universität wien

DISSERTATION

Titel der Dissertation

„Synthesis of Novel Antimalarials“

verfasst von

Christian Dank, BSc, MSc

angestrebter akademischer Grad

Doktor der Naturwissenschaften (Dr. rer. nat.)

Wien, 2015

Studienkennzahl lt. Studienblatt:	A 796 605 419
Dissertationsgebiet lt. Studienblatt:	Chemie
Betreuer:	Univ.-Prof. Mag. Dr. Walther Schmid

Danksagung

An erster Stelle möchte ich Dr. Hubert Gstach dafür danken, dass er mir diese schöne Arbeit ermöglicht hat und dass er mir täglich seinen unvergleichlichen Erfahrungsschatz sowie seine private Laborausrüstung zur Verfügung gestellt hat. Mit seinem unersättlichen Forschergeist wird er mir immer ein Vorbild sein!

Großer Dank gilt Prof. Walther Schmid, unter dessen Ägide diese Arbeit entstand. Für die Bereitstellung des schönsten Labors der Welt (Institut für Medizinische Chemie in der Währingerstraße 10, mit Ausblick auf die altehrwürdige Votivkirche) möchte ich mich bei Prof. Herbert Stangl bedanken. Eine solche Kulisse ist wahrlich kreativitätsfördernd. Darüber hinaus ist es ein Leichtes, mit bereichernden Kollegen wie Richard Wurzer BSc seine Forschung voranzutreiben.

Für das Starten dieses Projekts, an dem ich teilhaben durfte, möchte ich mich bei Prof. Peter Chiba und allen anderen involvierten Personen bedanken. Besonders hervorheben möchte ich dabei Matthias Mastalir MSc, der die meisten Verbindungen, die im Teil Preliminary Data aufgeführt sind, synthetisiert hat.

Ergebenst danke ich den MitarbeiterInnen unseres industriellen Kooperationspartners, der Marinomed Biotechnologie GmbH, darunter vor allem Dr. Andreas Grassauer, Dr. Eva Prieschl-Grassauer, Dr. Jan-Marcus Seifert, Dr. Martina Morokutti-Kurz, Franz Amberger sowie Tom Szewczyk.

Maßgeblich zur guten Atmosphäre am Institut und am Mittagstisch beigetragen haben die KollegInnen Dr. Hannes Steinkellner, Mag. Matthias Spork, Dr. Stefanie Fruhwürth, Dr. Yaprak Dönmez und natürlich unsere kommunikationskompetente und hinterfragende Labornachbarin Dr. Monika Praschberger.

Für Messungen am Chemischen Institut bin ich Dr. Hanspeter Kählig, Ing. Susanne Felsinger, Ing. Elena Macoratti, Prof. Eberhard Lorbeer und Dipl Ing. Alexander Roller zu großem Dank verpflichtet. Auch den ehemaligen Arbeitsgruppen Dr. Uwe Rinner und Prof. Johann Mulzer bin ich immer noch sehr dankbar für die einmalige Schule, die ich in diese Arbeit einfließen lassen konnte. Bei Simon Baldauf MSc, Dr. Martin Ariger und Dr. Martin Himmelbauer möchte ich mich darüber hinaus für die Abschiedsgeschenke bedanken.

Ich danke meinen Bandkollegen und Freunden von „Ramazuri“ (Helmut Barillari, Michael Barillari, Roland Gager, Sandro Kallinger, Philipp Kogler und Martin Liebentritt) für die schönen und produktiven Ablenkungen (Proben, Konzertreisen, CD-Aufnahmen) von meiner Arbeit. Diese Band begleitet mich schon fast mein halbes Leben, aus diesem Grund könnte ich das mit der Ablenkung fast umgekehrt formulieren.

Für Stimmungshochs und –tiefs, die teilweise wochenweise Periodizität hatten, möchte ich mich bei den Spielern und den Verantwortlichen des Fußballvereins „SK Rapid Wien“ bedanken. Das Leid, das durch die Tiefs hervorgerufen wurde, wurde glücklicherweise innerhalb des Fanklubs „PID-Freunde des Spaßes“ auf mehrere Schultern verteilt – danke dafür an die treuesten Freunde: Johannes Strehn, Armin Heinrich, Jakob Schnabl, Daniel Reisner, Ronald Heinrich, Georg Wind und Andreas Polt.

Besonders danken möchte ich den lieben Menschen, die mir das Abfüllen von Getränken im Zuge des „Big Frankies-Projects“ ermöglicht haben: Georg Wind, Andreas Polt, Paul Wagner und Rainer Haspel. Gleichermaßen danke ich den „Waschbärn 04“ für die schönen Jahre, die ich als Teil dieses Freizeitvereins erlebt habe.

Meinen Eltern, Isabella Appel und Gerhard Dank, und meiner Schwester Pia Milena Dank danke ich für einfach alles, das sie jemals für mich gemacht haben. Einen besseren Rückhalt kann man sich nicht wünschen. Dasselbe gilt für meine ganze Familie. Traurigerweise muss ich hier meinen Opa, Andreas Appel, und meinen Onkel, Josef „Pepi“ Dank, hervorheben, die die Fertigstellung dieser Arbeit leider nicht mehr erleben durften.

Ganz besonders möchte ich mich bei meiner Freundin Birgit Koch bedanken, die ein beispielloser Beistand in allen Lebenslagen ist.

Table of Contents

Abbreviations

ACT	artemisinin-based combination therapy
CAS	Chemical Abstracts Service
CAS RN	CAS Registry Number
COSY	correlation spectroscopy
CRT	chloroquine-resistance-transporter
CSP	circumsporozoite protein
d	days
DCC	*N,N*'-dicyclohexylcarbodiimide
DCM	dichloromethane
DDT	dichlorodiphenyltrichloroethane
DEET	*N*,*N*-diethyl-*m*-toluamide
DHPS	dihydropteroate synthetase
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
ee	enantiomeric excess
er	enantiomeric ratio
ESI	electrospray ionization
FACS	fluorescence-activated cell sorting
FBS	fetal bovine serum
FQ	ferroquine
G6PD	glucose-6-phosphate dehydrogenase
GFP	green fluorescent protein
h	hours
HATU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluoro-phosphate
hERG	human Ether-à-go-go-Related Gene
HMBC	heteronuclear multiple bond correlation
HOBt	Hydroxybenzotriazole
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectra
HSPGs	heparan sulfate proteoglycans
HSQC	heteronuclear single quantum coherence
Hz	Hertz
i.p.	intraperitoneal injection
IC_{50}	half maximal inhibitory concentration
IPA	isopropyl alcohol
IRS	indoor residual spraying
ITN	Insecticide-treated bed nets
LCMS	liquid chromatography–mass spectrometry
MDR	multi drug resistance
MHz	Megahertz
min	minutes
mp	melting point

MPLC	middle pressure chromatography
NADPH	nicotinamide adenine dinucleotide phosphate
NMR	nuclear magnetic resonance
NMRI	Naval Medical Research Institute
NOESY	Nuclear Overhauser Enhancement and Exchange Spectroscopy
p.o.	*per os* (oral administration)
PART	presumptive anti-relapse therapy
PQP	piperaquine phosphate
PV	parasitophorous vacuole
RBC	red blood cell
RDT	rapid diagnosis test
RMS	root mean square
RNA	ribonucleic acid
Swiss TPH	Swiss Tropical and Public Health Institute
TLC	thin-layer chromatography
TOF	time-of-flight
TRAP	thrombospondin-related adhesive/anonymous protein
UV	ultraviolet
WHO	World Health Organization

1. General Part

1.1 Malaria

Although the global malaria map has been shrinking over the past decades, today 3.4 billion people worldwide are estimated to be at risk of malaria.[1] This makes up 48 % of the world's population (7.137 billion in mid-2013)[2], therefore malaria is one of the world's most widespread infectious diseases.[3]

The species of parasite that affect humans all belong to the genus *Plasmodium*: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*. *Plasmodium falciparum*, which is beside *P. vivax* the most important species, is the most deadly form, and it is predominant in Africa.[1]

Access to affordable and effective medicines would be a giant leap in the global fight against malaria. The resistance against chloroquine, the traditional treatment, brought the at least ten times more costly artemisinins to the scene.[4] The increase of international disbursements to malaria-endemic countries from less than 100 million US $ in 2000 to nearly 2 billion US $ in 2013 moved malaria again to the spotlight. The contributions towards the fight against malaria with growth of research groups and scientific publications focused on antimalarial chemotherapy caused that malaria is no longer regarded as neglected tropical disease.[5]

1.1.1 Pathogenesis

The infection of a mammalian host starts by introduction of *Plasmodium* sporozoites into the skin. The sporozoites are present in the salivary glands of infected female *Anopheles* mosquitoes. A study published in 2007 showed in a model system that the majority of the infective sporozoites are at the injection site for hours and are slowly released into the circulation. Until then, it was considered that sporozoites immediately enter the circulation to enter hepatocytes, their unique target cell. The migration of the sporozoites from the infection site to the liver may take from 15 minutes to a few hours. It is suggested that not every infectious mosquito bite results in a patent blood stage infection, which leads to the assumption that a change of the host must constitute a bottleneck of the *Plasmodium* life cycle.[6-9]

Sporozoites movement occurs *via* gliding motility, which is made possible by the actomyosin motor of the parasite.[8,10,11] The transmembrane protein TRAP and related proteins mediate this form of substrate dependent locomotion. Sporozoites enter and leave cells by breaching their plasma membrane.[8,12] It was observed that rapid repair occurred after breaching the plasma membranes of host cells. The cytosols of several cells are traversed by sporozoites, before invading a hepatocyte.[13]

Once, sporozoites entered the blood circulation they rapidly head to the liver. It has been shown that interactions of the circumsporozoite protein (CSP), which is the major surface protein of sporozoites, with heparan sulfate proteoglycans (HSPGs), present on liver cells, is responsible for recognition and strong adhesion.[14-17] The transition through the sinusoidal barrier, possibly leads through Kupffer cells (liver resident macrophages). Then, sporozoites switch from the cell traversal phenotype to productive invasion phenotype.[16,18] This culminates in formation of a parasitophorous vacuole (PV), in which sporozoites develop into the next infective stage. It may be essential for completion of the life cycle that sporozoites must traverse several hepatocytes before forming the PV.[13]

The formation of the parasitophorous vacuole starts by constructing an intimate junction, by which the parasite finds its way to an invagination of the cell plasma membrane. Rapid remodeling of the host cell membrane by insertion of parasite proteins generates the membrane of the parasitophorous vacuole.[8] After productive invasion, *Plasmodium* sporozoites carry out an act of development and replication, by multiple rounds of nuclear divisions and segmentation, generating thousands of morozoites. This conversion is known as schizogony. Merozoites are contained in the membrane of the PV until they are released into the bloodstream to initiate the blood stage cycle.[8,16] It has been shown that manipulation of the host cells by the liver-stage parasites ensures migration of parasites into the blood stream and their protection from host immunity. Parasites induce the death and the detachments of their host liver-cell generating merosomes, parasite filled vesicles. These vesicles aid the parasite to safely pass the liver resident immune cells (Kupffer cells).[6,19,20]

A complicated process takes place when merozoites invade erythrocytes. First, recognition and reversible attachment of the merozoite to the membrane happens. Then, after orientation of the apical end of the merozoite towards the surface of the erythrocyte, an irreversible junction is formed. Simultaneous to the formation of a vacuole, invagination of the erythrocyte membrane by movement of the junction happens. This is accompanied by re-

moving the surface coat of the merozoite and resealing of the PV and the erythrocyte membranes, which concludes the invasion procedure. Then asexual division inside the erythrocytes starts and parasites develop therein. The earliest stage is the ring form with its eponymous morphology. Digestion of hemoglobin leads to formation of hemozoin (malaria pigment), a crystalline substance stored in the food vacuole, by polymerization of heme. "Trophozoite" is the term used for the intraerythrocytic growth phase. The final stage is the schizont. Each schizont releases between 16 and 32 merozoites, initiating a new erythrocytic infection cycle within seconds after release, upon rupture of the red blood cell (RBC).[6,8,16,21]

In a cycle of 48 to 72 hours parasites multiply and grow within RBCs, until these burst. Rupture sets free new parasites starting over the cycle again. Destruction of the host cells leads to fever, the guiding symptom of malaria. Increase of the body temperature is triggered by the release of cell components. In this context, glycosylphosphatidylinositol plays a special role, due to its similarity to bacterial antigens. Thereby, a massive fever reaction of the human organism is provoked.[22]

Instead of generating new invasive stages, some merozoites develop into gametocytes after seven to fifteen days for *Plasmodium falciparum* after starting the initial asexual cycle. This is where the sexual stage of malaria starts. The goal of the *Plasmodium* parasite is that a constant supply of mature male and female gametocytes, which develop over five stages[23], is available in mammalian host for uptake by a female *Anopheles* mosquito.[8,24-26]

When gametocytes reach their destination, they are transformed into gametes and egress out of erythrocytes, triggered by encounter of new compounds (xanthurenic acid, etc.) and an abrupt drop in temperature. Male gametocytes transform into eight highly motile gametes. This flagellar movement through blood was observed by Laveran (see section "1.1.4 History" starting on p. 15) which led to the discovery that *Plasmodium* parasites cause malaria. A diploid zygote is formed upon fertilization of female gametes. A zygote develops further to an ookinete, which penetrates the wall of a cell in the midgut of an Anopheles mosquito, where it evolves to the next stage: an oocyst. Sporozoites are produced within the oocyst until it ruptures to release the sporozoites, which then migrate to the salivary glands of the female *Anopheles* mosquito, to be transmitted to another mammalian host in the occasion of a blood meal.[6,8]

1.1.2 Symptoms and Pathogens

The first clinical symptoms of a malaria infection occur with the beginning of the erythrocytic phase. People suffer from high fever, cough, respiratory distress, shivering, headache, pain in the limbs, convulsions, nausea, vomiting and diarrhea. Often, a malaria infection is confused with a viral infection, due to similar indications.[27] Typically, fever attacks return regularly, due to synchronous asexual multiplication cycles (blood schizogony), and anemia may occur in severe cases of malaria.[6]

Malaria *tertiana*, which is caused by *Plasmodium ovale* and *P. vivax*, fever attacks return every 48 hours. *P. malariae* causes malaria *quartana* which returns in 72 hour rhythms. *P. knowlesi* is often misdiagnosed as *P. malariae*, due to morphological similarities.[28,29] Malaria *tropica*, which is caused by *Plasmodium falciparum*, occurs in irregular intervals.[6,22] This species is responsible for the most cases and deaths of malaria. Malaria *tropica* is the most aggressive type of malaria and may even lead to death. An adhesion protein (PfEMP1) mediates parasite binding to various receptors. It is expressed at the surface of infected erythrocytes.[30] With the adhesion protein on the surface, infected erythrocytes can bind to endothelium of various organs. Parasites are sequestered by themselves in several organs such as heart, lung, brain, liver, kidney, subcutaneous tissues and placenta. It is supposed that sequestration in the brain is associated to fatal cerebral malaria.[21,31]

Malaria is critical to pregnant women. It may cause premature birth or abortion, also maternal death is more likely. The probability for pregnant women to suffer from a severe case of malaria is three times higher compared to non-pregnant women. Severe cases of anemia are common, because the lack of iron and folic acid aggravates the infection.[32,33]

Although *P. falciparum* infections result in the most deaths, *P. vivax* is also sometimes complicated and life-threatening.[34-36] The global economic damage caused by *P. vivax* is believed to be up to four billion dollars per year. Because the burden of *P. vivax*, which is sometimes even called benign, is often underestimated, sometimes it is called a neglected disease.[37,38]

P. vivax and *P. ovale* infections also have an additional feature. In the human liver, hypnozoites are formed, which are in a state of quiescence. These hypnozoites may resume their development to mature schizonts in the liver after a long time, from months up to years after the infection. This means that cycles can start over and over once a human is infected with *P. vivax* or *P. ovale*.[39-41] This was discovered only in 1980.[42]

1.1.3 Epidemiology

Currently, malaria transmission is ongoing in 97 countries and territories. Seven countries are in the prevention of reintroduction phase. In total this sums up to 104 countries and territories in which malaria is presently considered endemic, a map is shown in Figure 1[43]. Globally, 3.4 billion people are estimated to be at risk of malaria. WHO estimates that 207 million cases of malaria occurred globally in 2012 and 627,000 deaths. Africa is worst affected with 80% of all cases and 90% of all global deaths caused by malaria. The disease is most fatal to children under 5 years of age, with 77% of all global deaths.[1]

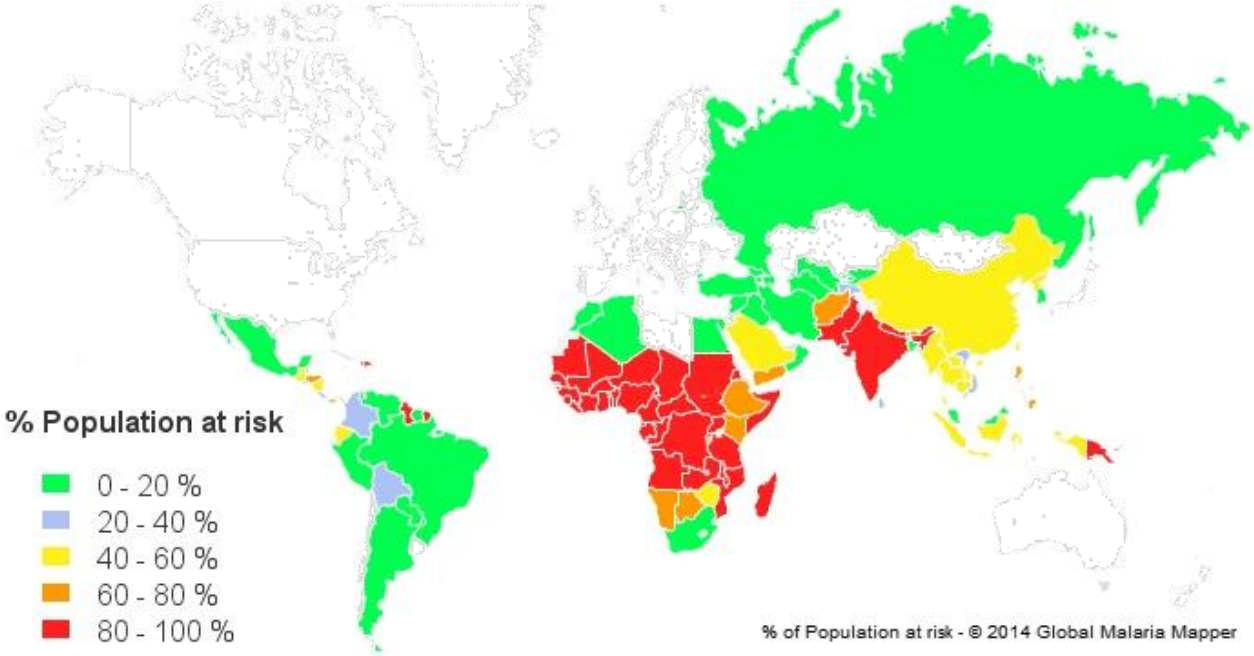


Figure 1. Percentage of Population at risk; Population at risk (High+Low): High=population living in areas (reported malaria incidence ≥ 1 per 1000/year) defined at administrative level 2 or lower. Low=population living in areas (reported malaria incidence < 1 per 1000/year). The map was created by the Medicines for Malaria Venture and the WHO Global Malaria Programme based on relevant data from the WHO World Malaria Report 2013.[43]

In West Africa, a region with intense transmission, *P. falciparum* is predominant. Except for Algeria, where also infections caused by *P. vivax* are reported. *P. vivax* is the only parasite species in West Africa. The populations of 15 of the 17 countries in this region are considered at high risk for malaria. In Central Africa also *P. falciparum* is predominant. In southern African countries with low transmission (Botswana, Namibia, South Africa, Swaziland and Zimbabwe) 80% of the population, about 55 million people, live in areas free of malaria. Nearly all of the reported cases are caused by *P. falciparum*, but transmission is highly sea-

sonal. In the rest of Africa (East Africa and southern African countries with high transmission) also *P. falciparum* is the only one parasite species, with the exception of Ethiopia and Eritrea where 45% of the reported cases are due to *P. vivax* infections.[1]

In both American continents *P. falciparum* caused less than 30% of all cases, and the disease is focused on very few countries. In 2012, 52% of all cases in this region were reported in Brazil. In this region substantial progress was observed over the past decade, emphasized through the decrease of reported malaria cases from 1.1 million in 2000 to 469,000 in 2012.[1]

In the eastern Mediterranean region high malaria transmission is still ongoing in areas of Afghanistan, Djibouti, Pakistan, Somalia, South Sudan, Sudan and Yemen. In Iran, Iraq and Saudi Arabia malaria case incidences were reduced by more than 75% between 2000 and 2012. The United Arab Emirates and Morocco are certified as malaria free since 2007 and 2010, respectively. Like Iraq, the Syrian Arab Republic, Oman and Egypt are in the prevention of re-introduction phase; Iran and Saudi Arabia are in the elimination phase. Except for Afghanistan, Iran and Pakistan where *P. vivax* is the dominant malaria species, also *P. falciparum* is predominant in the eastern Mediterranean region.[1]

In Azerbaijan, Georgia, Kyrgyzstan, Tajikistan, Turkey and Uzbekistan only 235 cases of malaria were reported in 2012. In contrast, 33,400 cases were reported in 2000. Interestingly these countries are termed as “European Region” by the WHO.[1]

One billion people are at high risk of malaria in the Southeastern Asian region, and another 1.6 billion people are at some risk. Except for Sri Lanka and Nepal where the most reported cases are due to *P. vivax*, *P. falciparum* is the predominant species of all malaria parasites in this region. Also in this region a decrease of reported cases was observed from the year 2000 (2.9 million) to the year 2012 (2 million). In the Western Pacific region, Papua New Guinea achieved the slowest decrease of malaria transmission since 2000. Unfortunately this is the country with the most reported cases and deaths of this region.[1]

In countries where malaria is eradicated, cases of reimported malaria occur as result of extensive travelling and temporary residence in places where malaria is endemic. Therefore, the possibility of malaria should be considered by physicians whenever a patient, who has recently been in malaria endemic areas, suffers from a febrile illness.[27,44] Between 1990 and 2000, 924 travel related cases of malaria were reported in Austria.[45] During the subsequent decade, this number decreased to 615 malaria cases which were reported to federal agen-

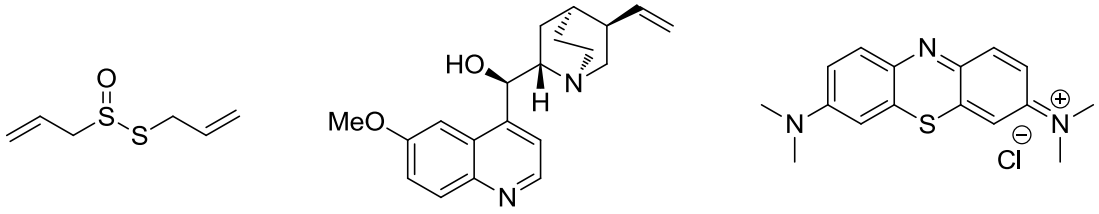
cies in Austria.[46] Currently, malaria prophylaxis recommendations for travellers in Europe are inhomogeneous as are the opinions of experts.[47] Recommendations regard preventive behavior, which includes the use of bed nets and repellents, chemoprophylaxis and, depending on the circumstances, stand-by emergency treatment.[48]

However, also in Austria *Anopheles* mosquitoes are endemic, therefore sporadic autochthonous malaria cases cannot be ruled out. Nevertheless, repatriation is hardly probable due to the fact that the Austrian health care system is covering all areas and social classes. Thus, an insufficient amount of gametocyte carriers would be available to keep up the parasite's life cycle.[49]

1.1.4 History

Malaria is accompanying mankind since the Neolithic Revolution, when humans became sedentary. Agriculture needed irrigation, which created suitable breeding places for malaria vectors. Advanced civilizations suffered from infectious diseases during warm periods in the valleys of the rivers Nile, Euphrates, Yellow River and Ganges.[50] The oldest archaeological finds containing ancient DNA of *P. falciparum* are mummies from the period of 3,500-1,600 BC.[51,52] DNA of *P. falciparum* was also found in Tutankhamun and his ancestors.[53] It was also discussed if Tutankhamun died because of malaria, sickle cell disease or Gaucher's disease.[54] Also, the bible passage "Then it happened that night that the angel of the Lord went out and struck 185,000 in the camp of the Assyrians; and when men rose early in the morning, behold, all of them were dead." (2 Kings 19:35), which reports the death of many soldiers in King Sanherib's army, is connected to malaria. Today it is assumed that the soldiers were infected with malaria in the deep and hot Jordan Valley, and that the outbreak came after the ascent of about 1,200 m to the cool mountain village of Jerusalem.[50]

Herodotus (484-425 BC), a Greek historian, reported that builders of the Egypt pyramids protected themselves from diseases of all kind by consumption of garlic (*Allium sativum*). It is assumed that the construction of this admired wonder of the world could not have been built without malaria control. Allicin (**1**), see Figure 2, an organosulfur compound found in garlic, has an insect-repellent effect, which is not yet shown for garlic consumption.[55] Furthermore, Herodotus made an interesting observation during his Egypt journey. He stated that that people living in the Nile Delta lived in elevated dwellings and slept under fishing nets it to keep out insects.[56]



allicin **1** quinine **2** methylene blue **3**

Figure 2. Historically relevant compounds.

Before malaria transmission was elucidated, people thought that infectious diseases were caused by *miasma*. This term was coined by Hippocrates of Cos (~460-377 BC), who described it as gaseous substance, caused by rottenness and decomposition, spreading over the air and causing illness. It was considered that infections were not passed from individuals to each other, but that the origin of the *miasmata* is soil. Hippocrates blamed the *miasma* of the swamps for the regular returning fevers that epidemically killed people. Therefore, he recommended not to settle in swampy areas or to drain swamps.[57] It was also Hippocrates who established the expressions "tertian fever" (tritaios pyretos, *febris tertiana*) and "quartan fever" (tetartaios pyretos, *febris quartana*).[50]

At least since 200 BC malaria was endemic in the Campagna, a region surrounding Rome. The importance of malaria in Italy grew until 1,000 AD. The death of the Roman Emperor Titus (81 AD) is also suspected to be caused by a malaria infection.[50]

When Attila the Hun led his army through Northern Italy, refugees built pile dwellings for protection in a saltwater lagoon. This habitation remained generally free of malaria, because local *Anopheles* mosquitoes do not lay their eggs in saltwater, and the distance between coast and habitation was beyond the action scope of the mosquitoes. The habitation developed to the beautiful trade city Venice, and Attila backed out with an army harassed by malaria to their Asian homeland.[50]

America was free of malaria until 1,500 AD, when European conquerors and conquistadores came, and with them their African slaves. From the local population Spanish missionaries learnt about remedies. Especially the bark of the *cinchona*, growing in the high forests of the Andes Mountains at 1,200 – 2,700 m above sea level from Bolivia to Venezuela, was of huge interest. Quinine (**2**, shown in Figure 2), the active agent of the bark, has a relaxing effect on muscular system and was used to treat muscle tremors in the colds of high mountains. The Jesuit brother Agostino Salumbrino (1561-1642), who also was pharmacist, learned about

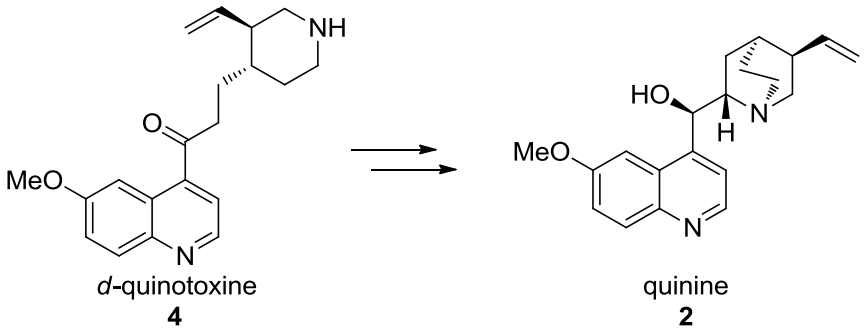
the application of *cinchona* bark from the Quechua people in Lima. The Jesuit Order propagated the use of the bark in Europe since 1632, but because of nondisclosure reasons it was imported as powder and labeled "Jesuit's Powder". Certainly, this label was not welcome in all parts of Europe due to religious conflicts. Oliver Cromwell, the leader of the English Protestants, died 1658 on a malaria infection because he refused the treatment with "Jesuit's Powder". His successor, King Charles II, was successfully treated with quinine (**2**), in secret, in 1678 or 1679.[50,58] It was Sir Robert Talbor who cured the English King. Later he travelled through Europe curing hundreds of royal and aristocratic persons. Among them was the son of Louis XIV, which provided him the additional title of Chevalier Talbot, and Louisa Maria, the Queen of Spain.

There are several different opinions about who used the term "malaria" for the first time. For sure it can be translated to "bad air" from Italian or Latin. In some references Francesco Torti[57] (1658-1741), an Italian physician, is considered as neoterist. But the term was used long before Torti by Leonardo Bruni[50] in the year 1476, and Cornaro[56] 1440. But without any doubt, the publication of the opus "Therapeutice Specialis ad Febres Periodicas Perniciosas" in 1712 was Torti's merit. This document was highly popular and prerequisite for the prevalence of *cinchona* therapies. Giovanni Maria Lancisi, a coeval of Torti, described black-brownish deposits in the spleen and brain of malaria patients. Lancisi is believed to be the founder of modern hygiene. Black brownish pigments also occurred to the German physician Heinrich Meckel in 1847 during the autopsy of a mentally disordered patient. He did not associate the pigment with malaria, two years later Virchow correctly associated the pigment with hematin crystals.[50] Now we know that this brown pigment is a product of the digestion of hemoglobin and is produced through biocrystallization by the malaria parasite.[59] The brown pigment (hemozoin) in organs at autopsy is a strong indicator of malarial infection.[60]

Modern malaria therapy started in 1820, when Pelletier and Caventou successfully isolated quinine (**2**), the most important alkaloid in *cinchona* bark.[61,62] This allowed correct dosage. Before 1820, dried *cinchona* bark was powdered and mixed with wine before it was drunk. Very often therapeutic effects were not observed due to wrong dosage.[50] The export of *cinchona* plants and seeds was then forbidden under death penalty by South American governments to maintain the monopoly on *cinchona* bark. Despite the risk, the English adventurer Charles Ledger smuggled 14 pounds of *cinchona* seed to England. In the end, he sold the seeds to the Dutch in 1865, which were planted in Java later.[63] Through reckless exploi-

tation in the South American Andes Mountains, then the Netherlands had the monopoly on quinine (**2**) at the end of the 19th century.[64]

Quinine (**2**) extraction from *cinchona* bark was expensive, so a cheap synthesis became an attractive task for ambitious chemists. In 1856, when William H. Perkin tried to synthesize Quinine he unfortunately did not reach his initial goal, instead he synthesized mauveine (the first organic chemical dye), which started a veritable industrial revolution.[64,65] The first synthetic antimalarial was methylene blue (**3**), which cured two malaria patients in Berlin, is shown in Figure 2. Although it never could challenge the dominant position of quinine (**2**), methylene blue is currently experiencing a renaissance and is, besides therapy, of importance for the fight on malaria as ingredient of Giemsa stain, used for histopathological diagnosis of malaria. This standard method is nowadays more and more replaced by "Rapid Diagnosis Test" (RDT).[50,66] The first total synthesis of quinine (**2**), which was not economical due to its complexity, succeeded in 1944. In fact it was only a formal synthesis, because Woodward and Doering described the synthesis of *d*-quinotoxine (**4**), which was converted before to quinine (**2**) by Rabe and Kindler in 1918.[50,65] The schematic conversion, which was performed within 3 steps under formation of various side products, is shown in Scheme 1.



d-quinotoxine
4

quinine
2

Scheme 1. Conversion of 4 **to quinine (**2**).**

The presence of parasites in the blood of malaria patients was discovered in 1880[50] by the French army surgeon Charles Louis Alphonse Laveran. It was Ronald Ross reporting mosquitoes to transmit malaria.[6] Laveran and Ross were awarded Nobel Prizes in 1907 and 1902, respectively. Giovanni Batista Grassi was the first to report the complete life cycle of *P. falciparum* in 1989, and to specify the term mosquitoes to female *Anopheles*, which are the only kind of mosquitoes to infect humans with malaria. There was a huge controversial between Ross and Grassi with Robert Koch interfering, with the more favorable outcome for Ross receiving the Nobel Prize alone.[50,67,68] Between 1885 and 1892, Camillo Golgi, who received a

Nobel Prize in 1906, fought the common idea that malaria was caused by a bacterium and found that different species of *Plasmodium* caused different types of malarial fevers. He also stated that rupture and release of merozoites into the bloodstream coincided with the paroxysm of fever.[60,69,70]

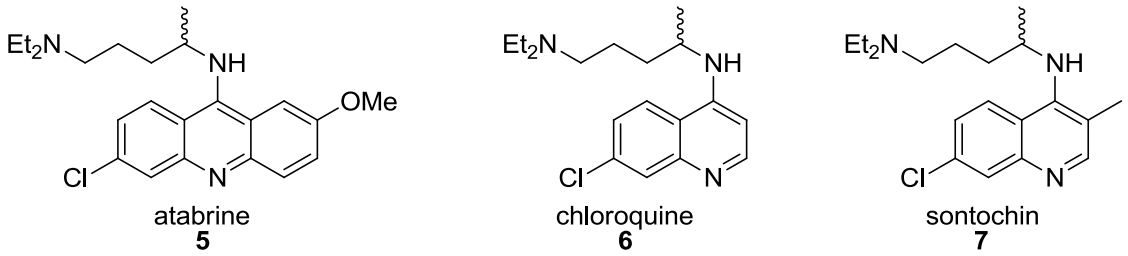


Figure 3. Approved 4-Aminoquinolines.

The development of synthetic antimalarials was considered as strategic necessity in times of war by developed countries in the beginning of the 20th century. In the Bayer research laboratory in Elberfeld, a municipal subdivision of the German city of Wuppertal, the workgroup of Fritz Mietzsch synthesized atabrine (**5**), which was shown by Walter Kikuth to be a promising malaria therapeutic. It entered the market as first full-value alternative to quinine (**2**) in 1932. Remarkably, the German antimalarial atabrine (**5**) had a huge contribution in the victory of the Allied over Japan in World War II. In 1934, Hans Andersag synthesized chloroquine (**6**, in first place he called it "resochin"), which has a quinoline ring instead of the acridine ring in atabrine (**5**). Chloroquine (**6**) was erroneously considered as too toxic, which delayed the use by many years.[71] During the African Campaign, sontochin (**7**) was used by German Wehrmacht, because it was believed to be less toxic than resochin (**6**). Hermann Göring may have profited of sontochin (**7**), because it is believed that he was the only patent proprietor.[50] In 1945 chloroquine (**6**) was introduced onto the market by American partners of IG-Farben, which was only known as "Resochin" until then.

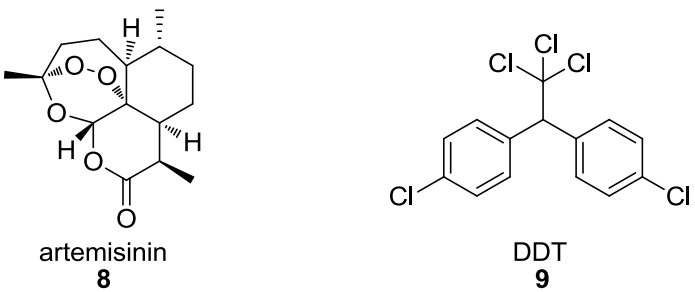


Figure 4. Important compounds in the second half of the 20th century.

Another natural remedy for malaria was found in the traditional Chinese medicine. At the time of the Vietnam War, the Chinese government initiated a revival of traditional treatments. In 1972 old manuscripts were found, in which for the first time the medicinal plant "quing-hao" (*Artemisia*, wormwood) is mentioned. According to Ge Hong (284-343), the extract of the plant was obtained by neutral extraction from dry plants at mild heat and drunk without further treatment. Of nearly 400 species of *Artemisia*, only *Artemisia annua*, *A. apiacea*, and *A. lancea* are known to produce the active antimalarial compound artemisinin (**8**, "qinghaosu").[50,72] Today, artemisinin (**8**) is mainly produced in semisynthetic manner starting from a precursor produced by yeast cells. Sanofi planned to produce 50 – 60 tons of artemisinin in 2014.[26,73,74]

As a result of changes in agricultural practices, land use and house construction and some targeted vector control, malaria was eliminated in the mid of the 20th century from most of Europe and the United States of America. A global eradication program initiated by the development of the highly active residual insecticide DDT (**9**) in the 1950s and 1960s showed only temporary successes in many countries such as India, Sri Lanka and the Soviet Union. These successes were not permanent, because of the appearance of resistances to DDT (**9**), the denial of repeated spraying in some communities and the high costs of the program. [75] The disappearance of malaria from most of Europe and North America led to a loss of interest in drug development for the next 25 years. This is emphasized by the fact that only 3 of 1,223 new drugs that were developed from 1975 to 1996 were antimalarials.[76]

1.2 The Fight Against Malaria

1.2.1 Prevention by Insect Control

Vector control is defined as one of four basic and most effective measures by the WHO. Primarily, vector control is carried out by usage of Insecticide-treated bed nets (ITNs) and Indoor residual spraying (IRS). The extensive use of chemical insecticides began in the 1940s. Organochlorines, organophosphates, carbamates and pyrethroids are compound classes of historically important insecticides.[77,78]

In sub-Saharan Africa, where most of the world's malaria burden occurs, endemic mosquitoes are highly specialized and almost rely on humans (*Anopheles funestus* and *An*. *gambiae*) or humans and their cattle (*An*. *arabiensis*). The required malaria transmission level to maintain populations of *P*. *falciparum* is exceeded 10,000 times by these exceptional vectors.[79]

Through the use of ITNs and IRS, transmission suppression by two orders of magnitude can be achieved. These methods, however, can rarely contribute towards elimination, since vectors also feed outdoors or upon cattle. Thereby they evade contact with insecticides. Nevertheless, there are some other species of *Anopheles* mosquitoes that actually were completely eliminated in some areas for some time. For instance, *An*. *funestus* disappeared from an area in Tanzania as a result of three years of IRS with dieldrin (**10**), which is shown with other synthetic insecticides in Figure 5. It took the species five years after the IRS was stopped to re-establish itself in the area. Notably, the speed of the re-appearance indicated that *An*. *funestus* was completely gone.[79] Also *An. sinensis*, the major malaria vector in China and other countries in Southeast Asia, were reported to possess high levels of resistance against deltamethrin (**11**), a nonvolatile pyrethroid, in China and Korea.[77] Pyrethroids are shown in Figure 6.

The same species was also rendered extinct in South Africa by IRS with DDT (**9**). It remained absent for four decades, and returned when DDT (**9**) was replaced by pyrethroids.[79]

Spraying DDT (**9**), which was subject of the Nobel Prize in 1948, is conversely discussed, due to concerns regarding environment and health. Despite these concerns DDT (**9**) was reported to be used in six African countries as residual spray in 2013.[1,80,81]

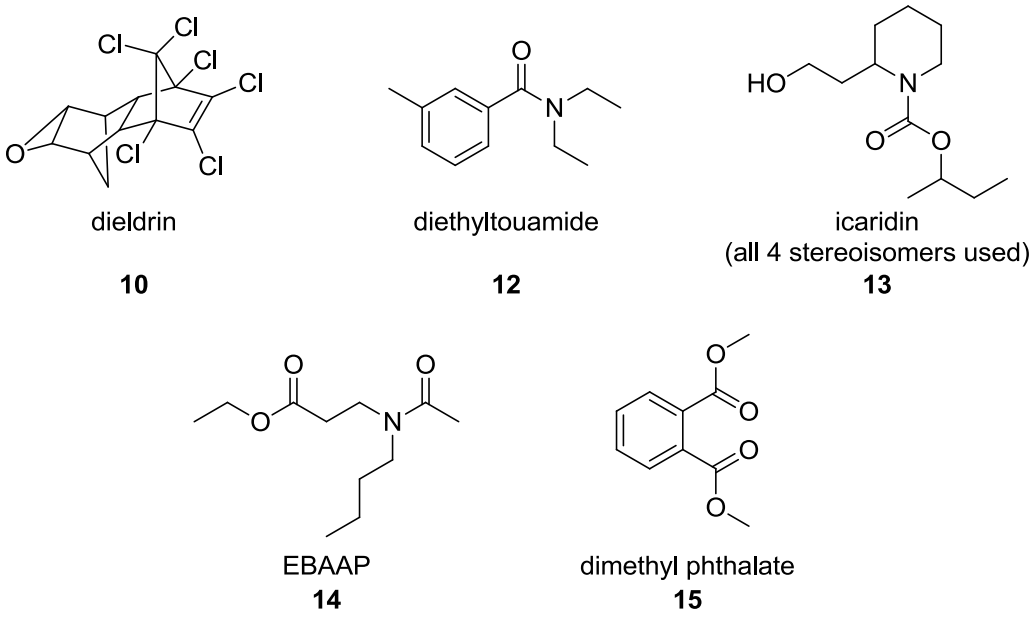


Figure 5. Synthetic insecticides.

Originally, *N*,*N*-diethyl-*m*-toluamide (**12**, DEET) was designed for soldiers of the US-Army. It developed to today's gold standard of repellents. It is estimated that about 200 million people use DEET (**12**) per year.[82,83]

The organic compounds that are part of pyrethrum, which is a natural insecticide made from different kinds of *Chrysanthemum*, possessing an insecticidal activity are called pyrethrins. These attack the nervous systems of all insects. In non-lethal amounts they still have an insect repellent effect. Compounds similar to pyrethrins are called pyrethroids. These compounds are the only approved insecticides for use on ITNs, because they pose only very low health risks to human and other mammals but are lethal to insects even at low doses.[83]

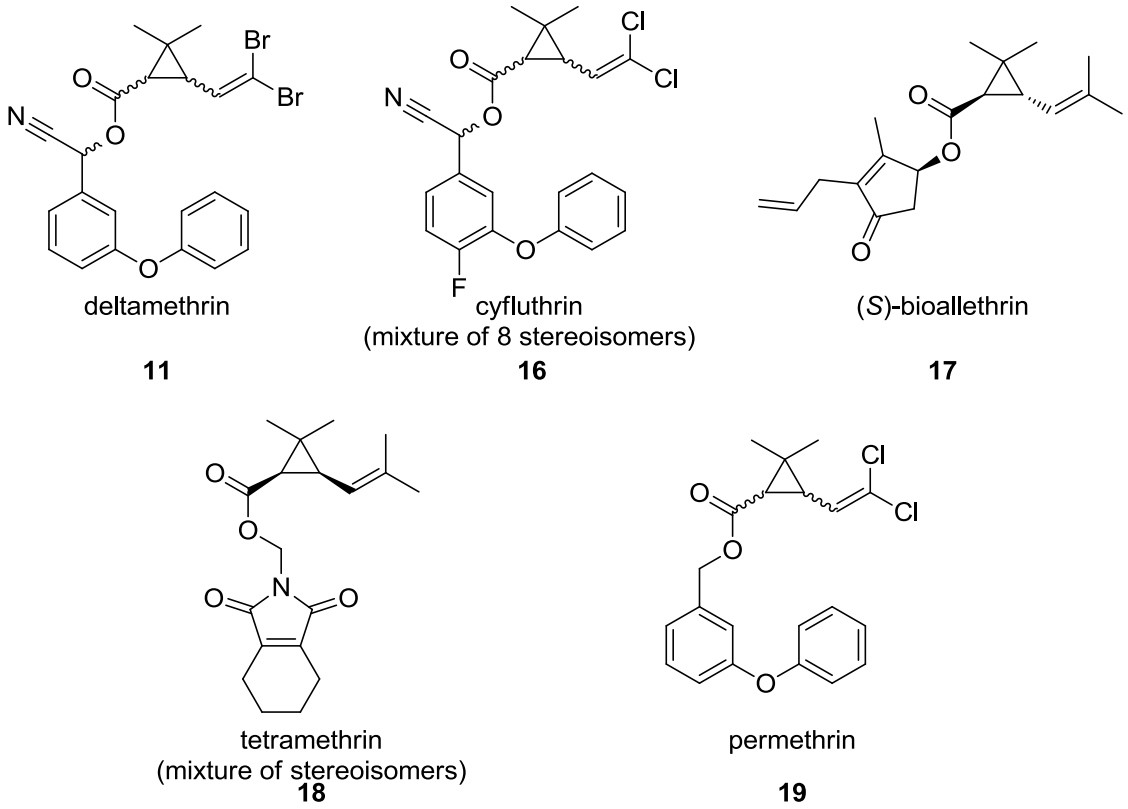


Figure 6. Pyrethroids 11 **and** 16-19**.**

1.2.2 Medications

Medications used to prevent and treat malaria belong to the following substance classes: aminoalcohols, 4-aminoquinolines, 8-aminoquinolines, artemisinins, antifolates, antibiotics and inhibitors of the respiratory chain.[84,85]

Table 1. The global malaria portfolio (Q2/2014); retrieved in August 2014 from MMV (Medicines for Malaria Venture, www.mmv.org). Translational stage (preclinical and human volunteers) was omitted.

Development			Access
Patient exploratory	**Patient confirmatory**	**Under review**	**Post Approval**
OZ439/PQP Sanofi	**Tafenoquine** GSK	**Rectal Artesunate** CIPLA/Strides/TDR	**Artemether-Lumefantrine**[1] Novartis
OZ439/FQ Sanofi	**DHA Piperaquine** *Paediatric* Sigma-Tau	**Sulfadox-ine/Pyrimethamine + Amodiaquine** Guilin	**Artemether-Lumefantrine Dispersible**[2] Novartis
KAE609[11] Novartis	**Co-trimoxazole Bactrim** Inst. of Trop. Med.	**Arterolane/PQP**[8] Ranbaxy	**Artesunate**[3] *for injection* Guilin
KAF156 Novartis	**Artemisinin-Naphthoquine**[9] KPC		**Dihydroartemisinin-Piperaquine**[4] Sigma-Tau
Methylene Blue/AQ Heidelberg	**Pyronaridine-Artesunate** *Paediatric* Shin Poong/Iowa		**Pyronaridine-Artesunate**[5] Shin Poong
SAR97276 Sanofi	**Artemether**[10] *sublingual spray* Proto-Pharma Ltd		**Artesunate Amodiaquine**[6] Sanofi/DNDi
Fosmidomycin Piperaquine Jomaa Pharma GmbH			**Artesunate Mefloquine**[7] CIPLA/DNDi
Artemisone UHKST			

1 Brand name: Coartem®, Generics by Ajanta, Cipla, Ipca, Strides, Macleods Pharma Ltd, Mylan Laboratories

2 Brand name: Coartem® Dispersible, Generic by Ajanta

3 Brand name: Artesun®

4 Brand name: Euratesim®

5 Brand name: Pyramax®

6 Brand name: Coarsucam™, ASAQ/Winthrop®, generics by Ajanta, Ipca, Guilin, Cipla, Strides (co-blistered)

7 Also Acino/Mepha product (co-blistered)

8 Brand name: Synriam™

9 Brand name: ARCO®

10 Brand name: ArTiMist™

11 Formerly known as NITD609

Aminoalcohols

Aminoalcohols, depicted in Figure 7, have in common a lipophilic aromatic system and a secondary or tertiary amino moiety close to a hydroxyl group. The synthetic compounds lumefantrine (**20**), halofantrine (**21**) and mefloquine (**22**) can be seen as simplification of the complex, historically very important, quinine (**2**). The mechanism of the antimalarial effect of this substance class is not known yet. The hemoglobin metabolism of the parasites is hindered, an effect which is also caused by 4-aminoquinolines, but apparently by a different mechanism. Aminoalcohols and 4-aminoquinolines may target the same membrane-target, but aminoalcohols hinder the release of Ca^{2+} ions and thereby prevent the fusion of transport-vesicles and the food-vacuole.[62,84,86]

The sensitivity of the parasites against aminoalcohols also depends on multi-drug resistance (MDR) effects. There are also some expectations that MDR1-transporters are the biological target of aminoalcohols.[84]

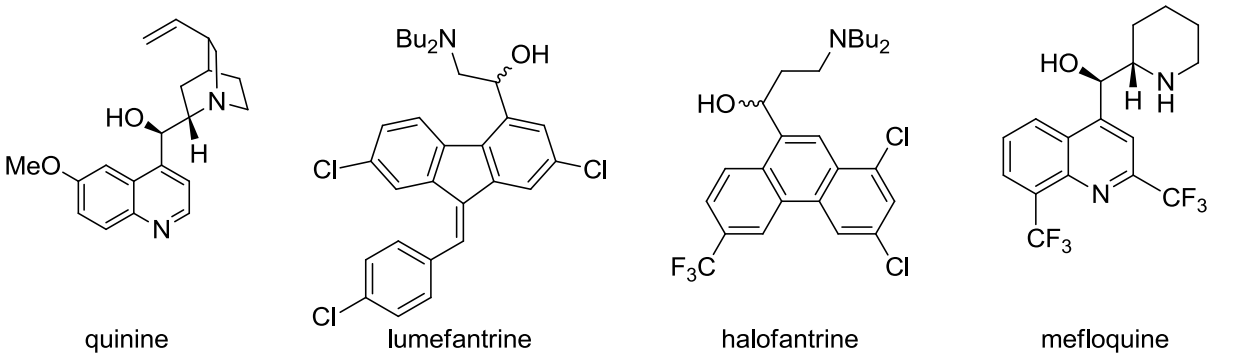


Figure 7. Aminoalcohols used for treatment of malaria.

Pure quinine (**2**) was used to treat malaria since 1820, nowadays it is still an important therapeutic, especially to parenterally treat complicated malaria. A French preparation, "Quinimax"®, contains 96% quinine (**2**). Apart from this, quinine (**2**) is no longer commercially available in finished dosage forms in most European countries.[84]

Mefloquine (**22**), see Figure 7, was introduced to the market as Lariam® in 1985. Due to its long half-life (21 days) administration is only needed once a week. Therefore, this substance was frequently used. Nevertheless, the scope of **22** is limited due to the high costs compared with other antimalarials and, even worse, it is associated with debilitating neurological effects in a small proportion of patients and milder concerning effects have also been ob-

served. The enantiomers of mefloquine (**22**), which is marketed in racemic form, differ in biological activity. (-)-11*R*,12*S*-Mefloquine possesses the same configuration as quinine (**2**), while the conformation of the (+)-enantiomer is similar to quinidine (**23**). These differences are reflected in biological activities, although there have also been studies, stating that all four stereoisomers of mefloquine are equally active against *P. berghei*.[84,87-90]

Halofantrine (**21**) shows high activity, but it is no longer available in most western countries, due to cardiac arrhythmias it caused. The structurally related lumefantrine (**20**) shows much less activity, but no cardiac effects were observed after administration of lumefantrine (**20**). The bioavailability of lumefantrine (**20**) is highly dependent on the nutrition. When lumefantrine is ingested with a fat-rich meal the resorption is 16 times higher. Often milk is recommended as best form of fat to increase the resorption. The reasonably priced lumefantrine (**20**) is only available as fixed dosage (containing 20mg artemether and 120 mg lumefantrine, Coartem®) with artemether (**24**), shown in Figure 10. The different pharmacokinetics of artemether (**24**) and lumefantrine (**20**) create a synergy. While artemether (**24**) is absorbed in a rapid manner, lumefantrine (**20**) eradicates the remaining parasites over a longer term. One of the great advantages of this fixed dosage is that only very few parasites are exposed to lumefantrine (**20**) alone and no parasites are exposed to artemether (**24**) and its metabolite dihydroartemisinin (**25**, see Figure 10) alone. Such artemisinin-based combination therapies (ACT) are recommended by WHO to replace artemisinin-based monotherapies to prevent or delay the development of resistances. It was shown that the desbutyl-metabolite of lumefantrine (**20**) shows even greater antimalarial potency than lumefantrine itself.[84,91-96]

4-Aminoquinolines

The common features of 4-aminoquinolines are a basic side chain connected to the nitrogen atom in the 4-position of the quinoline ring and a chlorine atom in the 7-position of the quinolone ring. The exact mechanism is also unknown for 4-aminoquinolines, but it is supposed that 4-aminoquinolines form stable complexes with the degradation product of hemoglobin. During the blood stage the parasite *P. falciparum* digests up to 80% of the hemoglobin present in an acidic food vacuole. Normally, hemozoin is formed from degradation products during the blood stage of the parasite, but the ferriprotoporphyrin complexes formed with 4-aminoquinolines are toxic for the parasite.[97]

Before the spread of chloroquine-resistant *P. falciparum*, chloroquine was considered as perfect antimalarial due to its efficacy, safety (even for pregnant women and newborns),

pharmacokinetics and its low costs.[5] Chloroquine-resistance-transporter (CRT), which belongs to the drug/metabolite-transporter superfamily, is responsible for the resistance of parasites against chloroquine (**6**) and other 4-aminoquinolines depicted in Figure 8. The physiological function of CRT, which is located in the membrane of the food vacuole, is unknown. It is also unknown whether the drug is actively transported or if the CRT-protein is just a channel which the drug has to pass in order to leave the food vacuole. The importance of chloroquine (**6**) nearly vanished, because chloroquine-resistant strains of *Plasmodium falciparum* can be found in the whole area of distribution of *P*. *falciparum*.[84]

Another important representative of the 4-aminoquinolines is amodiaquine (**26**). The phenyl group and the Mannich base moiety are characteristic for this compound. It is probably the aromatic side chain which is responsible for the reduced affinity of amodiaquine (**26**) to the CRT. However, in cases of high grade resistant strains against chloroquine (**6**) also amodiaquine (**26**) is not effective. Long prophylactic treatment with amodiaquine (**26**) leads to heavy damage to the liver. Also immune reactions against blood-building systems were observed upon longer treatment. Due to these crucial side effects which only occurred during longer treatment, amodiaquine (**26**) is used in Africa as cheap therapeutic agent in combination with artesunate (**27**) or sulfadoxine (**28**, see Figure 11)/pyrimethamine (**29**, see Figure 12).[84]

In the molecular structure of ferroquine (**30**, abbreviated as FQ), the first organometallic antimalarial, a ferrocenyl group is flanked by a basic alkylamine and a 4-aminoquinoline. This compound is currently under development, see Table 1. The antimalarial activity is related to the ability of ferroquine (**30**) to target lipids. FQ inhibits the formation of hemozoin and generation of reactive oxygen species.[98] With piperaquine (**31**) another member of the 4-aminoquinoline compound class is also present in four advanced projects (in two of them in phosphate formulation, as PQP) and one even post approval.

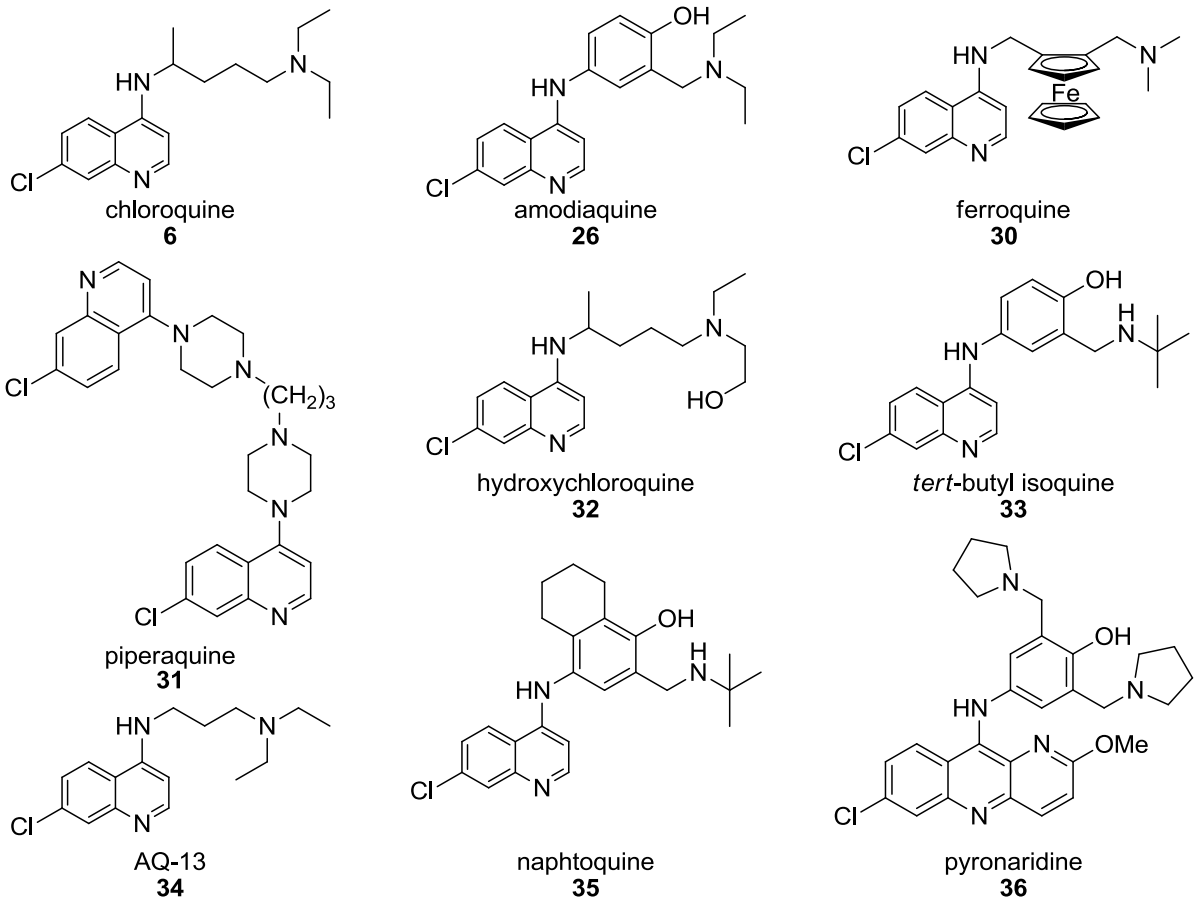


Figure 8. Antimalarial 4-aminoquinolines.

8-Aminoquinolines

The amino alkyl chain connected to the nitrogen atom in the 8-position of the quinolone ring system and the methoxy group in the 6-position of the quinolone ring system are characteristic parts of 8-aminoquinolines. Important representatives of this substance class are shown in Figure 9. The first 8-aminoquinoline used against malaria was diethylprimaquine (**37**), also known as pamaquine or plasmoquine, which was introduced in 1925. It was not widely used due to its toxic properties. The replacement of the diethyl amino group through a simple primary amino group resulted in primaquine (**38**), which is used since 1952. Primaquine (**38**) is the only antimalarial that destroys all liver stages of the parasites, including the enduring hypnozoites formed in case of *P. vivax* or *P. ovale* infections. Therefore, it can also be used for prophylaxis and for presumptive anti-relapse therapy (PART) in cases of extensive exposure to parasites. A contraindication is deficiency in glucose-6-phosphate dehydrogenase (G6PD), when primaquine would be administered lethal hemolysis may be caused. This also rules out pregnant women, because even a normal level of G6PD of the pregnant women does not tell anything about the fetus.[84,99]

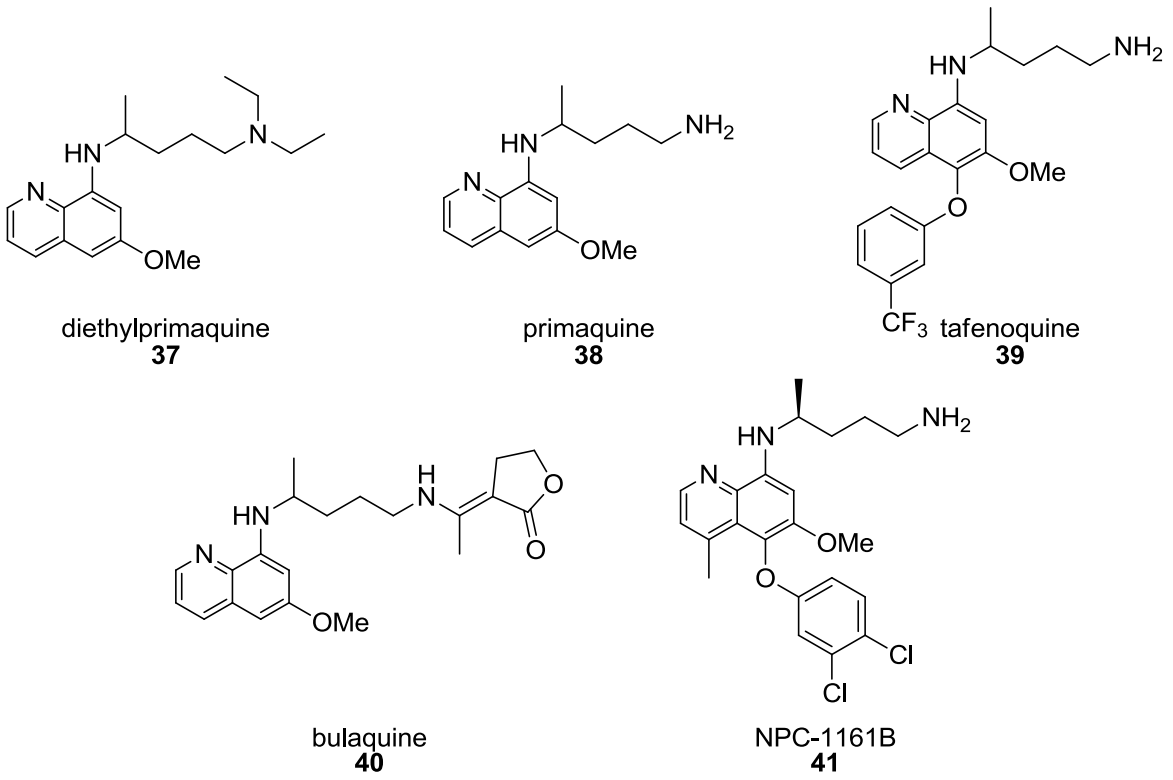


Figure 9. 8-Aminoquinolines 37-41**.**

Artemisinins and Other Endoperoxides

Artemisinin (**8**) is badly soluble in oil as well as in water. Therefore, only semisynthetic derivatives of artemisinin (**8**), see Figure 10, are used exclusively today. Dihydroartemisinin (**25**), which is not suitable to be used in pharmaceutical formulations due to its intrinsic instability, is the active form of all artemisinin related drugs.[100] Artesunate (**27**) is converted to dihydroartemisinin (**25**) during minutes, probably in a non-enzymatic way. The conversion of artemether (**24**) to dihydroartemisinin (**25**) happens *via* oxidative desalkylation and takes much longer. Artemisinins also take effect on ring stages, the early erythrocytic stages. The burden of the parasites is reduced by a factor 10^4 per asexual cycle. Therefore, artemisinins are the fastest and most effective drugs against malaria known today.[84] But monotherapies lead to a high rate of recrudescence despite the remarkable activity of artemisinin (**8**) and all its derivatives. Therefore the use of ACT is not only reasonable due to delay of growing artemisinin resistances but also in view of possible failure of artemisinin monotherapies.[101]

Unfortunately, the cost of ACT may be too high for malaria endemic countries with low income. Another issue is the discovery of upcoming resistances in South East Asia.[102,103]

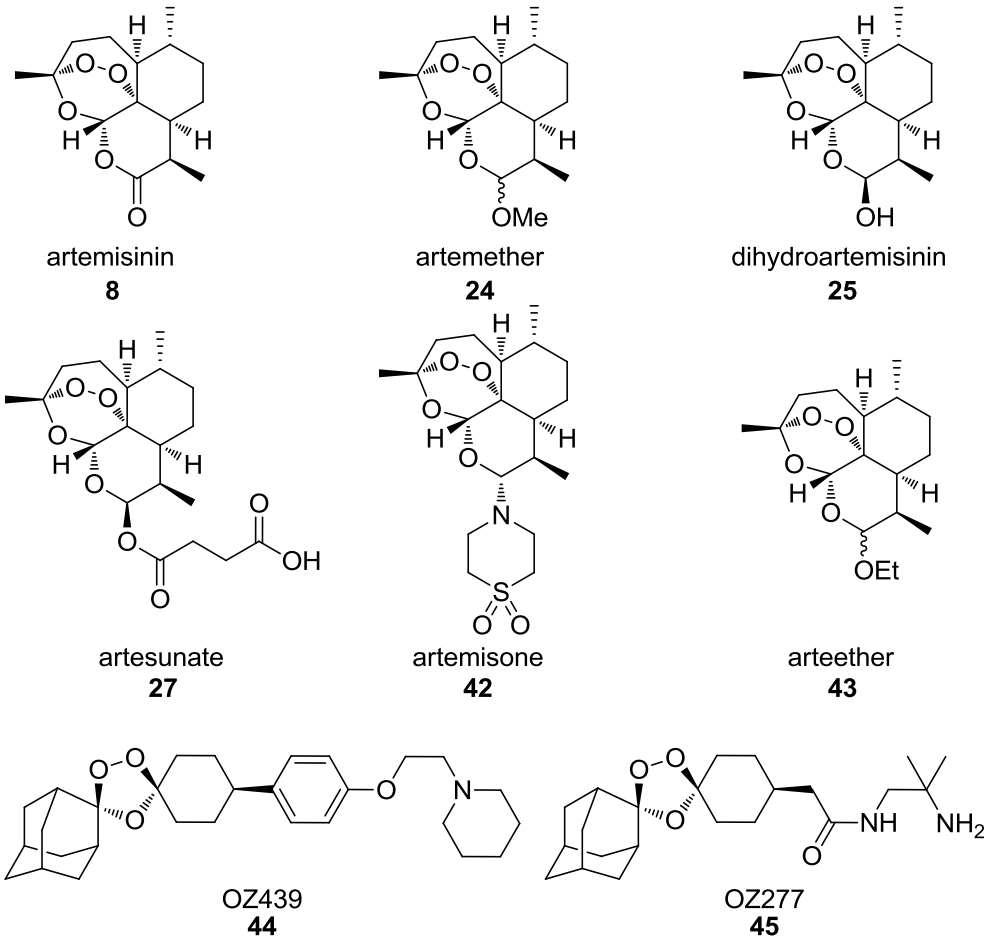


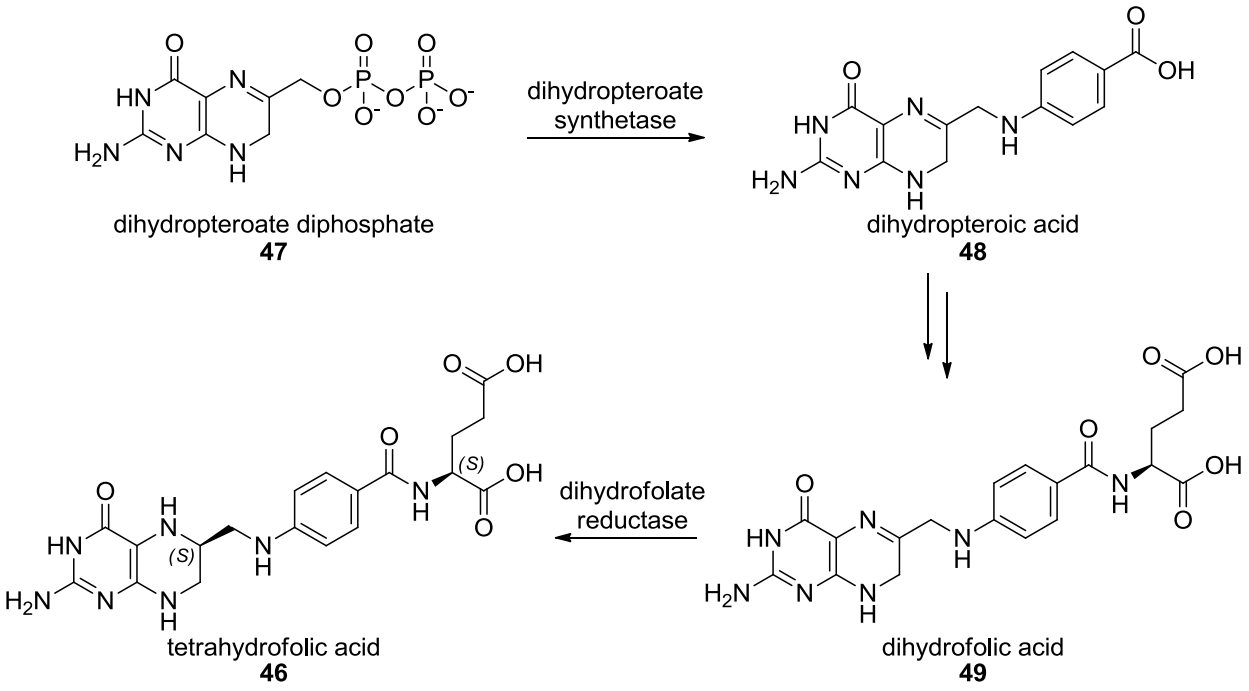
Figure 10. Artemisinin derivatives and other endoperoxides.

The essential structural feature responsible for antimalarial activity is the endoperoxide moiety. There are various theories about the mechanism of artemisinins. On one hand there is the martial picture of “iron-triggered cluster bombs”, which seems unlikely due to occurring resistances against artemisinins which cannot be explained by an unspecific mechanism like this. This thought is also unlikely because compounds without heme reactivity showed high activity. Also inhibition of heme formation does not stop artemisinin (**8**) from being active. On the other hand there is proposed that artemisinins inhibit a calcium-ATPase (*Pf*ATP6). If artemisinins have a specific target, such as *Pf*ATP6, then mutations could lead to resistances against artemisinins. This is also not really plausible, since tremendous variations in the artemisinin backbone and stereochemistry do not dramatically affect the antimalarial activity. In a third model artemisinin is believed to be activated by malaria mitochondria and surrounded molecules are non-specifically damaged by generated free radicals from the endoperoxide group.[84,104,105]

OZ277 (**45**) was the first synthetic ozonide which was clinically evaluated. It is also known as RBx11160 or arterolane maleate. Ozonides and artemisinins have the peroxide moiety in common, which can be seen as pharmacophore. Regardless of the convincing antimalarial activity of OZ277 (**45**), the half-life is only twice to threefold longer as that of the very instable dihydroartemisinin (**25**). Whereas OZ439 (**44**), another synthetic ozonide, is a more promising candidate and can be found in two advanced projects in Table 1.[106,107]

Antifolates

Unlike humans, which have to ingest folic acid with their food, bacteria and protozoa are not depending on the uptake of folic acid to generate the important cofactor tetrahydrofolic acid (**46**), which plays an important role in many reactions especially in the metabolism of amino acids and nucleic acids. Therefore, inhibition of one of the relevant enzymes, dihydropteroate synthetase (DHPS) or dihydrofolate reductase, is a classical principle in antimicrobial chemotherapy. A simplified pathway is outlined in Scheme 2.[84]



Scheme 2. Tetrahydrofolate synthesis pathway.

The substitution of the diphosphate moiety of **47** with *para*-amino benzoic acid is catalyzed by the enzyme dihydropteroate synthetase. Sulfonamides, such as these shown in Figure 11, inhibit this reaction due to structural similarity to *p*-amino benzoic acid. They also react instead of *p*-amino benzoic acid to give sulfa-dihydropteroates. These compounds show an-

tiparasitic effects, possibly by inhibition of dihydrofolate reductase, the second important enzyme shown in Scheme 2.[84]

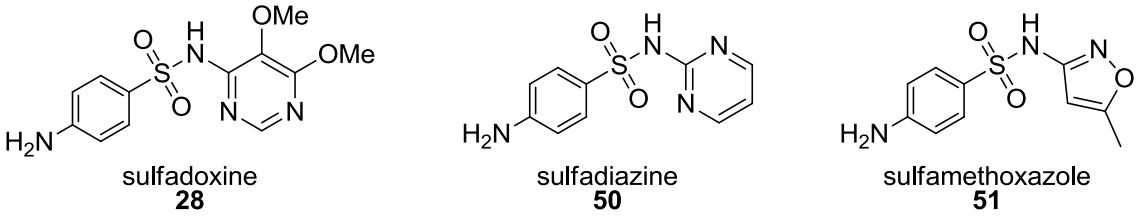


Figure 11. Sulfonamides 28**,** 49**, and** 50**.**

Sulfonamides, Figure 11, show only a weak antimalarial effect when they are administered on their own. But in combination with dihydrofolate reductase inhibitors, see Figure 12, a distinct synergism increases the activity of both compounds. In many strains, mutations in the gene of DHPS lead to decreased activity of DHPS inhibitors through replacement of amino acids. Nowadays, a combination of sulfadoxine (**28**) and pyrimethamine (**29**), distributed as Fansidar®, is widely used.[84]

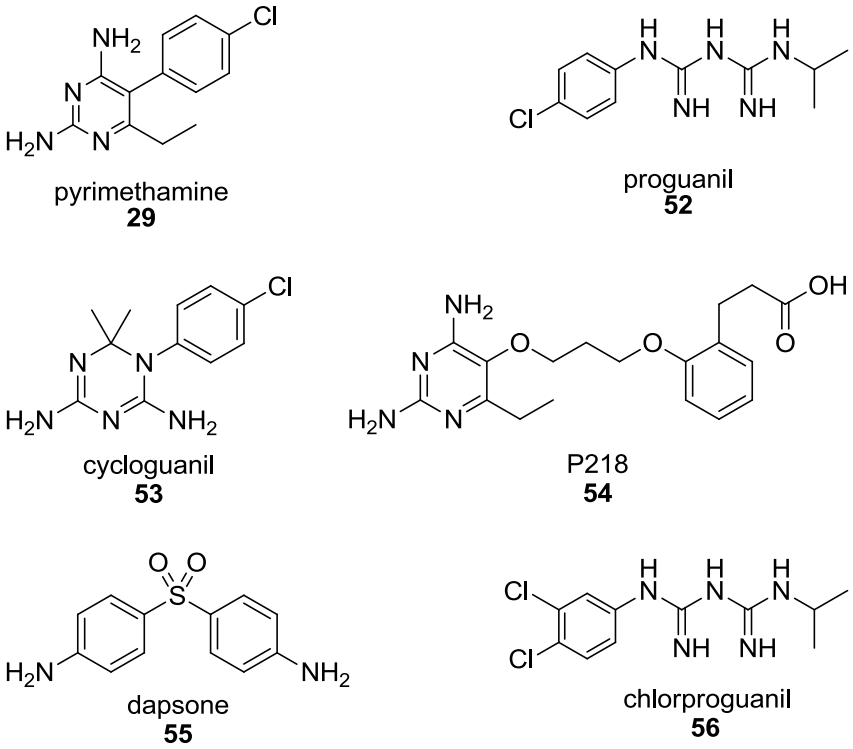


Figure 12. Inhibitors of dihydrofolate reductase.

The inhibitors of the enzyme dihydrofolate reductase, pyrimethamine (**29**) and proguanil (**52**) were introduced to malaria therapy in the late 1940s and early 1950s, respectively. Proguanil (**52**) is a prodrug, which is converted to cycloguanil (**53**) by oxidation.[84]

Antibiotics

Most of the used antibiotics assumedly take effect on the protein biosynthesis apparatus of the apicoplast. Proteins relevant for biosynthesis in the apicoplast (fatty acid synthesis, isopentenyl diphosphate synthesis, etc.) are coded by the nuclear DNA and are imported to the apicoplast. A variety of antibiotics is shown in Figure 13.

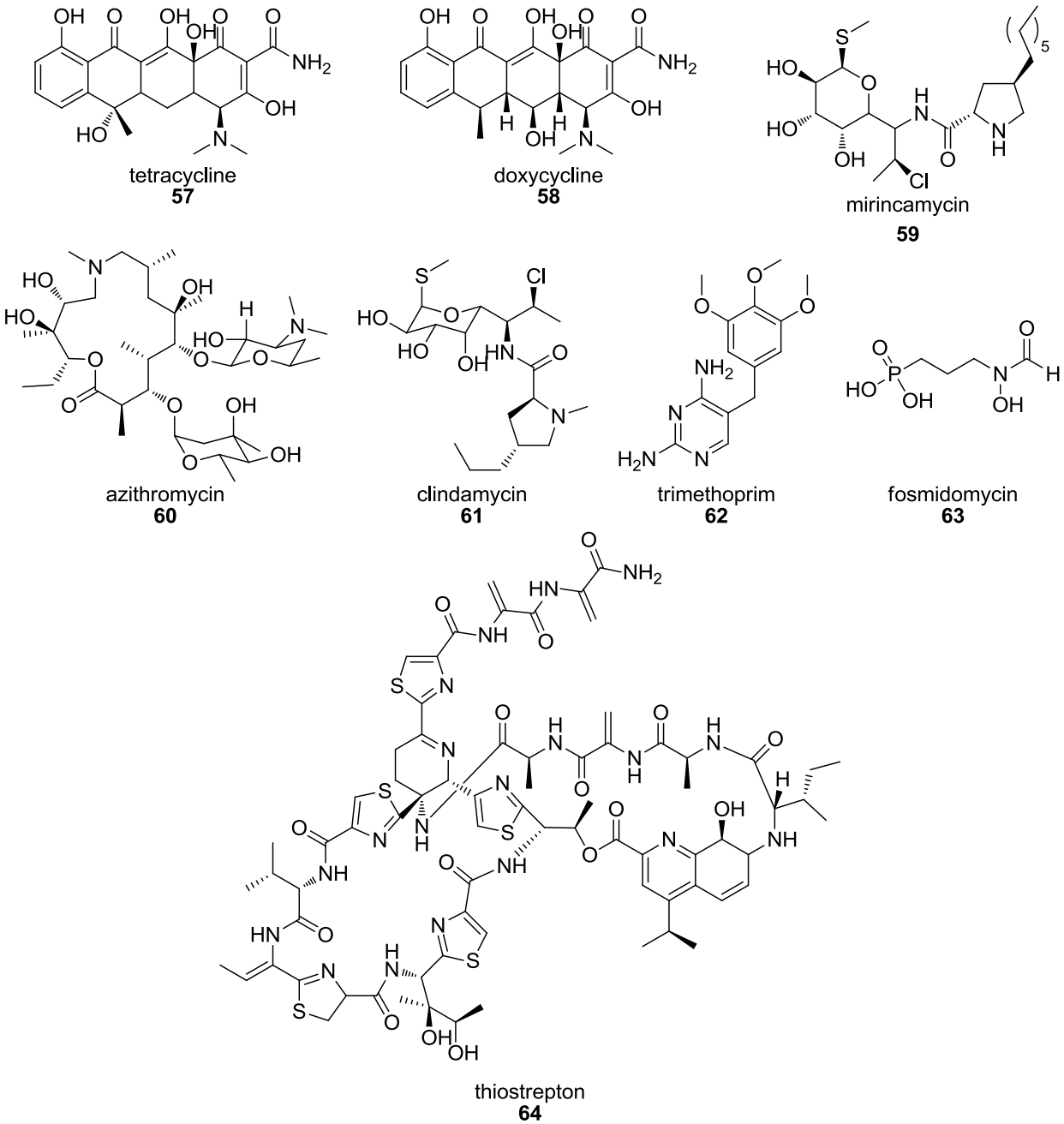


Figure 13. Antibiotics used for malaria treatment.

Characteristically, parasites show only little effects during the first asexual phase upon treatment with antibiotics. A delayed death effect is observed. It is therefore supposed that antibiotics hinder the synthesis of proteins, relevant for the import and processing of en-

zymes crucial for biosynthesis, in newly generated apicoplasts. If malaria is treated exclusively with antibiotics, improvement of the symptoms can be expected not until four days. This is often too late; hence, treatment with antibiotics is reasonable only in combination with a rapidly effective antimalarial, such as quinine (**2**) or artesunate (**27**).[84]

Inhibitors of the Respiratory Chain and Methylene Blue

Atovaquone (**65**), shown in Figure 14, is the first naphtoquinone which reached importance as an antiprotozoal agent with a broad spectrum in human medicine. It can be seen as structural analogon to ubiquinone, which plays an important role in the electron transport chain in mitochondria. The electron transport in the respiratory chain is interrupted by atovaquone (**65**) treatment leading to a collapse of the mitochondrial membrane potential. This causes quick die-off of the parasites. Mono therapy leads, however, to a quick selection of resistant mutants, which results in a therapy failure of 30%. Combined treatment of atovaquone (**65**) and proguanil (**52**) indicates positive interaction of both compounds. The concentration of atovaquone (**65**) needed for collapse of the membrane potential is drastically lowered when proguanil is also administered. On the other hand, the conversion of proguanil (**52**) to cycloguanil (**53**) is irrelevant to the therapeutic effect of atovaquone (**65**). The probability that resistances against the combination of atovaquone (**65**)/proguanil (**52**) (Malarone®) occur is very low. Because of the lipophilicity of atovaquone (**65**) it is better resorpted with a high-fat diet, in the manner of lumefantrine (**20**).[84]

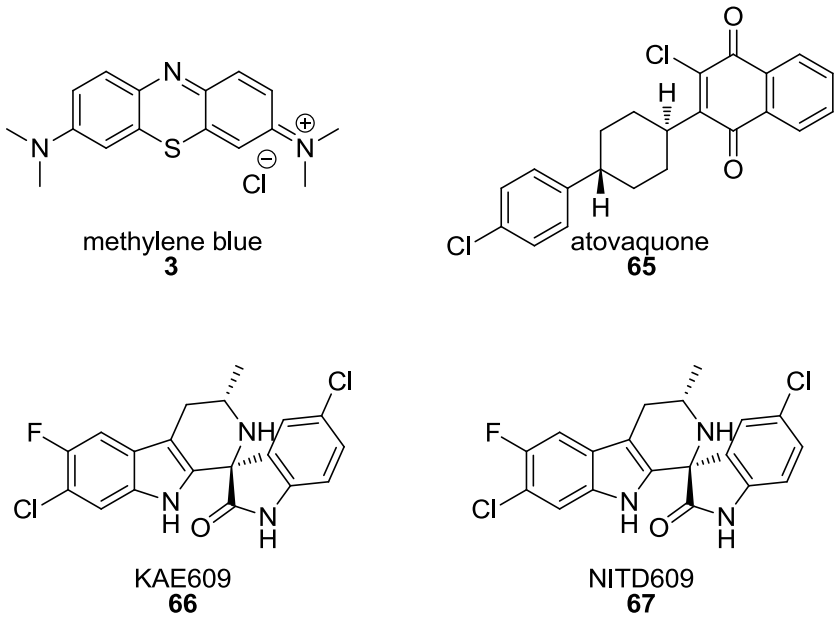


Figure 14. Methylene blue (3**), atovaquone (**65**) and spiroindolones** 66 **and** 67**.**

Also the world's first synthetic antimalarial is experiencing a renaissance. Methylene blue (**3**) is currently investigated at the University of Heidelberg. Combination with well-established antimalarials showed increased activity against gametocytes, which would help to prevent transmission back to mosquitoes. This might be helpful regarding malaria control and eradication in endemic areas.[108,109]

Spiroindolones

The compound class of spirotetrahydro-β-carbolines, or spiroindolones, was reported by Novartis in 2010 as a potent compound class for the treatment of malaria. A ^{35}S-radiolabeled methionine and cysteine incorporation assay revealed that protein synthesis was inhibited more rapidly than by treatment with mefloquine (**22**) and artemisinin (**8**), which indicates that the most promising compound KAE609 (**66**), at this time called NITD609, possessed a different mechanism of action than mefloquine (**22**) and artemisinin (**8**).[110,111]

Spiroindolones inhibit a plasma membrane Na^+-ATPase (PfATP4) of the parasite that regulates sodium and osmotic homeostasis.[112] In a phase 2 study two cohorts of adults infected with *P. vivax* and *P. falciparum* were successfully treated with KAE609 (**66**) at a dose of 30 mg per day for 3 days. Only mild adverse effects were observed.[113]

1.3 Ambition

Many antimalarials rapidly lost efficacy. High levels of resistance can occur by accumulation of multiple drug resistance mutations as revealed through the use of dihydrofolate reductase (DHFR)-targeting drugs.[114] As opposed to this, resistance to drugs, not targeting enzymes, such as chloroquine (**6**), happens much less rapidly.[115] Attempts of discovering new chemotypes directed at standing targets were unsuccessful in many cases. This may be caused by the rigid nature of the active sites in common drug targets, such as DHFR and thymidylate.[116]

A major constraint is the relatively small number of low molecular weight scaffolds with *in vivo* activity against *P. falciparum*. Even among the compounds that are active *in vivo*, only a small number of different scaffolds are found in clinical use.

A screen for antimalarial therapeutics done in 2006 identified the propafenone scaffold; see Figure 15, to have antimalarial activity.[117] Chiba et al. identified growth inhibitory potential of propafenone (**68**) and its derivatives in chloroquine resistant strains of *P. falciparum*. Propafenone (**68**), a class 1c antiarrhythmic drug, is used for treatment of ventricular arrhythmia.[118]

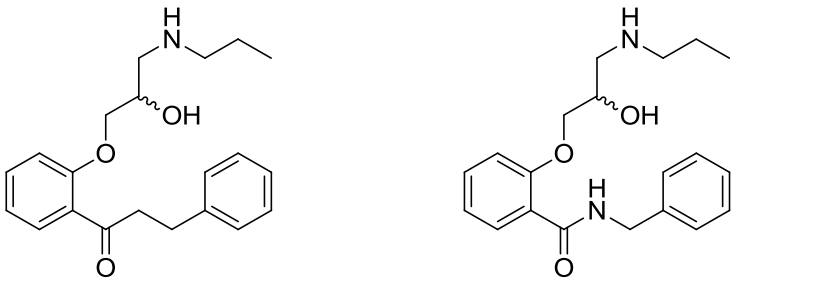


Figure 15. Propafenone (68**) and its aza-derivative (**69**).**

It is known that the β-adrenergic activity of propafenone (**68**) is decreased by substitution of the methylene group through a nitrogen atom, leading to salicylamide **69**, shown in Figure 15. Furthermore, the antiarrhythmic activity of these salicylamide derivatives was that low that these compounds were not capable to be developed to an antiarrhythmic drug.[119]

Unfortunately, the aza-propafenone (**69**) suffered a dramatic decrease in antimalarial activity compared to propafenone (propafenone **68**: IC_{50} (3D7) = 600 nM, aza-propafenone **69**: IC_{50} (3D7) = 20 µM; unpublished data from Medical University of Vienna). The activity prob-

lem can be overcome by modification of the amine components, which includes the amide substructure as well as the aminoalcohol moiety.[120]

Within this thesis, compounds similar to salicylamide **69** are synthesized and a structure-activity relationship is deduced.

Goals set are:

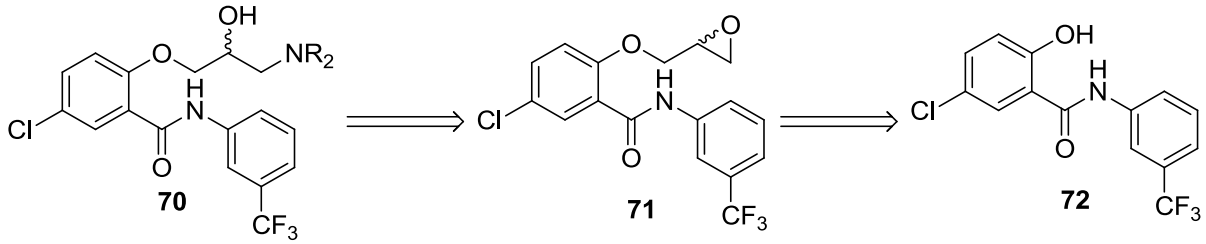
- To exceed the potency of approved antimalarial drugs, such as lumefantrine and artesunate, *in vitro*. Activities of lumefantrine, artesunate and other selected antimalarials are shown in Table 19 on p. 582
- Activity in an animal model (e.g. mouse *P. berghei*) shall be demonstrated
- Investigate the relevance of the stereogenic center towards antimalarial activity and relevant biological properties in the presented scaffold.
- Determine the structure of highly active compounds in solution (NMR) and in the solid state (X-ray)

2. Results and Discussion

2.1 Synthesis

2.1.1 Retrosynthetic Analysis

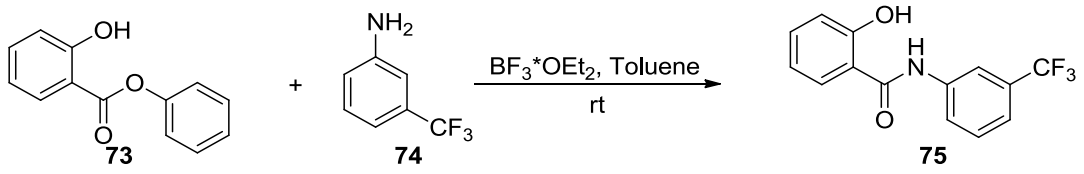
The aminoalcohol motif of a desired molecule as **70** can be derived from epoxide **71**. Nucleophilic attack of an amine leads to the desired regioisomer. Epoxide **71** can be obtained by reaction of anilide **72** with commercial available epichlorohydrin.



Scheme 3. Retrosynthetic analysis of target compounds.

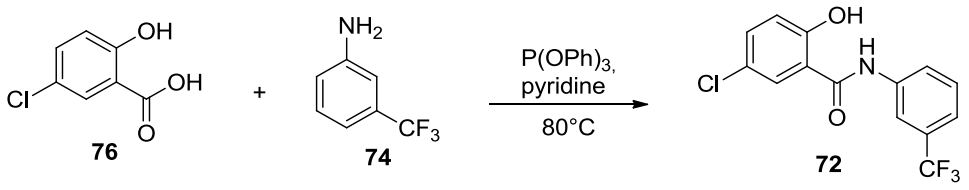
2.1.2 Synthesis of Salicylanilides

The first step in the synthesis of a compound with an unsubstituted salicyl diversity site (**75**) was performed by reaction of phenyl salicylate (**73**) with a derivate of aniline, such as **74**, under catalysis of BF_3 at room temperature.[121] In some cases BF_3 had to be added in stoichiometric amounts for completion of the reaction. The major drawback of this method is the bad solubility of phenyl esters of substituted salicylates, which are also not commercially available. Therefore, it was clear that switching to a different protocol for exploration of the salicylic diversity site would maintain the number of synthetic steps.



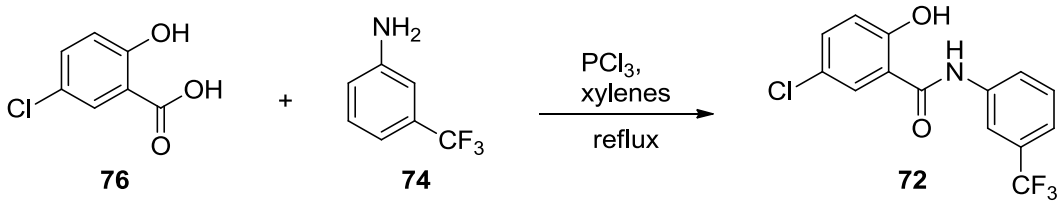
Scheme 4. Synthesis of anilide 75 ***via*** **BF_3*OEt_2.**

Derivatives of salicylic acid, such as 5-chlorosalicylic acid (**72**), are widely available. The reaction depicted in Scheme 5 has long reaction times similar to the reaction in Scheme 4, both reactions were stirred overnight. This means that each reaction time was at least 14 hours. The reaction in pyridine needs to be acidified during workup to remove basic molecules.



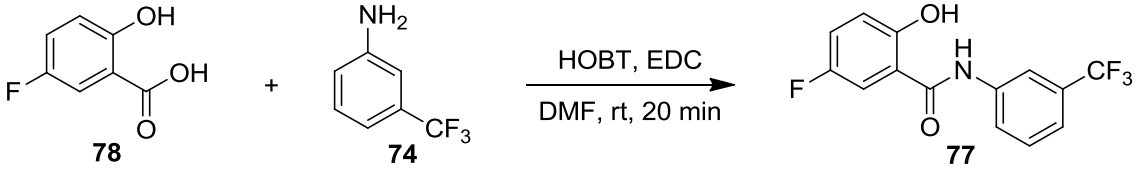
Scheme 5. Synthesis of anilide 72 ***via*** **$P(OPh)_3$.**

The most convenient method for the reaction of salicylic acids with anilines is shown in Scheme 6.[122] The greatest advantages of this protocol are the short reaction times, typically no longer than one hour, and that no real workup is needed; the reaction mixture is poured in a beaker while it is still hot. This removes a tarry residue which forms during the reaction. The solution of the product is stirred in a hood until xylenes are gone and pure product remains in the beaker.



Scheme 6. Synthesis of anilide 72 ***via*** **PCl_3.**

Beside the above discussed methods also syntheses *via* activated esters were tried, where HOBt proved to be better than HATU in combination with DCC. The reaction shown in Scheme 7 gave product **77** with 66% yield. Also, the reaction of the aniline with the *in situ* generated acid chloride did not prove advantageous (not even with acetyl protection of the phenol).



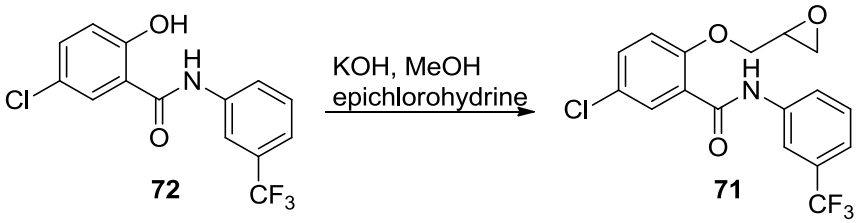
Scheme 7. Synthesis of anilide 77 ***via*** **coupling reaction with HOBt.**

It has to be mentioned that, surprisingly, some of the synthesized phenols are easily deprotonated by treatment with saturated $NaHCO_3$ solution during workup; this was observed for 3,5-dichloro-2-hydroxy-*N*-(3-(trifluoromethyl)phenyl)benzamide (**79**) and *N*-(4-chloro-3-(trifluoromethyl)phenyl)-5-cyano-2-hydroxybenzamide (**80**). This basic workup was only needed if unreacted salicylic acid was still present. Unreacted aniline can be removed by

washings with hexanes. Acidification did not make the residual anilines water-soluble in most cases.

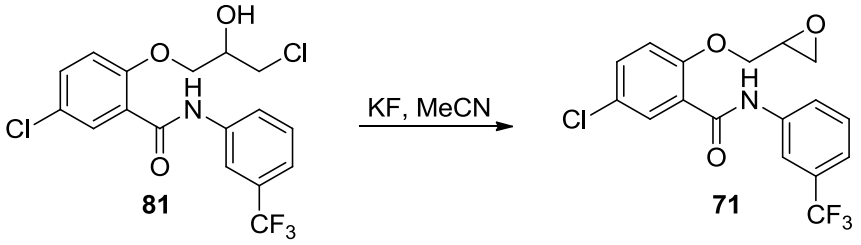
2.1.3 Synthesis of Epoxide Compounds

Epoxide intermediates, such as **71** (Scheme 8), can be synthesized by alkylation reactions of potassium salts of salicylanilides, such as **72**, with epichlorohydrin. The same reaction conditions also can be applied to acetyl protected anilides. But acetyl protected salicylic acids did not prove advantageous in comparison to unprotected acids. Therefore, only feasibility of the reaction of acetyl protected anilides is reported herein.



Scheme 8. Synthesis of epoxide 71 ***via alkylation reaction*.**

Due to occasionally large amounts of side product (chloroalcohol **81**) in this reaction, yields were not steady. A literature known conversion of chloroalcohol to epoxide with KF on Celite® (2 eq) in refluxing acetonitrile for 18 h improves the yield drastically and also simplifies purification.[123] This reaction, which is shown in Scheme 9, can be implemented directly after gaining the solvent free crude product of the reaction.

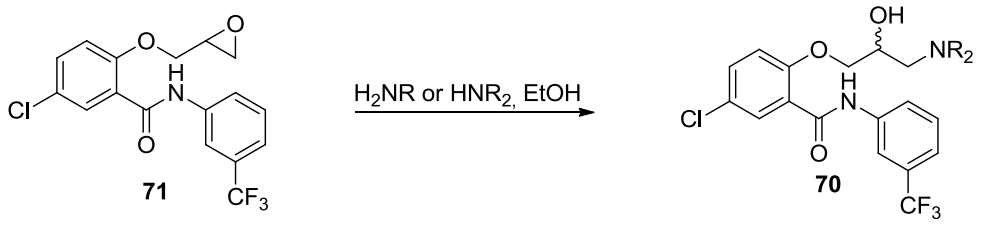


Scheme 9. Conversion of chloroalcohols to epoxides.

2.1.4 Synthesis of Target Molecules

The racemic target molecules (**71**) are obtained by epoxide ring-opening reactions, as shown in Scheme 10, with suitable amines. Epoxide opening at the more substituted site (C-2) was never observed. A variety of amines, which are considered suitable for biological investigations, are shown in Figure 16. Product amounts about 100 milligram and purity above 95% is

considered as sufficient for primary assessment of biological activities and safety (*in vitro*). For *in vivo* tests, purity above 98% is considered as sufficient.



Scheme 10. Synthesis of an active molecule from an epoxide intermediate.

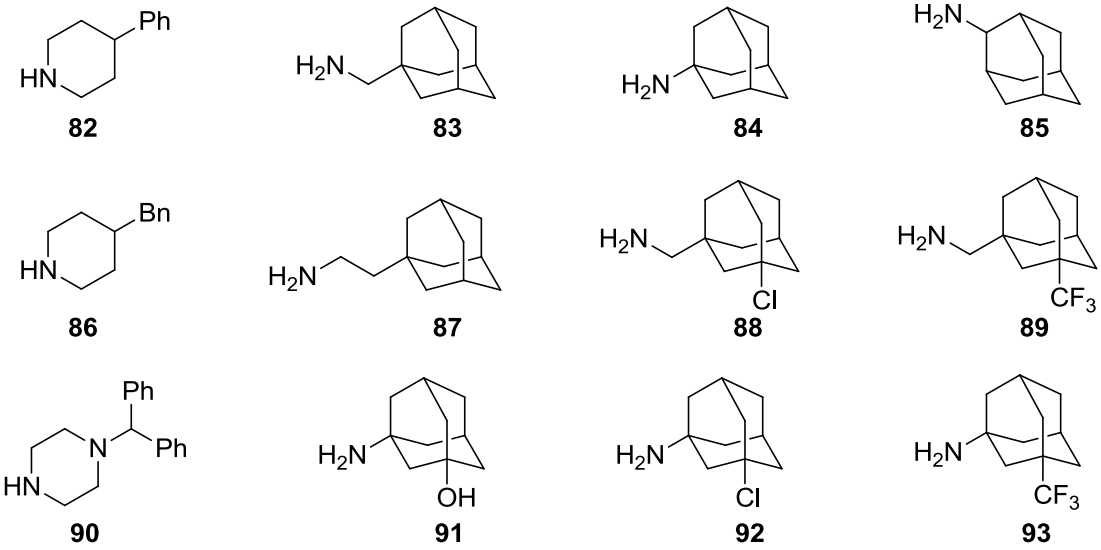
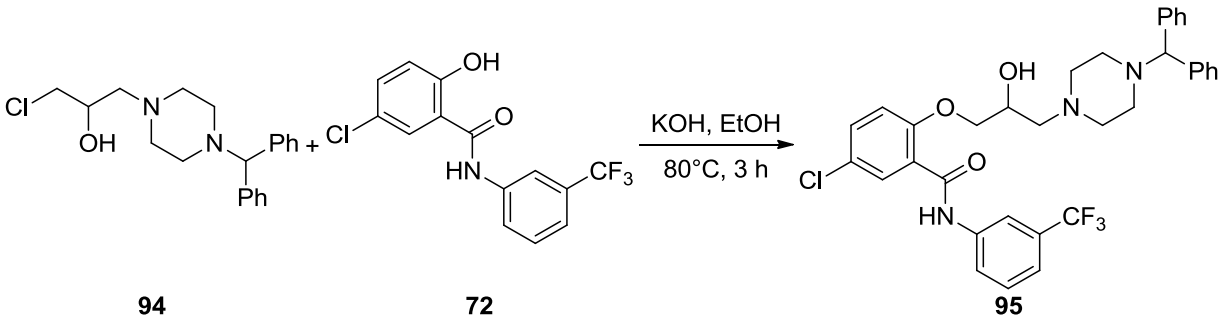


Figure 16. Examples for important amine compounds used in syntheses during the thesis.

Target molecules can also be obtained by reaction of 1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-2-ol (**94**) with anilides as shown in Scheme 11. Adduct **94**, prepared by reaction of benzhydryl piperazine and epichlorohydrin, is the only one of its kind that was synthesized because the synthetic route *via* 5-Chloro-2-oxiranylmethoxy-N-(3-trifluoromethyl-phenyl)-benzamide (**71**) enables exploration of the amine diversity site easier. Otherwise, the preparation of epichlorohydrin adducts of each amine would have been necessary.

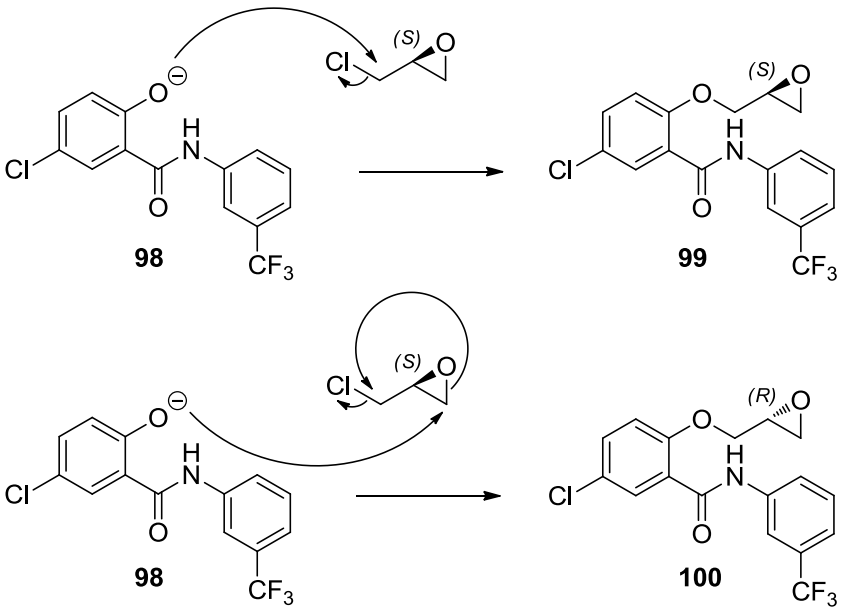


94 **72** **95**

Scheme 11. Alternative synthetic route to target molecule 95**.**

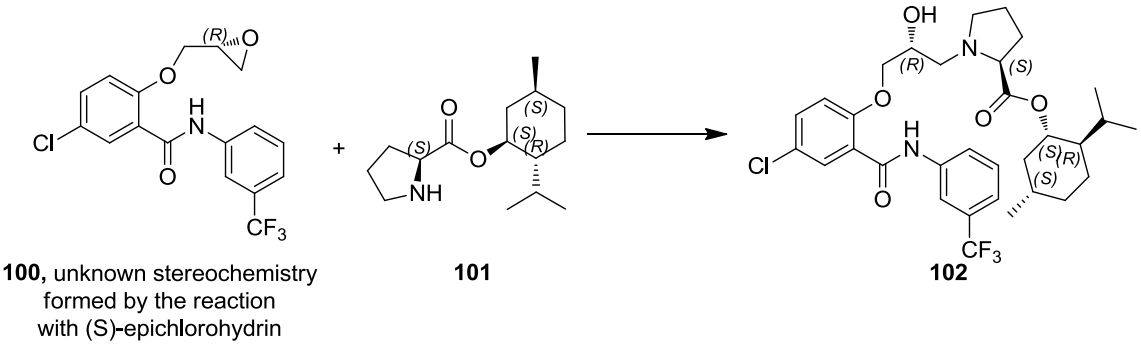
2.1.5 Stereochemical Investigations

Enantiopure target molecules (**96** and **97**) were synthesized using commercially available (*S*)-epichlorohydrin, as shown in Scheme 12, and (*R*)-epichlorohydrin, respectively. The reaction can proceed *via* S_N2 type reactions at the carbon bearing the chlorine atom, or ring opening at the less substituted carbon atom of the oxirane moiety. Varying reaction conditions can change the outcome of such reactions[124], therefore these investigations were made.



Scheme 12. Nucleophilic attack of phenolate 98 **is conceivable at the two different electrophilic sites of epichlorohydrin.**

The reaction product of the above shown reaction with (*S*)-epichlorohydrin was **100**. The absolute configuration of the chiral center was determined by epoxide opening with proline menthyl ester **101** as shown in Scheme 13. The structure of **102** was verified by x-ray structure analysis.



Scheme 13. Determining the configuration of epoxide 100 **by derivatization.**

The crystal structure of **102** (see Figure 17) shows that the nucleophilic attack of the phenolate occurs mainly at the epoxide. Therefore, an inversion of the configuration is observed.

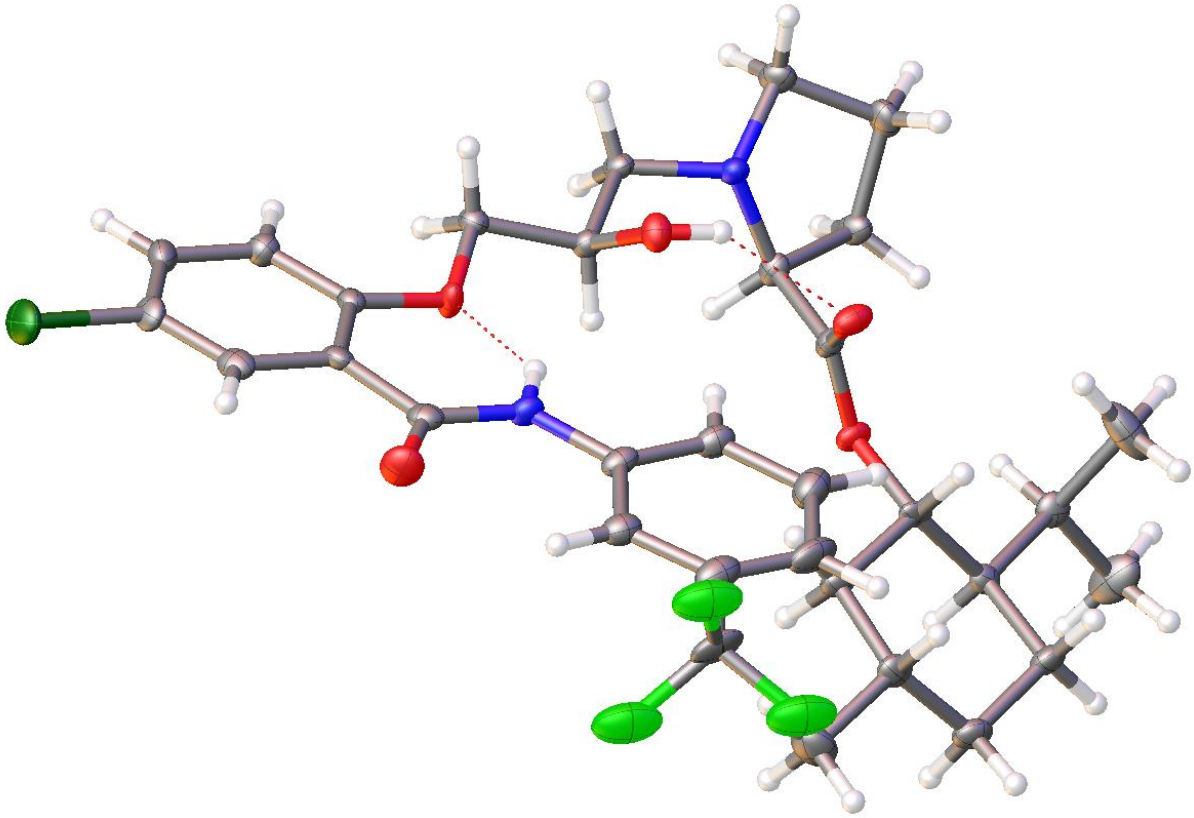


Figure 17. Crystal structure of (*S*)-(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl-1-((*R*)-3-(4-chloro-2-((3-(trifluoromethyl)phenyl)carbamoyl)phenoxy)-2-hydroxypropyl)pyrrolidine-2-carboxylate (102**).**

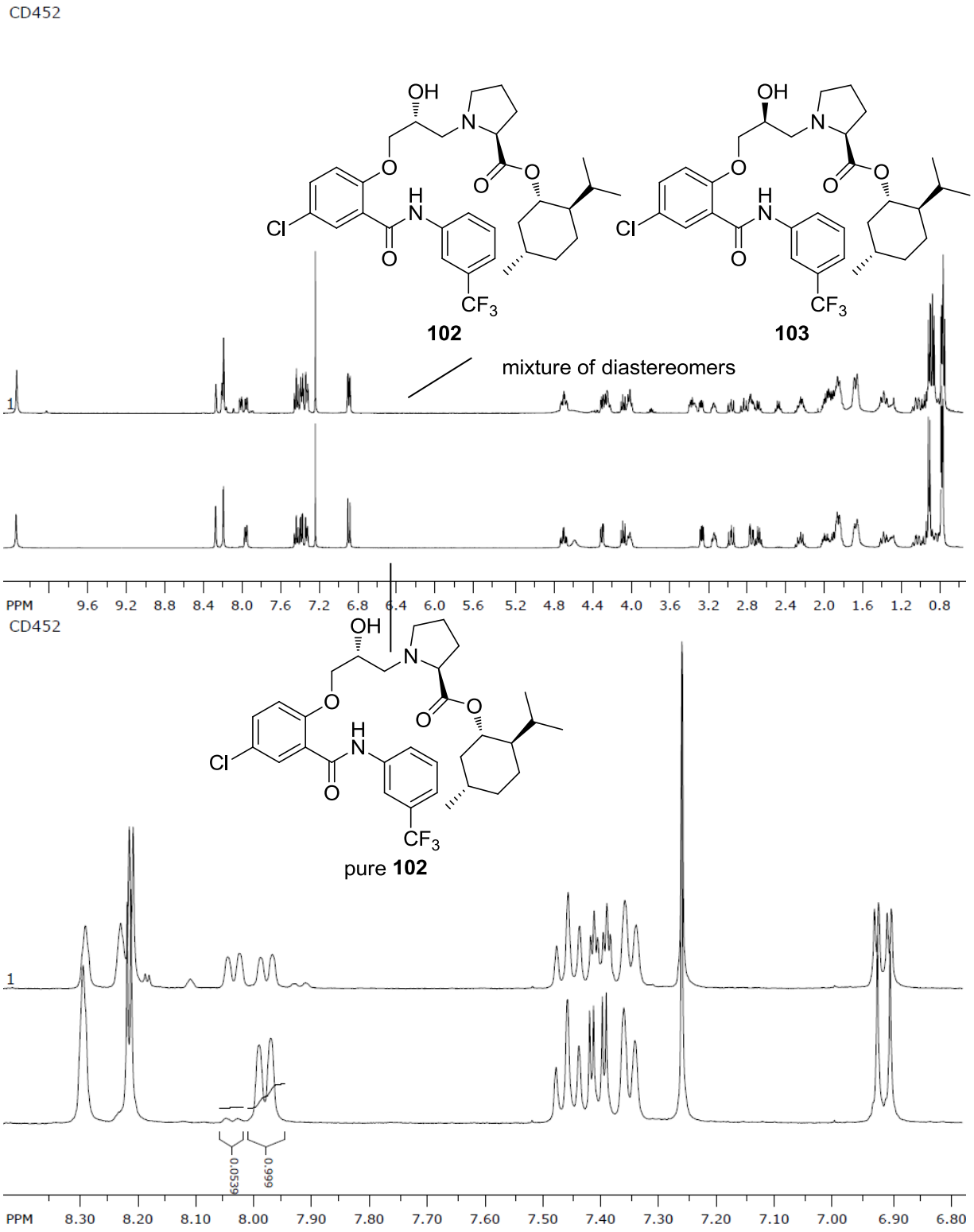


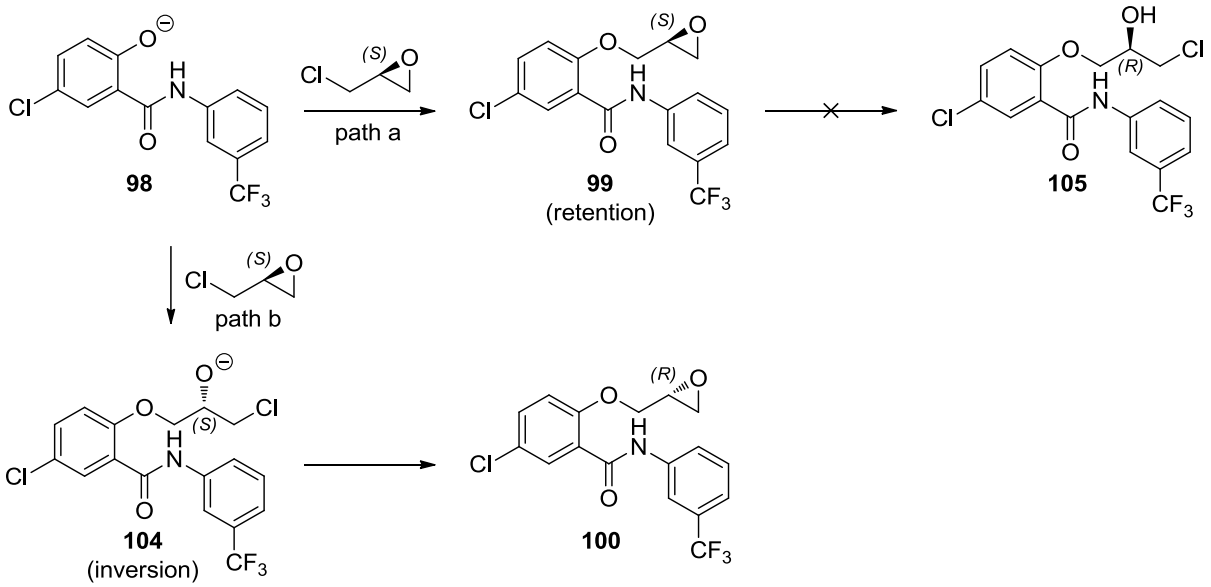
Figure 18. ^{1}H spectra of (*S*)-(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl-1-((*R*)-3-(4-chloro-2-((3-(trifluoromethyl)phenyl)carbamoyl)phenoxy)-2-hydroxypropyl)pyrrolidine-2-carboxylate (102**) and a mixture of** 103 **and its diastereomer.**

Figure 18 shows the ^{1}H spectra of (*S*)-(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl-1-((*R*)-3-(4-chloro-2-((3-(trifluoromethyl)phenyl)carbamoyl)phenoxy)-2-hydroxypropyl)pyrrolidine-2-

carboxylate (**102**) and in the upper traces a mixture of **102** and its diastereomer **103**, which was synthesized by reaction of proline menthyl ester **101** and the racemic epoxide **71**. Quantification of integrals, shown in the lower set of spectra in Figure 18, leads to an er (enantiomeric ratio) of 95:5 which is in perfect agreement with the er of the epoxide batch (exactly the same er determined by chiral HPLC, data not shown) used as starting material in this reaction. This states that no racemization occurs during the epoxide opening step, as assumed.

The crystal structure of **102** revealed two cooperative three-centered hydrogen bond networks. This intriguing network of hydrogen bonds in **102** is part of ongoing investigations.

With the knowledge that inversion happens, the mechanism was investigated and quantified *via* chiral HPLC, chromatograms are shown on p. 572. Reactions were performed with commercial available (*S*)-epichlorohydrin (97% ee) as shown in Scheme 14, as well as with commercial available (*R*)-epichlorohydrin (98% ee). The reaction products (epoxide and chloroalcohol) were separated and chiral separation was performed for a sample of epoxide first. Because no method to completely separate (baseline separation) enantiomeric chloroalcohols was found, these were converted to the corresponding epoxide *via* reaction with KF, as shown above in Scheme 9. Then, these epoxides, obtained from the corresponding chloroalcohols, were also separated on chiral HPLC. The results, which also take into account the available ee data of the commercial epichlorohydrin reagents, state that the reaction proceeds 95.3 % *via* path b for the depicted reaction with (*S*)-epichlorohydrin. Consistently, analysis of the reaction with (*R*)-epichlorohydrin gives percentage of 95.9% for path b.



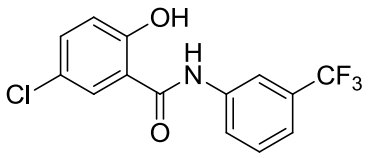
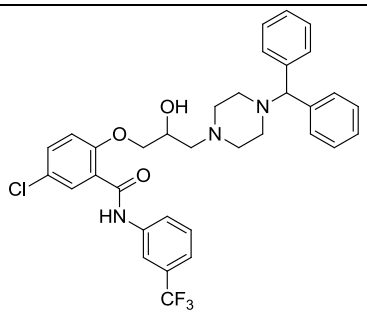
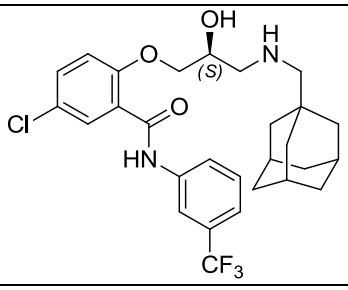
Scheme 14. Quantification of the mechanisms for reactions of phenolate 98 **with epichlorohydrin.**

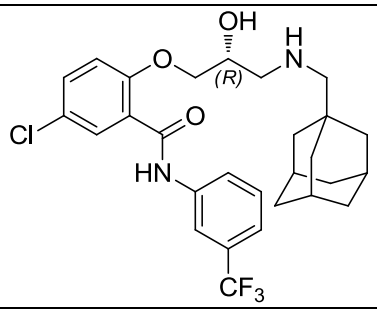
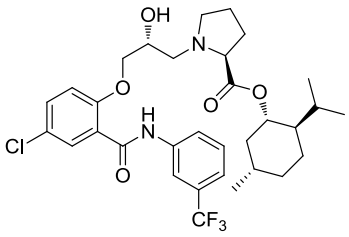
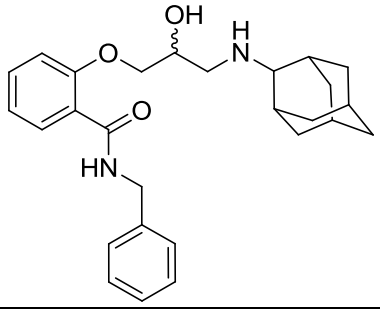
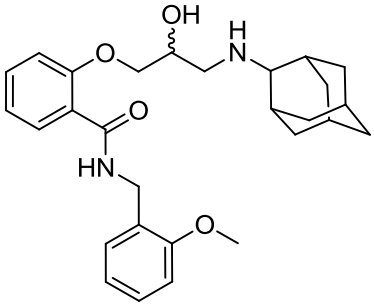
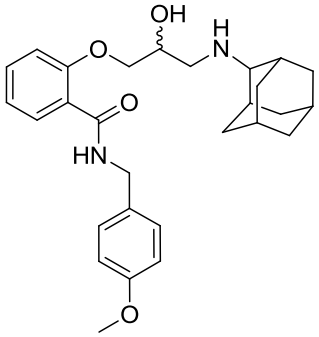
Furthermore, it was observed that the er of chloroalcohol **99**/**100** never drastically differed from the er of the used epichlorohydrin. Therefore, it can be assumed that all built chloroalcohol is formed by path b, and that no reaction from epoxide to chloroalcohol proceeds under the applied reaction conditions. To clarify, there is no back reaction from epoxide **100** to chloroalcohol **104** and there is no reaction from epoxide **99** to chloroalcohol **105**. Hence, (*R*)-chloroalcohol **105** is only formed *via* path b from (*R*)-epichlorohydrin present in (*S*)-epichlorohydrin, which consists of 98.5% (*S*)-epichlorohydrin and 1.5% (*R*)-epichlorohydrin.

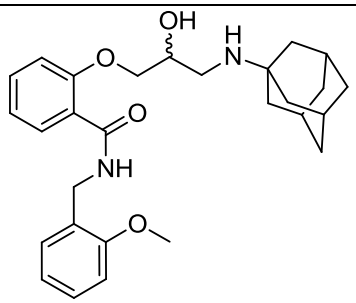
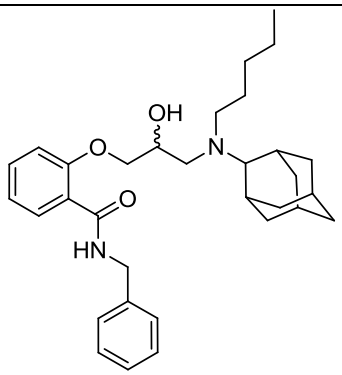
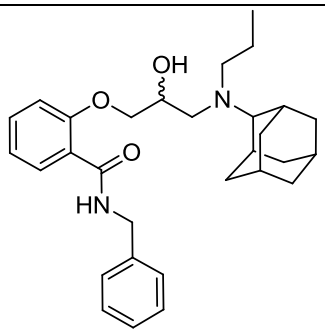
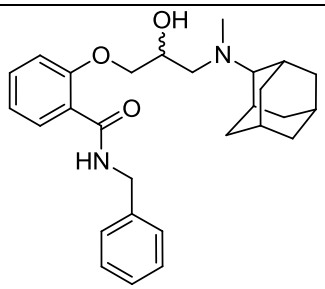
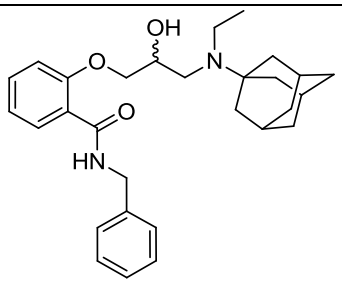
2.2 Structure Activity Relationship Analysis

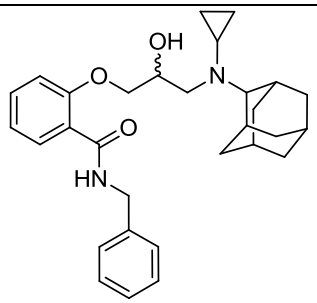
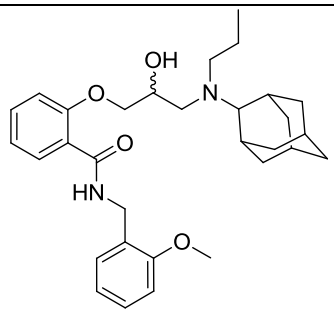
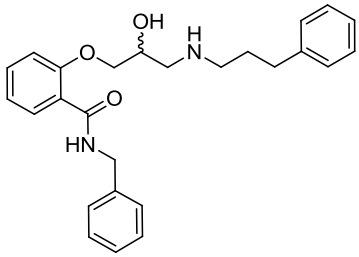
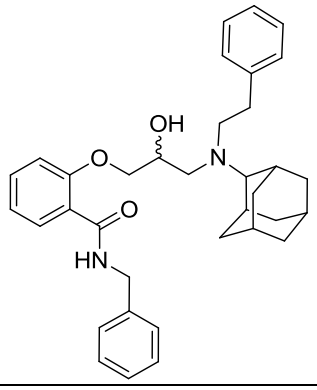
All available *in vitro* results, as well as microsomal stability data and cytotoxicity data are shown in Table 2. A [^{3}H]-hypoxanthine incorporation assay was used for assessment of inhibition of parasite growth. These tests were performed at Swiss Tropical and Public Health Institute (Swiss TPH, Sergio Wittlin), whereas tests for microsomal stability and cytotoxicity were performed at Marinomed Biotechnologie GmbH. In the course of this thesis more compounds have been synthesized than listed in this table. They were omitted in the table since there were no data available the thesis had to be finished. However, structures and experimental data of those compounds can be found in the respective sections.

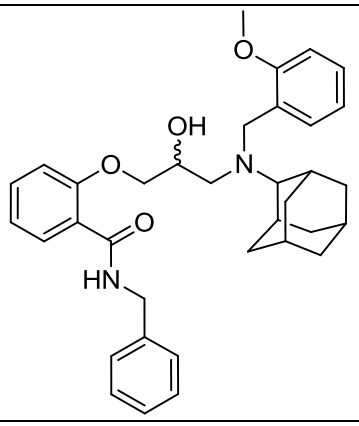
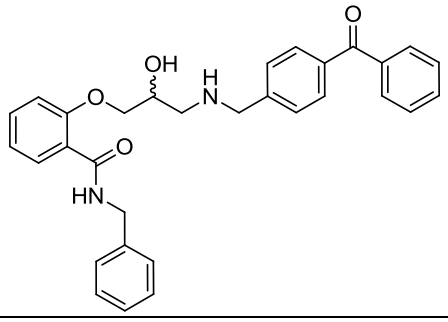
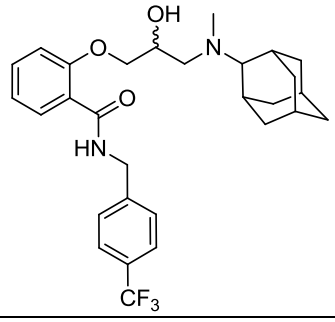
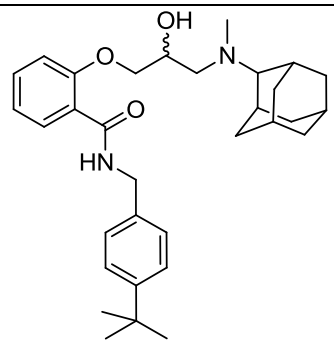
Table 2. Structures with corresponding activities on NF54 strain and chloroquine resistant K1 strain of *Plasmodium falciparum*. Furthermore, microsomal stability and cytotoxicity of tested compounds are listed, if available.

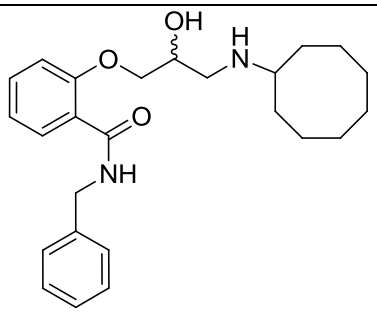
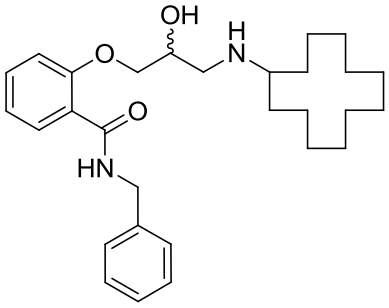
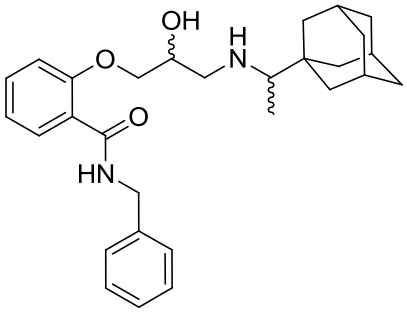
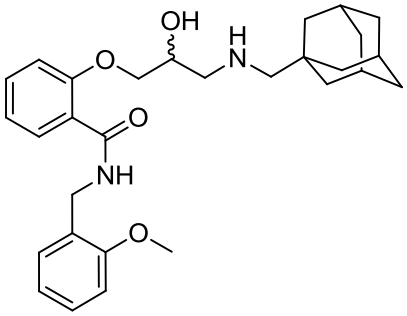
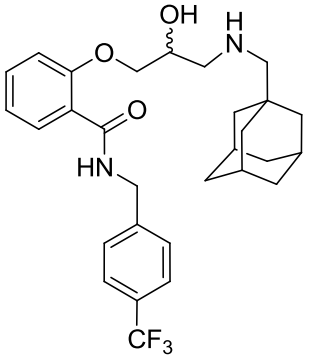
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability l normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
72		2296.0	1133.00				
95		5.7	1.20			90.3	140.4
96		1.9	0.52	40	23	-0.2	118.3

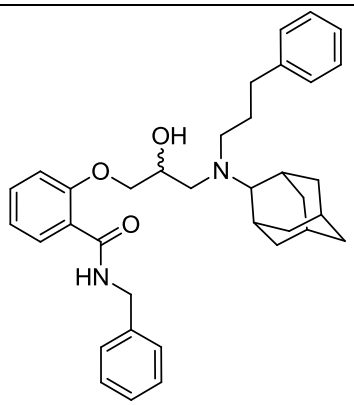
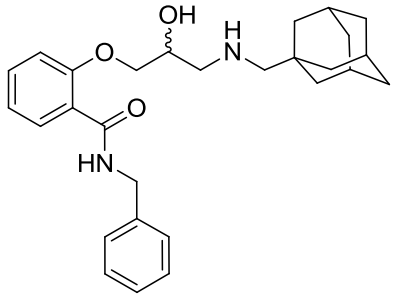
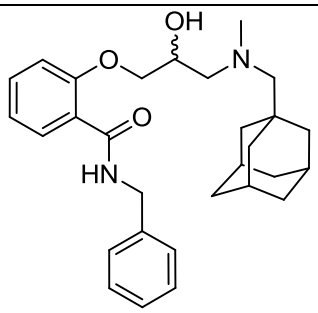
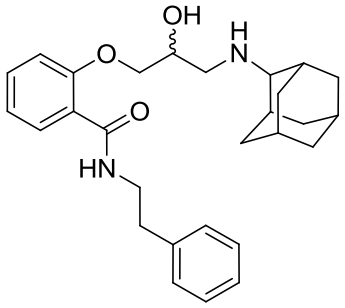
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
97		1.8	0.43	48	28	-0.2	109.6
102		117.0	29.00	62	27		
106		757.0	246.00				
107		238.0	78.00				
108		220.0	90.00				

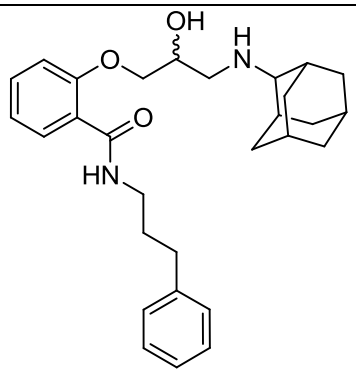
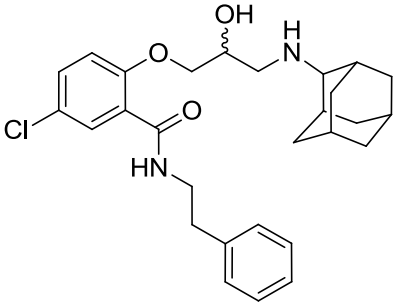
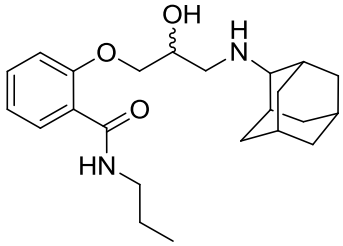
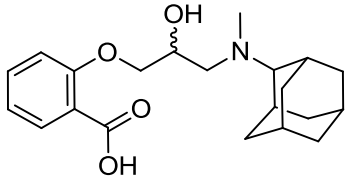
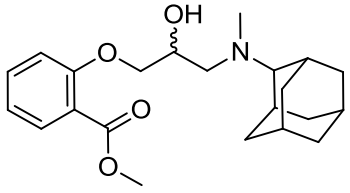
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
109		968.0	281.00				
110		218.0	73.00				
111		349.0	121.00			92.0	104.0
112		421.0	137.00			94.0	119.8
113		933.0	262.00				

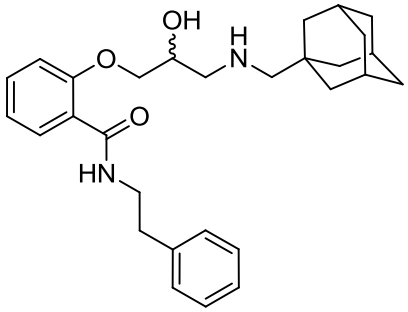
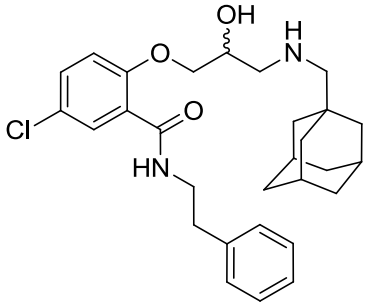
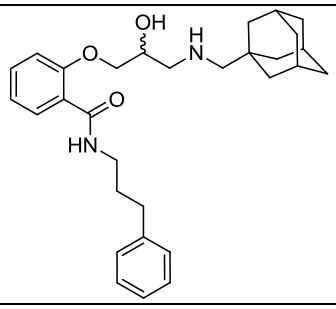
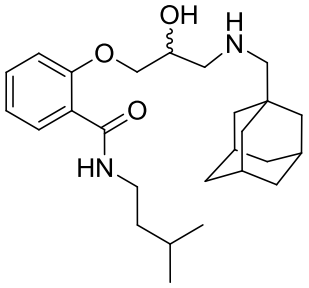
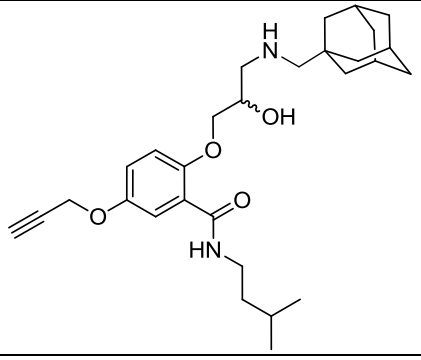
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
114		1156.0	433.00			113.0	92.0
115		290.0	132.00				
116		1091.0	510.00			82.0	91.0
117		580.0	212.00				

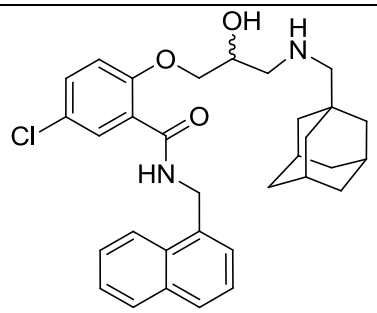
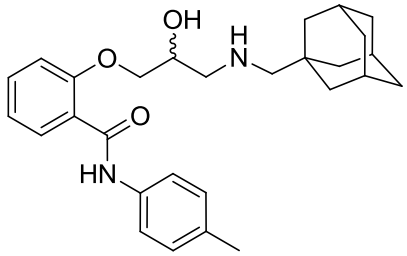
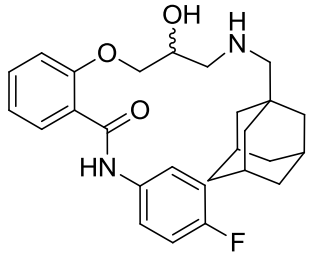
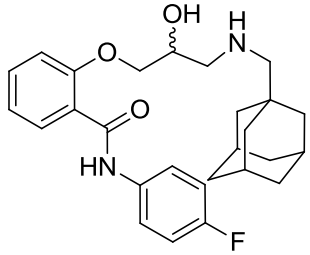
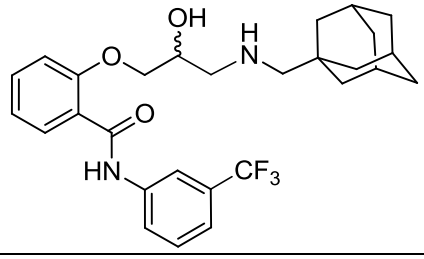
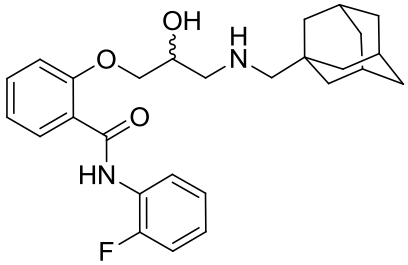
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
118		2051.0	707.00			88.0	115.0
119		2120.0	995.00			64.0	89.0
120		161.0	54.00			65.5	97.8
121		261.0	69.00			73.0	93.0

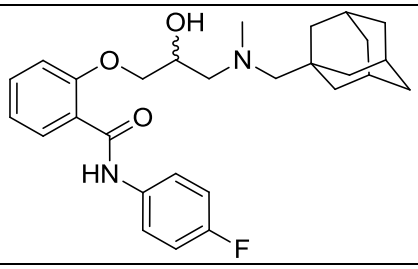
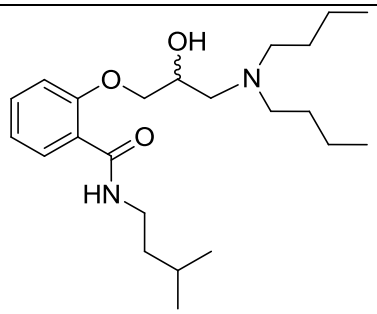
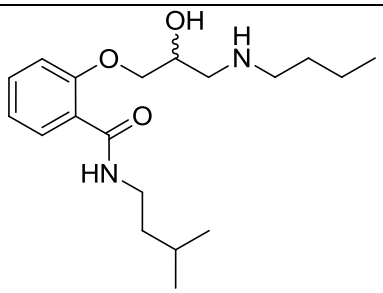
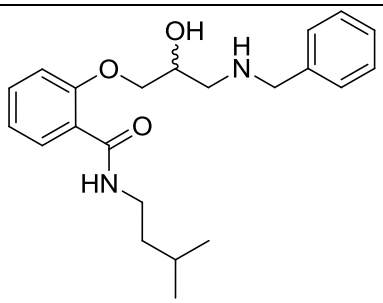
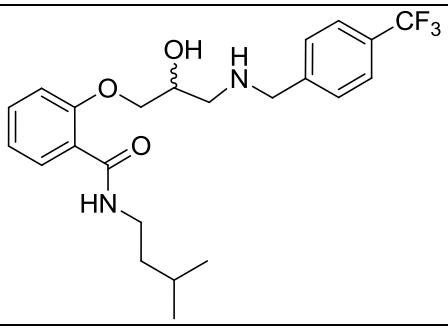
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
122		881.0	333.00				
123		262.0	70.00			3.0	89.0
124		79.0	20.00				
125		183.0	61.00				
126		57.0	18.00			0.5	104.7

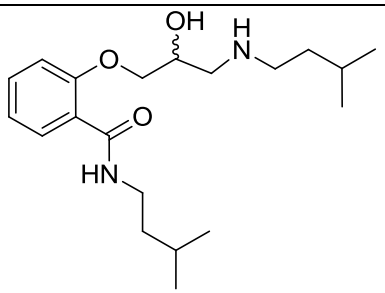
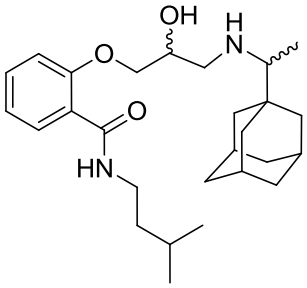
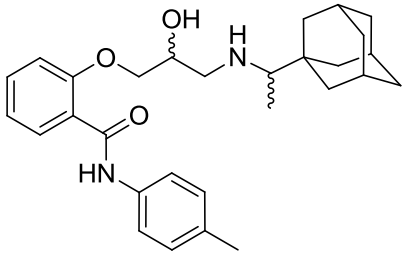
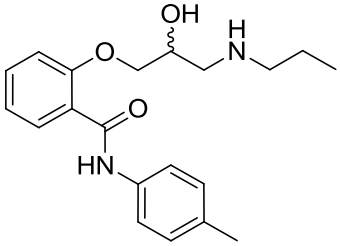
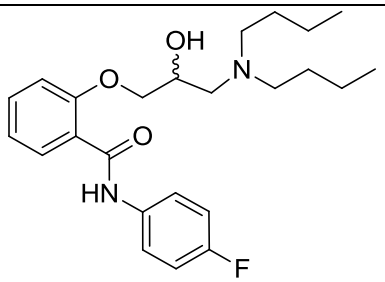
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
127		168.0	59.00			98.5	111.0
128		143.0	49.00				
129		670.0	182.00			81.1	125.7
130		281.0	101.00			53.7	115.5

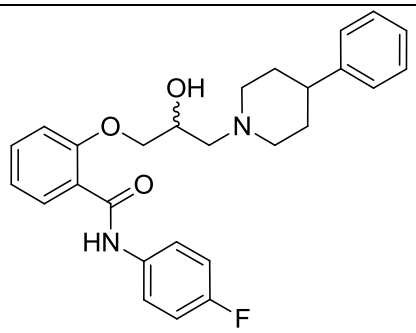
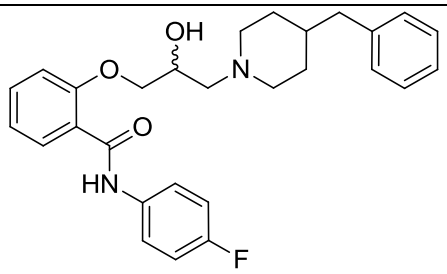
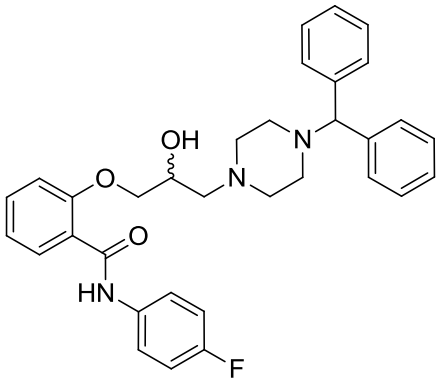
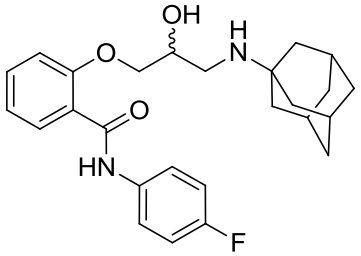
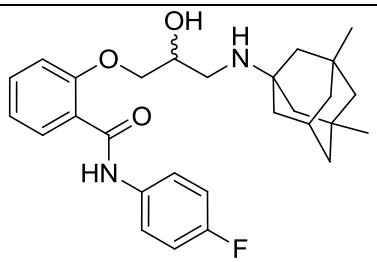
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Micro-some stability I nor-malized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
131		308.0	103.00				
132		96.0	26.00			0.2	66.0
133		614.0	174.00			57.0	99.0
134		<40000	<40000				
135		<40000	4611.00				

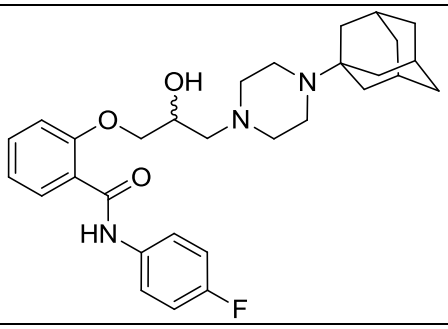
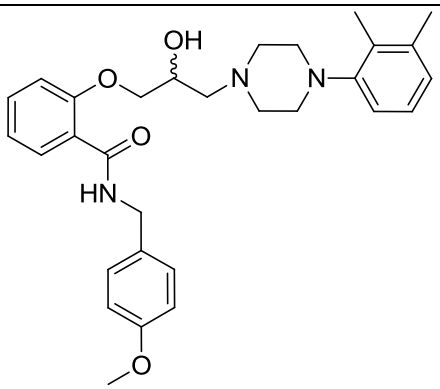
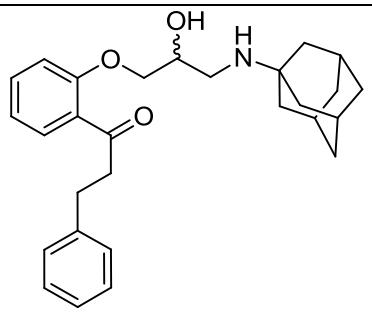
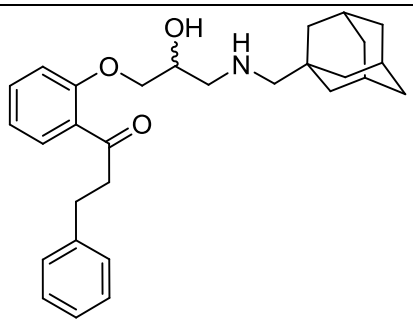
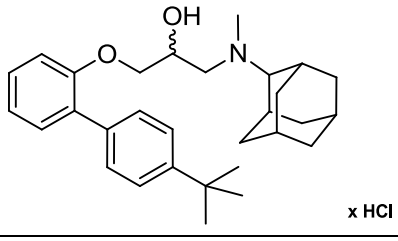
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
136		101.0	30.00			0.0	119.1
137		27.0	7.90			0.4	86.8
138		148.0	52.00			0.1	107.3
139		134.0	36.00			20.4	113.0
140		5380.0	2260.00				

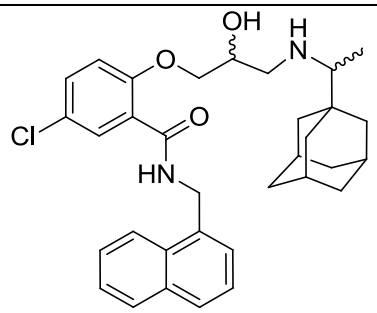
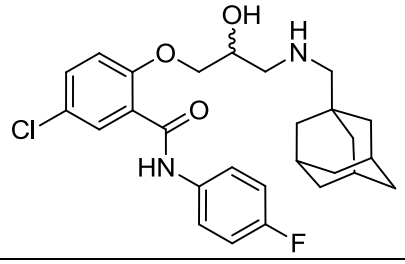
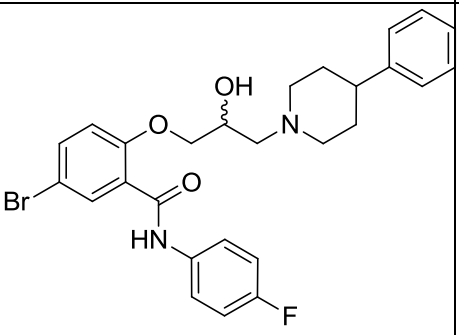
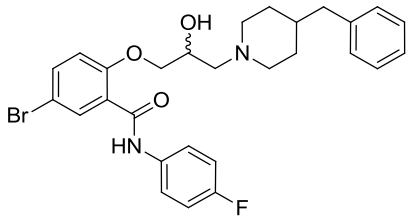
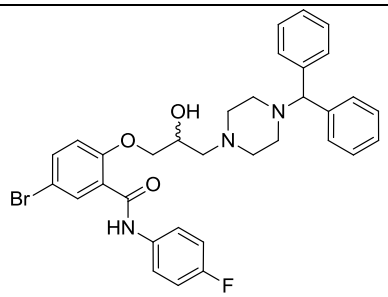
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
141		20.0	5.20			0.4	100.8
142		5.6	1.70			0.5	86.6
143		6.4	1.70			0.2	93.6
144		9.3	3.10			0.1	70.0
145		2.3	0.51			0.5	22.4
146		24.0	8.10			7.0	103.9

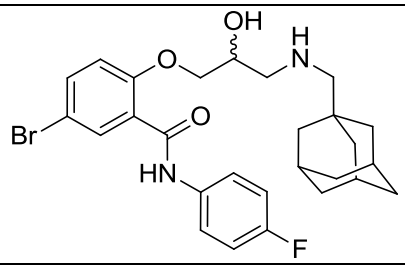
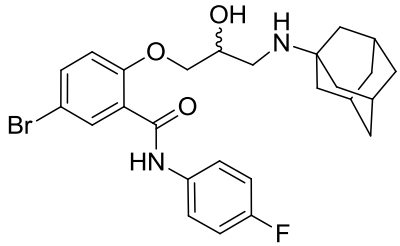
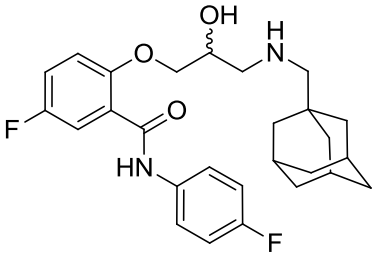
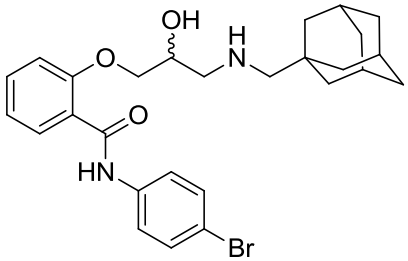
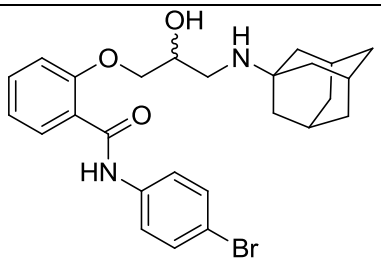
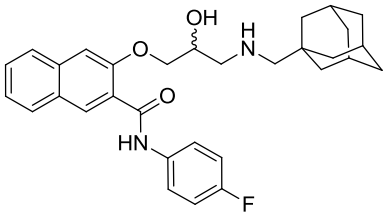
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
147		63.0	16.00			77.5	112.3
148		333.0	76.00			96.0	110.0
149		2751.0	827.00			94.0	107.0
150		1434.0	356.00				
151		1362.0	371.00			63.4	97.7

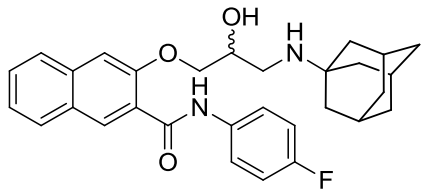
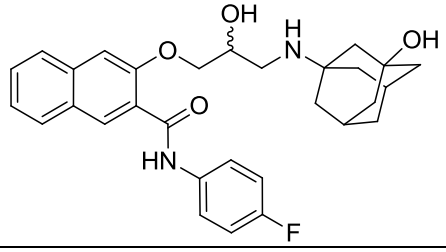
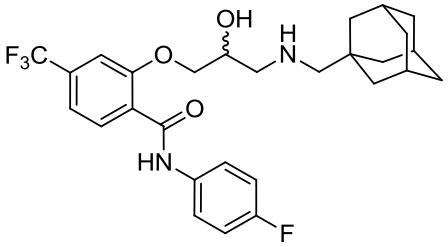
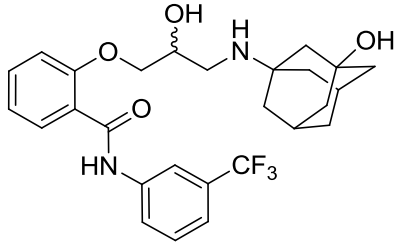
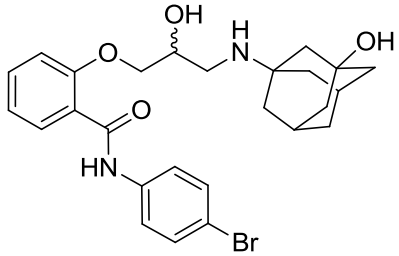
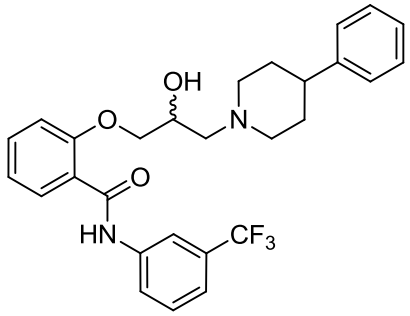
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
152		1693.0	467.00			98.0	100.0
153		74.0	18.00			0.1	107.6
154		5.6	1.50			0.5	117.6
155		156.0	72.00			77.0	108.0
156		18.0	5.70			69.9	88.7

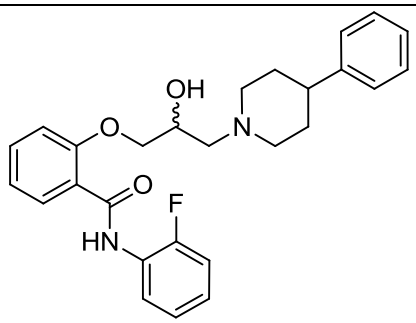
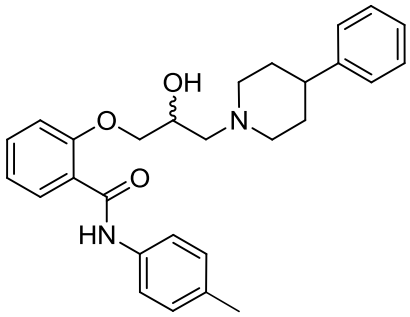
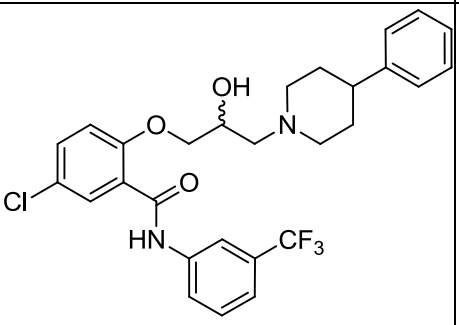
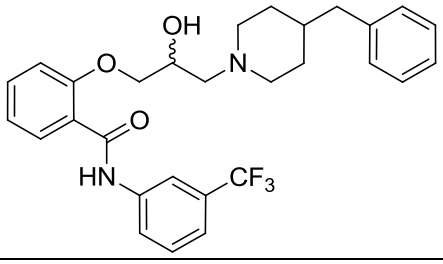
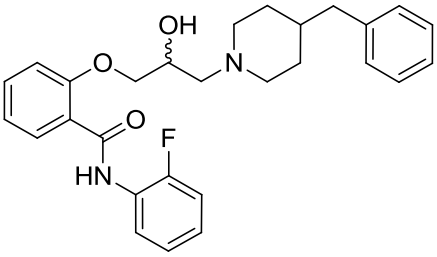
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
157		26.0	9.00			4.4	107.6
158		16.0	6.80			0.1	105.1
159		14.0	3.70			29.7	81.2
160		51.0	11.00			0.0	89.0
161		38.0	8.30			0.4	104.6

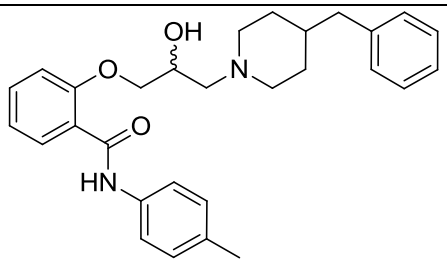
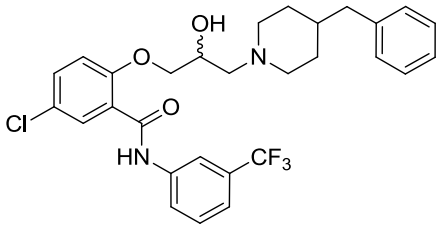
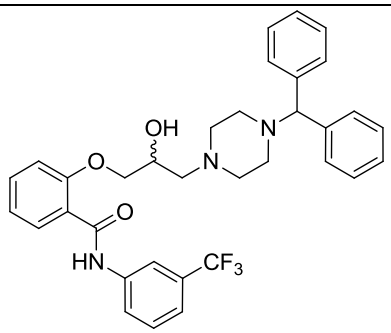
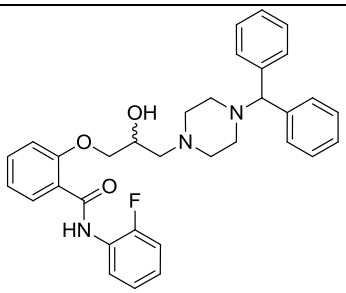
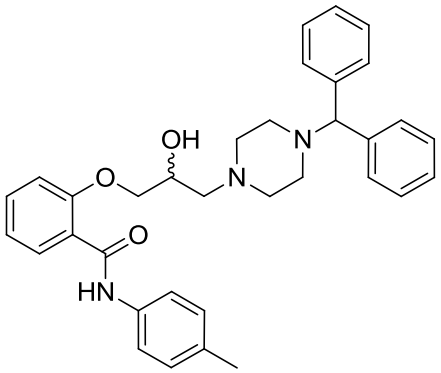
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
162		59.0	12.00			13.2	107.6
163		644.0	243.00			46.0	96.0
164		182.0	96.00			0.3	106.9
165		40.0	12.00			0.6	105.5
166	 x HCl	492.0	159.00			40.1	107.6

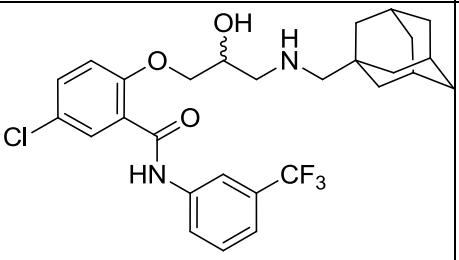
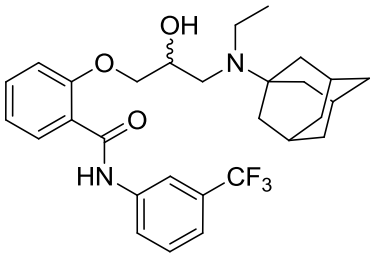
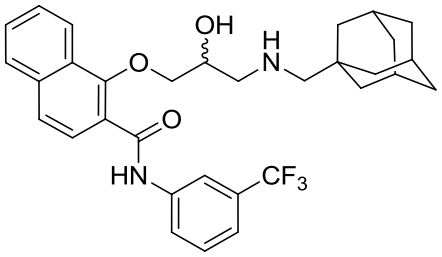
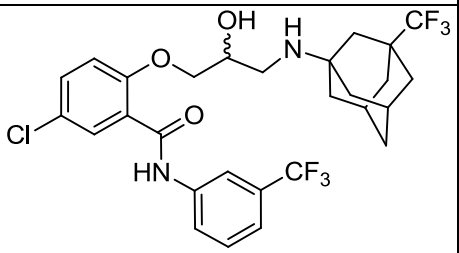
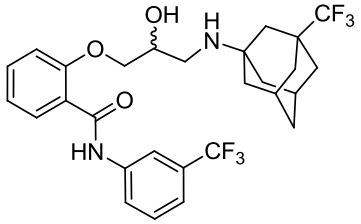
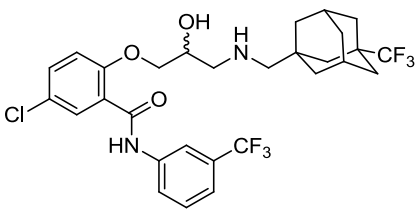
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
167		14.0	3.60			0.5	83.9
168		2.4	0.62			0.4	93.4
169		9.3	2.60			0.5	68.2
170		8.4	2.30			0.5	85.2
171		7.1	1.80			52.1	101.7

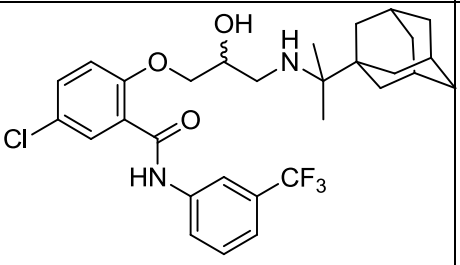
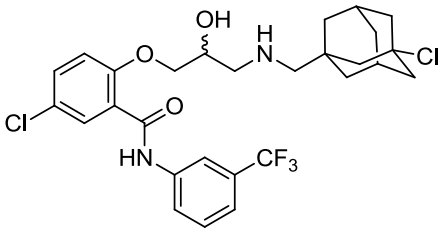
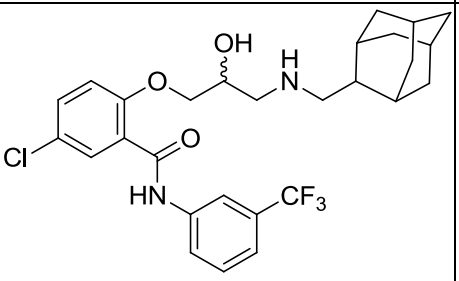
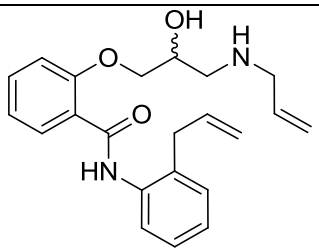
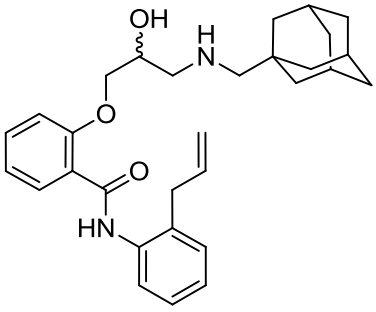
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
172		2.3	0.56			0.5	93.8
173		15.0	4.20			0.3	87.8
174		3.2	0.68			0.2	1.7
175		4.8	1.20			0.7	126.7
176		28.0	7.10			0.1	107.2
177		29.0	8.30			1.0	106.8

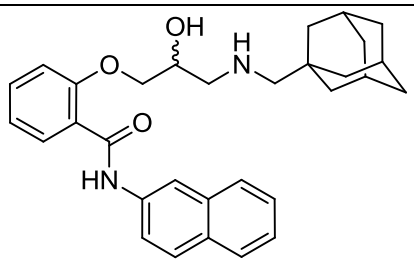
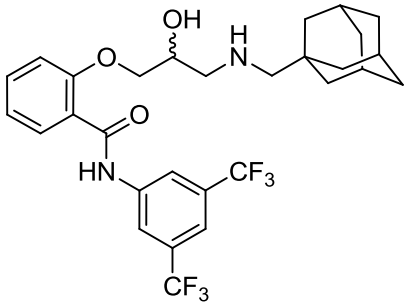
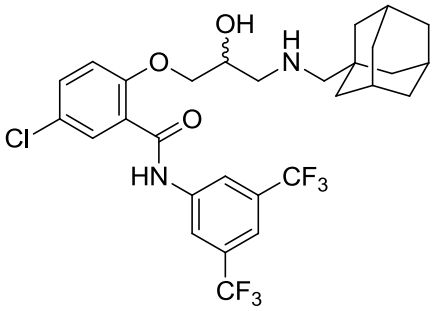
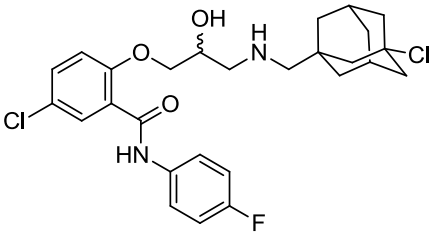
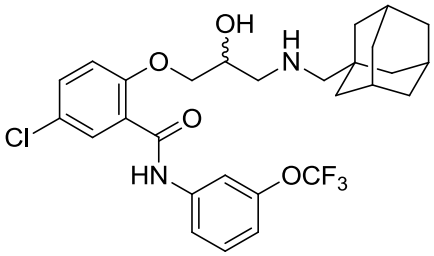
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
178		65.0	23.00			0.8	83.7
179		1303.0	816.00			53.6	100.1
180		1.5	0.55			0.0	1.5
181		1503.0	921.00			67.7	107.6
182		1572.0	1124.00			47.2	124.1
183		8.8	2.20			1.0	115.6

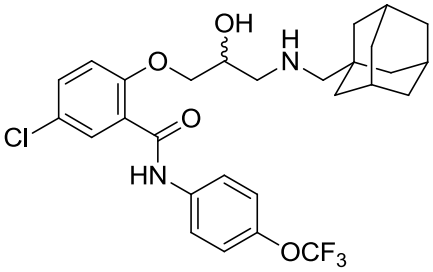
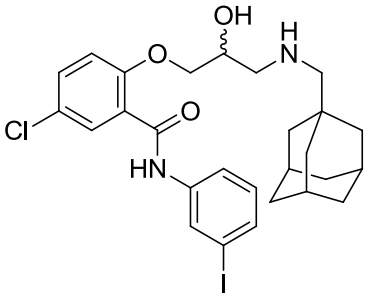
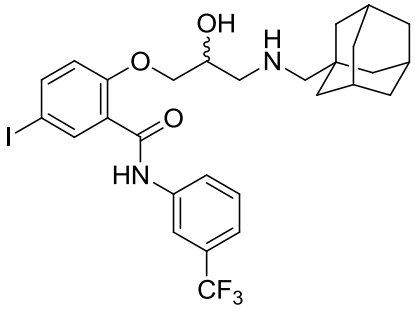
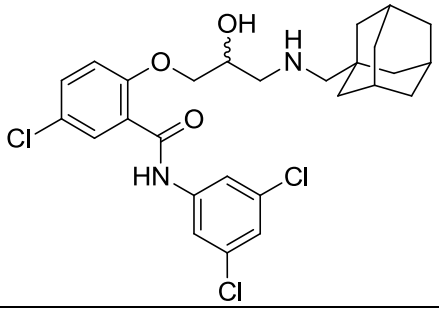
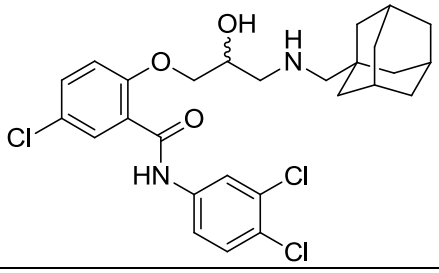
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
184		256.0	105.00			80.5	107.6
185		47.0	11.00			0.5	129.6
186		16.0	3.50			106.8	109.9
187		8.6	2.30			0.9	119.3
188		205.0	74.00			38.7	93.7

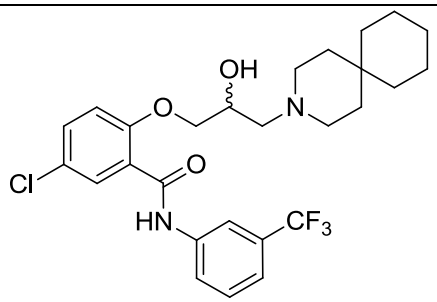
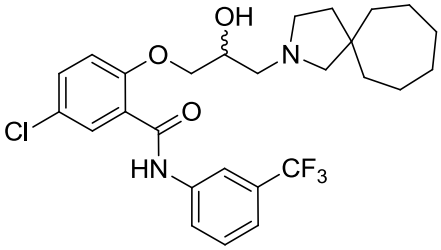
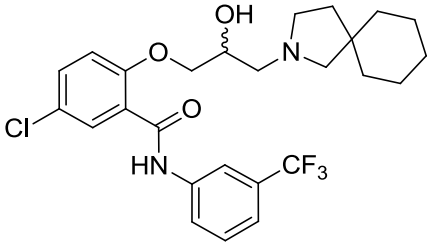
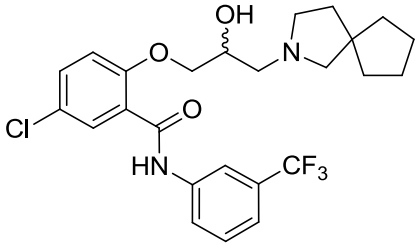
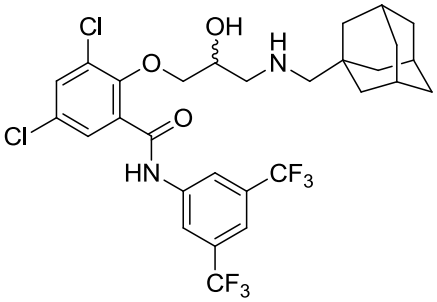
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
189		36.0	8.60			0.6	108.9
190		3.8	0.99			0.8	131.8
191		5.5	1.30			73.0	118.9
192		258.0	83.00			76.7	116.7
193		24.0	5.90			51.9	98.7

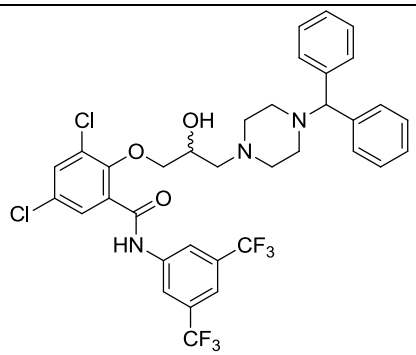
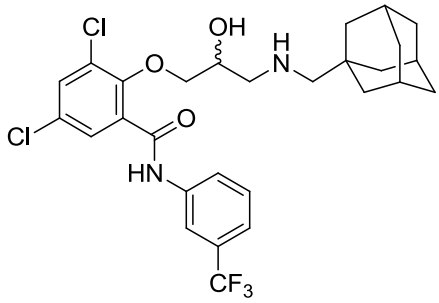
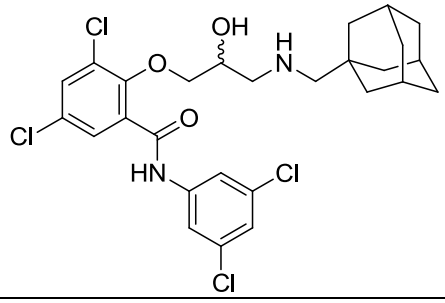
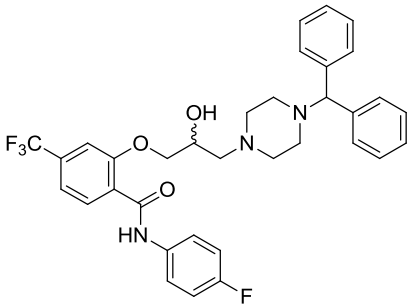
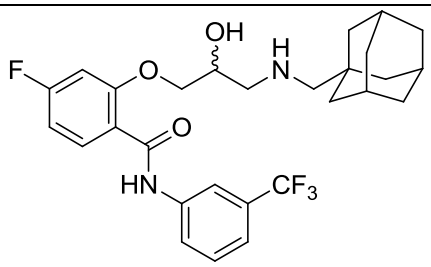
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
194		4.2	0.99	42	12	0.3	91.1
195		17.0	4.00			0.3	64.3
196		15.0	4.10			0.2	65.2
197		3.5	1.40			0.4	1.0
198		6.3	3.10			0.4	0.5
199		2.0	0.51			0.1	15.0

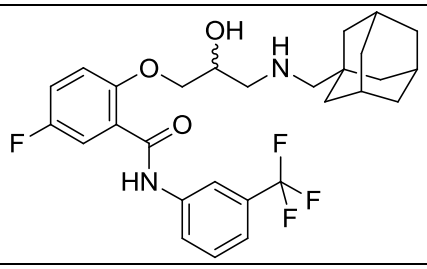
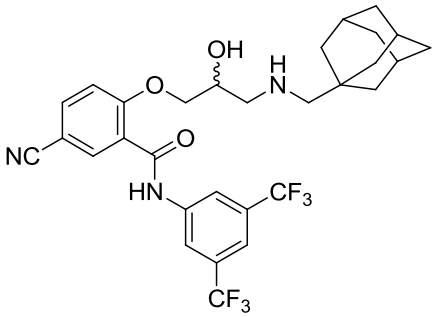
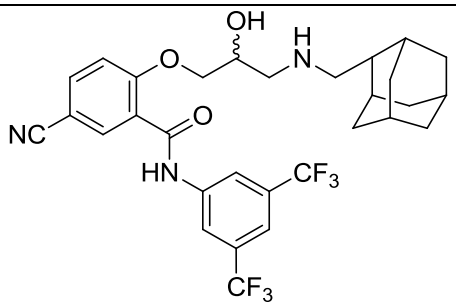
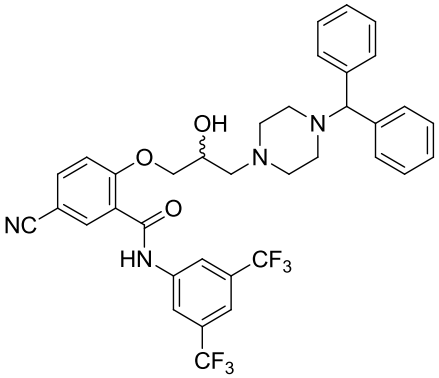
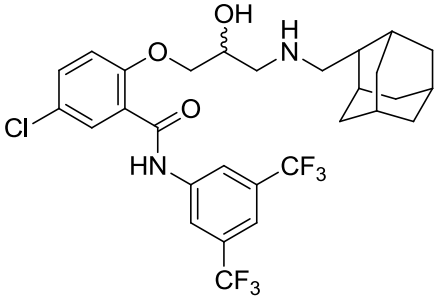
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Micro-some stability I nor-malized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
200		1.5	0.51			0.0	10.5
201		2.2	0.62			-0.1	9.1
202		2.1	0.46	49	25	0.1	105.6
203		2554.0	488.00			82.1	89.2
204		73.0	21.00			46.3	121.9

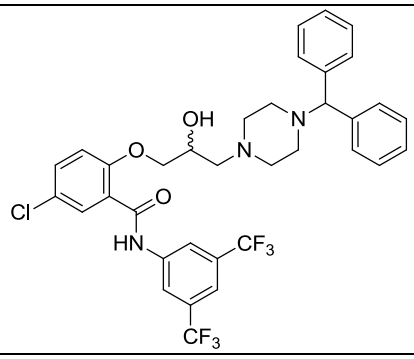
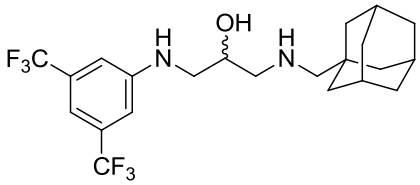
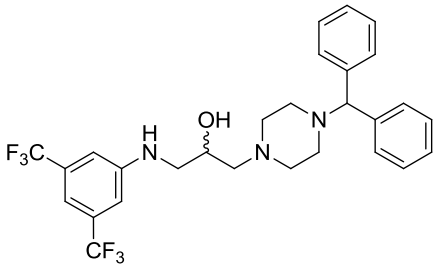
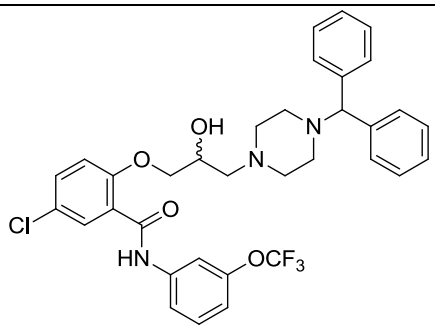
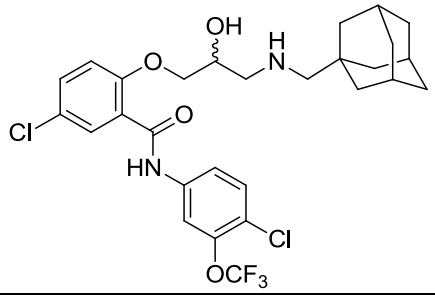
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
205		6.2	1.80			1.2	101.7
206		1.2	0.26			-0.2	64.2
207		1.1	0.19	53	31	0.0	109.8
208		3.6	1.50			0.1	0.4
209		1.0	0.20	23	17	0.2	84.9

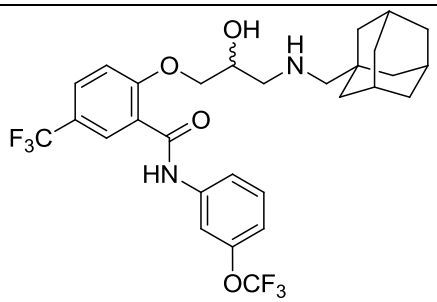
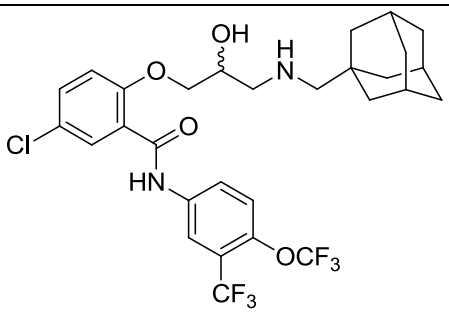
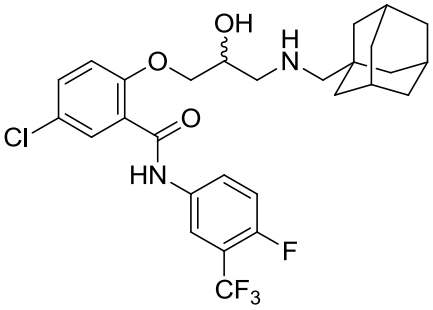
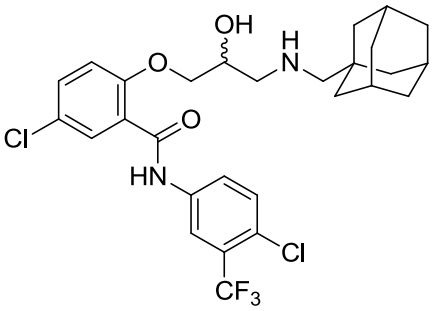
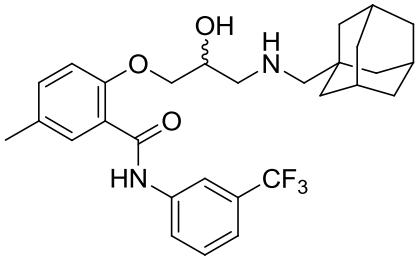
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
210		0.92	0.25	11	2	0.4	106.0
211		1.3	0.27	11	4	0.4	106.2
212		2.1	0.47	39	15	0.1	100.6
213		2.5	0.50	18	10	0.4	105.1
214		1.2	0.31	12	5	0.3	102.0

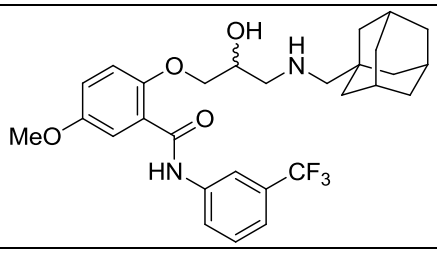
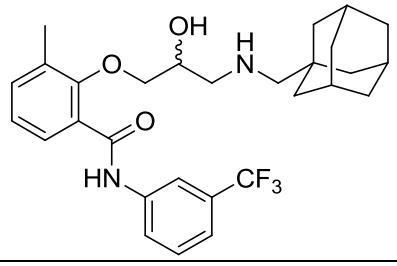
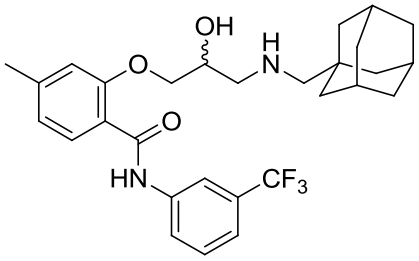
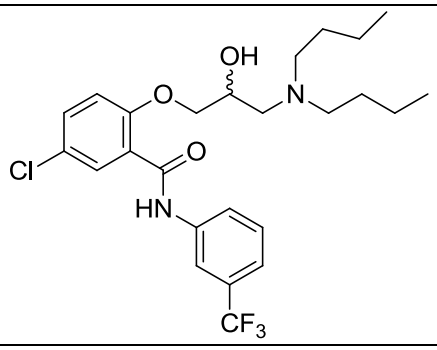
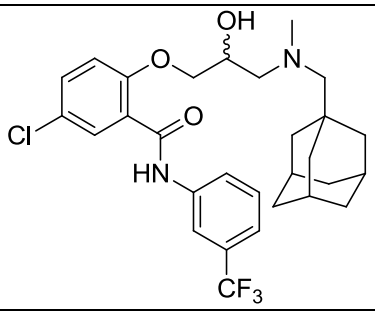
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
215		2.0	0.48			0.2	87.1
216		1.1	0.35	14	2	0.0	98.7
217		1.4	0.48			0.2	77.4
218		1.8	0.76	6	3	0.2	74.8
219		5.6	1.60	63	27	2.4	103.5

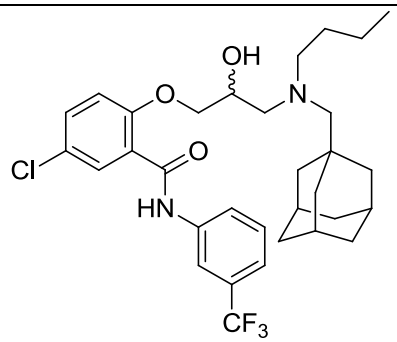
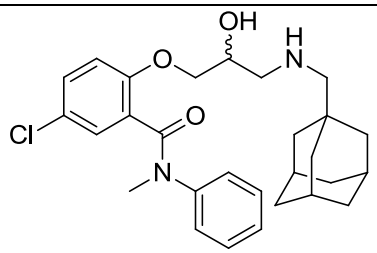
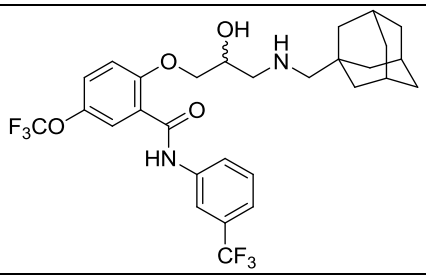
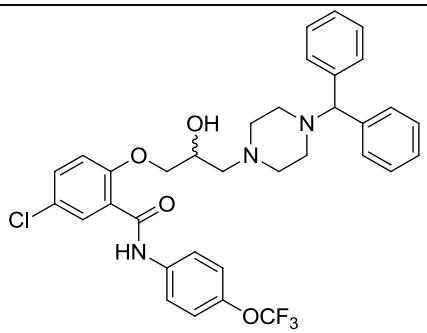
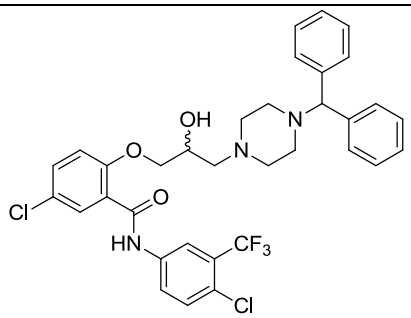
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
220		37.0	9.50	58	57	99.6	119.7
221		8.0	2.20	18	3	0.5	87.1
222		4.6	1.20	54	n.a.	29.3	101.8
223		8.3	2.60	10	1	82.7	121.9
224		2.7	0.61	45	10	0.0	90.0

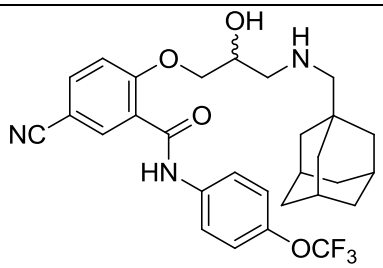
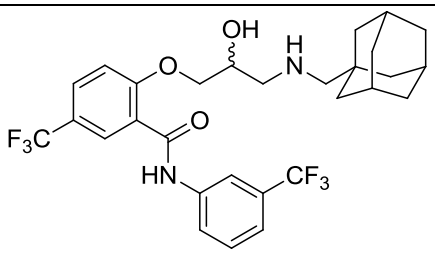
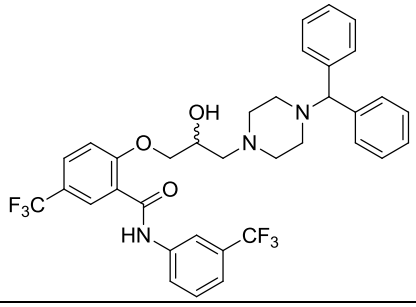
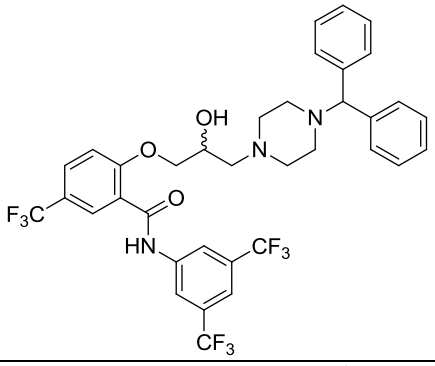
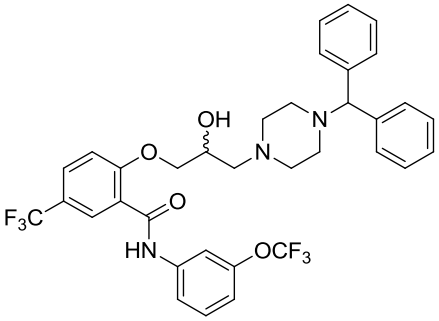
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Micro-some stability I nor-malized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
225		1.3	0.42	13	5	0.1	97.0
226		8.2	2.30	78	60	1.0	96.1
227		9.2	2.80	70	74	0.8	81.6
228		19.0	4.20	27	15	57.8	103.6
229		4.5	1.30	48	29	1.6	102.4

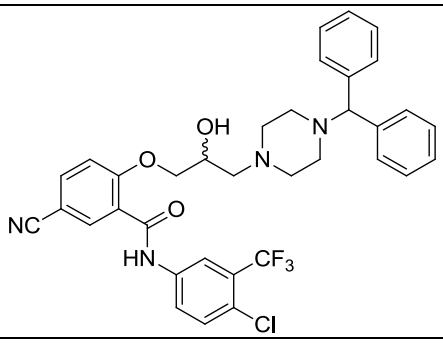
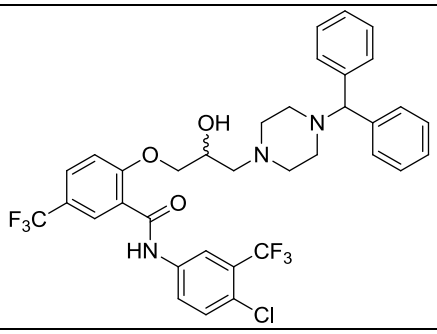
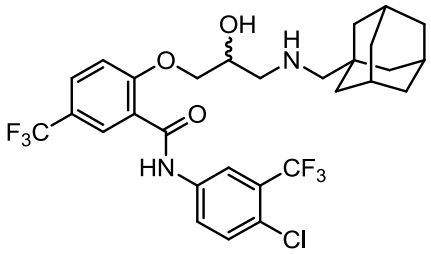
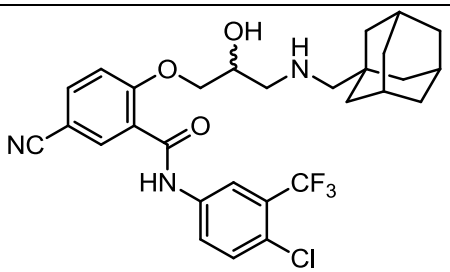
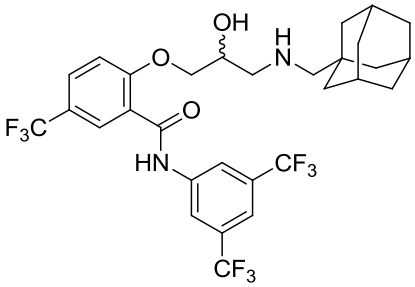
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
230		18.0	3.80	69	48	79.0	112.2
231		23.0	8.30	38	11	-0.1	101.7
232		611.0	1280.00	7	5	78.3	91.0
233		6.7	1.50	10	2	86.5	119.8
234		1.6	0.31	59	16	0.3	124.6

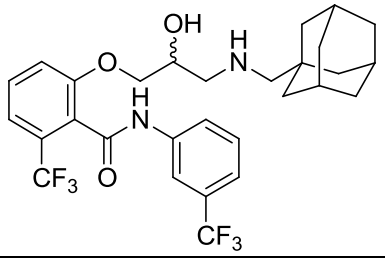
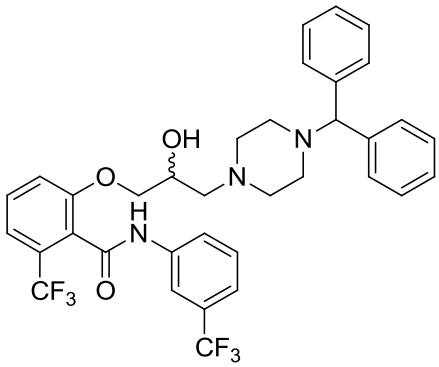
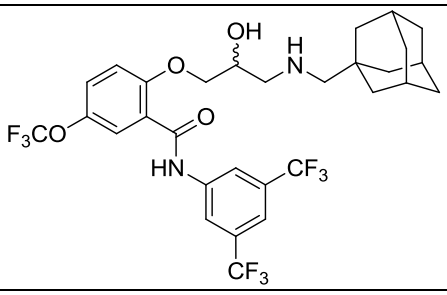
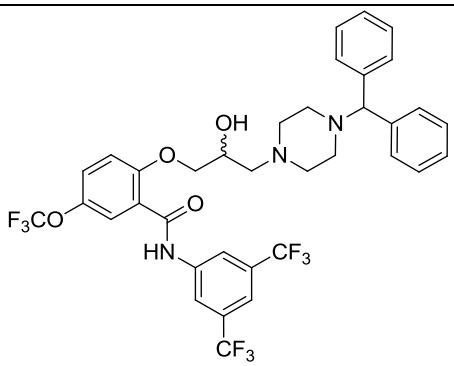
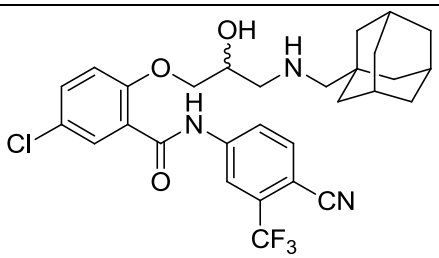
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Micro-some stability I nor-malized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
235		2.4	0.68	62	n.a.	1.6	92.7
236		1.3	0.27	36	11	0.3	127.2
237		1.6	0.40	27	15	0.0	118.9
238		1.5	0.36	28	9	-0.2	123.1
239		5.0	1.30	43	13	0.0	96.0

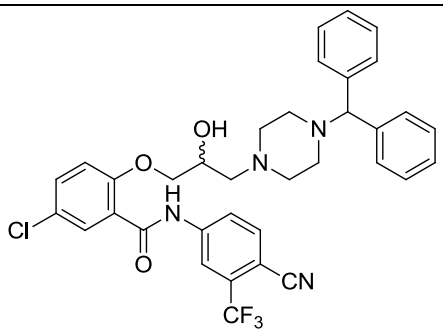
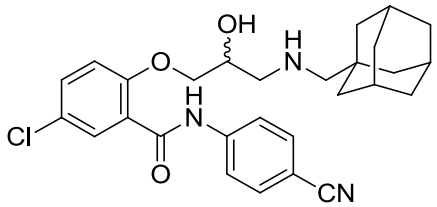
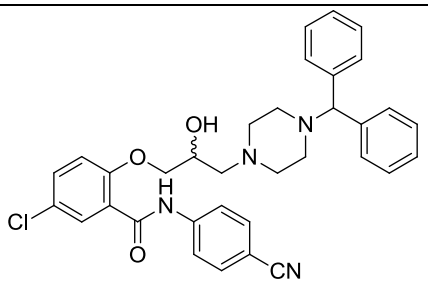
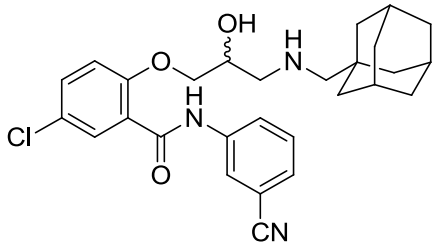
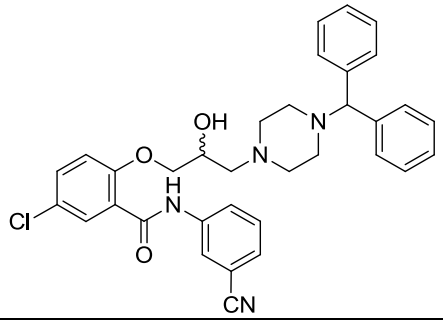
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Micro-some stability I nor-malized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
240		6.0	1.70	71	n.a.	0.0	97.0
241		38.0	16.00	32	4	0.0	104.0
242		4.1	0.83	58	20	41.0	93.0
243		5.5	1.50	15	4	60.2	94.7
244		22.0	6.90	20	4	82.0	110.4

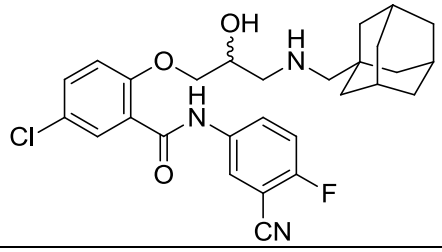
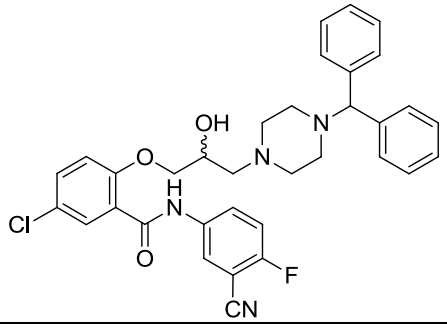
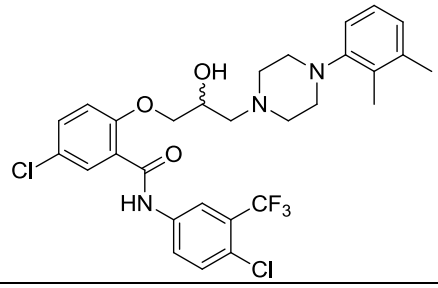
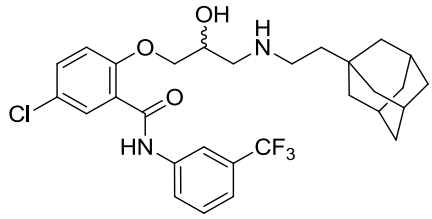
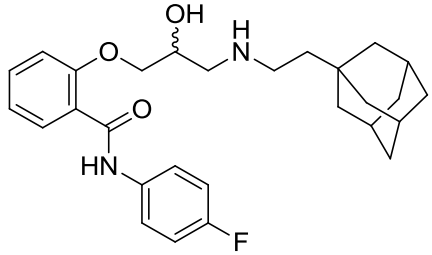
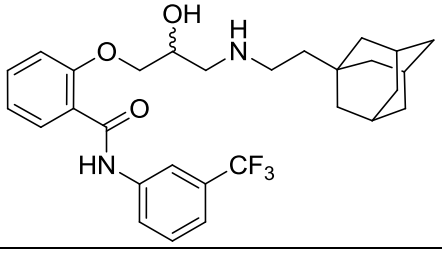
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
245		24.0	6.50	60	30	101.0	106.0
246		579.0	172.00	13	1	45.0	106.0
247		1.4	0.37	61	29	0.1	129.8
248		7.2	1.70	16	9	94.0	130.0
249		1.4	0.45	55	44	82.2	115.9

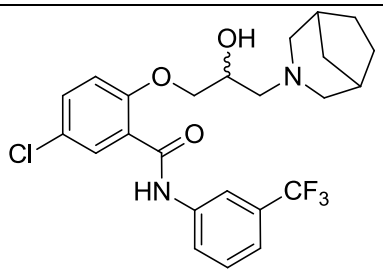
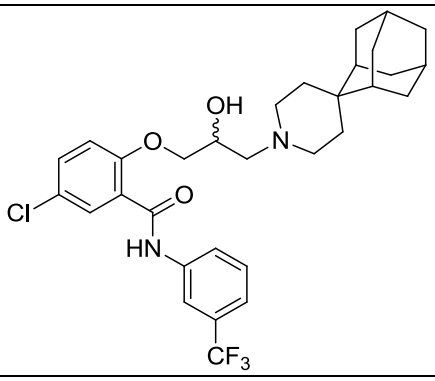
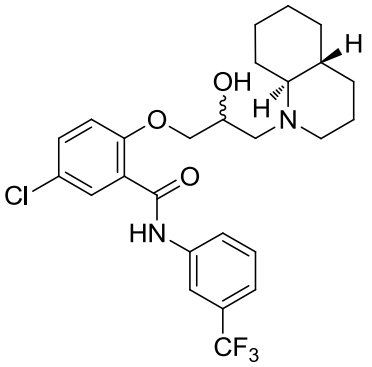
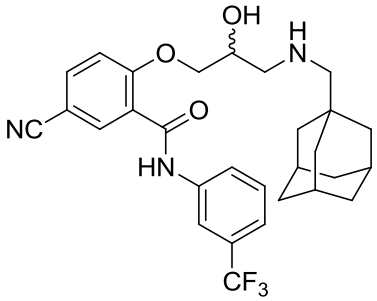
Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
250		11.0	3.60	31	13	1.5	101.3
251		2.8	0.82	43	18	1.5	81.2
252		7.3	1.90	28	12	53.9	83.6
253		16.0	4.00	50	29	26.6	97.0
254		6.8	1.60	21	4	67.8	99.9

Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
255		17.0	5.20	19	8	48.6	103.0
256		11.0	2.50	25	4	78.9	104.2
257		2.4	0.66	38	23	1.2	83.2
258		8.7	2.50	39	19	1.2	93.0
259		3.7	0.96	64	n.a.	0.7	88.9

Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Micro-some stability I nor-malized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
260		282.0	78.00	27	2		
261		354.0	114.00	39	2		
262		1.8	0.26	78	35.0		
263		5.8	1.10	57	22.0		
264		3.6	0.61	74	1		

Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
265		6.0	1.30	15	1		
266		5.6	1.60	22	0		
267		8.0	2.60	73	n.a.		
268		3.8	1.20	6	0		
269		3.6	1.00	7	n.a.		

Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Micro-some stability I nor-malized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
270		3.6	0.70	20	0		
271		5.0	1.00	15	1		
272		14.0	2.80				
273		2.7	0.95			-0.1	3.0
274		7.0	3.20			0.0	-0.1
275		9.8	2.00			0.3	124.1

Pos	Structure	NF54 STI	K1 STI	% 60min Microsome stability	t_1/2 calc Microsome stability I normalized to vinpocetin	Hep G2 Tox10 µM (% survival), AB	HepG2 Tox 1 µM (% survival), AB
276		4.6	1.40	74		93.6	119.5
277		4968.0	2633.00	10	n.a.	96.3	117.3
278		3.4	0.97	18	4	0.0	83.9
279		13.0	4.90	40	23	2.1	103.6

2.2.1 Preliminary Data

Antiplasmodial activity was determined using two strains of *P. falciparum*: the drug-sensitive NF54 strain, an airport strain of unknown origin, and the more robust K1 strain, a clone of a strain originating from Thailand, resistant to chloroquine (**6**) and pyrimethamine (**29**). The ratio of the IC_{50} values against NF54 and K1 strain are constantly in the same order of magnitude, to that effect that antiplasmodial activity of the presented compounds are two to five times more active against K1 strain than against NF54 strain.

The malaria project at the Medical University of Vienna was started in 2004. This thesis covers the period from late 2012 to mid-2015. In the following, preliminary data of important compounds will be discussed.

Propafenone (**68**), which was the starting point of this project, showed IC_{50} values of 302 nM[118] and 1.22 µM[125] against 3D7 strain. These values vary due to different assays used for determination of the activity. The 3D7 strain was derived from the NF54 strain by limiting dilution.[126] The problem with propafenone as lead is the antiarrhythmic activity of the scaffold. When the α carbon atom was replaced by a nitrogen atom, the antiarrhythmic potency was decreased in a manner that this compound was no longer considered as useful in treatment of cardiac diseases. Unfortunately, this modification also decreases malaria activity drastically, resulting in a 70-fold reduced activity against the chloroquine sensitive 3D7 strain.[120,127]

This effect can be overcome by replacement of the propyl residue on the basic nitrogen with more bulky alkyl residues. Data of "aza-propafenone" derivatives are shown in Table 3. For instance, the 2-adamantyl residue increases the activity so that **106** shows moderate antimalarial activity, comparable to that of propafenone (**68**), while antiarrhythmic activity should be ruled out by the salicylamide moiety. Further increase of activity is achieved by *ortho*- or *para*-methoxy substitution (**107**, **108**), in the benzylamide diversity site (R''). The position of the methoxy group has no noteworthy effect on the activity; **107** and **108** show roughly equal activity on each tested strain.

The 1-adamantyl residue in **109** shows less activity than its 2-adamantyl analog **107**. In the 2-adamantyl series with unsubstituted benzylamide, the presence of tertiary amines results in varying effects on the activity. While an additional *n*-pentyl (**110**), *n*-propyl (**111**), or methyl (**112**) residue increase activity (218 and 73 nM, 349 and 121 nM, and 421 and 137 nM, re-

spectively), an additional ethyl (**113**) or cyclopropyl (**114**) residue result in loss of activity (933 and 262 nM, and 156 and 433 nM, respectively).

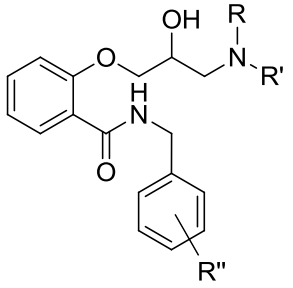
Combining structural beneficial features, *ortho*-methoxy benzylamide and a tertiary basic nitrogen with a 2-adamantyl residue and an *n*-propyl side chain in **115** shows an increase over **111**, but it is a retrograde step regarding **107**. The 3-phenylpropyl residue by itself (**116**) brings a worsening of activity, although in combination with a 2-adamantyl residue a bigger increase of activity compared to additional alkyl side chains (**110-114**) is caused.

The effect of 2-phenylethyl (**117**) residue is smaller than that of 3-phenylpropyl but still an increase over **106**, while substitution with a 2-methoxyphenylmethyl residue (**118**) leads to a drastic decrease of activity, which may be caused by the polarity of the methoxy group on the aromatic ring. Similar considerations also apply for **119**, with a 4-benzoylbenzyl residue on a secondary amine.

4-Trifluoromethyl (**120**) or 4-*tert*-butyl (**121**) groups in the benzylamide moiety act beneficial compared to the parenteral compound **102** containing a tertiary amine with a 2-adamantyl and a methyl residue. The effect of a cyclooctyl residue (**122**) in the amine diversity site is negative, whereas the larger cyclododecyl residue (**123**) increases activity. Activity is drastically increased to an IC_{50} of 79 nM (NF54) and 20 nM (K1) in **124** which features a 1-adamantan-1-ylethyl residue on a secondary amine. Unfortunately, this structure has 4 stereoisomers; therefore the 1-adamantan-1-ylethyl residue is not favorable. But also the adamantan-1-ylmethyl shows promising activity (79 nM on NF54 and 20 nM K1, respectively).

The beneficial effect of a 2-methoxy group in the benzylamide site in combination with a 2-adamantyl residue (**107**) seems adverse in combination with a 1-adamantanylmethyl residue on a secondary amine (**125**). In contrast, the beneficial effect of a 4-trifluoromethyl group in the benzylamide site is also observed in combination with a 1-adamantanylmethyl residue on a secondary amine (**126**). The IC_{50} of 57 nM (NF54) and 18 nM (K1) seems promising. Different from the 2-adamantyl series, in combination with adamantan-1-ylmethyl residues in the amine diversity site an additional alkyl group shows a decrease of activity. Within the entire benzylamide series, as far as tested no toxicity against Hep G2 cells was observed and no stability data were collected.

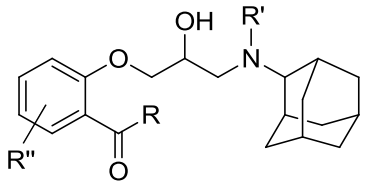
Table 3. Chemical structure and IC_{50} values (nM) of benzylamide derivatives.



	R	R'	R''	IC_{50} NF54	IC_{50} K1
106	2-adamantyl	H	-	757	246
107	2-adamantyl	H	2-methoxy	238	78
108	2-adamantyl	H	4-methoxy	220	90
109	1-adamantyl	H	2-methoxy	968	281
110	2-adamantyl	*n*-pentyl	-	218	73
111	2-adamantyl	*n*-propyl	-	349	121
112	2-adamantyl	methyl	-	421	137
113	2-adamantyl	ethyl	-	933	262
114	2-adamantyl	cyclopropyl	-	1156	433
115	2-adamantyl	*n*-propyl	2-methoxy	290	132
116	3-phenylpropyl	H	-	1091	510
117	2-adamantyl	2-phenylethyl	-	580	212
118	2-adamantyl	2-methoxyphenylmethyl	-	2051	707
119	4-benzoylbenzyl	H	-	2120	995
120	2-adamantyl	methyl	4-trifluoromethyl	161	54
121	2-adamantyl	methyl	4-*tert*-butyl	261	69
122	cyclooctyl	H	-	881	333
123	cyclododecyl	H	-	262	70
124	1-adamantan-1-ylethyl	H	-	79	20
125	adamantan-1-ylmethyl	H	2-methoxy	183	61
126	adamantan-1-ylmethyl	H	4-trifluoromethyl	57	18
127	2-adamantyl	3-phenylpropyl	-	168	59
128	adamantan-1-ylmethyl	H	-	143	49
129	adamantan-1-ylmethyl	methyl	-	670	182

Table 4 shows more structures of 2-adamantyl derivatives and their activities. Both the 2-phenylethyl amide (**130**) and the 3-phenylpropyl amide (**131**) have increased activities compared with the benzylamide analog **106**. The activity of the 2-phenylethyl amide can still be increased by 5-chloro modification in the salicylic ring (**132**), which seems to have negative influence on the cytotoxicity of the compound. Also aliphatic amides such as propyl amide **133** have at least moderate antimalarial activity. The importance of the amide group for activity can be shown by the inactive acid analog (**134**) and the corresponding inactive ester analog (**135**), respectively.

Table 4. Chemical structure and IC_{50} values (nM) of 2-adamantyl derivatives.

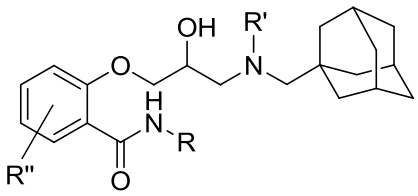


	R	R'	R''	IC_{50} NF54	IC_{50} K1
130	NHC_2H_4Ph	H	-	281	101
131	NHC_3H_6Ph	H	-	308	103
132	NHC_2H_4Ph	H	5-Cl	96	26
133	NHC_3H_7	H	-	614	174
134	OH	Me	-	inactive	inactive
135	OMe	Me	-	inactive	inactive

In the same manner as in the 2-adamantyl variation, the 5-chloro modification is also applicable to adamantan-1-ylmethyl derivatives; see **136** and **137** in Table 4. Not only activity is increased from 96 nM to 27 nM on NF54 and 26 nM to 7.9 nM on K1, also cytotoxicity is decreased from **137** to **132**. Also, the activity of **138**, featuring a 3-phenylpropyl amide succeeds the activity of the 2-adamantyl analog **131**. Aliphatic residues on the amide moiety such as isopentyl (**139**) lead to reasonable activities. The intolerance of the 5-prop-2-yn-1-yloxy group in the salicylic ring of **140** is obvious. Also a naphthalen-1-ylmethyl (**141**) residue is tolerated at the amide diversity site. Switching to salicyl anilides increases activity further. In combination with adamantan-1-ylmethyl, very high activity was observed for p-tolyl- (**142**), *N*-4-fluorophenyl- (**143**), *N*-2,4-difluorophenyl- (**144**), and *N*-3-(trifluoromethyl)phenylsalicylamide (**145**).

In the case of *N*-2-fluorophenylsalicylamide (**146**) activity is not that high due to sterical reasons; this consideration also affects *N*-2,4-difluorophenyl analog **144**. **147** shows that the adamantan-1-ylmethyl residue in the amine diversity site is better on a secondary amine than on a tertiary amine with an additional methyl substituent, this confirms the findings presented in Table 3 (**128** and **129**).

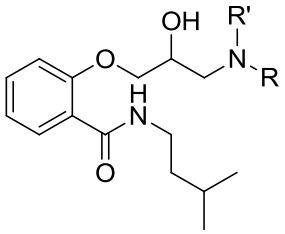
Table 5. Chemical structure and IC_{50} values (nM) of adamantan-1-ylmethyl derivatives.



	R	R'	R''	IC_{50} NF54	IC_{50} K1
136	2-phenylethyl	H	-	101	30
137	2-phenylethyl	H	5-Cl	27	7.9
138	3-phenylpropyl	H	-	148	52
139	isopentyl	H	-	134	36
140	isopentyl	H	5-prop-2-yn-1-yloxy	5380	2260
141	naphthalen-1-ylmethyl	H	5-Cl	20	5.2
142	*p*-tolyl	H	-	5.6	1.7
143	4-fluorophenyl	H	-	6.4	1.7
144	2,4-difluorophenyl	H	-	9.3	3.1
145	3-(trifluoromethyl)phenyl	H	-	2.3	0.51
146	2-fluorophenyl	H	-	24	8.1
147	4-fluorophenyl	Me	-	63	16

Compared to the salicylarylamides the salicylalkylamides presented in Table 6 show only low activities. Unlike lumefantrine (**20**)[96], dibutyl **148** shows greater activity than its monobutyl derivative **149**. The activities of the compounds **150**, **151**, and **152** suggest that the amine site has to be substituted with bulky alkyl side chains, which is splendidly confirmed by the activity shown by the 1-adamantan-1-ylethyl compound **153**, which is outstanding in respect of the non-ideal alkyl amide substitution.

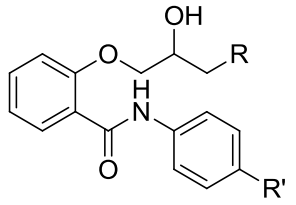
Table 6. Chemical structure and IC_{50} values (nM) of isopentyl amide derivatives.



	R	R'	IC_{50} NF54	IC_{50} K1
148	*n*-butyl	*n*-butyl	333	76
149	*n*-butyl	H	2751	827
150	benzyl	H	1434	356
151	4-trifluoromethylbenzyl	H	1362	371
152	isopentyl	H	1693	467
153	1-adamantan-1-ylethyl	H	74	18

Activities of salicylanilide derivatives are shown in Table 7. The 1-adamantan-1-ylethyl analog (**154**) of the above seen **142** is equally potent. The propyl amino analog **155** is much less active, which is another proof of the need for bulky alkyl residues in the amine diversity site. But, when changing to an *N*-4-fluorophenyl amide a minimal chain elongation from propyl- to butyl- we end up with a very active compound (**156**) again. More bulky residues do not change activity significantly (see compounds **157**-**162**).

Table 7. Chemical structure and IC_{50} values (nM) of salicylanilide derivatives.



	R	R'	IC_{50} NF54	IC_{50} K1
154	1-adamantan-1-ylethylamino	Me	5.6	1.5
155	*n*-propylamino	Me	156	72
156	*n*-dibutylamino	F	18	5.7
157	4-phenylpiperidin-1-yl	F	26	9
158	4-benzylpiperidin-1-yl	F	16	6.8
159	4-benzhydrylpiperazin-1-yl	F	14	3.7
160	1-adamantylamino	F	51	11
161	3,5-dimethyladamantan-1-ylamino	F	38	8.3
162	4-(adamantan-1-yl)piperazin-1-yl	F	59	12

163 with a 3,4-dimethylphenylpiperazine in the amine diversity site, see Figure 19, shows moderate activity and low cytotoxicity. The adamantyl derivatives of propafenone, **164** and **165**, show good activity. Biphenyl **166** shows moderate activity and low cytotoxicity. It is important to notice that this compound contains no amide or carbonyl group but activity remained. After all, compared with its benzylamido derivative **121** it shows half of the activity and is only slightly more cytotoxic. The naphthalen-1-ylmethylamido structure **167** shows more activity than its adamantan-1-ylmethyl derivative **141**. The additional methyl group seems to have a beneficial effect, but this data has to be treated with caution because this data is based on a diastereomeric mixture of compounds.

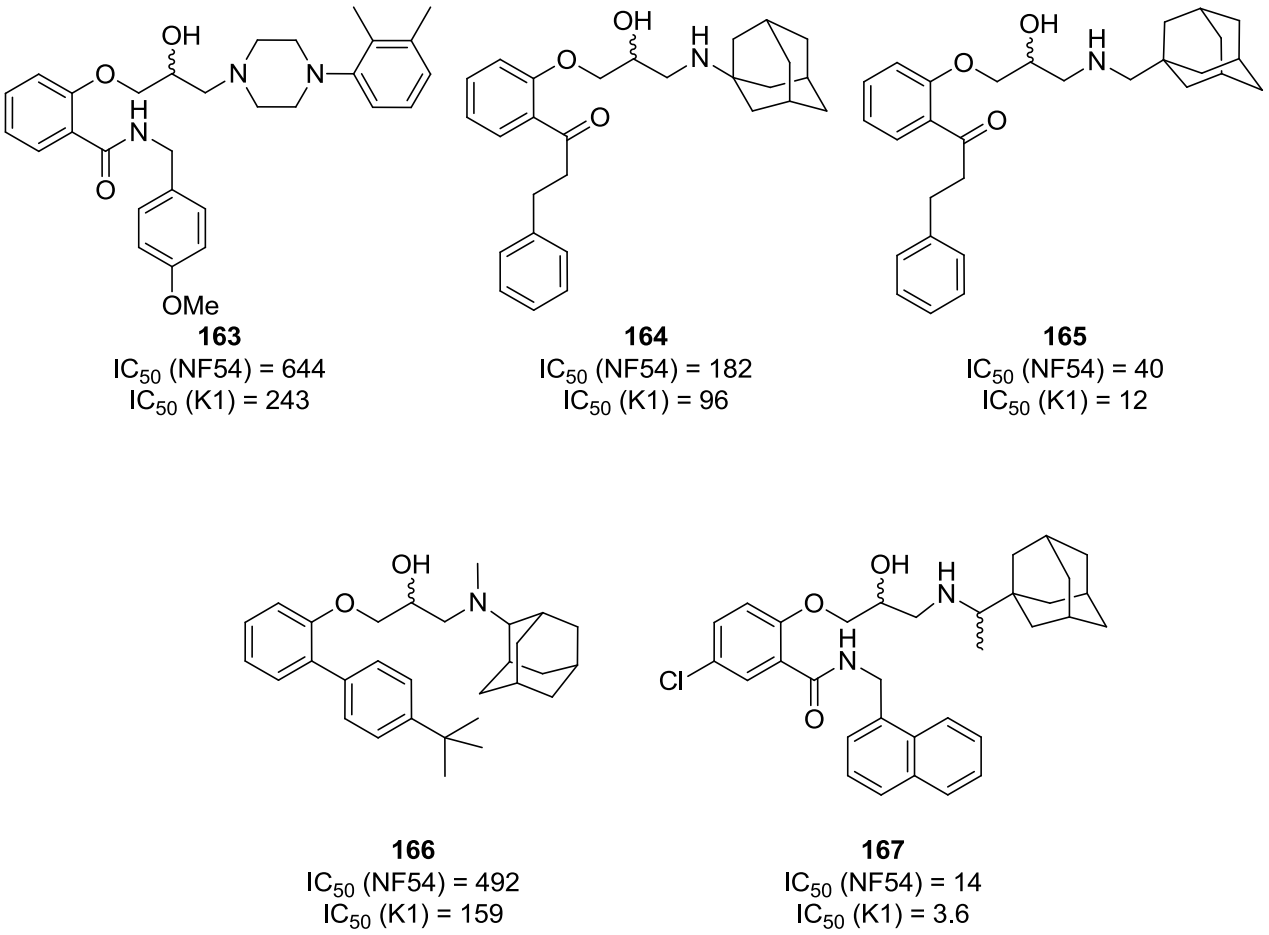


Figure 19. Other compounds examined for antiplasmodial activity (nM).

The drawn lessons from comparing preliminary data are quite simple. In the amide site the anilide structure is the most active group. 2-Phenylethyl amides are less active, and least active are the 3-phenylpropyl-, the benzyl, and the isopentylamides. In the amine diversity site the substituted rimantadines are the most active. However, they should be avoided because of the inconvenient, and therefore expensive, handling of diastereomers. Lumefantrine (**20**), having only one stereogenic center, acts as model because it can be administered as racemic mixture. Hence, adamantan-1-ylmethyl amines are considered as best choice because the shown activities of the presented compounds above (**137**, **141**-**146**, **154**, **156**-**159**, and **167**) look promising although cytotoxicity might be problematic, but not insurmountable. 2-Adamantyl amines are much less active, but still better than 1-adamantyl derivatives. In summary, the evaluation of preliminary data leads us to the scaffold shown in Figure 20.

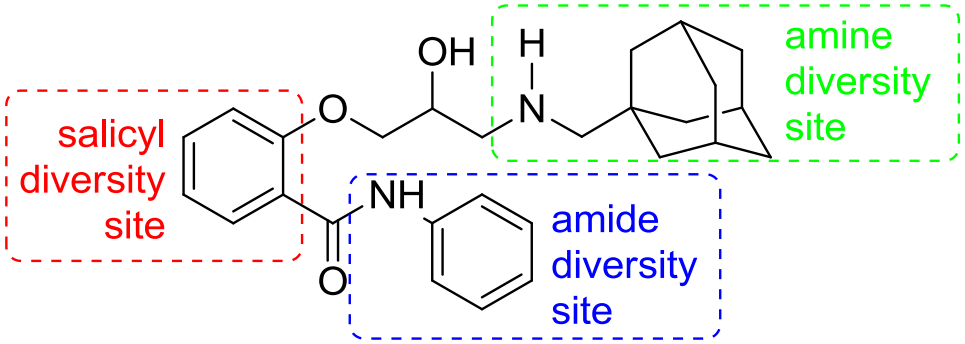
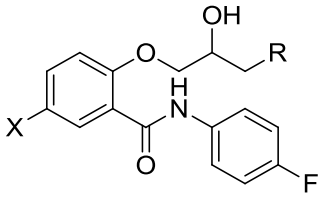


Figure 20. Simplified illustration of the ideal scaffold solution found through evaluation of preliminary data.

2.2.2 Data Collected During Thesis

One of the most promising substitution patterns from preliminary results was the *N*-4-fluoro substitution in the amide region: **143**, **147**, **156**-**159**, and **162**. Therefore this pattern was further investigated, see Table 8. It was considered as important to block the 5-postion in the salicylic ring, to avoid the metabolic production of *p*-hydroquinone. **168** shows excellent activity and acceptable cytotoxicity. In comparison to their unsubstituted analogs (**157**-**159**) the 5-bromo compounds (**169**, **170**, and **171**) show better activities. The 4-phenylpiperidine compound **169** shows more cytotoxic activity than its analog without the bromine atom, while the 5-bromo substitution seems to be beneficial in combination with a benzhydryl piperazine. When comparing **172** and **168** there seems to be no difference in activity or cytotoxicity between 5-bromo and 5-chloro substitution. The reduced activity of the 1-adamantane compound **173** in comparison with the CH_2-elongated **172** is another confirmation of our findings from evaluation of preliminary data. 5-Fluoro substitution in **174** shows slightly poorer activity than chloro or bromo analogs (**168** and **172**, respectively) but extreme cytotoxicity issues.

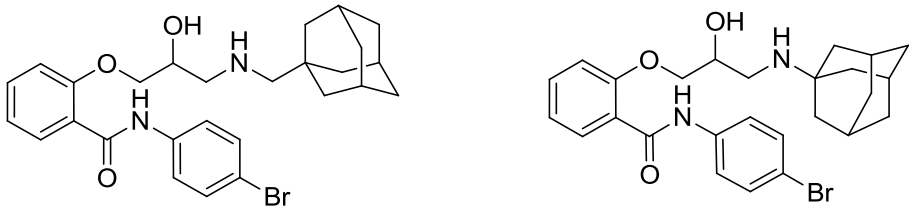
Table 8. Chemical structures and activities (nM) of 4-fluoro salicylanilides in combination with halogen substituents in the 5-position of the salicylic ring.



	X	R	IC_{50} NF54	IC_{50} K1
168	Cl	adamantan-1-ylmethylamino	2.4	0.62
169	Br	4-phenylpiperidin-1-yl	9.3	2.3
170	Br	4-benzylpiperidin-1-yl	8.4	2.3
171	Br	4-benzhydrylpiperazin-1-yl	7.1	1.8
172	Br	adamantan-1-ylmethylamino	2.3	0.56
173	Br	1-adamantylamino	15	4.2
174	F	adamantan-1-ylmethylamino	3.2	0.68

Compound **175**, shown in Figure 21, shows promising activity. Cytotoxicity data seems to be fair enough. However, in an animal experiment one of three mice treated with **175** died. The bromine atom in the aniline was considered as trigger of this effect. Therefore, incorporation of bromine was avoided hereafter. For the sake of completeness, 1-adamantylamine com-

pound **176** is less active than its adamantan-1-ylmethylamino analog **175**. This ranking of amines was observed before.



175
IC_{50} (NF54) = 4.8
IC_{50} (K1) = 1.2

176
IC_{50} (NF54) = 28
IC_{50} (K1) = 7.1

Figure 21. 2-(3-((Adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(4-bromophenyl)benzamide (175**) and 2-(3-(adamantan-1-ylamino)-2-hydroxypropoxy)-*N*-(4-bromophenyl)benzamide (**176**).**

As the diversity site in the salicylic region was not deeper investigated so far, the compounds shown in Figure 22 (**177**, **178**, **179**, and **200**) were synthesized. **177** is about five-fold less active than the unsubstituted salicylamide analog **143** (Table 5; 6.4 nM on NF54 and 1.7 nM on K1, respectively) while cytotoxicity remains the same. The 1-adamantyl amine **178** shows weaker activity than the 1-adamantyl amine salicyl-compound **160** (Table 7; 51 nM on NF54 and 11 nM on K1, respectively) but roughly on the same level. By installing a 3-hydroxy-1-adamantyl residue in the amine diversity site as in **179** activity is significantly reduced. This might be a mimic of potential metabolic intermediates when such a compound is degraded. When a trifluoromethyl group is in the 4-position of the salicylic ring (**180**) activity is extraordinarily good, but unfortunately at the expense of high cytotoxicity. At a concentration of 1 µM only 1.5 % of the tested Hep G2 cells survived.

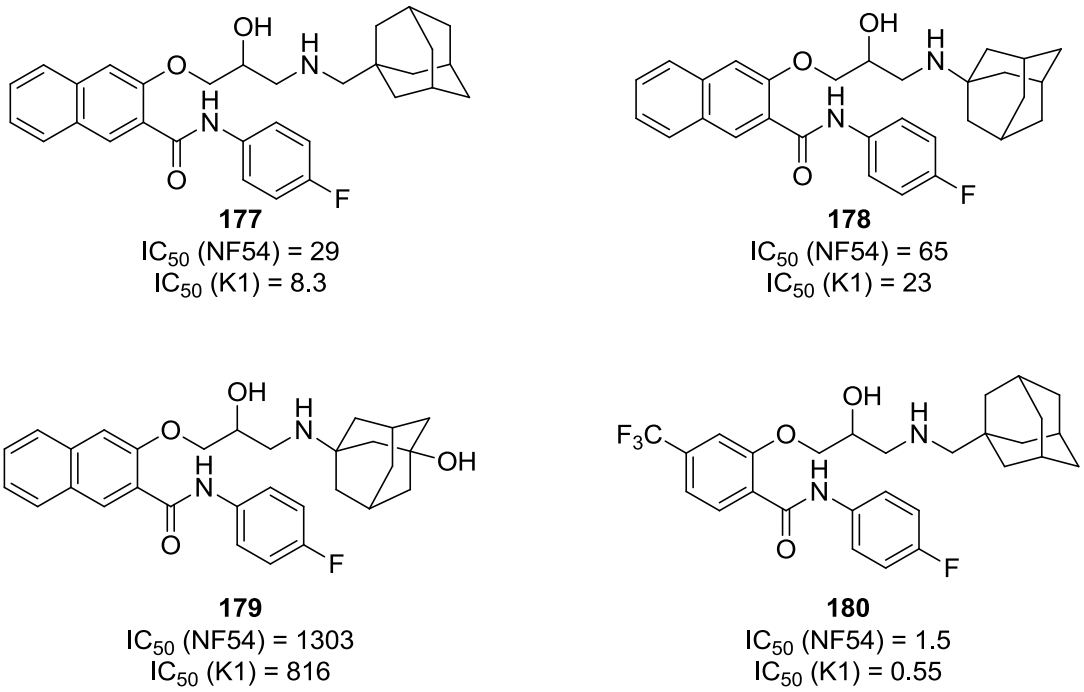


Figure 22. Structure and activity (nM) of 2-naphthamides 177**,** 178**, and** 179**; as well as the highly active 4-trifluoromethyl salicyl compound** 180**.**

To validate the low antiplasmodial activity found with **179** other derivatives carrying a 3-hydroxy-1-adamantyl residue (**181**, **182**) were synthesized (see Figure 23). Both derivatives revealed IC_{50}-values around 1 µM. All three of them are nontoxic to Hep G2 cells, which is also positive as it would suggest that metabolites of this type would exert no cytotoxicity.

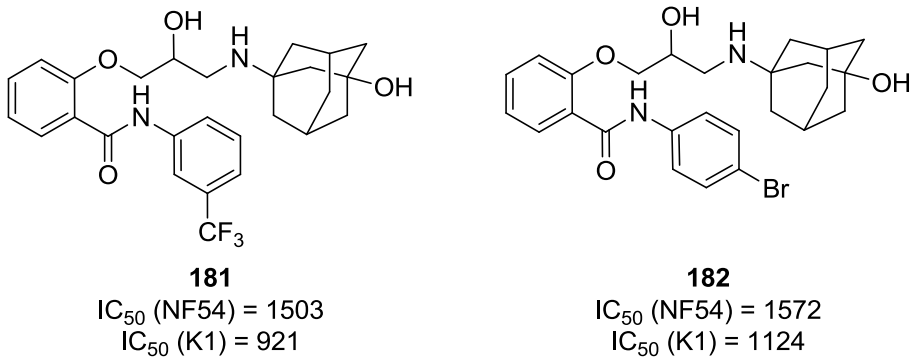
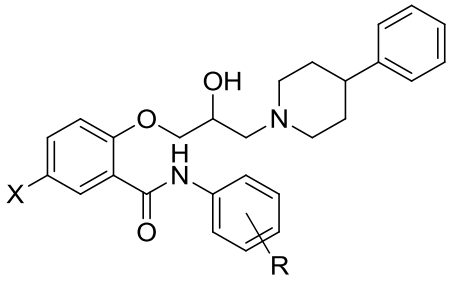


Figure 23. Derivatives with 3-hydroxy-1-adamantyl residues.

In compound **169** (Table 8; 9.3 nM and 2.3 nM, respectively) the 4-phenyl piperidine in the molecule looked promising. Further, compounds with this amine motif were synthesized and tested. Structures and activities are shown in Table 9. **183** showed slightly better but comparable activity while being less cytotoxic. The 2-fluoro group of **184** drastically reduces activity. On the other hand cytotoxicity is also drastically reduced. **185** offers no advantage in terms of cytotoxicity over **183** while being muss less active. The chlorine atom in **186** seems

to reduce activity which was not observed before. This compound has surprisingly very low solubility; the assay therefore might have failed.

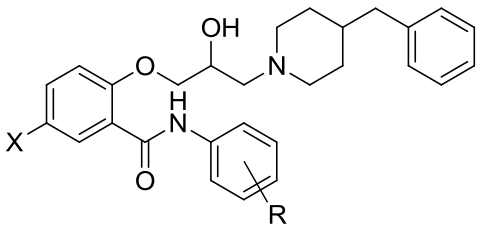
Table 9. 4-Phenyl piperidine derivatives 183-186**.**



	X	R	IC_{50} NF54	IC_{50} K1
183	H	3-trifluoromethyl	8.8	2.2
184	H	2-fluoro	256	105
185	H	4-methyl	47	11
186	Cl	3-trifluoromethyl	16	3.5

Since the 4-phenyl piperidine compounds did not provide satisfying results, the 4-benzyl piperidine motif was investigated. Compounds **187**-**190**, shown in Table 10, show no noteworthy improvement over their 4-phenyl analogs in Table 9. One exception is of course **190** which is much better soluble than its analog **186**. Therefore, activity is much better and concomitantly cytotoxicity is observed; this was not the case for **186**.

Table 10. 4-Benzyl piperidine derivatives 187-190**.**

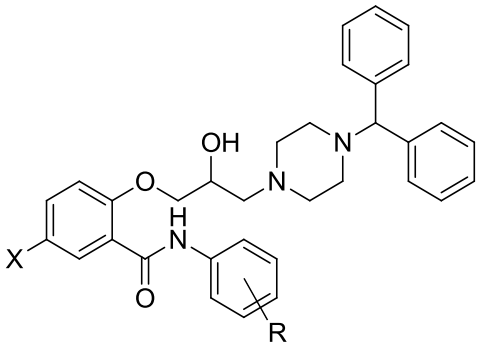


	X	R	IC_{50} NF54	IC_{50} K1
187	H	3-trifluoromethyl	8.6	2.3
188	H	2-fluoro	205	74
189	H	4-methyl	36	8.6
190	Cl	3-trifluoromethyl	3.8	0.99

When considering the 4-benzylpiperazine derivatives in Table 11 generally low cytotoxicity is observed. This might be an effect related to the benzhydryl piperazine moiety, because it is observed for all compounds shown in Table 11 and also **159** (see Table 7) shows low cytotoxicity. **191**, which is not cytotoxic, still shows half of the activity of adamantan-1-ylmethylamino compound **145,** which is highly toxic on Hep G2 cells. **192** shows only moderate activity, com-

parable to its piperidine analogs **184** and **188**. These also show only weak cytotoxicity; hence, **192** is no real advance and the 2-fluoro anilines can be ruled out as best solution. Benzhydryl piperazine **193** shows five-fold decreased activity than adamantan-1-ylmethylamino **142**. In return it is less cytotoxic. Interestingly 5-chloro salicyl compound **95** shows very similar results in activity and cytotoxicity to deschloro analog **191**. Both compounds are highly interesting since both offer promising activity, comparable to marketed antimalarial drugs, while being nontoxic on Hep G2 cells.

Table 11. 4-Benzhydryl piperazine derivatives 191-193**, and** 95**.**



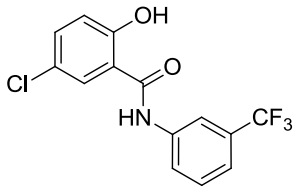
	X	R	IC_{50} NF54	IC_{50} K1
95	Cl	3-trifluoromethyl	5.7	1.2
191	H	3-trifluoromethyl	5.5	1.3
192	H	2-fluoro	258	83
193	H	4-methyl	24	5.9

Hitherto, the trifluoromethyl substituent in the 3-positon of the aniline has been promising; therefore, many more compounds showing this motif have been synthesized. These are shown in Figure 24. First, anilide **72** shows only very weak activity. Unfortunately, no toxicological data is available. This would have been interesting regarding the hazardousness of metabolites. Compound **194** shows good activity and acceptable cytotoxicity. The effect of an additional alkyl group on the amine was beneficial in preliminary tests in some cases. Compound **195** shows unfavorable cytotoxicity, while the activity is unrevealing because no comparable compound has been evaluated.

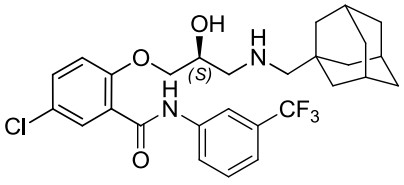
The effect of a 3,4-annulation in the salicylic ring as in compound **196** has unfavorable effects on the activity if it is compared to the simpler salicylic analog **145** which is sevenfold more active. A similar effect was observed above concerning 4,5-annulation, shown with the pair **143** and **177**. Both enantiomers, **96** and **97**, show the same activity and the same toxicological properties regarding Hep G2 cells. This would suggest that the compounds work the same way as for instance lumefantrine which is also administered as racemic mixture. Sur-

prisingly, the enantiomers show slightly more activity than the racemate. The trifluoromethyladamantyl compounds **197**, **198**, and **199** show good antimalarial activities but at the same time they are all seriously toxic on the tested Hep G2 cells. On the basis of the promising effect of 1-adamantan-1-ylethyl amine in compound **124** (see Table 3) a symmetrical 2-(adamantan-1-yl)propan-2-amine was incorporated in **200**. The result is good activity, comparable to the tested enantiomers **96** and **97**, but cytotoxicity on this level is unacceptable. The effect of a chloroadamantyl residue is comparable to the effect of the trifluoromethyladamantyl residue in the amine diversity site. **201** also shows good IC_{50}-values while being extremely cytotoxic. **202**, the 2-adamantyl version of **194** shows comparable activity and cytotoxicity data as the enantiomers **96** and **97**. Therefore, it can be assumed that the adamantan-2-ylmethyl group has no advantage over the adamantan-1-ylmethyl group.

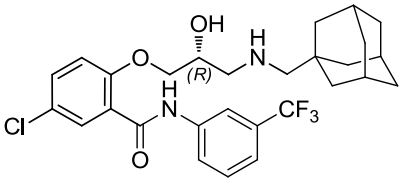
The low activity of 2-allyl anilide **203**, see Figure 25, can be overcome when a bulky alkyl residue is presented in the amine diversity site as in **204**. 2-Naphthylamine (**205**) seems to be well tolerated with regard to activity. Compound **205** also shows an acceptable level of cytotoxic activity against liver cells. Both bis(trifluoromethyl) aniline derivatives **206** and **207** are highly active. But chloro compound **207** is less cytotoxic than the deschloro version **206** while being equally active. Chloroadamantyl compound **208** is, similar to its 3-trifluoromethyl version, highly cytotoxic. 3-Trifluoromethoxy compound **209** shows very good activity, while being cytotoxic at an acceptable level; even more in contrast to the high activity. Changing the position of the trifluoromethoxy group from 3 to 4 yields **210**, which has an impressive IC_{50}-value of 920 pM at the NF54 strain and is even less cytotoxic than **209**. Also promising compounds are **211** which features a 3-iodoaniline and **212** with the iodine in the salicyl diversity site. For both derivatives, activities are good and cytotoxicity is tolerable. Dichloroaniline compounds **213** and **214** show both acceptable cytotoxicity and good activity, whereas the compound with the 3,4-substitution pattern (**214**) is twice as active as **213** with the 3,5-pattern.



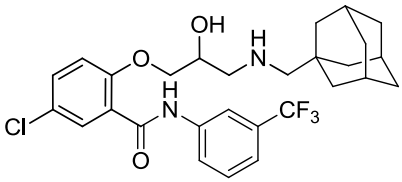
72
IC_{50} (NF54) = 2296
IC_{50} (K1) = 1133



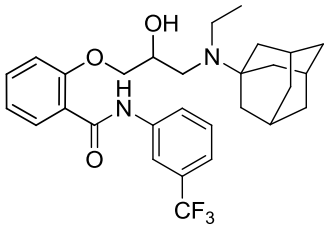
96
IC_{50} (NF54) = 1.9
IC_{50} (K1) = 0.52



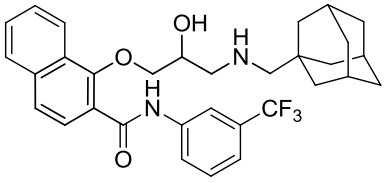
97
IC_{50} (NF54) = 1.8
IC_{50} (K1) = 0.43



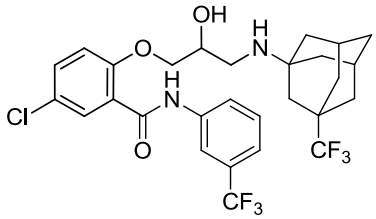
194
IC_{50} (NF54) = 4.2
IC_{50} (K1) = 0.9



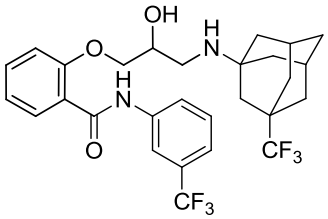
195
IC_{50} (NF54) = 17
IC_{50} (K1) = 4.0



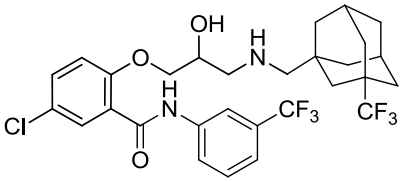
196
IC_{50} (NF54) = 15
IC_{50} (K1) = 4.1



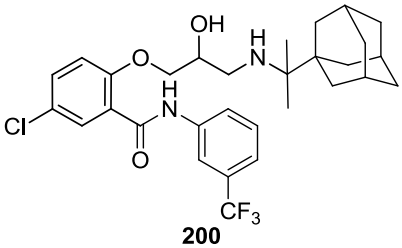
197
IC_{50} (NF54) = 3.5
IC_{50} (K1) = 1.4



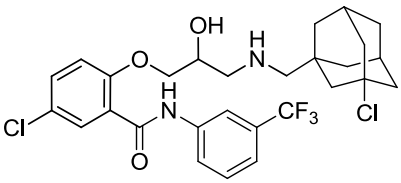
198
IC_{50} (NF54) = 6.3
IC_{50} (K1) = 3.1



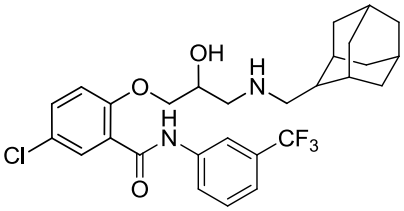
199
IC_{50} (NF54) = 2.0
IC_{50} (K1) = 0.51



200
IC_{50} (NF54) = 1.5
IC_{50} (K1) = 0.51



201
IC_{50} (NF54) = 2.2
IC_{50} (K1) = 0.62



202
IC_{50} (NF54) = 2.1
IC_{50} (K1) = 0.46

Figure 24. Structures and activities (nM) of further compounds containing a 3-trifluoromethyl anilide residue.

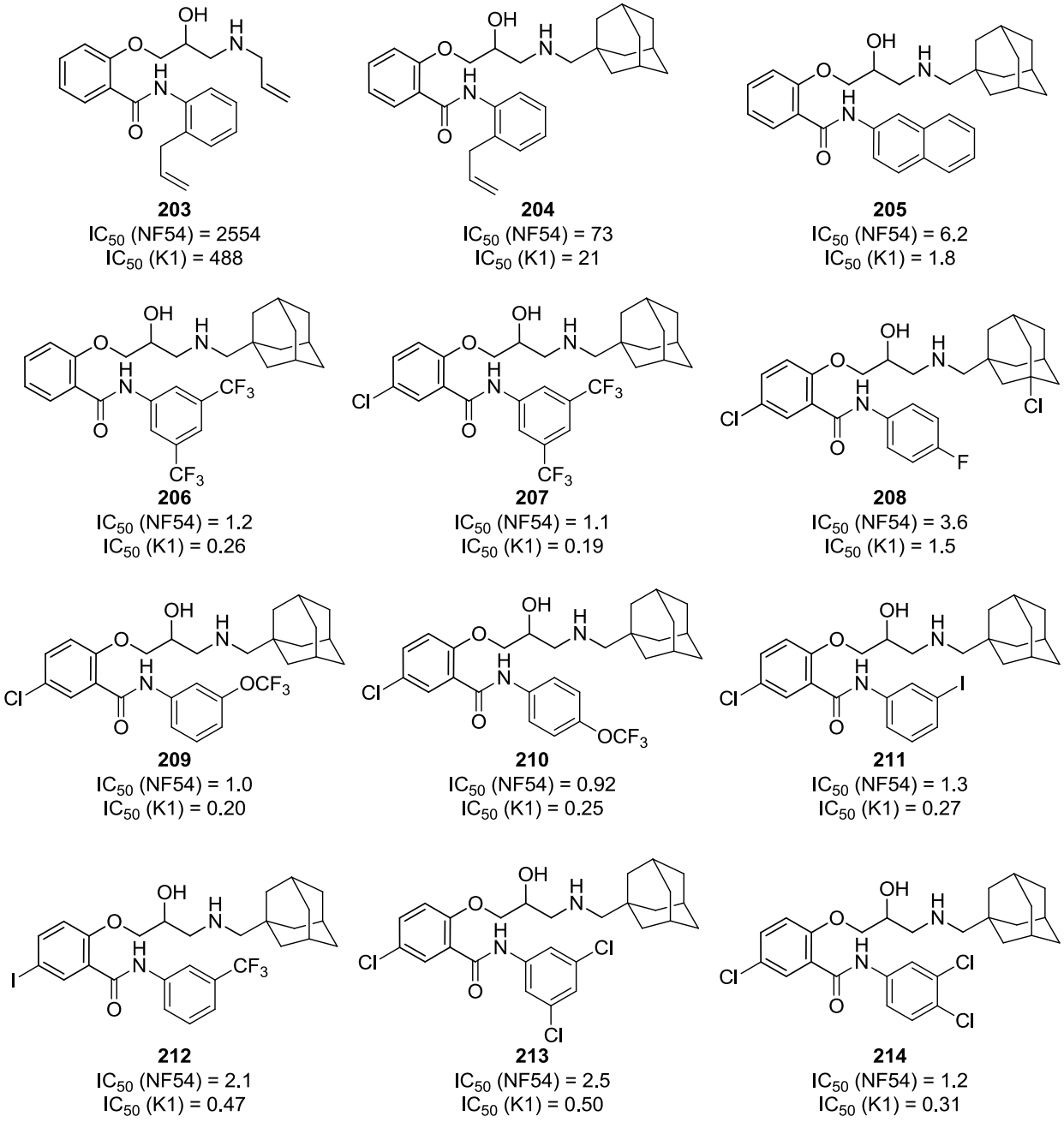


Figure 25. Structures and activities (nM) of compounds 203 **–** 214**.**

3-Azaspiro[5.5]undecan (**215**) as well as 2-azaspiro[4.6]undecan (**216**) show exceptional activity and acceptable cytotoxicity (for structures and activities see Figure 26). Compounds featuring the smaller 2-azaspiro[4.5]decan (**217**) or the even smaller 2-azaspiro[4.4]nonan (**218**) also show good activity but considerable cytotoxicity.

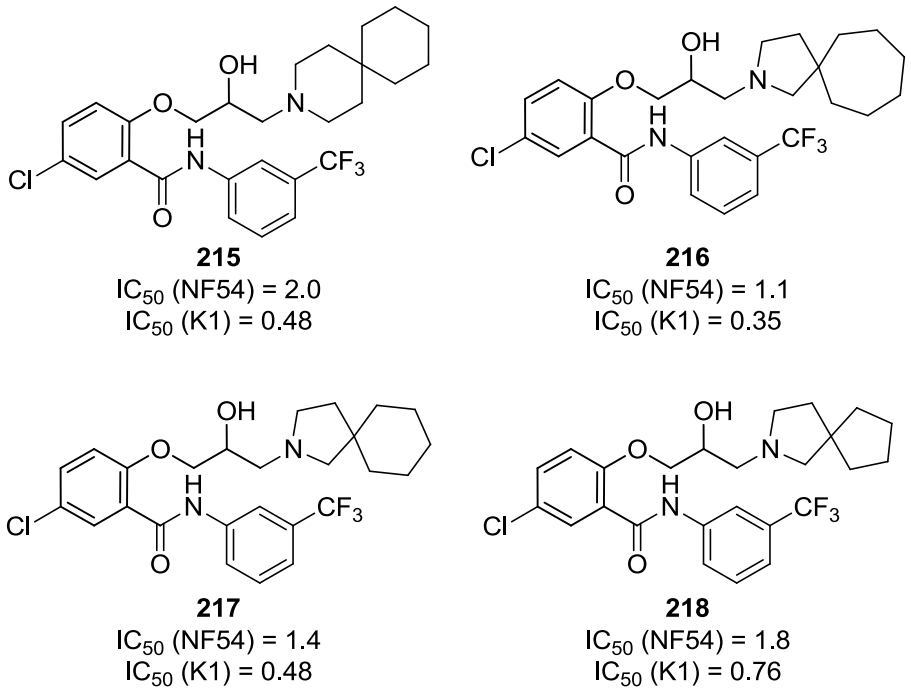


Figure 26. Structures and activities (nM) of spiroamino compounds 215 **–** 218**.**

Compounds disubstituted in the 3- and 5- position of the salicylic ring are depicted in Figure 27. An additional chlorine atom on highly active compound **207** (Figure 25; 1.1 nM on NF54 and 0.19 nM K1, respectively) leads to **219** which is fivefold less active and cytotoxicity stays on an equal level. The benzhydryl piperazine derivative **220** shows no cytotoxicity at all and shows impressive results in the microsome stability assay. Unfortunately, activity is not as high as desired. **221** is the dichloro derivative of **194** (Figure 24). Also in this case an additional chlorine atom in the 3-position of the salicylic ring lowers the activity, while no change regarding cytotoxicity was observed. Compound **222**, which contains four chlorine atoms, shows acceptable stability as well as antiplasmodial activity, while being less cytotoxic than most other compounds. **223** is the benzhydryl piperazine analog of **180** (Figure 22), which is highly active but also highly cytotoxic. The benzhydryl piperazine analog shows very low toxicity on Hep G2 cells though also lower activity than the adamantan-1-ylmethyl amine analog. 4-Fluoro salicyl compound **224** shows good activity, stability and cytotoxicity on an acceptable level.

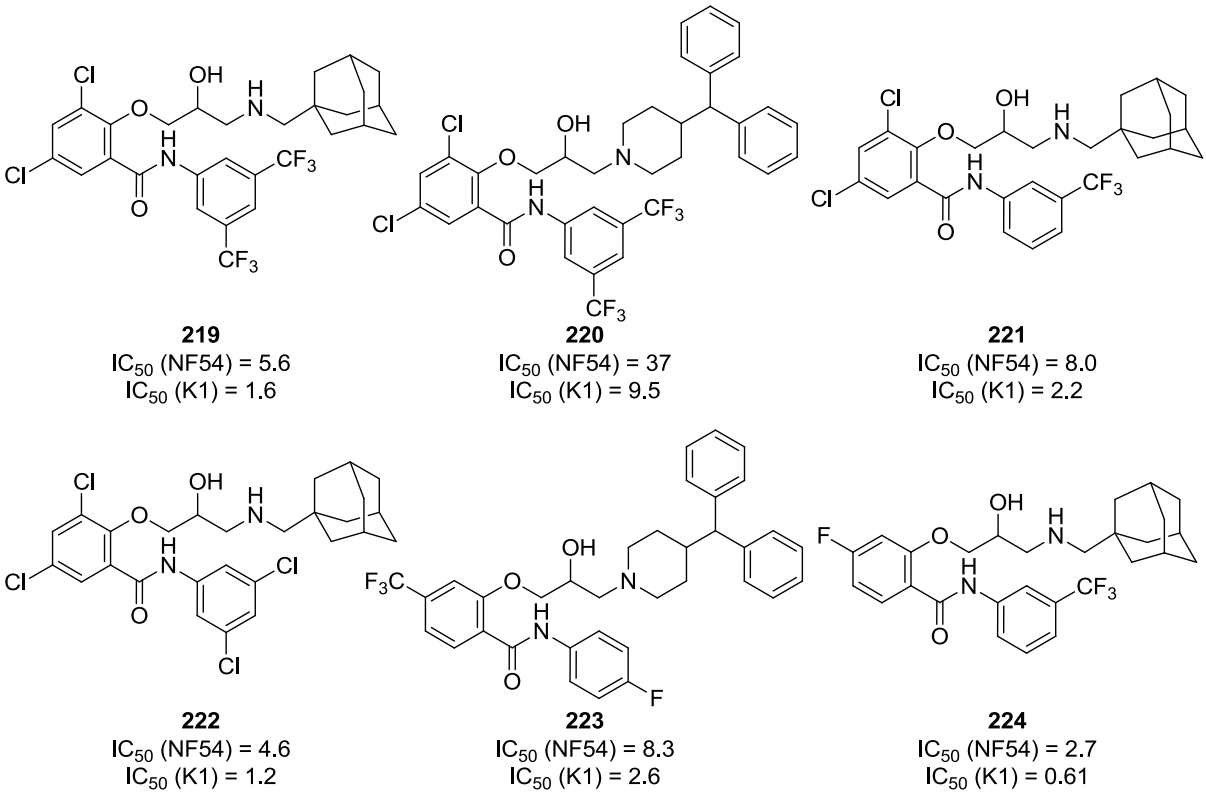


Figure 27. Structures and activities (nM) of 3,5-dichlorosalicylic compounds and further compounds substituted in the 4-position of the salicylic ring.

Comparison of the above shown **224** (Figure 27) with a fluorine atom in the 4-position of the salicylic ring with its regiomer **225**, having the fluorine atom in the 5-position, reveals that substitution in the 5-position leads to better activity while substitution in the 4-position seems to increase stability. Cyano compound **226** shows high stability and acceptable cytotoxicity and also acceptable activity although it clearly underperforms in comparison to other compounds. The adamantan-2-ylmethyl analog **227** is less favorable in all three concerns: activity, stability, and cytotoxicity. The benzhydryl piperazine motif in **228** lowers activity as well as stability and favorably cytotoxicity. Also, adamantan-2-ylmethyl compound **229** is less favorable in all respects than the adamantan-1-ylmethyl analog **207** (Figure 25). These findings (comparison of the pairs **227** / **226** and **229** / **207**, respectively) validate the assumption from above that the adamantan-2-ylmethyl group has no advantage over the adamantan-1-ylmethyl group which was derived from the comparison of **202** with **194**, **96**, and **97** (structures are depicted in Figure 24).

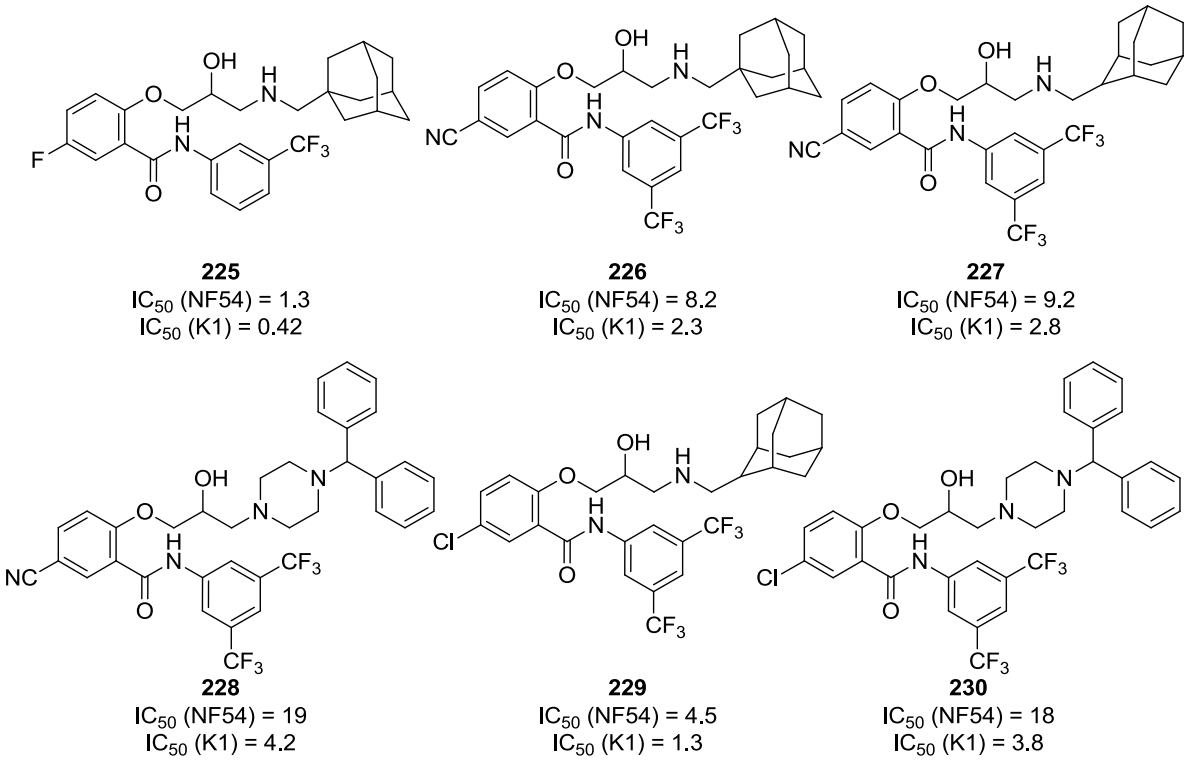


Figure 28. Structures and activities (nM) of compounds 225 **–** 230**.**

Surprisingly, the simple structure of **231** showed promising IC_{50} values of 23 nM against NF54 and 8 nM against K1 strain. Cytotoxicity was also on an acceptable level. Benzhydryl piperazine **232** showed only moderate activity on NF54 and, in contrast to all other compounds tested, it is more active against this strain than on the K1 strain. This observation could point towards a different mode of action of this scaffold. The two compounds shown in Figure 29 are the only ones synthesized featuring this simplified scaffold.

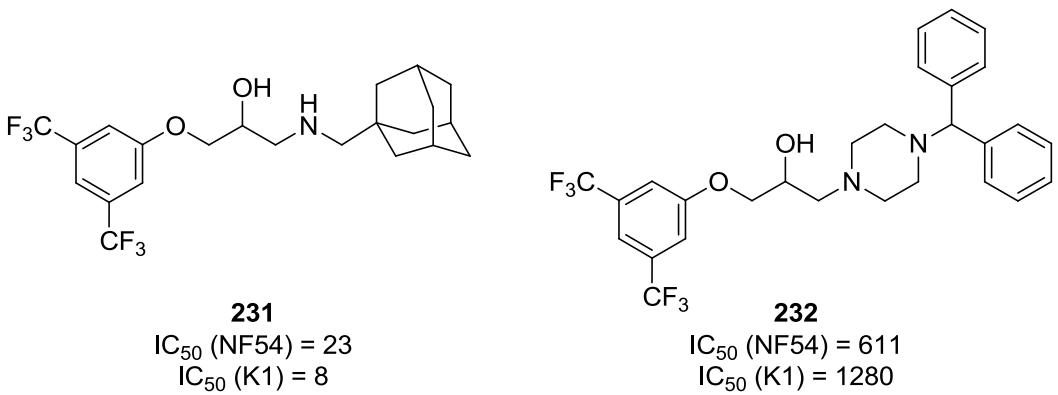


Figure 29. Structures and activities (nM) of 1-((adamantan-1-ylmethyl)amino)-3-(3,5-bis(trifluoromethyl)phenoxy)propan-2-ol (231**) and 1-(4-benzhydrylpiperazin-1-yl)-3-(3,5-bis(trifluoromethyl)phenoxy)propan-2-ol (**232**).**

Benzhydryl piperazine compound **233** is sevenfold less active than the corresponding adamantan-1-ylmethyl amine **209** (Figure 25), while being less cytotoxic (structures and activities are summarized in Figure 30). The effect of an additional chlorine atom in the 4-position of the aniline fragment of **234** is a decrease in activity, an enhanced stability and it appeals safer in cytotoxic concerns in comparison to **209** (Figure 25). For **235**, a similar effect is observed. Instead of adding a chlorine atom in the aniline, the chlorine atom in the salicylic region is replaced by a trifluoromethyl group. In comparison to **209** (Figure 25) activity is lower, but stability is increased while cytotoxicity roughly stays the same. The effect on stability is more marked in **235** than in **234**. When an additional trifluoromethoxy group is incorporated in the aniline ring in the 4-position (**236**) the activity is increased, while stability and cytotoxicity remain on the same level, in comparison to the results of the analog racemic **194** and the enantiopure compounds **96** and **97** (reference substances are shown in Figure 24). The same effects were observed when instead of a trifluoromethoxy group, as in **236**, an additional fluorine- (**237**) or chlorine atom (**238**) is present in the 4-position of the aniline.

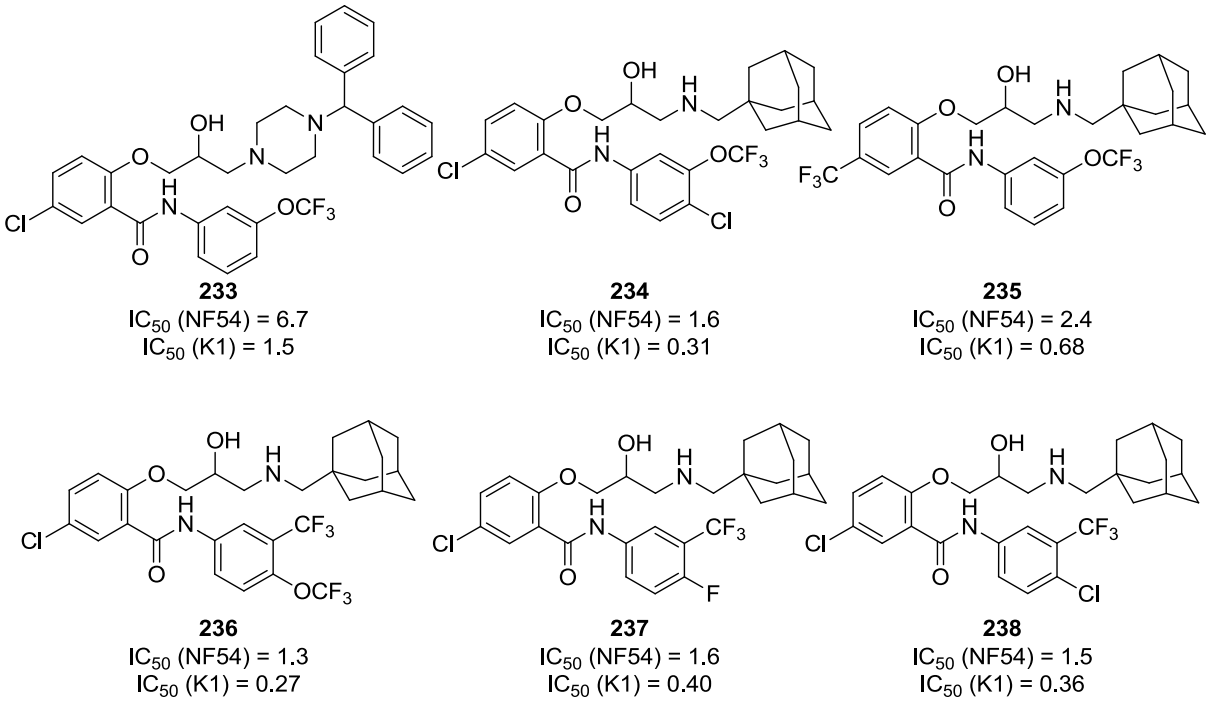
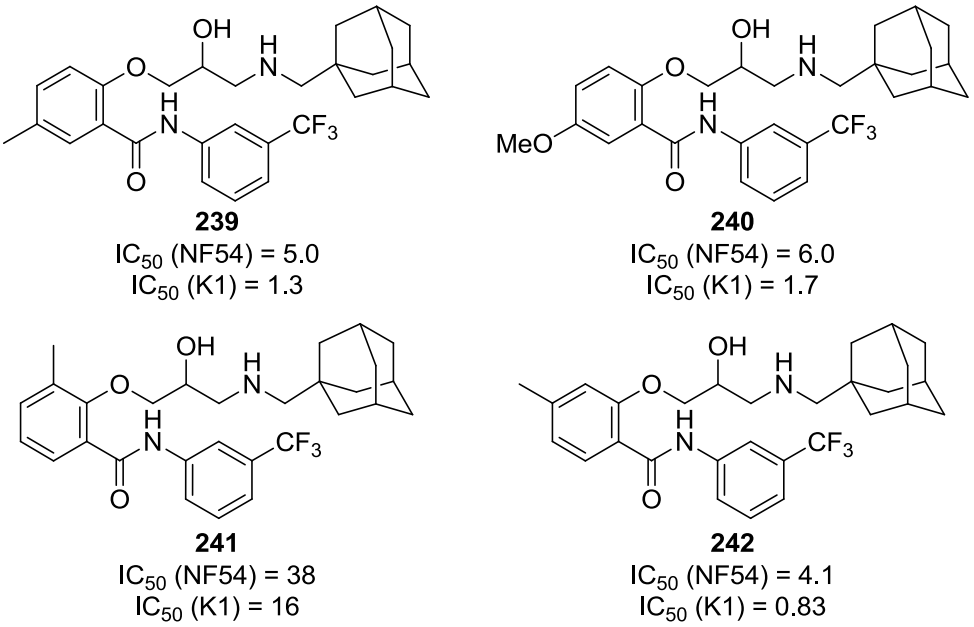


Figure 30. Activities (nM) and structures of analogs of 194 **and** 209**, respectively.**

Replacement of the chlorine atom of **194** (Figure 24) by a methyl group, as in **239** depicted in Figure 31, leads to a decrease in activity. Stability and cytotoxicity of these compounds are widely unaffected. A replacement by methoxy group (**240**) lowers the activity even further

but stability is increased, while cytotoxicity remains at the same acceptable level. The methyl group in the 3-position of **241** drastically reduces activity whereas stability and cytotoxicity are comparable to **194** (Figure 24). Derivative **242**, a 4-methyl analog, not only shows the best activity within the methyl series but also stability and cytotoxicity are on a satisfying level.



239
IC_{50} (NF54) = 5.0
IC_{50} (K1) = 1.3

240
IC_{50} (NF54) = 6.0
IC_{50} (K1) = 1.7

241
IC_{50} (NF54) = 38
IC_{50} (K1) = 16

242
IC_{50} (NF54) = 4.1
IC_{50} (K1) = 0.83

Figure 31. Structures and activities (nM) of compounds featuring a methyl or methoxy group in the salicylic part.

Dibutyl compound **243** (see Figure 32) shows promising activity and satisfyingly low cytotoxicity, only the stability is in need of improvement. Although with its dibutyl amine motif **243** is obviously an analog of lumefantrine (**20**) for which it is known that one butyl group is cleaved rapidly during metabolism. The resulting monodesbutyl metabolite is even more active than lumefantrine itself.[91] Lumefantrine (**20**) can be interpreted as prodrug. Similar considerations might be applicable to **243**.

Adding a methyl group to the basic amine of **194** (Figure 24) leads to tertiary amine **244**. This compound is less active than the desmethyl analog **194** but it is far less cytotoxic. When the methyl group is replaced by the larger butyl group as in **245** activity stays the same while cytotoxicity is even less than in the methylated analog **244**, but the greatest improvement is the stability.

When a tertiary anilide is combined with activity supporting substitution patterns on salicyl and amine site, such as in **246**, activity is drastically reduced. This observation underscores the importance of the intramolecular hydrogen bridge established within secondary anilides.

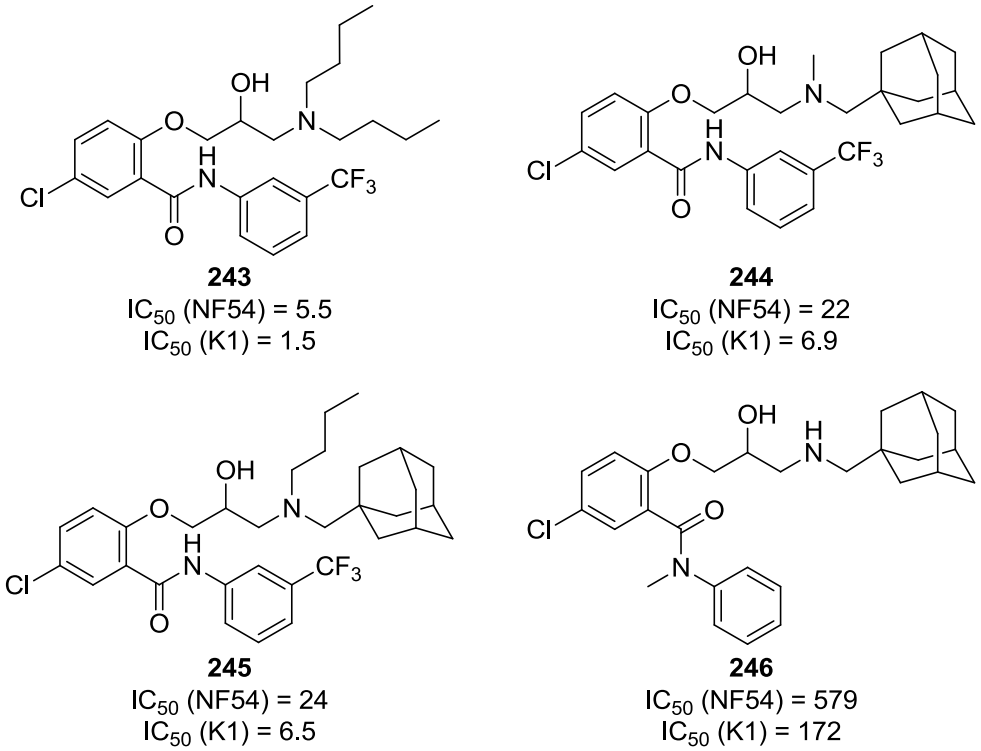


Figure 32. Structures and activities (nM) of tertiary adamantan-1-ylmethyl amines 243 - 245 **and tertiary amide** 246**.**

The trifluoromethoxy structure **247** (Figure 33) shows much more activity than the simple methoxy analog **240** (Figure 31). Stability decreased slightly but is still satisfying while also cytotoxicity is acceptable. The effect of a trifluoromethoxy group in the 4-position of the aniline diversity site (**248**) is comparable to compound **233** (Figure 30), which is the regioisomer carrying the trifluoromethoxy group in the 3-position. A real highlight is **249** which shows very good activity (1.4 nM on NF54 and 0.45 nM on K1 strain, respectively), good stability data, and nearly no cytotoxicity. **250**, the cyano analog of highly active **210** (Figure 25), drastically loses activity compared to the chlorine derivative. **251**, which is also an analog of **194** and its enantiopure forms **96** and **97** (**194**, **96**, and **97** are shown in Figure 24), shows less activity than both enantiopure forms and additionally offers no advantage in respect of stability and cytotoxicity. Also combined with the benzhydryl piperazine motif the trifluoromethyl group in the salicylic ring (**252**) shows less activity than the chloro analog **95** (Table 11), which also has the better cytotoxic properties. An additional trifluoromethyl group in the 5 position of the aniline once more reduces activity when **252** and **253** are compared.

However, stability is increased while cytotoxicity results seem paradoxical since **252** seems more cytotoxic than **253** at a concentration of 1 µM but is less cytotoxic at a concentration of 10 µM. Moreover, the 5-chloro salicyl variant (**233** shown in Figure 30) of **254**, which again features a 3-trifluoromethoxy group in the amide region, also proves the findings from above that a chlorine atom is the better option than a trifluoromethyl group in the 5-position of the salicylic ring. In particular, activity is comparable, also in terms of stability no noteworthy benefit was recorded, and chlorine variant **233** (Figure 30) has the more favorable cytotoxicity profile.

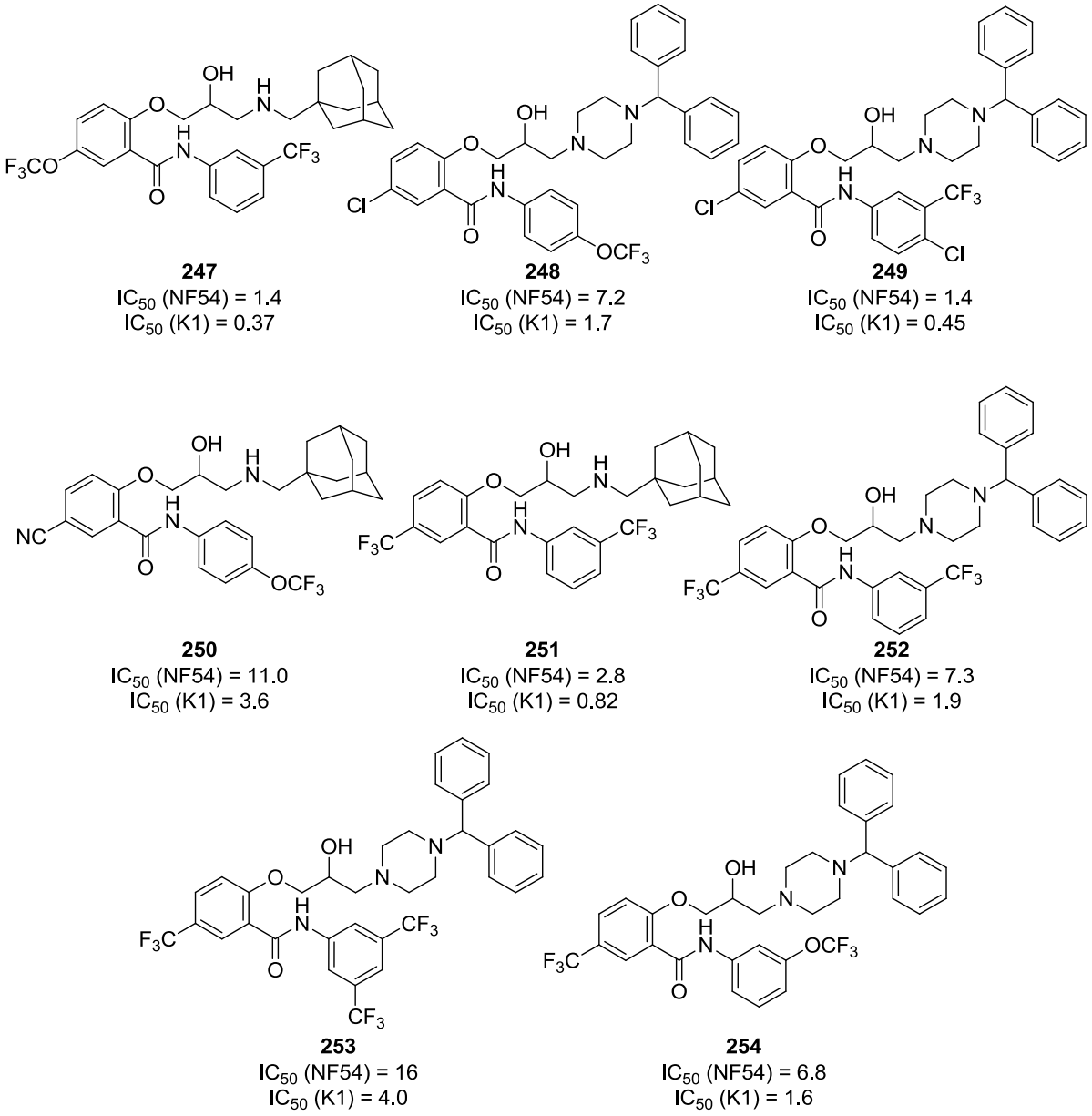


Figure 33. Structures and activities (nM) of compounds 247 **–** 254**.**

The trifluoromethyl analog **256**, shown in Figure 34, of the all over satisfying compound **249** (Figure 33) is less convincing in every aspect. Cyano analog **255** shows even worse results than trifluoromethyl analog **256**. In the adamantan-1-ylmethyl amine version the trifluoromethyl group (**257**) shows also more activity than the cyano derivative **258**. The stabilities of these compounds are similar, but both are not satisfying. Cytotoxicities are also similar and on an acceptable level. The tris(trifluoromethyl) compound **259** shows less activity than other trifluoromethyl salicyl adamantan-1-ylmethyl compounds but it is still on a remarkable niveau. Stability is surprisingly high, while cytotoxicity is on an acceptable level.

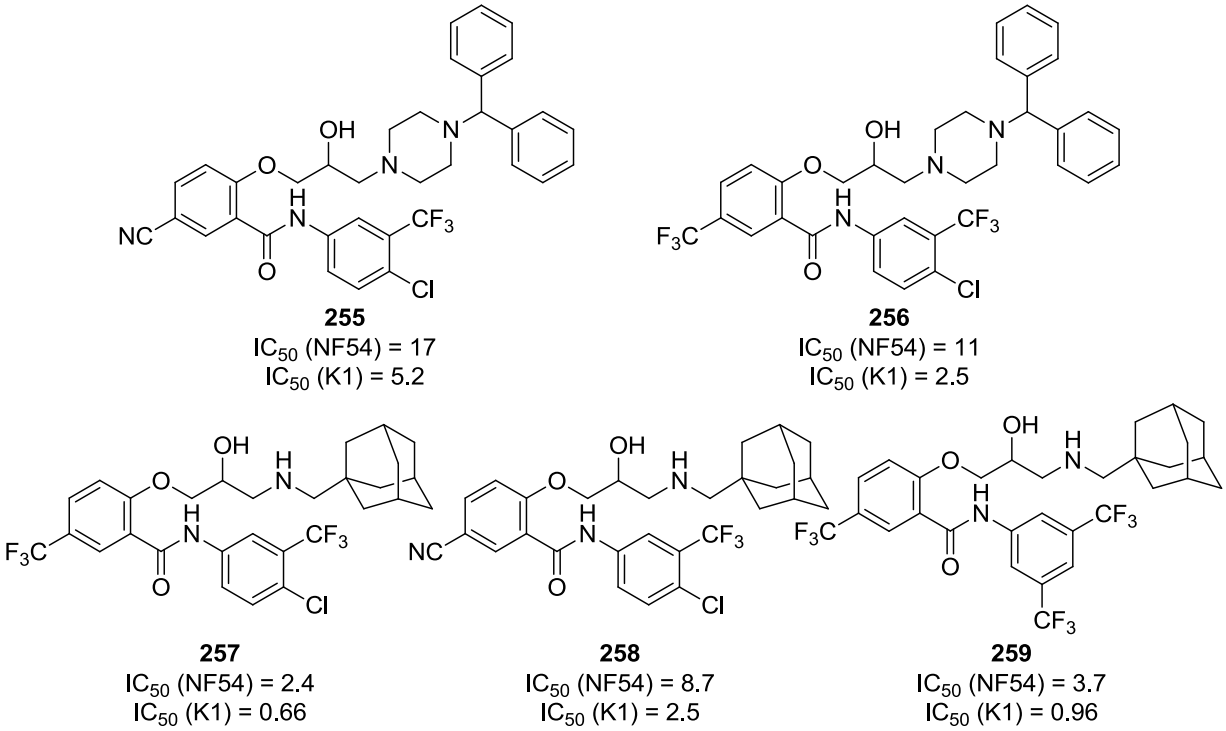
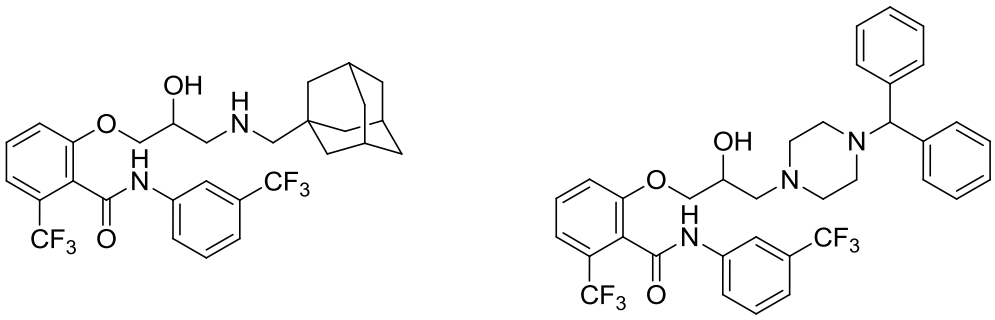


Figure 34. Structures and activities (nM) of compounds 255 **–** 259**.**

The drastically reduced activities of compounds **260** and **261**, shown in Figure 35, must be attributed to the trifluoromethyl groups in the 6-position of the salicylic ring. Substitution in this position seems momentous. The loss of activity upon substitution of the 6-position with a trifluoromethyl group can be attributed to disturbed resonance of the amide functionality with the aromatic salicyl core. Electronic repulsion between the trifluoromethyl substituent and the carbonyl rotates the amide out of plane of the aromatic ring, which would result in weakening or even loss of the intramolecular hydrogen bond.



260
IC_{50} (NF54) = 282
IC_{50} (K1) = 78

261
IC_{50} (NF54) = 354
IC_{50} (K1) = 114

Figure 35. Structures and activities (nM) of 6-trifluoromethylsalicyl compounds.

Compound **262**, shown in Figure 36, is slightly less active than **207** (1.1 nM on NF54 and 0.19 nM on K1 strain, respectively), which has a chlorine atom in the salicylic region instead of the trifluoromethoxy group. On the other hand, **263** is much more active than its chloro analog **230** (18.0 nM on NF54 and 3.8 nM on K1 strain, respectively). No significant effect was shown for the additional cyano group in the 4-position of the aniline site; **264** and **265** are not more active than their descant analogs **194** and **95**. Omitting the trifluoromethyl groups (**266** and **267**) reduces activity further. When the cyano groups are in the 3-position (**268** and **269**) instead of the 4-position (**266** and **267**) activity is improved. An additional fluorine atom in the 4-postion of the aniline shows slight beneficial effects on the activity in case of the adamantane compound (**270**) and unfavorable effects were observed for benzhydryl piperazine derivative **271**. The 2,3-dimethylphenyl piperazine compound **272** shows much less activity than the most promising compound **249**.

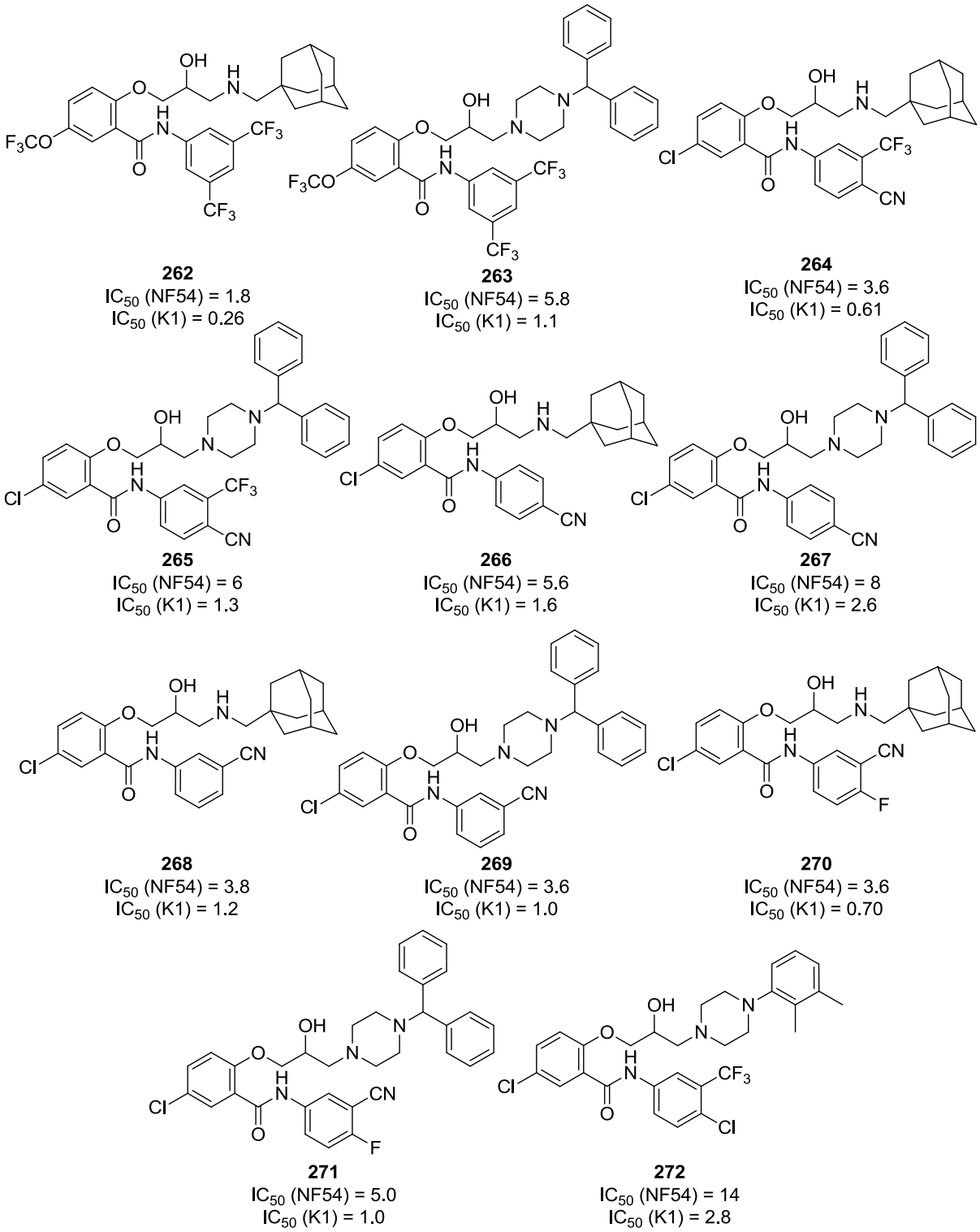
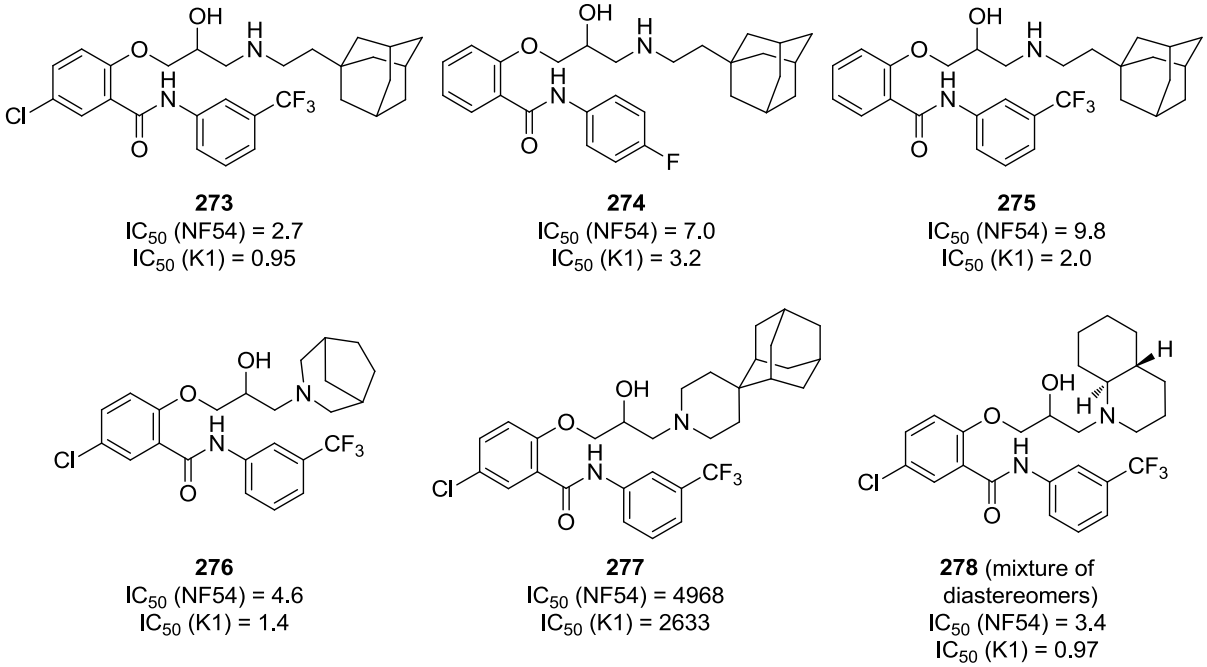


Figure 36. Structures and activities (nM) of compounds 262 **–** 272**.**

The 1-adamantanylethyl series (**273**, **274**, and **275**) shows no advantages over the 1-adamantanylmethyl series. While **273** shows comparable activity to its 1-adamantanylmethyl analogs (**96**, **97**, and **194**) it has more cytotoxic activity. The same is valid for **274** when it is compared to compound **143**. Only **275** is an exception. This compound is less active than its 1-adamantanylmethyl analog **145** but concomitantly also less cytotoxic on Hep G2 cells. Bi-

cyclic **276** shows high activity, very good microsomal stability and very low cytotoxicity. Spiroadamantane compound **277** loses antimalarial activity. A diastereomeric mixture of transdecalins (**278**) showed promising activity.



273
IC_{50} (NF54) = 2.7
IC_{50} (K1) = 0.95

274
IC_{50} (NF54) = 7.0
IC_{50} (K1) = 3.2

275
IC_{50} (NF54) = 9.8
IC_{50} (K1) = 2.0

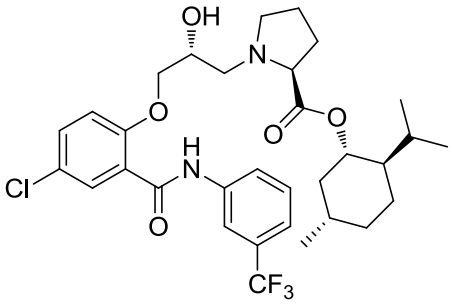
276
IC_{50} (NF54) = 4.6
IC_{50} (K1) = 1.4

277
IC_{50} (NF54) = 4968
IC_{50} (K1) = 2633

278 (mixture of diastereomers)
IC_{50} (NF54) = 3.4
IC_{50} (K1) = 0.97

Figure 37. Structures and activities (nM) of compounds 273 **–** 278**.**

Also the menthyl proline compound **102**, shown in Figure 38, possesses antimalarial activity. This compound was synthesized to determine the configuration of the alcohol moiety which originates from a corresponding epoxide precursor.



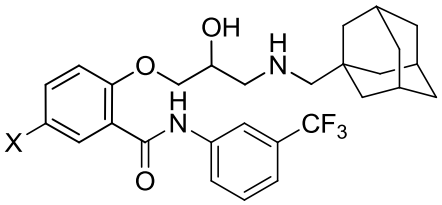
102
IC_{50} (NF54) = 117
IC_{50} (K1) = 29

Figure 38. Structure and activity (nM) of (*S*)-(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl-1-((*R*)-3-(4-chloro-2-((3-(trifluoromethyl)phenyl)carbamoyl)phenoxy)-2-hydroxypropyl)pyrrolidine-2-carboxylate (102**).**

2.2.3 Conclusions from SAR

Blocking the 5-position is a necessity to avoid the formation of quinoidal systems during metabolization. The effect of the substituent in this position on the activity is shown in Table 12. Halogens seem well tolerated at this position which is indicated by very high activities. The trifluoromethoxy substituent also shows very high activity. The cyano group is least suitable.

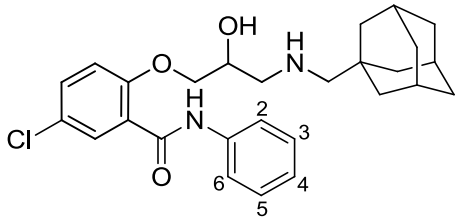
Table 12. Effects of substituents in the 5-position of the salicylic ring on the activity (nM).



	X	IC_{50} NF54	IC_{50} K1
145	H	2.3	0.51
194	Cl	4.2	0.99
212	I	2.1	0.47
225	F	1.3	0.42
239	Me	5.0	1.30
240	OMe	6.0	1.70
247	OCF_3	1.4	0.37
251	CF_3	2.8	0.82
279	CN	13.0	4.90

The effects of the various substitutions in the aniline diversity site on the activity are summarized in Table 13. The chlorine atom in the salicylic region was used in several target compounds. Therefore, it serves as good reference for substitutions in the aniline site. The extraordinary result of **210** which shows an activity of 900 pM on the NF54 strain is followed by its regioisomer **209**. In general, bulky substitution by halogens or other substituents with similar electronic effects such as the trifluoromethyl- and the trifluoromethoxy group, which are also bulky show very high activities; **207**, **211**, **214**, **234, 236**, **237** and **238**, show activities of 1.0 - 1.6 nM on the NF54 strain. The substitution pattern in both trichloro compounds **213** and **214** has some importance. The 3,4-substituted compound **214** is twice as active as 3,5-substituted **213**. Compounds bearing cyano groups show weaker but still good activities; **194**, **266**, **268**, **264**, and **270** show activities of 3.6 – 5.6 nM on the NF54 strain.

Table 13. Effects of various substitutions in the aniline diversity site on the antimalarial activity (nM).



	3	4	5	IC_{50} NF54	IC_{50} K1
168	H	F	H	2.4	0.62
194	CF_3	H	H	4.2	0.99
207	CF_3	H	CF_3	1.1	0.19
209	OCF_3	H	H	1.0	0.20
210	H	OCF_3	H	0.9	0.25
211	I	H	H	1.3	0.27
213	Cl	H	Cl	2.5	0.50
214	Cl	Cl	H	1.2	0.31
234	OCF_3	Cl	H	1.6	0.31
236	CF_3	OCF_3	H	1.3	0.27
237	CF_3	F	H	1.6	0.40
238	CF_3	Cl	H	1.5	0.36
264	CF_3	CN	H	3.6	0.61
266	H	CN	H	5.6	1.60
268	CN	H	H	3.8	1.20
270	CN	F	H	3.6	0.70

The adamantan-1-ylmethyl amino- and the benzhydryl piperazine-derivatives are the most promising groups in the amine diversity site. In general, adamantan-1-ylmethyl amino compounds show higher activity while benzhydryl piperazine compounds are safer regarding cytotoxicity. Tertiary adamantan-1-ylmethyl amines showed a similar behavior in the few examples synthesized. The salicyl aryl amide scaffold showed best results. 3,4 Annulations (**196**) as well as 4,5 annulations (**177** and **178**) in the salicylic region resulted in worse activities.

2.3 Analysis of Data from Animal Experiments

Animal experiments were performed to show activity of compounds *in vivo*. Acute toxicity was tested prior to animal experiments involving malaria infections. The compounds tested are shown in Figure 39. Some adverse effects (reduced activity, sunken flanks, increased reaction to touch, and hunching) were observed after administration of compounds **132**, **137**, and **146**, which are depicted in the top row. Even from the observations made for these compounds, no acute toxicity was derived.

Administration of other compounds was well tolerated. Therefore, the compound class can be considered as harmless regarding acute toxicity.

Table 14. Acute toxicology tested at Swiss TPH.

	series of test	route	observations	toxicity
32	1	p.o.	-	-
132	1	i.p.	after 30mg/kg: reduced activity, after 50mg/kg: reduced activity, sunken flank	-
137	1	p.o.	-	-
137	1	i.p	after 30mg/kg: reduced activity, after 50mg/kg: reduced activity, sunken flank	-
137	2	i.p.	after 30mg/kg: reduced activity	-
143	2	i.p.	-	-
144	2	i.p.	-	-
145	2	i.p.	-	-
146	1	p.o.	increased reaction to touch	-
146	1	i.p	after 30mg/kg: reduced activity, after 50mg/kg: reduced activity, hunched position, sunken flank	-
183	2	i.p.	-	-
187	2	i.p.	-	-
191	2	i.p.	-	-

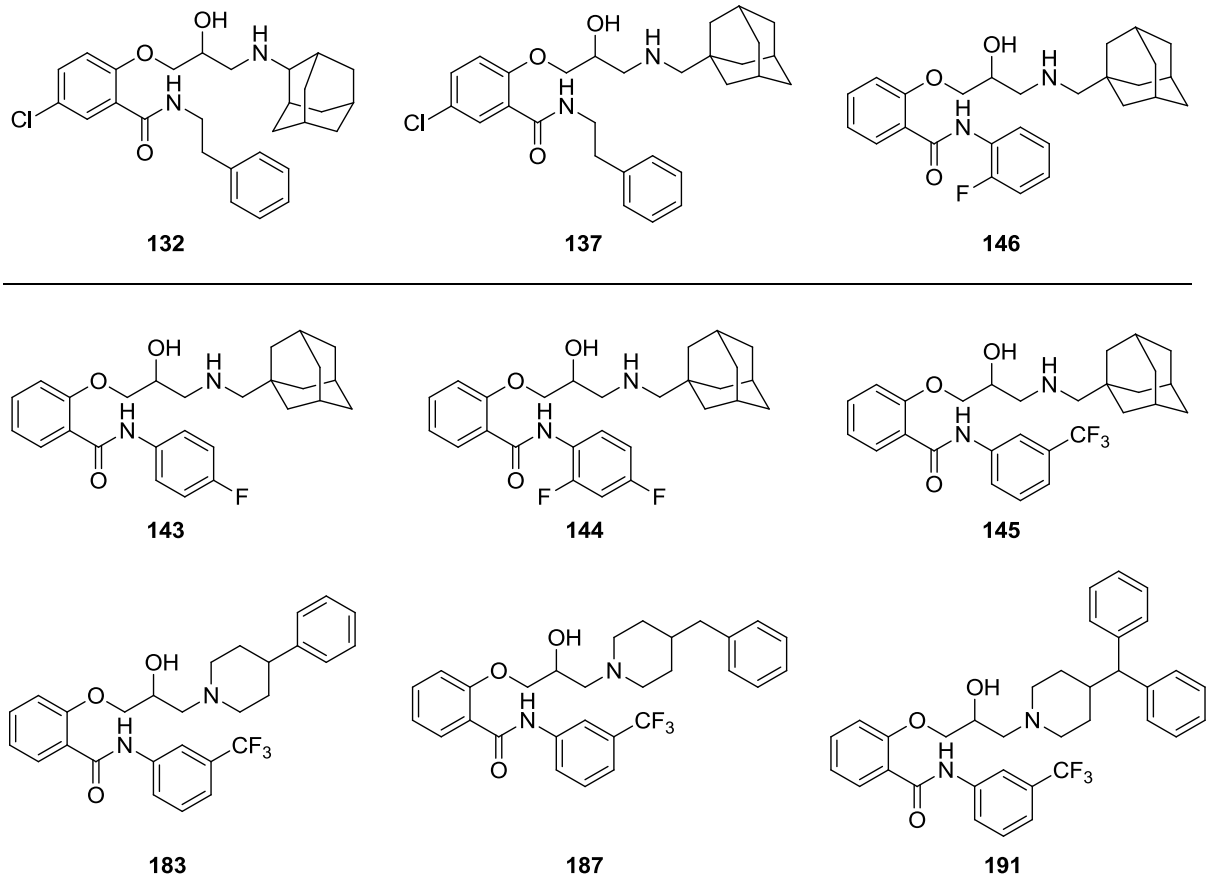


Figure 39. Compounds tested for acute toxicity. Adverse effects were observed for compounds 132**,** 137**, and** 146 **(top row).**

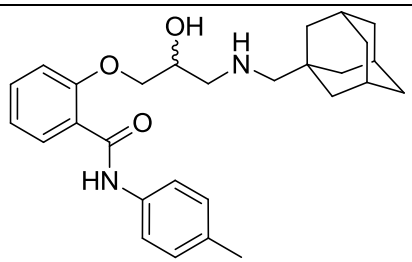
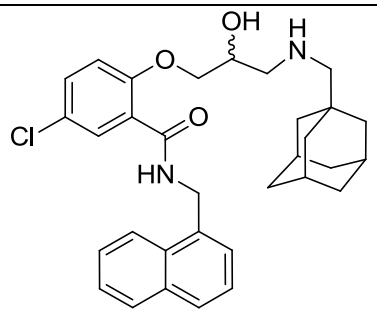
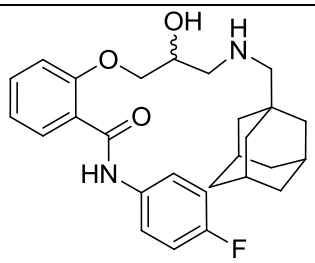
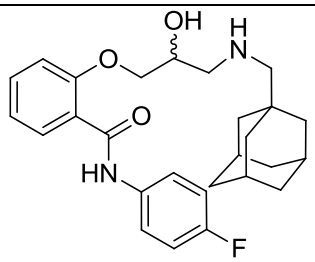
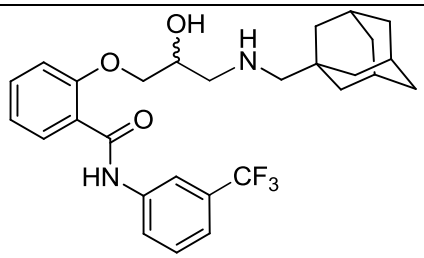
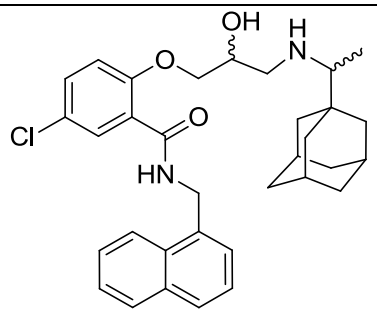
To demonstrate antimalarial activity *in vivo*, the four days Peter´s suppression test[128] is the most widely used test. Mice were infected with *Plasmodium berghei*, and afterwards treated for four days with 30 mg/kg test compound (daily dose). 24 hours after the last administration, residual parasitemia was determined and contrasted with the parasitemia of untreated mice. The column "activity" in Table 15 comprises these results. After the activity was determined, the time until death was determined. Untreated mice infected with *Plasmodium berghei* would die on day 4-6. Therefore, survival greater than seven days can be considered as prolongation of lifetime. Mice without parasitemia on day 30 post infection are considered cured. I.p. administration of compounds **141**, **142**, **143** and **144** did not prolong the survival of mice. The activities of these compounds were measureable but insufficient. **145** had much greater activity (97.76 %) but survival was only eight days, so this high activity was reflected in a prolongation of survival time of only one day. **167** and **154** showed insufficient activity to prolongate lifetime. **168** showed high activity (99.78%) and a survival of ten days. **205** showed an activity of 89% but a survival of only five days. **194** had an activity of 99.73%,

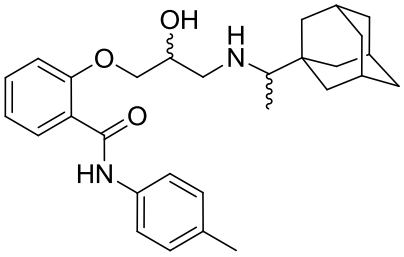
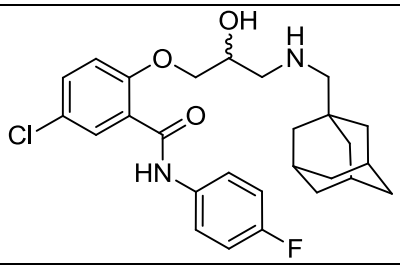
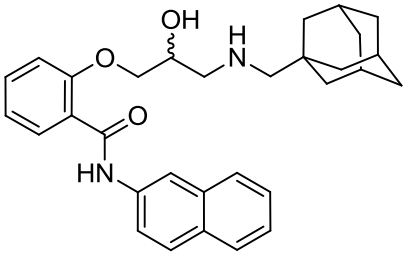
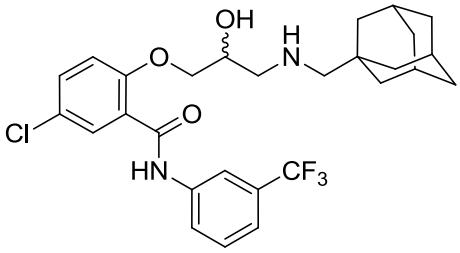
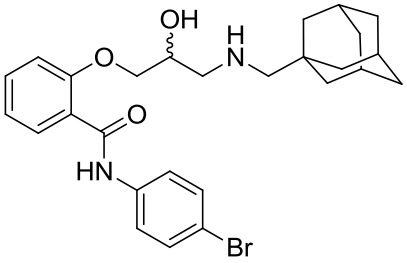
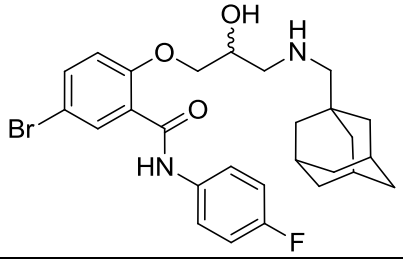
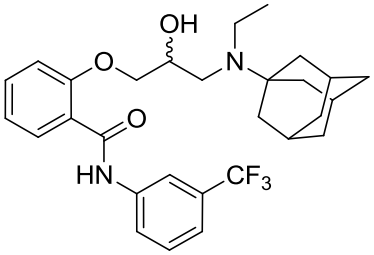
all three test mice survived until the experiment was finished after 30 days post infection. **175** and **172** both showed the same, very high activities (99.67% each) but drastically different survival times of 9 and 14 days, respectively. **195** showed only a very low activity. All above discussed results origin from i.p administration, the following results rely on data from p.o. administration. **142**, **143**, and **144** show less than half of the activity on the p.o. route, survival times were reduced from seven days (i.p.) to four days. Also the activities of **145** and **168** were drastically reduced, which also resulted in reduced survival time. Activity of **194** which cured the mice on the i.p. route was only 89.38% p.o. and survival time was limited to 9.7 days. For this promising compound also smaller daily doses were tested (i.p.), 10mg/kg doses achieved an activity of 71.96% and daily doses of 3mg/kg achieved an activity of only 13.75%. **175** and **172**, which were also promising in i.p. experiments were also much less active p.o. with activities smaller than 50% and survival times of only four days. **273** (86% activity), **202** (99.8% activity), and **209** (99.64% activity) showed with 10, 11.3 and 11 days the greatest survival times of the p.o. series.

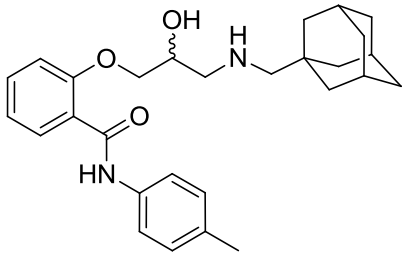
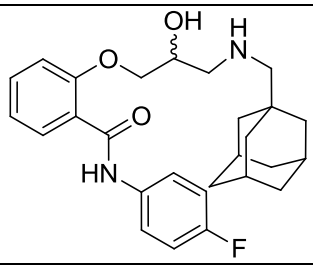
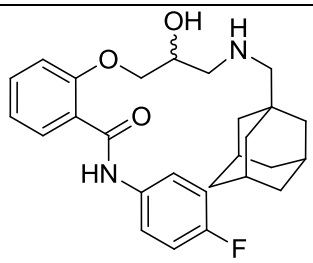
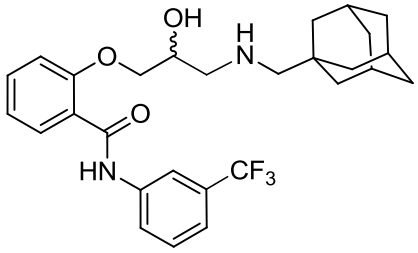
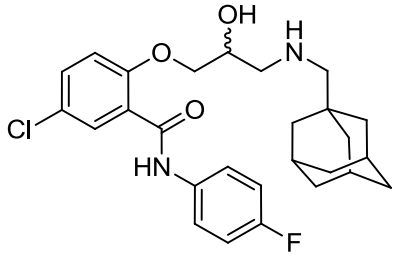
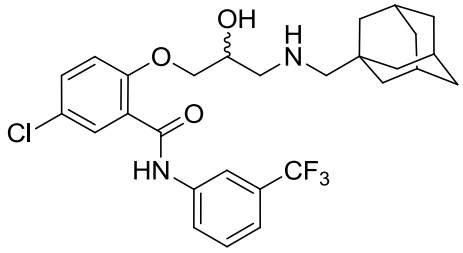
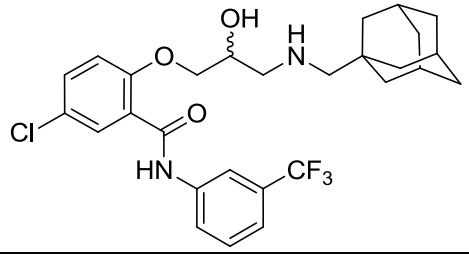
Additional *in vivo* experiments following the same experimental procedures as at Swiss TPH were performed at Marinomed Biotechnologie GmbH (i.p., data shown in Table 16), in which also **249**, **97** (the (*S*)-enantiomer of **194**), and **247** led to a cure as achieved by treatment with **194** in the tests of Swiss TPH.

The available data show impressively that *in vivo* tests are much more demanding than *in vitro* tests. Keeping in mind that not only antimalarial activity plays an important role in animal experiments, but also bioavailability, biological half-life, pharmacokinetics, as well as other possible targets of the tested compounds this becomes very clear. The importance of these issues is sowed quite plainly if i.p. and p.o. experiments are compared with each other. Bioavailability may be much better when compounds are administered *via* intraperitoneal injection than orally. However, *in vivo* activity was shown in both types of experiments. Further, by administration of **194** three mice infected with *Plasmodium berghei* were cured.

Table 15. Results of *in vivo* experiments performed at Swiss TPH.

route	pos	structure	% activity	daily dose [mg]	survival [d]
i.p.	**142**		58.24	30	7
i.p.	**141**		23.91	30	4
i.p.	**143**		67.35	30	7
i.p.	**144**		49.01	30	7
i.p.	**145**		97.76	30	8
i.p.	**167**		38.96	30	4

route	pos	structure	% activity	daily dose [mg]	survival [d]
i.p.	**154**		75.15	30	5.7
i.p.	**168**		99.78	30	10
i.p.	**205**		89.27	30	5
i.p.	**194**		99.73	30	30/30/30
i.p.	**175**		99.67	30	9
i.p.	**172**		99.67	30	14
i.p.	**195**		24.76	30	4

route	pos	structure	% activity	daily dose [mg]	survival [d]
p.o.	**142**		26.3	30	4
p.o.	**143**		25.04	30	4
p.o.	**144**		13.38	30	4
p.o.	**145**		50.65	30	6.7
p.o.	**168**		57.75	30	4
p.o.	**194**		89.38	30	9.7
p.o.	**194**		71.96	10	aborted

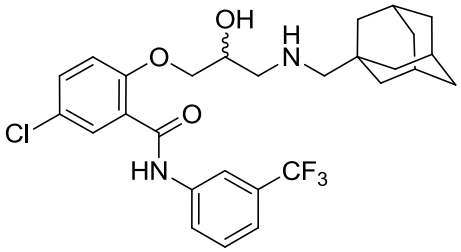
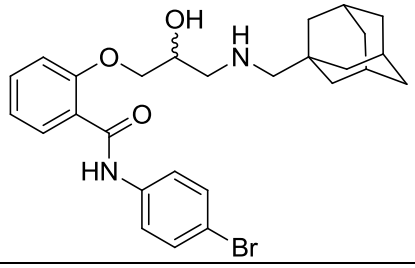
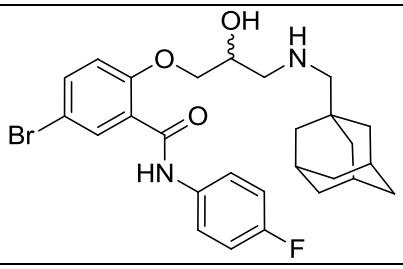
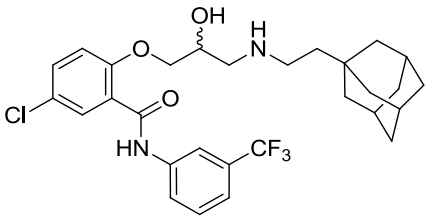
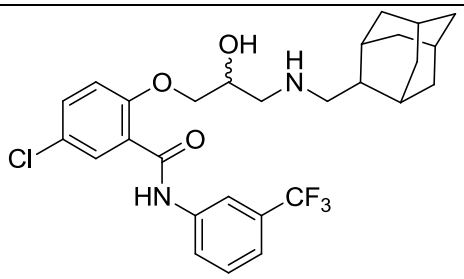
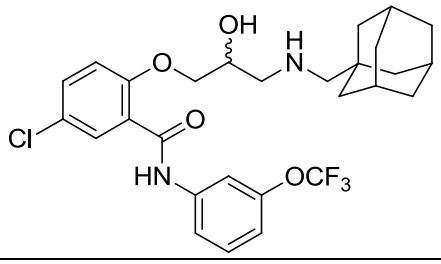
route	pos	structure	% activity	daily dose [mg]	survival [d]
p.o.	**194**		13.75	3	aborted
p.o.	**175**		47.5	30	4
p.o.	**172**		46.85	30	4
p.o.	**273**		86	30	10
p.o.	**202**		99.8	30	11.3
p.o.	**209**		99.6	30	11

Table 16. Summary of animal experiments performed at Swiss TPH (herein abbreviated as S) and Marinomed Biotechnologie GmbH (M).

	test site	4x30 mg i.p. % red. para	survival [d]	4x30 mg p.o. % red. para	survival [d]
142	S	58.24	7	26.3	4
141	S	23.91	4		
143	S	67.35	7	25.04	4
144	S	49.01	7	13.38	4
145	S	97.76	8	50.65	7
167	S	38.96	4		
154	S	75.15	6		
168	S	99.78	10	57.75	4
205	S	89.27	5		
194	S/M	99.73	30	89.38	10
175	S	99.67	9	47.5	4
186	M	92.88			
186	M	99.67	11		
172	S	99.67	14	46.85	4
195	S	24.76	4		
273	S			85.52	10
202	S/M	99.62		99.82	11
209	S/M			99.64	11
276	M	84.58			
222	M	99.58			
96	M	99.67			
97	M	99.98	30	75.39	7
220	M	94.07	8		
248	M	93.43	9		
249	M	99.96	30		
245	M	99.59	8		
Lumefantrine	S			99.78	30
Chloroquine	M	99.96	18		

2.4 Other Biological Data

A range of experiments were performed at Cerep (Poitiers, France). These include Ames test, inhibition of hERG channel, and inhibition of adrenergic receptors. Tests were performed with compounds **145** (in the tests at Cerep named: MAM-12.048), **168** (MAM-12.173), **190** (MAM-12.196), and **249** (MAM-12.255).

Inhibition of adrenergic receptors is summarized in Table 17. Only benzhydryl piperazine compound **249** shows no inhibition above 50% on all of the tested receptors. The other three compounds inhibited several adrenergic receptors, whereas the adamantane compounds were better tolerated than 4-benzyl piperidine **190**.

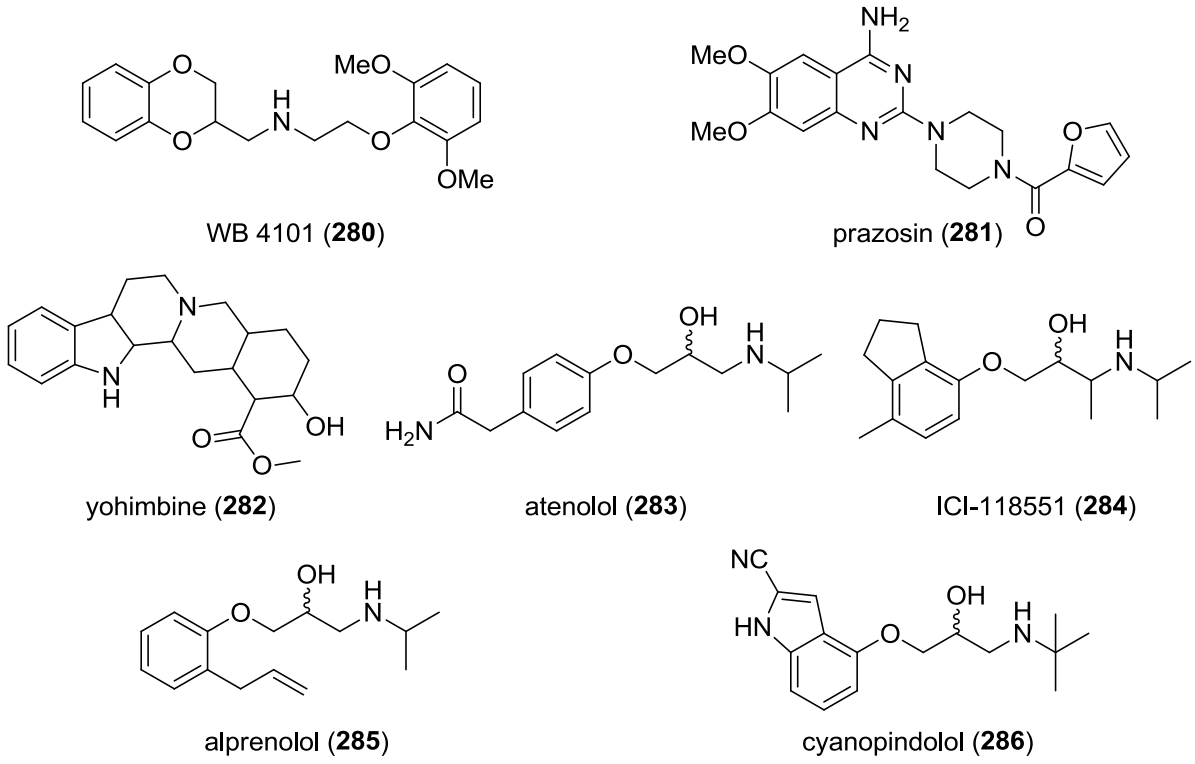


Figure 40. Structures of control compounds used by CEREP in the adrenoceptor assays.

Results for bacterial cytotoxicity, which is complementary to the Ames test to prevent wrong readouts, are shown for **145**, **168**, and **190** in Figure 41 and Figure 42, whereas results for **249** are shown in Figure 43. While **145**, **168**, and **190** are cytotoxic above concentrations of 5 µM, benzhydryl piperazine **249** showed no cytotoxicity as far as 100 µM.

Table 17. Results for inhibition of adrenergic receptors by compounds 145**,** 168**,** 190**, and** 249 **(in this table: 48, 173, 196, and 255). Test concentration: 10 µM.**[129]

ID	Assay	% Inhibition of Control Specific Binding	IC_{50} [nM]	Ref Com-pound	IC_{50} Ref [M]	K_i Ref [M]
48	α_{1A} (h) (ant rl)	70		WB 4101	3.1E-10	1.5E-10
173	α_{1A} (h) (ant rl)	86	2600	WB 4101	3.1E-10	1.5E-10
196	α_{1A} (h) (ant rl)	87	320	WB 4101	3.1E-10	1.5E-10
255	α_{1A} (h) (ant rl)	21		WB 4101	2.3E-10	1.2E-10
48	α_{1B} (h) (ant rl)	51		prazosin	2.7E-10	7.3E-11
173	α_{1B} (h) (ant rl)	49		prazosin	2.7E-10	7.3E-11
196	α_{1B} (h) (ant rl)	96	210	prazosin	2.7E-10	7.3E-11
255	α_{1B} (h) (ant rl)	27		prazosin	1.4E-10	3.7E-11
48	α_{1D} (h) (ant rl)	79		prazosin	2.0E-10	8.5E-11
173	α_{1D} (h) (ant rl)	50		prazosin	1.5E-10	6.4E-11
196	α_{1D} (h) (ant rl)	89		prazosin	1.5E-10	6.4E-11
255	α_{1D} (h) (ant rl)	7		prazosin	1.6E-10	6.7E-11
48	α_{2A} (h) (ant rl)	8		yohimbine	5.7E-09	2.5E-09
173	α_{2A} (h) (ant rl)	16		yohimbine	5.7E-09	2.5E-09
196	α_{2A} (h) (ant rl)	70		yohimbine	5.7E-09	2.5E-09
255	α_{2A} (h) (ant rl)	-3		yohimbine	3.2E-09	1.4E-09
48	α_{2B} (h) (ant rl)	-14		yohimbine	9.2E-09	6.1E-09
173	α_{2B} (h) (ant rl)	-20		yohimbine	9.2E-09	6.1E-09
196	α_{2B} (h) (ant rl)	13		yohimbine	9.2E-09	6.1E-09
255	α_{2B} (h) (ant rl)	-10		yohimbine	3.4E-09	2.3E-09
48	α_{2C} (h) (ant rl)	70		yohimbine	1.6E-09	5.0E-10
173	α_{2C} (h) (ant rl)	31		yohimbine	1.7E-09	5.4E-10
196	α_{2C} (h) (ant rl)	98	140	yohimbine	3.1E-09	1.0E-09
255	α_{2C} (h) (ant rl)	1		yohimbine	3.5E-09	1.1E-09
48	β_1 (h) (ag rl)	30		atenolol	2.2E-07	1.3E-07
173	β_1 (h) (ag rl)	8		atenolol	2.2E-07	1.3E-07
196	β_1 (h) (ag rl)	35		atenolol	2.2E-07	1.3E-07
255	β_1 (h) (ag rl)	4		atenolol	2.6E-07	1.5E-07
48	β_2 (h) (ag rl)	48		ICI 118551	4.1E-10	1.4E-10
173	β_2 (h) (ag rl)	25		ICI 118551	4.1E-10	1.4E-10
196	β_2 (h) (ag rl)	35		ICI 118551	4.1E-10	1.4E-10
255	β_2 (h) (ag rl)	-5		ICI 118551	8.8E-10	2.9E-10
48	β_3 (h) (ag rl)	7		cyanopindolol	2.2E-07	1.2E-07
173	β_3 (h) (ag rl)	5		cyanopindolol	2.2E-07	1.2E-07
196	β_3 (h) (ag rl)	-34		cyanopindolol	2.2E-07	1.2E-07
255	β_3 (h) (ag rl)	0		alprenolol	1.3E-07	9.7E-08

ant rl = antagonist radioligand

ag rl = agonist radiolig

Cerep Compound I.D.	Client Compound I.D.	Test Concentration	% of Control growth 1st	2nd	3rd	Mean	Cytotoxicity (% of control)	Flags 1st	2nd	3rd
Bacterial cytotoxicity (TA100 - S9)										
100010294-1	MAM-12.048	6.0E-07 M	103.3	106.6	106.7	105.6	106			
100010294-1	MAM-12.048	1.2E-06 M	99.0	97.8	104.9	100.6	101			
100010294-1	MAM-12.048	2.5E-06 M	92.0	91.6	61.0	81.6	82			
100010294-1	MAM-12.048	5.0E-06 M	32.1	33.5	39.5	**35.0**	35	CYTOX	CYTOX	CYTOX
100010294-1	MAM-12.048	1.0E-05 M	32.1	34.4	34.1	**33.5**	34	CYTOX	CYTOX	CYTOX
100010294-1	MAM-12.048	2.5E-05 M	33.0	33.5	44.8	**37.1**	37	CYTOX	CYTOX	CYTOX
100010294-1	MAM-12.048	5.0E-05 M	33.9	35.2	56.5	**41.9**	42	CYTOX	CYTOX	CYTOX
100010294-1	MAM-12.048	1.0E-04 M	42.5	39.6	65.5	**49.2**	49	CYTOX	CYTOX	CYTOX
100010294-2	MAM-12.173	6.0E-07 M	104.2	105.7	106.7	105.6	106			
100010294-2	MAM-12.173	1.2E-06 M	80.8	74.0	93.3	82.7	83			
100010294-2	MAM-12.173	2.5E-06 M	69.5	78.4	81.6	76.5	76			
100010294-2	MAM-12.173	5.0E-06 M	32.1	32.6	33.2	**32.6**	33	CYTOX	CYTOX	CYTOX
100010294-2	MAM-12.173	1.0E-05 M	32.1	33.5	35.0	**33.5**	34	CYTOX	CYTOX	CYTOX
100010294-2	MAM-12.173	2.5E-05 M	38.2	37.9	35.0	**37.0**	37	CYTOX	CYTOX	CYTOX
100010294-2	MAM-12.173	5.0E-05 M	44.3	45.8	40.4	**43.5**	43	CYTOX	CYTOX	CYTOX
100010294-2	MAM-12.173	1.0E-04 M	64.3	67.0	57.4	62.9	63			
100010294-3	MAM-12.196	6.0E-07 M	102.5	101.3	101.3	101.7	102			
100010294-3	MAM-12.196	1.2E-06 M	92.0	92.5	100.4	95.0	95			
100010294-3	MAM-12.196	2.5E-06 M	66.9	53.7	54.7	58.4	58	CYTOX	CYTOX	CYTOX
100010294-3	MAM-12.196	5.0E-06 M	92.0	85.5	96.0	91.2	91			
100010294-3	MAM-12.196	1.0E-05 M	43.4	33.5	68.2	**48.4**	48	CYTOX	CYTOX	CYTOX
100010294-3	MAM-12.196	2.5E-05 M	47.8	96.0	51.1	**49.4**	49	CYTOX	{}, CYTOX	CYTOX
100010294-3	MAM-12.196	5.0E-05 M	59.0	104.0	104.0	104.0	104	{}		
100010294-3	MAM-12.196	1.0E-04 M	88.6	89.9	85.2	87.9	88			
Bacterial cytotoxicity (TA1535 - S9)										
100010294-1	MAM-12.048	6.0E-07 M	106.2	109.6	111.2	109.0	109			
100010294-1	MAM-12.048	1.2E-06 M	97.1	106.2	106.0	103.1	103			
100010294-1	MAM-12.048	2.5E-06 M	73.3	31.9	88.5	80.9	81		{}	
100010294-1	MAM-12.048	5.0E-06 M	30.5	31.9	32.4	**31.6**	32	CYTOX	CYTOX	CYTOX
100010294-1	MAM-12.048	1.0E-05 M	30.5	31.9	32.4	**31.6**	32	CYTOX	CYTOX	CYTOX
100010294-1	MAM-12.048	2.5E-05 M	31.3	32.8	42.0	**35.4**	35	CYTOX	CYTOX	CYTOX
100010294-1	MAM-12.048	5.0E-05 M	32.1	34.5	36.8	**34.5**	34	CYTOX	CYTOX	CYTOX
100010294-1	MAM-12.048	1.0E-04 M	34.6	43.2	72.7	50.1	50	CYTOX	CYTOX	CYTOX
100010294-2	MAM-12.173	6.0E-07 M	104.5	108.8	111.2	108.2	108			
100010294-2	MAM-12.173	1.2E-06 M	94.7	102.7	108.6	102.0	102			
100010294-2	MAM-12.173	2.5E-06 M	78.2	78.6	70.9	75.9	76			
100010294-2	MAM-12.173	5.0E-06 M	30.5	31.9	37.7	**33.4**	33	CYTOX	CYTOX	CYTOX
100010294-2	MAM-12.173	1.0E-05 M	32.1	32.8	32.4	**32.4**	32	CYTOX	CYTOX	CYTOX
100010294-2	MAM-12.173	2.5E-05 M	40.3	36.3	35.9	**37.5**	38	CYTOX	CYTOX	CYTOX
100010294-2	MAM-12.173	5.0E-05 M	66.7	46.6	44.7	52.7	53	CYTOX	CYTOX	CYTOX
100010294-2	MAM-12.173	1.0E-04 M	54.3	92.4	62.2	69.6	70			
100010294-3	MAM-12.196	6.0E-07 M	102.1	107.1	112.1	107.1	107			
100010294-3	MAM-12.196	1.2E-06 M	99.6	107.9	107.7	105.1	105			
100010294-3	MAM-12.196	2.5E-06 M	84.8	85.5	120.9	97.0	97			
100010294-3	MAM-12.196	5.0E-06 M	56.8	70.8	70.1	65.9	66			
100010294-3	MAM-12.196	1.0E-05 M	51.0	85.5	37.7	58.1	58	CYTOX	CYTOX	CYTOX
100010294-3	MAM-12.196	2.5E-05 M	102.1	72.5	125.3	87.3	87			{}
100010294-3	MAM-12.196	5.0E-05 M	56.0	64.7	57.8	59.5	60	CYTOX	CYTOX	CYTOX
100010294-3	MAM-12.196	1.0E-04 M	78.2	82.0	86.7	82.3	82			

Figure 41. Bacterial cytotoxicity of 145 **(MAM-12.048),** 168 **(MAM-12.173),** 190 **(MAM-12.196). Part 1/2**

Cerep Compound I.D.	Client Compound I.D.	Test Concentration	% of Control growth 1st	2nd	3rd	Mean	Cytotoxicity (% of control)	Flags 1st	2nd	3rd
Bacterial cytotoxicity (TA98 - S9)										
100010294-1	MAM-12.048	6.0E-07 M	97.0	99.0	97.8	97.9	98			
100010294-1	MAM-12.048	1.2E-06 M	94.6	89.9	94.5	93.0	93			
100010294-1	MAM-12.048	2.5E-06 M	82.6	79.1	67.1	76.3	76			
100010294-1	MAM-12.048	5.0E-06 M	29.4	30.0	29.8	**29.7**	30	CYTOX	CYTOX	CYTOX
100010294-1	MAM-12.048	1.0E-05 M	29.4	30.8	30.7	**30.3**	30	CYTOX	CYTOX	CYTOX
100010294-1	MAM-12.048	2.5E-05 M	30.2	33.3	34.0	**32.5**	32	CYTOX	CYTOX	CYTOX
100010294-1	MAM-12.048	5.0E-05 M	31.8	33.3	40.6	**35.2**	35	CYTOX	CYTOX	CYTOX
100010294-1	MAM-12.048	1.0E-04 M	38.9	37.4	56.4	**44.2**	44	CYTOX	CYTOX	CYTOX
100010294-2	MAM-12.173	6.0E-07 M	93.0	98.2	95.3	95.5	95			
100010294-2	MAM-12.173	1.2E-06 M	76.3	84.9	86.2	82.5	82			
100010294-2	MAM-12.173	2.5E-06 M	69.9	70.7	92.8	77.8	78			
100010294-2	MAM-12.173	5.0E-06 M	28.6	30.0	29.8	**29.5**	29	CYTOX	CYTOX	CYTOX
100010294-2	MAM-12.173	1.0E-05 M	31.0	33.3	31.5	**31.9**	32	CYTOX	CYTOX	CYTOX
100010294-2	MAM-12.173	2.5E-05 M	37.4	39.1	36.5	**37.6**	38	CYTOX	CYTOX	CYTOX
100010294-2	MAM-12.173	5.0E-05 M	39.7	39.9	40.6	**40.1**	40	CYTOX	CYTOX	CYTOX
100010294-2	MAM-12.173	1.0E-04 M	67.5	59.1	54.7	60.4	60	CYTOX	CYTOX	CYTOX
100010294-3	MAM-12.196	6.0E-07 M	96.2	98.2	99.4	97.9	98			
100010294-3	MAM-12.196	1.2E-06 M	93.0	91.5	89.5	91.3	91			
100010294-3	MAM-12.196	2.5E-06 M	66.8	67.4	95.3	76.5	76			
100010294-3	MAM-12.196	5.0E-06 M	64.4	101.5	76.2	80.7	81			
100010294-3	MAM-12.196	1.0E-05 M	31.0	84.0	84.5	84.3	84	{}		
100010294-3	MAM-12.196	2.5E-05 M	39.7	81.6	126.8	60.6	61			{}
100010294-3	MAM-12.196	5.0E-05 M	50.9	56.6	53.0	53.5	53	CYTOX	CYTOX	CYTOX
100010294-3	MAM-12.196	1.0E-04 M	85.8	84.0	79.6	83.1	83			
Bacterial cytotoxicity (TA1537 - S9)										
100010294-1	MAM-12.048	6.0E-07 M	102.4	109.2	106.3	106.0	106			
100010294-1	MAM-12.048	1.2E-06 M	91.7	85.7	92.1	89.8	90			
100010294-1	MAM-12.048	2.5E-06 M	28.5	29.1	29.4	**29.0**	29	CYTOX	CYTOX	CYTOX
100010294-1	MAM-12.048	5.0E-06 M	28.5	29.9	28.6	**29.0**	29	CYTOX	CYTOX	CYTOX
100010294-1	MAM-12.048	1.0E-05 M	28.5	29.9	29.4	**29.3**	29	CYTOX	CYTOX	CYTOX
100010294-1	MAM-12.048	2.5E-05 M	30.0	29.9	37.3	**32.4**	32	CYTOX	CYTOX	CYTOX
100010294-1	MAM-12.048	5.0E-05 M	31.6	33.2	54.0	**39.6**	40	CYTOX	CYTOX	CYTOX
100010294-1	MAM-12.048	1.0E-04 M	34.7	66.3	146.0	50.5	50	CYTOX	CYTOX	{}, CYTOX
100010294-2	MAM-12.173	6.0E-07 M	97.0	108.4	105.6	103.7	104			
100010294-2	MAM-12.173	1.2E-06 M	54.7	84.1	66.7	68.5	68			
100010294-2	MAM-12.173	2.5E-06 M	28.5	29.9	30.2	**29.5**	30	CYTOX	CYTOX	CYTOX
100010294-2	MAM-12.173	5.0E-06 M	29.3	29.1	29.4	**29.2**	29	CYTOX	CYTOX	CYTOX
100010294-2	MAM-12.173	1.0E-05 M	30.8	30.7	30.2	**30.6**	31	CYTOX	CYTOX	CYTOX
100010294-2	MAM-12.173	2.5E-05 M	36.2	33.2	40.5	**36.6**	37	CYTOX	CYTOX	CYTOX
100010294-2	MAM-12.173	5.0E-05 M	37.7	38.8	42.9	**39.8**	40	CYTOX	CYTOX	CYTOX
100010294-2	MAM-12.173	1.0E-04 M	51.6	45.3	89.7	**48.4**	48	CYTOX	CYTOX	{}, CYTOX
100010294-3	MAM-12.196	6.0E-07 M	99.4	105.9	106.3	103.9	104			
100010294-3	MAM-12.196	1.2E-06 M	90.1	88.1	97.6	92.0	92			
100010294-3	MAM-12.196	2.5E-06 M	28.5	29.1	29.4	**29.0**	29	CYTOX	CYTOX	CYTOX
100010294-3	MAM-12.196	5.0E-06 M	29.3	29.1	29.4	**29.2**	29	CYTOX	CYTOX	CYTOX
100010294-3	MAM-12.196	1.0E-05 M	30.8	31.5	31.0	**31.1**	31	CYTOX	CYTOX	CYTOX
100010294-3	MAM-12.196	2.5E-05 M	38.5	40.4	38.9	**39.3**	39	CYTOX	CYTOX	CYTOX
100010294-3	MAM-12.196	5.0E-05 M	54.7	59.0	55.6	56.4	56	CYTOX	CYTOX	CYTOX
100010294-3	MAM-12.196	1.0E-04 M	93.2	91.4	89.7	91.4	91			

Notes:
1. Cytotoxicity is presented as % of control growth.
2. A cytotoxicity value of less than 60 % is flagged, and the compound is considered as toxic at the respective concentration.

