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DIPLOMARBEIT

„Towards the Synthesis of Novel Donepezil Analogues“

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Abstract

Donepezil, a drug that prevents the breakdown of the neurotransmitter acetylcholine by inhibiting the acetylcholinesterase (AChE), is used in the treatment of Alzheimer's disease. Donepezil is a member of *N*-benzylpiperidine-based AChE inhibitors that were developed by Eisai Company in Japan. After performing structure-activity analyses, different research groups came to the conclusion that donepezil does not interact directly with the catalytic triad of AChE and that through the variation of donepezil's structure, for example of the piperidine moiety, the binding of the molecule and therefore its binding affinity would be increased. It is believed that the drug's potency and its overall pharmacological profile would improve through these structure alterations. *N*-benzyl-4-piperidone is an important precursor in the synthesis of donepezil. Easy access to chiral, 2-substituted *N*-benzylic 4-piperidones is possible *via* a double *aza*-Michael cyclisation of divinyl ketones and primary amines. These compounds are versatile building blocks and can be used as key intermediates for the preparation of stereoselectively piperidine-substituted donepezil analogues.

Exposé

Das Medikament Donepezil, das in der Behandlung von Morbus Alzheimer verwendet wird, verhindert den Zerfall des wichtigen Neurotransmitters Acetylcholin durch Hemmung der Acetylcholinesterase (AChE). Donepezil gehört zu einer Reihe von *N*-benzylpiperidin-basierten AChE- Hemmern die von dem japanischen Unternehmen Eisai entwickelt wurden. Nachdem verschiedene Forschungsgruppen Struktur-Aktivität Analysen durchführten kam man zu dem Ergebnis, dass Donepezil nicht direkt mit dem katalytischen Zentrum von AChE interagiert und dass man durch Änderungen an gewissen Teilstrukturen, zum Beispiel am Piperidin-Ring, die Bindungsaffinität von Donepezil erhöhen könnte. Durch diese strukturellen Änderungen könnte sich die Wirksamkeit und das gesamte pharmakologische Profil verbessern. *N*-benzyl-4-piperidon ist ein wichtiger Vorläufer in der Donepezil- Synthese. Die Synthese von 2-substituierten *N*-benzylischen 4-Piperidonen ist möglich *via aza*-Michael-Zyklisierung von Divinylketonen und primären Aminen. Diese Verbindungen sind sehr vielseitig und können als Zwischenprodukte für die weitere Synthese von stereoselektiven Piperidin-substituierten Donepezil Analoga dienen.

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Abbreviations and Acronyms

Å	angstrom(s)
ACh	acetylcholine
AChE	acetylcholinesterase
AD	Alzheimer's disease
aqu.	aqueous
Ar	aryl
◦C	degree Celsius
^{13}C-NMR	carbon nuclear magnetic resonance
COSY	correlation spectroscopy
dd	doublet of doublet
ddd	doublet of doublets of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMF	*N,N*-dimethylformamide
dt	doublet of triplets
equiv	equivalent(s)
Et	ethyl
h	hour(s)
hAChE	human acetylcholinesterase
^{1}H-NMR	proton nuclear magnetic resonance
HMBC	heteronuclear multiple bond correlation
HSQC	heteronuclear single quantum correlation
Hz	hertz
IR	infrared
J	NMR coupling constant

LDA	lithium diisopropylamide
M	molar
m	multiplet (spectroscopic) or milli
m/z	mass to charge ratio
M+	parent molecular ion
MCI	mild cognitive impairment
Me	methyl
MHz	megahertz
min	minute(s)
mmol	millimole(s)
mol	mole(s)
mp	melting point
MS	molecular sieves or mass spectrometry
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Ph	phenyl
ppm	part(s) per million
q	quartet
R_f	retention factor
rt	room temperature
s	singlet (spectroscopic) or second(s)
t	triplet
temp	temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

1 Introduction

1.1 Alzheimer's disease (AD)

Alzheimer's disease is a neurodegenerative disease and the most common form of dementia, named after Alois Alzheimer, a German neuropathologist and psychiatrist, who first described the symptoms in 1906. [1] The word dementia includes various symptoms, like the loss of memory, mood changes and difficulties with reasoning and communication, that develop when the brain is damaged by certain diseases, including AD. Alzheimer's disease mostly affects people aged over 65; With a population that is getting older and older due to increased life expectancy Alzheimer's prevalence is increasing. In 2000, there were 4.5 million people in the United States with AD. A fairly small number, 0.3 million (7%), were between the ages of 65 and 74 years, 2.4 million (53%) were between the ages of 75 and 84 years, and 1.8 million (40%) were 85 years of age and older. Until 2050, prevalence is expected to increase almost 3-fold to 13.2 million people affected in 2050. [2, 3]

1.1.1 Pathophysiology

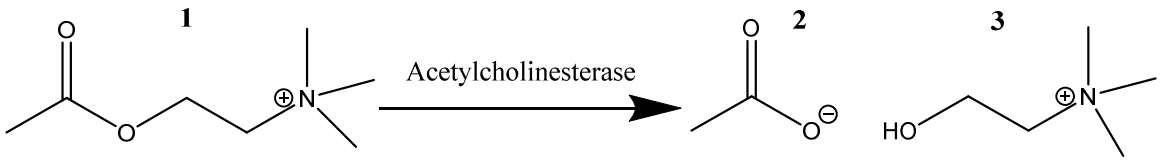
Alzheimer's disease is characterised by the loss of synapses and neurons in the cerebral cortex and other brain regions which leads to atrophy of the affected parts of the brain, as for example the temporal and the parietal lobe and the frontal cortex. [4] The two major pathological hallmarks of the disease appear to be neurofibrillary tangles and amyloid plaques in the brain, [3, 5] even Alzheimer himself spoke of "miliary bodies" and nerve cells whose interiors were choked by "dense bundles of fibrils" [6] after he autopsied the brain of the first known Alzheimer's Disease patient. The certain cause for Alzheimer's disease is still unknown, but there are several hypotheses trying to explain the cause of Alzheimer's disease.

Cholinergic hypothesis

The cholinergic hypothesis is the oldest hypothesis, suggesting that a decreased production of the neuronal transmitter Acetylcholine is the cause for AD.[7, 8, 9] The neurotransmitter Acetylcholine and associated neurons form a neurotransmitter system

that causes anti-excitatory actions, the so-called "cholinergic system". In the peripheral nervous system acetylcholine activates muscles, but it is also important in learning processes and is therefore one of the most important neurotransmitters.[10]

Therapeutics based on this hypothesis aim to preserve acetylcholine **1** by inhibiting acetylcholinesterases that normally breaks down acetylcholine to choline **3** and acetate **2**. (Scheme 1.1.1)



Scheme 1.1.1 Acetylcholinesterase catalyses the hydrolysis of acetylcholine to acetate and choline

Tau hypothesis

The Tau protein is a microtubule- associated protein that is responsible for the stabilisation of microtubules in the cell cytoskeleton. Microtubule- associated tau is essential for normal neuronal activity, and therefore for normal brain function. Tau protein itself is regulated by its degree of phosphorylation. Hyperphosphorylation, mutations that alter function, and mutations that alter isoform expression decrease its microtubule assembly activity and its ability to bind microtubules.[11, 12] In Alzheimer's Disease, tau protein in the brain is abnormally hyperphosphorylated, self-aggregates and eventually forms neurofibrillary tangles of paired helical filaments that lead to neuronal death,[13] as shown in Figure 1.1.1 [14] and Figure 1.1.2. [15]

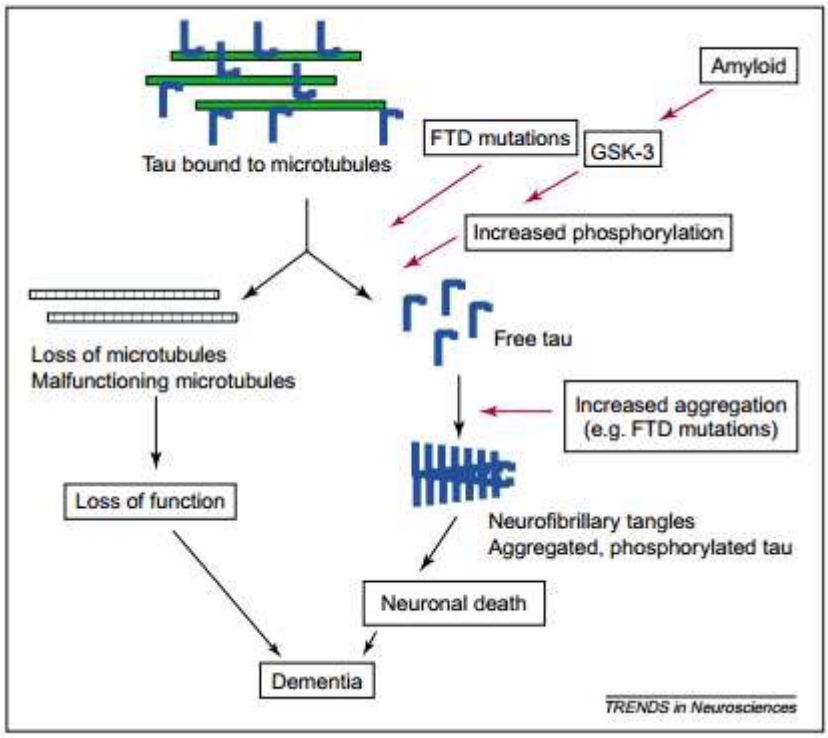


Figure 1.1.1 The tau and tangle hypothesis; GSK-3 = glycogen synthase kinase 3; FTD = fronto- temporal degeneration[14]

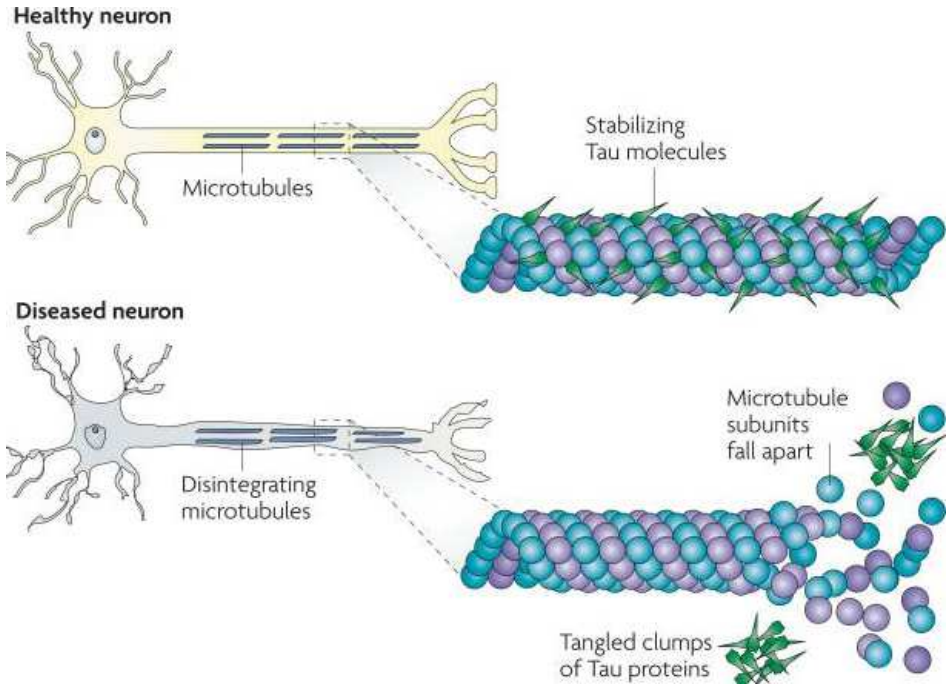


Figure 1.1.2 A healthy neuron compared to a neuron in tauopathies[15]

There are also several other central nervous disorders that share the same pathological feature of hyperphosphorylation and as a result the neurofibrillary degeneration and dementia, as AD. These disorders are called "tauopathies". (Table 1.1.1) [13, 15, 16]

Tauopathies characterised by hyperphosphorylation of tau
Alzheimer's Disease
Down Syndrome, adult cases
Guam parkinsonism dementia complex
Dementia pugilistica
Pick disease
Dementia with agyrophilic grains
Fronto-temporal dementia
Cortico- basal degeneration
Pallido- ponto- nigral degeneration
Progressive supranuclear palsy
Gerstmann- Sträussler- Scheinker disease with tangles

Table 1.1.1 Tauopathies

Amyloid hypothesis

Aβ, the main component of senile plaques, is a peptide that is derived from amyloid precursor protein (APP), which can be processed in two distinctive pathways (Figure 1.1.3). [14] Amyloid precursos protein (APP) is cleaved either by α-secretase resulting in sAPPα, which has neuroprotective properties, or by β-amyloid cleaving enzyme (BACE) and then γ-secretase to yield Aβ. The larger those Aβ42 peptides are, the more likely they are to self-aggregate and are more pathogenic.

The supporters of the amyloid hypothesis consider the abundant deposition of Aβ in the brain to be the main cause for AD, and the neurofibrillary tangles, cell loss and dementia as a direct result. [17] Support for this hypothesis comes from several studies that connect the location of the gene for APP on chromosome 21 and the prevalence of dementia AD in patients with Down syndrome, who almost certainly develop Alzheimer's around the age of 40. [6, 18] More evidence comes from studies with transgenic mice that overexpress mutated human amyloid precursor protein resulting in neurodegenerative changes in the brain similar to AD. [19]

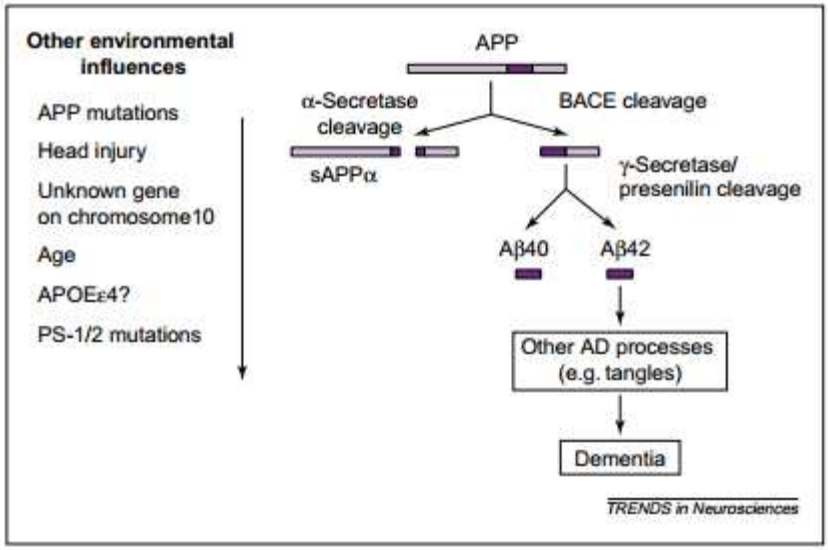


Figure 1.1.3. The amyloid cascade hyposthesis [14]

Genetics

There is a high heritability rate for Alzheimer's Disease, with a range from 58% to 79% based on numerous twin studies. [20] Various genetic risk factors have been found, but only rare AD cases can be attributed to specific gene mutations. One genetic susceptibility factor for AD is confirmed to be the ε4 allele of APOE (hereafter "APOE-ε4"), [21] but there is also a considerable number of studies which found a connection between AD and alleles in other genes. [22] All studies though come to the conclusion that non-genetic risk factors also play a very important role and might be relevant in preventive treatment.

Other hypotheses

There are many other hypotheses, one of them proposing that Herpes simplex virus type 1 in combination with the susceptible APOE-ε4 can play a causative role. [23, 24] Also, smoking, air pollution, oxidative stress, pesticides, metals and many other factors seem to be playing an important role in increasing the risk of developing AD. [25, 26, 27, 28, 29]

1.1.2 Stages and Symptoms

In 2011, new criteria and guidelines for diagnosing AD were proposed by the NIA (National Institute on Aging) and the Alzheimer's Association, updating the ones established in 1984. The three stages proposed by these new criteria are Preclinical AD, mild cognitive impairment (MCI) due to AD and dementia due to AD. The main

differences between these guidelines are that the 1984's criteria were manly based on a doctor's judgement of an individual's case, focused on whether or not the patient had already had decreased cogitation and severe memory loss, whereas the new criteria identify three stages of AD and involve biomarker tests, for example levels of Amyloid β and tau protein in the cerebrospinal fluid and in the blood. [30, 31, 32]

1.1.2.1 *Preclinical Alzheimer's disease*

In the preclinical stage biomarkers and brain changes can already be measured, but individuals do not show symptoms like memory loss or disorientation. The biochemical changes such as increased levels of tau protein or Amyloid β can precede the outbreak of severe symptoms up to 20 years. [30, 33]

1.1.2.2 *Mild cognitive impairment (MCI) due to Alzheimer's disease*

MCI is defined as a syndrome marked by cognitive decline to a greater extent than that expected for the patient's age but does not interfere with daily life.[34] Recently, MCI is subject of several studies that investigate whether MCI is a predictor for AD or a distinct and static aetiology.[33] Similar to dementia due to Alzheimer's disease, it is currently not possible to diagnose MCI by laboratory tests, but is judged by a physician.[35]

1.1.2.3 *Dementia due to Alzheimer's disease*

Dementia differs from MCI on whether or not there is a severe interference in daily life and work. This judgement is made by a clinician on the basis of the patient's descriptions of the individual circumstances and an informant, such as a family member.[31] The patients suffer from severe impairment of recent memory, and appear to "live in the past". Planning, organizing, logically thinking and also speaking becomes more and more difficult.[36] The ability to read and write deteriorate constantly, also the comprehension of texts becomes more and more difficult.[37, 38] The individuals are restless, often lose emotional control, are verbally or even physically aggressive. Up to 20% of the patients develop hallucinations, which may be caused by severe cholinergic deficit.[39] As the disease progresses almost all cognitive functions are impaired, language is reduced to simple phrases or even single words. Patients need support for all activities, even for basic motoric functions such as chewing or swallowing.[40] These patients with moderate to severe dementia due to AD need constant supervision and care, they cannot live alone.[41]

1.1.3 Treatment

There is no cure for Alzheimer's disease, treatment mainly focuses on improving the quality of life and maximising functional performance by enhancing cognition, mood and behaviour. The treatment can be divided into pharmacological and non-pharmacological treatment.

1.1.3.1 ***Non-pharmacological treatment***

Non-pharmacological treatments use other approaches than medication, such as cognitive training, behavioural interventions and caregiving. Many non-pharmacological treatments have been studied, but only few have proven supporting effectiveness.[30]

1.1.3.2 ***Pharmacological treatment***

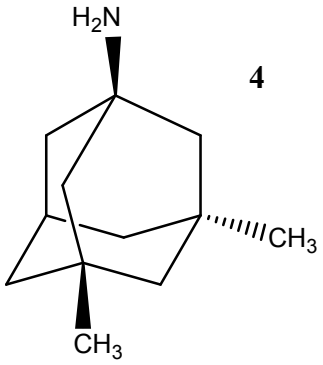
There are currently 5 pharmaceuticals for treating the cognitive symptoms of AD, four of them are cholinesterase inhibitors, donepezil, galantamine, rivastigmine and tacrine, and one is a NDMA receptor antagonist (memantine).

NMDA receptor antagonists

Glutamate is an excitatory neurotransmitter of the nervous system, found in the neural pathways associated with learning and memory. In patients with AD, glutamine synthetase in the brain is oxidized, which leads to excessively increased amount of glutamate. Excessive activation of NDMA receptors by the high levels of glutamate increase the neuron's vulnerability, leading to neuronal degeneration and cell death. memantine **4** blocks the NMDA receptor and thereby prevents the activity of the neurotransmitter glutamate.[42]

In contrast to cholinesterase inhibitors, which are only approved for treating mild to moderate stages of AD, memantine **4** is also approved in the severe stages of the disease. However the clinical efficacy is lower than that of the cholinesterase inhibitors.[43] After several studies indicate that targeting both the glutamate and the cholinergic pathway leads to better outcomes, memantine **4** is increasingly used as an adjuvant in cholinesterase therapy. [44]

The chemical structure of Memantine **4** is shown in Scheme 1.1.2



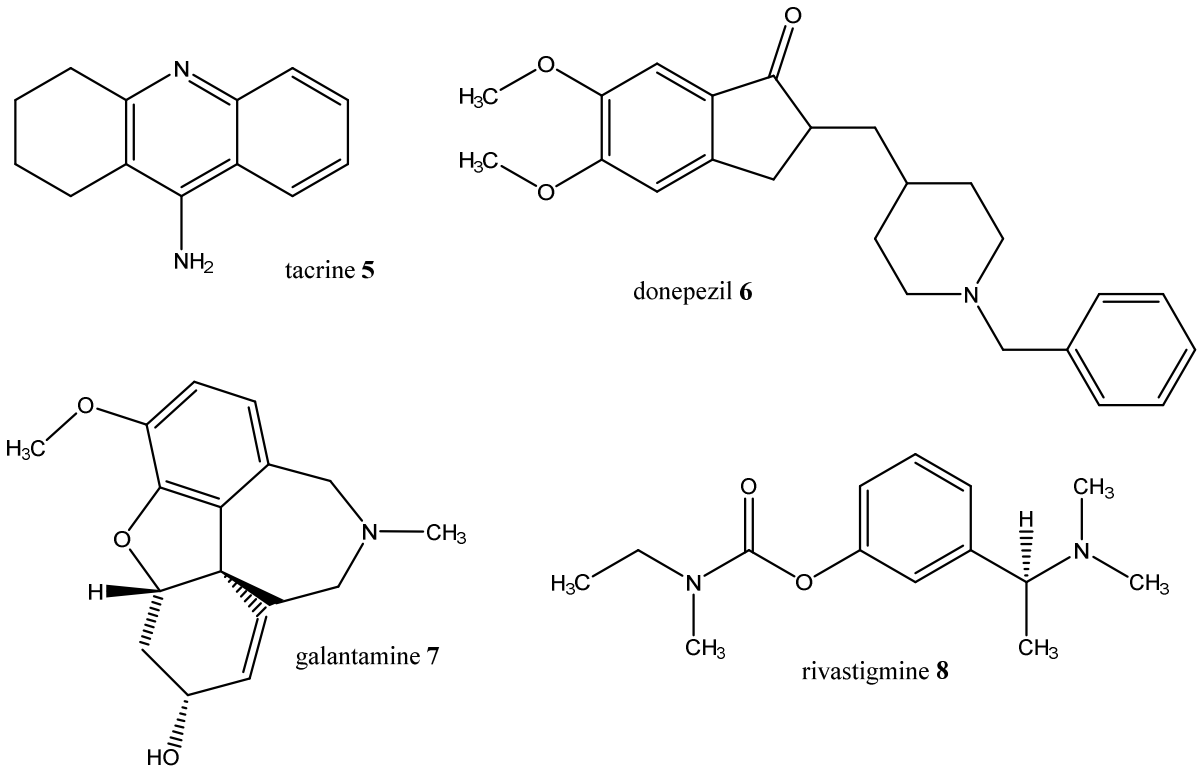
Scheme 1.1.2 Memantine

Cholinesterase inhibitors

The state of the art therapy of AD at present is the inhibition of the acetylcholine-esterase enzyme (AChE) with mainly cognitive symptomatic and weak disease-modifying effects.[45] ACh is an important neurotransmitter that has functions in the peripheral nervous system as well as in the central nervous system and it is well known since the 1970s that the activitiy of cholinergic neurons is decreased in Alzheimer-brains. Aceytylcholinesterase inhibitors (AChEI) are used to inhibit the AChE and thereby prevent it from breaking down acetylcholine, increasing the Ach level in the brain and compensating the loss of ACh by the death of cholinergic neurons to a certain extent.[9, 42, 46]

In 1993, the FDA approved the first cholinesterase inhibitor, tacrine **5**, followed by donepezil **6** (1996), rivastigmine **7**(2000) and Galantamine **8**(2001). The use of tacrine **5** has been limited due to poor oral bioavailability and adverse drug reactions. [44] Second generation cholinergics, including donepezil **6** (Aricept ®), galantamine **7** (Reminyl ®, U.S. trade name Razadyne ®) and rivastigmine **8** (Exelon ®) have fewer side effects, longer half-lives and greater efficacy.[42] Findings have shown that these drugs lead to small improvements in cognition and functionality, but no improvements were found in the progression of the disease, or the risk of entering institutional care.[45, 47, 48]

The four cholinesterase inhibitors are shown in Scheme 1.1.3.



Scheme 1.1.3 The cholinesterase inhibitors donepezil, galantamine, rivastigmine and tacrine

Donepezil

Donepezil, an important drug that prevents the degradation of the important neurotransmitter acetylcholine by inhibiting acetylcholinesterase, is used for the treatment of AD. Donepezil is a member of *N*-benzylpiperidine-based AChE inhibitors that were discovered by Eisai Company in Japan on the basis of QSAR (quantitative structure-activity relationship) studies[49, 50] prior to the elucidation of the 3D structure of AChE of the electric ray *Torpedo californica* (*Tc*AChE).[51] The experimental structure of donepezil- *Tc*AChE complex published by Kryger[52] shows that donepezil has indeed high affinity and selectivity, however it does not interact directly with the catalytic triad but only indirectly through solvent molecules.

In 2012, Cheung first described the structure of the human acetylcholinesterase (rhAChE) and showed that donepezil binds to rhAChE in a significantly different conformation than it does to *Tc*AChE, thereby showing the importance of using the human acetylcholinesterase in future drug binding models.[53] Interestingly, both research groups[52,53] came to the conclusion that through the variation of the structure at the piperidine moiety, the binding affinity of donepezil could be improved and therefore

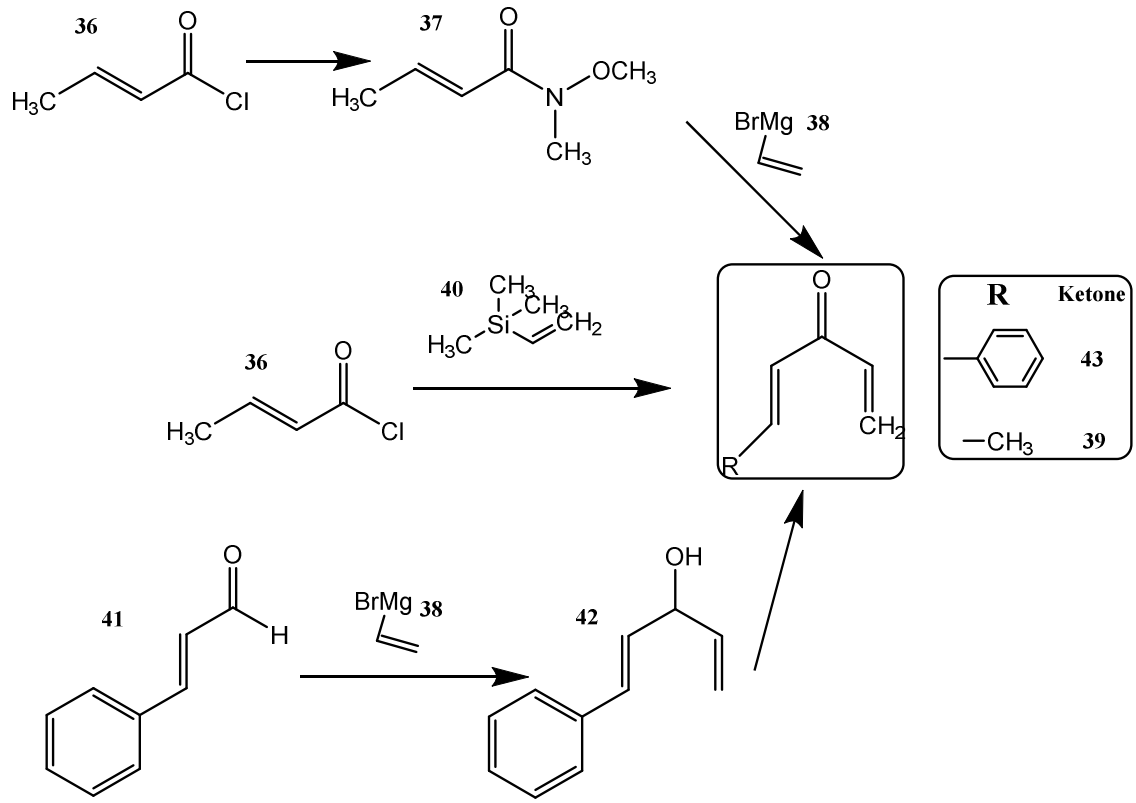
also its pharmacological profile. The piperidine moiety is an important substructure found in many pharmaceuticals, and most of these drugs, like donepezil, are limited to a simple 1, 4- disubstitution on the piperidine ring. Therefore the easy access to steroselectively substituted piperidines, such as *N*(1),C(2),C(4)- trisubstituted building blocks should be investigated.

1.2 Aim of project

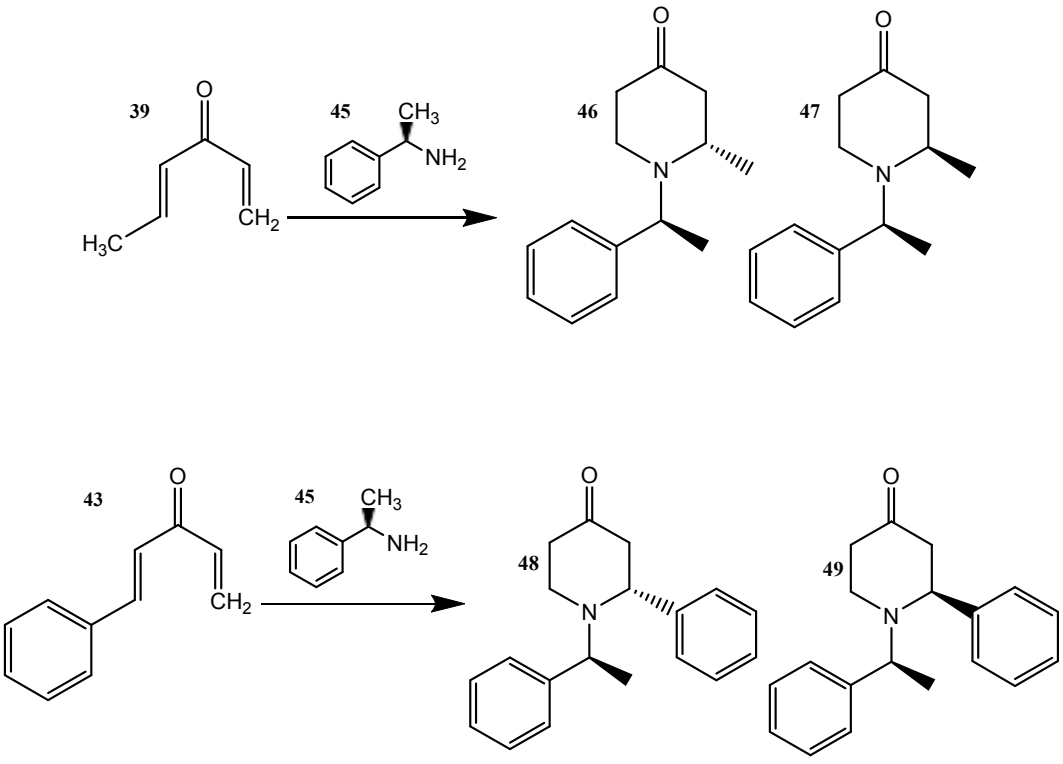
In most pharmaceuticals bearing a piperidine moiety disubstitution is limited to a 1,4-disubstitution. However, studies have shown that additional substituents on the piperidine can lead to products with higher binding affinity and therefore improved pharmaceutical profile.[54]

The aim of this project is to synthesise diastereomeric *N*(1),C(2),C(4)-trisubstituted piperidine blocks which can serve as key intermediates for the further preparation of novel donepezil analogues.

It is intended to achieve the synthesis diastereomeric 2-substituted 4-piperidones by initially synthesise divinyl ketones **39** and **43** (Scheme 1.2.1), which will be cyclised by a suitable chiral amine like *S*-*α*- phenylethylamine **45** in an *aza*- Michael reaction. (Scheme 1.2.2)



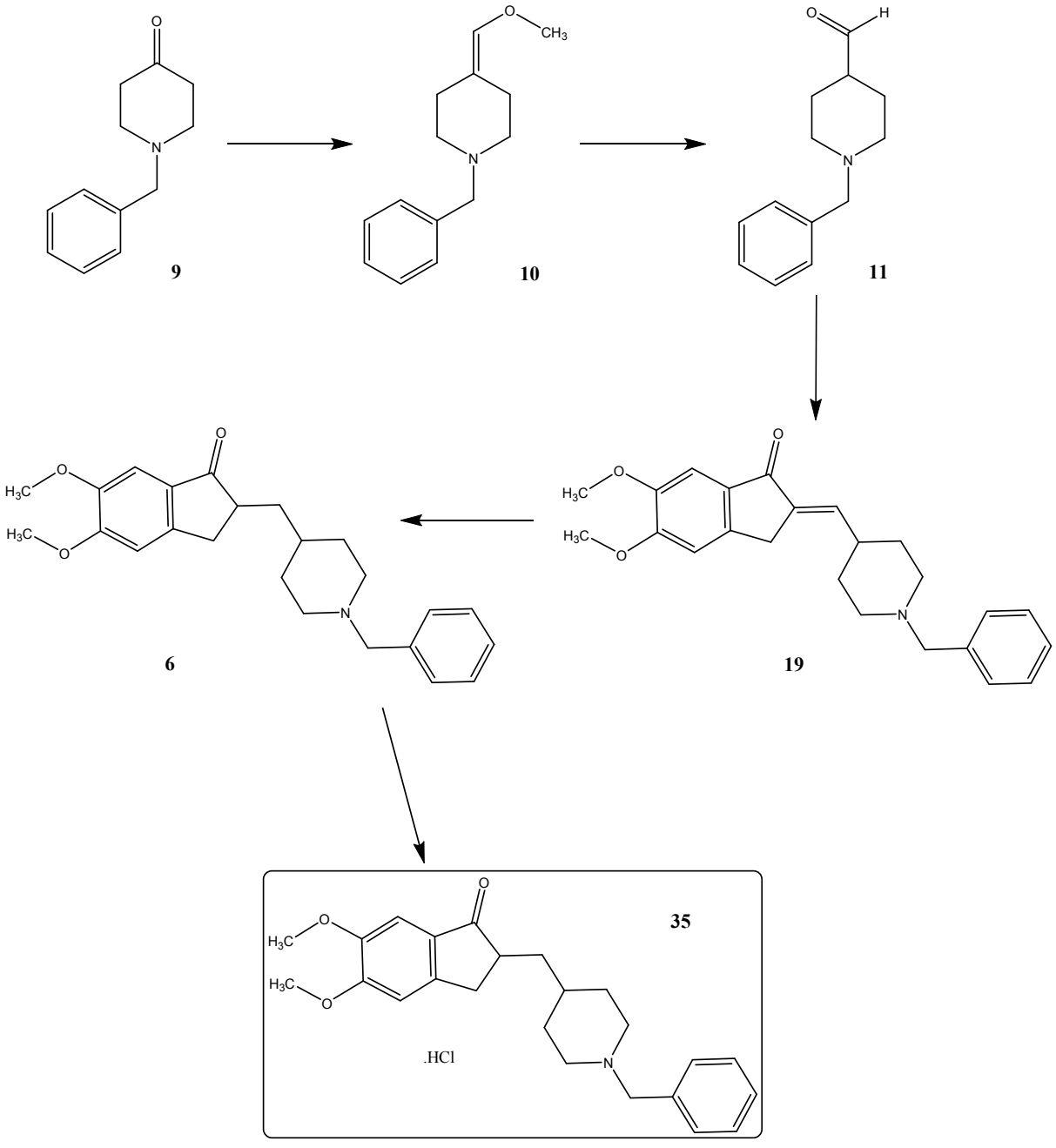
Scheme 1.2.1 Synthetic route to divinylketones 39& 43



Scheme 1.2.2 Synthetic route to the desired diastereomeric 2-substituted 4-piperidones

In an initial study it is intended to synthesise donepezil **6** according to Sugimoto[55] *via* a Wittig reaction to afford 1-Benzyl-4-(methoxymethylene)piperidine **10**, followed by

hydrolysis and an aldol condensation leading to the donepezil precursor **19**. Hydrogenation and treatment of Donepezil **6** with HCl consequently leads to the hydrochloride salt of Donepezil **35**. (Scheme 1.2.3)

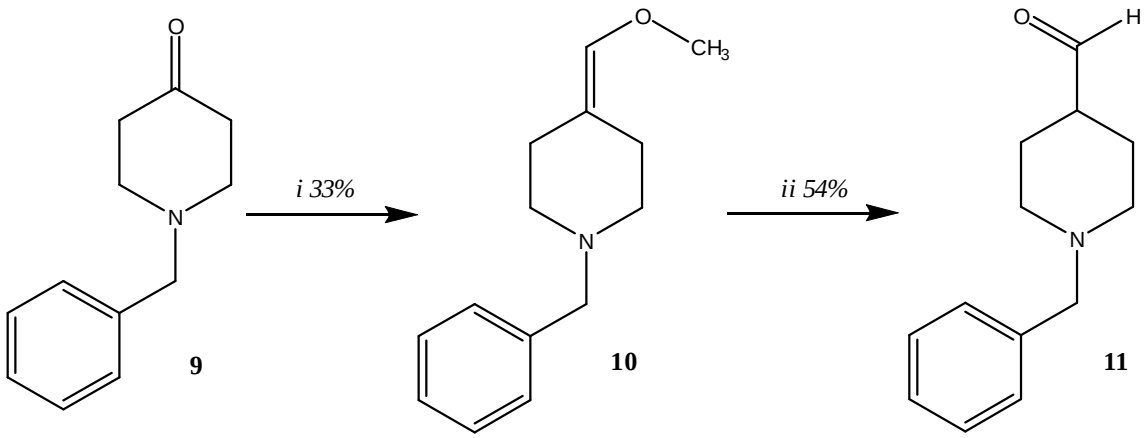


Scheme 1.2.3 Reaction path to donepezil HCl

2 Results & Discussion

2.1 Synthesis of Donepezil HCl

The first report of the preparation of donepezil was made by Sugimoto[55, 56], who chose the commercially available *N*-benzy-4-piperidone **9** as the starting material. (Scheme 2.1.1) Piperidone **9** is transformed to enol ether **10** via a Wittig reaction and subsequently hydrolysed under acidic conditions to obtain aldehyde **11** as key intermediate. We chose to follow the same route as described by Sugimoto,[55] we applied optimised reaction conditions in order to increase the yields of the desired unstable aldehyde intermiediate **11**.[57]

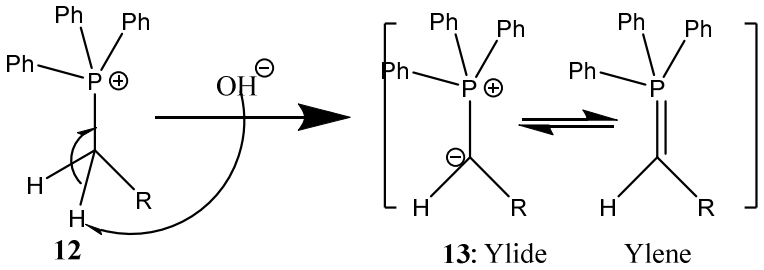


Scheme 2.1.1 Reaction conditions: *i*) $(C_6H_5)_3P(Cl)CH_2OCH_3$, Et_2O, *n*-BuLi, rt--> 0°C, Et_2O, 3h; *ii*) MeOH/1N HCl 1:1, reflux, 3h[55]

The Wittig reaction

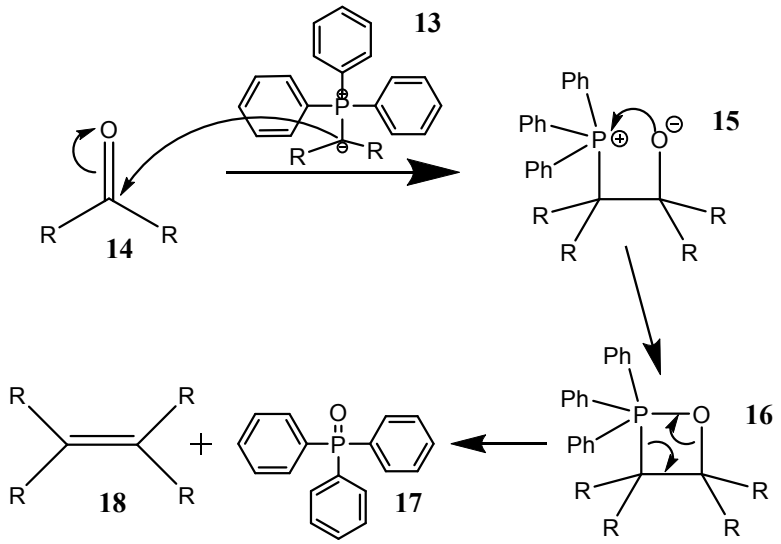
In the Wittig reaction (also Wittig olefination) an alkene and triphenylphosphine oxide are generated through the reaction between a carbonyl moiety and a phosphonium ylide (=Wittig reagent).[58, 59]

Ylides are molecules bearing a positively charged heteroatom adjacent to a carbanion. They are produced when a phosphonium salt **12** is deprotonated by a strong base, as shown in Scheme 2.1.2.



Scheme 2.1.2 Preparation of a phosphonium ylide

During the Wittig reaction the addition of ylide **13** to carbonyl compound **14** the zwitterionic intermediate betaine **15** is formed and further cyclises to give oxaphosphetane intermediate **16**. The ring opens, forming phosphinium oxide **17** and alkene **18**. As lithium salts stabilise the betaine intermediate, the formation of side products is promoted. Therefore, suitable bases in Wittig Reactions are NaH, NaOMe and NEt_3. The reaction mechanism is shown in Scheme 2.1.3.



Scheme 2.1.3 The Wittig reaction

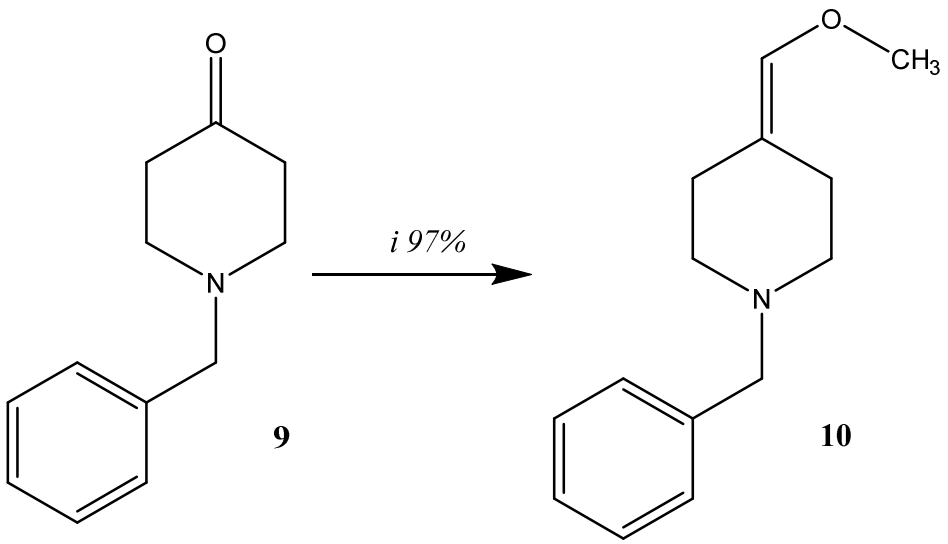
Diastereoselectivity is observed depending on the reaction conditions and reagents: Whether the resulting alkene of the Wittig reaction is an (*E*) - or (*Z*) - alkene depends on the reactivity of the ylide. If the ylide R is for instance a phenyl, the ylide is stabilized and not as reactive as if the ylide R was an alkyl. Non- stabilized ylides (R= alkyl) lead to (*Z*) - alkenes, whereas stabilized ylides (for example R= Ph) to (*E*)-alkenes.[60]

The Wittig reaction is a very popular reaction for the synthesis of alkenes because it forms the double bond reliably in one position, unlike other reaction types that may produce alkene regioisomers. However the numerous advantages of the Wittig reaction,

one limitation is the stereochemistry of the product. With simple, non- stabilized ylides the reaction affords mainly the Z-isomer. If the reaction's solvent is DMF and LiI or NaI are present, the Z- isomer is almost the only product. [61] If the wanted product is the E-isomer, the Schlosser Modification can be used. With the Schlosser modification it is possible to yield high E-isomer- selectivity even with non- stabilized ylides. [62]

Preparation of *N*-benzyl-4-formyl-piperidine *via* Wittig reaction and acidic hydrolysis

Ketone **9** was converted to 1-benzyl-4-(methoxymethylene) piperidine **10** by Wittig reaction, using (methoxymethyl)triphenylphosphonium chloride as the Wittig reagent and lithiumdiisopropylamide as the base to deprotonate the phosphonium salt. (Scheme 2.1.4)

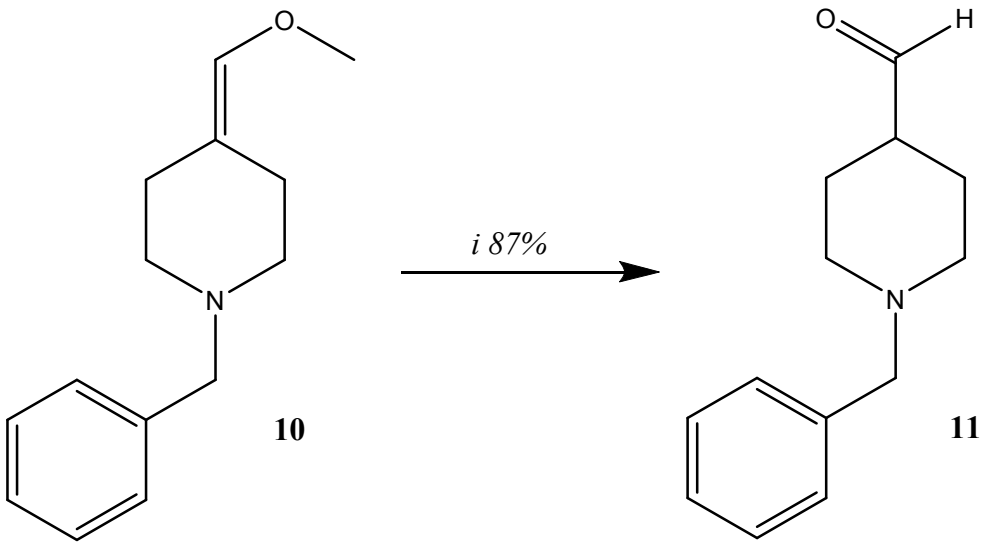


Scheme 2.1.4 Reaction conditions: *i)* $(C_6H_5)_3P(Cl)CH_2OCH_3$, LDA, THF, molecular sieves, - 70° → rt → - 20° → rt, 16h

To ensure a complete conversion to the ylide, an excess of 1.5 equivalents of (methoxymethyl)triphenylphosphonium chloride and lithiumdiisopropylamide were added and THF and molecular sieves were used to maintain anhydrous conditions throughout the reaction. Having added LDA at -70°C, the reaction was allowed to warm to room temperature.[63] The mixture developed the characteristic dark red colour, indicating the ylide formation. For the cautious adding of ketone **9** the mixture was cooled to – 20°C and subsequently allowed to warm to room temperature. Finally, while

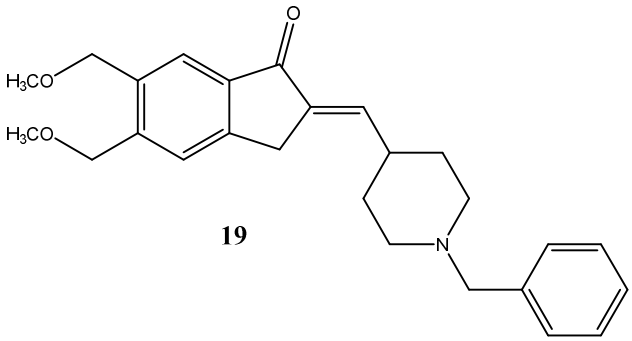
stirring the mixture for 16 h, decolouration from red over orange to light yellow was observed. Purification by column chromatography yielded pure Wittig product **10** in excellent yield (97%).

Having successfully prepared 1-benzyl-4-(methoxymethylene) piperidine **10**, it was used as substrate for the acidic hydrolysis to form aldehyde **11.** (Scheme 2.1.5) Sugimoto's original reaction conditions only led to a yield of 54%.[55] Using a slightly modified procedure,[57] enol ether **10** was stirred in a 1:1 solution of 1.6N HCl and THF, warmed to 45°C and stirred for 2 hours. After work up, the reaction afforded 87% of crude aldehyde **11**. NMR analysis of the crude residue showed that no starting material was left and that the product was of sufficient purity to be used in the next synthetic step.



Scheme 2.1.5 Reaction conditions: *i*) 1.6 N HCl/THF 1:1, 45°C, 2h

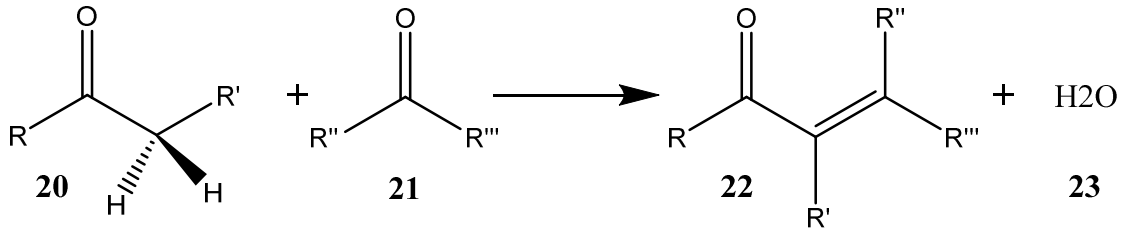
Having successfully prepared N-benzyl-4-formyl-piperidine, the next step would be an aldol condensation of **11**, to generate the donepezil precursor **19.**



Scheme 2.1.6 Donepezil precursor 19

The Aldol condensation

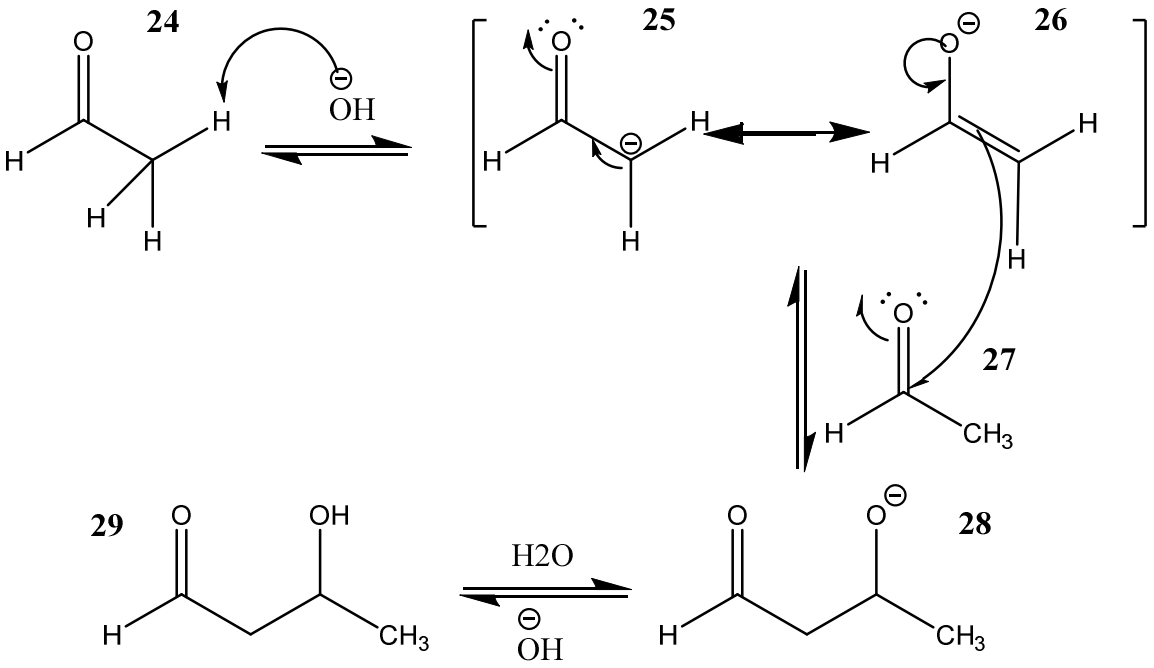
The Aldol condensation is a reaction of a carbonyl moiety with an enol or enolate ion that produces either a *β*-hydroxyaldehyde or a *β*-hydroxyketone ("aldol" from "*ald*ehyde + alcoh*ol*"), which is subsequently dehydrated to form a conjugated enone (Scheme 2.1.7).



Scheme 2.1.7 The Aldol condensation

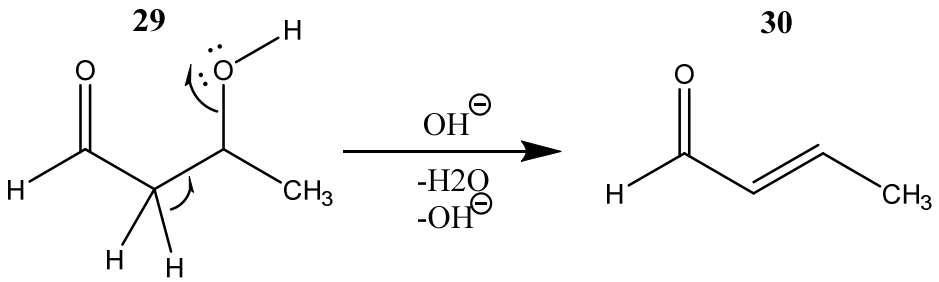
Nowadays the term "aldol condensation" is also used for all aldol reactions, even if they don't occur with dehydration. Aldol reactions combine two carbonyls forming a new β-hydroxy-carbonyl compound, so-called "aldols". Aldol reactions have two different mechanisms, the "enol mechanism" and the "enolate mechanism". [64]

The enolate mechanism: Carbonyl compounds **24** can be deprotonated to form enolates **25**. Enolates are more nucleophilic than enols or enol ethers and can attack electrophiles directly-the aldol reaction occurs via nucleophilic attack by the resonance-stabilized enolate **25** on the carbonyl group of another molecule **27**. Then the aldol **29** is formed. The catalyst is a moderate base. Scheme 2.1.8 shows a simplified mechanism for the base-catalyzed aldol reaction of an aldehyde with itself. [65]



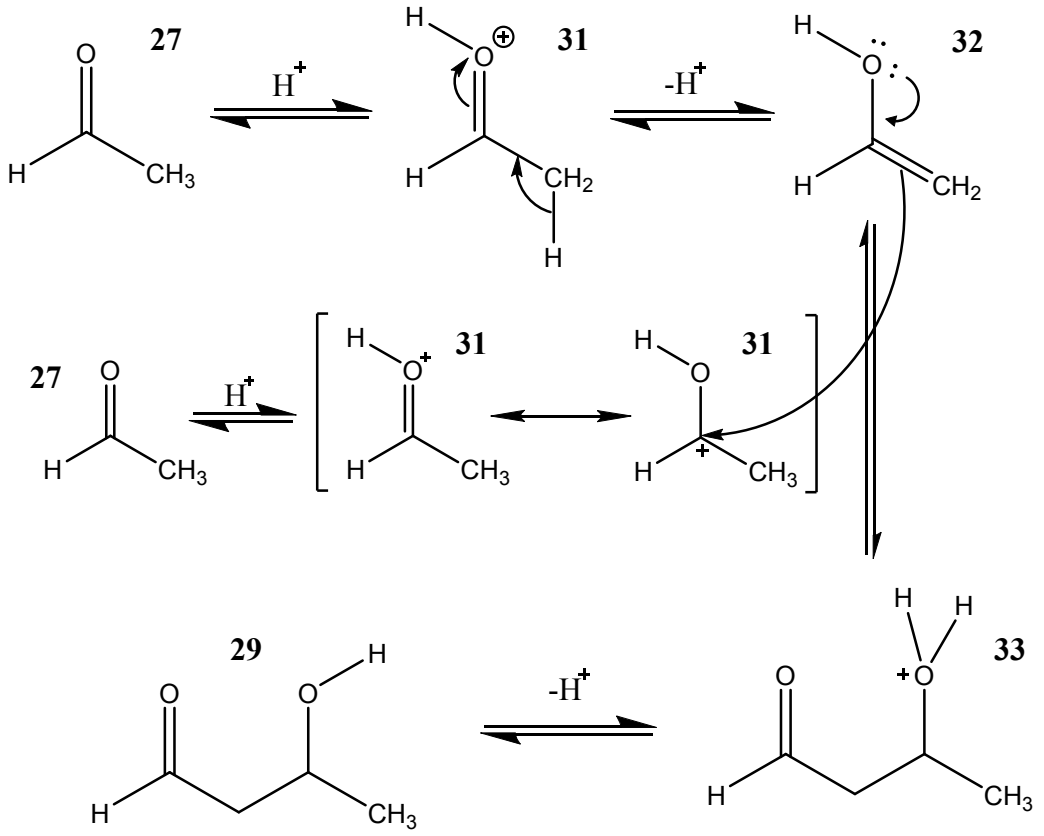
Scheme 2.1.8 Base-catalyzed Aldol reaction

The product of the aldol reaction **29** can be dehydrated to give an unsaturated carbonyl compound **30**, as seen in Scheme 2.1.9.



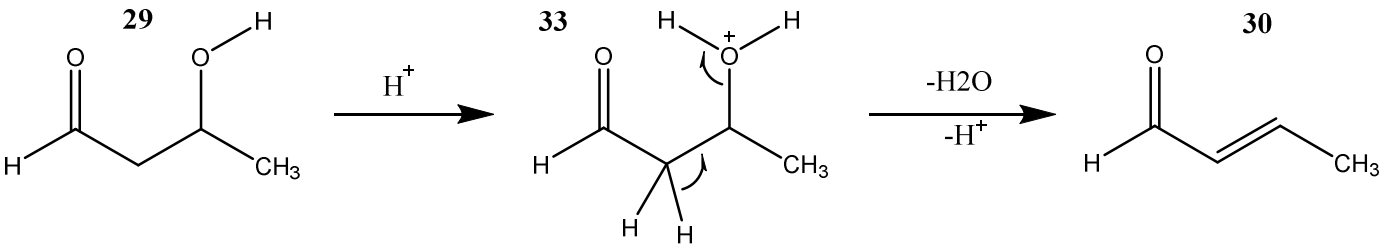
Scheme 2.1.9 Base- catalysed dehydration of the Aldol reaction product (Aldol condensation)

The enol mechanism: Aldehydes and ketones can be converted to enols **31** or enol ethers **32**, which are nucleophilic at the α-carbon. The catalysts in these reactions are acids, which catalyze the tautomerisation of the carbonyl to the enol and also protonate the carbonyl group of another molecule, making it highly electrophilic **31**. The nucleophilic enol attacks the protonated carbonyl, giving the aldol product **25** after deprotonation. [64, 65] The enol mechanism is shown in Scheme 2.1.10.



