universität wien

DISSERTATION

Titel der Dissertation

SYNTHESIS OF NEW ANTICANCER COMPOUNDS WITH A TETRACYCLIC NUCLEUS

Verfasser

M.Sc. Theerachart Leepasert

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Finally, I would regret my doctoral years at University of Vienna if I did not get the Technology Grants scholarship from Austrian Academic Exchange Service (Österreichischer Austausch Dienst: ÖAD). Without their support, my ambition to study abroad can hardly be realized. I would really like to thank ÖAD program. Joining this program was not only a turning point in my life, but also a wonderful experience.

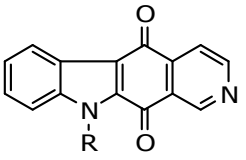
Theerachart Leepasert

Zusammenfassung

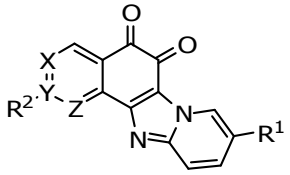
Synthese neuer krebshemmender Substanzen mit tetrazyklischer Grundstruktur

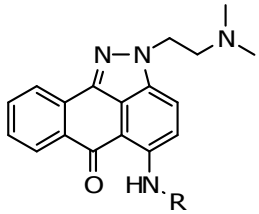
Theerachart Leepasert, Universität Wien Betreuer: Univ.-Prof. Dr. Helmut Spreitzer

Dissertation zur Erlangung des akademischen Grades Doktor der Naturwissenschaften
Im Zuge dieser Arbeit sollten drei Serien von DNA-interkalierenden Verbindungen synthetisiert sowie ein neuer synthetischer Zugang zu Ellipticin (**49**) geschaffen werden. In der ersten Serie (**107-109**, **114**, **120**, **124**) wurde eine Reihe Pyridin-anellierter Carbazole durch Anlagerung verschiedener Aminoalkyl- und Hydroxyalkylsulfidseitenketten an den Stickstoff des Pyrrolringes hergestellt. Sämtliche Verbindungen zeigten starke Zytotoxizität gegen NClH460 Zelllinien. Außerdem wiesen die Verbindungen **109**, **114** und **124** moderate Zytotoxizität gegen SKOV3 Zelllinien auf. Der zweiten Serie lag die Reaktion von 6,7-Dichlor-5,8-isochinolindion oder 6,7-Dichlor-5,8-Chinazolindion und als zweitem Edukt substituiertes 2-Aminopyridin oder unsubstituiertes 2-Aminopyridin zugrunde, die zu den Verbindungen **128(a,b)**, **134(a,b)**, **136a** und **143a** führten. Zusätzlich konnte an Substanz **128a** eine Aminoseitenkette eingeführt werden, wodurch die Darstellung von Verbindung **138b** ermöglicht wurde. Die dritte Serie wurde durch nukleophile aromatische Substitution an Anthrapyrazol mit verschiedenen Aminen realisiert, daraus resultierten die Verbindungen **155**, **157**, **159**, **161**, **163** und **165**. Die letzten beiden Serien werden derzeit noch auf ihre krebshemmende zytostatische Wirkung getestet. Für Ellipticin sollte eine neue, besonders kurze Synthese via Buchwald-Hartwig-Kopplung und anschließender Ringschlussmethode entwickelt werden. Dies konnte zwar nicht realisiert werden, die Synthese der Schlüsselverbindung **169** wurde jedoch erfolgreich auf drei Schritte verkürzt, was zumindest einer Optimierung der in den letzten Publikationen diskutierten Syntheseroute entspricht.



107: R = -$(CH_2)_2S(CH_2)_2OH$
108: R = -$(CH_2)_2$-N-morphorine
109: R = -$(CH_2)_2$-N-pyrrolidine
114: R = -$(CH_2)_2$-N-oxazolidine
120: R = -$(CH_2)_2$-N-1-methylpiperazine
124: R = -$(CH_2)_2NMe(CH_2)_2OH$





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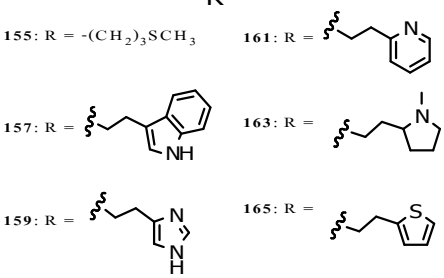
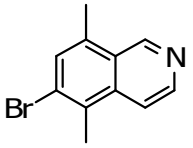


161: R =
157: R =
163: R =
159: R =
165: R =

128a: X = N, Y = C, Z = C ; R^1 = Cl, R^2 = H
128b: X = C, Y = N, Z = C ; R^1 = Cl, R^2 = H
134a: X = N, Y = C, Z = C ; R^1 = Br, R^2 = H
134b: X = C, Y = N, Z = C ; R^1 = Br, R^2 = H
136a: X = N, Y = C, Z = C ; R^1 = NO_2, R^2 = H
138b: X = N, Y = C, Z = C ; R^1 = Cl, R^2 = -$NMe(CH_2)_2NMe_2$
143a: X = N, Y = C, Z = N ; R^1 = H, R^2 = H



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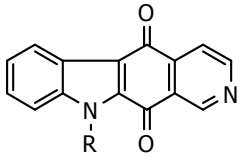
ABSTRACT

SYNTHESIS OF NEW ANTICANCER COMPOUNDS WITH A TETRACYCLIC NUCLEUS

Theerachart Leepasert, University of Vienna Thesis Advisor: Prof. Helmut Spreitzer

A Thesis submitted in partial fulfillment of the requirement for the degree of doctor of science

Three series of DNA intercalating agents were modified and synthesized and a novel synthetic approach to ellipticine **(49)** was investigated. In the first series (**107-109**, **114**, **120**, **124**), pyridocarbazoles have been assembled by attachment of various amino alkyl and hydroxy alkyl sulfide side chains on the nitrogen atom of pyrrole ring. All of them showed strong cytotoxicity against NClH460 cell lines. Moreover **109**, **114**, and **124** presented moderate cytotoxicity against SKOV3 cell lines. The second series was the reaction between 6,7-dichloro-5,8-isoquinolinedione/6,7-dichloro-5,8-quinazolinedione and substituted 2-aminopyridine/2-aminopyridine, yielding to new tetracyclic compounds **128(a,b)**, **134(a,b)**, **136a**, and **143a**. Moreover, **128a** could be introduced amine side chain at ring A to provide **138b**. The third series was synthesized by nucleophilic aromatic substitution of anthrapyrazole **(153)** with various amines, leading to **155**, **157**, **159**, **161**, **163**, and **165**. Both the second and the third series are being investigated concerning anticancer activity. Finally, Buchwald-Hartwig coupling and ring closure method could not be employed for the aspired shortest route to ellipticine. However, key intermediate **169** could be successfully synthesized in three steps, shorter than in recent reports described.



107: R = -$(CH_2)_2S(CH_2)_2OH$
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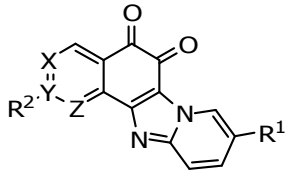
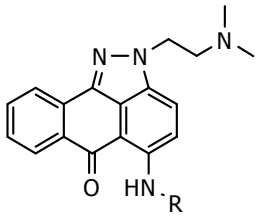


128a: X = N, Y = C, Z = C ; R^1 = Cl, R^2 = H
128b: X = C, Y = N, Z = C ; R^1 = Cl, R^2 = H
134a: X = N, Y = C, Z = C ; R^1 = Br, R^2 = H
134b: X = C, Y = N, Z = C ; R^1 = Br, R^2 = H
136a: X = N, Y = C, Z = C ; R^1 = NO_2, R^2 = H
138b: X = N, Y = C, Z = C ; R^1 = Cl, R^2 = $-NMe(CH_2)_2NMe_2$
143a: X = N, Y = C, Z = N ; R^1 = H, R^2 = H



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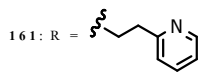

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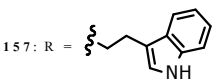

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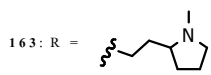

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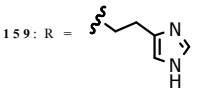

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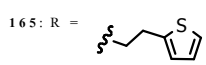

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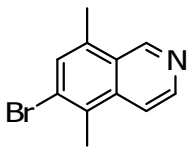

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ABBREVIATIONS

Ac_2O	acetic anhydride
$AlCl_3$	aluminium chloride
bp	boiling point
br	broad
$[BF_4][HP^tBu_3]$	tri(tert-butyl)phosphonium tetrafluoroborate
Bu_4NF	tetrabutylammonium fluoride
$CeCl_3.7H_2O$	cerium trichloride heptahydrate
$CDCl_3$	deuterochloroform
CH_2Cl_2	dichloromethane
CO_2	carbondioxide
d	doublet
dd	double doublet
DHFR	dihydrofolate reductase
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
EtOH	ethanol
eV	electron colt
g	gram
h	hour (s)
HCl	hydrochloric acid
HNO_3	nitric acid
HRMS	high resolution mass spectrometry
H_2SO_4	sulfuric acid
Hz	hertz
IR	infrared
J	coupling constant
K_2CO_3	potassium carbonate
KOH	potassium hydroxide
LDA	lithium diisopropylamide
$LiN[Si(CH_3)_3]_2$	lithium-bis(trimethylsilyl)amide

ABBREVIATIONS (CONT.)

m	multiplet
M	molar
MeOH	methanol
mg	milligram
MHz	megahertz
min	minute (s)
mL	milliliter
mmol	millimole
m/z	a value of mass divided by charge
M^+	molecular ion
mp	melting point
MS	mass spectrometry
NaH	sodium hydride
NaOH	sodium hydroxide
NaOMe	sodium methoxide
NaO^tBu	sodium tertiary butoxide
Na_2SO_4	sodium sulfate
NBS	N-bromosuccinimide
$Ni(PPh_3)_2Cl$	bis[triphenylphosphine]nickel(II)
NMR	nuclear magnetic resonance
$Pd(OAc)_2$	palladium(II)acetate
Ph	phenyl
$PhSO_2Cl$	benzenesulfonylchloride
ppm	part per million
p-TsOH.H_2O	para toluene sulfonic acid monohydrate
pyr	pyridine
RT	room temperature
s	singlet
SiO_2	silica gel
$SOCl_2$	thionyl chloride
t	triplet

ABBREVIATIONS (CONT.)

THF	tetrahydrofuran
TLC	thin layer chromatography
Zn	zinc metal
δ	chemical shift
υ_{max}	maximum absorptaion frequencies
^{o}C	degree celcius
%	percentage

CONTENTS

CONTENTS (CONT.)

CHAPTER I

INTRODUCTION

Cancer is a collective term used for a group of diseases that are characterized by the loss of control of the growth, division, and spread to other regions of the body through a process known as metastasis, which is the cause of 90% of cancer death. Cancer remains one of the most difficult diseases to treat and is responsible for 13% of all deaths worldwide, and this disease is increasing due to the aging of population in most countries, but especially in the developed ones.

1. Principles of cell cycle and cancer

1.1 The cell cycle

The cell cycle, or cell-division cycle, is the series of events that take place in a cell leading to its division and duplication (replication). In cells without a nucleus (prokaryotes), the cell cycle occurs via a process termed binary fission. In cells with a nucleus (eukaryotes), the cell cycle can be divided in two brief periods: interphase during which the cell grows, accumulating nutrients needed for mitosis and duplicating its DNA and the mitosis (M) phase, during which the cell splits itself into two distinct cells, often called "daughter cells". The cell-division cycle is a vital process where a single-celled fertilized egg develops into a mature organism, as well as the process where hair, skin, blood cells, and some internal organs are renewed.

The cell cycle consists of four distinct phases: G_1 phase, S phase (synthesis), G_2 phase (collectively known as interphase) and M phase (mitosis). M phase is itself composed of two tightly coupled processes: mitosis where the cell's chromosomes are divided into the two daughter cells, and cytokinesis where the cell's cytoplasm divides forming distinct cells. Activation of each phase is dependent on the proper progression and completion of the previous one. Cells that have temporarily or reversibly stopped dividing are said to have entered a state of quiescence called G_0 phase [1].

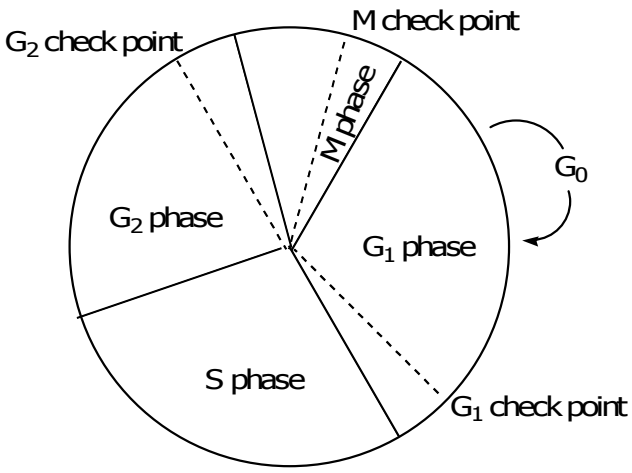


Figure 1. The eukaryotic cell cycle

G_1 phase : This phase is marked by synthesis of various enzymes that are required in S phase mainly those needed for DNA replication.

S phase : During this phase, the amount of DNA in the cell has effectively doubled, though the ploidy for the cell remains the same. Rate of RNA transcription and protein synthesis are very low during this phase.

G2 phase : Significant protein synthesis occurs during this phase, mainly involving the production of microtubules, which are required during the process of mitosis.

M phase : The M phase has been broken down into several distinct phases. Sequentially known as prophase, prometaphase, metaphase, anaphase, and telophase leading to cytokinesis.

1.2 Cancer

Cancer (medical term: malignant neoplasm) is a class of diseases in which a group of cells display uncontrolled growth (division beyond the normal limits), invasion (intrusion on and destruction of adjacent tissues), and sometimes metastasis (spread to other locations in the body via lymph or blood). These three malignant properties of cancers differentiate them from benign tumors, which are self-limited, do not invade or metastasize. Most cancers form a tumor but some, like leukemia, do not. The branch of medicine concerned with the study, diagnosis, treatment, and prevention of cancer is oncology.

Genetic abnormalities found in cancer typically affect two general classes of genes. Cancer-promoting oncogenes are typically activated in cancer cells, giving those cells new properties, such as hyperactive growth and division, protection against programmed cell death, loss of respect for normal tissue boundaries, and the ability to become established in diverse tissue environments. Tumor suppressor genes are then inactivated in cancer cells, resulting in the loss of normal functions in those cells, such as accurate DNA replication, control over the cell cycle, orientation and adhesion within tissues, and interaction with protective cells of the immune system.

2. A brief account of the role of chemistry in cancer chemotherapy

Chemistry has had varying roles in the discovery and development of anticancer drugs since the beginning of cancer therapies [2]. In its early history, chemical modification of sulfur mustard gas led to the serendipitous discovery of the still clinically useful nitrogen mustards. Since those years, synthetic chemistry has been extensively used to modify drug leads, especially those of natural origin, and to solve the problem of the often scarce supply of natural products by developing semisynthetic or synthetic strategies.

Since the 1950s, chemistry has also generated many antitumor drug leads through *in vitro* screening programs promoted by the National Cancer Institute (NCI) in the United States by using a range of cancer cell lines. In this early period transplantable rodent tumor models characterized by a high growth rate were used for *in vivo* screening. Later on, human tumor xenograft, based on transplantation of human tumor tissue into immune-tolerant animals, became also important tools for selecting drugs because the xenografts models allowed to stimulate a chemotherapeutic effect under conditions closer to man. In the late seventies and early eighties, the role of chemotherapy was extended to preoperative and postoperative adjuvants, radiosensitizers to enhance radiation effects and supportive therapy to increase the tolerance of the organism toward toxicity [3].

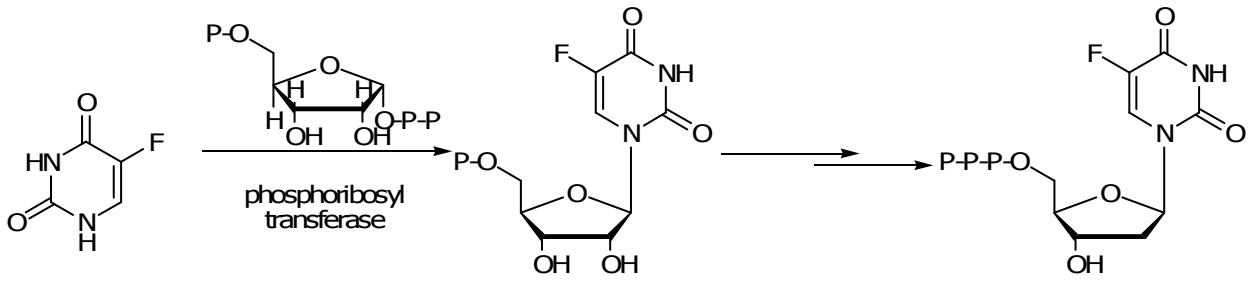
Cancer therapy is based on surgery and radiotherapy, which are, when possible, rather successful regional interventions, and on systemic chemotherapy. Approximately half of the cancer patients are not cured by these treatments and obtain only a prolonged survival or no benefit at all. The aim of most cancer chemotherapeutic drugs currently in clinical use is to kill malignant tumor cells by inhibiting some of the mechanism implied in cellular division.

Hence, the antitumor compounds developed through this approach are cytostatic or cytotoxic. However, the knowledge of tumor biology has exploded during the past decades and this may pave the way for more active, targeted cancer therapies.

2.1 Antimetabolites

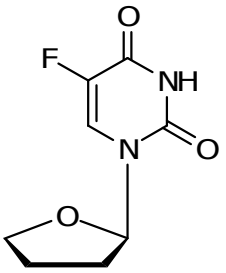
Antimetabolites can be defined as analogs of naturally occurring compounds that interfere with their formation, thus inhibiting essential metabolic routes. Although the enzymes inhibited by antimetabolites are also present in normal cells, some selectivity toward cancer cell is possible due to their faster division rates. Most antimetabolites interfere with nucleic acid synthesis and sometimes with RNA. Specific interference with the *de novo* nucleic acid pathway in cancer cell is probably not possible because tumor and normal cell use the same biosynthetic pathways. Nevertheless, some antimetabolites are remarkably effective against some human cancers and are still basic cancer therapeutics [4-5].

One of the most widely prescribed class of antimetabolites is 5-fluorouracil **(1)** (5-FU), it is used in the treatment of cancer of the aerodigestive tract, breast, head and neck and especially in colorectal cancer in combination therapies with oxaliplatin and irinotecan. Administered as a cream, it is also useful for the treatment of some skin cancers. 5-FU is a prodrug that enters the cell using the same facilitated transport mechanism as uracil and is activated to 5-fluoro-2'-deoxyuridine-monophosphate and more metabolites to active species 5-fluoro-2'-deoxyuridine-triphosphate, which eventually inhibit DNA synthesis.

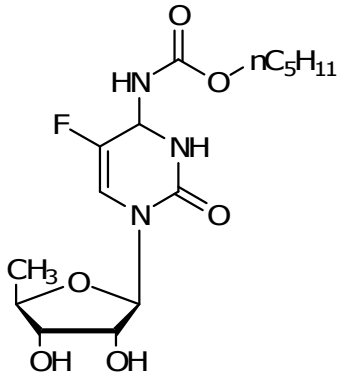


1: 5-Fluorouracil

5-FU requires intravenous administration and a number of oral prodrugs have been designed to avoid this limitation. One of them is ftorafur **(2)** which is completely absorbed in the gastrointestinal tract and metabolized to 5-FU. However it has shown cardiac toxicities. Thus, capecitabine **(3)** is a multiple prodrug, designed to be activated specifically with tumor cell. This compound has shown higher activity and less toxicity than ftorafur.



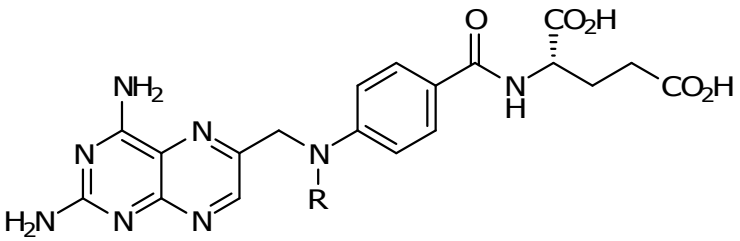
2: Ftorafur



3: Capecitabine

2.1.1 Inhibitors of dihydrofolate reductase (DHFR)

Folic acid and its metabolites are coenzymes of many essential biochemical transformations. Most importantly, they are involved in the transformation of one carbon unit in the DNA synthesis (thymidylic acid and purine nucleotides). Folate-dependent enzymes are obvious targets for cancer chemotherapy but until 1980 only DHFR was exploited in this regard. The most potent inhibitors of DHFR are folic acid analogs that differ from the natural ligand by carrying a 2,4-diaminopyridine unit, as shown by aminopterine **(4)**, methotrexate **(5)**, edatrexate **(6)** and 10-propagyl-10-deazaaminopterine (PDX) **(7)** which is under clinical investigation. The inhibitors where the side chain ends in a glutamic acid residue, like folic acid, are known as classical antifolates [6].



4: R = H; Aminopterine

5: R = CH_3; Methotrexate

6: R = CH_2CH_3; Edatrexate

7: R = $CH_2C{\equiv}CH$; PDX

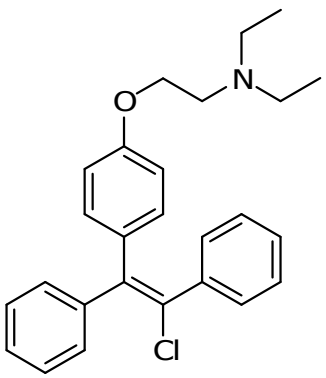
2.2 Anticancer drugs that inhibit hormone action

Hormones, and in particular steroid hormones, are the main determinants in induction and growth of several types of tumor or cancer and for this reason the search for antihormones has been one of the mainstays of cancer chemotherapy. Thus, compounds acting on estrogen and androgen receptors (ARs) are involved in the treatment of breast and prostatic cancers.

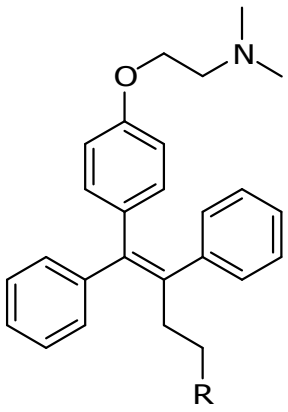
2.2.1 Nonsteroidal antiestrogen (SERMs)

The first discovered antiestrogen was clomiphene **(8)**, but its development for the treatment for advanced breast cancer was discontinued because of concerns about potential side effects [7]. In 1974, tamoxifene **(9)** was the first antiestrogen to be approved for the treatment of advanced breast cancer. Tamoxifene also binds with high affinity to other targets, such as the microsomal antiestrogen binding site, protein kinase C, calmodulin-dependent enzymes and acyl coenzyme A.

Tamoxifene has estrogenic agonist effects on other tissues such as bone and endometrium due to the nonspecific activation of their estrogen receptors (ERs). For this reason, several antiestrogen compounds, known as SERMs, have been developed that have a reduced agonist profile on breast. Some of these compounds belong to the triphenylethylene family, including toremifene **(10)**, droloxifene **(11)** and idoxifene **(12)**.

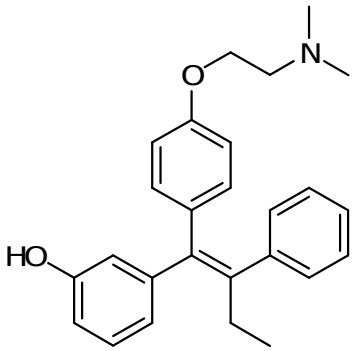


8: Clomiphene

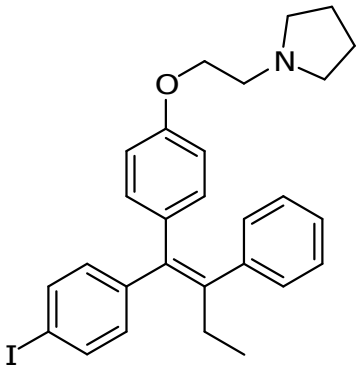


9: R = H; Tamoxifene

10: R = Cl; Toremifene



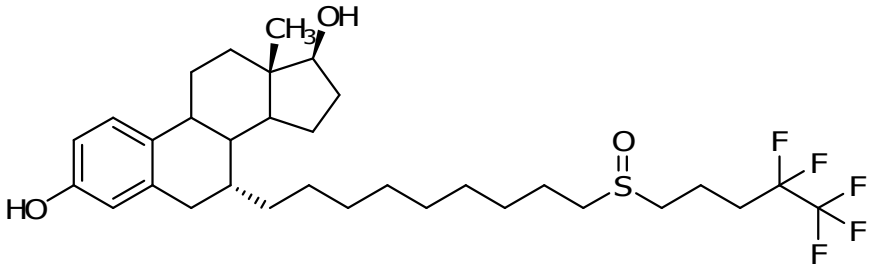
11: Droloxifene



12: Idoxifene

2.2.2 Steroidal antiestrogens

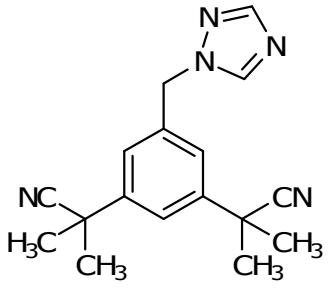
Structurally, the main family of selective estrogen antagonists are steroids carrying a long lipophilic chain at C-6, represented by fulvestrant (ICI-182786) **(13)** which has been approved for the treatment of postmenopausal women with hormone-sensitive advance breast cancer following prior endocrine therapy.



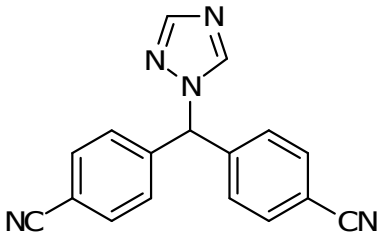
13: Fulvestrant

2.2.3 Nonsteroidal aromatase inhibitors

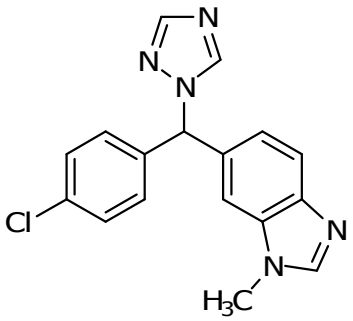
This group of inhibitors comprises structurally varied compounds that are able to bind to the active site of aromatase through the coordination of a heterocyclic nitrogen atom, usually an imidazole or triazole ring, to the iron atom of the heme group of the enzyme. Because of the similarity of aromatase with other essential enzymes of the cytochrome P450 group, the main problem to be solved is one of selectivity. On the contrary, they have the advantage over steroidal inhibitors of not being subject to metabolism by the cytochrome enzyme system. The structures of the main drugs belonging to this group are given below.



14: Anastrozole



15: Vorozole

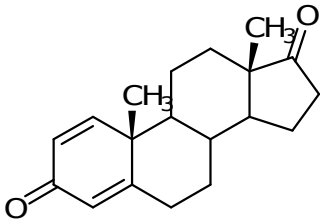


16: Letrozole

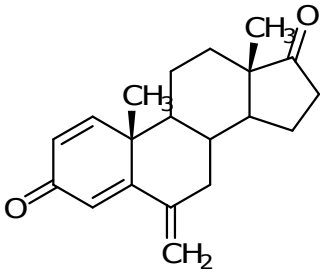
Nonsteroidal aromatase inhibitors include the triazole derivatives anastrozole **(14)**, vorozole **(15)**, and letrozole **(16)**, which are very potent and specific aromatase inhibitors that allow almost complete estrogen suppression [8].

2.2.4 Steroidal aromatase inhibitors

The first member of this class of compounds to be recognized as an aromatase inhibitor was subsequently 1,4-androstadiene-3,17-dione **(17)**. Among other more highly unsaturated compounds, the most relevant is the 6-methylene derivative, known as exemestane **(18)** [9]. Exemestane was approved more recently for clinical use in some countries and has the advantages over formestane of being more potent and, specially, of allowing oral administration [10].



17: 1,4-Androstadiene-3,17-dione

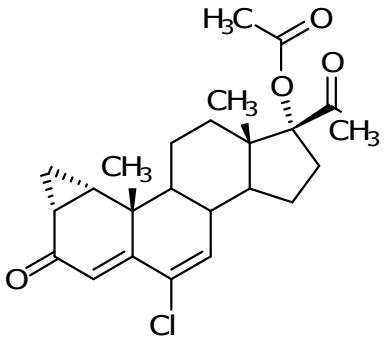


18: Exemestane

2.2.5. Antiandrogens

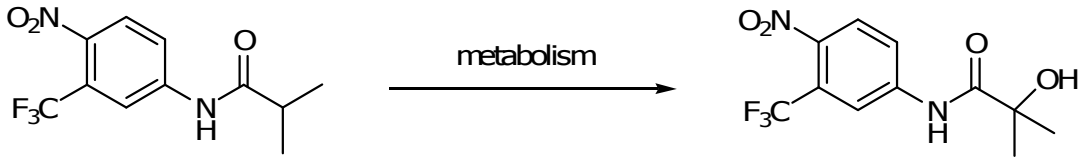
Androgen antagonists [11] bind to the receptor and prevent binding of the natural steroids, but they do not produce the correct conformational change in the receptor that is essential to elicit normal changes in gene expression. Cyproterone acetate **(19)** is a steroidal antiandrogen that was initially developed as a synthetic gestagen to be used as a contraceptive,

but the observation of feminization of the offspring in gestating rats led to its identification as a competitive inhibitor of the AR. It is used in prostatic carcinoma, but its side effects of gynecomastia and edema, which can be attributed to its analogy with natural gestagens and glucocorticoids, respectively, stimulated the search for nonsteroidal compounds with pure antiandrogenic action (SARM, selective androgen receptor modulators).



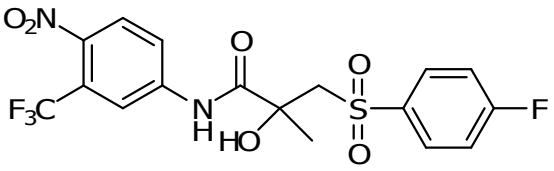
19: Cyproterone acetate

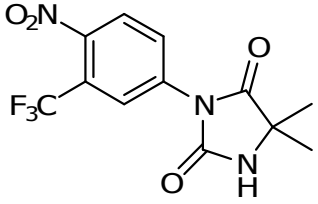
Flutamide **(20)** was the first nonsteroidal antiandrogen [12]. It does not act on androgen receptors, but it is metabolized by hydroxylation to the active species. This metabolite inhibits both androgen uptake and binding of androgens to their receptors in target tissues. Other antiandrogens that are in clinical use for the treatment of prostate cancer are bicalutamide **(21)** and nilutamide **(22)**, which have the advantage over flutamide by having a longer half-life that allows its administration only once daily.



20: Flutamide

Flutamide active metabolite





21: Bicalutamide

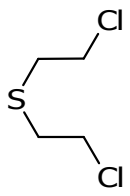
22: Nilutamide

2.3 DNA Alkylating Agents

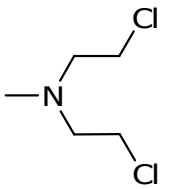
Anticancer drugs that target DNA have been used in clinic for more than 60 years. Despite the recent major advances in cancer research, the mechanism by which most clinically relevant anticancer drugs kill cells consist of interference with replication, which can be succeeded most simply by DNA alkylation. Alkylating agents can be defined as compounds capable of covalently binding an alkyl group to a biomolecule. DNA alkylating agents interact with resting and proliferating cells in any phase of the cell cycle, but they are more cytotoxic during the late G1 and S phases because there is not enough time available to repair the damage before DNA synthesis occurs. The main types of DNA alkylating drugs have been classified as follows: nitrogen mustards, aziridines (ethyleneimines), methansulfonates, and platinum complexes.

2.3.1 Nitrogen mustards

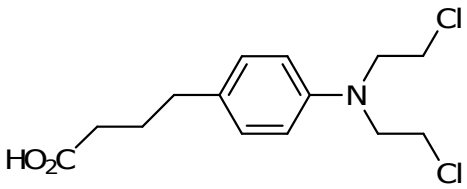
Sulfur mustard **(23)** was used in the World War I for chemical warfare. It is an extremely irritant agent. After that, it was realized that this compound could play a role in cancer treatment, but after an exploratory study, it was considered as too toxic for normal cells, and the nitrogen analog of sulfur mustard know as mechlorethamine (mustine) **(24)** was developed. It was applied to a lymphosarcoma patient in 1943. Afterwards, other nitrogen mustards for example chloramubucil **(25)**, melphalan **(26)**, bendamustin **(27)**, and uracyl mustard **(28)** [13] were developed for the reason of more activity and less toxicity than mustine.

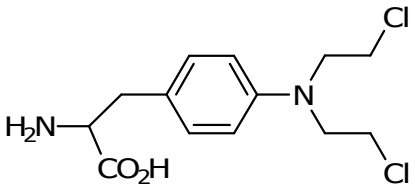


23: Sulfur mustard

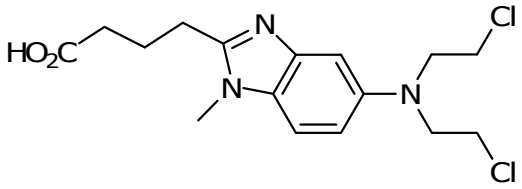


24: Mechlorethamine

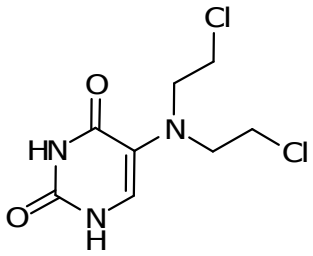




25: Chlorabucil



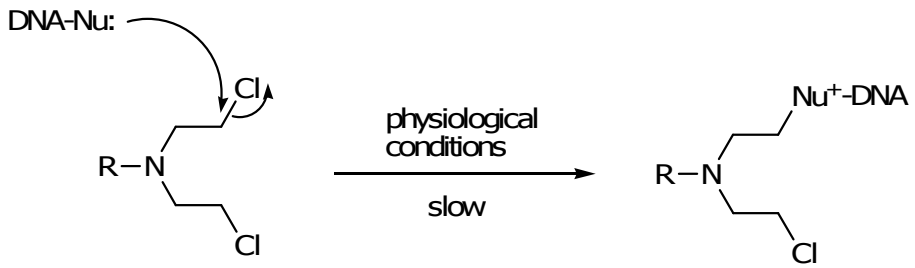
26: Melphalan

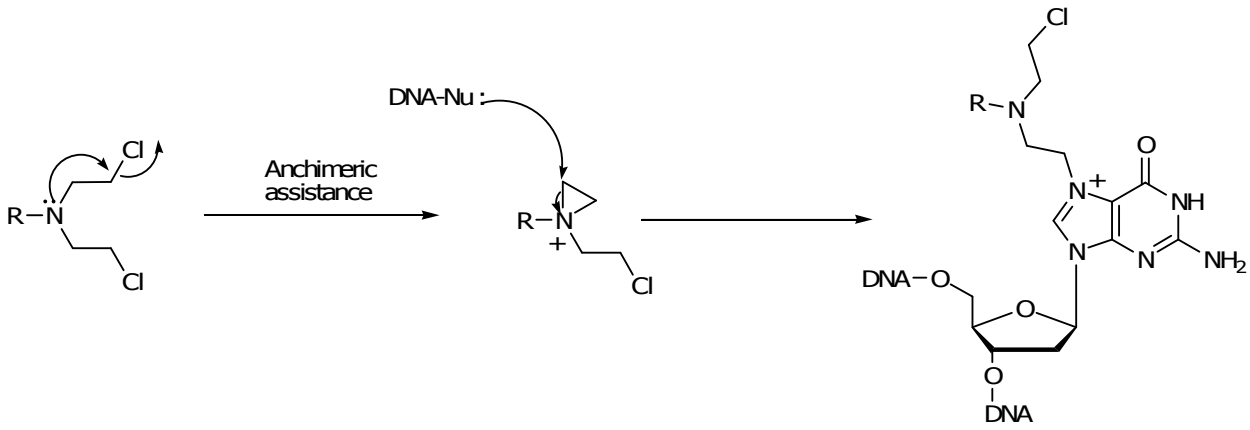


27: Bendamustin

28: Uracyl mustard

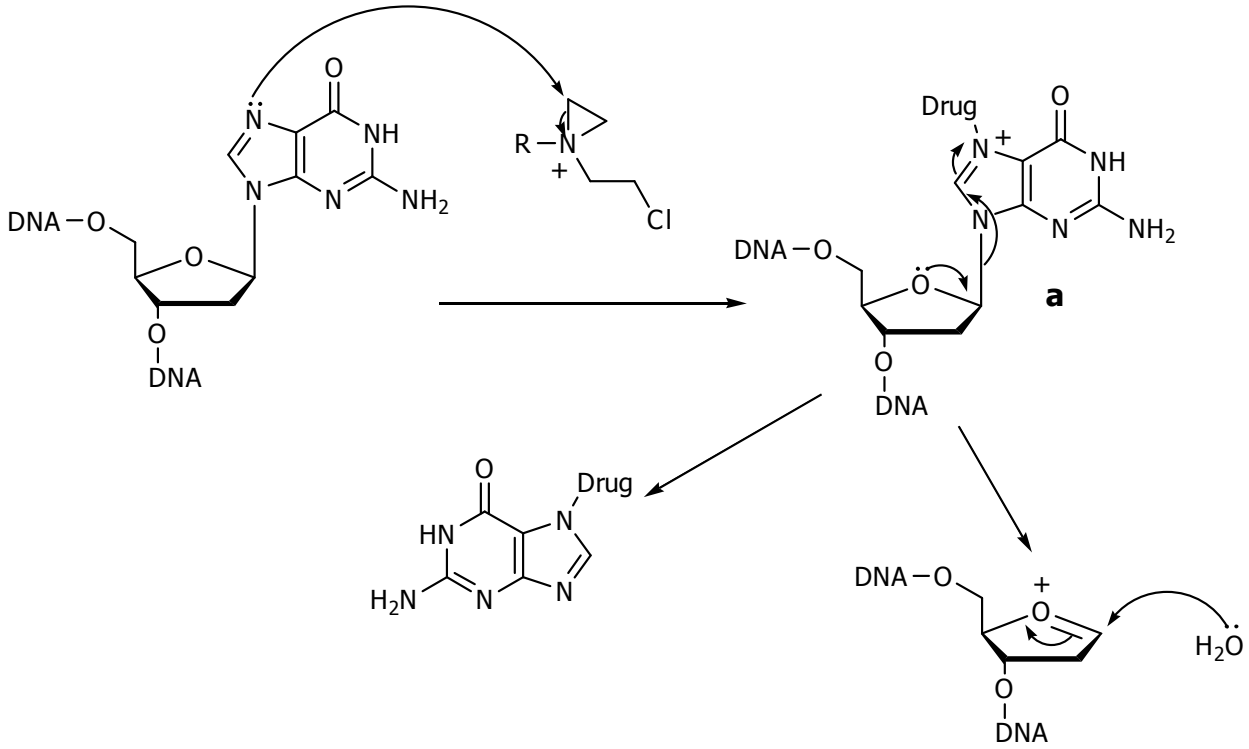
Because of the relative unreactivity of alkyl chloride as electrophiles, direct attack of DNA nucleophilic centers to nitrogen mustard under physiological condition is too slow because of therapeutic relevance. The reason why nitrogen mustards have a high reactivity as alkylating agents under mild conditions is the anchimeric assistance of the nitrogen atom. As a consequence of this the formation of an intramolecular aziridinium cation happens. The aziridinium cation is highly reactive because of its positive charge at the leaving group and high strain of the three membered ring. Since the most nucleophilic atom in DNA is the N-7 nitrogen of guanine, the most common species arising from alkylation as illustrated in scheme 1.

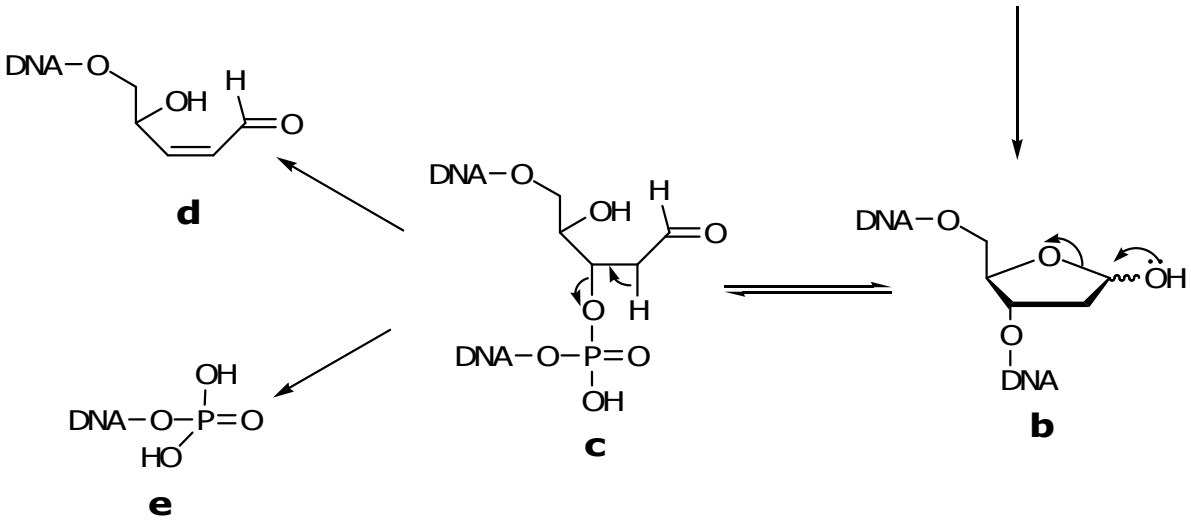




Scheme 1

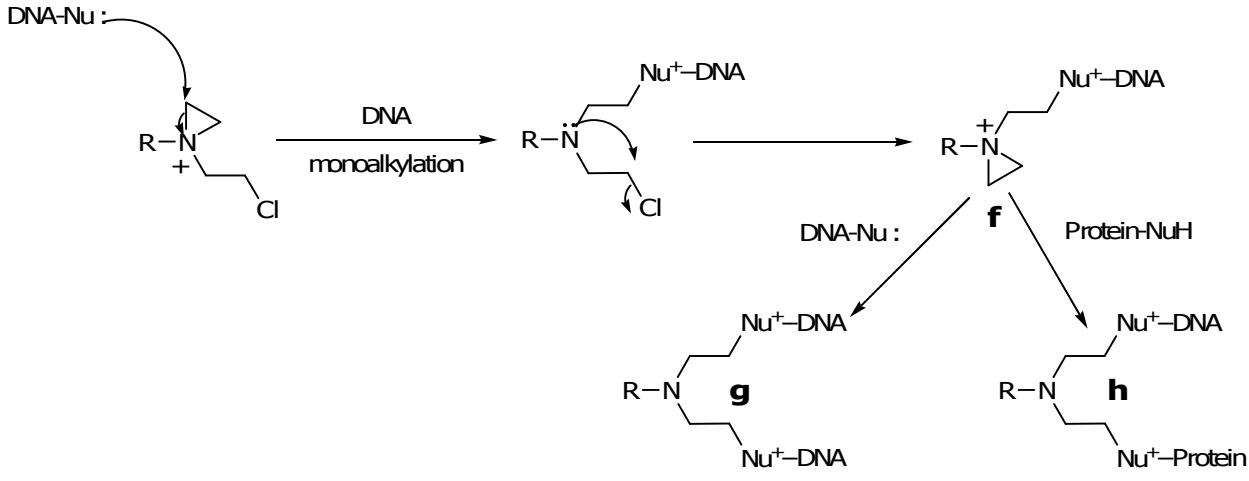
Another consequence of guanine alkylation is an increase in the electrophilicity of the position adjacent or conjugated to the positive charge of N-7, which leads to several hydrolytic reactions that alter the DNA structure. Thus, cleavage of the heteroside bond in structure (**a**) although slow [14], induces DNA depurination to give (**b**).This structure is in equilibrium with the open form (**c**), which has a good leaving group. This arrangement leads to an easy elimination process whereby DNA is fragmented to (**d**) and (**e**) as shown in scheme 2.





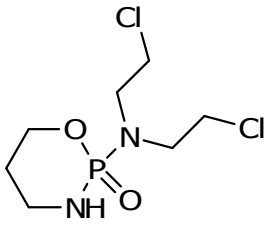
Scheme 2

Because nitrogen mustards are bifunctional alkyating agents, one of their cytotoxicity mechanisms is related to the ability of DNA-monoalkyated species (**f**) to give covalent DNA interstrand and intrastrand cross-links (**g**) or DNA-protein complexes (**h**) from the monoalkyated species (**f**), leading to disruption of replication or transcription process as shown in scheme 3.