CYTOX: Test compound appears to have cytotoxic effect.
{}: That replicate was excluded from the calculation

Figure 42. Bacterial cytotoxicity of 145 **(MAM-12.048),** 168 **(MAM-12.173),** 190 **(MAM-12.196). Part 2/2**

Cerep Compound I.D.	Client Compound I.D.	Test Concentration	%Effect 1st	%Effect 2nd	%Effect 3rd	Mean %Effect	Cytotoxicity (% of control)
Bacterial cytotoxicity (TA98 - S9)							
100018635-1	MAM-12.255	6.0E-07 M	115.7	103.0	97.1	105.3	105
100018635-1	MAM-12.255	1.2E-06 M	102.2	103.0	102.2	102.4	102
100018635-1	MAM-12.255	2.5E-06 M	97.1	92.0	92.9	94.0	94
100018635-1	MAM-12.255	5.0E-06 M	105.5	96.2	103.8	101.9	102
100018635-1	MAM-12.255	1.0E-05 M	101.3	97.1	99.6	99.3	99
100018635-1	MAM-12.255	2.5E-05 M	109.8	108.1	103.0	106.9	107
100018635-1	MAM-12.255	5.0E-05 M	122.4	112.3	113.1	115.9	116
100018635-1	MAM-12.255	1.0E-04 M	180.7	168.9	171.4	173.6	174
Bacterial cytotoxicity (TA100 - S9)							
100018635-1	MAM-12.255	6.0E-07 M	98.3	99.2	108.1	101.9	102
100018635-1	MAM-12.255	1.2E-06 M	108.1	95.3	102.2	101.9	102
100018635-1	MAM-12.255	2.5E-06 M	94.3	94.3	98.3	95.6	96
100018635-1	MAM-12.255	5.0E-06 M	99.2	100.2	99.2	99.6	100
100018635-1	MAM-12.255	1.0E-05 M	104.1	105.1	104.1	104.5	104
100018635-1	MAM-12.255	2.5E-05 M	129.7	121.8	115.0	122.2	122
100018635-1	MAM-12.255	5.0E-05 M	142.5	138.5	146.4	142.5	142
100018635-1	MAM-12.255	1.0E-04 M	195.5	185.7	177.8	186.4	186
Bacterial cytotoxicity (TA1535 - S9)							
100018635-1	MAM-12.255	6.0E-07 M	103.3	103.3	101.6	102.7	103
100018635-1	MAM-12.255	1.2E-06 M	105.0	101.6	103.3	103.3	103
100018635-1	MAM-12.255	2.5E-06 M	105.8	106.7	107.5	106.7	107
100018635-1	MAM-12.255	5.0E-06 M	114.4	117.8	116.9	116.4	116
100018635-1	MAM-12.255	1.0E-05 M	107.5	105.8	113.5	109.0	109
100018635-1	MAM-12.255	2.5E-05 M	114.4	105.8	111.8	110.7	111
100018635-1	MAM-12.255	5.0E-05 M	134.9	125.5	127.2	129.2	129
100018635-1	MAM-12.255	1.0E-04 M	163.9	169.8	175.0	169.6	170
Bacterial cytotoxicity (TA1537 - S9)							
100018635-1	MAM-12.255	6.0E-07 M	111.2	102.7	98.5	104.2	104
100018635-1	MAM-12.255	1.2E-06 M	110.4	103.6	106.1	106.7	107
100018635-1	MAM-12.255	2.5E-06 M	102.7	96.8	98.5	99.3	99
100018635-1	MAM-12.255	5.0E-06 M	98.5	90.8	93.4	94.2	94
100018635-1	MAM-12.255	1.0E-05 M	92.5	92.5	90.8	92.0	92
100018635-1	MAM-12.255	2.5E-05 M	104.4	96.8	101.0	100.8	101
100018635-1	MAM-12.255	5.0E-05 M	128.2	116.3	114.6	119.7	120
100018635-1	MAM-12.255	1.0E-04 M	167.3	162.2	157.1	162.2	162

Notes:
1. Cytotoxicity is presented as % of control growth.
2. A cytotoxicity value of less than 60 % is flagged, and the compound is considered as toxic at the respective concentration.

Figure 43. Bacterial cytotoxicity of 249 **(MAM-12.255).**

To test if the compounds can cause mutations **145**, **168**, **190**, and **249** were subjected to the Ames test for mutagenicity. Results are shown in Figure 44 and Figure 45 for compounds **145**, **168**, and **190**. Results for **249** can be found in Figure 46. No mutagenicity was found for the tested compounds.

Cerep Compound I.D.	Client Compound I.D.	Test Concentration	Count (# of wells)	Positive Significance (- to +++)	Fisher Exact Test (p-value)	Count Flag	Flags
Ames test (TA98 + S9)							
100010294-1	MAM-12.048	5.0E-06 M	3	-	0.5000	-	
100010294-1	MAM-12.048	1.0E-05 M	6	-	0.3700		
100010294-1	MAM-12.048	5.0E-05 M	0	-	0.0586	-	
100010294-1	MAM-12.048	1.0E-04 M	1	-	0.1808	-	
100010294-2	MAM-12.173	5.0E-06 M	3	-	0.5000	-	
100010294-2	MAM-12.173	1.0E-05 M	5	-	0.5000		
100010294-2	MAM-12.173	5.0E-05 M	5	-	0.5000		
100010294-2	MAM-12.173	1.0E-04 M	10	-	0.0732		
100010294-3	MAM-12.196	5.0E-06 M	10	-	0.0732		
100010294-3	MAM-12.196	1.0E-05 M	2	-	0.3387	-	
100010294-3	MAM-12.196	5.0E-05 M	12	+	0.0264		INTER
100010294-3	MAM-12.196	1.0E-04 M	15	++	0.0046		INTER
Ames test (TA100 - S9)							
100010294-1	MAM-12.048	5.0E-06 M	0	-	0.5000	-	
100010294-1	MAM-12.048	1.0E-05 M	0	-	0.5000	-	
100010294-1	MAM-12.048	5.0E-05 M	0	-	0.5000	-	
100010294-1	MAM-12.048	1.0E-04 M	0	-	0.5000	-	
100010294-2	MAM-12.173	5.0E-06 M	0	-	0.5000	-	
100010294-2	MAM-12.173	1.0E-05 M	0	-	0.5000	-	
100010294-2	MAM-12.173	5.0E-05 M	0	-	0.5000	-	
100010294-2	MAM-12.173	1.0E-04 M	0	-	0.5000	-	
100010294-3	MAM-12.196	5.0E-06 M	0	-	0.5000	-	
100010294-3	MAM-12.196	1.0E-05 M	0	-	0.5000	-	
100010294-3	MAM-12.196	5.0E-05 M	0	-	0.5000	-	
100010294-3	MAM-12.196	1.0E-04 M	0	-	0.5000	-	
Ames test (TA100 + S9)							
100010294-1	MAM-12.048	5.0E-06 M	10	-	1.0000		
100010294-1	MAM-12.048	1.0E-05 M	7	-	0.2969	-	
100010294-1	MAM-12.048	5.0E-05 M	0	-	0.0006	<<<	
100010294-1	MAM-12.048	1.0E-04 M	0	-	0.0006	<<<	
100010294-2	MAM-12.173	5.0E-06 M	5	-	0.1303	-	
100010294-2	MAM-12.173	1.0E-05 M	9	-	0.5000	-	
100010294-2	MAM-12.173	5.0E-05 M	4	-	0.0732	-	
100010294-2	MAM-12.173	1.0E-04 M	1	-	0.0038	<<	
100010294-3	MAM-12.196	5.0E-06 M	4	-	0.0732	-	
100010294-3	MAM-12.196	1.0E-05 M	2	-	0.0137	<	
100010294-3	MAM-12.196	5.0E-05 M	12	-	0.4043		
100010294-3	MAM-12.196	1.0E-04 M	4	-	0.0732	-	
Ames test (TA1535 - S9)							
100010294-1	MAM-12.048	5.0E-06 M	0	-	1.0000		
100010294-1	MAM-12.048	1.0E-05 M	0	-	1.0000		
100010294-1	MAM-12.048	5.0E-05 M	0	-	1.0000		
100010294-1	MAM-12.048	1.0E-04 M	0	-	1.0000		
100010294-2	MAM-12.173	5.0E-06 M	0	-	1.0000		
100010294-2	MAM-12.173	1.0E-05 M	0	-	1.0000		
100010294-2	MAM-12.173	5.0E-05 M	0	-	1.0000		
100010294-2	MAM-12.173	1.0E-04 M	0	-	1.0000		
100010294-3	MAM-12.196	5.0E-06 M	0	-	1.0000		
100010294-3	MAM-12.196	1.0E-05 M	0	-	1.0000		
100010294-3	MAM-12.196	5.0E-05 M	0	-	1.0000		
100010294-3	MAM-12.196	1.0E-04 M	0	-	1.0000		

Figure 44. Ames test of 145 **(MAM-12.048),** 168 **(MAM-12.173),** 190 **(MAM-12.196). Part 1/2**

Cerep Compound I.D.	Client Compound I.D.	Test Concentration	Count (# of wells)	Positive Significance (- to +++)	Fisher Exact Test (p-value)	Count Flag	Flags
Ames test (TA98 - S9)							
100010294-1	MAM-12.048	5.0E-06 M	0	-	1.0000		
100010294-1	MAM-12.048	1.0E-05 M	0	-	1.0000		
100010294-1	MAM-12.048	5.0E-05 M	0	-	1.0000		
100010294-1	MAM-12.048	1.0E-04 M	0	-	1.0000		
100010294-2	MAM-12.173	5.0E-06 M	0	-	1.0000		
100010294-2	MAM-12.173	1.0E-05 M	0	-	1.0000		
100010294-2	MAM-12.173	5.0E-05 M	0	-	1.0000		
100010294-2	MAM-12.173	1.0E-04 M	0	-	1.0000		
100010294-3	MAM-12.196	5.0E-06 M	0	-	1.0000		
100010294-3	MAM-12.196	1.0E-05 M	0	-	1.0000		
100010294-3	MAM-12.196	5.0E-05 M	0	-	1.0000		
100010294-3	MAM-12.196	1.0E-04 M	0	-	1.0000		
Ames test (TA1535 + S9)							
100010294-1	MAM-12.048	5.0E-06 M	1	-	0.0556	-	
100010294-1	MAM-12.048	1.0E-05 M	2	-	0.1339	-	
100010294-1	MAM-12.048	5.0E-05 M	0	-	0.0132	<	
100010294-1	MAM-12.048	1.0E-04 M	0	-	0.0132	<	
100010294-2	MAM-12.173	5.0E-06 M	2	-	0.1339	-	
100010294-2	MAM-12.173	1.0E-05 M	0	-	0.0132	<	
100010294-2	MAM-12.173	5.0E-05 M	0	-	0.0132	<	
100010294-2	MAM-12.173	1.0E-04 M	1	-	0.0556	-	
100010294-3	MAM-12.196	5.0E-06 M	1	-	0.0556	-	
100010294-3	MAM-12.196	1.0E-05 M	2	-	0.1339	-	
100010294-3	MAM-12.196	5.0E-05 M	0	-	0.0132	<	
100010294-3	MAM-12.196	1.0E-04 M	0	-	0.0132	<	
Ames test (TA1537-S9)							
100010294-1	MAM-12.048	5.0E-06 M	0	-	0.5000	-	
100010294-1	MAM-12.048	1.0E-05 M	0	-	0.5000	-	
100010294-1	MAM-12.048	5.0E-05 M	0	-	0.5000	-	
100010294-1	MAM-12.048	1.0E-04 M	0	-	0.5000	-	
100010294-2	MAM-12.173	5.0E-06 M	0	-	0.5000	-	
100010294-2	MAM-12.173	1.0E-05 M	0	-	0.5000	-	
100010294-2	MAM-12.173	5.0E-05 M	0	-	0.5000	-	
100010294-2	MAM-12.173	1.0E-04 M	0	-	0.5000	-	
100010294-3	MAM-12.196	5.0E-06 M	4	-	0.1808		
100010294-3	MAM-12.196	1.0E-05 M	1	-	1.0000		
100010294-3	MAM-12.196	5.0E-05 M	3	-	0.3085		
100010294-3	MAM-12.196	1.0E-04 M	3	-	0.3085		
Ames test (TA1537 + S9)							
100010294-1	MAM-12.048	5.0E-06 M	1	-	0.5000	-	
100010294-1	MAM-12.048	1.0E-05 M	6	-	0.1339		
100010294-1	MAM-12.048	5.0E-05 M	4	-	0.3387		
100010294-1	MAM-12.048	1.0E-04 M	0	-	0.2474	-	
100010294-2	MAM-12.173	5.0E-06 M	2	-	1.0000		
100010294-2	MAM-12.173	1.0E-05 M	0	-	0.2474	-	
100010294-2	MAM-12.173	5.0E-05 M	2	-	1.0000		
100010294-2	MAM-12.173	1.0E-04 M	7	-	0.0793		
100010294-3	MAM-12.196	5.0E-06 M	0	-	0.2474	-	
100010294-3	MAM-12.196	1.0E-05 M	2	-	1.0000		
100010294-3	MAM-12.196	5.0E-05 M	0	-	0.2474	-	
100010294-3	MAM-12.196	1.0E-04 M	1	-	0.5000	-	

Notes:
1. Weak positive, if $p < 0.05$, denoted as "+"
   Strong positive, if $p < 0.01$, denoted as "++"
   Very strong positive, if $p < 0.001$, denoted as "+++"
2. When possible, compounds which score significantly below background are flagged.
   This may indicate low level cytotoxicity undetectable by the growth assay.
   The compounds are flagged as described below.
   if $p < 0.05$, flagged as "<"
   if $p < 0.01$, flagged as "<<"
   if $p < 0.001$, flagged as "<<<"
3. Hyphens (-) indicate negative results.

INTER: Test compound interferes with the assay detection method.

Figure 45. Ames test of 145 **(MAM-12.048),** 168 **(MAM-12.173),** 190 **(MAM-12.196). Part 2/2**

Cerep Compound I.D.	Client Compound I.D.	Test Concentration	Count (# of wells)	Positive Significance (- to +++)	Fisher Exact Test (p-value)	Count Flag
Ames fluctuation test (TA98 - S9)						
100018635-1	MAM-12.255	5.0E-06 M	0	-	1.0000	
100018635-1	MAM-12.255	1.0E-05 M	0	-	1.0000	
100018635-1	MAM-12.255	5.0E-05 M	0	-	1.0000	
100018635-1	MAM-12.255	1.0E-04 M	1	-	0.5000	
Ames fluctuation test (TA98 + S9)						
3100018635-1	MAM-12.255	5.0E-06 M	1	-	1.0000	-
100018635-1	MAM-12.255	1.0E-05 M	0	-	0.5000	-
100018635-1	MAM-12.255	5.0E-05 M	0	-	0.5000	-
100018635-1	MAM-12.255	1.0E-04 M	0	-	0.5000	-
Ames fluctuation test (TA100 - S9)						
100018635-1	MAM-12.255	5.0E-06 M	0	-	0.5000	-
100018635-1	MAM-12.255	1.0E-05 M	1	-	1.0000	
100018635-1	MAM-12.255	5.0E-05 M	0	-	0.5000	-
100018635-1	MAM-12.255	1.0E-04 M	1	-	1.0000	
Ames fluctuation test (TA100 + S9)						
100018635-1	MAM-12.255	5.0E-06 M	3	-	0.3085	
100018635-1	MAM-12.255	1.0E-05 M	4	-	0.1808	
100018635-1	MAM-12.255	5.0E-05 M	0	-	0.5000	-
100018635-1	MAM-12.255	1.0E-04 M	0	-	0.5000	-
Ames fluctuation test (TA1535 - S9)						
100018635-1	MAM-12.255	5.0E-06 M	0	-	1.0000	
100018635-1	MAM-12.255	1.0E-05 M	0	-	1.0000	
100018635-1	MAM-12.255	5.0E-05 M	0	-	1.0000	
100018635-1	MAM-12.255	1.0E-04 M	0	-	1.0000	
Ames fluctuation test (TA1535 + S9)						
100018635-1	MAM-12.255	5.0E-06 M	0	-	0.0586	-
100018635-1	MAM-12.255	1.0E-05 M	2	-	0.3387	-
100018635-1	MAM-12.255	5.0E-05 M	0	-	0.0586	-
100018635-1	MAM-12.255	1.0E-04 M	0	-	0.0586	-
Ames fluctuation test (TA1537-S9)						
100018635-1	MAM-12.255	5.0E-06 M	0	-	1.0000	
100018635-1	MAM-12.255	1.0E-05 M	0	-	1.0000	
100018635-1	MAM-12.255	5.0E-05 M	0	-	1.0000	
100018635-1	MAM-12.255	1.0E-04 M	0	-	1.0000	
Ames fluctuation test (TA1537 + S9)						
100018635-1	MAM-12.255	5.0E-06 M	0	-	0.1211	-
100018635-1	MAM-12.255	1.0E-05 M	0	-	0.1211	-
100018635-1	MAM-12.255	5.0E-05 M	0	-	0.1211	-
100018635-1	MAM-12.255	1.0E-04 M	0	-	0.1211	-

Notes:
1. Weak positive, if $p < 0.05$, denoted as "+"
   Strong positive, if $p < 0.01$, denoted as "++"
   Very strong positive, if $p < 0.001$, denoted as "+++"
2. When possible, compounds which score significantly below background are flagged.
   This may indicate low level cytotoxicity undetectable by the growth assay.
   The compounds are flagged as described below.
   if $p < 0.05$, flagged as "<"
   if $p < 0.01$, flagged as "<<"
   if $p < 0.001$, flagged as "<<<"
3. Hyphens (-) indicate negative results.

Figure 46. Ames test of 249 **(MAM-12.255).**

Cardiac safety testing has been performed at CEREP by assessment of % inhibition of tail current in an automated hERG patch-clamp assay. All compounds (**145** (MAM-12.048), **168** (MAM-12.173), **190** (MAM-12.196), and **249** (MAM-12.255)) were tested at three concentrations 0.1, 1.0 and 10 µM, respectively. Inhibition of the hERG channel was also tested; results can be found in Figure 47 and Figure 48, respectively. The hERG channel is an undesired molecular target of propafenone (**68**), the parenteral compound of the salicylamides, also an undesired target of many marketed antimalarial drugs.

Inhibition of tail current at concentrations of 0.1 and 1.0 µM was found to be negligible for all four compounds. **168** achieved 50%-inhibition at 10 µM, slightly more than **249**. The remaining derivatives **145** and **190** reduced tail current only by 25% at the highest concentration tested (expected IC_{50} > 50 µM).

These results from hERG assay establish a significant advantage over existing drugs used in chemotherapy of malaria. All of the drugs on the market (lumefantrine, quinine, quinidine, mefloquine) containing an aminoalcohol motifs show IC_{50}-values below 10 µM for inhibition of hERG.

Cerep Compound I.D.	Client Compound I.D.	Test Concentration	% Inhibition of Tail current		
			1st	2nd	Mean
hERG (hERG-CHO, automated patch-clamp)					
100010294-1	MAM-12.048	1.0E-07 M	1.7	0.6	1
100010294-1	MAM-12.048	1.0E-06 M	5.9	4.5	5
100010294-1	MAM-12.048	1.0E-05 M	20.3	29.5	25
100010294-2	MAM-12.173	1.0E-07 M	6.0	7.9	7
100010294-2	MAM-12.173	1.0E-06 M	15.8	15.1	15
100010294-2	MAM-12.173	1.0E-05 M	45.1	55.4	50
100010294-3	MAM-12.196	1.0E-07 M	1.1	-3.6	-1
100010294-3	MAM-12.196	1.0E-06 M	1.6	-3.6	-1
100010294-3	MAM-12.196	1.0E-05 M	26.9	28.1	28

Figure 47. hERG inhibition of 145 **(MAM-12.048),** 168 **(MAM-12.173),** 190 **(MAM-12.196).**

Cerep Compound I.D.	Client Compound I.D.	Test Concentration	% Inhibition of Tail current		
			1st	2nd	Mean
hERG (hERG-CHO, automated patch-clamp)					
100018635-1	MAM-12.255	1.0E-07 M	12.8	23.3	18.0
100018635-1	MAM-12.255	1.0E-06 M	26.4	35.6	31.0
100018635-1	MAM-12.255	1.0E-05 M	42.4	48.6	45.5

Figure 48. hERG inhibition of 249 **(MAM-12.255).**

2.5 Structural Elucidation

It was shown that both enantiopure forms (**96** and **97**) of **194** possess the same antimalarial activity on NF54. It might be reasonably assumed that both enantiomers are able to adjust to an active conformation due to the flexible aminoalcohol moiety, unlike the pair of diastereoisomers shown in Figure 49. In the epiquinine molecule (**287**), which is practically inactive, the formation of a hydrogen bond in the α-aminoalcohol moiety may force the space demanding substituents in an unfavorable arrangement.[130] The diastereomeric centers of the quinine (**2**) molecule are in ideal premise for formation of a hydrogen bond between the hydroxy group and the tertiary amine while leaving the bulky rests in energetically favorable distance.[131] Unfortunately, no guest-free crystals of quinine (**2**) and epiquinine (**287**) are reported so far.[132]

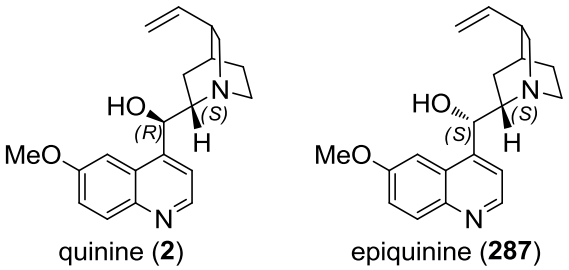


Figure 49. Quinine (2) and its diastereomer epiquinine (287).

The conformations of the synthesized molecules were investigated for molecules in the solid state *via* x-ray structure analysis and for molecules in solution *via* NMR analysis, respectively. The compounds synthesized in the course of this thesis form distinct patterns of hydrogen bondings. Such a network between the amide and the aminoalcohol site is depicted in Figure 50. While the hydrogen of the amide interacts with the phenyl ether as well as with the alcohol oxygen, the amine is interacting with the hydrogen of the hydroxy group. The three-center hydrogen bonding in combination with the two-center hydrogen bonding has a huge impact on the conformation of the molecules.

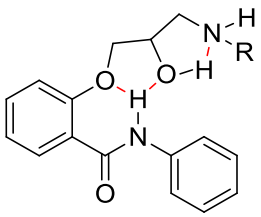


Figure 50. Hydrogen bonding network between amide and aminoalcohol site.

The importance of a network between the two regions of the molecule is suggested when the low activity of tertiary amide compound **246** (Figure 51; 579.0 nM on NF54 and 172 nM on K1 strain, respectively) is considered. In this compound no amide hydrogen is present, therefore only a two-centered hydrogen bonding motif can be formed. This two-centered hydrogen bonding of the aminoalcohol alone is enough to cause weak antimalarial activity; conformations similar to Figure 50 are needed to achieve highly active compounds.

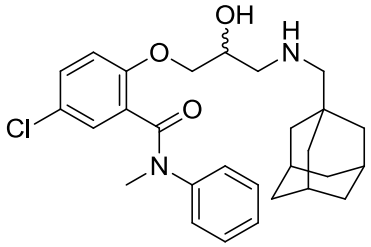


Figure 51. Structure of tertiary amide compound 246**.**

X-ray structure analysis of epoxide **100**, structure shown in Figure 52, reveals that the bifurcated hydrogen bond between amide and the glycidyl salicyl ether, which is the precursor of the aminoalcohol site, is already formed in the epoxide stage. The distance between amide nitrogen and glycidyl ether oxygen is 1.89 Å, while epoxide oxygen is 3.12 to 3.23 Å away from the amide hydrogen atom. It is also noteworthy that the trifluoromethyl group is not interacting with the epoxide in an intramolecular fashion.

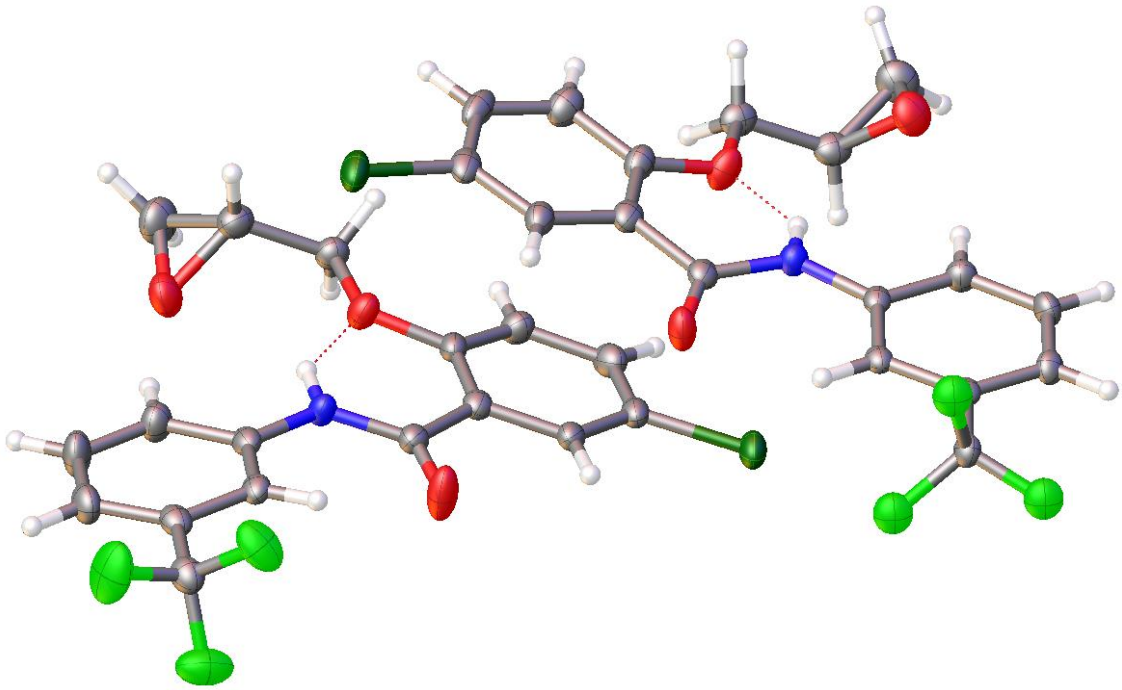


Figure 52. Crystal structure of (*R*)-(+)-5-chloro-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)-benzamide (100**).**

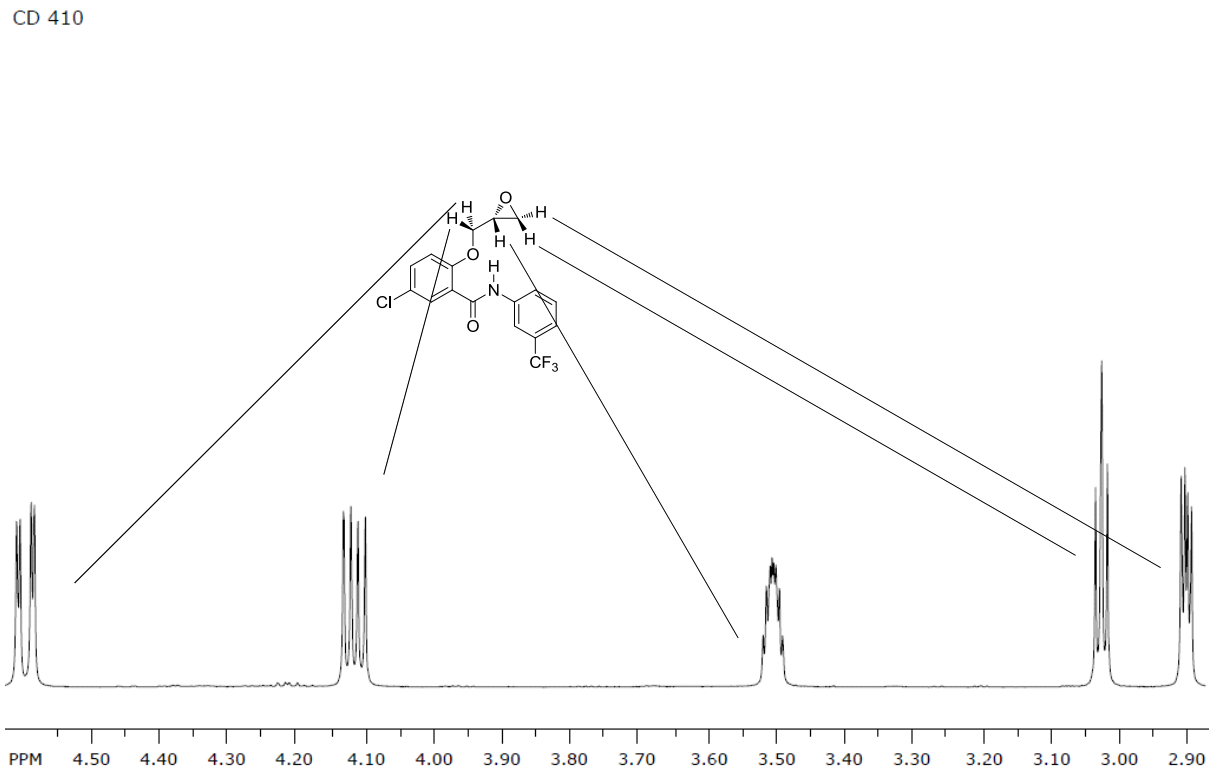


Figure 53. Assignment of the aminoalcohol signals in epoxide compound 100**.**

The ^{1}H NMR signals in the aminoalcohol, see Figure 53, can be assigned due to differences in coupling constants of the respective protons to the methine proton. Therefore, these diastereotopic protons are distinguishable.

The crystal structure of **186**, which is the aminoalcohol analog of the above discussed epoxide compound **100**, is shown in Figure 54. The network of hydrogen bonds, as depicted in Figure 50, is clearly visible in the crystal structure. It is also remarkable that the trifluoromethyl group also searches proximity to the piperidine. Interestingly, the three centered interaction between the amide hydrogen, phenyl ether oxygen and alcohol oxygen seems stronger than in the epoxide structure. The distances of 2.11 Å from amide hydrogen to the phenyl ether oxygen, instead of 1.89 Å in the epoxide, and 2.67 from the amide hydrogen to the alcohol oxygen, instead of 3.2 Å to the epoxide oxygen, clearly show that the bifurcation has grown stronger. This can be explained by the cooperative second hydrogen bond from the alcohol to the amine nitrogen. Concomitantly, with the piperidine moiety the trifluoromethyl group has found an intramolecular partner to interact with. This can either be interpreted as cause for the cooperative hydrogen bonding network or simply as result of it.

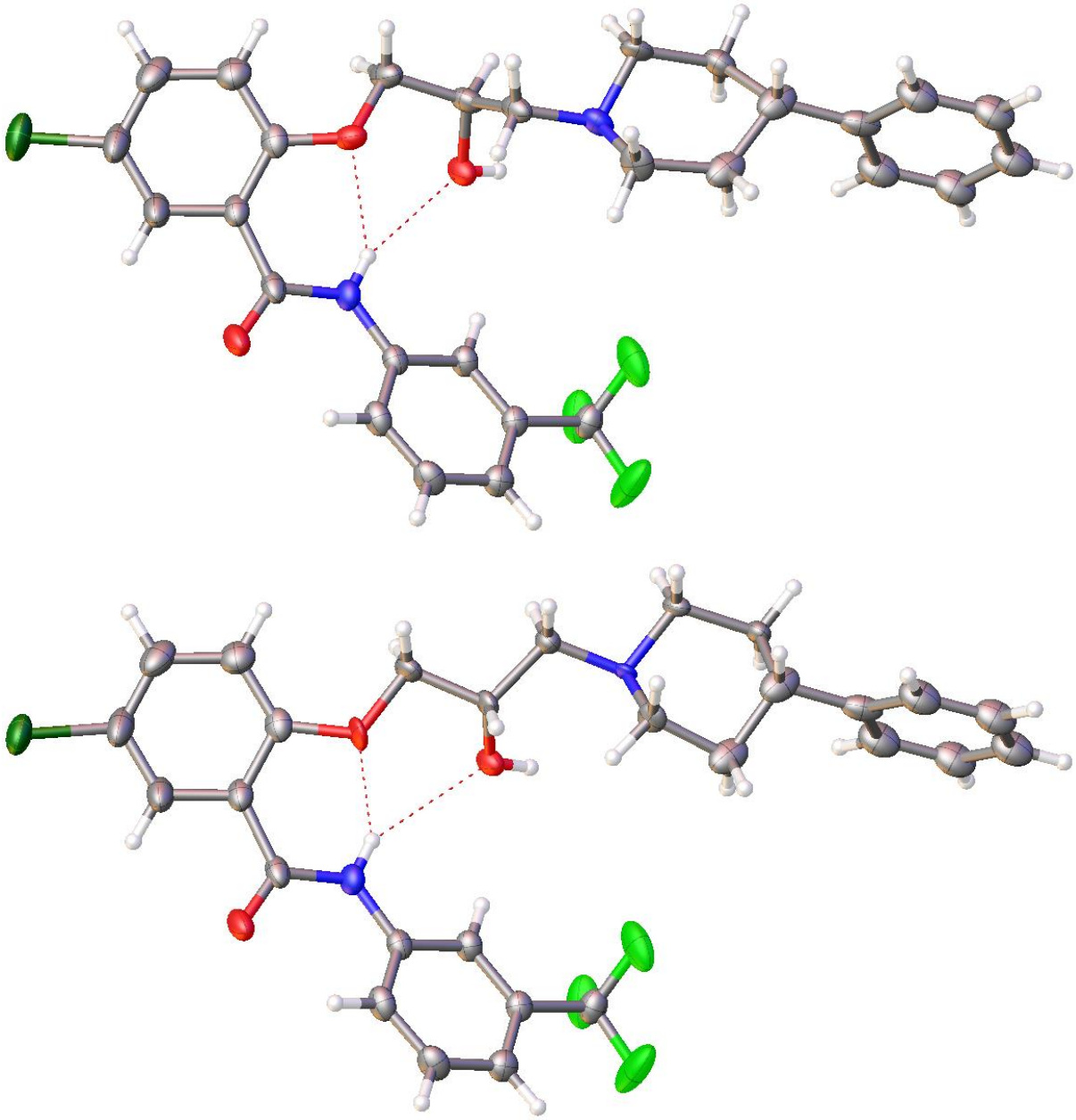


Figure 54. X-ray structure of 186**, which crystallized in two different structures.**

NMR spectra of highly active compounds show diastereotopicity of the hydrogens in the C-2 symmetric piperidine ring. As example, a HSQC of compound **190**, the benzyl analog of **186**, with very good activity (3.8 nM on NF54 and 0.99 nM on K1 strain, respectively) is shown in Figure 55. Axial and equatorial hydrogens of the 2- and 6-position of the piperidine have different shifts (axial hydrogens differ by 124 Hz and equatorial hydrogens differ by 127 Hz, respectively). This is even more apparent when the chemical shifts of the carbons are studied. The chemical shifts of C-2 (55.82 ppm) and C-6 (52.49 ppm) of the piperidine ring differ by 398 Hz. Interactions with the 3-trifluoromethyl aniline are responsible for this effect. It must be stated that these observations are only possible if the piperidine is fixed by the hy-

drogen bond to the alcohol hydrogen; otherwise dynamic effects would make C-2 and C-6 indistinguishable.

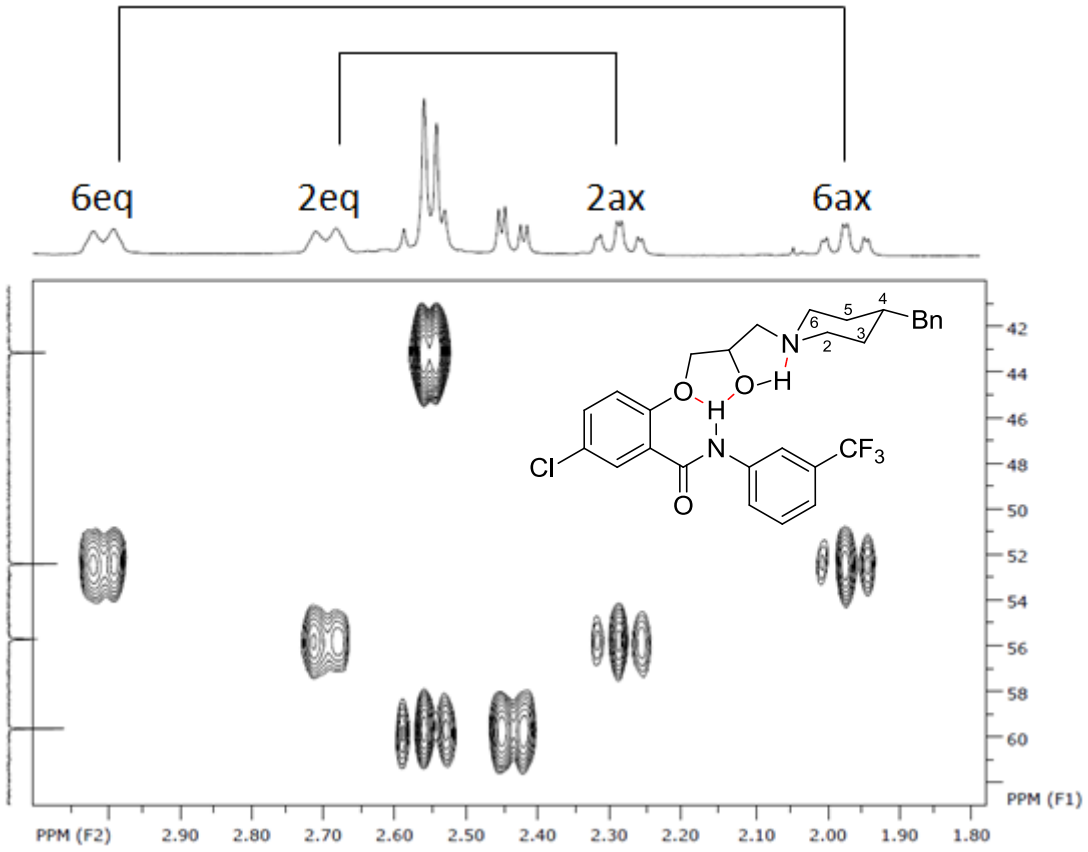


Figure 55. HSQC of 190**.**

Complementary to the crystal structure of **186**, also extensive NMR interpretation was carried out. In addition to the obligatory assignment of signals which is found on p. 253, the piperidine and the aminoalcohol spin-systems were simulated and a NOESY experiment was investigated. The simulated spectra and the relevant original regions of the spectrum are shown in Figure 56 and Figure 57, respectively. Input parameters are given on p. 576. The simulation reveals coupling constants for the piperidine spin system, mainly multiplets are observed for this moiety. The apparent coupling constants are in good agreement with the calculated coupling constants from the simulation.

NOESY-related screenshots are shown in Figures 58-63. Under omission of obvious cross-peaks which rise due to connectivity, such as between geminal protons, this NOESY reveals important conformational information. In Figure 59, showing the aliphatic region, crosspeaks between the methine hydrogen (4.25 ppm) and the equatorial hydrogen at C-6 (3.15 ppm) are visible; this is in good agreement with the crystal structure; see the upper structure in

Figure 54. This finding clearly allows attributing the signals to different sides of the molecule, because the equatorial hydrogen at C-2 (2.82 ppm) does not show this interaction. On the other hand this equatorial hydrogen at C-2 (2.82 ppm) shares a cross-peak with one hydrogen atom (2.62 ppm, having a large coupling constant indicating a dihedral angle close to 180° to methine H) of the in vicinity to the tertiary amine and also tells which of the 4 proton signals from 1.73-1.92 ppm must be assigned to C-3 and C-5.

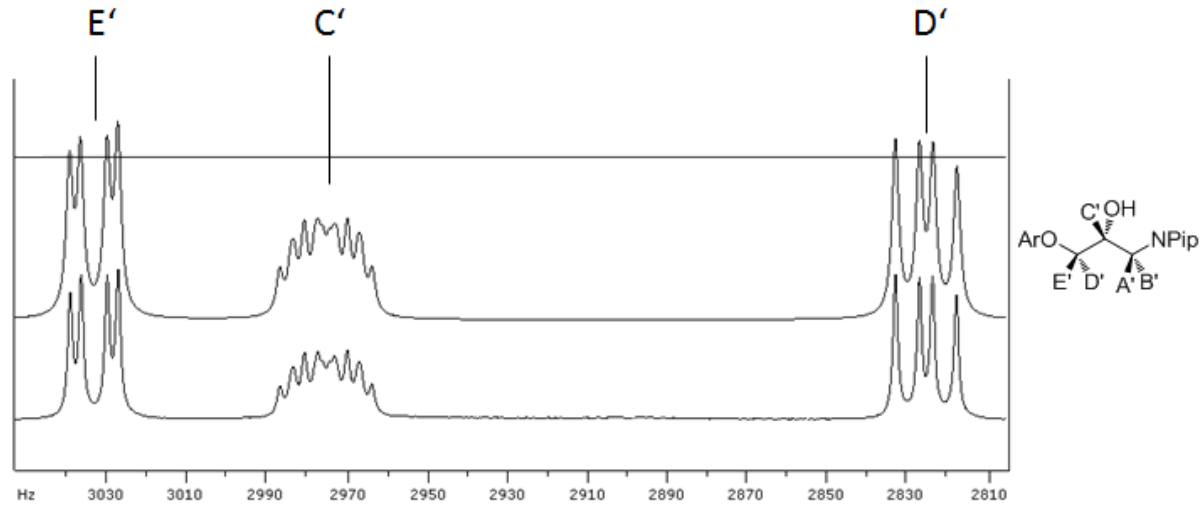


Figure 56. Simulation of the ^{1}H spectrum of the aminoalcohol region in 186 **between 2810 and 3050 Hz.**

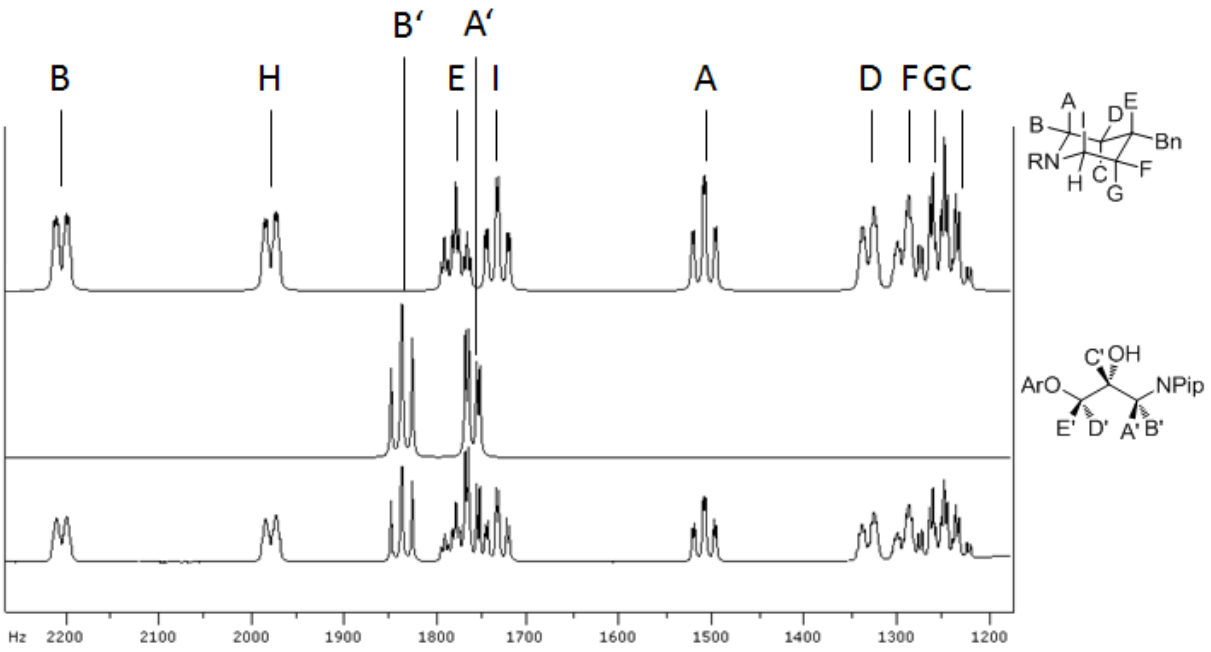


Figure 57. Simulation of the ^{1}H spectrum of 186**. Upper row shows the simulated piperidine spectrum. Second row shows the simulation of the aminoalcohol which has the amino methylene group in this region (1180-2250 Hz). In the bottom row the original spectrum is shown.**

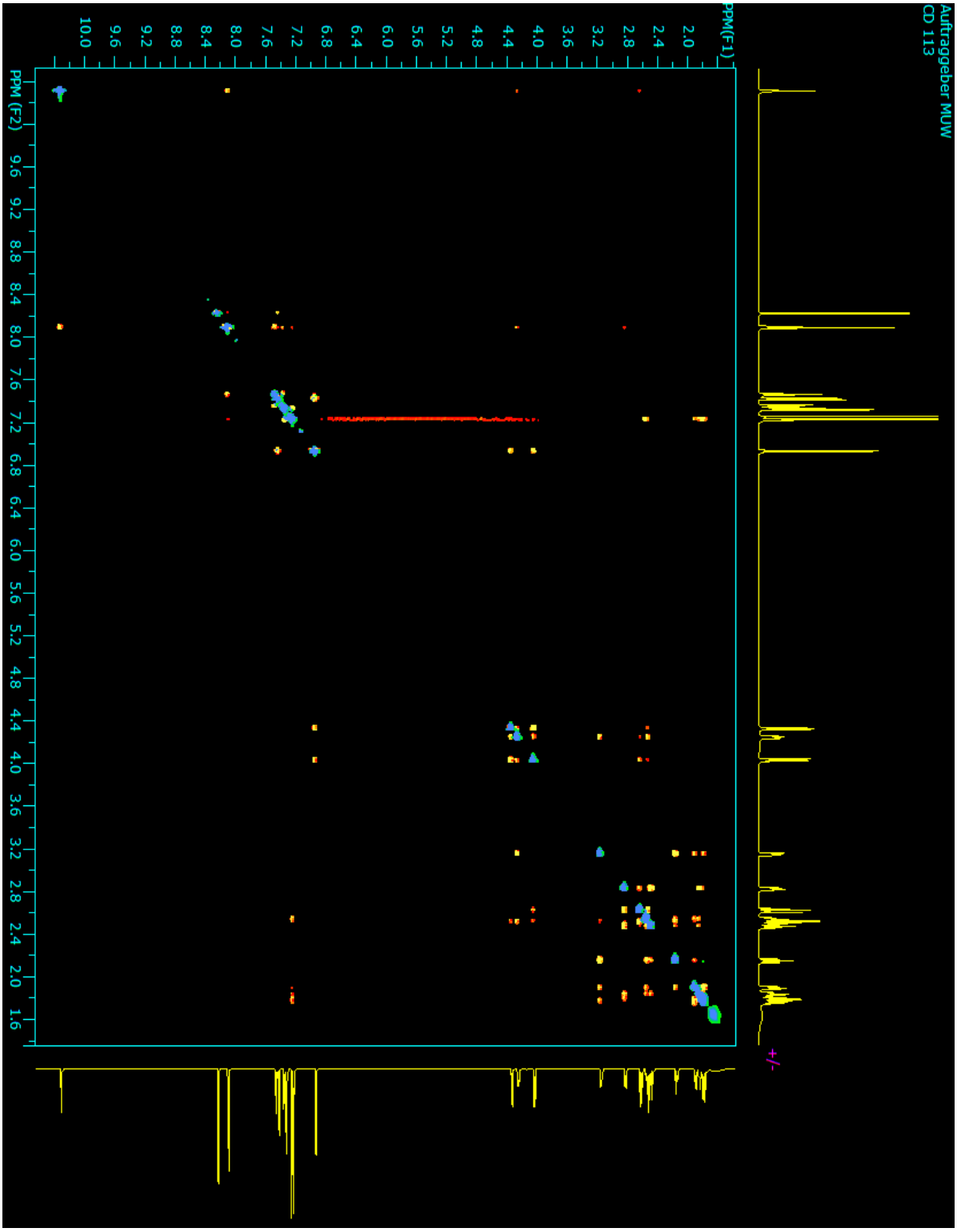


Figure 58. NOESY of 186**- total view.**

The carbon backbone of the aminoalcohol motif is obviously not predominantly arranged in a zig-zag manner in solution as the lower structure of Figure 54 suggests; otherwise, both hydrogens of the methylene group near the salicyl moiety (4.04 and 4.33 ppm) would inter-

act with both hydrogens of the methylene group in vicinity to the piperidine (2.51 and 2.62 ppm).

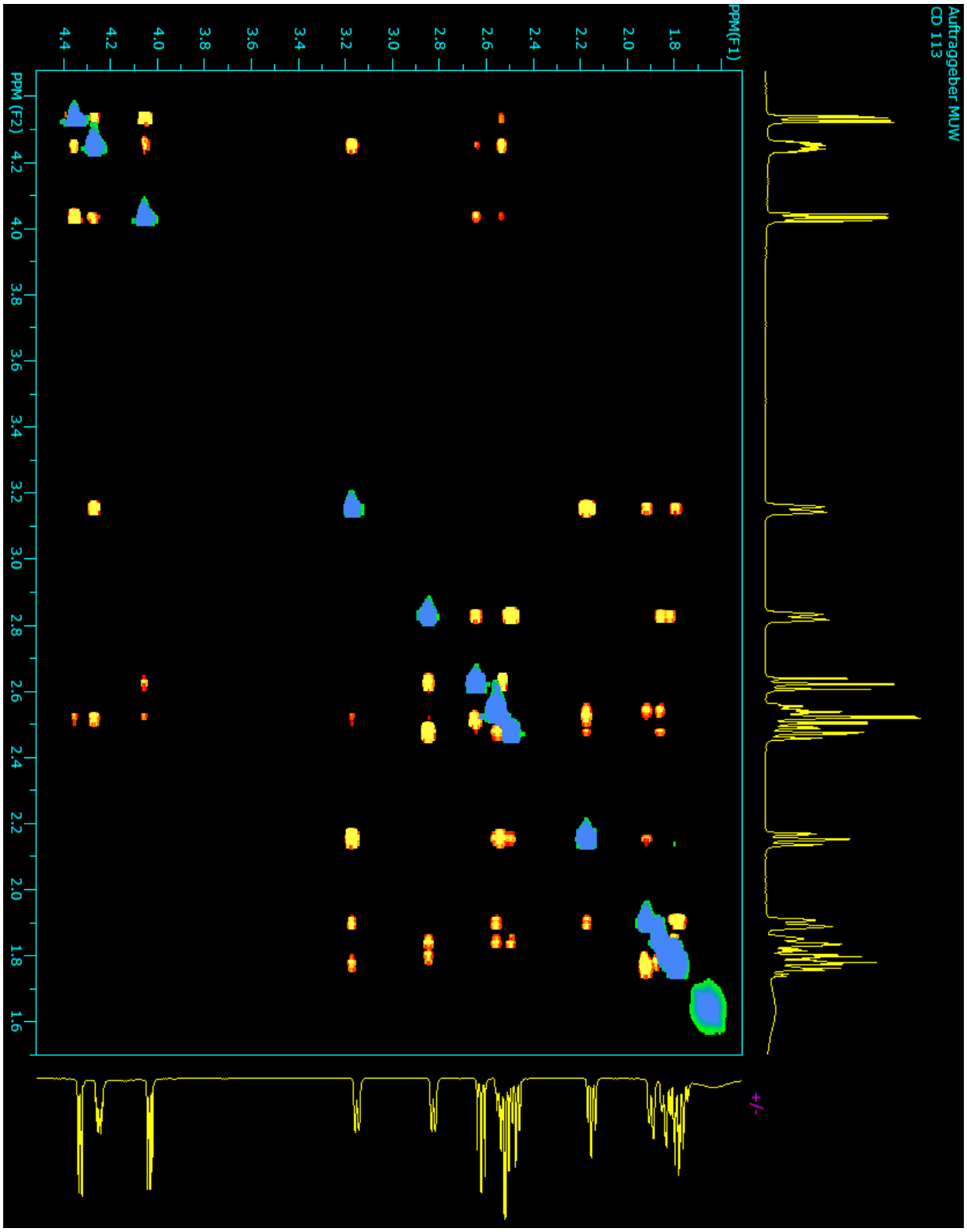


Figure 59. NOESY of 186- **aliphatic region.**

Interactions between aliphatic and aromatic region are shown in Figure 60 and Figure 61. The proton in the 3-postion of the salicylic ring interacts with both hydrogens of the meth-

ylene group next to the oxygen atom (4.04 and 4.33 ppm) in the same intensity, which is indicating that both hydrogens are symmetrical regarding the salicylic ring. This positioning was also observed in the lower structure in Figure 54.

Also crosspeaks between hydrogen atoms in the 2- and 6-position in the phenyl (7.21-7.24 ppm) and the axial protons attached to the 3-, 4-, and 5-carbon atom in the piperidine ring (1.73-1.82 and 2.54 ppm) are observed; these reasonable interactions are depicted in Figure 60 and Figure 61.

Weak interactions are observed for the hydrogen in the 2-position of the aniline (8.08 ppm) with the methine hydrogen (4.25 ppm) as well as the equatorial hydrogen in the 2-position of the piperidine ring (2.82 ppm); the corresponding crosspeaks are shown in Figure 62 and Figure 63, respectively. This is indicative for the proximity of the aniline region to the rest of the molecule, and an impressive argument for the diastereotopicity of the piperidine, which is also shown above for **190** in Figure 55. Furthermore, it is also shown that distances between H-2 of the aniline and methine H (in crystal structure 3.58 Å), as well as the distance between H-2 of the aniline and equatorial hydrogen in the 2 position of the piperidine (in crystal structure 3.89 Å) are also below 4 Å, which is a typical limit of NOESY experiments.

A closer look on the strong crosspeaks between the amide hydrogen (10.31 ppm) atom and the hydrogen atom in the 2-position of the aniline (8.08 ppm), see Figure 64, reveals that also the hydrogen atom in the 6-position of the aniline (8.10 ppm) interacts with the amide hydrogen. This minor interaction represents rapid exchange between conformations, because NOESY experiments, just as any other NMR experiments, show signals of all conformations averaged over time.

Evaluation of the discussed NOESY experiment, regarding the information from scalar coupling, allows complete consistent assignment of the signals to the respective sides of the molecule. Further, good agreement with crystallographic structure analysis of the same compound was found without any dissent.

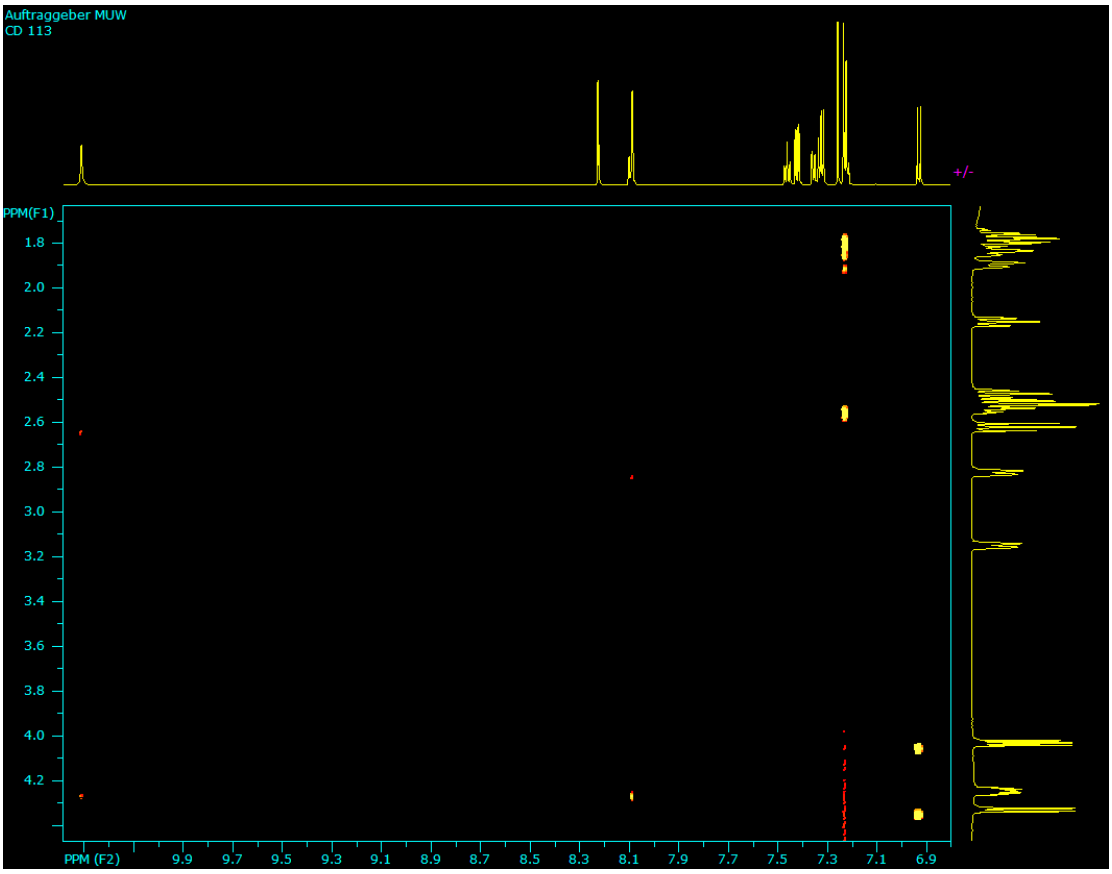


Figure 60. NOESY of 186- **aliphatic and aromatic interactions I.**

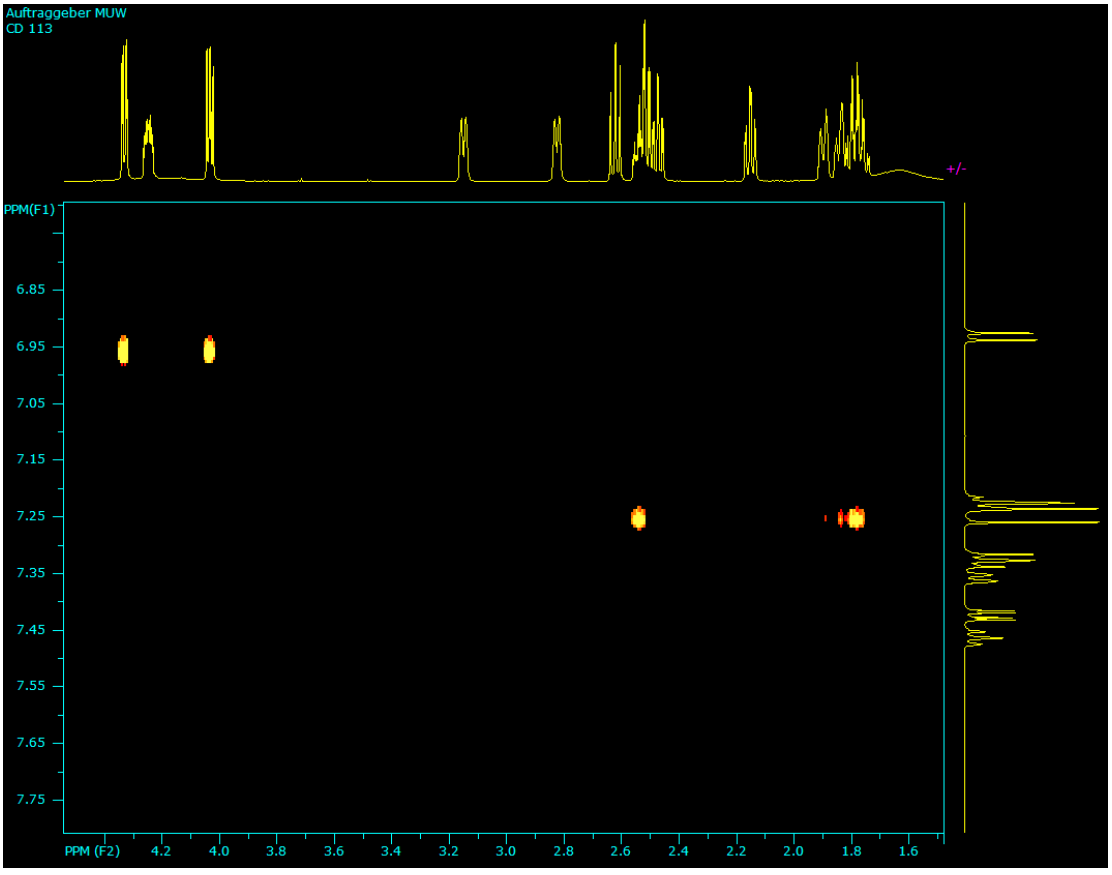


Figure 61. NOESY of 186- **aliphatic and aromatic interactions II.**

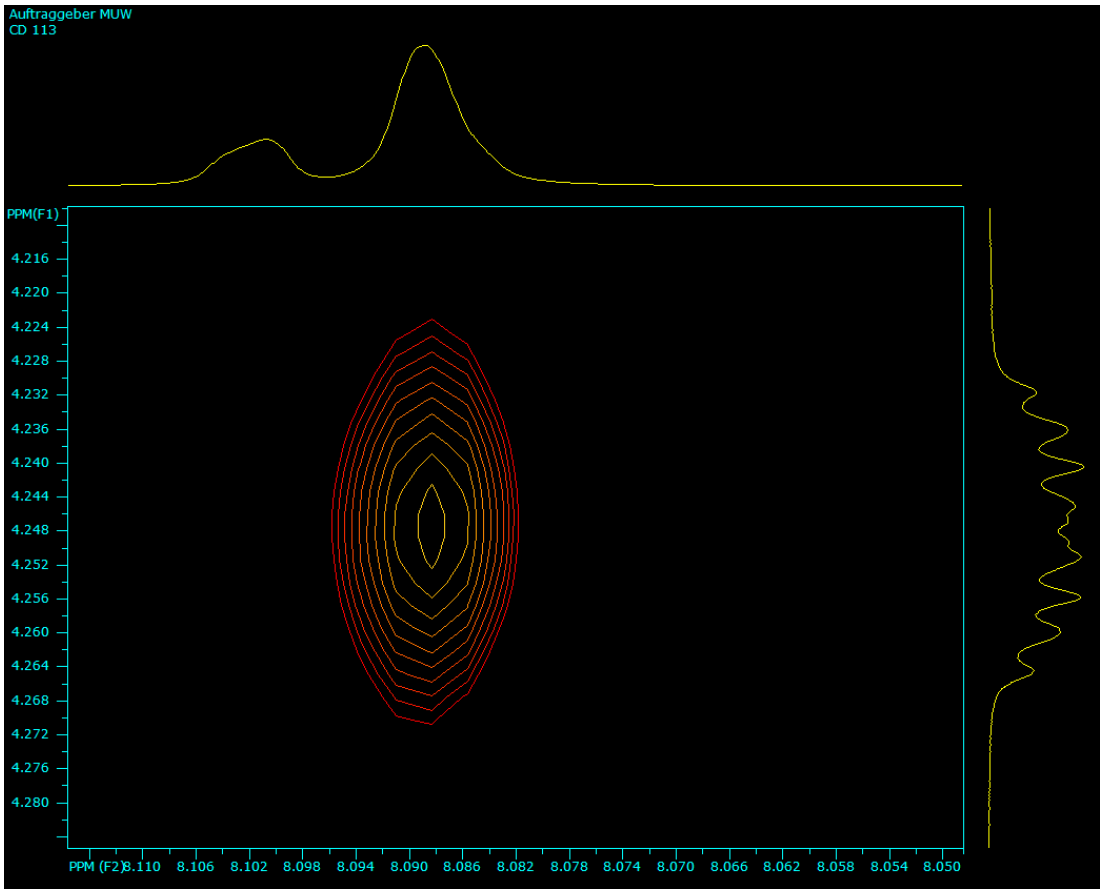


Figure 62. NOESY of 186- **cross-peak between methine hydrogen and H-2 of the aniline.**

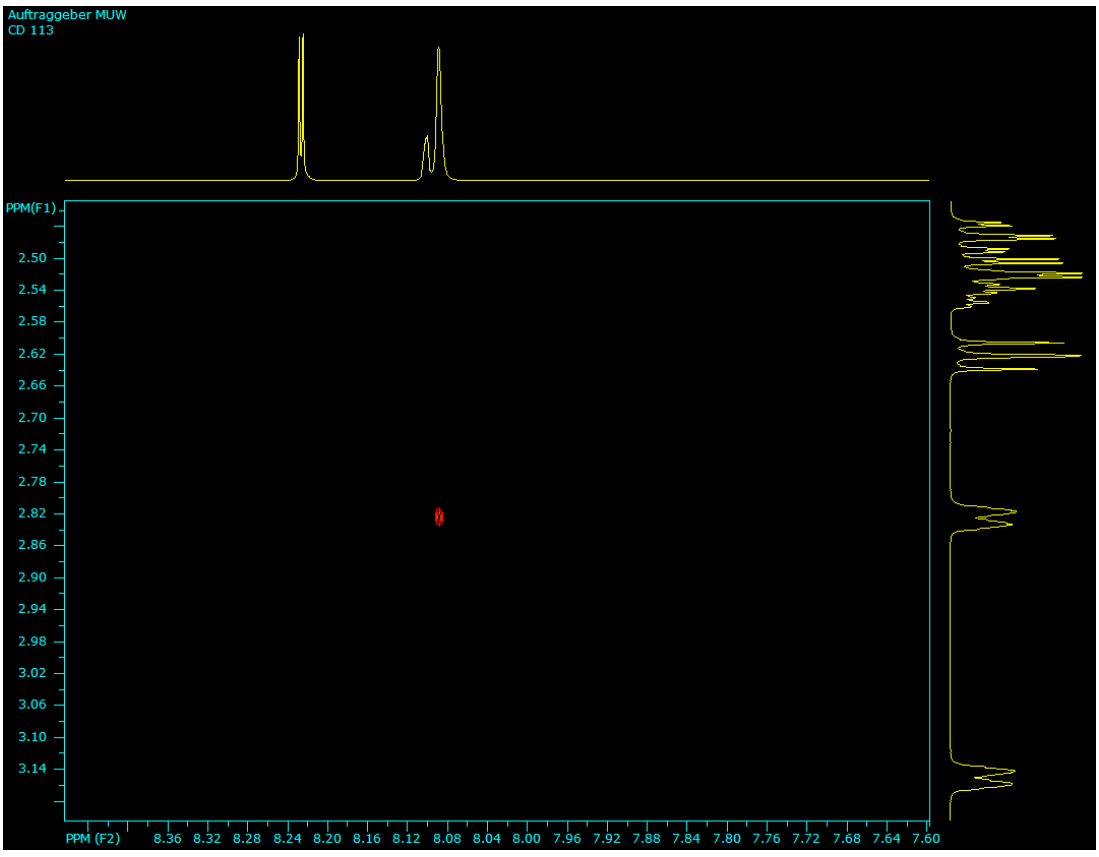


Figure 63. NOESY of 186- **cross-peak between the equatorial H-2 in the piperidine and H-2 of the aniline.**

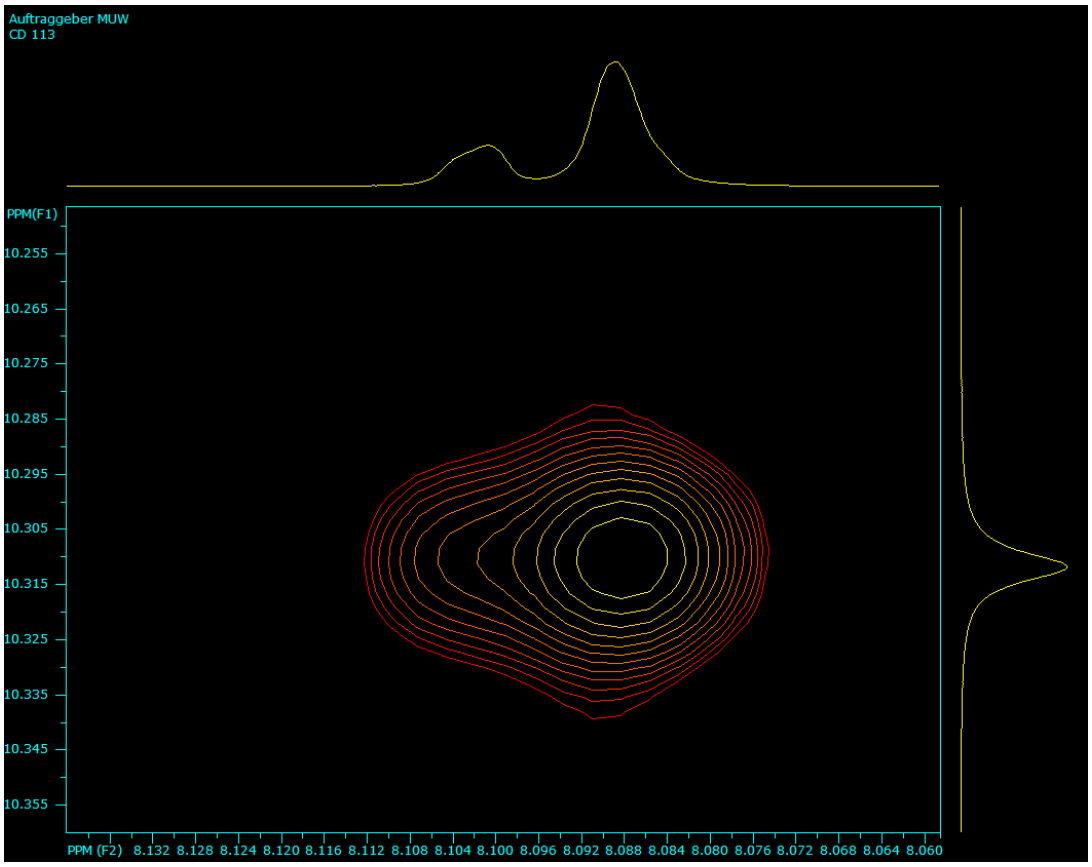


Figure 64. NOESY of 186- **cross-peak between amide hydrogen and H-2/H-6 of the aniline.**

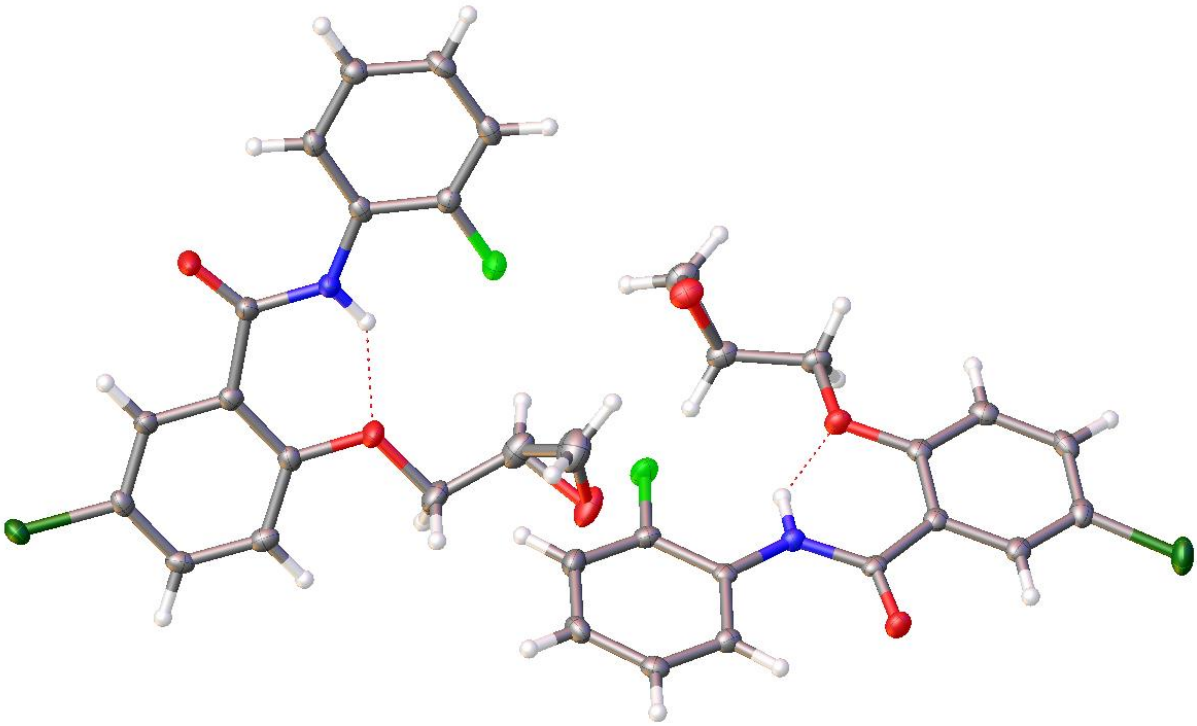


Figure 65. X-ray structure of 288**, which crystallized in two different structures.**

When the above discussed cooperative system is disturbed by presence of another acceptor as the fluorine atom in 5-chloro-*N*-(2-fluorophenyl)-2-(oxiran-2-ylmethoxy)benzamide (**288**)

then interaction between amide hydrogen and epoxide oxygen is no longer indicated. Distances in crystal structures are 3.82 Å in the right structure depicted in Figure 65, while in the left structure the epoxide is arranged in a manner that would not even let think about interactions because the oxygen is averted from the amide hydrogen. But even in this structures a three-centered hydrogen bond is observed between the amide, the phenyl ether and the fluorine atom. The distances of the noncovalent bonds from the amide hydrogen to the phenyl ether oxygen are 1.9 Å, while the distance between the hydrogen and the fluorine atom is 2.24 Å, in both structures. This indicates that fluorine atom and the oxygen in the oxirane are competing as acceptors for the amide hydrogen. Fluorine is in better position, because only the binding angle between the nitrogen and the aromatic ring is determining if an hydrogen bond is formed or not. Proximity of the oxirane, on the other hand, depends on three bonding angles (salicylic ring to oxygen, oxygen to methylene, and methylene to methine). As observed in the crystal structure of (*R*)-(+)-5-chloro-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)-benzamide (**100**), shown in Figure 66, interactions between oxirane and amide hydrogen are not well-marked, even without presence of another hydrogen acceptor. The bifurcation is distinctive in the cooperative system containing a three-centered and a two-centered interaction, see Figure 50.

Fortunately, also crystals of aminoalcohols featuring the *ortho*-fluorine anilide could be grown. According to x-ray structures of **184** and **188**, see Figure 68, the fluorine atom is involved in hydrogen bonding with the hydrogen of the amide and the methine hydrogen of the aminoalcohol. This additional hydrogen acceptor fluorine displaces the alcohol oxygen from the three-centered hydrogen bonding; a sketch is shown in Figure 67. The consequence regarding antimalarial activity is clearly shown, see Table 2. These *ortho*-fluorine compounds are drastically less active than their *meta*-trifluoromethyl analogs. This can be referred to the presence of the fluorine atom in ortho position of the aniline forces a drastical change in the dihedral bonding angles in the aminoalcohol region, which causes larger distances between the piperidine rings and the anilines in **184** and **188**.

A HSQC spectrum of **184** is shown in Figure 69. Both, axial and equatorial hydrogens of the 2- and 6-position of the piperidine have different shifts (axial hydrogens differ by 0.29 ppm and equatorial hydrogens differ by 0.28 ppm, respectively); this implies that they are diastereotopic which is, as pointed out above, explainable by a hindered rotation of the piperidine ring through the hydrogen bonding in the aminoalcohol motif.

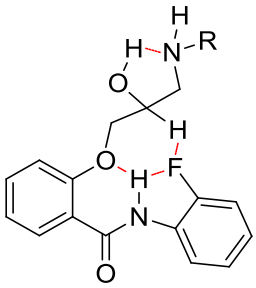


Figure 67. Hydrogen bonding network between amide and aminoalcohol site in *ortho*-fluoroaniline compounds.

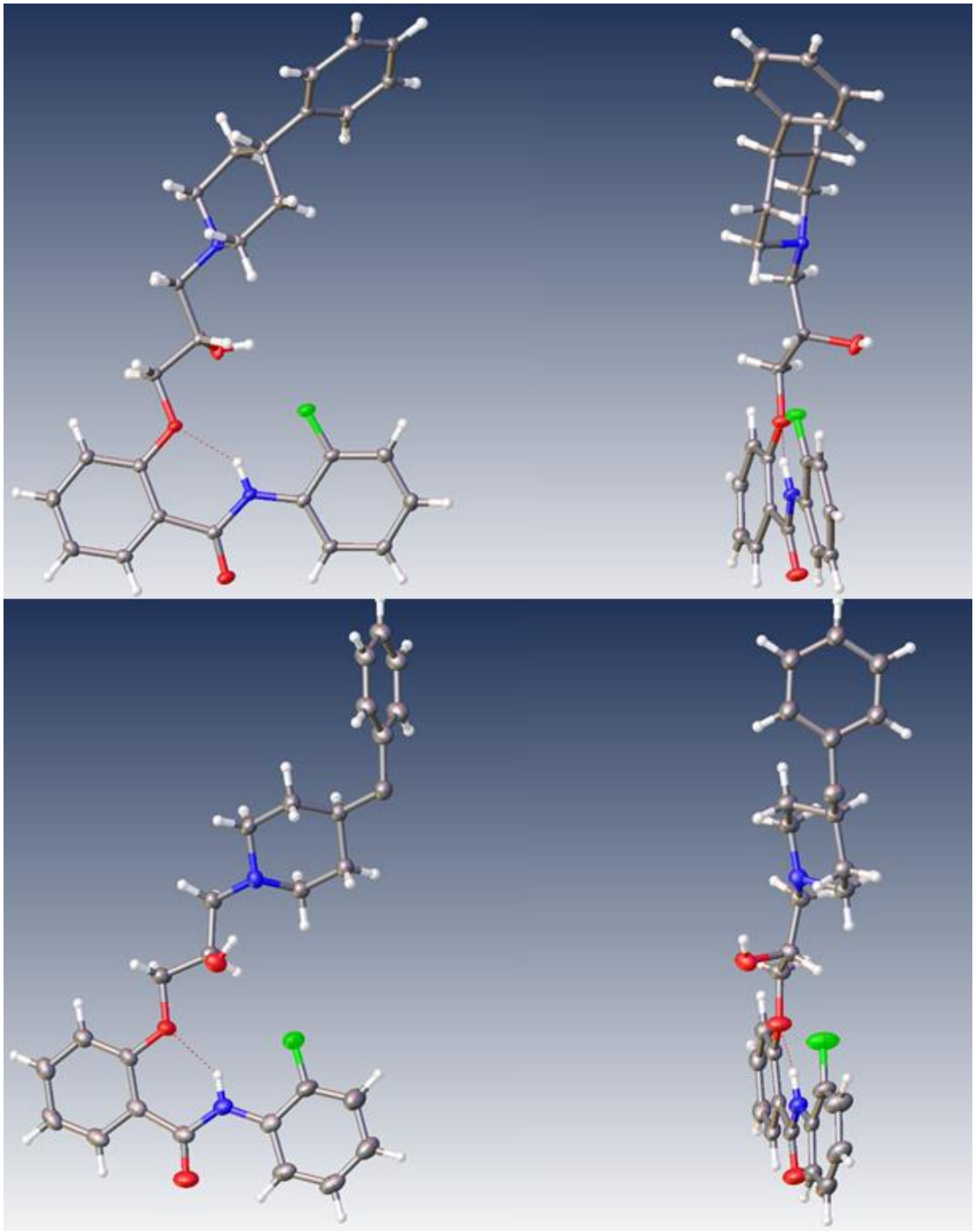


Figure 68. X-ray structures of 184 **(top row) and** 188 **(bottom row) in two angles each.**

Compound **184** shows reduced antimalarial activity (256 nM on NF54 and 105 nM on K1 strain, respectively) due to the influence of the *ortho*-fluoroaniline. In the case of **184** the structure consists of dimers; the formation of these dimers is only possible through the additional hydrogen acceptor in the form of the fluorine atom.

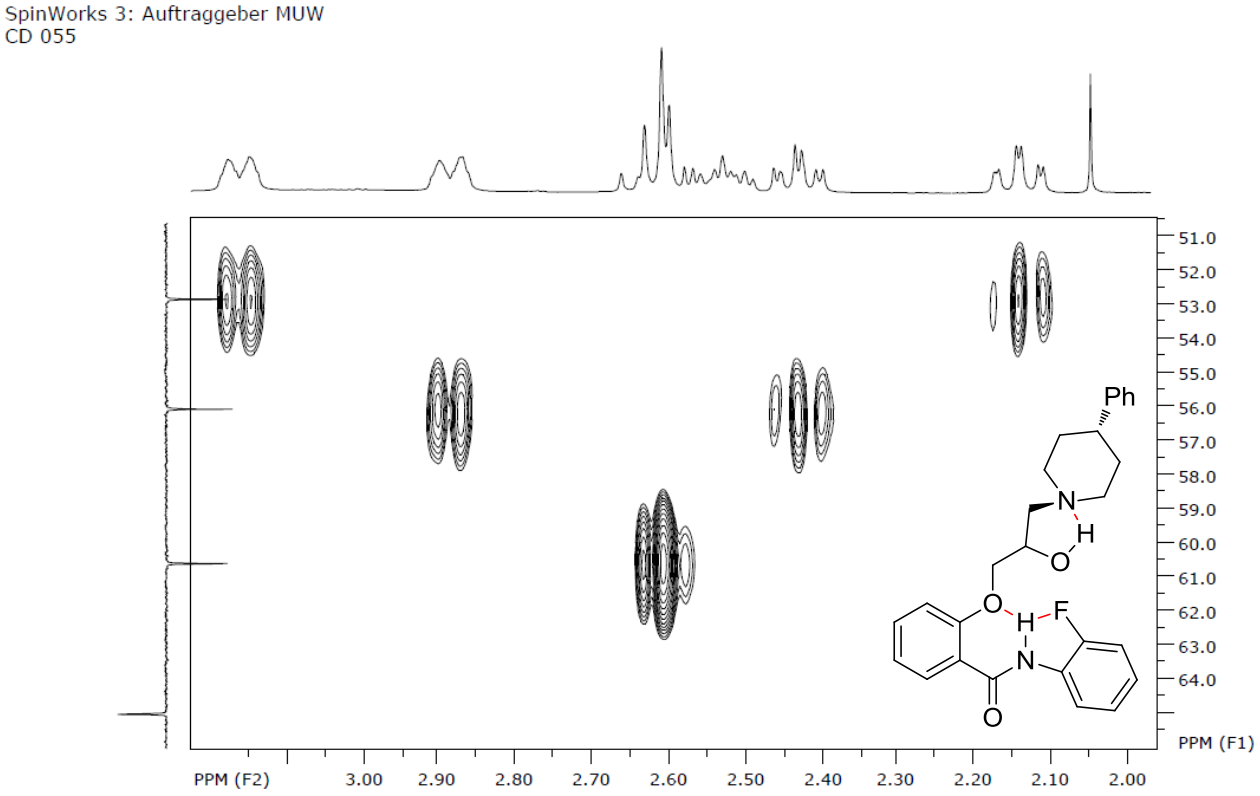


Figure 69. HSQC of 184**.**

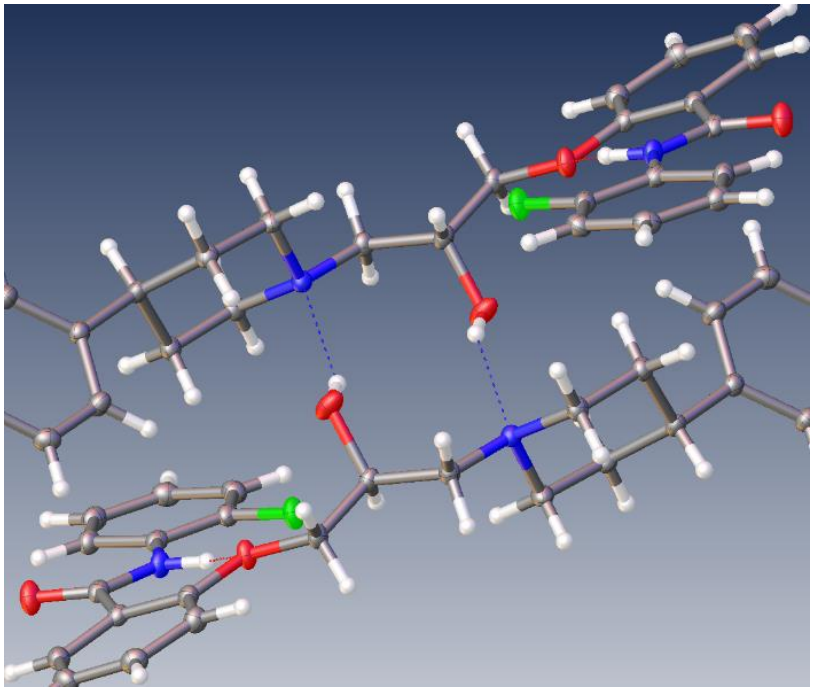


Figure 70. X-ray structure of 184 **(dimer).**

Distances and dihedral angles of several compounds were compared; data are shown in Table 18. The numbering for the atom labels is shown in Figure 71. As already pointed out above, distances between N(1) and O(3) are larger in ortho fluorine aniline compounds. The larger distances are related to larger angles in the dihedral angle (O(2)-C(8)-C(9)-O(3)) between the oxygen atoms O(2) and O(3) in the epoxide compounds as well as in the aminoalcohols. Further, it is observable that the dihedral angle in the salicylic ring and the amide nitrogen (C(2)-C(1)-C(7)-N(1)) near zero in the fluorine substituted crystal structures while highly active compounds show dihedral angles around 20°.

Other differences between both groups are the dihedral angles between the piperidine and the methine group (C(9)-C(10)-N(2)-C(p1)) as well as the dihedral angles between the oxygen and the nitrogen O(3)-C(9)-C(10)-N(2), which can be referred to communication between the amide and amine region.

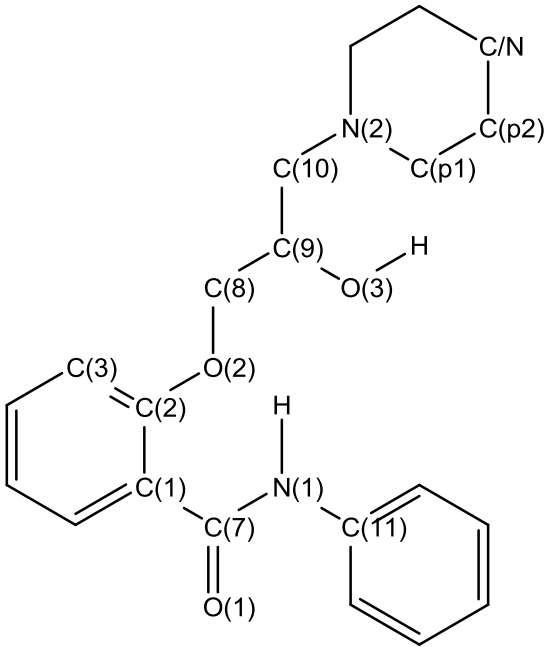


Figure 71. Atom numbering pattern in crystal structures, as used in Table 18.

Table 18. Distances and dihedral angles taken from crystal structures.

				2-F substituted							2H-substituted					
distances [Å]				**(*S*)-288**	**288**	**288**	**184**	**188** A	**188** B		**99** A	**99** B	**186** A	**186** B	**102**	**272**
N(1)-O(2)				2.653	2.657	2.667	2.676	2.659	2.658		2.624	2.648	2.749	2.537	2.64	2.627
N(1)-O(3)				4.563	4.656	5.59	4.440	4.209	4.207		3.936	4.060	3.451	3.384	3.639	3.634
O(3)-N(2)				-	-	-	3.099	2.733	2.735		-	-	2.965	2.876	2.773	2.897
O(2)-O(3)				3.133	3.163	3.638	2.864	2.832	2.833		2.888	2.925	2.653	2.666	2.718	2.691
torsion angles [°]																
O(2)	C(8)	C(9)	O(3)	84.2	163.8	88.9	69.9	-169.690	169.558		-68.1	-70.8	55.5	59.0	-60.9	58.0
C(2)	O(2)	C(8)	C(9)	174.4	178.2	169.7	-171.7	176.790	-176.872		-175.7	-173.9	-160.7	-173.2	-178.6	-172.2
C(8)	O(2)	C(2)	C(3)	4.6	-5.1	10.2	1.2	6.1	-6.0		2.3	-1.9	-23.9	-9.1	18.9	-7.0
C(7)	C(1)	C(2)	O(2)	-3.5	-2.6	-0.9	-2.5	2.8	-2.6		6.7	5.5	2.8	-1.5	3.0	-1.8
C(2)	C(1)	C(7)	N(1)	-0.8	-3.5	1.0	15.5	-1.2	1.1		-2.0	13.1	-20.2	-20.2	1.7	-19.5
C(11)	N(1)	C(7)	C(1)	-174.8	-173.8	179.7	178.2	177.770	-177.7		170.6	175.9	176.4	176.4	-177.2	-179.7
C(7)	N(1)	C(11)	C(12)	-175.6	178.4	-179.0	179.6	169.822	-169.900		19.1	-4.2	167.9	157.9	1.1	-179.7
C(11)	N(1)	C(7)	O(1)	4.0	5.2	-0.3	-0.5	1.7	1.7		-7.7	-1.0	-5.5	-5.5	1.7	-8.5
C(8)	C(9)	C(10)	N(2)	-	-	-	166.2	-168.1	169.1		-	-	-171.1	-170.6	167.6	-176.2
C(9)	C(10)	N(2)	C(p1)	-	-	-	-78.4	-78.1	78.2		-	-	-155.2	-60.0	71.8	-157.2
C(10)	N(2)	C(p1)	C(p2)	-	-	-	179.5	179.7	179.7		-	-	-175.4	174.2	-104.0	177.5
N(2)	C(p1)	C(p2)	O(5)	-	-	-	-	-	-		-	-	-	-	-9.9	-
O(3)	C(9)	C(10)	N(2)	-	-	-	-77.1	-48.8	48.7		-	-	68.3	-49.3	47.9	63.3

To investigate the conformation in polar environment, a series of NMR spectra were taken of 5-chloro-2-(2-hydroxy-3-(4-phenylpiperidin-1-yl)propoxy)-*N*-(3-(trifluoromethyl)phenyl)-benzamide (**186**) in different solvent mixtures ($CDCl_3$ and DMSO-d_6). Observation of changes of chemical shifts can reveal conformational changes when the solvent is gradually changed. The amide hydrogen and the hydrogen atom in the 6 position of the salicylic ring are nearly not affected from changes of polarity, see Figure 72. This indicates that the hydrogen bond between amide hydrogen and phenyl ether oxygen is still in place in polar environment. Only slight changes are observed for the chemical shift (+0.3 ppm from $CDCl_3$ to DMSO-d_6) of the H-2 in the aniline region. This may arise due to increased rotation of the aniline ring.

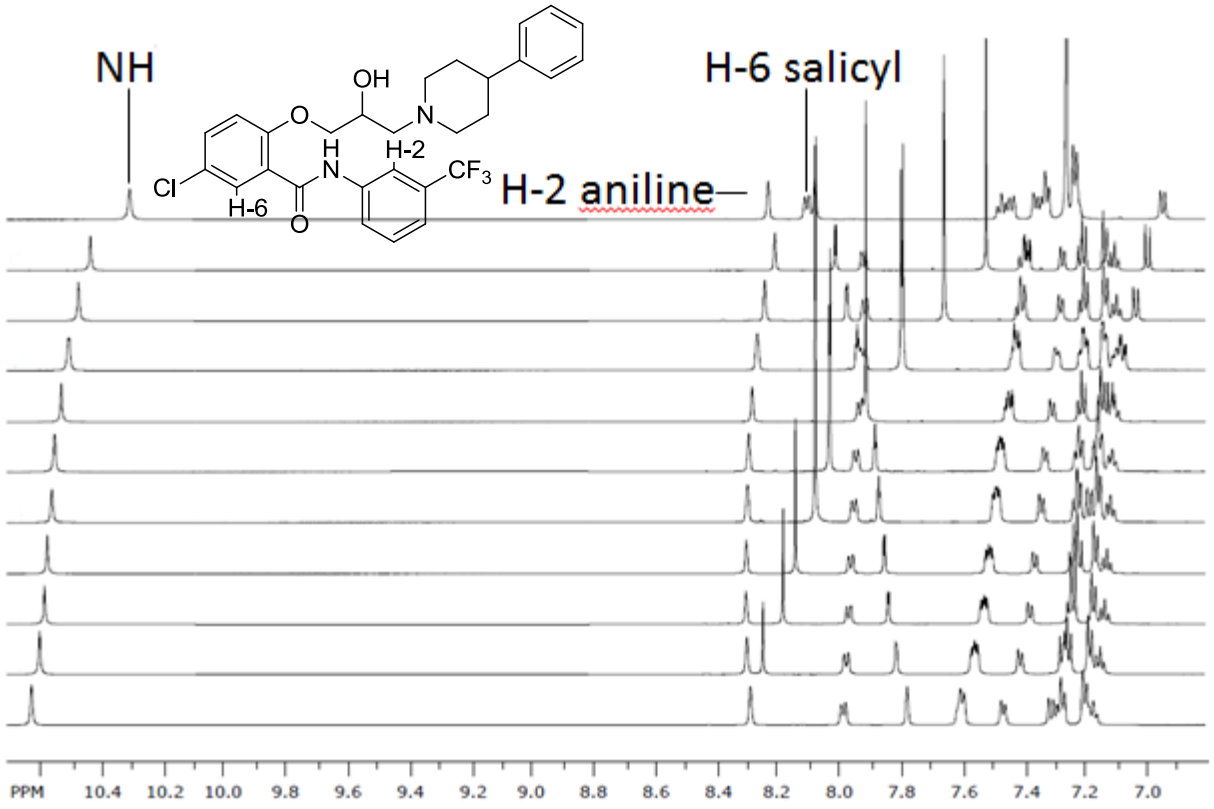


Figure 72. Conformational analysis of 186 **by solvent dependence of ^{1}H spectra – aromatic region. The top row shows a sample of** 186 **in pure $CDCl_3$, from top to bottom DMSO-d_6 content is ascending in steps of 10 percent, whereby the bottom row shows a spectrum in pure DMSO-d_6.**

In the aliphatic region, see Figure 73, the exchange of the alcohol proton is suppressed in presence of DMSO, and the relative positions of a hydrogen of the methylene group next to the phenyl ether oxygen and the methine hydrogen are switched; they have the nearly the same position when the ratio of $CDCl_3$ and DMSO-d_6 are 60:40. Further, the equatorial hydrogens at C-2 and C-6 in the piperidine ring change places; coalescence is reached when the ratio of $CDCl_3$ and DMSO-d_6 are 70:30. The axial hydrogen atoms, which are diastereotopic when their environment mainly consists of $CDCl_3$, also share nearly the same chemical shift

in polar environment. Addition of DMSO also cancels the well-defined coupling constants of the protons in the methylene group in vicinity of the amine nitrogen atom.

These observations indicate that the hydrogen bond between amine and alcohol is destroyed in presence of DMSO, while the three-centered interaction between amide hydrogen, phenyl ether and alcohol is still maintained in polar environment. Then, the 4-phenyl piperidine moiety is without fixation and is free to rotate starting with the methylene group.

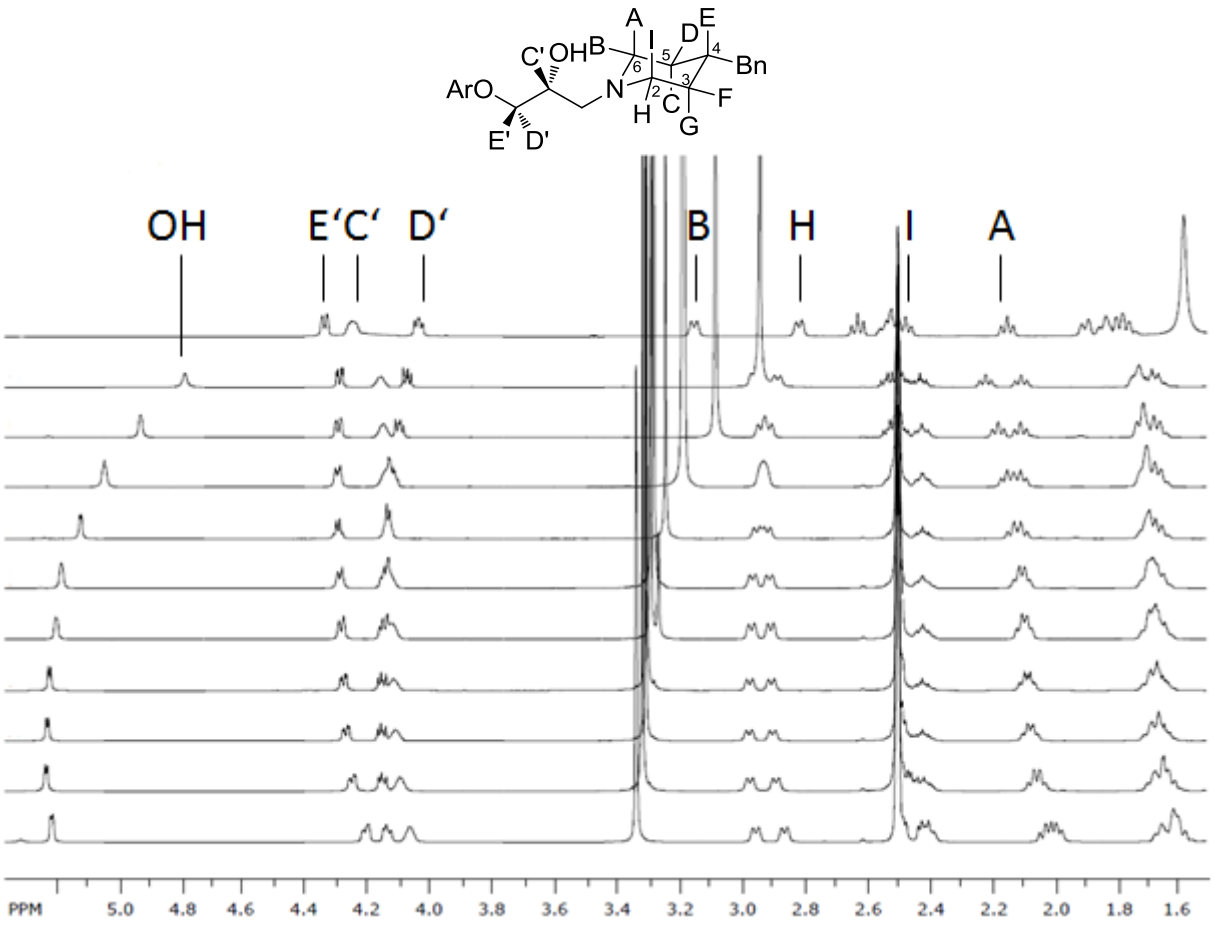


Figure 73. Conformational analysis of 186 **by solvent dependence of ^{1}H spectra – aliphatic region. The top row shows a sample of** 186 **in pure $CDCl_3$, from top to bottom DMSO-d_6 content is ascending in steps of 10 percent, whereby the bottom row shows a spectrum in pure DMSO-d_6. The same labels as in the simulation on p. 134 are used.**

The loss in activity if the three-centered bond is not formed was shown above by the low activity of tertiary amide compound **246** (Figure 51; 579.0 nM on NF54 and 172 nM on K1 strain, respectively). When the three-centered bond is formed but there is no cooperativity with the two-centered aminoalcohol hydrogen bond the activity is 256.0 nM on NF54 and 105.00 nM on K1 strain, respectively for **184**, and the activity of **188** 205.0 nM on NF54 and 74.00 nM on K1 strain, respectively.

The good agreement of observations made by NMR analysis and x-ray structure analysis suggest that the conformation is predominantly as discussed above in active compounds. Thus, the amide is forming a hydrogen bonding to the phenol ether oxygen and the alcohol oxygen; concomitantly the alcohol and the amine form another hydrogen bonding. As a direct consequence of this network of hydrogen bonds the alkyl part of the amine site and the aniline come in close proximity. If one of the hydrogen bondings is not formed, the contact between aniline and amine alkyl region cannot be established and activity is drastically lost. Each of the criteria must be met in order to establish the needed conformation to provide highly active compounds.

In order to be active against malaria, our aminoalcohols need to be in a hydrogen bonding network which hides away the polarity of the compound through intramolecular interactions. By doing so, no polar groups can interact with other molecules. This hypothesis is also applicable to commercial available aminoalcohols, which also have no more pharmacophore than the aminoalcohol motif, except the quinoline ring in some cases of course.

The compounds show all a very bad solubility, which is also in agreement with the intramolecular interactions. Furthermore, TLC staining with iodine did only develop brown spots after a very long period of time (hours), which is an indication that the alcohol hydrogen is protecting the lone-pair of the nitrogen atom. Therefore, slight staining occurs only slowly, within hours.

3. Conclusion

During this thesis more than 240 compounds were synthesized and characterized. Among these are 125 molecules with antimalarial activity. One of the highly ambitioned goals which were set at the beginning of the thesis was to exceed the potency of approved antimalarial drugs, such as lumefantrine (**20**) and artesunate (**27**). A comparison with activities of 37 "current and future" (published in 2012) antimalarial drugs[85], partly ascertained from persons also directly involved in the *in vitro* and *in vivo* testings of compounds presented within this thesis, shows that this goal was accomplished. Table 19 (page 582) shows the activities found in the above mentioned publication. Therein, lumefantrine (**20**) shows IC_{50} values of 2.8 nM (NF54) and 1.1 nM (K1) and artesunate (**27**) shows IC_{50} values of 3.5 nM (NF54) and 2.6 nM (K1). Within this thesis 34 compounds are presented having a lower IC_{50} value than 2.8 nM on the NF54 strain and 41 compounds having a lower IC_{50} value than 1.1 nM on the K1 strain. The most potent compound (**210**) on the NF54 strain presented in this thesis showed an IC_{50} value of 0.92 nM, in the above discussed publication only artemisone (**42**), and atovaquone (**65**) showed higher potencies, while halofantrine (**21**) showed roughly the same (0.9 nM) activity. The most potent compound (**207**) on the K1 strain presented in this thesis showed an IC_{50} value of 0.19 nM; again, halofantrine (**21**) showed roughly the same (0.2 nM) activity.

Activity in an animal model was shown in many cases. Furthermore, complete cure was impressively demonstrated for compounds **194**, **249**, **97**, and **247**. As far as known, no exclusion criteria by testing for hERG channel blocking, inhibition of adrenergic receptors, cytotoxicity, and mutagenicity were observed for benzhydryl piperazine compound **249**.

The relevance of the stereogenic center towards antimalarial activity in the presented scaffold was investigated. The investigations lead to the conclusion that the activity does not depend on the configuration the above mentioned stereogenic center. Also values found for microsome stability and cytotoxicity on Hep G2 cells were at comparable levels for both enantiopure forms of **194**.

In addition to the above discussed results, which exceeded all expectations, the structure of highly active compounds was elucidated in solution by methods of NMR spectroscopy. Also crystallographic data are available for highly active compounds, such as the most promising compound **249**, which represents the structure in the solid state. The structures in solution

and in the solid state are consistent, which again confirm the assumptions that all hydrogen donors and acceptors of highly active compounds have to form intramolecular hydrogen bonds. This hides away all polar information of the molecules, leaving only apolar regions to communicate with other molecules. This is also reflected in bad solubility, an issue that is also known for the marketed lumefantrine (**20**).[133]

One of the most important requirements regarding malaria, cheapness of the medications due to poverty in the endemic regions, was also met. Costs for building blocks for the most promising candidate **249** aggregate to less than 1€/g on a 100g scale when unambitious yields of 80% for each of the three synthetic steps are calculated, whereas during the thesis was also shown that convergent synthesis is also applicable. Beyond these achievements, structures of highly active compounds were elucidated and structural necessities were hypothesized.

To sum up, a malaria project was started in 2004 with propafenone (**68**), a class 1c antiarrhythmic drug used for treatment of ventricular arrhythmia, at the Medical University of Vienna. The scaffold was changed to the amidophenoxypropanolamine scaffold (Figure 15, p. 36). A hERG targeting motif was chemically engineered to a novel antimalarial scaffold. A structure-activity relationship was established leading to the salicylanilide motif as most promising amide component. During this thesis, the SAR was further supplemented, leading to highly auspicious candidates for treating malaria. Even full cures in animal experiments were demonstrated.

4. Experimental Part

4.1 General Information

4.1.1 Materials and Methods

Starting materials (amines, salicylic acid derivatives, reagents) were purchased from various commercial sources and were used without further purification. Solvents used in synthesis and chromatographic purification steps were distilled prior use (ethyl acetate, petrol ether, *n*-hexane). All air and moisture sensitive reactions were performed in vessels dried by repeated heating under vacuum (heat gun) followed by purging with dry argon. Reaction procedures were carried out under slight overpressure of argon (balloon) in dry solvents. Sensitive reagents or solutions were transferred *via* syringe or cannula through rubber septa.

4.1.2 Reaction Monitoring and Purification of Compounds

Reaction monitoring was performed by thin layer chromatography (TLC) on Merck silica gel 60-F_{254} glass plates, or on Macherey & Nagel POLYGRAM SIL G/UV 254 foils. The plates were developed with mixtures of hexane/ethyl acetate, neat ethyl acetate, methanol/ethyl acetate/aqueous ammonia. Compound spots were visualized by UV (254 nm) irradiation in a dual lamp CAMAG UV cabinet or in TLC-chamber containing iodine adsorbed on silica gel. Purification of compounds was performed by preparative separation by middle pressure chromatography (MPLC) on silica gel 60 from Merck (0.040-0.063 µm, 240-400 mesh). Stationary phase material and MPLC system consisting of unique home-built columns, Fluid Metering pump and Amersham Superfrac fraction collector were provided by H. Gstach from private fund.

4.1.3 Analytical Characterization

NMR Spectroscopy[134]

NMR-spectra were recorded on Bruker Avance 400 MHz and 600 MHz spectrometers (NMR-Center at the Faculty of Chemistry, University of Vienna). The software used for processing of 1D- (^{1}H, ^{13}C) and 2D- (COSY, HMBC, HSQC) NMR-spectra was SpinWorks 3.1.8.1 (copyright 2010, Kirk Marat, University of Manitoba). Coupling constants (*J*) are given in Hertz (Hz) and

refer to 1st order interpretation (apparent coupling constants J_{app} are given). ^{x}J refers to homonuclear H-H coupling over x bonds, $^{x}J_{HF}$ refers to heteronuclear $^{1}H/^{19}F$ coupling over x bonds, $_{x}J_{CF}$ refers to heteronuclear $^{13}C/^{19}F$ coupling over x bonds; $^{TS}J_{CF}$ refers to through space coupling. Solvents used for NMR spectroscopy: $CDCl_3$, chloroform-d_1 (CAS RN 865-49-6), was filtered through basic, activated aluminum oxide (Sigma Aldrich) prior use. DMSO-d_6, hexadeutero dimethyl sulfoxide (CAS RN 2206-27-1), was stored over molecular sieve (4Å). 2-D NMR techniques used for assignment of ^{1}H and ^{13}C resonance signals: HSQC (Hetero-nuclear Single Quantum Coherence), HMBC (Heteronuclear Mutliple Bond Correlation), and COSY (Correlation Spectroscopy). Chemical shift calibration[135]: $CDCl_3$: 1H δ = 7.26; ^{13}C δ = 77.16; DMSO-d_6: ^{1}H δ = 2.50; ^{13}C δ = 39.52.

Mass Spectroscopy

HRMS

Mass spectra are HRMS (high resolution mass spectra). These were taken with a Maxis Bruker spectrometer. The kind of ionization was ESI (electron spray ionization) and a TOF (time of flight) analyzer was used in all cases.

LCMS

LCMS was performed with a Waters Autopurification system. Mass spectra were taken with an ACQUITY QDa Detector (Waters Corporation, Milford, MA, USA). ESI+ and ESI- ionization were used.

HPLC

Chiral HPLC (normal phase) was performed with a module system from Shimadzu (SIL-20AHT auto sampler, CTO-20AC column thermostat, CBM-20A controller, LC-Solution software, UV-detector SPD-20A with temperature adjusted to 35°C) using a LC-20AT pump with LPGE valve and low pressure gradient unit. Low pressure gradient settings were used; solvents were mixed prior to entering the system without additional pressure.

Melting Point

Melting points (mp) were determined with a Bausch & Lomb microscope equipped with a Kofler melting-stage and are uncorrected.

Optical Rotation

Optical rotation was measured on a Perkin Elmer Polarimeter 341 in combination with a Julabo 5 thermostat. The measured temperature is stated in all cases. The wavelength of the light used is 589 nm (sodium D line) in all cases.

Crystallographic Structure Determination[134]

X-ray diffraction measurements were performed on Bruker D8 VENTURE diffractometers. Single crystals were positioned at 50, 35, and 40 mm from the detector, and 2281, 2534, and 3016 frames were measured, each for 16, 5.6, and 24 s over a 0.4° scan width for 9, 13, and 14, correspondingly. The data were processed using SAINT software[136]. Crystal data, data collection parameters and structure refinement details are given below the respective structure. The structures were solved by direct methods and refined by full-matrix least-squares techniques. Non-H atoms were refined with anisotropic displacement parameters. H atoms were inserted in the calculated positions and refined with a riding model. The following computer programs were used: structure solution, SHELXS-97, and refinement, SHELXL-97[137]; molecular diagrams, ORTEP[137].

4.1.4 Biological Data

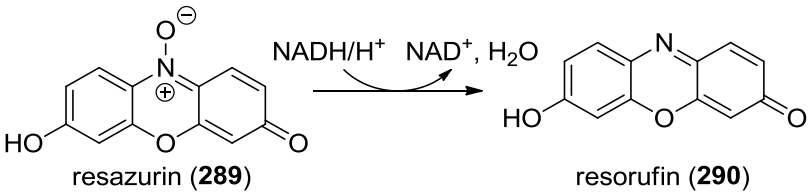
Assessment of antimalarial potency (IC_{50})

A [^{3}H]-hypoxanthine incorporation assay was used as markers for inhibition of parasite growth as previously described.[138] IC_{50} values have been assessed for K1 as well as for NF54 strain of *P. falciparum*. Chloroquine (**6**), lumefantrine (**20**), and artesunate (**27**) were included as controls. These tests were performed at Swiss Tropical and Public Health Institute (Swiss TPH).

Cytotoxicity on Hep G2 liver cells

Hep G2 cells (10,000 cells/well) were cultured in a 96 well format for 48 hours. The incubated cells were exposed to test compounds (1 and 10 µM, respectively) dissolved in culture medium (Minimal essential medium, 10% FBS, nonessential amino acids 1mM, 0.2% DMSO) for 72 hours. Viability was assessed using resazurin (alamarBlue®) sodium salt.

Resazurin (**289**) is reduced to resorufin (**290**), a highly fluorescent compound that is red in color. Viable cells continuously convert resazurin to resorufin, see Scheme 15. The percentage of viability was determined by comparing to an untreated control (100% viability), whereas staurosporin was used as positive control.[139] These tests were performed at Marinomed Biotechnologie GmbH.



resazurin (**289**) resorufin (**290**)

Scheme 15. Reduction of resazurin (289**) to fluorescent resorufin (**290**).**

Microsomal stability

Liver microsomes are a good source for drug metabolizing enzymes including cytochrome P-450. These subcellular particles are derived from the endoplasmic reticulum of hepatic cells by homogenization of liver. The microsomes are incubated (37°C) with test compounds in presence of co-factor NADPH. The disappearance of test compound was monitored over a 60 minute time period.

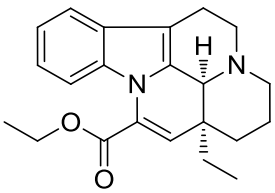
Reactions are terminated after (0), 5, 15, 30, and 60 min, respectively by the addition of methanol. Supernatant after centrifugation is analyzed *via* HPLC. Biological half-life of the substances was calculated from this data. Vinpocetin (**291**), see Figure 74, was used as a de-

gradable control (half-life of **291** is about 3 min) to guarantee the functionality of the membranes, because in this assay microsome activity was highly varying. Hence, half-lives were referenced to the half-life of vinpocetin (**291**) as pointed out in the following formula:

$$t\_1/2\ normalized\ to\ vin = \frac{t\_1/2\ of\ tested\ compound}{t\_1/2\ of\ vinpocetin}$$

In addition, compound **194** was added as positive control. When the referenced half-life of **194** was below 10 the experiments were repeated.

Where possible, an internal standard substance was included into the protocol to account for potential loss of substance during the preparation process. Very highly cleared compounds are generally considered to be unfavorable as they are likely to be rapidly cleared *in vivo* resulting in a short duration of action.[140] These tests were performed at Marinomed Biotechnologie GmbH.



vinpocetin (**291**)

Figure 74. Structure of reference compound vinpocetin (291**).**

Acute toxicity

Acute toxicity was determined using NMRI mice, the same kind of mice used later in the Peters' 4-day suppression test, prior first *in vivo* experiments to see adverse effects. The first application was 5mg/kg, 2 hours later 15mg/kg, 2 hours later 30mg/kg, and again 2 hours later 50mg/kg. Observations and were noted and toxicity derived from these observations are listed in Table 14. These tests were performed at Swiss TPH.

In vivo assay: Peters' 4-day suppression test against *Plasmodium berghei*

The four day Peter´s suppression test[128] is the most widely used test. The efficacy of a compound is assessed by comparison of blood parasitemia and mouse survival time of treated and untreated mice. Starting on day 0, mice of the experimental group (NMRI mice, female, age: 3-4 weeks, ~ 22 g, three each per compound) are infected with 0.2 mL of aliquot ($2*10^7$ parasitized erythrocytes, *Plasmodium berghei* ANKA 676m1cl1) intraperitoneally. Parasitemia of placebo treated mice (control group, also three each per series) is compared with the test drug treated group. The drugs are prepared at required concentration, as a solution or

suspension containing 7% Tween80/3% ethanol and administered 4 h post infection by appropriate routes.

On day 1 to 3 (24, 48, and 72 h after infection), the experimental groups are treated again (same dose and same route) as on day 0. On day 4, 96 h after infection, blood is taken and parasitemia is determined by FACS analysis. The transgenic line *Plasmodium berghei* ANKA 676m1cl1 expresses GFP-Luciferase constitutively during the whole life cycle, which allows determination of parasitemia easily by FACS analysis. The difference between the mean value of the control group (100%) and those of the experimental groups is calculated and expressed as percent reduction or activity using the following equation:

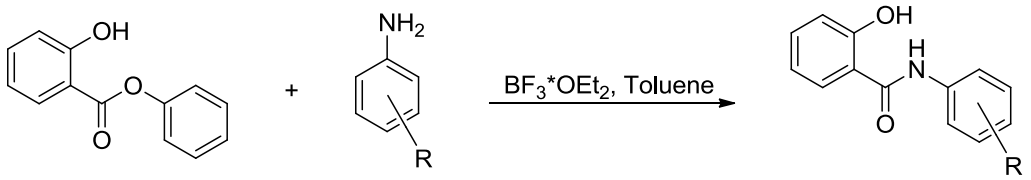
$$Activity = 100 - \frac{mean\ parasitemia\ treated}{mean\ parasitemia\ control} * 100$$

Untreated control mice typically die approximately one week after infection. For treated mice the survival-time (in days) is recorded and the mean survival time is calculated in comparison with the untreated and standard drug treated groups. Mice without parasitemia on day 30 of post-infection are considered cured. These tests were performed at Swiss TPH.

4.2 General Procedures

Most of the reactions performed follow the same protocols, below general procedures are described. While there are three different procedures that were carried out for the preparation of various anilides, only one protocol was used for alkylation and also only one protocol was used for epoxide opening to give desired aminoalcohols.

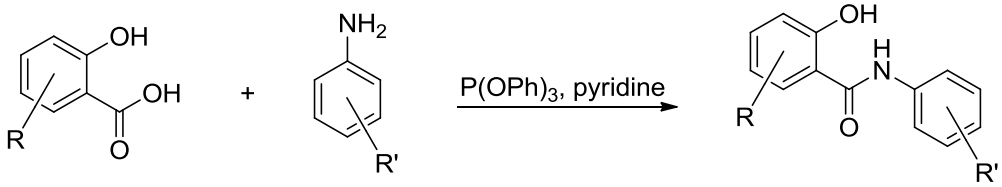
General Procedure A



BF_3*OEt_2 (1 eq) was added to a solution of phenyl 2-hydroxybenzoate (1 eq) and the particular aniline (1 eq) in toluene (reaction molarity = 1 M).

After 12 h of stirring at room temperature, the reaction mixture was filtered, and the precipitation was washed with hexane or diisopropyl ether.

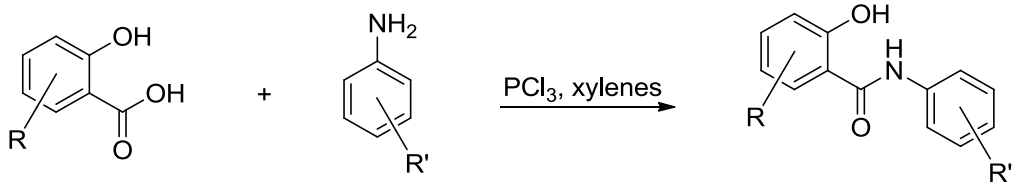
General Procedure B



Triphenyl phosphite (1 eq) was added to a stirred suspension of the particular salicylic acid (1 eq) and the particular aniline (1 eq) in pyridine (reaction molarity = 2 M). The reaction mixture was stirred at 80°C for 16 h.

Then, pyridine was widely removed by rotary evaporation. By addition of 6 M HCl, pH was adjusted to 1. Ethyl acetate was added and the layers were separated. The organic layer was washed three times with 2 M HCl, once each with water, saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The product was crystallized from diisopropyl ether, filtered and washed with diisopropyl ether.

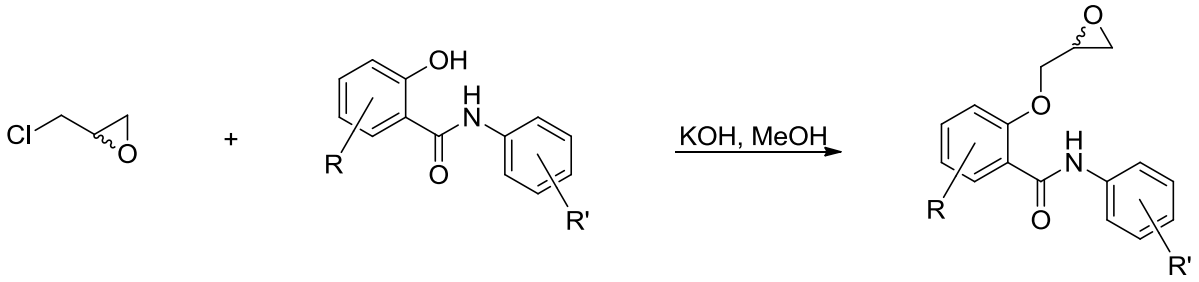
General Procedure C



To a stirred solution of the particular salicylic acid (1 eq) and the particular aniline (1 eq) in xylenes (reaction molarity = 0.4 M) at 160°C was added phosphorous trichloride (0.4 eq). After 30 min, the reaction mixture was rapidly transferred while hot by decanting to a beaker and allowed to cool under rapid stirring.

As the solution cooled the precipitated product and was filtered and washed with hexane or diisopropyl ether.

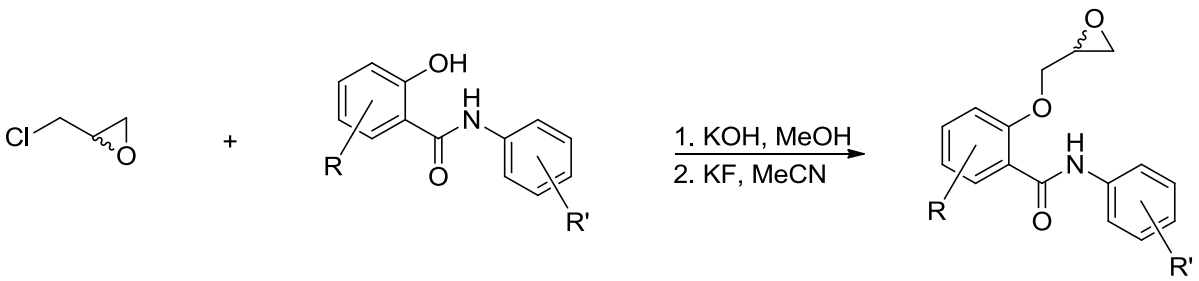
General Procedure D



Potassium hydroxide (1 eq) was loaded to a round bottom flask. MeOH and the particular salicyl anilide (1 eq) were added immediately. MeOH was removed on *via* rotary evaporation when the mixture was homogenous. An excess of (±)-epichlorohydrin (10 eq) was added to the solid residue, and the mixture was stirred at 85°C.

After complete consumption of anilide was observed, usually 20 min, unreacted epichlorohydrin was removed. The residue was extracted three times with ethyl acetate. The extracts were dried over Na_2SO_4, and concentrated under reduced pressure. The product was purified through column chromatography (ethyl acetate:hexane = 1:1).

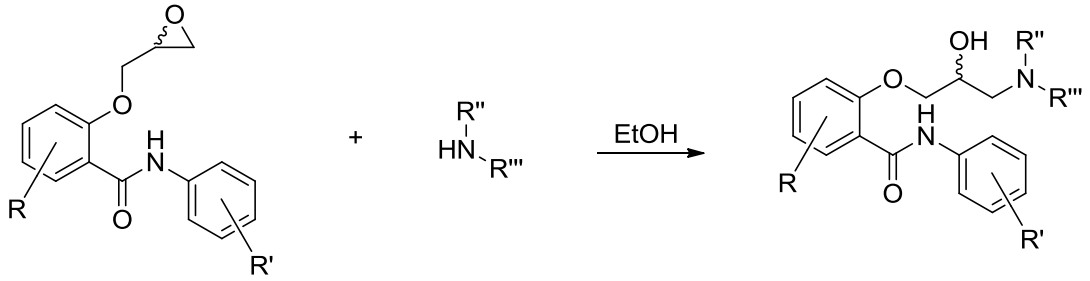
General Procedure D (KF method)[123]



Potassium hydroxide (1 eq) was loaded to a round bottom flask. MeOH and the particular salicyl anilide (1 eq) were added immediately. MeOH was removed on *via* rotary evaporation when the mixture was homogenous. An excess of (±)-epichlorohydrin (10 eq) was added to the solid residue, and the mixture was stirred at 85°C.

After complete consumption of anilide was observed, usually 20 min, unreacted epichlorohydrin was removed. KF on Celite (2 eq) and acetonitrile were added and the mixture was refluxed for 18 h. After full conversion the reaction mixture was filtrated to remove Celite. EtOAc and water were used to extract the solids. The layers were separated and the organic layer was dried over $NaSO_4$ and concentrated under reduced pressure. If needed, the product was purified through column chromatography (ethyl acetate:hexane=1:1).

General Procedure E



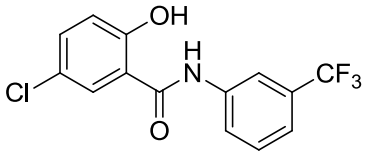
The particular amine (1 eq) and the particular 2-(oxiran-2-ylmethoxy)-*N*-phenylbenzamide (1 eq) in EtOH (4 mL) were stirred for 8 h at 80°C in a screw cap tube.

Then, the reaction mixture was concentrated under reduced pressure and the product was obtained after purification by column chromatography (ethyl acetate containing 2% MeOH).

4.3 Syntheses

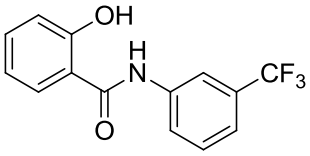
4.3.1 Anilides

5-chloro-2-hydroxy-*N*-(3-(trifluoromethyl)phenyl)benzamide (72)



72 was prepared following **general procedure B**, yielding 0.898 g (49%) of the desired product. Characterization (NMR) was in accordance with previously reported values (CAS: 1580-42-3[141]).

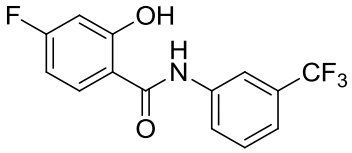
2-hydroxy-*N*-(3-(trifluoromethyl)phenyl)benzamide (75)



75 was prepared following **general procedure C**, yielding 45.706 g (87%) of the desired product. Characterization (NMR) was in accordance with previously reported values (CAS: 587-49-5[142]).

Melting point: 177-179°C.

4-fluoro-2-hydroxy-*N*-(3-(trifluoromethyl)phenyl)benzamide (77)



77 was prepared following **general procedure C**, yielding 0.619 g (63%) of the desired product.

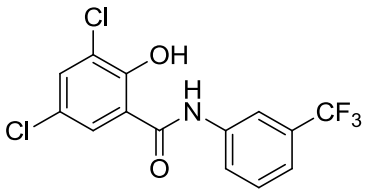
^{1}H NMR (400 MHz, DMSO-d$_6$, 23 °C): δ = 6.79-6.87 (m, 2H, *H*-3,5 salicyl), 7.48 (d, ^{3}J = 7.7, 1H, *H*-4 aniline), 7.61 (dd[t], ^{3}J = 7.9, 1H, *H*-5 aniline), 7.94 (d, ^{3}J = 8.4, 1H, *H*-6 aniline), 8.01 (m [dd], ^{3}J = 8.7, J_{HF} = 6.7, 1H, *H*-6 salicyl), 8.20 (br s, 1H, *H*-2 aniline), 10.55 (br s, 1H, CON*H*), 12.03 (br s, 1H, ArO*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d$_6$, 23 °C): δ = 103.81 ($^{2}J_{CF}$ = 23.9, *C*-3 salicyl), 106.58 ($^{2}J_{CF}$ = 22.1, *C*-5 salicyl), 114.79 ($^{4}J_{CF}$ = 2.7, *C*-1 salicyl), 116.91 (q, $^{3}J_{CF}$ = 4.1, *C*-2 aniline), 120.43 (q,

$^{3}J_{CF}$ = 3.8, *C*-4 aniline), 124.07 (q, $^{1}J_{CF}$ = -271.9, *C*F_3 aniline), 124.40 (*C*-6 aniline), 129.44 (q, $^{2}J_{CF}$ = 32.2, *C*-3 aniline), 129.92 (*C*-5 aniline), 131.54 ($^{3}J_{CF}$ = 11.3, *C*-6 salicyl), 138.97 (*C*-1 aniline), 160.22 ($^{3}J_{CF}$ = 12.9, *C*-2 salicyl), 164.98 ($^{1}J_{CF}$ = -250.0, C_q-4 salicyl), 166.08 (*C*ONH).

Melting point: 190°C.

3,5-dichloro-2-hydroxy-*N*-(3-(trifluoromethyl)phenyl)benzamide (79)



79 (CAS: 796-61-2) was prepared following **general procedure B**, yielding 1.643 g (44%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 7.53 (d, ^{3}J = 7.7, 1H, *H*-4 aniline), 7.64 (dd[t], ^{3}J = 7.8, 1H, *H*-5 aniline), 7.79-7.82 (m, 1H, *H*-4 salicyl), 7.98 (d, ^{3}J = 8.2, 1H, *H*-6 aniline), 8.06-8.08 (m, 1H, *H*-6 salicyl), 8.13 (br s, 1H, *H*-2 aniline), 10.82 (br s, 1H, CON*H*), 11.84-12.81 (br, 1H, ArO*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ 117.54 (q, $^{3}J_{CF}$ = 3.9, *C*-2 aniline), = 119.08 (C_q-1 salicyl), 121.11 (q, $^{3}J_{CF}$ = 3.7, *C*-2 aniline), 118.93 (C_q-3 salicyl), 122.86 (C_q-5 salicyl), 124.25 (q, $^{1}J_{CF}$ = -272.3, *C*F_3 aniline), 126.12 (*C*-6 aniline), 127.20 (*C*-6 salicyl), 129.54 (q, $^{2}J_{CF}$ = 31.5, *C*-3 in CF_3 aniline), 129.87 (*C*-5 aniline), 130.74 (*C*-4 salicyl), 140.91 (*C*-1 aniline), 164.96 (*C*-2 salicyl), 165.65 (*C*ONH).

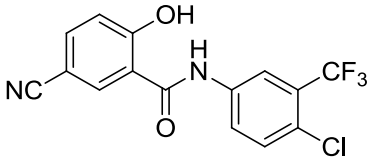
Na Salt:

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 7.24 (dd, ^{4}J = 3.0, 1H, *H*-4 salicyl), 7.33 (d, ^{3}J = 7.7, 1H, *H*-4 aniline), 7.53 (dd[t], ^{3}J = 8.0, 1H, *H*-5 aniline), 7.63 (d, ^{4}J = 3.0, 1H, *H*-6 salicyl), 7.75 (d, ^{3}J = 8.4, 1H, *H*-6 aniline), 8.28 (br s, 1H, *H*-2 aniline), 15.21 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 110.99 (C_q-5 salicyl), 115.34 (q, $^{3}J_{CF}$ = 4.0, *C*-2 aniline), 118.46 (q, $^{3}J_{CF}$ = 3.8, *C*-4 aniline), 118.93 (C_q-3 salicyl), 122.86 (*C*-6 aniline), 124.25 (q, $^{1}J_{CF}$ = -272.3, *C*F_3 aniline), 126.12 (C_q-1 salicyl), 127.20 (*C*-6 salicyl), 129.54 (q, $^{2}J_{CF}$ = 31.5, *C*-3 in CF_3 aniline), 129.87 (*C*-5 aniline), 130.74 (*C*-4 salicyl), 140.91 (*C*-1 aniline), 164.96 (*C*-2 salicyl), 165.65 (*C*ONH).

Melting point: 140-143°C.

N-(4-chloro-3-(trifluoromethyl)phenyl)-5-cyano-2-hydroxybenzamide (80)

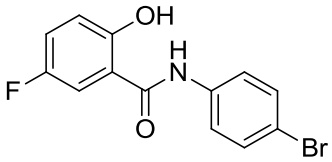


80 was prepared following **general procedure C**, yielding 0.360 g (90%) of the desired semi crystalline product.

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 7.14 (d, ^{3}J = 8.7, 1H, *H*-3 salicyl), 7.73 (d, ^{3}J = 8.9, 1H, *H*-5 aniline), 7.85 (dd, ^{3}J = 8.7, ^{3}J = 2.0, 1H, *H*-4 salicyl), 7.99 (d, ^{3}J = 8.9 ^{4}J = 2.1, 1H, *H*-6 aniline), 8.21 (d, ^{4}J = 2.0, 1H, *H*-6 salicyl), 8.31 (d, ^{4}J = 2.1, 1H, *H*-2 aniline), 10.73 (br s, 1H, CON*H*), 11.72-12.53 (br, 1H, ArO*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 101.38 (*C*-5 salicyl), 118.30 (*C*-3 salicyl), 118.68 (*C*N), 119.07 (q, $^{3}J_{CF}$ = 5.7, *C*-2 aniline), 120.95 (C_q-1 salicyl), 122.69 (q, $^{1}J_{CF}$ = -273.4, *C*F_3 aniline), 125.20 (*C*-6 aniline), 124.88 (q, $^{3}J_{CF}$ = 1.5, *C*-4 aniline), 126.76 (q, $^{2}J_{CF}$ = 30.3, *C*-3 in CF_3 aniline), 132.16 (*C*-5 aniline), 134.10 (*C*-6 salicyl), 136.58 (*C*-4 salicyl), 137.78 (*C*-1 aniline), 160.83 (*C*-2 salicyl), 164.74 (*C*ONH).

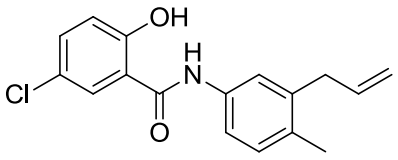
N-(4-bromophenyl)-5-fluoro-2-hydroxybenzamide (295)



295 was prepared following **general procedure B**, yielding 0.126 g (7%) of the desired product. Characterization (mp) was in accordance with previously reported values (CAS: 7103-89-1[143,144]).

Melting point: 219-221°C.

N-(3-allyl-4-methylphenyl)-5-chloro-2-hydroxybenzamide (296)



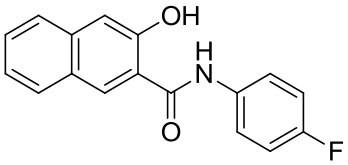
296 was prepared following **general procedure C**, yielding 1.063 g (72%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 2.23 (s, 3H, CH_3), 3.35 (d, ^{3}J = 6.3, 2H, CH_2CH=CH_2), 5.02 (d, $^{3}J_{trans}$ = 17.2, ^{2}J = 1.5 1H, CH_2CH=C$H_a$$H_b$), 5.08 (d, $^{3}J_{cis}$ = 10.1, ^{2}J = 1.5, 1H, CH_2CH=$CH_a$$H_b$), 5.88-6.01 (m, 1H, CH_2CH=CH_2), 7.00 (d, ^{3}J = 8.7, 1H, *H*-3 salicyl), 7.15 (d, ^{3}J = 7.9, 1H, *H*-5 aniline), 7.41-7.52 (m, 3H, *H*-4 salicyl, *H*-2,6 aniline), 8.00 (d, ^{4}J = 2.5, 1H, *H*-6 salicyl), 10.32 (br s, 1H, CON*H*), 11.98 (br s, 1H, ArO*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ =18.40 (*C*H_3), 37.16 (*C*H_2CH=CH_2), 115.89 (CH_2CH=*C*H_2), 118.88 (*C*-2 aniline), 119.05 (C_q-1 salicyl), 119.12 (*C*-3 salicyl), 121.50 (*C*-6 aniline), 122.65 (C_q-5 salicyl), 128.19 (*C*-6 salicyl), 130.14 (*C*-5 aniline), 132.07 (*C*-4 aniline), 133.06 (*C*-4 salicyl), 135.85 (*C*-1 aniline), 136.49 (CH_2*C*H=CH_2), 138.20 (*C*-3 aniline), 157.23 (*C*-2 salicyl), 165.03 (*C*ONH).

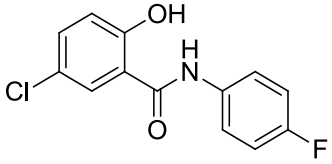
Melting point: 155-158°C.

N-(4-fluorophenyl)-3-hydroxy-2-naphthamide (297)



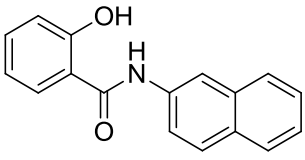
297 was prepared following **general procedure A**[121], yielding 2.78 g (87%) of the desired product. Characterization (NMR) was in accordance with previously reported values (CAS: 6267-93-2[145]).

5-chloro-*N*-(4-fluorophenyl)-2-hydroxybenzamide (298)



298 was prepared following **general procedure B**, yielding 7.1 g (66%) of the desired product. Characterization (NMR) was in accordance with previously reported values (CAS: 343-60-2[141]).

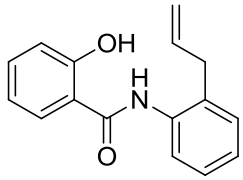
2-hydroxy-*N*-(naphthalen-2-yl)benzamide (299)



299 was prepared following **general procedure A**[121], yielding 1.031 g (84%) of the desired product. Characterization (mp) was in accordance with previously reported values (CAS: 5395-85-7[146]).

Melting point: 186-188°C.

N-(2-Allyl-phenyl)-2-hydroxy-benzamide (300)



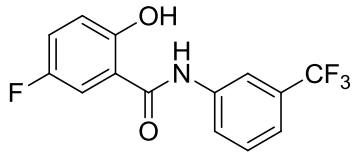
300 was prepared following **general procedure A**, yielding 0.654 g (65%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.47 (dt, *J* = 5.9 , *J* = 1.6, 2H, Ar-CH_2-HC= CH_2), 5.15 (dd, $^3J_{trans}$ = 17.3, ^2J = 1.6, 1H, CH_2-HC= C$H_{cis}$$H_{trans}$), 5.29 (dd, $^3J_{cis}$ = 10.1, ^2J = 1.5, 1H, CH_2-HC= $CH_{cis}H_{trans}$), 6.01-6.13 (m, 1H, CH_2-*H*C= CH_2), 6.88-6.93 (m, 1H, *H*-4 aniline), 7.04 (d, ^3J = 8.3, 1H, *H*-3 salicyl), 7.18-7.28 (m, 2H, *H*-3,5 aniline), 7.32-7.37 (m, 1H, *H*-5 salicyl), 7.41-7.48 (m, 2H, *H*-6 aniline *H*-4 salicyl), 7.86 (d, ^3J = 8.0, 1H, *H*-6 salicyl), 8.10 (br s, 1H, CON*H*), 12.11 (s, 1H, O*H* salicyl).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 37.23 (*C*H_2-HC= CH_2), 114.68 (*C*-1 salicyl), 117.16 (CH_2-HC= *C*H_2), 119.07 (*C*-3 salicyl), 119.12 (*C*-4 aniline), 124.74 (*C*-6 salicyl), 125.41 (*C*-6 aniline), 126.41 (*C*-3 aniline), 127.76 (*C*-5 salicyl), 130.75 (*C*-5 aniline), 131.30 (C_q-2 aniline), 134.79 (*C*-4 salicyl), 135.12 (C_q -1 aniline), 136.47 (CH_2-H*C*= CH_2), 162.17 (*C*ONH).

Melting point: 95-97°C.

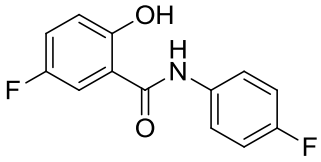
5-fluoro-2-hydroxy-*N*-(3-(trifluoromethyl)phenyl)benzamide (301)



301 was prepared following **general procedure B**, yielding 0.554 g (15%) of the desired product. Characterization (NMR) was in accordance with previously reported values (CAS: 1417658-34-4[141]).

Melting point: 214-215°C.

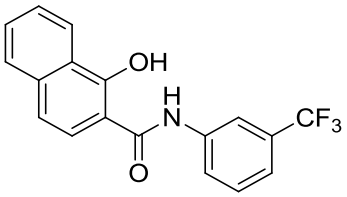
5-fluoro-*N*-(4-fluorophenyl)-2-hydroxybenzamide (302**)**



302 was prepared following **general procedure B**, yielding 0.476 g (21%) of the desired product. Characterization (mp) was in accordance with previously reported values (CAS: 363-28-0[143,144]).

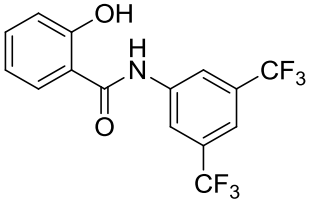
Melting point: 201-203°C.

1-hydroxy-*N*-(3-(trifluoromethyl)phenyl)-2-naphthamide (303**)**



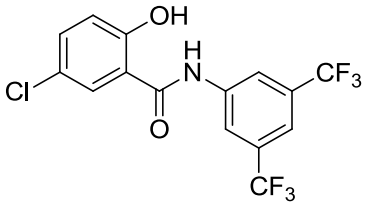
303 was prepared following **general procedure B**, yielding 6.481 g (62%) of the desired product. Characterization (NMR) was in accordance with previously reported values (CAS: 442-30-8[147]).

***N*-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxybenzamide (**304**)**



304 was prepared following **general procedure A**, yielding 0.231 g (5%) of the desired product. Characterization (NMR) was in accordance with previously reported values (CAS: 744-58-1[141]).

***N*-(3,5-bis(trifluoromethyl)phenyl)-5-chloro-2-hydroxybenzamide (**305**)**



Sodium methoxide (0.332 g, 6.15 mmol) was added to a solution of 5-chloro-2-hydroxybenzoic acid (1.0618 g, 6.15 mmol) in MeOH. MeOH was removed *via* rotary evapo-

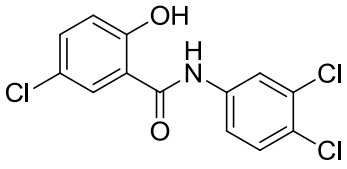
ration. Oxalyl chloride (2.004 mL, 22.89 mmol) and DCM (5 mL) were added. After gas evolution stopped, drops of DMF were added several times. Excess oxalyl chloride was removed by rotary evaporation. DCM (8 mL) triethyl amine (1 mL, 7.17 mmol) and DMAP (0.075 g, 0.615 mmol) were added. 3,5-Bis(trifluoromethyl)aniline (0.983 mL, 6.15 mmol) in 10mL DCM was added to an addition funnel. It was added dropwise under ice cooling. The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was washed three times with ethyl acetate, once with water, three times with $NaHCO_3$ and once with brine, dried over Na_2SO_4 and concentrated under reduced pressure. **305** (CAS: 978-62-1[141,148]) was obtained in 31% yield (0.720 g) after column chromatography (ethyl acetate:hexane=2:3).

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 7.04 (d, ^3J = 8.8, 1H, *H*-3 salicyl), 7.49 (dd, $^3J_1$ = 8.8, $^4J_2$ = 2.6, 1H, *H*-4 salicyl), 7.83 (br, s, 1H, *H*-4' in 3',5'-diCF_3), 7.86 (d, 1H, ^4J = 2.7, 1H, *H*-6 salicyl), 8.44 (br, s, 2H, *H*-2',6' in 3',5'-diCF_3), 10.84 (br, s, 1H, N*H*), 11.26-11.56 (br, 1H, O*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 116.86 (q, $^3J_{CF}$ = 4.0, *C*-2',6' in 3',5'-diCF_3-aniline), 119.03 (*C*-3 salicyl), 120.20 (C_q-1 salicyl), 120.33 (q, $^3J_{CF}$ = 3.8, *C*-4' in 3',5'-diCF_3-aniline), 122.77 (C_q-5 salicyl), 123.20 (q, $^1J_{CF}$ = -272.9, 2x *C*F_3), 128.57 (*C*-6 salicyl), 130.71 (q, $^2J_{CF}$ = 33.1, C_q-3',5' in 3',5'-diCF_3-aniline), 133.23 (*C*-4 salicyl), 140.24 (C_q-1' in 3',5'-diCF_3-aniline), 156.26 (C_q-2 salicyl), 165.50 (*C*ONH).

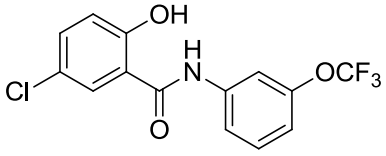
Melting point: 170-172°C.

5-chloro-*N*-(3,4-dichlorophenyl)-2-hydroxybenzamide (306)



306 was prepared following **general procedure B**, yielding 10.949 g (56%) of the desired product. Characterization (NMR) was in accordance with previously reported values (CAS: 642-84-2[149]).

5-chloro-2-hydroxy-*N*-(3-(trifluoromethoxy)phenyl)benzamide (307)



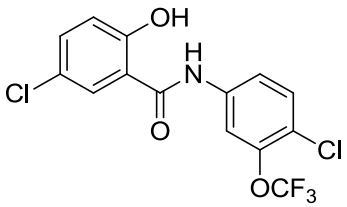
307 (CAS: 634185-96-9) was prepared following **general procedure B**, yielding 4.536 g (24%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 7.03 (d, ^{3}J = 8.9, 1H, *H*-3 salicyl), 7.13 (d, ^{3}J = 7.6, 1H, *H*-4 aniline), 7.45-7.52 (m, 2H, *H*-5 aniline, *H*-4 salicyl), 7.66 (d, ^{3}J = 8.4, 1H, *H*-6 aniline), 7.87-7.91 (m, 2H, *H*-2 aniline, *H*-6 salicyl), 10.58 (br s, 1H, CON*H*), 11.42-11.73 (br, 1H, ArO*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 112.68 (*C*-2 aniline), 116.19 (*C*-4 aniline), 118.99 (*C*-3 salicyl), 119.20 (*C*-6 aniline), 120.17 (one part of O*C*F_3 aniline visible), 122.70 (*C*-1 salicyl), 128.48 (*C*-6 salicyl), 130.46 (*C*-5 aniline), 132.99 (*C*-4 salicyl), 139.83 (*C*-1 aniline), 148.40 (*C*-3 aniline), 156.37 (*C*-2 salicyl), 165.08 (*C*ONH), *C*-5 salicyl not recorded.

Melting point: 190-193°C.

5-chloro-*N*-(4-chloro-3-(trifluoromethoxy)phenyl)-2-hydroxybenzamide (308)



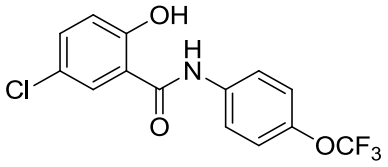
308 was prepared following **general procedure C**, yielding 0.565 g (33%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 7.03 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.49 (dd, ^{3}J = 8.8, ^{3}J = 2.6, 1H, *H*-4 salicyl), 7.58 (d, ^{3}J = 9.0, 1H, *H*-5 aniline), 7.75 (d, ^{3}J = 9.0 ^{4}J = 2.5, 1H, *H*-6 aniline), 7.86 (d, ^{4}J = 2.6, 1H, *H*-6 salicyl), 8.13 (d, ^{4}J = 2.5, 1H, *H*-2 aniline), 10.59 (br s, 1H, CON*H*), 11.52 (br s, 1H, ArO*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 118.99 (*C*-3 salicyl), 120.11 (q, $^{1}J_{CF}$ = -258.4, O*C*F_3 aniline), 120.14 (C_q-1 salicyl), 120.51 (*C*-6 aniline), 121.98 (*C*-2 aniline), 122.76 (C_q-5 salicyl), 123.55 (*C*-5 aniline), 126.05 (*C*-4 aniline), 128.51 (*C*-6 salicyl), 133.08 (*C*-4 salicyl), 138.44 (*C*-1 aniline), 139.76 (q, J_{CF} = 2.0, *C*-3 in 3-OCF_3 aniline), 156.27 (*C*-2 salicyl), 165.04 (*C*ONH).

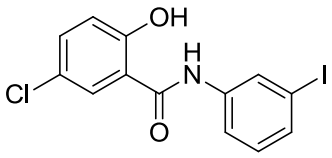
Melting point: 203°C.

5-chloro-2-hydroxy-*N*-(4-(trifluoromethoxy)phenyl)benzamide (309)



309 was prepared following **general procedure B**, yielding 4.736 g (25%) of the desired product. Characterization (NMR) was in accordance with previously reported values (CAS: 634186-00-8[141]).

5-chloro-2-hydroxy-*N*-(3-iodophenyl)benzamide (310)



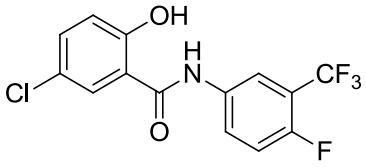
310 (CAS: 1040325-49-2) was prepared following **general procedure B**, yielding 5.136 g (60%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 7.03 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.17 (d, ^{3}J = 8.1, 1H, *H*-5 aniline), 7.46 (dd, ^{3}J = 8.8, ^{4}J = 2.7, 1H, *H*-4 salicyl), 7.50 (d, ^{3}J = 8.3, 1H, *H*-4 aniline), 7.68 (d, ^{3}J = 8.2, 1H, *H*-6 aniline), 7.91 (d, ^{4}J = 2.7, 1H, *H*-6 salicyl), 8.20 (m[t], 1H, *H*-2 aniline), 10.42 (s, 1H, CON*H*), 11.26-12.13 (br, 1H, ArO*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 94.43 (*C*-3 aniline), 119.04 (*C*-3 salicyl), 119.81 (*C*-1 salicyl), 119.89 (*C*-6 aniline), 122.69 (*C*-5 salicyl), 128.41 (*C*-6 salicyl), 128.77 (*C*-2 aniline), 130.74 (*C*-5 aniline), 132.72 (*C*-4 aniline), 133.02 (*C*-4 salicyl), 139.50 (*C*-1 aniline), 156.58 (*C*-2 salicyl), 164.97 (*C*ONH).

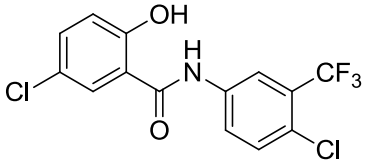
Melting point: 222-225°C.

5-chloro-*N*-(4-fluoro-3-(trifluoromethyl)phenyl)-2-hydroxybenzamide (311)



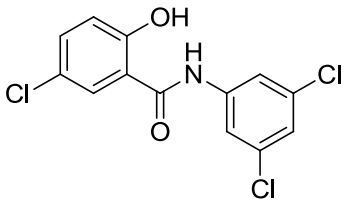
311 was prepared following **general procedure C**, yielding 3.584 g (94%) of the desired product. Characterization (NMR) was in accordance with previously reported values (CAS: 439144-73-7[141,148]).

5-chloro-*N*-(4-chloro-3-(trifluoromethyl)phenyl)-2-hydroxybenzamide (312)



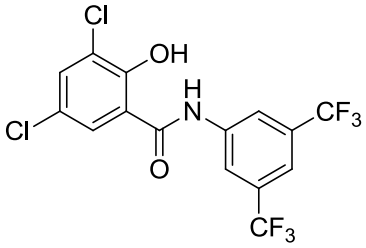
312 was prepared following **general procedure C**, yielding 4.718 g (76%) of the desired product. Characterization (NMR) was in accordance with previously reported values (CAS: 900-36-7[141]).

5-chloro-*N*-(3,5-dichlorophenyl)-2-hydroxybenzamide (313)



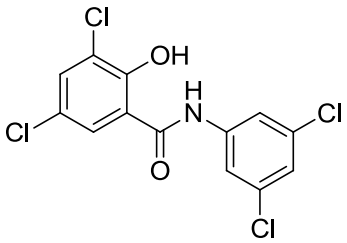
313 was prepared following **general procedure B**, yielding 4,536 g (23%) of the desired product. Characterization (NMR) was in accordance with previously reported values (CAS: 106480-60-8[141]).

N-(3,5-bis(trifluoromethyl)phenyl)-3,5-dichloro-2-hydroxybenzamide (314)



314 was prepared following **general procedure C**, yielding 3.093 g (68%) of the desired product. Characterization (NMR) was in accordance with previously reported values (CAS: 4554-46-5[141,150]).

3,5-dichloro-*N*-(3,5-dichlorophenyl)-2-hydroxybenzamide (315)



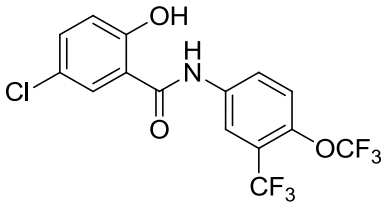
315 (CAS: 51543-48-7) was prepared following **general procedure C**, yielding 3.993 g (99%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 7.40 (m, ^4J = 1.8, 1H, *H*-4 aniline), 7.78-7.84 (m, 3H, *H*-2,6 aniline, *H*-4 salicyl), 7.98 (m, 1H, ^4J = 2.3, 1H, *H*-6 salicyl), 10.75 (br s, 1H, N*H*), 11.36-12.53 (br, 1H, O*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, DMSO-d_6, 23 °C): δ = 119.28 (*C*-2,6 aniline), 119.61 (C_q-3 salicyl), 122.58 (C_q-5 salicyl), 122.75 (C_q-1 salicyl), 123.89 (*C*-4 aniline), 126.60 (*C*-6 salicyl), 133.07 (*C*-4 salicyl), 134.01 (C_q-3,5 aniline), 140.05 (C_q-1 aniline), 153.93 (C_q-2 salicyl), 166.41 (*C*ONH).

Melting point: 170-173°C.

5-chloro-2-hydroxy-*N*-(4-(trifluoromethoxy)-3-(trifluoromethyl)phenyl)benzamide (316)



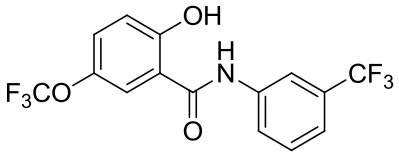
316 was prepared following **general procedure C**, yielding 0.998 g (57%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 7.03 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.47 (dd, ^{3}J = 8.8, ^{3}J = 2.5, 1H, *H*-4 salicyl), 7.68 (d, ^{3}J = 8.6, 1H, *H*-5 aniline), 7.87 (d, ^{4}J = 2.6, 1H, *H*-6 salicyl), 8.11 (d, ^{3}J = 9.1 ^{4}J = 2.5, 1H, *H*-6 aniline), 8.31 (d, ^{4}J = 2.4, 1H, *H*-2 aniline), 10.71 (br s, 1H, CON*H*), 11.49 (br s, 1H, ArO*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, DMSO-d_6, 23 °C): δ = 119.01 (*C*-3 salicyl), 119.04 (q, $^{3}J_{CF}$ = 5.2, *C*-2 aniline), 119.88 (q, $^{1}J_{CF}$ = -258.3, O*C*F_3 aniline), 120.04 (C_q-1 salicyl), 121.67 (q, $^{2}J_{CF}$ = 31.8, *C*-3 in CF_3 aniline), 122.33 (q, $^{1}J_{CF}$ = -272.4, *C*F_3 aniline), 122.54 (*C*-5 aniline), 122.74 (C_q-5 salicyl), 125.87 (*C*-6 aniline), 128.48 (*C*-6 salicyl), 133.14 (*C*-4 salicyl), 137.61 (*C*-1 aniline), 140.73 (q, $^{3}J_{CF}$ = 2.2, *C*-4 in CF_3 aniline), 156.38 (*C*-2 salicyl), 165.29 (*C*ONH).

Melting point: 178-180°C.

2-hydroxy-5-(trifluoromethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (317)



317 was prepared following **general procedure C**, yielding 1.278 g (73%) of the desired product.

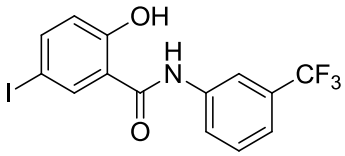
^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 7.10 (d, ^{3}J = 8.9, 1H, *H*-3 salicyl), 7.45 (dd, ^{3}J = 8.9, ^{3}J = 2.8, 1H, *H*-4 salicyl), 7.49 (d, ^{3}J = 7.9, 1H, *H*-4 aniline), 7.61 (dd[t], ^{3}J = 8.0 , 1H, *H*-5 aniline),

7.84 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 7.93 (d, ^{3}J = 8.3, 1H, *H*-6 aniline), 8.21 (br s, 1H, *H*-2 aniline), 10.63 (br s, 1H, CON*H*), 11.69 (br s, 1H, ArO*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, DMSO-d_6, 23 °C): δ = 116.74 (q, $^{3}J_{CF}$ = 4.0, *C*-2 aniline), 118.55 (*C*-3 salicyl), 119.75 (C_q-1 salicyl), 120.20 ($^{1}J_{CF}$ = -255.6, O*C*F_3 aniline), 120.51 (q, $^{3}J_{CF}$ = 3.8, *C*-4 aniline), 122.02 (*C*-6 salicyl), 124.05 (q, $^{1}J_{CF}$ = -272.5, *C*F_3 aniline), 124.22 (*C*-6 aniline), 126.46 (*C*-4 salicyl), 129.49 (q, $^{2}J_{CF}$ = 31.5, *C*-3 aniline), 129.97 (*C*-5 aniline), 138.93 (*C*-1 aniline), 140.26 (J_{CF} = 2.0, C_q-5 salicyl), 156.29 (*C*-2 salicyl), 164.82 (*C*ONH).

Melting point: 151-152°C.

2-hydroxy-5-iodo-*N*-(3-(trifluoromethyl)phenyl)benzamide (318)



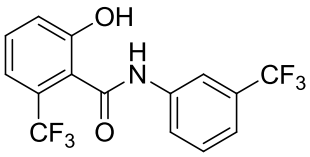
318 (CAS: 1494-09-3) was prepared following **general procedure C**, yielding 4.403 g (95%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 6.84 (d, ^{3}J = 8.6, 1H, *H*-3 salicyl), 7.49 (br d, ^{3}J = 8.0, 1H, *H*-4 aniline), 7.61 (dd [t], ^{3}J = 8.0, 1H, *H*-5 aniline), 7.72 (dd, $^{3}J_{1}$ = 8.6, ^{4}J = 2.2, 1H, *H*-4 salicyl), 7.94 (br d, ^{3}J = 8.3, 1H, *H*-6 aniline), 8.16 (d, 1H, ^{4}J = 2.2, 1H, *H*-6 salicyl), 8.19 (br, s, 1H, *H*-2 aniline), 10.60 (br, s, 1H, N*H*), 11.61 (br, 1H, O*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, DMSO-d_6, 23 °C): δ = 80.97 (C_q-5 salicyl), 116.80 (q, $^{3}J_{CF}$ = 4.0, *C*-2 aniline), 119.81 (*C*-3 salicyl), 120.50 (q, $^{3}J_{CF}$ = 3.8, *C*-4 aniline), 120.95 (C_q-1 salicyl), 124.13 (q, $^{1}J_{CF}$ = -272.4, *C*F_3), 124.28 (*C*-6 aniline), 129.44 (q, $^{2}J_{CF}$ = 31.4, C_q-3 aniline), 129.97 (*C*-5 aniline), 137.06 (*C*-6 salicyl), 138.97 (C_q-1 aniline), 141.62 (*C*-4 salicyl), 157.56 (C_q-2 salicyl), 165.27 (*C*ONH).

Melting point: 218-220°C.

2-hydroxy-6-(trifluoromethyl)-*N*-(3-(trifluoromethyl)phenyl)benzamide (319)



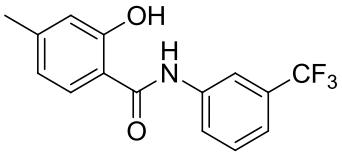
319 was prepared following **general procedure C**, yielding 0.271 g (22%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 7.23 (m, 2H, *H*-3,5 salicyl), 7.44 (d, ^{3}J = 7.8, 1H, *H*-4 aniline), 7.48 (dd [t], ^{3}J = 8.0, 1H, *H*-4 salicyl), 7.58 (dd[t], ^{3}J = 7.9 , 1H, *H*-5 aniline), 7.85 (d, ^{3}J = 8.4, 1H, *H*-6 aniline), 8.19 (br s, 1H, *H*-2 aniline), 10.51 (br s, 1H, ArO*H*), 10.76 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 115.08 (q, $^{3}J_{CF}$ = 4.1, *C*-2 aniline), 116.08 (q, $^{3}J_{CF}$ = 4.8, *C*-5 salicyl), 119.83 (q, $^{3}J_{CF}$ = 3.9, *C*-4 aniline), 120.04 (*C*-3 salicyl), 122.69 (*C*-6 aniline), 123.47 (q, $^{3}J_{CF}$ = 2.2, C_q-1 salicyl), 123.72 (q, $^{1}J_{CF}$ = -274.1, *C*F_3 aniline), 126.80 (q, $^{1}J_{CF}$ = -271.1, *C*F_3 salicyl), 126.92 (q, $^{2}J_{CF}$ = 30.9, *C*-6 salicyl), 129.52 (q, $^{2}J_{CF}$ = 31.9, *C*-3 aniline), 130.06 (*C*-4 salicyl), 130.57 (*C*-5 aniline), 139.91 (*C*-1 aniline), 154.95 (*C*-2 salicyl), 163.97 (*C*ONH).

Melting point: 160-166°C.

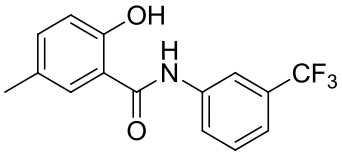
2-hydroxy-4-methyl-*N*-(3-(trifluoromethyl)phenyl)benzamide (320)



320 was prepared following **general procedure C**, yielding 5.026 g (89%) of the desired product. Characterization (NMR, mp) was in accordance with previously reported values (CAS: 1036619-32-5[151]).

Melting Point: 187-189°C.

2-hydroxy-5-methyl-*N*-(3-(trifluoromethyl)phenyl)benzamide (321)



321 (CAS: 16366-33-9) was prepared following **general procedure C**, yielding 4.926 g (85%) of the desired product.

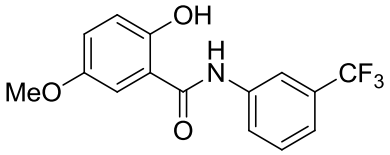
^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 2.28 (s, 3H, CH_3), 6.90 (d, ^{3}J = 8.4, 1H, *H*-3 salicyl), 7.26 (dd, $^{3}J_1$ = 8.4, ^{4}J = 1.9, 1H, *H*-4 salicyl), 7.47 (br d, ^{3}J = 7.8, 1H, *H*-4 aniline), 7.60 (dd [t], ^{3}J = 8.0, 1H, *H*-5 aniline), 7.75 (d, 1H, ^{4}J = 1.9, 1H, *H*-6 salicyl), 7.95 (br d, ^{3}J = 8.3, 1H, *H*-6 aniline), 8.21 (br, s, 1H, *H*-2 aniline), 10.57 (br, s, 1H, N*H*), 11.33 (br, 1H, O*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 20.01 (*C*H_3), 116.80 (q, $^{3}J_{CF}$ = 3.9, *C*-2 aniline), 117.07 (*C*-3 salicyl), 117.22 (C_q-1 salicyl), 120.29 (q, $^{3}J_{CF}$ = 3.8, *C*-4 aniline), 124.09 (q, $^{1}J_{CF}$ = -

272.5, *C*F_3), 124.27 (*C*-6 aniline), 127.78 (C_q-5 salicyl), 128.98 (*C*-6 salicyl), 129.44 (q, $^2J_{CF}$ = 31.6, C_q-3 aniline), 129.91 (*C*-5 aniline), 134.45 (*C*-4 salicyl), 139.13 (C_q-1 aniline), 156.05 (C_q-2 salicyl), 166.88 (*C*ONH).

Melting point: 162-163°C.

2-hydroxy-5-methoxy-*N*-(3-(trifluoromethyl)phenyl)benzamide (322)



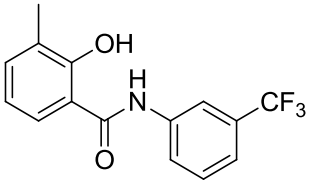
322 was prepared following **general procedure C**, yielding 4.386 g (74%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 3.76 (s, 3H, OC*H*$_3$), 6.95 (d, ^3J = 8.9, 1H, *H*-3 salicyl), 7.08 (dd, ^3J = 8.9, ^3J = 3.0, 1H, *H*-4 salicyl), 7.46-7.50 (m, 2H, *H*-4 aniline, *H*-6 salicyl), 7.61 (dd[t], ^3J = 8.0, 1H, *H*-5 aniline), 7.93 (d, ^3J = 8.4, 1H, *H*-6 aniline), 8.22 (br s, 1H, *H*-2 aniline), 10.61 (br s, 1H, CON*H*), 11.12 (br s, 1H, ArO*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 55.66 (O*C*H$_3$), 112.81 (*C*-6 salicyl), 116.85 (q, $^3J_{CF}$ = 4.1, *C*-2 aniline), 117.79 (*C*-1 salicyl), 118.15 (*C*-3 salicyl), 120.38 (q, $^3J_{CF}$ = 3.8, *C*-4 aniline), 120.63 (*C*-4 salicyl), 124.09 (q, $^1J_{CF}$ = -272.2, *C*F_3 aniline), 124.36 (*C*-6 aniline), 129.48 (q, $^2J_{CF}$ = 31.6, *C*-3 aniline), 129.93 (*C*-5 aniline), 139.06 (*C*-1 aniline), 151.90 (*C*-2 salicyl), 151.93 (*C*-5 salicyl), 166.25 (*C*ONH).

Melting point: 164°C.

2-hydroxy-3-methyl-*N*-(3-(trifluoromethyl)phenyl)benzamide (323)



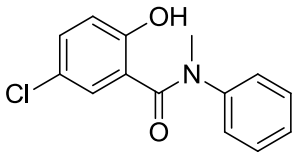
323 (CAS: 1041580-54-4) was prepared following **general procedure C**, yielding 3.448 g (56%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ =2.20 (s, 3H, C*H*$_3$), 6.90 (d, ^3J = 7.7, 1H, *H*-5 salicyl), 7.39 (d, $^3J_1$ = 7.3, 1H, *H*-4 salicyl), 7.52 (br d, ^3J = 7.8, 1H, *H*-4 aniline), 7.63 (dd [t], ^3J = 8.0, 1H, *H*-5 aniline), 7.91 (d, 1H, ^3J = 7.9, 1H, *H*-6 salicyl), 8.02 (br d, ^3J = 8.2, 1H, *H*-6 aniline), 8.15 (br, s, 1H, *H*-2 aniline), 10.64 (br, s, 1H, N*H*), 12.22 (br s, 1H, O*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, DMSO-d_6, 23 °C): δ = 15.54 (*C*H_3), 114.22 (C_q-1 salicyl), 117.75 (q, $^{3}J_{CF}$ = 4.2, *C*-2 aniline), 118.15 (*C*-5 salicyl), 120.82 (q, $^{3}J_{CF}$ = 3.8, *C*-4 aniline), 124.07 (q, $^{1}J_{CF}$ = -272.0, *C*F_3), 125.18 (*C*-6 aniline), 125.52 (*C*-6 salicyl), 126.26 (C_q-3 salicyl), 129.38 (q, $^{2}J_{CF}$ = 31.5, C_q-3 aniline), 129.91 (*C*-5 aniline), 135.30 (*C*-4 salicyl), 138.67 (C_q-1 aniline), 159.08 (C_q-2 salicyl), 169.39 (*C*ONH).

Melting point: 127-129°C.

5-chloro-2-hydroxy-*N*-methyl-*N*-phenylbenzamide (324)



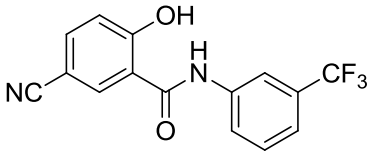
324 was prepared following **general procedure C**, yielding 2.153 g (67%) of the desired product. Characterization (MP) was in accordance with previously reported values (CAS: 54892-12-5[152]).

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 3.30 (s, 3H, NCH_3) 6.61-6.72 (m, 1H, *H*-arom), 7.03-7.12 (m, 2H, *H*-arom), 7.13-7.18(m, 1H, *H*-arom), 7.19-7.30(m, 4H, *H*-arom), 9.96 (br, 1H, O*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, DMSO-d_6, 23 °C): δ = 36.70 (dyn, N*C*H_3), 117.20 (*C*H-arom), 126.57 (C_q-5 salicyl), 126.64 (2x *C*H-aniline), 127.64 (*C*H-arom), 128.64 (2x *C*H-aniline), 129.46 (*C*H-arom), 143.45 (C_q-1 aniline), 152.31 (C_q-2 salicyl), 166.74 (*C*ONH).

Melting point: 143-145°C.

5-cyano-2-hydroxy-*N*-(3-(trifluoromethyl)phenyl)benzamide (325)



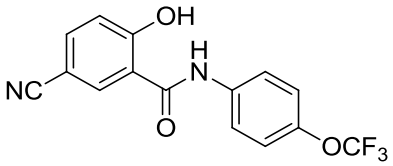
325 was prepared following **general procedure C**, yielding 2.484 g (66%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 7.14 (d, ^{3}J = 8.6, 1H, *H*-3 salicyl), 7.49 (d, ^{3}J = 7.8, 1H, *H*-4 aniline), 7.62 (dd[t], ^{3}J = 7.8, ^{3}J = 8.2, 1H, *H*-5 aniline), 7.85 (dd, ^{3}J = 8.6, ^{3}J = 2.0, 1H, *H*-4 salicyl), 7.94 (d, ^{3}J = 8.2, 1H, *H*-6 aniline), 8.20 (br s, 1H, *H*-2 aniline), 8.25 (d, ^{3}J = 2.0, 1H, *H*-6 salicyl), 10.64 (br s, 1H, CON*H*), 12.13 (br s, 1H, ArO*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, DMSO-d_6, 23 °C): δ = 101.44 (*C*-5 salicyl), 116.56 (q, $^{3}J_{CF}$ = 4.1, *C*-2 aniline), 118.32 (*C*-3 salicyl), 118.71 (*C*N), 120.55 (q, $^{3}J_{CF}$ = 3.8, *C*-4 aniline), 120.80 (*C*-1 salicyl), 124.06 (*C*-6 aniline), 124.06 (q, $^{1}J_{CF}$ = -272.1, *C*F_3 aniline), 129.49 (q, $^{2}J_{CF}$ = 31.6, *C*-3 aniline), 130.05 (*C*-5 aniline), 134.06 (*C*-6 salicyl), 136.56 (*C*-4 salicyl), 138.99 (*C*-1 aniline), 160.96 (*C*-2 salicyl), 164.80 (*C*ONH).

Melting point: 224-226°C.

5-cyano-2-hydroxy-*N*-(4-(trifluoromethoxy)phenyl)benzamide (326)



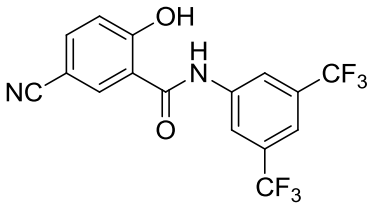
326 was prepared following **general procedure C**, yielding 3.205 g (81%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 7.13 (d, ^{3}J = 8.6, 1H, *H*-3 salicyl), 7.39 (d, ^{3}J = 8.6, 2H, *H*-3,5 aniline), 7.83 (m, 2H, *H*-2,6 aniline), 7.85 (dd, ^{3}J = 8.6, ^{3}J = 2.2, 1H, *H*-4 salicyl), 8.26 (d, ^{3}J = 2.2, 1H, *H*-6 salicyl), 10.54 (br s, 1H, CON*H*), 12.09-12.50 (br, 1H, ArO*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, DMSO-d_6, 23 °C): δ = 101.42 (*C*-5 salicyl), 118.33 (*C*-3 salicyl), 118.72 (*C*N), 120.13 ($^{1}J_{CF}$ = -256.0, O*C*F_3 aniline), 120.62 (*C*-1 salicyl), 121.63 (*C*-3,5 aniline), 122.00 (*C*-2,6 aniline), 134.01 (*C*-6 salicyl), 136.53 (*C*-4 salicyl), 137.33 (*C*-1 aniline), 144.29 (m, *C*-4 aniline), 161.08 (*C*-2 salicyl), 164.58 (*C*ONH).

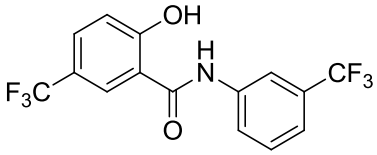
Melting point: 260-263°C.

N-(3,5-bis(trifluoromethyl)phenyl)-5-cyano-2-hydroxybenzamide (327)



327 was prepared following **general procedure C**, yielding 2.701 g (59%) of the desired product. Characterization (NMR) was in accordance with previously reported values (CAS: 439144-18-0[153]).

2-hydroxy-5-(trifluoromethyl)-*N*-(3-(trifluoromethyl)phenyl)benzamide (328)



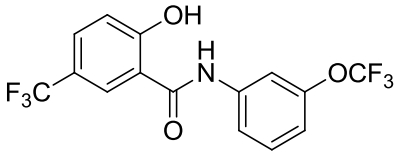
328 (CAS: 145132-81-6) was prepared following **general procedure C**, yielding 1.531 g (90%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d$_6$, 23 °C): δ = 7.18 (d, ^3J = 8.7, 1H, *H*-3 salicyl), 7.50 (br d, ^3J = 7.7, 1H, *H*-4 aniline), 7.62 (dd [t], ^3J = 8.0, 1H, *H*-5 aniline), 7.77 (dd, $^3J_1$ = 8.7, $^4J_2$ = 1.9, 1H, *H*-4 salicyl), 7.95 (br d, ^3J = 8.2, 1H, *H*-6 aniline), 8.18 (d, 1H, ^4J = 1.9, 1H, *H*-6 salicyl), 8.21 (br, s, 1H, *H*-2 aniline), 10.70 (br, s, 1H, N*H*), 12.10 (br, 1H, O*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d$_6$, 23 °C): δ = 116.78 (q, $^3J_{CF}$ = 4.0, *C*-2 aniline),117.97 (*C*-3 salicyl), 119.56 (*C*$_q$-1 salicyl), 119.72 (q, $^2J_{CF}$ = 32.6, *C*$_q$-5 salicyl), 120.55 (q, $^3J_{CF}$ = 3.8, *C*-4 aniline), 124.27 (*C*-6 aniline), 124.08 (q, $^1J_{CF}$ = -272.2, *C*F$_3$ salicyl), 124.31 (q, $^1J_{CF}$ = -271.8, *C*F$_3$ aniline), 126.82 (q, $^3J_{CF}$ = 3.8, *C*-6 salicyl), 129.48 (q, $^2J_{CF}$ = 32.0, *C*$_q$-3 aniline), 129.98 (q, $^3J_{CF}$ = 3.8, *C*-4 salicyl), 130.00 (*C*-5 aniline), 138.98 (*C*$_q$-1 aniline), 160.39 (*C*$_q$-2 salicyl), 165.17 (*C*ONH).

Melting point: 155-157°C.

2-hydroxy-*N*-(3-(trifluoromethoxy)phenyl)-5-(trifluoromethyl)benzamide (329)



329 was prepared following **general procedure C**, yielding 1.258 g (71%) of the desired product.

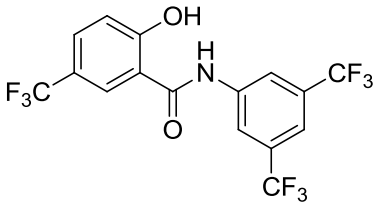
^{1}H NMR (400 MHz, DMSO-d$_6$, 23 °C): δ = 7.14 (d, ^3J = 8.2, ^4J = 1.1, 1H, *H*-4 aniline), 7.18 (d, ^3J = 8.7, 1H, *H*-3 salicyl), 7.51 (dd[t], ^3J = 8.2, ^3J = 8.0, 1H, *H*-5 aniline), 7.67 (d, ^3J = 8.0, 1H, *H*-6 aniline), 7.77 (dd, ^3J = 8.7, ^3J = 2.2, 1H, *H*-4 salicyl), 7.91 (br s, 1H, *H*-2 aniline), 8.17 (d, ^3J = 1.8, 1H, *H*-6 salicyl), 10.64 (s, 1H, CON*H*), 12.09 (br s, 1H, ArO*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d$_6$, 23 °C): δ = 112.74 (*C*-2 aniline), 116.26 (*C*-4 aniline), 117.92 (*C*-3 salicyl), 119.24 (*C*-6 aniline), 119.76 (*C*-1 salicyl), 119.78 (q, $^2J_{CF}$ = 32.6, *C*-5 salicyl), 120.12 (q, $^1J_{CF}$ = -255.3, O*C*F$_3$ aniline), 124.31 (q, $^1J_{CF}$ = -271.0, *C*F$_3$ salicyl), 126.86 (q, $^3J_{CF}$ =

3.9, *C*-6 salicyl), 129.92 (q, $^{3}J_{CF}$ = 3.5, *C*-4 salicyl), 130.49 (*C*-5 aniline), 139.87 (*C*-1 aniline), 148.46 (J_{CF} = 1.4, *C*-3 aniline), 160.22 (*C*-2 salicyl), 165.01 (*C*ONH).

Melting point: 142°C.

N-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxy-5-(trifluoromethyl)benzamide (330)



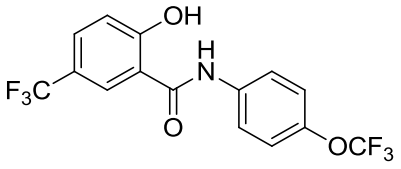
330 (CAS: 439144-33-9) was prepared following **general procedure C**, yielding 1.397 g (66%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d$_6$, 23 °C): δ = 7.19 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.77 (dd, $^{3}J_{1}$ = 8.8, $^{4}J_{2}$ = 1.8, 1H, *H*-4 salicyl), 7.83 (s, 1H, *H*-4 aniline), 8.14 (d, 1H, ^{4}J = 1.8, 1H, *H*-6 salicyl), 8.44 (s, 2H, *H*-2,6 aniline), 10.91 (br s, 1H, N*H*), 11.94 (br, 1H, O*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d$_6$, 23 °C): δ = 116.91 (m, $^{3}J_{CF}$ = 3.8, *C*-4 aniline), 117.94 (*C*-3 salicyl), 119.71 (C_q-1 salicyl), 119.77 (q, $^{2}J_{CF}$ = 32.9, C_q-5 salicyl), 120.35 (q, $^{3}J_{CF}$ = 3.3, *C*-2,6 aniline), 123.21 (q, $^{1}J_{CF}$ = -272.7, 2x *C*F$_3$), 124.26 (q, $^{1}J_{CF}$ = -271.2, *C*F$_3$ salicyl), 126.93 (q, $^{3}J_{CF}$=3.8, *C*-6 salicyl), 130.13 (q, $^{3}J_{CF}$=3.3, *C*-4 salicyl), 130.73 (q, $^{2}J_{CF}$ = 32.8, C_q-3,5 aniline), 140.25 (C_q-1 aniline), 160.13 (C_q-2 salicyl), 165.42 (*C*ONH).

Melting point: 163-165°C.

2-hydroxy-*N*-(4-(trifluoromethoxy)phenyl)-5-(trifluoromethyl)benzamide (331)



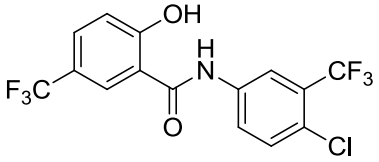
331 was prepared following **general procedure C**, yielding 1.323 g (73%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d$_6$, 23 °C): δ = 7.17 (d, ^{3}J = 8.4, 1H, *H*-3 salicyl), 7.38 (br d, ^{3}J = 8.9, 2H, *H*-3,5 aniline), 7.76 (dd, $^{3}J_{1}$ = 8.7, $^{4}J_{2}$ = 2.1, 1H, *H*-4 salicyl), 7.83 (m [d], ^{3}J = 9.1, 2H, *H*-2,6 aniline), 8.19 (d, 1H, ^{4}J = 1.8, 1H, *H*-6 salicyl), 10.59 (br, s, 1H, N*H*), 12.18 (br, 1H, O*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, DMSO-d_6, 23 °C): δ = 117.99 (*C*-3 salicyl), 119.37 (C_q-1 salicyl), 119.78 (q, $^{2}J_{CF}$ = 32.4, C_q-5 salicyl), 120.15 (q, $^{1}J_{CF}$ = -256.2, O*C*F_3 aniline), 121.60 (*C*-3,5 aniline), 122.22 (*C*-2,6 aniline), 124.32 (q, $^{1}J_{CF}$ = -270.8, *C*F_3 aniline), 126.80 (q, $^{3}J_{CF}$ = 3.8, *C*-6 salicyl), 129.95 (q, $^{3}J_{CF}$ = 3.3, *C*-4 salicyl), 137.31 (C_q-1 aniline), 144.34 (J_{CF} = 1.7, *C*-4 aniline), 160.49 (C_q-2 salicyl), 164.93 (*C*ONH).

Melting point: 160°C.

N-(4-chloro-3-(trifluoromethyl)phenyl)-2-hydroxy-5-(trifluoromethyl)benzamide (332)



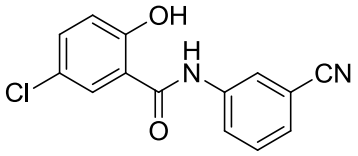
332 was prepared following **general procedure C**, yielding 1.602 g (93%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 7.18 (d, ^{3}J = 8.7, 1H, *H*-3 salicyl), 7.72 (d, ^{3}J = 8.7, 1H, *H*-5 aniline), 7.77 (dd, ^{3}J = 8.7, ^{3}J = 1.9, 1H, *H*-4 salicyl), 8.00 (d, ^{3}J = 8.7 ^{4}J = 2.4, 1H, *H*-6 aniline), 8.14 (d, ^{4}J = 1.9, 1H, *H*-6 salicyl), 8.31 (d, ^{4}J = 2.4, 1H, *H*-2 aniline), 10.73 (br s, 1H, CON*H*), 11.99 (br s, 1H, ArO*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, DMSO-d_6, 23 °C): δ = 117.93 (*C*-3 salicyl), 119.30 (q, $^{3}J_{CF}$ = 5.6, *C*-2 aniline), 119.72 (C_q-1 salicyl), 119.76 (q, $^{2}J_{CF}$ = 32.1, *C*-5 salicyl), 122.71 (q, $^{1}J_{CF}$ = -273.0, *C*F_3 aniline), 124.28 (q, $^{1}J_{CF}$ = -271.8, *C*F_3 salicyl), 124.91 (q, $^{3}J_{CF}$ = 2.2, *C*-4 aniline), 125.42 (*C*-6 aniline), 126.75 (q, $^{2}J_{CF}$ = 31.0, *C*-3 in CF_3 aniline), 126.85 (q, $^{3}J_{CF}$ = 3.8, *C*-6 salicyl), 130.02 (q, $^{3}J_{CF}$ = 3.5, *C*-4 salicyl), 132.11 (*C*-5 aniline), 137.75 (*C*-1 aniline), 160.17 (*C*-2 salicyl),165.14 (*C*ONH).

Melting point: 169-173°C.

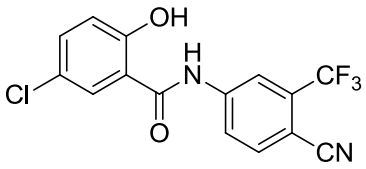
5-chloro-*N*-(3-cyanophenyl)-2-hydroxybenzamide (333)



333 was prepared following **general procedure C**, yielding 16.318 g (99%) of the desired product. Characterization (mp, NMR) was in accordance with previously reported values (CAS: 380656-56-4[141]).

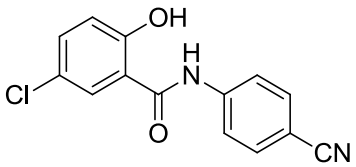
Melting point: 234°C

5-chloro-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-2-hydroxybenzamide (334)



334 was prepared following **general procedure C**, yielding 3.193 g (81%) of the desired product. Characterization (NMR) was in accordance with previously reported values (CAS: 634185-61-8[141]).

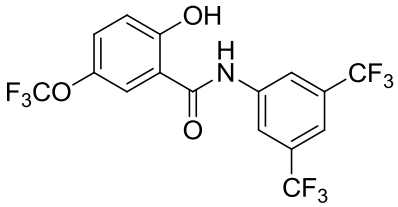
5-chloro-*N*-(4-cyanophenyl)-2-hydroxybenzamide (335)



335 was prepared following **general procedure C**, yielding 4.961 g (62%) of the desired product. Characterization (NMR, mp) was in accordance with previously reported values (CAS: 612087-80-6[154]).

Melting point: 245-246°C.

N-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxy-5-(trifluoromethoxy)benzamide (336)



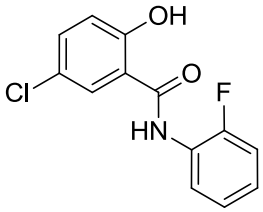
336 was prepared following **general procedure C**, yielding 2.583 g (76%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 7.10 (d, ^3J = 8.9, 1H, *H*-3 salicyl), 7.44 (dd, $^3J_1$ = 8.7, $^4J_2$ = 2.0, 1H, *H*-4 salicyl), 7.79(d, 1H, ^4J = 2.0, 1H, *H*-6 salicyl), 7.82 (br, s, 1H, *H*-4 aniline), 8.44 (br, s, 2H, *H*-2,6 aniline), 10.75-11.34 (br, 2H, N*H*, O*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, DMSO-d_6, 23 °C): δ = 116.77 (q, $^{3}J_{CF}$ = 3.4, *C*-4 aniline), 118.69 (*C*-3 salicyl), 119.79 (C_q-1 salicyl), 120.22 (q, $^{1}J_{CF}$ = -255.2, O*C*F_3), 120.28 (q, $^{3}J_{CF}$ = 3.2, *C*-2,6 aniline), 122.13 (*C*-6 salicyl), 123.22 (q, $^{1}J_{CF}$ = -272.3, 2x *C*F_3), 126.61 (*C*-4 salicyl), 130.74 (q, $^{2}J_{CF}$ = 32.8, C_q-3,5 aniline), 140.07 (d, J_{CF} = 1.2, C_q-5 salicyl), 140.30 (C_q-1 aniline), 156.55 (C_q-2 salicyl), 165.11 (*C*ONH).

Melting point: 174-176°C.

5-chloro-*N*-(2-fluorophenyl)-2-hydroxybenzamide (337)



337 (CAS 928770-44-9) was prepared following **general procedure C**, yielding 5.154 g (69%) of the desired product.

1H NMR (400 MHz, DMSO-d6 , 23 °C): δ = 7.05 (d, ^{3}J = 8.7, 1H, *H*-3 salicyl), 7.16-7.26 (m, br, 2H, *H*-4',5' in 2'-F-aniline), 7.29-7.35 (m, br, 1H, *H*-3' in 2'-F-aniline), 7.49 (dd, ^{3}J = 8.8, ^{4}J = 2.7, 1H, *H*-4 salicyl), 7.98 (d, ^{3}J = 2.8, 1H, *H*-6 salicyl), 8.18-8.23 (m, br, 1H, *H*-6' in 2'-F-aniline), 10.67 (s, 1H, N*H*CO), 12.15 (s, 1H, 2-O*H*).

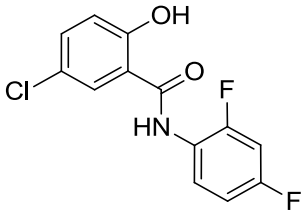
$^{13}C\{^{1}H\}$NMR (100 MHz, DMSO-d_6, 23 °C): δ = 115.30 (d, $^{2}J_{1CF}$ = 19.3, *C*-3' in 2'-F-aniline), 119.10 (*C*-3 salicyl), 119.33 (C_q-1 salicyl), 123.19 (*C*-6' in 2'-F-aniline), 123.35 (C_q-5 salicyl), 124.68 (d, $^{4}J_{CF}$ = 3.5, *C*-5' in 2'-F-aniline), 125.39 (d, $^{3}J_{CF}$ = 7.7, *C*-4' in 2'-F-aniline), 125.91 (d, $^{2}J_{CF}$ = 10.8, C_q-1' in 2'-F-aniline), 129.38 (*C*-6 salicyl), 133.38 (*C*-4 salicyl), 152.26 (d, $^{1}J_{CF}$ = -244.0, C_q-2' in 2'-F-aniline), 155.78 (C_q-2 salicyl), 163.18 (*C*ONH).

^{1}H NMR (600 MHz, $CDCl_3$, 23 °C): δ = 7.00 (d, ^{3}J = 8.9, 1H, *H*-3 salicyl), 7.15-7.24 (m, 3H, *H*-3',4',5' in 2'-F-aniline), 7.42 (dd, ^{3}J = 8.8, ^{4}J = 2.4, 1H, *H*-4 salicyl), 7.52 (d, ^{3}J = 2.4, 1H, *H*-6 salicyl), 8.10 (s, 1H, N*H*CO), 8.25-8.28 (m, br, 1H, *H*-6' in 2'-F-aniline), 11.72 (s, 1H, 2-O*H*).

$^{13}C\{^{1}H\}$NMR (150 MHz, $CDCl_3$, 23 °C): δ = 115.29 (d, $^{2}J_{1CF}$ = 19.0, *C*-3' in 2'-F-aniline), 115.51 (C_q-1 salicyl), 120.68 (*C*-3 salicyl), 122.84 (*C*-6' in 2'-F-aniline), 124.01 (C_q-5 salicyl), 124.93 (d, $^{4}J_{CF}$ = 3.7, *C*-5' in 2'-F-aniline), 125.14 (d, $^{2}J_{CF}$ = 10.1, C_q-1' in 2'-F-aniline), 125.32 (*C*-6 salicyl), 125.96 (d, $^{3}J_{CF}$ = 7.8, *C*-4' in 2'-F-aniline), 135.03 (*C*-4 salicyl), 160.52 (C_q-2 salicyl), 167.29 (*C*ONH). C_q-2' in 2'-F-aniline missing

Melting point: 227-228°C.

5-chloro-*N*-(2,4-difluorophenyl)-2-hydroxybenzamide (338)



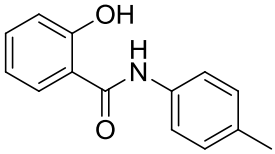
338 was prepared following **general procedure C**, yielding 4.226 g (78%) of the desired product. Characterization (^{1}H-NMR) was in accordance with previously reported values (CAS: 634189-17-6[141]).

^{1}H NMR (400 MHz, DMSO-d_6 , 23 °C): δ = 7.04 (d, ^3J = 8.7, 1H, *H*-3 salicyl), 7.09-7.16 (m, 1H, *H*-5' in 2,4-difluoroaniline), 7.34-7.42 (m, 1H, *H*-3' in 2,4-difluoroaniline), 7.48 (dd, ^3J = 8.7, ^4J = 2.6, 1H, *H*-4 salicyl), 7.97 (d, ^4J = 2.6, 1H, *H*-6 salicyl), 8.07-8.16 (m, 1H, *H*-6' in 2,4-difluoroaniline), 10.57 (s, 1H, CON*H*),12.11 (s, 1H, 2-O*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 104.14 (dd, $^2J_{1CF}$ = 24.1, $^2J_{1CF}$ = 26.9, *C*-3' in 2', 4'-difluoroaniline), 111.33 (dd, $^2J_{CF}$ = 21.9, $^4J_{CF}$ = 3.4, *C*-5' in 2', 4'-difluoroaniline), 118.97 (C_q-1 salicyl), 119.12 (*C*-3 salicyl), 122.39 (dd, $^2J_{1CF}$ = 11.1, $^4J_{CF}$ = 3.5, C_q-1' in 2', 4'-difluoroaniline), 123.25 (C_q-5 salicyl), 124.87 (dd, $^3J_{2CF}$ = 9.6, $^3J_{2CF}$ = 2.4, *C*-6' in 2', 4'-difluoroaniline), 129.19 (*C*-6 salicyl), 133.44 (*C*-4 salicyl), 153.75 (dd, $^1J_{1CF}$ = 247.0, $^3J_{2CF}$ = 12.9, *C*-4' in 2', 4'-difluoroaniline), 156.06 (C_q-2 salicyl), 158.62 (dd, $^1J_{1CF}$ = 244.2, $^3J_{2CF}$ = 12.0, *C*-2' in 2', 4'-difluoroaniline), 163.60 (*C*ONH).

Melting point: 238-240°C.

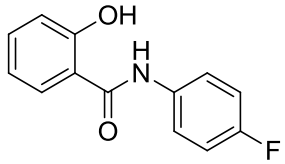
2-hydroxy-*N*-(p-tolyl)benzamide (339)



339 was prepared following **general procedure A**[121], yielding 0.81 g (76%) of the desired product. Characterization (NMR) was in accordance with previously reported values (CAS: 7164-80-9[155]).

Melting point: 155-156°C.

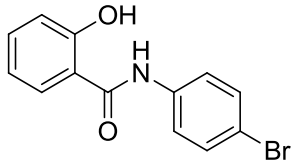
N-(4-fluorophenyl)-2-hydroxybenzamide (340)



340 was prepared following **general procedure A**[121], yielding 3.3 g (76%) of the desired product. Characterization (NMR) was in accordance with previously reported values (CAS: 7120-46-9[155]).

Melting point: 156-157°C.

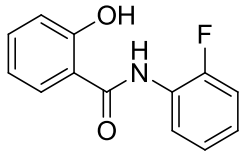
N-(4-bromophenyl)-2-hydroxybenzamide (341)



341 was prepared following **general procedure A**[121], yielding 8.3 g (61%) of the desired product. Characterization (NMR) was in accordance with previously reported values (CAS: 2627-77-2[156]).

Melting point: 170-171°C.

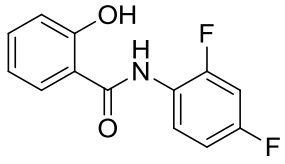
N-(2-fluorophenyl)-2-hydroxybenzamide (342)



342 was prepared following **general procedure A**[121], yielding 2.30 g (53%) of the desired product. Characterization (NMR) was in accordance with previously reported values (CAS: 866034-84-6[155]).

Melting point: 141-143°C.

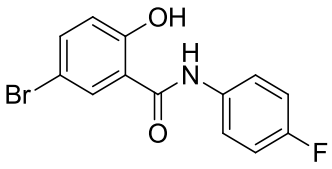
N-(2,4-difluorophenyl)-2-hydroxybenzamide (343)



343 was prepared following **general procedure A**[121], yielding 2.0 g (86%) of the desired product. Characterization (NMR) was in accordance with previously reported values (CAS: 316124-58-0[155]).

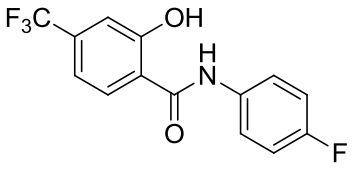
Melting point: 180-183°C.

5-bromo-*N*-(4-fluorophenyl)-2-hydroxybenzamide (344)



344 was prepared following **general procedure B**, yielding 2.9 g (68%) of the desired product. Characterization (NMR) was in accordance with previously reported values (CAS: 4294-89-7[157]).

N-(4-fluorophenyl)-2-hydroxy-4-(trifluoromethyl)benzamide (345)



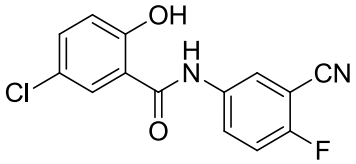
345 was prepared following **general procedure B**, yielding 5.8 g (77%) of the desired product. Characterization (mp) was in accordance with previously reported values (CAS: 175872-26-1[158]).

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 7.19-7.24 (m, 2H, *H*-3,5 aniline), 7.28 (s, 1H, *H*-3 salicyl), 7.28 (d, ^{3}J = 8.1, 1H, *H*-5 salicyl), 7.71-7.78 (m, 2H, *H*-2,6 aniline), 7.99 (d, ^{4}J = 8.1, 1H, *H*-6 salicyl), 10.51 (br s, 1H, CON*H*), 11.27-12.47 (br , 1H, ArO*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 113.50 (q, $^{3}J_{CF}$ = 3.7, *C*-3 salicyl), 115.33 (q, $^{3}J_{CF}$ = 3.8, *C*-5 salicyl), 115.44 ($^{2}J_{CF}$ = 22.3, *C*-3,5 aniline), 122.45 ($^{3}J_{CF}$ = 7.9, *C*-2,6 aniline), 123.50 (*C*-1 salicyl), 123.62 ($^{1}J_{CF}$ = -272.6, *C*F_3), 130.61 (*C*-6 salicyl), 132.56 ($^{2}J_{CF}$ = 31.9, *C*-4 salicyl), 134.65 ($^{4}J_{CF}$ = 2.5, *C*-1 aniline), 157.37 (*C*-2-salicyl), 158.62 ($^{1}J_{CF}$ = -241.1, *C*-4 aniline), 164.76 (*C*ONH).

Melting point: 175-178°C.

5-chloro-*N*-(3-cyano-4-fluorophenyl)-2-hydroxybenzamide (346)



346 (CAS: 1455386-89-6) was prepared following **general procedure C**, yielding 2.240 g (65%) of the desired product.

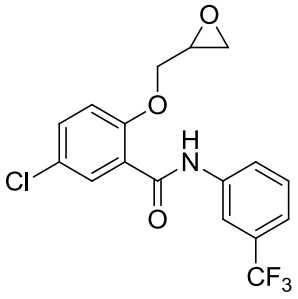
^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 7.03 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.47 (dd, ^{3}J = 8.8, ^{4}J = 2.7, 1H, *H*-4 salicyl), 7.55 (dd [t], ^{3}J =9.1, 1H, *H*-5 aniline), 7.86 (d, ^{4}J = 2.7, 1H, *H*-6 salicyl), 7.99-8.05 (m, 1H, *H*-6 aniline), 8.20-8.25 (m, 1H, *H*-2 aniline), 10.61 (br s, 1H, CON*H*), 11.58 (br s, 1H, O*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 100.00 (d, J_{CF}=16.4, *C*-3 aniline), 113.86 (*C*N), 117.08 (d, $^{2}J_{CF}$= 20.6, *C*-5 aniline), 119.04 (*C*-3 salicyl), 119.86 (*C*-1 salicyl), 122.79 (*C*-5 salicyl), 124.76 (*C*-2 aniline), 128.12 (d, $^{3}J_{CF}$= 8.3, *C*-6 aniline), 128.52 (*C*-6 salicyl), 133.17 (*C*-4 salicyl), 135.29 (d, $^{4}J_{CF}$= 2.8, *C*-1 aniline), 156.38 (*C*-2 salicyl), 158.70 (d, $^{1}J_{CF}$= 253.0, *C*-4 aniline), 165.00 (*C*ONH).

Melting point: 219-221°C.

4.3.2 Epoxides

(±)-5-Chloro-2-oxiranylmethoxy-*N*-(3-trifluoromethyl-phenyl)-benzamide (71)



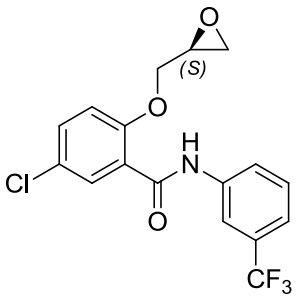
71 was prepared following **general procedure D**, yielding 0.432 g (46%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.90 (dd, *J* = 4.7 , *J* = 2.5, 1H, C*H*$_a$H$_b$ epoxide), 3.02 (dd[t], *J* = 4.5, 1H, CH$_a$*H*$_b$ epoxide), 3.47-3.53 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.12 (dd, ^2J = -10.6, ^3J = 5.4, 1H, OC*H*$_a$H$_b$CHOR), 4.60 (dd, ^2J = -10.6, ^3J = 2.3, 1H, OCH$_a$*H*$_b$CHOR), 6.94 (d, ^3J = 8.8, 1H, *H*-3 salicyl), 7.37 (d, ^3J = 7.9, 1H, *H*-4 aniline), 7.42 (dd, ^3J = 8.8, ^4J = 2.8, 1H, *H*-4 salicyl), 7.46 (dd [t], ^3J = 8.2, ^3J = 7.9, 1H, *H*-5 aniline), 7.92 (d, ^3J = 8.2, 1H, *H*-6 aniline), 8.19 (s [t], 1H, *H*-2 aniline), 8.22 (d, ^4J = 2.8, 1H, *H*-6 salicyl), 9.91 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.69 (*C*H$_2$ epoxide), 49.78 (*C*HO epoxide), 69.25 (O*C*H$_2$CHOR), 114.42 (*C*-3 salicyl), 117.18 ($^3J_{CF}$ = 3.8, *C*-2 aniline), 120.92 ($^3J_{CF}$ = 3.8, *C*-4 aniline), 123.36 (*C*-5 salicyl), 124.12 ($^1J_{CF}$ = -272.3, *C*F$_3$ aniline), 123.55 ([verbreitert], *C*-6 aniline), 128.05 (*C*-5 salicyl), 129.63 (*C*-5 aniline), 131.50 ($^2J_{CF}$ = 32.2, *C*-3 aniline), 132.54 (*C*-6 salicyl), 133.20 (*C*-4 salicyl), 139.00 (*C*-1 aniline), 154.53 (*C*-2 salicyl), 162.08 (*C*ONH).

Melting point: 95-104°C.

(*S*)-(-)-5-chloro-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (99)



99 was prepared following **general procedure D**, using (*S*)-(+)-epichlorohydrin, yielding 0.235 g (64%) of the desired product.

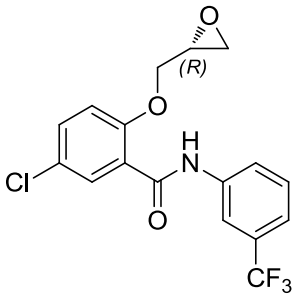
For NMR assignment see (±)-5-Chloro-2-oxiranylmethoxy-*N*-(3-trifluoromethyl-phenyl)-benzamide (**71**).

$[\alpha]_D^{20}$= -63.2°, c=1 in $CHCl_3$.

$[\alpha]_D^{20}$= -38.9°, c=1 in MeOH.

Melting point: 111-112°C.

(*R*)-(+)-5-chloro-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (100)



100 was prepared following **general procedure D**, using (*R*)-(-)-epichlorohydrin, yielding 0.277 g (58%) of the desired product.

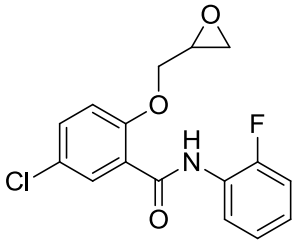
For NMR assignment see (±)-5-Chloro-2-oxiranylmethoxy-*N*-(3-trifluoromethyl-phenyl)-benzamide (**71**).

$[\alpha]_D^{20}$= +64.0°, c=1 in $CHCl_3$.

$[\alpha]_D^{20}$= +37.1°, c=1 in MeOH.

Melting point: 111-112°C.

5-chloro-*N*-(2-fluorophenyl)-2-(oxiran-2-ylmethoxy)benzamide (288)



288 was prepared following **general procedure D**, yielding 1.913 g (79%) of the desired product.

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ = 2.76 (dd, *J* = 4.9, *J* = 2.6, 1H, CH_aH$_b$ epoxide), 3.00 (dd[t], *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3.51 (m[sext], 1H, OCH$_a$H$_b$C*H*OH), 4.12 (dd, ^2J = -10.5, ^3J = 6.3, 1H,

OC*H*$_a$H$_b$CHOH), 4.41 (dd, ^2J = -10.6, ^3J = 3.3, 1H, OCH$_a$*H*$_b$CHOH), 6.96 (d, ^3J = 8.8, 1H, *H*-3 salicyl), 7.04-7.14 (m, 2H, *H*-3', *H*-4' in 2'-F-aniline), 7.15-7.19 (m[tr], 1H, *H*-5' in 2'-F-aniline), 7.42 (dd, ^3J = 8.8, ^4J = 2.8, 1H, *H*-4 salicyl), 8.26 (d, ^4J = 2.8, 1H, *H*-6 salicyl), 8.56 (ddd, $^3J = {}^3J_{HF}$ = 8.1, ^4J = 1.6, 1H, *H*-6' in 2'-F-aniline), 10.14 (br, s, 1H, CON*H*).

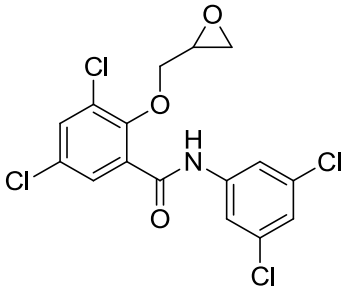
^{13}C{^{1}H}NMR (125 MHz, CDCl$_3$, 23 °C): δ = 44.93 (d, $^{TS}J_{CF}$ = 1.5, *C*H$_2$ oxirane), 49.41 (d, $^{TS}J_{CF}$ = 2.6, *C*H oxirane), 71.60 (salicyl-O*C*H$_2$-oxirane), 114.30 (*C*-3 salicyl), 114.83 (d, $^3J_{CF}$ = 19.2, *C*-3' aniline), 122.13 (*C*-6' aniline), 123.35 (*C*$_q$-5 salicyl), 124.41 (d, $^3J_{CF}$ = 7.9, *C*-4' in 2'-F-aniline), 124.83 (d, $^4J_{CF}$ = 3.5, *C*-5' in 2'-F-aniline), 126.93 (d, $^2J_{CF}$ = 9.8, *C*$_q$-1' in 2'-F-aniline), 127.81 (*C*$_q$-1 salicyl), 132.51 (*C*-6 salicyl), 133.19 (*C*-4 salicyl), 152.87 (d, $^1J_{CF}$ = -242.6, *C*$_q$-2' in 2'-F-aniline), 154.91 (*C*$_q$-2 salicyl), 161.77 (*C*ONH).

^{1}H NMR (500 MHz, DMSO-d$_6$, 23 °C): δ = 2.75 (dd, *J* = 4.7, *J* = 2.6, 1H, C*H*$_a$H$_b$ epoxide), 2.89 (dd[t], *J* = 4.5, 1H, CH$_a$*H*$_b$ epoxide), 3.44 (m[sext], 1H, OCH$_a$H$_b$C*H*OH), 4.10 (dd, ^2J = -11.0, ^3J = 6.6, 1H, OC*H*$_a$H$_b$CHOH), 4.55 (dd, ^2J = -11.0, ^3J = 2.5, 1H, OCH$_a$*H*$_b$CHOH), 7.17-7.26 (m, 2H, *H*-3', *H*-4' in 2'-F-aniline), 7.28 (d, ^3J = 8.8, 1H, *H*-3 salicyl), 7.32 (m[ddd], 1H, *H*-5' in 2'-F-aniline), 7.61 (dd, ^3J = 8.9, ^4J = 2.8, 1H, *H*-4 salicyl), 7.86 (d, ^4J = 2.7, 1H, *H*-6 salicyl), 8.18 (ddd, $^3J = {}^3J_{HF}$ = 7.8, ^4J = 2.0, 1H, *H*-6' in 2'-F-aniline), 10.17 (sharp, s, 1H, CON*H*).

^{13}C{^{1}H}NMR (125 MHz, DMSO-d$_6$, 23 °C): δ = 43.74 (*C*H$_2$ oxirane), 49.21 (d, $^{TS}J_{CF}$ = 1.4, *C*H oxirane), 71.00 (salicyl-O*C*H$_2$-oxirane), 115.32 (d, $^3J_{CF}$ = 19.0, *C*-3' aniline), 115.75 (*C*-3 salicyl), 123.22 (*C*-6' aniline), 124.08 (*C*$_q$-5 salicyl), 124.55 (d, $^4J_{CF}$ = 3.6, *C*-5' in 2'-F-aniline), 125.24 (*C*$_q$-1 salicyl), 125.38 (d, $^3J_{CF}$ = 7.9, *C*-4' in 2'-F-aniline), 125.94 (d, $^2J_{CF}$ = 9.8, *C*$_q$-1' in 2'-F-aniline), 129.98 (*C*-6 salicyl), 132.57 (*C*-4 salicyl), 153.23 (d, $^1J_{CF}$ = -242.6, *C*$_q$-2' in 2'-F-aniline), 154.86 (*C*$_q$-2 salicyl), 162.00 (*C*ONH).

Melting point: 146-149°C.

3,5-dichloro-*N*-(3,5-dichlorophenyl)-2-(oxiran-2-ylmethoxy)benzamide (347)



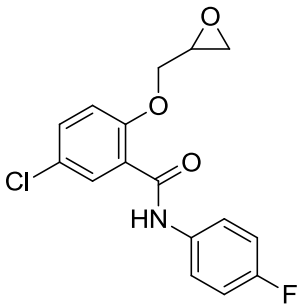
347 was prepared following **general procedure D**, yielding 1.219 g (44%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 2.61 (dd, *J* = 5.0, *J* = 2.7, 1H, CH_aH$_b$ epoxide), 2.75 (dd, *J* = 5.0, *J* = 4.3, 1H, CH$_a$$H_b$ epoxide), 3.24-3.29 (m, 1H, OCH$_a$H$_b$C*H*OR), 3.90 (dd, ^{2}J = -11.2, ^{3}J = 6.7, 1H, OCH_aH$_b$CHOR), 4.29 (dd, ^{2}J = -11.2, ^{3}J = 2.6, 1H, OCH$_a$$H_b$CHOR), 7.35 (d, ^{4}J = 1.8, 1H, *H*-4 aniline), 7.66 (d, ^{4}J = 2.6, 1H, *H*-6 salicyl), 7.77 (d, ^{3}J = 1.9, 2H, *H*-2,6 aniline), 7.87 (d, ^{4}J = 2.6, 1H, *H*-4 salicyl), 10.78 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 43.41 (*C*H$_2$ epoxide), 49.65 (*C*HO epoxide), 76.09 (O*C*H$_2$CHOR), 118.02 (*C*-2,6 aniline), 123.28 (*C*-4 aniline), 127.81 (*C*-6 salicyl), 128.71 (C_q-5 salicyl), 131.62 (*C*-4 salicyl), 133.28 (C_q-3 salicyl), 134.09 (C_q-3,5 aniline), 140.85 (*C*-1 aniline), 150.72 (*C*-2 salicyl), 163.12 (*C*ONH). C_q-1 saclicyl not recorded

Melting point: 163-164°C.

5-Chloro-*N*-(4-fluorophenyl)-2-oxiranylmethoxy-benzamide (348)



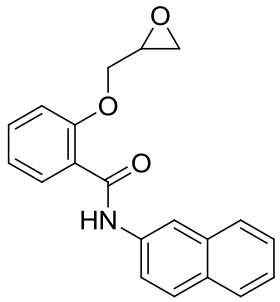
348 was prepared following **general procedure D**, yielding 0.932 g (65%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.88 (dd, *J* = 4.8 , *J* = 2.6, 1H, CH_aH$_b$ epoxide), 3.00 (dd[t], *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3.46 - 3.51 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.08 (dd, ^{2}J = -10.6, ^{3}J = 5.5, 1H, OCH_aH$_b$CHOR), 4.58 (dd, ^{2}J = -10.6, ^{3}J = 2.3, 1H, OCH$_a$$H_b$CHOR), 6.92 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.00 – 7.08 (m, 2H, *H*(3,5)-aniline), 7.40 (dd, ^{3}J = 8.8, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.70 - 7.78 (m, 2H, *H*(2,6)-aniline), 8.22 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 9.74 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.67 (*C*H$_2$ epoxide), 49.80 (*C*HO epoxide), 69.39 (O*C*H$_2$CHOR), 114.34 (*C*-3 salicyl), 115.75 ($^{2}J_{CF}$ = 22.6, *C*-3,5 aniline), 122.00 ($^{3}J_{CF}$ = 8.4, *C*-2,6 aniline), 123.86 (C-1 salicyl), 127.96 (C-5 salicyl), 132.48 (*C*-6 salicyl), 132.90 (*C*-4 salicyl), 134.52 ($^{4}J_{CF}$ = 2.5, *C*-1 aniline), 154.49 (*C*-2-salicyl), 159.50 ($^{1}J_{CF}$ = -243.6, *C*-4 aniline), 161.75 (*C*ONH).

Melting point: 102-107°C.

N-Naphthalen-2-yl-2-oxiranylmethoxy-benzamide (349)



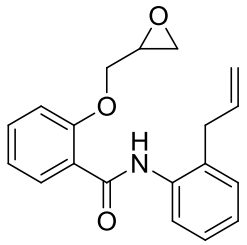
349 (CAS: 1510805-32-9[120]) was prepared following **general procedure D**, yielding 0.156 g (67%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.92 (dd, *J* = 4.8, *J* = 2.5, 1H, CH_aH$_b$ epoxide), 3.02 (dd[t], *J* = 4.3, 1H, CH$_a$$H_b$ epoxide), 3.51-3.56 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.17 (dd, ^2J = -10.6, ^3J = 5.4, 1H, OCH_aH$_b$CHOR), 4.61 (dd, ^2J = -10.6, ^3J = 2.4, 1H, OCH$_a$$H_b$CHOR), 7.01 (d, ^3J = 8.3, *J* = 0.4, 1H, *H*-3 salicyl), 7.15–7.21 (m[ddd], 1H, *H*-5 salicyl), 7.37–7.42 (m[ddd], 1H, *H*-6 napthalene), 7.43–7.48 (m, 1H, *H*-7 naphtalene), 7.48–7.52 (m, 1H, *H*-4 salicyl), 7.69 (dd, *J* = 8.7, *J* = 2.0, 1H, *H*-3 naphtalene), 7.78 (d, J = 8.0, 1H, *H*-5 naphtalene), 7.83 (d, 1H, *J* = 9.0, *H*-8 naphtalene), 7.85 (d, *J* = 8.3, 1H, *H*-4 naphtalene), 8.33 (dd, ^3J = 7.8, ^4J = 1.8, 1H, *H*-6 salicyl), 8.59 (d, ^4J = 1.8, 1H, *H*-1 naphtalene), 9.99 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.71 (*C*H$_2$ epoxide), 49.99 (*C*HO epoxide), 69.09 (O*C*H$_2$CHOR), 112.75 (*C*-3 salicyl), 117.07 (*C*-1 naphtalene), 120.57 (*C*-3 naphtalene), 122.51 (*C*-5 salicyl), 122.67 (*C*-1 salicyl), 124.93 (*C*-6 naphtalene), 126.46 (*C*-7 naphtalene), 127.64 (*C*-5 naphtalene), 128.04 (*C*- 8 naphtalene), 128.80 (*C*-4 Naphtalene), 130.79 (*C*-2 naphtalene), 132.91 (*C*-3 naphtalene), 133.33 (*C*-4 salicyl), 134.24 (*C*-5a naphtalene), 136.21 (*C*-8a naphthalene), 156.08 (*C*-2 salicyl), 163.38 (*C*ONH).

Melting point: 96-99°C.

N-(2-Allyl-phenyl)-2-oxiranylmethoxy-benzamide (350)

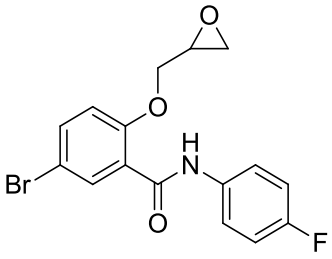


350 was prepared following **general procedure D**, yielding 0.609 g (78%) of the desired product as yellow/brown oil.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.75 (dd, *J* = 4.8 , *J* = 2.6, 1H, CH_aH$_b$ epoxide), 2.92 (dd[t], *J* = 4.5, 1H, CH$_a$$H_b$ epoxide), 3.37 – 3.42 (m, 1H, OCH$_a$H$_b$C*H*OR), 3.48 (dt, *J* = 6.1 , *J* = 1.5, 2H, Ar-CH_2-HC= CH_2), 4.13 (dd[m=überlagert], ^{2}J = -11.6, ^{3}J = 6.2, 1H, OCH_aH$_b$CHOR), 4.54 (dd, ^{2}J = -11.6, ^{3}J = 2.7, 1H, OCH$_a$$H_b$CHOR), 5.02 (dd, $^{3}J_{trans}$ = 17.1, ^{2}J = 1.6, 1H, CH_2-HC= CH_{cis}H$_{trans}$), 5.10 (dd, $^{3}J_{cis}$ = 5.8, ^{2}J = 1.6, 1H, CH_2-HC= CH$_{cis}$$H_{trans}$), 5.95 - 6.09 (m, 1H, CH_2-*H*C= CH_2), 7.06 (d, ^{3}J = 8.3, 1H, *H*-3 salicyl), 7.12 – 7.19 (m[t], 2H, *H*-4 anilide/ *H*-5 salicyl), 7.23 (dd, ^{3}J = 7.5, ^{4}J = 1.5, 1H, *H*-3 aniline), 7.27 – 7.32 (m, 1H, *H*-5 aniline), 7.44 – 7.52 (m, 1H, *H*-4 salicyl), 8.00 (d, ^{3}J = 8.0, 1H, *H*-6 aniline), 8.28 (dd, ^{3}J = 7.8, ^{4}J = 1.8, 1H, *H*-6 salicyl), 9.41 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 36.00 (*C*H_2-HC= CH_2), 44.81 (*C*H_2 epoxide), 49.81 (*C*HO epoxide), 70.46 (O*C*H_2CHOR), 113.04 (*C*-3 salicyl), 116.60 (CH_2-HC= *C*H_2), 122.36 (*C*-5 salicyl), 122.76 (*C*-1 salicyl), 124.67 (*C*-6 aniline), 125.50 (*C*-4 aniline), 127.24 (*C*-5 aniline), 129.89 (*C*-3 aniline), 131.57 (*C*-1 aniline), 132.97 (*C*-6 salicyl), 133.23 (*C*-4 salicyl), 136.01 (CH_2-H*C*= CH_2), 136.14 (*C*-2 aniline), 156.33 (*C*-2 salicyl), 163.66 (*C*ONH).

5-bromo-*N*-(4-fluorophenyl)-2-(oxiran-2-ylmethoxy)benzamide (351)



351 was prepared following **general procedure D**, yielding 0.583 g (48%) of the desired product.

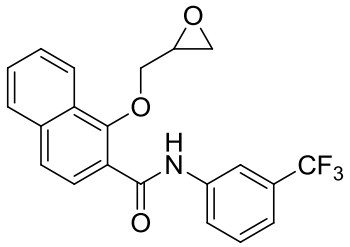
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.88 (dd, *J* = 4.7 , *J* = 2.6, 1H, CH_aH$_b$ epoxide), 3.00 (dd[t], *J* = 4.5, 1H, CH$_a$$H_b$ epoxide), 3.46 - 3.51 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.08 (dd, ^{2}J = -10.5, ^{3}J = 5.6, 1H, OCH_aH$_b$CHOR), 4.58 (dd, ^{2}J = -10.6, ^{3}J = 2.3, 1H, OCH$_a$$H_b$CHOR), 6.87 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.01–7.08 (m, 2H, *H*(3,5)-aniline), 7.55 (dd, ^{3}J = 8.7, ^{4}J = 2.7, 1H, *H*-4 salicyl), 7.71-7.78 (m, 2H, *H*(2,6)-aniline), 8.36 (d, ^{4}J = 2.6, 1H, *H*-6 salicyl), 9.72 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.67 (*C*H_2 epoxide), 49.79 (*C*HO epoxide), 69.31 (O*C*H_2CHOR), 114.69 (*C*-3 salicyl), 115.15 (C-5 salicyl), 115.75 ($^{2}J_{CF}$ = 22.1, *C*-3,5 aniline),

121.99 ($^3J_{CF}$ = 7.6, *C*-2,6 aniline), 124.19 (C-1 salicyl), 134.53 ($^4J_{CF}$ = 2.7, *C*-1 aniline), 135.44 (*C*-6 salicyl), 135.85 (*C*-4 salicyl), 155.00 (*C*-2-salicyl), 159.49 ($^1J_{CF}$ = -243.7, *C*-4 aniline), 161.64 (*C*ONH).

Melting point: 114-118°C.

1-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)-2-naphthamide (352)

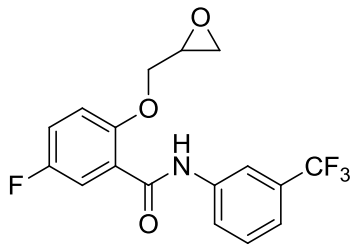


352 was prepared following **general procedure D**, yielding 1.935 g (75%) of the desired product as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.89 (dd, *J* = 4.8 , *J* = 2.6, 1H, CH_aH$_b$ epoxide), 2.99 (dd[t], *J* = 4.8, *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3.49-3.56 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.03 (dd, ^2J = -11.1, ^3J = 6.3, 1H, OCH_aH$_b$CHOR), 4.49 (dd, ^2J = -11.1, ^3J = 2.0, 1H, OCH$_a$$H_b$CHOR), 7.40 (d, br, ^3J = 7.7, 1H, *H*-4 aniline), 7.50 (dd[tr], ^3J = 7.8, 1H, *H*-5 aniline), 7.59-7.65 (m, 2H, *H*-6,7 napththyl), 7.75 (d, ^3J = 8.7, 1H, *H*-4 napththyl), 7.87-7.93 (m, 1H, *H*-5 napththyl), 8.02 (d, br, ^3J = 8.9, 1H, *H*-6 aniline), 8.16-8.22 (m, 2H, *H*-3 napththyl *H*-8 napththyl), 8.30 (s br, 1H, *H*-2' in 3'-CF_3-aniline), 10.08 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.51 (*C*H$_2$ oxirane), 50.18 (*C*H oxirane), 76.28 (OCH_2CHOR), 117.35 (q, $^3J_{CF}$ = 4.1, *C*-2 aniline), 120.90 (q, $^3J_{CF}$ = 3.8, *C*-4' in 3'-CF_3-aniline), 122.21 (C_q-2 naphthyl), 122.69 (*C*-8 naphthyl), 123.54 (*C*-6' in 3'-CF_3-aniline), 124.15 (q, $^1J_{CF}$ = -272.4, 3'-*C*F_3-aniline), 125.52 (*C*-4 naphthyl), 126.79 (*C*-3 naphthyl), 127.24 (*C*-7 naphthyl), 127.30 (C_q-4a naphthyl), 128.53 (*C*-5 naphthyl), 128.56 (*C*-6 naphthyl), 129.55 (*C*-5' in 3'-CF_3-aniline), 131.45 (q, $^2J_{CF}$ = 32.2, *C*-3' in 3'-CF_3-aniline), 137.01 (C_q-8a naphthyl), 139.07 (C_q-1' in 3'-F_3-aniline), 153.27 (C_q-1 naphthyl), 163.61 (*C*ONH).

5-fluoro-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (353)

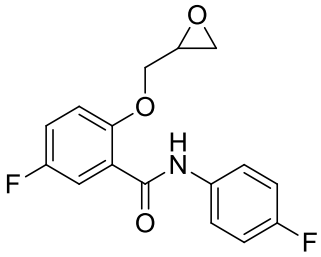


353 was prepared following **general procedure D**, yielding 0.120 g (23%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.90 (dd, *J* = 4.7, *J* = 2.6, 1H, CH_aH$_b$ epoxide), 3.02 (dd[t], *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3.48-3.53 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.12 (dd, ^{2}J = -10.5, ^{3}J = 5.4, 1H, OCH_aH$_b$CHOR), 4.60 (dd, ^{2}J = -10.5, ^{3}J = 2.3, 1H, OCH$_a$$H_b$CHOR), 6.97 (m, ^{3}J = 9.0, ^{F}J = 4.0 1H, *H*-3 salicyl), 7.18 (m, ^{3}J = 9.0, ^{4}J = 3.3, ^{F}J = 10.3, 1H, *H*-4 salicyl), 7.38 (d, ^{3}J = 7.8, 1H, *H*-4 aniline), 7.47 (dd [t], ^{3}J = 7.9, 1H, *H*-5 aniline), 7.92-8.00 (m, 2H, *H*-6 aniline, *H*-6 salicyl) 8.21 (s [t], 1H, *H*-2 aniline), 10.03 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.69 (*C*H$_2$ epoxide), 49.87 (*C*HO epoxide), 69.59 (OCH$_2$CHOR), 114.61 ($^{3}J_{CF}$= 7.8, *C*-3 salicyl), 117.23 (q, $^{3}J_{CF}$= 4.2, *C*-2 aniline), 119.11 ($^{2}J_{CF}$= 25.2, *C*-6 salicyl), 120.07 ($^{2}J_{CF}$= 23.7, *C*-4 salicyl), 120.91 (q, $^{3}J_{CF}$= 3.9, *C*-4 aniline), 123.39 (*C*-6 aniline), 124.13 ($^{1}J_{CF}$ = -242.0, CF_3), 123.77 ($^{3}J_{CF}$ = 6.8, C-1 salicyl), 129.62 (*C*-5 aniline), 131.50 ($^{2}J_{CF}$ = 32.6, *C*-3 aniline), 139.01 (*C*-1 aniline), 152.18 ($^{4}J_{CF}$ = 2.2, *C*-2-salicyl), 157.87 ($^{1}J_{CF}$ = -241.9, C-5 salicyl), 162.15 ($^{4}J_{CF}$ =1.7, *C*ONH).

5-fluoro-*N*-(4-fluorophenyl)-2-(oxiran-2-ylmethoxy)benzamide (354)



354 was prepared following **general procedure D**, yielding 0.295 g (85%) of the desired product.

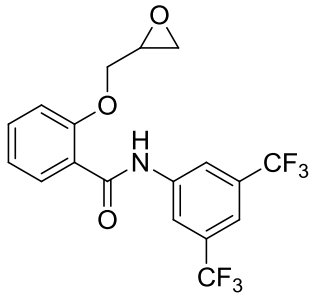
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.88 (dd, *J* = 4.7, *J* = 2.6, 1H, CH_aH$_b$ epoxide), 3.00 (dd[t], *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3.46-3.50 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.08 (dd, ^{2}J = -10.7, ^{3}J = 5.5, 1H, OCH_aH$_b$CHOR), 4.57 (dd, ^{2}J = -10.6, ^{3}J = 2.3, 1H, OCH$_a$$H_b$CHOR), 6.95 (dd, ^{3}J = 9.3, ^{F}J = 4.6 1H, *H*-3 salicyl), 7.01–7.08 (m, 2H, *H*(3,5)-aniline), 7.13-7.19 (m, 1H, *H*-4 salicyl), 7.73-7.78 (m, 2H, *H*(2,6)-aniline), 7.97 (dd, ^{F}J = 9.3, ^{4}J = 3.3, 1H, *H*-6 salicyl), 9.84 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.65 (*C*H$_2$ epoxide), 49.89 (*C*HO epoxide), 69.79 (OCH$_2$CHOR), 114.5 ($^{3}J_{CF}$ = 7.6, *C*-3 salicyl), 115.73 ($^{2}J_{CF}$ = 22.5, *C*-3,5 aniline), 119.05 ($^{2}J_{CF}$ = 25.2, *C*-6 salicyl),119.72 ($^{2}J_{CF}$ = 23.7, *C*-4 salicyl), 122.05 ($^{3}J_{CF}$ = 7.8, *C*-2,6 aniline), 124.12 ($^{3}J_{CF}$ =

6.9, C-1 salicyl), 134.53 ($^4J_{CF}$ = 2.7, *C*-1 aniline), 152.14 ($^4J_{CF}$ = 2.4, *C*-2-salicyl), 157.87 ($^1J_{CF}$ = -241.7, C-5 salicyl), 159.50 ($^1J_{CF}$ = -243.7, *C*-4 aniline), 160.71 ($^4J_{CF}$ =1.5, *C*ONH).

Melting point: 102-104

N-(3,5-bis(trifluoromethyl)phenyl)-2-(oxiran-2-ylmethoxy)benzamide (355)

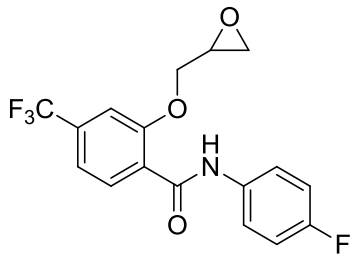


355 was prepared following **general procedure D**, yielding 0.168 g (71%) of the desired product.

^{1}H NMR (400 MHz, DMSO-D$_6$, 27 °C): δ = 2.74-2.78 (m[dd] 1H, C*H*$_a$H$_b$ epoxide), 2.84 (dd[t], *J* = 4.6, 1H, CH$_a$*H*$_b$ epoxide), 3.38–3.44 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.09 (dd, ^2J = -11.2, ^3J = 5.9, 1H, OC*H*$_a$H$_b$CHOR), 4.60 (dd, ^2J = -11.4, ^3J = 1.7, 1H, OCH$_a$*H*$_b$CHOR), 7.12 (dd [t], ^3J = 7.5, *H*-5 salicyl) 7.23 (d, ^3J = 8.4, 1H, *H*-3 salicyl), 7.37 (d, ^3J = 7.9, 1H, *H*-4 aniline), 7.54 (dd [t], ^3J = 8.2, 1H, *H*-4 salicyl), 7.69 (d, ^3J = 7.7, 1H, *H*-6 salicyl), 7.80 (br s, 1H, *H*-4 aniline), 8.45 (br s, 1H, *H*-2,6 aniline), 10.72 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-D$_6$, 27 °C): δ = 43.70 (*C*H$_2$ epoxide), 49.62 (*C*HO epoxide), 69.13 (OC*H*$_2$CHOR), 113.43 (*C*-3 salicyl), 116.27 (q, $^3J_{CF}$ = 3.1, *C*-4' in 3',5'-bis-CF$_3$-aniline), 119.21 (q, $^3J_{CF}$ = 3.1, *C*-2',6' in 3',5'-bis-CF$_3$-aniline), 121.11 (*C*-5 salicyl), 123.21 ($^1J_{CF}$ = -271.9, *C*F$_3$), 124,21 (*C*-1 salicyl),129.91 (*C*-6 salicyl), 130.81 ($^2J_{CF}$ = 32.7, *C*-3,5 in 3',5'-bis-CF$_3$-aniline), 132.72 (*C*-4 salicyl), 140.83 (*C*-1 in 3',5'-bis-CF$_3$-aniline), 155.58 (*C*-2 salicyl), 165.32 (*C*ONH).

N-(4-fluorophenyl)-2-(oxiran-2-ylmethoxy)-4-(trifluoromethyl)benzamide (356)



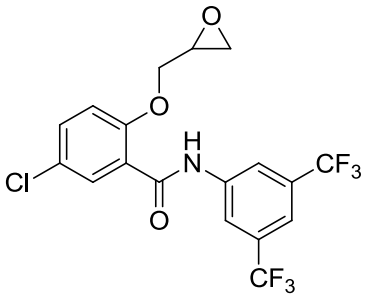
356 was prepared following **general procedure D**, yielding 4.560 g (98%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.91 (dd, *J* = 4.7, *J* = 2.7, 1H, CH_aH$_b$ epoxide), 3.03 (dd[t], *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3.50-3.54 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.15 (dd, ^{2}J = -10.4, ^{3}J = 5.6, 1H, OCH_aH$_b$CHOR), 4.67 (dd, ^{2}J = -10.4, ^{3}J = 2.1, 1H, OCH$_a$$H_b$CHOR), 7.05 (m, 2H, *H*(3,5)-aniline), 7.21 (s, 1H, *H*-3 salicyl), 7.40 (d, ^{3}J = 8.1, 1H, *H*-5 salicyl), 7.77 (m, 2H, *H*(2,6)-aniline), 8.36 (d, ^{4}J = 8.1, 1H, *H*-6 salicyl), 9.74 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.71 (*C*H$_2$ epoxide), 49.70 (*C*HO epoxide), 69.31 (O*C*H$_2$CHOR), 109.83 (q, $^{3}J_{CF}$ = 3.8, *C*-3 salicyl), 115.81 ($^{2}J_{CF}$ = 22.6, *C*-3,5 aniline), 119.11 (q, $^{3}J_{CF}$ = 3.7, *C*-5 salicyl), 122.08 ($^{3}J_{CF}$ = 7.8, *C*-2,6 aniline), 123.41 ($^{1}J_{CF}$ = -272.8, *C*F$_3$) 125.57 (*C*-1 salicyl), 133.65 (*C*-6 salicyl), 134.37 ($^{4}J_{CF}$ = 2.8, *C*-1 aniline), 134.85 ($^{2}J_{CF}$ = 32.8, *C*-4 salicyl), 155.89 (*C*-2-salicyl), 159.67 ($^{1}J_{CF}$ = -243.9, *C*-4 aniline), 161.82 (*C*ONH).

Melting point: 100-102°C.

N-(3,5-bis(trifluoromethyl)phenyl)-5-chloro-2-(oxiran-2-ylmethoxy)benzamide (357)



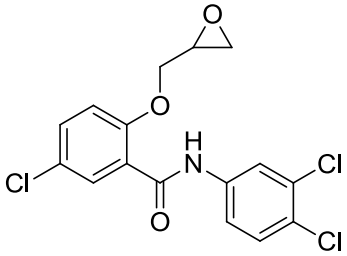
357 was prepared following **general procedure D**, yielding 0.443 g (100%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.93 (dd, *J* = 4.8 , *J* = 2.6, 1H, CH_aH$_b$ epoxide), 3.06 (dd[t], *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3.51-3.56 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.17(dd, ^{2}J = -10.5, ^{3}J = 5.0, 1H, OCH_aH$_b$CHOR), 4.64 (dd, ^{2}J = -10.5, ^{3}J = 2.3, 1H, OCH$_a$$H_b$CHOR), 6.97 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.46 (dd, ^{3}J = 8.8, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.62 (s, 1H, *H*-4 aniline), 8.22 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 8.38 (s, 2H, *H*-2,6 aniline), 10.14 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.78 (*C*H$_2$ epoxide), 49.81 (*C*HO epoxide), 68.82 (O*C*H$_2$CHOR), 114.60 (*C*-3 salicyl), 117.55 (m, $^{3}J_{CF}$ = 3.7, *C*-4 aniline), 120.17 (m, $^{3}J_{CF}$ = 3.6, *C*-2,6 aniline), 123.07 (*C*-1 salicyl), 123.37 ($^{1}J_{CF}$ = -273.0, 2x *C*F$_3$ aniline), 128.27 (*C*-5 salicyl), 132.40 (q, $^{3}J_{CF}$ = 33.5, *C*-3,5 aniline), 132.61 (*C*-6 salicyl), 133.62 (*C*-4 salicyl), 139.93 (*C*-1 aniline) 154.53 (*C*-2 salicyl), 162.37 (*C*ONH).

Melting point: 114-116°C.

5-chloro-*N*-(3,4-dichlorophenyl)-2-(oxiran-2-ylmethoxy)benzamide (358)



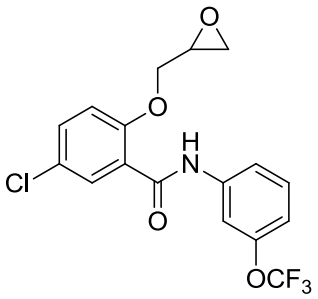
358 was prepared following **general procedure D**, yielding 2.769 g (73%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.89 (dd, *J* = 4.8 , *J* = 2.6, 1H, CH_aH$_b$ epoxide), 3.03 (dd[t], *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3.48-3.53 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.09 (dd, ^{2}J = -10.5, ^{3}J = 5.4, 1H, OCH_aH$_b$CHOR), 4.60 (dd, ^{2}J = -10.5, ^{3}J = 2.2, 1H, OCH$_a$$H_b$CHOR), 6.92 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.38 (d, ^{4}J = 8.7, 1H, *H*-5 aniline), 7.42 (dd, ^{3}J = 8.8, ^{4}J = 2.7, 1H, *H*-4 salicyl), 7.57 (dd, ^{3}J = 8.7, ^{4}J = 2.5, 1H, *H*-6 aniline), 8.10 (d, ^{4}J = 2.5, 1H, *H*-2 aniline), 8.19 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 9.82 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.75 (*C*H$_2$ epoxide), 49.80 (*C*HO epoxide), 69.19 (O*C*H$_2$CHOR), 114.37 (*C*-3 salicyl), 119.62 (*C*-6 aniline), 122.03 (*C*-2 aniline), 123.38 (*C*-1 salicyl), 127.44 (*C*-4 aniline), 128.05 (*C*-5 salicyl), 130.59 (*C*-5 aniline), 132.50 (*C*-6 salicyl), 132.82 (*C*-3 aniline), 133.25 (*C*-4 salicyl), 137.95 (*C*-1 aniline) 154.45 (*C*-2 salicyl), 161.94 (*C*ONH).

Melting point: 180-210°C.

5-chloro-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethoxy)phenyl)benzamide (359)



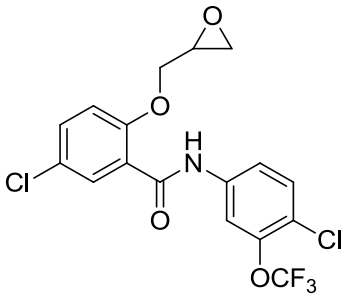
359 was prepared following **general procedure D**, yielding 0.590 g (26%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.89 (dd, *J* = 4.7 , *J* = 2.7, 1H, CH_aH$_b$ epoxide), 3.01 (dd[t], *J* = 4.5, 1H, CH$_a$$H_b$ epoxide), 3.46-3.52 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.12 (dd, ^{2}J = -10.5, ^{3}J = 5.4, 1H, OCH_aH$_b$CHOR), 4.60 (dd, ^{2}J = -10.5, ^{3}J = 2.3, 1H, OCH$_a$$H_b$CHOR), 6.92 (d, ^{3}J = 8.9, 1H, *H*-3 salicyl), 6.98 (d, ^{3}J = 8.2, 1H, *H*-4 aniline), 7.35 (dd [t], ^{3}J = 8.1, ^{3}J = 7.9, 1H, *H*-5 aniline), 7.41 (dd, ^{3}J = 8.9, ^{4}J = 2.9, 1H, *H*-4 salicyl), 7.63 (d, ^{3}J = 8.2, 1H, *H*-6 aniline), 7.89 (s [t], 1H, *H*-2 aniline), 8.22 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 9.86 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.67 (*C*H$_2$ epoxide), 49.78 (*C*HO epoxide), 69.22 (O*C*H$_2$CHOR), 113.14 (*C*-2 aniline), 114.35 (*C*-3 salicyl), 116.46 (*C*-4 aniline), 118.37 (*C*-6 aniline), 120.64 ($^{1}J_{CF}$ = -256.4, O*C*F$_3$ aniline), 123.58 (*C*-1 salicyl), 128.03(*C*-5 salicyl), 130.12(*C*-5 aniline), 132.55 (*C*-6 salicyl), 133.16 (*C*-4 salicyl), 139.88 (*C*-1 aniline), 149.75 (*C*-3 aniline), 154.50 (*C*-2 salicyl), 162.00 (*C*ONH).

Melting point: 83-85°C.

5-chloro-*N*-(4-chloro-3-(trifluoromethoxy)phenyl)-2-(oxiran-2-ylmethoxy)benzamide (360)



360 was prepared following **general procedure D**, yielding 0.251 g (54%) of the desired product.

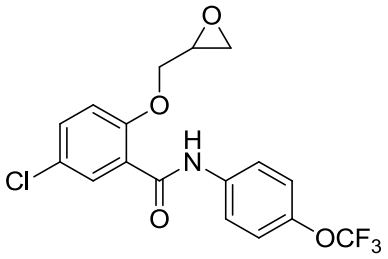
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.90 (dd, *J* = 4.7, *J* = 2.7, 1H, CH_aH$_b$ epoxide), 3.04(dd[t], *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3.48 - 3.53 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.10 (dd, ^{2}J = -10.5, ^{3}J = 5.5, 1H, OCH_aH$_b$CHOR), 4.61 (dd, ^{2}J = -10.5, ^{3}J = 2.2, 1H, OCH$_a$$H_b$CHOR), 6.93 (d, ^{3}J = 8.9, 1H, *H*-3 salicyl), 7.28 (m [dq], ^{3}J = 9.0, *J* = 1.2, 1H, *H*-5 aniline), 7.42 (dd, ^{3}J = 8.8, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.64 (dd, ^{3}J = 9.0 ^{4}J = 2.6, 1H, *H*-6 aniline), 8.12 (d, ^{4}J = 2.6, 1H, *H*-2 aniline), 8.19 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 9.87 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.78 (*C*H$_2$ epoxide), 49.81 (*C*HO epoxide), 69.18 (O*C*H$_2$CHOR), 114.41 (*C*-3 salicyl), 119.42 (*C*-6 aniline), 120.68 (q, $^{1}J_{CF}$ = -256 1, O*C*F$_3$ aniline), 122.34 (*C*-2aniline), 123.17 (*C*-5 aniline), 123.31 (*C*-1 salicyl), 127.95 (*C*-4 aniline), 128.10 (*C*-5

salicyl), 132.54 (*C*-6 salicyl), 133.33 (*C*-4 salicyl), 137.92 (*C*-1 aniline), 141.28 (q, J_{CF} = 1.6, *C*-4 aniline), 154.48 (*C*-2 salicyl), 162.02 (*C*ONH).

Melting point: 115-121°C.

5-chloro-2-(oxiran-2-ylmethoxy)-*N*-(4-(trifluoromethoxy)phenyl)benzamide (361)



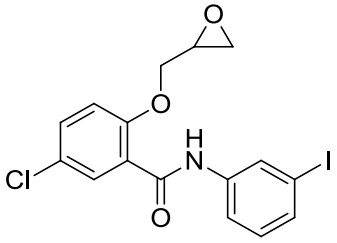
361 was prepared following **general procedure D**, yielding 3.009 g (85%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.89 (dd, *J* = 4.7 , *J* = 2.6, 1H, CH_aH$_b$ epoxide), 3.01 (dd[t], *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3.47-3.51 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.08 (dd, ^2J = -10.6, ^3J = 5.6, 1H, OCH_aH$_b$CHOR), 4.59 (dd, ^2J = -10.6, ^3J = 2.3, 1H, OCH$_a$$H_b$CHOR), 6.93 (d, ^3J = 8.8, 1H, *H*-3 salicyl), 7.21 (d, ^3J = 8.6, 2H, *H*-3,5 aniline), 7.41 (dd, ^3J = 8.7, ^4J = 2.8, 1H, *H*-4 salicyl), 7.83 (m, 2H, *H*-2,6 aniline), 8.22 (d, ^4J = 2.8, 1H, *H*-6 salicyl), 9.83 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.71 (*C*H$_2$ epoxide), 49.81 (*C*HO epoxide), 69.36 (OCH_2CHOR), 114.35 (*C*-3 salicyl), 120.67 ($^1J_{CF}$ = -256.2, OCF_3 aniline), 121.49 (*C*-2,6 aniline), 121.86 (*C*-3,5 aniline), 123.71 (*C*-1 salicyl), 128.03 (*C*-5 salicyl), 132.55 (*C*-6 salicyl), 133.07 (*C*-4 salicyl), 137.16 (*C*-1 aniline), 145.41 (q, J_{CF} = 1.5, *C*-4 aniline), 154.50 (*C*-2 salicyl), 161.90 (*C*ONH).

Melting point: 89-95°C.

5-chloro-*N*-(3-iodophenyl)-2-(oxiran-2-ylmethoxy)benzamide (362)



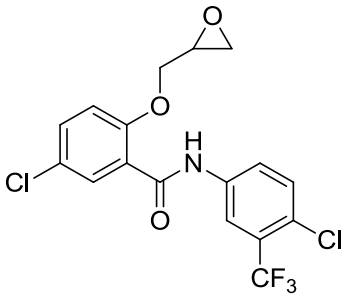
362 was prepared following **general procedure D**, yielding 2.385 g (72%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.88 (dd, *J* = 4.7, *J* = 2.6, 1H, C$H_a$$H_b$ epoxide), 3.02 (dd[t], *J* = 4.4, 1H, CH_aH_b epoxide), 3.46-3.51 (m, 1H, OCH_aH_bCHOR), 4.10 (dd, ^{2}J = -10.5, ^{3}J = 5.5, 1H, OCH_aH_bCHOR), 4.57 (dd, ^{2}J = -10.6, ^{3}J = 2.2, 1H, OCH_aH_bCHOR), 6.93 (d, ^{3}J = 8.9, 1H, *H*-3 salicyl), 7.061 (d, ^{3}J = 8.1, 1H, *H*-4 aniline), 7.41 (dd, ^{3}J = 8.8, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.46 (dq, ^{3}J = 7.9, *J* = 0.6, 1H, *H*-5 aniline), 7.68 (dq, ^{3}J = 8.2, *J* = 1.2, 1H, *H*-6 aniline), 8.20 (d, ^{4}J = 2.7, 1H, *H*-6 salicyl), 8.28 (s [t], 1H, *H*-2 aniline), 9.73 (br s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.69 (*C*H_2 epoxide), 49.78 (*C*HO epoxide), 69,39 (OCH_2CHOR), 94,38 (*C*-3 aniline), 114,38 (*C*-3 salicyl), 119,53 (*C*-6 aniline), 123,66 (*C*-1 salicyl), 128,00 (*C*-5 salicyl), 129,13 (*C*-2 aniline), 130,59 (*C*-4 aniline), 132,52 (*C*-6 salicyl), 133,10 (*C*-4 salicyl), 133,42 (*C*-5 aniline), 139,61 (*C*-1 aniline) 154,50 (*C*-2 salicyl), 161,85 (*C*ONH).

Melting point: 127-128°C.

5-chloro-*N*-(4-chloro-3-(trifluoromethyl)phenyl)-2-(oxiran-2-ylmethoxy)benzamide (363)



363 was prepared following **general procedure D**, yielding 1.145 g (26%) of the desired product.

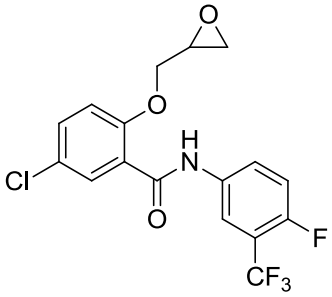
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.91 (dd, *J* = 4.7, *J* = 2.7, 1H, C$H_a$$H_b$ epoxide), 3.04 (dd[t], *J* = 4.4, 1H, CH_aH_b epoxide), 3.49-3.53 (m, 1H, OCH_aH_bCHOR), 4.13 (dd, ^{2}J = -10.4, ^{3}J = 5.2, 1H, OCH_aH_bCHOR), 4.61 (dd, ^{2}J = -10.4, ^{3}J = 2.3, 1H, OCH_aH_bCHOR), 6.94 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.44 (dd, ^{3}J = 8.8, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.45 (m , ^{3}J = 8.9, teilweise überlagert, 1H, *H*-5 aniline), 7.46 (dd, ^{3}J = 8.9 ^{4}J = 2.6, 1H, *H*-6 aniline), 8.21 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 8.23 (d, ^{4}J = 2.6, 1H, *H*-2 aniline), 9.96 (br s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.76 (*C*H_2 epoxide), 49.81 (*C*HO epoxide), 69.04 (OCH_2CHOR), 114.49 (*C*-3 salicyl), 119.47 (q, $^{3}J_{CF}$ = 5.6, *C*-2 aniline), 122.82 (q, $^{1}J_{CF}$ = -273.5, *C*F_3 aniline), 123.32 (*C*-1 salicyl), 124.27 (*C*-6 aniline), 126.81 (*C*-4 aniline), 128.18 (*C*-5 salicyl),

128.87 (q, $^{2}J_{CF}$ = 31.5, *C*-3 aniline), 132.08 (*C*-5 aniline), 132.58 (*C*-6 salicyl), 133.38 (*C*-4 salicyl), 137.39 (*C*-1 aniline), 154.50 (*C*-2 salicyl), 162.12 (*C*ONH).

Melting point: 116-118°C.

5-chloro-*N*-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(oxiran-2-ylmethoxy)benzamide (364)



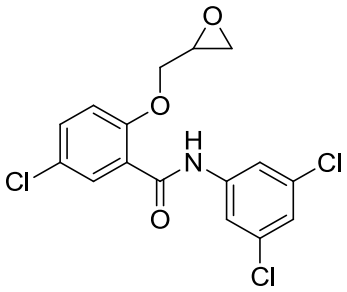
364 was prepared following **general procedure D**, yielding 1.093 g (36%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.90 (dd, *J* = 4.7, *J* = 2.6, 1H, CH_aH$_b$ epoxide), 3.03 (dd[t], *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3.48-3.53 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.10 (dd, ^{2}J = -10.6, ^{3}J = 5.5, 1H, OCH_aH$_b$CHOR), 4.60 (dd, ^{2}J = -10.6, ^{3}J = 2.2, 1H, OCH$_a$$H_b$CHOR), 6.92 (d, ^{3}J = 8.9, 1H, *H*-3 salicyl), 7.16 (dd [t], ^{3}J = 9.9, 1H, *H*-5 aniline), 7.41 (dd, ^{3}J = 8.9, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.93 (m, 1H, *H*-6 aniline), 8.17 (d, ^{4}J = 2.7, J_{HF} = 6.3, 1H, *H*-2 aniline), 8.18 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 9.91 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.74 (*C*H$_2$ epoxide), 49.79 (*C*HO epoxide), 69.08 (O*C*H$_2$CHOR), 114.49 (*C*-3 salicyl), 117.40 ($^{2}J_{CF}$ = 21.7, *C*-5 aniline), 118.55 (dd, $^{2}J_{CF}$ = 33.4 $^{2}J_{CF}$ = 13.3, *C*-3 aniline), 119.00 (q, J_{CF} = 5.2, *C*-2 aniline), 122.57 (q, $^{1}J_{CF}$ = -272.7, *C*F$_3$ aniline), 123.29 (*C*-1 salicyl), 125.42 ($^{3}J_{CF}$ = 7.9, *C*-6 aniline), 128.05 (*C*-5 salicyl), 132.44 (*C*-6 salicyl), 133.26 (*C*-4 salicyl), 134.73 ($^{4}J_{CF}$ = 3.1, *C*-1 aniline), 154.50 (*C*-2 salicyl), 156.05 ($^{1}J_{CF}$ = -253.2, *C*-4 aniline), 162.01 (*C*ONH).

Melting point: 123-124°C.

5-chloro-*N*-(3,5-dichlorophenyl)-2-(oxiran-2-ylmethoxy)benzamide (365)



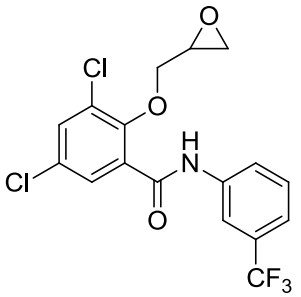
365 was prepared following **general procedure D**, yielding 2.162 g (77%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.89 (dd, *J* = 4.8 , *J* = 2.7, 1H, CH_aH$_b$ epoxide), 3.05 (dd[t], *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3.47-3.54 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.10 (dd, ^{2}J = -10.6, ^{3}J = 5.4, 1H, OCH_aH$_b$CHOR), 4.60 (dd, ^{2}J = -10.6, ^{3}J = 2.0, 1H, OCH$_a$$H_b$CHOR), 6.93 (d, ^{3}J = 8.7, 1H, *H*-3 salicyl), 7.10 (d, ^{4}J = 1.7, 1H, *H*-4 aniline), 7.42 (dd, ^{3}J = 8.8, ^{4}J = 2.7, 1H, *H*-4 salicyl), 7.77 (d, ^{3}J = 1.8, 2H, *H*-2,6 aniline), 8.17 (d, ^{4}J = 2.7, 1H, *H*-6 salicyl), 9.91 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.79 (*C*H$_2$ epoxide), 49.77 (*C*HO epoxide), 69.24 (OCH_2CHOR), 114.42 (*C*-3 salicyl), 118.63 (*C*-2,6 aniline), 123.24 (*C*-1 salicyl), 124.28 (*C*-4 aniline), 128.06 (*C*-5 salicyl), 132.52 (*C*-6 salicyl), 133.36 (*C*-4 salicyl), 135.26 (*C*-3,5 aniline), 140.24 (*C*-1 aniline), 154.47 (*C*-2 salicyl), 162.03 (*C*ONH).

Melting point: 150-157°C.

3,5-dichloro-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (366)



366 was prepared following **general procedure D**, yielding 1.214 g (100%) of the desired product.

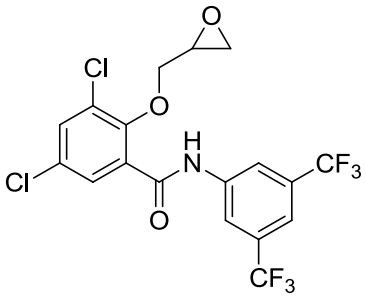
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.85 (dd, *J* = 4.6 , *J* = 2.6, 1H, CH_aH$_b$ epoxide), 2.86 (dd[t], *J* = 4.5, 1H, CH$_a$$H_b$ epoxide), 3.43-3.49 (m, 1H, OCH$_a$H$_b$C*H*OR), 3.98 (dd, ^{2}J = -10.7, ^{3}J = 6.2, 1H, OCH_aH$_b$CHOR), 4.50 (dd, ^{2}J = -10.8, ^{3}J = 2.1, 1H, OCH$_a$$H_b$CHOR), 7.41 (d, ^{3}J = 7.6, 1H,

H-4 aniline), 7.47 (dd [q], ^{3}J = 7.9, ^{3}J = 8.1, 1H, *H*-5 aniline), 7.58 (d, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.96 (d, ^{3}J = 8.3, 1H, *H*-6 aniline), 8.12 (d, ^{4}J = 2.7, 1H, *H*-6 salicyl), 8.21 (s, 1H, *H*-2 aniline), 9.86 (br s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.57 (*C*H_2 epoxide), 49.91 (*C*HO epoxide), 74.92 (O*C*H_2CHOR), 117.71 ($^{3}J_{CF}$ = 4.0, *C*-2 aniline), 121.45 ($^{3}J_{CF}$ = 3.7, *C*-4 aniline), 123.86 (*C*-6 aniline), 124.07 ($^{1}J_{CF}$ = -272.1, *C*F_3 aniline), 129.15 (*C*-1 salicyl), 129.44 (*C*-3 salicyl), 129.61 (*C*-5 aniline), 130.97 (*C*-6 salicyl), 131.49 (*C*-5 salicyl), 133.94(*C*-4 salicyl), 138.48 (*C*-1 aniline), 150.73 (*C*-2 salicyl), 160.99 (*C*ONH). *C*-3 Aniline not recorded

Melting point: 62-77°C.

N-(3,5-bis(trifluoromethyl)phenyl)-3,5-dichloro-2-(oxiran-2-ylmethoxy)benzamide (367)



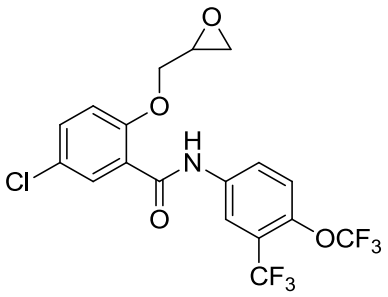
367 was prepared following **general procedure D**, yielding 0.311 g (53%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.90 (dd, *J* = 4.7 , *J* = 2.7, 1H, C$H_a$$H_b$ epoxide), 3.01 (dd[t], *J* = 4.5, 1H, C$H_a$$H_b$ epoxide), 3.46-3.51 (m, 1H, OC$H_a$$H_b$C*H*OR), 3.98 (dd, ^{2}J = -10.7, ^{3}J = 6.2, 1H, OC$H_a$$H_b$CHOR), 4.57 (dd, ^{2}J = -10.7, ^{3}J = 1.7, 1H, OC$H_a$$H_b$CHOR), 7.61 (d, ^{4}J = 2.6, 1H, *H*-4 salicyl), 7.65 (br s, 1H, *H*-4 aniline), 8.15 (d, ^{4}J = 2.6, 1H, *H*-6 salicyl), 8.41 (br s, 2H, *H*-2,6 aniline), 10.12 (br s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.68 (*C*H_2 epoxide), 49.90 (*C*HO epoxide), 74.62 (O*C*H_2CHOR), 118.07 (m, $^{3}J_{CF}$ = 3.8, *C*-4 aniline), 120.81 ($^{3}J_{CF}$ = 3.3, *C*-2,6 aniline), 123.32 (q, $^{1}J_{CF}$ = -273.3, 2x *C*F_3), 128.42 (C_q-5 salicyl), 129.52 (C_q-3 salicyl), 131.09 (*C*-6 salicyl), 131.66 (C_q -1 salicyl), 132.37 (q, $^{2}J_{CF}$ = 33.5, 2x *C*-3,5 aniline), 134.36 (*C*-4 salicyl), 139.41 (*C*-1 aniline), 150.71 (*C*-2 salicyl), 161.17 (*C*ONH).

Melting point: 150-153°C.

5-chloro-2-(oxiran-2-ylmethoxy)-*N*-(4-(trifluoromethoxy)-3-(trifluoromethyl)phenyl)benzamide (368)



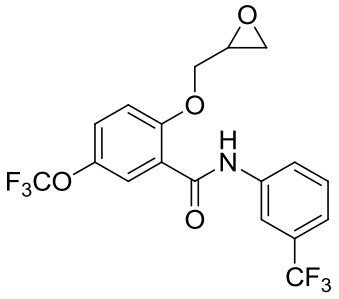
368 was prepared following **general procedure D**, yielding 0.679 g (66%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.92 (dd, *J* = 4.7, *J* = 2.6, 1H, CH_aH$_b$ epoxide), 3.04 (dd[t], *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3.49-3.54 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.13 (dd, ^2J = -10.4, ^3J = 5.4, 1H, OCH_aH$_b$CHOR), 4.62 (dd, ^2J = -10.4, ^3J = 2.2, 1H, OCH$_a$$H_b$CHOR), 6.95 (d, ^3J = 8.8, 1H, *H*-3 salicyl), 7.39 (d, ^3J = 9.0, 1H, *H*-5 aniline) 7.44 (dd, ^3J = 8.8, ^4J = 2.8, 1H, *H*-4 salicyl), 8.05 (dd, ^3J = 9.0 ^4J = 2.7, 1H, *H*-6 aniline), 8.21 (d, ^4J = 2.8, 1H, *H*-6 salicyl), 8.25 (d, ^4J = 2.7, 1H, *H*-2 aniline) 9.83 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.79 (*C*H$_2$ epoxide), 49.82 (*C*HO epoxide), 69.00 (O*C*H$_2$CHOR), 114.50 (*C*-3 salicyl), 119.29 (q, J_{CF} = 5.2, *C*-2 aniline), 122.08 (*C*-5 aniline), 120.47 ($^1J_{CF}$ = -259.1, O*C*F$_3$ aniline), 123.22 (*C*-1 salicyl), 123.70 (q, $^2J_{CF}$ = 17.6, *C*-3 aniline), 124.44 (q, $^1J_{CF}$ = -273.3, *C*F$_3$ aniline), 124.56 (*C*-6 aniline), 128.20 (*C*-5 salicyl), 132.58 (*C*-6 salicyl), 133.44 (*C*-4 salicyl), 137.09 (*C*-1 aniline), 142.35 (broadened signal, *C*-4 aniline), 154.51 (*C*-2 salicyl), 162.17 (*C*ONH).

Melting point: 100-115°C.

2-(oxiran-2-ylmethoxy)-5-(trifluoromethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (369)



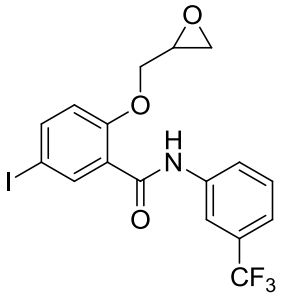
369 was prepared following **general procedure D**, yielding 0.566 g (73%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.91 (dd, *J* = 4.9, *J* = 2.7, 1H, CH_aH$_b$ epoxide), 3.04 (dd[t], *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3.49 - 3.54 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.15 (dd, ^{2}J = -10.5, ^{3}J = 5.3, 1H, OCH_aH$_b$CHOR), 4.64 (dd, ^{2}J = -10.5, ^{3}J = 2.3, 1H, OCH$_a$$H_b$CHOR), 7.02 (d, ^{3}J = 9.0, 1H, *H*-3 salicyl), 7.34 (dd, ^{3}J = 9.0, ^{4}J = 3.0, 1H, *H*-4 salicyl), 7.38 (d, ^{3}J = 7.7, 1H, *H*-4 aniline), 7.47 (dd [t], ^{3}J = 7.9, 1H, *H*-5 aniline), 7.93 (d, ^{3}J = 8.2, 1H, *H*-6 aniline), 8.15 (d, ^{4}J = 3.0, 1H, *H*-6 salicyl), 8.22 (s [t], 1H, *H*-2 aniline), 9.96 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.71 (*C*H$_2$ epoxide), 49.77 (*C*HO epoxide), 69.37 (OCH_2CHOR), 114.20 (*C*-3 salicyl), 117.22 (q, $^{3}J_{CF}$ = 3.9, *C*-6 aniline), 120.60 ($^{1}J_{CF}$ = -258.0, O*C*F$_3$ salicyl), 121.01 ($^{3}J_{CF}$ = 3.8, *C*-4 aniline), 123.37 ([verbreitert], *C*-6 aniline), 123.58 (*C*-1 salicyl), 124.10 ($^{1}J_{CF}$ = -273.4, *C*F$_3$ aniline), 125.57 (*C*-6 salicyl), 126.21 (*C*-4 salicyl), 129.66 (*C*-5 aniline), 131.54 ($^{2}J_{CF}$ = 32.2, *C*-3 aniline), 138.93 (*C*-1 aniline), 143.96 (J_{CF} = 2.3, *C*-5 salicyl), 154.34 (*C*-2 salicyl), 161.91 (*C*ONH).

Melting point: 109-114°C.

5-iodo-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (370)



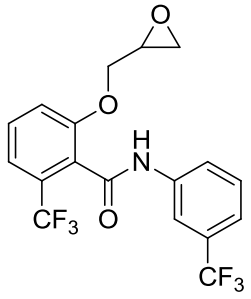
370 was prepared following **general procedure D**, yielding 3.204 g (91%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.89 (dd, *J* = 4.7, *J* = 2.4, 1H, CH_aH$_b$ epoxide), 3.02 (dd[t], *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3.47-3.52 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.11 (dd, ^{2}J = -10.4, ^{3}J = 5.3, 1H, OCH_aH$_b$CHOR), 4.58 (dd, ^{2}J = -10.4, ^{3}J = 2.2, 1H, OCH$_a$$H_b$CHOR), 6.75 (d, ^{3}J = 8.6, 1H, *H*-3 salicyl), 7.34-7.40 (m, überlagert, 1H, *H*-4 aniline), 7.46 (dd [t], ^{3}J = 8.0, 1H, *H*-5 aniline), 7.74 (dd, ^{3}J = 8.5, ^{4}J = 2.3, 1H, *H*-4 salicyl), 7.91 (d, ^{3}J = 8.0, 1H, *H*-6 aniline), 8.18 (s, 1H, *H*-2 aniline), 8.52 (d, ^{4}J = 2.3, 1H, *H*-6 salicyl), 9.86 (br s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.71 (*C*H_2 epoxide), 49.76 (*C*HO epoxide), 69.01 (O*C*H_2CHOR), 85.02 (*C*-5 salicyl), 115.09 (*C*-3 salicyl), 117.18 ($^{3}J_{CF}$ = 4.0, *C*-2 aniline), 120.92 ($^{3}J_{CF}$ = 3.8, *C*-4 aniline), 123.35 (*C*-6 aniline), 124.00 (*C*-1 salicyl), 124.11 ($^{1}J_{CF}$ = -272.6, *C*F_3 aniline), 129.64 (*C*-5 aniline), 131.50 ($^{2}J_{CF}$ = 32.3, *C*-3 aniline), 138.96 (*C*-1 aniline), 141.39 (*C*-6 salicyl), 142.10 (*C*-4 salicyl), 155.82 (*C*-2 salicyl), 161.95(*C*ONH).

Melting point: 104-107°C.

2-(oxiran-2-ylmethoxy)-6-(trifluoromethyl)-*N*-(3-(trifluoromethyl)phenyl)benzamide (371)

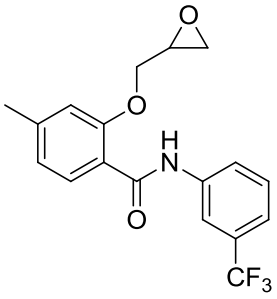


371 was prepared following **general procedure D**, yielding 0.202 g (86%) of the desired product as colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 2.66 (dd, *J* = 5.2, *J* = 2.7, 1H, C$H_a$$H_b$ epoxide), 2.75 (dd, *J* = 5.2, *J* = 4.4, 1H, CH_aH_b epoxide), 3.23-3.28 (m, 1H, OCH_aH_bCHOR), 4.06 (dd, ^{2}J = -11.7, ^{3}J = 5.9, 1H, OCH_aH_bCHOR), 4.48 (dd, ^{2}J = -11.7, ^{3}J = 2.3, 1H, OCH_aH_bCHOR), 7.41 (d, ^{3}J = 7.8 1H, *H*-5 salicyl), 7.47 (d, ^{3}J = 7.8, 1H, *H*-4 aniline), 7.52 (d, ^{3}J = 8.4 1H, *H*-3 salicyl), 7.60 (dd [t], ^{3}J = 8.4, ^{3}J = 7.8, 1H, *H*-4 salicyl), 7.66 (m [t], 1H, *H*-5 aniline), 7.84 (d, ^{3}J = 8.3, 1H, *H*-6 aniline), 8.14 (br s, 1H, *H*-2 aniline), 10.84 (br s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, DMSO-d_6, 23 °C): δ = 43.30 (*C*H_2 epoxide), 49.53 (*C*HO epoxide), 69.58 (O*C*H_2CHOR), 115.29 (q, $^{3}J_{CF}$ = 4.1, *C*-2 aniline), 117.49 (*C*-3 salicyl), 118.09 (q, $^{3}J_{CF}$ = 4.6, *C*-5 salicyl), 120.09 (q, $^{3}J_{CF}$ = 3.8, *C*-4 aniline), 122.93 (*C*-6 aniline), 123.50 (q, $^{1}J_{CF}$ = -274.6, *C*F_3 aniline), 124.05 (q, $^{1}J_{CF}$ = -272.6, *C*F_3 salicyl), 125.35 (q, $^{3}J_{CF}$ = 2.2, C_q-1 salicyl), 126.84 (q, $^{2}J_{CF}$ = 31.1, *C*-3 aniline), 129.57 (q, $^{2}J_{CF}$ = 31.4, *C*-6 salicyl), 130.14 (*C*-5 aniline), 131.07 (*C*-4 salicyl), 139.63 (*C*-1 aniline), 155.50 (*C*-2 salicyl), 163.20 (*C*ONH).

4-methyl-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (372)



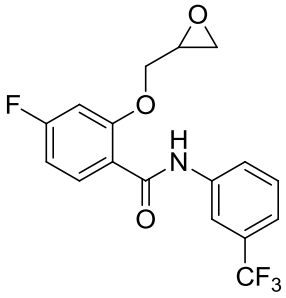
372 was prepared following **general procedure D**, yielding 0.882 g (28%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.40 (s, 3H, CH_3), 2.90 (dd, *J* = 4.7, *J* = 2.7, 1H, CH_aH$_b$ epoxide), 3.01 (dd[t], *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3.47-3.53 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.14 (dd, ^2J = -10.6, ^3J = 5.4, 1H, OCH_aH$_b$CHOR), 4.58 (dd, ^2J = -10.6, ^3J = 2.3, 1H, OCH$_a$$H_b$CHOR), 6.79 (s, 1H, *H*-3 salicyl), 6.96 (d, ^3J = 8.0, 1H, *H*-5 salicyl), 7.35 (d, ^3J = 7.7, 1H, *H*-4 aniline), 7.45 (dd [t], ^3J = 8.1, ^3J = 7.7, 1H, *H*-5 aniline), 7.93 (d, ^3J = 8.1 1H, *H*-6 aniline), 8.14 (d, ^3J = 8.0, 1H, *H*-6 salicyl), 8.23 (s, 1H, *H*-2 aniline), 9.98 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 21.86 (*C*H$_3$), 44.66 (*C*H$_2$ epoxide), 49.95 (*C*HO epoxide), 68.72 (O*C*H$_2$CHOR), 113.54 (*C*-3 salicyl), 117.09 (q, $^3J_{CF}$ = 3.9, *C*-2 aniline), 119.38 (*C*-1 salicyl), 120.46 (q, $^3J_{CF}$ = 3.9, *C*-4 aniline), 123.24 (*C*-6 aniline), 123.41 (*C*-5 salicyl), 124.20 (q, $^1J_{CF}$ = -272.5, *C*F$_3$ aniline), 129.52 (*C*-5 aniline), 131.43 (q, $^3J_{CF}$ = 32.2, *C*-3 aniline), 132.77 (*C*-6 salicyl), 139.46 (*C*-1 aniline), 144.71 (*C*-4 salicyl), 156.00 (*C*-2 salicyl), 163.56 (*C*ONH).

Melting point: 119-120°C.

4-fluoro-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (373)



373 was prepared following **general procedure D**, yielding 0.241 g (60%) of the desired product.

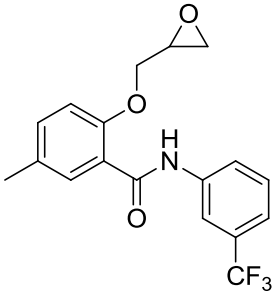
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.90 (dd, *J* = 4.7, *J* = 2.6, 1H, CH_aH$_b$ epoxide), 3.03 (dd[t], *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3.49-3.54 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.11 (dd, ^2J = -10.5, ^3J = 5.4, 1H,

OCH_aH$_b$CHOR), 4.59 (dd, ^2J = -10.5, ^3J = 2.3, 1H, OCH$_a$$H_b$CHOR), 6.71 (dd, J_{HF}=10.2, ^3J = 2.3, 1H, *H*-3 salicyl), 6.86 (m, 1H, *H*-5 salicyl), 7.36 (d, ^3J = 7.6, 1H, *H*-4 aniline), 7.46 (dd [t], ^3J = 8.1, ^3J = 7.6, 1H, *H*-5 aniline), 7.91 (d, ^3J = 8.1, 1H, *H*-6 aniline), 8.20 (s, 1H, *H*-2 aniline), 8.28(dd, J_{HF}= 7.0, ^2J = 8.9, 1H, *H*-3 salicyl), 9.83 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, CDCl$_3$, 23 °C): δ = 44.68 (*C*H$_2$ epoxide), 49.66 (*C*HO epoxide), 69.11 (OCH$_2$CHOR), 100.93 (d, $^2J_{CF}$ = 26.5, *C*-3 salicyl), 109.58 (d, $^2J_{CF}$ = 21.1, *C*-5 salicyl), 117.13 (q, $^3J_{CF}$ = 3.9, *C*-2 aniline), 118.42 (d,$^4J_{CF}$ = 3.5, *C*-1 salicyl), 120.73 (q, $^3J_{CF}$ = 3.9, *C*-4 aniline), 123.29 (*C*-6 aniline), 124.14 (q, $^1J_{CF}$ = -272.5, *C*F$_3$ aniline), 129.60 (*C*-5 aniline), 131.50 (q, $^3J_{CF}$ = 32.0, *C*-3 aniline), 134.94 (d, $^3J_{CF}$ = 10.8, *C*-6 salicyl), 139.18 (*C*-1 aniline), 157.28 (d, $^3J_{CF}$ = 10.3, *C*-2 salicyl), 162.55 (*C*ONH), 165.77 (d, $^1J_{CF}$ = -253.9, *C*-4 salicyl).

Melting point: 110-114°C.

5-methyl-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (374)



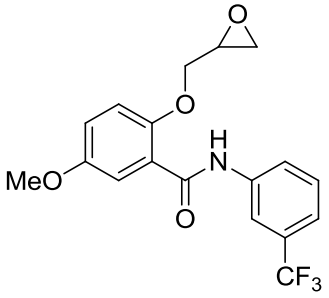
374 was prepared following **general procedure D**, yielding 0.472 g (16%) of the desired product.

^{1}H NMR (400 MHz, CDCl$_3$, 23 °C): δ = 2.35 (s, 3H, CH_3), 2.89 (dd, *J* = 4.7, *J* = 2.6, 1H, CH_aH$_b$ epoxide), 3.00 (dd[t], *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3.46-3.51 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.12 (dd, ^2J = -10.7, ^3J = 5.3, 1H, OCH_aH$_b$CHOR), 4.56 (dd, ^2J = -10.7, ^3J = 2.0, 1H, OCH$_a$$H_b$CHOR), 6.89 (d, 1H, ^3J = 8.0, *H*-3 salicyl), 7.28 (dd, 1H, ^3J = 8.6, ^4J = 2.3, *H*-4 salicyl), 7.36 (d, ^3J = 7.8, 1H, *H*-4 aniline), 7.46 (dd [t], ^3J = 8.2, ^3J = 7.8, 1H, *H*-5 aniline), 7.94 (d, ^3J = 8.2 1H, *H*-6 aniline), 8.07 (d, ^4J = 2.2, 1H, *H*-6 salicyl), 8.22 (s, 1H, *H*-2 aniline), 10.02 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, CDCl$_3$, 23 °C): δ = 20.56 (*C*H$_3$), 44.65 (*C*H$_2$ epoxide), 49.99 (*C*HO epoxide), 68.96 (OCH$_2$CHOR), 112.98 (*C*-3 salicyl), 117.14 (q, $^3J_{CF}$ = 4.2, *C*-2 aniline), 120.56 (q, $^3J_{CF}$ = 3.8, *C*-4 aniline), 121.69 (*C*-1 salicyl), 123.28 (*C*-6 aniline), 124.19 (q, $^1J_{CF}$ = -272.2, *C*F$_3$ aniline), 129.54 (*C*-5 aniline), 131.44 (q, $^2J_{CF}$ = 32.1, *C*-3 aniline), 132.10 (*C*-5 salicyl), 133.08 (*C*-6 salicyl), 134.09 (*C*-4 salicyl), 139.39 (*C*-1 aniline), 154.05 (*C*-2 salicyl), 163.63 (*C*ONH).

Melting point: 126-128°C.

5-methoxy-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (375)



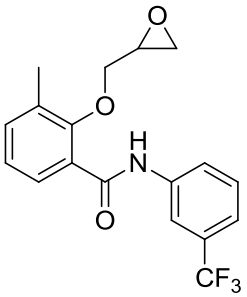
375 was prepared following **general procedure D**, yielding 2.282 g (96%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.89 (dd, *J* = 4.7, *J* = 2.8, 1H, CH_aH$_b$ epoxide), 3.00 (dd[t], *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3.45-3.52 (m, 1H, OCH$_a$H$_b$C*H*OR), 3.84 (s, 3H, CH_3), 4.09 (dd, ^{2}J = -10.6, ^{3}J = 5.5, 1H, OCH_aH$_b$CHOR), 4.55 (dd, ^{2}J = -10.7, ^{3}J = 2.2, 1H, OCH$_a$$H_b$CHOR), 6.95 (d, 1H, ^{3}J = 9.0, *H*-3 salicyl), 7.04 (dd, 1H, ^{3}J = 9.0, ^{4}J = 3.0, *H*-4 salicyl), 7.37 (d, ^{3}J = 7.8, 1H, *H*-4 aniline), 7.46 (dd [t], ^{3}J = 8.0, ^{3}J = 7.8, 1H, *H*-5 aniline), 7.81 (d, ^{4}J = 3.0, 1H, *H*-6 salicyl), 7.93 (d, ^{3}J = 8.0 1H, *H*-6 aniline), 8.26 (s, 1H, *H*-2 aniline), 10.13 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.66 (*C*H$_2$ epoxide), 50.02 (*C*HO epoxide), 55.97 (O*C*H$_3$), 69.79 (O*C*H$_2$CHOR), 114.99 (*C*-3 salicyl), 115.76 (*C*-6 salicyl), 117.23 (q, $^{3}J_{CF}$ = 3.8, *C*-2 aniline), 120.42 (*C*-4 salicyl), 120.69 (q, $^{3}J_{CF}$ = 3.8, *C*-4 aniline), 122.82 (*C*-1 salicyl), 123.34 (*C*-6 aniline), 124.18 (q, $^{1}J_{CF}$ = -272.3, *C*F$_3$ aniline), 129.55 (*C*-5 aniline), 131.47 (q, $^{2}J_{CF}$ = 32.5, *C*-3 aniline), 139.28 (*C*-1 aniline), 150.27 (*C*-5 salicyl), 154.87 (*C*-2 salicyl), 163.23 (*C*ONH).

Melting point: 116-118°C.

3-methyl-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (376)

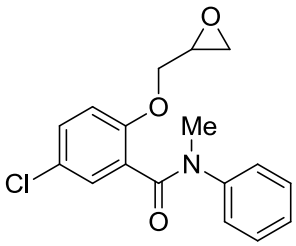


376 was prepared following **general procedure D**, yielding 2.3467 g (99%) of the desired semicrystalline product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.39 (s, 3H, CH_3), 2.80 (dd, *J* = 4.8, *J* = 2.6, 1H, CH_aH$_b$ epoxide), 2.92 (dd, *J* = 4.8, *J* = 4.3, 1H, CH$_a$$H_b$ epoxide), 3.38-3.42 (m, 1H, OCH$_a$H$_b$C*H*OR), 3.83 (dd, ^{2}J = -11.2, ^{3}J = 6.2, 1H, OCH_aH$_b$CHOR), 4.26 (dd, ^{2}J = -11.2, ^{3}J = 2.2, 1H, OCH$_a$$H_b$CHOR), 7.22 (dd [t], ^{3}J = 7.6, 1H, *H*-5 salicyl), 7.36-7.41 (m, 2H, *H*-4 aniline, *H*-4 salicyl), 7.47 (dd [t], ^{3}J = 8.0, 1H, *H*-5 aniline), 7.96 (d, ^{3}J = 8.0 1H, *H*-6 aniline), 8.02 (d, ^{3}J = 7.8, ^{4}J = 1.6, 1H, *H*-6 salicyl), 8.22 (s, 1H, *H*-2 aniline), 9.89 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 16.17 (*C*H_3), 44.45 (*C*H_2 epoxide), 50.08 (*C*HO epoxide), 74.53 (O*C*H_2CHOR), 117.35 (q, $^{3}J_{CF}$ = 3.9, *C*-2 aniline), 120.85 (q, $^{3}J_{CF}$ = 3.8, *C*-4 aniline), 123.53 (*C*-6 aniline), 124.15 (q, $^{1}J_{CF}$ = -272.1, teilweise überdeckt aber Wert zuverlässig, *C*F_3 aniline), 125.49 (*C*-5 salicyl), 126.57 (*C*-1 salicyl), 129.51 (*C*-5 aniline), 130.13 (*C*-6 salicyl), 131.45 (q, $^{2}J_{CF}$ = 32.4, *C*-3 aniline), 131.75 (*C*-3 salicyl), 135.60 (*C*-4 salicyl), 139.06 (*C*-1 aniline), 154.51 (*C*-2 salicyl), 163.68 (*C*ONH).

5-chloro-*N*-methyl-2-(oxiran-2-ylmethoxy)-*N*-phenylbenzamide (377)



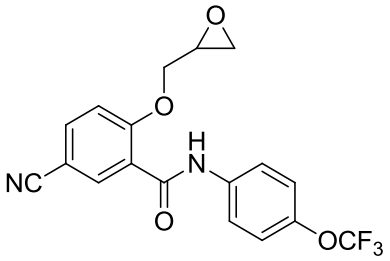
377 was prepared following **general procedure D**, yielding 1.349 g (56%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.70 (br s, 1H, CH_aH$_b$ epoxide), 2.88 (dd [t], *J* = 4.5, 1H, CH$_a$$H_b$ epoxide), 3.26 (m [br s], 1H, OCH$_a$H$_b$C*H*OR), 3.47 (s, 3H, C(O)NCH_3), 3.68 (m, ^{2}J = -11.2, ^{3}J = 6.2, 1H, OCH_aH$_b$CHOR), 4.09 (m [d], ^{2}J = -11.5, 1H, OCH$_a$$H_b$CHOR), 6.56 (d, 1H, ^{3}J = 8.8, *H*-3 salicyl), 7.03-7.14 (m, 4H, Ar*H*), 7.14-7.22 (m, 3H, Ar*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 37.29 (*C*H_3), 44.54 (*C*H_2 epoxide), 50.07 (*C*HO epoxide), 69.36 (dyn, O*C*H_2CHOR), 113.44 (*C*-3 salicyl), 126.08 (C_q), 126.40 (C_q), 127.02 (2x *C*H), 127.13 (*C*H), 128.71 (*C*H), 128.83 (2x *C*H), 129.37 (*C*H), 130.03 (*C*H), 143.48 (*C*-2 salicyl), 152.60 (*C*ONH).

Melting point: 69-73°C.

5-cyano-2-(oxiran-2-ylmethoxy)-*N*-(4-(trifluoromethoxy)phenyl)benzamide (378)



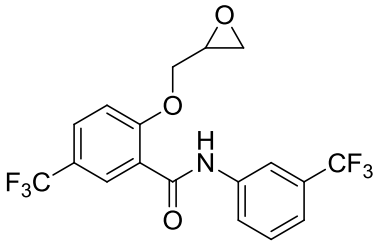
378 was prepared following **general procedure D**, yielding 0.191 g (15%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.92 (dd, *J* = 4.6, *J* = 2.6, 1H, C*H*$_a$H$_b$ epoxide), 3.06 (dd[t], *J* = 4.4, 1H, CH$_a$*H*$_b$ epoxide), 3.51-3.57 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.18 (dd, ^2J = -10.5, ^3J = 5.6, 1H, OC*H*$_a$H$_b$CHOR), 4.71 (dd, ^2J = -10.5, ^3J = 2.1, 1H, OCH$_a$*H*$_b$CHOR), 7.08 (d, 1H, ^3J = 8.6, *H*-3 salicyl), 7.22 (d, ^3J = 8.8, 2H, *H*-3,5 aniline), 7.76 (dd, ^3J = 8.6, ^4J = 2.2, 1H, *H*-4 salicyl), 7.82 (m, 2H, *H*-2,6 aniline), 8.56 (d, ^4J = 2.2, 1H, *H*-6 salicyl), 9.68 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.79 (*C*H$_2$ epoxide), 49.55 (*C*HO epoxide), 69.28 (OCH$_2$CHOR), 106.56 (*C*-5 salicyl), 113.54 (*C*-3 salicyl), 118.00 (*C*N), 121.56 (*C*-2,6 aniline), 121.94 (*C*-3,5 aniline), 123.51 (*C*-1 salicyl), 136.81 (*C*-1 aniline), 136.96 (*C*-4 salicyl), 137.33 (*C*-6 salicyl), 145.62 (q, J_{CF} = 2.3, *C*-4 aniline), 158.66 (*C*-2 salicyl), 161.06 (*C*ONH). One part of O*C*F$_3$ aniline (d) at 119.36, second part not visible.

Melting point: 162-164°C.

2-(oxiran-2-ylmethoxy)-5-(trifluoromethyl)-*N*-(3-(trifluoromethyl)phenyl)benzamide (379)



379 was prepared following **general procedure D**, yielding 1.649 g (100%) of the desired product.

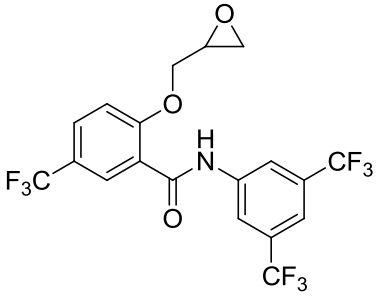
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.92 (dd, *J* = 4.7, *J* = 2.6, 1H, C*H*$_a$H$_b$ epoxide), 3.05 (dd[t], *J* = 4.4, 1H, CH$_a$*H*$_b$ epoxide), 3.51-3.56 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.20 (dd, ^2J = -10.5, ^3J = 5.4, 1H, OC*H*$_a$H$_b$CHOR), 4.69 (dd, ^2J = -10.5, ^3J = 2.3, 1H, OCH$_a$*H*$_b$CHOR), 7.09 (d, 1H, ^3J = 8.6, *H*-3

salicyl), 7.38 (d, ^{3}J = 7.8, 1H, *H*-4 aniline), 7.47 (dd [t], ^{3}J = 8.0, ^{3}J = 7.8, 1H, *H*-5 aniline), 7.73 (dd, 1H, ^{3}J = 8.6, ^{4}J = 2.3, *H*-4 salicyl), 7.93 (d, ^{3}J = 8.0 1H, *H*-6 aniline), 8.21 (s, 1H, *H*-2 aniline), 8.56 (d, ^{4}J = 2.3, 1H, *H*-6 salicyl), 9.88 (br s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.74 (*C*H_2 epoxide), 49.67 (*C*HO epoxide), 69.07 (O*C*H_2CHOR), 113.07 (*C*-3 salicyl), 117.19 (q, $^{3}J_{CF}$ = 4.0, *C*-2 aniline), 121.05 (q, $^{3}J_{CF}$ = 3.8, *C*-4 aniline), 122.59 (*C*-1 salicyl), 123.34 (*C*-6 aniline), 123.83 (q, $^{1}J_{CF}$ = -271.8, *C*F_3 salicyl), 124.09 (q, $^{1}J_{CF}$ = -272.6, *C*F_3 aniline), 125.02 (q, $^{2}J_{CF}$ = 33.6, *C*-5 salicyl), 129.69 (*C*-5 aniline), 130.48 (q, $^{4}J_{CF}$ = 3.8, *C*-4 salicyl), 130.53 (q, $^{4}J_{CF}$ = 3.8, *C*-6 salicyl), 131.55 (q, $^{2}J_{CF}$ = 32.2, *C*-3 aniline), 138.89 (*C*-1 aniline), 158.06 (*C*-2 salicyl), 162.03 (*C*ONH).

Melting point: 104-110°C.

N-(3,5-bis(trifluoromethyl)phenyl)-2-(oxiran-2-ylmethoxy)-5-(trifluoromethyl)benzamide (380)



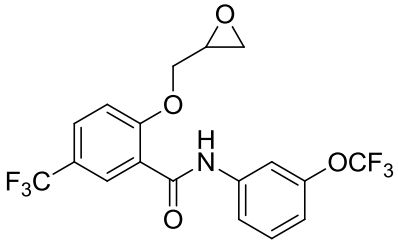
380 was prepared following **general procedure D**, yielding 0.743 g (57%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.96 (dd, *J* = 4.6 , *J* = 2.6, 1H, C$H_a$$H_b$ epoxide), 3.08 (dd[t], *J* = 4.4, 1H, C$H_a$$H_b$ epoxide), 3.54-3.60 (m, 1H, OC$H_a$$H_b$C*H*OR), 4.25 (dd, ^{2}J = -10.4, ^{3}J = 5.1, 1H, OC$H_a$$H_b$CHOR), 4.73 (dd, ^{2}J = -10.4, ^{3}J = 2.3, 1H, OC$H_a$$H_b$CHOR), 7.12 (d, ^{3}J = 8.6, 1H, *H*-3 salicyl), 7.63 (s, 1H, *H*-4 aniline), 7.76 (dd, ^{3}J = 8.6, ^{4}J = 2.3, 1H, *H*-4 salicyl), 8.39 (s, 2H, *H*-2,6 aniline), 8.56 (d, ^{4}J = 2.3, 1H, *H*-6 salicyl), 10.10 (br s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.84 (*C*H_2 epoxide), 49.69 (*C*HO epoxide), 68.67 (O*C*H_2CHOR), 113.29 (*C*-3 salicyl), 117.69 (m, $^{3}J_{CF}$ = 3.8, *C*-4 aniline), 120.17 (m, $^{3}J_{CF}$ = 3.4, *C*-2,6 aniline), 122.15 (*C*-1 salicyl), 123.35 ($^{1}J_{CF}$ = -272.5, *C*F_3 salicyl), 123.74 ($^{1}J_{CF}$ = -272.5, 2x *C*F_3 aniline), 125.26 (q, $^{2}J_{CF}$ = 33.4, *C*-5 salicyl), 130.62 (q, $^{3}J_{CF}$ = 3.8, *C*-6 salicyl), 130.87 (q, $^{3}J_{CF}$ = 3.8, *C*-4 salicyl), 132.47 (q, $^{2}J_{CF}$ = 33.2, *C*-3,5 aniline), 139.83 (*C*-1 aniline), 158.08 (*C*-2 salicyl), 162.32 (*C*ONH).

Melting point: 146-150°C.

2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethoxy)phenyl)-5-(trifluoromethyl)benzamide (381)



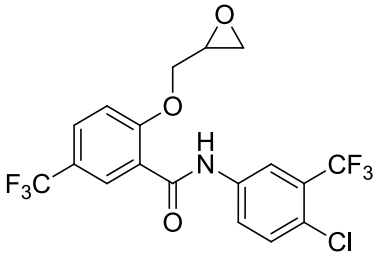
381 was prepared following **general procedure D**, yielding 0.774 g (57%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.92 (dd, *J* = 4.6 , *J* = 2.6, 1H, CH_aH$_b$ epoxide), 3.04 (dd[t], *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3.50-3.55 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.19 (dd, ^{2}J = -10.4, ^{3}J = 5.1, 1H, OCH_aH$_b$CHOR), 4.67 (dd, ^{2}J = -10.5, ^{3}J = 2.3, 1H, OCH$_a$$H_b$CHOR), 6.99 (m [dt], ^{3}J = 8.2, 1H, *H*-4 aniline), 7.08 (d, ^{3}J = 8.6, 1H, *H*-3 salicyl), 7.36 (dd [t], ^{3}J = 8.2, 1H, *H*-5 aniline), 7.64 (m [dd], ^{3}J = 8.2, 1H, *H*-6 aniline), 7.72 (dd, ^{3}J = 8.6, ^{4}J = 2.3, 1H, *H*-4 salicyl), 7.91 (br s, 1H, *H*-2 aniline), 8.55 (d, ^{4}J = 2.3, 1H, *H*-6 salicyl), 9.82 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.72 (*C*H$_2$ epoxide), 49.67 (*C*HO epoxide), 69.04 (OCH_2CHOR), 113.01 (*C*-3 salicyl), 113.15 (*C*-2 aniline), 116.61 (*C*-4 aniline), 118.35 (*C*-6 aniline), 120.63 (q, $^{1}J_{CF}$ = -272.5, O*C*F$_3$ aniline), 122.63 (*C*-1 salicyl), 123.82 ($^{1}J_{CF}$ = -271.3, *C*F$_3$ salicyl), 125.00 (q, $^{2}J_{CF}$ = 33.7, *C*-5 salicyl), 130.18 (*C*-5 aniline), 130.44 (q, $^{3}J_{CF}$ = 3.6, *C*-4 salicyl), 130.56 (q, $^{3}J_{CF}$ = 3.7, *C*-6 salicyl), 139.76 (*C*-1 aniline), 149.76 (q, J_{CF} = 2.4, *C*-3 aniline), 158.04 (*C*-2 salicyl), 161.94 (*C*ONH).

Melting point: 113-116°C.

N-(4-chloro-3-(trifluoromethyl)phenyl)-2-(oxiran-2-ylmethoxy)-5-(trifluoromethyl)benzamide (382)



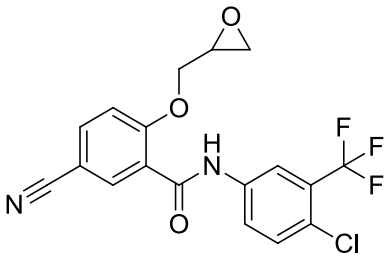
382 was prepared following **general procedure D**, yielding 1.145 g (68%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.94 (dd, *J* = 4.6 , *J* = 2.6, 1H, CH_aH$_b$ epoxide), 3.06 (dd[t], *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3.52-3.58 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.21 (dd, ^{2}J = -10.4, ^{3}J = 5.3, 1H, OCH_aH$_b$CHOR), 4.70 (dd, ^{2}J = -10.4, ^{3}J = 2.3, 1H, OCH$_a$$H_b$CHOR), 7.09 (d, ^{3}J = 8.6, 1H, *H*-3 salicyl), 7.47 (d, ^{3}J = 8.7, 1H, *H*-5 aniline), 7.74 (dd, ^{3}J = 8.7, ^{4}J = 2.4, 1H, *H*-4 salicyl), 7.96 (dd, ^{3}J = 8.7, ^{4}J = 2.5, 1H, *H*-6 aniline), 8.25 (d, ^{4}J = 2.6, 1H, *H*-2 aniline), 8.54 (d, ^{4}J = 2.4, 1H, *H*-6 salicyl), 9.92(br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.91 (*C*H$_2$ epoxide), 49.78 (*C*HO epoxide), 68.94 (O*C*H$_2$CHOR), 113.24 (*C*-3 salicyl), 119.54 (m, $^{3}J_{CF}$ = 5.8, *C*-2 aniline), 121.54 122.45 (*C*-1 salicyl), 122.90 ($^{1}J_{CF}$ = -273.2, *C*F$_3$ aniline), 123.89 ($^{1}J_{CF}$ = -273.5, *C*F$_3$ salicyl), 124.34 (*C*-6 aniline), 125.22 (q, $^{2}J_{CF}$ = 33.6, *C*-5 salicyl), 127.05 (m, $^{3}J_{CF}$ = 1.5, *C*-4 aniline), 128.99 (q, $^{2}J_{CF}$ = 31.5, *C*-3 aniline), 130.64 (q, $^{3}J_{CF}$ = 3.8, *C*-6 salicyl), 130.74 (q, $^{3}J_{CF}$ = 3.7, *C*-4 salicyl), 132.22 (*C*-5 aniline), 137.37 (*C*-1 aniline), 158.12 (*C*-2 salicyl), 162.15 (*C*ONH).

Melting point: 153-156°C.

N-(4-chloro-3-(trifluoromethyl)phenyl)-5-cyano-2-(oxiran-2-ylmethoxy)benzamide (383)



383 was prepared following **general procedure D**, yielding 0.536 g (46%) of the desired product.

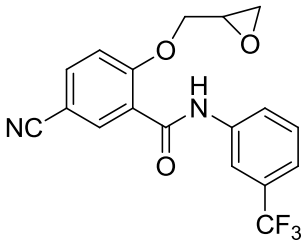
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.94 (dd, *J* = 4.5 , *J* = 2.6, 1H, CH_aH$_b$ epoxide), 3.07 (dd[t], *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3.53-3.58 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.21 (dd, ^{2}J = -10.5, ^{3}J = 5.3, 1H, OCH_aH$_b$CHOR), 4.72 (dd, ^{2}J = -10.5, ^{3}J = 2.2, 1H, OCH$_a$$H_b$CHOR), 7.09 (d, ^{3}J = 8.6, 1H, *H*-3 salicyl), 7.47 (d, ^{3}J = 8.8, 1H, *H*-5 aniline), 7.77 (dd, ^{3}J = 8.6, ^{4}J = 2.2, 1H, *H*-4 salicyl), 7.96 (dd, ^{3}J = 8.8, ^{4}J = 2.4, 1H, *H*-6 aniline), 8.20 (d, ^{4}J = 2.4, 1H, *H*-2 aniline), 8.53 (d, ^{4}J = 2.2, 1H, *H*-6 salicyl), 9.81 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.86 (*C*H$_2$ epoxide), 49.54 (*C*HO epoxide), 68.96 (O*C*H$_2$CHOR), 106.66 (*C*-5 salicyl), 113.69 (*C*-3 salicyl), 117.88 (*C*N), 119.47 (q, $^{3}J_{CF}$ = 5.5, *C*-2 aniline), 122.74 ($^{1}J_{CF}$ = -273.5, *C*F$_3$ aniline), 123.09 (*C*-1 salicyl), 124.30 (*C*-6 aniline), 127.16

(m, $^{3}J_{CF}$ = 1.5, *C*-4 aniline), 128.91 (q, $^{2}J_{CF}$ = 31.4, *C*-3 aniline), 132.16 (*C*-5 aniline), 137.04 (*C*-1 aniline), 137.20 (*C*-4 salicyl), 137.31 (*C*-6 salicyl), 158.64 (*C*-2 salicyl), 161.25 (*C*ONH).

Melting point: 153-156°C.

5-cyano-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (384)



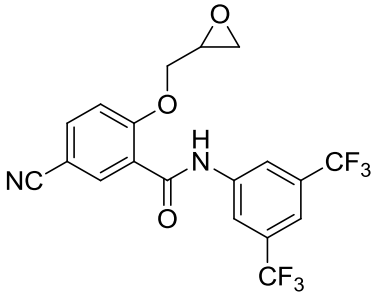
384 was prepared following **general procedure D**, yielding 1.214 g (93%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.93 (dd, *J* = 4.6, *J* = 2.5, 1H, C$H_a$$H_b$ epoxide), 3.06 (dd[t], *J* = 4.4, 1H, C$H_a$$H_b$ epoxide), 3.53-3.57 (m, 1H, OC$H_a$$H_b$C*H*OR), 4.20 (dd, ^{2}J = -10.6, ^{3}J = 5.5, 1H, OC$H_a$$H_b$CHOR), 4.71 (dd, ^{2}J = -10.6, ^{3}J = 2.3, 1H, OC$H_a$$H_b$CHOR), 7.09 (d, ^{3}J = 8.6, 1H, *H*-3 salicyl), 7.39 (d, ^{3}J = 7.9, 1H, *H*-4 aniline), 7.47 7.46 (dd [t], ^{3}J = 8.3, ^{3}J = 7.9, 1H, *H*-5 aniline), 7.75 (dd, ^{3}J = 8.6, ^{4}J = 2.2, 1H, *H*-4 salicyl), 7.92 (d, ^{3}J = 8.3, 1H, *H*-2 aniline), 8.16 (br s, 1H, *H*-2 aniline), 8.54 (d, ^{4}J = 2.2, 1H, *H*-6 salicyl), 9.77 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.79 (*C*H_2 epoxide), 49.53 (*C*HO epoxide), 69.20 (O*C*H_2CHOR), 106.55 (C_q-5 salicyl), 113.64 (*C*-3 salicyl), 117.20 ($^{3}J_{CF}$ = 4.0, *C*-2 aniline), 117.96 (*C*N), 121.26 ($^{3}J_{CF}$ = 3.7, *C*-4 aniline), 123.33 (C_q-1 salicyl), 123.42 (*C*-6 aniline), 124.04 ($^{1}J_{CF}$ = -273.6, *C*F_3 aniline), 129.75(*C*-5 aniline), 131.57 ($^{2}J_{CF}$ = 32.1, *C*-3 aniline), 137.06 (*C*-6 salicyl), 137.29 (*C*-4 salicyl), 138.64 (C_q-1 aniline) 158.69 (C_q-2 salicyl), 161.26 (*C*ONH).

Melting point: 125-128°C.

N-(3,5-bis(trifluoromethyl)phenyl)-5-cyano-2-(oxiran-2-ylmethoxy)benzamide (385)



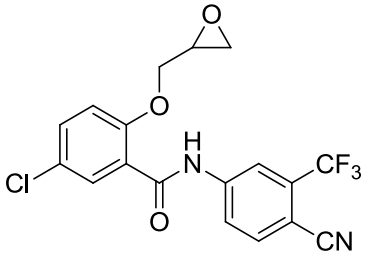
385 was prepared following **general procedure D**, yielding 1.262 g (75%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.96 (dd, *J* = 4.4 , *J* = 2.4, 1H, CH_aH$_b$ epoxide), 3.09 (dd[t], *J* = 4.3, 1H, CH$_a$$H_b$ epoxide), 3.55-3.61 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.26 (dd, ^{2}J = -10.5, ^{3}J = 5.1, 1H, OCH_aH$_b$CHOR), 4.75 (dd, ^{2}J = -10.5, ^{3}J = 2.0, 1H, OCH$_a$$H_b$CHOR), 7.13 (d, ^{3}J = 8.6, 1H, *H*-3 salicyl), 7.64 (s, 1H, *H*-4 aniline), 7.80 (dd, ^{3}J = 8.6, ^{4}J = 2.0, 1H, *H*-4 salicyl), 8.36 (s, 2H, *H*-2,6 aniline), 8.56 (d, ^{4}J = 2.0, 1H, *H*-6 salicyl), 10.00 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.89 (*C*H$_2$ epoxide), 49.56 (*C*HO epoxide), 68.78 (OCH$_2$CHOR), 106.84 (*C*-5 salicyl), 113.82 (*C*-3 salicyl), 117.81 (*C*N), 117.89 (m, $^{3}J_{CF}$ = 3.8, *C*-4 aniline), 120.21 (m, $^{3}J_{CF}$ = 3.4, *C*-2,6 aniline), 122.93 (*C*-1 salicyl), 123.29 ($^{1}J_{CF}$ = -272.6, 2x *C*F$_3$ aniline), 132.52 (q, $^{3}J_{CF}$ = 33.6, *C*-3,5 aniline), 137.39 (*C*-6 salicyl), 137.42 (*C*-4 salicyl), 139.62 (*C*-1 aniline), 158.68 (*C*-2 salicyl), 161.53 (*C*ONH).

Melting point: 166-168°C.

5-chloro-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-2-(oxiran-2-ylmethoxy)benzamide (386)



386 was prepared following **general procedure D**, yielding 0.998 g (43%) of the desired product.

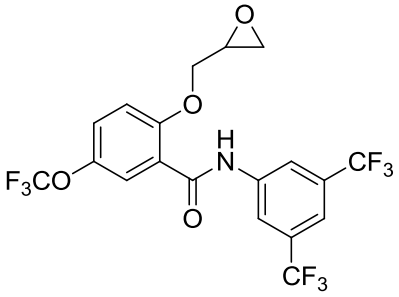
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.93 (dd, *J* = 4.6, *J* = 2.6, 1H, CH_aH$_b$ epoxide), 3.07 (dd[t], *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3.51-3.57 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.14 (dd, ^{2}J = -10.4, ^{3}J = 5.4, 1H, OCH_aH$_b$CHOR), 4.67 (dd, ^{2}J = -10.4, ^{3}J = 2.2, 1H, OCH$_a$$H_b$CHOR), 6.97 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.48 (dd, ^{3}J = 8.8, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.80 (d, ^{3}J = 8.5, 1H, *H*-5 aniline), 8.18 (dd, ^{3}J = 8.5, ^{4}J = 2.0, 1H, *H*-6 aniline), 8.21 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 8.38 (d, ^{4}J = 2.0, 1H, *H*-2 aniline), 10.23 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.92 (*C*H$_2$ epoxide), 49.83 (*C*HO epoxide), 68.93 (OCH$_2$CHOR), 104.30 (q, $^{3}J_{CF}$=2.2, C_q-3 aniline), 114.57 (*C*-3 salicyl), 115.91 (*C*N), 118.22 (q, J_{CF}=5.2, *C*-2 aniline), 122.40 (q, $^{1}J_{CF}$ = -273.8, *C*F$_3$), 122.62 (*C*-6 aniline), 122.82 (*C*-1 salicyl),

128.36 (*C*-5 salicyl), 132.70 (*C*-6 salicyl), 133.91 (*C*-4 salicyl), 134.06 (q, $^{2}J_{CF}$ = 32.7, *C*-3 aniline), 135.95 (*C*-5 aniline), 142.73 (*C*-1 aniline), 154.53 (*C*-2 salicyl),162.49 (*C*ONH).

Melting point: 187-190°C.

N-(3,5-bis(trifluoromethyl)phenyl)-2-(oxiran-2-ylmethoxy)-5-(trifluoromethoxy)benzamide (387)

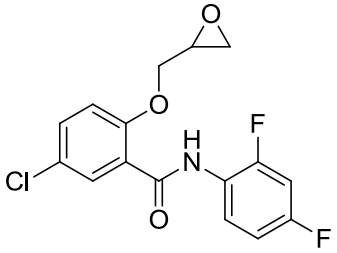


387 was prepared following **general procedure D**, yielding 1.062 g (48%) of the desired semicrystalline product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.94 (dd, *J* = 4.7, *J* = 2.7, 1H, CH_aH$_b$ epoxide), 3.07 (dd[t], *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3.52-3.58 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.20 (dd, ^{2}J = -10.5, ^{3}J = 5.1, 1H, OCH_aH$_b$CHOR), 4.68 (dd, ^{2}J = -10.5, ^{3}J = 2.3, 1H, OCH$_a$$H_b$CHOR), 7.05 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.38 (dd, ^{3}J = 8.8, ^{4}J = 3.0, 1H, *H*-4 salicyl), 7.63 (s, 1H, *H*-4 aniline), 8.15 (d, ^{4}J = 3.0, 1H, *H*-6 salicyl), 8.39 (s, 2H, *H*-2,6 aniline), 10.18 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.80 (*C*H$_2$ epoxide), 49.79 (*C*HO epoxide), 68.99 (OCH_2CHOR), 114.44 (*C*-3 salicyl), 117.65 (m, $^{3}J_{CF}$ = 3.8, *C*-4 aniline), 120.21 (m, $^{3}J_{CF}$ = 3.3, *C*-2,6 aniline), 120.58 ($^{1}J_{CF}$ = -257.8, O*C*F$_3$ aniline), 123.13 (*C*-1 salicyl), 123.36 ($^{1}J_{CF}$ = -272.7, 2x *C*F$_3$ aniline), 125.61 (*C*-6 salicyl), 126.64 (*C*-4 salicyl), 132.45 (q, $^{2}J_{CF}$ = 33.2, *C*-3,5 aniline), 139.88 (*C*-1 aniline), 144.08 (q, J_{CF} = 2.3, *C*-5 salicyl), 154.35 (*C*-2 salicyl), 162.20 (*C*ONH).

5-chloro-*N*-(2,4-difluorophenyl)-2-(oxiran-2-ylmethoxy)benzamide (388)



388 was prepared following **general procedure D**, yielding 0.444 g (57%) of the desired product.

^{1}H NMR (600 MHz, $CDCl_3$, 23 °C): δ = 2.77 (dd, *J* = 4.6, *J* = 2.6, 1H, C*H*$_a$H$_b$ epoxide), 3.01 (dd[t], *J* = 4.4, 1H, CH$_a$*H*$_b$ epoxide), 3.48-3.52 (m, 1H, OCH$_a$H$_b$C*H*OH), 4.10 (dd, ^{2}J = -10.6, ^{3}J = 6.4, 1H, OC*H*$_a$H$_b$CHOH), 4.45 (dd, ^{2}J = -10.6, ^{3}J = 3.2, 1H, OCH$_a$*H*$_b$CHOH), 6.87-6.94 (m, 2H, *H*-3',5' in 2,4-difluoroaniline), 6.96 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.43 (dd, ^{3}J = 8.8, ^{4}J = 2.8, 1H, *H*-4 salicyl), 8.26 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 8.49-8.54 (m, 1H, *H*-6' in 2,4-difluoroaniline), 10.06 (br, s, 1H, CON*H*).

^{13}C{^{1}H}NMR (150 MHz, $CDCl_3$, 23 °C): δ = 44.87 (d, $^{TS}J_{CF}$ = 1.1, *C*H$_2$ oxirane), 49.42 (d, $^{TS}J_{CF}$ = 2.3, *C*H oxirane), 71.51 (salicyl-O*C*H$_2$-oxirane), 103.63 (dd, $^{2}J_{1CF}$ = 23.3, $^{2}J_{1CF}$ = 26.7, *C*-3' in 2', 4'-difluoroaniline), 111.41 (dd, $^{2}J_{CF}$ = 21.5, $^{4}J_{CF}$ = 3.6, *C*-5' in 2', 4'-difluoroaniline), 114.22 (*C*-3 salicyl), 122.99 (dd, $^{3}J_{2CF}$ = 8.8, $^{3}J_{2CF}$ = 2.1, *C*-6' in 2', 4' difluoro-aniline), 123.03 (*C*$_q$-1 salicyl), 123.27 (dd, $^{2}J_{1CF}$ = 10.1, $^{4}J_{CF}$ = 3.7, *C*$_q$-1' in 2', 4'-difluoroaniline), 127.83 (*C*$_q$-5 salicyl), 132.49 (*C*-6 salicyl), 133.30 (*C*-4 salicyl), 152.80 (dd, $^{1}J_{1CF}$ = 246.0, $^{3}J_{2CF}$ = 11.7, *C*-4' in 2', 4'-difluoro-aniline), 154.86 (*C*$_q$-2 salicyl), 158.60 (dd, $^{1}J_{1CF}$ = 246.1, $^{3}J_{2CF}$ = 11.6, *C*-2' in 2', 4'-difluoro-aniline), 161.75 (*C*ONH).

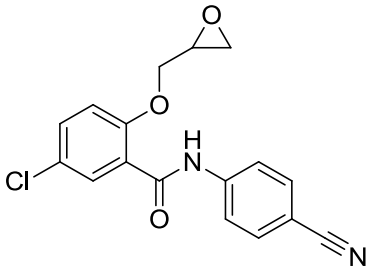
^{1}H NMR (400 MHz, DMSO-d$_6$, 23 °C): δ = 2.75 (dd, *J* = 5.0, *J* = 2.6, 1H, C*H*$_a$H$_b$ epoxide), 2.88 (dd[t], *J* = 4.6, 1H, CH$_a$*H*$_b$ epoxide), 3.41-3.45 (m, 1H, OCH$_a$H$_b$C*H*OH), 4.08 (dd, ^{2}J = -11.1, ^{3}J = 6.6, 1H, OC*H*$_a$H$_b$CHOH), 4.53 (dd, ^{2}J = -11.1, ^{3}J = 2.6, 1H, OCH$_a$*H*$_b$CHOH), 7.11-7.15 (m, 1H, *H*-5' in 2,4-difluoroaniline), 7.27 (d, ^{3}J = 8.9, 1H, *H*-3 salicyl), 7.37-7.42 (m, 1H, *H*-3' in 2,4-difluoroaniline), 7.60 (dd, ^{3}J = 8.9, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.81 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 8.06-8.11 (m, 1H, *H*-6' in 2,4-difluoroaniline), 10.11 (br, s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d$_6$, 23 °C): δ = 43.76 (*C*H$_2$ oxirane), 49.33 (d, $^{TS}J_{CF}$ = 1.3, *C*H oxirane), 70.83 (salicyl-O*C*H$_2$-oxirane), 104.23 (dd, $^{2}J_{1CF}$ = 26.9, $^{2}J_{1CF}$ = 23.8, *C*-3' in 2', 4'-difluoroaniline), 111.31 (dd, $^{2}J_{CF}$ = 21.9, $^{4}J_{CF}$ = 3.5, *C*-5' in 2', 4'-difluoroaniline), 115.73 (*C*-3 salicyl), 122.56 (dd, $^{2}J_{1CF}$ = 11.6, $^{4}J_{CF}$ = 3.7, *C*$_q$-1' in 2', 4'-difluoro-aniline), 124.32 (*C*$_q$-1 salicyl),

124.95 (dd, $^{3}J_{2CF}$ = 11.2, $^{3}J_{2CF}$ = 3.5, *C*-6' in 2', 4'-difluoroaniline), 125.18 (*C*$_q$-5 salicyl), 129.88 (*C*-6 salicyl), 132.53 (*C*-4 salicyl), 153.76 (dd, $^{1}J_{1CF}$ = 248.2, $^{3}J_{2CF}$ = 12.5, *C*-4' in 2', 4'-difluoroaniline), 154.86 (*C*$_q$-2 salicyl), 158.62 (dd, $^{1}J_{1CF}$ = 244.2, $^{3}J_{2CF}$ = 11.6, *C*-2' in 2', 4'-difluoroaniline), 162.32 (*C*ONH).

Melting point: 153-155°C.

5-chloro-*N*-(4-cyanophenyl)-2-(oxiran-2-ylmethoxy)benzamide (389**)**



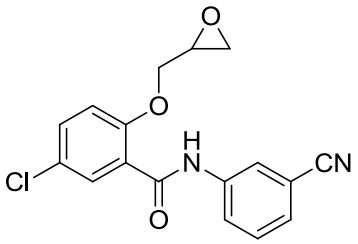
389 was prepared following **general procedure D**, yielding 3.709 g (68%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2,88 (dd, *J* = 4.7, *J* = 2.6, 1H, CH_aH$_b$ epoxide), 3,02 (dd[t], *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3,46-3,54 (m, 1H, OCH$_a$H$_b$C*H*OR), 4,05 (dd, ^2J = -10.4, ^3J = 5.8, 1H, OCH_aH$_b$CHOR), 4,61 (dd, ^2J = -10.4, ^3J = 2.2, 1H, OCH$_a$$H_b$CHOR), 6,92 (d, ^3J = 8.8, 1H, *H*-3 salicyl), 7,40 (dd, ^3J = 8.8, ^4J = 2.8, 1H, *H*-4 salicyl), 7,60 (d, ^3J = 8.7, 2H, *H*-3,5 aniline), 7,91 (d, ^3J = 8.7, 2H, *H*-2,6 aniline), 8,15 (d, ^4J = 2.8, 1H, *H*-6 salicyl), 9,99 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44,77 (*C*H$_2$ epoxide), 49,74 (*C*HO epoxide), 69,25 (OCH_2CHOR), 107,05 (C_q-4 aniline), 114,33 (*C*-3 salicyl), 119,11 (*C*N), 120,28 (*C*-2,6 aniline), 123,06 (C_q-1 salicyl), 127,92 (C_q-5 salicyl), 132,42 (*C*-6 salicyl), 133,29 (*C*-3,5 aniline), 133,44 (*C*-4 salicyl), 142,44 (C_q-1 aniline), 154,45 (C_q-2 salicyl), 162,14 (*C*ONH).

Melting point: 158°C.

5-chloro-*N*-(3-cyanophenyl)-2-(oxiran-2-ylmethoxy)benzamide (390**)**



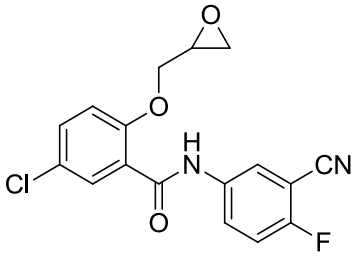
390 was prepared following **general procedure D**, yielding 0.502 g (16%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.90 (dd, *J* = 4.7, *J* = 2.6, 1H, CH_aH$_b$ epoxide), 3.04 (dd[t], *J* = 4.4, 1H, CH$_a$$H_b$ epoxide), 3.49-3.54 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.09 (dd, ^2J = -10.5, ^3J = 5.7, 1H, OCH_aH$_b$CHOR), 4.63 (dd, ^2J = -10.5, ^3J = 2.3, 1H, OCH$_a$$H_b$CHOR), 6.95 (d, ^3J = 8.9, 1H, *H*-3 salicyl), 7.36-7.48 (m, 3H, *H*-4,5 aniline, *H*-4 salicyl), 7.96 (dq, ^3J = 8.1, 1H, *H*-6 aniline), 8.20 (d, ^4J = 2.8, 1H, *H*-6 salicyl), 8.25 (s, 1H, *H*-2 aniline), 9.94 (br s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.83 (*C*H_2 epoxide), 49.79 (*C*HO epoxide), 69.30 (O*C*H_2CHOR), 113.12 (*C*-3 aniline), 114.45 (*C*-3 salicyl), 118.85 (*C*N), 123.29 (C_q-1 salicyl), 123.53 (*C*-2 aniline), 124.51 (*C*-6 aniline), 127.80 (C_q-5 salicyl), 128.10 (*C*-5 aniline), 129.96 (*C*-4 aniline), 132.56 (*C*-6 salicyl), 133.38 (*C*-4 salicyl), 139.30 (C_q-1 aniline), 154.51 (C_q-2 salicyl), 162.16 (*C*ONH).

Melting point: 155-158°C.

5-chloro-*N*-(3-cyano-4-fluorophenyl)-2-(oxiran-2-ylmethoxy)benzamide (391)



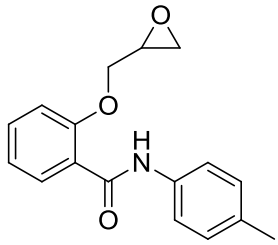
391 was prepared following **general procedure D**, yielding 0.484 g (25%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.91 (dd, *J* = 4.6, *J* = 2.5, 1H, C$H_a$$H_b$ epoxide), 3.05 (dd[t], *J* = 4.4, 1H, CH_aH_b epoxide), 3.49-3.57 (m, 1H, OCH_aH_bCHOR), 4.10 (dd, ^{2}J = -10.4, ^{3}J = 5.5, 1H, OCH_aH_bCHOR), 4.65 (dd, ^{2}J = -10.4, ^{3}J = 2.1, 1H, OCH_aH_bCHOR), 6.95 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.18 (dd [t], ^{3}J = 8.9, 1H, *H*-5 aniline), 7.43 (dd, ^{3}J = 8.8, ^{4}J = 2.7, 1H, *H*-4 salicyl), 7.91-7.99 (m, 1H, *H*-6 aniline), 8.18 (d, ^{4}J = 2.7, 1H, *H*-6 salicyl), 8.22-8.28 (m, 1H, *H*-2 aniline), 9.95 (br s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.89 (*C*H_2 epoxide), 49.83 (*C*HO epoxide), 69.12 (O*C*H_2CHOR), 101.60 (d, J_{CF}=16.4, *C*-3 aniline), 113.99 (*C*N), 114.55 (*C*-3 salicyl), 116.92 (d, $^{2}J_{CF}$= 20.6, *C*-5 aniline), 123.08 (*C*-1 salicyl), 124.52 (*C*-2 aniline), 126.81 (d, $^{3}J_{CF}$= 7.5, *C*-6 aniline), 128.14 (*C*-5 salicyl), 132.50 (*C*-6 salicyl), 133.45 (*C*-4 salicyl), 135.37 (d, $^{4}J_{CF}$= 2.7, *C*-1 aniline), 154.48 (*C*-2 salicyl), 159.53 (d, $^{1}J_{CF}$= 256.6, *C*-4 aniline),162.08 (*C*ONH).

Melting point: 153°C.

2-(oxiran-2-ylmethoxy)-*N*-(p-tolyl)benzamide (392)



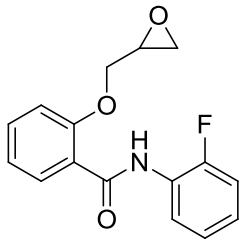
392 (CAS: 81500-04-1[120,159]) was prepared following **general procedure D**, yielding 1.688 g (43%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.33 (s, 3H, C*H*$_3$), 2.87-2.89 (m[dd], 1H, C*H*$_a$H$_b$-oxirane), 2.97-2.99 (m[t], 1H, CH$_a$*H*$_b$-oxirane), 3.46-3.50 (m, 1H, C*H*-oxirane), 4.13 (dd, ^2J = -10.6, ^3J = 5.4, 1H, salicyl-OC*H*$_a$H$_b$-oxirane), 4.55 (dd, ^2J = -10.6, ^3J = 2.4, 1H, salicyl-OCH$_a$*H*$_b$-oxirane), 6.97 (d, ^3J = 8.3, 1H, *H*-3 salicyl), 7.11-7.19 (m, AA' of AA'BB', 3H, *H*-3',5' in toluidine, *H*-5 salicyl), 7.46 (ddd, ^3J = 7.5, ^3J = 8.3, ^4J = 1.8, 1H, *H*-4 salicyl), 7.67, 7.69 (BB' of AA'BB', 2H, *H*-2',6' in toluidine), 8.27 (dd, ^3J = 7.8, ^4J = 1.8, 1H, *H*-6 salicyl), 9.74 (s, br, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 21.04 (CONH-1'-C_6H_4-4'-*C*H$_3$), 44.64 (*C*H$_2$ oxirane), 49.94 (*C*H oxirane), 69.07 (salicyl-O*C*H$_2$-oxirane), 112.73 (*C*-3 salicyl), 120.32 (*C*-2',6' in toluidine), 122.40 (*C*-3 salicyl), 122.77 (C_q-1 salicyl), 129.62 (*C*-3',5' in toluidine), 132.82 (*C*-6 salicyl), 133.12 (*C*-4 salicyl), 133.72 (C_q-4' in toluidine), 136.24 (C_q-1' in toluidine), 156.01 (C_q-2 salicyl),163.03 (*C*ONH).

Melting point: 136-138°C.

N-(2-fluorophenyl)-2-(oxiran-2-ylmethoxy)benzamide (393)



393 (CAS: 866034-84-6[120]) was prepared following **general procedure D**, yielding 1.402 g (75%) of the desired product.

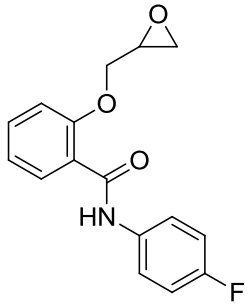
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.76-2.78 (m[dd], 1H, C*H*$_a$H$_b$-oxirane), 2.99-3.01 (m[t], 1H, CH$_a$*H*$_b$-oxirane), 3.51-3.55 (m, 1H, C*H*-oxirane), 4.18 (dd, ^2J = -10.6 , ^3J = 6.1, 1H, salicyl-OC*H*$_a$H$_b$-oxirane), 4.40 (dd, ^2J = -10.6, ^3J = 3.6, 1H, salicyl-OCH$_a$*H*$_b$-oxirane), 7.02 (d, ^3J = 8.2,

1H, *H*-3 salicyl), 7.04-7.20 (m, 4H, *H*-3',4', 5' in 2'-F-aniline, *H*-5 salicyl), 7.49 (ddd, $^{3}J_{1}$ = 7.3, $^{3}J_{2}$ = 8.3, ^{4}J = 1.8, 1H, *H*-4 salicyl), 8.31 (dd, ^{3}J = 7.8, ^{4}J = 1.8, 1H, *H*-6 salicyl), 8.60 (ddd, ^{3}J = $^{3}J_{HF}$ = 8.1, ^{4}J = 1.5, 1H, *H*-6' in 2'-F-aniline), 10.21 (s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 45.07, 45.09 (*C*H_2 oxirane), 49.53, 49.56 (*C*H oxirane), 71.11 (salicyl-O*C*H_2-oxirane), 112.69 (*C*-3 salicyl), 114.79 (d, $^{2}J_{CF}$ = 19.3, *C*-3' in 2'-F-aniline), 121.97 (C_q-1 salicyl), 122.14 (br, *C*-6' in 2'-F-aniline), 122.34 (*C*-5 salicyl), 124.08 (d, $^{3}J_{CF}$ = 7.7, *C*-4' in 2'-F-aniline), 124.80 (d, $^{4}J_{CF}$ = 3.3, *C*-5' in 2'-F-aniline), 127.29 (d, $^{2}J_{CF}$ = 9.7, C_q-1' in 2'-F-aniline), 132.92 (*C*-6 salicyl), 133.65 (*C*-4 salicyl), 152.89 (d, $^{1}J_{CF}$ = -242.6, C_q-2' in 2'-F-aniline), 156.43 (C_q-2 salicyl), 163.17 (*C*ONH).

Melting point: 108-111°C.

N-(4-Fluoro-phenyl)-2-oxiranylmethoxy-benzamide (394)



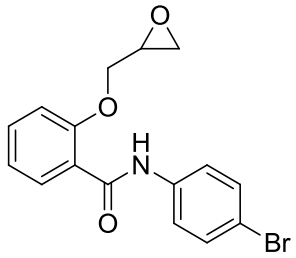
394 (CAS 1510805-23-8)[120] was prepared following **general procedure D**, yielding 0.274 g (22%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.88-2.90 (m[dd], 1H, C$H_a$$H_b$-oxirane), 2.98-3.01 (m[t], 1H, C$H_a$$H_b$-oxirane), 3.47-3.51 (m, 1H, C*H*-oxirane), 4.13 (dd, ^{2}J = -10.6 , ^{3}J = 5.4, 1H, salicyl-OC$H_a$$H_b$-oxirane), 4.59 (dd, ^{2}J = -10.6, ^{3}J = 2.3, 1H, salicyl-OC$H_a$$H_b$-oxirane), 6.98 (dd, ^{3}J = 8.2, ^{4}J = 0.6, 1H, *H*-3 salicyl), 7.01-7.08 (m[tr], 2H, *H*-3',5' in 4'-F-aniline), 7.15 (ddd[tr], $^{3}J_{1}$ = $^{3}J_{2}$ = 7.6, ^{4}J = 0.8, 1H, *H*-5 salicyl), 7.47 (ddd, $^{3}J_{1}$ = 7.3, $^{3}J_{2}$ = 8.3, ^{4}J = 1.8, 1H, *H*-4 salicyl), 7.75-7.80 (m, 2H, *H*-2',6' in 4'-F-aniline), 8.27 (dd, ^{3}J = 7.8, ^{4}J = 1.8, 1H, *H*-6 salicyl), 9.81 (s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.66 (*C*H_2 oxirane), 49.96 (*C*H oxirane), 68.91 (salicyl-O*C*H_2-oxirane), 112.78 (*C*-3 salicyl), 115.68 (d, $^{2}J_{CF}$ = 22.3, *C*-3',5' in 4'-F-aniline), 121.94 (d, $^{3}J_{CF}$ = 7.8, *C*-2',6' in 4'-F-aniline), 122.47 (C_q-1 salicyl), 122.50 (*C*-5 salicyl), 132.86 (*C*-6 salicyl), 133.33 (*C*-4 salicyl), 134.87 (d, $^{4}J_{CF}$ = 2.7, C_q-1' in 4'-F-aniline), 156.02 (C_q-2 salicyl), 159.36 (d, $^{1}J_{CF}$ = -243, C_q-4' in 4'-F-aniline), 163.12 (*C*ONH).

Melting point: 113-116°C.

N-(4-bromophenyl)-2-(oxiran-2-ylmethoxy)benzamide (395)



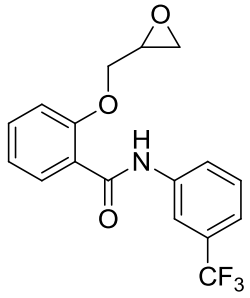
395 (CAS: 81500-06-3[159], no characterization) was prepared following **general procedure D**, yielding 4.320 g (52%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.86-2.88 (m[dd], 1H, CH_aH$_b$-oxirane), 2.97-2.99 (m[t], 1H, CH$_a$$H_b$-oxirane), 3.46-3.49 (m, 1H, C*H*-oxirane), 4.09 (dd, ^2J = -10.6 , ^3J = 5.5, 1H, salicyl-OCH_aH$_b$-oxirane), 4.59 (dd, ^2J = -10.6, ^3J = 2.3, 1H, salicyl-OCH$_a$$H_b$-oxirane), 6.96 (dd, ^3J = 8.3, ^4J = 0.6, 1H, *H*-3 salicyl), 7.13 (ddd[tr], $^3J_1$ = $^3J_2$ = 7.6, ^4J = 0.8, 1H, *H*-5 salicyl), 7.43, 7.45 (AA' of AA'BB', 2H, (*H*-3',5' aniline), 7.46 (ddd, $^3J_1$ = 7.4, $^3J_2$ = 8.5, ^4J = 1.8, 1H, *H*-4 salicyl), 7.70. 7.72 (BB' of AA'BB', 2H, (*H*-2',6' aniline), 8.24 (dd, ^3J = 7.8, ^4J = 1.8, 1H, *H*-6 salicyl), 9.84 (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.64 (*C*H$_2$ oxirane), 49.92 (*C*H oxirane), 68.82 (salicyl-O*C*H$_2$-oxirane), 112.73 (*C*-3 salicyl), 116.59 (C_q-4'aniline), 121.87 (*C*-2',6'aniline), 122.26 (C_q-1 salicyl), 122.45 (*C*-5 salicyl), 132.01 (*C*-3',5' aniline), 132.79 (*C*-6 salicyl), 133.46 (*C*-4 salicyl), 137.89 (C_q-1' aniline), 155.96 (C_q-2 salicyl), 163.21 (*C*ONH).

Melting point: 110-113°C.

2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (396)



396 (CAS: 1510805-26-1[120]) was prepared following **general procedure D**, yielding 22.531 g (75%) of the desired product.

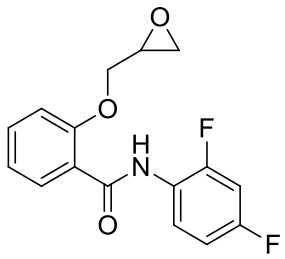
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.90-2.92 (m[dd], 1H, CH_aH$_b$-oxirane), 3.00-3.03 (dd[t], 1H, CH$_a$$H_b$-oxirane), 3.49-3.53 (m[sext], 1H, C*H*-oxirane), 4.16 (dd, ^2J = -10.6, ^3J = 5.3, 1H,

salicyl-OCH_aH$_b$), 4.61 (dd, ^2J = -10.6, ^3J = 2.3, 1H, salicyl-OCH$_a$$H_b$), 7.00 (dd, ^3J = 7.8, ^4J = 0.6, 1H, *H*-3 salicyl), 7.17 (ddd, $^3J_1$ = $^3J_2$ = 8.0, ^4J = 0.8, 1H, *H*-5 salicyl), 7.36 (d, br, 1H, *H*-4' in 3'-CF_3-aniline), 7.46 (m[tr], 1H, *H*-5' in 3'-CF_3-aniline), 7.49 ($^3J_1$ = 7.4, $^3J_2$ = 8.3, ^4J = 1.8, 1H, *H*-4 salicyl), 7.95 (d, br, 1H, *H*-6' in 3'-CF_3-aniline), 8.22 (m, br, 1H, *H*-2' in 3'-CF_3-aniline), 8.27 (dd, ^3J = 7.8, ^4J = 1.7, 1H, *H*-6 salicyl), 10.00 (s, br, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.69 (*C*H$_2$ oxirane), 49.94 (*C*H oxirane), 68.76 (salicyl-O*C*H$_2$-oxirane), 112.85 (*C*-3 salicyl), 117.17 (q, $^3J_{CF}$ = 3.9, *C*-2' in 3'-CF_3-aniline), 120.64 (q, $^3J_{CF}$ = 3.8, *C*-4' in 3'-CF_3-aniline), 122.18 (C_q-1 salicyl), 122.59 (*C*-5 salicyl), 123.31 (*C*-6' in 3'-CF_3-aniline), 123.86 (q, $^1J_{CF}$ = -273.3, 3'-*C*F_3-aniline), 129.57 (*C*-5' in 3'-CF_3-aniline), 131.50 (q, $^2J_{CF}$ = 32.3, *C*-3' in 3'-CF_3-aniline), 132.93 (*C*-6 salicyl), 133.64 (*C*-4 salicyl), 139.34 (C_q-1' in 3'-CF_3-aniline), 156.06 (C_q-2 salicyl), 163.46 (*C*ONH).