Scheme 2.1.10 Acid-catalyzed Aldol reaction

The Aldol reaction product **29** can be dehydrated to an unsaturated carbonyl compound **30.** (Scheme 2.1.11)

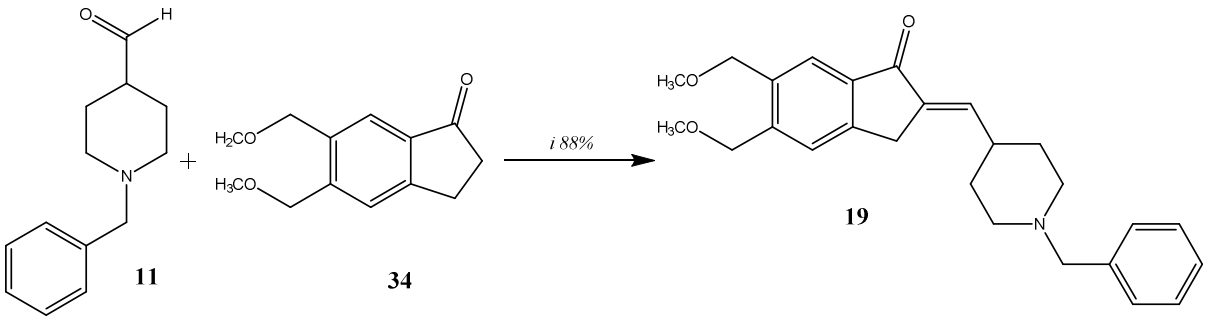


Scheme 2.1.11 Acid- catalyzed dehydration of the Aldol reaction product (Aldol condensation)

The aldol reaction is a common tool in organic chemistry, particularly in the synthesis of natural products. For example, a key step in the synthesis of Atorvastatin (®Pfizer, 1996) are two Aldol reactions. There is a range of other reactions that follow the same principle as the Aldol reaction, as the Claisen condensation,[66] the Henry reaction,[67] the Knoevenagel reaction [68] or the Hajos-Parrish-Eder-Sauer-Wiechert-reaction. [69, 70]

Preparation of Donepezil HCl

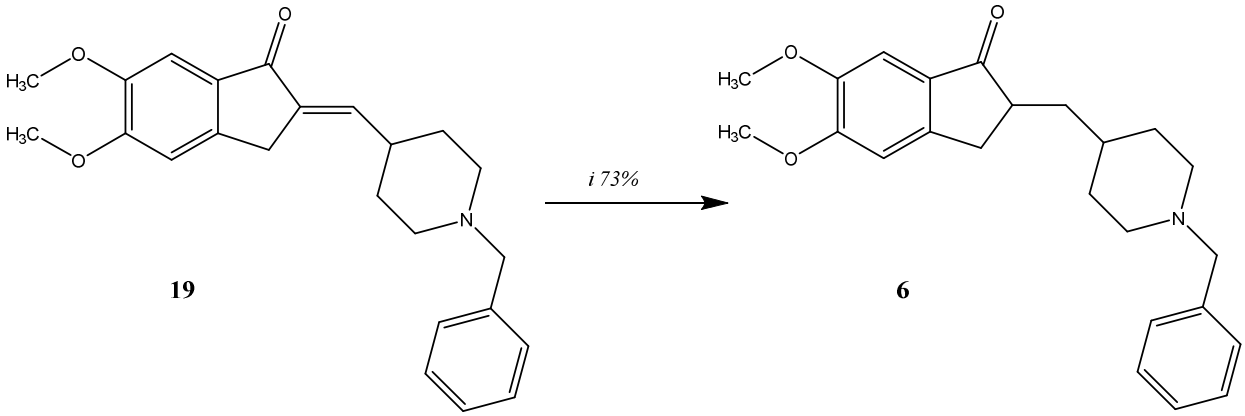
For the preparation of the enone precursor **19** we chose to follow a protocol published by Imai. [71] Aldehyde **11** was used for an Aldol condensation with 5, 6-dimethoxy-1-indanone **34**, shown in Scheme 2.1.12.



Scheme 2.1.12 Reaction conditions: *i*) MeOH, 80°C, $NaOCH_3$, 75 min, --> rt

The base catalysed enolate addition of 5, 6-dimethoxyindanone **34** and *N*-benzyl-4-formyl-piperidine **11** was carried out using methanol as the solvent and sodium methoxide as base. During stirring at reflux for 75 min deprotonation was achieved and the mixture was cooled down to room temperature to give crude product **19** in good yield (88%). The NMR analysis showed only minor impurities, so it was decided to proceed with the next step without further purification by column chromatography.

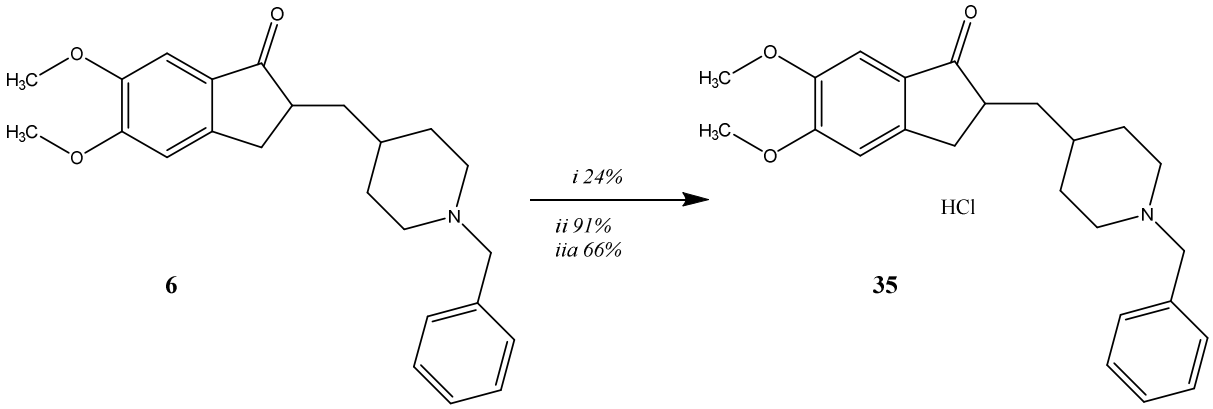
For the following step leading to Donepezil **6** we hydrogenated condensation product **19** according to Sugimoto [56] over palladium 10% on activated charcoal for 6h at 1.1 atm. After purification by column chromatography donepezil **6** was afforded in a good yield of 73%. (Scheme 2.1.13)



Scheme 2.1.13 Reaction conditions: *i*) THF, 10% Pd/C, 1.1 atm H_2, 6h

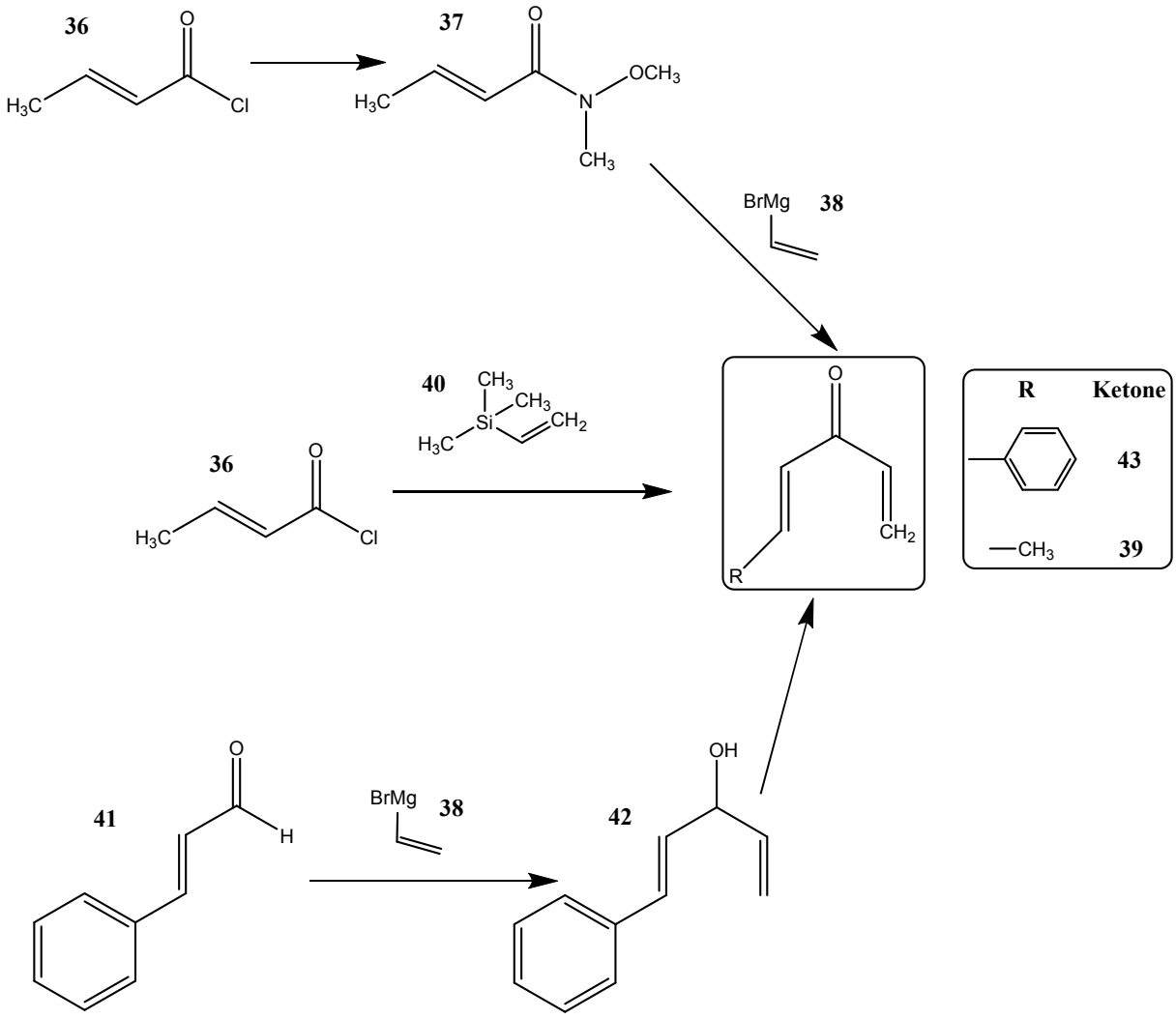
The salt donepezil hydrochloride **35** was prepared in two different ways; According to the procedure of Rao[72] donepezil was stirred in 1.5N aqu. HCl in ethyl acetate at room temperature, however only a poor yield (24%) was obtained. NMR analysis showed that the hydrochloride salt had been formed, but impurities were still present.

Due to the poor yield and the impurities, we searched the literature for better conditions and used a protocol by Dubey et al.[73] Instead of using aqueous 1.5 N HCl, concentrated HCl in ethyl acetate was used. The reaction led to good crude yields (66- 91%), and combined fractions of product **35** was subsequently recrystallized with MeOH/ isopropylether 1:1 according to Sugimoto [55] affording good yield (77%) (Scheme 2.1.14)



Scheme 2.1.14 Reaction conditions: *i*) 1.5N HCl/EtOAc; *ii*) conc. HCl/ EtOAc *iia*) Scale up, same conditions as *ii*)

2.2 Synthesis of divinyl ketones for the preparation of 2-substituted 4-piperidones



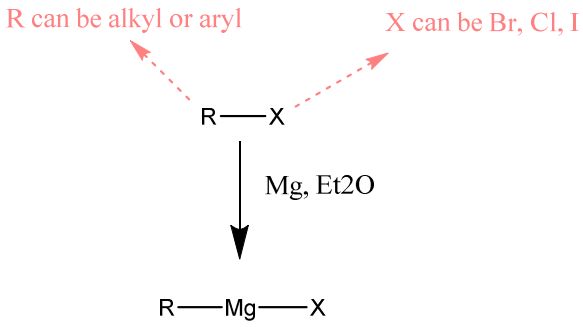
Scheme 2.2.1 Preparation of divinyl ketones

Firstly, we attempted to access important divinyl ketone **39** *via* a Weinreb Ketone synthesis followed by a Grignard reaction, which is an important tool for the new formation of carbon-carbon bonds and is explained in the following.

The Grignard reaction

In the Grignard reaction alkyl- or aryl- halides act as nucleophiles and attack electrophiles, such as carbonyl compounds, to form a new C-C bond, but the reaction can also be used to form carbon-phosphorus, carbon-silicon, carbon-tin, and carbon-boron bonds. [74] After the new bond is formed, hydrolysis generates a primary, secondary or tertiary alcohol as the Grignard reaction's product.

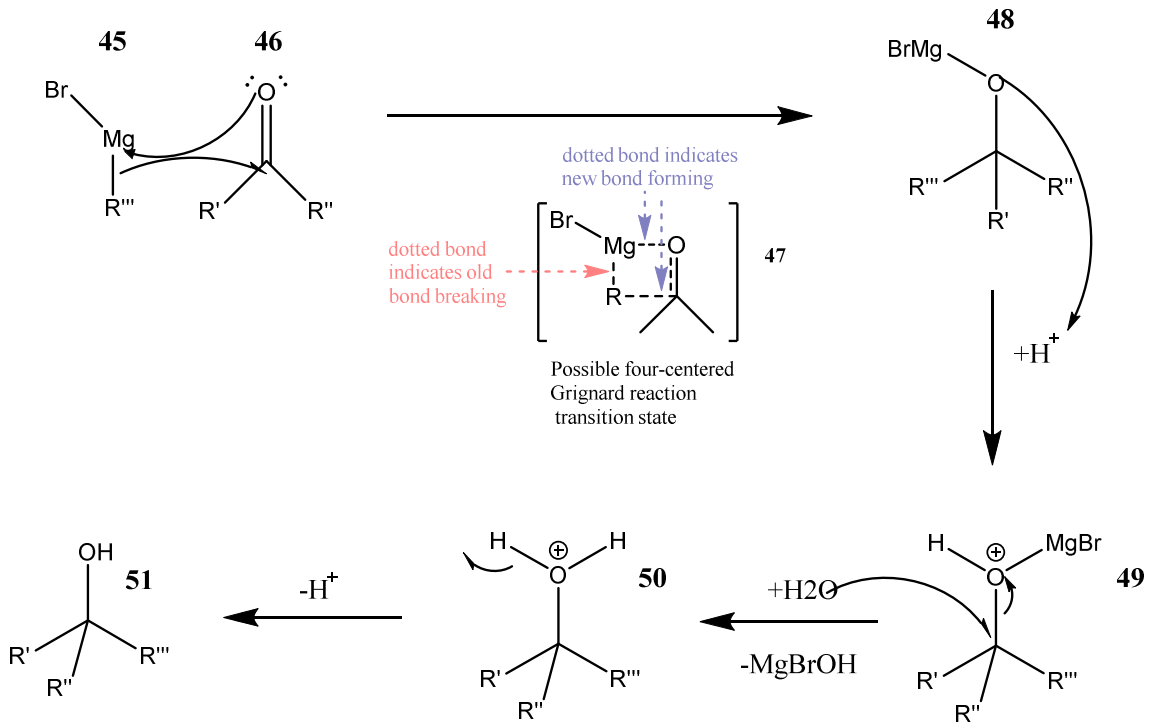
To synthesise a Grignard reagent, magnesium turnings react with alkyl- or aryl halides in ether solvents (such as Et_2O or THF) to form solutions of alkyl-/arylmagnesium halides. For this, iodides, bromides and chlorides can be used. Solvents are mostly ether solvents, but also dimethoxyethane or dioxane. In reactions using Grignard reagents it is necessary to exclude water and air to prevent degradation of the reagent caused by oxidation or protonolysis.[75] The general mechanism how to form a Grignard reagent is shown in Scheme 2.2.2.[64]



Scheme 2.2.2 Synthesis of a Grignard reagent[64]

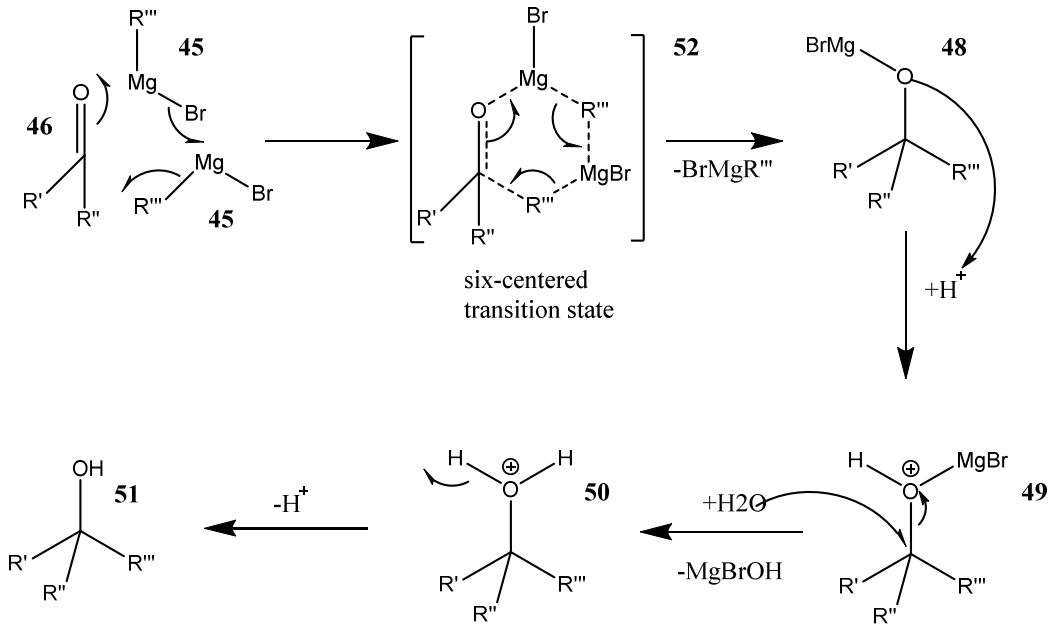
The mechanism involves an insertion of the magnesium into the newly formed carbon-halogen bond leading to a change of the magnesium's oxidation state- therefore the reaction is sometimes referred to as an "oxidative insertion" or "oxidative addition". As the reaction takes place on the surface of the metal, the state of the surface is important. Magnesium is usually covered by a thin coat of Magnesium oxide and because of that, an "initiation" is needed to make sure the metal comes in contact with the alkyl halide. To avoid the problems that are related to this initiation, commercially available Grignard reagents are used. [76, 77] The Grignard reagents **45** function as nucleophiles, attacking electrophiles **46**, and thereby generate a new bond. The exact reaction mechanism is uncertain, however there are two theories. One theory is that a four-centered transition

state is formed, allowing the Lewis acidic Mg+ to coordinate with the oxygen, thereby making the carbonyl group more electrophilic. At the same time, the nucleophile attacks the electrophilic carbonyl group, building the product with a new C-C bond **48** (Scheme 2.2.3).[64]



Scheme 2.2.3 Grignard reaction and possible four-centered transition state [64]

The second and more common version of the mechanism states that two molecules of the Grignard reagent **45** are involved in the reaction, building a six- membered ring as a transition state **52**, shown in Scheme 2.2.4.[64, 78]



Scheme 2.2.4 Grignard reaction with six-centered transition state [64]

Grignard reagents react with various electrophiles and gives different products, as seen in Table 2.2.1, but the most important use of the Grignard reaction is the preparation of primary, secondary or tertiary alcohols.

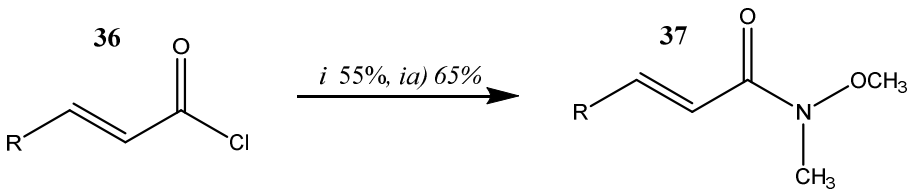
Substrate	Product
Formaldehyde	Primary alcohol
Aldehyde	Secondary alcohol
Formic acid ester	Secondary alcohol
Ketone	Tertiary alcohol
Carbonic acid ester	Tertiary alcohol
Carbon dioxide	Carbon acid
Nitrile	Ketone

Table 2.2.1 Various Grignard reaction substrates and their products

Preparation of (*E*)-hexa-1, 4-dien-3-one *via* Weinreb-ketone synthesis and Grignard reaction

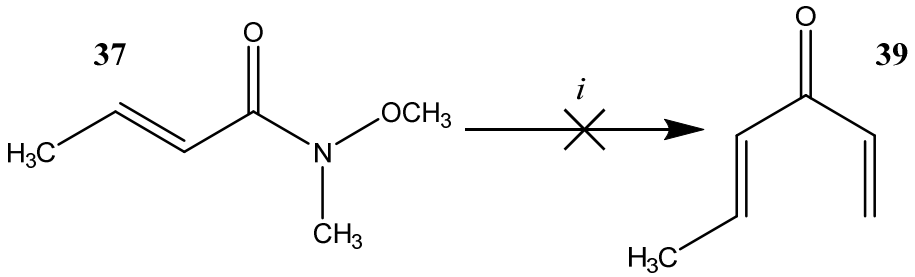
For the preparation of the desired divinylketone (*E*)-hexa-1,4-dien-3-one **39**, we followed a protocol by Solladie[79] and Evans et al,[80] and prepared the Weinreb amide (*E*)-*N*-methoxy-*N*-methylbut-2-enamide **37** through coupling of *N*,O-dimethylhydroxylamine

hydrochloride with *trans*-crotonyl chloride **36**. The reaction afforded a moderate yield of 55% using 3.08mmol of *N*,O-dimethylhydroxylamine hydrochloride, NMR analysis showed that the crude residue was sufficiently pure to be usedin the next step. Due to the unsatisfactory yield, the reaction was scaled up using 25.63mmol of *N*,O-dimethylhydroxylamine hydrochloride but under the same conditions, to increase the yield of the product. The scale-up afforded 65% pure product **37** after purification by column chromatography. (Scheme 2.2.5).



Scheme 2.2.5 Reaction conditions: *i*) MeONHMe-HCl, Pyridine, CH_2Cl_2, 0°C → rt; *ia*) Scale-up

Having prepared the Weinreb amide **37**, it was envisioned that subjecting it to a Grignard reaction utilising commercially available vinylmagnesium bromide **38** would afford divinylketone (*E*)-hexa-1, 4-dien-3-one **39**, following the protocol of Miltz et al.[81] (Scheme 2.2.6).



Scheme 2.2.6 Attempted preparation of (*E*)-hexa-1, 4-dien-3-one

The reaction was first carried out under oxygen free conditions and using tetrahydrofurane as the solvent and a slight excess of vinylmagnesium bromide (1.1 equiv) (Reaction 1), however on the TLCs no formation of the product was observed. NMR analysis showed that starting material was left as well as the formation of unwanted side products. Repeating the experiment with an increased amount of the vinylmagnesium bromide (1.3 equiv) and a reaction time of 3 hours, again led to no

product formation (as judged from the analysis of the crude NMR spectrum) (Reaction 2). Repeating the experiment with 1.1 equiv of vinylmagnesium bromide but with stirring at 0°C and an increased reaction time (4h) followed by prolonged stirring overnight showed no difference in the outcome (Reaction 3). We believed that the Grignard reagent was too old and therefore may have formed side products or might have been hydrolysed by humidity. We decided to repeat the experiment with an excess of 1.5 equiv of fresh vinylmagnesium bromide **38** this time letting the reaction stir overnight (Reaction 4). These changes in the reaction conditions however did not lead to the formation of the desired divinyl ketone **39**. The various attempts and their different reaction conditions to form the divinyl ketone are shown in Table 2.2.2.

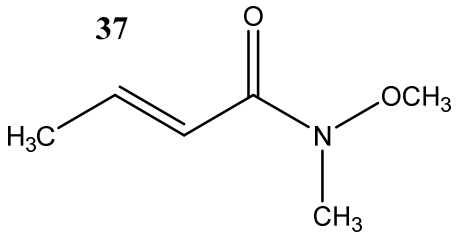
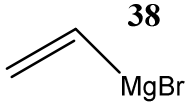
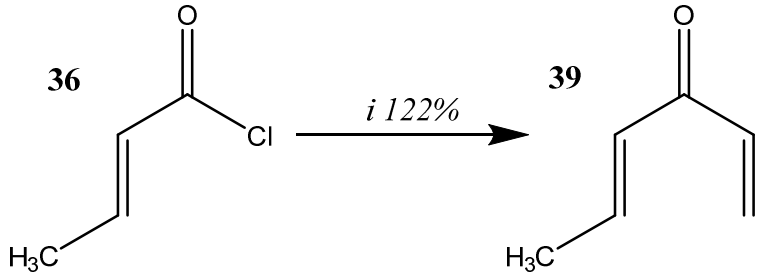
	37 	**38** 	**Temperature**	**Reaction time**
Reaction 1	200 mg (1.0 equiv)	1.1 equiv	Room temperature	1 hour
Reaction 2	200 mg (1.0 equiv)	1.3 equiv	Room temperture	3 hours
Reaction 3	200 mg (1.0 equiv)	1.1 equiv	0 °C	4 hours, overnight
Reaction 4	100 mg (1.0 equiv)	1.5 equiv	Room temperature	6 hours, overnight

Table 2.2.2 Various reaction conditions attempted to form divinylketone; Reaction conditions: THF, N_2, CH_2=CHMgBr

Preparation of the divinyl ketone *via* 2-*trans*-Crotonyl-chloride

Due to the unsatisfactory outcome of the attempt of preparing the desired molecule by Weinreb Ketone synthesis and Grignard reaction, another protocol for the preparation of divinyl ketone **39** was used. Following a protocol published by Blanco-Pallido et al,[82] we used 2-*trans*-crotonyl-chloride **36** in DCM as the starting material to react with vinyltrimethylsilane **40** in the presence of the Lewis acid aluminium chloride. The aluminium chloride was dissolved in dichlormethane at -35°C under oxygen free

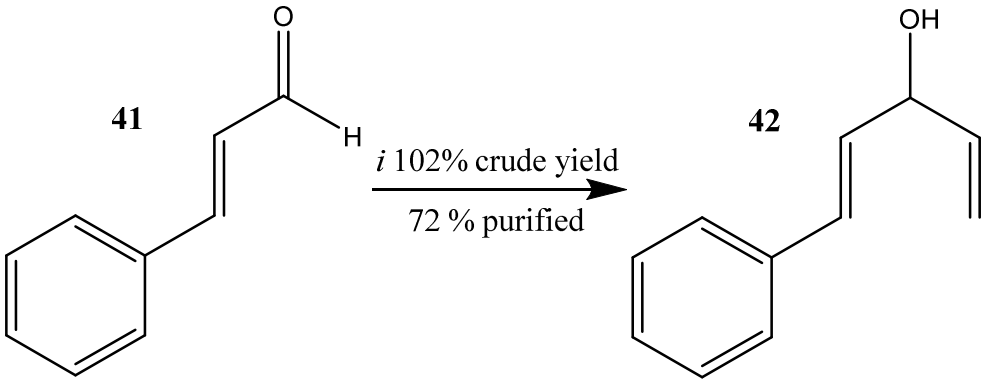
conditions, then 2-*trans*-crotonyl-chloride **36** was added slowly, and the reaction was stirred for 15 min. vinyltrimethylsilane **40** was cautiously added over 30 min, then stirred for 30 min and cooled to -50°C to facilitate the hydrolysis step. Subsequently a cold solution of potassium carbonate to quench the reaction was added, allowed to warm to room temperature and stirred vigorously for another 30 min (Scheme 2.2.7). NMR analysis showed the successful preparation of the desired divinylketone, in the presence of other impurities. As ketone **39** is highly unstable, it was decided to avoid further measures of purification and to use the crude residue for the next synthetic step.



Scheme 2.2.7, Reaction conditions: *i*) $AlCl_3$, -35°C, $(CH_3)_3SiCHCH_2$, → -50°C, K_2CO_3, → rt, 30min

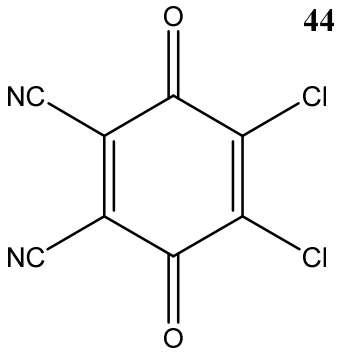
Preparation of (*E*)-1-phenylpenta-1, 4-dien-3-one *via* Grignard reaction and oxidation with DDQ

Following an example from the literature,[83] we used aldehyde **41** as the starting material and converted it to the desired divinyl alcohol intermediate **42** *via* Grignard reaction**.** (Scheme 2.2.8) We used a slight excess (1.1 eqiv) of the Grignard reagent **38** and reacted it with cinnamaldehyde **41** at 0°C, followed by stirring for one hour. The reaction was allowed to warm to room temperature. TLC analysis showed the successful conversion to crude divinyl alcohol **42**. Purification of divinyl alcohol **42** by column chromatography gave a yield of 72%



Scheme 2.2.8 Reaction conditions: *i*) CH_2=CHMgBr, THF, 1.5h, 0°C

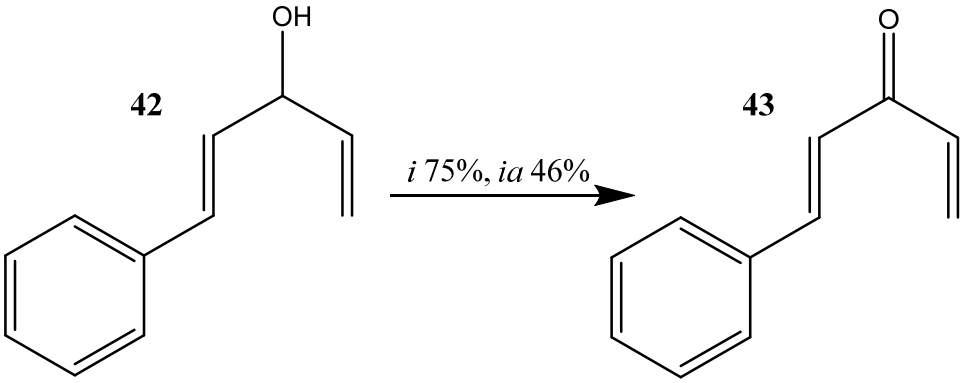
For the oxidation of divinyl alcohol **42** to divinyl ketone **43**, 2, 3-dichloro-5, 6-dicyano-*p*-quinone (DDQ) **44** a potent oxidising agent was chosen (Scheme 2.2.9).[57] DDQ easily oxidates benzylic alcohols and has the advantage that it can be used at room temperature. After the reaction it precipitates from the solution as its hydroquinone and can be easily filtered off. [84, 85]



Scheme 2.2.9 The oxidising agent 2, 3-dichloro-5, 6-dicyano-*p*-quinone

DDQ was added to pure divinyl alcohol **42** in dry DCM and stirred at room temperature for 24h, then the product was filtered and purification by column chromatography yielded 75% pure divinyl ketone **43** (Scheme 2.2.10).

The same experiment was repeated with a non-purified fraction of divinyl alcohol **42**, and purification by column chromatography gave 46% pure divinyl ketone **43**. It was concluded that it is important to purify after each reaction step to obtain a satisfactory yield.



Scheme 2.2.10 Reaction conditions *i*) DDQ, DCM, rt, 24h *ia*) same conditions, no preceding purification

2.3 Synthesis of diastereomeric 2-substituted *N*-*α* -4-piperidones

Having prepared the desired divinylketones **39** und **43**, it was envisioned to synthesise new diastereomeric 2- substituted *N*-*α*-phenylethyl-4-piperidones *via* an *aza*- Michael cyclisation with a suitable amine (Scheme 2.3.1). The commercially available *S*-*α*-phenylethylamine **45**, (Figure 2.3.1) which is both a nucleophile and a potential chiral auxiliary,[86,87] was chosen as a suitable primary amine for the reaction.

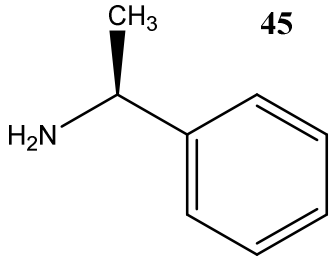
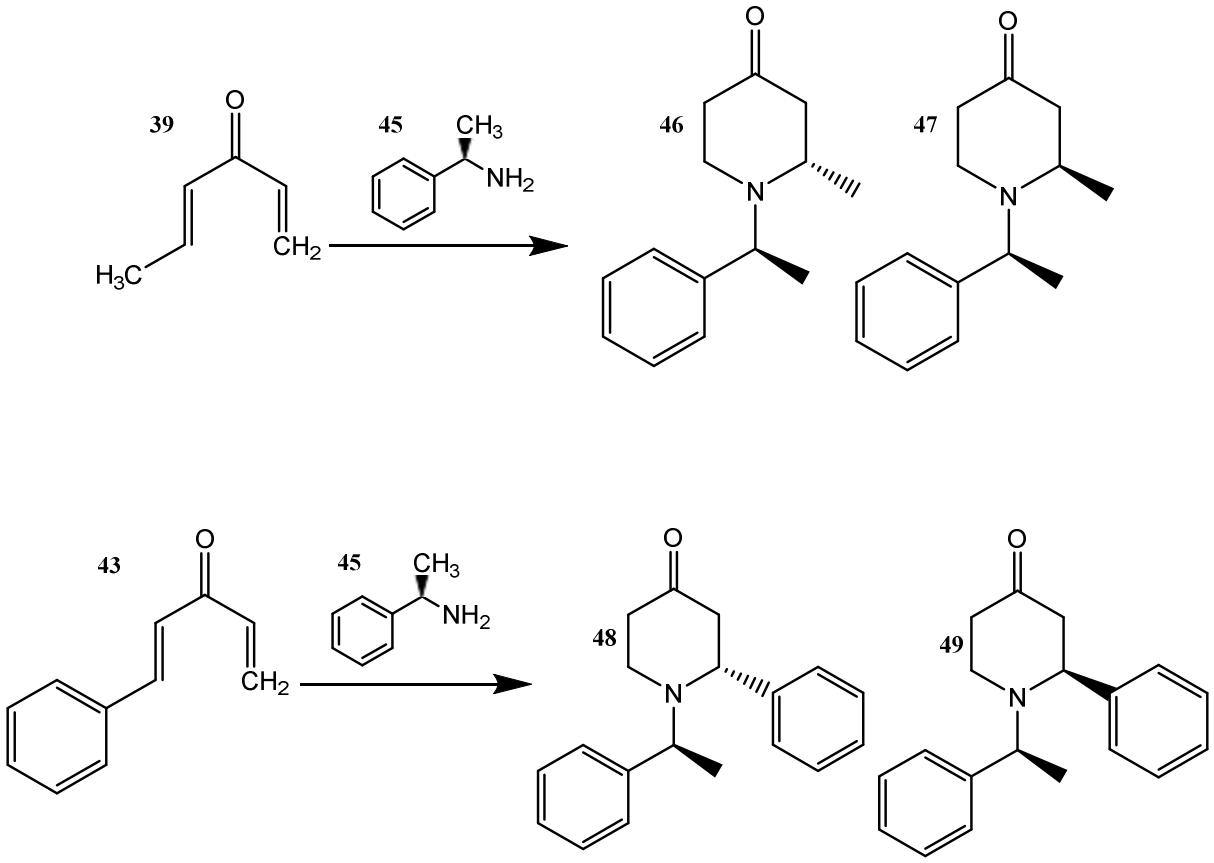


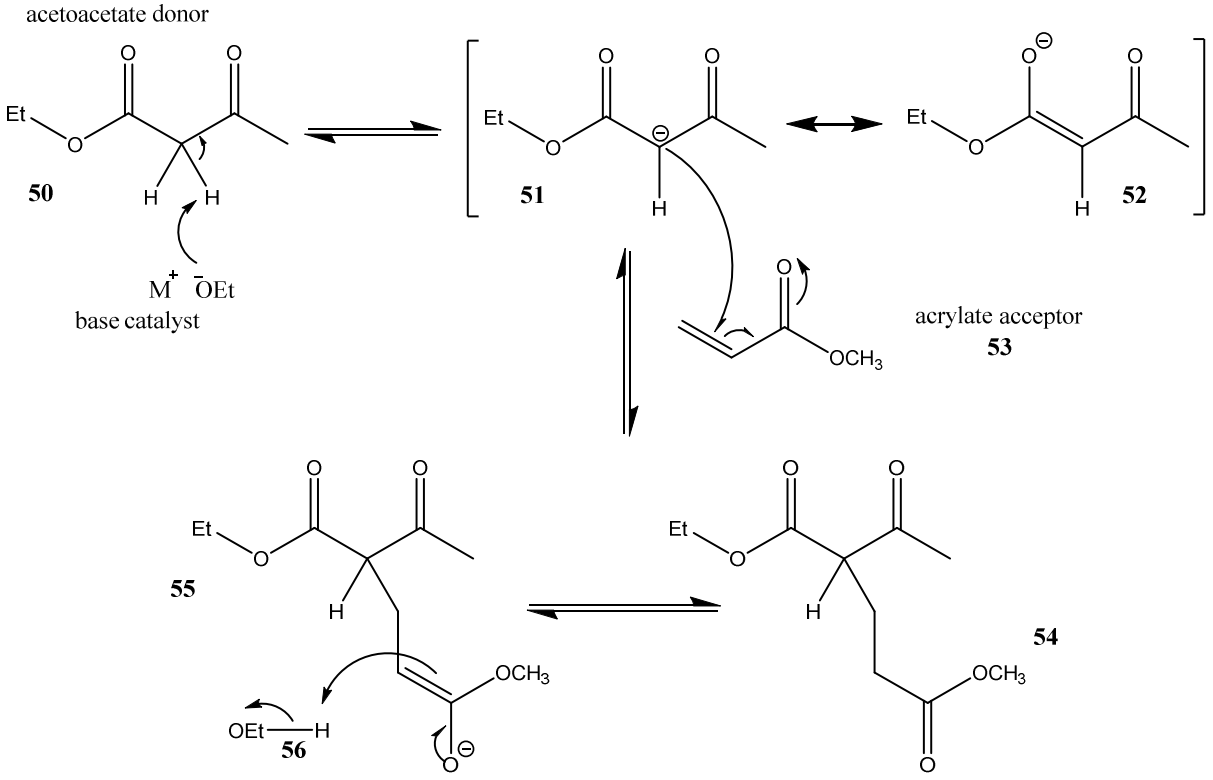
Figure 2.3.1 *S*-*α*- phenylethylamine



Scheme 2.3.1 Synthetic route to diastereomeric 2-substituted 4-piperidones

The *aza*- Michael reaction

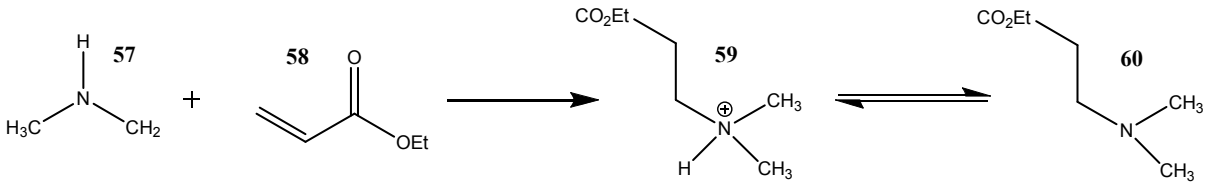
The typical Michael addition is a base- catalysed addition of a nucleophile (typically an enolate anion = Michael donor) to an activated *α, β*- unsaturated carbonyl compound (Michael acceptor) [88]. An example for the Michael addition mechanism is the base-catalysed addition ethyl acetoacetate to methyl acrylate [89], as shown in Scheme Scheme 2.3.2 [90]. The acetoacetate **50** is deprotonated by the base, forming an enolate anion (Michael donor) **51**. The nucleophilic enolate anion attacks the double bond of the methyl acrylate **53** (Michael acceptor). The resulting anion is stabilised by the carbonyl compound of the acrylate until protonation occurs (**54, 55**).



Scheme 2.3.2 Michael addition mechanism[90]

In a *hetero*- Michael addtition the donor is for example an amine, thiol or alcohol.[91, 92] When the Michael donor is an amine, the reaction is called an *aza*- Michael reaction. The *aza*- Michael reaction of dimethylamine with ethyl acrylate is shown in Scheme 2.3.3. [90]

The nucleophile in the *aza*-Michael reaction is either a primary or secondary amine, and as they are both nucleophilic and basic, there is normally no need for an extra base for the reaction to be successful. [90] In general, secondary amines are more nucleophilic than primary amines and therefore more reactive and do not need as harsh reaction conditions. [93]



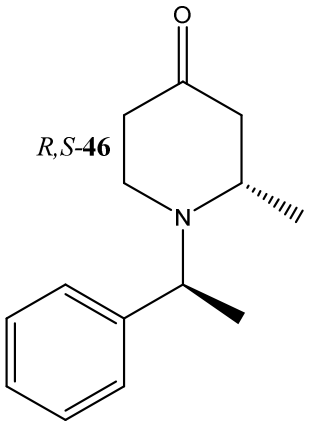
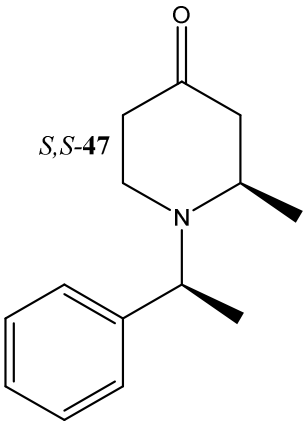
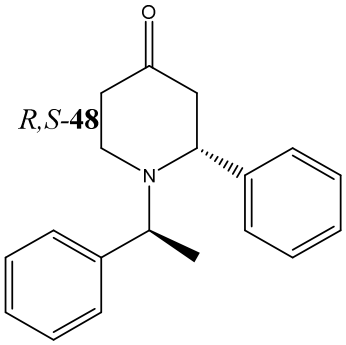
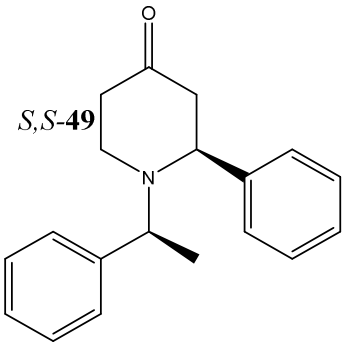
Scheme 2.3.3 *Aza*- Michael addition of dimethylamine with ethyl acrylate[90]

When the *aza*- Michael donors are not reactive enough, catalysts are used. They can either increase the amine's nucleophilicty or the acceptor's electrophilicity. [94, 95] Popular catalytic systems are Lewis acids such as copper and nickel complexes, triflates and transition and main-group metal chlorides,[96] Brønsted acids,[91, 97] lipases,[98] silica gel[99] and copper (II) oxide nanoparticles. [100, 101] Catalysts can improve the yield of *aza*-Michael reactions, but the results depend on the reaction conditions, solvents and the steric hindrance of the Michael acceptor and donor.

Preparation of diastereomeric 2-substituted-4-piperidones

For the preparation of diastereomeric 2-substituted 4-piperidones **46, 47, 48** & **49**, we used protocol based on a patent by Guzzo et al.[57,102] To a stirred solution of benzylamine in acetonitrile, aqueous $NaHCO_3$ solution was added and cooled to 16° C. Divinylketones **39** or **43** in acetonitrile were added slowly over 40 minutes. After addition, the solution was heated to reflux for 1h. The resulting solution was stirred for 15 minutes. Upon workup purification of the crude residue by column chromatography afforded the desired 2-substituted 4-piperidones as pure products in moderate to good combined yields. Table 2.3.1 records starting materials and yields of the diastereomeric piperidones that were synthesised.

Table 2.3.1 Synthesis of diastereomeric 2-substituted 4-piperidones

Ketone	Products	Yields
Ketone 39	 *R,S*-**46** +  *S,S*-**47**	19% (**46**) + 10% (**47**) + 3% (**46**&**47**)
Ketone 43	 *R,S*-**48** +  *S,S*-**49**	52% (**48**) + 8% (**49**) Scale up: 31% (**48**) + 5% (**49**) 4% (**48**&**49**)

Reaction conditions: Ketone, *S*-*α*- phenylethylamine, NaHCO3, CH3CN, 16°C, 40 min, 95°C, 1.5 h.

The isolation of these products proved to be quite difficult due to their similar R_f values, so column chromatography had to be repeated several times in order to obtain the pure diastereomers. A certain amount of mixed fractions was still present after repeating the column chromatography 3 times. The major products of the 2-phenyl diastereomeric piperidones possessed higher R_f values in comparison to the minor products. According to Pöschl,[57] the products with the higher R_f were assigned as *R,S*-**46** and *R,S*- **48**. Analysis of ^{1}H-NMR and ^{13}C-NMR showed the successful preparation of the desired pure products.

3 Experimental

Infrared (IR) spectra were recorded as either thin films on NaCl plates or as Durasampl IR II using a Perkin Elmer 100 FTIR spectrophotometer. Only significant absorptions (ν_{max}) are reported and alle absorptions are recorded in wavenumbers (cm^{-1}).

Proton magnetix resonance spectra (^{1}H-NMR) were recorded at 400 MHz using a Bruker spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to the residual protonated solvent peak. The order of citation in parentheses is (i) multiplicity (s, singulet; d, doublet; t, triplet; q, quartet and m, multiplet), (ii) soupling constant (*J*) quoted in Hertz to the nearest 0.5 Hz), (iii) number of equivalent nuclei (by integration), coupling constant (*J*) quoted in Hertz to the nearest 0.5 Hz, (iv) assignment.

Carbon magnetic resonance spectra (^{13}C-NMR) were recorded at 100.6 MHz using a Bruker spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to the appropriate solvent peak. The assignment is quoted in parentheses.

Low resolution mass spectra (m/z) were recorded using LCQ DECA XP instrument by electron spray ionization (ESI). Only molecular ions and major fragments of the molecular ions are reported. Accurate masses were determined using QTOF at King's College London.

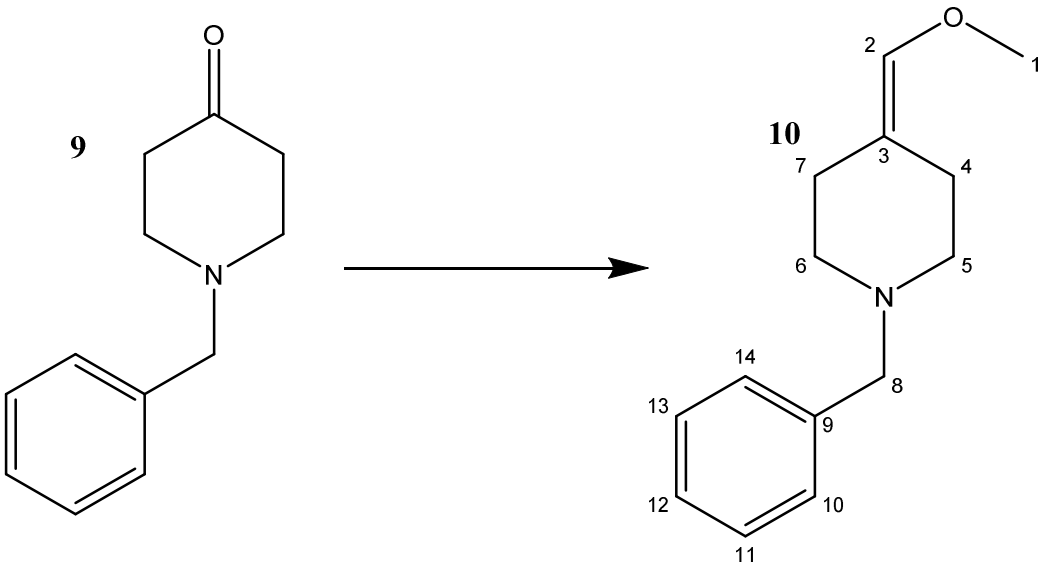
Melting points (mp) were measured on Barnstead Electrothermal 9100 apparatus and are uncorrected.

Flash Chromatography was carried out using Silica Gel (Aldrich, 230-400 mesh) as the stationary phase. Thin Layer Chromatography was carried out on aluminium plates precoated with Silica (Merck Silica Gel 60 F_{254} on aluminium) which was visualized by the quenching of ultraviolet fluorescence (λmax= 254nm) and / or by staining with potassium permanganate solution followed by heat.

All reactions were carried out at atmospheric pressure with stirring unless otherwise stated. All reagents were used as received unless otherwise stated. The fractions of light petroleum ether boiling between 40 and 60°C are referred to as "hexanes". Solvents were evaporated using a Büchi Rotavapor V800. Systematic names were derived using the IUPAC recommendations.

3.1 Experimental Procedures

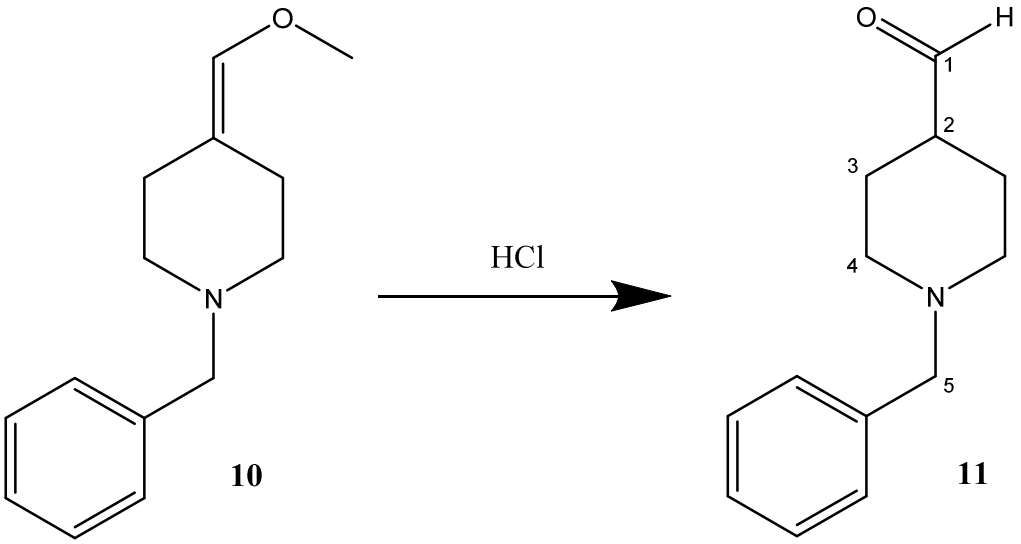
1-Benzyl-4-(methoxymethylene) piperidine 10



Methoxymethyltriphenylphosphonium chloride (2.17 g, 6.33 mol, 1.5 equiv) and molecular sieves (0.68 g) are placed in a dry flask and added with THF (11 ml) under N_2 atmosphere. The mixture was cooled down to -70°C in a dry ice/acetone cooling bath and a 2M solution of lithium diisopropylamide in THF/ heptane/ ethylbenzene (3.2 ml, 6.33 mol, 1.5 equiv) was added slowly, then the mixture was stirred at -70°C for 5 minutes and let it warm to room temperature while stirring for 20 min. Then the reaction was cooled to -20°C in an ice salt bath 3:1 and a solution of N-benzyl-4-piperidone **9** (0.8 g = 0.78 ml, 4.22 mol, 1.0 equiv) in absolute THF (7 ml) was added slowly. Then the reaction was stirred at -20°C for 15 min, then allowed to warm to room temperature and stirred for 16 h. 1M NH_4Cl solution (10 ml) and ethyl acetate (20 ml) were added and stirred vigorously for 5 min. The phases were separated in a separating funnel and the aqueous phase was again extracted with ethyl acetate. The combined organic layers were washed with water and brine and dried over $MgSO_4$, then filtered and the solvent was removed under reduced pressure. Purification by column chromatography (EA: Hex 1: 1.5) gave pale yellow oil **10** (888 mg, 97 %); R_f 0.40 (EA: Hex 2: 1); ν_{max} (film) 2931, 2795, 2174, 1691, 1584, 1453, 1339, 1225, 1121, 986, 839,

735, 697; δ_H (400 MHz,$CDCl_3$) 7.21-7.32 (5H, m, 5 x Ar. H), 5.76 (1H, s, H-2), 3.52 (3H, s, H-1), 3.49 (2H, s, H-8), 2.38 (4H, t, *J* 5.57 Hz, 2x H-5, 2x H-6), 2.29 (2H, t, *J* 5.6 Hz, 2x H-4), 2.05 (2H, t, *J* 5.35 Hz, 2x H-7); δ_C (100.6 MHz, $CDCl_3$) 139.77 (C2), 138.72 (*ipso* Ar. C-9), 129.38 (*ortho* Ar. C-10&14), 128.34 (*meta* Ar. C-11&13), 127.11 (*para* Ar. C-12), 114.98 (C-3), 63.43 (C-8), 59.57 (C-1), 55.43 (C-6), 54.25 (C-5), 29.89 (C-7), 25.36 (C-4);

_N_-Benzyl-4-formyl-piperidine 11



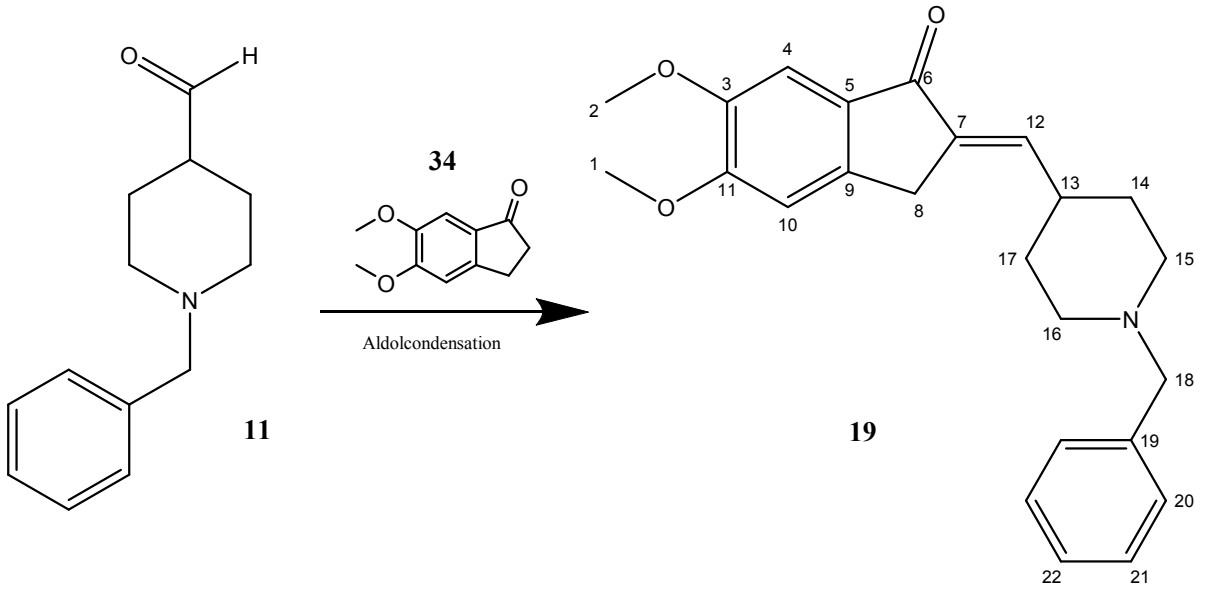
10 **11**

1.6 N HCl (8.5 ml) was added to 1- Benzyl-4-(methoxymethylene) piperidine **10** (850 mg, 3.91 mmol) in THF (8.5 ml) and stirred at 45°C for two hours. THF was then evaporated under reduced pressure and the residue was diluted with water. The pH was adjusted to 10 by the addition of an aqueous Na_2CO_3 solution. The aqueous phase was extracted with CH_2Cl_2 (3x 30ml) and the combined organic layers were washed with water and brine (50ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the aldehyde N-Benzyl- 4- formyl- piperidine **11** was obtained as pale yellow oil (695 mg, 87%); The product could be used for the next step without further purification; R_f 0.23 (EA: Hex 2:1); ν_{max} (film) 3004, 2929, 2757, 1688 (C=O), 1646, 1498, 1482, 1307, 1214, 1076, 906, 803, 732; δ_H (400 MHz,$CDCl_3$) 9.57 (d, 1H, *J* 1.15 Hz, -

C<u>H</u>O), 7.18-7.25 (m, 5H, 5x Ar. C), 3.43 (s, 2H, C-5), 2.75 (2H, dt, *J* 3.52 Hz, 7.51 Hz, 2x H4), 2.13-2.20 (1H, m, H-2), 2.04 (2H, td, *J* 2.54 Hz, 11.23 Hz, 2x H-4), 1.79-1.84 (2H, m, 2x H-3), 1.57-1.67 (2H, m, 2x H-3); δ_C (100.6 MHz, $CDCl_3$) 204.30 (C-1), 138.36 (*ipso* Ar.), 129.31 (*meta* Ar.), 128.43 (*ortho* Ar.), 127.27 (*para* Ar. C), 63.43 (C-5), 52.67 (C-4), 48.18 (C-2), 25.62 (C-3);

In agreement with published data [103, 104]

_E_- 2- ((1-Benzylpiperidin-4-yl) methylene)-5, 6- dimethoxy- 2, 3- dihydro- 1H-inden- 1-one[105] **19**

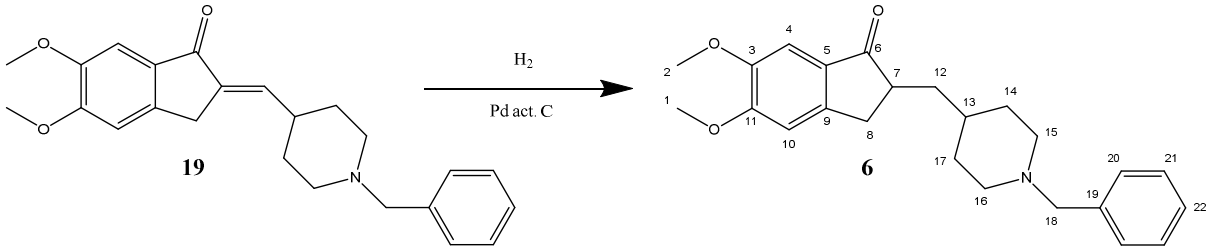


5, 6- Dimethoxy-1-indanone **34** (567.74 mg, 0.00295 mol, 1.0 equiv) was added to a solution of N-Benzyl-4-formyl-piperidine **11** (600 mg, 0.00295 mol, 1.0 equiv) in methanol (16 ml) and the system was put under an atmosphere of nitrogen. Then the mixture was heated to 80°C and a solution of sodium methoxide (28% in methanol,

0.192 ml, 3.54 mmol, 1.2 equiv) was added. The mixture was stirred under reflux for 75 min, then allowed to cool down to room temperature. The product was precipitated from the reaction mixture upon cooling with ice bath and filtrated. The filtrate was removed under reduced pressure. The reaction afforded product **19** (981.1 mg, 88 %) as pale pink solid; R_f 0.31 (EA: Methanol 9:1); melting point: 172- 175 °C; ν_{max} (solid) 2930, 1688 (C=O), 1586, 1498, 1452, 1369, 1309, 1214, 1070, 981, 733, 696; δ_H (400 MHz,$CDCl_3$) 7.24-7.31 (6H, m, 2x *ortho*, 2x *meta*, 1x *para*, H-4), 6.88 (1H, s, H-10), 6.64 (1H, d, *J* 9.69Hz, H-12), 3.95 (3H, s, H_3CO-C11), 3.91 (3H, s, H_3CO-C3), 3.57 (2H, "d", *J* 1.40, H-8), 3.51 (2H, s, H-18) 2.91 (2H, d, *J*11.14, 1x H-15, 1x H-16), 2.27-1.35 (1H, m, H-13), 2.03 (2H, dt, *J* 2.60Hz, 11.36 Hz, 1x H-15, 1x H-16), 159-1.69 (4H, m, H-14 & H-17); δ_C (100.6 MHz, $CDCl_3$) 192.83 (C5), 155.48 (C3), 149.69 (C11), 144.72 (C5), 140.10 (C12), 135.80 (C9), 132.07 (C7), 129.41 (C20), 128.40 (C21), 127.21 (C22), 107.42 (C10), 105.22 (C4), 63.73 (C18), 56.46 (C11-OCH_3), 56.36 (C3-OCH_3), 53.29 (C15&16), 37.51 (C13), 31.44 (C14&17), 29.70 (C8)

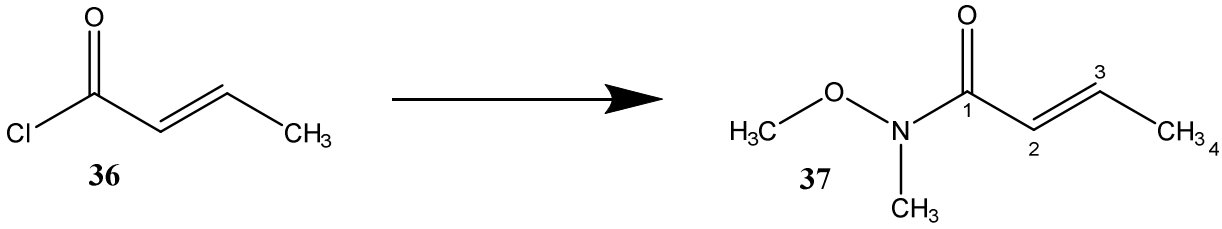
In agreement with published data [105,72]

2-((1-Benzylpiperidin-4-yl) methyl)-5, 6- dimethoxy-2, 3-dihydro-1H-inden-1-one (Donepezil) 6



A solution of E-2-((1-Benzylpiperidin-4-yl)methylene)-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one (300 mg, 0.795 mmol) in THF (23 ml) was hydrogenated over palladium 10% on activated charcoal (30 mg) for 6h at 1.1 atm. The reaction mixture was filtered through Celite and washed with CH_2Cl_2 (58 ml). The solvent was removed under reduced pressure and the product was obtained as white solid. Purification by column chromatography (CHCl3: Methanol 15: 1) afforded product **6** (220 mg, 73%) as pale yellow solid. R_f 0.35 (EA: Methanol 9:1); melting point: 86- 89 °C; ν_{max} (solid) 2915, 1687 (C=O), 1588, 1496, 1452, 1311, 1261, 1220, 1104, 1033, 731, 695; δ_H (400 MHz, $CDCl_3$) 7.21-7.30 (5H, m, Ar. H-20, 21, 22), 7.14 (1H, s, H-4), 6.83 (1H, s, H-10), 3.94 (3H, s, H_3CO-C11), 3.88 (3H, s, H_3CO-C3), 3.50 (2H, s, H-18), 3.17-3.24 (2H, dd, *J* 8.11, 17.64 1x H-8), 2.87-2.91 (2H, m, 1x H-15, 1x H-16), 2.66-2.70 (2H, m, 1x H-8, H-7), 1.86-1.98 (3H, m, 1x H-12, 1x H-15, 1x H-16), 1.63-1.73 (2H, m, 1x H-14, 1x H-17), 1.46-1.48 (1H, m, H-13), 1.26-1.38 (3H, m, 1x H-12, 1x H-14, 1x H-17); δ_C (100.6 MHz, $CDCl_3$) 207.96 (C6), 155.54 (C11), 149.51 (C3), 148.88 (C9), 138.50 (*ipso* Ar. C.), 129.35 (*ortho* Ar. C) 128.23 (*meta* Ar. C), 127.02 (*para* Ar. C), 107.44 (C10), 104.46 (C4), 63.57 (C18), 56.31 & 56.19 (1xC3 O$\underline{C}H_3$, 1xC11 O$\underline{C}H_3$), 53.88 & 53.86 (C 15& 16), 45.56 (C7), 38.81 (C12), 34.56 (C13), 33.44 (C8), 33.11& 31.88 (C14 & 17); *In agreement with published data* [106]

(*E*)- N- Methoxy- N- methylbut- 2- enamide 37



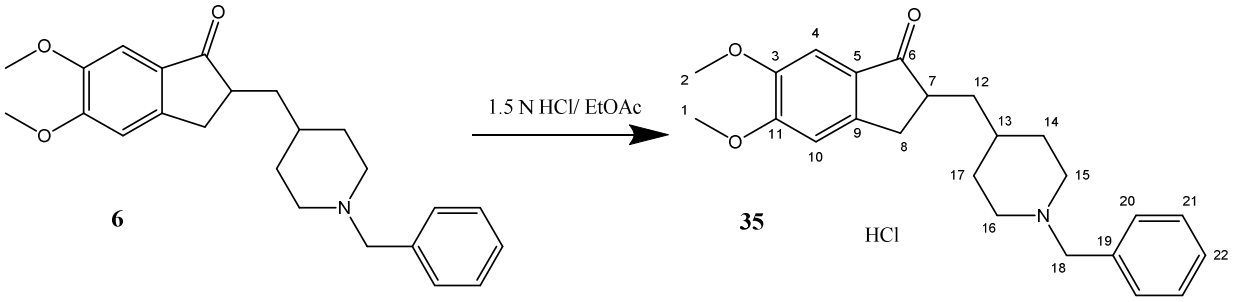
300 mg of N, O- dimethylhydroxylamine hydrochloride (3.08 mmol, 1.0 equiv), 8 ml dichlormethane and 397 mg = 0.34 ml trans-crotonylchloride (3.54 mmol, 1.15 equiv) was added to a 50 ml vacuum flame dried round bottom flask under N_2. The reaction mixture was stirred in an ice- water bath; 0.54 ml of pyridine (6.77 mmol, 2.2 equiv) was added to the flask dropwise. The mixture was then stirred at 0°C for 20 min, then allowed to warm to room temperature (30 min) and diluted with EtOAc (40 ml). The organic layer was washed with 30 ml of 1N HCl, 30 ml of saturated sodium bicarbonate & 30 ml of brine, then dried with $MgSO_4$ and filtrated. The filtrate was concentrated *in vacuo*. H-NMR of crude Weinreb Amide **37** (218 mg, 55 %) showed minor inpurifications, no purification was attempted.