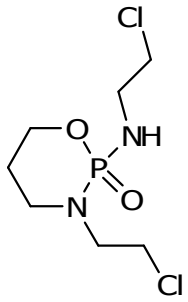


Scheme 3

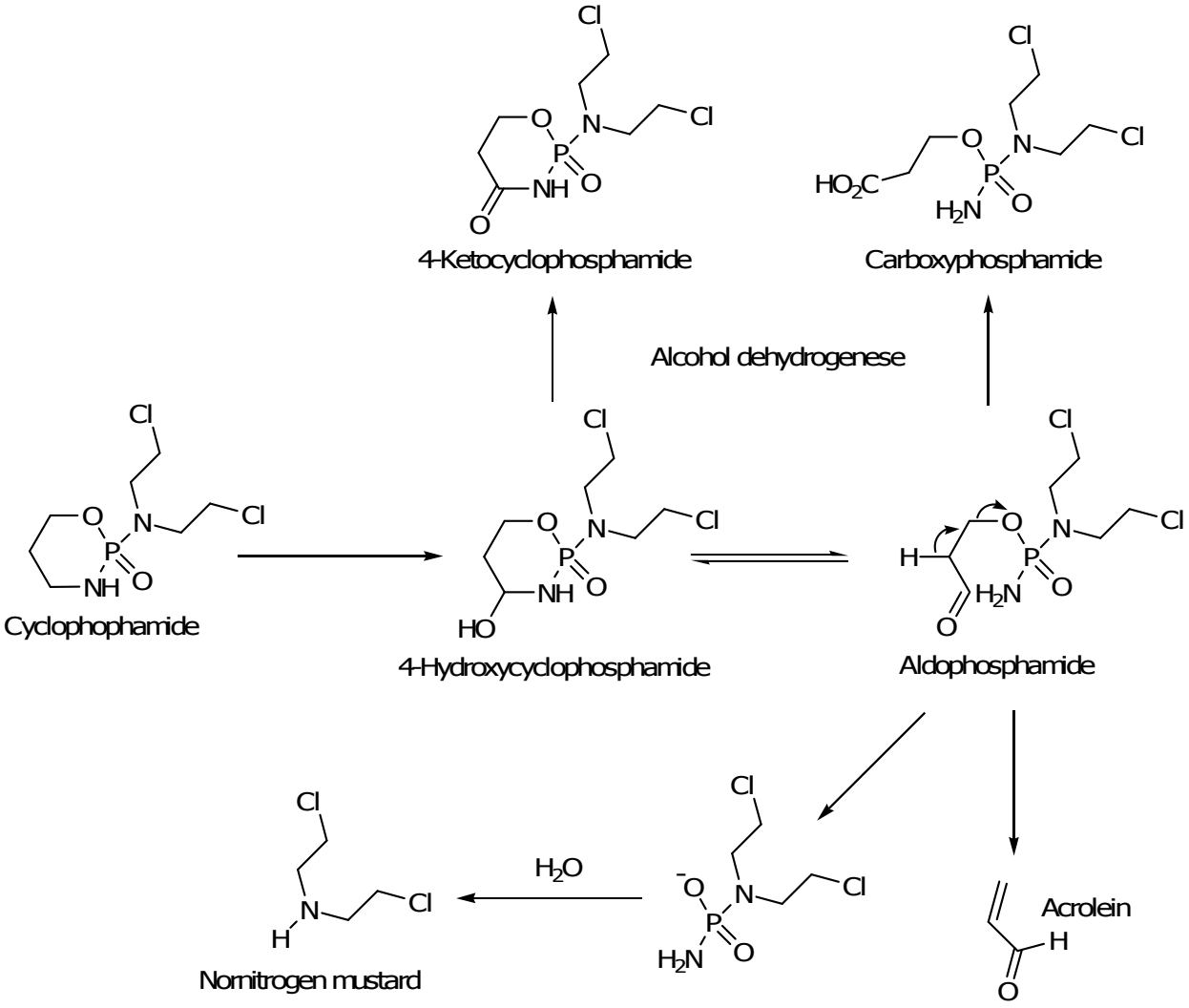
Another strategy for the development of site-directed nitrogen mustards can be the selective bioactivation of prodrug forms if biochemical differences can be found between a tumor and normal tissue. Thus, a report stating that some tumors contain high levels of phosphoramidase led to design of prodrug nitrogen mustards, which were expected to be activated by phosphoramide enzymatic hydrolysis. This assumption led to the preparation of cyclophosphamide (**29**), first reported in 1958, which has become the main antitumor drug of alkylating class, being used to treat lymphomas, leukemias, and often in combination with other drugs to treat breast cancer, leukemia, and overian cancer. Ifosfamide (**30**), a related compound, is used to treat testicular cancer. In both compounds the electron-withdrawing effect of the P=O bond prevents their activation to aziridinium cation. Finally, the negative charge on the phosphoramidate oxygen atom balances the electron-withdrawing effect of the P=O group, and allows its activation to an aziridinium cation. Phosphoramide mustard can be hydrolyzed to nornitrogen mustard, which is also active (scheme 4).



29: Cyclophosphamide



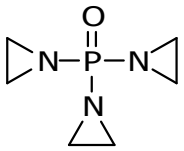
30: Ifosfamide



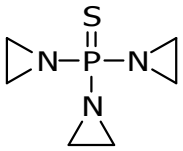
Scheme 4 Bioactivation of cyclophosphamide.

2.3.2 Aziridines

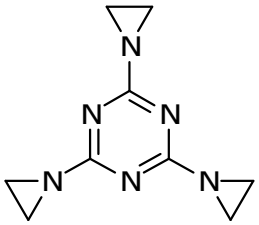
Since the active species involved in DNA alkylation by nitrogen mustards is an aziridinium cation, several aziridine derivatives were also tested as antitumor agents. Early studies showed that at least two aziridine units were necessary for good activity. The first compounds of this family to be introduced in therapeutics were triethylenemelamine (TEM) **(31)** and thiotepa **(32)**, so called because it is a sulfur analog of triethylenephosphoramide (TEPA) **(33)**.



31: TEPA

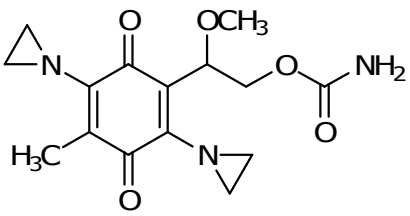


32: Thiotepa

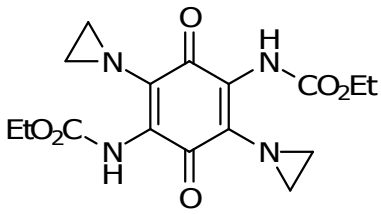


33: TEM

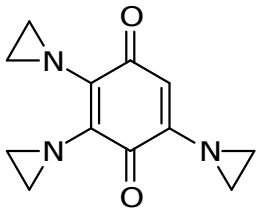
Other antitumor compounds contain two or three aziridine rings linked to a benzoquinone system and can act as DNA bisalkylators and cross-linking agents. They were designed to cross the blood-brain barrier because of their high lipophilicity and low ionization. Some of them have been used in clinic, as it is in the case of carboquone (carbazilquone) **(34)**, diaziquone (AZQ) **(35)**, triaziquone **(36)**, and BZQ **(37)**. AZQ, one of the most active compounds, has been studied in a number of clinical trials up to Phase II. In case of BZQ and triaziquone also underwent clinical trials [15], but finally, they were withdrawn due to their toxicity.



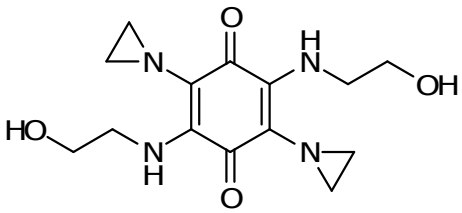
34: Carboquone



35: Diaziquone



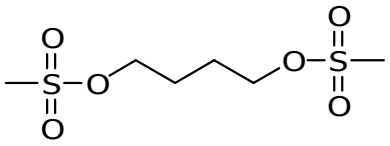
36: Triaziquone



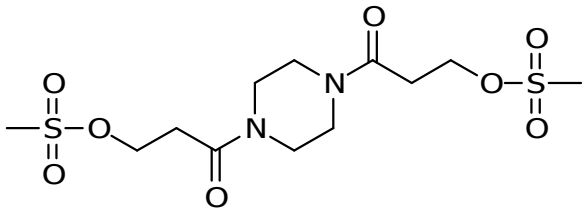
37: BZQ

2.3.3 Methanesulfonates

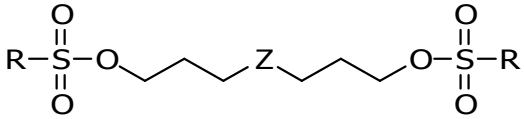
Methanesulfonate is a good leaving group because of the efficient delocalization of negative charge between three oxygen atoms. For this reason, several compounds containing two methansulfonate groups separated by a polymethylene chain were tested as antitumor agents, finding that the optimal activity corresponded to the compound with four carbon atoms (busulfan **(38)** [16]. Other members of this family are piposulfan **(39)**, improsulfan **(40)**, hepsulfan **(41)** and the diepoxide prodrug treosulfan **(42)**.



38: Busulfan

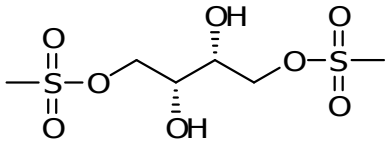


39: Piposulfan



40: R = CH_3, Z = NH; Improsufan

41: R = NH_2, Z = CH_2; Hepsulfan

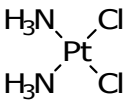


42: Treosulfan

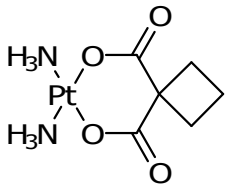
2.3.4 Platinum complexes

Cisplatin **(43)** (CDPP, cis-diaminedichloroplatinum II) provides an excellent example of serendipity in the discovery of antitumor drugs. In the course of the study of the effects of electric currents on cells, it was discovered that *Escherichia coli* cells formed long filaments, but they did not divide. Further research showed that inhibition of bacterial cell division was due to cisplatin, generated from the platinum electrodes and the ammonium chloride present

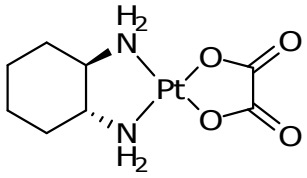
in the media. Because of the very high toxicity of cisplatin, thousands of analogs have been prepared in an effort to improve its selectivity and therapeutic index. The renal side effects are a great problem and dose-limiting. The causes for the renal side effects are interactions with renal components, leading to tubular necrosis of both proximal and distal renal tubules. Cisplatin analogs include tetragonal Pt(II) complexes, such as carboplatin **(44)**, oxaliplatin **(45)**, nedaplatin **(46)**, ZD-0473 **(47)**, and SKI 2053R **(48)** [17].



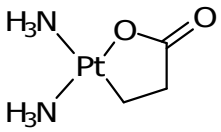
43: Cisplatin



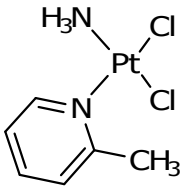
44: Carboplatin



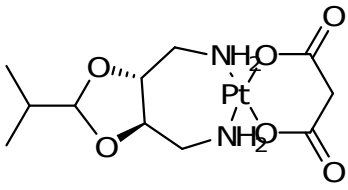
45: Oxaliplatin



46: Nedaplatin



47: ZD-0473



48: SKI 2053R

2.4 DNA intercalation and its consequences

Many anticancer drugs in clinical use (e.g. anthracyclins, mitoxantrone, dactinomycin) interact with DNA through intercalation, which can be defined as the process by which compounds containing planar aromatic or heteroaromatic ring systems are inserted between adjacent base pairs perpendicularly to the axis of helix and without disturbing the overall stacking pattern due to Watson-Crick hydrogen bonding.

The intercalation process starts with the transfer of the intercalating molecule from an aqueous environment to the hydrophobic space between two adjacent DNA base pairs. This process is thermodynamically favoured because of the positive entropy contribution associated to disruption of the organized shell of water molecules around the ligand (hydrophobic effect) [18]. In order to accommodate the ligand, DNA must undergo a conformational change involving an increase in chromophore. The double helix is thereby partially disturbed [19], which leads to distortions of the sugar-phosphate backbone and changes in the twist angle

between successive base pairs (Figure 2). Once the drug has been sandwiched between the DNA base pairs, the stability of the complex is optimized by a number of non-covalent interactions, including van der Waals and π-stacking interactions [20], reduction of coulombic repulsion between the DNA phosphate groups associated with the increased distance between the bases because of helix unwinding, ionic groups, and hydrogen bonding.

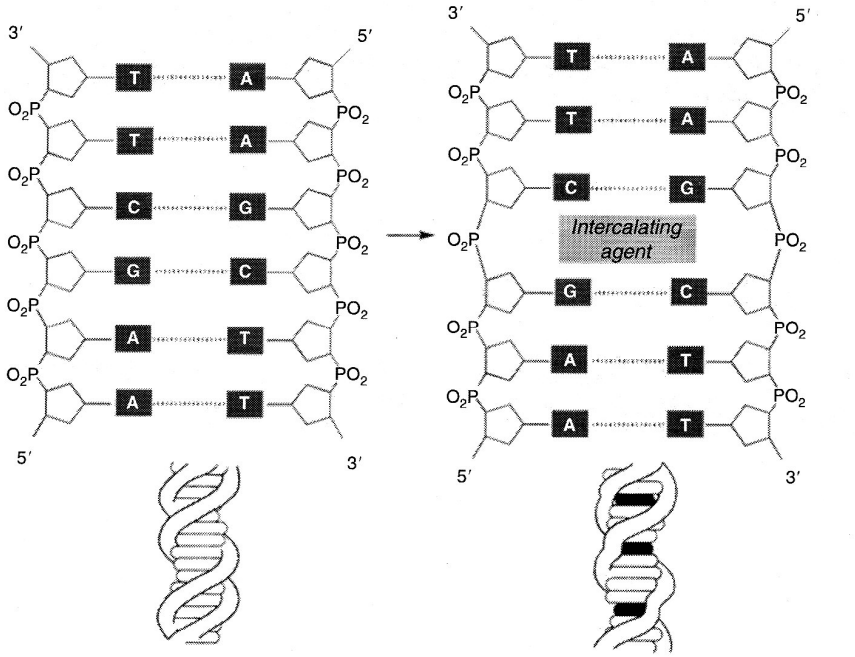
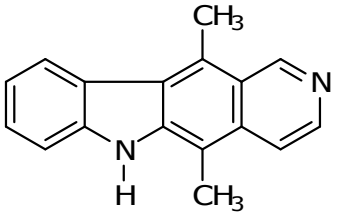
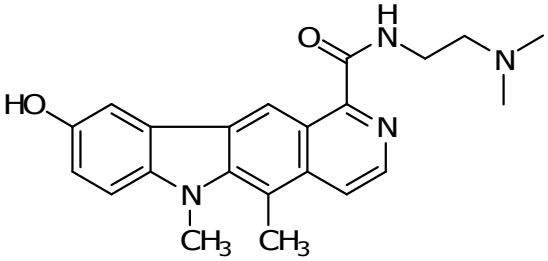


Figure 2 Deformation of DNA by an intercalating agent.

Ellipticine (**49**), an alkaloid isolated from the leave of *Ochrosia elliptica* and other *Apocymaceae* plants, is the prototype of intercalators based on the pyridocarbozole system and displays a broad spectrum of anticancer activity [21]. S-16020 (**50**) is another pyridocarbazole derivative, carrying a (dimethylamino)ethylcarboxamide side chain that increases its DNA-intercalating ability. This drug is a potent stimulator of topotisomerase II-mediated DNA cleavage. Despite its close similarity with ellipticine, both compounds show little cross-resistance.

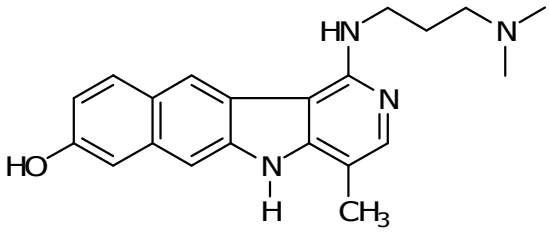


49: Ellipticine



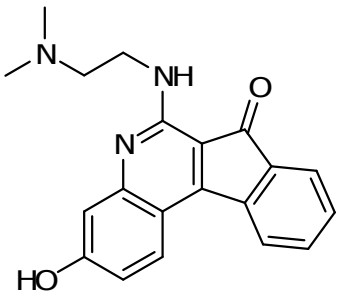
50: S-16020

Intoplicine **(51)** is an intercalating compound that can be considered as structurally related to the ellipticines. It behaves as a dual topoisomerase I and II poison at cleavage sites different to those of other known topoisomerase inhibitors [22]. From spectroscopic results two types of DNA complexes have been proposed an accounting for topoisomerase I- and II-mediated cleavages, involving a 'deep intercalation mode' or an 'outside binding mode', respectively [23]. Because of the high activity of intoplicine in preclinical cancer models, original mechanism of action and acceptable toxicity profile, it was further evaluated in several Phase I studies [24].



51: Intoplicine

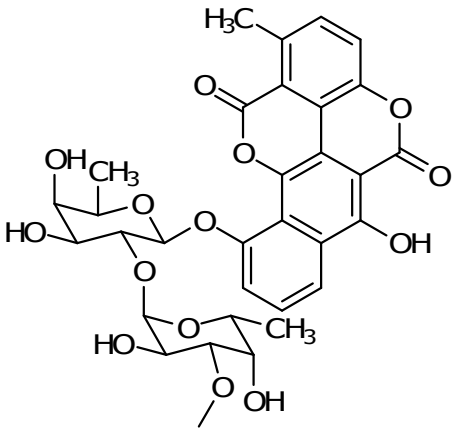
TAS-103 (**52**) is a dual topoisomerase I and II inhibitor that has marked efficacy against various lung metastatic cancers and a broad antitumor spectrum, and it has reached clinical trails for treatment of solid tumors. DNA binding and unwinding assays indicate that TAS-103 intercalates in to DNA [25].



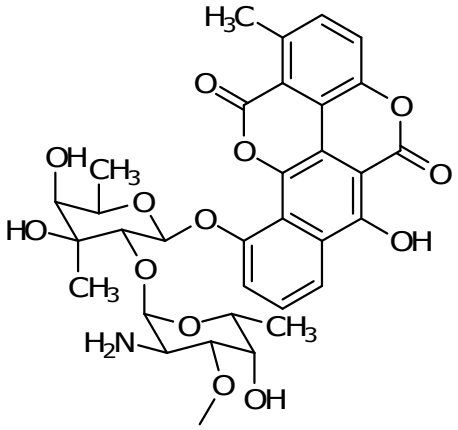
52: TAS-103

Chartreusin **(53)** and elsamicin A **(54)** are structurally related antitumor antibiotics that were isolated from *Streptomyces chartreusis* and from an unidentified actinomycete strain, respectively. Chartreusin suffers from unfavourable pharmacokinetics (slow oral absorption and biliar excretion) which prevented its clinical development. Semi-synthetic

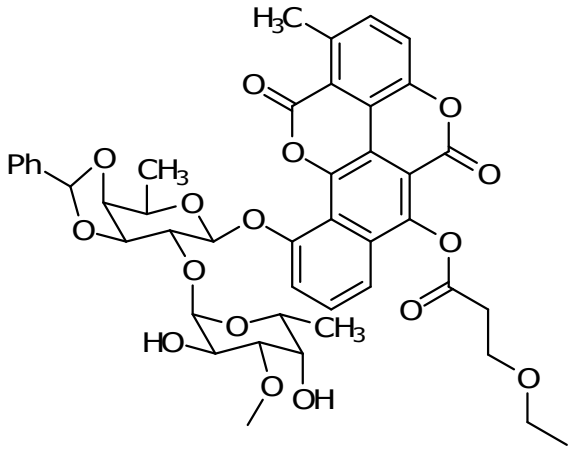
chartreusin analogs with improved pharmacokinetics have been developed. One of them, IST-622 **(55)**, is under Phase II clinical trials for the oral treatment of breast cancer [26].



53: Chartreusin

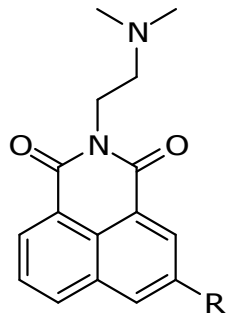


54: Elsamicin A



55: IST-622

Naphthalimide derivatives bearing an aminoalkyl side chain such as mitonafide **(56)** and amonafide **(57)** have shown interesting cytotoxic activity [27], which is due to intercalation and topoisomerase II inhibition [28]. Both mitonafide and amonafide have been extensively tested in clinical trials but have not been employed in therapeutics, although they have been used as leads in the design of bis-intercalators.



56: R = NO_2; Mitonafide

57: R = NH_2; Amonafide

In effort to increase the binding constant of intercalating compounds, bifunctional or even polyfunctional compounds have been designed. Bifunctional intercalators usually contain two intercalating two cationic units, separated by a spacer chain that must be long enough to allow double intercalation taking into account the neighbour exclusion principle as illustrated in figure 3.

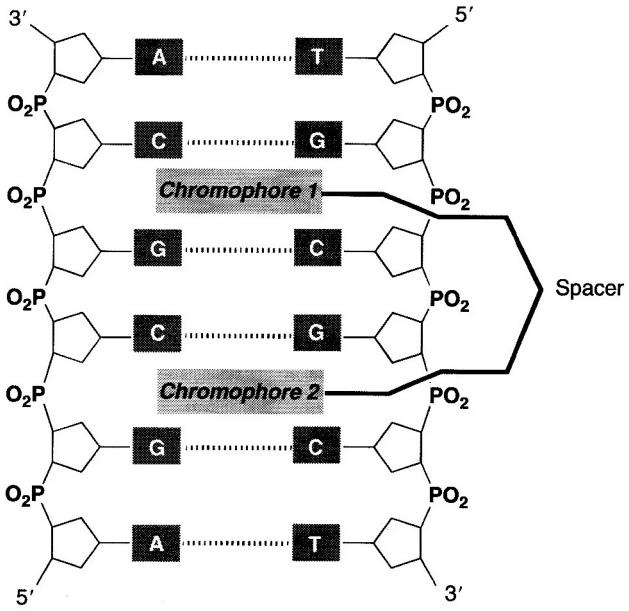
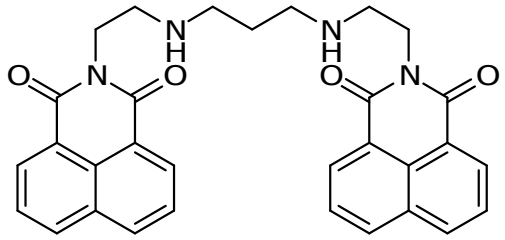


Figure 3 Interaction between a bis-intercalator and DNA.

Elinafide **(58)** is a bis-intercalator derived from naphthalimide pharmacophore [29] that showed antitumor activity and reached Phase I clinical trials, showing anti-neoplastic activity in ovarian cancer, breast cancer, and mesothelioma.



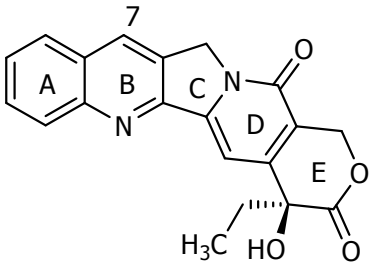
58: Elinafide

2.5 Topoisomerases inhibitors

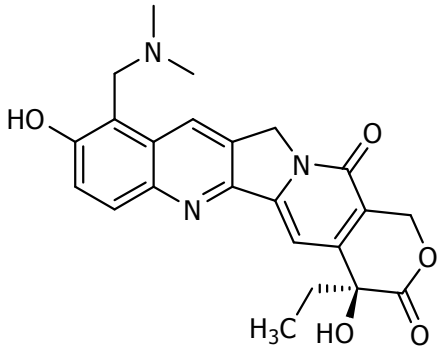
Topoisomerases are crucial for several DNA functions (e.g. replication and transcription). Topoisomerase I breaks a single DNA strand while Topoisomerase II brakes both strands and requires ATP for full activity. Drugs that can inhibit the topoisomerases, including some of the most widely used anticancer drugs.

2.5.1 Topoisomerase I inhibitor

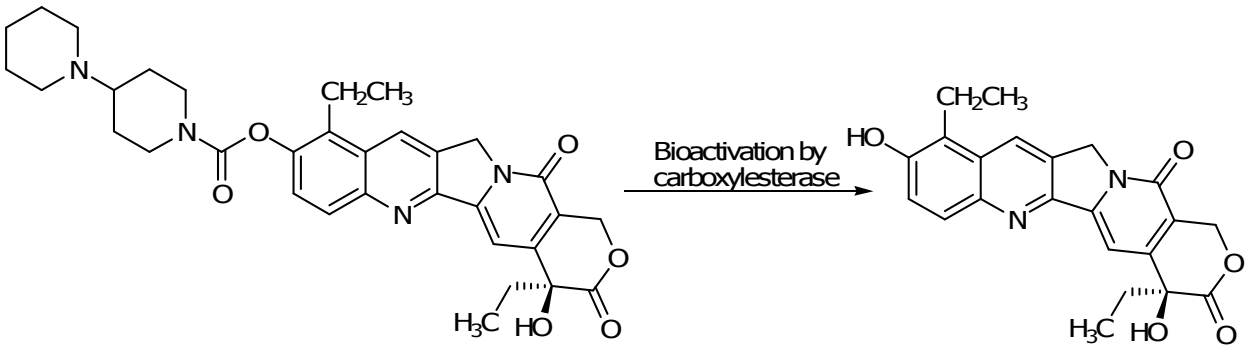
Topoisomerase I was validated as a target for cancer chemotherapy when it was identified as the sole target of camptothecin **(59)** (CPT). This compound was isolated in 1966 from the Chinese tree *Camptotheca acuminata* and its therapeutic development was initially limited by its poor solubility and unacceptable toxicity. The identification of topoisomerase I as its target prompted the search for water-soluble, more active, less toxic analogues. Structure activity relationship studies showed that substituents at ring A and at the C-7 position of ring B were allowed, whereas the ring E lactone was essential for activity. Two of these compounds are widely used in the clinic, namely topotecan **(60)** for the treatment of fluoropyrimidine-refractory ovarian and small cell lung cancers [30] and irinotecan (CPT-11). Irinotecan **(61)** is a prodrug that needs to be hydrolysed by carboxylesterase [31] to its active metabolite SN-38 **(62)** (Scheme 5) It is used in colorectal cancer, showing synergism with cisplatin, [32] and several studies have underscored the importance of pharmacogenetic considerations in its clinical application [33].



59: Camptothecin



60: Topotecan



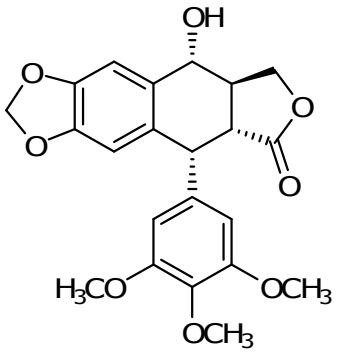
61: Irinotecan (prodrug)

62: SN-38

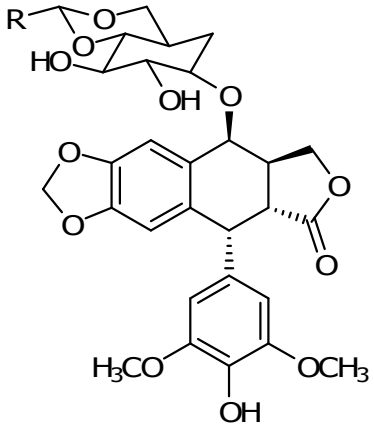
Scheme 5

2.5.2 Topoisomerase II inhibitor

Podophyllin resin derivatives have been used as folk medicines for centuries, its main active ingredient being podophyllotoxin **(63)**. In the 1950s, a search began to identify a more effective podophyllotoxin derivative [34] that eventually resulted in the development of a new class of anti-neoplastic agents which target topoisomerase II. The most important compounds are etoposide **(64)** and teniposide **(65)**, two semi-synthetic derivatives of 4-epipodophyllotoxin. Etoposide [35] is used mainly to treat testicular cancer which does not respond to other treatment and as a first-line treatment for small cell lung cancers. It is also used to treat chorionic carcinomas, Kaposi's sarcoma, lymphomas, and malignant melanomas.



63: Podophyllotoxin

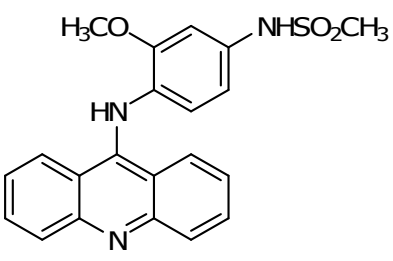


64: R = CH_3; Etoposide

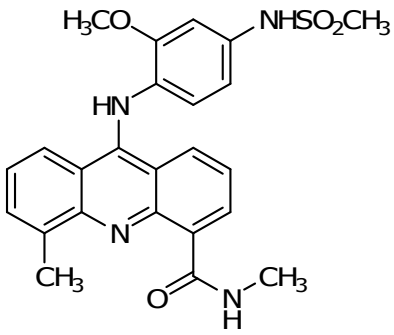
65: R = 2-thienyl; Teniposide

Etoposide and teniposide activity are cell cycle dependent and phase specific, with maximum effects on the S and G2 phases of cell division. They cause DNA damage through inhibition of topoisomerase II, and their mechanism of action has been studied specially for the case of etoposide. DNA religation inhibition by this compound seems to be due to inhibition of the release of ADP from the hydrolysis of ATP [36] and to its activation through oxidation–reduction reactions to produce derivatives that bind directly to DNA.

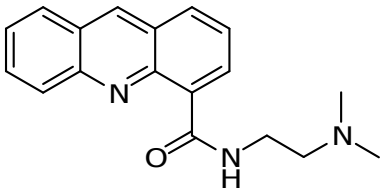
Amsacrine **(66)**, a large number of natural products and synthesis derivatives of acridines have been tested as anticancer agents and, so far, a few molecules have entered clinical trials and have been approved for chemotherapy. For instance, asulacrine **(67)** is an analog with a broader spectrum of activity in experimental tumors but without improved clinical antitumor activity. DACA (XR-5000) **(68)** is an acridinecarboxamide and a mixed topoisomerase I and II inhibitor that has undergone extensive clinical trials [37].



66: Amsacrine

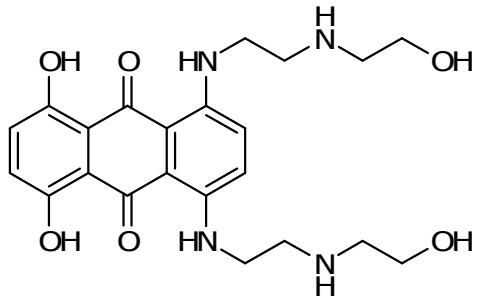


67: Asulacrine

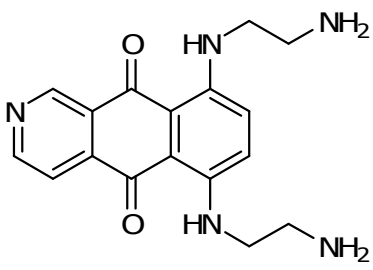


68: DACA

Mitoxantrone **(69)** is a simplified analog of the anthracyclines. It has a complex mechanism of action that includes generation of a stable drug-DNA-topoisomerase II ternary complex. Isosteric substitution of one or more carbons of the bezene ring by nitrogen atoms has been employed as a strategy for the design of mixtoxantrone analogs. Pixantrone **(70)** has a high level of activity in blood related tumors and is currently being studied in Phase III trials for the treatment of non-Hodgkin's lymphoma [38-39]. Another potential application of this drug is as an immunosuppressant in multiple sclerosis patients. The mechanism of action of pixantrone involves intercalation with DNA and interaction with topoisomerase II, causing DNA strands breaks.



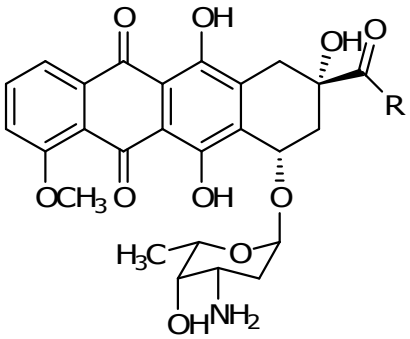
69: Mitoxantrone



70: Pixantrone

2.6 Antibiotics with anticancer activity

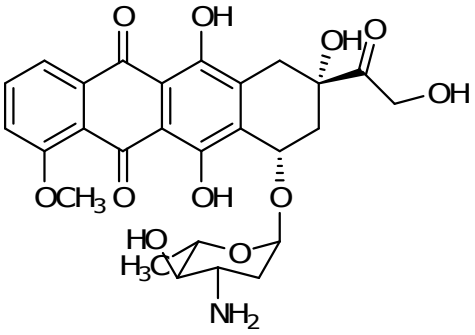
Anthracyclines are a group of antibiotics characterized by the presence of a planar chromophore containing an anthraquinone fragment, attached to an amino sugar. Doxorubicin (DOX) **(71)** and daunomycin or daunorubicin (DNR) **(72)** previously called adriamycin, were isolated from a *Streptomyces* species and were the first anthracycline antibiotics introduced in the clinic for cancer treatment. They are widely used for the treatment of human cancers, and, despite its very similar structure, their antitumor spectra of activity differ widely. Thus, daunorubicin is effective in acute lymphocytic and myeloid leukemia, while doxorubicin is an essential component of the chemotherapy of a large number of solid tumors, including breast cancer, childhood solid tumors, soft tissue sarcomas, and aggressive lymphomas.



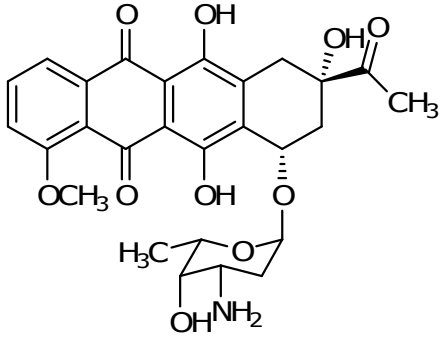
71: R = CH_2OH; Doxorubicin (DOX)

72: R = CH_3; Daunorubicin (daunomycin, DNR)

Epirubicin (EPI) **(73)** and idarubicin (IDA) **(74)** [40] can be mentioned as useful alternatives to DOX or DNR, respectively. EPI is an epimer of DOX at the daunosamine C-4'position that induces pharmacokinetic and metabolic changes related to the increased 4'-O-glucuronidation and increased elimination. In spite of this finding, clinical studies have shown that replacing DOX with EPI does not eliminate the risk of chronic cardiotoxicity. IDA, an analog of DNR obtained by removal of the methoxy group, has a broader spectrum of activity. This is probably related to its increased lipophilicity, which facilitates the cellular uptake and contributes to stabilize the ternary complex that forms the drug with DNA and topoisomerase II.



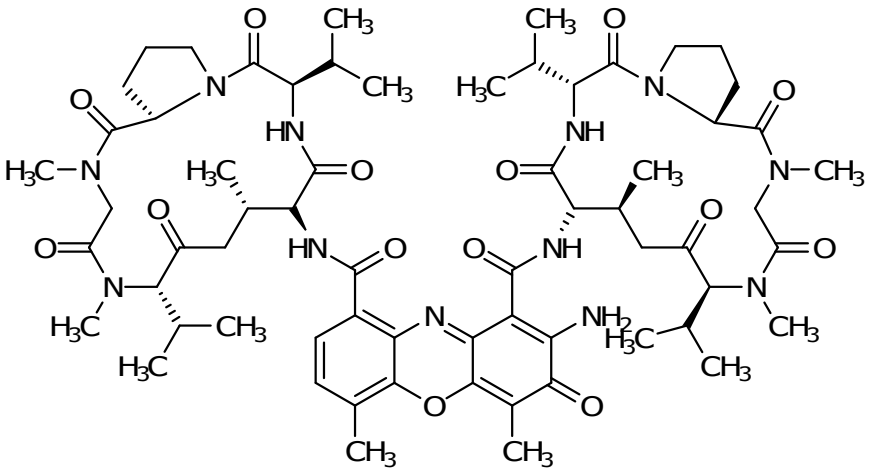
73: Epirubicin



74: Idarubicin

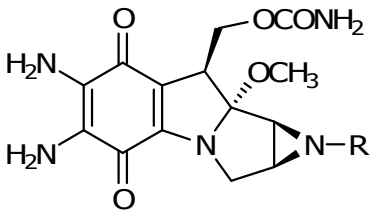
Actinomycin D **(75)** (dactinomycin) is a member of the actinomycin family of compounds, which was isolated from several *Streptomyces* strains. It contains a phenoxazine chromophore attached to two cyclic depsipeptides containing five amino acid residues. It can be considered as a hybrid compound that behaves both as a DNA intercalator and a minor

groove binding agent. Although it differs from most intercalating drugs in that it lacks a positive charge, it has been suggested that this is compensated by its high dipole moment, arising from a non-symmetrical distribution of polar substituent [41]. Dactinomycin is used to treat sarcomas, pediatric solid tumors (e.g. Wilms' tumor, a type of renal tumor), germ cell cancers (testicular cancer), and choriocarcinoma.



75: Actinomycin D (dactinomycin)

Mitomycin C **(76)** is a naturally occurring antitumor quinone from *Streptomyces caespitosus*, which contains quinone and aziridine units, although not directly linked. It has been used as a cytotoxin since the 1960 decade and is active against a variety of tumors, including breast, stomach, oesophagus, and bladder, [42] as well as non-small cell lung cancer [43]. The N-methyl derivative of mitomycin C is also a natural product called porfiromycin **(77)**, which has reached Phase III clinical studies for the treatment of head and neck cancer in combination with radiotherapy, with acceptable toxicity and encouraging activity [44].



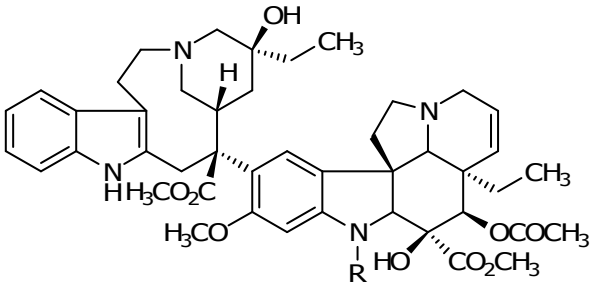
76: R = H; Mitomycin C

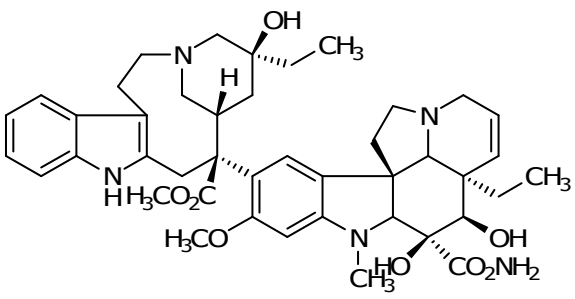
77: R = Me; Porfiromycin

2.7 Anticancer drugs targeting tubulin and microtubules

Drugs focusing on microtubules bind to several sites of tubulin and at different positions of the microtubules. As a consequence they all suppress microtubule dynamics, thereby blocking mitosis at the metaphase/ anaphase transition and inducing cell death. Some of the well-known drugs in this mode of action are vincristine (Oncovin®), vinblastine (Velbe®), vindesine (Eldisin®), vinorelbine (Navelbine®), paclitaxel (Taxol®), and docetaxel (Taxtere®)

Vincristine **(78)** and vinblastine **(79)** are complex molecules produced by the leaves of the rosy periwinkle plant *Catharanthus roseus* (*Vinca rosea*), whose potent cytotoxicity was discovered in 1958. They were introduced in cancer chemotherapy in the late 1960s and remain in widespread clinical usage to this day. Despite their very similar structures and common mechanism of action, they have different toxicological properties and antitumor spectra. Thus, vinblastine is currently used in the treatment of Hodgkin's disease and metastatic testicular tumors, where it is combined with bleomycin and cisplatin, while vincristine is used in the treatment of leukemia and lymphomas. Several semisynthetic analogs of these alkaloids [45] are also in clinical use, most notably vindesine **(80)**, used mainly to treat melanoma and lung carcinomas and, associated with other drugs, to treat uterine cancers, and the nor-derivative vinorelbine **(81)**, used for non-small cell lung cancer, metastatic breast cancer, and overian cancer.

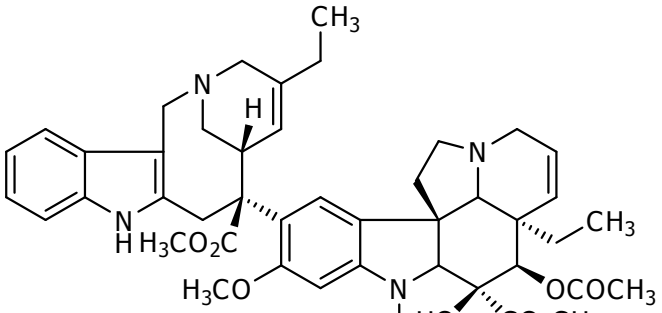




78: R = CHO; Vincristine (Oncovin®)

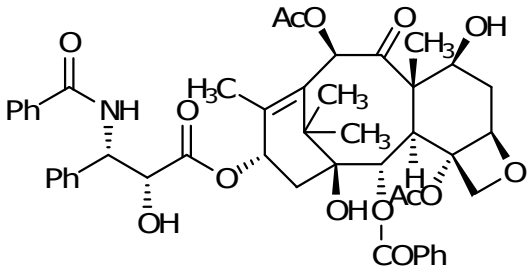
79: R = CH_3; Vinblastine (Velbe®)

80: Vindesine (Eldisin®)



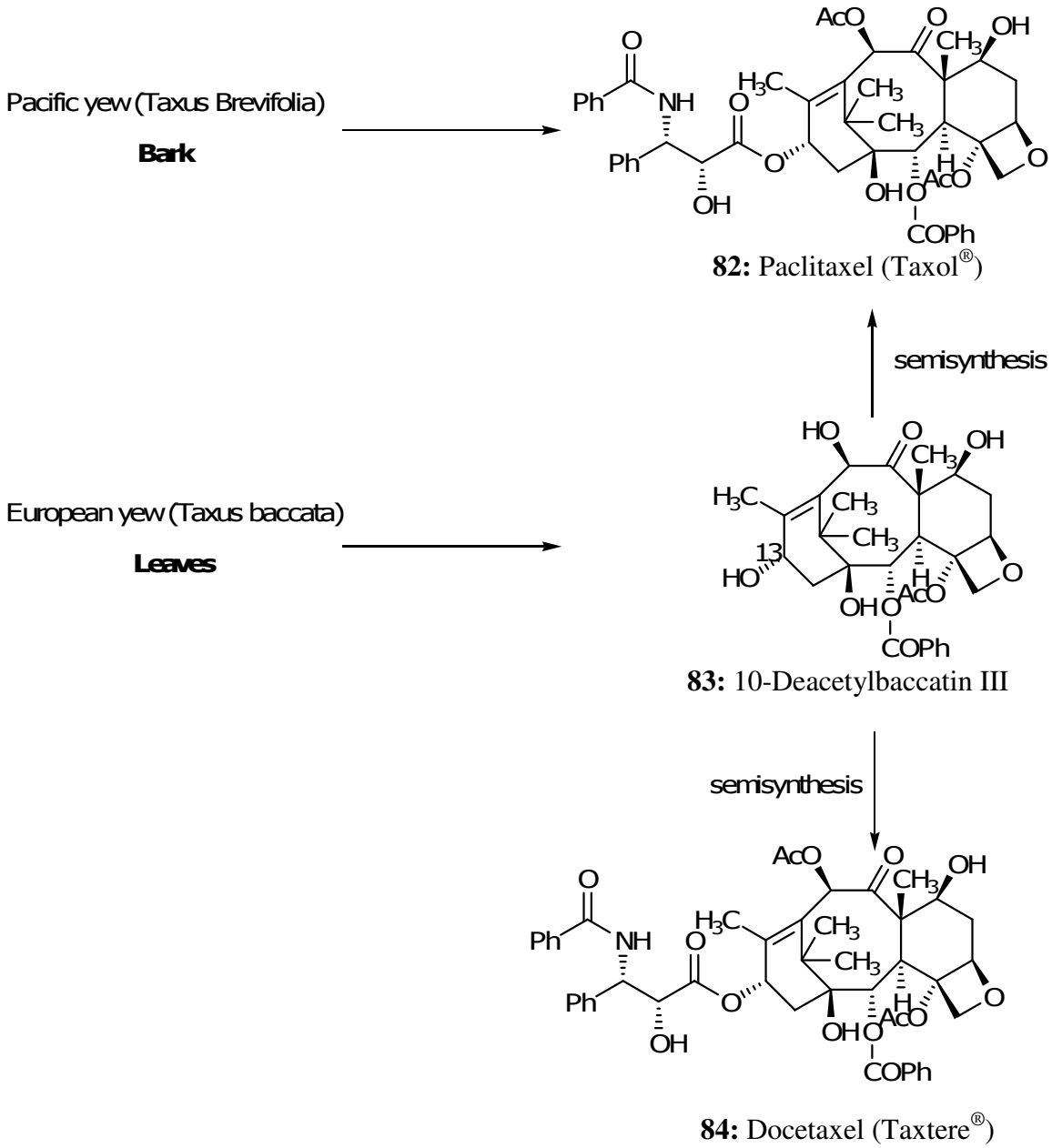
81: Vinorelbine (Navelbine®)

Paclitaxel **(82)** is the most important natural product in cancer chemotherapy and one of the most successful cancer drugs ever produced, being widely used in the treatment of breast, ovarian, and lung carcinomas. It was isolated from the Pacific yew *Taxus brevifolia*, and its anticancer activity was discovered on the 1960s during a large-scale plant-screening program sponsored by the National Cancer Institute (NCI).



82: Paclitaxel (Taxol®)

Enormous supply problems were found initially because the location of taxol in the bark required to sacrifice the tree to extract it, the concentration of the compound in yew bark is low, its extraction is complex and expensive, and the Pacific yew is a limited resource that grows very slowly. About 4,000 trees were required to provide 360 g of taxol for the early clinical trials, and 38,000 trees were necessary to isolate 25 kg of taxol to treat 12,000 cancer patients after approval of the use of taxol for treating advanced ovarian cancer in 1992. Fortunately, it was subsequently discovered that the twigs and needles of the European yew, *Taxus baccata*, were a high yielding (1 g/kg) and renewable source of a related compound, 10-deacetylbaccatin III **(83)**, lacking the C-13 side chain and the C-10 acetyl group, that could be transformed through a relatively simple semisynthetic route into paclitaxel and also into its more soluble and potent analog docetaxel **(84)**, which was approved for advanced breast cancer in 1996 (Scheme 6).



82: Paclitaxel (Taxol®)

83: 10-Deacetylbaccatin III

84: Docetaxel (Taxtere®)

Scheme 6 Semisynthetic route into paclitaxel and docetaxel.