Melting point: 85-87°C.

N-(2,4-difluorophenyl)-2-(oxiran-2-ylmethoxy)benzamide (397)



397 (CAS: 1510805-25-0[120]) was prepared following **general procedure D**, yielding 1.250 g (84%) of the desired product.

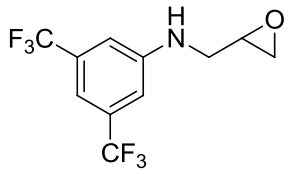
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.76-2.28 (m[dd], 1H, CH_aH$_b$-oxirane), 2.99-3.01 (dd[t], 1H, CH$_a$$H_b$-oxirane), 3.49-3.53 (m[sext], 1H, C*H*-oxirane), 4.15 (dd, ^2J = -10.7, ^3J = 6.3, 1H, salicyl-OCH_aH$_b$), 4.43 (dd, ^2J = -10.7, ^3J = 3.4, 1H, salicyl-OCH$_a$$H_b$), 6.86-6.94 (m, 2H, *H*-3',5' in 2,4-difluoroaniline), 7.01 (d, ^3J = 8.2, 1H, *H*-3 salicyl), 7.16 (ddd, $^3J_1$ = $^3J_2$ = 7.6, ^4J = 0.8, 1H, *H*-5 salicyl), 7.50 (ddd, $^3J_1$ = 7.4, $^3J_2$ = 8.3, ^4J = 1.8, 1H, *H*-4 salicyl), 8.30 (dd, ^3J = 7.8, ^4J = 1.7, 1H, *H*-6 salicyl), 8.52-8.58 (m, 1H, *H*-6' in 2,4-difluoroaniline), 10.11 (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.96, 44.97 (*C*H$_2$ oxirane), 49.52, 49.54 (*C*H oxirane), 71.04 (salicyl-O*C*H$_2$-oxirane), 103.57 (dd, $^2J_{1CF}$ = 23.4, $^2J_{1CF}$ = 26.6, *C*-3' in 2', 4'-difluoroaniline), 111.31 (dd, $^2J_{CF}$ = 21.5, $^4J_{CF}$ = 3.6, *C*-5' in 2', 4'-difluoroaniline), 112.70 (*C*-3 salicyl), 121.72 (C_q-1 salicyl), 122.38 (*C*-5 salicyl), 123.04 (dd, $^3J_{2CF}$ = 8.9, $^3J_{2CF}$ = 2.4, *C*-6' in 2', 4'-difluoroaniline), 123.62 (dd, $^2J_{1CF}$ = 9.9, $^4J_{CF}$ = 3.8, C_q-1' in 2', 4'-difluoroaniline), 132.89 (*C*-6

salicyl), 133.74 (*C*-4 salicyl), 152.84 (dd, $^{1}J_{1CF}$ = 246.1, $^{3}J_{2CF}$ = 11.8, *C*-4' in 2', 4'-difluoroaniline), 156.41 (C_q-2 salicyl), 158.47 (dd, $^{1}J_{1CF}$ = 245.7, $^{3}J_{2CF}$ = 11.8, *C*-2' in 2', 4'-difluoroaniline), 163.15 (*C*ONH).

Melting point: 117-118°C.

N-(oxiran-2-ylmethyl)-3,5-bis(trifluoromethyl)aniline (398)



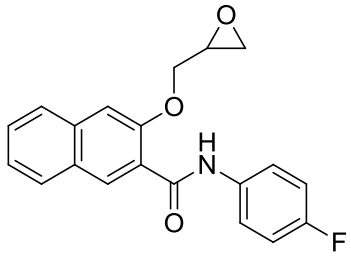
Crushed KOH (0.252 g, 4.49 mmol) was loaded to a 100 mL round bottom flask. 3,5-bis(trifluoromethyl)aniline (0.702 mL, 4.49 mmol) and epichlorohydrin (1.475 mL, 18.86 mmol) were added immediately and the mixture was stirred on the roatavapor at 85°C bath temperature. After complete consumption was observed *via* TLC (1h), unreacted epichlorohydrin was removed. The residue was extracted three times with ethyl acetate. The extracts were dried over Na_2SO_4, and concentrated under reduced pressure. **398** was obtained as yellow oil in 80% yield (1.025 g).

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.70 (dd, ^{2}J = -4.7, ^{3}J = 2.3, 1H, CH_aH$_b$ epoxide), 2.86 (dd, ^{2}J = -4.7, ^{3}J = 4.0, 1H, CH$_a$$H_b$ epoxide), 3.20-3.31 (m, 2H, OCH_aH$_b$CHOR, OCH$_a$H$_b$C*H*OR), 3.61-3.69 (m, 1H, OCH$_a$$H_b$CHOR), 4.34 (br s, 1H, N*H*), 6.99 (s, 2H, *H*-2,6 aniline), 7.18 (s, 1H, *H*-4 aniline).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.71 (*C*H$_2$ epoxide), 45.22 (N*C*H$_2$CHOR), 50.57 (*C*H epoxide), 110.97 (m, $^{3}J_{CF}$ = 4.0, *C*-4 aniline), 112.28 (q, $^{3}J_{CF}$ = 3.5, *C*-2,6 aniline), 123.64 ($^{1}J_{CF}$ = -273.0, *C*F$_3$ aniline), 132.68 (q, $^{2}J_{CF}$ = 31.9, *C*-3,5 aniline), 148.63 (*C*-1 aniline).

LCMS: $[M+H]^+$: calculated.: 286.07 found: 286.15, $[M-H]^-$: calculated.: 637.29 found: 637.21.

N-(4-fluorophenyl)-3-(oxiran-2-ylmethoxy)-2-naphthamide (399)



399 (CAS: 1174069-50-1[160]) was prepared following **general procedure D**, yielding 0.217 g (17%) of the desired product.

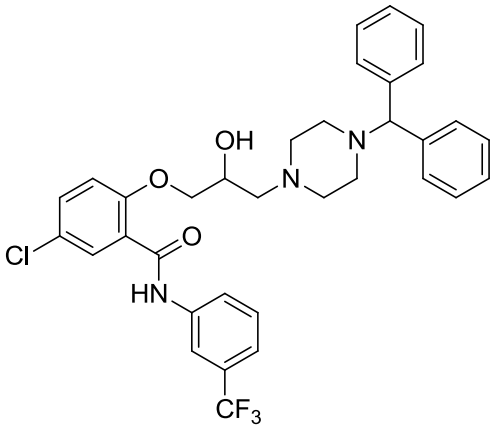
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.88 (dd, *J* = 4.8 , *J* = 2.7, 1H, CH_aH$_b$ epoxide), 2.97 (dd[t], *J* = 4.5, 1H, CH$_a$$H_b$ epoxide), 3.49-3.54 (m, 1H, OCH$_a$H$_b$C*H*OR), 4.04 (dd, ^{2}J = -11.2, ^{3}J = 6.4, 1H, OCH_aH$_b$CHOR), 4.48 (dd, ^{2}J = -11.2, ^{3}J = 2.1, 1H, OCH$_a$$H_b$CHOR), 7.04-7.11 (m[tr], 2H, *H*-3',5' in 4'-F-aniline), 7.59-7.63 (m, 2H, *H*-napththyl), 7.75 (d, 1H, *H*-napththyl), 7.81-7.86 (m, 2H, *H*-2',6' in 4'-F-aniline), 7.86-7.92 (m, 1H, *H*-napththyl), 8.17-8.22 (m, 2H, *H*-napththyl), 9.86 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 44.80 (*C*H$_2$ epoxide), 50.57 (*C*HO epoxide), 77.21 (O*C*H$_2$CHOR), 116.03 (d, $^{2}J_{CF}$ = 22.3, *C*-3',5' in 4'-F-aniline), 122.49 (d, $^{3}J_{CF}$ = 7.6, *C*-2',6' in 4'-F-aniline), 123.01 (*C*H naphthyl), 125.73 (*C*H naphthyl), 127.24 (*C*H naphthyl), 127.47 (*C*H naphthyl), 128.70 (*C*H naphthyl), 128.81 (*C*H naphthyl), 137.20 (C_q-1' in 4'-F-aniline), 153.42 (C_q-3 naphthyl), 159.75 (*C*-4' in 4'-F-aniline) by HMBC, 163.15 (*C*ONH) by HMBC. C_q-2,4a,8a naphthyl not recorded

Melting point: 108-111°C.

4.3.3 Final Compounds

2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (95)



95 was prepared following **general procedure E**, yielding 0.096 g (76%) of the desired product.

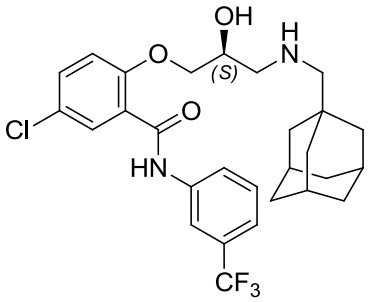
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.37-2.52 (m, 7H, NCH_{ax}-2'',6'', NCH_2-3''.5'' of piperazine, NCH_aH$_b$CH(OH)(dd, ^2J = -12.4, ^3J = 3.7)), 2.59 (dd, ^2J = -12.4, ^3J =10.8, 1H, NCH$_a$$H_b$CH(OH)), 2.68-2.78 (m, dyn, 2H, NCH_{eq}-2'',6'' of piperazine), 3.99 (dd, ^2J = -9.4, ^3J = 6.1, 1H, OCH_aH$_b$CH(OH)), 4.15-4.22 (m, 1H, C*H*(OH)), 4.26 (s, 1H, NC*H*(C_6H_5)$_2$), 4.29 (dd, ^2J = -9.4, ^3J = 2.7, 1H, OCH$_a$$H_b$CH(OH)), 6.90 (d, ^3J = 8.8, ^4J = 1.7, 1H, *H*-3 salicyl), 7.16-7.22 (m, 2H, 2x C*H*-4 phenyl), 7.24-7.31 (m, 4H, 2x *H*-3'',5'' phenyl), 7.33 (d, ^3J = 7.8, 1H, *H*-4 aniline), 7.39-7.44 (m, 6H, 2x *H*-2'',6'' phenyl, *H*-5 aniline, *H*-4 salicyl), 8.01-8.07 (m, 2H, *H*-2,6 aniline), 8.21 (d, ^4J = 2.8, 1H, *H*-6 salicyl), 10.26 (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 51.93 (*C*H_2-dyn, piperazine), 53.62 (*C*H_2-dyn, piperazine), 59.56 (N*C*H_2CH(OH)), 64.96 (*C*H(OH)), 71.69 (O*C*H_2CH(OH)), 76.18 (N-*C*H(C_6H_5)$_2$), 114.30 (*C*-3 salicyl), 117.29 (q, $^4J_{CF}$ = 4.1, *C*-2' in 3'-CF_3-aniline), 120.66 (q, $^4J_{CF}$ = 3.8, *C*-4' in 3'-CF_3-aniline), 123.48 (*C*-6' in 3'-CF_3-aniline), 123.62 (C_q-1 salicyl), 124.15 (q, $^1J_{CF}$ = -272.3, 3-*C*F_3-aniline), 127.17 (*C*-4'' phenyl), 127.59 (C_q-5 salicyl), 128.04 (*C*-2'',6'' phenyl), 128.66 (*C*-3'',5'' phenyl), 129.52 (*C*-5' in 3'-CF_3-aniline), 131.29 (q, $^2J_{CF}$ = 31.6, *C*-3' in 3'-CF_3-aniline), 132.39 (*C*-6 salicyl), 133.06 (*C*-4 salicyl), 139.27 (C_q-1' in 3'-CF_3-aniline), 142.64 (C_q-1'' phenyl), 155.14 (C_q-2 salicyl), 162.37 (*C*ONH).

HRMS: $[M+H]^+$: calculated.: 624.2245 found: 624.2241.

Melting point: 66-70°C.

(*S*)-(+)-2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (96)

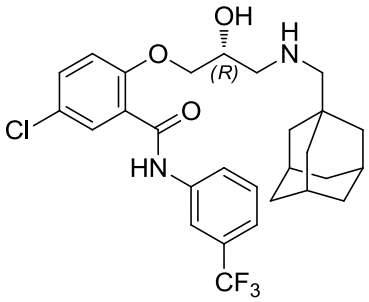


96 was prepared following **general procedure E**, using (*S*)-(-)-5-chloro-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (**99**), yielding 0.224 g (77%) of the desired product.

For NMR assignment see (±)-2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (**194**).

$[\alpha]_D^{20}$= 14.8°, c=1 in MeOH.

(*R*)-(-)-2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (97)

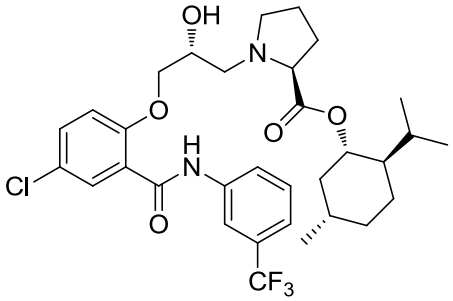


97 was prepared following **general procedure E**, using (*R*)-(+)-5-chloro-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (**100**), yielding 0.214 g (80%) of the desired product.

For NMR assignment see (±)-2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (**194**).

$[\alpha]_D^{20}$= 15.9°, c=1 in MeOH.

(*S*)-(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl-1-((*R*)-3-(4-chloro-2-((3-(trifluoromethyl)phenyl)carbamoyl)phenoxy)-2-hydroxypropyl)pyrrolidine-2-carboxylate (102)



102 was prepared following **general procedure E**, yielding 0.137 g (75%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 0.75 (d, ^{3}J = 7.0, 3H, CH_3 isopropyl), 0.76 (d, ^{3}J = 6.4, 3H, 5-CH_3 cyclohexyl), 0.80 (m, 1H, H_a-4 cyclohexyl), 0.89 (d, ^{3}J = 7.0, 3H, CH_3 isopropyl), 0.91 (m, 1H, H_a-6 cyclohexyl), 0.94-1.07 (m, 1H, H_a-3 cyclohexyl), 1.28 (m, 1H, *H*-5 cyclohexyl), 1.36 (m [tt], *J* = 12.0, *J* = 3.1, 1H, *H*-2 cyclohexyl), 1.58-1.70 (m, 2H, H_b-4 cyclohexyl, H_a-3 cyclohexyl), 1.77-2.01 (m, 5H, C*H* isopropyl, H_b-6 cyclohexyl, $H_{a,b}$-4 pyrrolidine, H_a-3 pyrrolidine), 2.16-2.28 (m, 1H, H_b-3 pyrrolidine), 2.66 (m, 1H, H_a-5 pyrrolidine), 2.73 (dd, ^{2}J = -12.7, ^{3}J = 3.2, 1H, CH(OH)CH_aH$_b$NH), 2.94 (dd, ^{2}J = -12.7, ^{3}J = 9.2, 1H, CH(OH)CH$_a$$H_b$NH), 3.09-3.16 (m, 1H, H_b-5 pyrrolidine), 3.25 (m, 1H, *H*-2 pyrrolidine), 3.95-4.03 (m, 1H, C*H*(OH)), 4.06 (dd, ^{2}J = -9.0, ^{3}J = 6.7, 1H, OCH_aH$_b$CH(OH)), 4.28 (dd, ^{2}J = -9.0, ^{3}J = 2.6, 1H, OCH$_a$$H_b$CH(OH)), 4.48-4.63 (m, 1H, CH(O*H*)), 4.68 (dd, J_{aa} = 10.6, J_{ae} = 4.3, 1H, C*H*-1 cyclohexyl), 6.91 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.35 1H (d, ^{3}J = 7.7, 1H, *H*-4'' in 3''-CF3-aniline), 7.40 (dd, ^{2}J = 8.8, ^{3}J = 2.7, 1H, *H*-4 salicyl), 7.46 (dd [t], ^{3}J = 7.9, 1H, *H*-5'' in 3''-CF3-aniline), 7.98 (d, ^{3}J = 8.1, 1H, *H*-6'' in 3''-CF3-aniline), 8.22 (d, ^{3}J = 2.7, 1H, *H*-6 salicyl), 8.30 (s, br, 1H, *H*-2''in 3''-CF3-aniline), 10.37 (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 16.09 (*C*H$_3$ isopropyl), 20.91 (*C*H$_3$ isopropyl), 21.96 (5-*C*H$_3$ cyclohexyl), 23.27 (*C*-3 cyclohexyl), 24.17 (*C*-4 pyrrolidine), 26.38 (*C*H isopropyl), 30.74 (*C*-3 pyrrolidine), 31.41 (*C*-5 cyclohexyl), 34.22 (*C*-4 cyclohexyl), 40.93 (*C*-6 cyclohexyl), 47.10 (*C*-2 cyclohexyl), 55.91 (*C*-5 pyrrolidine), 58.02 (N*C*H$_2$CH(OH)), 66.18 (*C*-2 pyrrolidine), 67.77 (*C*H(OH)), 71.53 (O*C*H$_2$CH(OH)), 75.37 (*C*-1 cyclohexyl), 114.18 (*C*-3 salicyl), 117.32 (q, $^{4}J_{CF}$ = 4.0, *C*-2' in 3'-CF_3-aniline), 120.63 (q, $^{4}J_{CF}$ = 3.7, *C*-4' in 3'-CF_3-aniline), 123.63 (overlay with C-6' aniline, C_q-1 salicyl), 123.66 (*C*-6' in 3'-CF_3-aniline), 124.21 (q, $^{1}J_{CF}$ = -272.5, 3-*C*F_3-aniline), 127.43 (C_q-5 salicyl), 129.41 (*C*-5' in 3'-CF_3-aniline), 131.34 (q, $^{2}J_{CF}$ = 32.2, *C*-3' in 3'-CF_3-

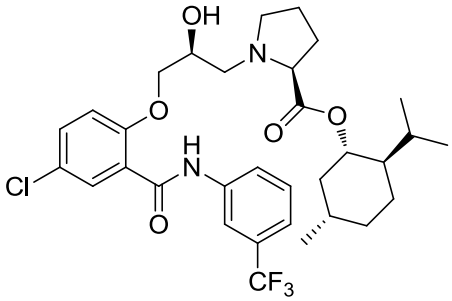
aniline), 132.40 (*C*-6 salicyl), 133.00 (*C*-4 salicyl), 139.39 (C_q-1' in 3'-CF_3-aniline), 155.23 (C_q-2 salicyl), 162.47 (*C*ONH), 175.43 (*C*OOR).

LCMS: $[M+H]^+$: calculated.: 625.27 found: 625.37, $[M-H]^-$: calculated.: 623.25 found: 623.46.

$[\alpha]_D^{20}$= +14.6°, c=1 in $CHCl_3$.

Melting point: 150-153°C.

(*S*)-(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl-1-((*S*)-3-(4-chloro-2-((3-(trifluoromethyl)phenyl)carbamoyl)phenoxy)-2-hydroxypropyl)pyrrolidine-2-carboxylate (103)



103 was prepared following **general procedure E**, yielding 0.063 g (93%) of the desired product.

^{1}H NMR (600 MHz, $CDCl_3$, 23 °C): δ = 0.73 (d, ^3J = 7.0, 3H, CH_3 isopropyl), 0.79-0.83 (m, 1H, H_a-4 cyclohexyl), 0.84 (d, ^3J = 6.5, 3H, 5-CH_3 cyclohexyl), 0.86 (d, ^3J = 7.0, 3H, CH_3 isopropyl), 0.90-0.96 (m, 1H, H_a-6 cyclohexyl), 0.97-1.05 (m, 1H, H_a-3 cyclohexyl), 1.32-1.44 (m, 2H, *H*-2 cyclohexyl, *H*-5 cyclohexyl), 1.57-1.69 (m, 2H, H_a-4 cyclohexyl, H_a-3 cyclohexyl), 1.77-1.99 (m, 5H, C*H* isopropyl, H_b-6 cyclohexyl, $H_{a,b}$-4 pyrrolidine, H_a-3 pyrrolidine), 2.16-2.25 (m, 1H, H_b-3 pyrrolidine), 2.45 (m, 1H, H_a-5 pyrrolidine), 2.72 (dd, ^2J = -12.1, ^3J = 2.2, 1H, CH(OH)CH_aH$_b$NH), 2.81 (dd, ^2J = -12.1, ^3J = 10.5, 1H, CH(OH)CH$_a$$H_b$NH), 3.30-3.34 (m, 1H, H_b-5 pyrrolidine), 3.36 (dd, ^3J = 8.6, ^3J = 5.7, 1H, *H*-2 pyrrolidine), 3.99 (dd, ^2J = -8.5, ^3J = 7.0, 1H, OCH_aH$_b$CH(OH)), 4.20-4.26 (m, 2H, C*H*(OH), OCH$_a$$H_b$CH(OH)), 4.68 (dd, J_{aa} = 10.6, J_{ae} = 4.3, 1H, C*H*-1 cyclohexyl), 6.92 (d, ^3J = 8.8, 1H, *H*-3 salicyl), 7.35 (d, ^3J = 7.7, 1H, *H*-4'' in 3''-CF3-aniline), 7.40 (dd, ^2J = 8.8, ^3J = 2.9, 1H, *H*-4 salicyl), 7.46 (dd [t], ^3J = 7.9, 1H, *H*-5'' in 3''-CF3-aniline), 8.04 (d, ^3J = 8.1, 1H, *H*-6'' in 3''-CF3-aniline), 8.22 (d, ^3J = 2.7, 1H, *H*-6 salicyl), 8.23 (s, br, 1H, *H*-2''in 3''-CF3-aniline), 10.37 (s, 1H, CON*H*).

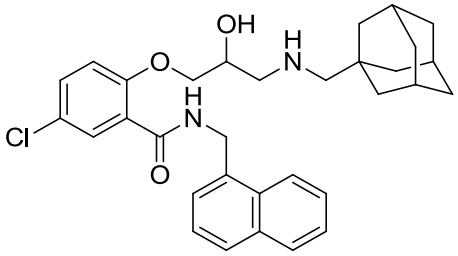
^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 16.06 (*C*H_3 isopropyl), 20.93 (*C*H_3 isopropyl), 22.04 (5-*C*H_3 cyclohexyl), 23.22 (*C*-3 cyclohexyl), 24.02 (*C*-4 pyrrolidine), 26.32 (*C*H isopropyl), 29.86

(*C*-3 pyrrolidine), 31.47 (*C*-5 cyclohexyl), 34.23 (*C*-4 cyclohexyl), 41.06 (*C*-6 cyclohexyl), 47.12 (*C*-2 cyclohexyl), 53.48 (*C*-5 pyrrolidine), 57.36 (N*C*H_2CH(OH)), 66.05 (*C*-2 pyrrolidine), 67.33 (*C*H(OH)), 72.17 (O*C*H_2CH(OH)), 75.22 (*C*-1 cyclohexyl), 114.48 (*C*-3 salicyl), 117.54 (q, $^4J_{CF}$ = 3.9, *C*-2' in 3'-CF_3-aniline), 120.60 (q, $^4J_{CF}$ = 3.7, *C*-4' in 3'-CF_3-aniline), 123.64 (overlay with C-6' aniline, C_q-1 salicyl), 123.82 (*C*-6' in 3'-CF_3-aniline), 124.23 (q, $^1J_{CF}$ = -272.5, 3-*C*F_3-aniline), 127.52 (C_q-5 salicyl), 129.43 (*C*-5' in 3'-CF_3-aniline), 131.20 (q, $^2J_{CF}$ = 32.0, *C*-3' in 3'-CF_3-aniline), 132.40 (*C*-6 salicyl), 132.97 (*C*-4 salicyl), 139.36 (C_q-1' in 3'-CF_3-aniline), 155.24 (C_q-2 salicyl), 162.49 (*C*ONH), 174.24 (*C*OOR).

$[\alpha]_D^{20}$= +8.7°, c=1 in MeOH.

Melting point: 127-135°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(naphthalen-1-ylmethyl)benzamide (141)



141 was prepared following **general procedure E**, yielding 0.457 g (76%) of the desired product.

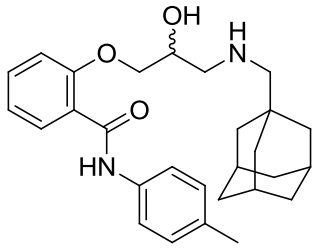
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.41 (s, br, 6H, CH in CH_2-adamantane), 1.60 - 1.67 (m, 3H, CH in CH_2-adamantane), 1.69 -1.78 (m, 3H, CH in CH_2-adamantane), 1.98 (s, br, 3H, C*H*-adamantane), 1.93, 1.96, 1.99, 2,02 (AB, $^2J_{AB}$ = -11.7, 2H, NHCH_2-1-adamantane), 2.10 (dd, ^2J = -12.0, ^3J = 9.6, 1H, C*H*(OH)C$H_a$$H_b$NH), 2.25 (dd, ^2J = -12.0, ^3J = 3.6, 1H, C*H*(OH)C$H_a$$H_b$NH), 3.40 (m[sext], 1H, C*H*(OH)), 3.81 (dd, ^2J = -9.4, ^3J = 5.1, 1H, OC$H_a$$H_b$CH(OH)), 3.94 (dd, ^2J = -9.4, ^3J = 3.7, OC$H_a$$H_b$CH(OH)), 5.03 (dd, ^2J = -14.6, ^3J = 4.7, 2H, CONHC$H_a$$H_b$-1-naphthyl), 5.14 (dd, ^2J = -14.6, ^3J = 5.2, 2H, CONHC$H_a$$H_b$-1-naphthyl), 6.80 (d, ^3J = 8.8, 1H, *H*-3 salicyl), 7.33 (dd, ^3J = 8.7, ^4J = 2.6, 1H, *H*-4 salicyl), 7.45 (dd[t], $^3J_1$ = $^3J_2$ = 7.5, 1H, *H*-3' naphthyl), 7.48-7.57 (m, 3H, *H*-2',6',7' in naphthyl), 7.82 (d, ^3J = 8.2, 1H, *H*-4' in naphthyl), 7.88 (dd, ^3J = 7.9, ^4J = 1.1, 1H, *H*-5' in naphthyl), 8.12 (d, ^3J = 8.0, 1H, *H*-8' in naphthyl), 8.23 (d, 1H, ^4J = 2.6, *H*-6 salicyl), 8.45 (t, br, ^2J = 4.0, 1H, CON*H*CH_2-1-naphthyl).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.53 (*C*H-adamantane), 33.48 (C_q-1 adamantane), 37.34 (*C*H_2-adamantane), 40.82 (*C*H_2-adamantane), 42.52 (CONH*C*H_2-1-naphthyl), 51.64 (CH(OH)*C*H_2NH), 62.02 (NH*C*H_2-1-adamantanyl), 66.73 (*C*H(OH)), 71.15 (O*C*H_2CH(OH)), 114.34 (*C*-3 salicyl), 123.61 (C_q-1 salicyl), 124.13 (*C*-8 in naphthyl), 125.63 (*C*-3 in naphthyl), 126.13 (*C*-6 in naphthyl), 126.73 (*C*-7 in naphthyl), 127.17 (*C*-2 in naphthyl), 128.59 (*C*-4 in naphthyl), 128.78 (*C*-5 in naphthyl), 131.86 (C_q-1 in naphthyl), 132.19 (*C*-6 salicyl), 132.36 (*C*-4 salicyl), 133.91 (C_q-8a in 1 naphthyl), 134.11 (C_q-4a in naphthyl), 155.60 (C_q-2 salicyl), 163.83 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 533.26 found: 533.37, $[M-H]^-$: calculated.: 531.24 found: 531.27.

Melting point: 111-116°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(p-tolyl)benzamide (142)



142 was prepared following **general procedure E**, yielding 0.179 g (38%) of the desired product.

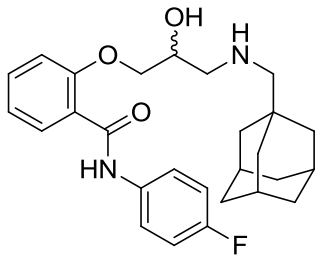
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.50 (d, br, 6H, CH in C*H*$_2$-adamantane), 1.60 - 1.67 (m, 3H, CH in C*H*$_2$-adamantane), 1.69 -1.77 (m, 3H, CH in C*H*$_2$-adamantane), 1.98 (s, br, 3H, C*H*-adamantane), 2.21, 2.24, 2.29, 2.32 (AB, $^{2}J_{AB}$ = -11.5, 2H, (-NHC*H*$_2$-adamantane), 2.33 (s, 3H, C*H*$_3$), 2.75 (dd, ^{2}J = -12,.3, ^{3}J = 9.0, 1H, CH(OH)C*H*$_a$H$_b$NH), 2.84 (dd, ^{2}J = -12.3, ^{3}J = 3.6, 1H, CH(OH)CH$_a$*H*$_b$NH), 4.02 – 4.12 (m, 2H,-OC*H*$_a$H$_b$CH(OH), C*H*(OH), 4.23 – 4.30 (m, 1H, OCH$_a$*H*$_b$CH(OH)), 6.97 (d, ^{3}J = 8.3, 1H, *H*-3 salicyl), 7.11 (dd[t], 2x ^{3}J = 7.4, 1H, *H*-5 salicyl), 7.13, 7.15 (m, 2H, AA' of AA'BB', *H*-3',5' toluidine), 7.45 (ddd, ^{3}J = 7.4, ^{3}J = 8.3, ^{4}J = 1.8, 1H, *H*-4 salicyl), 7.68, 7.70 (m, 2H, BB' of AA'BB', *H*-2',6' toluidine), 8.26 (dd, ^{3}J = 7.8, ^{4}J = 1.8, 1H, *H*-6 salicyl), 10.04 (s, br, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23°C): δ = 21.05 (4'-*C*H$_3$ toluidine), 28.54 (*C*H-adamantane), 33.65 (C_q-1 adamantane), 37.31 (*C*H_2-adamantane), 40.90 (*C*H_2-adamantane), 51.86 (CH(OH)*C*H_2NHCH$_2$), 62.45 (NH*C*H_2-1'-adamantane), 67.37 (*C*H(OH)), 71.22 (O*C*H_2CH(OH)),

112.69 (*C*-3 salicyl), 120.56 (*C*-2',6' toluidine), 121.92 (*C*-5 salicyl), 122.79 (C_q-1 salicyl), 129.50 (*C*-3',5' toluidine), 132.64 (*C*-6 salicyl), 132.99 (*C*-4 salicyl), 133.50 (C_q-4' toluidine), 136.50 (C_q-1' toluidine), 156.69 (C_q-2 salicyl), 163.37 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 449.28 found: 449.35, $[M-H]^-$: calculated.: 447.27 found: 447.33.

2-(3-((-adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(4-fluorophenyl)benzamide (143)



143 was prepared following **general procedure E**, yielding 0.206 g (44%) of the desired product.

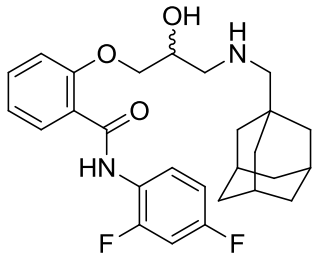
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.45-1.55 (m, 6H, CH in CH_2-adamantane), 1.60-1.67 (m, br, 3H, CH in CH_2-adamantane), 1.70-1.79 (m, br, 3H, CH in CH_2-adamantane), 1.99 (s, br, 3H, C*H*-adamantane), 2.22, 2.25, 2.30, 2.33 (AB, ^2J = -11.5, 2H, NHCH_aH_b-1-adamantane), 2.73 (dd, ^2J = -12.1, ^3J = 9.2, 1H, CH(OH)CH_aH$_b$NH), 2.85 (dd, ^2J = -12.1, ^3J = 3.8, 1H, CH(OH)CH$_a$$H_b$NH), 4.03 (dd, ^2J = -9.2, ^3J = 6.3, 1H, OCH_aH$_b$CH(OH)), 4.07-4.13 (m, 1H, C*H*(OH)), 4.27 (dd, ^2J = -9.2, ^3J = 2.7, 1H, OCH$_a$$H_b$CH(OH)), 6.92 (d, ^3J = 8.7, 1H, *H*-3 salicyl), 6.99-7.06 (m[t], 2H, *H*-3',5' in 4'F-aniline), 7.40 (dd, ^2J = 8.7, ^3J = 2.7, 1H, *H*-4 salicyl), 7.74-7.79 (m, 2H, *H*-2',6' in 4'F-aniline), 8.22 (d, ^4J = 2.7, 1H, *H*-6 salicyl), 10.11 (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.49 (*C*H-adamantane), 33.64 (C_q-1 adamantane), 37.26 (*C*H_2-adamantane), 40.89 (*C*H_2-adamantane), 51.63 (NCH_2CH(OH)), 62.41 (NH*C*H_2-1-adamantanyl), 67.13 (*C*H(OH)), 71.78 (OCH_2CH(OH)), 114.32 (*C*-3 salicyl), 115.58 (d, $^2J_{CF}$ = 22.5, *C*-3',5' in 4'-F-aniline), 122.24 (d, $^3J_{CF}$ = 7.8, *C*-2',6' in 4'-F-aniline), 123.99 (C_q-1 salicyl), 127.47 (C_q-5 salicyl), 132.34 (*C*-6 salicyl), 132.76 (*C*-4 salicyl), 134.83 (d, $^4J_{CF}$ = 2.2, C_q-1' in 4'-F-aniline), 155.20 (C_q-2 salicyl), 159.43 (d, $^1J_{CF}$ = -243, *C*-4' in 4'-F-aniline), 162.11 (*C*ONH-4'-F-aniline).

LCMS: $[M+H]^+$: calculated.: 453.25 found: 453.32, $[M-H]^-$: calculated.: 451.24 found: 451.30.

Melting point: 120-125°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(2,4-difluorophenyl)benzamide (144)



144 was prepared following **general procedure E**, yielding 0.194 g (42%) of the desired product.

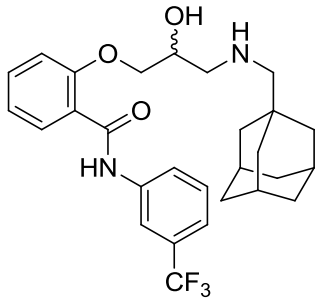
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.51 (s, br, 6H, CH_2-adamantane), 1.60-1.67 (m, 3H, CH_2-adamantane), 1.69-1.77 (m, 3H, CH_2-adamantane), 1.98 (s, br, 3H, C*H*-adamantane), 2.22, 2.25, 2,29, 2,32 (AB, J_{AB} = -11.6, 2H, NHCH_2-1-adamantane)), 2.72 (dd, ^{2}J = -12.3, ^{3}J = 8.6, 1H, CH(OH)CH_aH$_b$NH), 2.87 (dd, ^{2}J = -12.3, ^{3}J = 3.8, 1H, CH(OH)CH$_a$$H_b$NH), 4.09-4.16 (m[sext], 1H, C*H*(OH)), 4.17-4.24 (m, 2H, OCH_aH_bCH(OH)), 6.84-6.93 (m, 2H, *H*-3',5' in 2', 4'-difluoroaniline), 7.05 (d, ^{3}J = 8.2, 1H, *H*-3 salicyl), 7.13 (dd[t], $^{3}J_1$ = $^{3}J_2$ = 7.5, 1H, *H*-5 salicyl), 7.48 (ddd, $^{3}J_1$ = 7.5, $^{3}J_2$ = 8.3, ^{4}J = 1.8, 1H, *H*-4 salicyl), 8.26 (dd, ^{3}J = 7.8, ^{4}J = 1.7, 1H, *H*-6 salicyl), 8.40-8.48 (m, 1H, *H*-6' in 2', 4'-difluoroaniline), 10.05 (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.54 (*C*H-adamantane),33.67 (C_q-1'' adamantane), 37.31 (*C*H$_2$-adamantane), 40.91 (*C*H$_2$-adamantane), 52.36 (N*C*H$_2$CH(OH)), 62.60 (NH*C*H$_2$-1''-adamantane), 67.43 (*C*H(OH) doublet), 72.02 (O*C*H$_2$CH(OH)), 103.59 (dd, $^{2}J_{1CF}$ = 23.6, $^{2}J_{1CF}$ = 26.4, *C*-3' in 2', 4'-difluoroaniline), 111.28 (dd, $^{2}J_{CF}$ = 21.5, $^{4}J_{CF}$ = 3.8, *C*-5' in 2', 4'-difluoroaniline), 113.02 (*C*-3 salicyl), 121.76 (C_q-1 salicyl), 122.00 (*C*-5 salicyl), 123.42 (dd, $^{2}J_{2CF}$ = 10.3, $^{4}J_{1CF}$ = 3.8, C_q-1 in 2', 4'-difluoroaniline), 123.91 (dd, $^{3}J_{1CF}$ = 2.4, $^{3}J_{2CF}$ = 9.1, *C*-6' in 2', 4'-difluoroaniline), 132.72 (*C*-6 salicyl), 133.65 (*C*-4 salicyl), 154.37, 154.48 (part of C_q-4' in 2', 4'-difluoroaniline), 156.96 (C_q-2 salicyl), 158.66 (dd, $^{1}J_{1CF}$ = 245, $^{3}J_{2CF}$ = 11.7, C_q-2' in 2', 4'-difluoroaniline), 163.57 (*C*ONH).

HRMS: [M+H]+: calculated.: 471.2458 found: 471.2459.

Melting point: 101-105°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (145)



145 was prepared following **general procedure E**, yielding 0.209 g (13%) of the desired product.

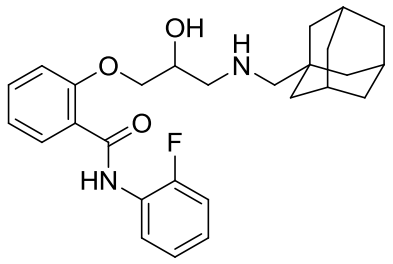
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.48-1.53 (m, br, 6H, CH in C*H*$_2$-adamantane), 1.60-1.67 (m, br, 3H, CH in C*H*$_2$-adamantane), 1.68-1.77 (m, br, 3H, CH in C*H*$_2$-adamantane), 1.98 (s, br, 3H, C*H*-adamantane), 2.23, 2.26, 2.30, 2.33 (AB, ^{2}J = -11.5, 2H, NHC*H*$_a$*H*$_b$-1-adamantane), 2.75 (dd, ^{2}J = -12.1, ^{3}J = 9.3, 1H, C*H*(OH)C*H*$_a$H$_b$NH), 2.84 (dd, ^{2}J = -12.1, ^{3}J = 3.8, 1H, C*H*(OH)CH$_a$*H*$_b$NH), 4.05 (dd, ^{2}J = -9.2, ^{3}J = 6.3, 1H, OC*H*$_a$H$_b$CH(OH)), 4.09-4.16 (m, 1H, C*H*(OH)), 4.31 (dd, ^{2}J = -9.2, ^{3}J = 2.8, 1H, OCH$_a$*H*$_b$CH(OH)), 6.99 (d, ^{3}J = 8.3, 1H, *H*-3 salicyl), 7.14 (dd[t], $^{3}J_1$ = $^{3}J_2$ = 7.5, $^{4}J_2$ = 0.8, 1H, *H*-5 salicyl), 7.34 (d, br, ^{3}J = 7.7, 1H, *H*-4' in 3'-CF_3-aniline), 7.44 (dd[t], $^{3}J_1$ = $^{3}J_2$ = 7.8, 1H, *H*-5' in 3'-CF_3-aniline), 7.48 (ddd, $^{3}J_1$ = 7.4, $^{3}J_2$ = 8.4, ^{4}J = 1.8, 1H, *H*-4 salicyl), 8.09 (d, br, ^{3}J = 8.3, 1H, *H*-6' in 3'-CF_3-aniline), 8.14 (s[t], br, 1H, *H*-2' in 3'-CF_3-aniline), 8.26 (dd, ^{3}J = 7.8, ^{4}J = 1.7, 1H, *H*-6 salicyl), 10.39 (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.51 (*C*H-adamantane), 33.60 (*C*$_q$-1 adamantane), 37.28 (*C*H$_2$-adamantane), 40.83 (*C*H$_2$-adamantane), 51.55 (N*C*H$_2$CH(OH)), 62.23 (NH*C*H$_2$-1-adamantanyl), 67.00 (*C*H(OH)), 71.34 (O*C*H$_2$CH(OH)), 112.78 (*C*-3 salicyl), 117.35 (q, $^{4}J_{CF}$ = 3.9, *C*-2' in 3'-CF_3-aniline), 120.38 (q, $^{4}J_{CF}$ = 3.8, *C*-4' in 3'-CF_3-aniline), 122.10 (*C*-5 salicyl), 122.20 (*C*$_q$-1 salicyl), 123.56 (*C*-6' in 3'-CF_3-aniline), 129.44 (*C*-5' in 3'-CF_3-aniline), 131.29 ($^{2}J_{CF}$ = 32.6, *C*-3' in 3'-CF_3-aniline), 132.74 (*C*-6 salicyl), 133.48 (*C*-4 salicyl), 139.67 (*C*$_q$-1' in 3'-CF_3-aniline), 156.77 (*C*$_q$-2 salicyl), 163.79 (*C*ONH). *C*F_3 not recorded

HRMS: [M+H]+: calculated.: 503.2515 found: 503.2521.

Melting point: 123-127°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(2-fluorophenyl)benzamide (146)



146 was prepared following **general procedure E**, yielding 0.436 g (100%) of the desired product.

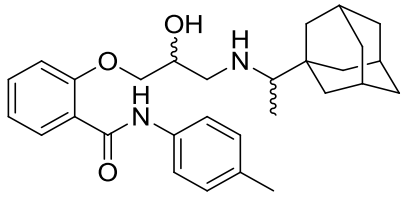
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.48-1.53 (m, br, 6H, CH in CH_2-adamantane), 1.59-1.67 (m, br, 3H, CH in CH_2-adamantane), 1.68-1.76 (m, br, 3H, CH in CH_2-adamantane), 1.97 (s, br, 3H, C*H*-adamantane), 2.22, 2.25, 2.29, 2.32 (AB, ^2J = -11.5, 2H, NHCH_aH_b-1-adamantane), 2.73 (dd, ^2J = -12.4, ^3J = 8.0, 1H, NCH_aH$_b$CH(OH)), 2.89 (dd, ^2J = -12.4, ^3J = 3.8, 1H, NCH$_a$$H_b$CH(OH)), 4.12-4.27 (m, 3H, salicyl-OCH_aH_b, C*H*(OH)), 7.02-7.12 (m, 3H, *H*-3 salicyl, *H*-3, *H*-5, in 2'-F-aniline), 7.12-7.20 (m, 2H, *H*-4 in 2'-F-aniline, *H*-5 salicyl), 7.49 (ddd, $^3J_1$ = 7.4, $^3J_2$ = 8.4, ^4J = 1.8, 1H, *H*-4 salicyl), 8.28 (dd, ^3J = 7.8, ^4J = 1.8, 1H, *H*-6 salicyl), 8.53 (ddd, ^3J = 7.5, $^4J_{HF}$ = 7.5, ^4J = 1.5, 1H, *H*-6 in 2'-F-aniline), 10.12 (s, br, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.56 (*C*H-adamantane), 33.68 (C_q-1 adamantane), 37.34 (*C*H_2-adamantane), 40.91 (*C*H_2-adamantane), 52.51 (CH(OH)*C*H_2NH), 62.63 (NH*C*H_2-1-adamantane), 67.51 (*C*H(OH), doublet), 72.08 (O*C*H_2CH(OH)), 112.98 (*C*-3 salicyl), 114.86 (d, $^2J_{CF}$ = 19.3, *C*-3' in 2'-F-aniline), 121.95 (*C*-5 salicyl), 121.97 (C_q-1 salicyl), 122.78 (br, *C*-6' in 2'-F-aniline), 124.25 (d, $^3J_{CF}$ = 7.7, *C*-4' in 2'-F-aniline), 124.78 (d, $^4J_{CF}$ = 3.3, *C*-5' in 2'-F-aniline), 127.17 (d, $^2J_{CF}$ = 10.0, C_q-1' in 2'-F-aniline), 132.75 (*C*-6 salicyl), 133.59 (*C*-4 salicyl), 153.08 (d, $^1J_{CF}$ = -243.4, C_q-2' in 2'-F-aniline), 156.94 (C_q-2 salicyl),163.55 (*C*ONH-4'-F-aniline).

LCMS: $[M+H]^+$: calculated.: 453.25 found: 453.32, $[M-H]^-$: calculated.: 451.24 found: 451.22.

Melting point: 66°C.

2-(3-((1-(adamantan-1-yl)ethyl)amino)-2-hydroxypropoxy)-*N*-(p-tolyl)benzamide (154)



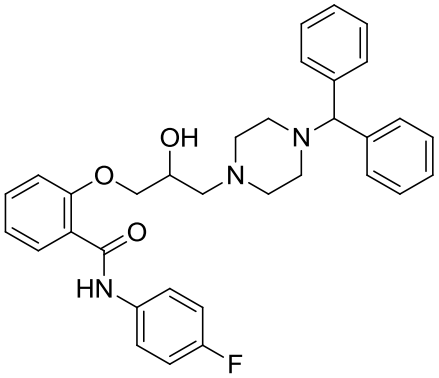
154 was prepared following **general procedure E**, yielding 0.122 g (25%) of the desired diastereomeric products.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 0.962, 0.967 (d, 3H, NCH(C*H*$_3$)-1-adamantane), 1.39-1.50 (m, br, 3H, 3H in C*H*$_2$-adamantane), 1.55-1.67 (m, br, 6H, 6H in C*H*$_2$-adamantane), 1.68-1.76 (m, br, 3H, 3H in C*H*$_2$-adamantane), 1.94-2.07(m, br, 4H, NHC*H*(CH_3)-1-adamantane, 3x C*H*-adamantane), 2.32 (s, 3H, C*H*$_3$ toluidine), 2.53 (dd, ^{2}J = -12.1, ^{3}J = 9.6, 1H, NC*H*$_a$H$_b$CH(OH), D1), 2.76-2.85 (m, 2H, NC*H*$_a$*H*$_b$CH(OH), D2), 3.06 (dd, ^{2}J = -12.1, ^{3}J = 3.7, 1H, NCH$_a$*H*$_b$CH(OH), D1), 3.98-4.14 (m, 2H, C*H*(OH), OC*H*$_a$H$_b$CH(OH)), 4.23-4.31 (m, 1H, OCH$_a$*H*$_b$CH(OH)), 6.97 (d, ^{3}J = 8.2, 1H, *H*-3 salicyl), 7.09-7.16 (m, 3H, *H*-5 salicyl, AA' of AA'BB', *H*-3',5' toluidine), 7.45 (ddd, ^{3}J = 7.6, ^{3}J = 8.3, ^{4}J = 1.8, 1H, *H*-4 salicyl), 7.65, 7.67; 7.69, 7.71 (BB' of AA'BB', 2H, *H*-2',6' toluidine, D1; D2), 8.25, 8.26 (2x d[t]d[t], ^{3}J = 7.8, ^{4}J = 1.9, 1H, *H*-6 salicyl, D1, D2), 10.02, 10.08 (2x s, br, 1H, CON*H*, D1, D2).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 13.73 (NHCH(*C*H3)-1-adamantane, D1), 14.27 (NHCH(*C*H3)-1-adamantane, D2), 21.05 (4'-*C*H$_3$ toluidine), 28.65 (*C*H-adamantane, D2), 28.68 (*C*H-adamantane, D1), 37.41 (*C*H$_2$-adamantane, D1, D2), 36.25 (*C*$_q$-1 adamantane), 38.87 (*C*H$_2$-adamantane, D1), 38.93 (*C*H$_2$-adamantane, D2), 49.23 (N*C*H$_2$CH(OH), D1), 50.88 (N*C*H$_2$CH(OH), D2), 61.71 (N*C*H(CH_3)-1-adamantane, D1), 63.88 (N*C*H(CH_3)-1-adamantane, D2), 67.32 (*C*H(OH), D1), 68.98 (*C*H(OH), D2), 70.95 (O*C*H$_2$CH(OH), D2), 71.37 (O*C*H$_2$CH(OH), D1), 112.63 (*C*-3 salicyl, D1), 112.68 (*C*-3 salicyl, D2), 120.51 (*C*-2',6' toluidine, D1), 120.70 (*C*-2',6' toluidine, D2), 121.91 (*C*-5 salicyl), 122.82 (*C*$_q$-1 salicyl), by HMBC 129.47 (*C*-3',5' toluidine, D1), 129.52 (*C*-3',5' toluidine, D2), 132.65 (*C*-6 salicyl), 132.99 (*C*-4 salicyl), 133.70 (*C*$_q$-1' toluidine), by HMBC 136.43 (*C*$_q$-4' toluidine), by HMBC 156.84 (*C*$_q$-2 salicyl), by HMBC 163.21 (*C*ONH). Concentration to low for recording of all quaternary carbons

LCMS: $[M+H]^+$: calculated.: 463.30 found: 463.36, $[M-H]^-$: calculated.: 461.28 found: 461.26.

2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(4-fluorophenyl)benzamide (159)



159 was prepared following **general procedure E**, yielding 0.761 g (66%) of the desired product.

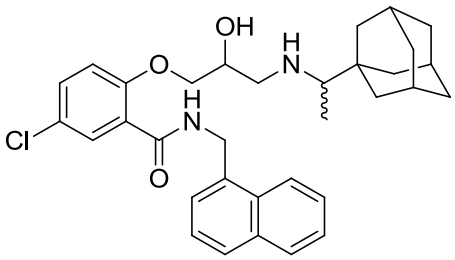
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.22-2.54 (m,br[dyn], 6H, *H*-piperazine), 2.46 (dd, ^{2}J = -12.3, ^{3}J = **3.5**, 1H, NC$H_a$$H_b$CH(OH)), 2.63 (dd, ^{2}J = -12.3, ^{3}J = **10.9**, 1H, NC$H_a$$H_b$CH(OH)), 2.67-2.79 (m,br[dyn], 2H, *H*-piperazine), 3.80-4.00 (br, 1H, CH(O*H*)), 4.02 (dd, ^{2}J = -9.6, ^{3}J = 5.5, 1H, OC$H_a$$H_b$CH(OH)), 4.13-4.20 (m, 1H, C*H*(OH)), 4.26 (s, 1H, NC*H*$(C_6H_5)_2$), 4.30 (dd, ^{2}J = -9.5, ^{3}J = 2.8, 1H, OC$H_a$$H_b$CH(OH)), 6.95 (d, ^{3}J = 8.2, 1H, *H*-3 salicyl), 6.97-7,03 (m[tr], 2H, *H*-3',5' in 4'-F-aniline), 7.12 (ddd[tr], $^{3}J_1$ = $^{3}J_2$ = 7.6, ^{4}J = 0.6, 1H, *H*-5 salicyl), 7.16-7.22 (m[tr], 2H, *H*-4'' CH(phenyl)$_2$), 7.26-7.31 (m[tr], 4H, *H*-3'',5' CH(phenyl)$_2$), 7.38-7.42 (m[d], 4H, *H*-2'',6' CH(phenyl)$_2$, 7.45 (ddd, $^{3}J_1$ = 7.6, $^{3}J_2$ = 8.3, ^{4}J = 1.8, 1H, *H*-4 salicyl), 7.71-7.77 (m, 2H, *H*-2',6' in 4'-F-aniline), 8.24 (dd, ^{3}J = 7.8, ^{4}J = 1.8, 1H, *H*-6 salicyl), 10.11 (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 51.98 (sharp, *C*-piperazine), 53.57 (br[dyn], *C*-piperazine), 59.73 (N*C*H_2CH(OH)), 65.09 (*C*H(OH), 70.97 (O*C*H_2CH(OH)), 76.20 (N*C*H$(C_6H_5)_2$), 112.70 (*C*-3 salicyl), 115.50 (d, $^{2}J_{CF}$ = 22.3, *C*-3',5' in 4'-F-aniline), 122.04 (*C*-5 salicyl), 122.08 (d, $^{3}J_{CF}$ = 7.5, *C*-2',6' in 4'-F-aniline), 122.48 (C_q-1 salicyl), 127.19 (*C*-4'' NCH(phenyl)$_2$), 128.05 (*C*-3'', 5'' NCH(phenyl)$_2$), 128.67 (*C*-2'', 6'' NCH(phenyl)$_2$), 132.67 (*C*-6 salicyl), 133.20 (*C*-4 salicyl), 135.08 (d, $^{4}J_{CF}$ = 2.5, C_q-1' in 4'-F-aniline), 142.52, 142.59 (C_q-1 NCH(phenyl)$_2$), 156.58 (C_q-2 salicyl), 159.24 (d, $^{1}J_{CF}$ = -242, C_q-4' in 4'-F-aniline), 163.42 (*C*ONH).

HRMS: [M+H]+: calculated.: 540.2664 found: 540.2662.

Melting point: 150-153°C.

2-(3-((1-(adamantan-1-yl)ethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(naphthalen-1-ylmethyl)benzamide (167)

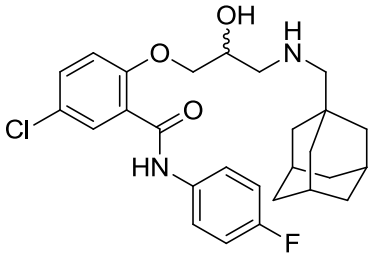


167 was prepared following **general procedure E**, yielding 0.243 g (47%) of the diastereomeric product.

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): 13.50, 14.20 (NHCH(*C*H_3)-1-adamantane), 28.65, 28.62 (*C*H-adamantane), 36.43, 36.01 (C_q-1 adamantane), 37.43, 37.40 (*C*H_2-adamantane), 38.82, 38.79 (*C*H_2-adamantane), 42.53, 42.38 (CONH*C*H_2-1-naphthyl), 50.61, 48.92 (CH(OH)*C*H_2NH), 63.56, 61.48 (N*C*H(CH_3)-1-adamantane), 68.58, 66.85 (*C*H(OH)), 71.53, 70.83 (O*C*H_2CH(OH)), 114.30, 114.43 (*C*-3 salicyl), 123.57, 123.72 (C_q-1 salicyl), 123.97, 124.18 (*C*-8 in naphthyl), 125.59, 125.65 (*C*-3 in naphthyl), 126.07, 126.13 (*C*-6 in naphthyl), 126.66 (*C*-7 in naphthyl, D1), 126.70 (*C*-2 in naphthyl, D1), 126.73 (*C*-7 in naphthyl, D2), 127.25 (*C*-2 in naphthyl, D2), 128.45, 128.62 (*C*-4 in naphthyl), 128.77, 128.82 (*C*-5 in naphthyl), 131.78, 131.89 (C_q-1 in naphthyl), 132.14, 132.22 (*C*-6 salicyl), 132.35 (2x *C*-4 salicyl), 133.95, 134.07 (C_q-8a in 1 naphthyl), 134.15, 133.90 (C_q-4a in naphthyl), 155.61, 155.65 (C_q-2 salicyl), 163.82, 163.92 (*C*ONH).

HRMS: $[M+H]^+$: calculated.: : 547.2727 found: 547.2747.

2-(3-((-adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(4-fluorophenyl)benzamide (168)



168 was prepared following **general procedure E**, yielding 0.142 g (40%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.45-1.55 (m, 6H, CH in CH_2-adamantane), 1.60-1.67 (m, br, 3H, CH in CH_2-adamantane), 1.70-1.79 (m, br, 3H, CH in CH_2-adamantane), 1.99 (s, br, 3H,

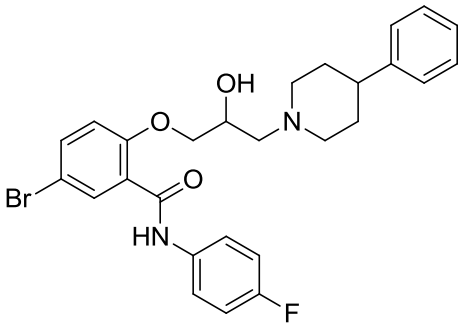
C*H*-adamantane), 2.22, 2.25, 2.30, 2.33 (AB, ^{2}J = -11.5, 2H, NHCH_aH_b-1-adamantane), 2.73 (dd, ^{2}J = -12.1, ^{3}J = 9.2, 1H, CH(OH)CH_aH$_b$NH), 2.85 (dd, ^{2}J = -12.1, ^{3}J = 3.8, 1H, CH(OH)CH$_a$$H_b$NH), 4.03 (dd, ^{2}J = -9.2, ^{3}J = 6.3, 1H, OCH_aH$_b$CH(OH)), 4.07-4.13 (m, 1H, C*H*(OH)), 4.27 (dd, ^{2}J = -9.2, ^{3}J = 2.7, 1H, OCH$_a$$H_b$CH(OH)), 6.92 (d, ^{3}J = 8.7, 1H, *H*-3 salicyl), 6.99-7.06 (m[t], 2H, *H*-3',5' in 4'F-aniline), 7.40 (dd, ^{2}J = 8.7, ^{3}J = 2.7, 1H, *H*-4 salicyl), 7.74-7.79 (m, 2H, *H*-2',6' in 4'F-aniline), 8.22 (d, ^{4}J = 2.7, 1H, *H*-6 salicyl), 10.11 (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.49 (*C*H-adamantane), 33.64 (C_q-1 adamantane), 37.26 (*C*H$_2$-adamantane), 40.89 (*C*H$_2$-adamantane), 51.63 (N*C*H$_2$CH(OH)), 62.41 (NH*C*H$_2$-1-adamantanyl), 67.13 (*C*H(OH)), 71.78 (O*C*H$_2$CH(OH)), 114.32 (*C*-3 salicyl), 115.58 (d, $^{2}J_{CF}$ = 22.5, *C*-3',5' in 4'-F-aniline), 122.24 (d, $^{3}J_{CF}$ = 7.8, *C*-2',6' in 4'-F-aniline), 123.99 (C_q-1 salicyl), 127.47 (C_q-5 salicyl), 132.34 (*C*-6 salicyl), 132.76 (*C*-4 salicyl), 134.83 (d, $^{4}J_{CF}$ = 2.2, C_q-1' in 4'-F-aniline), 155.20 (C_q-2 salicyl), 159.43 (d, $^{1}J_{CF}$ = -243, *C*-4' in 4'-F-aniline), 162.11 (*C*ONH-4'-F-aniline).

HRMS: $[M+H]^+$: calculated.: 487.2154 found: 487.2163.

Melting point: 148-149°C.

5-bromo-*N*-(4-fluorophenyl)-2-(2-hydroxy-3-(4-phenylpiperidin-1-yl)propoxy)benzamide (169)



169 was prepared following **general procedure E**, yielding 0.134 g (95%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.71-1.94 (m, 4H, H_{ax} H_{eq}-3,5 in piperidine), 2.16 (1H), (ddd, ^{2}J = -11.8, $^{3}J_{axax}$ = 11.8, $^{3}J_{axeq}$ = 2.1, 1H, H_{ax}-6 in piperidine), 2.46 (ddd, ^{2}J = -11.3, $^{3}J_{axax}$ = 11.3, $^{3}J_{axeq}$ = 2.9, 1H, H_{ax}-2 in piperidine), 2.50 (dd, ^{2}J = -12.2, ^{3}J = 3.6, 1H, CH(OH)CH_aH$_b$NH), 2.55 (tt, 1H, $^{3}J_{1axax}$ = $^{3}J_{2axax}$ = 11.8, $^{3}J_{1axeq}$ = $^{3}J_{2aeqx}$ = 3.9, piperidine-C*H*-4'-phenyl), 2.64 (dd, ^{2}J = -12.1, ^{3}J = 10.5, 1H, CH(OH)CH$_a$$H_b$NH), 2.84 (1H), (m[d], br, 1H, H_{eq}-2 in CH_2 piperidine), 3.14 (m[d], br, 1H, H_{eq}-6 in CH_2 piperidine), 4.02 (dd, ^{2}J = -9.5, ^{3}J = 5.7, 1H, OCH_aH$_b$CH(OH)), 4.18-

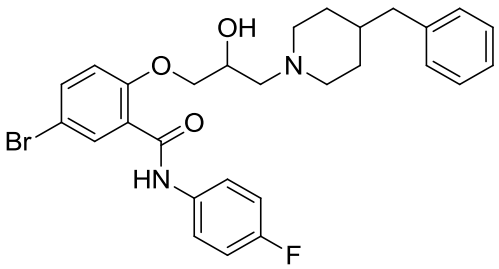
4.25 (m, 1H, C*H*(OH)), 4.31 (dd, ^{2}J = -9.5, ^{3}J = 2.8, 1H, OCH$_a$*H$_b$*CH(OH)), 6.86 (d, ^{3}J = 8.7, 1H, *H*-3 salicyl), 7.00-7.07 (m[t], 2H, *H*-3',5' in 4'F-aniline), 7.20 -7.25 (3H), (m, 3H, *H*-2'',6'' phenyl, *H*-4'' phenyl), 7.30-7.36 (m, 2H, *H*-3'',5'' phenyl), 7.54 (dd, ^{2}J = 8.7, ^{3}J = 2.6, 1H, *H*-4 salicyl), 7.73-7.79 (m, 2H, *H*-2',6' in 4'F-aniline), 8.36 (d, ^{4}J = 2.6, 1H, *H*-6 salicyl), 10.07 (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 33.40 (NCH$_2$*C*H$_2$-piperidine), 33.74 (NCH$_2$*C*H$_2$-piperidine), 42.35 (piperidine-*C*H-4-phenyl), 52.94 (N*C*H$_2$CH$_2$-piperidine), 56.31 (N*C*H$_2$CH$_2$-piperidine), 59.99 (N*C*H$_2$CH(OH)), 65.16 (*C*H(OH), 71.51 (O*C*H$_2$CH(OH)), 114.65 (*C*-5 salicyl), 114.68 (*C*-3 salicyl), 115.57 (d, $^{2}J_{CF}$ = 22.3, *C*-3',5' in 4'-F-aniline), 122.20 (d, $^{3}J_{CF}$ = 7.8, *C*-2',6' in 4'-F-aniline), 124.29 (C_q-1 salicyl), 126.51 (*C*-4'' phenyl), 126.88 (*C*-2'',6'' phenyl), 128.66 (*C*-3'',5'' phenyl), 134.79 (d, $^{4}J_{CF}$ = 2.2, C_q-1' in 4'-F-aniline), 135.24 (*C*-6 salicyl), 135.73 (*C*-4 salicyl), 145.79 (C_q-1'' phenyl), 155.62 (C_q-2 salicyl), 159.41 (d, $^{1}J_{CF}$ = -243, *C*-4' in 4'-F-aniline), 162.01 (*C*ONH-4'-F-aniline).

HRMS: $[M+H]^+$: calculated.: 527.1351 found: 527.1345.

Melting point: 137-149°C.

2-(3-(4-benzylpiperidin-1-yl)-2-hydroxypropoxy)-5-bromo-*N*-(4-fluorophenyl)benzamide (170)



170 was prepared following **general procedure E**, yielding 0.146 g (95%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.23-1.37 (m, 2H, H in 3,5-C*H*$_2$ piperidine), 1.50-1.60 (m, 1H, C*H*(CH$_2$)-phenyl), 1.61-1.70 (m, 2H, H in 3,5-C*H*$_2$ piperidine), 1.97 (ddd, ^{2}J = -11.8, $^{3}J_{aa}$ = 11.8, $^{3}J_{ae}$ = 2.2, 1H, H in 2,6-C*H*$_2$ piperidine), 2.27 (ddd, ^{2}J = -11.7, $^{3}J_{aa}$ = 11.6, $^{3}J_{ae}$ = 2.3, 1H, H in 2,6-C*H*$_2$ piperidine), 2.42 (dd, ^{2}J = -12.6, ^{3}J = 3.8, 1H, CH(OH)C*H$_a$*H$_b$NH),2.53-2.61 (m, 3H, C*H*$_2$-benzyl, CH(OH)CH$_a$*H$_b$*NH), 2.70 (m[d], br, 1H, H in 2,6-C*H*$_2$ piperidine), 2.99 (m[d], br, 1H, H in 2,6-C*H*$_2$ piperidine), 3.97 (dd, ^{2}J = -9.6, ^{3}J = 5.7, 1H, OC*H$_a$*H$_b$CH(OH)), 4.13-4.20 (m, 1H, C*H*(OH)), 4.26 (dd, ^{2}J = -9.6, ^{3}J = 2.8, 1H, OCH$_a$*H$_b$*CH(OH)), 6.83 (d, ^{3}J = 8.7, 1H, *H*-3 salicyl), 6.99-7.06 (m[t], 2H, *H*-3',5' in 4'F-aniline), 7.11-7.16 (m[d], 2H, *H*-2''',6''' phenyl), 7.18-7.23

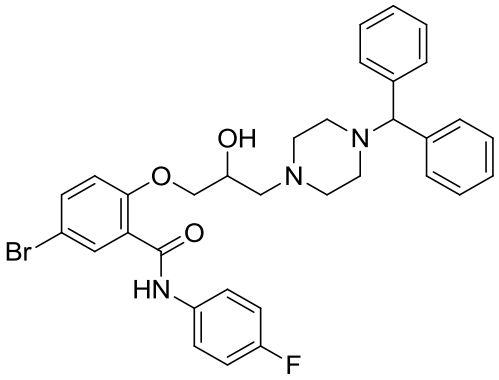
(m, 1H, *H*-4''' phenyl), 7.25-7.32 (m[t], 2H, *H*-3''',5''' phenyl), 7.52 (dd, ^{2}J = 8.7, ^{3}J = 2.7, 1H, *H*-4 salicyl), 7.71-7.77 (m, 2H, *H*-2',6' in 4'F-aniline), 8.34 (d, ^{4}J = 2.7, 1H, *H*-6 salicyl), 10.04 (s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 32.10 (NCH_2CH_2-piperidine), 32.43 (NCH_2CH_2-piperidine), 37.76 (*C*H-4''' piperidine), 43.13 (CH(*C*H_2)-phenyl), 52.57 (N*C*H_2-piperidine), 55.78 (N*C*H_2-piperidine), 59.89 (N*C*H_2CH(OH)), 65.04 (*C*H(OH)), 71.49 (O*C*H_2CH(OH)), 114.63 (*C*-5 salicyl), 114.65 (*C*-3 salicyl), 115.56 (d, $^{2}J_{CF}$ = 22.3, *C*-3',5' in 4'-F-aniline), 122.19 (d, $^{3}J_{CF}$ = 7.8, *C*-2',6' in 4'-F-aniline), 124.29 (C_q-1 salicyl), 126.09 (*C*-4'' phenyl), 128.39 (*C*-2'',6'' phenyl), 129.23 (*C*-3'',5'' phenyl), 134.78 (d, $^{4}J_{CF}$ = 2.2, C_q-1' in 4'-F-aniline), 135.23 (*C*-6 salicyl), 135.70 (*C*-4 salicyl), 140.42 (C_q-1'' phenyl), 155.61 (C_q-2 salicyl), 159.41 (d, $^{1}J_{CF}$ = -243, *C*-4' in 4'-F-aniline), 162.00 (*C*ONH-4'-F-aniline).

HRMS: $[M+H]^+$: calculated.: 541.1495 found: 541.1502.

Melting point: 96-102°C.

2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-5-bromo-*N*-(4-fluorophenyl)benzamide (171)



171 was prepared following **general procedure E**, yielding 0.166 g (100%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.35-2.52 (6H), (m[dyn], br, 6H, H_{ax} H_{eq}-3,5 in piperazine, H_{ax}-2,6 in CH_2 piperazine), 2.46 (dd, ^{2}J = -12.3, ^{3}J = 3.5, 1H, CH(OH)C$H_a$$H_b$NH), 2.61 (dd, ^{2}J = -12.2, ^{3}J = 10.7, 1H, CH(OH)C$H_a$$H_b$NH), 2.67-2.78 (2H), (m[d], br, 2H, H_{eq}-2,6 in CH_2 piperazine), 3.98 (dd, ^{2}J = -9.6, ^{3}J = 5.8, 1H, OC$H_a$$H_b$CH(OH)), 4.12-4.20 (m, 1H, C*H*(OH)), 4.26 (s, 1H, NC*H*(C_6H_5)$_2$), 4.27 (dd, ^{2}J = -9.3, ^{3}J = 2.8, 1H, OC$H_a$$H_b$CH(OH)), 6.84 (d, ^{3}J = 8.7, 1H, *H*-3 salicyl), 6.96-7.03 (m[t], 2H, *H*-3',5' in 4'F-aniline), 7.16-7.22 (m, 2H, 2x C*H*-4 phenyl), 7.25-7.31 (m, 4H, 2x *H*-3'',5'' phenyl), 7.38-7.44 (4H), (m, 4H, 2x *H*-2'',6'' phenyl), 7.53 (dd, ^{3}J =

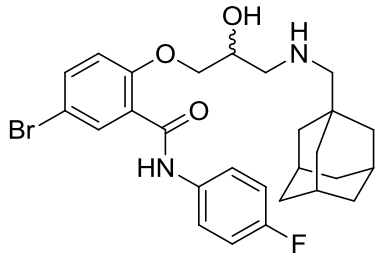
8.7, ^{4}J = 2.6, 1H, *H*-4 salicyl), 7.68-7.74 (m, 2H, *H*-2',6' in 4'F-aniline), 8.35 (d, ^{4}J = 2.6, 1H, *H*-6 salicyl), 10.02 (s, 1H (CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 51.92 (*C*H_2-3'',5'' piperazine), 53.55 (dyn, *C*H_2-2'',6'' piperazine), 59.63 (N*C*H_2CH(OH)), 64.99 (*C*H(OH)), 71.43 (O*C*H_2CH(OH)), 76.18 (N*C*H(C_6H_5)$_2$), 114.65 (*C*-5 salicyl), 114.69 (*C*-3 salicyl), 115.57 (d, $^{2}J_{CF}$ = 22.3, *C*-3',5' in 4'-F-aniline), 122.14 (d, $^{3}J_{CF}$ = 7.8, *C*-2',6' in 4'-F-aniline), 124.28 (C_q-1 salicyl), 127.20 (*C*-4'' phenyl), 128.05 (*C*-2'',6'' phenyl), 128.68 (*C*-3'',5'' phenyl), 134.75 (d, $^{4}J_{CF}$ = 2.2, C_q-1' in 4'-F-aniline), 135.27 (*C*-6 salicyl), 135.72 (*C*-4 salicyl), 142.47 (C_q-1'' phenyl[1]), 142.54 (C_q-1'' phenyl[2]), 155.59 (C_q-2 salicyl), 159.38 (d, $^{1}J_{CF}$ = -243, *C*-4' in 4'-F-aniline), 161.97 (*C*ONH-4'-F-aniline).

HRMS: $[M+H]^+$: calculated.: 618.1762 found: 618.1767.

Melting point: 135-152°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-bromo-*N*-(4-fluorophenyl)benzamide (172)



172 was prepared following **general procedure E**, yielding 0.067 g (46%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.48-1.54 (s, br, 6H, CH in C*H*$_2$-adamantane), 1.60-1.67 (m, 3H, CH in C*H*$_2$-adamantane), 1.70-1.77 (m, 3H, CH in C*H*$_2$-adamantane), 1.98 (s, br, 3H, C*H*-adamantane), 2.22, 2.25, 2.29, 2.32 (AB, ^{2}J = -11.7, 2H, NHC*H*$_a$*H*$_b$-1-adamantane), 2.70 (dd, ^{2}J = -12.2, ^{3}J = 9.2, 1H, CH(OH)C*H*$_a$H$_b$NH), 2.83 (dd, ^{2}J = -12.2, ^{3}J = 3.8, 1H, CH(OH)CH$_a$*H*$_b$NH), 4.00 (dd, ^{2}J = -9.3, ^{3}J = 6.5, 1H, OC*H*$_a$H$_b$CH(OH)), 4.05-4.11 (m[oct], 1H, C*H*(OH)), 4.24 (dd, ^{2}J = - 9.3, ^{3}J = 2.6, 1H, OCH$_a$*H*$_b$CH(OH)), 6.84 (d, ^{3}J = 8.7, 1H, *H*-3 salicyl), 6.97-7.04 (m[t], 2H, *H*-3',5' in 4'F-aniline), 7.51 (dd, ^{3}J = 8.7, ^{4}J = 2.6, 1H, *H*-4 salicyl), 7.72-7.78 (m, 2H, *H*-2',6' in 4'F-aniline), 8.34 (d, ^{4}J = 2.6, 1H, *H*-6 salicyl), 10.09 (s, 1H (CON*H*).

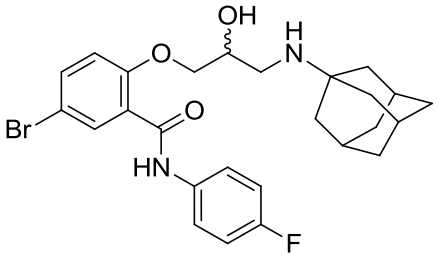
$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.49 (*C*H-adamantane), 33.64 (C_q-1 adamantane), 37.26 (*C*H_2-adamantane), 40.89 (*C*H_2-adamantane), 51.64 (N*C*H_2CH(OH)), 62.44 (NH*C*H_2-1-adamantanyl), 67.18 (*C*H(OH)), 71.73 (O*C*H_2CH(OH)), 114.58 (*C*-5 salicyl), 114.70 (*C*-3 salicyl),

115.54 (d, $^{2}J_{CF}$ = 22.3, *C*-3',5' in 4'-F-aniline), 122.21 (d, $^{3}J_{CF}$ = 7.8, *C*-2',6' in 4'-F-aniline), 124.22 (C_q-1 salicyl), 134.83 (d, $^{4}J_{CF}$ = 2.2, C_q-1' in 4'-F-aniline), 135.19 (*C*-6 salicyl), 135.70 (*C*-4 salicyl), 155.70 (C_q-2 salicyl), 159.40 (d, $^{1}J_{CF}$ = -243, *C*-4' in 4'-F-aniline), 162.02 (*C*ONH-4'-F-aniline).

HRMS: $[M+H]^+$: calculated.: 531.1666 found: 531.1658.

Melting point: 132-147°C.

2-(3-(adamantan-1-ylamino)-2-hydroxypropoxy)-5-bromo-*N*-(4-fluorophenyl)benzamide (173)



173 was prepared following **general procedure E**, yielding 0.090 g (64%) of the desired product.

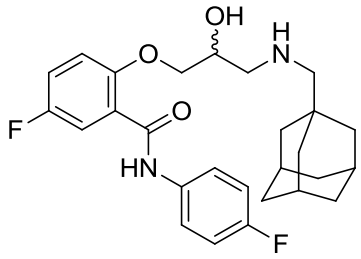
^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 1.41-1.52 (m, 9H, CH in CH_2-adamantane), 1.54-1.62 (m, 3H, CH in CH_2-adamantane), 1.94 (s, br, 3H, C*H*-adamantane), 2.59-2.70 (m, 2H, NC$H_a$$H_b$CH(OH)), 3.83-3.89 (m, 1H, C*H*(OH)), 4.12 (dd, ^{2}J = -9.6, ^{3}J = 5.6, 1H, OCH_aH$_b$CH(OH)), 4.21 (dd, ^{2}J = - 9.6, ^{3}J = 4.6, 1H, OCH$_a$$H_b$CH(OH)), 7.14-7.20 (m[t], 2H, *H*-3',5' in 4'F-aniline), 7.20 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.68 (dd, ^{3}J = 8.8, ^{4}J = 2.6, 1H, *H*-4 salicyl), 7.76-7.82 (m, 2H, *H*-2',6' in 4'-F-aniline), 7.89 (d, ^{4}J = 2.6, 1H, *H*-6 salicyl), 10.34 (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 28.88 (*C*H-adamantane), 36.21 (*C*H$_2$-adamantane), 41.97 (*C*H$_2$-adamantane), 42.79 (N*C*H$_2$CH(OH)), 49.79 (C_q-1 adamantane), 68.86 (*C*H(OH)), 71.94 (O*C*H$_2$CH(OH)), 112.31 (*C*-5 salicyl), 115.26 (d, $^{2}J_{CF}$ = 22.2, *C*-3',5' in 4'-F-aniline), 116.07 (*C*-3 salicyl), 121.61 (d, $^{3}J_{CF}$ = 7.8, *C*-2',6' in 4'-F-aniline), 125.59 (C_q-1 salicyl), 132.50 (*C*-6 salicyl), 134.99 (*C*-4 salicyl), 135.07 (d, $^{4}J_{CF}$ = 2.7, C_q-1' in 4'-F-aniline), 155.53 (C_q-2 salicyl), 158.31 (d, $^{1}J_{CF}$ = -240, *C*-4' in 4'-F-aniline), 162.14 (*C*ONH-4'-F-aniline).

HRMS: $[M+H]^+$: calculated.: 517.1495 found: 517.1502.

Melting point: 131-139°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-fluoro-N-(4-fluorophenyl)benzamide (174)



174 was prepared following **general procedure E**, yielding 0.093 g (45%) of the desired product.

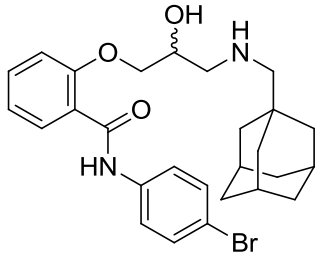
^{1}H NMR (400 MHz, DMSO-d$_6$, 23 °C): δ = 1.39-1.46 (br, 6H, C*H*$_2$-adamantane), 1.52-1.60 (m, 3H, C*H*$_2$-adamantane), 1.62-1.69 (m, 3H, C*H*$_2$-adamantane), 1.89 (br, 3H, C*H*-adamantane), 2.13 (s, 2H, NHC*H*$_2$-1-damantane), 2.59-2.71 (m, 2H, CH(OH)C*H*$_2$NH), 3.93-4.02 (m, 1H, C*H*(OH)), 4.12 (dd, ^{2}J = -9.6, ^{3}J = 5.8, 1H, OC*H*$_a$H$_b$CH(OH)), 4.21 (dd, ^{2}J = -9.6, ^{3}J = 4.1, 1H, OCH$_a$*H*$_b$CH(OH)), 7.15-7.22 (m, 2H, *H*(3,5)-aniline), 7.26 (dd, ^{3}J = 9.1, ^{F}J = 4.3 1H, *H*-3 salicyl), 7.35-7.42 (m, 1H, *H*-4 salicyl), 7.60 (dd, ^{F}J = 9.1, ^{4}J = 3.3, 1H, *H*-6 salicyl), 7.77-7.83 (m, 2H, *H*(2,6)-aniline), 10.41 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d$_6$, 23 °C): δ = 27.81 (*C*H-adamantane), 33.23 (*C*$_q$-1'' adamantane), 36.73 (*C*H$_2$-adamantane), 40.26 (*C*H$_2$-adamantane), 53.34 (N*C*H$_2$CH(OH)), 62.37 (NH*C*H$_2$-1''-adamantane), 67.90 (*C*H(OH)), 72.24 (O*C*H$_2$CH(OH)), 115.31 ($^{2}J_{CF}$ = 22.2, *C*-3,5 aniline), 115.58 ($^{3}J_{CF}$ = 7.8, *C*-3 salicyl), 116.49 ($^{2}J_{CF}$ = 24.1, *C*-6 salicyl), 119.14 ($^{2}J_{CF}$ = 22.7, *C*-4 salicyl), 121.59 ($^{3}J_{CF}$ = 7.9, *C*-2,6 aniline), 135.09 ($^{4}J_{CF}$ = 2.7, *C*-1 aniline), 152.68 ($^{4}J_{CF}$ = 1.7, *C*-2-salicyl), 156.21 ($^{1}J_{CF}$ = -237.7, C-5 salicyl), 158.31 ($^{1}J_{CF}$ = -240.6, *C*-4 aniline), 162.20 ($^{4}J_{CF}$ =1.5, *C*ONH). C-1 salicyl not recorded

HRMS: [M+H]$^{+}$: calculated.: 471.2469 found: 471.2459.

Melting point: 135-143°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(4-bromophenyl)benzamide (175)



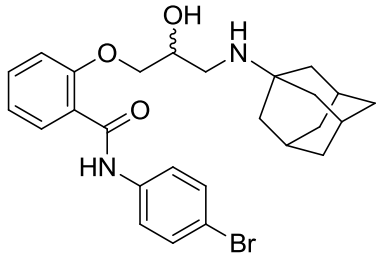
175 was prepared following **general procedure E**, yielding 0.300 g (41%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.51 (br s[d], *J* = 1.9, 6H, C*H*$_2$-adamantane), 1.64 (d, ^{2}J = -12.2, 3H, C*H*$_2$-adamantane), 1.74 (d, ^{2}J = -12.2, 3H, C*H*$_2$-adamantane), 1.99 (br s, 3H, C*H*-adamanthyl), 2.23 (d, ^{2}J = -11.6, 1H, RNHC*H*$_a$H$_b$-adamanthyl), 2.34 (d, ^{2}J = -11.6, 1H, RNHCH$_a$*H*$_b$-adamanthyl), 2.74 (dd, ^{2}J = -12.3, ^{3}J = 3.7, 1H, $OCH_2CHOHCH_aH_bNHR$), 2.86 (dd, ^{2}J = -12.3, ^{3}J = 9.3, 1H, $OCH_2COHCH_aH_bNHR$), 4.04 (dd, ^{2}J = -9.4, ^{3}J = 6.1, 1H, OC*H*$_a$H$_b$CHOH), 4.15 (m, 1H, OCH_2CHOCH_2NHR), 4.27 (dd, ^{2}J = -9.4, ^{3}J = 2.9, 1H, OCH_aH_bCHOH), 6.95 (d, ^{3}J = 8.4, 1H, *H*-3 salicyl), 7.12 (m, 1H, *H*-5 salicyl), 7.43 (d, ^{3}J = 8.8, 2H, *H*(3,5)-aniline), 7.45 (m, 1H, *H*-4 salicyl), 7.74 (d, ^{3}J = 8.8, 2H, *H*(2,6)-aniline), 8.23 (dd, ^{3}J = 7.9, ^{4}J = 1.7, 1H, *H*-6 salicyl), 10.17 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.47 (*tert*-*C*H-adamanthyl), 33.60 (*C*$_q$-adamanthyl), 37.21 (chair-*C*H_2-adamanthyl), 40.83 (*C*H_2-adamanthyl next to C_q), 51.93 ($OCH_2CHOHCH_2NHR$), 62.42 ($RHNCH_2$-adamanthyl), 67.17 ($OCH_2CHOHCH_2NHR$), 71.21 ($OCH_2CHOHCH_2NHR$), 112.73 (*C*-3 salicyl), 116.45 (*C*-4 aniline), 122.04 (*C*-5 salicyl), 122.17 (*C*-2,6 aniline), 122.38 (*C*-1 salicyl), 131.91 (*C*-3,5 aniline), 132.65 (*C*-6 salicyl), 133.34 (*C*-4 salicyl), 138.18 (*C*-1 aniline), 156.64 (*C*-2 salicyl), 163.59 (*C*ONH).
HRMS: $[M+H]^+$: calculated.: 513.1747 found: 513.1753.

Melting point: 125-130°C.

2-(3-(adamantan-1-ylamino)-2-hydroxypropoxy)-*N*-(4-bromophenyl)benzamide (176)



176 was prepared following **general procedure E**, yielding 0.119 g (82%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.52-1.69 (m, 12H, CH in C*H*$_2$-adamantane), 2.04 (s[br], 3H, C*H*-adamantane), 2.72 (dd, ^{2}J = -12.0, ^{3}J = 8.8, 1H, NC*H*$_a$H$_b$CH(OH)), 2.90 (dd, ^{2}J = -12.1, ^{3}J = 2.8, 1H, $NCH_aH_bCH(OH)$), 4.02-4.28 (m, 3H, C*H*(OH), OC*H*$_a$H$_b$CH(OH)), 6.95 (d, ^{3}J = 8.3, 1H,

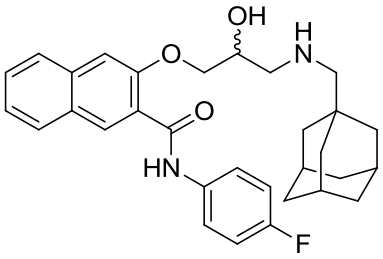
H-3 salicyl), 7.12 (m [t], 1H, *H*-4 salicyl), 7.40-7.49 (m, 3H, *H*-5 salicyl, *H*-3',5' in 4'-bromoaniline), 7.71-7.76 (m, 2H, *H*-2',6' in 4'-bromoaniline), 8.21 (dd, ^{3}J = 7.8, ^{4}J = 1.5, 1H, *H*-6 salicyl), 10.13 (s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 29.53 (*C*H-adamantane), 36.49 (*C*H_2-adamantane), 42.35 (N*C*H_2CH(OH)), 42.42 (*C*H_2-adamantane), 51.72 (C_q-adamantane), 67.89 (*C*H(OH), 71.29 (O*C*H_2CH(OH)), 112.67 (*C*-3 salicyl), 116.47 (C_q-4' in 4'-bromoaniline), 122.02 (*C*-5 salicyl), 122.31 (*C*-2',6' in 4'-bromoaniline), 122.43 (C_q-1 salicyl), 131.87 (*C*-3',5' in 4'-bromoaniline), 132.60 (*C*-6 salicyl), 133.31 (*C*-4 salicyl), 138.13 (C_q-1' in 4'-bromoaniline), 156.61 (C_q-2 salicyl), 163.64 (*C*ONH).

HRMS: $[M+H]^+$: calculated.: 499.1591 found: 499.1596.

Melting point: 129-139°C.

3-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(4-fluorophenyl)-2-naphthamide (177)



177 was prepared following **general procedure E**, yielding 0.050 g (31%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.51 (6H), (s, br, 6H, C*H*$_2$-adamantane), 1.60-1.67 (3H), (m, 3H, C*H*$_2$-adamantane), 1.70-1.77 (3H), (m, 3H, C*H*$_2$-adamantane), 1.98 (3H), (s, br, 3H, C*H*-adamantane), 2.26 (1H), (d, ^{2}J = -11.6, 1H, RNHC*H*$_a$H$_b$-1-adamantane), [2.24/2.27/2.30/2.33] 2.32 (1H), (d, ^{2}J = -11.6, 1H, RNHCH$_a$*H*$_b$-1-adamantane), 2.79 (1H), (dd, ^{2}J = -11.9, ^{3}J = 8.6-8.9, 1H, OCH$_2$CHOHC*H*$_a$H$_b$NHR), 2.86 (1H), (dd, ^{2}J = -11.9, ^{3}J = 4.1, 1H, OCH$_2$COHCH$_a$*H*$_b$NHR), 4.07-4.13 (m, 1H, OC*H*$_a$H$_b$CHOH), 4.14-4.21 (m, 2H, OCH$_a$*H*$_b$C*H*(OH)), 7.06 (m, 2H, *H*(3,5)-aniline), 7.59 (m, 2H, *H*-7,9 naphthyl), 7.73 (d, *J* = 8.7, 1H, *H*-1 naphthyl), 7.84 (m, 2H, *H*(2,6)-aniline), 7.89 (m, 1H, *H*-9 naphthyl), 8.20 (m, 1H, *H*-6 naphthyl), 8.24 (d, *J* = 8.7, 1H, *H*-4 naphthyl), 10.16 (br s, 1H, CON*H*).

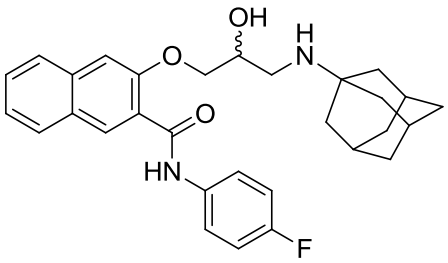
$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.51 (*C*H-adamantane), 33.63 (C_q-adamantane), 37.28 (*C*H_2-adamantane), 40.90 (*C*H_2-adamantane), 51.64 (OCH$_2$CHOH*C*H$_2$NHR), 62.45

(RHN*C*H_2-1''-adamantane), 68.06 (OCH_2*C*HOHCH_2NHR), 78.53 (O*C*H_2CHOHCH_2NHR), 115.54 (d, $^2J_{CF}$ = 22.2, *C*-3',5' in 4'-F-aniline), 122.39 (C_q-2 naphthalene), 122.60 (d, $^3J_{CF}$ = 7.8, *C*-2',6' in 4'-F-aniline), 122.99 (*C*H naphthyl), 125.07 (*C*-1 naphthyl), 126.89 (*C*H), 127.08 (*C*-4 naphthyl), 127.60 (C_q), 128.23 (*C*H), 128.46 (*C*-9 naphthyl), 134.83 ($^4J_{CF}$ = 2.8, *C*-1 aniline), 136.97 (C_q), 153.90 (*C*-3 naphthyl), 159.49 (d, $^1J_{CF}$ = -243, *C*-4' in 4'-F-aniline), 163.51 (*C*ONH).

HRMS: $[M+H]^+$: calculated.: 503.2721 found: 503.2710.

Melting point: 138-151°C.

3-(3-(adamantan-1-ylamino)-2-hydroxypropoxy)-*N*-(4-fluorophenyl)-2-naphthamide (178)



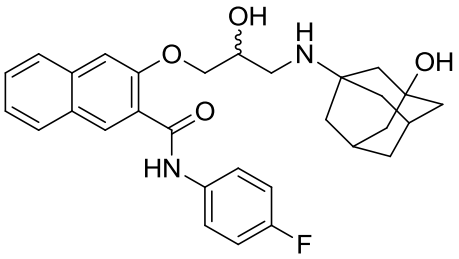
178 was prepared following **general procedure E**, yielding 0.074 g (51%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 1.55-1.81 (12H), 2.10 (3H), 2.89 (1H), 3.02 (1H), 4.12 (1H), 4.17 (1H), 4.35 (1H), 7.00-7.07 (2H), 7.71 (1H), 7.78-7.88 (3H), 8.14-8.20 (2H), 9.99 (1H). ^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 29.41, 36.24, 41.42, 53.52, 68.11, 78.21, 115.58, 122.53, 122.72, 122.89, 125.13, 126.89, 126.99, 127.49, 128.24, 128.45, 134.69, 136.88, 153.63, 159.53, 163.67.

HRMS: $[M+H]^+$: calculated.: 489.2559 found: 489.2553.

Melting point: 147-149°C.

N-(4-fluorophenyl)-3-(2-hydroxy-3-((3-hydroxyadamantan-1-yl)amino)propoxy)-2-naphthamide (179)



179 was prepared following **general procedure E**, yielding 0.028 g (19%) of the desired product.

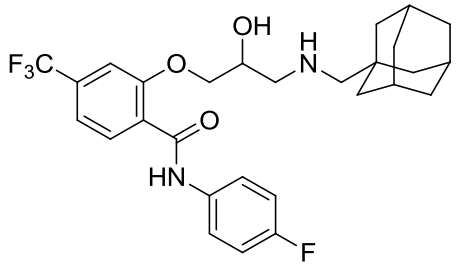
^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 1.32-1.50 (12H), 2.07 (2H), 2.61-2.73 (2H), 3.87-3.94 (1H), 4.01-4.12 (2H), 7.15-7.24 (2H), 7.61-7.66 (2H), 7.71-7.87 (4H), 7.97-8.02 (1H), 8.38-8.43 (1H), 10.51 (1H).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 30.14, 35.02, 40.79, 43.24, 43.54 ($CH_2CHOHCH_2NHR$), 44.39 (CH_2-adamantane), 44.40 (CH_2-adamantane), 49.12 (CH_2-adamantane), 50.09 (CH_2-adamantane), 67.15 (C_q-3 adamantane), 69.48 ($OCH_2CHOHCH_2NHR$), 78.28 ($OCH_2CHOHCH_2NHR$), 115.21 ($^{2}J_{CF}$ = 22.1, *C*-3,5 aniline), 121.84 ($^{3}J_{CF}$ = 7.6, *C*-2,6 aniline), 123.06 (*C*-9 naphthyl), 123.70 (*C*H), 124.38 (*C*-3 naphthyl), 125.84 (*C*-1 naphthyl), 126.62 (*C*-4 naphthyl), 127.36 (*C*-5 naphthyl), 127.75 (*C*-6 naphthyl), 127.94 (*C*H), 135.40 ($^{4}J_{CF}$ = 2.9, *C*-1 aniline), 135.43 (*C*-10 naphthyl), 152.83 (*C*-2 naphthyl), 158.29 ($^{1}J_{CF}$ = -241.0, *C*-4 aniline), 164.62 (*C*ONH).

HRMS: $[M+H]^+$: calculated.: 505.2501 found: 505.2502.

Melting point: 152-155°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(4-fluorophenyl)-4-(trifluoromethyl)benzamide (180)



180 was prepared following **general procedure E**, yielding 0.226 g (57%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.45-1.52 (br, 6H, CH in C*H*$_2$-adamantane), 1.55-1.63 (m, 3H, CH in C*H*$_2$-adamantane), 1.67-1.76 (m, 3H, CH in C*H*$_2$-adamantane), 1.97 (s, br, 3H, *CH*-adamantane), 2.36, 2.39, 2.57, 2.60 (AB, $^{2}J_{AB}$ = -11.4, 2H, NHC*H*$_2$-1-damantane), 3.01 (dd, ^{2}J = -12.1, ^{3}J = 10.0, 1H, CH(OH)C*H*$_a$H$_b$NH), 3.12 (dd, ^{2}J = -12.1, ^{3}J = 3.2, 1H, CH(OH)CH$_a$*H*$_b$NH), 4.16 (dd, ^{2}J = -9.4, ^{3}J = 4.8, 1H, OC*H*$_a$H$_b$CH(OH)), 4.30 (dd, ^{2}J = -9.4, ^{3}J = 3.1, 1H, OCH$_a$*H*$_b$CH(OH)), 4.50-4.58 (m, 1H, C*H*(OH)), 6.98-7.05 (m[t], 2H, *H*-3',5' in 4'-F-aniline), 7.16

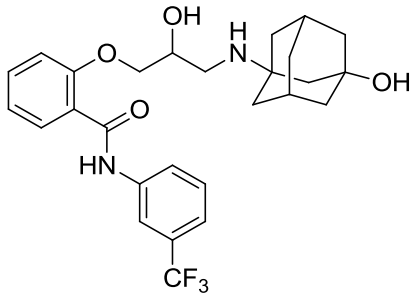
(s, br, 1H, *H*-3 salicyl), 7.39 (d, ^{3}J = 9.1, 1H, *H*-5 salicyl), 7.74-7.81 (m, 2H, *H*-2',6' in 4'-F-aniline), 8.28 (d, ^{3}J = 7.8, 1H, *H*-6 salicyl), 9.89 (s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.06 (*C*H-adamantane), 32.97 (C_q-1'' adamantane), 36.60 (*C*H_2-adamantane), 40.06 (*C*H_2-adamantane), 52.41 (N*C*H_2CH(OH)), 61.55 (NH*C*H_2-1''-adamantane), 65.47 (*C*H(OH)), 71.26 (O*C*H_2CH(OH)), 109.89 (q, $^{3}J_{CF}$ = 3.7, *C*-3 salicyl) 115.73 (d, $^{2}J_{CF}$ = 22.2, *C*-3',5' in 4'-F-aniline), 118.98 (q, $^{3}J_{CF}$ **= 3.6,** *C*-5 salicyl), 122.30 (d, $^{3}J_{CF}$ = 7.8, *C*-2',6' in 4'-F-aniline), 126.20 (C_q-1 salicyl), 133.33 (*C*-6 salicyl), 134.58 (d, $^{4}J_{CF}$ = 2.4, C_q-1' in 4'-F-aniline), 134.71 (q, $^{2}J_{CF}$ = 31, C_q-4 salicyl), 156.20 (C_q-2 salicyl), 159.55 (d, $^{1}J_{CF}$ = -243, C_q-4' in 4'-F-aniline),162.34 (*C*ONH). *C*F_3 not recorded

LCMS: $[M+H]^+$: calculated.: 521.24 found: 521.32, $[M-H]^-$: calculated.: 519.23 found: 519.29.

Melting point: 195-200°C.

2-(2-hydroxy-3-((-3-hydroxyadamantan-1-yl)amino)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (181)



181 was prepared following **general procedure E**, yielding 0.074 g (79%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 1.31-1.51 (m, br, 13H, CH_2-adamantane), 2.05 (s, br, 2H, C*H*-adamantane), 2.69 (dd, ^{2}J = -11.5, ^{3}J = 7.1, 1H, NC$H_a$$H_b$CH(OH)), 2.74 (dd, ^{2}J = -11.5, ^{3}J = 5.1, 1H, NC$H_a$$H_b$CH(OH)), 3.90-3.98 (m[q], 1H, C*H*(OH)), 4.14-4.25 (m, 2H, OC$H_a$$H_b$CH(OH)), 7.11 (d,d[t], 1H, (dd[t], $^{3}J_1$ = $^{3}J_2$ = 7.4, 1H, *H*-5 salicyl), 7.22 (d, 1H, (d, ^{3}J = 8.3, 1H, *H*-3 salicyl), 7.43 (d, 1H, (d, br, ^{3}J = 7.7, 1H, *H*-4' in 3'-CF_3-aniline), 7.51-7.61 (m, 2H, *H*-4 salicyl, *H*-5' in 3'-CF_3-aniline), 7.83 (dd, ^{3}J = 7.7, ^{4}J = 1.6, 1H, *H*-6 salicyl), 7.96 (d, br, 1H, ^{3}J = 8.3, *H*-6' in 3'-CF_3-aniline), 8.35 (s, 1H, br, 1H, *H*-2' in 3'-CF_3-aniline), 10.63 (s, 1H, CON*H*).

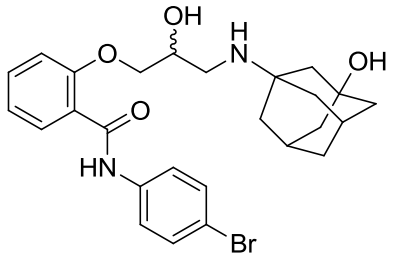
$^{13}C\{^{1}H\}$NMR (100 MHz, DMSO-d_6, 23 °C): δ = 30.07 (*C*H of adamantane), 34.92 (*C*H_2 of adamantane), 40.22 (*C*H_2 of adamantane), 43.12 (N*C*H_2CH(OH)), 44.29 (*C*H_2 of adamantane), 49.55 (*C*H_2-2 of adamantane), 53.56 (C_q-1 adamantane), 67.56 (C_q-3-OH adamantane), 68.35

(*C*H(OH)), 71.44 (O*C*H$_2$CH(OH)), 113.52 (*C*-3 salicyl), 115.84 ($^4J_{CF}$ = 4.1, *C*-2' in 3'-CF$_3$-aniline), 119.85 ($^4J_{CF}$ = 3.8, *C*-4' in 3'-CF$_3$-aniline), 121.00 (*C*-5 salicyl), 123.17 (C_q-1 salicyl), 123.40 (*C*-6' in 3'-CF$_3$-aniline), 124.14 (q, C_q, $^1J_{CF}$ = -272.3, 3'-*C*F$_3$-aniline), 129.51 ($^2J_{CF}$ = 31.6, *C*-3' in 3'-CF$_3$-aniline), 129.89 (*C*-5' in 3'-CF$_3$-aniline), 130.57 (*C*-6 salicyl), 133.02 (*C*-4 salicyl), 139.71 (C_q-1' in 3'-CF$_3$-aniline), 156.28 (C_q-2 salicyl), 164.27 (*C*ONH).

HRMS: $[M+H]^+$: calculated.: 505.2320 found: 505.2314.

Melting point: 139-145°C.

N-(4-bromophenyl)-2-(2-hydroxy-3-((3-hydroxyadamantan-1-yl)amino)propoxy)benzamide (182)



182 was prepared following **general procedure E**, yielding 0.122 g (81%) of the desired product.

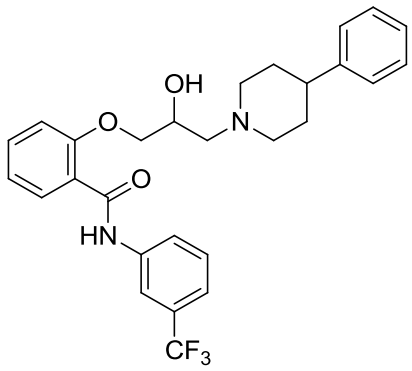
^{1}H NMR (400 MHz, DMSO-d$_6$, 23 °C): δ = 1.33-1.49 (m, br, 12H, C*H*$_2$-adamantane), 2.06 (s, br, 2H, C*H*-adamantane), 2.61-2.70 (m, 2H, NC*H*$_a$*H*$_b$CH(OH)), 3.84-3.92 (m, 1H, C*H*(OH)), 4.12 (dd, ^2J = -9.6, ^3J = 6.0, 1H, OC*H*$_a$H$_b$CH(OH)), 4.22 (dd, ^2J = -9.6, ^3J = 4.0, 1H, OCH$_a$*H*$_b$CH(OH)), 7.10 (dd[t], 1H, *H*-5 salicyl), 7.21 (d, ^3J = 8.2, 1H, *H*-3 salicyl), 7.48-7.56 (m, 3H, *H*-4 salicyl, *H*-3',5' in 4'-bromoaniline), 7.77 (m[d], 2H, *H*-2',6' in 4'-bromoaniline), 7.83 (dd, ^3J = 7.6, ^4J = 3.5, 1H, *H*-6 salicyl), 10.40 (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d$_6$, 23 °C): δ = 30.20 (*C*H of adamantane), 35.10 (*C*H$_2$ of adamantane), 40.83 (*C*H$_2$ of adamantane), 43.28 (N*C*H$_2$CH(OH)), 44.42 (*C*H$_2$ of adamantane), 50.11 (*C*H$_2$-2 of adamantane), 53.07 (C_q-1 adamantane), 67.73 (C_q-3-OH adamantane), 68.94 (*C*H(OH)), 71.60 (O*C*H$_2$CH(OH)), 113.56 (*C*-3 salicyl), 115.23 (C_q-4' in 4'-bromoaniline), 121.04 (*C*-5 salicyl), 121.79 (*C*-2',6' in 4'-bromoaniline), 123.21 (C_q-1 salicyl), 130.66 (*C*-6 salicyl), 131.56 (*C*-3',5' in 4'-bromoaniline), 133.01 (*C*-4 salicyl), 138.34 (C_q-1' in 4'-bromoaniline), 156.33 (C_q-2 salicyl), 163.84 (*C*ONH).

HRMS: $[M+H]^+$: calculated.: 515.1553 found: 515.1545.

Melting point: 179-194°C.

2-(2-hydroxy-3-(4-phenylpiperidin-1-yl)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (183)



183 was prepared following **general procedure E**, yielding 0.074 g (43%) of the desired product.

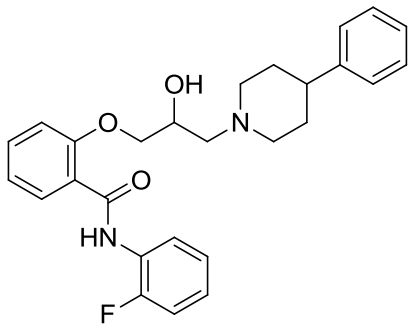
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.74-1.94 (m, 4H, *H*-3,5 in piperidine), 2.18 (ddd, 1H, H_{ax}-2 in piperidine), 2.42-2.59 (m, 3H, H_{ax}-6 in piperidine, NC$H_a$$H_b$CH(OH), H_{ax}-4 in piperidine), 2.69 (dd[t], 1H, $NCH_aH_bCH(OH)$), 2.86-2.92 (m, 1H, H_{eq}-6 in piperidine), 3.15-3.22 (m, 1H, H_{eq}-2 in piperidine), 4.06 (dd, ^{2}J = -9.1, ^{3}J = 5.6, 1H, OC$H_a$$H_b$CH(OH)), 4.24-4.35 (m, 2H, $OCH_aH_bCH(OH)$, C*H*(OH)), 4.35-4.55 (br, 1H, CH(O*H*)), 6.97 (d, 1H, ^{3}J = 8.2, 1H, *H*-3 salicyl), 7.14 (dd[t], ^{3}J = ^{3}J = 7.5, 1H, *H*-5 salicyl), 7.20-7.25 (m, 3H, *H*-2'',6''-phenyl, *H*-4 phenyl), 7.30-7.37 (m, 3H, *H*-3'',5''-phenyl, *H*-4' in 3'-CF_3-aniline), 7.42-7.50 (m, 2H, *H*-4 salicyl, *H*-5' in 3'-CF_3-aniline), 8.10 (d, br, 1H, *H*-6' in 3'-CF_3-aniline), 8.16 (s, br, 1H, *H*-2' in 3'-CF_3-aniline), 8.25 (dd, ^{3}J = 7.8, ^{4}J = 1.8, 1H, *H*-6 salicyl), 10.37 (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 33.15 (NCH_2CH_2-piperidine), 33.43 (NCH_2CH_2-piperidine), 42.27 (piperidine-*C*H-4-phenyl), 52.88 (NCH_2CH_2-piperidine), 56.25 (NCH_2CH_2-piperidine), 60.07 ($NCH_2CH(OH)$), 65.20 (*C*H(OH), 71.27 ($OCH_2CH(OH)$), 112.73 (*C*-3 salicyl), 117.25 (q, $^{3}J_{CF}$ = 3.9, *C*-2' in 3'-CF_3-aniline), 120.38 (q, $^{3}J_{CF}$ = 3.7, *C*-4' in 3'-CF_3-aniline), 122.08 (*C*-5 salicyl), 122.17 (C_q-1 salicyl), 123.47 (*C*-6' in 3'-CF_3-aniline), 124.08 (q, $^{1}J_{CF}$ = -272, 3'-*C*F_3-aniline), 126.48 (*C*-4'' phenyl), 126.88 (*C*-2'',6'' phenyl), 128.63 (*C*-3'',5'' phenyl), 129.46 (*C*-5' in 3'-CF_3-aniline), 131,23 (q, $^{2}J_{CF}$ = 32.6, *C*-3' in 3'-CF_3-aniline), 132.63 (*C*-6 salicyl), 133.50 (*C*-4 salicyl), 139.60 (*C*-1' in 3'-CF_3-aniline), 145.74 (C_q-1'' phenyl), 156.65 (C_q-2 salicyl), 163.82 (*C*ONH).

HRMS: $[M+H]^+$: calculated.: 499.2206 found: 499.2208.

Melting point: 154-159°C.

_N_-(2-fluorophenyl)-2-(2-hydroxy-3-(4-phenylpiperidin-1-yl)propoxy)benzamide (184)



184 was prepared following **general procedure E**, yielding 0.148 g (95%) of the desired product.

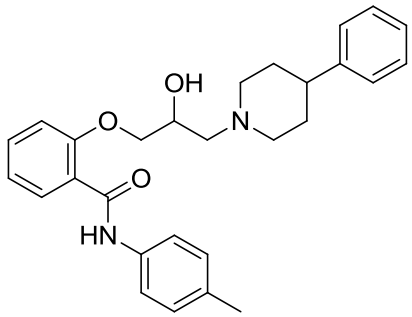
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.72-1.92 (m, 4H, H_{ax} H_{eq}-3,5 in piperidine), 2.14 (ddd, ^{2}J = -11.6, $^{3}J_{axax}$ = 11.3, $^{3}J_{axeq}$ = 2.5, 1H, H_{ax}-6 in piperidine), 2.43 (ddd, ^{2}J = -11.3, $^{3}J_{axax}$ = 11.3, $^{3}J_{axeq}$ = 3.1, 1H, H_{ax}-2 in piperidine), 2.48-2.67 (m, 2H, piperidine-C*H*-4'-phenyl, NCH_aH_bCH(OH)), 2.85-2.92 (m[d], br, 1H, H_{eq}-2 in CH_2 piperidine), 3.13-3.20 (m[d], br, 1H, H_{eq}-6 in CH_2 piperidine), 4.22- 4.32 (m, 2H, OCH_aH_bCH(OH), CH(O*H*)), 7.03-7.25 (m, 8H, *H*-2'',6'' phenyl, *H*-3,5 salicyl, 3',4',5' aniline, 4'' phenyl), 7.28-7.34 (m, 2H, *H*-3'',5'' phenyl), 7.50 (ddd, $^{3}J_1$ = 7.4, $^{3}J_2$ = 8.3, ^{4}J = 1.8, 1H, *H*-4 salicyl), 8.28 (dd, ^{3}J = 7.8, ^{4}J = 1.8, 1H, *H*-6 salicyl), 8.53 (ddd, ^{3}J = 8.0, $^{4}J_{HF}$ = 7.5, ^{4}J = 1.7, 1H, *H*-6 in 2'-F-aniline), 10.10 (s, 1H (CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 33.45 (NCH$_2$*C*H$_2$-piperidine), 33.80 (NCH$_2$*C*H$_2$-piperidine), 42.48 (piperidine-*C*H-4-phenyl), 52.91 (N*C*H$_2$CH$_2$-piperidine), 56.17 (N*C*H$_2$CH$_2$-piperidine), 60.75 (N*C*H$_2$CH(OH)), 65.21 (*C*H(OH), 72.16 (O*C*H$_2$CH(OH)), 113.00 (*C*-3 salicyl), 114.87 (d, $^{2}J_{CF}$ = 19.3, *C*-3' in 2'-F-aniline), 121.99 (*C*-5 salicyl), 122.08 (C_q-1 salicyl), 122.90 (br, *C*-6' in 2'-F-aniline), 124.32 (d, $^{3}J_{CF}$ = 7.7, *C*-4' in 2'-F-aniline), 124.74 (d, $^{4}J_{CF}$ = 3.5, *C*-5' in 2'-F-aniline), 126.41 (*C*-4'' phenyl), 126.93 (*C*-2'',6'' phenyl), 127.12 (d, $^{2}J_{CF}$ = 10.1, C_q-1' in 2'-F-aniline), 128.61 (*C*-3'',5'' phenyl), 132.75 (*C*-6 salicyl), 133.58 (*C*-4 salicyl), 146.08 (C_q-1'' phenyl), 153.14 (d, $^{1}J_{CF}$ = -243.4, C_q-2' in 2'-F-aniline), 156.93 (C_q-2 salicyl), 163.60 (*C*ONH-2'-F-aniline).

HRMS: $[M+H]^+$: calculated.: 449.2254 found: 449.2240.

Melting point: 72-92°C.

2-(2-hydroxy-3-(4-phenylpiperidin-1-yl)propoxy)-*N*-(p-tolyl)benzamide (185)



185 was prepared following **general procedure E**, yielding 0.150 g (96%) of the desired product.

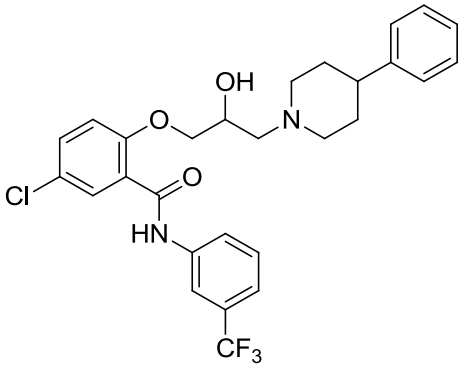
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.71-1.93 (4H), (m, 4H, H_{ax} H_{eq}-3,5 in piperidine), 2.14 (1H), (ddd, ^{2}J = -11.6, $^{3}J_{axax}$ = 11.3, $^{3}J_{axeq}$ = 2.5, 1H, H_{ax}-6 in piperidine), 2.32 (3H), (s, 3H, 4-CH_3C$_6$H$_4$NHCO), 2.44 (1H), (ddd, ^{2}J = -11.3, $^{3}J_{axax}$ = 11.3, $^{3}J_{axeq}$ = 3.1, 1H, H_{ax}-2 in piperidine), 2.48-2.58 (2H), (m, 2H, piperidine-C*H*-4'-phenyl; ^{2}J = -12.2, ^{3}J = 3.5, NCH_aH$_b$CH(OH)), 2.70 (1H), (dd, ^{2}J = -12.2, ^{3}J = 10.9, 1H, NCH$_a$$H_b$CH(OH)), 2.79-2.86 (1H), (m[d], br, 1H, H_{eq}-2 in CH_2 piperidine), 3.12-3.19 (1H), (m[d], br, 1H, H_{eq}-6 in CH_2 piperidine), 4.08 (1H), (dd, ^{2}J = -9.5, ^{3}J = 5.1, 1H, OCH_aH$_b$CH(OH)), 4.19-4.26 (1H), (m, 1H, C*H*(OH)), 4.33 (1H), (dd, ^{2}J = -9.5, ^{3}J = 3.0, 1H, OCH$_a$$H_b$CH(OH)), 6.98 (1H), (dd[d], ^{3}J = 8.2, ^{4}J = 0.6, 1H, *H*-3 salicyl), 7.10-7.18 (3H), (m, 3H, *H*-5 salicyl, *H*-3',5' toluidine), 7.20-7.25 (3H), *H*-4'' phenyl. *H*-2'',6'' phenyl), 7.29-7.36 (2H), *H*-3'',5'' phenyl), 7.46 (1H), (ddd, $^{3}J_1$ = 7.7, $^{3}J_2$ = 8.8, ^{4}J = 1.7, 1H, *H*-4 salicyl), 7.66-7.72 (2H), (m, 2H, *H*-2',6' toluidine), 8.26 (1H), (dd, ^{3}J = 7.8, ^{4}J = 1.7, 1H, *H*-6 salicyl), 10.02 (1H), (s, 1H (CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 21.04 (4-*C*H$_3$ in toluidine), 33.45 (NCH$_2$*C*H$_2$-piperidine), 33.80 (NCH$_2$*C*H$_2$-piperidine), 42.43 (piperidine-*C*H-4-phenyl), 52.85 (N*C*H$_2$CH$_2$-piperidine), 56.30 (N*C*H$_2$CH$_2$-piperidine), 60.17 (N*C*H$_2$CH(OH)), 65.25 (*C*H(OH)), 70.94 (O*C*H$_2$CH(OH)), 112.63 (*C*-3 salicyl), 120.55 (*C*-2',6' toluidine), 121.97 (*C*-5 salicyl), 122.84 (C_q-1 salicyl), 126.47 (*C*-4''phenyl), 126.92 (*C*-3'',5''phenyl), 128.65 (*C*-2'',6''phenyl), 129.48 (*C*-3',5' toluidine), 132.67 (*C*-6 salicyl), 133.02 (*C*-4 salicyl), 133.57 (C_q-4' toluidine), 136.47 (C_q-1' toluidine), 145.97 (C_q-1'' phenyl), 156.62 (C_q-2 salicyl), 163.39 (*C*ONH).

HRMS: $[M+H]^+$: calculated.: 445.2495 found: 445.2491.

Melting point: 129-140°C.

5-chloro-2-(2-hydroxy-3-(4-phenylpiperidin-1-yl)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (186**)**



186 was prepared following **general procedure E**, yielding 0.087 g (60%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 1.55-1.72 (m, 4H, *H*-3,5 in piperidine), 1.96-2.09 (2H), (m, 2H, H_{ax}-2,6 in piperidine), 2.35-2.56 (3H), (m, 2H, NCH_aH_bCH(OH), H_{ax}-4 in piperidine), 2.83-2.91 (1H), (m[d], br, 1H, H_{eq}-2 in CH_2 piperidine), 2.92-3.01 (1H), (m[d], br, 1H, H_{eq}-6 in CH_2 piperidine), 4.03-4.11 (1H), (m, 1H, C*H*(OH)), 4.12-4.27 (2H), (m, 2H, OCH_aH_bCH(OH)), 5.19 (1H), (d, 1H, CH(O*H*)) 7.14-7.23 (m, 3H, *H*-2'',4'',6'' phenyl), 7.24-7.34 (m, 3H, *H*-3 salicyl, *H*-3'',5'' phenyl), 7.46 (m[d], 1H, *H*-4' in 3'-CF_3-aniline), 7.56-7.64 (m, 2H, *H*-4 salicyl, *H*-5' in 3'-CF_3-aniline), 7.79 (d, ^{4}J = 2.5, 1H, *H*-6 salicyl), 7.99 (d, br, 1H, *H*-6' in 3'-CF_3-aniline), 8.29 (s, br, 1H, *H*-2'' in 3''-CF3-aniline), 10.62 (s, 1H (CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 33.08 (NCH$_2$*C*H$_2$-piperidine), 41.67 (piperidine-*C*H-4-phenyl), 54.46 (N*C*H$_2$CH$_2$-piperidine), 61.13 (N*C*H$_2$CH(OH)), 66.38 (*C*H(OH), 72.32 (O*C*H$_2$CH(OH)), 115.81 (*C*-3 salicyl), 115.90 (q, $^{3}J_{CF}$ = 3.8, *C*-2' in 3'-CF_3-aniline), 120.13 (q, $^{3}J_{CF}$ = 3.7, *C*-4' in 3'-CF_3-aniline), 123.41 (*C*-6' in 3'-CF_3-aniline), 124.58 (q, $^{1}J_{CF}$ = -272.3, 3-*C*F_3-aniline), 124.82 (C_q-1 salicyl), 125.10 (C_q-5 salicyl), 125.93 (*C*-4'' phenyl), 126.59 (*C*-2'',6'' phenyl), 128.28 (*C*-3'',5'' phenyl), 129.51 (q, $^{2}J_{CF}$ = 31.6, *C*-3' in 3'-CF_3-aniline), 129.61 (*C*-5' in 3'-CF_3-aniline), 129.99 (*C*-6 salicyl), 132.34 (*C*-4 salicyl), 139.45 (*C*-1' in 3'-CF_3-aniline), 146.24 (C_q-1'' phenyl), 155.18 (C_q-2 salicyl), 162.93 (*C*ONH).

^{1}H NMR (700 MHz, $CDCl_3$, 23 °C): δ = 1.73-1.82 (m[2x dddd], 2H, H-3_{ax}/H-5_{ax} in piperidine), 1.82-1.86 (m, 1H, H_{eq}-3 in piperidine), 1.87-1.92 (m, 1H, H_{eq}-5 in piperidine), 2.15 (ddd, 1H, H_{ax}-6 in piperidine), 2.47 (ddd, 1H, H_{ax}-2 in piperidine), 2.51 (dd, ^{2}J = -12.2, ^{3}J = 3.4, 1H, CH(OH)CH_aH_bNH), 2.54 (tt, 1H, H_{ax}-4 in piperidine), 2.62 (dd, ^{2}J = -12.2, ^{3}J = 11.2, 1H, CH(OH)CH_aH_bNH), 2.82 (m[d], br, 1H, H_{eq}-2 in piperidine), 3.15 (m[d], br, 1H, H_{eq}-6 in piperi-

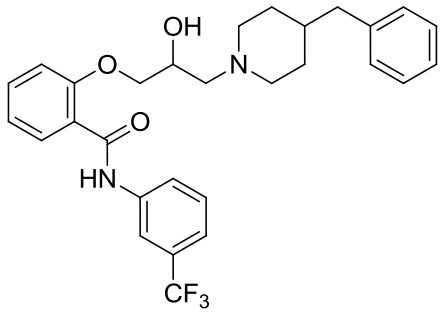
dine), 4.04 (m, 1H, ^{2}J = -9.2, ^{3}J = 6.0, OCH_aH$_b$CH(OH)), 4.25 (m[octet], 1H, CH(O*H*)) 4.33 (m, 1H, ^{2}J = -9.2, ^{3}J = 2.6, OCH$_a$$H_b$CH(OH)), 6.94 (d, ^{3}J = 8.7, 1H, *H*-3 salicyl), 7.21-7.24 (m, 3H, *H*-2'', 4'', 6'' phenyl), 7.31-7.34 (m, 2H, *H*-3'',5'' phenyl), 7.36 (m[d], 1H, *H*-4' in 3'-CF_3-aniline), 7.43 (m, 1H, ^{2}J = -8.7, ^{3}J = 2.7, *H*-4 salicyl), 7.47 (m[t], 1H, *H*-5' in 3'-CF_3-aniline), 8.08 (s, br, 1H, *H*-2' in 3'-CF3-aniline), 8.10 (d, br, 1H, *H*-6' in 3'-CF_3-aniline), 8.23 (d, ^{4}J = 2.7, 1H, *H*-6 salicyl), 10.31 (s, 1H (CON*H*).

^{13}C{1H}NMR (175 MHz, $CDCl_3$, 23 °C): δ = 33.42 (NCH$_2$*C*(5)H$_2$-piperidine), 33.75 (NCH$_2$*C*(3)H$_2$-piperidine), 42.45 (piperidine-*C*H-4-phenyl), 52.77 (NC(6)*H$_2$CH$_2$*-piperidine), 56.38 (N*C*(2)H$_2$CH$_2$-piperidine), 59.87 (N*C*H$_2$CH(OH)), 65.11 (*C*H(OH), 71.74 (O*C*H$_2$CH(OH)), 114.30 (*C*-3 salicyl), 117.34 (q, $^{3}J_{CF}$ = 3.9, *C*-2' in 3'-CF_3-aniline), 120.70 (q, $^{3}J_{CF}$ = 3.4, *C*-4' in 3'-CF_3-aniline), 123.54 (*C*-6' in 3'-CF_3-aniline), 123.66 (C_q-1 salicyl), 124.18 (q, $^{1}J_{CF}$ = - 272, *C*F_3), 126.49 (*C*-2'', 6'' phenyl), 126.92 (br, *C*-3'', 4', 5'' phenyl), 127.60 (C_q-5 salicyl), 128.66 (*C*-2'',6'' phenyl), 129.57 (*C*-5' in 3'-CF_3-aniline), 131.33 ($^{2}J_{CF}$ = 32.1, *C*-3' in 3$_q$'-CF_3-aniline), 132.41 (*C*-6 salicyl), 133.09 (*C*-4 salicyl), 139.30 (*C*-1' in 3'-CF_3-aniline), 145.89 (C_q-1'' phenyl), 155.19 (C_q-2 salicyl), 162.43 (*C*ONH).

HRMS: $[M+H]^+$: calculated.: 533.1831 found: 533.1819.

Melting point: 198-202°C.

2-(3-(4-benzylpiperidin-1-yl)-2-hydroxypropoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (187)



187 was prepared following **general procedure E**, yielding 0.147 g (96%) of the desired product as colorless oil.

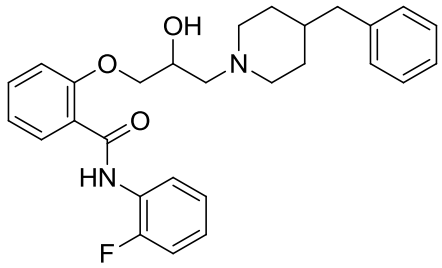
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.24-1.36 (m, 2H, H in 3,5-C*H*$_2$ piperidine), 1.50-1.59 (m, 1H, C*H*(CH$_2$)-phenyl), 1.59-1.71 (m[t], 2H, H in 3,5-C*H*$_2$ piperidine), 1.97 (ddd, ^{2}J = -11.7, $^{3}J_{aa}$ = 11.6, $^{3}J_{ae}$ = 2.2, 1H, H_{ax}-2 piperidine), 2.27 (ddd, ^{2}J = -11.6, $^{3}J_{aa}$ = 11.7, $^{3}J_{ae}$ = 2.3, 1H, H_{ax}-6 piperidine), 2.43 (dd, ^{2}J = -12.3, ^{3}J = 3.6, 1H, CH(OH)CH_aH$_b$NH), 2.52-2.60 (m, 3H, CH(CH_2)-

phenyl, CH(OH)CH$_a$H$_b$NH), 2.67-2.74 (m[d], br, 1H, H_{eq}-6 in piperidine), 2.97-3.04 (m[d], br, 1H, H_{eq}-2 in piperidine), 3.99 (dd, ^2J = -9.3, ^3J = 5.9, 1H, OCH$_a$H$_b$CH(OH)), 4.15-4.23 (br, 1H, CH(OH)), 4.27 (dd, ^2J = -9.3, ^3J = 2.7, 1H, OCH$_a$H$_b$CH(OH)), 6.93 (d, ^3J = 8.2, 1H, *H*-3 salicyl), 7.11 (ddd[t], $^3J_1$ = $^3J_2$ = 7.5, ^4J = 0.7, 1H, *H*-5 salicyl,), 7.13-7.17 (m, 2H, *H*-2'',6''-phenyl), 7.18-7.24 (m, 1H, *H*-4'-phenyl), 7.27-7.32 (m, 3H, *H*-3'',5''-phenyl), 7.33-7.37 (d, br, 1H, *H*-4' in 3'-CF_3-aniline), 7.40-7.47 (m, 2H, *H*-4 salicyl, *H*-4' in 3'-CF_3-aniline), 8.07 (d, br, 1H, *H*-6' in 3'-CF_3-aniline), 8.18 (s, br, 1H, *H*-2' in 3'-CF_3-aniline), 8.24 (dd, ^3J = 7.8, ^4J = 1.8, 1H, *H*-6 salicyl), 10.39 (s, 1H (CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 32.04 (NCH$_2$*C*H$_2$-piperidine), 32.29 (NCH$_2$*C*H$_2$-piperidine), 37.69 (piperidine-4-*C*H-CH$_2$C$_6$H$_5$), 43.08 (CH(*C*H$_2$)-phenyl), 52.47 (N*C*H$_2$-piperidine), 55.65 (N*C*H$_2$-piperidine), 59.85 (N*C*H$_2$CH(OH)), 65.10 (*C*H(OH), 71.26 (O*C*H$_2$CH(OH)), 112.70 (*C*-3 salicyl), 117.20 (q, $^3J_{CF}$ = 3.9, *C*-2' in 3'-CF_3-aniline), 120.28 (q, $^3J_{CF}$ = 3.7, *C*-4' in 3'-CF_3-aniline), 121.94 (*C*-5 salicyl), 122.01 (C_q-1 salicyl), 123.40 (*C*-6' in 3'-CF_3-aniline), 124.22 (q, $^1J_{CF}$ = -272, 3'-*C*F$_3$-aniline), 125.98 (*C*-4'' phenyl), 128.30 (*C*-2'',6'' phenyl), 129.16 (*C*-3'',5'' phenyl), 129.39 (*C*-5' in 3'-CF_3-aniline), 131.15 (q, $^2J_{CF}$ = 32.6, *C*-3' in 3'-CF_3-aniline), 132.51 (*C*-6 salicyl), 133.44 (*C*-4 salicyl),139.58 (*C*-1' in 3'-CF_3-aniline), 140.46 (C_q-1'' phenyl), 156.64 (C_q-2 salicyl), 163.76 (*C*ONH-3'-CF_3-aniline).

HRMS: $[M+H]^+$: calculated.: 513.2359 found: 513.2365.

2-(3-(4-benzylpiperidin-1-yl)-2-hydroxypropoxy)-*N*-(2-fluorophenyl)benzamide (188)



188 was prepared following **general procedure E**, yielding 0.151 g (94%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.22-1.36 (2H) (m, 2H, H in 3,5-C*H*$_2$ piperidine), 1.48-1.59 (1H), (m, 1H, C*H*(CH$_2$)-phenyl), 1.59-1.69 (2H), (m[t], 2H, H in 3,5-C*H*$_2$ piperidine), 1.93 (1H), (ddd, ^2J = -11.7, $^3J_{aa}$ = 11.7, $^3J_{ae}$ = 2.3, 1H, H in 2,6-C*H*$_2$ piperidine), 2.23 (1H), (ddd, ^2J = -11.6, $^3J_{aa}$ = 11.7, $^3J_{ae}$ = 2.3, 1H, H in 2,6-C*H*$_2$ piperidine), 2.47-2.57 (4H), (m, 4H, CH(C*H*$_2$)-

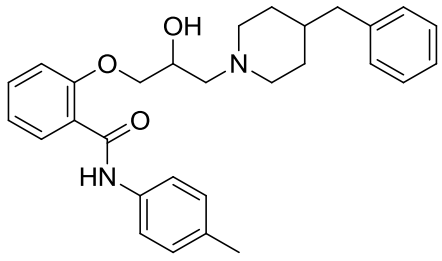
phenyl, NCH_aH_bCH(OH)), 2.69-2.76 (1H), (m[d], br, 1H, H in 2,6-CH_2 piperidine), 2.96-3.03 (1H), (m[d], 1H, H in 2,6-CH_2 piperidine), 4.16-4.26 (3H), (m, 3H, CH(OH), OCH_aH_bCH(OH)), 7.02-7.22 (8H), (m, 8H, *H*-2'',6'' phenyl, *H*-3,5 salicyl, 3',4',5' aniline, 4'' phenyl), 7.24-7.32 (2H), (m, 2H, *H*-3'',5'' phenyl), 7.48 (1H), (ddd, $^3J_1$ = 7.4, $^3J_2$ = 8.3, ^4J = 1.8, 1H, *H*-4 salicyl), 8.28 (1H), (dd, ^3J = 7.8, ^4J = 1.8, 1H, *H*-6 salicyl), 8.51 (1H), (ddd, ^3J = 8.0, $^4J_{HF}$ = 7.5, ^4J = 1.7, 1H, *H*-6 in 2'-F-aniline), 10.09 (1H) (s, 1H (CON*H*).

$^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 32.30 (NCH$_2$*C*H$_2$-piperidine), 32.60 (NCH$_2$*C*H$_2$-piperidine), 37.88 (piperidine-4-*C*H-CH$_2$C$_6$H$_5$), 43.26 (CH(*C*H$_2$)-phenyl), 52.52 (N*C*H$_2$-piperidine), 55.64 (N*C*H$_2$-piperidine), 60.66 (N*C*H$_2$CH(OH)), 65.13 (*C*H(OH), doublet), 72.22 (O*C*H$_2$CH(OH)), 112.98 (*C*-3 salicyl), 114.87 (d, $^2J_{CF}$ = 19.3, *C*-3' in 2'-F-aniline), 121.95 (*C*-5 salicyl), 122.04 (C_q-1 salicyl), 122.89 (br, *C*-6' in 2'-F-aniline), 124.29 (d, $^3J_{CF}$ = 7.7, *C*-4' in 2'-F-aniline), 124.71 (d, $^4J_{CF}$ = 3.5, *C*-5' in 2'-F-aniline), 126.01 (*C*-4'' phenyl), 127.12 (d, $^2J_{CF}$ = 10.1, C_q-1' in 2'-F-aniline), 128.35 (*C*-2'',6'' phenyl), 129.24 (*C*-3'',5'' phenyl), 132.75 (*C*-6 salicyl), 133.55 (*C*-4 salicyl), 140.66 (C_q-1'' phenyl), 153.14 (d, $^1J_{CF}$ = -243.4, C_q-2' in 2'-F-aniline), 156.95 (C_q-2 salicyl), 163.58 (*C*ONH-2'-F-aniline).

HRMS: $[M+H]^+$: calculated.: 463.2404 found: 463.2397.

Melting point: 120-126°C.

2-(3-(4-benzylpiperidin-1-yl)-2-hydroxypropoxy)-*N*-(p-tolyl)benzamide (189)



189 was prepared following **general procedure E**, yielding 0.136 g (80%) of the desired product.

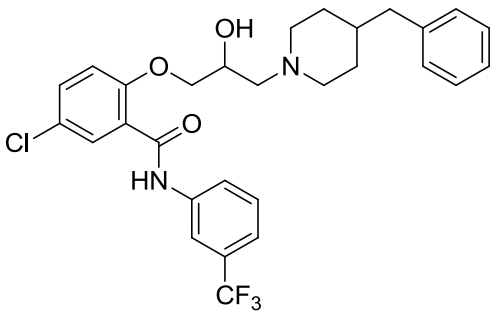
^1H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.25-1.37 (m, 2H, H in 3,5-CH_2 piperidine), 1.49-1.70 (m, 3H, CH(CH$_2$)-phenyl, 2H in 3,5-CH_2 piperidine), 1.96 (ddd, ^2J = -11.7, $^3J_{aa}$ = 11.6, $^3J_{ae}$ = 2.2, 1H, H in 2,6-CH_2 piperidine), 2.24 (ddd, ^2J = -11.6, $^3J_{aa}$ = 11.6, $^3J_{ae}$ = 2.2, 1H, H in 2,6-CH_2 piperidine), 2.33 (s, 3H, 4-CH_3C$_6$H$_4$NHCO), 2.43 (dd, ^2J = -12.4, ^3J = 3.5, 1H, NCH_aH$_b$CH(OH)), 2.55 (d, 2H, ^3J = 7.0, CH(CH_2)-phenyl), 2.62 (1H), (dd, ^2J = -12.4, ^3J = 10.5, 1H, NCH$_a$$H_b$CH(OH)), 2.66-2.72 (m[d], br, 1H, H in 2,6-CH_2 piperidine), 2.96-3.04 (m[d], br, 1H, H in 2,6-CH_2

piperidine), 4.03 (dd, ^{2}J = -9.5, ^{3}J = 5.1, 1H, OCH_aH$_b$CH(OH)), 4.14-4.22 (m, 1H, C*H*(OH)), 4.28 (dd, ^{2}J = -9.5, ^{3}J = 3.1, 1H, OCH$_a$$H_b$CH(OH)), 6.95 (dd, ^{3}J = 8.2, 1H, *H*-3 salicyl), 7.08-7.17 (m, 5H, *H*-3',5' toluidine, *H*-2'',6'' phenyl, *H*-5 salicyl), 7.18 -7.23 (m, 1H, *H*-4'' phenyl), 7.27-7.32 (m, 2H, *H*-3'',5'' phenyl), 7.43 (ddd, $^{3}J_1$ = 7.6, $^{3}J_2$ = 8.4, ^{4}J = 1.8, 1H, *H*-4 salicyl), 7.64-7.70 (*H*-2',6' toluidine), 8.24 (dd, ^{3}J = 7.8, ^{4}J = 1.7, 1H, *H*-6 salicyl), 10.00 (s, 1H (CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 21.03 (4-*C*H$_3$ in toluidine), 32.09 (NCH$_2$*C*H$_2$-piperidine), 32.39 (NCH$_2$*C*H$_2$-piperidine), 37.74 (piperidine-4-*C*H-CH$_2$C$_6$H$_5$), 43.15 (piperidine-4-CH(*C*H$_2$)-phenyl), 52.53 (N*C*H$_2$-piperidine), 55.69 (N*C*H$_2$-piperidine), 60.12 (N*C*H$_2$CH(OH)), 65.14 (*C*H(OH), 70.96 (O*C*H$_2$CH(OH)), 112.61 (*C*-3 salicyl), 120.51 (*C*-2',6' toluidine), 121.90 (*C*-5 salicyl), 122.79 (*C*$_q$-1 salicyl), 126.06 (*C*-4'' phenyl), 128.36 (*C*-3'',5'' phenyl), 129.21 (*C*-2'',6'' phenyl), 129.45 (*C*-3',5' toluidine), 132.59 (*C*-6 salicyl), 132.98 (*C*-4 salicyl), 133.49 (*C*$_q$-4' toluidine), 136.44 (*C*$_q$-1' toluidine), 140.49 (*C*$_q$-1'' phenyl), 156.58 (*C*$_q$-2 salicyl), 163.37 (*C*ONH-toluidine).

HRMS: $[M+H]^+$: calculated.: 459.2641 found: 459.2647.

2-(3-(4-benzylpiperidin-1-yl)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (190)



190 was prepared following **general procedure E**, yielding 0.074 g (49%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.24-1.37 (m, 2H, H in 3,5-C*H*$_2$ piperidine), 1.49-1.72 (m, 3H, C*H*(CH$_2$)-phenyl),H in 3,5-C*H*$_2$ piperidine), 1.97 (ddd, ^{2}J = -11.6, $^{3}J_{aa}$ = 11.6, $^{3}J_{ae}$ = 2.4, 1H, H in 2,6-C*H*$_2$ piperidine), 2.29 (ddd, ^{2}J = -11.7, $^{3}J_{aa}$ = 11.6, $^{3}J_{ae}$ = 2.2, 1H, H in 2,6-C*H*$_2$ piperidine), 2.43 (dd, ^{2}J = -12.4, ^{3}J = 3.6, 1H, NCH_aH$_b$CH(OH)), 2.52-2.60 (m, 3H, CH(C*H*$_2$)-phenyl), NCH$_a$$H_b$CH(OH)), 2.70 (m[d], br, 1H, H in 2,6-C*H*$_2$ piperidine), 3.01 (m[d], br, 1H, H in 2,6-C*H*$_2$ piperidine), 4.00 (dd, ^{2}J = -9.3, ^{3}J = 6.0, 1H, OCH_aH$_b$CH(OH)), 4.16-4.24 (m, 1H, C*H*(OH)), 4.29 (dd, ^{2}J = -9.4, ^{3}J = 2.5, 1H, OCH$_a$$H_b$CH(OH)), 6.91 (d, ^{3}J = 8.7,1H, *H*-3 salicyl), 7.12-7.16 (m[d], 2H, H-2''',6''' phenyl), 7.17-7.22 (m, 1H, *H*-4''' phenyl), 7.24-7.32 (m[t], 2H,

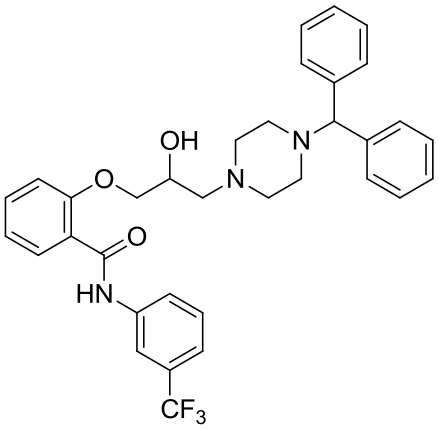
H-3’’’,5’’’ phenyl), 7.37 (d, 1H, *H*-4’’ in 3’’-CF3-aniline), 7.42 (dd, ^{3}J = 8.7, ^{4}J = 2.7, 1H, *H*-4 salicyl), 7.46 (t, 1H, *H*-5’’ in 3’’-CF3-aniline), 8.08 (m[d], 2H, *H*-2’’, *H*-6’’ in 3’’-CF3-aniline), 8.22 (d, ^{3}J = 2.7, 1H, *H*-6 salicyl), 10.28 (s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 32.13 (NCH_2CH_2-piperidine), 32.40 (NCH_2CH_2-piperidine), 37.80 (*C*H-4’’’ piperidine), 43.15 (CH(*C*H_2)-phenyl), 52.49 (NCH_2-piperidine), 55.82 (NCH_2-piperidine), 59.78 (N*C*H_2CH(OH)), 65.03 (*C*H(OH)), 71.80 (O*C*H_2CH(OH)), 114.32 (*C*-3 salicyl), 117.35 (q, $^{4}J_{CF}$ = 3.8, *C*-2’ in 3’-CF_3-aniline), 120.68 (q, $^{4}J_{CF}$ = 3.7, *C*-4’ in 3’-CF_3-aniline), 123.55 (*C*-6’ in 3’-CF_3-aniline), 123.69 (C_q-1 salicyl), 124.21 (q, $^{1}J_{CF}$ = -272.3, 3-*C*F_3-aniline), 126.07 (*C*-4’’’ phenyl), 127.58 (C_q-5 salicyl), 128.39 (*C*-2’’,6’’ phenyl), 129.23 (*C*-3’’,5’’ phenyl), 129.55 (*C*-5’ in 3’-CF_3-aniline), 131.31 (q, $^{2}J_{CF}$ = 31.6, C_q-3’ in 3’-CF_3-aniline), 132.39 (*C*-6 salicyl), 133.06 (*C*-4 salicyl), 139.31 (C_q-1’ in 3’-CF_3-aniline), 140.51 (C_q-1’’ phenyl), 155.19 (C_q-2 salicyl), 162.43 (*C*ONH).

HRMS: $[M+H]^+$: calculated.: 547.1968 found: 547.1975.

Melting point: 101-109°C.

2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (191)



191 was prepared following **general procedure E**, yielding 0.081 g (47%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.34-2.48 (6H), (m, dyn, 6H, NCH_{eq}-2’’,6’’, NCH_2-3’’.5’’ of piperazine), 2.49 (1H), (dd, ^{2}J = -12.2, ^{3}J = 3.4, 1H, NC$H_a$$H_b$CH(OH)), 2.63 (1H), (dd, ^{2}J = -12.2, ^{3}J = 10.8, 1H, $NCH_aH_bCH(OH)$), 2.69-2.79 (2H), (m, dyn, 2H, NCH_{ax}-2’’,6’’ of piperazine), 4.04 (1H), (dd, ^{2}J = -9.4, ^{3}J = 5.7, 1H, OC$H_a$$H_b$CH(OH)), 4.18-4.25 (1H), (m, 1H, C*H*(OH)), 4.26 (1H), (s, 1H, NC*H*(C_6H_5)$_2$), 4.33 (1H), (dd, ^{2}J = -9.5, ^{3}J = 2.7, 1H, $OCH_aH_bCH(OH)$), 6.97 (1H), (d, ^{3}J =

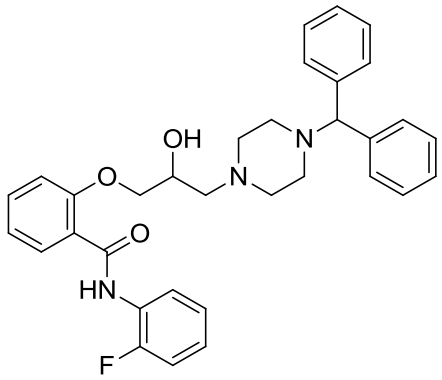
8.2, 1H, *H*-3 salicyl), 7.14 (1H), (ddd[t], $^{3}J_{1}$ = $^{3}J_{2}$ = 7.5, ^{4}J = 0.7, 1H, *H*-5 salicyl), 7.16-7.22 (2H) (m, 2H, 2x C*H*-4 phenyl), 7.24-7.31 (4H), (m, 4H, 2x *H*-3'',5'' phenyl), 7.33(1H), (d, br, 1H, *H*-4' in 3'-CF_3-aniline), 7.39-7.44 (5H), (m, 5H, 2x *H*-2'',6'' phenyl, *H*-5' in 3'-CF_3-aniline), 7.48 (1H), (ddd, $^{3}J_{1}$ = 7.4, $^{3}J_{2}$ = 8.4, ^{4}J = 1.7, 1H, *H*-4 salicyl, 8.06 (1H), (d, br, 1H, *H*-6' in 3'-CF_3-aniline), 8.09 (1H), (s, br, 1H, *H*-2' in 3'-CF_3-aniline), 8.26 (1H), (dd, ^{3}J = 7.8, ^{4}J = 1.7, 1H, *H*-6 salicyl), 10.32 (1H); (s, 1H (CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 51.92 (dyn, *C*H_2-3'',5'' piperazine), 53.58 (br), (dyn, *C*H_2-2'',6'' piperazine), 59.72 (N*C*H_2CH(OH)), 65.05 (*C*H(OH)), 71.15 (O*C*H_2CH(OH)), 76.19 (N*C*H(C_6H_5)$_2$), 112.72 (*C*-3 salicyl), 117.25 (q, $^{3}J_{CF}$ = 4.1, *C*-2' in 3'-CF_3-aniline), 120.40 (q, $^{3}J_{CF}$ = 3.7, *C*-4' in 3'-CF_3-aniline), 122.16 (*C*-5 salicyl), 122.19 (C_q-1 salicyl), 123.43 (*C*-6' in 3'-CF_3-aniline), 127.17 (*C*-4'' phenyl), 128.05 (*C*-2'',6''phenyl), 128.67 (*C*-3'',5''phenyl), 129.47 (*C*-5' in 3'-CF_3-aniline), 132.74 (*C*-6 salicyl), 133.50 (*C*-4 salicyl), 139.57 (*C*-1' in 3'-CF_3-aniline), 142.62 (C_q-1'' phenyl), 142.66 (C_q-1'' phenyl), 156.66 (C_q-2 salicyl), 163.76 (*C*ONH). *C*F_3, *C*-3' in 3'-CF_3-aniline not recorded

HRMS: $[M+H]^+$: calculated.: 590.2634 found: 590.2630.

Melting point: 67-70°C.

2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(2-fluorophenyl)benzamide (192)



192 was prepared following **general procedure E**, yielding 0.164 g (88%) of the desired product as oil.

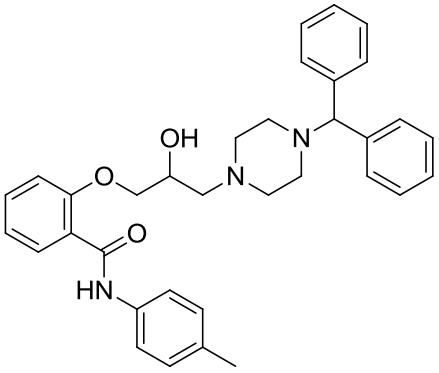
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.34-2.50 (m, dyn, 6H, N*C*H_{ax}-2'',6'', N*C*H_2-3''.5'' of piperazine), 2.54 (dd, ^{2}J = -12.2, ^{3}J = 4.0, 1H, N*C*$H_a$$H_b$CH(OH)), 2.60 (dd, ^{2}J = -12.2, ^{3}J =9.0, 1H, NCH$_a$$H_b$CH(OH)), 2.65-2.78 (m, dyn, 2H, N*C*H_{eq}-2'',6'' of piperazine), 4.17-4.27 (m, 4H, O*C*H_2CH(OH), C*H*(OH), N*C*H(C_6H_5)$_2$), 7.00-7.22 (m, 7H *H*-3,5 salicyl, *H*-3,4,5 aniline, 2x C*H*-4

phenyl), 7.23-7.32 (m, 4H, 2x *H*-3'',5'' phenyl), 7.37-7.43 (m, 4H, 2x *H*-2'',6'' phenyl), 7.48 (m, 1H, *H*-4 salicyl), 8.27 (d, ^{3}J = 7.8, ^{4}J = 1.7, 1H, *H*-6 salicyl), 8.51 (m, 1H, *H*-6 F-aniline), 10.08 (s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 52.06 (*C*H_2-dyn, piperazine), 53.50 (*C*H_2-dyn, piperazine), 60.35 (N*C*H_2CH(OH)), 65.12 (*C*H(OH), doublet), 72.15 (O*C*H_2CH(OH)), 76.31 (N-*C*H(C_6H_5)$_2$), 112.97 (*C*-3 salicyl), 114.87 (d, $^{2}J_{CF}$ = 19.3, *C*-3' in 2'-F-aniline), 121.99 (*C*-5 salicyl), 122.04 (C_q-1 salicyl), 122.87 (br, *C*-6' in 2'-F-aniline), 124.29 (d, $^{3}J_{CF}$ = 7.7, *C*-4' in 2'-F-aniline), 124.72 (d, $^{3}J_{CF}$ = 3.2, *C*-5' in 2'-F-aniline), 127.13 (*C*-4'' phenyl), 128.05 (*C*-2'',6'' phenyl), 128.65 (*C*-3'',5'' phenyl), 132.76 (*C*-6 salicyl), 133.56 (*C*-4 salicyl), 142.73, 142.78, 2x (C_q-1'' phenyl), 153.10 (d, $^{1}J_{CF}$ = -243.4, C_q-2' in 2'-F-aniline), 156.91 (C_q-2 salicyl), 163.56 (*C*ONH). C_q-1 aniline not recorded.

HRMS: $[M+H]^+$: calculated.: 540.2670 found: 540.2662.

2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(p-tolyl)benzamide (193)



193 was prepared following **general procedure E**, yielding 0.193 g (100%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.29 (s, 3H, 4-C*H*$_3$C$_6$H$_4$NHCO), 2.34- 2.53 (m, dyn, 6H, NC*H*$_{ax}$-2'',6'', NC*H*$_2$-3''.5'' of piperazine), 2.46 (dd, ^{2}J = -12.3, ^{3}J = 3.5, 1H, NC*H*$_a$H$_b$CH(OH)), 2.61-2.76 (m, dyn, 2H, NC*H*$_{eq}$-2'',6'' of piperazine), 2.65 (dd, ^{2}J = -12.2, ^{3}J = 10.8, 1H, NCH$_a$*H*$_b$CH(OH)), 4.03 (dd, ^{2}J = -9.5, ^{3}J = 5.1, 1H, OC*H*$_a$H$_b$CH(OH)), 4.12-4.19 (m, 1H, C*H*(OH)), 4.25 (s, 1H, NC*H*(C_6H_5)$_2$), 4.29 (dd, ^{2}J = -9.5, ^{3}J = 3.0, 1H, OCH$_a$*H*$_b$CH(OH)), 6.95 (dd[d], ^{3}J = 8.2, ^{4}J = 0.6, 1H, *H*-3 salicyl), 7.07-7.14 (m, 3H, *H*-5 salicyl, *H*-3'',5'' toluidine), 7.16-7.22 (m, 2H, 2x C*H*-4 phenyl), 7.25-7.31 (m, 4H, 2x *H*-3'',5'' phenyl), 7.38-7.47 (m, 5H, *H*-4 salicyl, 2x *H*-2'',6''

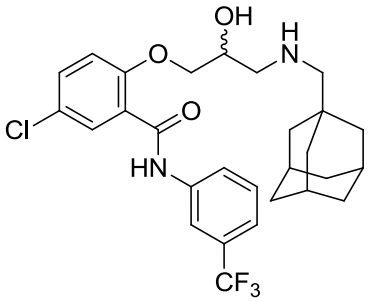
phenyl), 7.62-7.67 (m, 2H, *H*-2'',6'' toluidine), 8.24 (dd, ^{3}J = 7.8, ^{4}J = 1.9, 1H, *H*-6 salicyl), 9.99 (s, 1H (CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 20.85 (4-*C*H_3 in toluidine), 51.86 (dyn, *C*H_2-3'',5'' piperazine), 53.40 (dyn, *C*H_2-2'',6'' piperazine), 59.63 (N*C*H_2CH(OH)), 64.96 (*C*H(OH)), 70.73 (O*C*H_2CH(OH)), 76.09 (N*C*H(C_6H_5)$_2$), 112.46 (*C*-3 salicyl), 120.33 (*C*-2'',6'' toluidine), 121.79 (*C*-5 salicyl), 122.64 (C_q-1 salicyl), 127.01 (*C*-4 phenyl), 127.89 (*C*-2'',6''phenyl), 128.50 (*C*-3'',5''phenyl), 129.30 (*C*-3'',5'' toluidine), 132.48 (*C*-6 salicyl), 132.83 (*C*-4 salicyl), 133.33 (C_q-4' toluidine), 136.26 (C_q-1 toluidine), 142.46 (C_q-1'' phenyl[1]), 142.52 (C_q-1'' pheny[2]l), 156.42 (C_q-2 salicyl), 163.18 (*C*ONH).

HRMS: $[M+H]^+$: calculated.: 536.2923 found: 536.2913.

Melting point: 125-138°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (194)



194 was prepared following **general procedure E**, yielding 0.599 g (41%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.49-1.53 (s, br, 6H, CH_2-adamantane), 1.60-1.67 (m, 3H, CH_2-adamantane), 1.67-1.77 (m, 3H, CH_2-adamantane), 1.98 (s, br, 3H, C*H*-adamantane), 2.24, 2.27,2.31,2.33 (AB, J_{AB} = -11.6, 2H, NHCH_2-1-adamantane), 2.73 (dd, ^{2}J = -12.2, ^{3}J = 9.8, 1H, CH(OH)C$H_a$$H_b$NH), 2.84 (dd, ^{2}J = -12.2, ^{3}J = 3.7, 1H, CH(OH)C$H_a$$H_b$NH), 4.01 (dd, ^{2}J = -9.2, ^{3}J = 6.7, 1H, OC$H_a$$H_b$CH(OH)), 4.09-4.16 (m, 1H, C*H*(OH)), 4.28 (dd, ^{2}J = -9.2, ^{3}J = 2.3, 1H, OC$H_a$$H_b$CH(OH)), 6.92 (dd, ^{3}J = 8.7, ^{4}J = 1.7, 1H, *H*-3 salicyl), 7.33-7.47 (m, 3H, *H*-4 salicyl, *H*-4'', *H*-5'' in 3''-CF3-aniline), 8.07 (d, br, 1H, *H*-6'' in 3''-CF3-aniline), 8.11 (s, br, 1H, *H*-2''in 3''-CF3-aniline), 8.22 (d, ^{3}J = 2.7,1H, *H*-6 salicyl), 10.33 (s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.49 (*C*H-adamantane), 33.57 33.09 (C_q-1'' adamantane), 37.25 (*C*H_2-adamantane), 40.80 (*C*H_2-adamantane), 51.46 (N*C*H_2CH(OH)), 62.20

(NH*C*H_2-1''-adamantane), 66.86 (*C*H(OH)), 71.84 (O*C*H_2CH(OH)), 114.36 (*C*-3 salicyl), 117.40 (q, $^4J_{CF}$ = 4.0, *C*-2' in 3'-CF_3-aniline), 120.66 (q, $^4J_{CF}$ = 3.8, *C*-4' in 3'-CF_3-aniline), 123.62 (*C*-6' in 3'-CF_3-aniline), 123.58 (C_q-1 salicyl), 124.17 (q, $^1J_{CF}$ = -272.0, 3'-*C*F_3-aniline), 127.54 (C_q-5 salicyl), 129.50 (*C*-5' in 3'-CF_3-aniline), 131.32 (q, $^2J_{CF}$ = 31.6, C_q-3' in 3'-CF_3-aniline), 132.39 (*C*-6 salicyl), 133.04 (*C*-4 salicyl), 139.35 (C_q-1' in 3'-CF_3-aniline), 155.25 (C_q-2 salicyl), 162.44 (*C*ONH).

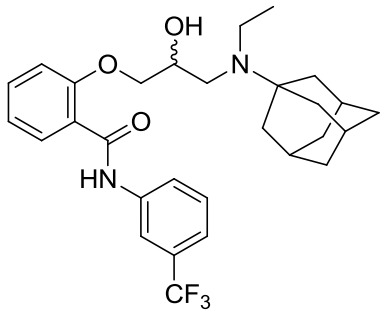
^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 1.37-1.42 (s, br, 6H, CH_2-adamantane), 1.52-1.58 (m, 3H, CH_2-adamantane), 1.61-1.68 (m, 3H, CH_2-adamantane), 1.87 (s, br, 3H, C*H*-adamantane), 2.08 (s, 2H, NHCH_2-1-adamantane), 2.56-2.67 (m, 2H, CH(OH)CH_2NH), 3.91-3.99 (m, 1H, C*H*(OH)), 4.12-4.23 (m, 1H, OCH_2CH(OH)), 5.25 (br, 1H, CH(O*H*)), 7.28 (d, ^3J = 9.0, 1H, *H*-3 salicyl), 7.46 (br d, ^3J = 7.8, 1H, *H*-4 aniline), 7.56-7.62 (m, 2H, *H*-4 salicyl, *H*-5 aniline), 7.78 (d, ^3J = 2.8, 1H, *H*-6 salicyl), 7.96 (br d, ^3J = 8.3, 1H, *H*-6 aniline), 8.28 (br s, 1H, *H*-2 aniline), 10.59 (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 27.81 (*C*H-adamantane), 33.24 (C_q-1'' adamantane), 36.75 (*C*H_2-adamantane), 40.27 (*C*H_2-adamantane), 53.36 (N*C*H_2CH(OH)), 62.40 (NH*C*H_2-1''-adamantane), 67.92 (*C*H(OH)), 71.99 (O*C*H_2CH(OH)), 115.74 (*C*-3 salicyl), 115.87 (q, $^4J_{CF}$ = 4.2, *C*-2 aniline), 120.13 (q, $^4J_{CF}$ = 4.0, *C*-4 aniline), 123.33 (*C*-6' in 3'-CF_3-aniline), 124.12 (q, $^1J_{CF}$ = -272.3, 3'-*C*F_3-aniline), 124.81 (C_q-1 salicyl), 125.03 (C_q-5 salicyl), 129.54 (q, $^2J_{CF}$ = 31.3, C_q-3 aniline), 129.63 (*C*-6 aniline), 129.97 (*C*-5 aniline), 132.35 (*C*-4 salicyl), 139.43 (C_q-1 aniline), 155.15 (C_q-2 salicyl), 162.90 (*C*ONH).

HRMS: $[M+H]^+$: calculated.: 537.2124 found: 537.2132.

Melting point: 110-120°C.

2-(3-(adamantan-1-yl(ethyl)amino)-2-hydroxypropoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (195)



195 was prepared following **general procedure E**, yielding 0.174 g (73%) of the desired product.

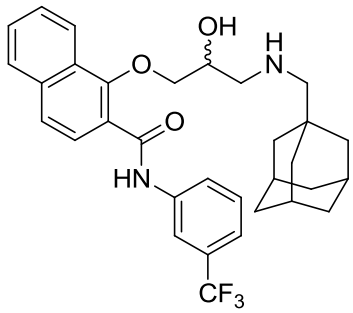
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.07 (3H), 1.49-1.75 (12H), 1.99 (br, 3H), 2.50-2.61 (1H), 2.63 (1H), 2.75 (1H), 2.79-2.89 (1H), 3.99-4.07 (2H), 4.31 (1H), 7.00 (1H), 7.14 (1H), 7.33 (1H), 7.44 (1H), 7.48 (1H), 8.10 (1H), 8.16 (1H) 8.26 (1H), 10.43 (1H).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 17.13 ($NCH_2\mathit{C}H_3$), 29.64 (*C*H-adamantane), 36.64 ($\mathit{C}H_2$-adamantane), 40.20 ($\mathit{C}H_2$-adamantane), 42.95 ($N\mathit{C}H_2CH_3$), 49.52 ($CH(OH)\mathit{C}H_2NH$), 55.64 (C_q-1 adamantane), 66.05 ($CH_2\mathit{C}H(OH)CH_2$), 71.74 (salicyl-$O\mathit{C}H_2CH(OH)CH_2$), 112.78 (*C*-3 salicyl), 117.60 (q, $^{3}J_{CF}$ = 3.9, *C*-2' in 3'-CF_3-aniline), 120.30 (q, $^{3}J_{CF}$ = 3.9, *C*-4' in 3'-CF_3-aniline), 122.04 (*C*-5 salicyl), 122.28 (C_q-1 salicyl), 123.73 (*C*-6' in 3'-CF_3-aniline), 129.39 (*C*-5' in 3'-CF_3-aniline), 132.69 (*C*-6 salicyl), 133.43 (*C*-4 salicyl), 139.68 (C_q-1' in 3'-CF_3-aniline), 156.87 (C_q-2 salicyl), 163.84 (*C*ONH). $\mathit{C}F_3$, *C*-3' in 3'-CF_3-aniline not recorded

HRMS: $[M+H]^+$: calculated.: 517.2682 found: 517.2678.

Melting point: 90-92°C.

1-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(3-(trifluoromethyl)phenyl)-2-naphthamide (196)



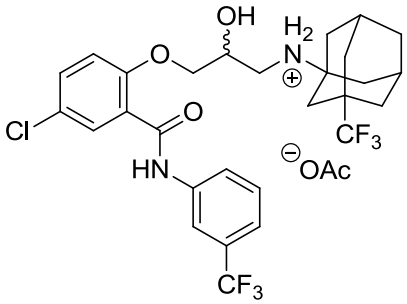
196 was prepared following **general procedure E**, yielding 0.078 g (11%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 1.33-1.40 (m, br, 6H, CH in $C\mathit{H}_2$-adamantane), 1.51-1.57 (m, br, 3H, CH in $C\mathit{H}_2$-adamantane), 1.60-1.68 (m, br, 3H, CH in $C\mathit{H}_2$-adamantane), 1.86 (s, br, 3H, C*H*-adamantane), 2.04 (br s, 2H, $NHC\mathit{H}_2$-1-adamantane), 2.60 (dd, ^{2}J = -12.0, ^{3}J = 6.6, 1H, $C\mathit{H}(OH)C\mathit{H}_aH_bNH$), 2.67 (dd, ^{2}J = -12.0, ^{3}J = 5.4, 1H, $C\mathit{H}(OH)CH_a\mathit{H}_bNH$), 3.95-4.02 (m, 1H, C*H*(OH)), 4.02-4.13 (m, 2H, $OC\mathit{H}_2CH(OH)$), 5.16 (br s, 1H, CH(O*H*)) 7.46 (d, br, ^{3}J = 7.6, 1H, *H*-4' in 3'-CF_3-aniline), 7.57-7.69 (m, 3H), 7.74-7.83 (m [q], 2H), 7.98-8.05 (m, 2H), 8.33 (br s, 1H, *H*-2' in 3'-CF_3-aniline), 8.38 (dd, ^{3}J = 7.5, ^{4}J = 1.6, 1H, *H*-6 salicyl), 10.75 (s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, DMSO-d_6, 23 °C): δ = 27.79 (*C*H-adamantane), 33.13 (C_q-1 adamantane), 36.73 (CH_2-adamantane), 40.24 (*C*H_2-adamantane), 53.38 (N*C*H_2CH(OH)), 62.36 (NH*C*H_2-1-adamantanyl), 68.62 (*C*H(OH)), 78.60 (O*C*H_2CH(OH)), 116.01 (q, $^{3}J_{CF}$ = 3.8, *C*-4' in 3'-CF3-aniline), 119.94 (q, $^{3}J_{CF}$ = 3.8, *C*-2' in 3'-CF3-aniline), 123.04 (*C*-6 salicyl), 123.49 (*C*-6' in 3'-CF3-aniline), 123.81, 124.00 (C_q-1 salicyl), 124.12 (q, $^{1}J_{CF}$ = -273.2, *C*F_3 in 3'-CF_3-aniline), 125.77, 126.69, 127.33 (C_q-3 salicyl), 127.90, 127.97, 129.43 (q, $^{2}J_{CF}$ = 31.6, *C*-3' in 3'-CF_3-aniline),129.82, 135.54 (*C*q-4 salicyl), 139.78 (C_q-1' in 3'-CF_3-aniline), 153.13 (C_q-2 salicyl), 165.08 (*C*ONH).

HRMS: $[M+H]^+$: calculated.: 553.2682 found: 553.2678.

5-chloro-2-(2-hydroxy-3-((3-(trifluoromethyl)adamantan-1-yl)amino)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide acetate (197)



197 was prepared following **general procedure E** and subsequent reaction with acetic acid, yielding 0.090 g (58%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.53-1.76 (m, 12H, C*H*$_2$-adamantane), 1.99 (s, 3H, C*H*$_3$-acetate), 2.20 (br s, 2H, C*H*-adamantane), 2.91 (dd, ^{2}J = -11.8, ^{3}J = 9.3, 1H, CH(OH)C*H*$_a$H$_b$NH), 2.97 (dd, ^{2}J = -11.8, ^{3}J = 2.6, 1H, CH(OH)CH$_a$*H*$_b$NH), 4.09 (dd, ^{2}J = -9.5, ^{3}J = 5.0, 1H, OC*H*$_a$H$_b$CH(OH)), 4.23 (dd, ^{2}J = -9.5, ^{3}J = 2.5, 1H, OCH$_a$*H*$_b$CH(OH)), 4.26-4.33 (m, 1H, C*H*(OH)), 6.87 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.35 (d, ^{3}J = 7.6, 1H, *H*-4 aniline), 7.40 (ddd, ^{3}J = 8.8, ^{4}J = 2.6, ^{5}J = 0.9, 1H, *H*-4 salicyl), 7.44 (dd [t], ^{3}J = 7.9, 1H, *H*-5 aniline), 7.94 (d, ^{3}J = 8.0, 1H, *H*-6 aniline), 8.14 (dd, ^{4}J = 2.6, ^{5}J = 0.9, 1H, *H*-6 salicyl), 8.15 (s, br, 1H, *H*-2 aniline), 10.10 (s, 1H, CON*H*).

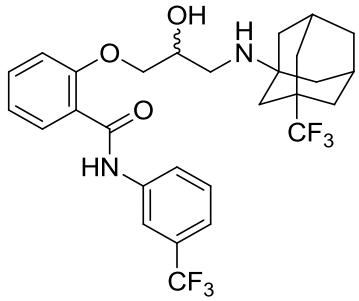
$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 22.81 (*C*H_3-acetate), 28.20 (2x *C*H-adamantane), 33.54 (2x *C*H_2-adamantane), 34.77 (*C*H_2-adamantane), 37.95 (*C*H_2-adamantane), 39.29 (*C*H_2-adamantane), 39.54 (*C*H_2-adamantane), 41.02 (q, $^{2}J_{CF}$ = 26.1, C_q-3 adamantane), 42.95 (N*C*H_2CH(OH)), 53.89 (C_q-1 adamantane), 66.67 (*C*H(OH)), 71.38 (O*C*H_2CH(OH)), 114.27 (*C*-3 salicyl), 117.38 (q, $^{3}J_{CF}$ = 3.9, *C*-2' in 3'-CF_3-aniline), 120.81 (q, $^{3}J_{CF}$ = 3.7, *C*-4' in 3'-CF_3-aniline),

123.71 (*C*-6' in 3'-CF_3-aniline), 123.94 (C_q-1 salicyl), 124.15 (q, $^1J_{CF}$ = -272.0, 3-*C*F_3-aniline), 127.58 (q, $^1J_{CF}$ = -272.3, 3-*C*F_3-adamantane), 127.72 (C_q-5 salicyl), 129.57 (*C*-5' in 3'-CF_3-aniline), 131.34 (q, $^2J_{CF}$ = 32.3, *C*-3' in 3'-CF_3-aniline), 132.24 (*C*-6 salicyl), 133.07 (*C*-4 salicyl), 139.17 (C_q-1' in 3'-CF_3-aniline), 154.85 (C_q-2 salicyl), 162.63 (*C*ONH) 177.95 (*C*OO^-).

HRMS: $[M+H]^+$: calculated.: 591.1840 found: 591.1849.

Melting point: 139°C.

2-(2-hydroxy-3-((3-(trifluoromethyl)adamantan-1-yl)amino)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (198)



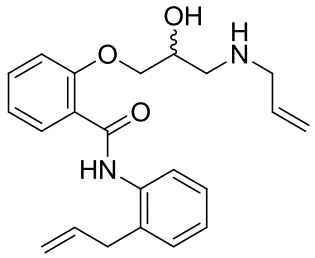
198 was prepared following **general procedure E**, yielding 0.261 g (80%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.50-1.89 (m, 12H, CH_2-adamantane), 2.20 (br s, 2H, C*H*-adamantane), 2.97-3.18 (br s. 2H, CH(OH)CH_2NH), 4.14-4.20 (m [br d], 1H, OC$H_a$$H_b$CH(OH)), 4.21-4.29 (m [br d], 1H, OC$H_a$$H_b$CH(OH)), 4.41-4.57 (m, 1H, C*H*(OH)), 6.92 (d, ^3J = 8.3, 1H, *H*-3 salicyl), 7.14 (dd [t], ^3J = 7.5, 1H, *H*-5 salicyl), 7.33 (d, ^3J = 7.6, 1H, *H*-4 aniline), 7.43 (dd [t], ^3J = 7.6, 1H, *H*-5 aniline), 7.45-7.50 (m, 1H, *H*-4 salicyl), 7.89 (d, ^3J = 7.9, 1H, *H*-6 aniline), 8.14 (dd, ^3J = 7.8, ^4J = 1.8, 1H, *H*-6 salicyl), 8.25 (s, br, 1H, *H*-2 aniline), 10.02 (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.03 (2x *C*H-adamantane), 33.27 (2x *C*H_2-adamantane), 34.41 (*C*H_2-adamantane), 36.64 (br, *C*H_2-adamantane), 37.79 (br, *C*H_2-adamantane), 38.10 (br, *C*H_2-adamantane), 41.01 (q, $^2J_{CF}$ = 27.1, C_q-3 adamantane), 43.44 (N*C*H_2CH(OH)), 56.04 (C_q-1 adamantane), 65.74 (*C*H(OH)), 70.73 (O*C*H_2CH(OH)), 112.68 (*C*-3 salicyl), 117.31 (q, $^3J_{CF}$ = 3.9, *C*-2' in 3'-CF_3-aniline), 120.62 (q, $^3J_{CF}$ = 3.7, *C*-4' in 3'-CF_3-aniline), 122.36 (*C*-5 salicyl), 122.60 (C_q-1 salicyl), 123.65 (*C*-6' in 3'-CF_3-aniline), 124.18 (q, $^1J_{CF}$ = -272.5, *C*F_3 aniline), 127.32 (q, $^1J_{CF}$ = -280.1, *C*F_3 adamantane), 129.55 (*C*-5' in 3'-CF_3-aniline), 131.34 (q, $^2J_{CF}$ = 32.3, *C*-3' in 3'-CF_3-aniline), 132.44 (*C*-6 salicyl), 133.55 (*C*-4 salicyl), 139.35 (C_q-1' in 3'-CF_3-aniline), 156.13 (C_q-2 salicyl), 164.16 (*C*ONH).

HRMS: $[M+H]^+$: calculated.: 557.2223 found: 557.2239.

2-(3-(allylamino)-2-hydroxypropoxy)-*N*-(2-allylphenyl)benzamide (203)



203 was prepared following **general procedure E**, yielding 0.080 g (67%) of the desired product.

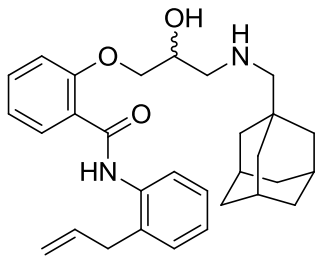
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.39-2.64 (2H, br), (br, 2H, O*H*, N*H*), 2.69 (1H), (dd, ^2J = -12.1, ^3J = 9.2, 1H, CH(OH)CH_aH$_b$NH), 2.85 (1H), (dd, ^2J = -12.1, ^3J = 3.8, 1H, CH(OH)CH$_a$$H_b$NH), 3.16-3.29 (2H), (m, 1H, CH_2=CHCH_2-NH-CH(OH)), 3.47 (2H), (m, 1H, *C*H_2=CHCH_2-2'-aniline), 4.04-4.12 (1H), (m, 1H, C*H*(OH)), 4.14 (1H), (dd, ^2J = -9.8, ^3J = 6.4, 1H, OCH_aH$_b$CH(OH)), 4.26 (1H), (dd, ^2J = -9.8, ^3J = 3.4, 1H, OCH$_a$$H_b$CH(OH)), 4.98-5.18 (4H), (m, 4H, CH_2=CHCH$_2$-NH-CH(OH), CH_2=CHCH$_2$-2'-aniline), 5.74-5.87 (1H), (m, 1H, CH_2=C*H*CH$_2$-NH-CH(OH)), 5.93-6.05 (1H), (m, 1H, CH_2=C*H*CH$_2$-2'-aniline), 7.04 (1H), (d, ^3J = 8.3, 1H, *H*-3 salicyl), 7.12 (1H), (dd[t], ^3J = ^3J = 7.5, 1H, *H*-5 salicyl,), 7.17 (1H), (m, *H*-4 aniline), 7.21-7.30 (2H), (m, *H*-3 aniline, *H*-5 aniline), 7.46 (1H), (ddd, $^3J_1$ = 8.4, $^3J_2$ = 7.6, $^4J_2$ = 1.2, 1H, *H*-4 salicyl,), 7.80 (1H), (d, ^3J = 7.8, 1H, *H*-6 aniline), 8.18 (1H), (dd, ^2J = 7.8, ^3J = 1.0, 1H, *H*-6 salicyl), 9.42 (1H); (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 36.06 (CH_2=CH*C*H$_2$-2'-aniline), 50.84 (N*C*H$_2$CH(OH)), 52.11(CH_2=CH*C*H$_2$-NH-CH(OH)), 67.77 (*C*H(OH)), 72.10 (O*C*H$_2$CH(OH)), 113.38 (*C*-3 salicyl), 116.54 (*C*H_2=CHCH$_2$-2'-aniline), 116.81 (*C*H_2=CHCH$_2$-NH-CH(OH)), 122.01 (*C*-5 salicyl), 123.05 (C_q-1 salicyl), 125.56 (*C*-6' aniline), 125.89 (*C*-4' aniline), 127.12 (*C*-5' aniline), 129.84 (*C*-3' aniline), 132.44 (*C*-6 salicyl), 132.93 (C_q-2' aniline), 133.07 (*C*-4 salicyl), 136.05 (C_q-1' aniline), 136.09 (CH_2=*C*HCH$_2$-NH-CH(OH)), 136.39 (CH_2=C*H*CH$_2$-2'-aniline), 156.87 (C_q-2 salicyl), 164.25 (*C*ONH-2'-allyl-aniline).

HRMS: $[M+H]^+$: calculated.: 367.2018 found: 367.2021.

Melting point: 98-99°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(2-allylphenyl)benzamide (204)



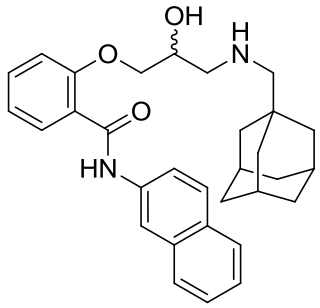
204 was prepared following **general procedure E**, yielding 0.083 g (53%) of the desired semi-crystalline product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.40-1.48 (s, br, 6H, CH_2-adamantane), 1.54-1.62 (m, 3H, CH_2-adamantane), 1.65-1.73 (m, 3H, CH_2-adamantane), 1.89-1.98 (s, br, 3H, C*H*-adamantane), 2.20, 2.23, 2.40, 2.43, (AB, J_{AB} = -11.9, 2H, NHCH_2-1-adamantane)), 2.76-2.88 (dd, ^{2}J = -12.0, ^{3}J = 9.5, 1H, CH(OH)CH_aH$_b$NH), 2.92-3.02 (dd, ^{2}J = -12.0, ^{3}J = 1.8, 1H, CH(OH)CH$_a$$H_b$NH), 3.40-3.52 (CH$_2$=CHC$H_2$-2'-aniline), 4.16 (dd, ^{2}J = -9.7, ^{3}J = 4.8, 1H, OCH_aH$_b$CH(OH)), 4.22 (dd, ^{2}J = -9.2, ^{3}J = 5.0, 1H, OCH$_a$$H_b$CH(OH)), 4.24-4.30 (m, 1H, C*H*(OH)), 4.99-5.10 (CH_2=CHCH$_2$-2'-aniline), 5.90-6.03 (CH$_2$=C*H*CH$_2$-2'-aniline), 7.02 (dd, ^{3}J = 7.8, ^{4}J = 1.7, 1H, *H*-6 salicyl), 7.12 (dd[t], ^{3}J = ^{3}J = 7.5, 1H, *H*-5 salicyl), 7.09-7.19 (m, *H*-4 aniline), 7.21-7.29 (m, *H*-3 aniline, *H*-5 aniline), 7.46 (ddd, br, $^{3}J_1$ = 8.2, $^{3}J_2$ = 7.5, $^{4}J_2$ = 1.5, 1H, *H*-4 salicyl), 7.78 (d, ^{3}J = 7.8, 1H, *H*-6 aniline), 8.15 (dd, ^{2}J = 7.7, ^{3}J = 1.5, 1H, *H*-6 salicyl), 9.37 (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.20 (*C*H-adamantane), 33.09 (C_q-1'' adamantane), 36.11 (CH$_2$=CH*C*H$_2$-2'-aniline), 36.83 (*C*H$_2$-adamantane), 40.22 (*C*H$_2$-adamantane), 52.45 (N*C*H$_2$CH(OH)), 61.67 (NH*C*H$_2$-1''-adamantane), 66.02 (*C*H(OH)), 71.56 (O*C*H$_2$CH(OH)), 113.34 (*C*-3 salicyl), 116.61 (*C*H$_2$=CHCH$_2$-2'-aniline), 122.09 (*C*-5 salicyl), 123.17 (C_q-1 salicyl), 125.49 (*C*-6' aniline), 125.93 (*C*-4' aniline), 127.11 (*C*-5' aniline), 129.89 (*C*-3' aniline), 132.37 (*C*-6 salicyl), 133.06 (*C*-4 salicyl), 133.09 (*C*-4 salicyl), 136.00 (C_q-1' aniline), 136.32 (CH$_2$=C*H*CH$_2$-2'-aniline), 156.68 (C_q-2 salicyl), 164.30 (*C*ONH).

HRMS: $[M+H]^+$: calculated.: 475.2961 found: 475.2960.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(naphthalen-2-yl)benzamide (205)



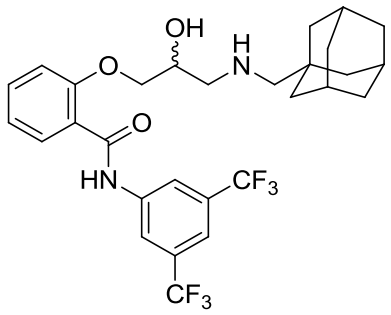
205 was prepared following **general procedure E**, yielding 0.076 g (50%) of the desired semi-crystalline product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.45-1.50 (6H), (s, br, 6H, C*H*$_2$-adamantane), 1.55-1.63 (3H), (m, 3H, C*H*$_2$-adamantane), 1.66-1.74 (3H), (m, 3H, C*H*$_2$-adamantane), 1.91-1.97 (3H), (s, br, 3H, C*H*-adamantane), 2.19-2.34 (2H), 2.19, 2.22, 2.31, 2.34 (AB, J_{AB} = -11.6, 2H, NHC*H*$_2$-1-adamantane)), 2.79 (1H), (dd, ^{2}J = -12.2, ^{3}J = 9.0, 1H, CH(OH)CH_aH$_b$NH), 2.86 (1H), (dd, ^{2}J = -12.2, ^{3}J = 3.6, 1H, CH(OH)CH$_a$$H_b$NH), 3.57-3.98 (br, 2H, O*H*, N*H*), 4.04 (1H), (dd, ^{2}J = -9.2, ^{3}J = 5.6, 1H, OCH_aH$_b$CH(OH)), 4.18-4.28 (2H), (m, 2H, C*H*(OH), OCH$_a$$H_b$CH(OH)), 6.93 (1H), (d, ^{3}J = 8.2, 1H, *H*-3 salicyl), 7.12 (1H), (dd[t], $^{3}J_1$ = $^{3}J_2$ = 7.8, 1H, *H*-5 salicyl), 7.34-7.39 (1H), (m, 1H, *H*-naphthalene), 7.40-7.46 (2H), (m, 1H, *H*-4 salicyl), 7.73 (1H), (d, 1H, *H*-8' naphthalene), 7.76-7.79 (2H), (m, 1H, *H*-4' naphthalene), 7.83 (1H), (d, 1H, *H*-5'-naphthalene), 8.27 (1H), (dd, ^{3}J = 7.8, ^{4}J = 1.8, 1H, *H*-6 salicyl), 8.53 (1H), (s, br, 1H, *H*-1' naphthalene), 10.26 (1H); (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.39 (*C*H-adamantane), 33.43 (C_q-1'' adamantane), 37.10 (*C*H$_2$-adamantane), 40.65 (*C*H$_2$-adamantane), 52.07 (N*C*H$_2$CH(OH)), 62.16 (NH*C*H$_2$-1''-adamantane), 66.96 (*C*H(OH)), 71.09 (O*C*H$_2$CH(OH)), 112.65 (*C*-3 salicyl), 117.14 (*C*-1' naphthalene), 120.89 (*C*-6' naphthalene), 121.96 (*C*-5 salicyl), 122.58 (C_q-1 salicyl), 124.83 (*C*-4a' naphthalene), 126.33 (*C*-7' naphthalene), 127.58 (*C*H), 127.96 (*C*-4' naphthalene), 128.60 (*C*H), 130.70 (C_q- naphthalene), 132.57 (*C*-6 salicyl), 133.21 (*C*-4 salicyl), 134.17 (C_q-4a' naphthalene), 136.48 (C_q-1' naphthalene), 156.62 (C_q-2 salicyl), 163.76 (*C*ONH).

HRMS: $[M+H]^+$: calculated.: 485.2808 found: 485.2804.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)benzamide (206**)**



206 was prepared following **general procedure E**, yielding 0.095 g (50%) of the desired product.

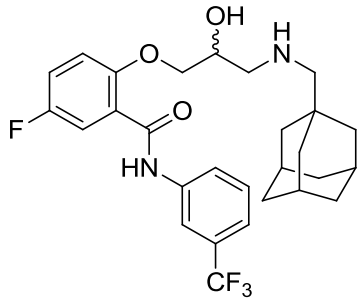
^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 1.48-1.55 (br, 6H, CH in C*H*$_2$-adamantane), 1.59-1.78 (br, 6H, CH in C*H*$_2$-adamantane), 1.98 (m, 3H, CH in C*H*$_2$-adamantane), 2.25, 2.28, 2.31, 2.34 (AB, $^{2}J_{AB}$ = -11.4, 2H, NHC*H*$_2$-1-damantane), 2.70-2.88 (m, 2H, CH(OH)C*H*$_2$NH), 3.98-4.05 (m, 1H, C*H*(OH)), 4.12-4.27 (m, 2H, OC*H*$_2$CH(OH)), 7.00 (dd [t], ^{3}J = 7.5, 1H, *H*-5 salicyl), 7.15 (d, ^{3}J = 8.3, 1H, *H*-3 salicyl), 7.58 (m, 1H, *H*-4 salicyl), 7.80 (br s, 1H, *H*-4-aniline), 7.81 (dd, ^{3}J = 7.8, 1H, *H*-6 salicyl), 8.44 (br s, 2H, *H*-2,6-aniline), 10.68 (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 28.50 (*C*H-adamantane), 33.55 (C_q-1'' adamantane), 37.26 (*C*H$_2$-adamantane), 40.79 (*C*H$_2$-adamantane), 51.28 (N*C*H$_2$CH(OH)), 62.07 (NH*C*H$_2$-1''-adamantane), 66.76 (*C*H(OH)), 71.51 (O*C*H$_2$CH(OH)), 112.92 (*C*-3 salicyl), 116.96 (q, $^{3}J_{CF}$ = 3.7, *C*-4' in 3',5'-bis-CF$_3$-aniline), 120.31 (q, $^{3}J_{CF}$ = 3.4, *C*-2',6' in 3',5'-bis-CF$_3$-aniline), 121.70 (C_q-1 salicyl), 122.27 (*C*-5 salicyl), 123.52 (q, C_q, $^{1}J_{CF}$ = -272.0, 3',5'-bis-*C*F$_3$-aniline), 132.13 (q, $^{2}J_{CF}$ = 33.2, C_q-3',5' in 3',5'-bis-CF$_3$-aniline), 132.77 (*C*-6 salicyl), 133.86 (*C*-4 salicyl), 140.65 (C_q-1' in 3',5'-bis-*C*F$_3$-aniline), 156.81 (C_q-2 salicyl), 164.04 (*C*ONH).

HRMS: $[M+H]^+$: calculated.: 571.2402 found: 571.2395.

Melting point: 144-161°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-fluoro-*N*-(3-(trifluoromethyl)phenyl)benzamide (225)



225 was prepared following **general procedure E**, yielding 0.104 g (35%) of the desired product.

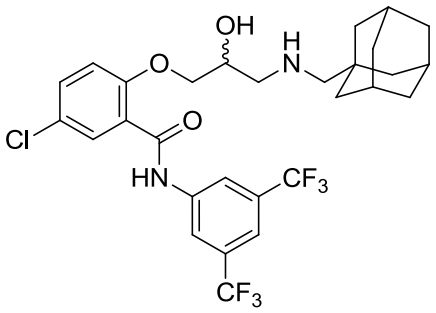
^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 1.37-1.44 (s, br, 6H, CH_2-adamantane), 1.51-1.58 (m, 3H, CH_2-adamantane), 1.61-1.68 (m, 3H, CH_2-adamantane), 1.88 (s, br, 3H, C*H*-adamantane), 2.09 (s, 2H, NHCH_2-1-adamantane)), 2.57-2.69 (m, 2H, CH(OH)CH_2NH), 3.92-3.99 (m, 1H, C*H*(OH)), 4.14 (dd, ^{2}J = -9.7, ^{3}J = 5.4, 1H, OCH_aH$_b$CH(OH)), 4.20 (dd, ^{2}J = -9.2, ^{3}J = 2.3, 1H, OCH$_a$$H_b$CH(OH)), 7.28 (dd, ^{3}J = 9.1, ^{4}J = 4.3, 1H, *H*-3 salicyl), 7.37-7.44 (m, 1H, *H*-4 salicyl), 7.46 (d, 1H, ^{3}J = 7.6, *H*-4'' in 3''-CF3-aniline), 7.55-7.63 (m, 2H, *H*-5'' in 3''-CF3-aniline, *H*-6 salicyl), 7.97 (d, br, 1H, ^{3}J = 8.4, *H*-6'' in 3''-CF3-aniline), 8.30 (s, br, 1H, *H*-2''in 3''-CF3-aniline), 10.65 (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 27.82 (*C*H-adamantane), 33.25 (C_q-1'' adamantane), 36.75(*C*H$_2$-adamantane), 40.28 (*C*H$_2$-adamantane), 53.36 (N*C*H$_2$CH(OH)), 62.41 (NH*C*H$_2$-1''-adamantane), 67.98 (*C*H(OH)), 72.27 (O*C*H$_2$CH(OH)), 115.61 (d, $^{3}J_{CF}$ = 7.6, *C*-3 salicyl), 115.91 (q, $^{4}J_{CF}$ = 4.1, *C*-2' in 3'-CF$_3$-aniline), 116.48 (d, $^{2}J_{CF}$ = 24.9, *C*-6 salicyl), 119.35 (d, $^{2}J_{CF}$ = 23.1, *C*-4 salicyl), 120.12 (q, $^{4}J_{CF}$ = 3.9, *C*-4' in 3'-CF$_3$-aniline), 123.36 (*C*-6' in 3'-CF$_3$-aniline), 124.08 (q, $^{1}J_{CF}$ = -272.3, *C*F$_3$-aniline), 124.42 (d, $^{3}J_{CF}$ = 6.8, C_q-1 salicyl), 129.55 (q, $^{2}J_{CF}$ = 31.5, C_q-3' in 3'-CF$_3$-aniline), 129.96 (*C*-5' in 3'-CF$_3$-aniline), 139.42 (C_q-1' in 3'-CF$_3$-aniline), 152.76 (q, $^{4}J_{CF}$ = 1.5, C_q-2 salicyl), 156.20 (d, $^{1}J_{CF}$ = -238.0, C_q-5 salicyl), 162.88 (q, $^{4}J_{CF}$ = 1.5, *C*ONH).

LCMS: [M+H]$^{+}$: calculated.: 521.24 found: 521.39, [M-H]$^{-}$: calculated.: 519.23 found: 519.42.

Melting point: 125-130°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-chlorobenzamide (207)



207 was prepared following **general procedure E**, yielding 0.112 g (32%) of the desired product.

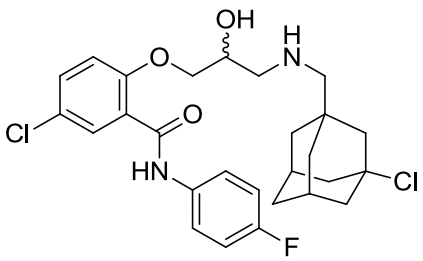
^{1}H NMR (400 MHz, DMSO-d$_6$, 23 °C): δ = 1.34-1.39 (m, 6H, CH in C*H*$_2$-adamantane), 1.49-1.57 (m, 3H, CH in C*H*$_2$-adamantane), 1.60-1.67 (m, br, 3H, CH in C*H*$_2$-adamantane), 1.86 (s, br, 3H, C*H*-adamantane), 2.05 (2H, NHC*H*$_a$*H*$_b$-1-adamantane), 2.56-2.69 (2H, C*H*(OH)C*H*$_a$*H*$_b$NH), 3.91-3.98 (m, 1H, C*H*(OH)), 4.13-4.18 (2H, OC*H*$_a$*H*$_b$CH(OH)), 5.31 (br, 1H, CH(O*H*)), 7.29 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.60 (dd, $^{3}J_2$ = 8.8, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.76 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 7.82 (s, br, *H*-4 aniline), 8.46 (s, br, *H*-2, *H*-6 aniline), 10.88 (br, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d$_6$, 23 °C): δ = 27.78 (*C*H-adamantane), 33.15 (*C*$_q$-1'' adamantane), 36.70 (*C*H$_2$-adamantane), 40.19 (*C*H$_2$-adamantane), 53.27 (N*C*H$_2$CH(OH)), 62.22 (NH*C*H$_2$-1''-adamantane), 67.74 (*C*H(OH)), 71.90 (O*C*H$_2$CH(OH)), 115.76 (*C*-3 salicyl), 116.59 (q, $^{3}J_{CF}$ = 4.8, *C*-4' in 3',5'-bis-CF$_3$-aniline), 119.43 (q, $^{3}J_{CF}$ = 3.9, *C*-2',6' in 3',5'-bis-CF$_3$-aniline), 123.18 (q, *C*$_q$, $^{1}J_{CF}$ = -272.0, 3',5'-bis-*C*F$_3$-aniline), 124.81 (*C*$_q$-1 salicyl), 124.96 (*C*$_q$-5 salicyl), 129.48 (*C*-6 salicyl), 130.86 (q, $^{2}J_{CF}$ = 32.8, *C*$_q$-3',5' in 3',5'-bis-CF$_3$-aniline), 132.56 (*C*-4 salicyl), 140.58 (*C*$_q$-1' in 3',5'-bis-*C*F$_3$-aniline), 155.14 (*C*$_q$-2 salicyl), 163.57 (*C*ONH).

LCMS: [M+H]$^{+}$: calculated.: 605.20 found: 605.29.

Melting point: 135-148°C.

5-chloro-2-(3-(((3-chloroadamantan-1-yl)methyl)amino)-2-hydroxypropoxy)-*N*-(4-fluorophenyl)benzamide (208)



208 was prepared following **general procedure E**, yielding 0.332 g (72%) of the desired product.

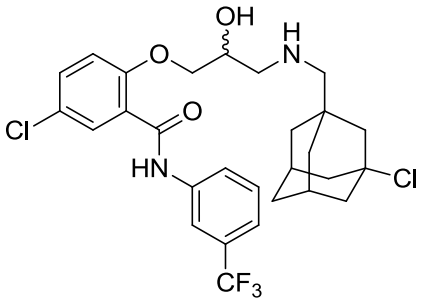
^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 1.30-1.37 (m, br, 2H, CH in C*H*$_2$-adamantane), 1.37-1.44 (m, br, 2H, CH in C*H*$_2$-adamantane), 1.44-1.51 (m, br, 1H, CH in C*H*$_2$-adamantane), 1.55-1.62 (m, br, 1H, CH in C*H*$_2$-adamantane), 1.81-1.85 (br s, 2H, C_qC*H*$_2$CCl-adamantane), 1.92-1.99 (m, br, 2H, CH in C*H*$_2$-adamantane), 2.00-2.07 (m, br, 2H, CH in C*H*$_2$-adamantane), 2.11 (2H), (s, br, 2H, C*H*-adamantane), 2.19 (m, 2H, NHC*H*$_2$-1-adamantane), 2.58-2.69 (m, 2H, CH(OH)C*H*$_2$NH), 3.92-4.00 (m, 1H, C*H*(OH)), 4.13 (dd, ^{2}J = -9.7, ^{3}J = 5.7, 1H, OC*H*$_a$H$_b$CH(OH)), 4.22 (dd, ^{2}J = -9.8, ^{3}J = 4.2, 1H, OCH$_a$*H*$_b$CH(OH)), 7.15-7.22 (m[t], 2H, *H*-3',5' in 4'F-aniline), 7.27 (d, ^{3}J = 9.0, 1H, *H*-3 salicyl), 7.57 (dd, ^{2}J = 8.9, ^{3}J = 2.8, 1H, *H*-4 salicyl), 7.76-7.84 (3H, *H*-6 salicyl, *H*-2',6' in 4'F-aniline), 10.36 (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 31.04 (*C*H-adamantane), 34.52 (CH*C*H$_2$CH-adamantane), 38.22 (CH*C*H$_2$C$_q$-adamantane), 46.89 (CH*C*H$_2$CCl-adamantane), 50.28 (C$_q$*C*H$_2$CCl-adamantane), 53.36 (N*C*H$_2$CH(OH)), 60.92 (NH*C*H$_2$-1-adamantanyl), 67.96 (*C*H(OH)), 70.30 (*C*$_q$Cl-adamantane), 71.94 (O*C*H$_2$CH(OH)), 115.33(d, $^{2}J_{CF}$ = 22.2, *C*-3',5' in 4'-F-aniline), 115.72 (*C*-3 salicyl), 121.56 (d, $^{3}J_{CF}$ = 7.8, *C*-2',6' in 4'-F-aniline), 124.81 (*C*$_q$-1 salicyl), 125.11 (*C*$_q$-5 salicyl), 129.69 (*C*-6 salicyl), 132.15 (*C*-4 salicyl), 135.09 (d, $^{4}J_{CF}$ = 2.3, *C*$_q$-1' in 4'-F-aniline), 155.10 (*C*$_q$-2 salicyl), 158.30 (d, $^{1}J_{CF}$ = -243, *C*-4' in 4'-F-aniline), 162.16 (*C*ONH). Ada-C$_q$ not recorded

LCMS: $[M+H]^+$: calculated.: 521.18 found: 521.24, $[M-H]^-$: calculated.: 519.16 found: 519.22.

Melting point: 125-131°C.

5-chloro-2-(3-(((3-chloroadamantan-1-yl)methyl)amino)-2-hydroxypropoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (201)



201 was prepared following **general procedure E**, yielding 0.300 g (79%) of the desired product.

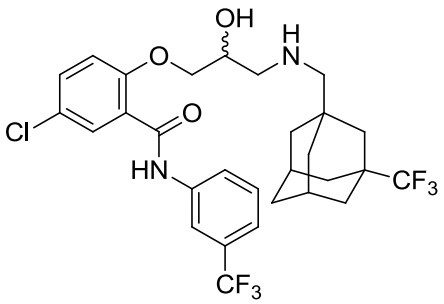
^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 1.28-1.43 (m, 4H, C*H* of CH_2 adamantane), 1.43-1.50 (m, 1H, C*H* of CH_2 adamantane), 1.54-1.62, (m, 1H, C*H* of CH_2 adamantane), 1.78-1.84 (m, 2H, C*H* of CH_2 adamantane), 1.91-2.06 (m, 4H, C*H* of CH_2 adamantane), 2.07-2.12 (s, br, 2H, C*H*-adamantane), 2.17 (br, 2H, NHCH_2-1-adamantane), 2.58-2.70 (m, 2H, CH(OH)CH_aH_bNH), 3.91-3.99 (m, 1H, C*H*(OH)), 4.12-4.23 (m, 2H, OCH_aH_bCH(OH)), 7.28 (d, ^3J = 8.8, 1H, *H*-3 salicyl), 7.46 (m, 1H, *H*-4'' in 3''-CF3-aniline), 7.55-7.63 (m, 2H, *H*-4 salicyl, *H*-5'' in 3''-CF3-aniline), 7.78 (d, ^3J = 2.6, 1H, *H*-6 salicyl), 7.96 (d, br, 1H, *H*-6'' in 3''-CF3-aniline), 8.28 (s, br, 1H, *H*-2''in 3''-CF3-aniline), 10.59 (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 31.03 (*C*H-adamantane), 34.50 (*C*H_2-adamantane), 38.17 (C_q-1'' adamantane), 38.19 (*C*H_2-adamantane), 46.87 (*C*H_2-adamantane), 50.25 (*C*H_2-adamantane), 53.28 (N*C*H_2CH(OH)), 60.83 (NH*C*H_2-1''-adamantane), 67.87 (*C*H(OH)), 70.22 (*C*-3'', adamantane), 71.89 (O*C*H_2CH(OH)), 115.71 (*C*-3 salicyl), 115.82 (q, $^3J_{CF}$ = 3.9, *C*-2' in 3'-CF_3-aniline), 120.13 (q, $^3J_{CF}$ = 3.7, *C*-4' in 3'-CF_3-aniline), 123.32 (*C*-6' in 3'-CF_3-aniline), 124.07 (C_q, $^1J_{CF}$ = -272.0, 3-*C*F_3-aniline), 124.82 (C_q-1 salicyl) 125.07 (C_q-5 salicyl), 129.56 (q, $^2J_{CF}$ = 31.5, C_q-3' in 3'-CF_3-aniline), 129.63 (*C*-6 salicyl), 129.98 (*C*-5' in 3'-CF_3-aniline), 132.34 (*C*-4 salicyl), 139.45 (C_q-1' in 3'-CF_3-aniline), 155.13 (C_q-2 salicyl), 162.91 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 571.17 found: 571.26, $[M-H]^-$: calculated.: 569.16 found: 569.23.

Melting point: 99-133°C.

5-chloro-2-(2-hydroxy-3-(((3-(trifluoromethyl)adamantan-1-yl)methyl)amino)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (199)



199 was prepared following **general procedure E**, yielding 0.303 g (88%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 1.32-1.45 (m, 6H, C*H* of CH_2 adamantane), 1.52-1.68 (m, 6H, C*H* of CH_2 adamantane), 2.01-2.08 (m, 2H, C*H* of CH_2 adamantane), 2.17 (br, 2H,

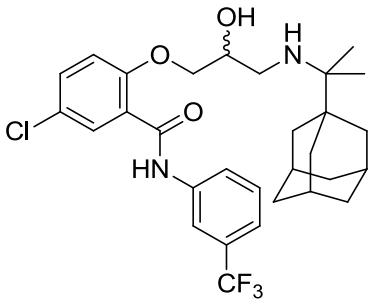
NHCH_2-1-adamantane), 2.58-2.70 (m, 2H, CH(OH)CH_2NH), 3.91-4.00 (m, 1H, C*H*(OH)), 4.11-4.24 (m, 2H, OCH_2CH(OH)), 7.28 (d, ^3J = 8.8, 1H, *H*-3 salicyl), 7.44-7.48 (m, 1H, *H*-4'' in 3''-CF3-aniline), 7.55-7.62 (m, 2H, *H*-4 salicyl, *H*-5'' in 3''-CF3-aniline), 7.77 (d, ^3J = 2.7, 1H, *H*-6 salicyl), 7.97 (d, br, 1H, *H*-6'' in 3''-CF3-aniline), 8.27 (s, br, 1H, *H*-2''in 3''-CF3-aniline), 10.59 (s, 1H, CON*H*).

$^{13}C\{^1H\}$NMR (100 MHz, DMSO-d_6, 23 °C): δ = 26.83 (*C*H-adamantane), 33.19 (*C*H_2-adamantane), 33.71 (br, *C*H_2-adamantane), 35.21 (C_q-1'' adamantane), 37.00 (*C*H_2-adamantane), 38.38 (C_q-3'' adamantane), 38.89 (*C*H_2-adamantane), 53.33 (N*C*H_2CH(OH)), 61.27 (NH*C*H_2-1''-adamantane), 67.84 (*C*H(OH)), 71.88 (O*C*H_2CH(OH)), 115.69 (*C*-3 salicyl), 115.84 (q, $^3J_{CF}$ = 4.0, *C*-2' in 3'-CF_3-aniline), 120.10 (q, $^3J_{CF}$ = 3.7, *C*-4' in 3'-CF_3-aniline), 123.31 (*C*-6' in 3'-CF_3-aniline), 124.06 (C_q, $^1J_{CF}$ = -272.0, 3'-*C*F_3-aniline), 124.81 (C_q-1 salicyl), 125.14 (C_q-5 salicyl), 128.53 (C_q, $^1J_{CF}$ = -281, 3''-*C*F_3-adamantane), 129.56 (q, $^2J_{CF}$ = 31.5, C_q-3' in 3'-CF_3-aniline), 129.59 (*C*-6 salicyl), 129.97 (*C*-5' in 3'-CF_3-aniline), 132.30 (*C*-4 salicyl), 139.46 (C_q-1' in 3'-CF_3-aniline), 155.11 (C_q-2 salicyl), 162.95 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 605.20 found: 605.25, $[M-H]^-$: calculated.: 603.19 found: 603.22.

Melting point: 127-129°C.

2-(3-((2-(adamantan-1-yl)propan-2-yl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (200)



200 was prepared following **general procedure E**, yielding 0.245 g (81%) of the desired product.

^1H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 0.78 (NHC[CH_{3a}CH_{3b}]-1-adamantane), 0.80 (NHC[CH_{3a}CH_{3b}]-1-adamantane), 1.49-1.64 (m, 12H, C*H* of CH_2 adamantane), 1.90 (m, 3H, C*H* of CH_2 adamantane), 2.61-2.69 (m, 2H, CH(OH)CH_2NH), 3.87-3.95 (m, 1H, C*H*(OH)), 4.15-4.24 (m, 2H, OCH_2CH(OH)), 7.28 (d, ^3J = 9.0, 1H, *H*-3 salicyl), 7.43-7.48 (br d, 1H, ^3J = 7.7, *H*-4'' in 3''-CF3-aniline), 7.55-7.61 (m, 2H, *H*-4 salicyl, *H*-5'' in 3''-CF3-aniline), 7.77 (d, ^4J = 2.7, 1H, *H*-

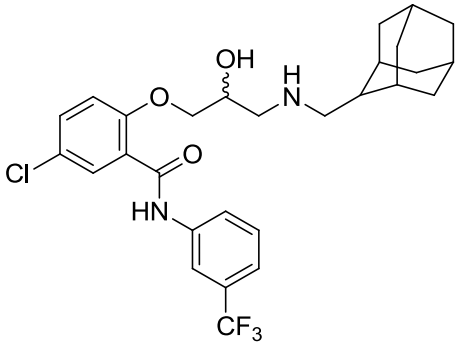
6 salicyl), 7.96 (d, br, ^{3}J = 8.3, 1H, *H*-6'' in 3''-CF3-aniline), 8.27 (s, br, 1H, *H*-2''in 3''-CF3-aniline), 10.60 (s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, DMSO-d_6, 23 °C): δ = 19.81 (NHC[*C*H_{3a}CH_{3b}]-1-adamantane), 19.89 (NHC[CH$_{3a}$*C*H$_{3b}$]-1-adamantane), 28.11 (*C*H-adamantane), 35.46 (*C*H_2-adamantane), 36.71 (*C*H_2-adamantane), 38.29 (C_q-1'' adamantane), 44.95 (N*C*H_2CH(OH)), 56.17 (NH*C*$(CH_3)_2$-1-adamantane), 68.76 (*C*H(OH)), 71.97 (O*C*H_2CH(OH)), 115.66 (*C*-3 salicyl), 115.90 (q, $^{3}J_{CF}$ = 4.0, *C*-2' in 3'-CF_3-aniline), 120.12 (q, $^{3}J_{CF}$ = 3.7, *C*-4' in 3'-CF_3-aniline), 123.33 (*C*-6' in 3'-CF_3-aniline), 124.77 (C_q-1 salicyl), 125.10 (C_q-5 salicyl), 129.51 (q, $^{2}J_{CF}$ = 31.5, C_q-3' in 3'-CF_3-aniline), 129.59 (*C*-6 salicyl), 129.95 (*C*-5' in 3'-CF_3-aniline), 132.31 (*C*-4 salicyl), 139.42 (C_q-1' in 3'-CF_3-aniline), 155.13 (C_q-2 salicyl), 162.94 (*C*ONH). *C*F3 not recorded

LCMS: $[M+H]^+$: calculated.: 565.24 found: 565.42, $[M-H]^-$: calculated.: 563.23 found: 563.24.

Melting point: 129-138.

2-(3-((adamantan-2-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (202)



202 was prepared following **general procedure E**, yielding 0.220 g (65%) of the desired product.

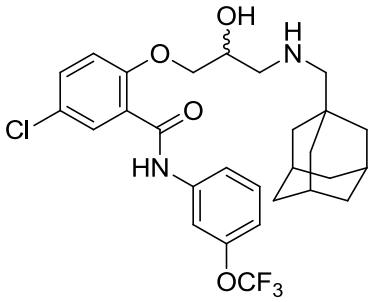
^{1}H NMR (400 MHz, $CDCl_3$, 27 °C): δ = 1.50-1.57 (m, 2H, C*H*$_2$-adamantane), 1.68-1.93 (m, 13H, C*H*$_2$,C*H*--adamantane,), 2.70 (dd, , ^{2}J = -11.8, ^{3}J = 7.0, 1H, NHC*H*$_a$-2-adamantane)), 2.75-2.84 (m, 2H, NHC*H*$_b$-2-adamantane, CH(OH)C*H*$_a$H$_b$NH), 2.90 (dd, ^{2}J = -12.3, ^{3}J = 3.3, 1H, CH(OH)CH$_a$*H*$_b$NH), 4.03 (dd, ^{2}J = -9.0, ^{3}J = 6.4, 1H, OC*H*$_a$H$_b$CH(OH)), 4.13-4.21 (m, 1H, C*H*(OH)), 4.27 (dd, ^{2}J = -9.3, ^{3}J = 1.5, 1H, OCH$_a$*H*$_b$CH(OH)), 6.90 (dd, ^{3}J = 8.8, ^{4}J = 0.7, 1H, *H*-3 salicyl), 7.34 (d, ^{3}J = 7.6, 1H, *H*-4'' in 3''-CF3-aniline), 7.37-7.46 (m, 2H, *H*-4 salicyl, *H*-5'' in 3''-CF3-aniline), 7.99 (d, ^{3}J = 8.0, 1H, *H*-6'' in 3''-CF3-aniline), 8.14 (s, br, 1H, *H*-2''in 3''-CF3-aniline), 8.19 (m, ^{3}J = 2.7, 1H, *H*-6 salicyl), 10.28 (s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 27 °C): δ = 27.84 (*C*H-adamantane), 28.23 (*C*H-adamantane), 30.31 (*C*H-adamantane), 30.49 (*C*H-adamantane), 31.68 (*C*H_2-adamantane), 31.78 (*C*H_2-adamantane), 38.11 (*C*H_2-adamantane), 38.85 (*C*H_2-adamantane), 38.89 (*C*H_2-adamantane), 44.35 (RNHCH_2*C*H-adamantane), 51.04 (NH*C*H_2-2''-adamantane), 51.93 (N*C*H_2CH(OH)), 66.93 (OCH_2*C*HOHCH_2NHR), 71.66 (O*C*H_2CH(OH)), 114.20 (*C*-3 salicyl), 117.22 (q, $^{4}J_{CF}$ = 4.0, *C*-2' in 3'-CF_3-aniline), 120.54 (q, $^{4}J_{CF}$ = 3.6, *C*-4' in 3'-CF_3-aniline), 123.43 (*C*-6' in 3'-CF_3-aniline), 123.48 (C_q-1 salicyl), 124.02 (q, $^{1}J_{CF}$ = -272.9, 3-*C*F_3-aniline), 127.40 (C_q-5 salicyl), 129.33 (*C*-5' in 3'-CF_3-aniline), 131.14 (q, $^{2}J_{CF}$ = 32.1, C_q-3' in 3'-CF_3-aniline), 132.18 (*C*-6 salicyl), 132.90 (*C*-4 salicyl), 139.14 (C_q-1' in 3'-CF_3-aniline), 155.02 (C_q-2 salicyl), 162.32 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 537.21 found: 537.34, $[M-H]^-$: calculated.: 535.20 found: 535.24.

Melting point: 115-125°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethoxy)phenyl)benzamide (209)



209 was prepared following **general procedure E**, yielding 0.216 g (50%) of the desired product.

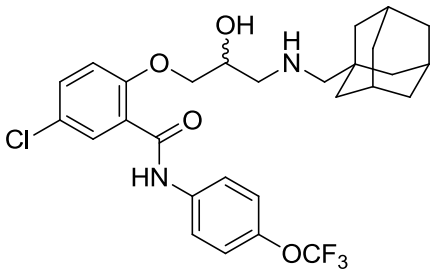
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.49-1.53 (s, br, 6H, C*H*$_2$-adamantane), 1.60-1.66 (m, 3H, C*H*$_2$-adamantane), 1.70-1.76 (m, 3H, C*H*$_2$-adamantane), 1.98 (s, br, 3H, C*H*-adamantane), 2.25, 2.28,2.36,2.39 (AB, J_{AB} = -11.9, 2H, NHC*H*$_2$-1-adamantane)), 2.77 (dd, ^{2}J = -12.2, ^{3}J = 9.5, 1H, CH(OH)C*H*$_a$H$_b$NH), 2.88 (dd, ^{2}J = -12.2, ^{3}J = 3.6, 1H, CH(OH)CH$_a$*H*$_b$NH), 4.02 (dd, ^{2}J = -9.3, ^{3}J = 6.2, 1H, OC*H*$_a$H$_b$CH(OH)), 4.16-4.22 (m, 1H, C*H*(OH)), 4.27 (dd, ^{2}J = -9.2, ^{3}J = 2.9, 1H, OCH$_a$*H*$_b$CH(OH)), 6.91 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 6.96 (d, ^{3}J = 8.1, 1H, *H*-4 aniline), 7.33 (dd [t], ^{3}J = 8.2, 1H, *H*-5 aniline), 7.40 (dd, ^{3}J = 8.8, ^{4}J = 2.7, 1H, *H*-4 salicyl), 7.73 (d, ^{3}J = 8.2, 1H, *H*-6 aniline), 7.84 (s [t], 1H, *H*-2 aniline), 8.20 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 10.22 (br s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.42 (*C*H-adamantane), 33.48 (C_q-1'' adamantane), 37.13 (CH_2-adamantane), 40.69 (CH_2-adamantane), 51.72 ($NCH_2CH(OH)$), 62.12 ($NHCH_2$-1''-adamantane), 66.71 (*C*H(OH)), 71.72 ($OCH_2CH(OH)$), 113.30 (*C*-2' in 3'-OCF_3-aniline), 114.30 (*C*-3 salicyl), 116.26 (*C*-4' in 3'-OCF_3-aniline), 118.66 (*C*-6' in 3'-OCF_3-aniline), 120.66 ($^{1}J_{CF}$ = -258.0, OCF_3 aniline), 123.75 (*C*-1 salicyl), 127.57 (*C*-5 salicyl), 129.99 (*C*-5' in 3'-OCF_3-aniline), 132.39 (*C*-6 salicyl), 133.01 (*C*-4 salicyl), 140.21 (C_q-1' in 3'-CF_3-aniline), 149.66 (*C*-3' in 3'-OCF_3-aniline), 155.14 (C_q-2 salicyl), 162.39 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 553.21 found: 553.36, $[M-H]^-$: calculated.: 551.19 found: 551.32.

Melting point: 94-107 °C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(4-(trifluoromethoxy)phenyl)benzamide (210)



210 was prepared following **general procedure E**, yielding 0.167 g (41%) of the desired product.

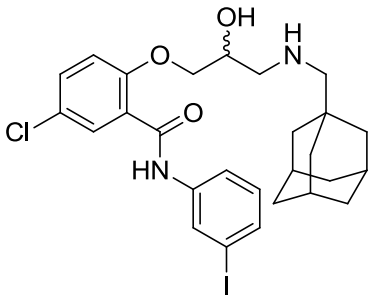
^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 1.39-1.44 (m, 6H, CH in CH_2-adamantane), 1.52-1.59 (m, 3H, CH in CH_2-adamantane), 1.61-1.68 (m, br, 3H, CH in CH_2-adamantane), 1.88 (s, br, 3H, C*H*-adamantane), 2.10 (s, 2H, NHCH_aH_b-1-adamantane), 2.57-2.67 (m, 2H, C*H*(OH)CH_aH_bNH), 3.92-3.99 (m, 1H, C*H*(OH)), 4.13 (dd, ^{2}J = -9.7, ^{3}J = 5.7, 1H, OC$H_a$$H_b$CH(OH)), 4.21 (dd, ^{2}J = -9.7, ^{3}J = 4.3, 1H, $OCH_aH_bCH(OH)$), 7.28 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.35 (d, ^{4}J = 8.7, 2H, *H*-3,5 aniline), 7.57 (dd, ^{3}J = 8.8, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.78 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 7.88 (m [d], ^{3}J = 9.0, 2H, *H*-2,6 aniline), 10.47 (br s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, DMSO-d_6, 23 °C): δ = 27.82 (*C*H-adamantane), 33.26 (C_q-1'' adamantane), 36.75 (CH_2-adamantane), 40.31 (CH_2-adamantane), 53.43 ($NCH_2CH(OH)$), 62.50 ($NHCH_2$-1''-adamantane), 67.97 (*C*H(OH)), 72.03 ($OCH_2CH(OH)$), 115.73 (*C*-3 salicyl), 120.12 ($^{1}J_{CF}$ = -256.4, OCF_3 aniline), 121.17 (*C*-2,6 aniline), 121.57 (*C*-3,5 aniline), 124.82 (*C*-1 salicyl), 125.00 (C_q-5 salicyl), 129.68 (*C*-6 salicyl), 132.28 (*C*-4 salicyl), 137.85 (C_q-1 aniline) 143.93 (J_{CF} = 1.5, C_q-4 aniline), 155.14 (C_q-2 salicyl), 162.46 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 553.21 found: 553.36, $[M-H]^-$: calculated.: 551.19 found: 551.26.

Melting point: 123-140°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3-iodophenyl)benzamide (211)



211 was prepared following **general procedure E**, yielding 0.165 g (40%) of the desired product.

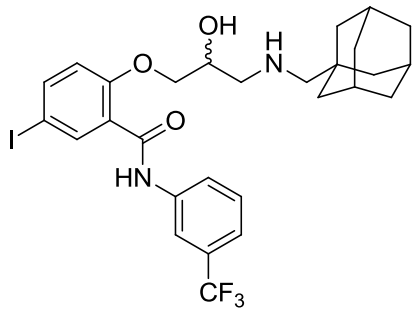
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.48-1.54 (m, br, 6H, CH in CH_2-adamantane), 1.59-1.66 (m, br, 3H, CH in CH_2-adamantane), 1.68-1,76 (m, br, 3H, CH in CH_2-adamantane), 1.97 (s, br, 3H, C*H*-adamantane), 2.25, 2.28, 2.33, 2.36 (AB, ^2J = -11.6, 2H, NHCH_aH_b-1-adamantane), 2.75 (dd, ^2J = -12.2, ^3J = 9.6, 1H, C*H*(OH)CH_aH$_b$NH), 2.85(dd, ^2J = -12.2, ^3J = 3.8, 1H, C*H*(OH)CH$_a$$H_b$NH), 4.00 (dd, ^2J = -9.4, ^3J = 6.0, 1H, OCH_aH$_b$CH(OH)), 4.10-4.17 (m, 1H, C*H*(OH)), 4.24 (dd, ^2J = -9.4, ^3J = 3.0, 1H, OCH$_a$$H_b$CH(OH)), 6.88 (d, ^3J = 8.8, 1H, *H*-3 salicyl), 7.03 (m[t], ^2J = 8.0, 1H, *H*-5' in 3'-I-aniline), 7.38 (dd, $^3J_1$ = 8.8, $^4J_2$ = 2.8, 1H, *H*-4 salicyl), 7.42 (d[dt], $^3J_1$ = 7.9, $^4J_2$ = 1.2 1H, *H*-4' in 3'-I-aniline), 7.80 (dd, $^3J_1$ = 8.2, $^4J_2$= 1.8 1H, *H*-6' in 3'-I-aniline), 8.17 (d, ^4J = 2.8, 1H, *H*-6 salicyl), 8.20 (s[t], br, 1H, *H*-2' in 3'-I-aniline), 10.08 (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ = 28.46 (*C*H-adamantane), 33.53 (C_q-1 adamantane), 37.19 (*C*H$_2$-adamantane), 40.76 (*C*H$_2$-adamantane), 51.62 (NCH_2CH(OH)), 62.07 (NH*C*H$_2$-1-adamantanyl), 66.67 (*C*H(OH)), 71.68 (OCH_2CH(OH)), 94.19 (C_q-3' in 3'-I-aniline), 114.29 (*C*-3 salicyl), 119.77 (*C*-6' in 3'-I-aniline), 123.72 (C_q-1 salicyl), 127.46 (C_q-5 salicyl), 129.30 (*C*-2' in 3'-I-aniline), 130.50 (*C*-5' in 3'-I-aniline), 132.29 (*C*-6 salicyl), 132.95 (*C*-4 salicyl), 133.17 (*C*-4' in 3'-I-aniline), 139.97 (C_q-1' in 3'-I-aniline), 155.14 (C_q-2 salicyl), 162.24 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 595.12 found: 595.21, $[M-H]^-$: calculated.: 593.11 found: 593.27.

Melting point: 127-143°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-iodo-*N*-(3-(trifluoromethyl)phenyl)benzamide (212**)**



212 was prepared following **general procedure E**, yielding 0.215 g (50%) of the desired product.

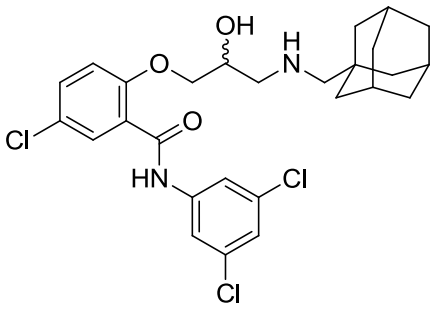
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.49-1.52 (s, br, 6H, CH_2-adamantane), 1.60-1.65 (m, 3H, CH_2-adamantane), 1.70-1.76 (m, 3H, CH_2-adamantane), 1.98 (m, 3H, C*H*-adamantane), 2.24, 2.27, 2.33, 2.36 (AB, J_{AB} = -11.8, 2H, NHCH_2-1-adamantane), 2.75 (dd, ^{2}J = -12.2, ^{3}J = 9.5, 1H, CH(OH)CH_aH$_b$NH), 2.85 (dd, ^{2}J = -12.2, ^{3}J = 3.9, 1H, CH(OH)CH$_a$$H_b$NH), 4.01 (dd, ^{2}J = -9.3, ^{3}J = 6.4, 1H, OCH_aH$_b$CH(OH)), 4.13-4.19 (m, 1H, C*H*(OH)), 4.27 (dd, ^{2}J = -9.3, ^{3}J = 2.9, 1H, OCH$_a$$H_b$CH(OH)), 6.74 (d, ^{3}J = 8.7, 1H, *H*-3 salicyl), 7.35 (d, ^{3}J = 7.7, 1H, *H*-6 aniline), 7.44 (dd [t], ^{3}J = 7.7, ^{3}J = 8.3, 1H, *H*-5 aniline), 7.73 (dd, ^{3}J = 8.7, ^{4}J = 2.3, 1H, *H*-4 salicyl), 8.04 (d, ^{3}J = 8.3, 1H, *H*-4 aniline), 8.12 (s, 1H, *H*-2 aniline), 8.51(d, ^{4}J = 2.4, 1H, *H*-6 salicyl), 10.26 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.44 (*C*H-adamantane), 33.50 (C_q-1'' adamantane), 37.17 (*C*H$_2$-adamantane), 40.72 (*C*H$_2$-adamantane), 51.57 (N*C*H$_2$CH(OH)), 62.10 (NH*C*H$_2$-1''-adamantane), 66.69 (*C*H(OH)), 71.58 (O*C*H$_2$CH(OH)), 84.47 (*C*-5 salicyl), 115.11 (*C*-3 salicyl), 117.39 (q, $^{3}J_{CF}$ = 3.9, *C*-2 aniline), 120.67 (q, $^{3}J_{CF}$ = 3.9, *C*-4 aniline), 123.60 (*C*-6 aniline), 124.17 ($^{1}J_{CF}$ = -272.6, *C*F$_3$ aniline), 124.22 (*C*-1 salicyl), 129.51 (*C*-5 aniline), 131.32 ($^{2}J_{CF}$ = 32.1, *C*-3 aniline), 139.32 (*C*-1 aniline), 141.20 (*C*-6 salicyl), 141.92 (*C*-4 salicyl), 156.48 (*C*-2 salicyl), 162.29 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 629.15 found: 629.28, $[M-H]^-$: calculated.: 627.13 found: 627.18.

Melting point: 135-138°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3,5-dichlorophenyl)benzamide (213)



213 was prepared following **general procedure E**, yielding 0.210 g (44%) of the desired product.

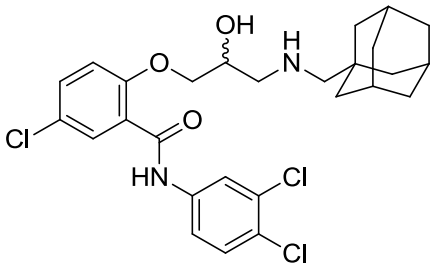
^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 1.41-1.44 (m, 6H, CH in CH_2-adamantane), 1.54-1.59 (m, 3H, CH in CH_2-adamantane), 1.62-1.67 (m, br, 3H, CH in CH_2-adamantane), 1.89 (s, br, 3H, C*H*-adamantane), 2.12 (s, 2H, NHCH_aH_b-1-adamantane), 2.59-2.70 (m, 2H, C*H*(OH)CH_aH_bNH), 3.93-3.99 (m, 1H, C*H*(OH)), 4.12-4.18 (m, 2H, OCH_aH_bCH(OH)), 7.26 (d, ^{3}J = 9.0, 1H, *H*-3 salicyl), 7.32 (d, ^{4}J = 1.9, 1H, *H*-4 aniline), 7.58 (dd, ^{3}J = 8.9, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.72 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 7.85 (d, ^{3}J = 1.8, 2H, *H*-2,6 aniline), 10.58 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 27.80 (*C*H-adamantane), 33.15 (C_q-1'' adamantane), 36.70 (*C*H_2-adamantane), 40.19 (*C*H_2-adamantane), 53.23 (N*C*H_2CH(OH)), 62.13 (NH*C*H_2-1''-adamantane), 67.59 (*C*H(OH)), 71.83 (O*C*H_2CH(OH)), 115.69 (*C*-3 salicyl), 117.86 (*C*-2,6 aniline), 122.98 (*C*-4 aniline), 124.79 (*C*-1 salicyl), 125.11 (*C*-5 salicyl), 129.48 (*C*-6 salicyl), 132.39 (*C*-4 salicyl), 134.12 (*C*-3,5 aniline), 141.00 (*C*-1 aniline) 155.02 (*C*-2 salicyl), 163.16 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 537.15 found: 537.26, $[M-H]^-$: calculated.: 535.13 found: 535.24.

Melting point: 160-190°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3,4-dichlorophenyl)benzamide (214)



214 was prepared following **general procedure E**, yielding 0.106 g (39%) of the desired product.

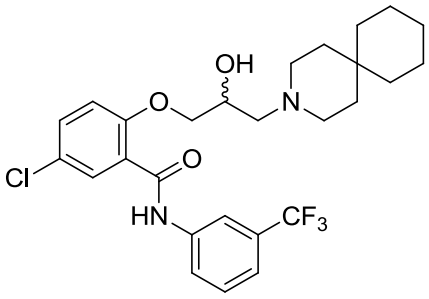
^{1}H NMR (400 MHz, DMSO-d$_6$, 23 °C): δ = 1.39-1.41 (m, 6H, CH in C*H*$_2$-adamantane), 1.53-1.58 (m, 3H, CH in C*H*$_2$-adamantane), 1.62-1.67 (m, br, 3H, CH in C*H*$_2$-adamantane), 1.88 (s, br, 3H, C*H*-adamantane), 2.06 (s, 2H, NHC*H*$_a$*H*$_b$-1-adamantane), 2.55-2.68 (m, 2H, C*H*(OH)C*H*$_a$*H*$_b$NH), 3.89-3.97 (m, 1H, C*H*(OH)), 4.10-4.19 (m, 2H, OC*H*$_2$CH(OH)), 7.26 (d, ^{3}J = 8.9, 1H, *H*-3 salicyl), 7.57 (dd, ^{3}J = 8.9, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.59 (d, ^{3}J = 8.6, 1H, *H*-5 aniline), 7.72 (dd, ^{3}J = 8.9, ^{3}J = 2.4, 1H, *H*-6 aniline), 7.73 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 8.11 (d, ^{4}J = 2.4, 1H, *H*-5 aniline), 10.52 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d$_6$, 23 °C): δ = 27.83 (*C*H-adamantane), 33.24 (*C*$_q$-1'' adamantane), 36.75 (*C*H$_2$-adamantane), 40.29 (*C*H$_2$-adamantane), 53.46 (N*C*H$_2$CH(OH)), 62.43 (NH*C*H$_2$-1''-adamantane), 67.90 (*C*H(OH)), 71.92 (O*C*H$_2$CH(OH)), 115.70 (*C*-3 salicyl), 119.75 (*C*-6 aniline), 120.92 (*C*-2 aniline), 124.79 (*C*$_q$ -1 salicyl), 125.11 (*C*$_q$ -5 salicyl), 125.26 (*C*$_q$-4 aniline), 129.50 (*C*-6 salicyl), 130.67 (*C*-5 aniline), 131.05 (*C*$_q$ -3 aniline), 132.32 (*C*-4 salicyl), 138.77 (*C*$_q$-1 aniline), 155.07 (*C*$_q$-2 salicyl), 162.86 (*C*ONH).

LCMS: [M+H]$^{+}$: calculated.: 537.15 found: 537.26, [M-H]$^{-}$: calculated.: 535.13 found: 535.16.

Melting point: 122-139°C.

5-chloro-2-(2-hydroxy-3-(3-azaspiro[5.5]undecan-3-yl)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (215)



215 was prepared following **general procedure E**, yielding 0.367 g (100%) of the desired product.

^{1}H NMR (600 MHz, CDCl$_3$, 25 °C): δ = 1.30-1.37 (m, 4H, dyn, C*H*$_2$-2,6-cyclohexyl), 1.39-1.43 (m, 6H, dyn, C*H*$_2$-3,4,5-cyclohexyl), 1.44-1.52 (m, 4H, , 3,5 piperidine C*H*$_2$), 2.31-2.36 (m, 2H, C*H*$_{ax}$-2,6 piperidine), 2.46 (dd, , ^{2}J = -12.2, ^{3}J = 3.6, 1H, CH(OH)C*H*$_a$H$_b$NH), 2.57 (dd [t], ^{2}J = -12.1, ^{3}J = 10.1, 1H, CH(OH)CH$_a$*H*$_b$NH), 2.61-2.66 (m, 2H, C*H*$_{eq}$-2,6 piperidine), 3.99 (dd, ^{2}J = -

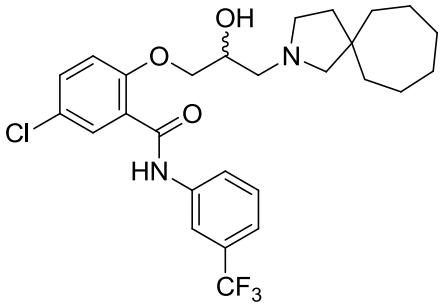
9.2, ^{3}J = 6.1, 1H, OCH_aH$_b$CH(OH)), 4.19-4.23 (m, 1H, CH(OH)), 4.28 (dd, ^{2}J = -9.2, ^{3}J = 2.8, 1H, OCH$_a$$H_b$CH(OH)), 6.90 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.35 (d, ^{3}J = 7.6, 1H, *H*-4'' in 3''-CF3-aniline), 7.40 (dd, ^{3}J = 8.7, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.45 (t,^{3}J = 8.0, 1H, *H*-5'' in 3''-CF3-aniline), 7.99 (d, ^{3}J = 8.5, 1H, *H*-6'' in 3''-CF3-aniline), 8.14 (s, br, 1H, *H*-2''in 3''-CF3-aniline), 8.20 (d, ^{3}J = 2.7, 1H, *H*-6 salicyl), 10.29 (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (150 MHz, $CDCl_3$, 25 °C): δ = 21.57 (*C*-3,5-cyclohexyl), 26.90 (*C*-4-cyclohexyl), 30.77 (C_q-spiro undecane), 36.28 (*C*-3,5 piperidine, *C*-2,6-cyclohexyl), 49.63 (*C*-2,6 piperidine), 59.85 (N*C*H$_2$CH(OH)), 64.92 (OCH$_2$*C*HOHCH$_2$NHR), 71.84 (O*C*H$_2$CH(OH)), 114.29 (*C*-3 salicyl), 117.33 (q, $^{4}J_{CF}$ = 4.1, *C*-2' in 3'-CF$_3$-aniline), 120.67 (q, $^{4}J_{CF}$ = 3.7, *C*-4' in 3'-CF$_3$-aniline), 123.53 (*C*-6' in 3'-CF$_3$-aniline), 123.63 (C_q-1 salicyl), 124.17 (q, $^{1}J_{CF}$ = -272.2, 3-*C*F$_3$-aniline), 127.51 (C_q-5 salicyl), 129.52 (*C*-5' in 3'-CF$_3$-aniline), 131.31 (q, $^{2}J_{CF}$ = 32.2, C_q-3' in 3'-CF$_3$-aniline), 132.34 (*C*-6 salicyl), 133.05 (*C*-4 salicyl), 139.29 (C_q-1' in 3'-CF$_3$-aniline), 155.19 (C_q-2 salicyl), 162.45 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 525.21 found: 525.28, $[M-H]^-$: calculated.: 523.20 found: 523.10.

Melting point: 139-142°C.

5-chloro-2-(2-hydroxy-3-(2-azaspiro[4.6]undecan-2-yl)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (216)



216 was prepared following **general procedure E**, yielding 0.400 g (91%) of the desired product as orange oil.

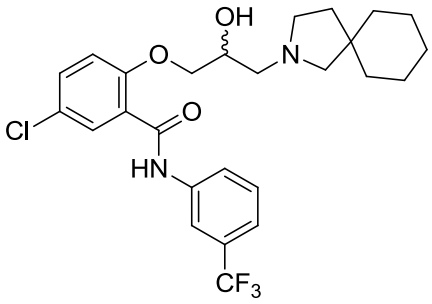
^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.38-1.50 (m, 4H, dyn, CH_2 spiro-alkyl), 1.50-1.60 (m, 8H, dyn, CH_2 spiro-alkyl), 1.64 (dd [t], *J* = 7.0, 2H, CH_2 spiro-alkyl), 2.32 (d, ^{2}J = -9.2, 1H *H* in NCH$_2$C$_q$), 2.48 (dd, ^{2}J = -12.0, ^{3}J = 3.5, 1H, CH(OH)CH_aH$_b$NH), 2.59 (d, ^{2}J = -9.2, 1H, *H* in NCH_2C$_q$), 2.61 (m, 1H, überlagert *H* in NCH_2CH$_2$), 2.80 (m, 1H, überlagert *H* in NCH_2CH$_2$), 2.85 (dd, ^{2}J = -12.0, ^{3}J = 10.6, 1H, CH(OH)CH$_a$$H_b$NH), 4.01 (dd, ^{2}J = -9.3, ^{3}J = 6.1, 1H, OCH_aH$_b$CH(OH)), 4.16-4.23 (m, 1H, CH(OH)), 4.28 (dd, ^{2}J = -9.3, ^{3}J = 2.8, 1H, OCH$_a$$H_b$CH(OH)),

6.91 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.35 (d, ^{3}J = 7.5, 1H, *H*-4'' in 3''-CF3-aniline), 7.40 (dd, ^{3}J = 8.8, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.44 (dd [t], ^{3}J = 8.0, 1H, *H*-5 aniline), 8.05 (d, ^{3}J = 8.2, 1H, *H*-6'' in 3''-CF3-aniline), 8.11 (s, br, 1H, *H*-2''in 3''-CF3-aniline), 8.21 (d, ^{3}J = 2.7, 1H, *H*-6 salicyl), 10.29 (s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (150 MHz, $CDCl_3$, 25 °C): δ = 23.95 (*C*H_2 spiro-alkyl), 23.99 (*C*H_2 spiro-alkyl), 29.57 (2x *C*H_2 spiro-alkyl), 39.16 (*C*H_2 spiro-alkyl), 41.42 (*C*H_2 spiro-alkyl), 41.55 (*C*H_2 spiro-alkyl), 45.42 (C_q spiro-alkyl), 53.83 (N*C*H_2CH_2), 57.77 (N*C*H_2CH(OH)), 66.48 (OCH_2*C*HOHCH_2NHR), 67.70 (N*C*H_2C_q), 71.80 (O*C*H_2CH(OH)), 114.32 (*C*-3 salicyl), 117.38 (q, $^{4}J_{CF}$ = 3.9, *C*-2' in 3'-CF_3-aniline), 120.67 (q, $^{4}J_{CF}$ = 3.9, *C*-4' in 3'-CF_3-aniline), 123.55 (C_q-1 salicyl), 123.67 (*C*-6' in 3'-CF_3-aniline), 124.17 (q, $^{1}J_{CF}$ = -272.4, 3-*C*F_3-aniline), 127.55 (C_q-5 salicyl), 129.52 (*C*-5' in 3'-CF_3-aniline), 131.32 (q, $^{2}J_{CF}$ = 32.1, *C*-3' in 3'-CF_3-aniline), 132.36 (*C*-6 salicyl), 133.05 (*C*-4 salicyl), 139.32 (C_q-1' in 3'-CF_3-aniline), 155.19 (C_q-2 salicyl), 162.44 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 525.21 found: 525.28, $[M-H]^-$: calculated.: 523.20 found: 523.26.

5-chloro-2-(2-hydroxy-3-(2-azaspiro[4.5]decan-2-yl)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (217)



217 was prepared following **general procedure E**, yielding 0.389 g (93%) of the desired product.

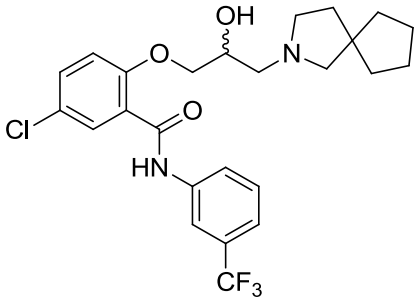
^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.33-1.49 (m, 10H, dyn, C*H*$_2$-spiro-alkyl), 1.61-1.65 (m, 2H, C*H*$_2$-spiro-alkyl), 2.31 (d, ^{2}J = -9.0, 1H *H* in NCH_2C_q), 2.43 (dd, ^{2}J = -11.9, ^{3}J = 3.6, 1H, CH(OH)C*H*$_a$H$_b$NH), 2.54-2.58 (m, 1H, *H* in NC*H*$_2$CH$_2$), 2.59 (d, ^{2}J = -9.1, 1H, *H* in NC*H*$_2C_q$), 2.75-2.80 (m, 1H, *H* in NC*H*$_2$CH$_2$), 2.82 (dd, ^{2}J = -11.9, ^{3}J = 11.0, 1H, CH(OH)CH$_a$*H*$_b$NH), 4.00 (dd, ^{2}J = -9.2, ^{3}J = 6.0, 1H, OC*H*$_a$H$_b$CH(OH)), 4.15-4.20 (m, 1H, C*H*(OH)), 4.28 (dd, ^{2}J = -9.2, ^{3}J = 2.7, 1H, OCH$_a$*H*$_b$CH(OH)), 6.90 (d, ^{3}J = 8.9, 1H, *H*-3 salicyl), 7.35 (d, ^{3}J = 7.5, 1H, *H*-4'' in 3''-CF3-aniline), 7.40 (dd, ^{3}J = 8.7, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.44 (t,^{3}J = 8.0, 1H, *H*-5'' in 3''-CF3-aniline), 8.05 (d, ^{3}J = 8.0, 1H, *H*-6'' in 3''-CF3-aniline), 8.10 (s, br, 1H, *H*-2''in 3''-CF3-aniline), 8.21 (d, ^{3}J = 2.8, 1H, *H*-6 salicyl), 10.29 (s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (150 MHz, $CDCl_3$, 25 °C): δ = 23.69 (*C*H_2 spiro-alkyl), 23.71 (*C*H_2 spiro-alkyl), 26.06 (*C*H_2 spiro-alkyl), 37.37 (*C*H_2 spiro-alkyl), 38.35 (*C*H_2 spiro-alkyl), 38.50 (*C*H_2 spiro-alkyl), 42.07 (C_q spiro-alkyl), 53.73 (N*C*H_2CH_2), 57.62 (N*C*H_2CH(OH)), 66.40 (N*C*H_2C_q), 66.52 (OCH$_2$*C*HOHCH$_2$NHR), 71.78 (O*C*H_2CH(OH)), 114.30 (*C*-3 salicyl), 117.34 (q, $^{4}J_{CF}$ = 4.0, *C*-2' in 3'-CF_3-aniline), 120.64 (q, $^{4}J_{CF}$ = 3.6, *C*-4' in 3'-CF_3-aniline), 123.51 (*C*-6' in 3'-CF_3-aniline), 123.57 (C_q-1 salicyl), 124.16 (q, $^{1}J_{CF}$ = -272.9, 3-*C*F_3-aniline), 127.49 (C_q-5 salicyl), 129.51 (*C*-5' in 3'-CF_3-aniline), 131.29 (q, $^{2}J_{CF}$ = 32.3, C_q-3' in 3'-CF_3-aniline), 132.34 (*C*-6 salicyl), 133.05 (*C*-4 salicyl), 139.31 (C_q-1' in 3'-CF_3-aniline), 155.20 (C_q-2 salicyl), 162.42 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 511.20 found: 511.28, $[M-H]^-$: calculated.: 509.18 found: 509.26.

Melting point: 80-88°C.

5-chloro-2-(2-hydroxy-3-(2-azaspiro[4.4]nonan-2-yl)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (218)



218 was prepared following **general procedure E**, yielding 0.423 g (95%) of the desired semi-crystalline product.

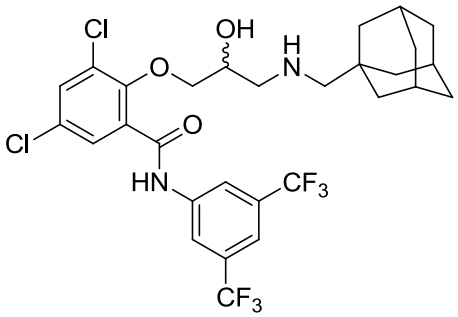
^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.33-1.66 (m, 8H, dyn, C*H*$_2$-spiro-alkyl), 1.71-1.80 (m, 2H, C*H*$_2$-spiro-alkyl), 2.52 (d, ^{2}J = -9.2, 1H *H* in NCH_2C_q), 2.59 (dd, ^{2}J = -12.0, ^{3}J = 3.2, 1H, CH(OH)CH_aH$_b$NH), 2.70-2.78 (m, 2H, *H* in N*C*H_2CH_2, *H* in NCH_2C_q), 2.87-2.95 (m, 2H, *H* in N*C*H_2CH_2, CH(OH)CH$_a$*H*$_b$NH), 4.02 (dd, ^{2}J = -9.2, ^{3}J = 5.8, 1H, OCH_aH$_b$CH(OH)), 4.20-4.25 (m, 1H, C*H*(OH)), 4.27 (dd, ^{2}J = -9.2, ^{3}J = 2.8, 1H, OCH$_a$*H*$_b$CH(OH)), 6.89 (d, ^{3}J = 8.9, 1H, *H*-3 salicyl), 7.35 (d, ^{3}J = 7.8, 1H, *H*-4'' in 3''-CF3-aniline), 7.39 (dd, ^{3}J = 8.7, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.44 (t,^{3}J = 7.9, 1H, *H*-5'' in 3''-CF3-aniline), 8.04 (d, ^{3}J = 8.1, 1H, *H*-6'' in 3''-CF3-aniline), 8.12 (s, br, 1H, *H*-2''in 3''-CF3-aniline), 8.18 (d, ^{3}J = 2.8, 1H, *H*-6 salicyl), 10.27 (s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (150 MHz, $CDCl_3$, 25 °C): δ = 24.40 (*C*H_2 spiro-alkyl), 24.41 (*C*H_2 spiro-alkyl), 37.83 (*C*H_2 spiro-alkyl), 39.27 (*C*H_2 spiro-alkyl), 39.39 (*C*H_2 spiro-alkyl), 49.58 (C_q spiro-alkyl), 54.34 (N*C*H_2CH_2), 58.18 (N*C*H_2CH(OH)), 66.28 (N*C*H_2C_q), 66.38 (OCH$_2$*C*HOHCH$_2$NHR), 71.70

(O*C*H$_2$CH(OH)), 114.28 (*C*-3 salicyl), 117.32 (q, $^4J_{CF}$ = 4.0, *C*-2' in 3'-CF$_3$-aniline), 120.67 (q, $^4J_{CF}$ = 3.8, *C*-4' in 3'-CF$_3$-aniline), 123.55 (J_{CF} = 0.4, *C*-6' in 3'-CF$_3$-aniline), 123.65 (C_q-1 salicyl), 124.15 (q, $^1J_{CF}$ = -272.5, 3-*C*F$_3$-aniline), 127.51 (C_q-5 salicyl), 129.53 (*C*-5' in 3'-CF$_3$-aniline), 131.28 (q, $^2J_{CF}$ = 32.3, C_q-3' in 3'-CF$_3$-aniline), 132.28 (*C*-4 salicyl), 133.04 (*C*-6 salicyl), 139.28 (C_q-1' in 3'-CF$_3$-aniline), 155.11 (C_q-2 salicyl), 162.48 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 497.18 found: 497.28, $[M-H]^-$: calculated.: 495.17 found: 495.18.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)-3,5-dichlorobenzamide (219)



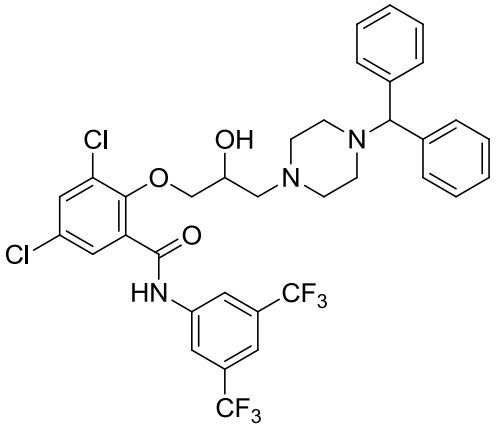
219 was prepared following **general procedure E**, yielding 0.137 g (20%) of the desired semi-crystalline product.

^{1}H NMR (400 MHz, CDCl$_3$, 23 °C): δ = 1.50-1.53 (s, br, 6H, C*H*$_2$-adamantane), 1.60-1.65 (m, 3H, C*H*$_2$-adamantane), 1.70-1.74 (m, 3H, C*H*$_2$-adamantane), 1.98 (s, br, 3H, C*H*-adamantane), 2.28, 2.31,2.35,2.38 (AB, J_{AB} = -11.7, 2H, NHC*H*$_2$-1-adamantane)), 2.84 (dd, ^2J = -12.3, ^3J = 9.6, 1H, CH(OH)C*H*$_a$H$_b$NH), 2.91 (dd, ^2J = -12.3, ^3J = 4.0, 1H, CH(OH)CH$_a$*H*$_b$NH), 4.03 (dd, ^2J = -9.5, ^3J = 5.5, 1H, OC*H*$_a$H$_b$CH(OH)), 4.09-4.15 (m, 1H, C*H*(OH)), 4.27 (dd, ^2J = -9.5, ^3J = 2.2, 1H, OCH$_a$*H*$_b$CH(OH)), 7.58 (dd, ^4J = 2.8, 1H, *H*-4 salicyl), 7.62 (s, 1H, *H*-4 aniline), 8.18 (d, ^4J = 2.8, 1H, *H*-6 salicyl), 8.43 (s, 2H, *H*-2,6 aniline), 10.56 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, CDCl$_3$, 23 °C): δ = 28.44 (*C*H-adamantane), 33.54 (C_q-1'' adamantane), 37.17 (*C*H$_2$-adamantane), 40.72 (*C*H$_2$-adamantane), 50.97 (N*C*H$_2$CH(OH)), 62.01 (NH*C*H$_2$-1''-adamantane), 66.99 (*C*H(OH)), 76.57 (O*C*H$_2$CH(OH)), 117.77 (m, $^3J_{CF}$ = 3.8, *C*-4' in 3',5'-bis-CF$_3$-aniline), 121.22 (q, $^3J_{CF}$ = 3.1, *C*-2',6' in 3',5'-bis-CF$_3$-aniline), 123.42 ($^1J_{CF}$ = -273.4, 2x *C*F$_3$ aniline), 128.36 (*C*-5 salicyl), 129.40 (*C*-1 salicyl), 131.15 (*C*-3 salicyl), 131.19 (*C*-6 salicyl), 132.10 ($^2J_{CF}$ = 33.6, *C*-3,5 in 3',5'-bis-CF$_3$-aniline), 134.24 (*C*-4 salicyl), 139.81 (*C*-1 in 3',5'-bis-CF$_3$-aniline) 151.38 (*C*-2 salicyl), 161.35 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 639.16 found: 639.16, $[M-H]^-$: calculated.: 637.15 found: 637.06.

2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)-3,5-dichlorobenzamide (220)



220 was prepared following **general procedure E**, yielding 0.194 g (34%) of the desired product.

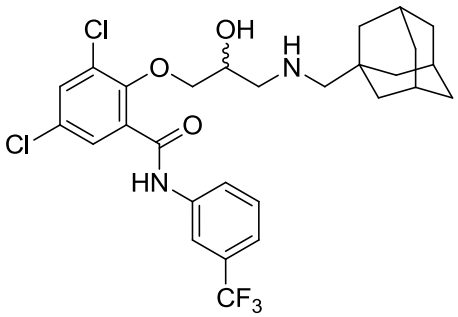
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.33-2.61 (m[dyn], br, 7H, CH(OH)C$H_a$$H_b$NH, H_{ax} H_{eq}-3,5 in piperazine, H_{ax}-2,6 in CH_2 piperazine), 2.68-2.81 (m, 3H, H_{eq}-2,6 in CH_2 piperazine, CH(OH)C$H_a$$H_b$NH), 4.02 (dd, ^{2}J = -9.6, ^{3}J = 5.3, 1H, OC$H_a$$H_b$CH(OH)), 4.11-4.18 (m, 1H, C*H*(OH)), 4.25 (s, 1H, NC*H*$(C_6H_5)_2$), 4.27 (dd, ^{2}J = -9.6, ^{3}J = 2.1, 1H, OC$H_a$$H_b$CH(OH)), 7.16-7.22 (m, 2H, 2x C*H*-4 phenyl), 7.25-7.31 (m, 4H, 2x *H*-3'',5'' phenyl), 7.37-7.46 (m, 4H, 2x *H*-2'',6'' phenyl), 7.58 (d, ^{3}J = 2.6, 1H, *H*-4 salicyl), 7.63 (br s, 1H, *H*-4 aniline), 8.18 (d, ^{4}J = 2.7, 1H, *H*-6 salicyl), 8.39 (br s, 2H, *H*-2,6 aniline), 10.51 (s, 1H (CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 51,96 (*C*H_2-3'',5'' piperazine), 52.85 (dyn, *C*H_2-2'',6'' piperazine), 58,88 (N*C*H_2CH(OH)), 65,31 (*C*H(OH)), 76,25 (O*C*H_2CH(OH)), 76,26 (N*C*H$(C_6H_5)_2$), 117,84 (m, $^{3}J_{CF}$ = 3.9, *C*-4 aniline), 121.25 (*C*-2,6 aniline), 122.31 (C_q-1 salicyl), 123.40 ($^{1}J_{CF}$ = -273.2, 2x *C*F_3 aniline), 127,20 (*C*-4'' phenyl), 128,01 (*C*-2'',6'' phenyl), 128,29 (*C*-3 salicyl), 128,70 (*C*-3'',5'' phenyl), 129,35 (*C*-5 salicyl), 131,20 (*C*-6 salicyl), 132.08 (d, $^{2}J_{CF}$ = 33.4, *C*-3,5 aniline), 134,29 (*C*-4 salicyl), 139,73 (*C*-1 aniline), 142,66 (2x C_q-1'' phenyl), 151,32 (C_q-2 salicyl), 161,32 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 726.17 found: 726.27, $[M-H]^-$: calculated.: 724.16 found: 724.24.

Melting point: 78-82°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-3,5-dichloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (221)



221 was prepared following **general procedure E**, yielding 0.087 g (21%) of the desired product.

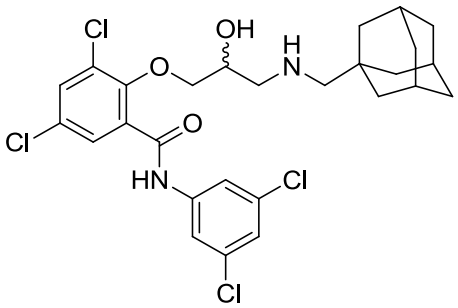
^{1}H NMR (400 MHz, DMSO-d$_6$, 23 °C): δ = 1.34-1.38 (s, br, 6H, C*H*$_2$-adamantane), 1.60-1.65 (m, 3H, C*H*$_2$-adamantane), 1.70-1.74 (m, 3H, C*H*$_2$-adamantane), 1.87 (s, br, 3H, C*H*-adamantane), 1.99 (s, 2H, NHC*H*$_2$-1-adamantane)), 2.78 (m, von DMSO überlagert, 1H, CH(OH)C*H*$_a$H$_b$NH), 2.61 (dd, ^{2}J = -12.2, ^{3}J = 4.3, 1H, CH(OH)CH$_a$*H*$_b$NH), 3.81-3.87 (m, 1H, C*H*(OH)), 3.95-4.01 (m, 2H, OC*H*$_2$CH(OH)), 7.48 (d, ^{3}J = 7.8, 1H, *H*-4 aniline), 7.60 (dd [t], ^{3}J = 8.0, 1H, *H*-5 aniline), 7.67 (d, ^{4}J = 2.6, 1H, *H*-6 salicyl), 7.84 (d, ^{4}J = 2.6, 1H, *H*-4 salicyl), 7.92 (d, ^{3}J = 8.3, 1H, *H*-6 aniline), 8.22 (s, 1H, *H*-2 aniline), 10.78 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d$_6$, 23 °C): δ = 27.77 (*C*H-adamantane), 33.04 (*C*$_q$-1'' adamantane), 36.69 (*C*H$_2$-adamantane), 40.14 (*C*H$_2$-adamantane), 53.41 (N*C*H$_2$CH(OH)), 62.02 (NH*C*H$_2$-1''-adamantane), 68.03 (*C*H(OH)), 77.25 (O*C*H$_2$CH(OH)), 115.97 (q, $^{3}J_{CF}$ = 4.0, *C*-2 in 3CF$_3$-aniline) 120.34 (q, $^{3}J_{CF}$ = 3.6, *C*-4 in 3CF$_3$-aniline), 123.44 (slightly broadened ~0.5 Hz, *C*-4 in 3CF$_3$-aniline), 124.06 ($^{1}J_{CF}$ = -272.6, *C*F$_3$ aniline), 127.96 (*C*-6 salicyl), 128.32 (*C*-5 salicyl), 128.37 (*C*-1 salicyl), 129.49 ($^{2}J_{CF}$ = 31.4, *C*-3 in 3-CF$_3$-aniline),129.98 (slightly broadened ~0.8 Hz, *C*-5 in 3CF$_3$-aniline), 131.58 (*C*-4 salicyl), 133.07 (*C*-3 salicyl), 139.38 (*C*-1 in 3CF$_3$-aniline), 151.05 (*C*-2 salicyl), 163.00 (*C*ONH).

LCMS: [M+H]$^{+}$: calculated.: 571.17 found: 571.28, [M-H]$^{-}$: calculated.: 569.16 found: 569.25.

Melting point: 132-134°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-3,5-dichloro-*N*-(3,5-dichlorophenyl)benzamide (222)



222 was prepared following **general procedure E**, yielding 0.200 g (47%) of the desired product.

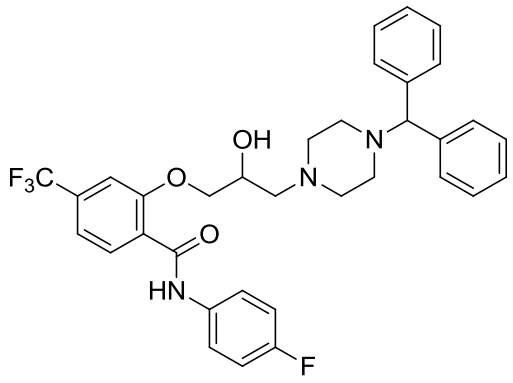
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.49-1.53 (s, br, 6H, CH_2-adamantane), 1.61-1.66 (m, 3H, CH_2-adamantane), 1.69-1.76 (m, 3H, CH_2-adamantane), 1.97 (s, br, 3H, C*H*-adamantane), 2.27, 2.29,2.32,2.35 (AB, J_{AB} = -11.7, 2H, NHCH_2-1-adamantane)), 2.81-2.89 (m, 2H, CH(OH)CH_2NH), 3.99-4.07 (m, 2H, OC$H_a$$H_b$CH(OH), C*H*(OH)), 4.23 ([d], ^{3}J = 7.2, 1H, OCH$_a$$H_b$CH(OH)), 7.11 (m [t], ^{4}J = 1.8, 1H, *H*-4 aniline), 7.55 (dd, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.81 (d, ^{4}J = 1.8, 2H, *H*-2,6 aniline), 8.11 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 10.15 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.48 (*C*H-adamantane), 33.61 (C_q-1'' adamantane), 37.23 (*C*H_2-adamantane), 40.82 (*C*H_2-adamantane), 51.13 (N*C*H_2CH(OH)), 62.24 (NH*C*H_2-1''-adamantane), 67.30 (*C*H(OH)), 76.81 (O*C*H_2CH(OH)), 119.63 (*C*-2,6 in 3,5-di-Cl-aniline), 124.62 (*C*-4 in 3,5-di-Cl-aniline), 128.81 (*C*-6 salicyl), 129.23 (*C*-5 salicyl), 130.93 (*C*-1 salicyl), 131.00 (*C*-3 salicyl), 134.00 (*C*-4 salicyl), 135.05 (C_q-3,5 aniline), 140.07 (C_q-1 in 3,5-di-Cl-aniline), 151.41 (*C*-2 salicyl), 161.26 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 571.11 found: 571.16, $[M-H]^-$: calculated.: 569.09 found: 569.12.

Melting point: 99-102°C.

2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(4-fluorophenyl)-4-(trifluoromethyl)benzamide (223)



223 was prepared following **general procedure E**, yielding 0.190 g (61%) of the desired product.

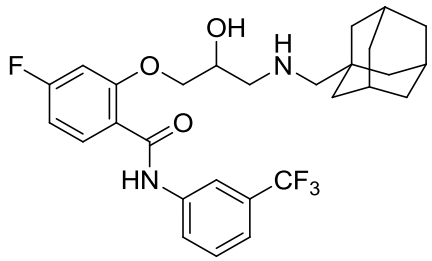
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.35-2.59 (m[dyn], br, 7H, CH(OH)C$H_a$$H_b$NH, H_{ax} H_{eq}-3,5 in piperazine, H_{ax}-2,6 in CH_2 piperazine), 2.65 (dd, ^{2}J = -12.3, ^{3}J = 10.7, 1H, CH(OH)C$H_a$$H_b$NH), 2.70-2.78 (m[t], br, 2H, H_{eq}-2,6 in CH_2 piperazine), 4.06 (dd, ^{2}J = -9.4, ^{3}J = 5.8, 1H, OC$H_a$$H_b$CH(OH)), 4.17-4.24 (m, 1H, C*H*(OH)), 4.27 (s, 1H, NC*H*$(C_6H_5)_2$), 4.35 (dd, ^{2}J = -9.4, ^{3}J = 2.6, 1H, C$H_a$$H_b$CH(OH)), 7.01 (m, 2H, *H*-3',5' aniline), 7.17-7.22 (m, 3H, 2x C*H*-4 phenyl, *H*-3 salicyl) 7.26-7.31 (m, 4H, 2x *H*-3'',5'' phenyl), 7.37-7.43 (m, 5H, *H*-5 salicyl, 2x *H*-2'',6'' phenyl), 7.74 (m, 2H, *H*-2',6' aniline), 8.35 (d, ^{4}J = 8.1, 1H, *H*-6 salicyl), 10.04 (s, 1H (CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 51.86 (*C*H_2-3'',5'' piperazine), 53.65 (dyn, *C*H_2-2'',6'' piperazine), 59.64 (N*C*H_2CH(OH)), 64.93 (*C*H(OH)), 71.51 (O*C*H_2CH(OH)), 76.16 (N*C*H$(C_6H_5)_2$), 109.84 (q, $^{3}J_{CF}$ = 3.6, *C*-3 salicyl), 115.63 (d, $^{2}J_{CF}$ = 22.3, *C*-3,5 aniline), 118.73 (q, $^{3}J_{CF}$ = 3.7, *C*-5 salicyl), 122.23 (d, $^{4}J_{CF}$ = 7.7, *C*-2,6 aniline), 123.51 (q, $^{1}J_{CF}$ = -272.6, *C*F_3 salicyl), 125.74 (C_q-1 salicyl), 127.23 (*C*-4'' phenyl), 128.04 (*C*-2'',6'' phenyl), 128.69 (*C*-3'',5'' phenyl), 133.48 (*C*-6 salicyl), 134.64 (d, $^{4}J_{CF}$ = 2.6, *C*-1 aniline), 134.70 (q, $^{2}J_{CF}$ = 32.7, *C*-4 salicyl), 142.44 (C_q-1'' phenyl[1]), 142.50 (C_q-1'' phenyl[2]), 156.51 (C_q-2 salicyl), 159.47 (d, $^{1}J_{CF}$ = -244.1, *C*-4 aniline), 162.11 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 608.25 found: 608.36, $[M-H]^-$: calculated.: 606.34 found: 606.24.

Melting point: 77-80°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-4-fluoro-*N*-(3-(trifluoromethyl)phenyl)benzamide (224)



224 was prepared following **general procedure E**, yielding 0.130 g (44%) of the desired product.

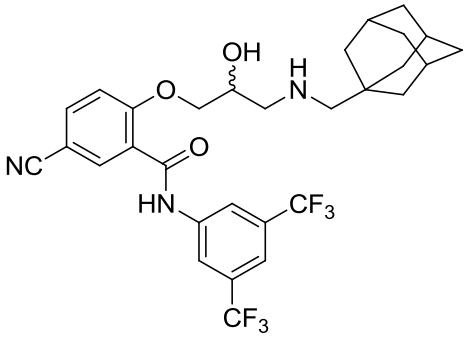
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.48-1.55 (s, br, 6H, CH_2-adamantane), 1.61-1.67 (m, 3H, CH_2-adamantane), 1.70-1.77 (m, 3H, CH_2-adamantane), 1.98 (s, br, 3H, C*H*-adamantane), 2.23, 2.26, 2.30, 2.32 (AB, J_{AB} = -11.5, 2H, NHCH_2-1-adamantane), 2.73 (dd, ^{2}J = -12.3, ^{3}J = 9.5, 1H, CH(OH)CH_aH$_b$NH), 2.84 (dd, ^{2}J = -12.3, ^{3}J = 3.8, 1H, CH(OH)CH$_a$$H_b$NH), 4.01 (dd, ^{2}J = -9.2, ^{3}J = 6.5, 1H, OCH_aH$_b$CH(OH)), 4.09-4.16 (m, 1H, C*H*(OH)), 4.27 (dd, ^{2}J = -10.2, ^{3}J = 2.3, 1H, OCH$_a$$H_b$CH(OH)), 6.69 (dd, J_{HF}=10.2, ^{3}J = 2.3, 1H, *H*-3 salicyl), 6.83 (m, 1H, *H*-5 salicyl), 7.34 (d, ^{3}J = 7.8, 1H, *H*-4 aniline), 7.43 (dd [t], ^{3}J = 8.1, ^{3}J = 7.8, 1H, *H*-5 aniline), 8.06 (d, ^{3}J = 8.1, 1H, *H*-6 aniline), 8.12 (s, 1H, *H*-2 aniline), 8.27 (dd, J_{HF}=6.8, ^{2}J = 8.8, 1H, *H*-3 salicyl), 10.24 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.49 (*C*H-adamantane), 33.58 (C_q-1'' adamantane), 37.25 (*C*H$_2$-adamantane), 40.81 (*C*H$_2$-adamantane), 51.40 (N*C*H$_2$CH(OH)), 62.21 (NH*C*H$_2$-1''-adamantane), 66.80 (*C*H(OH)), 71.68 (O*C*H$_2$CH(OH)), 100.79 (d, $^{2}J_{CF}$ = 26.0, *C*-3 salicyl), 109.10 (d, $^{2}J_{CF}$ = 21.1, *C*-5 salicyl), 117.30 (q, $^{3}J_{CF}$ = 3.9, *C*-2 aniline), 118.45 (d,$^{4}J_{CF}$ = 3.0, *C*-1 salicyl), 120.47 (q, $^{3}J_{CF}$ = 3.7, *C*-4 aniline), 123.51 (*C*-6 aniline), 124.20 (q, $^{1}J_{CF}$ = -272.8, *C*F$_3$ aniline), 129.46 (*C*-5 aniline), 131.28 (q, $^{2}J_{CF}$ = 32.2, *C*-3 aniline), 134.71 (d, $^{3}J_{CF}$ = 10.8, *C*-6 salicyl), 139.51 (*C*-1 aniline), 158.03 (d, $^{3}J_{CF}$ = 10.7, *C*-2 salicyl), 162.90 (*C*ONH), 165.78 (d, $^{1}J_{CF}$ = -253.9, *C*-4 salicyl).

LCMS: $[M+H]^+$: calculated.: 521.24 found: 521.32, $[M-H]^-$: calculated.: 519.23 found: 519.29.

Melting point: 143-144°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-cyanobenzamide (226)



226 was prepared following **general procedure E**, yielding 0.108 g (30%) of the desired product.

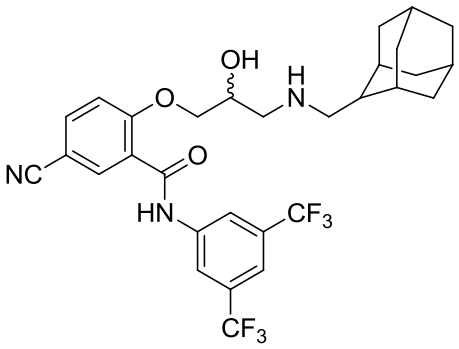
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.50-1.53 (s, br, 6H, C*H*$_2$-adamantane), 1.61-1.66 (m, 3H, C*H*$_2$-adamantane), 1.71-1.77 (m, 3H, C*H*$_2$-adamantane), 1.98 (s, br, 3H, C*H*-adamantane), 2.25, 2.28, 2.31, 2.34 (AB, J_{AB} = -11.5, 2H, überlagert von Austauschpeak NHC*H*$_2$-1-adamantane), 2.72 (dd, ^{2}J = -12.3, ^{3}J = 9.8, , 1H, CH(OH)C*H*$_a$H$_b$NH), 2.86 (dd, ^{2}J = -12.3, ^{3}J = 3.8, 1H, CH(OH)CH$_a$*H*$_b$NH), 4.06 (m, ^{2}J = -9.0, ^{3}J = 7.3, 1H, OC*H*$_a$H$_b$CH(OH)), 4.15-4.21 (m, 1H, C*H*(OH)), 4.40 (dd, ^{2}J = -9.0, ^{3}J = 2.7, 1H, OCH$_a$*H*$_b$CH(OH)), 7.09 (d, 1H, ^{3}J = 8.7, *H*-3 salicyl), 7.61 (s, 1H, *H*-4 aniline), 7.78 (dd, 1H, ^{3}J = 8.7, ^{4}J = 2.2, *H*-4 salicyl), 8.40 (s, 2H, *H*-2,6 aniline), 8.56 (d, 1H, ^{4}J = 2.2, *H*-6 salicyl), 10.48 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.45 (*C*H-adamantane), 33.54 (*C*$_q$-1'' adamantane), 37.21 (*C*H$_2$-adamantane), 40.77 (*C*H$_2$-adamantane), 50.97 (N*C*H$_2$CH(OH)), 62.08 (NH*C*H$_2$-1''-adamantane), 66.42 (*C*H(OH)), 72.09 (O*C*H$_2$CH(OH)), 106.31 (*C*-5 salicyl), 113.79 (*C*-3 salicyl), 117.59 (J_{CF} =3.8, *C*-4 aniline), 118.03 (*C*N), 120.40 (J_{CF} =3.4, *C*-2,6 aniline), 123.02 (*C*-1 salicyl), 123.38 (q, $^{1}J_{CF}$ = -272.6, 2x *C*F3), 132.30 (q, $^{2}J_{CF}$ = 33.2, *C*-3,5 aniline), 137.26 (*C*-4,6 salicyl), 140.03 (*C*-1 aniline), 159.49 (*C*-2 salicyl), 161.85 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 596.23 found: 596.38, $[M-H]^-$: calculated.: 594.22 found: 594.28.

Melting point: 143-145°C.

2-(3-((adamantan-2-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-cyanobenzamide (227)



227 was prepared following **general procedure E**, yielding 0.267 g (61%) of the desired product.

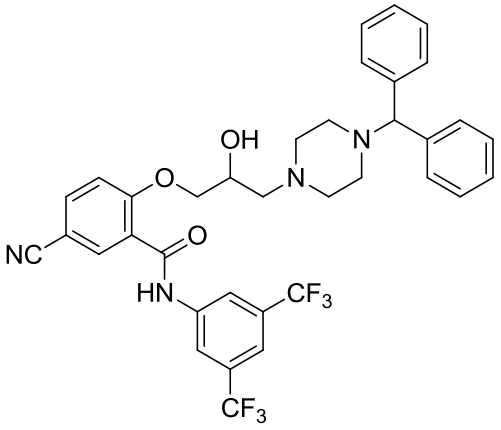
^{1}H NMR (400 MHz, $CDCl_3$, 27 °C): δ = 1.51-1.58 (m, 2H, CH_2-adamantane), 1.70-1.93 (m, 13H, CH_2,C*H*--adamantane,), 2.67-2.83 (m, 3H, NHCH_2-2-adamantane, CH(OH)CH_aH$_b$NH), 2.93 (dd, ^{2}J = -12.2, ^{3}J = 3.8, 1H, CH(OH)CH$_a$$H_b$NH), 4.09 (dd, ^{2}J = -9.0, ^{3}J = 7.1, 1H, OCH_aH$_b$CH(OH)), 4.15-4.22 (m, 1H, C*H*(OH)), 4.41 (dd, ^{2}J = -9.0, ^{3}J = 2.6, 1H, OCH$_a$$H_b$CH(OH)), 7.09 (d, ^{3}J = 8.6, 1H, *H*-3 salicyl), 7.61 (s, 1H, *H*-4 aniline), 7.78 (dd, ^{3}J = 8.6, ^{4}J = 2.2, 1H, *H*-4 salicyl), 8.39 (s, 2H, *H*-2,6 aniline), 8.56 (d, ^{4}J = 2.2, 1H, *H*-6 salicyl), 10.46 (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 27 °C): δ = 28.02 (*C*H-adamantane), 28.44 (*C*H-adamantane), 30.52 (*C*H-adamantane), 30.68 (*C*H-adamantane), 31.84 (*C*H_2-adamantane), 31.96 (*C*H_2-adamantane), 38.29 (*C*H_2-adamantane), 39.04 (*C*H_2-adamantane), 39.09 (*C*H_2-adamantane), 44.91 (RNHCH$_2$*C*H-adamantane), 50.70 (NH*C*H_2-2''-adamantane), 52.10 (N*C*H_2CH(OH)), 66.83 (OCH$_2$*C*HOHCH$_2$NHR), 72.02 (O*C*H_2CH(OH)), 106.33 (C_q-5 salicyl), 113.80 (*C*-3 salicyl), 117.62 (m, J_{CF} = 3.8, *C*-4 aniline), 118.02 (*C*N), 120.39 (q, $^{3}J_{CF}$ = 3.3, *C*-2,6 aniline), 123.02 (C_q-1 salicyl), 123.73 (q, $^{1}J_{CF}$ = -273.1, 2x*C*F$_3$), 132.31 (q, $^{2}J_{CF}$ = 33.5, C_q-3,5 aniline), 137.27 (*C*-4,6 salicyl), 140.00 (C_q-1 aniline), 159.49 (C_q-2 salicyl), 161.84 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 596.23 found: 596.30, $[M-H]^-$: calculated.: 594.22 found: 594.20.

Melting point: 187-188°C.

2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-cyanobenzamide (228**)**



228 was prepared following **general procedure E**, yielding 0.139 g (46%) of the desired product.

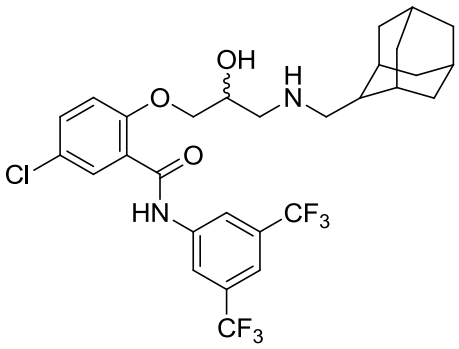
^{1}H NMR (400 MHz, DMSO-d$_6$, 23 °C): δ = 2.12-2.47 (m[dyn], br, 10H, CH(OH)C*H$_a$H$_b$*NH, *H*$_{ax}$ *H*$_{eq}$-3,5 in piperazine, *H*$_{ax}$ *H*$_{eq}$ -2,6 in C*H*$_2$ piperazine), 3.93-4.02 (m, 1H, C*H*(OH)), 4.17 (d, ^{3}J = 4.6, 2H, OC*H*$_2$CH(OH)), 4.19 (s, 1H, NC*H*(C$_6$H$_5$)$_2$), 5.11 (m, 1H, CH(O*H*)), 7.17 (m, 2H, 2x C*H*-4 phenyl), 7.27 (m, 4H, 2x *H*-3'',5'' phenyl), 7.34-7.43 (m, 5H, *H*-3 salicyl, 2x *H*-2'',6'' phenyl), 7.79 (s, 1H, *H*-4 aniline), 8.00 (dd, ^{4}J = 8.7, ^{4}J = 2.2, 1H, *H*-4 salicyl), 8.11 (d, ^{4}J = 2.2, 1H, *H*-6 salicyl), 8.41 (s, 2H, *H*-2',6' aniline), 10.88 (s, 1H (CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d$_6$, 23 °C): δ = 51.40 (*C*H$_2$-dyn, piperazine), 53.46 (*C*H$_2$-dyn, piperazine), 60.79 (N*C*H$_2$CH(OH)), 66.02 (*C*H(OH)), 72.13 (O*C*H$_2$CH(OH)), 75.10 (N-*C*H(C$_6$H$_5$)$_2$), 103.32 (*C*-5 salicyl), 114.61 (*C*-3 salicyl), 116.61 (m, *C*-4' in 3',5'-bis-CF$_3$-aniline), 118.33 (*C*N), 119.29 (q, $^{3}J_{CF}$ = 3.1, *C*-2',6' in 3',5'-bis-CF$_3$-aniline), 123.15 ($^{1}J_{CF}$ = -272.9, 2x *C*F$_3$ aniline), 125.24 (*C*-1 salicyl), 126.77 (*C*-4'' phenyl), 127.47 (*C*-2'',6'' phenyl), 128.42 (*C*-3'',5'' phenyl), 130.87 ($^{2}J_{CF}$ = 32.8, *C*-3,5 in 3',5'-bis-CF$_3$-aniline), 133.98 (*C*-6 salicyl), 136.85 (*C*-4 salicyl), 140.56 (*C*-1 in 3',5'-bis-CF$_3$-aniline), 142.84 (C$_q$-1'' phenyl), 142.89 (C$_q$-1'' phenyl), 159.35 (*C*$_q$-2 salicyl), 163.50 (*C*ONH).

LCMS: [M+H]$^{+}$: calculated.: 683.25 found: 683.33, [M-H]$^{-}$: calculated.: 681.23 found: 681.36.

Melting point: 215-220°C.

2-(3-((adamantan-2-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-chlorobenzamide (229)



229 was prepared following **general procedure E**, yielding 0.119 g (22%) of the desired product.

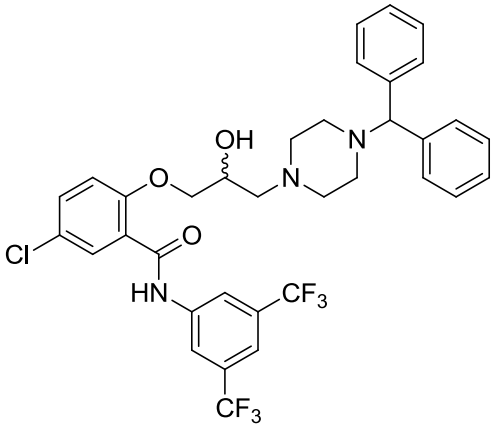
^{1}H NMR (400 MHz, DMSO-d$_6$, 23 °C): δ = 1.36-1.43 (m, 2H, C*H*$_2$-adamantane), 1.57-1.82 (m, 13H, C*H*$_2$,C*H*--adamantane,), 2.52 (m, 2H, überlagert von DMSO, NHC*H*$_2$-2-adamantane), 2.61-2.73 (m, 2H, CH(OH)C*H*$_2$NH), 3.92-4.00 (m, 1H, C*H*(OH)), 4.17 (d, *J* = 4.9, 2H, OC*H*$_2$CH(OH)), 7.29 (d, 1H, ^{3}J = 8.8, *H*-3 salicyl), 7.60 (dd, 1H, ^{3}J = 8.8, ^{4}J = 2.8, *H*-4 salicyl), 7.76 (d, 1H, ^{4}J = 2.8, *H*-6 salicyl), 7.81 (s, 1H, *H*-4 aniline), 8.46 (s, 2H, *H*-2,6 aniline), 10.88 (br, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d$_6$, 23 °C): δ = 27.32 (*C*H-adamantane), 27.73 (*C*H-adamantane), 29.66 (*C*H-adamantane), 29.72 (*C*H-adamantane), 31.24 (2x *C*H$_2$-adamantane), 37.74 (*C*H$_2$-adamantane), 38.47 (2x *C*H$_2$-adamantane), 43.67 (RNHCH$_2$*C*H-adamantane), 51.82 (NH*C*H$_2$-2''-adamantane), 52.15 (N*C*H$_2$CH(OH)), 67.69 (OCH$_2$*C*HOHCH$_2$NHR), 71.89 (O*C*H$_2$CH(OH)), 115.76 (*C*-3 salicyl), 116.61 (m, $^{4}J_{CF}$ = 3.9, *C*-4 aniline), 119.49 (q, $^{4}J_{CF}$ = 3.5, *C*-2,6 aniline), 123.20 (q, $^{1}J_{CF}$ = -273.1, 2x *C*F$_3$-aniline), 124.83 (*C*$_q$-1 salicyl), 124.87 (*C*$_q$-5 salicyl), 129.55 (*C*-6 salicyl), 130.85 (q, $^{2}J_{CF}$ = 32.7, *C*$_q$-3,5 aniline), 132.60 (*C*-4 salicyl), 140.58 (*C*$_q$-1 aniline), 155.15 (*C*$_q$-2 salicyl), 163.57 (*C*ONH).

LCMS: $[M+H]^{+}$: calculated.: 605.20 found: 605.32, $[M-H]^{-}$: calculated.: 603.19 found: 603.22.

Melting point: 143-146°C.

2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-chlorobenzamide (230)



230 was prepared following **general procedure E**, yielding 0.167 g (22%) of the desired product.

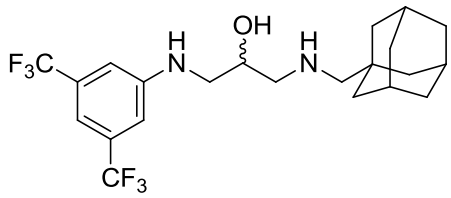
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.35-2.56 (m[dyn], br, 8H, CH(OH)C*H*$_2$NH, H_{ax} H_{eq}-3,5 in piperazine, H_{ax}-2,6 in C*H*$_2$ piperazine), 2.69-2.79 (m[t], br, 2H, H_{eq}-2,6 in C*H*$_2$ piperazine), 3.97 (dd, ^{2}J = -9.2, ^{3}J = 6.9, 1H, OCH_aH$_b$CH(OH)), 4.19-4.24 (m, 1H, C*H*(OH)), 4.26 (s, 1H, NC*H*(C_6H_5)$_2$), 4.31 (dd, ^{2}J = -9.2, ^{3}J = 2.4, 1H, OCH$_a$$H_b$CH(OH)), 6.92 (d, ^{3}J = 8.7, 1H, *H*-3 salicyl), 7.19 (m, 2H, 2x C*H*-4 phenyl), 7.26-7.31 (m, 4H, 2x *H*-3'',5'' phenyl), 7.39-7.45 (m, 5H, *H*-4 salicyl, 2x *H*-2'',6'' phenyl), 7.58 (s, 1H, *H*-4 aniline), 8.21 (d, ^{4}J = 2.7, 1H, *H*-6 salicyl), 8.37 (s, 2H, *H*-2',6' aniline), 10.55 (s, 1H (CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 51.92 (*C*H$_2$-dyn, piperazine), 52.94 (*C*H$_2$-dyn, piperazine), 59.35 (N*C*H$_2$CH(OH)), 64.89 (*C*H(OH)), 72.02 (O*C*H$_2$CH(OH)), 76.15 (N-*C*H(C_6H_5)$_2$), 114.46 (*C*-3 salicyl), 117.26 (m, J_{CF} = 3.6, *C*-4' in 3',5'-bis-CF_3-aniline), 120.23 (q, $^{3}J_{CF}$ = 3.4, *C*-2',6' in 3',5'-bis-CF_3-aniline), 123.12 (*C*-1 salicyl), 123.42 ($^{1}J_{CF}$ = -272.5, 2x *C*F_3 aniline), 127.18 (*C*-4'' phenyl), 127.81 (*C*-5 salicyl), 128.03 (*C*-2'',6'' phenyl), 128.67 (*C*-3'',5'' phenyl), 132.19 ($^{2}J_{CF}$ = 33.5, *C*-3,5 in 3',5'-bis-CF_3-aniline), 132.43 (*C*-6 salicyl), 133.46 (*C*-4 salicyl), 140.24 (*C*-1 in 3',5'-bis-CF_3-aniline), 142.60 (C_q-1'' phenyl), 142.63 (C_q-1'' phenyl), 155.17 (C_q-2 salicyl), 162.63 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 692.21 found: 692.28, $[M-H]^-$: calculated.: 690.20 found: 690.34.

Melting point: 180-181°C.

1-((adamantan-1-ylmethyl)amino)-3-((3,5-bis(trifluoromethyl)phenyl)amino)propan-2-ol (231)



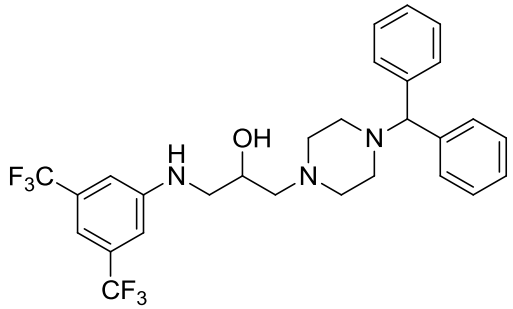
231 was prepared following **general procedure E**, yielding 0.181 g (70%) of the desired product as yellow oil.

^{1}H NMR (400 MHz, DMSO-d$_6$, 23 °C): δ = 1.46-1.49 (s, br, 6H, C*H$_2$*-adamantane), 1.55-1.61 (m, 3H, C*H$_2$*-adamantane), 1.63-1.70 (m, 3H, C*H$_2$*-adamantane), 1.91 (m, 3H, C*H*-adamantane), 2.17 (s, 2H, NHC*H$_2$*-1-adamantane), 2.51-2.59 (m, 2H, CH(OH)C*H$_2$*NHCH$_2$-1''-adamantane), 3.01-3.09 (m, 1H, ArNHC*H$_a$*H$_b$CH(OH)), 3.22-3.29 (m, 1H, ArNHCH$_a$*H$_b$*CH(OH)), 3.66-3.73 (m, 1H, C*H*(OH)), 6.70 (m [t], *J* = 5.7, 1H, N*H* -aniline), 6.99 (s, 1H, *H*-4 aniline), 7.14 (s, 2H, *H*-2,6 aniline).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d$_6$, 23 °C): δ = 27.86 (*C*H-adamantane), 33.26 (*C$_q$*-1'' adamantane), 36.77 (*C*H$_2$-adamantane), 40.39 (*C*H$_2$-adamantane), 47.11 (ArNH*C*H$_2$CH(OH)), 54.60 (CH(OH)*C*H$_2$NHCH$_2$-1''-adamantane), 62.56 (NH*C*H$_2$-1''-adamantane), 68.07 (*C*H(OH)), 106.64 (m, $^{3}J_{CF}$ = 3.8, *C*-4 aniline), 111.12 (broadened, *C*-2,6 aniline), 123.71 ($^{1}J_{CF}$ = -272.1, 2x*C*F$_3$ aniline), 130.83 (q, $^{2}J_{CF}$ = 31.7, *C*-3,5 aniline), 150.30 (*C*-1 aniline).

LCMS: [M+H]$^{+}$: calculated.: 451.22 found: 451.40.

1-(4-benzhydrylpiperazin-1-yl)-3-((3,5-bis(trifluoromethyl)phenyl)amino)propan-2-ol (232)



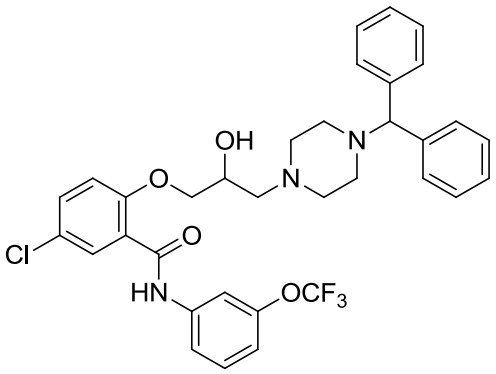
1-Benzhydrylpiperazine (0.229 g, 0.908 mmol) and *N*-(oxiran-2-ylmethyl)-3,5-bis(trifluoromethyl)aniline (**398**, 0.259 g, 0.908 mmol) in EtOH (4 mL) were stirred for 5 h at 80°C. **232** was obtained in 62% yield (0.300 g) as yellow oil after column chromatography (ethyl acetate:hexane=1:1).

^{1}H NMR (400 MHz, $CDCl_3$, 27 °C): δ = 2.37-2.55 (m[dyn], br, 8H, CH(OH)C*H*$_2$NH, H_{ax} H_{eq}-3,5 in piperazine, H_{ax}-2,6 in CH_2 piperazine), 2.65-2.77 (m[t], br, 2H, H_{eq}-2,6 in CH_2 piperazine), 3.05 (dd, ^{2}J = -12.1, ^{3}J = 6.2, 1H, ArNHCH_aH$_b$CH(OH)), 3.30 (dd, ^{2}J = -12.1, ^{3}J = 2.3, 1H, ArNHCH$_a$$H_b$CH(OH)), 3.92-3.99 (m, 1H, C*H*(OH)), 4.24 (s, 1H, NC*H*(C_6H_5)$_2$), 6.95 (s, 2H, *H*-2,6 aniline), 7.14 (s, 1H, *H*-4 aniline), 7.17-7.21 (m, 2H, 2x C*H*-4 phenyl), 7.26-7.31 (m, 4H, 2x *H*-3'',5'' phenyl), 7.39-7.44 (m, 4H, 2x *H*-2'',6'' phenyl).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 47.13 (ArNH*C*H$_2$CH(OH)), 52.04 (*C*H$_2$, piperazine), 52.68 (dyn-*C*H$_2$, piperazine), 61.28 (pip-N*C*H$_2$CH(OH)), 64.93 (*C*H(OH)), 76.30 (*N*-*C*H(C_6H_5)$_2$), 110.42 (m, $^{3}J_{CF}$ = 4.0, *C*-4 aniline), 112.25 (q, $^{3}J_{CF}$ = 3.3, *C*-2,6 aniline), 123.71 (q, $^{1}J_{CF}$ = -273.6, 2x *C*F$_3$ aniline), 127.16 (*C*-4'' phenyl), 128.03 (*C*-2'',6'' phenyl), 128.67 (*C*-3'',5'' phenyl), 132.49 (q, $^{2}J_{CF}$ = 32.2, *C*-3,5 aniline), 142.67 (C_q-1'' phenyl), 142.69 (C_q-1'' phenyl), 149.15 (*C*$_q$-1 aniline).

LCMS: $[M+H]^+$: calculated.: 538.23 found: 538.35, $[M-H]^-$: calculated.: 536.21 found: 536.17.

2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethoxy)phenyl)benzamide (233)



233 was prepared following **general procedure E**, yielding 0.266 g (100%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.25-2.50 (m[dyn], br, 7H, CH(OH)CH_aH$_b$NH, H_{ax} H_{eq}-3,5 in piperazine, H_{ax}-2,6 in CH_2 piperazine), 2.53 (dd, ^{2}J = -12.1, ^{3}J = 10.7, 1H, CH(OH)CH$_a$$H_b$NH), 2.62-2.71 (m[t], br, 2H, H_{eq}-2,6 in CH_2 piperazine), 3.91 (dd, ^{2}J = -9.4, ^{3}J = 6.0, 1H, OCH_aH$_b$CH(OH)), 4.09-4.15 (m, 1H, C*H*(OH)), 4.19 (s, 1H, NC*H*(C_6H_5)$_2$), 4.21 (dd, ^{2}J = -9.4, ^{3}J = 2.7, 1H, CH$_a$$H_b$CH(OH)), 6.82 (d, ^{3}J = 8.9, 1H, *H*-3 salicyl), 6.87 (d, ^{3}J = 8.2, 1H, *H*-4 aniline), 7.10-7.15 (m, 2H, 2x C*H*-4 phenyl), 7.18-7.24 (m, 5H, *H*-5 aniline, 2x *H*-3'',5'' phenyl), 7.30-

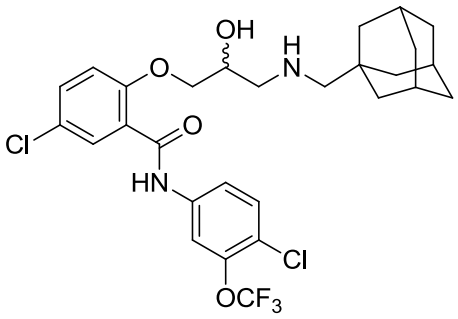
7.36 (m, 5H, *H*-4 salicyl, 2x *H*-2'',6'' phenyl), 7.66 (d, ^{3}J = 8.2, 1H, *H*-6 aniline), 7.69 (br s, 1H, *H*-2 aniline), 8.13 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 10.13 (s, 1H (CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 51.90 (*C*H_2-3'',5'' piperazine), 53.56 (dyn, *C*H_2-2'',6'' piperazine), 59.56 (N*C*H_2CH(OH)), 64.95 (*C*H(OH)), 71.62(O*C*H_2CH(OH)), 76.22 (N*C*H(C_6H_5)$_2$), 113.11 (*C*-2 aniline), 114.26 (*C*-3 salicyl), 116.22 (*C*-4 aniline), 118.54 (*C*-6 aniline), 120.66 ($^{1}J_{CF}$ = -257.1, O*C*F_3 aniline), 123.66 (C_q-1 salicyl), 127.18 (*C*-4'' phenyl), 127.56 (*C*-5 salicyl), 128.04 (*C*-2'',6'' phenyl), 128.66 (*C*-3'',5'' phenyl), 130.00 (*C*-5 aniline), 132.39 (*C*-6 salicyl), 133.02 (*C*-4 salicyl), 140.14 (*C*-1 aniline), 142.57 (d, J_{CF} = 3.4, *C*-3 aniline), 149.60 (C_q-1'' phenyl[1]), 149.61 (C_q-1'' phenyl[2]), 155.10 (C_q-2 salicyl), 162.30 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 640.22 found: 640.32, $[M-H]^-$: calculated.: 638.20 found: 638.30.

Melting point: 71-74°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(4-chloro-3-(trifluoromethoxy)phenyl)benzamide (234)



234 was prepared following **general procedure E**, yielding 0.144 g (56%) of the desired semi-crystalline product.

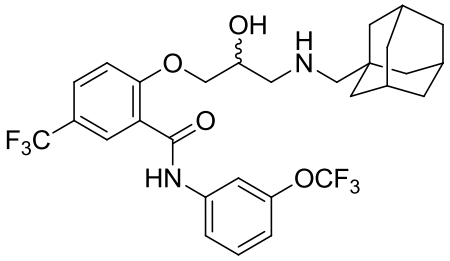
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.51-1.54 (s, br, 6H, C*H*$_2$-adamantane), 1.61-1.67 (m, 3H, C*H*$_2$-adamantane), 1.71-1.76 (m, 3H, C*H*$_2$-adamantane), 1.98 (s, br, 3H, C*H*-adamantane), 2.26, 2.28, 2.31, 2.34 (AB, J_{AB} = -11.5, 2H, NHC*H*$_2$-1-adamantane), 2.72 (dd, ^{2}J = -12.2, ^{3}J = 9.6, 1H, CH(OH)C*H*$_a$H$_b$NH), 2.84 (dd, ^{2}J = -12.2, ^{3}J = 3.9, 1H, CH(OH)CH$_a$*H*$_b$NH), 3.99 (dd, ^{2}J = -9.2, ^{3}J = 6.7, 1H, OC*H*$_a$H$_b$CH(OH)), 4.09-4.15 (m, 1H, C*H*(OH)), 4.28 (dd, ^{2}J = -9.2, ^{3}J = 2.7, 1H, OCH$_a$*H*$_b$CH(OH)), 6.91 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.26 (m [dq], ^{3}J = 9.0, *J* = 1.2, 1H, *H*-5 aniline), 7.40 (dd, ^{3}J = 8.8, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.78 (dd, ^{3}J = 9.0 ^{4}J = 2.6, 1H, *H*-6 aniline), 8.04 (d, ^{4}J = 2.6, 1H, *H*-2 aniline), 8.19 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 10.28 (br s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.49 (*C*H-adamantane), 33.63 (C_q-1'' adamantane), 37.25 (*C*H_2-adamantane), 40.87 (*C*H_2-adamantane), 51.33 (N*C*H_2CH(OH)), 62.24 (NH*C*H_2-1''-

adamantane), 66.87 (*C*H(OH)), 71.89 (O*C*H_2CH(OH)), 114.38 (*C*-3 salicyl), 119.68 (*C*-6 aniline), 120.71 ($^1J_{CF}$ = -256 1, O*C*F_3 aniline), 122.49 (*C*-2 aniline), 123.02 (*C*-5 aniline), 123.43 (*C*-1 salicyl), 127.57 (*C*-5 salicyl), 127.69 (*C*-4 aniline), 132.36 (*C*-6 salicyl), 133.16 (*C*-4 salicyl), 138.33 (*C*-1 aniline), 141.12 (*C*-3 aniline), 155.23 (*C*-2 salicyl), 162.41 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 587.17 found: 587.36, $[M-H]^-$: calculated.: 585.15 found: 585.20.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(3-(trifluoromethoxy)phenyl)-5-(trifluoromethyl)benzamide (235)



235 was prepared following **general procedure E**, yielding 0.226 g (54%) of the desired product.

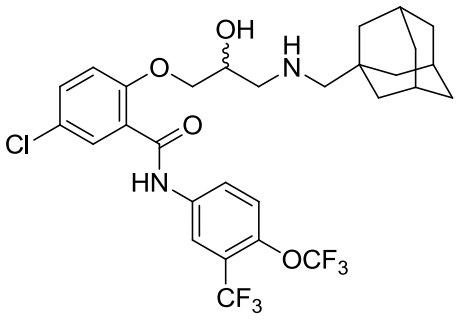
^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 1.39-1.43 (s, br, 6H, CH_2-adamantane), 1.52-1.58 (m, 3H, CH_2-adamantane), 1.61-1.68 (m, 3H, CH_2-adamantane), 1.88 (s, br, 3H, C*H*-adamantane), 2.11 (s, 2H, NHCH_2-1-adamantane)), 2.59-2.71 (m, 2H, CH(OH)CH_2NH), 3.96-4.02 (m, 1H, C*H*(OH)), 4.21-4.29 (d, ^3J = 4.8, 2H, OCH_2CH(OH)), 7.11 (d, ^3J = 8.4, 1H, *H*-4 aniline), 7.44 (d, ^3J = 8.9, 1H, *H*-3 salicyl), 7.48 (dd[t], ^3J = 8.2, 1H, *H*-5 aniline), 7.71 (dd, ^3J = 8.2, ^4J = 1.1, 1H, *H*-6 aniline), 7.89 (dd, ^3J = 8.8, ^4J = 2.2, 1H, *H*-4 salicyl), 7.95 (br s, 1H, *H*-2 aniline), 8.06 (d, ^4J = 2.2, 1H, *H*-6 salicyl), 10.56 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 27.82 (*C*H-adamantane), 33.21 (C_q-1'' adamantane), 36.73 (*C*H_2-adamantane), 40.24 (*C*H_2-adamantane), 53.25 (N*C*H_2CH(OH)), 62.30 (NH*C*H_2-1''-adamantane), 67.72 (*C*H(OH)), 71.88 (O*C*H_2CH(OH)), 111.90 (*C*-2 aniline), 114.35 (*C*-3 salicyl), 115.85 (*C*-4 aniline), 118.40 (*C*-6 aniline), 120.10 ($^1J_{CF}$ = -256.1, O*C*F_3 aniline), 121.46 ($^2J_{CF}$ = 32.5, *C*-5 salicyl), 124.11 ($^1J_{CF}$ = -271.6, *C*F_3 salicyl), 124.22 (*C*-1 salicyl), 127.35 (q, J_{CF} = 3.7, *C*-6 salicyl), 129.77 (q, J_{CF} = 3.3, *C*-4 salicyl), 130.52 (*C*-5 aniline), 140.28 (*C*-1 aniline), 148.53 (q, J_{CF} = 1.5, *C*-3 aniline), 158.95 (*C*-2 salicyl), 162.97 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 587.23 found: 587.36, $[M-H]^-$: calculated.: 585.22 found: 585.39.

Melting point: 130-133°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(4-(trifluoromethoxy)-3-(trifluoromethyl)phenyl)benzamide (236)



236 was prepared following **general procedure E**, yielding 0.168 g (41%) of the desired product.

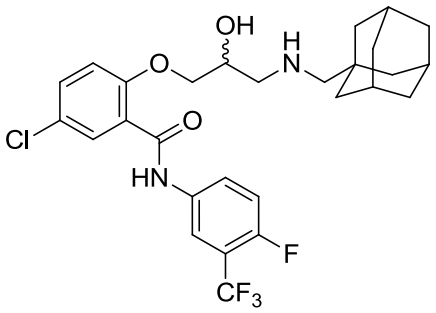
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.51-1.53 (s, br, 6H, CH_2-adamantane), 1.61-1.65 (m, 3H, CH_2-adamantane), 1.71-1.76 (m, 3H, CH_2-adamantane), 1.98 (s, br, 3H, C*H*-adamantane), 2.26, 2.29, 2.34, 2.37 (AB, J_{AB} = -11.6, 2H, NHCH_2-1-adamantane)), 2.74 (dd, ^{2}J = -12.3, ^{3}J = 9.9, 1H, CH(OH)CH_aH$_b$NH), 2.87 (dd, ^{2}J = -12.3, ^{3}J = 3.8, 1H, CH(OH)CH$_a$$H_b$NH), 4.00 (dd, ^{2}J = -9.2, ^{3}J = 6.7, 1H, OCH_aH$_b$CH(OH)), 4.14-4.19 (m, 1H, C*H*(OH)), 4.29 (dd, ^{2}J = -9.2, ^{3}J = 2.7, 1H, OCH$_a$$H_b$CH(OH)), 6.92 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.37 (d, ^{3}J = 8.7, 1H, *H*-5 aniline), 7.42 (dd, ^{3}J = 8.8, ^{4}J = 2.8, 1H, *H*-4 salicyl), 8.16-8.22 (m, 3H, *H*-2,6 aniline, *H*-6 salicyl), 10.43 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.44 (*C*H-adamantane), 33.54 (C_q-1'' adamantane), 37.17 (*C*H$_2$-adamantane), 40.76 (*C*H$_2$-adamantane), 51.42 (N*C*H$_2$CH(OH)), 62.15 (NH*C*H$_2$-1''-adamantane), 66.72 (*C*H(OH)), 71.90 (O*C*H$_2$CH(OH)), 114.46 (*C*-3 salicyl), 119.50 (q, J_{CF} = 5.2, *C*-2 aniline), 120.50 ($^{1}J_{CF}$ = -256 1, O*C*F$_3$ aniline), 121.95 ($^{3}J_{CF}$ =1.4, *C*-5 aniline), 123.38 (*C*-1 salicyl), 124.75 (*C*-6 aniline), 125.23 (q, $^{1}J_{CF}$ = -273.6, *C*F$_3$ aniline), 127.72 (*C*-5 salicyl), 132.41 (*C*-6 salicyl), 133.27 (*C*-4 salicyl), 137.48 (*C*-1 aniline), 142.18 (*C*-4 aniline), 155.21 (*C*-2 salicyl), 162.52 (*C*ONH). *C*-3 aniline not recorded

LCMS: $[M+H]^+$: calculated.: 621.20 found: 621.27, $[M-H]^-$: calculated.: 619.18 found: 619.25.

Melting point: 146-148°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(4-fluoro-3-(trifluoromethyl)phenyl)benzamide (237**)**



237 was prepared following **general procedure E**, yielding 0.202 g (58%) of the desired product.

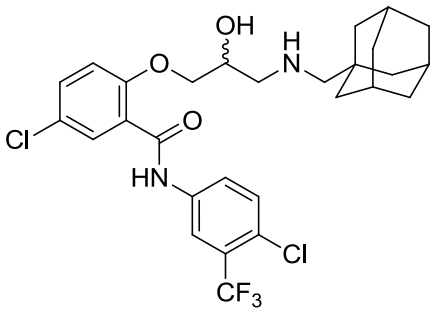
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.49-1.53 (s, br, 6H, C*H*$_2$-adamantane), 1.61-1.67 (m, 3H, C*H*$_2$-adamantane), 1.71-1.77 (m, 3H, C*H*$_2$-adamantane), 1.98 (m, 3H, C*H*-adamantane), 2.24, 2.27, 2.30, 2.33 (AB, J_{AB} = -11.8, 2H, NHC*H*$_2$-1-adamantane), 2.71 (dd, ^{2}J = -12.2, ^{3}J = 9.6, 1H, CH(OH)C*H*$_a$H$_b$NH), 2.84 (dd, ^{2}J = -12.2, ^{3}J = 3.8, 1H, CH(OH)CH$_a$*H*$_b$NH), 3.99 (dd, ^{2}J = -9.3, ^{3}J = 6.9, 1H, OC*H*$_a$H$_b$CH(OH)), 4.08-4.14 (m, 1H, C*H*(OH)), 4.28 (dd, ^{2}J = -9.3, ^{3}J = 2.7, 1H, OCH$_a$*H*$_b$CH(OH)), 6.92 (d, ^{3}J = 8.7, 1H, *H*-3 salicyl), 7.15 (dd [t], ^{3}J = 9.6, 1H, *H*-5 aniline), 7.41 (dd, ^{3}J = 8.7, ^{4}J = 2.3, 1H, *H*-4 salicyl), 8.06-8.12 (m, 2H, *H*-2,6 aniline), 8.20 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 10.35 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.49 (*C*H-adamantane), 33.60 (*C*$_q$-1'' adamantane), 37.25 (*C*H$_2$-adamantane), 40.84 (*C*H$_2$-adamantane), 51.36 (N*C*H$_2$CH(OH)), 62.27 (NH*C*H$_2$-1''-adamantane), 66.91 (*C*H(OH)), 71.94 (O*C*H$_2$CH(OH)), 114.45 (*C*-3 salicyl), 117.23 (d, $^{2}J_{CF}$ = 21.7, *C*-5 aniline), 118.36 (dd, $^{2}J_{CF}$ = 32.9 $^{2}J_{CF}$ = 13.0, *C*-3 aniline), 119.22 (q, J_{CF} = 4.7, *C*-2 aniline), 122.65 (q, $^{1}J_{CF}$ = -273.2, *C*F$_3$ aniline), 123.46 (*C*-1 salicyl), 125.65 ($^{3}J_{CF}$ = 7.8, *C*-6 aniline), 127.60 (*C*-5 salicyl), 132.33 (*C*-6 salicyl), 133.11 (*C*-4 salicyl), 135.11 ($^{4}J_{CF}$ = 3.2, *C*-1 aniline), 155.24 (*C*-2 salicyl), 155.95 ($^{1}J_{CF}$ = -253.3, *C*-4 aniline), 162.37 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 555.20 found: 555.31, $[M-H]^-$: calculated.: 553.19 found: 553.29.

Melting point: 140-143°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(4-chloro-3-(trifluoromethyl)phenyl)benzamide (238)



238 was prepared following **general procedure E**, yielding 0.167 g (41%) of the desired product.

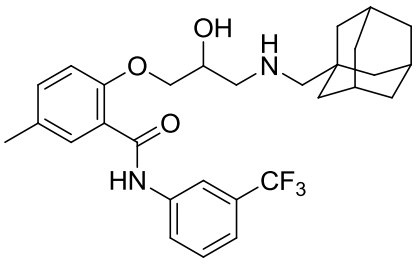
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.50-1.53 (s, br, 6H, C*H*$_2$-adamantane), 1.62-1.67 (m, 3H, C*H*$_2$-adamantane), 1.71-1.78 (m, 3H, C*H*$_2$-adamantane), 1.99 (m, 3H, C*H*-adamantane), 2.23, 2.26, 2.30, 2.33 (AB, J_{AB} = -11.5, 2H, NHC*H*$_2$-1-adamantane), 2.70 (dd, ^{2}J = -12.3, ^{3}J = 9.7, 1H, CH(OH)C*H*$_a$H$_b$NH), 2.84 (dd, ^{2}J = -12.3, ^{3}J = 3.8, 1H, CH(OH)CH$_a$*H*$_b$NH), 3.98 (dd, ^{2}J = -9.2, ^{3}J = 6.9, 1H, OC*H*$_a$H$_b$CH(OH)), 4.08-4.14 (m, 1H, C*H*(OH)) 4.29 (dd, ^{2}J = -9.2, ^{3}J = 2.7, 1H, OCH$_a$*H*$_b$CH(OH)), 6.92 (d, ^{3}J = 8.9, 1H, *H*-3 salicyl), 7.41 (dd, ^{3}J = 8.8, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.44 (m, überlagert *J* = 8.3, 1H, *H*-5 aniline), 8.11 (dd, ^{3}J = 8.7, ^{4}J = 2.4, 1H, *H*-6 aniline), 8.14 (d, ^{4}J = 2.4, 1H, *H*-2 aniline), 8.20 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 10.40 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.50 (*C*H-adamantane), 33.61 (*C*$_q$-1'' adamantane), 37.26 (*C*H$_2$-adamantane), 40.85 (*C*H$_2$-adamantane), 51.33 (N*C*H$_2$CH(OH)), 62.27 (NH*C*H$_2$-1''-adamantane), 66.90 (*C*H(OH)), 71.93 (O*C*H$_2$CH(OH)), 114.42 (*C*-3 salicyl), 119.69 (q, $^{3}J_{CF}$ = 5.8, *C*-2 aniline), 122.90 (q, $^{1}J_{CF}$ = -273.5, *C*F$_3$ aniline), 123.36 (*C*-1 salicyl), 124.47 (*C*-6 aniline), 126.48 (*C*-4 aniline), 127.62 (*C*-5 salicyl), 128.63 (q, $^{2}J_{CF}$ = 30.9, *C*-3 aniline), 131.94 (*C*-5 aniline), 132.36 (*C*-6 salicyl), 133.21 (*C*-4 salicyl), 137.77 (*C*-1 aniline), 155.24 (*C*-2 salicyl), 162.45 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 571.17 found: 571.26, $[M-H]^-$: calculated.: 569.16 found: 569.08.

Melting point: 128-130°C

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-methyl-*N*-(3-(trifluoromethyl)phenyl)benzamide (239)



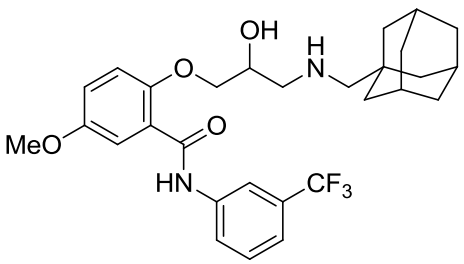
239 was prepared following **general procedure E**, yielding 0.160 g (21%) of the desired semi-crystalline product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.48-1.53 (s, br, 6H, CH_2-adamantane), 1.61-1.66 (m, 3H, CH_2-adamantane), 1.70-1.76 (m, 3H, CH_2-adamantane), 1.98 (s, br, 3H, C*H*-adamantane), 2.23, 2.26, 2.31, 2.34 (AB, J_{AB} = -11.8, 2H, NHCH_2-1-adamantane), 2.35 (s, 3H, CH_3), 2.76 (dd, ^2J = -12.2, ^3J = 9.5, 1H, CH(OH)CH_aH$_b$NH), 2.84 (dd, ^2J = -12.2, ^3J = 3.8, 1H, CH(OH)CH$_a$$H_b$NH), 4.02 (dd, ^2J = -9.4, ^3J = 6.3, 1H, OCH_aH$_b$CH(OH)), 4.10-4.17 (m, 1H, C*H*(OH)), 4.28 (dd, ^2J = -9.4, ^3J = 2.7, 1H, OCH$_a$$H_b$CH(OH)), 6.88 (d, 1H, ^3J = 8.3, *H*-3 salicyl), 7.27 (dd, 1H, überlagert, ^4J = 2.3, *H*-4 salicyl), 7.34 (d, ^3J = 7.8, 1H, *H*-4 aniline), 7.44 (dd [t], ^3J = 7.9, 1H, *H*-5 aniline), 8.05-8.10 (m, 2H, *H*-6 aniline, *H*-6 salicyl), 8.14 (s, 1H, *H*-2 aniline), 10.40 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 20.59 (*C*H$_3$), 28.48 (*C*H-adamantane), 33.55 (*C*$_q$-1'' adamantane), 37.23 (*C*H$_2$-adamantane), 40.78 (*C*H$_2$-adamantane), 51.61 (N*C*H$_2$CH(OH)), 62.16 (NH*C*H$_2$-1''-adamantane), 66.96 (*C*H(OH)), 71.45 (O*C*H$_2$CH(OH)), 112.86 (*C*-3 salicyl), 117.34 (q, $^3J_{CF}$ = 3.9, *C*-2 aniline), 120.33 (q, $^3J_{CF}$ = 3.8, *C*-4 aniline), 121.73 (*C*-1 salicyl), 123.53 (*C*-6 aniline), 129.43 (*C*-5 aniline), 131.26 (q, $^2J_{CF}$ = 32.3, *C*-3 aniline), 131.57 (*C*-5 salicyl), 132.91 (*C*-6 salicyl), 133.96 (*C*-4 salicyl), 139.69 (*C*-1 aniline), 154.70 (*C*-2 salicyl), 163.97 (*C*ONH). CF_3 not recorded

LCMS: $[M+H]^+$: calculated.: 517.27 found: 517.38, $[M-H]^-$: calculated.: 515.25 found: 515.41.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-methoxy-*N*-(3-(trifluoromethyl)phenyl)benzamide (240)



240 was prepared following **general procedure E**, yielding 0.251 g (44%) of the desired product.

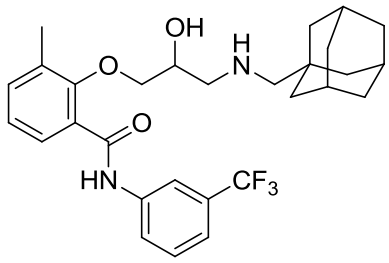
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.49-1.52 (s, br, 6H, C*H*$_2$-adamantane), 1.60-1.66 (m, 3H, C*H*$_2$-adamantane), 1.70-1.76 (m, 3H, C*H*$_2$-adamantane), 1.97 (s, br, 3H, C*H*-adamantane), 2.22, 2.25, 2.29, 2.32 (AB, J_{AB} = -11.5, 2H, NHC*H*$_2$-1-adamantane), 2.72 (dd, ^{2}J = -12.3, ^{3}J = 9.7, 1H, CH(OH)C*H*$_a$H$_b$NH), 2.82 (dd, ^{2}J = -12.3, ^{3}J = 3.8, 1H, CH(OH)CH$_a$*H*$_b$NH), 3.84 (s, 3H, OC*H*$_3$), 3.99 (dd, ^{2}J = -9.3, ^{3}J = 6.3, 1H, OC*H*$_a$H$_b$CH(OH)), 4.06-4.13 (m, 1H, C*H*(OH)), 4.25 (dd, ^{2}J = -9.3, ^{3}J = 2.7, 1H, OCH$_a$*H*$_b$CH(OH)), 6.92 (d, 1H, ^{3}J = 8.9, *H*-3 salicyl), 7.02 (dd, 1H, ^{3}J = 9.0, ^{4}J = 3.2, *H*-4 salicyl), 7.34 (d, ^{3}J = 7.7, 1H, *H*-4 aniline), 7.43 (dd [t], ^{3}J = 7.9, 1H, *H*-5 aniline), 7.80 (d, 1H, ^{4}J = 3.2, *H*-6 salicyl), 8.06 (d, ^{3}J = 8.1, 1H, *H*-6 aniline), 8.18 (s, 1H, *H*-2 aniline), 10.52 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.49(*C*H-adamantane), 33.57 (*C*$_q$-1'' adamantane), 37.26 (*C*H$_2$-adamantane), 40.81 (*C*H$_2$-adamantane), 51.52 (N*C*H$_2$CH(OH)), 55.96 (O*C*H$_3$), 62.22 (NH*C*H$_2$-1''-adamantane), 67.10 (*C*H(OH)), 72.14 (O*C*H$_2$CH(OH)), 114.67 (*C*-3 salicyl), 115.56 (*C*-6 salicyl), 117.41 (q, $^{3}J_{CF}$ = 4.1, *C*-2 aniline), 120.33 (*C*-4 salicyl), 120.42 (q, $^{3}J_{CF}$ = 3.8, *C*-4 aniline), 122.66 (*C*-1 salicyl), 123.57 (*C*-6 aniline), 124.23 (q, $^{1}J_{CF}$ = -272.2, *C*F3), 129.39 (*C*-5 aniline), 131.26 (q, $^{2}J_{CF}$ = 32.1, *C*-3 aniline), 139.59 (*C*-1 aniline), 150.99 (*C*-5 salicyl), 154.47 (*C*-2 salicyl), 163.56 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 533.26 found: 533.30, $[M-H]^-$: calculated.: 531.25 found: 531.27.

Melting point: 133-136°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-3-methyl-*N*-(3-(trifluoromethyl)phenyl)benzamide (241)



241 was prepared following **general procedure E**, yielding 0.132 g (27%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.46-1.51 (s, br, 6H, C*H*$_2$-adamantane), 1.60-1.65 (m, 3H, C*H*$_2$-adamantane), 1.70-1.75 (m, 3H, C*H*$_2$-adamantane), 1.96 (s, br, 3H, C*H*-adamantane),

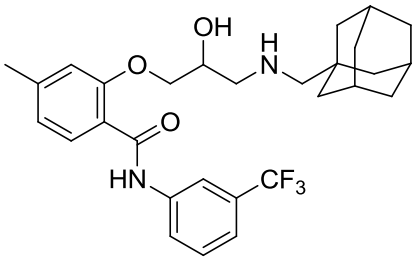
2.21, 2.24, 2.27, 2.30 (AB, J_{AB} = -11.5, 2H, NHCH_2-1-adamantane), 2.37 (s, 3H, CH_3), 2.73 (dd, ^2J = -12.1, ^3J = 9.3, 1H, CH(OH)CH_aH$_b$NH), 2.80 (dd, ^2J = -12.1, ^3J = 4.1, 1H, CH(OH)CH$_a$$H_b$NH), 3.87 (dd, ^2J = -9.9, ^3J = 6.2, 1H, OCH_aH$_b$CH(OH)), 3.97 (dd, ^2J = -9.9, ^3J = 2.6, 1H, OCH$_a$$H_b$CH(OH)), 4.01-4.08 (m, 1H, C*H*(OH)), 7.20 (dd [t], 1H, ^3J = 7.7, *H*-5 salicyl), 7.37 (m [t], 2H, *H*-4 aniline, *H*-4 salicyl), 7.45 (dd [t], ^3J = 7.9, 1H, *H*-5 aniline), 8.07 (m [d], 2H, *H*-6 aniline, *H*-6 salicyl), 8.18 (s, 1H, *H*-2 aniline), 10.23 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 16.38 (*C*H$_3$), 28.49 (*C*H-adamantane), 33.58 (C_q-1'' adamantane), 37.26 (*C*H$_2$-adamantane), 40.82 (*C*H$_2$-adamantane), 51.44 (N*C*H$_2$CH(OH)), 62.26 (NH*C*H$_2$-1''-adamantane), 67.70 (*C*H(OH)), 76.52 (O*C*H$_2$CH(OH)), 117.75 (q, $^3J_{CF}$ = 4.0, *C*-2 aniline), 120.61 (q, $^3J_{CF}$ = 3.7, *C*-4 aniline), 123.90 (*C*-6 aniline), 125.13 (*C*-5 salicyl), 126.38 (*C*-1 salicyl), 129.35 (*C*-5 aniline), 130.19 (*C*-6 salicyl), 131.70 (*C*-3 salicyl), 135.59 (*C*-4 salicyl), 139.34 (*C*-1 aniline), 155.17 (*C*-2 salicyl), 163.80 (*C*ONH). C-3 Aniline and CF3 not recorded.

LCMS: $[M+H]^+$: calculated.: 517.27 found: 517.32, $[M-H]^-$: calculated.: 515.25 found: 515.35.

Melting point: 55-58°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-4-methyl-*N*-(3-(trifluoromethyl)phenyl)benzamide (242)



242 was prepared following **general procedure E**, yielding 0.134 g (45%) of the desired product.

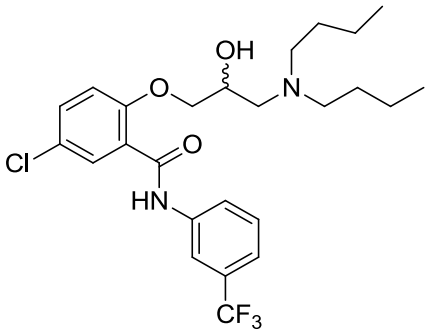
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.48-1.54 (s, br, 6H, CH_2-adamantane), 1.61-1.66 (m, 3H, CH_2-adamantane), 1.70-1.76 (m, 3H, CH_2-adamantane), 1.98 (s, br, 3H, C*H*-adamantane), 2.23, 2.26, 2.30,2.33 (AB, J_{AB} = -11.5, 2H, NHCH_2-1-adamantane), 2.39 (s, 3H, CH_3), 2.75 (dd, ^2J = -12.2, ^3J = 9.5, 1H, CH(OH)CH_aH$_b$NH), 2.83 (dd, ^2J = -12.2, ^3J = 3.8, 1H, CH(OH)CH$_a$$H_b$NH), 4.02 (dd, ^2J = -9.3, ^3J = 6.3, 1H, OCH_aH$_b$CH(OH)), 4.08-4.15 (m, 1H, C*H*(OH)), 4.28 (dd, ^2J = -9.3, ^3J = 2.8, 1H, OCH$_a$$H_b$CH(OH)), 6.77 (s, 1H, *H*-3 salicyl), 6.93 (d, 1H, ^3J = 7.9, *H*-5 salicyl), 7.32 (d, ^3J = 7.7, 1H, *H*-4 aniline), 7.42 (dd [t], ^3J = 7.7, ^3J = 8.2, 1H, *H*-5 aniline), 8.07 (d, ^3J = 8.2, 1H, *H*-6 aniline), 8.12-8.16 (m, 2H, *H*-2 aniline, *H*-6 salicyl), 10.37 (br s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 21.87 (*C*H_3), 28.49 (*C*H-adamantane), 33.56 (C_q-1'' adamantane), 37.26 (*C*H_2-adamantane), 40.80 (*C*H_2-adamantane), 51.59 (N*C*H_2CH(OH)), 62.20 (NH*C*H_2-1''-adamantane), 67.01 (*C*H(OH)), 71.23 (O*C*H_2CH(OH)), 113.43(*C*-3 salicyl), 117.26 (q, $^{3}J_{CF}$ = 3.9, *C*-2 aniline), 119.35 (*C*-1 salicyl), 120.21 (q, $^{3}J_{CF}$ = 3.8, *C*-4 aniline), 122.93 (*C*-5 salicyl), 123.47 (*C*-6 aniline), 126.96 (q, $^{1}J_{CF}$ = -271.7, *C*F3), 129.39 (*C*-5 aniline), 131.21 (q, $^{2}J_{CF}$ = 32.1, *C*-3 aniline), 132.58 (*C*-6 salicyl), 139.76 (*C*-1 aniline), 144.50 (*C*-4 salicyl), 156.68 (*C*-2 salicyl), 163.90 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 517.27 found: 617.27, $[M-H]^-$: calculated.: 515.25 found: 515.25.

Melting point: 144-148°C.

5-chloro-2-(3-(dibutylamino)-2-hydroxypropoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (243)



243 was prepared following **general procedure E**, yielding 0.495 g (68%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 0.87 (m, 6H, 2x C*H*$_3$) 1.19-1.33 (m, 4H, 2x C*H*$_2$) 1.34-1.45 (m, 4H, 2x C*H*$_2$) 2.42-2.45 (2H), 2.50-2.62 (m, 4H, 2x C*H*$_2$) 2.75-3.26 (m, br, 1H, NC*H*$_2$CH(OH)), 3.99 (dd, ^{2}J = -9.3, ^{3}J = 6.5, 1H, OC*H*$_a$H$_b$CH(OH)), 4.10-4.17 (m, 1H, C*H*(OH)), 4.28 (dd, ^{2}J = -9.3, ^{3}J = 2.6, 1H, OCH$_a$*H*$_b$CH(OH)), 6.92 (d, ^{3}J = 8.9, 1H, *H*-3 salicyl), 7.35 (d, ^{3}J = 7.8, 1H, *H*-4 aniline), 7.39-7.47 (m, 2H, *H*-4 salicyl, *H*-5 aniline)), 8.07-8.11 (m, 2H *H*-2,6 aniline), 8.22 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 10.35 (br s, 1H, CON*H*).

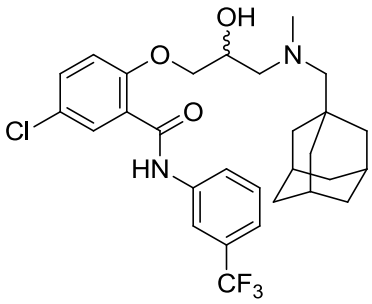
$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 14.04 (N($CH_2CH_2CH_2$*C*H_3)$_2$), 20.57 (N(CH_2CH_2*C*H_2CH_3)$_2$), 29.35 (N(CH_2*C*$H_2CH_2CH_3$)$_2$), 54.01 (CH(OH)*C*H_2N), 56.29 (N(*C*$H_2CH_2CH_2CH_3$)$_2$), 65.54 (*C*H(OH)), 71.85 (O*C*H_2CH(OH)), 114.28 (*C*-3 salicyl), 117.47 (q, $^{3}J_{CF}$ = 4.0, *C*-2' in 3'-CF_3-aniline), 120.64 (q, $^{3}J_{CF}$ = 3.8, *C*-4' in 3'-CF_3-aniline),123.63 (*C*-6' in 3'-CF_3-aniline), 124.17 (q, $^{1}J_{CF}$ = -272.5, *C*F_3), 124.23 (C_q-1 salicyl), 127.51 (C_q-5 salicyl), 129.46 (*C*-5'

in 3'-CF_3-aniline), 131.27 (q, $^2J_{CF}$ = 32.3, C_q-3' in 3'-CF_3-aniline), 132.37 (*C*-6 salicyl), 133.03 (*C*-4 salicyl), 139.32 (C_q-1' in 3'-CF_3-aniline), 155.23 (C_q-2 salicyl), 162.44 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 501.21 found: 501.32, $[M-H]^-$: calculated.: 499.20 found: 499.22.

Melting point: 58-60°C.

2-(3-((adamantan-1-ylmethyl)(methyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (244)



244 was prepared following **general procedure E**, yielding 0.599 g (93%) of the desired product.

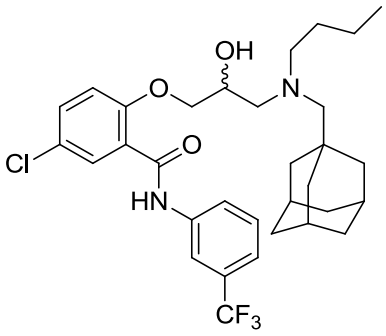
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.45-1.50 (s, br, 6H, CH_2-adamantane), 1.53-1.60 (m, 3H, CH_2-adamantane), 1.64-1.72 (m, 3H, CH_2-adamantane), 1.91 (s, br, 3H, C*H*-adamantane), 2.09-2.18 (m [s mit starken 13C Satelliten], 2H, NCH_2-1-adamantane)), 2.35 (s, 3H, NCH_3), 2.47-2.58 (m, 2H, CH(OH)CH_2NH), 4.00 (dd, ^2J = -9.2, ^3J = 6.6, 1H, OC$H_a$$H_b$CH(OH)), 4.09-4.16 (m, 1H, C*H*(OH)), 4.27 (dd, ^2J = -9.2, ^3J = 2.6, 1H, OCH$_a$$H_b$CH(OH)), 6.92 (d, ^3J = 8.9, 1H, *H*-3 salicyl), 7.35 (d, ^3J = 7.7, 1H, *H*-4 aniline), 7.39-7.47 (m, 2H, *H*-5 aniline, *H*-4 salicyl), 8.08 (d, ^3J = 8.1, 1H, *H*-6 aniline), 8.14 (s [t], 1H, *H*-2 aniline), 8.23 (d, ^4J = 2.8, 1H, *H*-6 salicyl), 10.36 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.47 (*C*H-adamantane), 34.90 (C_q-1'' adamantane), 37.12 (*C*H_2-adamantane), 41.42 (*C*H_2-adamantane), 45.80 (N*C*H_3), 62.74 (N*C*H_2CH(OH)), 66.28 (*C*H(OH)), 71.78 (O*C*H_2CH(OH)), 72.17 (N(CH_3)*C*H_2-1-adamantane), 114.34 (*C*-3 salicyl), 117.48 (q, $^3J_{CF}$ = 4.0, *C*-2' in 3'-CF_3-aniline), 120.65 (q, $^3J_{CF}$ = 3.8, *C*-4' in 3'-CF_3-aniline), 123.60 (*C*-6' in 3'-CF_3-aniline), 123.64 (C_q-1 salicyl), 124.19 (q, $^1J_{CF}$ = -271, *C*F3), 127.56 (C_q-5 salicyl), 129.47 (*C*-5' in 3'-CF_3-aniline), 131.28 (q, $^2J_{CF}$ = 32.3, C_q-3' in 3'-CF_3-aniline), 132.40 (*C*-6 salicyl), 133.04 (*C*-4 salicyl), 139.33 (C_q-1' in 3'-CF_3-aniline), 155.20 (C_q-2 salicyl), 162.40 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 551.23 found: 551.34, $[M-H]^-$: calculated.: 549.21 found: 549.24.

Melting point: 140-143°C.

2-(3-((adamantan-1-ylmethyl)(butyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (245)



245 was prepared following **general procedure E**, yielding 0.467 g (97%) of the desired product.

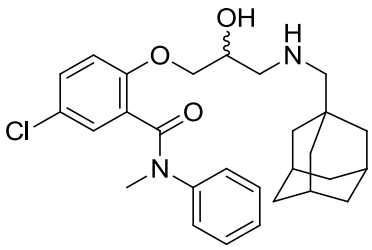
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.20 (t, 3H, C*H*$_3$), 1.29-1.36 (m, 2H, C*H*$_2$CH$_3$), 1.43-1.46 (m, 2H, C*H*$_2$CH$_2$CH$_3$), 1.49-1.52 (s, br, 6H, C*H*$_2$-adamantane), 1.54-1.61 (m, 3H, C*H*$_2$-adamantane), 1.66-1.72 (m, 3H, C*H*$_2$-adamantane), 1.93 (s, br, 3H, C*H*-adamantane), 2.10, 2.14, 2.21, 2.24 (AB, J_{AB} = -14.1, 2H, NHC*H*$_2$-1-adamantane), 2.37-2.46 (m, 1H, NHC*H*$_a$H$_b$CH$_2$CH$_2$CH$_3$), 2.47-2.60 (m, 3H, CH(OH)C*H*$_2$NH, NHCH$_a$*H*$_b$CH$_2$CH$_2$CH$_3$), 4.00 (dd, ^{2}J = -9.1, ^{3}J = 6.9, 1H, OC*H*$_a$H$_b$CH(OH)), 4.07-4.14 (m, 1H, C*H*(OH)), 4.25(dd, ^{2}J = -9.1, ^{3}J = 2.6, 1H, OCH$_a$*H*$_b$CH(OH)), 6.92 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.35 (d, ^{3}J = 7.8, 1H, *H*-4 aniline), 7.41 (d, ^{3}J = 8.8, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.43 (dd [t], ^{3}J = 7.8, 1H, *H*-5 aniline), 8.08 (d, ^{3}J = 7.8, 1H, *H*-6 aniline), 8.16 (br s, 1H, *H*-2 aniline), 8.24 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 10.38 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 14.09 (*C*H$_3$), 20.63 (*C*H$_2$CH$_3$), 28.52 (*C*H-adamantane), 29.73 (*C*H$_2$CH$_2$CH$_3$), 34.66 (*C*$_q$-1'' adamantane), 37.13 (*C*H$_2$-adamantane), 41.66 (*C*H$_2$-adamantane), 57.16 (N*C*H$_2$), 59.23 (N*C*H$_2$CH(OH)), 66.16 (*C*H(OH)), 69.32 (N(CH$_3$)*C*H$_2$-1-adamantane), 71.91 (O*C*H$_2$CH(OH)), 114.34 (*C*-3 salicyl), 117.53 (q, $^{3}J_{CF}$ = 3.9, *C*-2' in 3'-CF_3-aniline), 120.63 (q, $^{3}J_{CF}$ = 3.7, *C*-4' in 3'-CF_3-aniline), 123.60 (*C*-6' in 3'-CF_3-aniline), 123.65 (*C*$_q$-1 salicyl), 124.21 (q, $^{1}J_{CF}$ = -272.9, *C*F$_3$), 127.56 (*C*$_q$-5 salicyl), 129.42 (*C*-5' in 3'-CF_3-aniline), 131.29 (q, $^{2}J_{CF}$ = 32.2, *C*$_q$-3' in 3'-CF_3-aniline), 132.42 (*C*-6 salicyl), 133.02 (*C*-4 salicyl), 139.38 (*C*$_q$-1' in 3'-CF_3-aniline), 155.24 (*C*$_q$-2 salicyl), 162.39 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 593.28 found: 593.42, $[M-H]^-$: calculated.: 591.26 found: 519.25.

Melting point: 129-133°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-methyl-*N*-phenylbenzamide (246)



246 was prepared following **general procedure E**, yielding 0.163 g (46%) of the desired product.