Scale up:

2.5 g of N, O- dimethylhydroxylamine hydrochloride (25.63 mmol, 1.0 equiv), 67 ml dichlormethane and 3.5 g = 3.25 ml trans-crotonylchloride (29.47 mmol, 1.15 equiv) was added to a 250 ml vacuum flame dried round bottom flask under N_2. The reaction mixture was stirred in an ice- water bath; 4.5 ml of pyridine (56.39 mmol, 2.2 equiv) was added to the flask dropwise. The mixture was then stirred at 0°C for 20 min, then allowed to warm to room temperature (30 min) and diluted with EtOAc (333 ml). The organic layer was washed with 250 ml of 1N HCl, 250ml of saturated sodium bicarbonate & 250 ml of brine, then dried with $MgSO_4$ and filtrated. The filtrate was concentrated *in vacuo*. The Weinreb Amide was purified by column chromatography (Hexane: ethyl acetate 3:1 → 1:1). The reaction afforded product **37** (2.15 g, 65 %) as pale yellow oil; R_f 0.28 (EtOAc: Hex 1:1); ν_{max} (film) 2969, 1667, 1634, 1446, 1411, 1379, 1178, 1083, 1009, 963, 912, 815, 674, 620; δ_H (400 MHz, $CDCl_3$) 6.91-7.00 (1H, m, H-3), 6.39 (1H, dd, *J* 1.23 Hz, 15.14 Hz, H-2), 3.67 (3H, s, OC$\underline{H_3}$), 3.21 (3H, s, NC$\underline{H_3}$), 1.88 (3H,

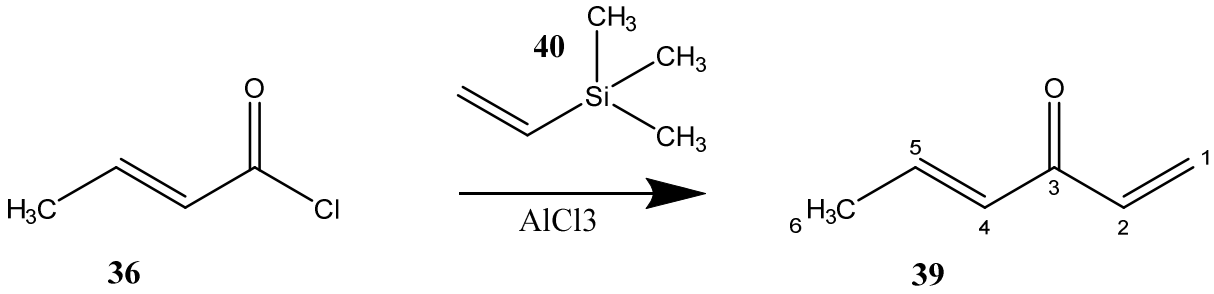
m, H-4); δ_C (100.6 MHz, $CDCl_3$) 167.18 (C1), 143.14 (C3), 120.34 (C2), 61.86 ($O\underline{C}H_3$), 32.51 ($N\underline{C}H_3$), 18.43 (C4)

2- ((1- benzylpiperidin- 4- yl) methyl)- 5, 6- dimethoxy- 2, 3- dihydro- 1H- inden- 1- one hydrochloride (Donepezil HCl)



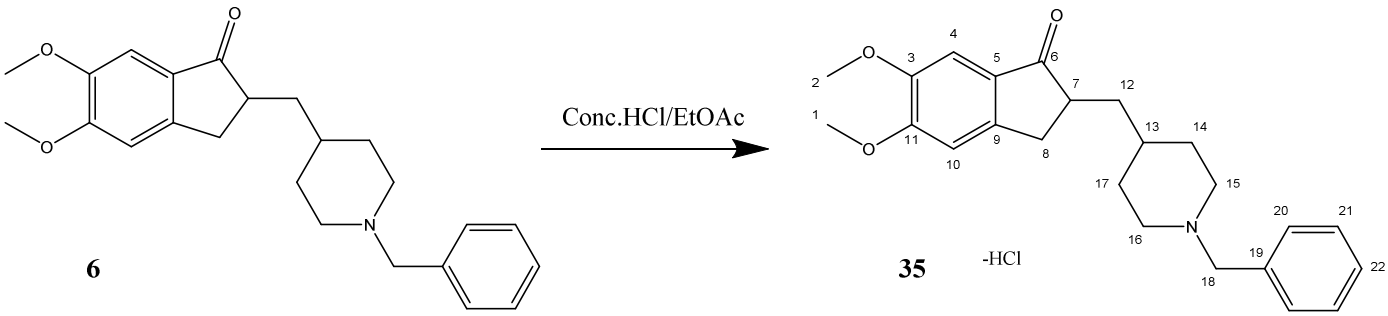
To 70 mg Donepezil (0.184594 mmol) 1.5 N aqueous HCl (0.32 ml) was added and stirred for 15 min at room temperature. Then 0.21 ml of demineralized water was added to see phase separation better and stirred for another 15 min at r.t. The aqueous phase was extracted with EtOAc (2x 20 ml) and the organic layer was discarded. Then the aqueous phase was extracted with $CHCl_3$ (2x 20 ml), and the organic phase was washed with demineralized water (2x 20 ml) and brine (20 ml). The $CHCl_3$ layers were dried over $MgSO_4$ and the solvent was evaporated. The reaction afforded product **35** (18.5 mg 24%) as white solid. R_f 0.34 (EtOAc: Methanol 9:2); Melting point: 206- 210 °C; ν_{max} (solid) 2928, 2485, 1686, 1590, 1500, 1455, 1314, 1265, 1117, 1035, 748, 698, 559; δ_H (400 MHz, $CDCl_3$) 7.32-7.42 (5H, m, Ar. H), 7.12 (1H, s, H-4), 6.83 (1H, s, H-10), 3.94 (3H, s, H-2), 3.88 (3H s, H-1), 3.72 (2H, m, H-8), 3.23 (1H, dd, *J* 9.26Hz, 17. 32 Hz, H-7), 2.62-2.68 (2H, m), 1.84-2.02 (2H, m), 1.63-1.84 (6H, m, H-12, H-14, H-17), 1.23-1.39 (4H, m); δ_C (100.6 MHz, $CDCl_3$) 207.60 (C6), 155.70 (C11), 149.63 (C9), 148.86 (C3), 131.31 (C19), 129.82 (C5), 129.30 (C20& 21), 128.76 (C22), 107.37 (C10), 104.49 (C4), 59.66 (C18), 56.37 (C1& 2), 56.23 (C15& 16), 45.12 (C7), 38.28 (C12), 33.73 (C8), 31.37 (C14 & 17), 29.83 (C13)

_E_- 1, 4- Hexadien- 3- one 39



3.99 g of Aluminium chloride (29.93 mmol, 1.0 equiv) in 5.87 ml Dichlormethane was put under an atmosphere of nitrogen and cooled to -35 °C with an ethylene glycol / ethanol (70%/ 30%) bath. Then 2.87 ml of 2-trans-crotonyl chloride in 5.87 ml CH_2Cl_2 were added cautiously and the mixture was stirred for 15 min. 4.35 ml vinyltrimethylsilane in CH_2Cl_2 were added slowly over 30 min, and the mixture was stirred for 30 min and cooled down to – 50°C with an ethylene glycol/ ethanol (50%/ 50%) bath. Then 49.88 ml of a cold 3M potassium carbonate solution was added cautiously and the reaction flask was allowed to warm to room temperature and the mixture was kept stirring for another 30 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x 60 ml). The organic phases were combined, washed with water (60 ml) and brine (60 ml), dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure, affording product **39** (3.5 g, 122 %) as crude red oil; R_f 0.4 (EtOAc: Hex 1:5); ν_{max} (film) 2968, 1694, 1667, 1629, 1441, 1376, 1288, 1128, 1085, 968, 842, 741, 659; δ_H (400 MHz, $CDCl_3$) 6.96 (1H, dq, *J* 15.5 Hz, 6.8 Hz, H-5), 6.59 (1H, dd, *J* 17.4 Hz, 10.6 Hz, H-2), 6.39 (1H, dq, *J* 15.6 Hz, 1.6 Hz, H-4), 6.28 (1H, dd, *J* 17.4 Hz, 1.3 Hz, H-1 *trans*), 5.81 (1H, dd, *J* 10.6 Hz, 1.3 Hz, H-1 *cis*), 1.94 (3H, dd, *J* 6.8 Hz, 1.6 Hz, H-6); δ_C (100.6 MHz, $CDCl_3$) 189.83 (C3), 144.31 (C5), 134.98 (C2), 129.87, 128.51, 18.64 (C6)

2- ((1- benzylpiperidin- 4- yl) methyl)- 5, 6- dimethoxy- 2, 3- dihydro- 1H- inden- 1- one hydrochloride (Donepezil HCl)



6 **35**

To 57 mg of Donepezil (0.15031 mmol) in ethyl acetate & 2 ml demineralized water conc. HCl was added until a pH of 2. The EtOAc layer was discarded and the acidic aqueous layer was extracted with CH_2Cl_2 (3x 20 ml). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent was evaporated. The reaction gave crude product **35** (70 mg, 91%) as white solid.

Scale up:

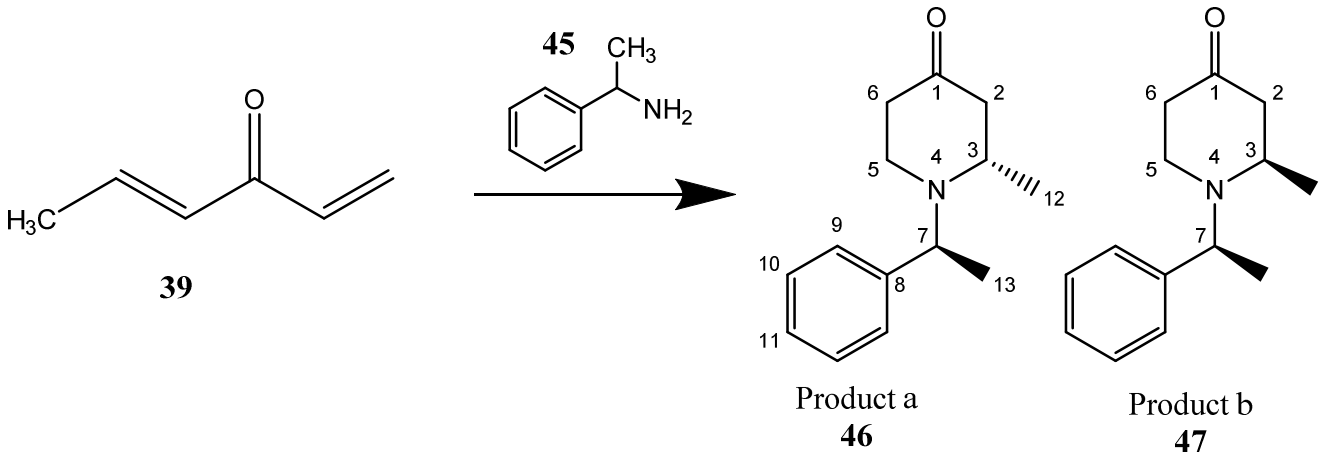
To 70 mg of Donepezil (0.184594 mmol) in ethyl acetate & 2 ml demineralized water conc. HCl was added until a pH of 2. The EtOAc layer was discarded and the acidic aqueous layer was extracted with CH_2Cl_2 (3x 30 ml). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent was evaporated. The reaction gave crude product **35** (50.8 mg, 66%) as white solid. R_f 0.34 (EtOAc: Methanol 9:2); Melting point: 206- 210 °C; ν_{max} (solid) 2928, 2485, 1686, 1590, 1500, 1455, 1314, 1265, 1117, 1035, 748, 698, 559; δ_H (400 MHz, $CDCl_3$) 7.40 (3H, t, *J* 2.86 Hz, Ar. H), 7.09 (1H, s, H-4), 6.82 (1H, s, H-10), 4.07-4.12 (2H, m, H-18), 3.93 (3H, s, H-2), 3.87 (3H, s, H-1), 3.35 (2H, m, H-8), 3.25 (1H, dd, *J* 7.97 Hz, 17.39 Hz, H-7), 2.59-2.67 (4H, m, H-15, H-16), 1.81-1.87 (6H, m, H-12, H-14, H-17), 1.45-1.49 (1H, m, H-13); δ_C (100.6 MHz, $CDCl_3$) 207.27 (C6), 155.91 (C11), 149.77 (C9), 148.89 (C3), 131.50 (C19), 130.02 (C5), 129.40 (C20& 21), 129.14 (C22), 107.56 (C10), 104.50 (C4), 60.59 (C18), 56.46 (C1& 2), 56.29 (C15& 16), 44.59 (C7), 38.34 (C12), 34.06 (C8), 31.12 (C14 & 17), 29.66, 28.85 (C13)

Recrystallisation of Donepezil HCl

112 mg of Donepezil HCl (0.27 mmol) were recrystallised in MeOH/ isopropylether (1:1, 2 ml), after 1 h of stirring at 5°C, the product was filtered and washed with isopropylether (2 ml), and dried in vacuum at 30 mm for 6 h at room temperature to afforded Donepezil HCl (86 mg, 77%) as white solid; δ_H (400 MHz, $CDCl_3$) 7.45(m, 3H, Ar. H), 7.11 (1H, s, H-4), 6.84 (1H, s, H-10), 4.13 (2H, m, H-18), 3.96 (3H, s, H-2), 3.89 (3H, s, H-1), 3.44-3.49 (2H, m, H-8), 3.30 (1H, m, H-7), 2.66 (4H, m, H-15, H-16), 1.60-2.11 (6H, m, H-12, H-14, H-17), 1.41 (1H, m, H-13); δ_C (100.6 MHz, $CDCl_3$) 207.16 (C6), 155.88 (C11), 149.77 (C9), 148.85 (C3), 131.75 (C19), 130.31 (C5), 129.48-129.07 (C20& 21), 128.21 (C22), 107.55 (C10), 104.45 (C4), 61.33 (C18), 56.24- 56.44 (C1& 2), 52.57-52.77 (C15& 16), 44.29 (C7), 38.36 (C12), 34.39 (C8), 32.36, 29.67, 28.55

(*R*)- 2- methyl- 1- ((*S*)- 1- phenylethyl) piperidin- 4- one 46

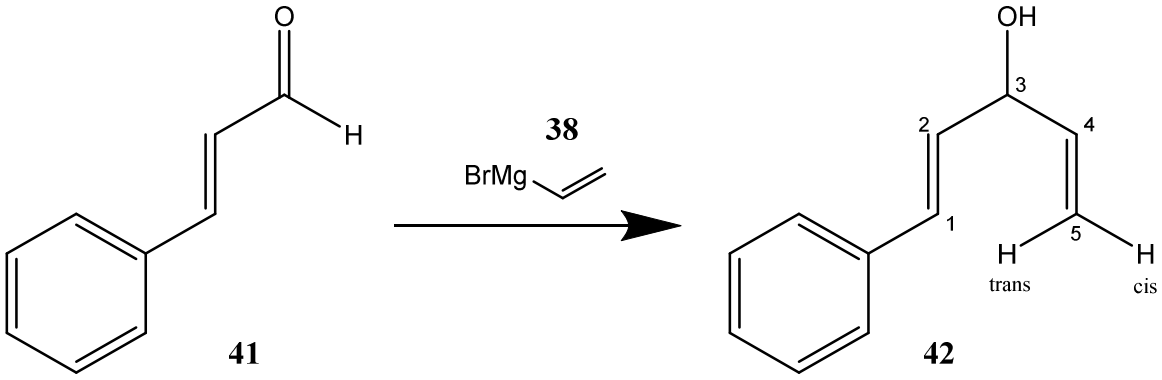
(*S*)- 2- methyl- 1- ((*S*)- 1- phenylethyl) piperidin- 4- one 47



L- alpha- Methylbenzylamine **45** (5.007 g, 41.356 mmol, 1.4 equiv) was dissolved in acetonitrile (30 ml) and a solution of aqueous $NaHCO_3$ (18.05 ml of 1.8M solution ≙ 2.729g $NaHCO_3$, 1.1 equiv) was added. The suspension was cooled to 16°C and *E*- 1, 4- Hexadien- 3- one **39** (2.84 g, 29.54 mmol, 1. 0 equiv) in acetonitrile (30.5 ml) was added slowly. The reaction mixture was stirred at reflux for 1.5h and acetonitrile was evaporated *in vacuo*. Then ethyl acetate was added (60 ml) and the solution was stirred for 15 min, layers were separated, and the aqueous layer was again extracted with ethyl acetate (2x 60 ml). The combined organic layers were washed with water (60 ml) and brine (60 ml), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by column chromatography (Hex: EtOAc 6:1 → 3:1) afforded **product 46** as yellow oil, eluting first (1.23 g, 19%); R_f 0.25 (EtOAc: Hex 1: 4); ν_{max} (film) 2968, 1716 (C=O), 1492, 1451, 1377, 1229, 1138, 1080, 924, 764, 699, 563; δ_H (400 MHz, $CDCl_3$) 7.21- 7.43 (5H, m, Ar. H), 3.96- 4.01 (1H, q, *J* 6.01 Hz, H-7), 3.32-3.39 (1H, m, H-3), 2.59- 2.76 (3H, m, 1x H-2, H-5), 2.14-2.34 (3H, m, 1x H-2, H-6), 1.31 (3H, d, *J* 6.71 Hz), 1.12 (3H, d, *J* 6.51 Hz); δ_C (100.6 MHz, $CDCl_3$) 210.59 (C1), 145.40 (C8), 128.53 (C9), 127.42 (C10), 127.06 (C11), 57.84 (C7), 52.62 (C3), 48.97 (C5), 44.06 (C2), 41.54 (C6), 16.55 (C13), 16.41 (C12) *In agreement with published data* [81]

and **prodcut 47** as yellow solid (661.1 mg, 10%); R_f 0.11 (EtOAc: Hex 1: 4); melting point: 72- 74 °C; ν_{max} (solid) 2967, 2816, 1715 (C=O), 1453, 1375, 1350, 1284, 1227, 1075, 767, 701, 553; δ_H (400 MHz, $CDCl_3$) 7.23-7.33 (5H, m, Ar. H), 3.87-3.92 (1H, q, *J* 6.37 Hz, H-7), 3.10-3.18 (1H, m, H-3), 2.88-2.98 (2H, m, H-5), 2.47- 2.57 (2H, m, 1x H- 2, 1x H-6), 2.26-2.33 (1H, m, 1x H-6), 2.05-2.10 (1H, m, 1x H-2), 1.40 (3H, d, *J* 6.68), 1.02 (3H, d, *J* 6.58 Hz); δ_C (100.6 MHz, $CDCl_3$) 210.59 (C1), 144.21 (C8), 128.63 (C9), 127.43 (C10), 127.29 (C11), 58.94 (C7), 52.53 (C3), 48.45 (C5), 43.27 (C2), 41.78 (C6), 21.99 (C13), 14.88 (C12) *In agreement with published data* [107]

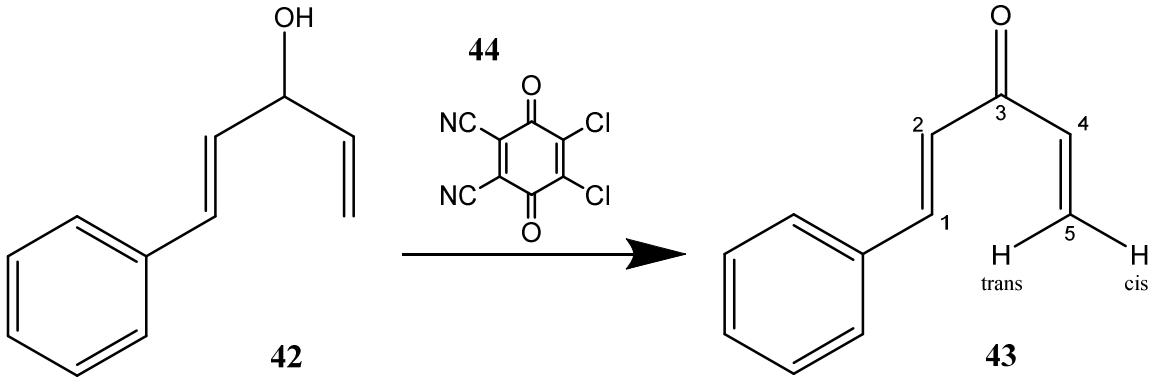
(*E*)-1-phenylpenta-1, 4-dien-3-ol 42



To an ice cooled solution of vinylmagnesium bromide in THF (0.7M in THF; 118 ml, 83.24 mmol) Cinnamaldehyde **41** (10 g = 9.524 ml, 75.67 mmol, 1.0 equiv) was added dropwise under an atmosphere of nitrogen. After stirring at room temperature for 1.5 h the mixture was poured into a mixture of saturated NH_4Cl (70 ml) & ice (70 g) and stirred for 15 min. Then the aqueous phase was extracted with ether and the combined organic layers were dried over $MgSO_4$. Concentration *in vacuo* afforded crude product **42** (12.30 g, 101.56 %) as red oil. 6g of crude product **42** were purified by column chromatography before going on with the next step. Column chromatography EA: Hex 1: 8 → 1: 4 afforded pure product **42** as yellow oil (4.329 g, 72%); R_f 0.19 (EA: Hex 1: 4); ν_{max} (film) 3354 (C-OH), 2922, 1657, 1598, 1493, 1449, 1331, 966, 924, 750, 692, 567; δ_H (400 MHz, $CDCl_3$) 7.15- 7.33 (5H, m, Ar. H), 6.55 (1H, d, *J* 15.95 Hz, H-1), 6.17 (1H, dd, *J* 6.42 Hz, 15.94 Hz, H-2), 5.87- 5.95 (1H, m, H-4), 5.27 (1H, dt, *J* 1.36 Hz, 17.21 Hz, H-5 *trans*), 5.13 (1H, dt, *J* 1.29 Hz, 10.37 Hz, H-5 *cis*), 4.74 (1H, "d", *J* 2.52 Hz, H-3); δ_C (100.6 MHz, $CDCl_3$) 139.48, 136.80 (C1), 131.08 (C4), 130.56 (C6), 128.80 (C8), 128.02 (C9), 126.77 (C7), 115.65 (C5), 74.06 (C3) *In agreement with published data* [108]

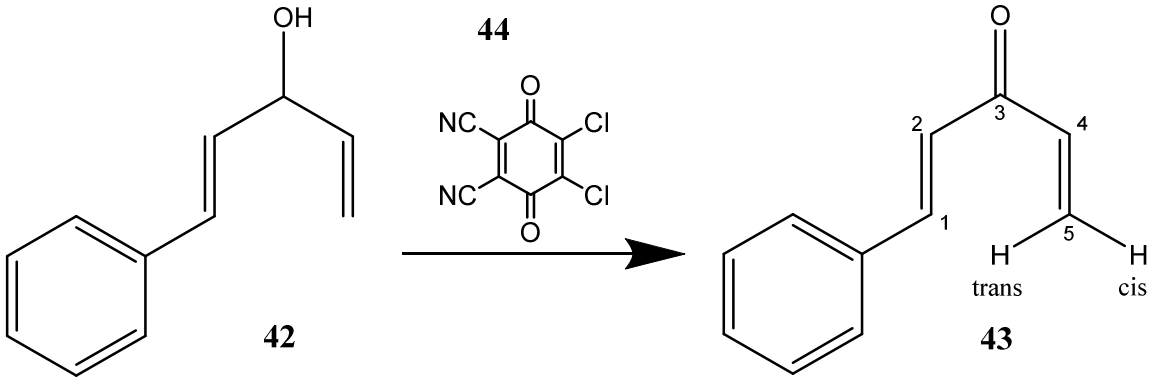
6g of crude product **42** were used for the next step without further purification

(*E*)- 1- phenylpenta- 1, 4- dien- 3- one 43



To pure alcohol **42** (4.33 g, 27.04 mmol, 1.0 equiv) in dry DCM (117 ml) 2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone (DDQ) **44** (7.37 g, 32.45 mmol, 1.2 equiv) was added and stirred at room temperature for 24h, then filtered and washed with dichlormethane (85 ml). Concentration under reduced pressure, purification by column chromatography (EA: Hex 1: 10) gave product **43** as yellow oil (3.2 g, 75%); R_f 0.25 (EA: Hex 1: 8); ν_{max} (film) 3026, 2921, 1655 (C=O), 1621, 1593, 1449, 1401, 1198, 1102, 982, 779, 687; δ_H (400 MHz, $CDCl_3$): 7.68 (1H, d, *J* 16.02 Hz, H-1), 7.57-7.60 (2H, m, *ortho* -H), 7.40-7.41 (3H, m, 2x *meta*- H, 1x *para*-H), 7.01 (1H, d, *J* 7.01 Hz, H-2), 6.72 (1H, dd, *J* 10.61 Hz, 17.42 Hz, H-4), 6.38 (1H, dd, *J* 1.22 Hz, 17.42 Hz, H-5 *trans*), 5.89 (1H, dd, *J* 1.22 Hz, 10.61 Hz, H-5 *cis*); δ_C (100.6 MHz, $CDCl_3$) 189.67 (C3), 144.10 (C1), 135.61 (C4), 134.81 (*ipso* C), 130.73 (*para* C), 129.11 (*meta* C), 128.69 (C5), 128.52 (*ortho* C), 124.30 (C2) *In agreement with published data* [109, 110]

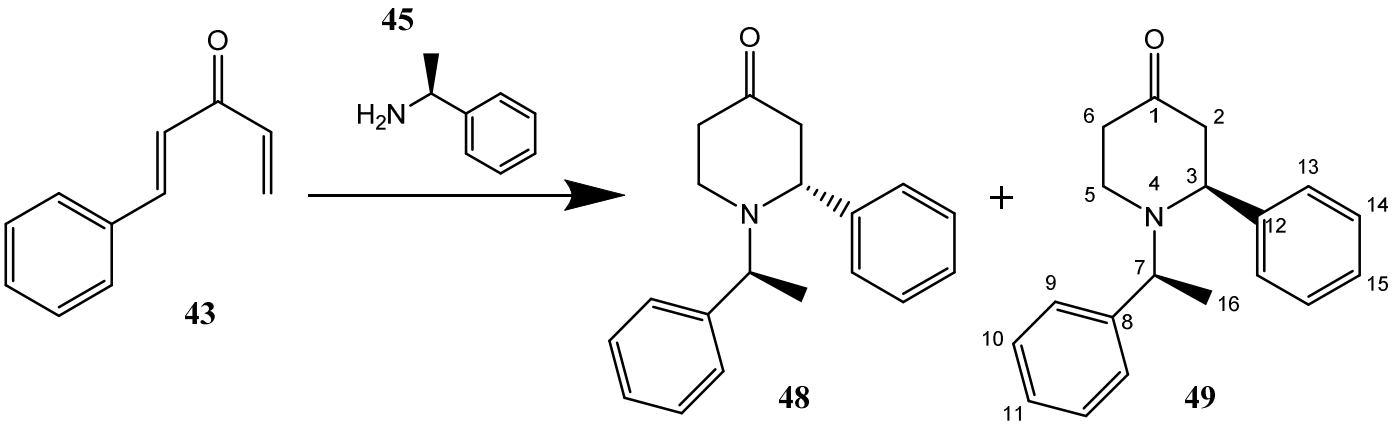
(*E*)- 1- phenylpenta- 1, 4- dien- 3- one 43



To crude alcohol **42** (6 g, 37.48 mmol, 1.0 equiv) in dry DCM (117 ml) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (10.22 g, 44.98 mmol, 1.2 equiv) was added and stirred at room temperature for 24h, then filtered and washed with dichloromethane (110 ml). Concentration under reduced pressure, purification by column chromatography (EA: Hex 1:10) gave crude ketone **43** as yellow oil (2.72 g, 46%) R_f 0. 25 (EA: Hex 1: 8) ν_{max} (film) 3026, 2921, 1655 (C=O), 1621, 1593, 1449, 1401, 1198, 1102, 982, 779, 687; δ_H (400 MHz, $CDCl_3$) 7.68 (1H, d, *J* 16.02 Hz, H-1), 7.58-7.60 (2H, m, *ortho* Ar. H), 7.40-7.41 (3H, m, *meta* Ar. H, *para* Ar. H), 7.01 (1H, d, *J* 16.01 Hz, H-2), 6.68-6.75 (1H, m, H-4), 6.38 (1H, dd, *J* 1.21 Hz, 17.42 Hz, *trans* H-5), 5.89 (1H, dd, *J* 1.19 Hz, 10.62 Hz, *cis* H-5)**;** δ_C (100.6 MHz, $CDCl_3$) 189.67 (C3), 144.10 (C1), 135.61 (C4), 134.81 (ipso Ar. C), 130.73 (*para* Ar. C), 129.11 (*meta* Ar. C), 128.69 (C5), 128.52 (*ortho* Ar. C), 124.30 (C2) *In agreement with published data* [109,110]

(*R*)- 2- phenyl- 1- ((*S*) - 1- phenylehtyl) piperidin- 4- one **48**

(*S*)- 2- phenyl- 1- ((*S*) -1- phenylehtyl) piperidin- 4- one **49**



L-(-) α- methylbenzylamine (199.17 mg, 1.64 mol, 1.3 equiv) was dissolved in acetonitrile (4 ml). After adding a solution of $NaHCO_3$ (0.4 g $NaHCO_3$ + 2.6 ml H_2O ≙4.74 mol, 3.8 equiv) the resulting suspension was cooled to 16°C and ketone (*E*)-1-phenylpenta-1, 4-dien-3-one **43** (200 mg, 1.27 mmol, 1.0 equiv) in acetonitrile was slowly added over 40 min. After the addition of the ketone, the mixture was stirred at reflux (93- 96°C) for 1.5 h. The acetonitrile was evaporated under reduced pressure, followed by the addition of ethyl acetate (8 ml). The solution was stirred for another 20 min, the layers were separated and the organic layer was washed with water (8 ml) und brine (8 ml). Then the organic phase was dried over Na_2SO_4 and filtered. The solvent was evaporated and purified by column chromatography (EA: Hex 1:5), affording product **48**, eluting first as yellow solid (183 mg, 52%); R_f 0.28 (EA: Hex 1: 8) and product **49** as yellow oil (27 mg, 8%); R_f 0.16 (EA: Hex 1: 8)

Scale up:

L-(-) α- methylbenzylamine (5.65 g, 46.6 mmol, 1.3 equiv) was dissolved in acetonitrile (114 ml). After adding a solution of $NaHCO_3$ (11.3 g $NaHCO_3$ + 75 ml H_2O, 134.51 mmol, 3.75 equiv) the resulting suspension was cooled to 16°C and ketone (*E*)-1-phenylpenta-

1, 4-dien-3-one **43** (5.67 g, 35.85 mmol, 1.0 equiv) in acetonitrile was slowly added over 40 min. After the addition of the ketone, the mixture was stirred at reflux (93-96°C) for 1.5h. Then the acetonitrile was evaporated under reduced pressure, followed by the addition of ethyl acetate (228 ml). The solution was stirred for another 20 min, the layers were separated and the organic layer was washed with water (200 ml) und brine (200 ml). Then the organic phase was dried over Na_2SO_4 and filtered. The solvent was evaporated and purified by column chromatography (EA: Hex 1:5),

affording **product 48**, eluting first as yellow solid (3.1 g, 30%); R_f 0.28 (EA: Hex 1: 8); melting point: 88- 91 °C; *m/z* (CI) 312 $[m+H+CH_3OH]^+$, 280 $[M+H]^+$, 176, 147, 129; ν_{max} (solid) 2974, 2823, 1712 (C=O), 1492, 1447, 1365, 1330, 1240, 1169, 1011, 761, 706, 696; δ_H (400 MHz, $CDCl_3$) 7.10-7.38 (10H, m, Ar. H), 3.98- 4.03 (2H, m, H-3, H-7), 2.77-2.82 (1H, m, 1x H-5), 2.57-2.63 (1H, m, 1x H-2), 2.37-2.52 (3H, m, 1x H-2, 1x H-5, 1x H-6), 2.17-2.21 (1H, m, 1x H-6), 1.10- 1.16 (3H, m, H-16); δ_C (100.6 MHz, $CDCl_3$) 209.01 (C1), 143.96 (1x *ipso* Ar. C), 142.35 (1x *ipso* Ar. C), 129.12 (1x *ortho* Ar. C), 128.25 (1x *ortho* Ar. C), 127.96 (1x *meta* A. C), 127.59 (1x *meta* Ar. C), 127.49 (1x *para* Ar. C), 126. 83 (1x *para* Ar. C), 64.90 (C3), 55.03 (C7), 50.35 (C2), 44.16 (C5), 42.02 (C6), 9.60 (C16);

and **product 49** as yellow oil (543 mg, 5%); R_f 0.16 (EA: Hex 1: 8); *m/z* (CI) 312 $[m+H+CH_3OH]^+$, 280 $[M+H]^+$, 176, 147, 129; ν_{max} (film) 3028, 2970, 2162, 1717 (C=O), 1600, 1453, 1361, 1227, 1167, 1028, 758, 700, 606; δ_H (400 MHz, $CDCl_3$) 7.07- 7.48 (10H, m, Ar. H), 4.03 (1H, q, *J* 7.04, H-7), 3.68 (1H, dd, *J* 4.58, 9.24, H-3), 3.31-3.36 (1H, m, 1x H-5), 2.38-2.67 (4H, m, H-2, H-6), 2.19-2.25 (1H, m, 1x H-5), 1.44 (3H, d, *J* 7.07, H-16); δ_C (100.6 MHz, $CDCl_3$) 208.74 (C1), 143.13 (1x *ipso* Ar. C), 139.15 (1x *ipso* Ar. C), 127.38-129.12 (8x Ar. C), 64.61 (C3), 56.72 (C7), 50.48 (C2), 44.53 (C5), 41.83 (C6), 19.59 (C16)

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5 Appendix

5.1 Spectra

Appendix

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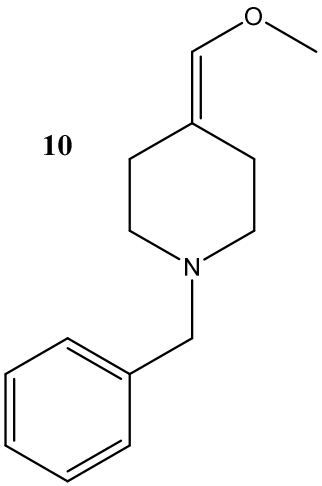
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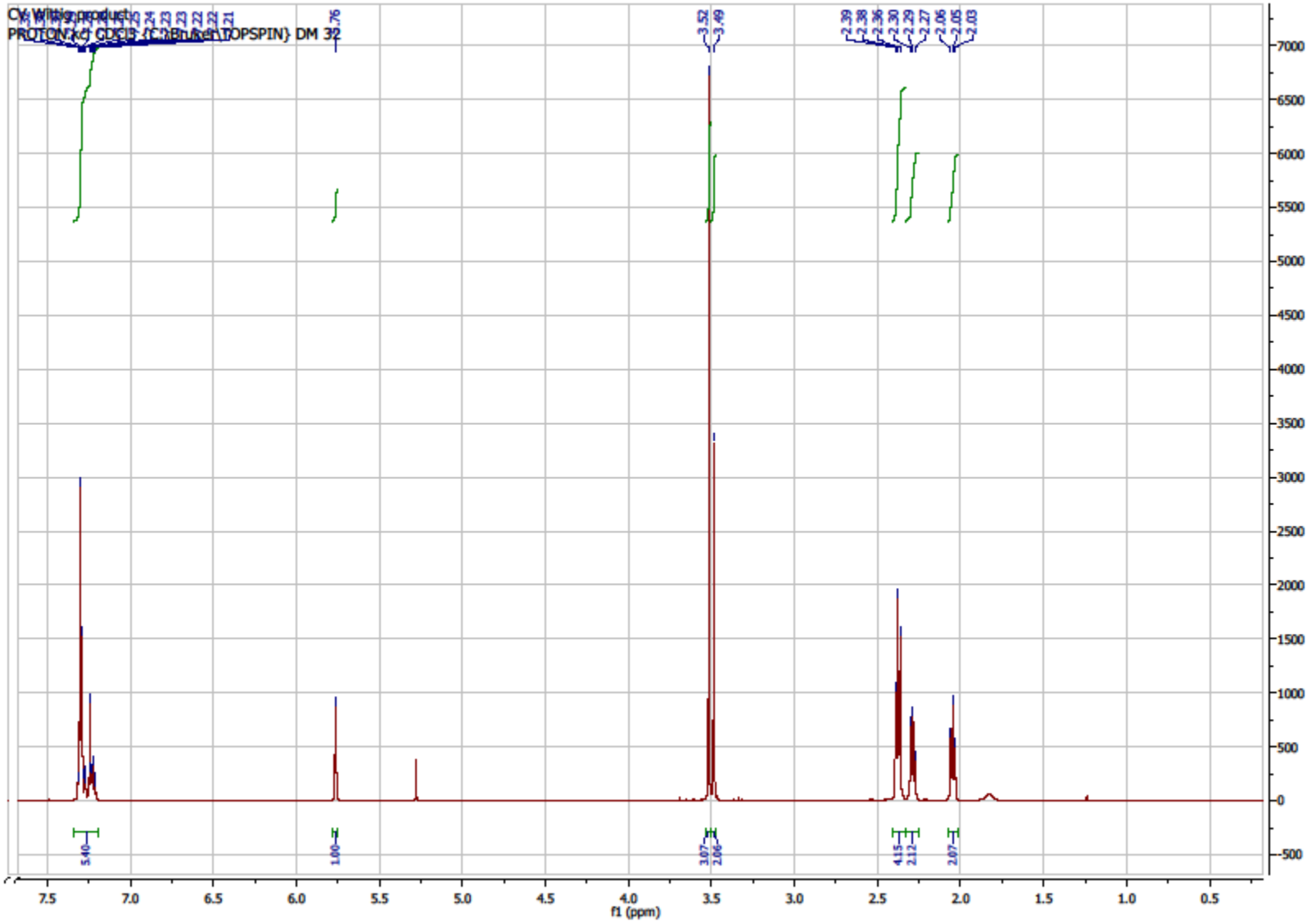
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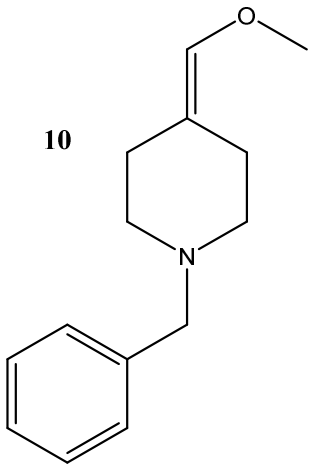
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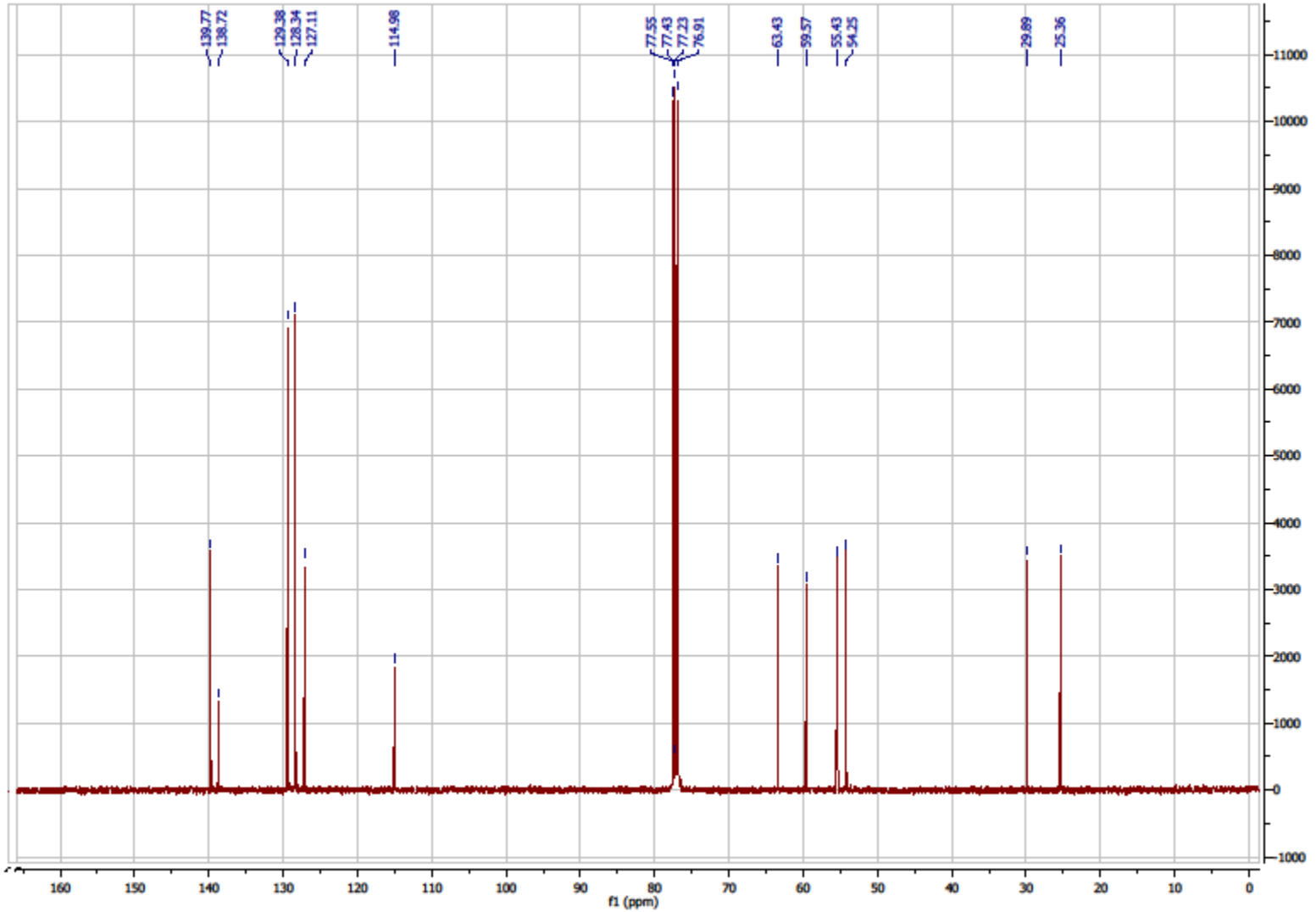
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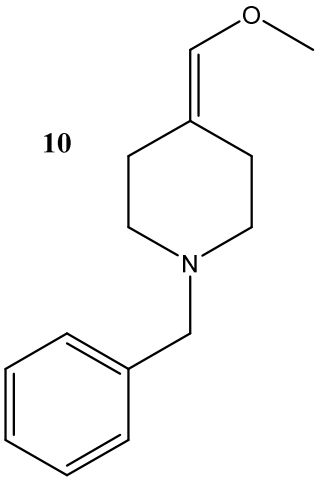
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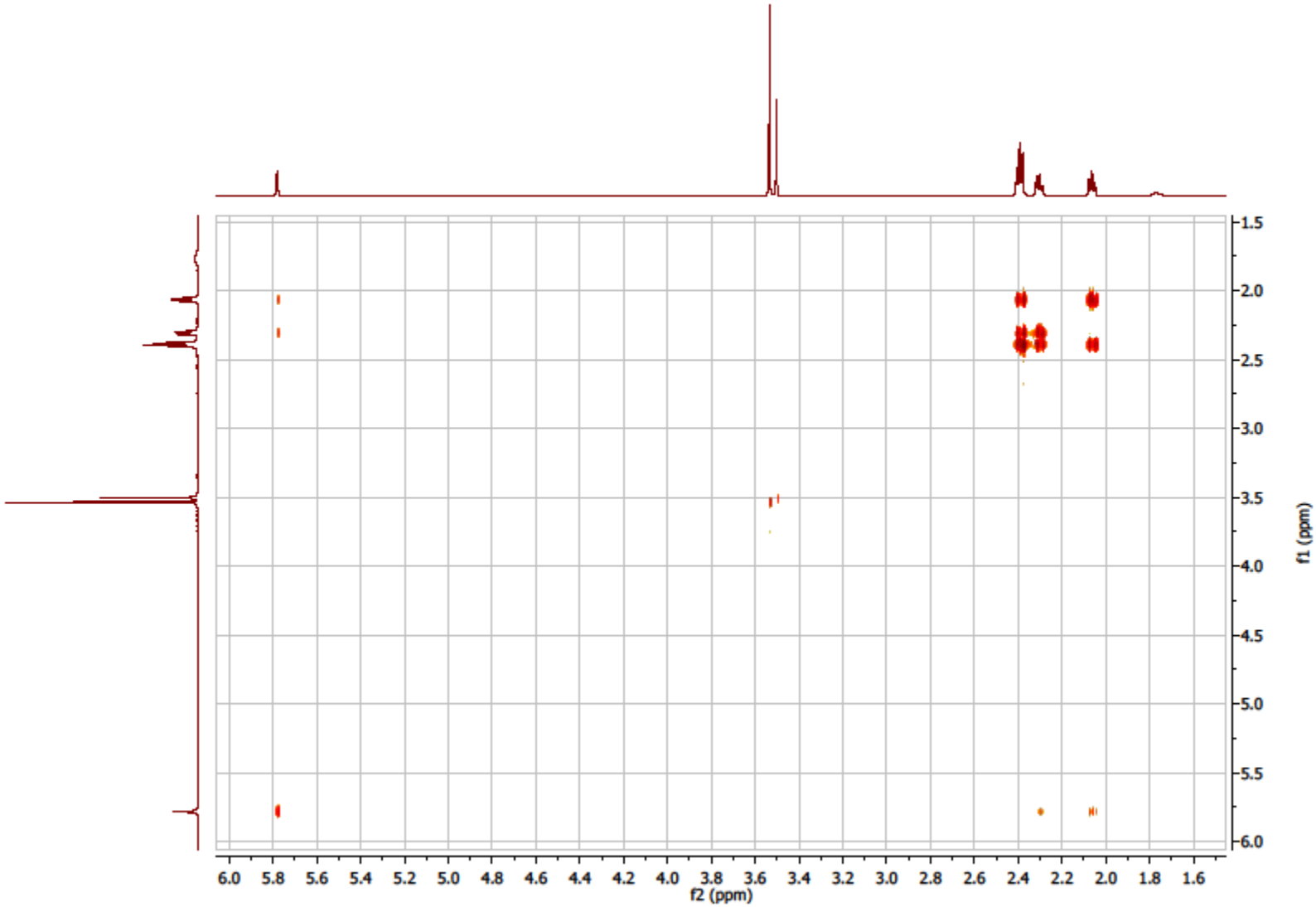
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f1 (ppm)

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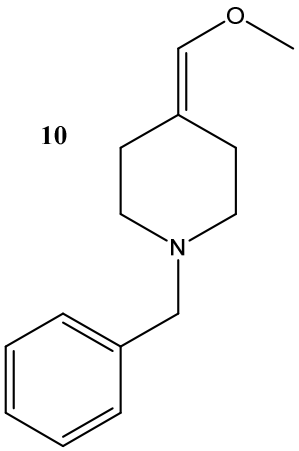
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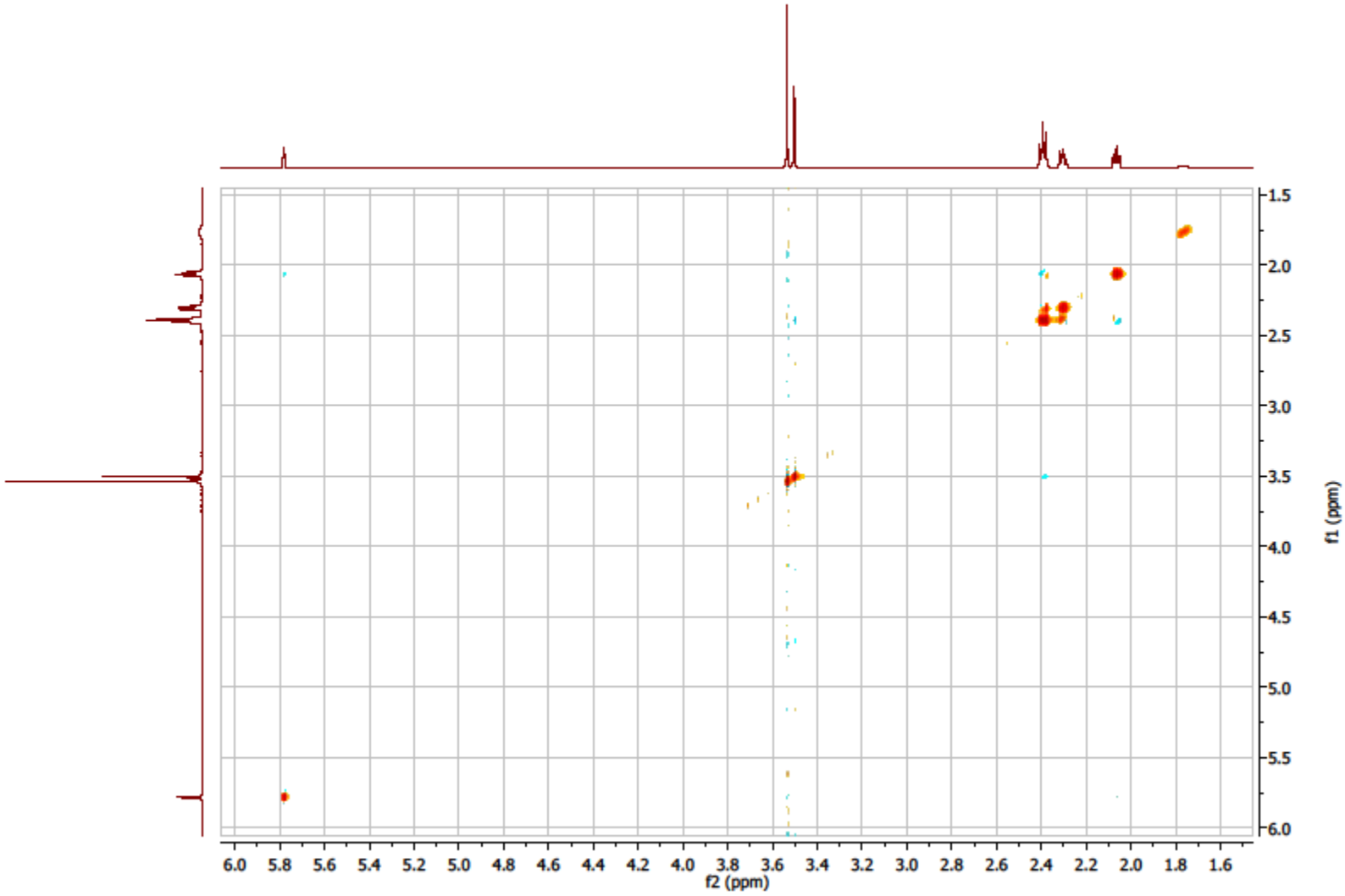
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f1 (ppm)

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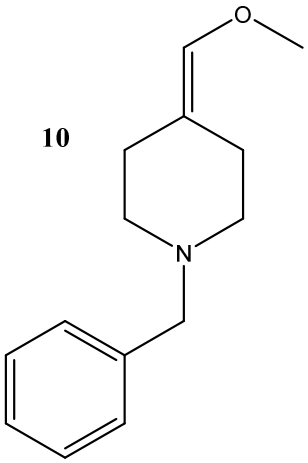
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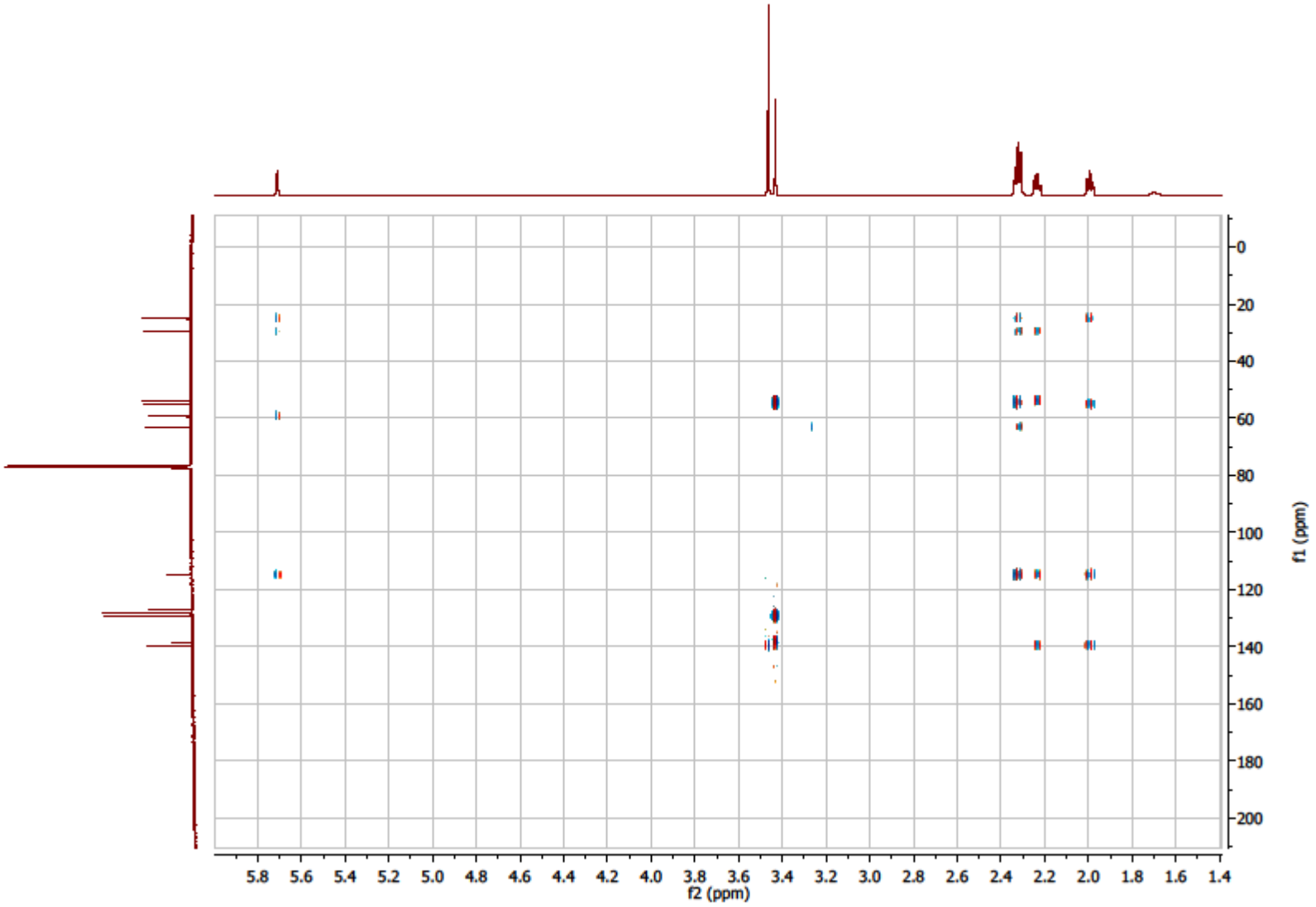
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f2 (ppm)