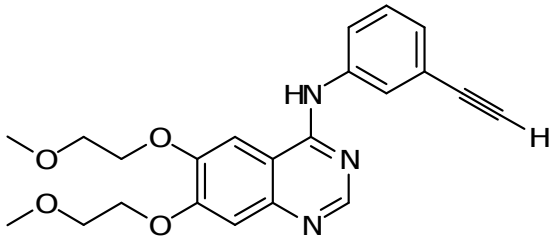
2.8 Drugs that inhibit signaling pathways for tumor cell growth and proliferation

Intra- or inter-cellular communication disorders are a major cause of pathogenic mechanisms. For this reason, modern drug research has become increasingly focused on signal transduction therapy and many of the recently validated targets are transduction-related macromolecules, especially kinases.

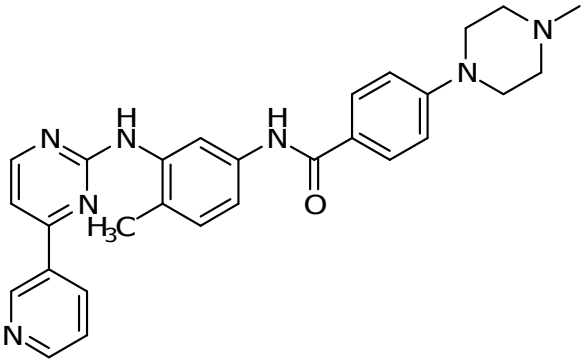
Protein kinases (PTKs) are enzymes that regulate the biological activity of proteins by phosphorylation of specific amino acids with ATP as the source of phosphate, thereby inducing a conformational change from an inactive to an active form of the protein.

Targeting PTKs is a compelling approach to cancer chemotherapy because in many cancers there is an overexpression of PTKs or their associated messengers. In fact that, following the discovery in the early 1980s that the protooncogene Src was in fact a PTK, it has subsequently been proved that most PTKs are related to oncogenes.

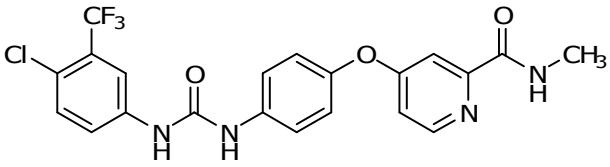
A number of substructures related to kinase inhibitors have been in therapeutic usage These include compounds identified from screening studies and they include erlotinib (Tarceva®) **(85)**, imatinib (Glivec®) **(86)**, sorafenib (Nexavar®) **(87)**, and dasatimib (Sprycel®) **(88)**, natural products and their analogues such as flavopiridol **(89)**, staurosporine **(90)**, and structural analogues of ATP like roscovitine (Seliciclib®) **(91)** [46].



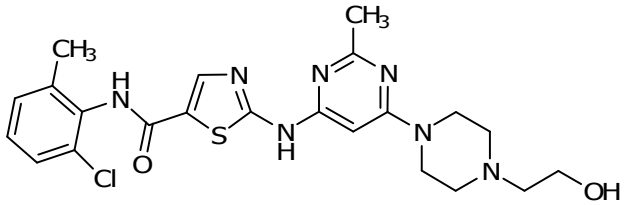
85: Erlotinib (Tarceva®)



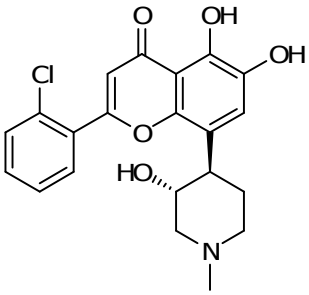
86: Imatinib (Glivec®)



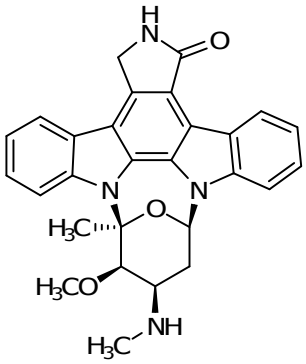
87: Sorafenib (Nexavar®)



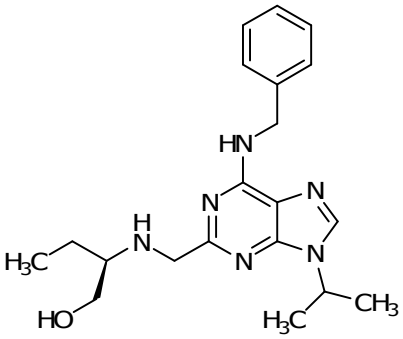
88: Dasatinib (Sprycel®)



89: Flavopiridol

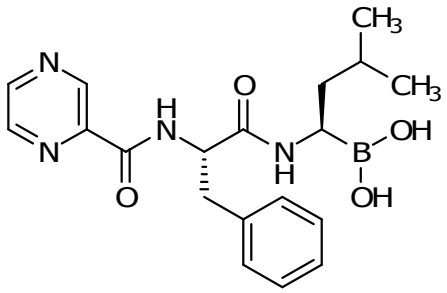


90: Staurosporine



91: Roscovitine (Seliciclib®)

Bortezomib (Velcade®) **(92)** was approved in 2003 for the treatment of multiple myeloma, the second most common hematological cancer, and is currently being clinically evaluated for various other malignancies. Bortezomib (PS-341, LDP-341, MLN-341) affects multiple signaling cascades within the cell because of proteasome inhibition and induces G2/M phase arrest followed by apoptosis in cancer cells [47].

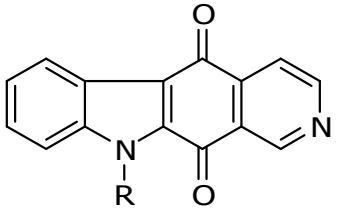


92: Bortezomib (Velcade®)

3. The aim of the studies

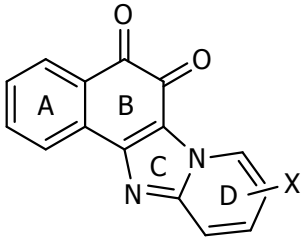
The aim of this research was to synthesize and modify the three core structures which were previously synthesized in the cancer research group to enhance their anti cancer activities. In continuation of these works, these studies focused on the three DNA intercalating core structures and a new synthetic approach to ellipticine should be examined.

3.1 The first building block the study focused on was the tetracyclic carbazole derivatives **93**. In previous works of S. Leber [48], it was shown that compound **94** is highly active against different cancer cell lines. Previous studies unveiled that the attachment of akylating side chains to this tetracyclic intercalating core resulted unexpectedly in lower activities than the fixation of basic side chains. As a consequence of these results and in continuation of these studies a number of basic or hydroxyl substituted side chains should connected to the carbazole nucleus and the consequences in regard to the anticancer activity should be evaluated. Basic substituents can enhance the activity of the intercalating structures by inter-action with the phosphate backbone of DNA, hydroxyl groups could interact via H-bridges, respectively.



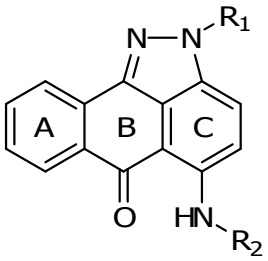
93: R = H; 10H-Pyrido[3,4-b]carbazole-5,11-dione **94:** R = $CH_2CH_2N(CH_3)_2$

3.2 The second structure focused on in this work, was benzo[a]fluorene-5,6-dione **95**. Since similar structures are described as highly active anticancer compounds further variations of ring A and D were of considerable interest [49].



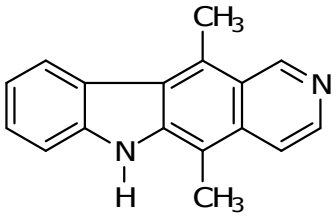
95: Benzo[a]fluorene-5,6-dione

3.3 The third goal was to attach new side chains to the tetracyclic anthrapyrazole nucleus **96**. The rationale for focusing on this anthrapyrazole nucleus was the fact that derivatives of **96** exhibit anticancer activities lacking cardiotoxic side effects [50] (the major drawback of the anticancer drugs doxorubicin, daunorubicin, mitroxantrone etc.) Since previous syntheses of derivatives of **96** resulted in the formation of highly active cystatic compounds new derivatives should be made accessible.



96: Anthrapyrazole

3.4 Finally a new route to the antitumor alkaloid ellipticine **49** should be developed.



49: Ellipticine

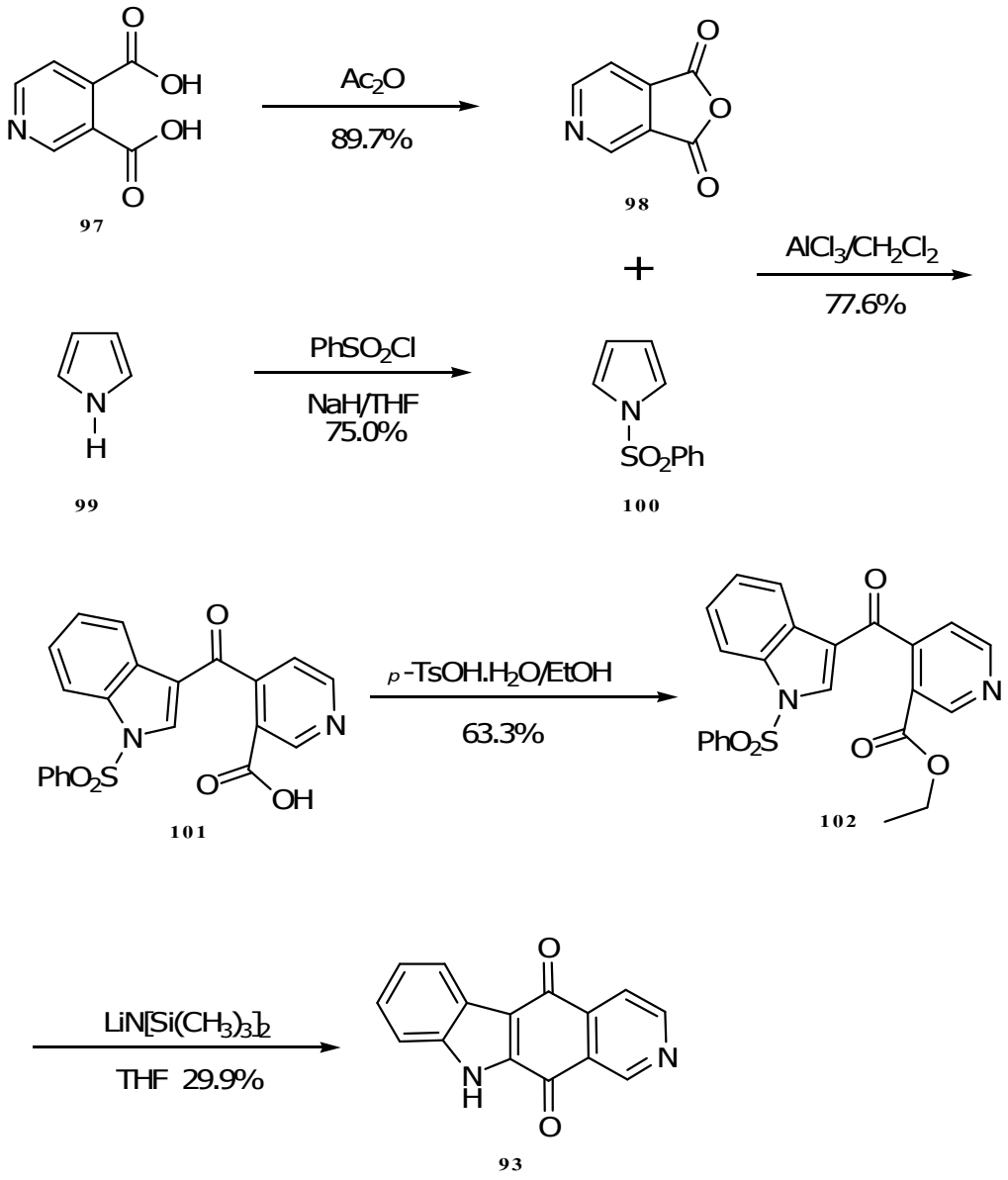
In fact of the fact that this naturally occurring substance exhibits very interesting anticancer properties a new synthetic pathway should open the road to new analogs. Moreover new applications of microwave irradiation to Buchwald-Hartwig coupling and ring closure reaction should be examined in the course of this study.

CHAPTER II

RESULT AND DISCUSSION

1. Synthesis of 10H-pyrido[3,4-b]carbazole-5,11-dione and its derivatives

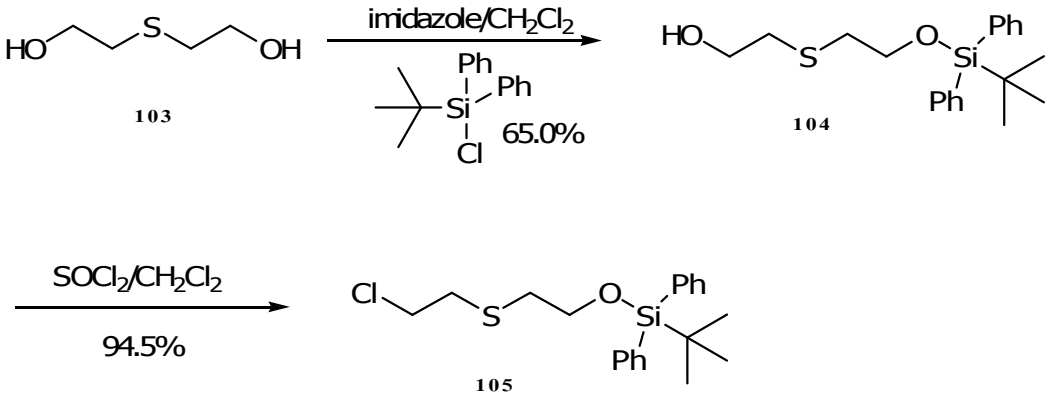
1.1 Synthesis of 10H-pyrido[3,4-b]carbazole-5,11-dione (93)

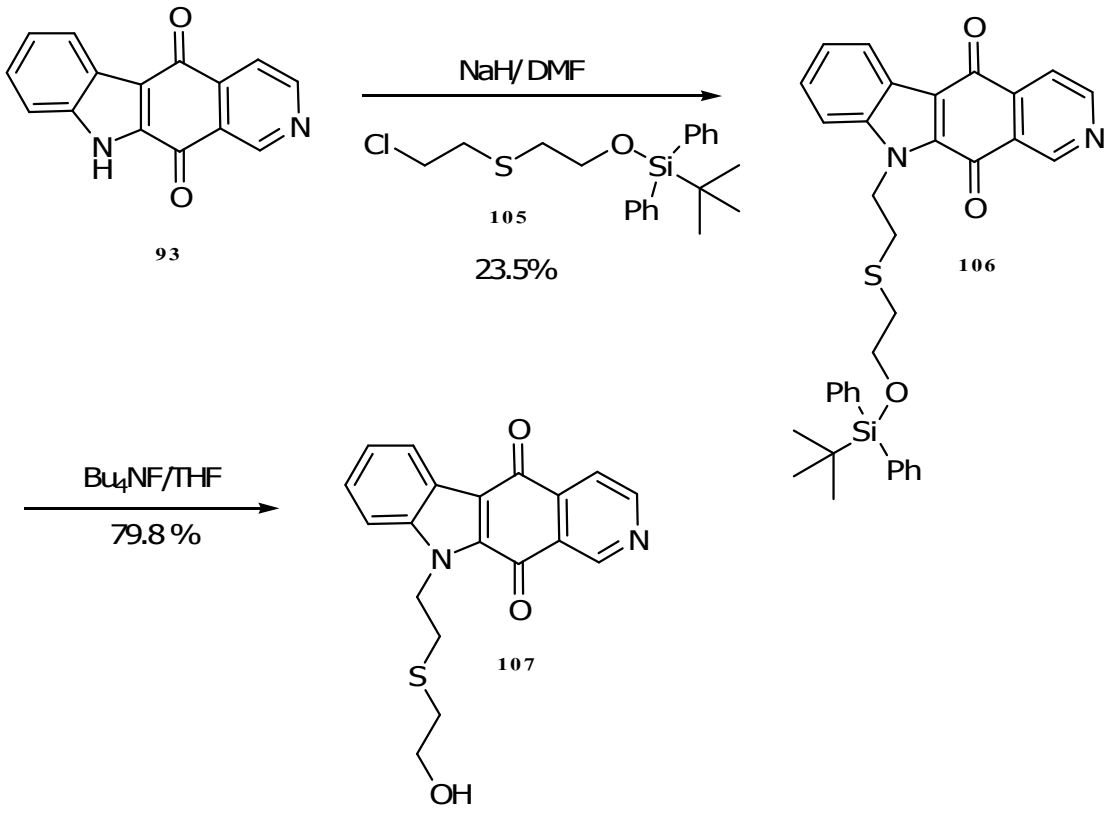


Scheme 7

Compound **93** was the starting material for the synthesis of the targeted derivatives. The synthesis started from the commercially available 3,4-dicarboxylpyridine **97** which was refluxed in freshly distilled acetic anhydride to yield the anhydride **98** in very good yield. The following intramolecular acylation reaction of **98** with the N-protected indole [51] under the catalysis of aluminium trichloride led to keto acid **101** which was subsequently esterified to ethyl ester **102** [52]. Reaction with lithium-bis(trimethylsilyl)amide [53] at -40 ^{o}C for 2 hours efforted the desired structure **93** in four steps in 13.1% over all yield as depicted in scheme 7.

1.2 Synthesis of 10-((2-[tert-Butyl-diphenyl-silanyloxy]-ethylsulfanyl)-ethanol)-10H-pyrido[3,4-b]carbazole-5,11-dione (107)



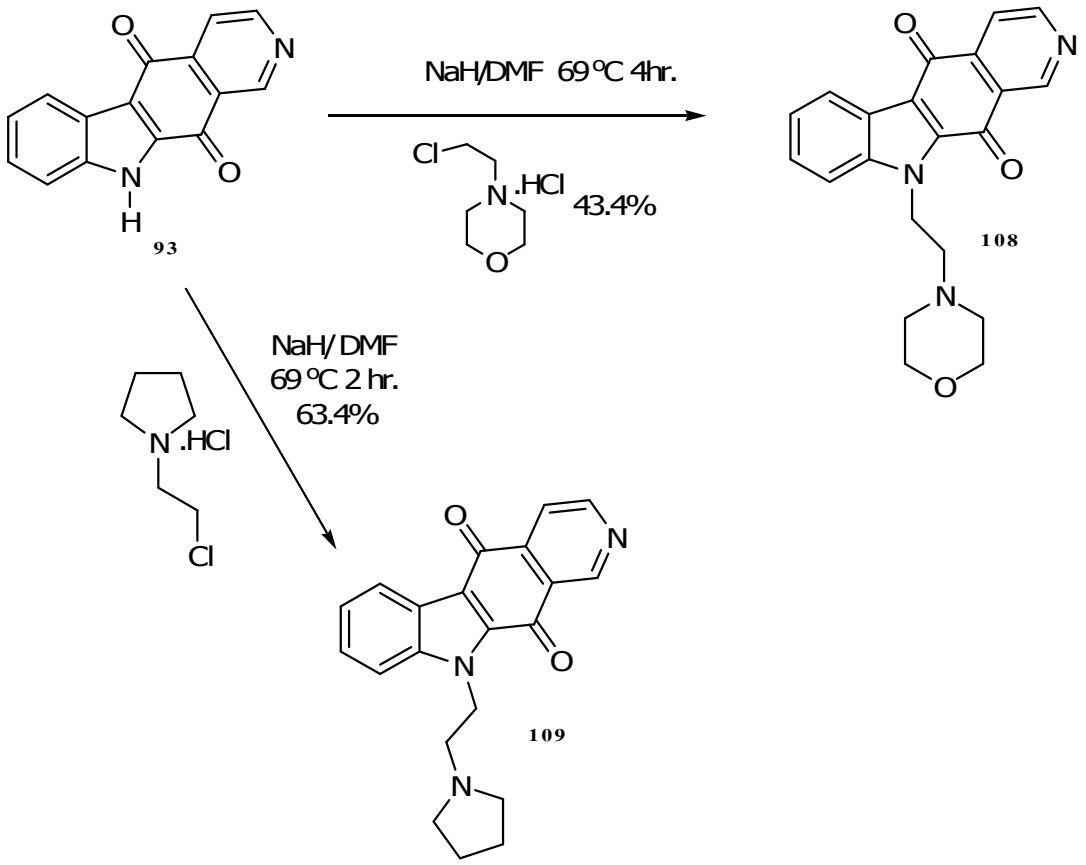


Scheme 8

The attachment of the hydroxyl alkylsulfide side chain to compound **93** should be achieved by N-alkylation. First of all, the alkylchloride **105** had to be synthesized from compound **103**. Monoprotection was realized by reaction with equimolar amounts of tert-butyldiphenylchlorosilane to produce the protected alcohol **104** which was subsequently converted by treatment with thionylchloride in dichloromethane to alkyl chloride **105.** In the following, N-alkylation of **93** with **105** could be realized by using sodium hydride in absolute DMF to yield **106**. Following deprotection of **106** led to **107** in good yield (79.8%) as shown in scheme 8. IR spectrum of **107** shows the signal of hydroxyl absorption broad band at 3452 cm^{-1}. ^{1}H NMR spectrum shows the signal (ppm) at 2.95 (s, 2H), 2.67 (t, 2H, J = 6.4 Hz), 3.85 (d, 2H, J = 6.5 Hz), and 4.82 (t, 2H, J = 4.5 Hz) which are attributed to alcohol sulfide side chain.

1.3 Synthesis of 10-(2-morpholinoethyl)-10H-pyrido[3,4-b]carbazole-5,11-dione (108) and 10-(2-pyrolidineethyl)-10H-pyrido[3,4-b]carbazole-5,11-dione (109)

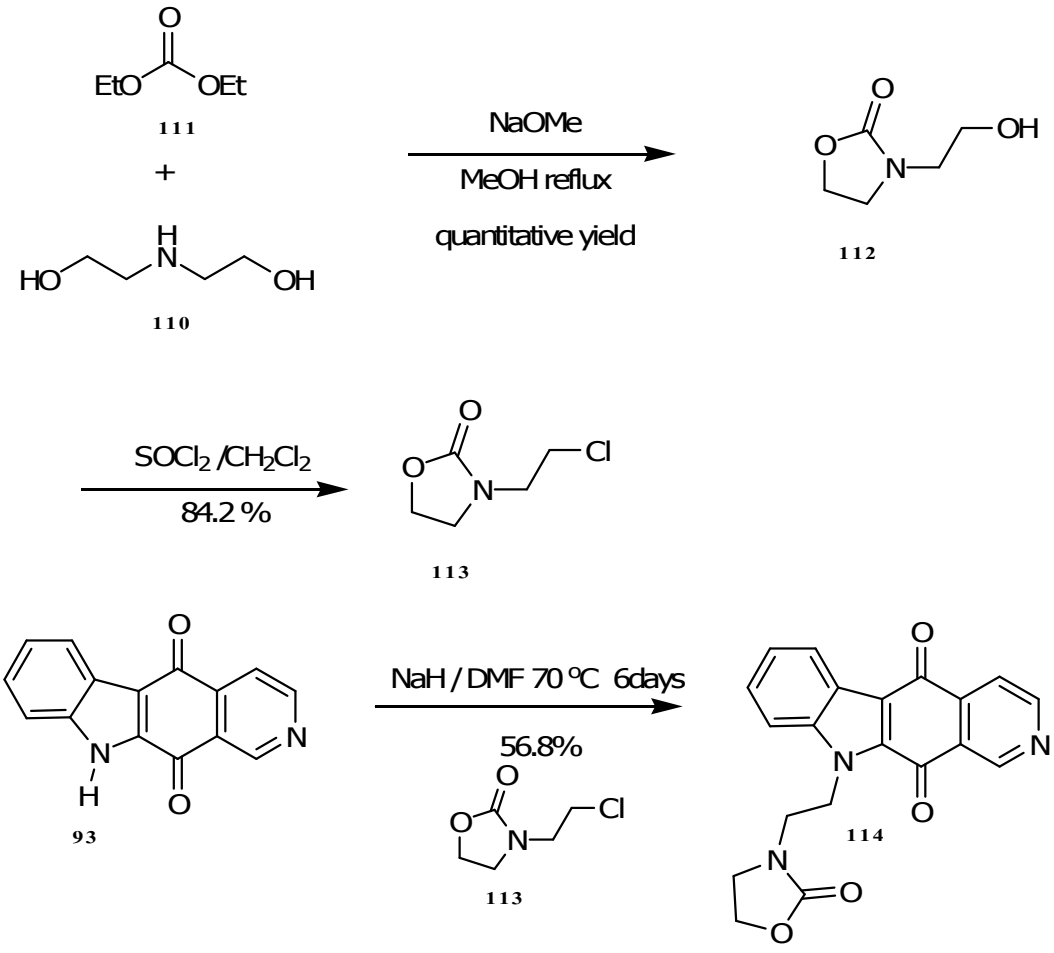
Morpholine and pyrolidine ethyl groups were chosen as next chains connected to **93**. The commercially available starting material, 4-(2-chloroethyl)morpholine hydrochloride and 4-(2-chloroethyl)pyrrolidine, respectively, gave the desired N-alkylation product **108** and **109** in 43.4% and 63.4% yield, respectively, as illustrated in scheme 9.



Scheme 9

IR spectrum of **108** shows a signal of strong absorption band of ether of morpholine ring at 1112 cm^{-1}. ^1H NMR spectrum exhibits the signal at 2.72 (d, 2H, J = 6.4 Hz) and 4.85 (d, 2H, J = 6.8 Hz) that are attributed to two methylene protons between chromophore and morpholine. The signals at 2.48 (s, 7H) and 3.84 (t, 4H, J = 4.9 Hz) are assigned to the methylene protons of morpholine. ^1H NMR spectrum of **109** shows the signal (ppm) of two methylene protons of the ethylene group at 2.92 (t, 2H) and 4.87 (t, 2H, J = 7.4 Hz) and the signal of pyrrolidine protons are at 1.77-1.84 (m, 4H) and 2.66 (d, 4H, J = 5.1 Hz).

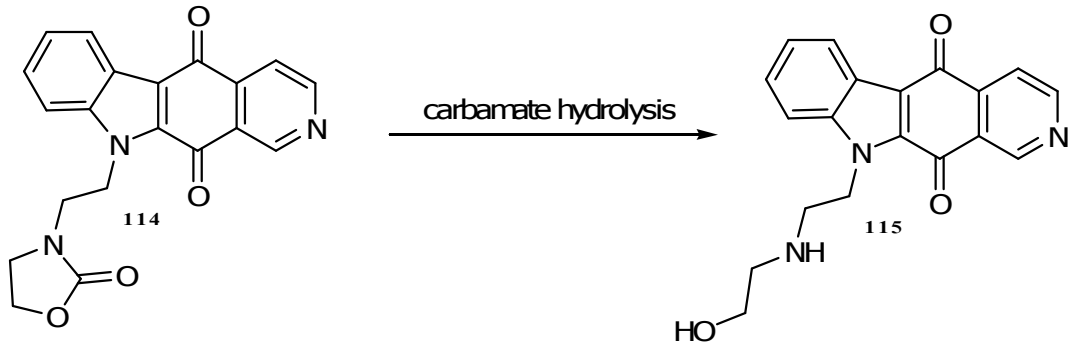
1.4 Synthesis of 10-[(2-ethyl)-2-oxazolidone]-10H-pyrido[3,4-b]carbazole-5,11-dione (114)



Scheme 10

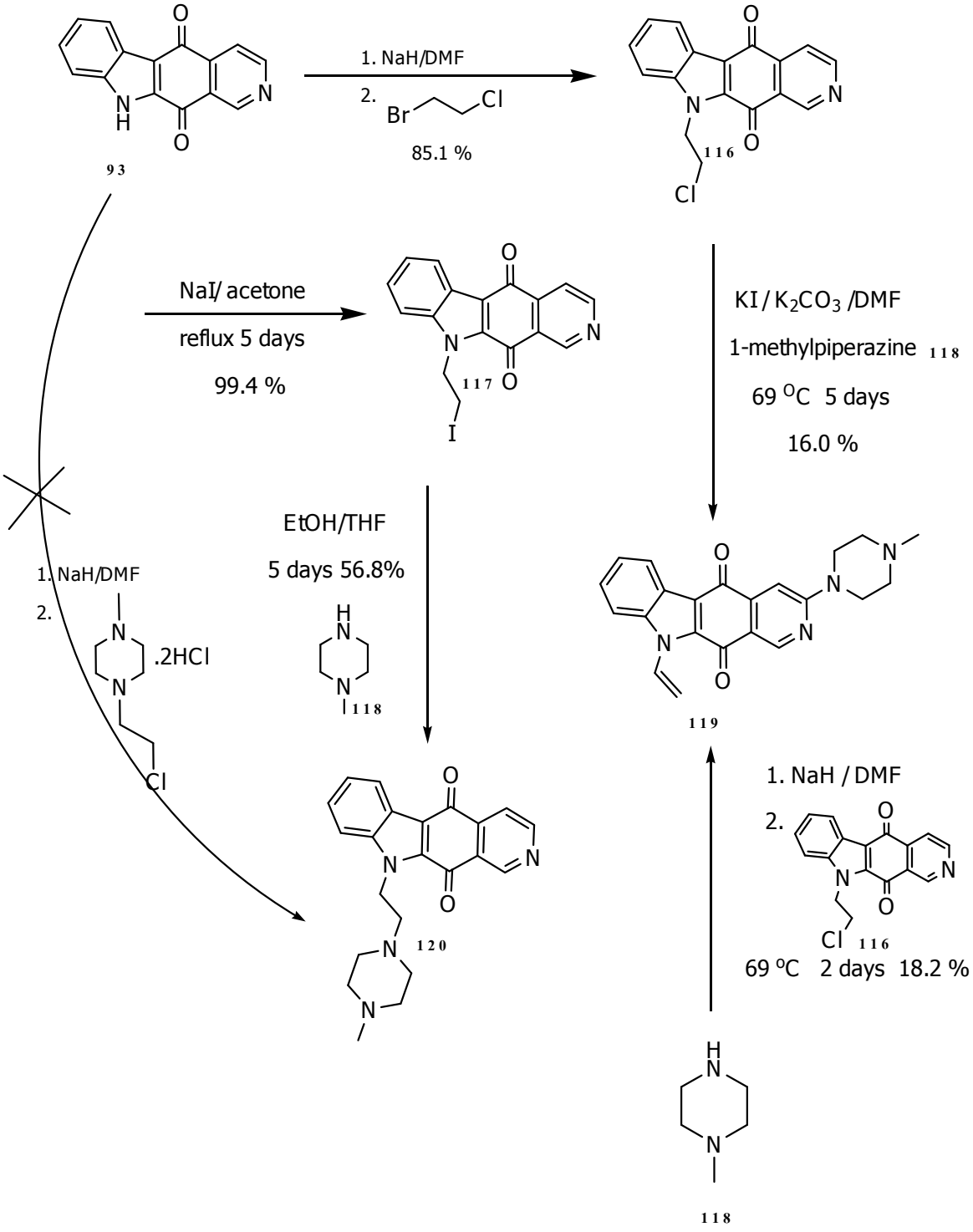
Moreover, after preparing the morpholine and pyrrolidine derivatives **108** and **109**, respectively, the consequences of an oxazolidine moiety to the biological activities were of interest. For that intention N-(2'-hydroxyethyl)-2-oxazolidone **112** had to be synthesized as starting material: diethanolamine **110** reacted smoothly with diethyl carbonate **111** and sodium methoxide to the hydroxyl ethanol derivative **112** which was treated with thionylchloride in dichloromethane and a small amount of absolute dimethylformamide to obtain N-(2'-chloroethyl)-2-oxazolidone **113** [54]. In the following compound **93** was treated with sodium hydride in absolute dimethylformamide in the presence of **113.** Surprisingly, it was necessary to heat at 70 ^{o}C for 6 days to obtain desired product **114** as shown in scheme 10.

^{1}H NMR spectrum of **114** shows signals (ppm) at 3.76 (t, 2H, J = 6.3 Hz) and 4.93 (t, 2H, J = 6.3 Hz) which are assigned to the side chain whereas the signal at 3.37 (t, 2H, J = 7.5 Hz) and 4.11 (t, 2H, J = 7.5 Hz) are attributed to two methylene protons of oxazolidine ring. The IR spectrum of **114** shows definitely a strong absorption band of carbonyl of oxazolidine ring at 1744 cm^{-1}. Since the carbamate moiety is susceptible to enzymatic hydrolysis compound **114** should act as precursor thus releasing the hydroxyl ethylamine derivative as active compound **115** as illustrated in scheme 11.



Scheme 11

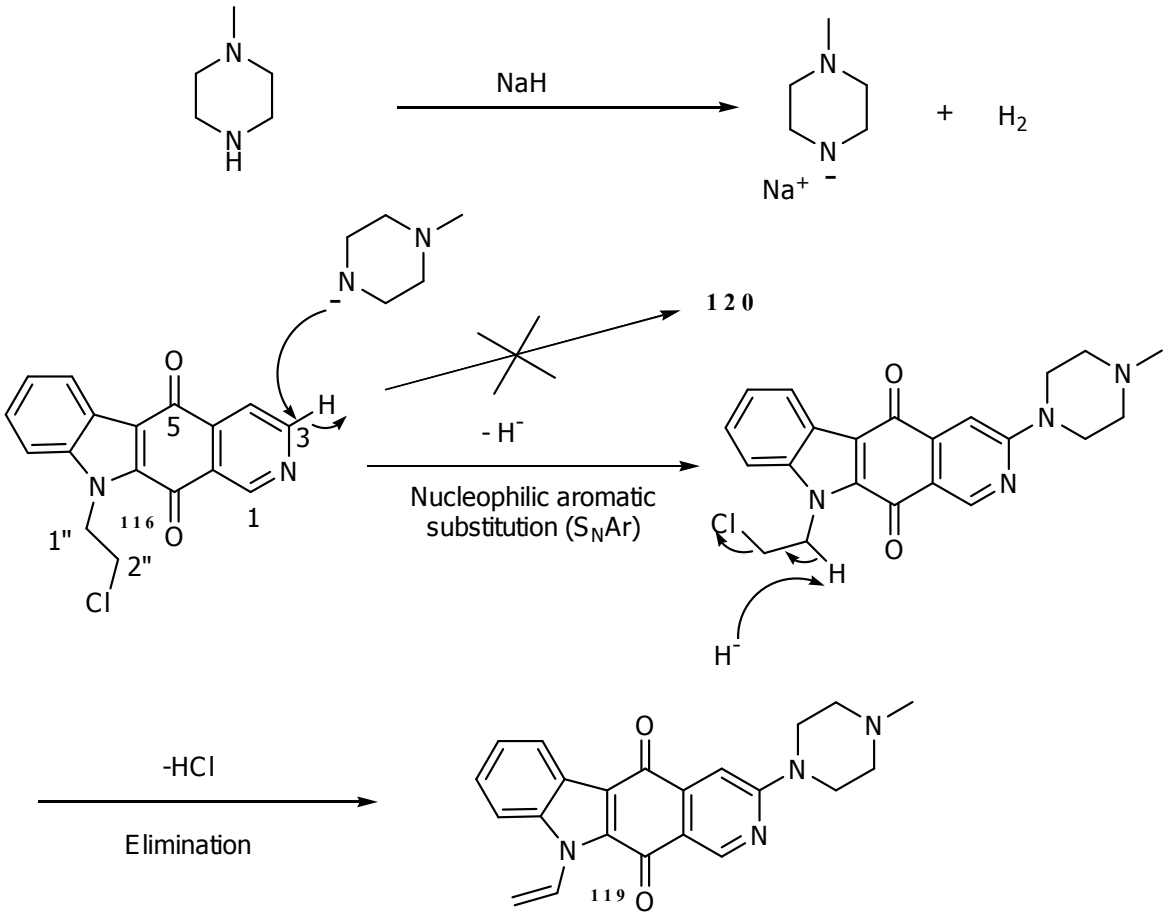
1.5 Synthesis of 3-(4-methylpiperazin-1-yl)-10-vinyl-10H-pyrido[3,4-b]carbazole-5,11-dione (119) and Synthesis of 10-[4-(1-methylpiperazine)]-10H-pyrido[3,4-b]carbazole-5,11-dione (120)



Scheme 12

Attempts to attach the 4-chloroethyl-1-methylpiperazine to compound **93** by simple N-alkylation to give **120** failed (Scheme 12), a route via chlorotheyl derivative **116** and subsequent alkylation with N-methyl piperazine seemed promising. Indeed, compound **116** was easily accessible by alkylation **93** with 1-bromo-2-chloroethane in 85.1% yield.

Surprisingly, reaction of 1-methylpiperazine/NaH with **116** in DMF did not furnish the desired product **120**. NMR elucidation (Figure 5) led to the confirmation of structure **119** as main product of this reaction. It is evident that the sodium amide generated of N-methyl piperazine attacked the pyridine ring which suffers from a distinct electron deficit. In the following the basic conditions led to HCl elimination finally leading to unexpected product **119**, as illustrated in scheme 13.



Scheme 13 The possible mechanism of the formation of **119**

The elucidation of **119** was determined by 2D-NMR and Nuclear Overhauser Enhancement (NOE) as depicted in figure 5. There was an effect to detect of H-6' and H-4 while there was no effect between H-2'' and H-2' and H-6'. Moreover, H-2''-trans and H-2''-cis had an effect on H-9 and H-1'', respectively. The spectroscopy analysis obviously confirmed structure **119**.

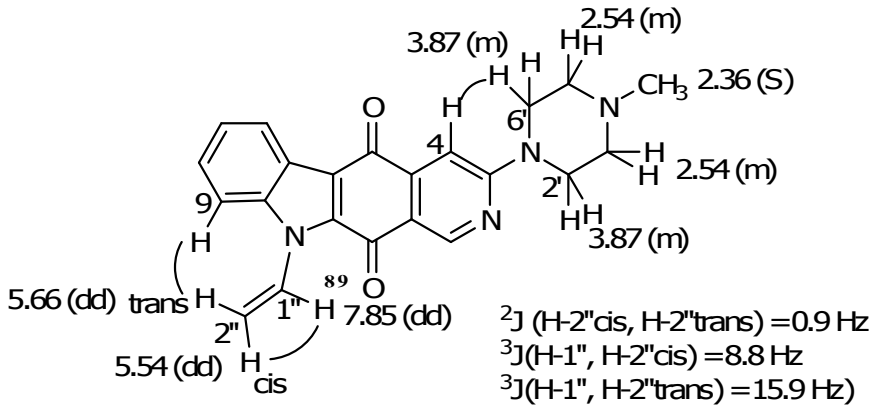


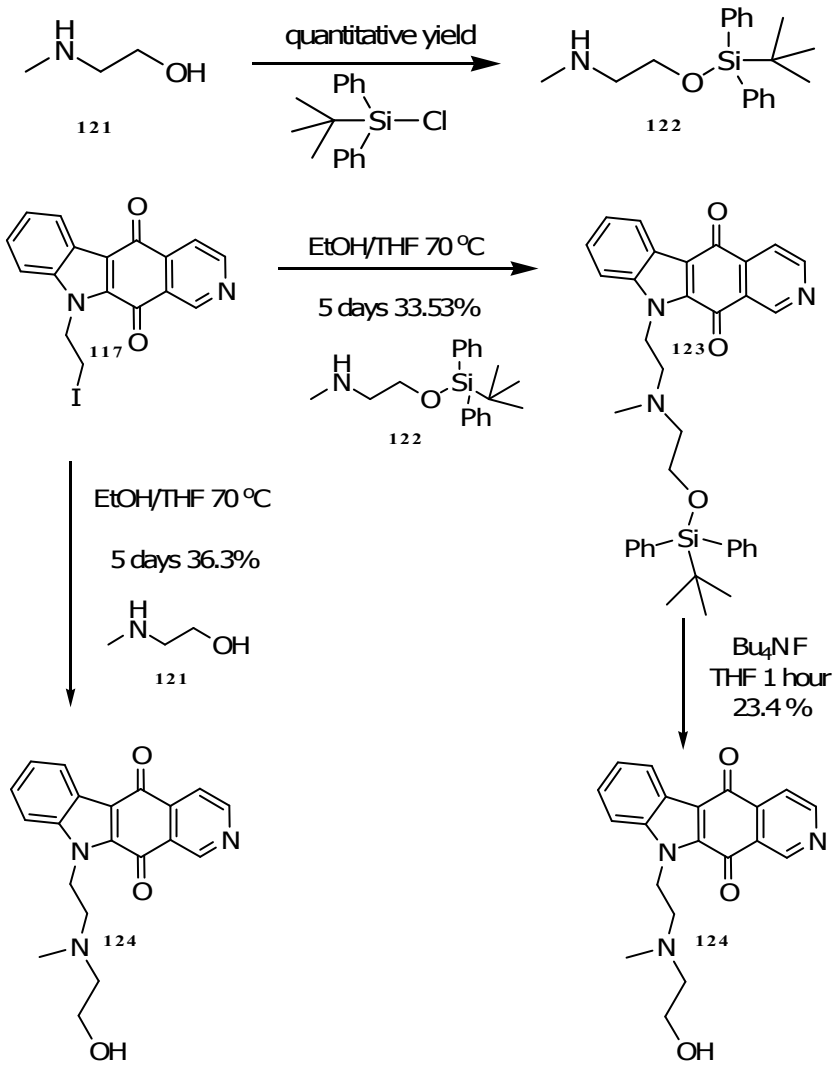
Figure 5 Observed NOE of **119**

In the same way the use of KI/K_2CO_3 in DMF [55] produced olefin **119** in 16.0%. Finally the synthesis of the target compound **119** was enforced by preparing the iodo derivative **117** (Scheme 12), from **116** with NaI in acetone. The mass spectrum shows m/z 402 (M^+) and the shift of the adjacent methylene carbon indicated the successful halide exchange.

In the following the iodo compound **117** smoothly reacted with N-methyl piperazine to the desired product **120** by exclusive nucleophilic substitution as shown in scheme 12. ^1H NMR spectrum of **120** shows the signal at 2.24 (s, 3H), 2.39 (s, 4H), 2.61 (s, 4H), 2.77 (t, 2H, J = 7.0 Hz), 4.83 (t, 2H, J = 6.9 Hz) which are attributed to the piperazine moiety.

1.6 Synthesis of 10-(2-((2-hydroxylethyl)(methyl)amino)ethyl)-10H-pyrido[3,4-b] carbazol-5,11-dione (124)

The production of **124** was realized by two synthetic routes: First 2-(methylamino)ethanol **121** was protected by tert-butyldiphenylchlorosilane to provide protected amine **122** in quantitative yield. The reaction of **117** and O-protected amino alcohol **122** afforded after refluxing for 5 days compound **123** in 33.5% which was deprotected the use of Bu_4NF to obtain alcohol **124** in 23.4%. On the one hand, target compound **124** could be directly synthesized from **117** and the use of the unprotected amine **121** by simply nucleophilic substitution in EtOH and THF, as shown in scheme 13.

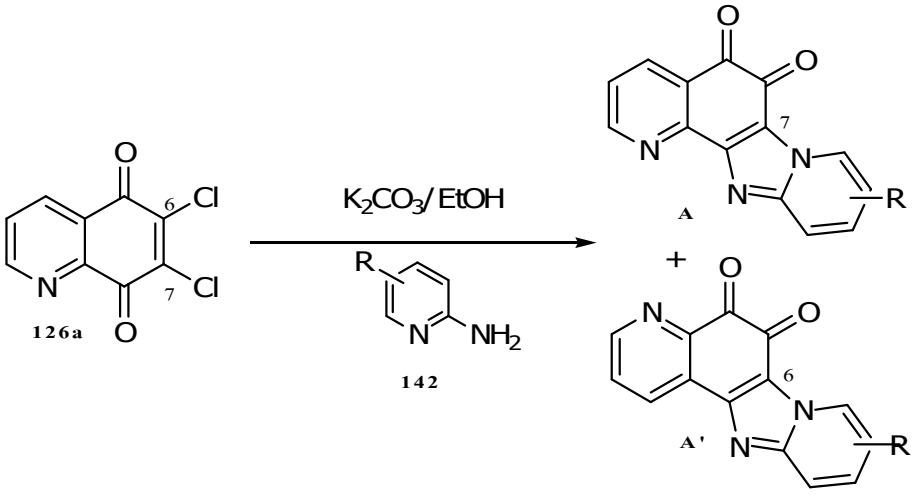


Scheme 13

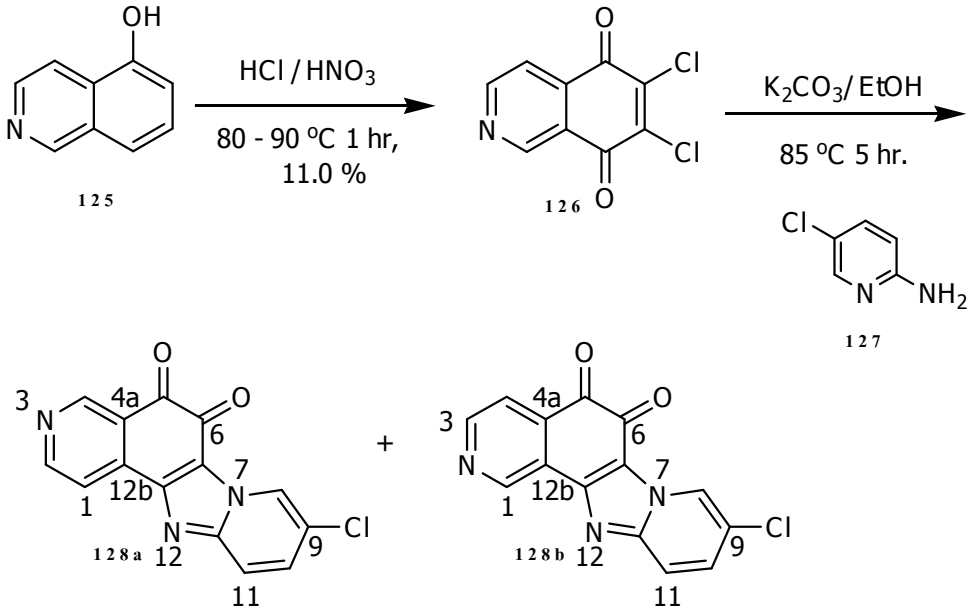
Both synthetic pathways showed the same results of spectroscopic data. The IR spectrum of **124** exhibits the signal of hydroxyl absorption broad band at 3422 cm^{-1}. The ^{1}H NMR spectrum of **124** shows signals at 2.44 (s, 3H), 2.64 (t, 2H, J = 5.3 Hz), 2.91 (t, 2H, J = 7.0 Hz), 3.50 (t, 2H, J = 3.5 Hz), and 4.81 (t, 2H, J = 6.8 Hz) which are attributed to amino alcohol side chain, attached to the chromophore.