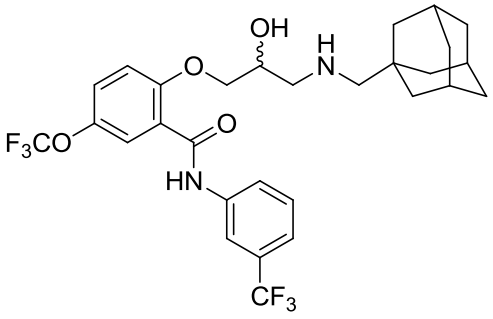
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.51-1.55 (s, br, 6H, CH_2-adamantane), 1.62-1.66 (m, 3H, CH_2-adamantane), 1.69-1.74 (m, 3H, CH_2-adamantane), 1.97 (s, br, 3H, C*H*-adamantane), 2.25, 2.28, 2.30, 2.33 (AB, J_{AB} = -11.6, 2H, NHCH_2-1-adamantane), 2.66-2.81 (m, 2H, CH(OH)CH_2NH), 3.46 (br s, 3H, C(O)NCH_3), 3.87-3.95 (m, 1H, C*H*(OH)), 3.97-4.05 (m, 2H, CH(OH)C$H_a$$H_b$NH), 6.70 (d, ^{3}J = 8.7, 1H, *H*-3 salicyl), 6.96 (br s, 1H, *H*-6 salicyl), 7.04-7.23 (m, 6H Ar*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.55 (*C*H-adamantane), 33.66 (C_q-1'' adamantane), 37.32 (*C*H_2-adamantane), 37.35 (C(O)N*C*H_3), 40.93 (*C*H_2-adamantane), 52.51 (N*C*H_2CH(OH)), 62.84 (NH*C*H_2-1''-adamantane), 68.03 (O*C*H_2CH(OH)), 72.99 (*C*H(OH)), 115.09 (*C*-3 salicyl), 125.86 (*C*-1 salicyl), 126.71 (*C*-2,6 aniline), 127.36 (*C*-4 aniline), 128.26 (*C*-6 salicyl), 128.95 (*C*-5 salicyl), 129.15 (*C*-3,5 aniline), 130.07 (*C*-4 salicyl), 143.53 (*C*-1 aniline), 154.00 (*C*-2 salicyl), 168.02 (*C*ONMe).

LCMS: $[M+H]^+$: calculated.: 483.24 found: 483.35.

Melting point: 83-90°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-(trifluoromethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (247)



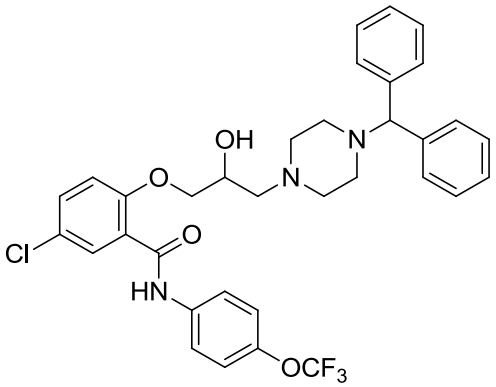
247 was prepared following **general procedure E**, yielding 0.019 g (42%) of the desired semi-crystalline product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.50-1.53(s, br, 6H, CH_2-adamantane), 1.61-1.65 (m, 3H, CH_2-adamantane), 1.70-1.76 (m, 3H, CH_2-adamantane), 1.98 (s, br, 3H, C*H*-adamantane), 2.26, 2.29, 2.35, 2.38 (AB, J_{AB} = -11.7, 2H, NHCH_2-1-adamantane), 2.78 (dd, ^{2}J = -12.3, ^{3}J = 9.7, 1H, CH(OH)CH_aH$_b$NH), 2.89 (dd, ^{2}J = -12.3, ^{3}J = 3.5, 1H, CH(OH)CH$_a$$H_b$NH), 4.05 (dd, ^{2}J = -9.2, ^{3}J = 6.3, 1H, OCH_aH$_b$CH(OH)), 4.18-4.23 (m, 1H, C*H*(OH)), 4.30 (dd, ^{2}J = -9.2, ^{3}J = 2.8, 1H, OCH$_a$$H_b$CH(OH)), 6.98 (d, ^{3}J = 8.9, 1H, *H*-3 salicyl), 7.32 (dd, ^{3}J = 8.9, ^{4}J = 3.0, 1H, *H*-4 salicyl), 7.36 (d, ^{3}J = 7.9, 1H, *H*-6 aniline), 7.45 (dd [t], ^{3}J = 7.9, ^{3}J = 8.0, 1H, *H*-5 aniline), 8.05 (d, ^{3}J = 8.0, 1H, *H*-4 aniline), 8.13 (d, ^{4}J = 3.0, 1H, *H*-6 salicyl), 8.15 (s, 1H, *H*-2 aniline), 10.33 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.43 (*C*H-adamantane), 33.51 (C_q-1'' adamantane), 37.15 (*C*H$_2$-adamantane), 40.71 (*C*H$_2$-adamantane), 51.71 (N*C*H$_2$CH(OH)), 62.13 (NH*C*H$_2$-1''-adamantane), 66.69 (*C*H(OH)), 71.90 (O*C*H$_2$CH(OH)), 114.09 (*C*-3 salicyl), 117.43 (q, $^{3}J_{CF}$ = 3.9, *C*-2 aniline), 120.64 ($^{1}J_{CF}$ = -257.7, O*C*F$_3$ aniline), 120.77 (q, $^{3}J_{CF}$ = -3.8, *C*-4 aniline), 123.64 (*C*-6 aniline), 124.17 ($^{1}J_{CF}$ = -273.0, *C*F$_3$ aniline), 125.42 (*C*-6 salicyl), 126.08 (*C*-4 salicyl), 129.53 (*C*-5 aniline), 131.37 ($^{2}J_{CF}$ = 32.1, *C*-3 aniline), 139.27 (*C*-1 aniline), 143.69 (q, J_{CF} = 1.5, *C*-5 salicyl), 155.01 (*C*-2 salicyl), 162.27 (*C*ONH). C-1 salicyl not recorded

LCMS: $[M+H]^+$: calculated.: 587.23 found: 587.28, $[M-H]^-$: calculated.: 585.22 found: 585.18.

2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-5-chloro-*N*-(4-(trifluoromethoxy)phenyl)benzamide (248)



248 was prepared following **general procedure E**, yielding 0.178 g (93%) of the desired product.

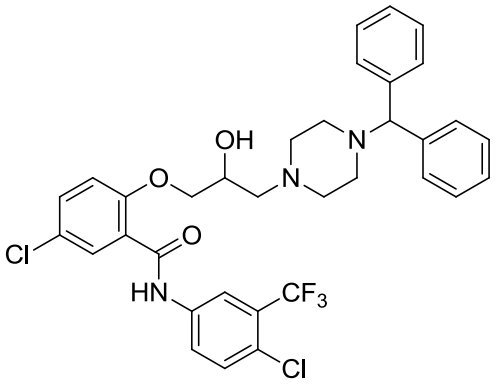
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.30-2.56 (m[dyn], br, 7H, CH(OH)C$H_a$$H_b$NH, H_{ax} H_{eq}-3,5 in piperazine, H_{ax}-2,6 in CH_2 piperazine), 2.61 (dd, ^{2}J = -12.3, ^{3}J = 10.8, 1H, CH(OH)C$H_a$$H_b$NH), 2.66-2.80 (m[t], br, 2H, H_{eq}-2,6 in CH_2 piperazine), 3.98 (dd, ^{2}J = -9.5, ^{3}J = 5.9, 1H, OC$H_a$$H_b$CH(OH)), 4.15-4.21 (m, 1H, CH(OH)), 4.26 (s, 1H, NCH(C_6H_5)$_2$), 4.28 (dd, ^{2}J = -9.3, ^{3}J = 2.8, 1H, OC$H_a$$H_b$CH(OH)), 6.89 (d, ^{3}J = 8.7, 1H, *H*-3 salicyl), 7.14-7.22 (m, 4H, *H*-3',5' aniline, 2x C*H*-4 phenyl), 7.26-7.31 (m, 4H, 2x *H*-3'',5'' phenyl), 7.37-7.43 (m, 5H, *H*-4 salicyl, 2x *H*-2'',6'' phenyl), 7.79 (m, 2H, *H*-2',6' aniline), 8.20 (d, ^{4}J = 2.7, 1H, *H*-6 salicyl), 10.12 (s, 1H (CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 51.87 (*C*H_2-3'',5'' piperazine), 53.63 (dyn, *C*H_2-2'',6'' piperazine), 59.62 (N*C*H_2CH(OH)), 64.97 (*C*H(OH)), 71.54 (O*C*H_2CH(OH)), 76.17 (N*C*H(C_6H_5)$_2$), 114.30 (*C*-3 salicyl), 120.65 ($^{1}J_{CF}$ = -257.1, O*C*F_3 aniline), 121.66 (*C*-2,6 aniline), 121.68 (*C*-3,5 aniline), 123.82 (C_q-1 salicyl), 127.22 (*C*-4'' phenyl), 127.56 (*C*-5 salicyl), 128.04 (*C*-2'',6'' phenyl), 128.67 (*C*-3'',5'' phenyl), 132.37 (*C*-6 salicyl), 132.94 (*C*-4 salicyl), 137.38 (*C*-1 aniline), 142.46 (d, $^{3}J_{CF}$ = 8.3, *C*-4 aniline), 145.26 (C_q-1'' phenyl[1]), 145.28 (C_q-1'' phenyl[2]), 155.07 (C_q-2 salicyl), 162.24 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 640.22 found: 640.25, $[M-H]^-$: calculated.: 638.20 found: 638.15.

Melting point: 155-165°C.

2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-5-chloro-*N*-(4-chloro-3-(trifluoromethyl)phenyl)benzamide (249)



249 was prepared following **general procedure E**, yielding 0.311 g (95%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.36-2.63 (m[dyn], br, 8H, CH(OH)C$H_a$$H_b$NH, CH(OH)C$H_a$$H_b$NH, H_{ax} H_{eq}-3,5 in piperazine, H_{ax}-2,6 in CH_2 piperazine), 2.72-2.80 (m[t], br, 2H, H_{eq}-2,6 in CH_2 piperazine), 3.97 (dd, ^{2}J = -9.2, ^{3}J = 6.4, 1H, OC$H_a$$H_b$CH(OH)), 4.19-4.26 (m, 1H, C*H*(OH)), 4.27 (s, 1H, NC*H*(C_6H_5)$_2$), 4.29 (dd, ^{2}J = -9.2, ^{3}J = 2.6, überlagert, 1H,

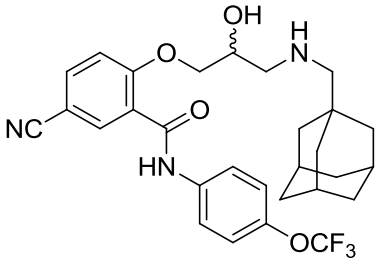
$OCH_aH_bCH(OH)$), 6.89 (d, ^3J = 8.7, 1H, *H*-3 salicyl), 7.17-7.22 (m, 2H, 2x C*H*-4 phenyl), 7.25-7.31 (m, 4H, 2x *H*-3'',5'' phenyl), 7.39-7.45 (m, 6H, *H*-5 aniline, *H*-4 salicyl, 2x *H*-2'',6'' phenyl), 8.07-8.11 (m, 2H, *H*-2,6 aniline), 8.19 (d, ^4J = 2.8, 1H, *H*-6 salicyl), 10.32 (s, 1H (CON*H*).

$^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 51.77 (CH_2-3'',5'' piperazine), 53.63 (dyn, CH_2-2'',6'' piperazine), 59.52 ($NCH_2CH(OH)$), 64.91 (*C*H(OH)), 71.81 ($OCH_2CH(OH)$), 76.13 ($NCH(C_6H_5)_2$), 114.36 (*C*-3 salicyl), 119.56 (q, $^3J_{CF}$ = 5.5, *C*-2 aniline), 122.87 ($^1J_{CF}$ = -273.1, CF_3 aniline), 123.38 (C_q-1 salicyl), 124.33 (*C*-6 aniline), 126.54 (*C*-4 aniline), 127.22 (*C*-4'' phenyl), 127.70 (*C*-5 salicyl), 128.04 (*C*-2'',6'' phenyl), 128.69 (*C*-3'',5'' phenyl), 131.98 (*C*-5 aniline), 132.37 (*C*-6 salicyl), 133.22 (*C*-4 salicyl), 137.70 (*C*-1 aniline), 142.48 (C_q-1'' phenyl[1]), 142.52 (C_q-1'' phenyl[2]), 155.08 (C_q-2 salicyl), 162.39 (*C*ONH). Only one part of the quartett of *C*-3 aniline visible at 128.44

LCMS: $[M+H]^+$: calculated.: 658.18 found: 658.29, $[M-H]^-$: calculated.: 656.17 found: 656.19.

Melting point: 162-165°C; diphosphate: 191-195°C, citrate: 155-156.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-cyano-*N*-(4-(trifluoromethoxy)phenyl)benzamide (250)



250 was prepared following **general procedure E**, yielding 0.057 g (19%) of the desired product.

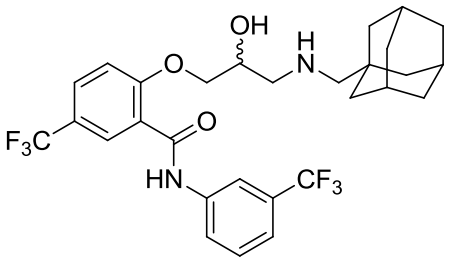
^1H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.49-1.54 (s, br, 6H, CH_2-adamantane), 1.60-1.65 (m, 3H, CH_2-adamantane), 1.71-1.76 (m, 3H, CH_2-adamantane), 1.98 (s, br, 3H, C*H*-adamantane), 2.25, 2.28, 2.34, 2.36 (AB, J_{AB} = -11.6, 2H, NHCH_2-1-adamantane), 2.75 (dd, ^2J = -12.2, ^3J = 9.4, 1H, CH(OH)CH_aH_bNH), 2.89 (dd, ^2J = -12.3, ^3J = 3.7, 1H, CH(OH)CH_aH_bNH), 4.10 (m, ^2J = -9.1, ^3J = 6.4, 1H, $OCH_aH_bCH(OH)$), 4.14-4.22 (m, 1H, C*H*(OH)), 4.35 (dd, ^2J = -9.1, ^3J = 2.6, 1H, $OCH_aH_bCH(OH)$), 7.05 (d, 1H, ^3J = 8.6, *H*-3 salicyl), 7.16-7.21 (m, 2H, *H*-3,5 aniline), 7.73 (dd, 1H, ^3J = 8.6, ^4J = 2.2, *H*-4 salicyl), 7.81-7.85 (m, 2H, *H*-2,6 aniline), 8.53 (d, 1H, ^4J = 2.2, *H*-6 salicyl), 10.07 (br s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.41 (*C*H-adamantane), 33.56 (C_q-1'' adamantane), 37.13 (CH_2-adamantane), 40.79 (CH_2-adamantane), 51.56 ($NCH_2CH(OH)$), 62.32 ($NHCH_2$-1''-adamantane), 66.78 (*C*H(OH)), 71.77 ($OCH_2CH(OH)$), 105.99 (*C*-5 salicyl), 113.61 (*C*-3 salicyl), 118.20 (*C*N), 121.73 (*C*-3,5 aniline), 121.77 (*C*-2,6 aniline), 123.63 (*C*-1 salicyl), 136.83 (*C*-4 salicyl), 137.14 (*C*-6 salicyl), 145.32 (q, J_{CF} =1.5, *C*-4 aniline), 159.41 (*C*-2 salicyl), 161.47 (*C*ONH). *C*-1 aniline and O*C*F3 not recorded.

LCMS: $[M+H]^+$: calculated.: 544.24 found: 544.34, $[M-H]^-$: calculated.: 542.23 found: 542.16.

Melting point: 90-93°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-(trifluoromethyl)-*N*-(3-(trifluoromethyl)phenyl)benzamide (251)



251 was prepared following **general procedure E**, yielding 0.145 g (40%) of the desired product.

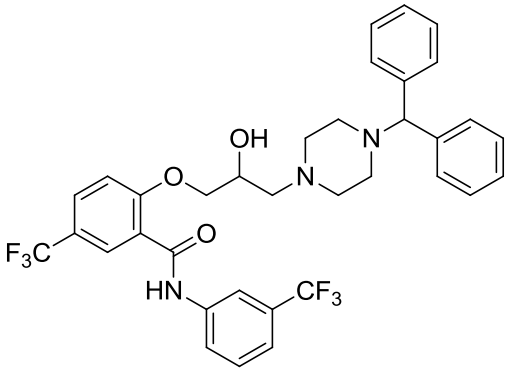
^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 1.37-1.41 (s, br, 6H, CH_2-adamantane), 1.51-1.57 (m, 3H, CH_2-adamantane), 1.61-1.66 (m, 3H, CH_2-adamantane), 1.87 (s, br, 3H, C*H*-adamantane), 2.07 (s, 2H, NHCH_2-1-adamantane), 2.59-2.68 (m, 2H, CH(OH)CH_2NH), 3.94-4.00 (m, 1H, C*H*(OH)), 4.21-4.29 (m, 2H, OCH_2CH(OH)), 7.42-7.49 (m, 2H, *H*-4 aniline, *H*-3 salicyl), 7.60 (dd [t], ^3J = 7.9, 1H, *H*-5 aniline), 7.90 (dd, ^3J = 8.7, ^4J = 2.2, 1H, *H*-4 salicyl), 7.97 (d, ^3J = 8.2, 1H, *H*-6 aniline), 8.06 (d, ^4J = 2.2, 1H, *H*-6 salicyl), 8.28 (s, 1H, *H*-2 aniline), 10.61 (br s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, DMSO-d_6, 23 °C): δ = 27.83 (*C*H-adamantane), 33.26 (C_q-1'' adamantane), 36.76 (CH_2-adamantane), 40.28 (CH_2-adamantane), 53.37 ($NCH_2CH(OH)$), 62.42 ($NHCH_2$-1''-adamantane), 67.86 (*C*H(OH)), 71.92 ($OCH_2CH(OH)$), 114.36 (*C*-3 salicyl), 115.88 (q, $^3J_{CF}$ = 3.8, *C*-2 aniline), 120.21 (q, $^3J_{CF}$ = 3.6, *C*-4 aniline), 121.44 (q, $^2J_{CF}$ = 32.7, *C*-5 salicyl), 123.34 (*C*-6 aniline), 124.09 ($^1J_{CF}$ = -272.6, CF_3 aniline), 124.11 ($^1J_{CF}$ = -271.7, CF_3 salicyl), 124.28 (*C*-1 salicyl), 127.30 (q, J_{CF} = 3.9, *C*-6 salicyl), 129.58 (q, $^2J_{CF}$ = 31.6, *C*-3 aniline), 129.77 (q, J_{CF} = 3.5, *C*-4 salicyl), 130.03 (*C*-5 aniline), 139.43 (*C*-1 aniline), 158.98 (*C*-2 salicyl), 163.10 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 571.24 found: 571.33, $[M-H]^-$: calculated.: 569.22 found: 569.23.

Melting point: 118-120°C.

2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-5-(trifluoromethyl)-*N*-(3-(trifluoromethyl)phenyl)benzamide (252)



252 was prepared following **general procedure E**, yielding 0.193 g (54%) of the desired product.

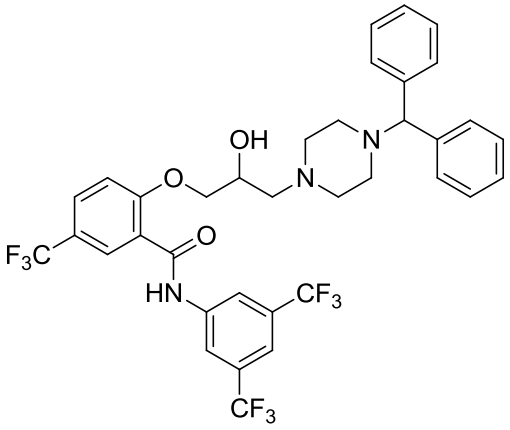
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.36-2.57 (m[dyn], br, 7H, CH(OH)CH_aH$_b$NH (^2J = -12.3, ^3J = 3.6), H_{ax} H_{eq}-3,5 in piperazine, H_{ax}-2,6 in CH_2 piperazine), 2.61 (dd, ^2J = -12.3, ^3J = 10.7, 1H, CH(OH)CH$_a$$H_b$NH), 2.71-2.77 (m[t], br, 2H, H_{eq}-2,6 in CH_2 piperazine), 4.06 (dd, ^2J = -9.4, ^3J = 6.2, 1H, OCH_aH$_b$CH(OH)), 4.19-4.25 (m, 1H, C*H*(OH)), 4.26 (s, 1H, NC*H*(C_6H_5)$_2$), 4.37 (dd, ^2J = -9.4, ^3J = 2.6, 1H, OCH$_a$$H_b$CH(OH)), 7.05 (d, ^3J = 8.7, 1H, *H*-3 salicyl), 7.17-7.22 (m, 2H, 2x C*H*-4 phenyl), 7.26-7.31 (m, 4H, 2x *H*-3'',5'' phenyl), 7.34 (d, 1H, *H*-4 aniline), 7.40-7.46 (m, ^3J = 7.8, 5H, *H*-5 aniline, 2x *H*-2'',6'' phenyl), 7.71 (dd, ^3J = 8.7, ^3J = 2.4, 1H, *H*-4 salicyl), 8.04 (d, ^3J = 8.3, 1H, *H*-6 aniline), 8.07 (s, 1H, *H*-2 aniline), 8.55 (d, ^3J = 2.4, 1H, *H*-6 salicyl), 10.23 (s, 1H (CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 51.89 (*C*H_2-dyn, piperazine), 52.83 (*C*H_2-dyn, piperazine), 59.51 (N*C*H_2CH(OH)), 64.86 (*C*H(OH)), 71.61 (O*C*H_2CH(OH)), 76.17 (N-*C*H(C_6H_5)$_2$), 113.00 (*C*-3 salicyl), 117.28 (q, $^3J_{CF}$ = 4.0, *C*-2 aniline), 120.79 (q, $^3J_{CF}$ = 3.7, *C*-4 aniline), 122.69 (*C*-1 salicyl), 123.46 (*C*-6 aniline), 123.93 ($^1J_{CF}$ = -272.0, *C*F_3 aniline), 124.12 ($^1J_{CF}$ = -273.0, *C*F_3 salicyl), 124.63 ($^2J_{CF}$ = 33.6, *C*-5 salicyl), 127.19 (*C*-4'' phenyl), 128.03 (*C*-2'',6'' phenyl), 128.67 (*C*-3'',5'' phenyl), 129.58 (*C*-5 aniline), 130.34 (q, $^3J_{CF}$ = 3.6, *C*-4 salicyl), 130.39 (q, $^3J_{CF}$ = 3.8, *C*-6 salicyl), 131.34 ($^2J_{CF}$ = 32.1, *C*-3 aniline), 139.17 (*C*-1 aniline), 142.57 (C_q-1'' phenyl), 142.60 (C_q-1'' phenyl), 158.69 (C_q-2 salicyl), 162.33 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 658.25 found: 658.37, $[M-H]^-$: calculated.: 656.24 found: 656.27.

Melting point: 70-72°C.

2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)benzamide (253)



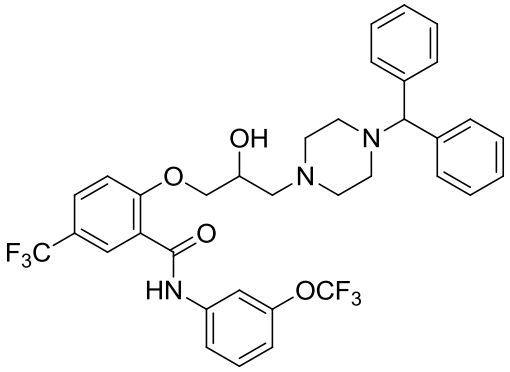
253 was prepared following **general procedure E**, yielding 0.176 g (56%) of the desired semi-crystalline product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.41-2.61 (m[dyn], br, 8H, CH(OH)CH_2NH, H_{ax} H_{eq}-3,5 in piperazine, H_{ax}-2,6 in CH_2 piperazine), 2.72-2.80 (m[t], br, 2H, H_{eq}-2,6 in CH_2 piperazine), 4.05 (dd, ^{2}J = -9.2, ^{3}J = 7.0, 1H, OC$H_a$$H_b$CH(OH)), 4.22-4.29 (m, 2H, C*H*(OH), NC*H*$(C_6H_5)_2$), 4.39 (dd, ^{2}J = -9.2, ^{3}J = 2.6, 1H, OCH$_a$$H_b$CH(OH)), 7.07 (d, ^{3}J = 8.7, 1H, *H*-3 salicyl), 7.17-7.22 (m, 2H, 2x C*H*-4 phenyl), 7.27-7.31 (m, 4H, 2x *H*-3'',5'' phenyl), 7.38-7.45 (m, 4H, 2x *H*-2'',6'' phenyl), 7.59 (s, 1H, *H*-4 aniline), 7.75 (dd, ^{3}J = 8.7, ^{3}J = 2.4, 1H, *H*-4 salicyl), 8.39 (s, 2H, *H*-2,6 aniline), 8.55 (d, ^{4}J = 2.4, 1H, *H*-6 salicyl), 10.52 (s, 1H (CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 51.89 (*C*H_2-dyn, piperazine), 52.55 (*C*H_2-dyn, piperazine), 59.27 (N*C*H_2CH(OH)), 64.81 (*C*H(OH)), 71.99 (O*C*H_2CH(OH)), 76.14 (N-*C*H$(C_6H_5)_2$), 113.19 (*C*-3 salicyl), 117.39 (m, J_{CF} = 3.9, *C*-4' in 3',5'-bis-CF_3-aniline), 120.22 (q, $^{3}J_{CF}$ = 3.3, *C*-2',6' in 3',5'-bis-CF_3-aniline), 122.21 (*C*-1 salicyl), 123.40 ($^{1}J_{CF}$ = -273.0, 2x *C*F_3 aniline), 123.84 ($^{1}J_{CF}$ = -272.0, *C*F_3 salicyl), 124.85 ($^{2}J_{CF}$ = 33.7, *C*-5 salicyl), 127.19 (*C*-4'' phenyl), 128.03 (*C*-2'',6'' phenyl), 128.68 (*C*-3'',5'' phenyl), 130.45 (q, $^{3}J_{CF}$ = 3.6, *C*-6 salicyl), 130.71 (q, $^{3}J_{CF}$ = 3.6, *C*-4 salicyl), 132.26 ($^{2}J_{CF}$ = 33.5, *C*-3,5 in 3',5'-bis-CF_3-aniline), 140.15 (*C*-1 in 3',5'-bis-CF_3-aniline), 142.58 (C_q-1'' phenyl), 142.60 (C_q-1'' phenyl), 158.74 (C_q-2 salicyl), 162.59 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 726.24 found: 726.29, $[M-H]^-$: calculated.: 724.22 found: 724.45.

2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(3-(trifluoromethoxy)phenyl)-5-(trifluoromethyl)benzamide (254)



254 was prepared following **general procedure E**, yielding 0.133 g (32%) of the desired product.

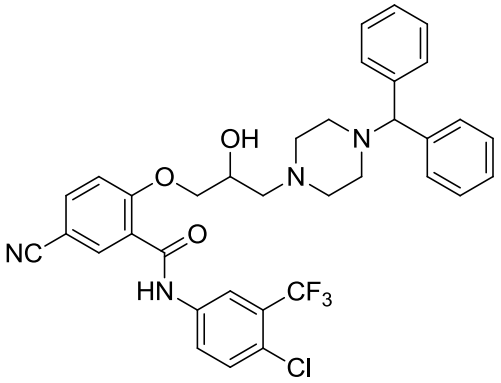
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.39-2.52 (m[dyn], br, 7H, CH(OH)C$H_a$$H_b$NH (dd, ^{2}J = -12.3, ^{3}J = 3.6), H_{ax} H_{eq}-3,5 in piperazine, H_{ax}-2,6 in CH_2 piperazine), 2.62 (dd, ^{2}J = -12.3, ^{3}J = 10.8, 1H, CH(OH)C$H_a$$H_b$NH), 2.71-2.78 (m[t], br, 2H, H_{eq}-2,6 in CH_2 piperazine), 4.06 (dd, ^{2}J = -9.4, ^{3}J = 6.1, 1H, OC$H_a$$H_b$CH(OH)), 4.19-4.24 (m, 1H, C*H*(OH)), 4.25 (s, 1H, NC*H*(C_6H_5)$_2$), 4.37 (dd, ^{2}J = -9.4, ^{3}J = 2.6, 1H, OC$H_a$$H_b$CH(OH)), 6.95 (d, ^{3}J = 8.2, 1H, *H*-4 aniline), 7.05 (d, ^{3}J = 8.7, 1H, *H*-3 salicyl), 7.19 (m, 2H, 2x C*H*-4 phenyl), 7.28 (m, 4H, 2x *H*-3'',5'' phenyl), 7.32 (dd [t], ^{3}J = 8.1, 1H, *H*-5 aniline), 7.41 (m, 4H, 2x *H*-2'',6'' phenyl), 7.71 (dd, ^{3}J = 8.7, ^{3}J = 2.3, 1H, *H*-4 salicyl), 7.74 (m, 1H, *H*-6 aniline), 7.77 (br s, 1H, *H*-2 aniline), 8.54 (d, ^{4}J = 2.3, 1H, *H*-6 salicyl), 10.17 (s, 1H (CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 51.91 (*C*H_2-dyn, piperazine), 52.97 (*C*H_2-dyn, piperazine), 59.48 (N*C*H_2CH(OH)), 64.86 (*C*H(OH)), 71.53 (O*C*H_2CH(OH)), 76.22 (N-*C*H(C_6H_5)$_2$), 112.96 (*C*-3 salicyl), 113.10 (*C*-2 aniline), 116.36 (*C*-4 aniline), 118.53 (*C*-6 aniline), 120.63 ($^{1}J_{CF}$ = -257.2, O*C*F_3 aniline), 122.74 (*C*-1 salicyl), 123.93 ($^{1}J_{CF}$ = -271.8, *C*F_3 salicyl), 124.62 (q, $^{2}J_{CF}$ = 33.5, *C*-5 salicyl), 127.20 (*C*-4'' phenyl), 128.04 (*C*-2'',6'' phenyl), 128.68 (*C*-3'',5'' phenyl), 130.07 (*C*-5 aniline), 130.30 (q, J_{CF} = 3.5, *C*-6 salicyl), 130.43 (q, J_{CF} = 3.8, *C*-4 salicyl), 140.05 (*C*-1 aniline), 142.54 (C_q-1'' phenyl), 142.58 (C_q-1'' phenyl), 149.63 (broadened, *C*-3 aniline), 158.67 (C_q-2 salicyl), 162.25 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 674.24 found: 674.31, $[M-H]^-$: calculated.: 672.23 found: 672.21.

Melting point: 69-72°C.

2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(4-chloro-3-(trifluoromethyl)phenyl)-5-cyanobenzamide (255)



255 was prepared following **general procedure E**, yielding 0.209 g (69%) of the desired product.

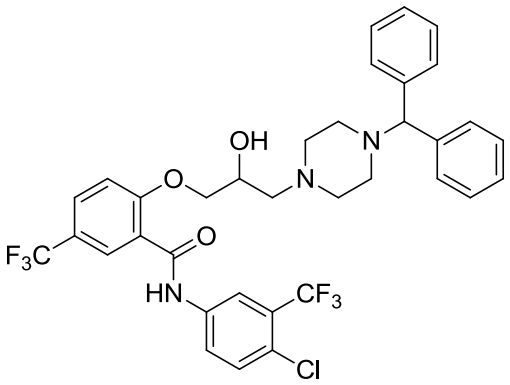
^{1}H NMR (400 MHz, DMSO-d$_6$, 23 °C): δ = 2.10-2.47 (m[dyn], br, 10H, CH(OH)C*H$_a$H$_b$*NH, *H*$_{ax}$ *H*$_{eq}$-3,5 in piperazine, *H*$_{ax}$ *H*$_{eq}$ -2,6 in C*H*$_2$ piperazine), 3.94-4.03 (m, 1H, C*H*(OH)), 4.17 (m, 2H, OC*H*$_2$CH(OH)), 4.21 (s, 1H, NC*H*(C$_6$H$_5$)$_2$), 5.09 (m, 1H, CH(O*H*)), 7.17 (m, 2H, 2x C*H*-4 phenyl), 7.27 (m, 4H, 2x *H*-3'',5'' phenyl), 7.36-7.42 (m, 5H, *H*-3 salicyl, 2x *H*-2'',6'' phenyl), 7.69 (d, 1H, ^{3}J = 8.7, *H*-5 aniline), 7.98 (dd, ^{3}J = 8.8, ^{4}J = 2.1, 1H, *H*-4 salicyl), 8.02 (dd, ^{3}J = 8.7, ^{4}J = 2.3, 1H, *H*-6 aniline), 8.10 (d, ^{4}J = 2.1, 1H, *H*-6 salicyl), 8.28 (d, ^{4}J = 2.3, 1H, *H*-2 aniline), 10.65 (s, 1H (CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d$_6$, 23 °C): δ = 51.43 (*C*H$_2$, piperazine), 53.48 (*C*H$_2$, piperazine), 60.75 (N*C*H$_2$CH(OH)), 66.03 (*C*H(OH)), 72.12 (O*C*H$_2$CH(OH)), 75.10 (N-*C*H(C$_6$H$_5$)$_2$), 103.30 (*C*-5 salicyl), 122.65 (q, $^{1}J_{CF}$ = -272.9, *C*F$_3$ aniline), 114.60 (*C*-3 salicyl), 118.32 (q, $^{3}J_{CF}$ = 5.5, *C*-2 aniline), 118.37 (*C*N), 124.37 (*C*$_q$-6 aniline), 124.51 (*C*-4 aniline), 125.36 (*C*$_q$-1 salicyl), 126.78 (*C*-4'' phenyl), 126.82 (q, $^{2}J_{CF}$ = 30.5, *C*-3 aniline), 127.51 (*C*-2'',6'' phenyl), 128.44 (*C*-3'',5'' phenyl), 132.20 (*C*-5 aniline), 134.01 (*C*-6 salicyl), 136.70 (*C*-4 salicyl), 138.12 (*C*$_q$-1 aniline), 142.85 (C$_q$-1'' phenyl), 142.87 (C$_q$-1'' phenyl), 159.34 (*C*$_q$-2 salicyl), 163.00 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 649.22 found: 649.27, $[M-H]^-$: calculated.: 647.20 found: 647.25.

Melting point: 209-211°C.

2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)benzamide (256)



256 was prepared following **general procedure E**, yielding 0.305 g (94%) of the desired product.

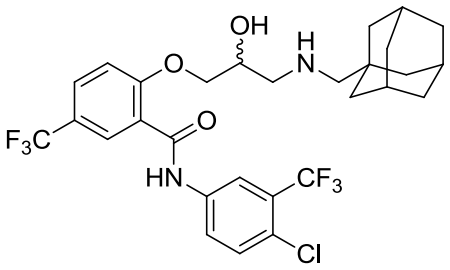
^{1}H NMR (400 MHz, DMSO-d$_6$, 23 °C): δ = 2.16-2.48 (m[dyn], br, 10H, CH(OH)CH_aH_bNH, H_{ax} H_{eq}-3,5 in piperazine, H_{ax} H_{eq} -2,6 in CH_2 piperazine), 4.00-4.04 (m, 1H, C*H*(OH)), 4.16 (dd, ^{2}J = -9.7, ^{3}J = 5.5, 1H, OCH_aH$_b$CH(OH)), 4.19-4.24 (m, 2H, NC*H*(C$_6$H$_5$)$_2$, OCH_aH$_b$CH(OH)), 5.15 (m, 1H, CH(O*H*)), 7.17 (m, 2H, 2x C*H*-4 phenyl), 7.27 (m, 4H, 2x *H*-3'',5'' phenyl), 7.36-7.44 (m, 5H, *H*-3 salicyl, 2x *H*-2'',6'' phenyl), 7.70 (d, 1H, ^{3}J = 8.8, *H*-5 aniline), 7.88 (dd, ^{3}J = 8.8, ^{4}J = 2.3, 1H, *H*-4 salicyl), 8.01-8.06 (m, 2H, *H*-6 aniline, *H*-6 salicyl), 8.31 (d, ^{4}J = 2.5, 1H, *H*-2 aniline), 10.67 (s, 1H (CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d$_6$, 23 °C): δ = 51.44 (*C*H$_2$, piperazine), 53.50 (*C*H$_2$, piperazine), 60.77 (N*C*H$_2$CH(OH)), 66.07 (*C*H(OH)), 72.18 (O*C*H$_2$CH(OH)), 75.11 (N-*C*H(C$_6$H$_5$)$_2$), 114.38 (*C*-3 salicyl), 118.46 (q, $^{3}J_{CF}$ = 5.3, *C*-2 aniline), 121.45 (q, $^{2}J_{CF}$ = 32.3, *C*-5 salicyl), 122.67 (q, $^{1}J_{CF}$ = -273.3, *C*F$_3$ aniline), 124.08 (q, $^{1}J_{CF}$ = -271.8, *C*F$_3$ salicyl), 124.32 (*C*$_q$-1 salicyl), 124.49 (*C*-6 aniline), 124.53 (*C*$_q$-4 aniline), 126.78 (*C*-4'' phenyl), 126.82 (q, $^{2}J_{CF}$ = 30.7, *C*-3 aniline), 127.15 (broadened, *C*-6 salicyl), 127.51 (*C*-2'',6'' phenyl), 128.44 (*C*-3'',5'' phenyl), 129.81 (q, $^{3}J_{CF}$ = 3.7, *C*-4 salicyl), 132.17 (*C*-5 aniline), 138.12 (*C*$_q$-1 aniline), 142.85 (C$_q$-1'' phenyl), 142.88 (C$_q$-1'' phenyl), 158.92 (*C*$_q$-2 salicyl), 163.27 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 692.21 found: 692.12, $[M-H]^-$: calculated.: 690.20 found: 690.10.

Melting point: 162-167°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)benzamide (257)



257 was prepared following **general procedure E**, yielding 0.187 g (47%) of the desired product.

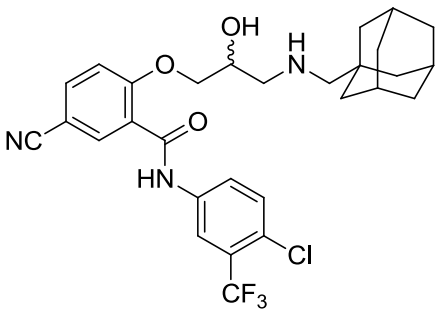
^{1}H NMR (400 MHz, DMSO-d$_6$, 23 °C): δ = 1.36-1.40 (s, br, 6H, C*H$_2$*-adamantane), 1.51-1.57 (m, 3H, C*H$_2$*-adamantane), 1.61-1.67 (m, 3H, C*H$_2$*-adamantane), 1.87 (s, br, 3H, C*H*-adamantane), 2.04 (s, 2H, NHC*H$_2$*-1-adamantane)), 2.57-2.65 (m, 2H, CH(OH)C*H$_2$*NH), 3.92-3.98 (m, 1H, C*H*(OH)), 4.22 (d, ^{3}J = 4.9, 2H, OC*H$_2$*CH(OH)), 7.43 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.72 (d, ^{3}J = 8.8, 1H, *H*-5 aniline), 7.89 (dd, ^{3}J = 8.8, ^{4}J = 2.2, 1H, *H*-4 salicyl), 8.00-8.05 (m, 2H, *H*-6 aniline, *H*-6 salicyl), 8.35 (d, ^{4}J = 2.2 1H, *H*-2 aniline), 10.69 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d$_6$, 23 °C): δ = 27.83 (*C*H-adamantane), 33.22 (*C*$_q$-1'' adamantane), 36.75 (*C*H$_2$-adamantane), 40.27 (*C*H$_2$-adamantane), 53.44 (N*C*H$_2$CH(OH)), 62.42 (NH*C*H$_2$-1''-adamantane), 67.82 (*C*H(OH)), 71.83 (O*C*H$_2$CH(OH)), 114.33 (*C*-3 salicyl), 118.39 (q, J_{CF} = 5.9, *C*-2 aniline), 121.44 (q, $^{2}J_{CF}$ = 32.9, *C*-5 salicyl), 122.69 ($^{1}J_{CF}$ = -273.0, *C*F$_3$ aniline), 124.10 ($^{1}J_{CF}$ = -271.4, *C*F$_3$ salicyl), 124.32 (*C*-1 salicyl), 124.47 (*C*-6 aniline), 124.55 (*C*-4 aniline), 126.86 (q, $^{2}J_{CF}$ = 30.7, *C*-3 aniline), 127.17 (q, J_{CF} = 3.7, *C*-6 salicyl), 129.82 (q, J_{CF} = 3.3, *C*-4 salicyl), 132.21 (*C*-5 aniline), 138.16 (*C*-1 aniline), 158.92 (*C*-2 salicyl), 163.29 (*C*ONH).

LCMS: [M+H]$^{+}$: calculated.: 605.20 found: 605.25, [M-H]$^{-}$: calculated.: 603.19 found: 603.22.

Melting point: 144-148°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(4-chloro-3-(trifluoromethyl)phenyl)-5-cyanobenzamide (258)



258 was prepared following **general procedure E**, yielding 0.149 g (51%) of the desired product.

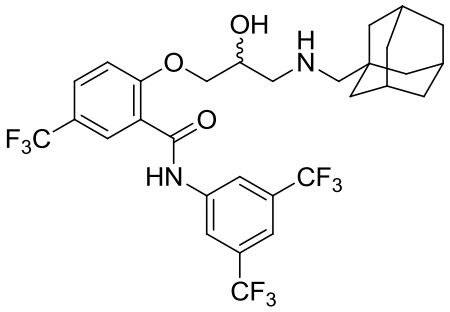
^{1}H NMR (400 MHz, DMSO-d$_6$, 23 °C): δ = 1.34-1.39 (s, br, 6H, C*H*$_2$-adamantane), 1.51-1.57 (m, 3H, C*H*$_2$-adamantane), 1.61-1.66 (m, 3H, C*H*$_2$-adamantane), 1.87 (s, br, 3H, C*H*-adamantane), 2.00-2.07 (m, 2H, NHC*H*$_2$-1-adamantane)), 2.54-2.67 (m, 2H, CH(OH)C*H*$_2$NH), 3.90-3.97 (m, 1H, C*H*(OH)), 4.20 (d, ^{3}J = 4.8, 2H, OC*H*$_2$CH(OH)), 7.41 (d, ^{3}J = 8.7, 1H, *H*-3 salicyl), 7.72 (d, ^{3}J = 8.8, 1H, *H*-5 aniline), 7.97-8.03 (m, 2H, *H*-6 aniline, *H*-4 salicyl), 8.10 (d, ^{4}J = 2.2, 1H, *H*-6 salicyl), 8.32 (d, ^{4}J = 2.3, 1H, *H*-2 aniline), 10.67 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d$_6$, 23 °C): δ = 27.80 (*C*H-adamantane), 33.15 (*C*$_q$-1'' adamantane), 36.71 (*C*H$_2$-adamantane), 40.20 (*C*H$_2$-adamantane), 53.33 (N*C*H$_2$CH(OH)), 62.25 (NH*C*H$_2$-1''-adamantane), 67.60 (*C*H(OH)), 71.72 (O*C*H$_2$CH(OH)), 103.30 (*C*-5 salicyl), 114.54 (*C*-3 salicyl), 118.25 (q, $^{3}J_{CF}$ = 5.5, *C*-2 aniline), 118.37 (*C*N), 122.68 ($^{1}J_{CF}$ = -272.9, *C*F$_3$ aniline), 124.36 (*C*-6 aniline), 124.55 (*C*-4 aniline), 125.41 (*C*-1 salicyl), 126.87 ($^{2}J_{CF}$ = 30.5, *C*-3 aniline), 132.23 (*C*-5 aniline), 134.01 (*C*-6 salicyl), 136.70 (*C*-4 salicyl), 138.17 (*C*-1 aniline), 159.31 (*C*-2 salicyl), 163.03 (*C*ONH).

LCMS: [M+H]$^{+}$: calculated.: 562.21 found: 562.23, [M-H]$^{-}$: calculated.: 560.19 found: 560.13.

Melting point: 146-148°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)benzamide (259)



259 was prepared following **general procedure E**, yielding 0.166 g (54%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d$_6$, 23 °C): δ = 1.34-1.38 (s, br, 6H, C*H*$_2$-adamantane), 1.49-1.54 (m, 3H, C*H*$_2$-adamantane), 1.60-1.66 (m, 3H, C*H*$_2$-adamantane), 1.85 (s, br, 3H, C*H*-adamantane), 2.03 (s, 2H, NHC*H*$_2$-1-adamantane)), 2.57-2.66 (m, 2H, CH(OH)C*H*$_2$NH), 3.93-3.98 (m, 1H, C*H*(OH)), 4.24 (d, ^{3}J = 4.7, 2H, OC*H*$_2$CH(OH)), 7.45 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.83 (s, 1H, *H*-4

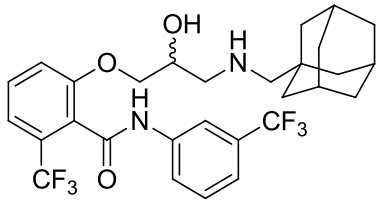
aniline), 7.91 (dd, ^{3}J = 8.8, ^{4}J = 2.2, 1H, *H*-4 salicyl), 8.04 (d, ^{4}J = 2.2, 1H, *H*-6 salicyl), 8.46 (s, 2H, *H*-2,6 aniline), 10.90 (br s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, DMSO-d_6, 23 °C): δ = 27.80 (*C*H-adamantane), 33.19 (C_q-1'' adamantane), 36.72 (*C*H_2-adamantane), 40.23 (*C*H_2-adamantane), 53.34 (N*C*H_2CH(OH)), 62.32 (NH*C*H_2-1''-adamantane), 67.77 (*C*H(OH)), 71.84 (O*C*H_2CH(OH)), 114.37 (*C*-3 salicyl), 116.67 (m, *C*-4 aniline), 119.44 (q, J_{CF} = 3.5, *C*-2,6 aniline), 121.46 ($^{2}J_{CF}$ = 32.6, *C*-5 salicyl), 123.19 ($^{1}J_{CF}$ = -272.5, 2x *C*F_3 aniline), 124.07 ($^{1}J_{CF}$ = -272.5, *C*F_3 salicyl), 124.18 (*C*-1 salicyl), 127.19 (q, J_{CF} = 3.8, *C*-6 salicyl), 129.98 (q, J_{CF} = 3.9, *C*-4 salicyl), 130.90 ($^{2}J_{CF}$ = 32.9, *C*-3,5 aniline), 140.57 (*C*-1 aniline), 158.97 (*C*-2 salicyl), 163.76 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 639.23 found: 639.39, $[M-H]^-$: calculated.: 637.29 found: 637.21.

Melting point: 120-121°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-6-(trifluoromethyl)-*N*-(3-(trifluoromethyl)phenyl)benzamide (260)



260 was prepared following **general procedure E**, yielding 0.048 g (63%) of the desired product.

^{1}H NMR (600 MHz, $CDCl_3$, 23 °C): δ = 1.41-1.43 (s, br, 6H, C*H*$_2$-adamantane), 1.53-1.57 (m, 3H, C*H*$_2$-adamantane), 1.65-1.69 (m, 3H, C*H*$_2$-adamantane), 1.92 (s, br, 3H, C*H*-adamantane), 2.20, 2.22, 2.29, 2.31 (AB, J_{AB} = -11.4, 2H, NHC*H*$_2$-1-adamantane), 2.96 (dd, ^{2}J = -12.1, ^{3}J = 9.8, 1H, CH(OH)C*H*$_a$H$_b$NH), 3.10 (dd, ^{2}J = -12.3, ^{3}J = 2, 1H, CH(OH)CH$_a$*H*$_b$NH), 4.05-4.08 (m, 2H, OC*H*$_2$CH(OH)), 4.24-4.29 (m, 1H, C*H*(OH)), 7.05 (d, 1H, ^{3}J = 8.3, *H*-3 salicyl), 7.19 (d, 1H, ^{3}J = 7.8, *H*-5 salicyl), 7.34 (dd [t], 1H, ^{3}J = 8.2, *H*-4 salicyl), 7.39 (d, ^{3}J = 7.7, 1H, *H*-4 aniline), 7.45 (dd [t], ^{3}J = 8.0, 1H, *H*-5 aniline), 7.86 (d, ^{3}J = 6.8, 1H, *H*-6 aniline), 8.05 (s, 1H, *H*-2 aniline), 9.30 (br s, 1H, CON*H*).

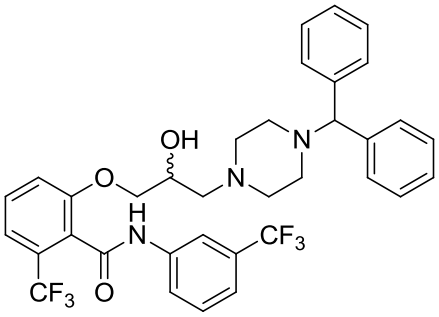
$^{13}C\{^{1}H\}$NMR (150 MHz, $CDCl_3$, 23 °C): δ = 27.90 (*C*H-adamantane), 32.50 (C_q-1'' adamantane), 36.37 (*C*H_2-adamantane), 39.51 (*C*H_2-adamantane), 52.79 (N*C*H_2CH(OH)), 60.93 (NH*C*H_2-1''-adamantane), 65.51 (*C*H(OH)), 70.54 (O*C*H_2CH(OH)), 116.38 (*C*-3 salicyl), 116.97 (q, $^{3}J_{CF}$ = 4.0, *C*-2 aniline), 118.93 (q, $^{3}J_{CF}$ = 4.2, *C*-5 salicyl), 121.30 (q, $^{3}J_{CF}$ = 3.7, *C*-4 aniline), 123.30 ($^{1}J_{CF}$=

274.0, *C*F_3 aniline), 123.59 (*C*-6 aniline), 124.01 ($^1J_{CF}$= 272.2, *C*F_3 salicyl), 124.99 (J_{CF}= 1.7, *C*-1 salicyl), 128.82 ($^2J_{CF}$= 31.8, *C*-6 salicyl), 129.80 (*C*-5 aniline), 131.11 (*C*-4 salicyl), 131.48 ($^2J_{CF}$= 32.4, *C*-3 aniline), 138.82 (*C*-1 aniline), 155.29 (*C*-2 salicyl), 164.42 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 571.24 found: 571.35, $[M-H]^-$: calculated.: 569.22 found: 569.44.

Melting point: 130-132°C.

2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-6-(trifluoromethyl)-*N*-(3-(trifluoromethyl)phenyl)benzamide (261)



261 was prepared following **general procedure E**, yielding 0.095 g (89%) of the desired product.

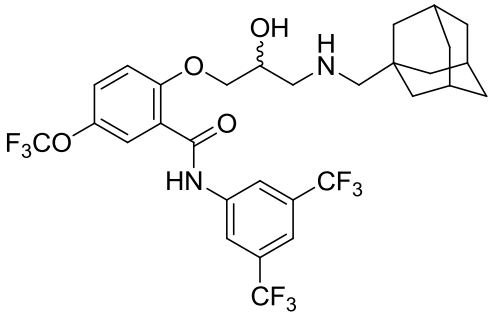
^{1}H NMR (600 MHz, $CDCl_3$, 27 °C): δ = 2.22-2.63 (m[dyn], br, 10H, CH(OH)C$H_a$$H_b$NH ($^2J$ = -12.6, ^3J = 3.4), CH(OH)C$H_a$$H_b$NH ($^2J$ = -12.6, ^3J = 9.9), H_{ax} H_{eq}-3,5 in piperazine, H_{ax}-2,6 in CH_2 piperazine), 3.98-4.03 (m, 2H, OC$H_a$$H_b$CH(OH), C*H*(OH)), 4.13-4.17 (m, 1H, OC$H_a$$H_b$CH(OH)), 4.20 (br s, 1H, NC*H*(C_6H_5)$_2$), 7.15 (d, ^3J = 8.6, 1H, *H*-3 salicyl), 7.17-7.20 (m, 2H, 2x C*H*-4 phenyl), 7.25-7.29 (m, 4H, 2x *H*-3'',5'' phenyl), 7.32 (d, ^3J = 8.1, 1H, *H*-5 salicyl), 7.34 (d, ^3J = 7.8, 1H, *H*-4 aniline), 7.37-7.39 (m, 4H, 2x *H*-2'',6'' phenyl), 7.42 (dd [t], ^3J = 7.9, 1H, *H*-5 aniline, 7.46 (dd [t], ^3J = 8.1, 1H, *H*-4 salicyl), 7.87 (s, 1H, *H*-2 aniline), 7.90 (d, ^3J = 8.2, 1H, *H*-6 aniline), 8.48-8.52 (br, 1H, CON*H*).

^{13}C{^{1}H}NMR (150 MHz, $CDCl_3$, 23 °C): δ = 51.47 (*C*H_2-dyn, piperazine), 53.83 (*C*H_2-dyn, piperazine), 59.56 (N*C*H_2CH(OH)), 65.24 (*C*H(OH)), 71.93 (O*C*H_2CH(OH)), 76.04 (*N*-*C*H(C_6H_5)$_2$), 116.72 (q, $^3J_{CF}$ = 4.0, *C*-2 aniline), 117.03 (*C*-3 salicyl), 119.15 (q, $^3J_{CF}$ = 4.8, *C*-5 salicyl), 121.11 (q, $^3J_{CF}$ = 3.7, *C*-4 aniline), 123.30 (*C*-6 aniline), 123.42 ($^1J_{CF}$= 274, *C*F_3 aniline), 123.96 ($^1J_{CF}$= 272.0, *C*F_3 salicyl), 125.36 (q, $^3J_{CF}$ = 1.8, *C*-1 salicyl), 127.17 (*C*-4'' phenyl), 127.97 (*C*-2'',6'' phenyl), 128.65 (*C*-3'',5'' phenyl), 129.44 ($^2J_{CF}$= 33.2, *C*-6 salicyl), 129.73 (*C*-5 aniline), 131.14 (br, *C*-4 salicyl), 131.47 ($^2J_{CF}$= 32.5, *C*-3 aniline), 138.73 (*C*-1 aniline), 142.50 (C_q-1'' phenyl), 142.52 (C_q-1'' phenyl), 156.16 (C_q-2 salicyl), 163.69 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 658.25 found: 658.36, $[M-H]^-$: calculated.: 656.23 found: 656.51.

Melting point: 85°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethoxy)benzamide (262)



262 was prepared following **general procedure E**, yielding 0.242 g (44%) of the desired product.

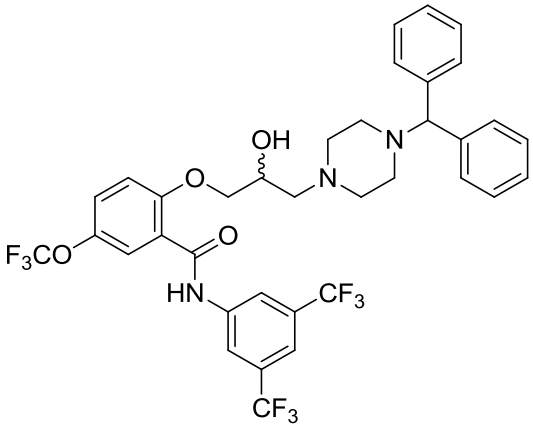
^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 1.33-1.39 (s, br, 6H, CH_2-adamantane), 1.49-1.55 (m, 3H, CH_2-adamantane), 1.60-1.67 (m, 3H, CH_2-adamantane), 1.85 (s, br, 3H, C*H*-adamantane), 2.04 (s, 2H, NHCH_2-1-adamantane)), 2.56-2.68 (m, 2H, CH(OH)CH_2NH), 3.92-3.99 (m, 1H, C*H*(OH)), 4.19 (d, ^3J = 4.7, 2H, OCH_2CH(OH)), 7.37 (d, ^3J = 9.1, 1H, *H*-3 salicyl), 7.58 (dd, ^3J = 8.7, ^4J = 3.0, 1H, *H*-4 salicyl), 7.72 (d, ^4J = 2.9, 1H, *H*-6 salicyl), 7.82 (s, 1H, *H*-4 aniline), 8.47 (s, 2H, *H*-2,6 aniline), 10.91 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 27.80 (*C*H-adamantane), 33.15 (C_q-1'' adamantane), 36.71 (*C*H_2-adamantane), 40.20 (*C*H_2-adamantane), 53.26 (N*C*H_2CH(OH)), 62.23 (NH*C*H_2-1''-adamantane), 67.75 (*C*H(OH)), 72.00 (O*C*H_2CH(OH)), 115.40 (*C*-3 salicyl), 116.66 (m, *C*-4 aniline), 119.46 (q, J_{CF} = 3.5, *C*-2,6 aniline), 120.13 ($^1J_{CF}$= 255.7, O*C*F_3 salicyl), 122.82 (*C*-6 salicyl), 123.19 ($^1J_{CF}$ = -273.8, 2x *C*F_3 aniline), 124.49 (*C*-1 salicyl), 125.99 (*C*-4 salicyl), 130.90($^2J_{CF}$ = 32.9, *C*-3,5 aniline), 140.53 (*C*-1 aniline), 141.67 (J_{CF} = 1.6, *C*-5 salicyl), 155.14 (*C*-2 salicyl), 163.43 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 655.22 found: 655.30, $[M-H]^-$: calculated.: 653.21 found: 653.46.

Melting point: 158-160°C.

2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethoxy)benzamide (263)



263 was prepared following **general procedure E**, yielding 0.381 g (61%) of the desired product.

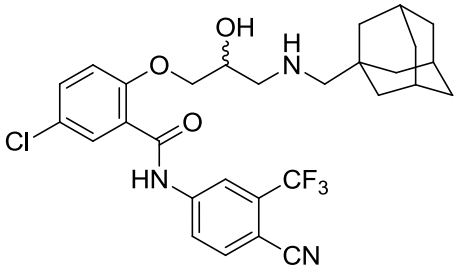
^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 2.14-2.48 (m[dyn], br, 10H, CH(OH)C$H_a$$H_b$NH ($^{2}J$ = -12.5, ^{3}J = 6.8), CH(OH)C$H_a$$H_b$NH ($^{2}J$ = -12.5, ^{3}J = 5.7) H_{ax} H_{eq}-3,5 in piperazine, H_{ax} H_{eq}-2,6 in CH_2 piperazine), 3.98-4.05 (m, 1H, C*H*(OH)), 4.12-4.17 (m, 2H, OCH_2CH(OH)), 4.20 (s, 1H, NC*H*(C_6H_5)$_2$), 5.15-5.26 (br, 1H, CH(O*H*)), 7.14-7.19 (m, 2H, 2x C*H*-4 phenyl), 7.24-7.29 (m, 4H, 2x *H*-3'',5'' phenyl), 7.33-7.40 (m, 5H, *H*-3 salicyl, 2x *H*-2'',6'' phenyl), 7.56 (dd, ^{3}J = 8.9, ^{3}J = 2.8, 1H, *H*-4 salicyl), 7.71 (d, ^{3}J = 2.8, 1H, *H*-6 salicyl), 7.78 (s, 1H, *H*-4 aniline), 8.45 (s, 2H, *H*-2,6 aniline), 10.91 (s, 1H (CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 51.42 (*C*H_2, piperazine), 53.47 (*C*H_2, piperazine), 60.78 (NCH_2CH(OH)), 66.14 (*C*H(OH)), 72.38 (OCH_2CH(OH)), 75.13 (N-*C*H(C_6H_5)$_2$), 115.46 (*C*-3 salicyl), 116.58 (m, *C*-4 aniline), 119.49 (q, $^{3}J_{CF}$ = 3.4, *C*-2,6 aniline), 120.12 ($^{1}J_{CF}$= 255.0, O*C*F_3 salicyl), 122.78 (*C*-6 salicyl), 123.16 ($^{1}J_{CF}$= 272.4, 2x*C*F_3 aniline), 124.53 (*C*-1 salicyl), 125.95 (*C*-4 salicyl), 126.77 (*C*-4'' phenyl), 127.47 (*C*-2'',6'' phenyl), 128.41 (*C*-3'',5'' phenyl), 130.86 ($^{2}J_{CF}$= 32.6, *C*-3,5 aniline), 140.51 (*C*-1 aniline), 141.68 (d, J_{CF}= 1.4, *C*-5 salicyl), 142.85 (C_q-1'' phenyl), 142.89 (C_q-1'' phenyl), 155.14 (C_q-2 salicyl), 163.43 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 742.23 found: 742.31, $[M-H]^-$: calculated.: 740.22 found: 740.53.

Melting point: 188-190°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(4-cyano-3-(trifluoromethyl)phenyl)benzamide (264**)**



264 was prepared following **general procedure E**, yielding 0.170 g (46%) of the desired product.

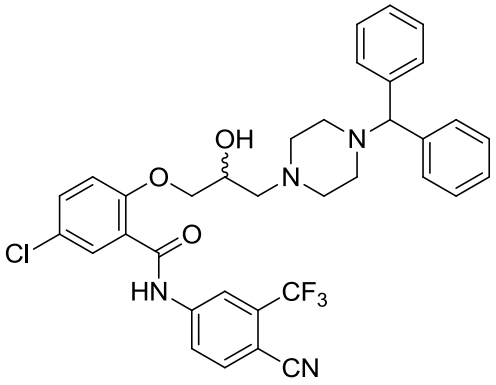
^{1}H NMR (400 MHz, DMSO-d$_6$, 23 °C): δ = 1.33-1.40 (s, br, 6H, C*H*$_2$-adamantane), 1.51-1.57 (m, 3H, C*H*$_2$-adamantane), 1.61-1.68 (m, 3H, C*H*$_2$-adamantane), 1.87 (s, br, 3H, C*H*-adamantane), 2.03 (s, 2H, NHC*H*$_2$-1-adamantane), 2.53-2.68 (m, 2H, CH(OH)C*H*$_2$NH), 3.89-3.96 (m, 1H, C*H*(OH)), 4.09-4.19 (m, 2H, OC*H*$_2$CH(OH)), 7.29 (d, ^{3}J = 8.9, 1H, *H*-3 salicyl), 7.60 (dd, ^{3}J = 8.9, ^{4}J = 2.7, 1H, *H*-4 salicyl), 7.74 (d, ^{4}J = 2.7, 1H, *H*-6 salicyl), 8.11-8.20 (m, 2H, *H*-5,6 aniline), 8.43 (br s, 1H, *H*-2 aniline), 10.76-11.22 (br, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d$_6$, 23 °C): δ = 27.81 (*C*H-adamantane), 33.18 (*C*$_q$-1'' adamantane), 36.73 (*C*H$_2$-adamantane), 40.25 (*C*H$_2$-adamantane), 53.40 (N*C*H$_2$CH(OH)), 62.34 (NH*C*H$_2$-1''-adamantane), 67.79 (*C*H(OH)), 71.88 (O*C*H$_2$CH(OH)), 102.13 (q, J_{CF} = 2.2, *C*$_q$-4 aniline), 115.69 (*C*N), 115.71 (*C*-3 salicyl), 117.04 (q, J_{CF} = 5.4, *C*-2 aniline), 122.42 ($^{1}J_{CF}$ = -273.7, *C*F$_3$), 122.54 (*C*-6 aniline), 124.82 (*C*$_q$-1 salicyl), 124.90 (*C*$_q$-5 salicyl), 129.48 (*C*-6 salicyl), 131.81 (q, $^{2}J_{CF}$ = 31.7, *C*-3 aniline), 132.69 (*C*-4 salicyl), 136.58 (*C*-5 aniline), 143.26 (*C*-1 aniline), 155.14 (*C*$_q$-2 salicyl), 163.77 (*C*ONH).

LCMS: $[M+H]^{+}$: calculated.: 562.21 found: 562.32, $[M-H]^{-}$: calculated.: 560.19 found: 560.35.

Melting point: 163-165°C.

2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-5-chloro-*N*-(4-cyano-3-(trifluoromethyl)phenyl)benzamide (265)



265 was prepared following **general procedure E**, yielding 0.480 g (94%) of the desired product.

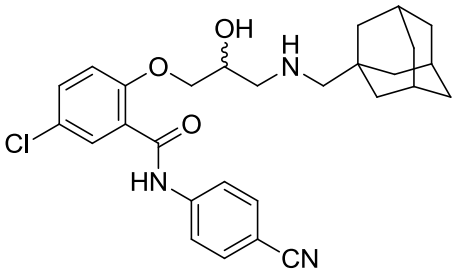
^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 2.05-2.49 (m[dyn], br, 10H, CH(OH)CH_2NH, H_{ax} H_{eq}-3,5 in piperazine, H_{ax}-2,6 in CH_2 piperazine), 3.97 (m, 1H, C*H*(OH)), 4.04-4.09 (d, ^{2}J =-9.7, ^{3}J =5.4, 1H, OCH_aH$_b$CH(OH)), 4.14 (d, ^{2}J =-9.7, ^{3}J =4.1, 1H, OCH$_a$$H_b$CH(OH)), 4.22 (br s, 1H, NC*H*(C_6H_5)$_2$), 5.12-5.26 (m, 1H, CH(O*H*)), 7.14-7.20 (m, 2H, 2x C*H*-4 phenyl), 7.24-7.31 (m, 5H, *H*-3 salicyl, 2x *H*-3'',5'' phenyl), 7.35-7.41 (m, 4H, 2x *H*-2'',6'' phenyl), 7.59 (dd, ^{3}J = 8.9, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.74 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 8.13 (d, ^{3}J = 8.6, 1H, *H*-5 aniline), 8.19 (dd, ^{3}J = 8.6, ^{4}J = 1.7, 1H, *H*-6 aniline), 8.39 (d, ^{4}J = 1.7, 1H, *H*-2 aniline), 10.94 (br, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 51.37 (*C*H_2 piperazine), 53.46 (*C*H_2 piperazine), 60.74 (NCH_2CH(OH)), 66.04 (*C*H(OH)), 72.25 (OCH_2CH(OH)), 75.08 (*N*-*C*H(C_6H_5)$_2$), 102.11 (q, J_{CF} = 2.2, C_q-4 aniline), 115.70 (*C*N), 115.78 (*C*-3 salicyl), 117.12 (q, J_{CF} = 5.0, *C*-2 aniline), 122.39 ($^{1}J_{CF}$ = -274.0, *C*F_3), 122.57 (*C*-6 aniline), 124.82 (C_q-1 salicyl), 124.85 (C_q-5 salicyl), 126.79 (*C*-4'' phenyl), 127.50 (*C*-2'',6'' phenyl), 128.45 (*C*-3'',5'' phenyl), 129.52 (*C*-6 salicyl), 131.76 (q, $^{2}J_{CF}$ = 31.9, *C*-3 aniline), 132.71 (*C*-4 salicyl), 136.55 (*C*-5 aniline), 142.82 (C_q-1'' phenyl), 142.84 (C_q-1'' phenyl), 143.21 (*C*-1 aniline), 155.14 (C_q-2 salicyl), 163.72 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 649.22 found: 649.33, $[M-H]^-$: calculated.: 647.20 found: 647.42.

Melting point: 160-162°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(4-cyanophenyl)benzamide (266**)**



266 was prepared following **general procedure E**, yielding 0.242 g (41%) of the desired product.

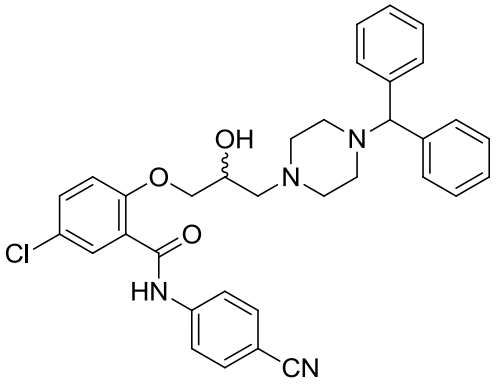
^{1}H NMR (400 MHz, DMSO-d$_6$, 23 °C): δ = 1.36-1.44 (s, br, 6H, C*H*$_2$-adamantane), 1.52-1.59 (m, 3H, C*H*$_2$-adamantane), 1.61-1.68 (m, 3H, C*H*$_2$-adamantane), 1.84-1.92 (s, br, 3H, C*H*-adamantane, *H* in exchange), 2.08 (s, 2H, NHC*H*$_2$-1-adamantane), 2.55-2.69 (m, 2H, CH(OH)C*H*$_2$NH), 3.92-4.00 (m, 1H, C*H*(OH)), 4.09-4.21 (m, 2H, OC*H*$_2$CH(OH)), 7.27 (d, ^{3}J = 8.9, 1H, *H*-3 salicyl), 7.58 (dd, ^{3}J = 8.9, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.73 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 7.81 (d, ^{3}J = 8.6, 2H, *H*-3,5 aniline), 7.96 (d, ^{3}J = 8.6, 2H, *H*-2,6 aniline), 10.70 (br, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d$_6$, 23 °C): δ = 27.79 (*C*H-adamantane), 33.15 (*C*$_q$-1'' adamantane), 36.69 (*C*H$_2$-adamantane), 40.19 (*C*H$_2$-adamantane), 53.34 (N*C*H$_2$CH(OH)), 62.17 (NH*C*H$_2$-1''-adamantane), 67.59 (*C*H(OH)), 71.80 (O*C*H$_2$CH(OH)), 105.52 (*C*$_q$-4 aniline), 115.64 (*C*-3 salicyl), 118.97 (*C*N), 119.81 (*C*-2,6 aniline), 124.75 (*C*$_q$-1 salicyl), 125.22 (*C*$_q$-5 salicyl), 129.52 (*C*-6 salicyl), 132.38 (*C*-4 salicyl), 133.28 (*C*-3,5 aniline), 142.89 (*C*$_q$-1 aniline), 155.05 (*C*$_q$-2 salicyl), 163.24 (*C*ONH).

LCMS: [M+H]$^{+}$: calculated.: 494.22 found: 494.37, [M-H]$^{-}$: calculated.: 492.21 found: 492.46.

Melting point: 174-176°C.

2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-5-chloro-*N*-(4-cyanophenyl)benzamide (267)



267 was prepared following **general procedure E**, yielding 0.721 g (100%) of the desired product.

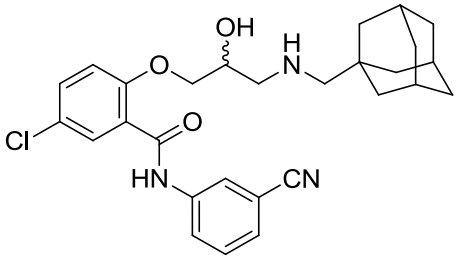
^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 2.08-2.47 (m[dyn], br, 10H, CH(OH)CH_2NH, H_{ax} H_{eq}-3,5 in piperazine, H_{ax}-2,6 in CH_2 piperazine), 3.97-4.04 (m, 1H, C*H*(OH)), 4.07 (d, ^{2}J =-9.5, ^{3}J =6.0, 1H, OCH_aH$_b$CH(OH)), 4.18 (d, ^{2}J =-9.5, ^{3}J =3.8, 1H, OCH$_a$$H_b$CH(OH)), 4.23 (br s, 1H, NC*H*(C_6H_5)$_2$), 5.13-5.22 (m, 1H, CH(O*H*)), 7.15-7.20 (m, 2H, 2x C*H*-4 phenyl), 7.24-7.31 (m, 5H, *H*-3 salicyl, 2x *H*-3'',5'' phenyl), 7.37-7.41 (m, 4H, 2x *H*-2'',6'' phenyl), 7.57 (dd, ^{3}J = 8.7, ^{4}J = 2.7, 1H, *H*-4 salicyl), 7.75 (d, ^{4}J = 2.7, 1H, *H*-6 salicyl), 7.79 (d, ^{3}J = 8.6, 2H, *H*-3,5 aniline), 7.94 (d, ^{3}J = 8.6, 2H, *H*-2,6 aniline), 10.64 (br, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 51.45 (*C*H$_2$ piperazine), 53.51 (*C*H$_2$ piperazine), 60.80 (NCH$_2$CH(OH)), 66.05 (*C*H(OH)), 72.26 (OCH$_2$CH(OH)), 75.10 (*N*-*C*H(C_6H_5)$_2$), 105.55 (C_q-4 aniline), 115.77 (*C*-3 salicyl), 118.95 (*C*N), 119.87 (*C*-2,6 aniline), 124.83 (C_q-1 salicyl), 124.96 (C_q-5 salicyl), 126.79 (*C*-4'' phenyl), 127.53 (*C*-2'',6'' phenyl), 128.46 (*C*-3'',5'' phenyl), 129.63 (*C*-6 salicyl), 132.48 (*C*-4 salicyl), 133.23 (*C*-3,5 aniline), 142.81 (C_q-1 aniline), 142.84 (C_q-1'' phenyl), 142.85 (C_q-1'' phenyl), 155.12 (*C*-2 salicyl), 163.09 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 581.23 found: 581.33, $[M-H]^-$: calculated.: 579.22 found: 579.35.

Melting point: 174-176°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3-cyanophenyl)benzamide (268**)**



268 was prepared following **general procedure E**, yielding 0.151 g (49%) of the desired product.

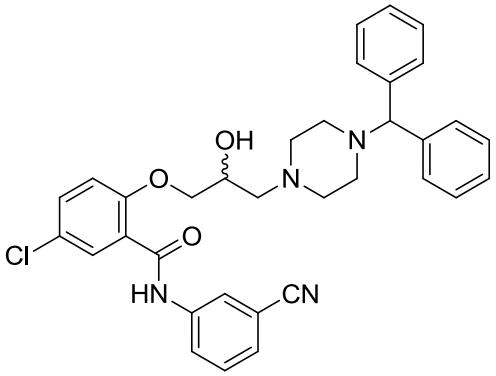
^{1}H NMR (400 MHz, DMSO-d$_6$, 23 °C): δ = 1.39-1.43 (s, br, 6H, C*H*$_2$-adamantane), 1.53-1.59 (m, 3H, C*H*$_2$-adamantane), 1.62-1.68 (m, 3H, C*H*$_2$-adamantane), 1.88 (s, br, 3H, C*H*-adamantane), 2.09 (s, 2H, NHC*H*$_2$-1-adamantane), 2.57-2.68 (m, 2H, CH(OH)C*H*$_2$NH), 3.92-3.99 (m, 1H, C*H*(OH)), 4.13 (d, ^{2}J =-9.7, ^{3}J =5.6, 1H, OC*H*$_a$H$_b$CH(OH)), 4.20 (d, ^{2}J =-9.7, ^{3}J =4.3, 1H, OCH$_a$*H*$_b$CH(OH)), 7.28 (d, ^{3}J = 8.9, 1H, *H*-3 salicyl), 7.55-7.61 (m, 3H, *H*-4,5 aniline, *H*-4 salicyl), 7.77 (d, ^{4}J = 2.7, 1H, *H*-6 salicyl), 8.01-8.07 (m, 1H, *H*-6 aniline), 8.20 (br s, 1H, *H*-2 aniline), 10.59 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d$_6$, 23 °C): δ = 27.83 (*C*H-adamantane), 33.25 (*C*$_q$-1'' adamantane), 36.75 (*C*H$_2$-adamantane), 40.29 (*C*H$_2$-adamantane), 53.40 (N*C*H$_2$CH(OH)), 62.43 (NH*C*H$_2$-1''-adamantane), 67.88 (*C*H(OH)), 72.00 (O*C*H$_2$CH(OH)), 111.69 (*C*-3 aniline), 115.80 (*C*-3 salicyl), 118.63 (*C*N), 122.43 (*C*-2 aniline), 124.35 (*C*-6 aniline), 124.85 (*C*$_q$-1 salicyl), 124.91 (*C*$_q$-5 salicyl), 127.34 (*C*-5 aniline), 129.64 (*C*-6 salicyl), 130.29 (*C*-4 aniline), 132.46 (*C*-4 salicyl), 139.49 (*C*$_q$-1 aniline), 155.15 (*C*$_q$-2 salicyl), 162.94 (*C*ONH).

LCMS: [M+H]$^{+}$: calculated.: 494.22 found: 494.37, [M-H]$^{-}$: calculated.: 492.21 found: 492.46.

Melting point: 149-152°C.

2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-5-chloro-*N*-(3-cyanophenyl)benzamide (269**)**



269 was prepared following **general procedure E**, yielding 0.320 g (90%) of the desired product.

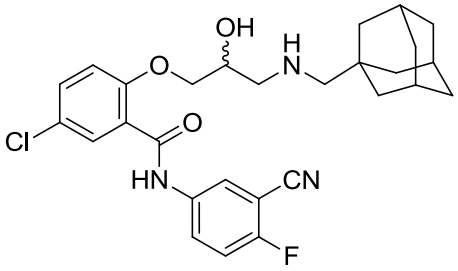
^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 2.12-2.49 (m[dyn], br, 10H, CH(OH)CH_2NH, H_{ax} H_{eq}-3,5 in piperazine, H_{ax}-2,6 in CH_2 piperazine), 3.98-4.06 (m, 1H, C*H*(OH)), 4.08 (d, ^{2}J =-9.6, ^{3}J =5.7, 1H, OCH_aH$_b$CH(OH)), 4.18 (d, ^{2}J =-9.6, ^{3}J =3.6, 1H, OCH$_a$$H_b$CH(OH)), 4.23 (br s, 1H, NC*H*(C_6H_5)$_2$), 5.18-5.29 (m, 1H, CH(O*H*)), 7.13-7.20 (m, 2H, 2x C*H*-4 phenyl), 7.24-7.31 (m, 5H, *H*-3 salicyl, 2x *H*-3'',5'' phenyl), 7.36-7.41 (m, 4H, 2x *H*-2'',6'' phenyl), 7.52-7.55 (m, 2H, *H*-4,5 aniline), 7.57 (dd, ^{3}J = 8.9, ^{4}J = 2.8,, 1H, *H*-4 salicyl), 7.77 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 8.00-8.06 (m, 1H, *H*-6 aniline), 8.20 (m, 1H, *H*-2 aniline), 10.58 (br, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 51.45 (*C*H$_2$ piperazine), 53.53 (*C*H$_2$ piperazine), 60.84 (NCH$_2$CH(OH)), 66.04 (*C*H(OH)), 72.33 (OCH$_2$CH(OH)), 75.11 (*N*-*C*H(C_6H_5)$_2$), 111.63 (*C*-3 aniline), 115.85 (*C*-3 salicyl), 118.63 (*C*N), 122.49 (*C*-2 aniline), 124.39 (*C*-6 aniline), 124.80 (C_q-1 salicyl), 124.88 (C_q-5 salicyl), 126.77 (*C*-4'' phenyl), 127.30 (*C*-5 aniline), 127.53 (*C*-2'',6'' phenyl), 128.46 (*C*-3'',5'' phenyl), 129.67 (*C*-6 salicyl), 130.23 (*C*-4 aniline), 132.48 (*C*-4 salicyl), 139.45 (C_q-1 aniline), 142.86 (C_q-1'' phenyl), 142.87 (C_q-1'' phenyl), 155.15 (C_q-2 salicyl), 162.87 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 581.23 found: 581.39, $[M-H]^-$: calculated.: 579.22 found: 579.35.

Melting point: 189°C.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3-cyano-4-fluorophenyl)benzamide (270**)**



270 was prepared following **general procedure E**, yielding 0.152 g (51%) of the desired product.

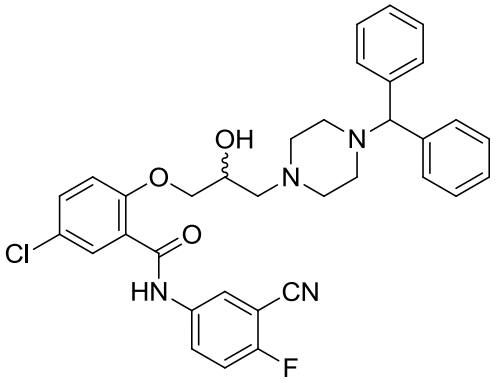
^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 1.38-1.44 (s, br, 6H, CH_2-adamantane), 1.53-1.59 (m, 3H, CH_2-adamantane), 1.62-1.68 (m, 3H, CH_2-adamantane), 1.88 (s, br, 3H, C*H*-adamantane), 2.10 (s, 2H, NHCH_2-1-adamantane)), 2.58-2.68 (m, 2H, CH(OH)CH_2NH), 3.93-4.00 (m, 1H, C*H*(OH)), 4.12 (d, ^{2}J =-9.8, ^{3}J =5.5, 1H, OCH_aH$_b$CH(OH)), 4.19 (d, ^{2}J =-9.8, ^{3}J =4.4, 1H, OCH$_a$$H_b$CH(OH)), 7.28 (d, ^{3}J = 8.9, 1H, *H*-3 salicyl), 7.52-7.61 (m, 2H, *H*-5 aniline, *H*-4 salicyl) 7.75 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 8.08 (m, 1H, *H*-6 aniline), 8.22 (m, 1H, *H*-2 aniline), 10.61 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 27.82 (*C*H-adamantane), 33.21 (C_q-1'' adamantane), 36.73 (*C*H$_2$-adamantane), 40.26 (*C*H$_2$-adamantane), 53.38 (N*C*H$_2$CH(OH)), 62.37 (NH*C*H$_2$-1''-adamantane), 67.79 (*C*H(OH)), 71.99 (O*C*H$_2$CH(OH)), 100.04 (d, J_{CF}=16.2, *C*-3 aniline), 113.86 (*C*N), 115.83 (*C*-3 salicyl), 117.16 (d, $^{2}J_{CF}$= 20.5, *C*-5 aniline), 123.52 (*C*-2 aniline), 124.85, 124.86 (*C*-1,5 salicyl), 127.05 (d, $^{3}J_{CF}$= 8.2, *C*-6 aniline), 129.57 (*C*-6 salicyl), 132.46 (*C*-4 salicyl), 135.86 (d, $^{4}J_{CF}$= 1.4, *C*-1 aniline), 155.13 (*C*-2 salicyl), 158.43 (d, $^{1}J_{CF}$= 252.5, *C*-4 aniline), 162.86 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 512.21 found: 512.36.

Melting point: 140-141°C.

2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-5-chloro-*N*-(3-cyano-4-fluorophenyl)benzamide (271)



271 was prepared following **general procedure E**, yielding 0.305 g (87%) of the desired product.

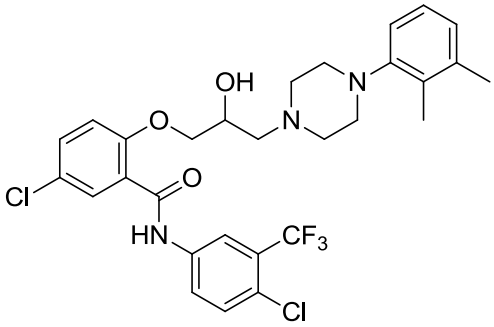
^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 2.13-2.48 (m[dyn], br, 10H, CH(OH)CH_2NH, H_{ax} H_{eq}-3,5 in piperazine, H_{ax}-2,6 in CH_2 piperazine), 3.98-4.11 (m, 2H, C*H*(OH), OC$H_a$$H_b$CH(OH)), 4.18 (d, ^{2}J =-9.2, ^{3}J =3.5, 1H, OCH$_a$$H_b$CH(OH)), 4.23 (br s, 1H, NC*H*(C_6H_5)$_2$), 5.18-5.32 (m, 1H, CH(O*H*)), 7.14-7.19 (m, 2H, 2x C*H*-4 phenyl), 7.24-7.31 (m, 5H, *H*-3 salicyl, 2x *H*-3'',5'' phenyl), 7.36-7.42 (m, 4H, 2x *H*-2'',6'' phenyl), 7.52 (dd[t], ^{3}J =9.1, 1H, *H*-5 aniline), 7.57 (dd, ^{3}J = 8.7, ^{4}J = 2.8,, 1H, *H*-4 salicyl), 7.76 (d, ^{4}J = 2.8,, 1H, *H*-6 salicyl), 8.04-8.10 (m, 1H, *H*-6 aniline), 8.20-8.25(m, 1H, *H*-2 aniline), 10.60 (br, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 51.45 (*C*H_2 piperazine), 53.54 (*C*H_2 piperazine), 60.86 (N*C*H_2CH(OH)), 66.02 (*C*H(OH)), 72.36 (O*C*H_2CH(OH)), 75.11 (*N*-*C*H(C_6H_5)$_2$), 100.00 (d, J_{CF}=16.2, *C*-3 aniline), 113.88 (*C*N), 115.91 (*C*-3 salicyl), 117.11 (d, $^{2}J_{CF}$= 20.6, *C*-5 aniline), 123.62 (*C*-2 aniline), 124.64 (*C*-1 salicyl), 124.91 (*C*-5 salicyl), 126.78 (*C*-4'' phenyl), 127.11 (d, $^{3}J_{CF}$= 8.2, *C*-6 aniline), 127.52 (*C*-2'',6'' phenyl), 128.45 (*C*-3'',5'' phenyl), 129.65 (*C*-6 salicyl), 132.53 (*C*-4 salicyl), 135.80 (d, $^{4}J_{CF}$= 1.7, *C*-1 aniline), 142.85 (C_q-1'' phenyl), 142.87 (C_q-1'' phenyl), 155.16 (*C*-2 salicyl), 158.41 (d, $^{1}J_{CF}$=-252.5, *C*-4 aniline), 162.75 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 599.22 found: 599.38, $[M-H]^-$: calculated.: 597.21 found: 597.41.

Melting point: 211-213°C.

5-chloro-*N*-(4-chloro-3-(trifluoromethyl)phenyl)-2-(3-(4-(2,3-dimethylphenyl)piperazin-1-yl)-2-hydroxypropoxy)benzamide (272)



272 was prepared following **general procedure E**, yielding 0.305 g (70%) of the desired product.

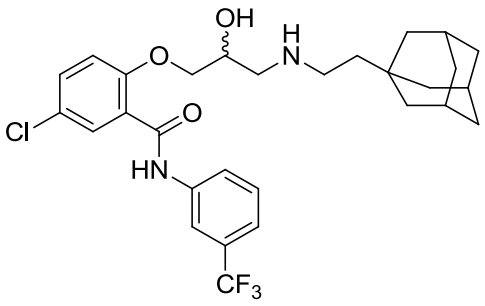
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 2.22 (s, 3H, 2-C*H*$_3$), 2.28 (s, 3H, 3-C*H*$_3$), 2.53-2.69 (m[dyn], 4H, CH(OH)C*H*$_2$NH, 2H in piperazine), 2.83-3.02 (m[dyn], br, 6H in piperazine), 4.02 (dd, ^{2}J = -9.0, ^{3}J = 6.5, 1H, OC*H*$_a$H$_b$CH(OH)), 4.13 (br, 1H, O*H*), 4.24-4.31 (m, 1H, C*H*(OH)), 4.34 (dd, ^{2}J = -9.0, ^{3}J = 2.3, 1H, OCH$_a$*H*$_b$CH(OH)), 6.90-6.97 (m, 3H, *H*-3 salicyl, *H*-4,6 phenyl), 7.11 (d, ^{3}J = 7.7, 1H, *H*-5 phenyl), 7.43 (dd, ^{3}J = 8.7, ^{4}J = 2.7, 1H, *H*-4 salicyl), 7.46 (d, ^{3}J = 8.9, 1H, *H*-5 aniline), 8.11 (d, ^{4}J = 2.1, 1H, *H*-2 aniline), 8.16 (dd, ^{3}J = 8.9, ^{4}J = 2.1, 1H, *H*-6 aniline), 8.21 (d, ^{4}J = 2.7, 1H, *H*-6 salicyl), 10.38 (s, 1H (CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 14.06 (2-*C*H$_3$), 20.77 (3-*C*H$_3$), 52.25 (*C*H$_2$-3'',5'' piperazine), 54.96 (dyn, *C*H$_2$-2'',6'' piperazine), 59.61 (N*C*H$_2$CH(OH)), 64.99 (*C*H(OH)), 71.84 (O*C*H$_2$CH(OH)), 114.34 (*C*-3 salicyl), 116.80 (*C*-6 phenyl), 119.53 (q, $^{3}J_{CF}$ = 5.6, *C*-2 aniline), 122.89 ($^{1}J_{CF}$ = -273.0, *C*F$_3$ aniline), 123.34 (C_q-1 salicyl), 124.31 (*C*-6 aniline), 125.40 (*C*-4 phenyl), 126.09 (*C*-5 phenyl), 126.47 (q, $^{3}J_{CF}$ = 2.2, *C*-4 aniline), 127.70 (C_q-5 salicyl), 128.61 (q, $^{2}J_{CF}$ = 31.3, *C*-3 aniline), 131.37 (C_q-2 phenyl), 132.02 (*C*-5 aniline), 132.39 (*C*-6 salicyl), 133.25 (*C*-4 salicyl), 137.73 (*C*-1 aniline), 138.22 (C_q-3 phenyl), 151.28 (C_q-1 phenyl), 155.11 (C_q-2 salicyl), 162.40 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 596.17 found: 596.26.

Melting point: 186-190°C.

2-(3-((2-(adamantan-1-yl)ethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (273)



273 was prepared following **general procedure E**, yielding 0.164 g (53%) of the desired product.

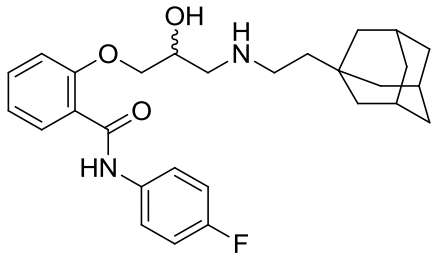
^{1}H NMR (400 MHz, DMSO-d$_6$, 23 °C): δ = 1.21-1.28 (m, 2H, C*H*$_2$CH$_2$N), 1.32-1.41 (s, br, 6H, C*H*$_2$-adamantane), 1.53-1.60 (m, 3H, C*H*$_2$-adamantane), 1.61-1.68 (m, 3H, C*H*$_2$-adamantane), 1.84-1.92 (s, br, 3H, C*H*-adamantane), 2.54-2.63 (m, 2H, CH$_2$C*H*$_2$N), 2.78 (dd, ^2J = -12.3, ^3J = 7.5, 1H, CH(OH)C*H*$_a$H$_b$NH), 2.89 (dd, ^2J = -12.3, ^3J = 4.3, 1H, CH(OH)CH$_a$*H*$_b$NH), 4.06-4.14 (m, 1H, C*H*(OH)), 4.14-4.23 (m, 2H, OC*H*$_2$CH(OH)), 7.27 (d, ^3J = 9.0, 1H, *H*-3 salicyl), 7.45 (d, ^3J = 7.8, 1H, *H*-4 aniline), 7.57 (d, ^3J = 9.0, ^4J = 2.6, 1H, *H*-4 salicyl), 7.57-7.61 (m, 1H, *H*-5 aniline), 7.72 (d, ^4J = 2.8, 1H, *H*-6 salicyl), 7.95 (d, ^4J = 8.3, 1H, *H*-6 aniline), 8.32 (br s, 1H, *H*-2 aniline), 10.67 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d$_6$, 23 °C): δ = 27.91 (*C*H-adamantane), 31.18 (*C*$_q$-1 adamantane), 36.47 (*C*H$_2$-adamantane), 41.35 (*C*H$_2$-adamantane), 41.71 (NHCH$_2$*C*H$_2$-1-adamantane), 43.20 (NH*C*H$_2$CH$_2$-1-adamantane), 50.86 (N*C*H$_2$CH(OH)), 66.20 (*C*H(OH)), 71.27 (O*C*H$_2$CH(OH)), 115.49 (*C*-3 salicyl), 115.79 (q, $^4J_{CF}$ = 3.9, *C*-2' in 3'-CF$_3$-aniline), 120.09 (q, $^4J_{CF}$ = 3.7, *C*-4' in 3'-CF$_3$-aniline), 123.39 (*C*-6' in 3'-CF$_3$-aniline), 124.76 (*C*$_q$-1 salicyl) 124.09 (q, *C*$_q$, $^1J_{CF}$ = -272.0, 3-*C*F$_3$-aniline), 125.70 (Cq) (*C*$_q$-5 salicyl), 129.42 (*C*-5' in 3'-CF$_3$-aniline), 129.51 (q, $^2J_{CF}$ = 31.5, *C*$_q$-3' in 3'-CF$_3$-aniline), 129.94 (*C*-6 salicyl), 132.05 (*C*-4 salicyl), 139.53 (*C*$_q$-1' in 3'-CF$_3$-aniline), 154.73 (*C*$_q$-2 salicyl), 163.29 (*C*ONH).

LCMS: [M+H]$^+$: calculated.: 551.23 found: 551.26, [M-H]$^-$: calculated.: 549.21 found: 549.16.

Melting point: 210°C.

2-(3-((2-(adamantan-1-yl)ethyl)amino)-2-hydroxypropoxy)-*N*-(4-fluorophenyl)benzamide (274)



274 was prepared following **general procedure E**, yielding 0.129 g (50%) of the desired product.

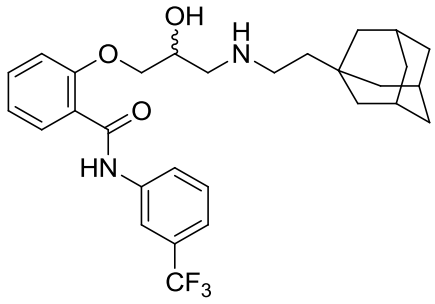
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.16-1.26 (m, 2H, CH_2CH_2N), 1.38-1.45 (s, br, 6H, CH_2-adamantane), 1.54-1.60 (m, 3H, CH_2-adamantane), 1.60-1.69 (m, 3H, CH_2-adamantane), 1.89 (s, br, 3H, C*H*-adamantane), 2.46-2.51 (m, 2H, CH_2CH_2N), 2.68 (dd, ^{2}J = -12.0, ^{3}J = 6.9, 1H, CH(OH)C$H_a$$H_b$NH), 2.75 (dd, ^{2}J = -12.0, ^{3}J = 5.1, 1H, CH(OH)C$H_a$$H_b$NH), 3.99-4.07 (m, 1H, C*H*(OH)), 4.14 (dd, ^{2}J = -9.7, ^{3}J = 5.6, 1H, OC$H_a$$H_b$CH(OH)), 4.21 (dd, ^{2}J = -9.7, ^{3}J = 4.3, 1H, OC$H_a$$H_b$CH(OH)), 7.06-7.12 (m, 1H, *H*-5 salicyl), 7.13-7.19 (m, 2H, *H*-3,5 aniline), 7.21 (d, ^{3}J = 8.4, 1H, *H*-3 salicyl), 7.49-7.54 (m, 1H, *H*-4 salicyl), 7.79-7.87 (m, 3H, *H*-2,6 aniline, *H*-6 salicyl), 10.38 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 27.99 (*C*H-adamantane), 31.28 (C_q-1 adamantane), 36.58 (*C*H_2-adamantane), 41.98 (*C*H_2-adamantane), 43.20 (NHCH_2*C*H_2-1-adamantane), 43.60 (NH*C*H_2CH_2-1-adamantane), 51.99 (N*C*H_2CH(OH)), 67.45 (*C*H(OH)), 71.36 (O*C*H_2CH(OH)), 113.43 (*C*-3 salicyl), 115.22 (d, $^{2}J_{CF}$ = 22.1, *C*-3',5' in 4'-F-aniline), 120.95 (*C*-5 salicyl), 121.44 (d, $^{3}J_{CF}$ = 7.7, *C*-2',6' in 4'-F-aniline), 123.40 (C_q-1 salicyl), 130.55 (*C*-6 salicyl), 132.72 (*C*-4 salicyl), 135.41 (d, $^{4}J_{CF}$ = 2.4, C_q-1' in 4'-F-aniline), 156.15 (C_q-2 salicyl), 158.14 (d, $^{1}J_{CF}$ = -240, C_q-4' in 4'-F-aniline), 163.58 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 467.27 found: 467.40, $[M-H]^-$: calculated.: 465.26 found: 465.38.

Melting point: 128-130°C.

2-(3-((2-(adamantan-1-yl)ethyl)amino)-2-hydroxypropoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (275)



275 was prepared following **general procedure E**, yielding 0.122 g (32%) of the desired product.

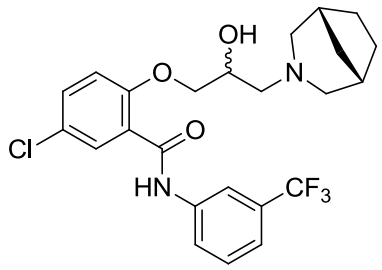
^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 1.14-1.21 (2H), 1.36-1.41 (6H), 1.51-1.68 (6H), 1.88 (br, 3H), 2.46-2.54 (2H), 2.67-2.81 (2H), 3.97-4.05 (1H), 4.12-4.23 (2H), 7.12 (1H), 7.23 (1H), 7.42-7.47 (1H), 7.51-7.61 (2H), 7.81 (1H), 7.93-7.98 (1H), 8.34 (1H), 10.59 (1H).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6, 23 °C): δ = 27.95 (*C*H-adamantane), 31.24 (C_q-1 adamantane), 36.54 (*C*H_2-adamantane), 41.91 (*C*H_2-adamantane), 42.97 (NHCH_2*C*H_2-1-adamantane), 43.55 (NH*C*H_2CH_2-1-adamantane), 51.78 (N*C*H_2CH(OH)), 67.29 (*C*H(OH)), 71.26 (O*C*H_2CH(OH)), 113.45 (*C*-3 salicyl), 115.76 (q, $^{3}J_{CF}$ = 4.0, *C*-2' in 3'-CF_3-aniline), 119.84 (q, $^{3}J_{CF}$ = 3.7, *C*-4' in 3'-CF_3-aniline), 121.00 (*C*-5 salicyl), 123.27 (*C*-6' in 3'-CF_3-aniline), 123.34 (C_q-1 salicyl), 129.89 (*C*-5' in 3'-CF_3-aniline), 130.48 (*C*-6 salicyl), 132.95 (*C*-4 salicyl), 139.73 (C_q-1' in 3'-CF_3-aniline), 156.15 (C_q-2 salicyl), 164.36 (*C*ONH). *C*F_3, *C*-3 aniline not recorded.

LCMS: $[M+H]^+$: calculated.: 517.27 found: 517.35, $[M-H]^-$: calculated.: 515.25 found: 515.25.

Melting point: 78°C.

2-(3-(3-azabicyclo[3.2.1]octan-3-yl)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (276)



276 was prepared following **general procedure E**, yielding 0.127 g (34%) of the desired product.

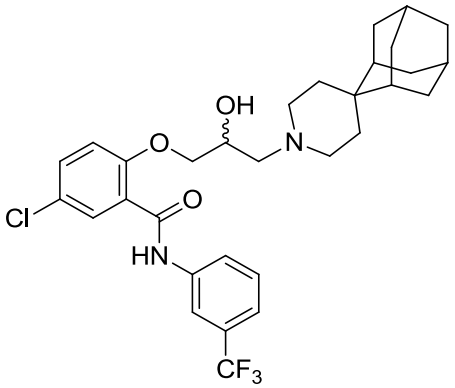
^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.23-1.27 (m, 1H, dyn, CH in CH_2), 1.33-1.40 (m, 1H, dyn, CH in CH_2), 1.42-1.59 (m, 4H, 2x CH_2), 1.95-2.05 (m, 4H, CH_2, 2x CH in CH_2), 2.32-2.44 (m, 2H, CH(OH)CH_aH_bNH), 2.50-2.54 (m, 1H, CH in CH_2, DMSO interfering), 2.59-2.64 (m, 1H CH in CH_2), 3.98-4.05 (m, 1H, C*H*(OH)), 4.16 (dd, ^{2}J = -9.4, ^{3}J = 5.4, 1H, OCH_aH$_b$CH(OH)), 4.24 (dd, ^{2}J = -9.6, ^{3}J = 3.6, 1H, OCH$_a$$H_b$CH(OH)), 7.28 (d, ^{3}J = 9.0, 1H, *H*-3 salicyl), 7.45 (d, ^{3}J = 7.8, 1H, *H*-4'' in 3''-CF3-aniline), 7.56-7.62 (m, 2H, *H*-4 salicyl, *H*-5'' in 3''-CF3-aniline), 7.80 (d, ^{3}J = 2.9, 1H, *H*-6 salicyl), 7.98 (d, ^{3}J = 8.3, 1H, *H*-6'' in 3''-CF3-aniline), 8.26 (s, br, 1H, *H*-2''in 3''-CF3-aniline), 10.61 (s, 1H, CON*H*).

^{13}C{^{1}H}NMR (150 MHz, $CDCl_3$, 25 °C): δ = 28.21 (CH*C*$H_2$$CH_2$CH), 28.36 (CHC$H_2$*C*$H_2$CH), 34.60 (*C*HC$H_2$$CH_2$CH), 34.69 (CHC$H_2$$CH_2$*C*H), 37.05 (CH*C*$H_2$CH), 60.02 (N*C*$H_2$CH(OH)),60.04 (N*C*$H_2$CH), 60.58 (N*C*$H_2$CH), 66.20 (OC$H_2$*C*HOHC$H_2$NHR), 72.19 (O*C*$H_2$CH(OH)), 115.74 (*C*-3 salicyl), 115.92 (q, $^{4}J_{CF}$ = 4.0, *C*-2' in 3'-CF_3-aniline), 120.12 (q, $^{4}J_{CF}$ = 3.7, *C*-4' in 3'-CF_3-aniline), 123.36 (*C*-6' in 3'-CF_3-aniline), 124.06 (q, $^{1}J_{CF}$ = -271.8, 3-*C*F_3-aniline), 124.83 (C_q-1 salicyl), 124.92 (C_q-5 salicyl), 129.69 (*C*-6 salicyl), 129.97 (*C*-5' in 3'-CF_3-aniline), 132.44 (*C*-4 salicyl), 139.41 (C_q-1' in 3'-CF_3-aniline), 155.31 (C_q-2 salicyl), 162.83 (*C*ONH). *C*-3 Aniline not recorded

LCMS: $[M+H]^+$: calculated.: 483.17 found: 483.27, $[M-H]^-$: calculated.: 481.15 found: 481.17.

Melting point: 122-143°C.

5-chloro-2-(2-hydroxy-3-(spiro[adamantane-2,4'-piperidin]-1'-yl)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (277)



277 was prepared following **general procedure E**, yielding 0.271 g (57%) of the desired product.

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 1.41-1.52 (m, 6H, CH_2-adamantane), 1.53-1.59 (m, 4H, CH_2-3,5-piperidine), 1.62 (br s, 2H, CH_2-adamantane), 1.78 (br s, 2H, C*H*-adamantane), 1.89-1.98 (m [d], 4H, CH_2-adamantane), 2.27 (m [t], 4H, CH_2-2,6-piperidine), 2.32-2.45 (s, 2H,

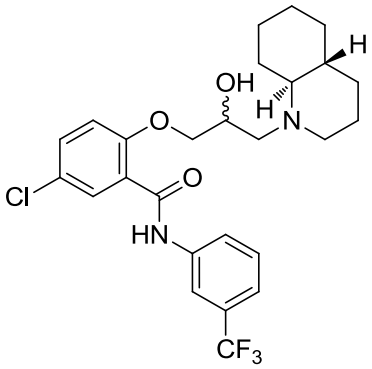
NHC*H*$_2$-1-adamantane)), 3.99-4.05 (m, 1H, C*H*(OH)), 4.10 (dd, ^2J = -9.6, ^3J = 5.3, 1H, OC*H*$_a$H$_b$CH(OH)), 4.16 (dd, ^2J = -9.5, ^3J = 4.2, 1H, OCH$_a$*H*$_b$CH(OH)), 5.12 (m, 1H, CH(O*H*)), 7.27 (d, ^3J = 8.9, 1H, *H*-3 salicyl), 7.45 (d, ^3J = 7.8, 1H, *H*-6 aniline), 7.55-7.61 (m, 2H, *H*-4 salicyl, *H*-5 aniline)), 7.76 (d, ^4J = 2.8, 1H, *H*-6 salicyl), 7.98 (d, ^3J = 8.3, 1H, *H*-4 aniline), 8.26 (s, 1H, *H*-2 aniline), 10.59 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, DMSO-d$_6$, 23 °C): δ = 27.62 (*C*H-adamantane), 31.77 (*C*H$_2$-adamantane, *C*H$_2$ 3,5-piperidine), 33.59 (*C*H$_2$-adamantane), 34.80 (*C*$_q$-2'' adamantane), 39.01 (*C*H$_2$-adamantane), 49.02 (N*C*H$_2$ 2,6-piperidine), 61.26 (N*C*H$_2$CH(OH)), 66.18 (*C*H(OH)), 72.31 (O*C*H$_2$CH(OH)), 115.76 (*C*-3 salicyl), 115.86 (q, $^3J_{CF}$ = 4.1, *C*-2 aniline), 120.06 (q, $^3J_{CF}$ = 3.6, *C*-4 aniline), 123.35 (*C*-6 aniline), 124.07 ($^1J_{CF}$ = -272.3, *C*F$_3$ aniline), 124.80 (*C*-1 salicyl), 125.18 (*C*-5 salicyl), 129.50 ($^2J_{CF}$ = 31.6, *C*-3 aniline), 129.56 (*C*-6 salicyl), 129.92 (*C*-5 aniline), 132.29 (*C*-4 salicyl), 139.45 (*C*-1 aniline), 155.13 (*C*-2 salicyl), 162.95 (*C*ONH).

LCMS: [M+H]$^+$: calculated.: 577.24 found: 577.32, [M-H]$^-$: calculated.: 575.23 found: 575.30.

Melting point: 163-165°C.

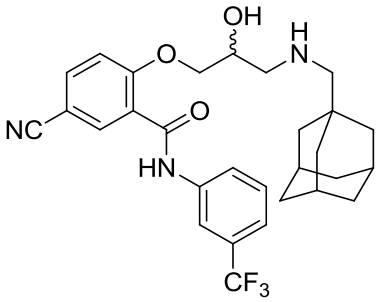
5-chloro-2-(2-hydroxy-3-(octahydroquinolin-1(2H)-yl)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (278)



278 was prepared following **general procedure E**, yielding 0.387 g (54%) of the desired diastereomeric products.

LCMS: [M+H]$^+$: calculated.: 511.20 found: 511.28, [M-H]$^-$: calculated.: 509.18 found: 509.18.

2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-cyano-*N*-(3-(trifluoromethyl)phenyl)benzamide (279)



279 was prepared following **general procedure E**, yielding 0.132 g (45%) of the desired product.

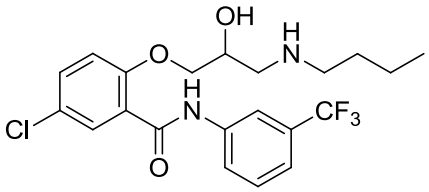
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.46-1.53 (s, br, 6H, C*H*$_2$-adamantane), 1.60-1.66 (m, 3H, C*H*$_2$-adamantane), 1.70-1.77 (m, 3H, C*H*$_2$-adamantane), 1.98 (s, br, 3H, C*H*-adamantane), 2.25, 2.28, 2.32, 2.35 (AB, J_{AB} = -11.4, 2H, NHC*H*$_2$-1-adamantane), 2.76 (dd, ^{2}J = -12.2, ^{3}J = 9.6, 1H, CH(OH)C*H*$_a$H$_b$NH), 2.87 (dd, ^{2}J = -12.3, ^{3}J = 3.8, 1H, CH(OH)CH$_a$*H*$_b$NH), 4.10 (m, ^{2}J = -9.1, ^{3}J = 6.6, 1H, OC*H*$_a$H$_b$CH(OH)), 4.15-4.22 (m, 1H, C*H*(OH)), 4.37 (dd, ^{2}J = -9.1, ^{3}J = 2.6, 1H, OCH$_a$*H*$_b$CH(OH)), 7.06 (d, 1H, ^{3}J = 8.7, *H*-3 salicyl), 7.37 (d, ^{3}J = 7.6, 1H, *H*-4 aniline), 7.45 (dd [t], ^{3}J = 7.9, 1H, *H*-5 aniline), 7.73 (dd, 1H, ^{3}J = 8.6, ^{4}J = 2.3, *H*-4 salicyl), 8.05 (d, ^{3}J = 8.4, 1H, *H*-6 aniline), 8.08 (s, 1H, *H*-2 aniline), 8.53 (d, 1H, ^{4}J = 2.3, *H*-6 salicyl), 10.19 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 28.42 (*C*H-adamantane), 33.51 (C_q-1'' adamantane), 37.16 (*C*H$_2$-adamantane), 40.73 (*C*H$_2$-adamantane), 51.36 (N*C*H$_2$CH(OH)), 62.13 (NH*C*H$_2$-1''-adamantane), 66.56 (*C*H(OH)), 71.84 (O*C*H$_2$CH(OH)), 106.03 (*C*-5 salicyl), 113.65 (*C*-3 salicyl), 117.40 (q, $^{3}J_{CF}$ = 4.0, *C*-2 aniline), 118.17 (*C*N), 120.98 (q, $^{3}J_{CF}$ = 3.7, *C*-4 aniline), 121.01 (*C*-1 salicyl), 123.67 (*C*-6 aniline), 124.09 (q, $^{1}J_{CF}$ = -272.3, *C*F3), 129.61 (*C*-5 aniline), 131.74 (q, $^{2}J_{CF}$ = 32.1, *C*-3 aniline), 136.93 (*C*-4 salicyl), 137.14 (*C*-6 salicyl), 139.01 (*C*-1 aniline), 159.45 (*C*-2 salicyl), 161.64 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 528.25 found: 528.32, $[M-H]^-$: calculated.: 526.23 found: 526.29.

Melting point: 110-112°C.

2-(3-(butylamino)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (292)



292 was prepared following **general procedure E**, yielding 0.302 g (81%) of the desired product.

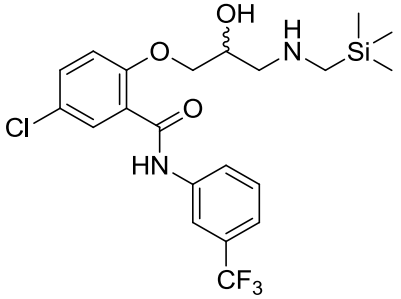
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 0.91 (t, ^{3}J = 7.2, 3H, CH_3), 1.29-1.38 (m, 2H, CH_2), 1.42-1.50 (m, 2H, CH_2), 2.55-2.69 (m, 2H, CH_2), 2.73 (dd, ^{2}J = -12.3, ^{3}J = 9.3, 1H, CH(OH)CH_aH$_b$NH), 2.87 (dd, ^{2}J = -12.3, ^{3}J = 3.9, 1H, CH(OH)CH$_a$$H_b$NH), 4.02 (dd, ^{2}J = -9.2, ^{3}J = 6.5, 1H, OCH_aH$_b$CH(OH)), 4.07-4.14 (m, 1H, CH(OH)), 4.27 (dd, ^{2}J = -9.2, ^{3}J = 2.7, 1H, OCH$_a$$H_b$CH(OH)), 6.90 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.34 (d, ^{3}J = 7.7, 1H, *H*-4 aniline), 7.39 (d, ^{3}J = 8.8, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.43 (dd [t], ^{3}J =7.9, 1H, *H*-5 aniline), 8.02 (d, ^{3}J = 8.2, 1H, *H*-6 aniline), 8.11 (br s, 1H, *H*-2 aniline), 8.20 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 10.31 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 14.03 (NCH$_2$CH$_2$CH$_2$*C*H$_3$), 20.39 (NCH$_2$CH$_2$*C*H$_2$CH$_3$), 32.39 (NCH$_2$*C*H$_2$CH$_2$CH$_3$), 49.43 (N*C*H$_2$CH$_2$CH$_2$CH$_3$), 51.03 (CH(OH)*C*H$_2$N), 67.37 (*C*H(OH)), 71.86 (O*C*H$_2$CH(OH)), 114.33 (*C*-3 salicyl), 117.33 (q, $^{3}J_{CF}$ = 4.1, *C*-2' in 3'-CF_3-aniline), 120.67 (q, $^{3}J_{CF}$ = 3.8, *C*-4' in 3'-CF_3-aniline), 123.53 (C_q-1 salicyl), 123.58 (*C*-6' in 3'-CF_3-aniline), 124.18 (q, $^{1}J_{CF}$ = -272.0, *C*F$_3$), 127.48 (C_q-5 salicyl), 129.50 (*C*-5' in 3'-CF_3-aniline), 131.27 (q, $^{2}J_{CF}$ = 32.0, C_q-3' in 3'-F_3-aniline), 132.32 (*C*-6 salicyl), 133.05 (*C*-4 salicyl), 139.29 (C_q-1' in 3'-CF_3-aniline), 155.21 (C_q-2 salicyl), 162.46 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 445.15 found: 445.29, $[M-H]^-$: calculated.: 443.14 found: 443.32.

Melting point: 87-89°C.

5-chloro-2-(2-hydroxy-3-(((trimethylsilyl)methyl)amino)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (293)



293 was prepared following **general procedure E**, yielding 0.364 g (91%) of the desired product.

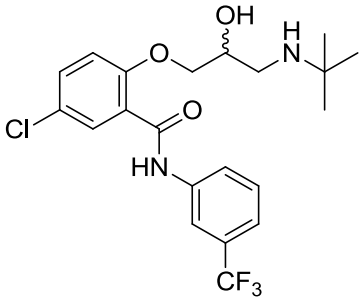
^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 0.06 (s, 9H, 3x SiCH_3), 1.97,2.00,2.17,2.21 (AB, J_{AB} = -13.4, 2H, NHCH_2Si$(CH_3)_3$), 2.74-2.85 (m, 2H, CH(OH)CH_2NH), 4.01 (dd, ^{2}J = -9.3, ^{3}J = 6.6, 1H, OCH_aH$_b$CH(OH)), 4.12-4.19 (m, 1H, CH(OH)), 4.28 (dd, ^{2}J = -9.3, ^{3}J = 2.7, 1H, OCH$_a$$H_b$CH(OH)), 6.90 91 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.34 (d, ^{3}J = 7.7, 1H, *H*-4 aniline), 7.39 (d, ^{3}J = 8.8, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.43 (dd [t], ^{3}J =8.2, 1H, *H*-5 aniline), 8.07 (br s, 1H, *H*-2 aniline), 8.08 (m, 1H, *H*-6 aniline), 8.20 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 10.33 (br s, 1H, CON*H*).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = -2.74 (3x Si*C*H$_3$), 39.79 (*C*H$_2$SiCH$_3$), 55.07 (N*C*H$_2$CH(OH)), 66.46 (*C*H(OH)), 71.88 (O*C*H$_2$CH(OH)), 114.31 (*C*-3 salicyl), 117.31 (q, $^{3}J_{CF}$ = 4.0, *C*-2' in 3'-CF$_3$-aniline), 120.63 (q, $^{3}J_{CF}$ = 3.8, *C*-4' in 3'-CF$_3$-aniline), 123.51 (C_q-1 salicyl), 124.17 (q, $^{1}J_{CF}$ = -272.4, *C*F$_3$), 123.56 (*C*-6' in 3'-CF$_3$-aniline), 127.46 (C_q-5 salicyl), 129.51 (*C*-5' in 3'-CF$_3$-aniline), 131.26 (q, $^{2}J_{CF}$ = 32.5, C_q-3' in 3'-CF$_3$-aniline), 132.33 (*C*-6 salicyl), 133.04 (*C*-4 salicyl), 139.32 (C_q-1' in 3'-CF$_3$-aniline), 155.23 (C_q-2 salicyl), 162.43 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 475.14 found: 475.30, $[M-H]^-$: calculated.: 473.13 found: 473.33.

Melting point: 95-99°C.

2-(3-(tert-butylamino)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (294)



294 was prepared following **general procedure E**, yielding 0.344 g (87%) of the desired product.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 1.07 (s, 9H, 3x CH_3), 2.63 (dd, ^{2}J = -12.2, ^{3}J = 8.8, 1H, CH(OH)CH_aH$_b$NH), 2.87 (dd, ^{2}J = -12.2, ^{3}J = 3.6, 1H, CH(OH)CH$_a$$H_b$NH), 3.96-4.06 (m, 2H, OCH_aH$_b$CH(OH), CH(OH)), 4.23-4.30 (m, 1H, OCH$_a$$H_b$CH(OH)), 6.91 (d, ^{3}J = 8.8, 1H, *H*-3 salicyl), 7.34 (d, ^{3}J = 7.8, 1H, *H*-4 aniline), 7.40 (d, ^{3}J = 8.8, ^{4}J = 2.8, 1H, *H*-4 salicyl), 7.44 (dd [t], ^{3}J =8.0,

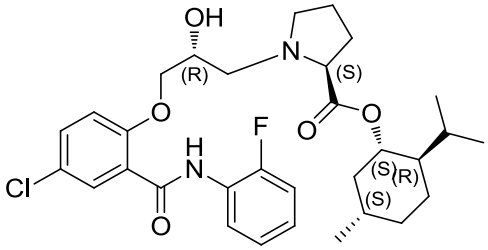
1H, *H*-5 aniline), 8.03 (d, ^{3}J = 8.0, 1H, *H*-6 aniline), 8.13 (br s, 1H, *H*-2 aniline), 8.20 (d, ^{4}J = 2.8, 1H, *H*-6 salicyl), 10.32 (br s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 29.21 (3x *C*H_3), 44.10 (N*C*H_2CH(OH)), 50.72 (C_q-*tert*-butyl), 68.25 (*C*H(OH)), 71.96 (O*C*H_2CH(OH)), 114.32 (*C*-3 salicyl), 117.43 (q, $^{3}J_{CF}$ = 3.9, *C*-2' in 3'-CF_3-aniline), 120.67 (q, $^{3}J_{CF}$ = 3.8, *C*-4' in 3'-CF_3-aniline), 123.58 (C_q-1 salicyl), 123.67 (*C*-6' in 3'-CF_3-aniline), 124.19 (q, $^{1}J_{CF}$ = -272.4, *C*F_3), 127.47 (C_q-5 salicyl), 129.49 (*C*-5' in 3'-CF_3-aniline), 131.24 (q, $^{2}J_{CF}$ = 32.4, C_q-3' in 3'-CF_3-aniline), 132.33 (*C*-6 salicyl), 133.04 (*C*-4 salicyl), 139.28 (C_q-1' in 3'-CF_3-aniline), 155.25 (C_q-2 salicyl), 162.47 (*C*ONH).

LCMS: $[M+H]^+$: calculated.: 445.15 found: 445.29, $[M-H]^-$: calculated.: 443.14 found: 473.32.

Melting point: 114-127°C.

(*S*)-(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 1-((*R*)-3-(4-chloro-2-((2-fluorophenyl)carbamoyl)phenoxy)-2-hydroxypropyl)pyrrolidine-2-carboxylate (400)



400 was prepared following **general procedure E**, yielding 0.171 g (96%) of the desired product.

^{1}H NMR (600 MHz, $CDCl_3$, 23 °C): δ = 0.74 (d, ^{3}J = 7.0, 3H, CH_3 isopropyl), 0.80-0.85 (m, 1H, H_a-4 cyclohexyl), 0.86 (d, ^{3}J = 6.7, 3H, 5-CH_3 cyclohexyl), 0.88 (d, ^{3}J = 7.0, 3H, CH_3 isopropyl), 0.91-0.98 (m, 1H, H_a-6 cyclohexyl) 1.00-1.08 (m, 1H, H_a-3 cyclohexyl), 1.34-1.41 (m [tt], 1H, *H*-2 cyclohexyl), 1.41-1.50 (m, 1H, *H*-5 cyclohexyl), 1.64-1.70 (m, 3H, H_a-4 pyrrolidine, H_b-4 cyclohexyl, CHO*H*), 1.78-1.89 (m, 3H, C*H* isopropyl, H_b-3 cyclohexyl, H_b-4 yrrolidine), 1.89-1.98 (m, 2H, H_b-6 cyclohexyl, H_a-3 pyrrolidine), 2.13-2.21 (m, 1H, H_b-3 pyrrolidine), 2.62 (m [q, ^{3}J = 8.1], 1H, H_a-5 pyrrolidine), 2.86 (dd, ^{2}J = -12.9, ^{3}J = 4.1, 1H, CH(OH)C$H_a$$H_b$NH), 2.90 (dd, ^{2}J = -12.9, ^{3}J = 7.5, 1H, CH(OH)C$H_a$$H_b$NH), 3.09-3.13 (m, 1H, H_b-5 pyrrolidine), 3.29 (dd, ^{3}J = 9.3, ^{3}J = 5.2, 1H, *H*-2 pyrrolidine), 4.06-4.12 (m, 1H, C*H*(OH)), 4.20 (dd, ^{2}J = -9.4, ^{3}J = 5.7, 1H, OC$H_a$$H_b$CH(OH)), 4.27 (dd, ^{2}J = -9.4, ^{3}J = 5.0, 1H, OC$H_a$$H_b$CH(OH)), 4.71 (ddd, J_{aa} = 11.0, J_{ae} = 4.3, 1H, C*H*-1 cyclohexyl), 7.03 (d, ^{3}J = 8.9, 1H, *H*-3 salicyl), 7.05-7.09 (m, 1H, *H*-5'' in 2''-F-aniline), 7.09-7.13 (m, 1H, *H*-3'' in 2''-F-aniline), 7.15-7.19 (m, 1H, *H*-4'' in 2''-F-aniline), 7.42

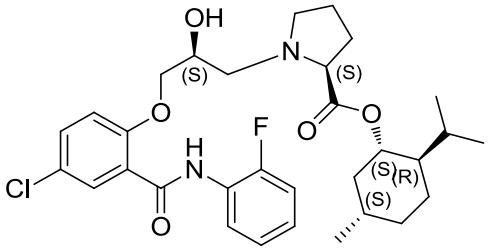
(dd, ^{2}J = 8.8, ^{3}J = 2.8, 1H, *H*-4 salicyl), 8.23 (d, ^{3}J = 2.8, 1H, *H*-6 salicyl), 8.45-8.49 (m, 1H, *H*-6'' in 2''-F-aniline), 10.08 (s, 1H, CON*H*).

$^{13}C\{^{1}H\}$NMR (150 MHz, $CDCl_3$, 23 °C): δ = 16.10 (*C*H_3 isopropyl), 20.94 (*C*H_3 isopropyl), 22.10 (5-*C*H_3 cyclohexyl), 23.25 (*C*-3 cyclohexyl), 24.12 (*C*-4 pyrrolidine), 26.33 (*C*H isopropyl), 30.35 (*C*-3 pyrrolidine), 31.50 (*C*-5 cyclohexyl), 34.27 (*C*-4 cyclohexyl), 40.97 (*C*-6 cyclohexyl), 47.14 (*C*-2 cyclohexyl), 55.51 (*C*-5 pyrrolidine), 58.24 (N*C*H_2CH(OH)), 66.42 (*C*-2 pyrrolidine), 67.63 (d, $^{TS}J_{CF}$ = 1.3, *C*H(OH)), 72.32 (O*C*H_2CH(OH)), 75.13 (*C*-1 cyclohexyl), 114.55 (*C*-3 salicyl), 114.92 ($^{2}J_{CF}$ = 19.2, *C*-3' in 2-F-aniline), 122.78 (*C*-6' in 2'F-aniline), 123.23 (C_q-1 salicyl), 124.59 ($^{3}J_{CF}$ = 7.7, *C*-4' in 2'-F-aniline), 124.80 ($^{4}J_{CF}$ = 3.7, *C*-5' in 3'-F-aniline), 126.79 ($^{2}J_{CF}$ = 10.2, C_q-1' in 2-F-aniline), 127.31 (C_q-5 salicyl), 132.32 (*C*-6 salicyl), 133.18 (*C*-4 salicyl), 153.08 (d, $^{1}J_{CF}$ = -243.4, *C*-2' in 2-F-aniline), 155.40 (C_q-2 salicyl), 162.21 (*C*ONH), 175.07 (*C*OOR).

$[\alpha]_D^{20}$= -4.0°, c=1 in MeOH.

Melting point: 106-116°C.

(*S*)-(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl-1-((*S*)-3-(4-chloro-2-((2-fluoro-5-(trifluoromethyl)phenyl)carbamoyl)phenoxy)-2-hydroxypropyl)pyrrolidine-2-carboxylate (401)



401 was prepared following **general procedure E**, yielding 0.180 g (100%) of the desired product.

^{1}H NMR (600 MHz, $CDCl_3$, 23 °C): δ = 0.73 (d, ^{3}J = 7.0, 3H, CH_3 isopropyl), 0.80 (m, 1H, H_a-4 cyclohexyl), 0.86 (d, ^{3}J = 6.6, 3H, 5-CH_3 cyclohexyl), 0.87 (d, ^{3}J = 7.0, 3H, CH_3 isopropyl), 0.90-0.96 (m, 1H, H_a-6 cyclohexyl), 1.00-1.06 (m, 1H, H_a-4 pyrrolidine), 1.32-1.39 (m [tt], 1H, *H*-2 cyclohexyl), 1.40-1.49 (m, 1H, *H*-5 cyclohexyl), 1.63-1.69 (m, 2H, H_a-4 cyclohexyl, H_a-3 cyclohexyl), 1.79-1.87 (m, 2H, C*H* isopropyl, H_b-3 cyclohexyl), 1.87-1.97 (m, 3H, H_b-6 cyclohexyl, H_a-3 pyrrolidine, H_b-4 pyrrolidine), 2.13-2.21 (m, 1H, H_b-3 pyrrolidine), 2.38-2.43 (m, 1H, H_a-5 pyrrolidine), 2.74-2.82 (m, 2H, CH(OH)CH_2NH), 3.28-3.34 (m, 2H, *H*-2 pyrrolidine, H_b-5 pyrrolidine), 4.13 (dd, ^{2}J = -11.5, ^{3}J = 7.3, 1H, OC$H_a$$H_b$CH(OH)), 4.21-4.26 (m, 2H, OC$H_a$$H_b$CH(OH),

C*H*(OH)), 4.69 (dd, J_{aa} = 10.9, J_{ae} = 4.4, 1H, C*H*-1 cyclohexyl), 7.04 (d, ^{3}J = 8.9, 1H, *H*-3 salicyl), 7.06-7.13 (m, 2H, *H*-3,4'' in 2''-F-aniline), 7.15-7.19 (m, 1H, *H*-5'' in 2''-F-aniline), 7.42 (dd, ^{2}J = 8.8, ^{3}J = 2.8, 1H, *H*-4 salicyl), 8.23 (d, ^{3}J = 2.8, 1H, *H*-6 salicyl), 8.46-8.50 (m, 1H, *H*-6'' in 2''-F-aniline), 10.09 (s, 1H, CON*H*).

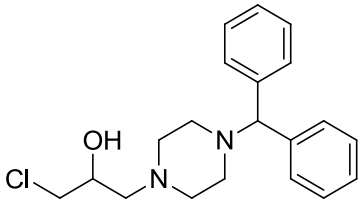
$^{13}C\{^{1}H\}$NMR (150 MHz, $CDCl_3$, 23 °C): δ = 16.09 (*C*H_3 isopropyl), 20.94 (*C*H_3 isopropyl), 22.08 (5-*C*H_3 cyclohexyl), 23.21 (*C*-3 cyclohexyl), 23.99 (*C*-4 pyrrolidine), 26.28 (*C*H isopropyl), 29.74 (*C*-3 pyrrolidine), 31.50 (*C*-5 cyclohexyl), 34.25 (*C*-4 cyclohexyl), 41.03 (*C*-6 cyclohexyl), 47.06 (*C*-2 cyclohexyl), 53.43 (*C*-5 pyrrolidine), 58.21 (N*C*H_2CH(OH)), 66.14 (*C*-2 pyrrolidine), 67.14 (d, $^{TS}J_{CF}$ = 1.5, *C*H(OH)), 72.91 (O*C*H_2CH(OH)), 75.06 (*C*-1 cyclohexyl), 114.74 (*C*-3 salicyl), 114.90 ($^{2}J_{CF}$ = 19.3, *C*-3' in 2-F-aniline), 122.76 (*C*-6' in 2'F-aniline), 123.30 (C_q-1 salicyl), 124.55 ($^{3}J_{CF}$ = 7.7, *C*-4' in 2'-F-aniline), 124.77 ($^{4}J_{CF}$ = 3.5, *C*-5' in 3'-F-aniline), 126.84 ($^{2}J_{CF}$ = 10.1, C_q-1' in 2-F-aniline), 127.36 (C_q-5 salicyl), 132.28 (*C*-6 salicyl), 133.18 (*C*-4 salicyl), 153.10 (d, $^{1}J_{CF}$ = -243.7, *C*-2' in 2-F-aniline), 155.49 (C_q-2 salicyl), 162.19 (*C*ONH), 174.21 (*C*OOR).

$[\alpha]_D^{20}$= +12.5°, c=1 in MeOH.

Melting point: 70-75°C.

4.3.4 Additions

1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-2-ol (94)



An excess of (±)-epichlorohydrin (3.1 mL, 10 eq) was added to 1-benzhydrylpiperazine (1.021 g), and the mixture was stirred at 85°C.

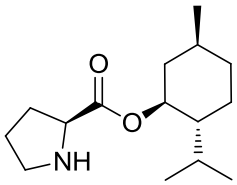
After complete consumption of anilide was observed (3 h) unreacted epichlorohydrin was removed. The residue was extracted three times with ethyl acetate. The extracts were dried over Na_2SO_4, and concentrated under reduced pressure to give 0.552 g colorless oil (40% yield).

^{1}H NMR (400 MHz, $CDCl_3$, 27 °C): δ = 2.33-2.52 (m[dyn], br, 6H, H_{ax} H_{eq}-3,5 in piperazine, H_{ax}-2,6 in CH_2 piperazine), 2.61-2.73 (m[t], br, 2H, H_{eq}-2,6 in CH_2 piperazine), 3.51-3.59 (m, 2H,

CH(OH)CH_2Cl), 3.69 (d, ^3J = 5.3, 2H, NCH_2CH(OH)), 3.86-3.94 (m, 1H, C*H*(OH)), 4.23 (br s, 1H, NC*H*(C_6H_5)$_2$), 7.16-7.21 (m, 2H, 2x C*H*-4 phenyl), 7.24-7.30 (m, 4H, 2x *H*-3'',5'' phenyl), 7.39-7.43 (m, 4H, 2x *H*-2'',6'' phenyl).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 23 °C): δ = 45.90 (N*C*H_2CH(OH)), 47.26 (Cl*C*H_2CH(OH)), 52.02 (*C*H_2-dyn, piperazine), 53.65 (*C*H_2-dyn, piperazine), 66.58 (*C*H(OH)), 76.27 (*N*-*C*H(C_6H_5)$_2$), 127.08 (*C*-4'' phenyl), 127.99 (*C*-2'',6'' phenyl), 128.61 (*C*-3'',5'' phenyl), 142.70 (C_q-1'' phenyl), 142.72 (C_q-1'' phenyl).

(*S*)-(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl pyrrolidine-2-carboxylate (101)



A reaction mixture of L-prolin (5.76 g, 50 mmol), (1S,2R,5S)-(+)-menthol (12.03 g, 77 mmol), *p*-toluenesulfonic acid monohydrate (12.00 g, 63.1 mmol) and 100 mL toluene were refluxed in a Dean and Stark distillation apparatus for 16 hr. The nascent water (~2 mL) was removed azeotropically. The insoluble materials were removed by filtration, and the solvent was evaporated to about 30 mL in vacuo. To this was added about 30 mL of ether, and then the acidic material was extracted with 8% sodium hydrogen carbonate. The organic layer was washed once with water and dried with anhydrous sodium sulfate. The dried solution was concentrated in vacuo, then 20 mL hydrogen chloride (4M) in dioxane were added. Crystallization was started by addition of hexane and cooling to 0°C. The crystals were filtered and washed with ether and petroleum ether. Two crops gave 7.385g (51%) of the hydrochloride as colorless crystals. 1g of the hydrochloride was neutralized with 2M $NaHCO_3$ to yield 0.856g (98%) of the free base as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 0.74 (d, ^3J = 7.0, 3H, CH_3 isopropyl), 0.80-0.87 (m, 1H, H_a-4 cyclohexyl), 0.89 (d, ^3J = 7.0, 3H, CH_3 isopropyl), 0.90 (d, ^3J = 6.4, 3H, 5-CH_3 cyclohexyl), 0.93-1.10 (m, 2H, H_a-6 cyclohexyl, H_a-3 cyclohexyl), 1.40 (m [tt], J = 11.0, J = 3.0, 1H, *H*-2 cyclohexyl), 1.45-1.55 (m, 1H, *H*-5 cyclohexyl), 1.63-1.91 (m, 6H, H_a-3 cyclohexyl, H_b-4 cyclohexyl, $H_{a,b}$-4 pyrrolidine, H_a-3 pyrrolidine, C*H* isopropyl, 1.99 (m, 1H, H_b-6 cyclohexyl), 2.06 (br s, 1H, N*H*), 2.09-2.18 (m, 1H, H_b-3 pyrrolidine), 2.85-2.92 (m, 1H, H_a-5 pyrrolidine), 3.05-3.12 (m, 1H, H_b-5 pyrrolidine), 3.70 (m, 1H, *H*-2 pyrrolidine), 4.70 (dd, J_{aa} = 10.8, J_{ae} = 4.4, 1H, C*H*-1 cyclohexyl).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$, 23 °C): δ = 16.19 (*C*H_3 isopropyl), 20.94 (*C*H_3 isopropyl), 22.13 (5-*C*H_3 cyclohexyl), 23.38 (*C*-3 cyclohexyl), 25.66 (*C*-4 pyrrolidine), 26.36 (*C*H isopropyl), 30.64 (*C*-3 pyrrolidine), 31.53 (*C*-5 cyclohexyl), 34.37 (*C*-4 cyclohexyl), 40.97 (*C*-6 cyclohexyl), 47.14 (*C*-5 pyrrolidine), 47.16 (*C*-2 cyclohexyl), 60.30 (*C*-2 pyrrolidine), 74.98 (*C*-1 cyclohexyl), 175.19 (*C*OOR).

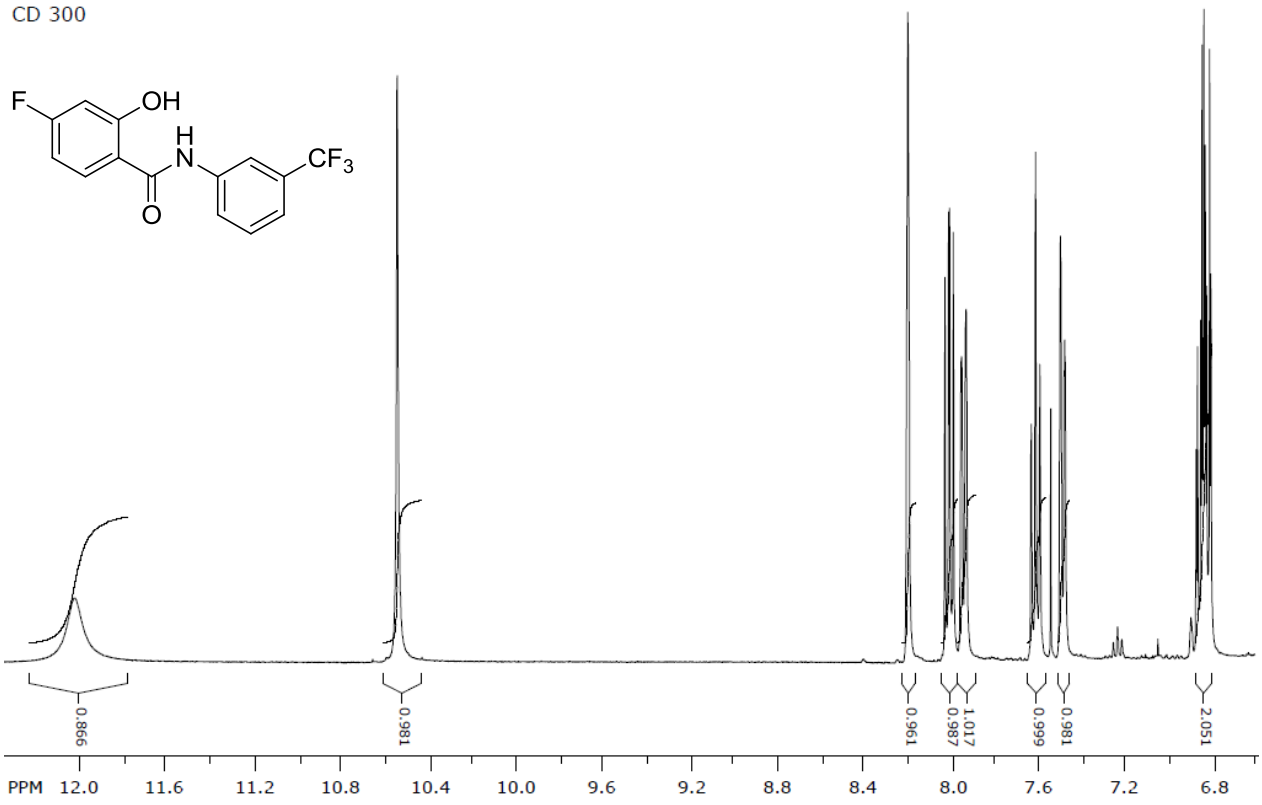
LCMS: $[M+H]^+$: calculated.: 254.21 found: 254.29.

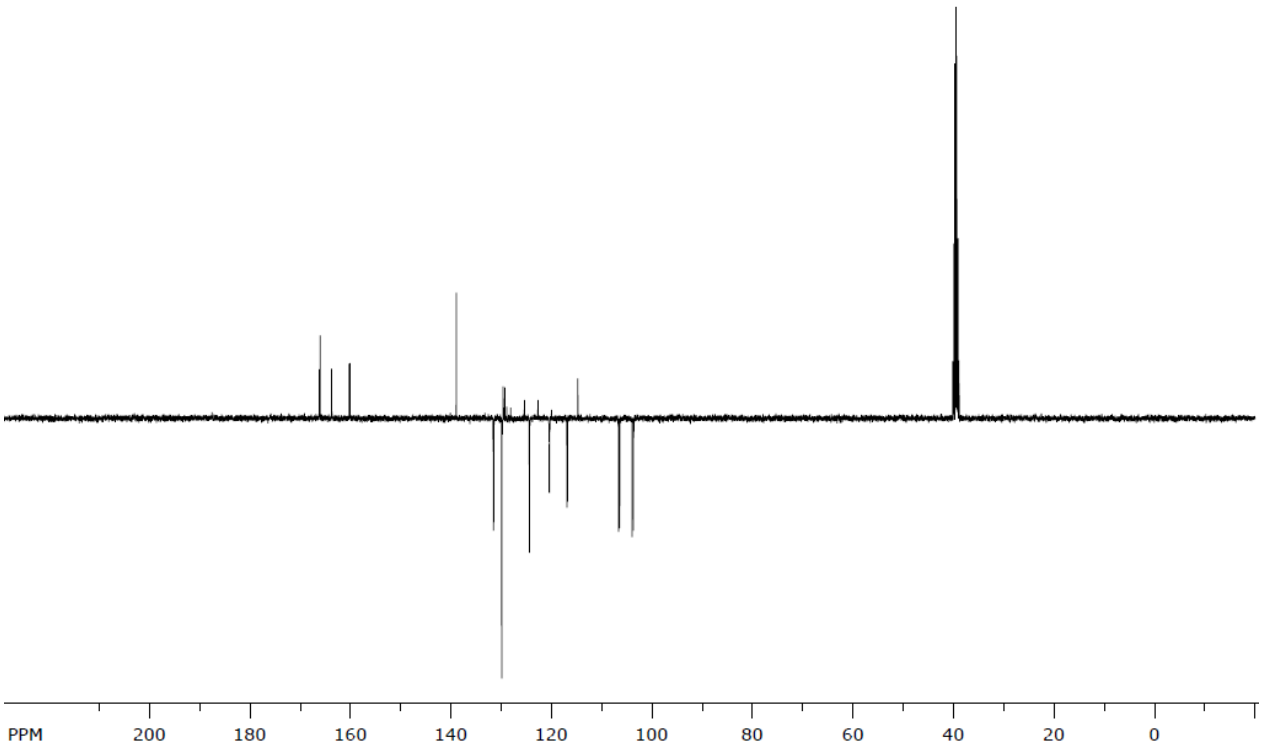
$[\alpha]_D^{20}$= +36.2°, c=1 in MeOH.

4.4 Spectra

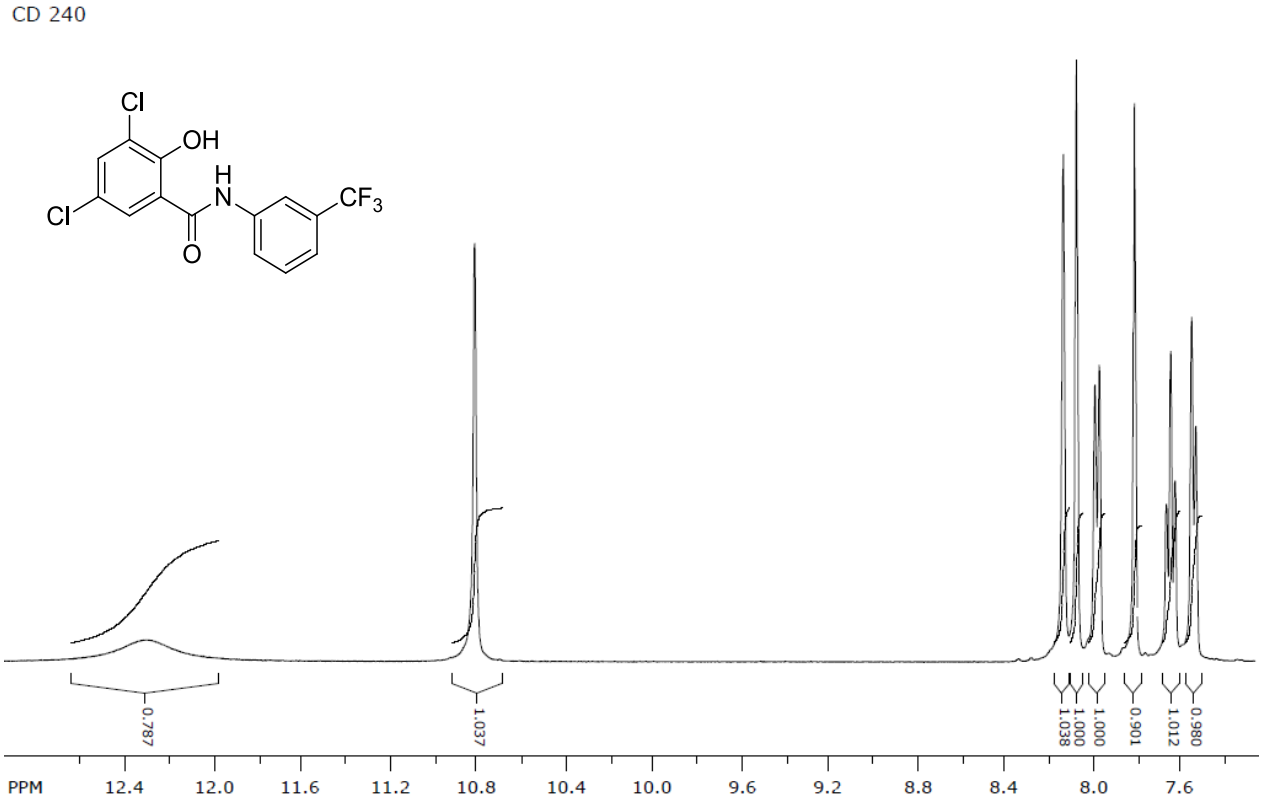
4.4.1 Anilides

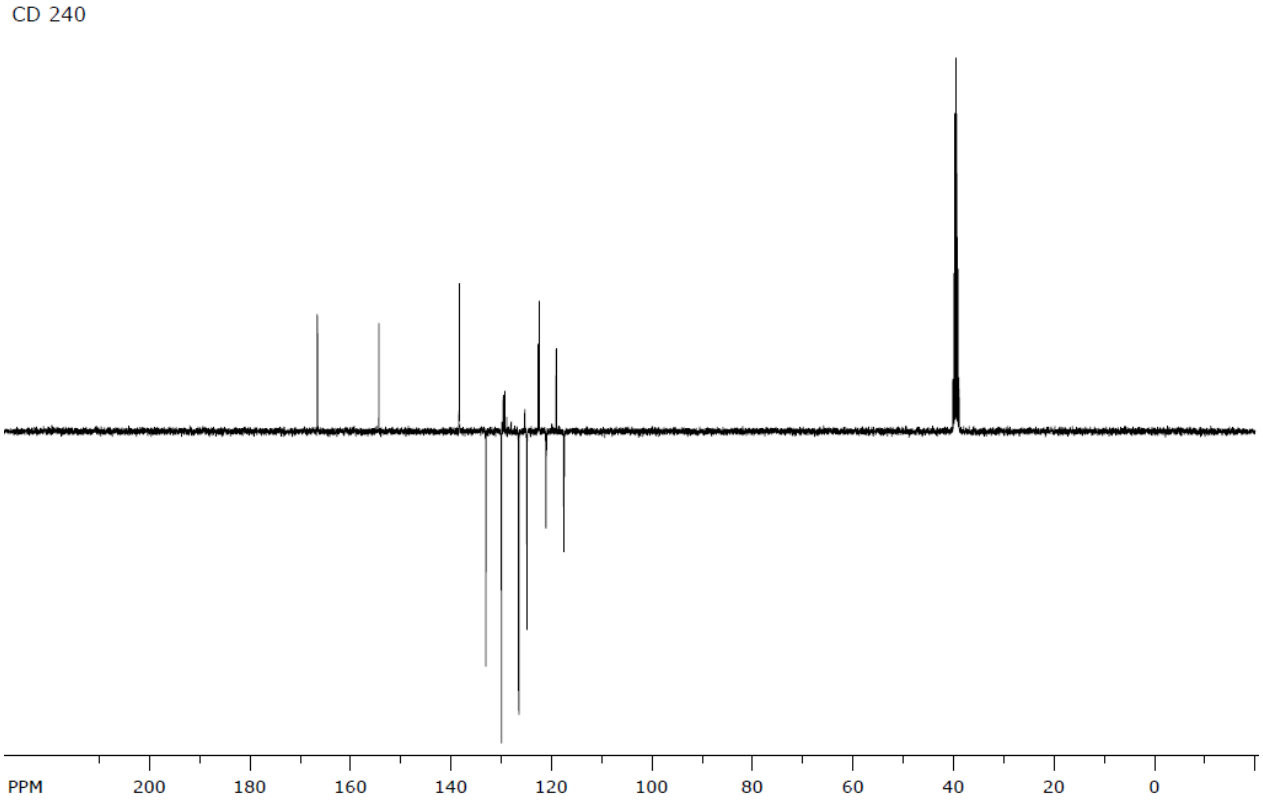
4-fluoro-2-hydroxy-*N*-(3-(trifluoromethyl)phenyl)benzamide (77)





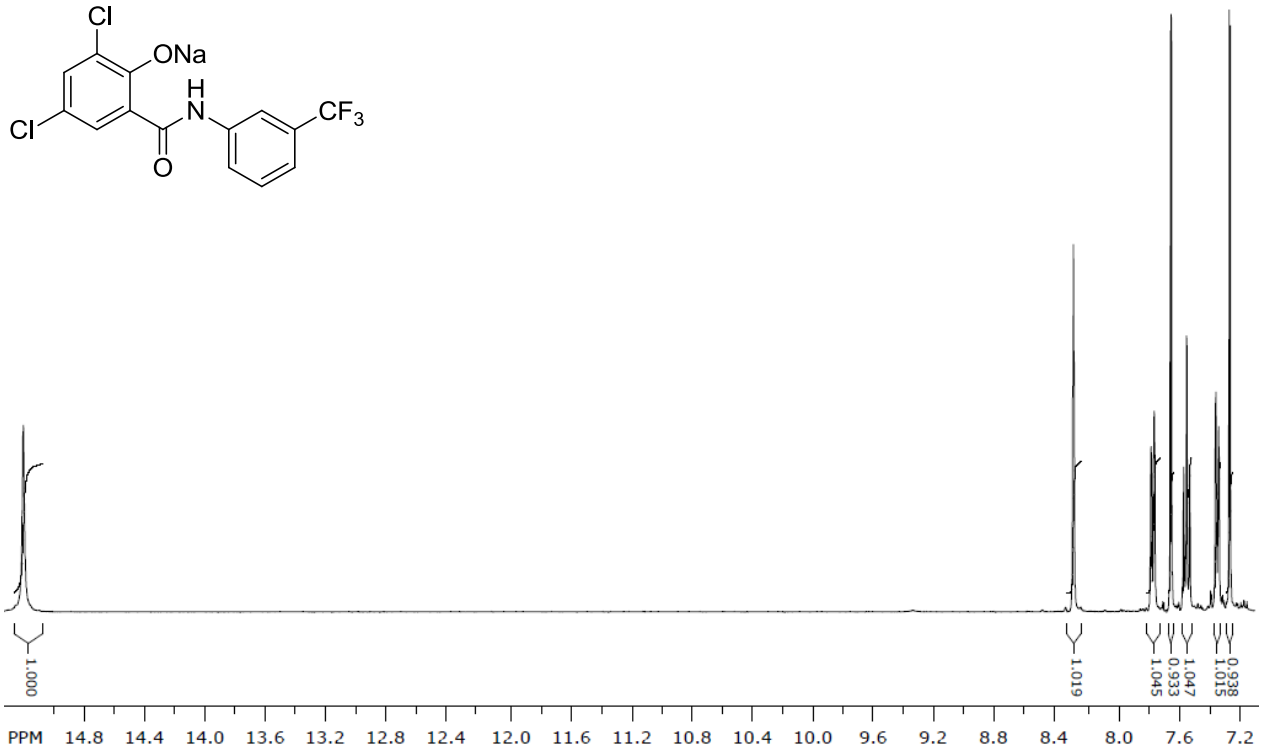
3,5-dichloro-2-hydroxy-*N*-(3-(trifluoromethyl)phenyl)benzamide (79)



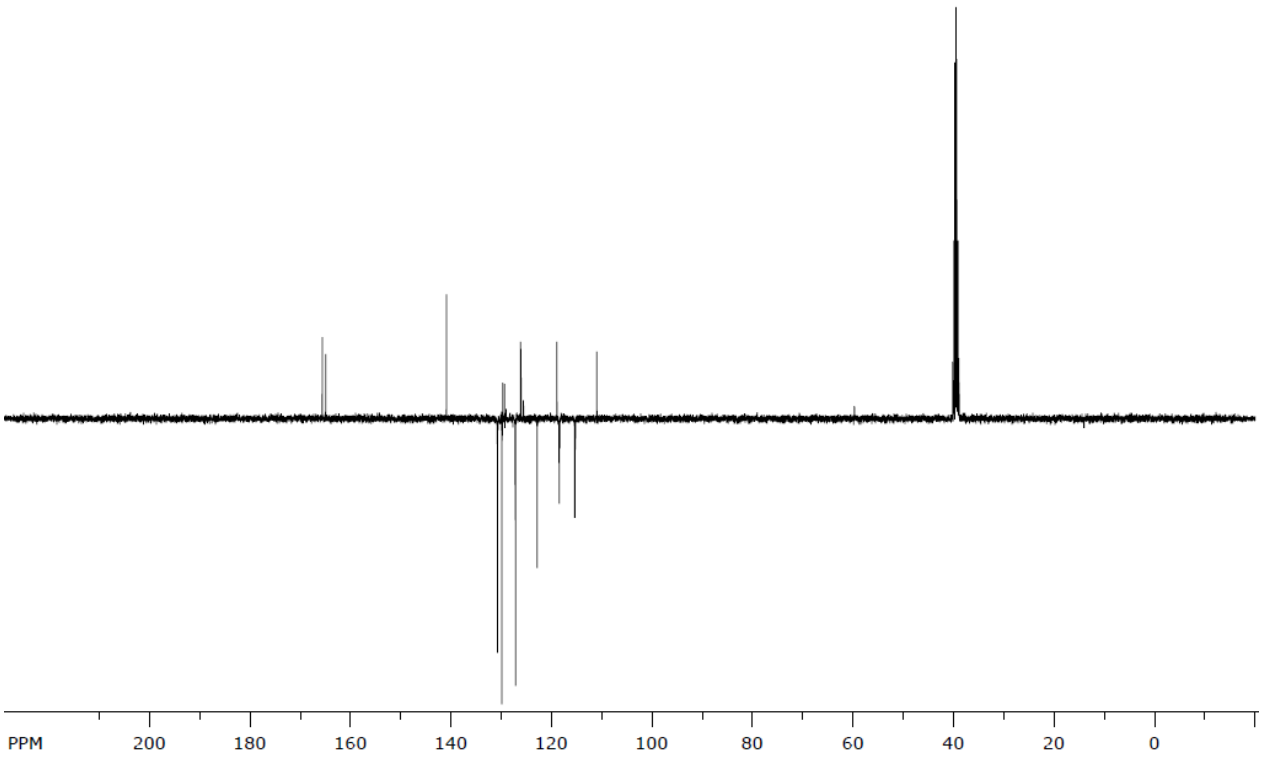


sodium 2,4-dichloro-6-((3-(trifluoromethyl)phenyl)carbamoyl)phenolate (Na salt of 79)

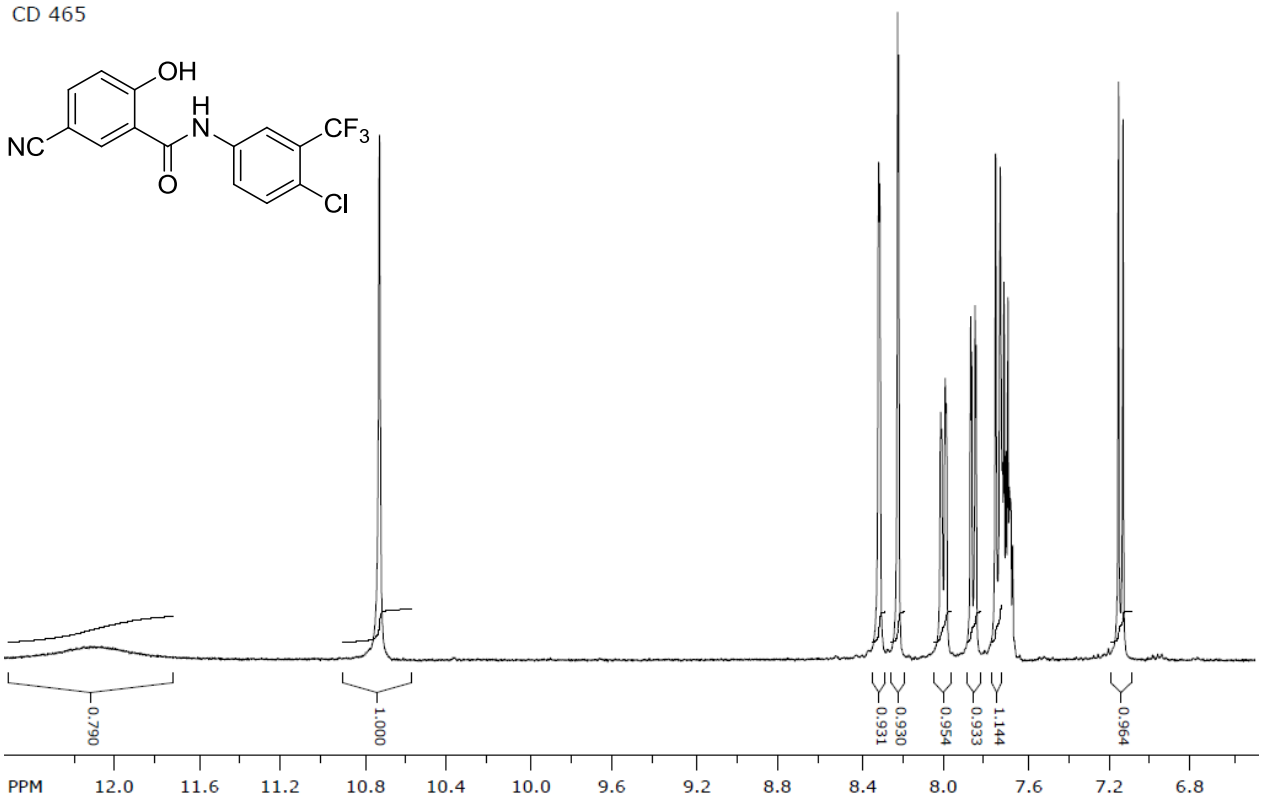
CD 214

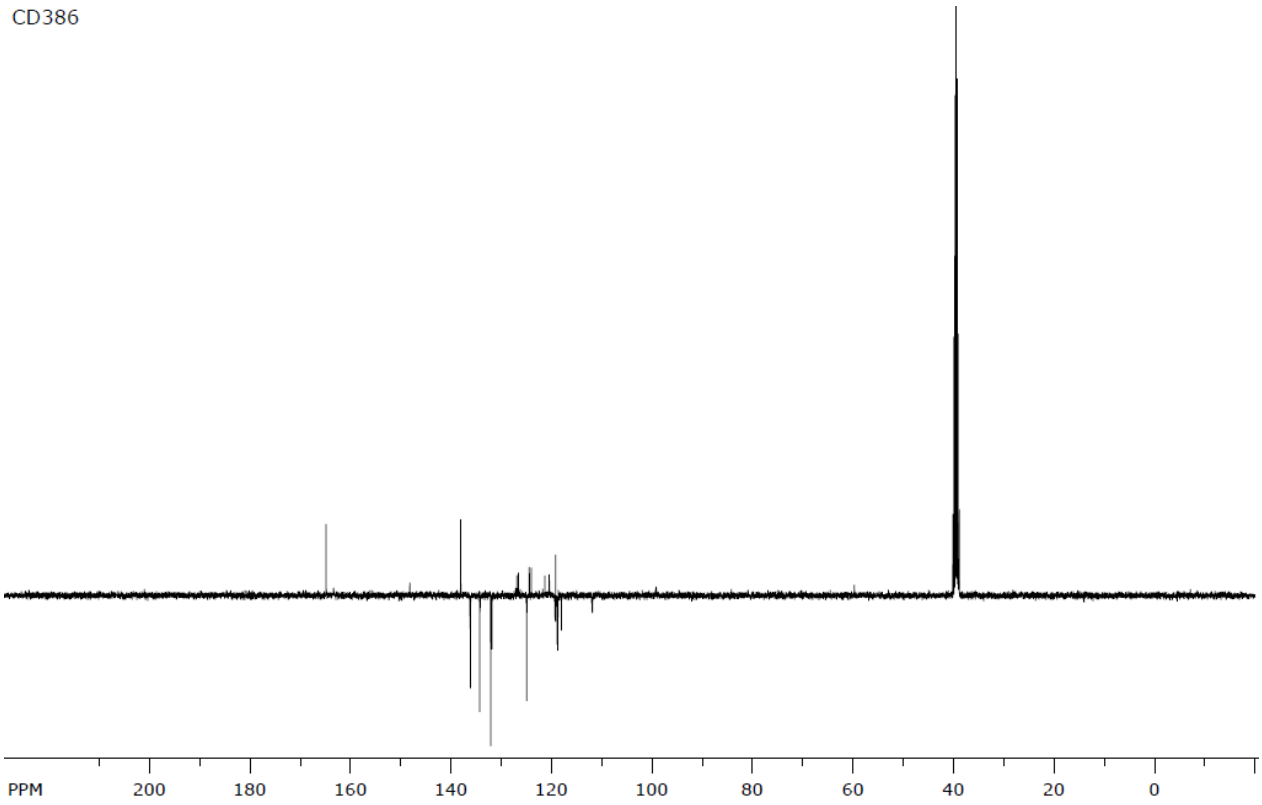


CD 214

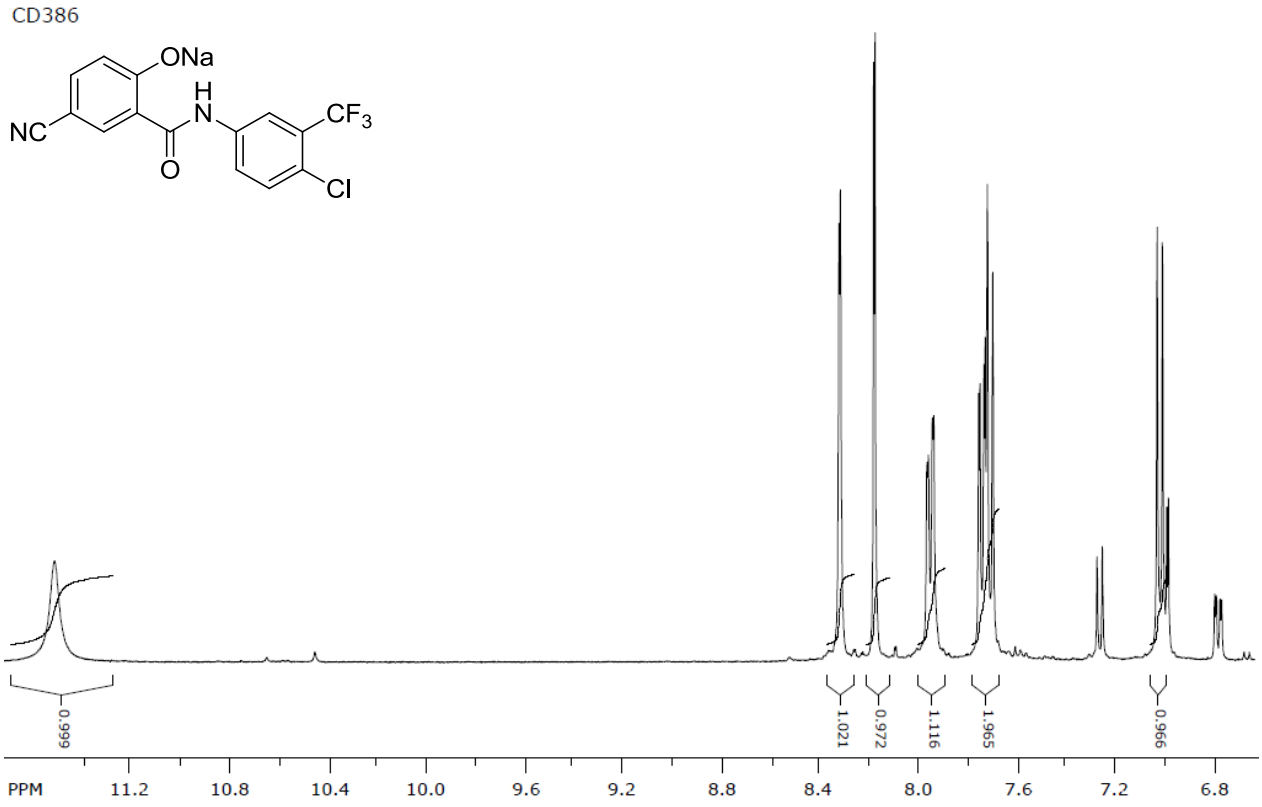


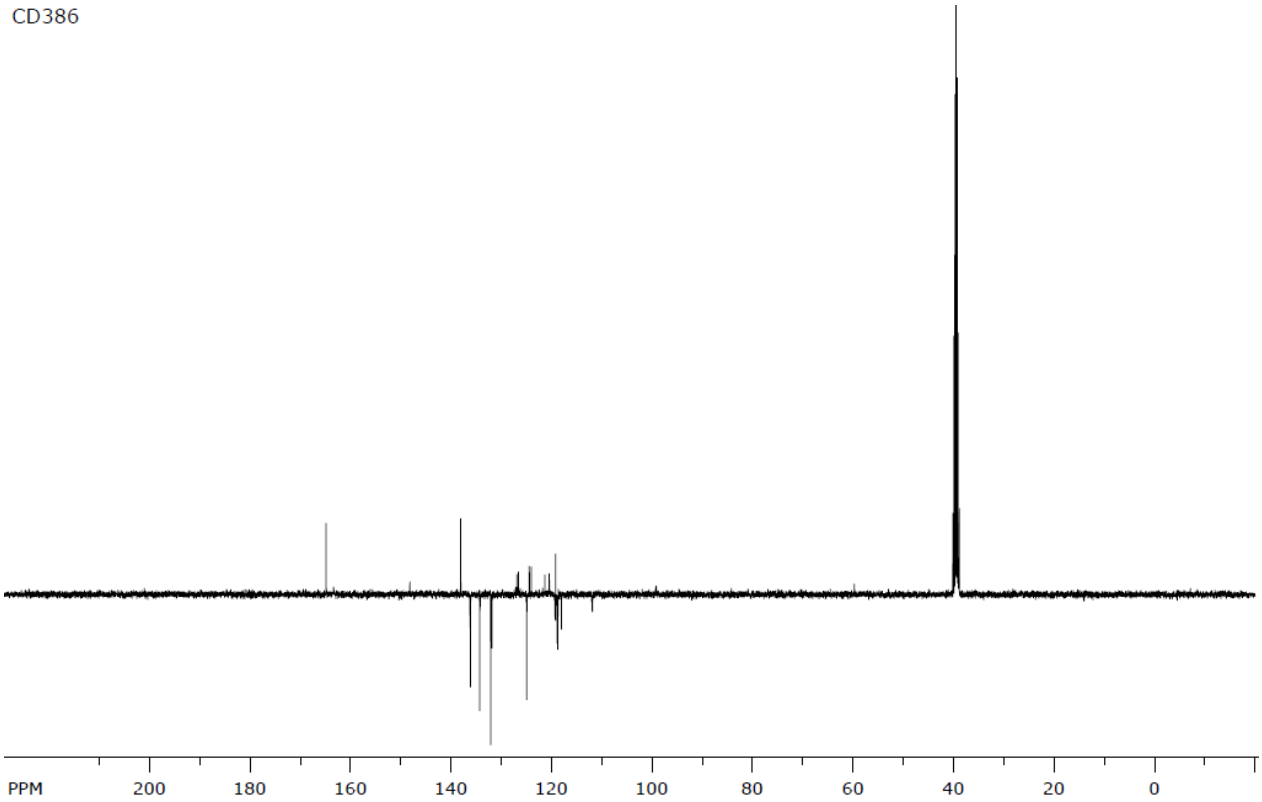
_N_-(4-chloro-3-(trifluoromethyl)phenyl)-5-cyano-2-hydroxybenzamide (80)



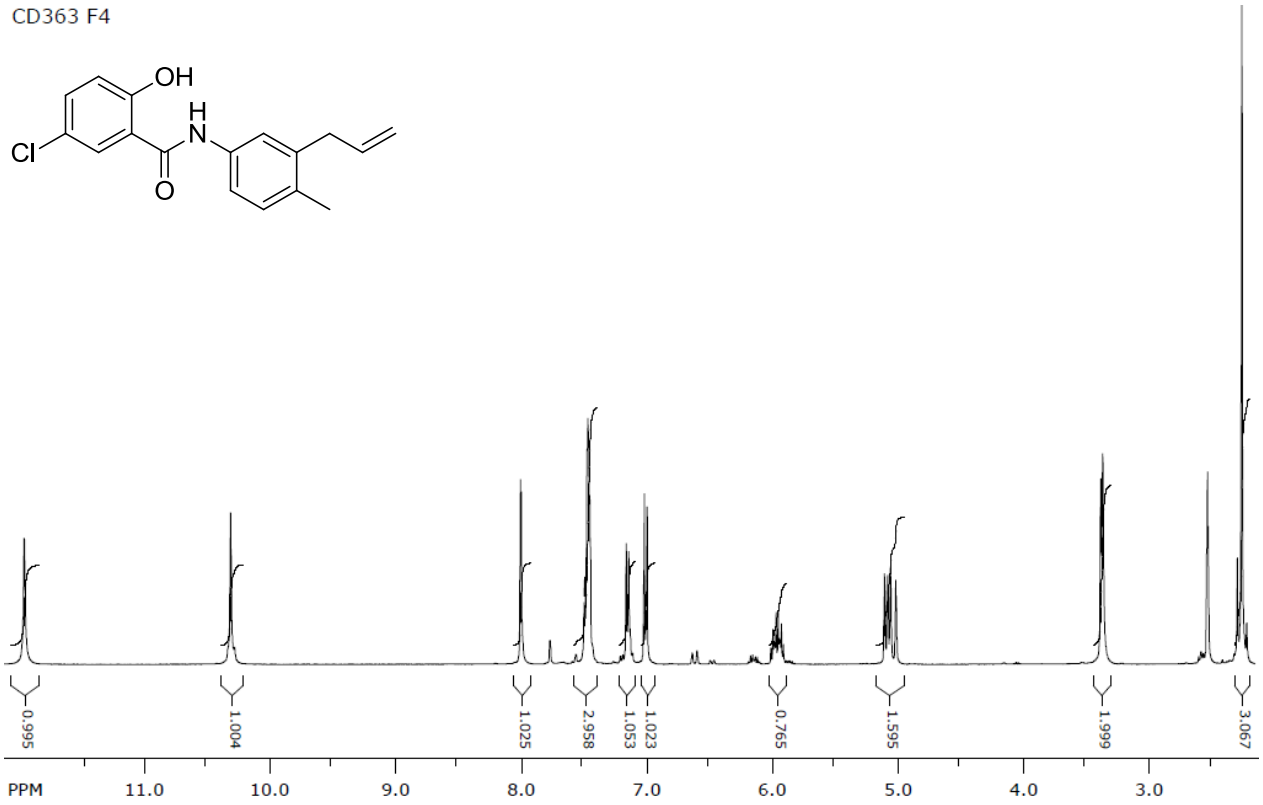


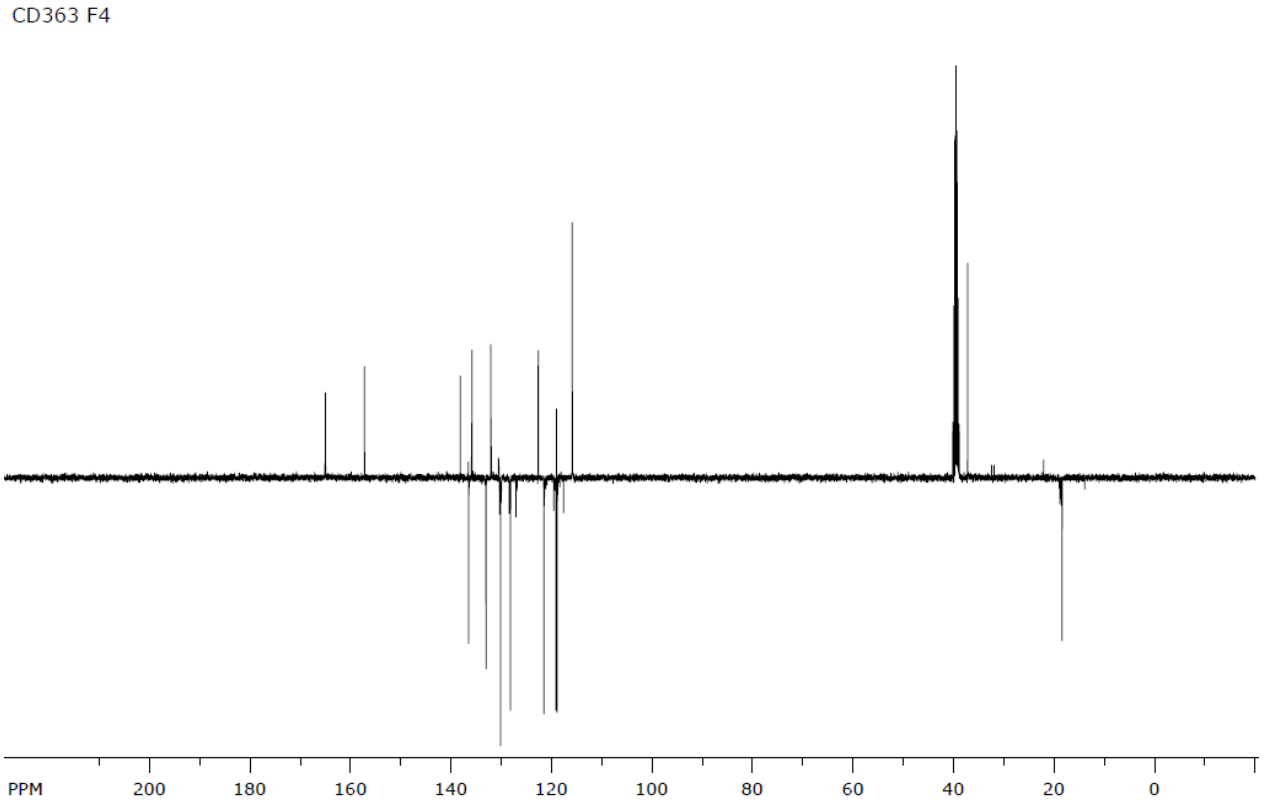
sodium 2-((4-chloro-3-(trifluoromethyl)phenyl)carbamoyl)-4-cyanophenolate (Na salt of 80)



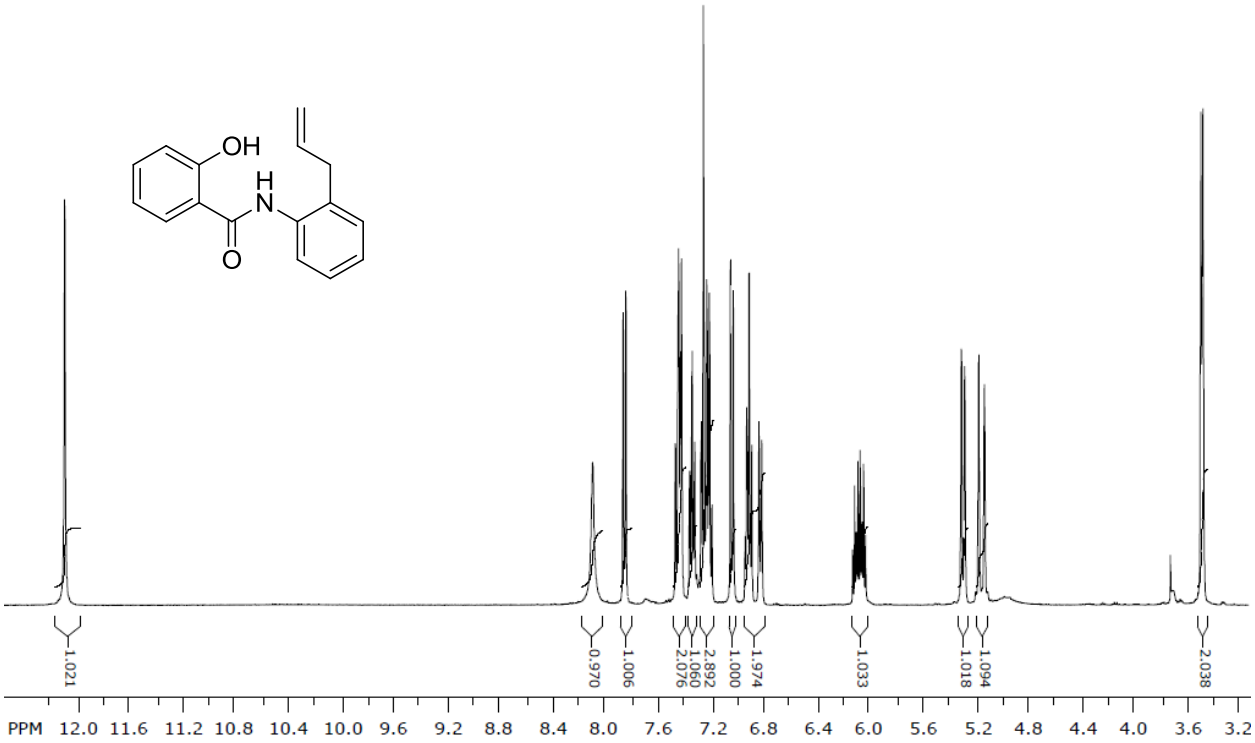


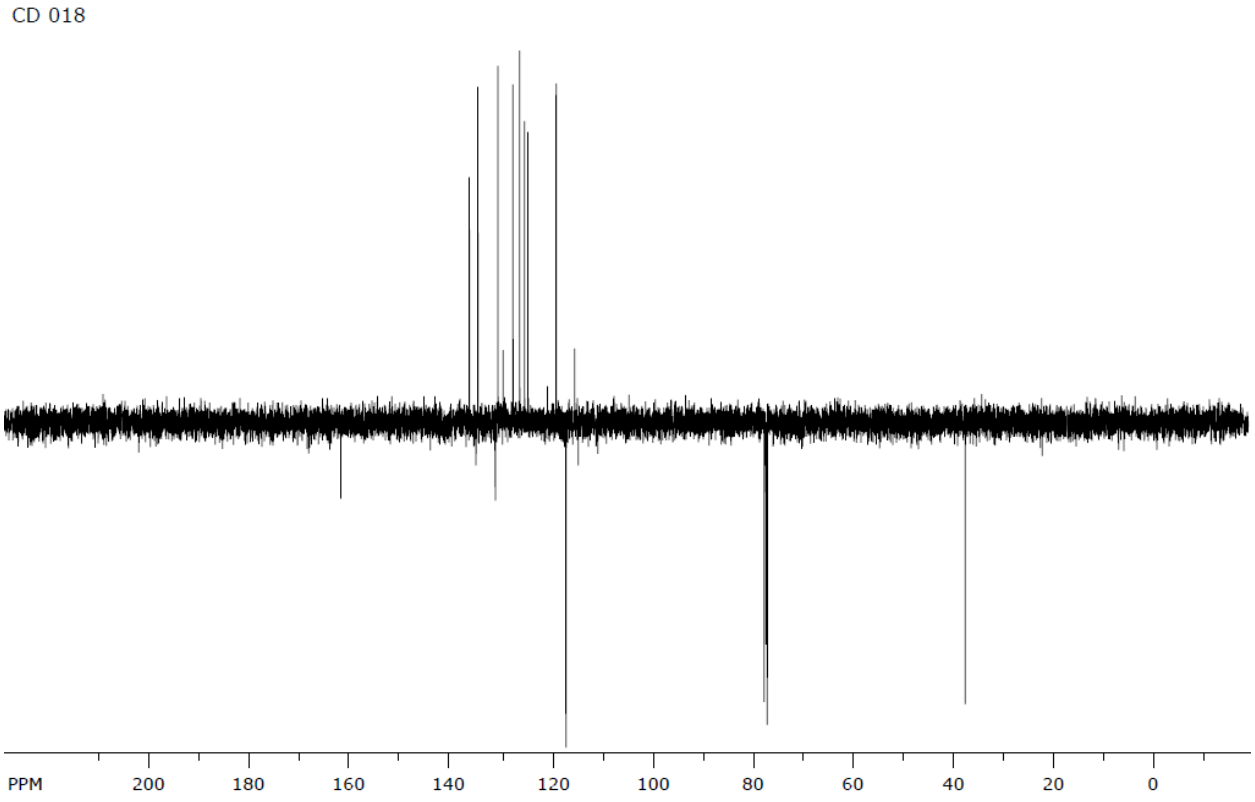
N-(3-allyl-4-methylphenyl)-5-chloro-2-hydroxybenzamide (296)



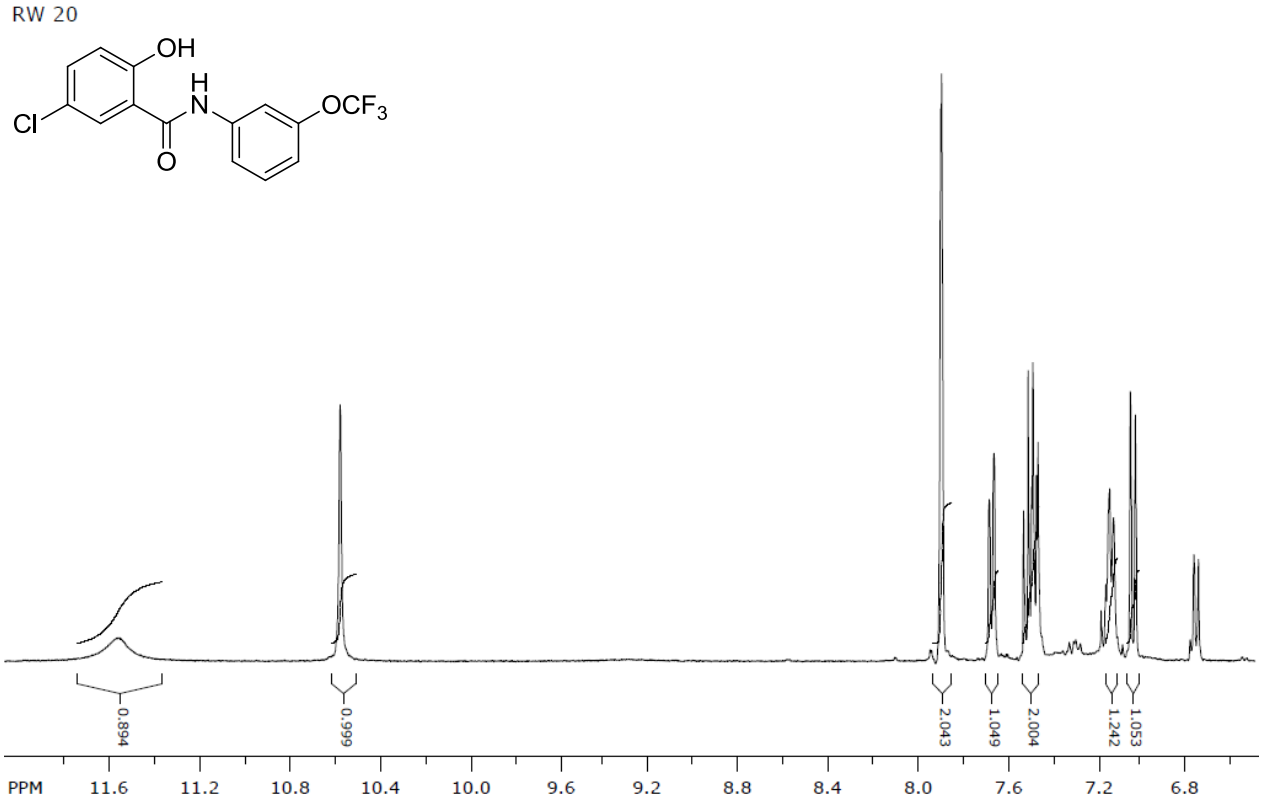


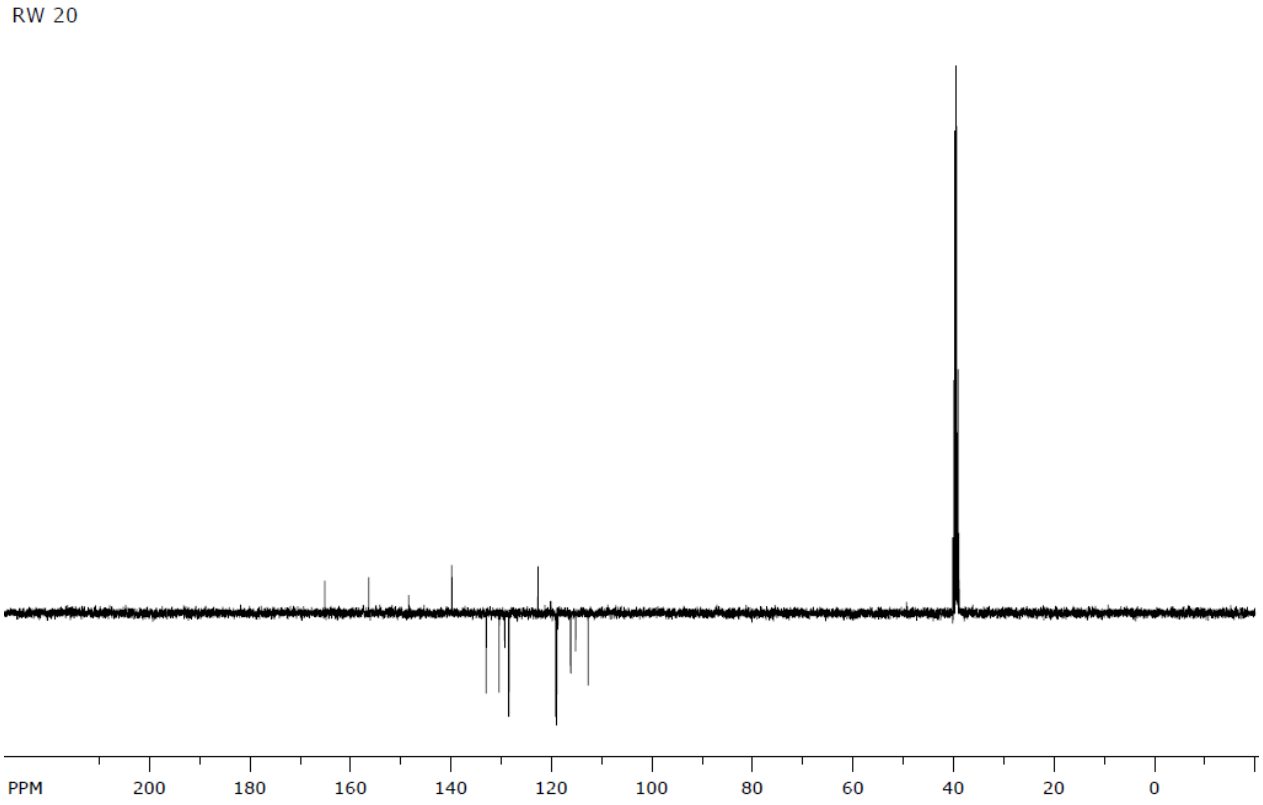
_N_-(2-allylphenyl)-2-hydroxybenzamide (300)



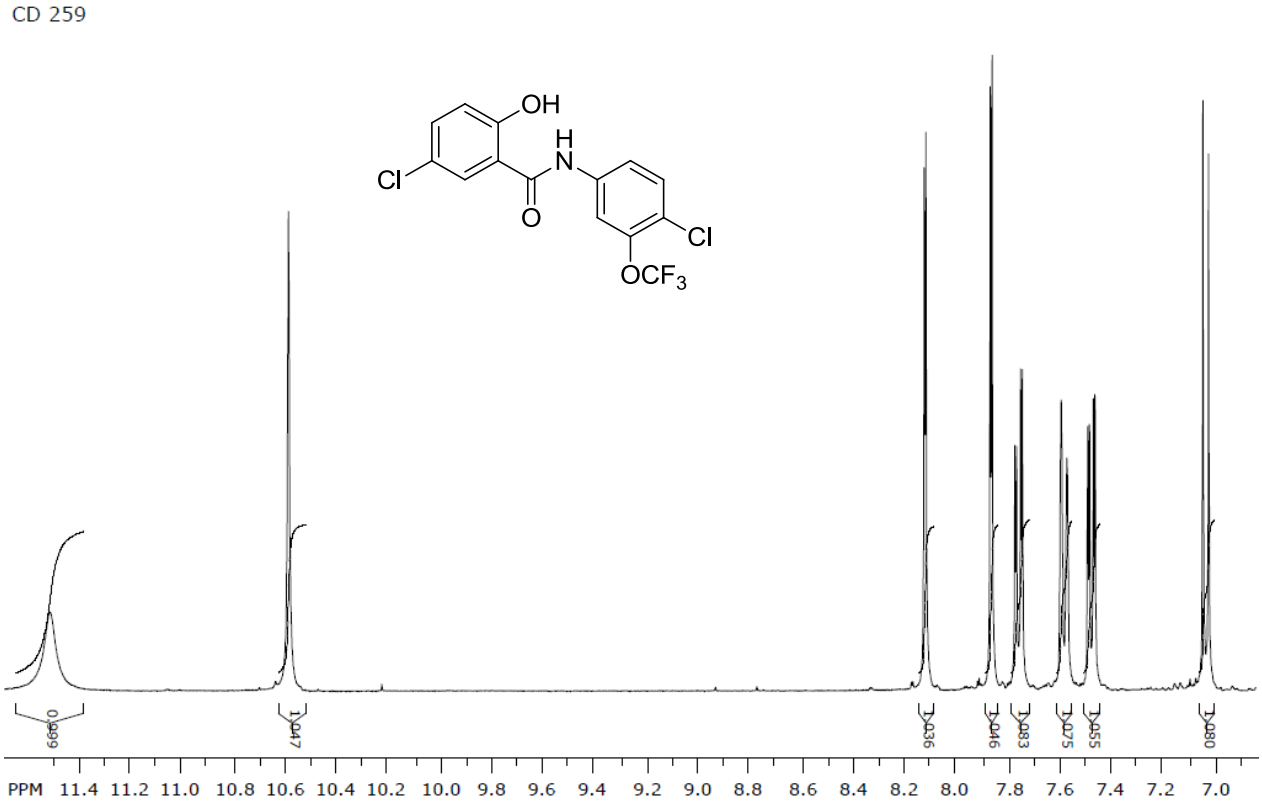


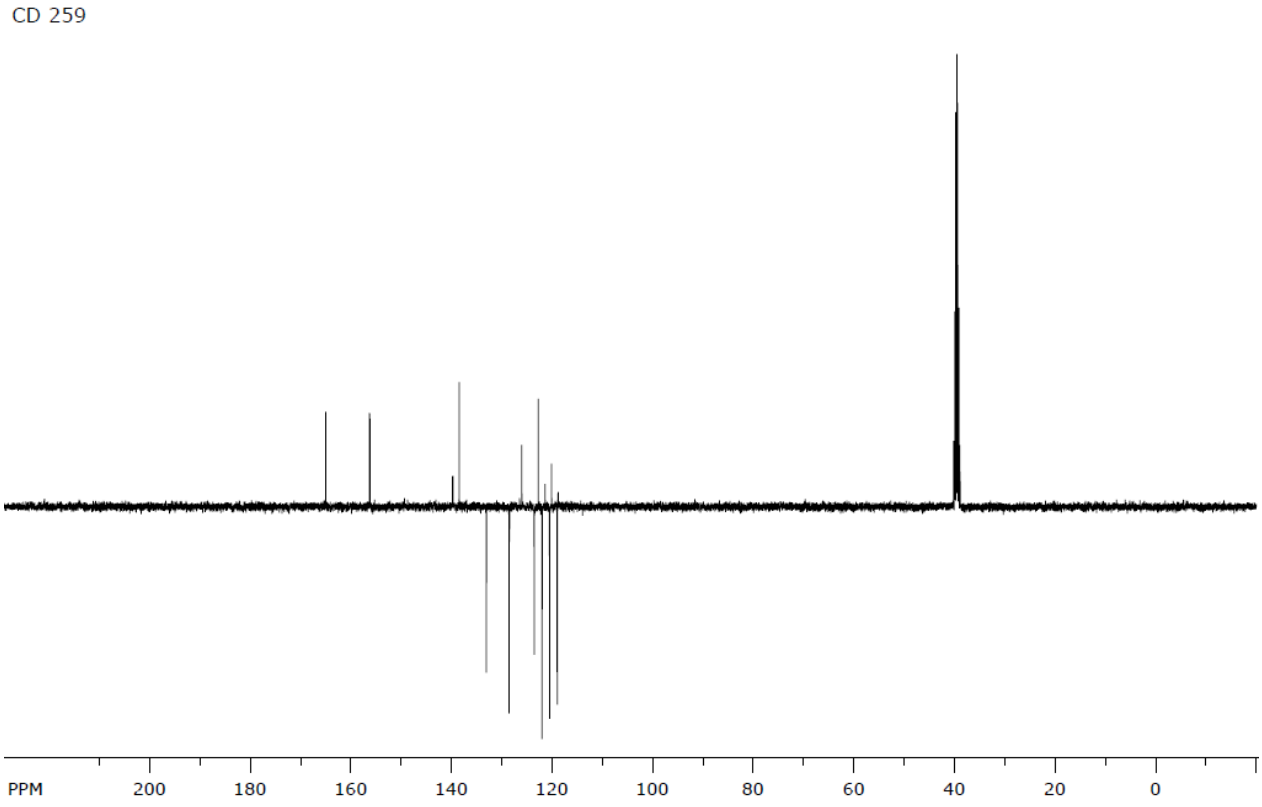
5-chloro-2-hydroxy-*N*-(3-(trifluoromethoxy)phenyl)benzamide (307)



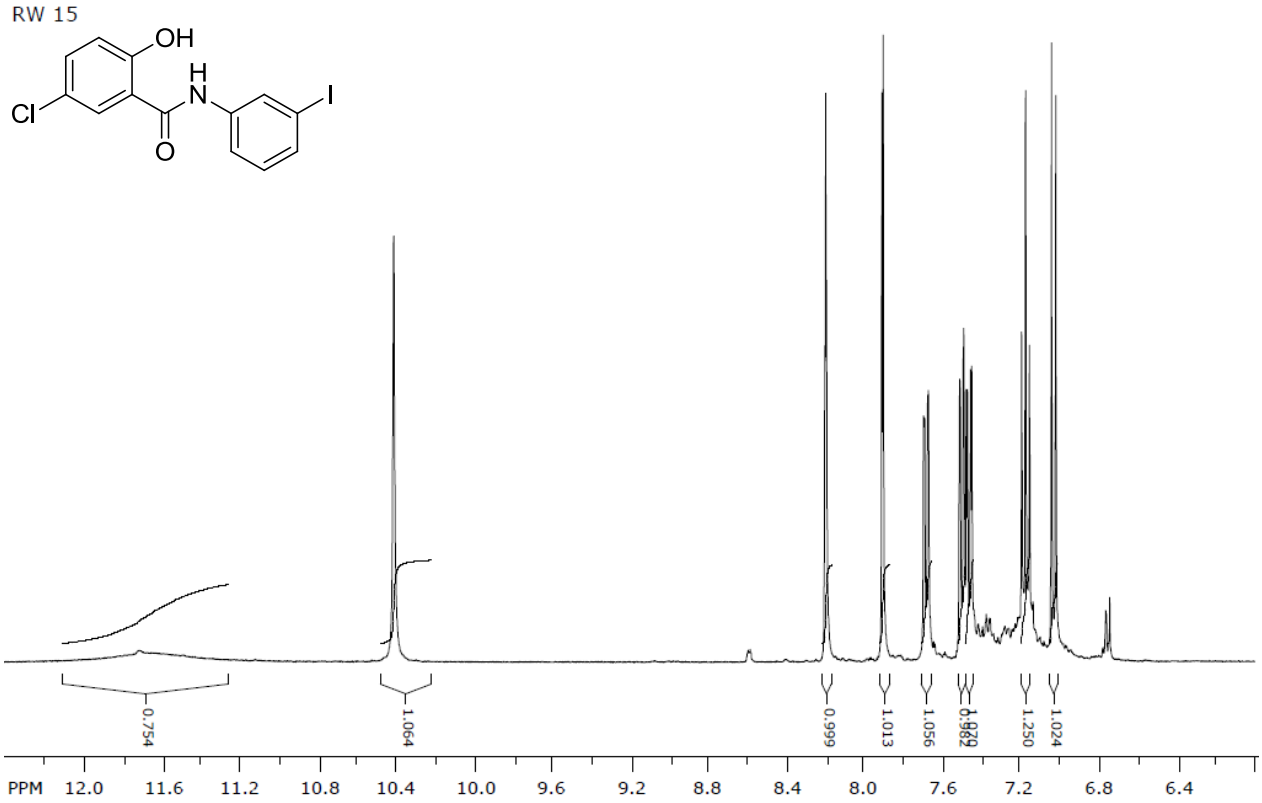


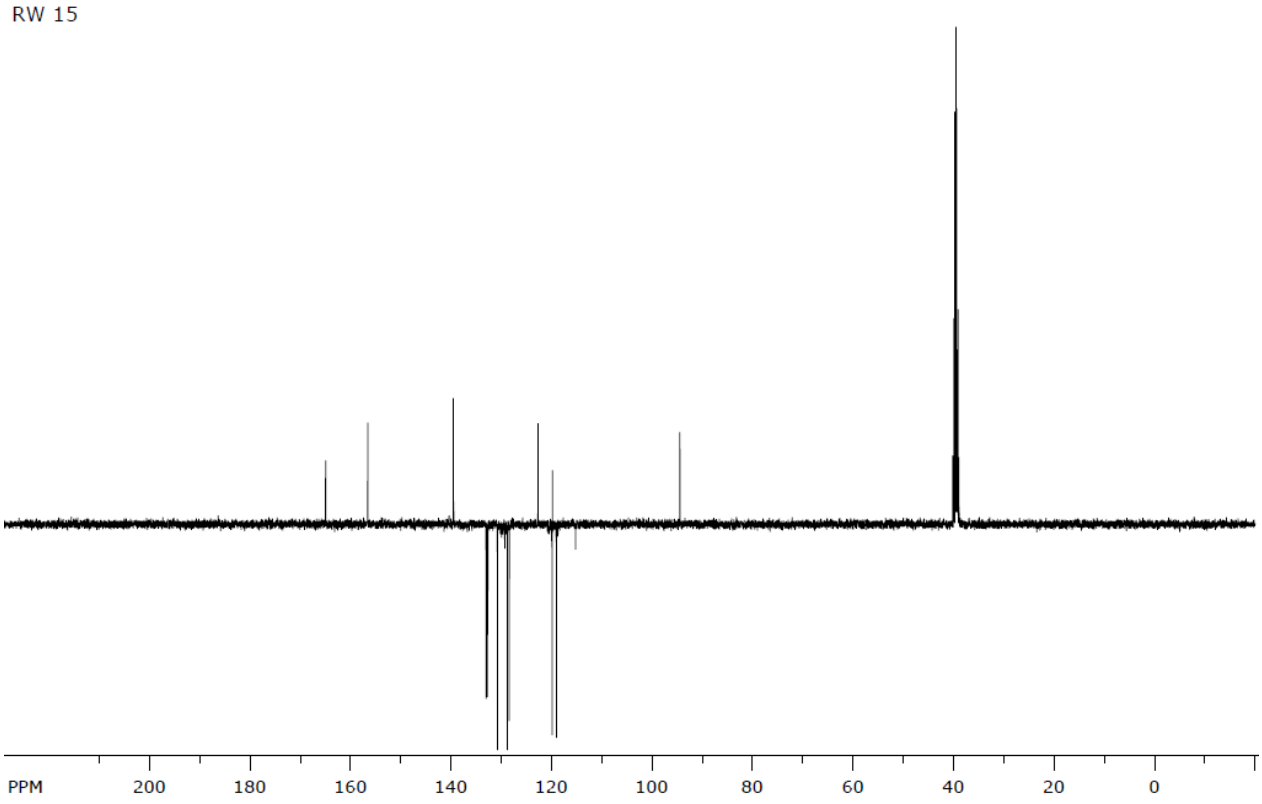
5-chloro-*N*-(4-chloro-3-(trifluoromethoxy)phenyl)-2-hydroxybenzamide (308)



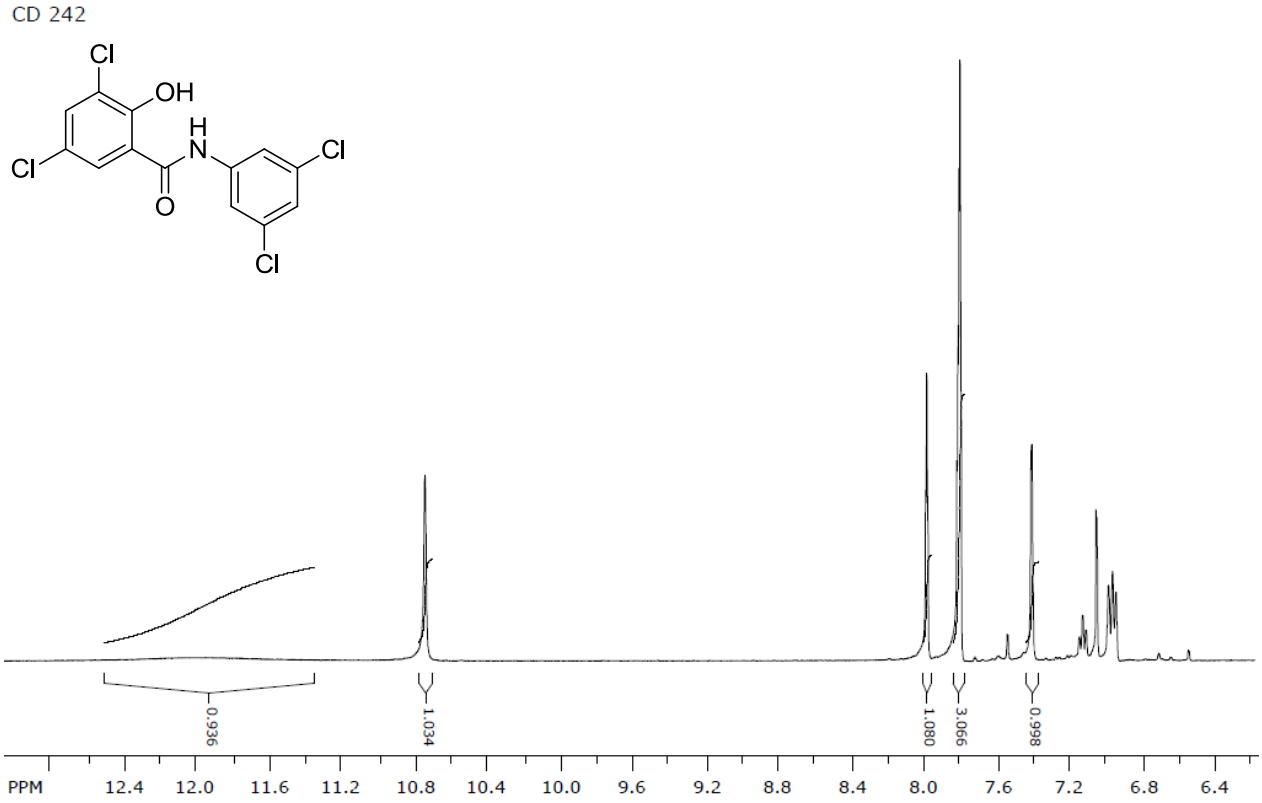


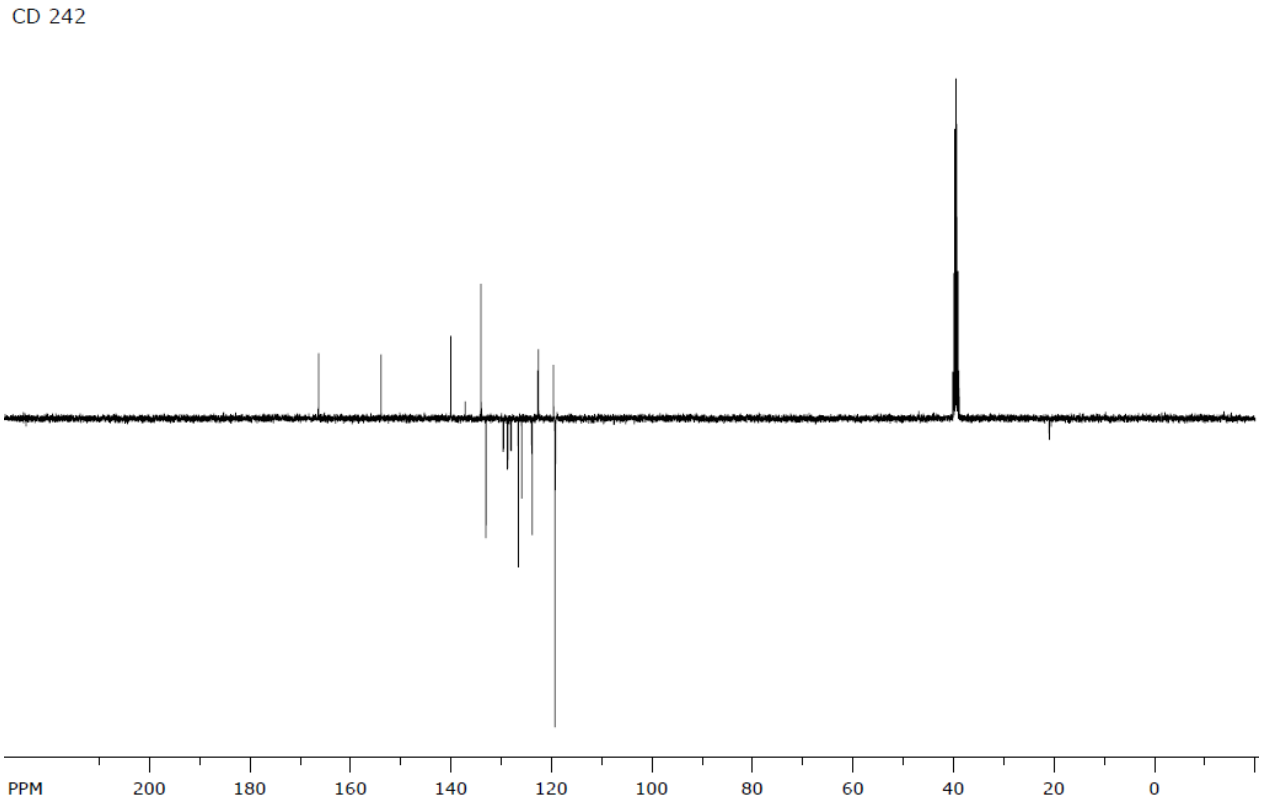
5-chloro-2-hydroxy-*N*-(3-iodophenyl)benzamide (310)



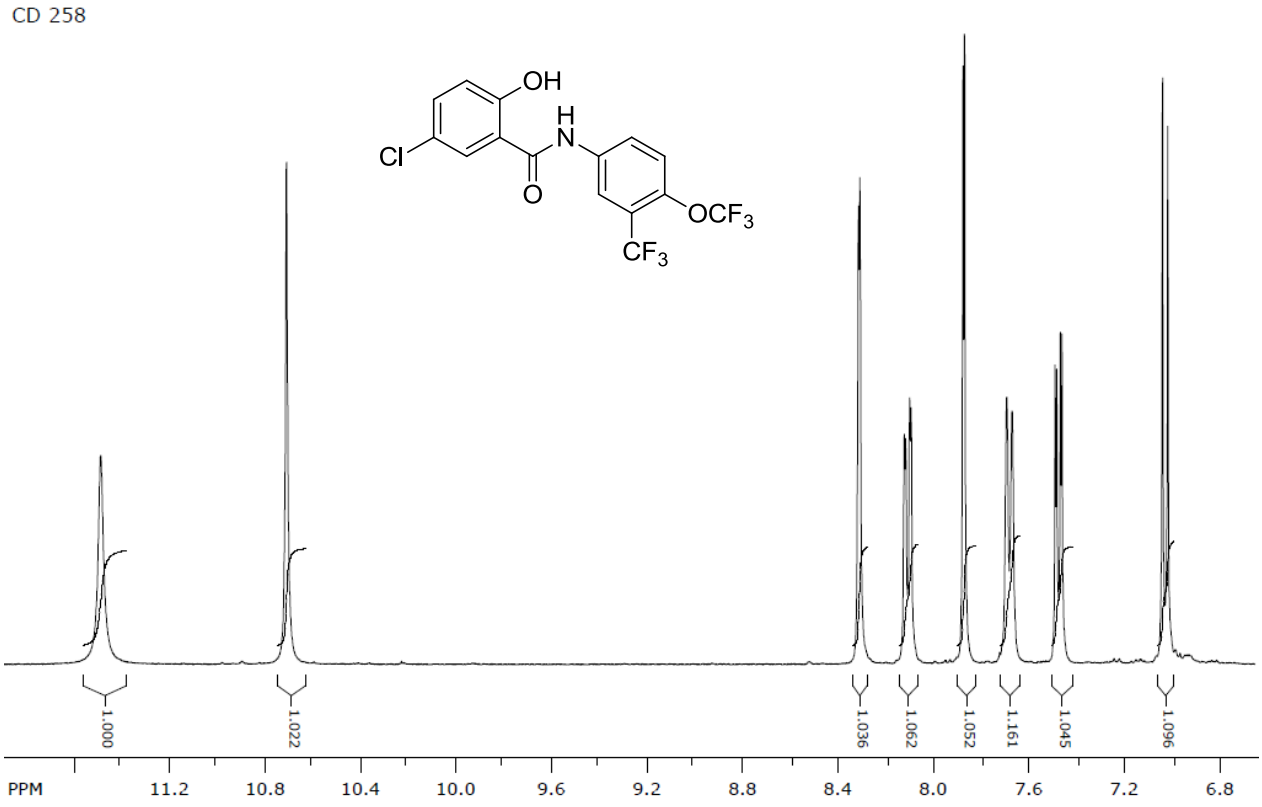


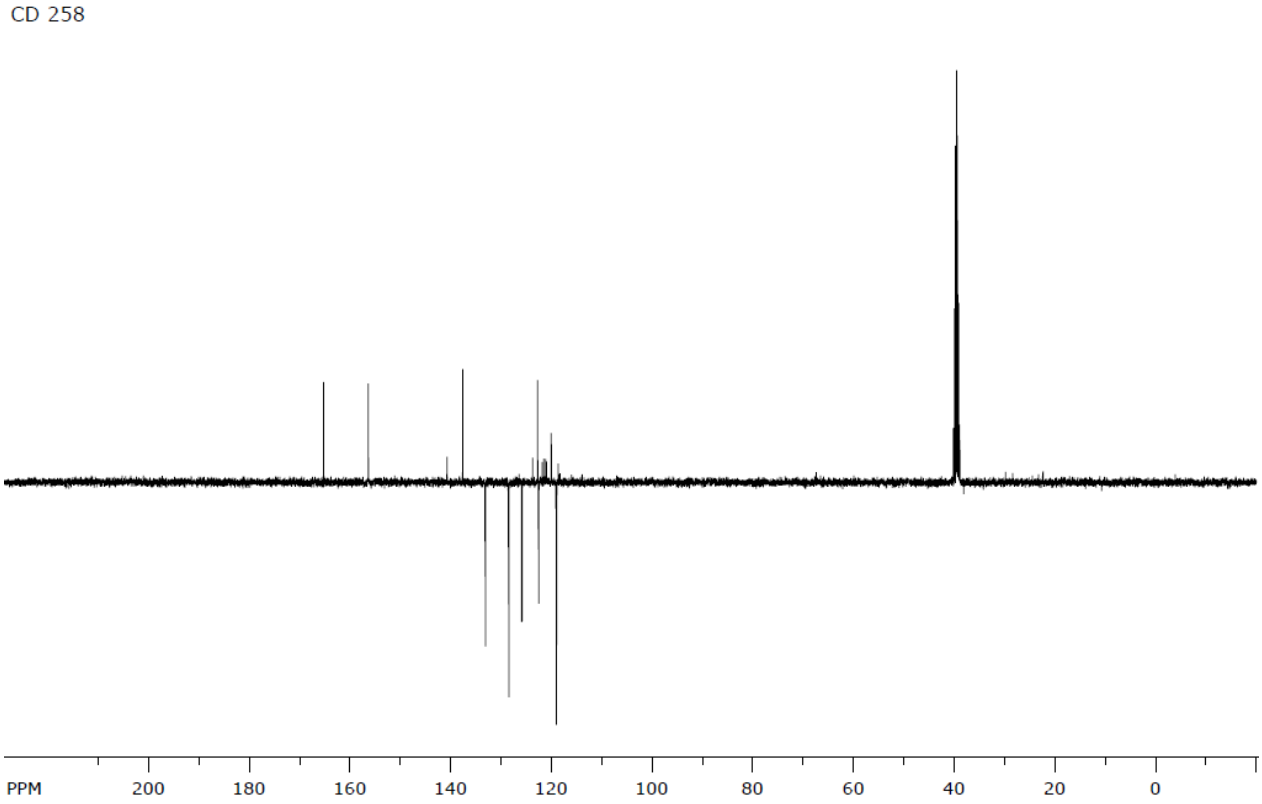
3,5-dichloro-*N*-(3,5-dichlorophenyl)-2-hydroxybenzamide (315)



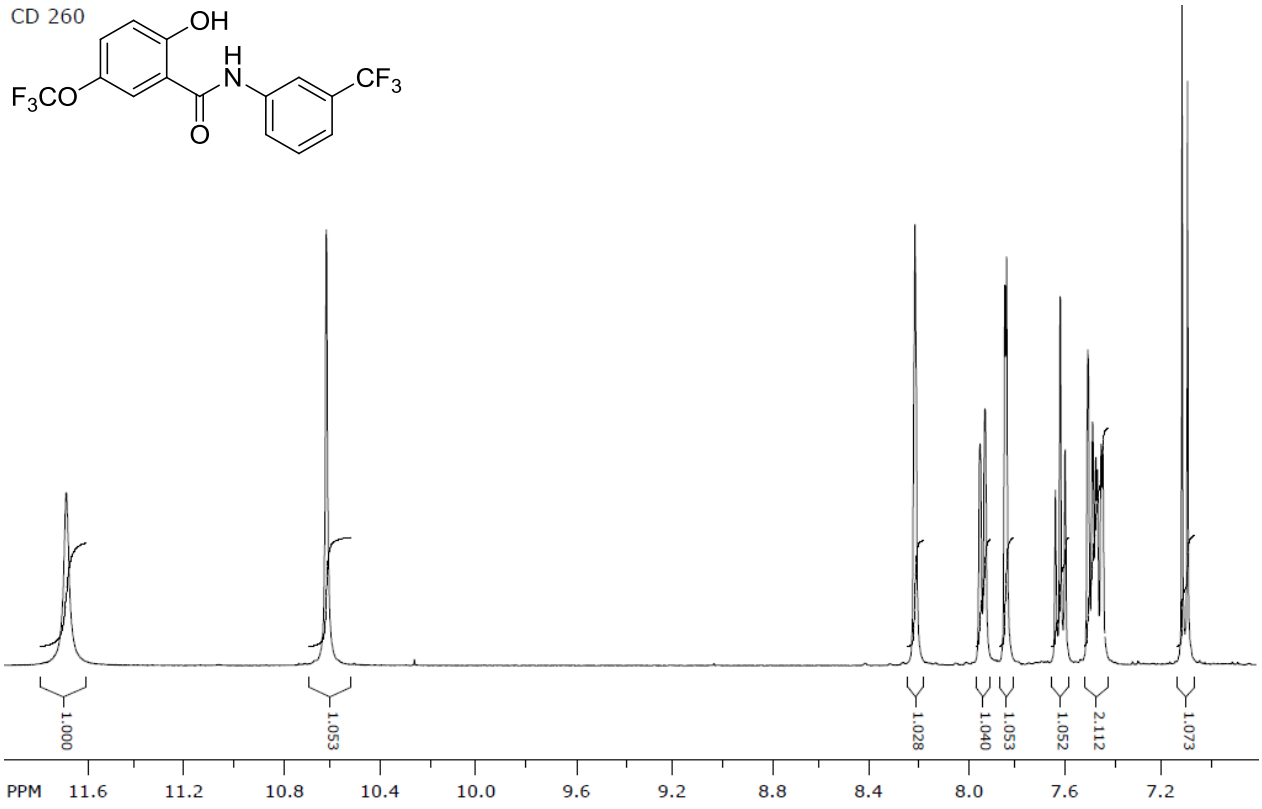


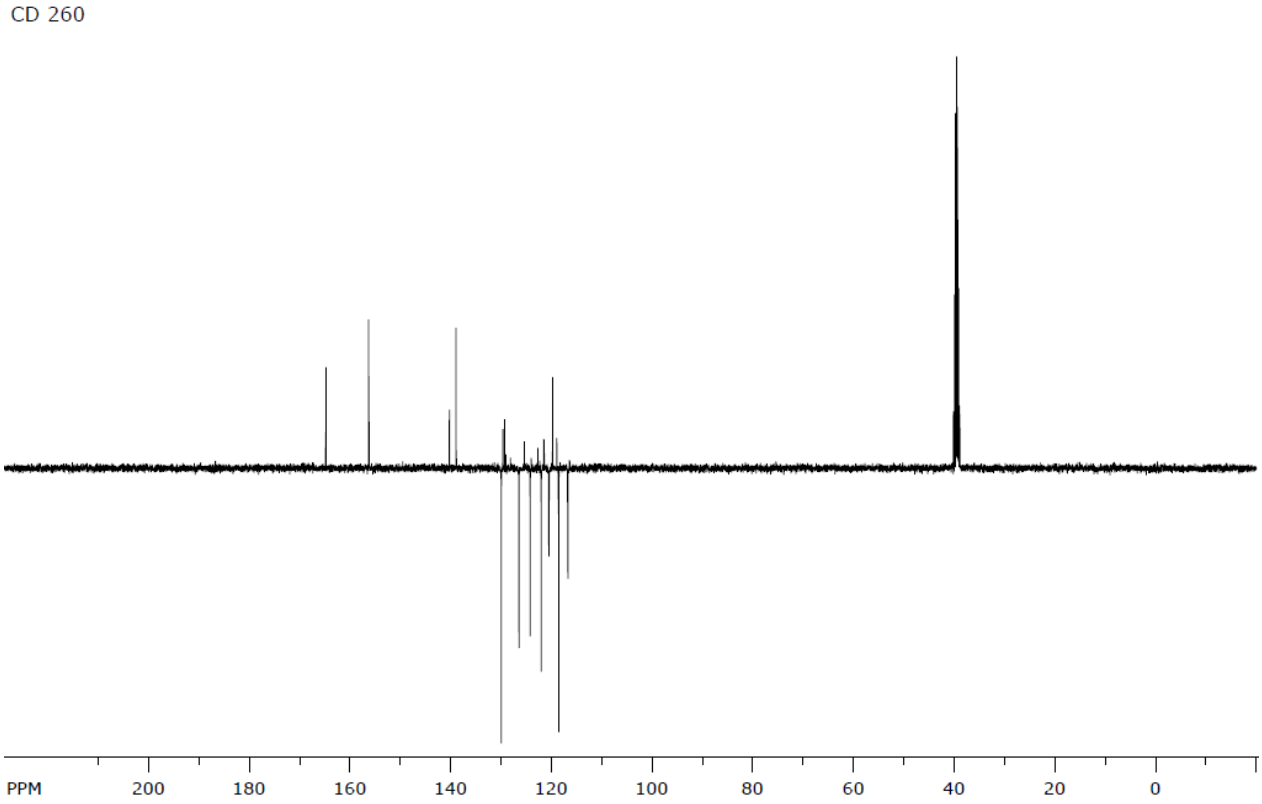
5-chloro-2-hydroxy-*N*-(4-(trifluoromethoxy)-3-(trifluoromethyl)phenyl)benzamide (316)



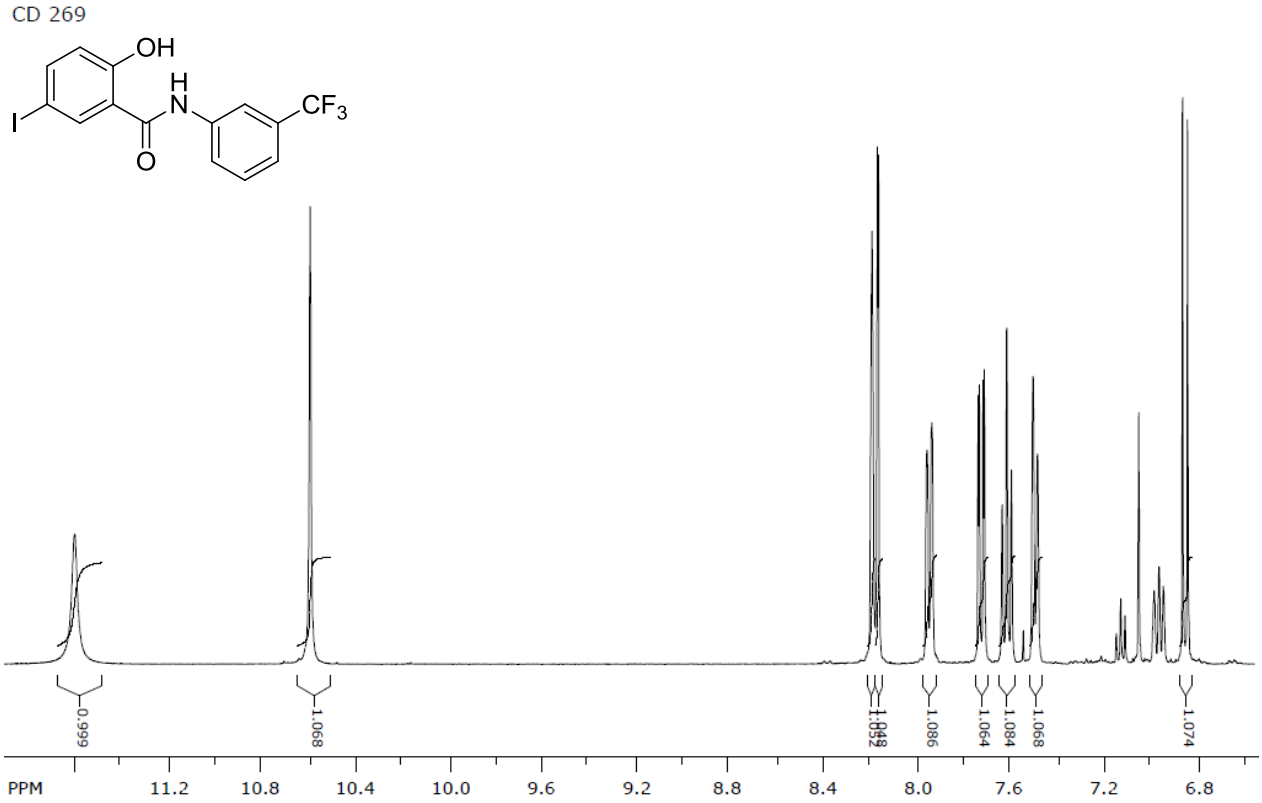


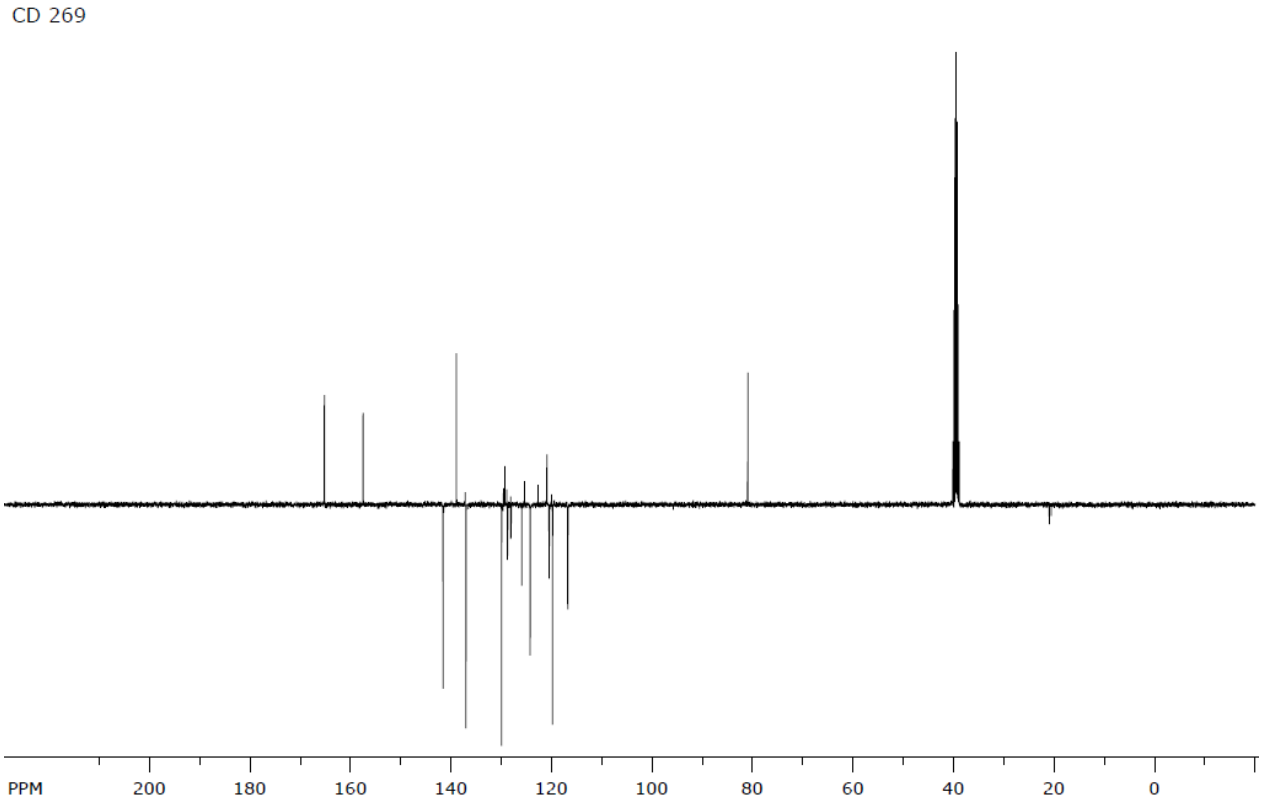
2-hydroxy-5-(trifluoromethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (317)



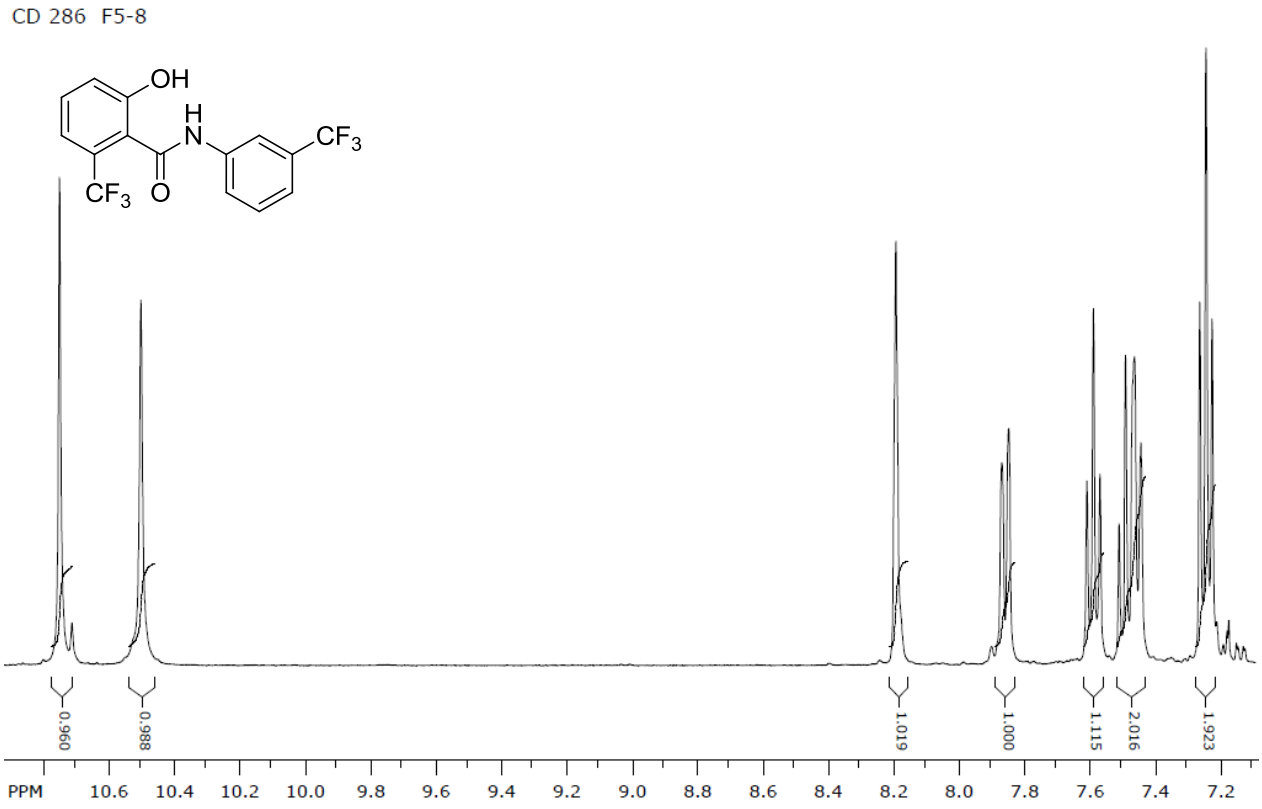


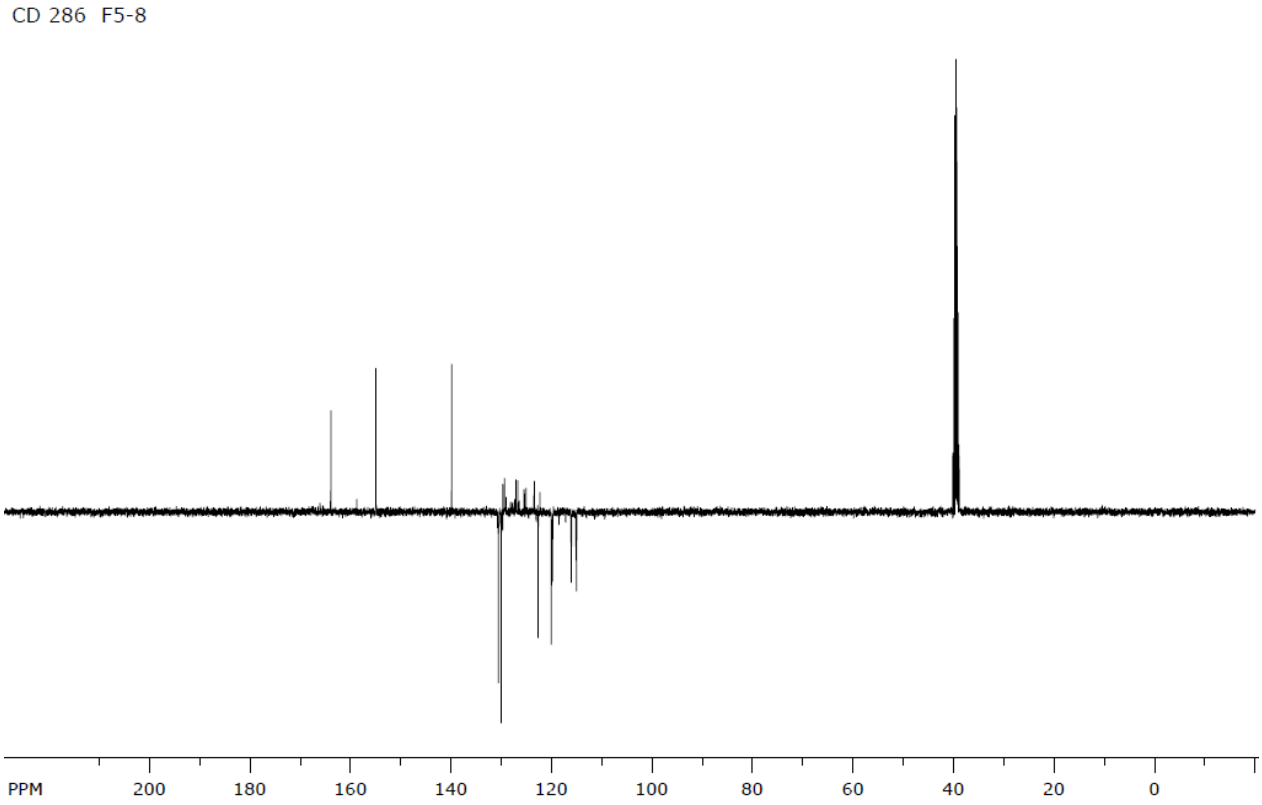
2-hydroxy-5-iodo-*N*-(3-(trifluoromethyl)phenyl)benzamide (318)



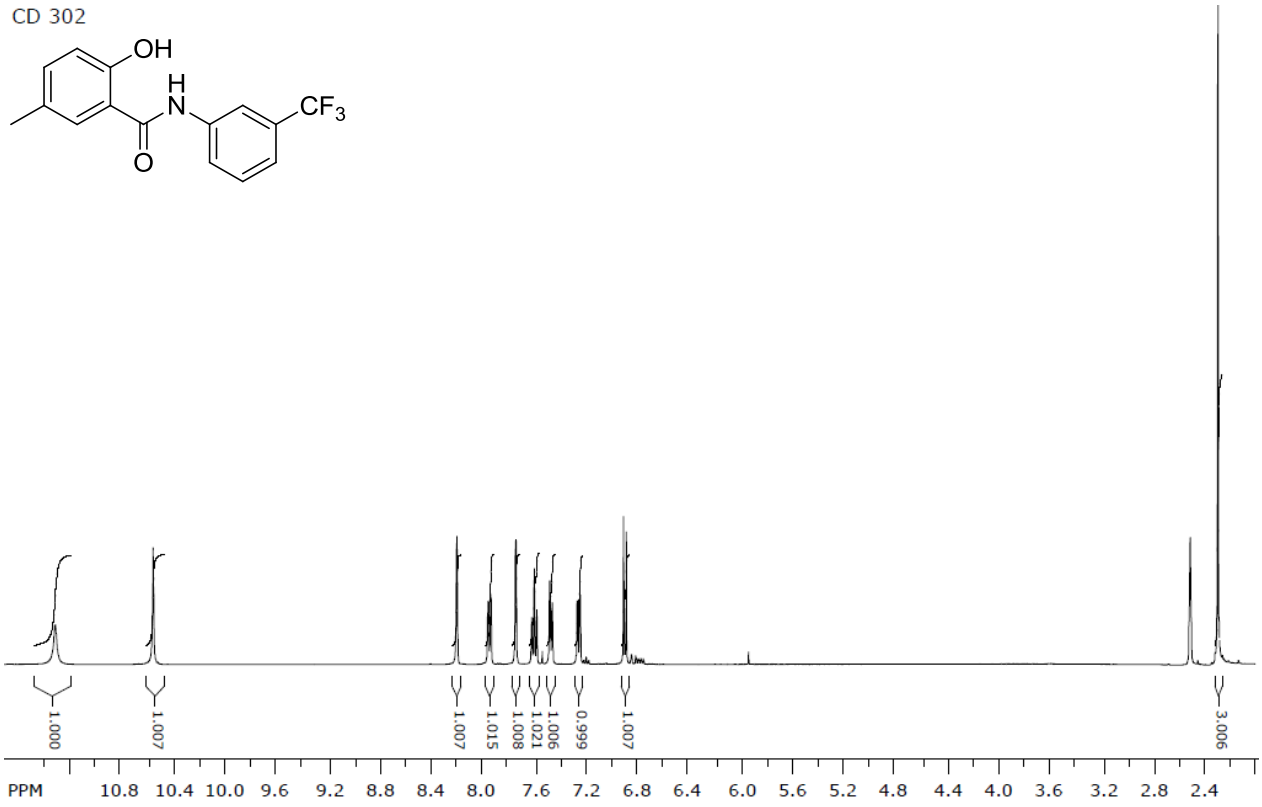


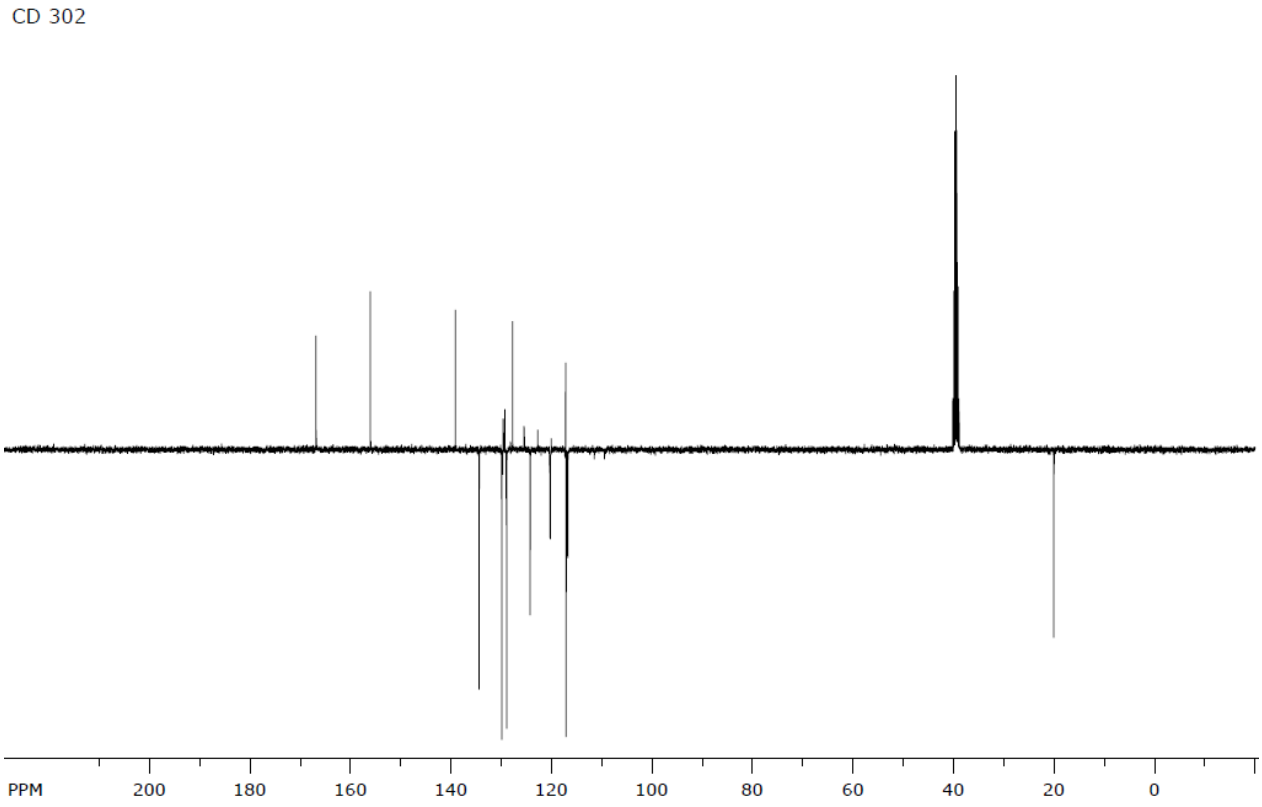
2-hydroxy-6-(trifluoromethyl)-*N*-(3-(trifluoromethyl)phenyl)benzamide (319)



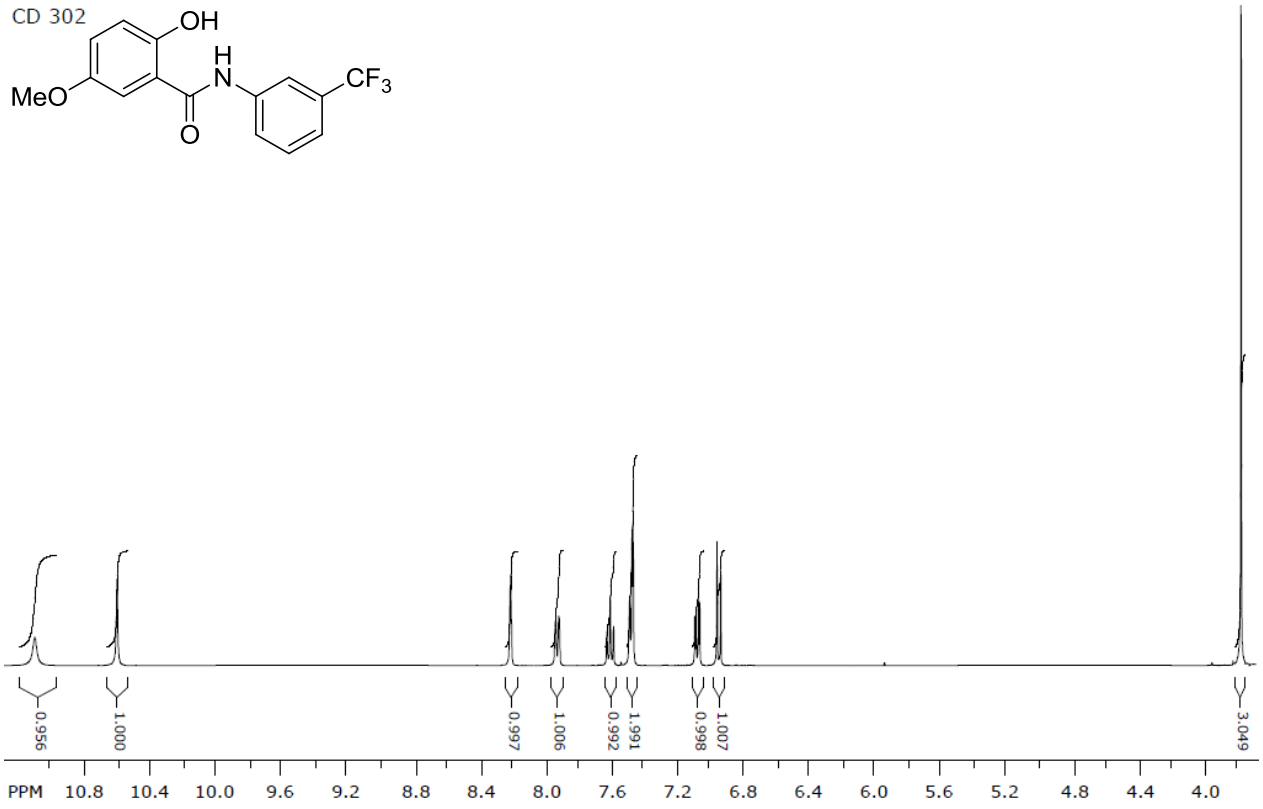


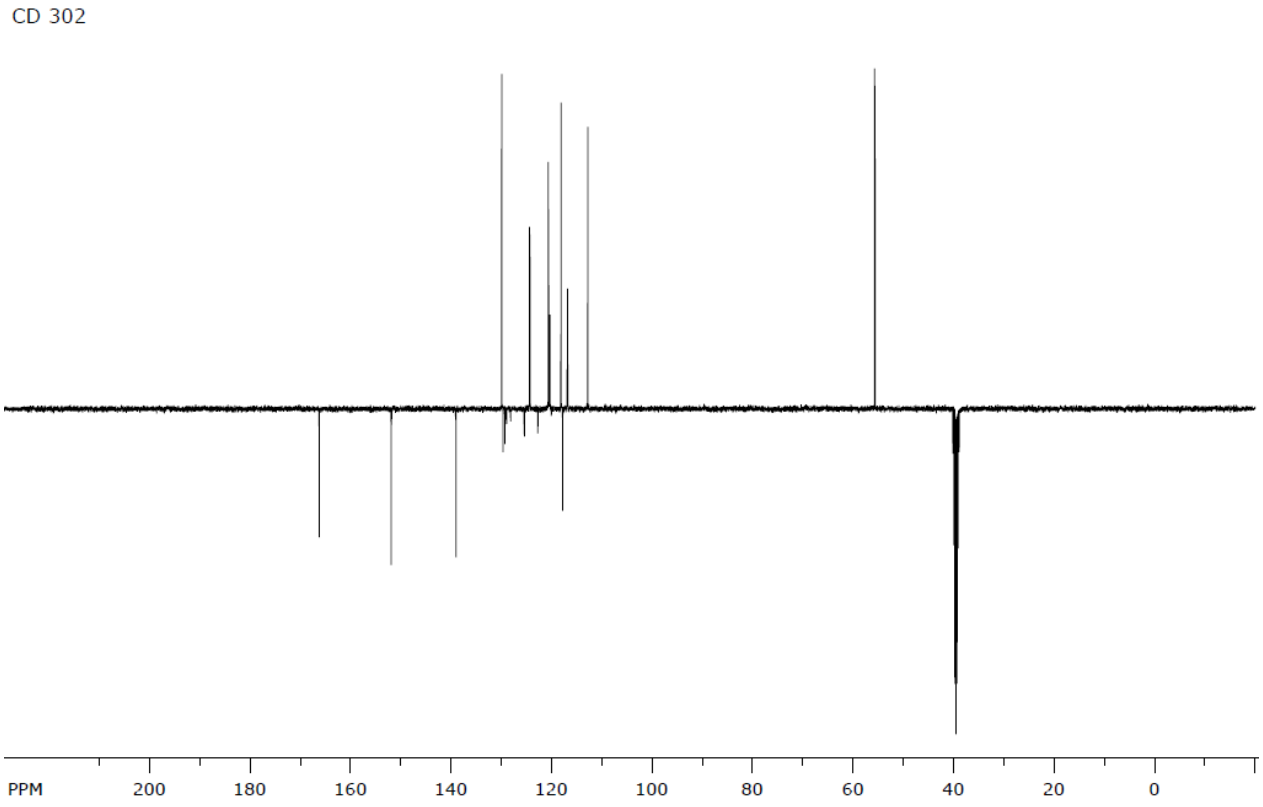
2-hydroxy-5-methyl-*N*-(3-(trifluoromethyl)phenyl)benzamide (321)





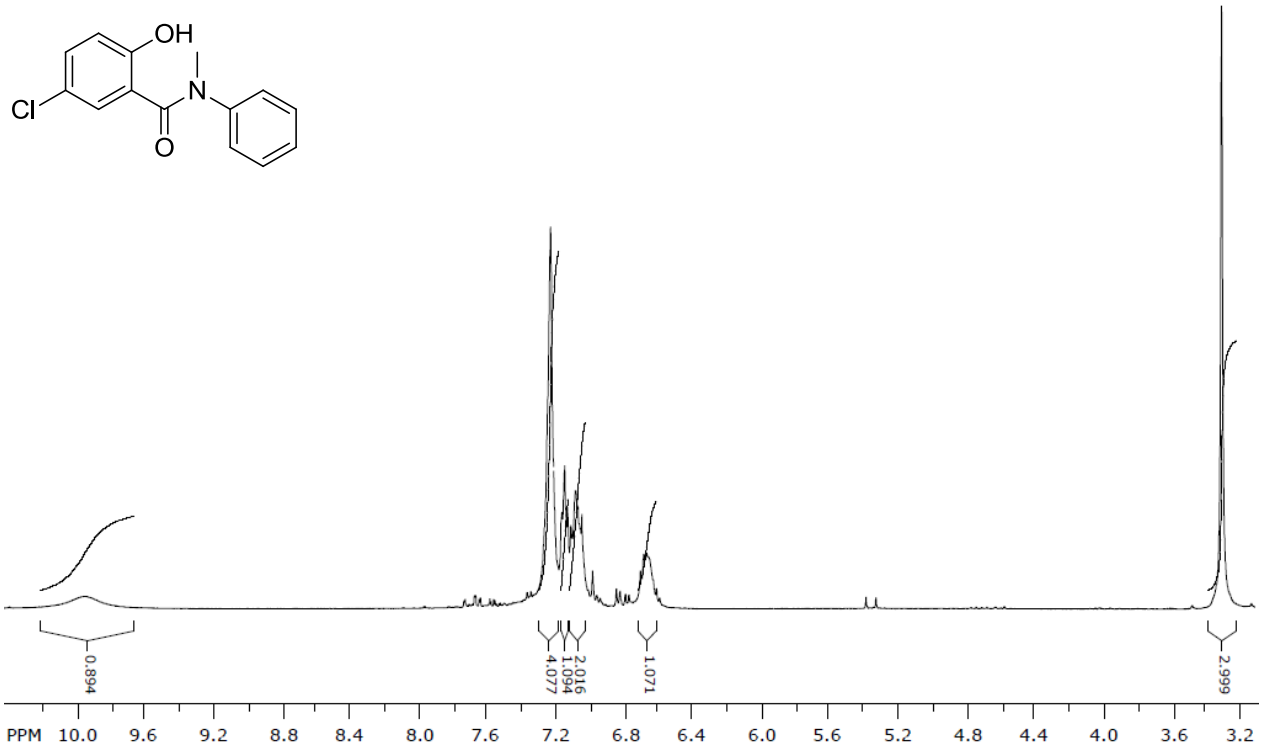
2-hydroxy-5-methoxy-*N*-(3-(trifluoromethyl)phenyl)benzamide (322)



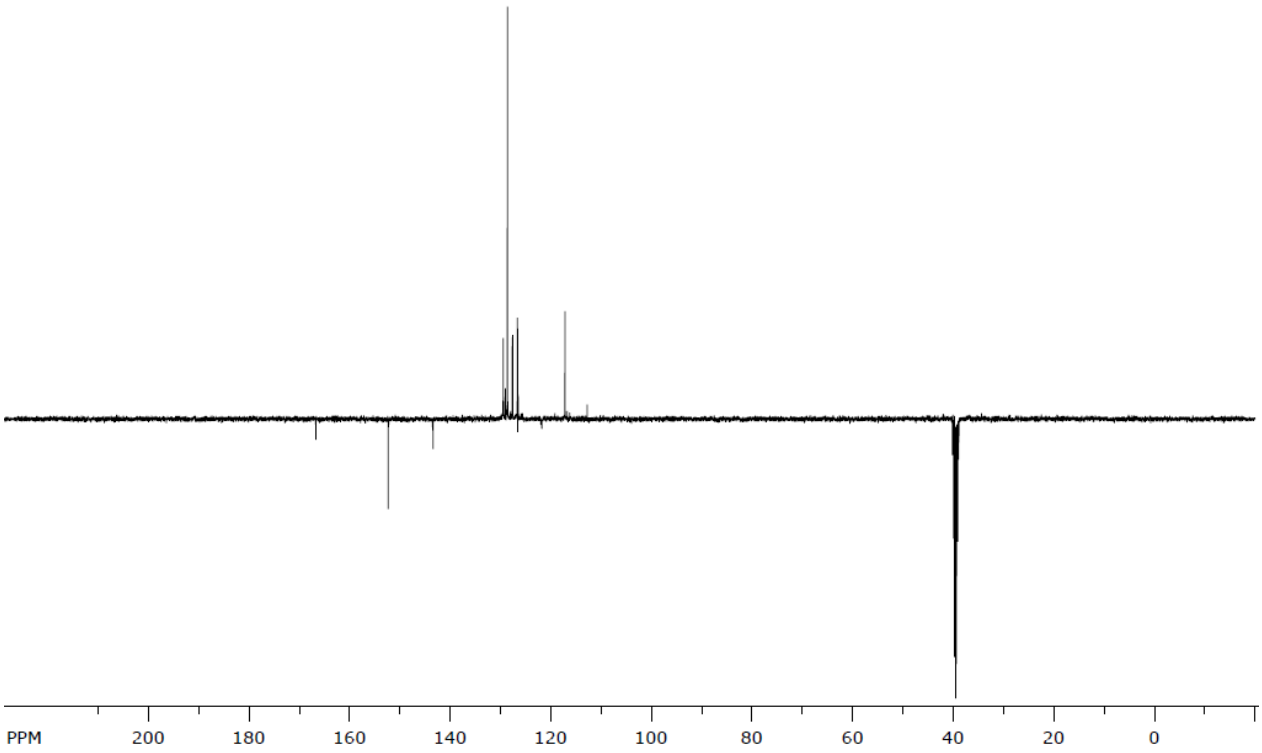


5-chloro-2-hydroxy-*N*-methyl-*N*-phenylbenzamide (324)

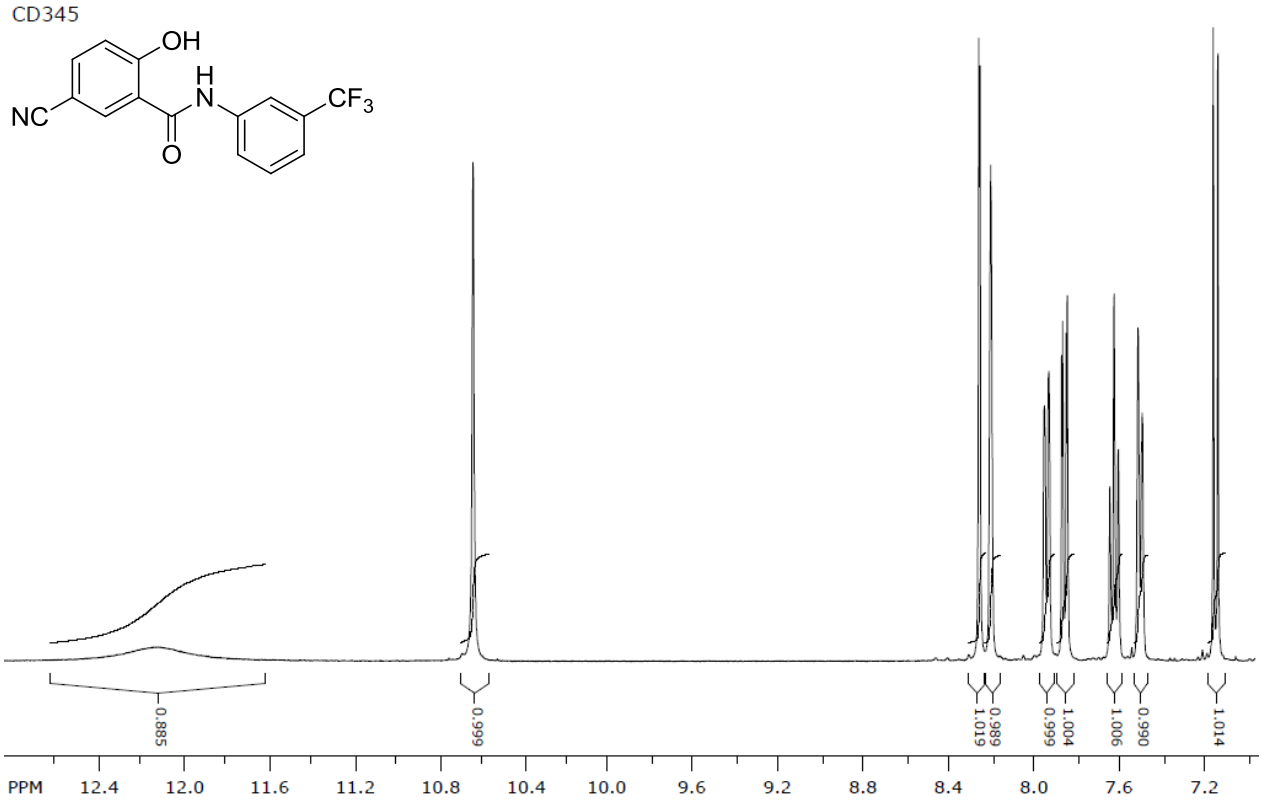
CD 317

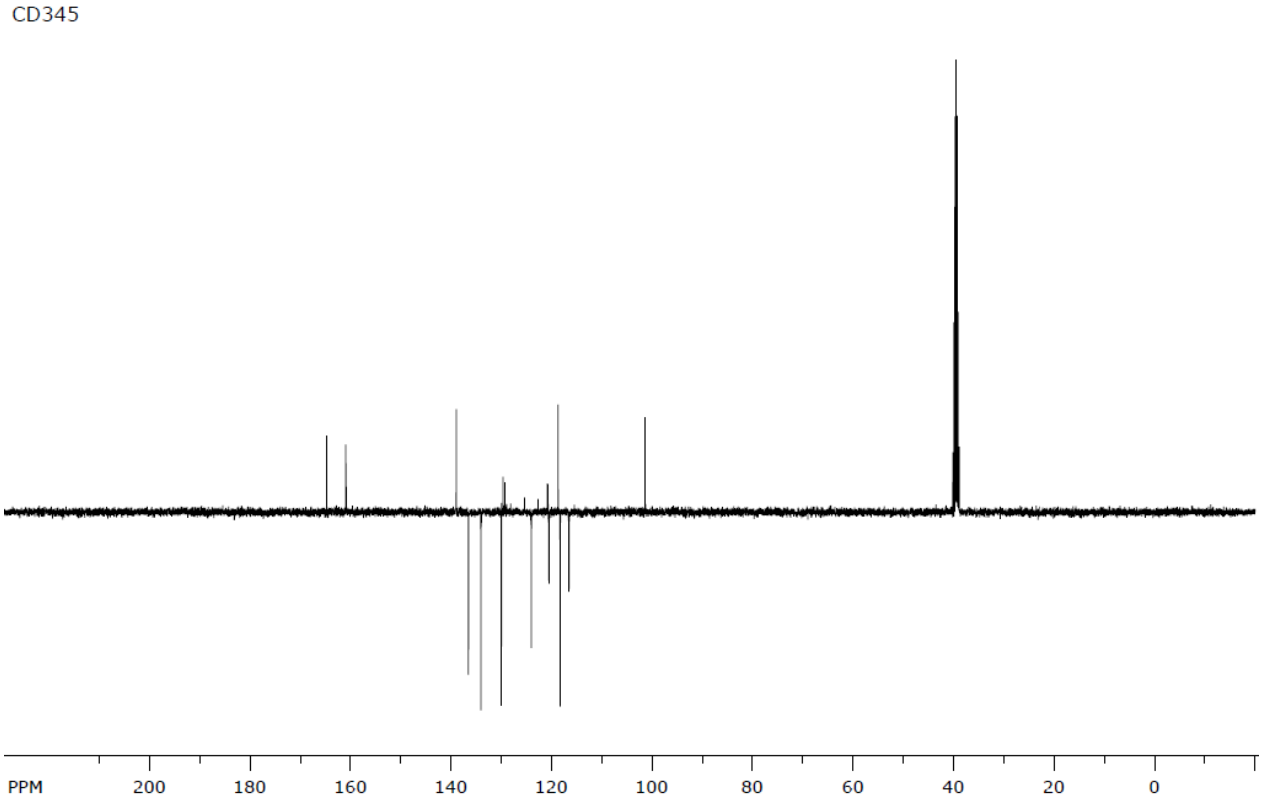


CD 317

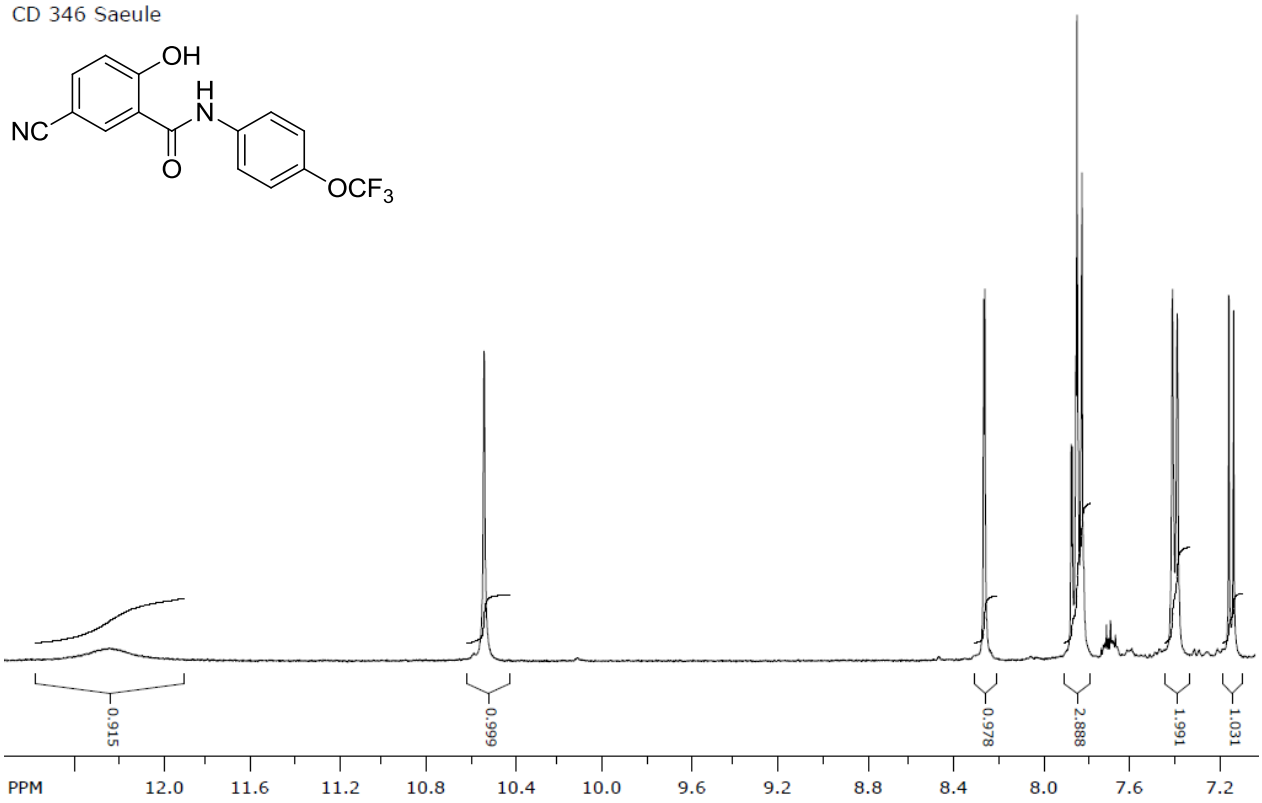


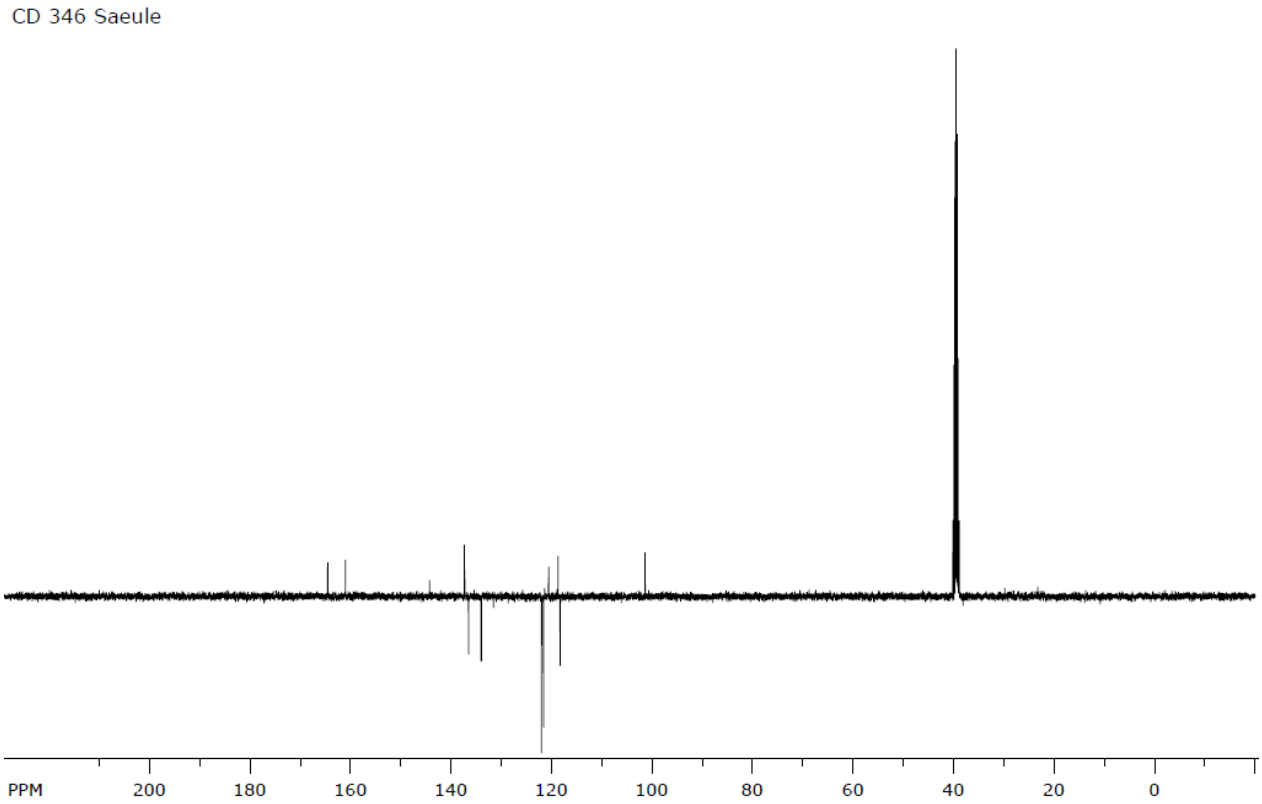
5-cyano-2-hydroxy-*N*-(3-(trifluoromethyl)phenyl)benzamide (325)



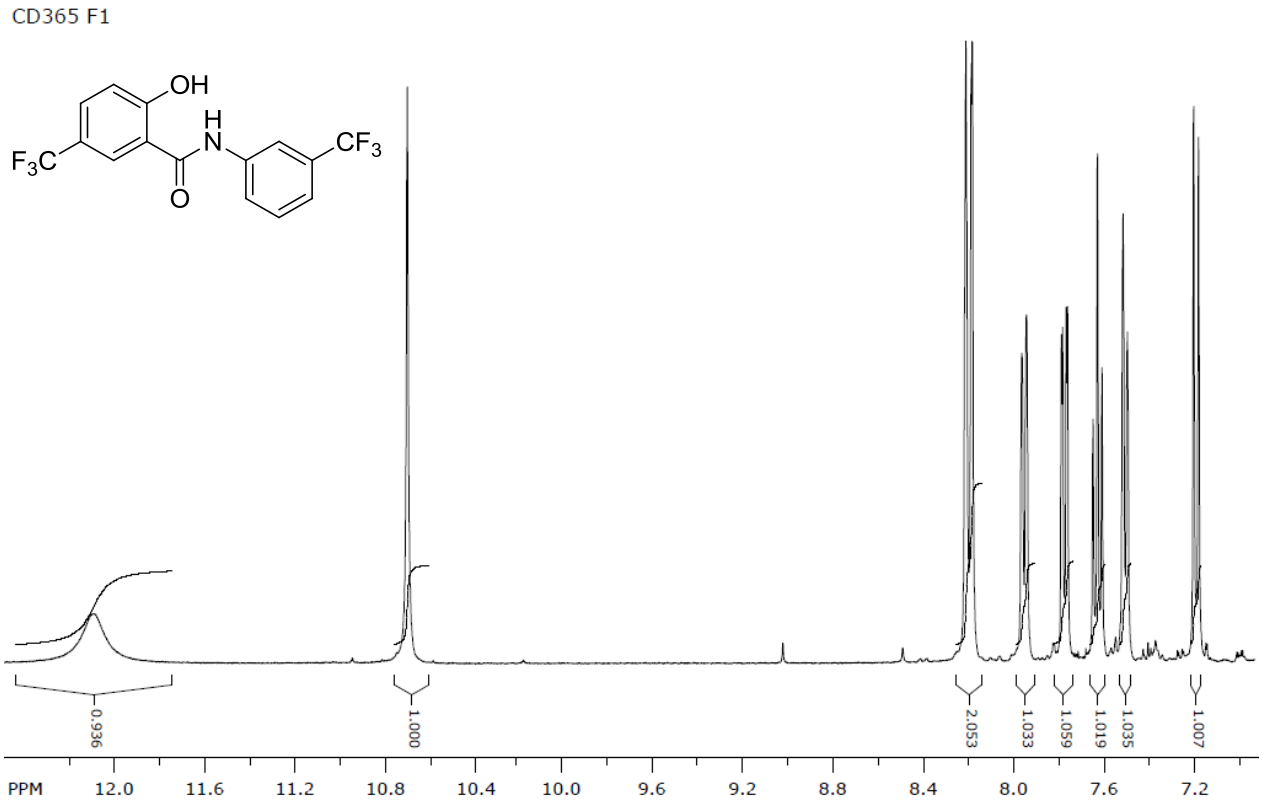


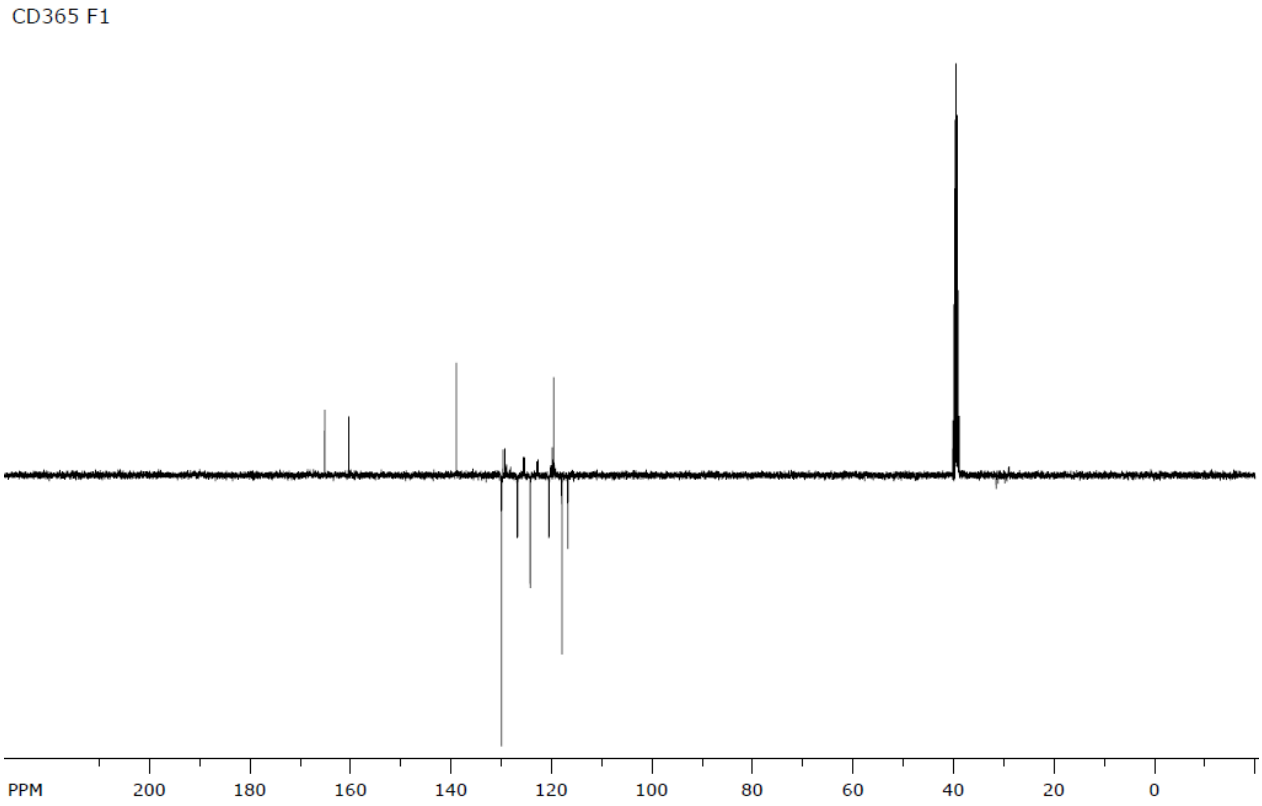
5-cyano-2-hydroxy-*N*-(4-(trifluoromethoxy)phenyl)benzamide (326)



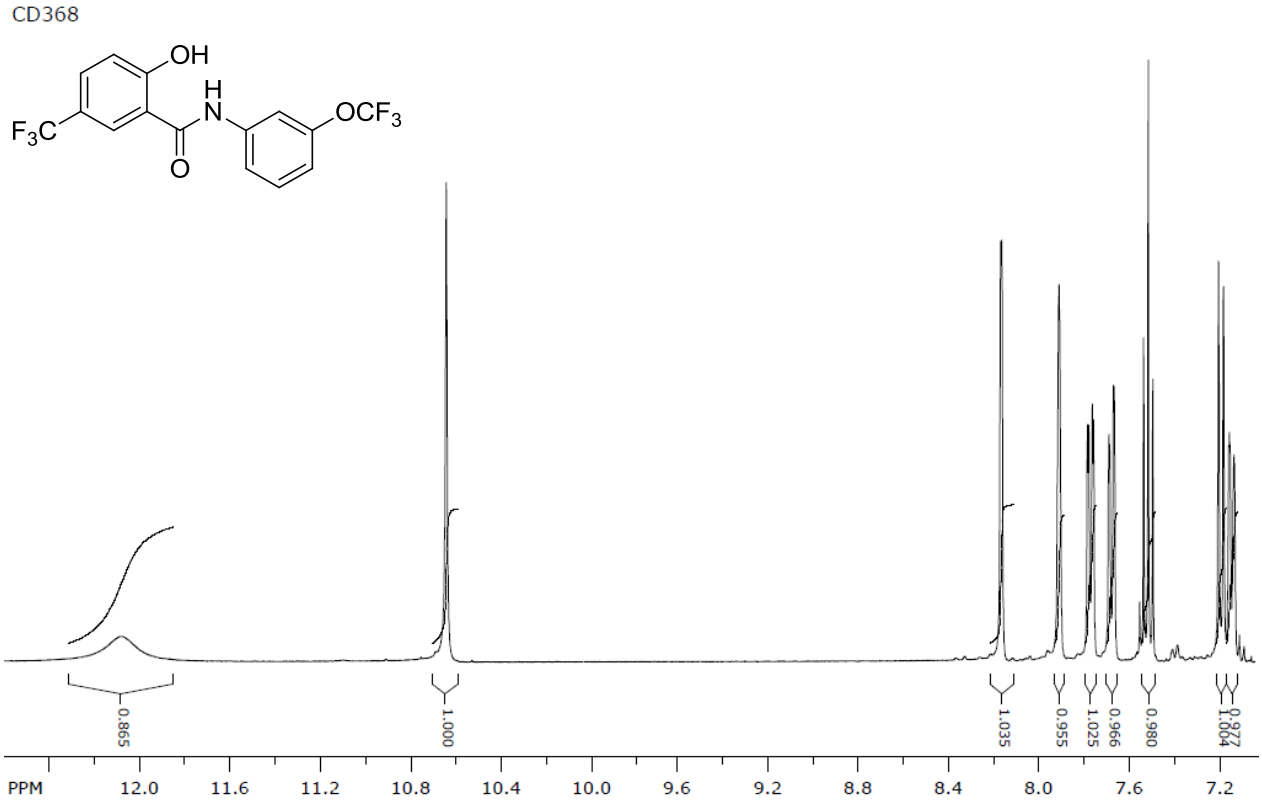


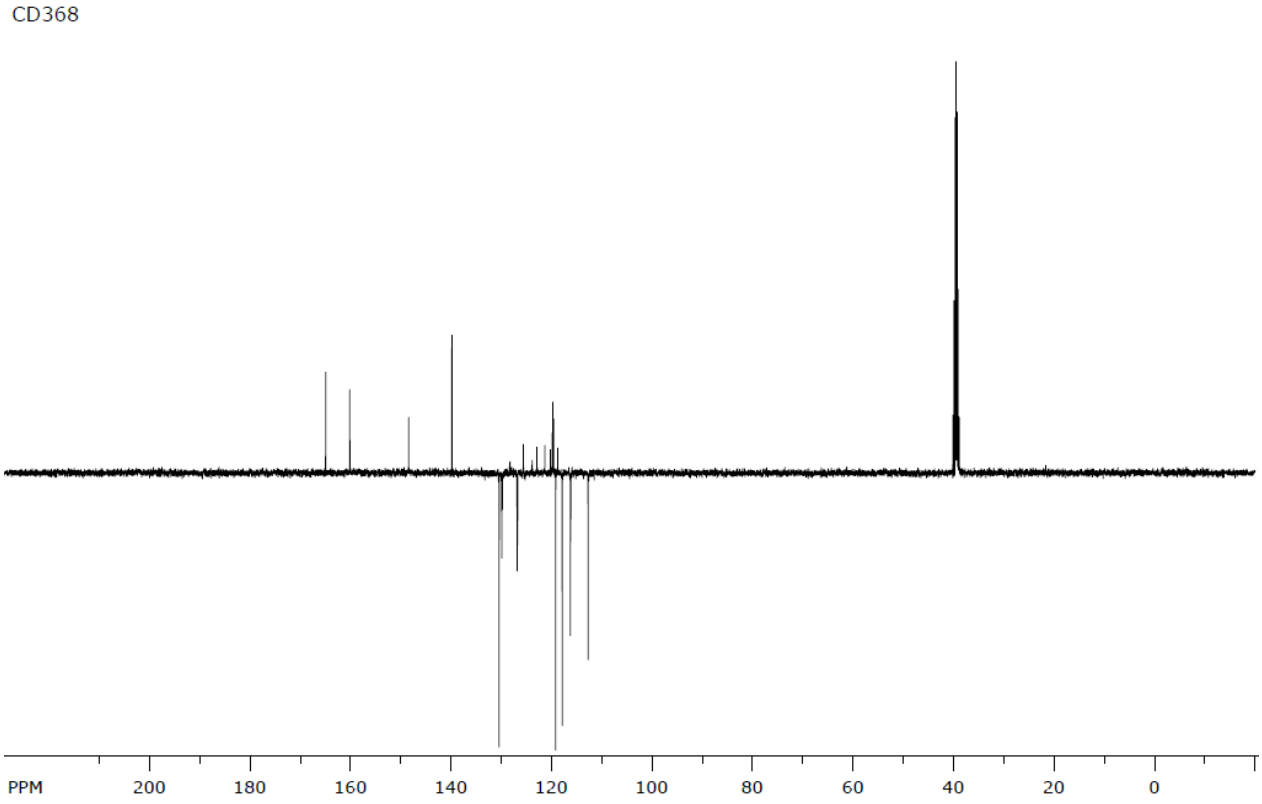
2-hydroxy-5-(trifluoromethyl)-*N*-(3-(trifluoromethyl)phenyl)benzamide (328)



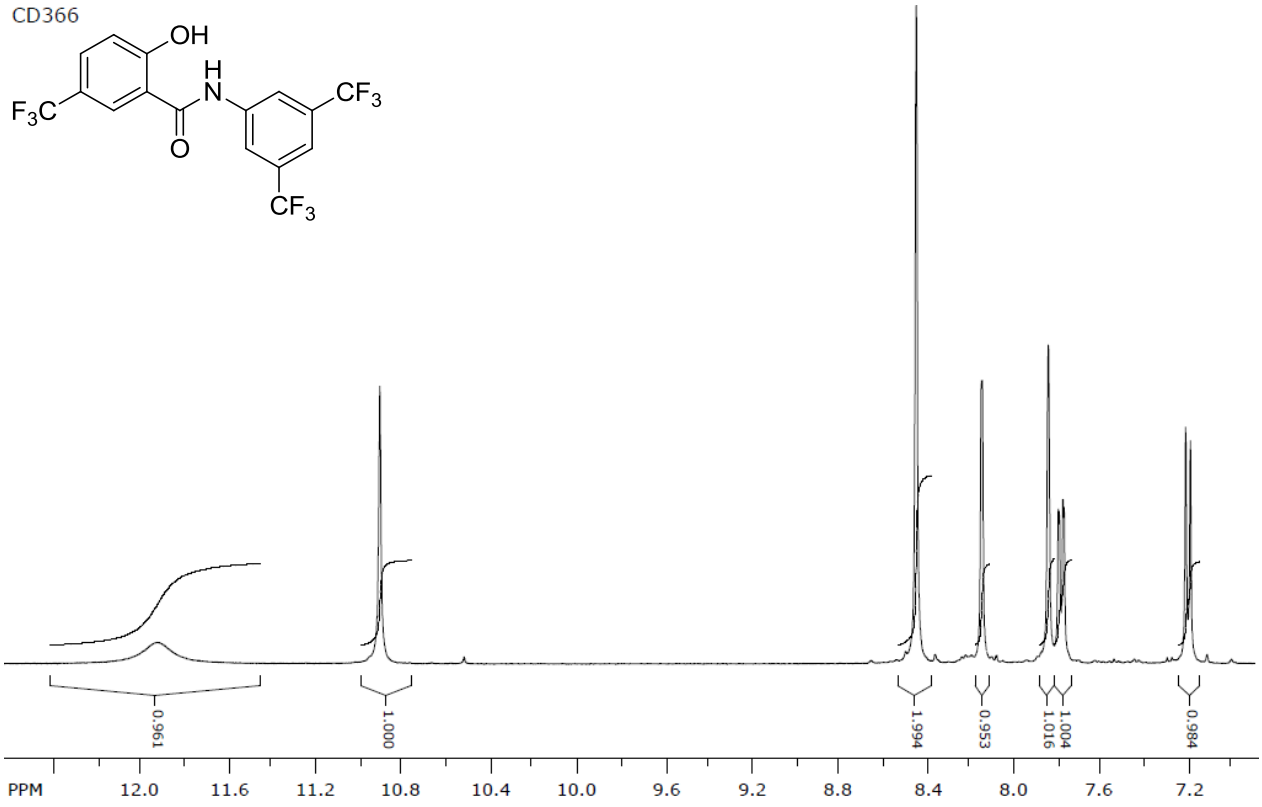


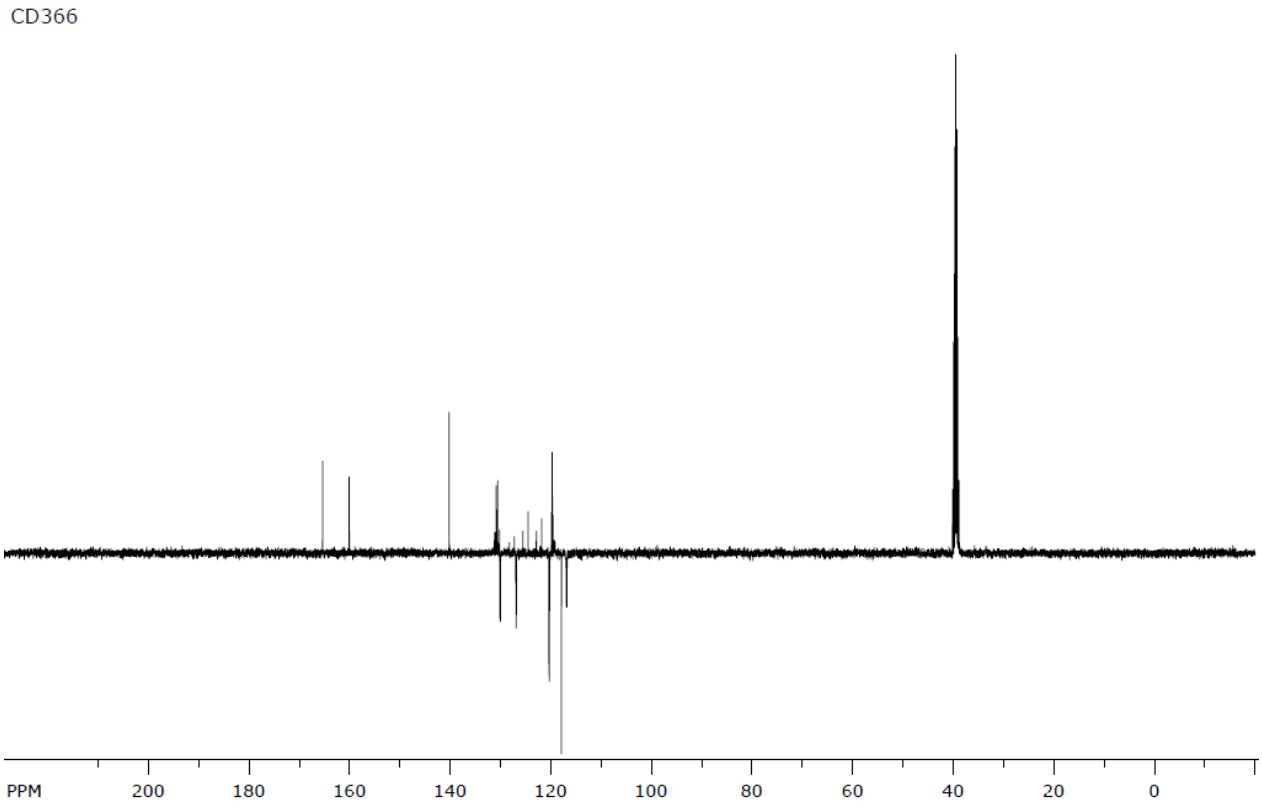
2-hydroxy-*N*-(3-(trifluoromethoxy)phenyl)-5-(trifluoromethyl)benzamide (329)



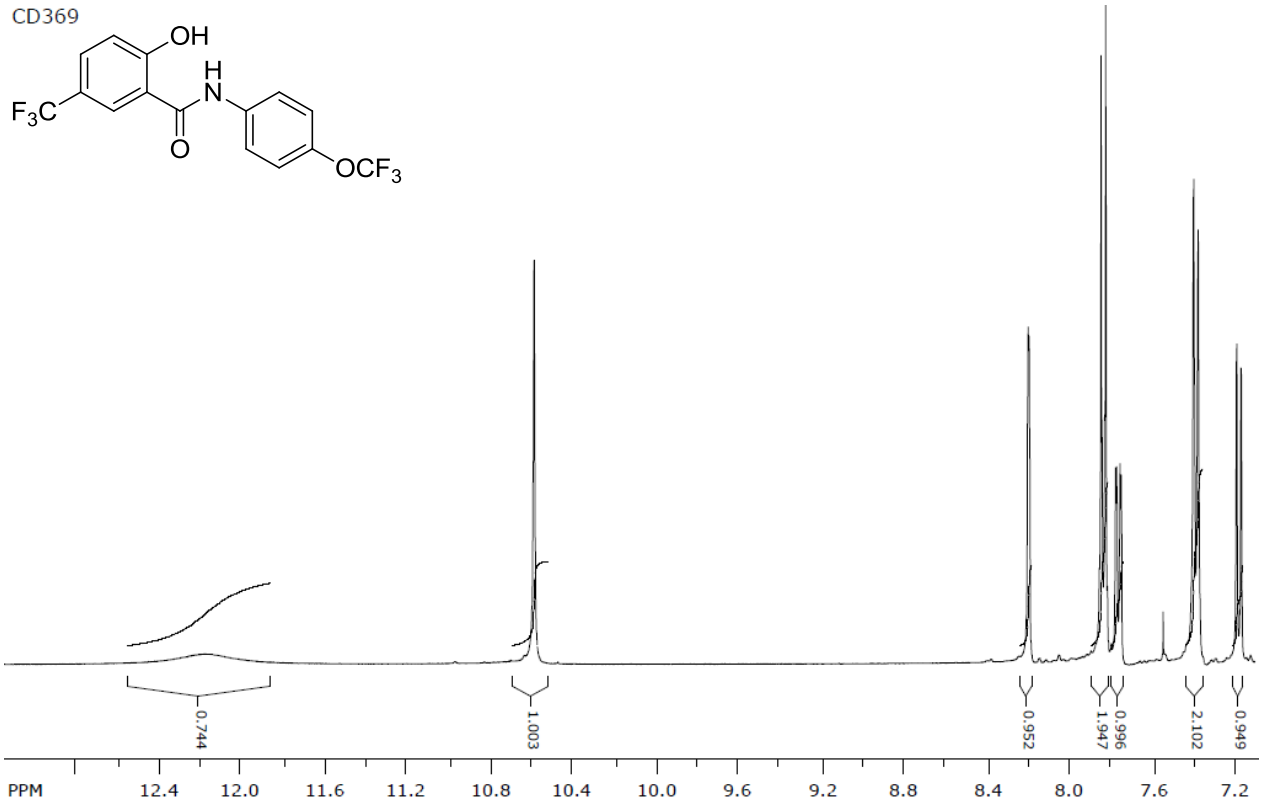


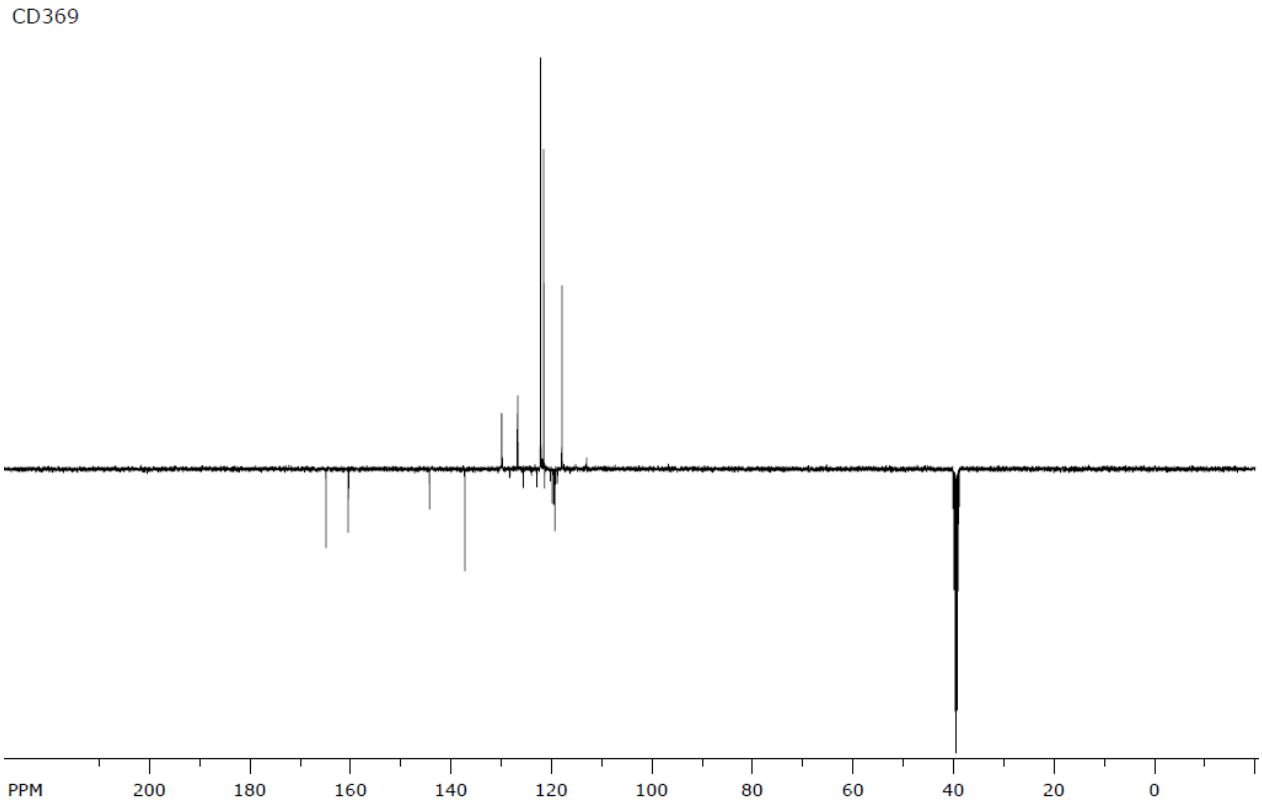
_N_-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxy-5-(trifluoromethyl)benzamide (330)



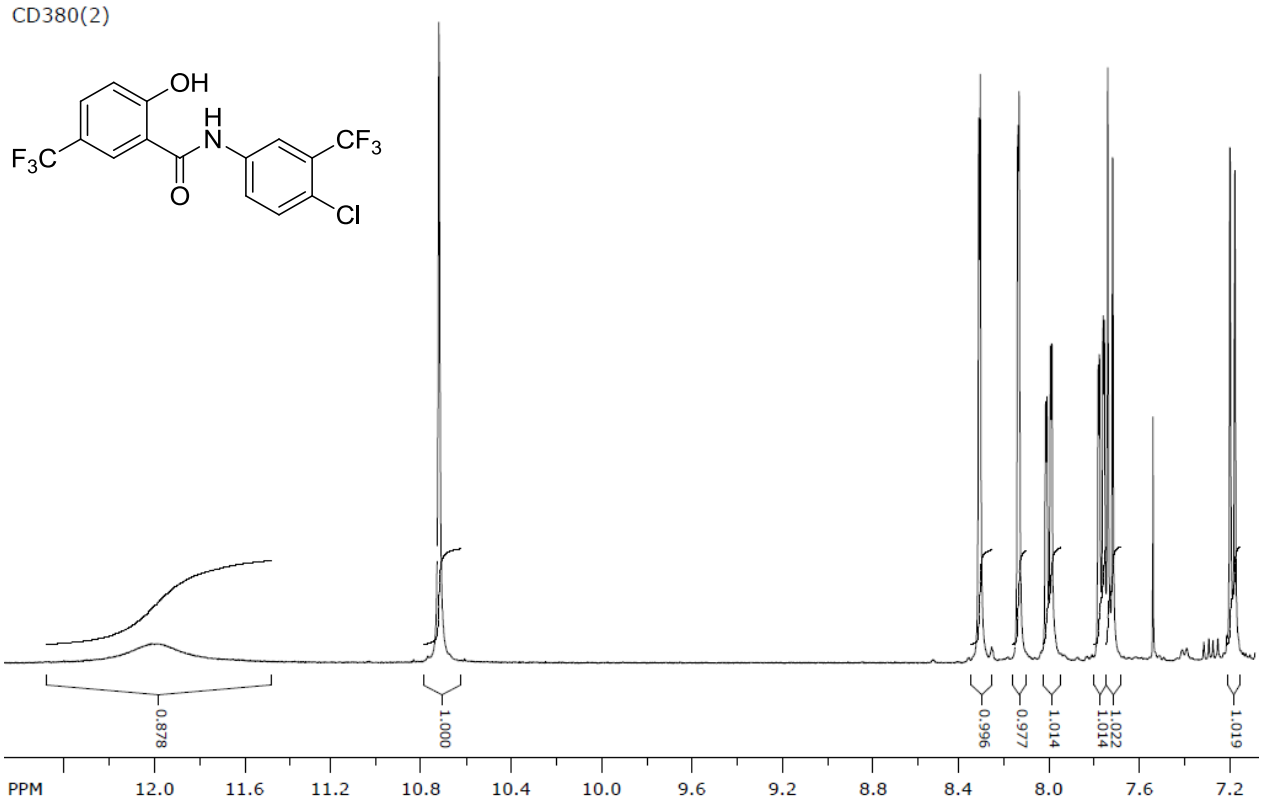


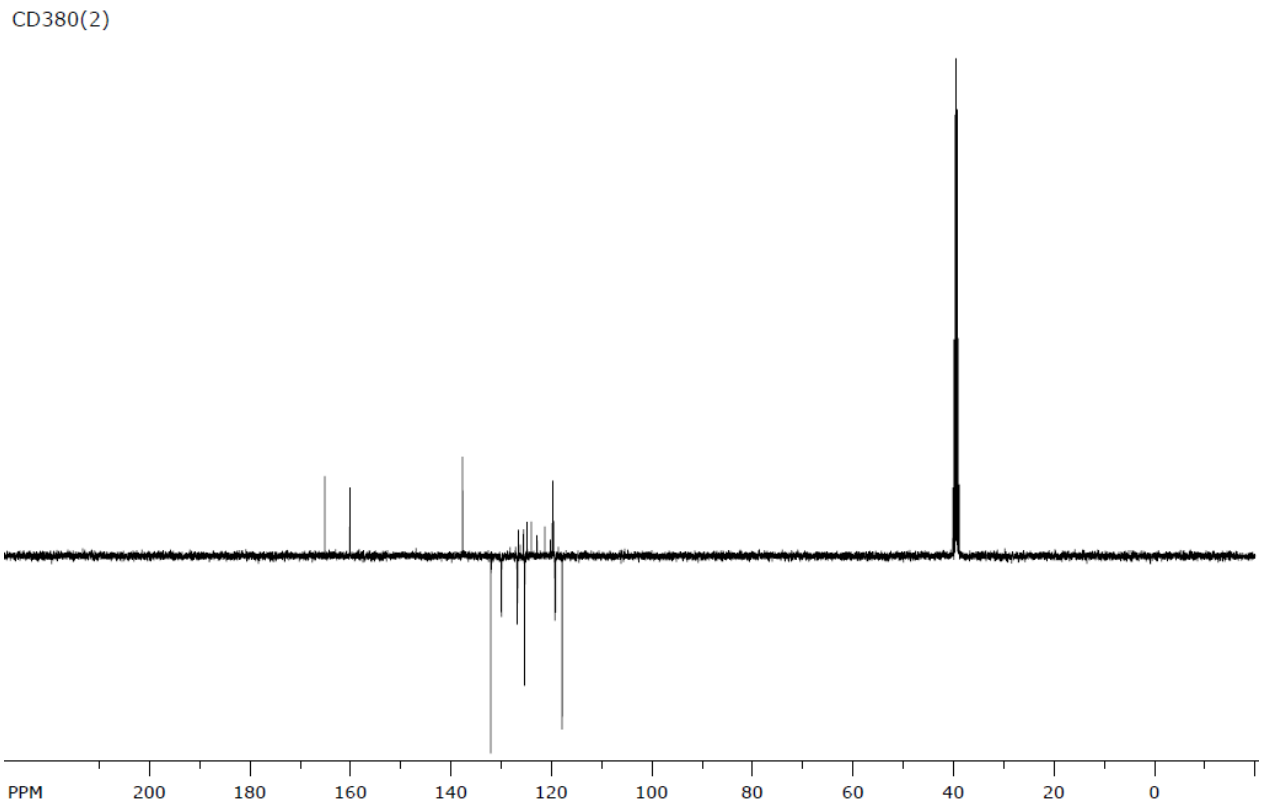
2-hydroxy-*N*-(4-(trifluoromethoxy)phenyl)-5-(trifluoromethyl)benzamide (331)





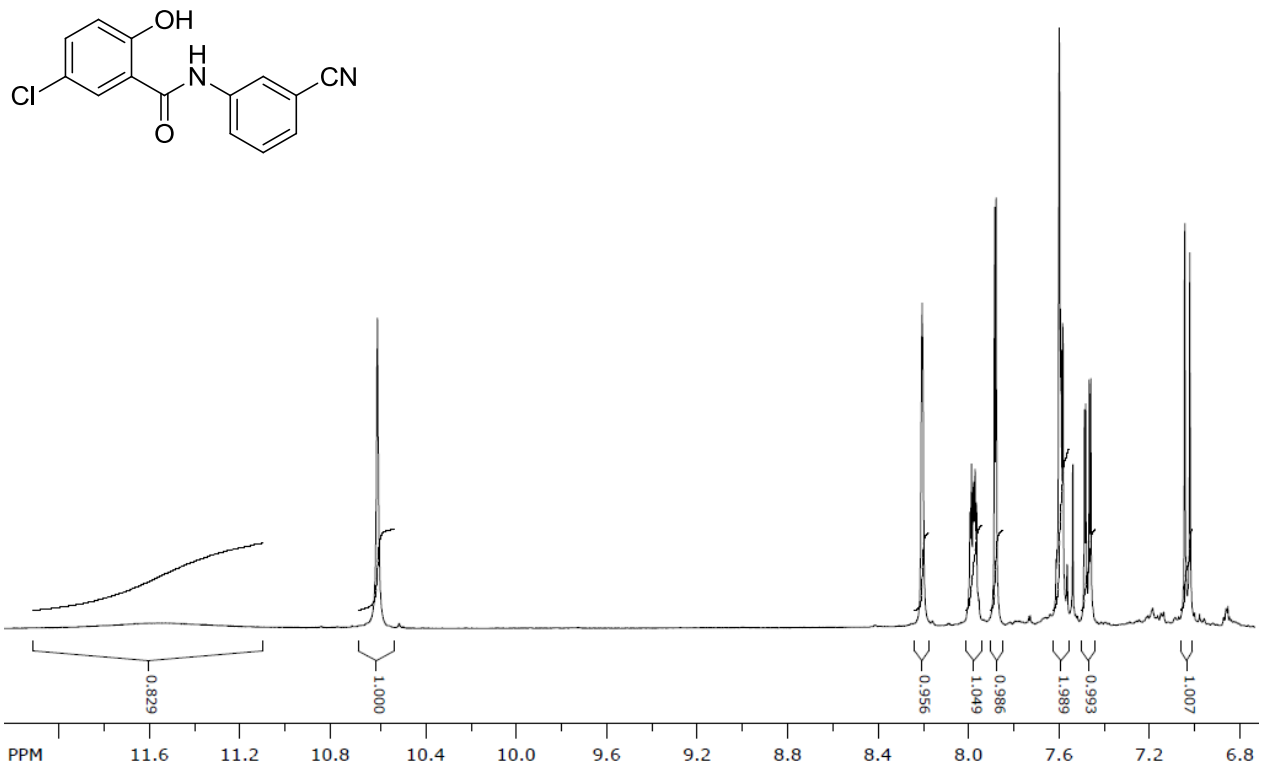
_N_-(4-chloro-3-(trifluoromethyl)phenyl)-2-hydroxy-5-(trifluoromethyl)benzamide (332)



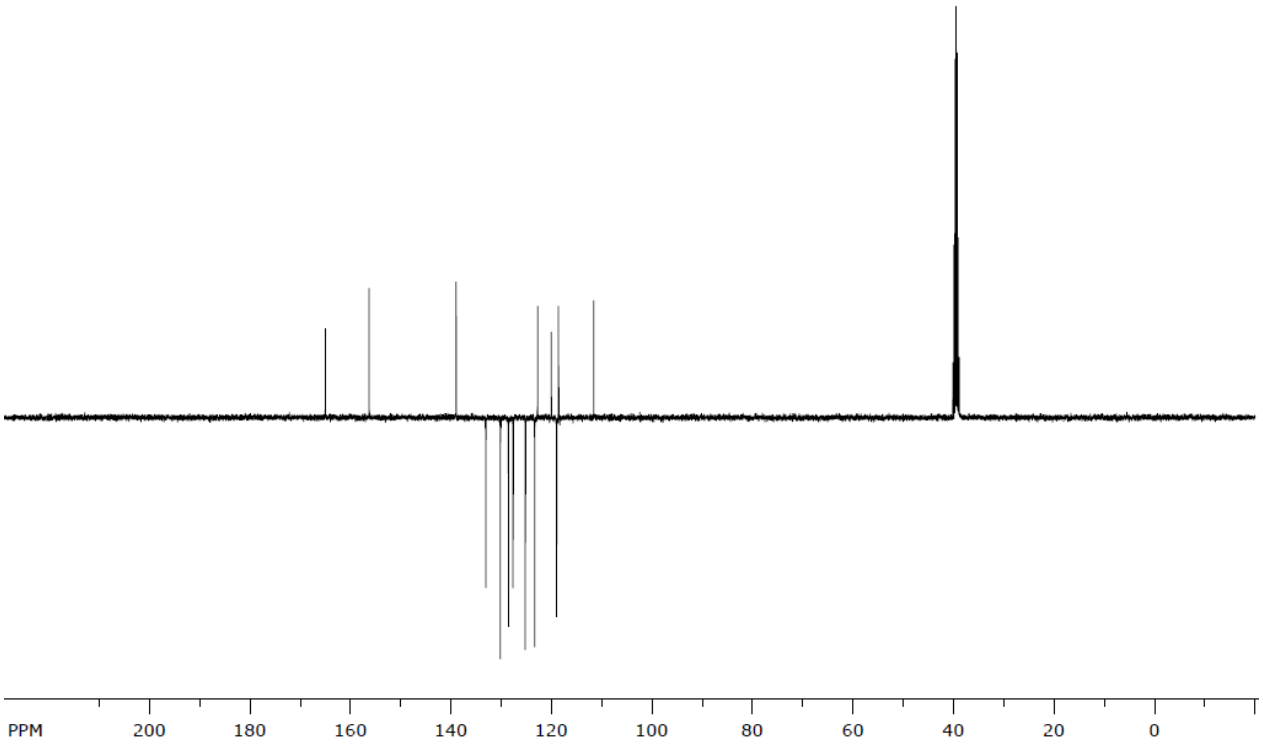


5-chloro-*N*-(3-cyanophenyl)-2-hydroxybenzamide (333)

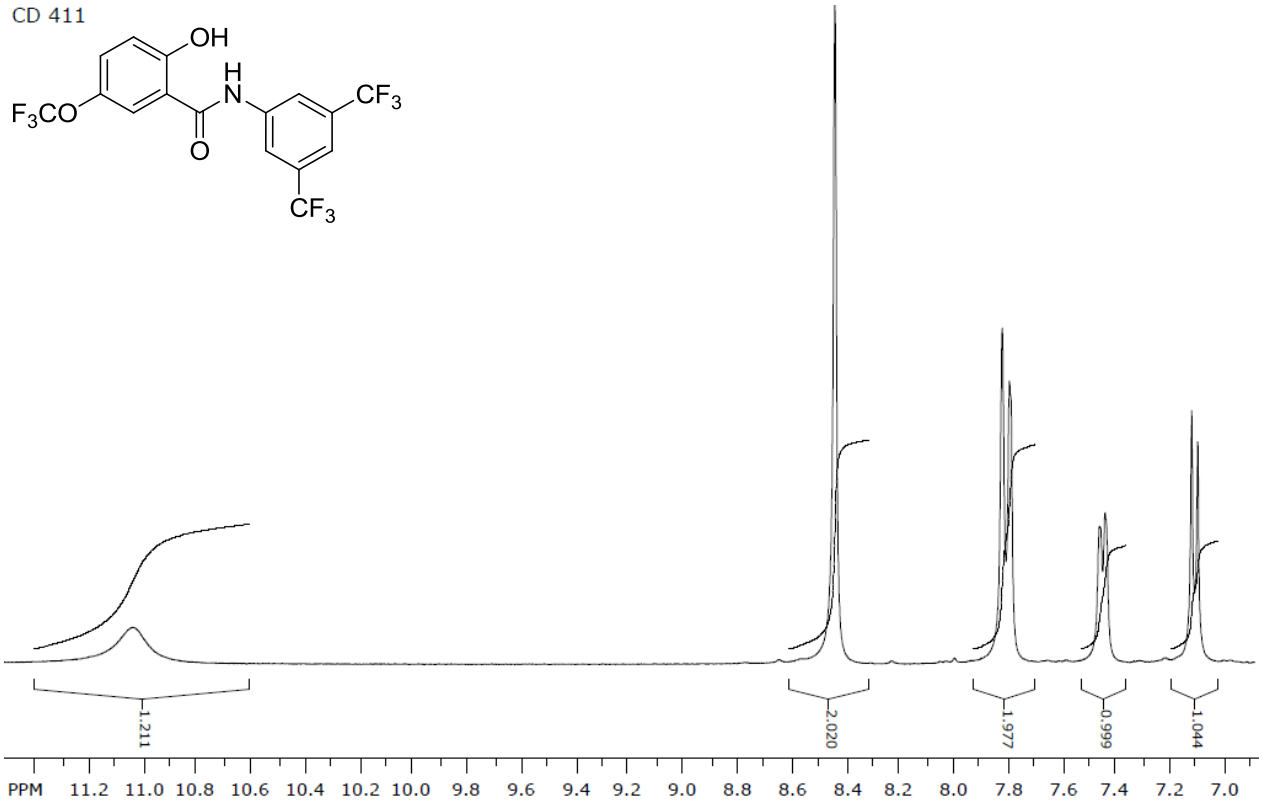
CD423

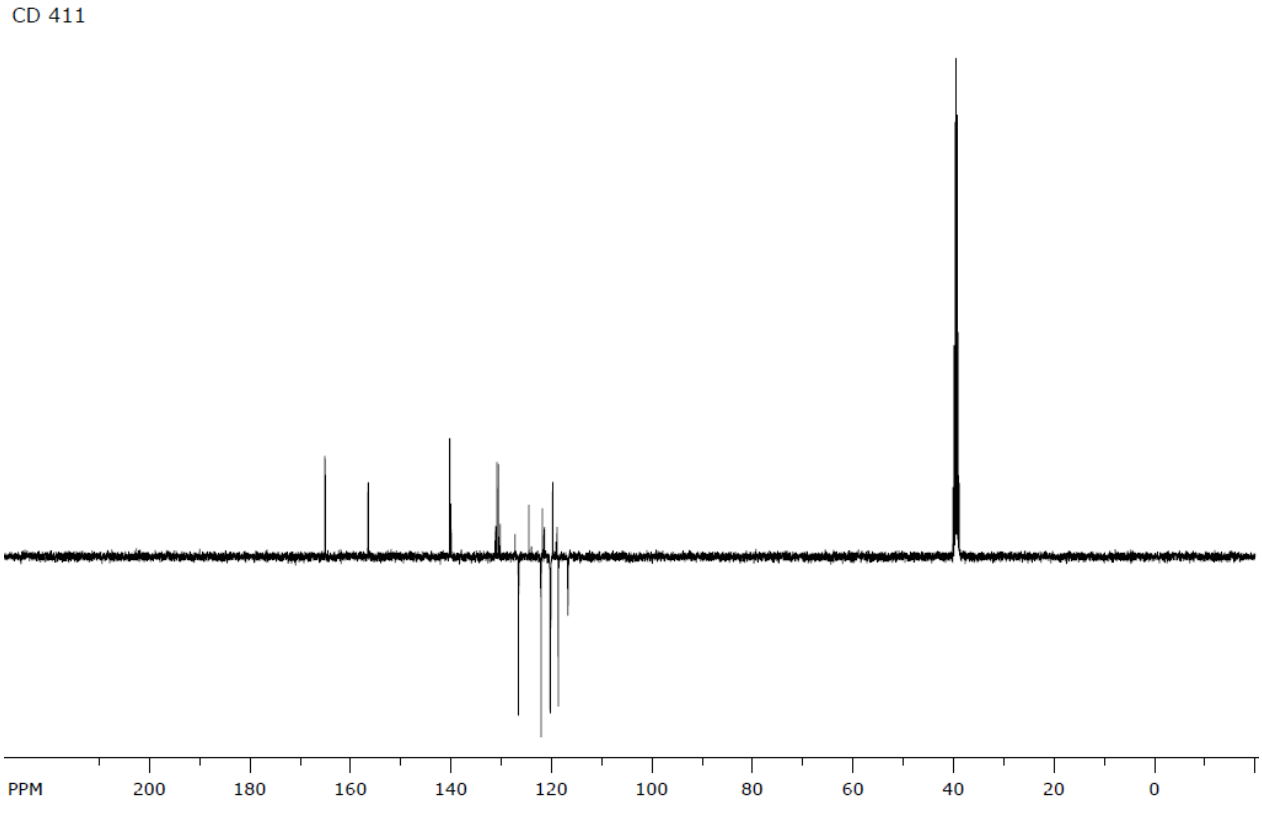


CD423

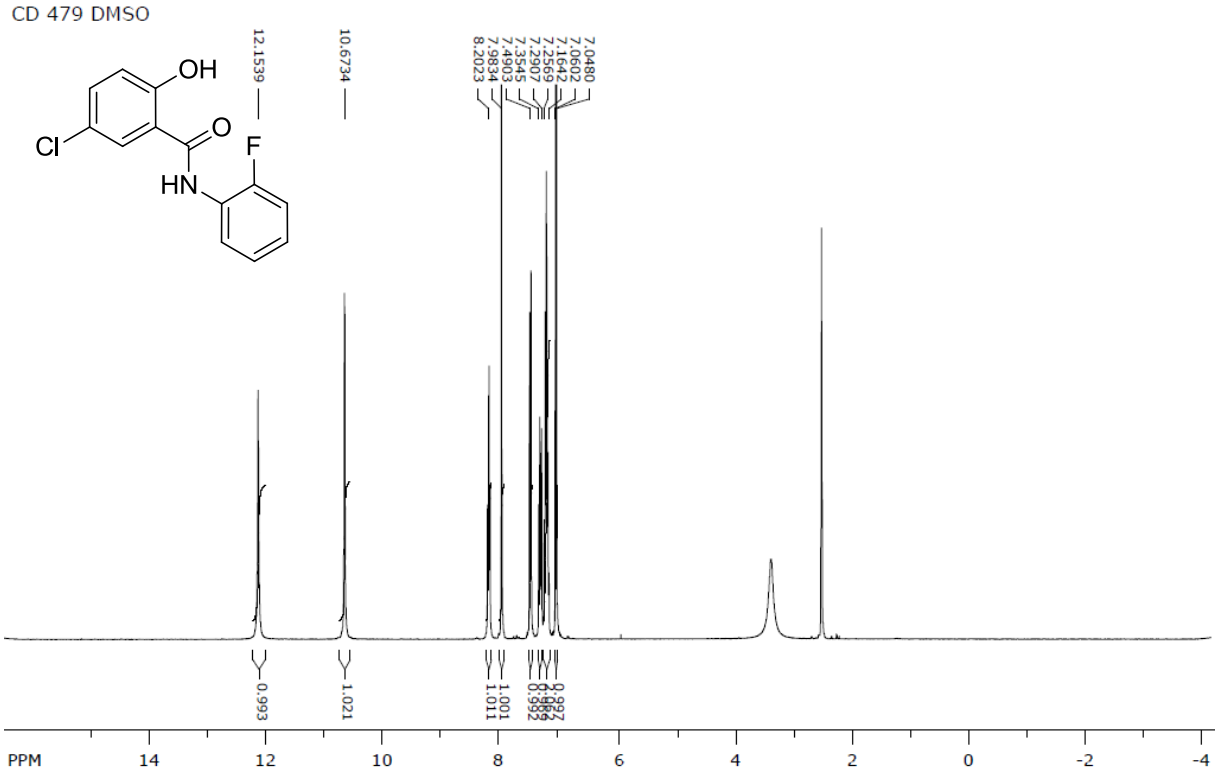


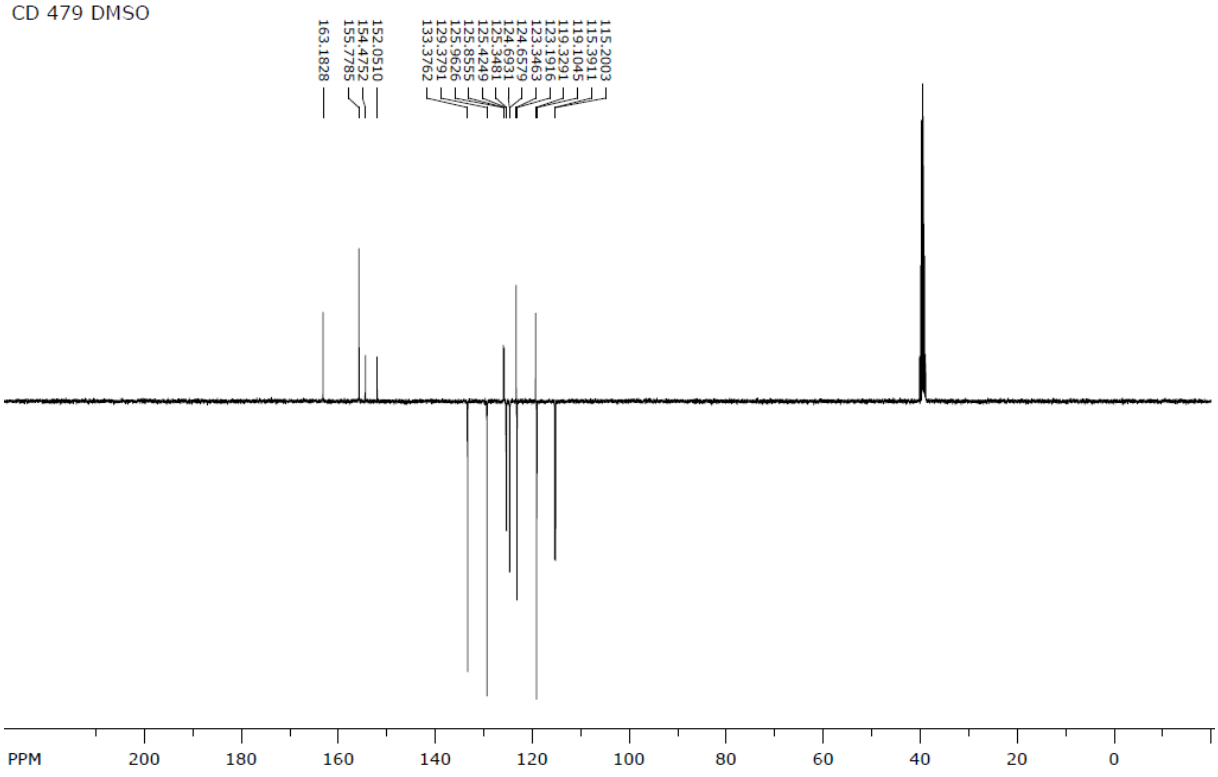
_N_-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxy-5-(trifluoromethoxy)benzamide (336)



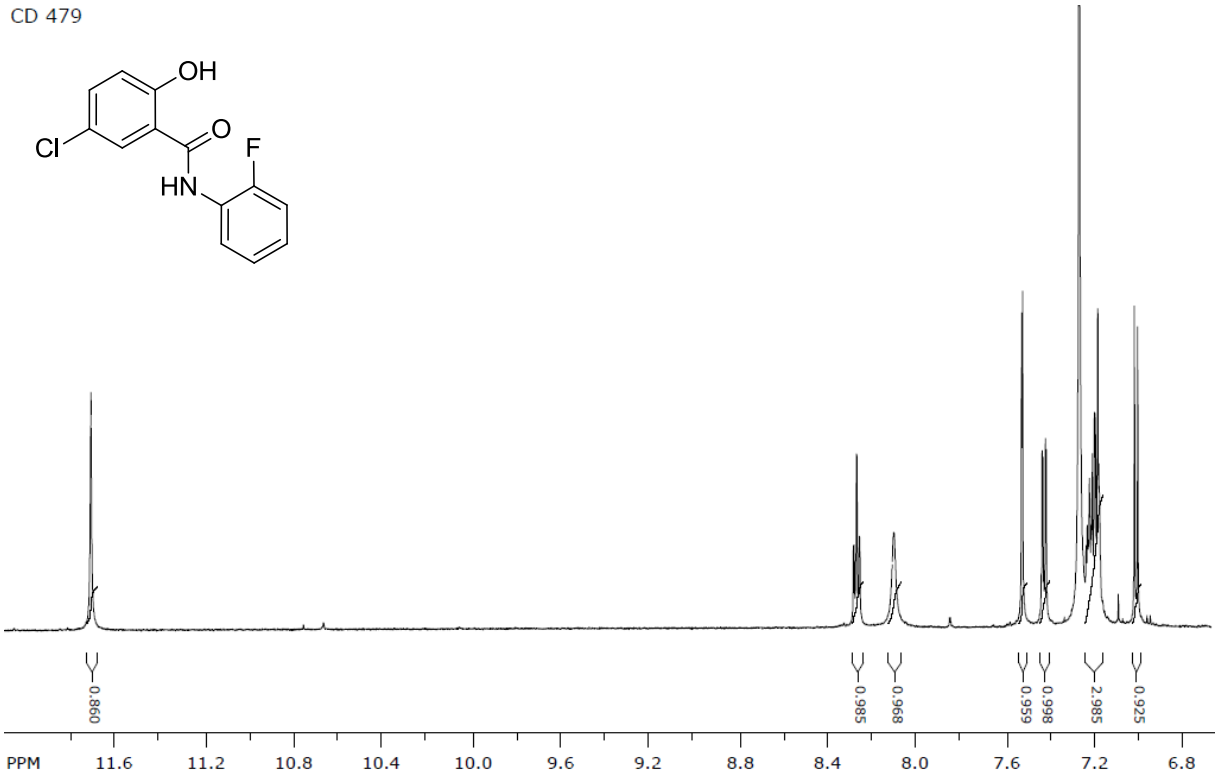


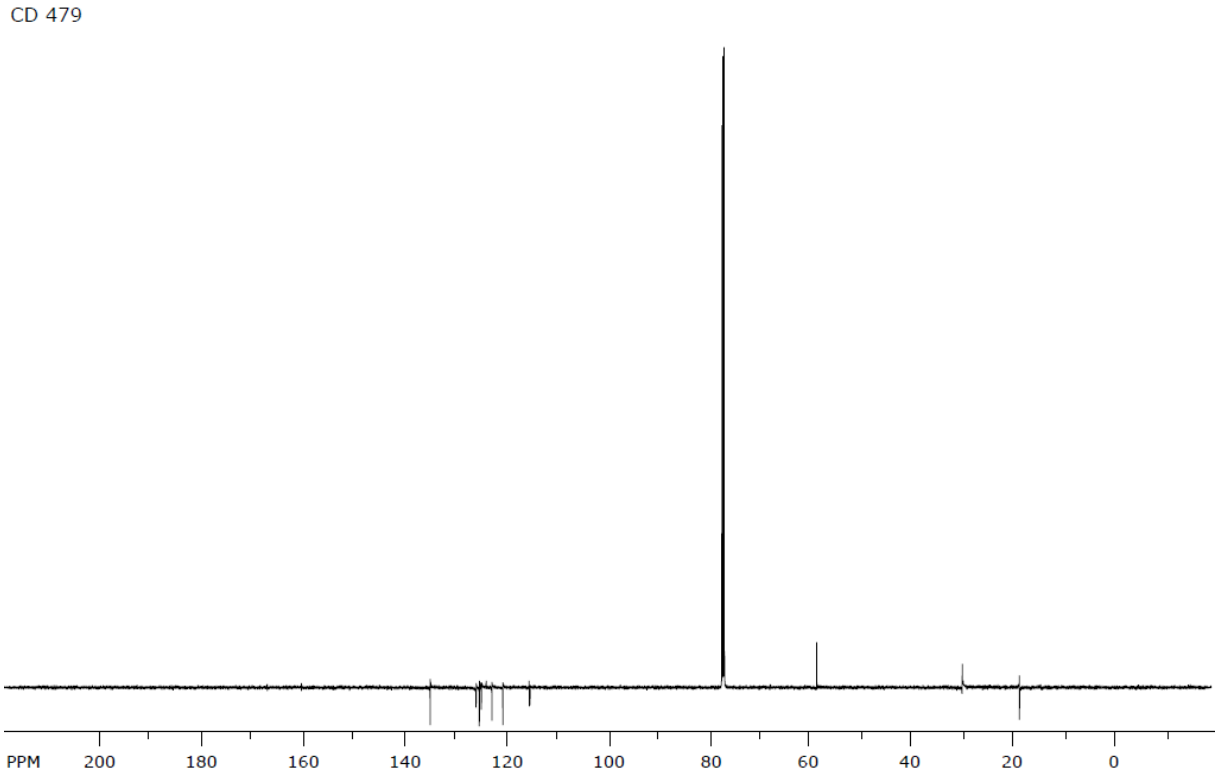
5-chloro-*N*-(2-fluorophenyl)-2-hydroxybenzamide (337)



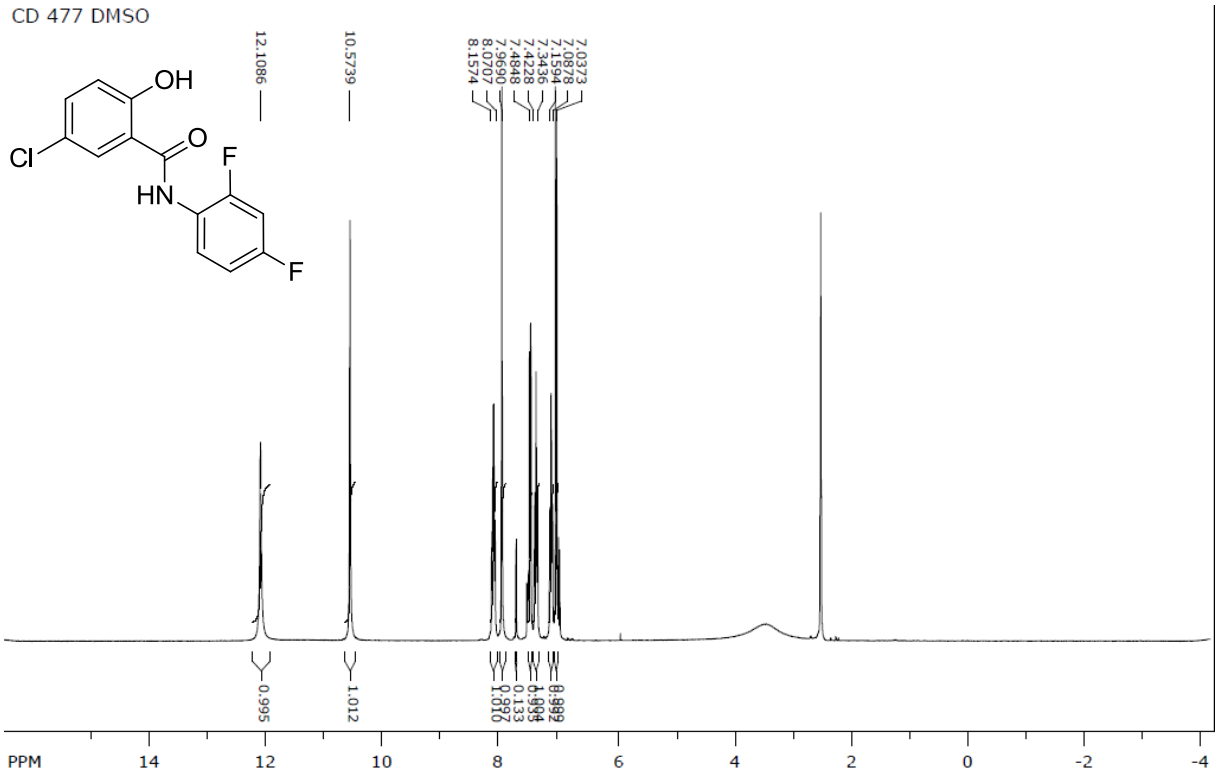


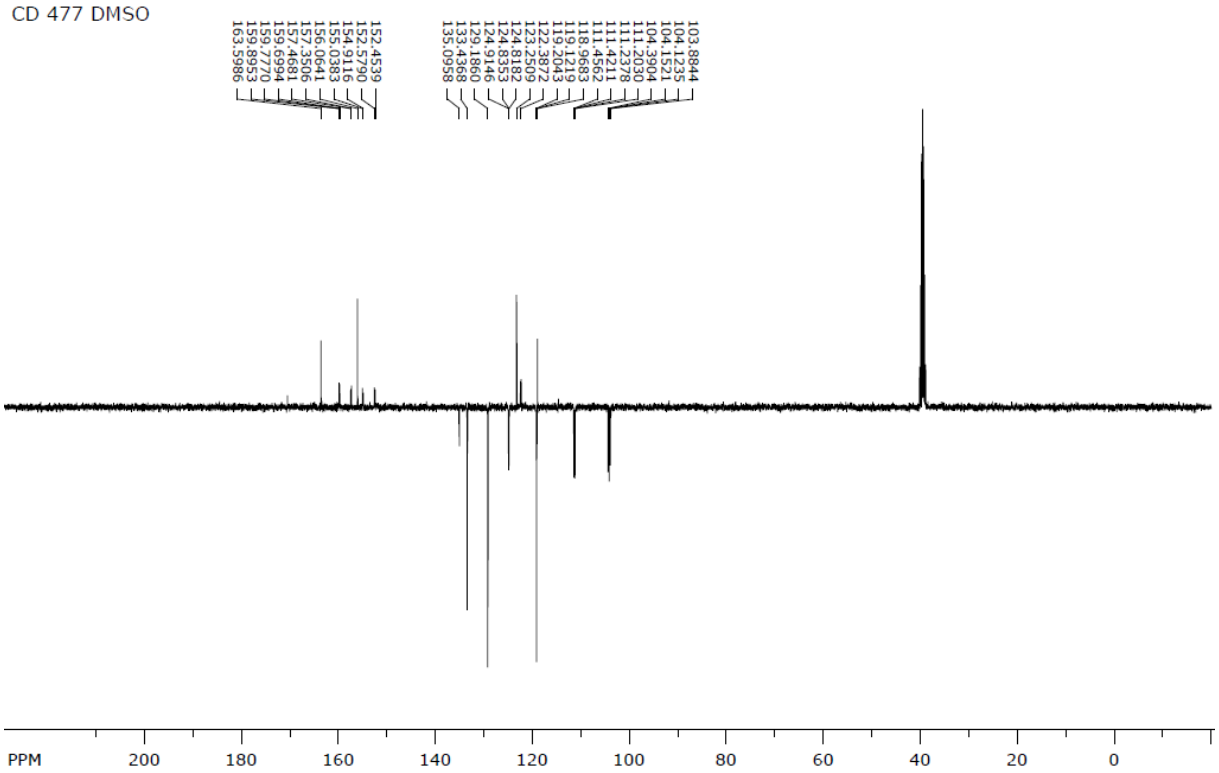
5-chloro-*N*-(2-fluorophenyl)-2-hydroxybenzamide (337)