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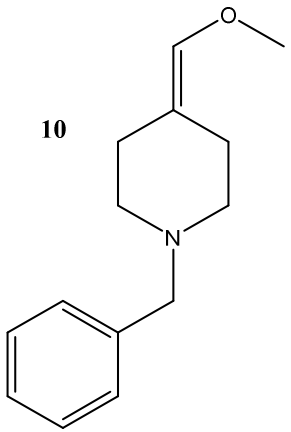
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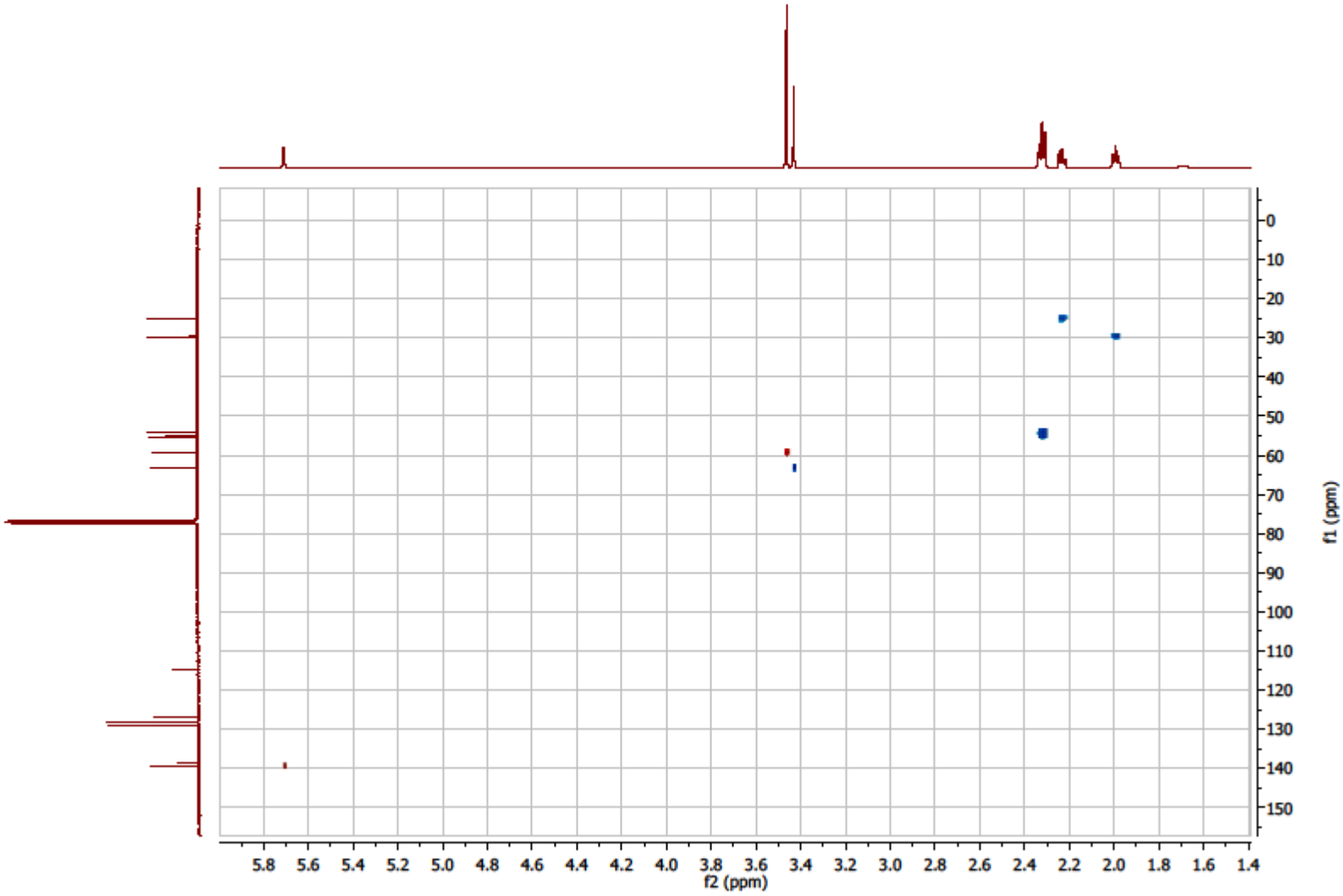
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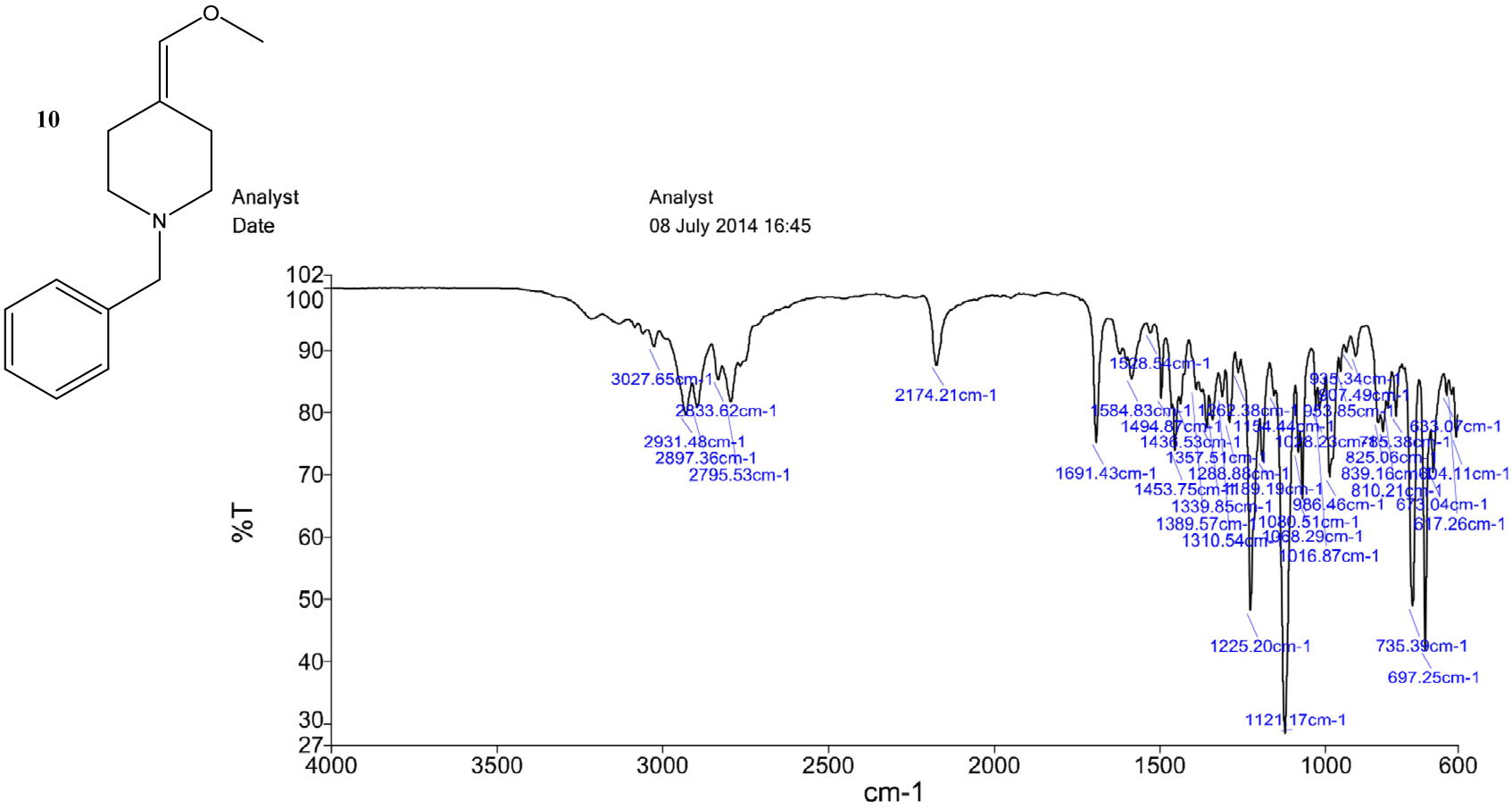
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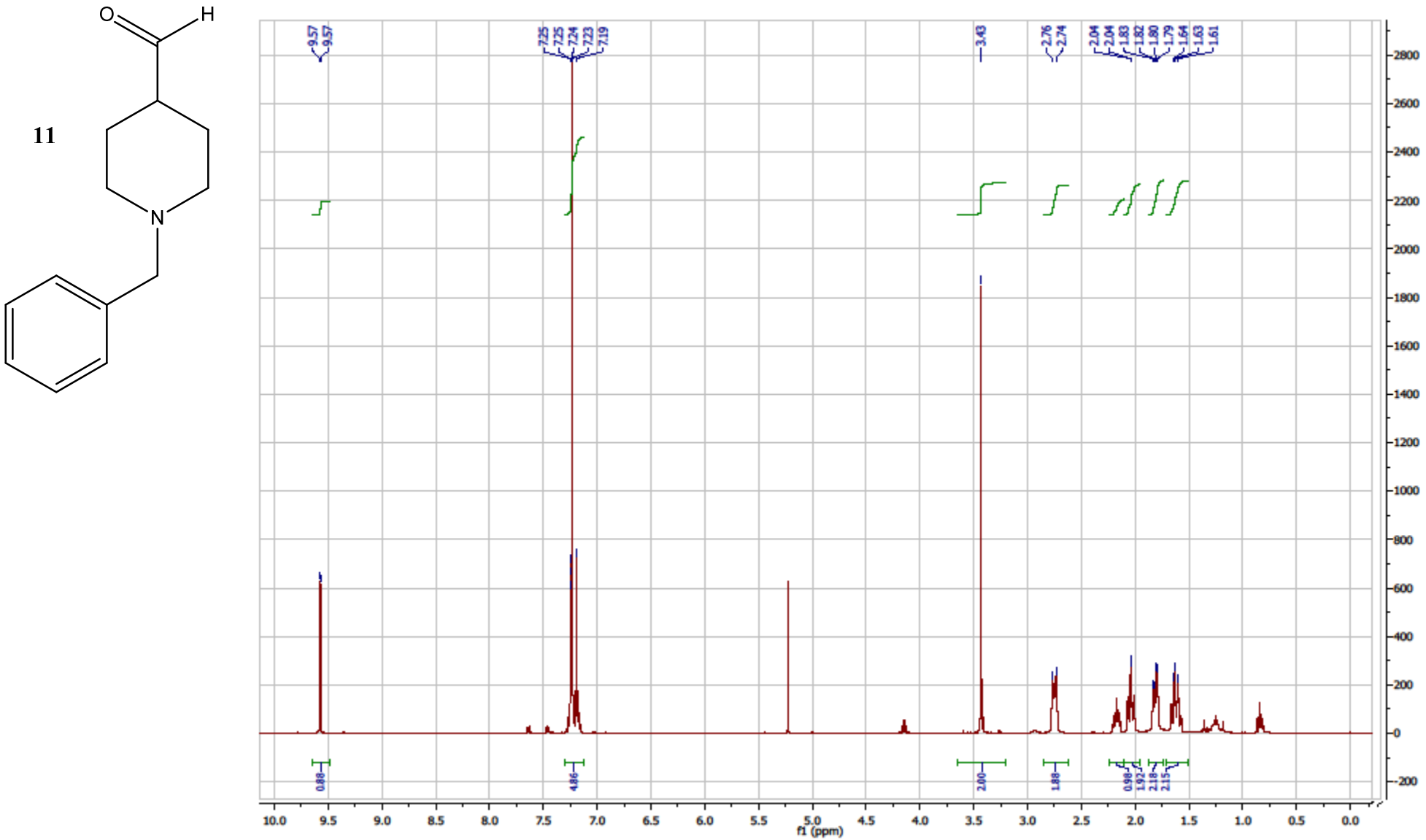
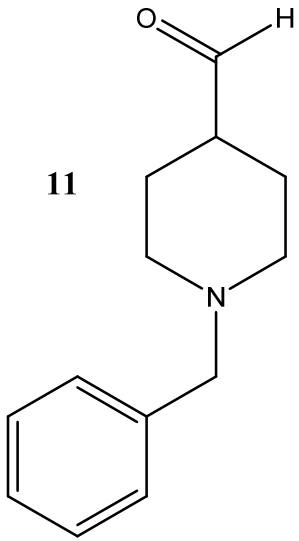
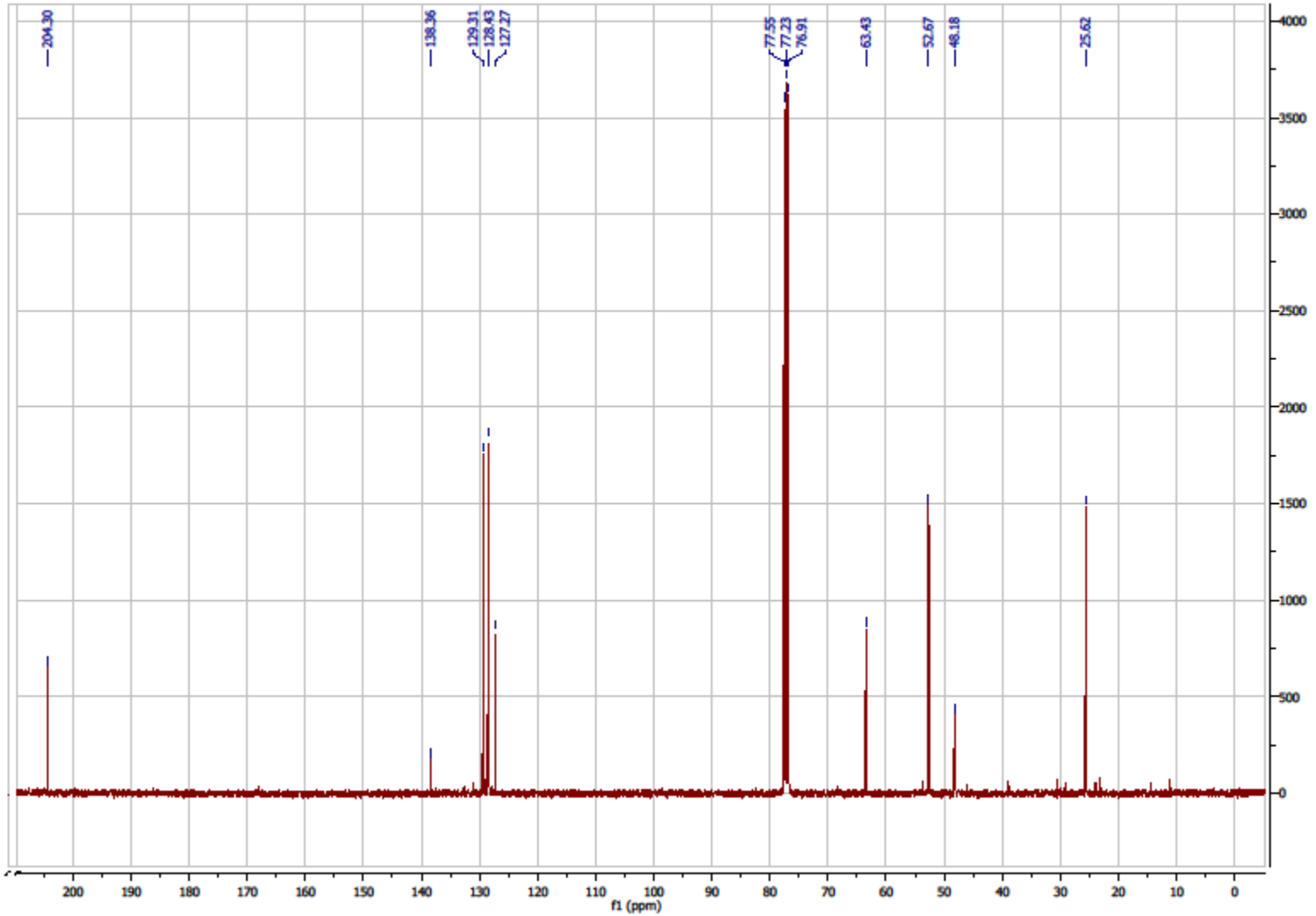
Wittig_reaction1 Sample 216 By Analyst Date Tuesday, July 01 2014

11

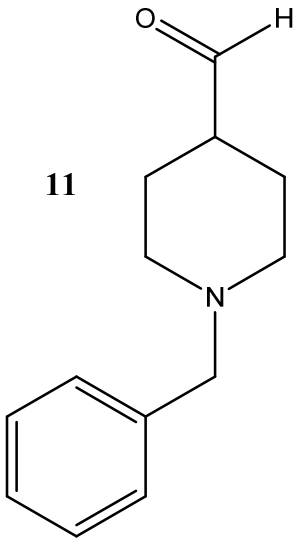

O
H
N
9.57
9.57
7.25
7.25
7.24
7.23
7.19
3.43
2.76
2.74
2.04
2.04
1.83
1.82
1.80
1.79
1.64
1.63
1.61
0.88
4.86
2.00
1.88
0.98
1.92
2.18
2.15
f1 (ppm)

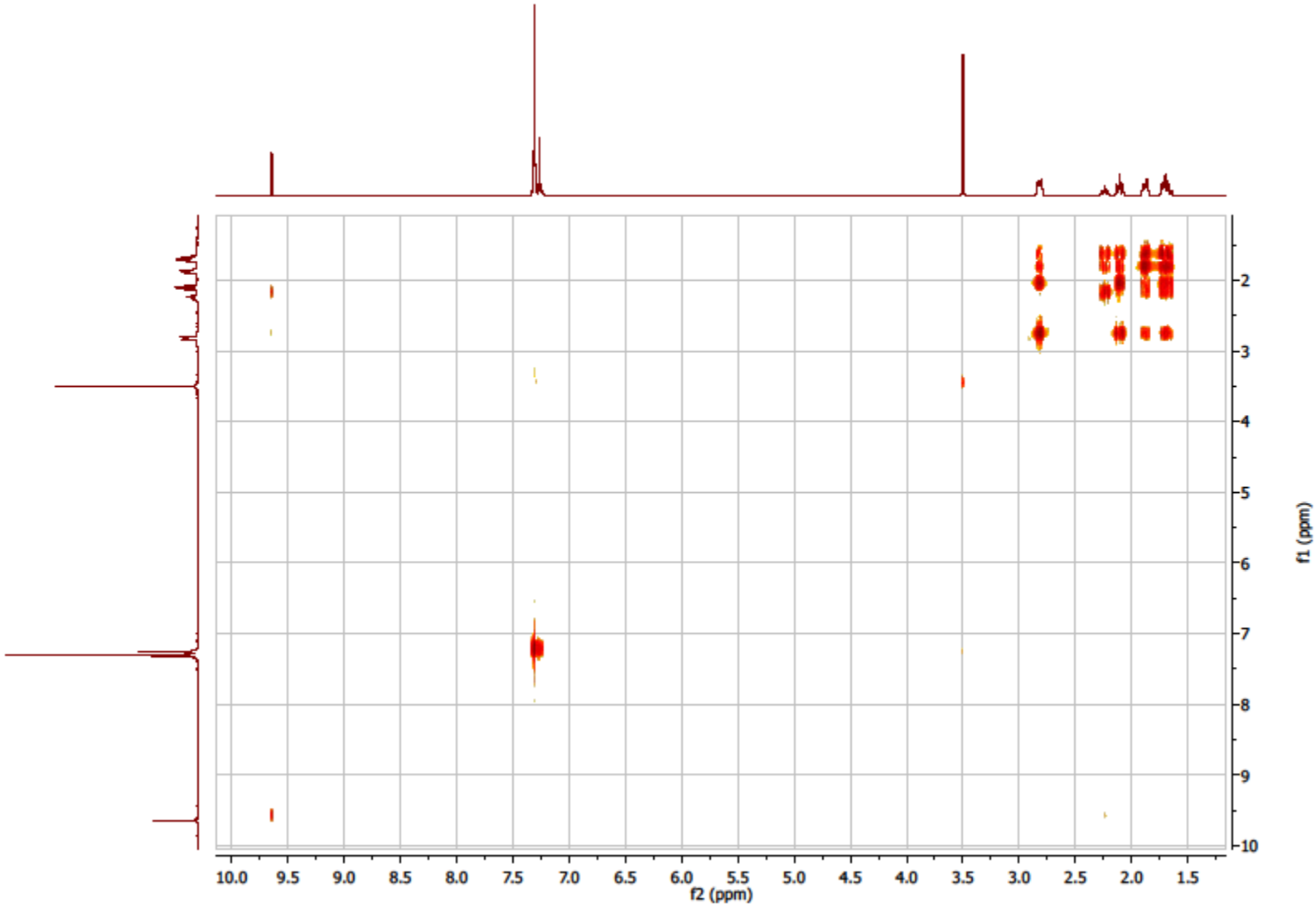
11


O
H
N


204.30
138.36
129.31
128.43
127.27
77.55
77.23
76.91
63.43
52.67
48.18
25.62
f1 (ppm)

11


O
H
N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9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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1.5
f2 (ppm)
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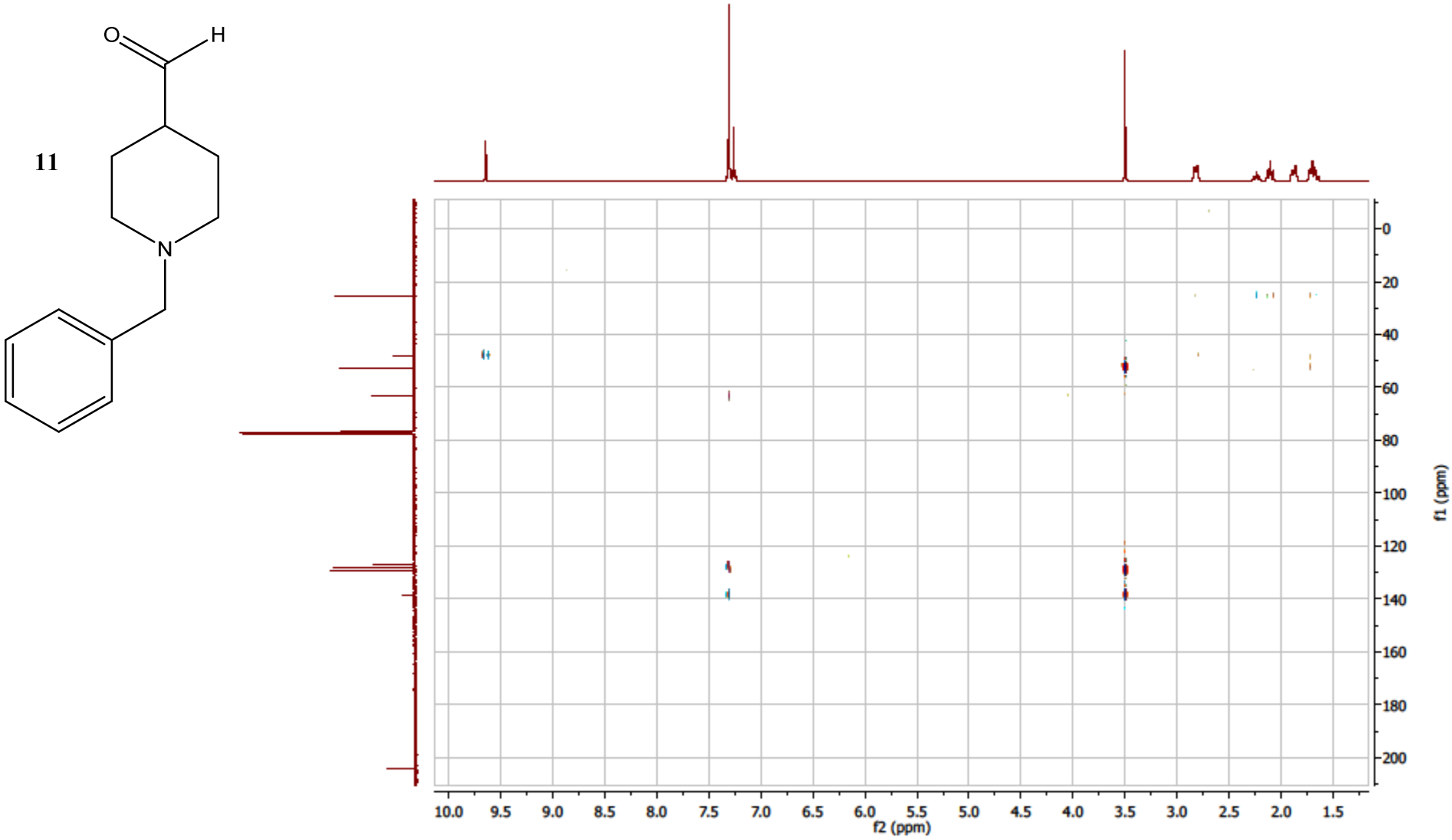
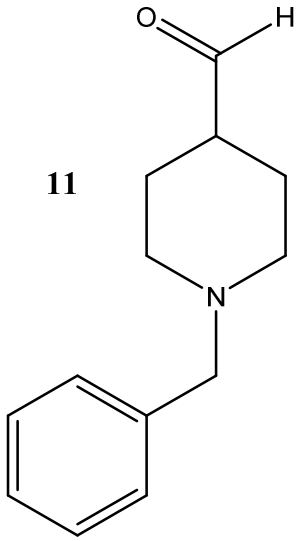
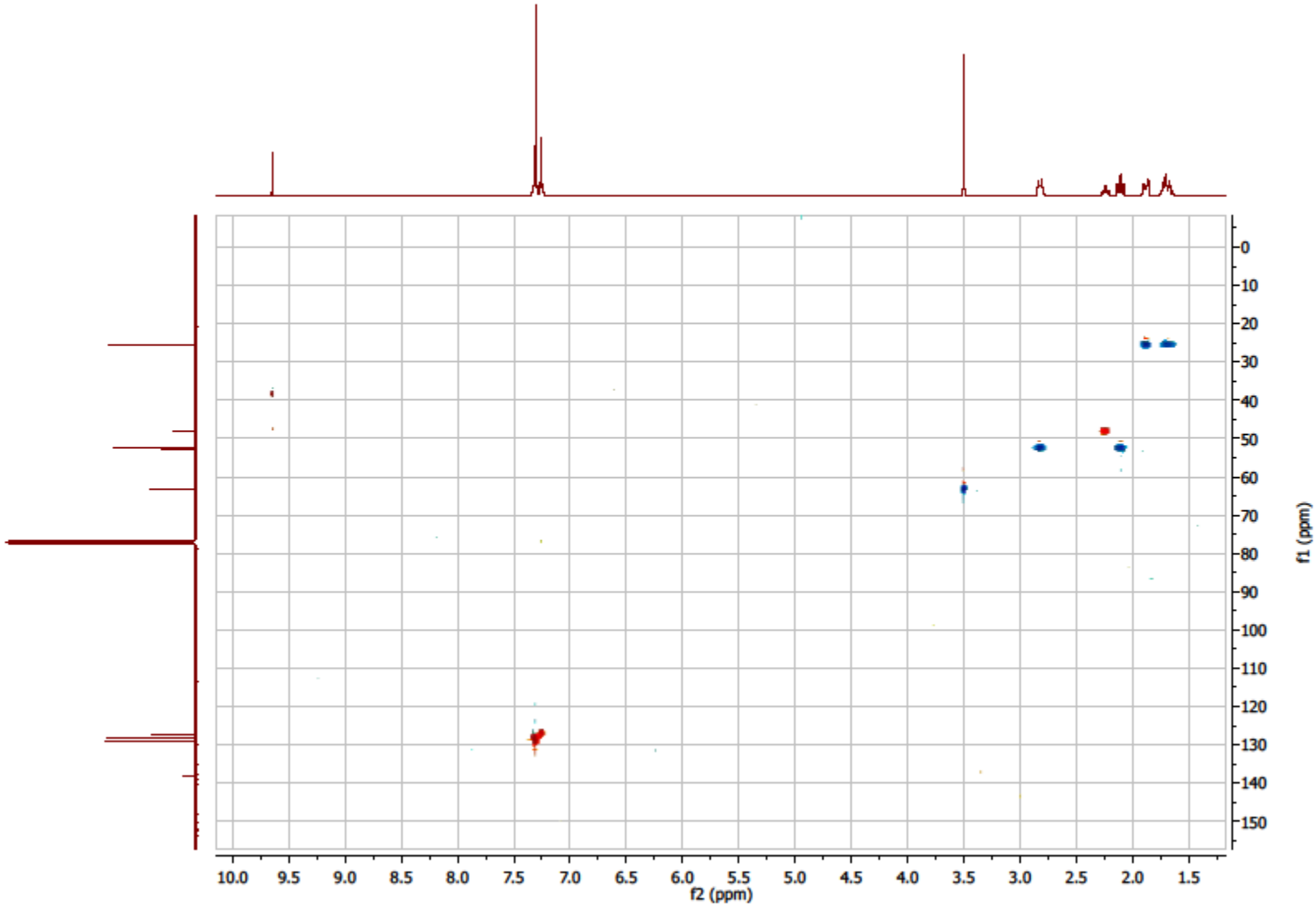
3
4
5
6
7
8
9
10
f1 (ppm)

11

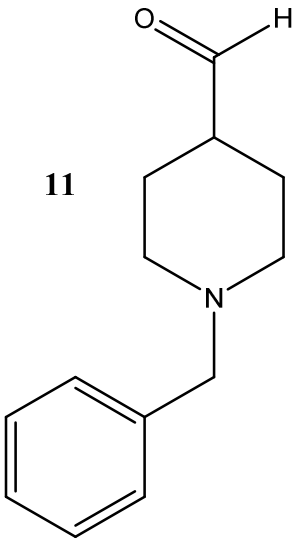

O
H
N
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f2 (ppm)
0
20
40
60
80
100
120
140
160
180
200
f1 (ppm)

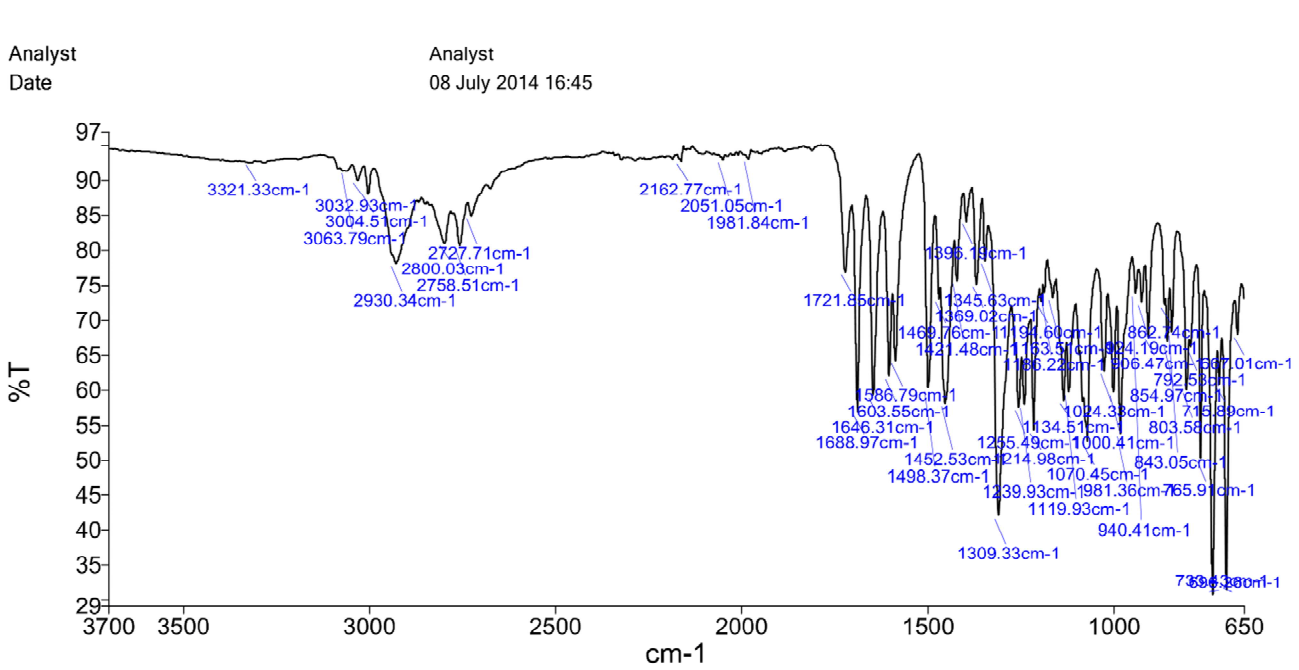
11


O
H
N

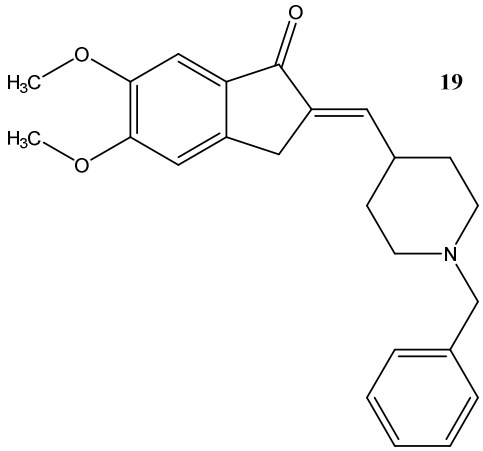

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f2 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)

11

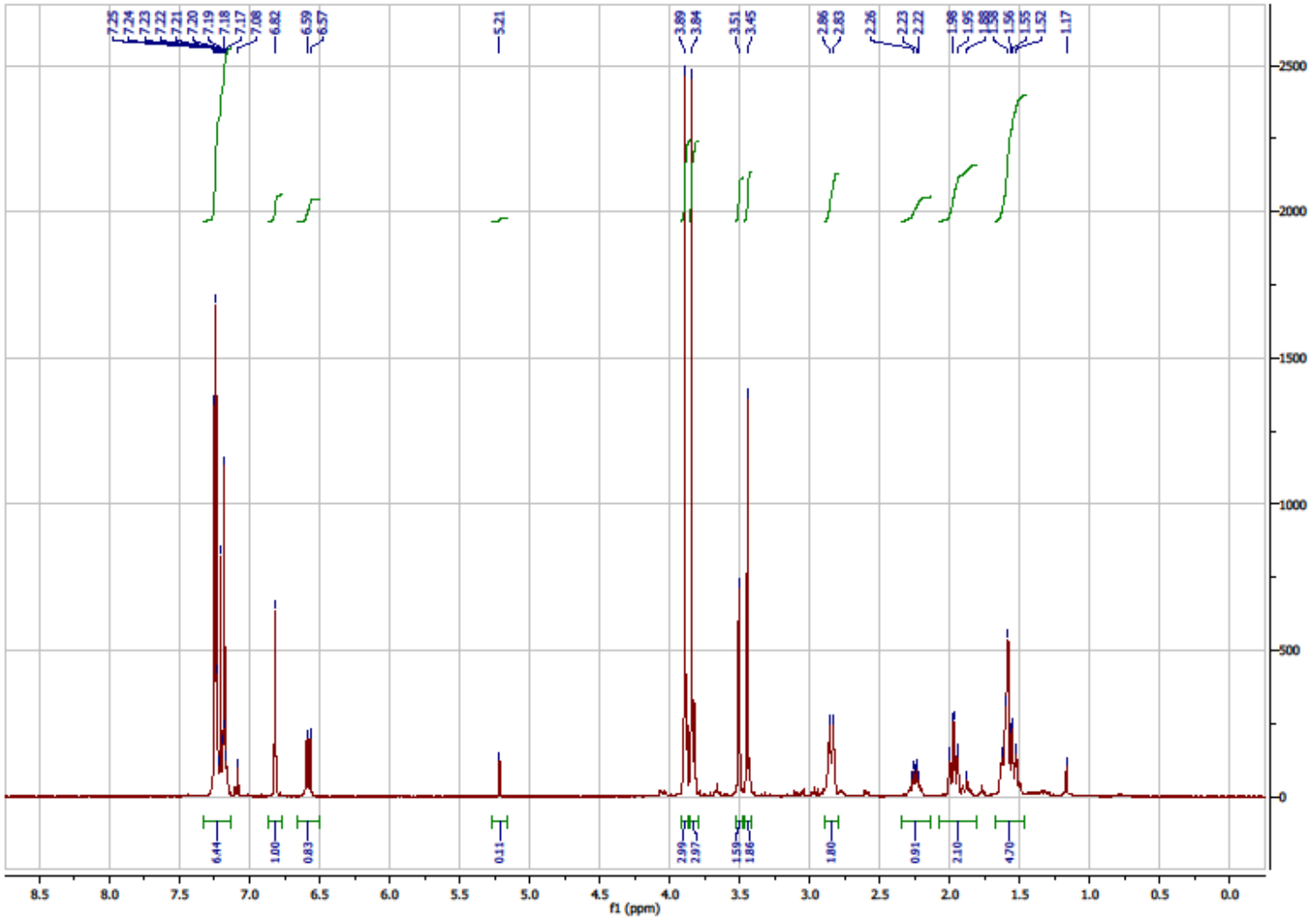

O
H
N


PerkinElmer Spectrum Version 10.4.00
08 July 2014 16:45
Analyst
Date
Analyst
08 July 2014 16:45
%T
cm-1
3321.33cm-1
3032.93cm-1
3004.51cm-1
3063.79cm-1
2727.71cm-1
2800.03cm-1
2758.51cm-1
2930.34cm-1
2162.77cm-1
2051.05cm-1
1981.84cm-1
1721.85cm-1
1345.63cm-1
1369.02cm-1
1469.76cm-1
1421.48cm-1
1586.79cm-1
1603.55cm-1
1646.31cm-1
1688.97cm-1
1452.53cm-1
1498.37cm-1
1309.33cm-1
1239.93cm-1
1119.93cm-1
1070.45cm-1
1024.38cm-1
1134.51cm-1
1255.49cm-1
1214.98cm-1
1000.41cm-1
981.36cm-1
940.41cm-1
854.97cm-1
803.58cm-1
843.05cm-1
765.91cm-1
715.89cm-1
N-Benzyl-4-formyl-piperidone Sample 191 By Analyst Date Monday, June 02 2014

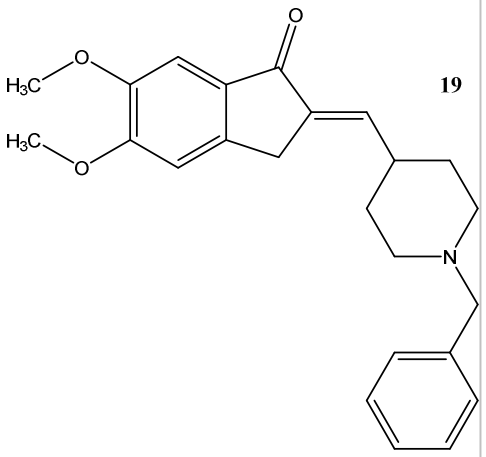
Appendix


O
H3C
O
H3C
O
N

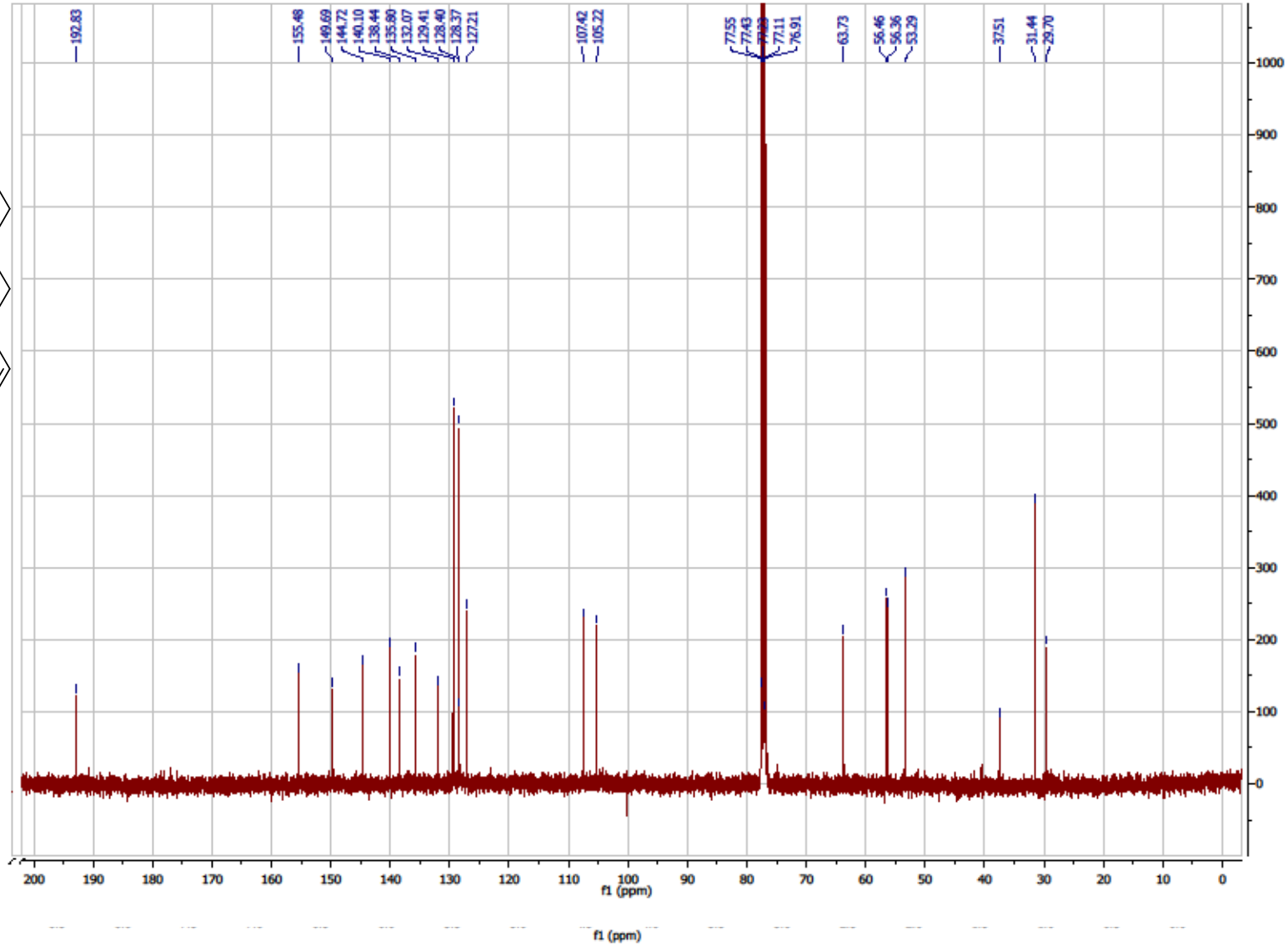
19

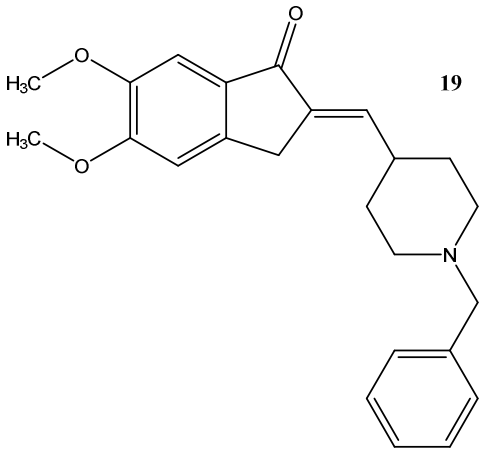

7.25
7.24
7.23
7.22
7.21
7.20
7.19
7.18
7.17
7.08
6.82
6.59
6.57
5.21
3.89
3.84
3.51
3.45
2.86
2.83
2.26
2.23
2.22
1.98
1.95
1.88
1.58
1.56
1.55
1.52
1.17
6.44
1.00
0.83
0.11
2.99
2.97
1.59
1.86
1.80
0.91
2.10
4.70
f1 (ppm)

Appendix

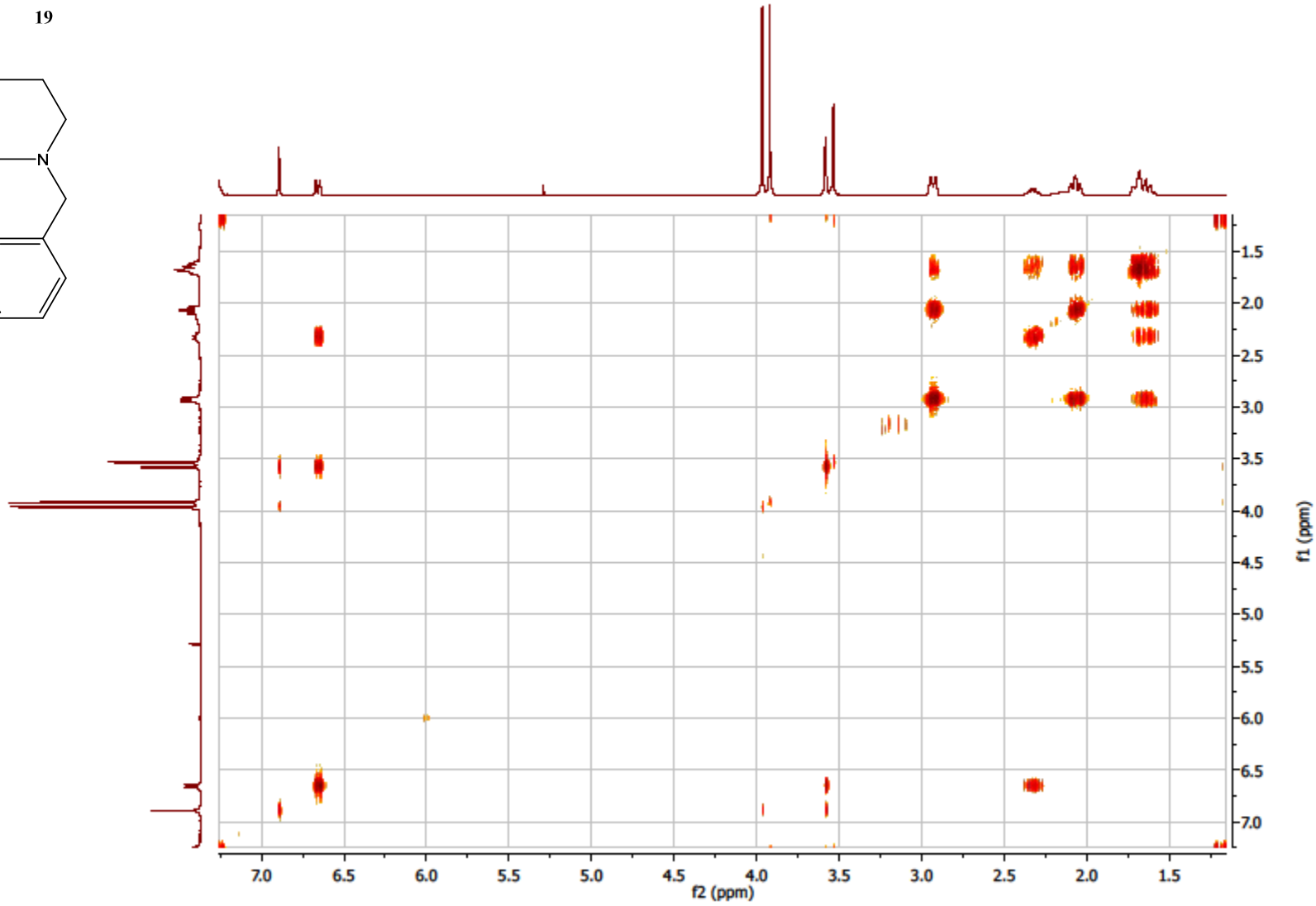

O
O
H3C
O
H3C
N

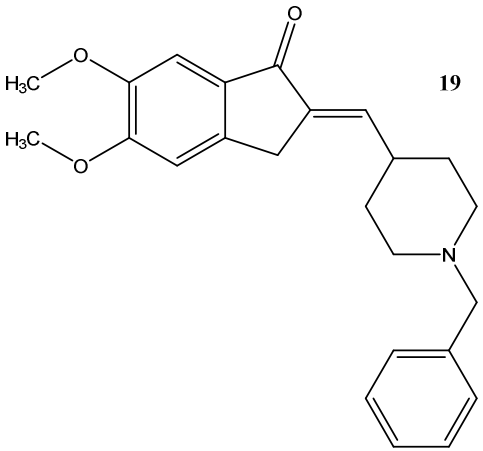
19


192.83
155.48
149.69
144.72
140.10
138.44
135.80
132.07
129.41
128.40
128.37
127.21
107.42
105.22
77.55
77.43
77.11
76.91
63.73
56.46
56.36
53.29
37.51
31.44
29.70
f1 (ppm)
f1 (ppm)

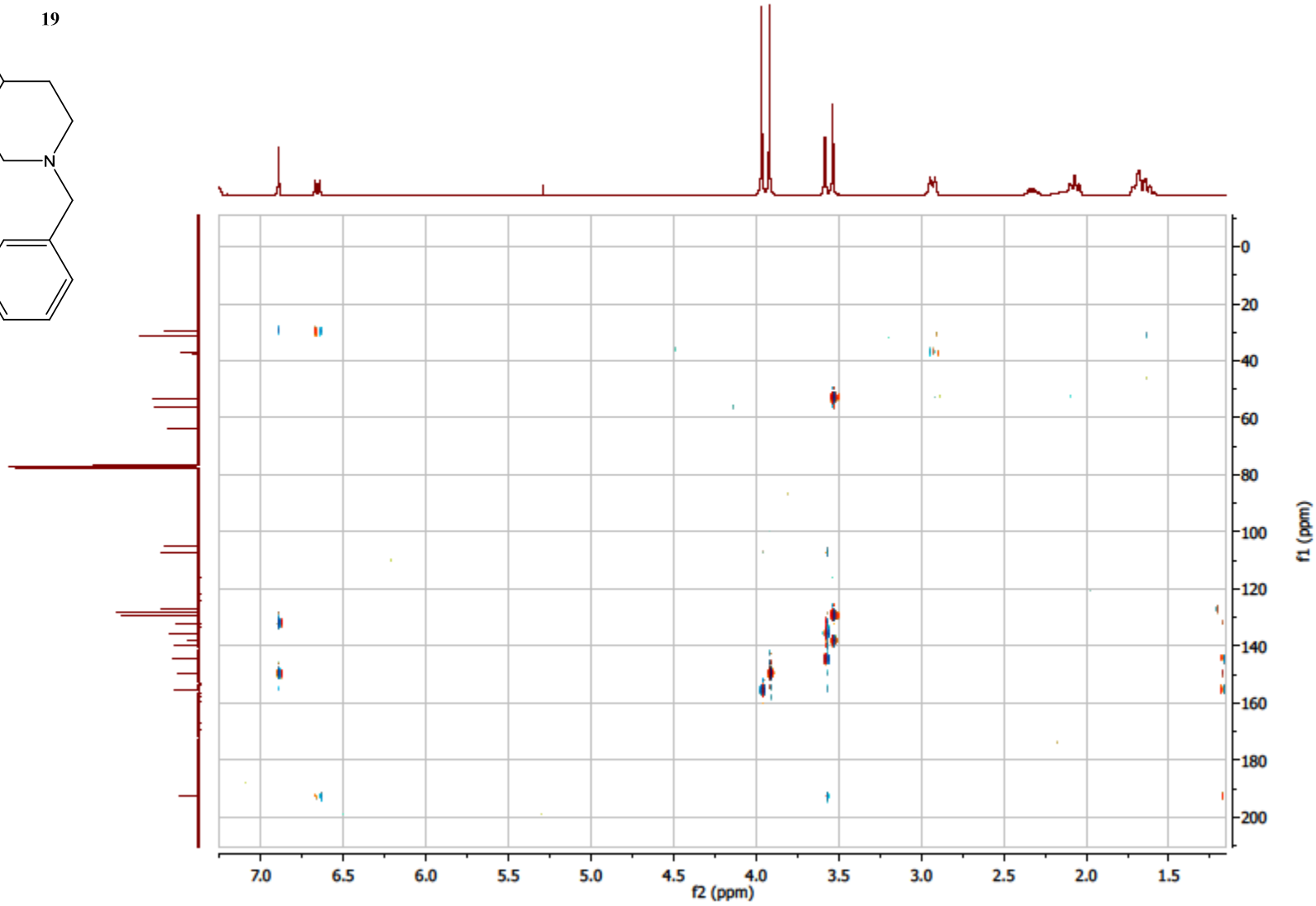

O
H3C
O
H3C
O
N

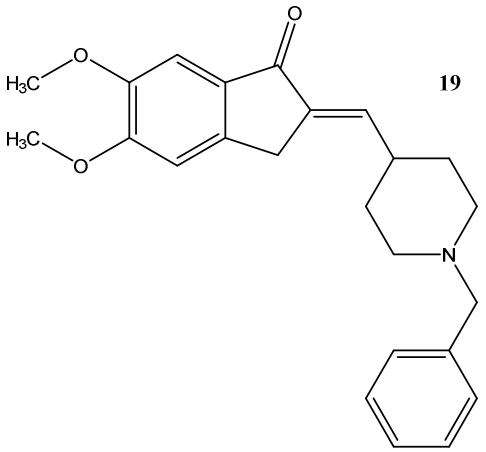
19


7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f2 (ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
f1 (ppm)

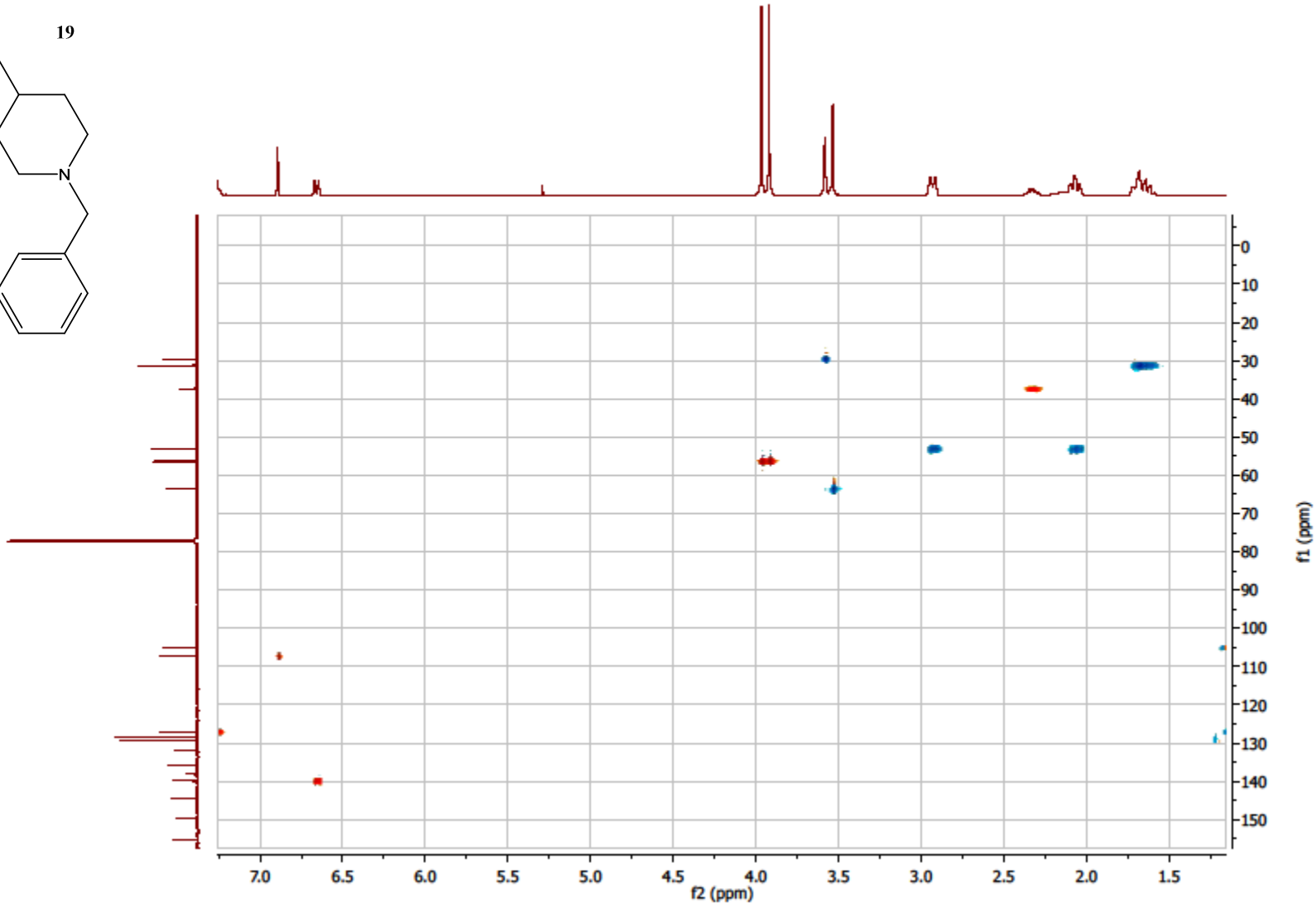

O
H3C
O
H3C
O
N

19

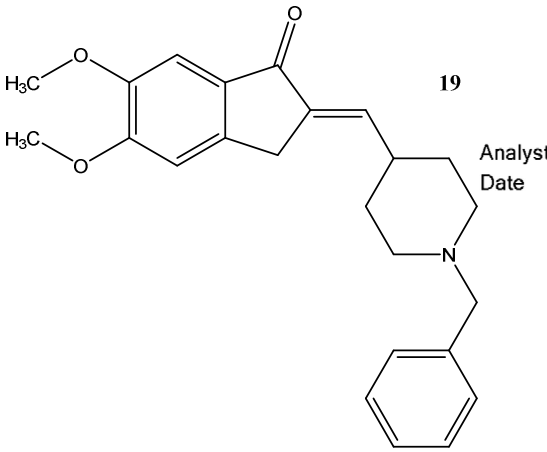

0
20
40
60
80
100
120
140
160
180
200
f1 (ppm)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f2 (ppm)


O
H3C
O
H3C
O
N

19


0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f2 (ppm)

Appendix



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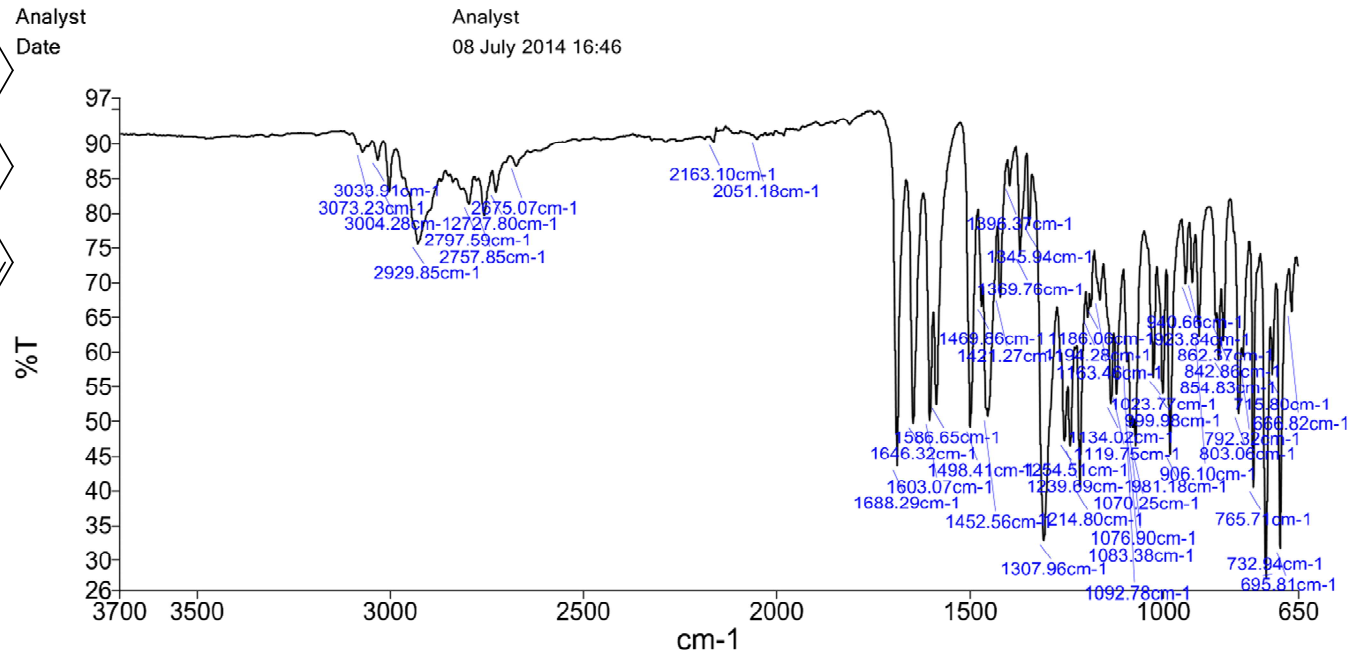