2. Synthesis of benzo[a]fluorene-5,6-dione derivatives

Since it was shown in previous papers that 6,7-dichloroquinoline-5,8-dione **126a** reacted with 2-aminopyridine **142** derivatives to tetracyclic ortho-quinone systems like **A** and **A'** [56] the behavior of the aza-isomer **126** in similar reactions should be studied. Moreover this tetracyclic nucleus seems to exhibit anticancer activity.



2.1 Synthesis of 5-chloropyrido[1',2'-1,2]imidazo[4,5-f]isoquinoline-5,6-dione (128a) and 5-chloropyrido[1',2'-2,3]imidazo[4,5-f]isoquinoline-5,6-dione (128b)



Scheme 14

Chloroxidation of **125** by using $NaClO_3$ in concentrated hydrochloric acid had been published. They obtained **126** in 3% from **125**. However, this yield could be raised to 11% by substituting concentrated nitric acid in stead of $NaClO_3$ [57].

The reaction between **126** and **127** under refluxing in ethanol in the presence of potassium bicarbonate produced two isomers of 4-membered ring **128a** and **128b** [49] which were confirmed by 2D NMR technique. For **128a**, the irradiation at δ 8.92 ppm (H-2) and δ 7.88 ppm (H-10) had an effect on δ 8.02 ppm (H-1) and δ 8.05 ppm (H-11), respectively. This result indicated that the proton at δ 8.92 ppm (H-2) is adjacent to the proton at δ 8.02 ppm and the proton at δ 7.88 ppm is close to the proton at δ 8.05 ppm. The comparison of the proton and carbon chemical shift of both is shown in figure 6**.** Mass spectra of both isomers show m/z 283 (M^+) and a prominent peak at m/z 255 (M^+-C=O).

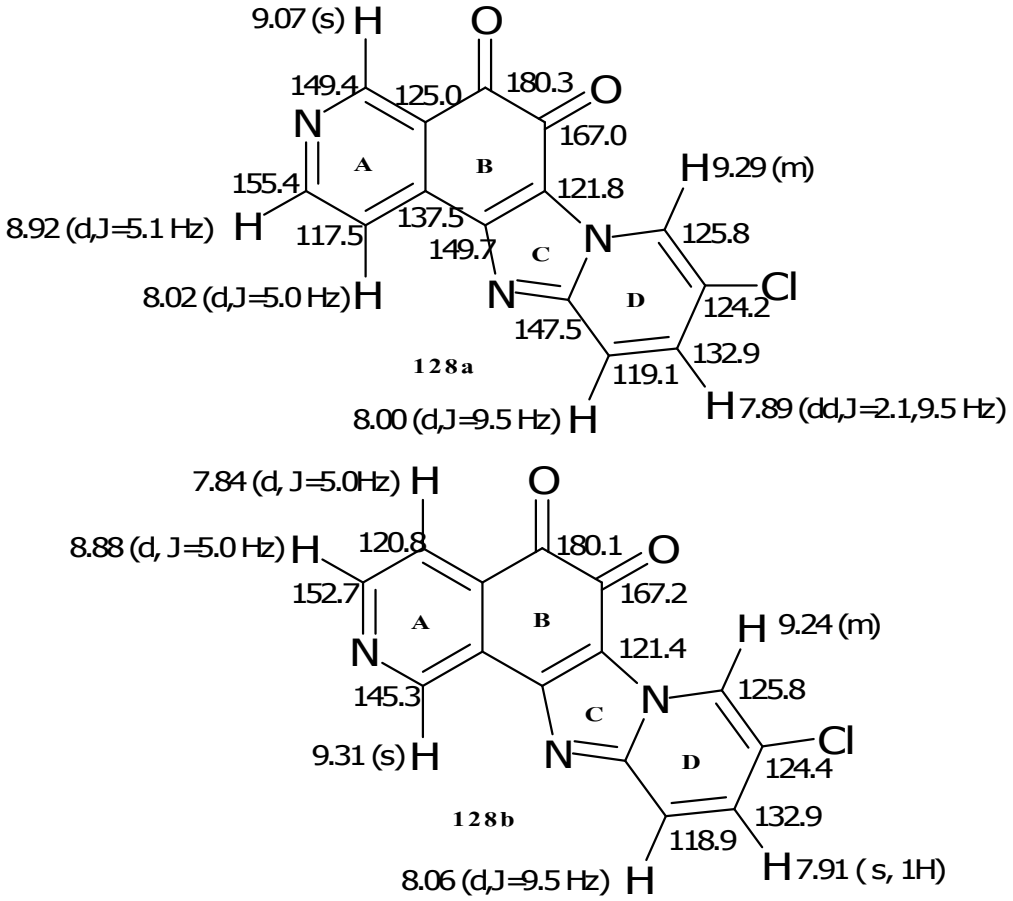
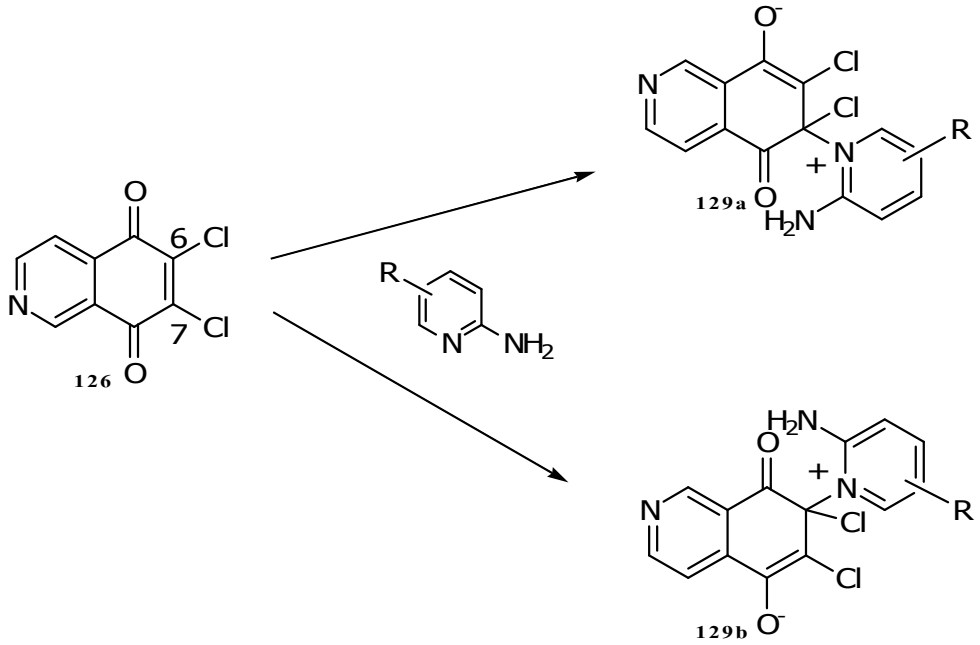
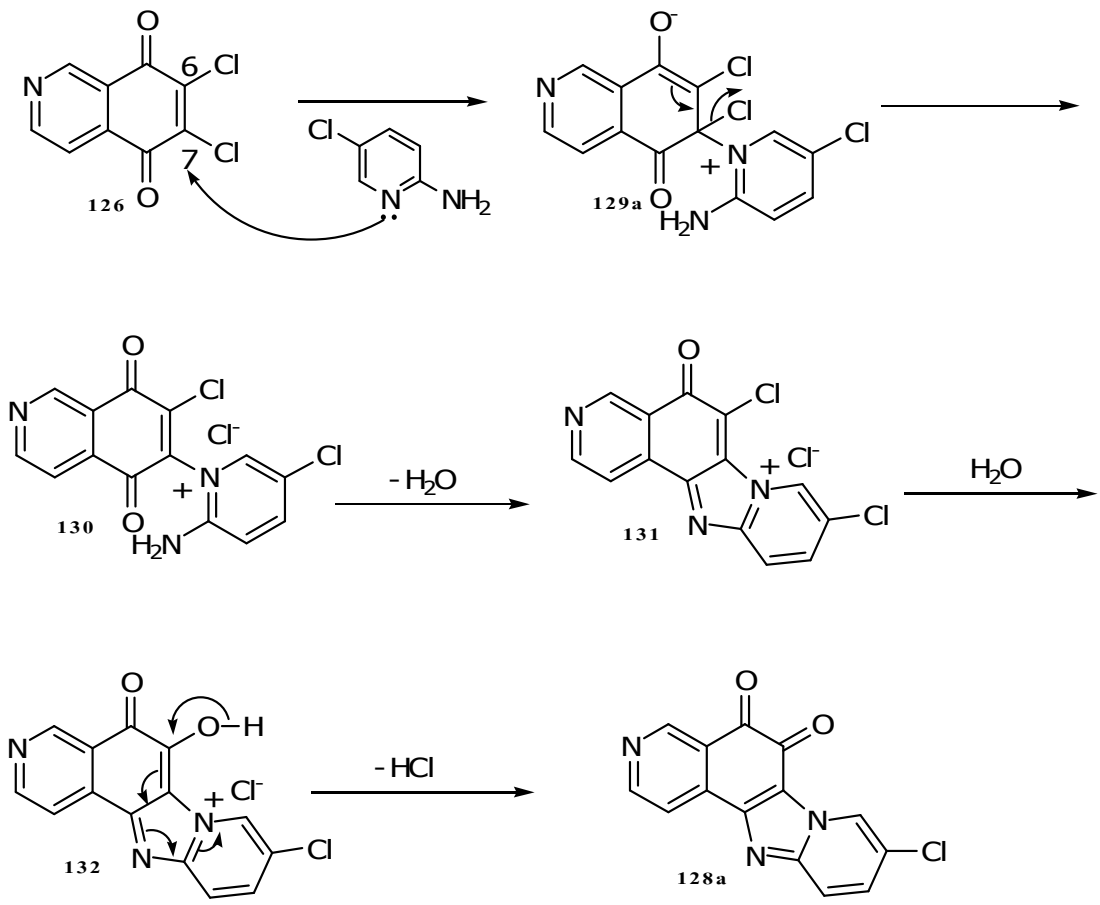


Figure 6 The comparison of ^1H and ^{13}C NMR signal (ppm) of **128a** and **128b**.

There are two possible ways to form two intermediates **129a** and **129b** [56, 58-59]. Not only nucleophilic attacks on C-6 of **126**, but also attacks on C-7 provide the resulting intermediates as shown in scheme 15**.** The predicted mechanism of the formation of **128a** is illustrated in scheme 16.

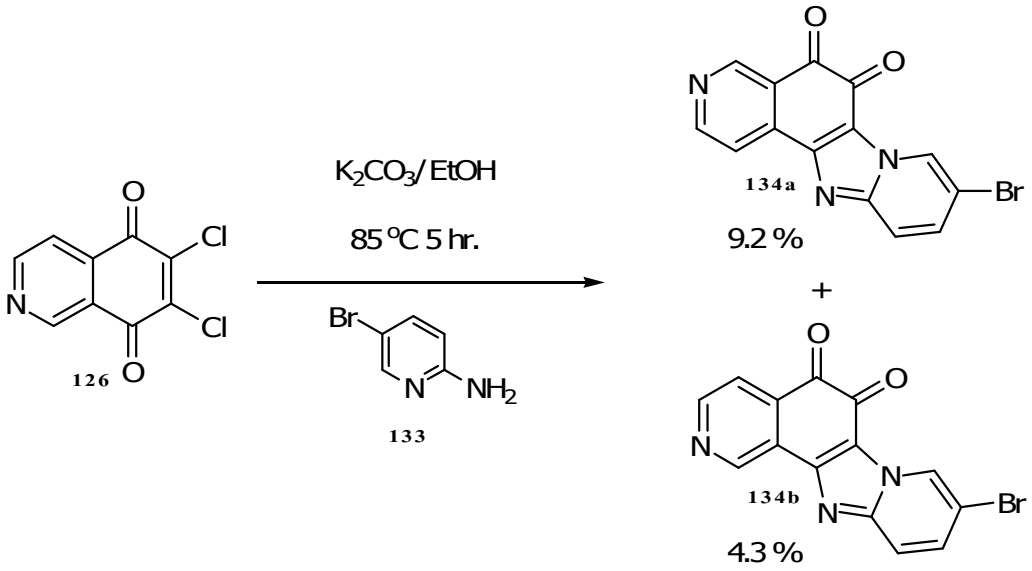


Scheme 15 The formation of the initial substitution products.



Scheme 16 The purposed reaction mechanism of the formation of **128a**.

2.2 Synthesis of 5-bromopyrido[1',2'-1,2]imidazo[4,5-f]isoquinoline-5,6-dione (134a) and 5-bromopyrido[1',2'-2,3]imidazo[4,5-f]isoquinoline-5,6-dione (134b)



Refluxing in ethanol, compound **126** reacted with 2-amino-5-bromopyridine **133** in the presence of potassium bicarbonate to provide again two isomers of tetracyclic fused ring **134a** and **134b** which show the close R_f values (Rate of flow) in 4:4:1 ethylacetate: light petroleum:methanol. The R_f value of **134a** is 0.36 and **134b** is 0.45. Thus, **134b** could not be definitely separated from **134a** due to the close R_f values of both compounds. It is less soluble than **134a** in DMSO-d_6. ^1H and ^{13}C NMR in DMSO-d_6 of it mainly consist of **134a** but it shows the different proton chemical shift on ring A. Moreover, two carbonyl groups of **134b** show a little different carbon chemical shift from **134b**. Therefore, there could not be elucidated whole protons and carbons of **134b** because of contamination with **134a**. The comparison of ^1H and ^{13}C NMR of both is shown in figure 7. However, both mass spectra show a prominent peak at m/z 312 (M^+).

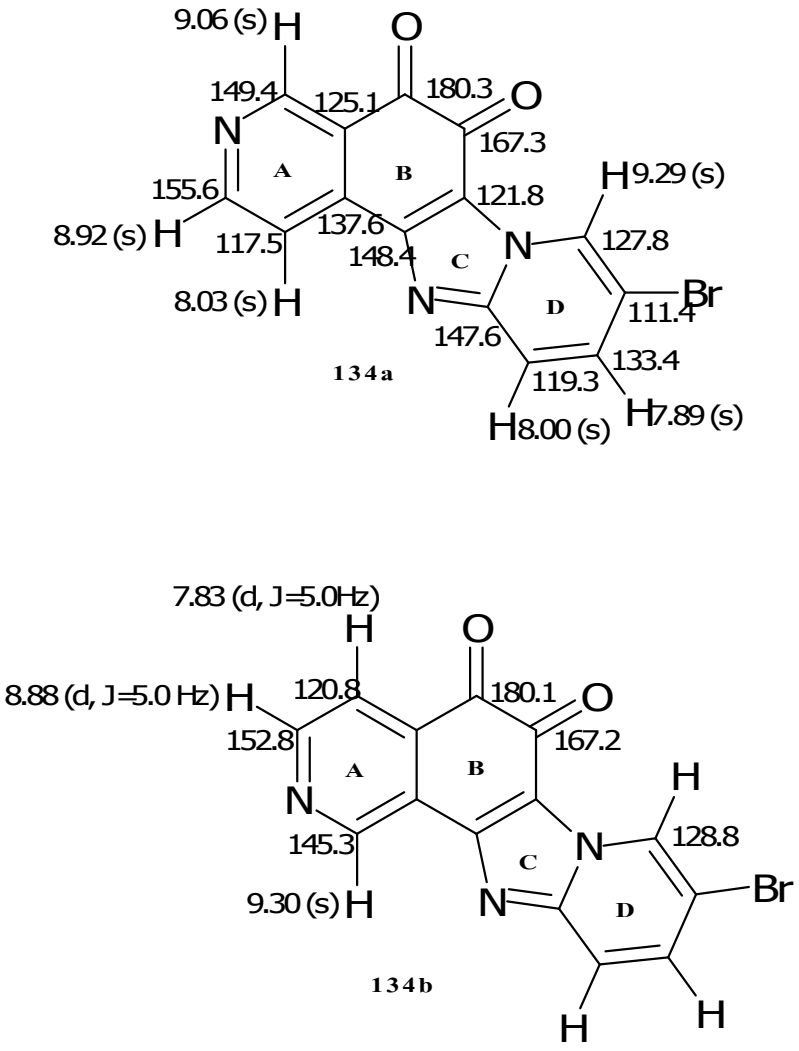
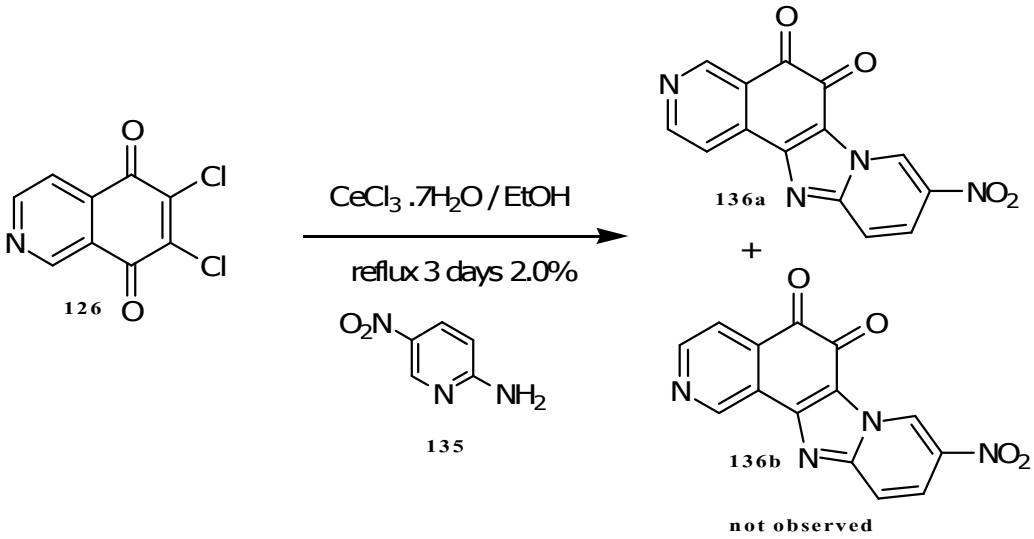


Figure 7 The comparison of ^{1}H and ^{13}C NMR signal (ppm) of **134a** and **134b**.

2.3 Synthesis of 5-nitropyrido[1',2'-1,2]imidazo[4,5-f]isoquinoline-5,6-dione (136)



In case of strong electron withdrawing groups such as nitro group on pyridine ring, the tetracyclic fused ring **136a** or its isomer **136b** could not be observed when **126** was treated with **135** under basic conditions. Otherwise, acid conditions were considered to prepare **136a**. Ceriumtrichloride heptahydrate was used instead of potassium bicarbonate in this reaction and furnished **136a**. Its structure was clearly elucidated by 2D NMR technique. The assignment of protons and carbons are illustrated in figure 8. The mass spectrum of **136a** shows m/z 249 (M^+) and a prominent peak at m/z 221 (M^+-C=O).

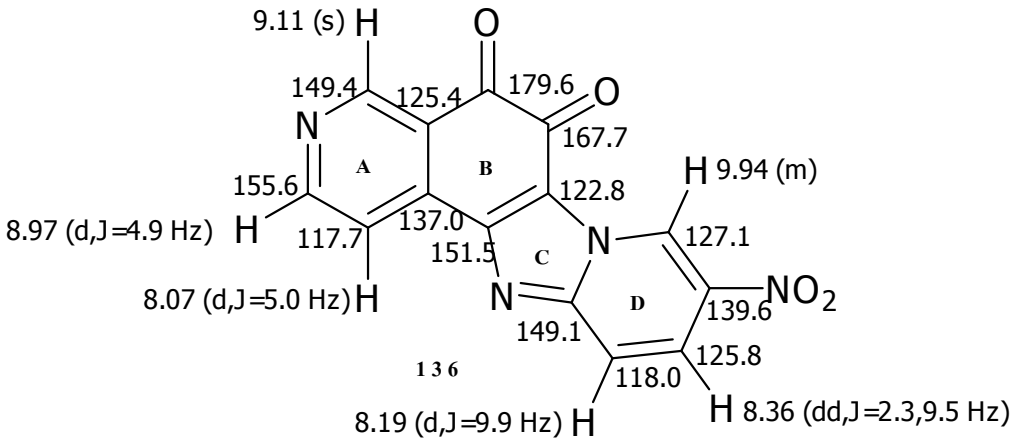
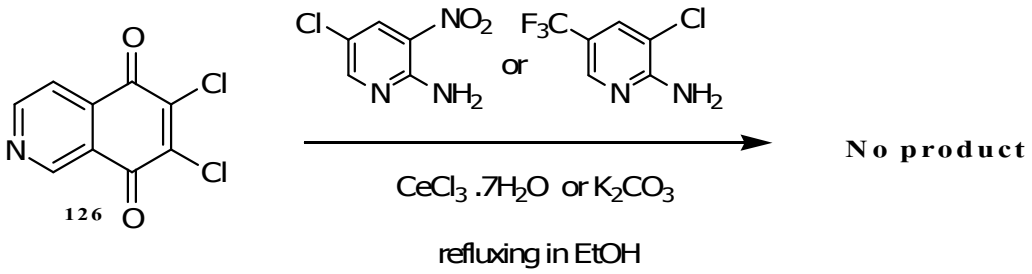


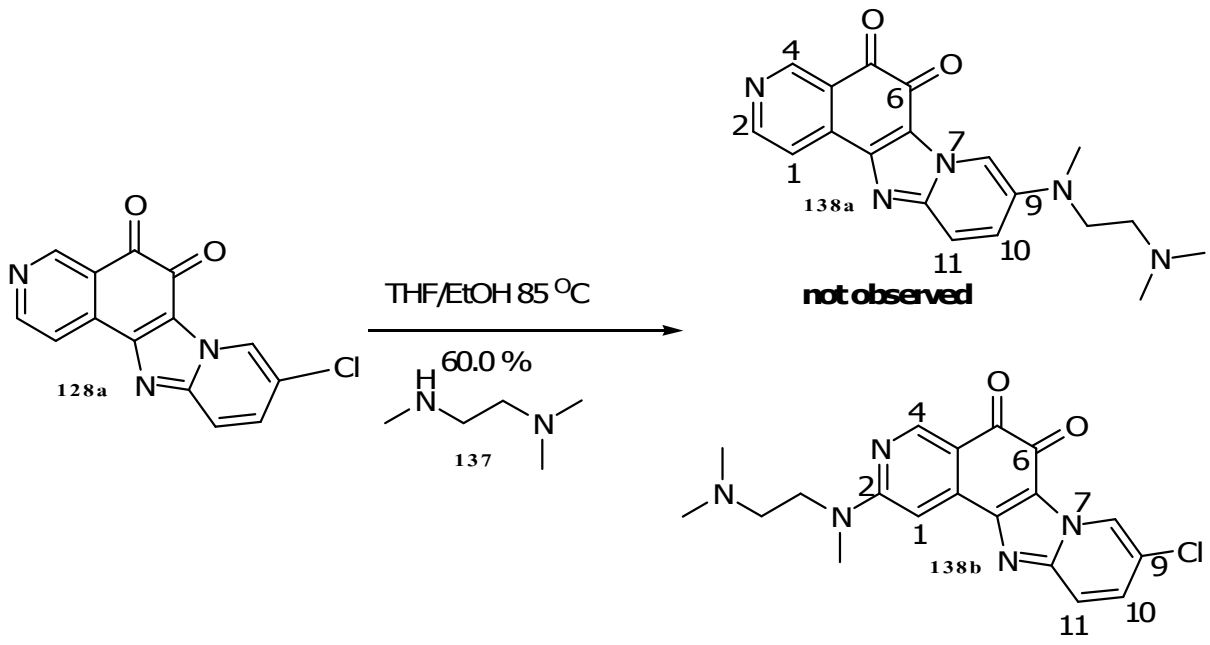
Figure 8 Assignment of ^{1}H and ^{13}C NMR of **136.**

Moreover, it was not possible to obtain the product from the reaction between quinone **126** and substituted aminopyridines which have more than two electron withdrawing groups. The reaction could not realized, neither in the presence of potassium bicarbonate nor cerium trichloride heptahydrate, as illustrated in scheme 17.



Scheme 17

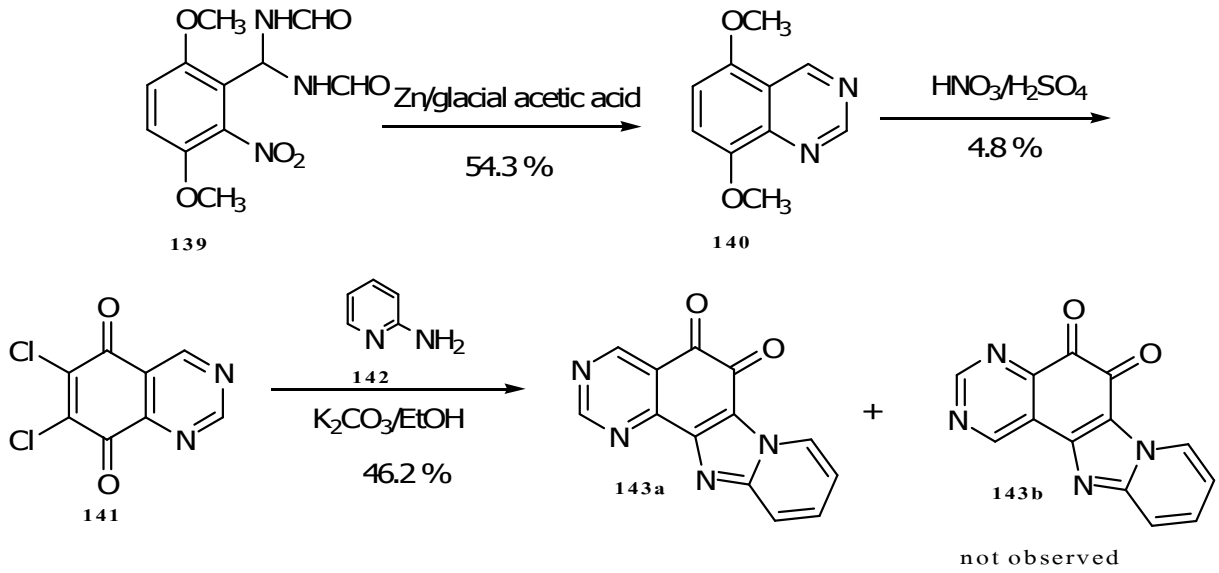
2.4 Synthesis of 5-chloropyrido[1',2'-1,2]imidazo[4,5-f]-2-((2-(dimethylamino)ethyl) methylamino) isoquinoline-5,6-dione (138b)



Since the tetracyclic nucleus of **128a** is flat and therefore can act as DNA-intercalator a basic side chain should be attached to improve eventually the anticancer activity. Therefore, nucleophilic substitution of **128a** with secondary amine **137** should give **138a**.

But nucleophilic aromatic substitution of **128a** with secondary amine **137** [60-61] afforded undesired product **138b**. The structure of **138b** was determined by 2D-NMR technique. The irradiation of proton at δ 7.60 ppm, attributed to H-10, had an effect on δ 7.75 ppm (H-11) and showed the same coupling constant AB system (J = 9.5 Hz). Moreover, the irradiated proton at δ 7.18 ppm (H-1) culminated in the proton of the methyl group at δ 3.31 ppm (-NCH_3) while irradiation of proton methyl group influenced the proton at δ 7.18 ppm (H-1). That result confirmed that amine **137** obviously attacked on C-2. HRMS shows 385.12 m/z (M^++1) as a prominent peak.

2.5 Synthesis of pyrido[1',2'-1,2]imido[4,5-f]quinazoline-5,6-dione (143a)



Scheme 18

The reductive cyclization of **139** with Zn metal in glacial acetic acid provided pyrimidine **140** which was oxidized to **141** by concentrated hydrochloric acid and nitric acid [57]. In refluxing EtOH compound **141** was treated with 2-aminopyridine **142** in the presence of potassium bicarbonate. The reaction proceeded straightforward furnishing solely **143a**. Isomer **143b** could not be detected. There were expected two tentative isomers **143a** and **143b** from the reaction between **141** and **142** under basic conditions as shown in scheme 18. The best confirmation is 2D NMR technique, HMQC, which showed that H-4 has an effect on C-5 as shown in figure 9.

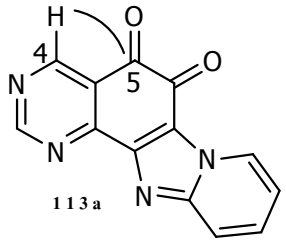
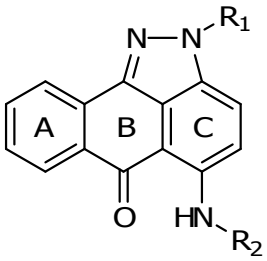


Figure 9 Observed NOE of **143a**

Finally the hitherto unstudied reaction of pyrimidine quinone **141** with 2-aminopyridine **142** should be examined.

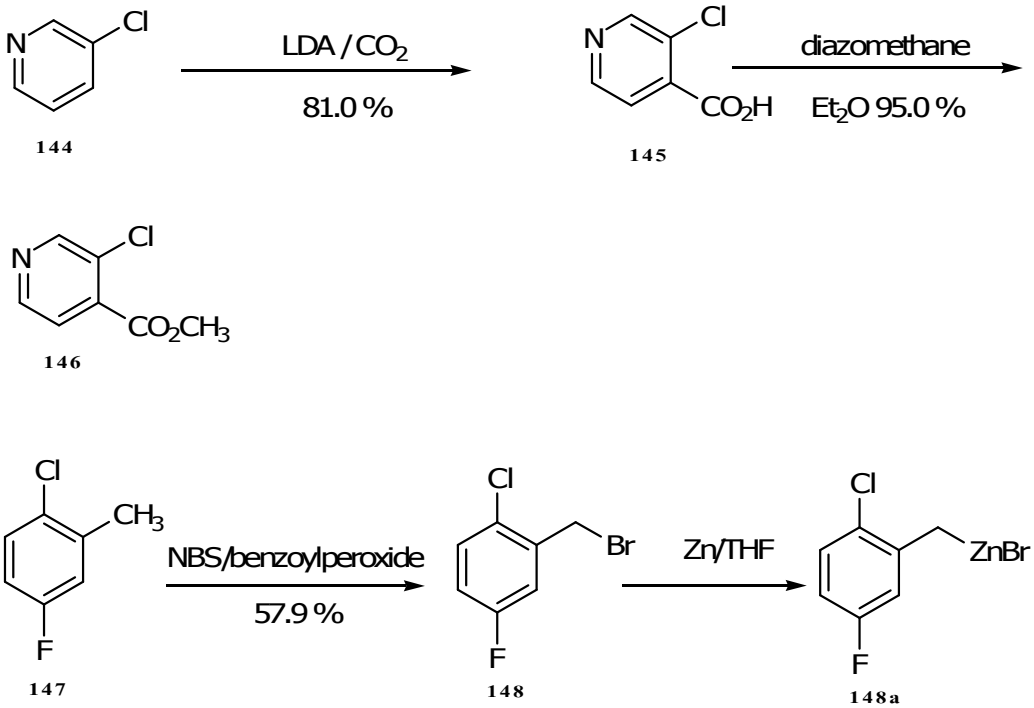
3. Synthesis of anthrapyrazole derivatives

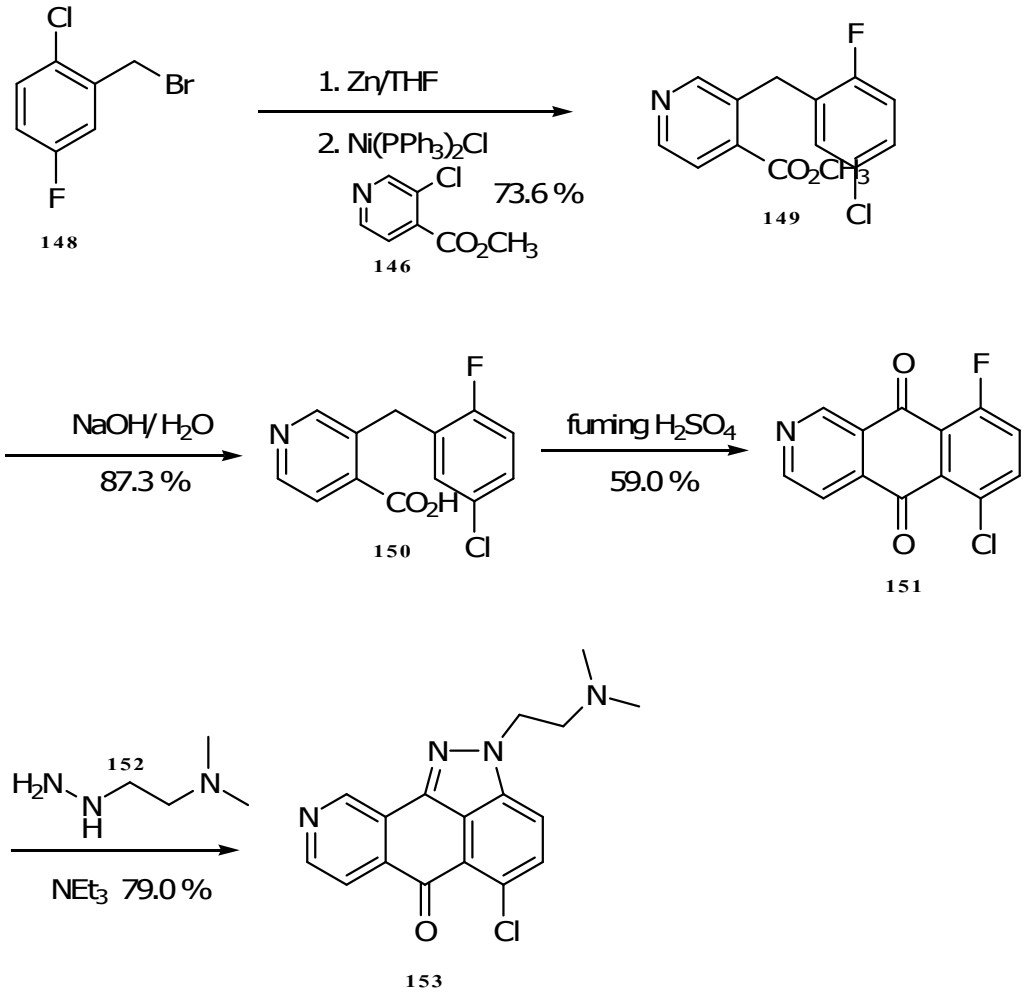
3.1 Synthesis of 2-(2-(dimethylamino)ethyl)-5-chloroindazolo[4,3-gh]isoquinoline-6(2H)-one (153)



96: anthrapyrazole

The syntheses of derivatives of **96** starts from the tetracyclic nucleus **153** as depicted in scheme 19. It has been proven that the tetracyclic nucleus interacts with the DNA by intercalation [62]. In continuation of previous studies the effect of new side chains attached to the tetracyclic core should be examined.



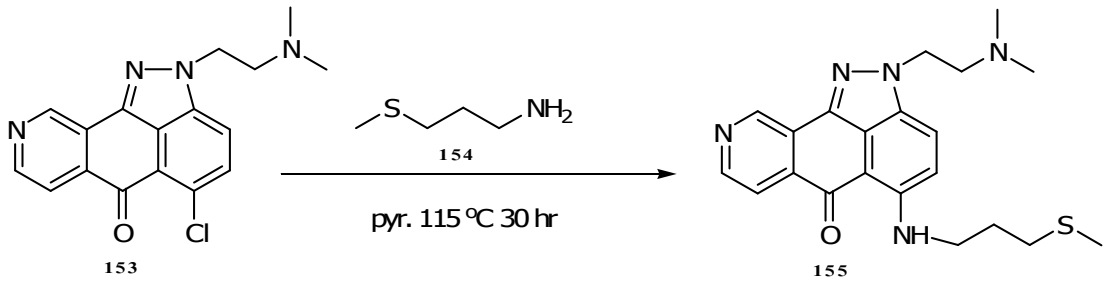


Scheme 19

Commercially available 3-chloropyridine **144** on treatment with lithium diisopropylamide and carbon dioxide gas led to acid **145** which was converted to ester **146** by diazomethane. The key step was the nickel mediated coupling of ester **146** with **148a**. This organo zinc bromide reagent was easily prepared by treatment of **148** with zinc dust in tetrahydrofurane. Benzyl bromide **148** was prepared by treatment of **147** with N-bromosuccinimide in carbon tetrachloride. The addition of a tetrahydrofuran solution of **148a** to ester to **146** in the presence of bis[triphenylphosphine]nickel(II) chloride led to coupled product **149**. Basic hydrolysis of **149** gave acid **150**. Cyclization and oxidation of **150** with fuming sulfuric acid with concomitant demethylation, led to **151**. The incorporation of pyrazol ring was successfully accomplished by treatment of **151** with hydrazine **152** to give satisfactory yields of **153** [63] after purification.

3.2 Synthesis of 2-(2-(dimethylamino)ethyl)-5-((3-methylthio)propylamino)indazolo[4,3-gh]isoquinoline-6(2H)-one (155)

Nucleophilic aromatic substitution (S_NAr) of the 5-chloro substituted compound **153** by 3-(methylthio)propylamine **154** in absolute pyridine for 30 hours at 115 ^oC provided product **155** in 58.1 %.



The ^1H NMR spectrum of compound **155** shows the signal as a singlet at 2.13 (s, 3H) which is attributed to the methyl group, adjacent to sulfur atom. The signals at 2.07 (t, 2H, J = 6.8 Hz), 2.91 (t, 3H, J = 6.7 Hz), and 3.60 (m, 2H) are the protons of three methylene groups of amino sulfide side chain that connected to compound **153**. The amine proton, adjacent to the aromatic ring, shows a triplet at 9.20 (br., 1H, J = 5.4 Hz). ^{13}C NMR of the side chain shows signals at 15.5, 28.5, 31.4, and 41.6 ppm. IR of **155** shows the signal of the –NH stretching band at 3273 cm^{-1}. The ^1H and ^{13}C NMR in $CDCl_3$ of the chromophore compound **155** is shown in figure 10.

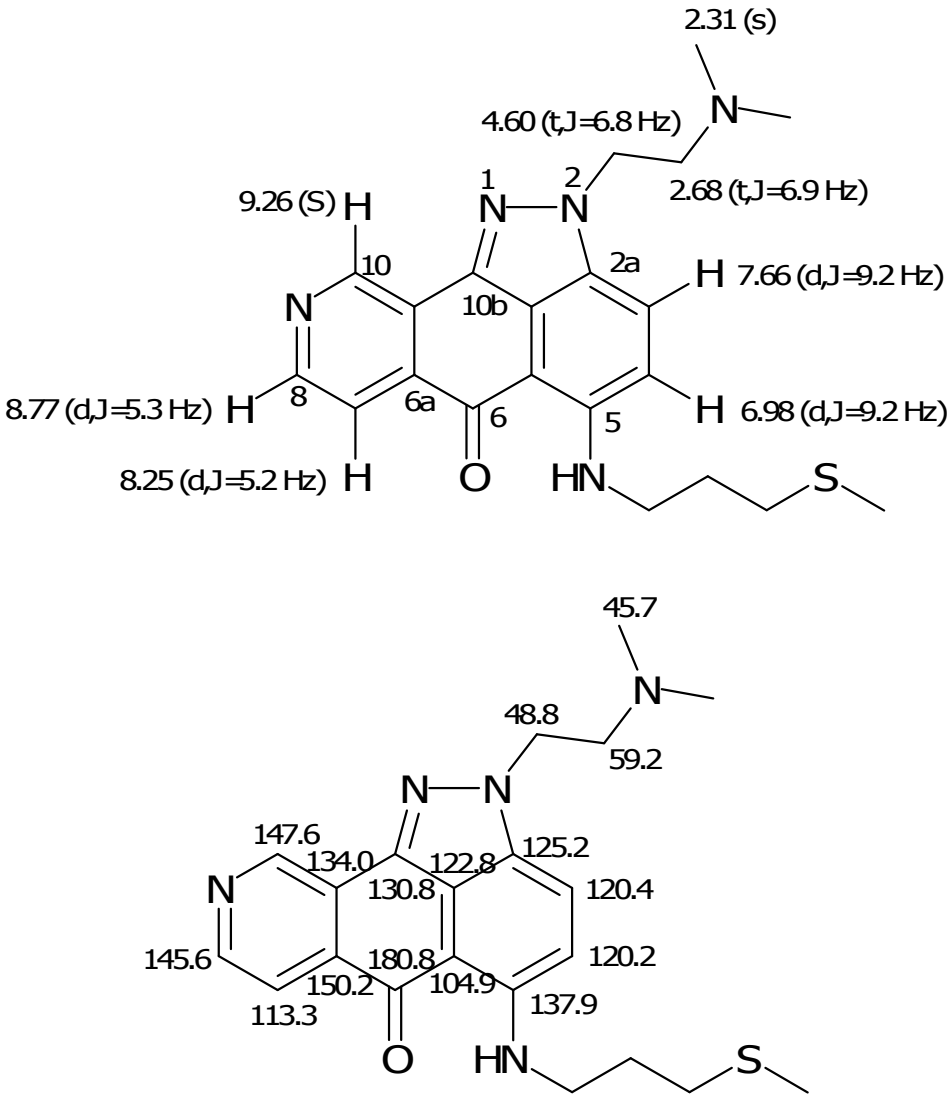
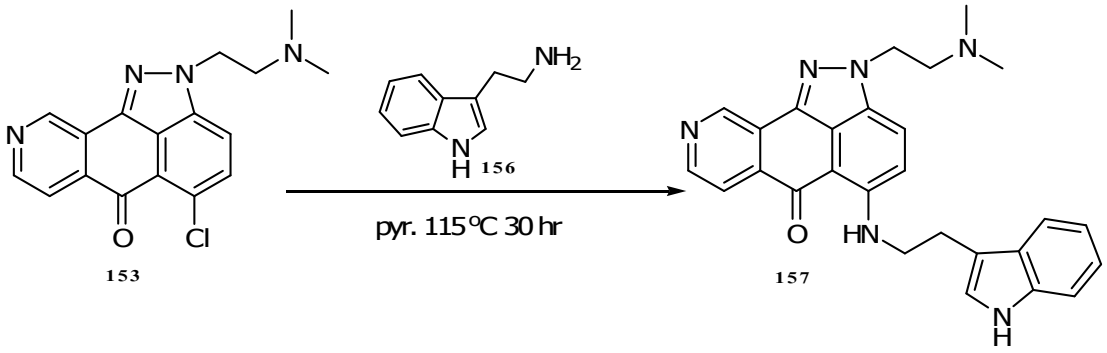


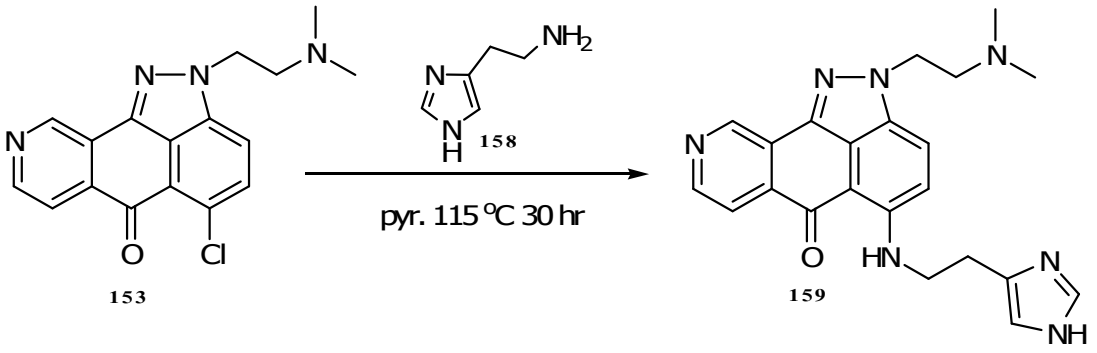
Figure 10 Assignment of ^{1}H and ^{13}C NMR of **155**.

3.3 Synthesis of 5-(2-(1H-indol-3-yl)ethylamino)-2-(2-(dimethylamino)ethyl)indazolo[4,3-gh]isoquinoline-6(2H)-one (157)



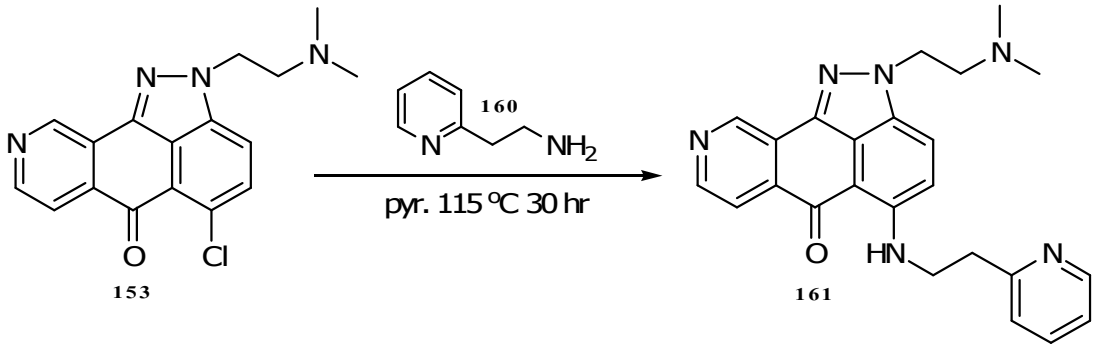
Displacement of the 5-chloro substituted compound **153** by tryptamine **156** in absolute pyridine for 30 hours at 115 ^{o}C led to product **157** in 61.5 % yield. The ^{1}H NMR spectrum of compound **157** shows the protons signal at 3.23 (t, 2H, J = 6.7 Hz), 3.73 (m, 2H), 7.10-7.20 (m, 3H), 7.38 (m, 2H), and 9.20 (t, 1H, J = 5.2 Hz) ppm which are attributed to tryptamine side chain. ^{13}C NMR spectrum of compound **157** shows signals at 24.4, 45.1, 110.8 111.4, 120.0, 121.0, 122.0, 123.3, 127.0, and 136.3 ppm which are attributed to carbon frame of the tryptamine. IR of **157** shows the signal of –NH stretching band at 3258 cm^{-1}.