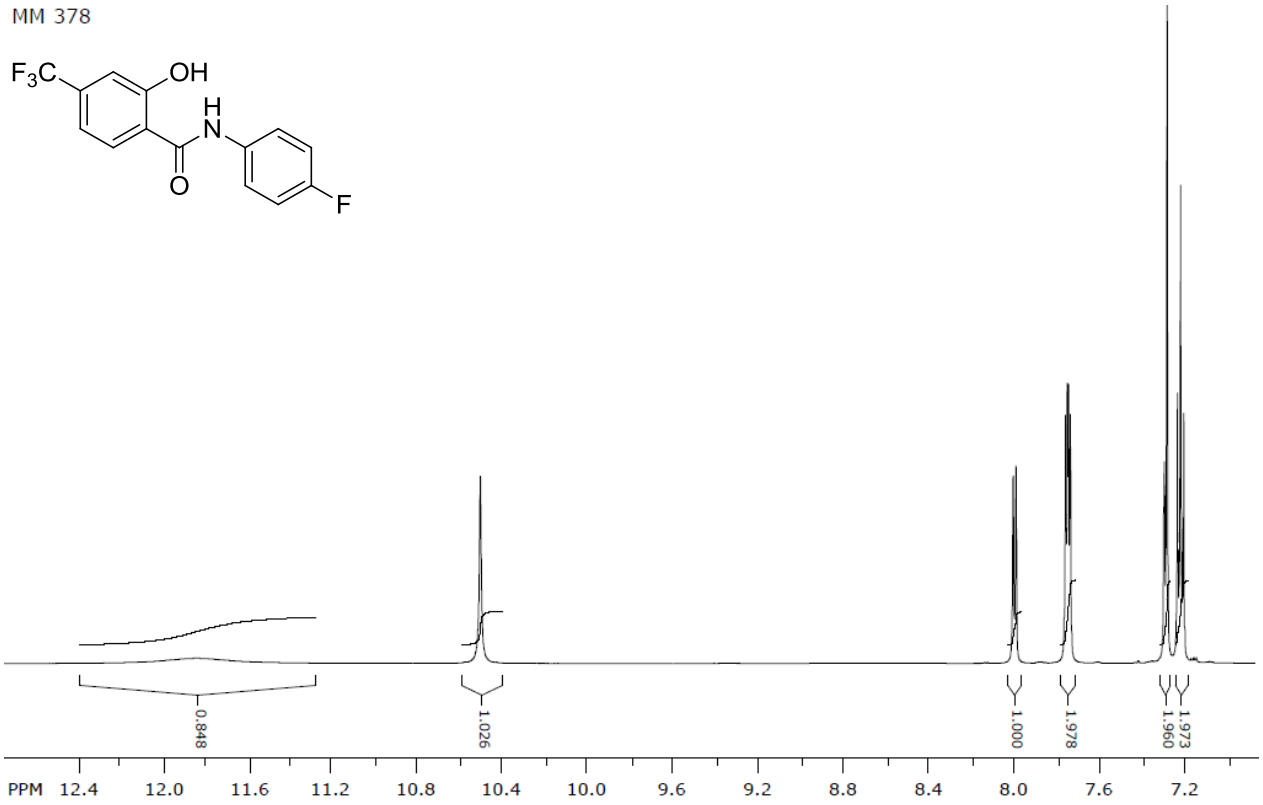


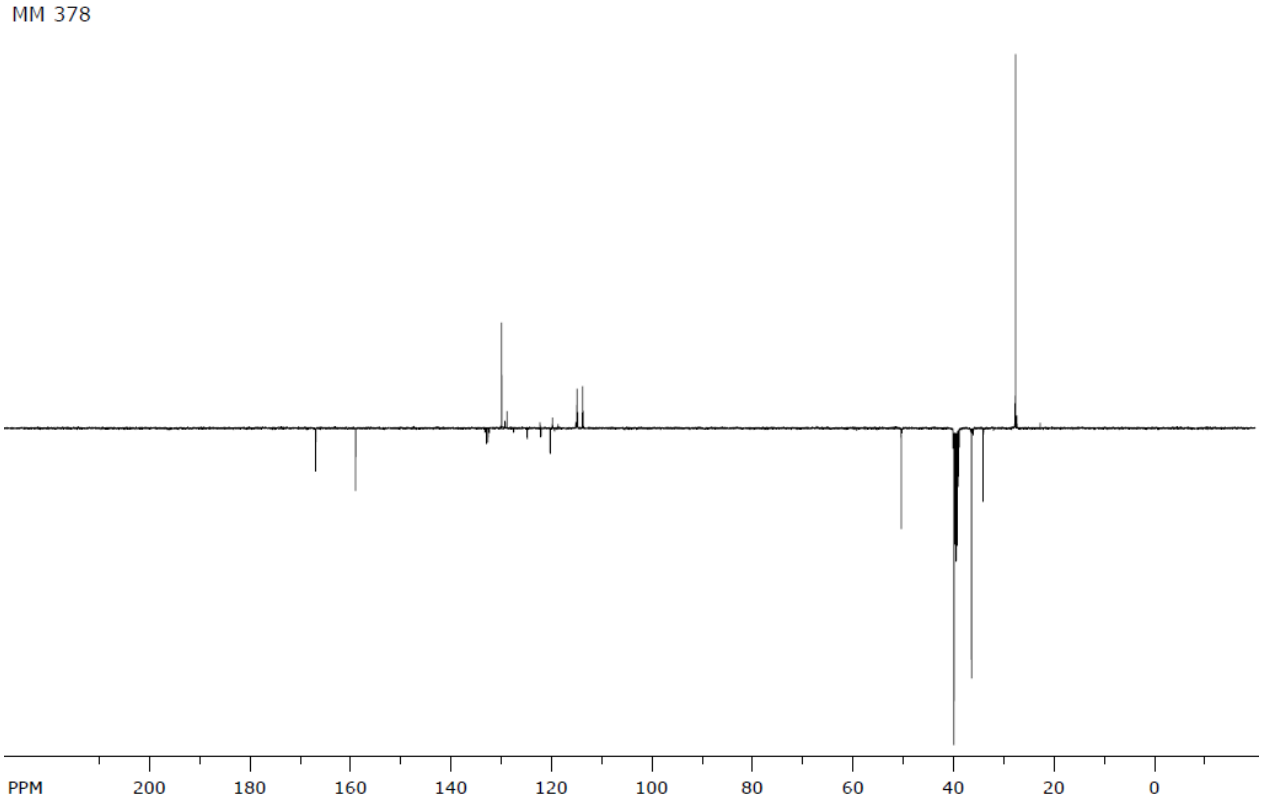
5-chloro-*N*-(2,4-difluorophenyl)-2-hydroxybenzamide (338)



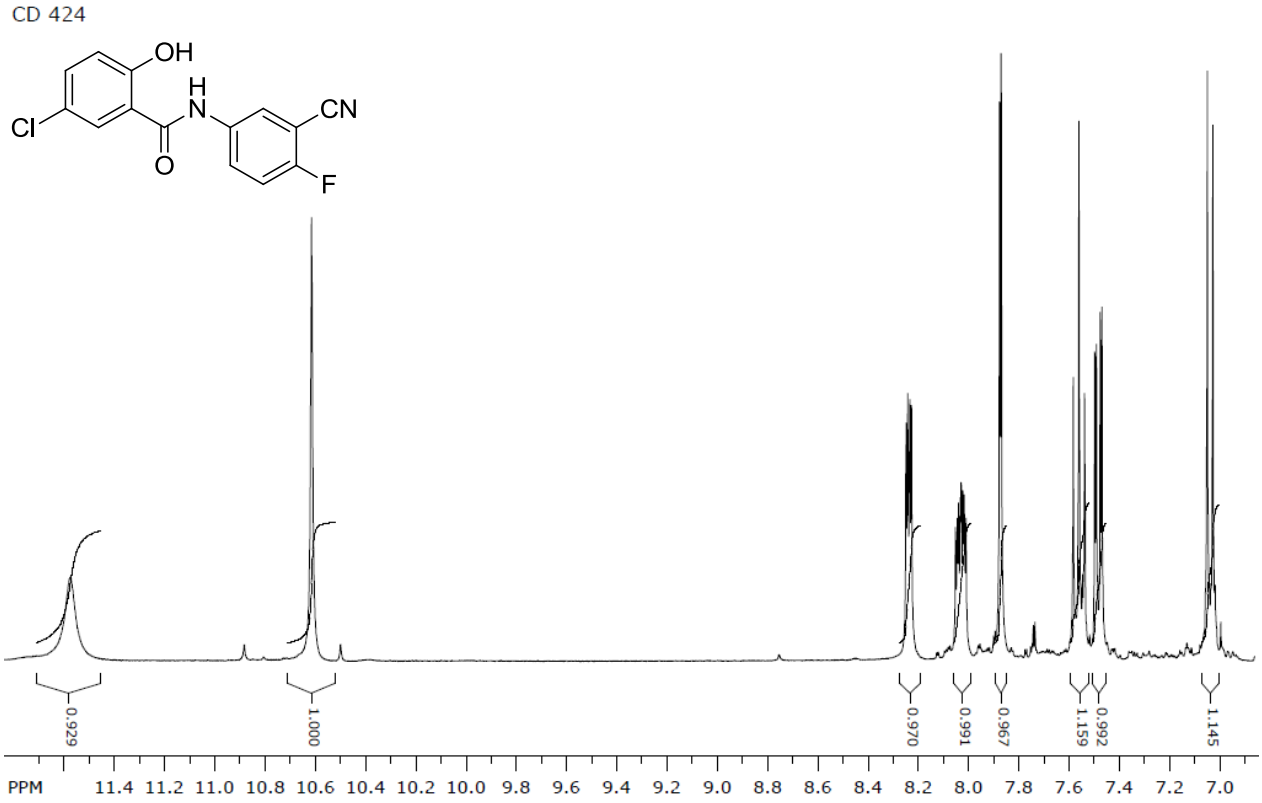


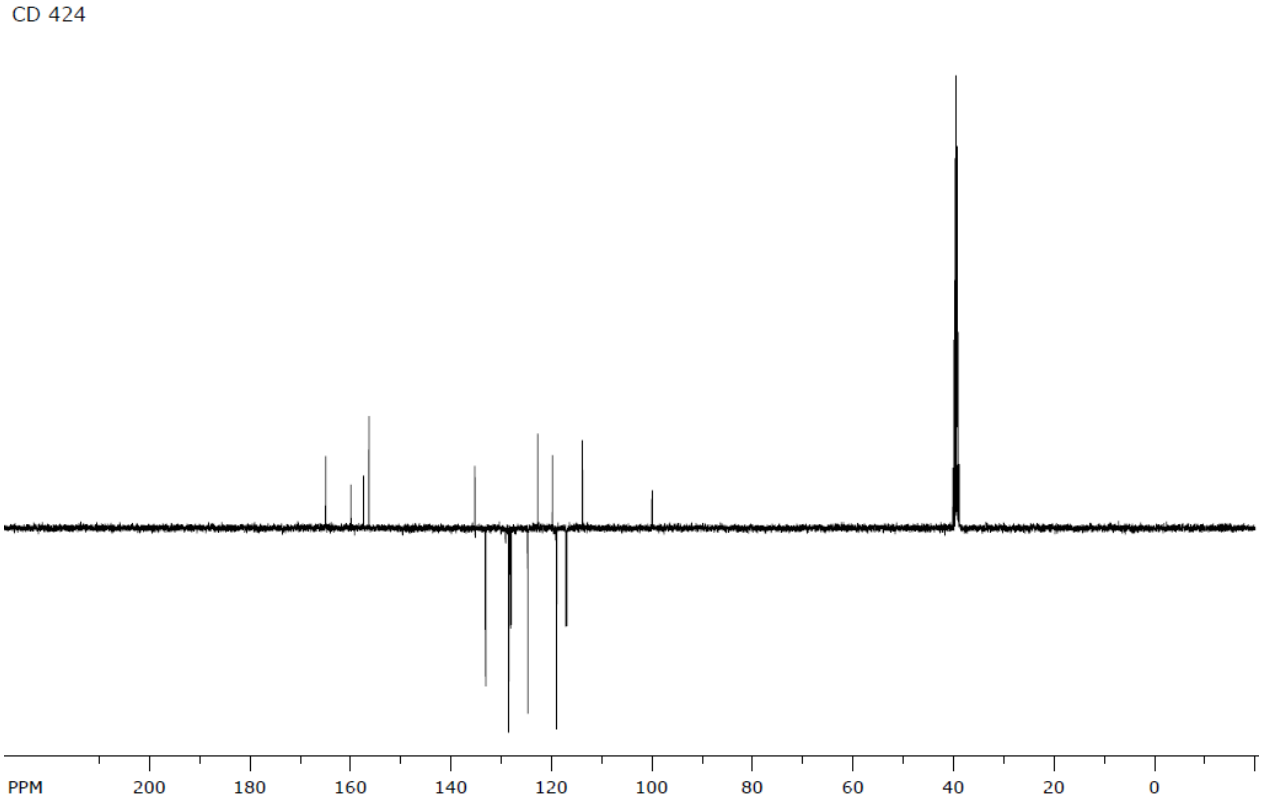
_N_-(4-fluorophenyl)-2-hydroxy-4-(trifluoromethyl)benzamide (345)





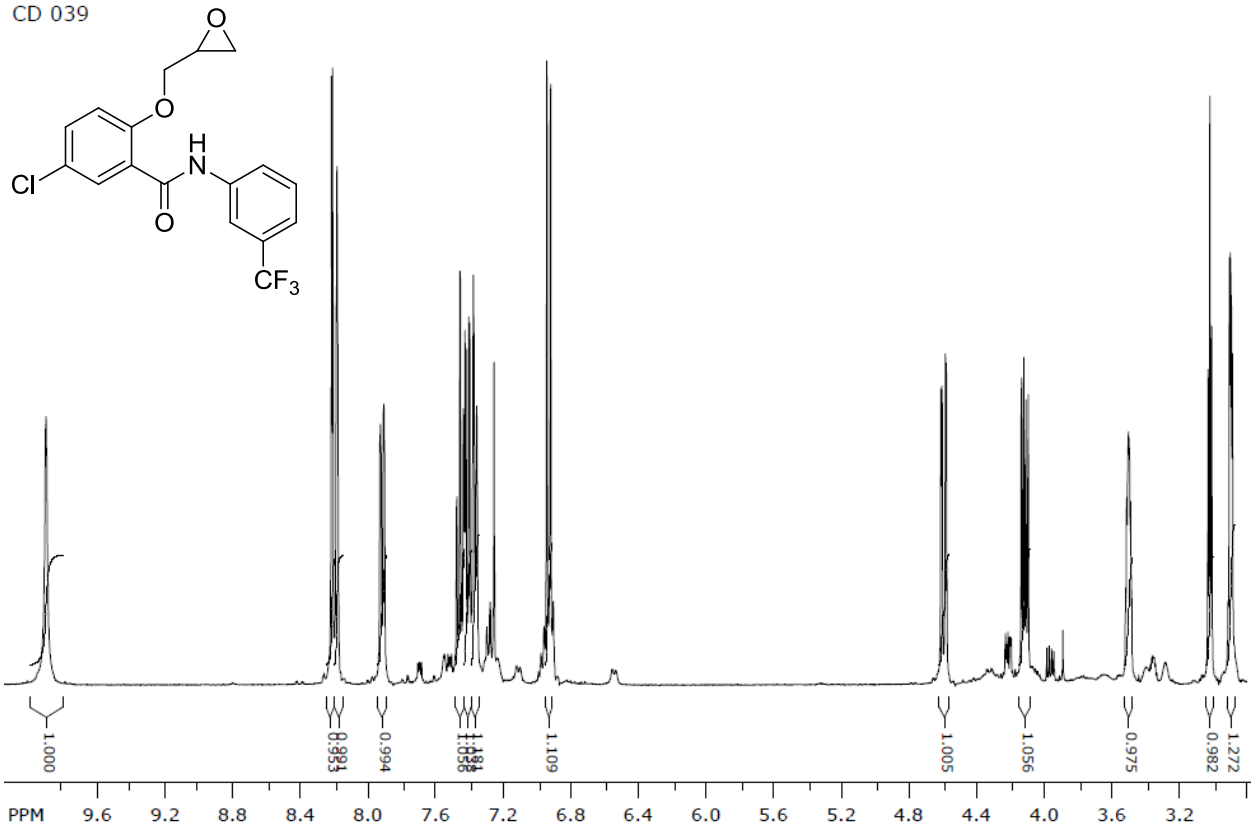
5-chloro-*N*-(3-cyano-4-fluorophenyl)-2-hydroxybenzamide (346)

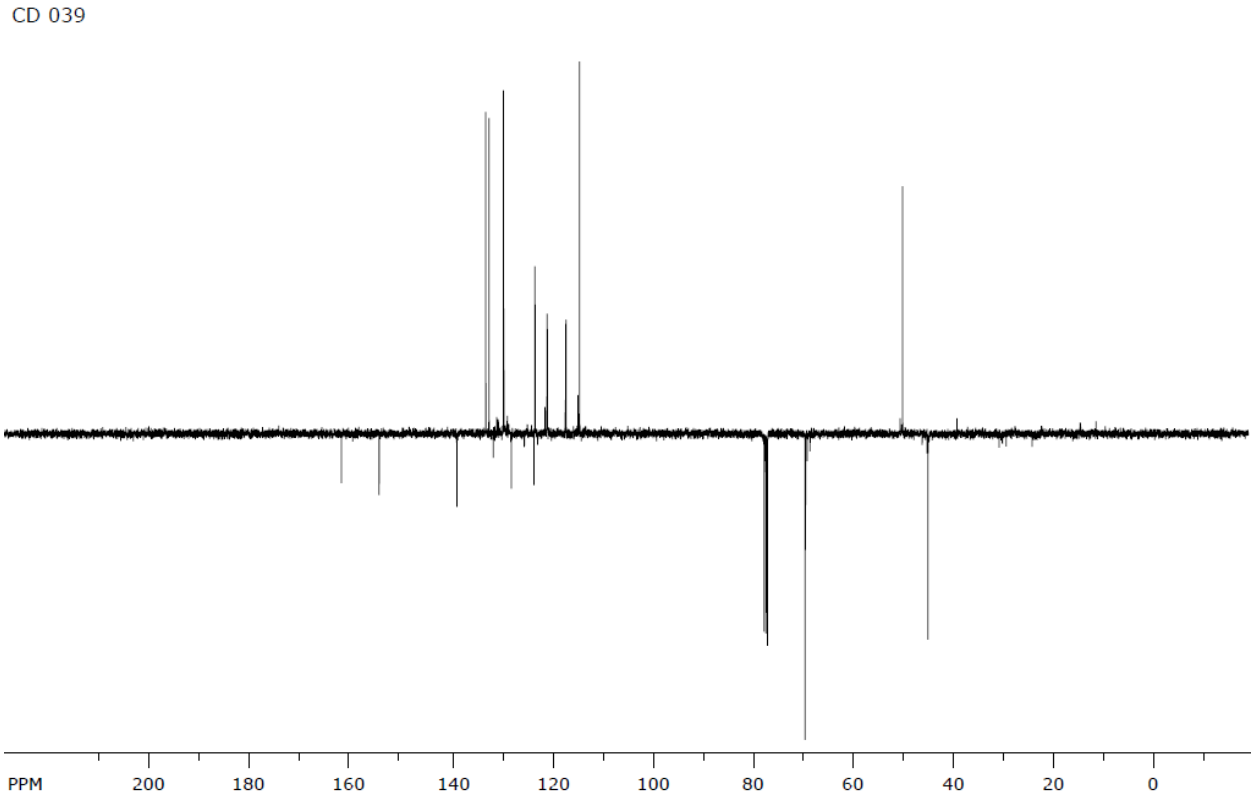




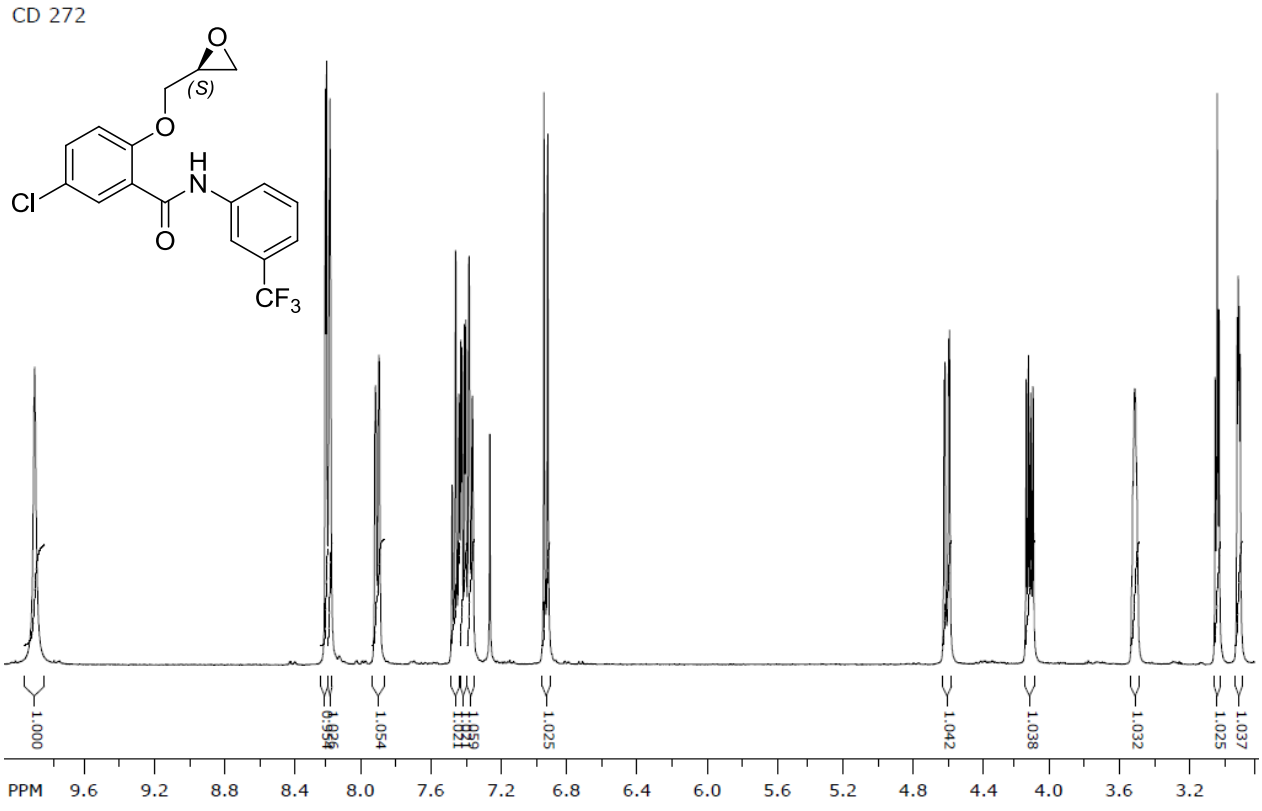
4.4.2 Epoxides

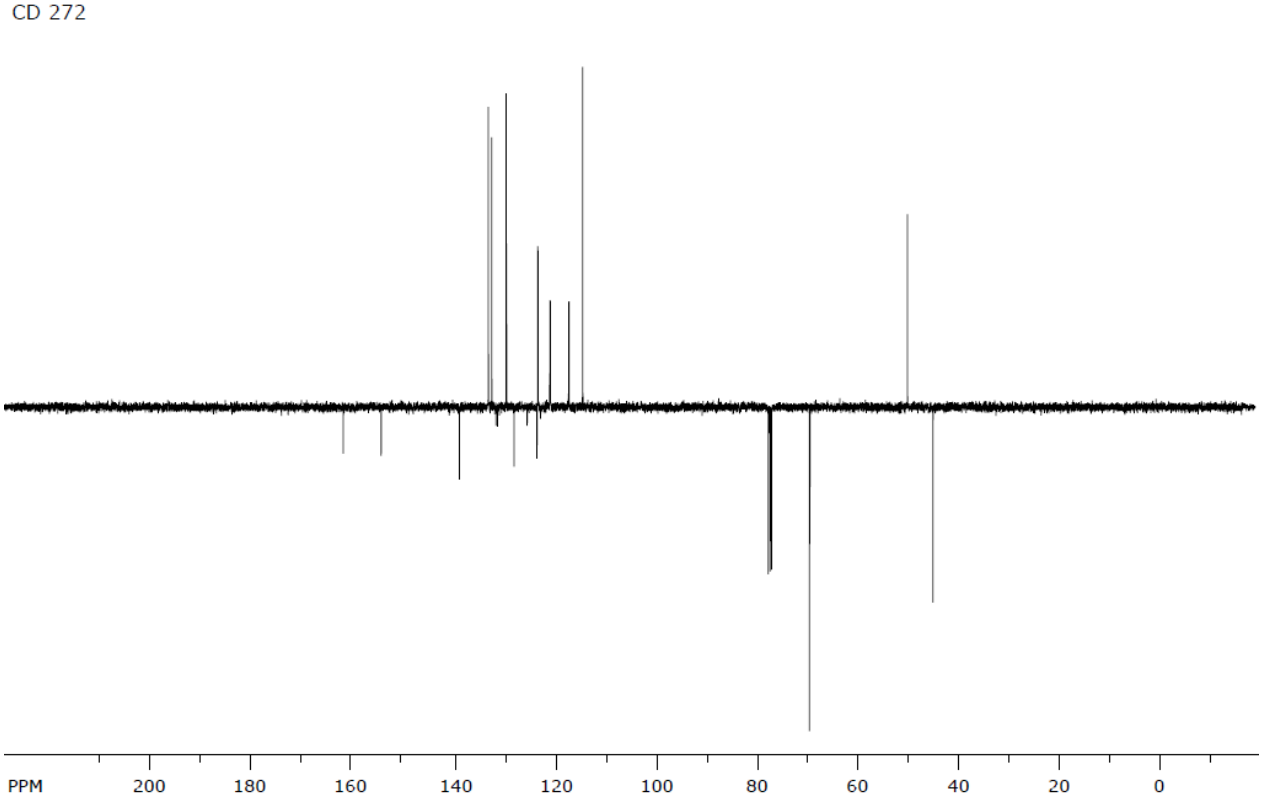
5-chloro-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (71)



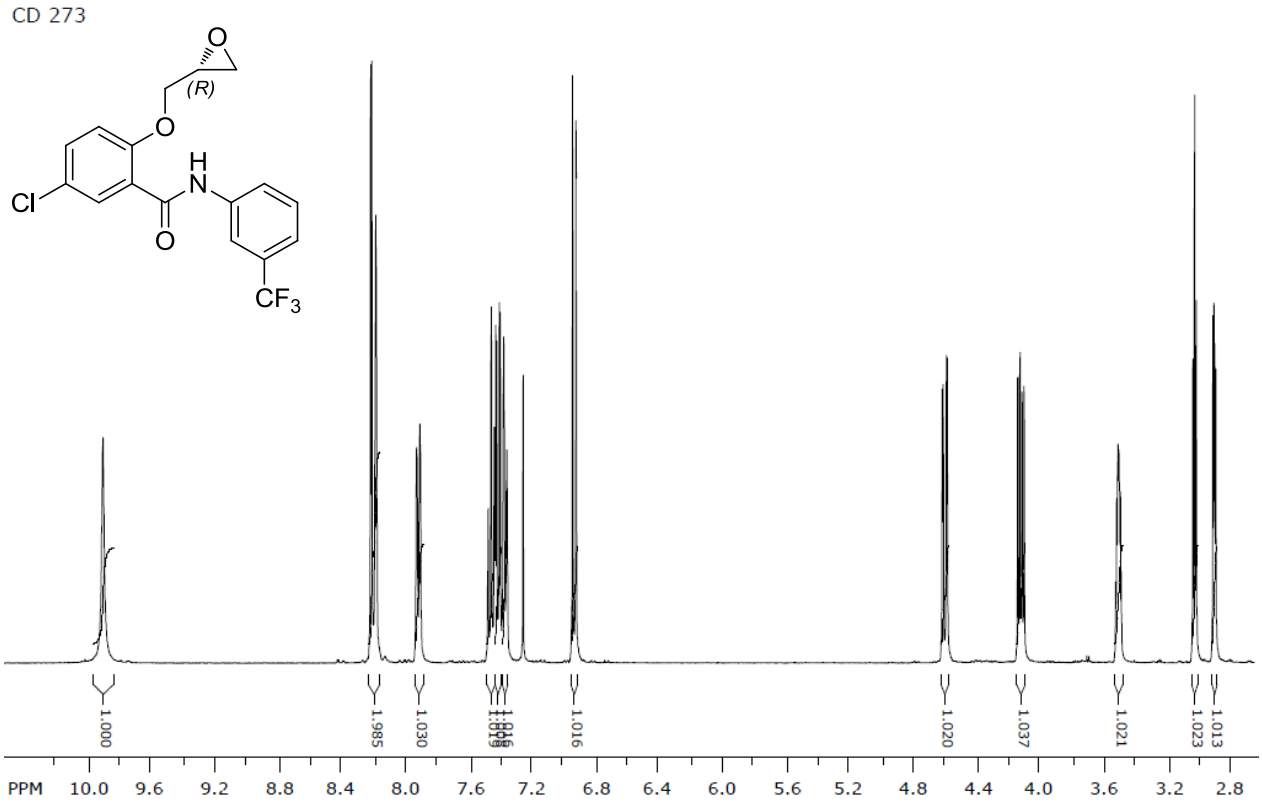


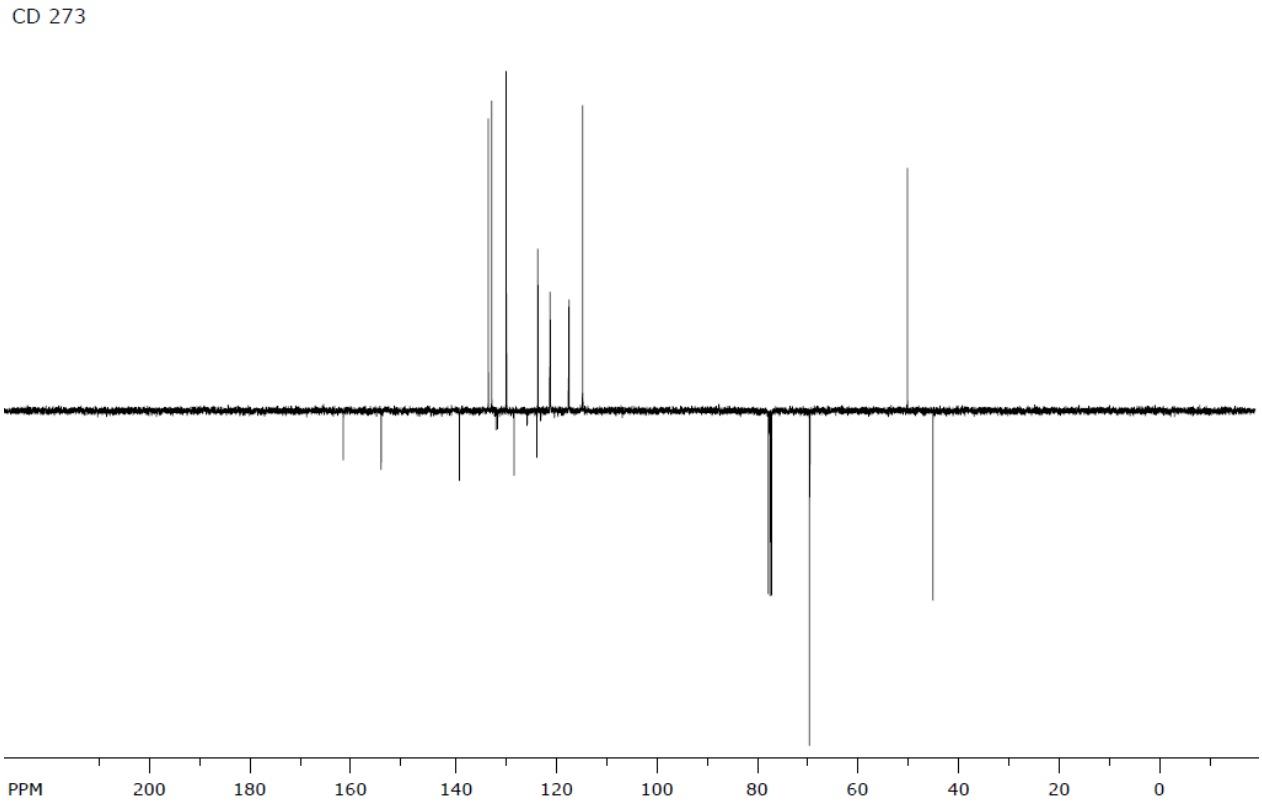
(*S*)-(-)-5-chloro-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (99)



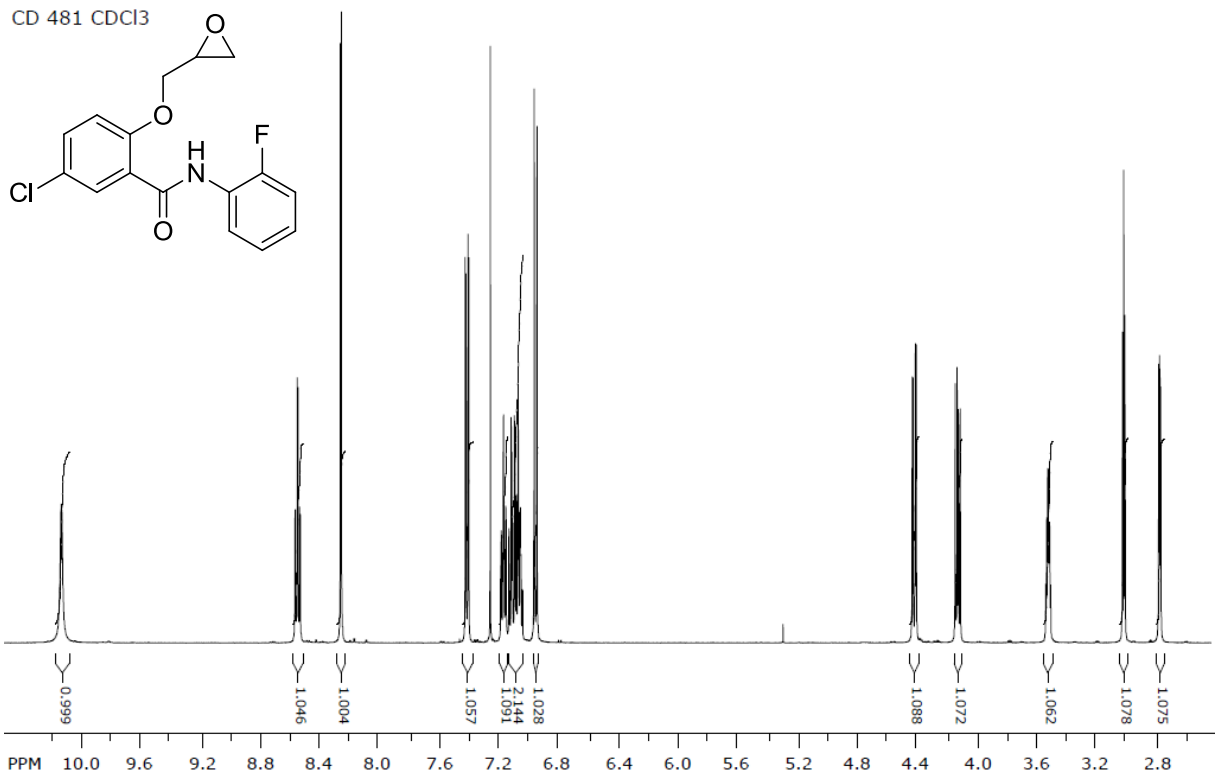


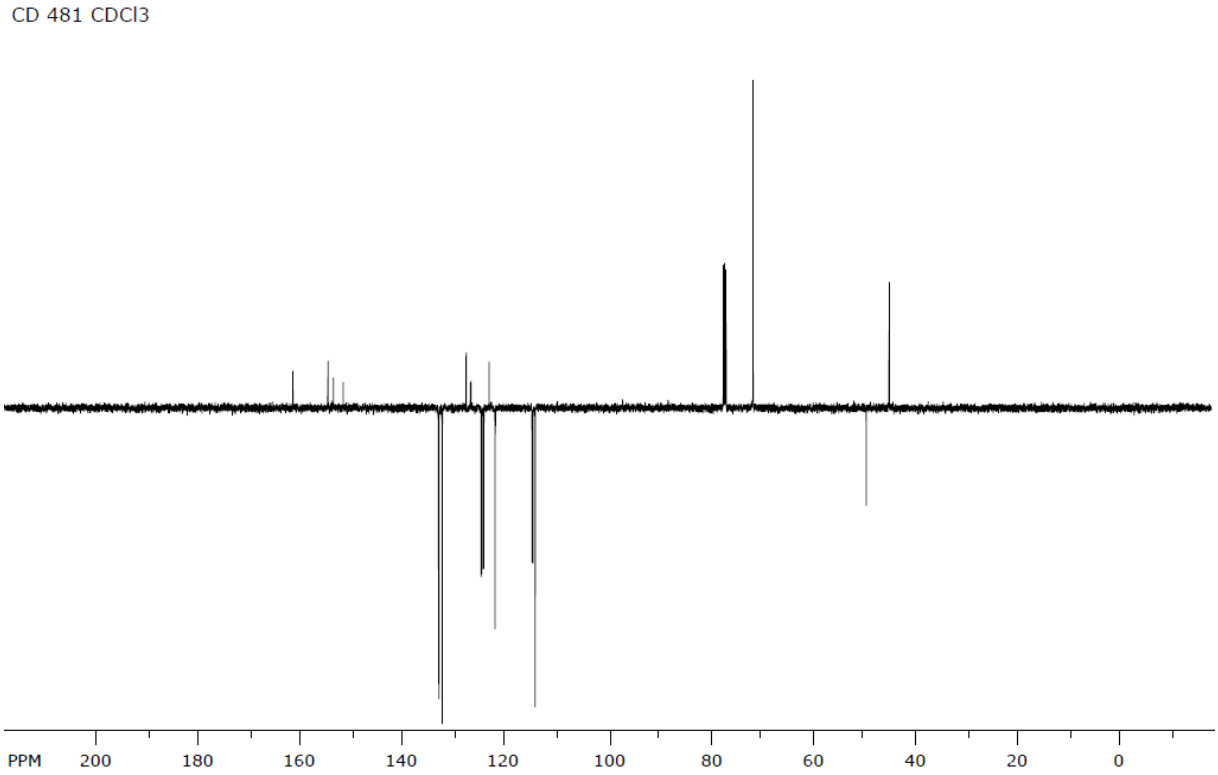
(*R*)-(+)-5-chloro-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (100)



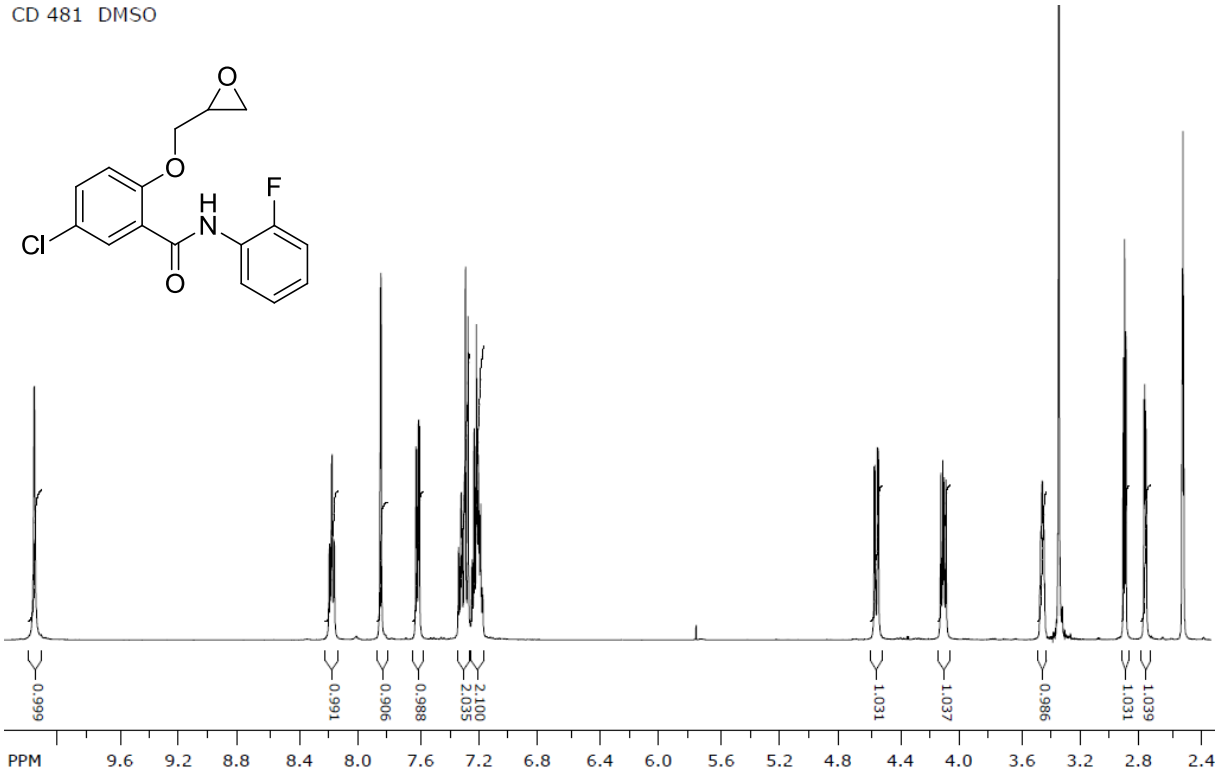


5-chloro-*N*-(2-fluorophenyl)-2-(oxiran-2-ylmethoxy)benzamide (288)

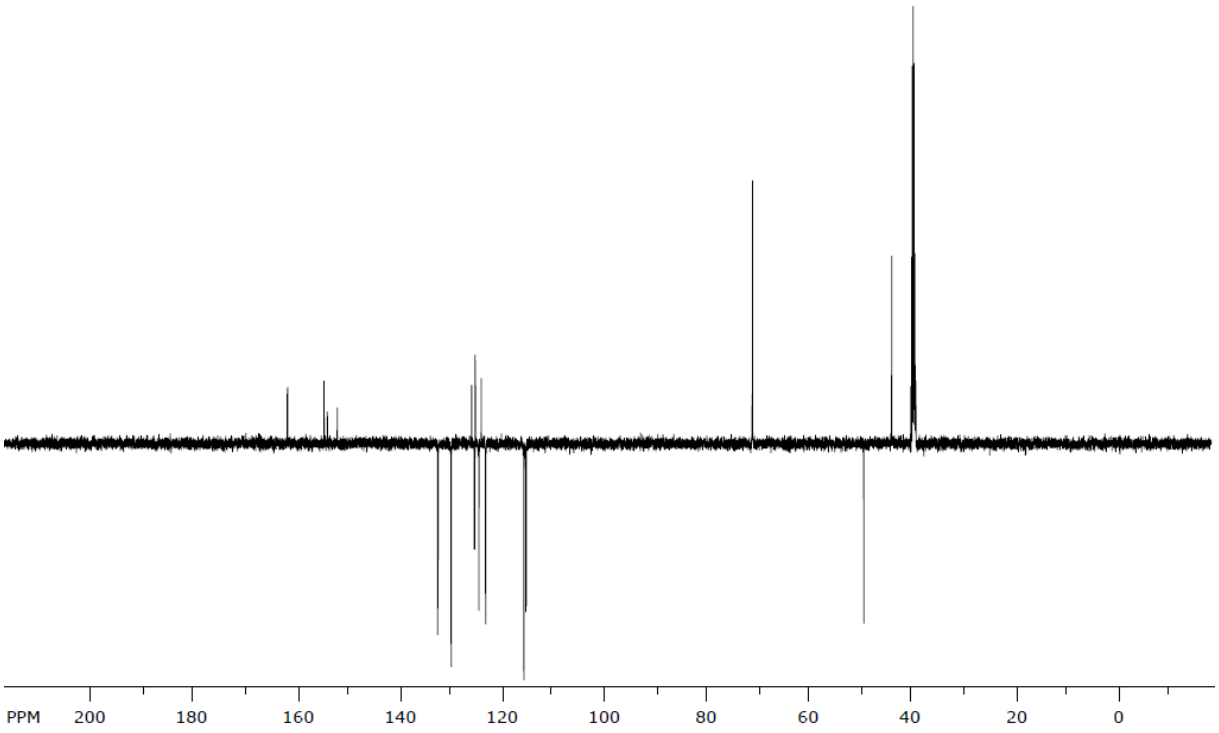




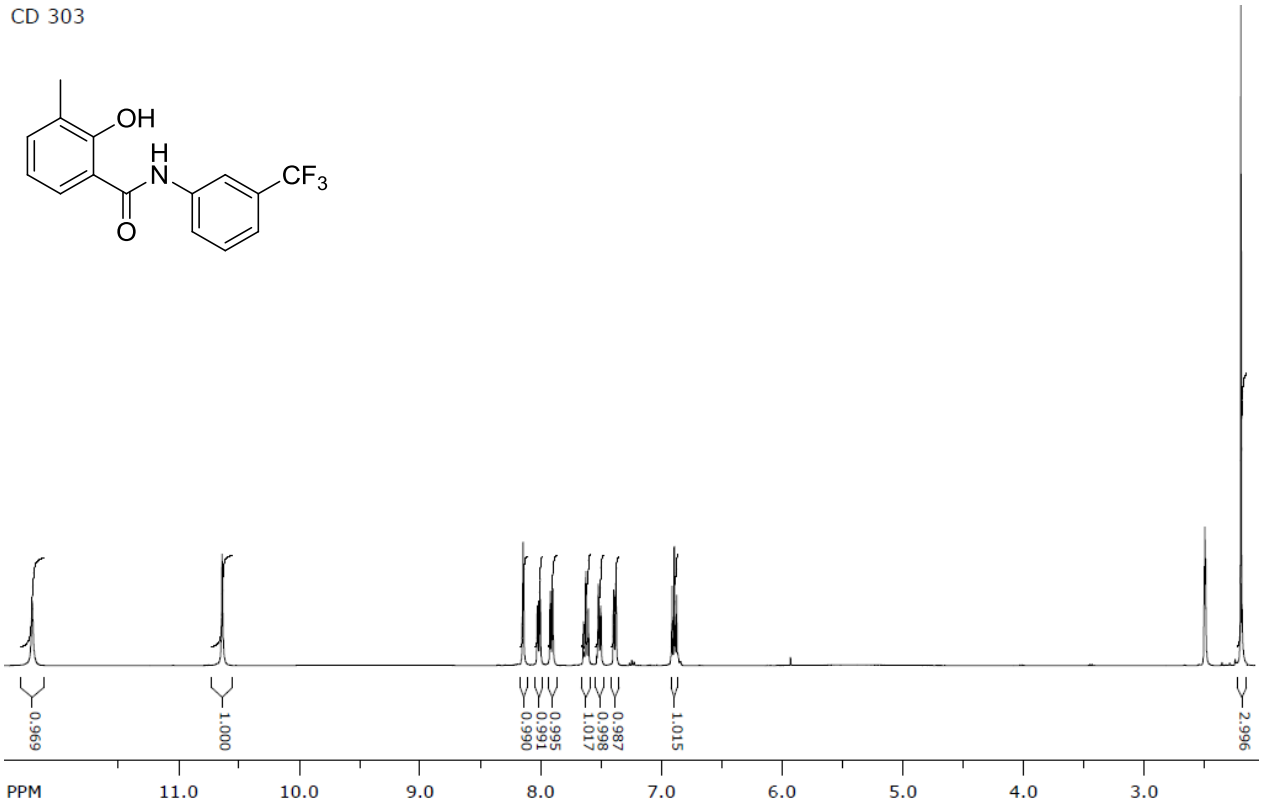
CD 481 DMSO

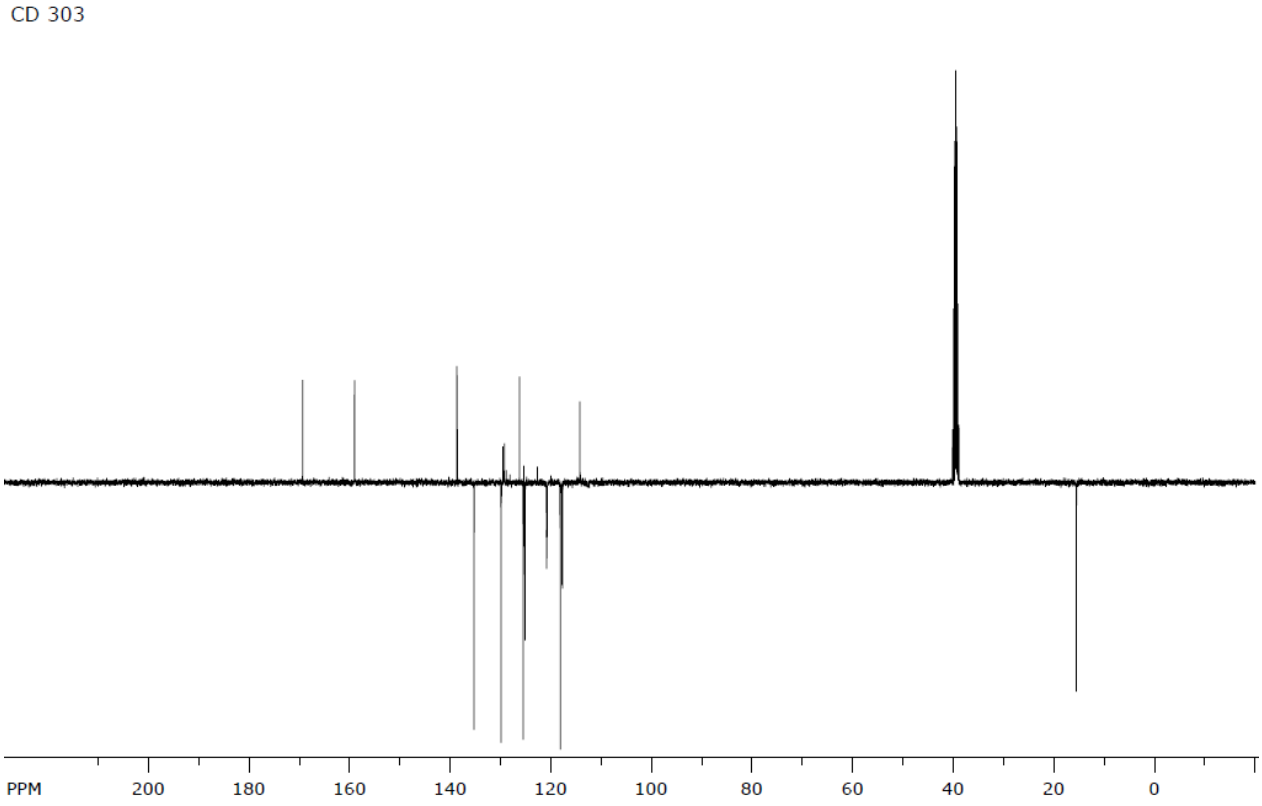


CD 481 DMSO

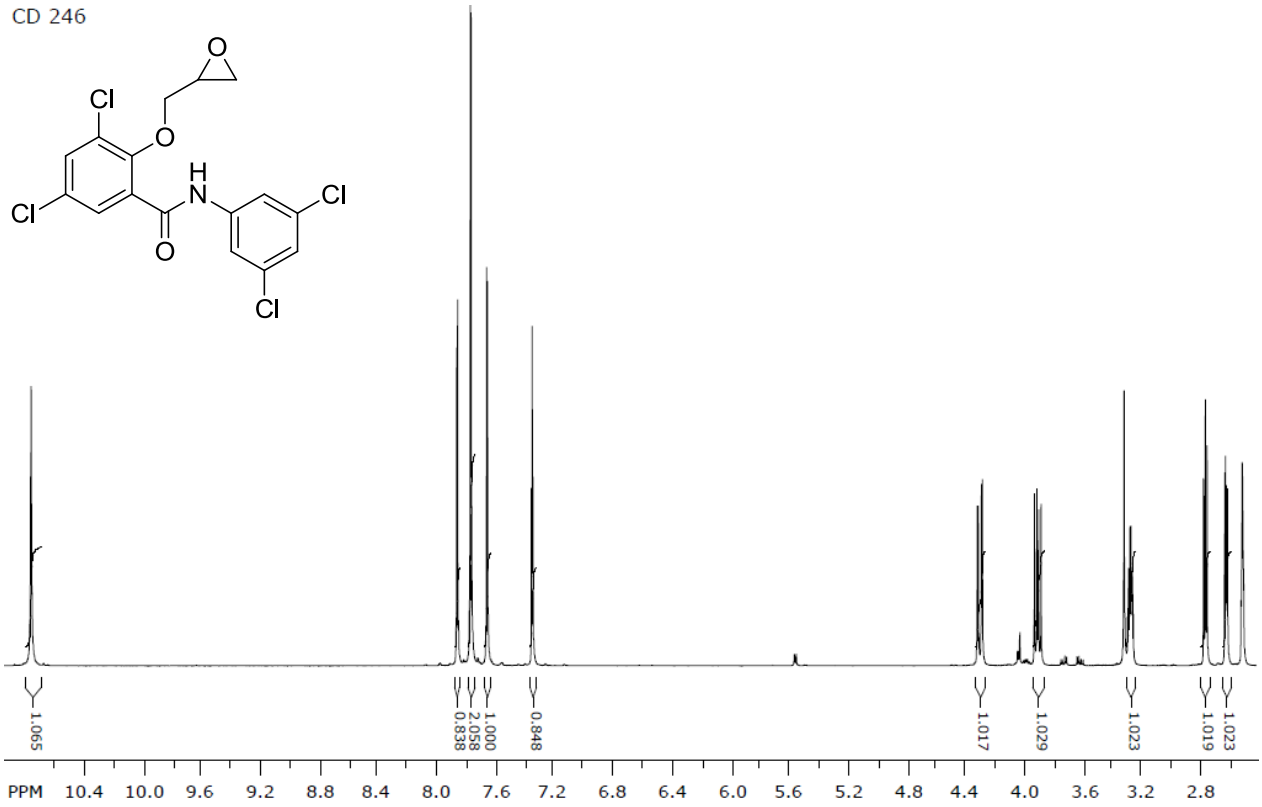


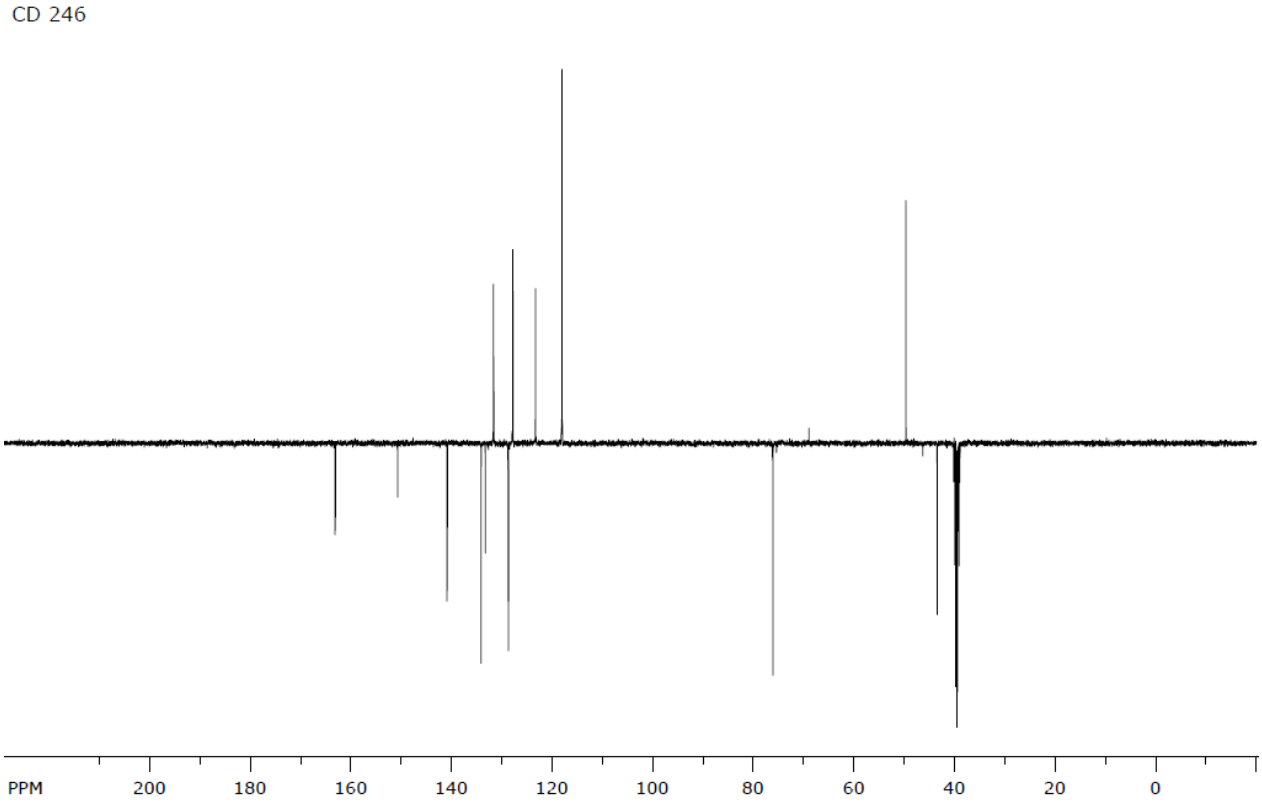
2-hydroxy-3-methyl-*N*-(3-(trifluoromethyl)phenyl)benzamide (323)



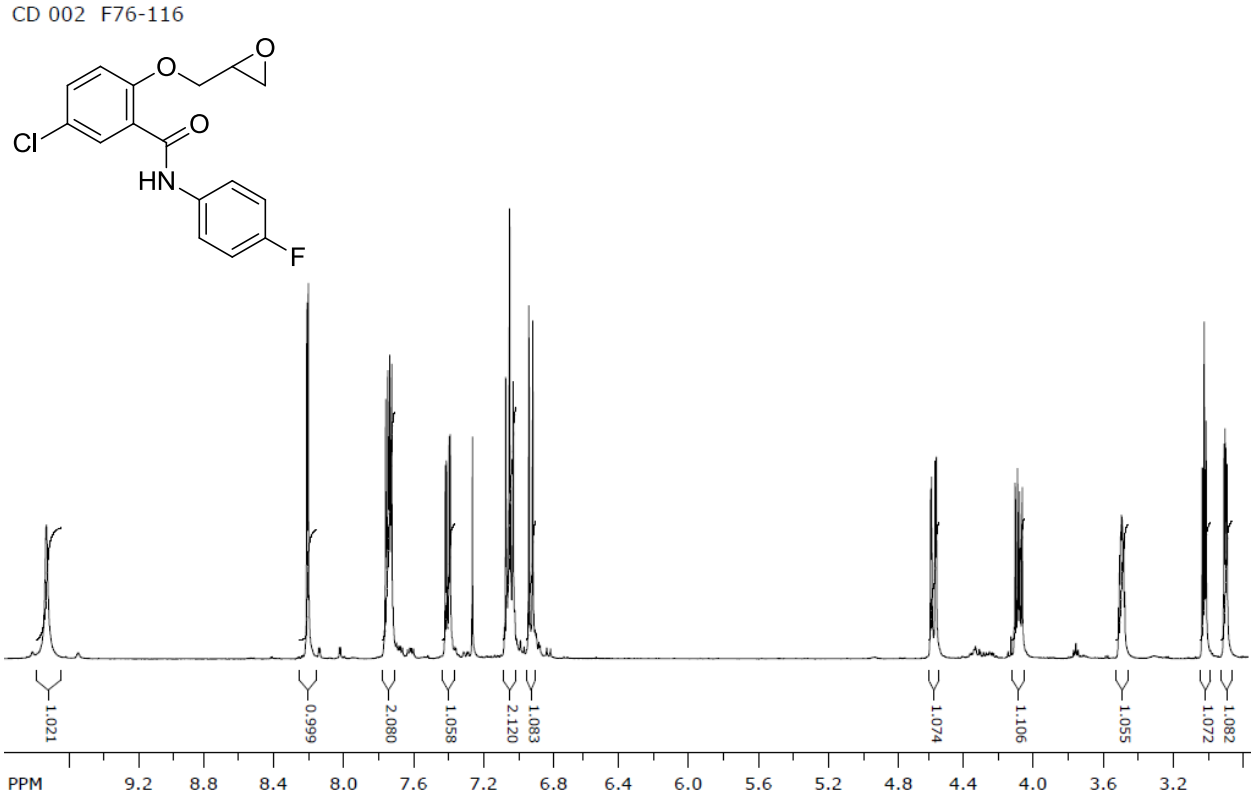


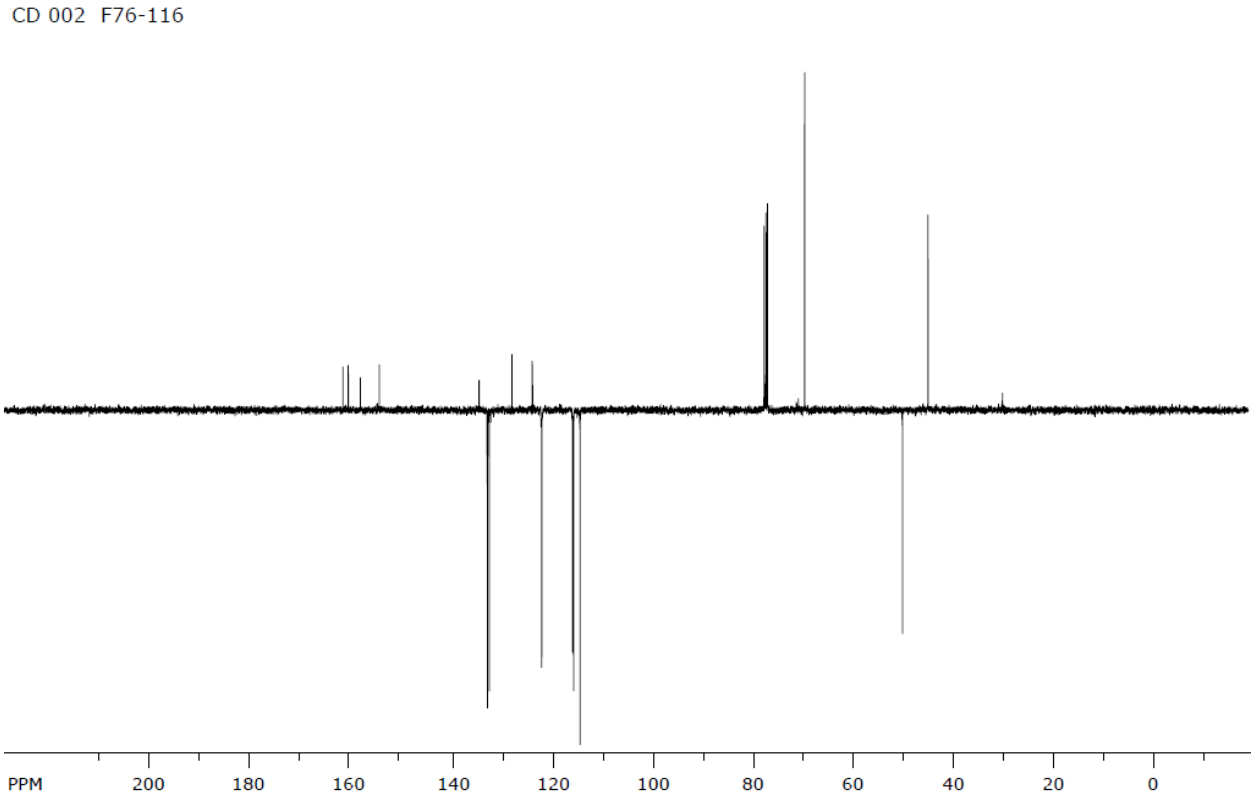
3,5-dichloro-*N*-(3,5-dichlorophenyl)-2-(oxiran-2-ylmethoxy)benzamide (347)





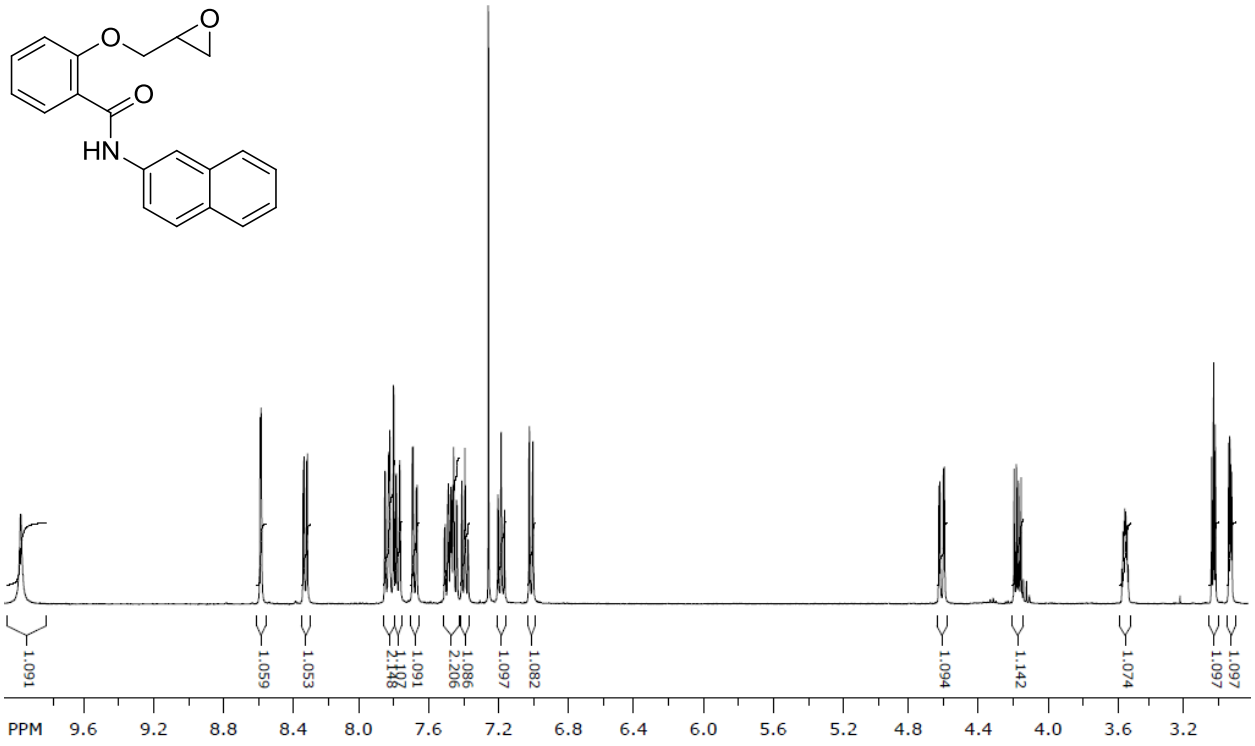
5-chloro-*N*-(4-fluorophenyl)-2-(oxiran-2-ylmethoxy)benzamide (348)



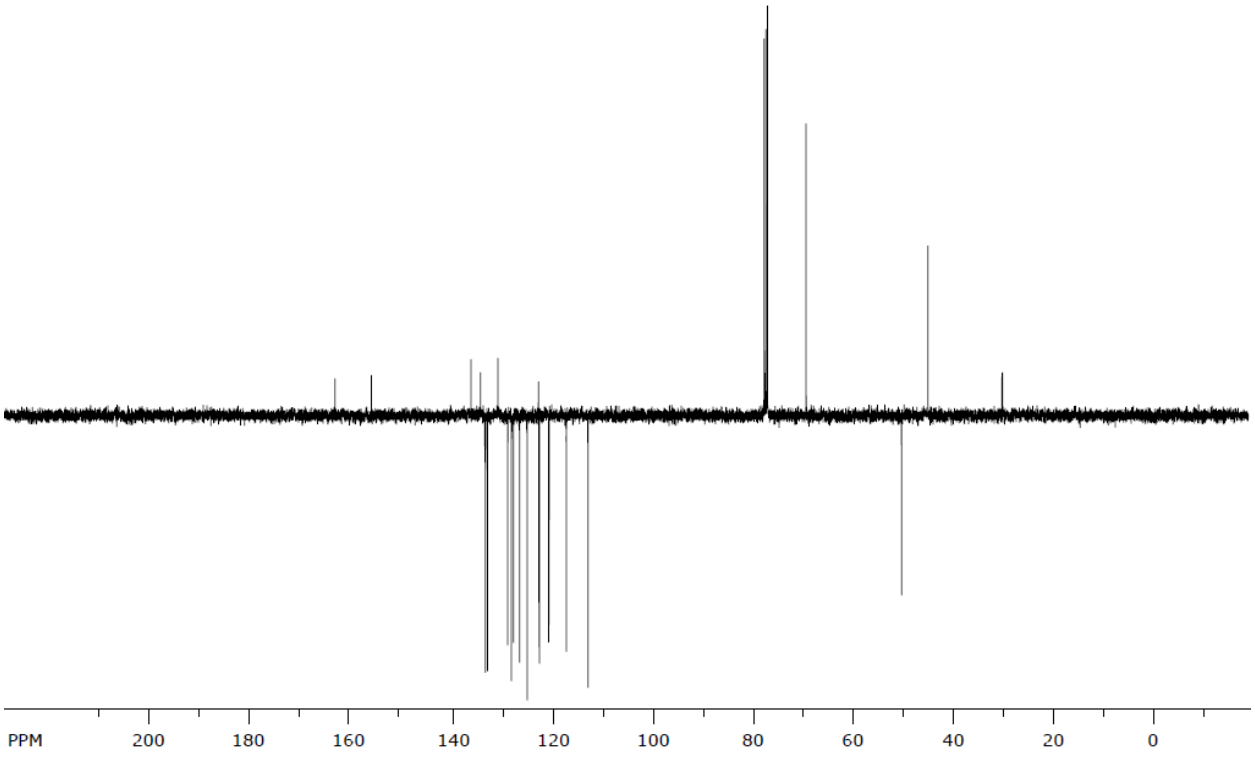


N-(naphthalen-2-yl)-2-(oxiran-2-ylmethoxy)benzamide (349)

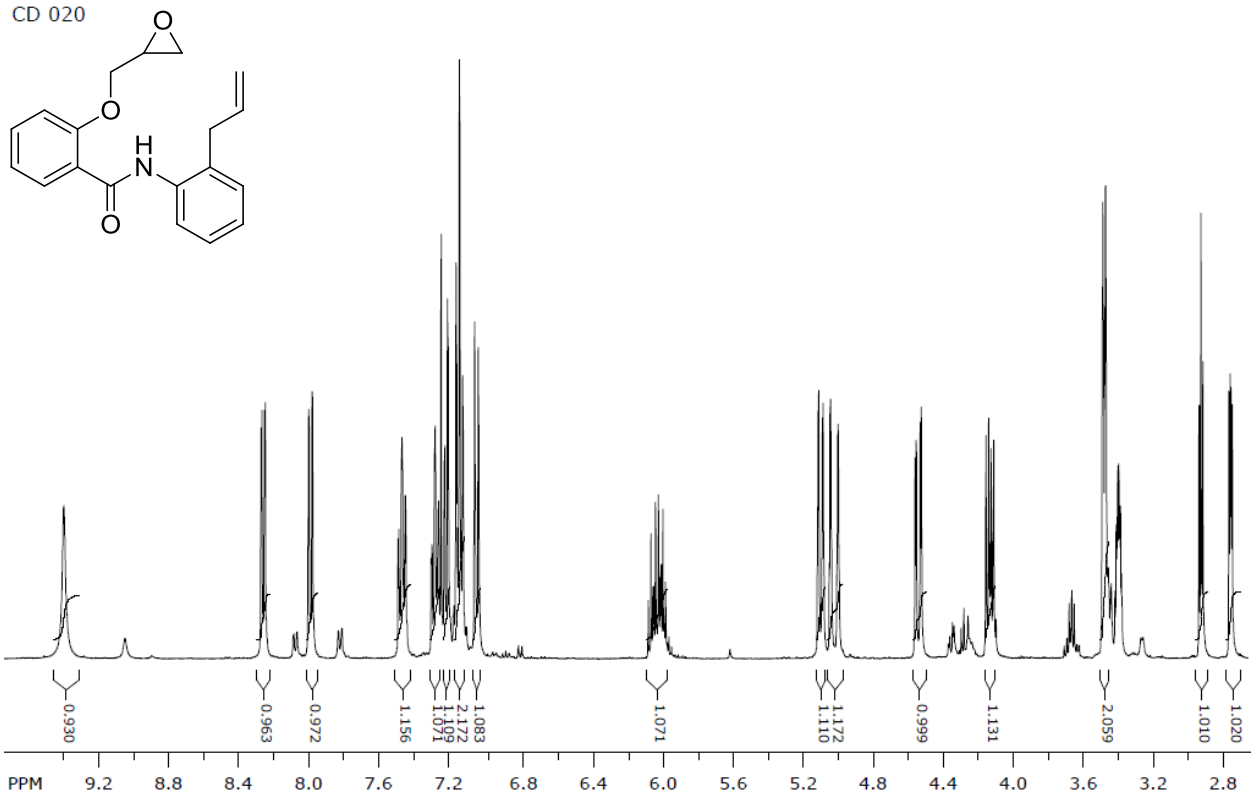
CD 014 F11-25

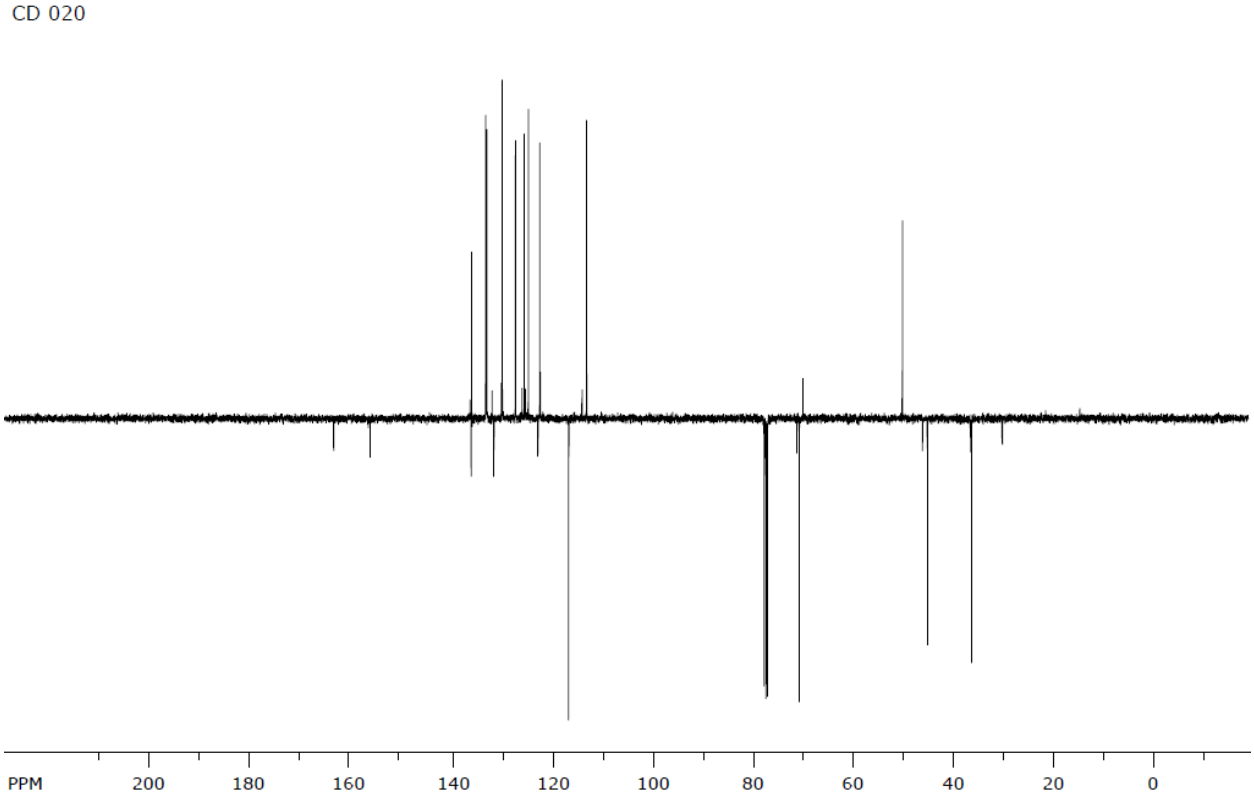


CD 014 F11-25

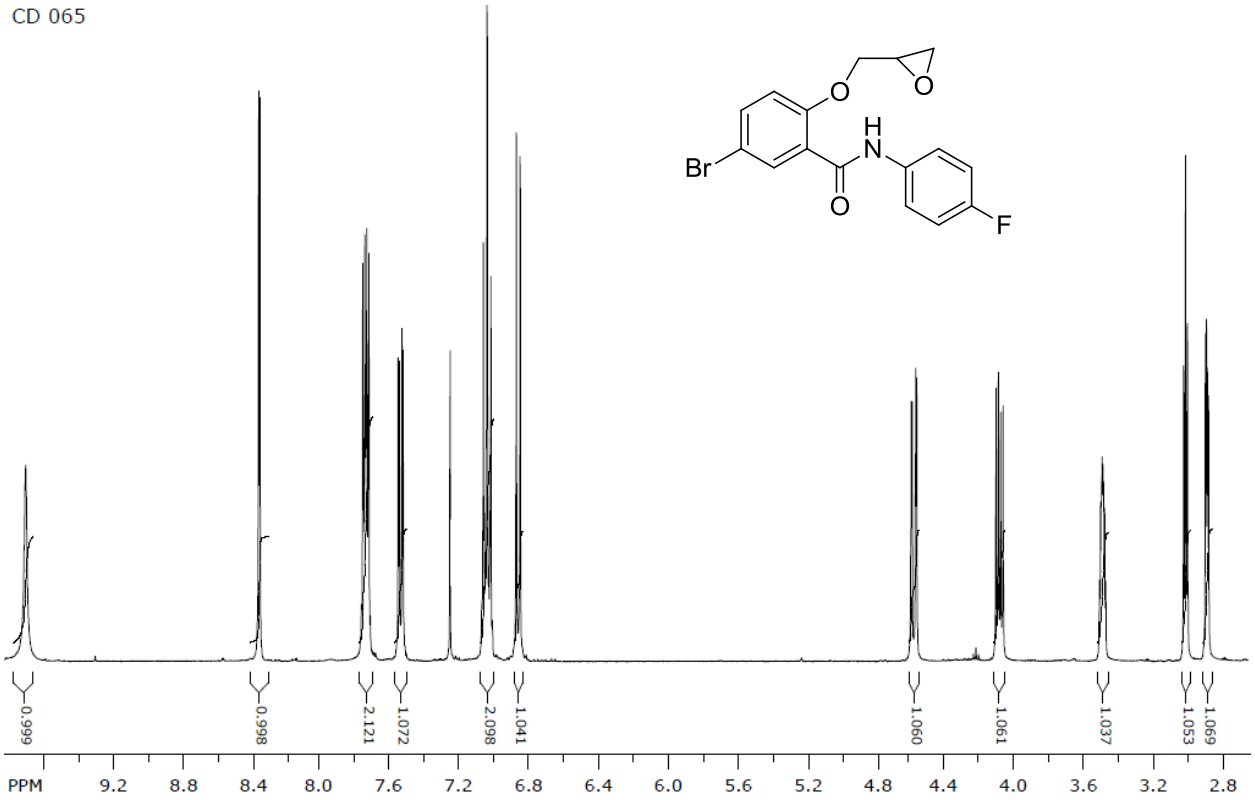


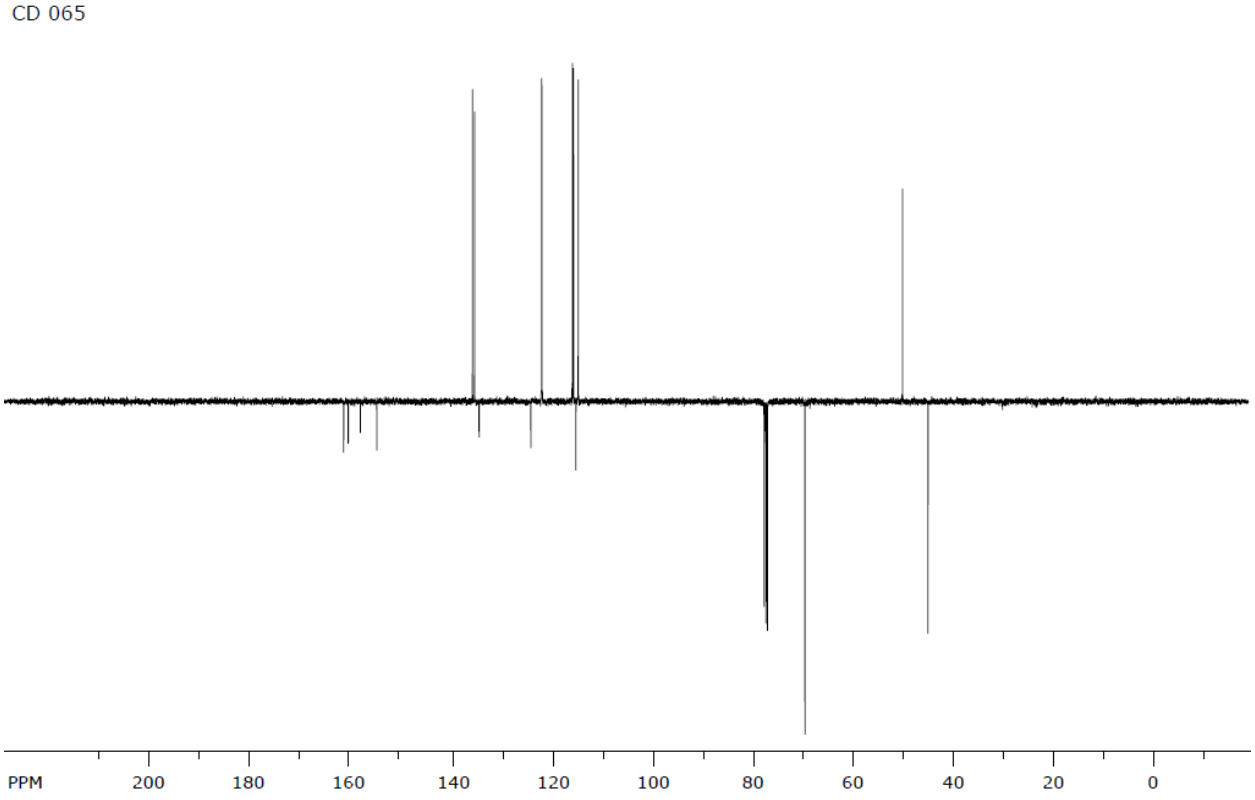
_N_-(2-allylphenyl)-2-(oxiran-2-ylmethoxy)benzamide (350)



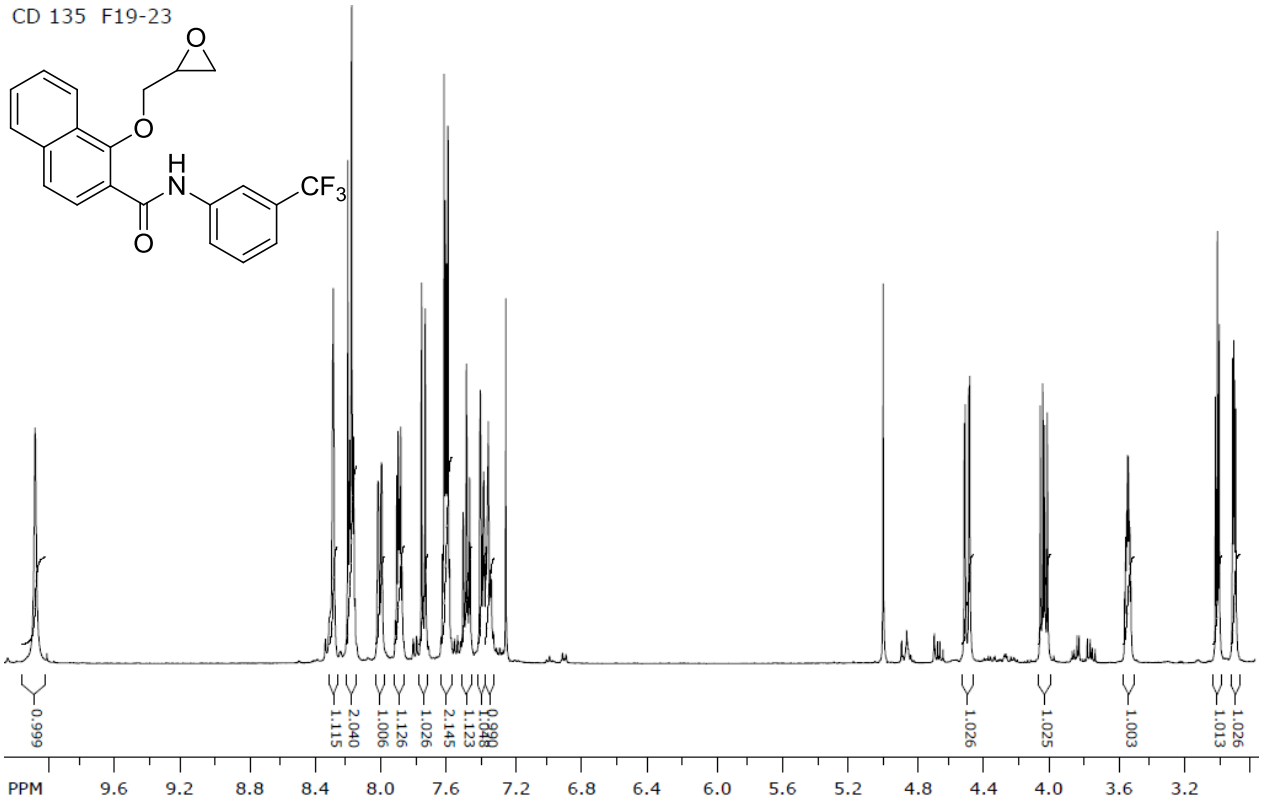


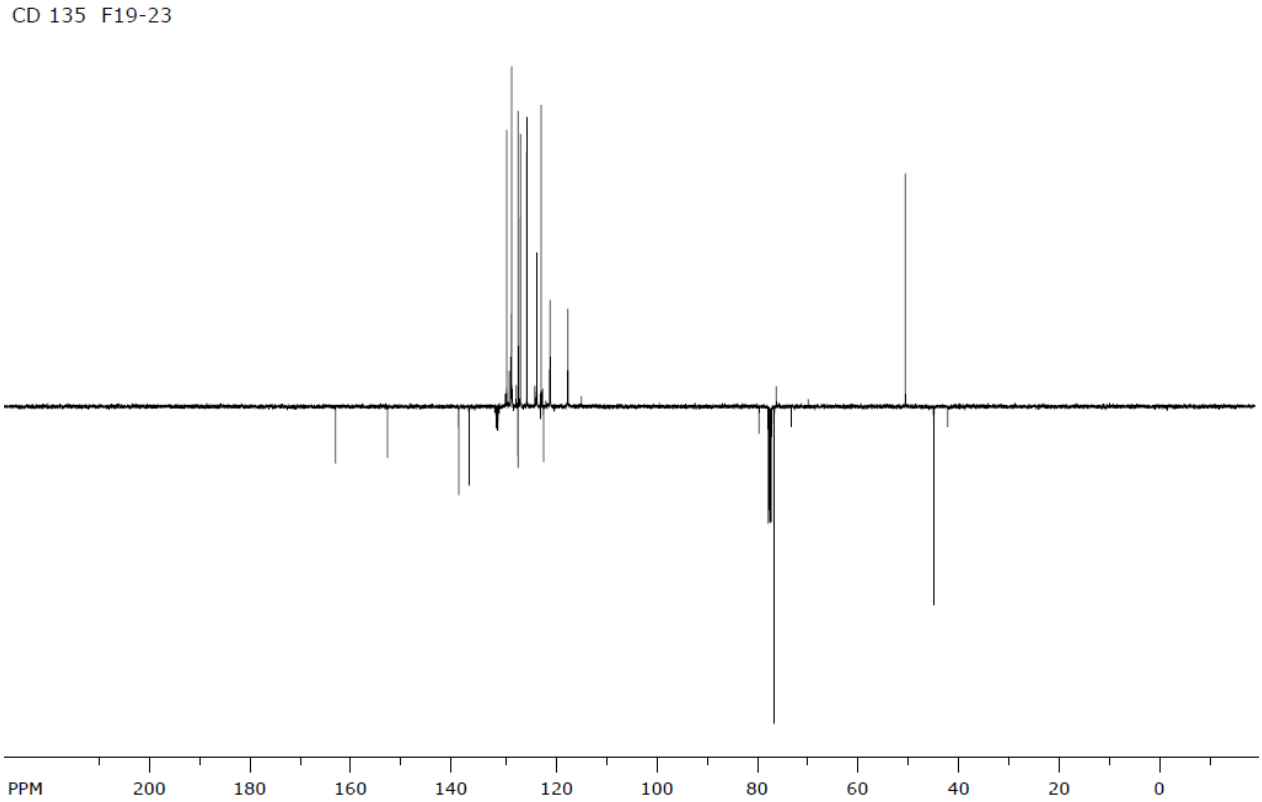
5-bromo-*N*-(4-fluorophenyl)-2-(oxiran-2-ylmethoxy)benzamide (351)



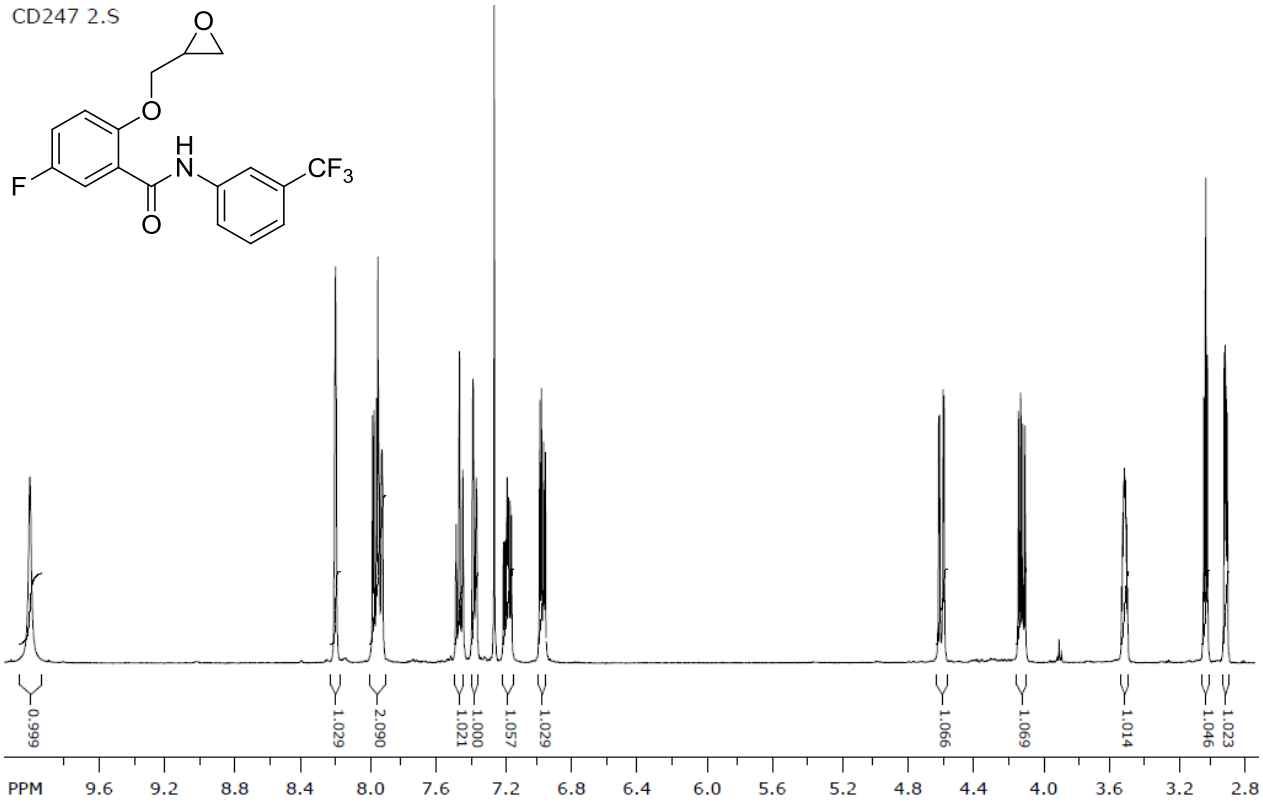


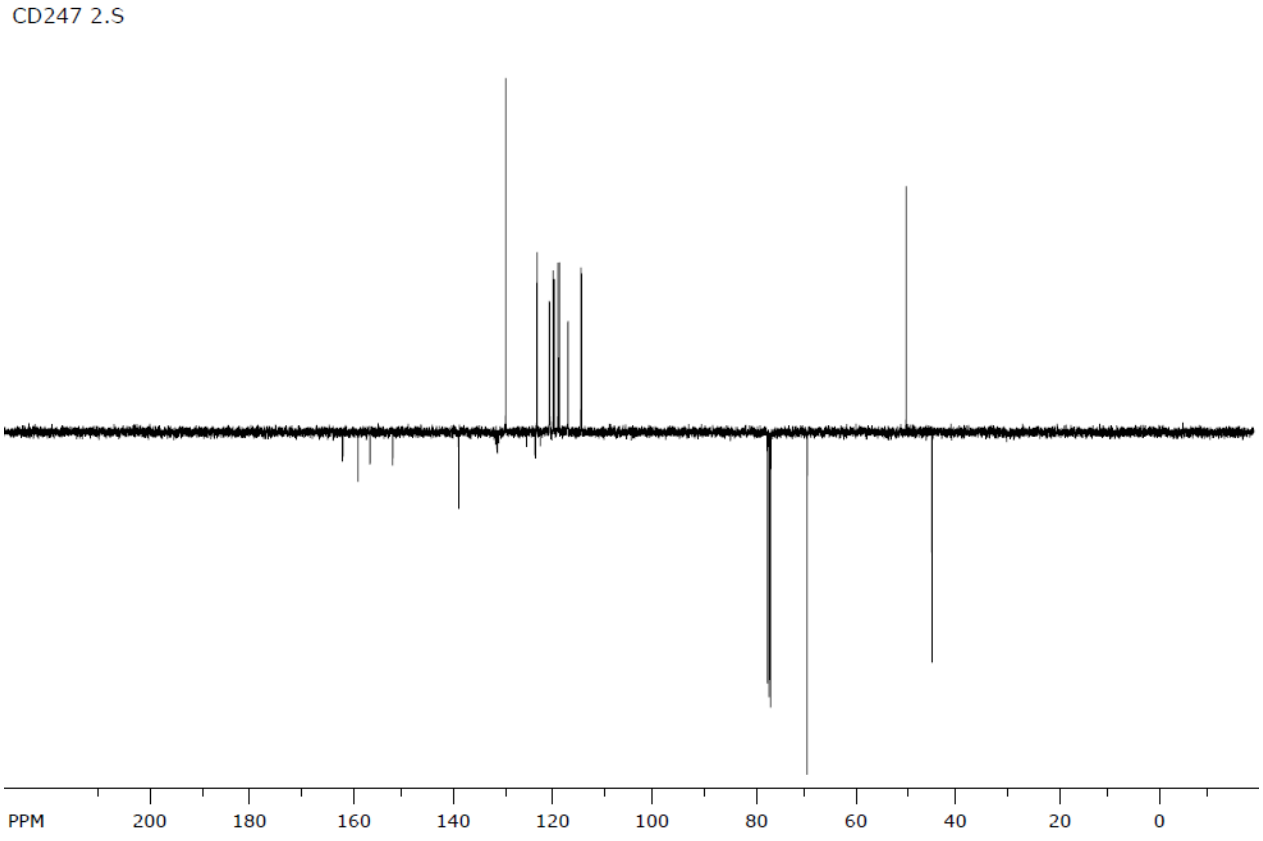
1-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)-2-naphthamide (352)



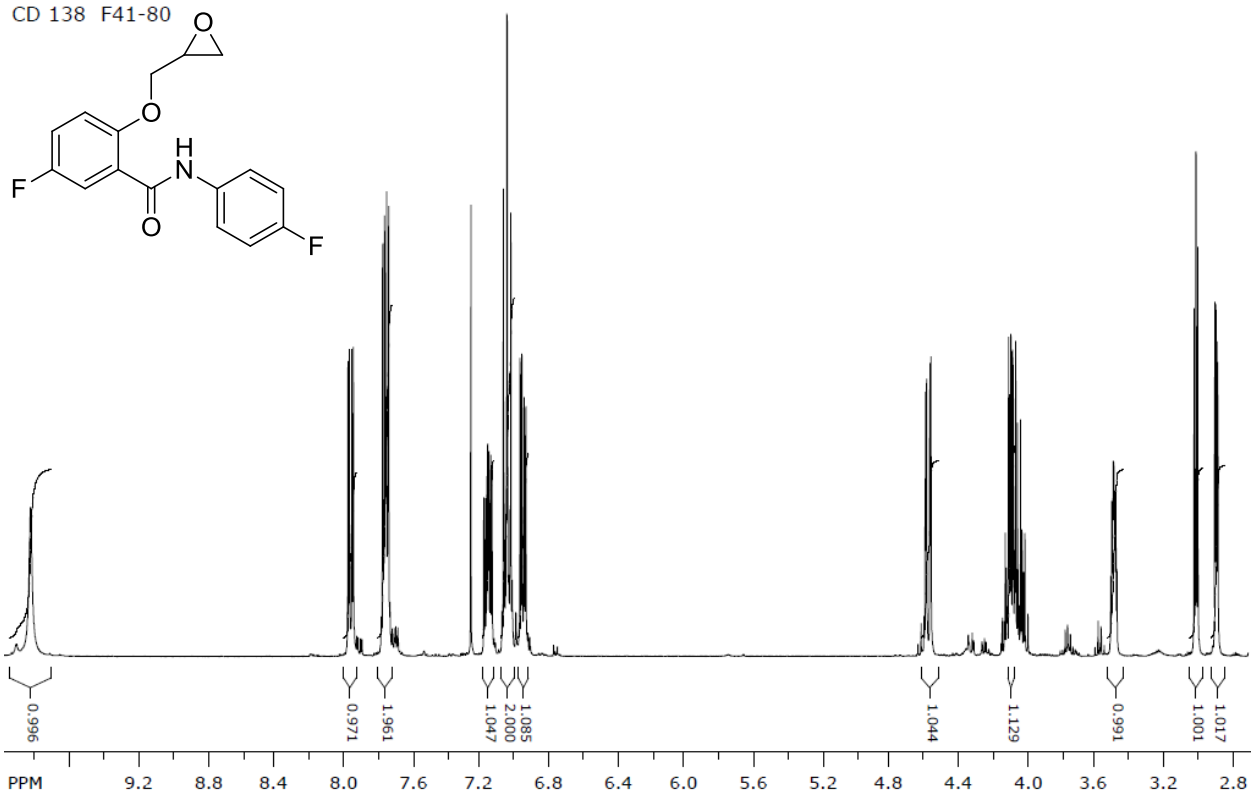


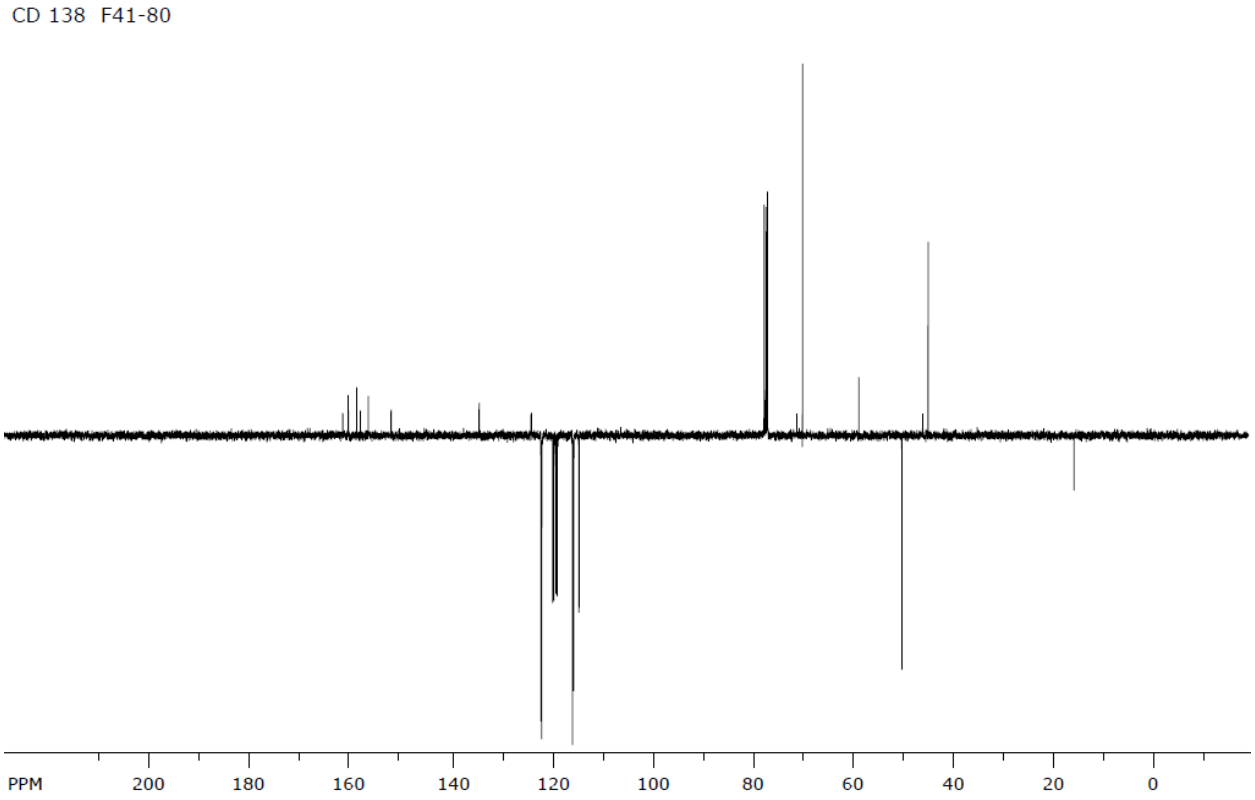
5-fluoro-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (353)



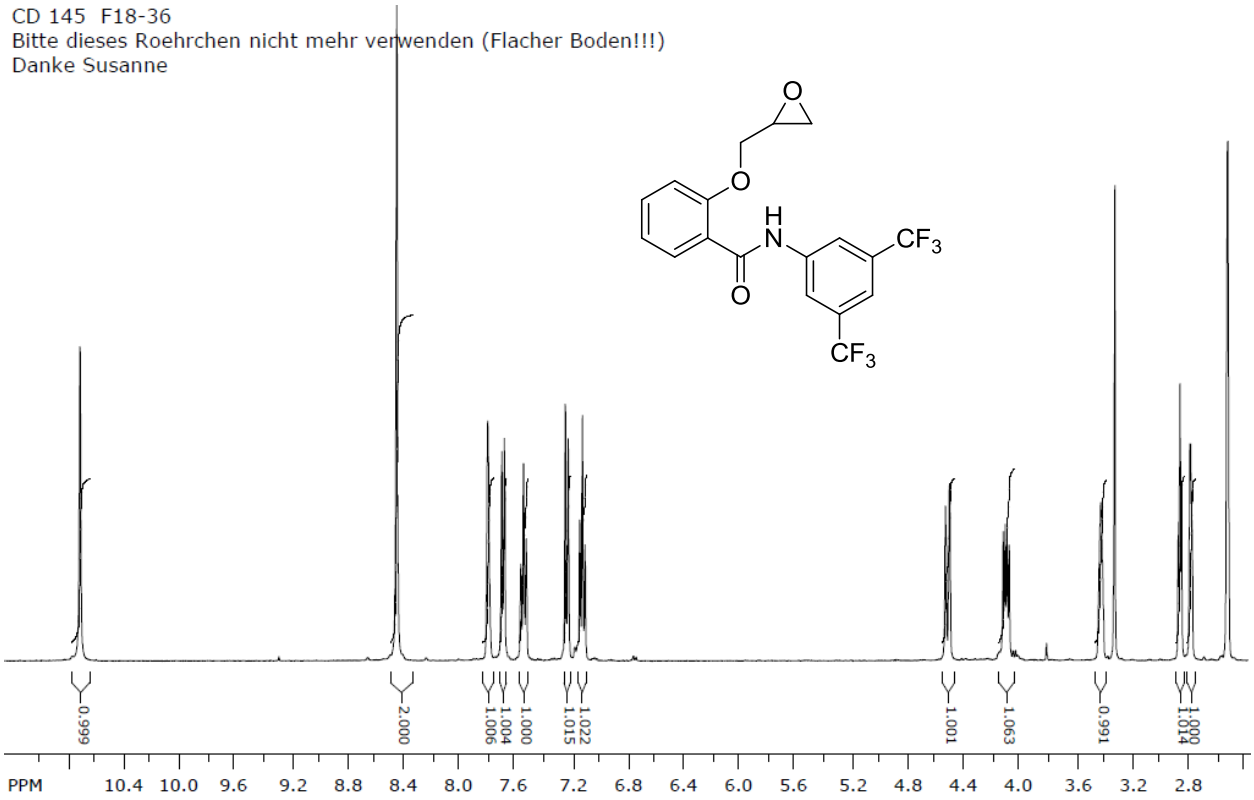


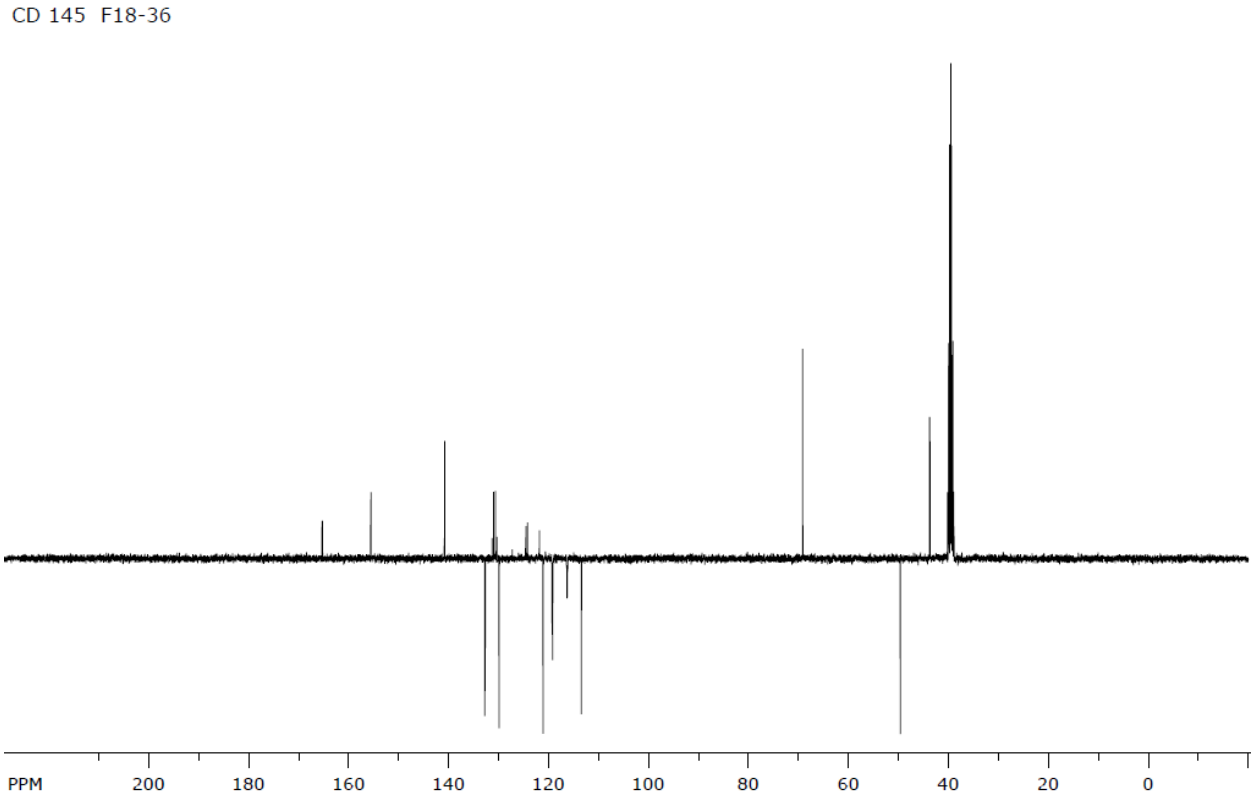
5-fluoro-*N*-(4-fluorophenyl)-2-(oxiran-2-ylmethoxy)benzamide (354)



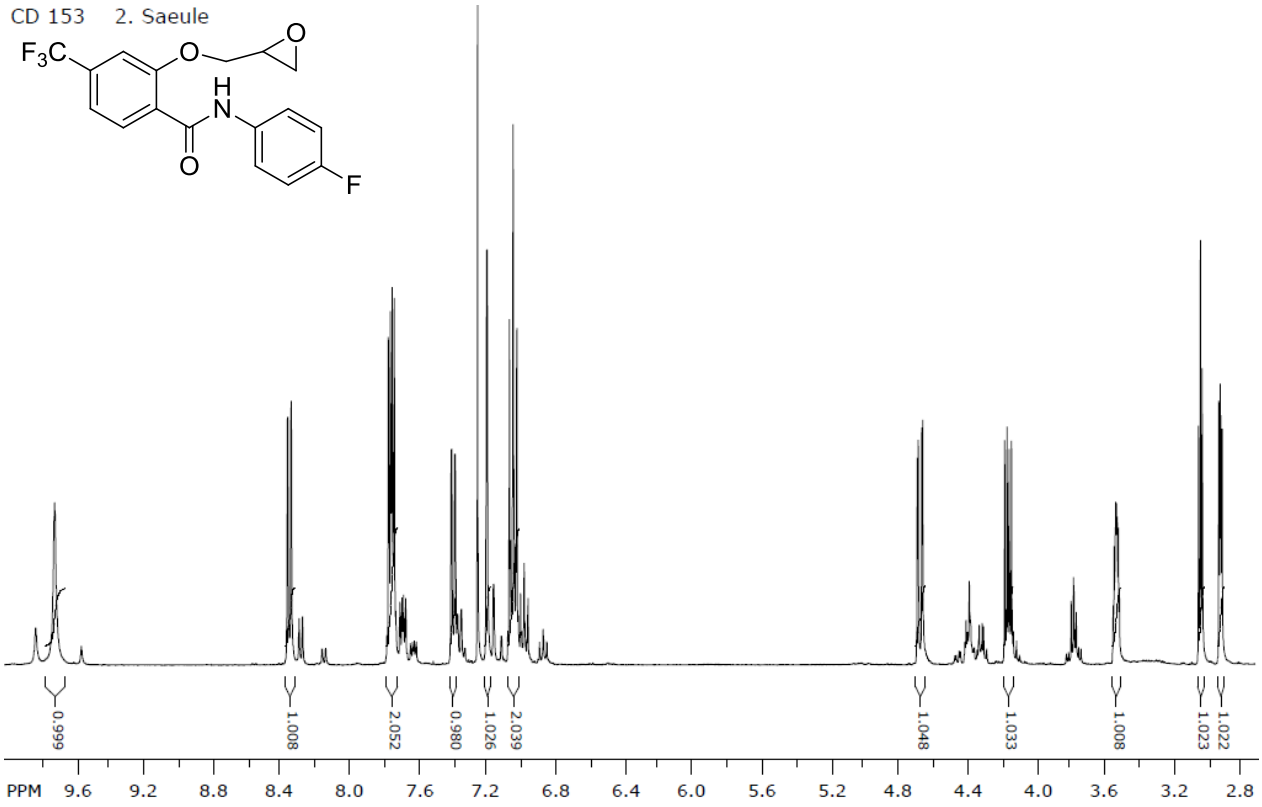


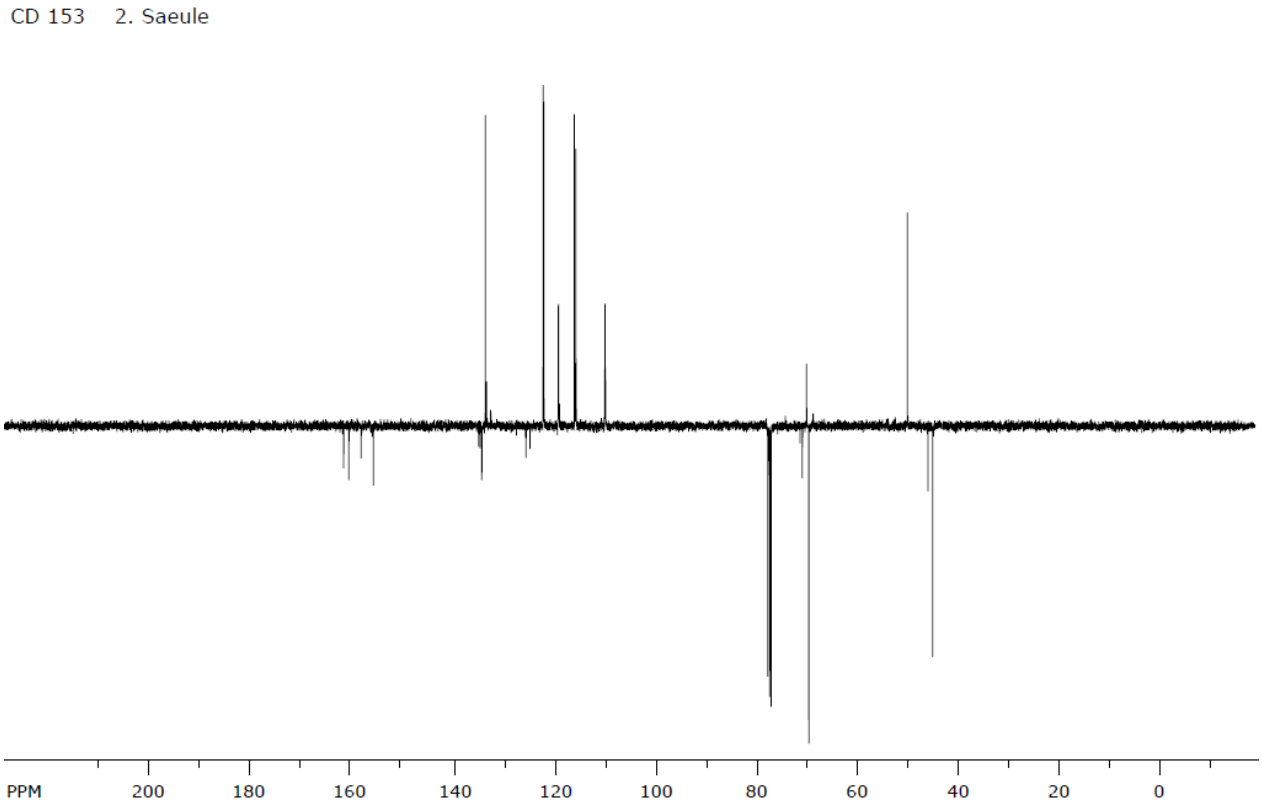
N-(3,5-bis(trifluoromethyl)phenyl)-2-(oxiran-2-ylmethoxy)benzamide (355)



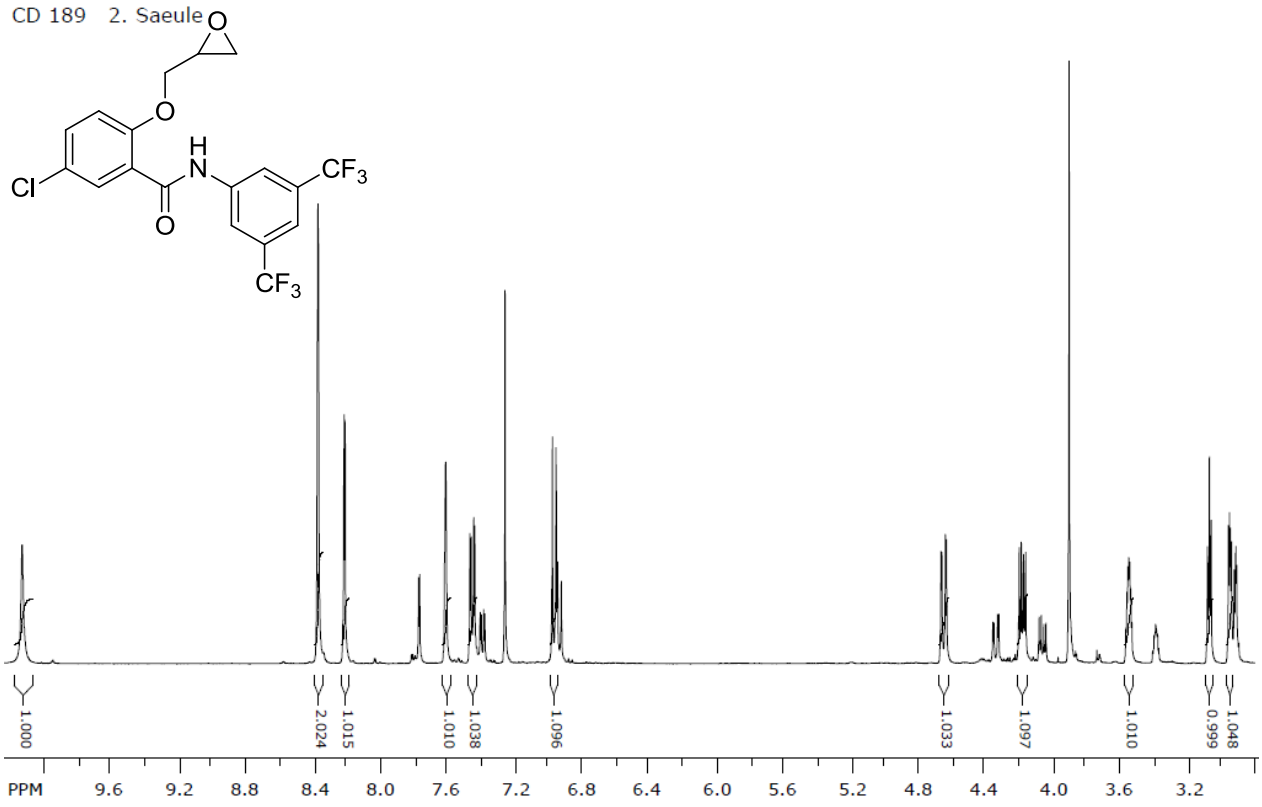


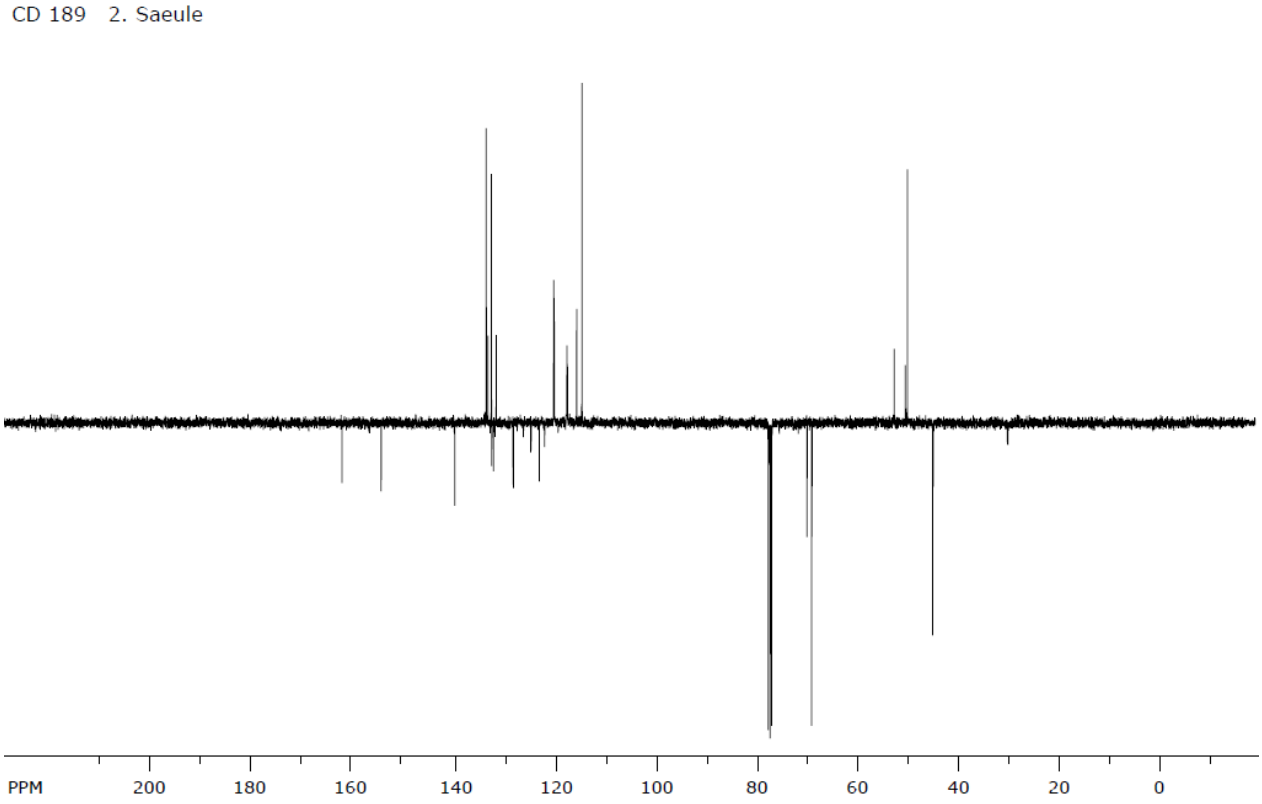
_N_-(4-fluorophenyl)-2-(oxiran-2-ylmethoxy)-4-(trifluoromethyl)benzamide (356)



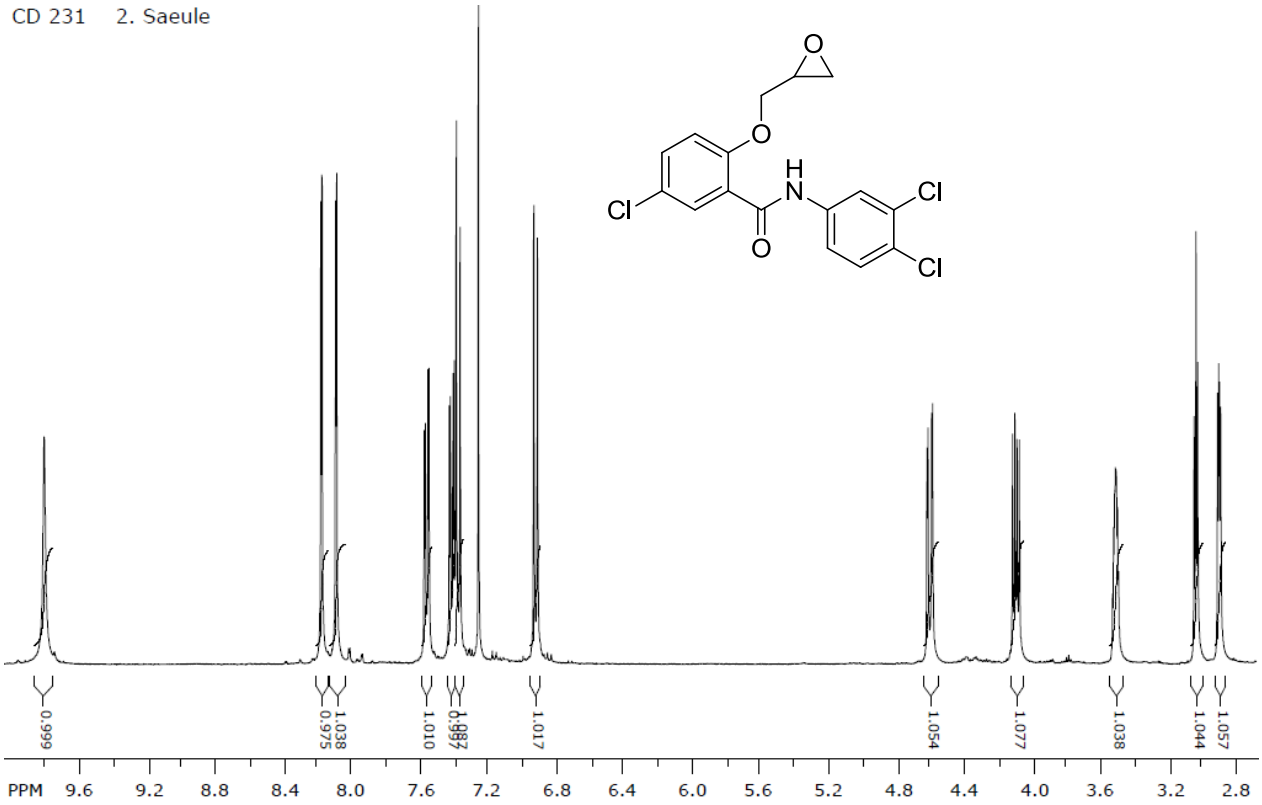


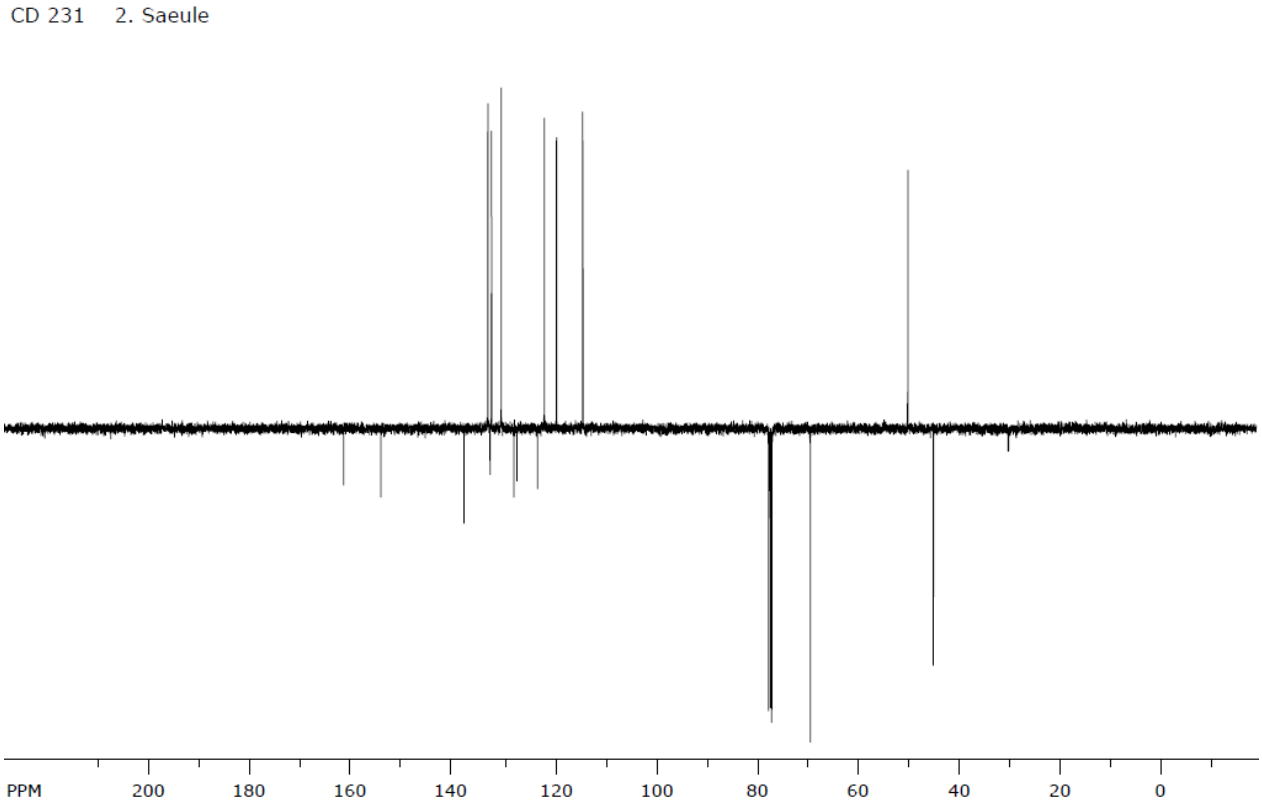
_N_-(3,5-bis(trifluoromethyl)phenyl)-5-chloro-2-(oxiran-2-ylmethoxy)benzamide (357)



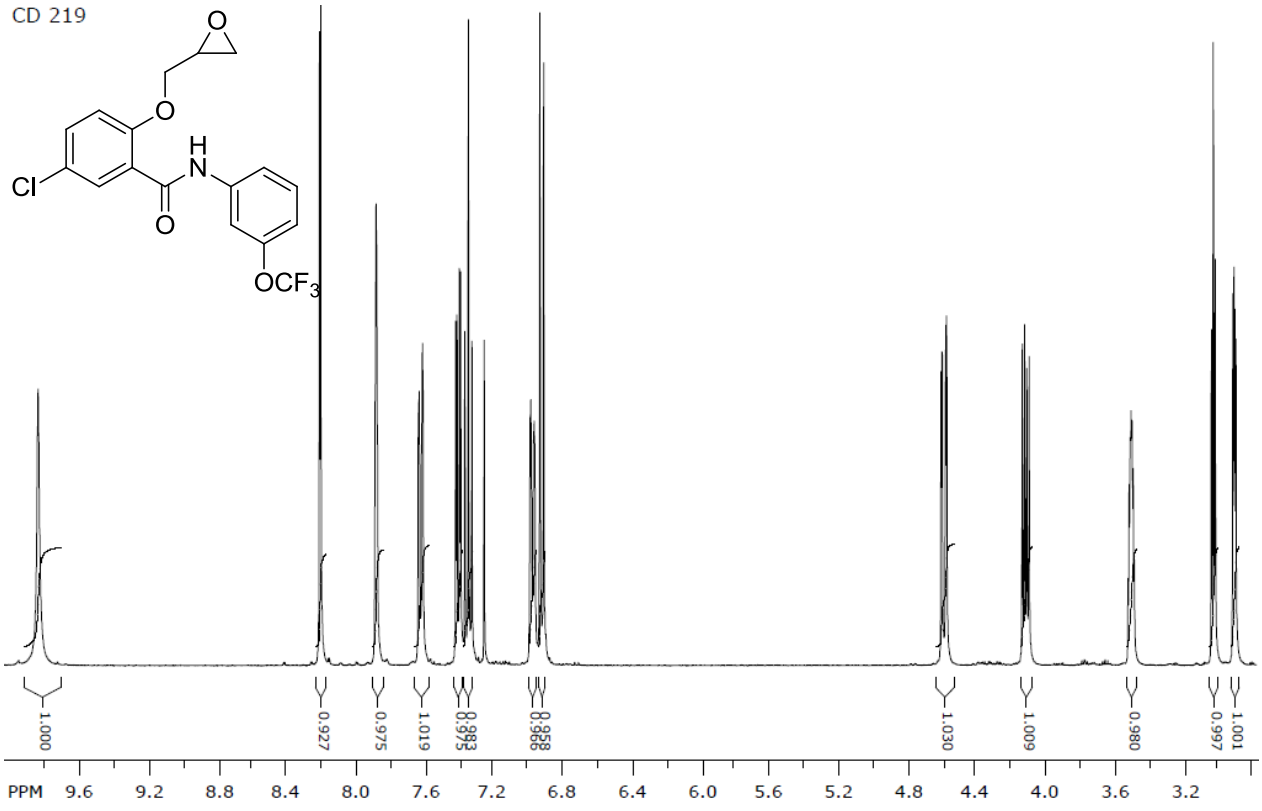


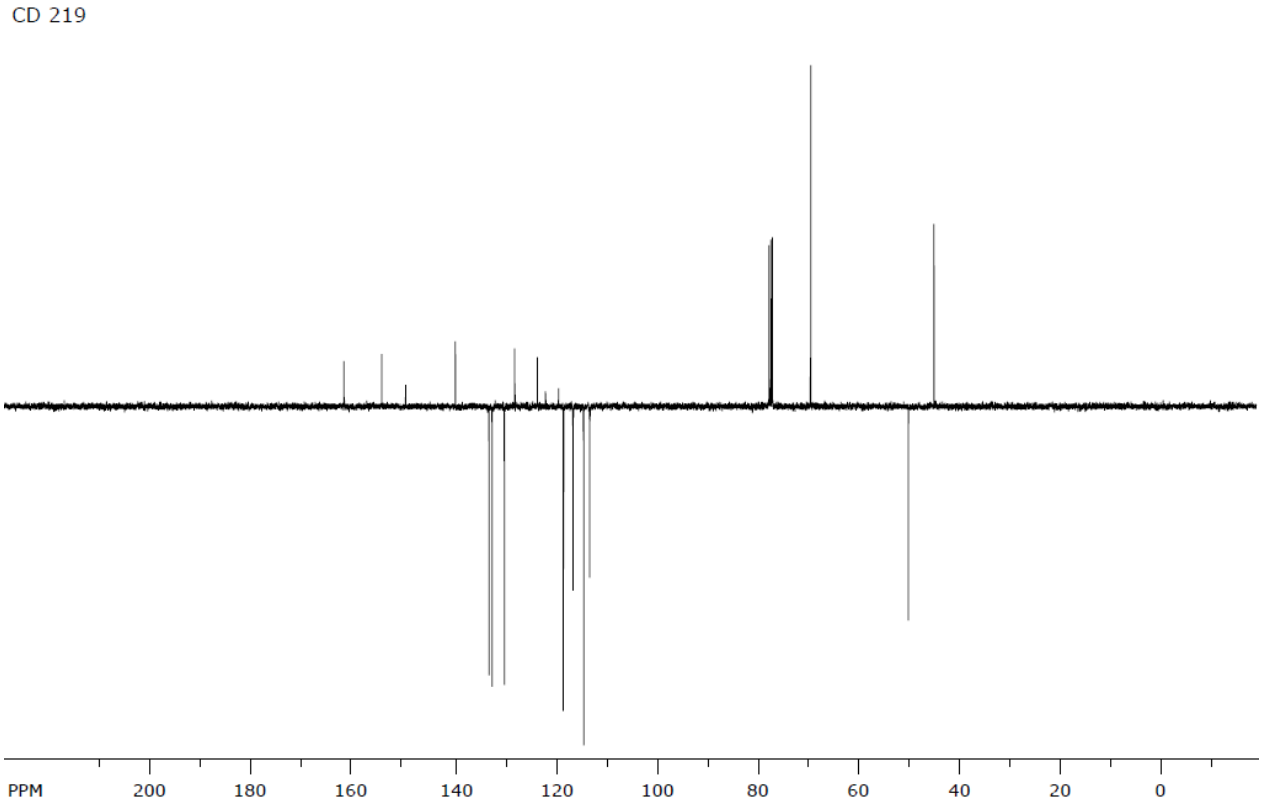
5-chloro-*N*-(3,4-dichlorophenyl)-2-(oxiran-2-ylmethoxy)benzamide (358)



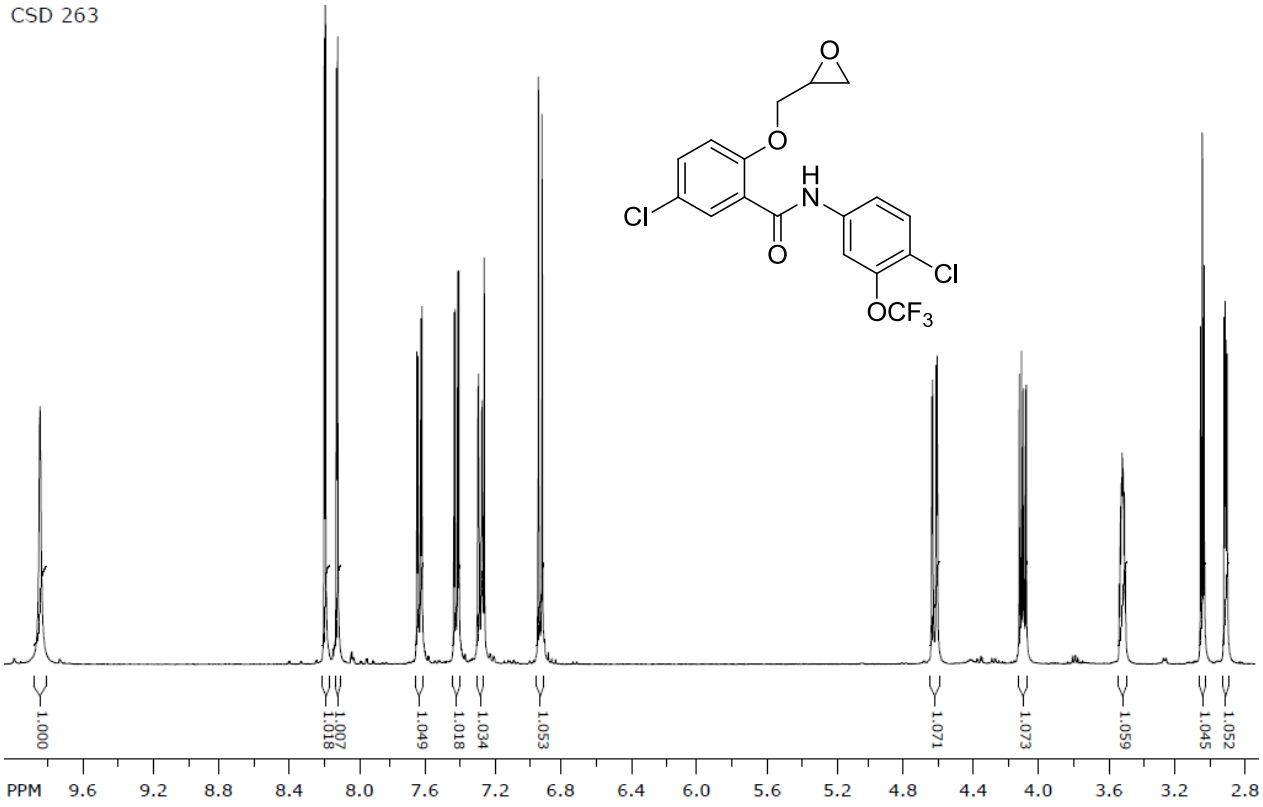


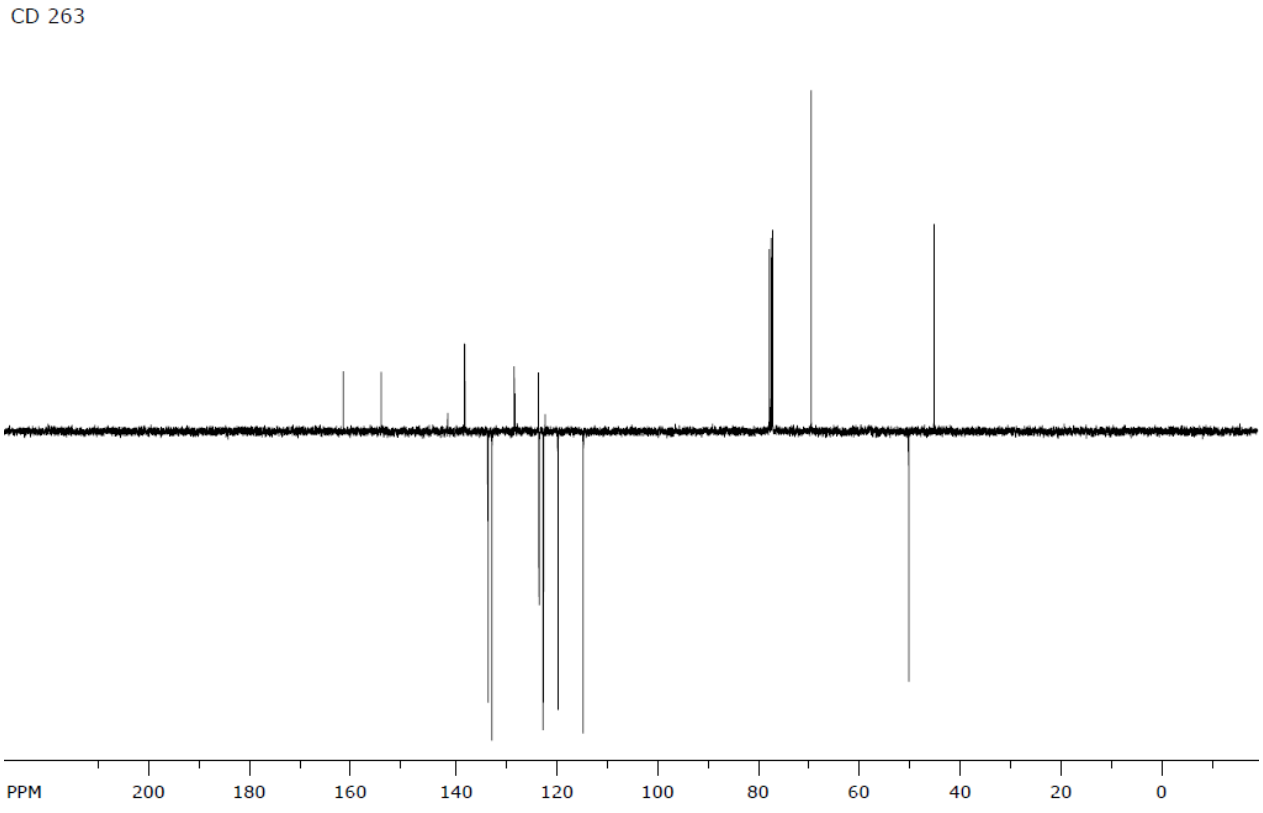
5-chloro-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethoxy)phenyl)benzamide (359)



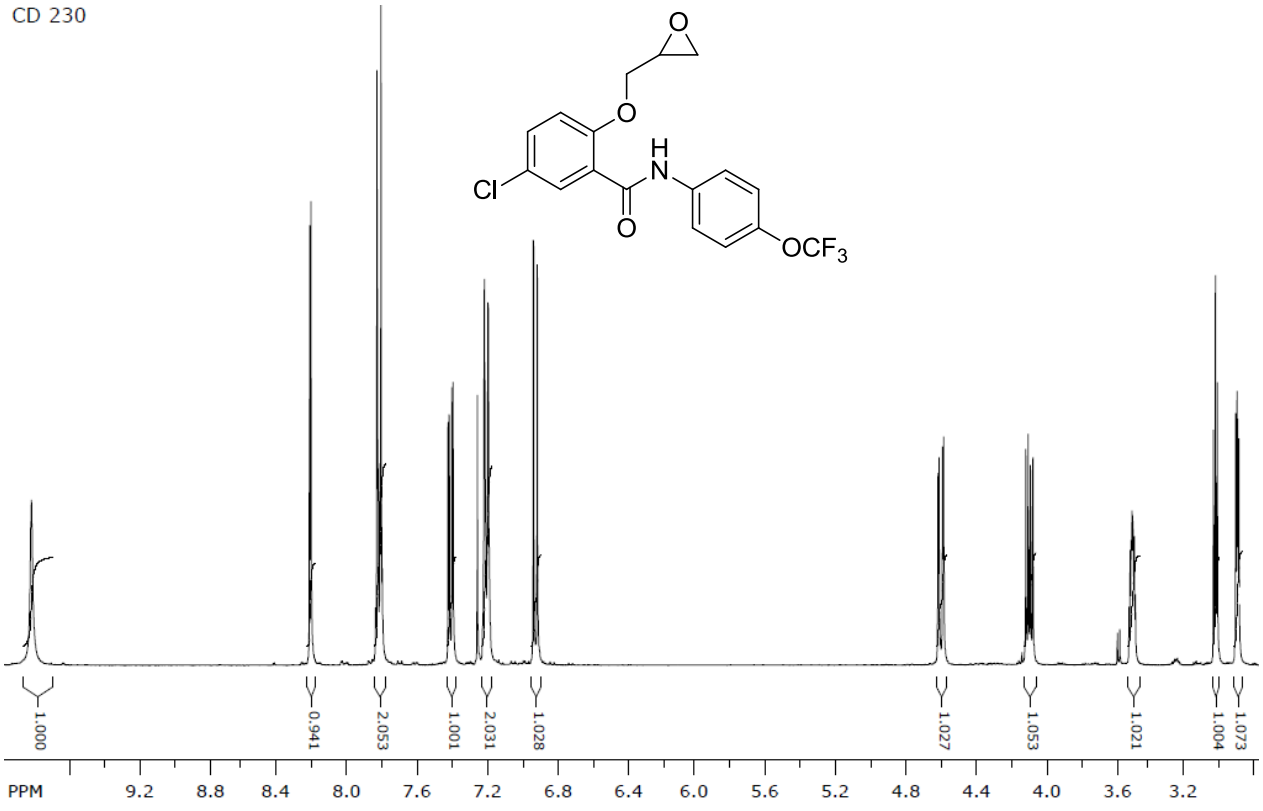


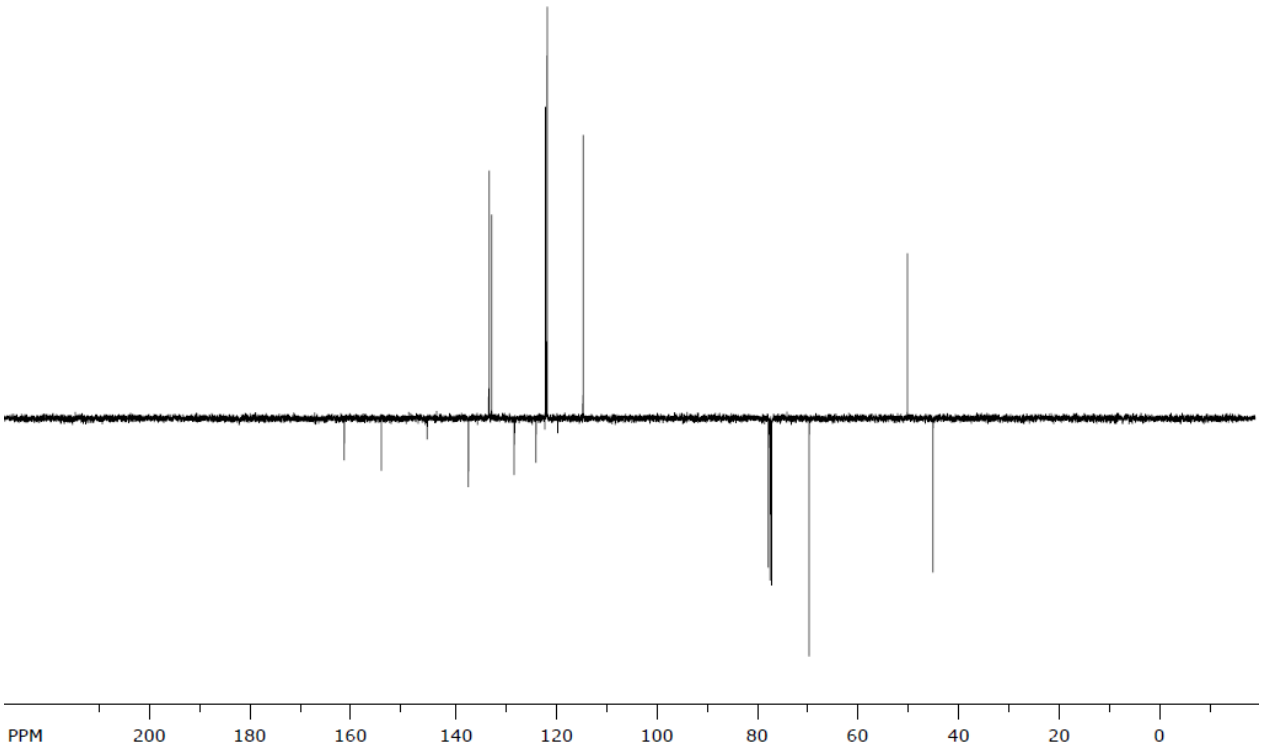
5-chloro-*N*-(4-chloro-3-(trifluoromethoxy)phenyl)-2-(oxiran-2-ylmethoxy)benzamide (360)



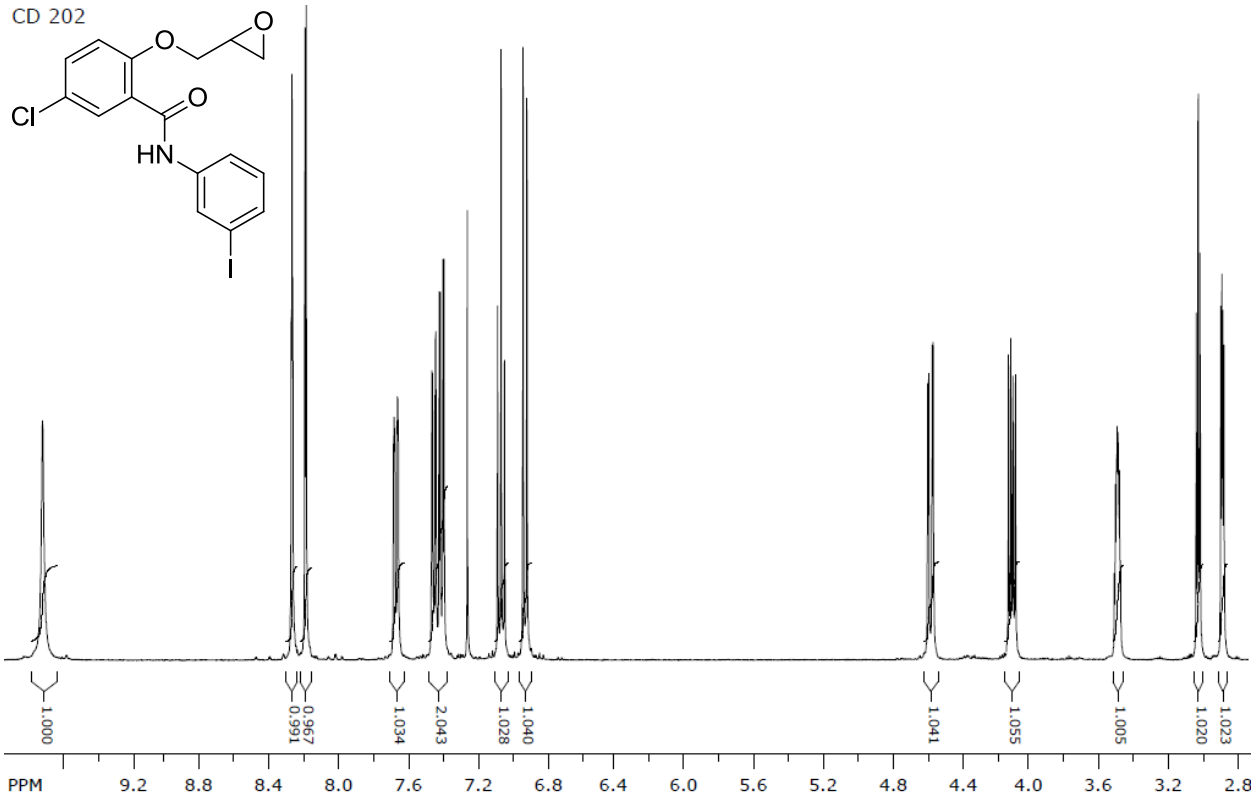


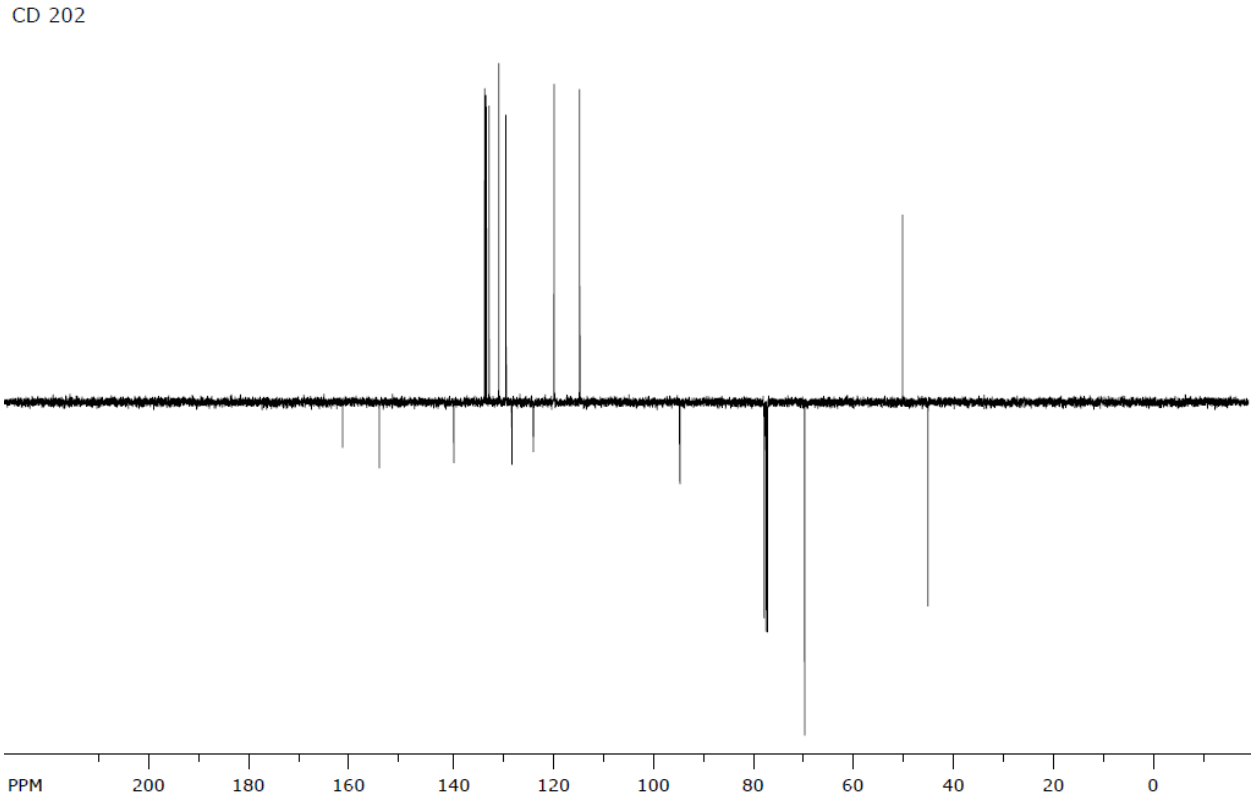
5-chloro-2-(oxiran-2-ylmethoxy)-*N*-(4-(trifluoromethoxy)phenyl)benzamide (361)



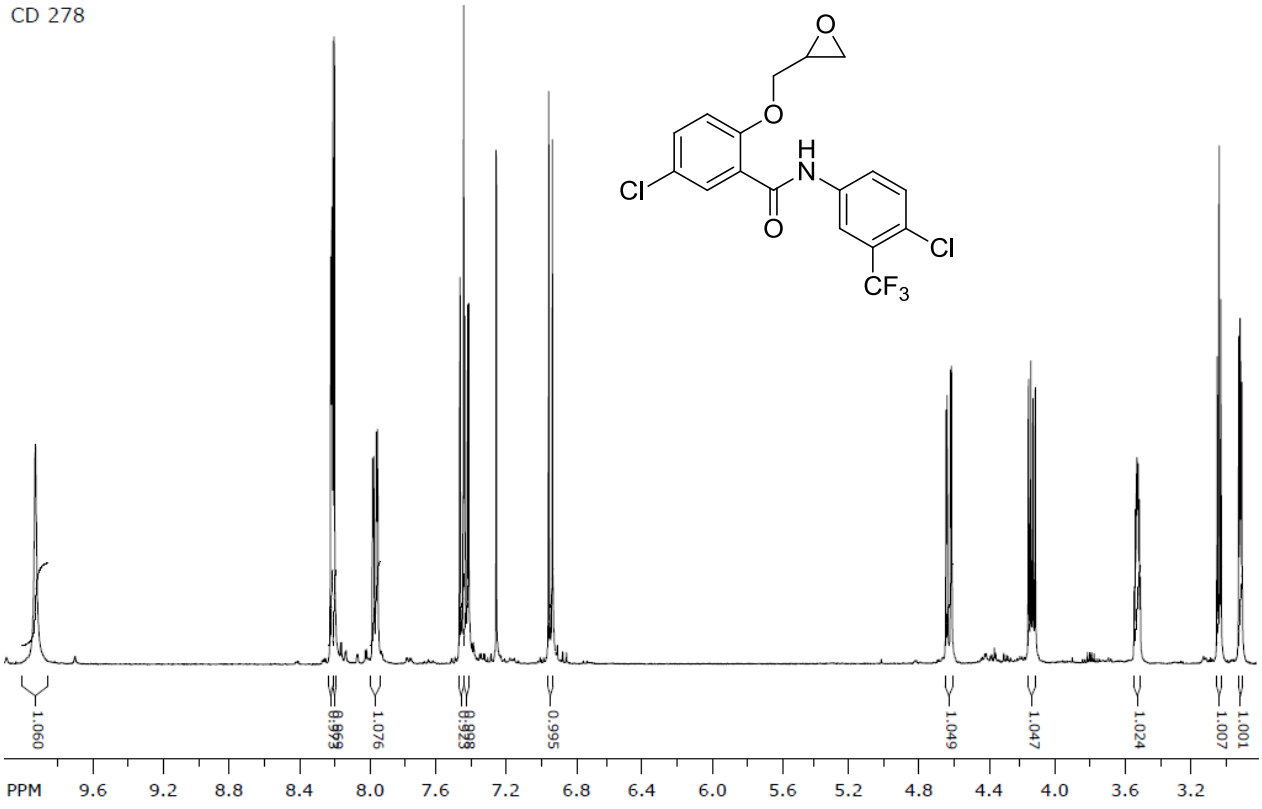


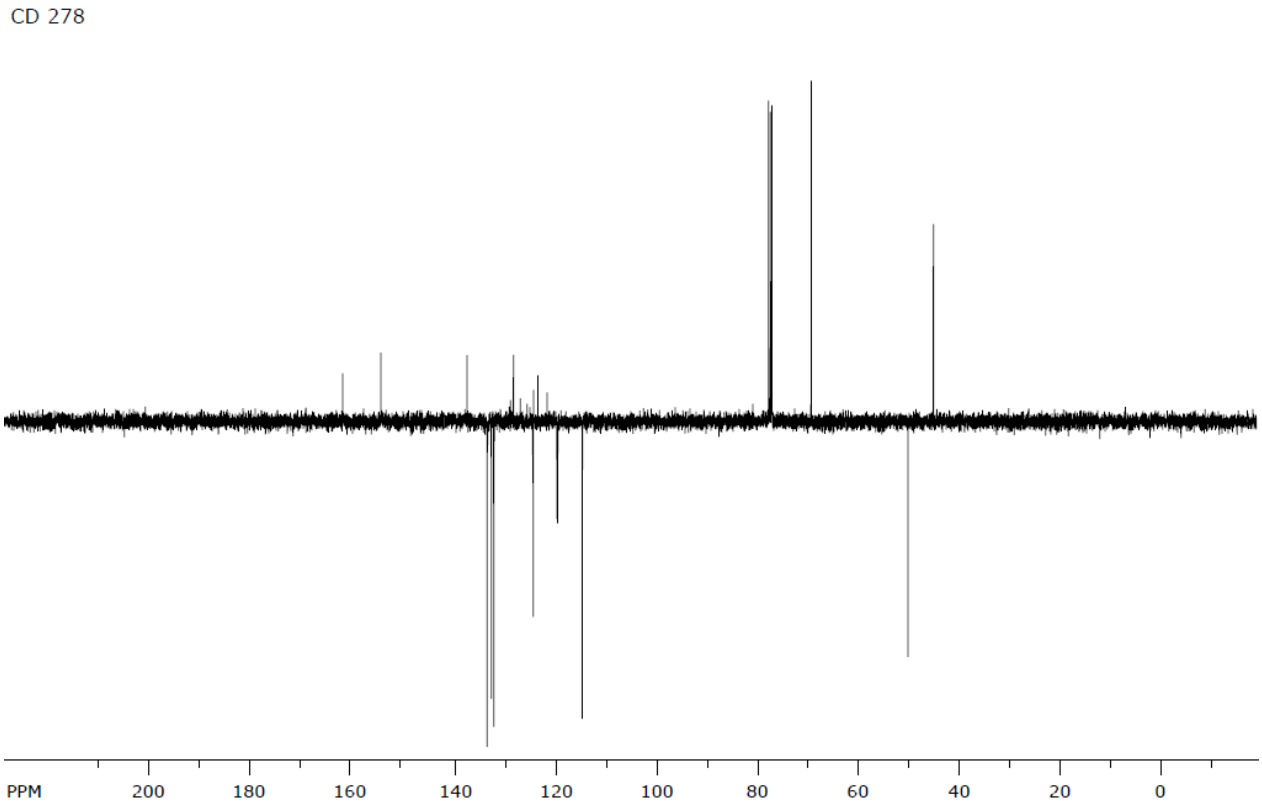
5-chloro-*N*-(3-iodophenyl)-2-(oxiran-2-ylmethoxy)benzamide (362)



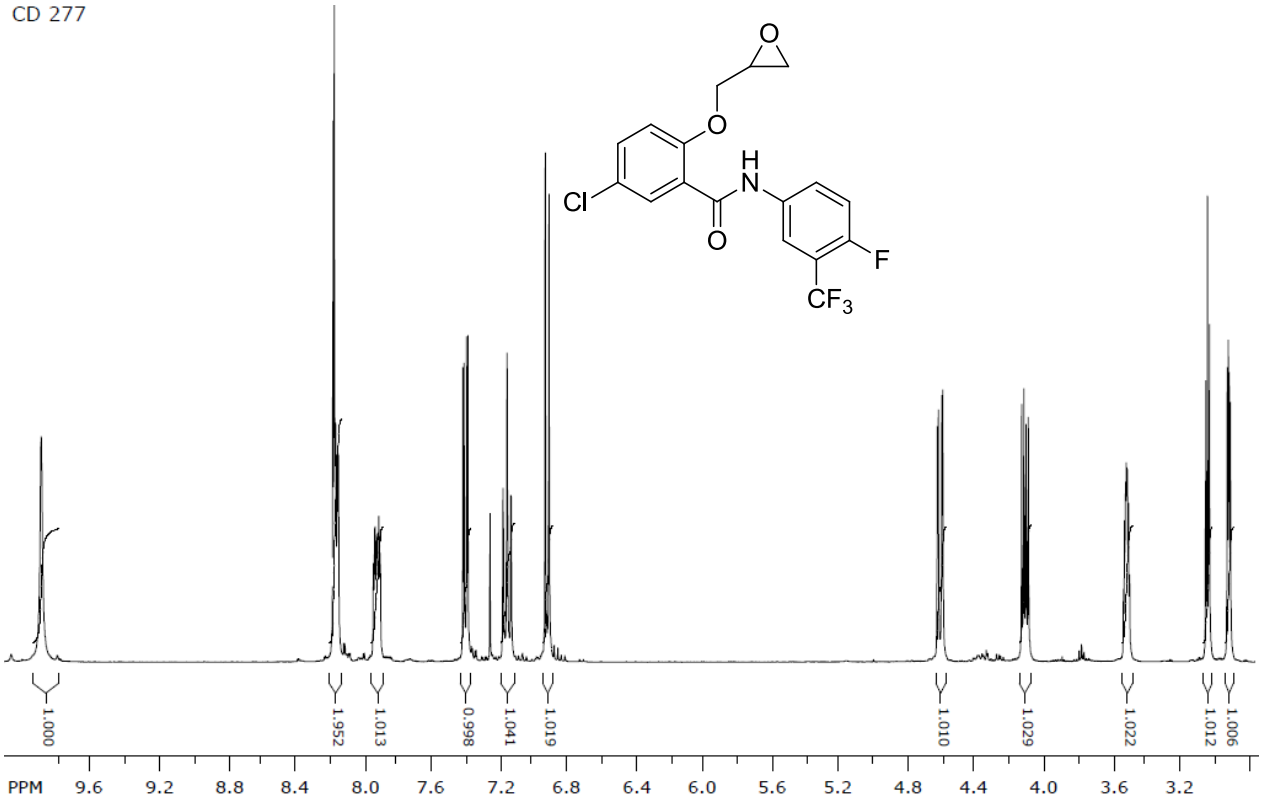


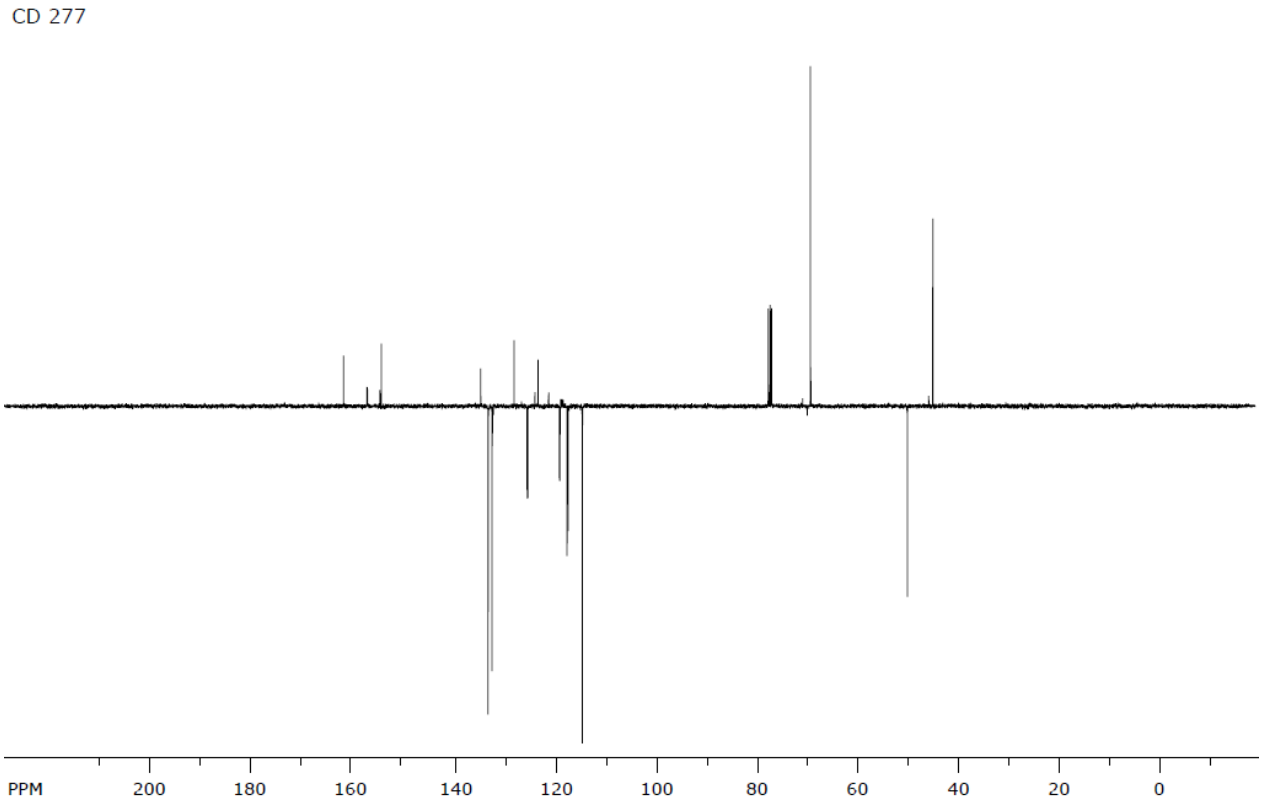
5-chloro-*N*-(4-chloro-3-(trifluoromethyl)phenyl)-2-(oxiran-2-ylmethoxy)benzamide (363)



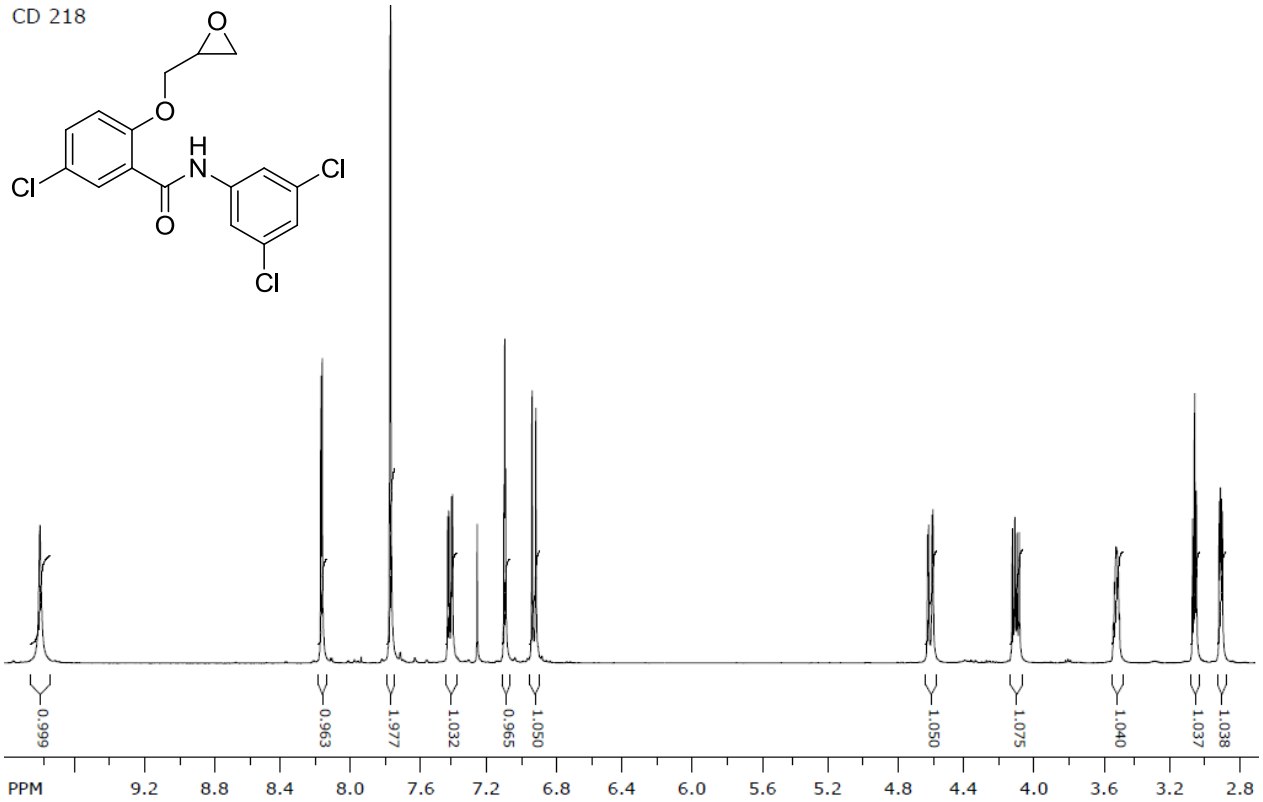


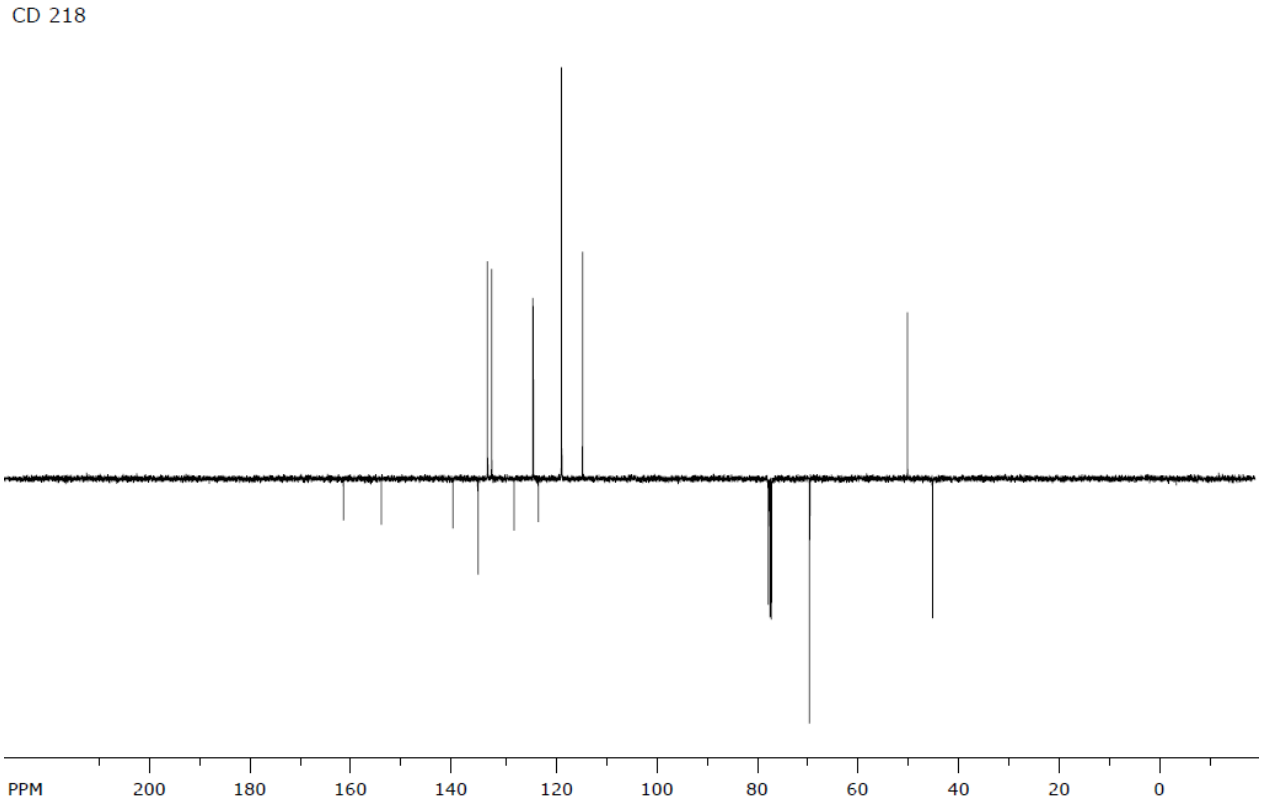
5-chloro-*N*-(4-fluoro-3-(trifluoromethyl)phenyl)-2-(oxiran-2-ylmethoxy)benzamide (364**)**



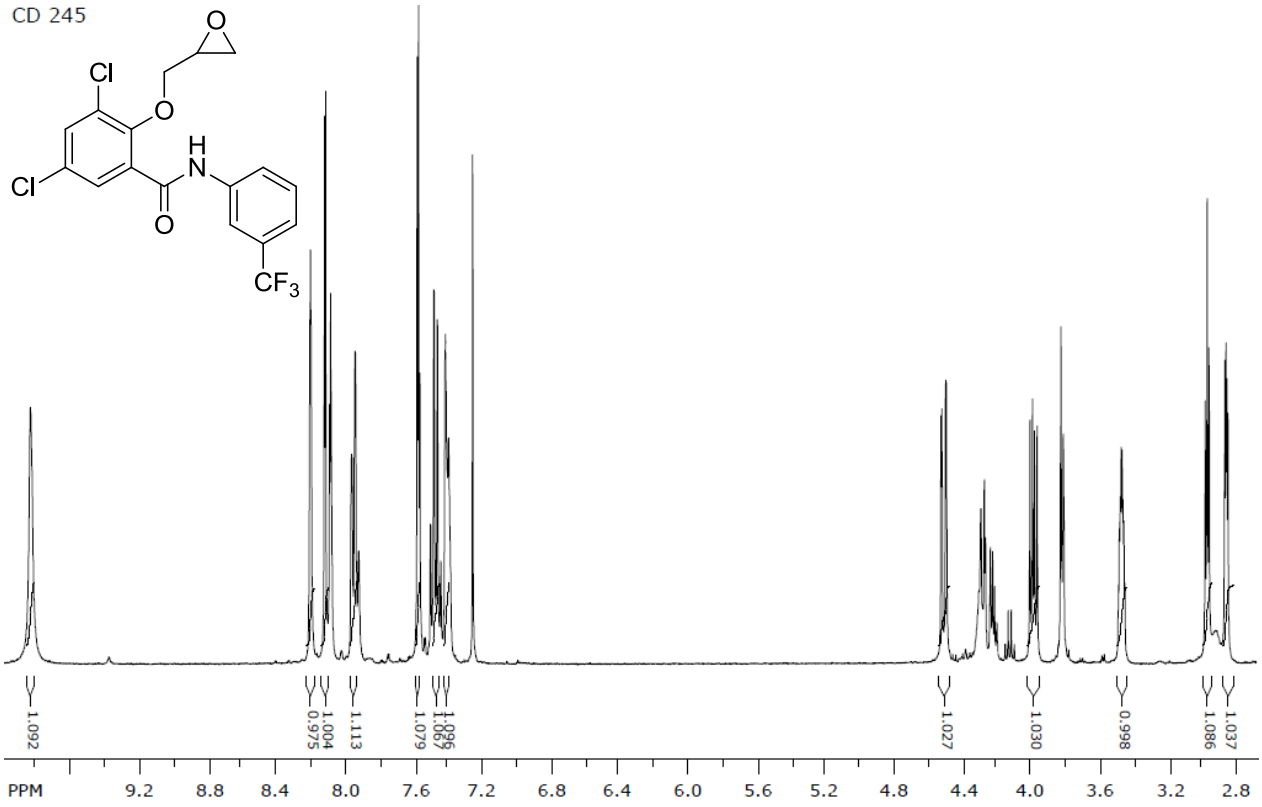


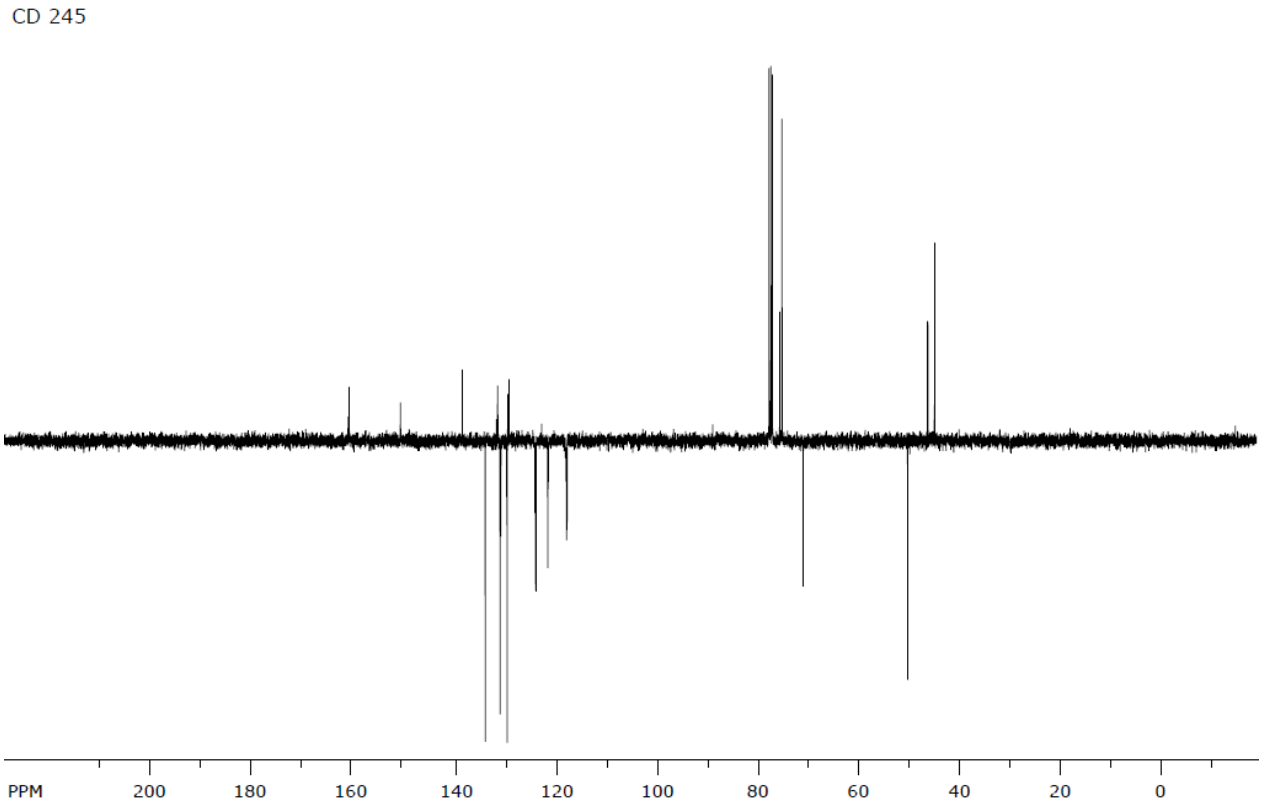
5-chloro-*N*-(3,5-dichlorophenyl)-2-(oxiran-2-ylmethoxy)benzamide (365)



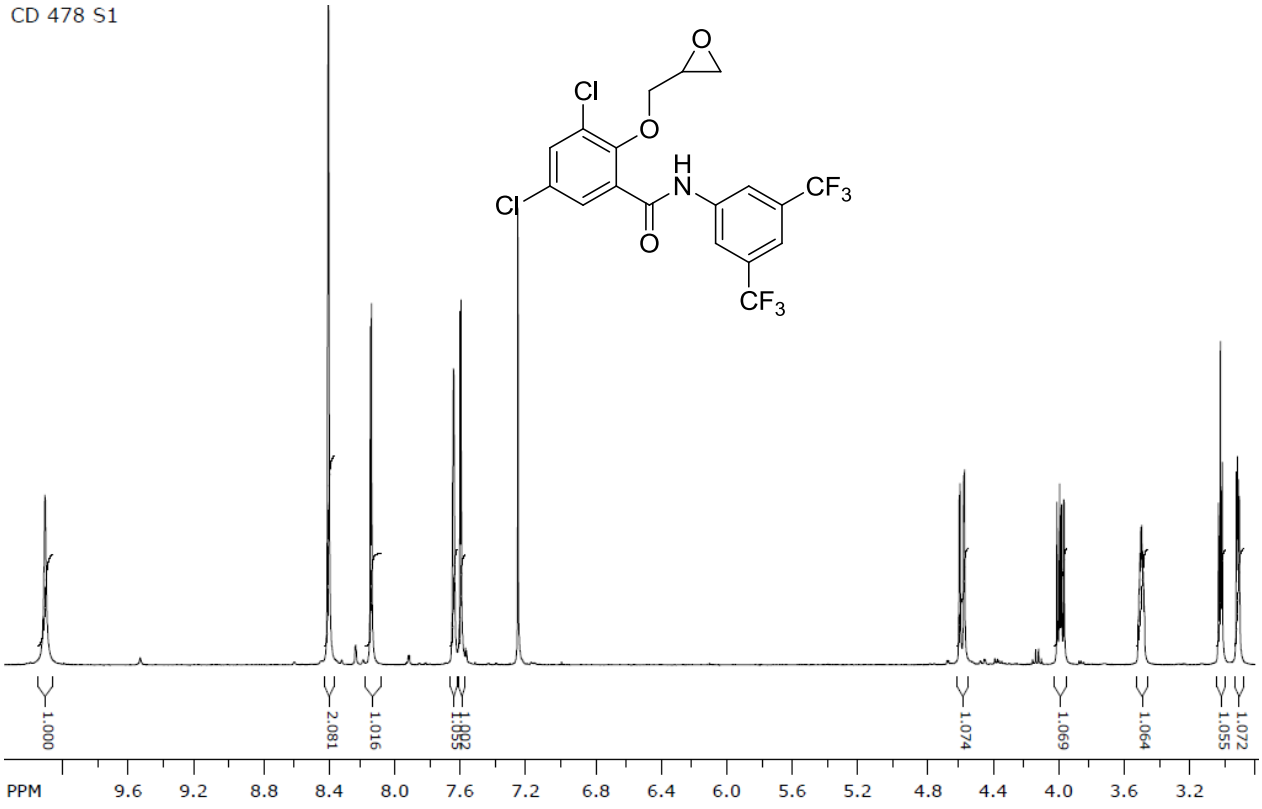


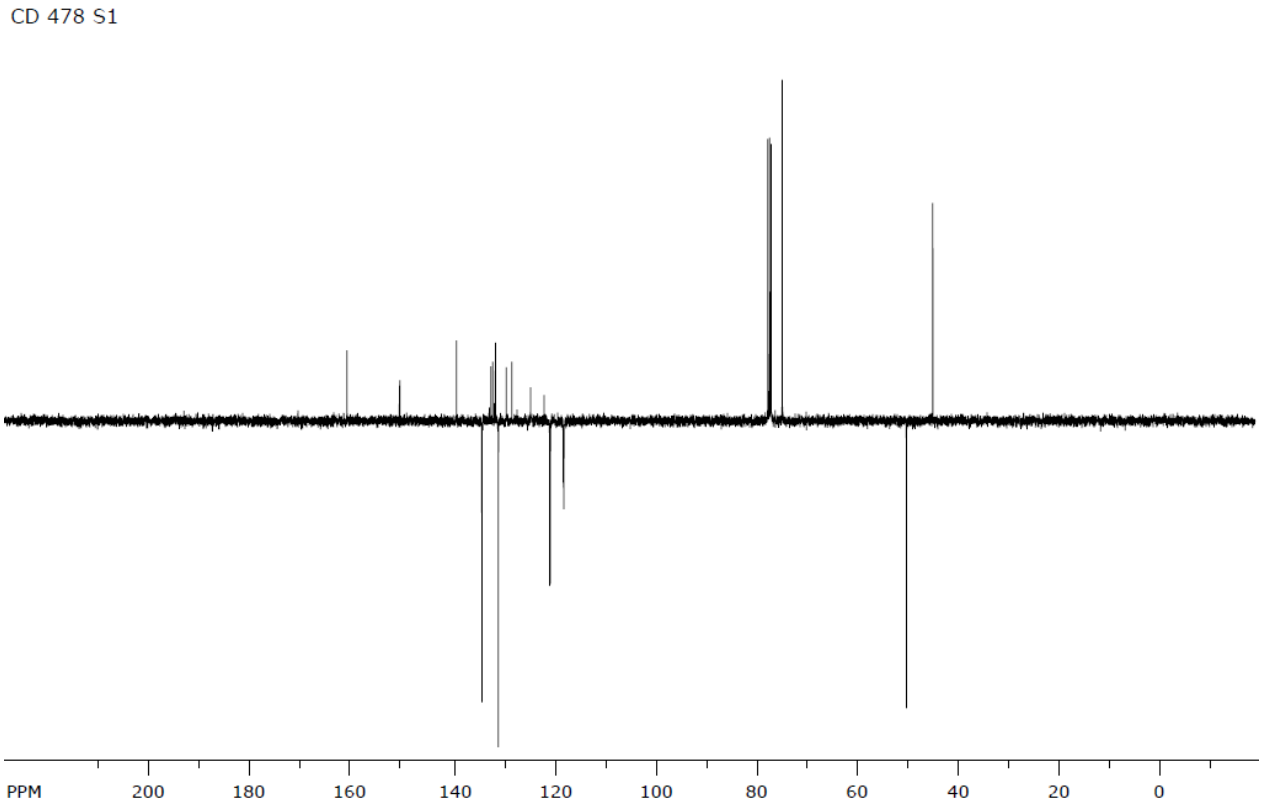
3,5-dichloro-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (366)



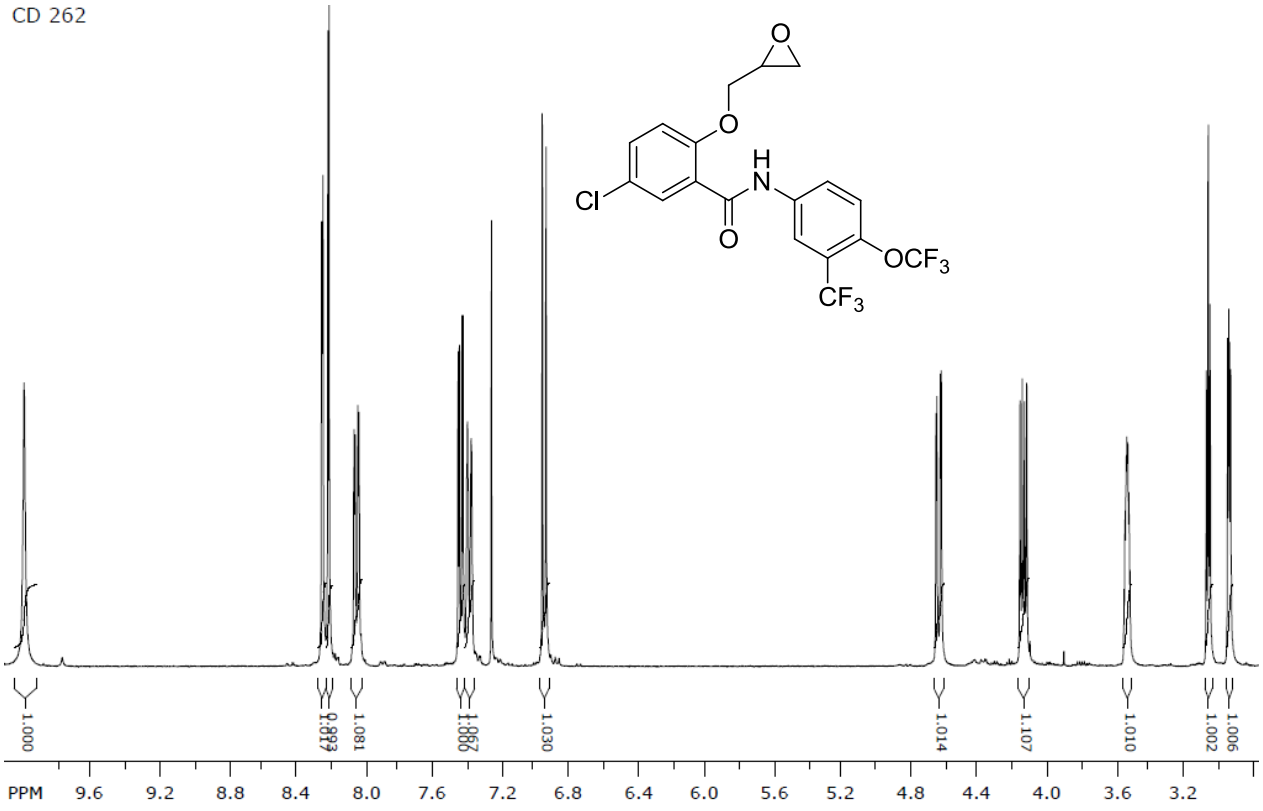


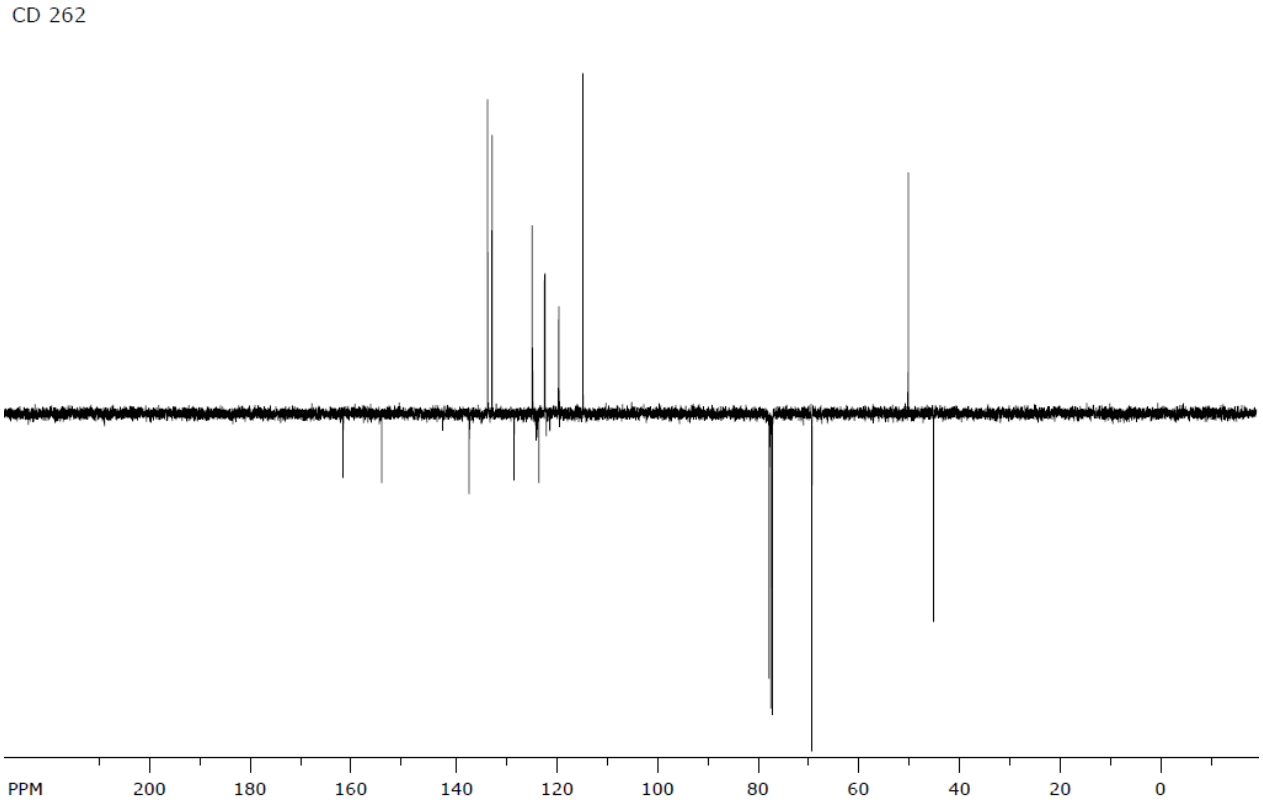
_N_-(3,5-bis(trifluoromethyl)phenyl)-3,5-dichloro-2-(oxiran-2-ylmethoxy)benzamide (367)



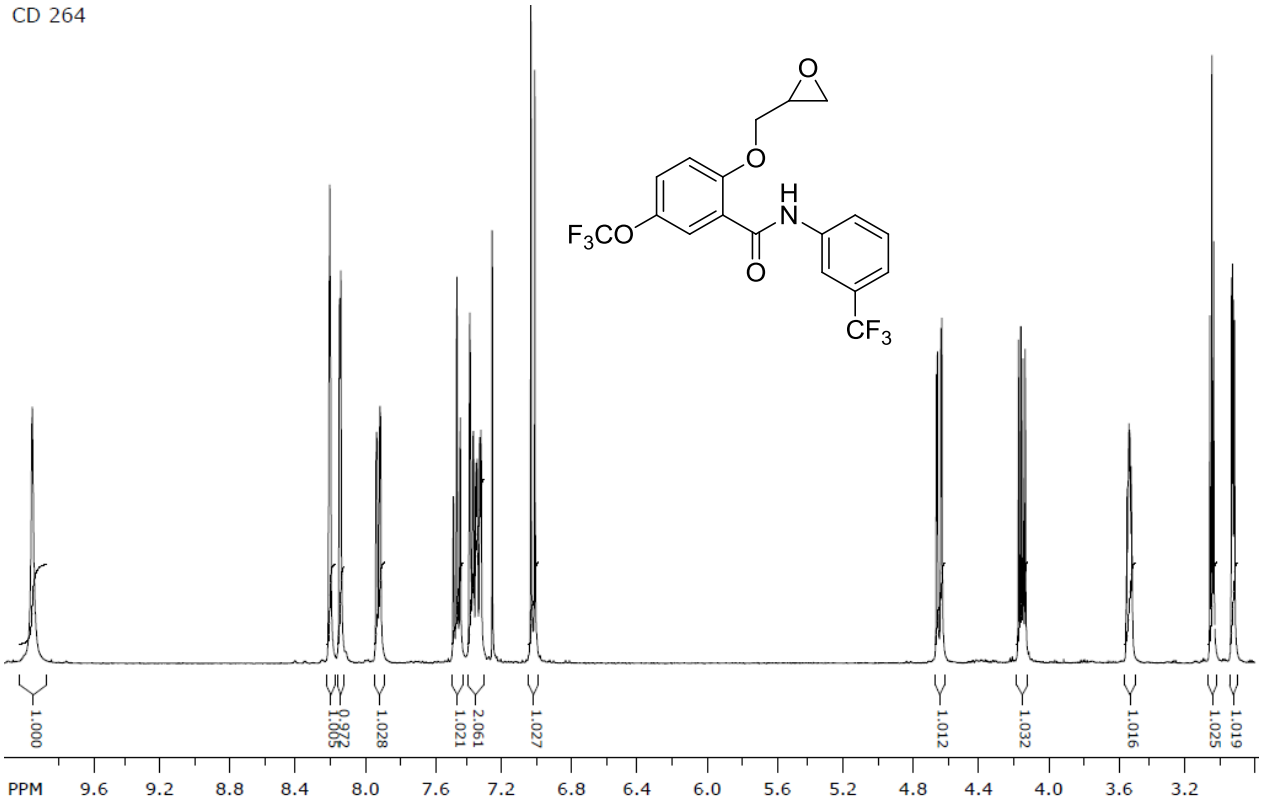


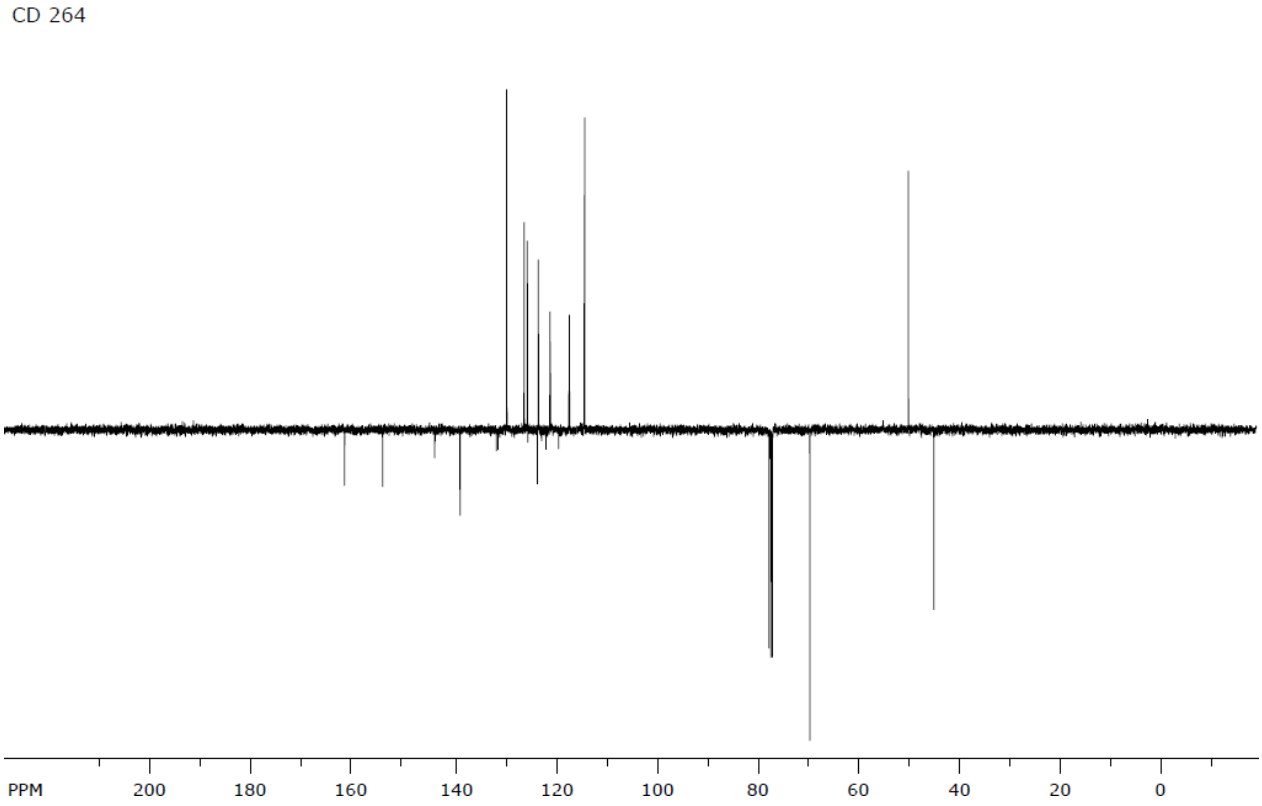
5-chloro-2-(oxiran-2-ylmethoxy)-*N*-(4-(trifluoromethoxy)-3-(trifluoromethyl)phenyl)benzamide (368)



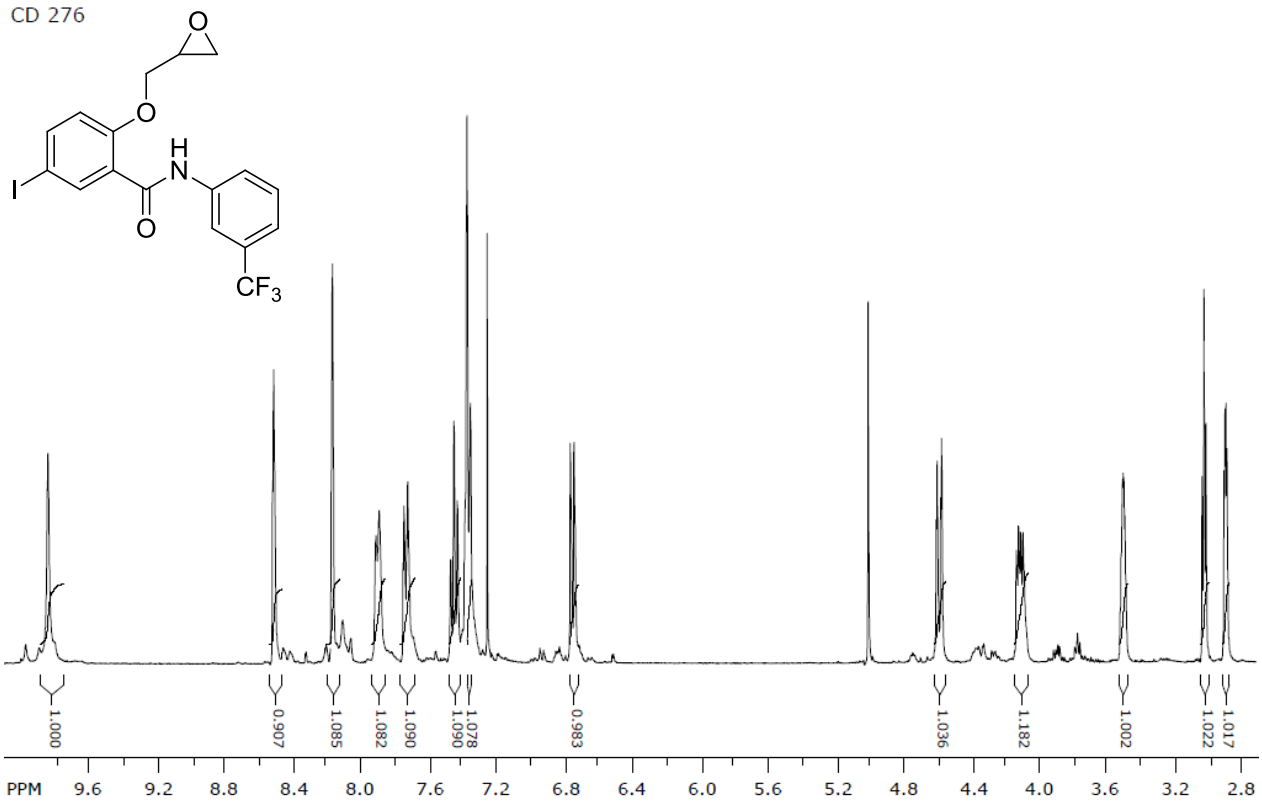


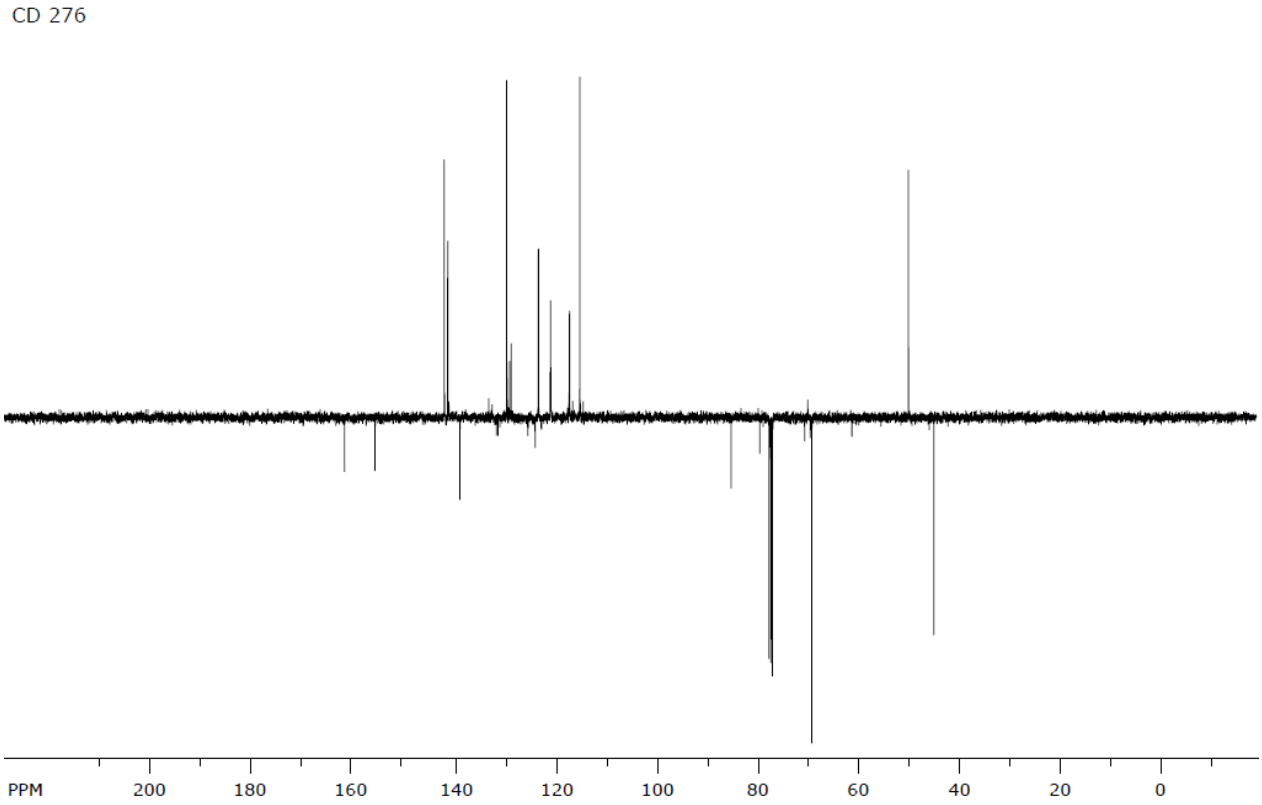
2-(oxiran-2-ylmethoxy)-5-(trifluoromethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (369)



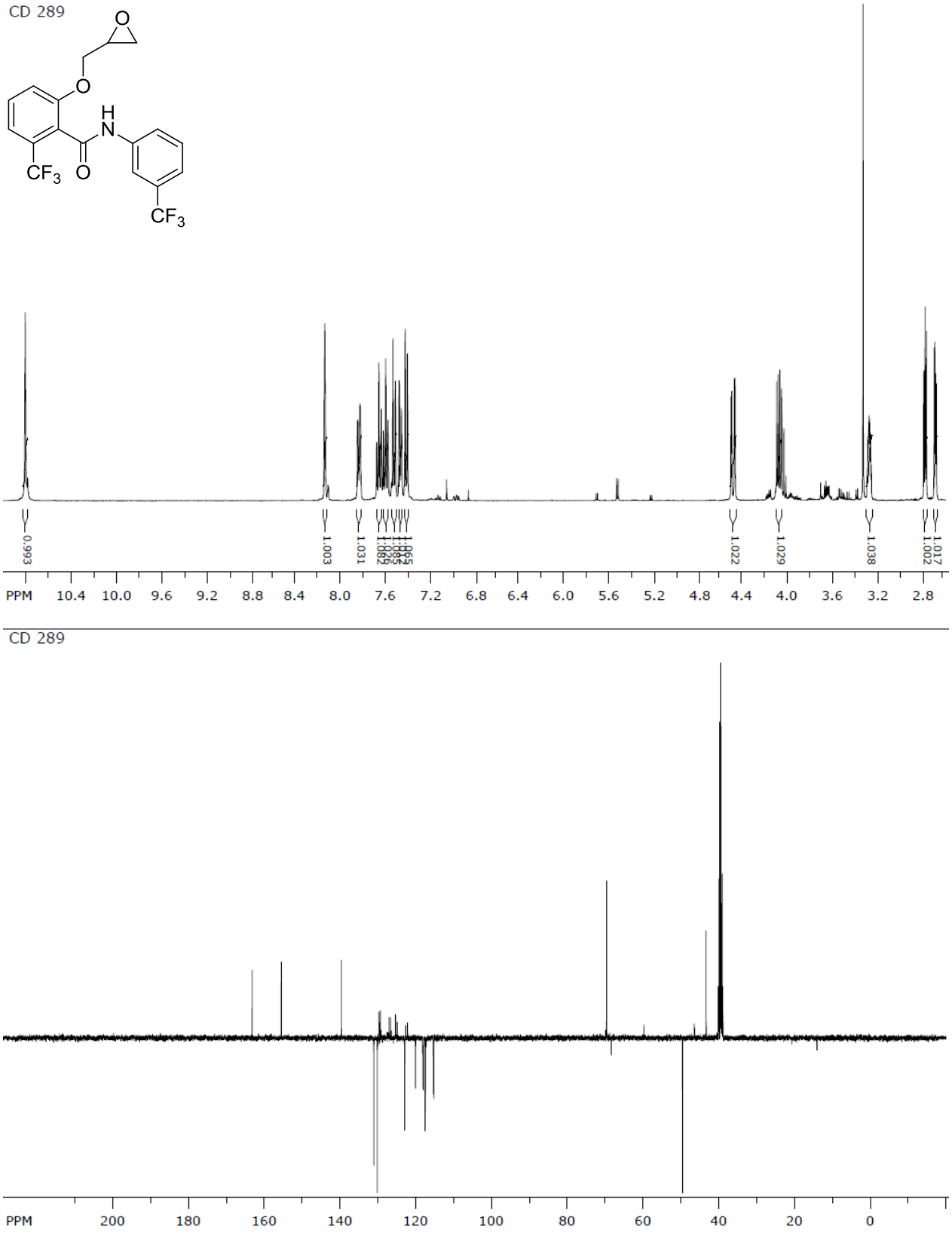


5-iodo-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (370)

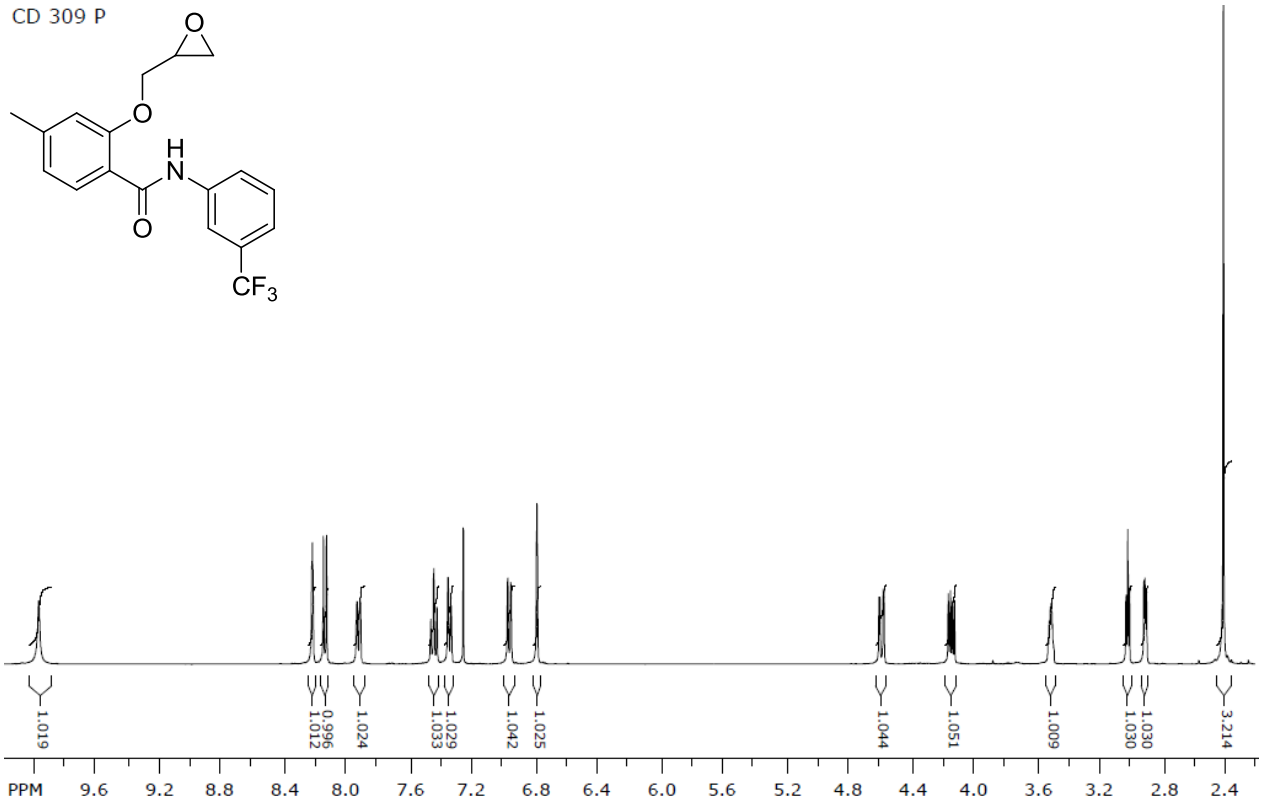


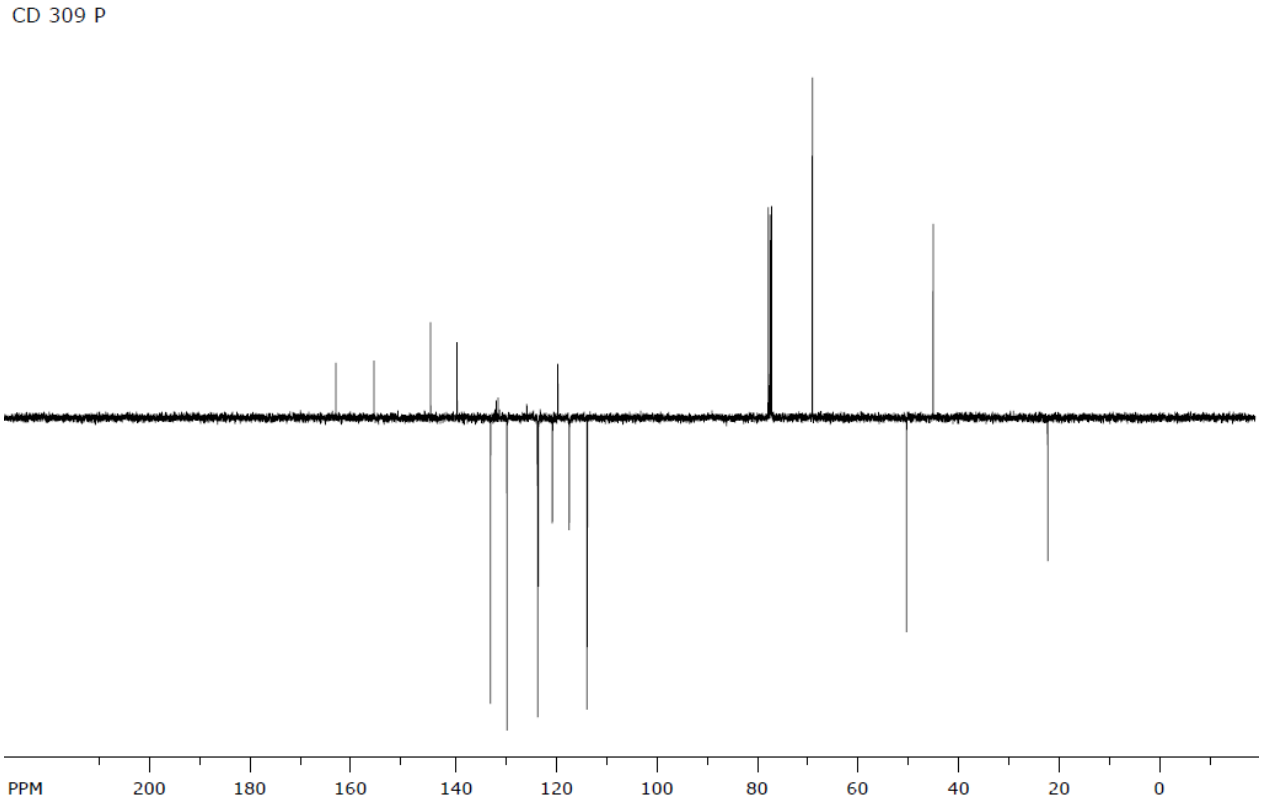


2-(oxiran-2-ylmethoxy)-6-(trifluoromethyl)-*N*-(3-(trifluoromethyl)phenyl)benzamide (371)

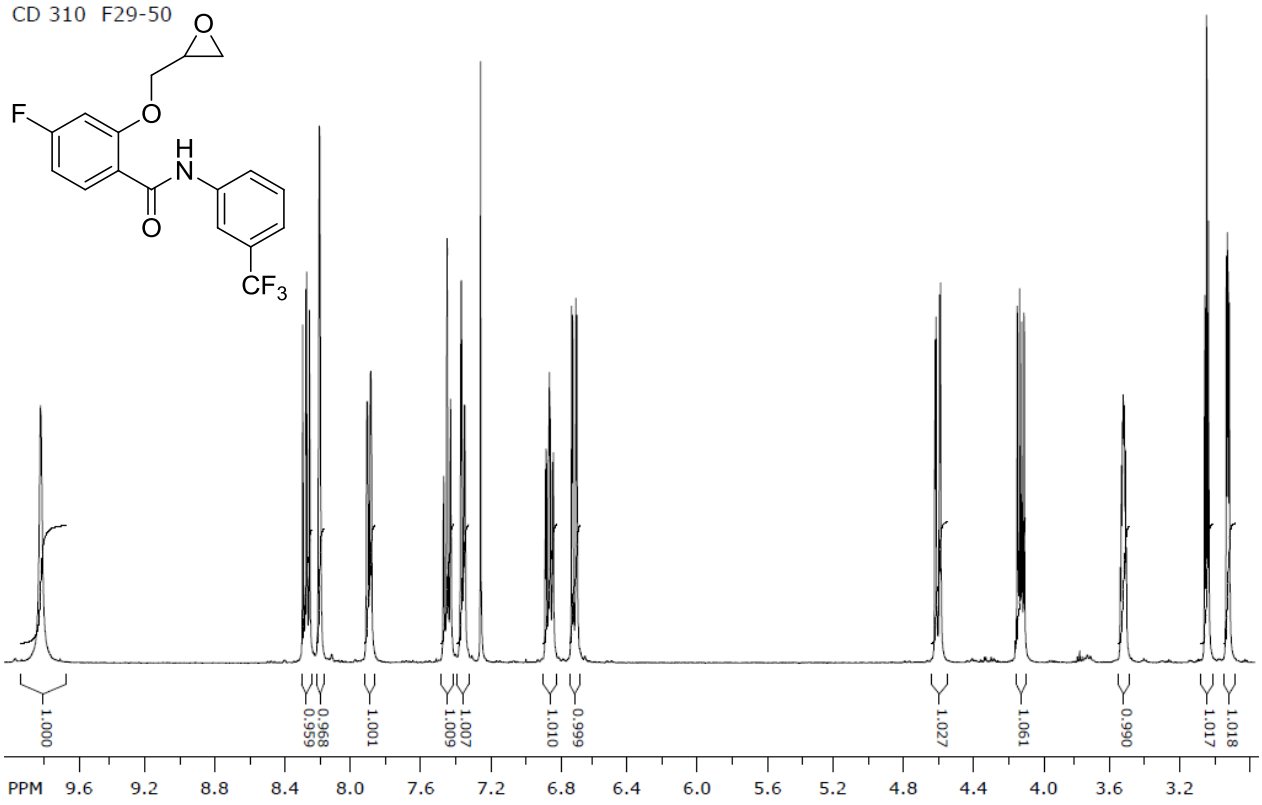


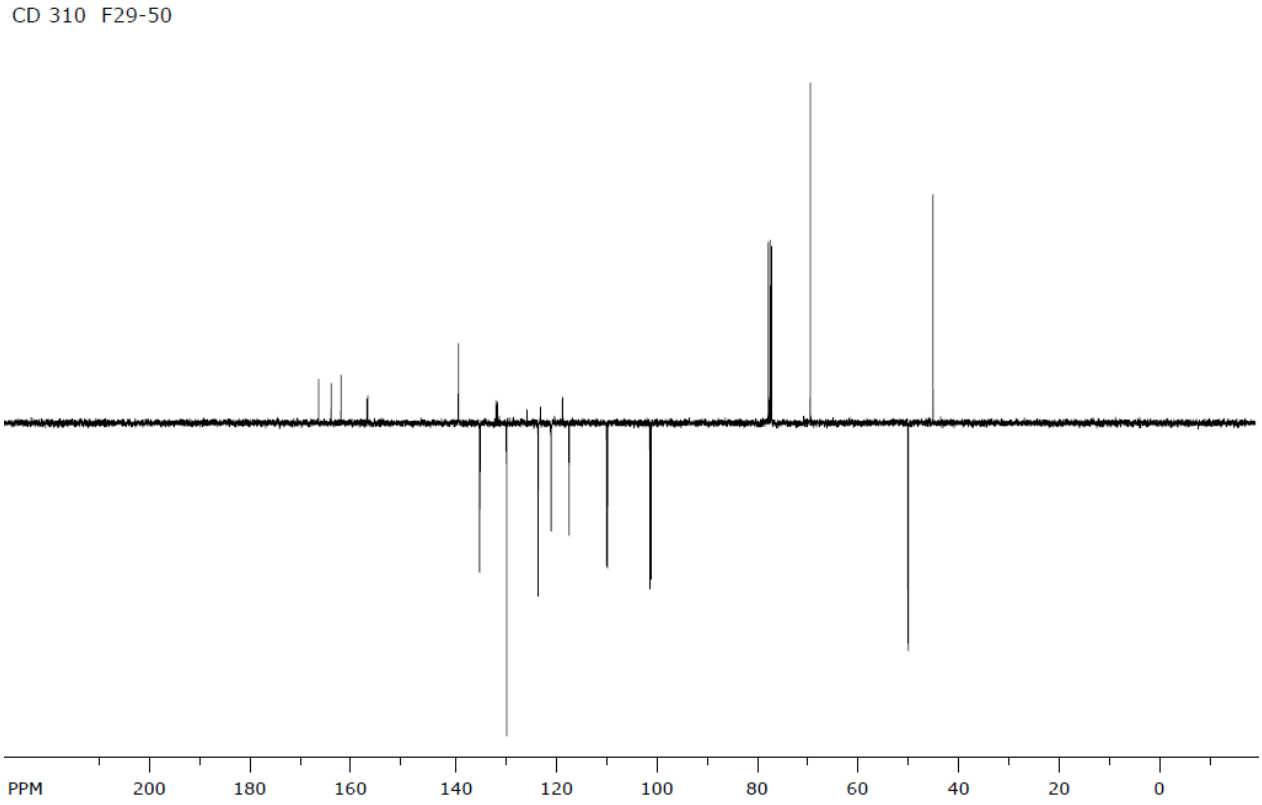
4-methyl-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (372)



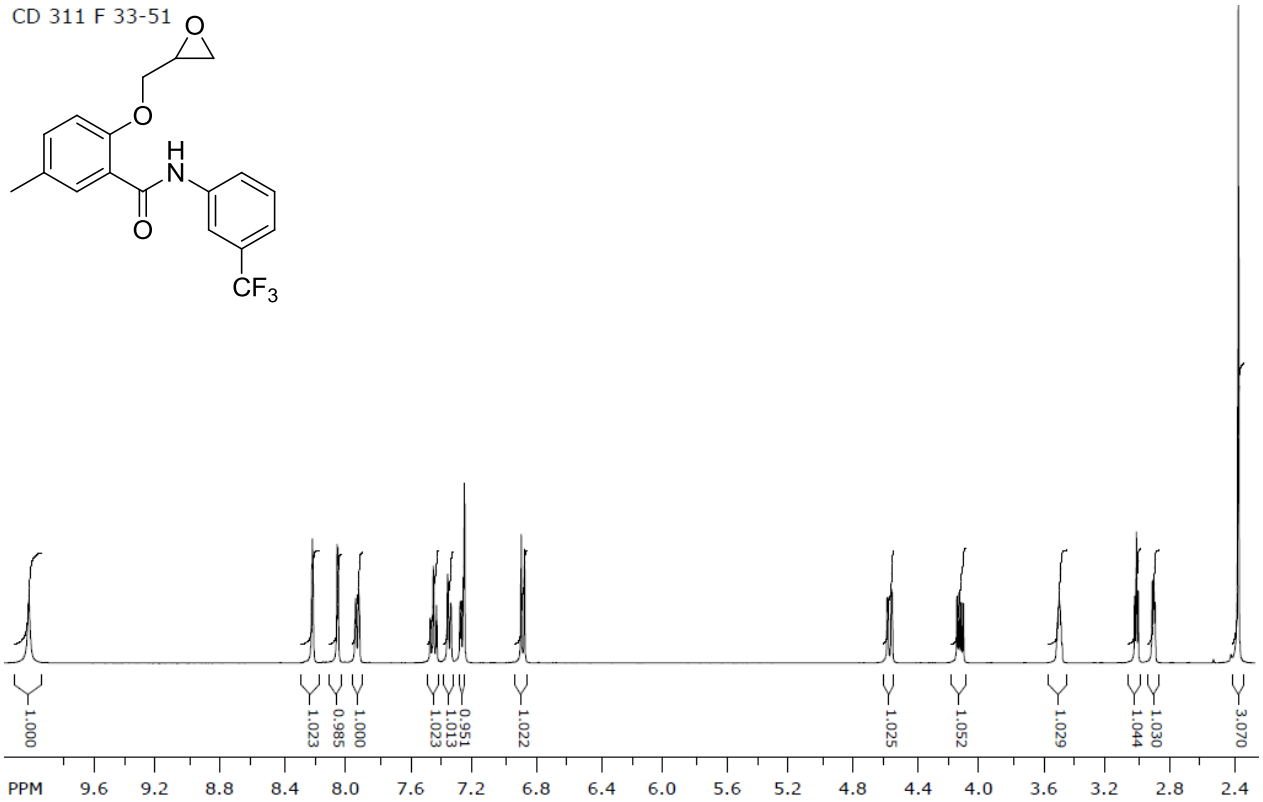


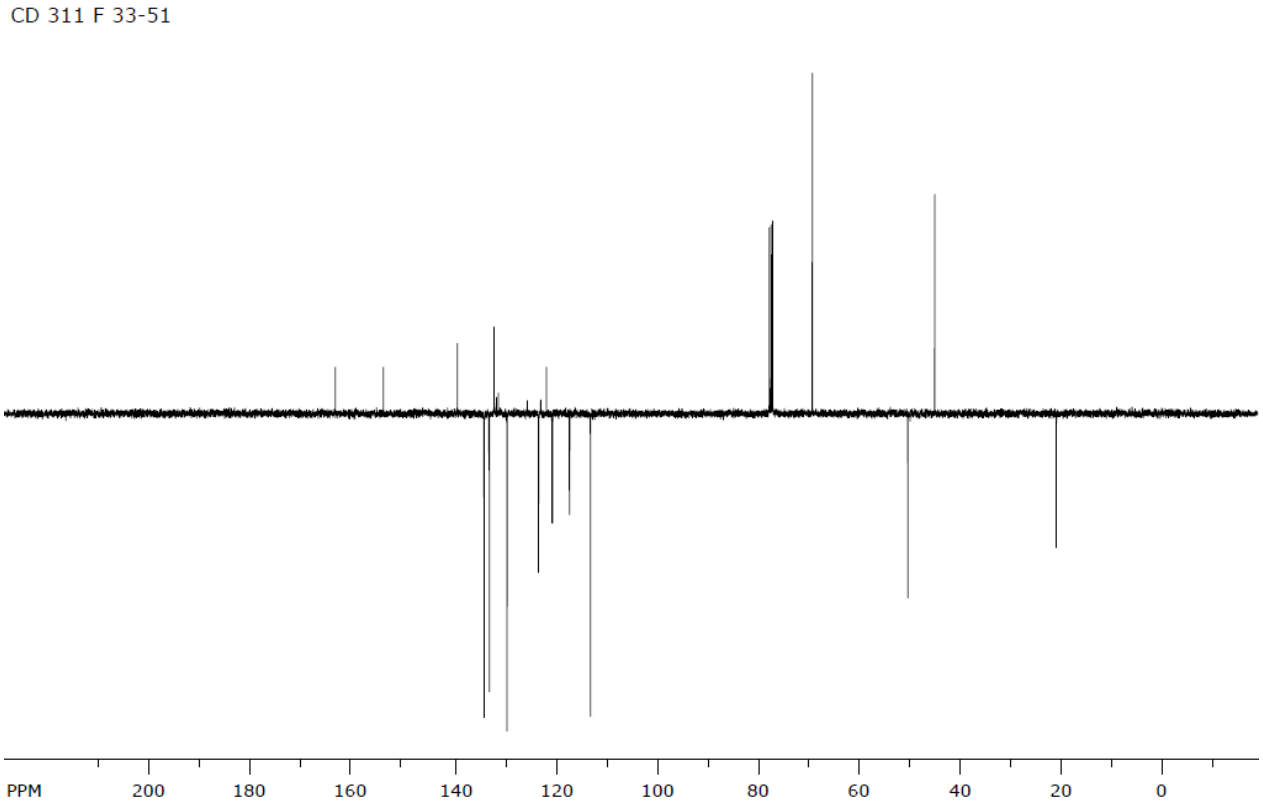
4-fluoro-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (373)



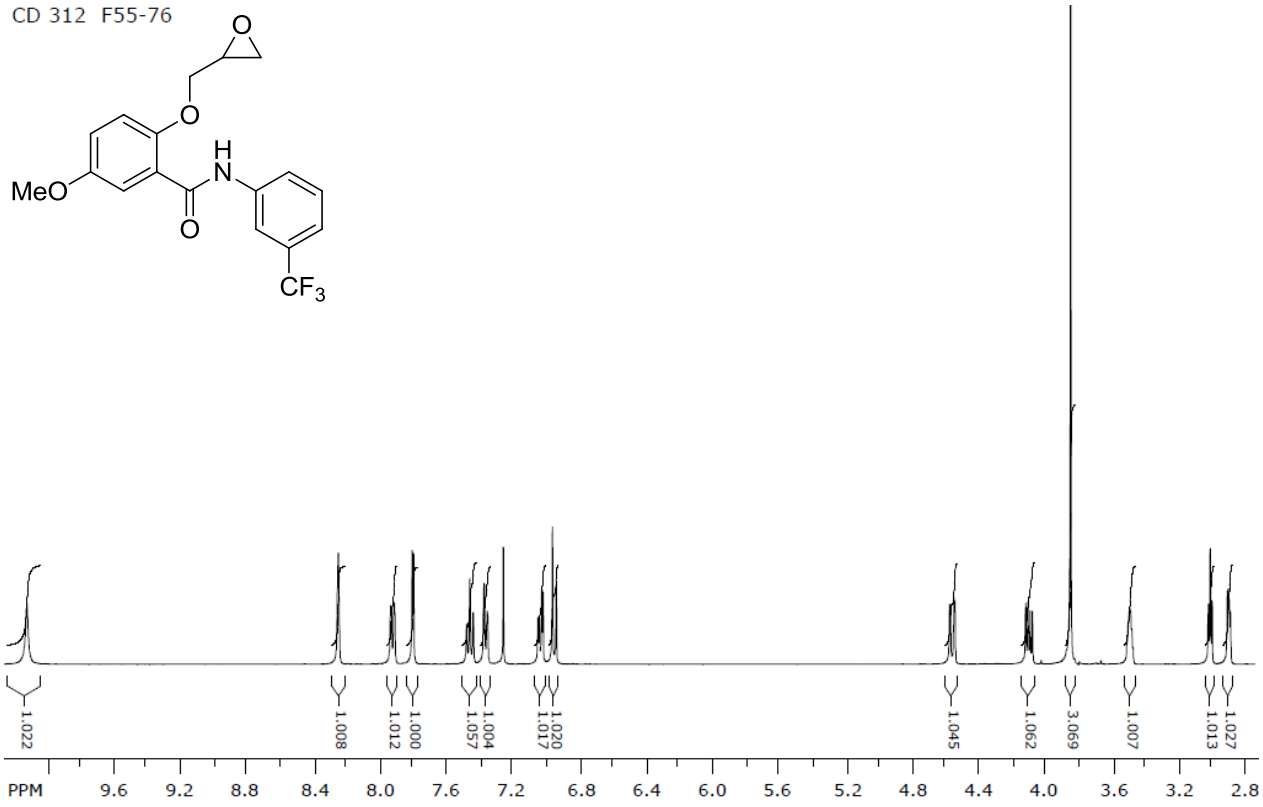


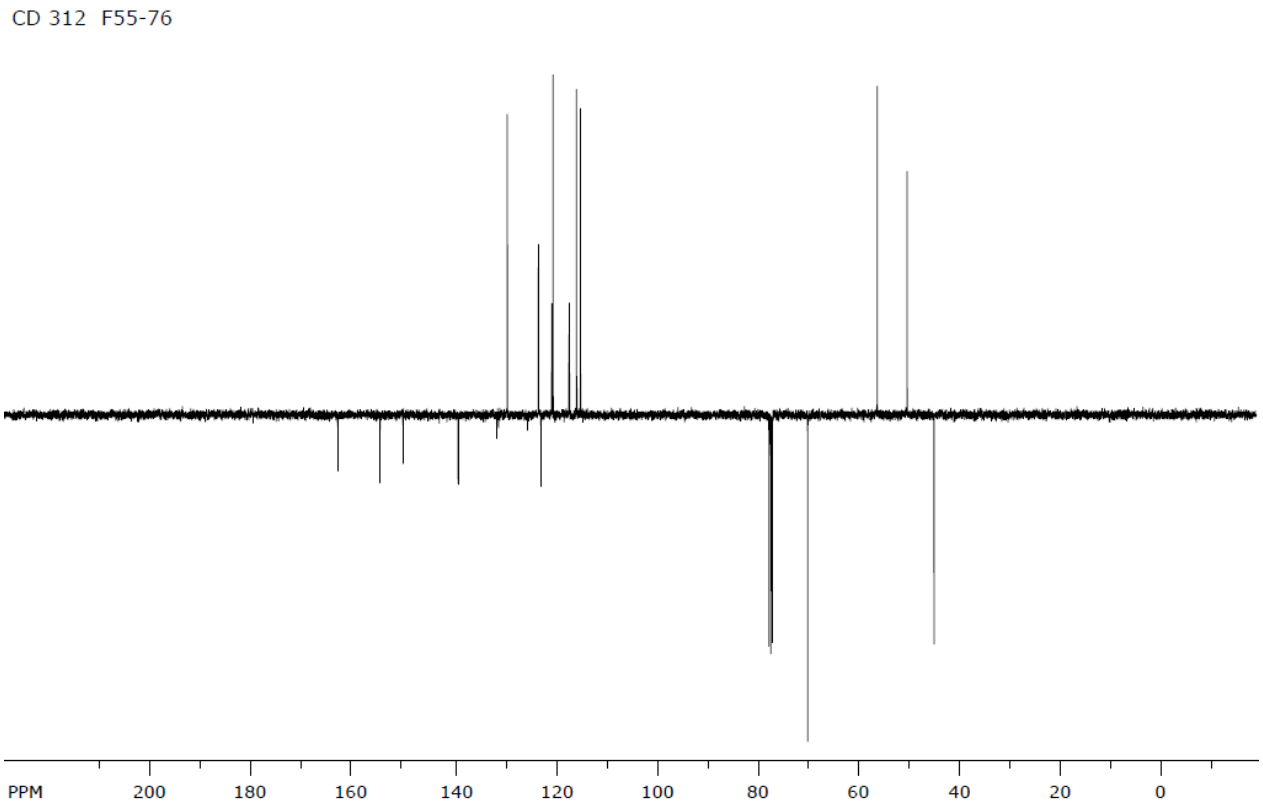
5-methyl-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (374)



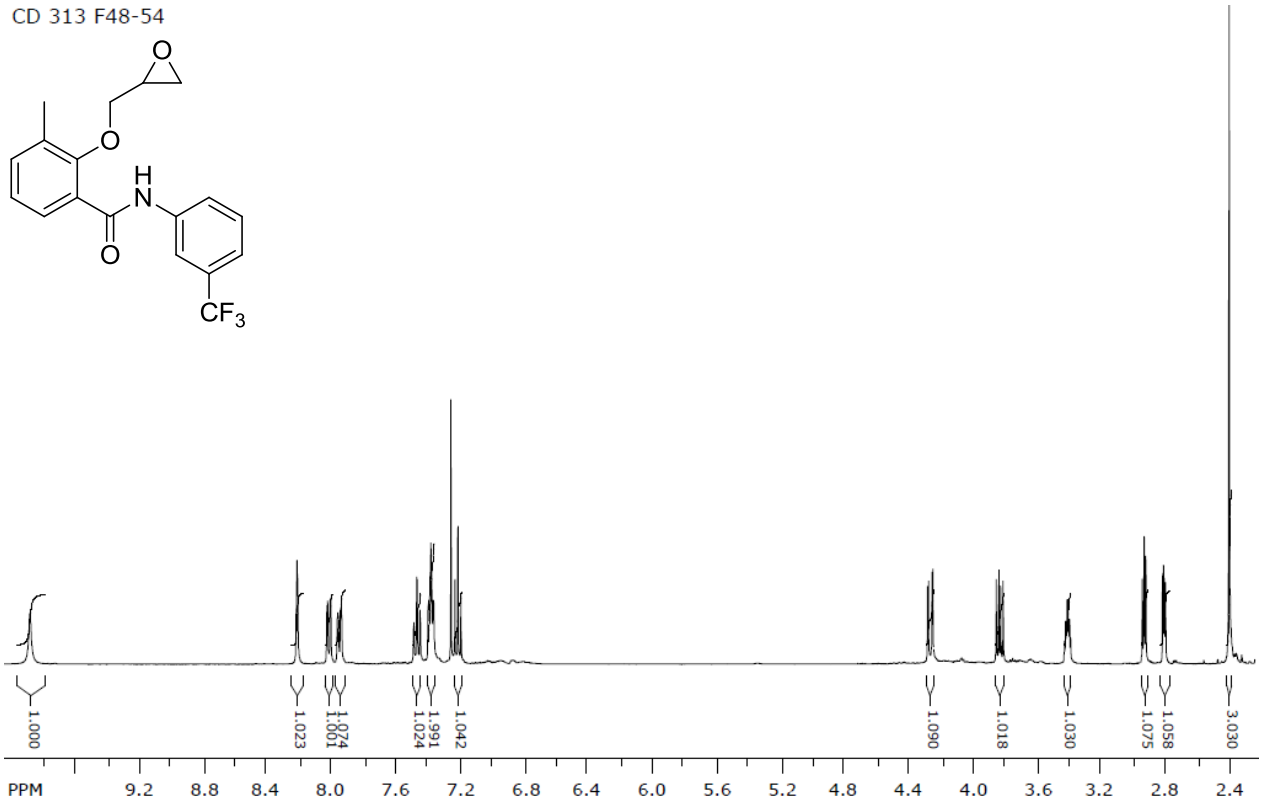


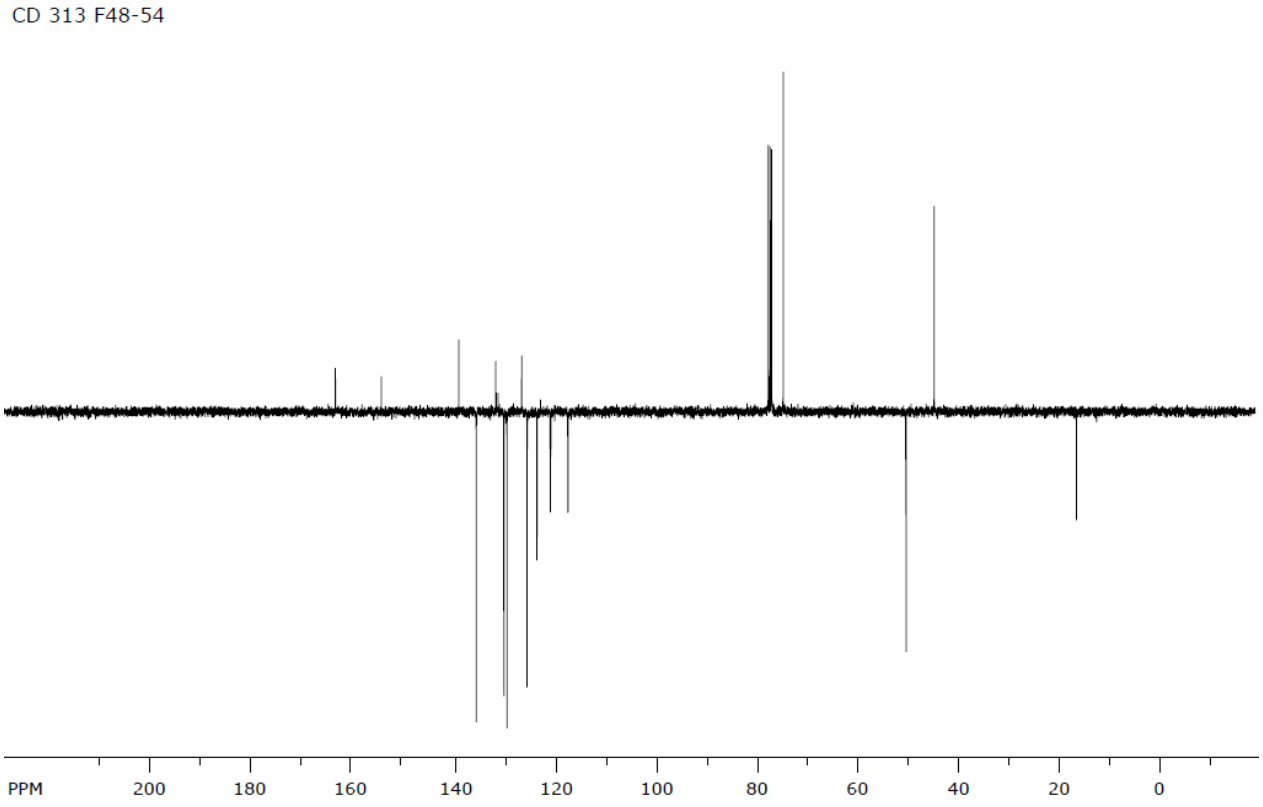
5-methoxy-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (375)



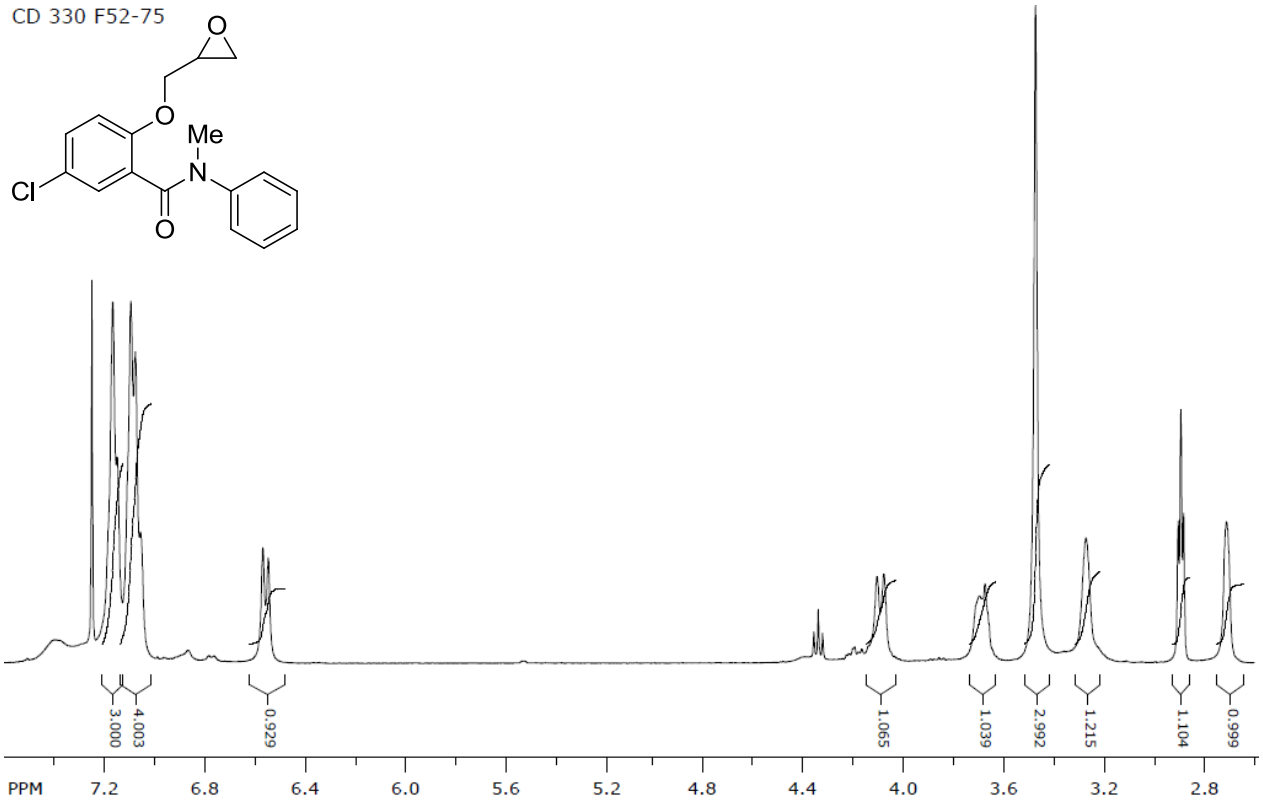


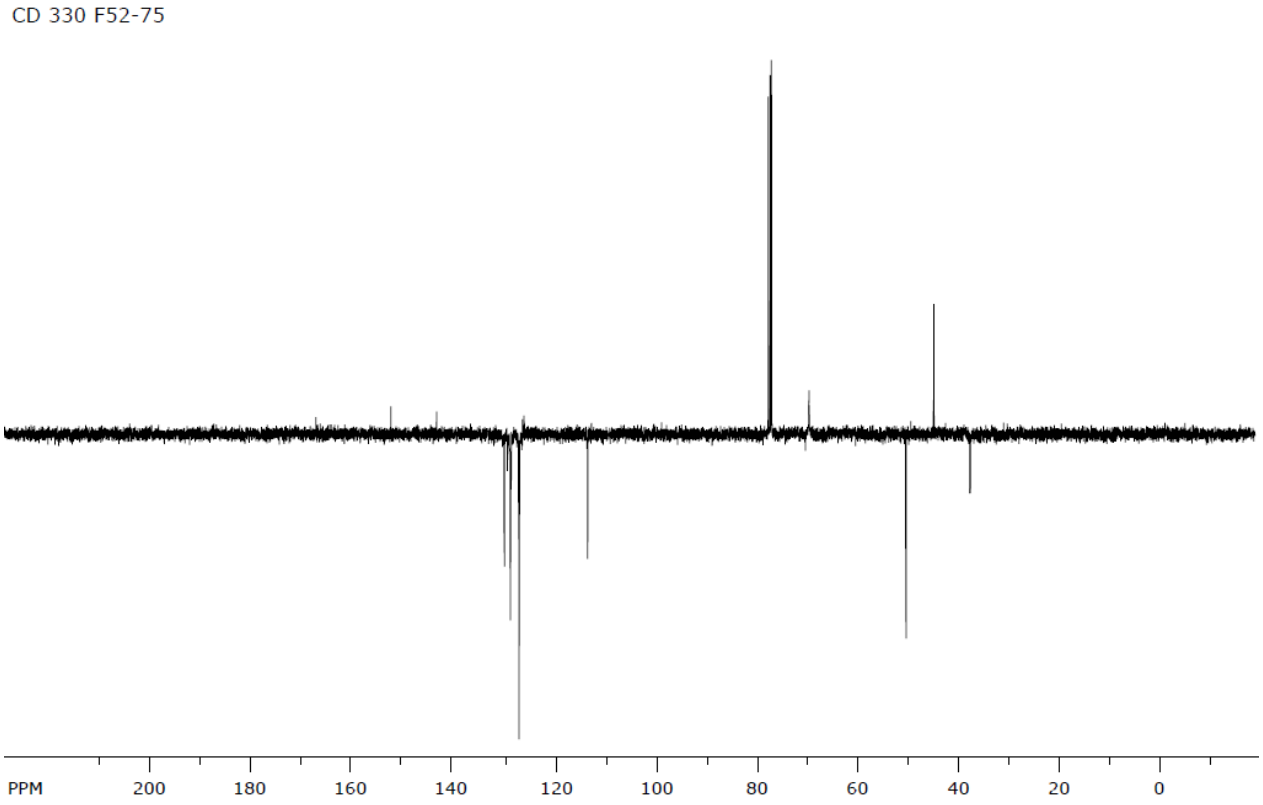
3-methyl-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (376)



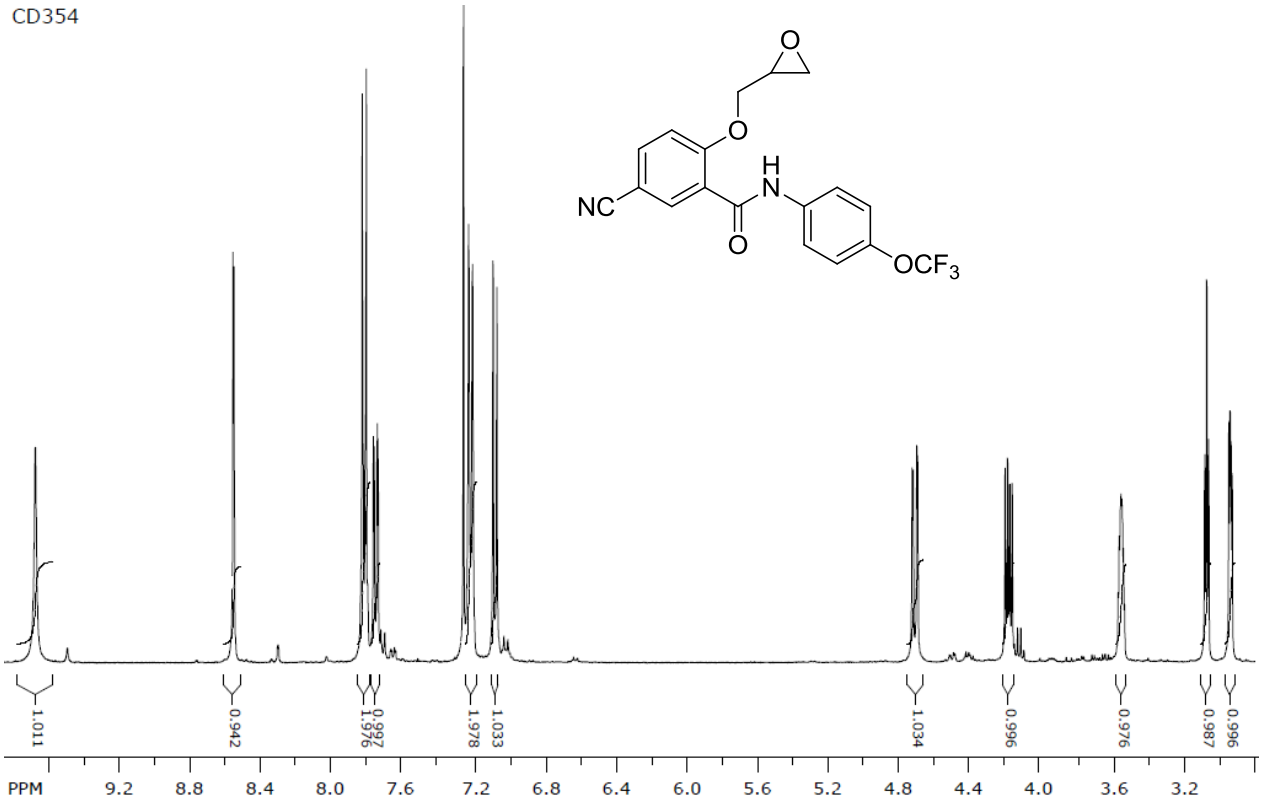


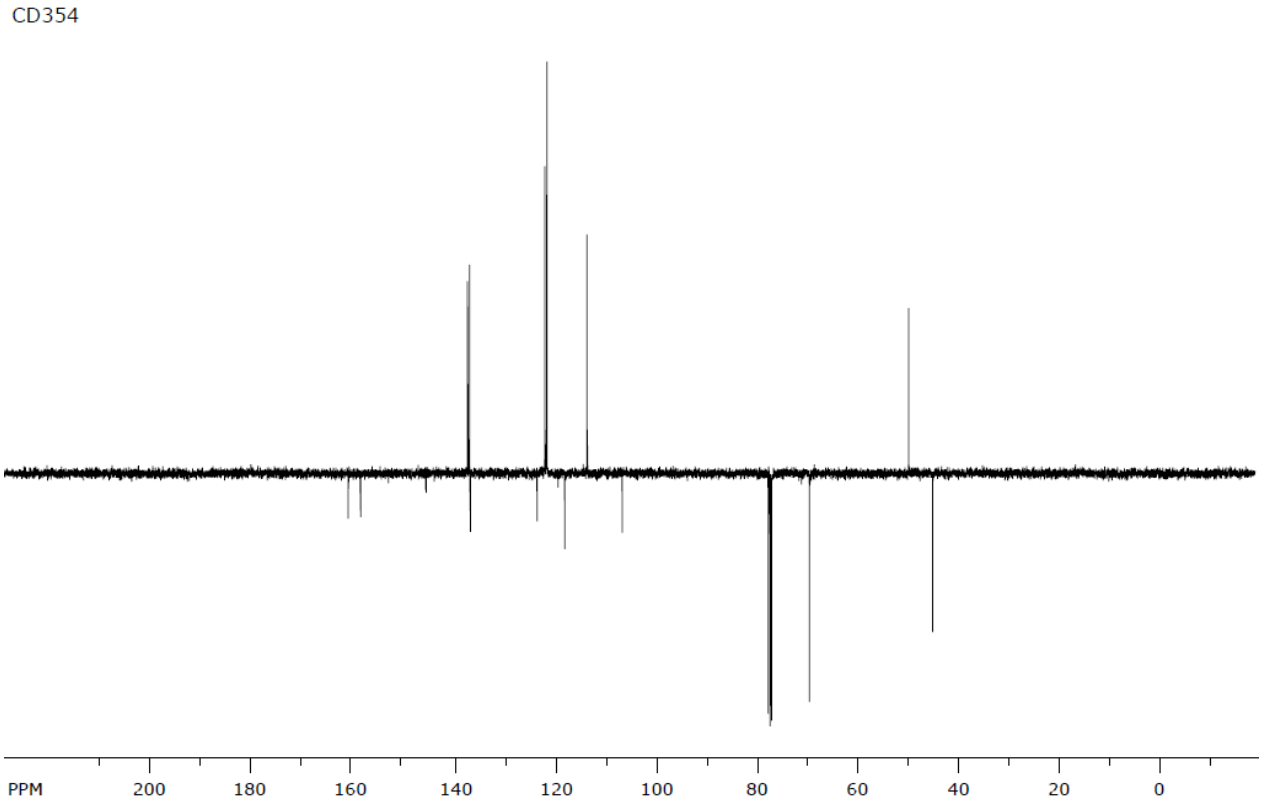
5-chloro-*N*-methyl-2-(oxiran-2-ylmethoxy)-*N*-phenylbenzamide (377)



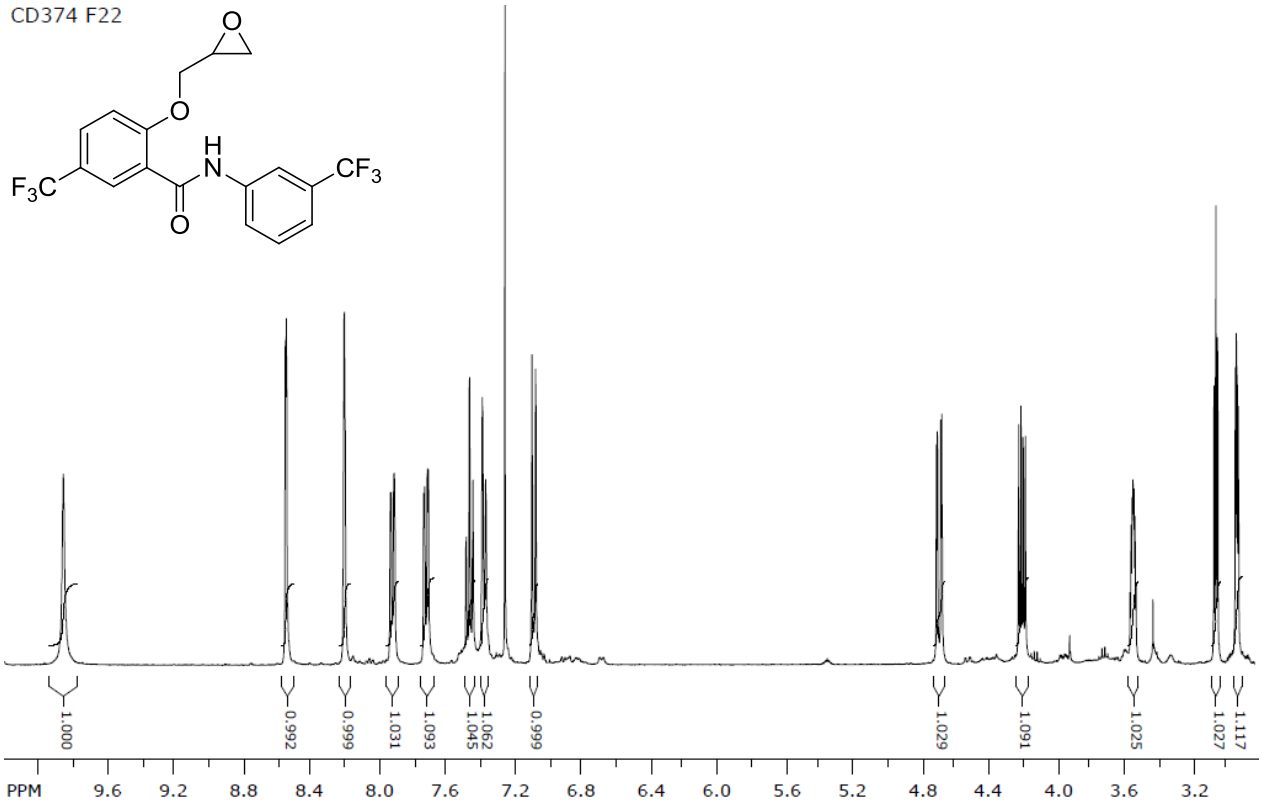


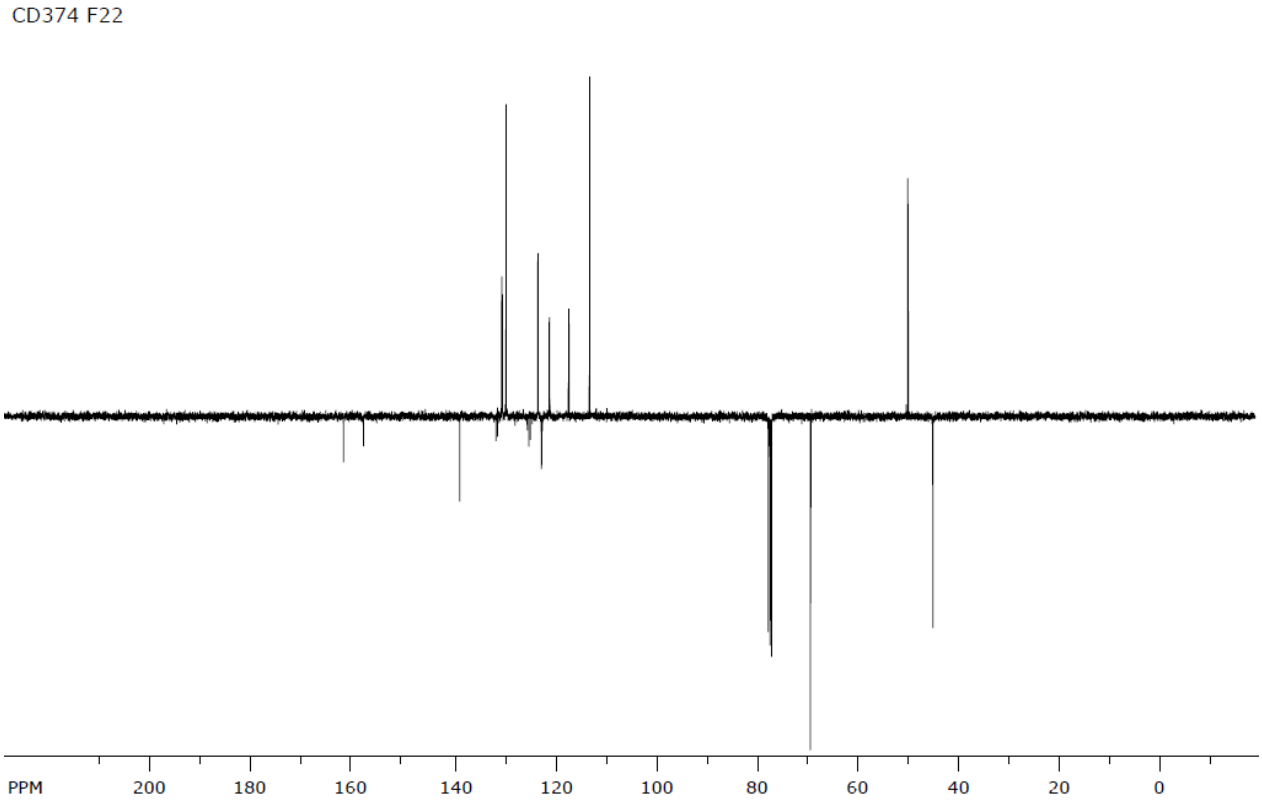
5-cyano-2-(oxiran-2-ylmethoxy)-*N*-(4-(trifluoromethoxy)phenyl)benzamide (378)



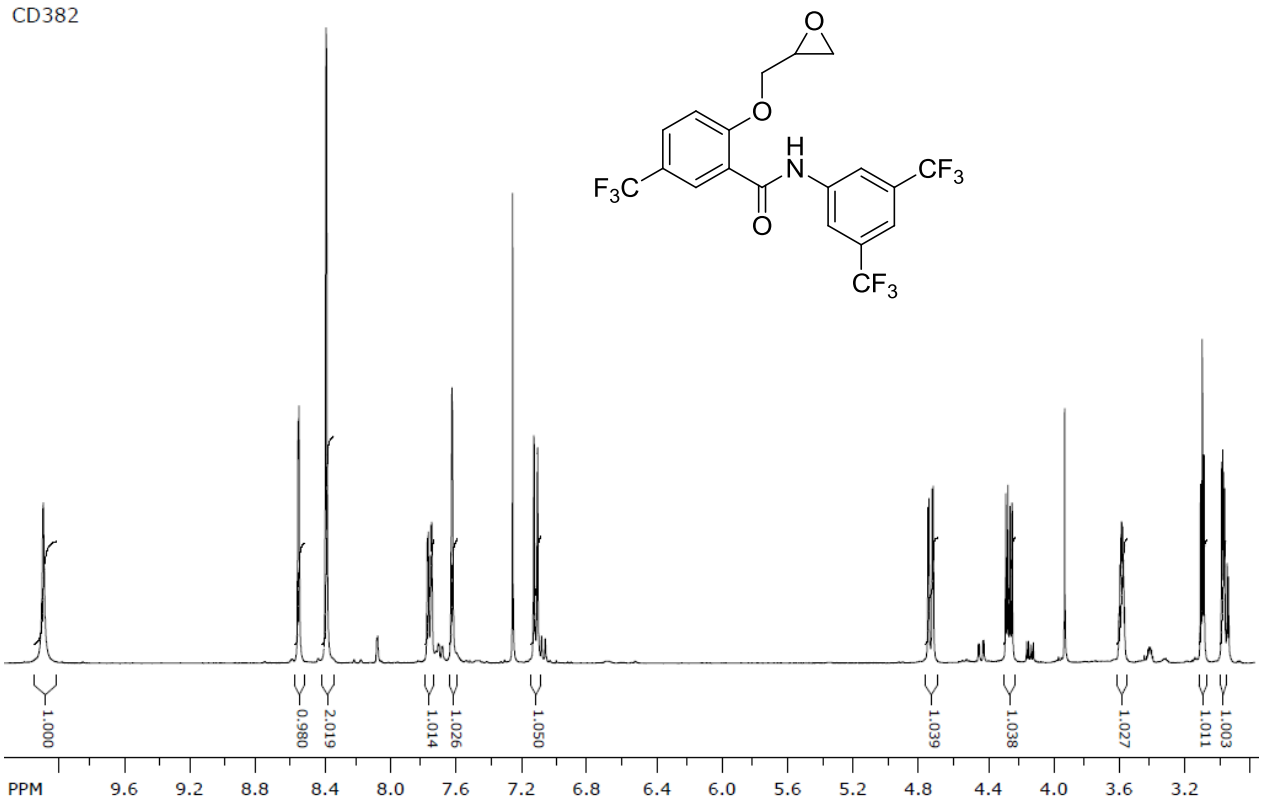


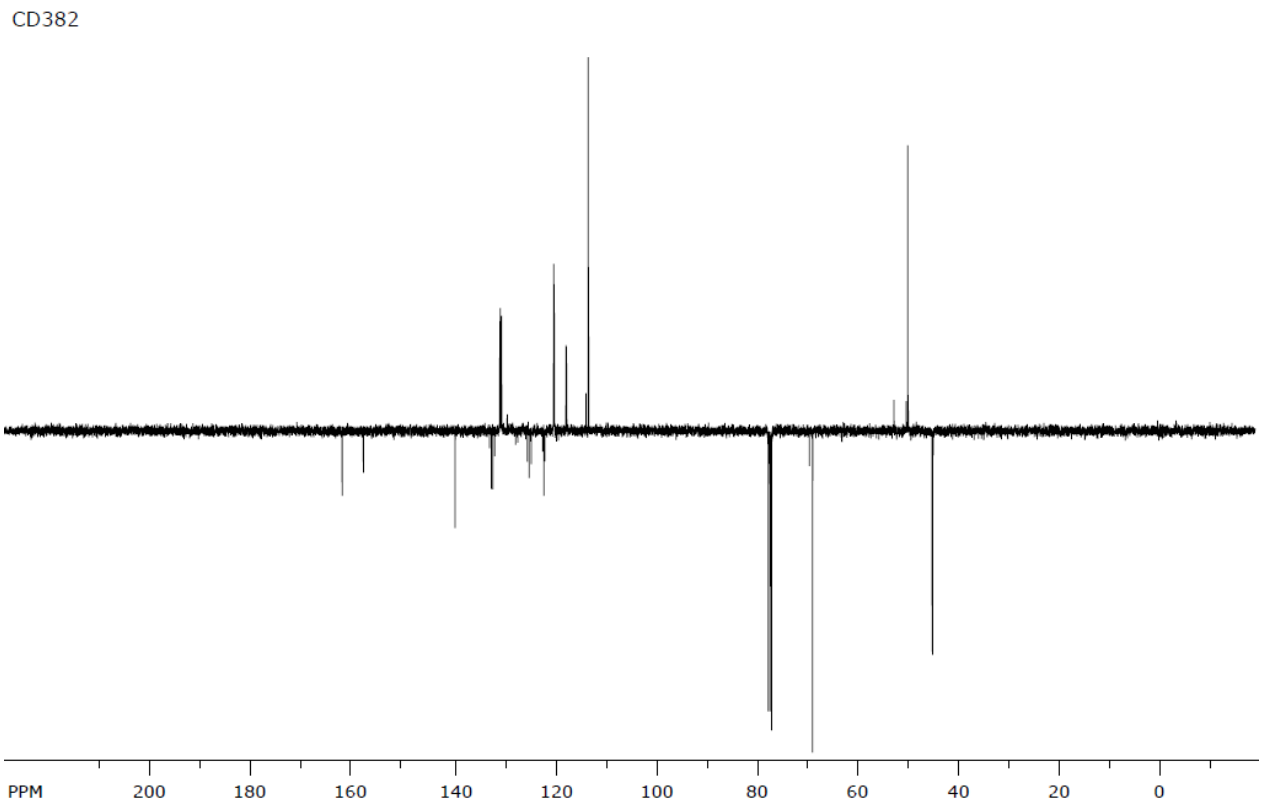
2-(oxiran-2-ylmethoxy)-5-(trifluoromethyl)-*N*-(3-(trifluoromethyl)phenyl)benzamide (379)



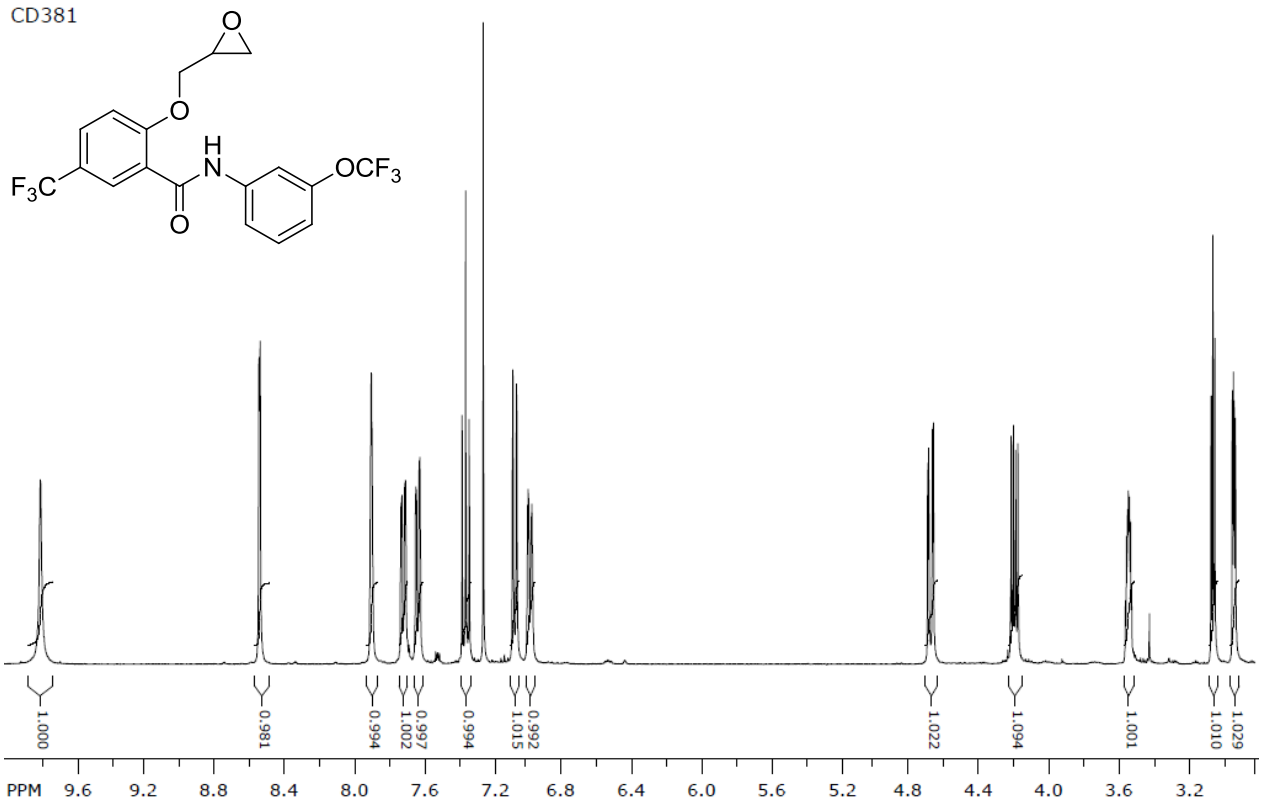


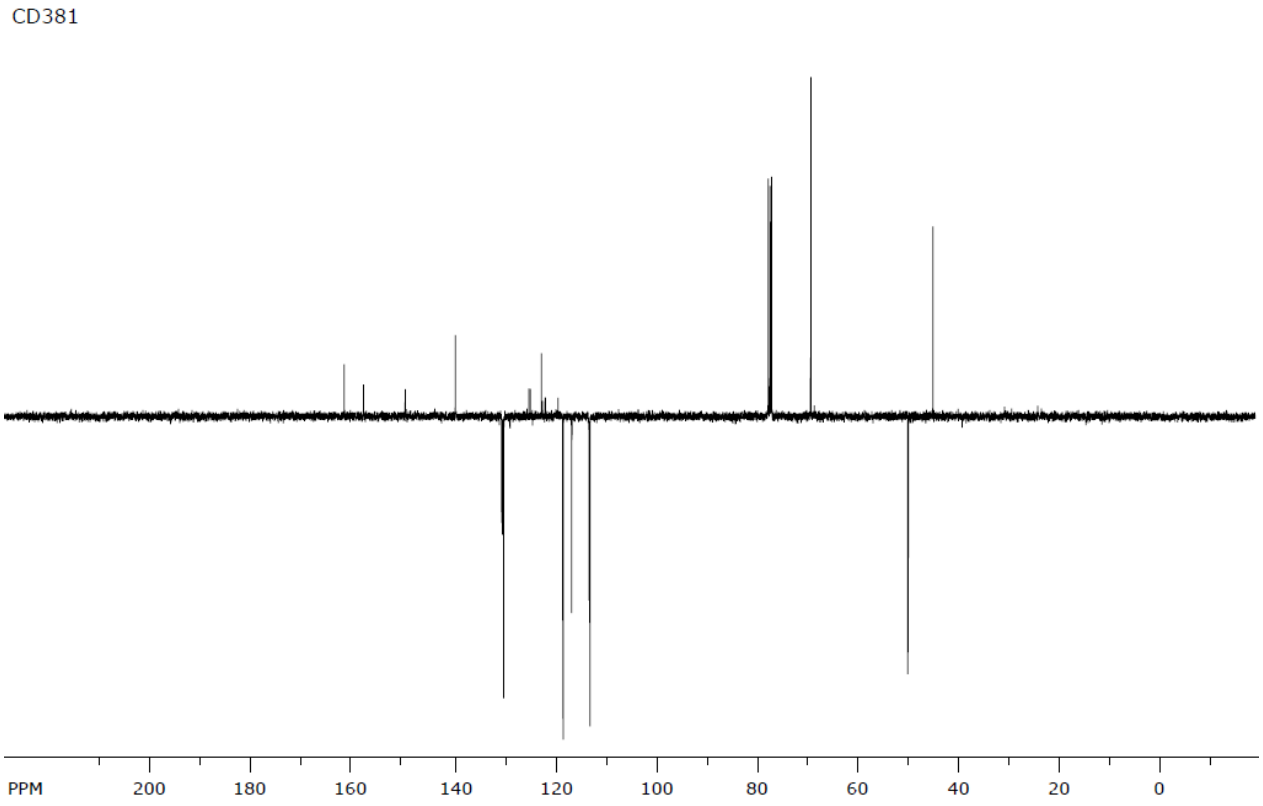
_N_-(3,5-bis(trifluoromethyl)phenyl)-2-(oxiran-2-ylmethoxy)-5-(trifluoromethyl)benzamide (380)



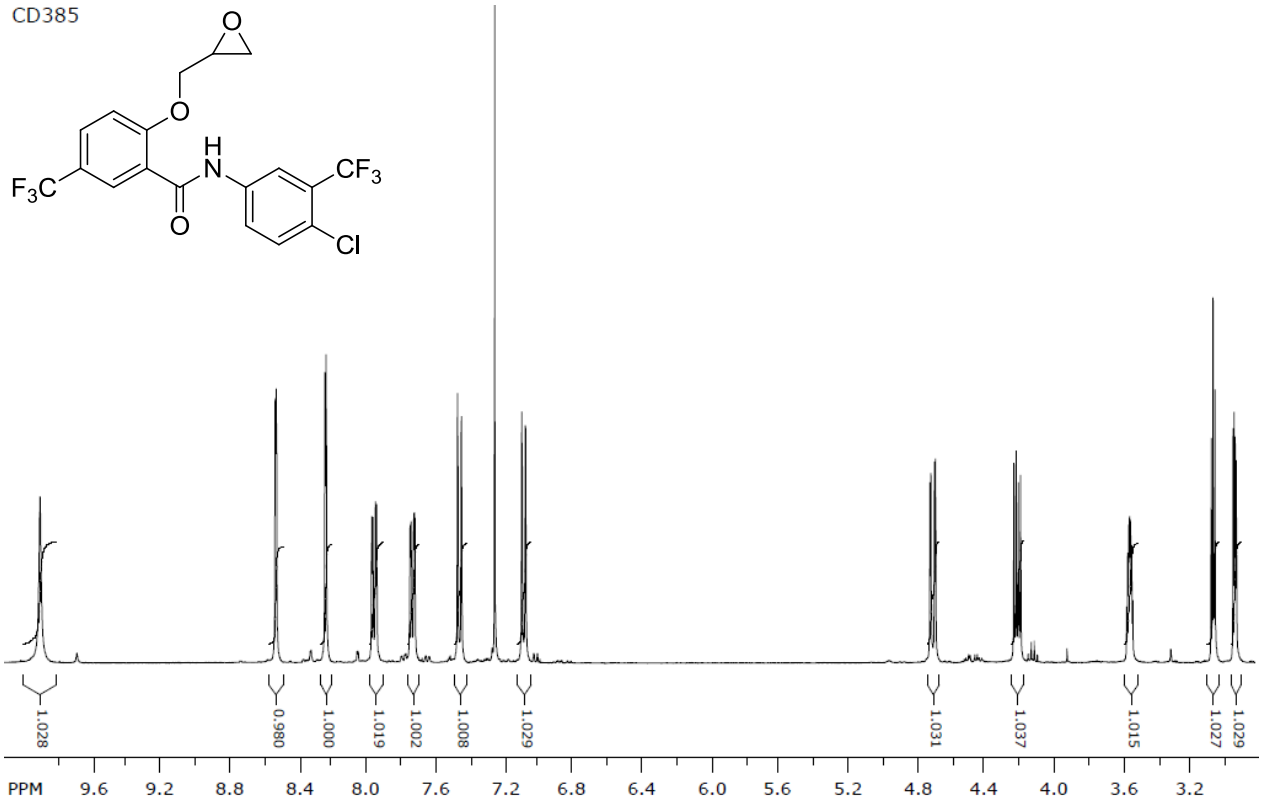


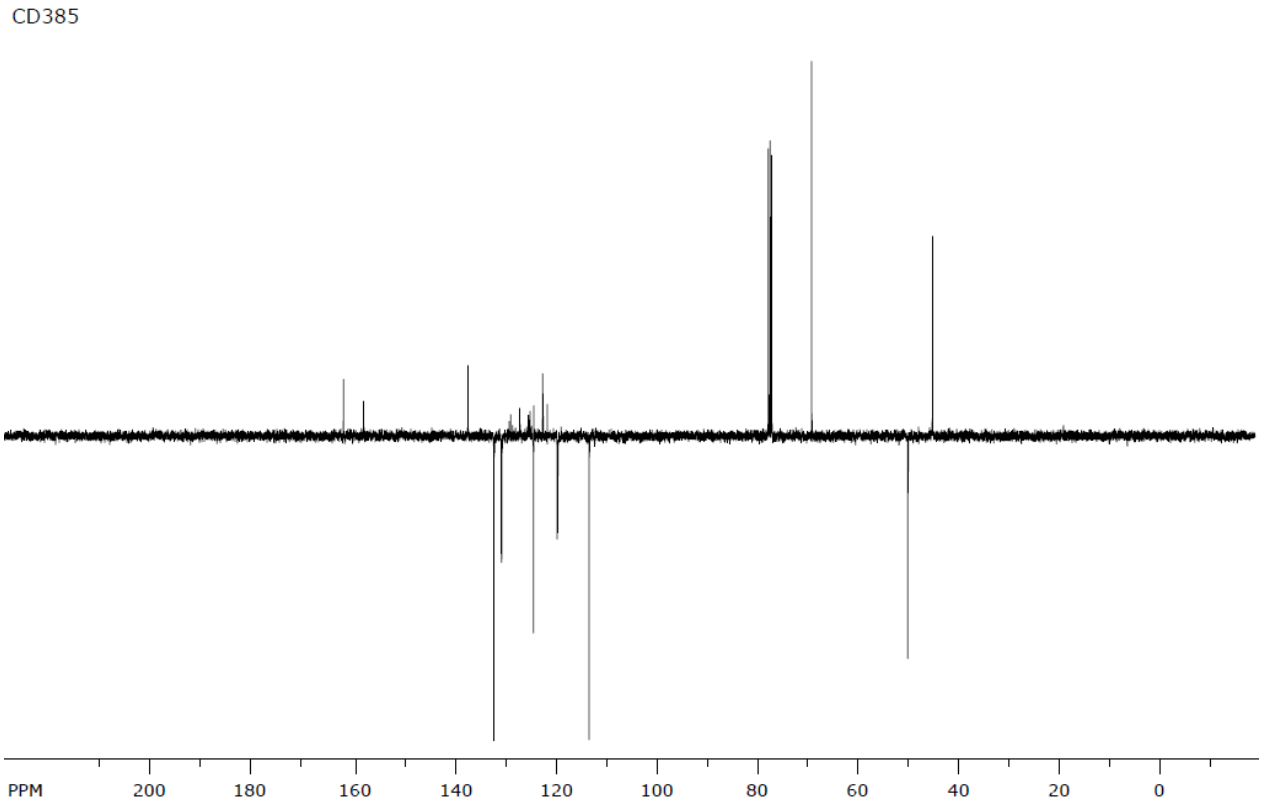
2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethoxy)phenyl)-5-(trifluoromethyl)benzamide (381)



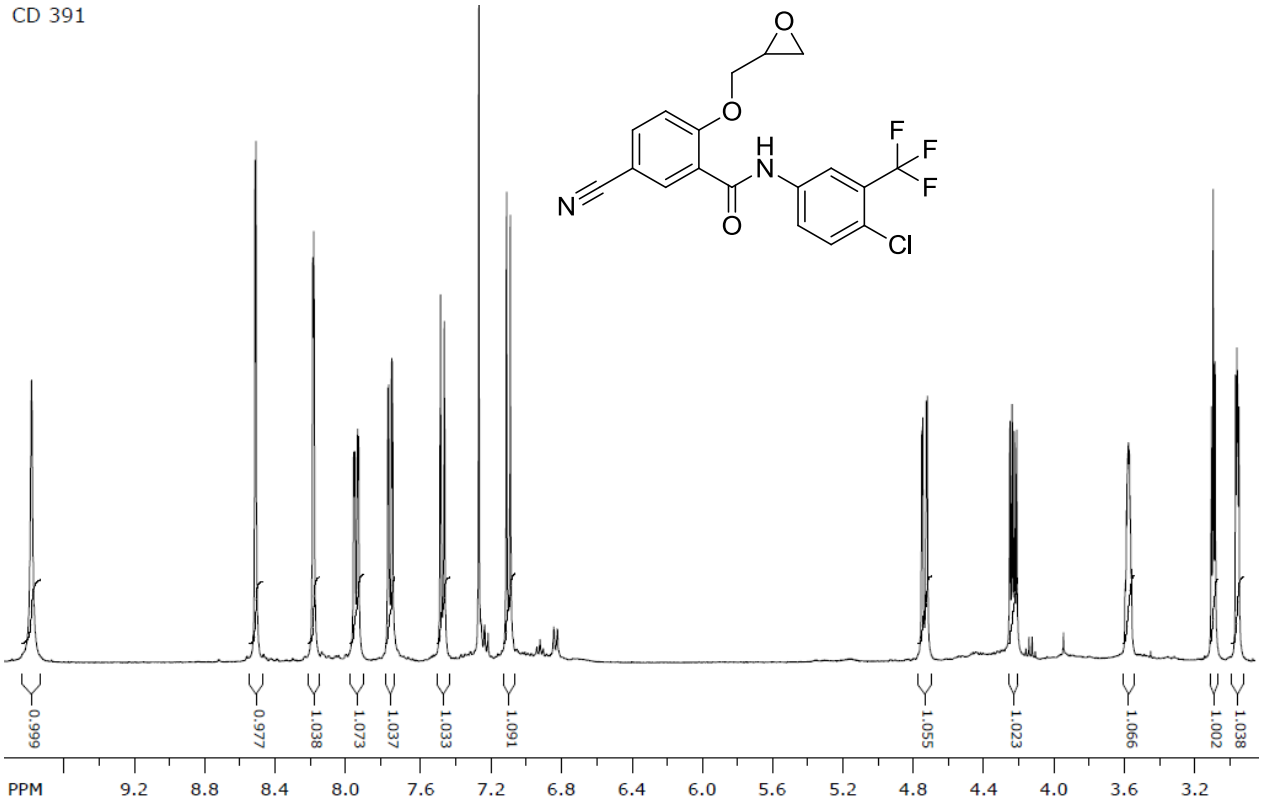


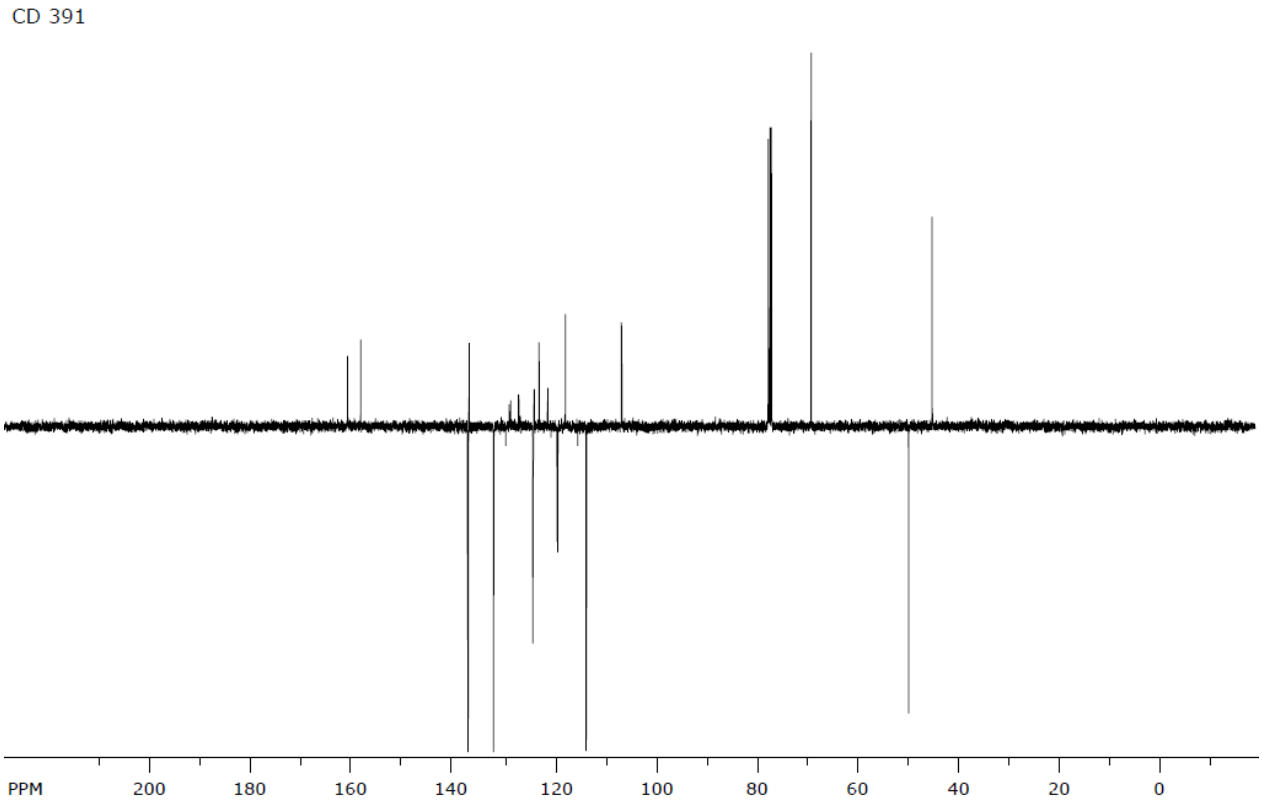
_N_-(4-chloro-3-(trifluoromethyl)phenyl)-2-(oxiran-2-ylmethoxy)-5-(trifluoromethyl)benzamide (382)



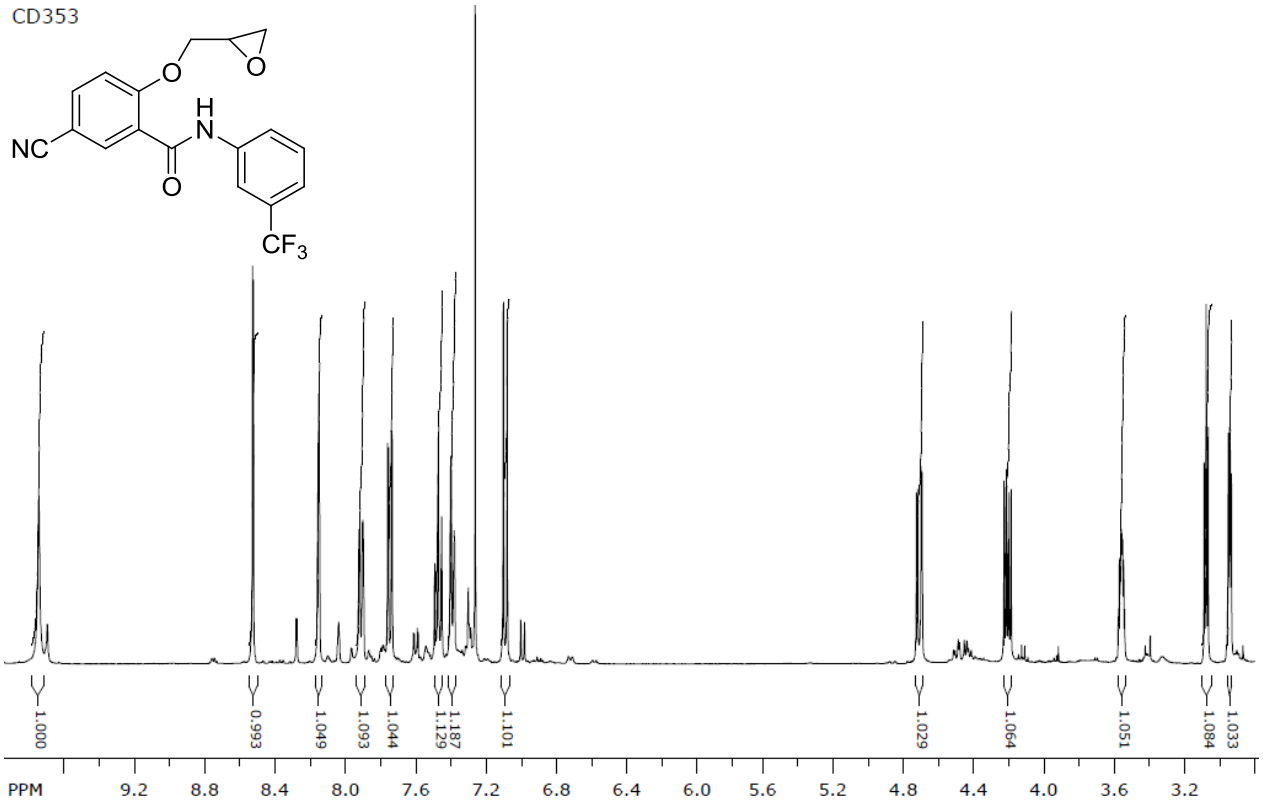


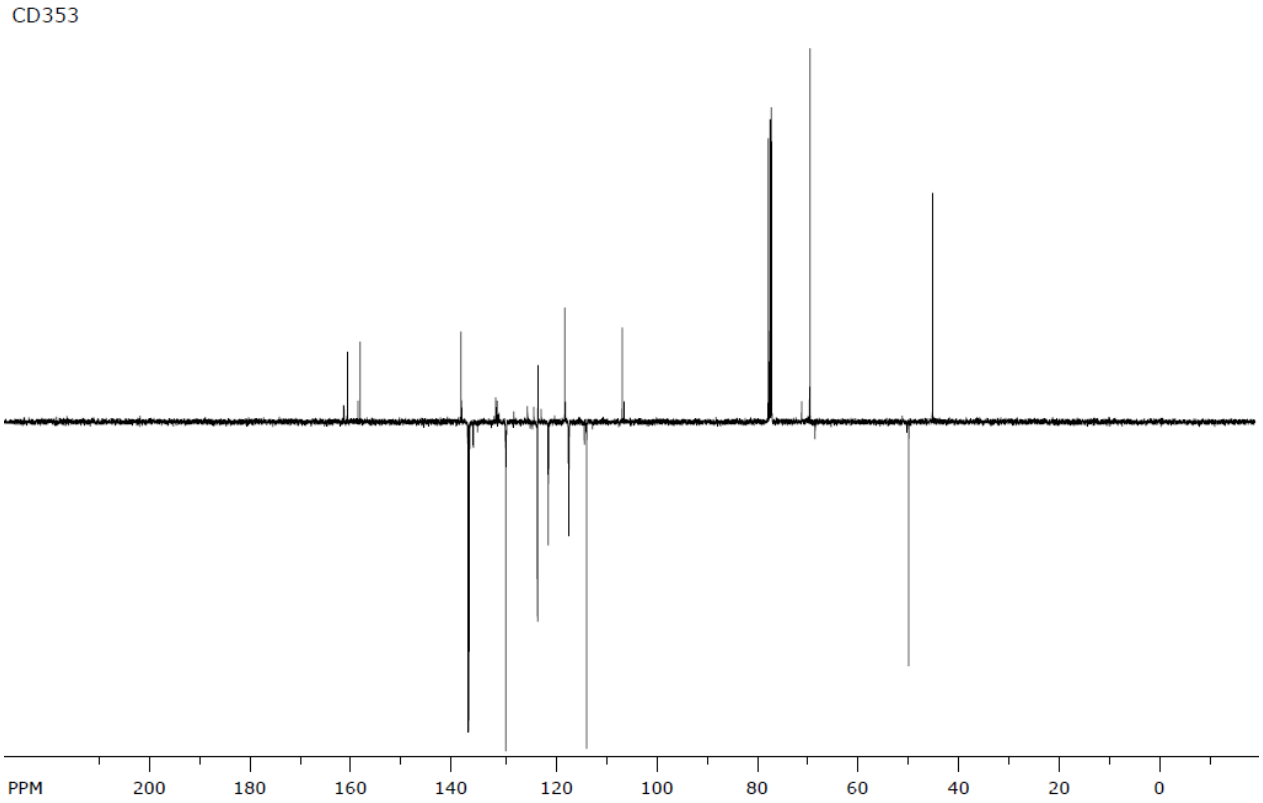
_N_-(4-chloro-3-(trifluoromethyl)phenyl)-5-cyano-2-(oxiran-2-ylmethoxy)benzamide (383**)**



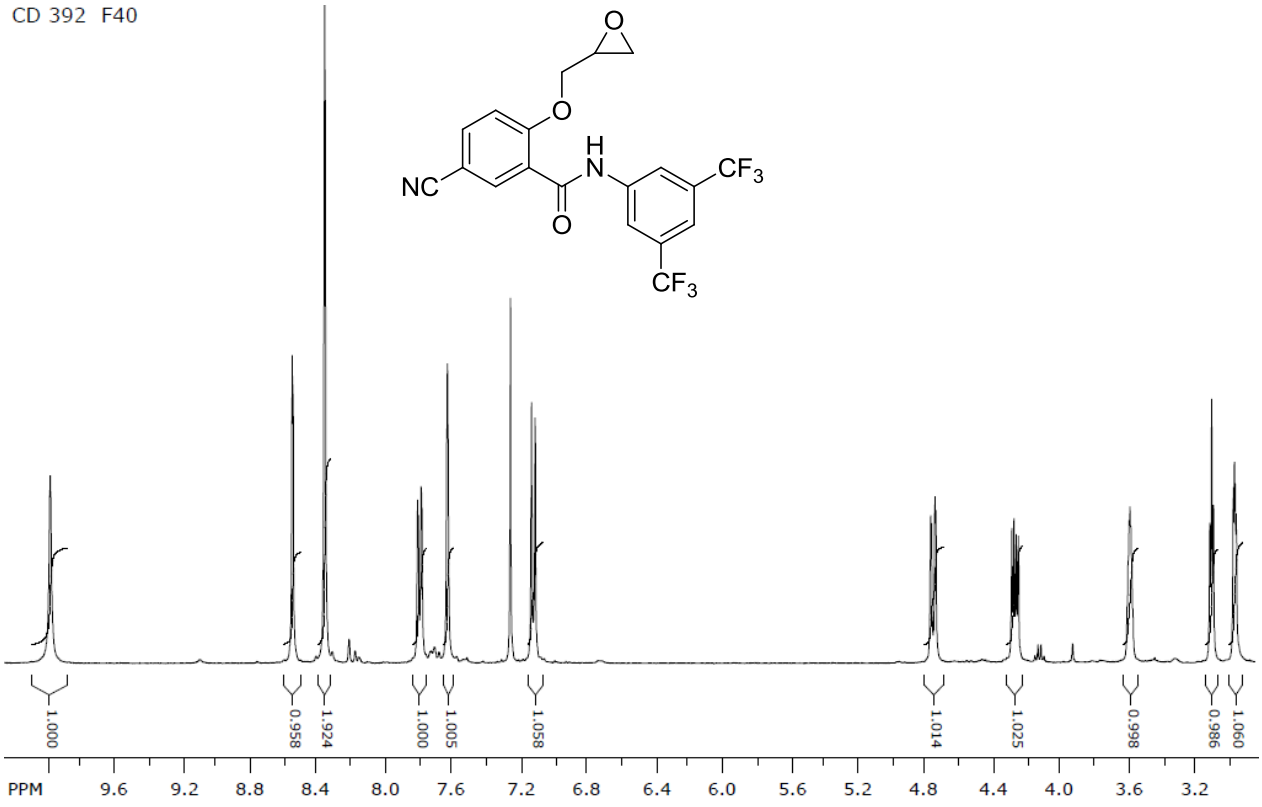


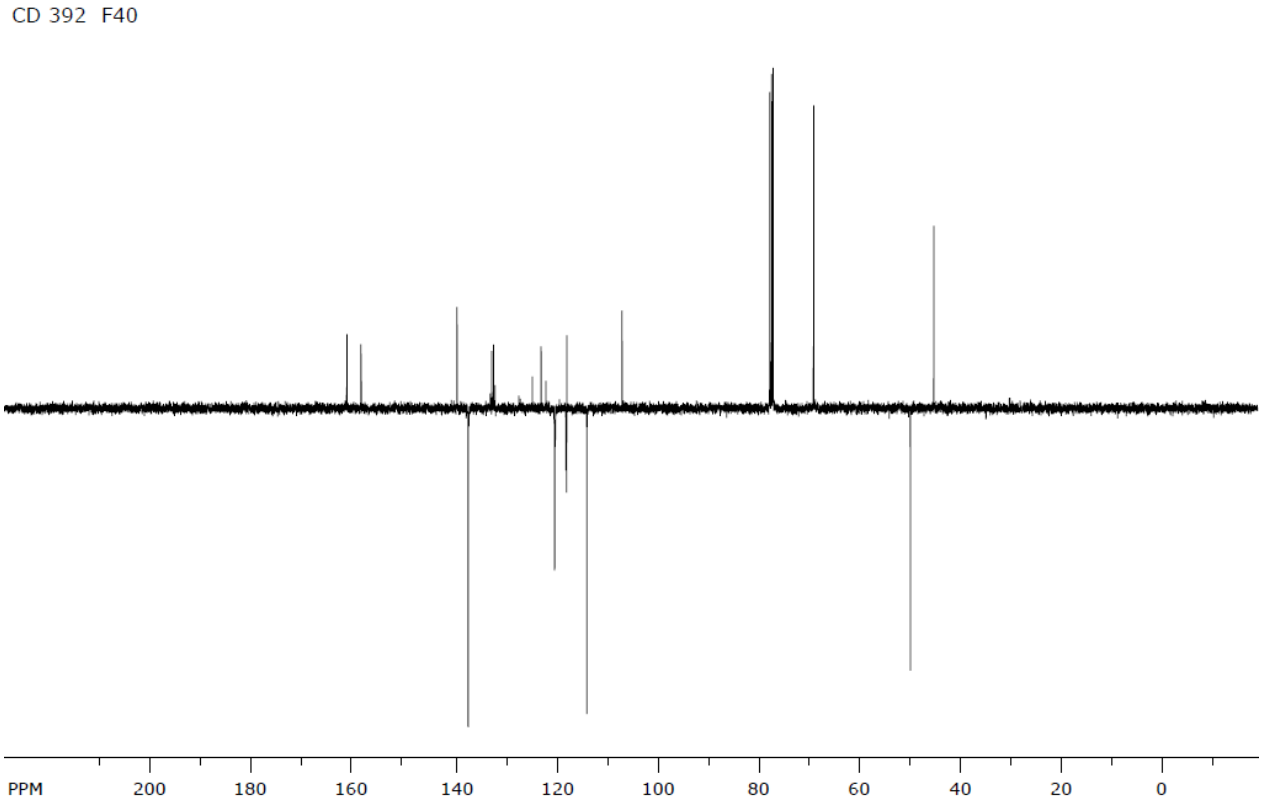
5-cyano-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (384)



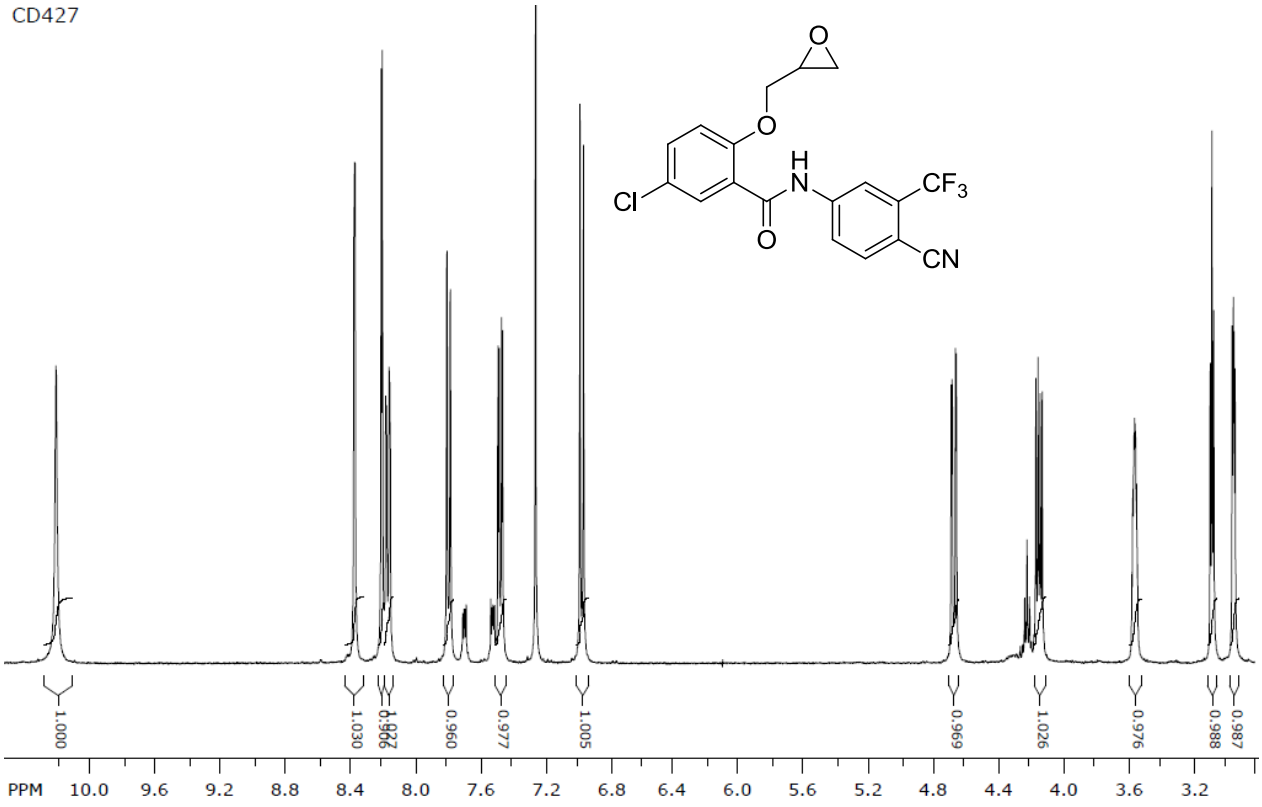


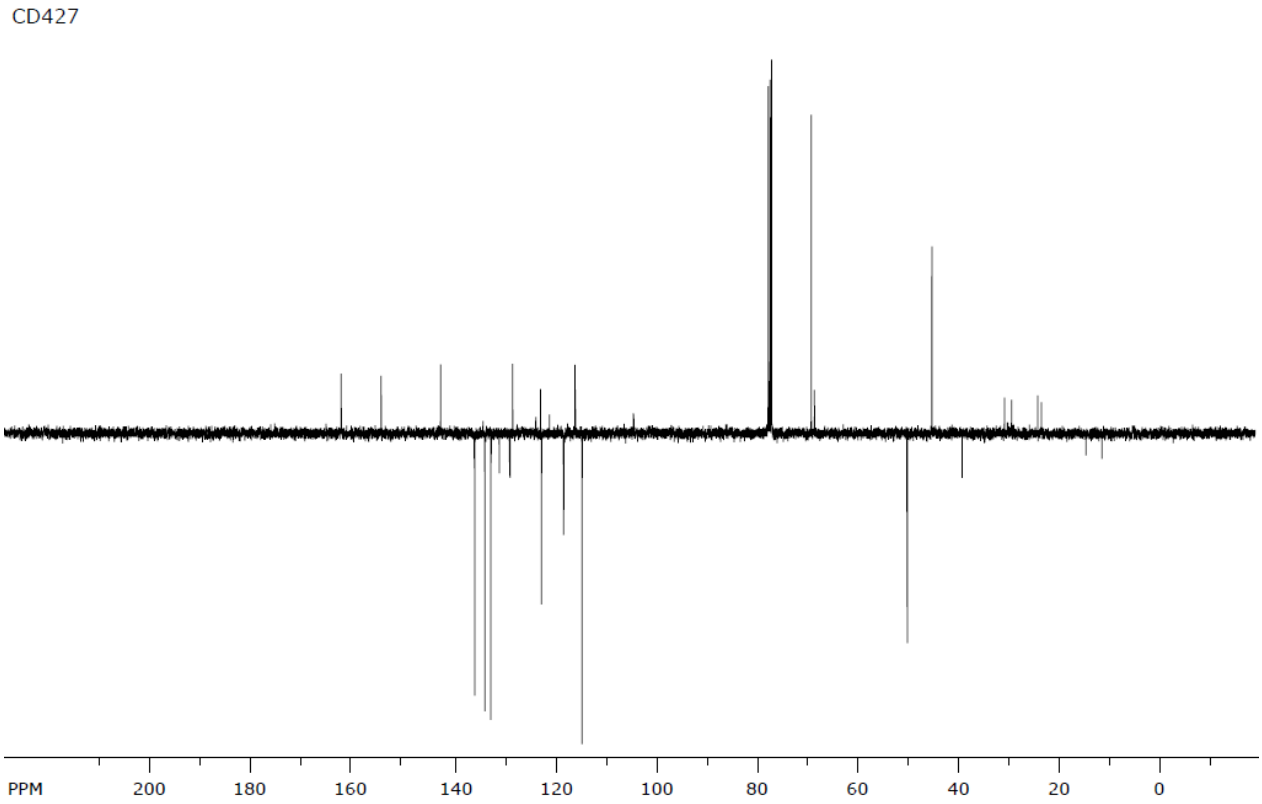
_N_-(3,5-bis(trifluoromethyl)phenyl)-5-cyano-2-(oxiran-2-ylmethoxy)benzamide (385)





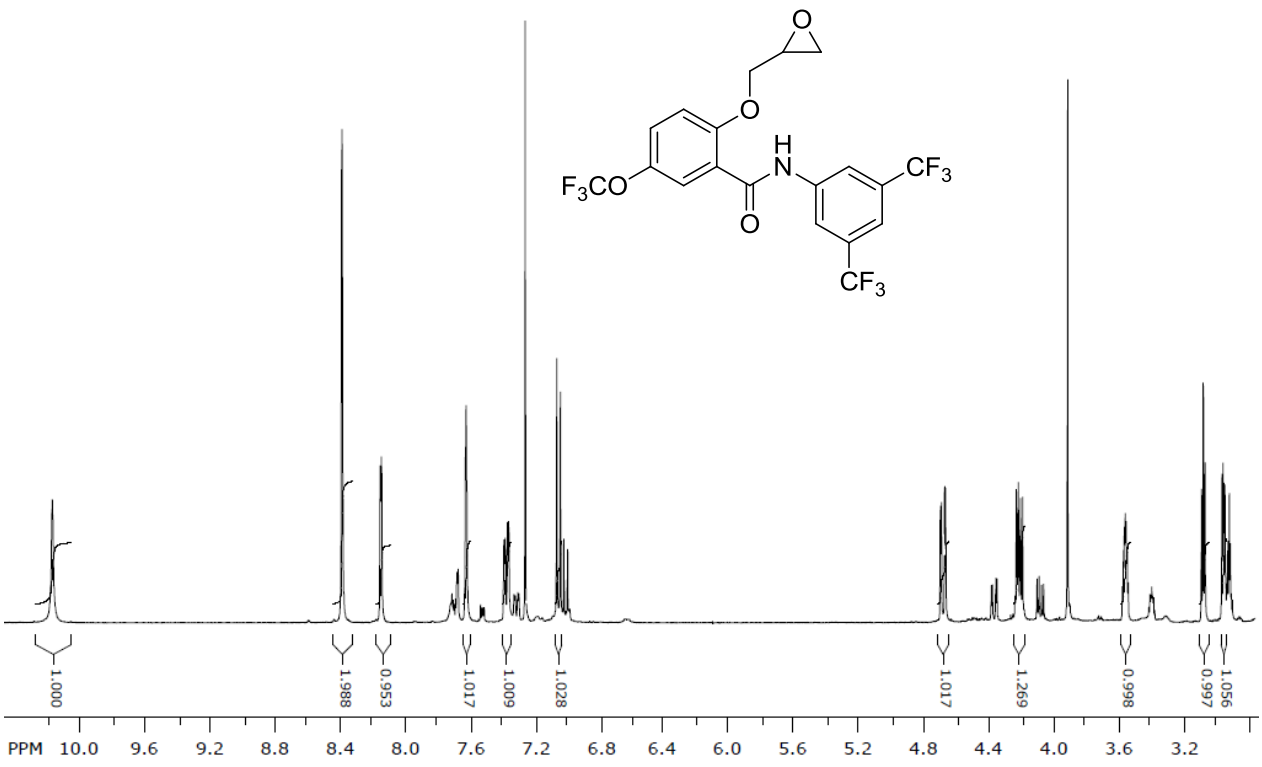
5-chloro-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-2-(oxiran-2-ylmethoxy)benzamide (386)



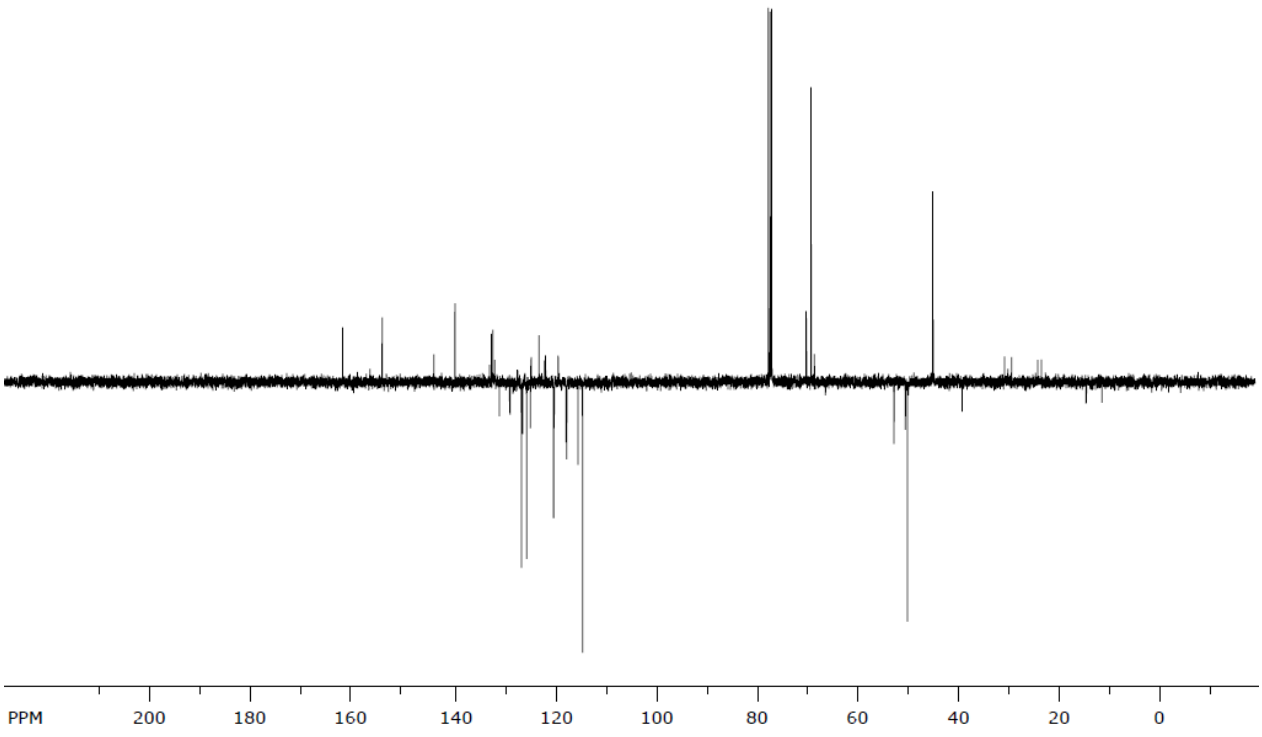


_N_-(3,5-bis(trifluoromethyl)phenyl)-2-(oxiran-2-ylmethoxy)-5-(trifluoromethoxy)benzamide (387)

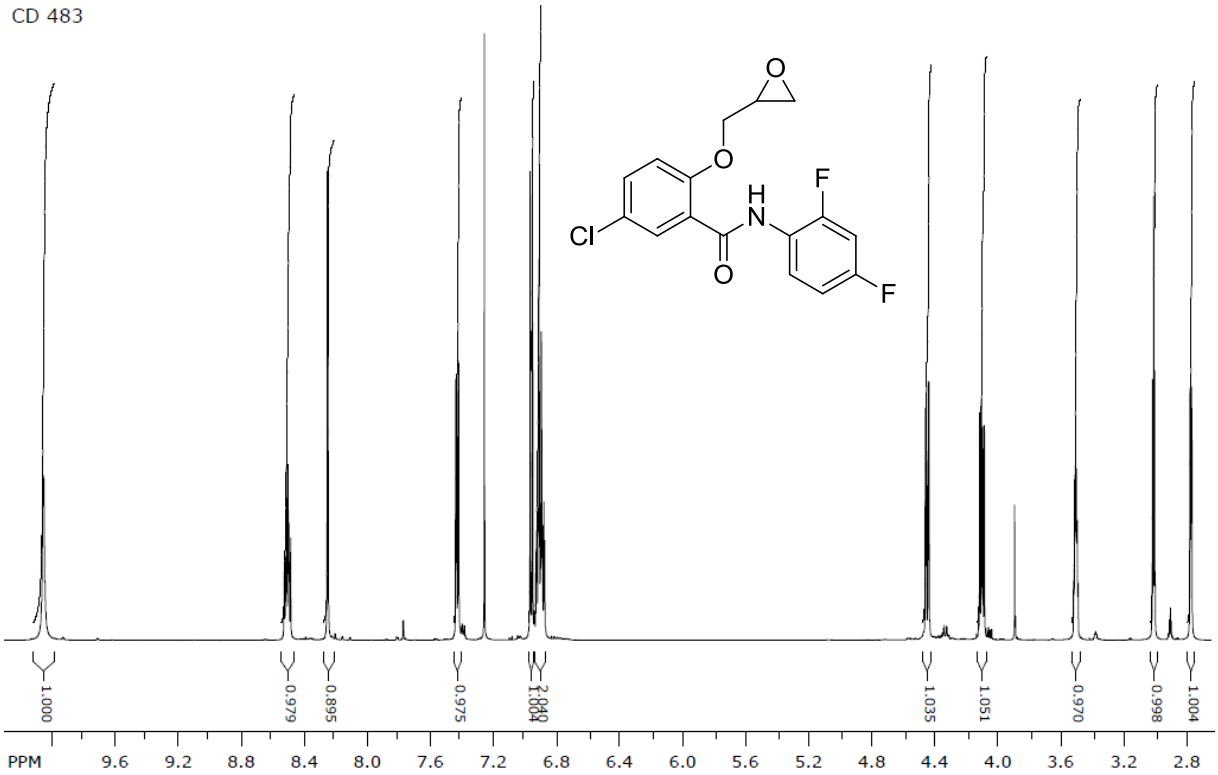
CD415

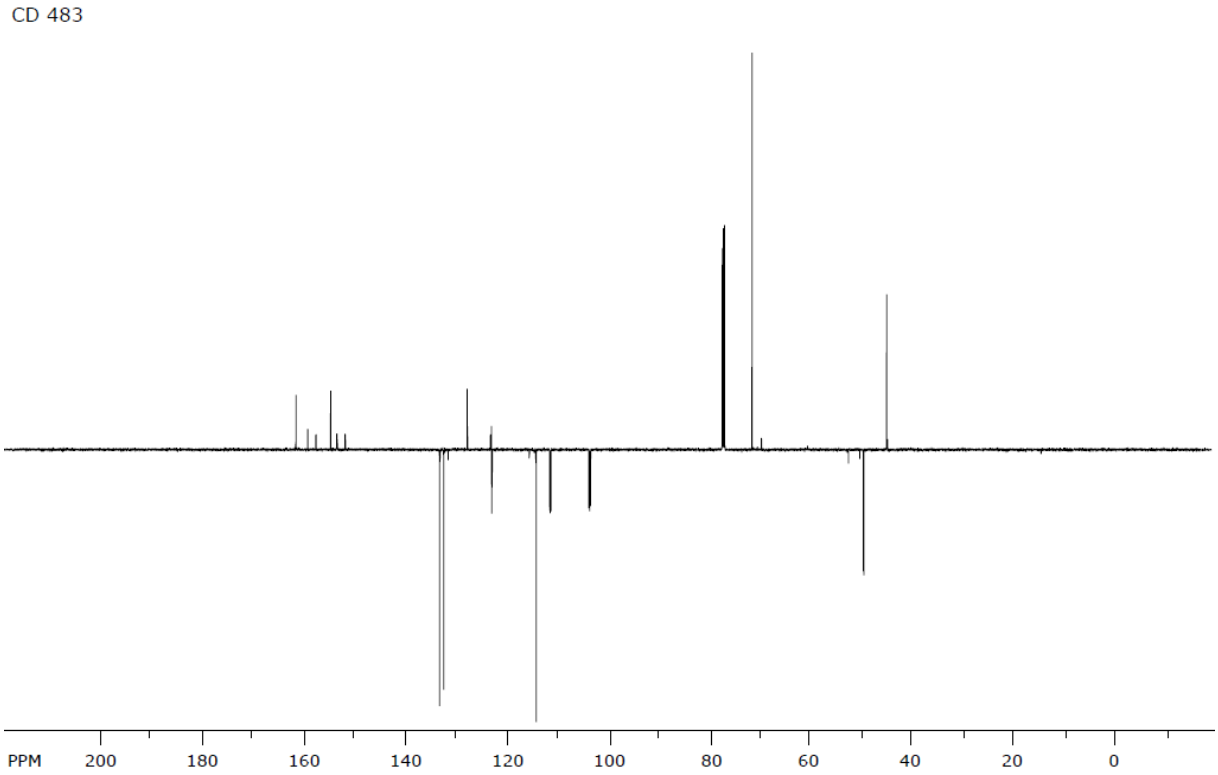


CD415

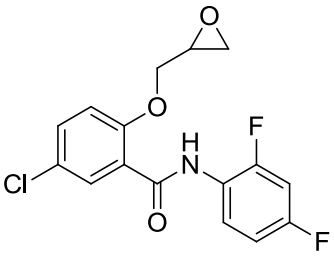


5-chloro-*N*-(2,4-difluorophenyl)-2-(oxiran-2-ylmethoxy)benzamide (388)



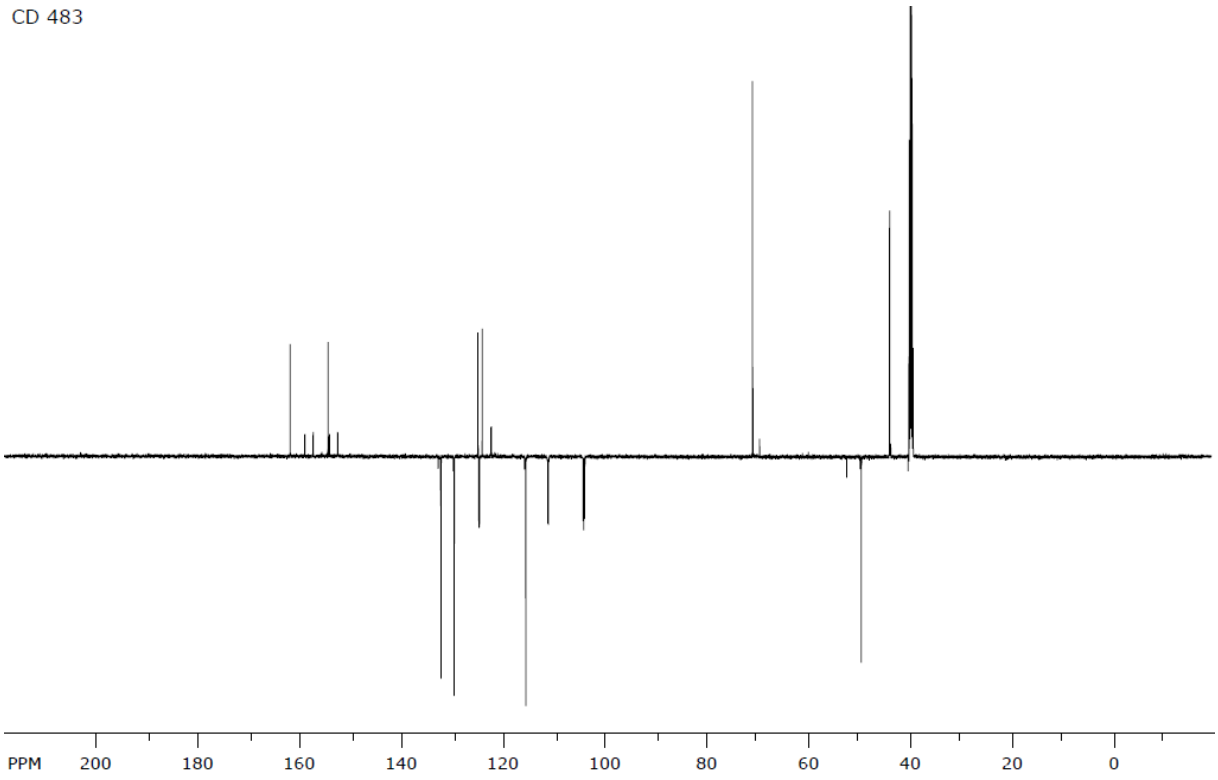


CD 483

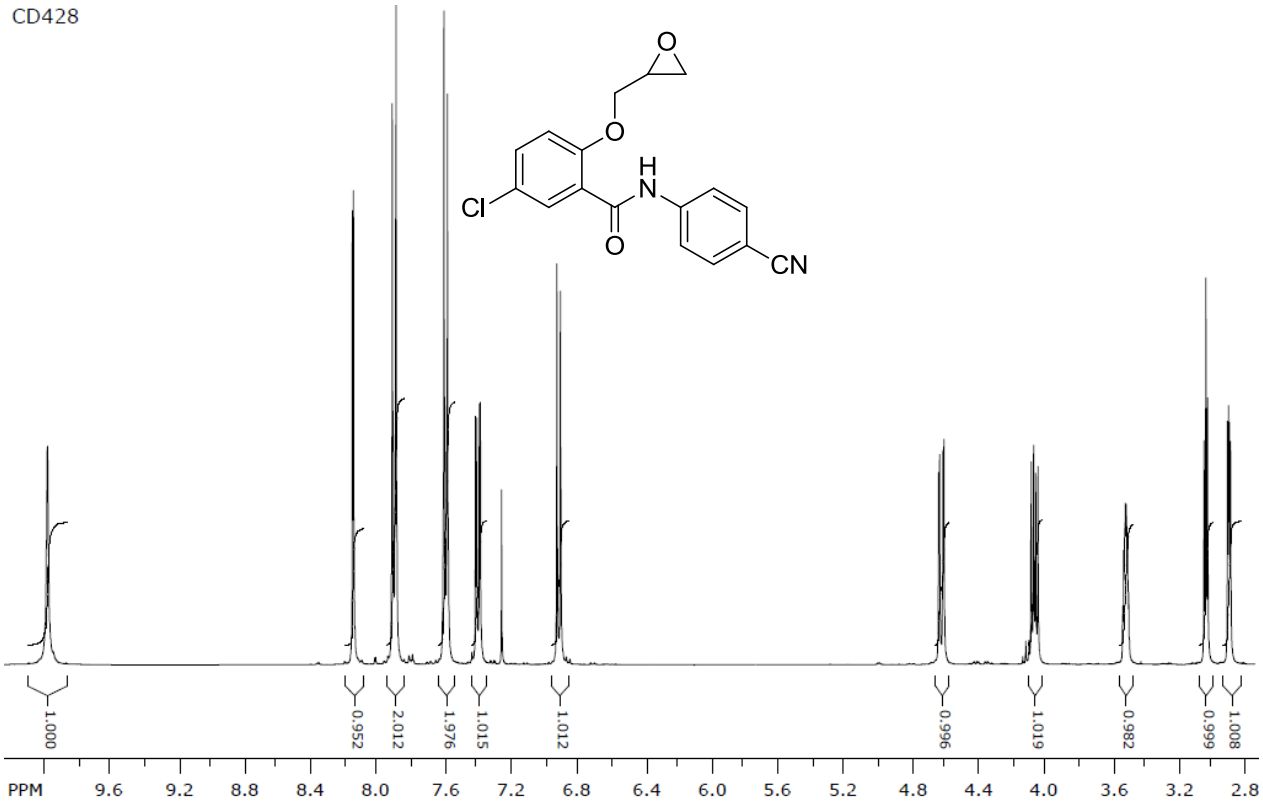

O
O
H
N
Cl
O
F
F

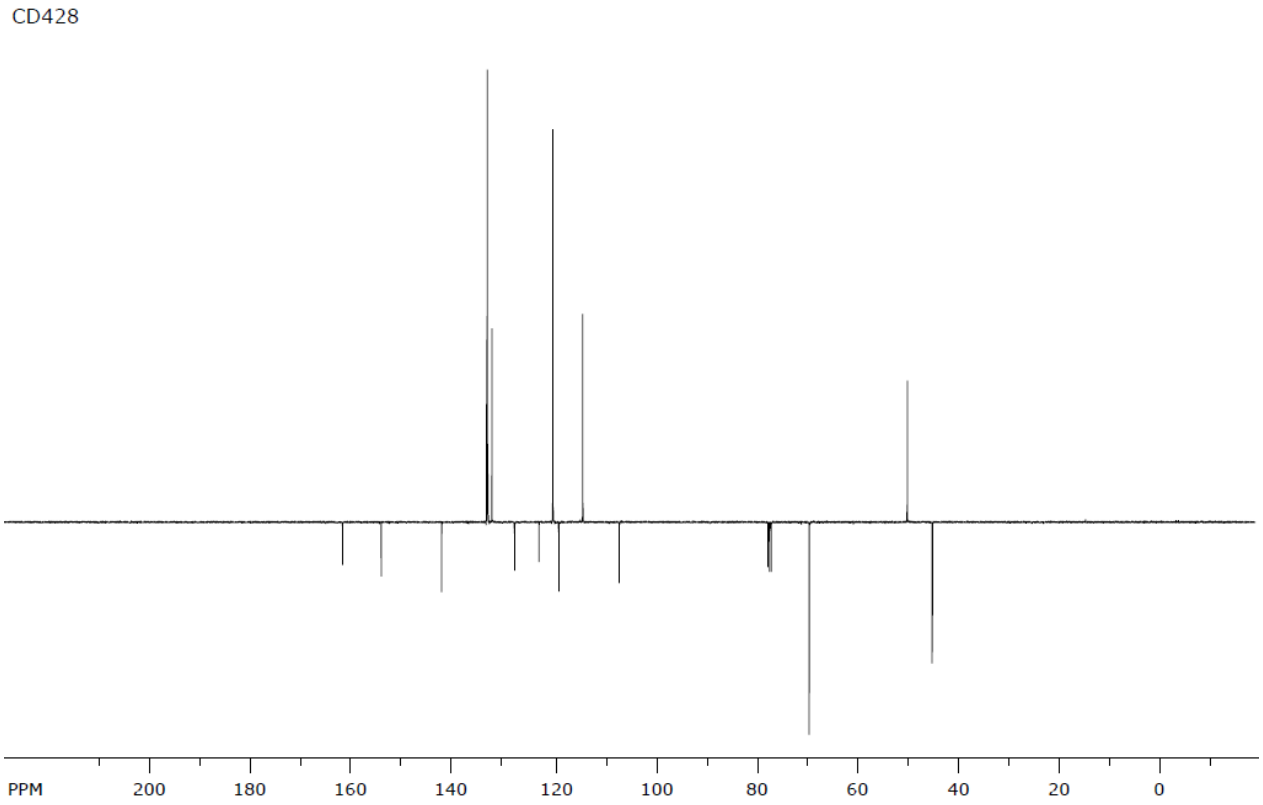
10.1131
8.1107
8.0630
7.8085
7.6039
7.4188
7.3720
7.2701
7.1541
7.1117
4.5343
4.0781
3.4452
3.4095
3.3557
2.8784
2.7498
PPM
14
12
10
8
6
4
2
0
-2