PerkinElmer Spectrum Version 10.4.00
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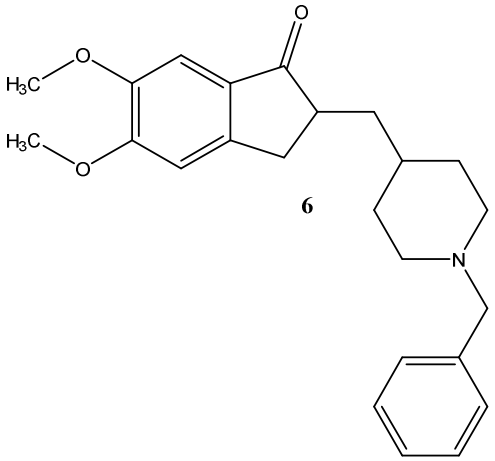
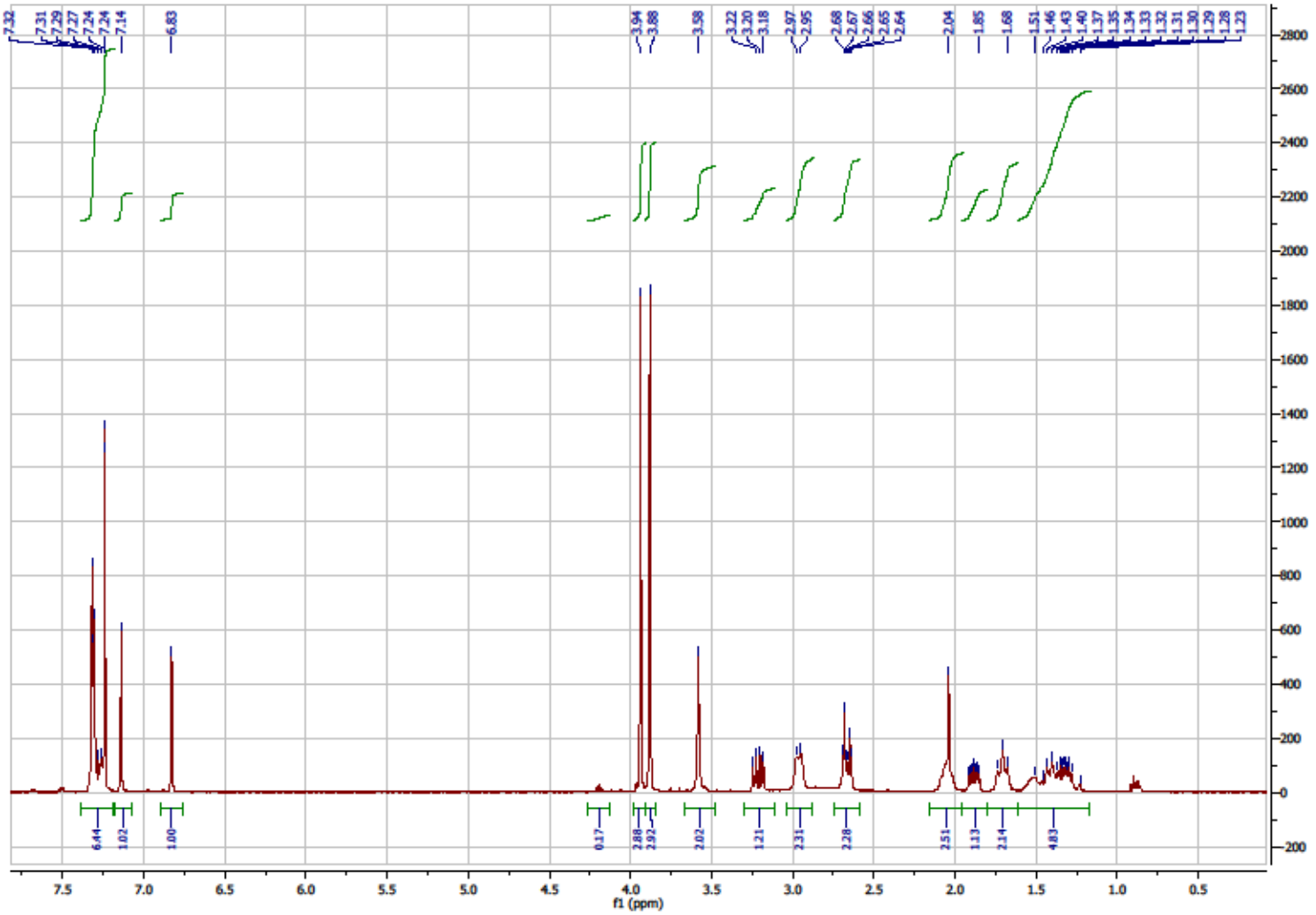
3_Aldolcondensation Sample 190 By Analyst Date Monday, June 02 2014

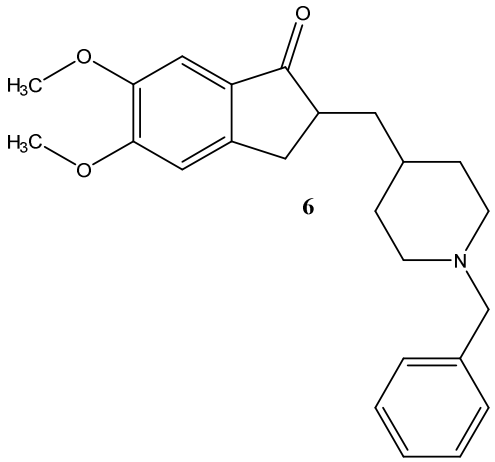
Appendix


O
H3C
O
H3C
O
N

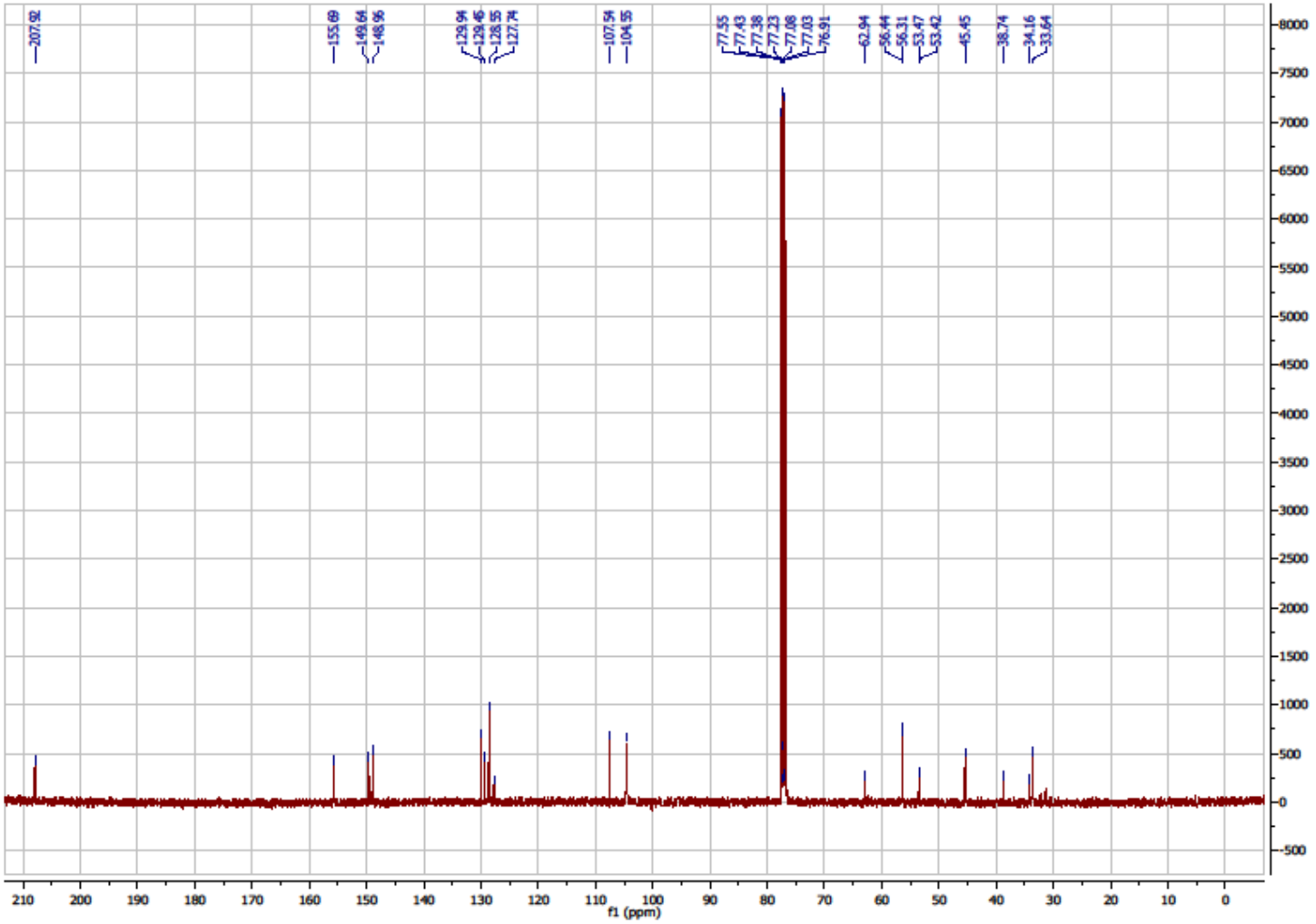
6

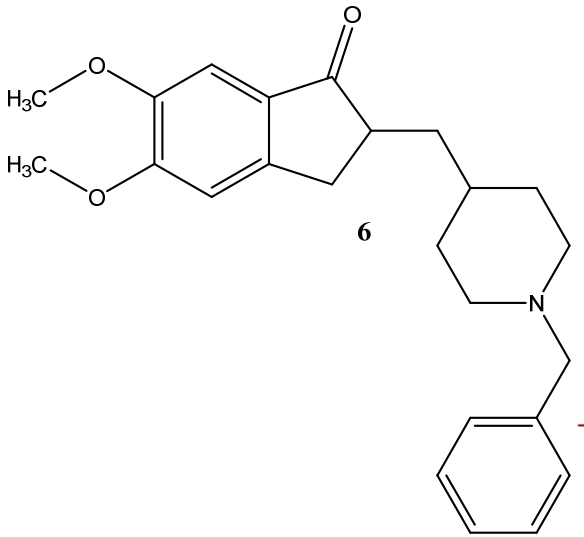

7.32
7.31
7.29
7.27
7.24
7.24
7.14
6.83
3.94
3.88
3.58
3.22
3.20
3.18
2.97
2.95
2.68
2.67
2.66
2.65
2.64
2.04
1.85
1.68
1.51
1.46
1.43
1.40
1.37
1.35
1.34
1.33
1.32
1.31
1.30
1.29
1.28
1.23
6.44
1.02
1.00
0.17
2.88
2.92
2.02
1.21
2.31
2.28
2.51
1.13
2.14
4.83
f1 (ppm)

Appendix

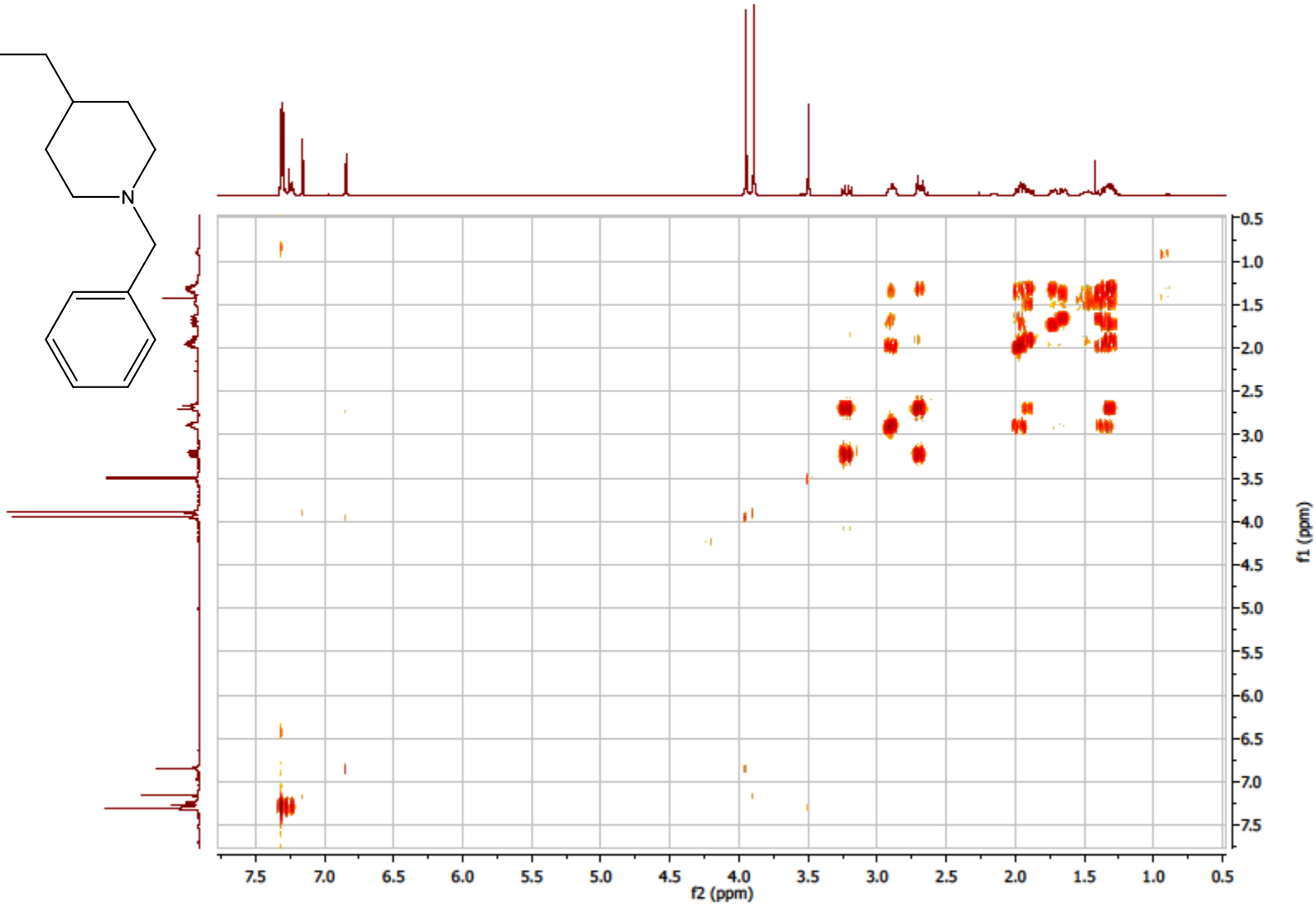

O
H3C
O
H3C
O
N

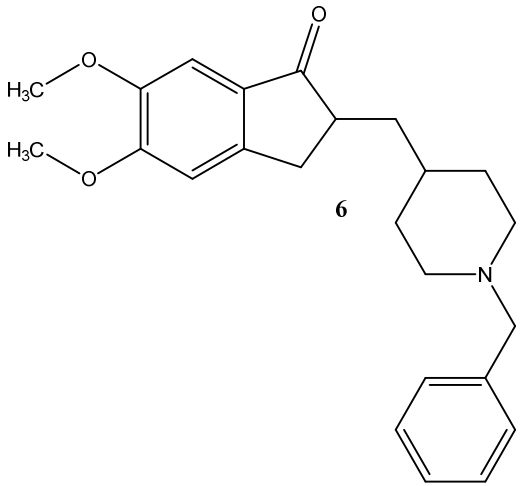
6


207.92
155.69
149.64
148.96
129.94
129.46
128.55
127.74
107.54
104.55
77.55
77.43
77.38
77.23
77.08
77.03
76.91
62.94
56.44
56.31
53.47
53.42
45.45
38.74
34.16
33.64
f1 (ppm)

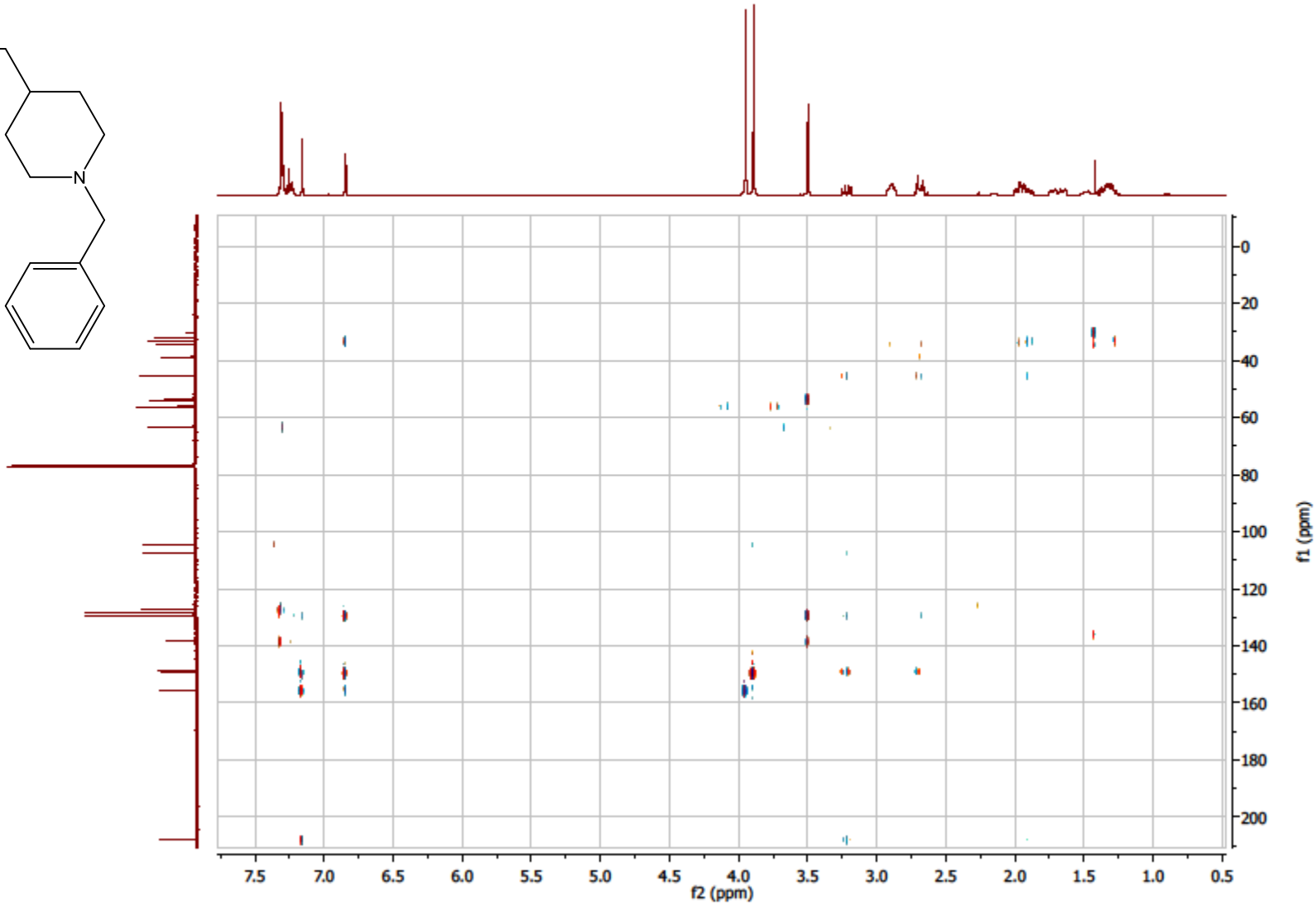

O
O
H3C
O
H3C
N

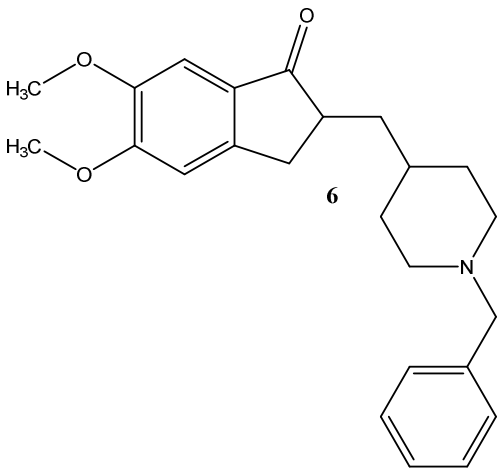
6


7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)

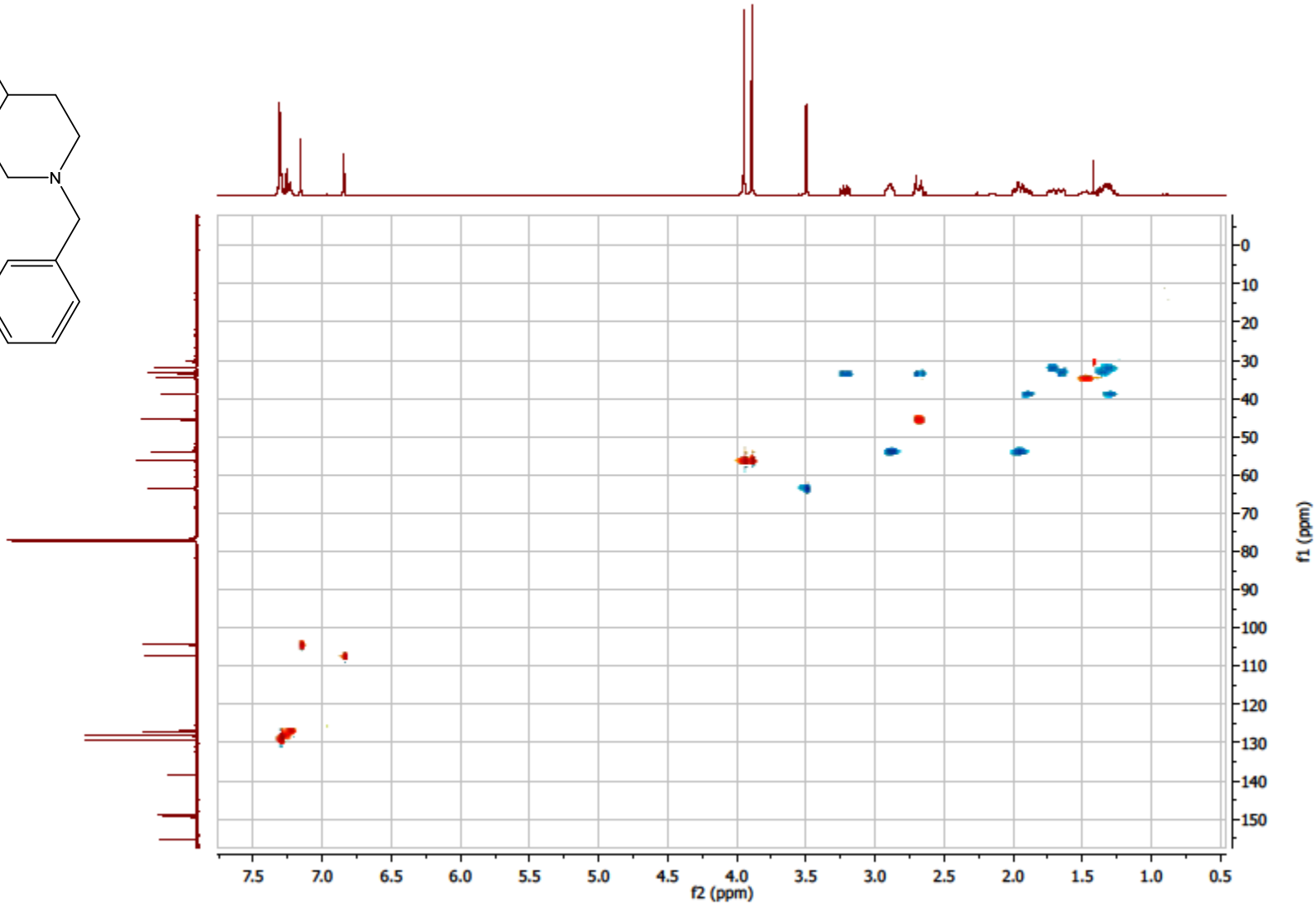

O
H3C
O
H3C
O
N

6

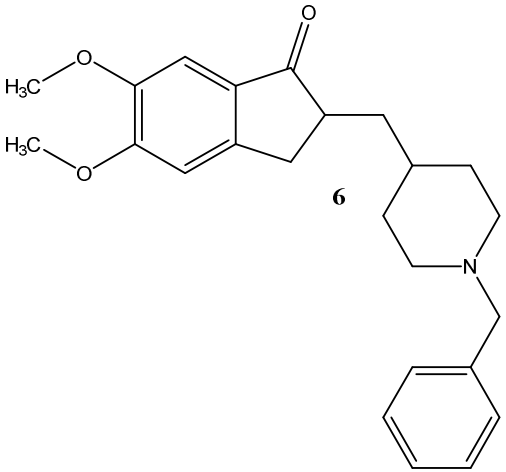

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
0
20
40
60
80
100
120
140
160
180
200
f1 (ppm)


O
O
H3C
O
H3C
N

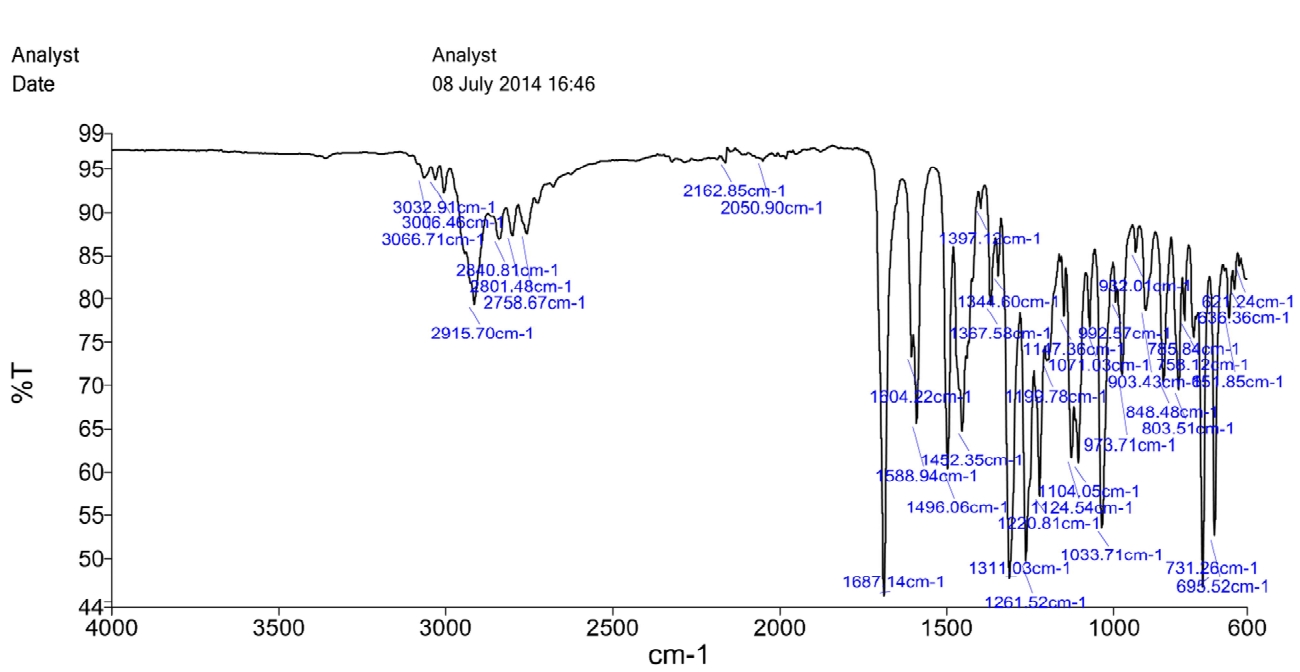
6

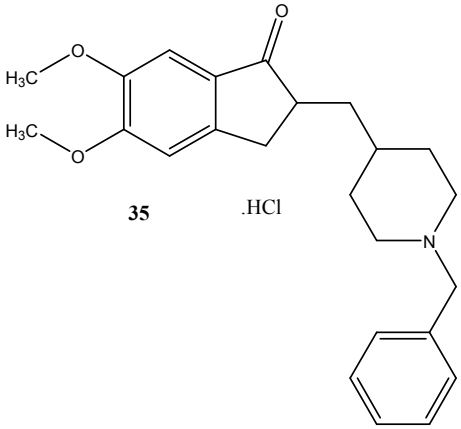

0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)

Appendix

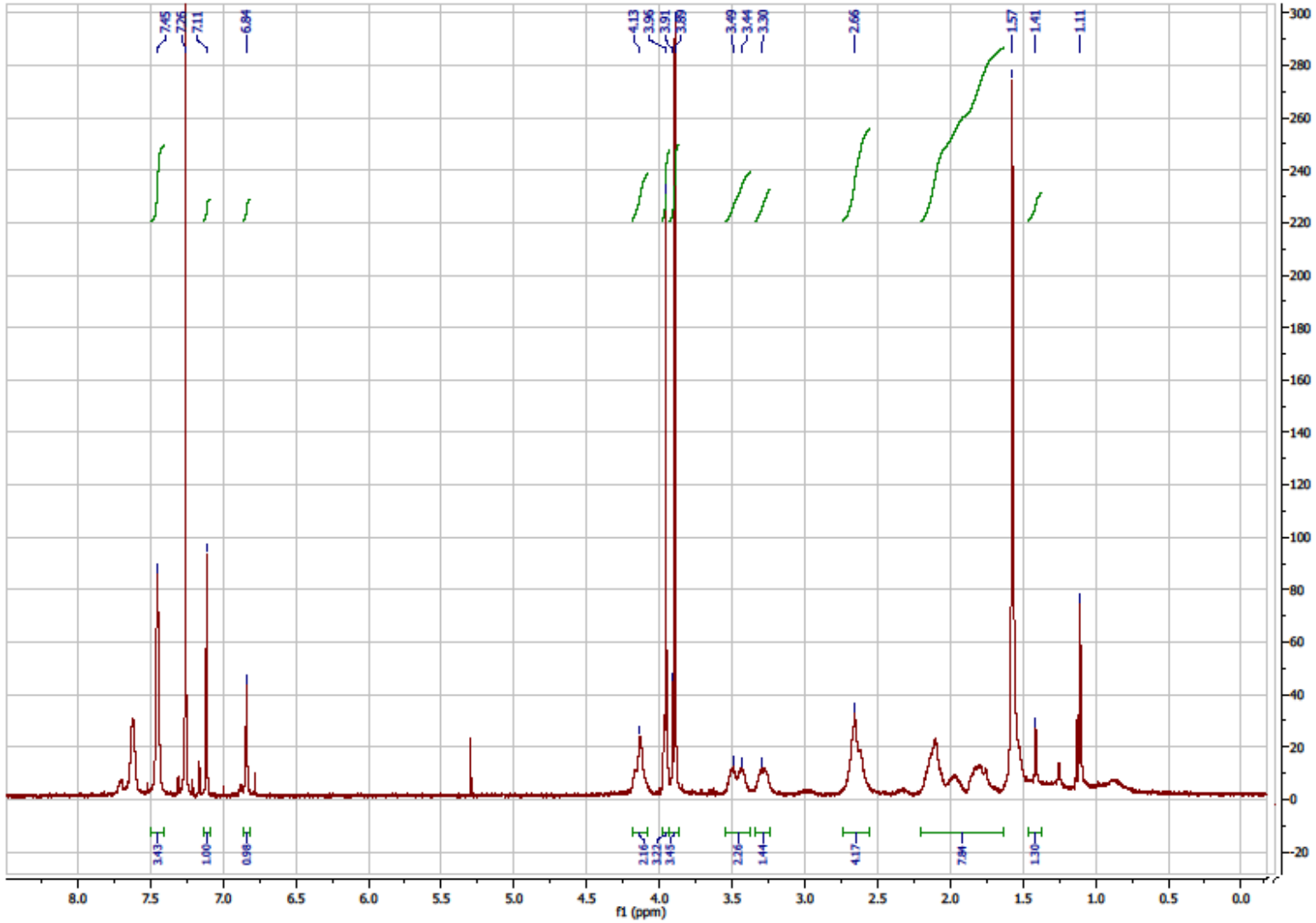

O
H3C
O
H3C
O
N

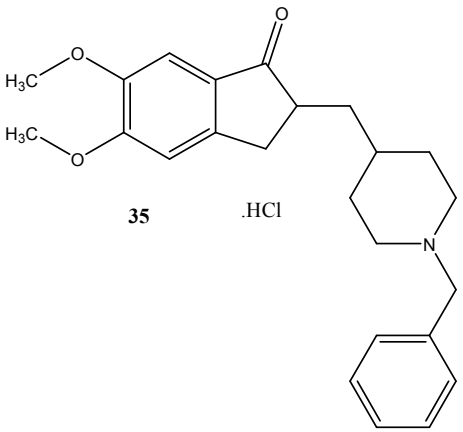
6


Analyst
Date
Analyst
08 July 2014 16:46
PerkinElmer Spectrum Version 10.4.00
08 July 2014 16:46
%T
cm-1
3032.91cm-1
3006.46cm-1
3066.71cm-1
2840.81cm-1
2801.48cm-1
2758.67cm-1
2915.70cm-1
2162.85cm-1
2050.90cm-1
1397.11cm-1
1344.60cm-1
1387.58cm-1
1604.22cm-1
1588.94cm-1
1496.06cm-1
1452.35cm-1
1687.14cm-1
1311.03cm-1
1261.52cm-1
1220.81cm-1
1198.78cm-1
1124.54cm-1
1104.05cm-1
1107.36cm-1
1071.03cm-1
1033.71cm-1
992.57cm-1
982.01cm-1
973.71cm-1
903.43cm-1
848.48cm-1
803.51cm-1
785.84cm-1
758.12cm-1
731.26cm-1
695.52cm-1
651.85cm-1
621.24cm-1
595.36cm-1
Donepezil Sample 217 By Analyst Date Tuesday, July 01 2014

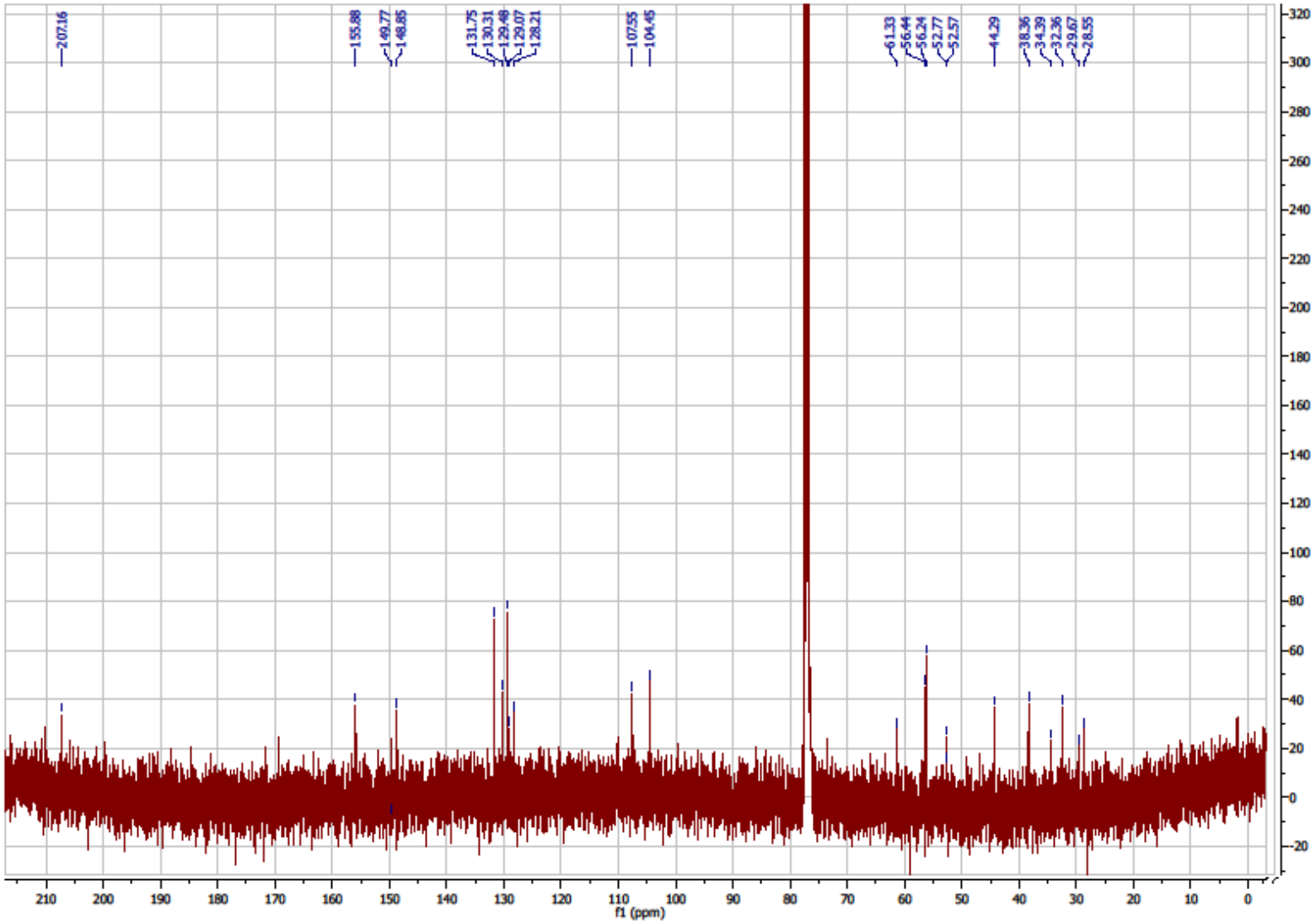

O
H3C
O
H3C
O
N

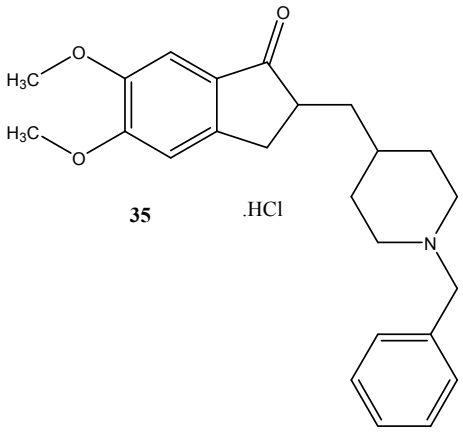
35 .HCl


7.45
7.26
7.11
6.84
4.13
3.96
3.91
3.89
3.49
3.44
3.30
2.66
1.57
1.41
1.11
3.43
1.00
0.98
2.16
3.23
3.43
2.26
1.44
4.17
7.84
1.30
f1 (ppm)

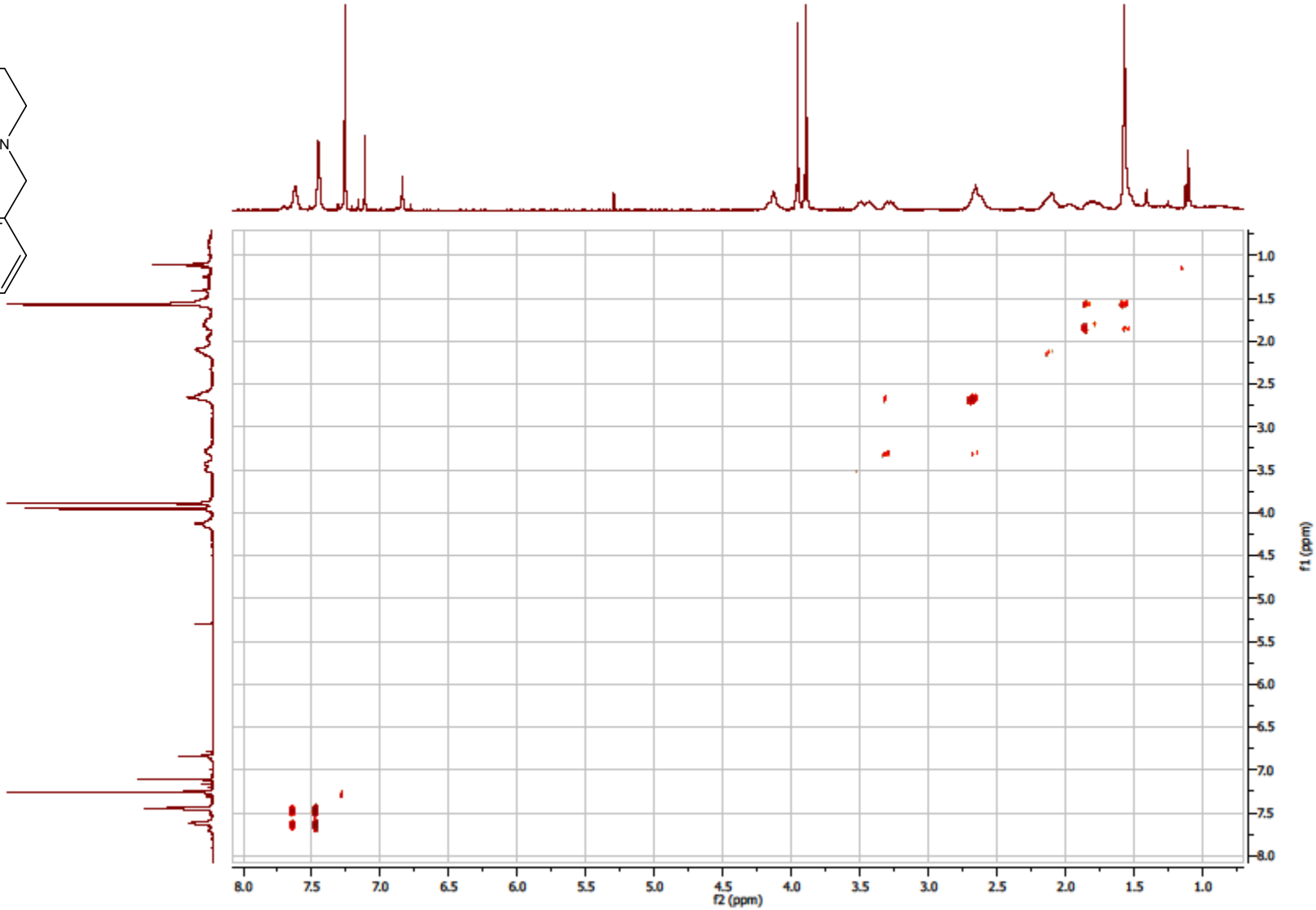

O
H3C
O
H3C
O
N

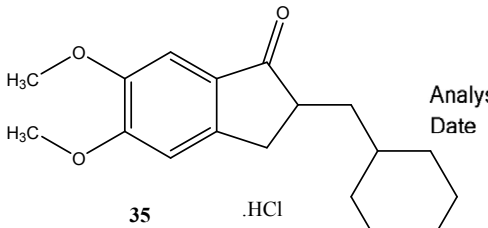
35 .HCl


207.16
155.88
149.77
148.85
131.75
130.31
129.48
129.07
128.21
107.55
104.45
61.33
56.44
56.24
52.77
52.57
44.29
38.36
34.39
32.36
29.67
28.55
f1 (ppm)

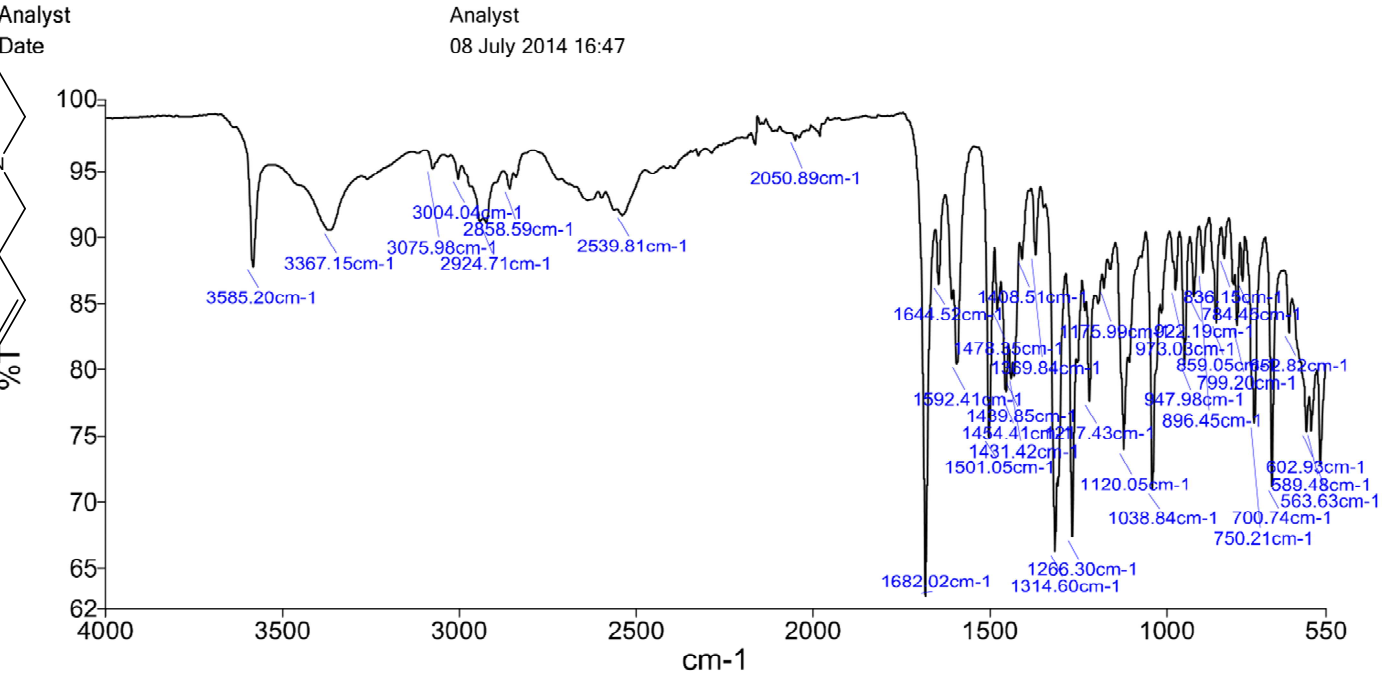

O
H3C
O
H3C
O
N

35 .HCl


8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
f1 (ppm)



35 .HCl



R21DonepezilHClrecr Sample 234 By Analyst Date Friday, July 04 2014

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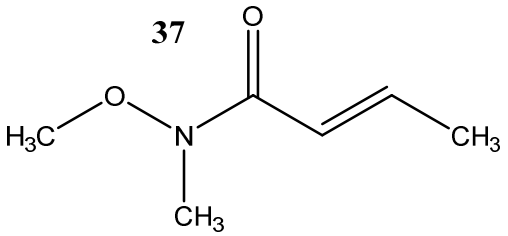
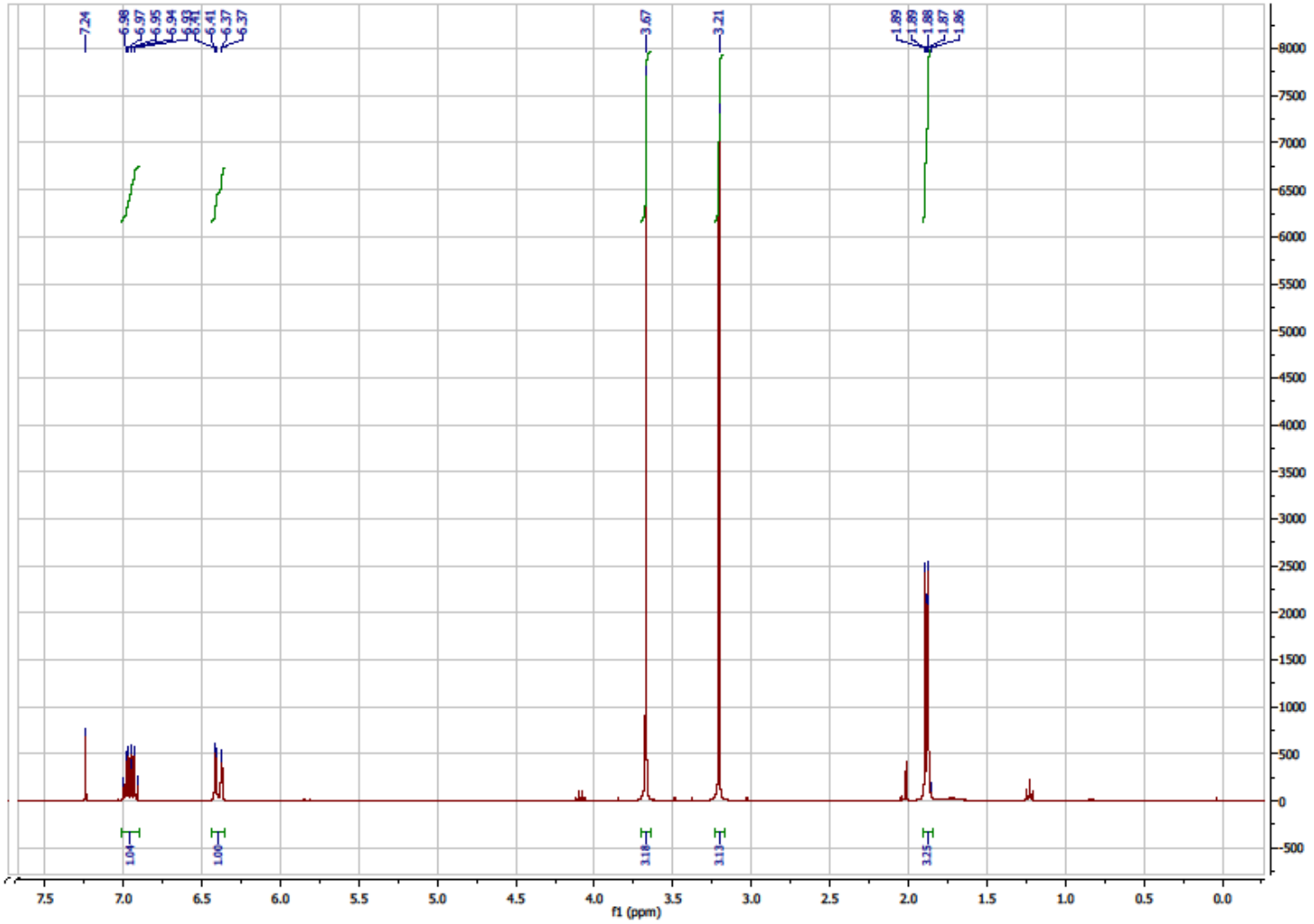
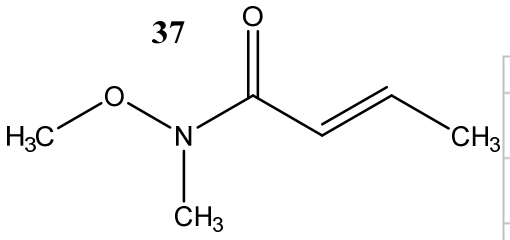
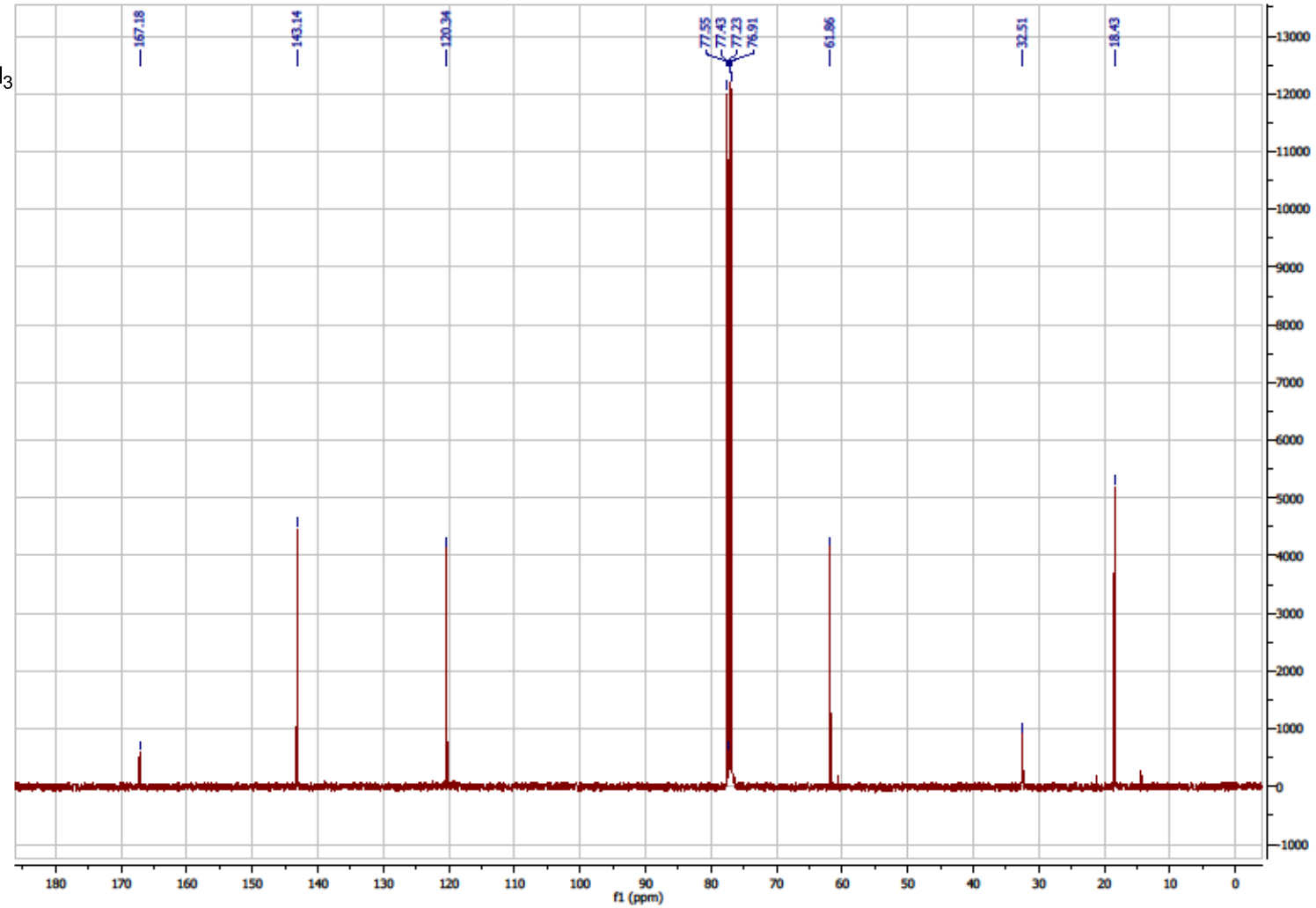

O
O
N
H3C
CH3
CH3

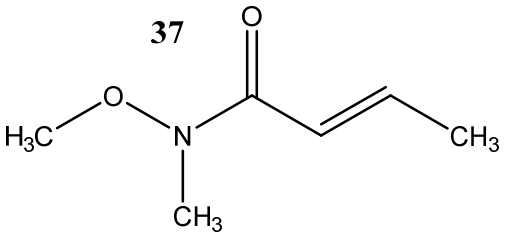

7.24
6.98
6.97
6.95
6.94
6.93
6.41
6.37
6.37
3.67
3.21
1.89
1.89
1.88
1.87
1.86
1.04
1.06
3.18
3.13
3.25
f1 (ppm)

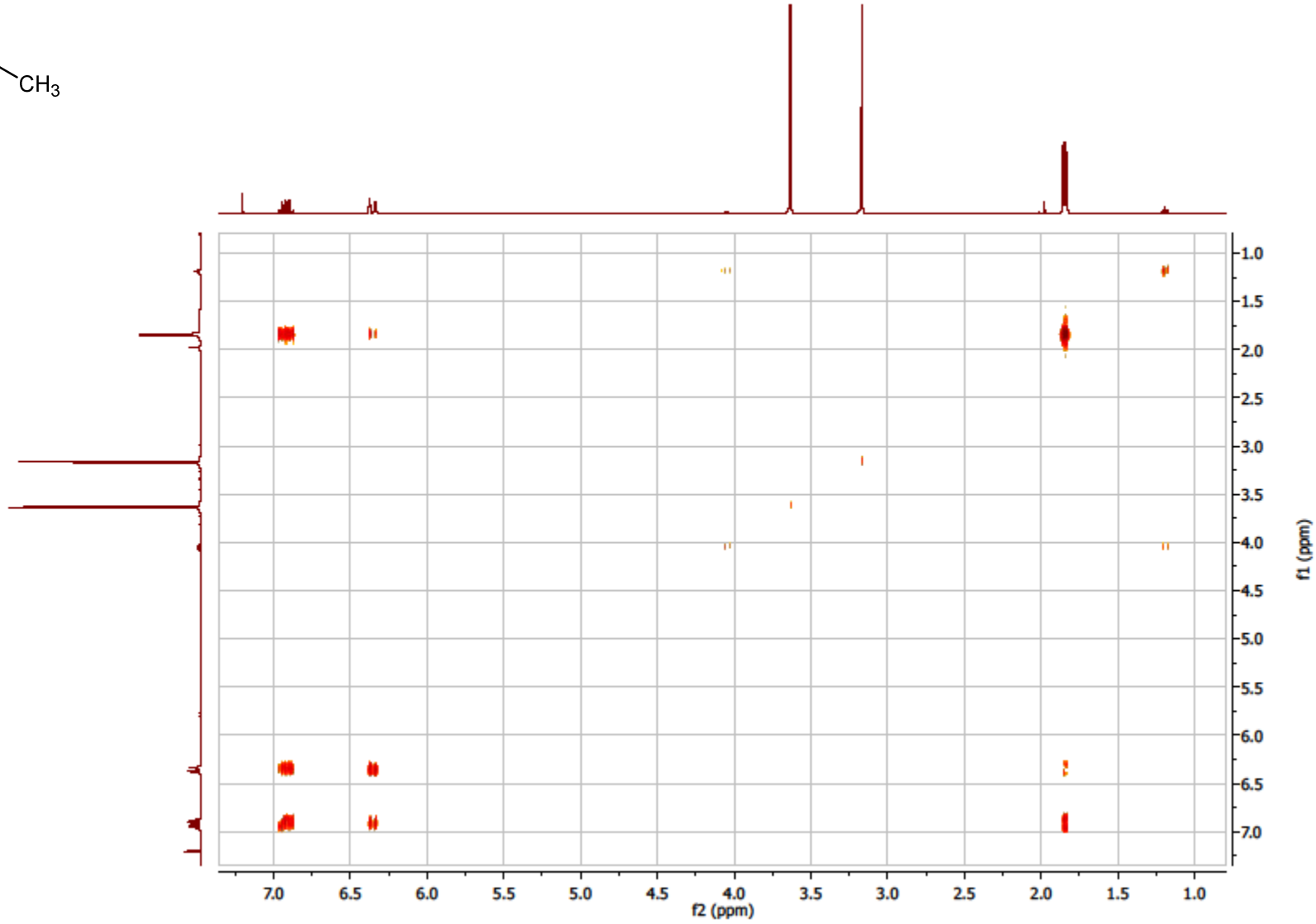
37


O
H3C
O
N
CH3
CH3

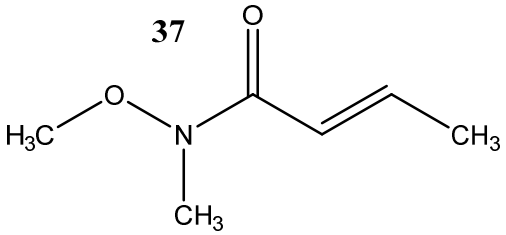

167.18
143.14
120.34
77.55
77.43
77.23
76.91
61.86
32.51
18.43
f1 (ppm)

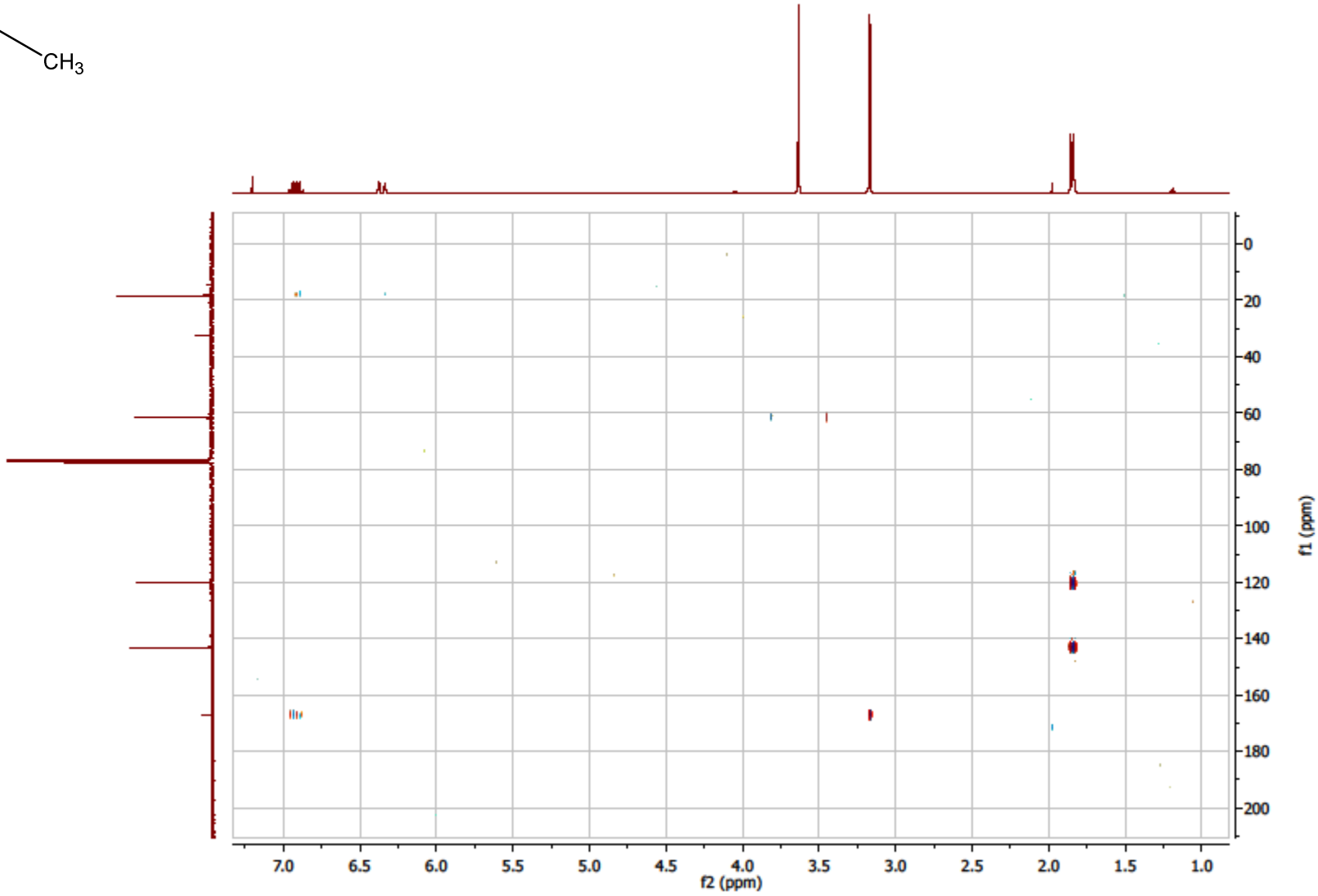
37


O
O
H3C
N
CH3
CH3

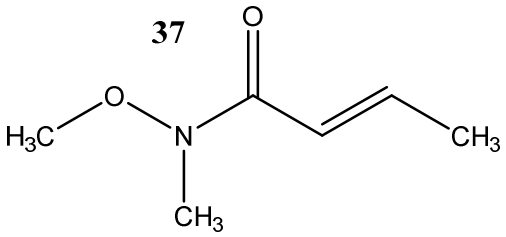

7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
f1 (ppm)