3.4 Synthesis of 5-(2-(1H-imidazol-4-yl)ethylamino)-2-(2-(dimethylamino)ethyl) indazolo[4,3-gh]isoquinoline-6(2H)-one (159)



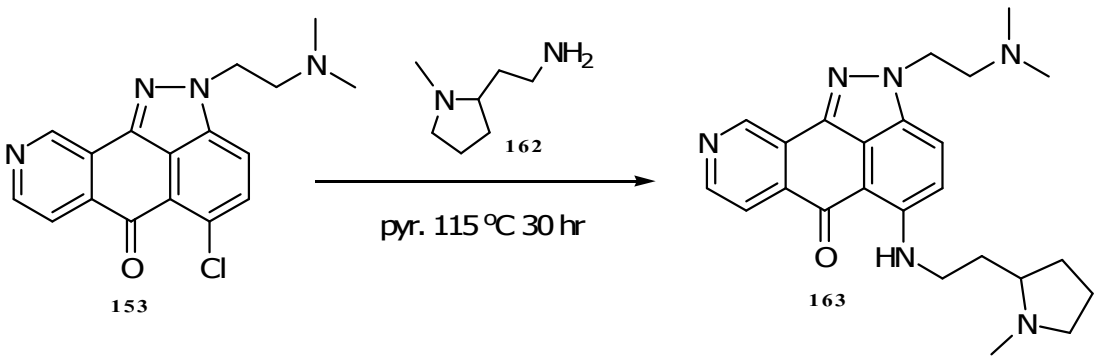
Displacement of the 5-chloro substituted compound **153** by histamine **158** in absolute pyridine for 30 hours at 115 ^{o}C provided product **159** in 58.3 % yield. The ^{1}H NMR spectrum of compound **159** shows proton signals at 3.03 (d, 2H, J = 6.2 Hz), 3.65 (d, 2H, J = 5.8 Hz), 6.96 (s, 1H), and 7.61 (s, 1H) ppm which are attributed to histamine side chain. ^{13}C NMR spectrum of compound **159** shows the signal at 29.6, 43.0, 116.2, 135.2, and 135.5ppm which are attributed to carbon frame of histamine. IR of **159** shows the signal of –NH stretching band at 3422 cm^{-1}.

3.5 Synthesis of 2-(2-dimethylamino)ethyl)-5-(2-(pyridin-2yl) ethylamino)indazolo[4,3-gh]isoquinoline-6(2H)-one (161)



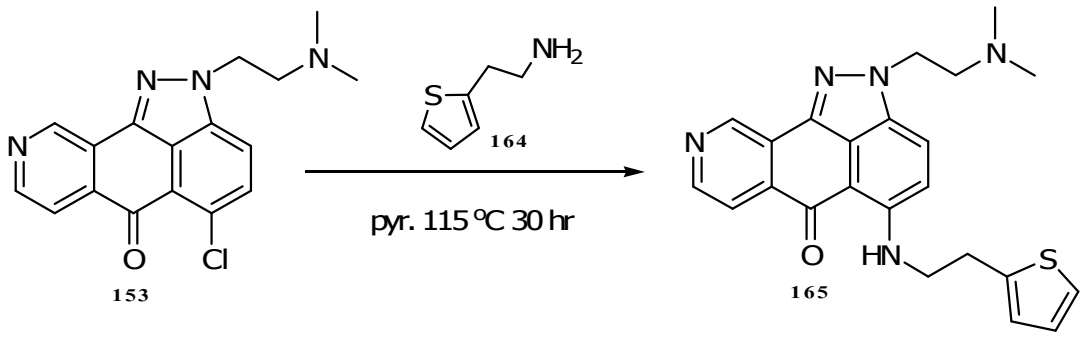
Displacement of the 5-chloro substituted compound **153** by 2-(2-aminoethyl)pyridine **160** in absolute pyridine for 30 hours at 115 ^{o}C gave product **161** in 47.4 %. The ^{1}H NMR spectrum of compound **161** shows the protons signal at 3.23 (t, 2H, J = 6.7 Hz), 3.73 (m, 2H), 7.13-7.22 (m, 3H), 8.6 (d, 1H, J= 4.7 Hz), and 9.31 (t, 1H, J = 5.3 Hz) which are attributed to pyridine side chain. ^{13}C NMR spectrum of compound **161** shows signals at 38.0, 42.8, 121.8, 123.6, 149.6, and 158.2 ppm which are attributed to the pyridine side chain. IR of **161** shows the signal of –NH stretching band at 3289 cm^{-1}.

3.6 Synthesis of 2-(2-(dimethylamino)ethyl)-5-(2-(1-methylpyrrolidin-2-yl)ethylamino) indazolo[4,3-gh]isoquinoline-6(2H)-one (163)



Displacement of the 5-chloro substituted compound **153** by 2-(2-aminoethyl)-1-methylpyrrolidine **162** in absolute pyridine for 30 hours at 115 ^{o}C led to product **163** in good yield (85.8 %). The ^{1}H NMR spectrum of compound **163** shows proton signals at 1.72-1.86 (m, 6H), 3.52 (m, 4H), and 9.23 (br., s, 1H) which are attributed to pyrrolidine side chain. ^{13}C NMR spectrum of compound **163** shows the signal at 33.1, 40.5, 40.6, 32.0, 30.6, 57.1, and 63.9 ppm which are attributed to carbon frame of the pyrrolidine side arm. IR of **163** shows the signal of –NH stretching band at 3282 cm^{-1}.

3.7 Synthesis of 2-(2-(dimethylamino)ethyl)-5-(2-(thiophen-2-yl) ethylamino)indazolo[4,3-gh]isoquinoline-6(2H)-one (165)

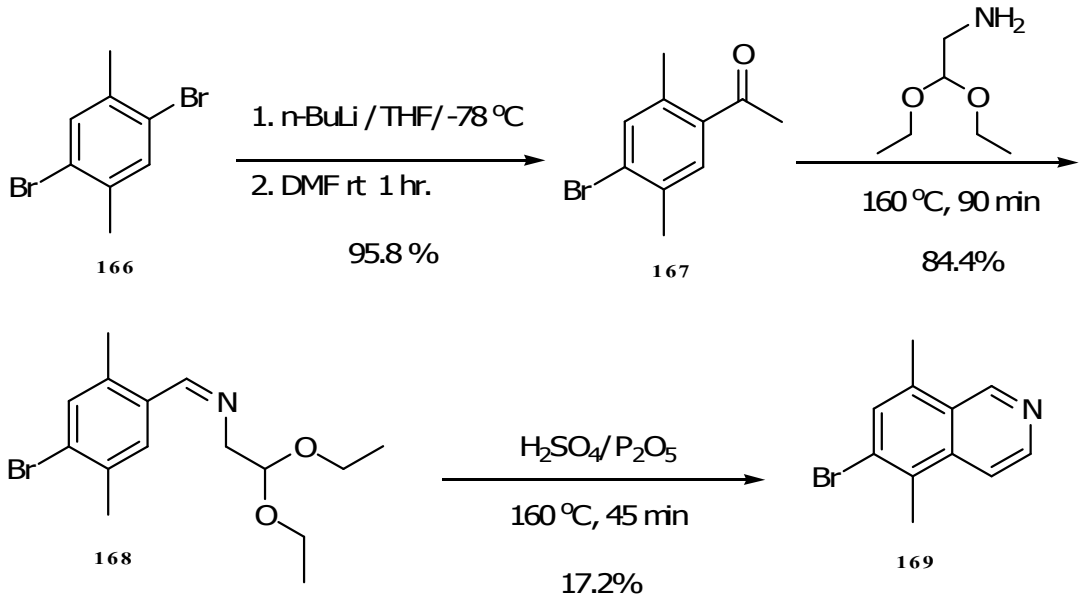


Displacement of the 5-chloro substituted of compound **153** by 2-thiopheneethylamine **164** in absolute pyridine for 30 hours at 115 ^{o}C gave product **165** in 58.3 % yield. The ^{1}H NMR spectrum of compound **165** shows proton signals at 3.29 (t, 2H, J = 7.0 Hz), 3.75 (m, 2H), 7.10-7.20 (m, 3H), 7.38 (m, 2H), 6.37 (m, 3H) , 7.18 (m, 1H), and 9.27 (t, 1H, J = 5.6 Hz) ppm. The integration of proton signals at 6.37 are three protons. One of them belongs to H-4. ^{13}C NMR spectrum shows the signals at 30.0, 48.8, 125.2, 125.7, and 127.1 ppm which are attributed to the thiophene side chain. IR of **165** shows the signal of –NH stretching band at 3286 cm^{-1}.

4.Synthesis of ellipticine (49)

Finally a new and very short route to ellipticine **49** should be opened: starting from bromoisoquinoline derivative **169** a two step approach should be tried. A Buchwald-Hartwig reaction followed by an intermolecular reaction should be lead on the shortest route to ellipticine.

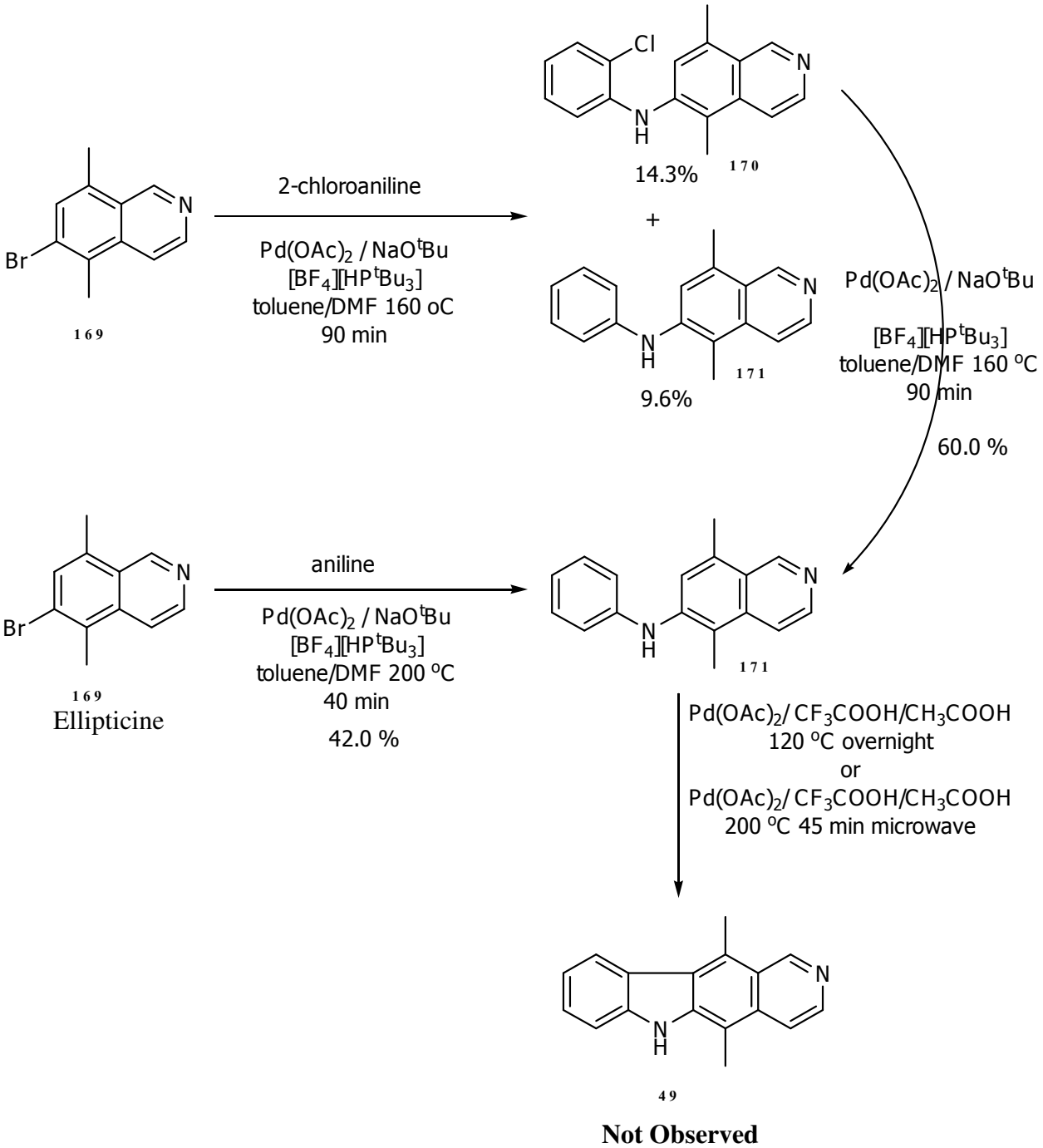
4.1 Synthesis of 7-bromo-5,8-dimethylisoquinoline (169)



Scheme 20

Treatment of 1,4-dibromo-2,5-dimethylbenzene **166** with n-BuLi followed by the addition of DMF produced the aldehyde **167** [64] which could be converted to imine **168** by refluxing in aminoacetaldehyde diethyl acetal to yield the expected product [64]. The ^{1}H NMR spectrum of **168** shows a singlet 8.48 which is attributed to the proton of imine. The signal of 1.19 (t, 6H, J = 7.0 Hz), 3.55 (dd, 2H, J = 2.2, 7.0 Hz), 3.68 (dd, 2H, J = 2.3, 7.0 Hz), 3.76 (d, 2H, J = 2.0 Hz), and 4.79 (t, 1H, J = 2.0 Hz) which are the proton of acetal moiety. Imine **168** allowed to cyclize in hot H_2SO_4/P_2O_5 to provide isoquinoline **169**. The ^{1}H NMR signals of **169** exhibit 7.74 (s, 1H), 7.75 (d, 1H, J = 5.9 Hz), 8.60 (d, 1H, J = 5.9 Hz), and 9.37 (s, 1H) which are the protons of aromatic isoquinoline ring (Scheme 20). The synthesis of intermediate **169** has been reported recently [65] in 8 steps, while it can be done now in 3 steps with this strategy.

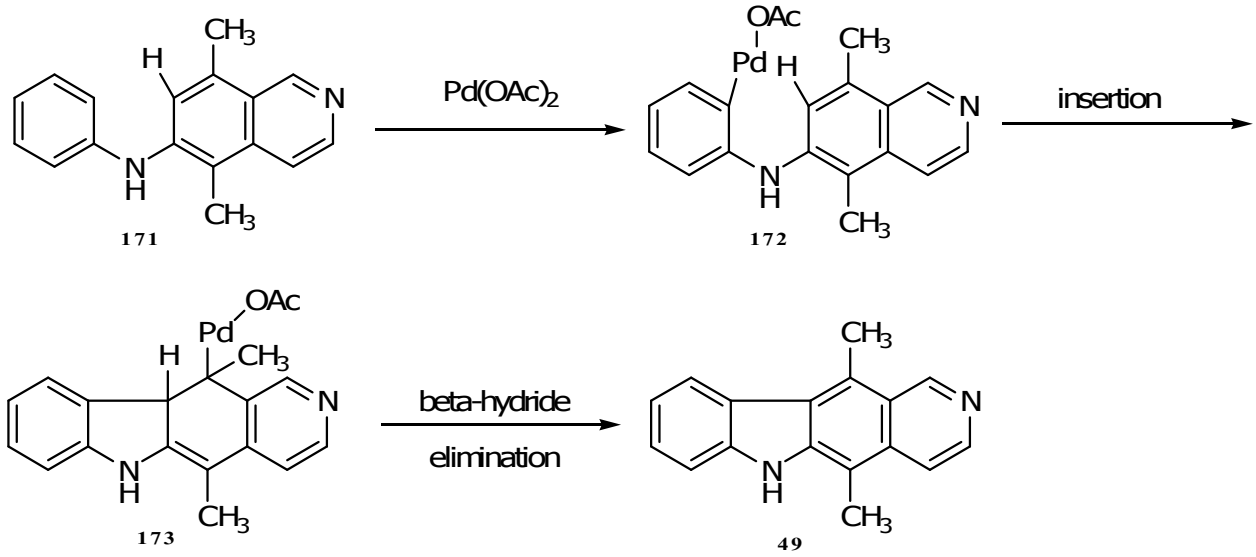
4.2 Attempts to synthesis of ellipticine (49)



Scheme 21

The Pd-catalyzed amination of **169** with 2-chloroaniline in the presence of $Pd(OAc)_2$, P^tBu_3, and NaO^tBu led to product **170** (14.3%) and **171** (9.6%) [66]. Unfortunately, ellipticine **49** could not be done in a tandem reaction by Buchwald-Hartwig coupling and ring closure in one pot. Moreover, subsequent intramolecular Heck reaction of compound **170** gave only **171**. Besides that compound **171** could be directly achieved from **169** and aniline by Buchwald-Hartwig reaction in 42.0%.

The attempts to cyclize **171** to ellipticine **(49)** by intramolecular Heck reaction using $Pd(OAc)_2$, could not realized, neither under conventional conditions nor under microwave assistance. The possible reason of this step it might be steric hindrance from methyl group that blocks the insertion step (Scheme 22). This seems reasonable because similar cyclization with adducts lacking this unfavorable methyl group occur smoothly [67].

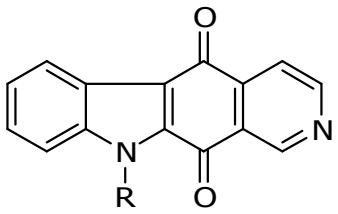


Scheme 22 Mechanism of intremoleculaer Heck reaction to form elliptine.

5. Biological activities test of synthesized compounds

All synthesized compounds were tested the biological activites *in vitro* at Zentaris GmbH. The antiproliferative activities were evaluated on two different cell lines; NClH460: lung carcinoma, SKOV3: ovrian carcinoma. The primary screen was carried out at constant concentration of 3.16 µg/ml.

For the first series, carbazole nucleus (Scheme 23) compound **107-109**, **114**, **120**, and **124** showed strongly antiproliferative activity against NClH460 cell lines. In case of SKOV3 cell lines, compound **109**, **114**, and **120** exhibited moderately antiproliferative activity whereas compound **107**, **108**, and **124** showed higher than the concentration constant at 3.16 µg/ml especially **107** and **124** as shown in table 1.



107: R = -$(CH_2)_2S(CH_2)_2OH$ **108:** R = -$(CH_2)_2$-N-morphorine

109: R = -$(CH_2)_2$-N-pyrrolidine **114:** R = -$(CH_2)_2$-N-oxazolidine

120: R = -$(CH_2)_2$-N-1-methylpiperazine **124:** R = -$(CH_2)_2NMe(CH_2)_2OH$

Scheme 23

Table 1 Cytotoxicity of the series of carbazole nucleus

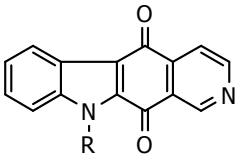
Cell lines / Compounds	NClH460 EC_{50} (µg/ml)	SKOV3 EC_{50} (µg/ml)
107	0.6388	9999
108	0.7924	3.9310
109	0.2562	0.5944
114	0.3099	2.3770
120	0.5275	1.3390
124	0.8301	9999

The biological activity test of the series of benzo[a]fluorine-5,6-dione **(95)** and anthrapyrazole **(96)** are under progress.

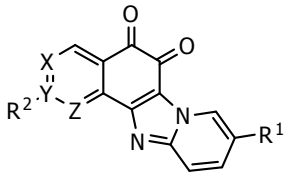
CHAPTER III

CONCLUSION

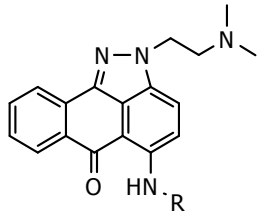
The derivatives of three structures, 10H-pyrido[3,4-b]carbazol-5,11-dione **(93)**, benzo[a]fluorine-5,6-dione **(95)**, and anthrapyrazole (**96**), were designed and synthesized. First series, carbazole derivatives were modified by N-alkylation with various side chains, leading to product **107-109**, **114**, **120**, and **124** which showed strong anticancer activity against NClH460 cell lines whereas especially **109**, **114**, and **120** presented moderate cytotoxicity against SKOV3 cell lines. Nevertheless the high anticancer activities of the previously synthesized amines could not be exceeded. The second series was the reaction between 6,7-dichloro-5,8-isoquinoline dinone/6,7-dichloro-5,8-quinazoline and substituted 2-aminopyridine/2-aminopyridine led to **128(a-b)**, **134(a-b)**, **136a** and **143a**. Surprisingly, **128a** could be substituted by secondary amine at C-2 to provide **138b**. The third series anthrapyrazole was synthesized by nucleophilic aromatic substitution (S_NAr) of the 5-chloro substituted **153**, leading to **155**, **157**, **159**, **161**, **163**, and **165**. For the second and the third series the testing of anticancer activity are in progress and therefore conclusion about structure activity relationships can not be drawn at this time. Finally, a new and extreme short route to ellipticine **(49)** could not be realized by a tandem Buchwald-Hartwig coupling and Heck reaction. However, the key intermediate **169** which can be converted to ellipticine, could be done in 3 steps.



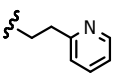
107: R = -$(CH_2)_2S(CH_2)_2OH$ **108**: R = -$(CH_2)_2$-N-morphorine
109: R = -$(CH_2)_2$-N-pyrrolidine **114**: R = -$(CH_2)_2$-N-oxazolidine
120: R = -$(CH_2)_2$-N-1-methylpiperazine **124**: R = -$(CH_2)_2NMe(CH_2)_2OH$



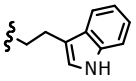
128a: X = N, Y = C, Z = C ; R^1 = Cl, R^2 = H **128b**: X = C, Y = N, Z = C ; R^1 = Cl, R^2 = H
134a: X = N, Y = C, Z = C ; R^1 = Br, R^2 = H **134b**: X = C, Y = N, Z = C ; R^1 = Br, R^2 = H
136a: X = N, Y = C, Z = C ; R^1 = NO_2, R^2 = H **138b**: X = N, Y = C, Z = C ; R^1 = Cl, R^2 = -$NMe(CH_2)_2NMe_2$
143a: X = N, Y = C, Z = N ; R^1 = H, R^2 = H



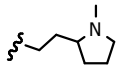
155: R = -$(CH_2)_3SCH_3$ **161**: R =



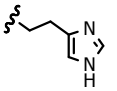
157: R =



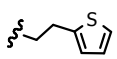
163: R =

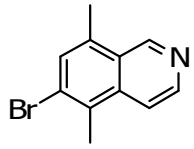


159: R =



165: R =





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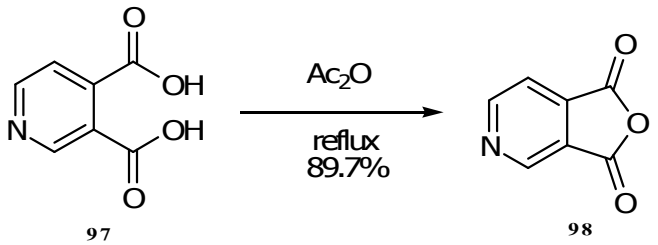
CHAPTER IV

Experimental Part

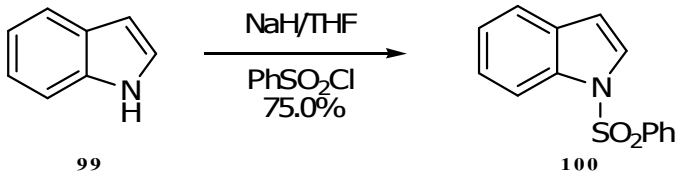
1.Synthesis of 10-H-pyrido[3,4-b]carbazole-5,11-dione and its derivatives.

1.1 Synthesis of furo[3,4-c]pyridine-1,3-dione (98)



A solution of 3,4-dicarboxylpyridine **97** (15.00 g, 0.09 mol) in 54 mL distilled acetic anhydride was refluxed for 30 min. After cooling down to room temperature, the excess of solvent was removed by vacuum distillation (20 mbar at 70 -100 ^{o}C) until total dryness. The dark brown semi-solid was kept in KOH a desiccator over night. The solid was purified by sublimation to yield **98** (12.00 g, 89.7 %) as solorless crystals. The full characterization of compound **98** is in reference [52].

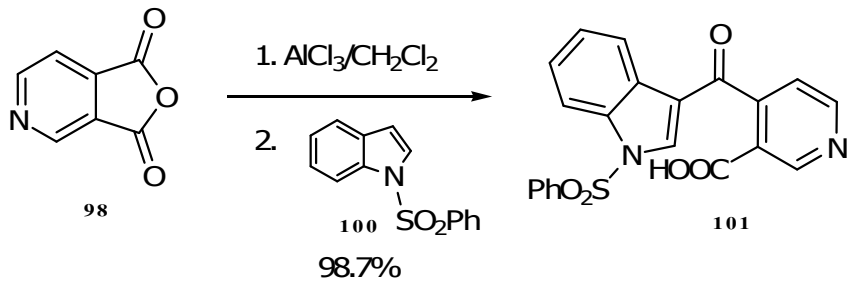
1.2 Synthesis of 1-phenylsulfonyl-1H-indole (100)



During 20 min, NaH (2.60 g, 0.108 mol, 60% in paraffin) was added to a stirred solution of indole **99** (10.00 g, 0.085 mol) in 100 mL anhydrous THF at 0 ^{o}C. After stirring at RT for 1 h, benzenesulfonylchloride (11mL, 0.086 mol) was added slowly. The reaction mixture was stirred for an additional 1 hr and then poured into 900 mL of 5% $NaHCO_3$ and extracted with ether (5 x 300 mL). The combined organic layers were dried with Na_2SO_4 and the sol-

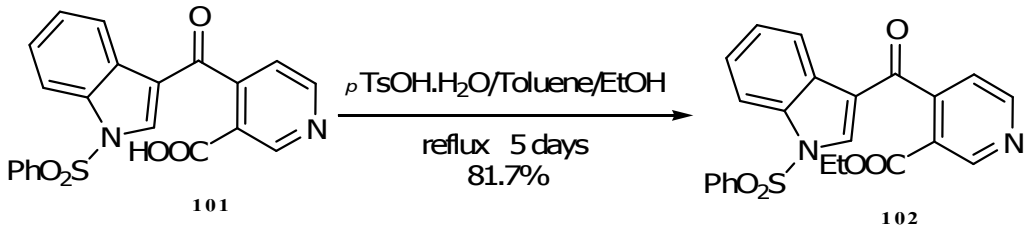
vent was removed under reduced pressure to give a beige solid. Recrystallization with ethanol gave the compound **100** (16.57 g, 75.0%) as colorless crystals, mp 75-78 ^{o}C. The full characterization of compound **100** is in reference [51].

1.2 Synthesis of 1-(phenylsufonyl)indol-3yl-3-carboxy-4-pyridyl ketone (101)



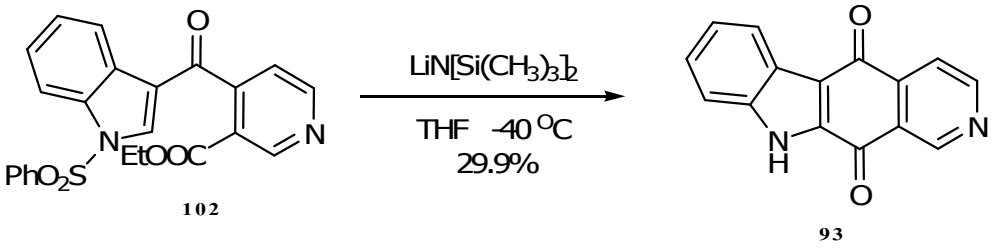
To a magnetically stirred suspension of $AlCl_3$ (12.51 g, 0.093 mol) in CH_2Cl_2 (250 mL) was added pyridine-3,4-dicarboxylic acid anhydride **98** (7.19 g, 0.048 mol), and the mixture was stirred for 30 min at RT. A solution of 1-phenylsulfonyl-1H-indole **100** (3.40 g, 0.013 mol) in CH_2Cl_2 (50 mL) was added dropwise via an additional funnel, and the solution was stirred for 2 hr at RT. The mixture was quenched with ice-water (250 mL), and the resulting solid was collected and dried in a desiccator over night. The solid was dissolved in acetone (350 mL) and refluxed for 1 h. Concentration of the solution to half volume gave white crystals which were collected in three crops, affording **101** (3.52 g, 99.7 %) as pale yellow crystal. The full characterization of compound **101** is in reference [52].

1.4 Synthesis of 1-(phenylsufonyl)indol-3-yl-3-carbethoxy-4-pyridyl ketone (102)



A mixture of keto acid **101** (4.84g, 11.9 mmol), absolute EtOH (200 mL), toluene (500 mL) and *p*-toluenesulfonic acid monohydrate (3.60 g, 18.9 mmol) was refluxed for 5 days under azeotropic removal of water. The solvent was removed in vacuo, ethyl acetate (400 mL) was added, and then the mixture was washed with 10% aqueous $NaHCO_3$ (3 x 250 mL). The organic layer was washed 2 times with water (200 mL) and dried with Na_2SO_4. After filtration, the solvent was removed to yield a beige solid. The crude product was purified by column chromatography using 1:1 THF/EtOAc as eluent to give 4.22 g (81.7%) **102** as colorless crystals. The full characterization of compound **102** is in reference [52].

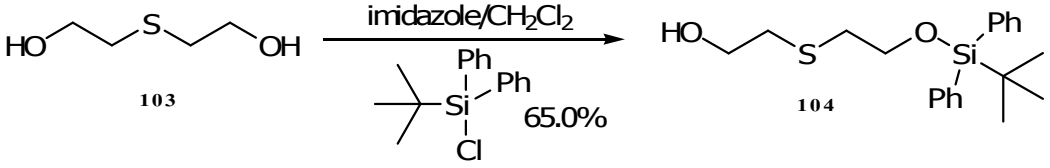
1.5 Synthesis of 10H-pyrido[3,4-b]carbazole-5,11-dione (93)



To a solution of keto ester **102** (2.20 g, 46 mmol) in anhydrous THF (100 mL) at -76 ^oC was slowly added 1.0M Li-bis(trimethylsilyl)amide (10.40 mL, 10.4 mmol). The mixture was allowed to warm up to -40 ^oC for 2 h under argon atmosphere. Then the mixture was warmed up to RT and the solvent was removed in vacuo to give a dark oil. The resulting oil was quenched with saturated NH_4Cl solution (200 mL) and extracted with EtOAc (5 x 150 mL). The combined organic phases were dried with Na_2SO_4 and the solvent was evaporated.

The crude product was purified by column chromatography, using 40% light petroleum/EtOAc as eluent to obtain product **93** as orange crystals, mp 318-320 ^{o}C (0.358 g, 29.88%). The fully characterization of compound **93** is in reference [52].

1.6 Synthesis of 2-[2-(tert-butyl-diphenyl-silanyloxy)-ethylsulfanyl]-ethanol (104)



A solution of tert-butyldiphenylchlorosilane **103** (7.52 mL, 29.4 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of bis-(2-hydroxyethyl)-sulfide (2.94 mL, 29.4 mmol) in CH_2Cl_2 (34 mL) and stirred at 0 ^{o}C for 1 h. Then the mixture was allowed to warm up to RT and was continuously stirred for 2 h. After that water was added and the mixture was extracted by EtOAc. The combined organic layers were washed with water and dried with Na_2SO_4 and the solvent was evaporated. The crude product was purified by column chromatography, using 30% EtOAc/light petroleum as eluent to provide **104** (6.89 g, 65.0%) as colorless liquid.

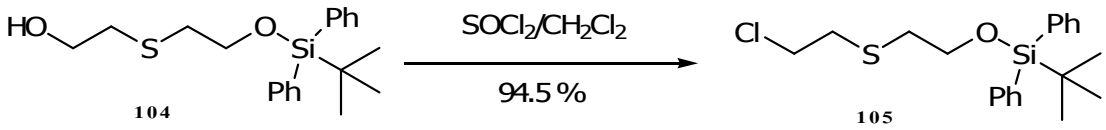
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.07 (s, 9H, -C($\underline{CH_3}$)$_3$), 2.33 (s, 1H, -O$\underline{H}$), 2.64-2.67 (m,4H, -$\underline{CH_2}$S$\underline{CH_2}$-), 3.63 (s, brs, HO$\underline{CH_2}$CH$_2$S-), 3.81 (t, 2H, J = 6.8 Hz,-SCH$_2\underline{CH_2}$ OSi-), 7.39-7.45 (m, 4H, Ph), 7.66-7.71 (m, 6H, Ph).

^{13}C NMR (50MHz, $CDCl_3$): δ = 19.1 ($\underline{C}$(CH$_3$)$_3$), 26.7 (C($\underline{C}$H$_3$)$_3$), 33.6 (HOCH$_2\underline{C}$H$_2$S-),35.5 (-S$\underline{C}$H$_2$CH$_2$OSi-), 60.4 (HOCH$_2\underline{C}$H$_2$S-), 63.7 (-SCH$_2\underline{C}$H$_2$OSi-), 127.7 (Ph), 129.7, (Ph),133.3 (Ph), 135.5 (Ph).

MS m/e (% relative intensity): 225(100), 199(24.1), 181(59.2), 105(8.9), 77(12.2) 61(7.1), 45(8.5).

IR (NaCl disc) υ_{max}: 3405, 2956, 2930, 2857, 1472, 1427, 1112, 823 cm^{-1}.

1.7 Synthesis of tert-butyl-[2-(2-chloro-ethylsulfanyl)-ethoxy]-diphenylsilane (105)



104 105

The alcohol **104** (2.24 g, 6.2 mmol) was dissolved in absolute CH_2Cl_2 (7 mL) then $SOCl_2$ (1.80 mL, 24.9 mmol) was added dropwise to the resulting solution. Afterwards, the mixture was stirred for 40 min at RT. Saturated $NaHCO_3$ (200 mL) was added and stirred for 10 min. The water layer was extracted with CH_2Cl_2 (100 mL x 2). The combined organic phases were washed with saturated $NaHCO_3$ (190 mL) and dried with Na_2SO_4. The solvent was evaporated to give 2.234g (94.5%) of **105** as beige liquid.

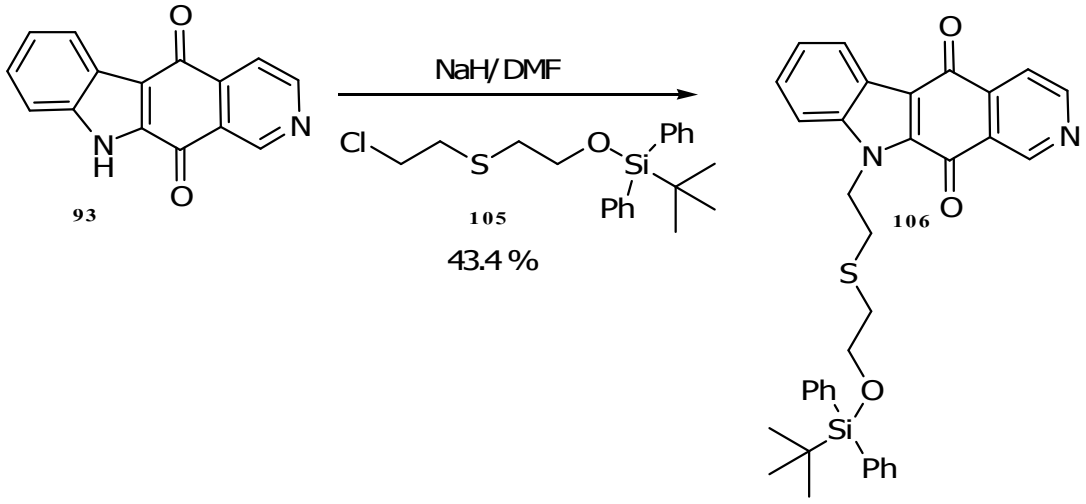
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.06 (s, 9H, -C($\underline{CH_3}$)$_3$), 2.67 (t, 2H, J = 6.8 Hz -S$\underline{CH_2}$$CH_2$ OSi-), 2.79 (t, 2H, J = 8.3 Hz, Cl$CH_2$$\underline{CH_2}$S-), 3.52 (t, 2H, J = 7.7 Hz, Cl$\underline{CH_2}$$CH_2$S-), 3.80 (t, 2H, J = 6.8 Hz, -S$CH_2$$\underline{CH_2}$OSi-), 7.39-7.45 (m, 4H, Ph), 7.65-7.67 (m, 6H, Ph).

^{13}C NMR (50MHz, $CDCl_3$): δ = 19.1 ($\underline{C}(CH_3)_3$), 26.8 (C($\underline{C}H_3$)$_3$), 34.2 (Cl$CH_2$$\underline{C}H_2$S-),34.4 (-S$\underline{C}H_2CH_2$OSi-), 43.0 (Cl$CH_2$$\underline{C}H_2$S-), 63.9 (-S$CH_2$$\underline{C}H_2$OSi-), 127.7 (Ph), 129.8 (Ph), 133.3 (Ph), 135.5 (Ph).

MS m/e (% relative intensity): 323(12.1), 321(27.4), 217(57.7), 181(24.7), 157(14.8), 105(100), 77(15.3), 45(17.6).

IR (NaCl disc) υ_{max}: 3070, 2958, 2930, 2857, 1472, 1427, 1112, 823 cm^{-1}.

1.8 Synthesis of 10-((2-[tert-butyl-diphenyl-silanyloxy]-ethylsulfanyl)-ethanol)-10H-pyrido[3,4-b]carbazole-5,11-dione (106)



A solution of amine **93** (0.13 g, 0.54 mmol) in absolute DMF (5 mL) was added dropwise to a cooled (-5 to -10 ^{o}C) suspension of NaH (54 mg, 1.35 mmol, 60% in paraffin, washed twice with hexane) in DMF (3 mL), after 30 min of stirring sulfide **105** (0.45 g, 1.09 mmol) in DMF (5 mL) was added slowly and the reaction mixture was stirred at 67 ^{o}C for 6 days. After quenching with 50 mL of water the mixture was extracted several times with EtOAc and the combined organic phases were dried with Na_2SO_4. The solvent was removed under reduced pressure to give a crude product which was purified by column chromatography, using 40% EtOAc/ petroleumether as eluent to obtain **106** (65 mg, 43.4%) as orange crystals, mp 94-95 ^{o}C.

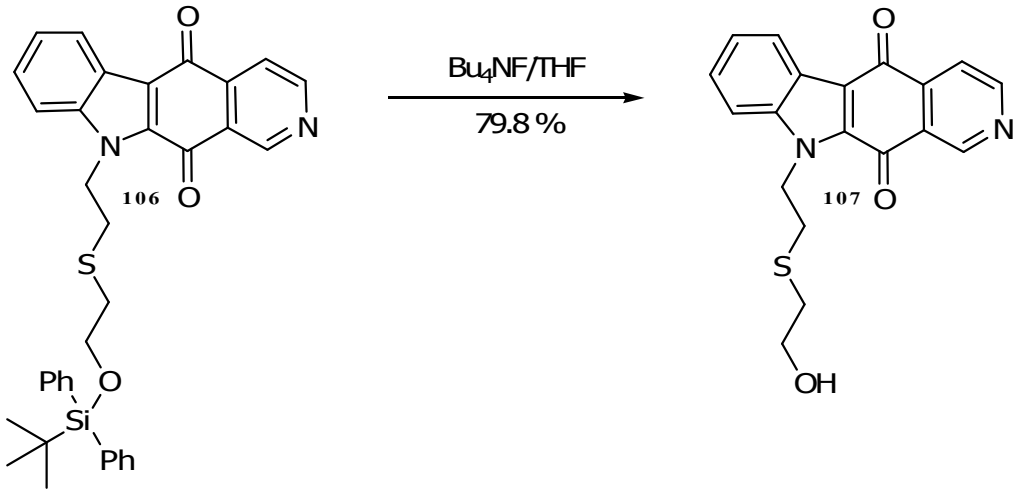
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.02 (s, 9H, -C($\underline{CH_3}$)$_3$), 2.79 (t, 2H, J = 6.4 Hz, -S$\underline{CH_2}$CH$_2$O Si-), 2.97 (t, 2H, J = 7.4 Hz, -NCH$_2\underline{CH_2}$S-), 3.85 (t, 2H, J = 6.5Hz, -SCH$_2\underline{CH_2}$OSi-), 4.88 (t, 2H, 7.2 Hz, -N$\underline{CH_2}$CH$_2$S-), 7.36-7.46 (m, 8H), 7.49 (s, 3H), 7.63-7.68 (m, 5H), 8.43 (d, 1H, J = 6.9 Hz).

^{13}C NMR (50MHz, $CDCl_3$): δ = 19.1 ($\underline{C}(CH_3)_3$), 26.7 (C($\underline{CH_3}$)$_3$), 32.0 (-NCH$_2\underline{C}$H$_2$S-),34.6 (-S$\underline{C}$H$_2$CH$_2$OSi-), 45.2 (-N$\underline{C}$H$_2$CH$_2$S-), 63.8 (-SCH$_2\underline{C}$H$_2$OSi-), 111.1 (C-9), 118.5 (C-4), 119.1 (C-5a), 123.6 (C-5b), 123.8 (C-6), 125.1 (C-11a),127.6 (Ph), 127.9 (C-8), 129.6 (Ph), 133.3 (Ph), 134.0 (C-10a), 135.5 (Ph), 139.2 (C-4a, C-9a), 148.2 (C-1), 155.5 (C-3), 178.0 (C-11), 179.5 (C-5).

HRMS (M^++1) calculated $C_{35}H_{25}O_3N_2SSi$ 591.2138, found 591.2146.

IR (KBr disc) υ_{max}: 2958, 2930, 2857, 1661, 1586, 1513, 1471, 1263, 1110, 701 cm^{-1}.

1.9 Synthesis of 10-(2-(2-hydroxyethylthio)ethyl)-10H-pyrido[3,4-b]carbazole-5,11-dione (107)



A solution of 1M Bu_4NF (1.2 mL, 1.2 mmol) in THF was added to a solution of compound **106** (0.28 g, 0.48 mmol) in absolute THF (10 mL) and the resulting mixture was stirred at RT for 10 min, quenched with water (100 mL) and extracted with EtOAc. The organic layer was washed with water and brine, and dried with Na_2SO_4. After filtration and concentration of the filtrate in vacuo, the crude product was purified by chromatography, using EtOAc as eluent to obtain **107** (0.135 g, 79.8%) as orange crystals, mp 184-185 ^oC.

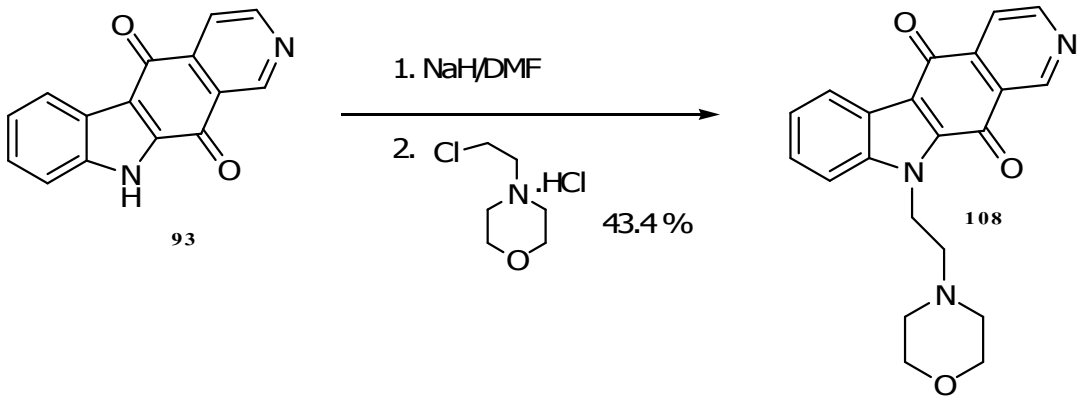
^1H NMR (200 MHz, DMSO-d_6): δ = 2.67 (t, 2H, J = 6.4 Hz, S$\underline{CH_2}CH_2OH$), 2.95 (s,2H,$NCH_2\underline{CH_2}S$), 3.58 (t, 2H, J = 6.5Hz, $SCH_2\underline{CH_2}OH$), 4.82 (d, 2H, J = 4.5 Hz, N$\underline{CH_2}CH_2S$-), 7.85 (s, 2H, H-7, H-8), 7,85 (s, 2H, H-4, H-9), 8.18 (s, 1H, H-6), 9.03 (s, 1H, H-3), 9.18 (d, 1H, H-1).

^{13}C NMR (50MHz, DMSO-d6): δ = 31.4 (-$NCH_2\underline{C}H_2S$-), 34.6(-S$\underline{C}H_2CH_2OSi$-), 45.1 (-N$\underline{C}H_2CH_2S$-), 61.3 (-$SCH_2\underline{C}H_2OSi$-), 112.8 (C-9), 118.3 (C-5a), 118.6 (C-4), 122.8 (C-6), 123.2 (C-5b), 134.8 (C-10a, C-4a), 139.3 (C-9a), 147.7 (C-1), 156.0 (C-3), 177.9 (C-11), 179.4 (C-5).

HRMS (M^++1) calculated $C_{19}H_{17}O_3N_2S$ 353.0960, found 353.0950.

IR (KBr disc) υ_{max}: 3432, 2923, 2862, 2360, 1653, 1585, 1510, 1472, 1264 cm^{-1}

1.10 Synthesis of 10-(2-morpholinoethyl)-10H-pyrido[3,4-b]carbazole-5,11-dione (108)



A solution of amine **93** (0.10 g, 0.41 mmol) in absolute DMF (5 mL) was added dropwise to a cooled (-5 to -10 ^{o}C) suspension of NaH (57 mg, 1.42 mmol, 60% in paraffin, washed twice with hexane) in DMF (3 mL), after 30 min of stirring 4-(2-chloroethyl) morpholine hydrochloride (0.15 g, 0.84 mmol) in DMF (5 mL) was added slowly and the reaction mixture was stirred at 69 ^{o}C for 4 h. After quenching with 50 mL of water the mixture was extracted several times with EtOAc and the combined organic phases were dried with Na_2SO_4. The solvent was removed by reduced pressure to give a crude product which was purified by column chromatography using 40% light petroleum/EtOAc to 5% MeOH/EtOAc as eluent to obtain compound **108** (65 mg, 43.4%) as red crystals, mp. 194-195 ^{o}C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.53 (s, 7H, overlapped with DMSO peak,-$\underline{CH_2}O\underline{CH_2}$-morpholine ring), 2.73 (t, 2H, J = 6.4 Hz, $NCH_2\underline{CH_2}$N-morpholine ing), 3.49 (t, 4H, J = 4.4 Hz, -$\underline{CH_2}N\underline{CH_2}$- morpholine ring), 4.86 (t, 2H, J = 6.5 Hz, $N\underline{CH_2}CH_2$N-morpholine), 7.46-7.57 (m, 2H, H-7, H-8), 7.85 (d, 1H, J =8.2 Hz, H-9), 7.95 (d, 1H, J = 4.9 Hz, H-4), 8.27 (d, 1H, J = 7.7 Hz, H-6), 9.10 (d, 1H, J = 4.9 Hz, H-3), 9.26 (s, 1H, H-1).