CD 483

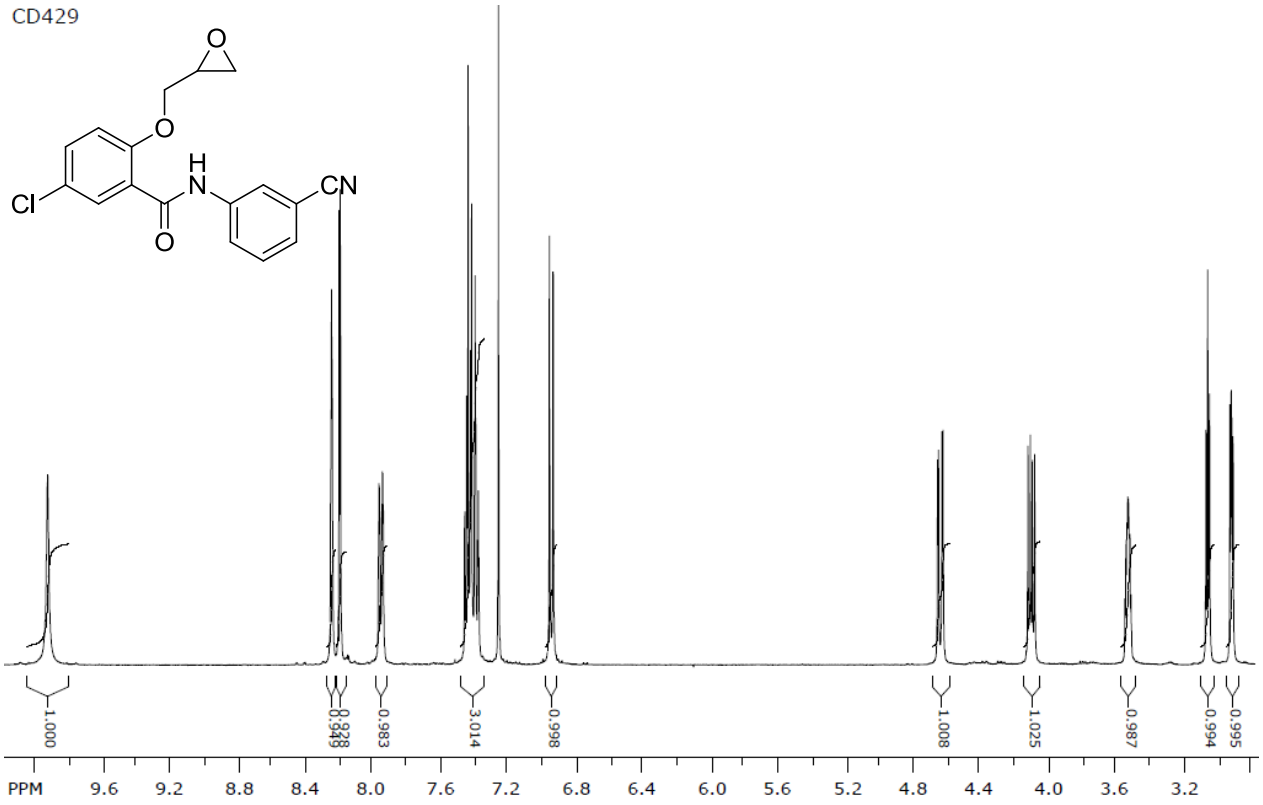

PPM
200
180
160
140
120
100
80
60
40
20
0

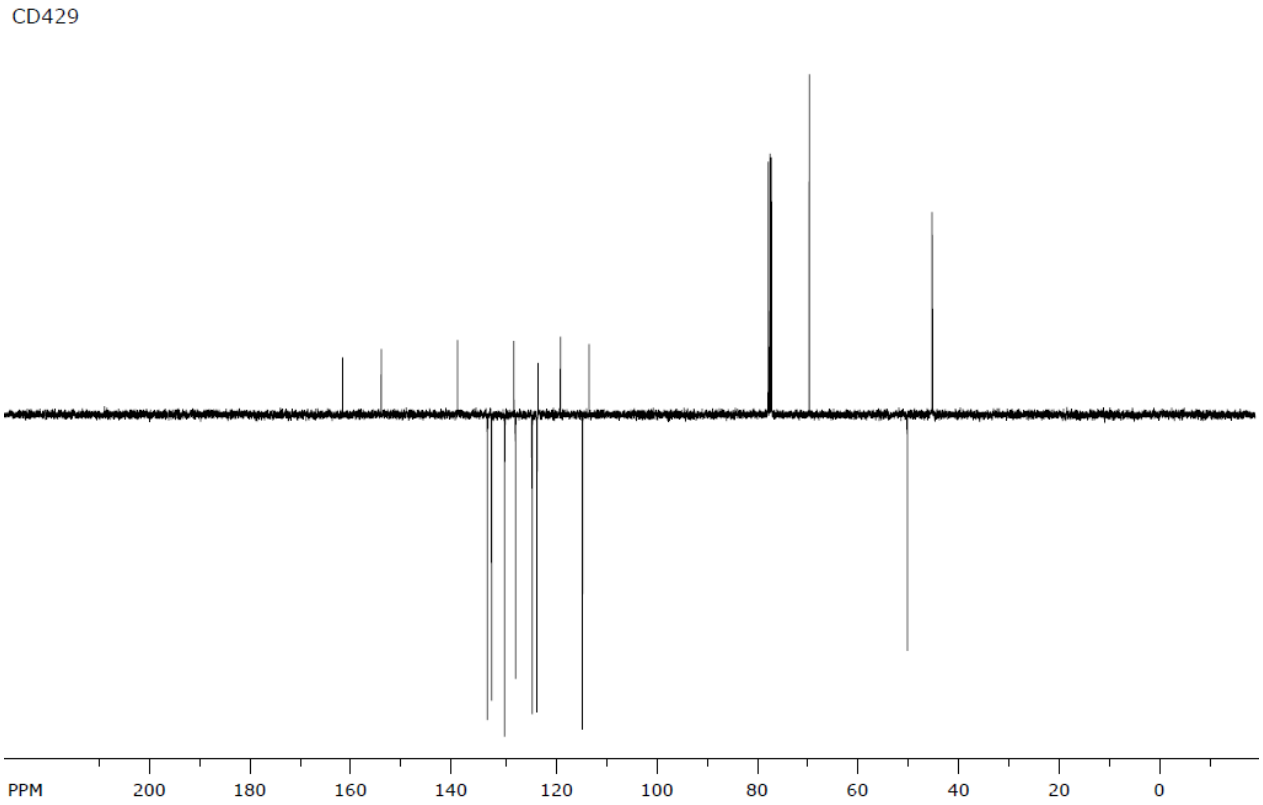
5-chloro-*N*-(4-cyanophenyl)-2-(oxiran-2-ylmethoxy)benzamide (389**)**



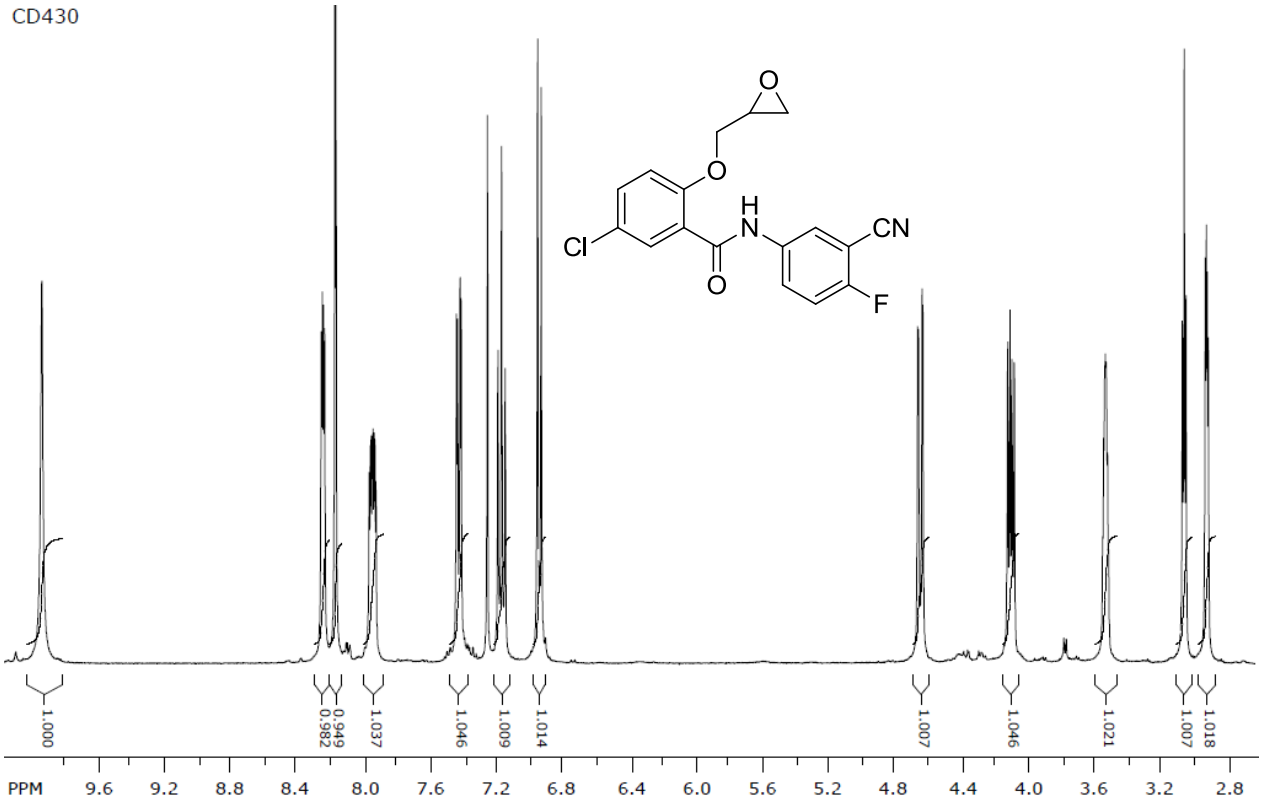


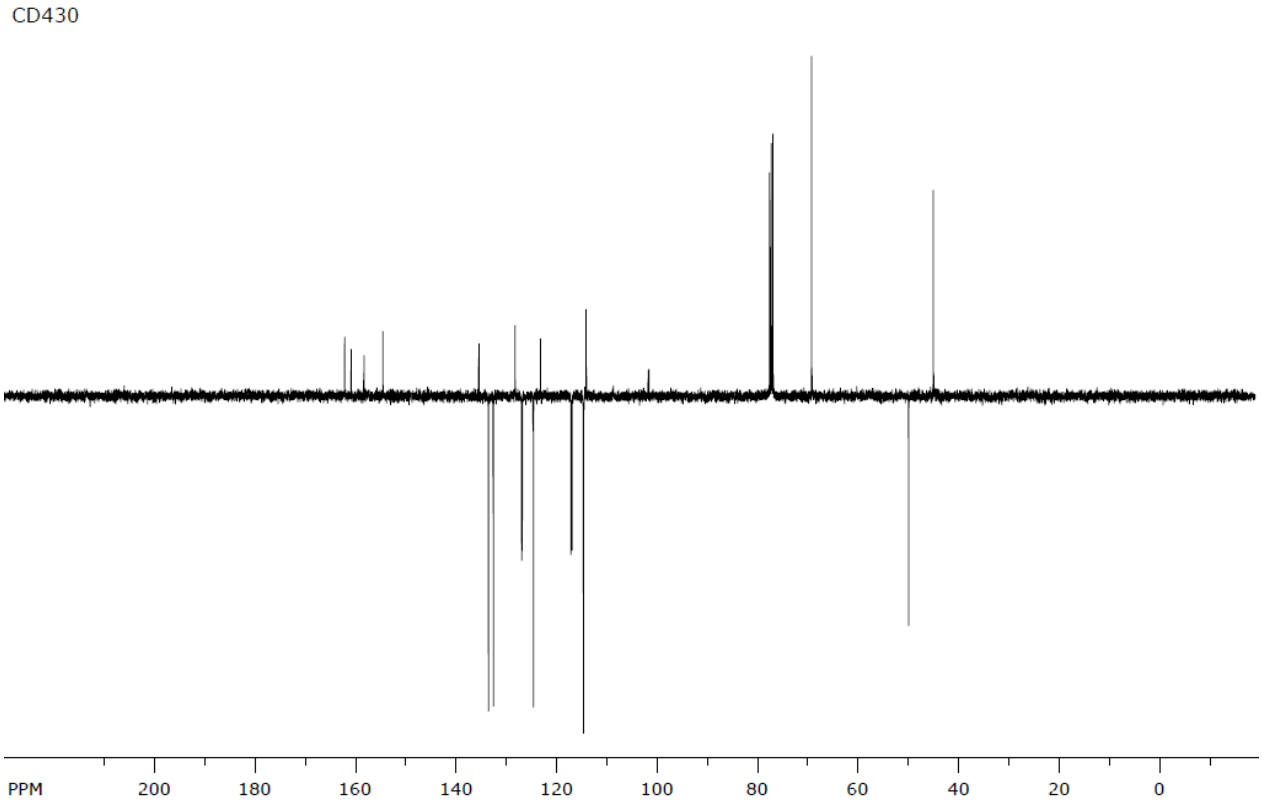
5-chloro-*N*-(3-cyanophenyl)-2-(oxiran-2-ylmethoxy)benzamide (390)



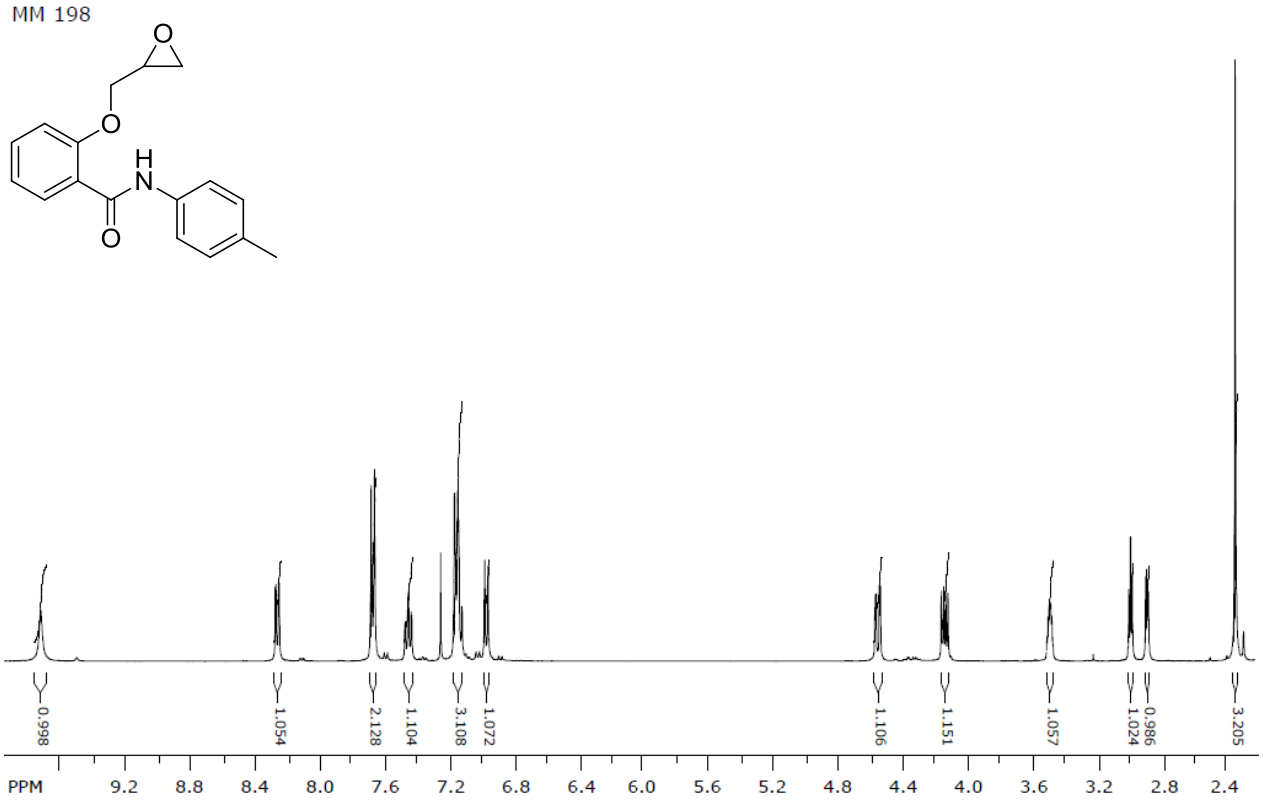


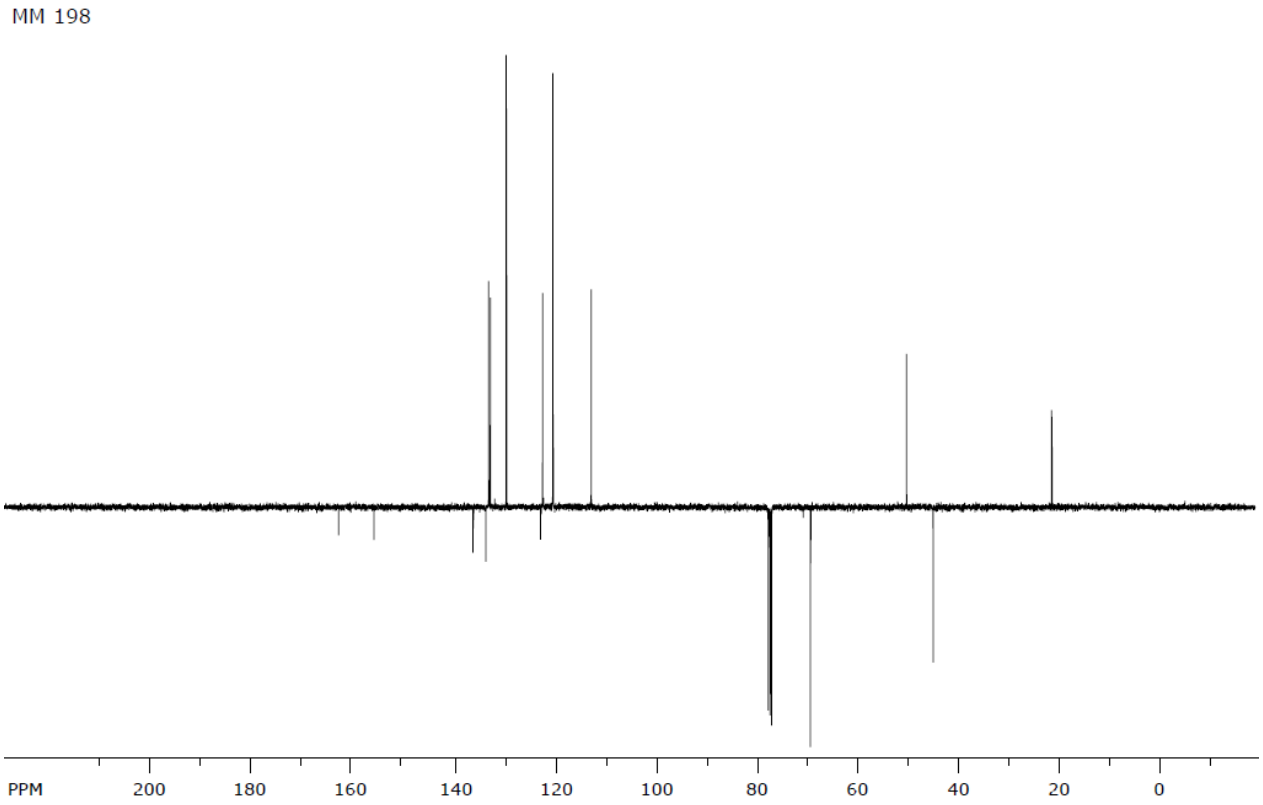
5-chloro-*N*-(3-cyano-4-fluorophenyl)-2-(oxiran-2-ylmethoxy)benzamide (391)



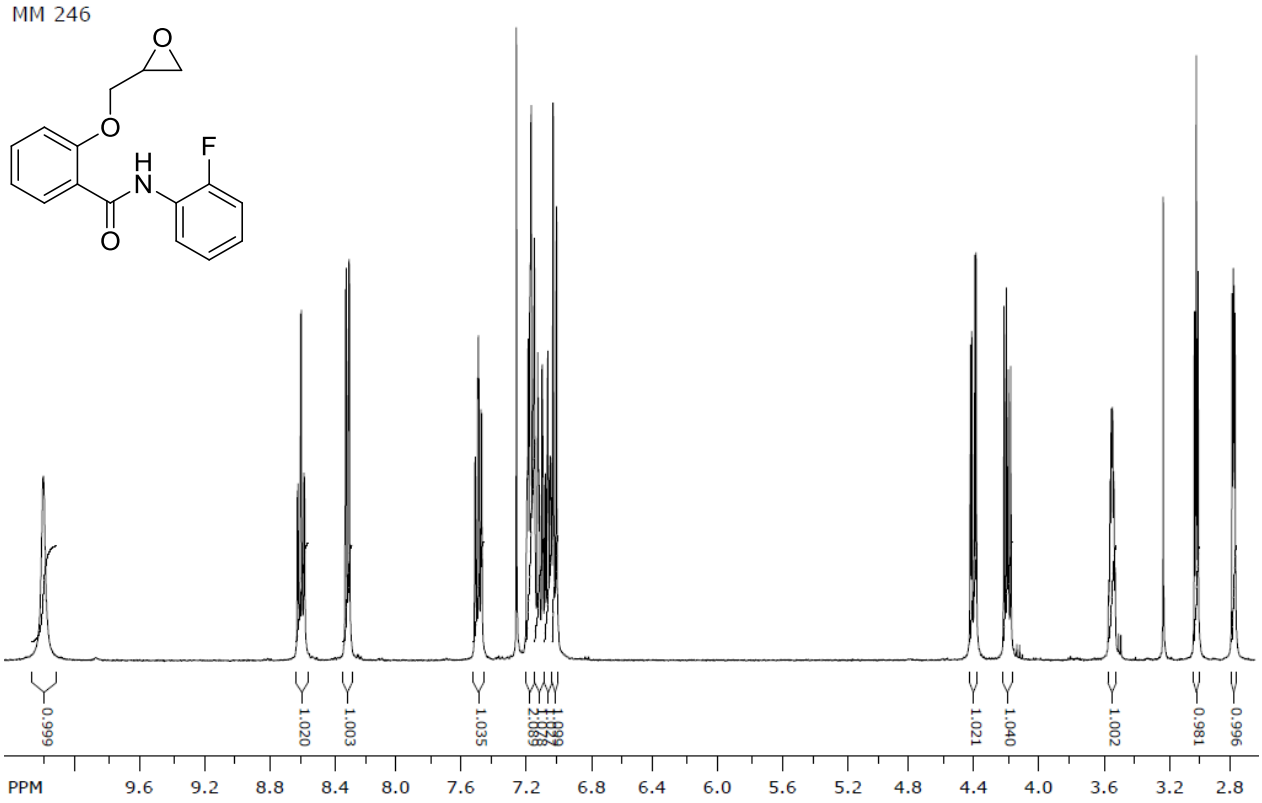


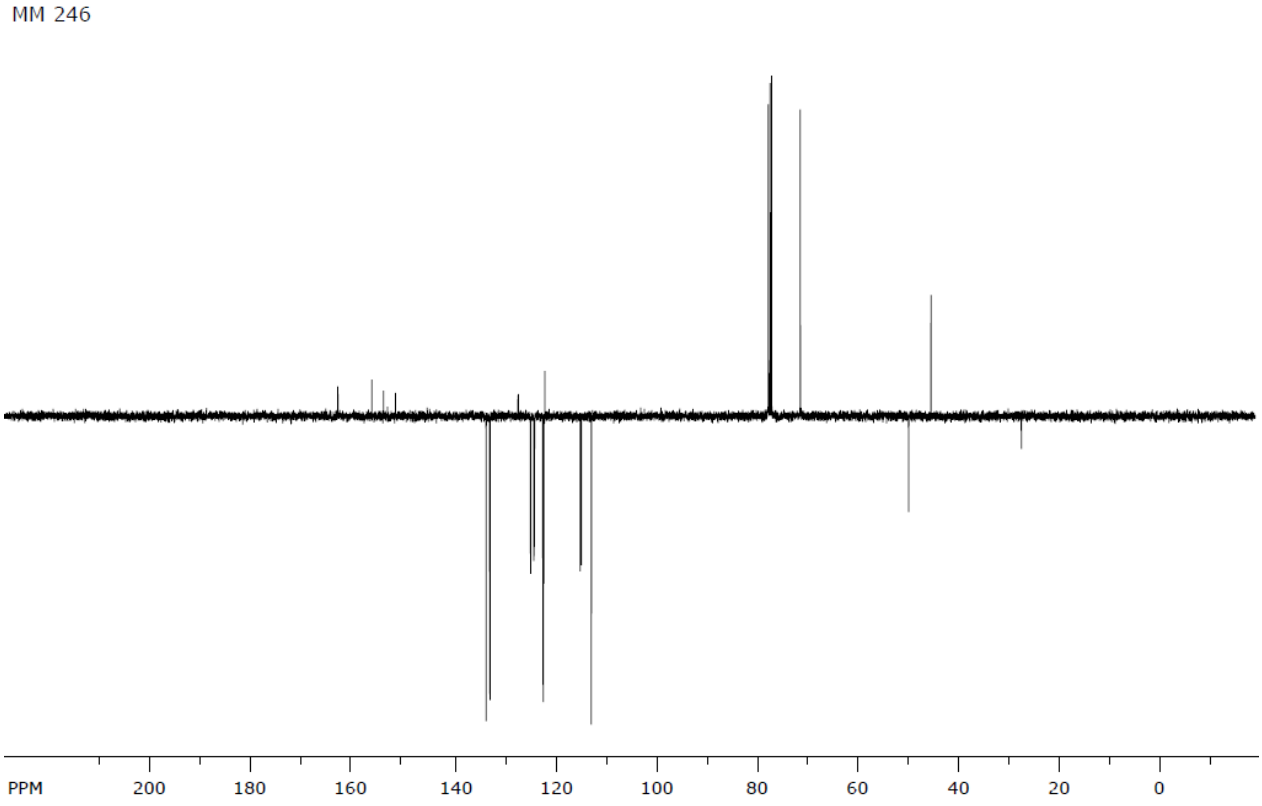
2-(oxiran-2-ylmethoxy)-*N*-(p-tolyl)benzamide (392)



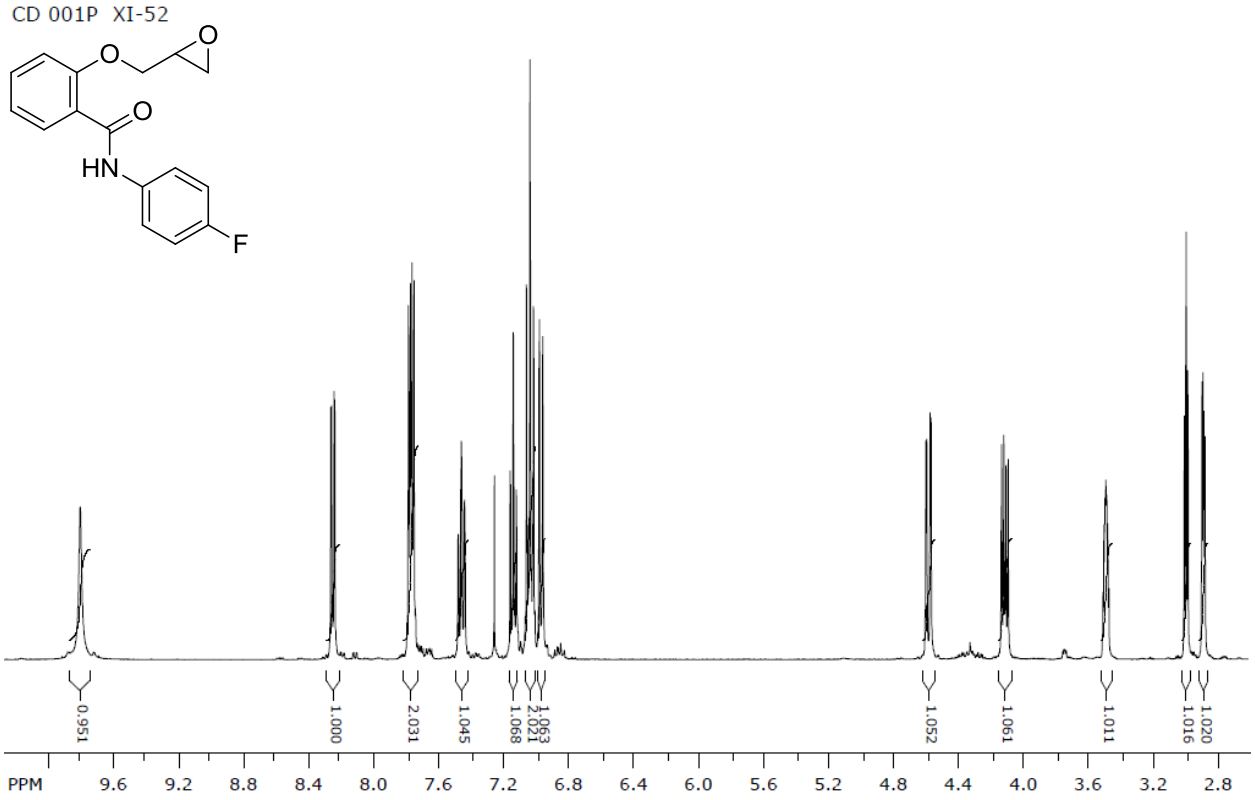


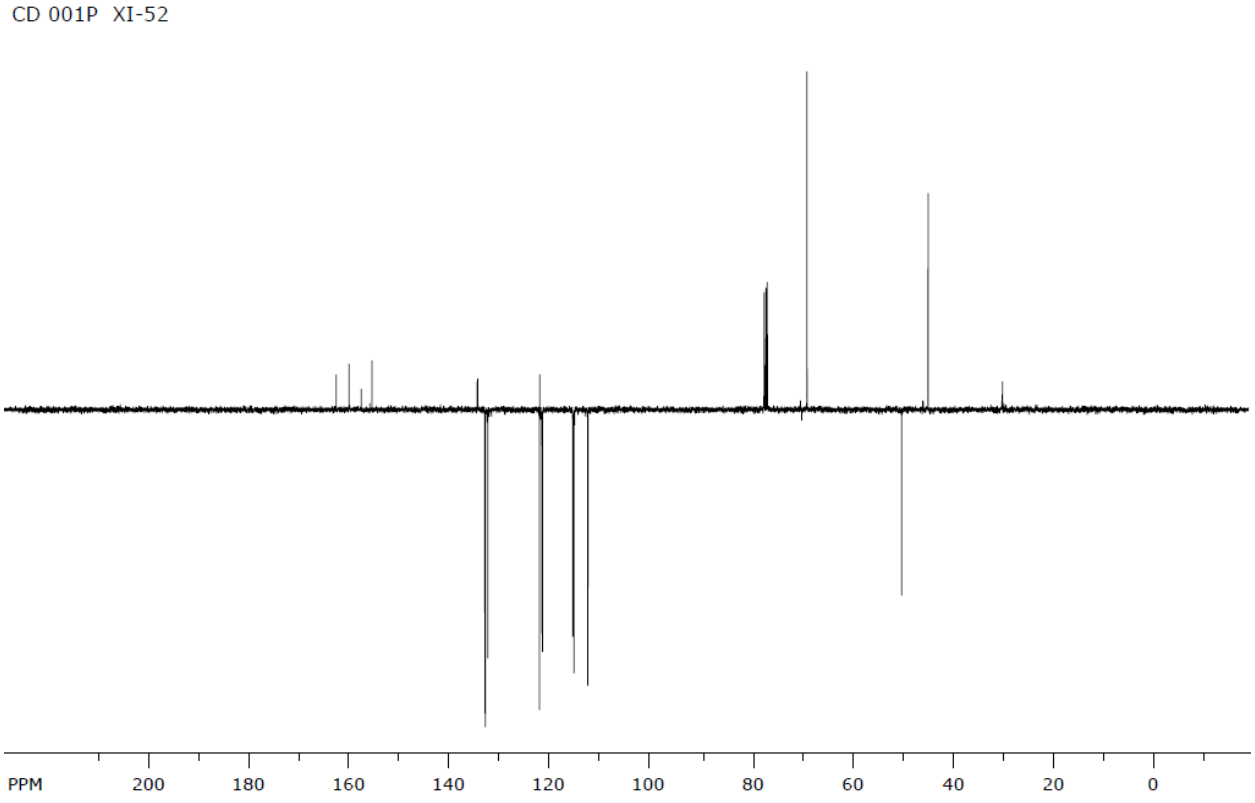
N-(2-fluorophenyl)-2-(oxiran-2-ylmethoxy)benzamide (393)



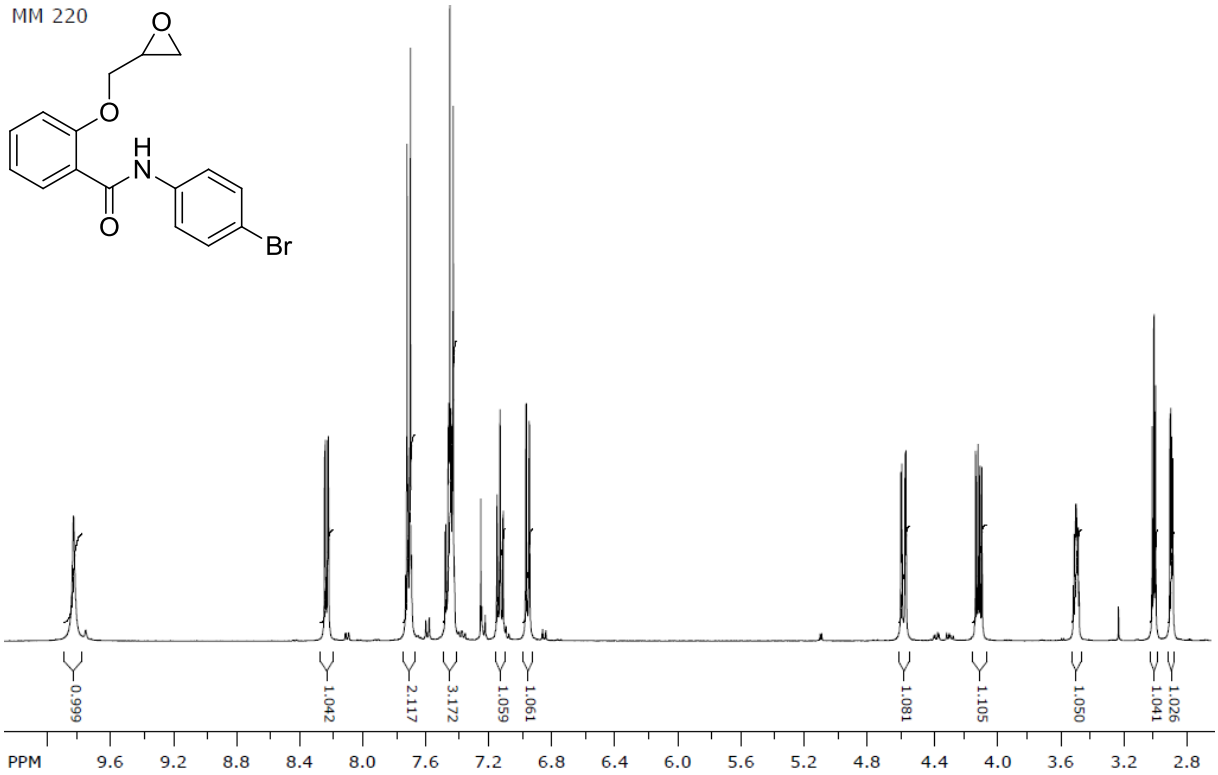


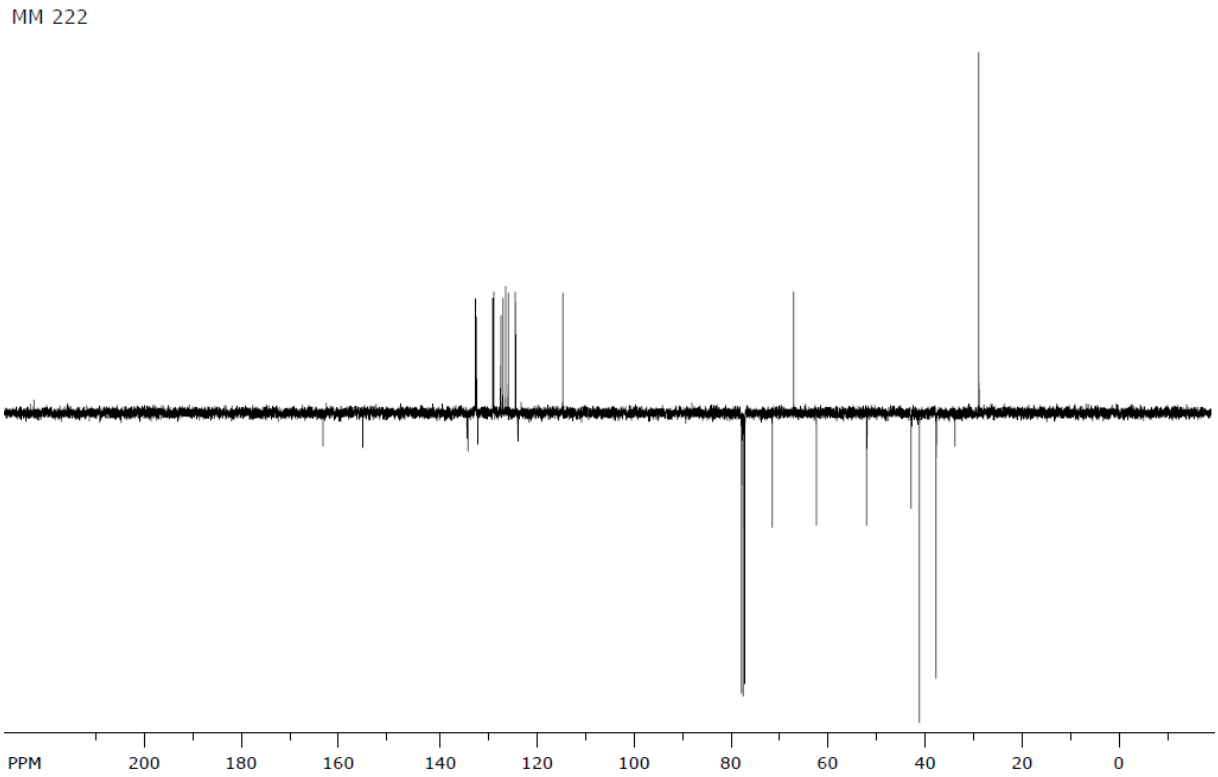
_N_-(4-fluorophenyl)-2-(oxiran-2-ylmethoxy)benzamide (394)



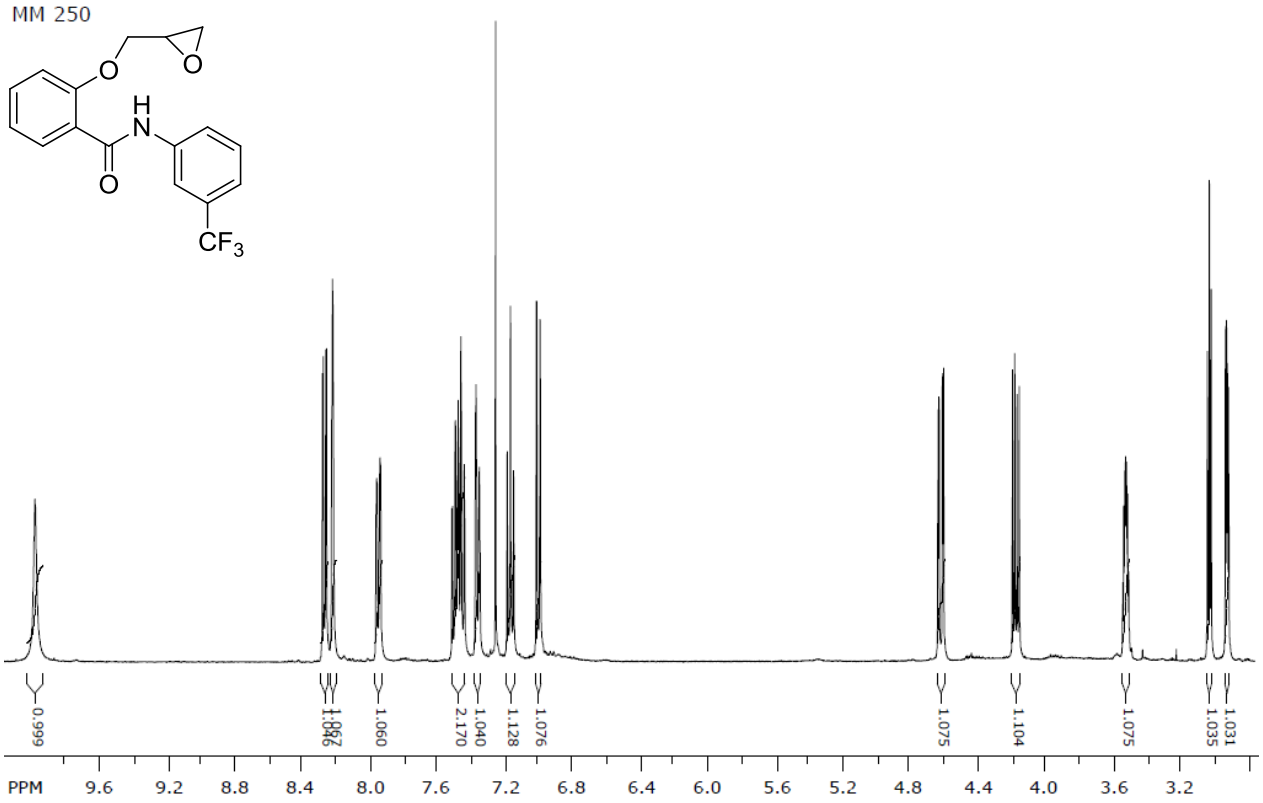


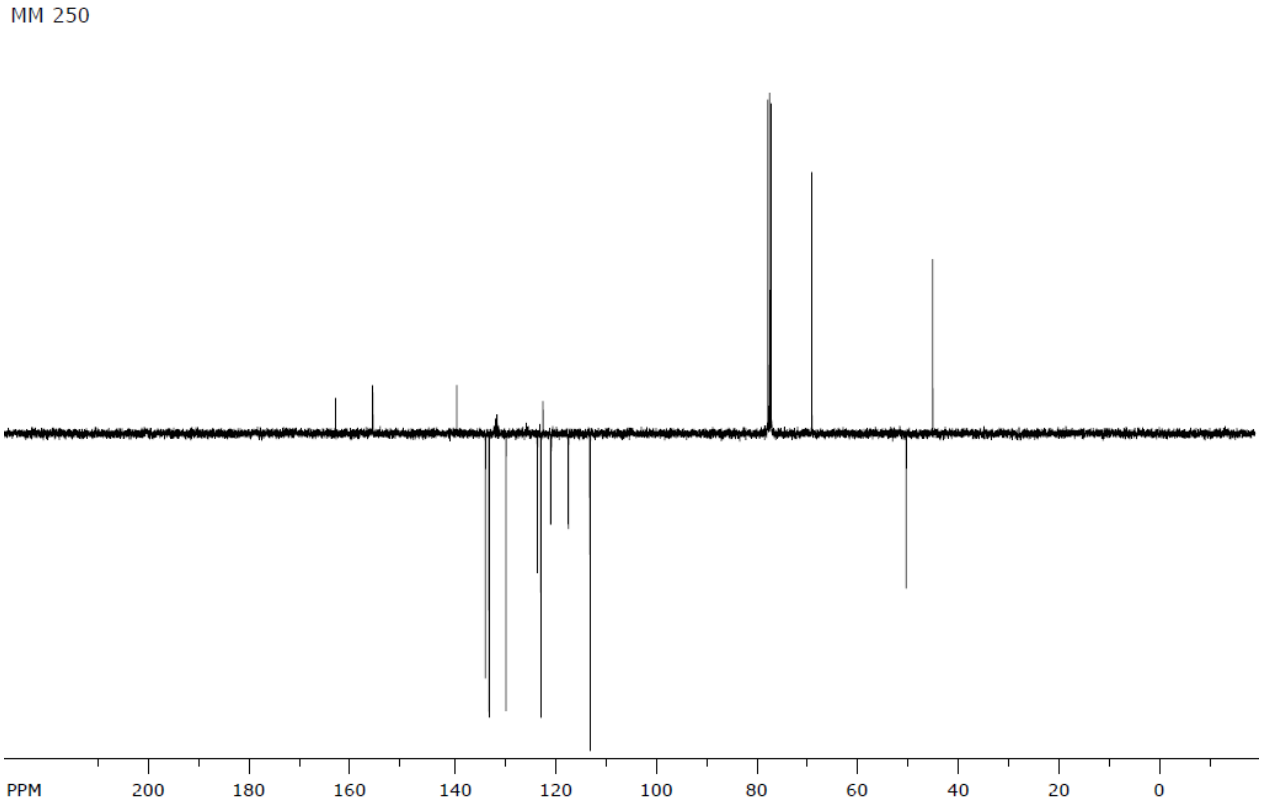
N-(4-bromophenyl)-2-(oxiran-2-ylmethoxy)benzamide (395)



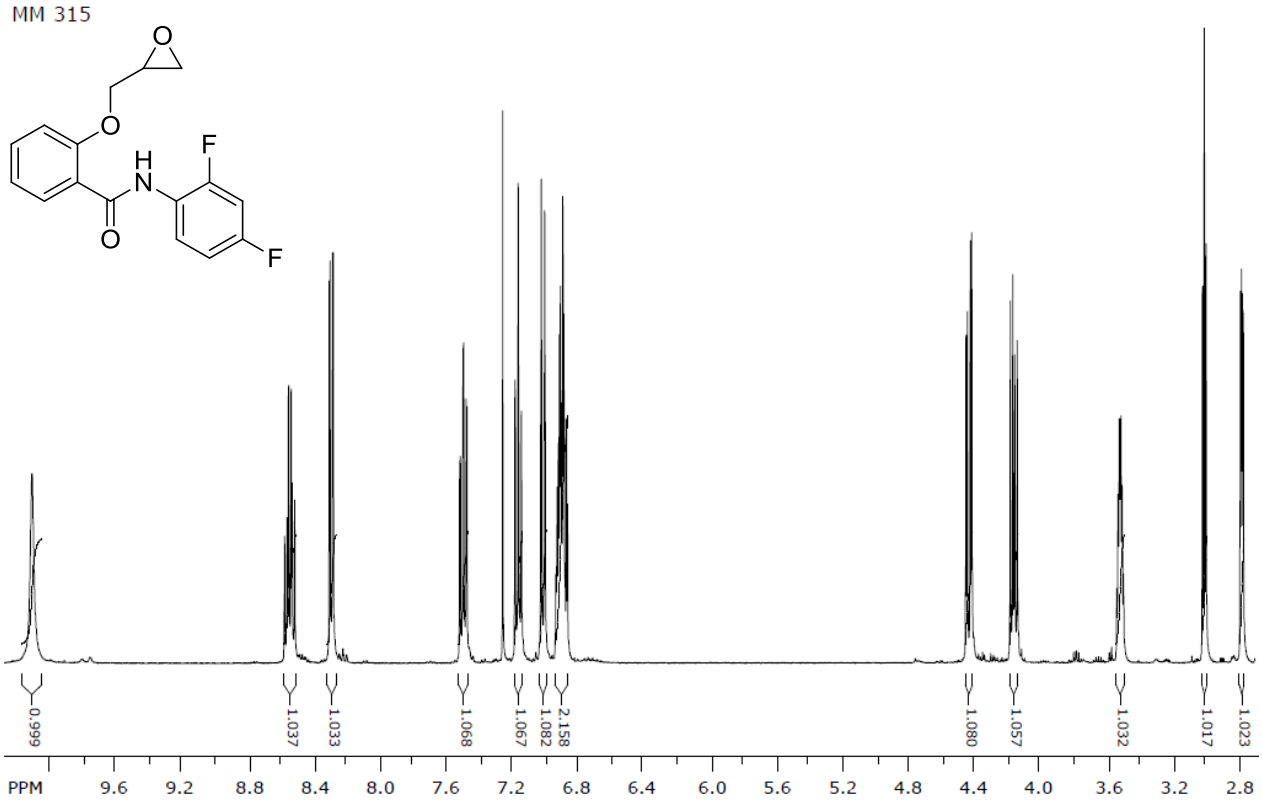


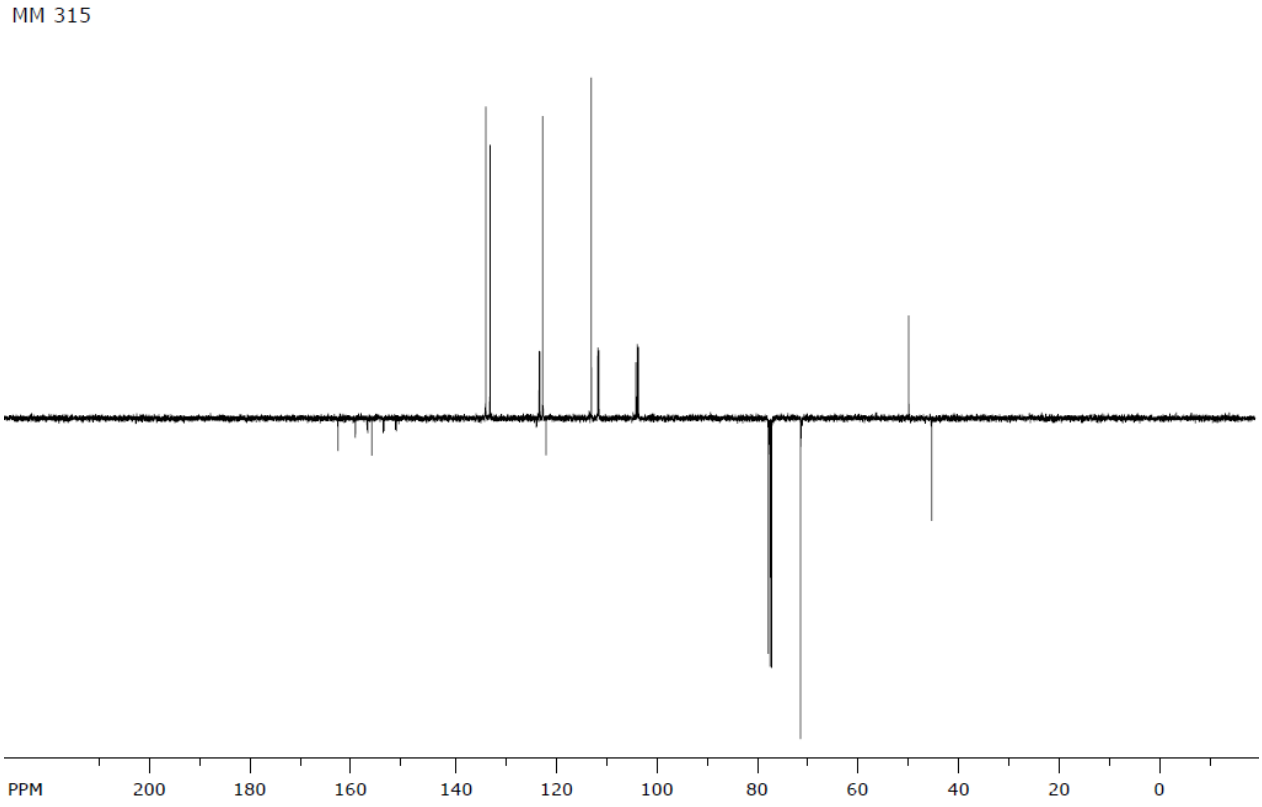
2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (396)



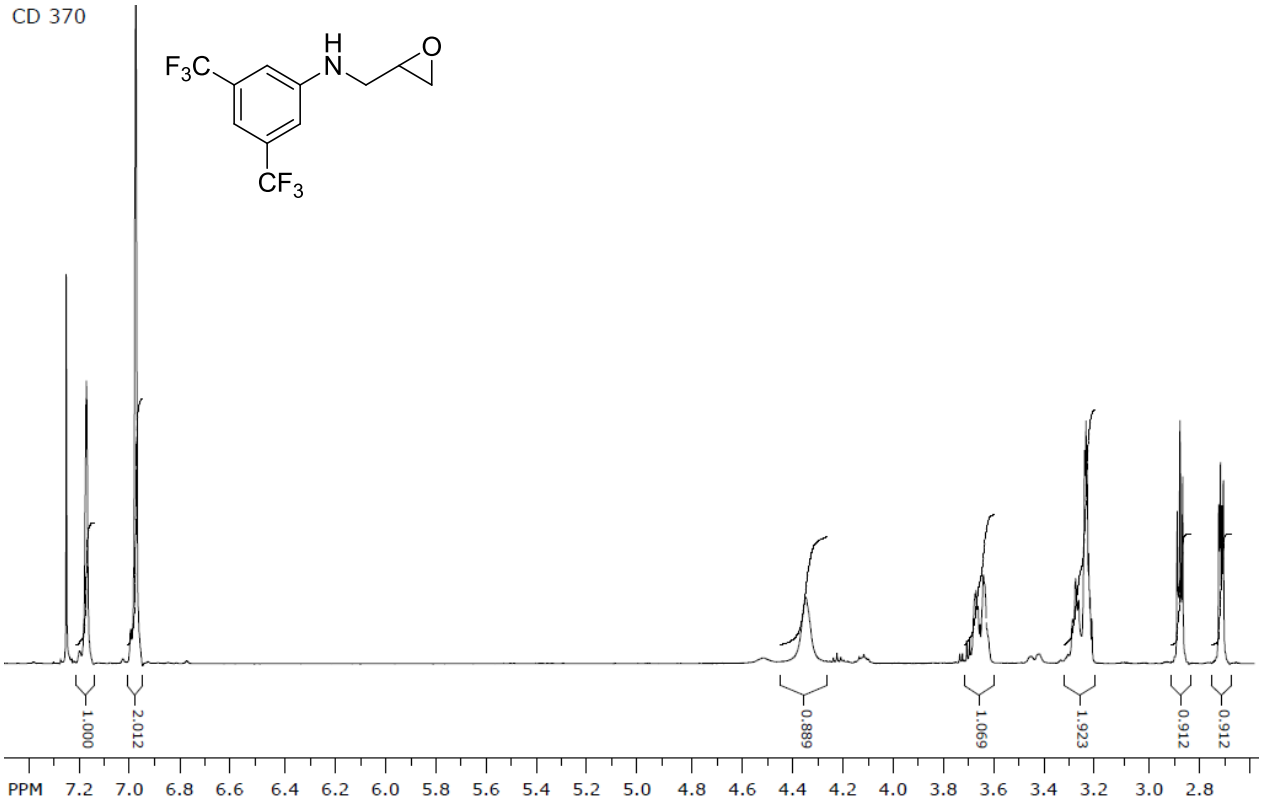


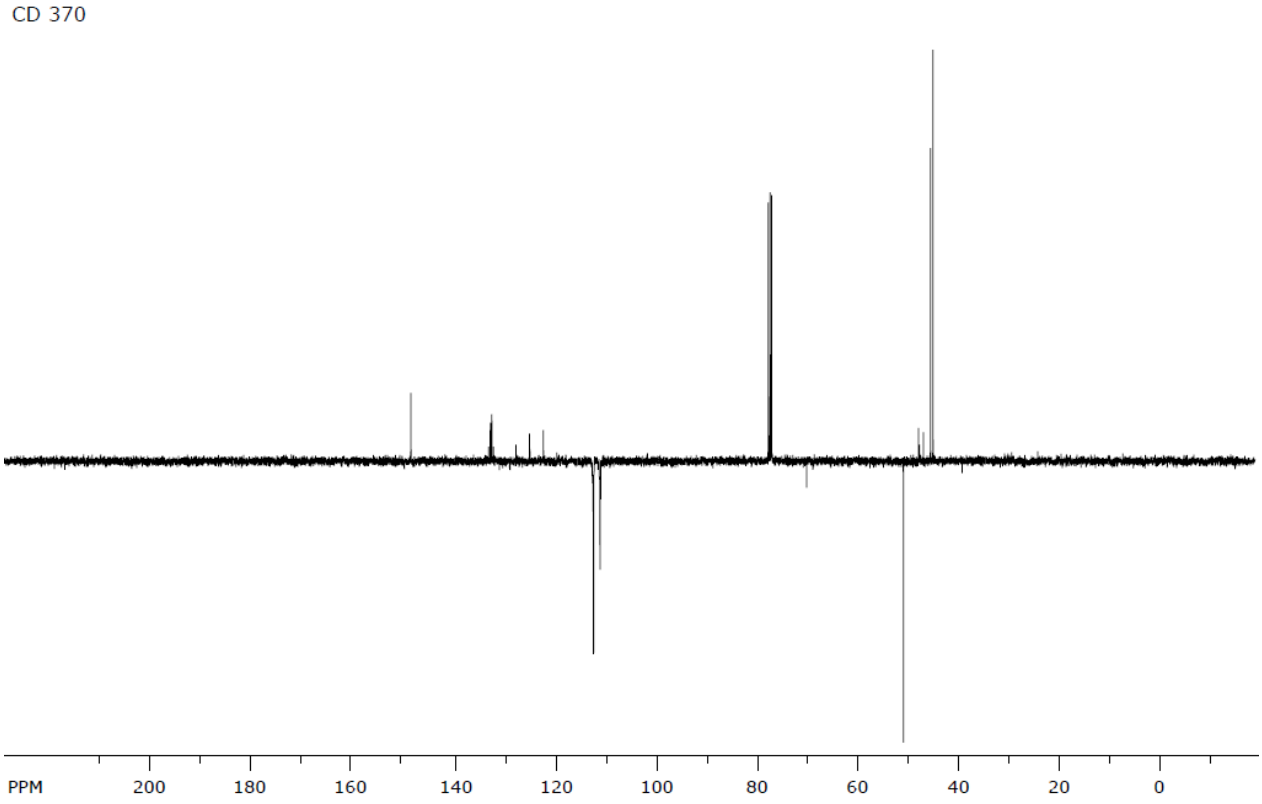
***Spektrum N*-(2,4-difluorophenyl)-2-(oxiran-2-ylmethoxy)benzamide (397)**



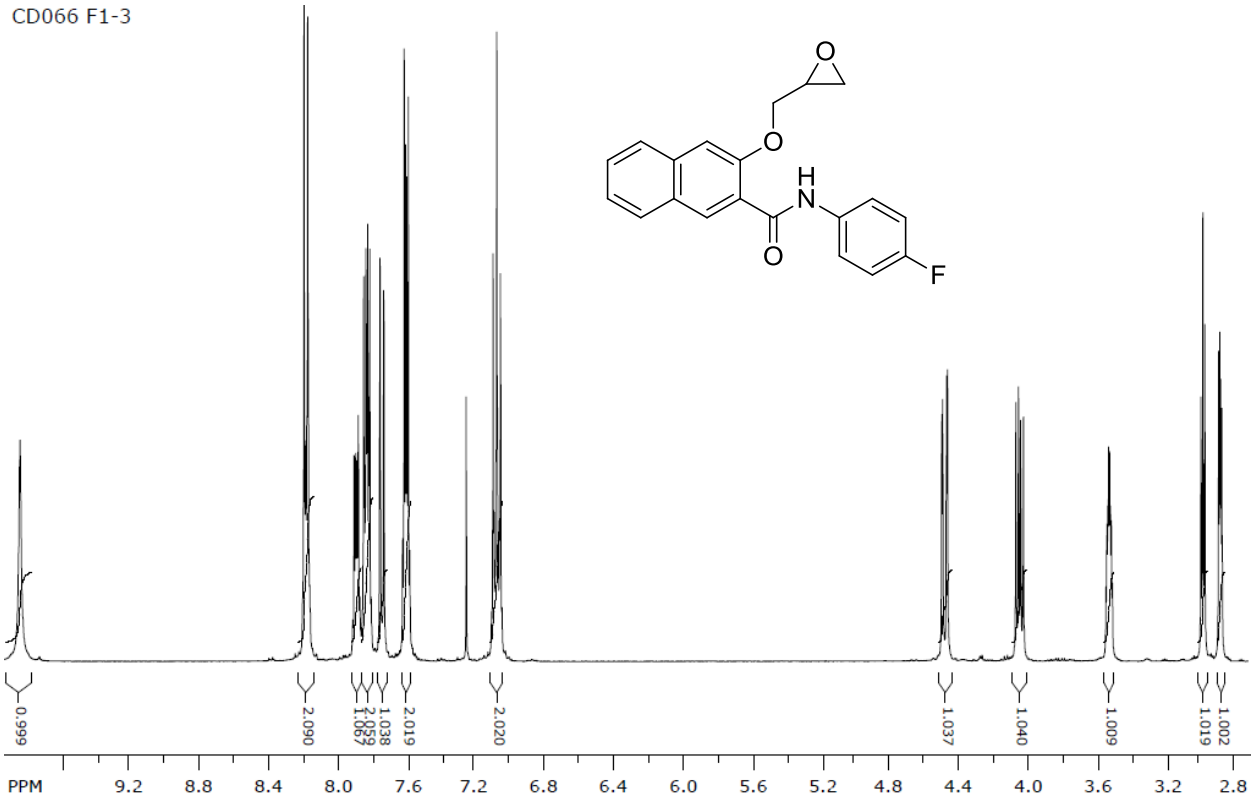


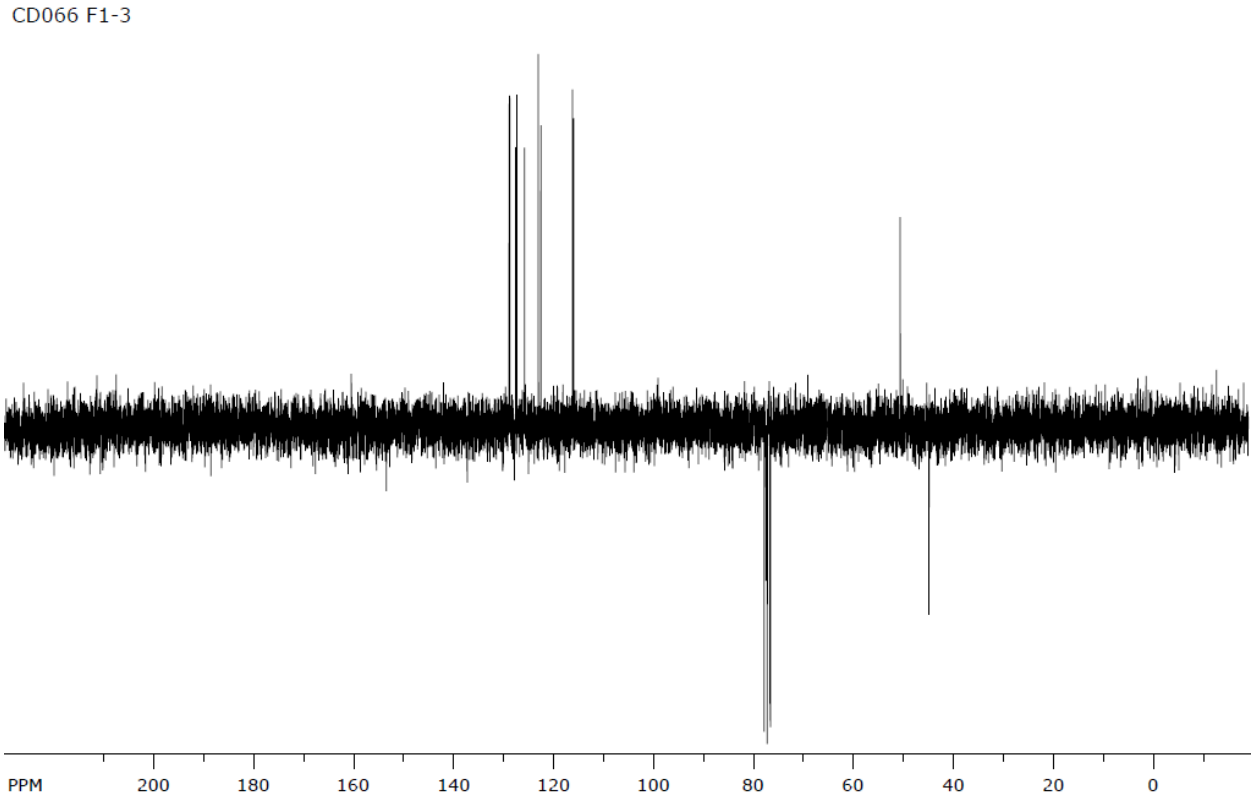
_N_-(oxiran-2-ylmethyl)-3,5-bis(trifluoromethyl)aniline (398)





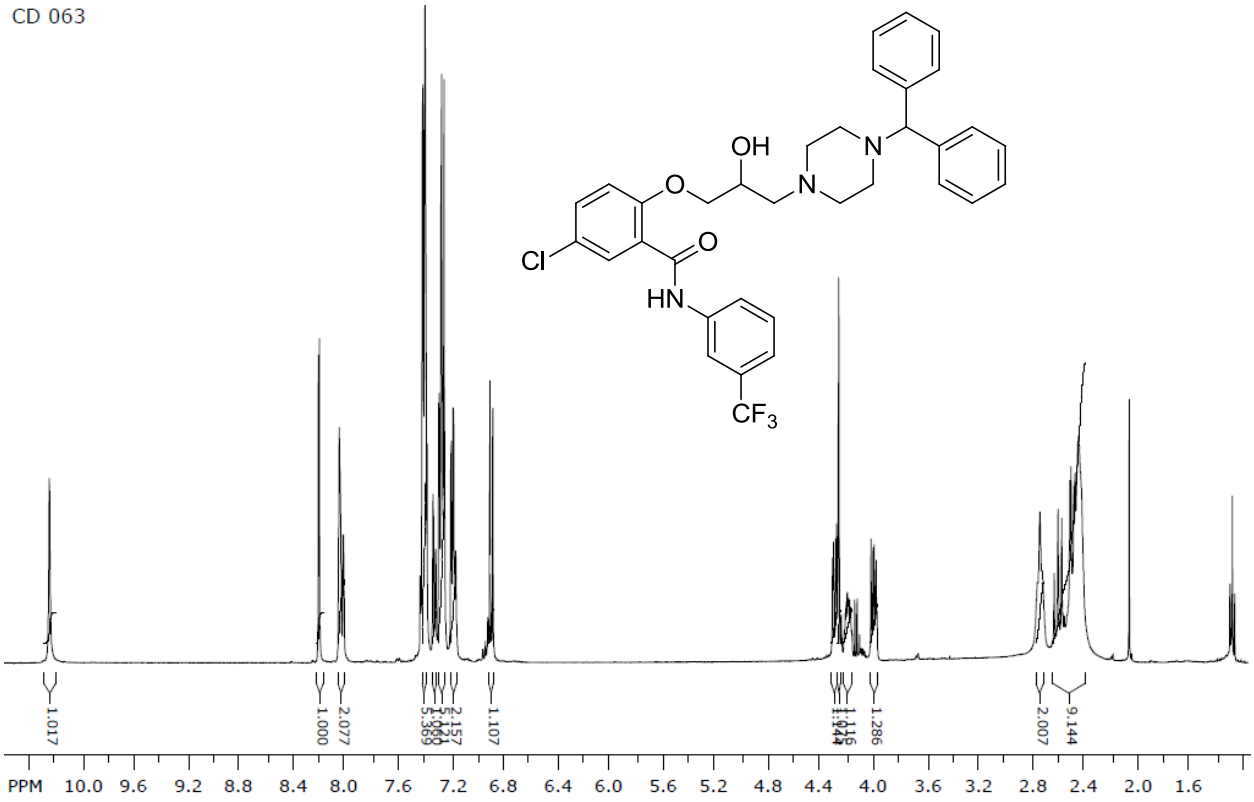
N-(4-fluorophenyl)-3-(oxiran-2-ylmethoxy)-2-naphthamide (399)

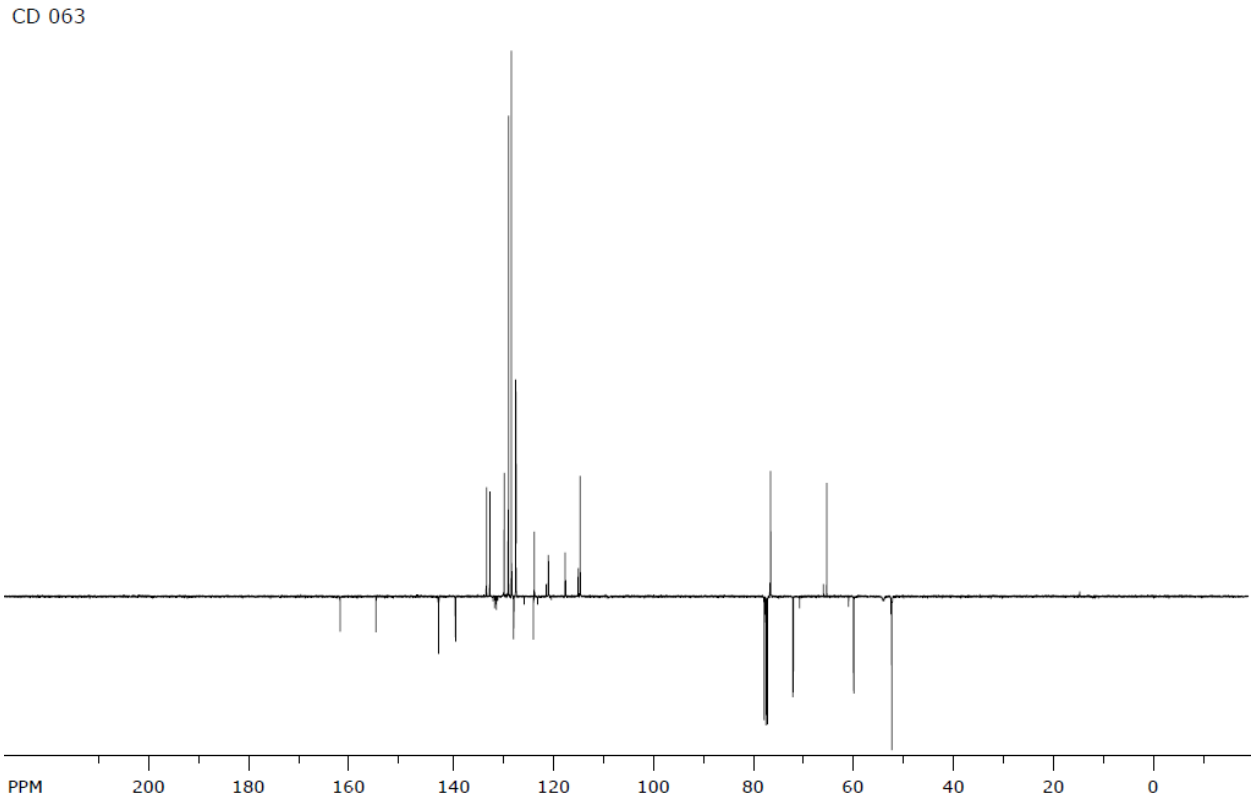




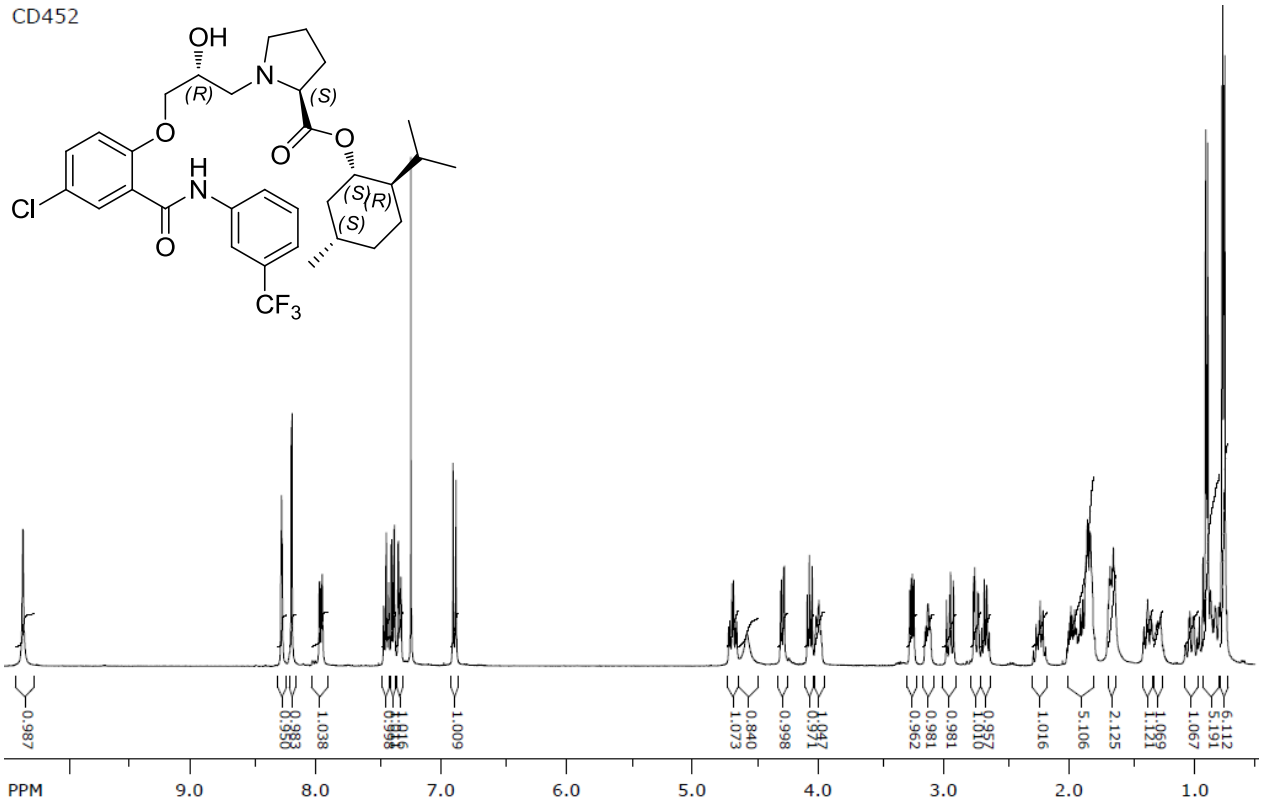
4.4.3 Final Compounds

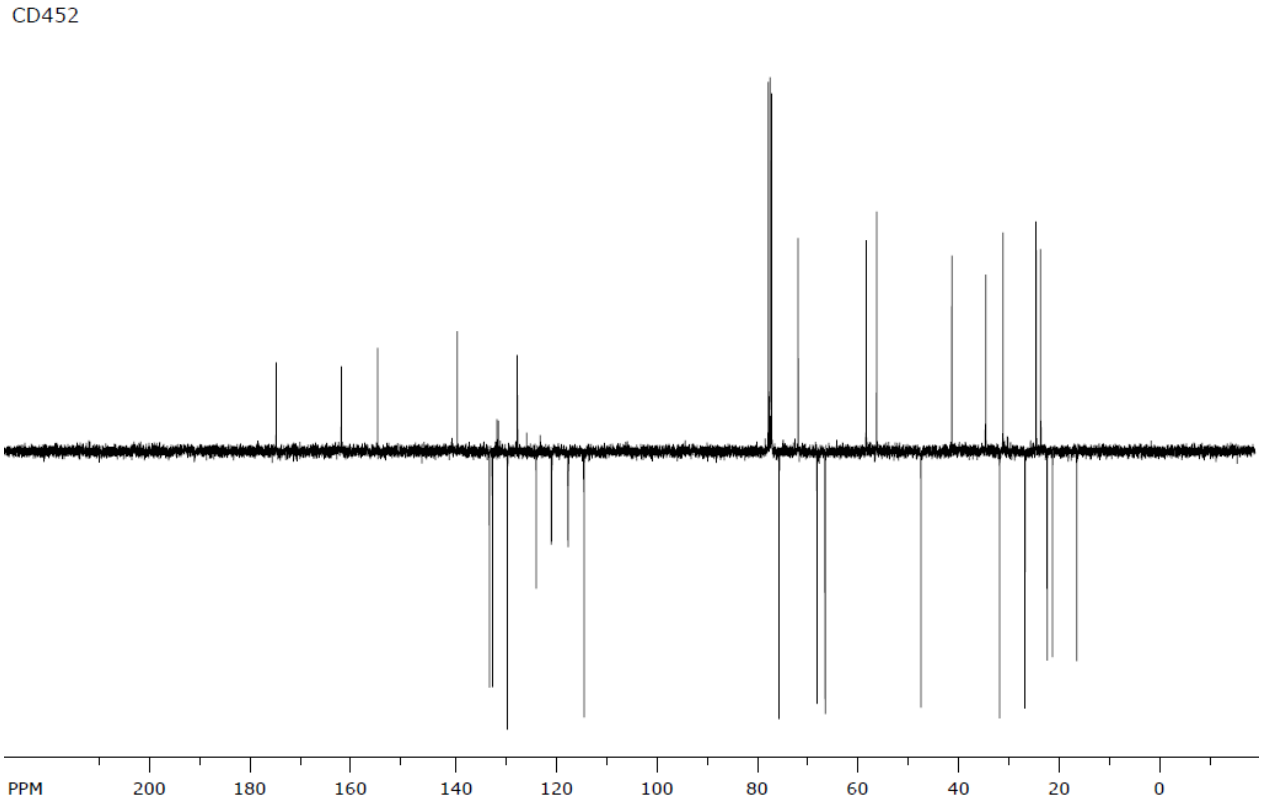
2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (95)



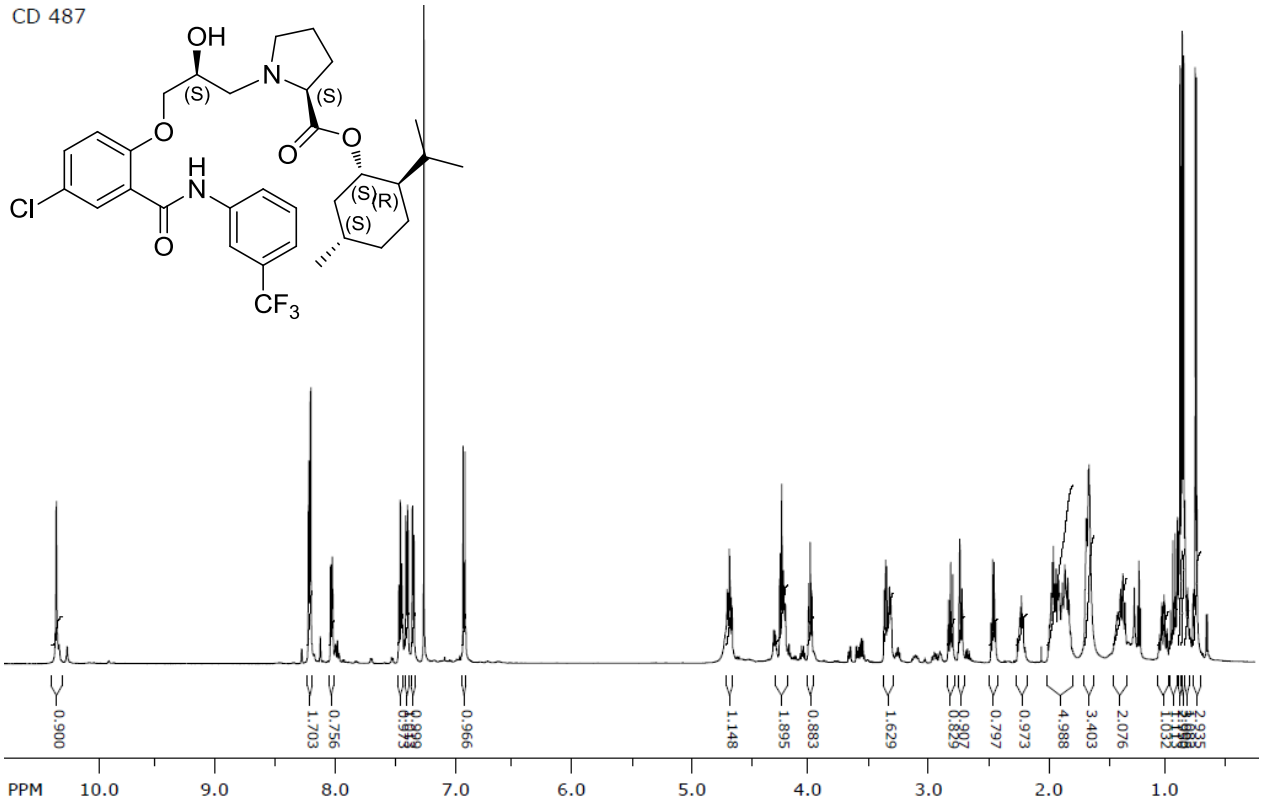


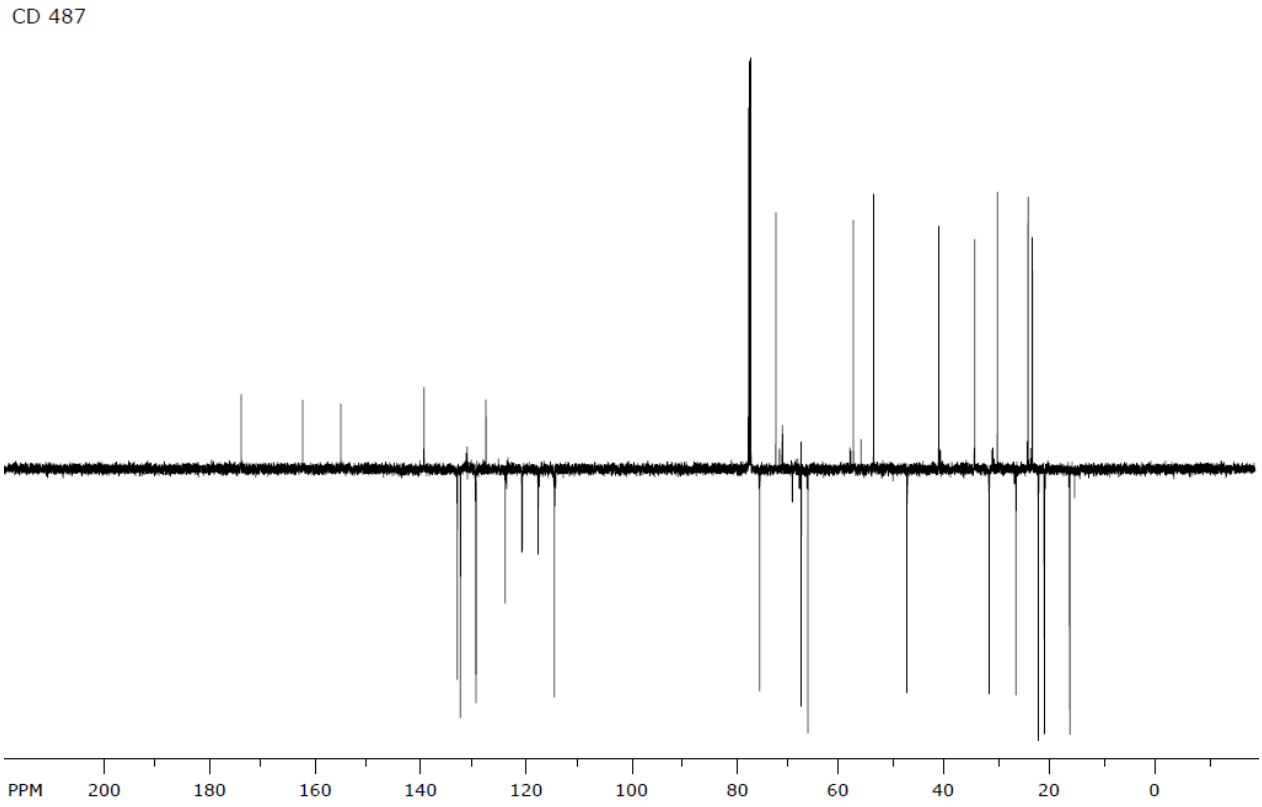
(*S*)-(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl-1-((*R*)-3-(4-chloro-2-((3-(trifluoromethyl)phenyl)carbamoyl)phenoxy)-2-hydroxypropyl)pyrrolidine-2-carboxylate (102)



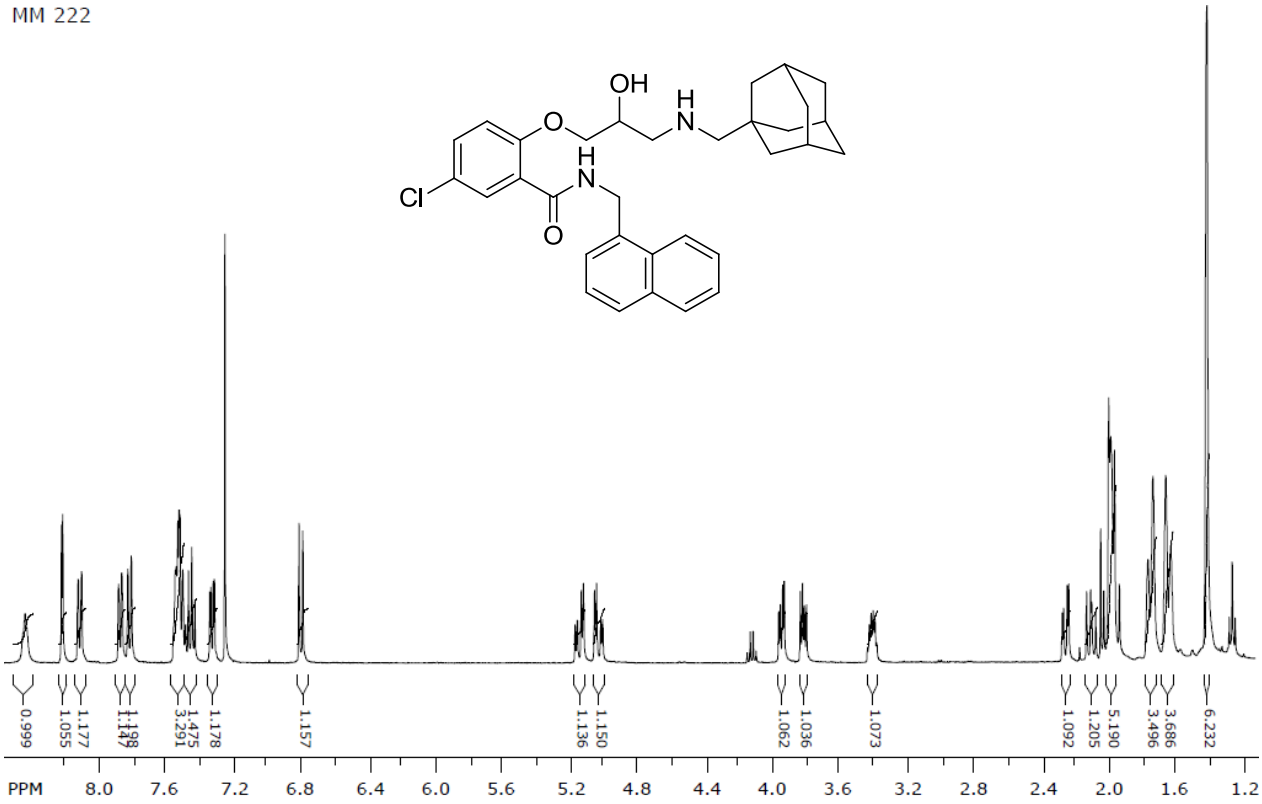


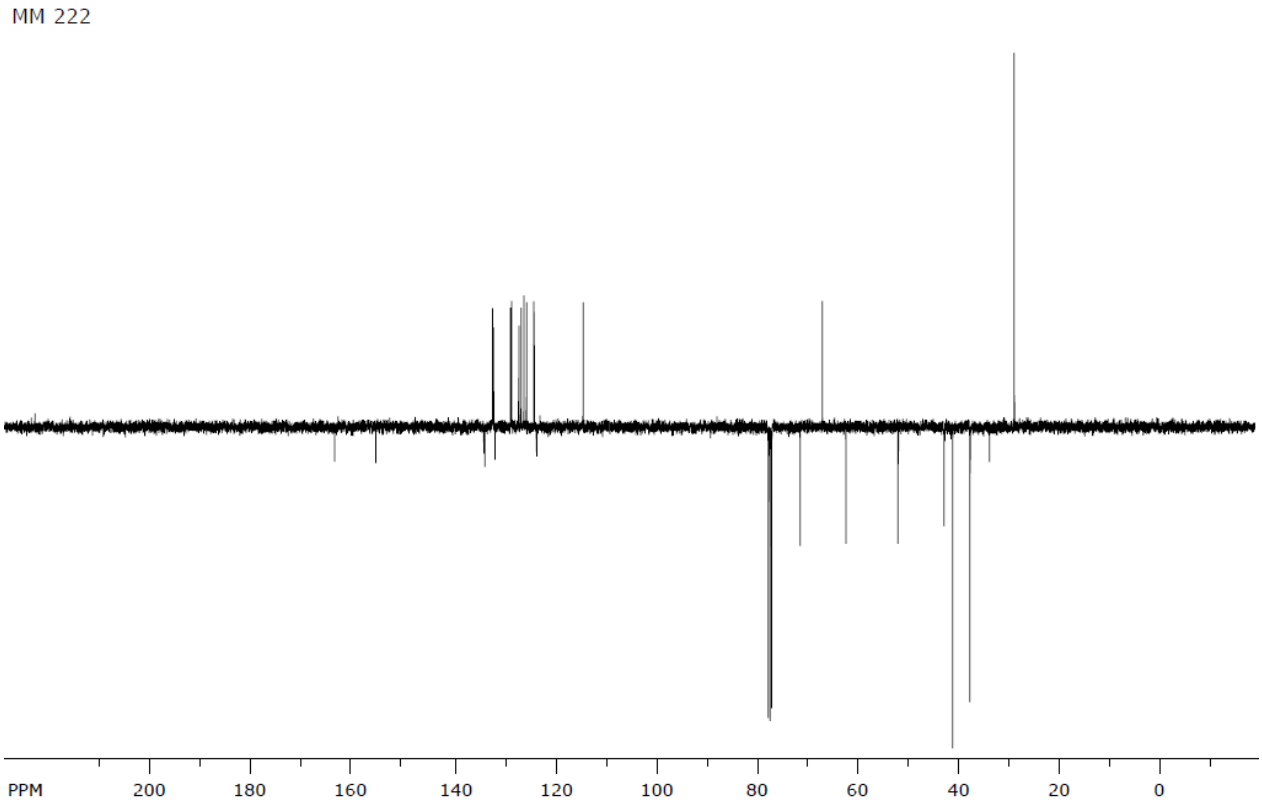
(*S*)-(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl-1-((*S*)-3-(4-chloro-2-((3-(trifluoromethyl)phenyl)carbamoyl)phenoxy)-2-hydroxypropyl)pyrrolidine-2-carboxylate (103)



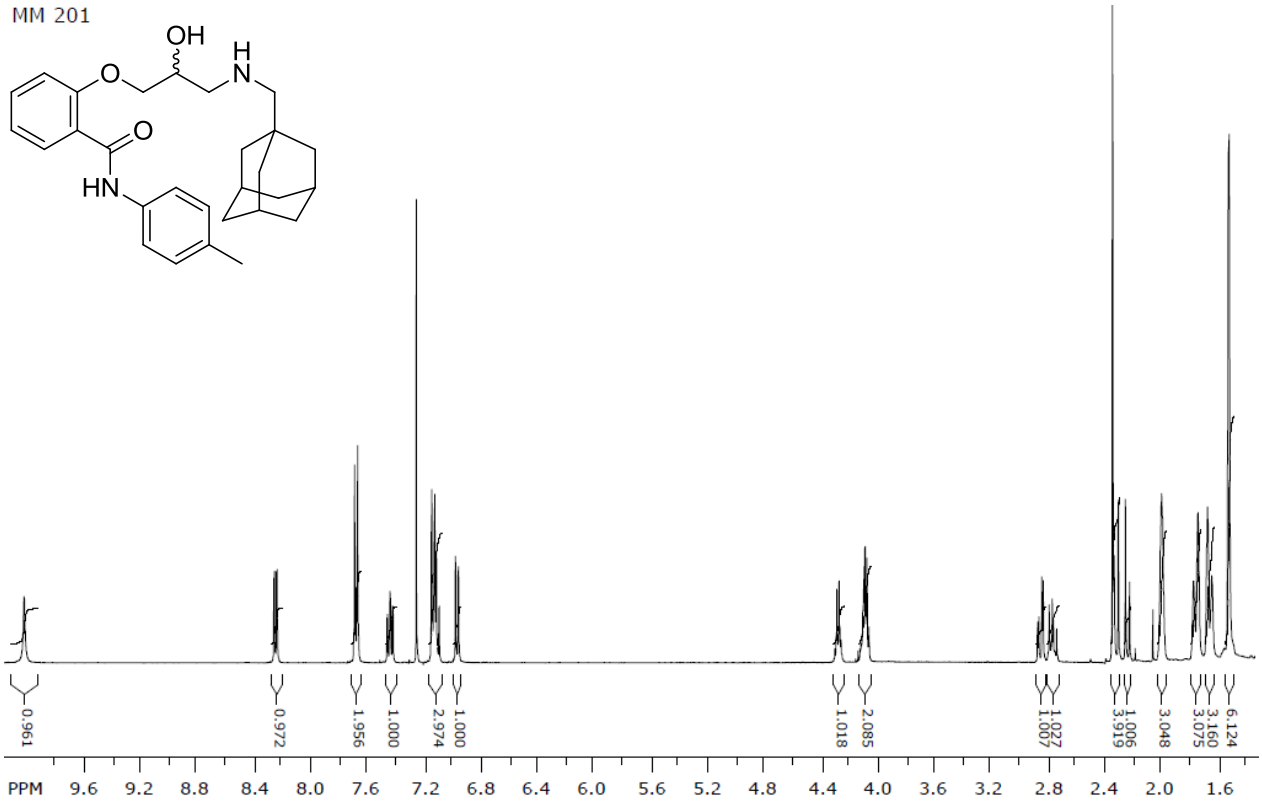


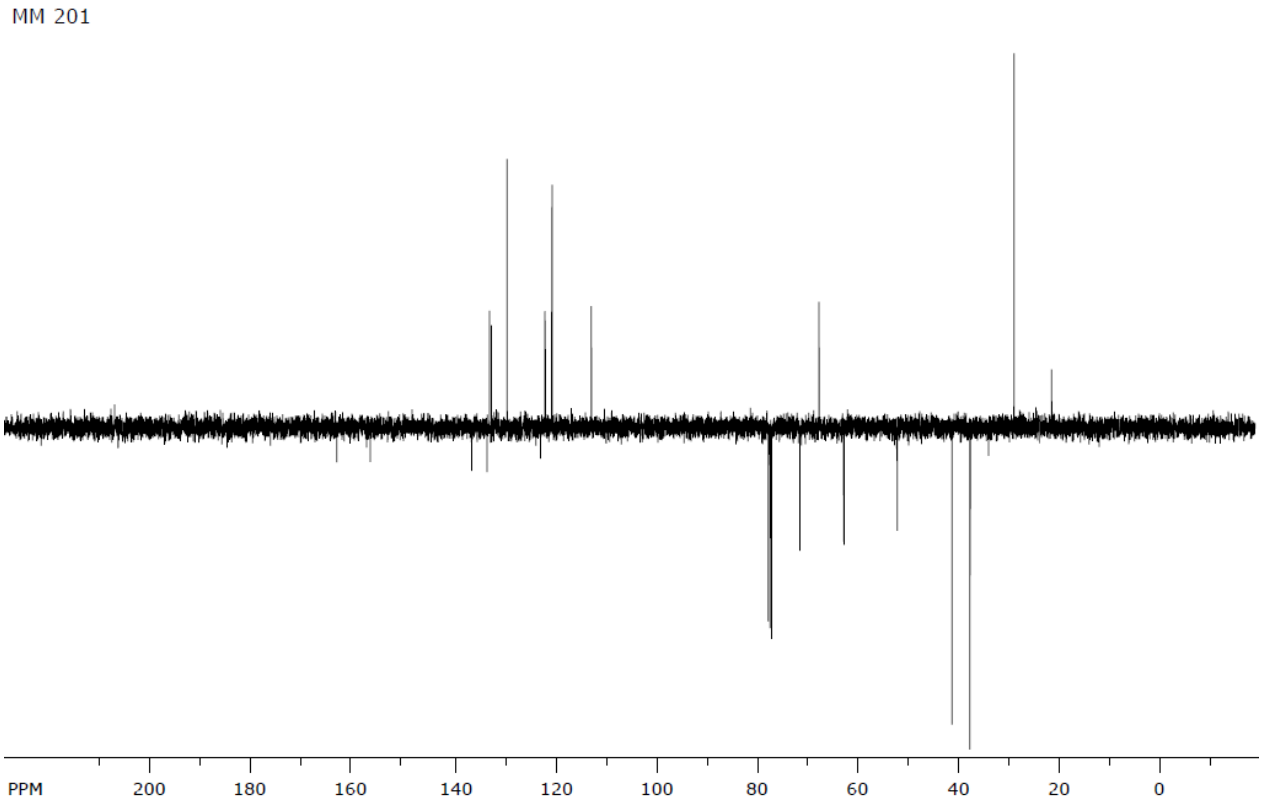
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(naphthalen-1-ylmethyl)benzamide (141)



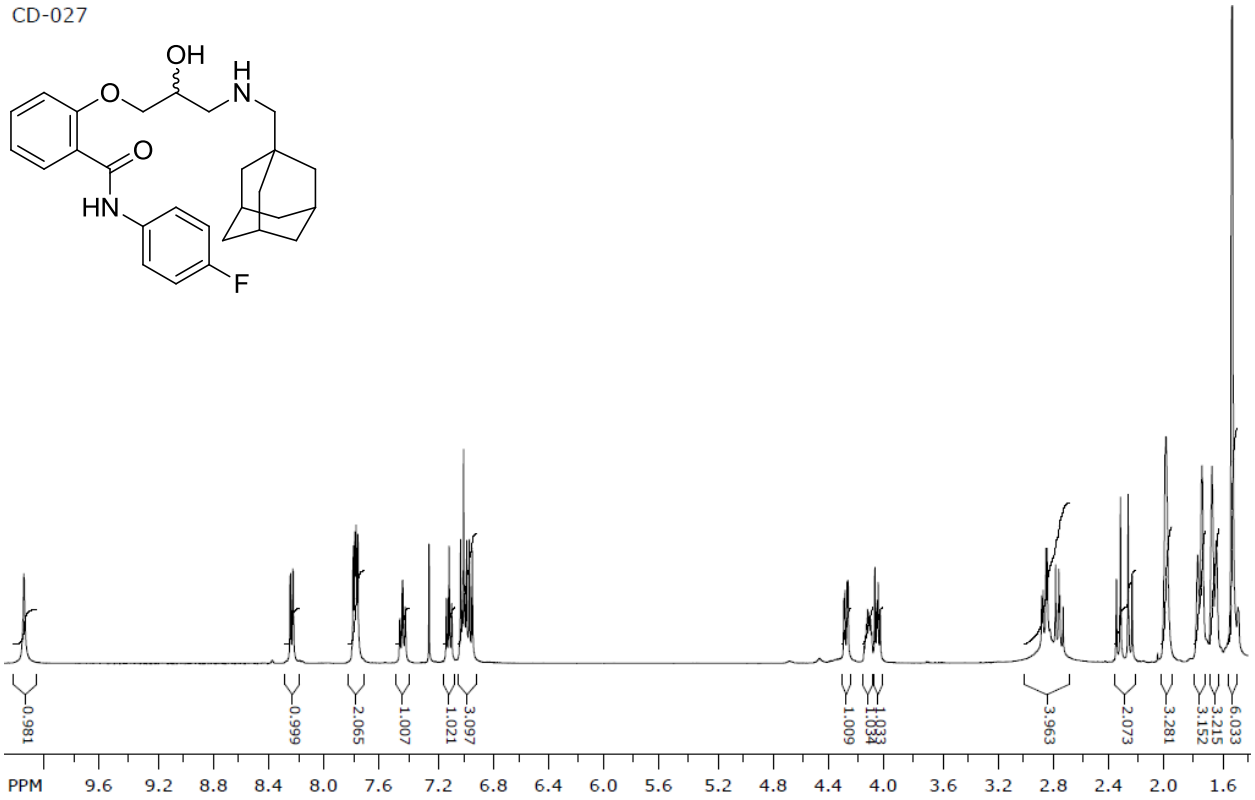


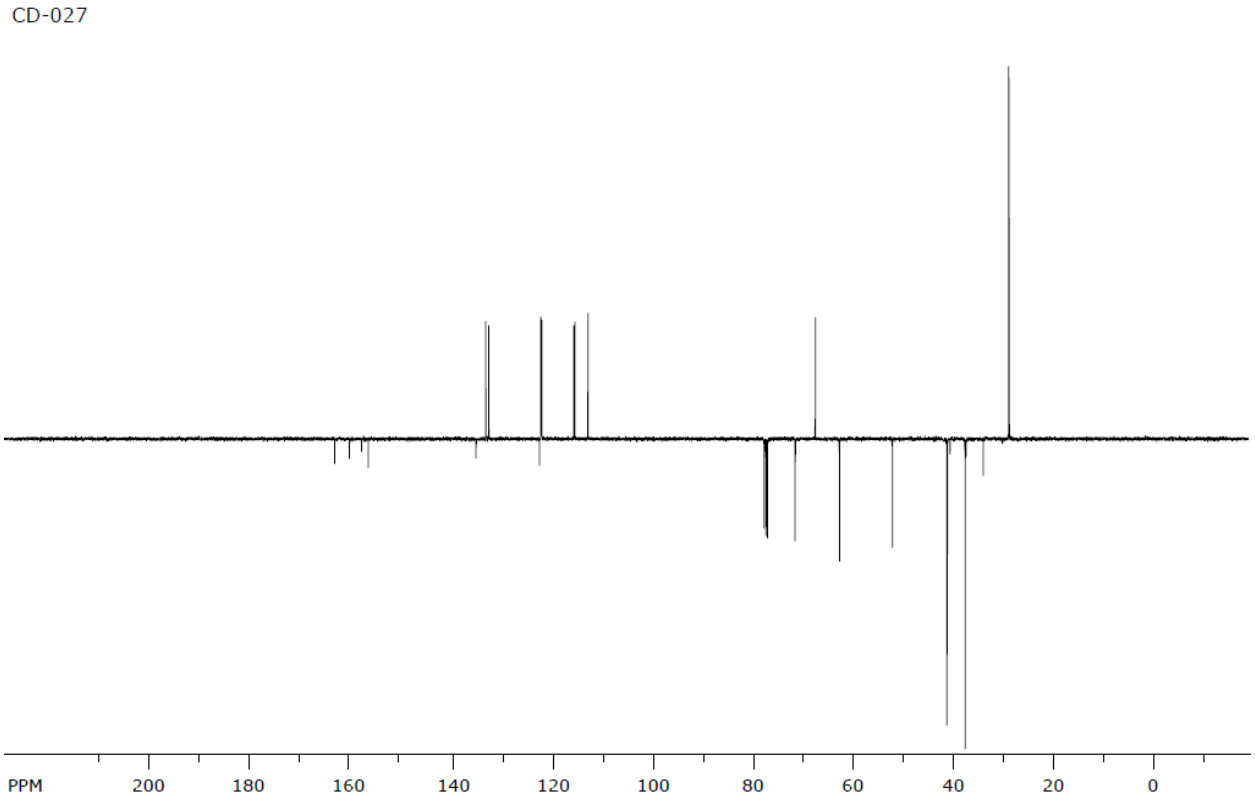
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(p-tolyl)benzamide (142)



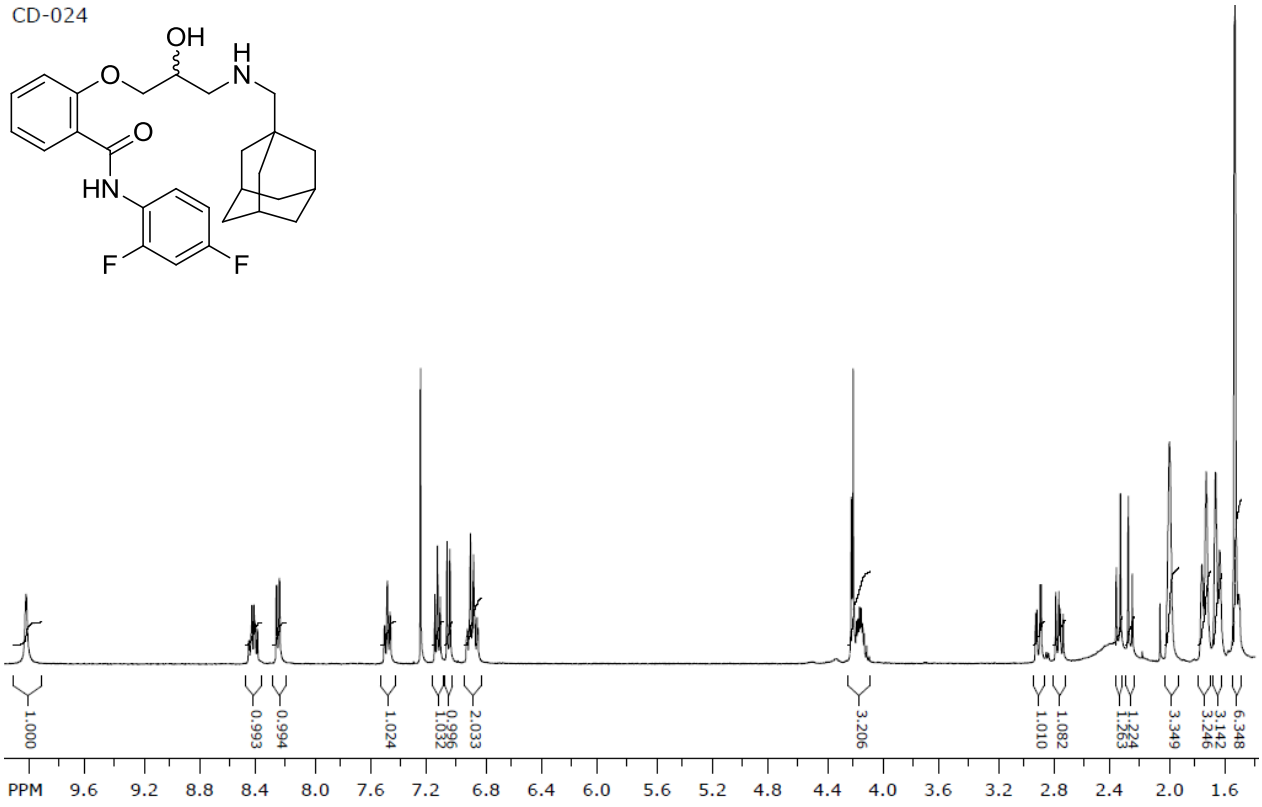


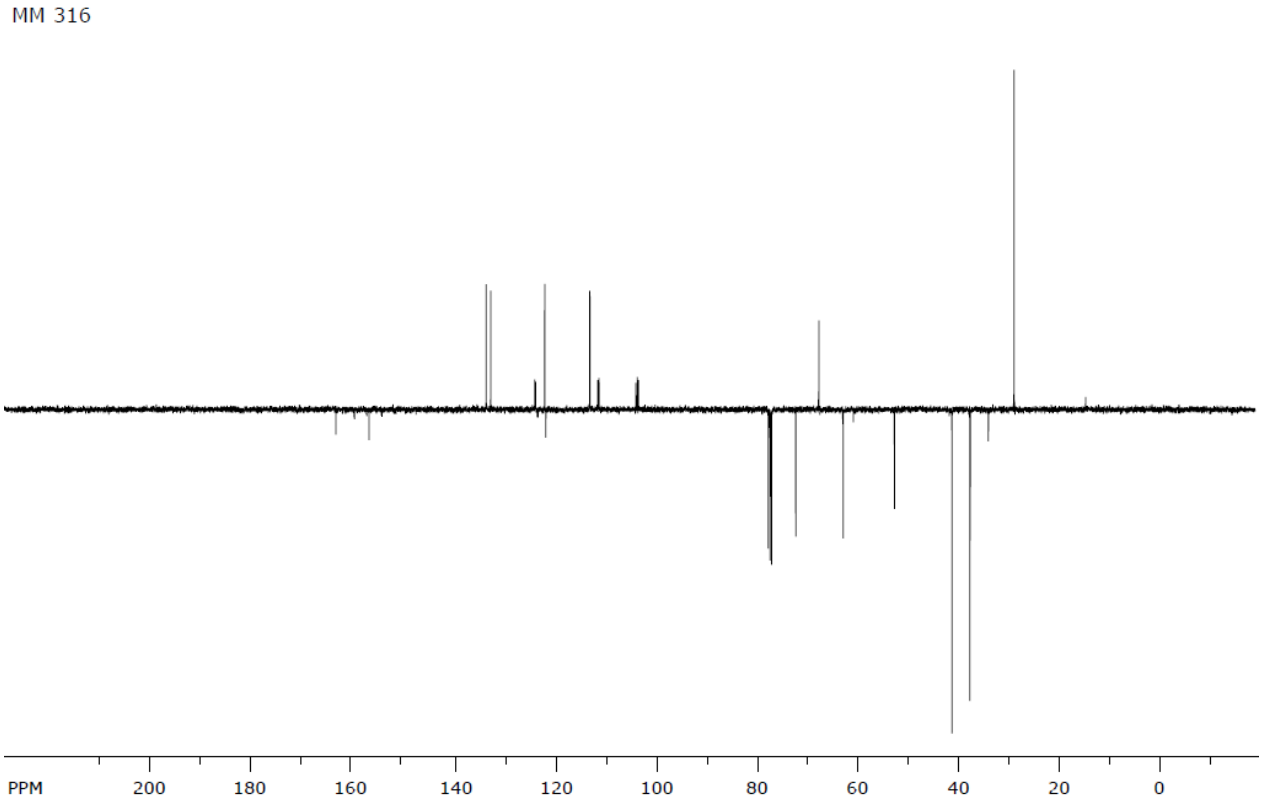
2-(3-((-adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(4-fluorophenyl)benzamide (143)



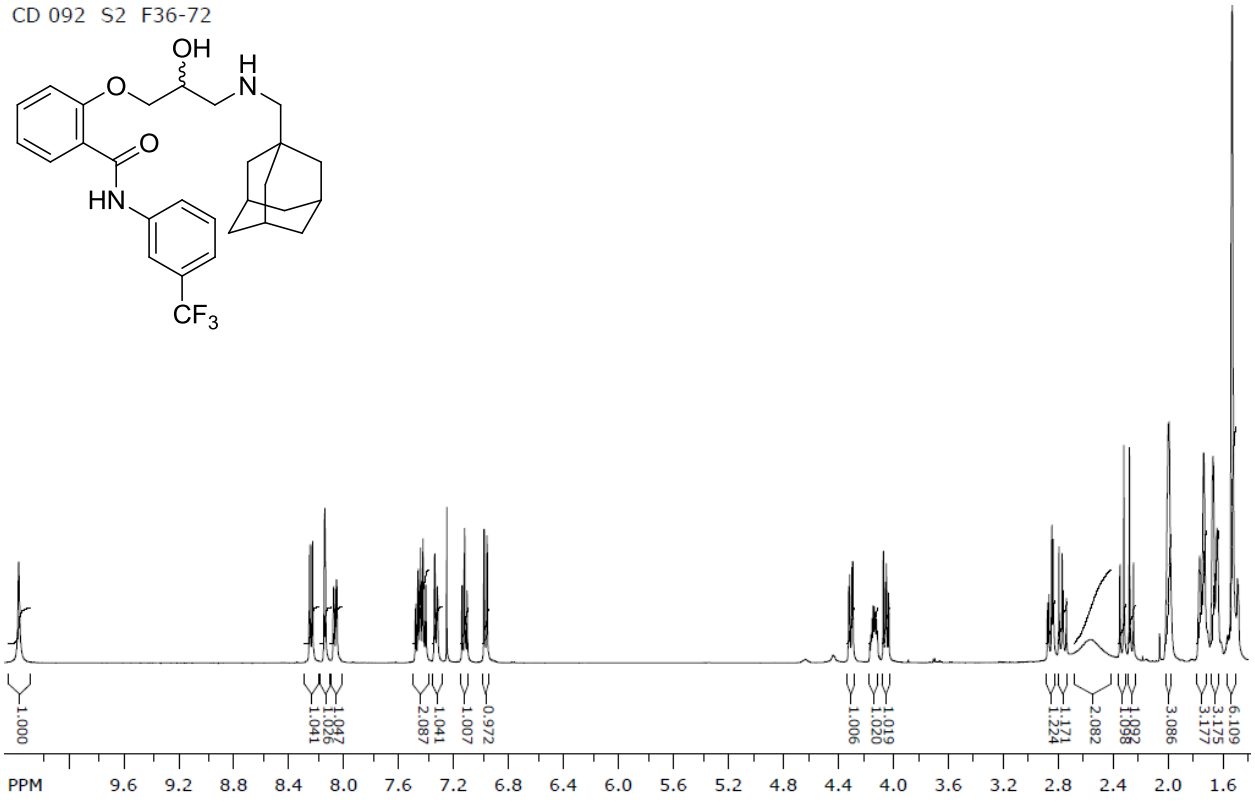


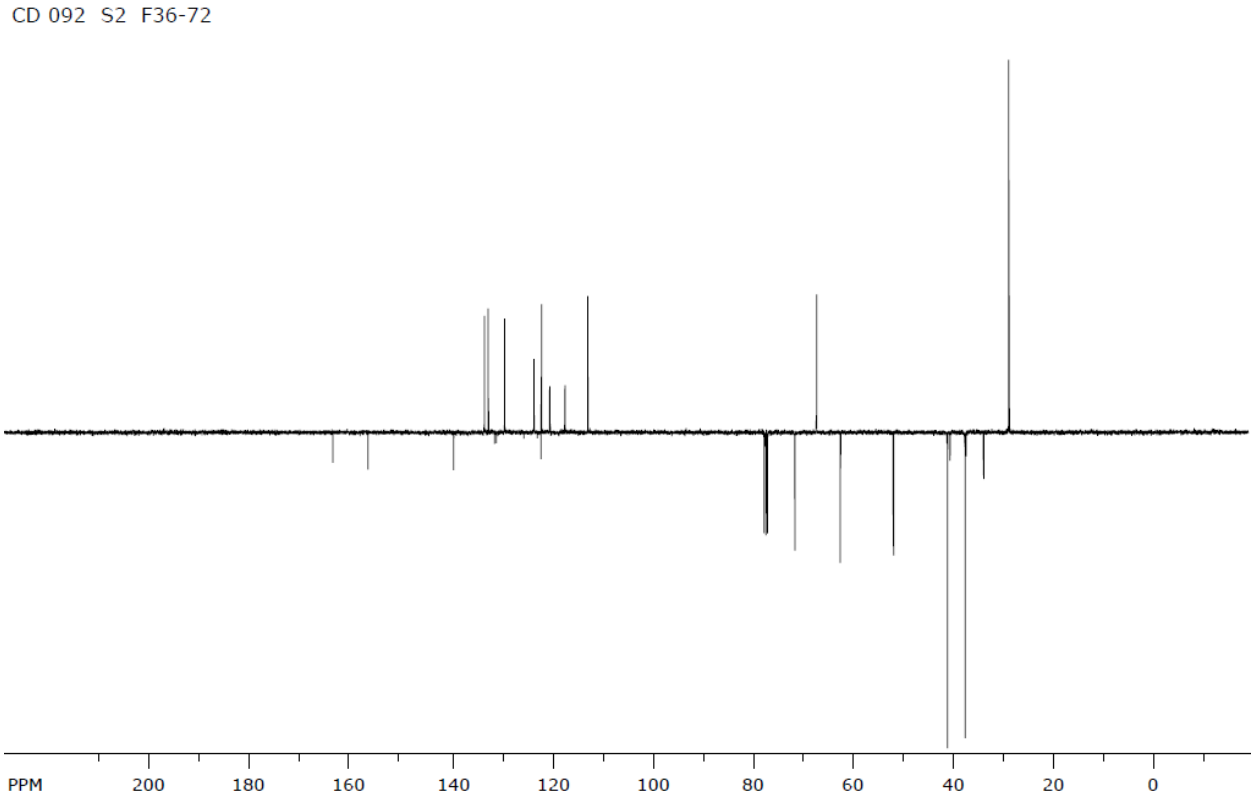
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(2,4-difluorophenyl)benzamide (144)



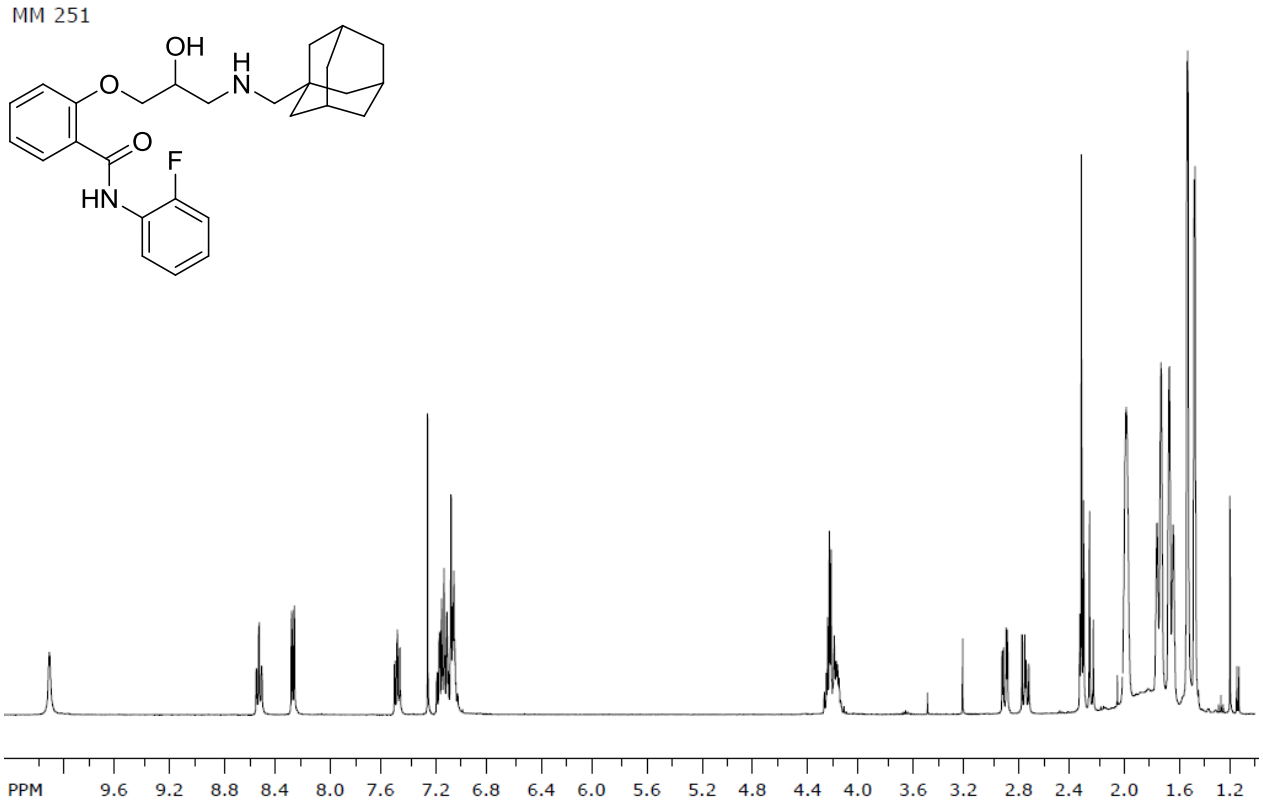


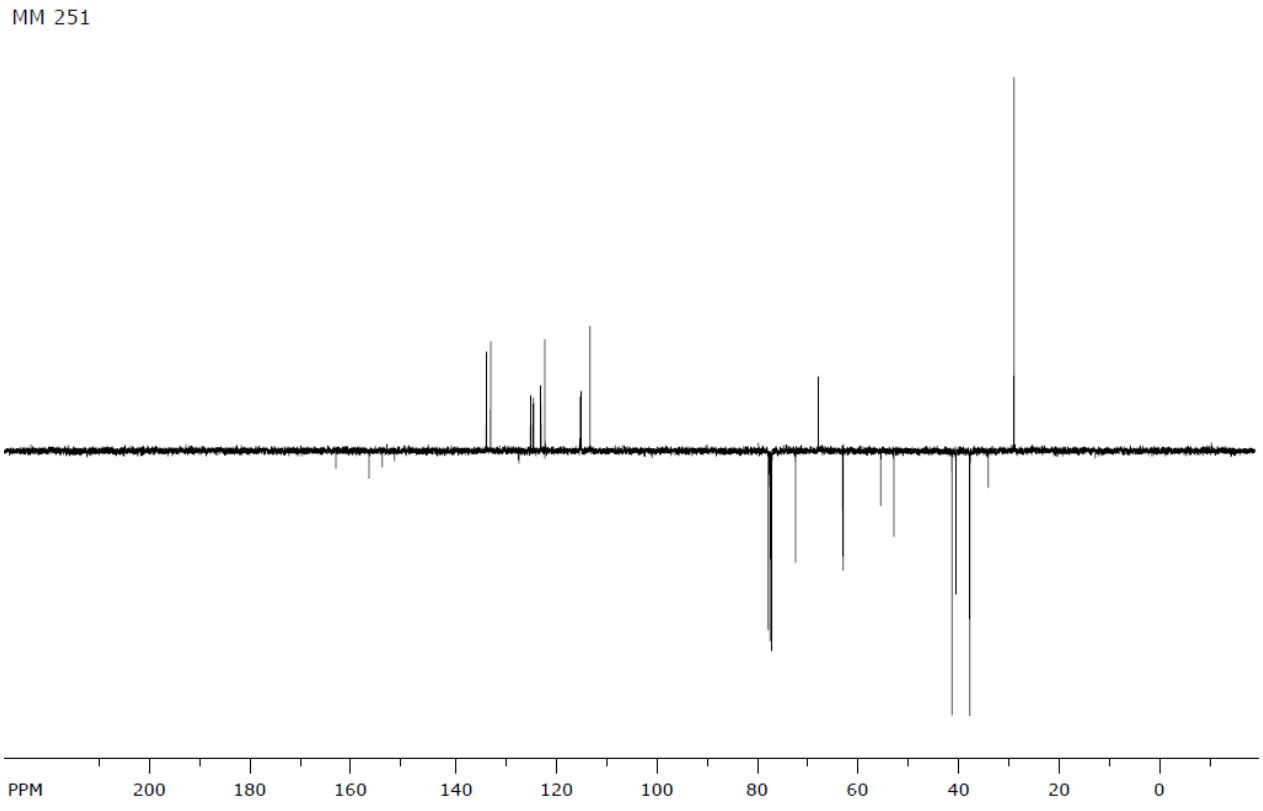
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (145)





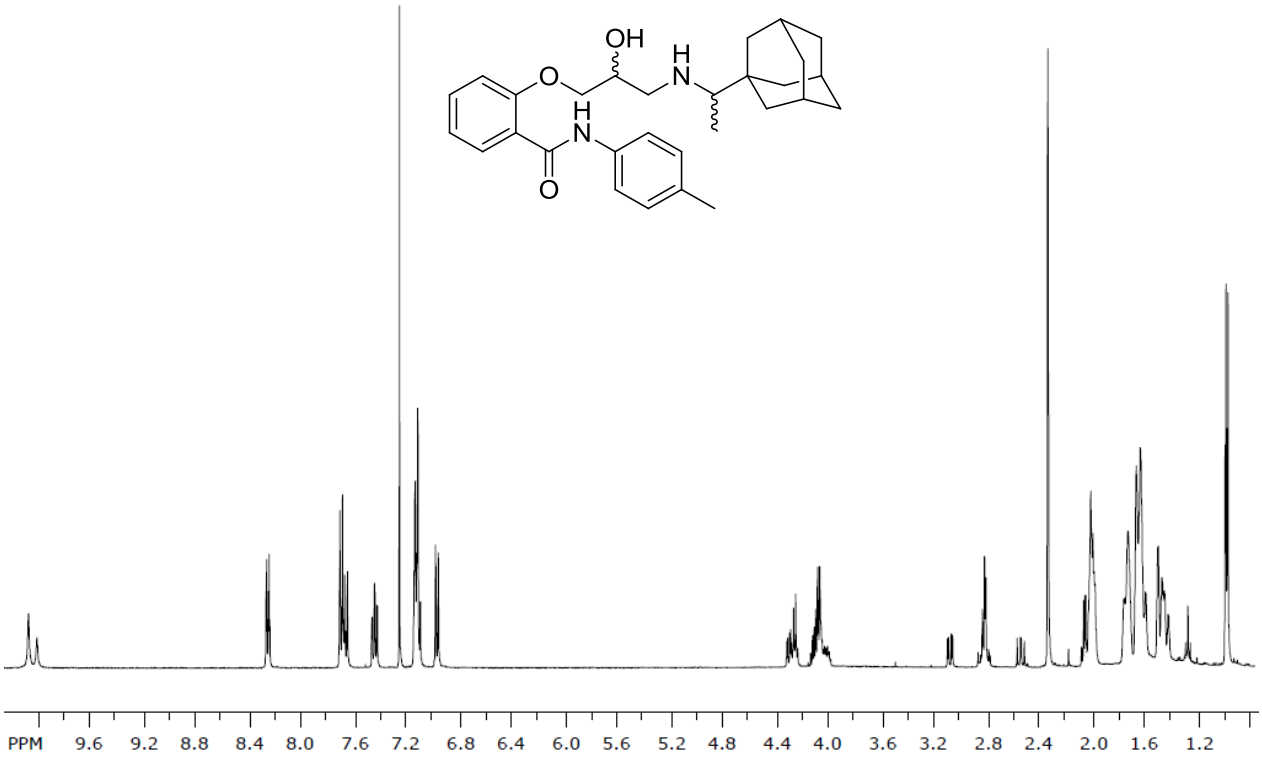
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(2-fluorophenyl)benzamide (146**)**



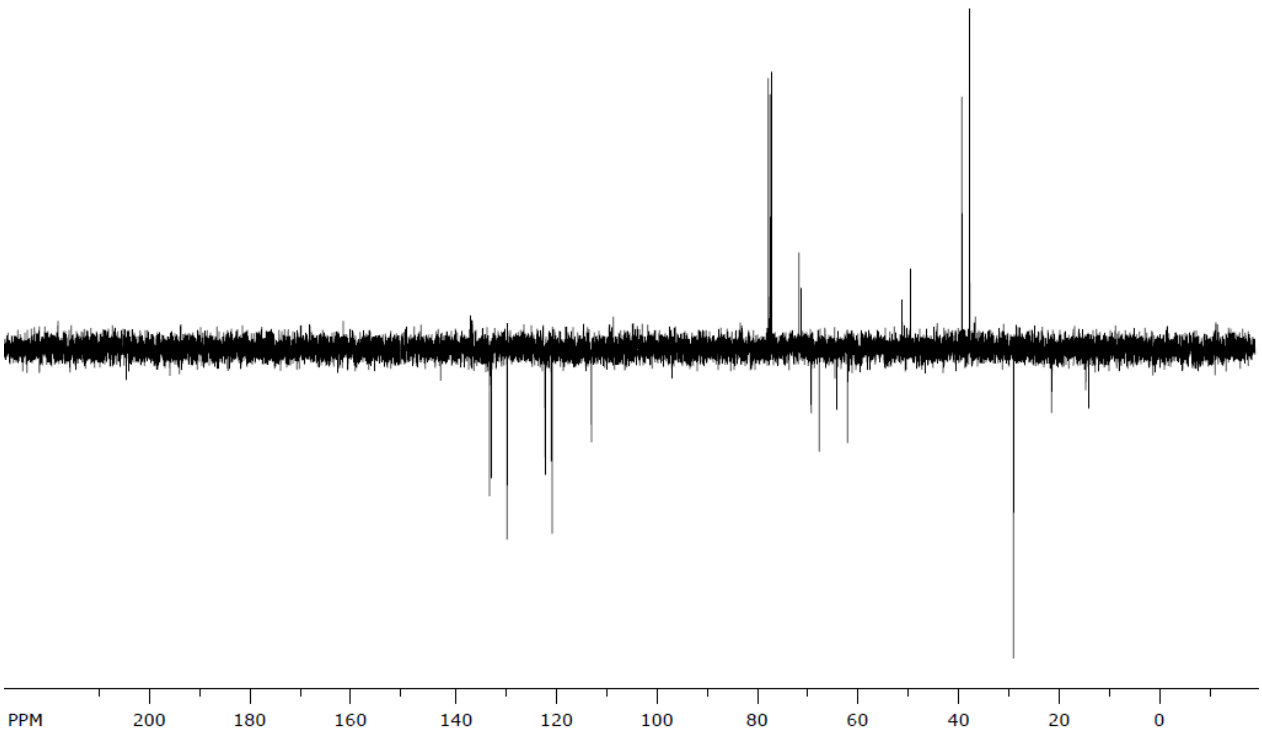


2-(3-((1-(adamantan-1-yl)ethyl)amino)-2-hydroxypropoxy)-*N*-(p-tolyl)benzamide (154)

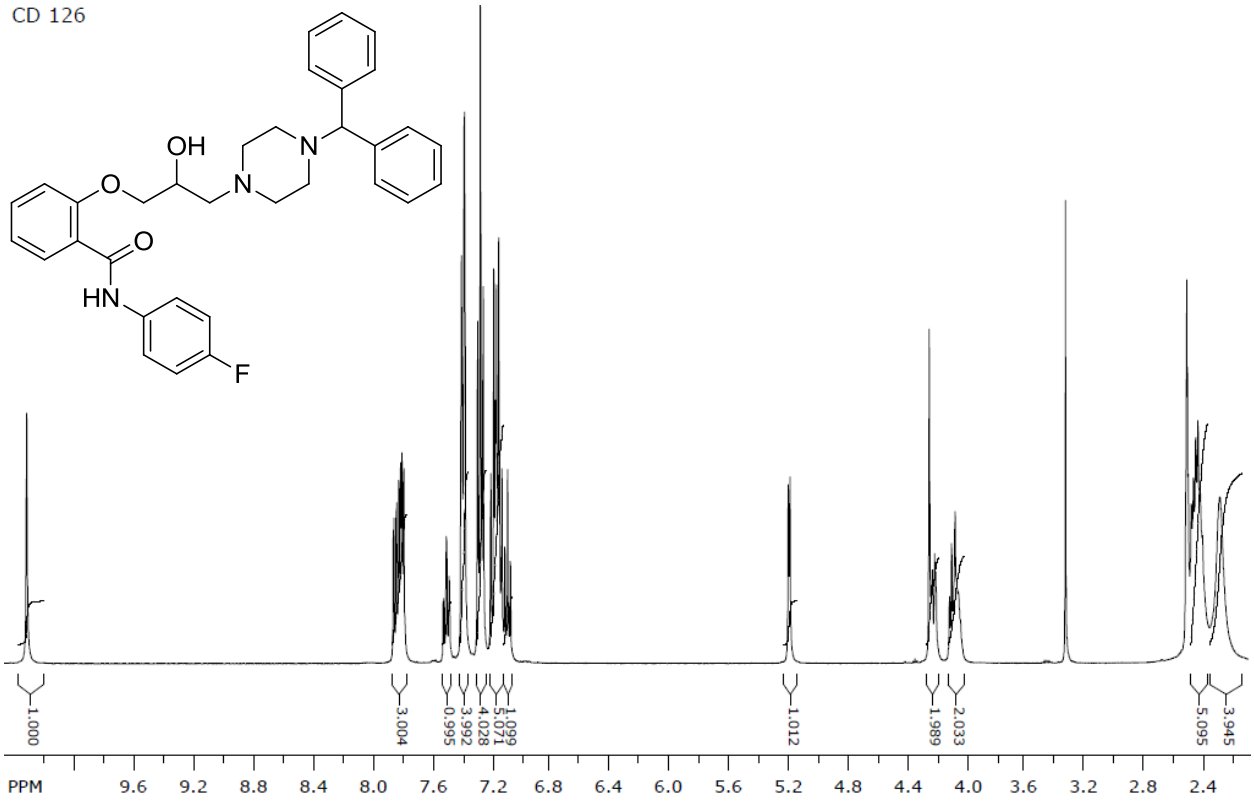
MM 202

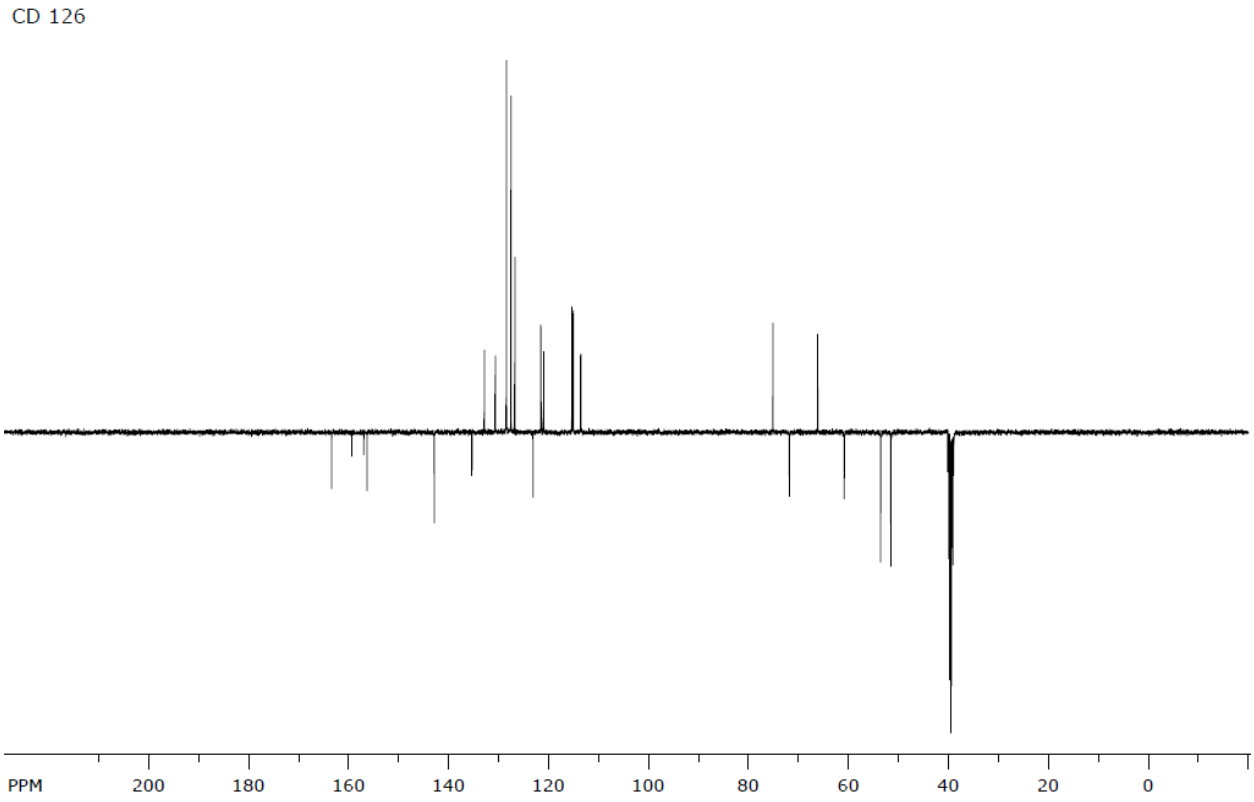


MM 202

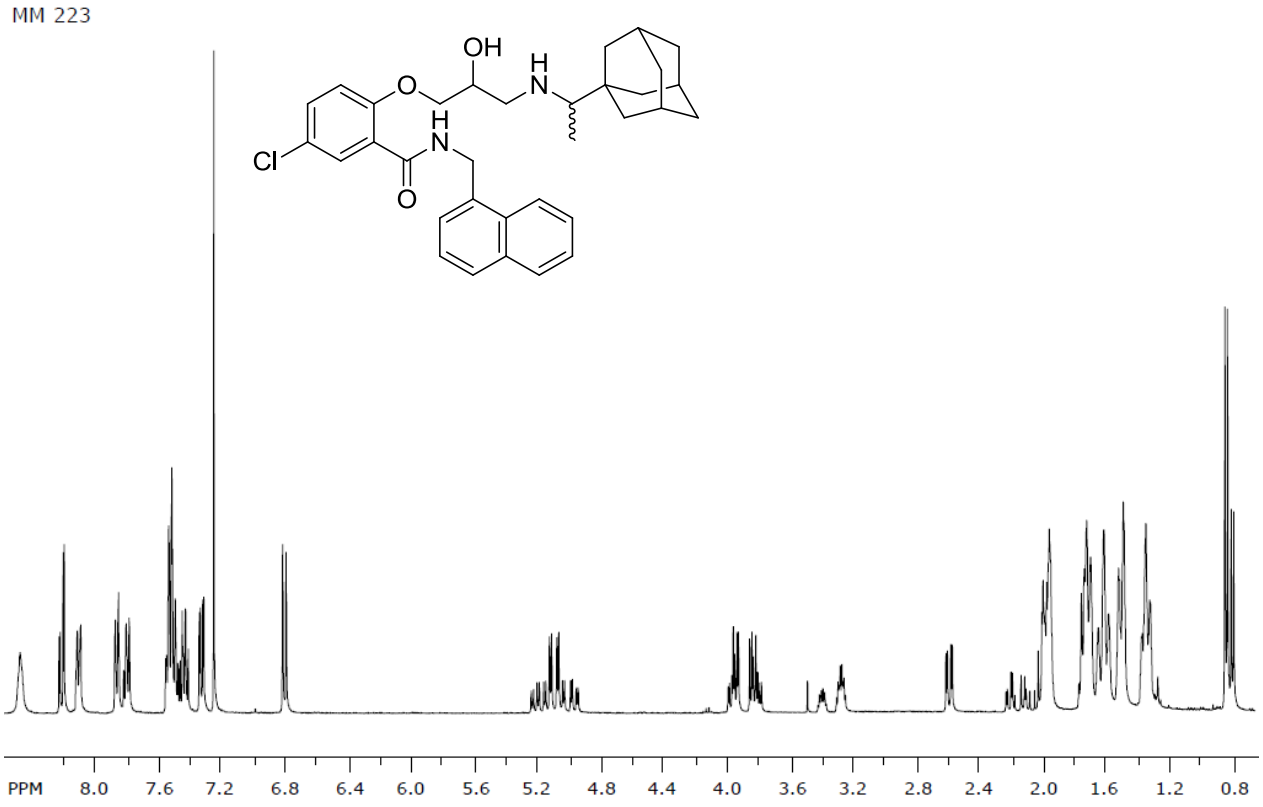


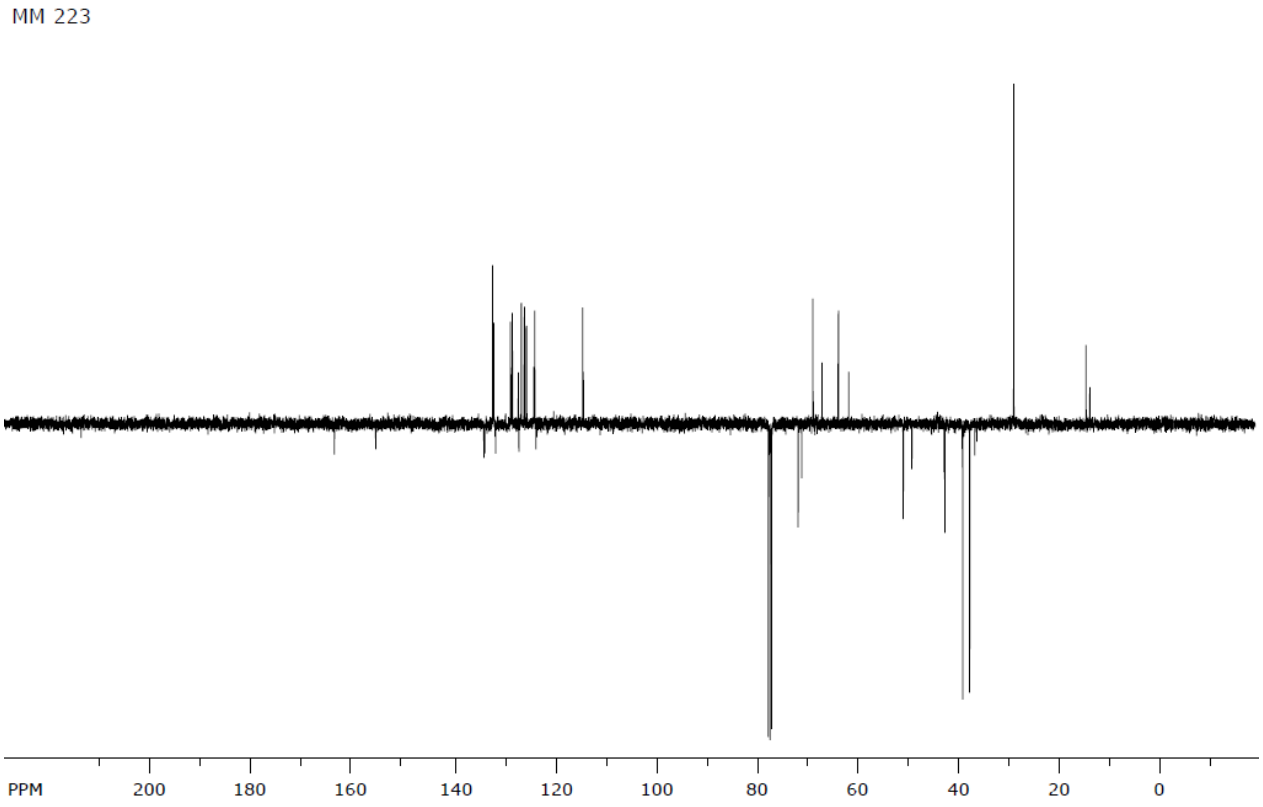
2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(4-fluorophenyl)benzamide (159**)**



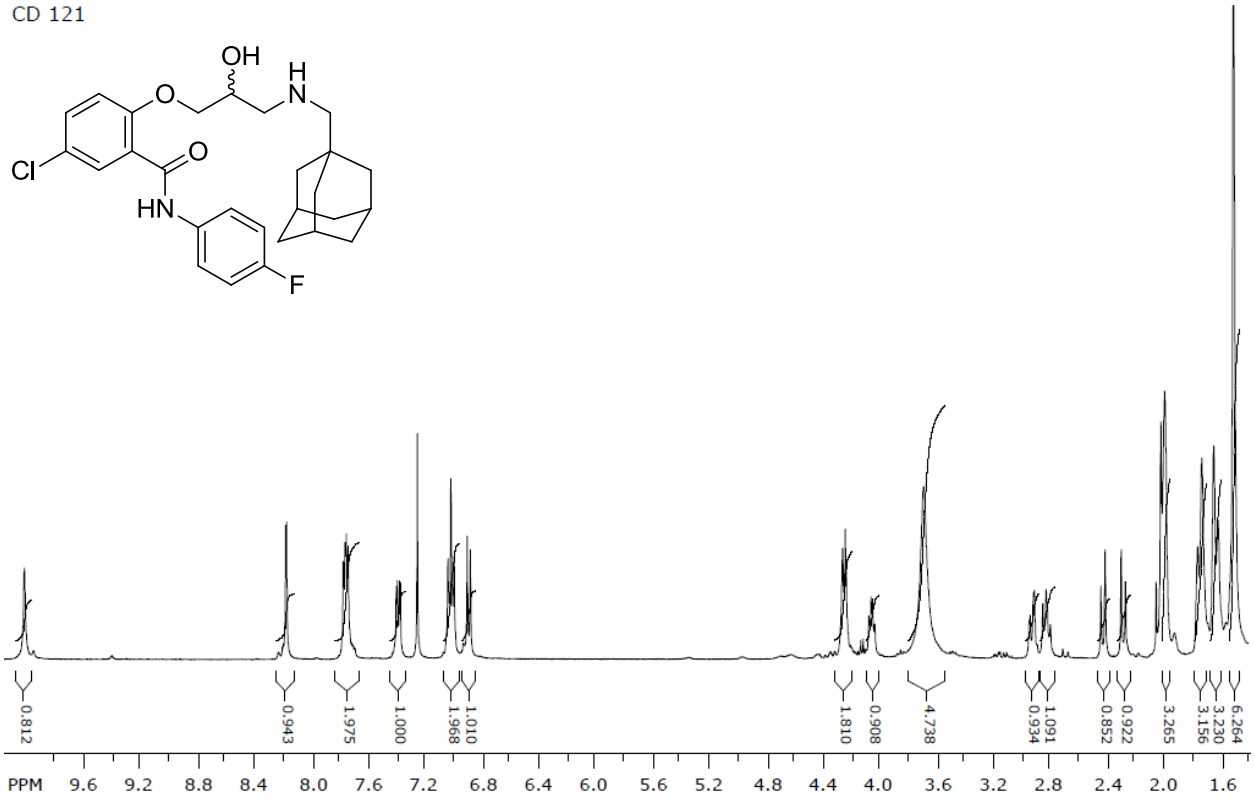


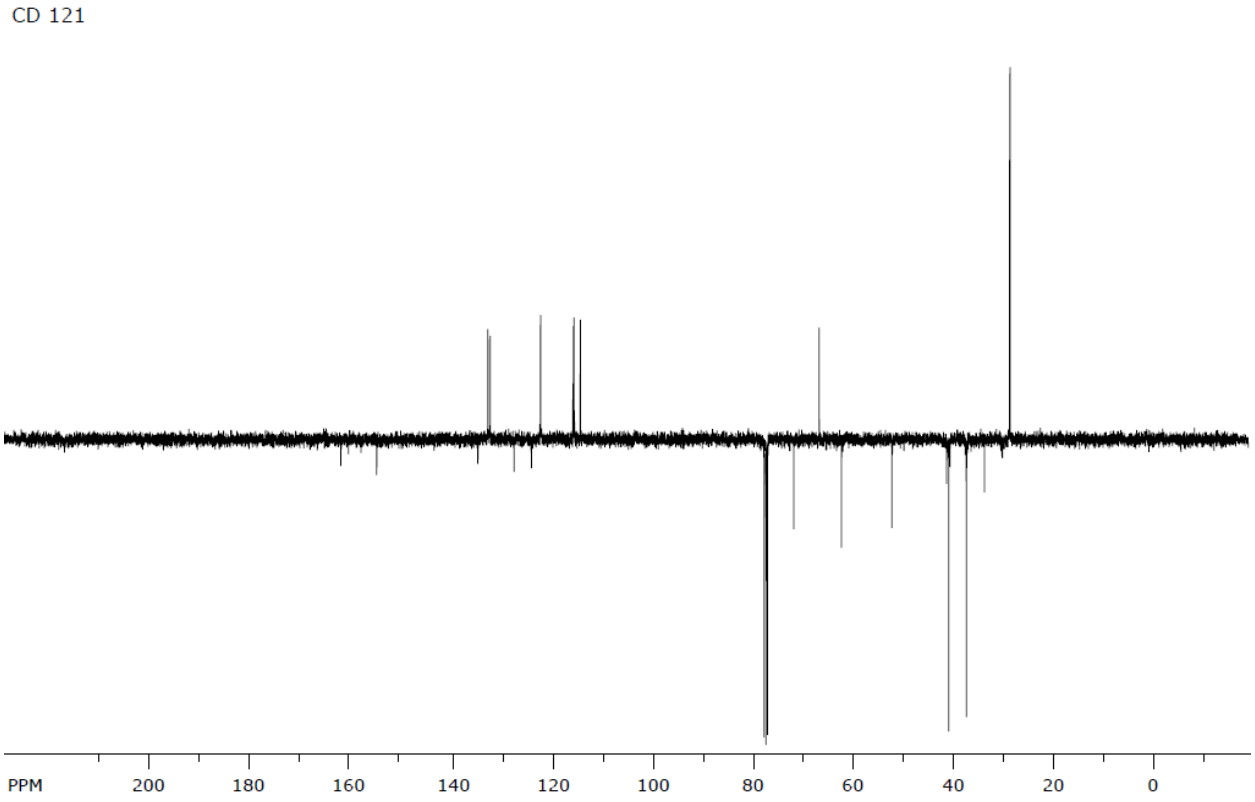
2-(3-((1-(adamantan-1-yl)ethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(naphthalen-1-ylmethyl)benzamide (167)



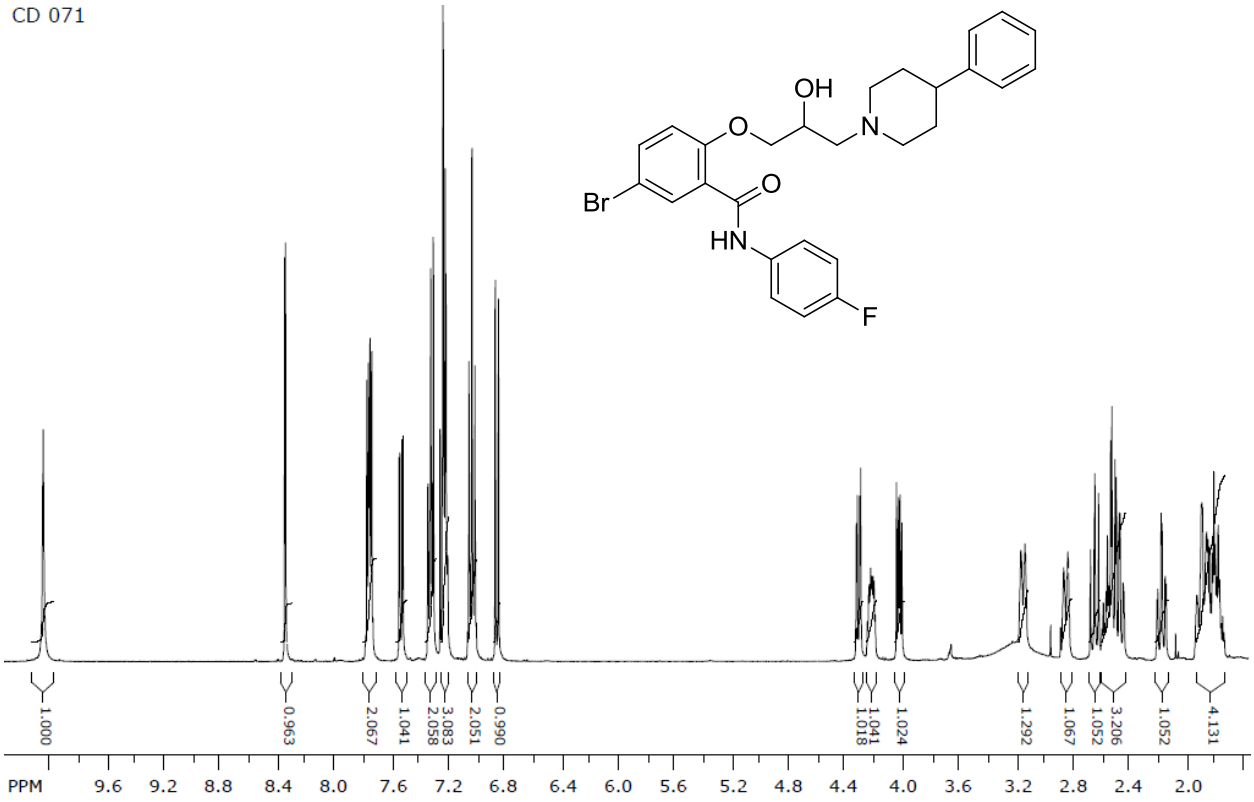


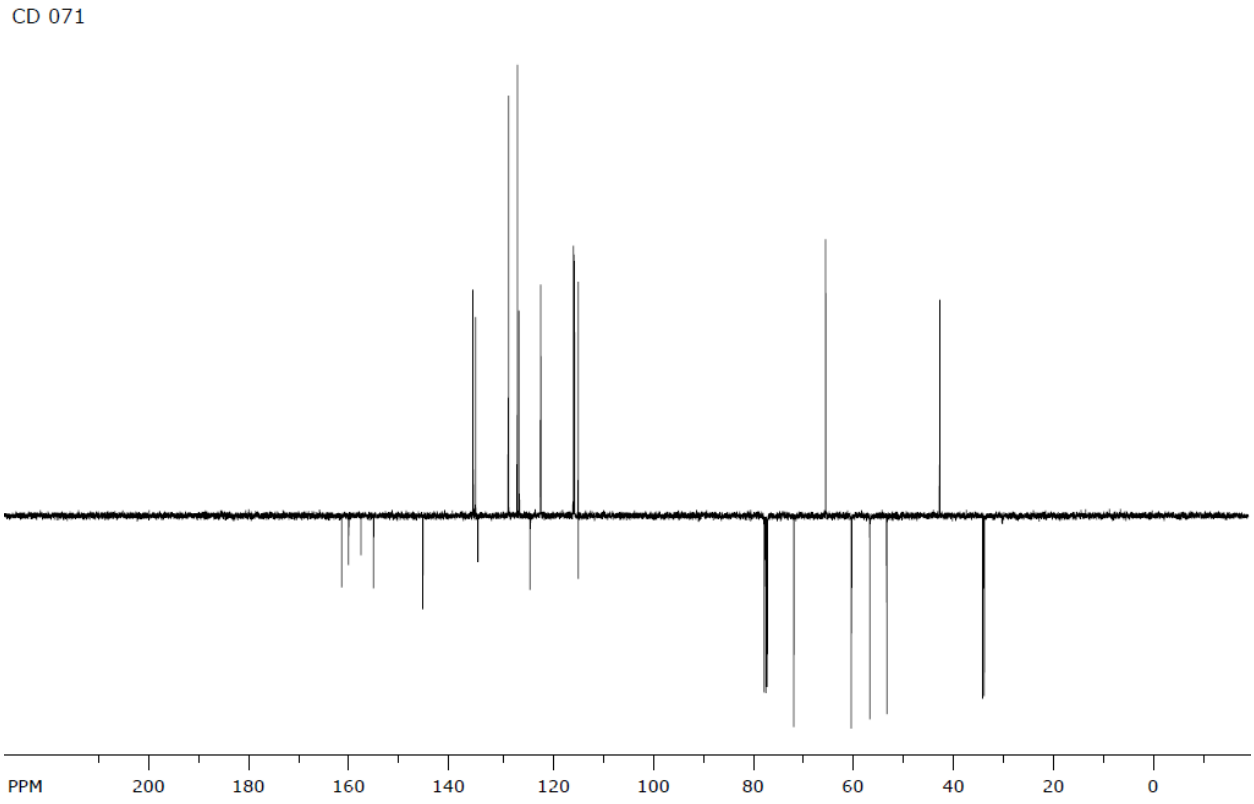
2-(3-((-adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(4-fluorophenyl)benzamide (168**)**



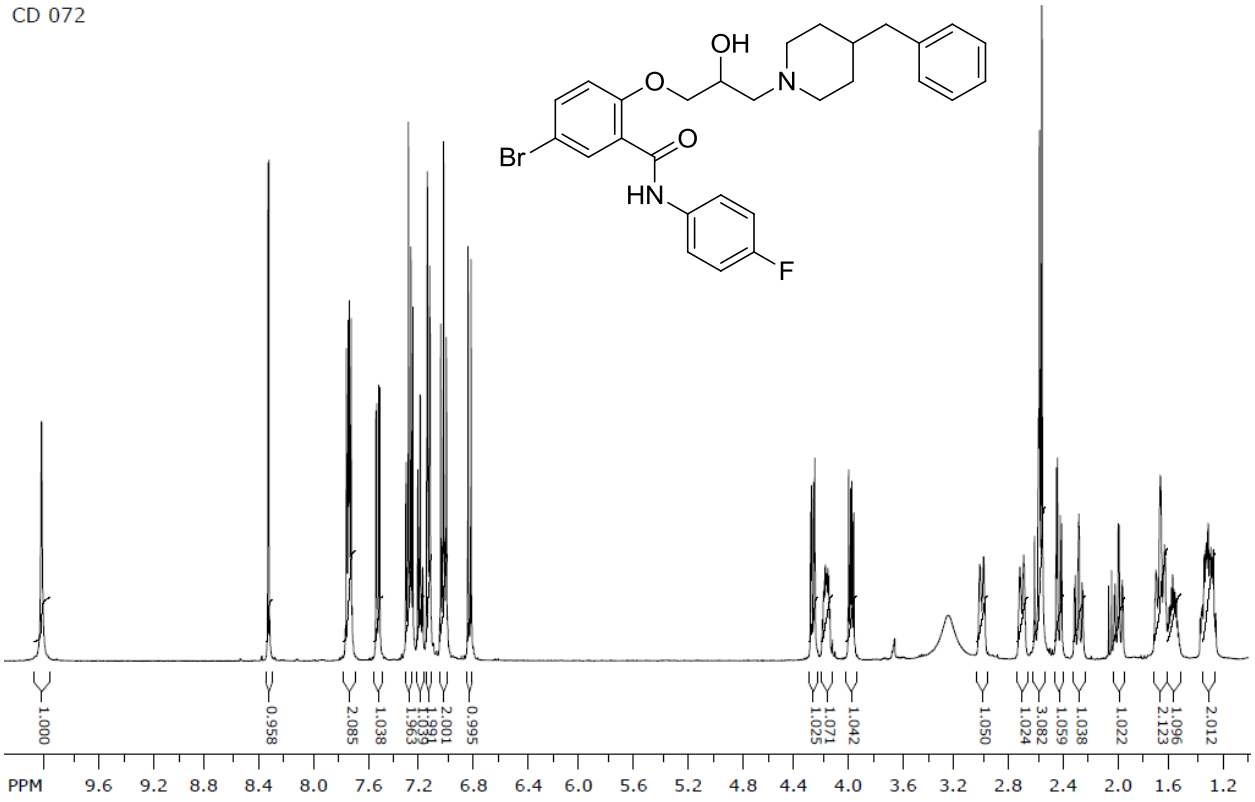


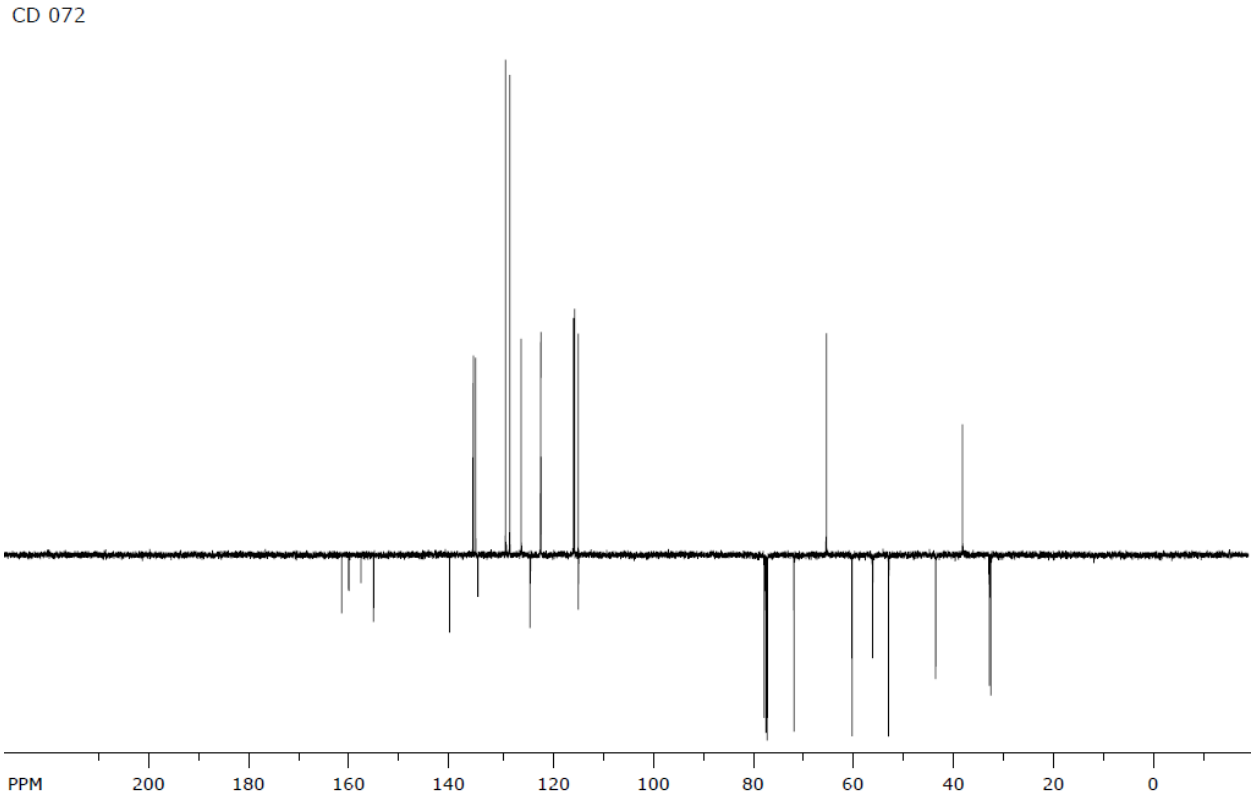
5-bromo-*N*-(4-fluorophenyl)-2-(2-hydroxy-3-(4-phenylpiperidin-1-yl)propoxy)benzamide (169**)**



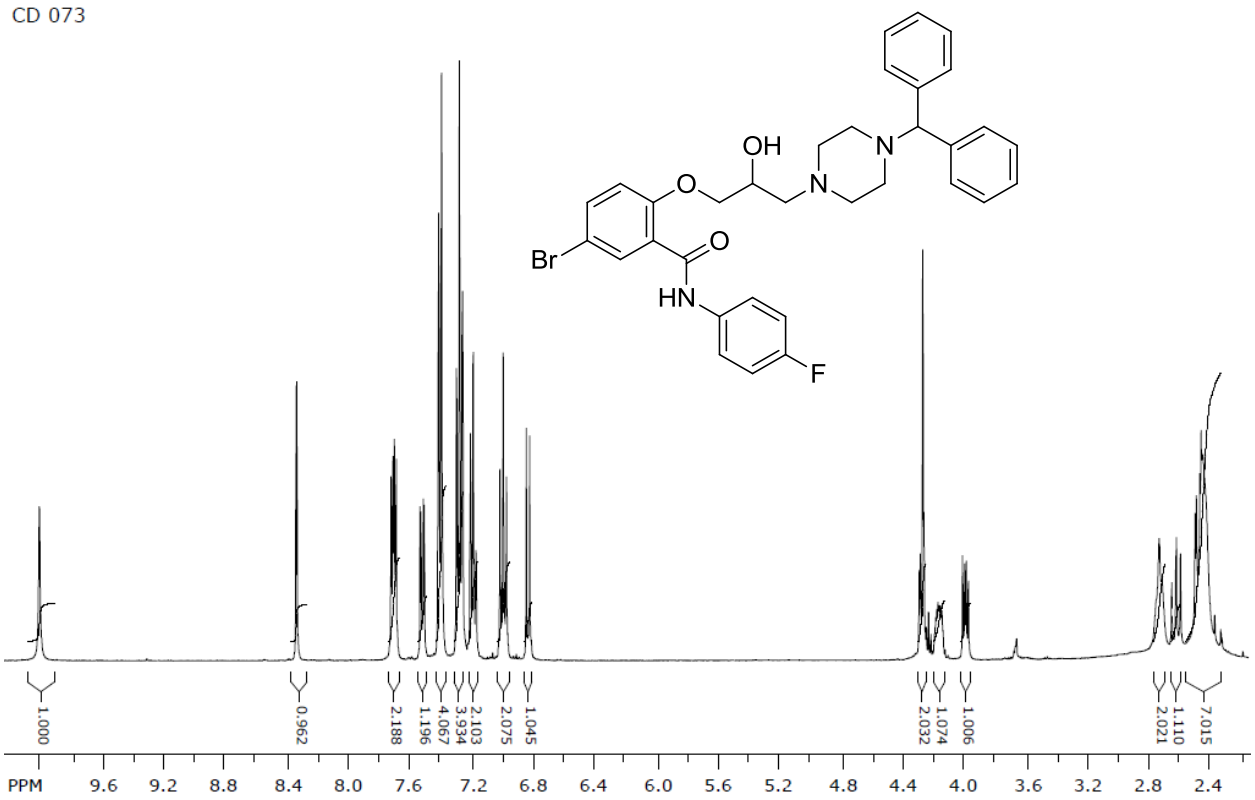


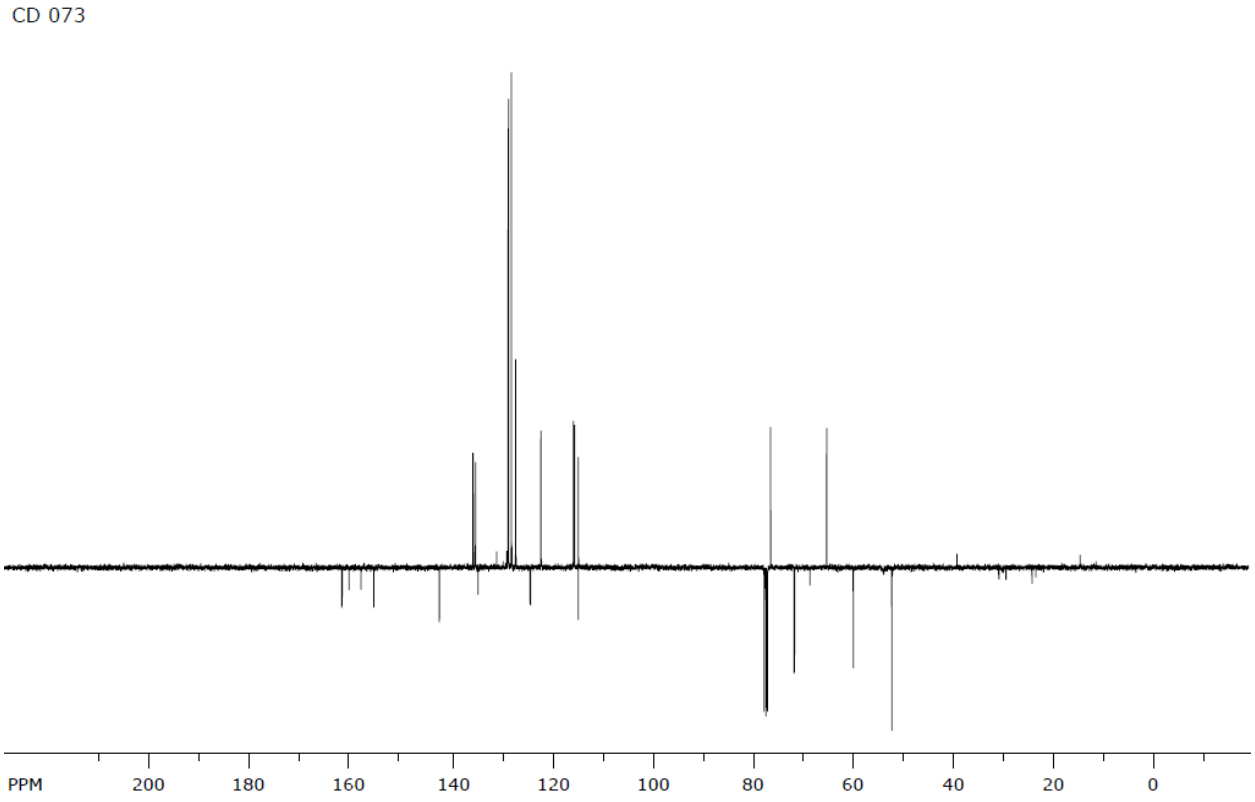
2-(3-(4-benzylpiperidin-1-yl)-2-hydroxypropoxy)-5-bromo-*N*-(4-fluorophenyl)benzamide (170)



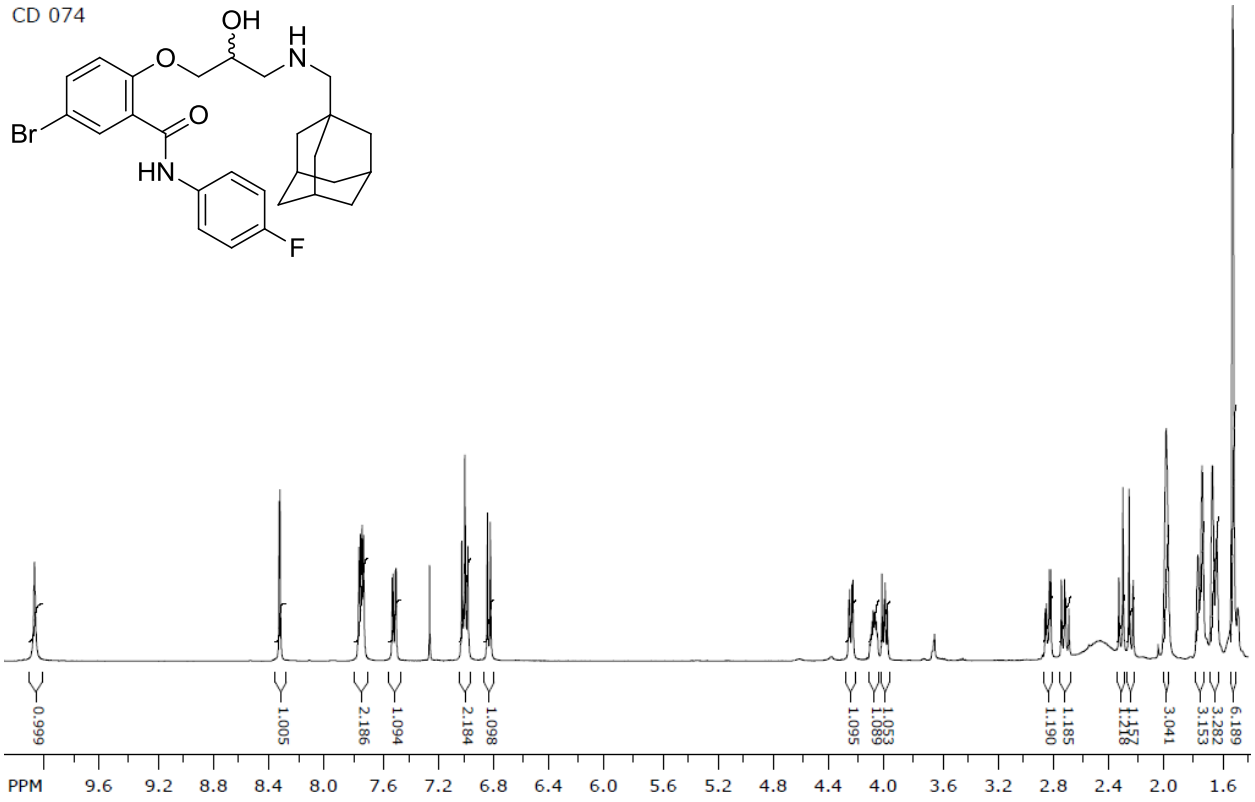


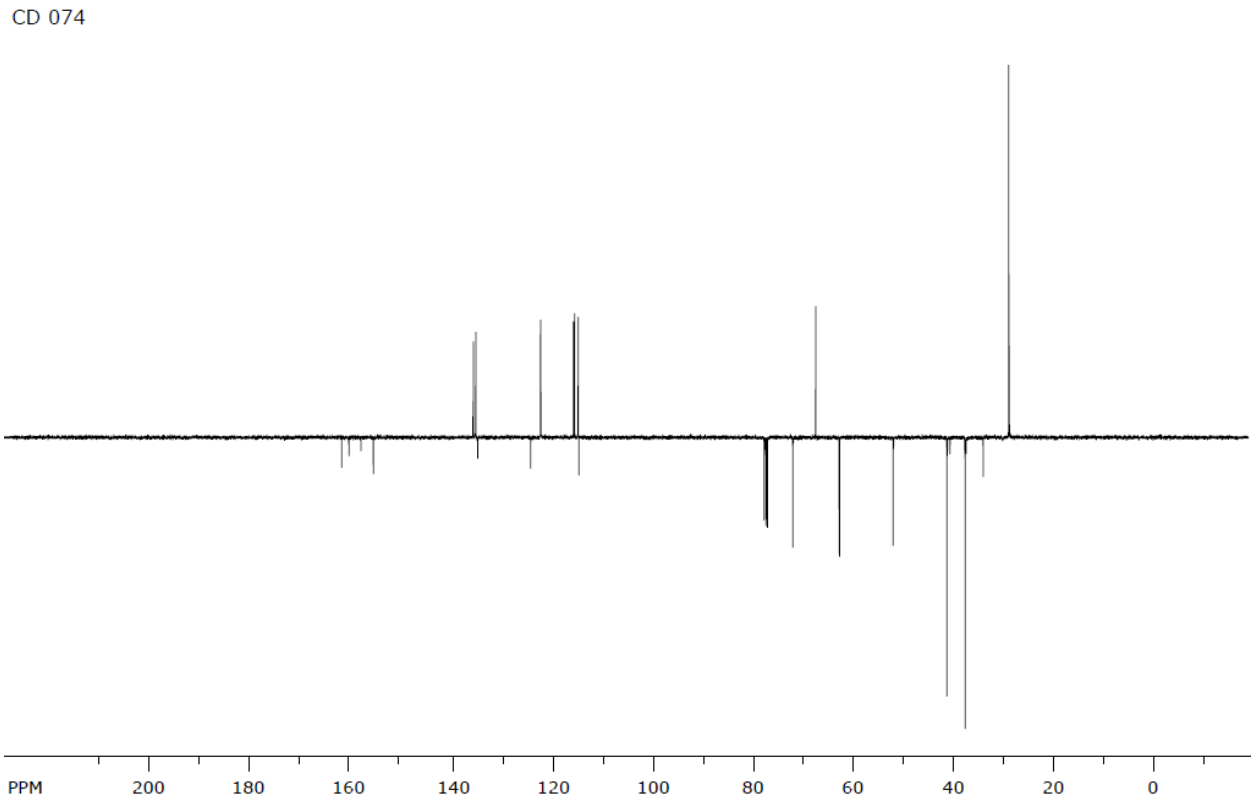
2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-5-bromo-*N*-(4-fluorophenyl)benzamide (171)



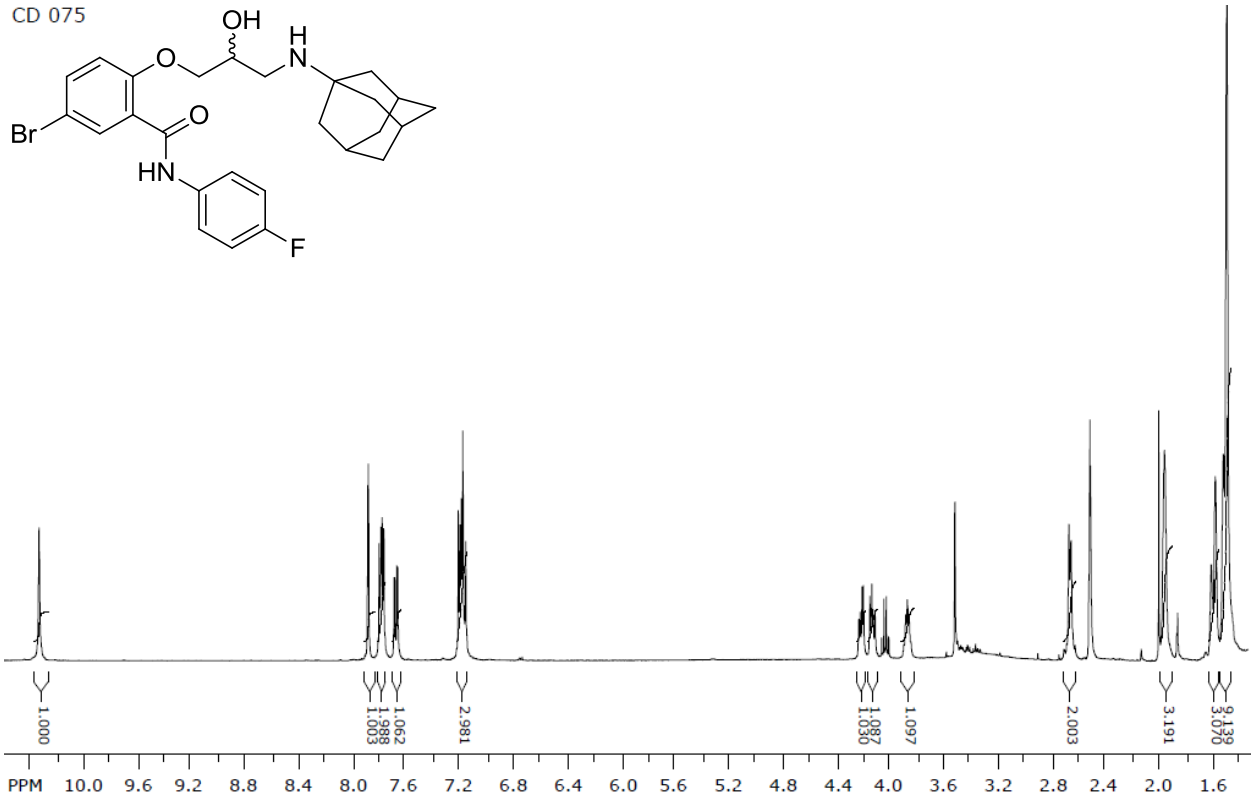


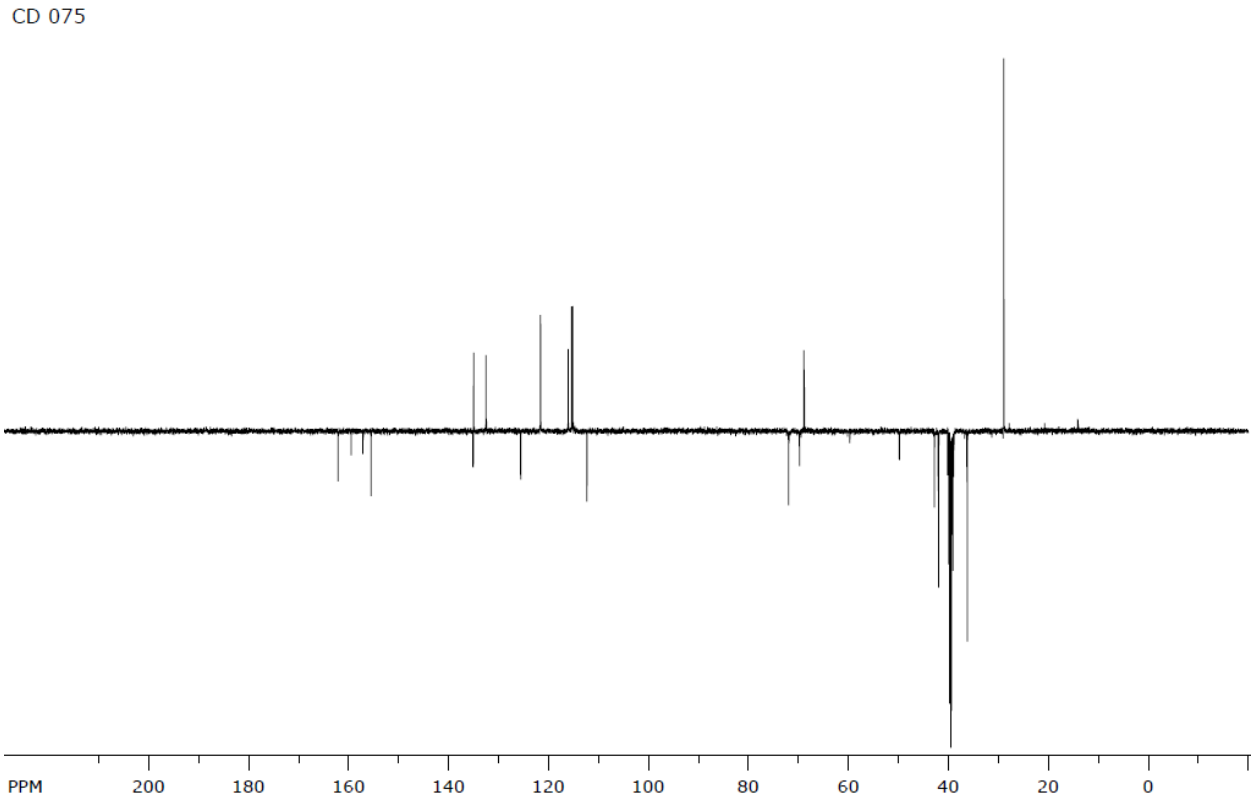
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-bromo-*N*-(4-fluorophenyl)benzamide (172)



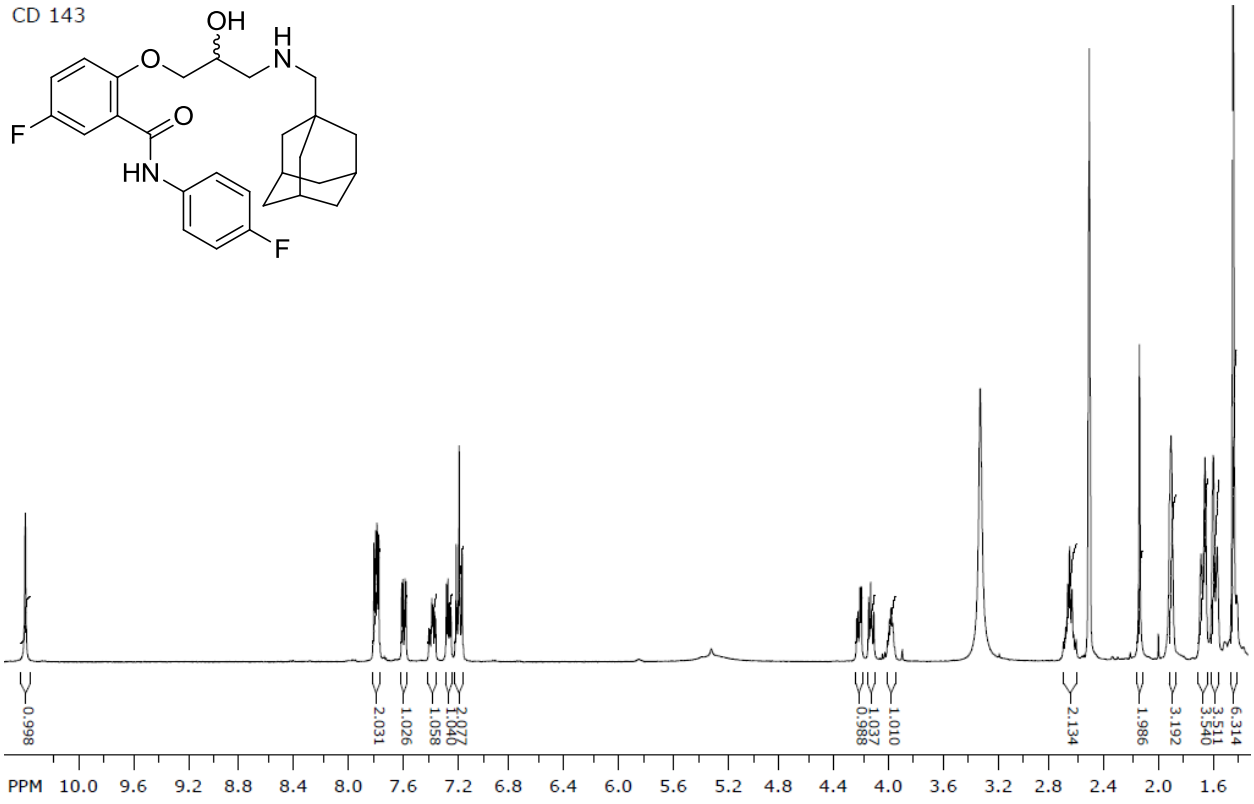


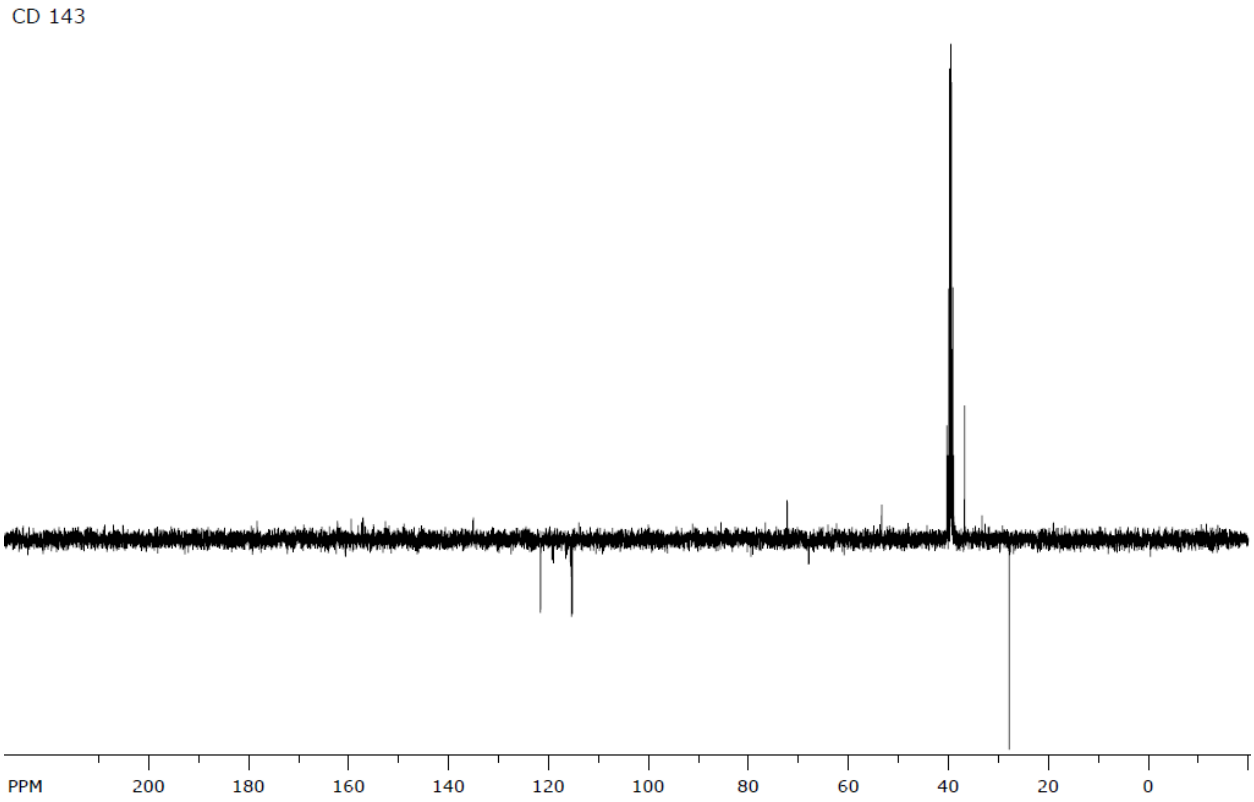
2-(3-(adamantan-1-ylamino)-2-hydroxypropoxy)-5-bromo-*N*-(4-fluorophenyl)benzamide (173)



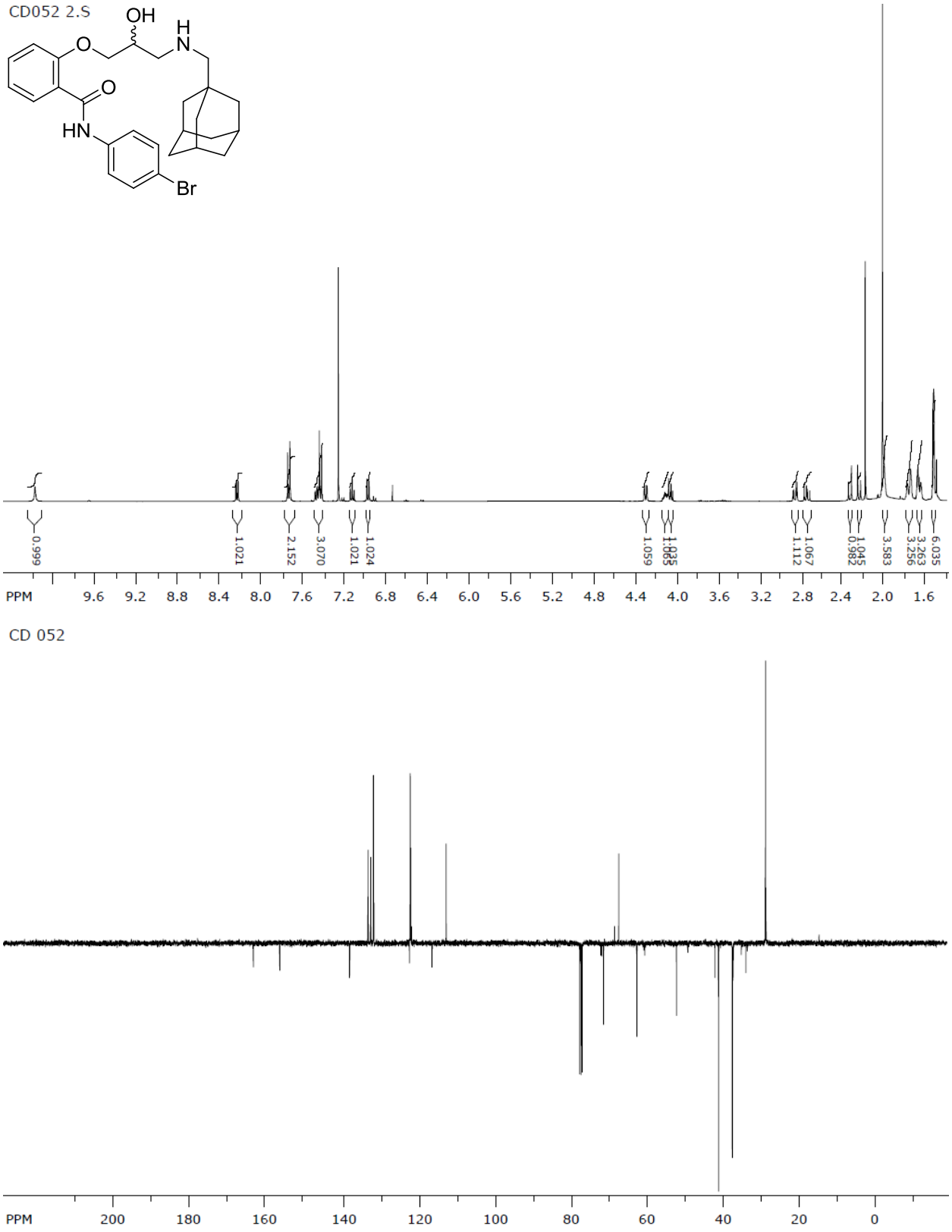


2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-fluoro-*N*-(4-fluorophenyl)benzamide (174**)**

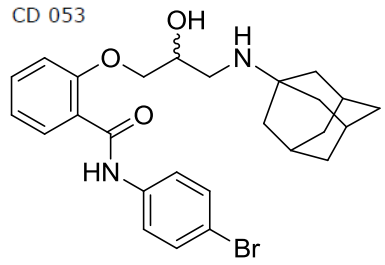


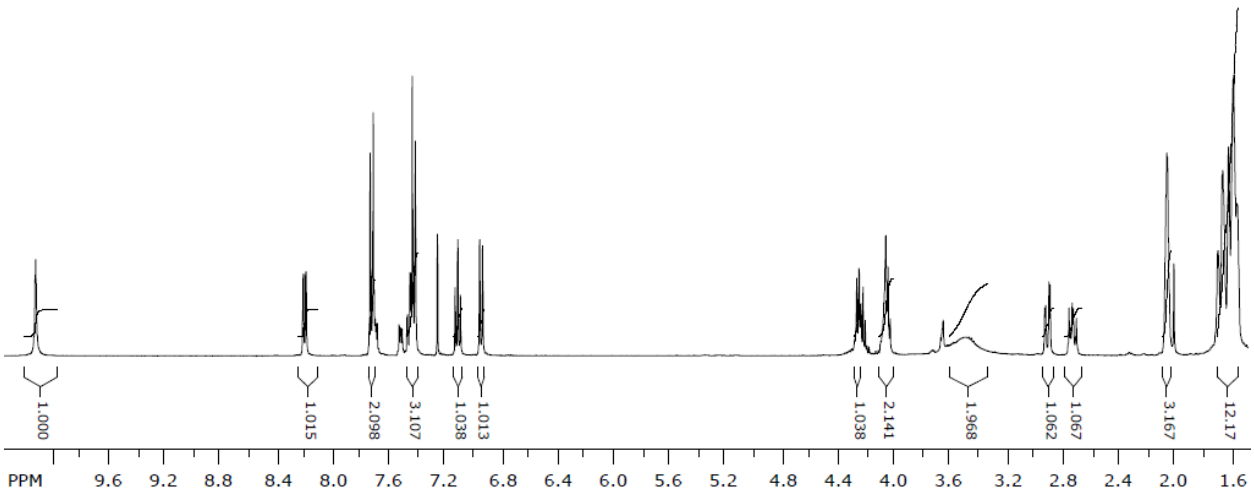


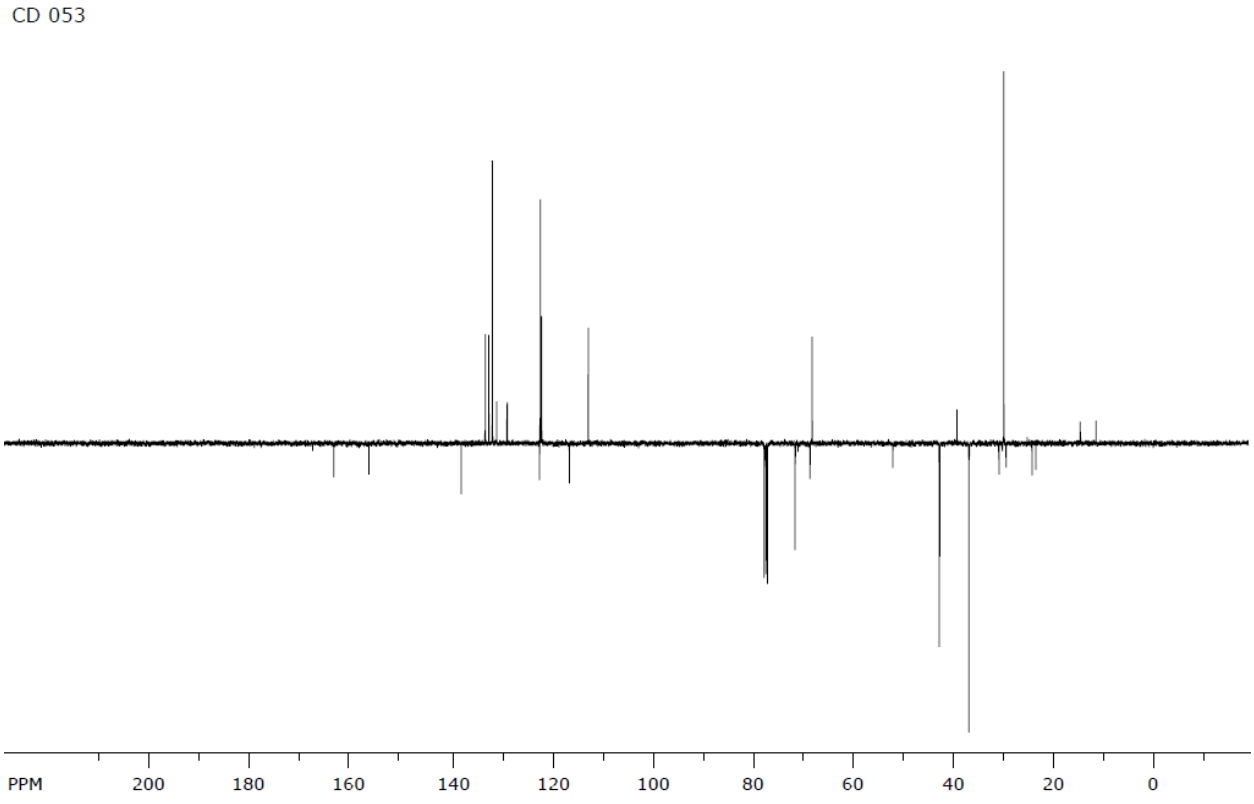
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(4-bromophenyl)benzamide (175)



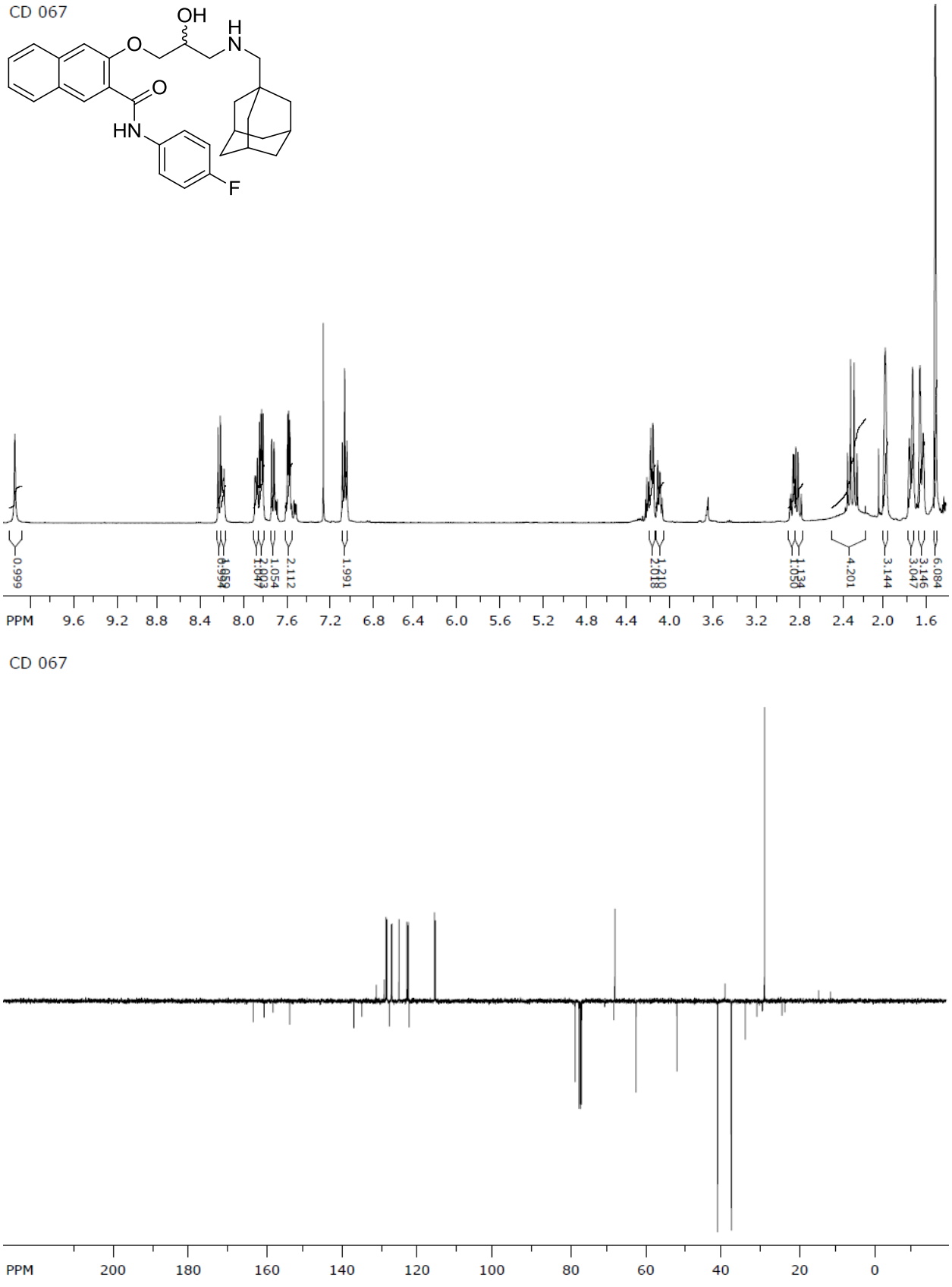
2-(3-(adamantan-1-ylamino)-2-hydroxypropoxy)-*N*-(4-bromophenyl)benzamide (176)



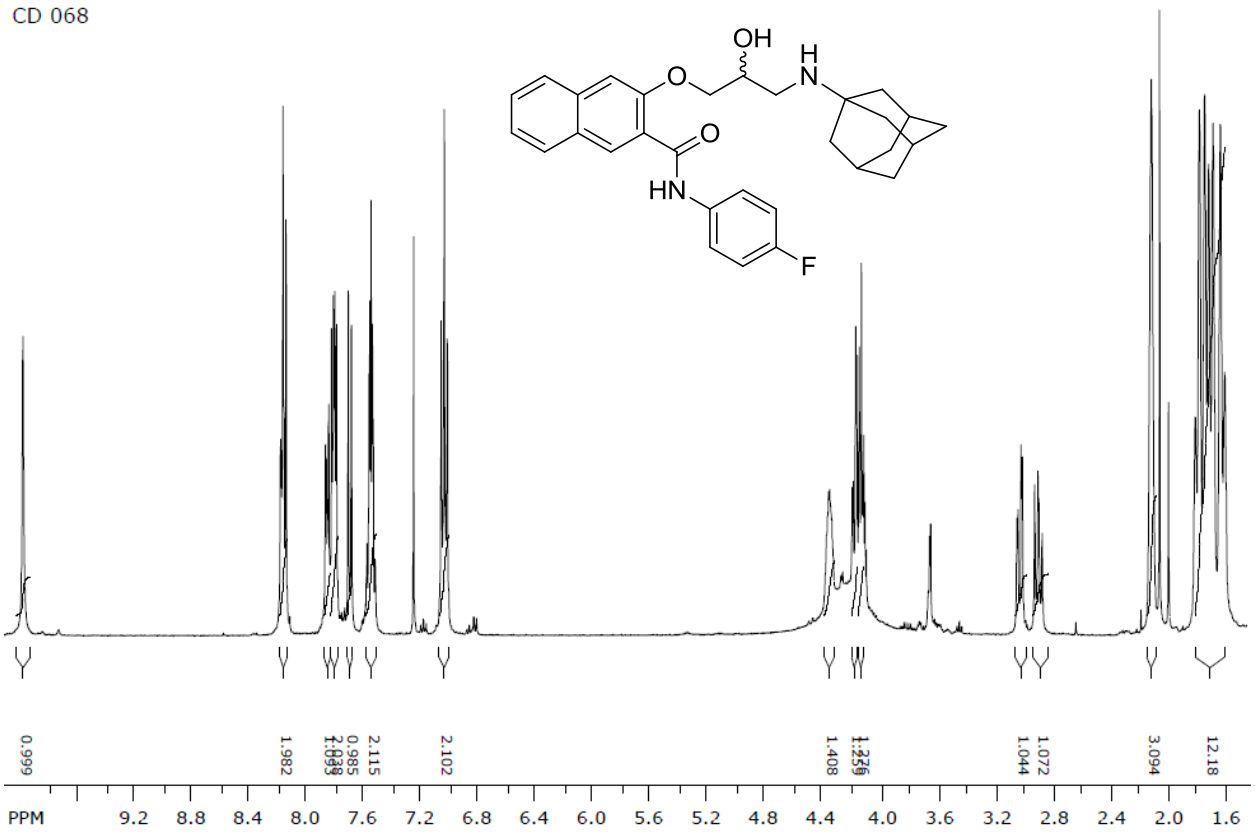


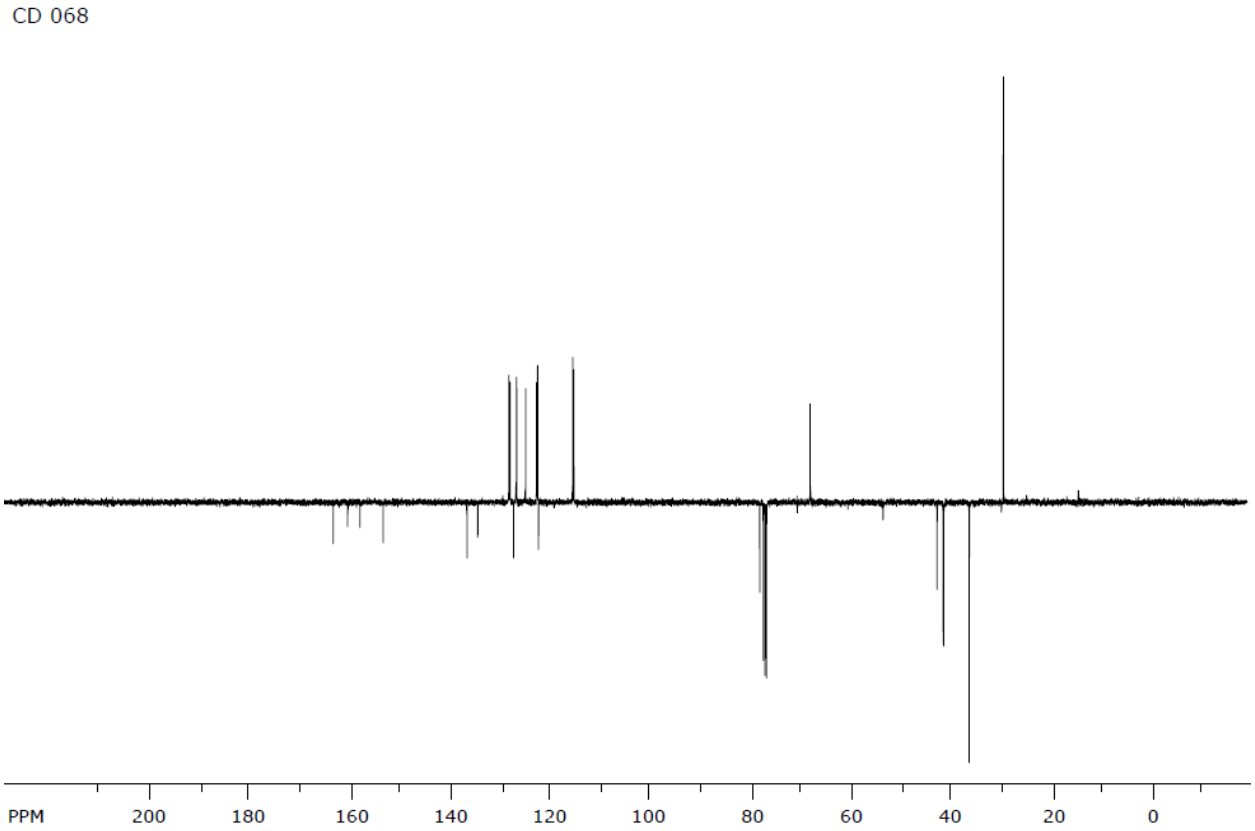


3-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(4-fluorophenyl)-2-naphthamide (177)

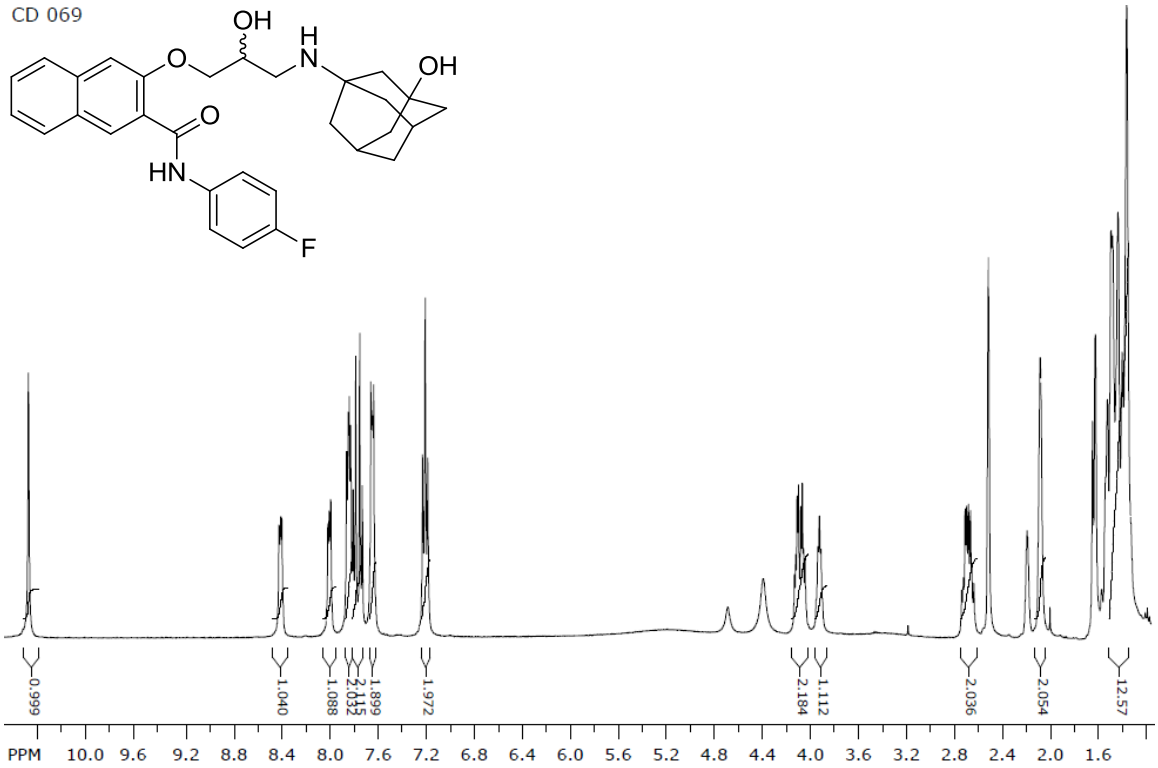


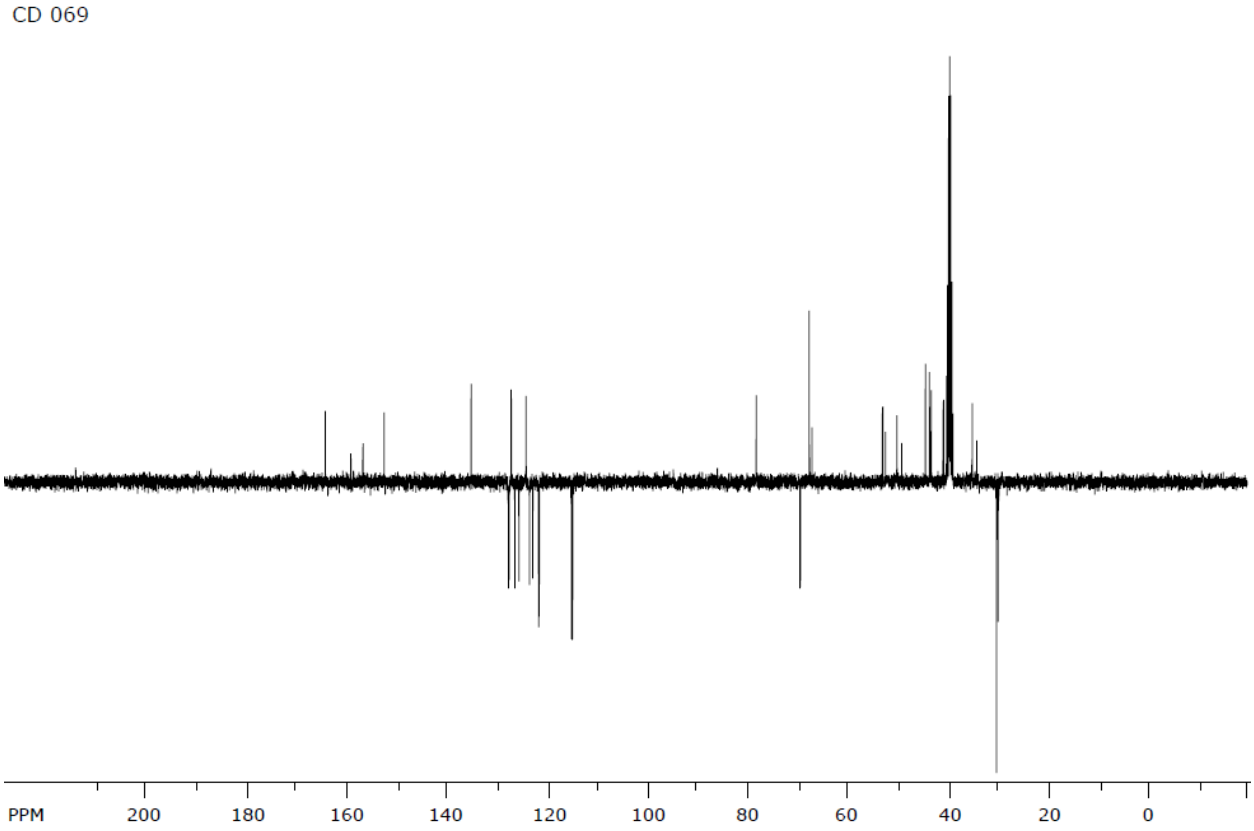
3-(3-(adamantan-1-ylamino)-2-hydroxypropoxy)-*N*-(4-fluorophenyl)-2-naphthamide (178**)**



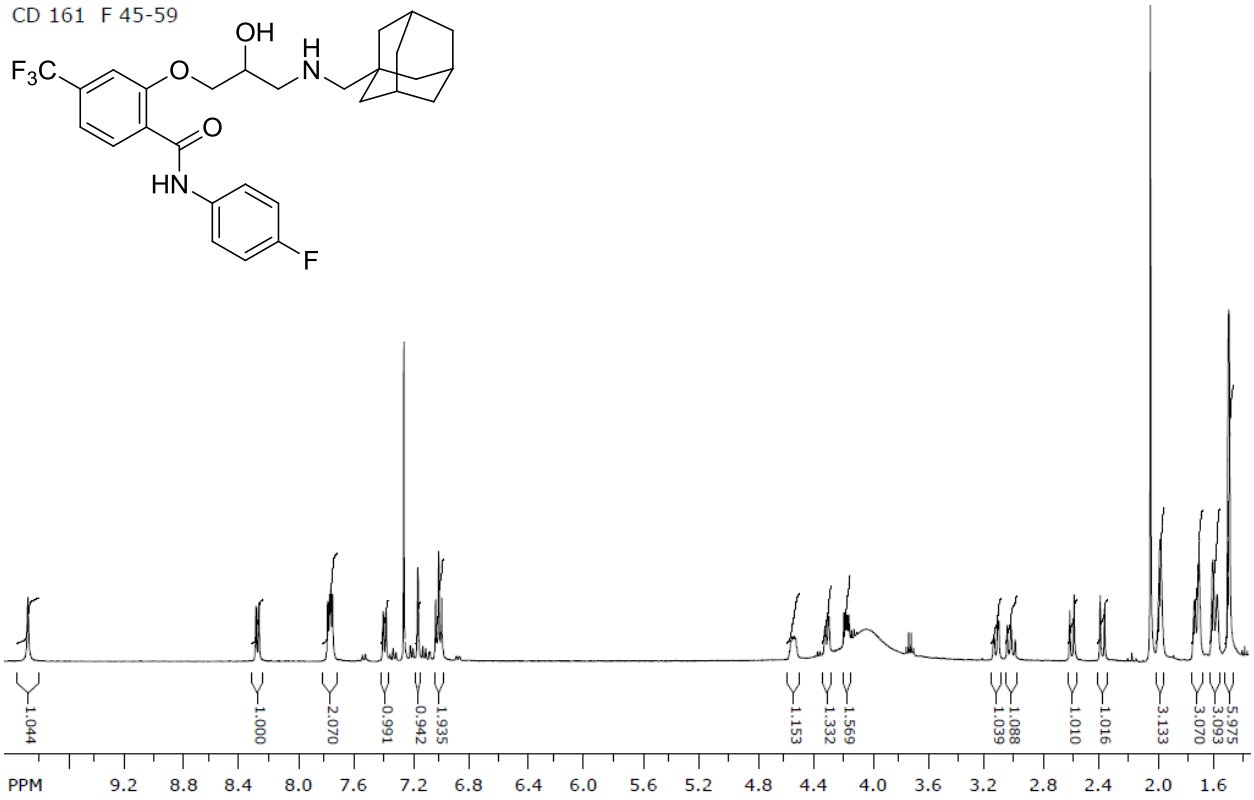


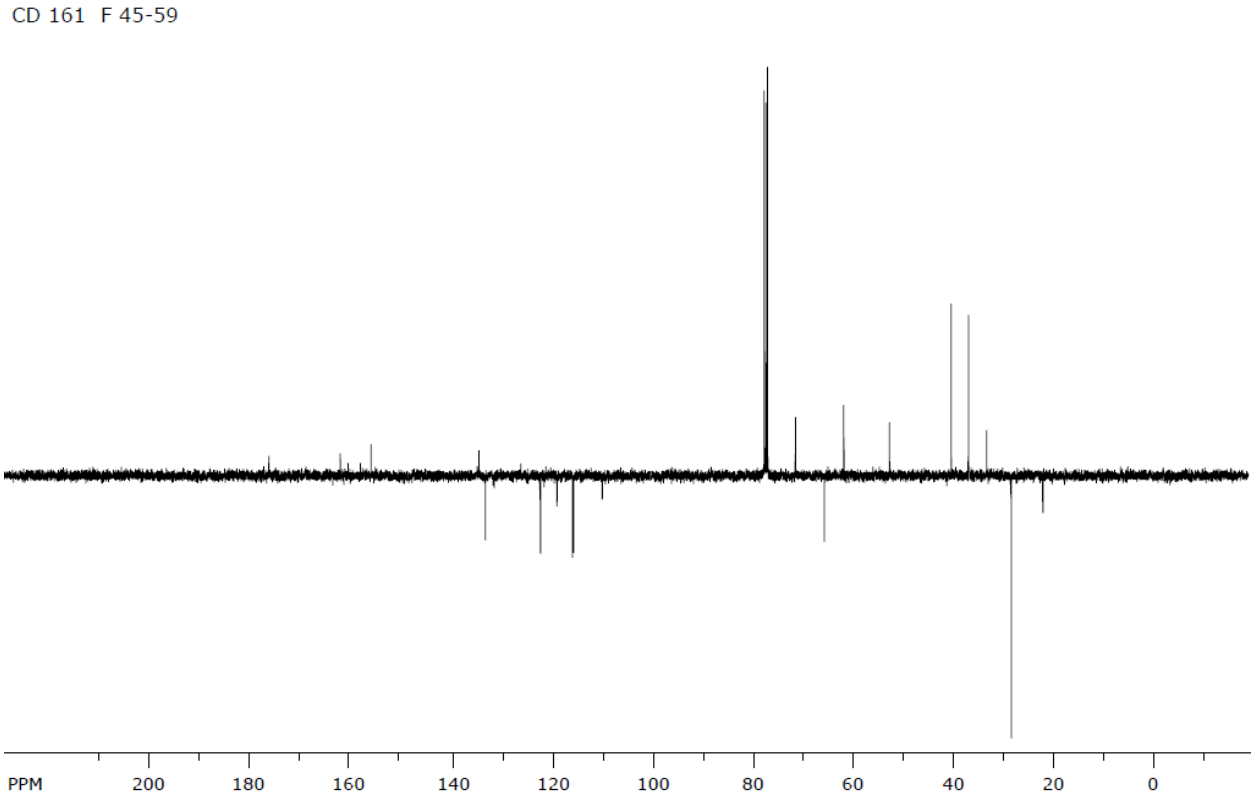
_N_-(4-fluorophenyl)-3-(2-hydroxy-3-((3-hydroxyadamantan-1-yl)amino)propoxy)-2-naphthamide (179)



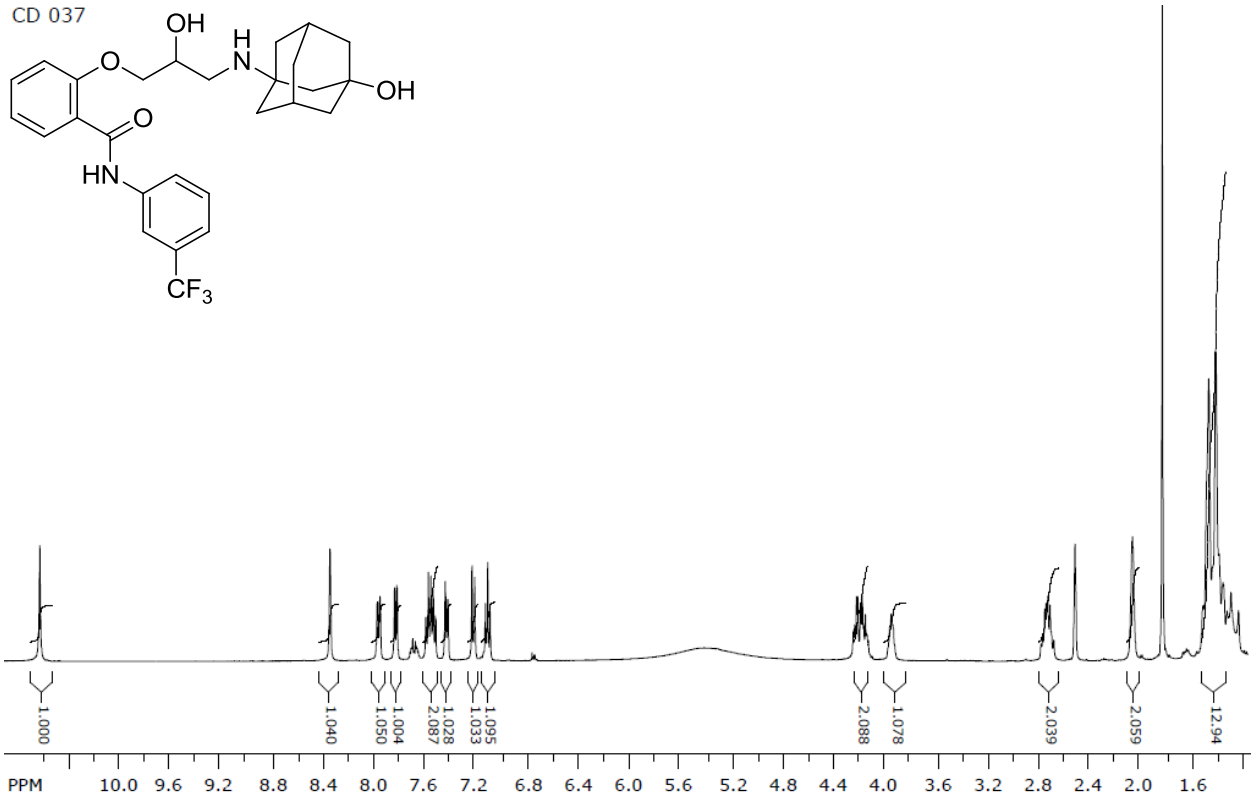


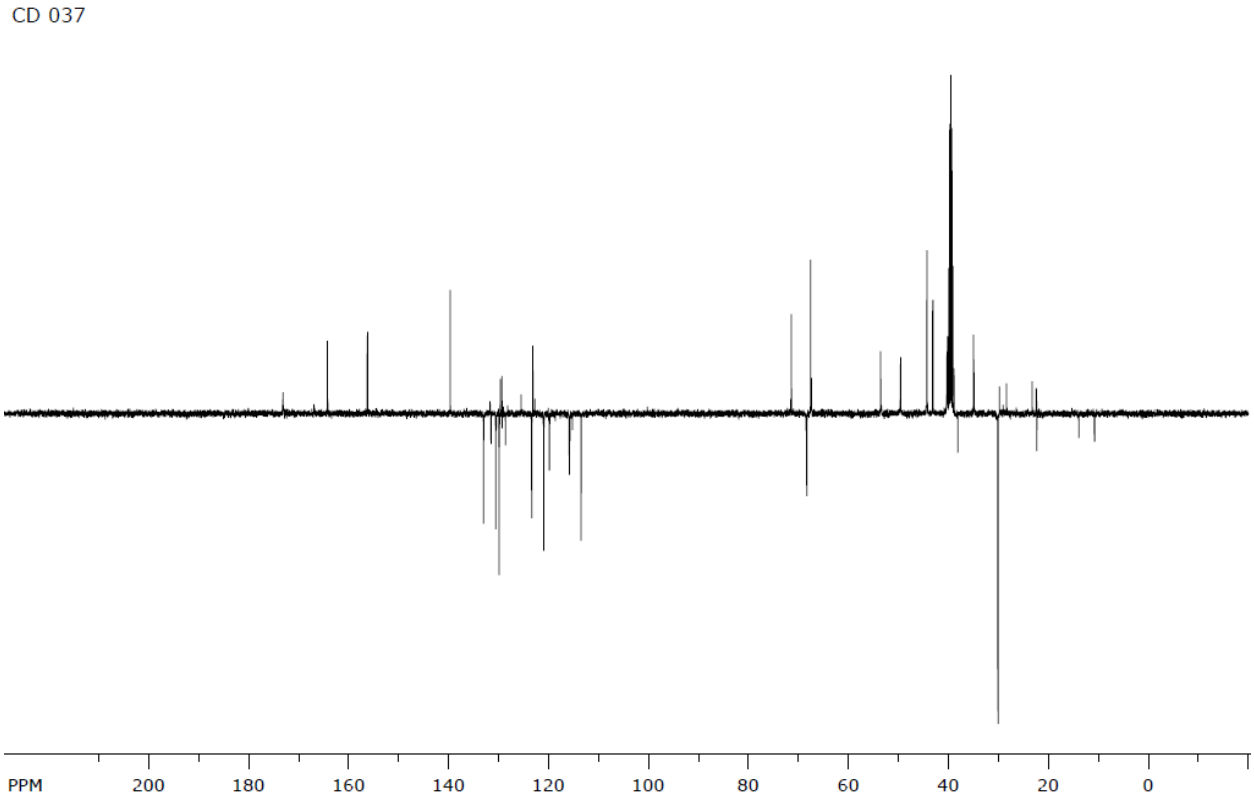
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(4-fluorophenyl)-4-(trifluoromethyl)benzamide (180**)**



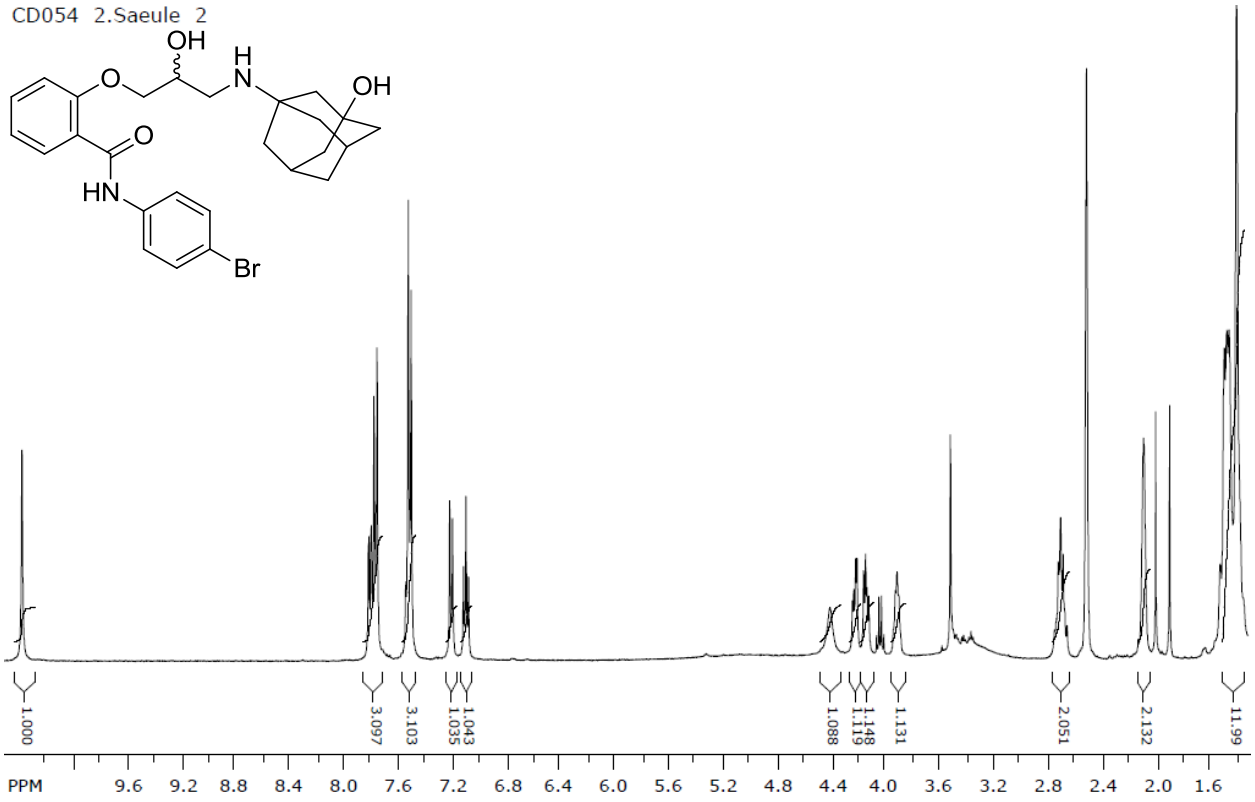


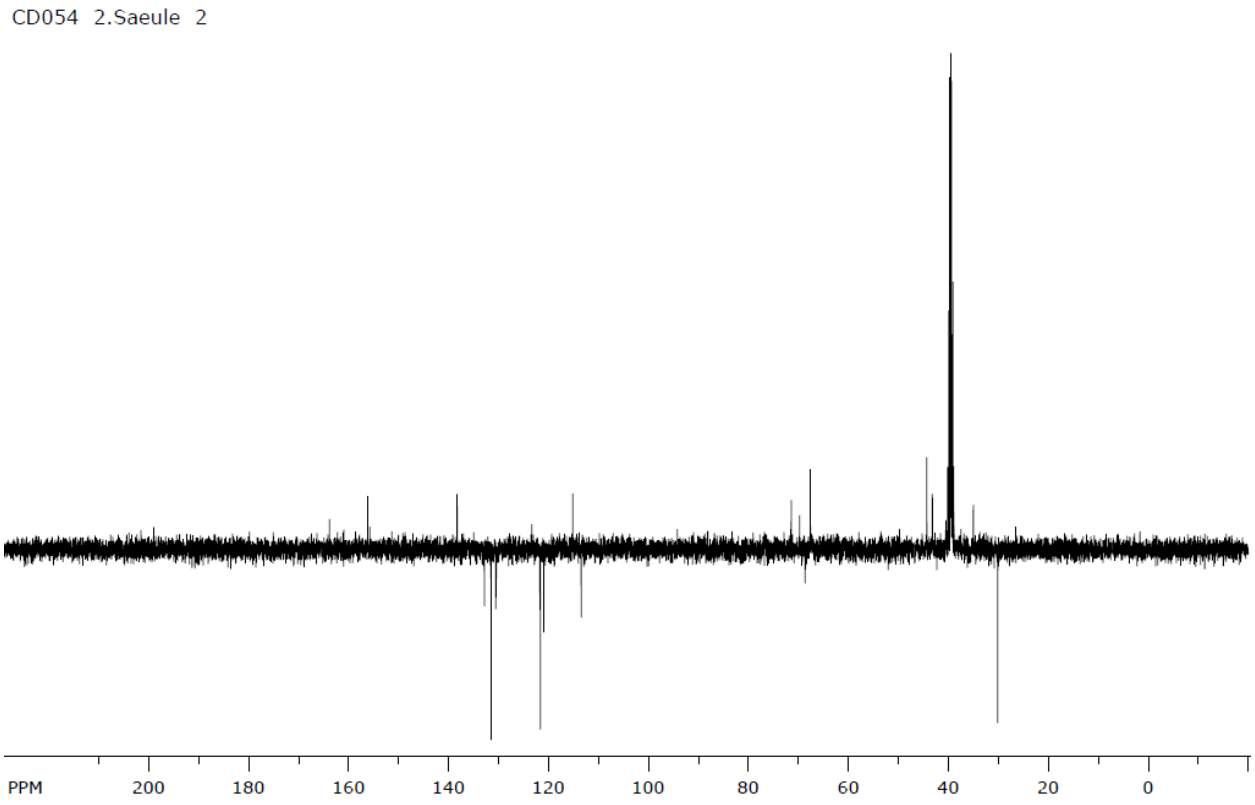
2-(2-hydroxy-3-((-3-hydroxyadamantan-1-yl)amino)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (181**)**



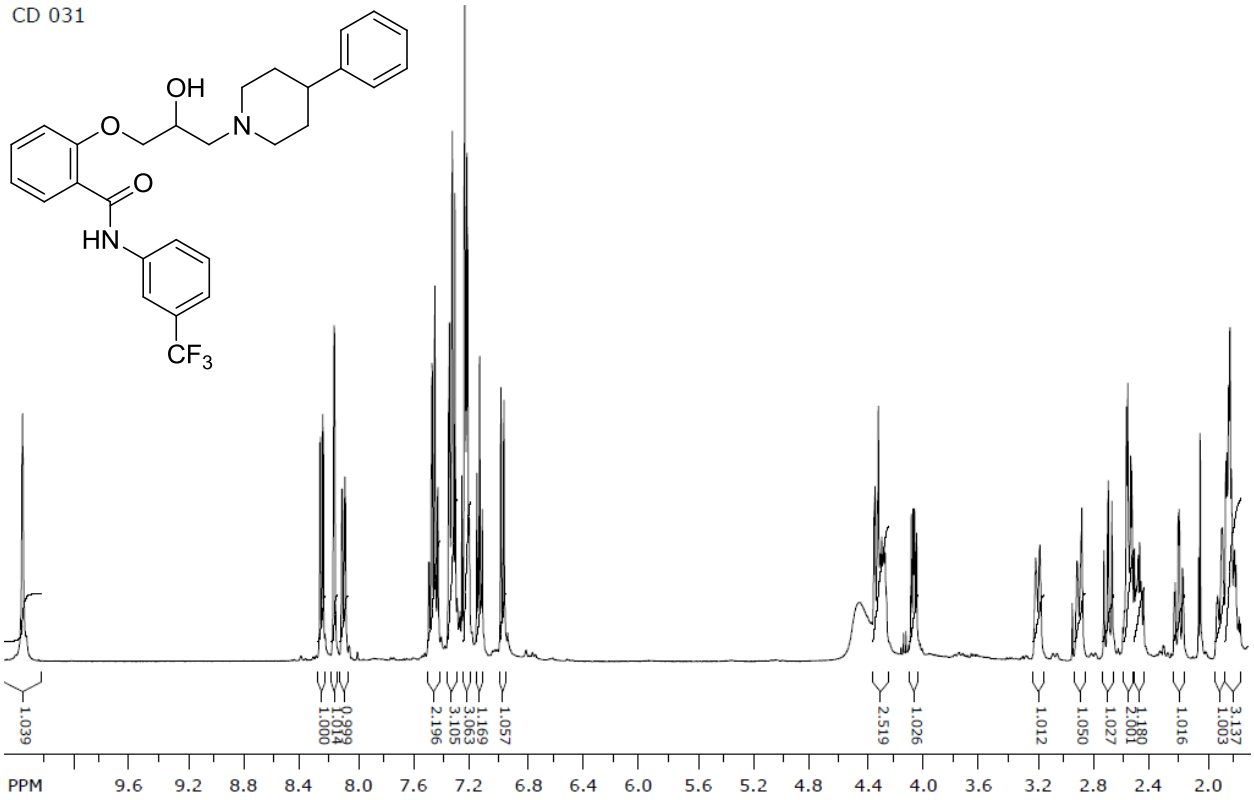


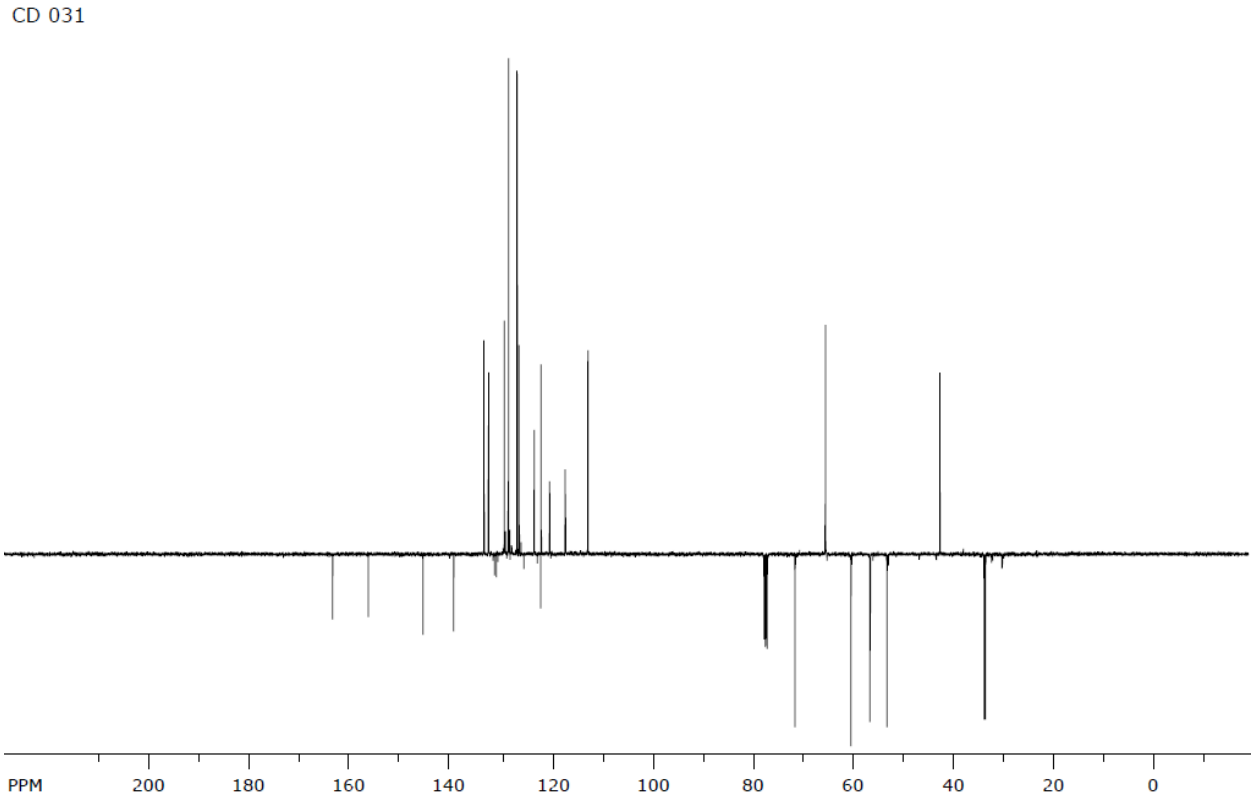
_N_-(4-bromophenyl)-2-(2-hydroxy-3-((3-hydroxyadamantan-1-yl)amino)propoxy)benzamide (182**)**



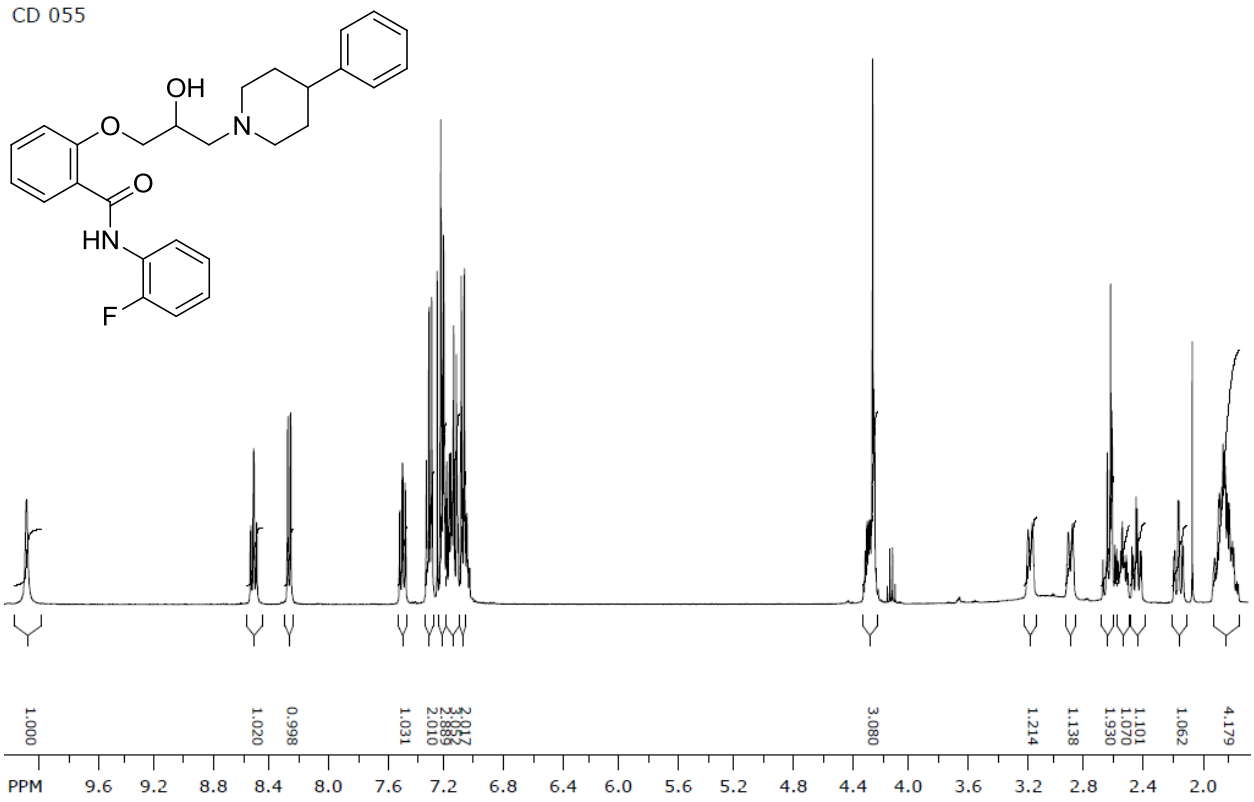


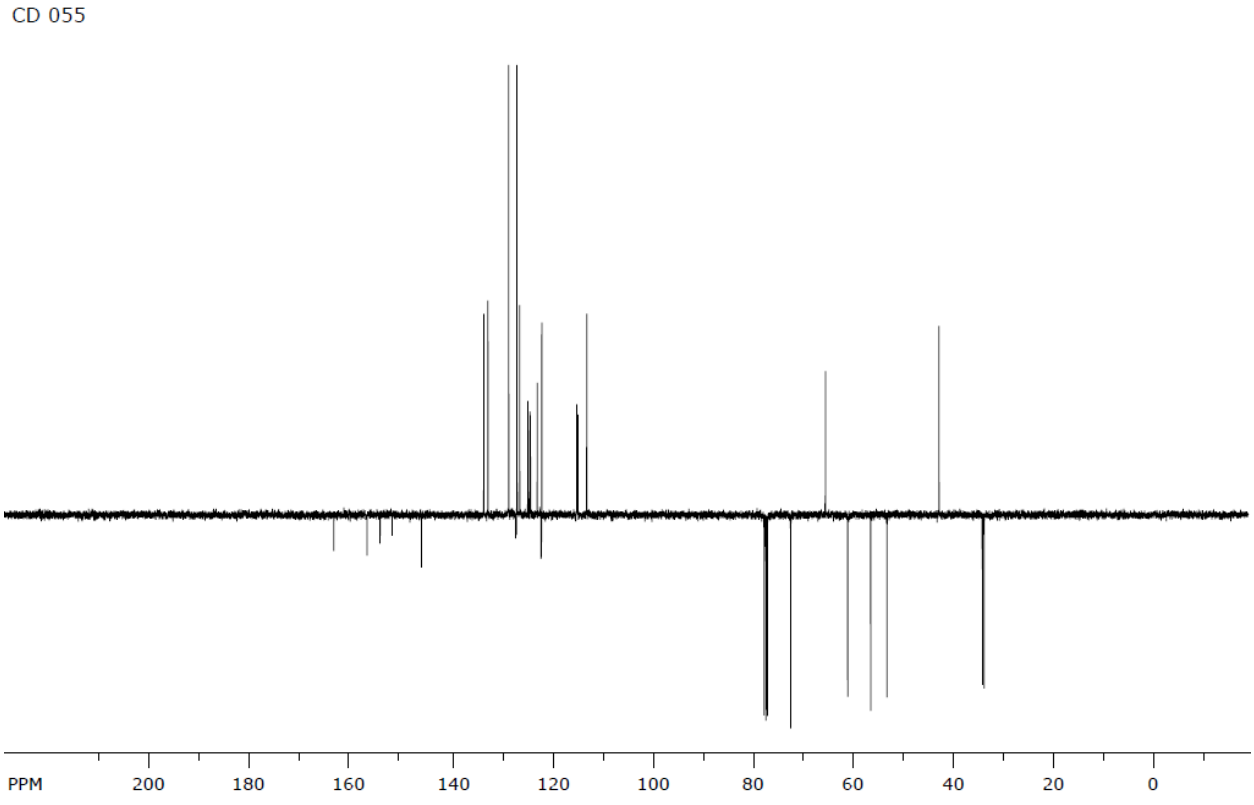
2-(2-hydroxy-3-(4-phenylpiperidin-1-yl)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (183)



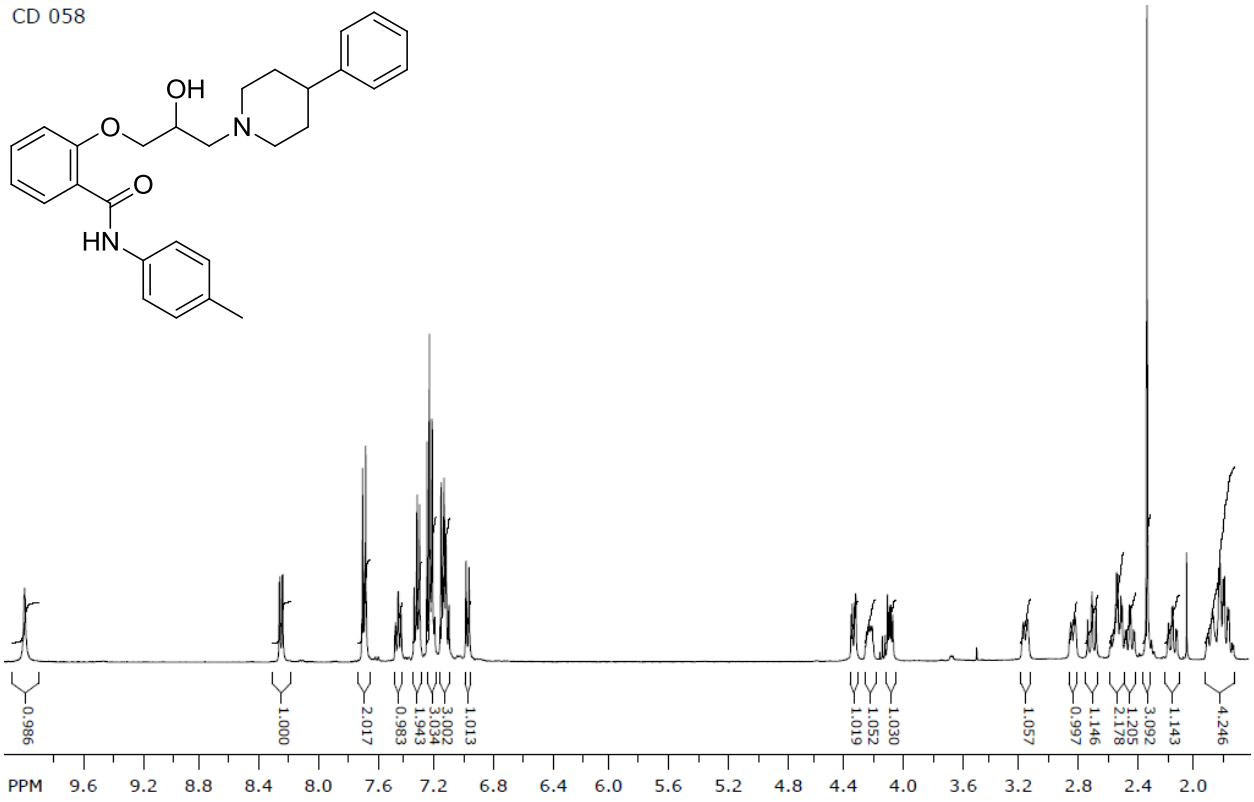


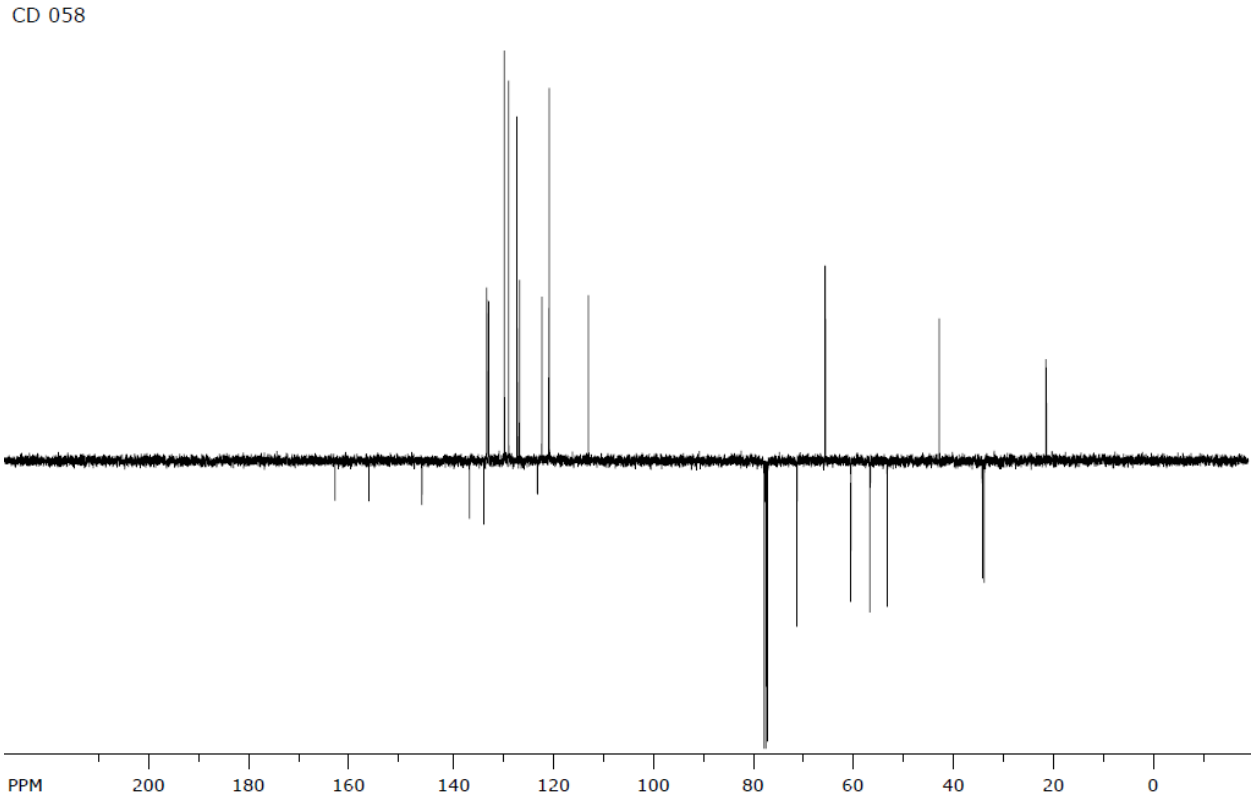
_N_-(2-fluorophenyl)-2-(2-hydroxy-3-(4-phenylpiperidin-1-yl)propoxy)benzamide (184)



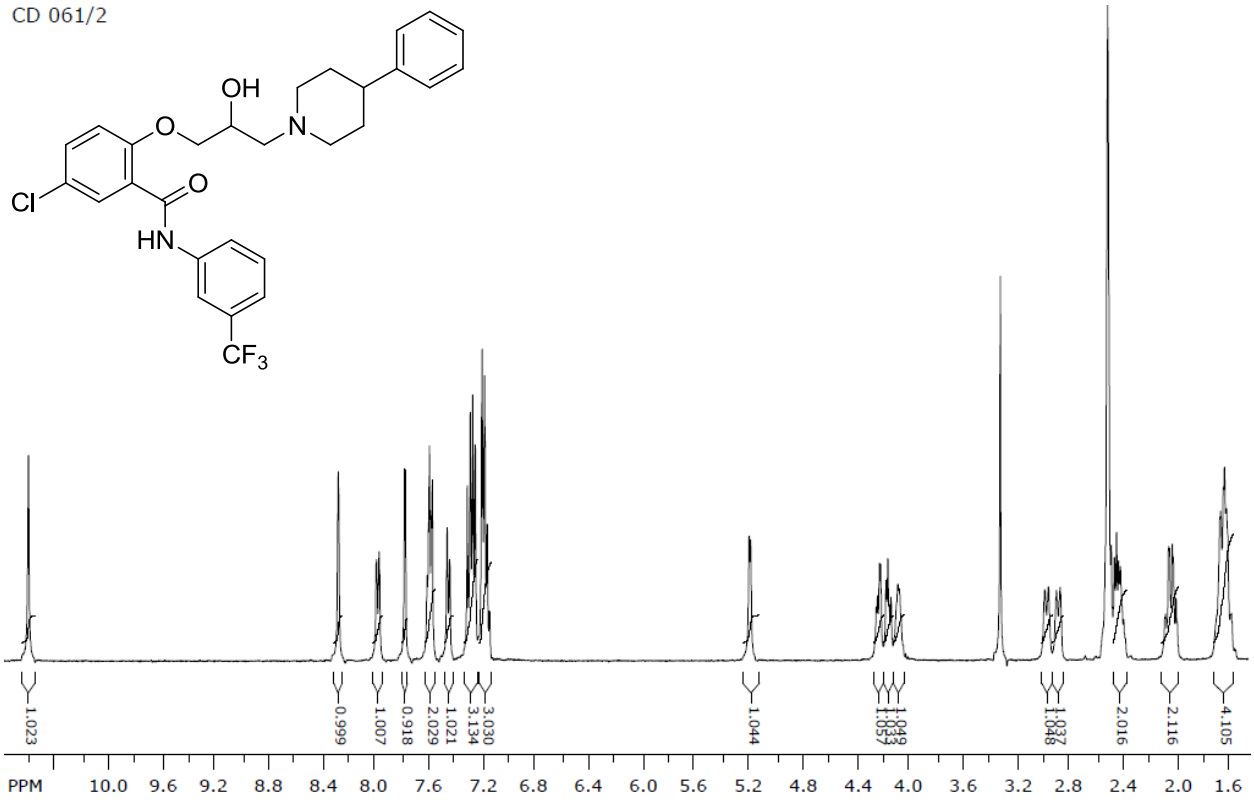


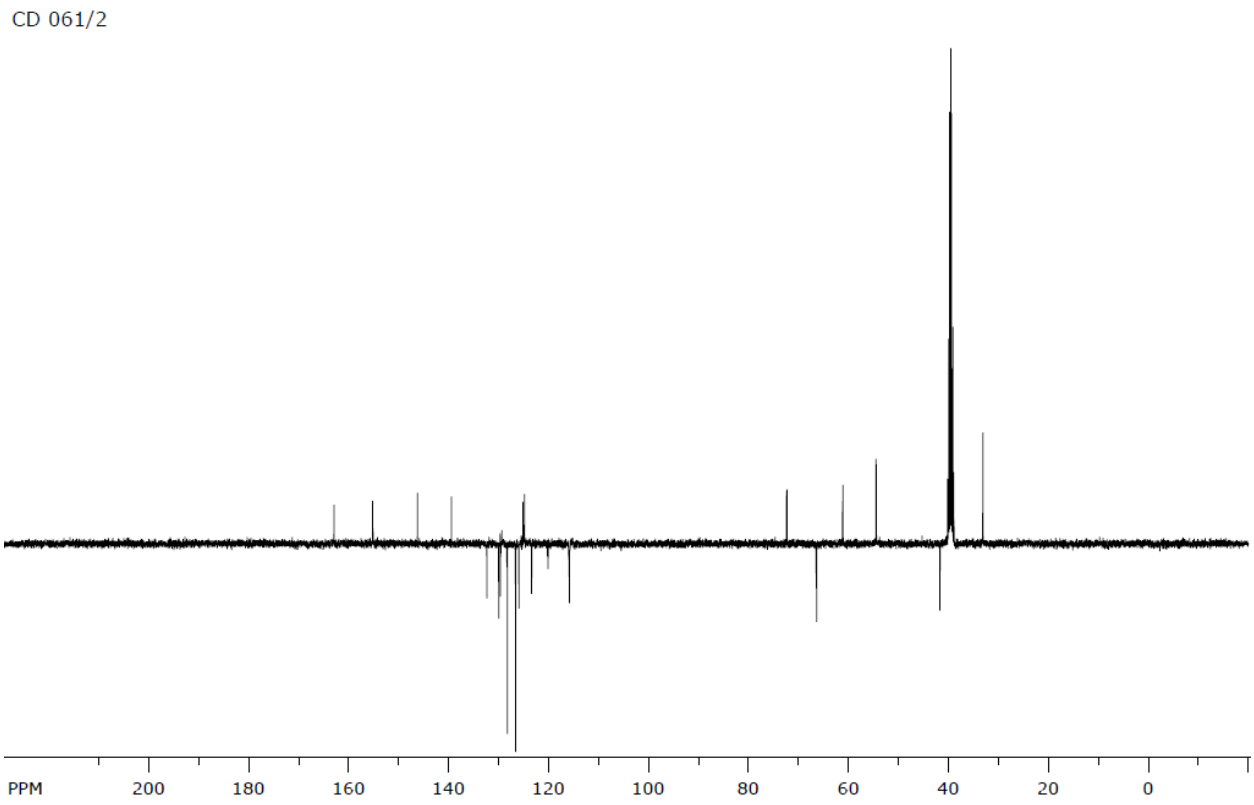
2-(2-hydroxy-3-(4-phenylpiperidin-1-yl)propoxy)-*N*-(p-tolyl)benzamide (185)



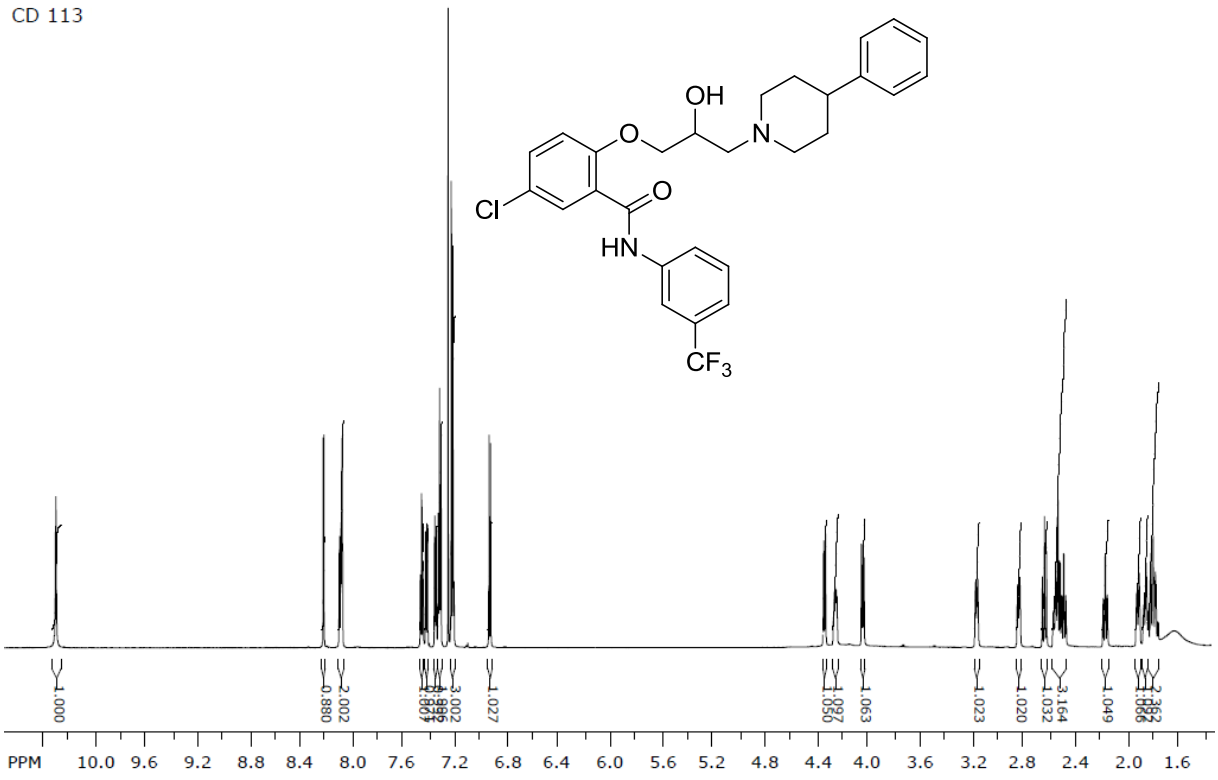


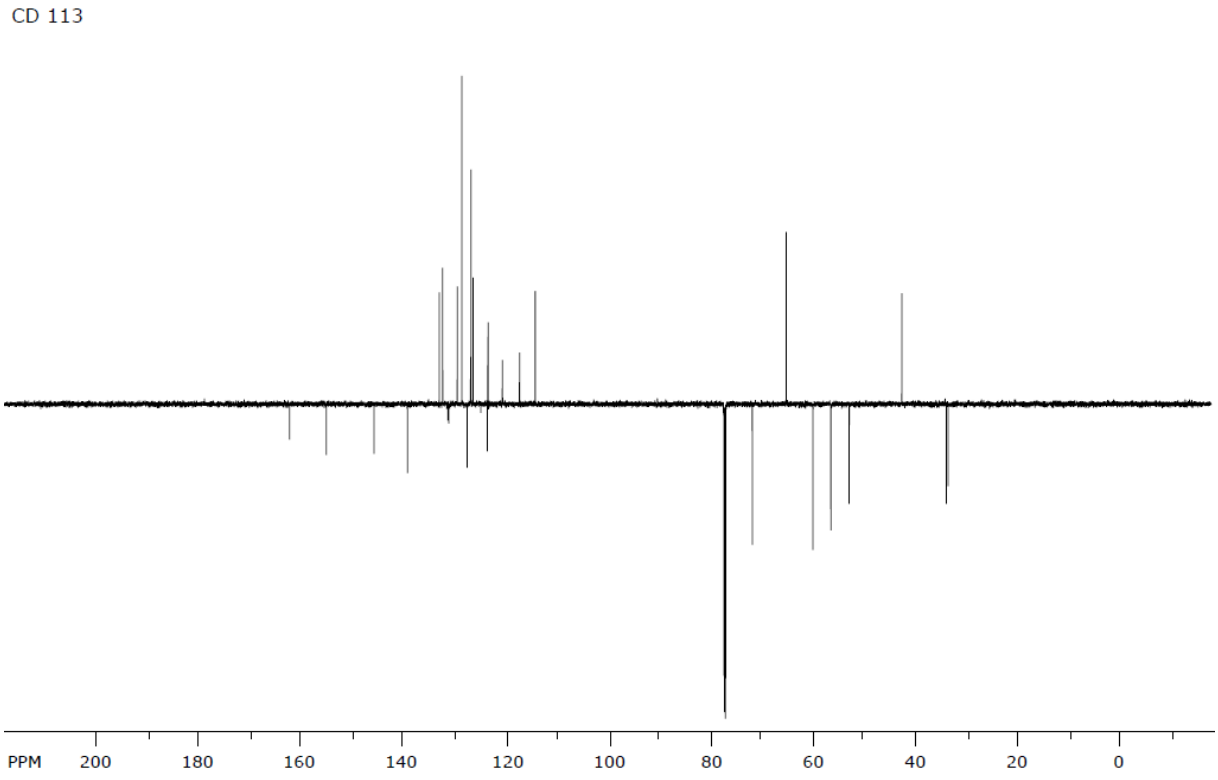
5-chloro-2-(2-hydroxy-3-(4-phenylpiperidin-1-yl)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (186**)**



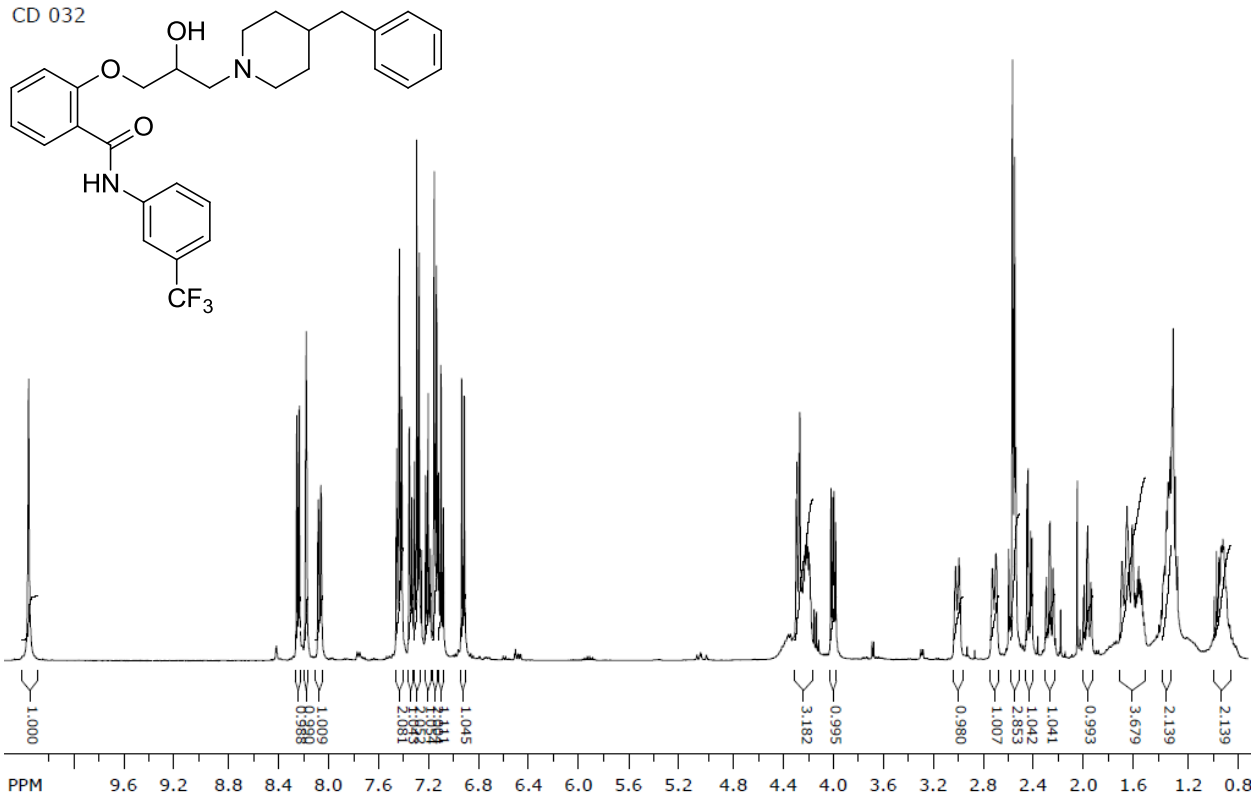


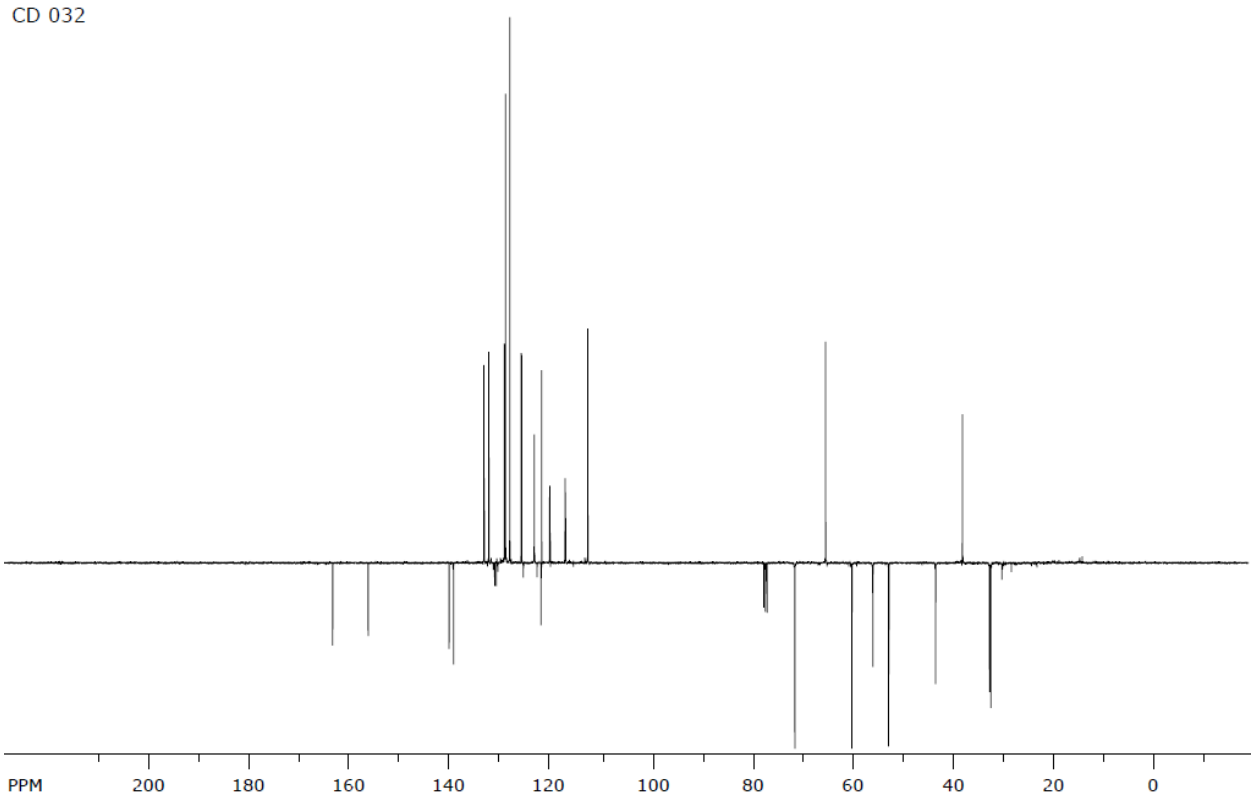
5-chloro-2-(2-hydroxy-3-(4-phenylpiperidin-1-yl)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (186)



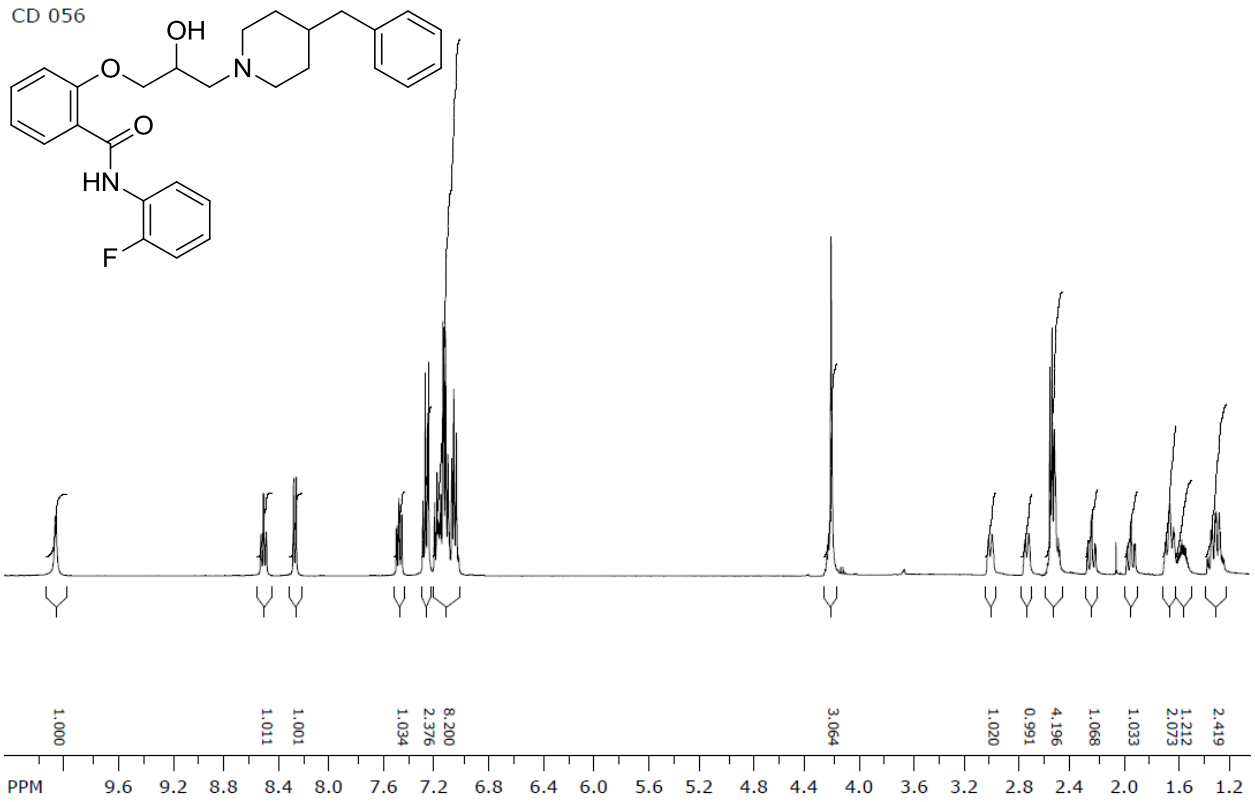


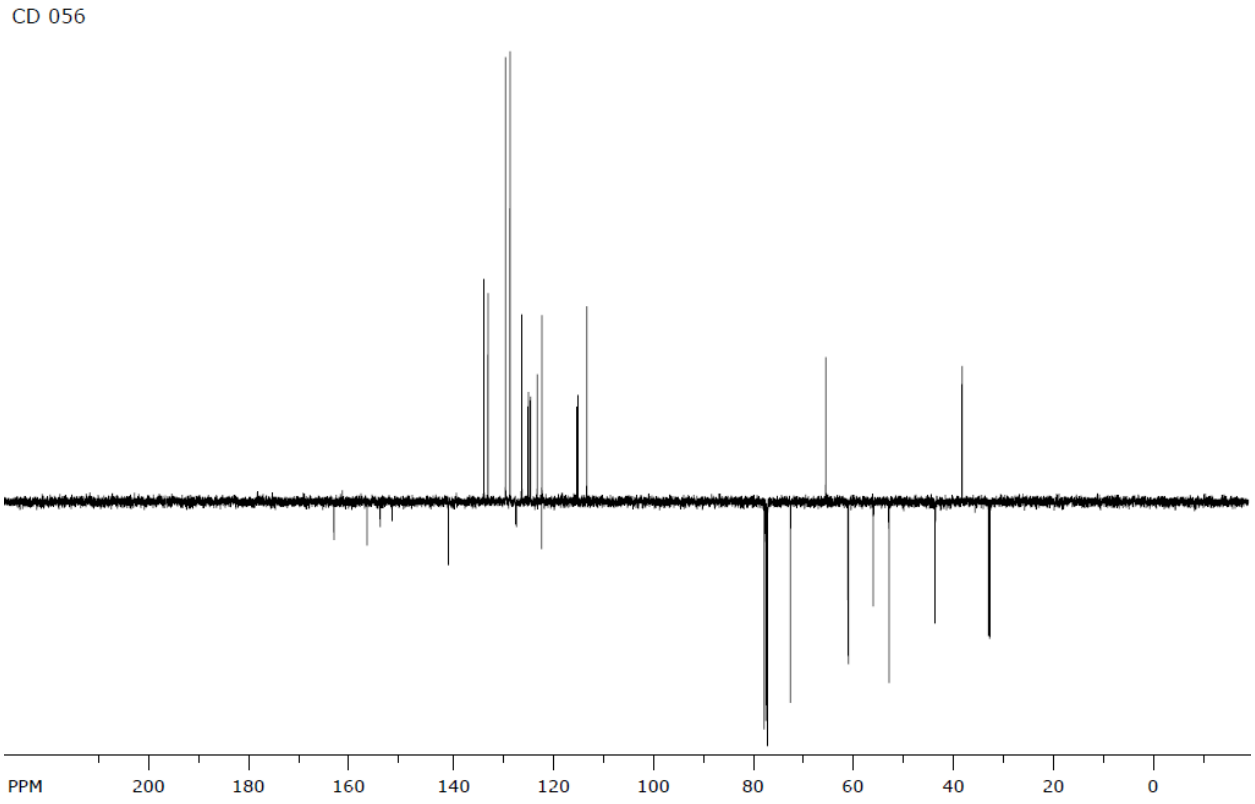
2-(3-(4-benzylpiperidin-1-yl)-2-hydroxypropoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (187**)**



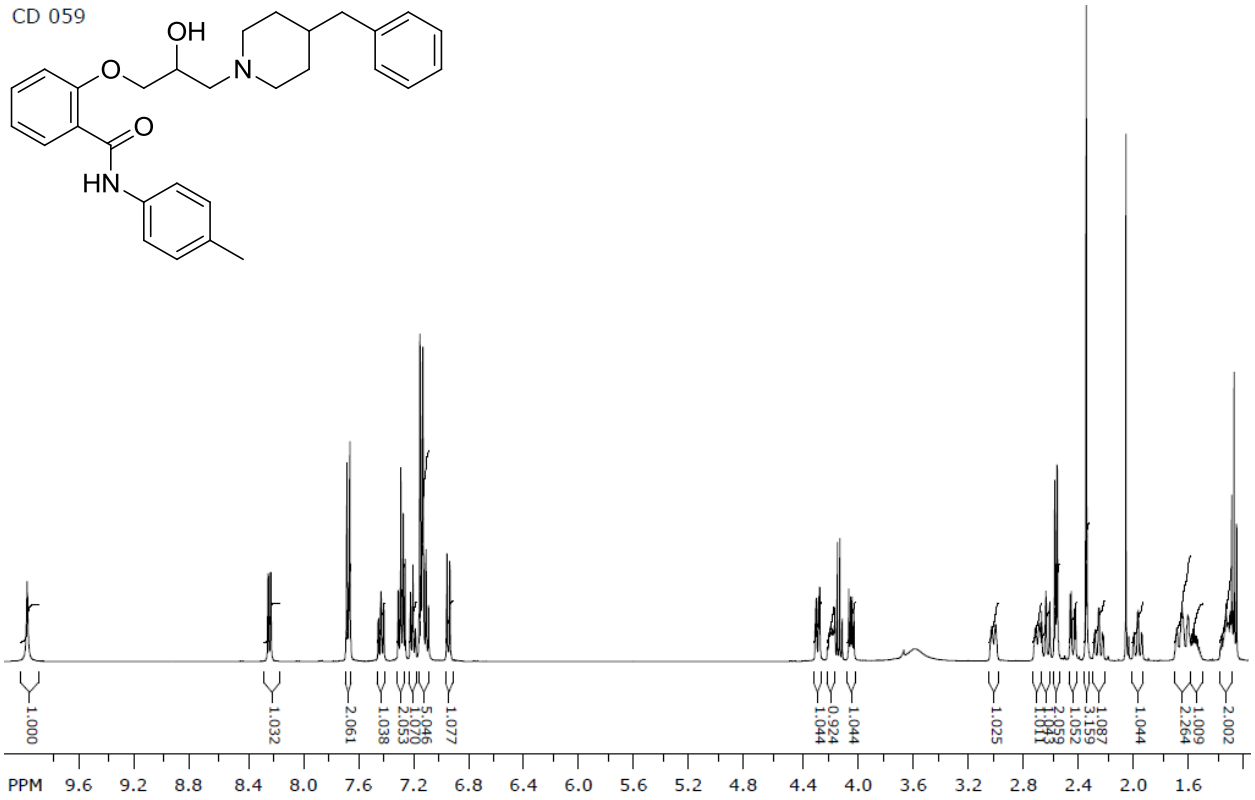


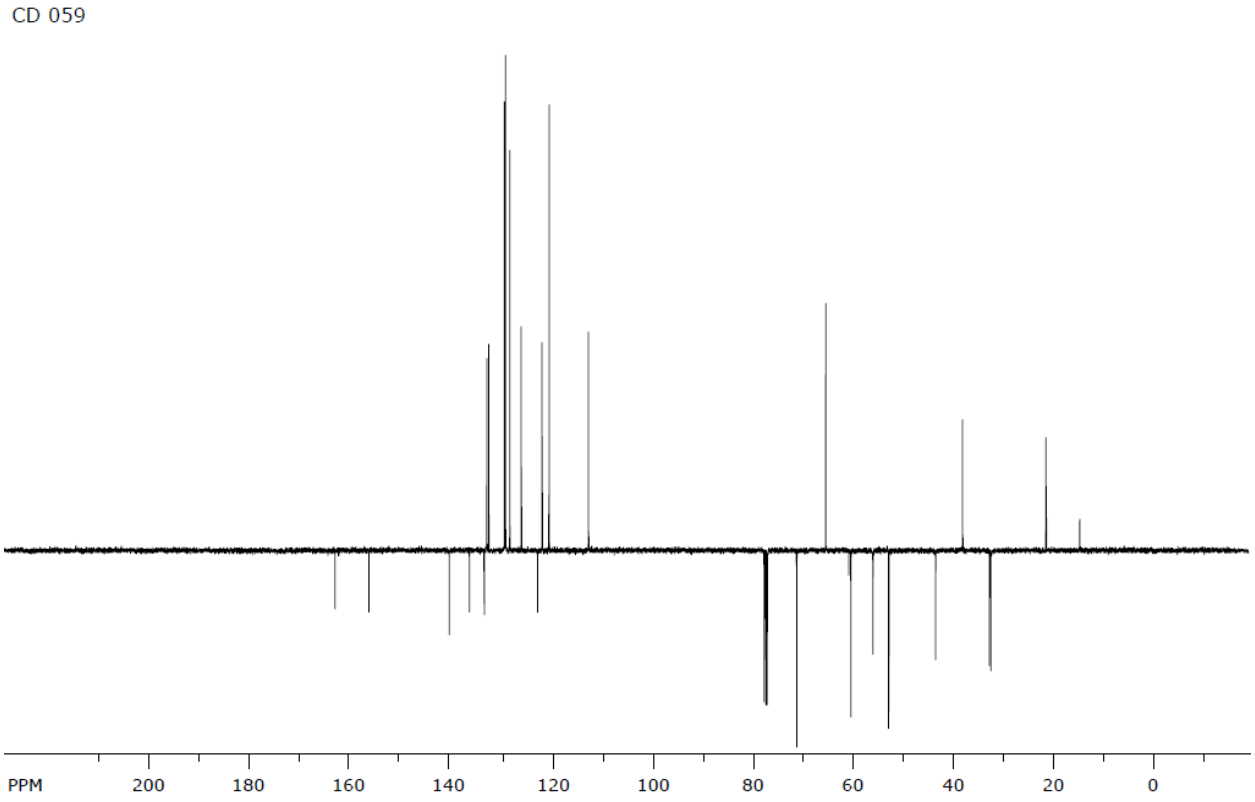
2-(3-(4-benzylpiperidin-1-yl)-2-hydroxypropoxy)-*N*-(2-fluorophenyl)benzamide (188)



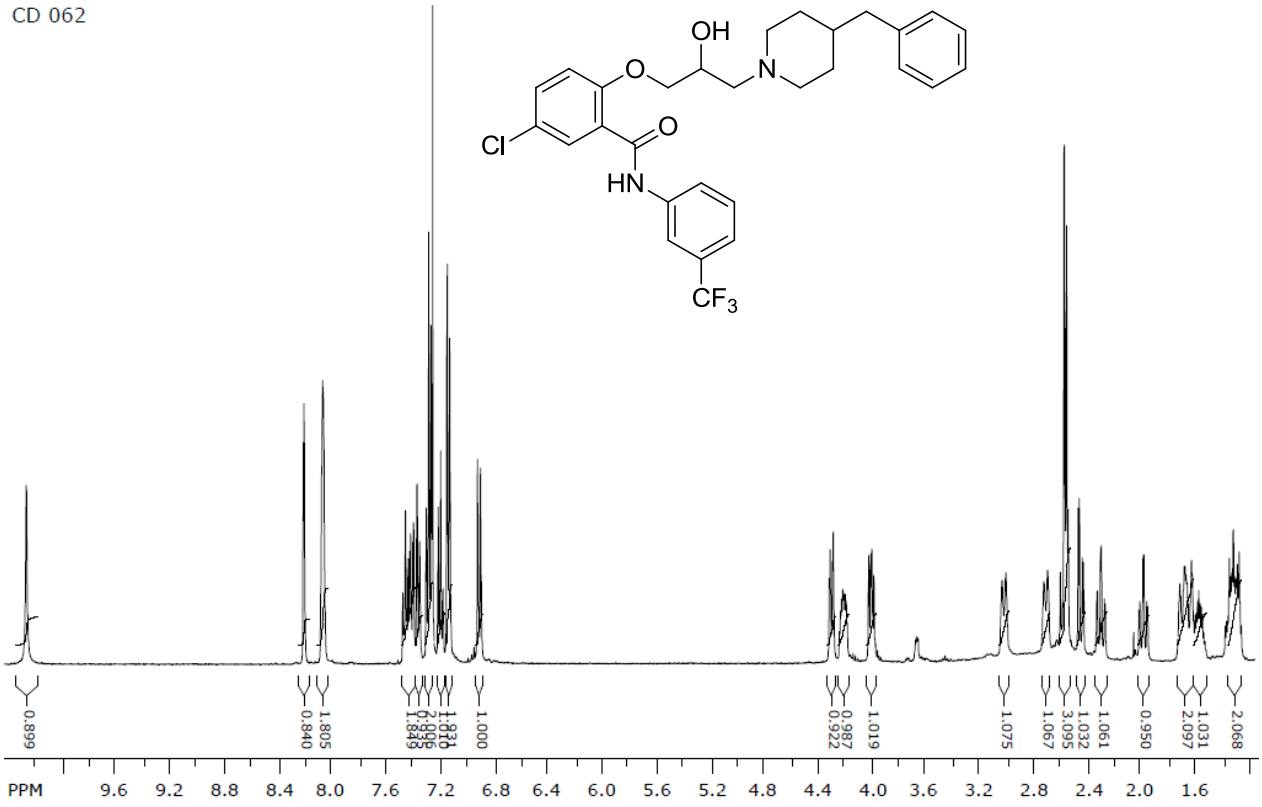


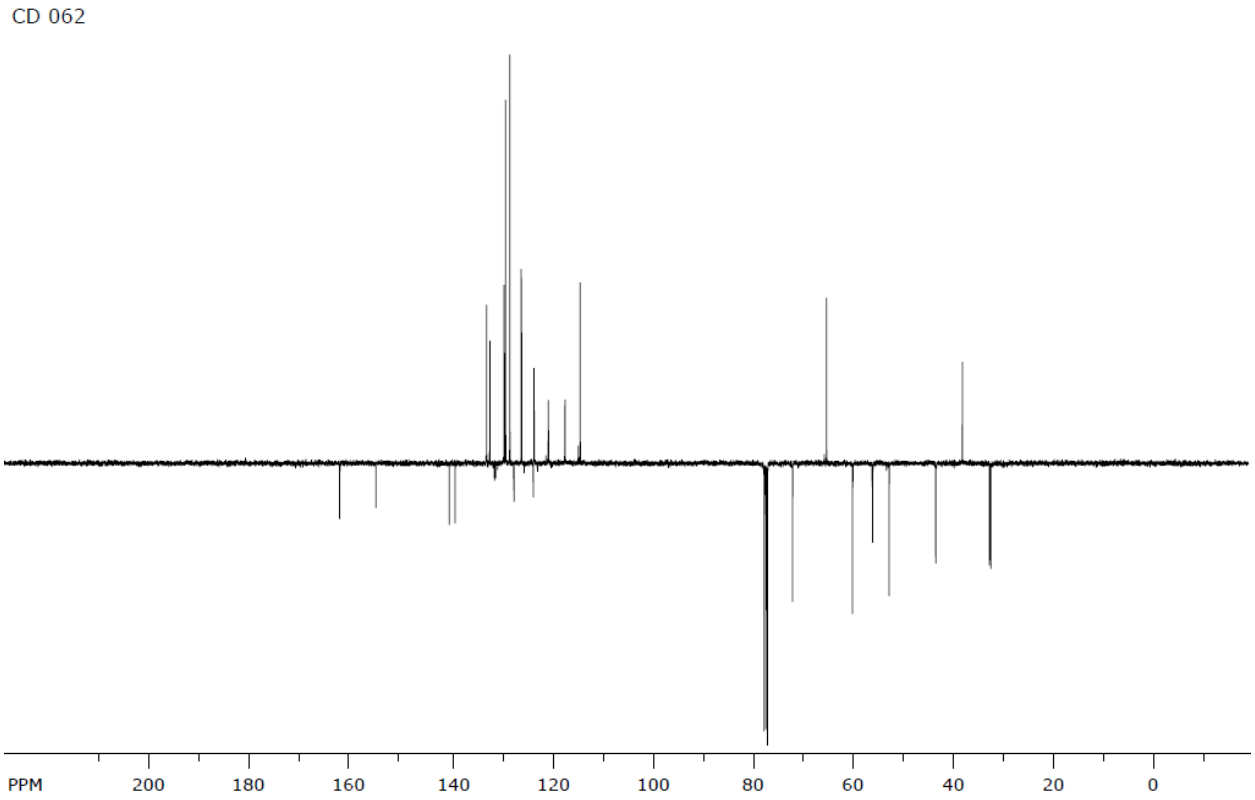
2-(3-(4-benzylpiperidin-1-yl)-2-hydroxypropoxy)-*N*-(p-tolyl)benzamide (189**)**



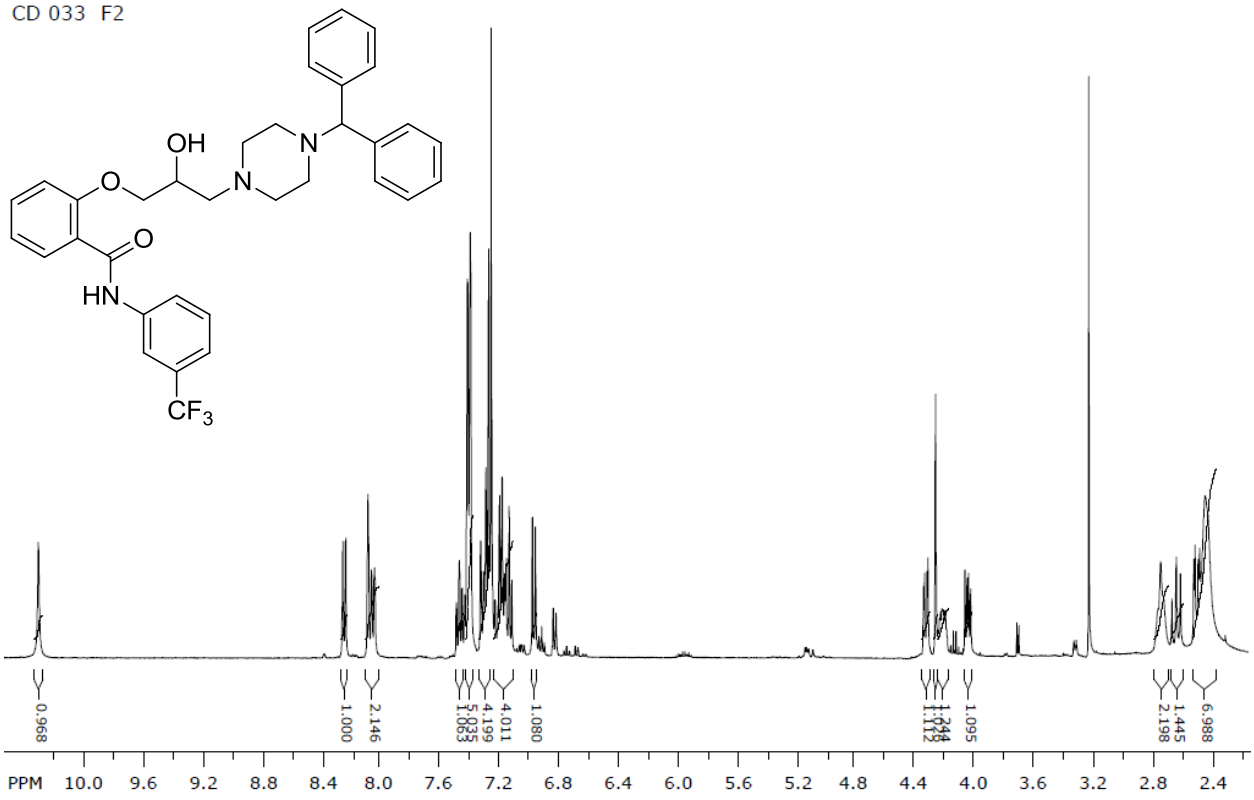


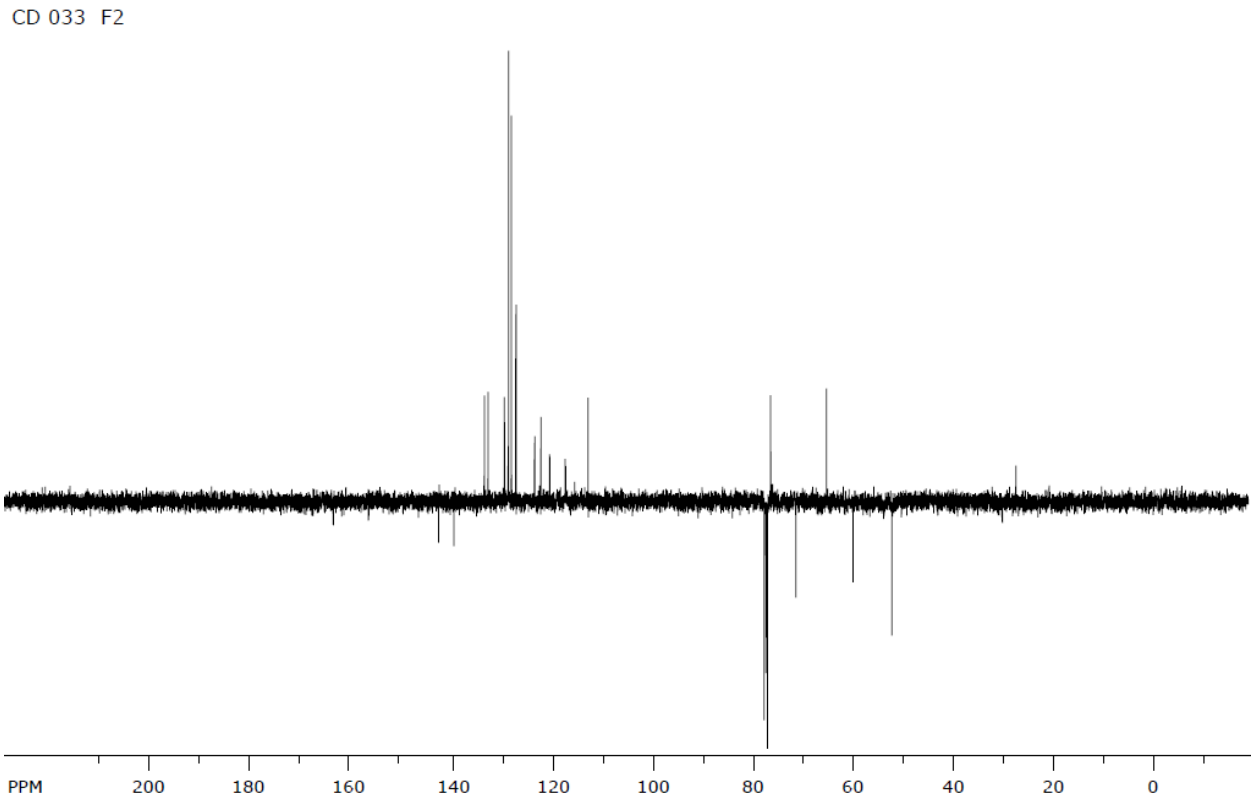
2-(3-(4-benzylpiperidin-1-yl)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (190**)**



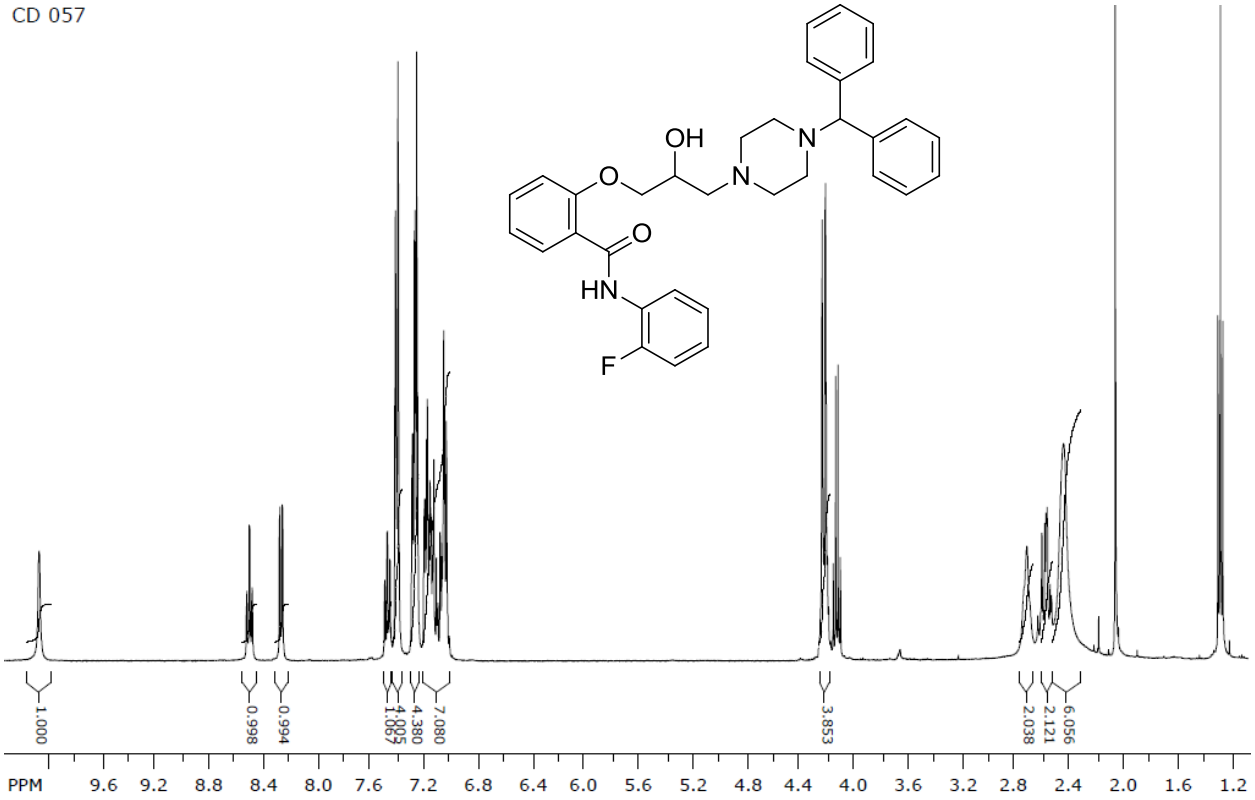


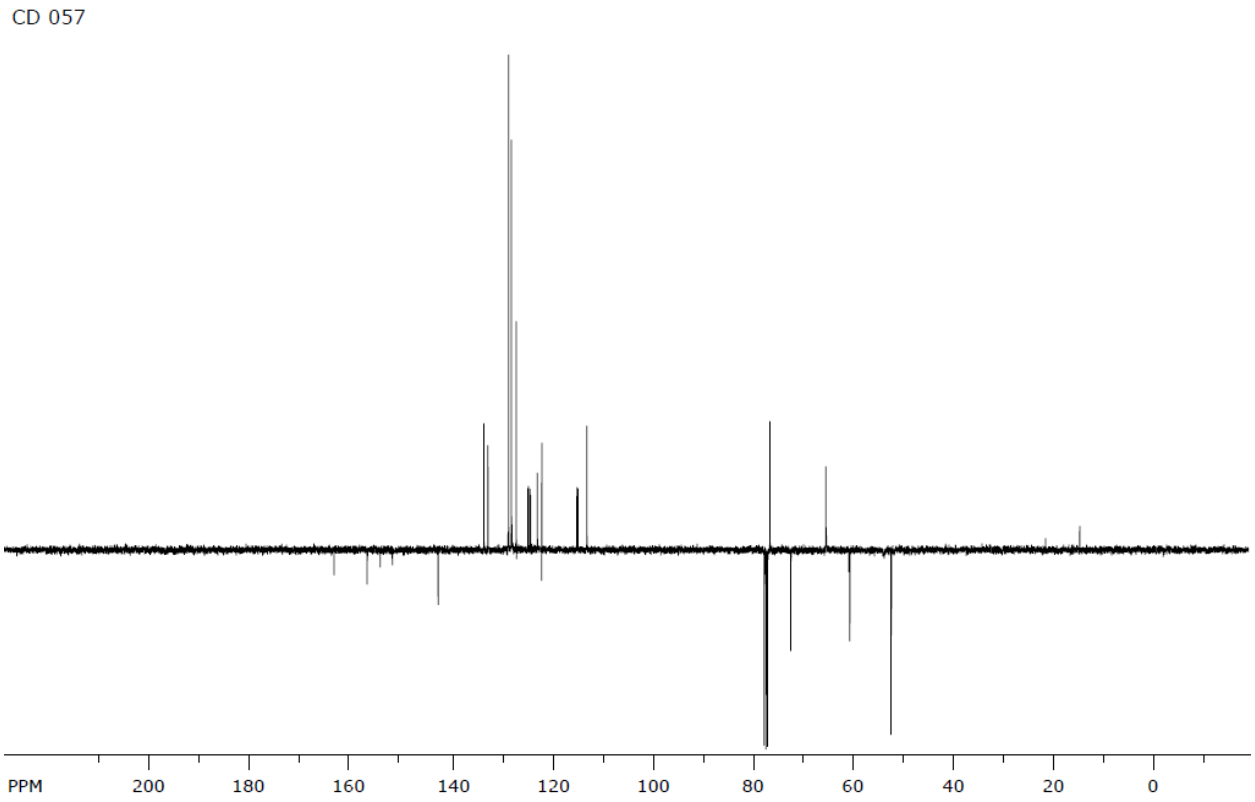
2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (191**)**



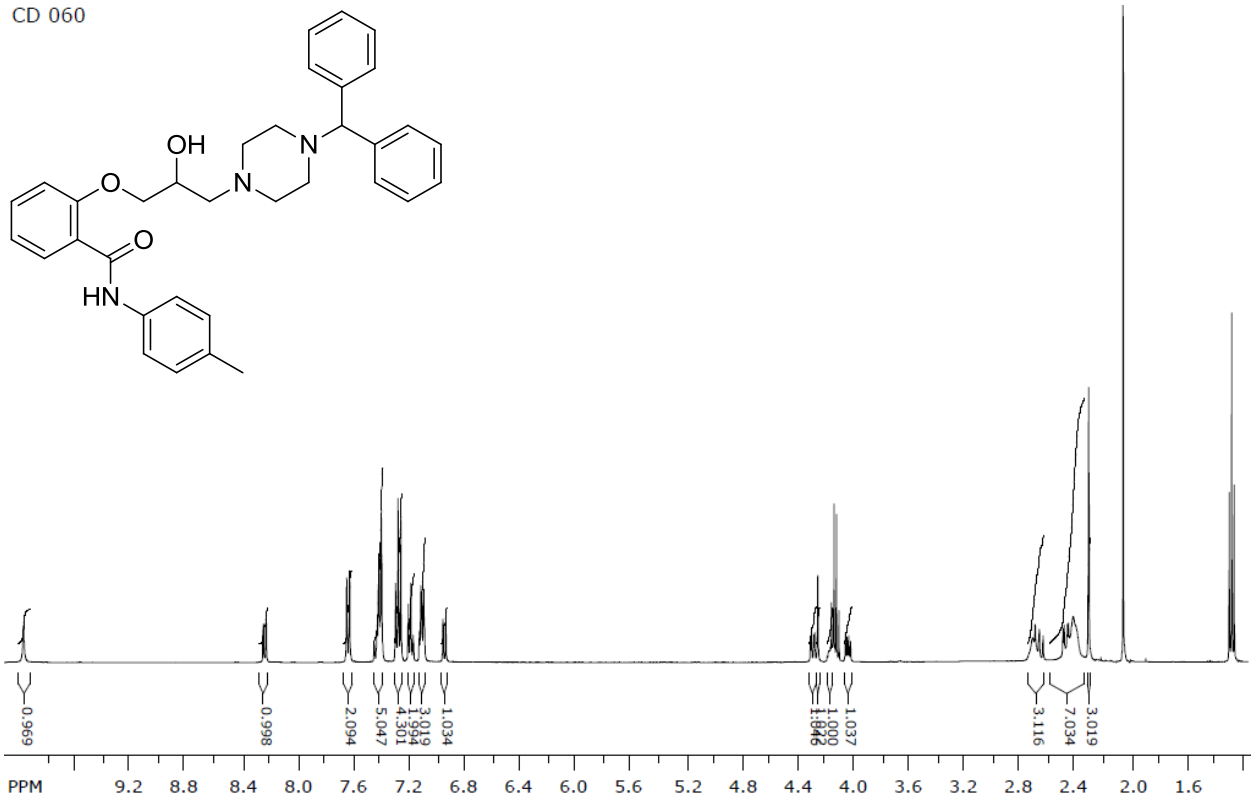


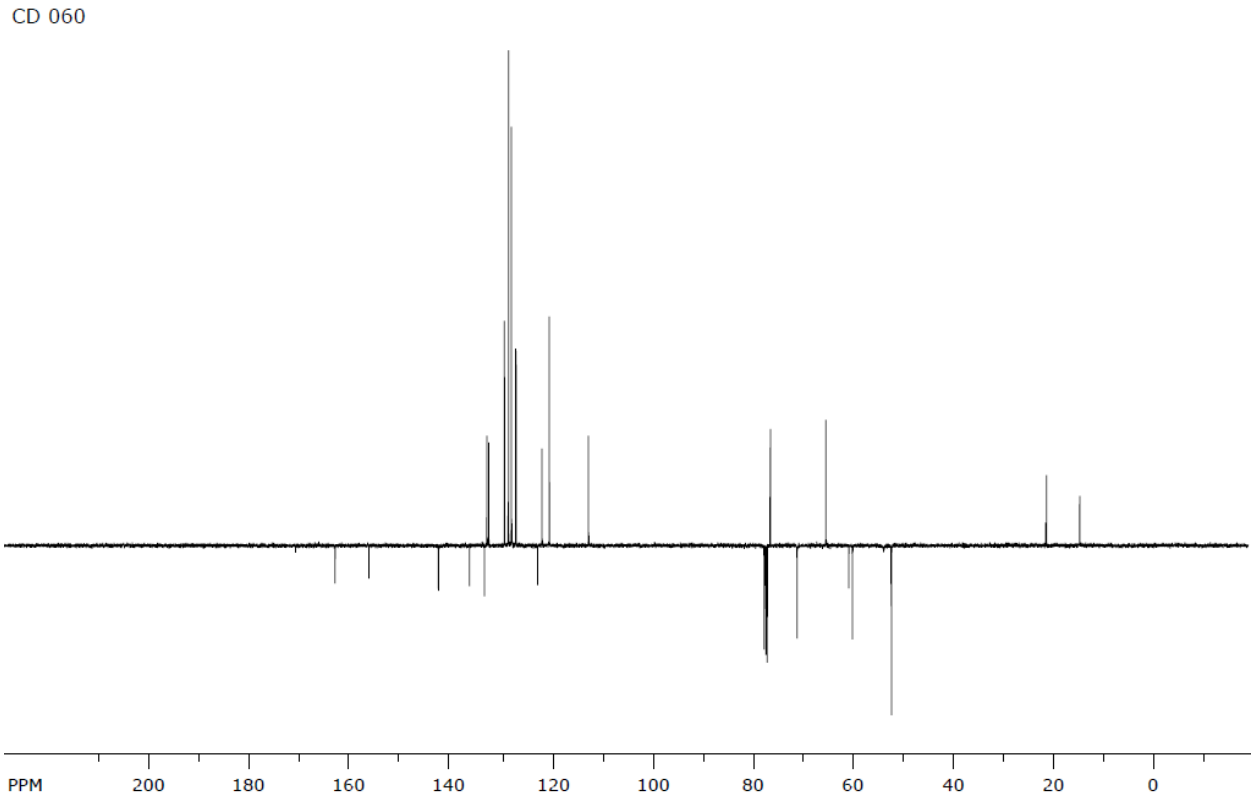
2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(2-fluorophenyl)benzamide (192**)**



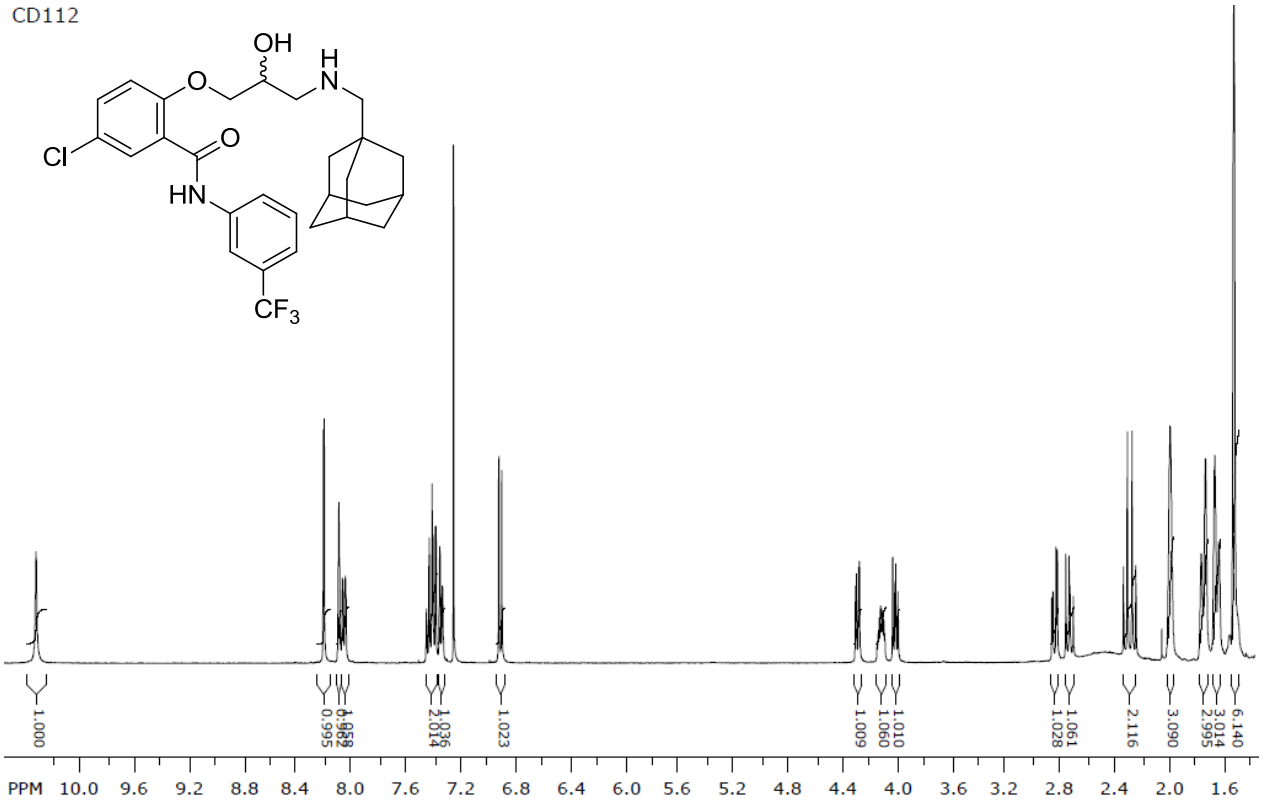


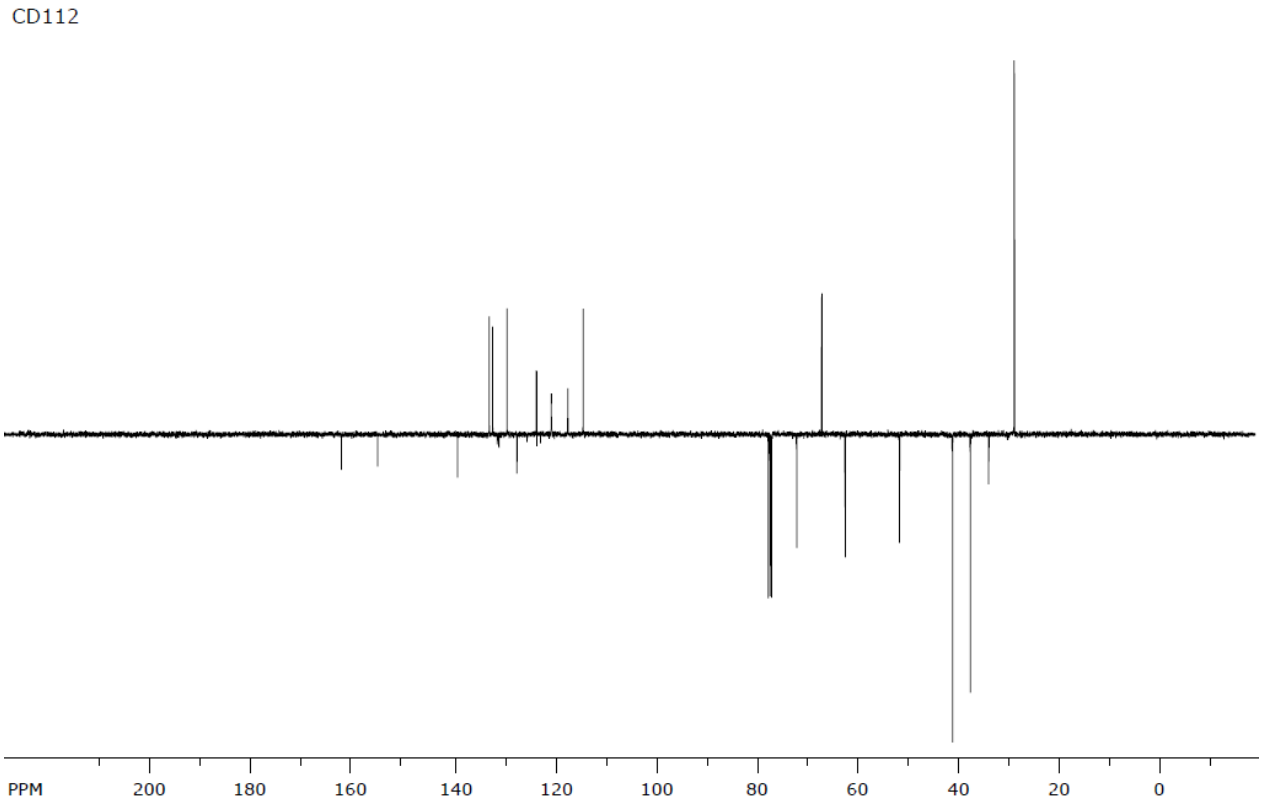
2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(p-tolyl)benzamide (193)



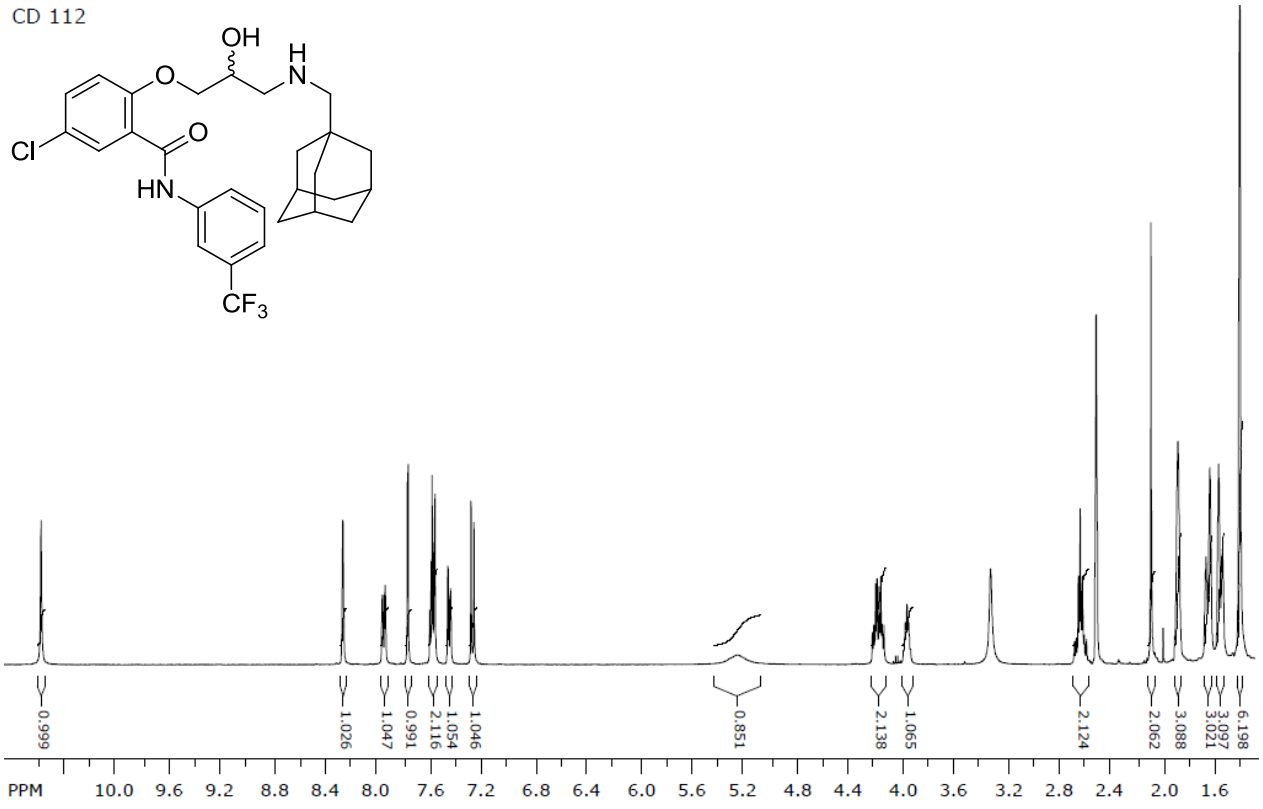


2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (194**)**

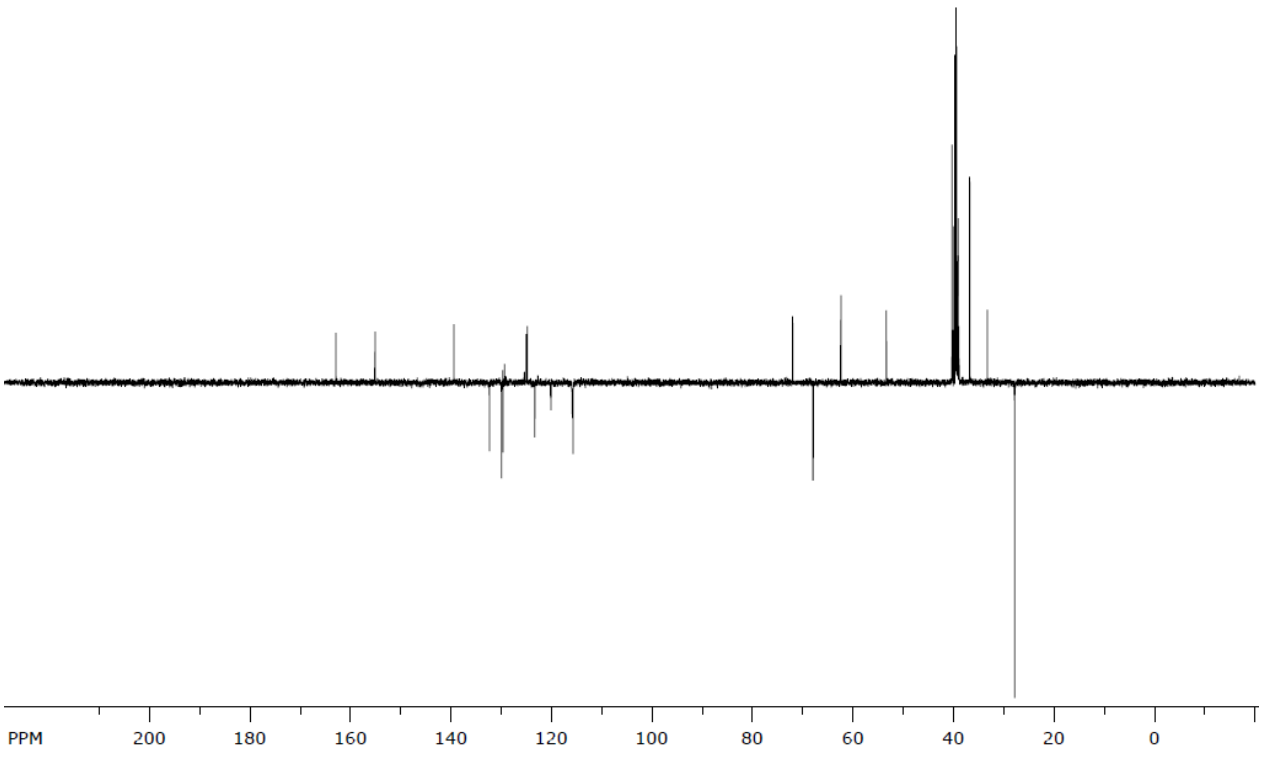




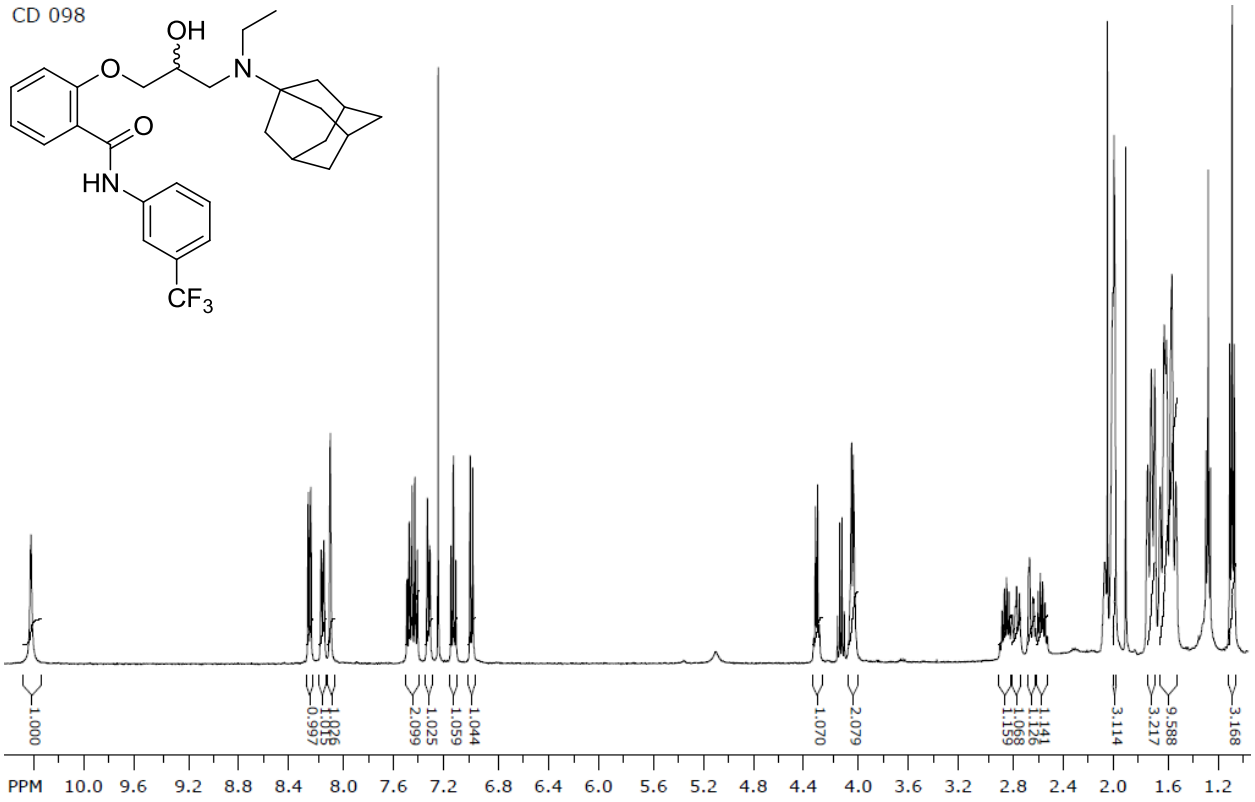
CD 112

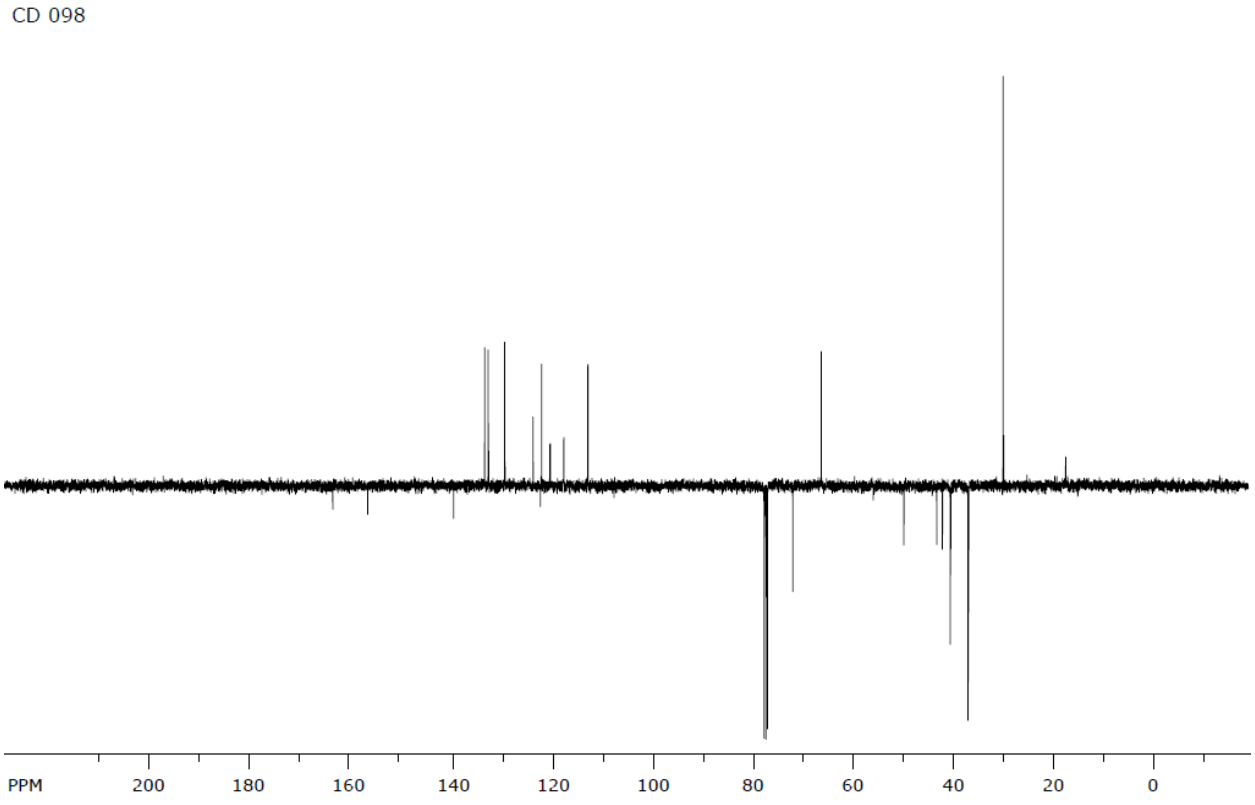

OH
H
N
O
Cl
O
HN
CF3
0.999
1.026
1.047
0.991
2.116
1.054
1.046
0.851
2.138
1.065
2.124
2.062
3.088
3.021
3.097
6.198
PPM
10.0 9.6 9.2 8.8 8.4 8.0 7.6 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6