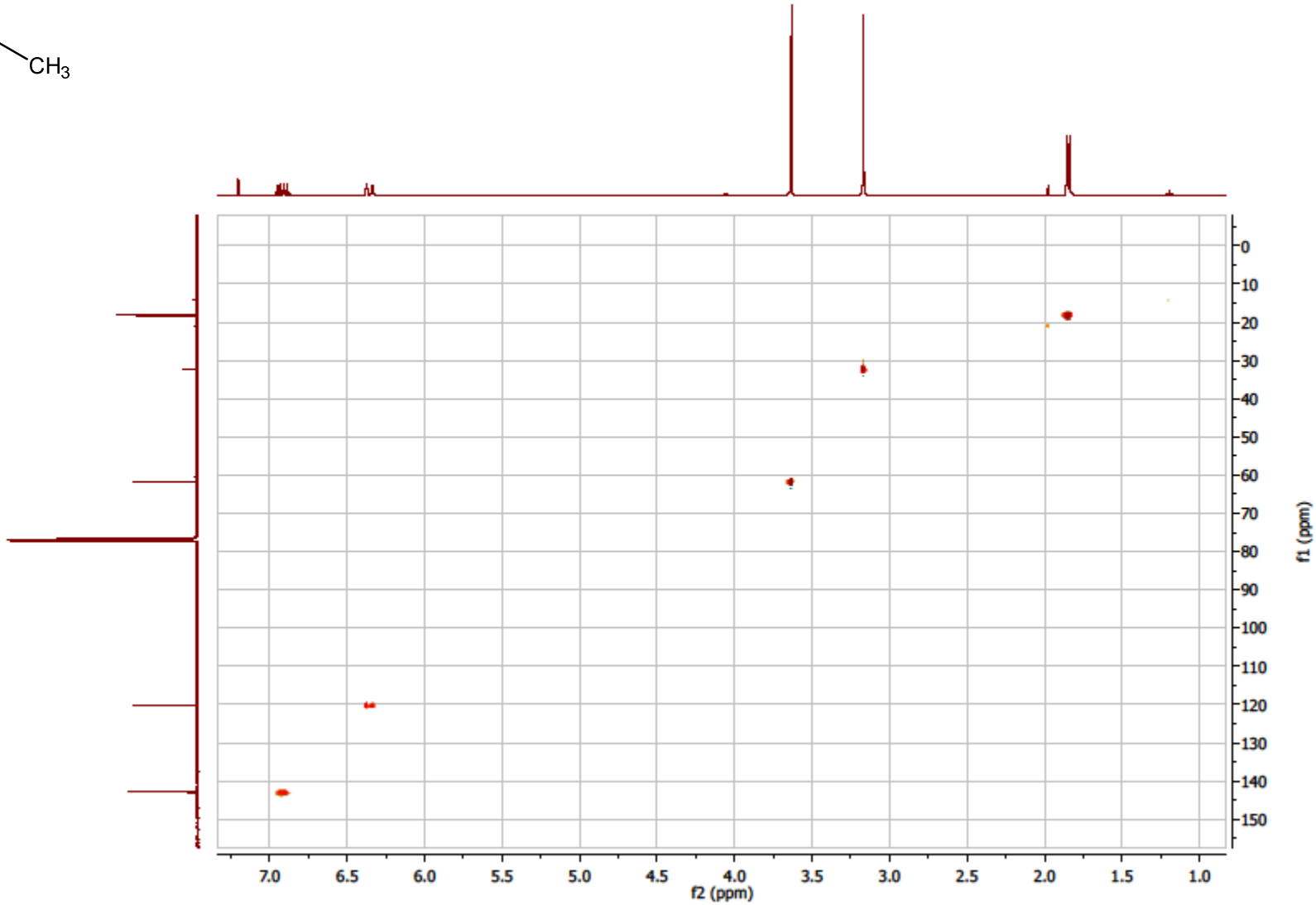
37


O
O
H3C
N
CH3
CH3


0
20
40
60
80
100
120
140
160
180
200
f1 (ppm)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)

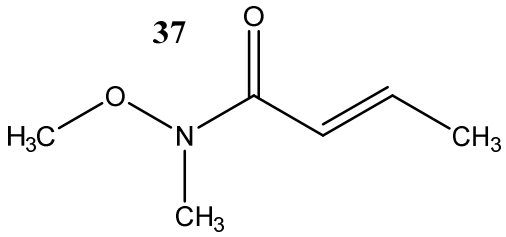
37


O
O
H3C
N
CH3
CH3


0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)

Appendix

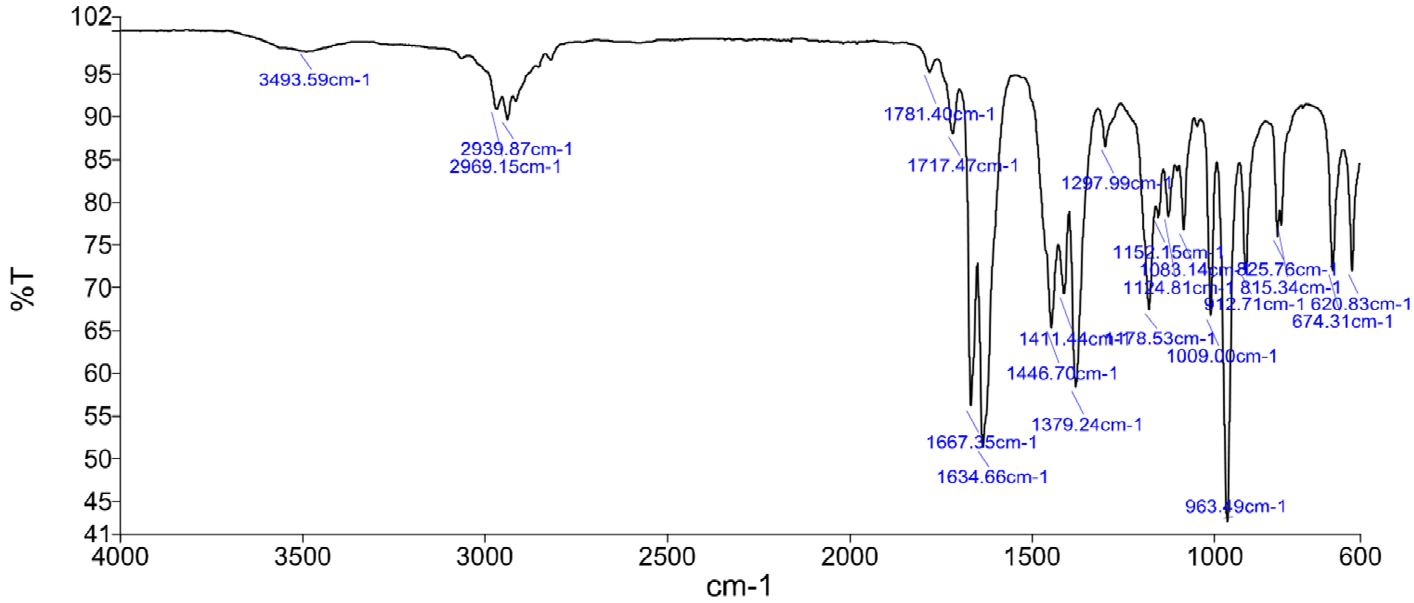
37



PerkinElmer Spectrum Version 10.4.00
08 July 2014 16:47

Analyst
Date

Analyst
08 July 2014 16:47



Weinreb_Amide Sample 218 By Analyst Date Tuesday, July 01 2014

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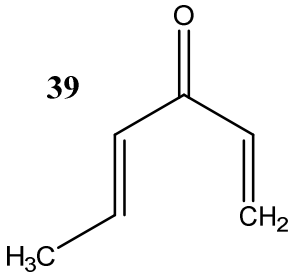
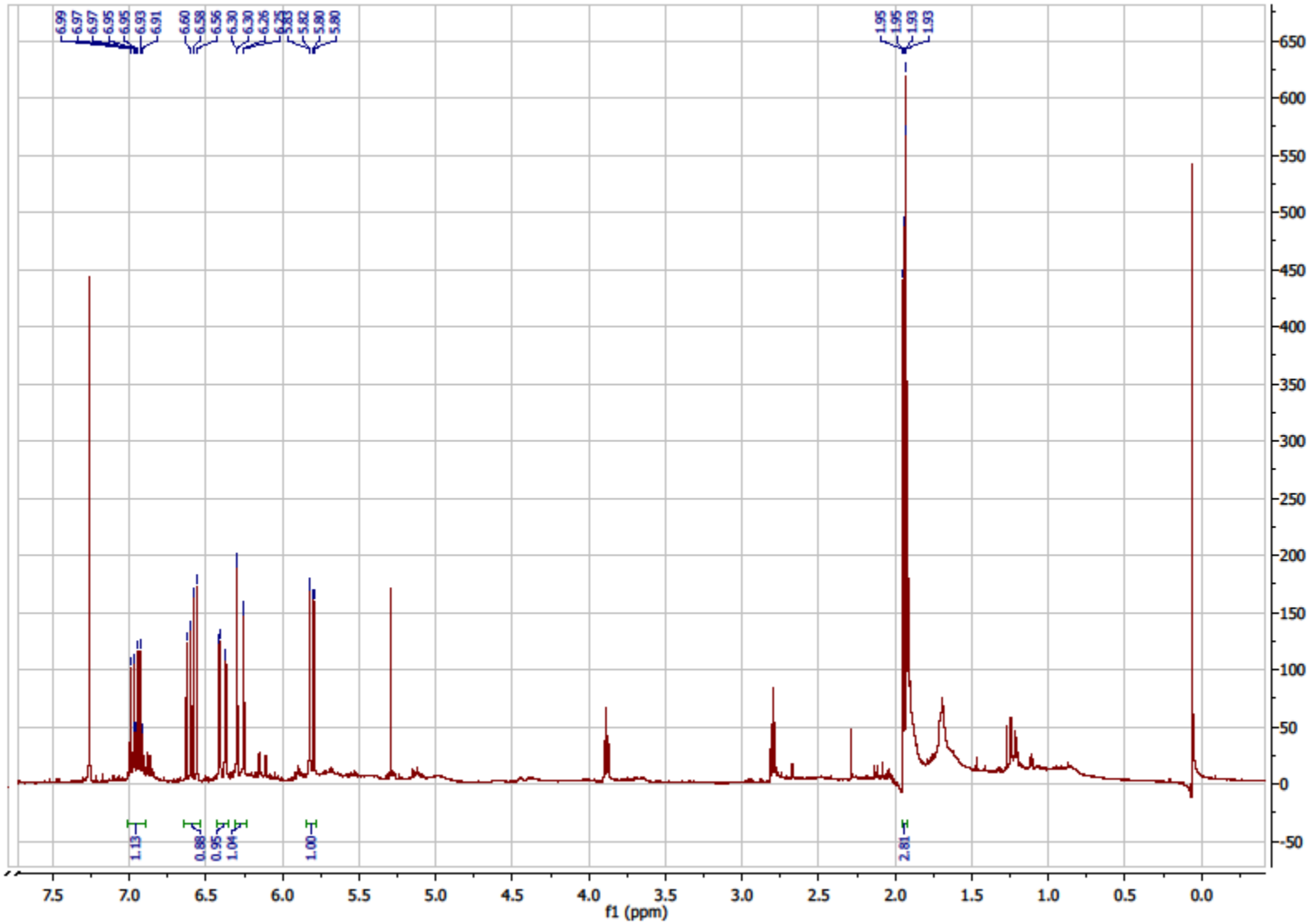
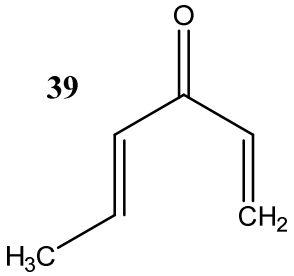
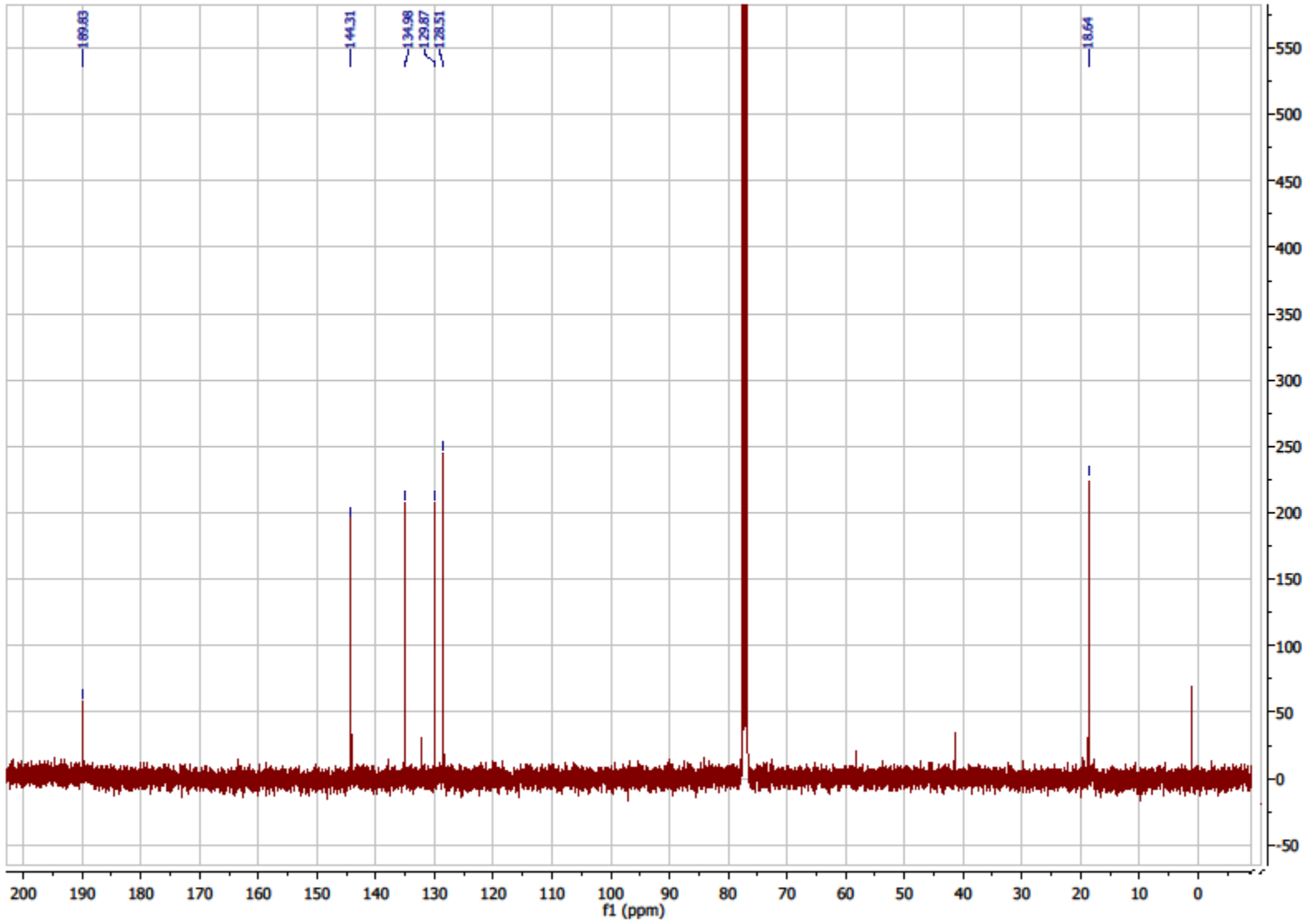

O
CH2
H3C

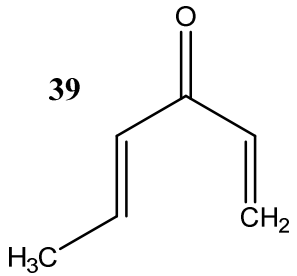

6.99
6.97
6.97
6.95
6.95
6.93
6.91
6.60
6.58
6.56
6.30
6.30
6.26
5.82
5.80
5.80
1.95
1.95
1.93
1.93
1.13
0.88
0.95
1.04
1.00
2.81
f1 (ppm)

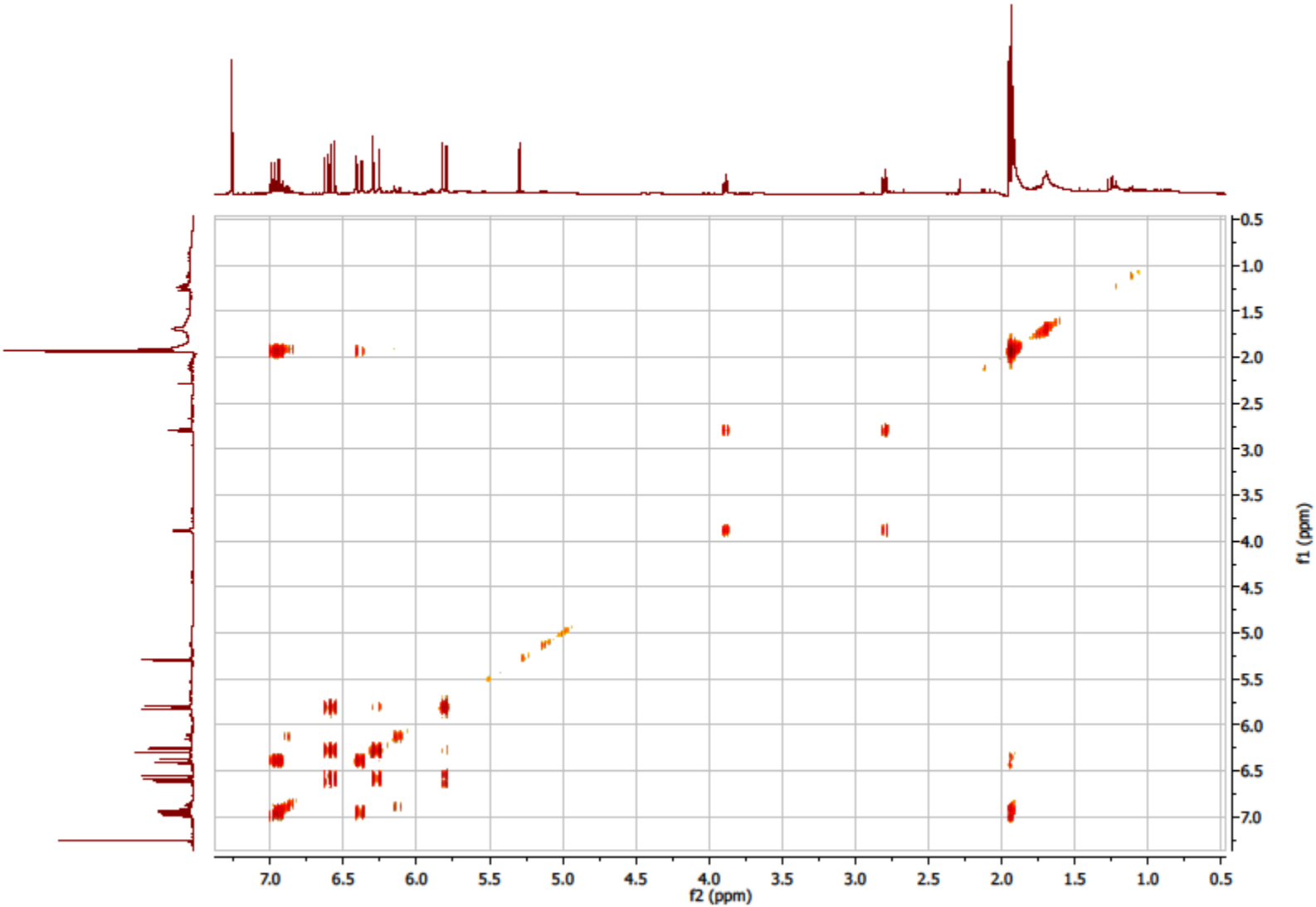
39



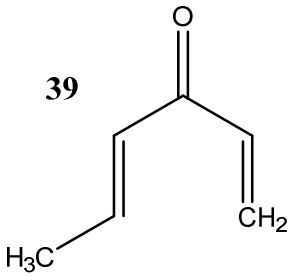


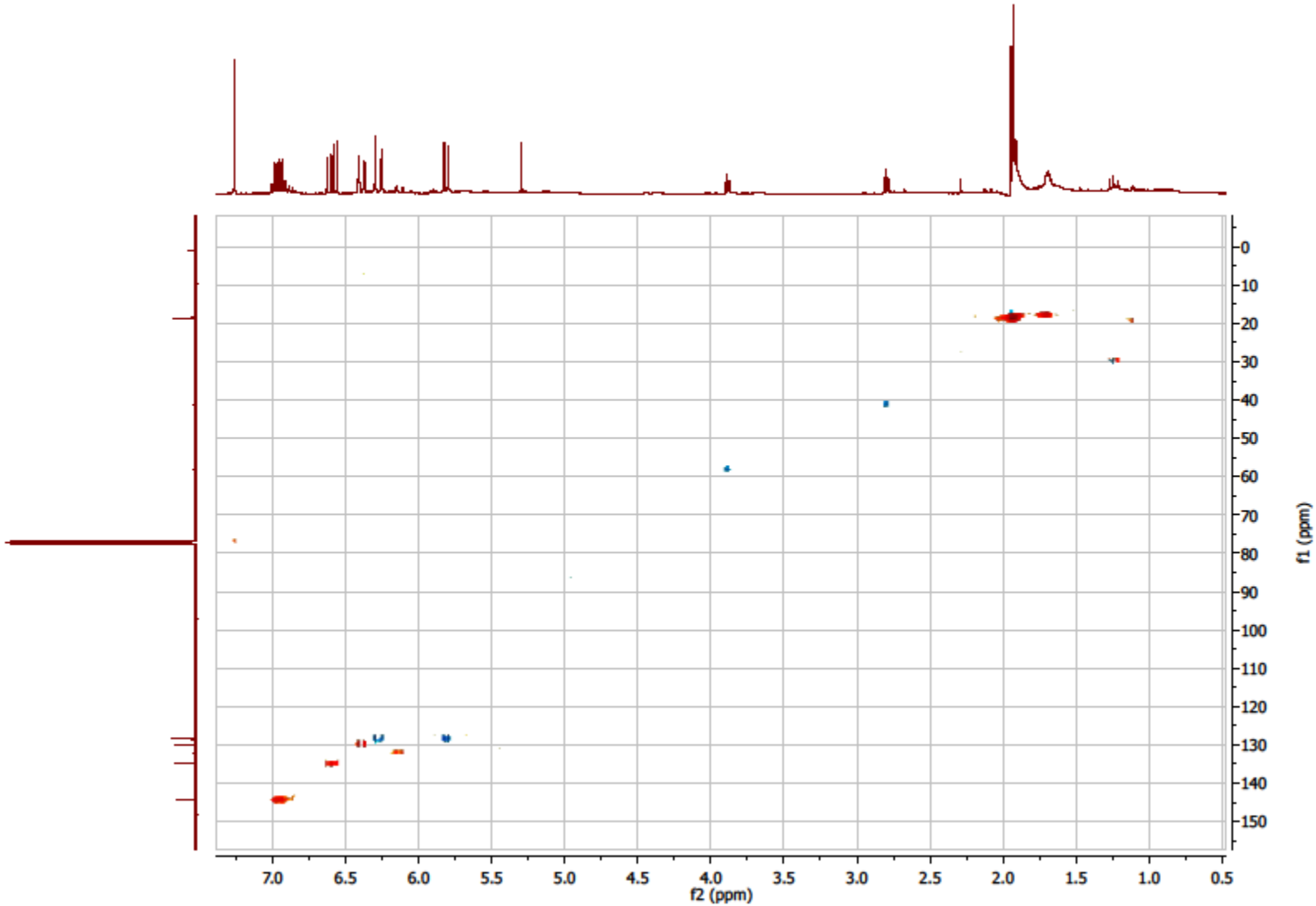
39



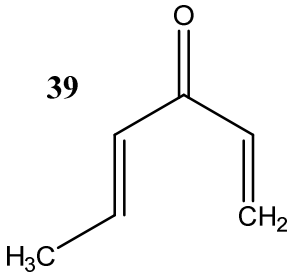


39


O
H3C
CH2


0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)

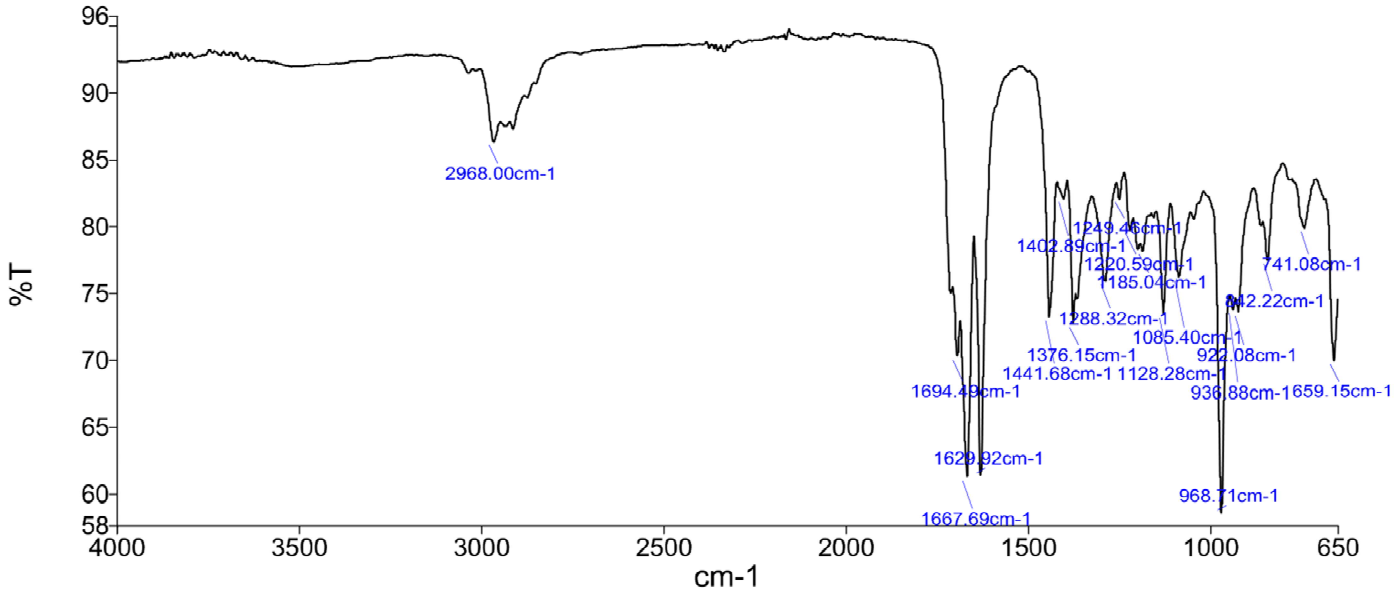
39



PerkinElmer Spectrum Version 10.4.00
11 July 2014 16:05

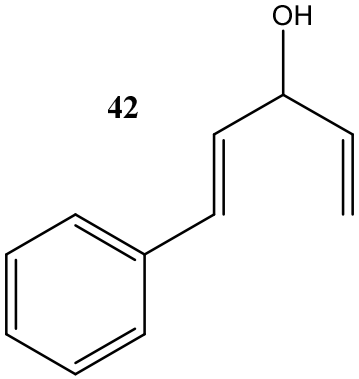
Analyst
Date

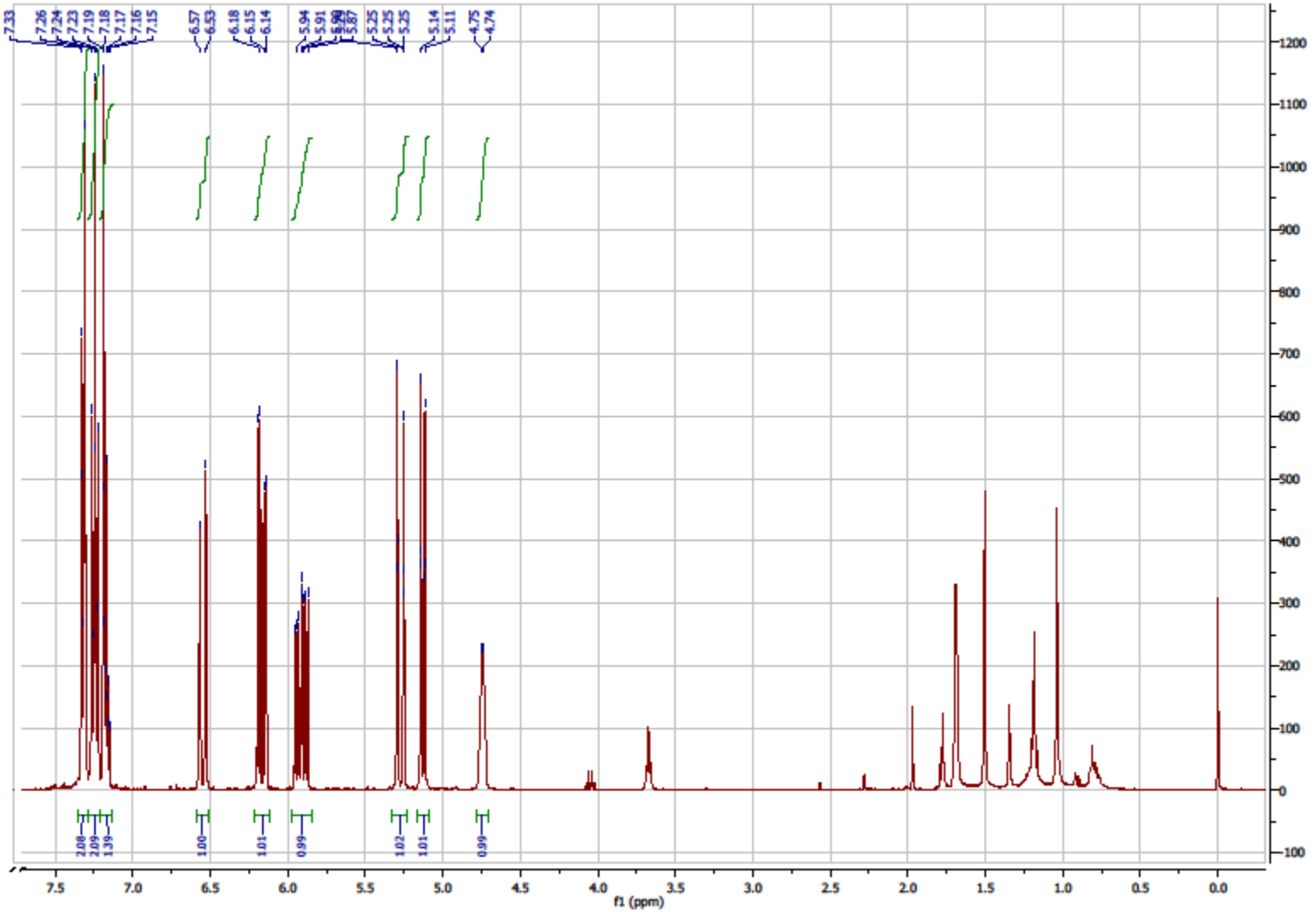
Analyst
11 July 2014 16:05



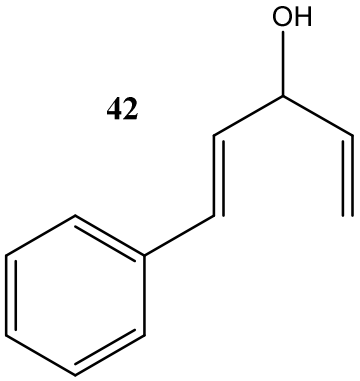
Analyst 343 Sample 343 By Analyst Date Friday, July 11 2014

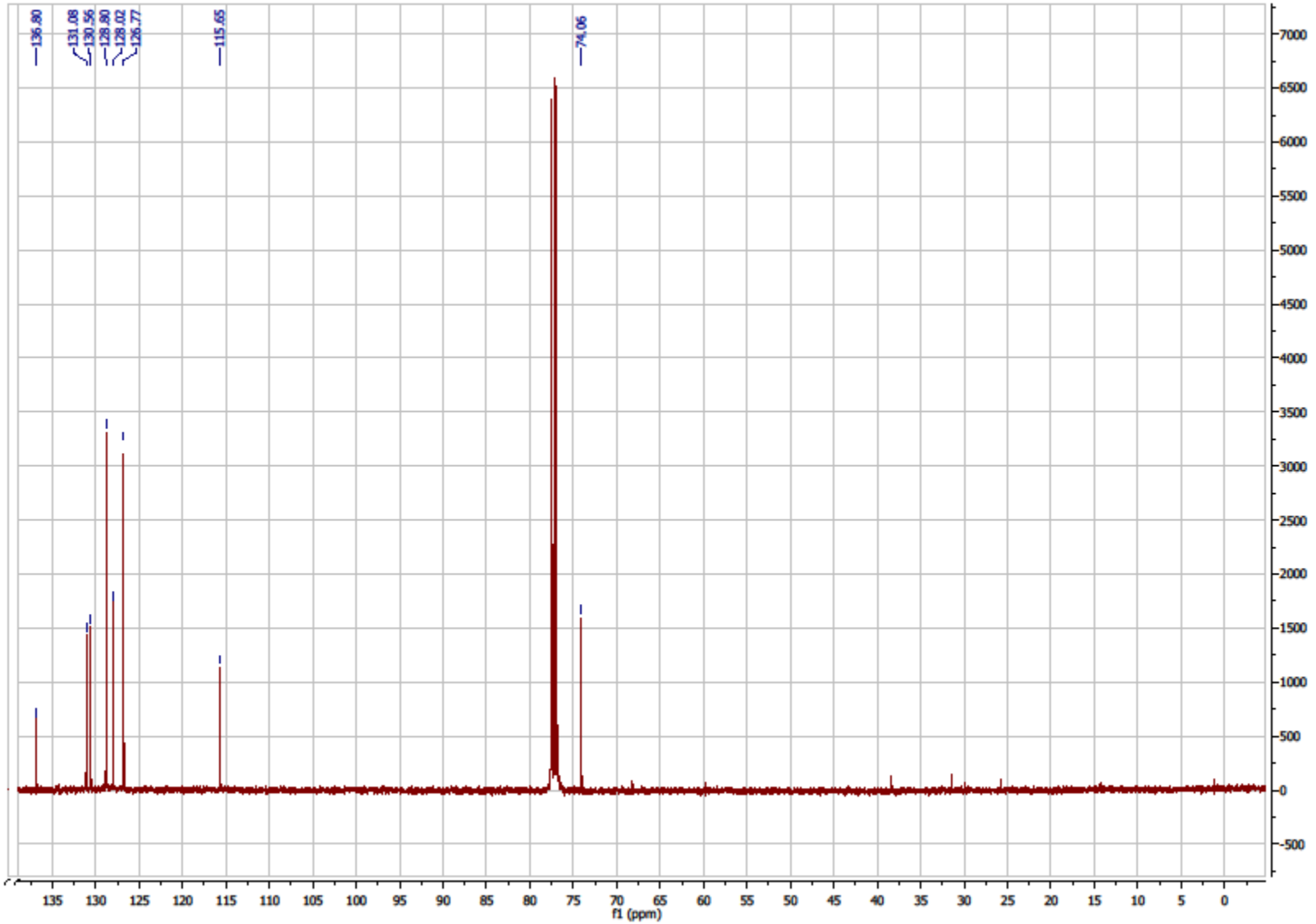
42


OH

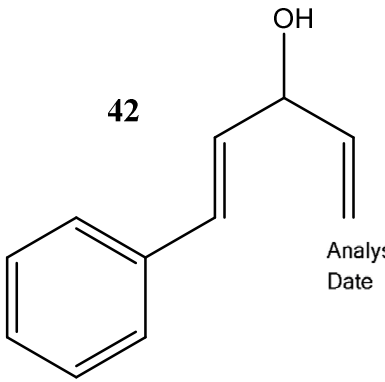

7.33
7.26
7.24
7.23
7.19
7.18
7.17
7.16
7.15
6.57
6.53
6.18
6.15
6.14
5.94
5.91
5.25
5.25
5.25
5.14
5.11
4.75
4.74
2.08
2.09
1.39
1.00
1.01
0.99
1.02
1.01
0.99
f1 (ppm)

42

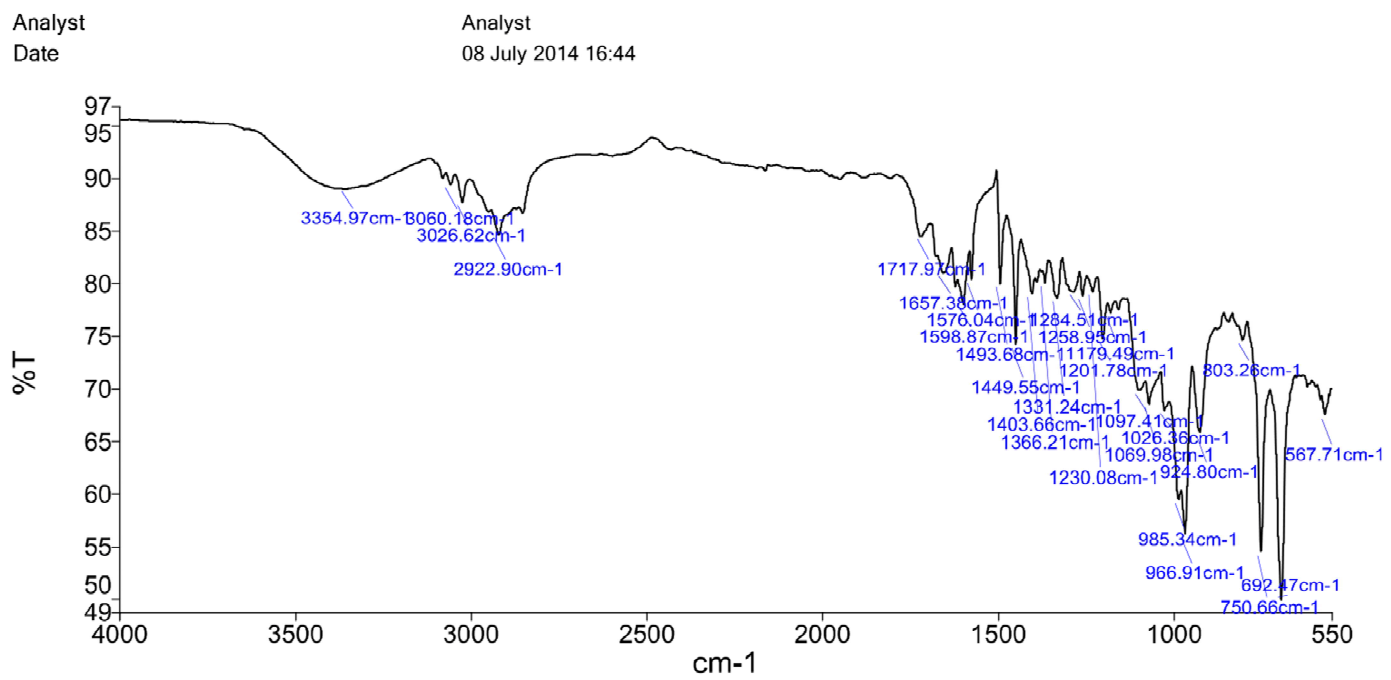


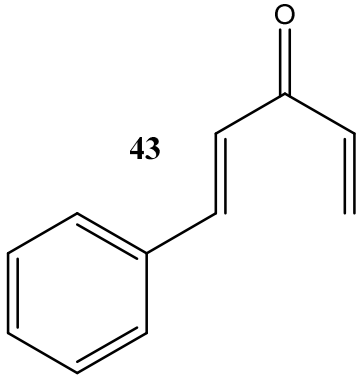


Appendix

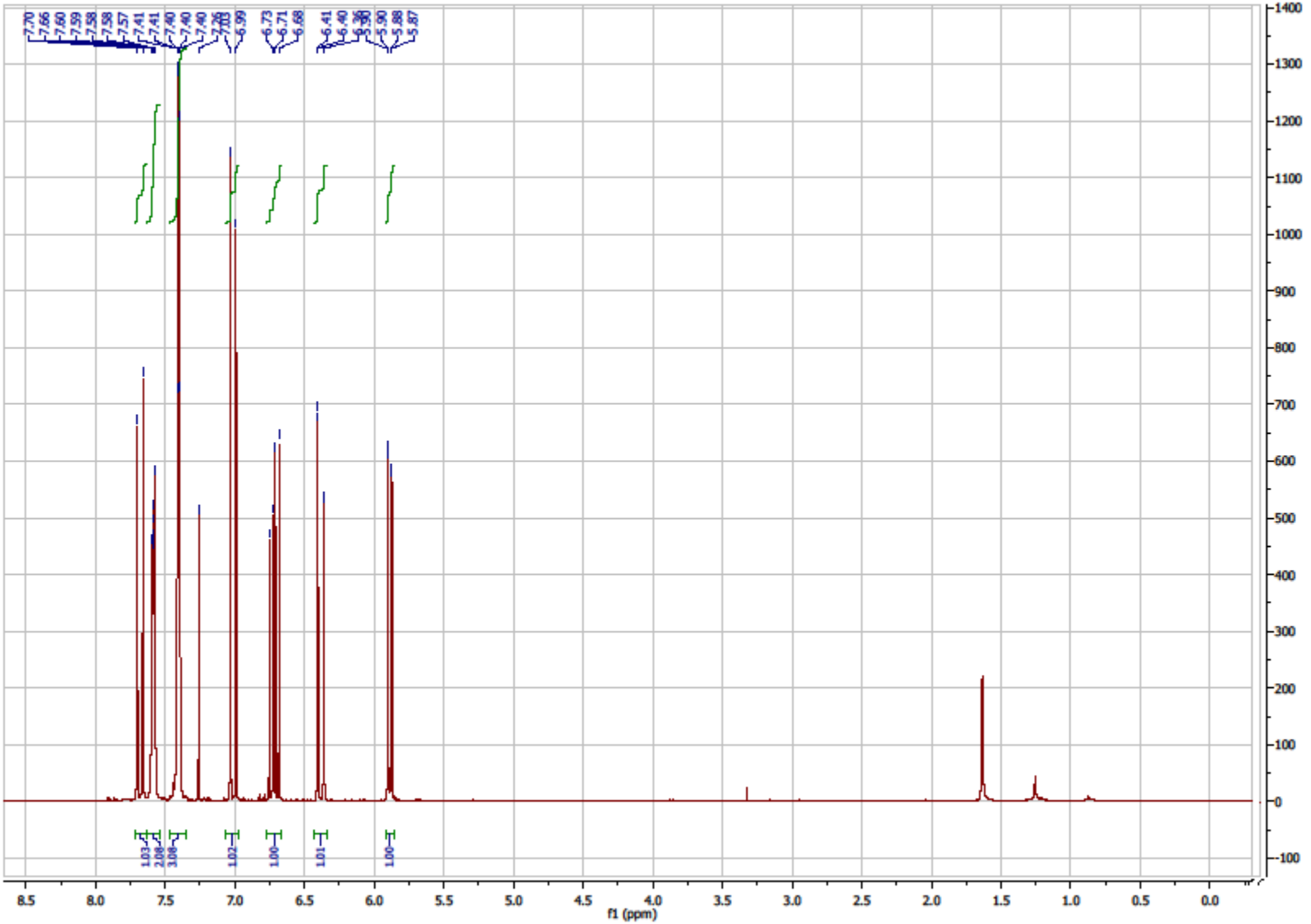

OH

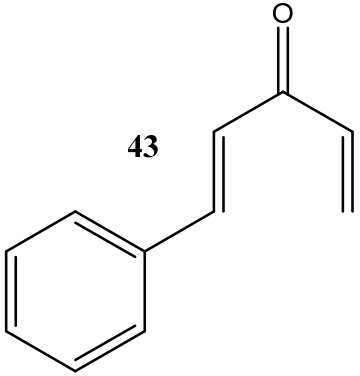
42


PerkinElmer Spectrum Version 10.4.00
08 July 2014 16:44
Analyst
Date
Analyst
08 July 2014 16:44
%T
cm-1
3354.97cm-1
3060.18cm-1
3026.62cm-1
2922.90cm-1
1717.97cm-1
1657.38cm-1
1576.04cm-1
1598.87cm-1
1493.68cm-1
1449.55cm-1
1403.66cm-1
1366.21cm-1
1331.24cm-1
1284.51cm-1
1258.95cm-1
1179.49cm-1
1201.78cm-1
1097.41cm-1
1026.36cm-1
1069.98cm-1
1230.08cm-1
924.80cm-1
985.34cm-1
966.91cm-1
803.26cm-1
692.47cm-1
750.66cm-1
567.71cm-1
R15 alcohol Sample 233 By Analyst Date Friday, July 04 2014

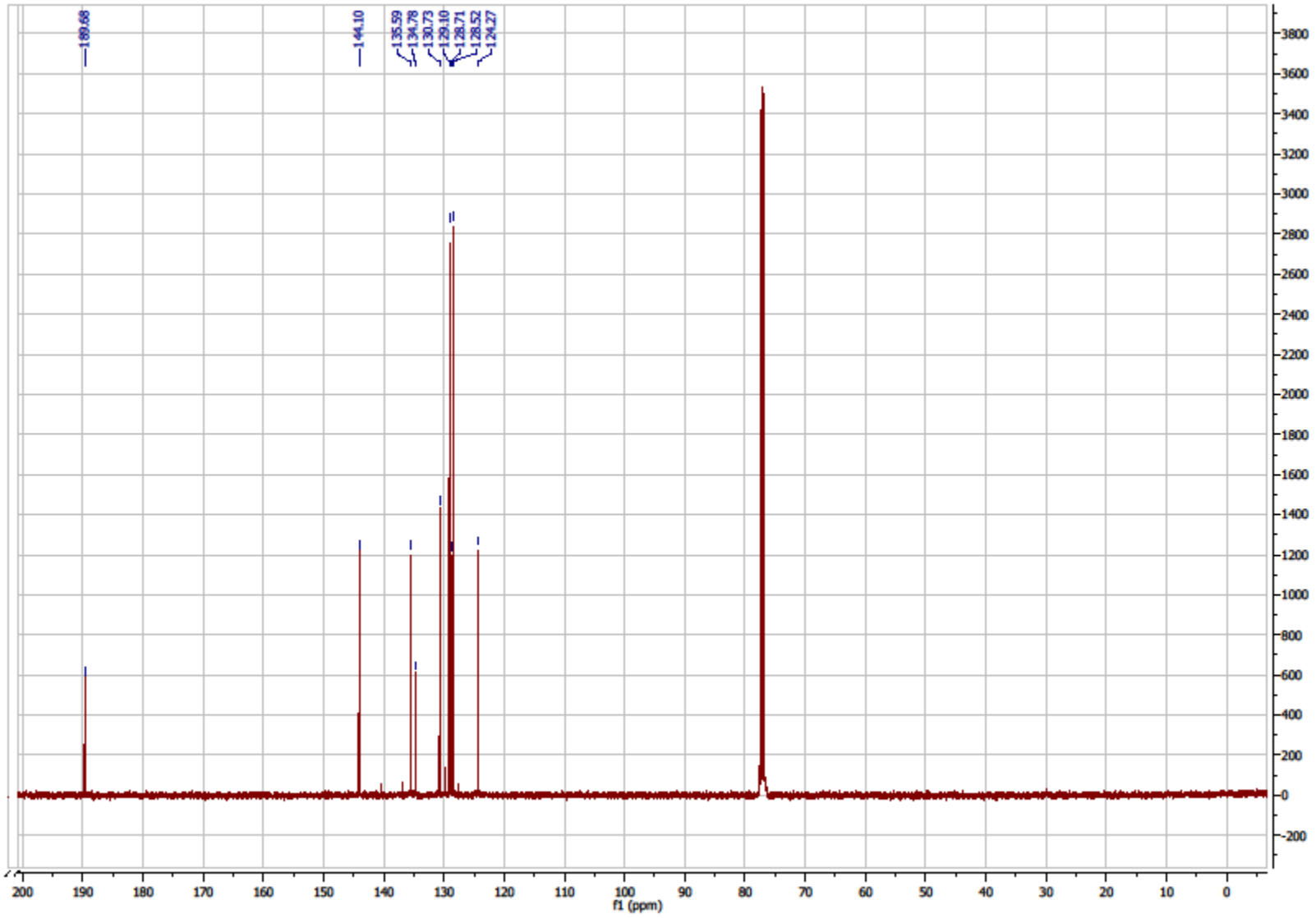


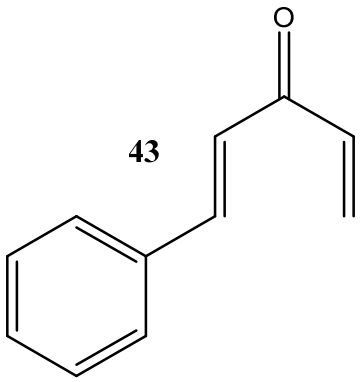
43


7.70
7.66
7.60
7.59
7.58
7.58
7.57
7.41
7.41
7.40
7.40
7.40
7.26
7.03
6.99
6.73
6.71
6.68
6.41
6.40
5.90
5.88
5.87
1.03
2.08
3.08
1.02
1.00
1.01
1.00
f1 (ppm)

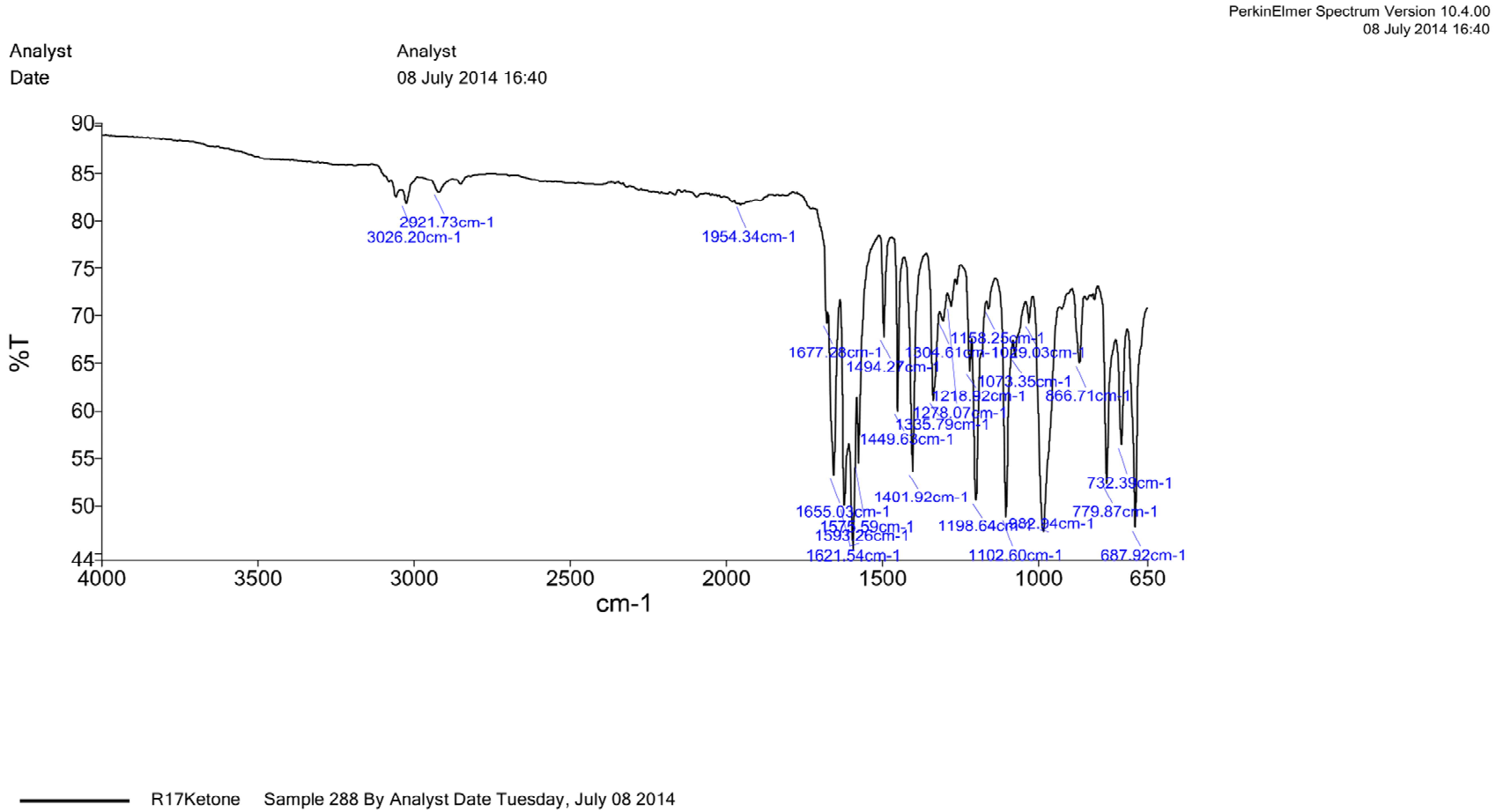


43


189.68
144.10
135.59
134.78
130.73
129.10
128.71
128.52
124.27
f1 (ppm)


O

43


PerkinElmer Spectrum Version 10.4.00
08 July 2014 16:40
Analyst
Date
Analyst
08 July 2014 16:40
%T
cm-1
2921.73cm-1
3026.20cm-1
1954.34cm-1
1677.28cm-1
1655.03cm-1
1621.54cm-1
1593.26cm-1
1578.59cm-1
1494.27cm-1
1449.63cm-1
1401.92cm-1
1335.79cm-1
1278.07cm-1
1218.92cm-1
1198.64cm-1
1158.25cm-1
1102.60cm-1
1073.35cm-1
1019.03cm-1
882.24cm-1
866.71cm-1
779.87cm-1
732.39cm-1
687.92cm-1
R17Ketone Sample 288 By Analyst Date Tuesday, July 08 2014

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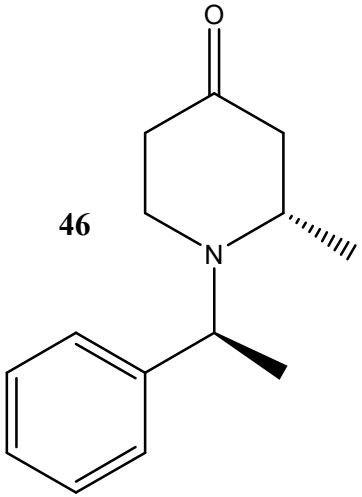
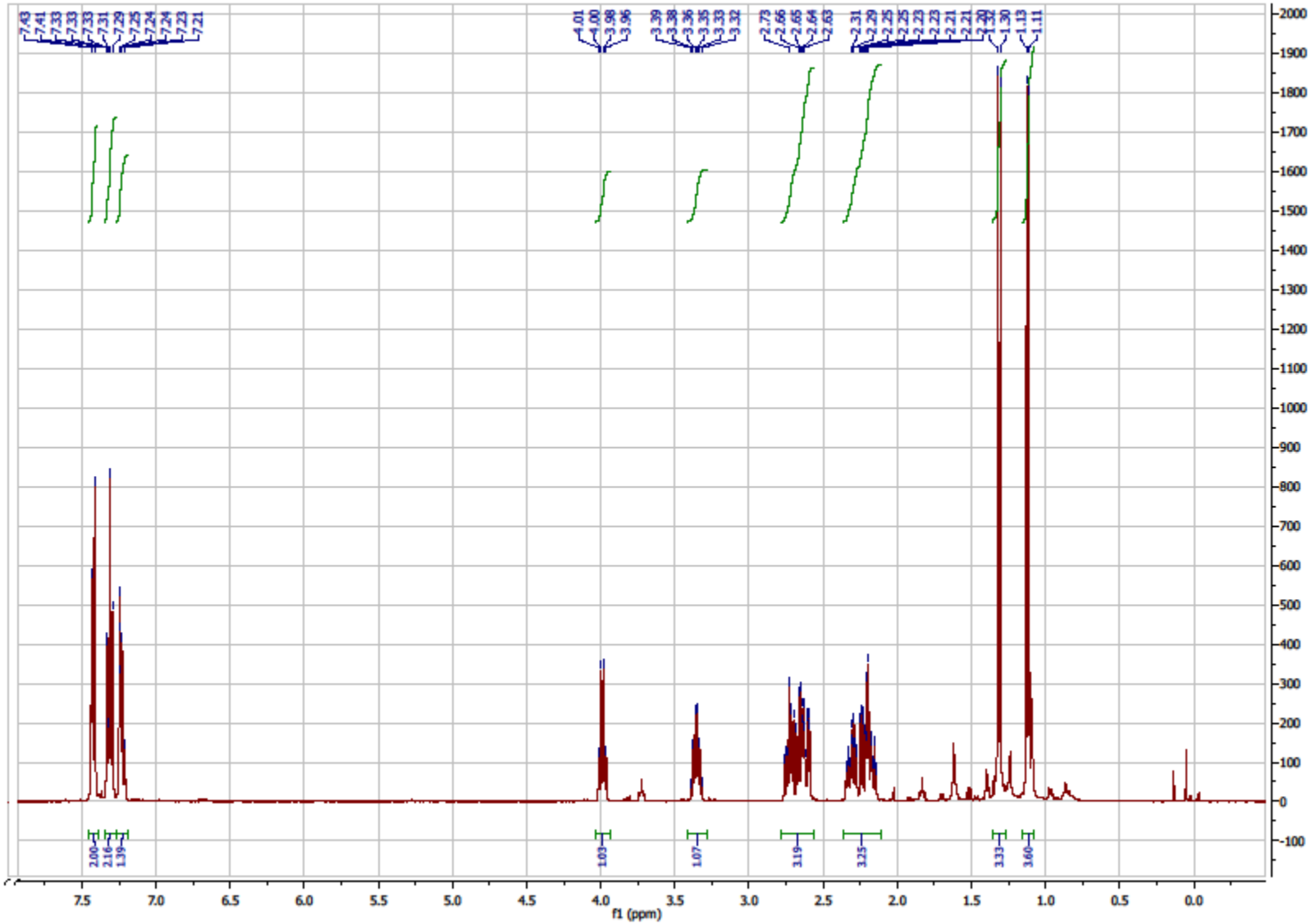
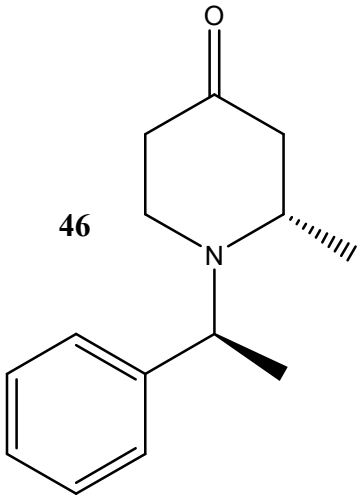
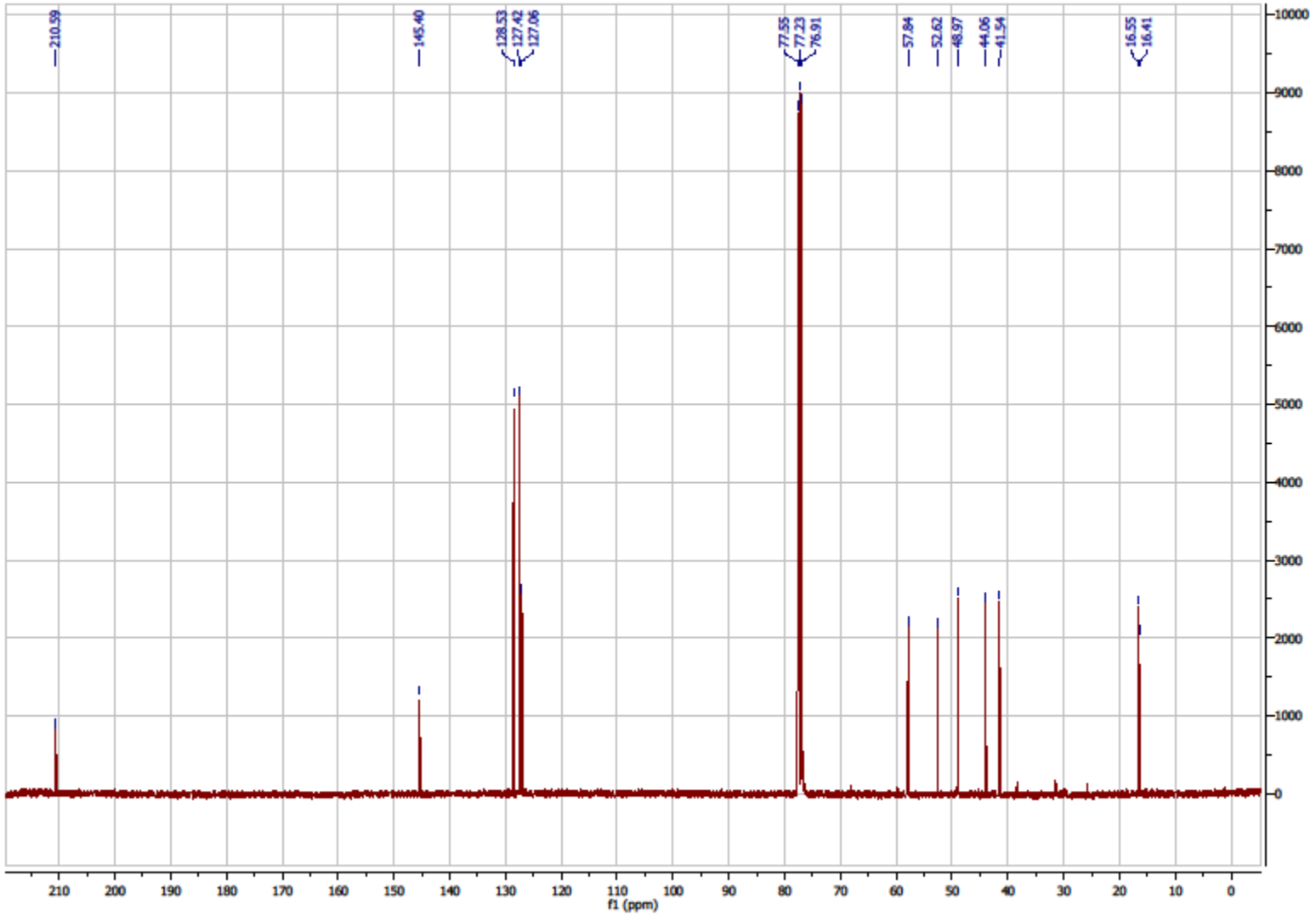