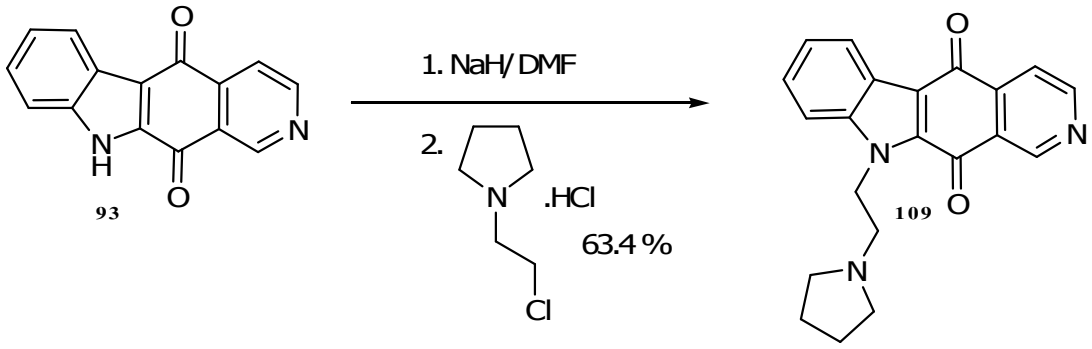
^{13}C NMR (50 MHz, DMSO-d_6): δ = 42.2 ($N\underline{C}H_2CH_2$N-morpholine), 53.4 ($NCH_2\underline{C}H_2$-morpholine), 57.4 (-$\underline{C}H_2N\underline{C}H_2$- morpholine ring), 66.2 (-$\underline{C}H_2O\underline{C}H_2$-morpholine),

112.6 (C-9), 117.9 (C-5a), 118.3 (C-4), 122.4 (C-6), 122.9 (C-5b), 134.8 (C-10a), 139.0 (C-4a), 139.2 (C-9a), 147.4 (C-1), 155.7 (C-3), 177.7 (C-11), 179.2 (C-5).

HRMS (M^++1) calculated $C_{21}H_{20}O_3N_3$ 362.1505, found 362.1498.

IR (KBr disc) υ_{max}: 2953, 2836, 1658, 1585, 1512, 1476, 1262, 1112 cm^{-1}.

1.11 Synthesis of 10-(2-pyrrolidineethyl)-10H-pyrido[3,4-b]carbazole-5,11-dione (109)



A solution of amine **93** (0.14 g, 0.58 mmol) in absolute DMF (5 mL) was added dropwise to a cooled (-5 to -10 ^oC) suspension of NaH (58 mg, 1.45 mmol, 60% in paraffin, washed twice with hexane) in DMF (3 mL). After 30 min of stirring 4-(2-chloroethyl)pyrrolidine hydrochloride (0.147g, 0.87 mmol) in DMF (5 mL) was added slowly and the reaction mixture was stirred at 69 ^oC for 2 h. After quenching with 50 mL of water the mixture was extracted several times with EtOAc and the combined organic phases were dried with Na_2SO_4. The solvent was removed by reduced pressure to give a crude product which was purified by column chromatography using 40% light petroleum/EtOAc to 5% MeOH/EtOAc as eluent to obtain compound **109** (0.13 g, 63.4%) as yellow-green crystals, mp 180-181 ^oC.

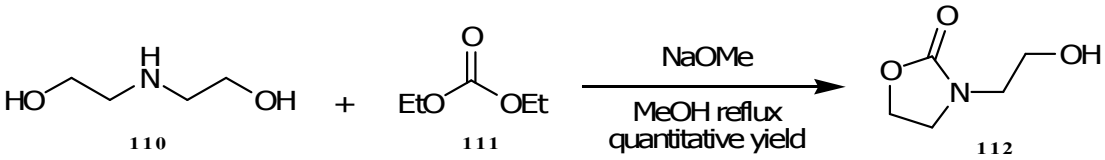
^1H NMR (200 MHz, $CDCl_3$): δ = 1.77-1.84 (m, 4H, -$\underline{CH_2}\underline{CH_2}$-pyrrolidine), 2.66 (d, 4H, J = 5.1 Hz, -$\underline{CH_2}N\underline{CH_2}$-pyrrolidine), 2.92 (t, 2H, J = 7.4 Hz, $NCH_2\underline{CH_2}$N-pyrrolidine ring), 4.87 (t, 2H, J = 7.4 Hz, $N\underline{CH_2}CH_2$N-pyrrolidine), 7.37-7.57 (m, 3H, H-7, H-8, H-9), 7.99 (d, 1H, J = 4.9 Hz, H4), 8.42 (d, 1H, J = 7.5 Hz, H-6), 9.03 (d, 1H, J = 4.9 Hz, H-3), 9.38 (s, 1H, H-1).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.6 (-$\underline{C}H_2\underline{C}H_2$-pyrrolidine), 44.5 ($NCH_2\underline{C}H_2$-pyrrolidine), 54.4 (-$\underline{C}H_2N\underline{C}H_2$-pyrrolidine), 55.3 ($N\underline{C}H_2CH_2N$-pyrolidine), 111.2 (C-9), 118.6 (C-4), 119.1 (C-5a), 123.8 (C-6), 125.1 (C-7), 126.5 (C-11a), 127.9 (C-8) 134.5 (C-10a), 139.5 (C-4a,C-9a), 148.2 (C-1), 155.3 (C-3), 178.0 (C-11), 179.5 (C-5).

HRMS (M^++1) calculated $C_{21}H_{20}O_2N_3$ 346.1556, found 346.1568.

IR (KBr disc) υ_{max}: 2926, 2795, 1661, 1585, 1478 cm^{-1}.

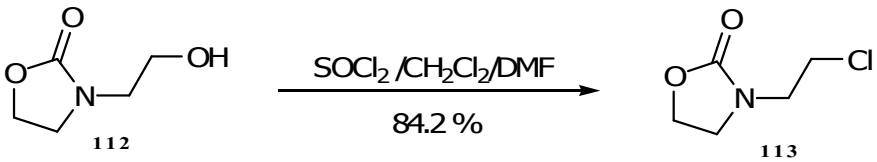
1.12 Synthesis of N-(2'-hydroxy ethyl)-2-oxazolidone (112)



To a solution of diethanolamine **110** (31.00 g, 29.4 mmol) and diethyl carbonate **111** (44.0 mL, 36.3 mmol) was added NaOMe (0.14 g, 2.6 mmol) in one portion and the resulting mixture was refluxed for 2 h. Ethanol formed in the reaction was removed by distillation under reduced pressure to give compound **112** in quantitative yield as colorless oil. The full characterization of compound **112** is in reference [54].

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.15 (t, 2H, J = 5.3 Hz), 3.47-3.55 (m, 4H), 4.14 (t, 2H, J = 2.6 Hz).

1.13 Synthesis of N-(2'-chloroethyl)-2-oxazolidone (113)

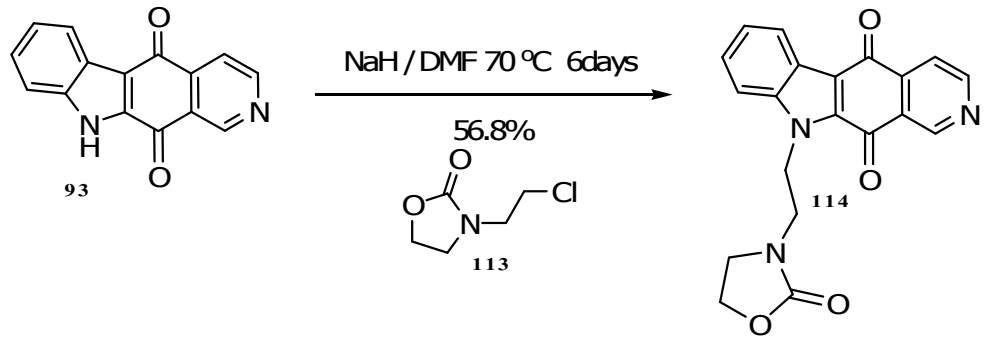


To a solution of alcohol **112** (10.2g, 77.0 mmol) in dry CH_2Cl_2 was slowly added thionylchloride (6.2 mL, 85.4 mmol) and 2 drops of DMF. The mixture was continuously stirred at RT until the formed CO_2 was completely gone. Saturated Na_2CO_3 (50 mL) was carefully added and the mixture was extracted with CH_2Cl_2. The combined organic layer we-

re washed with water and dried with Na_2SO_4 and the solvent was evaporated to obtain **113** (9.66g, 84.2 %) as a pale yellow oil. The full characterization of compound **113** is in reference [54].

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.46-3.69 (m, 6H), 4.29 (t, 2H, J = 8.3 Hz).

1.14 Synthesis of 10-[(2-ethyl)-2-oxazolidone]-10H-pyrido[3,4-b]carbazole-5,11-dione (114)



A solution of **93** (0.15 g, 0.62 mmol) in absolute DMF (5 mL) was added dropwise to a cooled (-5 to -10 °C) suspension of NaH (27mg, 0.67 mmol, 60% in paraffin, washed twice with hexane) in DMF (3 mL), after 30 min of stirring, a solution of compound **113** (0.14 g, 0.94 mmol) in DMF (5 mL) was added slowly and the reaction mixture was stirred at 69 °C for 6 days. After quenching with 50 mL of water the mixture was extracted several times with EtOAc and the combined organic phases were dried with Na_2SO_4. The solvent was removed by reduced pressure to give a crude product which was purified by column chromatography, using EtOAc to 5% MeOH/EtOAc as eluent to obtain compound **114** (54 mg, 56.8%) as yellow solid, mp 230-231 °C.

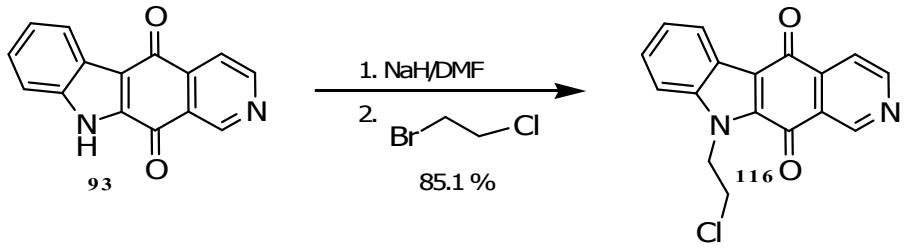
^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.37 (t,2H, J = 8.2 Hz, -$NCH_2\underline{CH_2}O$-), 3.76 (t, 2H J = 6.3 Hz, -$NCH_2\underline{CH_2}$N-oxazolidone), 4.11 (t, 2H, J = 7.5 Hz, -$N\underline{CH_2}CH_2O$-), 4.93 (t, 2H, J = 6.3 Hz, -$N\underline{CH_2}CH_2$N-oxazolidone), 7.41-7.66 (m, 3H, H-7, H-8, H-9), 8.01 (d, 1H, J = 4.9 Hz, H4), 8.43 (d, 1H, J = 8.0Hz, H-6), 9.05 (d, 1H, J = 4.9 Hz, H-3), 9.38 (s, 1H, H-1).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 43.1 (-$NCH_2\underline{C}H_2$N-oxazolidone), 44.2 (-$N\underline{C}H_2CH_2$N-oxazolidone), 45.7 (-$N\underline{C}H_2CH_2O$-), 62.0 (-$NCH_2\underline{C}H_2O$-) 111.0 (C-9), 118.7 (C-4), 119.7 (C-5a), 123.6 (C-5b), 123.9 (C-6) 125.5 (C-7), 126.3 (C-11a), 128.6 (C-8) 133.3 (C-10a), 139.5 (C-4a), 139.9 (C-9a), 148.2 (C-1), 155.8 (C-3), 158.4 (C=O, oxazolidone), 178.0 (C-11), 179.5 (C-5).

HRMS (M^++1) calculated $C_{21}H_{18}O_4N_3$ 362.1107, found 362.1133.

IR (KBr disc) υ_{max}: 2956, 2922, 1744, 1653, 1585, 1468, 1260 cm^{-1}.

1.15 Synthesis of 10-(2-chloroethyl)-10H-pyrido[3,4-b]carbazole-5,11-dione (116)



A solution of **93** (0.15 g, 0.61 mmol) in absolute DMF (5 mL) was added dropwise to a cooled (-5 to -10 ^oC) suspension of NaH (27 mg, 0.67 mmol, 60% in paraffin, washed twice with hexane) in DMF (3 mL), after 30 min of stirring a solution of 1-bromo-2-chloroethane (0.10 mL, 0.122 mmol) in DMF (5 mL) was added slowly and the reaction mixture was stirred at 69 ^oC for 3 h. After quenching with 50 mL of water the mixture was extracted several times with EtOAc and the combined organic phases were dried with Na_2SO_4. The solvent was removed by reduced pressure to give a crude product which was purified by column chromatography using 40% EtOAc/light petroleum as eluent to obtain compound **116** (0.16 g, 85.1%) as orange crystals, mp 193-194 ^oC.

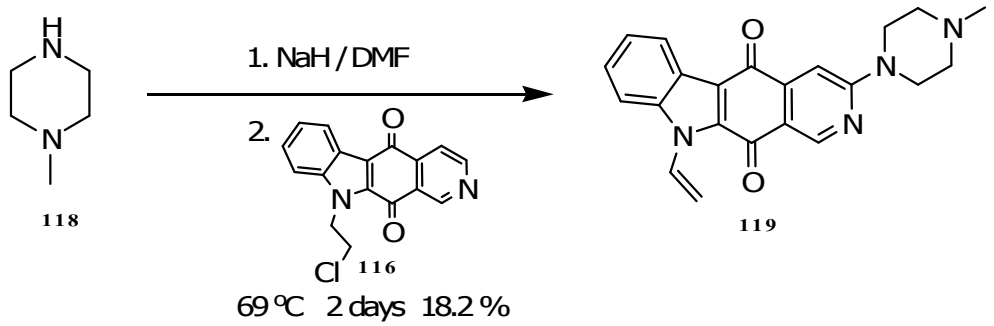
^{1}H NMR (200 MHz, DMSO-d_6): δ = 4.08 (t, 2H, J = 5.8 Hz, $NCH_2\underline{CH_2}Cl$), 5.06 (t, 2H J = 5.8 Hz, $N\underline{CH_2}CH_2Cl$), 7.39-7.57 (m, 2H, H-7, H-8), 7.90 (t, 2H, J = 4.4 Hz, H-4, H-9), 8.24 (d, 1H, J = 7.5 Hz, H6), 9.06 (d, 1H, J = 4.8 Hz, H-3), 9.22 (s, 1H, H- 1).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 43.0 ($NCH_2\underline{C}H_2Cl$), 46.0 ($N\underline{C}H_2CH_2Cl$), 112.8 (C-9),118.0 (C-4), 118.3(C-5a), 122.3 (C-6), 122.6 (C-5b), 125.0 (C-7), 126.2 (C-11a), 127.6 (C-8), 134.7 (C-10a), 138.6 (C-4a), 139.5 (C-9a), 147.4 (C-1), 155.7 (C-3), 177.6 (C-11), 179.3 (C-5).

MS m/e (% relative intensity): M^+ 310(28.8), 283(22.6), 275(100), 261(58.2), 248(19.8), 220(21.8), 191(17.6), 177(8.7), 164(24.3), 151(11.3), 137(22.0), 137(22.0), 114(14.5), 101(7.5), 88(14.1), 63(15.0), 50(19.2).

IR (KBr disc) υ_{max}: 3044, 2923, 2852, 1660, 1584, 1511, 1471, 754 cm^{-1}.

1.16 Synthesis of 3-(4-methylpiperazin-1-yl)-10-vinyl-10H-pyrido[3,4-b] carbazole-5,11-dione (119)



A solution of amine **118** (0.10 mL, 0.90 mmol) in absolute DMF (5 mL) was added dropwise to a cooled (-5 to -10 °C) suspension of NaH (27 mg, 0.67 mmol, 60% in paraffin, washed twice with hexane) in DMF (3 mL), after 30 min of stirring **116** (94 mg, 0.30mmol) in DMF (5 mL) was added slowly and the reaction mixture was stirred at 69 °C for 2 days. After quenching with 50 mL of water the mixture was extracted several times with EtOAc and the combined organic phases were dried with Na_2SO_4. The solvent was removed by reduced pressure to give the crude product which was purified by column chromatography, using EtOAc to 5% MeOH/EtOAc as eluent to obtain compound **119** (21mg, 18.2%) as red crystals, mp. 199-200 °C.

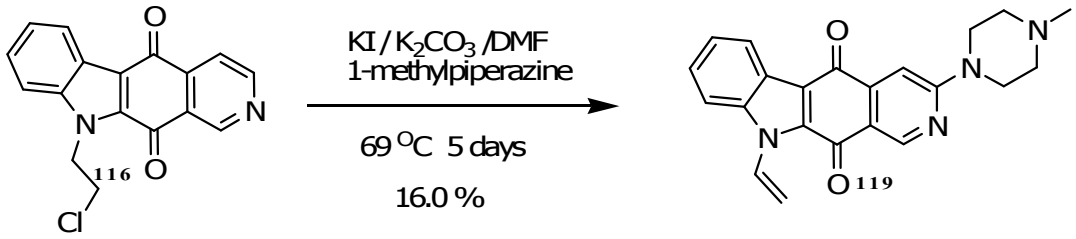
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.36 (s, 3H, N$\underline{CH_3}$), 2.54 (m, 4H, $(CH_3)N\underline{CH_2})_2$-piperazine), 3.87 (m, 4H, (-N($\underline{CH_2}$)$_2$-piperazine), 5.54 (dd,1H, J = 0.9, 8.8 Hz, $\underline{CH_2}$=CH), 5.66 (dd, 1H, J = 0.9, 15.9 Hz) 7.24 (s, 1H, H-4), 7.40 (d, 1H, J = 5.0 Hz, H-7) 7.44 (d, 1H, J = 5.0 Hz, H-8), 7.76 (d, 1H, J = 8.8 Hz, H-9), 7.85 (dd, 1H, J = 8.8, 15.9 Hz, CH_2=$\underline{CH}$), 8.40 (d, 1H, J = 5.0 Hz, H-6), 8.88 (s, 1H, H-1).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 44.8 (-N($\underline{C}H_2)_2$-piperazine), 46.1 (N$\underline{C}H_3$), 54.7 ((CH_3)N $\underline{C}H_2)_2$- piperazine), 101.5 (C-4), 110.8 ($\underline{C}H_2$=CH), 112.9 (C-9), 116.9(C-11a), 119.1 (C-5a), 123.6 (C-6), 124.9 (C-7), 127.7 (C-8), 131.6 (CH_2=$\underline{C}$H), 137.8 (C-9a), 141.2 (C-4a), 149.8 (C-1), 161.1 (C-3), 176.8 (C-11), 180.6 (C5).

HRMS (M^++1) calculated $C_{22}H_{21}O_2N_4$ 373.1665, found 373.1673.

IR (KBr disc) υ_{max}: 2963, 2925, 2854, 2793, 1659, 1595, 1518, 145, 1285 cm^{-1}.

1.17 Synthesis of 3-(4-methylpiperrazin-1-yl)-10-vinyl-10H-pyrido[3,4-b] carbazole-5,11-dione (119)



K_2CO_3 (65 mg, 0.69 mmol), KI (85 mg, 0.51 mmol) and 1-methypeperazine (0.08 mL, 0.36 mmol) were added to a solution of compound **116** (0.105g, 0.33 mmol) in dry DMF (6 mL). The mixture was stirred for 5 days at 69 °C, poured into water (50mL) and extract with EtOAc. The organic layer was washed with brine, dried with Na_2SO_4 and evaporated. The residue was purified by chromatography, using EtOAc to 5% MeOH/EtOAc as eluent to obtain compound **119** (20 mg, 16.1%) as red crystals, mp 199-200 °C.

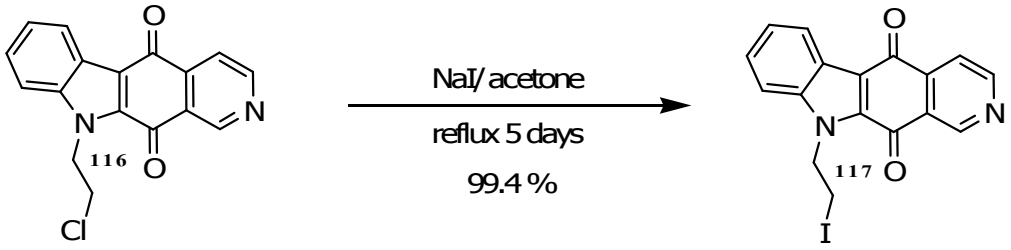
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.36 (s, 3H, N$\underline{C}H_3$), 2.54 (m, 4H, CH_3N($\underline{C}H_2)_2$-piperazine), 3.87 (m, 4H, -N($\underline{C}H_2)_2$-piperazine), 5.54 (dd,1H, J = 0.9, 8.8 Hz, $\underline{C}H_2$=CH), 5.66 (dd, 1H, J = 0.9, 15.9 Hz) 7.24 (s, 1H, H-4), 7.40 (d, 1H, J = 5.0 Hz, H-7) 7.44 (d, 1H, J = 5.0 Hz, H-8), 7.76 (d, 1H, J = 8.8 Hz, H-9), 7.85 (dd, 1H, J = 8.8, 15.9 Hz, CH_2=$\underline{C}$H), 8.40 (d, 1H, J = 5.0 Hz, H-6), 8.88 (s, 1H, H-1).

^{13}C NMR (125MHz, $CDCl_3$): δ = 44.8 (-N($\underline{C}H_2)_2$-piperazine), 46.1 (N$\underline{C}H_3$), 54.7 CH_3)N $\underline{C}H_2)_2$- piperazine), 101.5 (C-4), 110.8 ($\underline{C}H_2$=CH), 112.9 (C-9), 116.9(C-11a), 119.1 (C-5a), 123.6 (C-6), 124.9 (C-7), 127.7 (C-8), 131.6 (CH_2=$\underline{C}$H), 137.8 (C-9a), 141.2 (C-4a), 149.8 (C-1), 161.1 (C-3), 176.8 (C-11), 180.6 (C5).

HRMS (M^++1) calculated $C_{22}H_{21}O_2N_4$ 373.1665, found 373.1673.

IR (KBr disc) υ_{max}: 2963, 2925, 2854, 2793, 1659, 1595, 1518, 145, 1285 cm^{-1}.

1.18 Synthesis of 10-(2-iodoethyl)-10H-pyrido[3,4-b]carbazole-5,11-(10H)-dione (117)



To a solution of compound **116** (0.25 g, 0.81 mmol) in acetone (30 mL) was added NaI (1.22 g, 8.14 mmol) in one portion and the resulting mixture was refluxed for 5 days. After cooling down to RT, acetone was removed by distillation under reduced pressure to give a crude product which was purified by column chromatography, using 40% EtOAc/ light petroleum as eluent to obtain compound **117** (0.325g, 99.4%) as orange crystals, mp 209-210 ^{o}C.

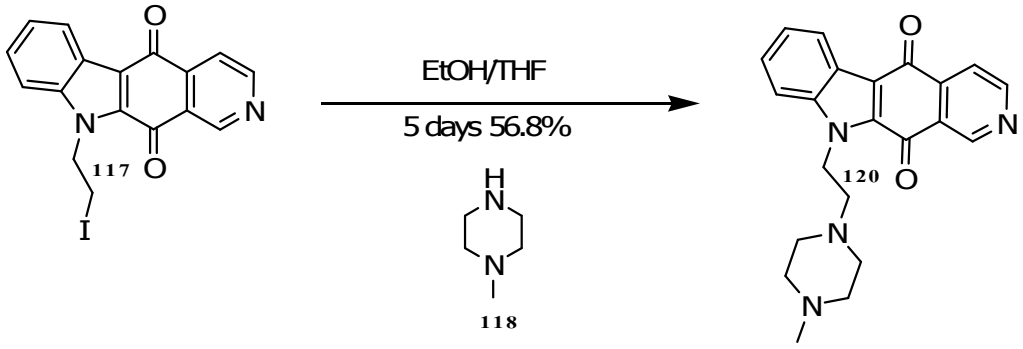
^{1}H NMR (200 MHz, DMSO-d_6): δ = 3.58 (t, 2H, J = 7.2 Hz, $NCH_2\underline{CH_2}I$), 5.04 (t, 2H J = 7.2 Hz, $N\underline{CH_2}CH_2I$), 7.39-7.57 (m, 2H, H-7, H-8), 7.88 (t, 2H, J = 4.9 Hz, H-4, H-9), 8.22 (d, 1H, J = 7.7 Hz, H6), 9.06 (d, 1H, J = 4.9 Hz, H-3), 9.21 (s, 1H, H-1).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 2.5 ($NCH_2\underline{C}H_2I$), 46.4 ($N\underline{C}H_2CH_2I$), 112.6 (C-9),118.1 (C-5a), 118.3 (C-4) 122.4 (C-6), 122.8 (C-5b), 125.1 (C-7), 126.2 (C-11a), 127.6 (C-8) 134.3 (C-10a), 138.7 (C-4a), 138.8 (C-9a), 147.4 (C-1), 155.7 (C-3), 177.6 (C-11), 179.3 (C-5).

MS m/e (% relative intensity): M+ 402(8.7), 275(100), 261(14.8), 219(14.1), 191(16.3), 164(23.2), 137(19.8), 50(28.2).

IR (KBr disc) υ_{max}: 3041, 2924, 1653, 1584, 1511, 1472 cm^{-1}.

1.19 Synthesis of 10-[4-(1-methypeperazine)]-10H-pyrido[3,4-b]carbazole-5,11-dione (120)



1-Methylpiperazine **118** (0.69 mL, 6.3 mmol) was added into the solution of compound **117** (0.126g, 0.31 mmol) in ethanol (10 mL) and THF (2 mL) in a sealed tube. The mixture was heated for 7 days at 75 ^{o}C. After the solvent was evaporated, the residue was purified by column chromatography, using EtOAc to 10% MeOH/EtOAc as eluent to obtain compound **120** (67 mg, 56.8%) as orange crystals, mp 163-164 ^{o}C.

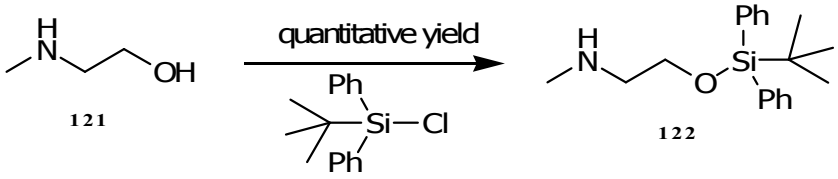
^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.24 (s, 3H, -N$\underline{C}H_3$), 2.39 (s, 4H, $CH_3N(\underline{C}H_2)_2$-piperazine) 2.61 (s, 4H, -$CH_2N(\underline{C}H_2)_2$-piperazine), 2.77 (t, 2H, J = 7.0 Hz)4.83 (t, 2H, J = 6.9), 7.40-7.49 (m, 3H, H-7, H-8, H-9), 7.97 (d, 1H, J = 4.9 Hz, H4), 8.40 (d, 1H, J = 7.3 Hz, H-6), 9.01 (d, 1H, J = 4.9 Hz, H-3), 9.35 (s, 1H, H-1).

^{13}C NMR (50MHz, $CDCl_3$): δ = 43.0 (-$NCH_2\underline{C}H_2N$-), 45.9 (-NCH_3), 53.3 ($CH_3N(\underline{C}H_2)_2$-piperazine), 55.0 (-$N(\underline{C}H_2)_2$-piperazine), 57.2 (-$N\underline{C}H_2CH_2N$-), 111.2 (C-9), 118.6 (C-4), 119.1 (C-5a), 123.8 (C-6), 124.3 (C-5b), 125.0 (C-7), 126.5 (C-11a), 127.7 (C-8), 134.6 (C-10a), 139.4 (C-4a, C-9a), 148.2 (C-1), 155.5 (C-3), 178.1 (C-11), 179.5 (C-5).

HRMS (M^++1) calculated $C_{22}H_{23}O_2N_4$ 375.1821, found 375.1671.

IR (KBr disc) υ_{max}: 2963, 2925, 2854, 2793, 1659, 1595, 1518, 145, 1285 cm^{-1}.

1.20 Synthesis of tert-butyl-[2-(methylamino)ethanol]-diphenylsilane (122)



To solution of tert-butyldiphenylchlorosilane (8.0 mL, 31.2 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of 2-(methylamino)ethanol **121** (2.5 mL, 31.2 mmol) in CH_2Cl_2 (34 mL) and allowed cool at 0 ^oC for 1 h. Then the mixture was warm up to RT and continuously stirred for 2 h. Then the water was added and the mixture was extracted with EtOAc. The combined organic layers were washed with water and dried with Na_2SO_4 and the solvent was evaporated to give compound **122** in quantitative yield as colorless oil.

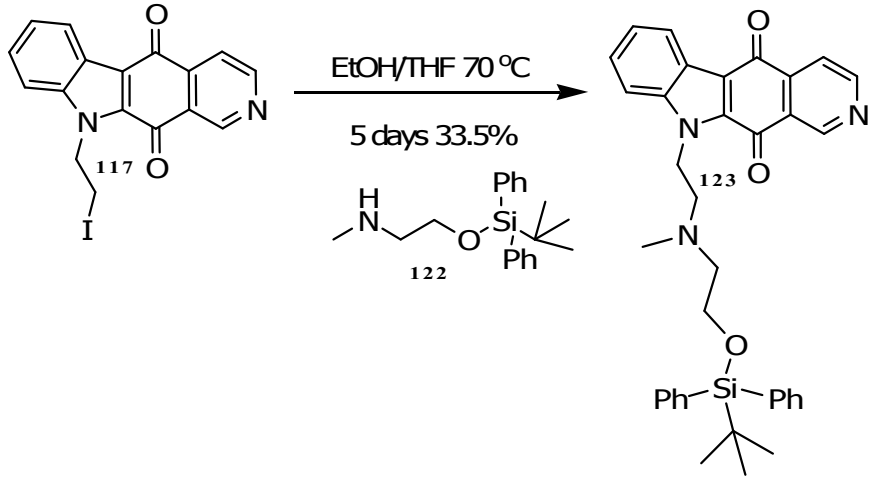
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.06 (s, 9H, C($\underline{CH_3}$)$_3$), 2.49 (s, 3H, N$\underline{CH_3}$), 2.77 (t, 2H, J =5.3 Hz,NHCH$_2\underline{CH_2}$O), 3.53 (s, 1H, N$\underline{H}$), 3.81 (t, 2H, J = 5.1 Hz, NH$\underline{CH_2}$CH$_2$O), 7.37-7.41 (m, 6H, Ph), 7.64-7.68 (m, 4H, Ph).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.0 ($\underline{C}$(CH$_3$)$_3$), 26.6 (C($\underline{C}$H$_3$)$_3$), 35.7 (N$\underline{C}$H$_3$), 53.0 (NH$\underline{C}$H$_2$CH$_2$O), 62.3 (NHCH$_2\underline{C}$H$_2$O), 127.5 (Ph), 129.5 (Ph), 133.2 (Ph), 135.3 (Ph).

MS m/e (% relative intensity): 256(100), 211(4.4), 199(18.6), 183(11.9), 178(49.3), 105(15.3), 77(11.0), 44(84.5).

IR (NaCl disc) υ_{max}: 3471, 3049, 2931, 2790, 2460, 1589, 1471, 1427, 1103, 947,705 cm^{-1}.

1.21 Synthesis of 10-(2-((2-(tert-butyldiphenylsilyloxy)ethyl)(methyl)amino)ethyl) -10H-pyrido[3,4-b]carbazol-5,11-dione (123)



Compound **122** (0.93 g, 2.98 mmol) was added into the solution of compound **117** (0.12g, 0.29 mmol) in ethanol (10 mL) and THF (2 mL) in a sealed tube. The mixture was heated for 6 days at 70 °C. After the solvent was evaporated, the residue was purified by column chromatography, using 40% EtOAc/light petroleum as eluent to afford compound **123** (57 mg, 33.5%) as orange crystals, mp 65-66 °C.

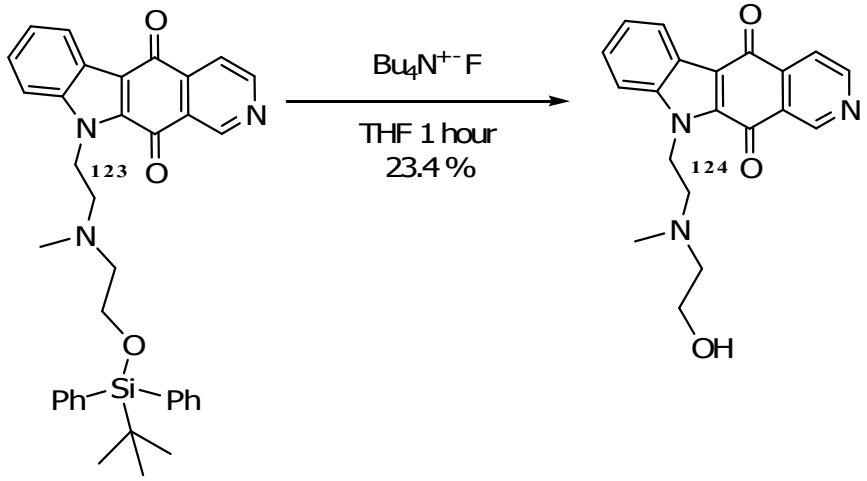
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.99 (s, 9H, C($\underline{C}H_3)_3$), 2.39 (s,3H, N$\underline{C}H_3$), 2.67 (t, 2H, J = 6.2 Hz, NCH$_2\underline{C}H_2$O), 2.85 (t, 2H, J = 7.2 Hz, NCH$_2\underline{C}H_2$N), 3.64 (t, 2H, J = 6.2 Hz, N$\underline{C}H_2$CH$_2$O), 4.77 (t, 2H, J = 6.9 Hz, N$\underline{C}H_2$CH$_2$N), 7.32-7.44 (m, 9H), 7.59-7.63 (m, 4H), 7.89 (d, 1H, J = 4.8 Hz), 9.02 (d, 1H, J = 4.9 Hz), 9.35 (s, 1H).

^{13}C NMR (50MHz, $CDCl_3$): δ = 19.0 ($\underline{C}(CH_3)_3$), 26.7 (C($\underline{C}H_3)_3$), 43.3(N$\underline{C}H_3$) 43.7 (N$\underline{C}H_2$CH$_2$O-) 57.2 (NCH$_2\underline{C}H_2$N), 59.5 (-N$\underline{C}H_2$CH$_2$N), 62.3 (NCH$_2\underline{C}H_2$O), 111.3 (C-9), 118.6 (C-4), 119.0 (C-5a), 123.0 (C-5b), 123.7 (C-6), 125.0 (C-7), 126.5 (C-11a), 127.6 (Ph), 127.7 (C-8), 129.6 (Ph), 133.5 (Ph), 134.4 (C-10a), 135.5 (Ph), 139.5 (C-4a, C-9a), 148.3 (C-1), 155.4 (C-3), 178.0 (C-11), 179.5 (C-5).

HRMS (M^++1) calculated $C_{36}H_{38}O_3N_3Si$ 588.2682, found 588.2683.

IR (KBr disc) υ_{max}: 3070, 2928, 2855, 1663, 1585, 1509, 1472, 1112, 748, 703 cm^{-1}.

1.22 Synthesis of 10-(2-((2-hydroxylethyl)(methyl)amino)ethyl)-10H-pyrido[3,4-b]carbazol-5,11-dione (124)



A solution of 1M Bu_4NF (0.4 mL, 0.4 mmol) in THF was added to the solution of compound **123** (92 mg, 0.15 mmol) in absolute THF (10 mL) and the resulting mixture was stirred at RT for 1 h, quenched with water (100 mL) and extracted with EtOAc. The organic layer was washed with water and brine, and dried with Na_2SO_4. After filtration and concentration of the filtrate in vacuo, the crude product was purified by chromatography, using 10% MeOH/CH_2Cl_2 as eluent to obtain **124** (11 mg, 23.4%) as red crystals, mp.102-103 ^oC.

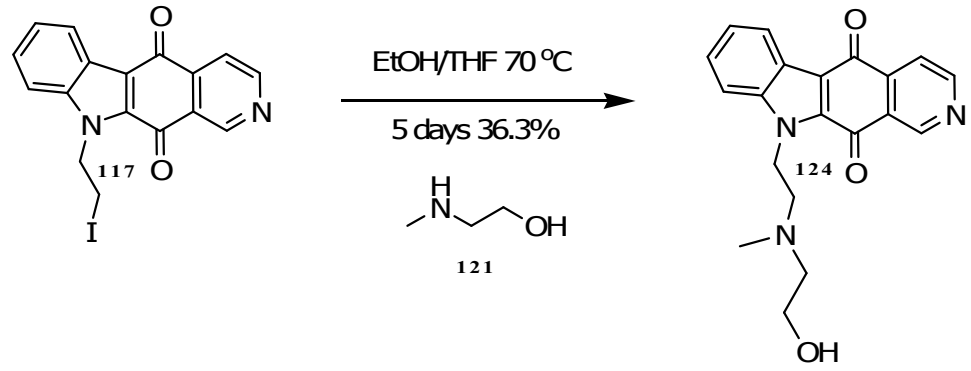
^1H NMR (200 MHz, $CDCl_3$): δ = 2.44 (s,3H, N$\underline{C}H_3$), 2.64 (t, 2H, J = 5.3 Hz, $NCH_2\underline{C}H_2O$), 2.91 (t, 2H, J = 7.0 Hz, $NCH_2\underline{C}H_2N$), 3.50 (t, 2H, J = 5.2 Hz, N$\underline{C}H_2CH_2O$), 4.81 (t, 2H, J = 6.8Hz, N$\underline{C}H_2CH_2N$), 7.41 (dd, 1H, J = 4.0, 7.8Hz, H-8), 7.48 (m, 2H, H-7, H-9), 7.95 (d, 1H, J = 4.9 Hz, H-4), 8.39 (d, 1H, J = 7.7 Hz, H-6), 9.01 (d, 1H, J = 4.9 Hz, H-3), 9.35 (s, 1H, H-1).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 42.1 (N$\underline{C}H_3$) 43.4 (N$\underline{C}H_2CH_2O$-), 56.9 ($NCH_2\underline{C}H_2N$), 58.5 (-N$\underline{C}H_2CH_2N$), 59.1($NCH_2\underline{C}H_2O$), 111.3 (C-9), 118.6 (C-4), 119.2 (C-5a), 123.6 (C-5b), 123.9 (C-6), 125.1 (C-7), 126.4 (C-11a), 128.0 (C-8), 134.1 (C-10a), 139.4 (C-4a), 139.5 (C-9a), 148.2 (C-1), 155.5 (C-3), 178.1 (C-11), 179.4 (C-5).

HRMS (M^++1) calculated $C_{20}H_{20}O_3N_3$ 350.1505 found, 350.1503.

IR (KBr disc) υ_{max}: 3422, 2942, 2850, 1758, 1585, 1514, 1476, 1260 cm^{-1}.

1.23 Synthesis of 10-(2-((2-hydroxylethyl)(methyl)amino)ethyl)-10H-pyrido[3,4-b]carbazol-5,11-dione (124)



Amine **121** (0.27 mL, 3.30 mmol) was added into the solution of compound **117** (69 mg, 0.17 mmol) in ethanol (10 mL) and THF (2 mL) in sealed tube. The mixture was heated for 5 days at 70 ^{o}C. After the solvent was evaporated, the residue was purified by column chromatography, using 10% MeOH/CH_2Cl_2 as eluent to obtain compound **124** (19 mg, 36.3%) as red crystals, mp 102-103 ^{o}C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.44 (s,3H, N$\underline{C}H_3$), 2.64 (t, 2H, J = 5.3 Hz, $NCH_2\underline{C}H_2O$), 2.91 (t, 2H, J = 7.0 Hz, $NCH_2\underline{C}H_2N$), 3.50 (t, 2H, J = 5.2 Hz, -N$\underline{C}H_2CH_2O$), 4.81 (t, 2H, J = 6.8 Hz, N$\underline{C}H_2CH_2N$), 7.41 (dd, 1H, J = 4.0, 7.8 Hz, H-8), 7.48 (m, 2H, H-7, H-9), 7.95 (d,1H, J = 4.9 Hz, H-4), 8.39 (d, 1H, J = 7.7 Hz, H-6), 9.01 (d, 1H, J = 4.9 Hz, H-3), 9.35 (s, 1H, H-1).

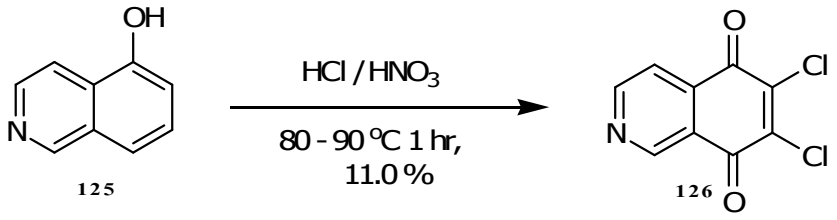
^{13}C NMR (50 MHz, $CDCl_3$): δ = 42.1 (N$\underline{C}H_3$) 43.4 (N$\underline{C}H_2CH_2O$-), 56.9 ($NCH_2\underline{C}H_2N$), 58.5 (-N$\underline{C}H_2CH_2N$), 59.1 ($NCH_2\underline{C}H_2O$), 111.3 (C-9), 118.6 (C-4), 119.2 (C-5a), 123.6 (C-5b), 123.9 (C-6), 125.1 (C-7), 126.4 (C-11a), 128.0 (C-8), 134.1(C-10a), 139.4 (C-4a), 139.5(C-9a), 148.2 (C-1), 155.5 (C-3), 178.1 (C-11), 179.4 (C-5).

HRMS (M^++1) calculated $C_{20}H_{20}O_3N_3$ 350.1505 found, 350.1503.

IR (KBr disc) υ_{max}: 3422, 2942, 2850, 1758, 1585, 1514, 1476, 1260 cm^{-1}

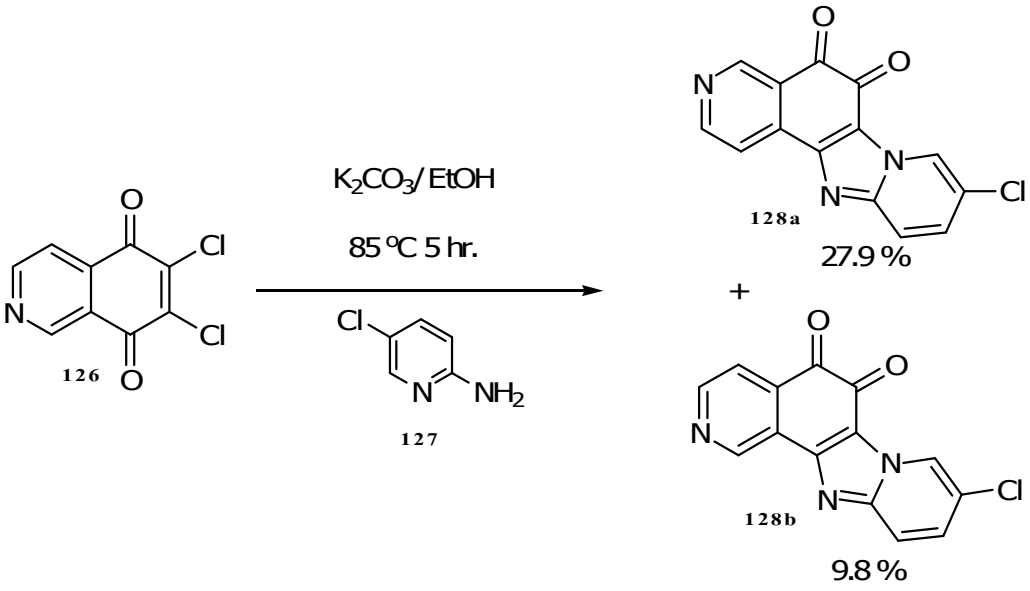
2. Synthesis of benzo[a]fluorine-5,6-dione derivatives

2.1 Synthesis of 6,7-dichloro-5,8-isoquinolinedione (126)



Concentrated HNO_3 (10 mL) was added in portions over 30 minutes to a stirred suspension of 5-hydroxyisoquinoline **125** (11.00 g, 75 mmol) in concentrated HCl (190 mL) at 80-90 ^oC. The resulting mixture was diluted to 2 L by ice water and extracted with ether. The organic phases were combined, extracted with water and dried over Na_2SO_4. After filtration and concentration of the filtrate in vacuo, the crude product was purified by column chromatography, using 1:1 ether:light petroleum as eluent to afforded **126** (1.45 g, 8.44%) as pale-green crystals, mp. 180-181 ^oC. The full characterization of compound **126** is in reference [57].

2.2 Synthesis of 5-chloropyrido[1',2'-1,2]imidazo[4,5-f]isoquinoline-5,6-dione (128a) and 5-chloropyrido[1',2'-2,3]imidazo[4,5-f]isoquinoline-5,6-dione (128b)



K_2CO_3 (0.27 g, 2.2 mmol) and 2-amino-5-chloropyridine **127** (0.37 g, 2.9 mmol) were added to a solution of quinone **126** (0.50g, 2.2 mmol) in ethanol (25 mL). The resulting mixture was refluxed for 5 h then cooled down to RT. The solvent was evaporated and the residue was extracted several times with CH_2Cl_2. The combined organic phases were washed with water and dried with Na_2SO_4, concentrated and then the residue was purified by column chromatography, using EtOAc: light petroleum: MeOH (4:4:1) as eluent to afford **128a** (0.17 g, 27.9%) and **128b** (6 mg, 9.8 %) as yellow crystals, mps: 309-310 ^oC and 251-253 ^oC, respectively.