CD 112

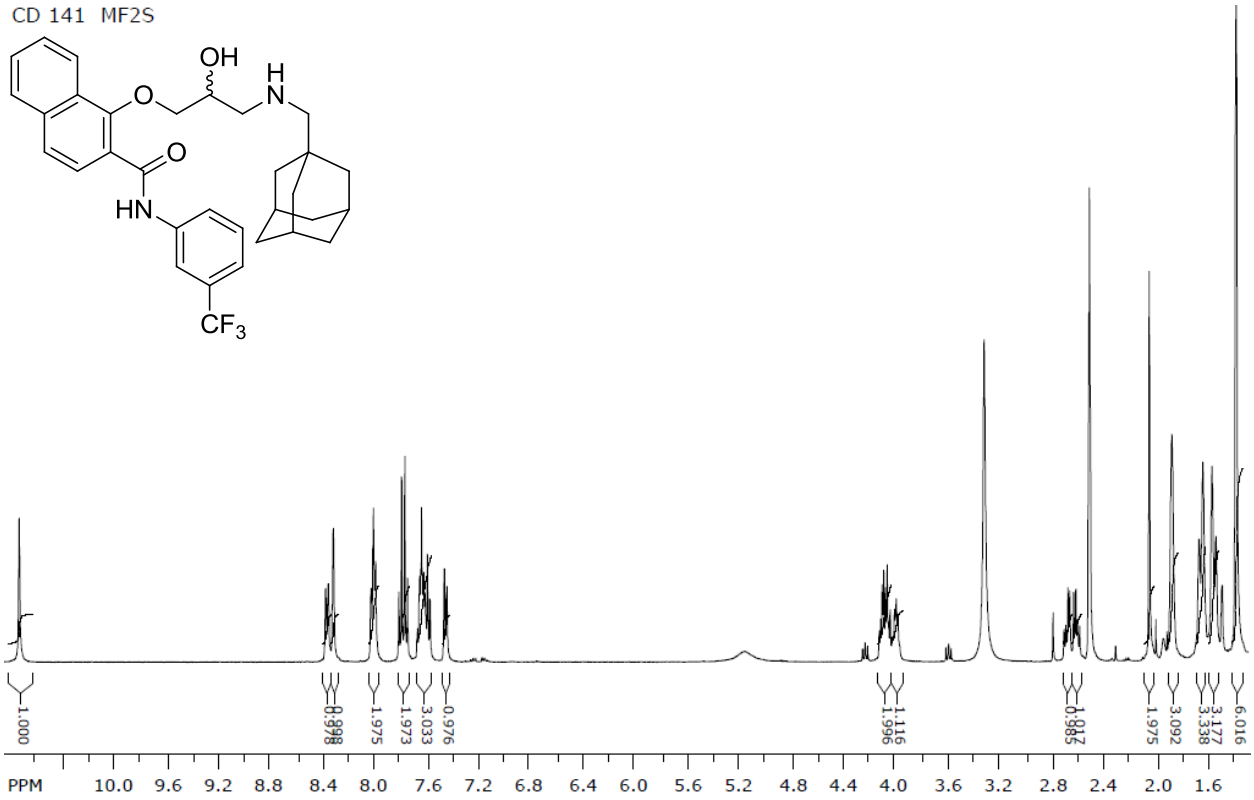

PPM
200 180 160 140 120 100 80 60 40 20 0

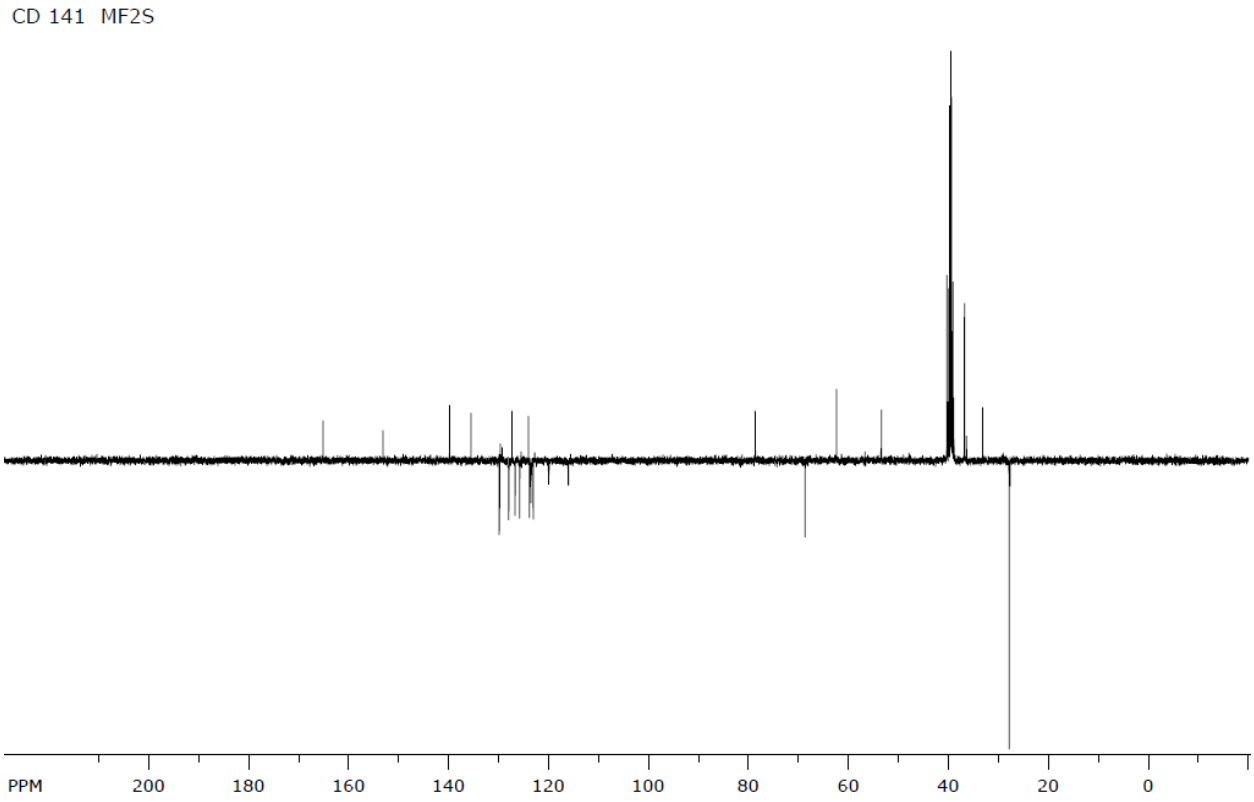
2-(3-(adamantan-1-yl(ethyl)amino)-2-hydroxypropoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (195)



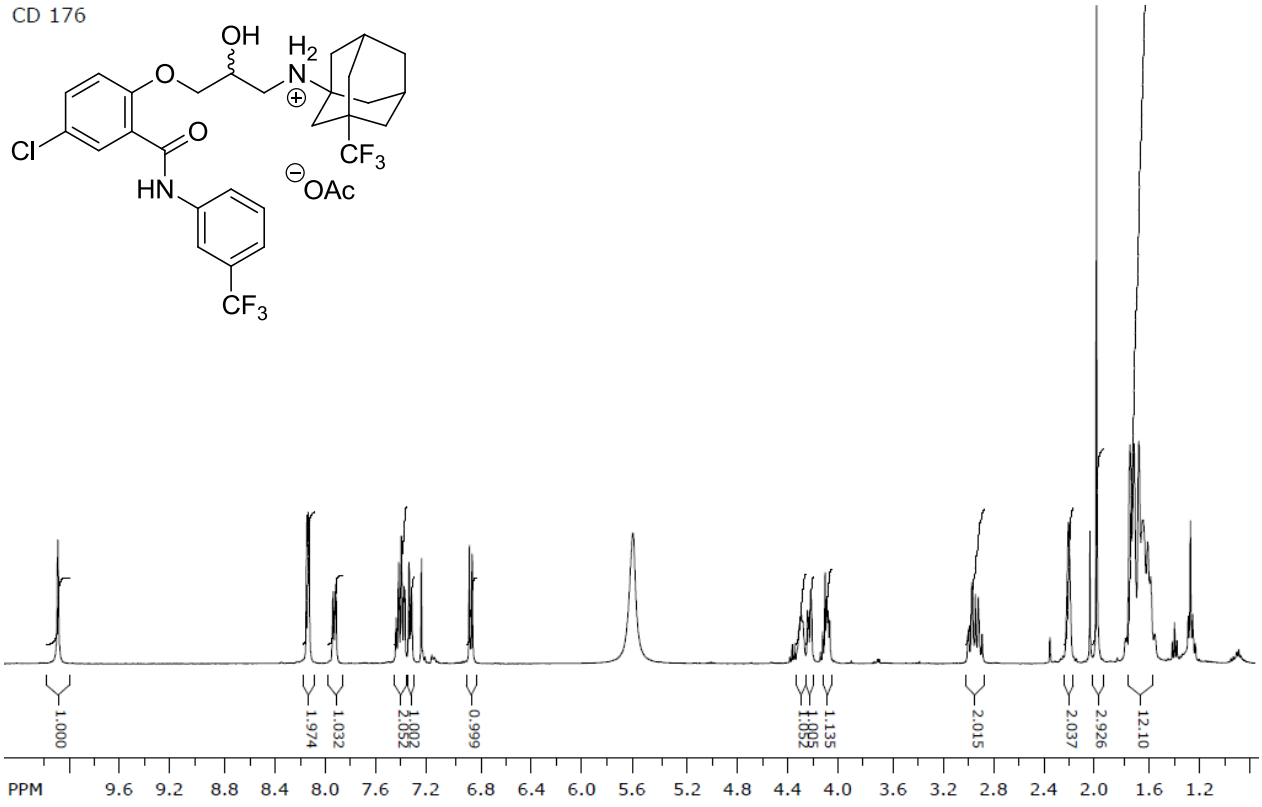


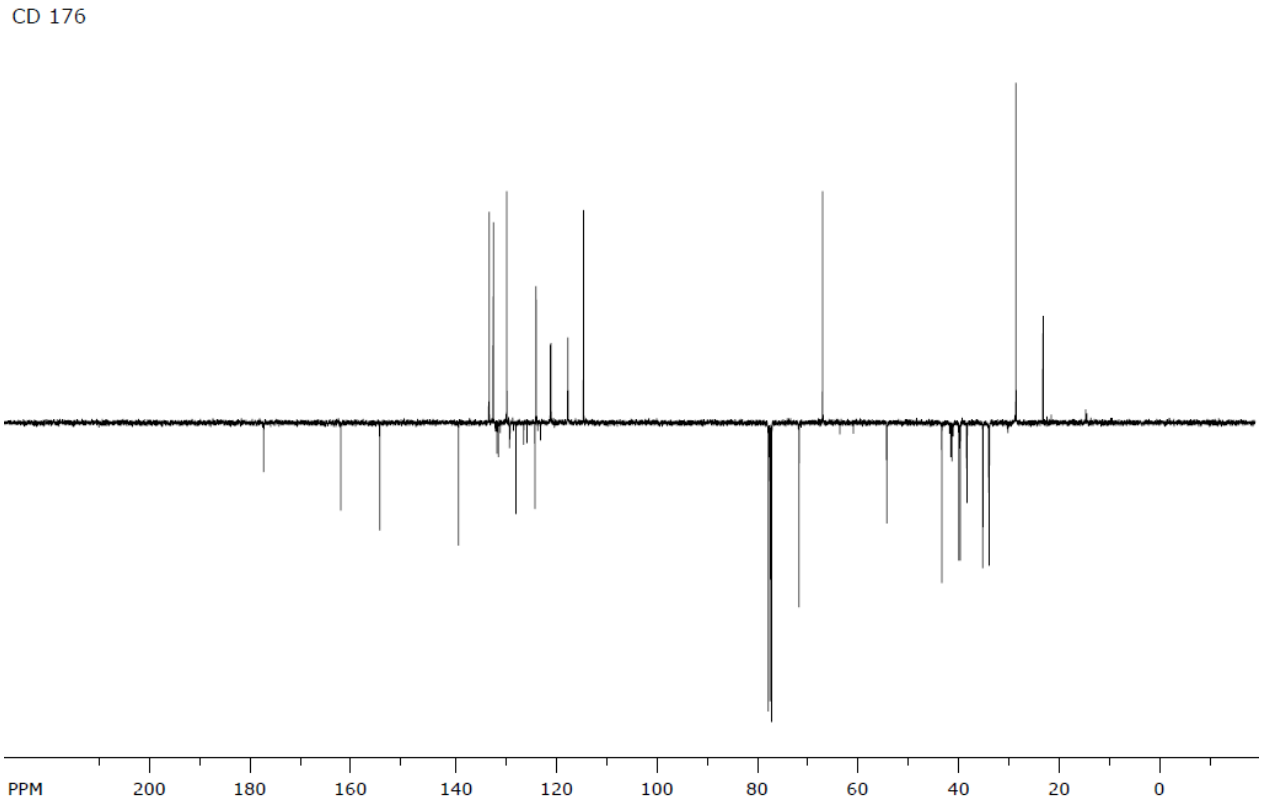
1-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(3-(trifluoromethyl)phenyl)-2-naphthamide (196)



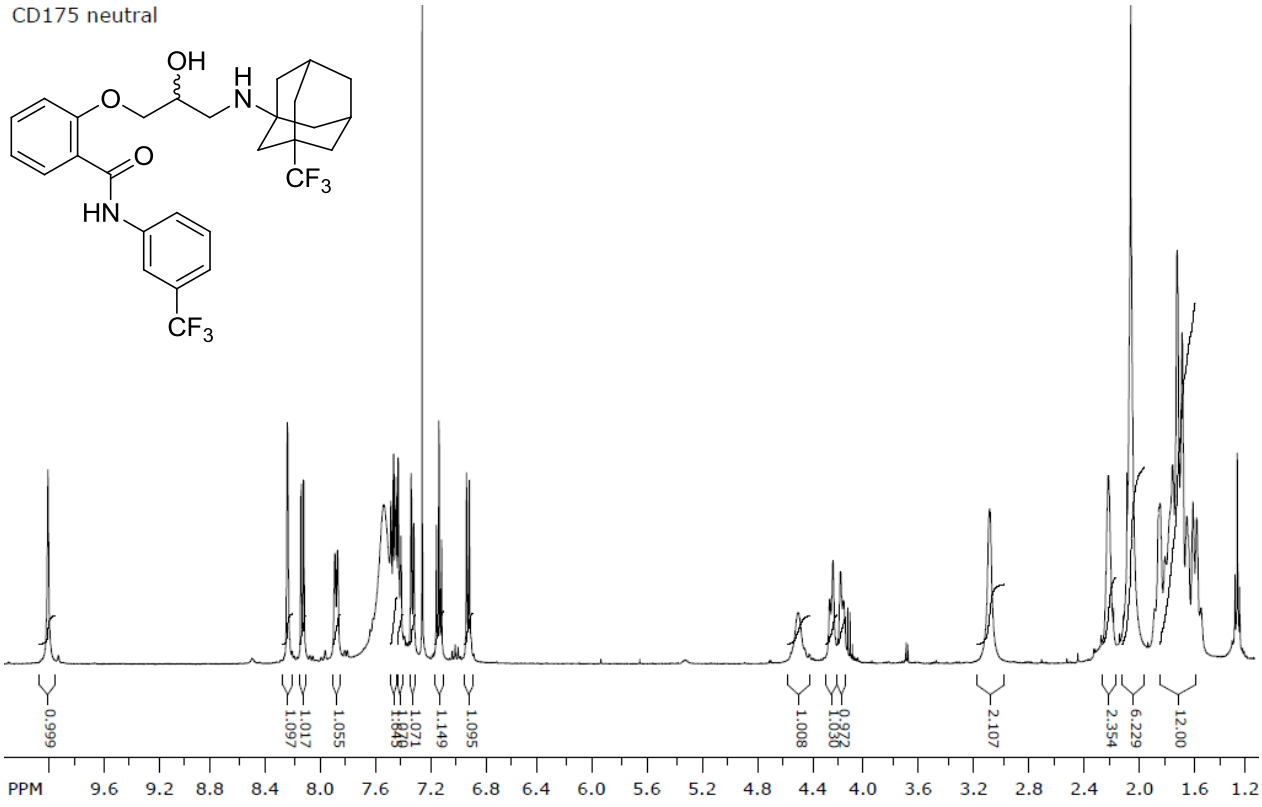


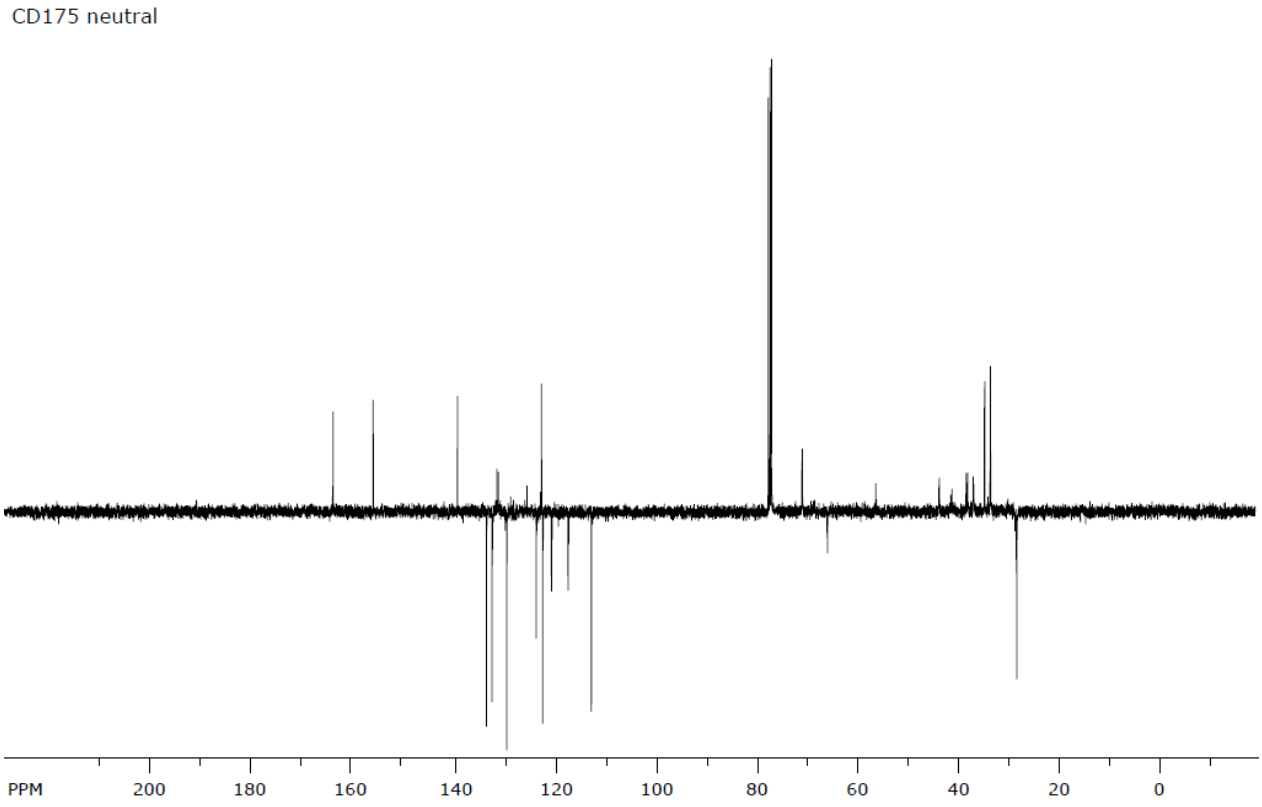
5-chloro-2-(2-hydroxy-3-((3-(trifluoromethyl)adamantan-1-yl)amino)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide acetate (197)



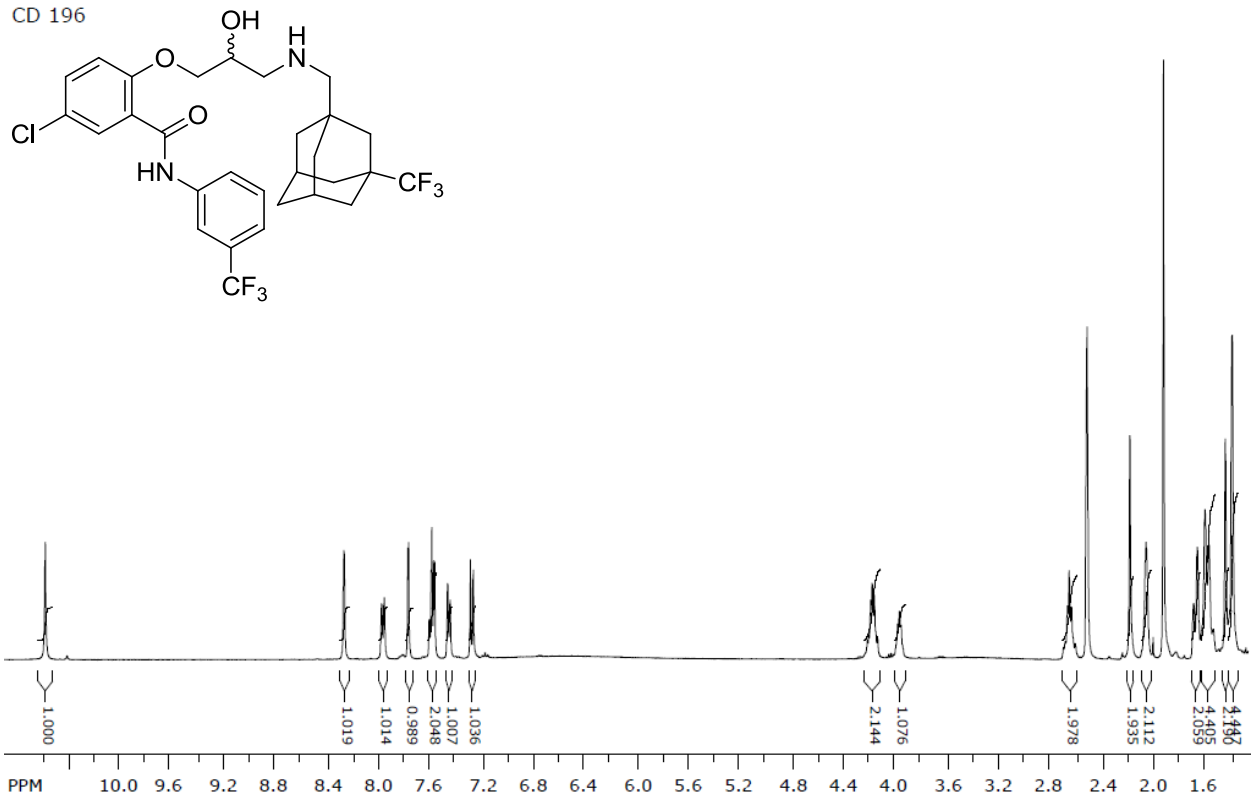


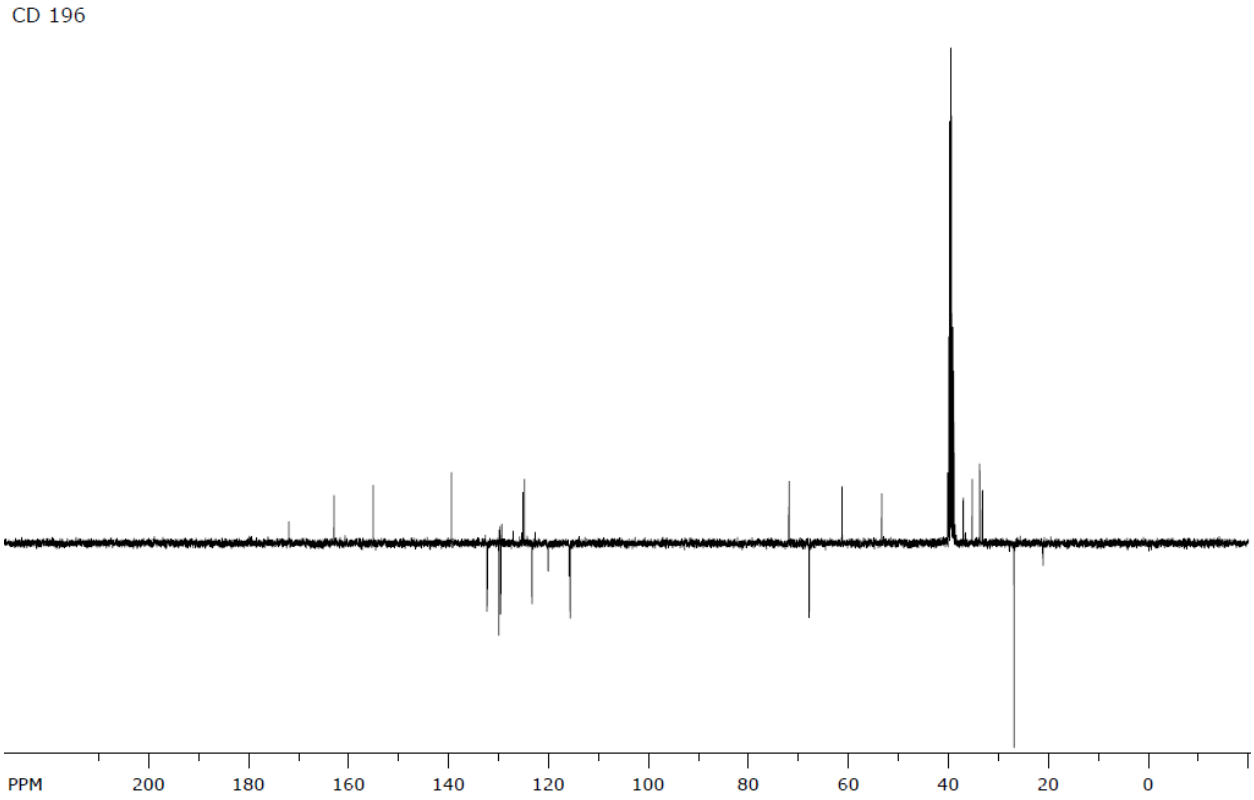
2-(2-hydroxy-3-((3-(trifluoromethyl)adamantan-1-yl)amino)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (198**)**



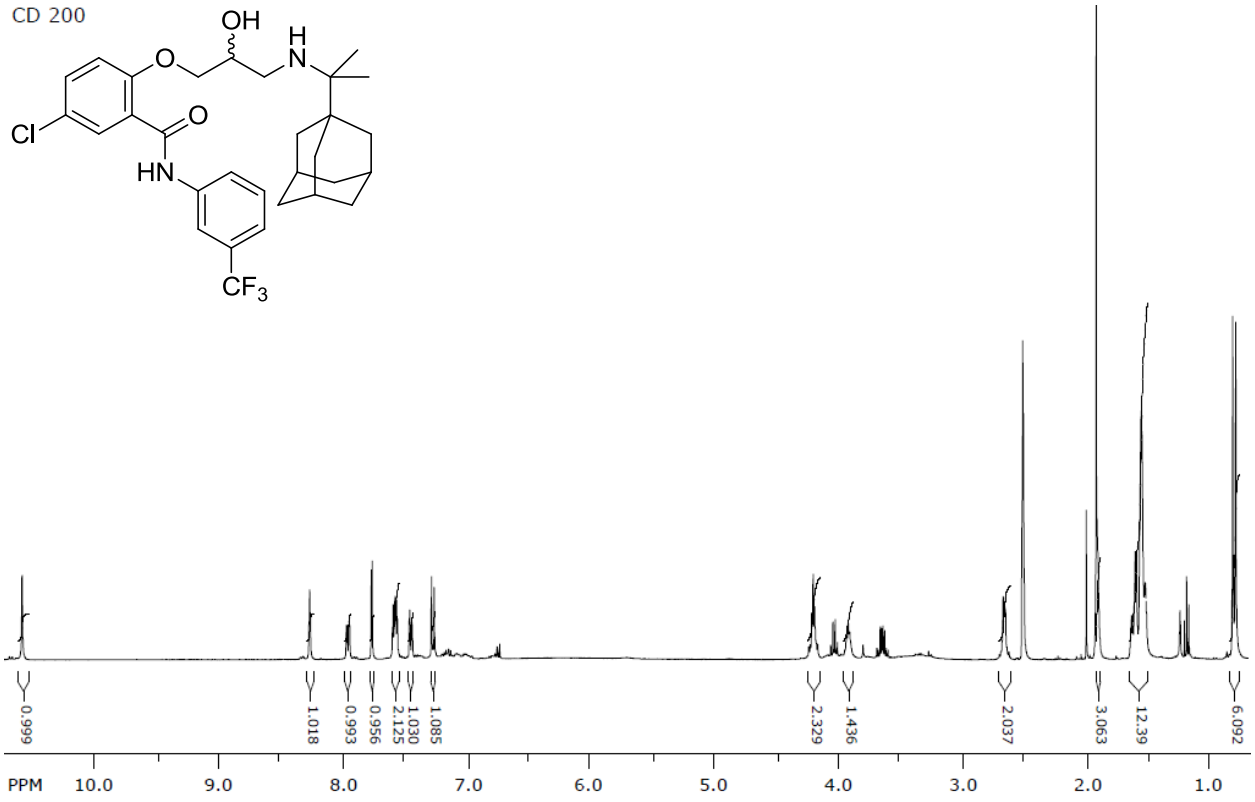


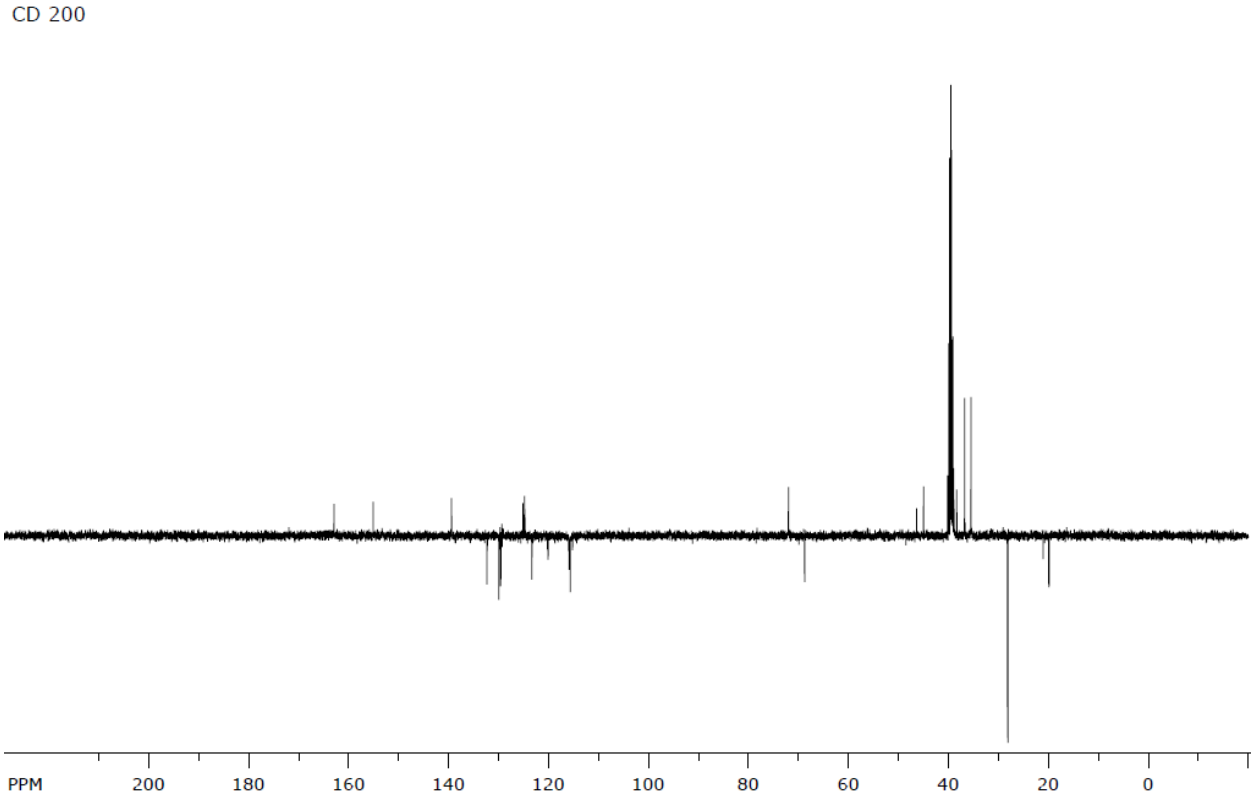
5-chloro-2-(2-hydroxy-3-(((3-(trifluoromethyl)adamantan-1-yl)methyl)amino)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (199)



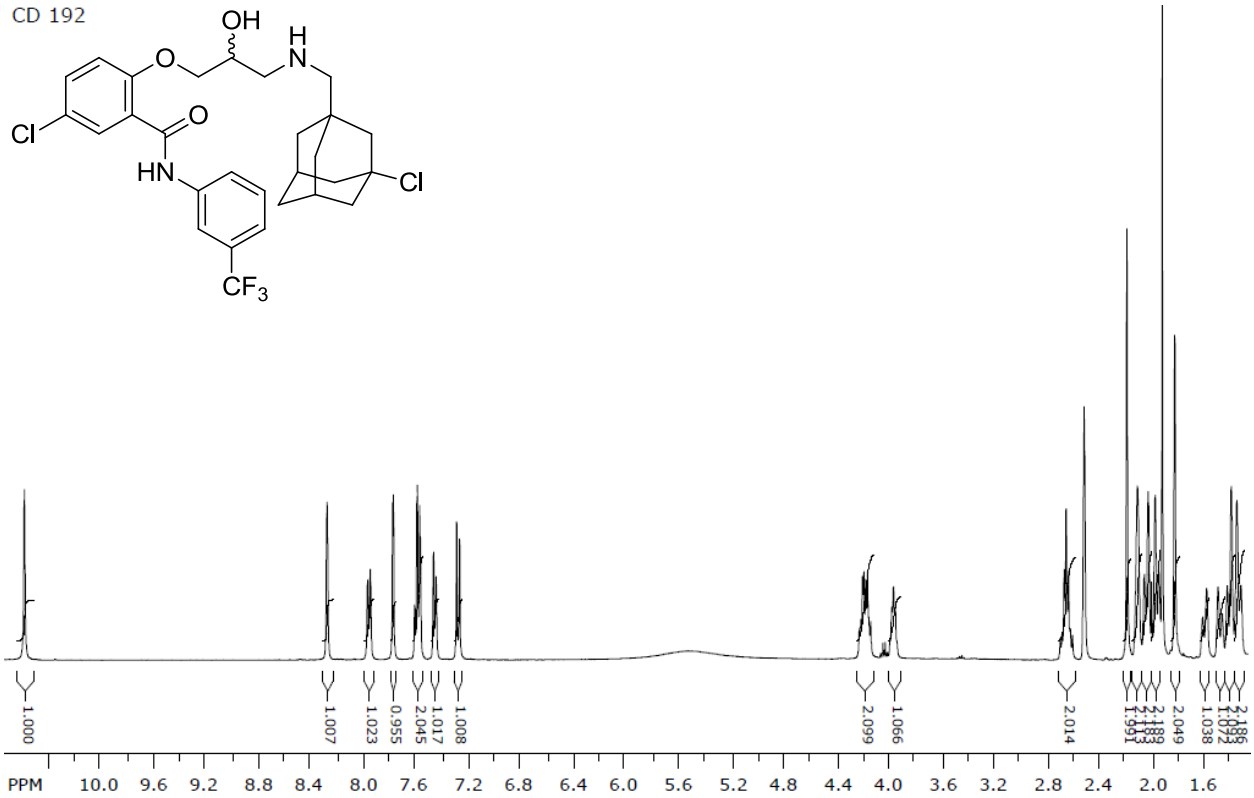


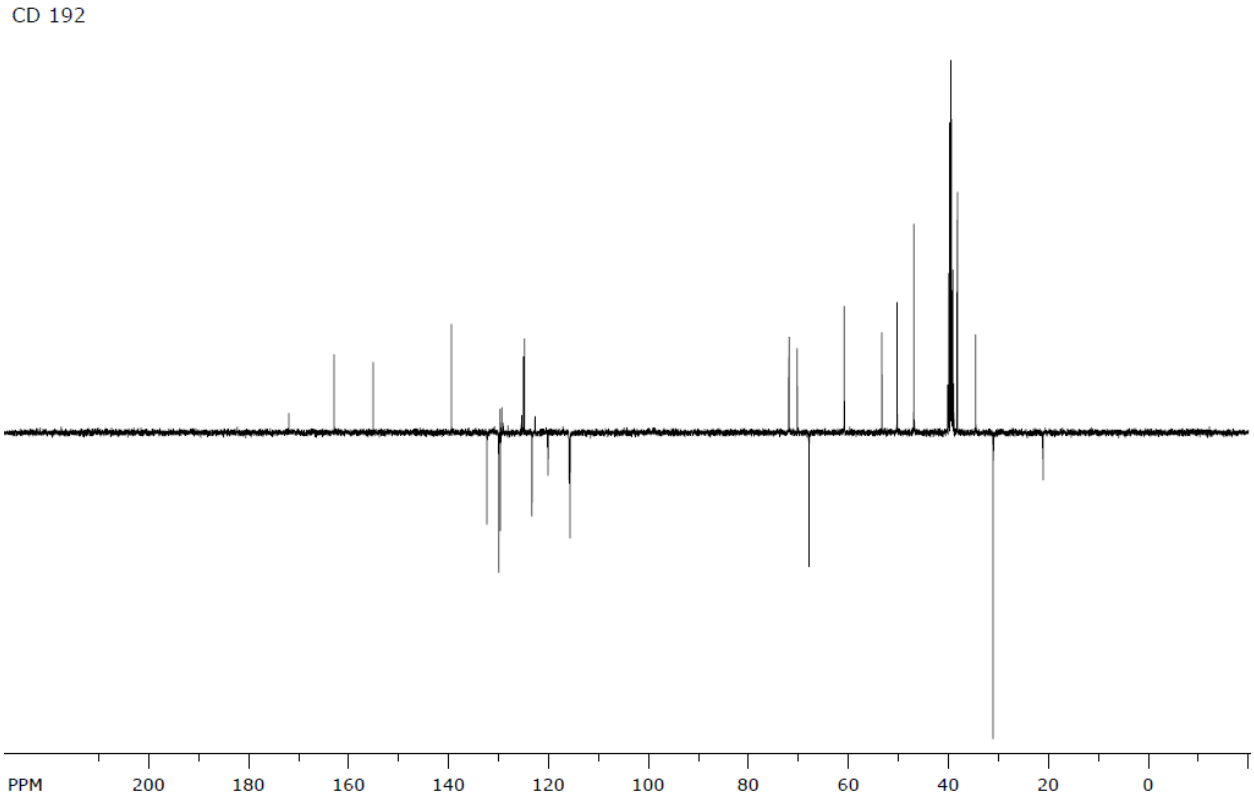
2-(3-((2-(adamantan-1-yl)propan-2-yl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (200)



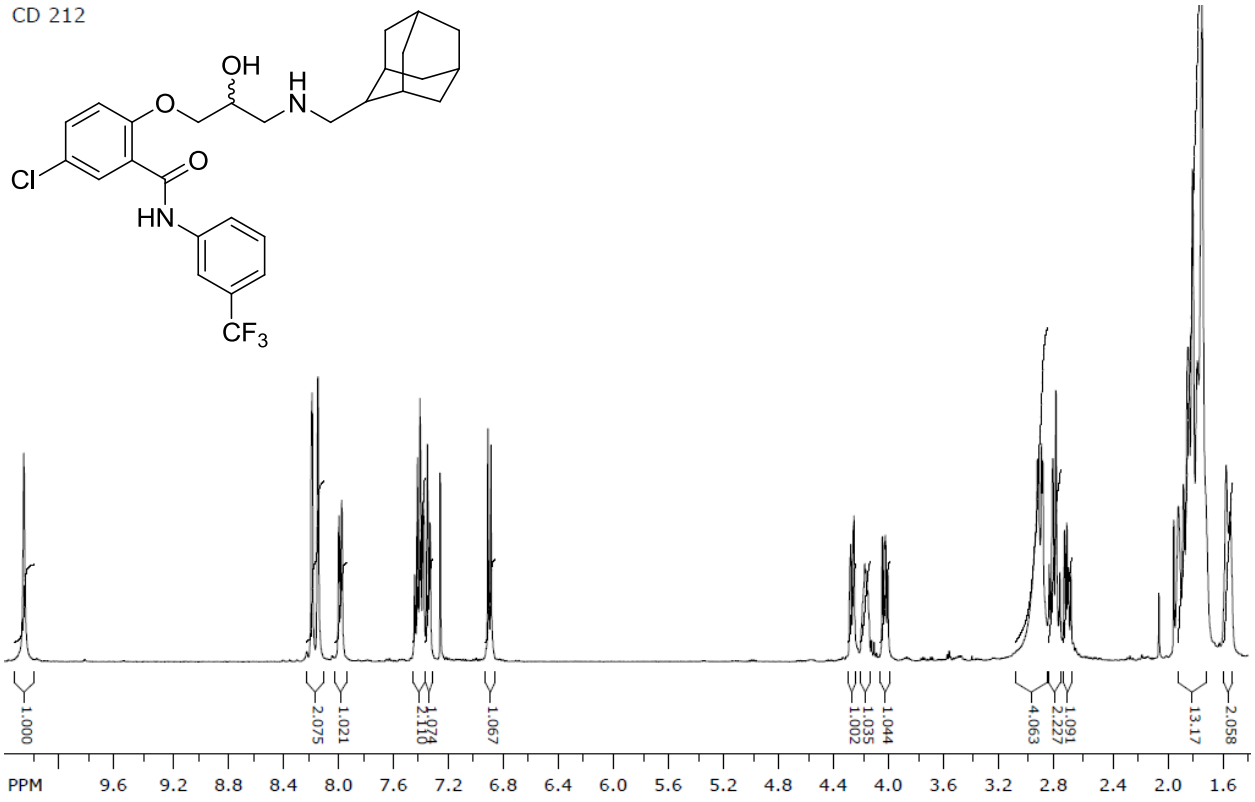


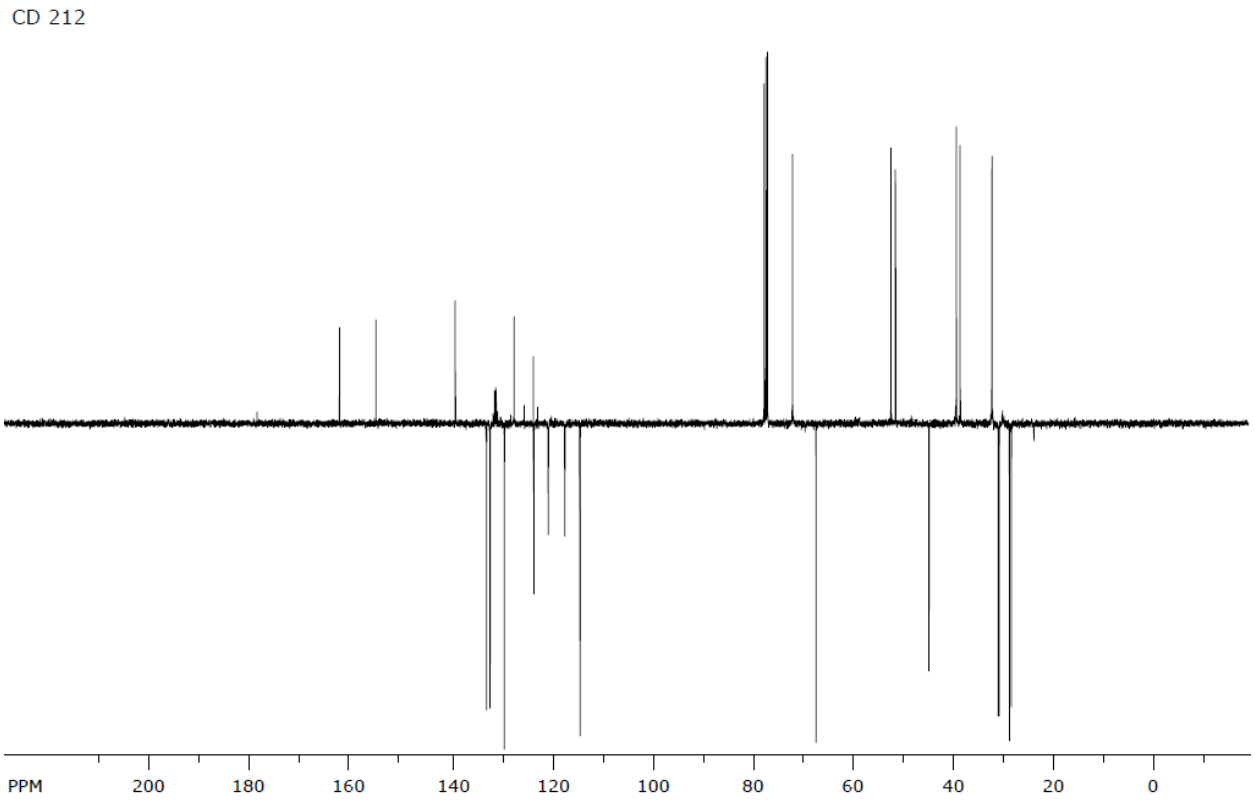
5-chloro-2-(3-(((3-chloroadamantan-1-yl)methyl)amino)-2-hydroxypropoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (201)



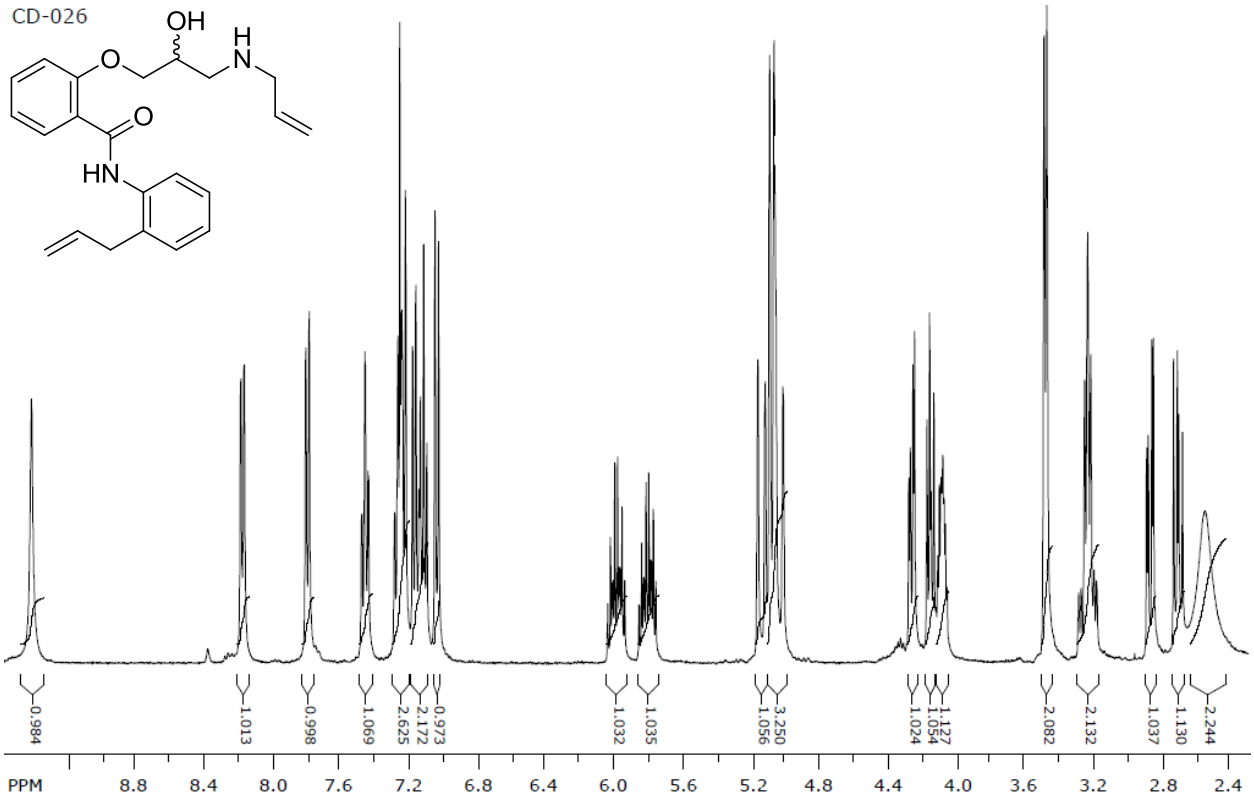


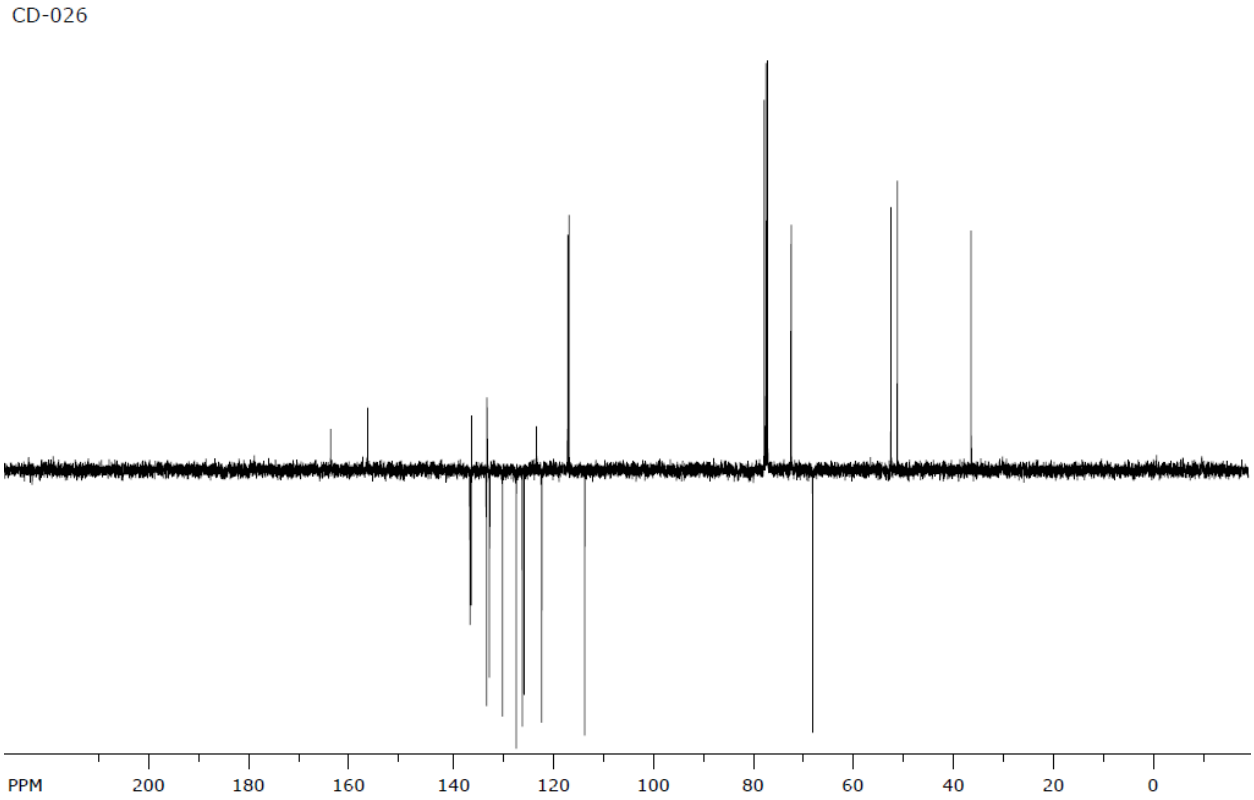
2-(3-((adamantan-2-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (202**)**



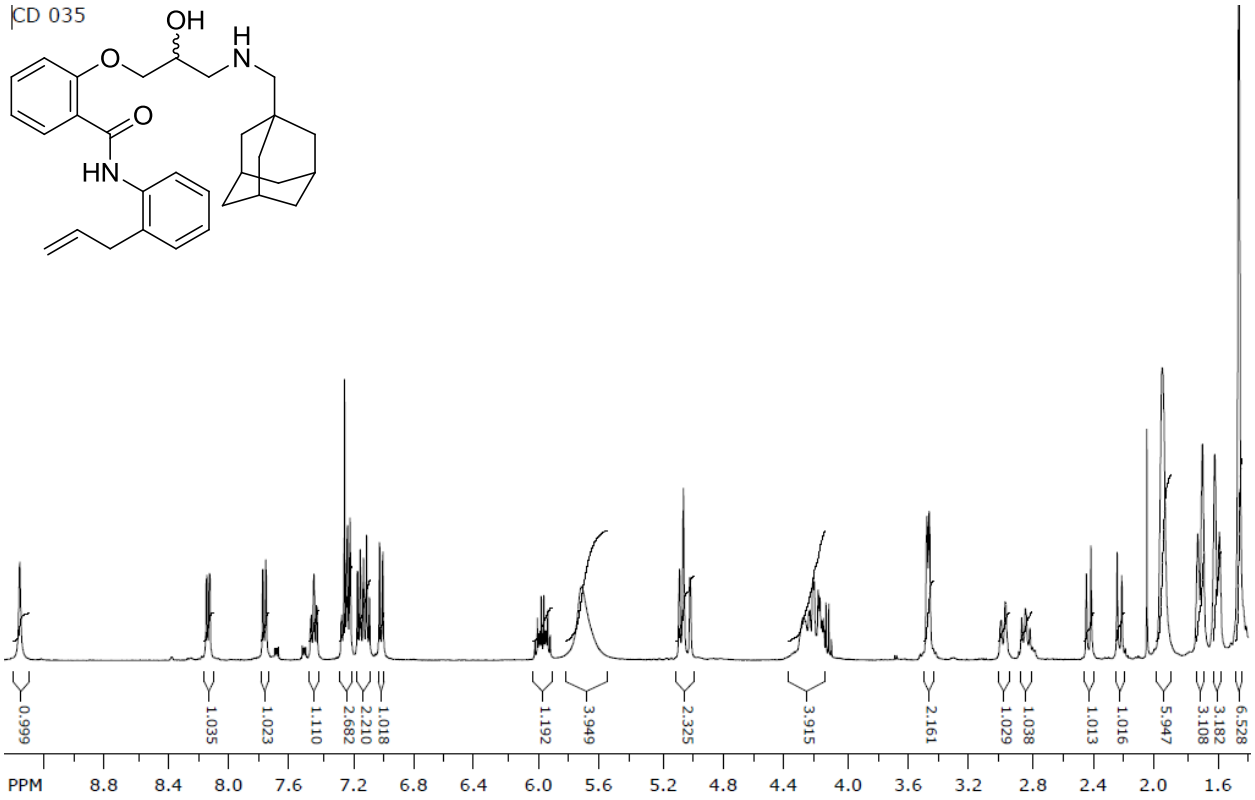


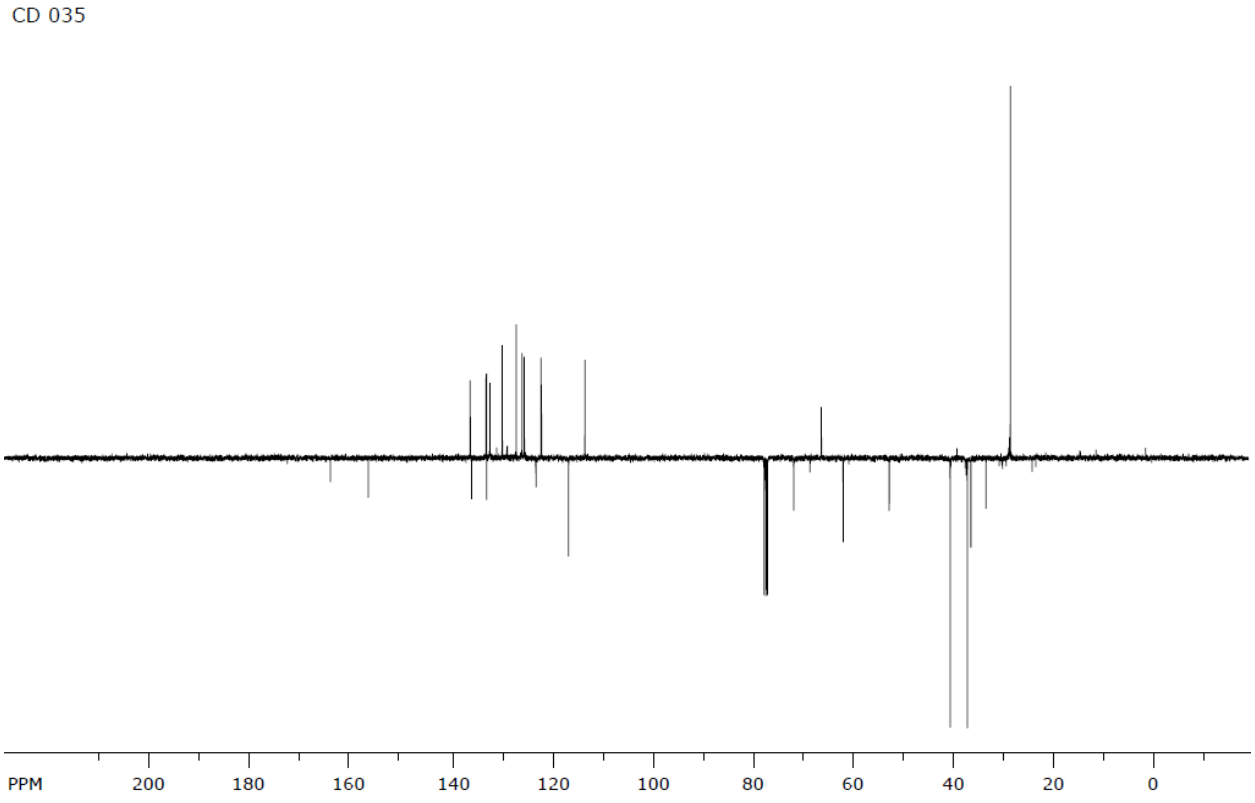
2-(3-(allylamino)-2-hydroxypropoxy)-*N*-(2-allylphenyl)benzamide (203)



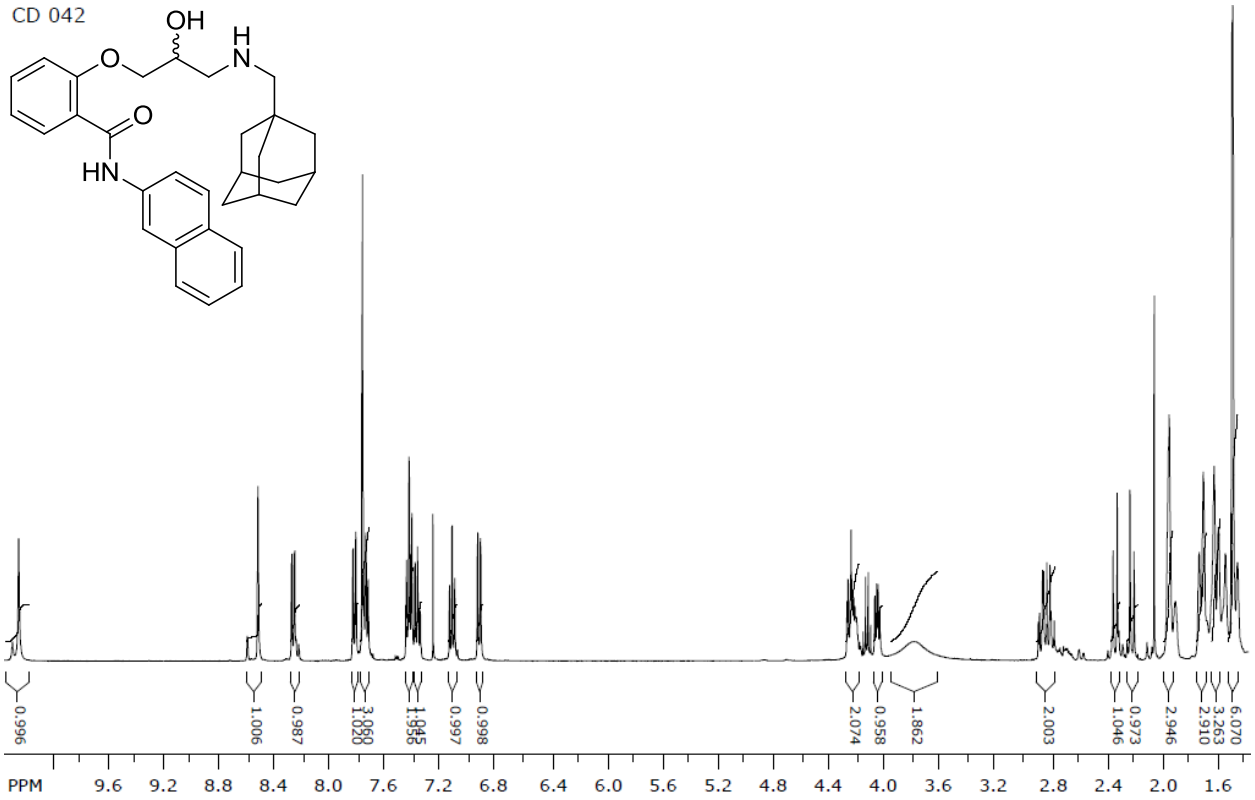


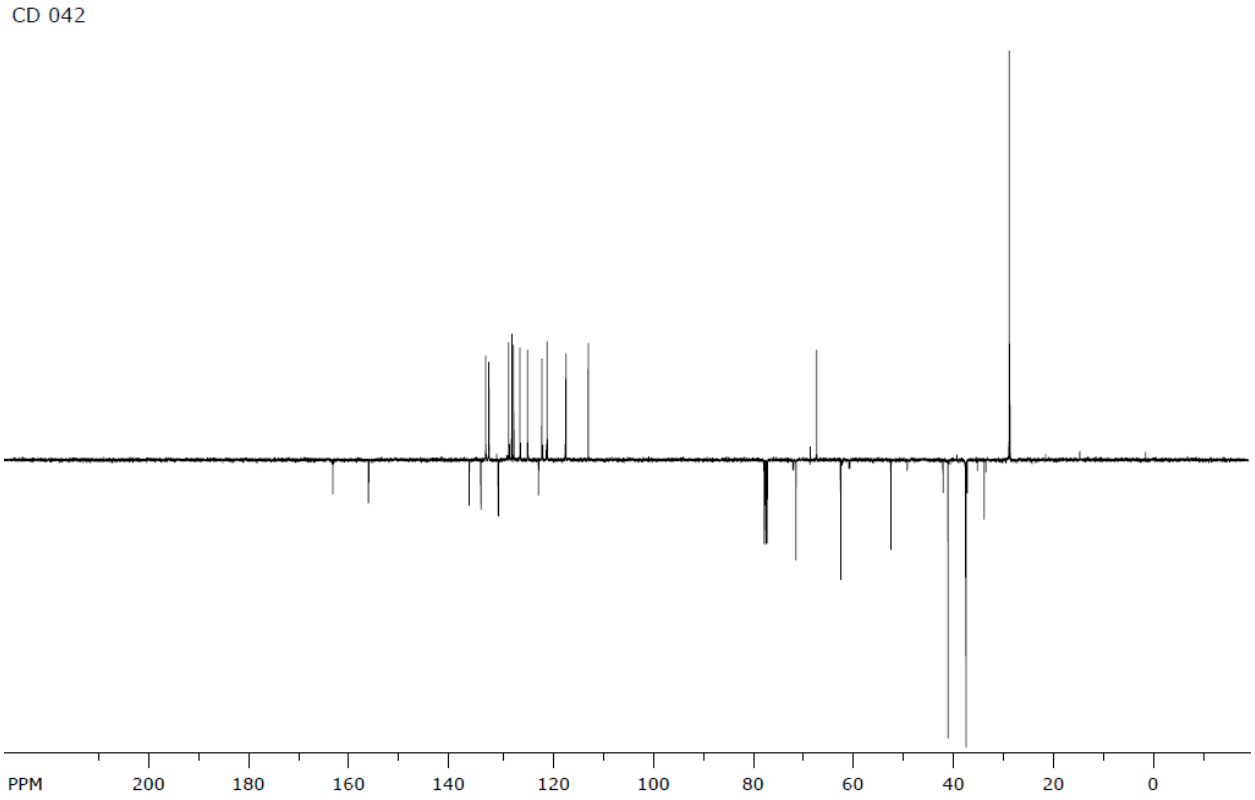
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(2-allylphenyl)benzamide (204**)**



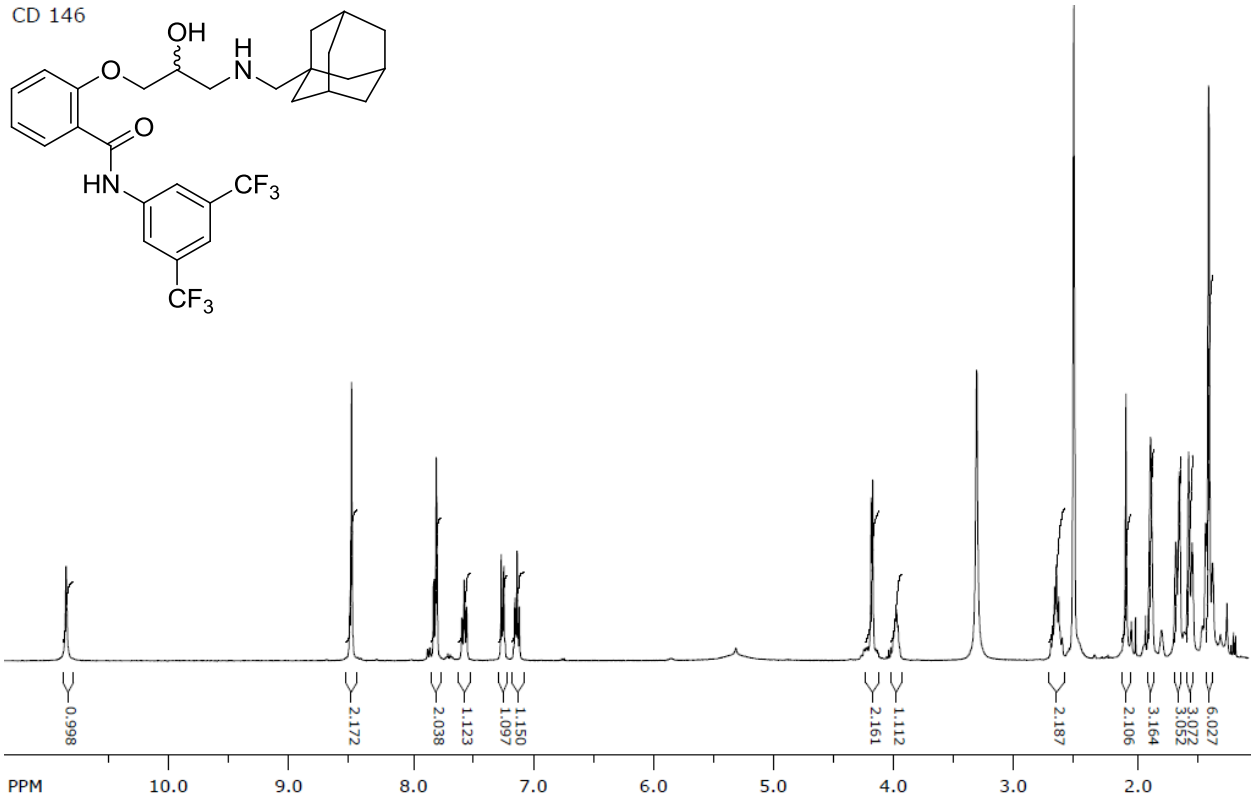


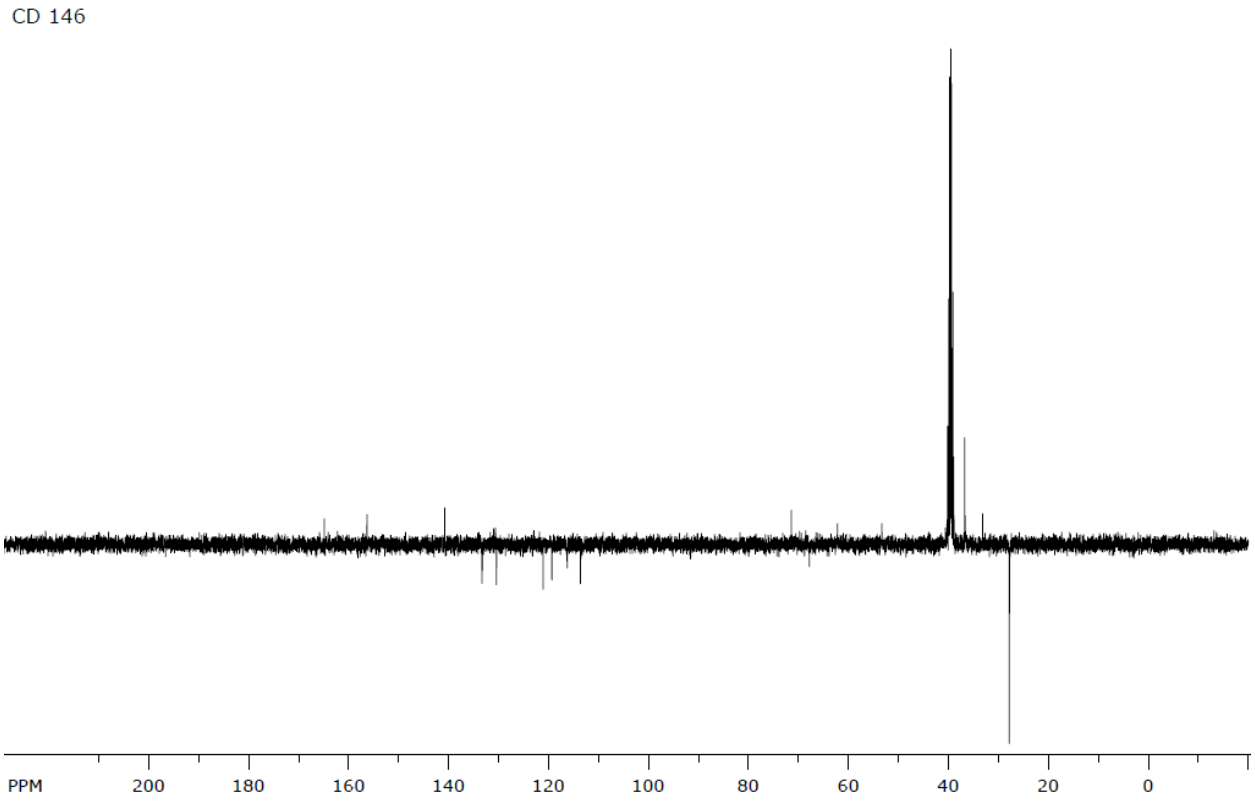
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(naphthalen-2-yl)benzamide (205)



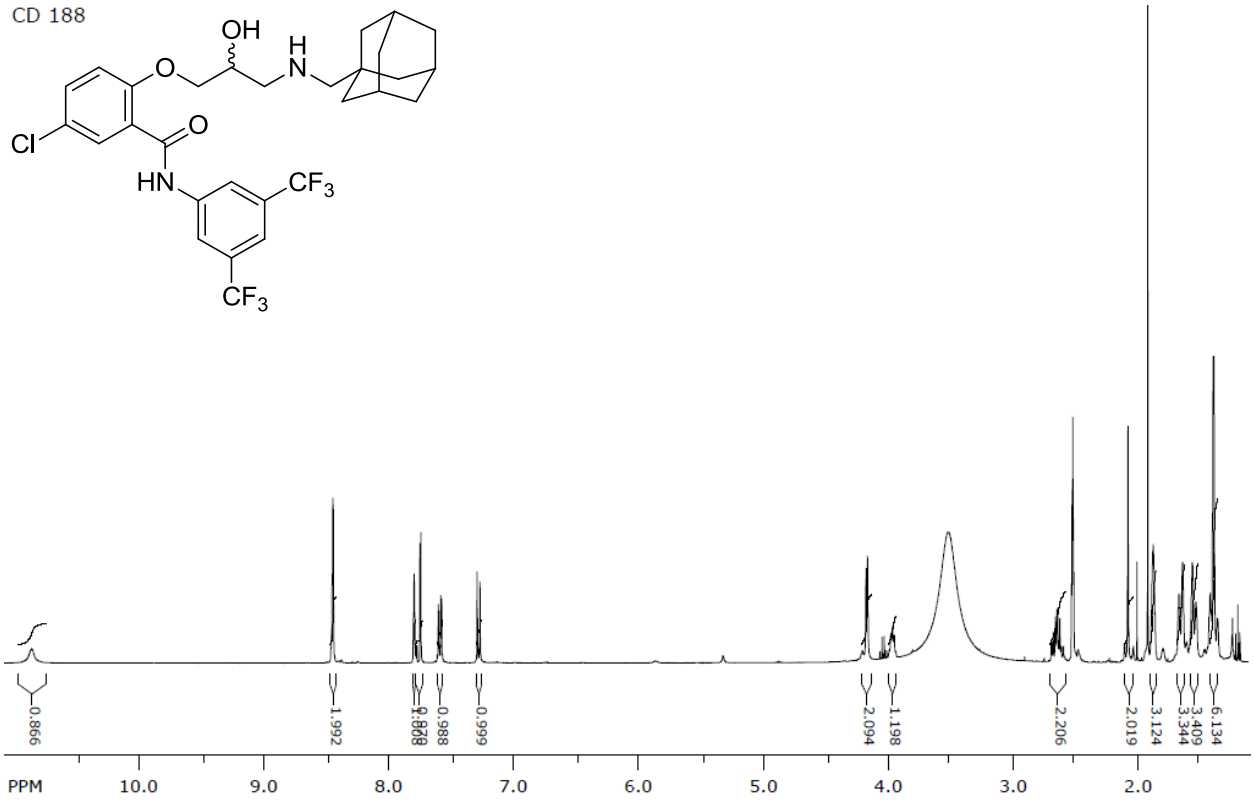


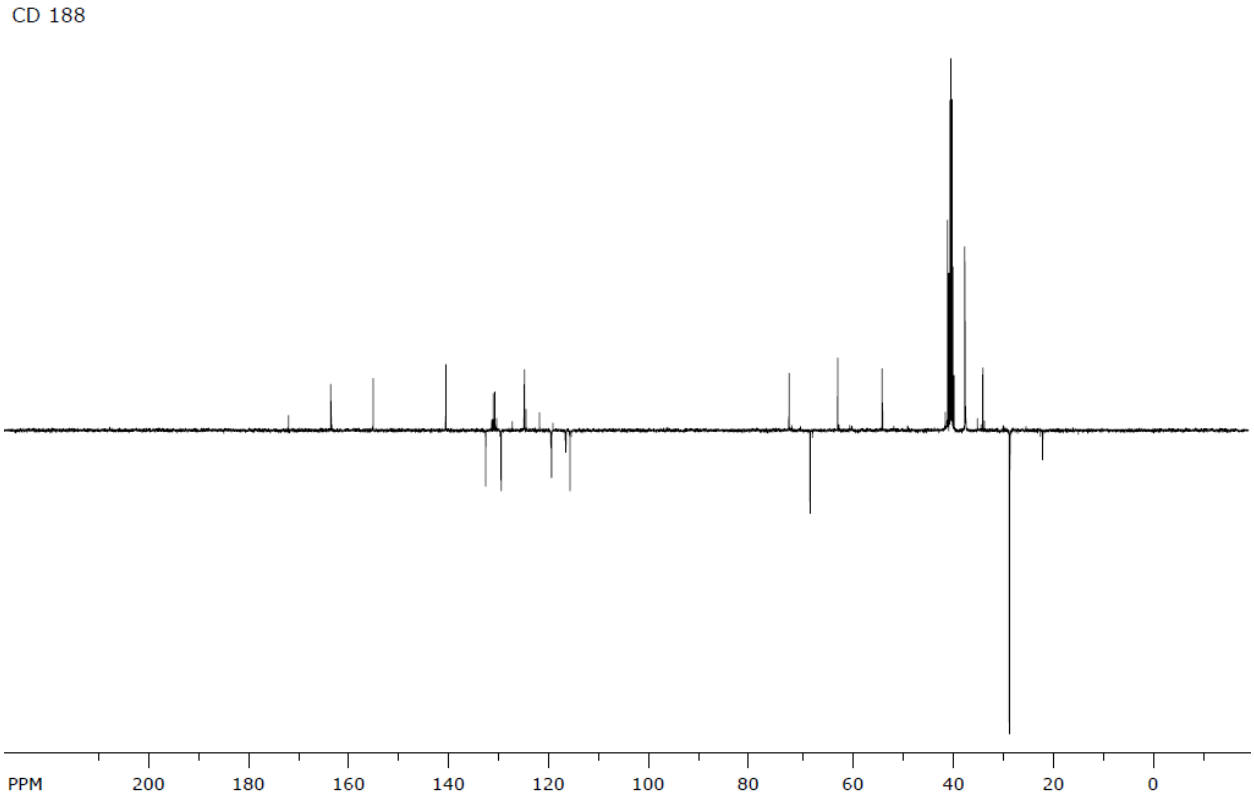
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)benzamide (206**)**



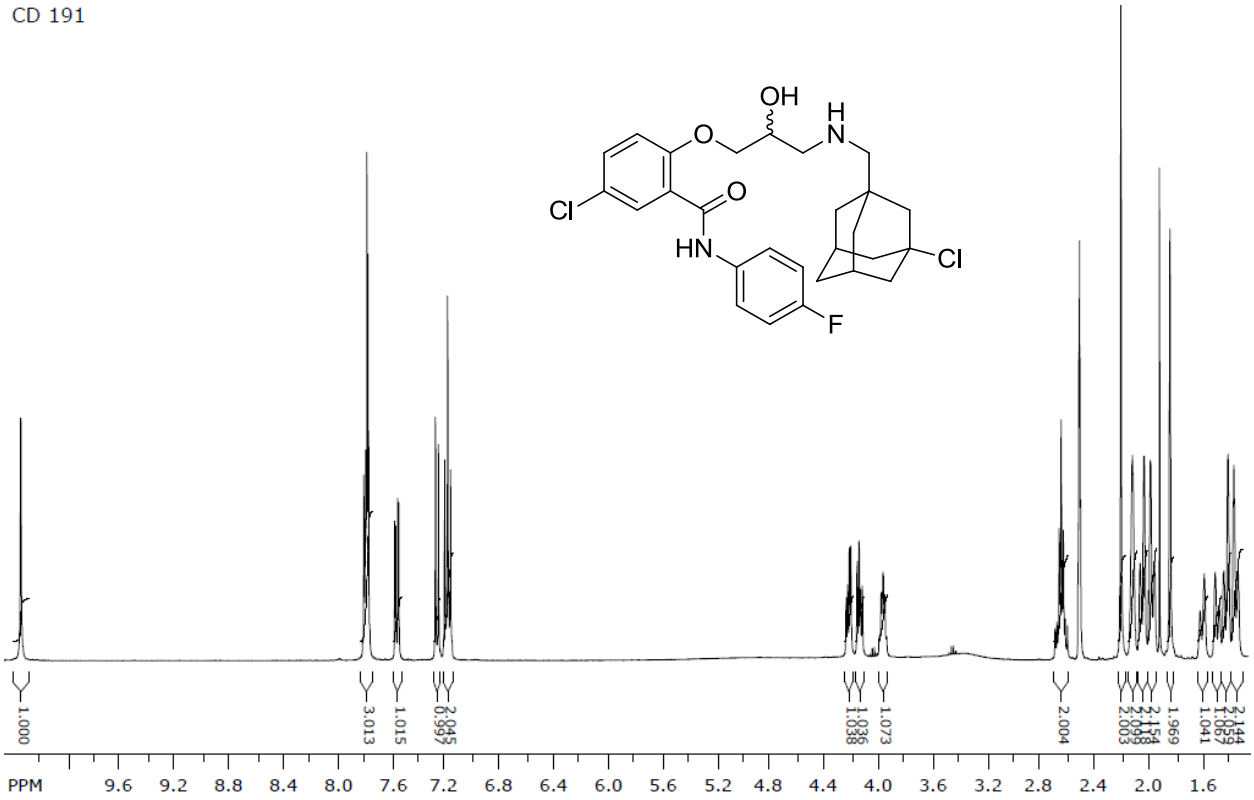


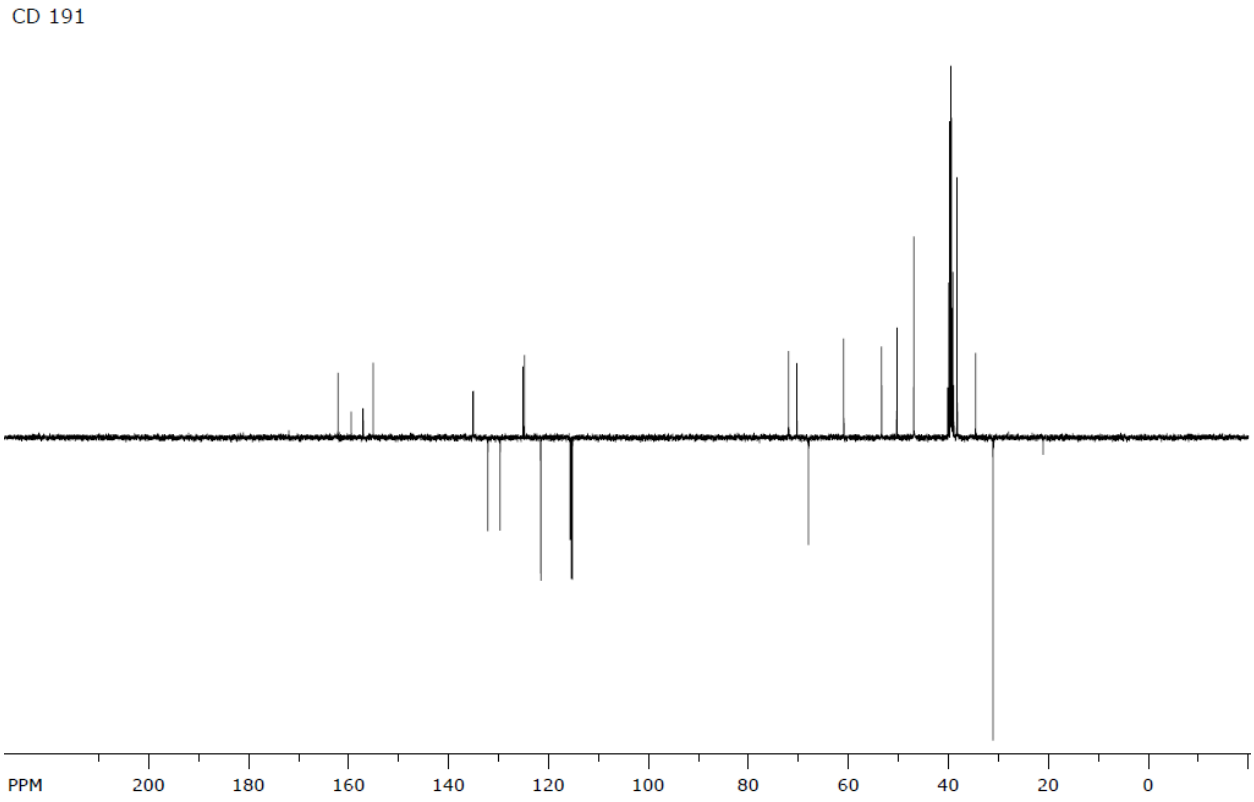
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-chlorobenzamide (207)



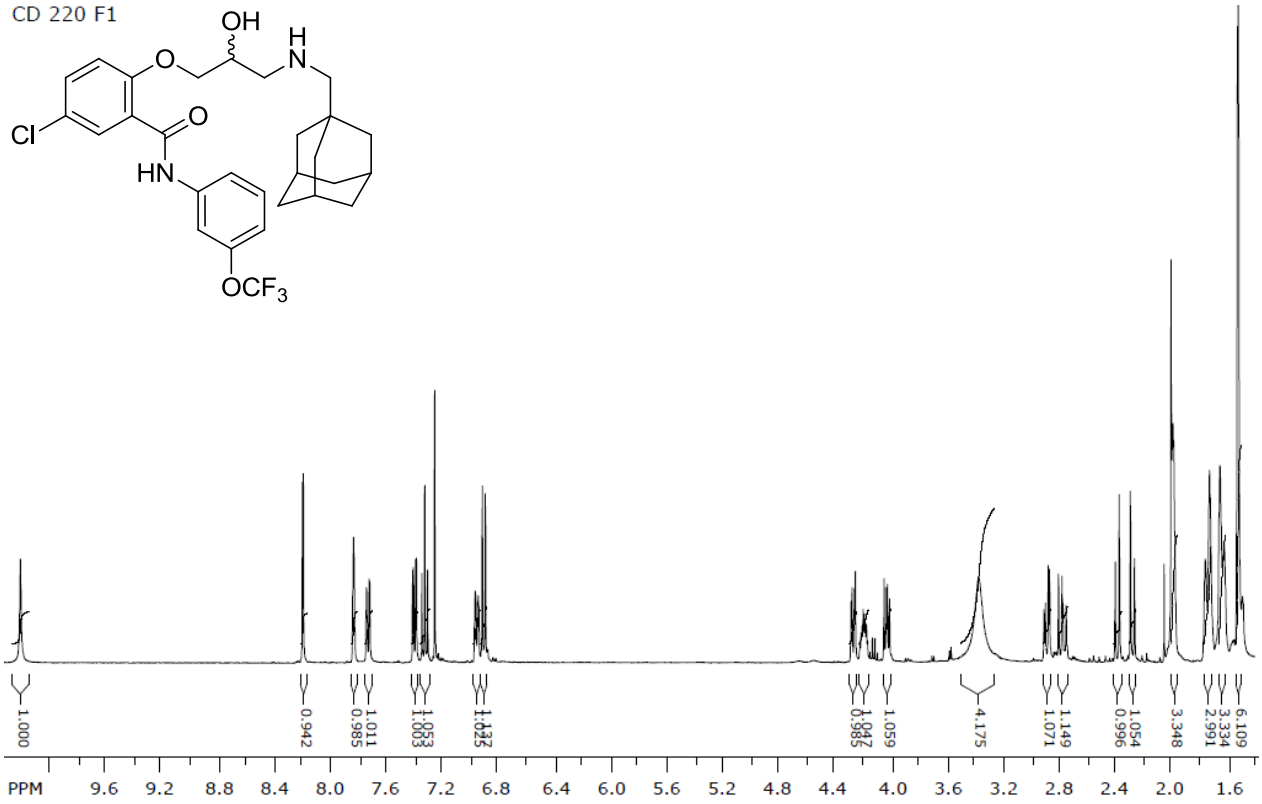


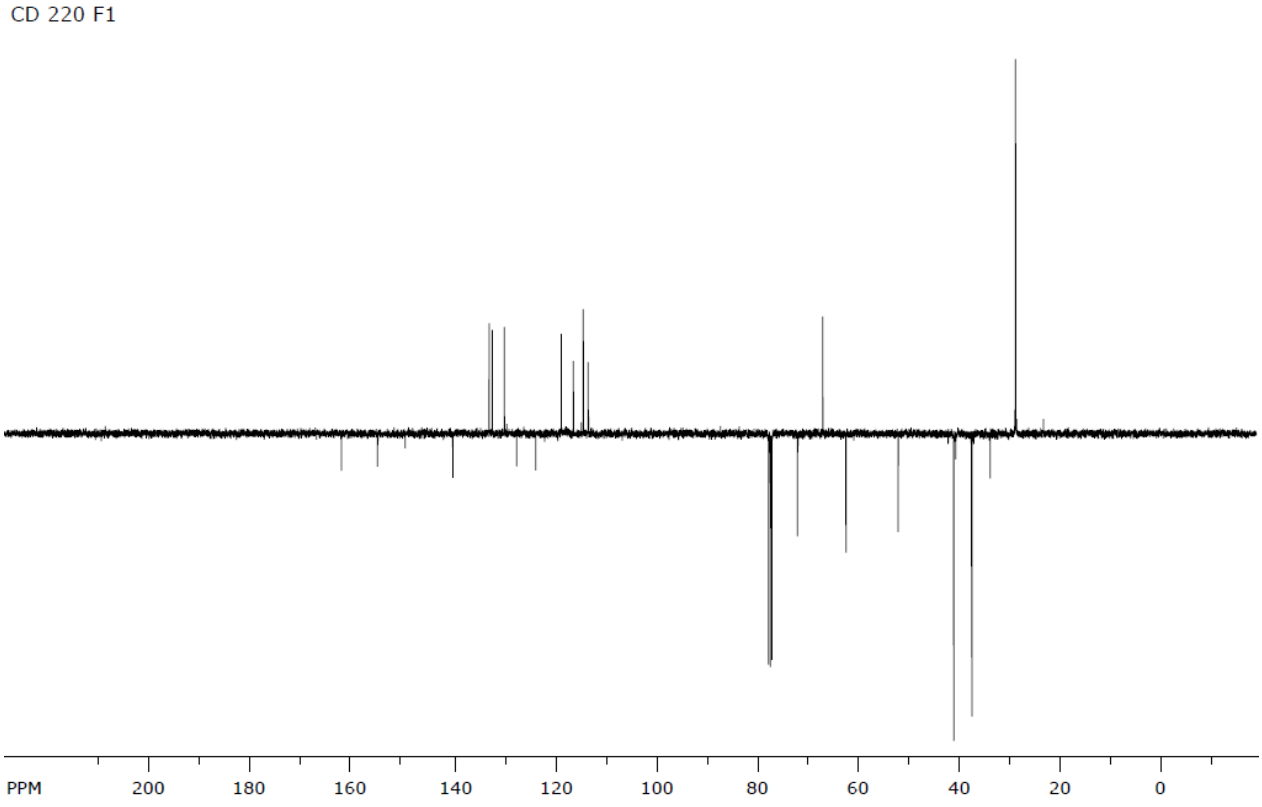
5-chloro-2-(3-(((3-chloroadamantan-1-yl)methyl)amino)-2-hydroxypropoxy)-*N*-(4-fluorophenyl)benzamide (208)



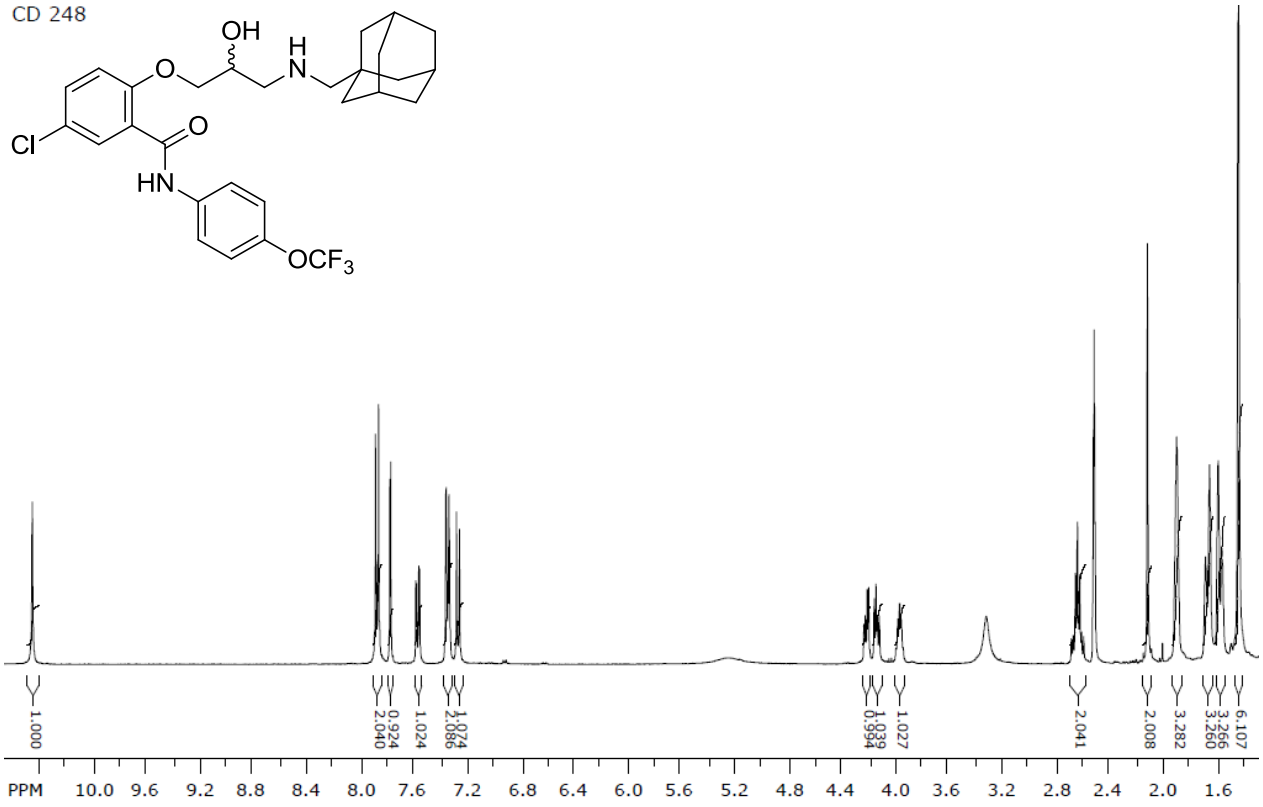


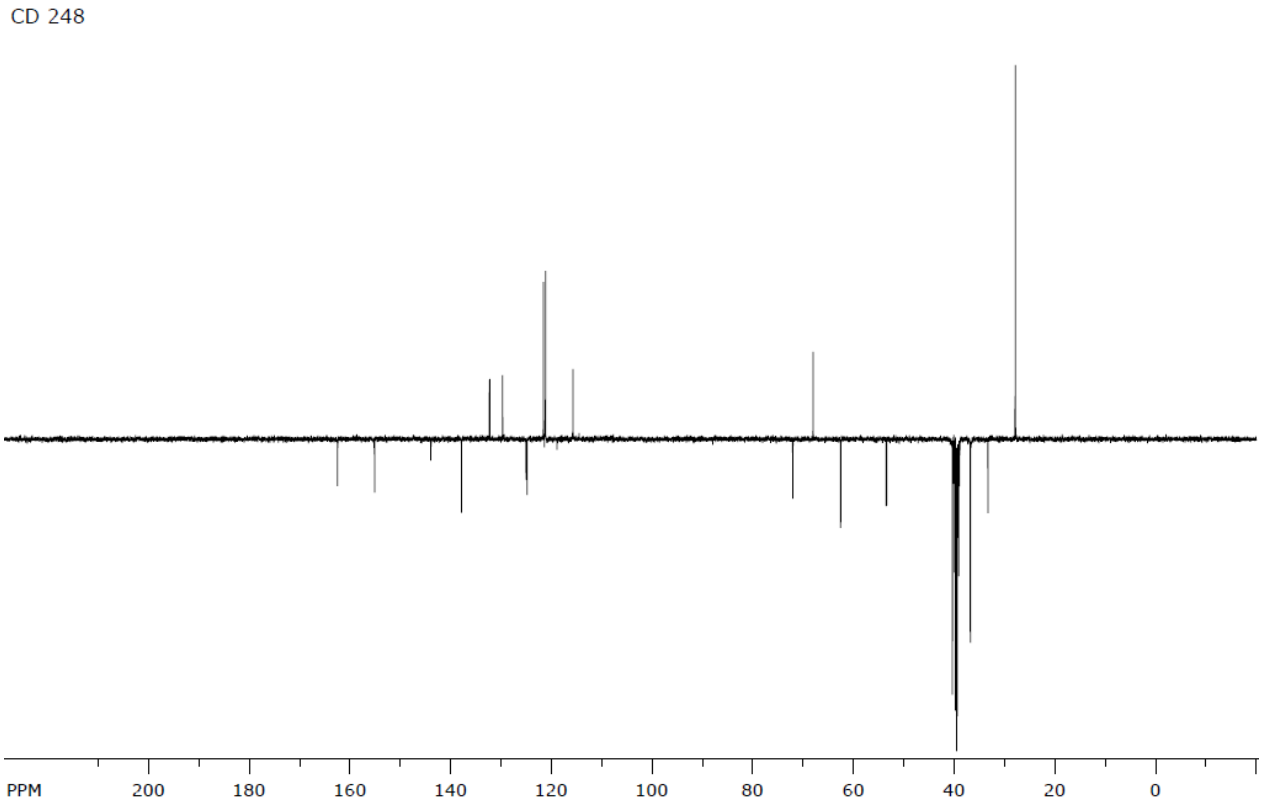
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethoxy)phenyl)benzamide (209)



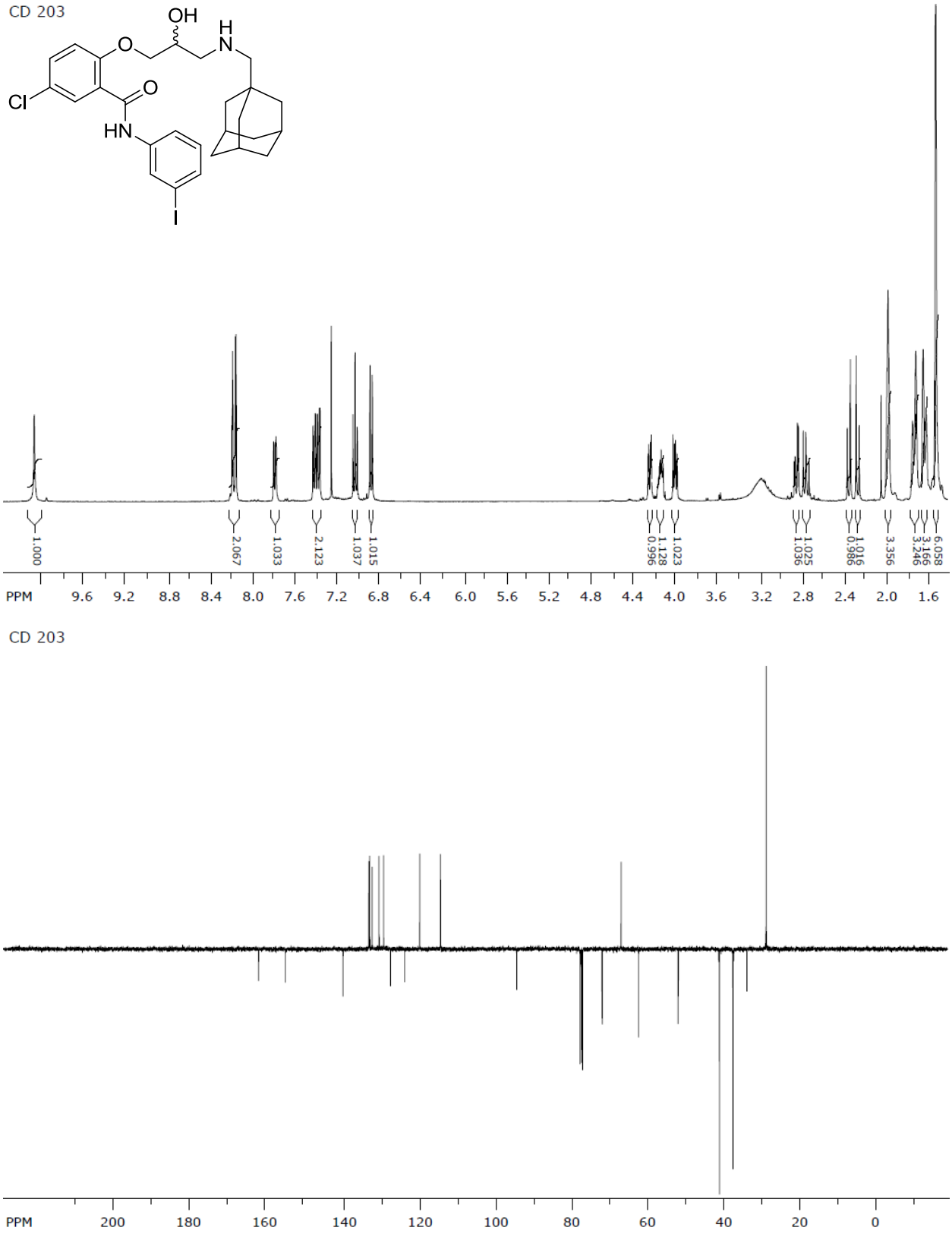


2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(4-(trifluoromethoxy)phenyl)benzamide (210**)**

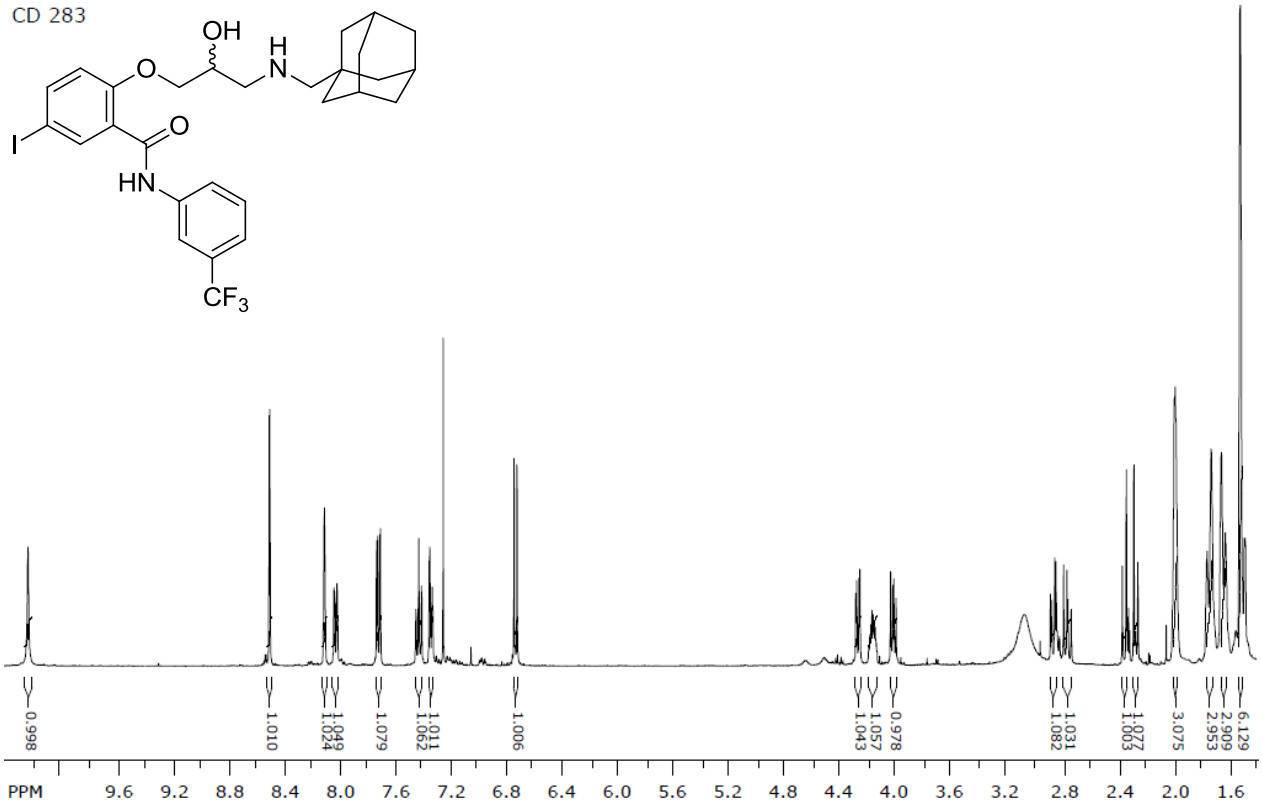


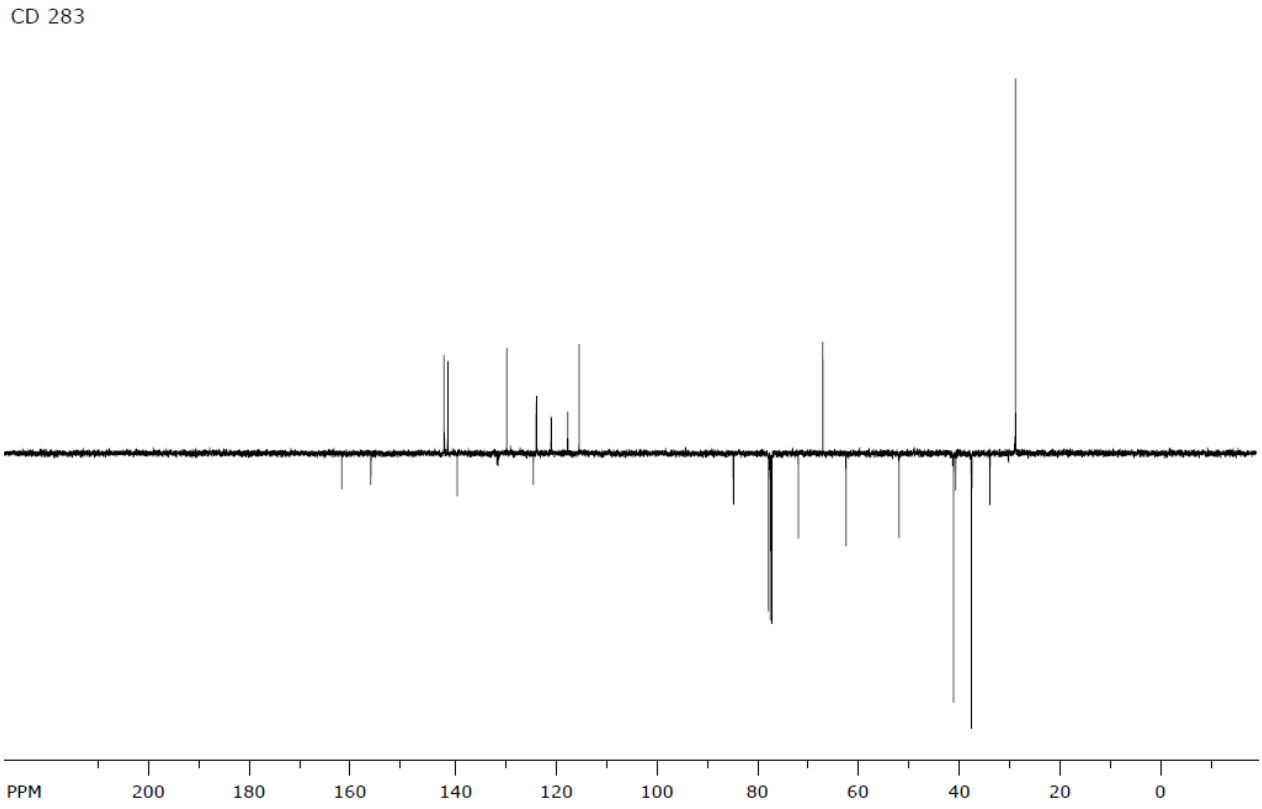


2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3-iodophenyl)benzamide (211**)**

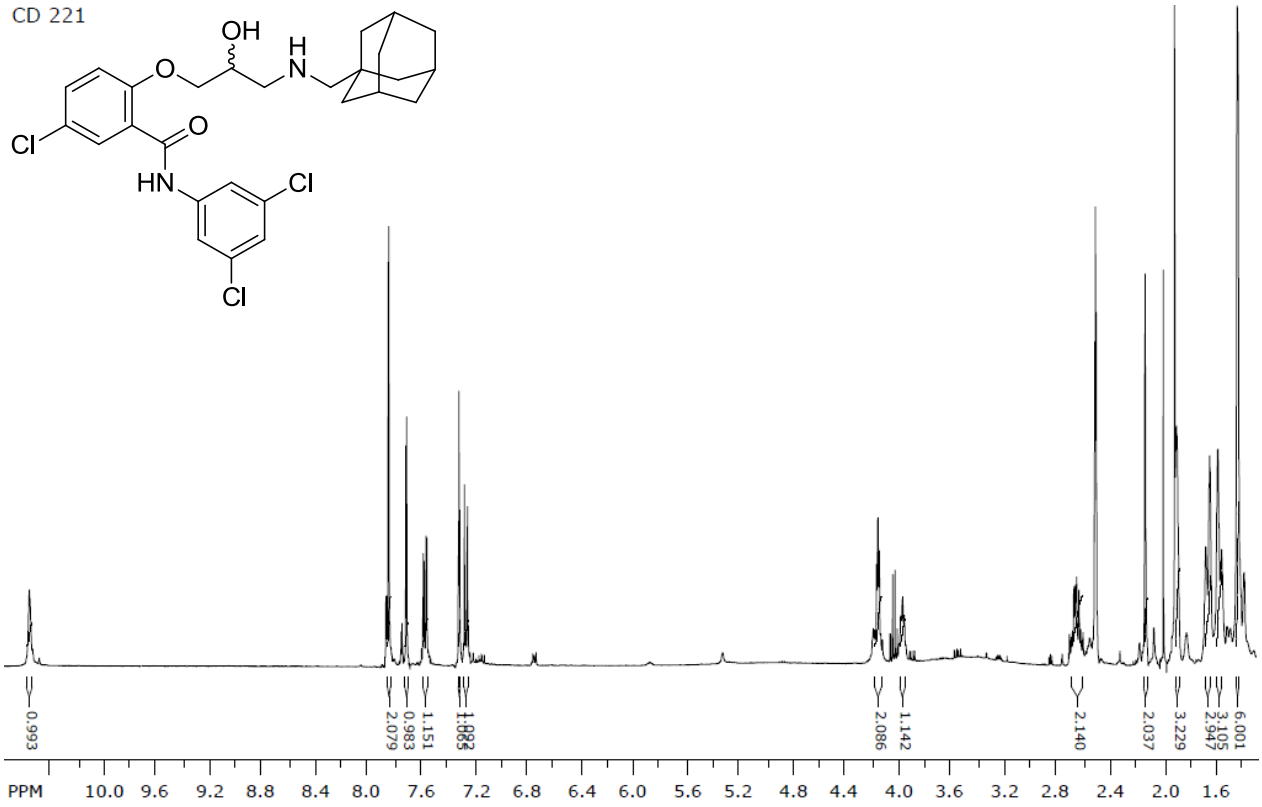


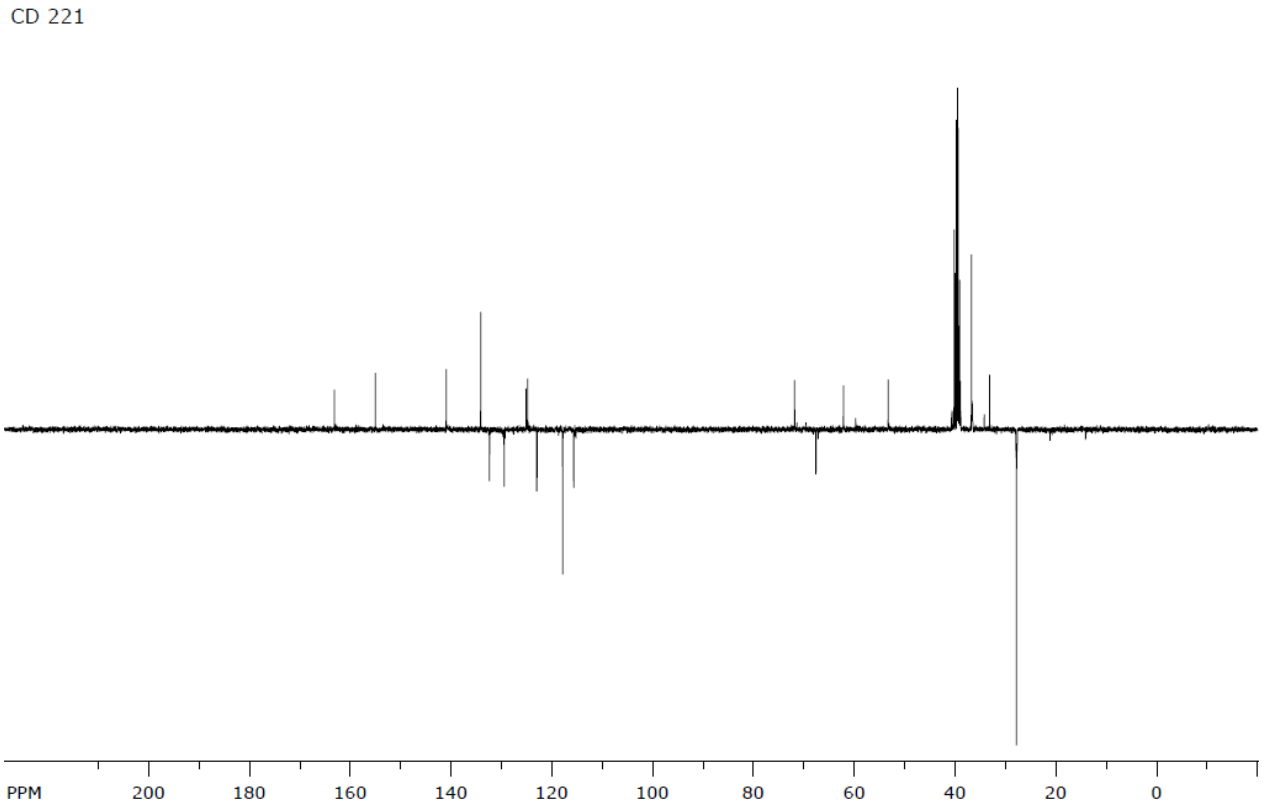
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-iodo-*N*-(3-(trifluoromethyl)phenyl)benzamide (212)



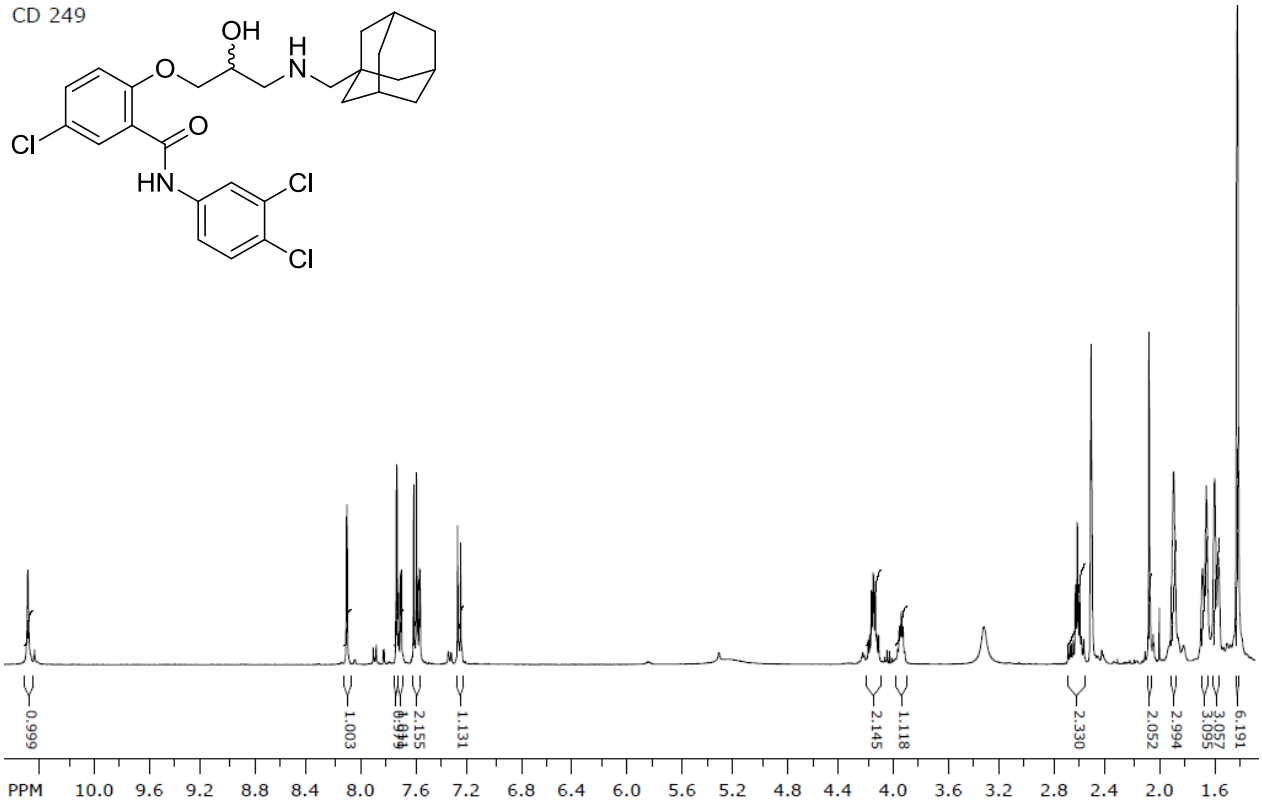


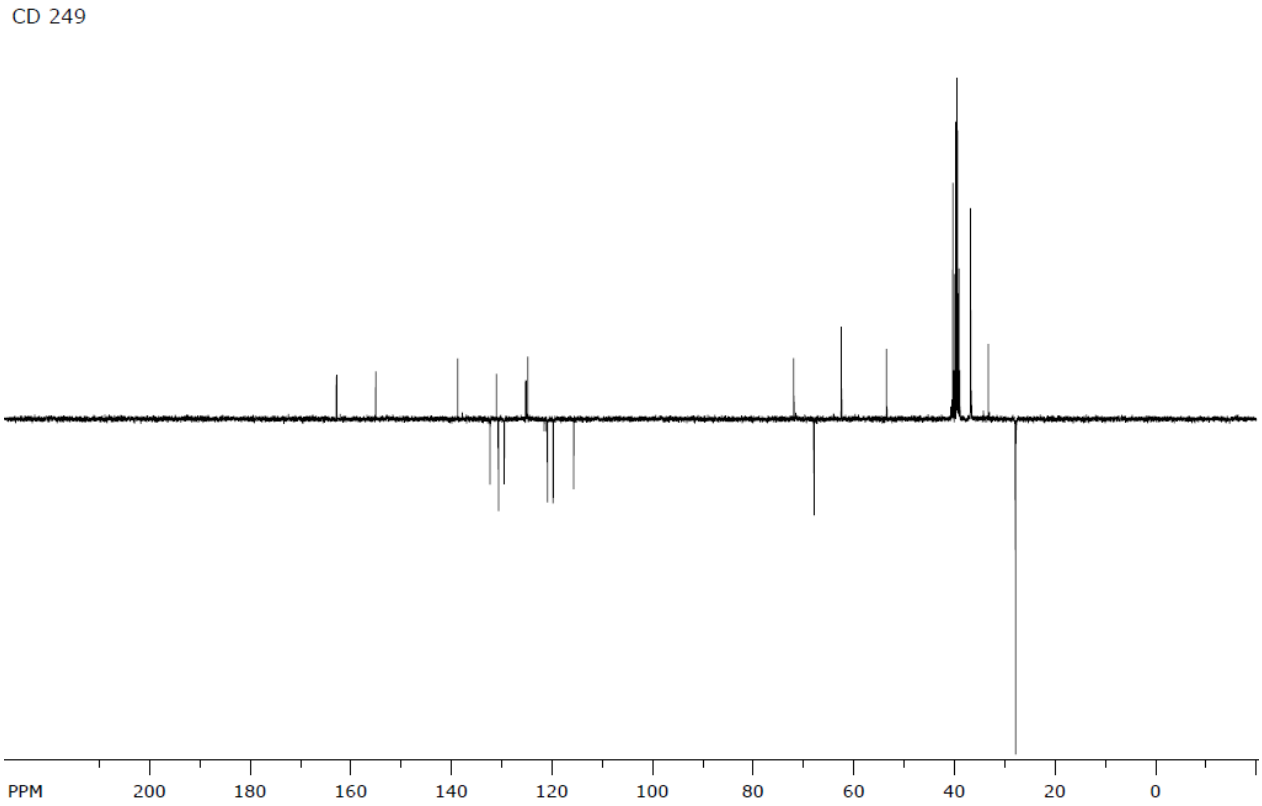
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3,5-dichlorophenyl)benzamide (213)



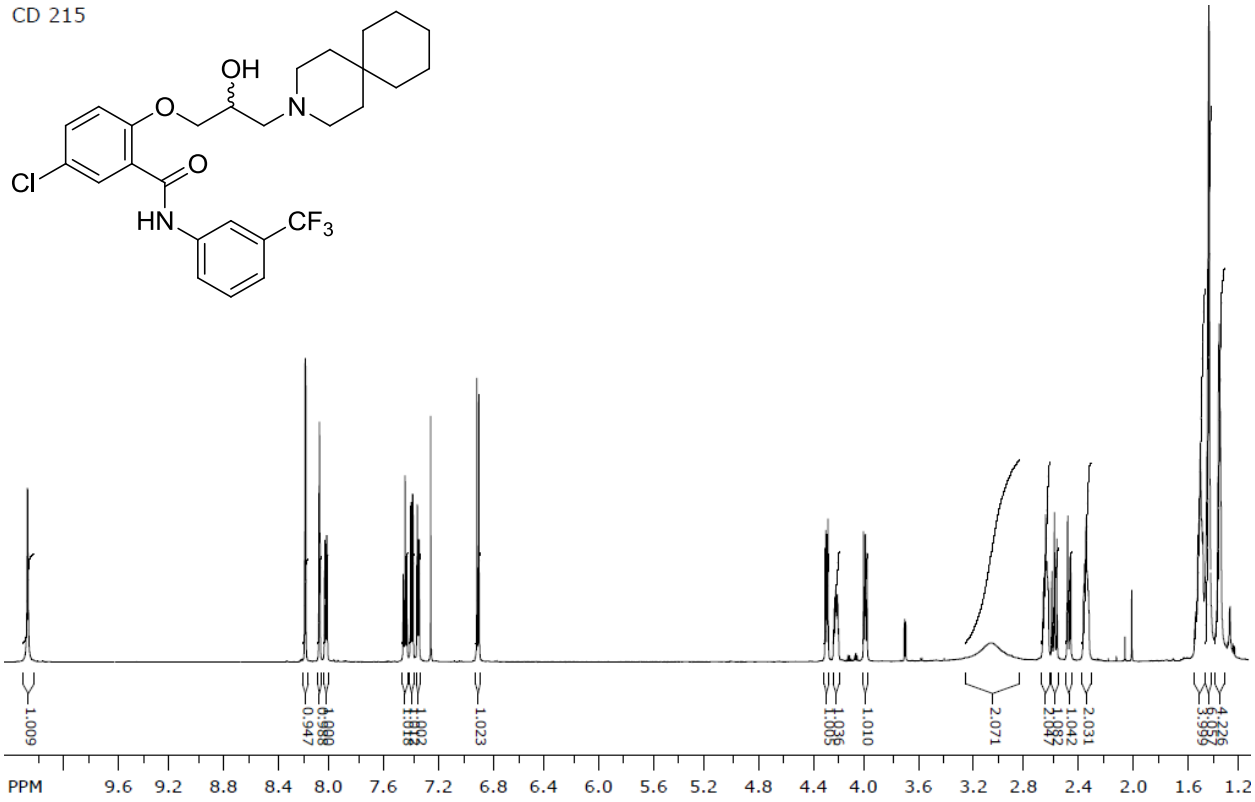


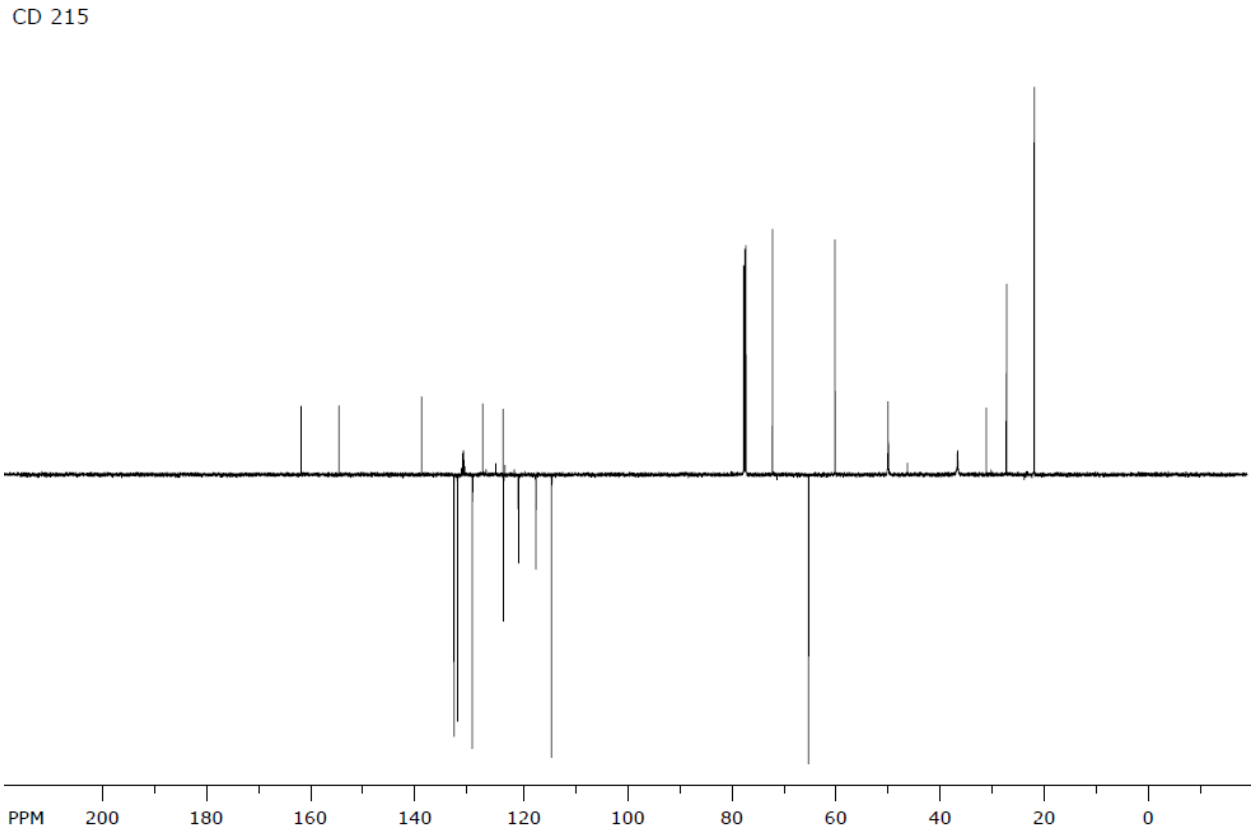
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3,4-dichlorophenyl)benzamide (214)



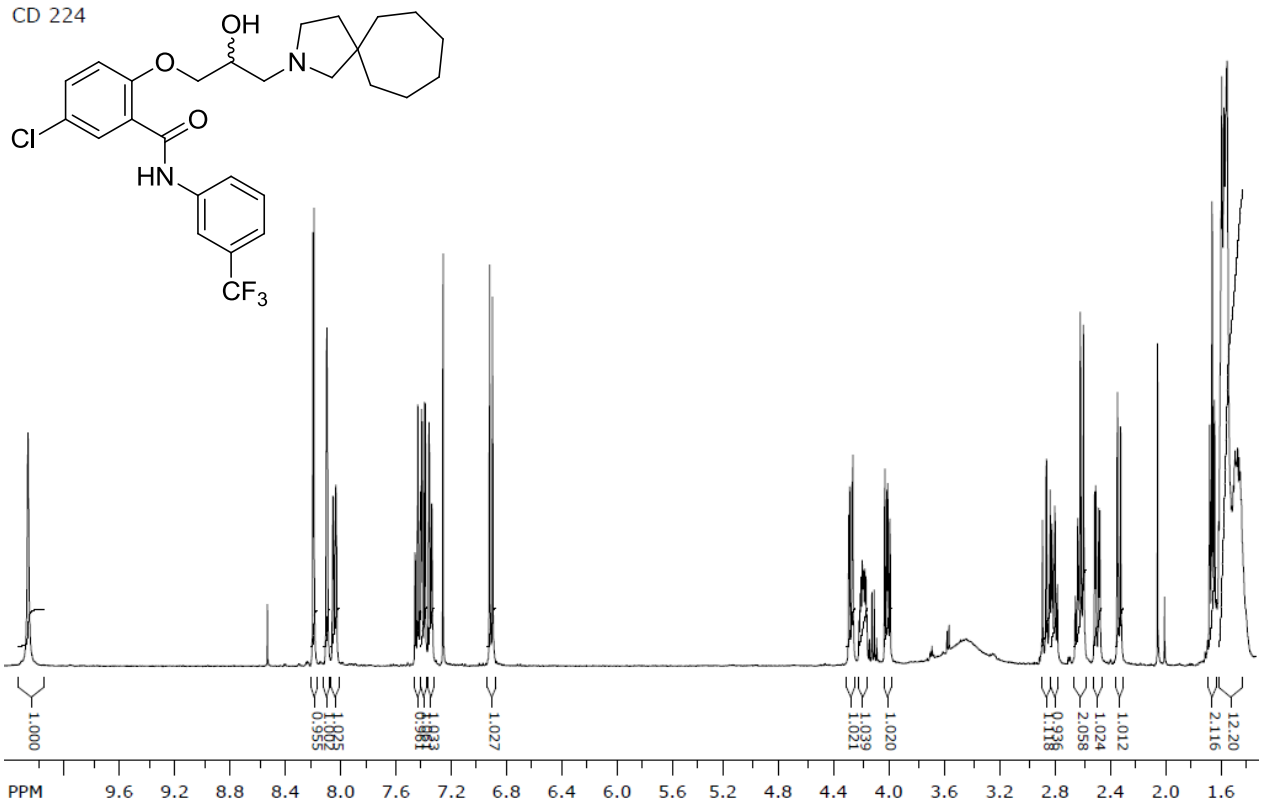


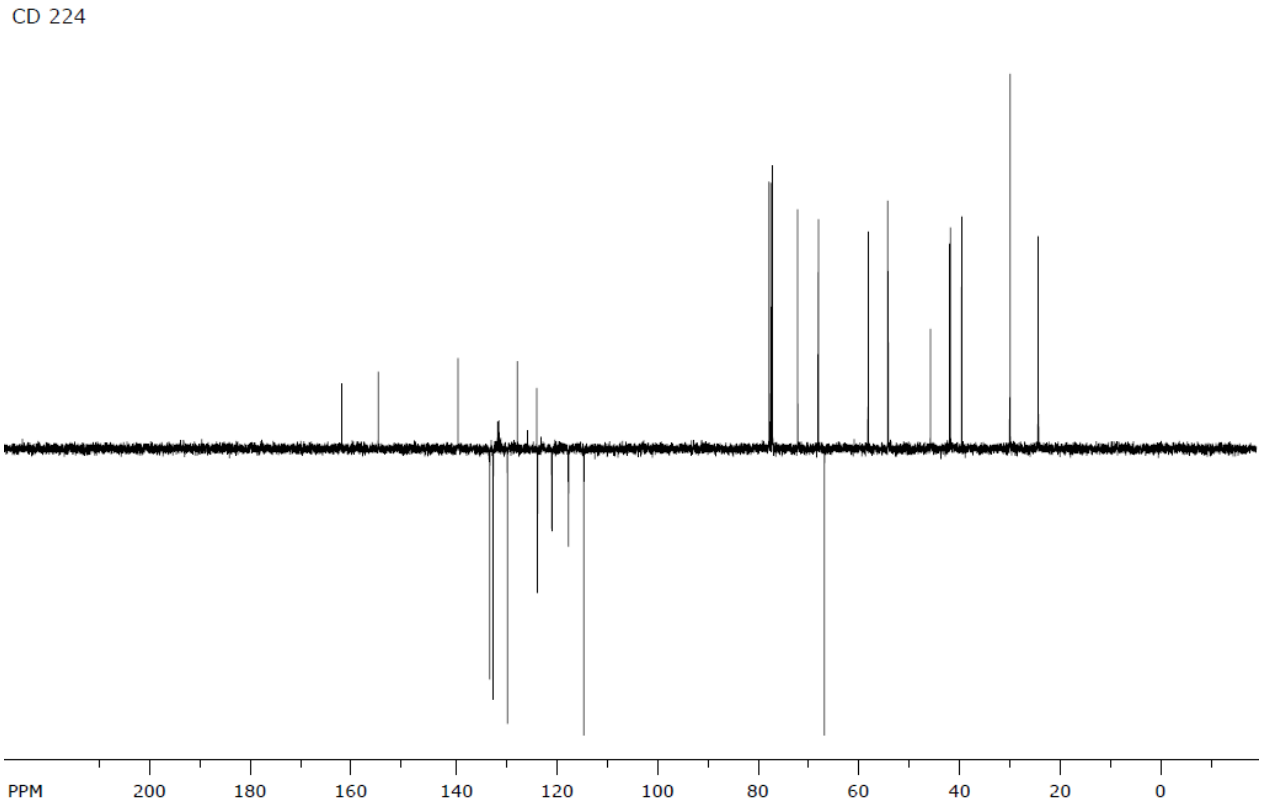
5-chloro-2-(2-hydroxy-3-(3-azaspiro[5.5]undecan-3-yl)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (215)



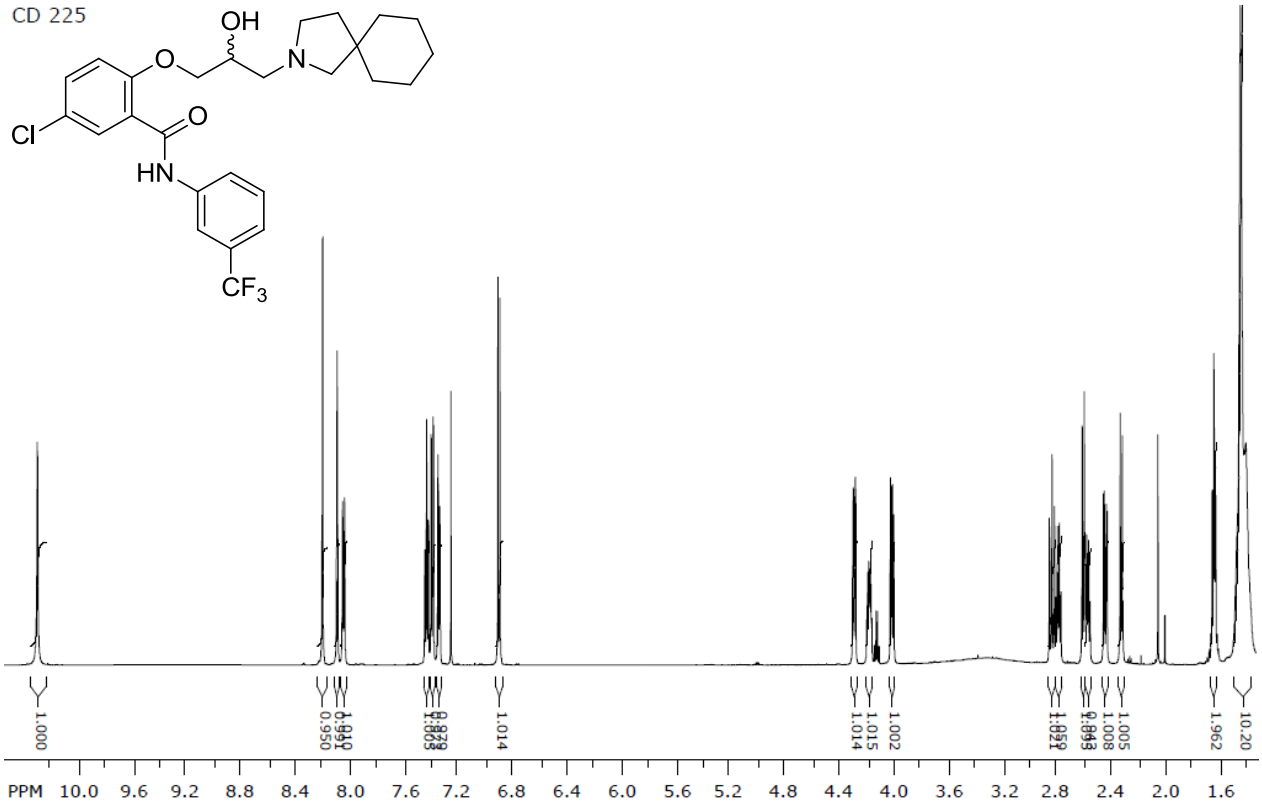


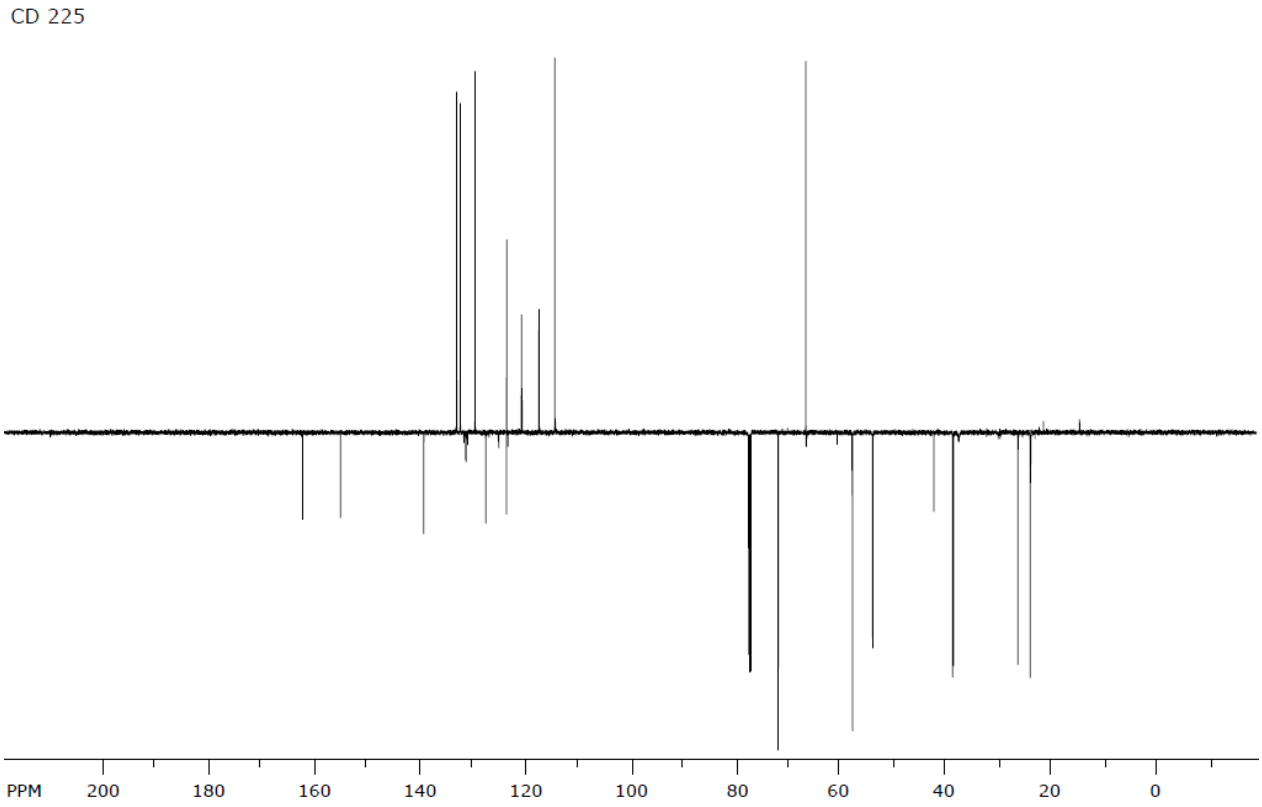
5-chloro-2-(2-hydroxy-3-(2-azaspiro[4.6]undecan-2-yl)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (216)



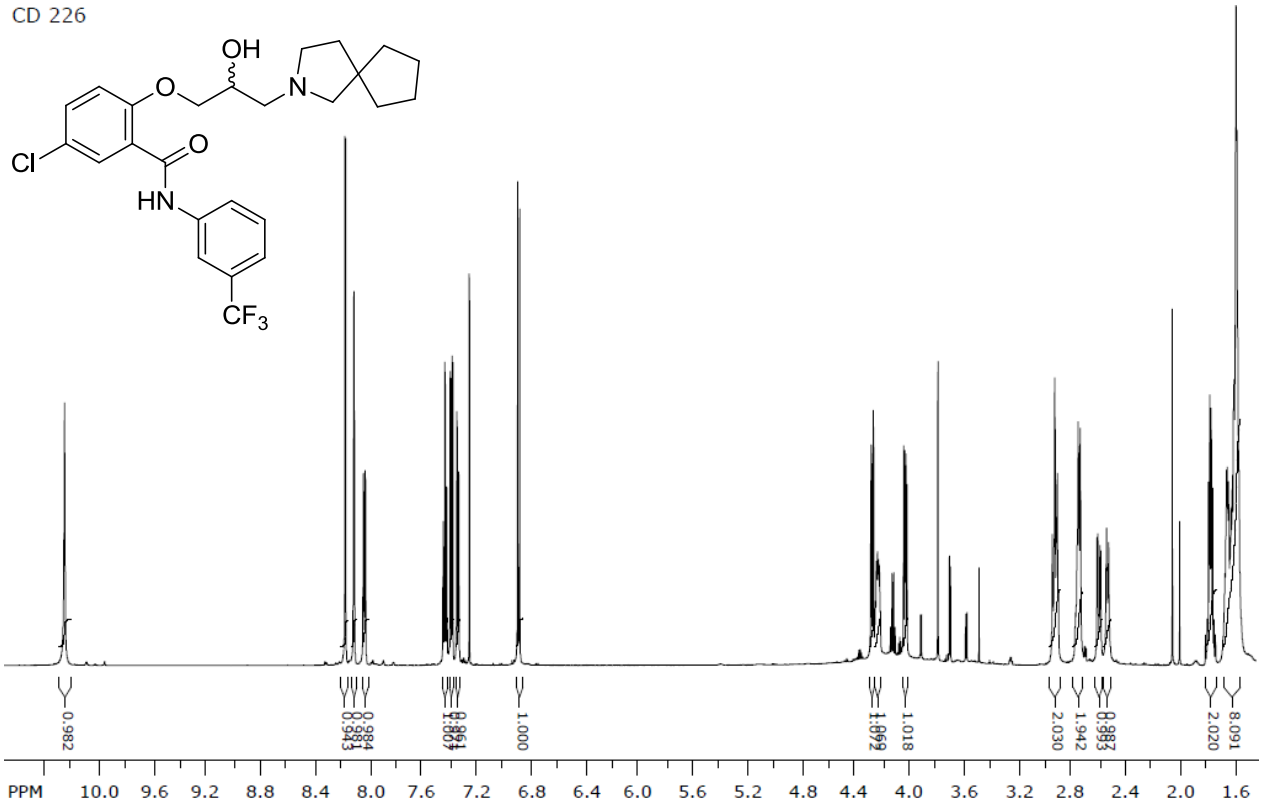


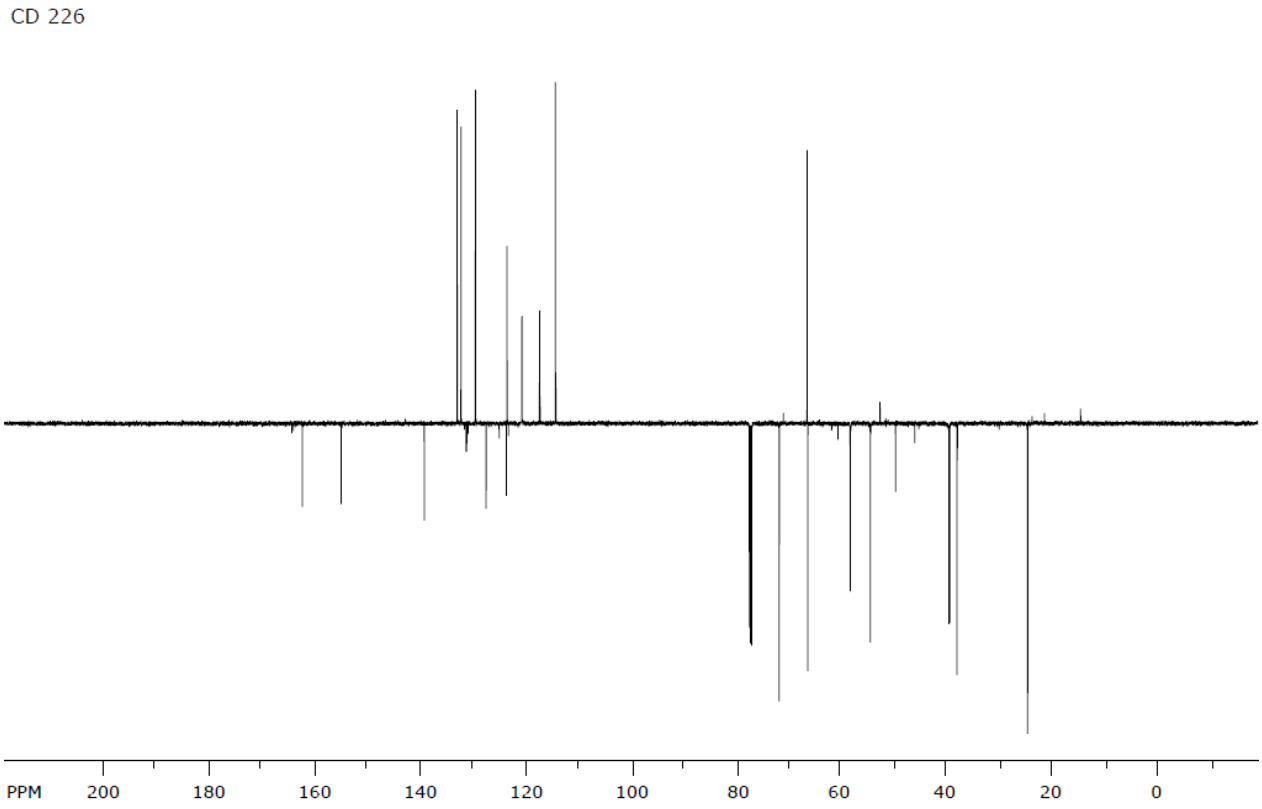
5-chloro-2-(2-hydroxy-3-(2-azaspiro[4.5]decan-2-yl)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (217)



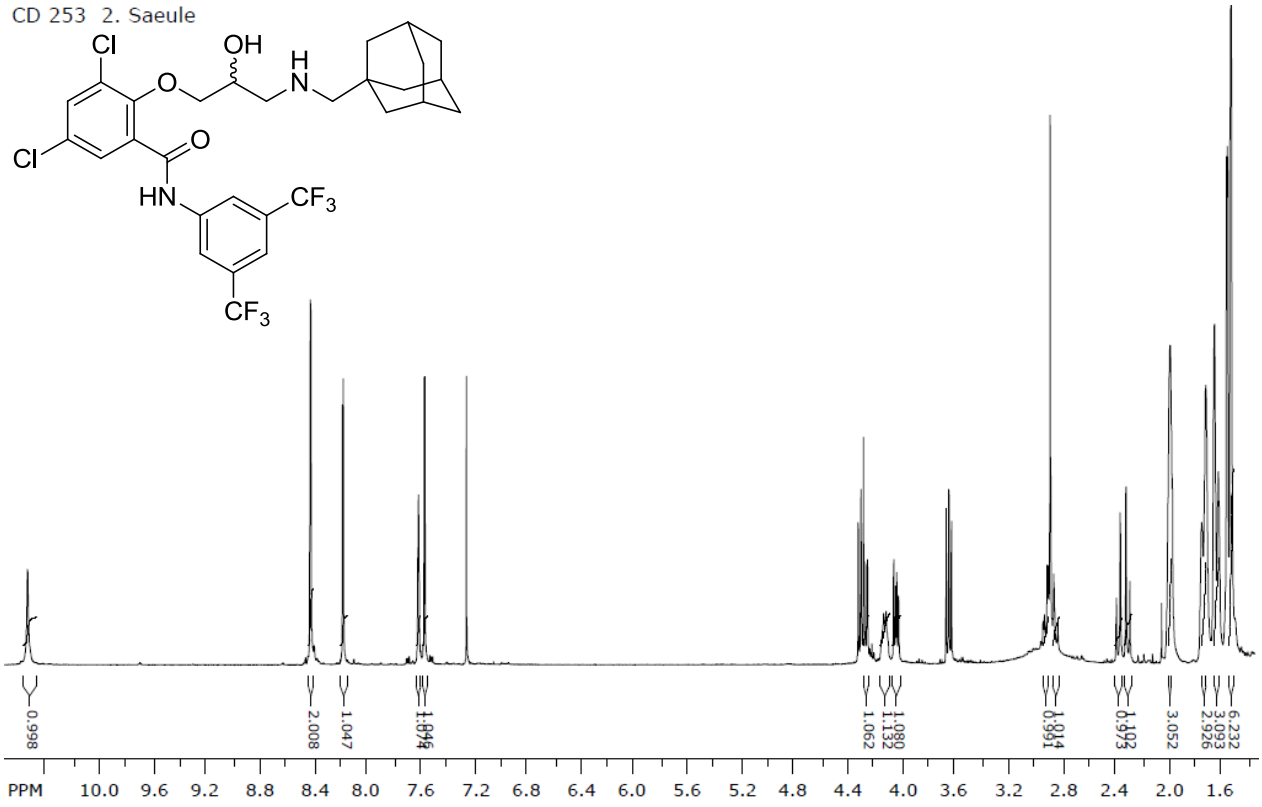


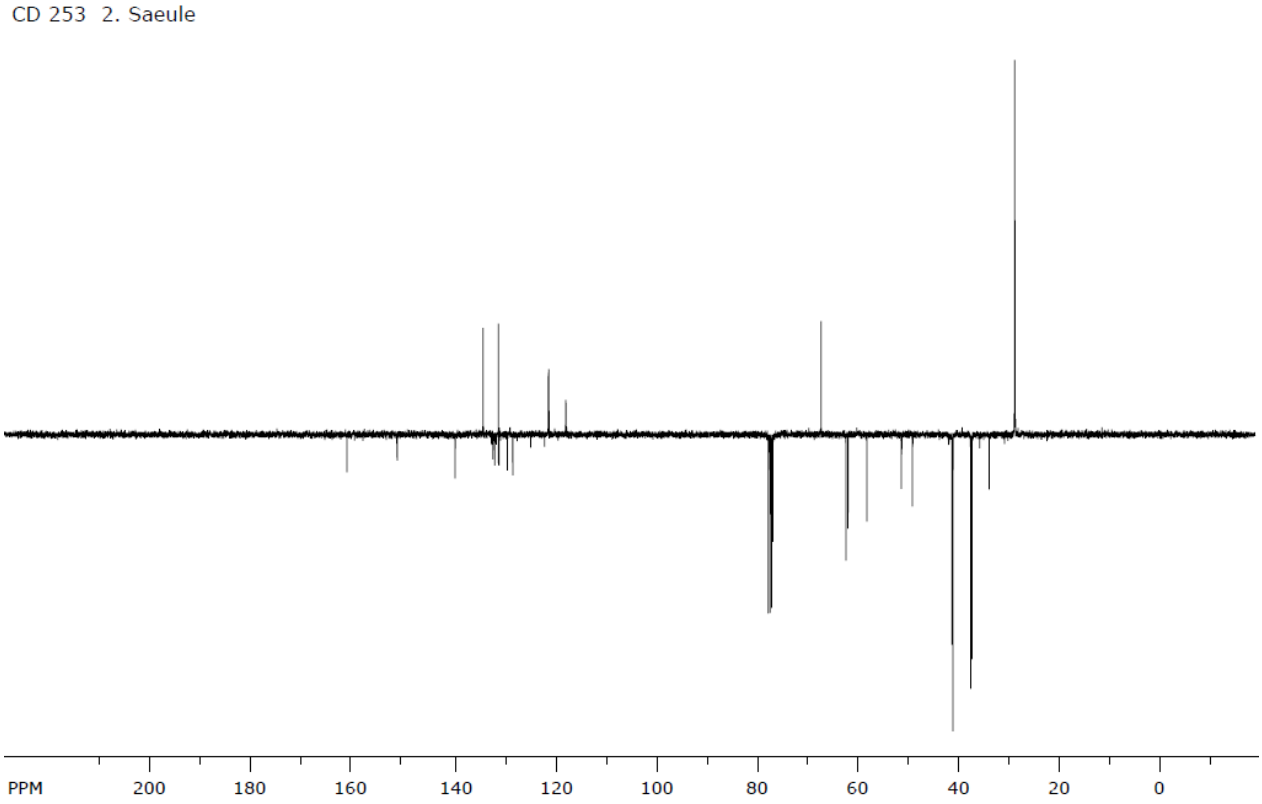
5-chloro-2-(2-hydroxy-3-(2-azaspiro[4.4]nonan-2-yl)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (218)



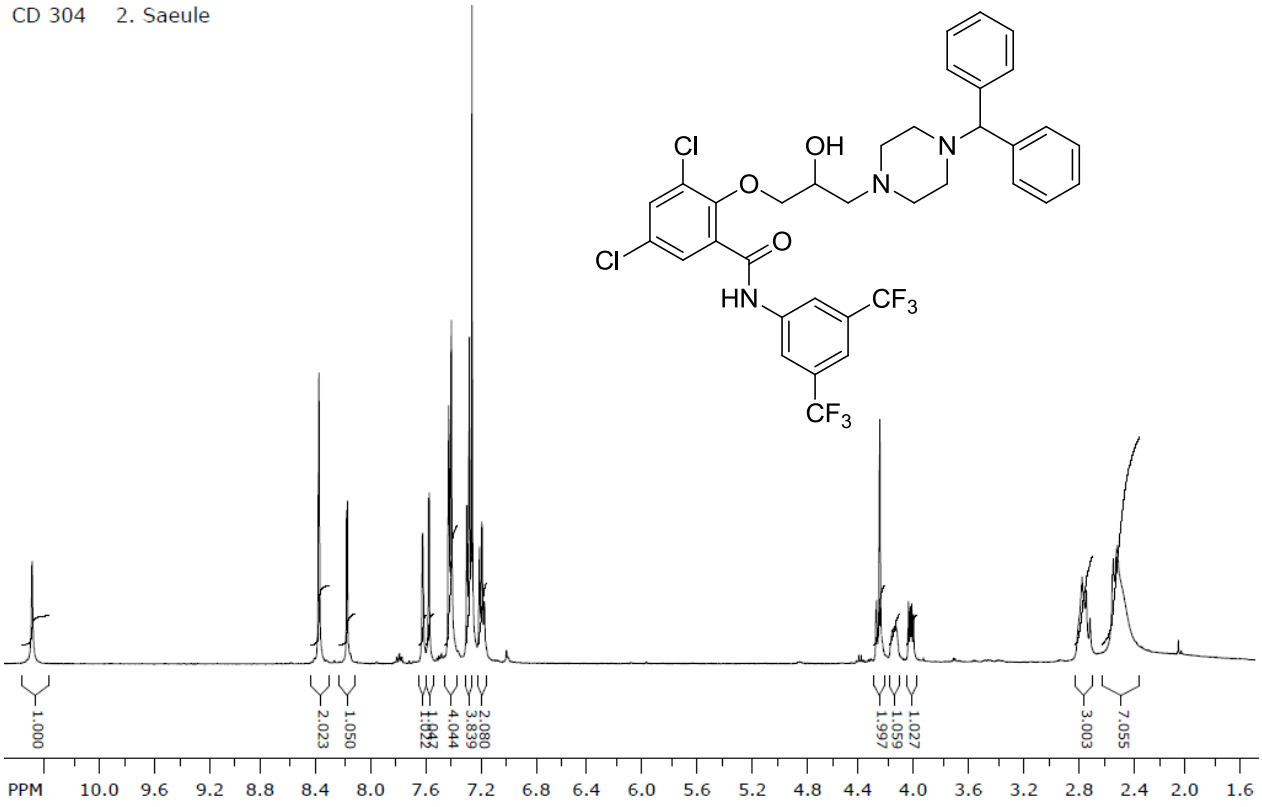


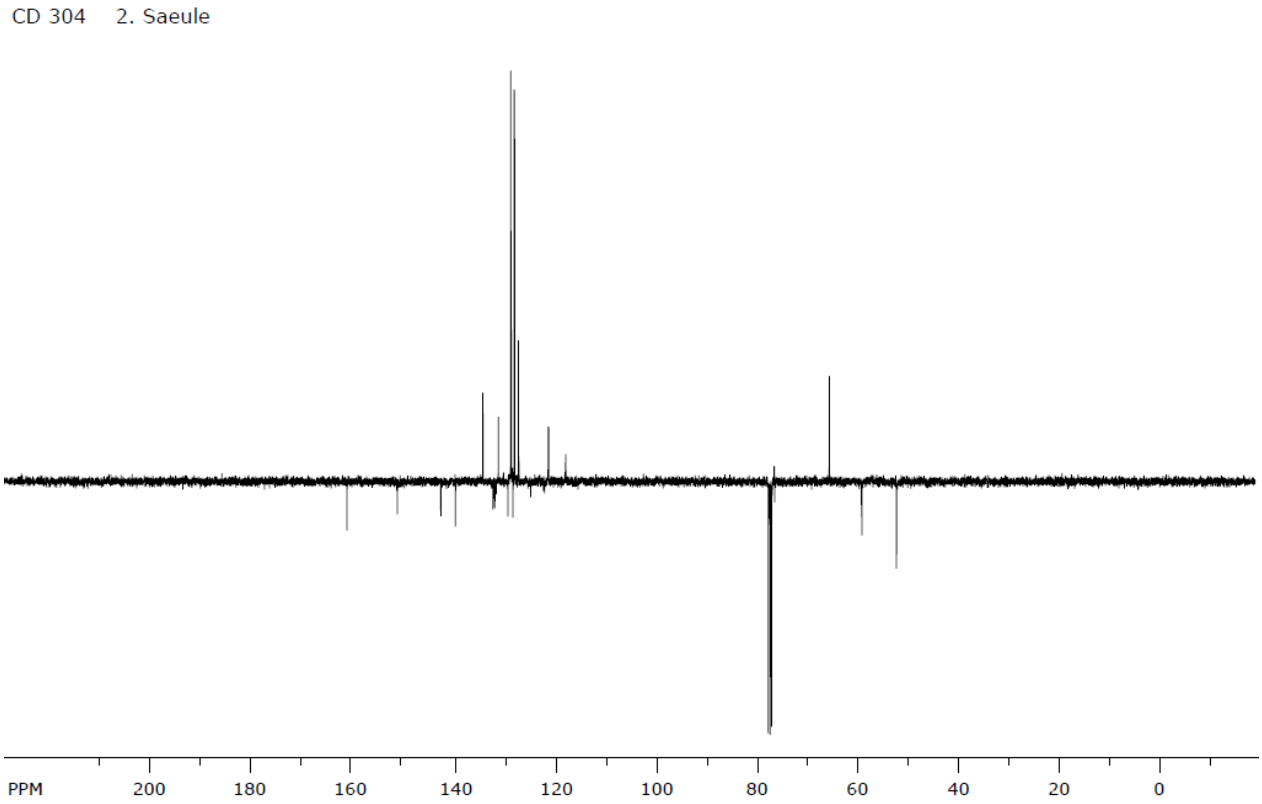
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)-3,5-dichlorobenzamide (219)



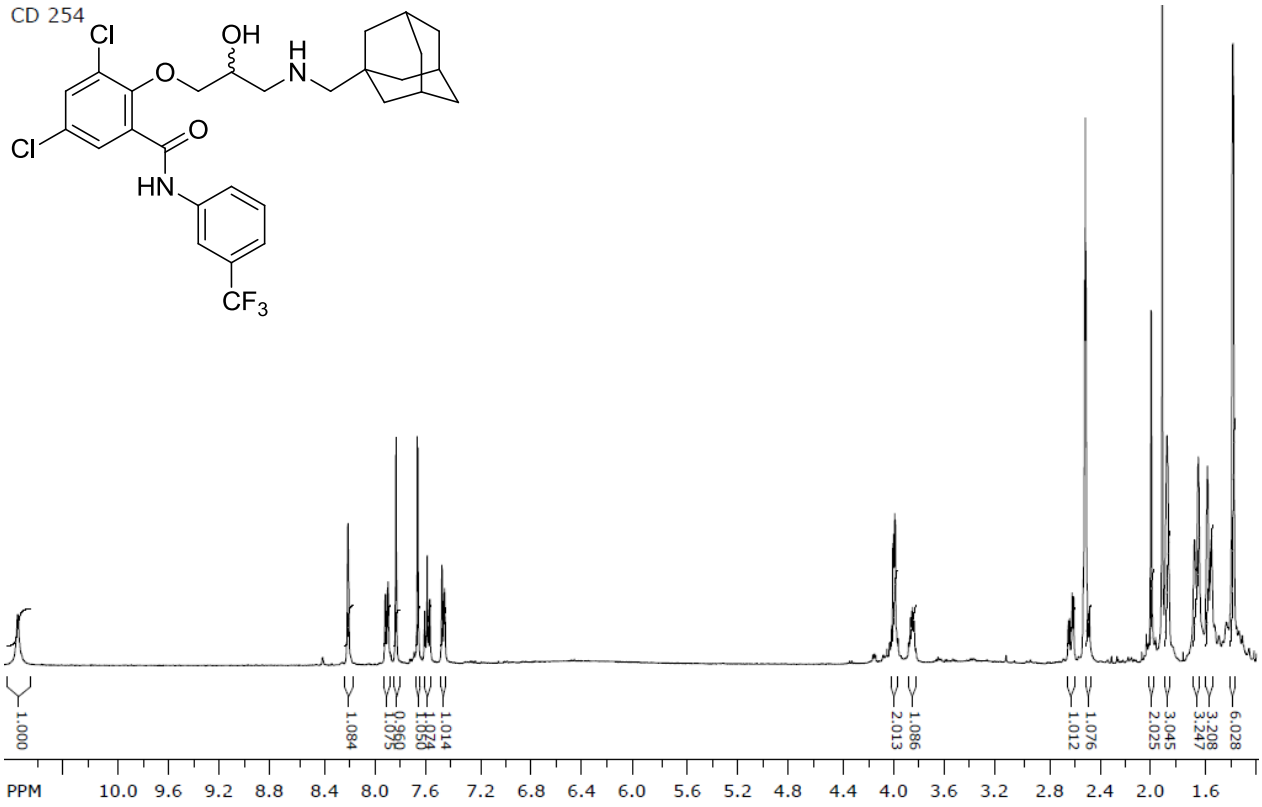


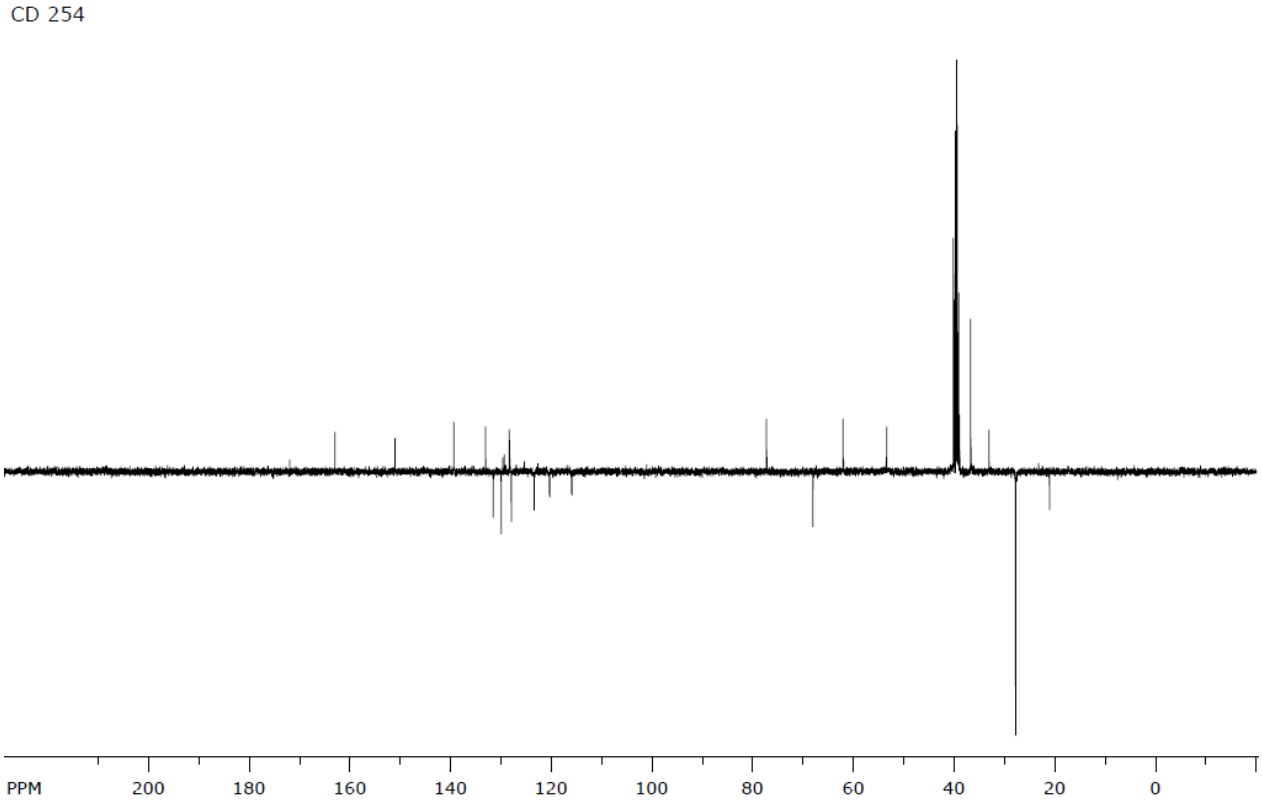
2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)-3,5-dichlorobenzamide (220)



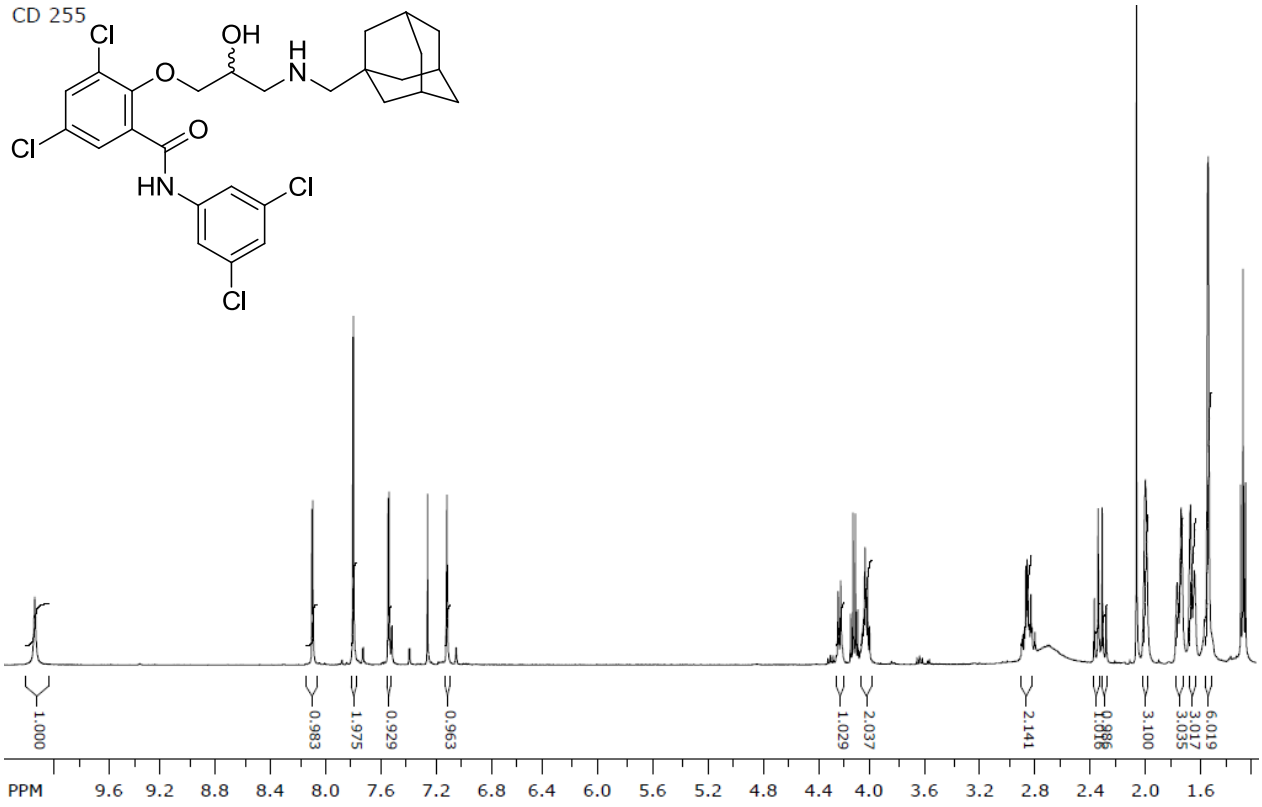


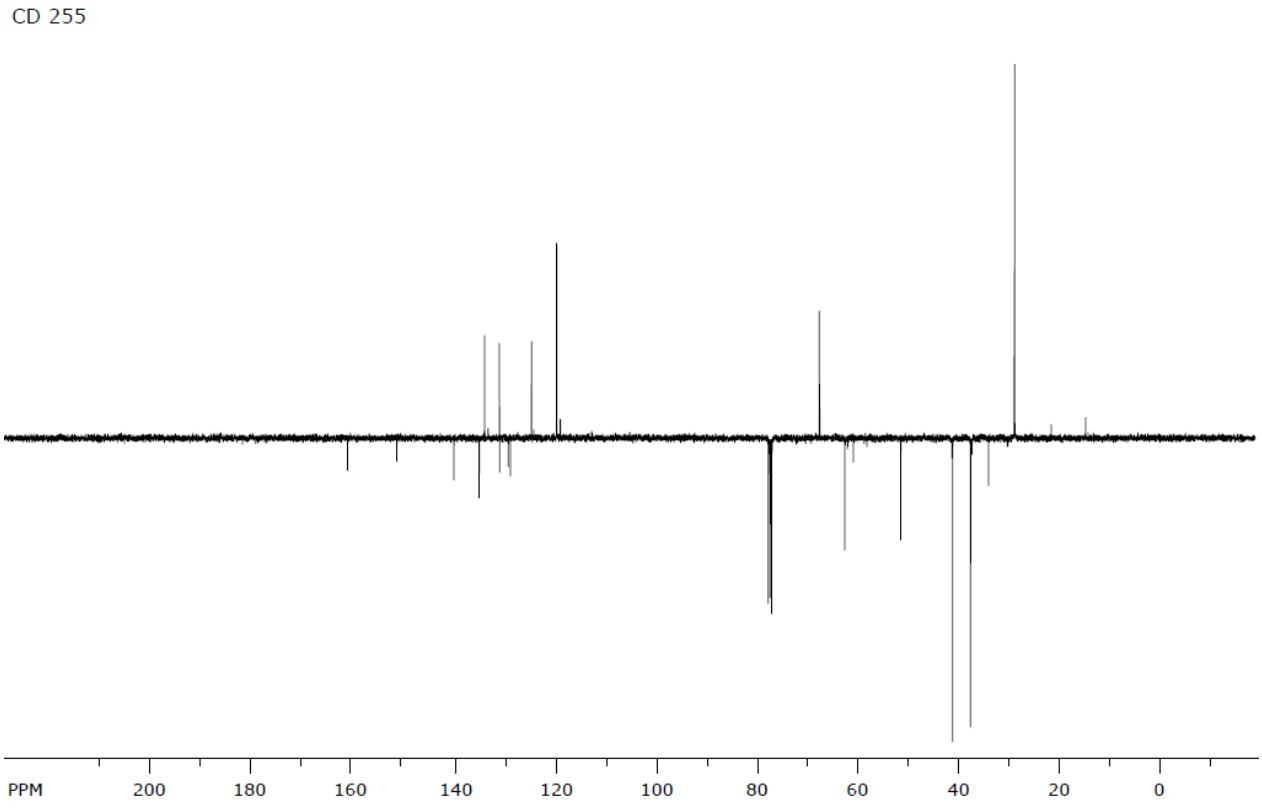
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-3,5-dichloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (221)



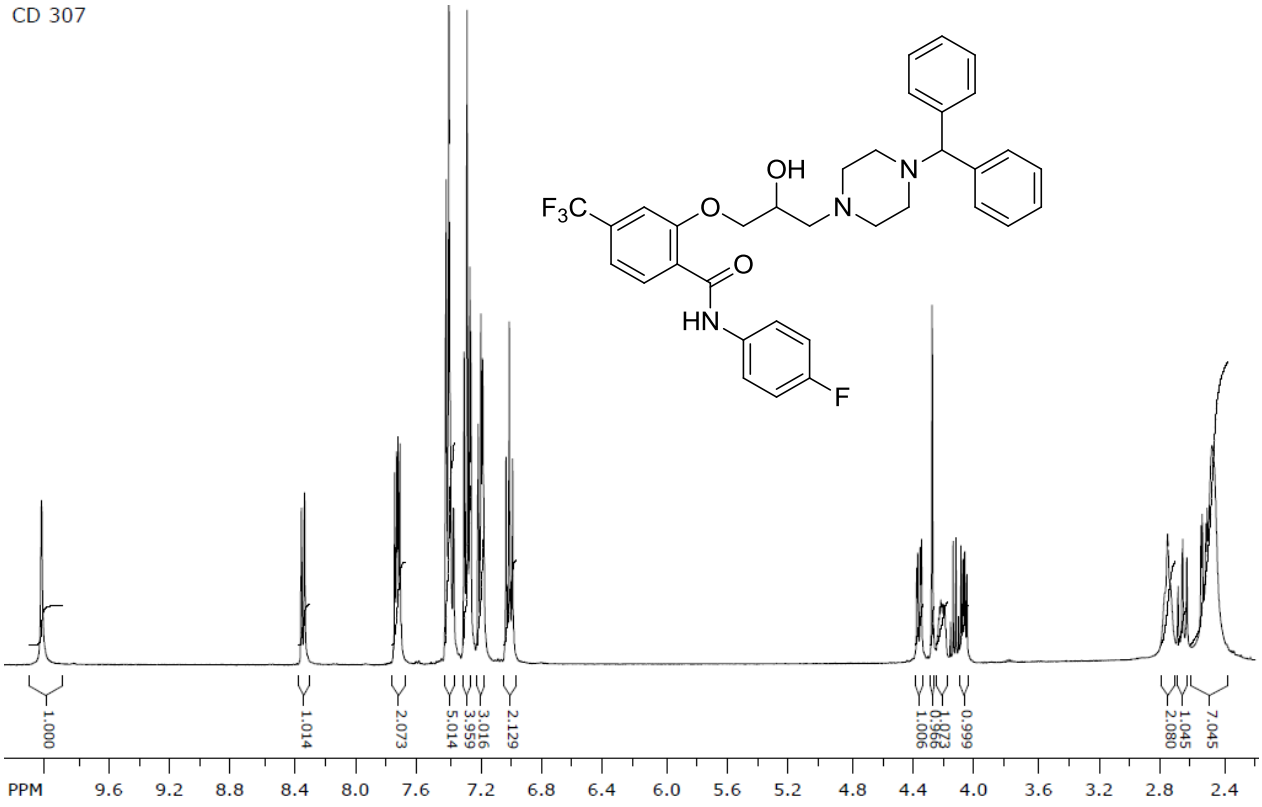


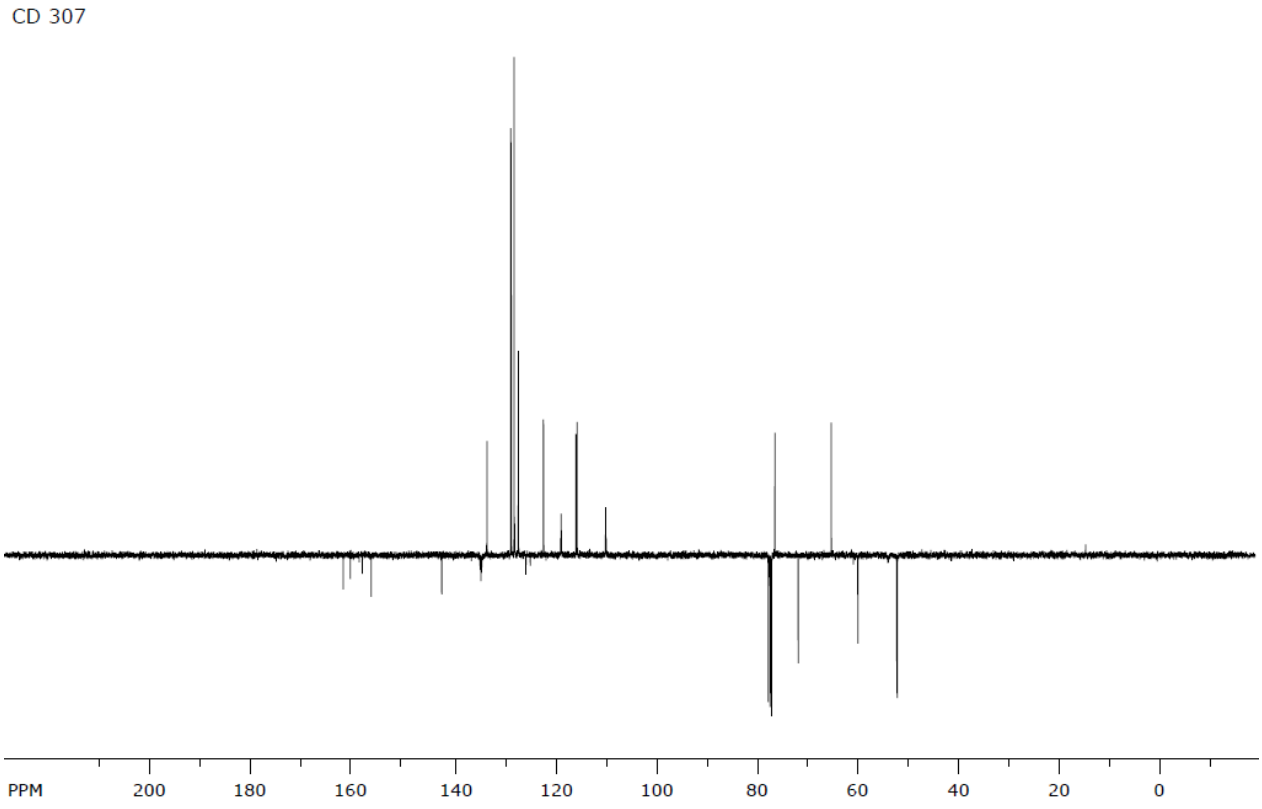
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-3,5-dichloro-*N*-(3,5-dichlorophenyl)benzamide (222)



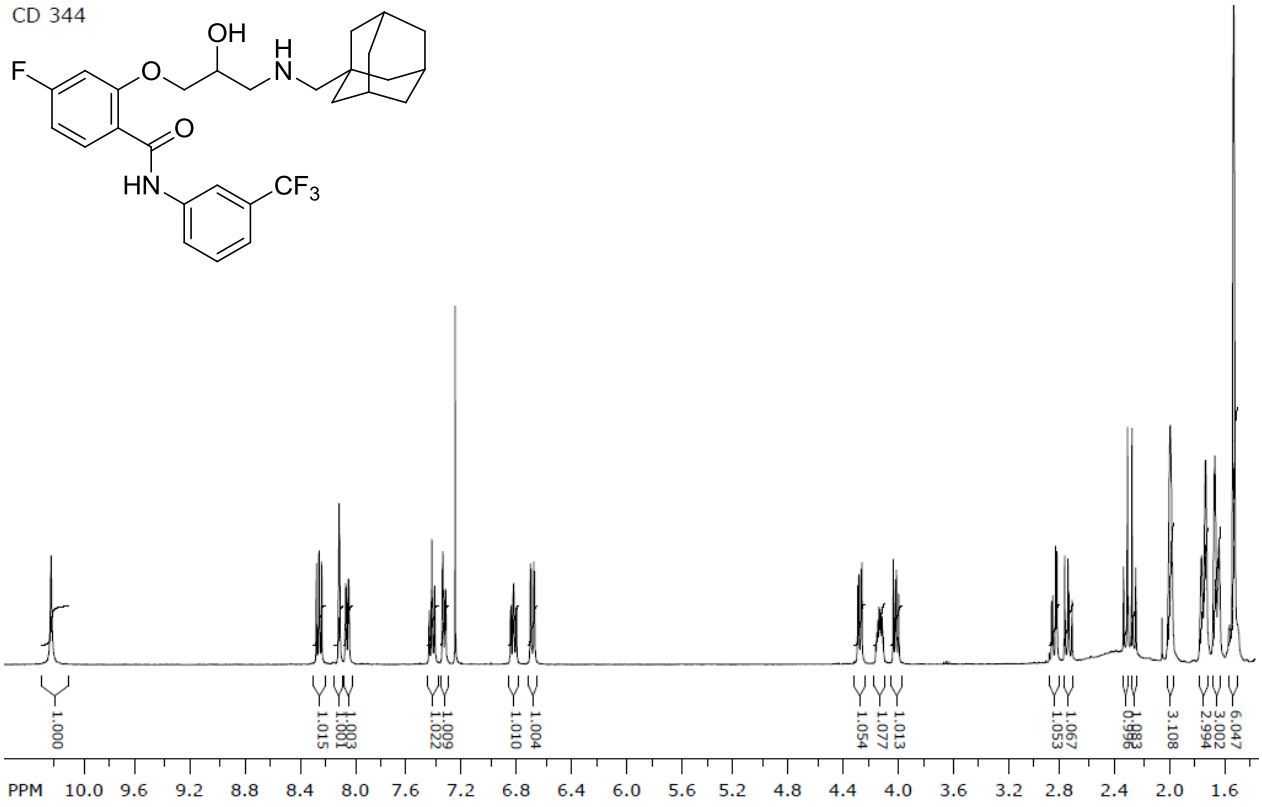


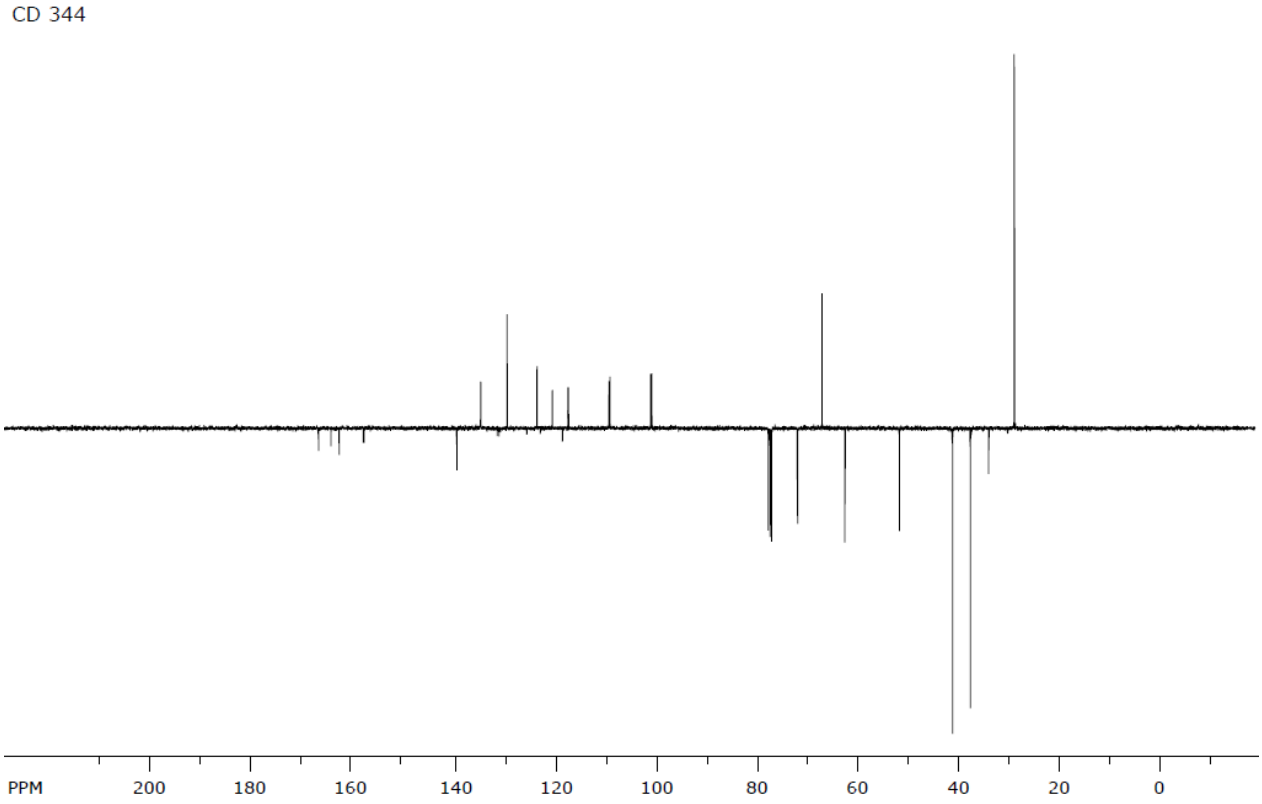
2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(4-fluorophenyl)-4-(trifluoromethyl)benzamide (223)



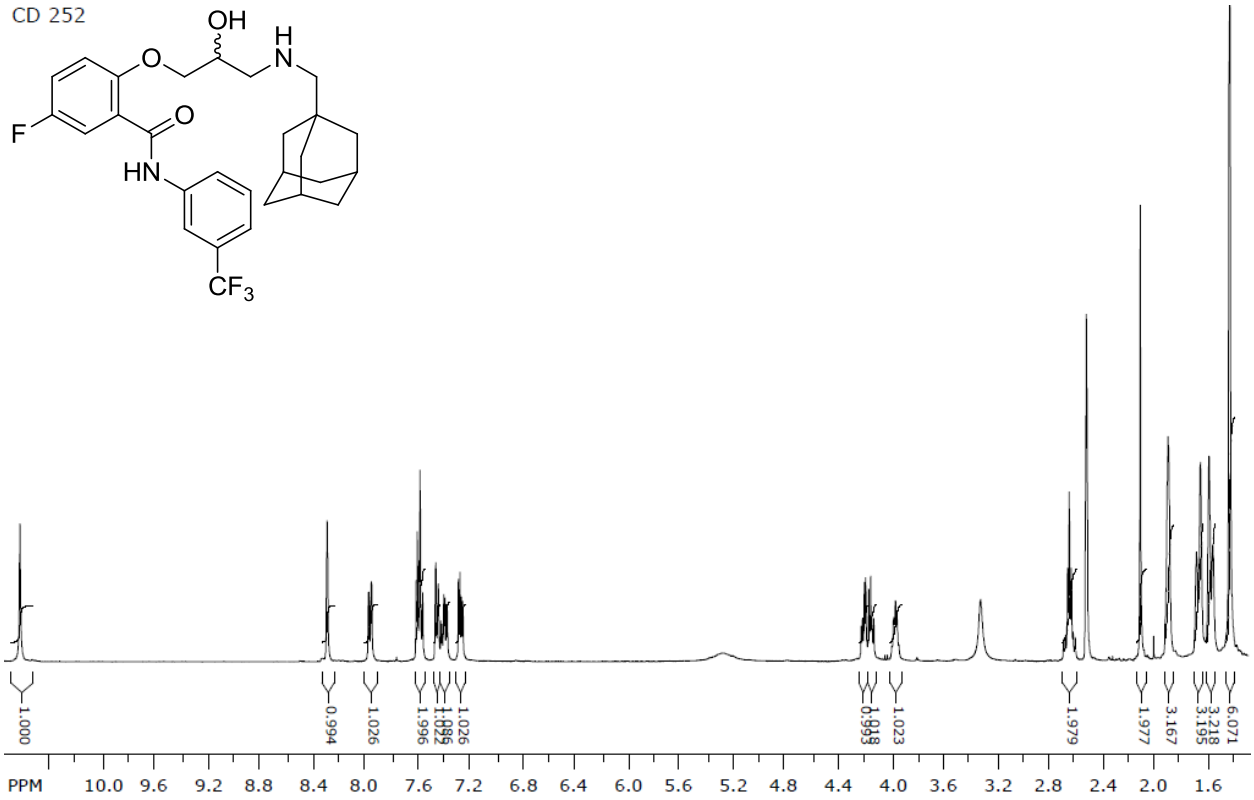


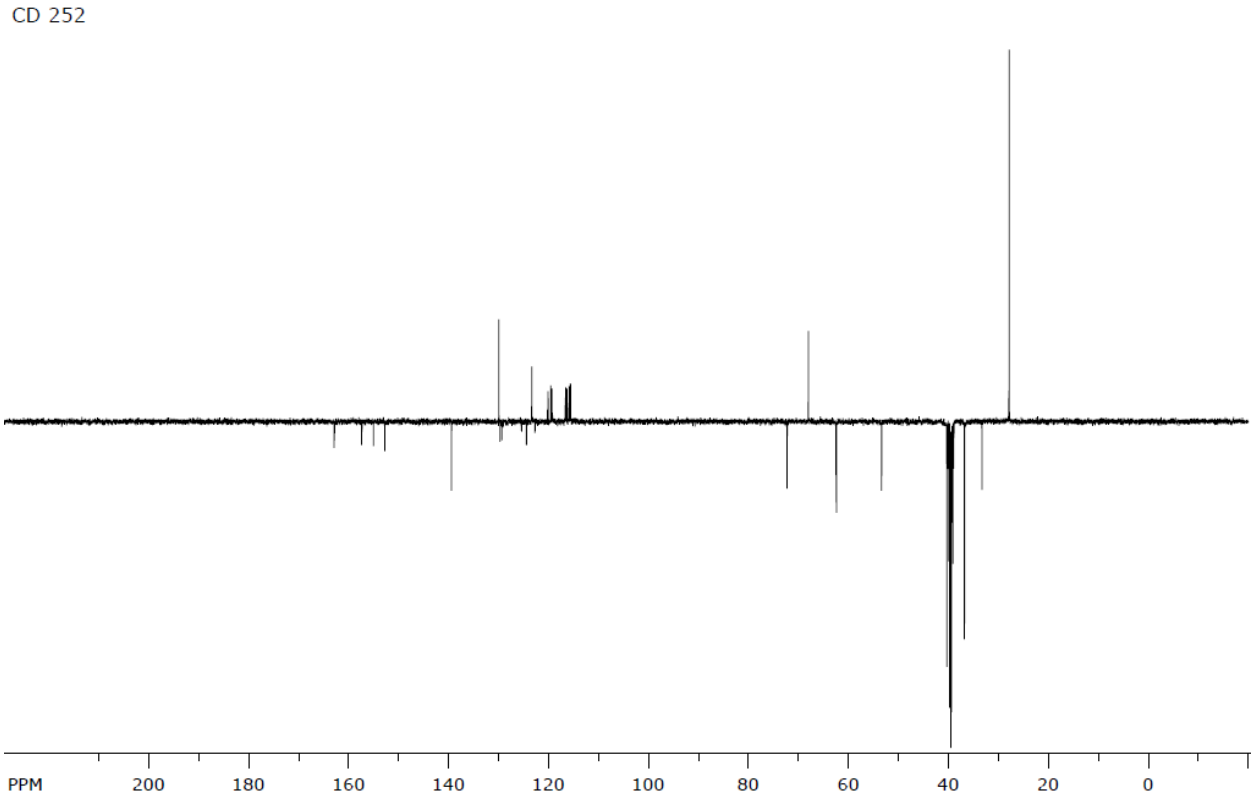
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-4-fluoro-*N*-(3-(trifluoromethyl)phenyl)benzamide (224)



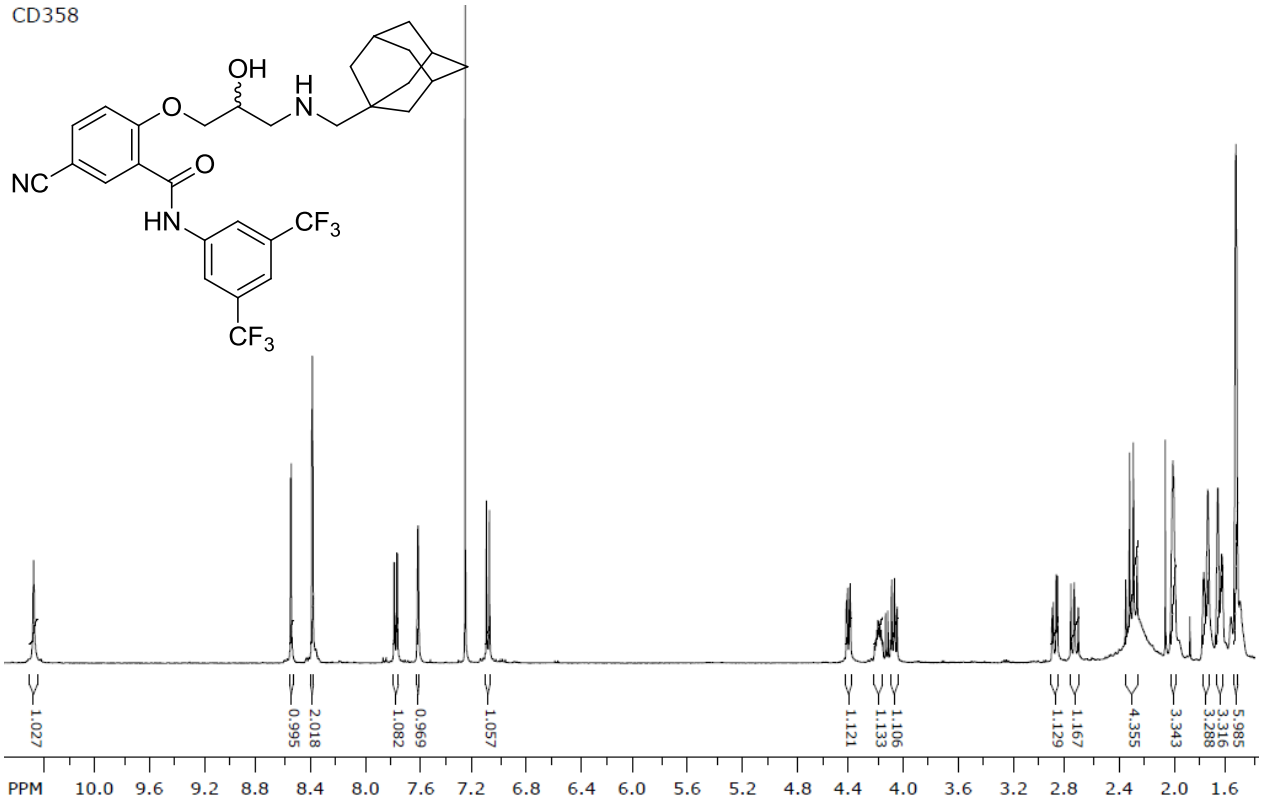


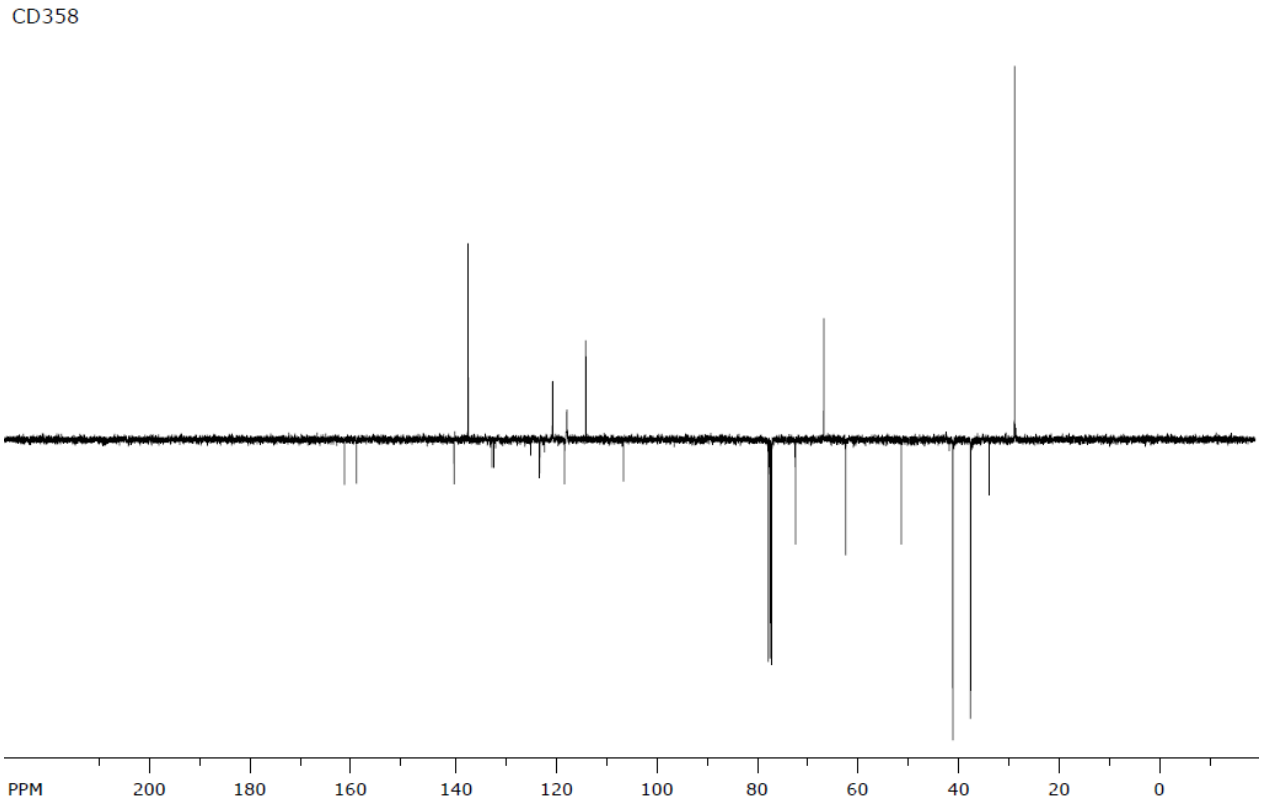
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-fluoro-*N*-(3-(trifluoromethyl)phenyl)benzamide (225)



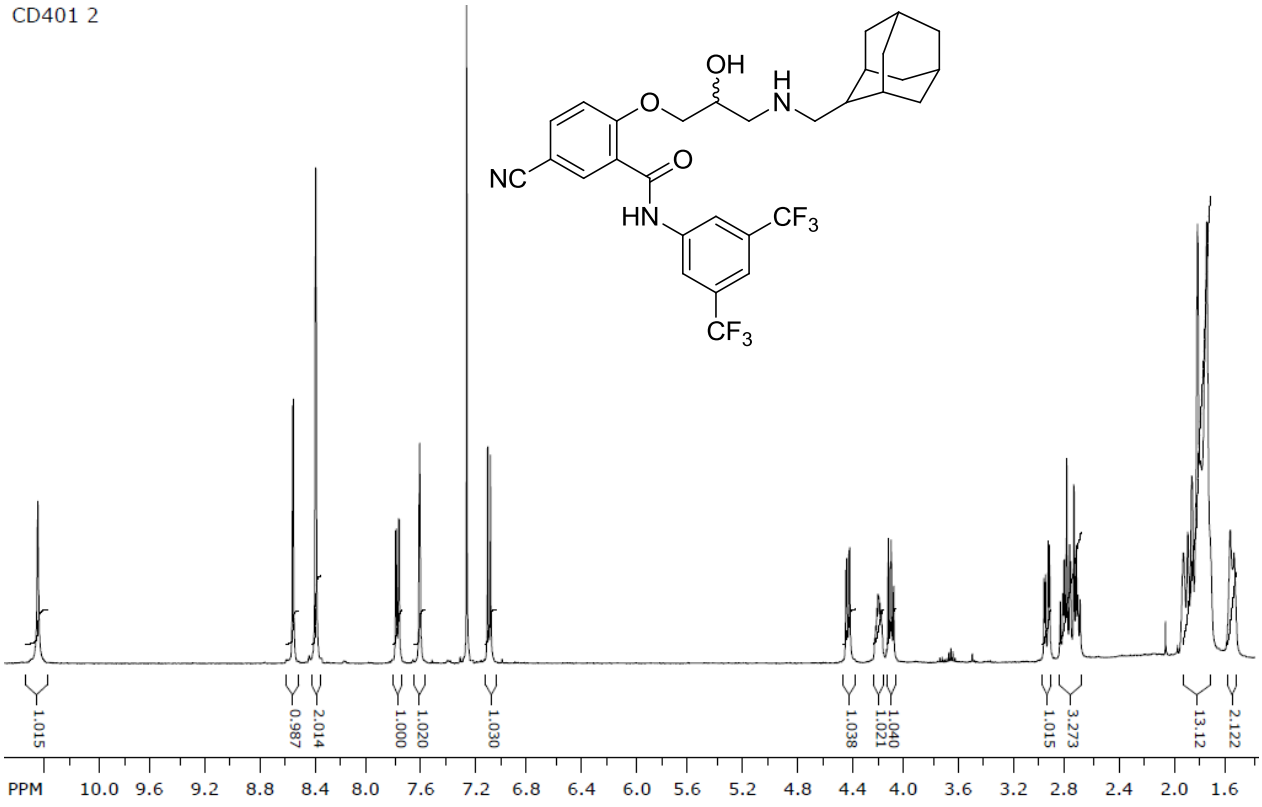


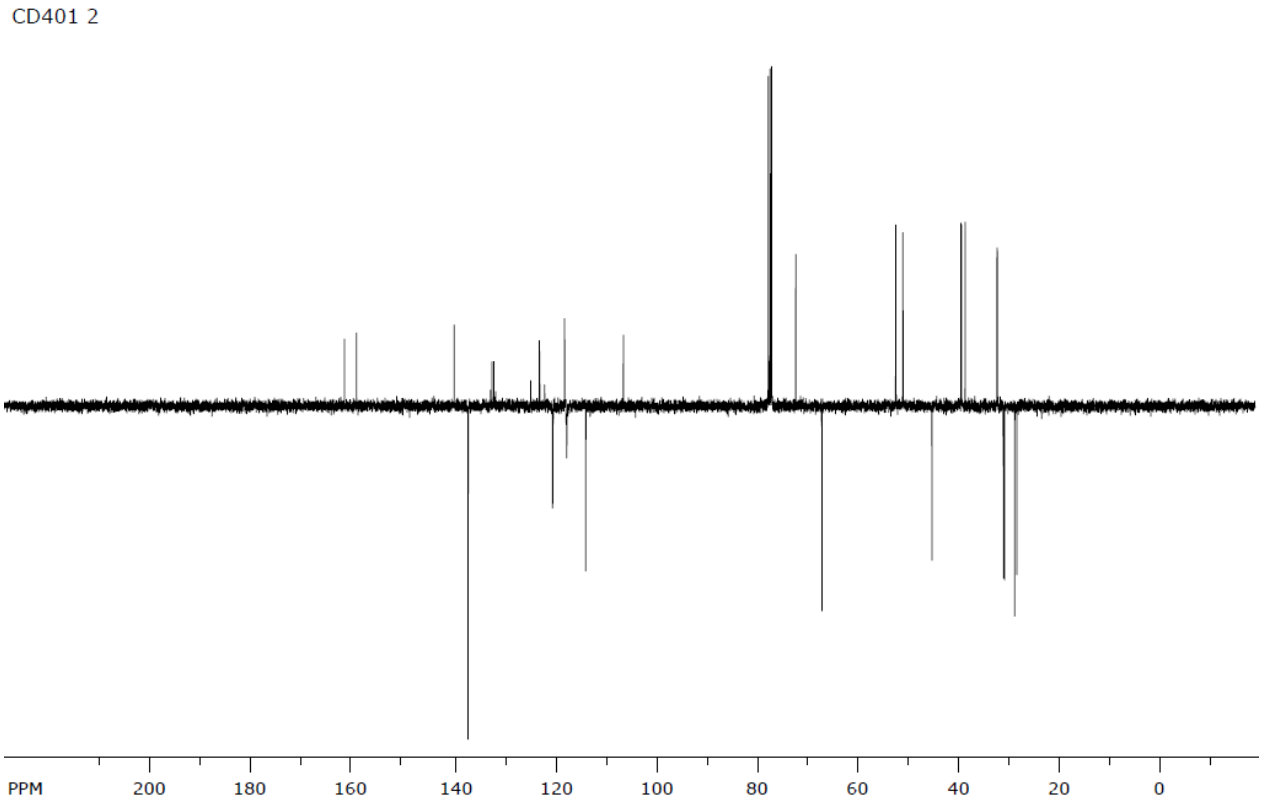
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-cyanobenzamide (226)



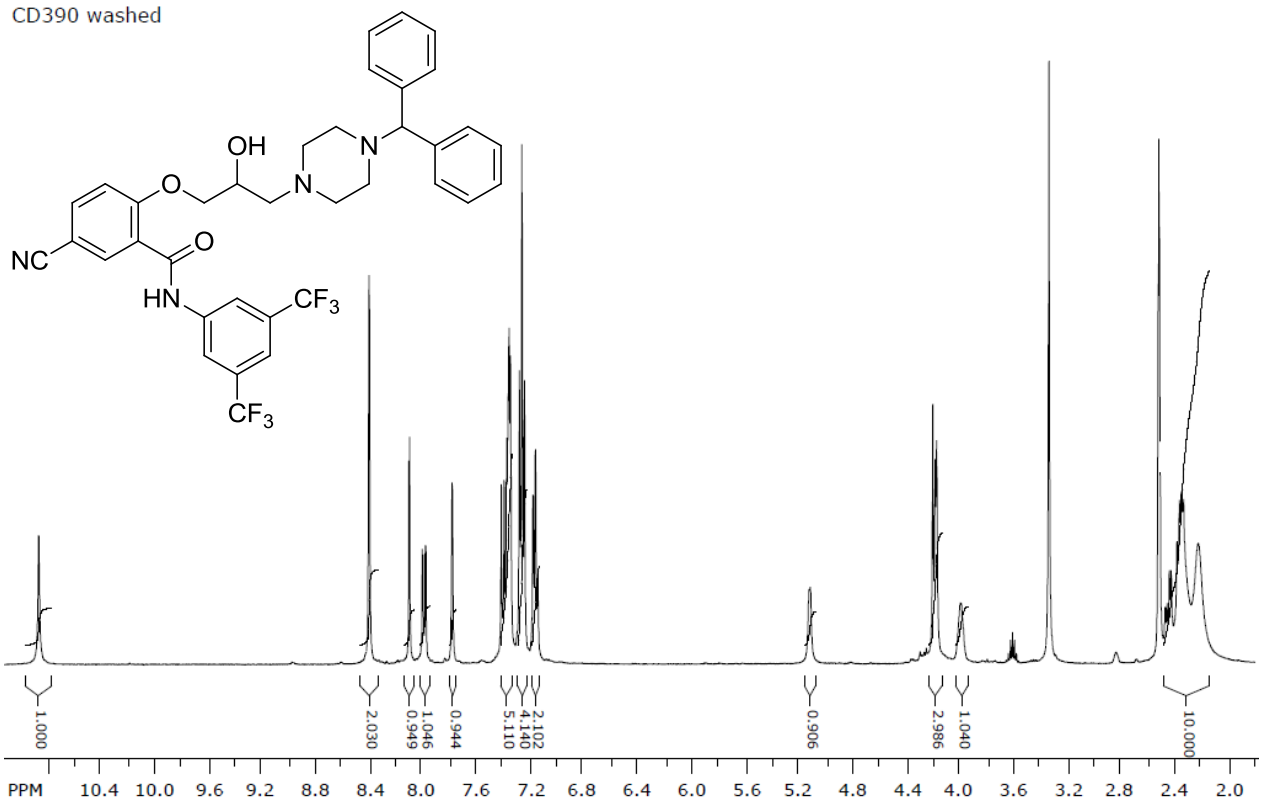


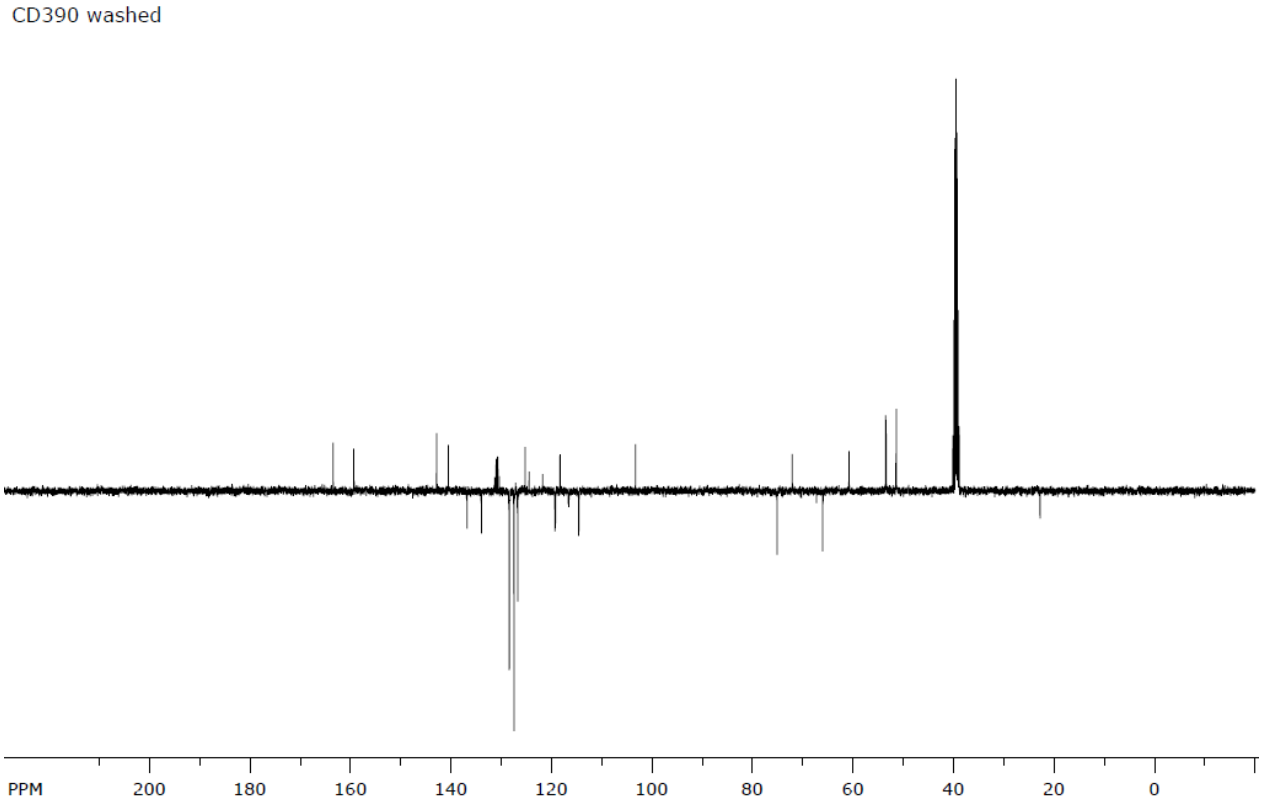
2-(3-((adamantan-2-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-cyanobenzamide (227)



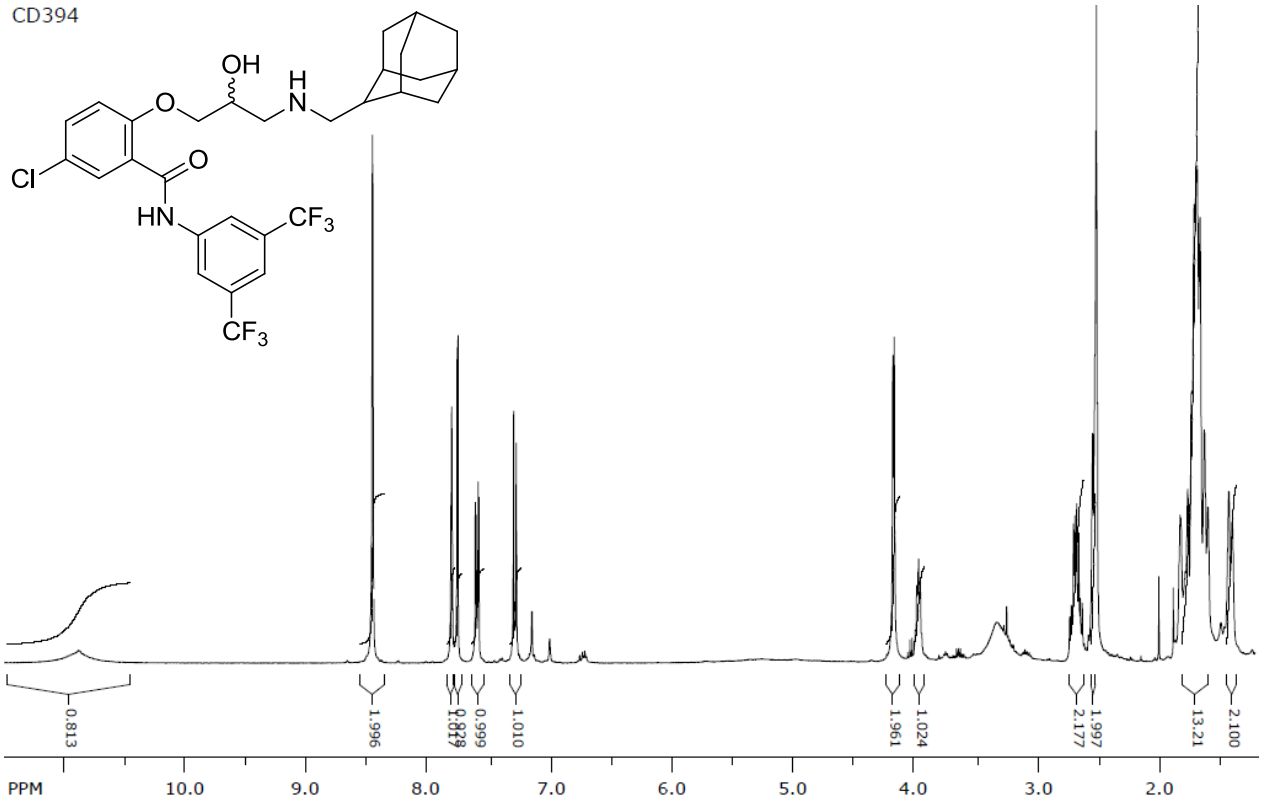


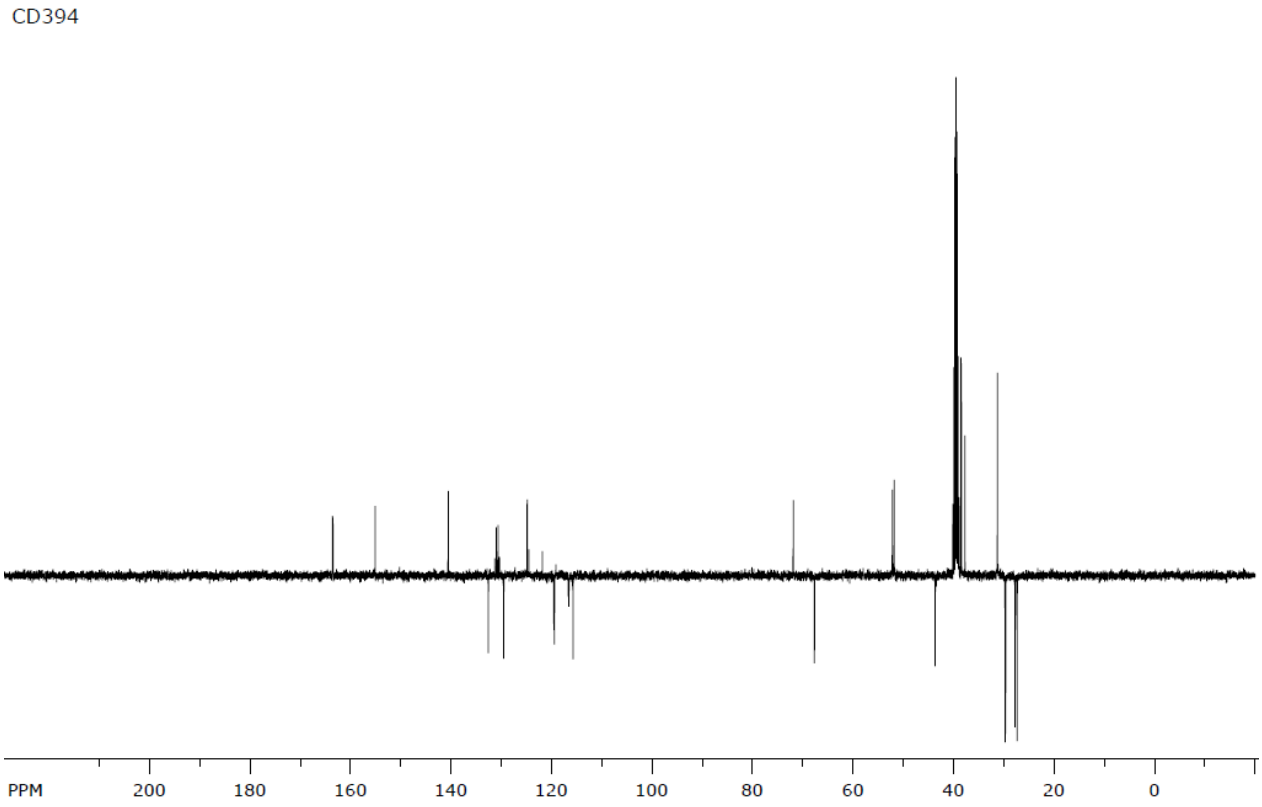
2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-cyanobenzamide (228)



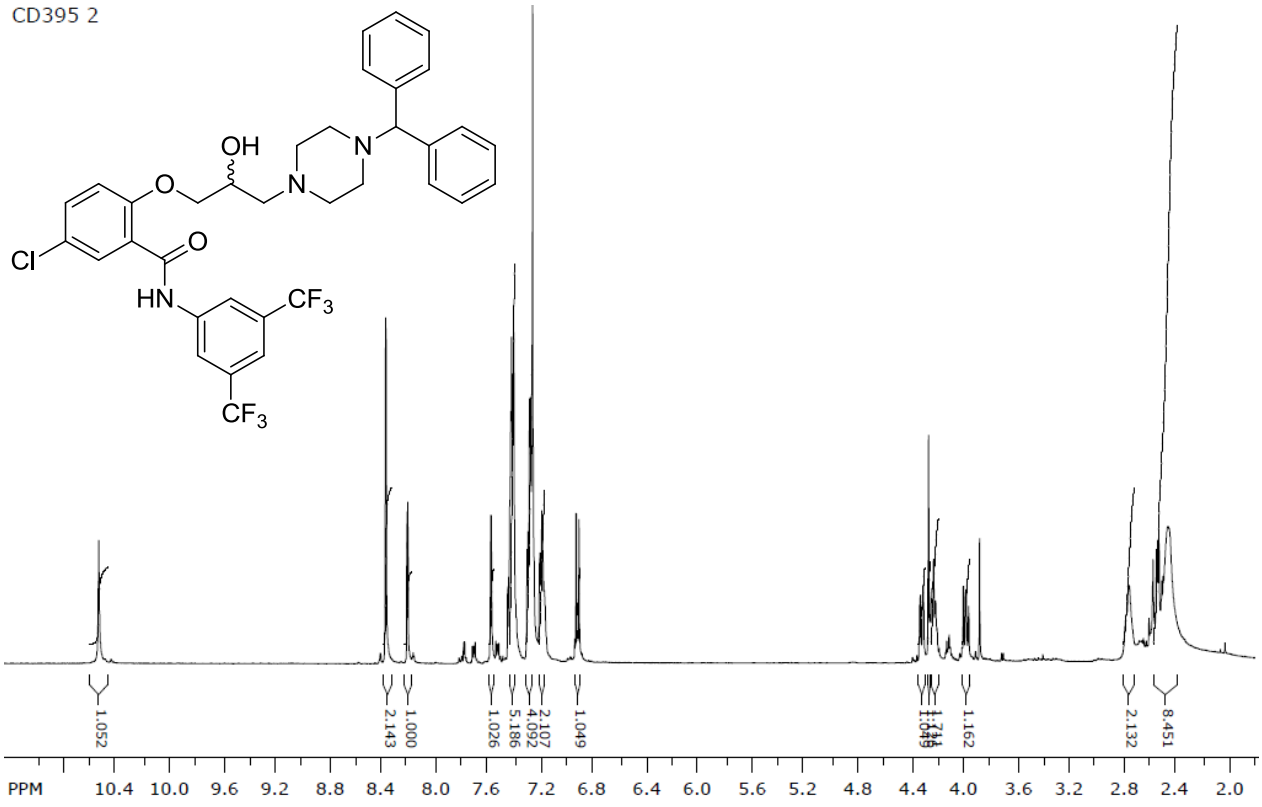


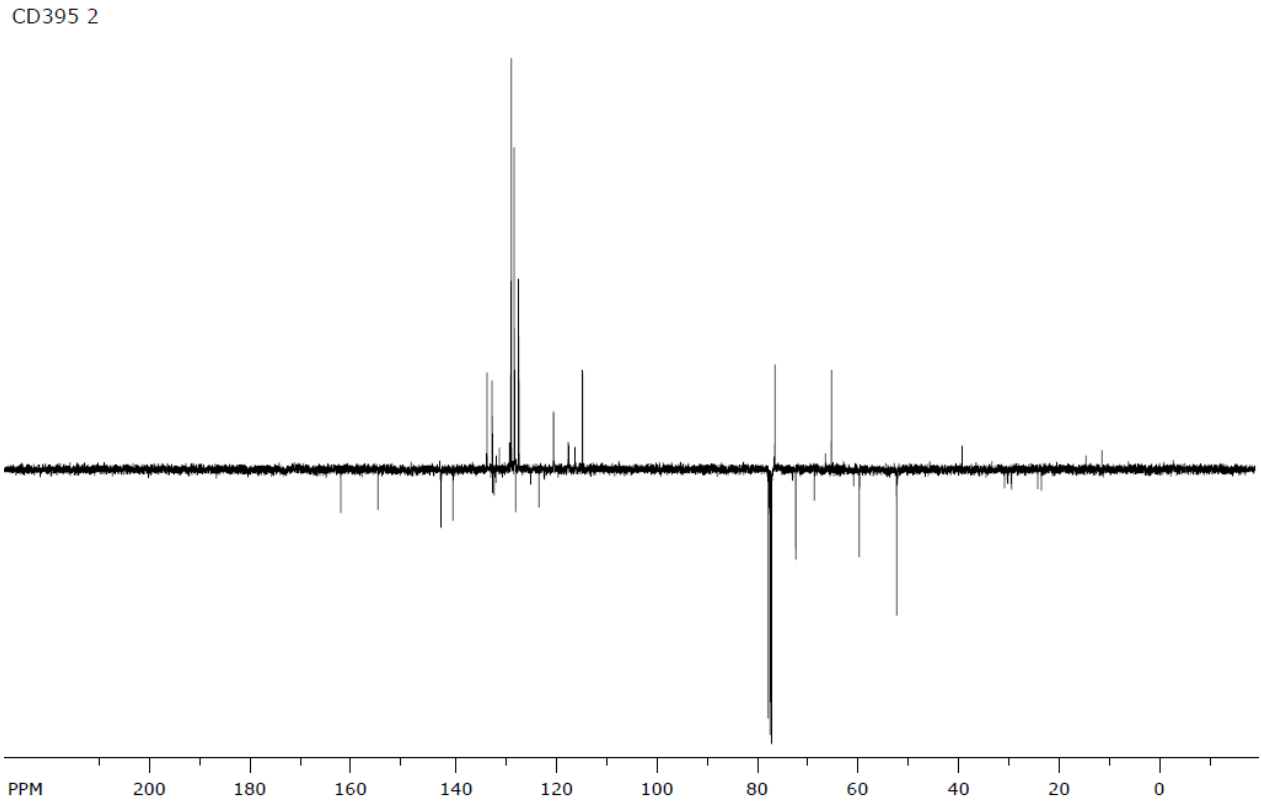
2-(3-((adamantan-2-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-chlorobenzamide (229)



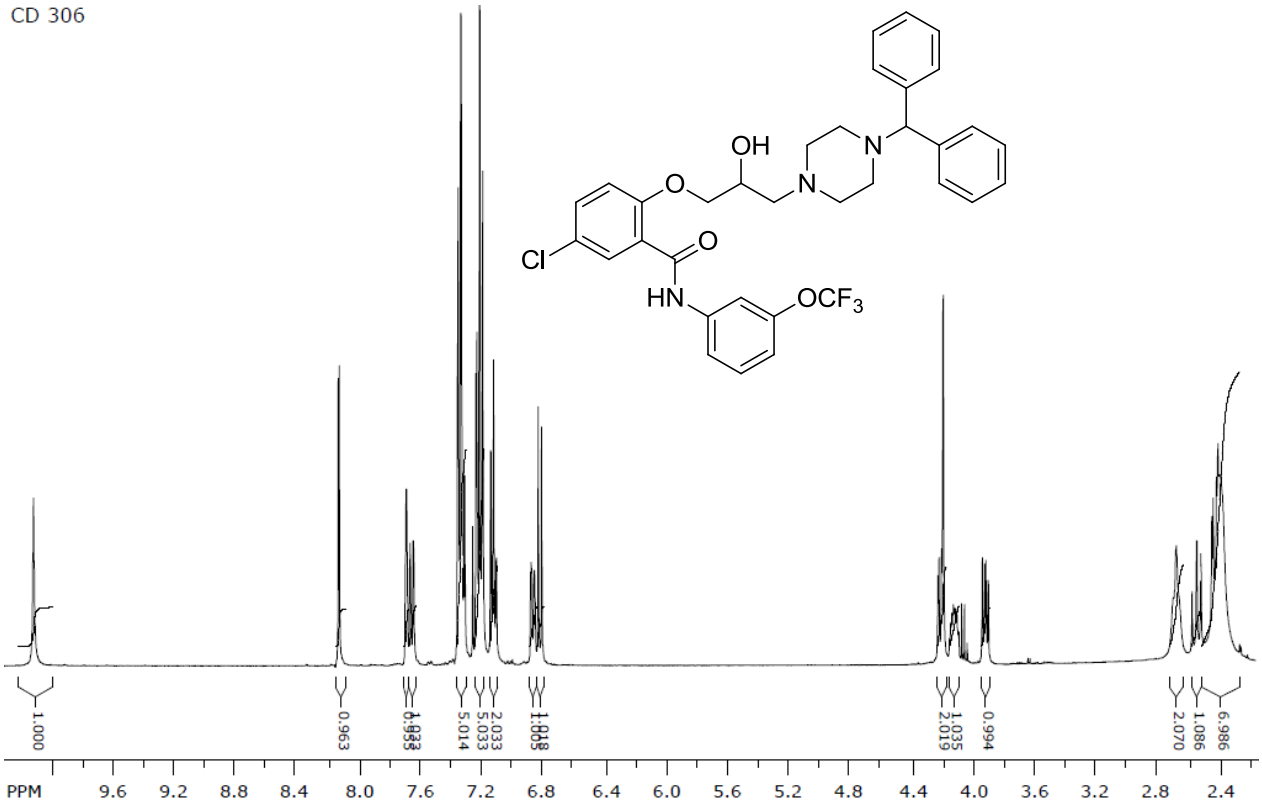


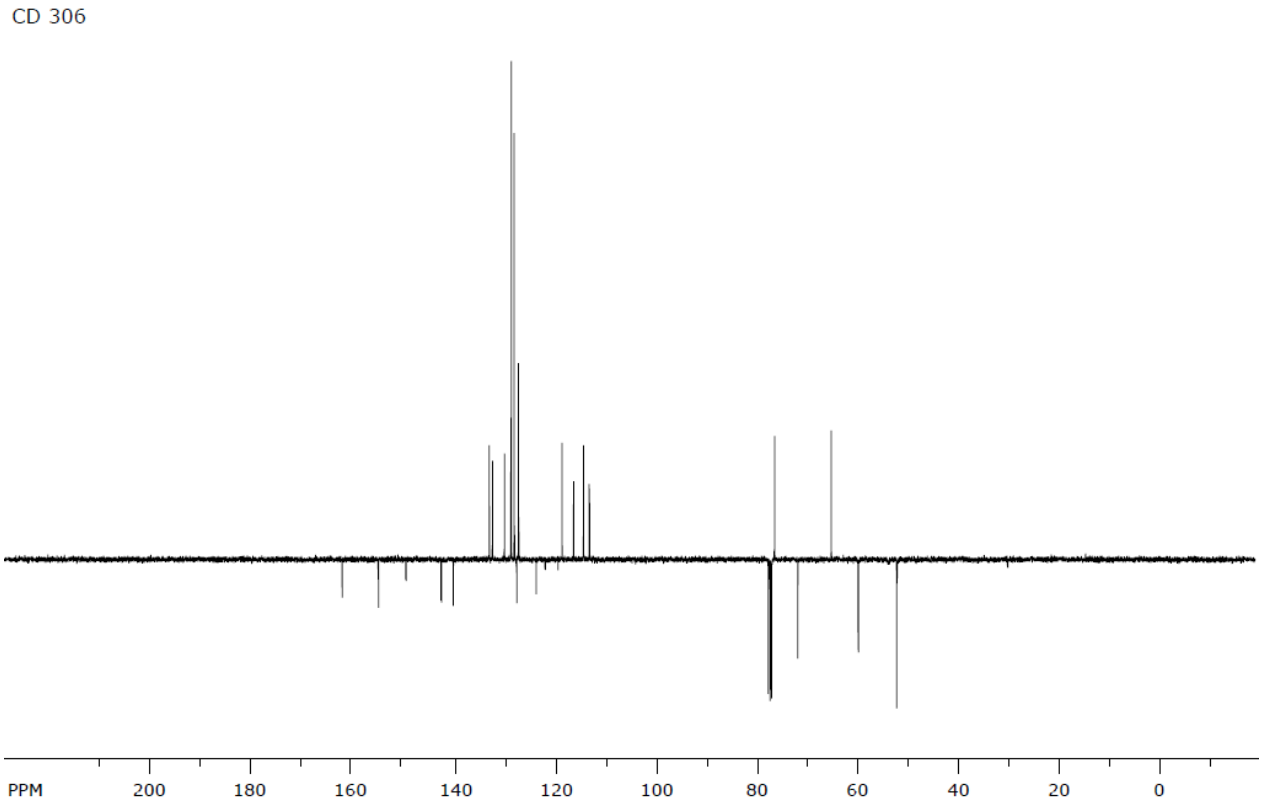
2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-chlorobenzamide (230)



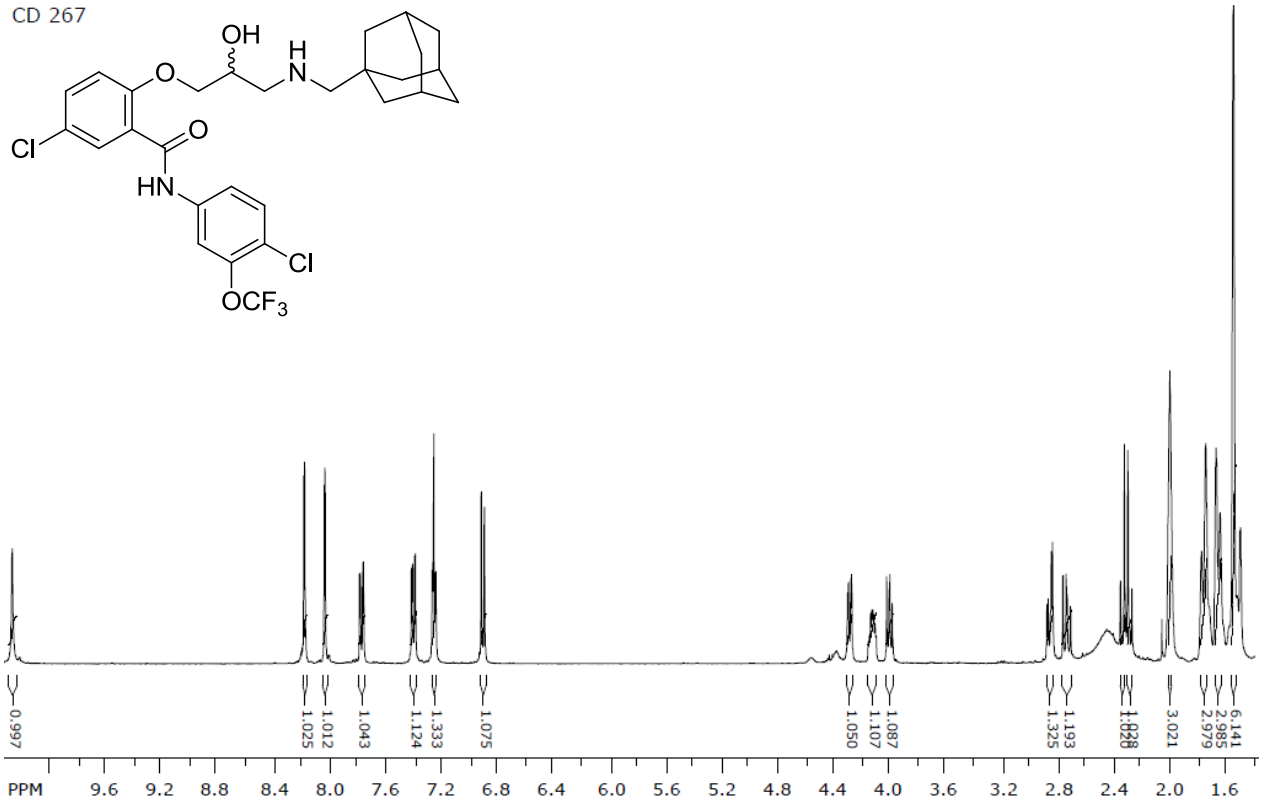


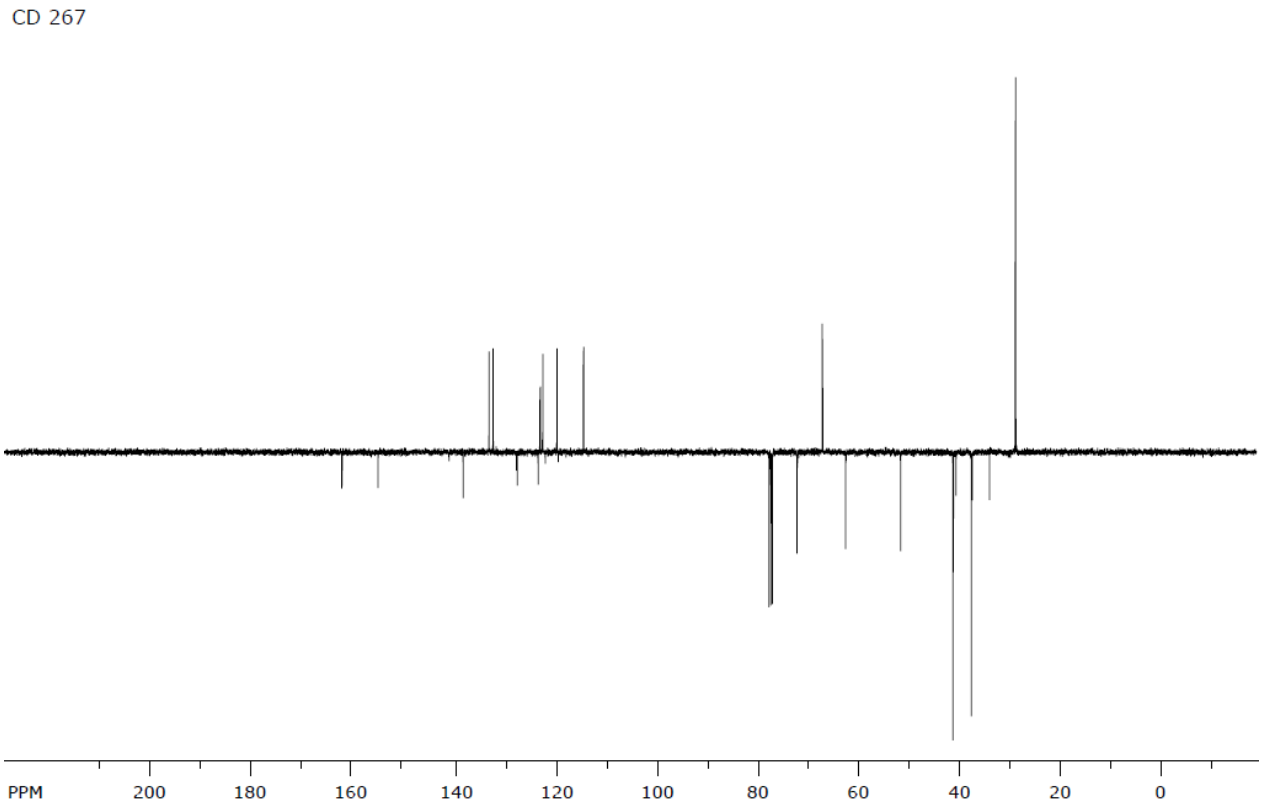
2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethoxy)phenyl)benzamide (233)



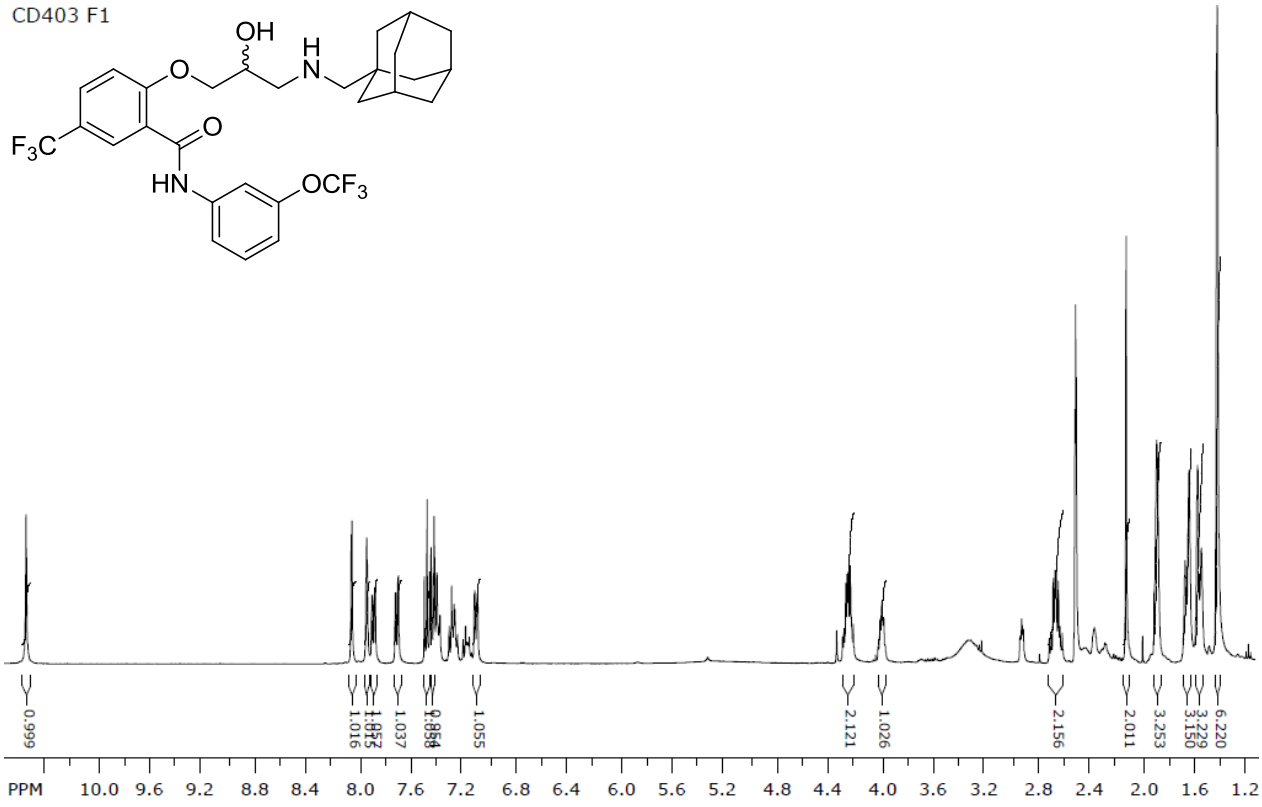


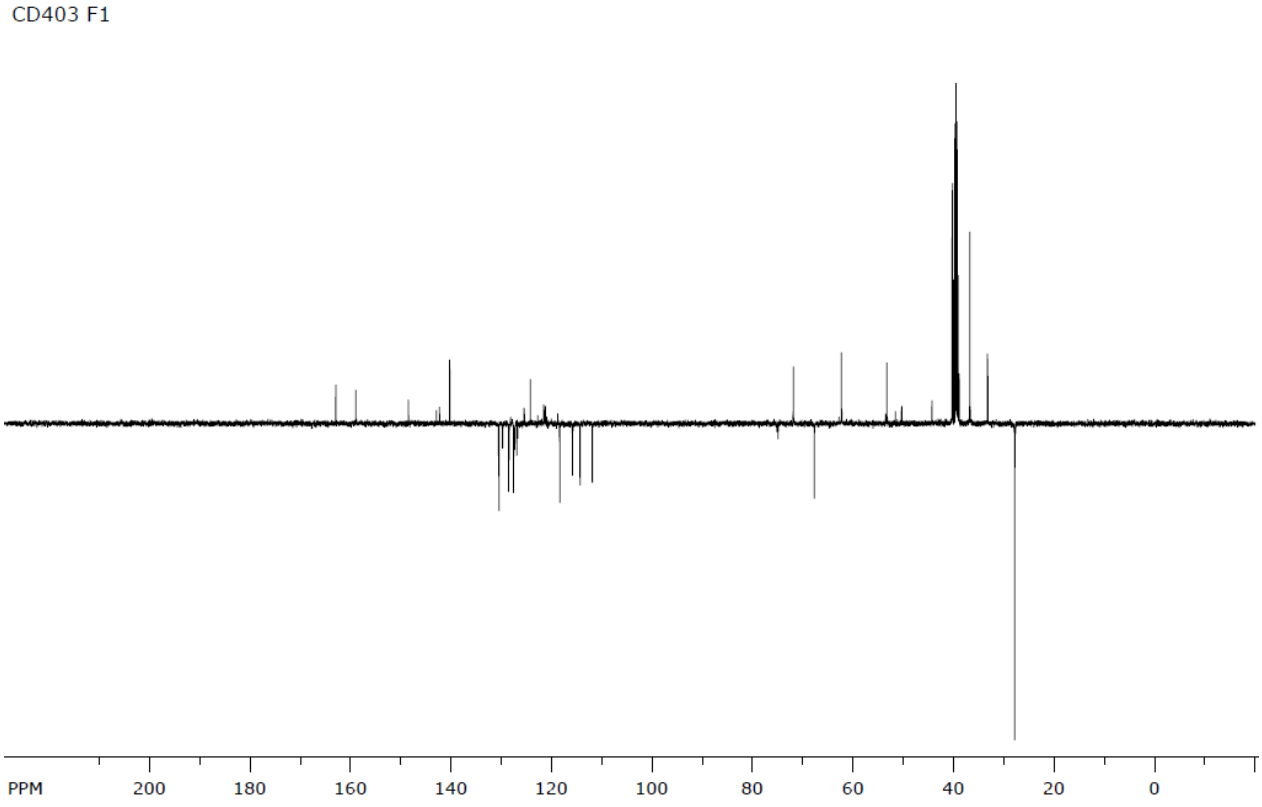
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(4-chloro-3-(trifluoromethoxy)phenyl)benzamide (234)



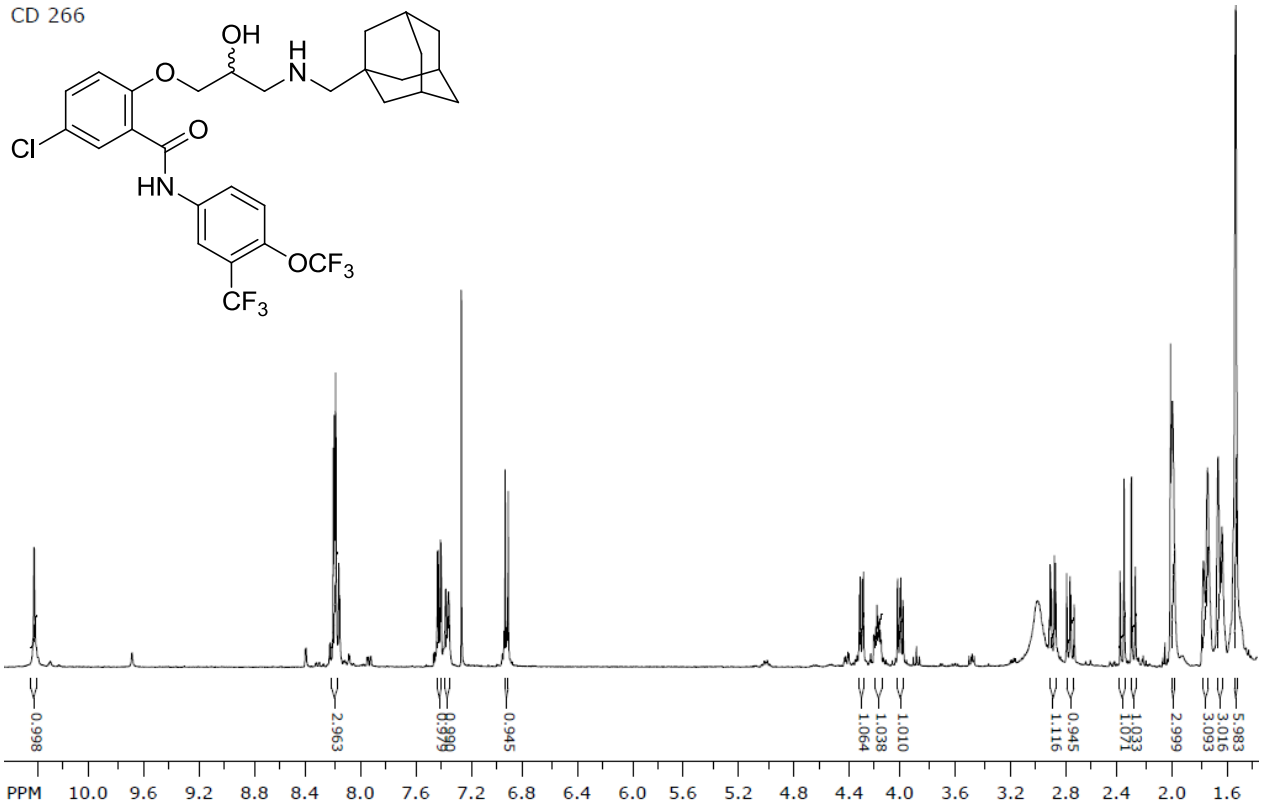


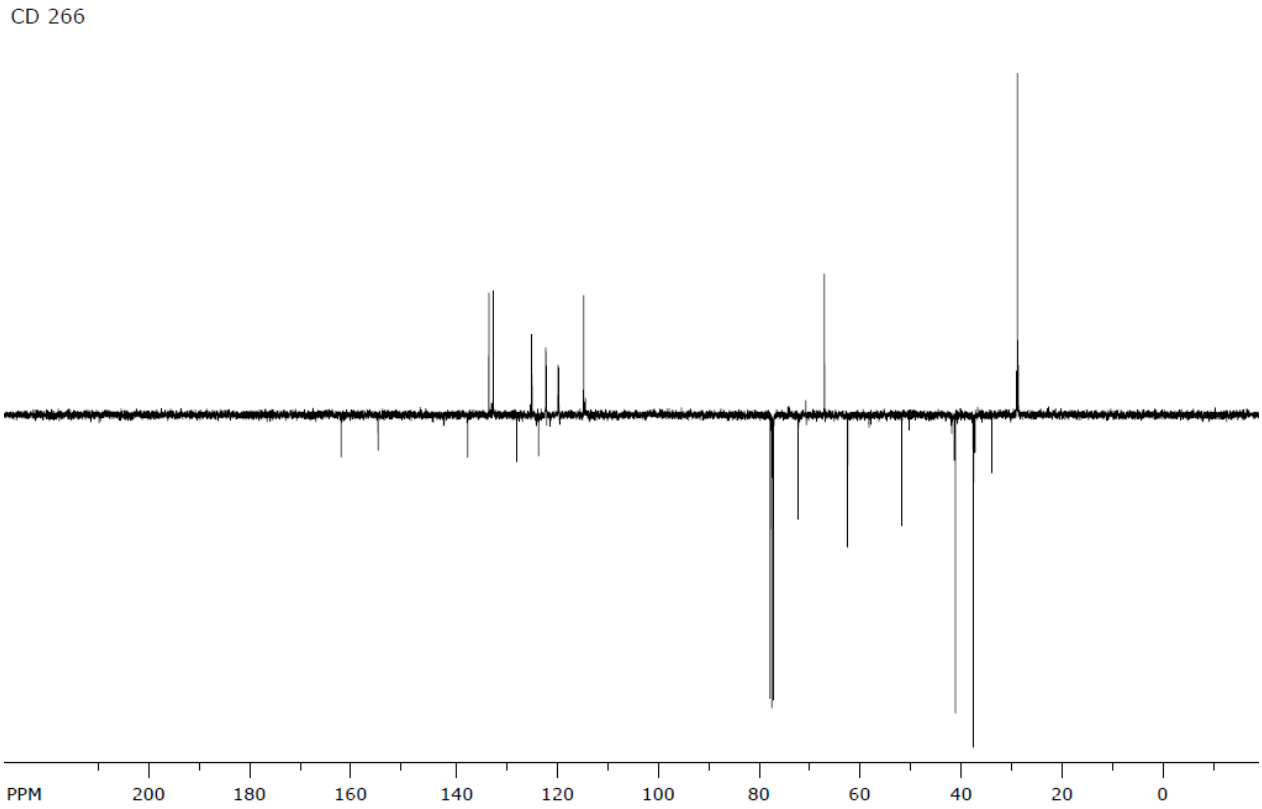
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(3-(trifluoromethoxy)phenyl)-5-(trifluoromethyl)benzamide (235)



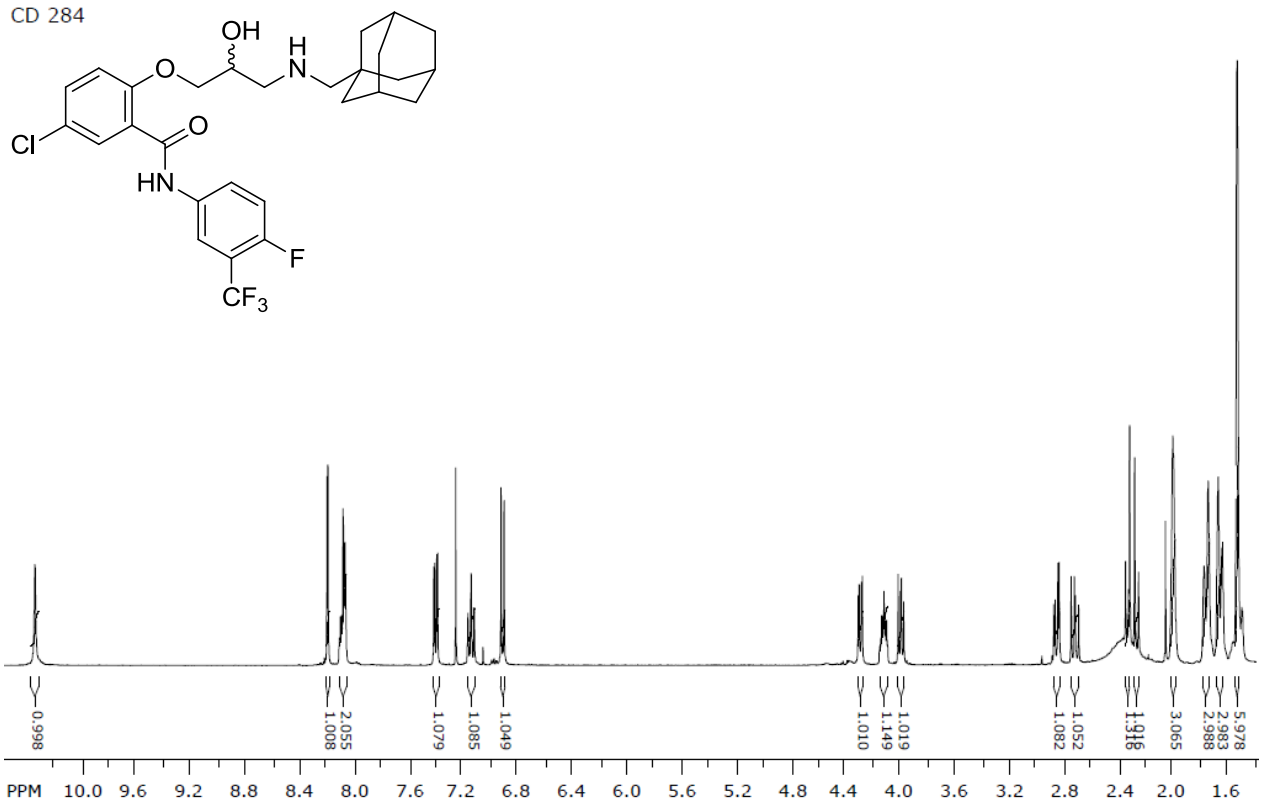


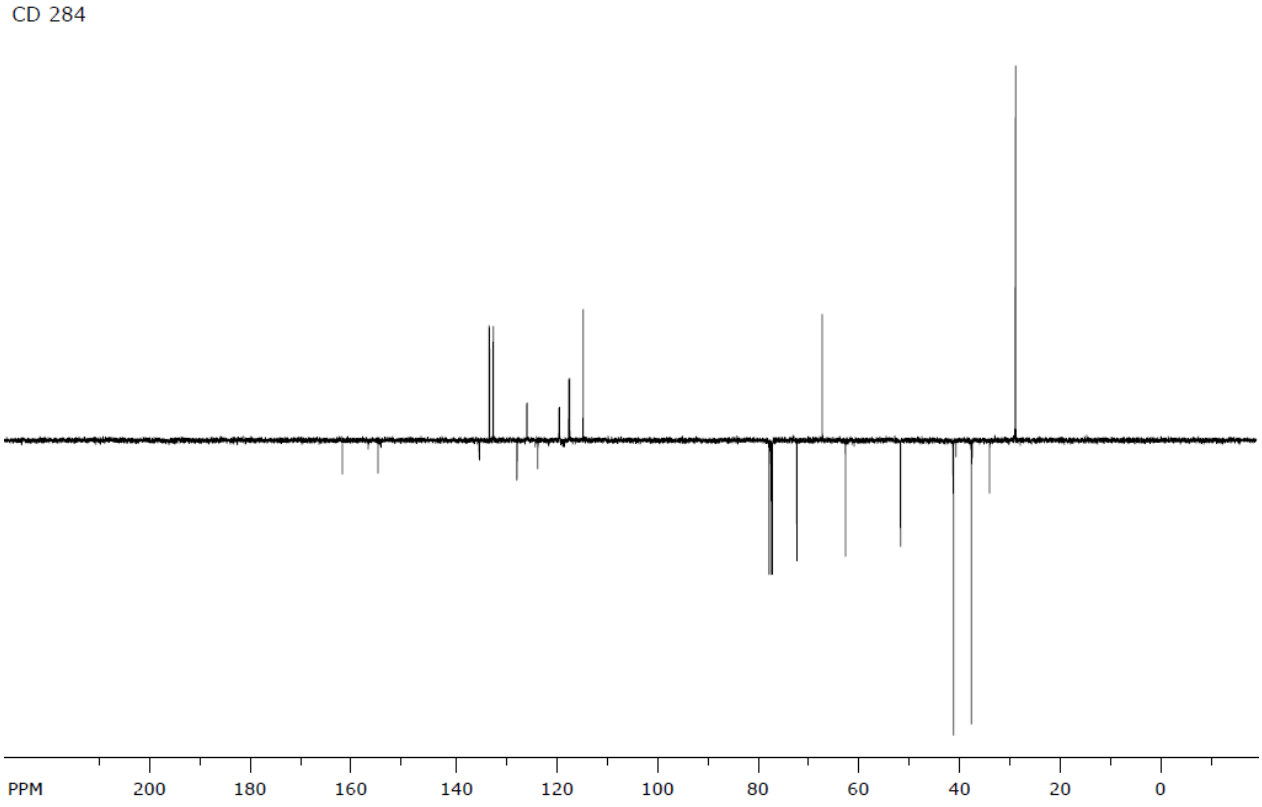
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(4-(trifluoromethoxy)-3-(trifluoromethyl)phenyl)benzamide (236)



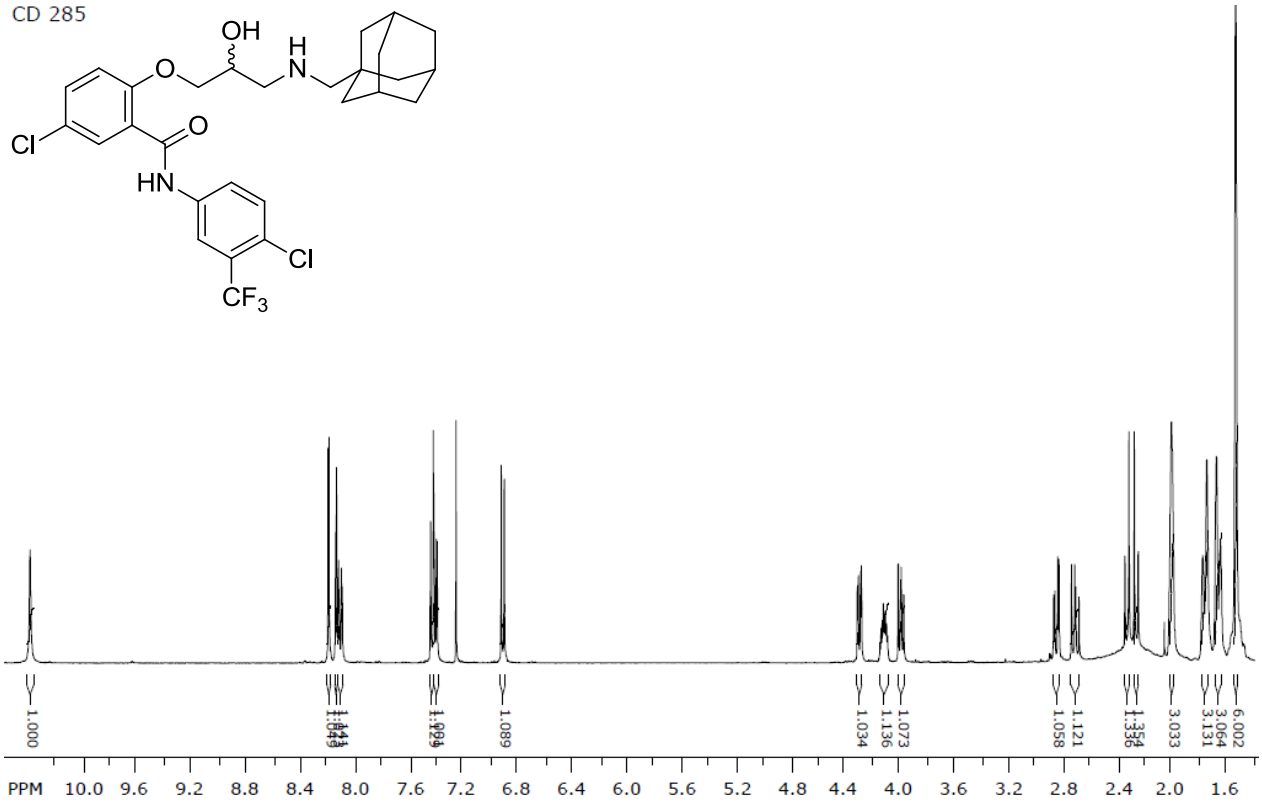


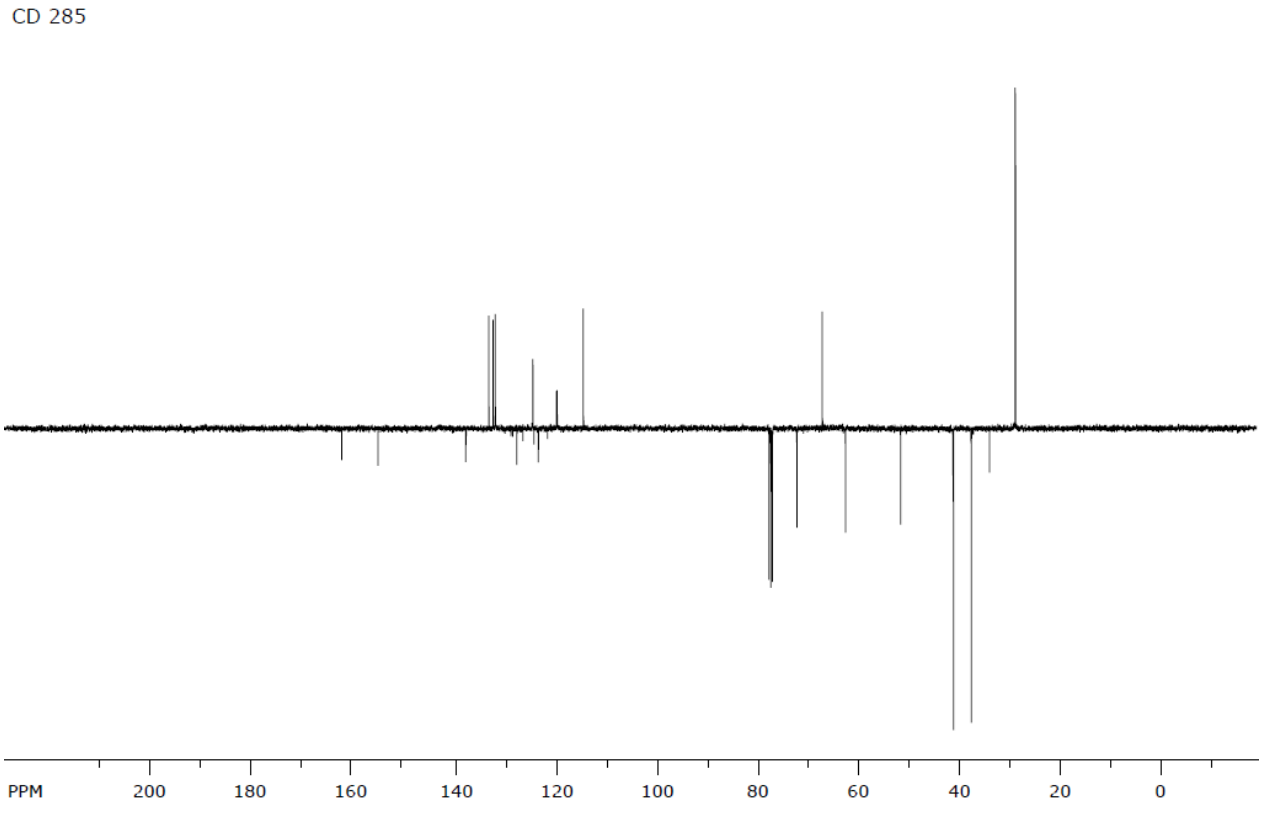
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(4-fluoro-3-(trifluoromethyl)phenyl)benzamide (237)



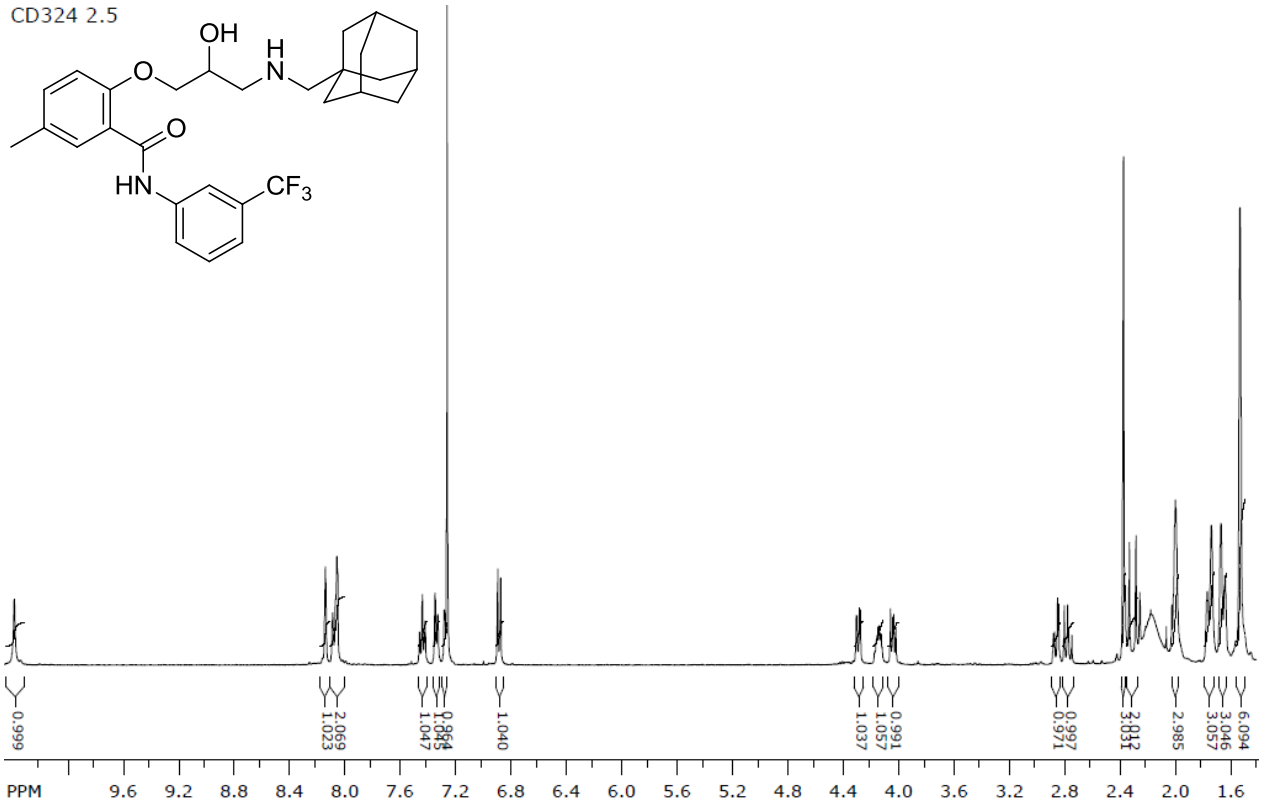


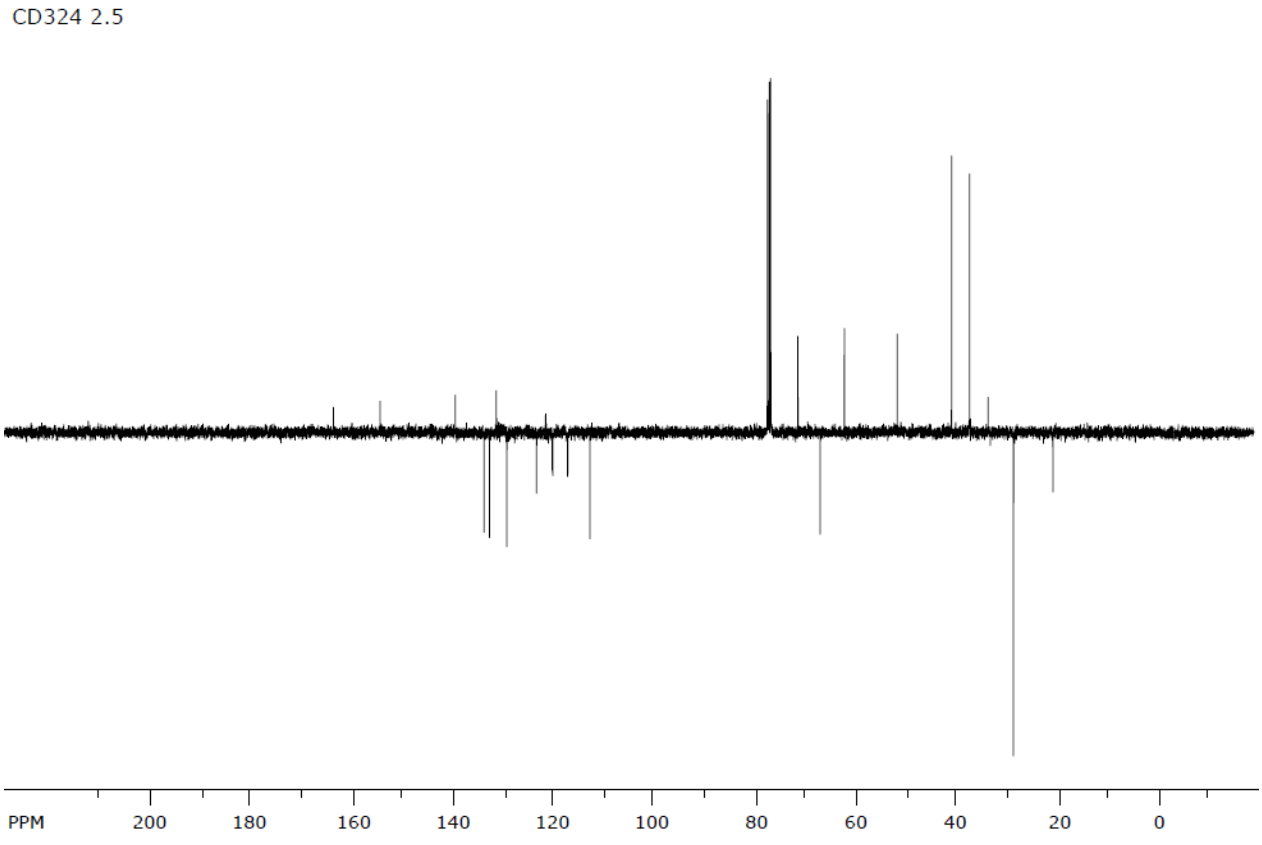
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(4-chloro-3-(trifluoromethyl)phenyl)benzamide (238)



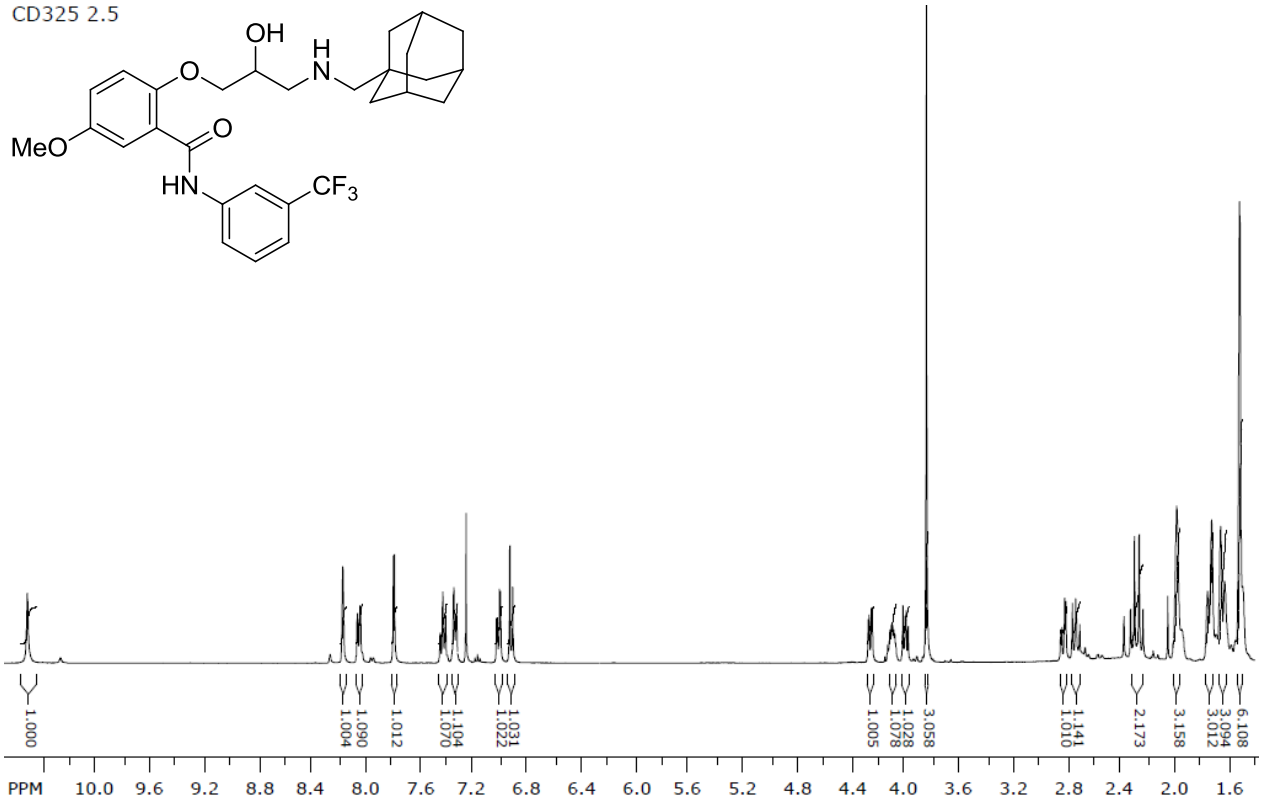


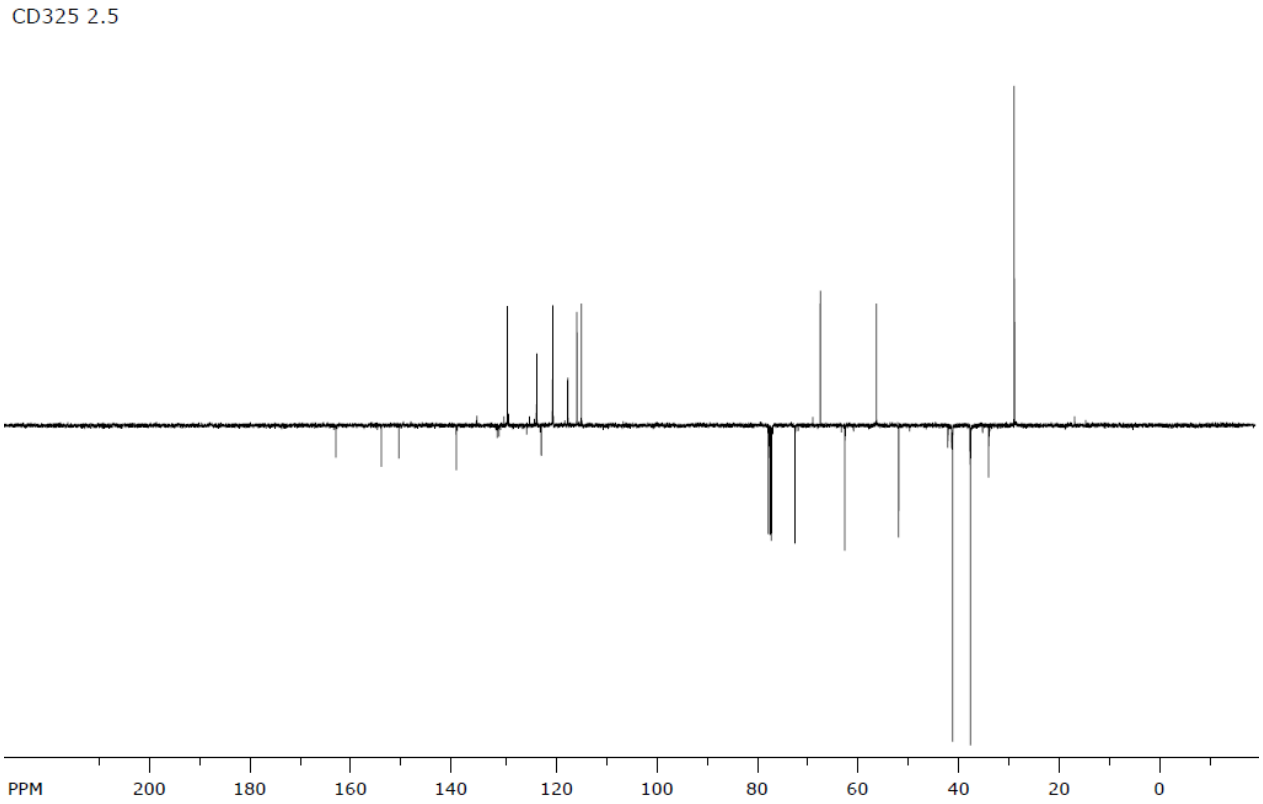
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-methyl-*N*-(3-(trifluoromethyl)phenyl)benzamide (239**)**



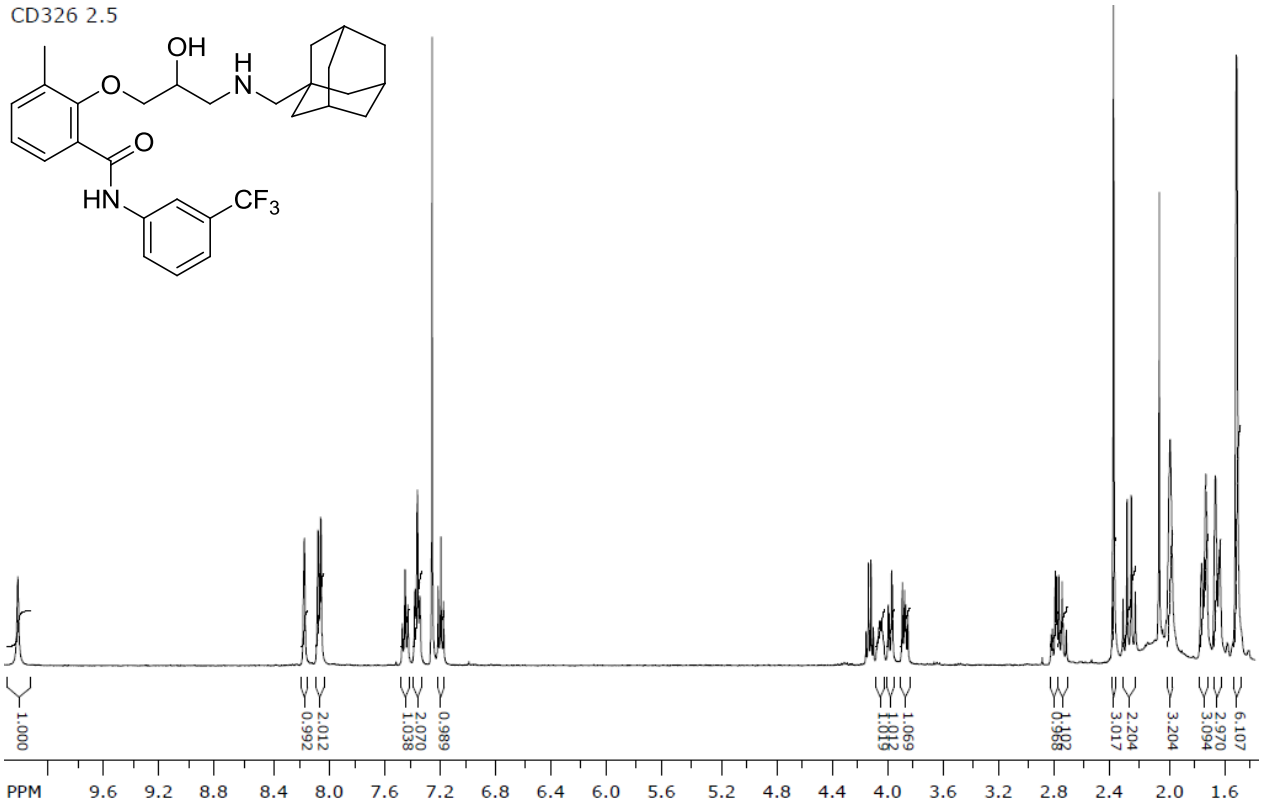


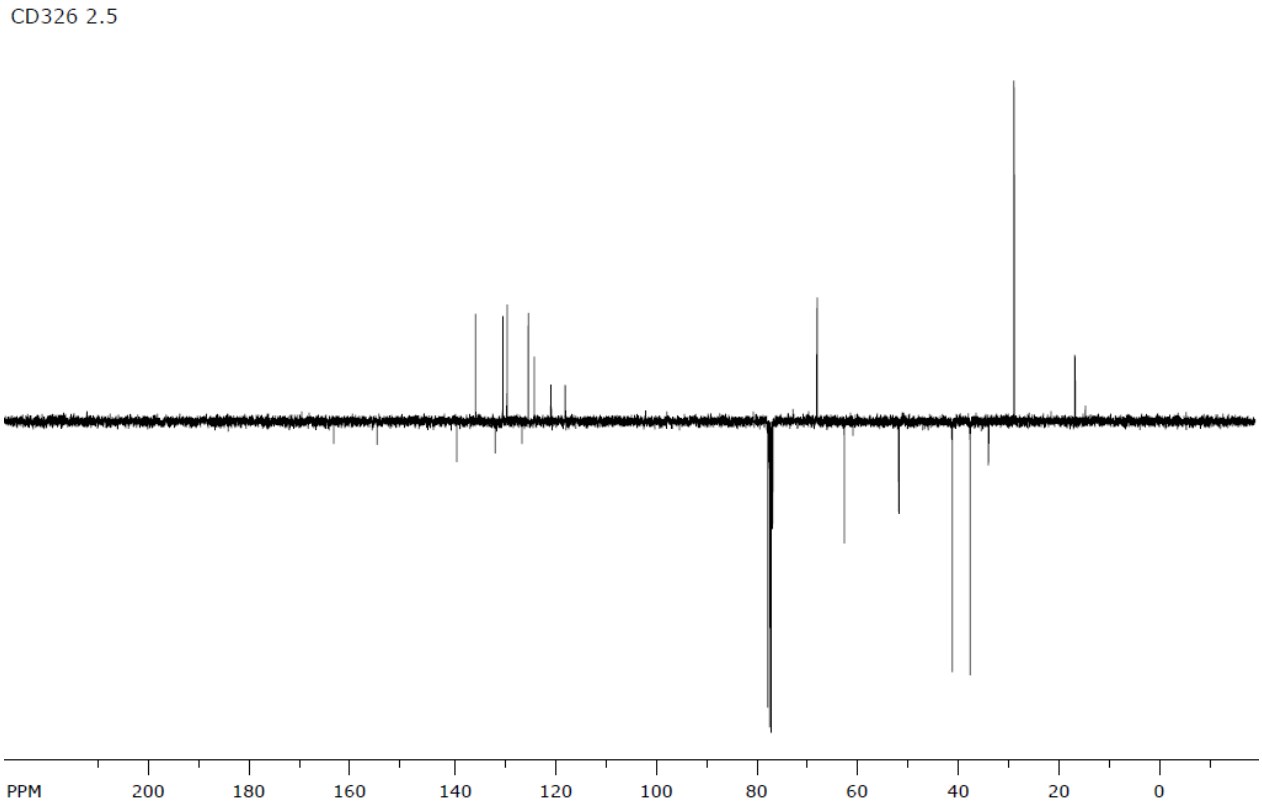
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-methoxy-*N*-(3-(trifluoromethyl)phenyl)benzamide (240)



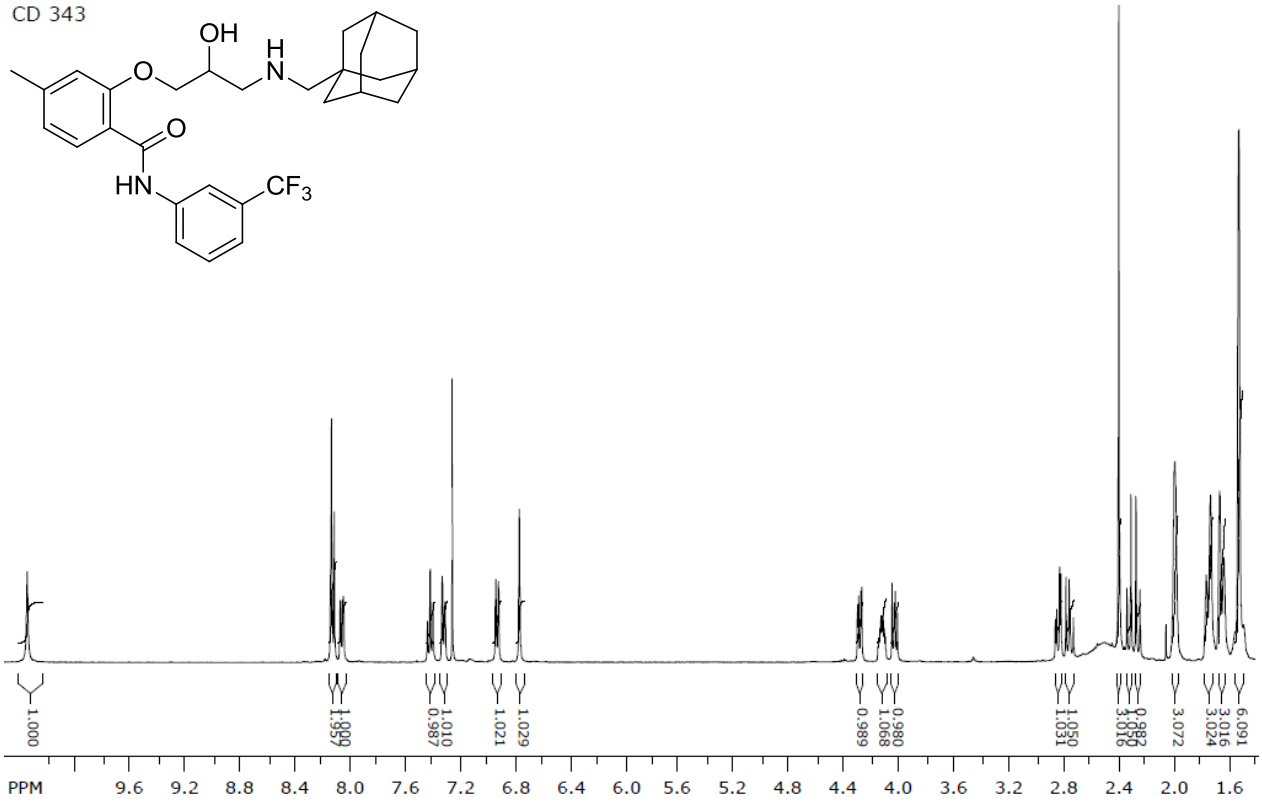


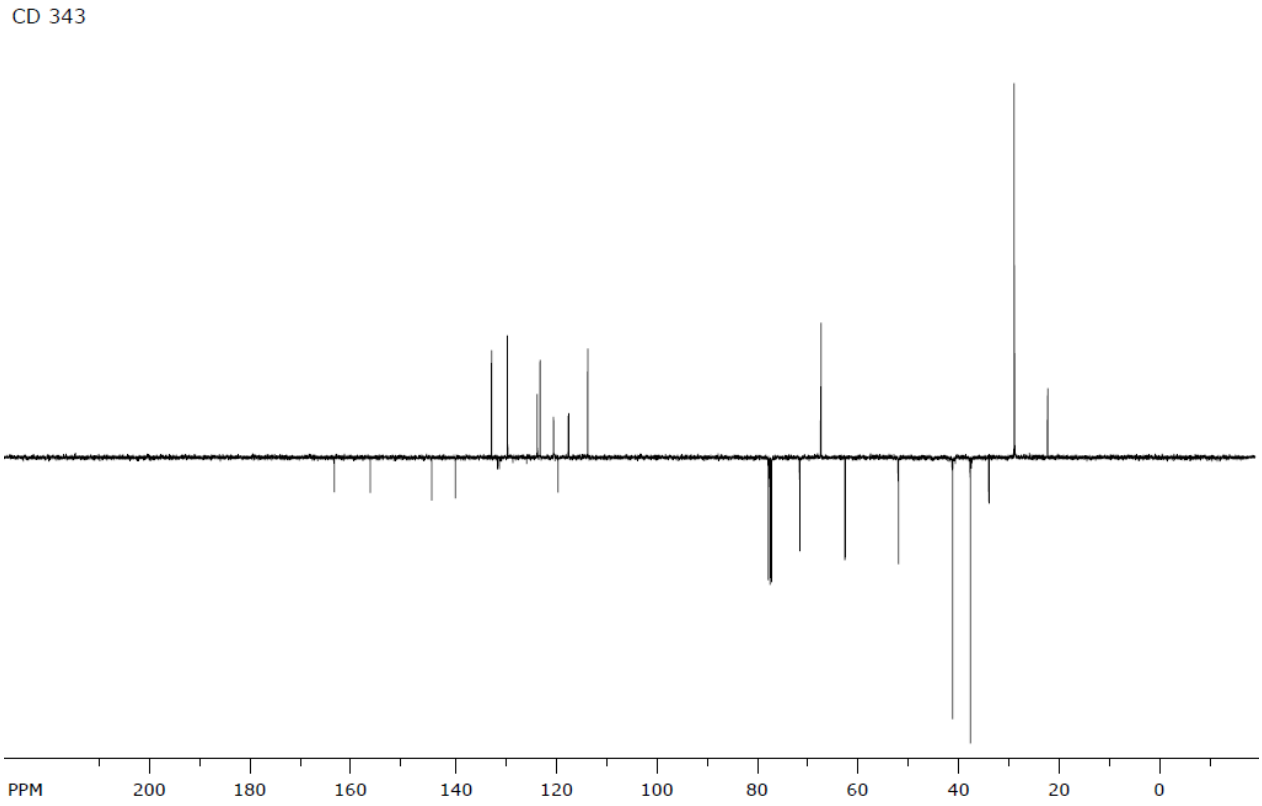
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-3-methyl-*N*-(3-(trifluoromethyl)phenyl)benzamide (241)



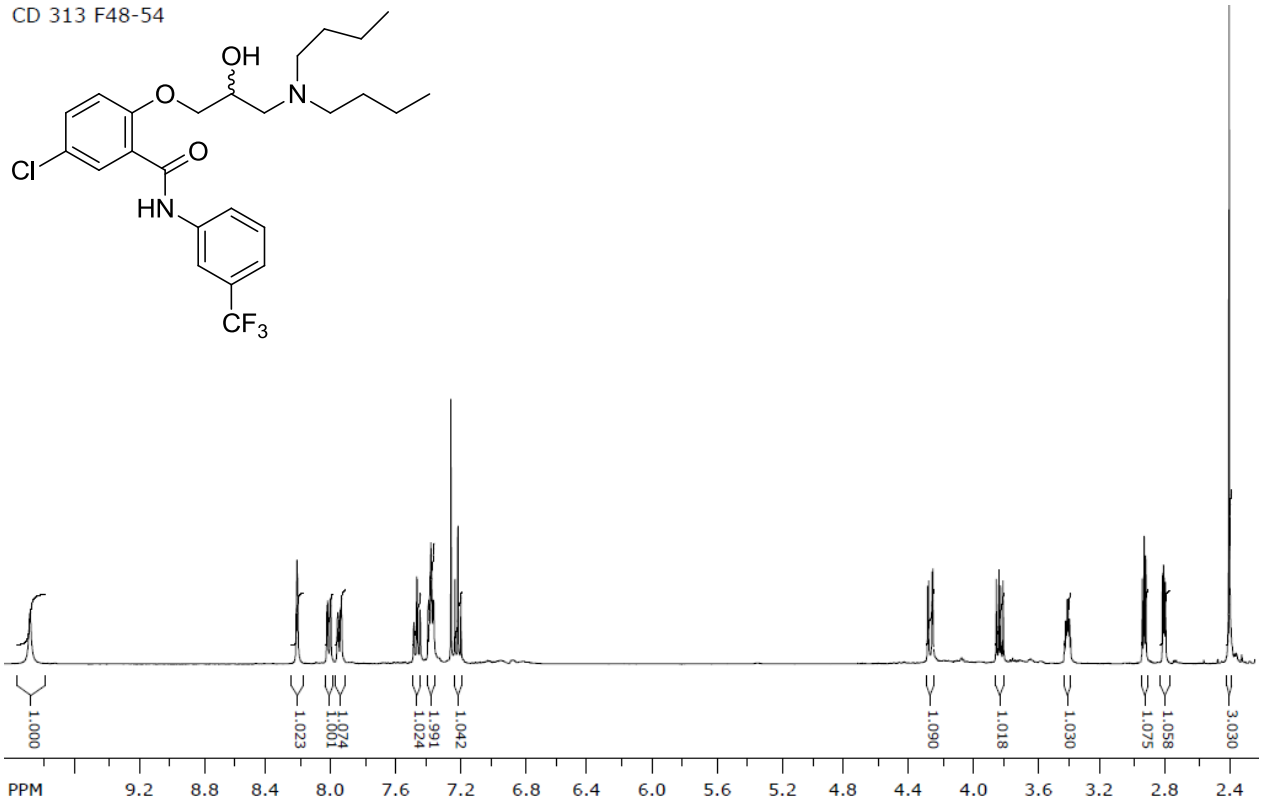


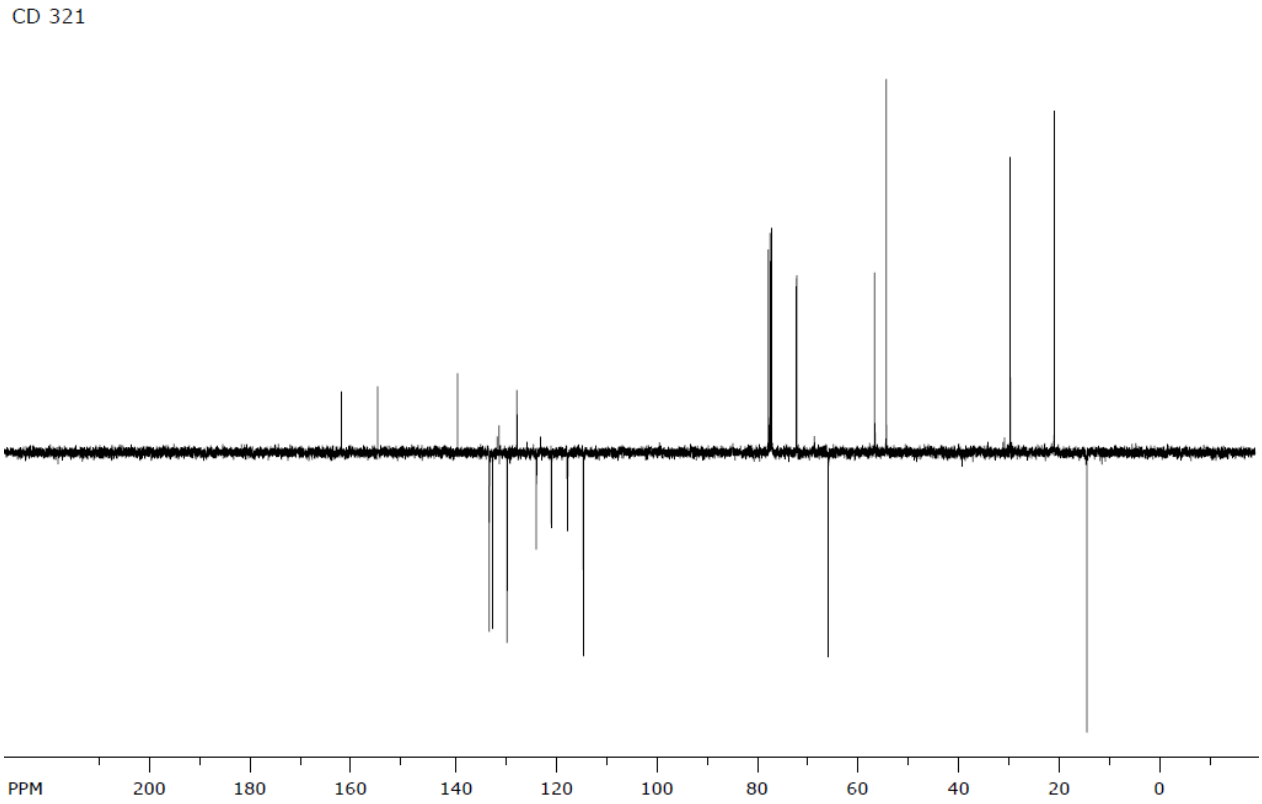
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-4-methyl-*N*-(3-(trifluoromethyl)phenyl)benzamide (242)



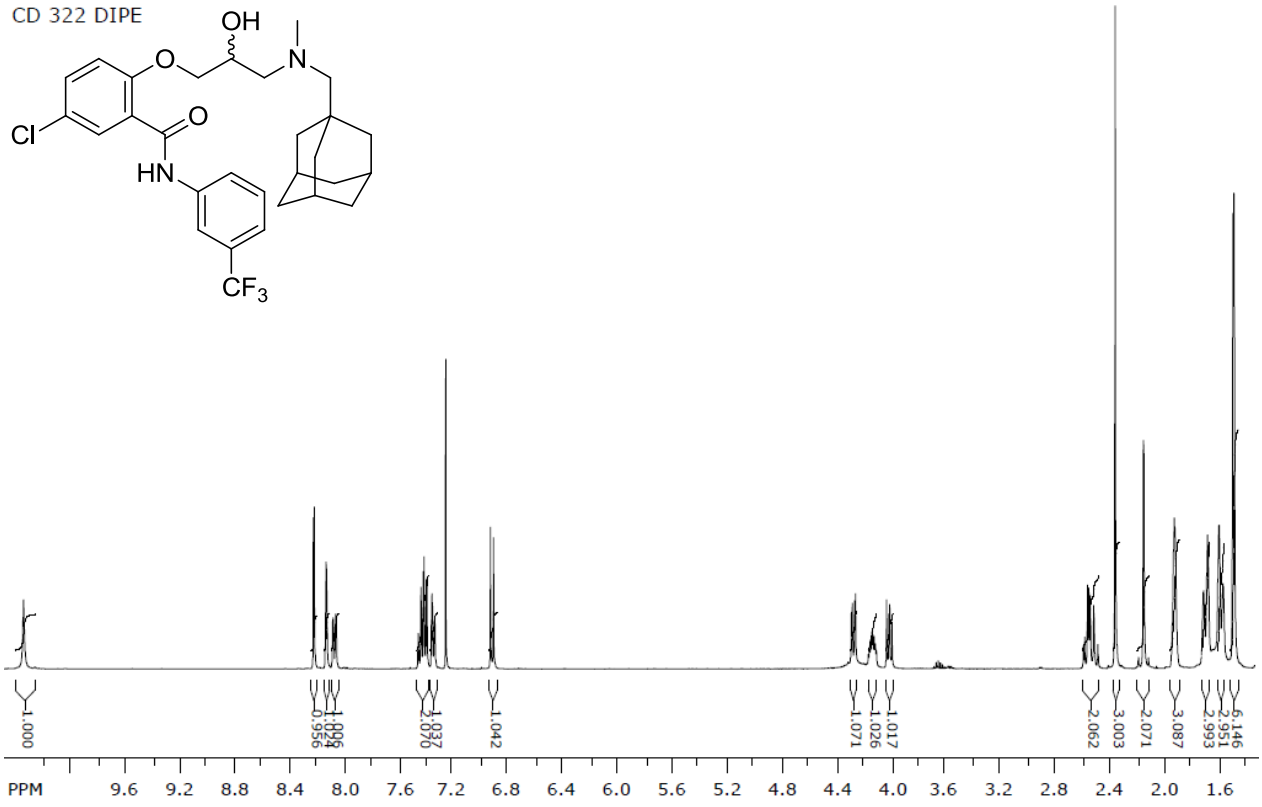


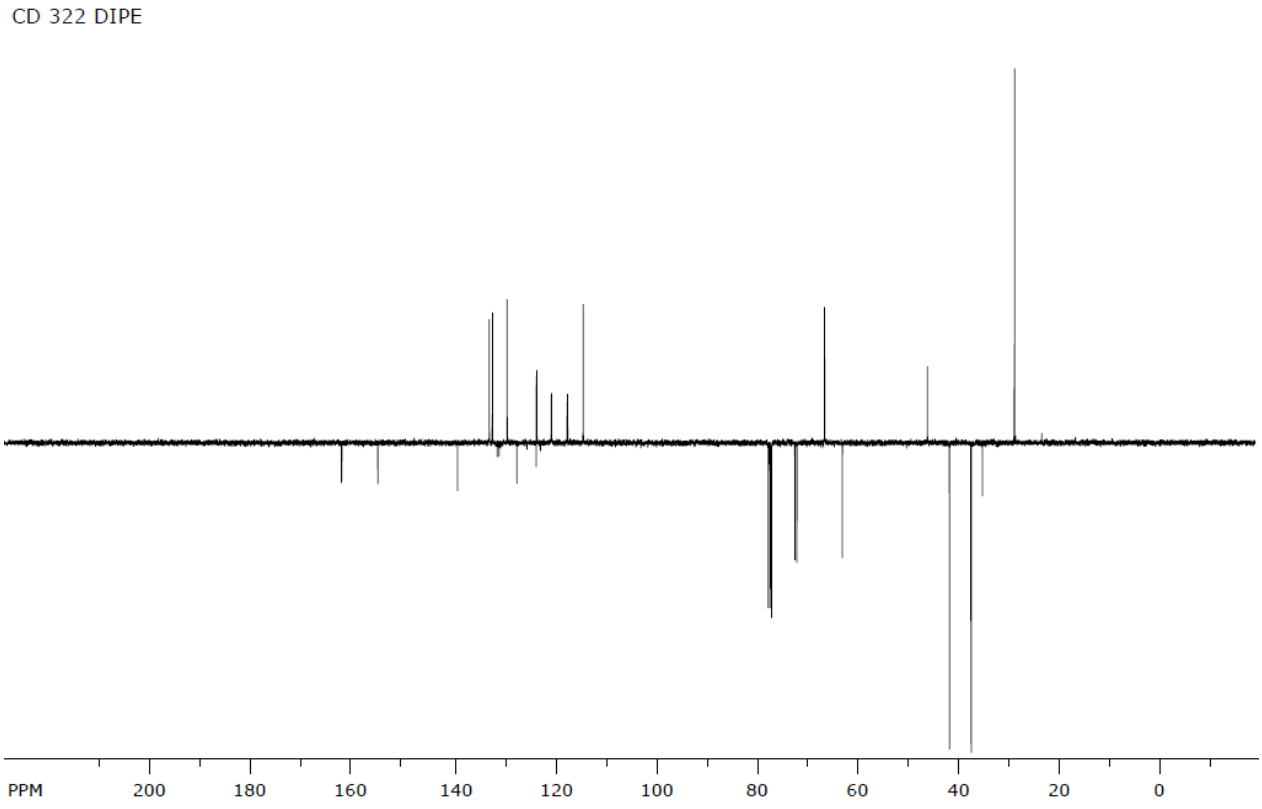
5-chloro-2-(3-(dibutylamino)-2-hydroxypropoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (243)



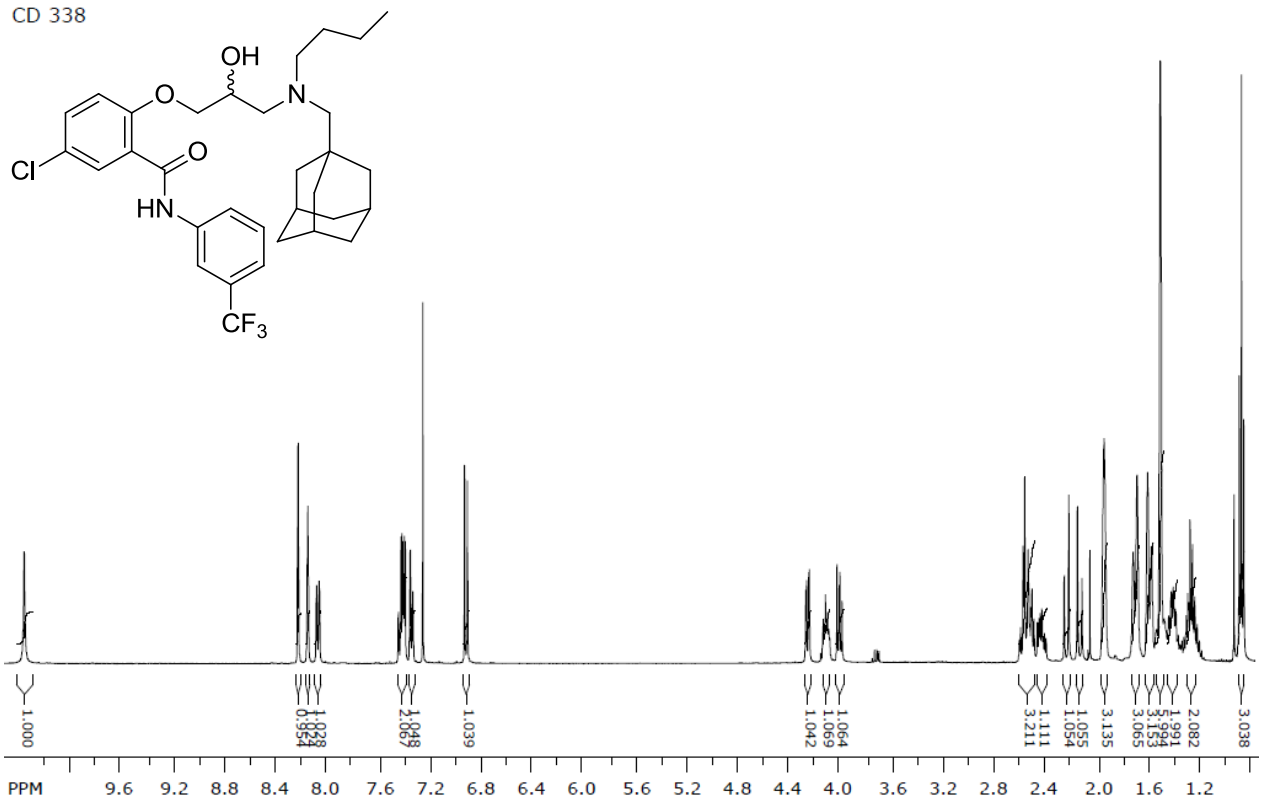


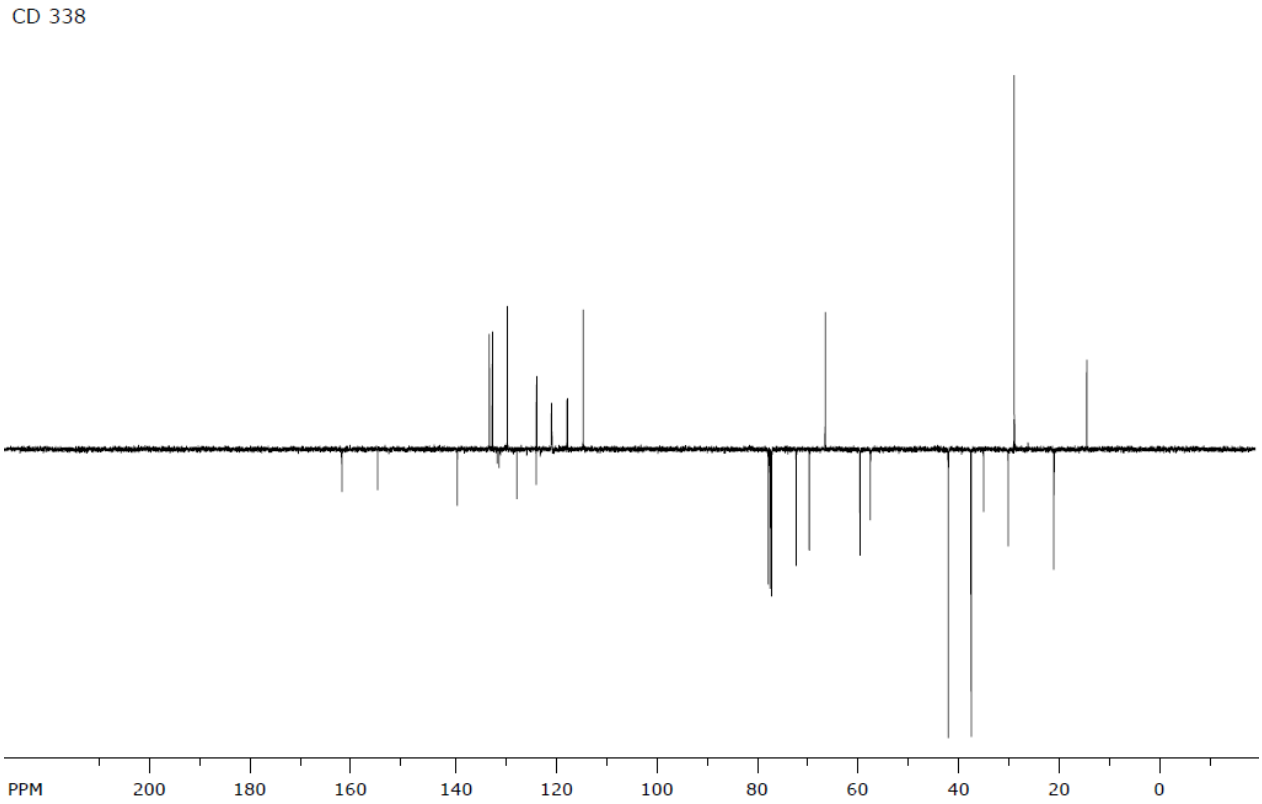
2-(3-((adamantan-1-ylmethyl)(methyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (244)



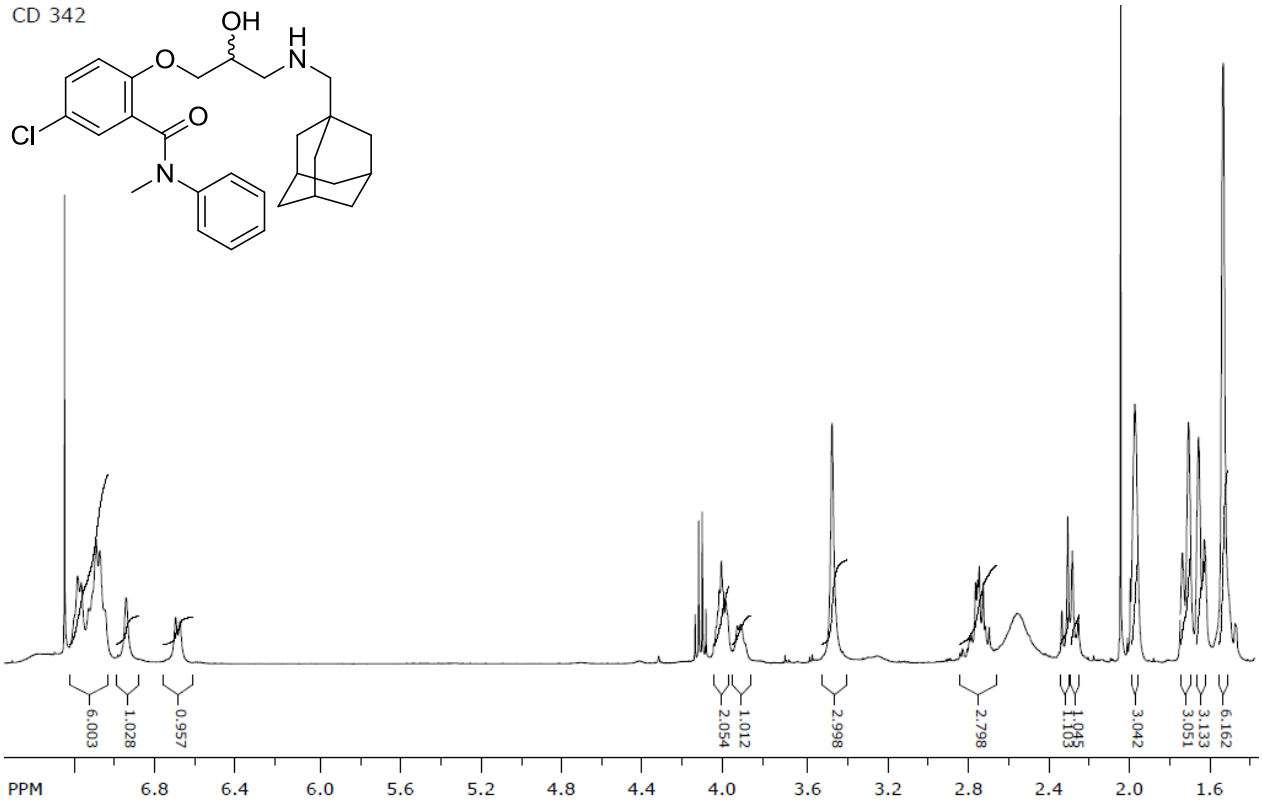


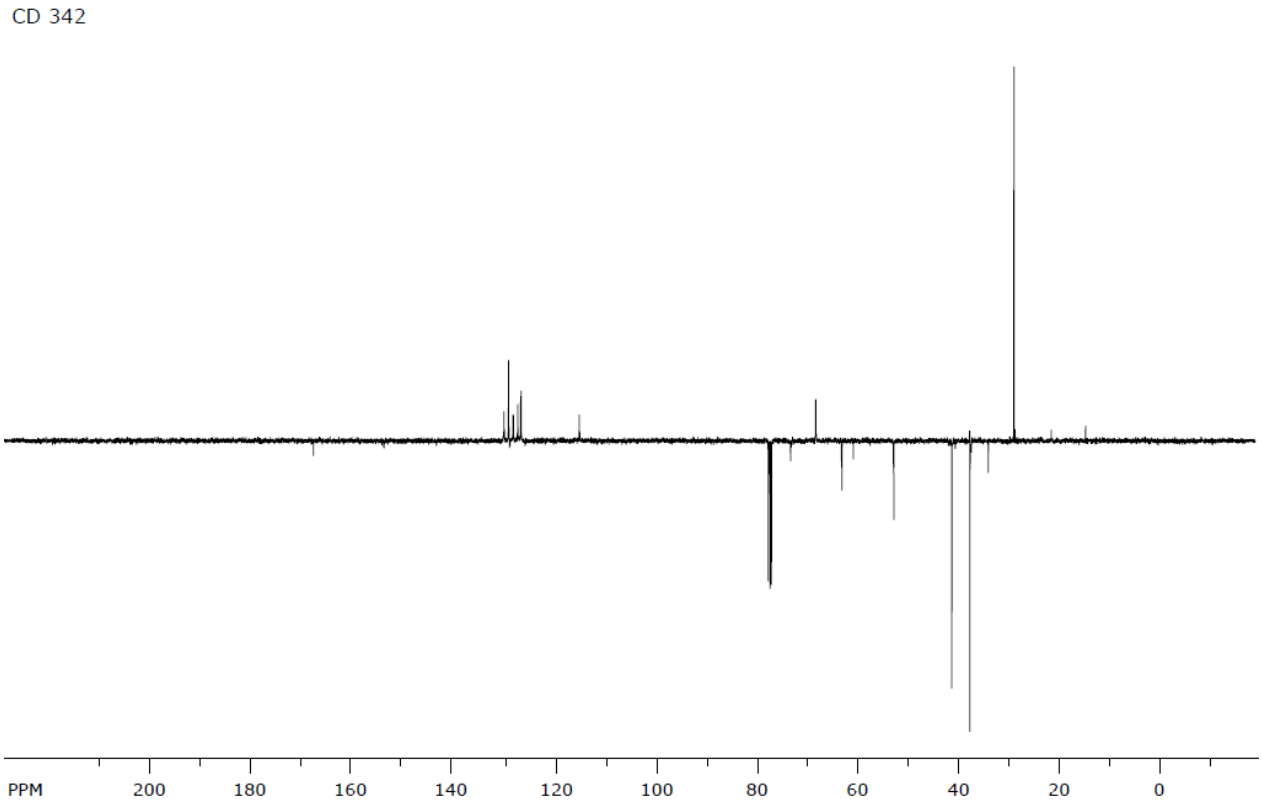
2-(3-((adamantan-1-ylmethyl)(butyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (245)



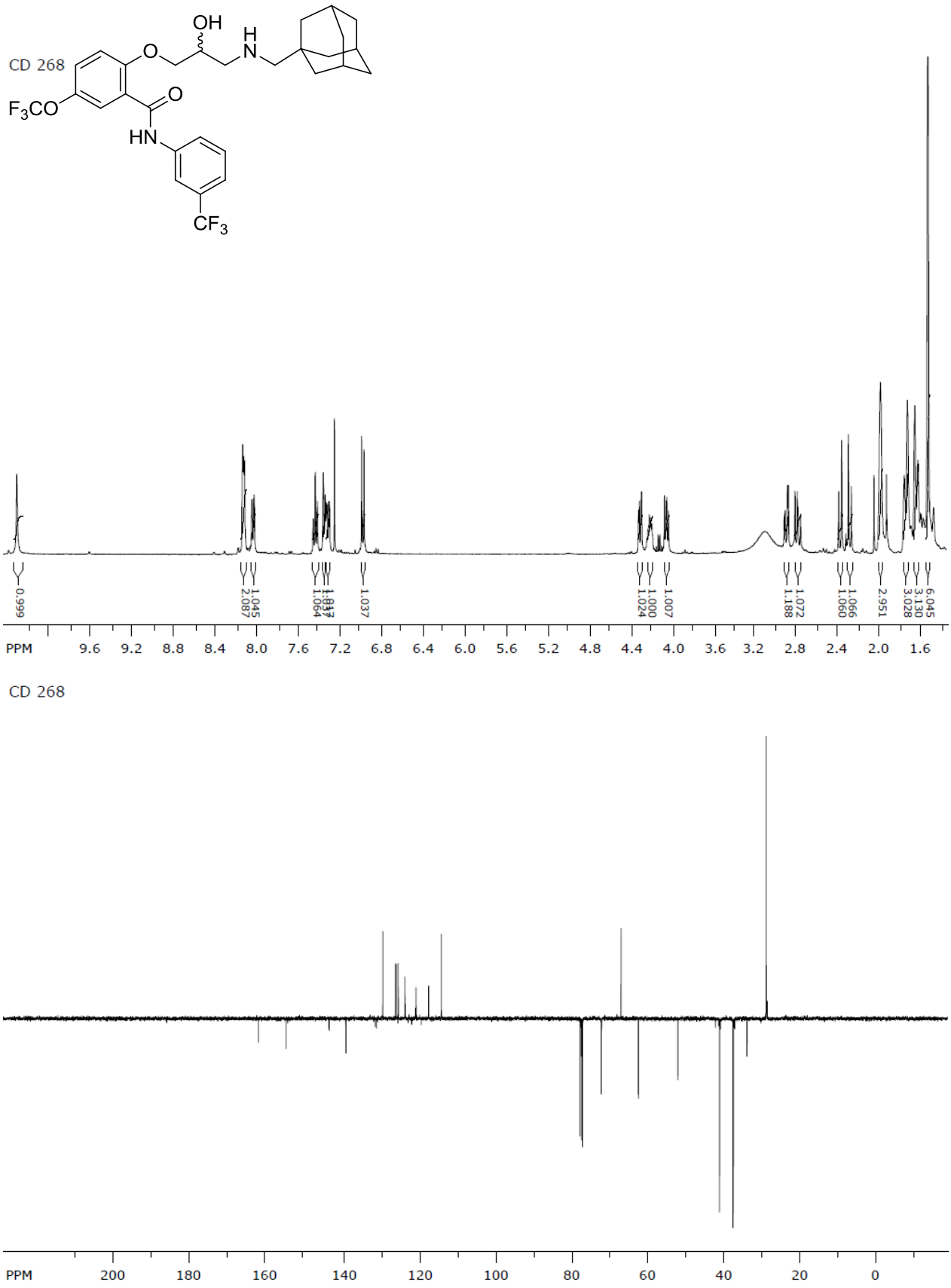


2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-methyl-*N*-phenylbenzamide (246)

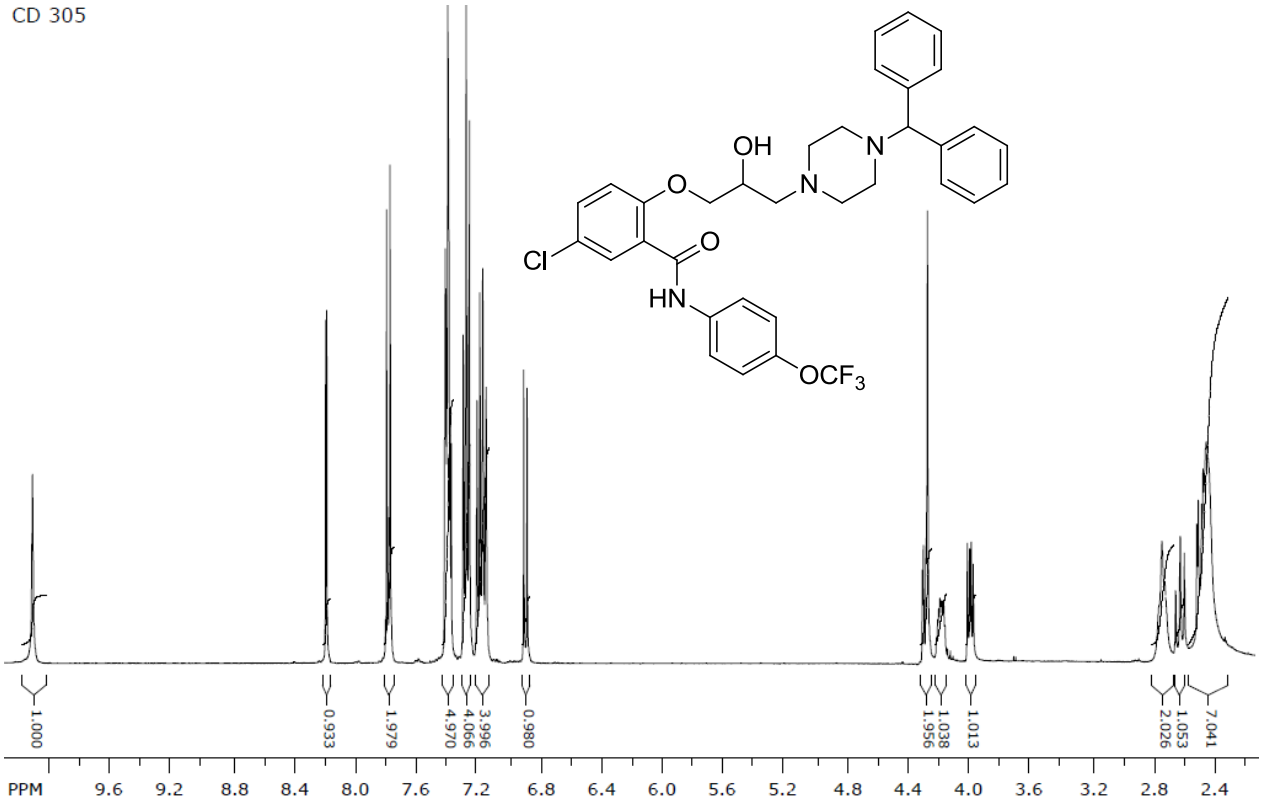


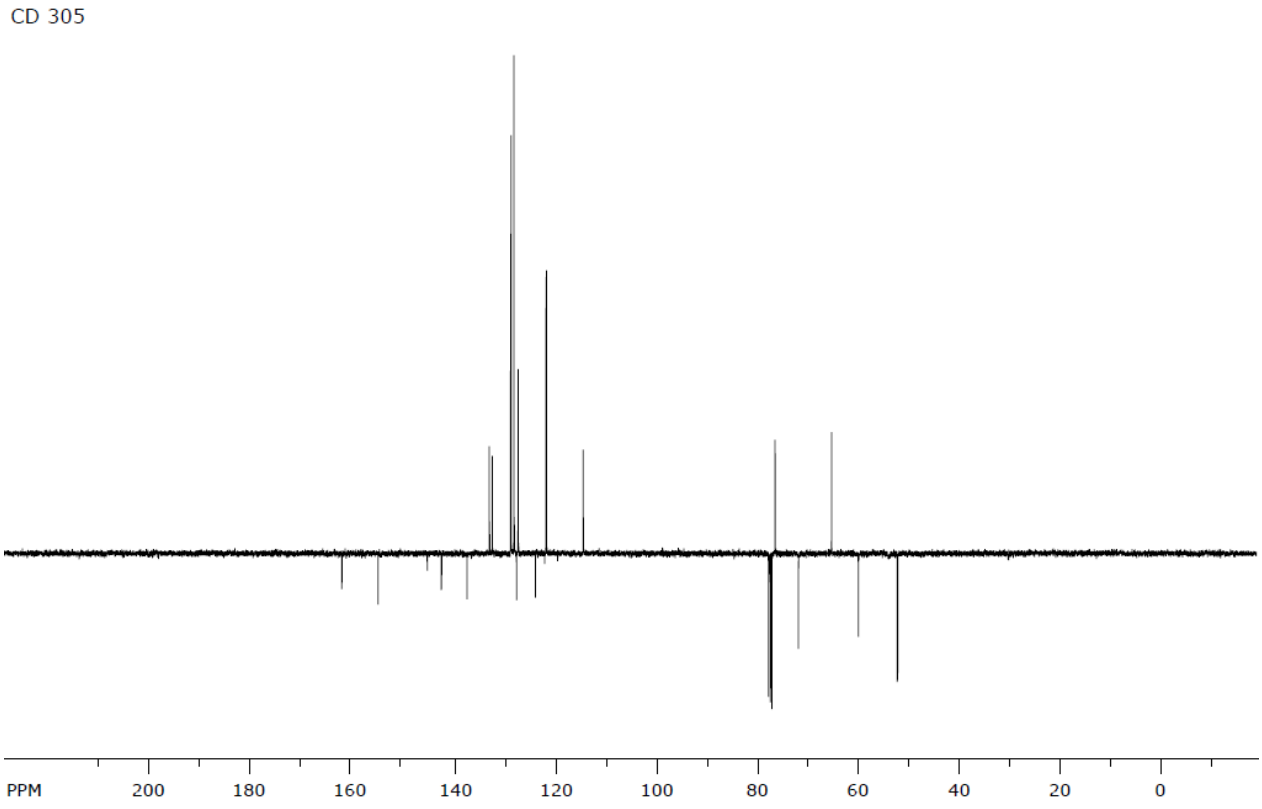


2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-(trifluoromethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (247)