O
N

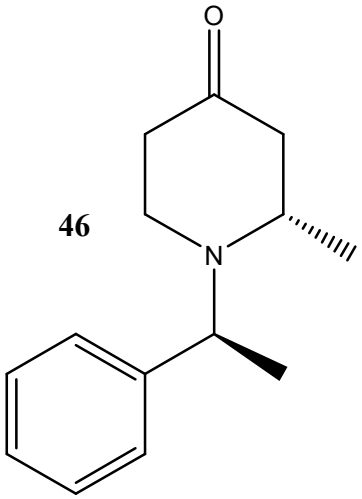

7.43
7.41
7.33
7.33
7.33
7.31
7.29
7.25
7.24
7.24
7.23
7.21
4.01
4.00
3.98
3.96
3.39
3.38
3.36
3.35
3.33
3.32
2.73
2.66
2.65
2.64
2.63
2.31
2.29
2.25
2.25
2.23
2.23
2.21
2.21
1.32
1.30
1.13
1.11
2.00
2.16
1.39
1.03
1.07
3.19
3.25
3.33
3.60
f1 (ppm)

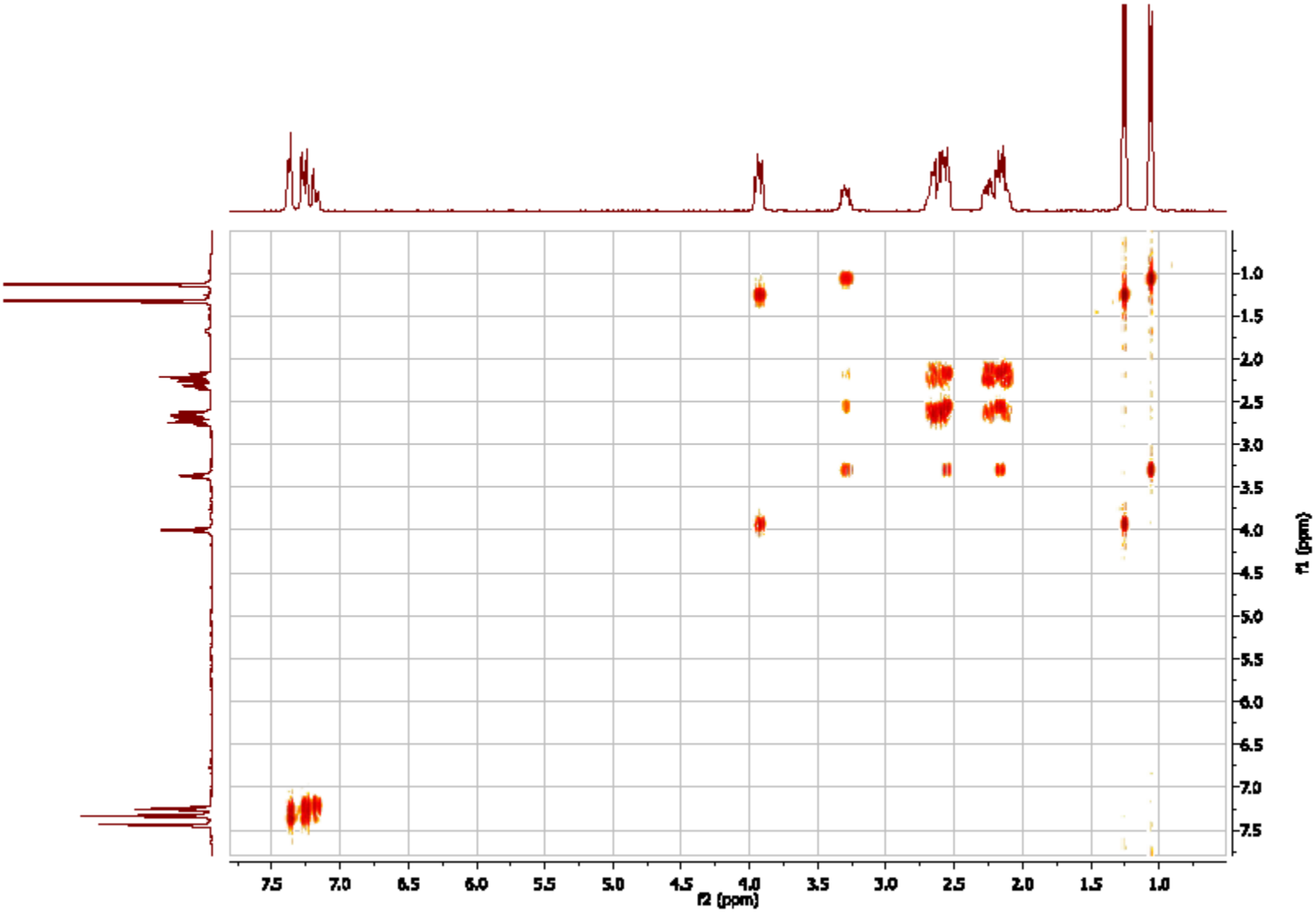
46


O
N

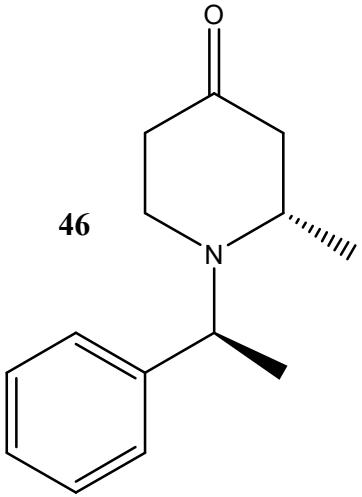

210.59
145.40
128.53
127.42
127.06
77.55
77.23
76.91
57.84
52.62
48.97
44.06
41.54
16.55
16.41
f1 (ppm)

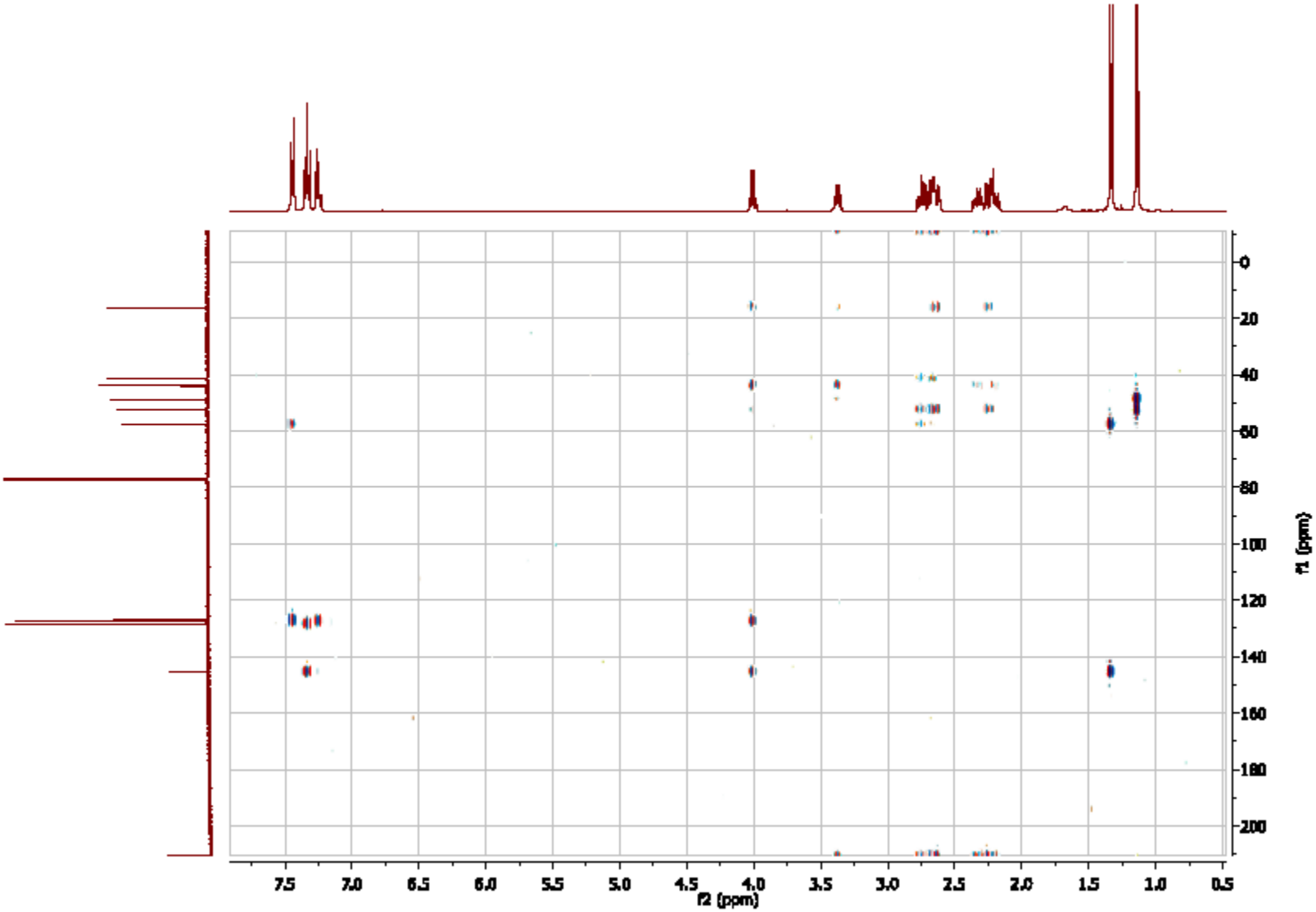
46


O
N

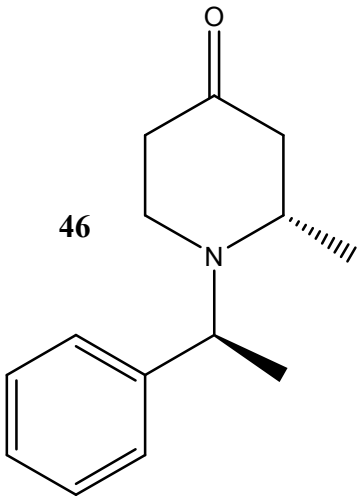

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)

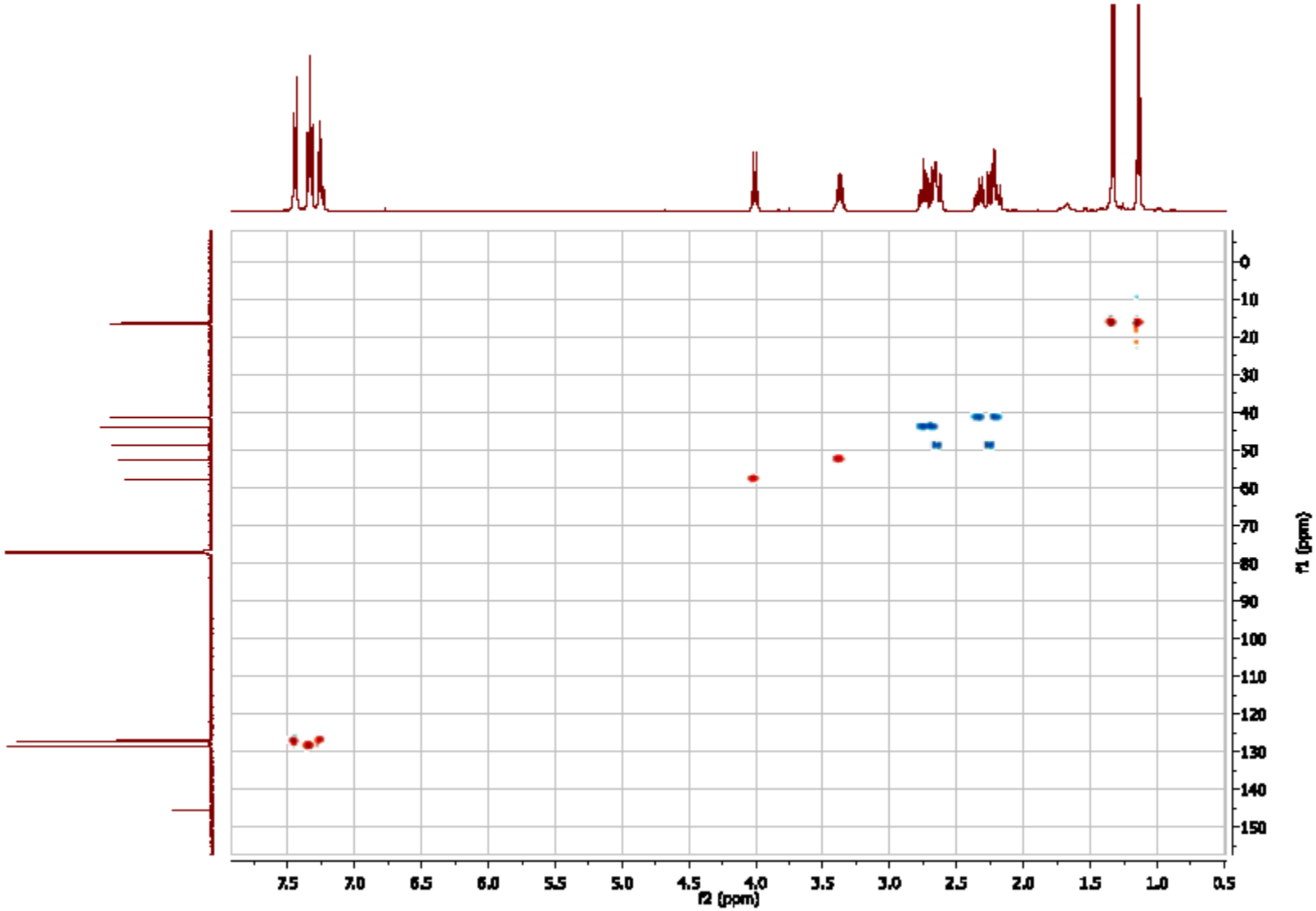
46


O
N

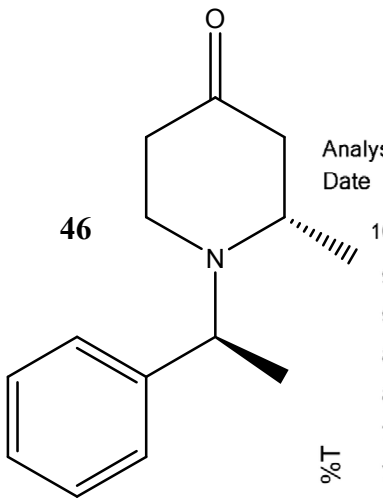

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
0
20
40
60
80
100
120
140
160
180
200
f1 (ppm)

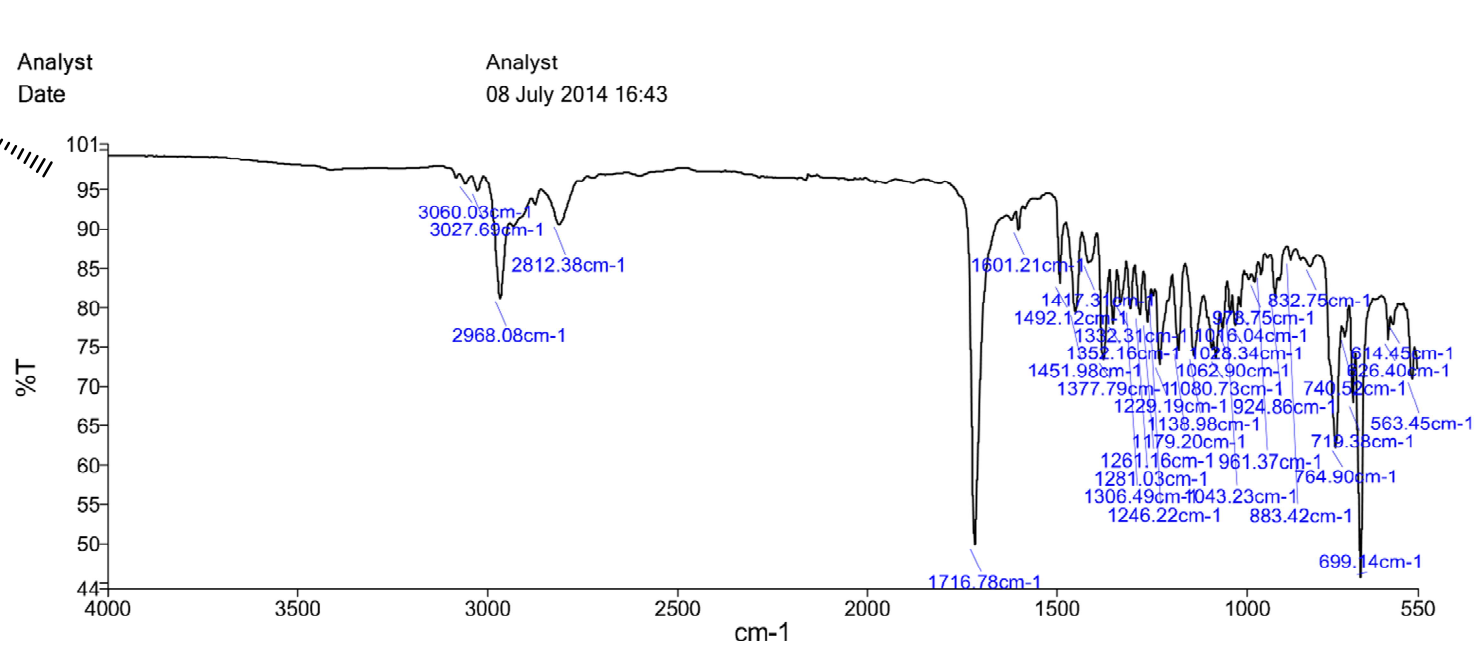
46


O
N

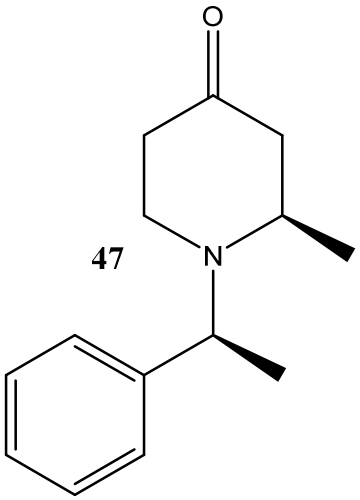

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)

46

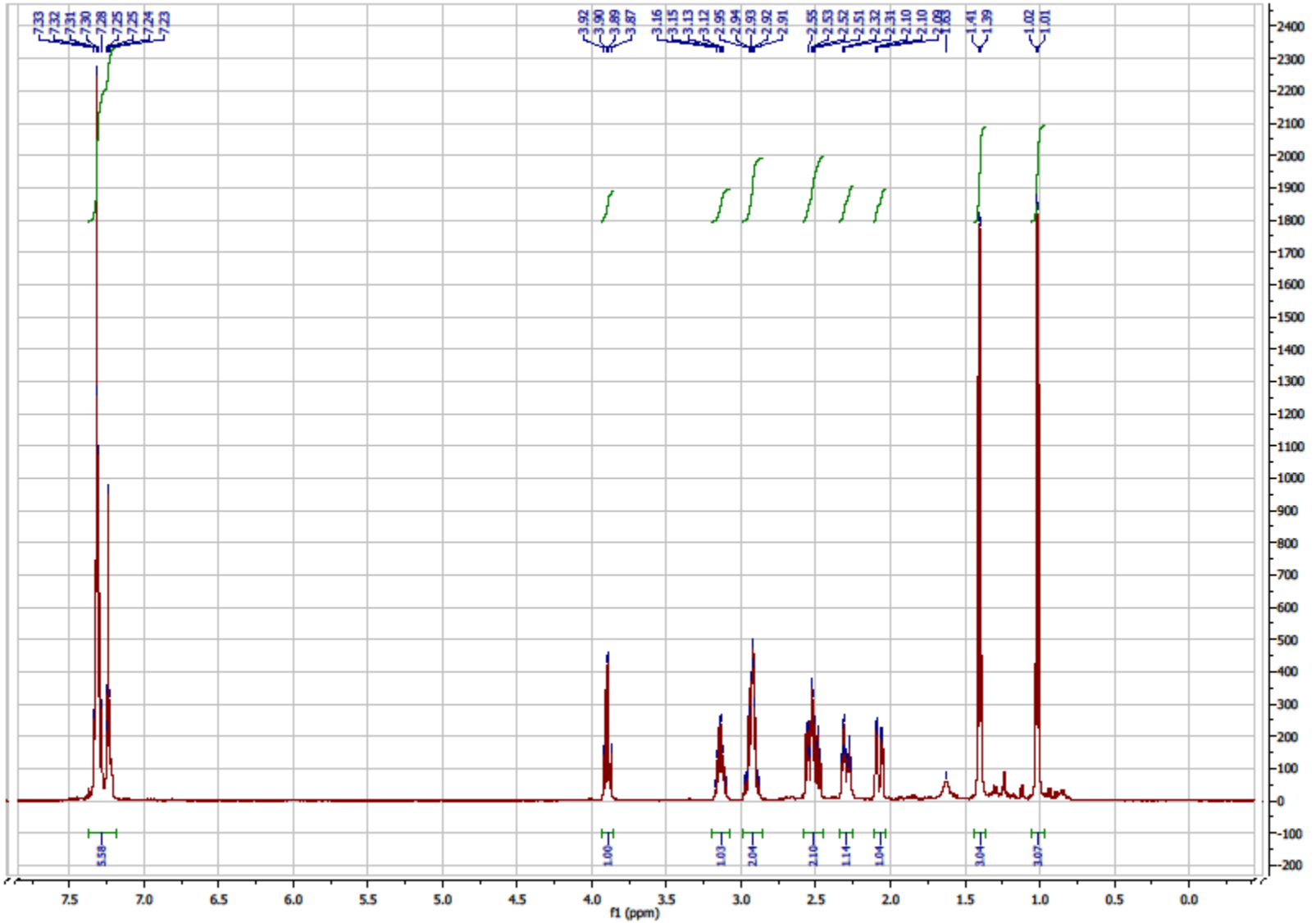


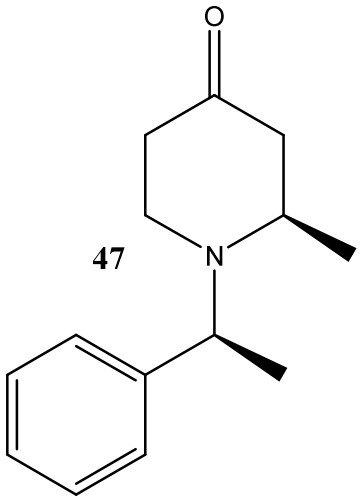


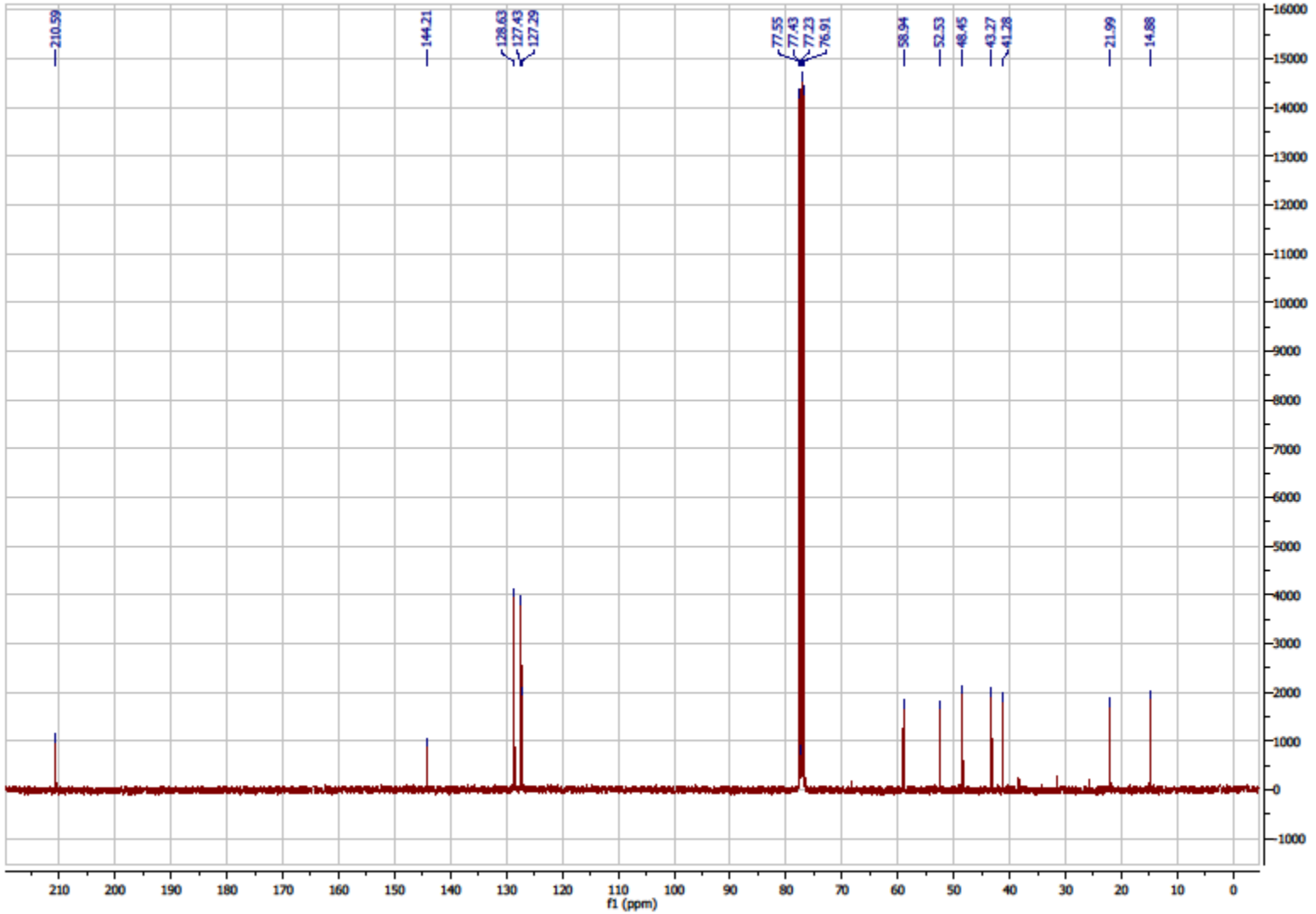
Sample Name	Description	Quality Checks
R14 Spot1	Sample 231 By Analyst Date Friday, July 04 2014	The Quality Checks do not report any warnings for the sample.

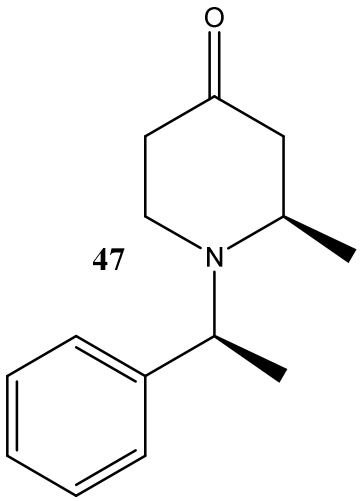

O
N

47

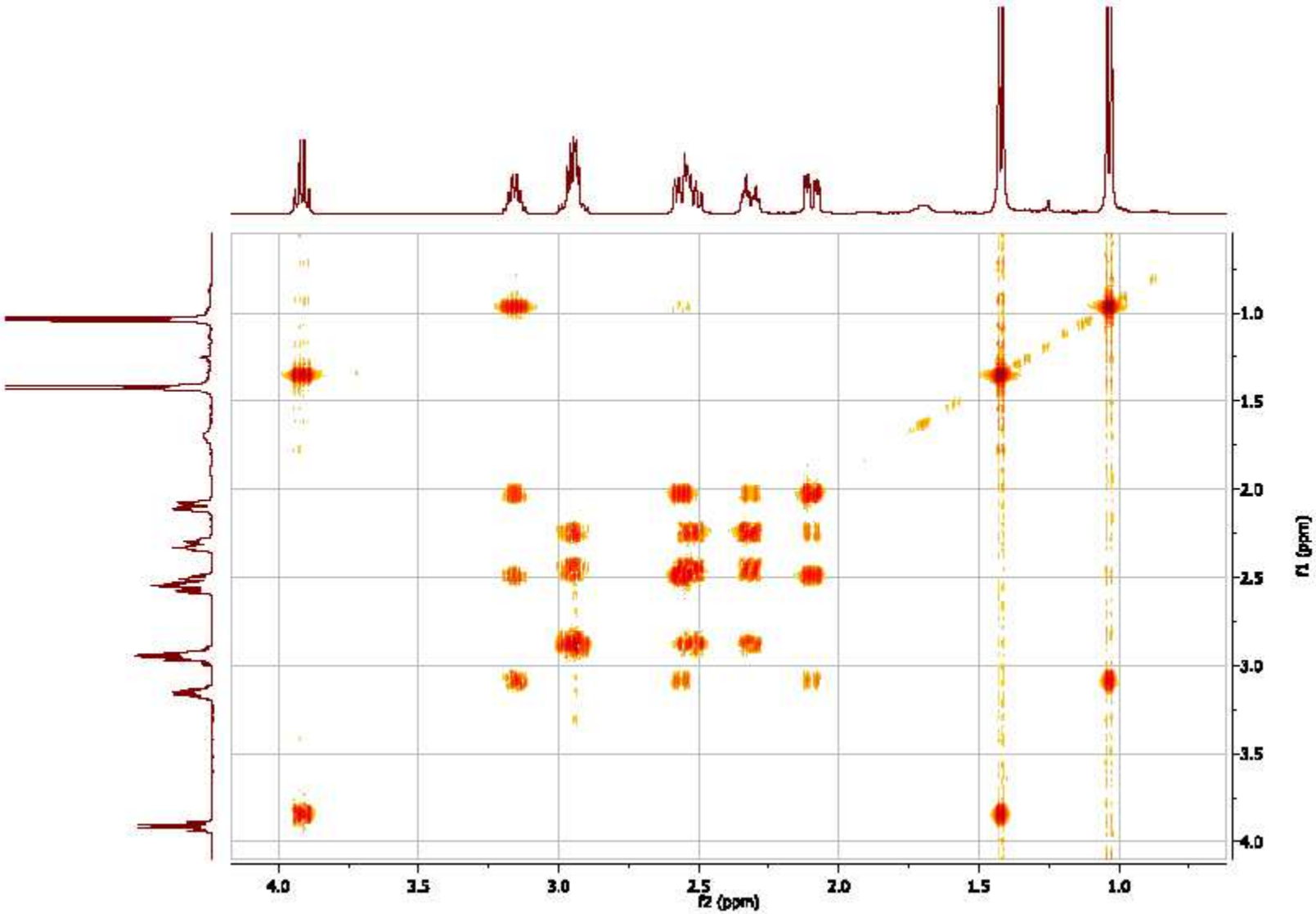

7.33
7.32
7.31
7.30
7.28
7.25
7.25
7.24
7.23
3.92
3.90
3.89
3.87
3.16
3.15
3.13
3.12
2.95
2.94
2.93
2.92
2.91
2.55
2.53
2.52
2.51
2.32
2.31
2.10
2.10
2.08
1.63
1.41
1.39
1.02
1.01
5.58
1.00
1.03
2.04
2.10
1.14
1.04
3.04
3.07
f1 (ppm)

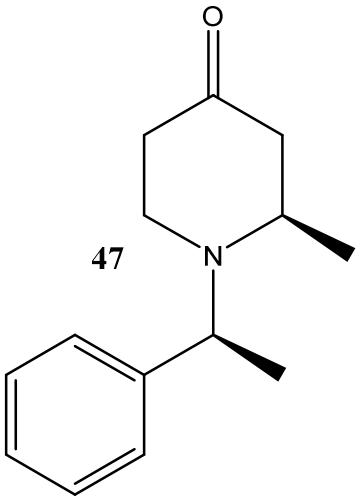

O
47
N


210.59
144.21
128.63
127.43
127.29
77.55
77.43
77.23
76.91
58.94
52.53
48.45
43.27
41.28
21.99
14.88
f1 (ppm)

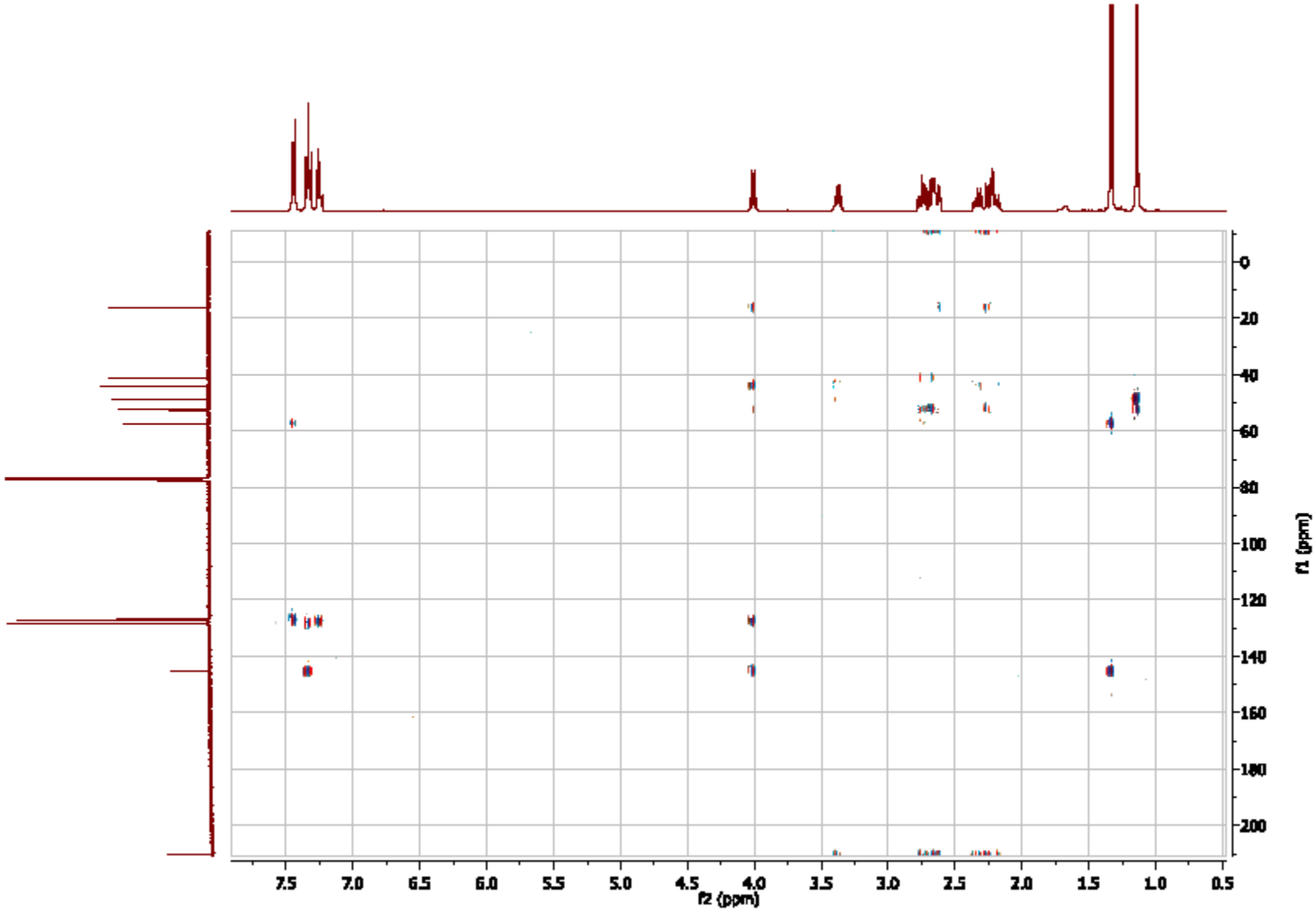


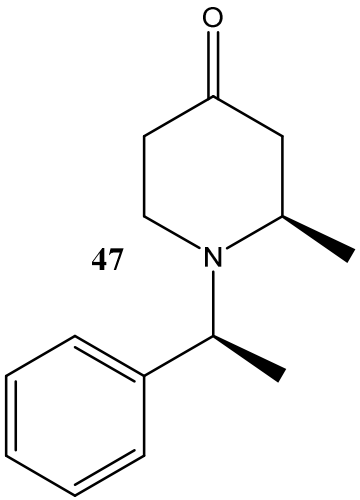
47



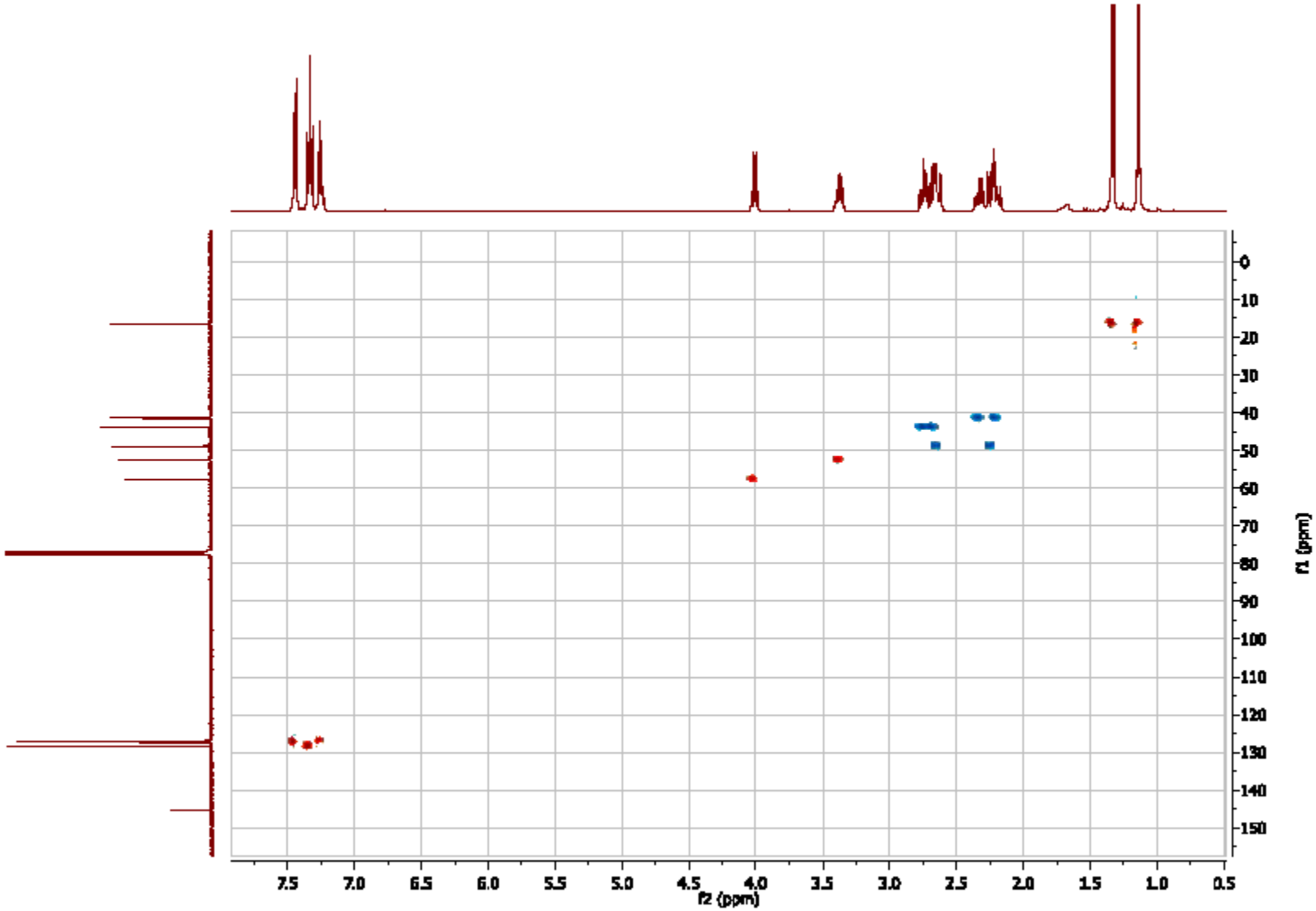

O
N

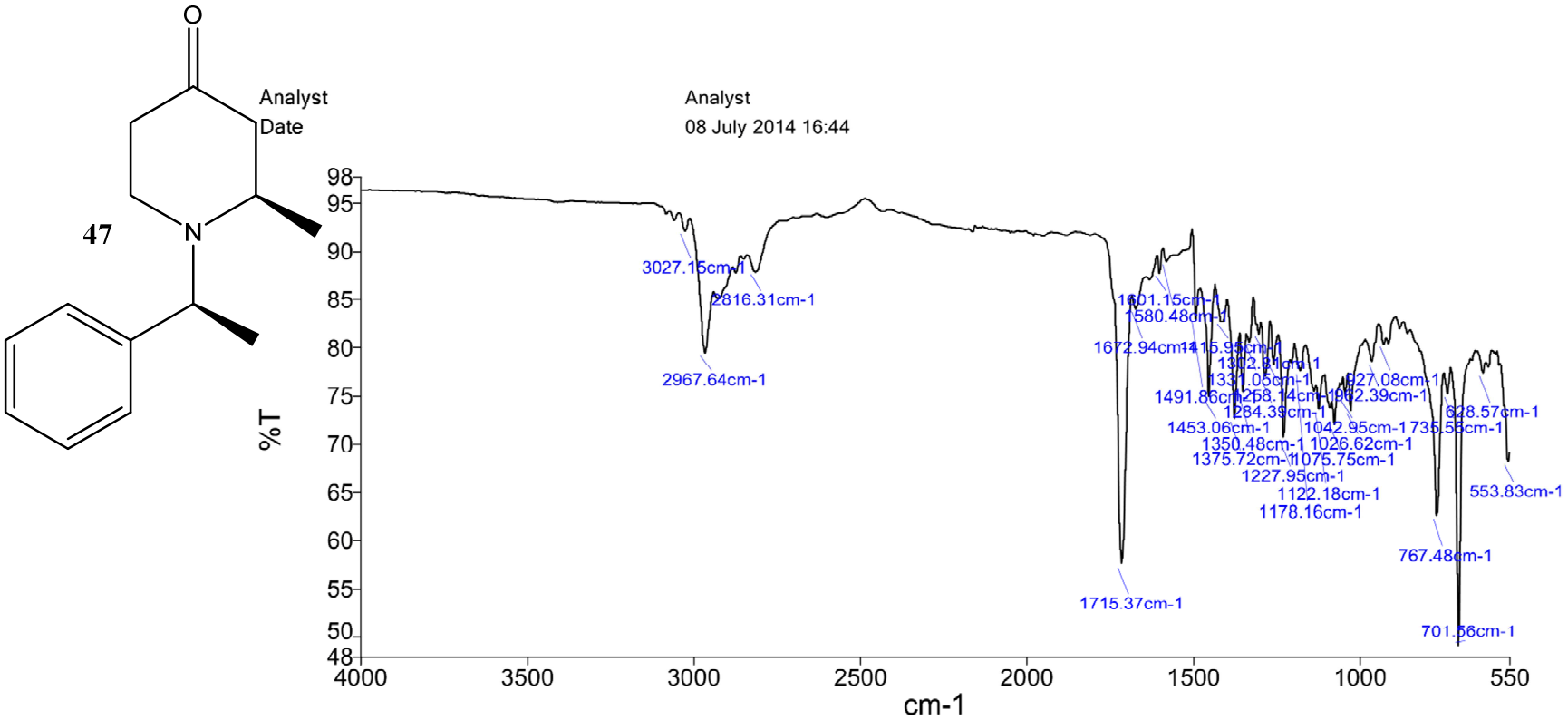
47


0
20
40
60
80
100
120
140
160
180
200
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)

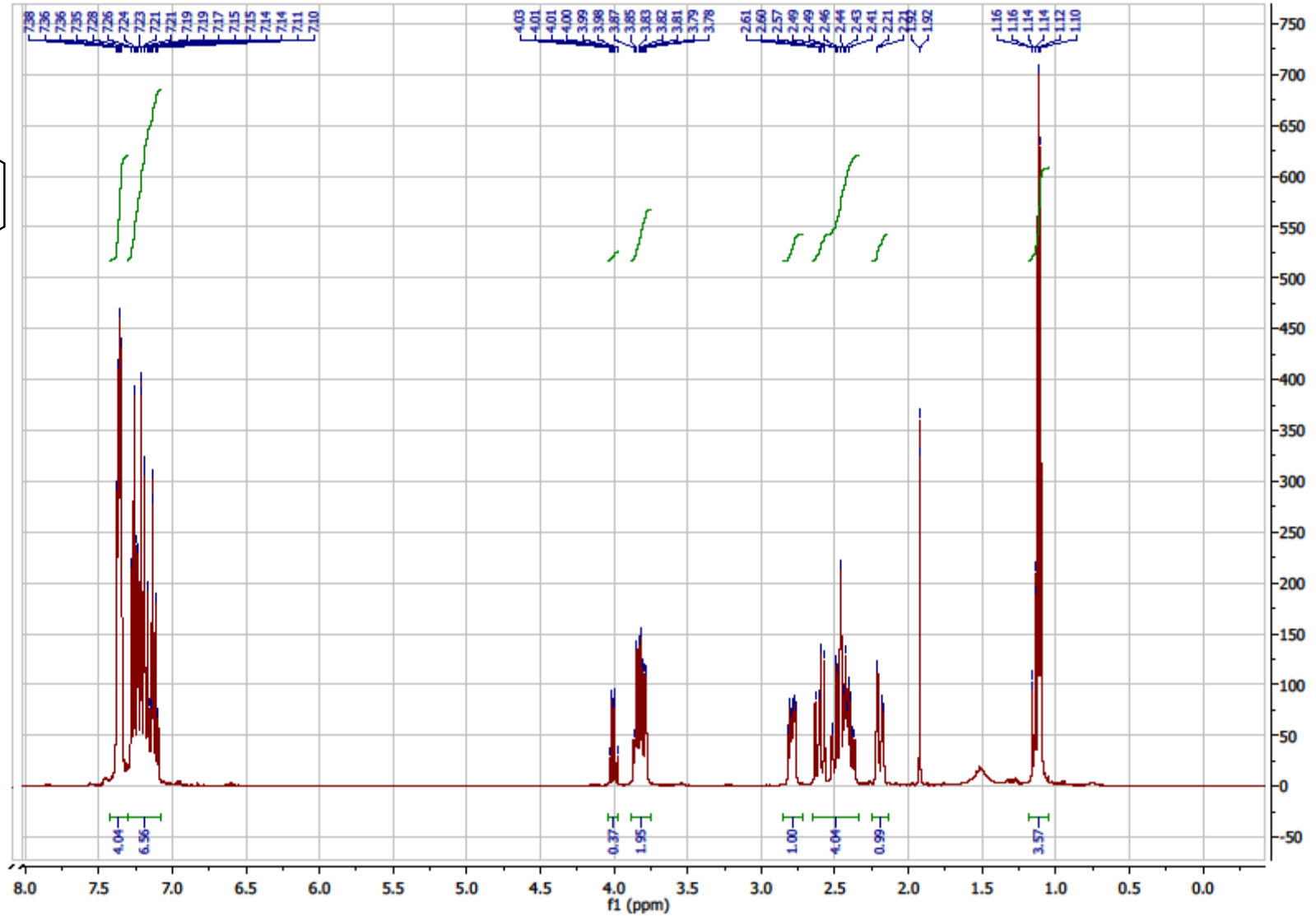

O
N

47

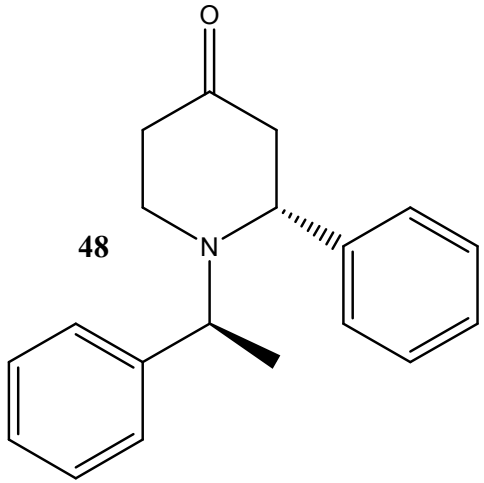

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)

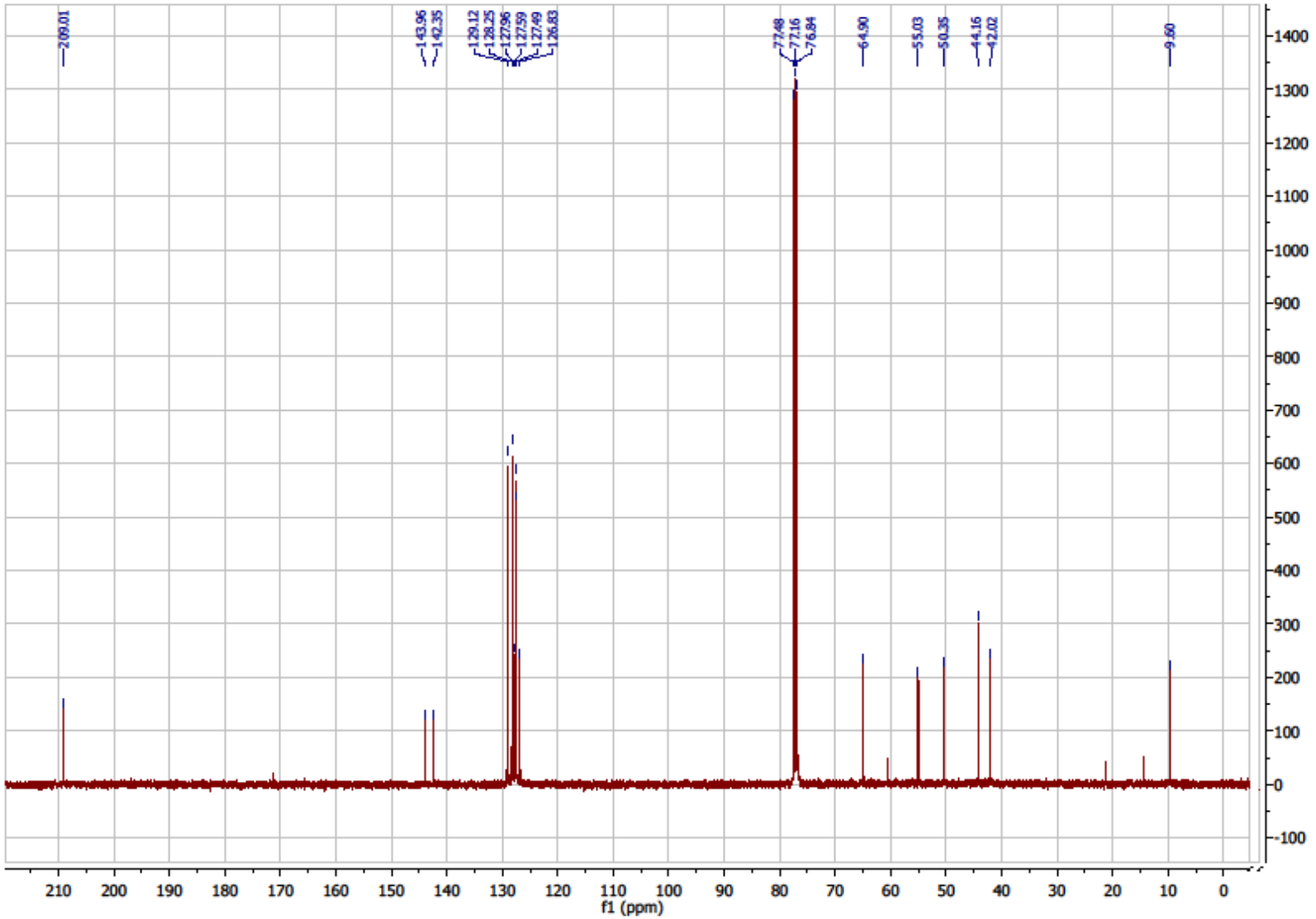

47
Analyst
Date
Analyst
08 July 2014 16:44
PerkinElmer Spectrum Version 10.4.00
08 July 2014 16:44
%T
cm-1
3027.15cm-1
2816.31cm-1
2967.64cm-1
1672.94cm-1
1715.37cm-1
1491.86cm-1
1453.06cm-1
1350.48cm-1
1375.72cm-1
1227.95cm-1
1122.18cm-1
1178.16cm-1
1042.95cm-1
1026.62cm-1
1075.75cm-1
767.48cm-1
701.56cm-1
553.83cm-1
R14 Spot2 Sample 232 By Analyst Date Friday, July 04 2014

48

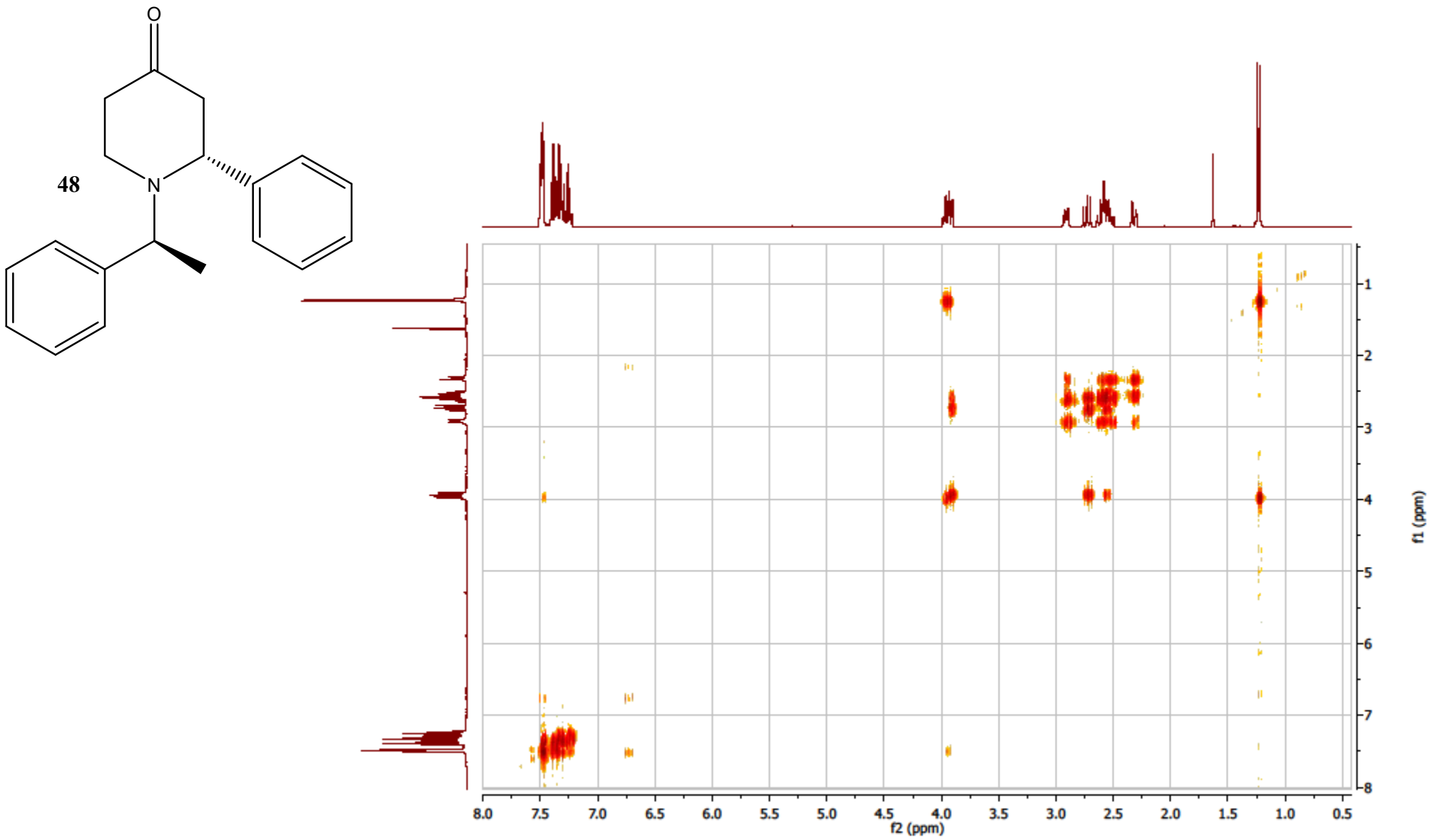

7.38 7.36 7.36 7.35 7.28 7.26 7.24 7.23 7.21 7.21 7.19 7.19 7.17 7.15 7.15 7.14 7.14 7.11 7.10
4.03 4.01 4.01 4.00 3.99 3.98 3.87 3.85 3.83 3.82 3.81 3.79 3.78
2.61 2.60 2.57 2.49 2.49 2.46 2.44 2.43 2.41 2.21 1.92 1.92
1.16 1.16 1.14 1.14 1.12 1.10
4.04 6.56 0.37 1.95 1.00 4.04 0.99 3.57
f1 (ppm)