128a: mp 309-310 ^oC.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.88 (dd, 1H, J = 2.1, 9.5 Hz, H-10), 8.02 (d, 1H, J = 5.0 Hz, H-1), 8.05 (d, 1H, J = 9.5 Hz, H-11), 8.92 (d, 1H, J = 5.1 Hz, H-2), 9.07 (s, 1H, H-4), 9.24 (m, 1H, J = 2.1 Hz, H-8).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 117.5 (C-1), 119.1 (C-11), 121.8 (C-6a), 124.2 (C-9), 125.0 (C-4a), 125.8 (C-8), 132.9 (C-10), 137.5 (C-12b), 147.4 (C-11a), 149.4 (C-4), 149.7 (C-12a), 155.4 (C-2), 167.0 (C-6), 180.3 (C-5).

MS m/e (% relative intensity): M^+ 283(22.7), 255 (100), 227(16.0), 220(8.4), 192(22.8), 165(17.1), 138(7.9), 114(23.8), 100(15.7), 88(27.0), 76(45.0), 57(27.6), 43(24.6).

IR (KBr disc) υ_{max}: 3101, 2923, 2852, 1700, 1651, 1595, 1487, 1408, 821 cm^{-1}.

128b: mp 251-253 ^oC.

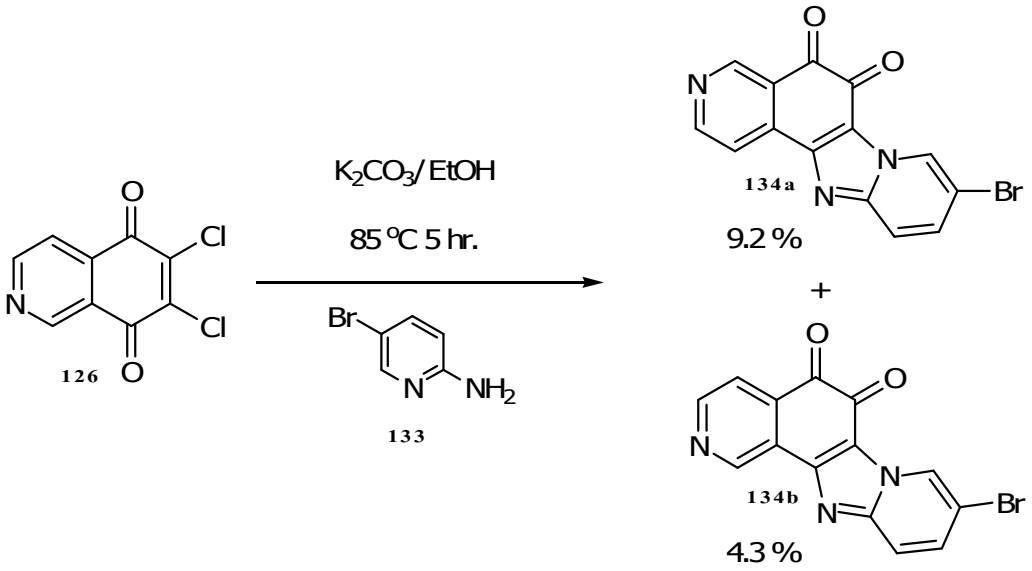
^1H NMR (500 MHz, DMSO-d_6): δ = 7.84 (dd, 1H, J = 5.1 Hz, H-4), 7.91 (S, 1H), 8.06 (d,1H, J = 9.5 Hz, H-11), 8.88 (d, 1H, J = 5.0 Hz, H-3), (d, 1H, J = 5.1 Hz, H-2), 9.24 (s, 1H, H-8), 9.31 (s, 1H, H-1).

^{13}C NMR (125 MHz, DMSO-d_6):δ = 118.9 (C-11), 120.7 (C-4), 121.4 (C-6a), 124.8 (C-9), 125.8 (C-8), 132.9 (C-10), 145.3 (C-1), 152.7 (C-6), 180.1 (C-5).

MS m/e (% relative intensity): M^+ 283(22.7), 255 (100), 227(16.0), 220(8.4), 192(22.8), 165(17.1), 138(7.9), 114(23.8), 100(15.7), 88(27.0), 76(45.0), 57(27.6), 43(24.6).

IR (KBr disc) υ_{max}: 3035, 2923, 1706, 1649, 1494, 1247, 832 cm^{-1}.

2.3. Synthesis of 5-bromopyrido[1',2'-1,2]imidazo[4,5-f]isoquinoline-5,6-dione (134a) and 5-bromopyrido[1',2'-2,3]imidazo[4,5-f]isoquinoline-5,6-dione (134b)



K_2CO_3 (0.32 g, 2.3 mmol) and 2-amino-5-bromopyridine **133** (0.50 g, 2.9 mmol) were added to a solution of quinone **126** (0.52 g, 2.3 mmol) in ethanol (25 mL). The resulting mixture was refluxed for 5 h then cooled down to RT. The solvent was evaporated and extracted with CH_2Cl_2 several times. The combined organic phases were washed with water and dried with Na_2SO_4, concentrated and then the residue was purified by column chromatography, using EtOAc: light petroleum: MeOH (4:4:1) as eluent to afford **134a** (69mg, 9.2%) as red-brown crystals and compound **134b** (32 mg, 4.3%) as red crystals, mps: 249-250 °C and 309-310 °C, respectively.

134a: mp 249-250 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.89 (s, 1H, H-10), 8.00 (s, 1H, H-11), 8.03 (s, 1H, H-1), 8.92 (s, 1H, H-2), 9.06 (s, 1H, H-4), 9.29 (s, 1H, H-8).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 111.4 (C-9), 117.5 (C-1), 119.3 (C-11), 121.8 (C-6a) 125.1 (C-4a), 127.8 (C-8), 133.4 (C-10), 137.6 (C-12b), 147.6 (C-11a), 149.4 (C-4, C12a), 155.6 (C-2), 167.3 (C-6), 180.3 (C-5).

MS m/e (% relative intensity): M^+ 312(100), 312(4.7), 299(16.2), 267(6.8), 218(14.3), 191(10.4), 177(5.3), 156(30.8), 88(20.8), 76(85.9), 63(19.7), 43(20.2).

IR (KBr disc) υ_{max}: 3029, 2923, 2853, 1706, 1646, 1604, 1492, 1249 cm^{-1}.

134b: mp 309-310 ^{o}C.

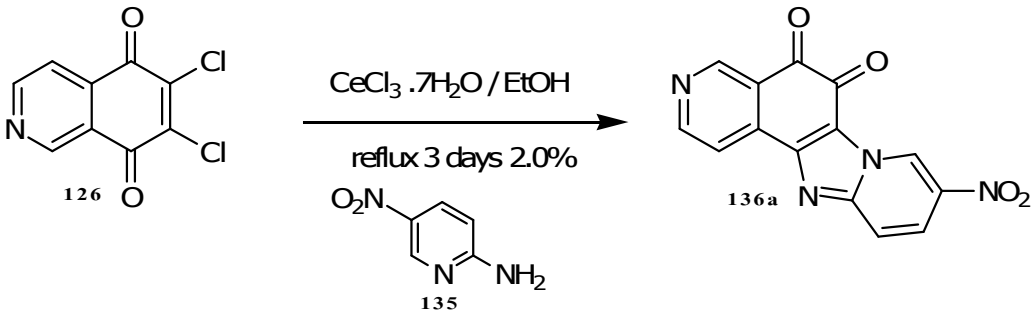
^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.83 (d, 1H, J = 5.0 Hz), 8.88 (d, 1H, J = 5.0 Hz), 9.30 (s, 1H).

^{13}C NMR (125MHz, DMSO-d_6): δ = 120.8 (C-4), 128.8 (C-8), 145.3 (C-1), 152.8 (C-3), 167.2 (C-6), 180.1 (C-5).

MS m/e (% relative intensity): M^{+} 312(100), 312(4.7), 299(16.2), 267(6.8), 218(14.3), 191(10.4), 177(5.3), 156(30.8), 88(20.8), 76(85.9), 63(19.7), 43(20.2).

IR (KBr disc) υ_{max}: 3015, 2923, 2853, 1691, 1641, 1603, 1409, 1251 cm^{-1}.

2.4 Synthesis of 5-nitropyrido[1',2'-1,2]imidazo[4,5-f]isoquinoline-5,6-dione (136a)



$CeCl_3.7H_2O$ (0.63 g, 1.7 mmol) and 2-amino-5-nitropyridine **135** (0.23 g, 1.7 mmol) were added to a solution of quinone **126** (0.39g, 1.7 mmol) in ethanol (25 mL). The resulting mixture was refluxed for 3 days then cooled down to RT. The solvent was evaporated and extracted with CH_2Cl_2 several times. The combined organic phases were washed with water and dried with Na_2SO_4, concentrated and then the residue was purified by column chromatography, using EtOAc:light petroleum:MeOH (4:4:1) as eluent to afford **136a** (40 mg, 2.0%) as yellow crystals, mp 144-145 ^{o}C.

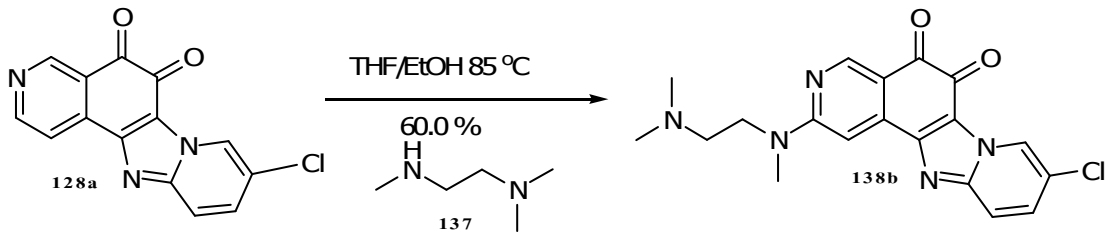
^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.07 (s, 1H), 8.19 (d, 1H, J = 9.9 Hz), 8.46 (dd,1H, J = 2.3, 9.9 Hz), 8.97 (d, 1H, J = 4.9 Hz), 9.11 (s, 1H), 9.94 (dd, 1H, J = 2.3 Hz).

^{13}C NMR (125MHz, DMSO-d_6): δ = 117.7 (C-1), 118.0 (C-11), 122.8 (C-6a), 125.4 (C-4a), 125.8 (C-10), 127.1 (C-8), 137.0 (C-12b), 139.6 (C-9), 149.1 (C-11a), 149.4 (C-4), 151.5 (C-12a), 155.6 (C-2), 167.7 (C-6), 179.6 (C-5).

MS m/e (% relative intensity): M^+ 249(24.2), 221(100), 193(26.9), 166(10.8),139(7.1), 88(11.5), 78(14.5), 51(16.0).

IR (KBr disc) υ_{max}: 3048, 2923, 2852, 1647, 1550, 1305 cm^{-1}.

2.5 Synthesis of 5-chloropyrido[1',2'-1,2]imidazo[4,5-f]-2-((2-(dimethylamino)ethyl)methylamino)isoquinoline-5,6-dione (138b)



N,N,N'-trimethylethylenediamine **137** (0.05 mL, 0.3 mmol) was added to a solution of compound **128a** (25 mg, 0.08 mmol) in ethanol (8 mL) and THF (2 mL) in a sealed tube. The mixture was heated for 5 h at 85 °C. After the solvent was evaporated, the residue was purified by column chromatography, using 10% MeOH/EtOAc as eluent to obtain (18 mg, 60.0%) **138b** as red solid, mp 230-231 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.34 (s, 6H, N($\underline{CH_3}$)$_2$), 2.62 (t, 2H, J = 6.9 Hz,$(CH_3)_2N\underline{CH_2}$), 3.31 (s, 3H, $N\underline{CH_3}$), 3.92 (s, brs, 2H, $(CH_3)_2NCH_2\underline{CH_2}$), 7.18 (s,1H, H-1), 7.58 (d, 1H, J = 9.5 Hz, H-10), 7.75 (d, 1H, J = 9.5 Hz, H-11), 8.90 (s, 1H, H-4), 9.37 (s, 1H, H-8).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.3 ($N\underline{C}H_3$), 45.6 (N($\underline{C}H_3$)$_2$), 48.3 $(CH_3)_2NCH_2\underline{C}H_2$), 56.7 $(CH_3)_2N\underline{C}H_2$), 99.7 (C-1), 114.7 (C-4a), 118.3 (C-11), 121.7 (C-6a), 124.8 (C-9), 126.6 (C-8), 132.7 (C-10), 138.1 (C-12b), 147.8 (C-11a), 151.3 (C-12a), 159.8 (C-4), 160.9 (C-2), 170.1 (C-6), 178.4 (C-5).

HRMS (M^++1) calculated $C_{19}H_{19}O_2ClN_2$ 384.1227 found 384.1225.

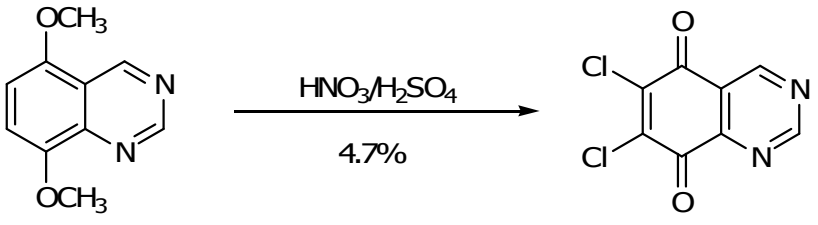
IR (KBr disc) υ_{max}: 2924, 2853, 1649, 1600, 1540, 730 cm^{-1}.

2.6 Synthesis of 5,8-dimethoxyquinazoline (140)

139 140

To a suspension of compound **139** (21.70 g, 76.6 mmol) in ice (210 g), glacial acetic acid (102 mL) and Zn metal (69.0g) were added in small portions during 1 h while the reaction mixture was vigorously stirred in an ice bath. The resulting mixture then was warmed to RT, and additional Zn (19.0 g) was added in small portions. Stirring was continued for a further 1.5 h. The reaction mixture was filtered into a solution of 50% NaOH (480 mL). The yellow suspension was extracted with ether. The combined organic phases were washed with water, dried with Na_2SO_4 and evaporated to give a light yellow solid which was used without purification for the next step. The full characterization of compound **140** is in reference [57].

2.7 Synthesis of 6,7-dichloro-5,8-quinazolinedione (141)

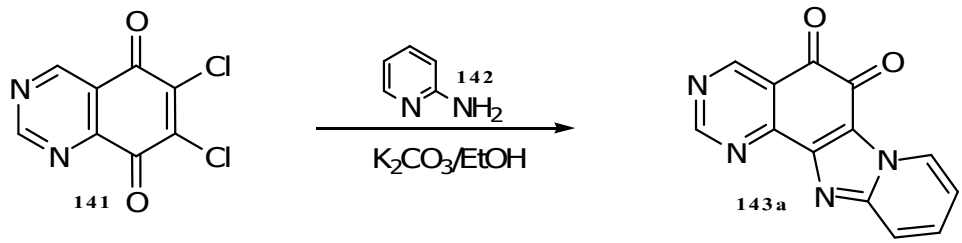


140 141

Concentrated HNO_3 (5 mL) was added in portions over 15 min to a stirred solution of compound **140** (7.60g, 40 mmol) in concentrated HCl (100 mL) at 80-90 ^oC. The solution mixture was cooled to RT and diluted with water (1L) and extracted with ether. The combined organic layers were washed with water and brine and dried with Na_2SO_4. After,

filtration and concentration of the filtrate in vacuo, the crude product was purified by chromatography, using 1:1 ether: light petroleum as eluent to give **141** (1.73 g, 4.76%) as pale-yellow, mp 135-136 ^{o}C crystals. The full characterization of compound **141** is in reference [57].

2.8 Synthesis of pyrido[1',2'-1,2]imido[4,5-f]quinazoline-5,6-dione (143a)



K_2CO_3 (60 mg, 0.4 mmol) and 2-aminopyridine **142** (49 mg, 0.5 mmol) were added to a solution of quinone **141** (99 mg, 0.4 mmol) in ethanol 20 mL. The resulting mixture was refluxed for 4 h, then cooled down to RT. The solvent was evaporated and the residue was extracted with CH_2Cl_2 several times. The combined organic phases were washed with water and dried with Na_2SO_4, concentrated and then the residue was purified by column chromatography, using EtOAc:light petroleum:MeOH (4:4:1) as eluent to afford compound **143a** (50 mg, 46.2%) as red crystals, mp: 273 ^{o}C (decomp.).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48 (m, 1H, H-9), 7.85 (m, 1H, H-10), 8.07 (m, 1H, H-11), 9.20 (s,1H, H-4), 9.29 (m, 1H, H-8), 9.46 (s, 1H, H-2).

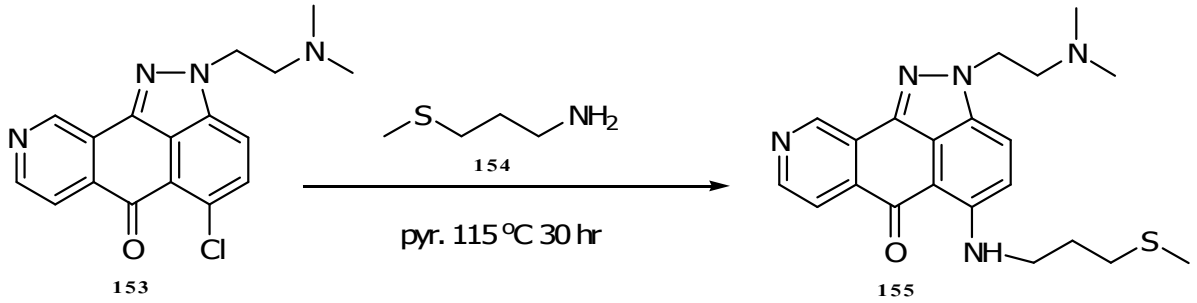
^{13}C NMR (125 MHz, $CDCl_3$): δ = 118.2 (C-9), 118.9 (C-11), 123.9 (C-6a), 124.7 (C-4a)128.2 (C-8), 132.6 (C-10), 149.0 (C-11a), 149.1 (C12a), 156.0 (C-4), 156.2 (C-12b), 161.9 (C-2), 166.7 (C-6), 179.4 (C-5).

MS m/e (% relative intensity): M^+ 250(18.2), 222(100), 194(18.6), 167(43.1), 84 (19.1), 78(36.0), 51(37.4).

IR (KBr disc) υ_{max}: 3123, 3029, 2923, 1709, 1669, 1653, 1646, 1363 cm^{-1}.

3. Synthesis of anthrapyrazole derivatives

3.1 Synthesis of 2-(2-(dimethylamino)ethyl)-5-(3-(methylthio)propylamino)indazolo[4,3-gh] isoquinoline-6(2H)-one (155)



A solution of 3-(methylthio)-propylamine **154** (0.14 g, 1.31 mmol) in absolute pyridine (2 mL) was added to a solution of compound **153** (0.1g, 0.30 mmol) in absolute pyridine (6 mL). The resulting mixture was then heated to 115 ^{o}C under argon atmosphere. After 30 h, the solvent was removed in vacuo and the water was added and extracted with CH_2Cl_2 several times. The combined organic phases were washed with water and dried with Na_2SO_4, concentrated and the residue was purified by column chromatography, using 10% MeOH/CH_2Cl_2 as eluent to afford **155** (70 mg, 58.3%) as brown crystals, mp 70-71 ^{o}C.

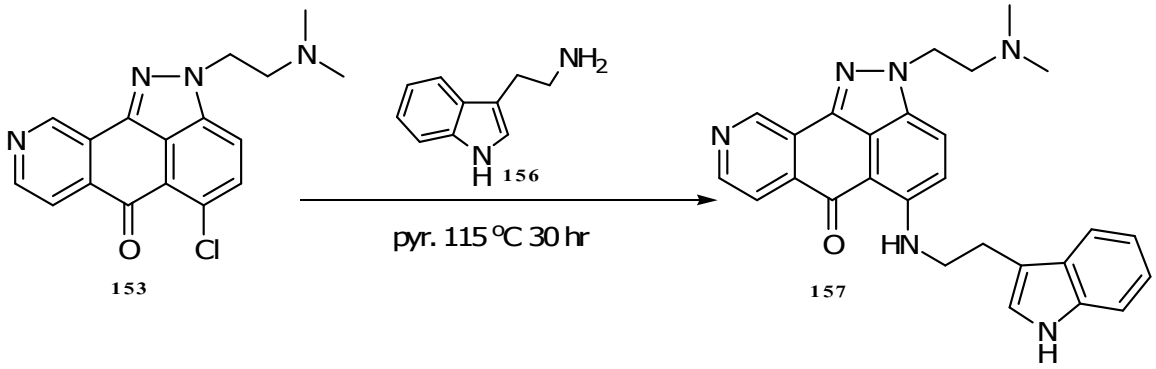
^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.07 (t, 2H, J = 6.8 Hz, $\underline{CH_2}SCH_3$) 2.13 (s, 3H, $S\underline{CH_3}$),2.31 (s, 6H, $N(\underline{CH_3})_2$), 2.68 (t, 2H, J = 6.9 Hz, $CH_2\underline{CH_2}N(CH_3)_2$), 2.91 (t, 2H, J = 6.7 Hz, $NH\underline{CH_2}$),3.60 (m, 2H, $NHCH_2\underline{CH_2}CH_2S$), 4.60 (t, 2H, J = 6.8 Hz, $\underline{CH_2}CH_2N(CH_3)_2$), 6.98 (d, 1H, J = 9.2 Hz, H-4), 7.66 (d, 1H, J = 9.2 Hz, H-3), 8.25 (d, 1H, J = 5.2 Hz, H-7) 8.77 (d, 1H, J = 5.3 Hz, H-8), 9.20 (t, 1H, J = 5.4 Hz N$\underline{H}$), 9.62 (s, 1H, H-10).

^{13}C NMR (50MHz, $CDCl_3$): δ = 15.5 ($S\underline{C}H_3$), 28.5 ($\underline{C}H_2SCH_3$), 31.4 ($NHCH_2\underline{C}H_2$), 41.6 ($NH\underline{C}H_2$), 45.7 ($N(\underline{C}H_3)_2$), 48.8 ($\underline{C}H_2CH_2N(CH_3)_2$), 59.2 ($CH_2\underline{C}H_2N(CH_3)_2$), 104.9 (C- 5a), 113.3 (C-7), 120.2 (C-4), 120.4 (C-3), 122.8 (C-10c), 125.2 (C-2a), 130.8 (C-10b), 134.0 (C-10a), 137.9 (C-5), 145.6 (C-8), 147.6 (C-10), 150.2 (C-6a), 180.8 (C-6).

HRMS (M^{+}+1) calculated $C_{21}H_{26}ON_5S$ 396.1858, found 396.1847.

IR (KBr disc) υ_{max}: 3273, 2948, 2921, 2855, 1652, 1604, 1604, 1559 cm^{-1}.

3.2 Synthesis of 5-(2-(1H-indol-3-yl)ethylamino)-2-(2-(dimethylamino)ethyl)indazolo [4,3-gh]isoquinoline-6(2H)-one (157)



A solution of tryptamine **156** (0.44 g, 2.74 mmol) in absolute pyridine (2 mL) was added to a solution of compound **153** (0.18g, 0.55 mmol) in absolute pyridine (6 mL). The resulting mixture was then heated to 115 ^{o}C under argon atmosphere. After 30 h, the solvent was removed in vacuo and the water was added and extracted with CH_2Cl_2 several times. The combined organic phases were washed with water and dried with Na_2SO_4, concentrated and the residue was purified by column chromatography, using 10% MeOH/CH_2Cl_2 as eluent to afford **157** (0.15 g, 61.5%) as reddish crystals, mp 126-127 ^{o}C.

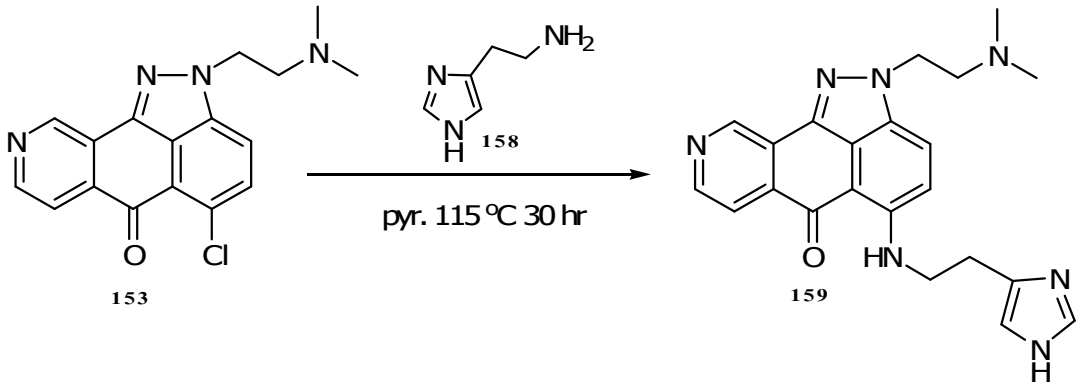
^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.33 (s, 6H, N($\underline{CH_3}$)$_2$), 2.90 (t, 2H, J = 6.8 Hz, $CH_2\underline{CH_2}N(CH_3)_2$), 3.23 (t, 2H, J = 6.7 Hz, $\underline{CH_2}$-indole), 3.73 (m, 2H, NH$\underline{CH_2}$), 4.54 (t, 2H, J = 6.8 Hz, $\underline{CH_2}CH_2N(CH_3)_2$), 6.79 (d, 1H, J = 9.2 Hz, H-4), 7.10-7.20 (m, 3H, indole), 7.38 (m, 2H, indole), 7.65 (d, 1H, J = 6.7 Hz, H-3), 8.21 (d, 1H, J = 7.2 Hz, H-7), 8.55 (s, brs, 1H, N$\underline{H}$ indole), 8.75 (d, 1H, J = 5.3 Hz, H-8), 9.20 (t, 1H, J = 5.2 Hz, N$\underline{H}CH_2$), 9.55 (s, 1H, H-10).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 24.9 ($\underline{C}H_2$-indole), 43.0 (N($\underline{C}H_3$)$_2$), 45.1 (NH$\underline{C}H_2$), 47.9($\underline{C}H_2CH_2N(CH_3)_2$), 58.8 ($CH_2\underline{C}H_2N(CH_3)_2$), 103.5 (C-5a), 110.8 (C- indole), 111.4 (C- indole), 113.9 (C-7), 118.3 (C-3,C-4), 120.0 (C-indole), 121.0 (C-indole), 121.7 (C-10c), 122.0 (C- indole), 123.3 (C- indole),124.6 (C-2a), 127.0 (C- indole), 130.7 (C-10b), 132.5 (C-10a), 136.3 (C- indole), 137.2 (C-5), 144.8 (C-8), 147.3 (C-10), 149.8 (C-6a), 178.9 (C-6).

HRMS (M^{+}+1) calculated $C_{27}H_{27}ON_6$ 451.2246, found 451.2236.

IR (KBr disc) υ_{max}: 3258, 2922, 2857, 1653, 1603, 1506 cm^{-1}.

3.3 Synthesis of 5-(2-(1H-imidazol-4-yl)ethylamino)-2-(2-(dimethylamino)ethyl)indazolo[4,3-gh]isoquinoline-6(2H)-one (159)



A solution of histamine **158** (0.21 g, 1.92 mmol) in absolute pyridine (2 mL) was added to a solution of compound **153** (0.10 g, 0.30 mmol) in absolute pyridine (6 mL). The resulting mixture was then heated to 115 ^{o}C under argon atmosphere. After 30 h, the solvent was removed in vacuo and the water was added and extracted with CH_2Cl_2 several times. The combined organic phases were washed with water and dried with Na_2SO_4, concentrated and the residue was purified by column chromatography, using 30% MeOH/CH_2Cl_2 as eluent to afford **159** (70 mg, 58.3%) as red crystals, mp 147-148 ^{o}C.

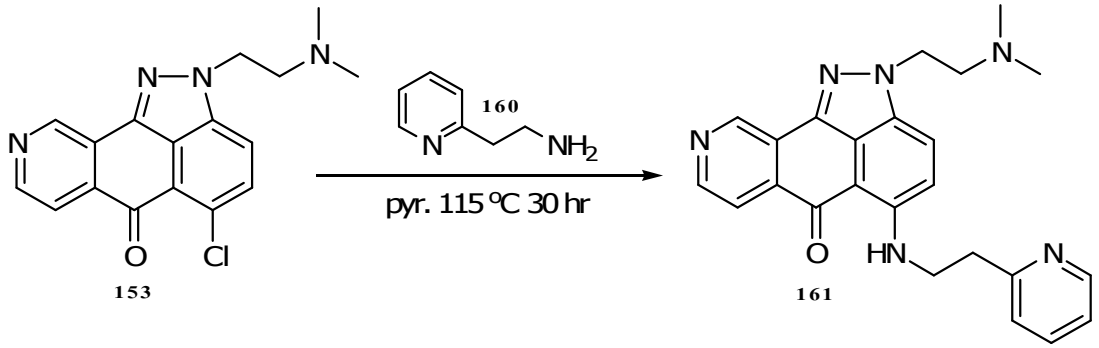
^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.28 (s, 6H, N($\underline{CH_3}$)$_2$), 2.85 (t, 2H, J = 6.5 Hz, $CH_2\underline{CH_2}N(CH_3)_2$) 3.03 (d, 2H, J = 6.2 Hz, $\underline{CH_2}$-imidazole), 3.65 (d, 2H, J = 5.8 Hz, NH$\underline{CH_2}$), 4.45 (t, 2H, J = 6.5 Hz, $\underline{CH_2}CH_2N(CH_3)_2$), 6.70 (d, 1H, J = 6.5 Hz, H-4), 6.96 (s, 1H, imidazole), 7.37 (d, 1H, J = 9.2 Hz, H-3), 7.61 (s, 1H, imidazole), 8.05 (d, 1H, J = 5.2 Hz, H-7), 8.65 (d, 1H, J = 5.3 Hz, H-8), 9.01 (s, 1H, N$\underline{H}$), 9.39 (s, 1H, H-10).

^{13}C NMR (50MHz, $CDCl_3$): δ = 29.6 ($\underline{C}H_2$-imidazole), 43.0 (NH$\underline{C}H_2$), 45.5 (N($\underline{C}H_3$)$_2$), 48.5 ($CH_2\underline{C}H_2N(CH_3)_2$), 59.0 ($\underline{C}H_2CH_2N(CH_3)_2$), 104.5 (C-5a), 113.2 (C-7), 116.2 (C-imidazole), 119.9 (C-4), 120.0 (C-3), 122.4 (C-10c), 124.9 (C-2a), 130.5 (C-10b), 133.5 (C-10a), 135.2 (C-imidazole), 135.5 (C-imidazole), 137.7 (C-5), 145.2 (C-8), 147.2 (C-10), 149.8 (C-6a), 180.0 (C-6).

HRMS (M^++1) calculated $C_{22}H_{22}ON_7$ 402.2042, found 402.2025.

IR (KBr disc) υ_{max}: 3422, 2925, 2864, 2653, 1603, 1560, 1223 cm^{-1}

3.4 Synthesis of 2-(2-(dimethylamino)ethyl)-5-(2-(pyridin-2yl)ethylamino)indazolo[4,3-gh]isoquinoline-6(2H)-one (161)



153 161

A solution of 2-(2-aminoethyl)pyridine **160** (0.2 mL, 1.67 mmol) in absolute pyridine (2 mL) was added to a solution of compound **153** (0.10 g, 0.30 mmol) in absolute pyridine (6 mL). The resulting mixture was then heated to 115 ^{o}C under argon atmosphere. After 30 h, the solvent was removed in vacuo and the water was added and extracted with CH_2Cl_2 several times. The combined organic phases were washed with water and dried with Na_2SO_4, concentrated and the residue was purified by column chromatography, using 20% MeOH/CH_2Cl_2 as eluent to afford **161** (0.10 g, 47.4%) as reddish oil.

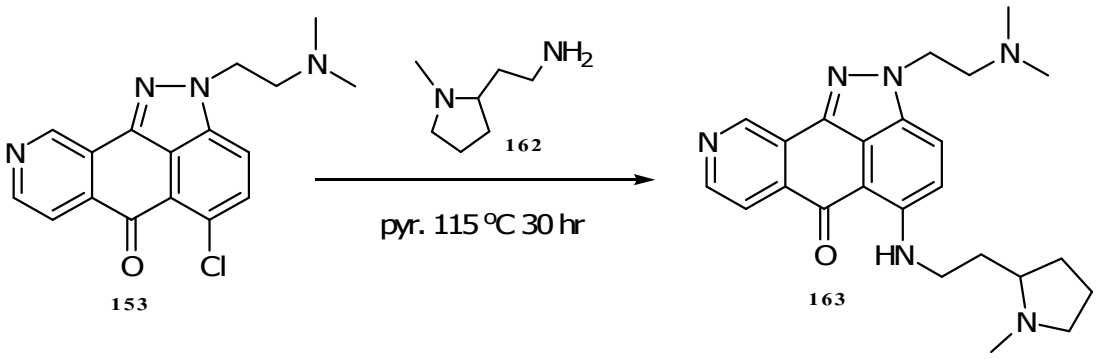
^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.31 (s, 6H, N($\underline{CH_3}$)$_2$), 2.92 (t, 2H, J = 6.9 Hz, $CH_2\underline{CH_2}N(CH_3)_2$), 3.23 (t, 2H, J = 7.0 Hz, $\underline{CH_2}$-pyridine), 3.92 (m, 2H, NH$\underline{CH_2}$), 4.61 (t, 2H, J = 6.7 Hz, $\underline{CH_2}CH_2N(CH_3)_2$), 7.03 (d, 1H, J = 9.0 Hz,H-4), 7.13-7.22 (m, 3H, pyridine), 7.59 (dd, 1H, J = 2.0, 7.7 Hz, H-3), 8.26 (d, 1H, J = 5.3 Hz, H-7), 8.60 (d, 1H, J = 4.7 Hz, pyridine), 8.76 (d, 1H, J = 5.1 Hz, H-8), 9.31 (t, 1H, J = 5.3 Hz, N$\underline{H}$), 9.63 (s, 1H, H-10).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 38.0 ($\underline{C}H_2$-pyridine), 42.8 (NH$\underline{C}H_2$), 45.6 (N($\underline{C}H_3$)$_2$), 48.8 ($CH_2\underline{C}H_2N(CH_3)_2$), 59.1 ($\underline{C}H_2CH_2N(CH_3)_2$), 105.0 (C-5a), 113.5 (C-7), 120.3 (C-3, C-4), 121.8 (C-pyridine), 122.9 (C-10a), 123.6 (C-pyridine), 125.2 (C-2a), 130.9 (C-10b), 134.1 (C-10a), 136.6 (C-pyridine), 138.0 (C-5), 145.6 (C-8), 147.6 (C-10), 149.6 (C-pyridine), 150.1 (C-6a), 158.2(C-pyridine), 180.8 (C-6).

HRMS (M^++1) calculated $C_{24}H_{25}ON_6$ 413.2090, found 413.2099.

IR (NaCl disc) υ_{max}: 3289, 3053, 1947, 2854, 2824, 1653, 1607, 1560, 1265, 737 cm^{-1}.

3.5 Synthesis of 2-(2-(dimethylamino)ethyl)-5-(2-(1-methylpyrrolidine-2-yl)ethylamino)indazolo[4,3-gh]isoquinoline-6(2H)-one (163)



A solution of 2-(2-aminoethyl)-1-methylpyrrolidine **162** (0.3 mL, 1.31 mmol) in absolute pyridine (2 mL) was added to a solution of compound **153** (0.12 g, 0.37 mmol) in absolute pyridine (6 mL). The resulting mixture was then heated to 115 ^{o}C under argon atmosphere. After 30 h, the solvent was removed in vacuo and the water was added and extracted with CH_2Cl_2 several times. The combined organic phases were washed with water and dried with Na_2SO_4, concentrated and the residue was purified by column chromatography, using 30% MeOH/CH_2Cl_2 as eluent to provide **163** (0.14 g, 85.8%) as dark oil.

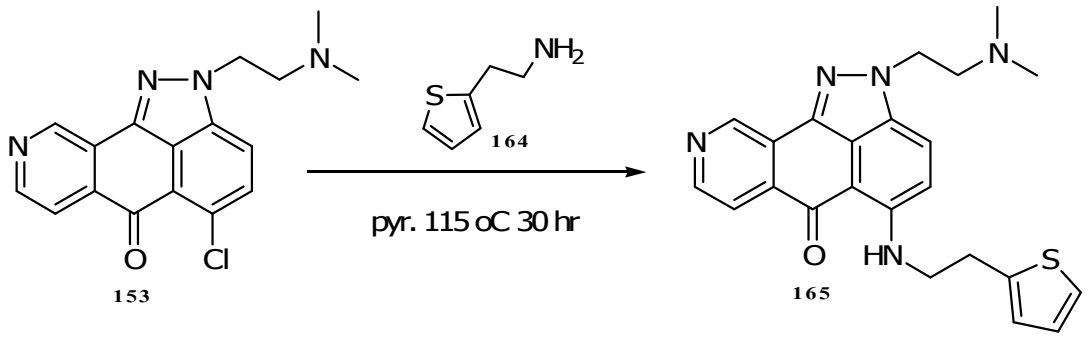
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.72-1.86 (m, 6H, pyrolidine), 2.31 (s, 3H $\underline{CH_3}$-pyrolidine), 2.35 (s, 6H, N($\underline{CH_3}$)$_2$), 2.92 (t, 2H, J = 6.7 Hz, $CH_2\underline{CH_2}N(CH_3)_2$), 3.08 (m, 1H, pyrolidine) 3.52 (m, 4H, NH$\underline{CH_2}\underline{CH_2}$-pyrolidine), 4.61 (t, 2H, J = 6.7 Hz, $\underline{CH_2}CH_2N(CH_3)_2$), 6.98 (d, 1H, J = 9.2 Hz, H-4), 7.69 (d, 1H, J = 9.1 Hz, H-3), 8.27 (d, 1H, J = 5.3 Hz, H-7), 8.78 (d, 1H, J = 9.1 Hz, H-8), 9.23 (s, brs, 1H, N$\underline{H}$), 9.64 (s, 1H, H-10)

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.0 (C-pyrolidine), 30.6 (C-pyrolidine), 33.1 ($\underline{C}H_2$-pyrrolidine), 40.5 (NH$\underline{C}H_2$), 40.6 (N$\underline{C}H_3$), 45.7 (N($\underline{C}H_3$)$_2$), 48.9 ($CH_2\underline{C}H_2N(CH_3)_2$ 57.1 (C- pyrolidine) 59.2 ($\underline{C}H_2CH_2N(CH_3)_2$), 63.9 (C- pyrolidine), 104.9 (C-5a), 113.4 (C-7), 120.3 (C-3), 120.4 (C-4), 122.9 (C-10a), 125.2 (C-2a), 130.8 (C-10b), 134.1 (C-10a), 138.0 (C-5), 145.7 (C-8), 147.5 (C-10), 150.2 (C-6a), 180.8 (C-6).

MS m/e (% relative intensity): M^+ 417(1.0), 246(1.0), 320(0.9), 249(1.1), 233(0.9) 111(0.8), 97(10.5), 78(36.0), 63(16.0), 51(37.4).

IR (NaCl disc) υ_{max}: 3282, 3051, 2977, 2780, 1651, 1605, 1504, 1265, 1027 cm^{-1}.

3.6 Synthesis of 2-(2-(dimethylamino)ethyl)-5-(2-(thiophen-2-yl)ethylamino)indazolo[4,3-gh]isoquinoline-6(2H)-one (165)



A solution of 2-thiopheneethylamine **164** (0.2 mL, 1.70 mmol) in absolute pyridine (2 mL) was added into a solution of compound **153** (0.12 g, 0.36 mmol) in absolute pyridine (6 mL). The resulting mixture was then heated to 115 ^{o}C under argon atmosphere. After 30 h, the solvent was removed in vacuo and the water was added and extracted with CH_2Cl_2 several times. The combined organic phases were washed with water and dried with Na_2SO_4, concentrated and the residue was purified by column chromatography, using 10% MeOH/CH_2Cl_2 as eluent to afford **165** (70 mg, 58.3%) as red oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.32 (s, 6H, N($\underline{CH_3}$)$_3$), 2.92 (t, 2H, J = 6.7 Hz, $CH_2\underline{CH_2}$ N(CH_3)$_2$), 3.29 (t, 2H, J =7.0 Hz, $\underline{CH_2}$-thiophene), 3.75 (m, 2H, NH$\underline{CH_2}$), 4.60 (t, 2H, J = 6.8 Hz, $\underline{CH_2}CH_2N(CH_3)_2$), 6.97 (m, 3H, H-4, thiophene), 7.18 (m, 1H, H-thiophene) 7.67 (d, 1H, J = 9.0 Hz, H-3), 8.26 (d, 1H, J = 5.3 Hz, H-7), 8.77 (d, 1H, J = 5.3 Hz, H-8), 9.27 (t, 1H, J = 5.6 Hz, N$\underline{H}$), 9.62 (s, 1H, H-10).

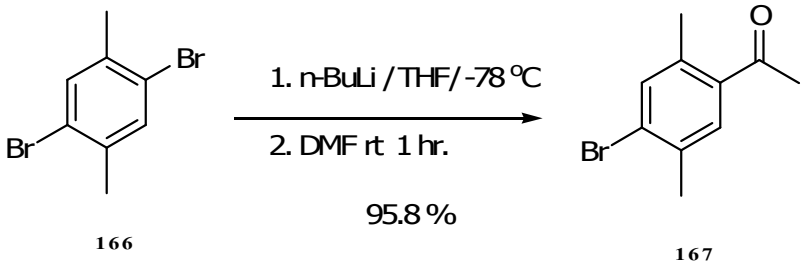
^{13}C NMR (50MHz, $CDCl_3$): δ = 30.0 ($\underline{C}H_2$-thiophene), 44.8 ($CH_2\underline{C}H_2$-thiophene), 45.6 (NH(CH_3)$_2$), 48.8 ($CH_2\underline{C}H_2N(CH_3)_2$), 59.1 ($\underline{C}H_2CH_2N(CH_3)_2$), 105.0 (C-5a), 113.2 (C-7), 120.31 (C-4), 120.35 (C-3), 122.9 (C-10c), 124.1 (C-thiophene), 125.2 (C-2a), 125.7 (C-thiophene), 127.1(C-thiophene), 30.9(C-10b), 134.1 (C-10a), 137.9 (C-5), 140.3 (C-thiophene), 145.6 (C-8), 147.6 (C-10), 149.7 (C-6a), 180.9 (C-6).

HRMS (M^++1) calculated $C_{24}H_{30}ON_6$ 418.2481, found 418.1712.

IR (NaCl disc) υ_{max}: 3286, 3051, 2947, 2860, 2860, 2824, 2775, 1652, 1605, 1568, 1475, 1265 cm^{-1}.

4. Attempts of a new synthesis of ellipticine (49)

4.1 Synthesis of 4-bromo-2,5-dimethylbezaldehyade (167)



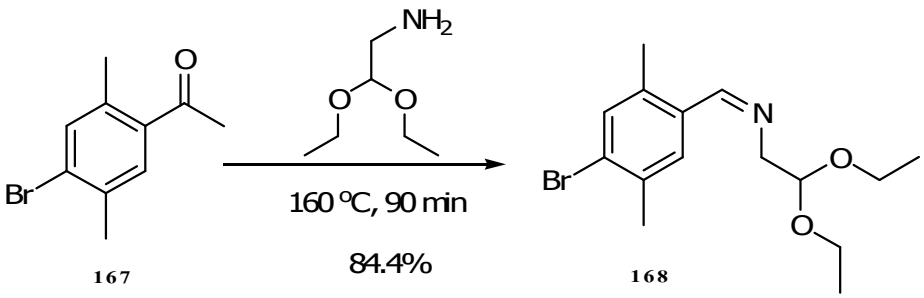
166 167

To a solution of 1,4-dibromo-2,5-dimethylbenzene **166** (5.28g, 20 mmol) in anhydrous THF (3 mL) n-BuLi (14 mL, 22 mmol, 1.6 M in hexane) was slowly added dropwise at -78 ^{o}C for 30 min. After 30 min N,N-dimethylformamide (3 mL, 40 mmol) was added, then the resulting mixture was warmed to RT and continuously stirred for 1 h. Saturated NH_4Cl (30 mL) was added. The aqueous phase was extracted with ether (2x100 mL). The organic layer was washed with brine (100 mL), dried with Na_2SO_4 and concentrated in vacuo to obtain the pure product (4.05 g, 95.8%) as a white solid, mp 57-59 ^{o}C. The fully characterization of compound **167** is in reference [64].

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.31 (s, 3H), 2.48 (s, 3H), 7.34 (s, 1H), 7.50 (s, 1H), 10.0 (s, 1H).

^{13}C NMR (50MHz, $CDCl_3$): δ = 18.5, 22.1, 131.2, 132.9, 133.5, 135.3, 136.0, 139.2, 191.7.

4.2 Synthesis of N-(4-bromo-2,5-dimethylbenzulidene)diethhoxymethanamine (143)



167 168

A mixture of 4-bromo-2,5-dimethylbezaldehyde **167** (0.5 g, 2.37 mmol) and aminoacetaldehyde diethyl acetal (0.7 mL, 4.78 mmol) was refluxed at 160 ^{o}C. After 90 min,

the reaction mixture was allowed to cool and the resulting liquid was removed and the distillation of the remaining acetal in vacuo to give the acetal **168** (0.681 g, 87.61%) as beige oil.