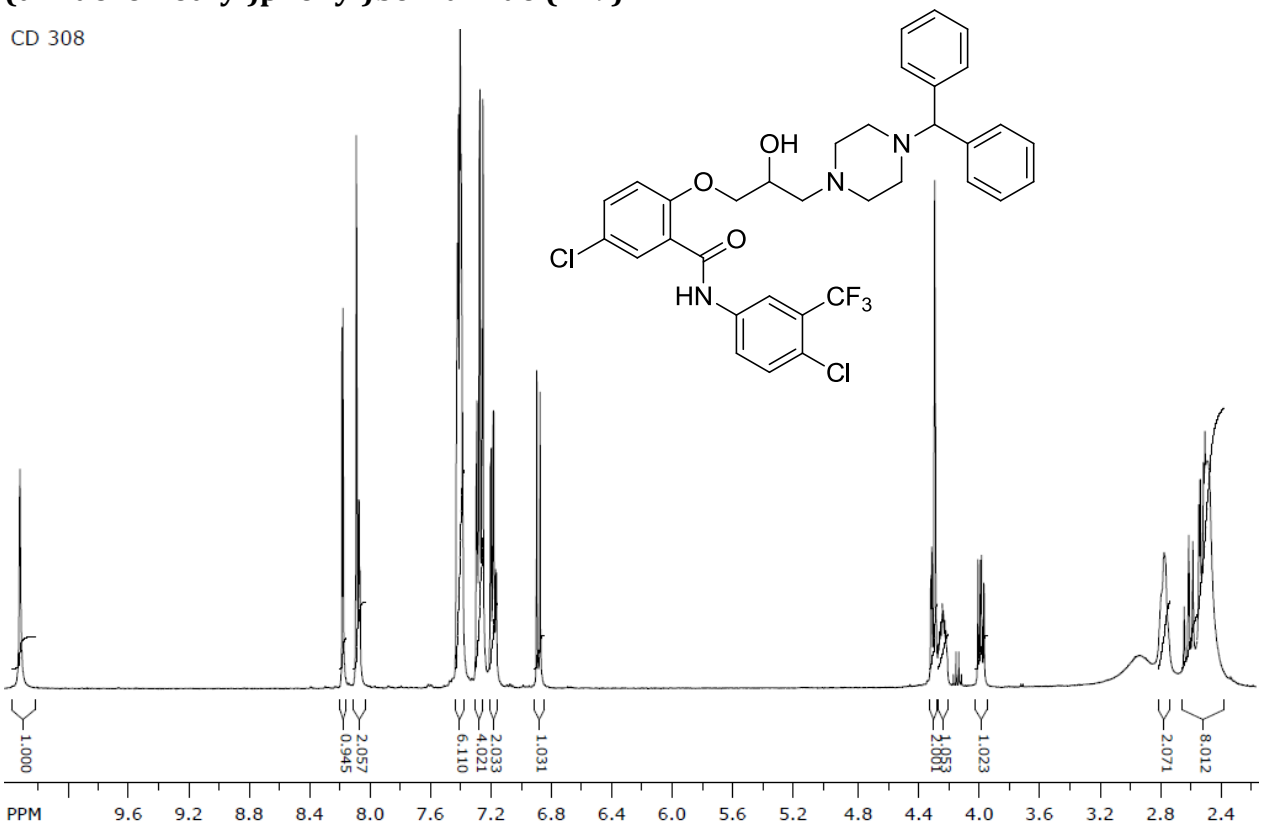


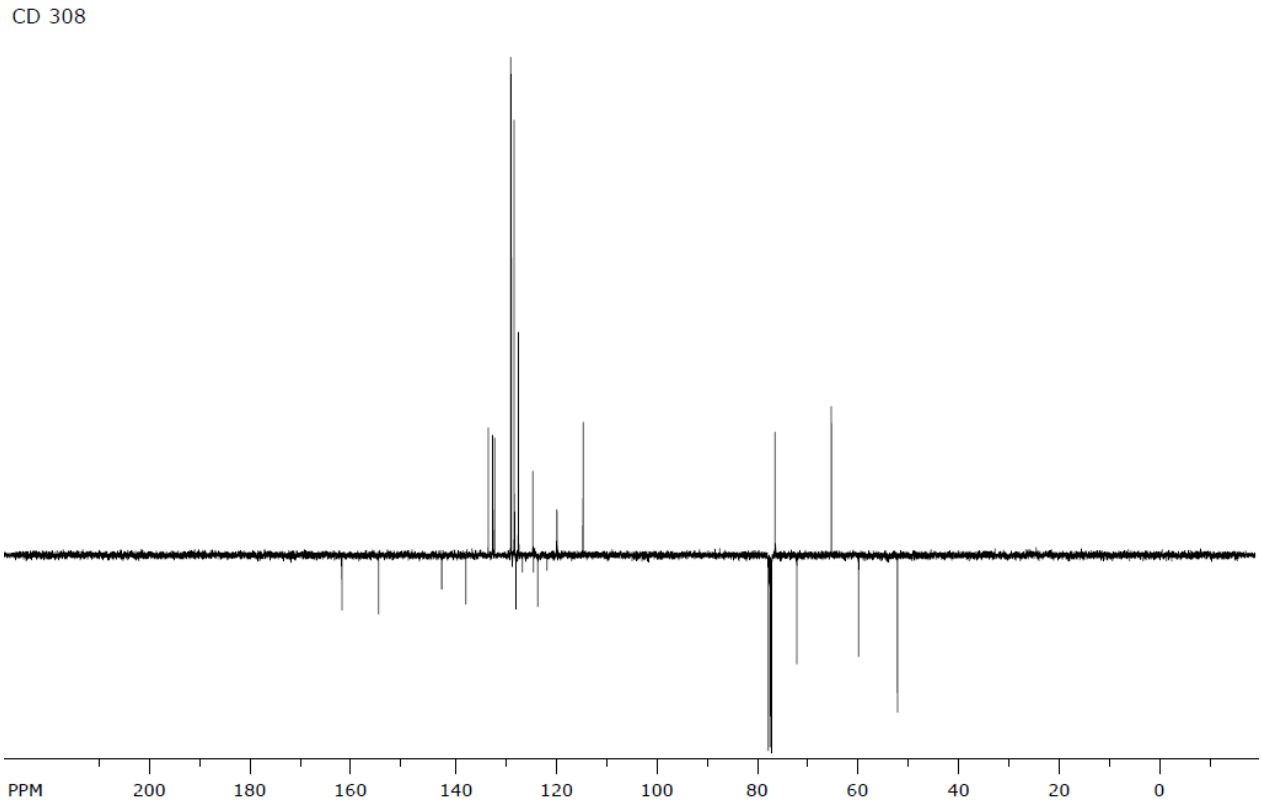
2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-5-chloro-*N*-(4-(trifluoromethoxy)phenyl)benzamide (248)



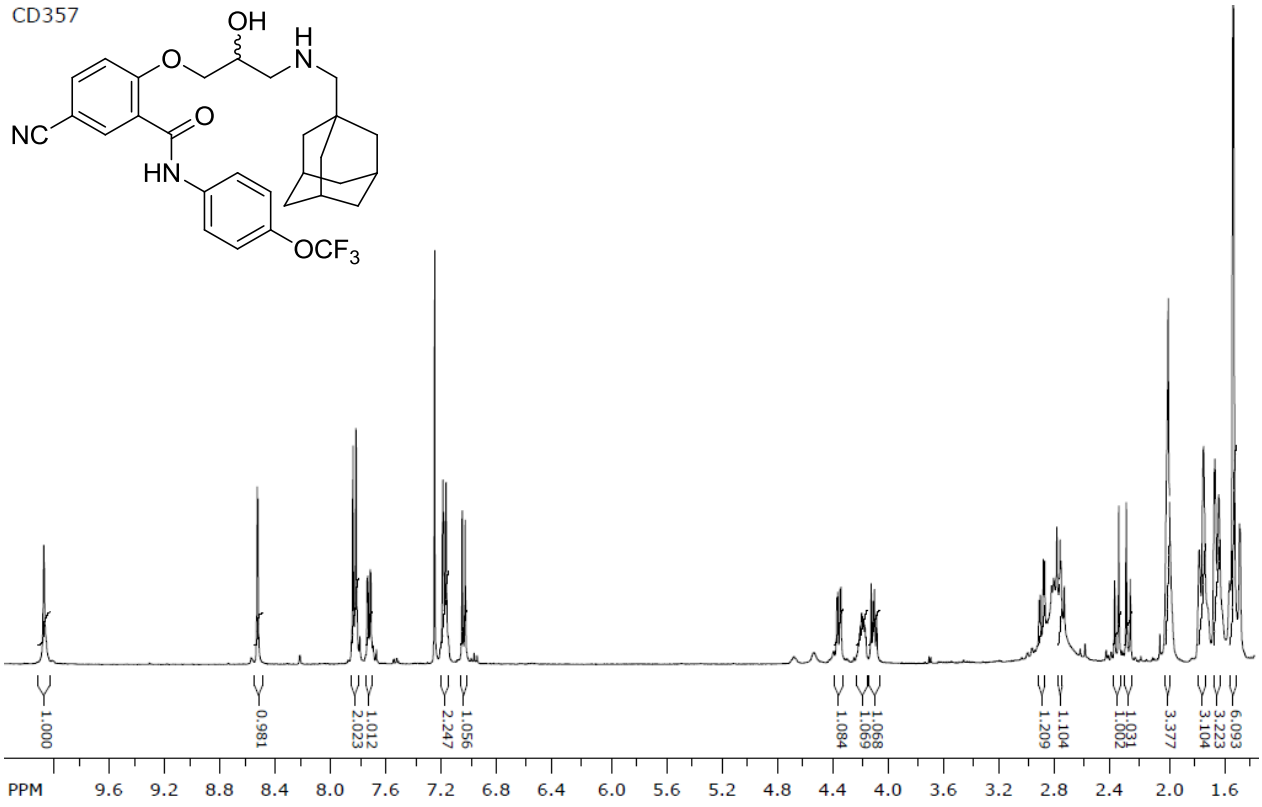


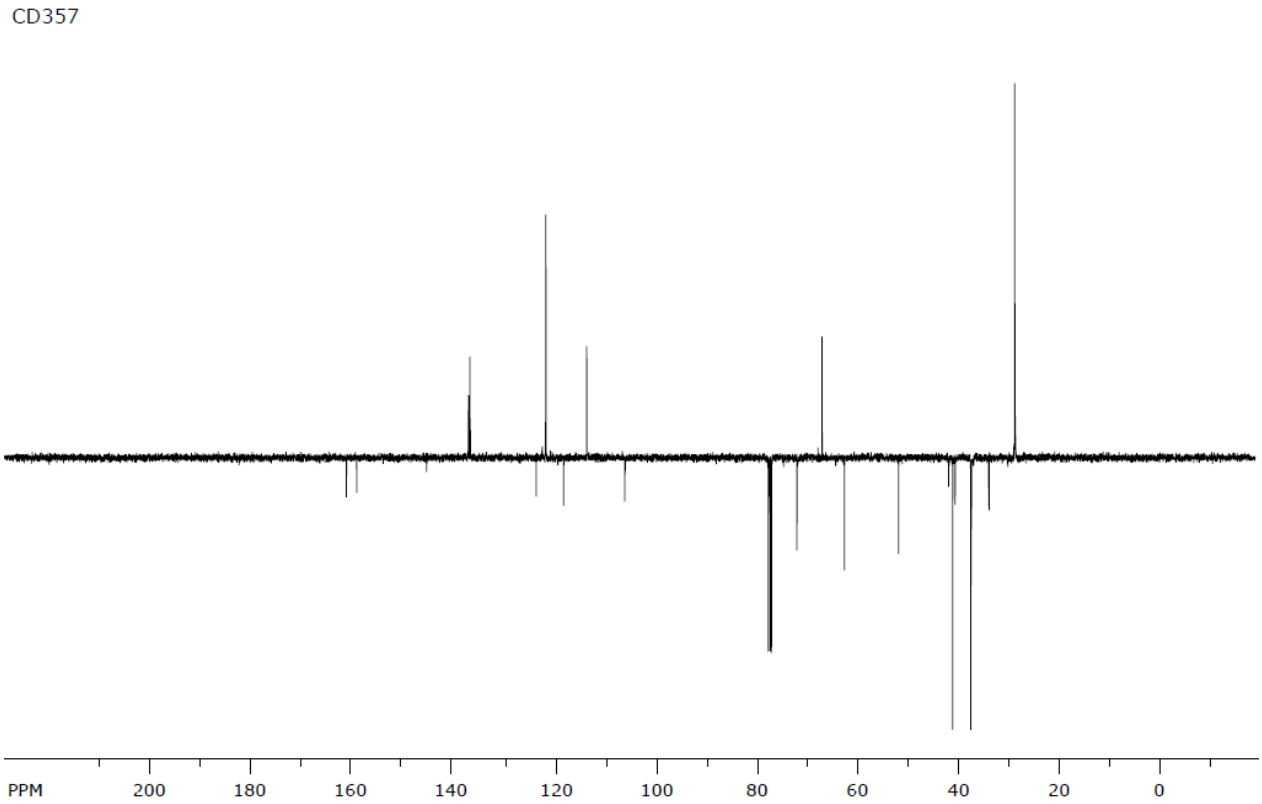
2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-5-chloro-*N*-(4-chloro-3-(trifluoromethyl)phenyl)benzamide (249)



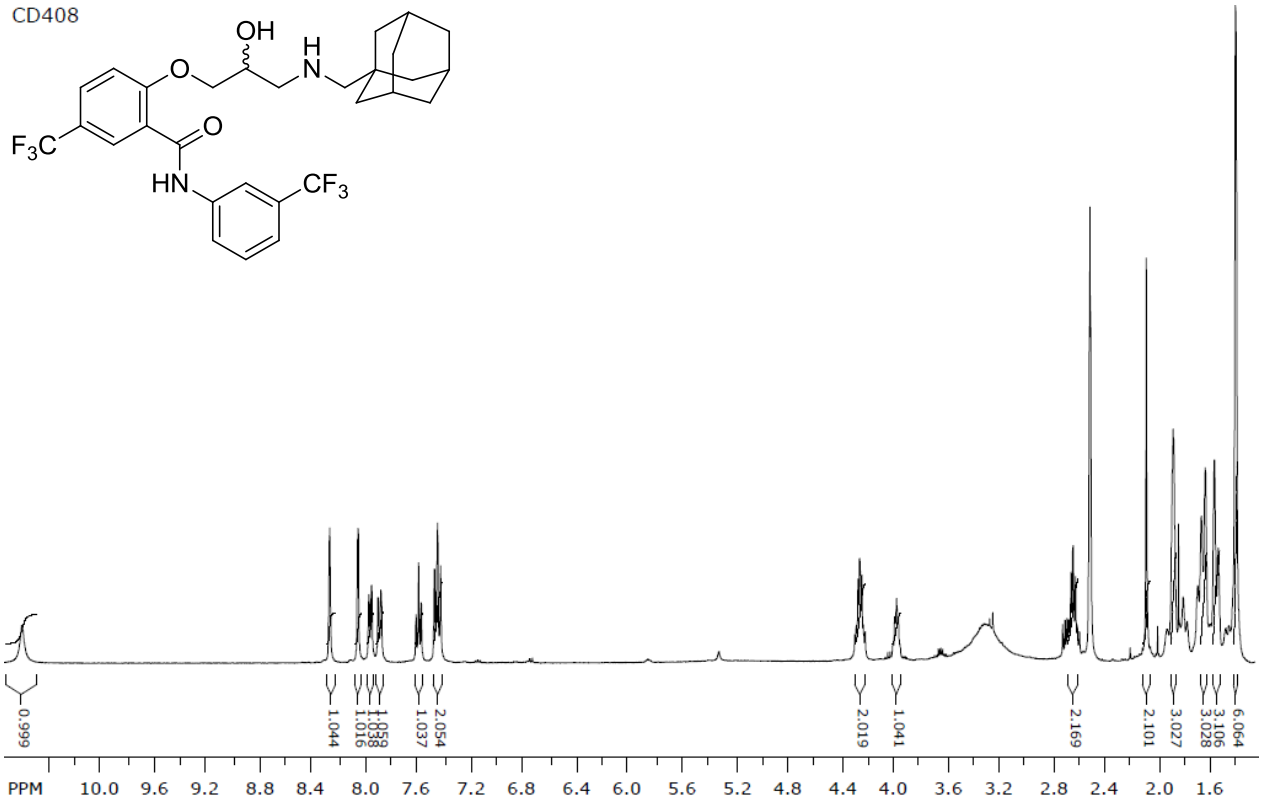


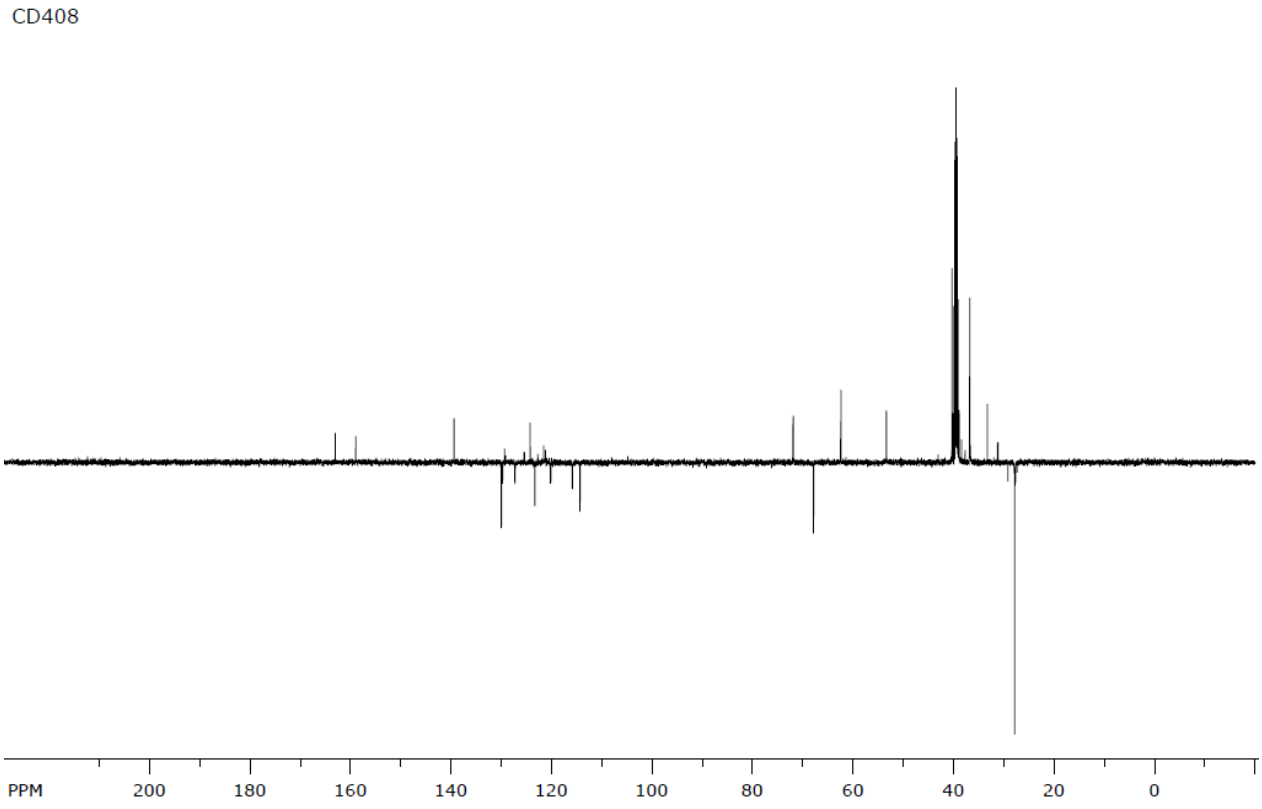
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-cyano-*N*-(4-(trifluoromethoxy)phenyl)benzamide (250)



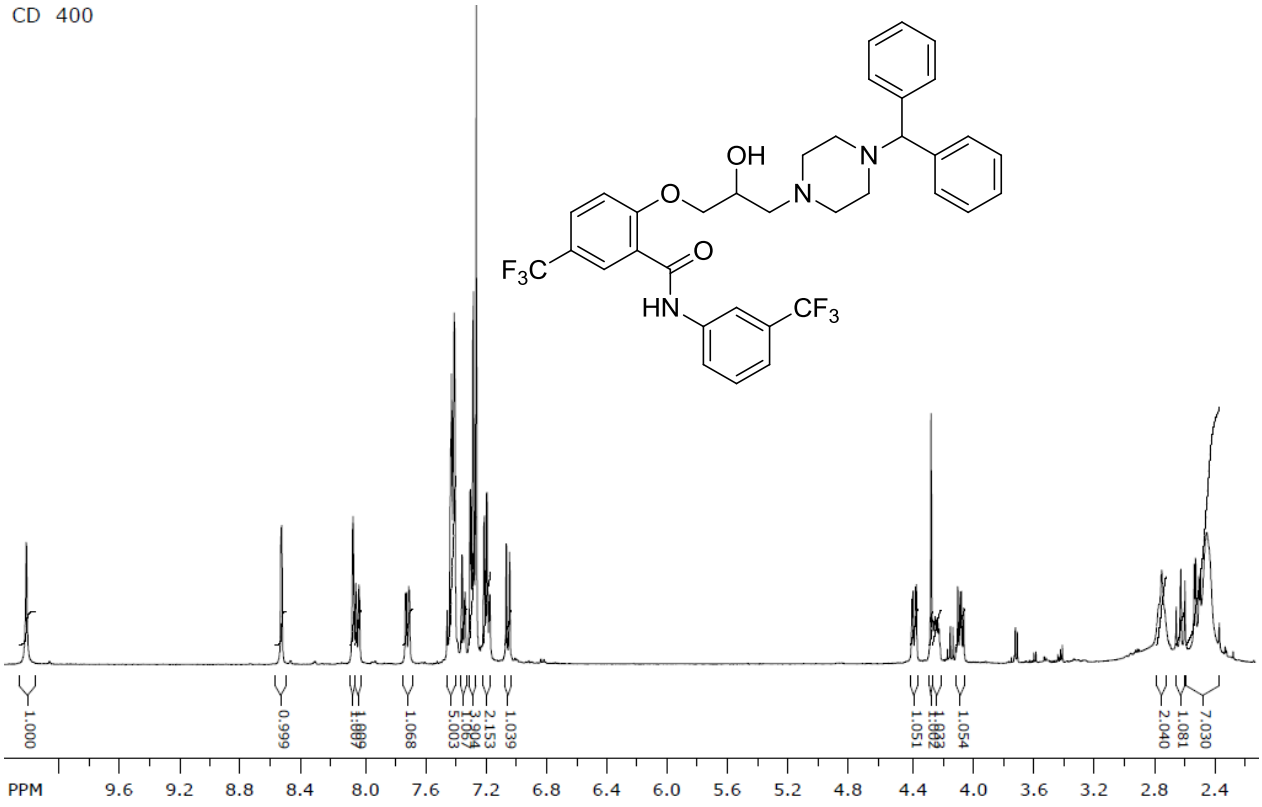


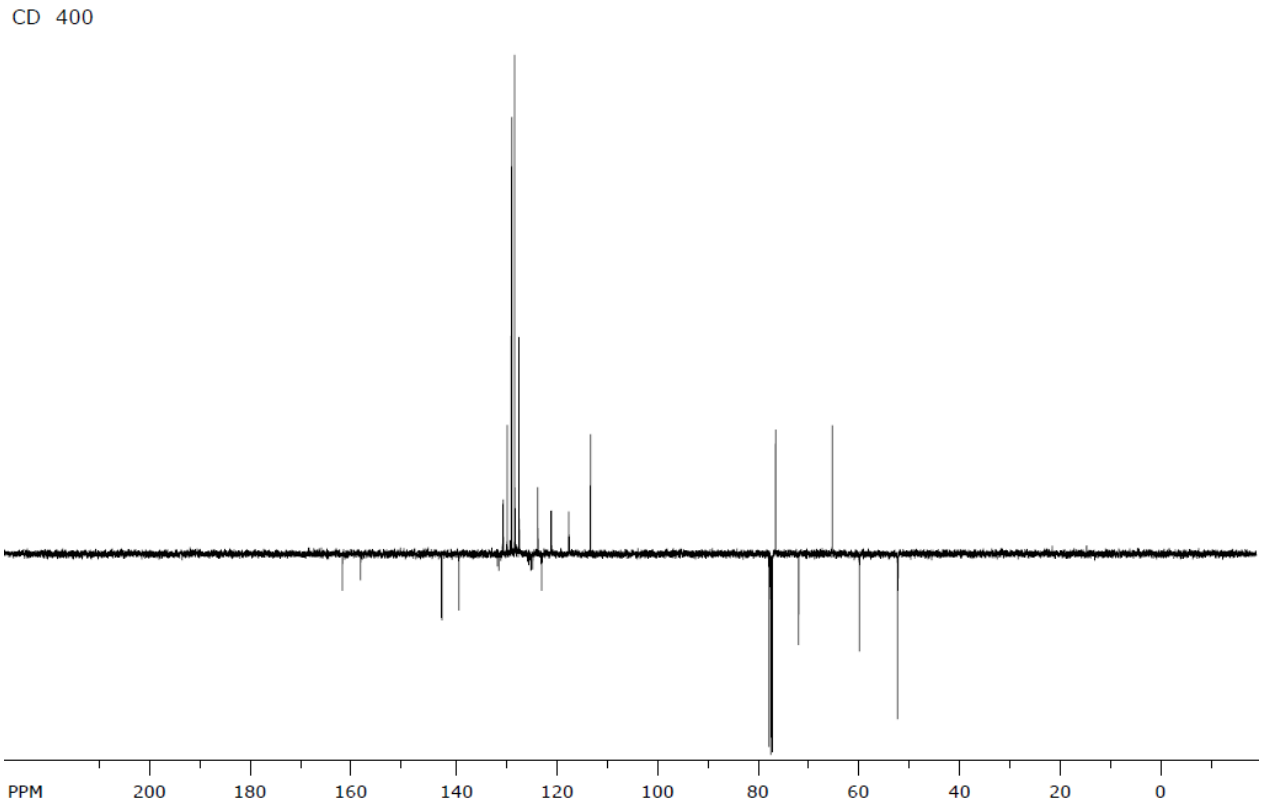
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-(trifluoromethyl)-*N*-(3-(trifluoromethyl)phenyl)benzamide (251)



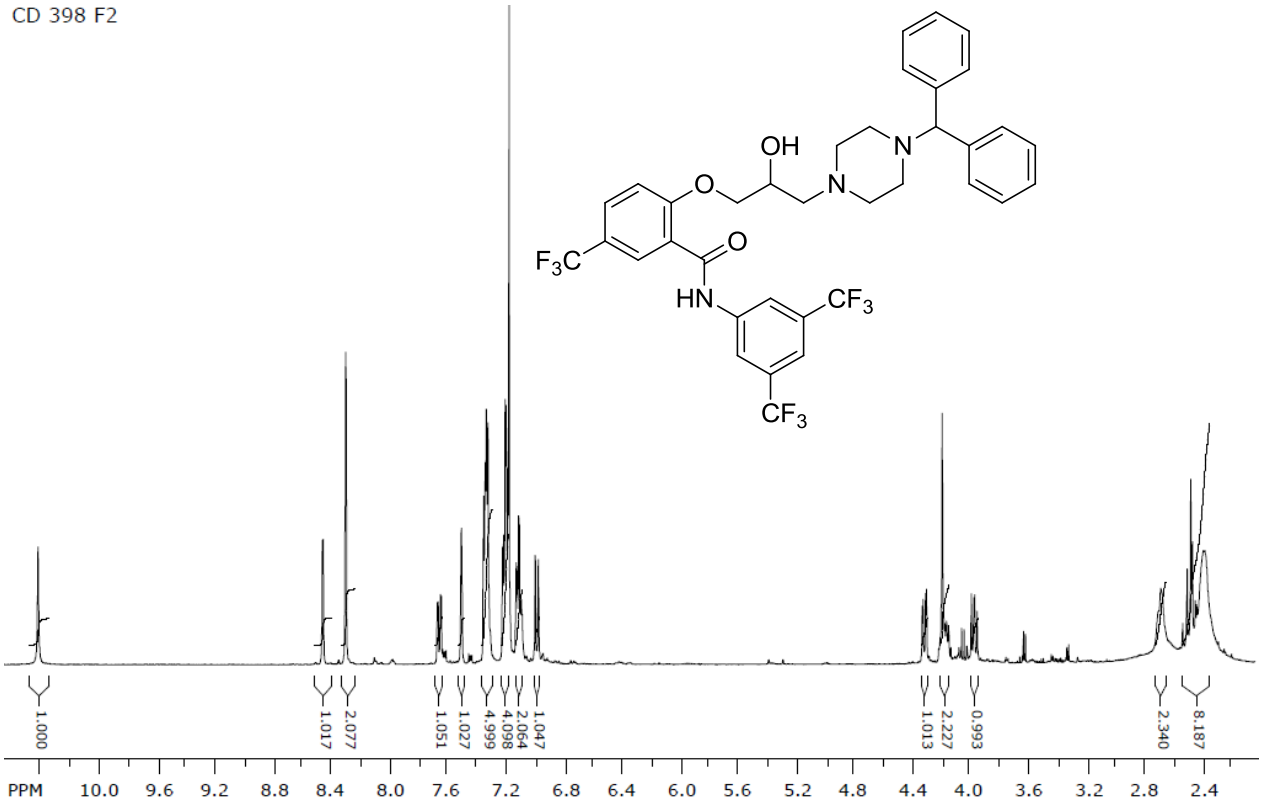


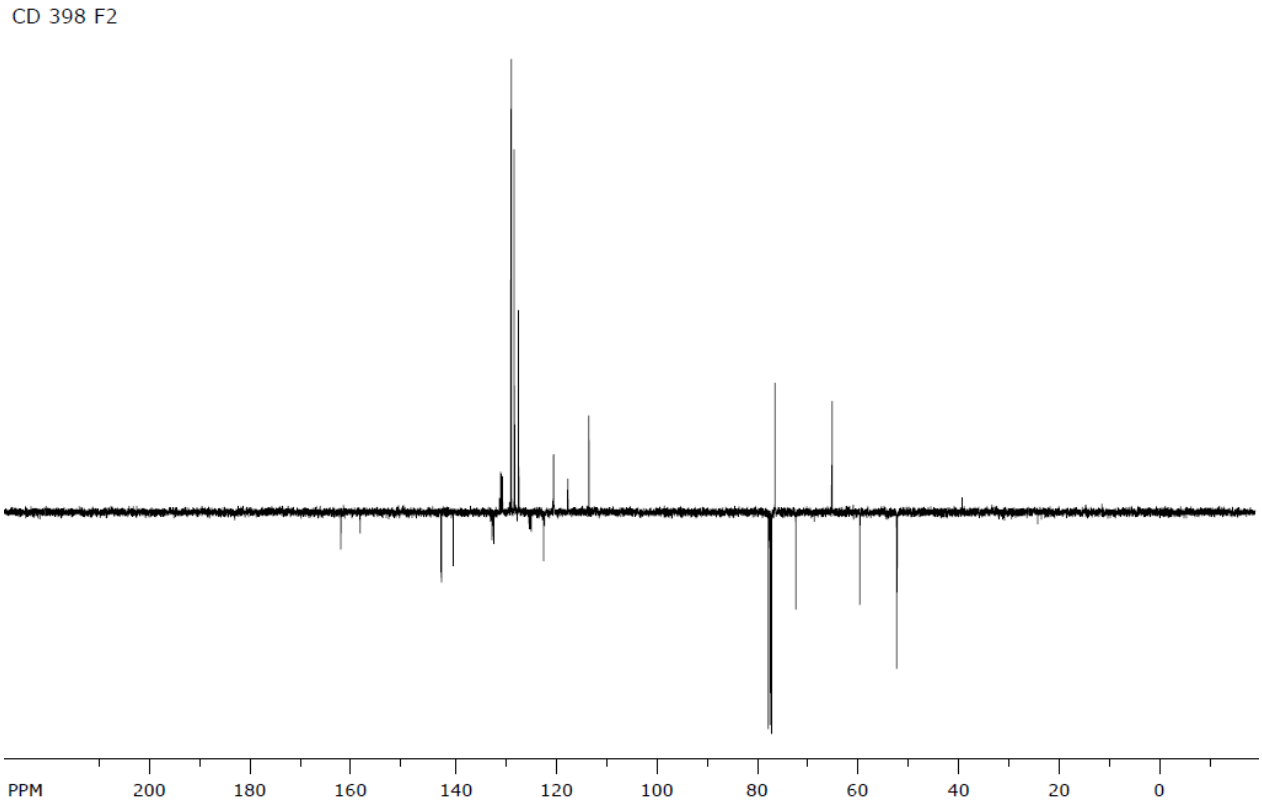
2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-5-(trifluoromethyl)-*N*-(3-(trifluoromethyl)phenyl)benzamide (252)



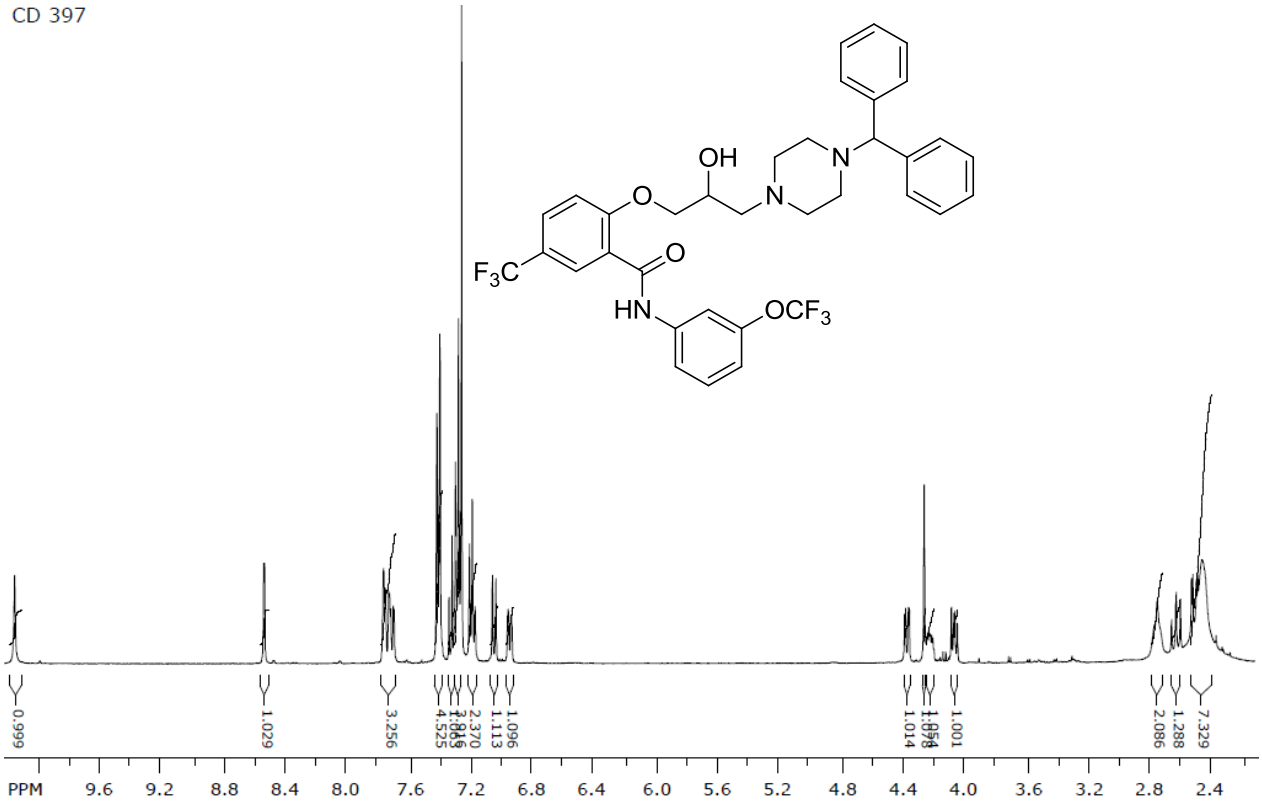


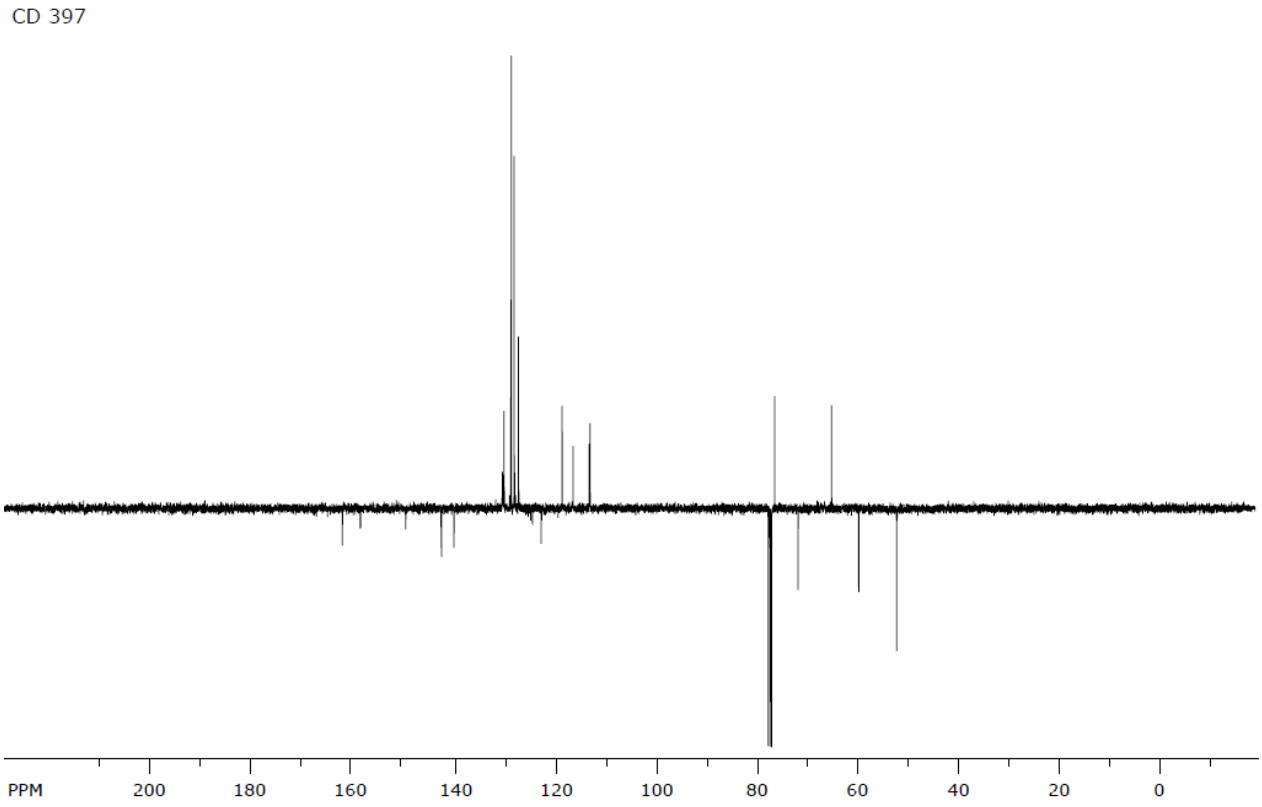
2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)benzamide (253)



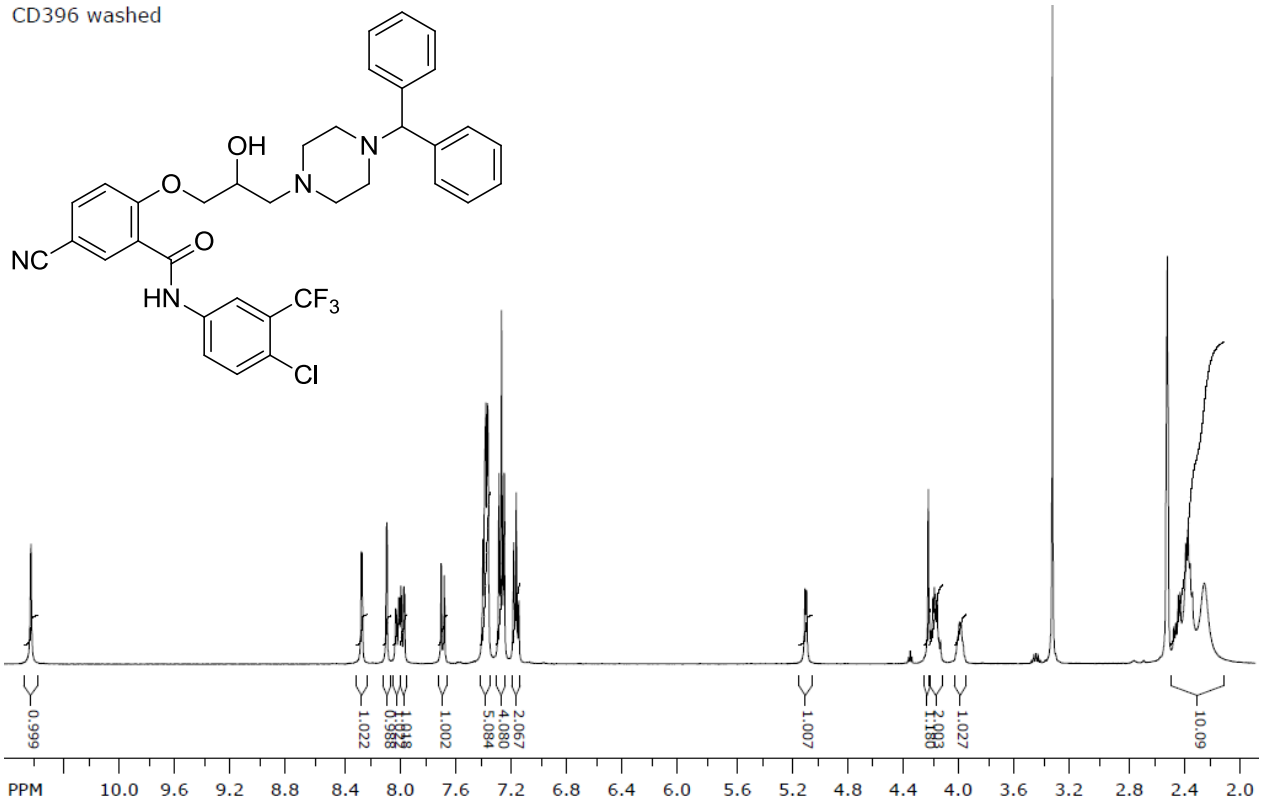


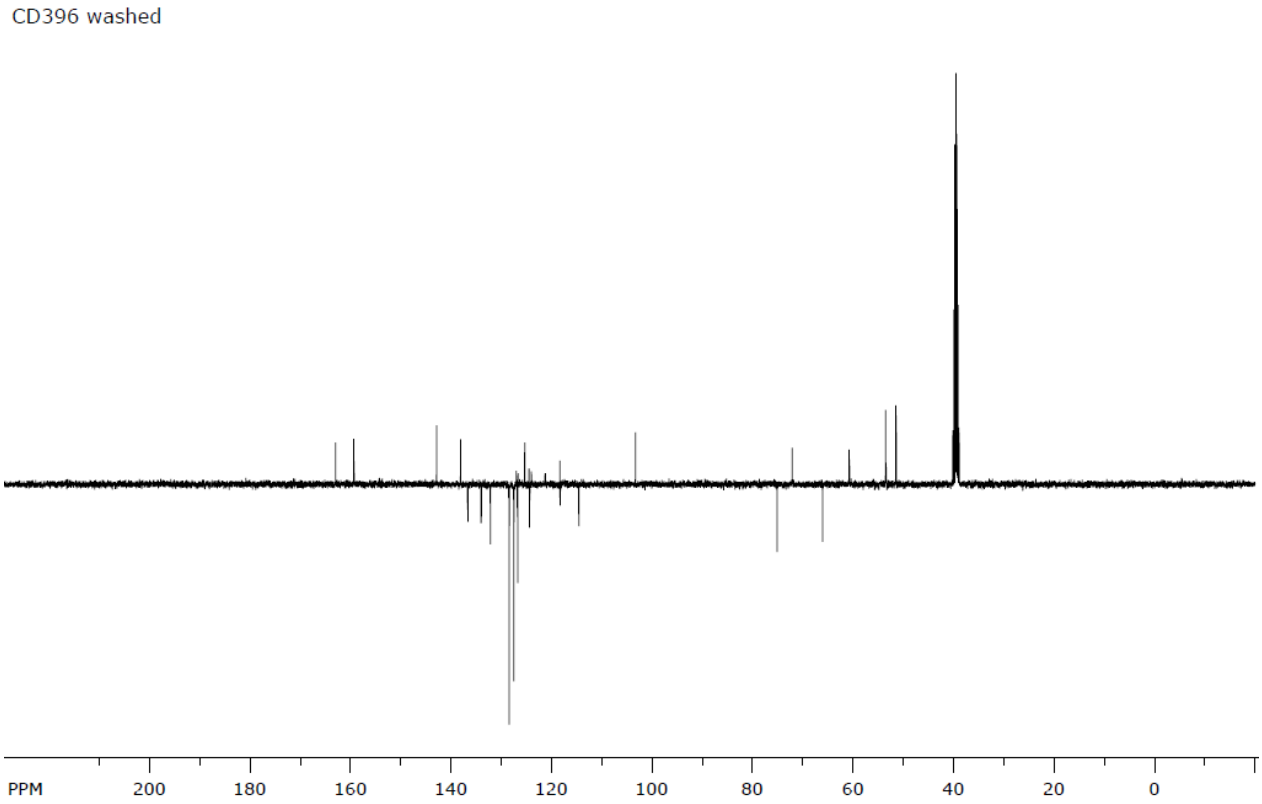
2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(3-(trifluoromethoxy)phenyl)-5-(trifluoromethyl)benzamide (254)



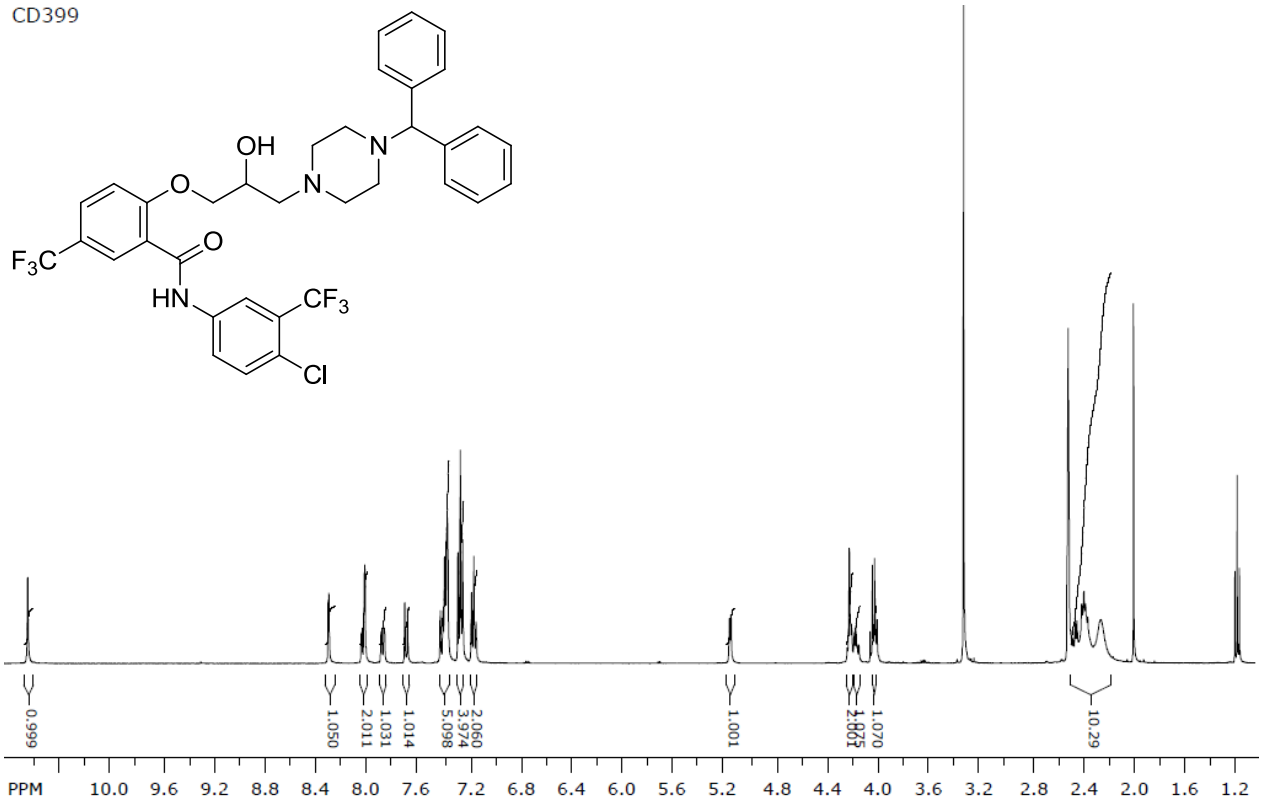


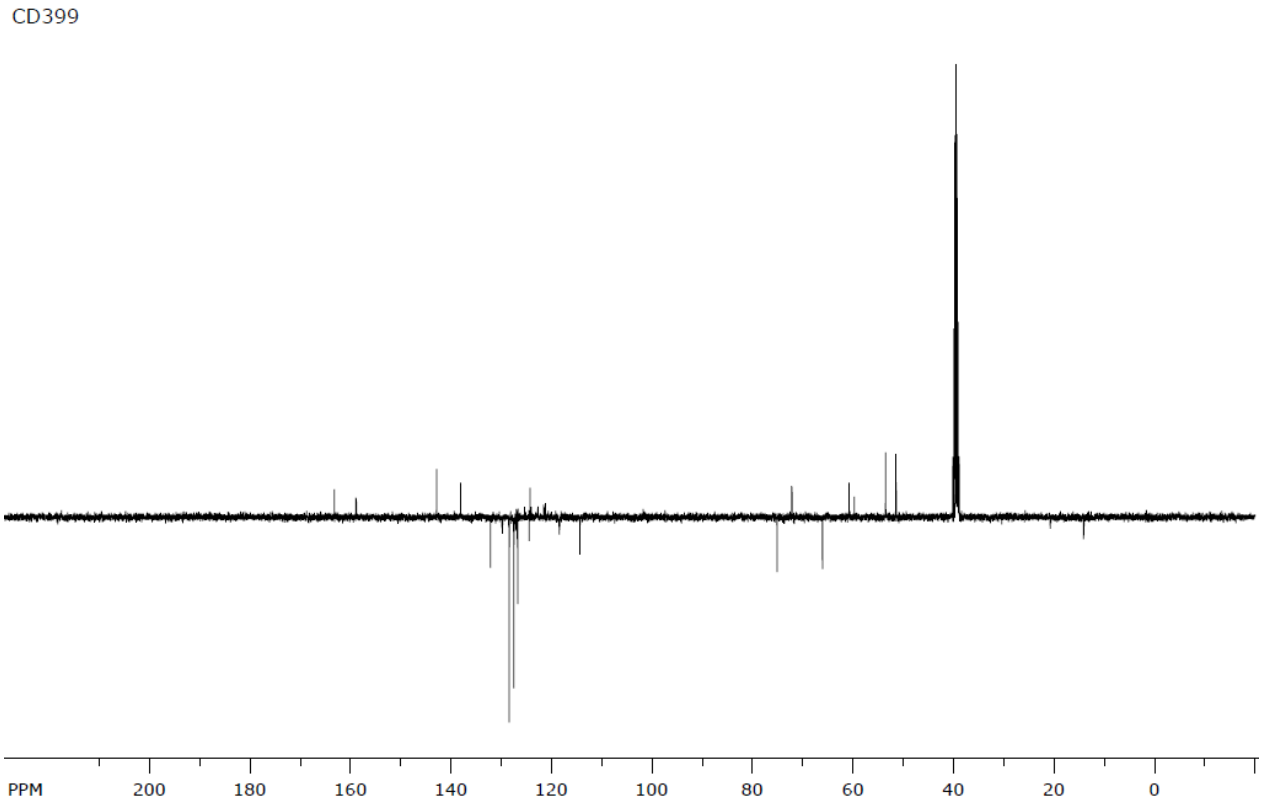
2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(4-chloro-3-(trifluoromethyl)phenyl)-5-cyanobenzamide (255)



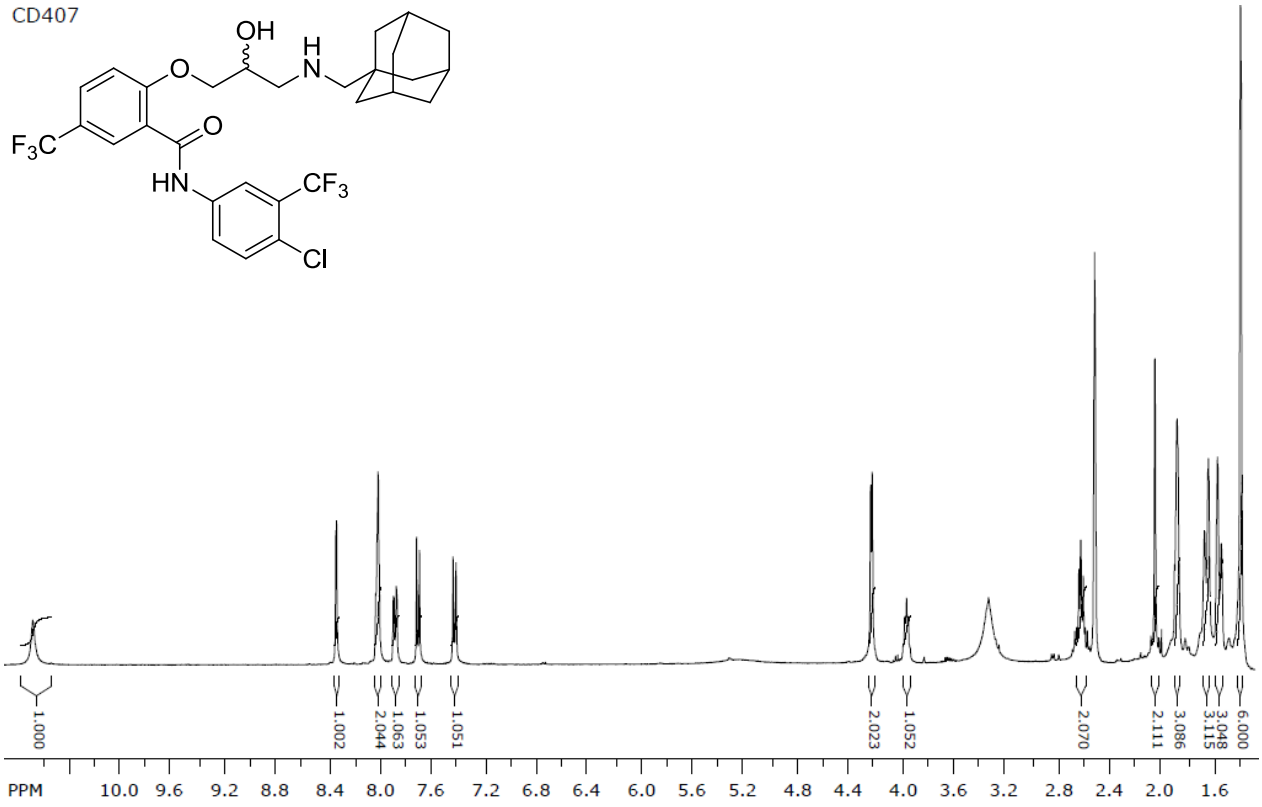


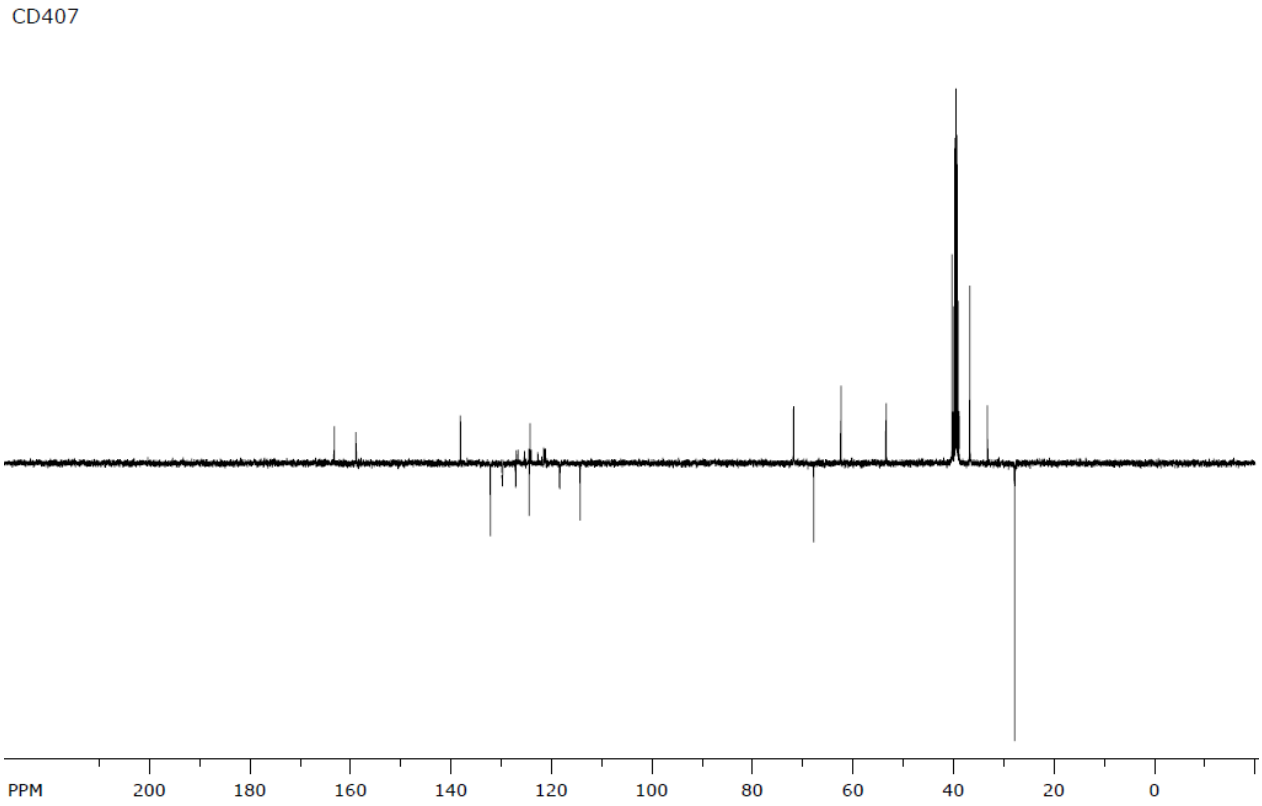
2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)benzamide (256)



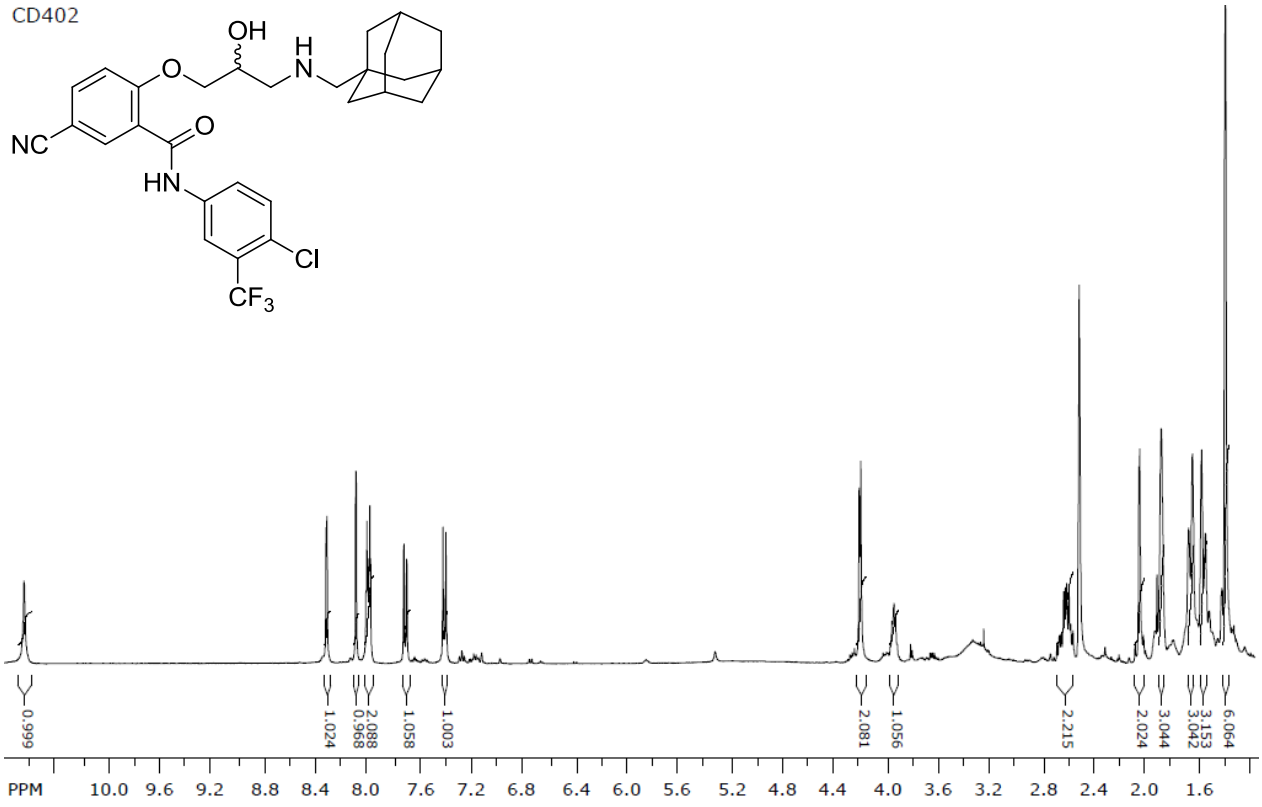


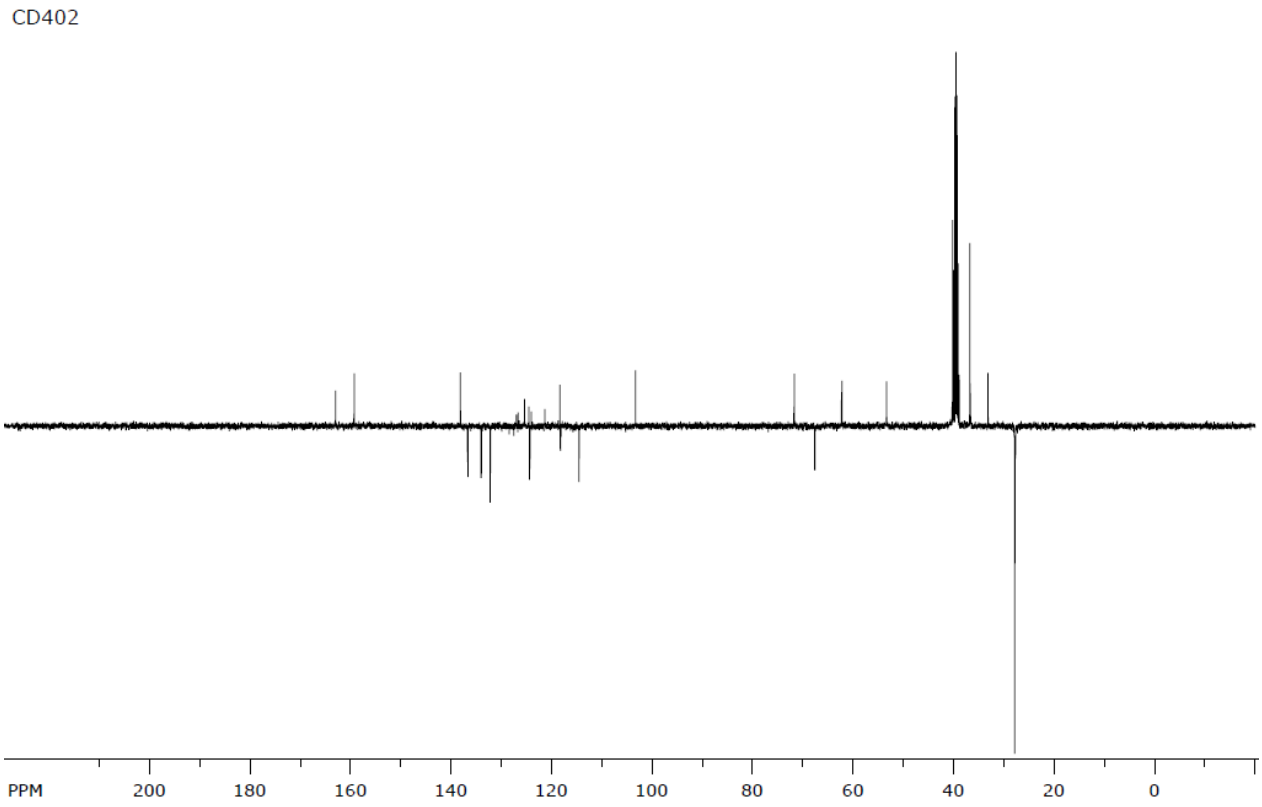
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)benzamide (257)



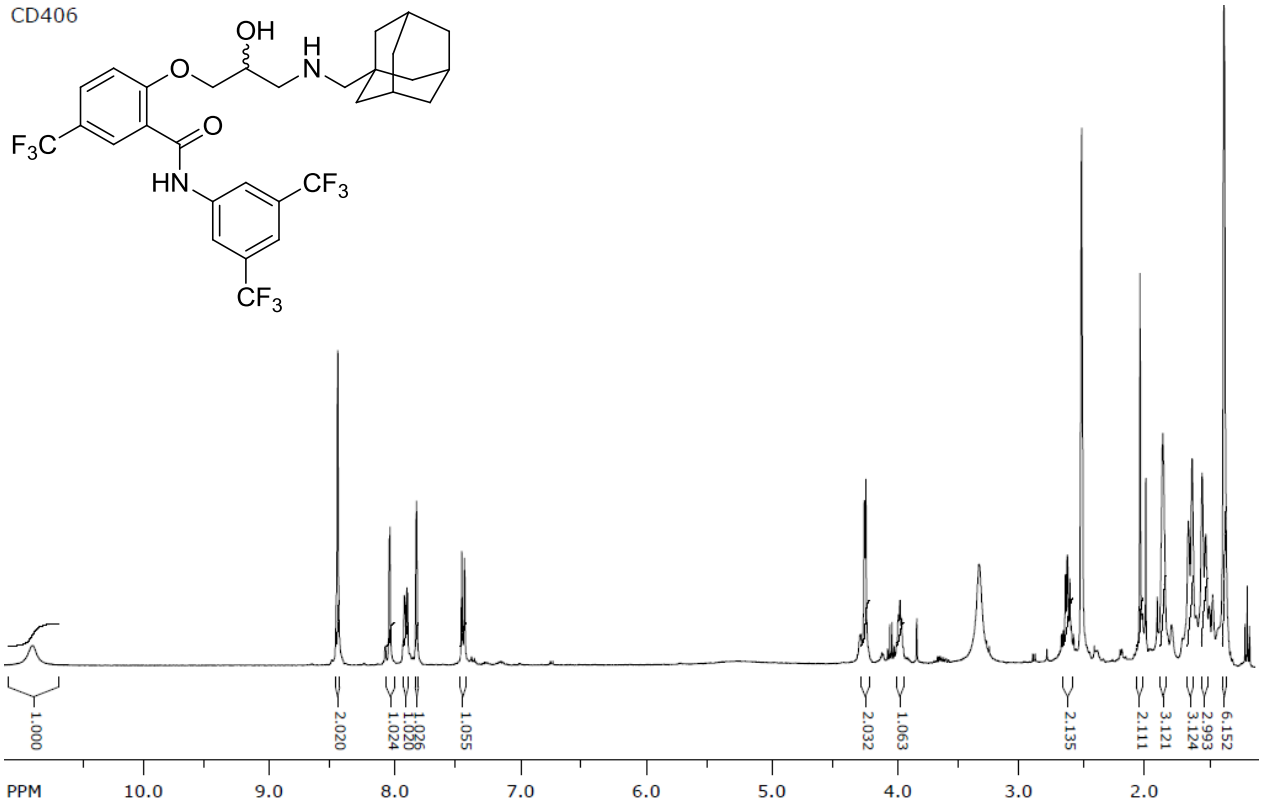


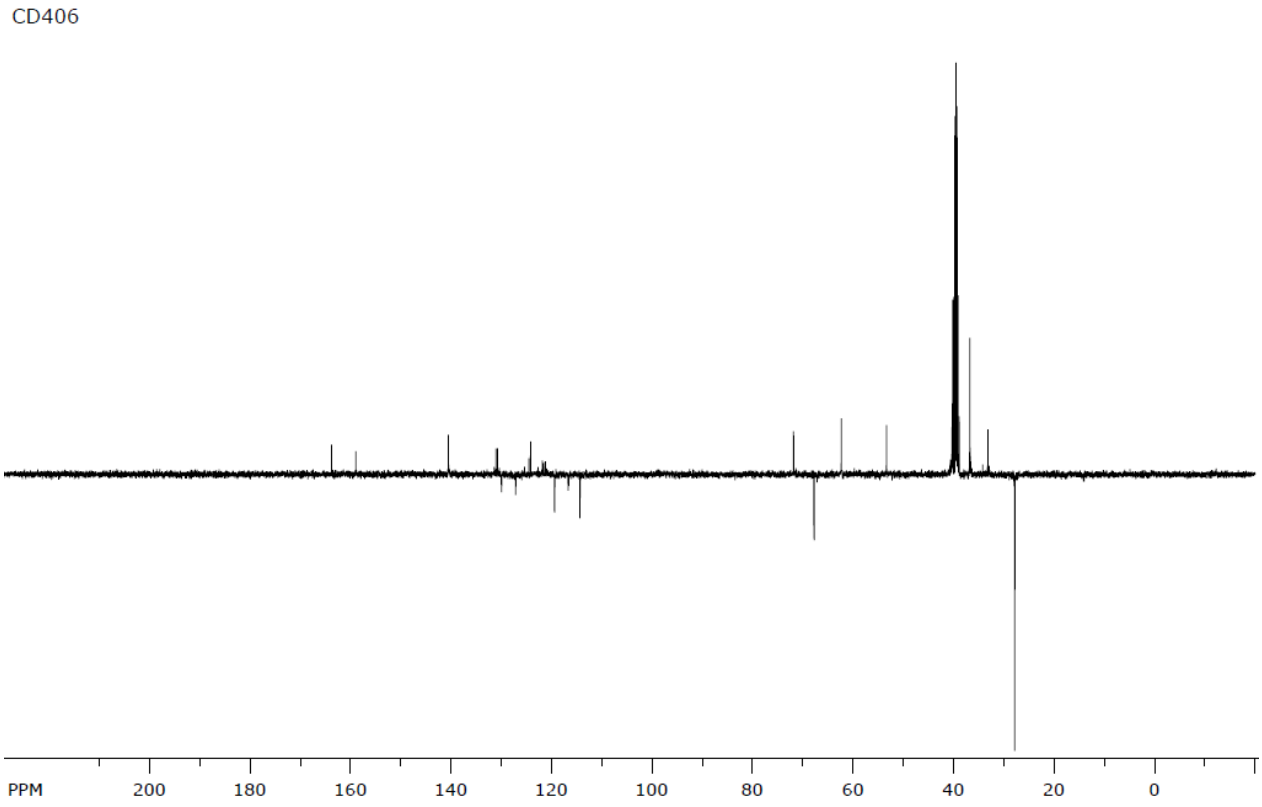
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(4-chloro-3-(trifluoromethyl)phenyl)-5-cyanobenzamide (258)



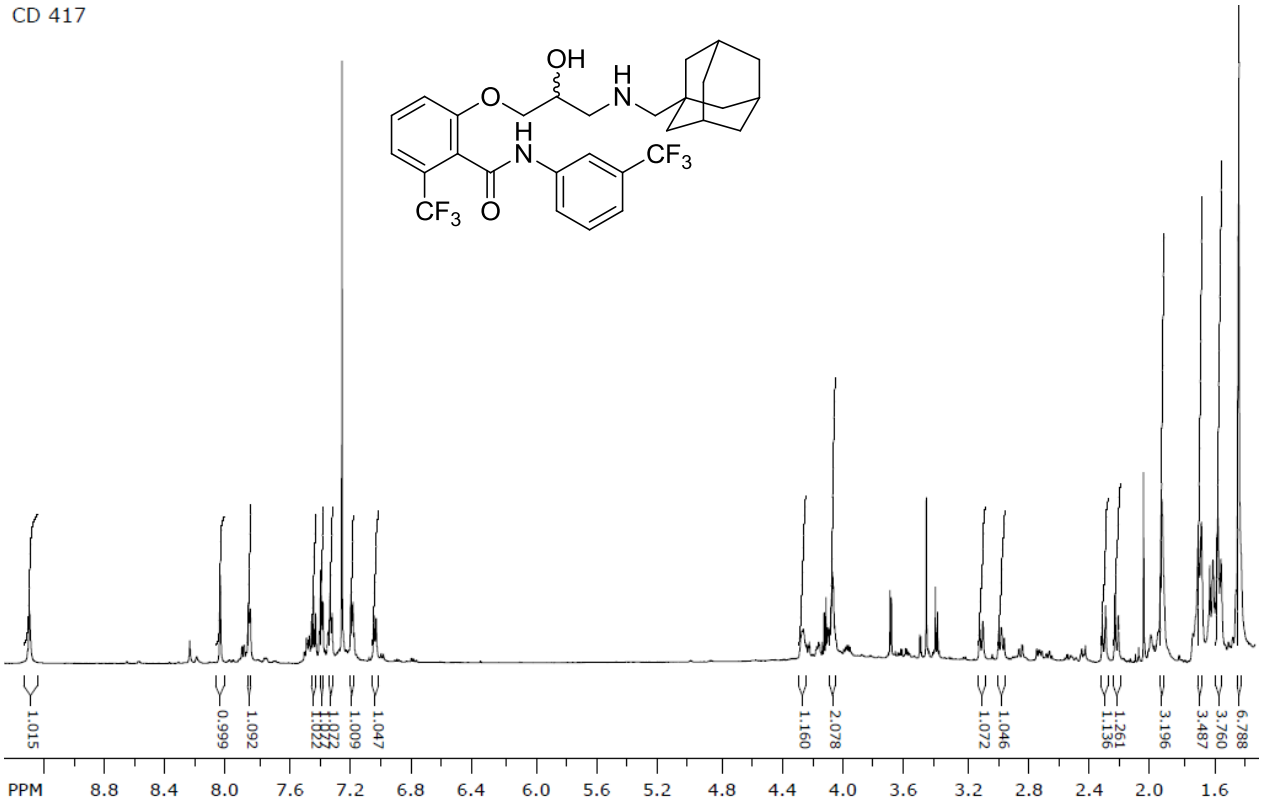


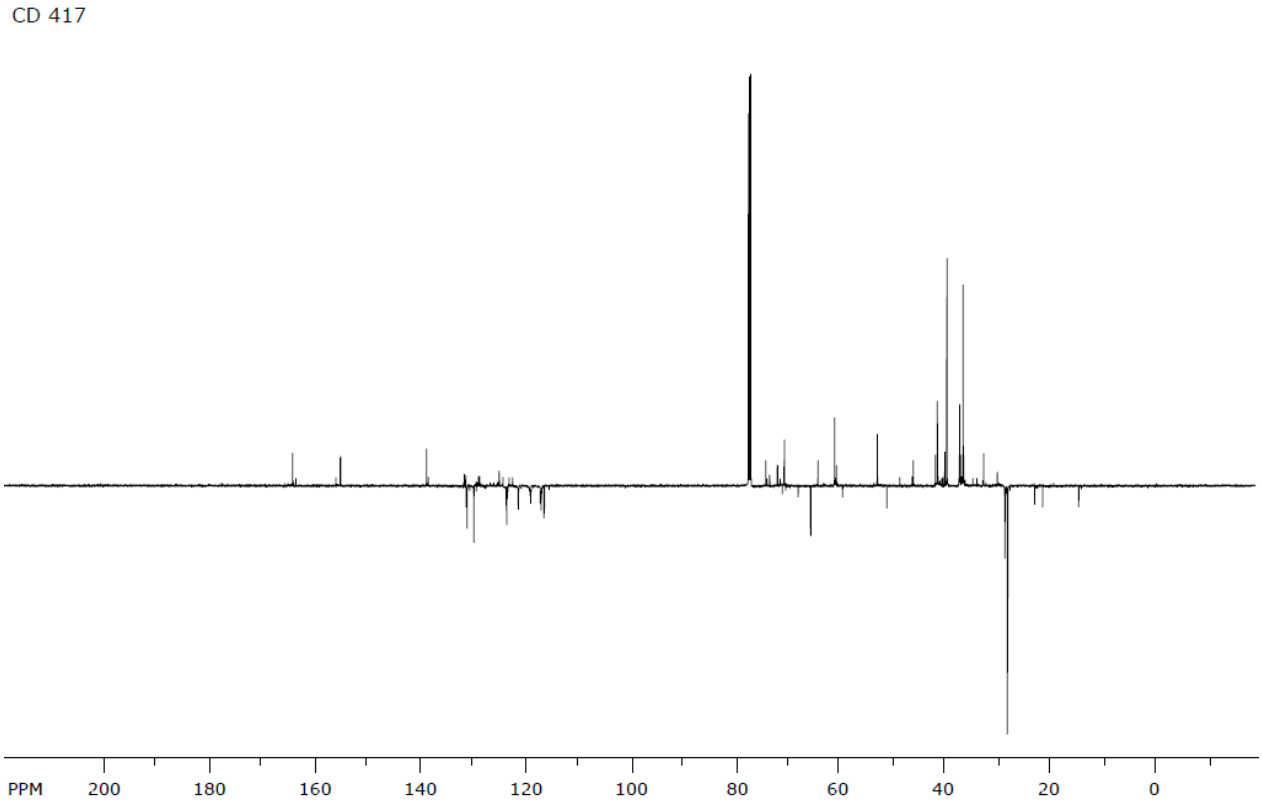
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)benzamide (259)



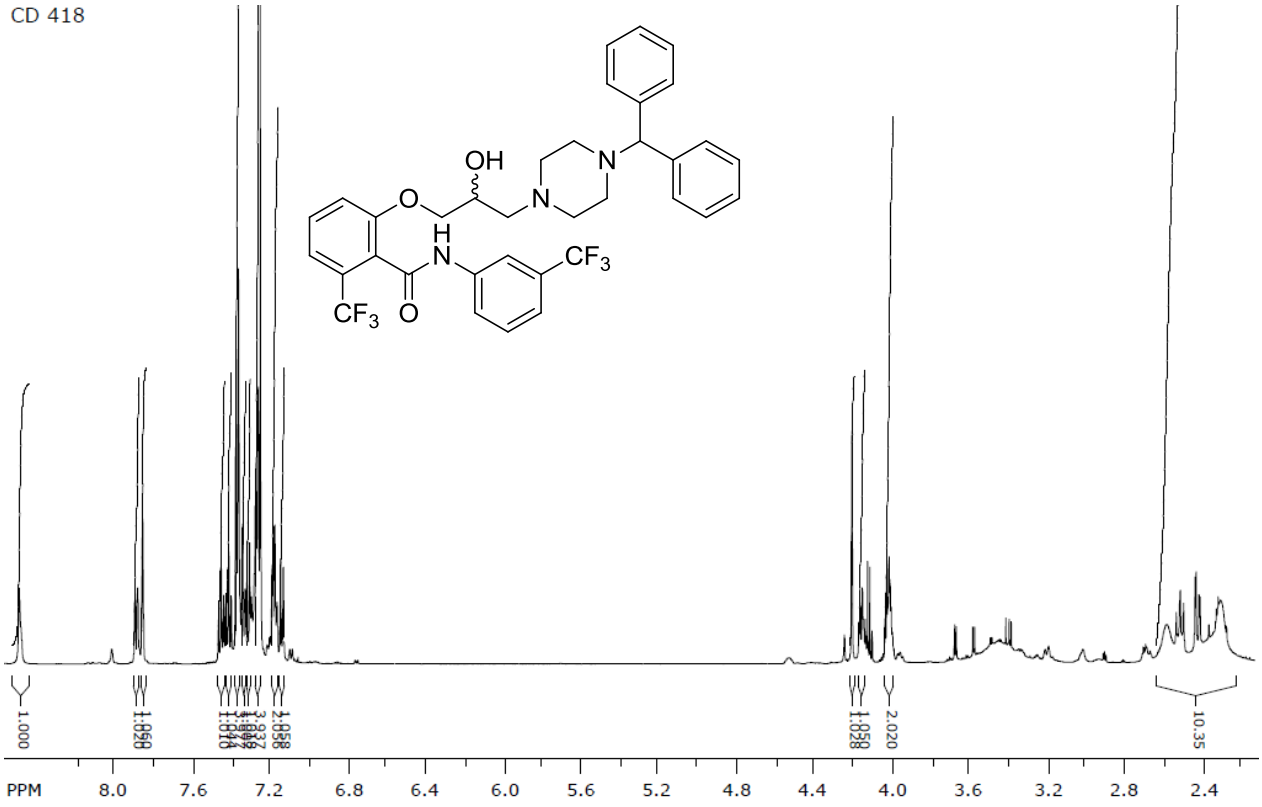


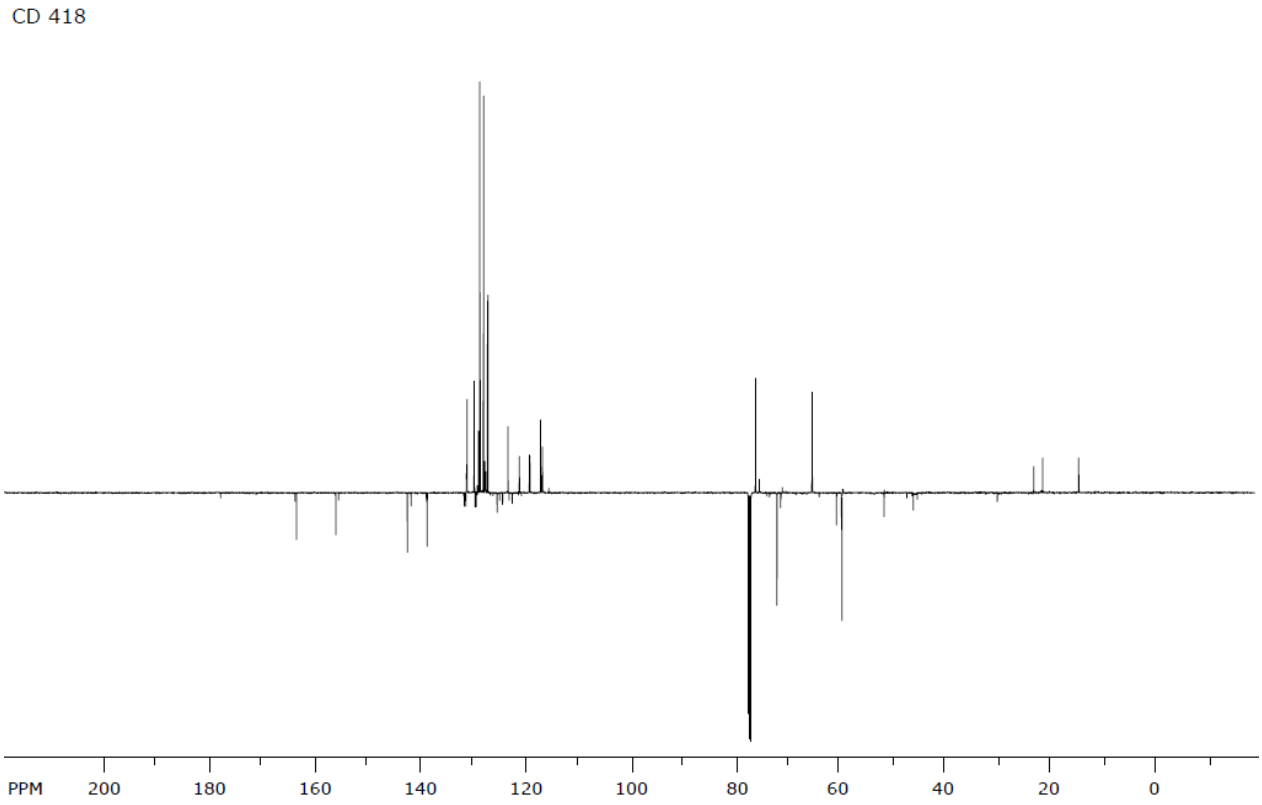
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-6-(trifluoromethyl)-*N*-(3-(trifluoromethyl)phenyl)benzamide (260)



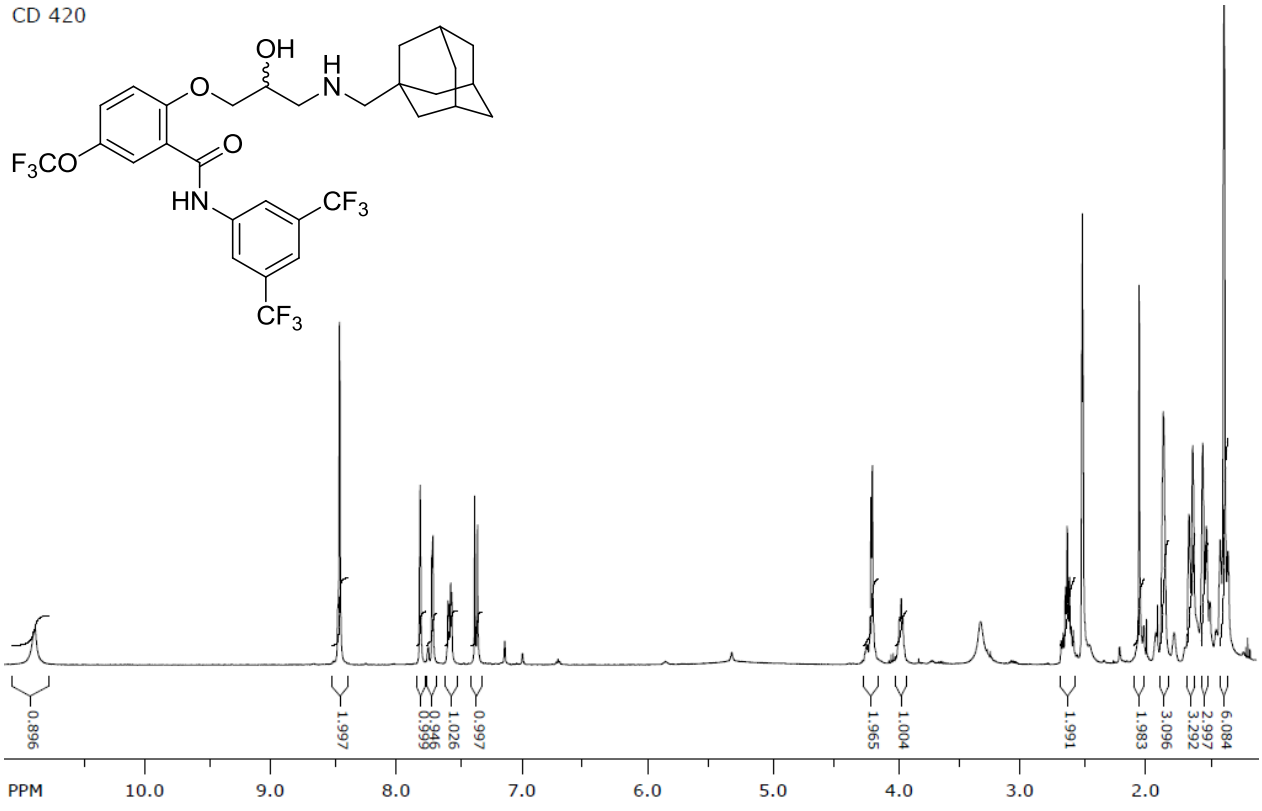


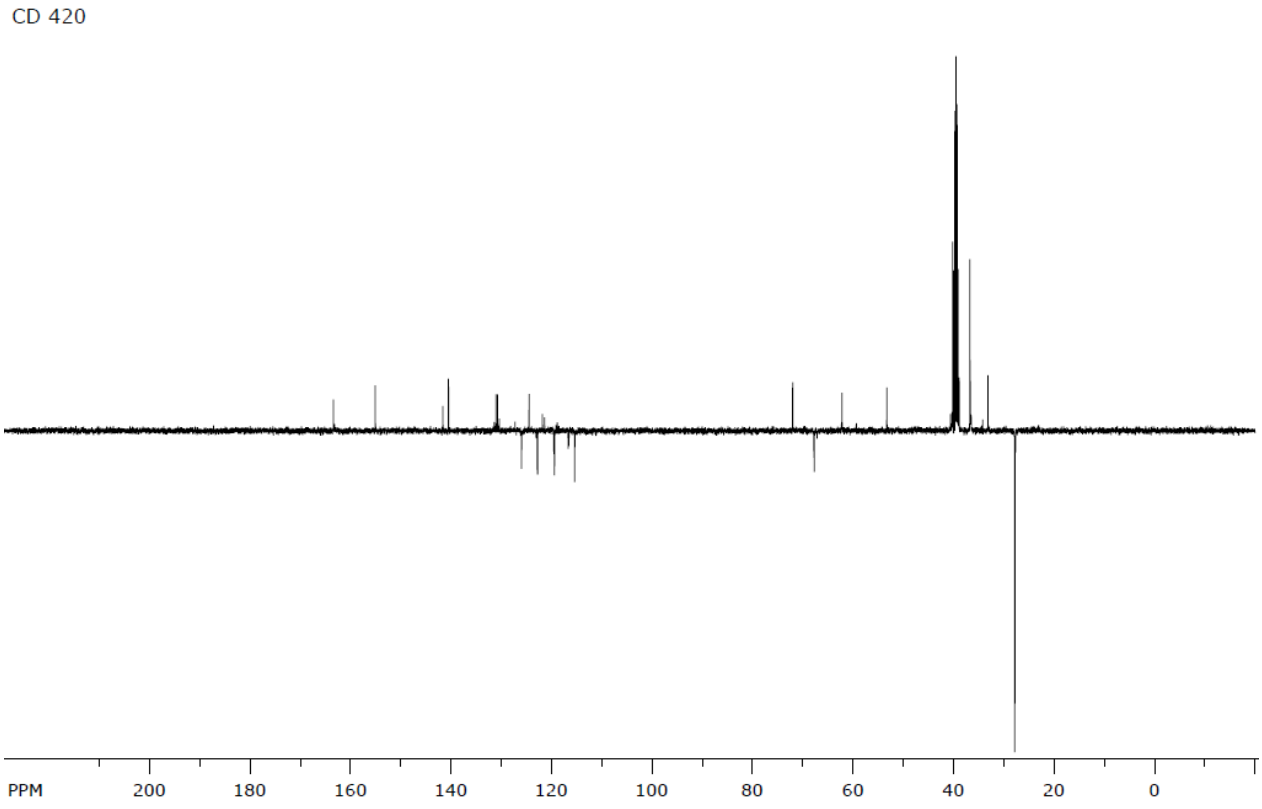
2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-6-(trifluoromethyl)-*N*-(3-(trifluoromethyl)phenyl)benzamide (261)



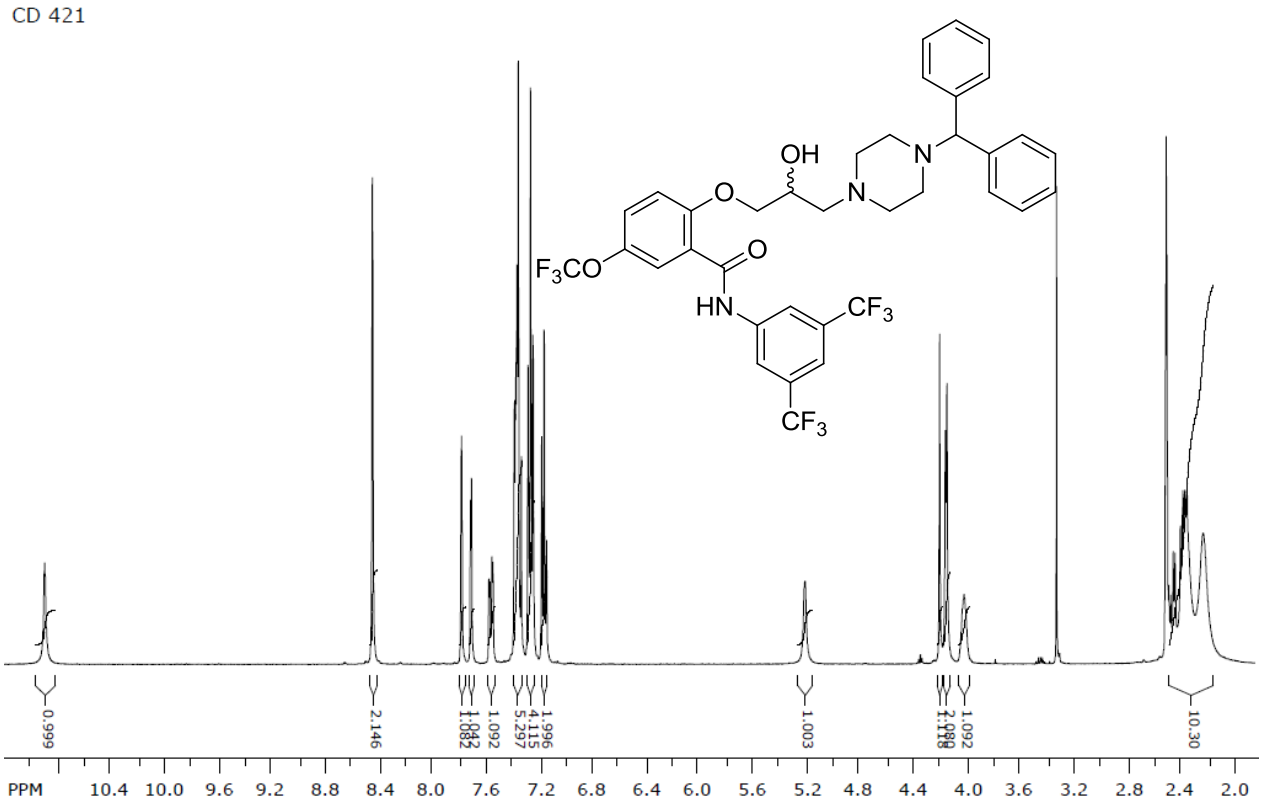


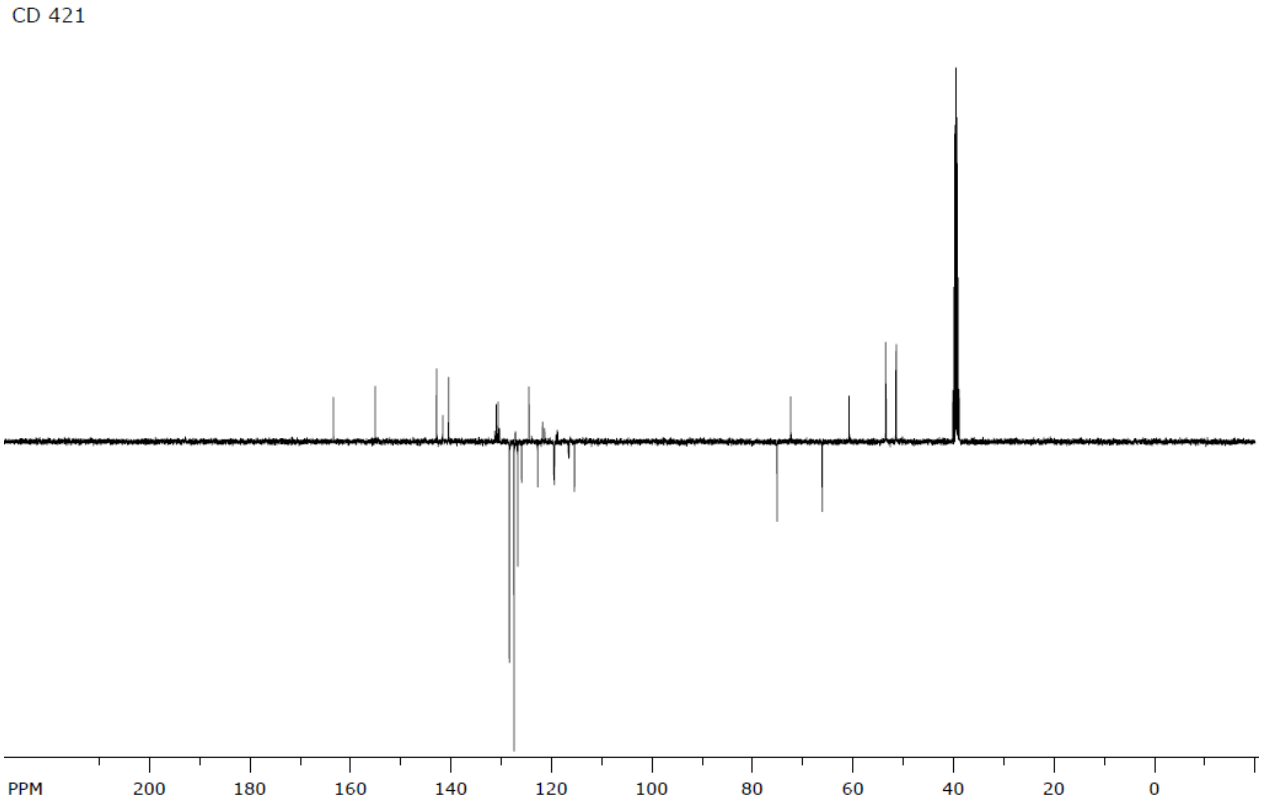
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethoxy)benzamide (262)



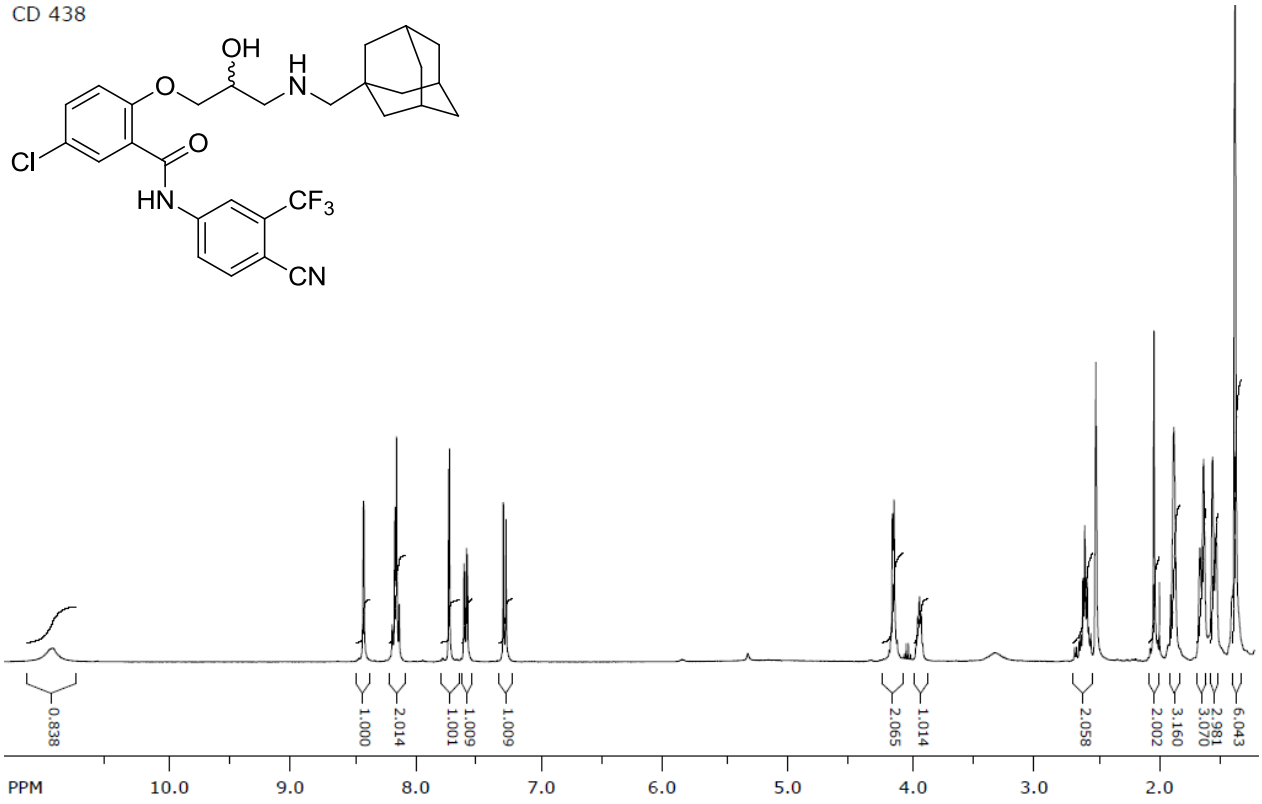


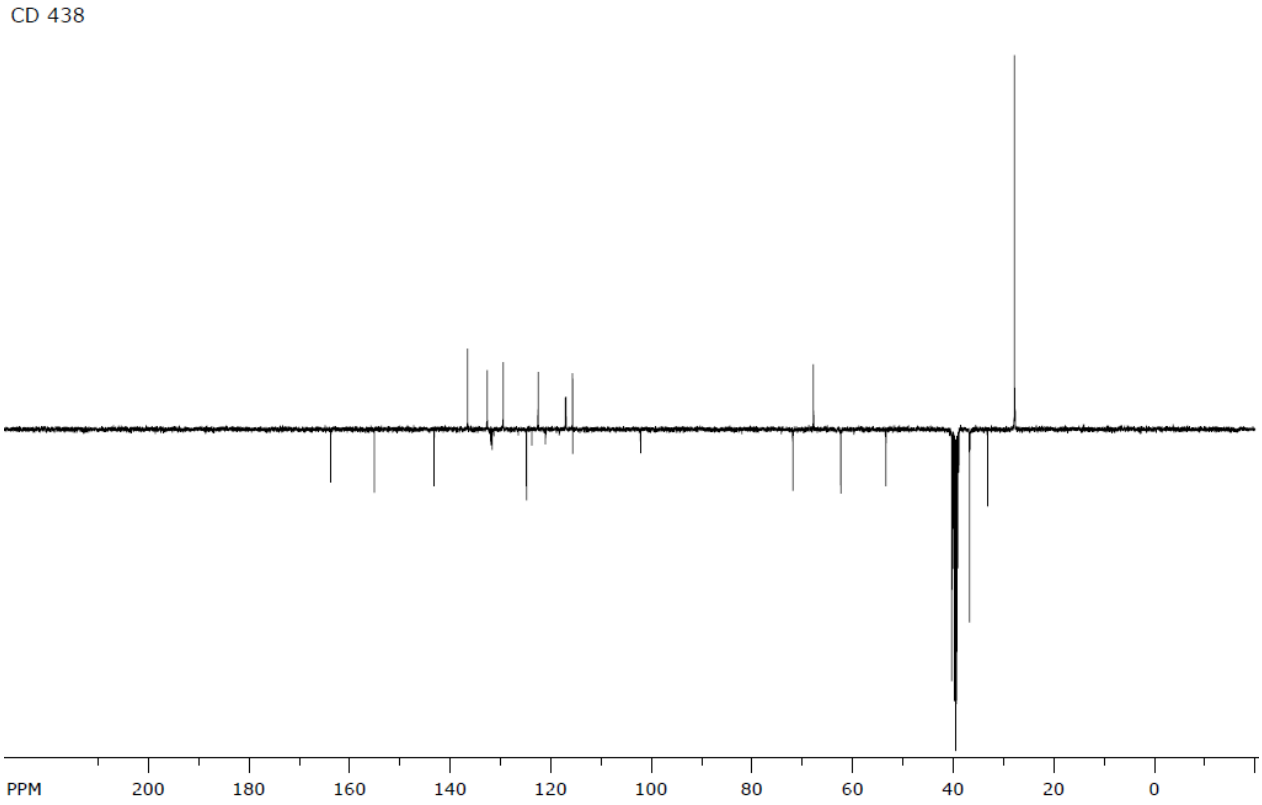
2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethoxy)benzamide (263)



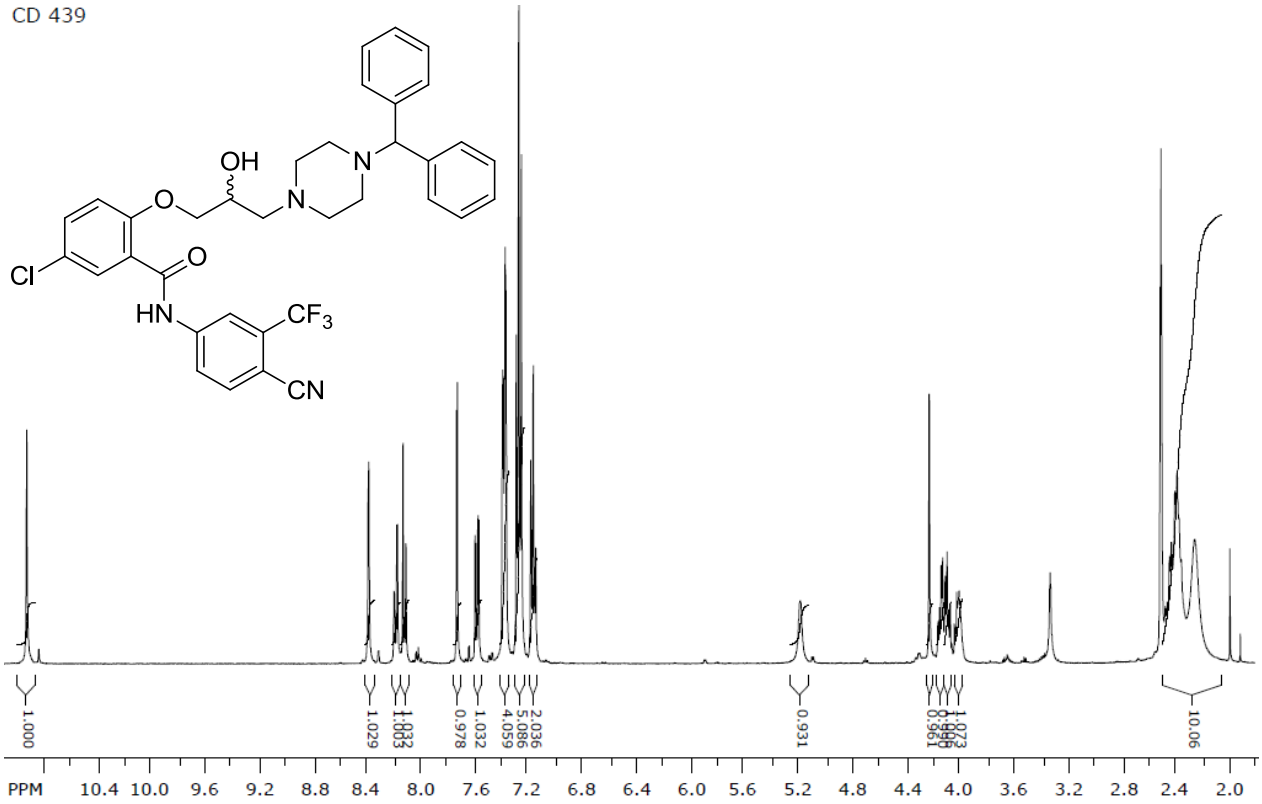


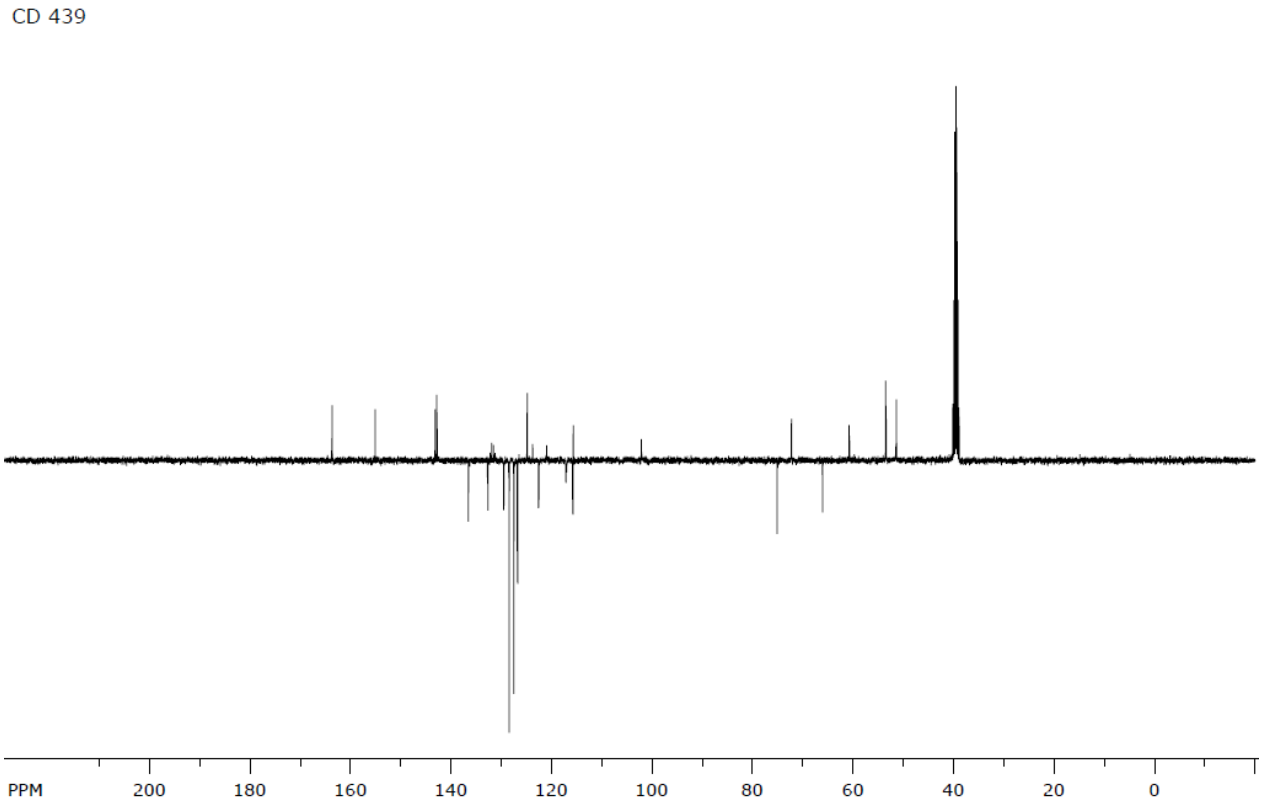
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(4-cyano-3-(trifluoromethyl)phenyl)benzamide (264**)**



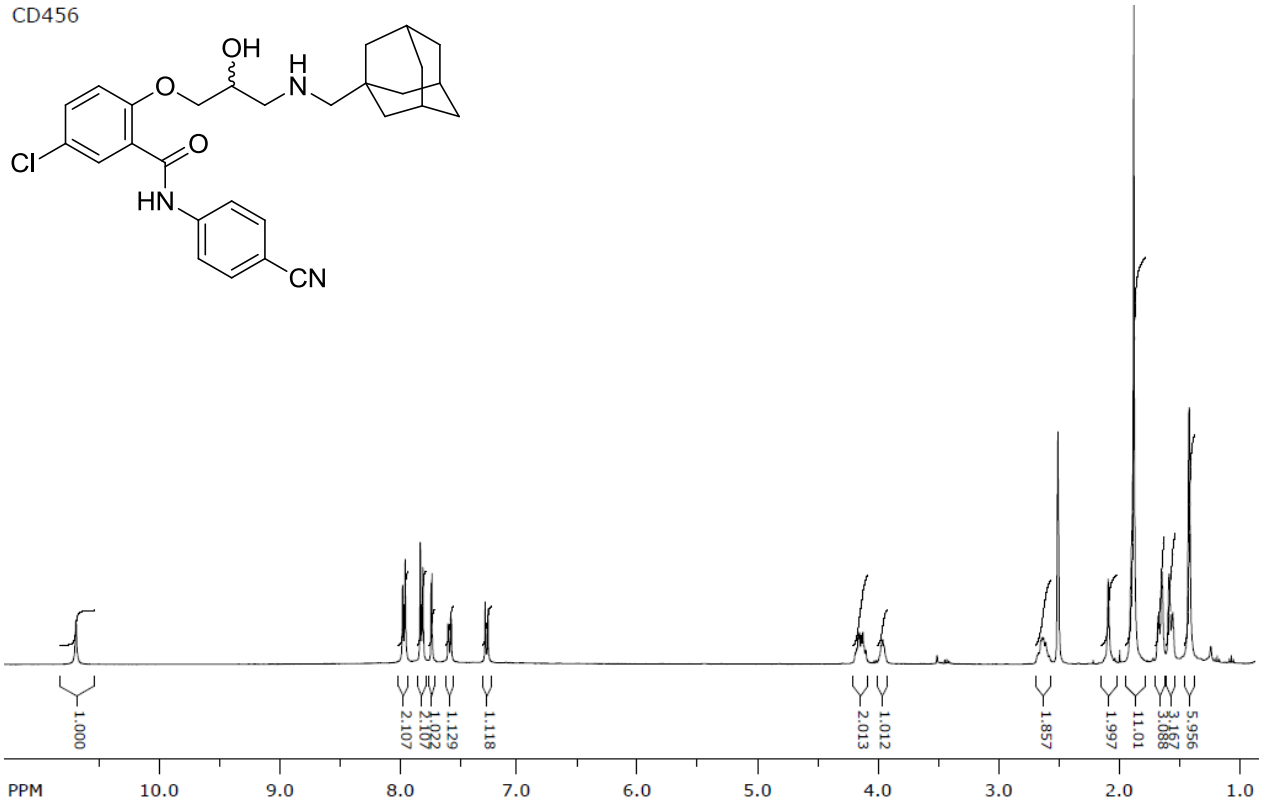


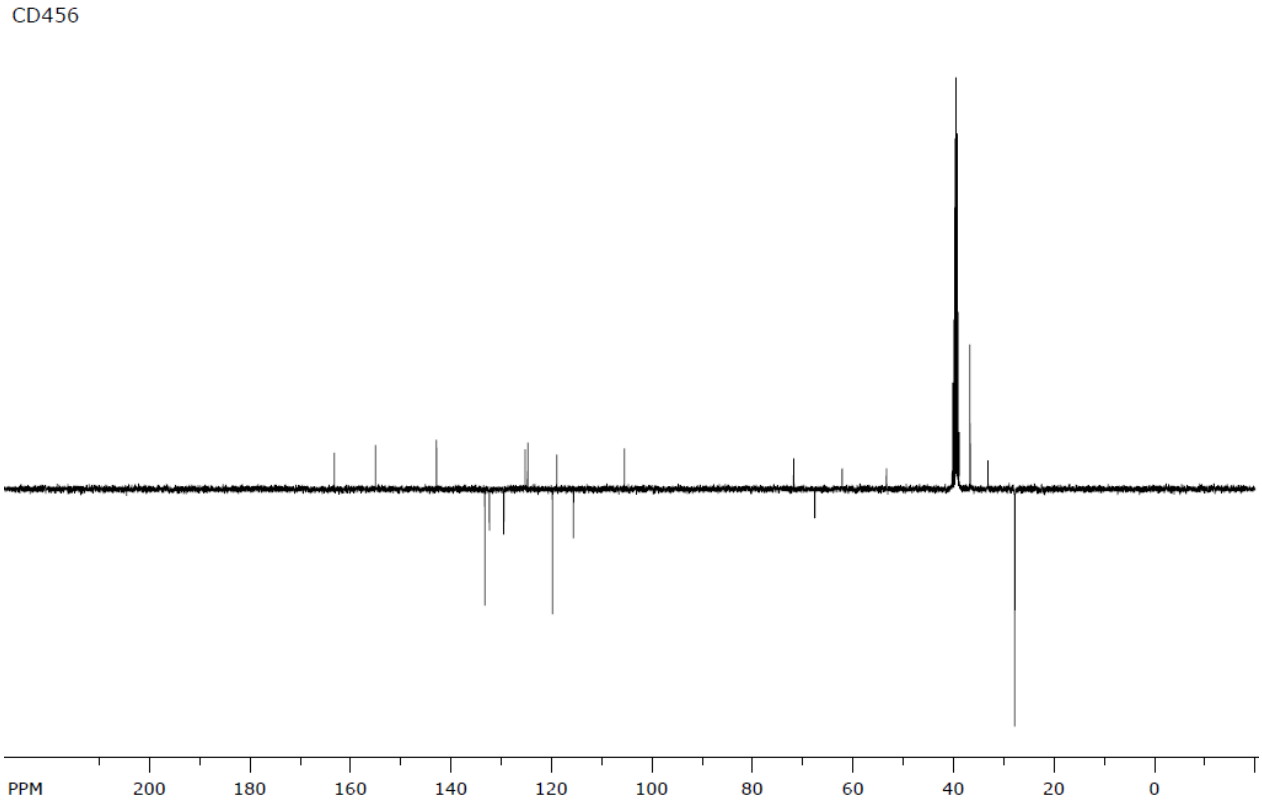
2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-5-chloro-*N*-(4-cyano-3-(trifluoromethyl)phenyl)benzamide (265)



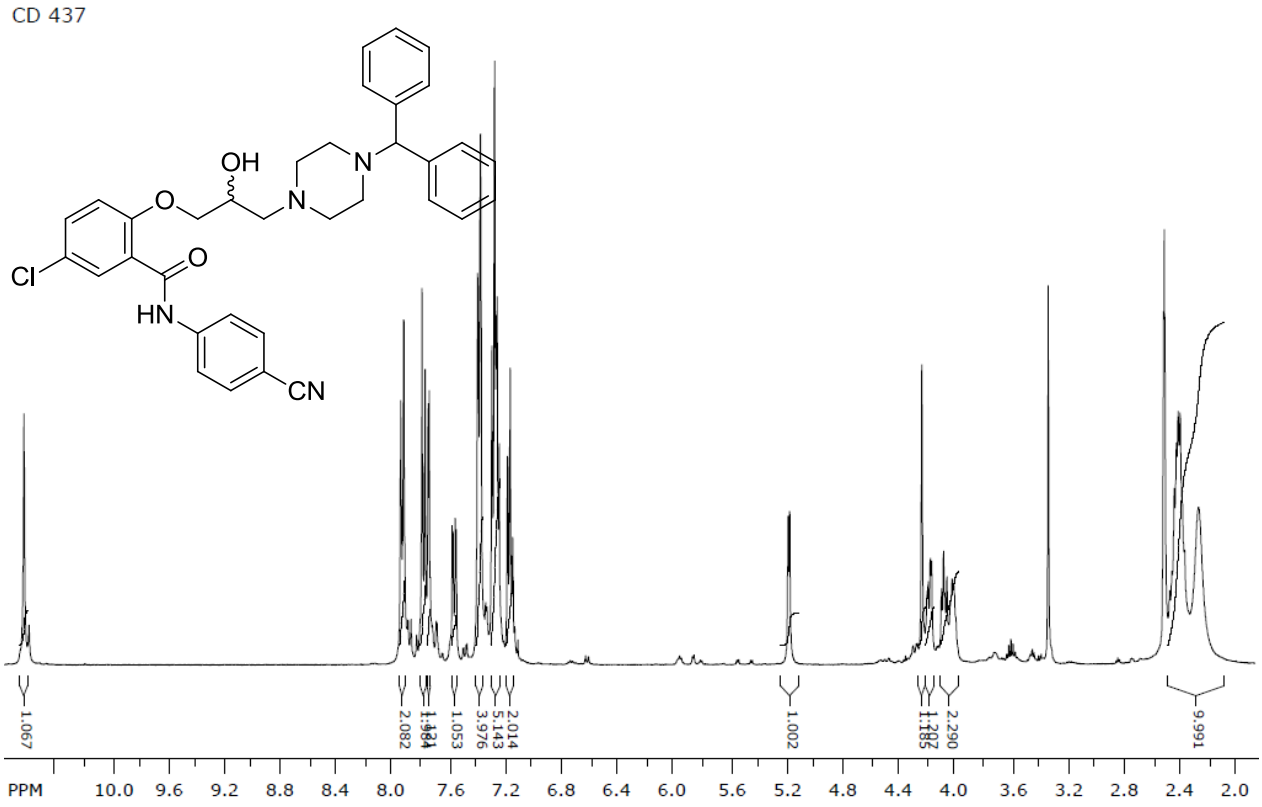


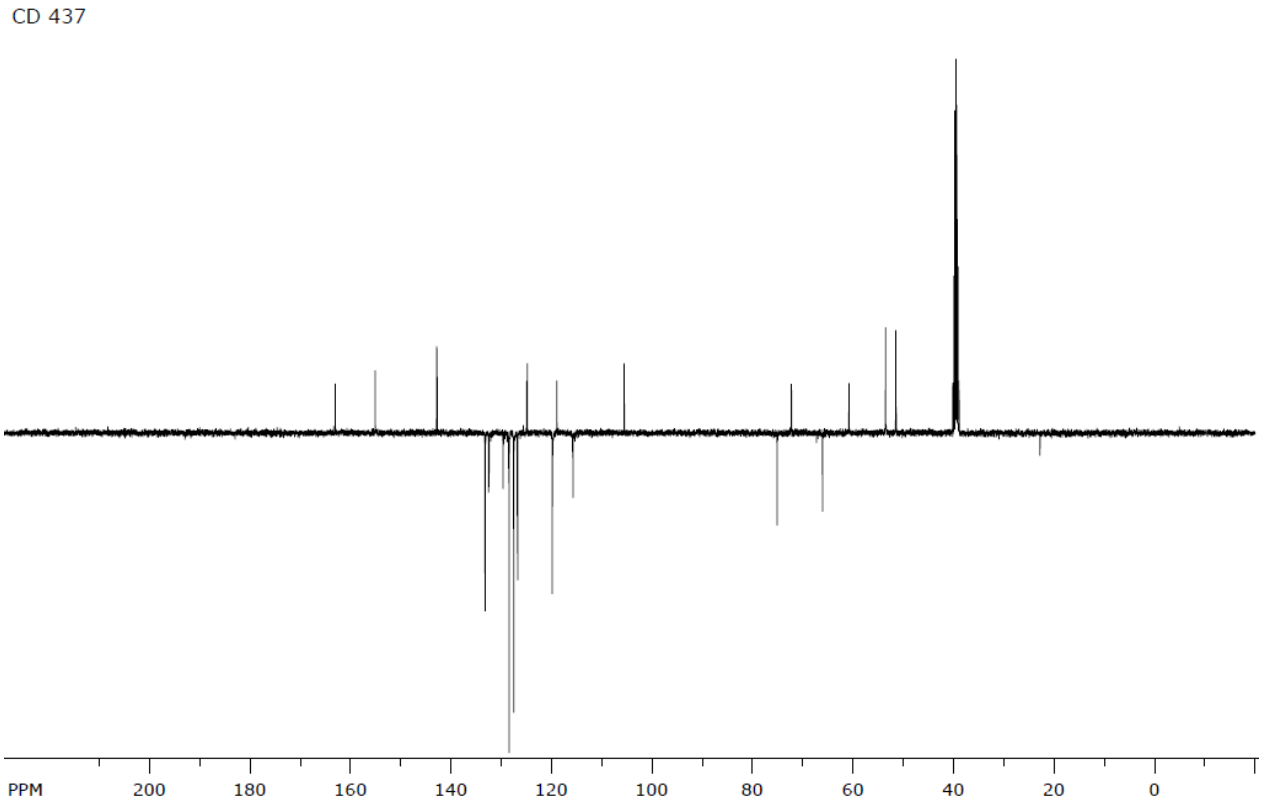
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(4-cyanophenyl)benzamide (266)



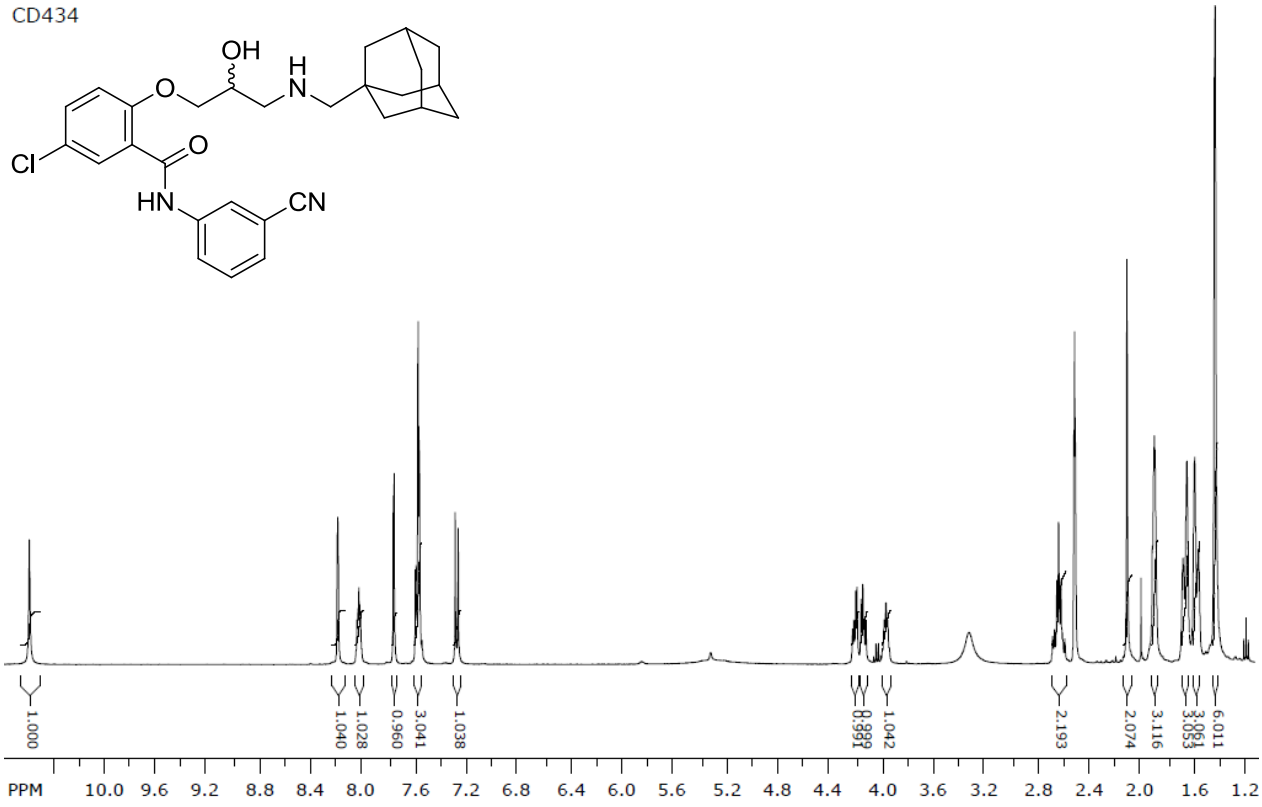


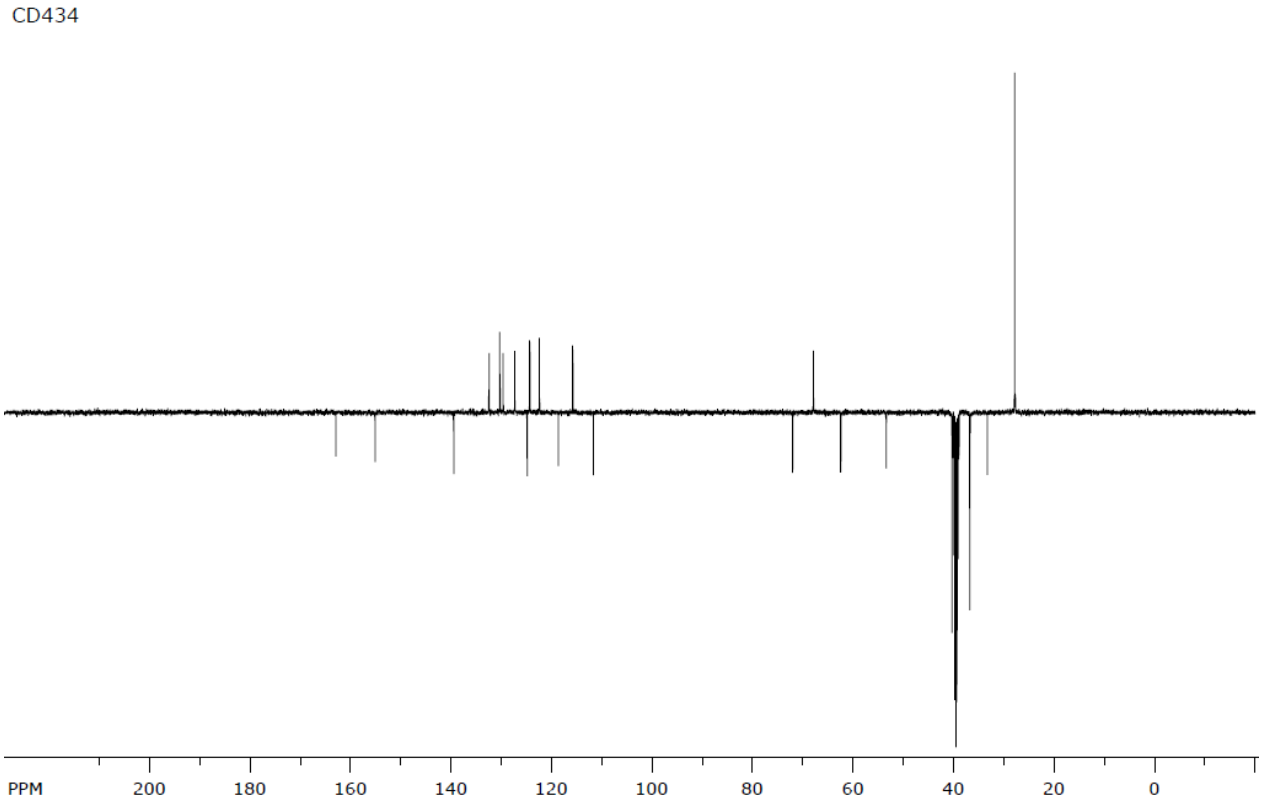
2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-5-chloro-*N*-(4-cyanophenyl)benzamide (267)



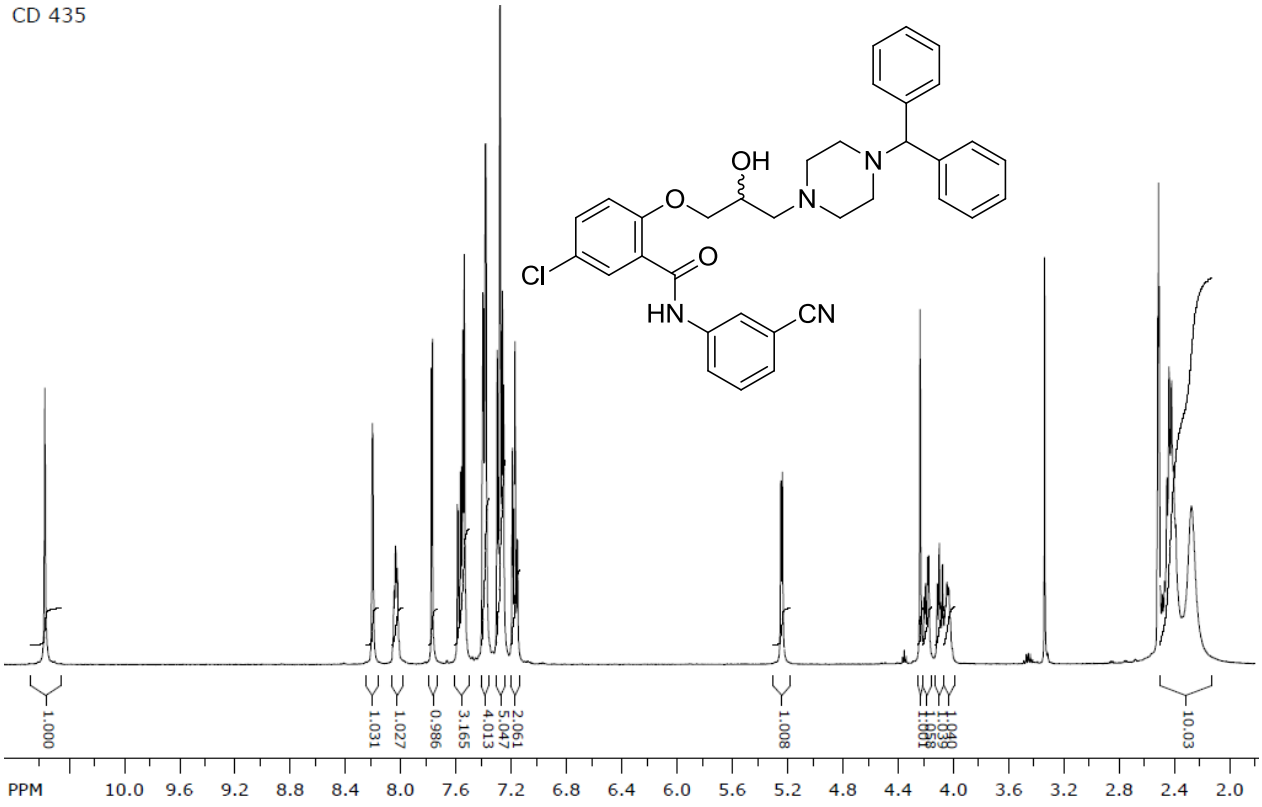


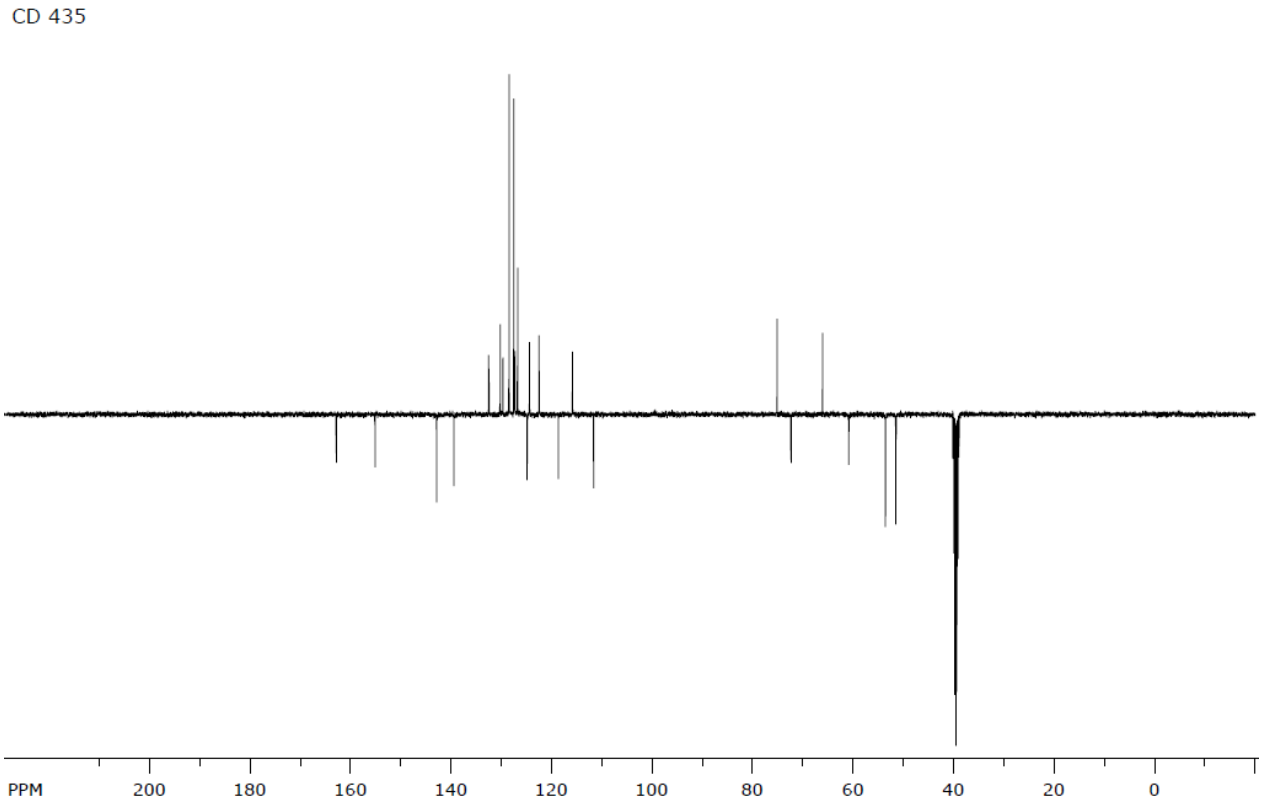
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3-cyanophenyl)benzamide (268)



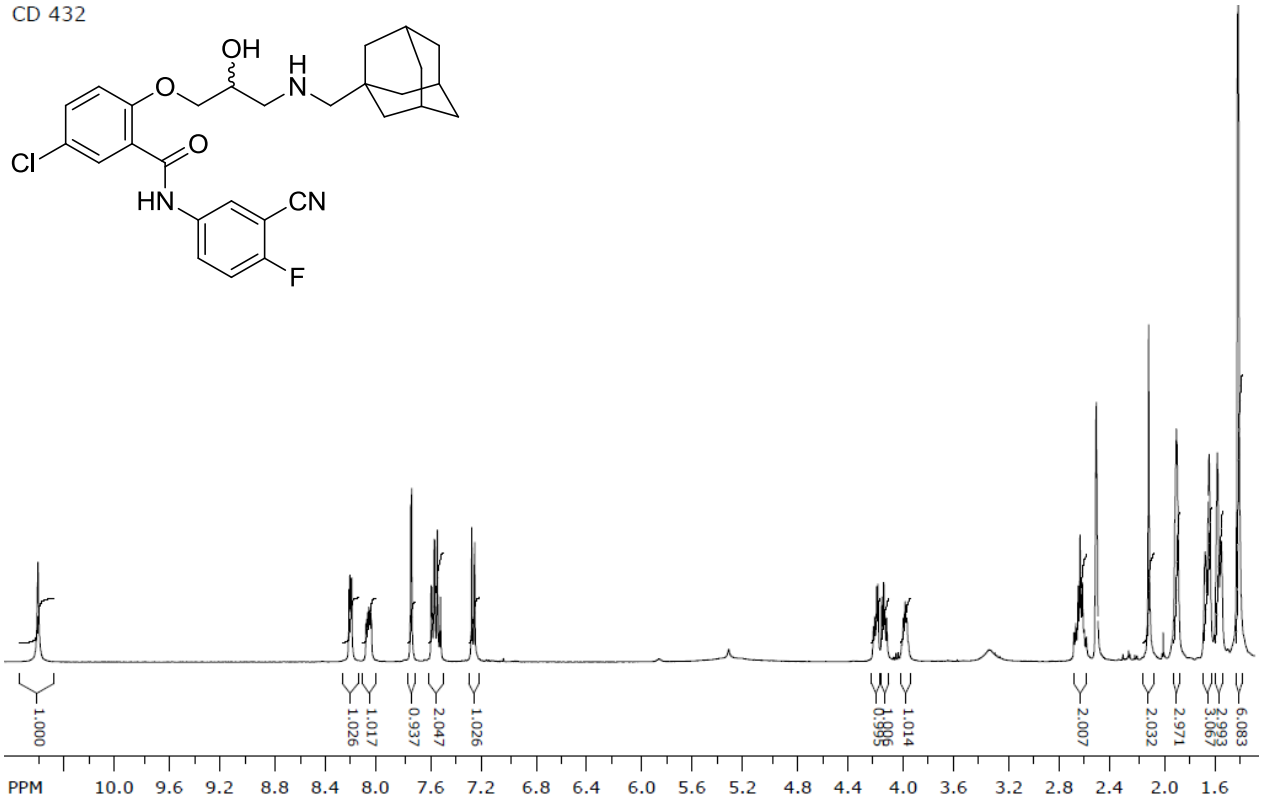


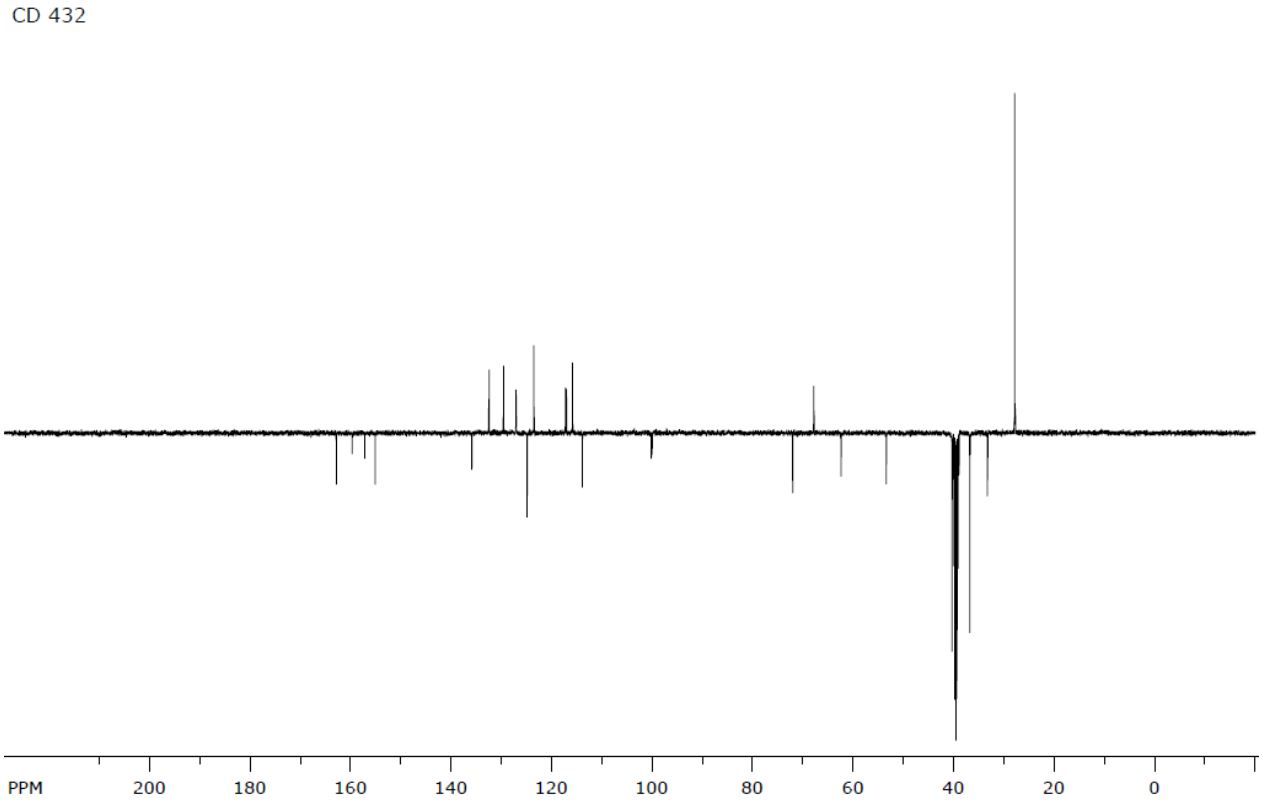
2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-5-chloro-*N*-(3-cyanophenyl)benzamide (269)



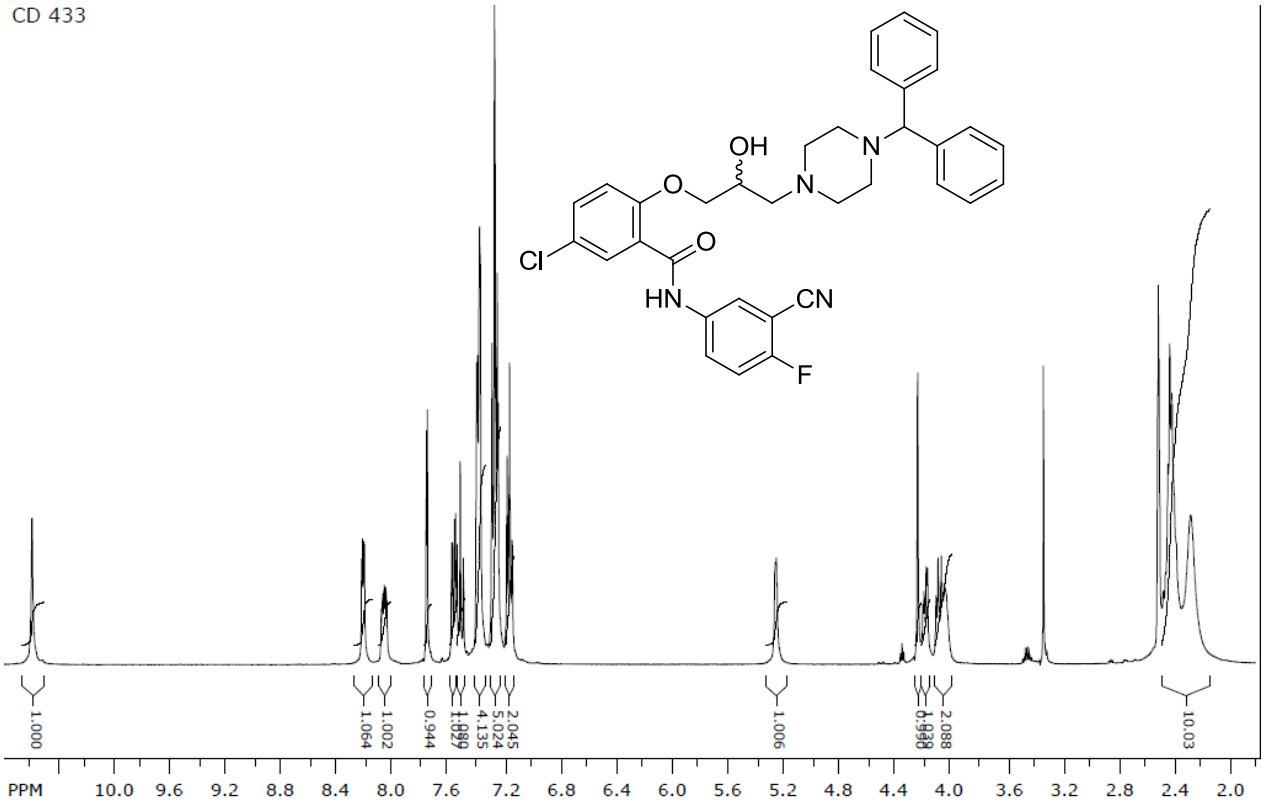


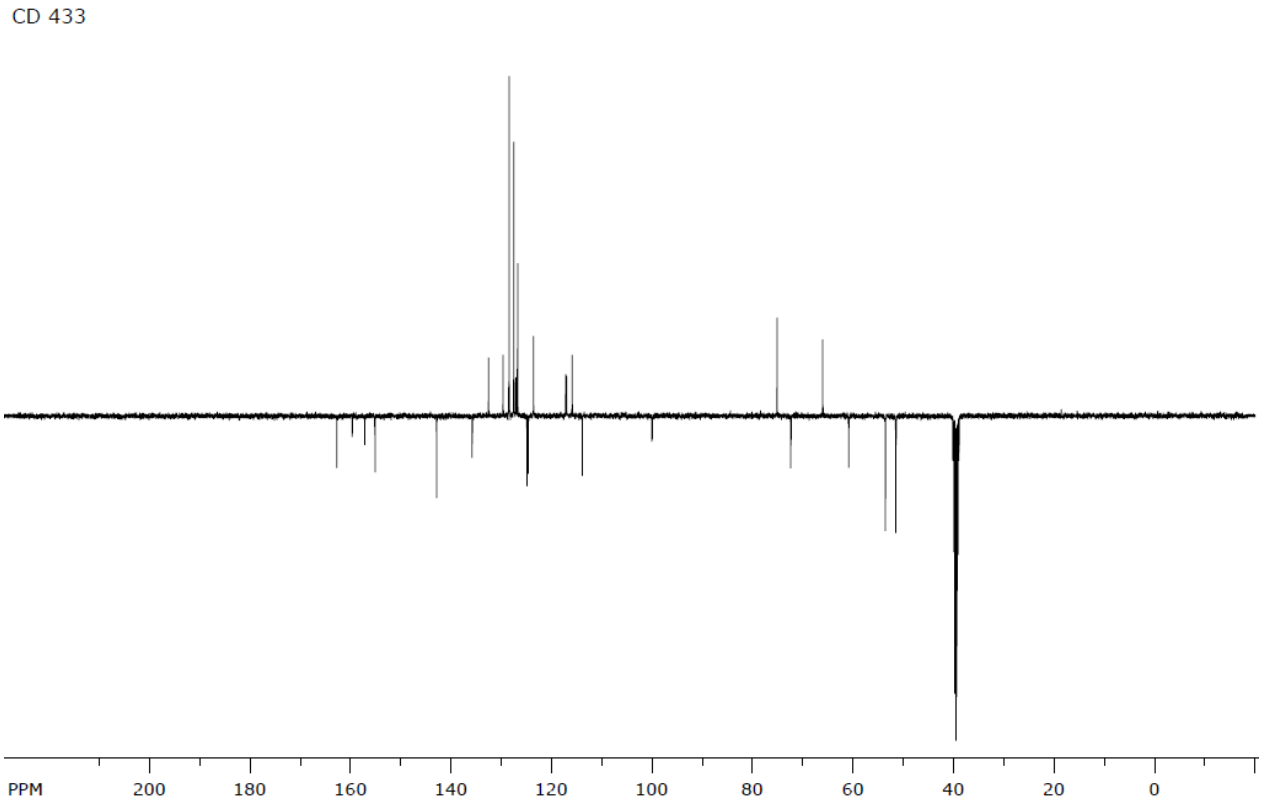
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3-cyano-4-fluorophenyl)benzamide (270)



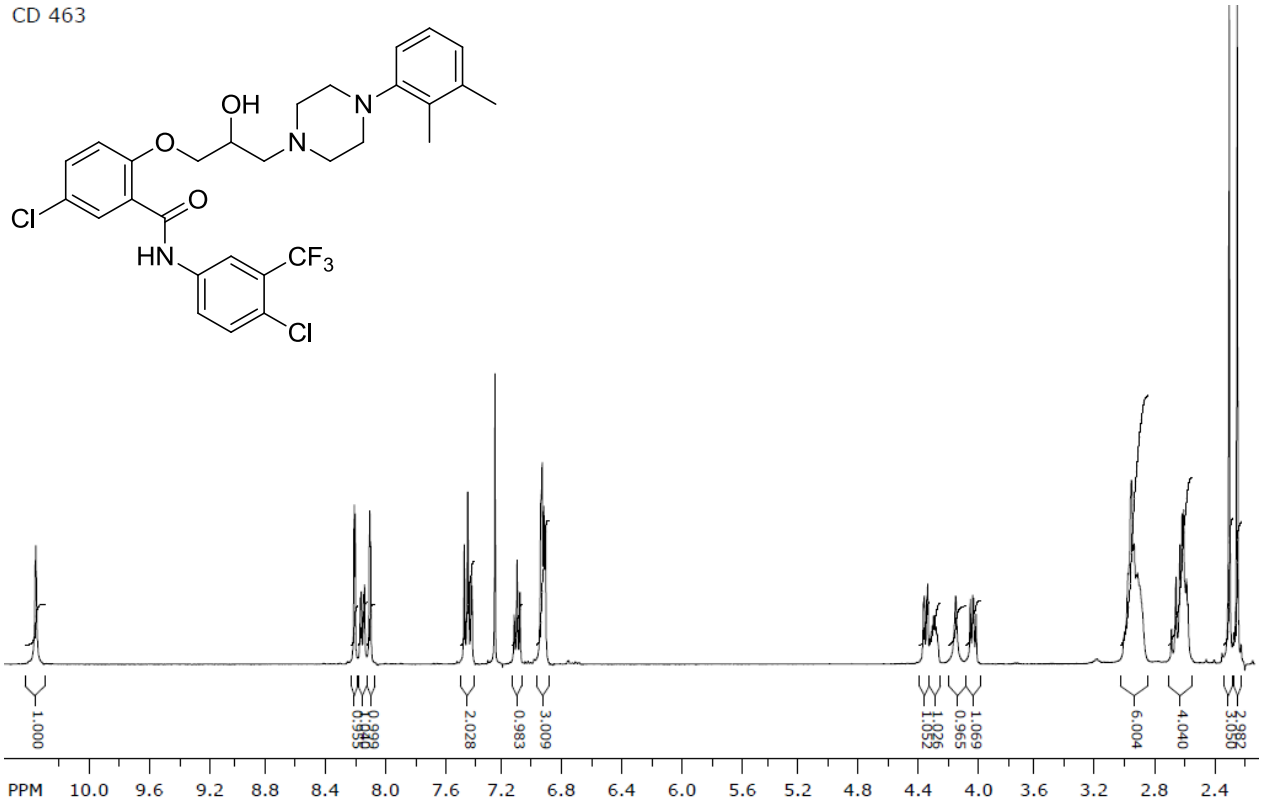


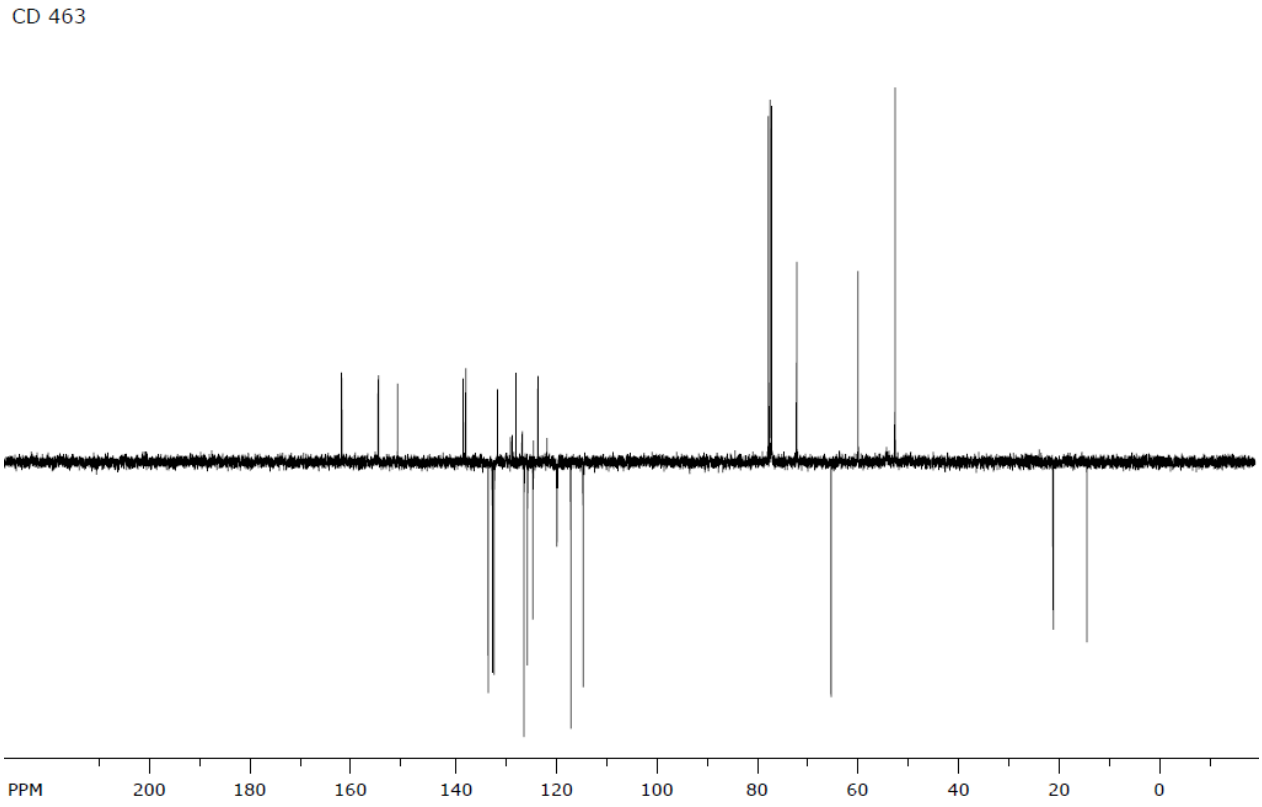
2-(3-(4-benzhydrylpiperazin-1-yl)-2-hydroxypropoxy)-5-chloro-*N*-(3-cyano-4-fluorophenyl)benzamide (271)



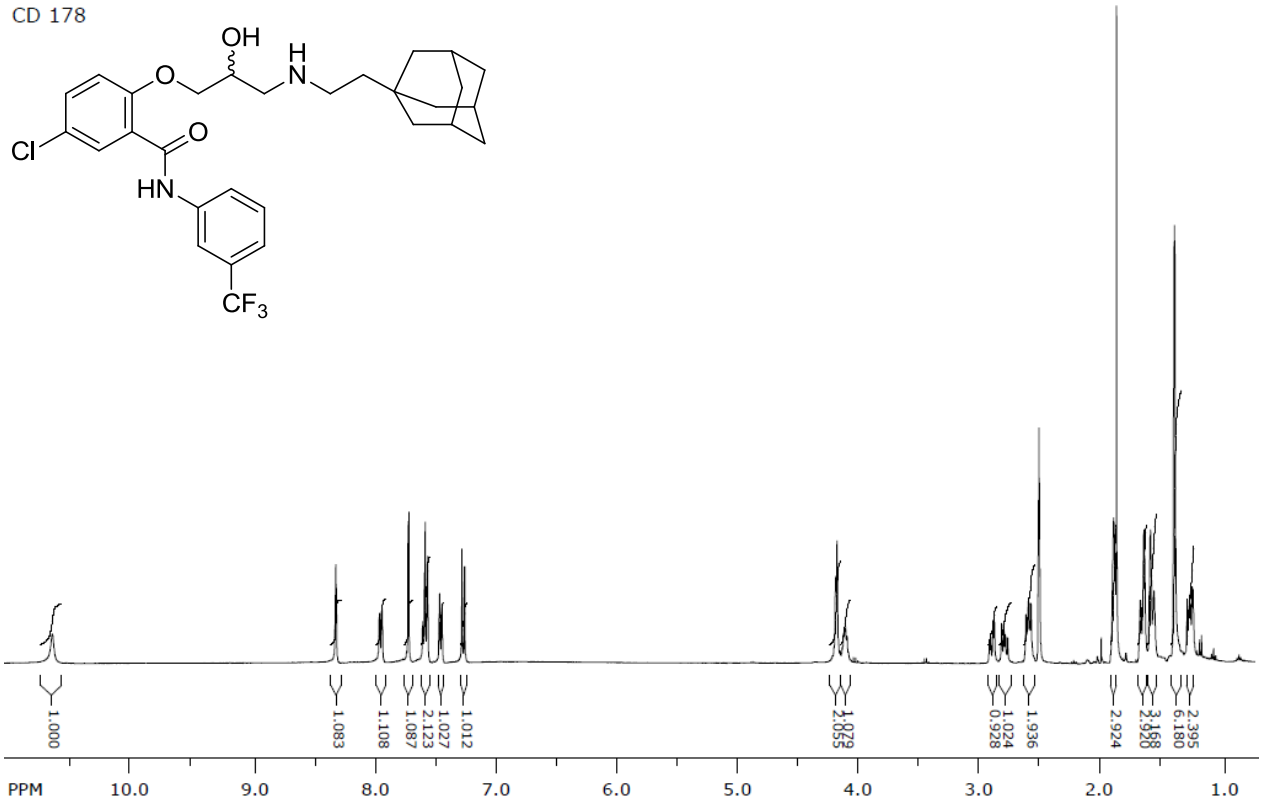


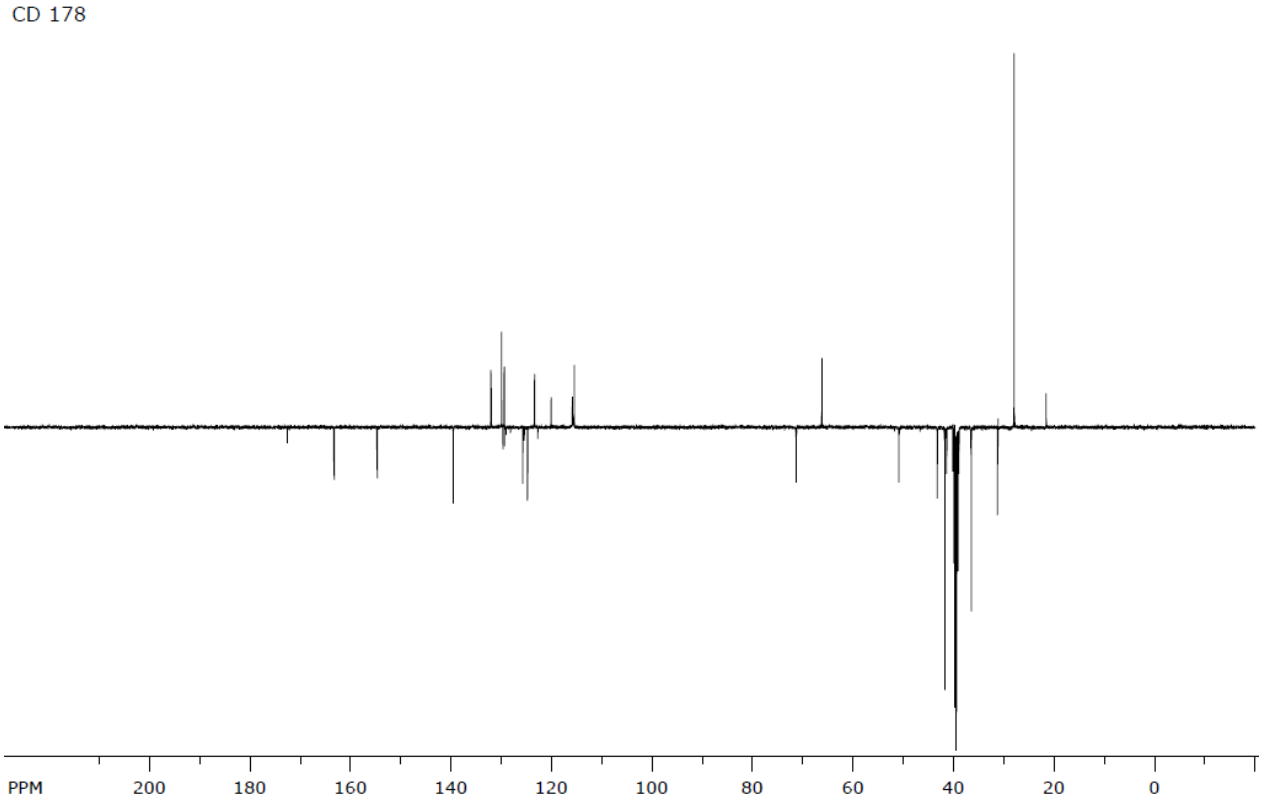
5-chloro-*N*-(4-chloro-3-(trifluoromethyl)phenyl)-2-(3-(4-(2,3-dimethylphenyl)piperazin-1-yl)-2-hydroxypropoxy)benzamide (272)



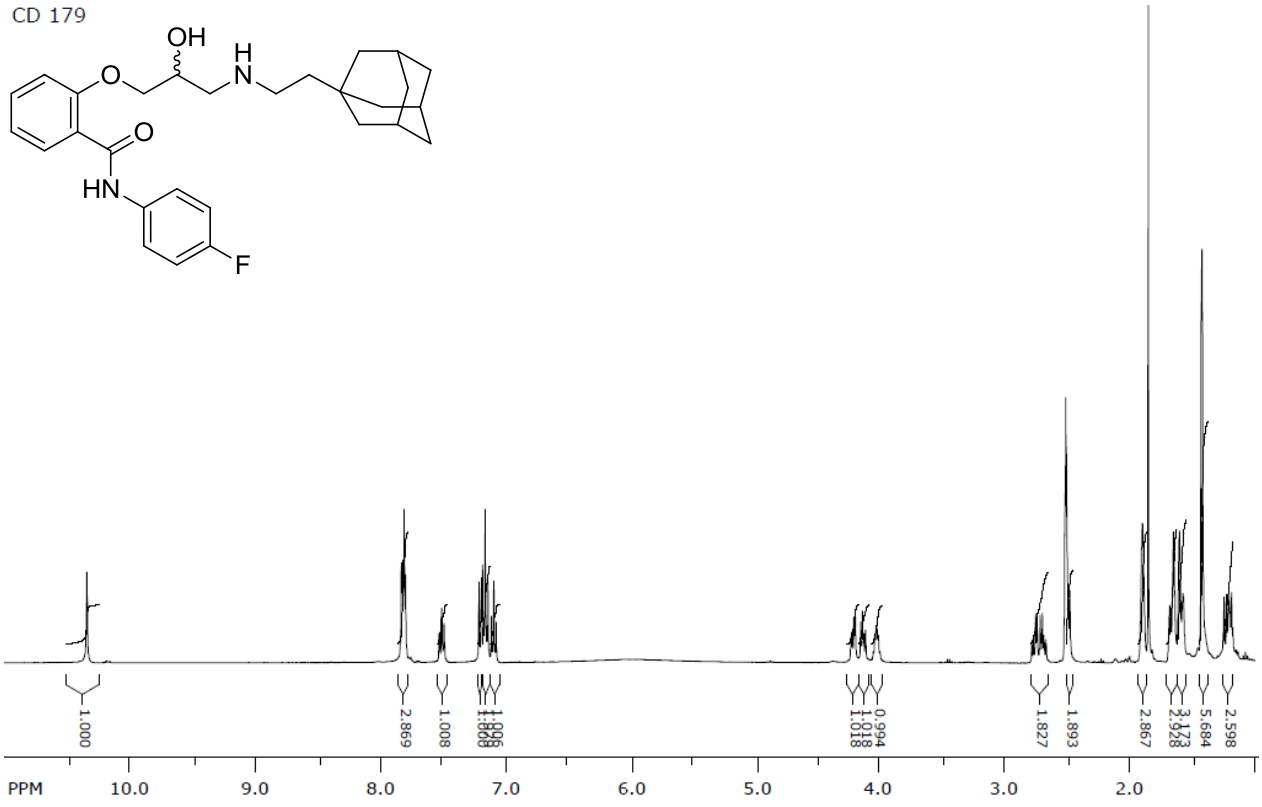


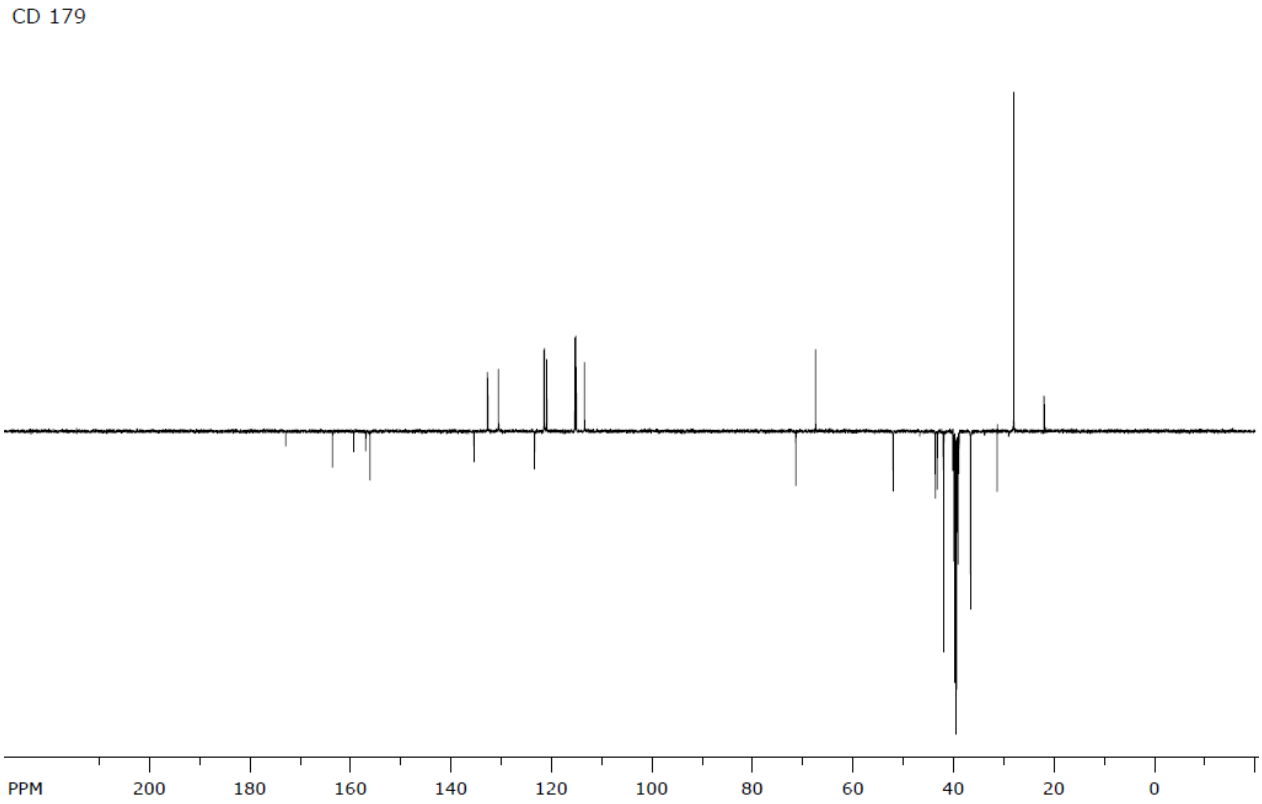
2-(3-((2-(adamantan-1-yl)ethyl)amino)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (273)



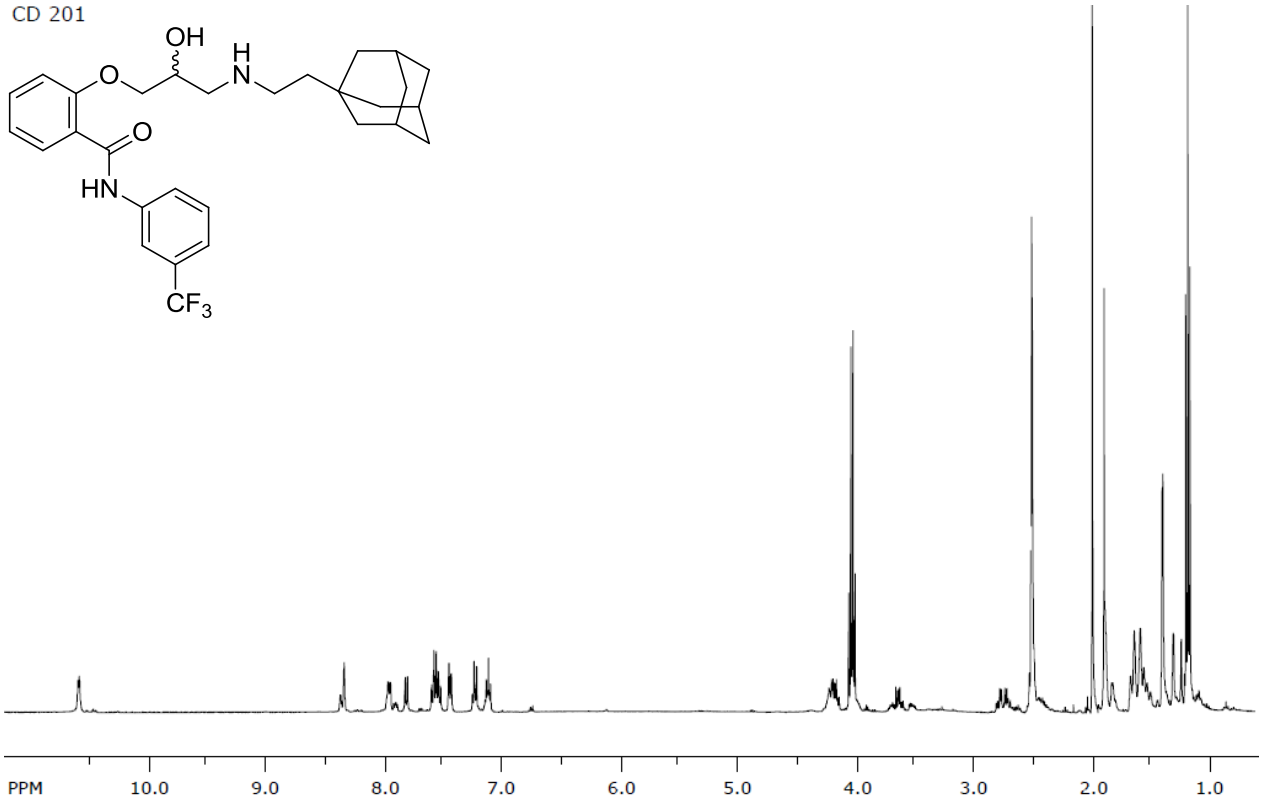


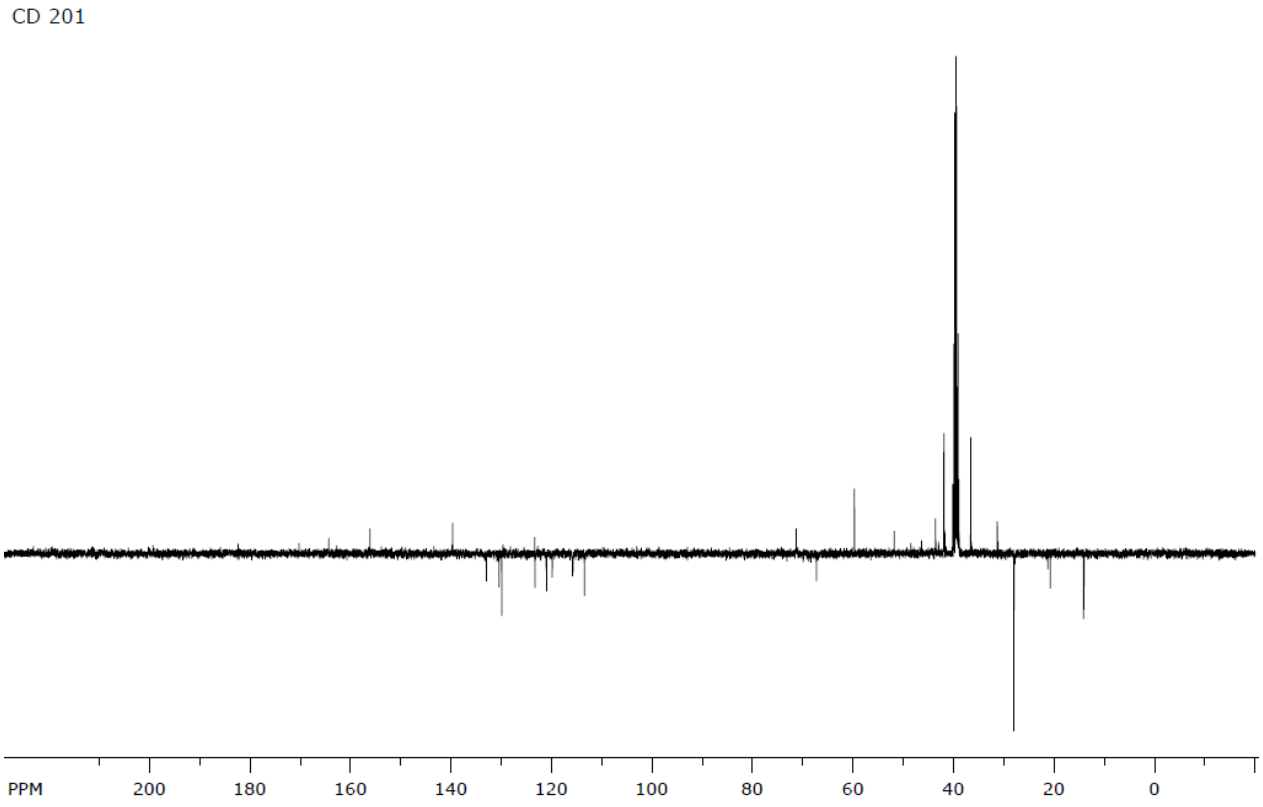
2-(3-((2-(adamantan-1-yl)ethyl)amino)-2-hydroxypropoxy)-*N*-(4-fluorophenyl)benzamide (274)



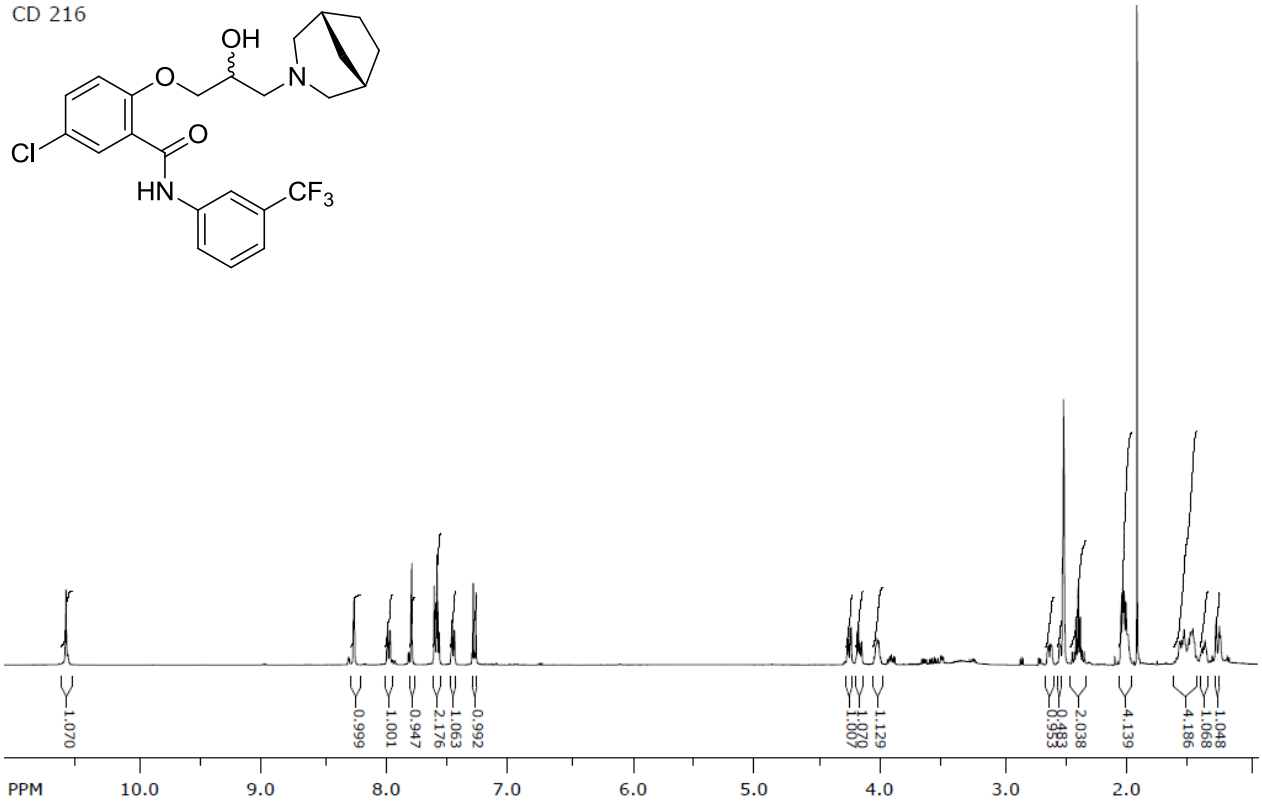


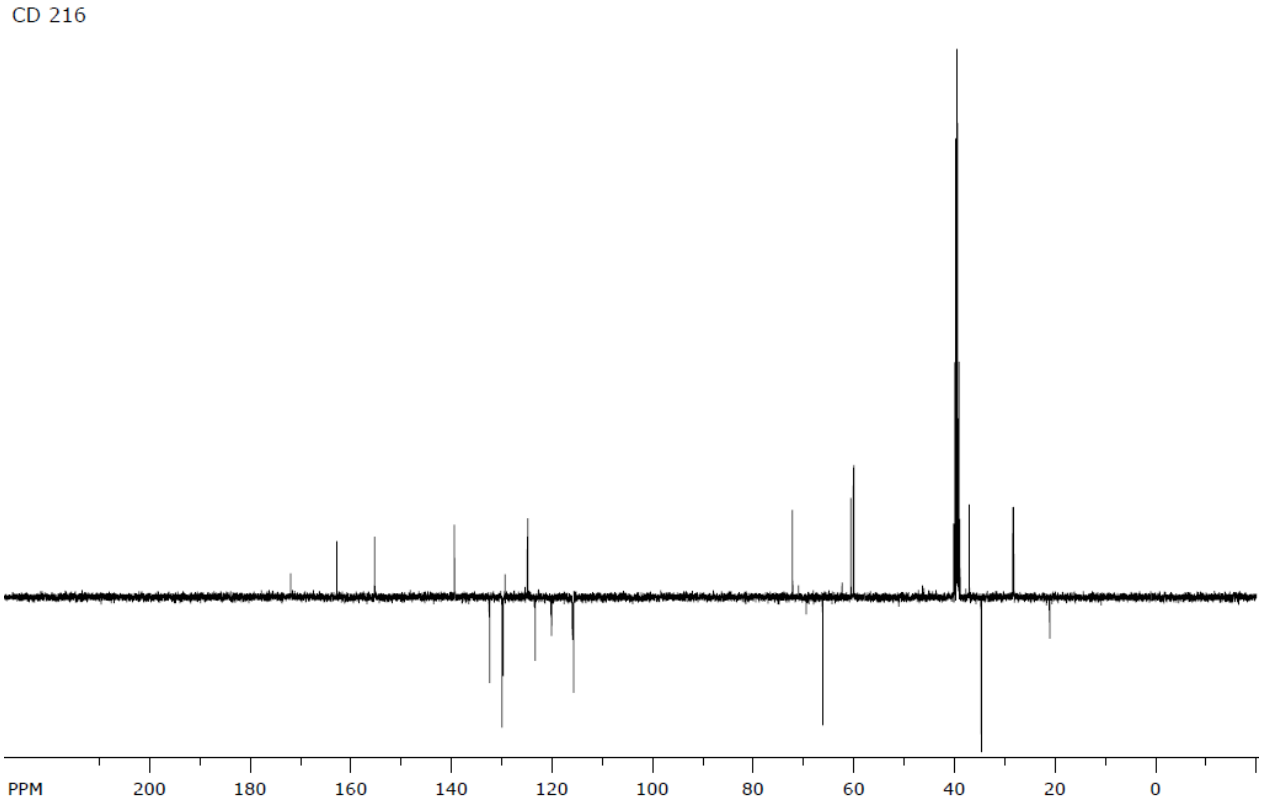
2-(3-((2-(adamantan-1-yl)ethyl)amino)-2-hydroxypropoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (275)



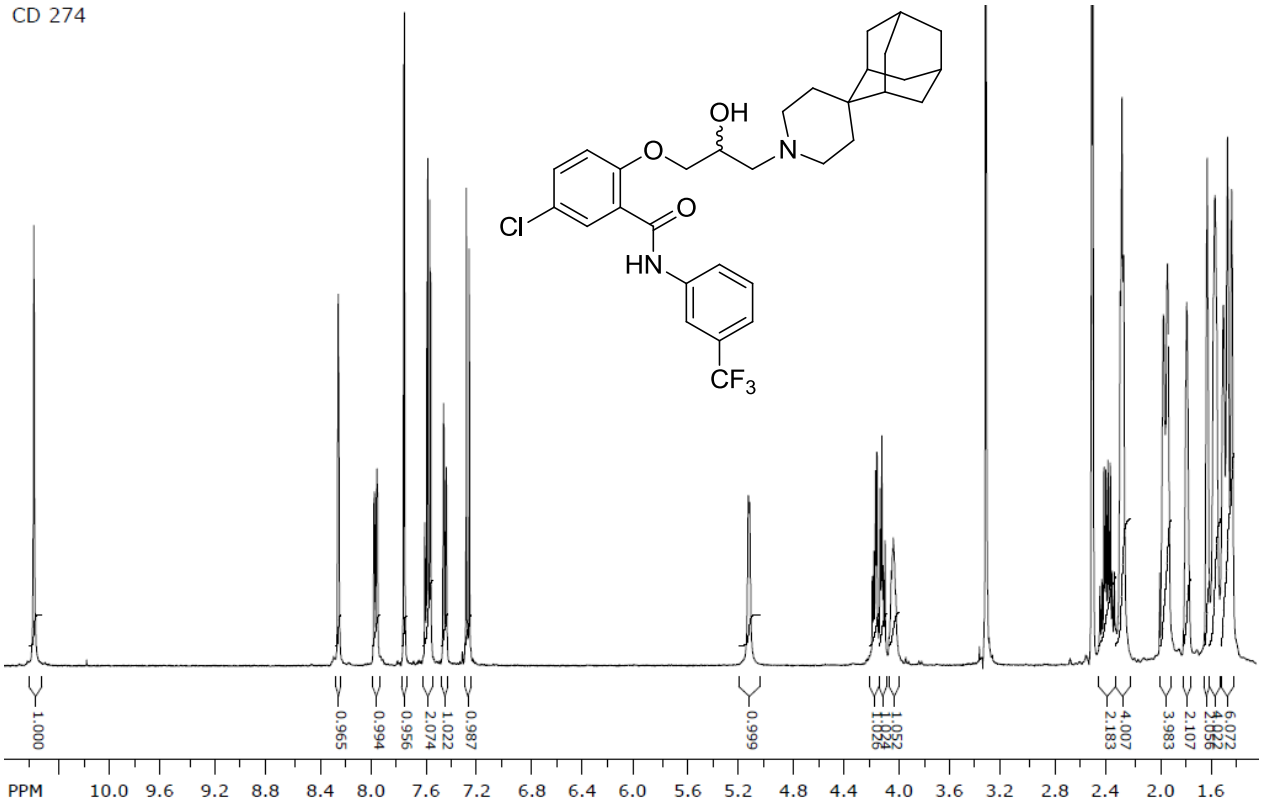


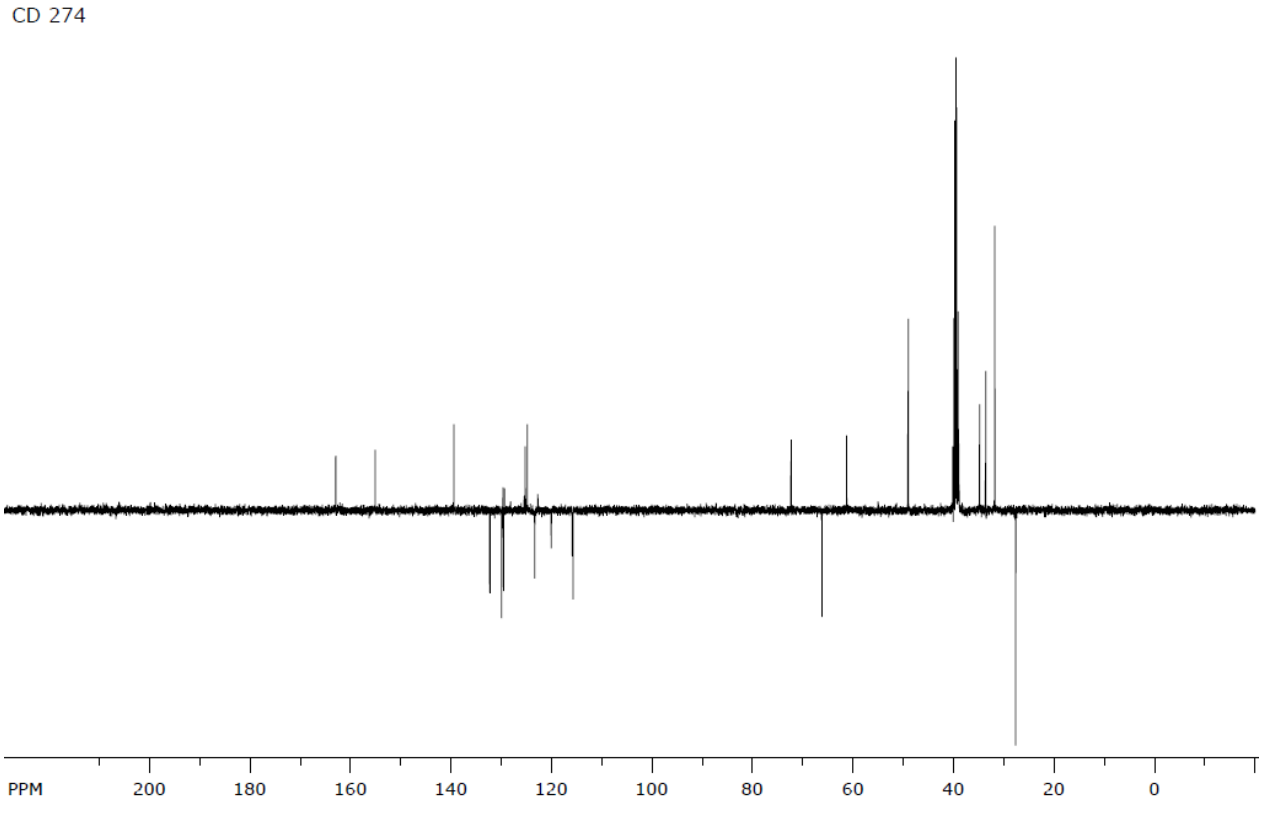
2-(3-(3-azabicyclo[3.2.1]octan-3-yl)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (276)



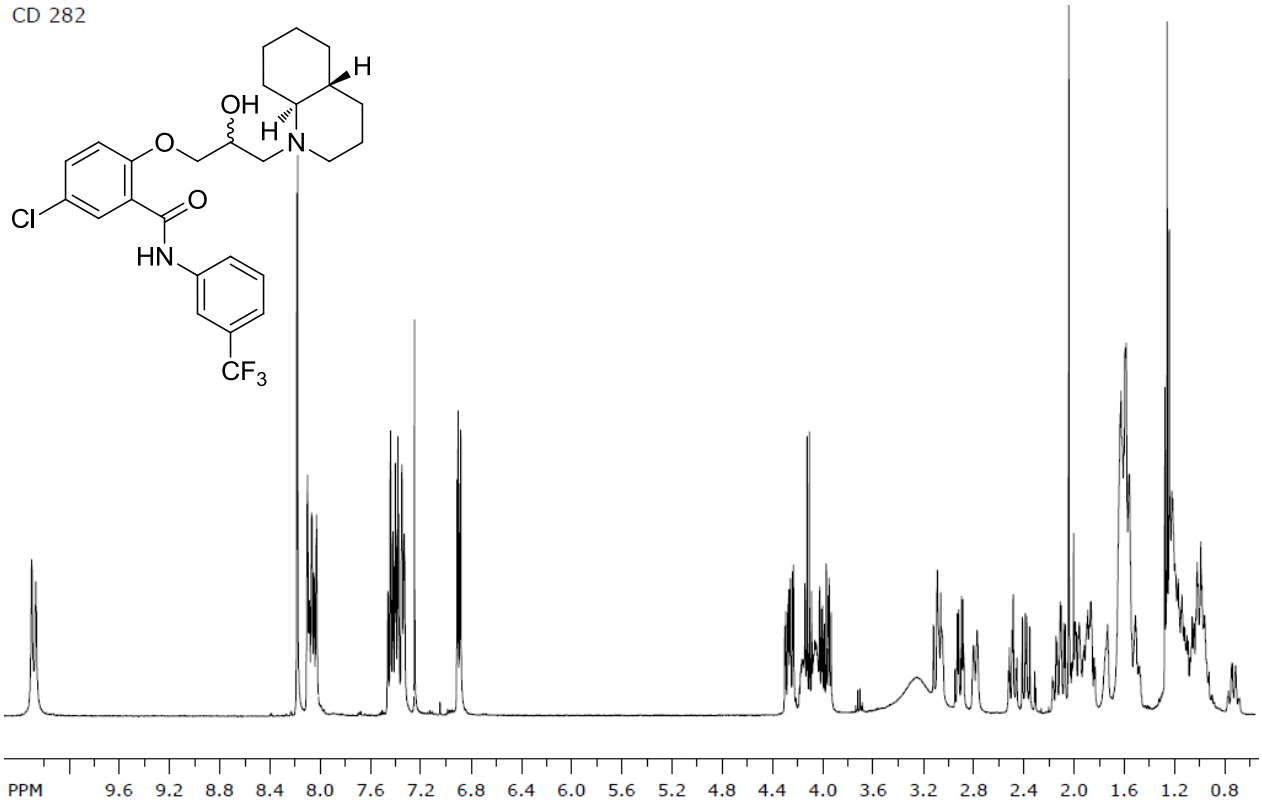


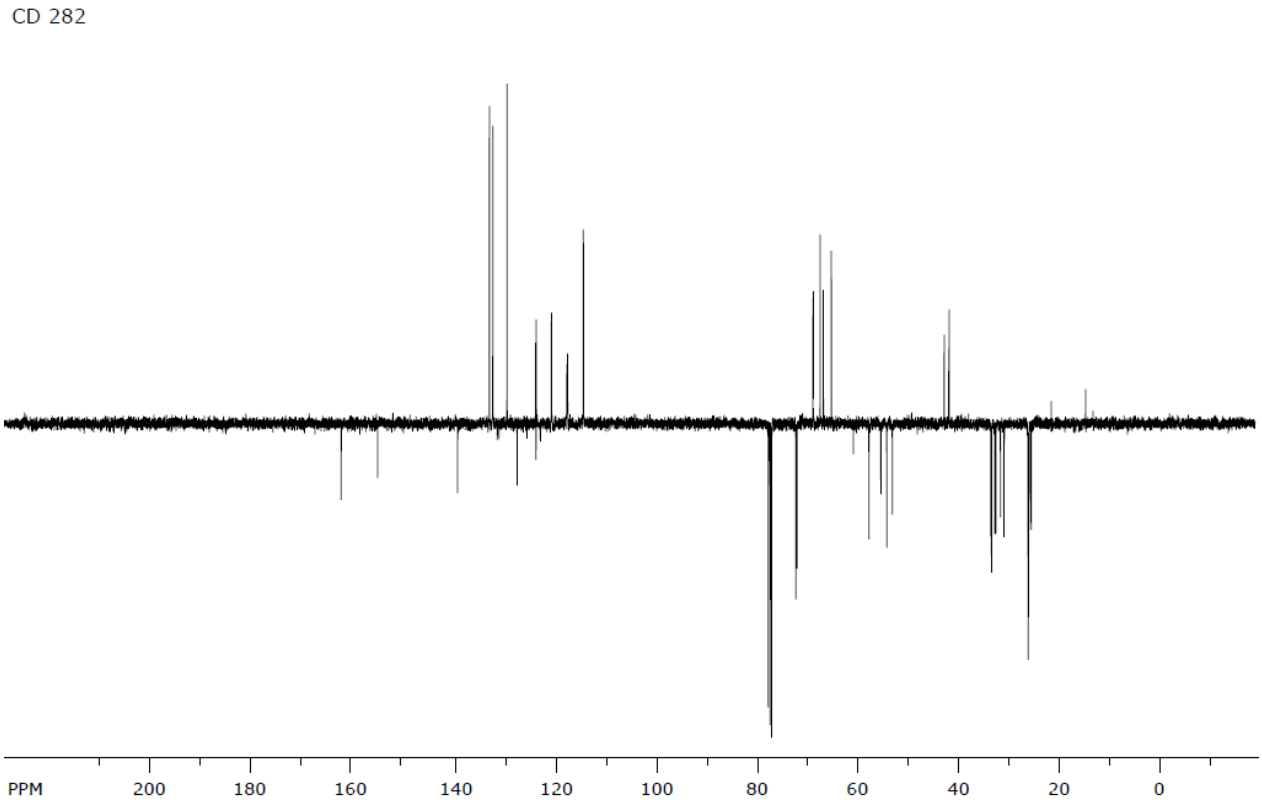
5-chloro-2-(2-hydroxy-3-(spiro[adamantane-2,4'-piperidin]-1'-yl)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (277)



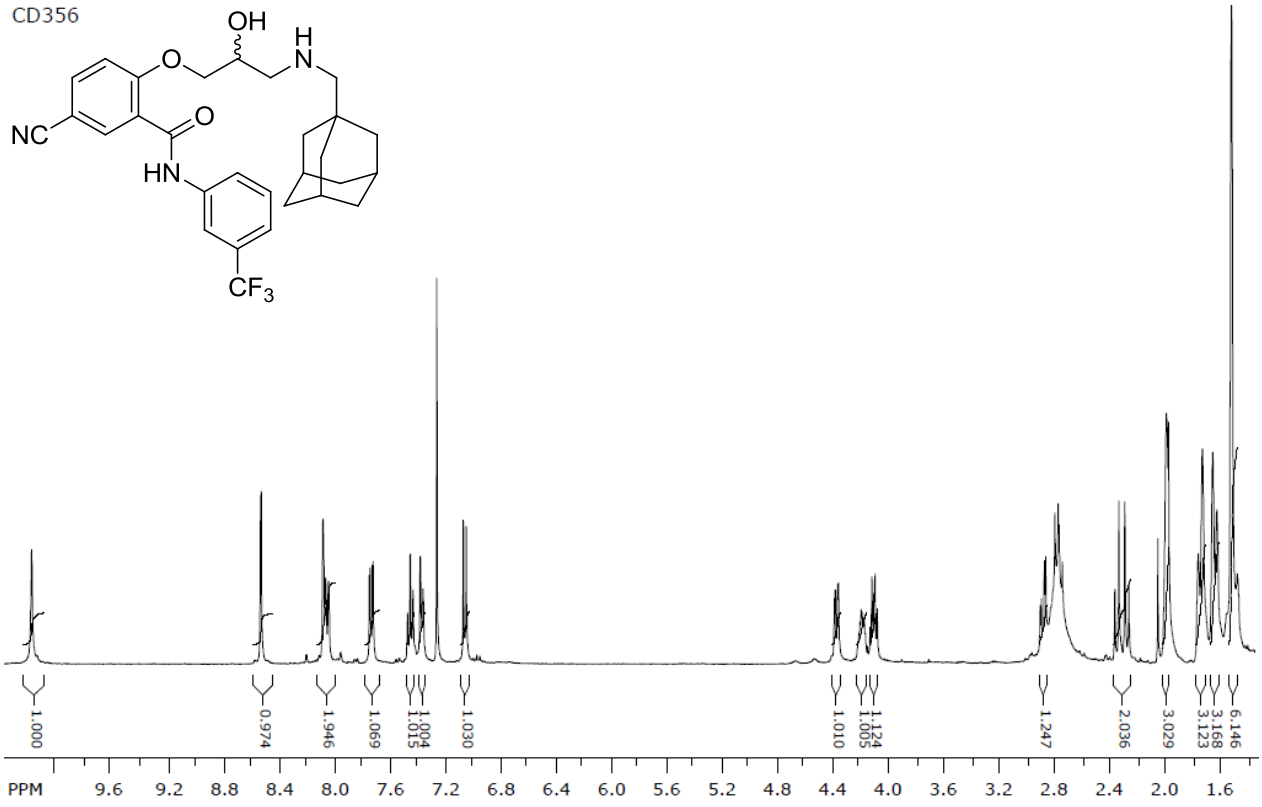


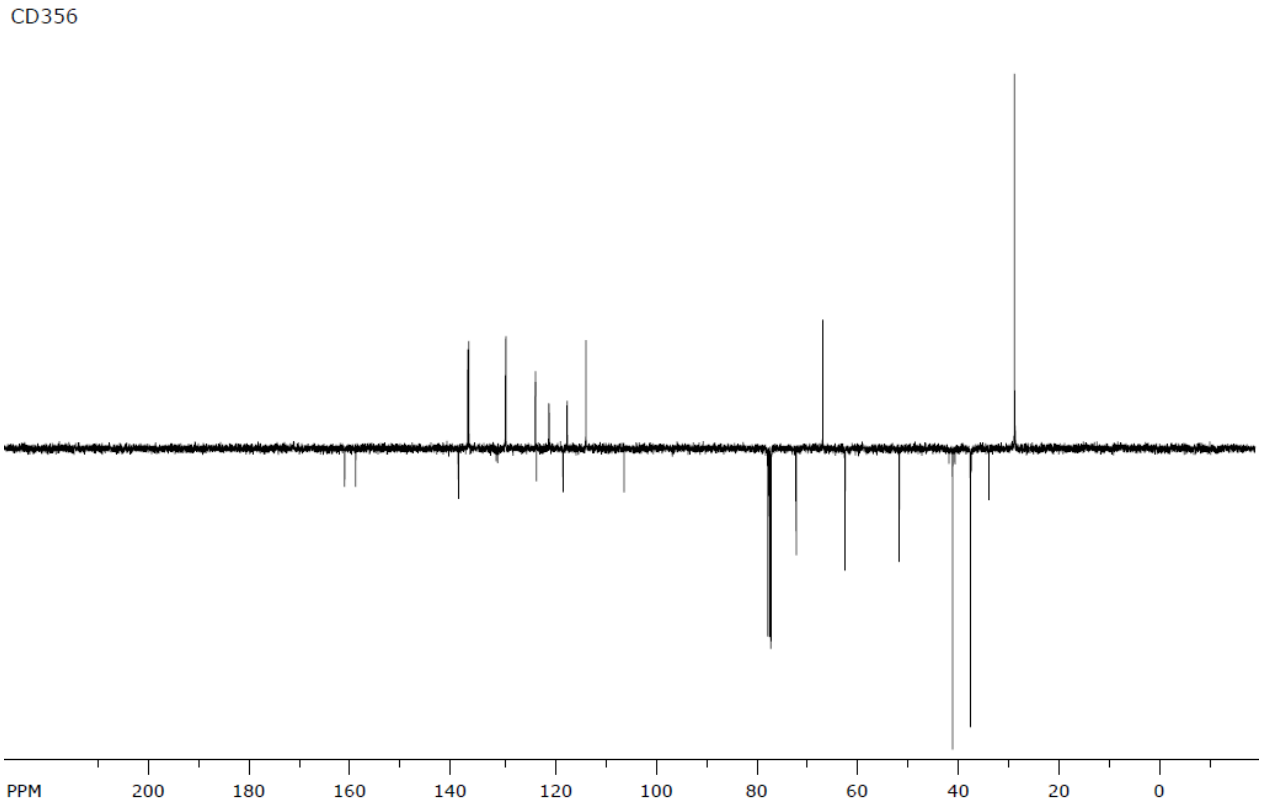
5-chloro-2-(2-hydroxy-3-(octahydroquinolin-1(2H)-yl)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (278)



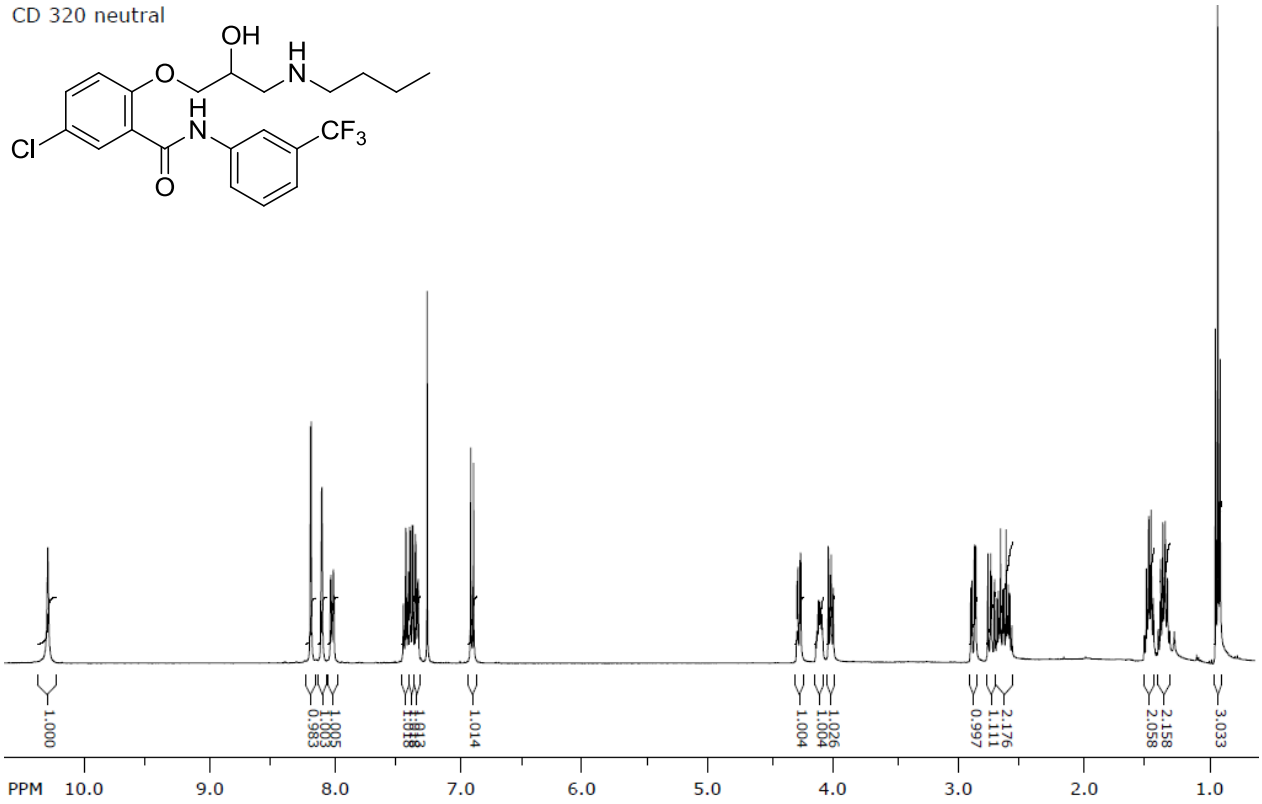


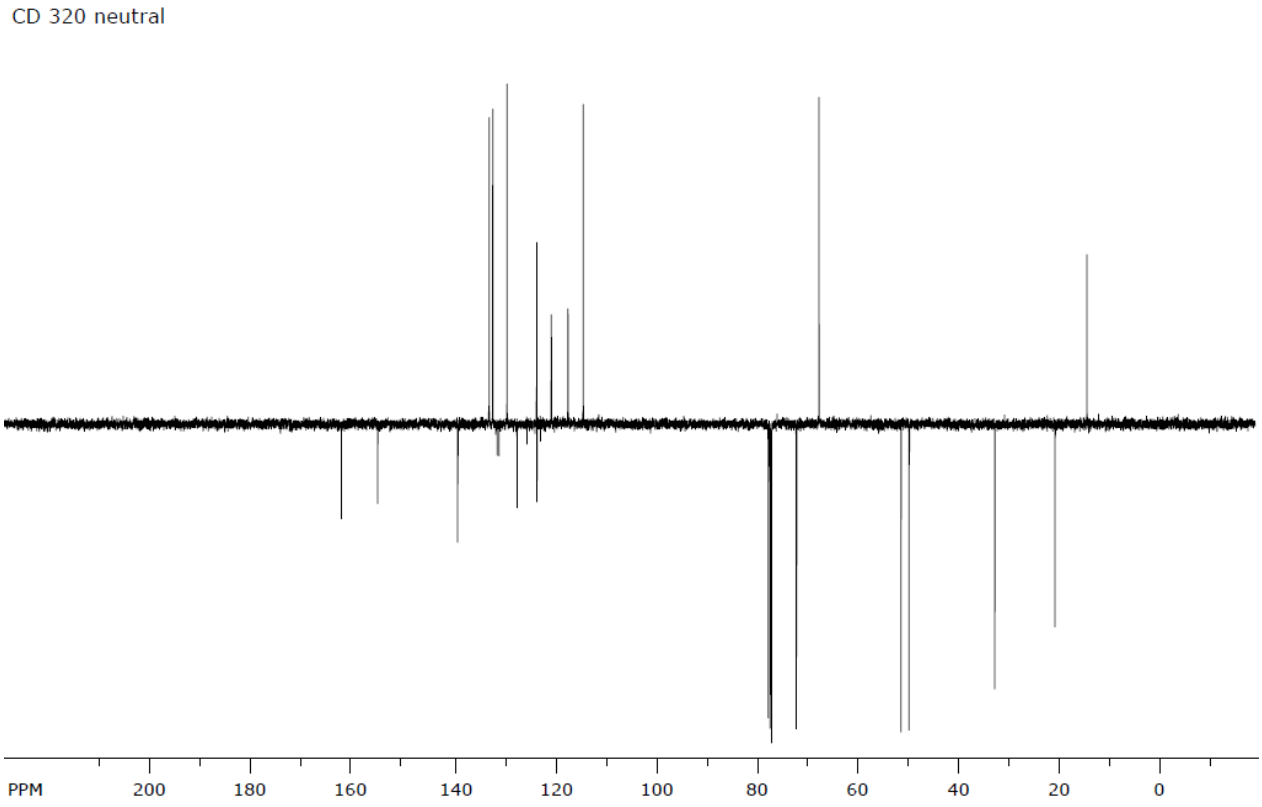
2-(3-((adamantan-1-ylmethyl)amino)-2-hydroxypropoxy)-5-cyano-*N*-(3-(trifluoromethyl)phenyl)benzamide (279)



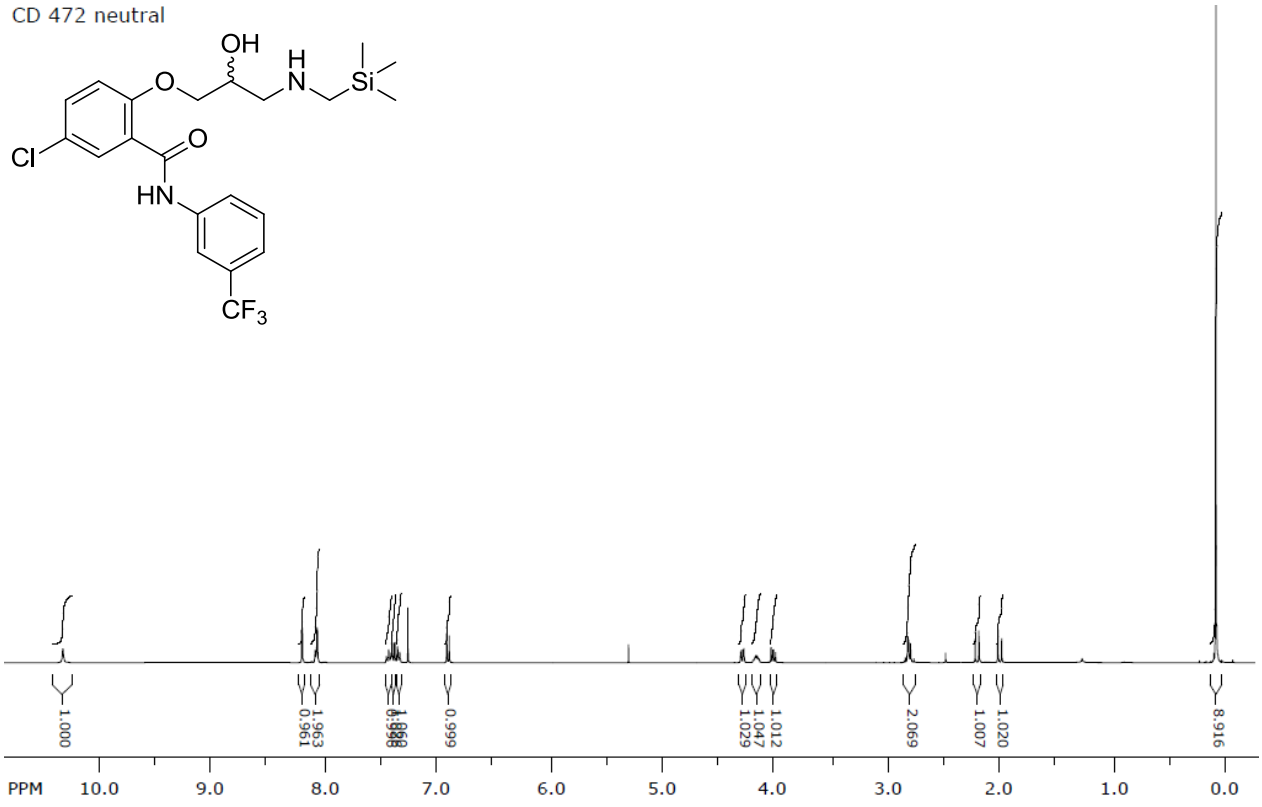


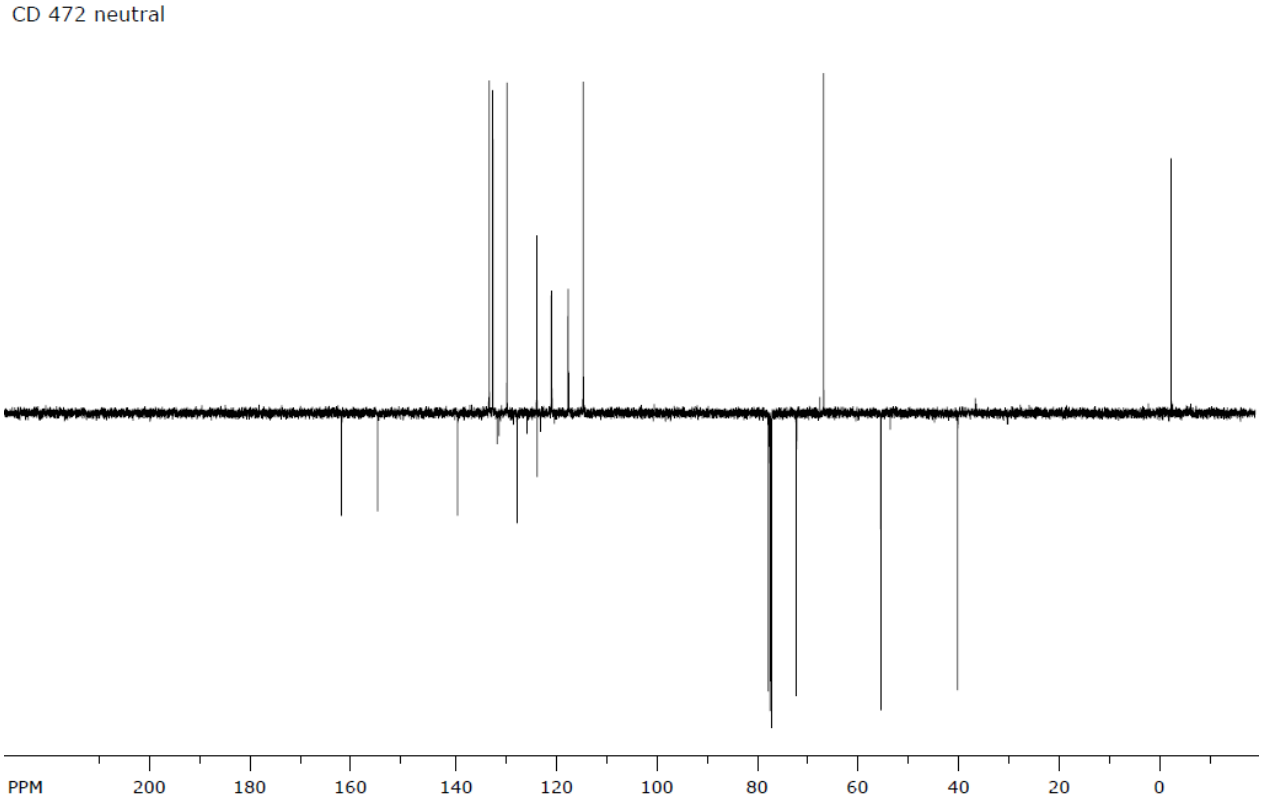
2-(3-(butylamino)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (292)



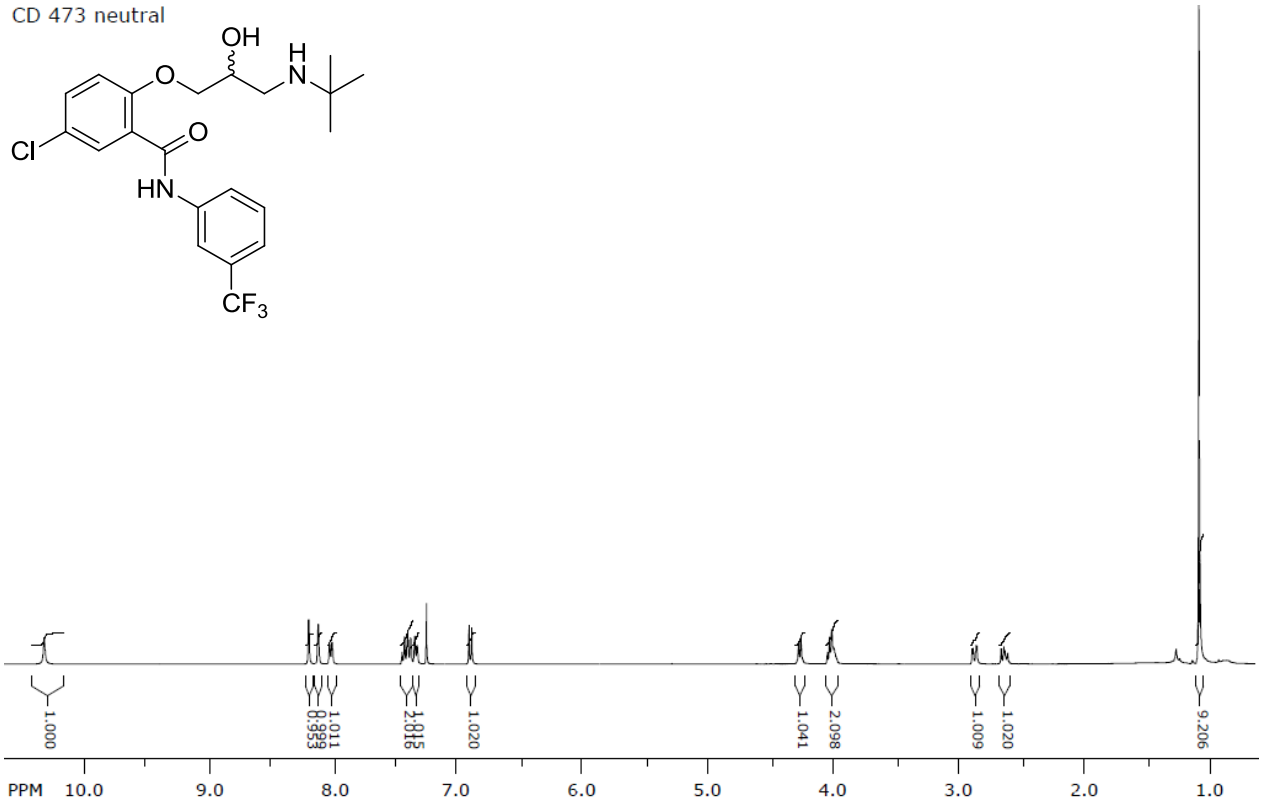


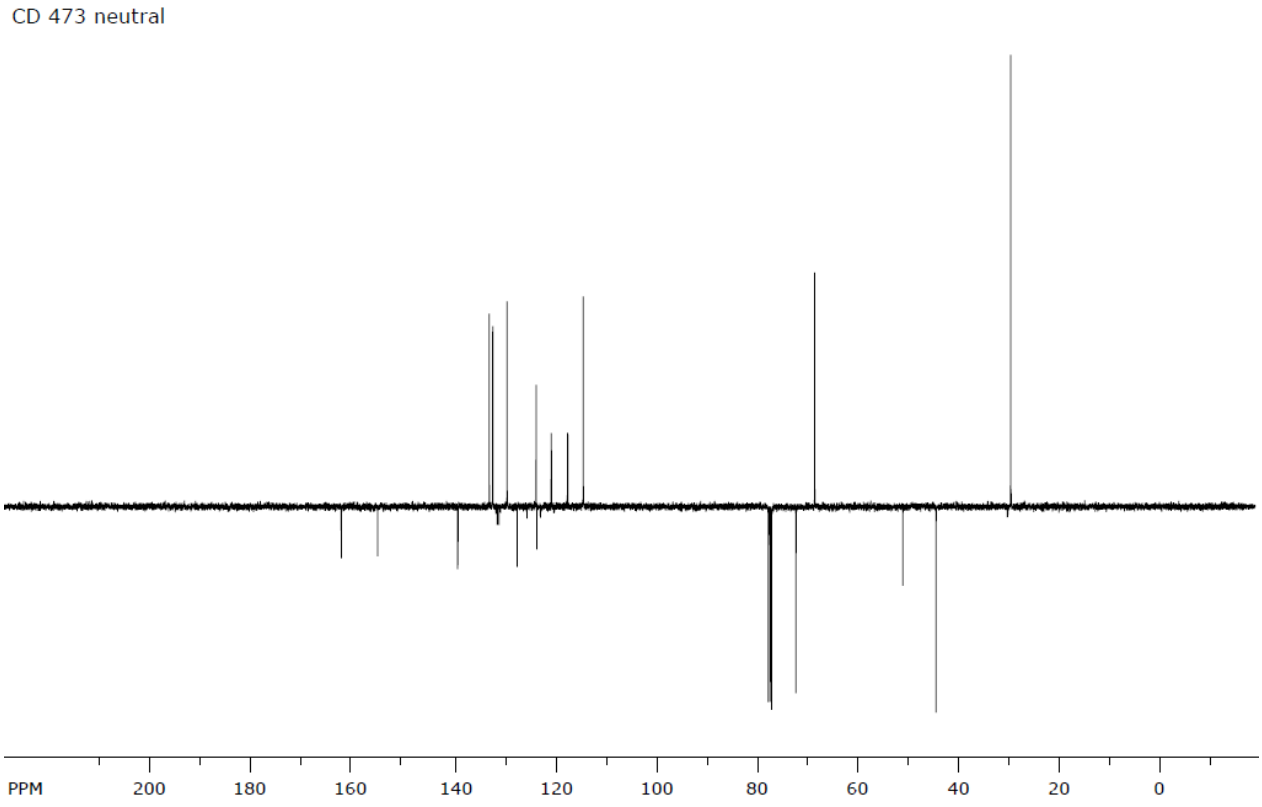
5-chloro-2-(2-hydroxy-3-(((trimethylsilyl)methyl)amino)propoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (293)



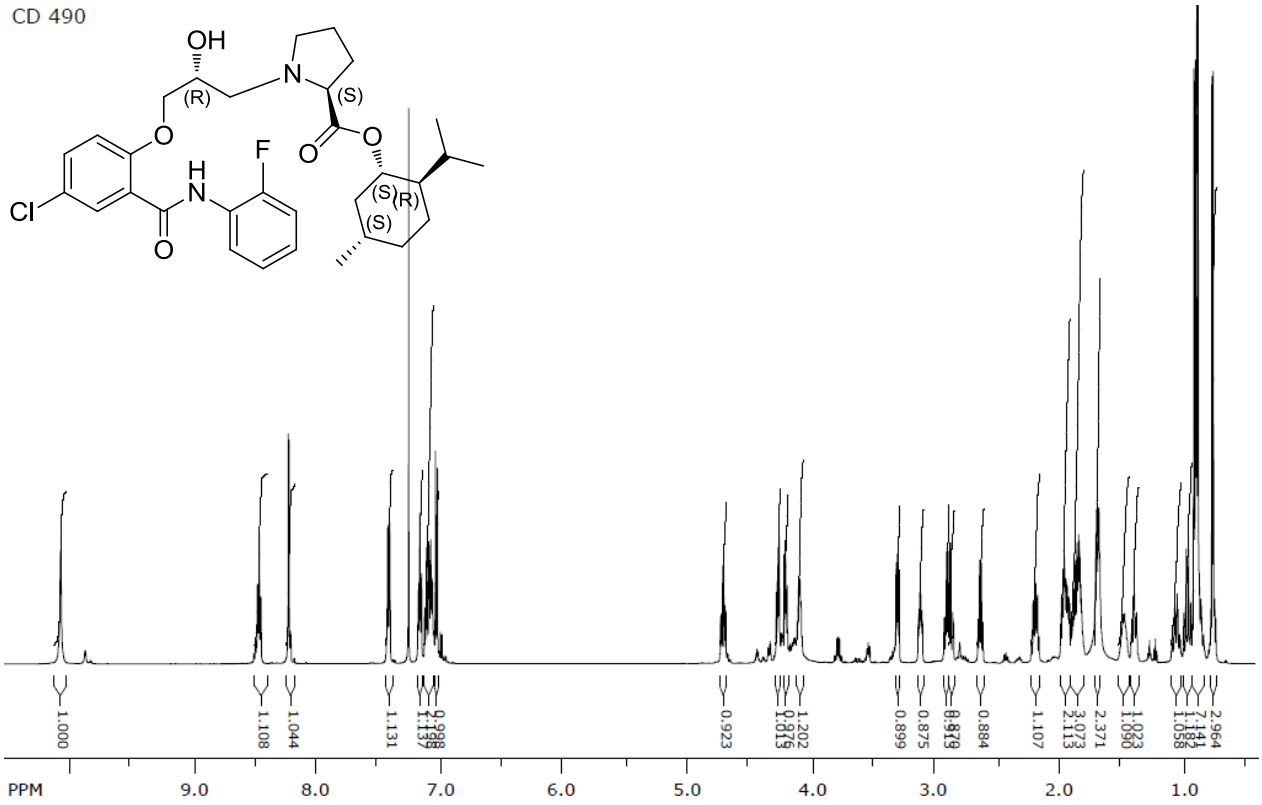


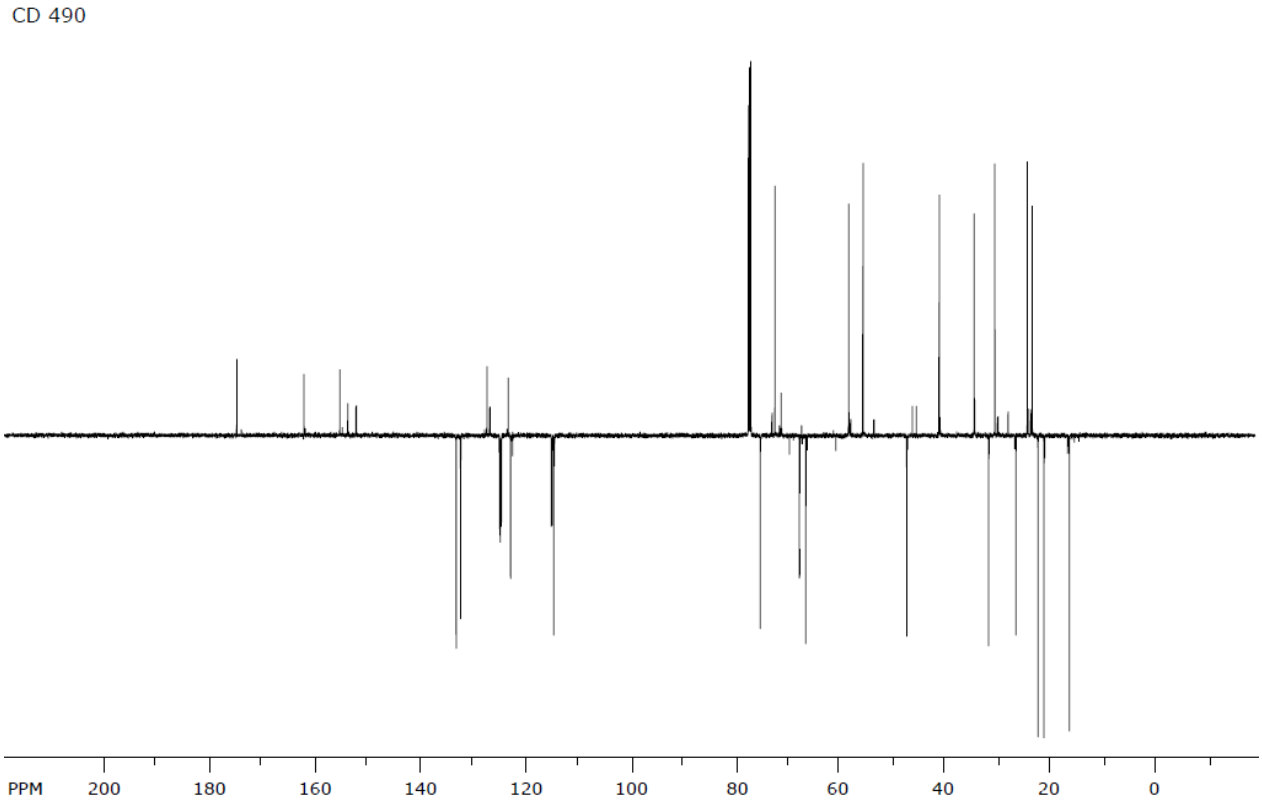
2-(3-(tert-butylamino)-2-hydroxypropoxy)-5-chloro-*N*-(3-(trifluoromethyl)phenyl)benzamide (294)





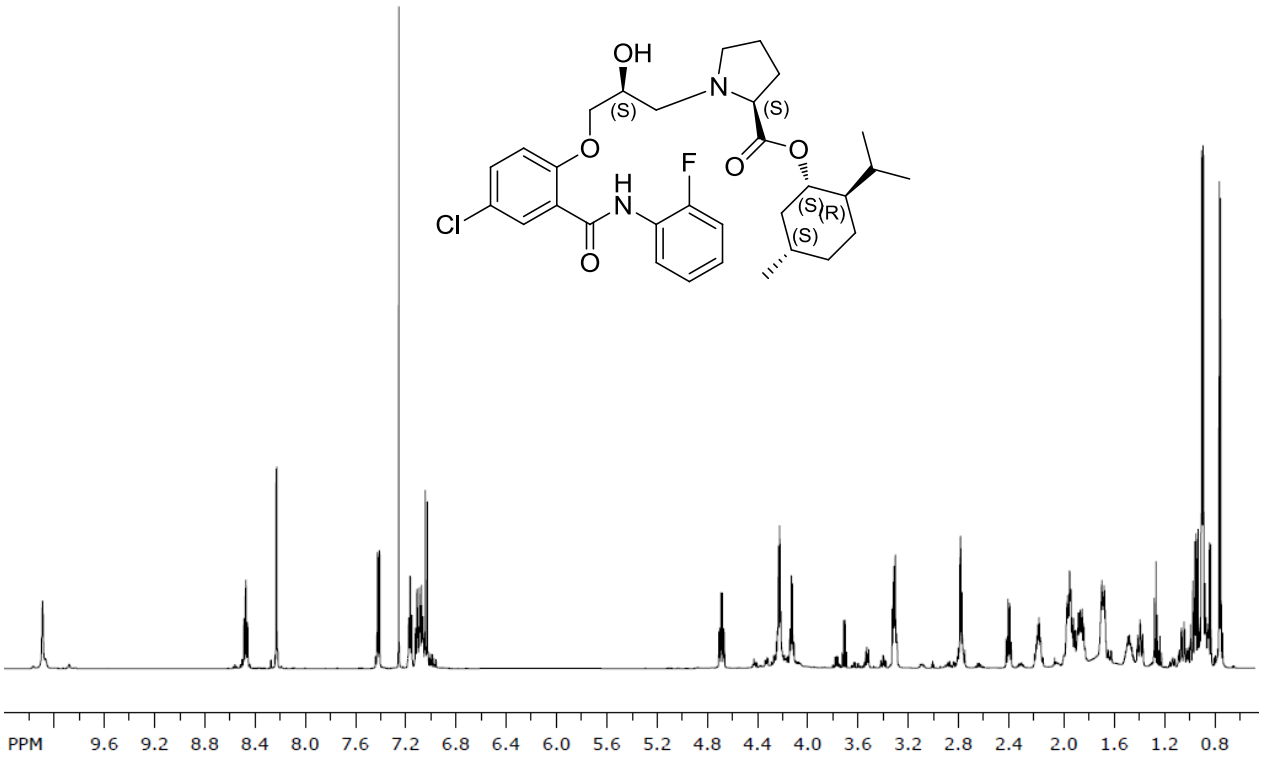
(*S*)-(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 1-((*R*)-3-(4-chloro-2-((2-fluorophenyl)carbamoyl)phenoxy)-2-hydroxypropyl)pyrrolidine-2-carboxylate (400)



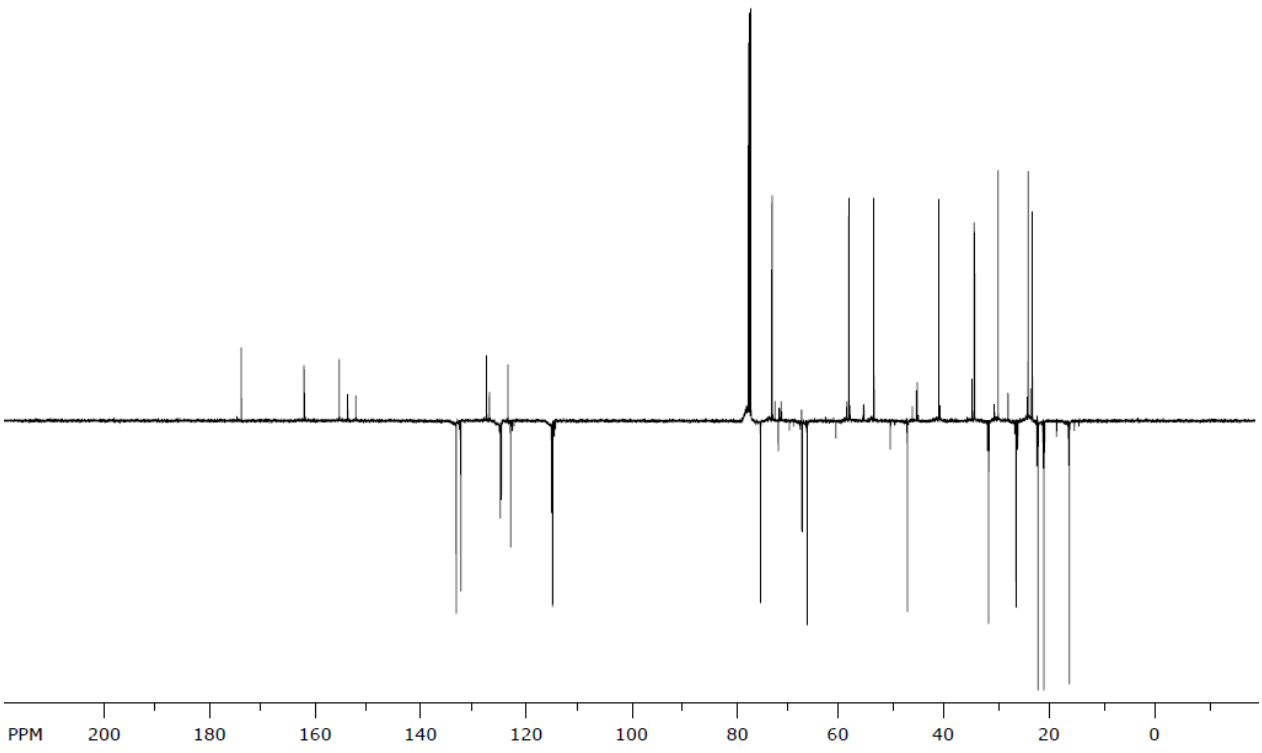


(*S*)-(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl-1-((*S*)-3-(4-chloro-2-((2-fluoro-5-(trifluoromethyl)phenyl)carbamoyl)phenoxy)-2-hydroxypropyl)pyrrolidine-2-carboxylate (401)

CD 491

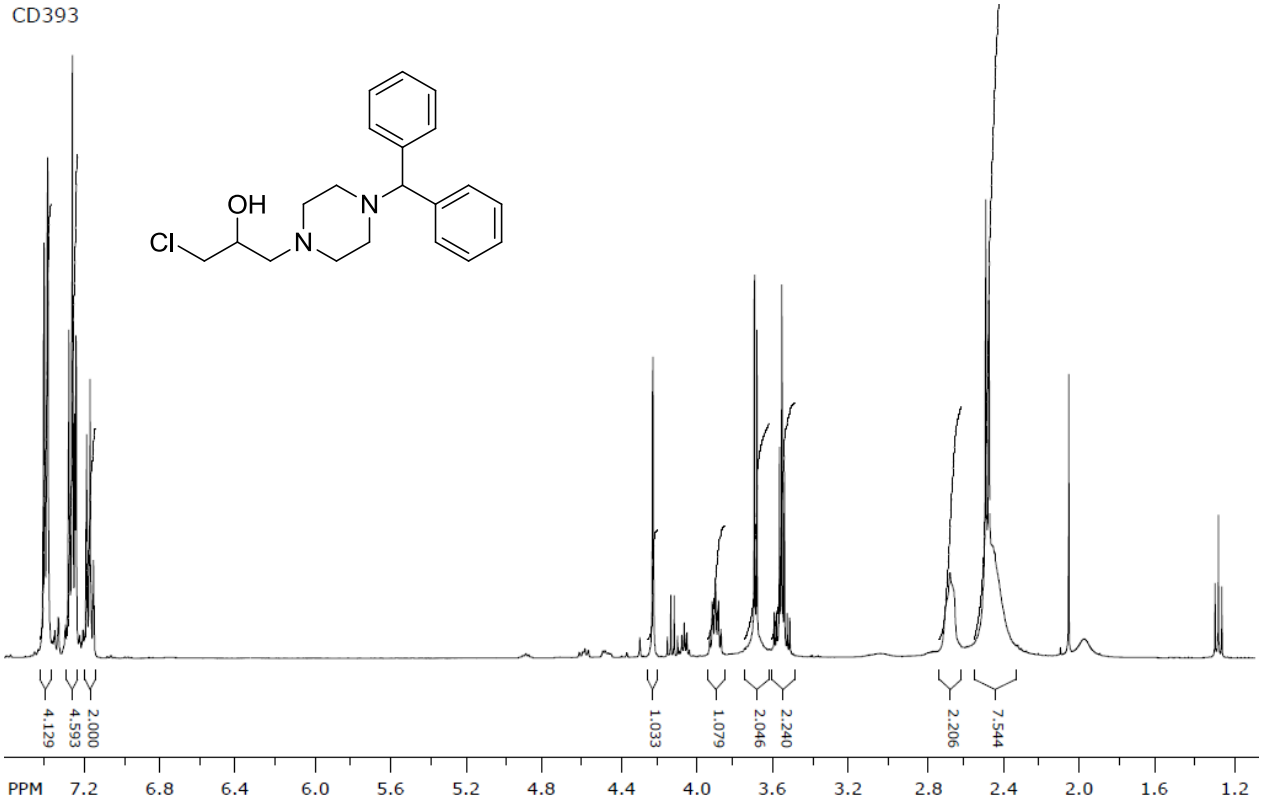


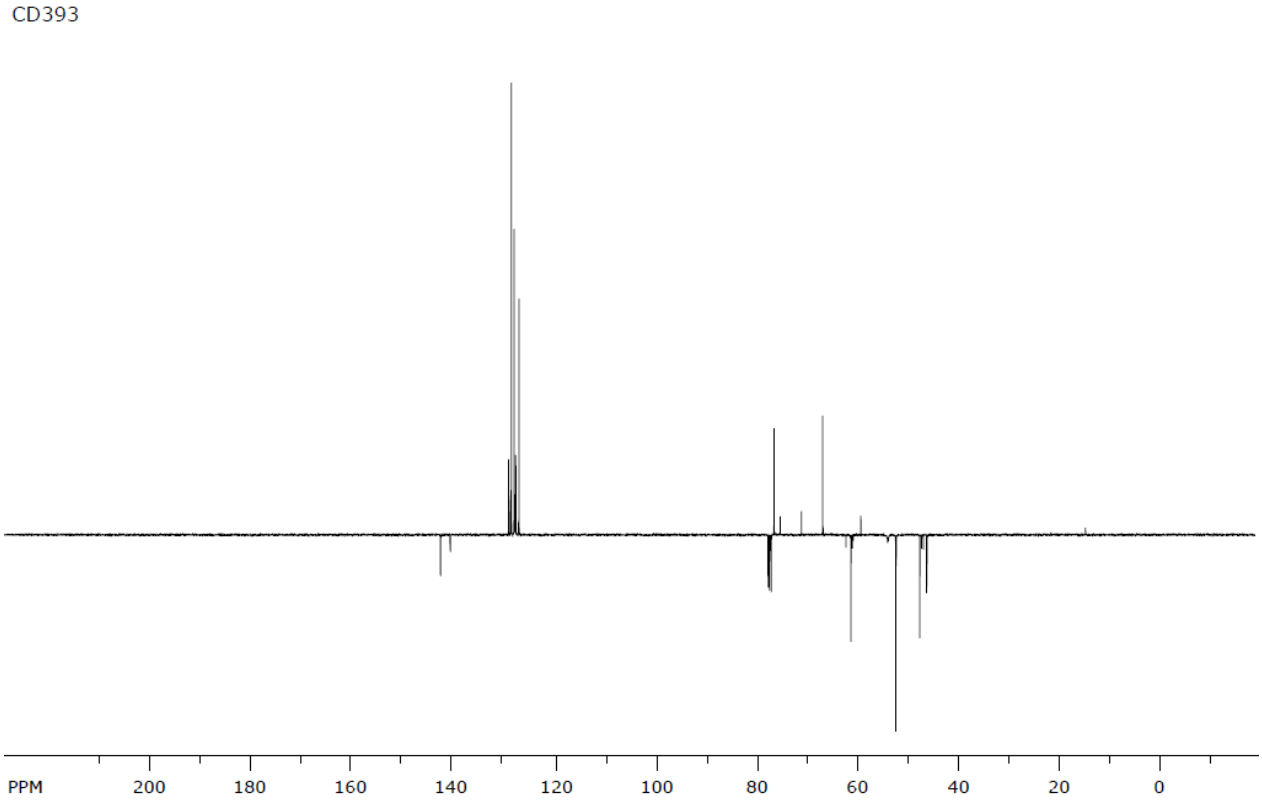
CD 491



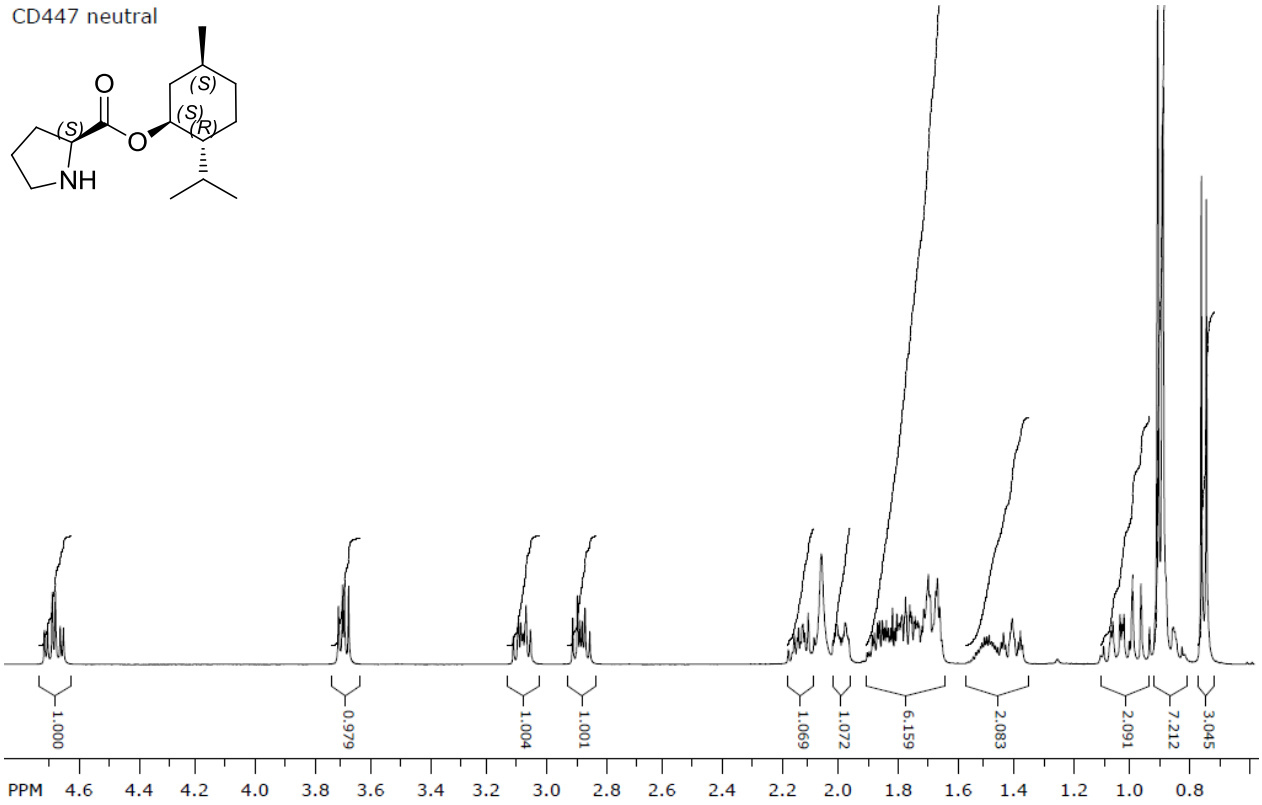
4.4.4 Additions

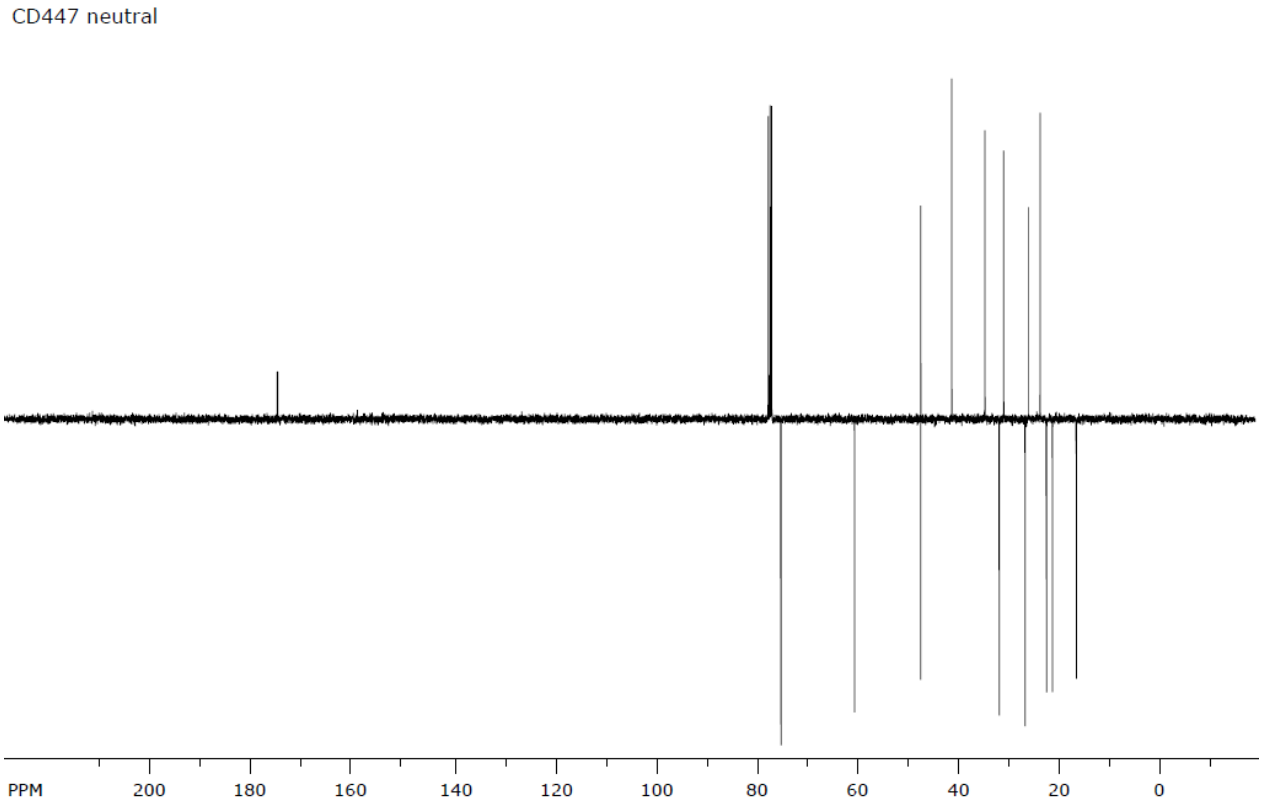
1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-2-ol (94)



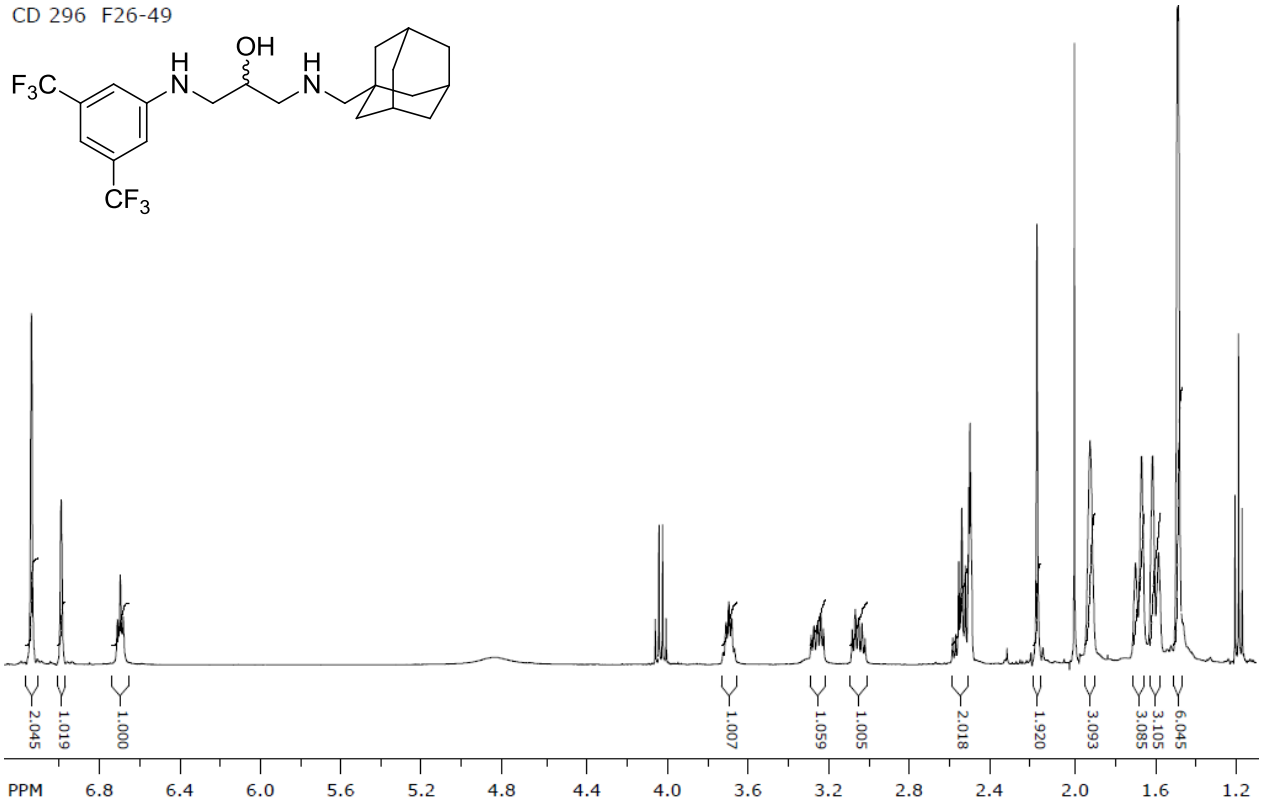


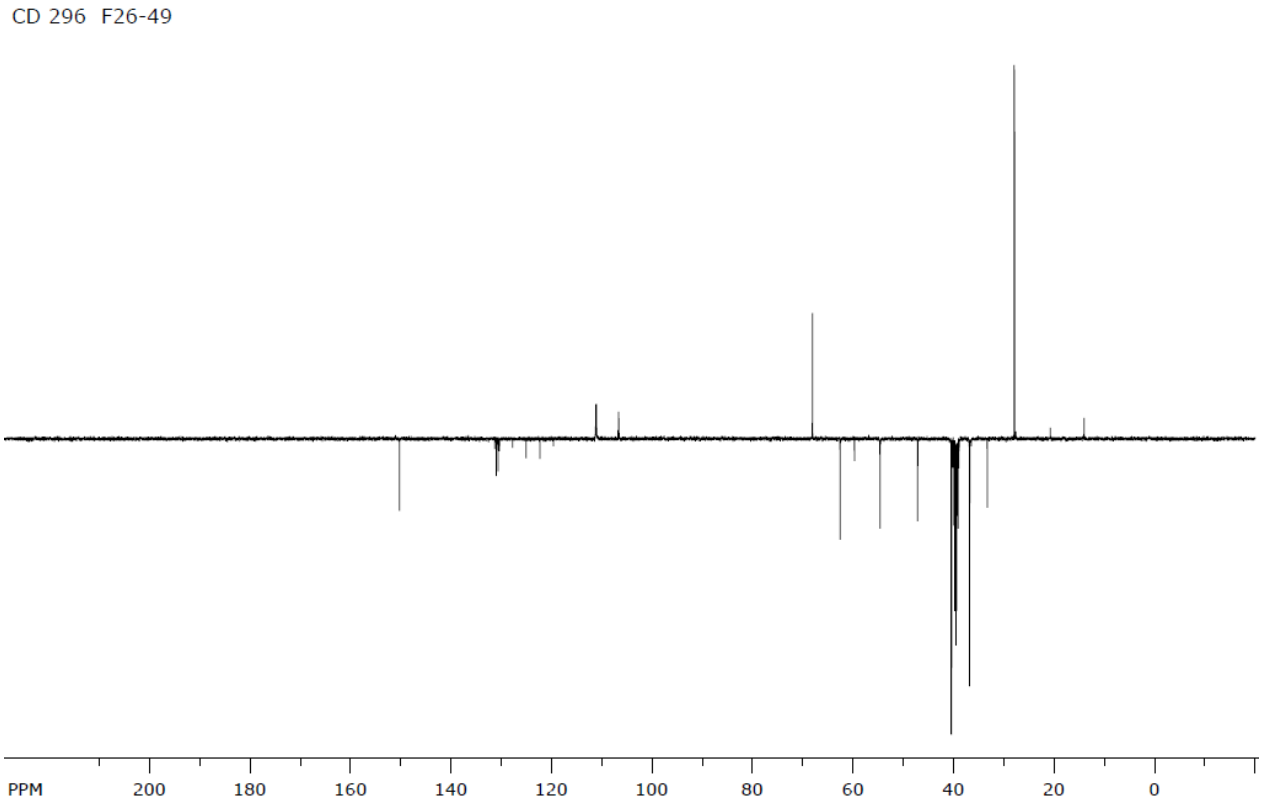
(*S*)-(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl pyrrolidine-2-carboxylate (101)



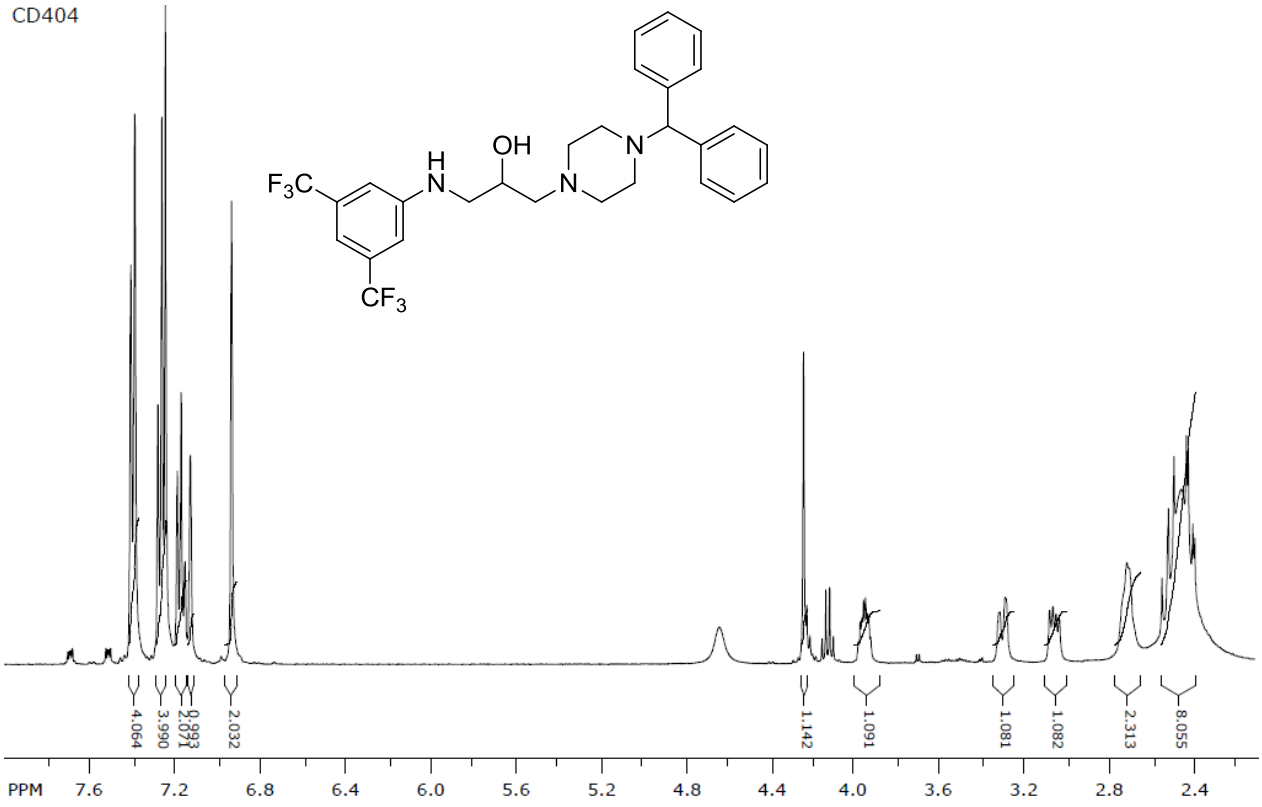


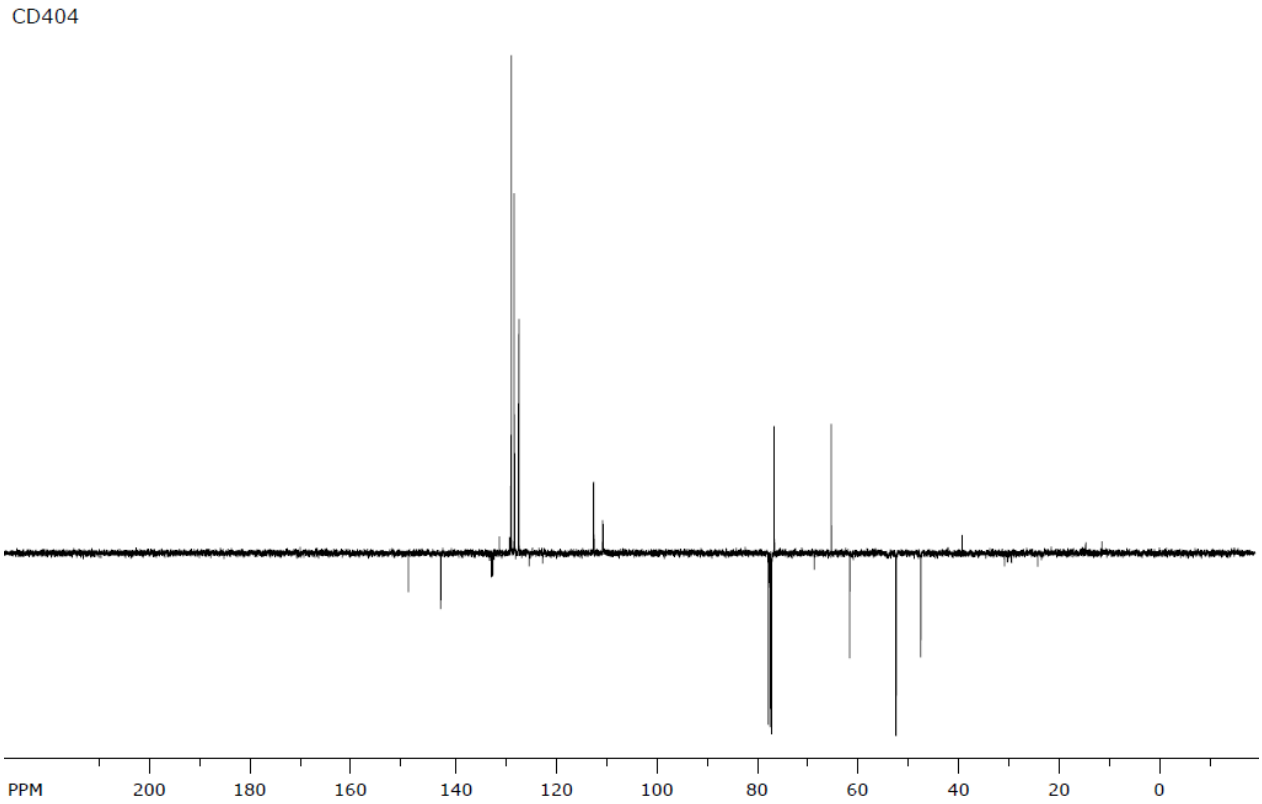
1-((adamantan-1-ylmethyl)amino)-3-((3,5-bis(trifluoromethyl)phenyl)amino)propan-2-ol (231)





1-(4-benzhydrylpiperazin-1-yl)-3-((3,5-bis(trifluoromethyl)phenyl)amino)propan-2-ol (232)





4.5 Chiral HPLC

Experiment description

Separtation method for 5-Chloro-2-oxiranylmethoxy-*N*-(3-trifluoromethyl-phenyl)-benzamide:

Column: Chiralpak AS-3 150 x 4.6 mm

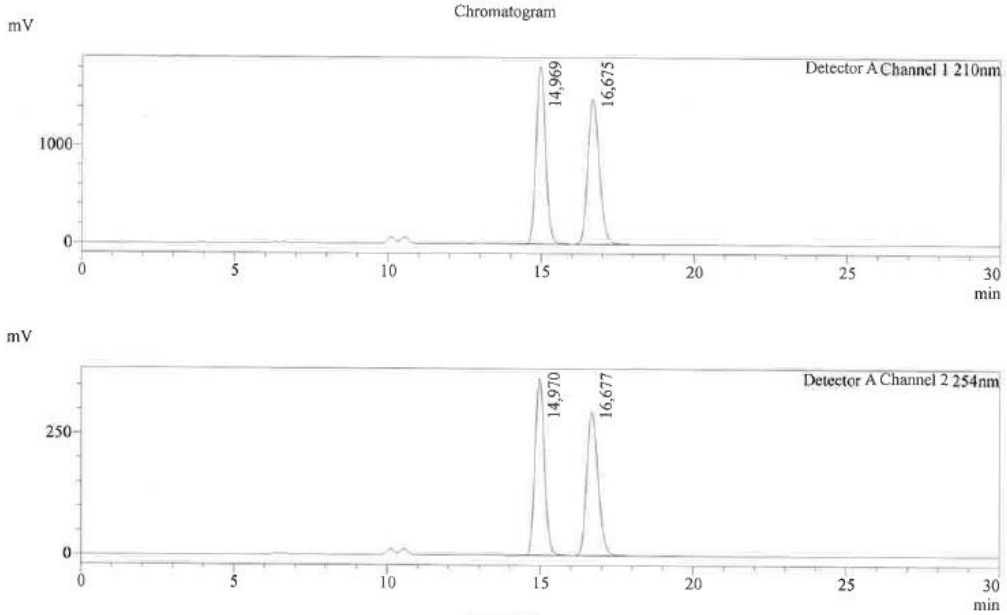
Solvent System: *n*-Heptan + 0.1% IPA/EtOH 9:1

Flow: 0.5 mL/min

T=25°C

P=24 bar

(±)-5-Chloro-2-oxiranylmethoxy-*N*-(3-trifluoromethyl-phenyl)-benzamide (71)



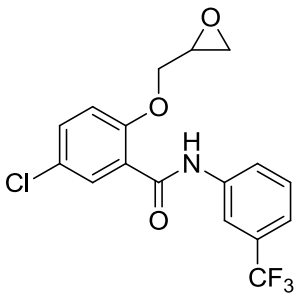
Peak Table

Detector A Channel 1 210nm

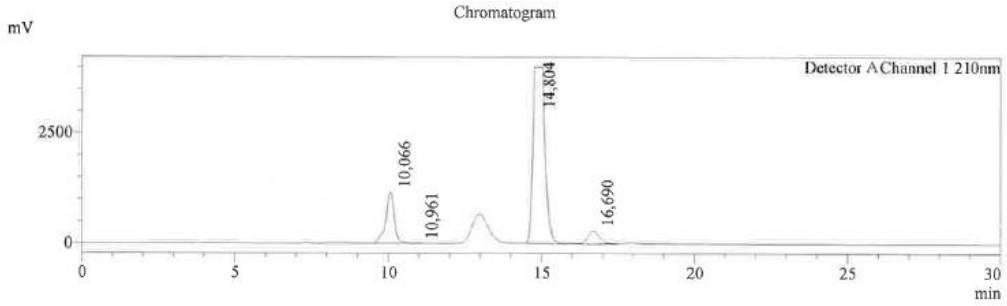
Peak#	Ret. Time	Area	Area%
1	14,969	38771928	49,879
2	16,675	38959807	50,121
Total		77731735	100,000

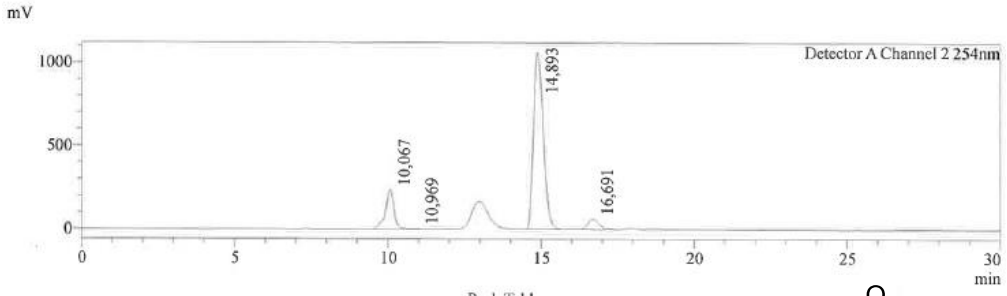
Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	14,970	7746185	49,956
2	16,677	7759804	50,044
Total		15505989	100,000



(*R*)-(+)-5-chloro-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (100)





Peak Table

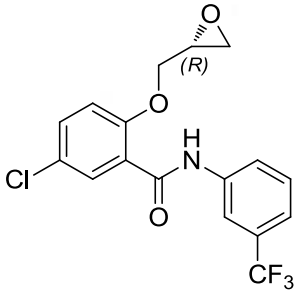
Detector A Channel 1 210nm

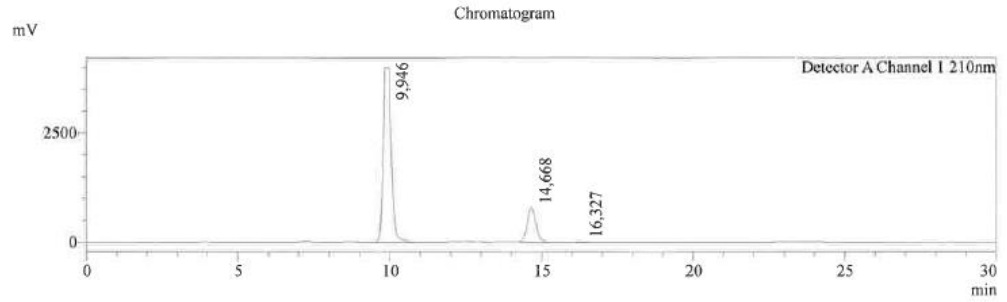
Peak#	Ret. Time	Area	Area%
1	10,066	22814306	16,390
2	10,961	102829	0,074
3	14,804	108436685	77,900
4	16,690	7845441	5,636
Total		139199261	100,000

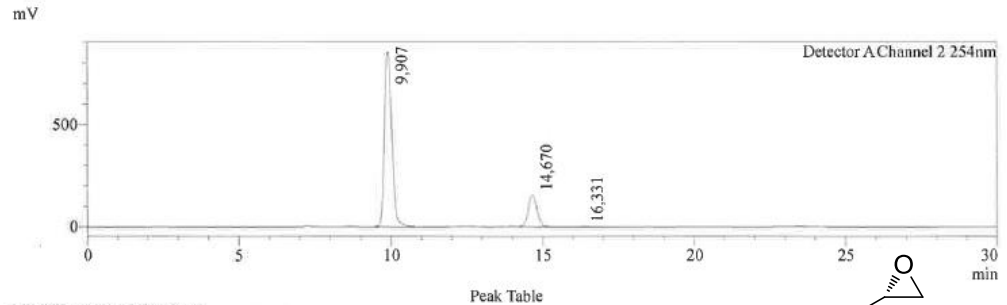
chloroalcohol : 5
epoxid 5

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	10,067	4617264	15,698
2	10,969	19408	0,066
3	14,893	23302163	79,225
4	16,691	1473969	5,011
Total		29412804	100,000







Peak Table

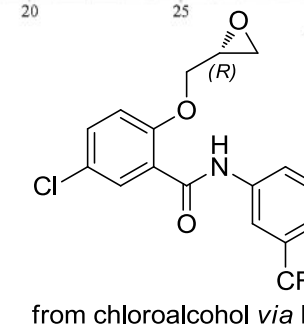
Detector A Channel 1 210nm

Peak#	Ret. Time	Area	Area%
1	9,946	73162047	81,975
2	14,668	15881258	17,794
3	16,327	206384	0,231
Total		89249689	100,000

EPOXID

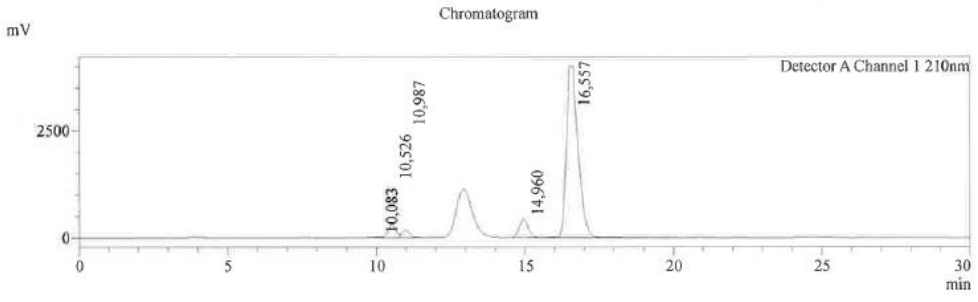
Detector A Channel 2 254nm

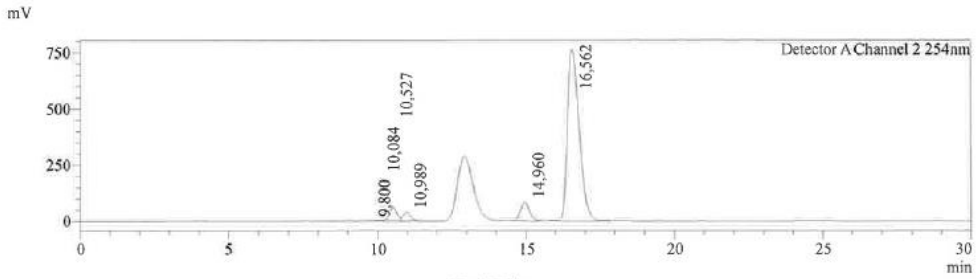
Peak#	Ret. Time	Area	Area%
1	9,907	14430722	82,095
2	14,670	3107760	17,680
3	16,331	39583	0,225
Total		17578065	100,000



from chloroalcohol *via* KF

(*S*)-(-)-5-chloro-2-(oxiran-2-ylmethoxy)-*N*-(3-(trifluoromethyl)phenyl)benzamide (99)





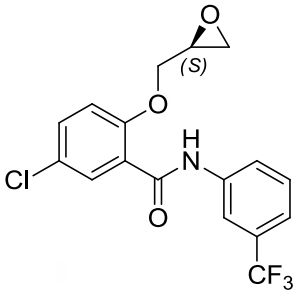
Peak Table

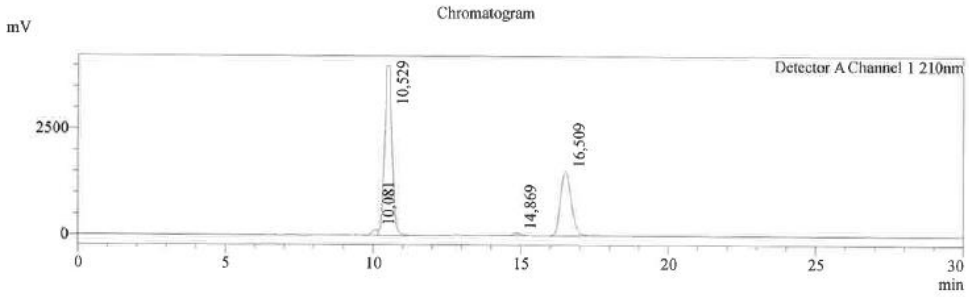
Detector A Channel 1 210nm

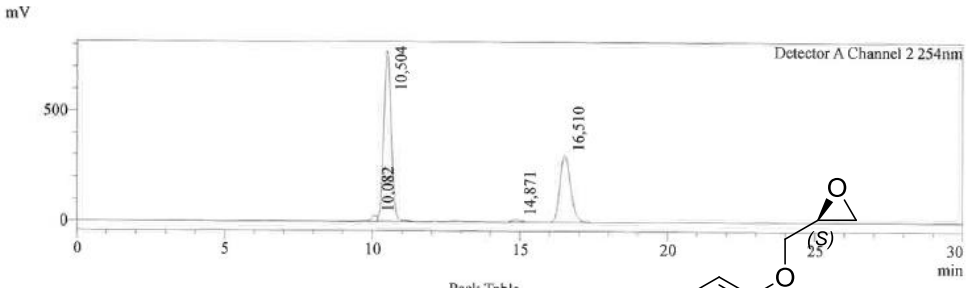
Peak#	Ret. Time	Area	Area%
1	10,083	318983	0,251
2	10,526	5742012	4,524
3	10,987	3241220	2,554
4	14,960	8853137	6,976
5	16,557	108754697	85,694
Total		126910050	100,000

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	9,800	16859	0,068
2	10,084	41964	0,170
3	10,527	1140348	4,613
4	10,989	709874	2,872
5	14,960	1756925	7,107
6	16,562	21054597	85,170
Total		24720566	100,000







Peak Table

Detector A Channel 1 210nm

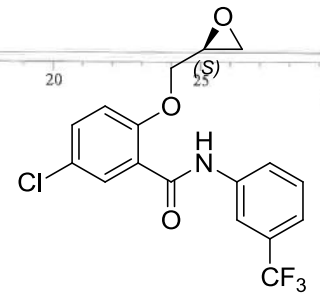
Peak#	Ret. Time	Area	Area%
1	10,081	1684813	1,518
2	10,529	69928867	63,008
3	14,869	1105721	0,996
4	16,509	38264589	34,478
Total		110983990	100,000

rac-Alcohol

epoxiol

Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	10,082	329450	1,523
2	10,504	13498928	62,383
3	14,871	218213	1,008
4	16,510	7592092	35,086
Total		21638683	100,000



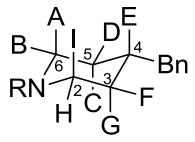
from chloroalcohol *via* KF

4.6 NMR Simulation

Simulations were performed in SpinWorks 3.1.7 (copyright 2010, Kirk Marat, University of Manitoba). Here, input parameters are listed, coupling constants and chemical shifts are given in Hz:

Piperidine Spin-System of 186

Opimize shifts and couplings =	0
Ignore bad transitions =	1
Auto assign observed peaks =	1
Maximum number of iterations =	30
RMS convergence limit =	0.020
RMS below this for autoassign =	0.250
Trans. freq. this * RMS ignored =	2.400



Groups and chemical shifts:

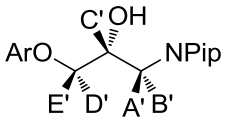
#	name	shift	spins	species	spin	sym
1	A	1507.391	1	1	1	1
2	B	2206.870	1	1	1	1
3	C	1239.020	1	1	1	1
4	D	1328.600	1	1	1	1
5	E	1777.726	1	1	1	1
6	F	1290.215	1	1	1	1
7	G	1255.340	1	1	1	1
8	H	1979.006	1	1	1	1
9	I	1732.637	1	1	1	1

Scalar coupling constants:

j[1, 2] =	j[A,B] =	-12.000000
j[1, 3] =	j[A,C] =	12.600000
j[1, 4] =	j[A,D] =	2.200000
j[1, 5] =	j[A,E] =	0.000000
j[1, 6] =	j[A,F] =	0.000000
j[1, 7] =	j[A,G] =	0.000000

j[1, 8] =	j[A,H] =	0.000000
j[1, 9] =	j[A,I] =	0.000000
j[2, 3] =	j[B,C] =	3.800000
j[2, 4] =	j[B,D] =	2.200000
j[2, 5] =	j[B,E] =	0.000000
j[2, 6] =	j[B,F] =	0.000000
j[2, 7] =	j[B,G] =	0.000000
j[2, 8] =	j[B,H] =	2.000000
j[2, 9] =	j[B,I] =	0.000000
j[3, 4] =	j[C,D] =	-12.500000
j[3, 5] =	j[C,E] =	12.500000
j[3, 6] =	j[C,F] =	0.000000
j[3, 7] =	j[C,G] =	0.000000
j[3, 8] =	j[C,H] =	0.000000
j[3, 9] =	j[C,I] =	0.000000
j[4, 5] =	j[D,E] =	3.500000
j[4, 6] =	j[D,F] =	2.500000
j[4, 7] =	j[D,G] =	0.000000
j[4, 8] =	j[D,H] =	0.000000
j[4, 9] =	j[D,I] =	0.000000
j[5, 6] =	j[E,F] =	3.500000
j[5, 7] =	j[E,G] =	12.500000
j[5, 8] =	j[E,H] =	0.000000
j[5, 9] =	j[E,I] =	0.000000
j[6, 7] =	j[F,G] =	-12.500000
j[6, 8] =	j[F,H] =	2.200000
j[6, 9] =	j[F,I] =	2.300000
j[7, 8] =	j[G,H] =	3.800000
j[7, 9] =	j[G,I] =	12.400000
j[8, 9] =	j[H,I] =	-11.700000

Aminoalcohol Spin-System of 186



Opimize shifts and couplings =	0
Ignore bad transitions =	1
Auto assign observed peaks =	1
Maximum number of iterations =	30
RMS convergence limit =	0.020
RMS below this for autoassign =	0.250
Trans. freq. this * RMS ignored =	2.400

Groups and chemical shifts:

#	name	shift	spins	species	spin	sym
1	A’	1760.011	1	1	1	1
2	B’	1836.295	1	1	1	1
3	C’	2975.348	1	1	1	1
4	D’	2824.991	1	1	1	1
5	E’	3033.545	1	1	1	1

Scalar coupling constants:

j[1, 2] =	j[A’,B’] =	-12.140000
j[1, 3] =	j[A’,C’] =	3.570000
j[1, 4] =	j[A’,D’] =	0.000000
j[1, 5] =	j[A‘,E‘] =	0.000000
j[2, 3] =	j[B‘,C‘] =	10.900000
j[2, 4] =	j[B‘,D‘] =	0.000000
j[2, 5] =	j[B‘,E‘] =	0.000000
j[3, 4] =	j[C‘,D‘] =	6.040000
j[3, 5] =	j[C‘,E‘] =	2.740000
j[4, 5] =	j[D‘,E‘] =	-9.440000

4.7 Crystallographic Data

	(S)-288	288	99
Identification code	chda485_P212121	chda481_P21	chda410_C2
Empirical formula	$C_{17}H_{14}Cl_4FNO_3$	$C_{32}H_{26}Cl_2F_2N_2O_6$	C17H13ClF3NO3
Formula weight	441.09	643.45	371.73
Temperature/K	100	100	100
Crystal system	orthorhombic	monoclinic	monoclinic
Space group	$P2_12_12_1$	$P2_1$	C2
a/Å	6.6885(2)	4.38680(10)	14.1520(11)
b/Å	15.1174(4)	23.9789(7)	7.3478(5)
c/Å	17.9992(5)	13.4893(4)	30.8381(19)
α/°	90	90	90
β/°	90	94.9386(8)	97.622(3)
γ/°	90	90	90
Volume/Å^3	1819.95(9)	1413.68(7)	3178.4(4)
Z	4	2	8
ρ_{calc}g/cm^3	1.61	1.512	1.554
μ/mm^{-1}	6.172	2.623	0.29
F(000)	896	664	1520
Crystal size/mm^3	0.296 × 0.106 × 0.065	0.25 × 0.16 × 0.15	0.513 × 0.133 × 0.026
Radiation	CuKα (λ = 1.54178)	CuKα (λ = 1.54178)	MoKα (λ = 0.71073)
2Θ range for data collection/°	7.636 to 136.964	6.576 to 137.032	1.332 to 50.698
Index ranges	-8 ≤ h ≤ 7, -17 ≤ k ≤ 18, -21 ≤ l ≤ 21	-5 ≤ h ≤ 5, -28 ≤ k ≤ 26, -16 ≤ l ≤ 16	-16 ≤ h ≤ 16, -8 ≤ k ≤ 8, -37 ≤ l ≤ 37
Reflections collected	14356	27276	19323
Independent reflections	3343 [R_{int} = 0.0496, R_{sigma} = 0.0315]	5145 [R_{int} = 0.0286, R_{sigma} = 0.0192]	5823 [Rint = 0.0679, Rsigma = 0.0557]
Data/restraints/parameters	3343/0/235	5145/1/397	5823/1/456
Goodness-of-fit on F^2	1.081	1.049	1.063
Final R indexes [I>=2σ (I)]	R_1 = 0.0264, wR_2 = 0.0664	R_1 = 0.0251, wR_2 = 0.0662	R1 = 0.0403, wR2 = 0.1009
Final R indexes [all data]	R_1 = 0.0280, wR_2 = 0.0671	R_1 = 0.0259, wR_2 = 0.0663	R1 = 0.0436, wR2 = 0.1037
Largest diff. peak/hole / e Å^{-3}	0.35/-0.38	0.43/-0.19	0.51/-0.39
Flack parameter	-0.011(5)	0.003(5)	-0.02(3)

	186	**102**	**272**
Identification code	chda113_P21c	chda452_P21	chda463_P21c
Empirical formula	$C_{28}H_{28}ClF_3N_2O_3$	$C_{32}H_{40}ClF_3N_2O_5$	$C_{29}H_{30}Cl_2F_3N_3O_3$
Formula weight	532.97	625.11	596.46
Temperature/K	100	100	100
Crystal system	monoclinic	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1$	$P2_1/c$
a/Å	7.8911(3)	5.0502(2)	8.4110(2)
b/Å	13.1163(4)	20.5929(7)	14.0688(4)
c/Å	24.2013(9)	14.9076(6)	23.3165(6)
α/°	90	90	90
β/°	91.1717(16)	92.1788(17)	95.2927(12)
γ/°	90	90	90
Volume/Å^3	2504.36(15)	1549.25(10)	2747.34(12)
Z	4	2	4
ρ_{calc}g/cm^3	1.414	1.34	1.442
μ/mm^{-1}	0.209	0.184	0.294
F(000)	1112	660	1240
Crystal size/mm^3	0.228 × 0.066 × 0.014	0.092 × 0.036 × 0.014	0.25 × 0.2 × 0.2
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.58 to 50.776	2.734 to 50.694	3.384 to 60.158
Index ranges	-9 ≤ h ≤ 9, -15 ≤ k ≤ 15, -29 ≤ l ≤ 29	-6 ≤ h ≤ 6, -24 ≤ k ≤ 24, -17 ≤ l ≤ 17	-11 ≤ h ≤ 11, -19 ≤ k ≤ 19, -32 ≤ l ≤ 32
Reflections collected	51975	20442	64135
Independent reflections	4600 [R_{int} = 0.0721, R_{sigma} = 0.0291]	5626 [R_{int} = 0.0537, R_{sigma} = 0.0469]	8027 [R_{int} = 0.0515, R_{sigma} = 0.0302]
Data/restraints/parameters	4600/16/407	5626/1/389	8027/0/364
Goodness-of-fit on F^2	1.104	1.071	1.033
Final R indexes [I>=2σ (I)]	R_1 = 0.0534, wR_2 = 0.1116	R_1 = 0.0517, wR_2 = 0.1299	R_1 = 0.0434, wR_2 = 0.1030
Final R indexes [all data]	R_1 = 0.0692, wR_2 = 0.1189	R_1 = 0.0727, wR_2 = 0.1745	R_1 = 0.0611, wR_2 = 0.1103
Largest diff. peak/hole / e Å^{-3}	0.35/-0.28	0.74/-0.76	0.67/-0.29
Flack parameter		0.00(3)	

	184	**188**
Identification code	chda055	chda056b
Empirical formula	C27 H29 F N2 O3	C28 H31 F N2 O3
Formula weight	448.52	462.55
Temperature	100(2) K	100(2) K
Wavelength	0.71073 A	1.54178 A
Crystal system, space group	triclinic, P-1	monoclinic, P21/n
Unit cell dimensions	a = 10.3385(4) A alpha = 82.5529(16) deg.	a = 18.086(2) A alpha = 90 deg.
	b = 11.3651(5) A beta = 63.2473(14) deg.	b = 5.2184(7) A beta = 107.734(7) deg.
	c = 11.4395(5) A gamma = 72.7590(16) deg.	c = 26.169(3) A gamma = 90 deg.
Volume	1146.30(8) A^3	2352.5(5) A^3
Z, Calculated density	2, 1.299 Mg/m^3	4, 1.306 Mg/m^3
Absorption coefficient	0.090 mm^-1	0.730 mm^-1
F(000)	476	984
Crystal size	0.35 x 0.17 x 0.06 mm	0.15 x 0.04 x 0.03 mm
Theta range for data collection	1.99 to 30.12 deg.	3.54 to 68.79 deg.
Index ranges	-14 ≤ h ≤ 14, -16 ≤ k ≤ 16, -16 ≤ l ≤ 16	-21 ≤ h ≤ 21, -6 ≤ k ≤ 6, -31 ≤ l ≤ 26
Reflections collected / unique	52269 / 6718 [R(int) = 0.0330]	26908 / 4320 [R(int) = 0.0476]
Completeness to 2theta =	30.12 99.7%	68.79 98.9%
Max. and min. transmission	0.9943 and 0.9688	0.9784 and 0.8984
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	6718 / 0 / 299	4320 / 1 / 273
Goodness-of-fit on F^2	1.02	0.997
Final R indices [I>2sigma(I)]	R1 = 0.0386, wR2 =0.1028	R1 = 0.0605, wR2 = 0.1360
R indices (all data)	R1 = 0.0459, wR2 = 0.108	R1 = 0.0823, wR2 = 0.1512
Largest diff. peak and hole	0.471 and -0.213 e.A^-3	0.809 and -0.684 e.A^-3

Appendix

Table 19.[85] The numerical potencies of selected antimalarials against asexual blood stages. Taken from the Supportin Information of "The Activities of Current Antimalarial Drugs on the Life Cycle Stages of *Plasmodium*: A Comparative Study with Human and Rodent Parasites" by Delves, M.; Plouffe, D.; Scheurer, C.; Meister, S.; Wittlin, S.; Winzeler, E. A.; Sinden, R. E.; Leroy, D. *Plos Med* 2012, *9*.

P. falciparum strains	NF54		K1		W2		7G8		TM90C2A		D6		V1/S	
Antimalarials	IC50 (nM)	SD	IC50 (nM)	SD	IC50 (nM)	SD	IC50 (nM)	SD	IC50 (nM)	SD	IC50 (nM)	SD	IC50 (nM)	SD
artemether	3.5	1.0	2.2	0.3	3.5	0.3	1.4	0.3	5.1	1.8	3.5	0.6	2.9	0.6
artemisinin	5.8	2.3	5.4	1.0	7.1	1.2	3.0	0.7	15.1	4.0	11.1	1.8	6.8	1.1
artemisone	0.8	0.1	0.4	0.1	0.5	0.0	0.5	0.1	0.6	0.2	0.8	0.1	0.6	0.2
dihydro artemisinin	1.1	0.1	0.8	0.0	1.2	0.1	0.7	0.2	1.0	0.3	1.5	0.1	1.0	0.2
artesunate	3.5	1.7	2.6	0.4	2.9	0.6	2.1	0.7	4.1	1.2	5.0	0.8	3.1	1.0
OZ439	3.0	0.5	1.8	0.1	3.3	0.2	1.7	0.1	3.2	1.1	2.8	0.4	2.4	0.5
OZ277	1.5	0.4	0.9	0.2	1.6	0.3	0.9	0.2	1.5	0.5	1.1	0.2	1.4	0.4
amodiaquine	3.9	1.9	7.7	1.6	10.8	1.6	9.9	1.6	5.8	1.7	4.6	0.8	9.4	0.5
AQ-13	5.3	1.0	20.0	0.8	27.0	4.5	14.7	1.2	10.8	5.2	7.8	1.1	32.0	1.6
chloroquine	11.2	2.7	198.0	24.1	268.3	51.5	70.3	12.0	105.8	52.7	8.8	0.3	304.0	18.8
hydroxychloroquine	16.3	1.7	962.0	131.4	1277.3	220.2	422.7	36.5	565.2	264.8	15.0	2.3	1735.3	104.4
naphthoquine	3.2	2.2	4.2	2.6	4.6	0.9	2.1	0.1	5.2	3.3	3.0	0.7	2.8	0.6
piperaquine	8.3	1.0	9.0	1.9	9.6	1.3	8.2	0.3	7.9	1.0	8.6	1.0	10.5	1.9
pyronaridine	4.9	0.8	6.7	2.7	9.5	3.9	5.9	0.7	4.6	2.3	4.1	0.8	6.9	3.5
tert-butyl Isoquine	5.4	2.0	13.3	2.1	10.1	1.4	3.9	0.4	6.0	2.2	6.5	1.7	16.0	0.0
bulaquine	1785.3	1099.0	1278.0	355.0	1573.3	332.0	831.7	304.0	1248.4	647.0	2499.1	1156.0	1155.5	300.0
NPC-1161B	419.0	91.0	140.3	27.0	192.3	73.0	41.7	13.0	150.1	89.0	461.7	252.0	138.3	38.0
diethylprimaquine	2670.0	504.0	768.3	123.0	949.0	249.0	841.3	180.0	882.0	387.0	2088.6	1197.0	746.3	59.0
primaquine	1191.0	275.0	557.0	182.0	675.7	79.0	441.3	155.0	629.7	294.0	1518.5	850.0	542.7	104.0
tafenoquine	631.0	233.0	185.3	39.0	121.3	22.0	52.5	5.0	297.3	190.0	1378.0	825.0	167.0	62.0
mefloquine (+ RS)	12.1	2.0	3.5	1.0	3.4	2.0	3.5	9.0	16.1	3.0	9.4	3.0	5.3	1.0
mefloquine (Racemic)	10.7	1.0	3.8	1.0	4.4	1.0	3.0	5.0	14.5	4.0	8.8	2.0	5.7	1.0
halofantrine	0.9	7.0	0.2	1.0	0.3	6.0	0.2	3.0	1.1	4.0	0.7	1.0	0.3	7.0
lumefantrine	2.8	6.0	1.1	2.0	1.6	2.0	1.2	1.0	5.9	1.0	4.1	1.0	1.3	4.0
pyrimethamine	17.0	8.0	10000.0	NA	10000.0	NA	6688.7	793.0	8231.0	NA	4.6	4.0	10000.0	NA
cycloguanil	4.5	2.0	445.0	69.0	1001.7	101.0	365.7	48.0	4261.7	2473.0	1.7	2.0	10000.0	NA
proguanil	1115.3	712.0	4011.3	1423.0	838.4	724.0	462.3	419.0	2674.1	2500.0	165.3	92.0	5535.0	2368.0
azithromycin	2643.0	1950.0	1423.7	265.0	1280.0	509.0	2231.0	865.0	299.0	99.0	2365.0	1875.0	783.7	114.0
thiostrepton	387.7	91.0	569.5	72.0	410.7	74.0	162.3	50.0	253.4	101.0	413.4	264.0	533.7	38.0
doxycyclin	1903.5	873.0	6239.5	522.0	1850.7	359.0	1558.3	564.0	2284.5	124.0	2058.7	794.0	6227.0	335.0
trimethoprim	940.3	23.0	10000.0	0.0	10000.0	NA	10000.0	NA	10000.0	NA	305.9	4.0	10000.0	NA
atovaquone	0.6	0.1	1.1	0.2	0.2	0.1	0.3	0.1	0.5	0.3	0.1	0.0	1.4	0.4
riboflavin	10000.0	NA	10000.0	NA	7561.3	2063.0	8096.7	1189.0	7586.7	NA	10000.0	NA	10000.0	NA
DHEA	10000.0	0.0	10000.0	NA	10000.0	NA	10000.0	NA	10000.0	NA	10000.0	NA	10000.0	NA
cycloheximide	83.3	4.0	121.3	25.0	341.6	445.0	97.3	26.0	78.8	11.0	93.7	2.0	100.7	1.0

IC50 >= 10,000 nM are indicated as 10,000 nM.

References

(1) World Health Organisation *World Malaria Report 2013* **2013**.

(2) Stiftung Weltbevölkerung *Datenreport 2013* **2013**.

(3) Wells, T. N. C.; Alonso, P. L.; Gutteridge, W. E. *Nat Rev Drug Discov* **2009**, *8*, 879.

(4) Laxminarayan, R.; Gelband, H. *Health Affair* **2009**, *28*, 949.

(5) Teixeira, C.; Vale, N.; Perez, B.; Gomes, A.; Gomes, J. R.; Gomes, P. *Chemical reviews* **2014**.

(6) Tuteja, R. *Febs J* **2007**, *274*, 4670.

(7) Yamauchi, L. M.; Coppi, A.; Snounou, G.; Sinnis, P. *Cell Microbiol* **2007**, *9*, 1215.

(8) Hafalla, J. C.; Silvie, O.; Matuschewski, K. *Immunol Rev* **2011**, *240*, 297.

(9) Tall, A.; Sokhna, C.; Perraut, R.; Fontenille, D.; Marrama, L.; Ly, A. B.; Sarr, F. D.; Toure, A.; Trape, J. F.; Spiegel, A.; Rogier, C.; Druilhe, P. *Malaria journal* **2009**, *8*.

(10) Menard, R. *Cell Microbiol* **2001**, *3*, 63.

(11) Baum, J.; Richard, D.; Healer, J.; Rug, M.; Krnajski, Z.; Gilberger, T. W.; Green, J. L.; Holder, A. A.; Cowman, A. F. *J Biol Chem* **2006**, *281*, 5197.

(12) Sultan, A. A.; Thathy, V.; Frevert, U.; Robson, K. J. H.; Crisanti, A.; Nussenzweig, V.; Nussenzweig, R. S.; Menard, R. *Cell* **1997**, *90*, 511.

(13) Mota, M. M.; Pradel, G.; Vanderberg, J. P.; Hafalla, J. C. R.; Frevert, U.; Nussenzweig, R. S.; Nussenzweig, V.; Rodriguez, A. *Science* **2001**, *291*, 141.

(14) Coppi, A.; Pinzon-Ortiz, C.; Hutter, C.; Sinnis, P. *J Exp Med* **2005**, *201*, 27.

(15) Montagna, G. N.; Matuschewski, K.; Buscaglia, C. A. *Front Biosci-Landmrk* **2012**, *17*, 726.

(16) Silvie, O.; Mota, M. M.; Matuschewski, K.; Prudencio, M. *Curr Opin Microbiol* **2008**, *11*, 352.

(17) Frevert, U.; Engelmann, S.; Zougbede, S.; Stange, J.; Ng, B.; Matuschewski, K.; Liebes, L. *Plos Biol* **2005**, *3*, 1034.

(18) Baer, K.; Roosevelt, M.; Clarkson, A. B.; van Rooijen, N.; Schnieder, T.; Frevert, U. *Cell Microbiol* **2007**, *9*, 397.

(19) Sturm, A.; Amino, R.; van de Sand, C.; Regen, T.; Retzlaff, S.; Rennenberg, A.; Krueger, A.; Pollok, J. M.; Menard, R.; Heussler, V. T. *Science* **2006**, *313*, 1287.

(20) Graewe, S.; Rankin, K. E.; Lehmann, C.; Deschermeier, C.; Hecht, L.; Froehlke, U.; Stanway, R. R.; Heussler, V. *Plos Pathog* **2011**, *7*.

(21) Miller, L. H.; Baruch, D. I.; Marsh, K.; Doumbo, O. K. *Nature* **2002**, *415*, 673.

(22) Stich, A. *Pharmazie in unserer Zeit* **2009**, *38*, 508.

(23) Field, J. W.; Shute, P. G. *The microscopic diagnosis of human malaria*; Malaya: Kuala Lumpur, 1948.

(24) Talman, A. M.; Domarle, O.; McKenzie, F. E.; Ariey, F.; Robert, V. *Malaria journal* **2004**, *3*.

(25) Kooij, T. W. A.; Matuschewski, K. *Curr Opin Microbiol* **2007**, *10*, 547.

(26) Saul, A. *Nat Med* **2004**, *10*, 455.

(27) Falisevac, J. *Bulletin of the World Health Organization* **1974**, *50*, 159.

(28) Lee, K. S.; Cox-Singh, J.; Brooke, G.; Matusop, A.; Singh, B. *Int J Parasitol* **2009**, *39*, 1125.

(29) Cox-Singh, J.; Davis, T. M. E.; Lee, K. S.; Shamsul, S. S. G.; Matusop, A.; Ratnam, S.; Rahman, H. A.; Conway, D. J.; Singh, B. *Clin Infect Dis* **2008**, *46*, 165.

(30) Baruch, D. I. *Best Pract Res Cl Ha* **1999**, *12*, 747.

(31) Taylor, T. E.; Fu, W. J.; Carr, R. A.; Whitten, R. O.; Mueller, J. S.; Fosiko, N. M.; Lewallen, S.; Liomba, N. G.; Molyneux, M. E. *Nat Med* **2004**, *10*, 435.

(32) Bruce-Chwatt, L. J. *Br Med J (Clin Res Ed)* **1983**, *286*, 1457.

(33) Schantz-Dunn, J.; Nour, N. M. *Reviews in obstetrics and gynecology* **2009**, *2*, 186.

(34) Kumar, S.; Melzer, M.; Dodds, P.; Watson, J.; Ord, R. *Scand J Infect Dis* **2007**, *39*, 255.

(35) Saleri, N.; Gulletta, M.; Matteelli, A.; Caligaris, S.; Tomasoni, L. R.; Antonini, B.; Perandin, F.; Castelli, F. *Journal of travel medicine* **2006**, *13*, 112.

(36) Beg, M. A.; Khan, R.; Baig, S. M.; Gulzar, Z.; Hussain, R.; Smego, R. A. *Am J Trop Med Hyg* **2002**, *67*, 230.

(37) Carlton, J. M.; Sina, B. J.; Adams, J. H. *Plos Neglect Trop D* **2011**, *5*.

(38) Price, R. N.; Tjitra, E.; Guerra, C. A.; Yeung, S.; White, N. J.; Anstey, N. M. *Am J Trop Med Hyg* **2007**, *77*, 79.

(39) Dembele, L.; Franetich, J. F.; Lorthiois, A.; Gego, A.; Zeeman, A. M.; Kocken, C. H. M.; Le Grand, R.; Dereuddre-Bosquet, N.; van Gemert, G. J.; Sauerwein, R.; Vaillant, J. C.; Hannoun, L.; Fuchter, M. J.; Diagana, T. T.; Malmquist, N. A.; Scherf, A.; Snounou, G.; Mazier, D. *Nat Med* **2014**, *20*, 307.

(40) Collins, W. E.; Jeffery, G. M. *Clin Microbiol Rev* **2005**, *18*, 570.

(41) Barnwell, J. W.; Galinski, M. R. *Nat Med* **2014**, *20*, 237.

(42) Cui, L. W.; Escalante, A. A.; Imwong, M.; Snounou, G. *Trends Parasitol* **2003**, *19*, 220.

(43) World Health Organization *"Global Malaria Mapper"* **2014**, *http://www.worldmalariareport.org/*.

(44) Gkrania-Klotsas, E.; Lever, A. M. L. *Blood Rev* **2007**, *21*, 73.

(45) Strauss, R.; Pfeifer, C. *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin* **2003**, *8*, 91.

(46) Auer-Hackenberg, L.; Staudinger, T.; Bojic, A.; Locker, G.; Leitner, G. C.; Graninger, W.; Winkler, S.; Ramharter, M.; Worel, N. *Malaria journal* **2012**, *11*.

(47) Calleri, G. *Infection* **2014**, 1.

(48) Castelli, F.; Odolini, S.; Autino, B.; Foca, E.; Russo, R. *Pharmaceuticals* **2010**, *3*, 3212.

(49) Seidel, B.; Silbermayr, K.; Kolodziejek, J.; Indra, A.; Nowotny, N.; Allerberger, F. *Wien Klin Wochenschr* **2013**, *125*, 139.

(50) Hempelmann, E.; Tesarowicz, I.; Oleksyn, B. J. *Pharmazie in unserer Zeit* **2009**, *38*, 500.

(51) Nerlich, A. G.; Schraut, B.; Dittrich, S.; Jelinek, T.; Zink, A. R. *Emerg Infect Dis* **2008**, *14*, 1317.

(52) Khairat, R.; Ball, M.; Chang, C. C. H.; Bianucci, R.; Nerlich, A. G.; Trautmann, M.; Ismail, S.; Shanab, G. M. L.; Karim, A. M.; Gad, Y. Z.; Pusch, C. M. *J Appl Genet* **2013**, *54*, 309.

(53) Hawass, Z.; Gad, Y. Z.; Ismail, S.; Khairat, R.; Fathalla, D.; Hasan, N.; Ahmed, A.; Elleithy, H.; Ball, M.; Gaballah, F.; Wasef, S.; Fateen, M.; Amer, H.; Gostner, P.; Selim, A.; Zink, A.; Pusch, C. M. *Jama-J Am Med Assoc* **2010**, *303*, 638.

(54) Timmann, C.; Meyer, C. G. *Trop Med Int Health* **2010**, *15*, 1278.

(55) Katz, T. M.; Miller, J. H.; Hebert, A. A. *J Am Acad Dermatol* **2008**, *58*, 865.

(56) Retief, F., Cilliers, L. *Acta Classica* **2004**, *47*.

(57) Stagl, V.; Sattmann, H.; Horweg, C. *Wien Klin Wochenschr* **2010**, *122*, 6.

(58) Reiter, P. *Emerg Infect Dis* **2000**, *6*, 1.

(59) Hempelmann, E. *Parasitology research* **2007**, *100*, 671.

(60) Hempelmann, E.; Krafts, K. *Malaria journal* **2013**, *12*.

(61) Kaufman, T. S.; Ruveda, E. A. *Angew Chem Int Edit* **2005**, *44*, 854.

(62) Dassonville-Klimpt, A. J., A.; Pillon, M.; Mullié, C.; Sonnet, P. *Science against microbial pathogens: communicating current research and technological advances* **2011**, *1*, 23.

(63) Bruce-Chwatt, L. J. *Br Med J (Clin Res Ed)* **1988**, *296*, 1486.

(64) Souza, K. A. F. D.; Porto, P. A. *J Chem Educ* **2012**, *89*, 58.

(65) Seeman, J. I. *Angew Chem Int Edit* **2007**, *46*, 1378.

(66) Abba, K.; Deeks, J. J.; Olliaro, P.; Naing, C. M.; Jackson, S. M.; Takwoingi, Y.; Donegan, S.; Garner, P. *Cochrane Db Syst Rev* **2011**.

(67) Manson-Bahr, P. *Proceedings of the Royal Society of Medicine* **1961**, *54*, 91.

(68) Capanna, E. *Int Microbiol* **2006**, *9*, 69.

(69) Muscatello, U. *Brain Res Rev* **2007**, *55*, 3.

(70) Cox, F. E. G. *Parasite Vector* **2010**, *3*.

(71) Baird, J. K. *Antimicrob Agents Ch* **2004**, *48*, 4075.

(72) Hsu, E. *Brit J Clin Pharmaco* **2006**, *61*, 666.

(73) Hale, V.; Keasling, J. D.; Renninger, N.; Diagana, T. T. *Am J Trop Med Hyg* **2007**, *77*, 198.

(74) Kupferschmidt, K. *Science* **2012**, *336*, 798.

(75) Greenwood, B.; Mutabingwa, T. *Nature* **2002**, *415*, 670.

(76) Trouiller, P.; Olliaro, P. L. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases* **1998**, *3*, 61.

(77) Zhong, D. B.; Chang, X. L.; Zhou, G. F.; He, Z. B.; Fu, F. Y.; Yan, Z. T.; Zhu, G. D.; Xu, T. L.; Bonizzoni, M.; Wang, M. H.; Cui, L. W.; Zheng, B.; Chen, B.; Yan, G. Y. *Plos One* **2013**, *8*.

(78) Yakob, L.; Dunning, R.; Yan, G. Y. *J R Soc Interface* **2011**, *8*, 799.

(79) Killeen, G. F.; Seyoum, A.; Sikaala, C.; Zomboko, A. S.; Gimnig, J. E.; Govella, N. J.; White, M. T. *Parasite Vector* **2013**, *6*.

(80) Bouwman, H.; van den Berg, H.; Kylin, H. *Environ Health Persp* **2011**, *119*, 744.

(81) Seagren, E. A. *J Environ Eng-Asce* **2005**, *131*, 1617.

(82) Kitau, J.; Oxborough, R.; Matowo, J.; Mosha, F.; Magesa, S. M.; Rowland, M. *Parasite Vector* **2014**, *7*.

(83) M. Altenkämper, M. S. *Pharmazeutische Zeitung* **2008**, 18.

(84) Schlitzer, M. *Pharmazie in unserer Zeit* **2009**, *38*, 512.

(85) Delves, M.; Plouffe, D.; Scheurer, C.; Meister, S.; Wittlin, S.; Winzeler, E. A.; Sinden, R. E.; Leroy, D. *Plos Med* **2012**, *9*.

(86) Foley, M.; Tilley, L. *Pharmacol Therapeut* **1998**, *79*, 55.

(87) Karle, J. M.; Karle, I. L. *Antimicrob Agents Ch* **2002**, *46*, 1529.

(88) Skorska, A.; Sliwinski, J.; Oleksyn, B. J. *Bioorg Med Chem Lett* **2006**, *16*, 850.

(89) Dow, G. S.; Heady, T. N.; Bhattacharjee, A. K.; Caridha, D.; Gerena, L.; Gettayacamin, A.; Lanteri, C. A.; Obaldia, N.; Roncal, N.; Shearer, T.; Smith, P. L.; Tungtaeng, A.; Wolf, L.; Cabezas, M.; Yourick, D.; Smith, K. S. *Antimicrob Agents Ch* **2006**, *50*, 4132.

(90) Basco, L. K.; Gillotin, C.; Gimenez, F.; Farinotti, R.; Lebras, J. *Brit J Clin Pharmaco* **1992**, *33*, 517.

(91) Wong, R. P. M.; Salman, S.; Ilett, K. F.; Siba, P. M.; Mueller, I.; Davis, T. M. E. *Antimicrob Agents Ch* **2011**, *55*, 1194.

(92) Djimde, A.; Lefevre, G. *Malaria journal* **2009**, *8*.

(93) Basco, L. K.; Bickii, J.; Ringwald, P. *Antimicrob Agents Ch* **1998**, *42*, 2347.

(94) Kokwaro, G.; Mwai, L.; Nzila, A. *Expert Opin Pharmaco* **2007**, *8*, 75.

(95) Colussi, D.; Parisot, C.; Legay, F.; Lefevre, G. *Eur J Pharm Sci* **1999**, *9*, 9.

(96) Starzengruber, P.; Wernsdorfer, G.; Parizek, M.; Rojanawatsirivet, C.; Kollaritsch, H.; Wernsdorfer, W. H. *Wien Klin Wochenschr* **2007**, *119*, 60.

(97) de Villiers, K. A.; Egan, T. J. *Molecules* **2009**, *14*, 2868.

(98) Dubar, F.; Khalife, J.; Brocard, J.; Dive, D.; Biot, C. *Molecules* **2008**, *13*, 2900.

(99) Hill, D. R.; Baird, J. K.; Parise, M. E.; Lewis, L. S.; Ryan, E. T.; Magill, A. J. *Am J Trop Med Hyg* **2006**, *75*, 402.

(100) Jansen, F. H. *Malaria journal* **2010**, *9*.

(101) Teuscher, F.; Gatton, M. L.; Chen, N. H.; Peters, J.; Kyle, D. E.; Cheng, Q. *J Infect Dis* **2010**, *202*, 1362.

(102) Ashley, E. A.; Dhorda, M.; Fairhurst, R. M.; Amaratunga, C.; Lim, P.; Suon, S.; Sreng, S.; Anderson, J. M.; Mao, S.; Sam, B.; Sopha, C.; Chuor, C. M.; Nguon, C.; Sovannaroth, S.; Pukrittayakamee, S.; Jittamala, P.; Chotivanich, K.; Chutasmit, K.; Suchatsoonthorn, C.; Runcharoen, R.; Hien, T. T.; Thuy-Nhien, N. T.; Thanh, N. V.; Phu, N. H.; Htut, Y.; Han, K. T.; Aye, K. H.; Mokuolu, O. A.; Olaosebikan, R. R.; Folaranmi, O. O.; Mayxay, M.; Khanthavong, M.; Hongvanthong, B.; Newton, P. N.; Onyamboko, M. A.; Fanello, C. I.; Tshefu, A. K.; Mishra, N.; Valecha, N.; Phyo, A. P.; Nosten, F.; Yi, P.; Tripura, R.; Borrmann, S.; Bashraheil, M.; Peshu, J.; Faiz, M. A.; Ghose, A.; Hossain, M. A.; Samad, R.; Rahman, M. R.; Hasan, M. M.; Islam, A.; Miotto, O.; Amato, R.; MacInnis, B.; Stalker, J.; Kwiatkowski, D. P.; Bozdech, Z.; Jeeyapant, A.; Cheah, P. Y.; Sakulthaew, T.; Chalk, J.; Intharabut, B.; Silamut, K.; Lee, S. J.; Vihokhern, B.; Kunasol, C.; Imwong, M.; Tarning, J.; Taylor, W. J.; Yeung, S.; Woodrow, C. J.; Flegg, J. A.; Das, D.; Smith, J.; Venkatesan, M.; Plowe, C. V.; Stepniewska, K.; Guerin, P. J.; Dondorp, A. M.; Day, N. P.; White, N. J. *The New England journal of medicine* **2014**, *371*, 411.

(103) Dondorp, A. M.; Nosten, F.; Yi, P.; Das, D.; Phyo, A. P.; Tarning, J.; Lwin, K. M.; Ariey, F.; Hanpithakpong, W.; Lee, S. J.; Ringwald, P.; Silamut, K.; Imwong, M.; Chotivanich, K.; Lim, P.; Herdman, T.; An, S. S.; Yeung, S.; Singhasivanon, P.; Day, N. P.; Lindegardh, N.; Socheat, D.; White, N. J. *The New England journal of medicine* **2009**, *361*, 455.

(104) Li, J.; Zhou, B. *Molecules* **2010**, *15*, 1378.

(105) Tang, Y. Q.; Dong, Y. X.; Vennerstrom, J. L. *Med Res Rev* **2004**, *24*, 425.

(106) Charman, S. A.; Arbe-Barnes, S.; Bathurst, I. C.; Brun, R.; Campbell, M.; Charman, W. N.; Chiu, F. C. K.; Chollet, J.; Craft, J. C.; Creek, D. J.; Dong, Y. X.; Matile, H.; Maurer, M.; Morizzi, J.; Nguyen, T.; Papastogiannidis, P.; Scheurer, C.; Shackleford, D. M.; Sriraghavan, K.; Stingelin, L.; Tang, Y. Q.; Urwyler, H.; Wang, X. F.; White, K. L.; Wittlin, S.; Zhou, L.; Vennerstrom, J. L. *P Natl Acad Sci USA* **2011**, *108*, 4400.

(107) O'Neill, P. M.; Amewu, R. K.; Nixon, G. L.; ElGarah, F. B.; Mungthin, M.; Chadwick, J.; Shone, A. E.; Vivas, L.; Lander, H.; Barton, V.; Muangnoicharoen, S.; Bray, P. G.; Davies, J.; Park, B. K.; Wittlin, S.; Brun, R.; Preschel, M.; Zhang, K. S.; Ward, S. A. *Angew Chem Int Edit* **2010**, *49*, 5693.

(108) Coulibaly, B.; Pritsch, M.; Bountogo, M.; Meissner, P. E.; Nebie, E.; Klose, C.; Kieser, M.; Berens-Riha, N.; Wieser, A.; Sirima, S. B.; Breitkreutz, J.; Schirmer, R. H.; Sie, A.; Mockenhaupt, F. P.; Drakeley, C.; Bousema, T.; Muller, O. *J Infect Dis* **2014**.

(109) Coulibaly, B.; Zoungrana, A.; Mockenhaupt, F. P.; Schirmer, R. H.; Klose, C.; Mansmann, U.; Meissner, P. E.; Muller, O. *Plos One* **2009**, *4*.

(110) Rottmann, M.; McNamara, C.; Yeung, B. K. S.; Lee, M. C. S.; Zou, B.; Russell, B.; Seitz, P.; Plouffe, D. M.; Dharia, N. V.; Tan, J.; Cohen, S. B.; Spencer, K. R.; Gonzalez-Paez, G. E.; Lakshminarayana, S. B.; Goh, A.; Suwanarusk, R.; Jegla, T.; Schmitt, E. K.; Beck, H. P.; Brun, R.; Nosten, F.; Renia, L.; Dartois, V.; Keller, T. H.; Fidock, D. A.; Winzeler, E. A.; Diagana, T. T. *Science* **2010**, *329*, 1175.

(111) Yeung, B. K. S.; Zou, B.; Rottmann, M.; Lakshminarayana, S. B.; Ang, S. H.; Leong, S. Y.; Tan, J.; Wong, J.; Keller-Maerki, S.; Fischli, C.; Goh, A.; Schmitt, E. K.; Krastel, P.; Francotte, E.; Kuhen, K.; Plouffe, D.; Henson, K.; Wagner, T.; Winzeler, E. A.; Petersen, F.; Brun, R.; Dartois, V.; Diagana, T. T.; Keller, T. H. *J Med Chem* **2010**, *53*, 5155.

(112) Spillman, N. J.; Allen, R. J. W.; McNamara, C. W.; Yeung, B. K. S.; Winzeler, E. A.; Diagana, T. T.; Kirk, K. *Cell Host Microbe* **2013**, *13*, 227.

(113) White, N. J.; Pukrittayakamee, S.; Phyo, A. P.; Rueangweerayut, R.; Nosten, F.; Jittamala, P.; Jeeyapant, A.; Jain, J. P.; Lefevre, G.; Li, R. B.; Magnusson, B.; Diagana, T. T.; Leong, F. J. *New Engl J Med* **2014**, *371*, 403.

(114) Sridaran, S.; McClintock, S. K.; Syphard, L. M.; Herman, K. M.; Barnwell, J. W.; Udhayakumar, V. *Malaria journal* **2010**, *9*, 247.

(115) Sanchez, C. P.; Dave, A.; Stein, W. D.; Lanzer, M. *Int J Parasitol* **2010**, *40*, 1109.

(116) Guiguemde, W. A.; Shelat, A. A.; Garcia-Bustos, J. F.; Diagana, T. T.; Gamo, F. J.; Guy, R. K. *Chem Biol* **2012**, *19*, 116.

(117) Weisman, J. L.; Liou, A. P.; Shelat, A. A.; Cohen, F. E.; Guy, R. K.; DeRisi, J. L. *Chem Biol Drug Des* **2006**, *67*, 409.

(118) Tasanor, O.; Ernst, M.; Thriemer, K.; Ecker, G. F.; Noedl, H.; Chiba, P. *Wien Klin Wochenschr* **2007**, *119*, 83.

(119) Brana, M. F.; Rodriguez, M. L. L.; Moran, M. *An Quim* **1990**, *86*, 565.

(120) Gstach, H.; Chiba, P.; Mastalir, M. *AU2013276702 (A1)* **2012-06-13**.

(121) Mastalir, M. *Bachelor Thesis, University of Natural Resources and Life Sciences, Vienna* **2011**.

(122) Wood, R. D.; McLeod, R.; Mui, E.; Fomovska, A.; Welsh, W. *US 2013/0324555 A1* **2013-05-29**.

(123) Pace, V.; Hoyos, P.; Sinisterra, J. V.; Alcantara, A. R.; Holzer, W. *Synlett* **2011**, 1831.

(124) McClure, D. E.; Arison, B. H.; Baldwin, J. J. *J Am Chem Soc* **1979**, *101*, 3666.

(125) Lotharius, J.; Gamo-Benito, F. J.; Angulo-Barturen, I.; Clark, J.; Connelly, M.; Ferrer-Bazaga, S.; Parkinson, T.; Viswanath, P.; Bandodkar, B.; Rautela, N.; Bharath, S.; Duffy, S.; Avery, V. M.; Mohrle, J. J.; Guy, R. K.; Wells, T. *Malaria J* **2014**, *13*.

(126) Walliker, D.; Quakyi, I. A.; Wellems, T. E.; Mccutchan, T. F.; Szarfman, A.; London, W. T.; Corcoran, L. M.; Burkot, T. R.; Carter, R. *Science* **1987**, *236*, 1661.

(127) Brana, M. F.; Lopez Rodriguez, M. L.; Moran, M. *An. Quim.* **1990**, *86*, 565.

(128) Peters, W. *Annals of tropical medicine and parasitology* **1975**, *69*, 155.

(129) Townsend-Nicholson, A.; Schofield, P. R. *J Biol Chem* **1994**, *269*, 2373.

(130) Karle, J. M.; Karle, I. L. *Acta Crystallogr C* **1992**, *48*, 1975.

(131) Silva, T. H. A.; Oliveira, A. B.; Dos Santos, H. F.; De Almeida, W. B. *Struct Chem* **2001**, *12*, 431.

(132) Hisaki, I.; Hiraishi, E.; Sasaki, T.; Orita, H.; Tsuzuki, S.; Tohnai, N.; Miyata, M. *Chem-Asian J* **2012**, *7*, 2607.

(133) Ashley, E. A.; Stepniewska, K.; Lindegårdh, N.; Annerberg, A.; Kham, A.; Brockman, A.; Singhasivanon, P.; White, N. J.; Nosten, F. *Trop Med Int Health* **2007**, *12*, 195.

(134) Dank, C.; Kirchknopf, B.; Mastalir, M.; Kahlig, H.; Felsinger, S.; Roller, A.; Arion, V. B.; Gstach, H. *Molecules* **2015**, *20*, 1686.

(135) Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J Org Chem* **1997**, *62*, 7512.

(136) Pressprich, M. R.; Chambers, J. *SAINT-Plus, version 7.06a and APEX2; Bruker-Nonius AXS Inc.: Madison, WI, USA,* **2004**.

(137) Sheldrick, G. M. *Acta Crystallogr A* **2008**, *64*, 112.

(138) Fidock, D. A.; Rosenthal, P. J.; Croft, S. L.; Brun, R.; Nwaka, S. *Nat Rev Drug Discov* **2004**, *3*, 509.

(139) Miret, S.; De Groene, E. M.; Klaffke, W. *J Biomol Screen* **2006**, *11*, 184.

(140) Asha, S.; Vidyavathi, M. *Appl Biochem Biotech* **2010**, *160*, 1699.

(141) Lee, I. Y.; Gruber, T. D.; Samuels, A.; Yun, M.; Nam, B.; Kang, M.; Crowley, K.; Winterroth, B.; Boshoff, H. I.; Barry, C. E. *Bioorgan Med Chem* **2013**, *21*, 114.

(142) Chang, D.; Huang, H. *US2012/0232105 (A1)* **2012-06-13**.

(143) Waisser, K.; Hladuvkova, J.; Kunes, J.; Kubicova, L.; Klimesova, V.; Karajannis, P.; Kaustova, J. *Chem Pap-Chem Zvesti* **2001**, *55*, 121.

(144) Ciampa, G.; Grieco, C. *Chim Ind-Milan* **1966**, *48*, 748.

(145) Gonec, T.; Kos, J.; Zadrazilova, I.; Pesko, M.; Govender, R.; Keltosova, S.; Chambel, B.; Pereira, D.; Kollar, P.; Imramovsky, A.; O'Mahony, J.; Coffey, A.; Cizek, A.; Kralova, K.; Jampilek, J. *Molecules* **2013**, *18*, 9397.

(146) Senier, A.; Shepheard, F. G. *J Chem Soc* **1909**, *95*, 441.

(147) Gonec, T.; Kos, J.; Zadrazilova, I.; Pesko, M.; Keltosova, S.; Tengler, J.; Bobal, P.; Kollar, P.; Cizek, A.; Kralova, K.; Jampilek, J. *Bioorgan Med Chem* **2013**, *21*, 6531.

(148) Muto, S.; T., N.; Saotome, T.; Itai, A. *EP1352650 (A1)* **2003-10-15**.

(149) SDBSWeb: http://sdbs.riodb.aist.go.jp (National Institute of Advanced Industrial Science and Technology, d. o. a.

(150) Muto, S.; Itai, A. *EP1510210 (A1)* **2005-03-02**.

(151) Yuan, M.; Li, J. M.; He, G. W.; Zhong, G. C.; Zhang, Y. C. *Yao xue xue bao = Acta pharmaceutica Sinica* **2013**, *48*, 874.

(152) Schraufstatter, E.; Gonnert, R.; Meiser, W. *Z Naturforsch Pt B* **1961**, *B 16*, 95.

(153) Kang, S.; Min, H. J.; Kang, M. S.; Jung, M. G.; Kim, S. *Bioorg Med Chem Lett* **2013**, *23*, 1748.

(154) Waisser, K.; Bures, O.; Holy, P.; Kunes, J.; Oswald, R.; Jiraskova, L.; Pour, M.; Klimesova, V.; Kubicova, L.; Kaustova, J. *Arch Pharm* **2003**, *336*, 53.

(155) Zhu, Z. W.; Shi, L.; Ruan, X. M.; Yang, Y.; Li, H. Q.; Xu, S. P.; Zhu, H. L. *J Enzym Inhib Med Ch* **2011**, *26*, 37.

(156) Waisser, K.; Pesina, M.; Holy, P.; Pour, M.; Bures, O.; Kunes, J.; Klimesova, V.; Buchta, V.; Kubanova, P.; Kaustova, J. *Arch Pharm* **2003**, *336*, 322.

(157) Kral'ova, K.; Sersen, F.; Pesko, M.; Waisser, K.; Kubicova, L. *Chem Pap* **2014**, *68*, 46.

(158) Kuhnt, D.; Haug, M.; Jelich, K.; Stenzel, K.; Dehne, H. W.; Hänszler, G.; Wachendorff-Neumann, U.; Erdelen, C.; Kugler, M.; Schrage, H. *DE4428380 (A1)* **1996-02-15**.

(159) Kulkarni, V. M.; Achhra, C. V. *Eur J Med Chem* **1982**, *17*, 93.

(160) Vattipalli, R.; Shirodkar, P. Y.; Somani, R. R.; Kadam, V. J. *Indian J Chem B* **2008**, *47*, 1587.

Curriculum Vitae

Personal Data

Name:	Christian Dank, MSc
Date of Birth	January 8th, 1986
Place of Birth:	Oberpullendorf, Burgenland, Austria
Citizenship:	Austria

School and Education

August/2013	Setting up a company for production of food
March/2013	Immatriculation at Vienna University of Economics and Business for the Bachelor program in Business Administration
January/2013	Beginning with doctoral thesis "**New Antiinfective Agents**" under supervision of Dr. Hubert Gstach and Prof. Dr. Walther Schmid
October/2012	Obtaining the academic degree „Master of Science" (MSc) at the university of Vienna
April/2011	Beginning with master's thesis "**Concise and flexible synthesis of the five-membered ring synthon of highly oxygenated jatrophane diterpenes**" under supervision of Prof. Dr. Johann Mulzer
May/2011	Obtaining the academic degree „Bachelor of Science" (BSc) at the university of Vienna after a change of the curriculum
December/2009	End of the first study section
Oct/2004-Sep/2005	Community service in the hospital "Barmherzige Brüder" in Eisenstadt, Austria
October/2005	Start of diploma study in chemistry, University of Vienna
October/2004	Matriculation
Sep/1996 – June/2004	"Oberstufenrealgymnasium Oberpullendorf"
Sep/1996 – June/2000	"Gymnasium und Realgymnasium Oberpullendorf"

Publications

Dank, C.; Kirchknopf, B.; Mastalir, M.; Kählig, H.; Felsinger, S.; Roller, A.; Arion, V.B.; Gstach, H. Hybrids of Salicylalkylamides and Mannich Bases: Control of the Amide Conformation by Hydrogen Bonding in Solution and in the Solid State. *Molecules* **2015**, *20*, 1686-1711.

Presentations at Conferences

14th Austrian Chemistry Days:	Towards the Total Synthesis of Euphosalicin: Synthesis of the Important 5-Membered Ring Fragment - Poster presentation

Abstract

Despite its big role in history, nearly half of the world's population is estimated to be at risk of malaria at the present day. World Health Organization (WHO) estimates that 207 million cases of malaria occurred globally in 2012 and estimates that 627,000 deaths are attributable to malaria. There is still a long way to go until malaria will be eradicated and a vast number of medications became useless due to development of resistances. Therefore, new antimalarial agents are still much in demand.

Within this thesis, a structure-activity relationship of amidophenoxypropanolamines, which were primordially derived from the antiarrhythmic agent propafenone, is presented. Among them are a vast number of highly active compounds, more active than lumefantrine and artesunate. Furthermore, mice infected with *Plasmodium berghei* were cured with compounds synthesized in the course of this thesis. This proves the drug-likeness featured by the presented compounds. In addition, cytotoxicity, receptor binding, genetic toxicity and cardiac toxicity assays were performed, stating that the tested class of compounds may serve as a rich source for serious drug candidates.

Structural elucidation with crystallographic structure analysis and methods of nuclear magnetic resonance (NMR) spectroscopy revealed an intriguing intramolecular network of hydrogen bonds in these aminoalcohols is responsible for the antimalarial activity.

Zusammenfassung

Die Tropenkrankheit Malaria spielte eine große und einflussreiche Rolle in der Geschichte der Menschheit. Noch am heutigen Tag ist beinahe die halbe Weltbevölkerung gefährdet, mit Malaria infiziert zu werden. Nach Schätzungen der Weltgesundheitsorganisation (WHO) gab es im Jahr 2012 noch 207 Millionen Fälle von Malariainfektionen mit 627.000 Todesopfern. Nachdem die vollständige Ausrottung von Malaria in weiter Ferne scheint und eine Vielzahl von eingeführten Medikamenten durch Resistenzentwicklung der Parasiten unbrauchbar wurde, ist die Entwicklung neuer Wirkstoffe mit neuen Wirkmechanismen und verbesserten pharmakologischen Profilen ein Gebot der Stunde.

Synthese und Ableitung einer Struktur-Wirkungsbeziehung von Amidophenoxypropanolaminen, deren Struktur ursprünglich vom Antiarrhythmikum Propafenon abgeleitet wurde, ist Gegenstand dieser Dissertation. Unter den synthetisierten Verbindungen befindet sich eine Vielzahl hochaktiver Verbindungen, die aktiver als Lumefantrin und Artesunat sind. Darüber hinaus konnte die Tauglichkeit der synthetisierten Derivate in Tierversuchen durch die vollständige Heilung von mit *Plasmodium berghei* infizierten Mäusen gezeigt werden. Zusätzlich wurde durch eine Reihe von Assays (Zytotoxizität, Ligandenbindungstests, Ames-Test, Kardiotoxizitätstests) gezeigt, dass die präsentierte Verbindungsklasse eine reichhaltige Quelle für potenzielle Wirkstoffe darstellen kann.

Strukturaufklärung an ausgewählten Verbindungen mit Hilfe von Kristallstrukturanalysen und Methoden der Kernspinresonanzspektroskopie enthüllten ein neuartiges Netzwerk von kooperativen Wasserstoffbrückenbindungen in den präsentierten Aminoalkoholen, dessen Integrität direkt mit der Antimalaria-Aktivität verknüpft ist.