48

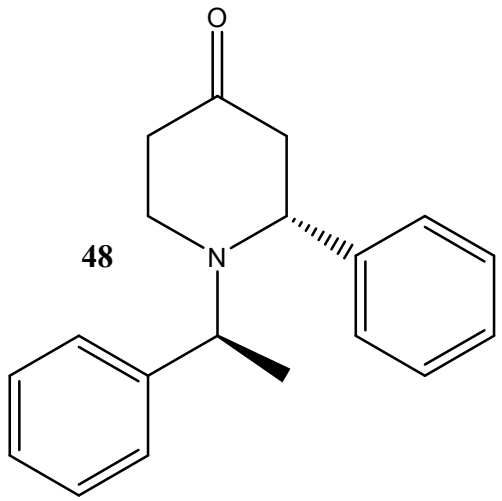

O
N

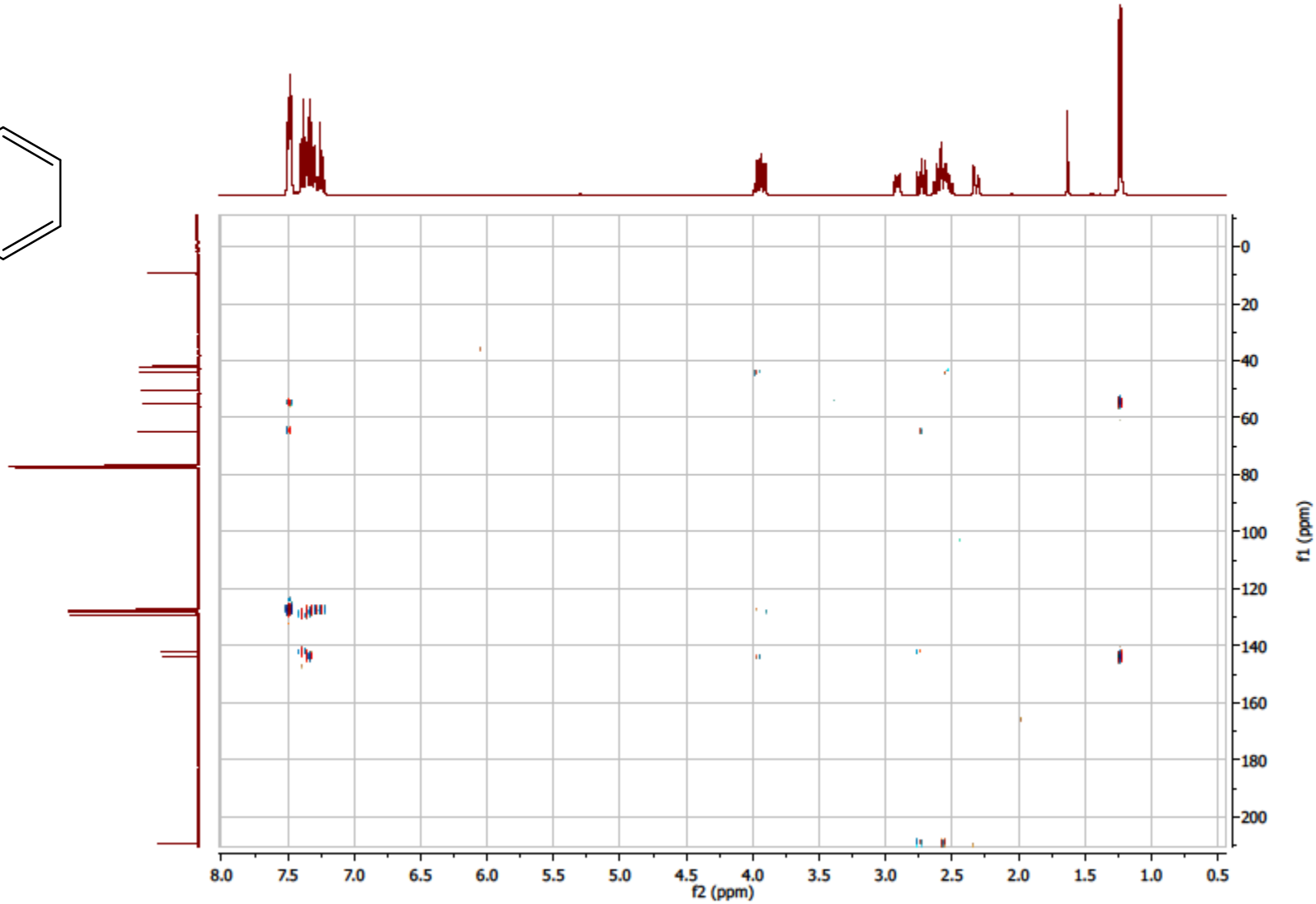

209.01
143.96
142.35
129.12
128.25
127.96
127.59
127.49
126.83
77.48
77.16
76.84
64.90
55.03
50.35
44.16
42.02
9.60
f1 (ppm)

48

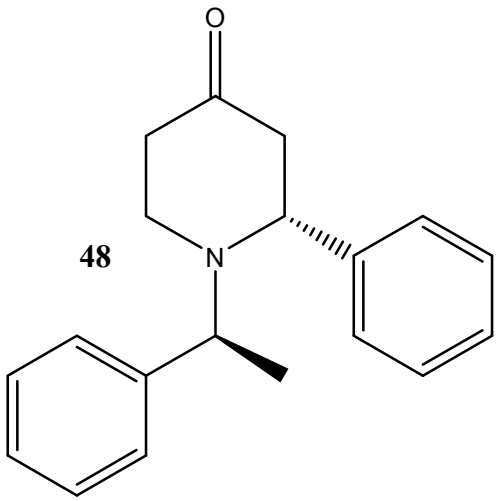

O
N
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
1
2
3
4
5
6
7
8
f1 (ppm)

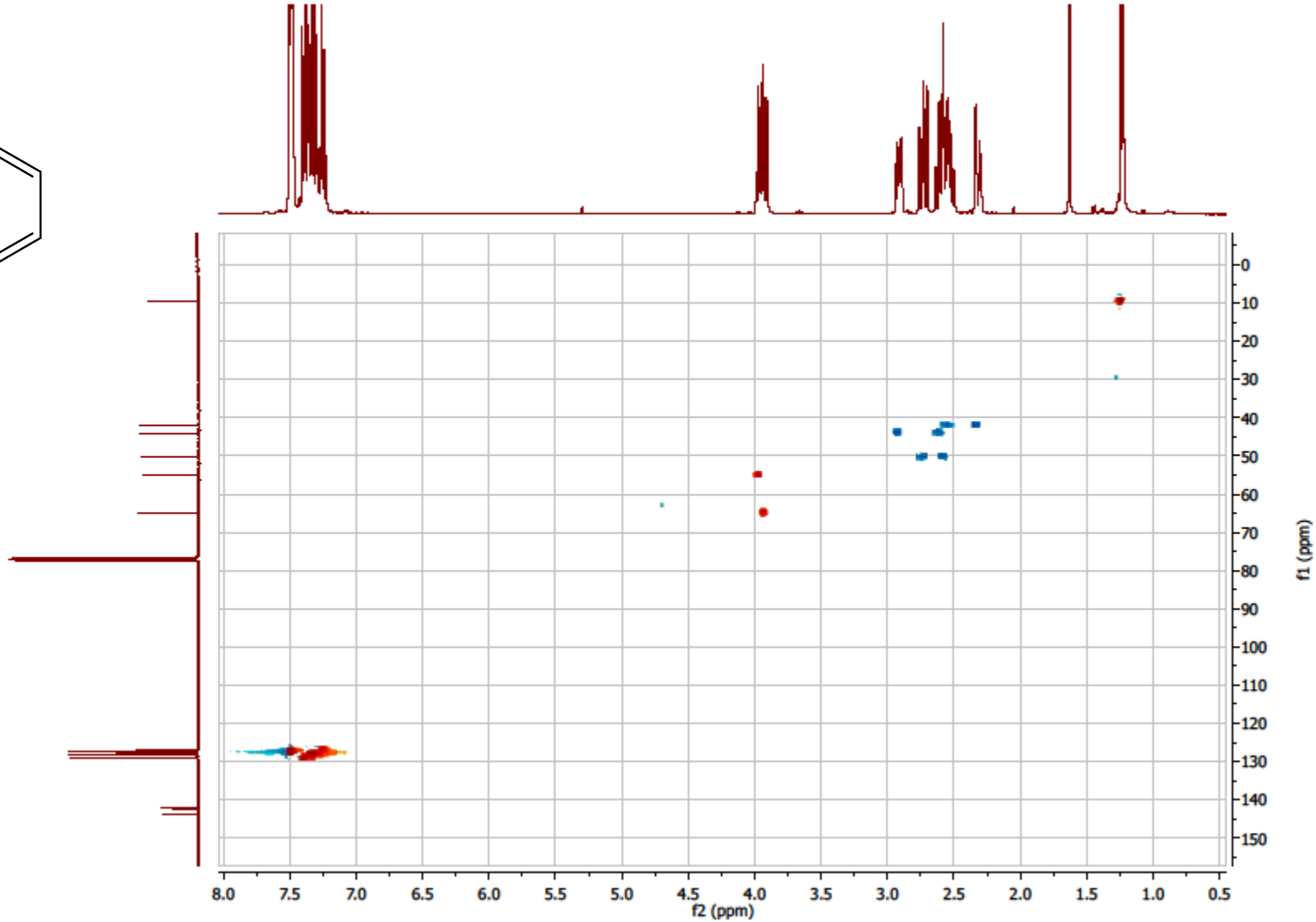
48


O
N

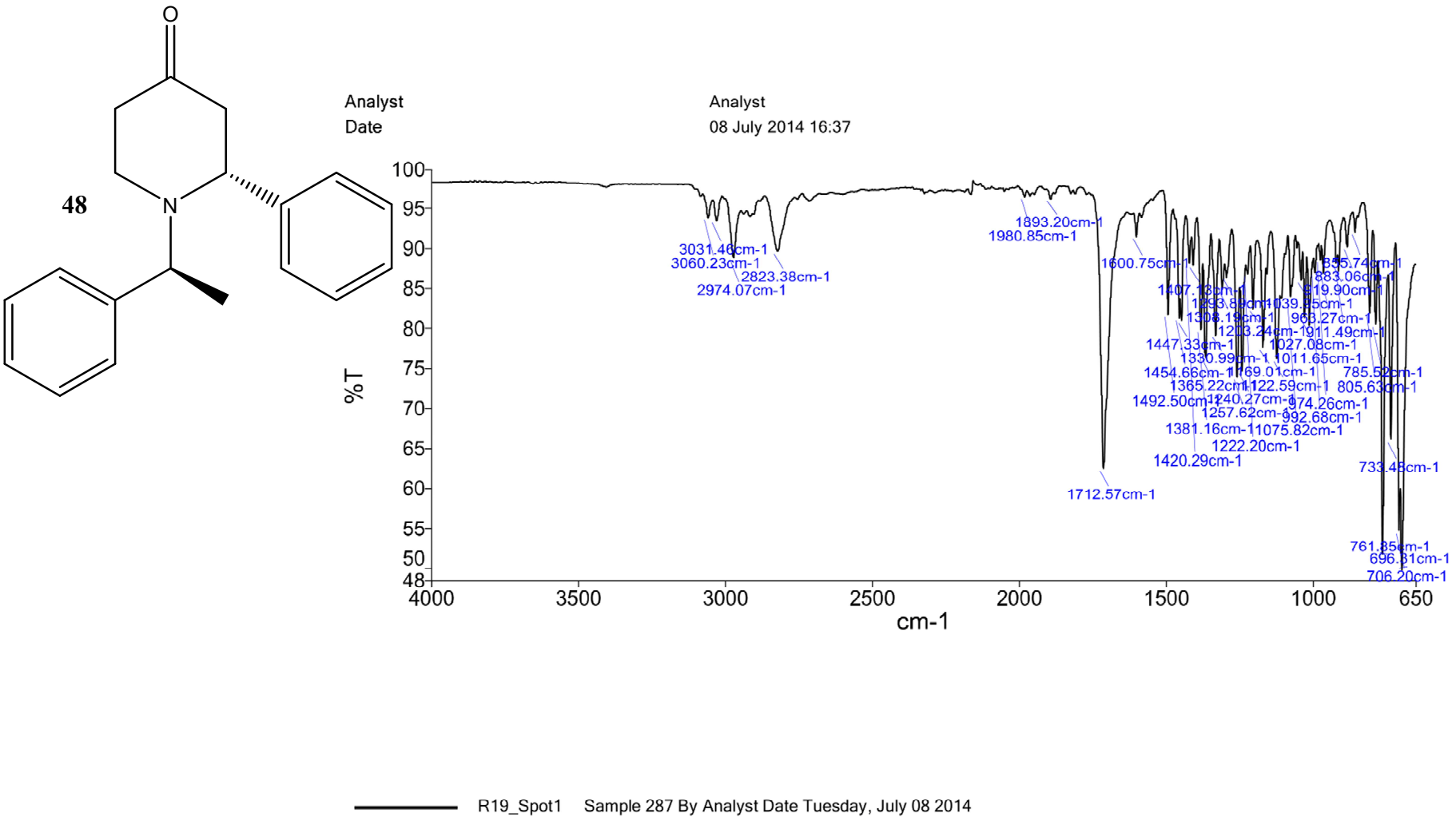

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
0
20
40
60
80
100
120
140
160
180
200
f1 (ppm)

48

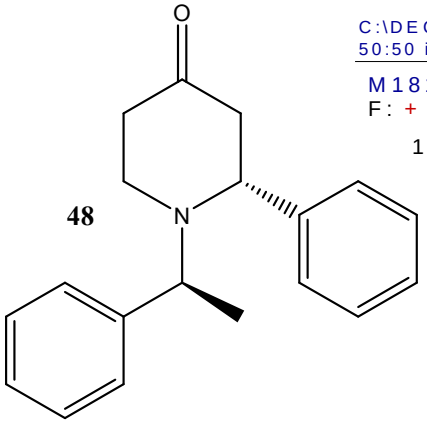

O
N


8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)

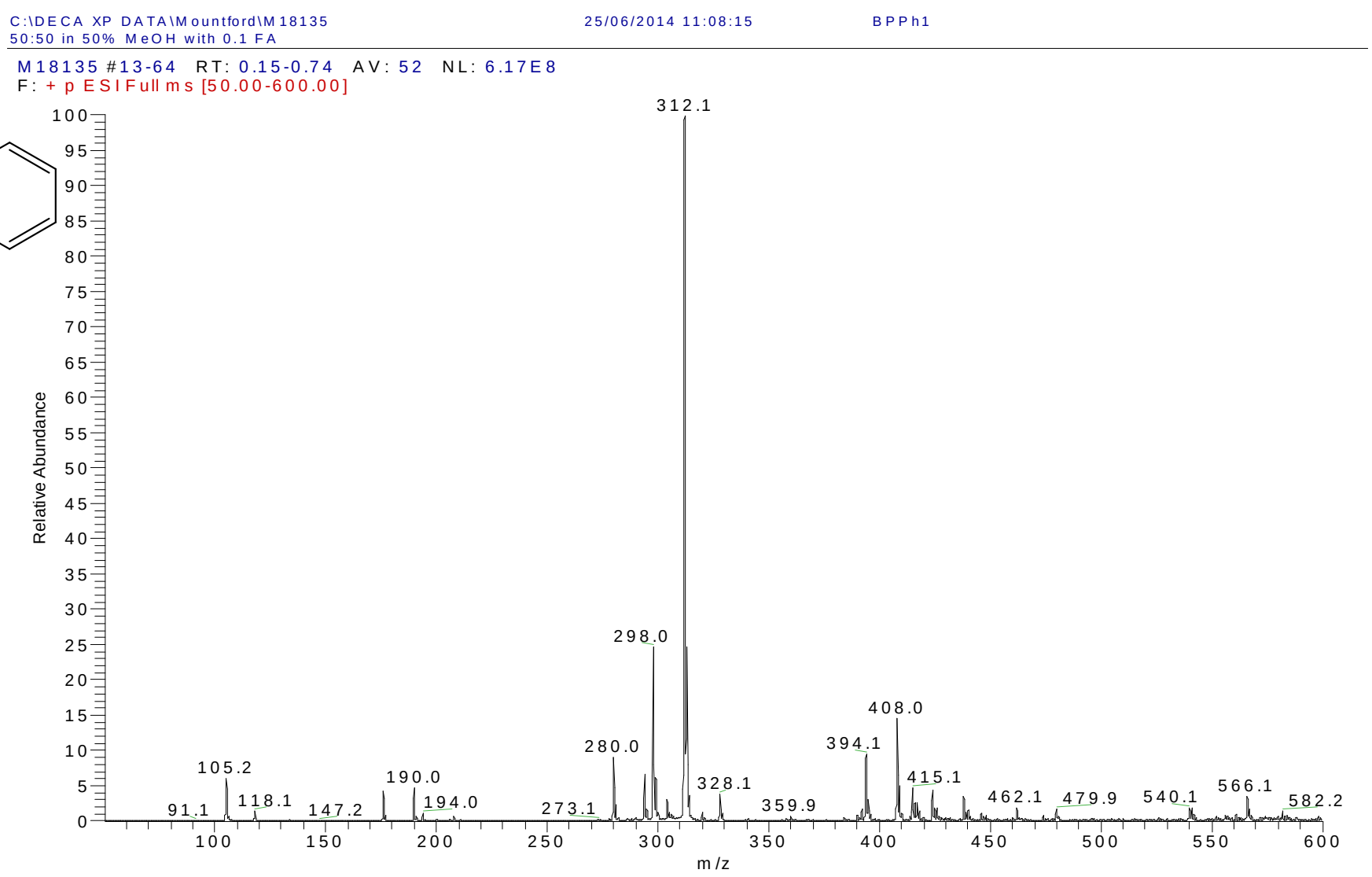
48


PerkinElmer Spectrum Version 10.4.00
08 July 2014 16:37
Analyst
Date
Analyst
08 July 2014 16:37
%T
cm-1
3031.46cm-1
3060.23cm-1
2823.38cm-1
2974.07cm-1
1893.20cm-1
1980.85cm-1
1600.75cm-1
1712.57cm-1
1447.33cm-1
1454.66cm-1
1492.50cm-1
1420.29cm-1
1381.16cm-1
1365.22cm-1
1330.99cm-1
1257.62cm-1
1222.20cm-1
1240.27cm-1
1203.24cm-1
1169.01cm-1
1122.59cm-1
1075.82cm-1
1027.08cm-1
1011.65cm-1
992.68cm-1
974.26cm-1
963.27cm-1
911.49cm-1
819.90cm-1
805.63cm-1
785.52cm-1
733.45cm-1
761.85cm-1
696.31cm-1
706.20cm-1
R19_Spot1 Sample 287 By Analyst Date Tuesday, July 08 2014

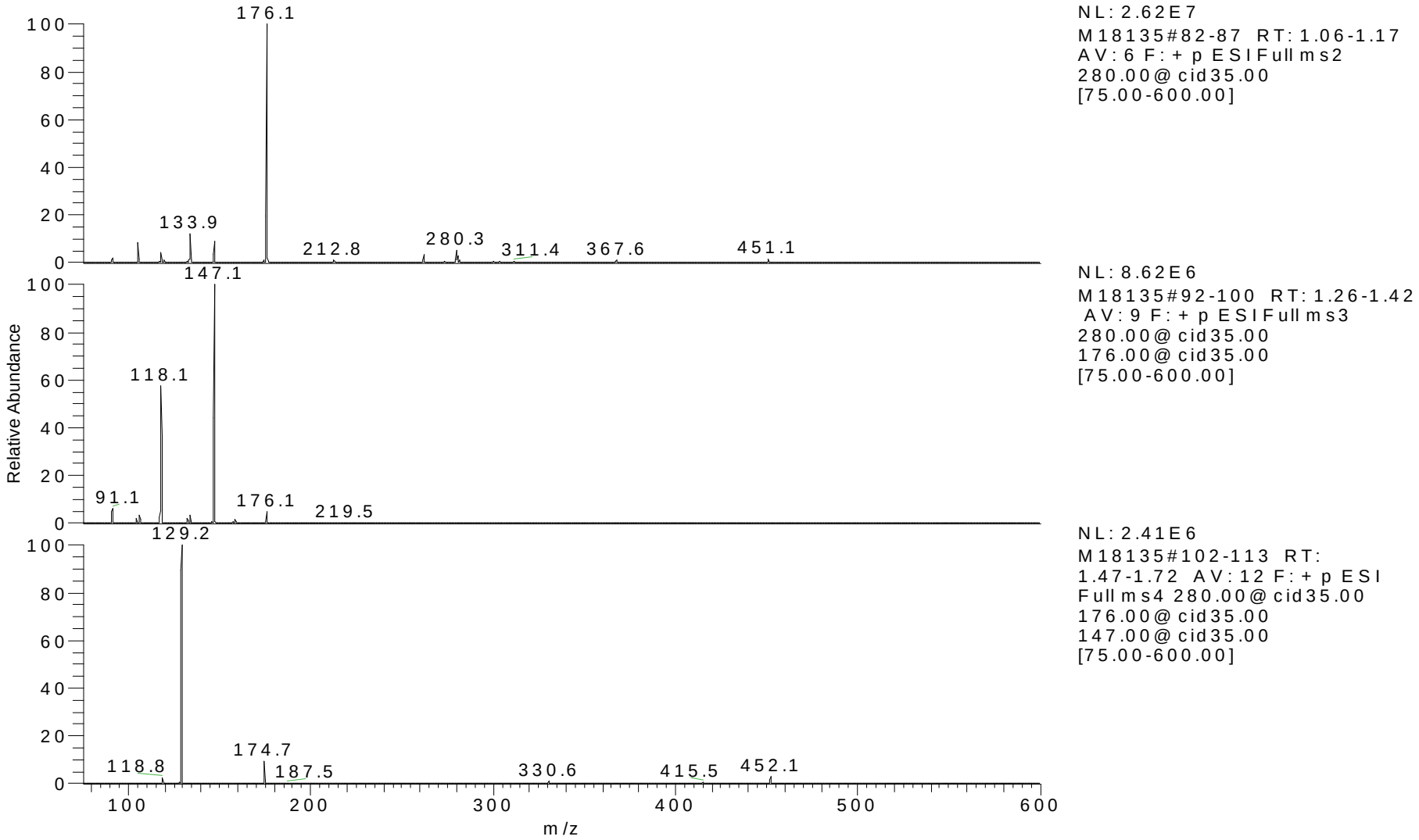
Sample BPPh1 diluted 50:50 with 50% MeOH containing 0.1% FA



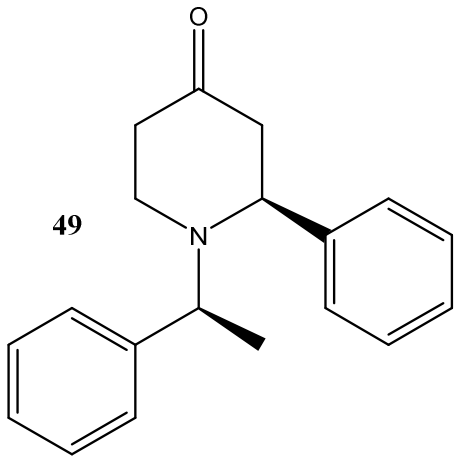
48

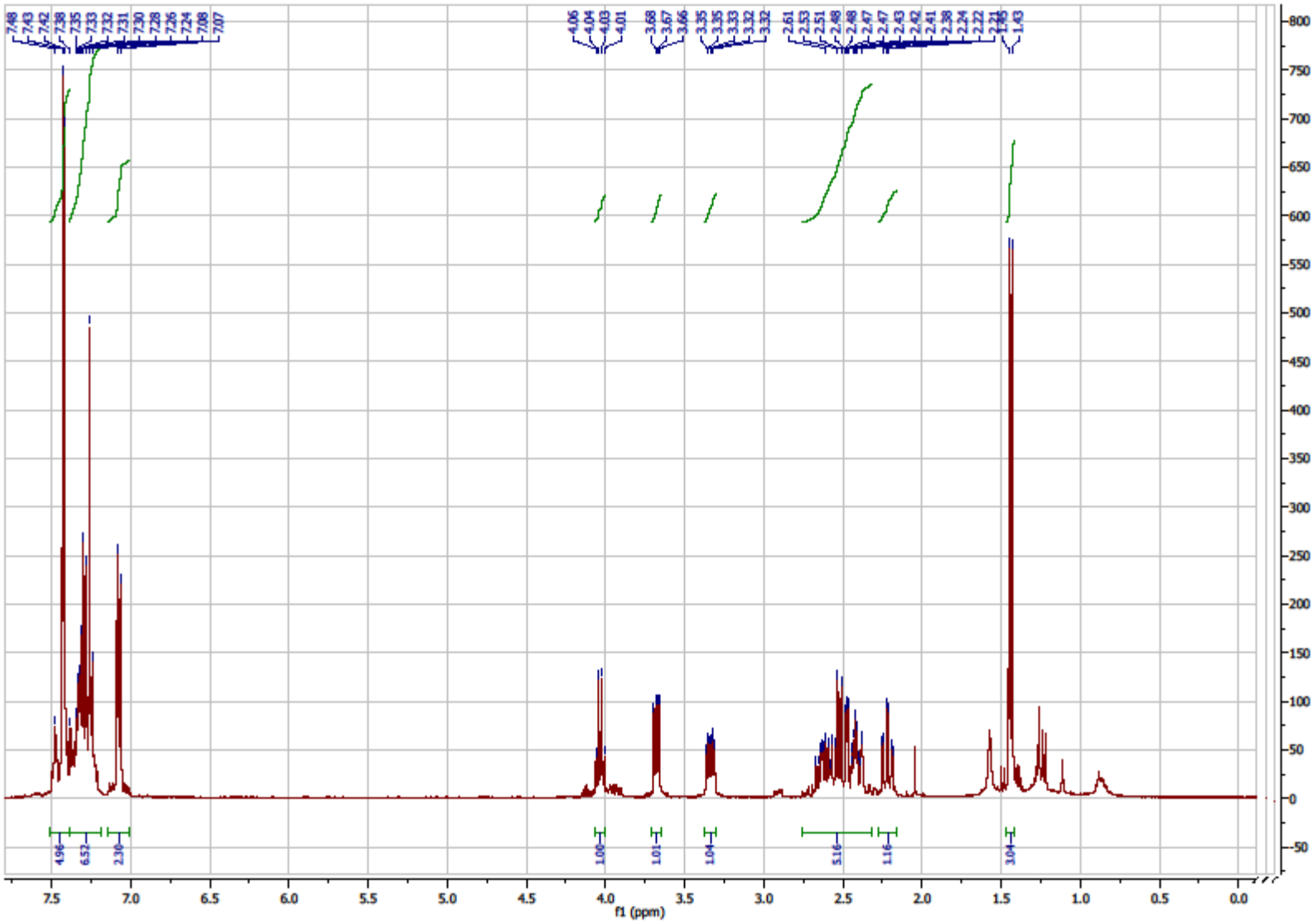


C:\DECA XP DATA\Mountford\M18135 25/06/2014 11:08:15 BPPh1
50:50 in 50% MeOH with 0.1 FA

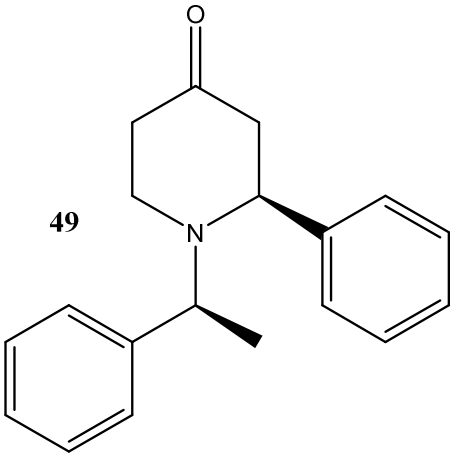


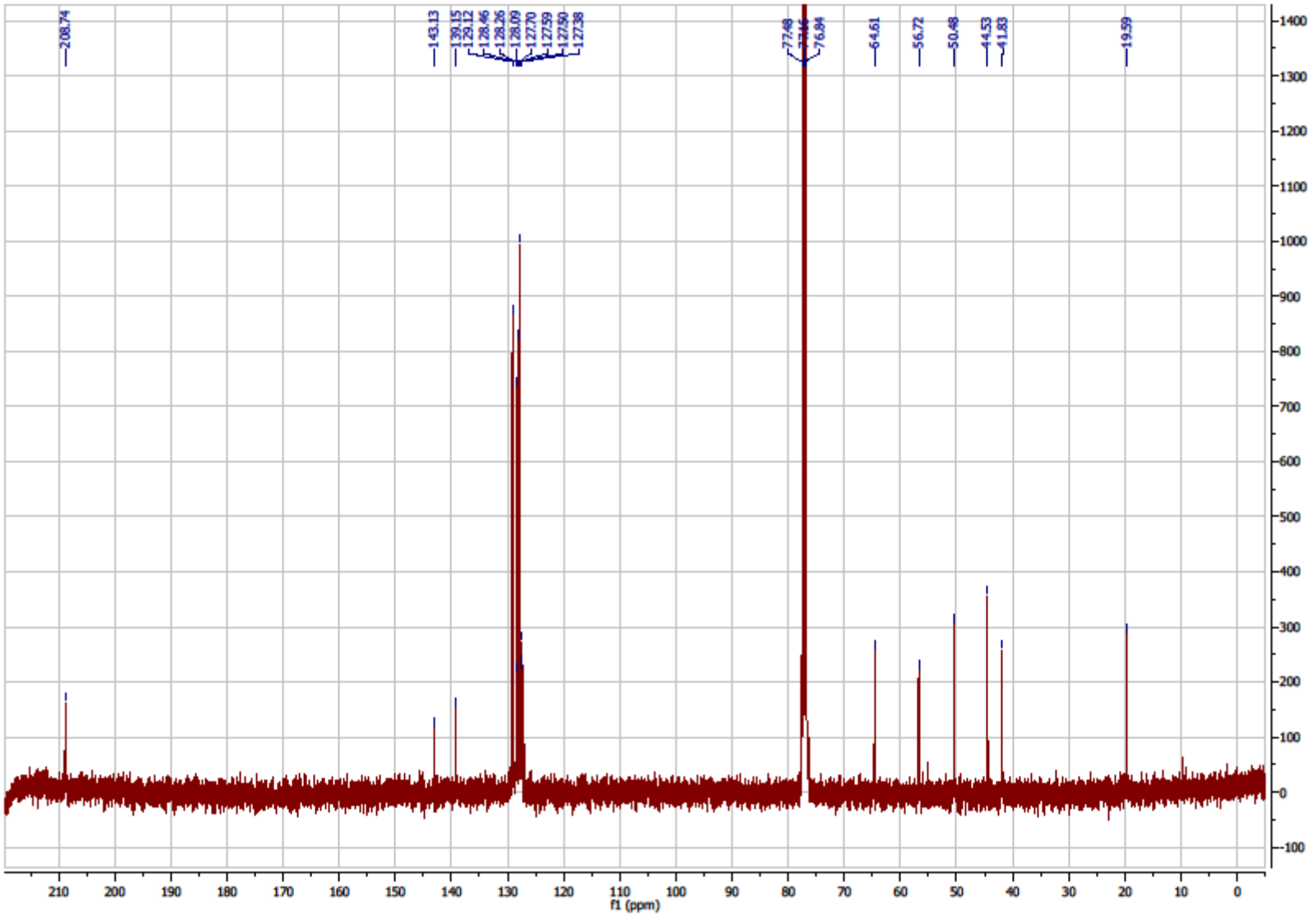
49


O
N

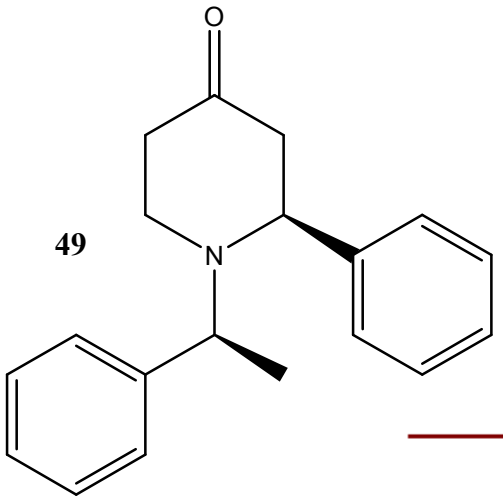

7.48
7.43
7.42
7.38
7.35
7.33
7.32
7.31
7.30
7.28
7.26
7.24
7.08
7.07
4.06
4.04
4.03
4.01
3.68
3.67
3.66
3.35
3.35
3.33
3.32
3.32
2.61
2.53
2.51
2.48
2.48
2.47
2.43
2.42
2.41
2.38
2.24
2.22
2.21
1.45
1.43
4.96
6.53
2.30
1.00
1.01
1.04
5.16
1.16
3.04
f1 (ppm)

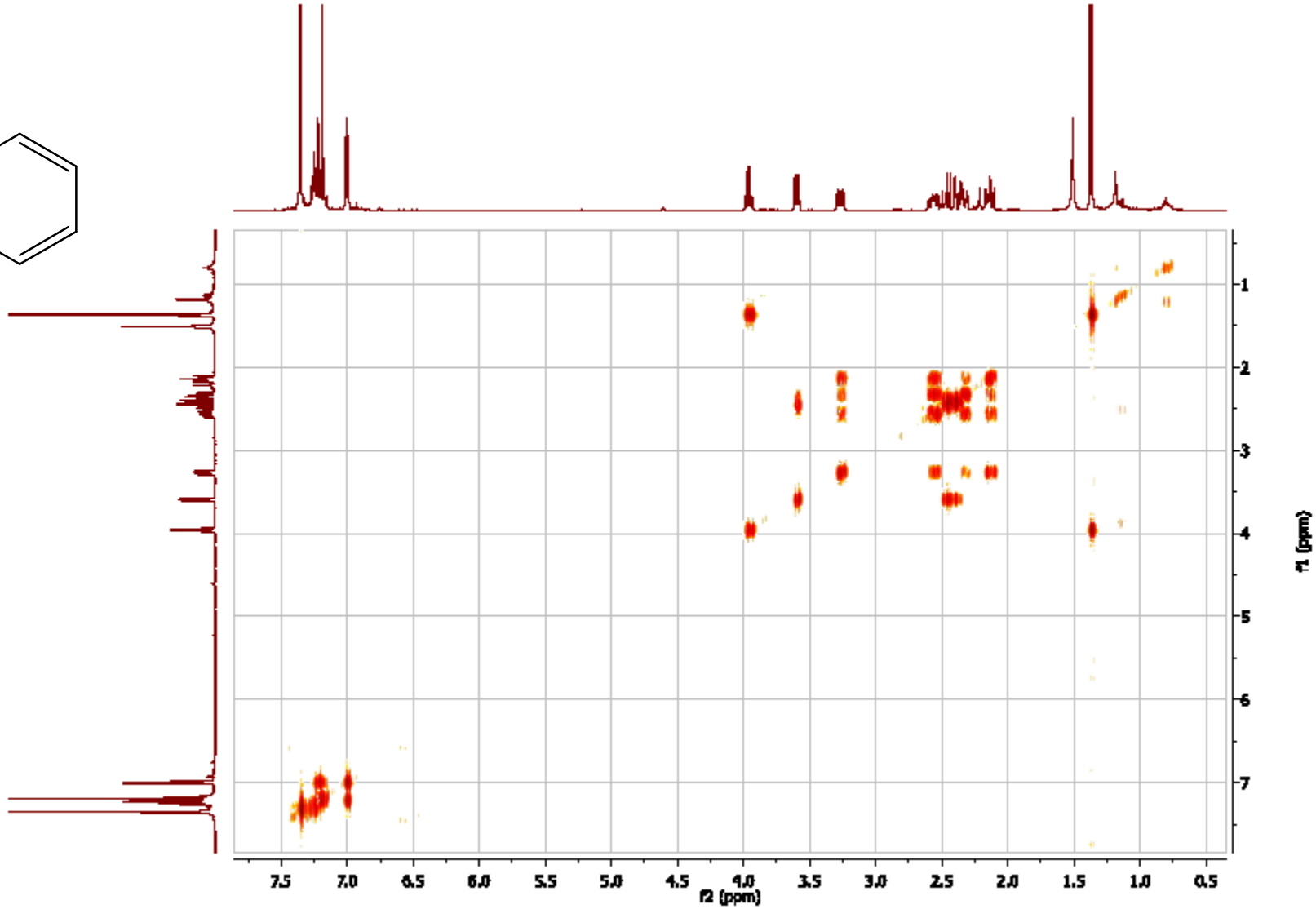
49


O
N

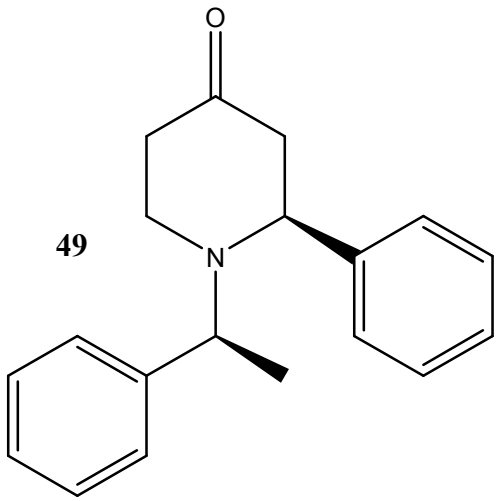

208.74
143.13
130.15
129.12
128.46
128.26
128.09
127.70
127.59
127.50
127.38
77.48
77.16
76.84
64.61
56.72
50.48
44.53
41.83
19.59
f1 (ppm)

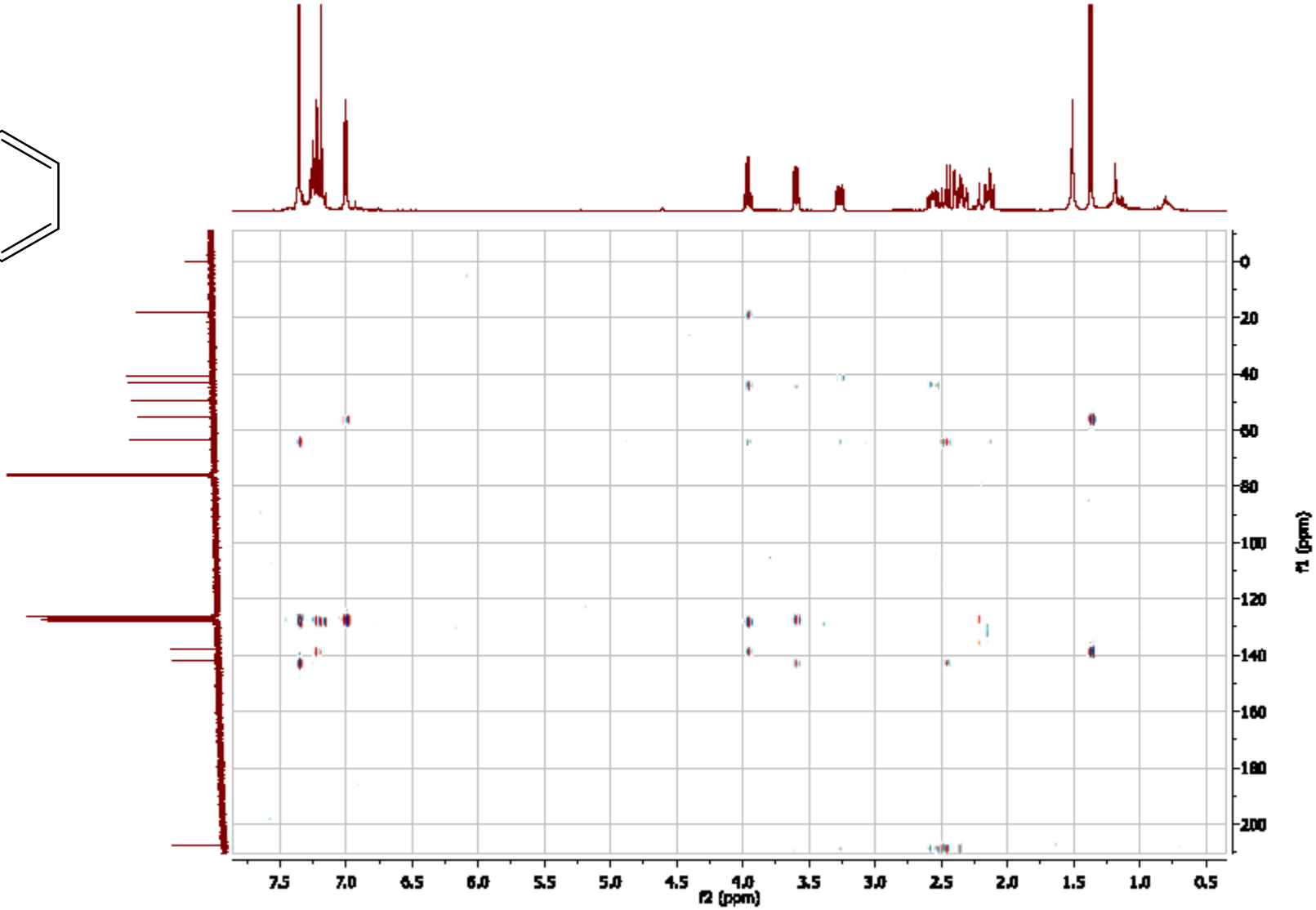
49



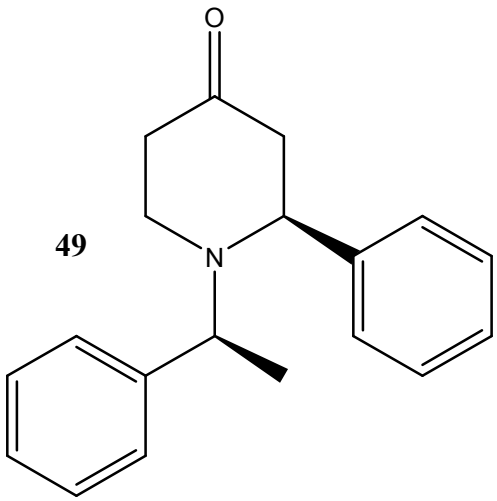


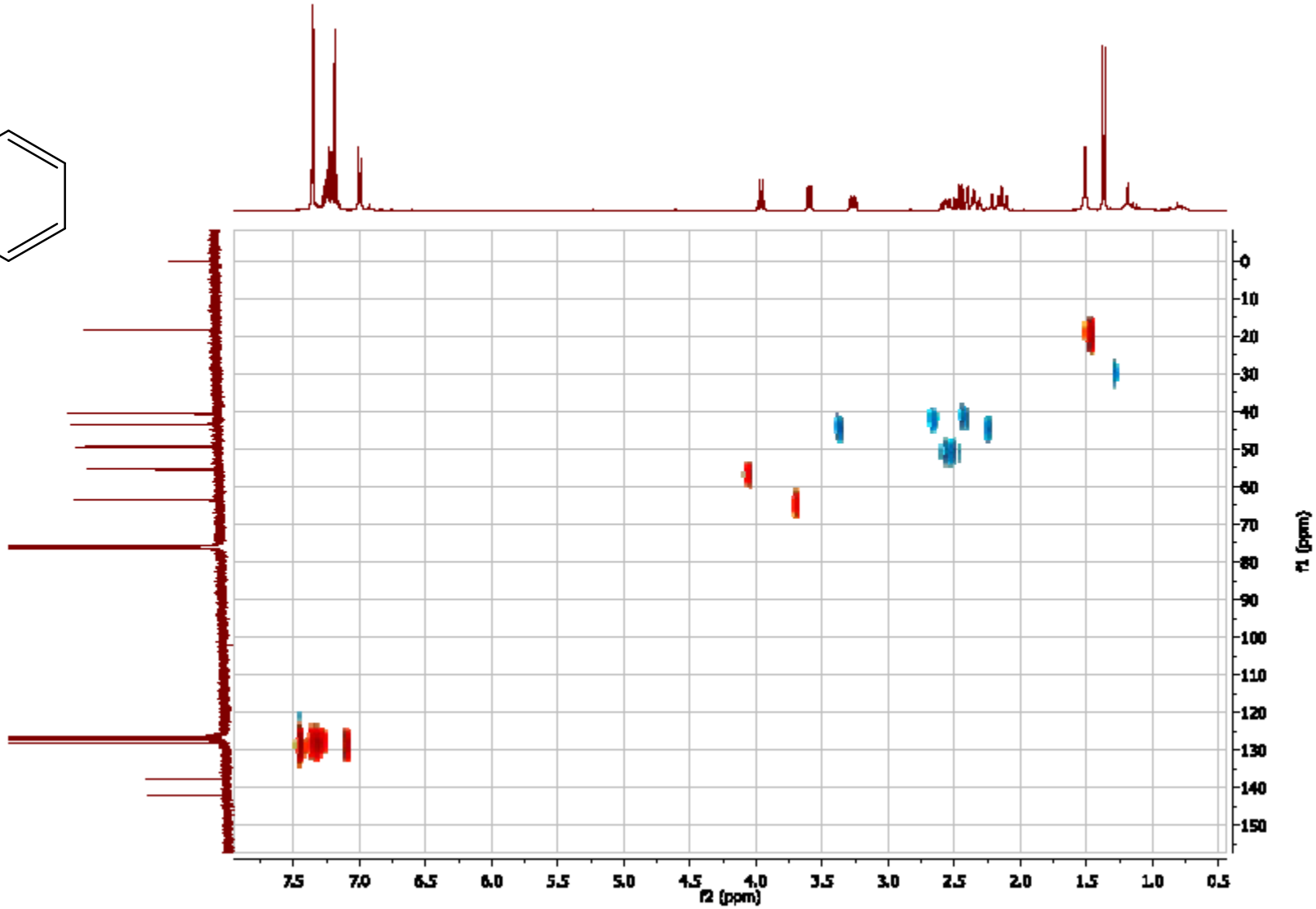
49


O
N


7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
0
20
40
60
80
100
120
140
160
180
200
f1 (ppm)

49





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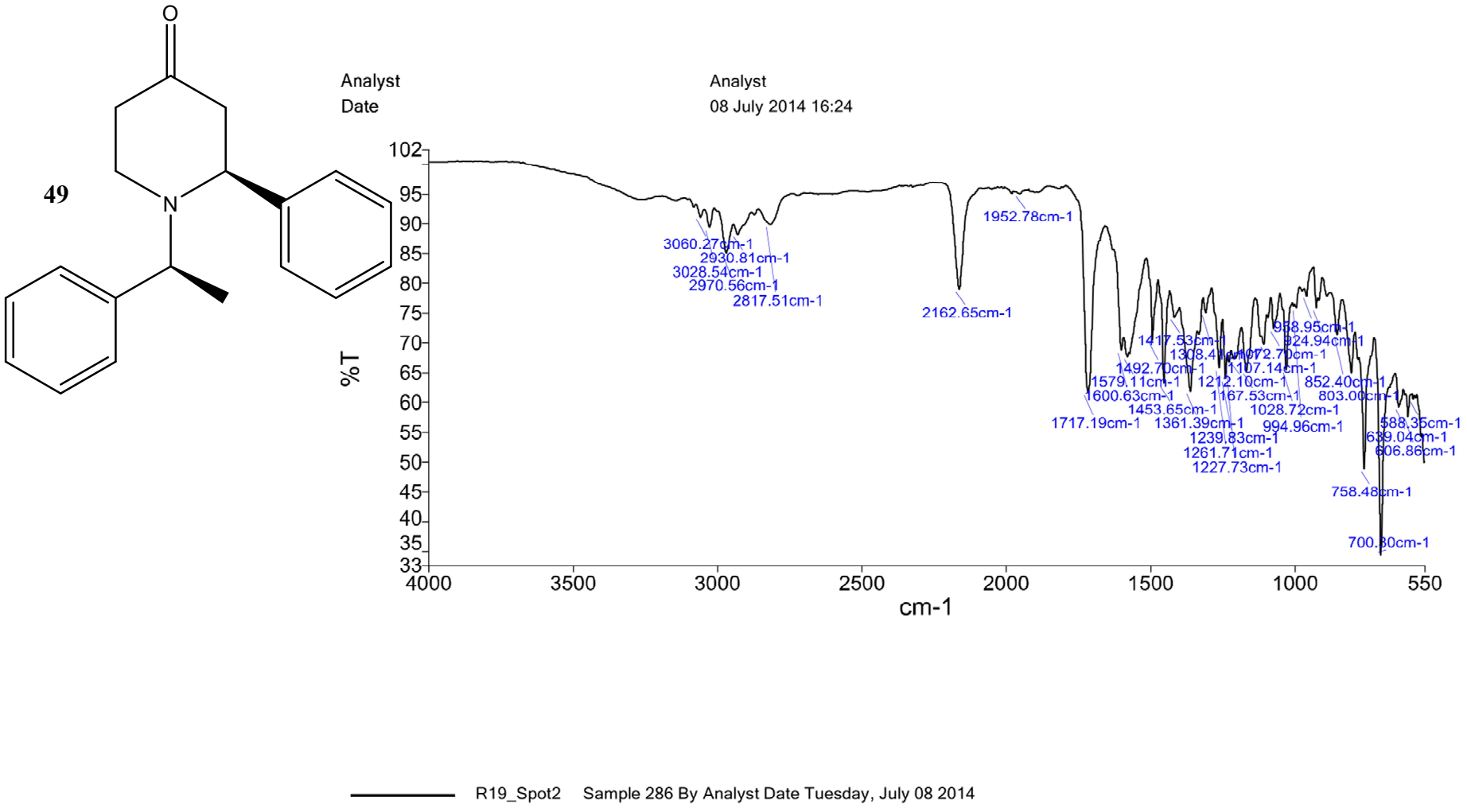
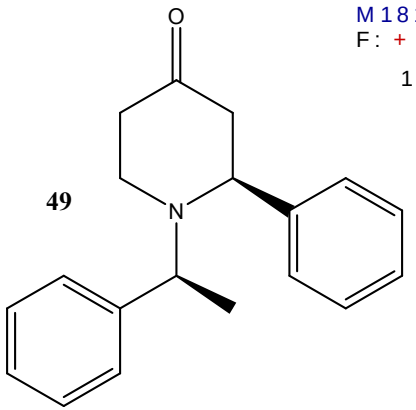
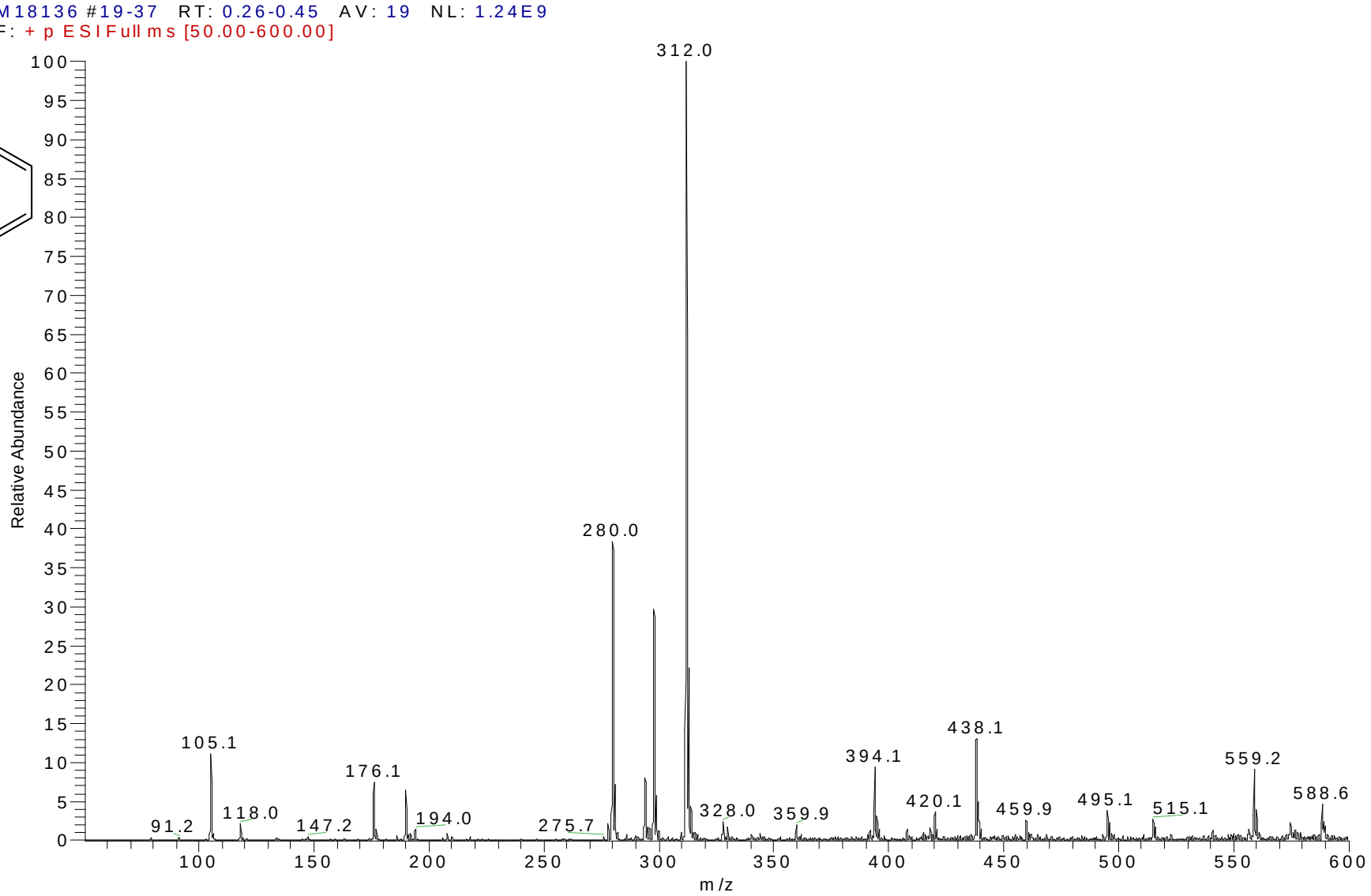

PerkinElmer Spectrum Version 10.4.00
08 July 2014 16:24
Analyst
Date
Analyst
08 July 2014 16:24
%T
cm-1
3060.27cm-1
2930.81cm-1
3028.54cm-1
2970.56cm-1
2817.51cm-1
2162.65cm-1
1952.78cm-1
1717.19cm-1
1600.63cm-1
1579.11cm-1
1492.70cm-1
1453.65cm-1
1417.53cm-1
1361.39cm-1
1308.44cm-1
1261.71cm-1
1239.83cm-1
1227.73cm-1
1212.10cm-1
1167.53cm-1
1107.14cm-1
1072.70cm-1
1028.72cm-1
994.96cm-1
958.95cm-1
924.94cm-1
852.40cm-1
803.00cm-1
758.48cm-1
700.80cm-1
639.04cm-1
606.86cm-1
588.35cm-1
R19_Spot2 Sample 286 By Analyst Date Tuesday, July 08 2014

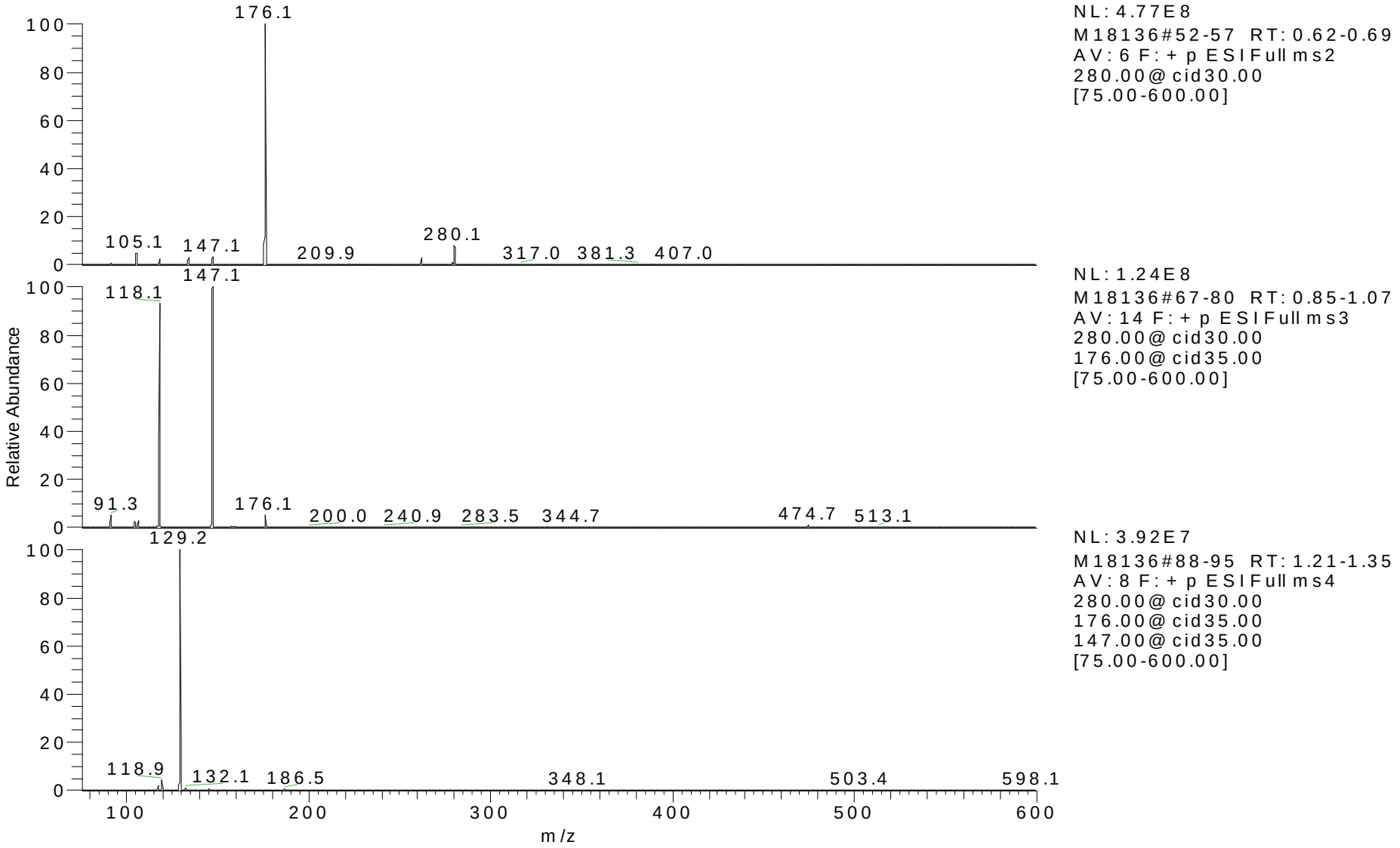
Sample BPPh2 diluted 50:50 with 50% MeOH containing 0.1% FA



49



C:\DECA XP DATA\Mountford\M18136 25/06/2014 10:47:43 BPPh2
50:50 in 50% MeOH with 0.1 FA



5.2 Curriculum vitae

Personal details

Name	Claudia Vater
Date of birth	25th November 1990
Nationality	Austria
Address	Ilse-Arlt Straße 23/15
	1220 Wien

Academic studies

since 2009	Diploma study at the University of Vienna
Jan 2014- Jul 2014	Erasmus student at King's College London,
	Department of Medicinal Chemistry,
	Diploma thesis project

Education

Sept 2001 – Jun 2009	Grammar school Waidhofen/Thaya
Sept 1997 – Jun 2001	Primary school Heidenreichstein

Work experience

10/2011 –01/2014	**University of Vienna**, Tutor
07/2013- 07/2013	**Internship:** ***Apotheke zur heiligen Margaretha***, 3860 Heidenreichstein
07/2011 –07/2011	**Internship:** ***Apotheke zur heiligen Margaretha***, 3860 Heidenreichstein
07/2010 –07/2010	**Internship:** ***Apotheke zur heiligen Margaretha***, 3860 Heidenreichstein
07/2009 – 08/2009	**Internship:** ***Schirmbar Heidenreichstein***, Nöbauer GmbH, 3860 Heidenreichstein

08/2008-08/2008 **Internship: *Billa Heidenreichstein***, Billa AG, 3860 Heidenreichstein

08/2007-08/2007 **Internship: *Billa Heidenreichstein***, Billa AG, 3860 Heidenreichstein

Language skills

German – native

English – fluent (spoken and written)

French – moderate

Spanish – basic