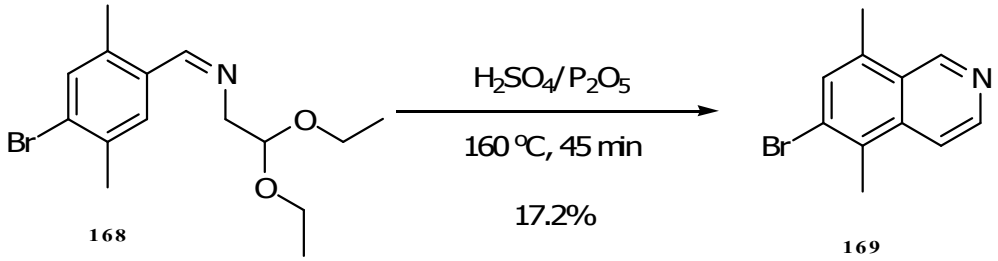
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.19 (t, 6H, J = 7.0 Hz), 2.35 (s, 3H), 2.41 (s, 3H), 3.55 (dd, 2H, J = 2.2, 7.0 Hz), 3.68 (dd, 2H, J = 2.3, 7.0 Hz), 3.76 (d, 2H, J =2.0 Hz), 4.79 (t, 1H, J = 2.0 Hz), 7.35 (s, 1H), 7.71 (s, 1H), 8.48 (s, 1H).

^{13}C NMR (50MHz, $CDCl_3$): δ = 15.3, 18.2, 22.1, 62.2, 64.9, 101.9, 127.1, 129.1, 133.1, 134.2, 135.5, 136.5, 161.3.

MS m/e (% relative intensity): M^+ 327(0.5), 264(40.0), 183(31.8), 103(100.0), 75(58.6), 47 (88.9).

IR (KBr disc) υ_{max}: 2974, 2925, 2881, 1648, 1598, 1481, 1443, 1129, 1068, 967 cm^{-1}

4.3 Synthesis of 7-bromo-5,8-dimethylisoquinoline (169)

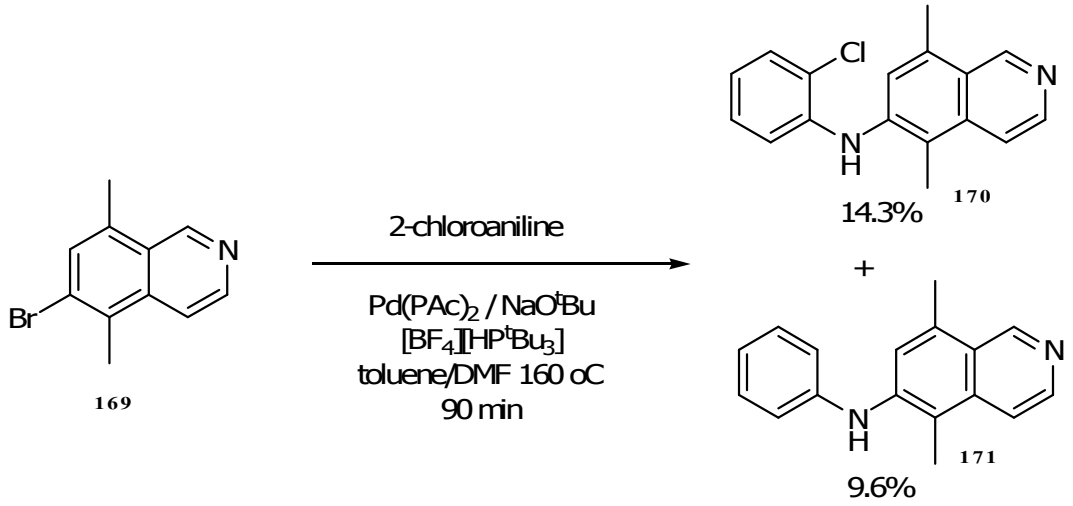


A mixture of P_2O_5 (35.6 g) and conc. H_2SO_4 (150 mL) was heated in a 160 ^{o}C oil bath. N-(4-bromo-2,5-dimethylbenzylidene)diethoxymethanamine **168** (8.41 g, 25.7 mmol) was dissolved in conc. H_2SO_4 (50 mL) and then the resulting solution was added rapidly to the reaction mixture. The mixture was allowed to react for 45 min. After that the mixture was cooled to RT, poured into ice (1 L) and basified using Na_2CO_3. The mixture was extracted with CH_2Cl_2 several times. The organic layer was dried with Na_2SO_4 and evaporated to give a brown residue. Chromatography on silica gel (40%EtOAc in petroleumether) gave 1.04 g (17.2%) of product as a yellowless solid, mp 102-103 ^{o}C. The fully characterization of compound **169** is in reference [64].

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.70 (s, 6H), 7.74 (s, 1H), 7.75 (d, 1H, J = 5.9 Hz), 8.60 (d, 1H, J = 5.9 Hz), 9.37 (s, 1H).

^{13}C NMR (50MHz, $CDCl_3$): δ = 17.9, 117.3, 126.6, 126.9, 130.7, 131.9, 134.6, 136.2, 143.8, 149.7.

4.4 Synthesis of N-(2-chlorophenyl)-2,5-dimethyl-6-isoquinoline (170)



NaO^tBu (91 mg, 0.94 mmol), $Pd(OAc)_2$ (7 mg, 0.03 mmol), and $[BF_4][HP^tBu_3]$ (14 mg, 0.05 mmol) were suspended in toluene (9 mL) and DMF (3 mL). 2-Chloroaniline (0.05 mL, 1.0 mmol) and 7-bromo-2,5-dimethylisoquinoline **169** (109 mg, 0.46 mmol) were added, and the microwave tube was sealed. The reaction mixture was heated in a microwave reactor at 160 °C for 90 min. After that, the mixture was cooled to RT and quenched by addition with 2 N HCl (2x20 mL). The organic layer was extracted with CH_2Cl_2 (3x100 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give crude product, purified by chromatography (40% light petroleum in EtOAc) to give **170** (34 mg, 11.0 %) as yellow crystals, mp 140-142 °C and **171** (20 mg, 9.6%) as yellow crystal, mp 172-173 °C.

170:

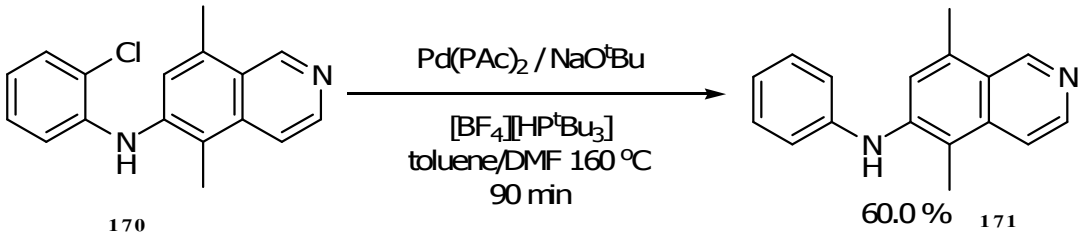
^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 2.63 (s, 3H), 6.81 (dd, 1H, J = 1.4, 8.1 Hz), 6.93 (dt, 1H, J = 1.4, 8.0 Hz), 7.07 (s, 1H), 7.18 (dt, 1H, J = 1.4, 8.0 Hz), 7.45 (dd, 1H, J = 1.4, 8.0 Hz), 7.59 (s, 1H), 7.79 (d, 1H, J = 6.0 Hz), 8.46 (d, 1H, J = 6.0 Hz), 9.27 (s, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 12.3, 18.0, 116.8, 118.9, 122.0, 123.40, 123.43, 124.1, 127.9, 129.9, 133.8, 136.5, 140.8, 141.6, 143.1, 149.0.

MS m/e (% relative intensity): M^+ 282(28.0), 247(87.2), 232(76.1), 171(34.8), 144(25.8), 127(43.8), 115(53.1), 102(57.7), 75(62.0), 44(100).

IR (KBr disc) υ_{max}: 3238, 3063, 2964, 1612, 1588, 1466, 1292, 1032, 738 cm^{-1}.

4.5 Synthesis of 5,8-dimethyl-N-phenyl-6-isoquinoliamine (171)



170 171

NaO^tBu (27.0 mg, 0.283 mmol), $Pd(OAc)_2$ (1.5 mg, 0.007 mmol), and $[BF_4][HP^tBu_3]$ (3.3 mg, 0.0014 mmol) were suspend in toluene (9 mL) and DMF (3 mL). N-(2-Chlorophenyl)-2,5-dimethyl-6-isoquinoline **170** was then added, and the microwave tube was sealed. The reaction mixture was heated in microwave reactor at 160 ^oC for 90 min. After that, the mixture was cooled to RT and quenched by addition of 2 N HCl (2x5 mL). The organic layer was extracted with CH_2Cl_2 (3x30 mL) and dried with Na_2SO_4. The solvent was removed under reduced pressure to give crude product, purified by chromatography (40% light petroleum in EtOAc) to yield **171** (21 mg, 60.0 %), mp 172-173 ^oC.

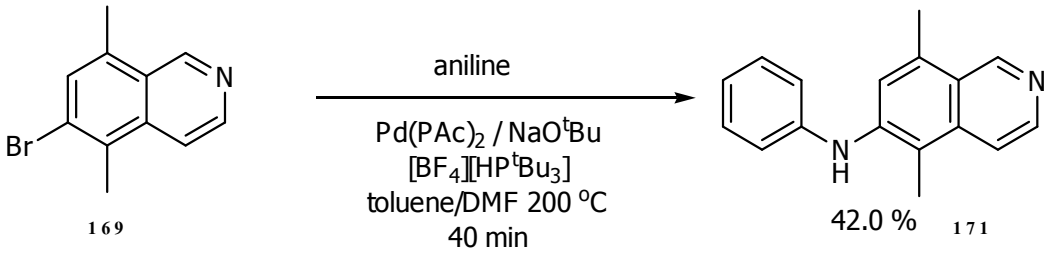
^1H NMR (200 MHz, $CDCl_3$): δ = 2.45 (s, 3H), 2.67 (s, 3H), 5.90 (s, 1H), 7.01 (m, 1), 7.04 (m, 2H), 7.32 (m, 2H), 7.69 (dd, 1H, J = 6.0 Hz), 8.48 (d, 1H, J = 6.0 Hz), 9.27 (d, 1H, J = 0.9 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 11.7, 18.5, 115.7, 116.5, 118.7, 120.9, 121.8, 124.2, 129.4 134.3, 137.1, 142.7, 141.8, 143.1, 149.1.

MS m/e (% relative intensity): M^+ 248(100), 233(17.6), 171(27.9), 116(47.2), 102(21.3), 51(17.9).

IR (KBr disc) υ_{max}: 3246, 3069, 2919, 1614, 1593, 1342, 1280, 1033, 808, 700 cm^{-1}.

4.6 Synthesis of 5,8-dimethyl-N-phenyl-6-isoquinolinamine (171)



NaO^tBu (0.4 g, 4.2 mmol), $Pd(OAc)_2$ (24 mg, 0.01 mmol), and $[BF_4][HP^tBu_3]$ (62 mg, 0.2 mmol) were suspend in DMA (12 mL). Aniline (0.20 mL, 2.1 mmol) and 7-bromo-2,5-dimethylisoquinoline **169** (0.5 g, 2.1 mmol) were then added, and the microwave tube was sealed. The reaction mixture was heated in microwave reactor at 160 °C for 45 min. After that, the mixture was cooled to RT and quenched by addition of 2 N HCl (2x20 mL). The organic layer was extracted with CH_2Cl_2 (3x75 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give crude product, purified by column chromatography (40% light petroleum in EtOAc) to yield **171** (0.25 g, 42.0 %), mp 172-173 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.45 (s, 3H), 2.67 (s, 3H), 5.90 (s, 1H), 7.01 (m, 1), 7.04 (m, 2H), 7.32 (m, 2H), 7.69 (dd, 1H, J = 6.0 Hz), 8.48 (d, 1H, J = 6.0 Hz), 9.27 (d, 1H, J = 0.9 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz) δ = 11.7, 18.5, 115.7, 116.5, 118.7, 120.9, 121.8, 124.2, 129.4 134.3, 137.1, 142.7, 141.8, 143.1, 149.1.

MS m/e (% relative intensity): M^+ 248(100), 233(17.6), 171(27.9), 116(47.2), 102(21.3), 51(17.9).

IR (KBr disc) υ_{max}: 3246, 3069, 2919, 1614, 1593, 1342, 1280, 1033, 808, 700 cm^{-1}.

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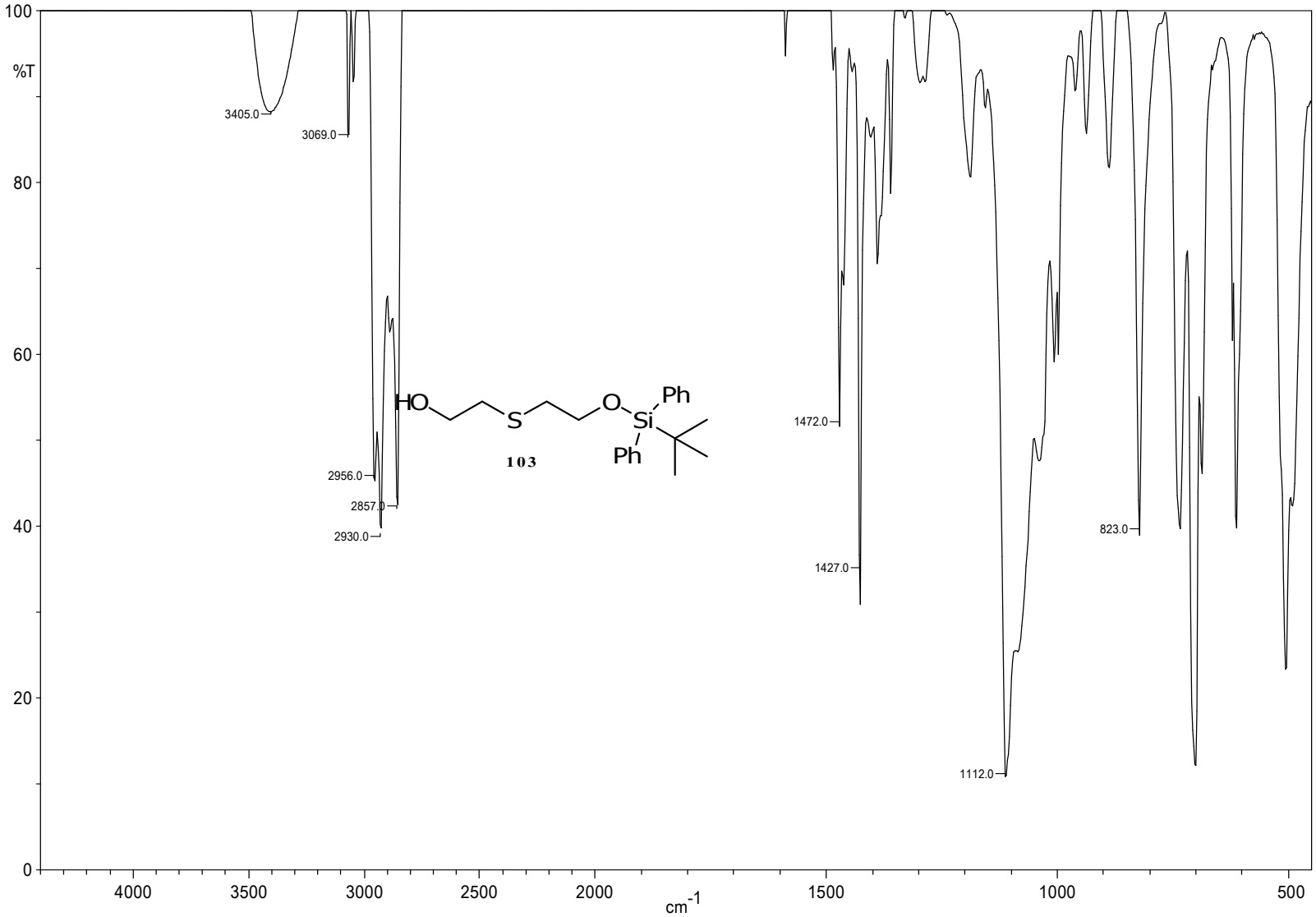
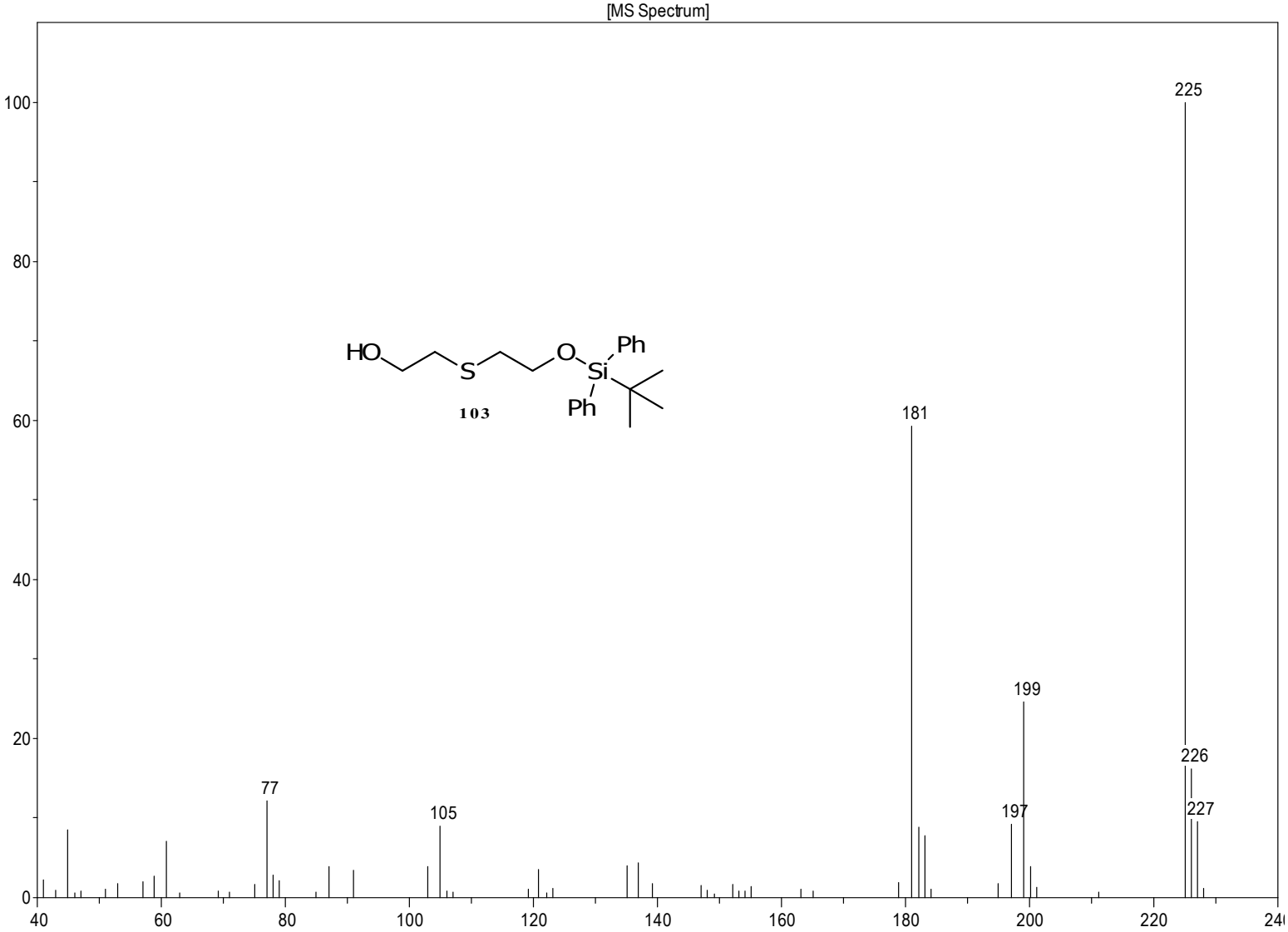
Appendix

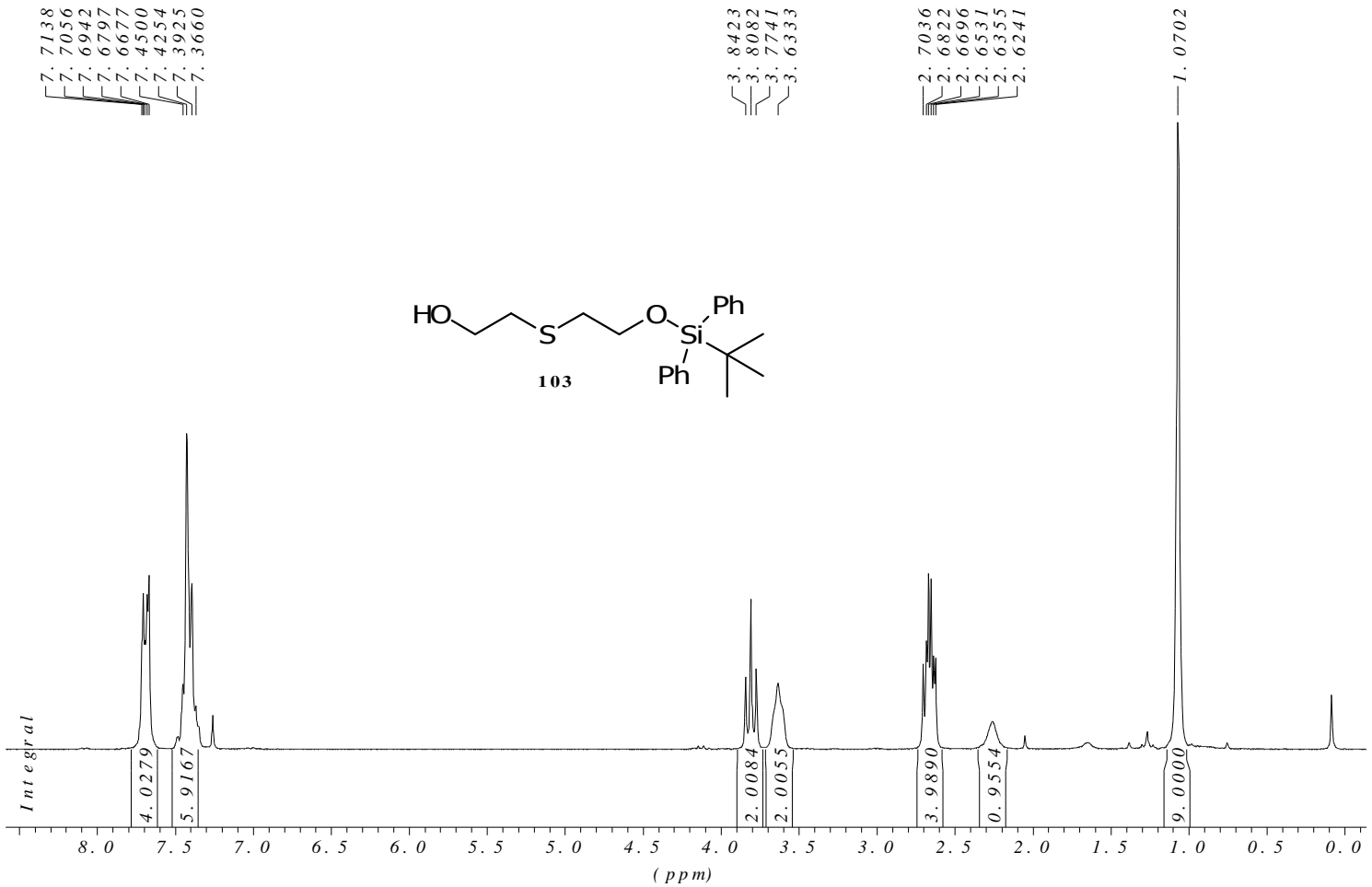
IR spectrum of **103** (NaCl).



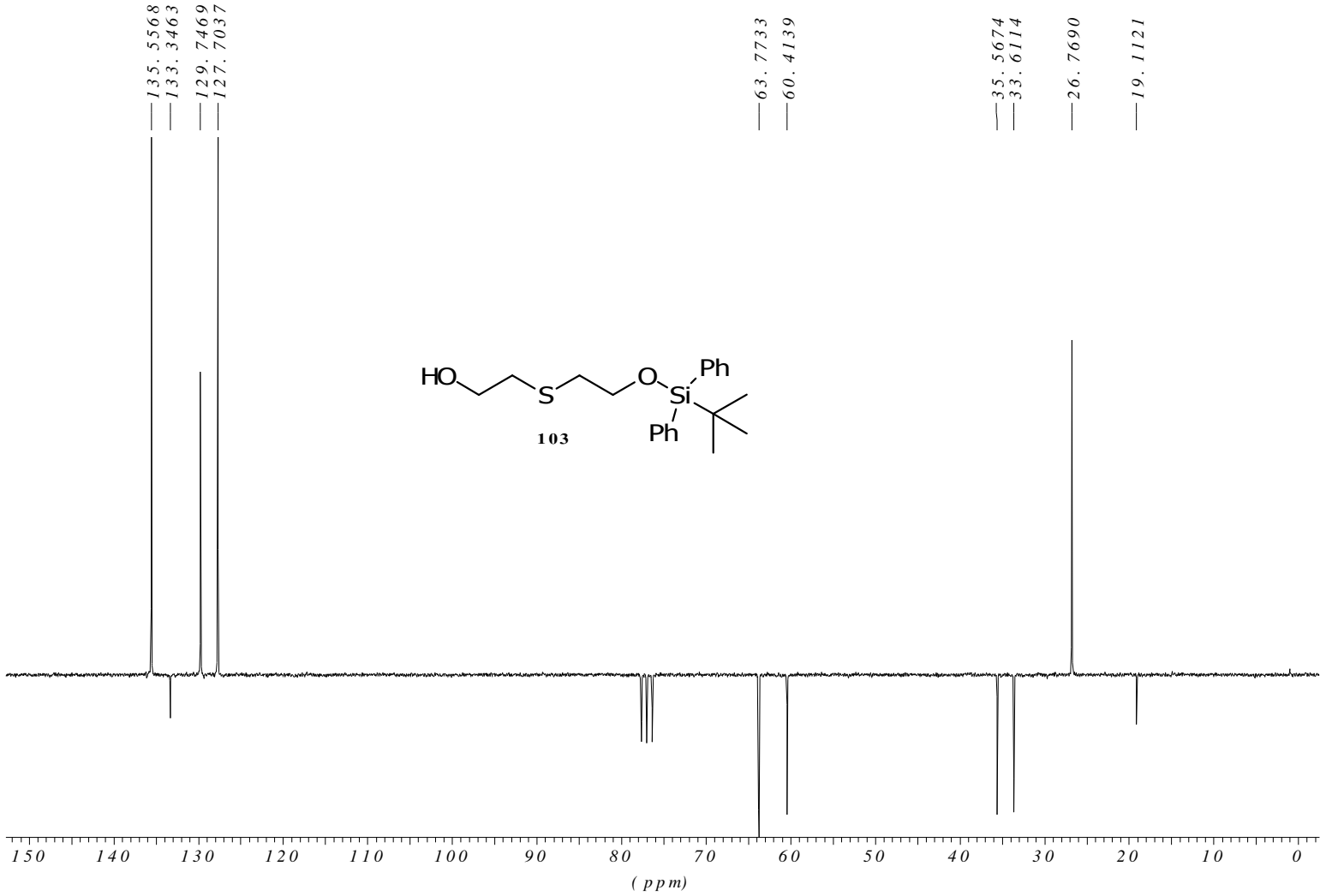
Mass spectrum of **103**.



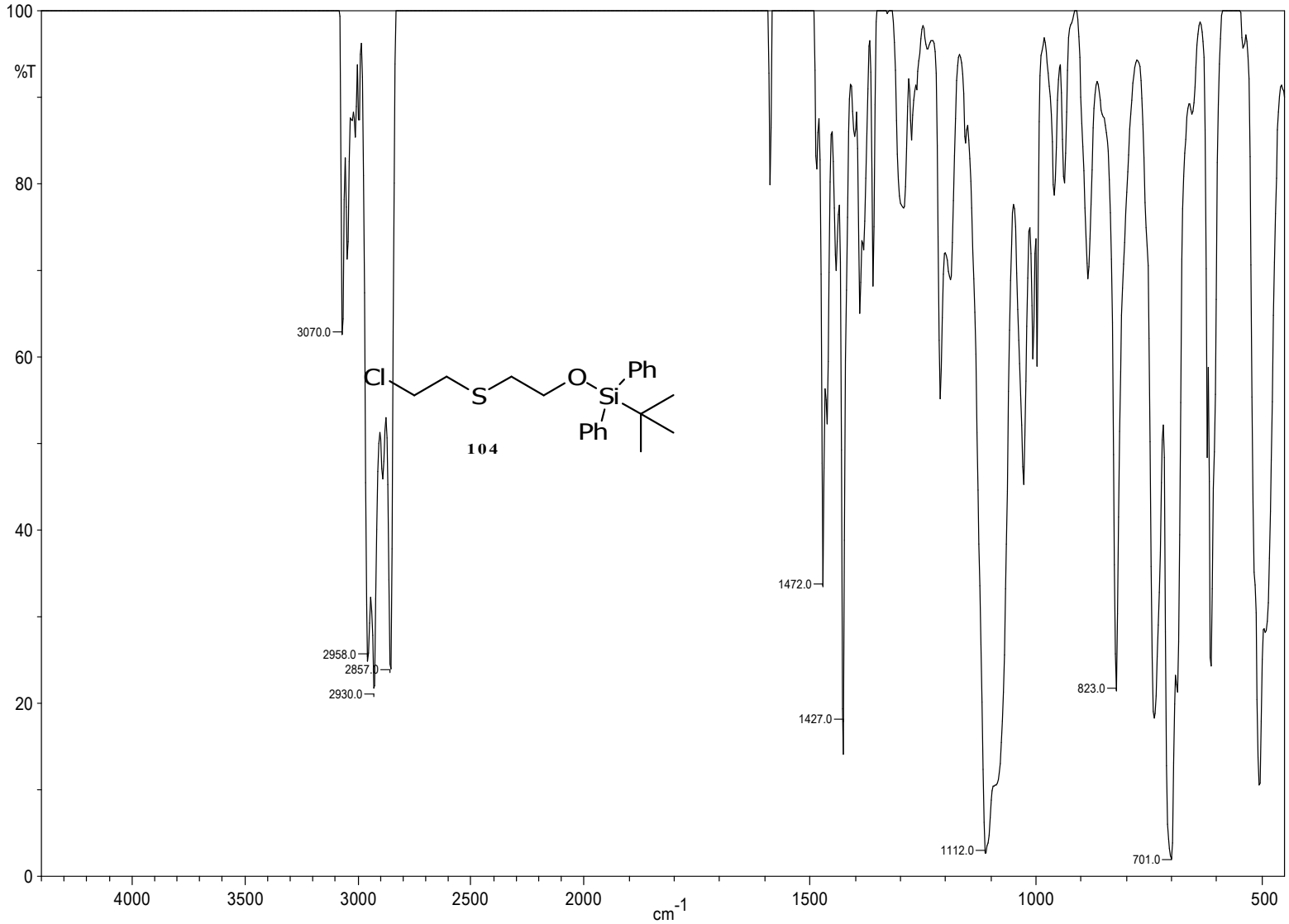
^{1}H NMR spectrum of **103** in $CDCl_3$.



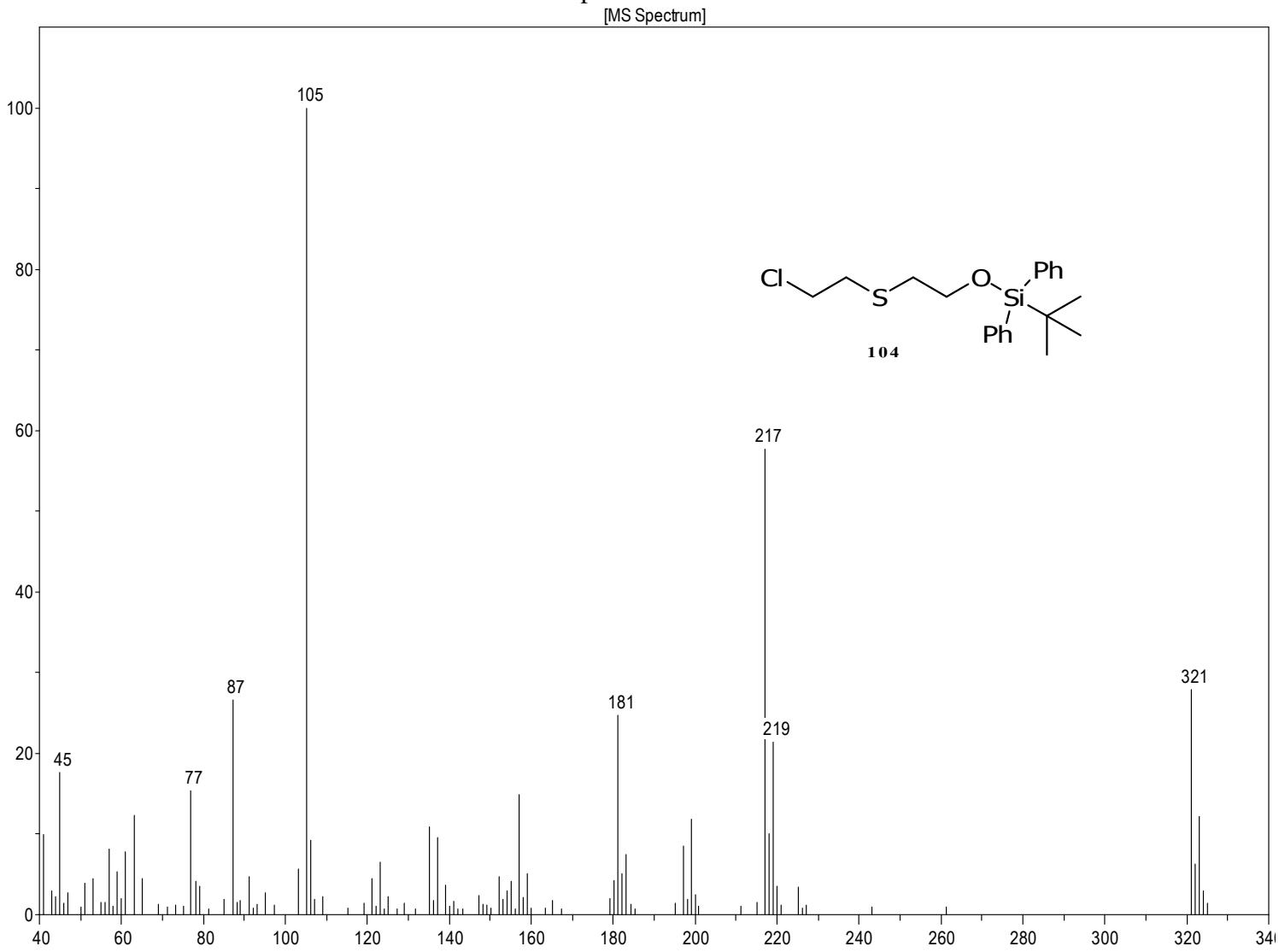
^{13}C NMR spectrum of **103** in $CDCl_3$.



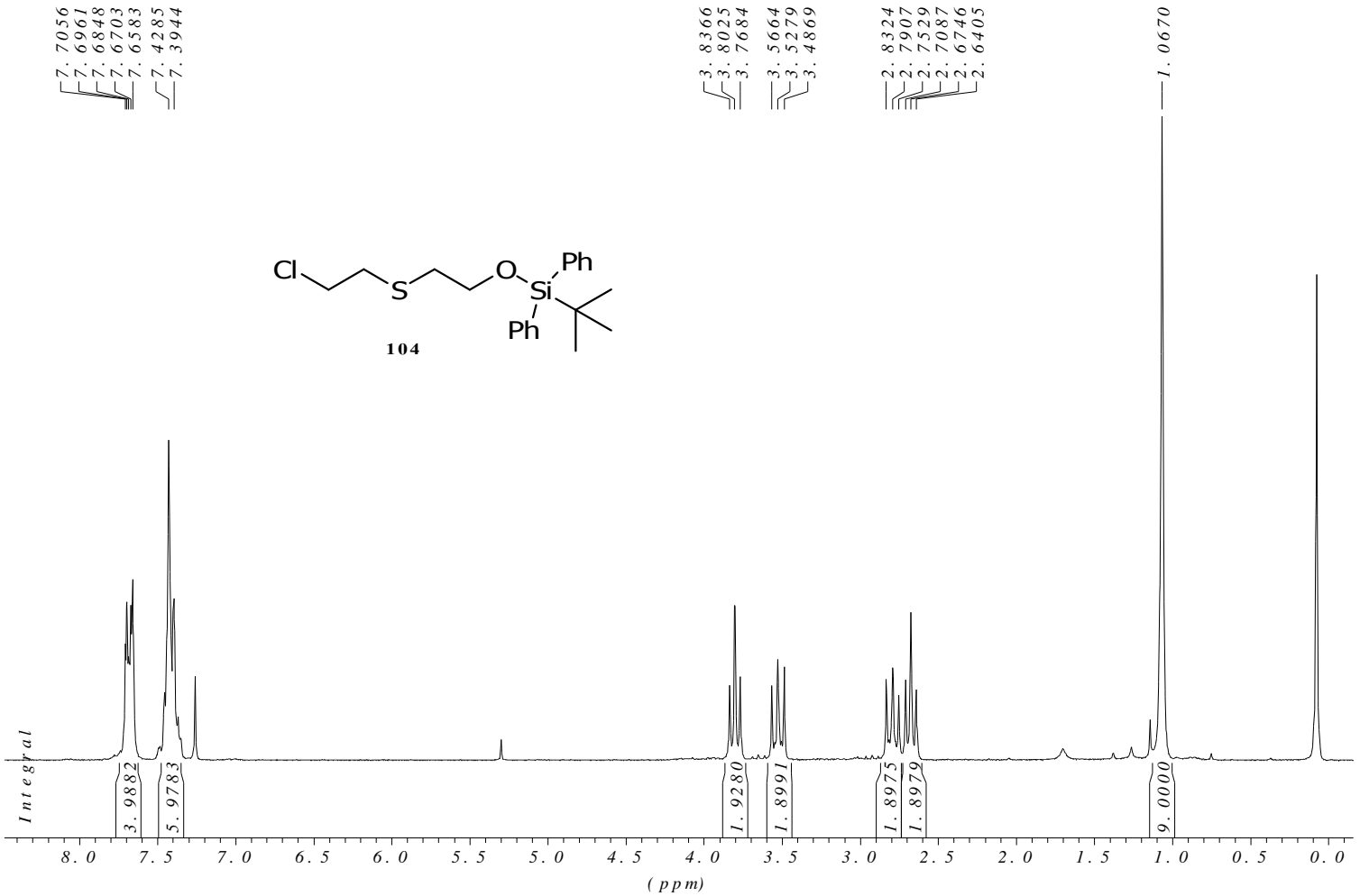
IR spectrum of **104** (NaCl).



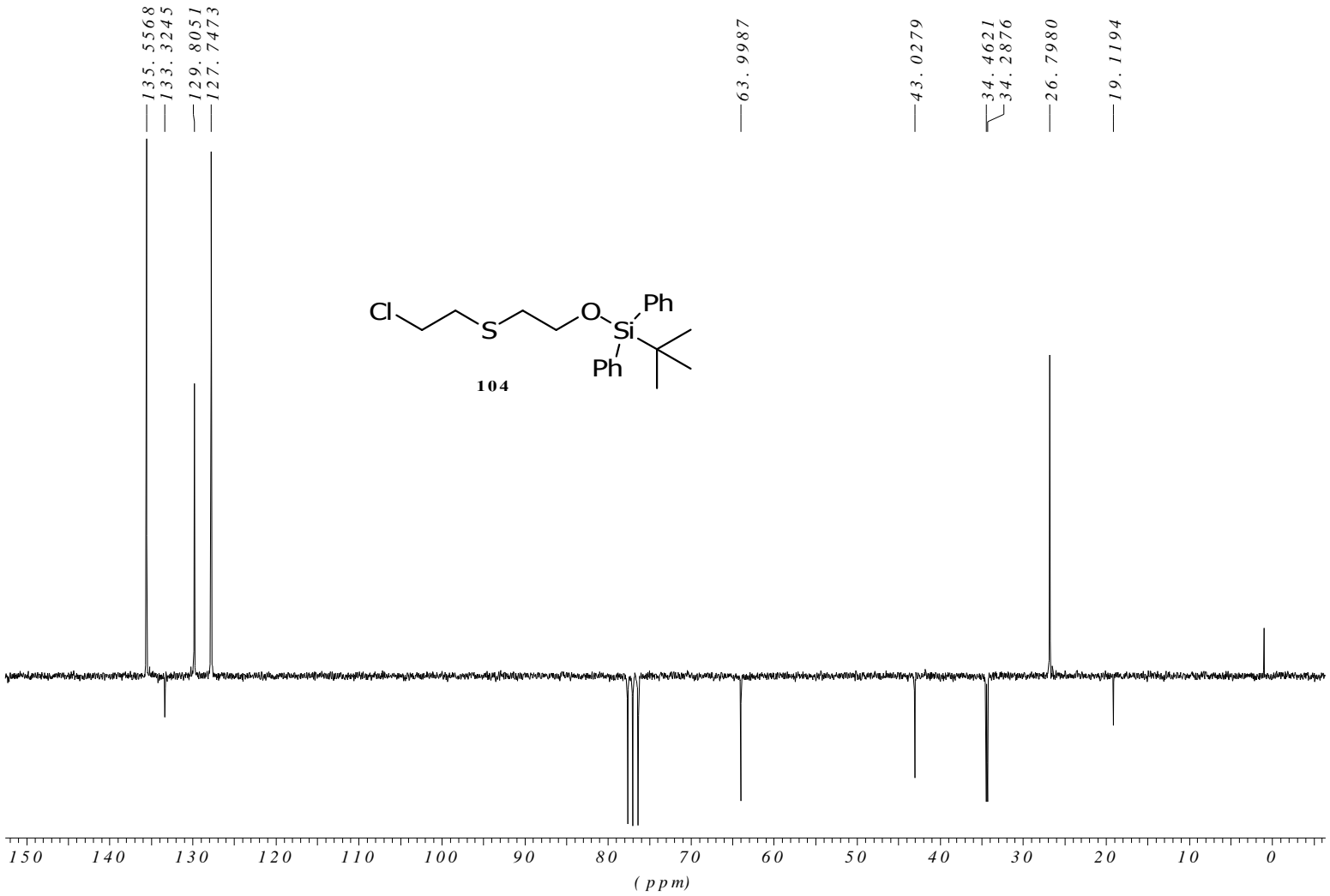
Mass spectrum of **104**.



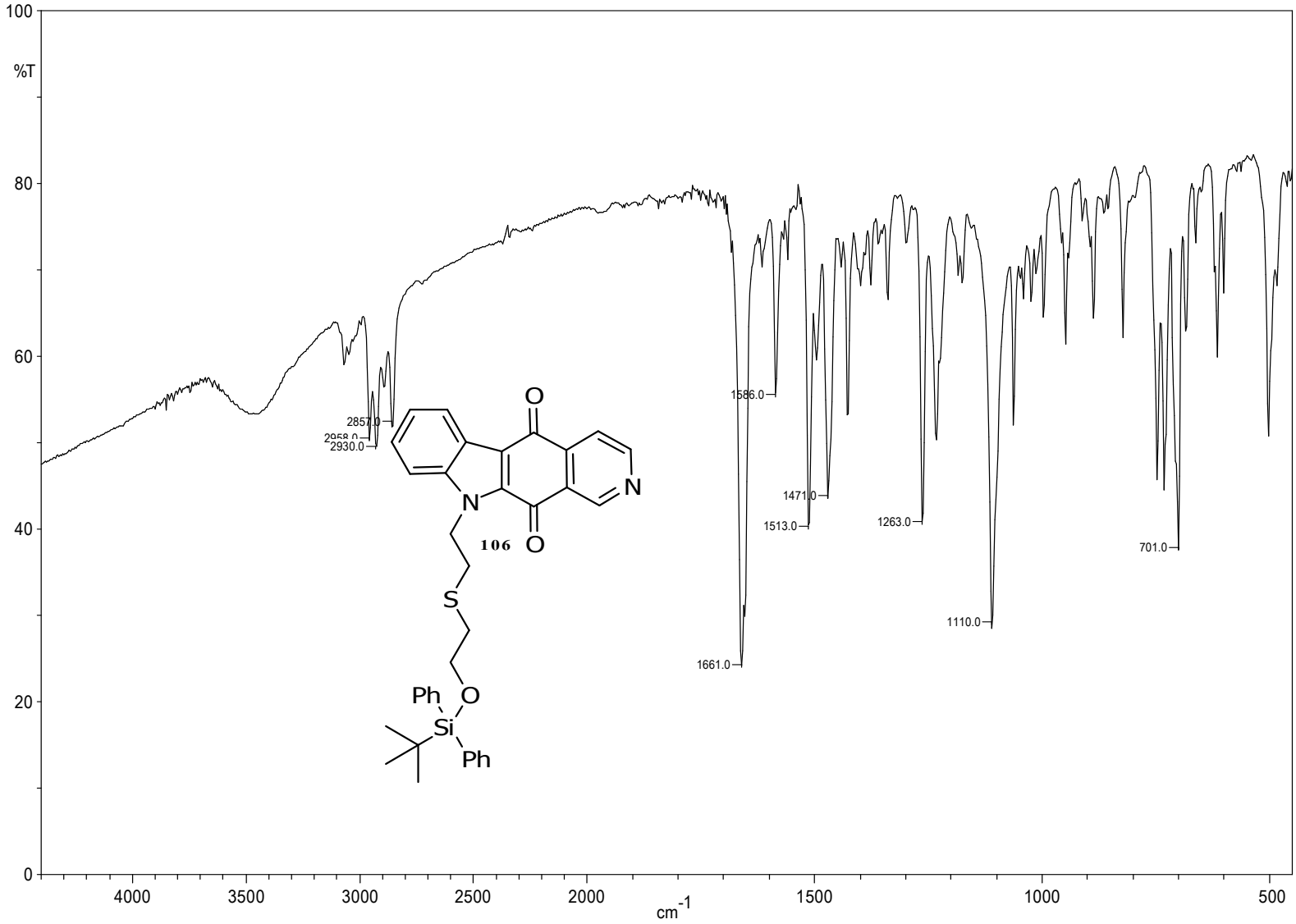
^{1}H NMR spectrum of **104** in $CDCl_3$.



^{13}C NMR spectrum of **104** in $CDCl_3$.

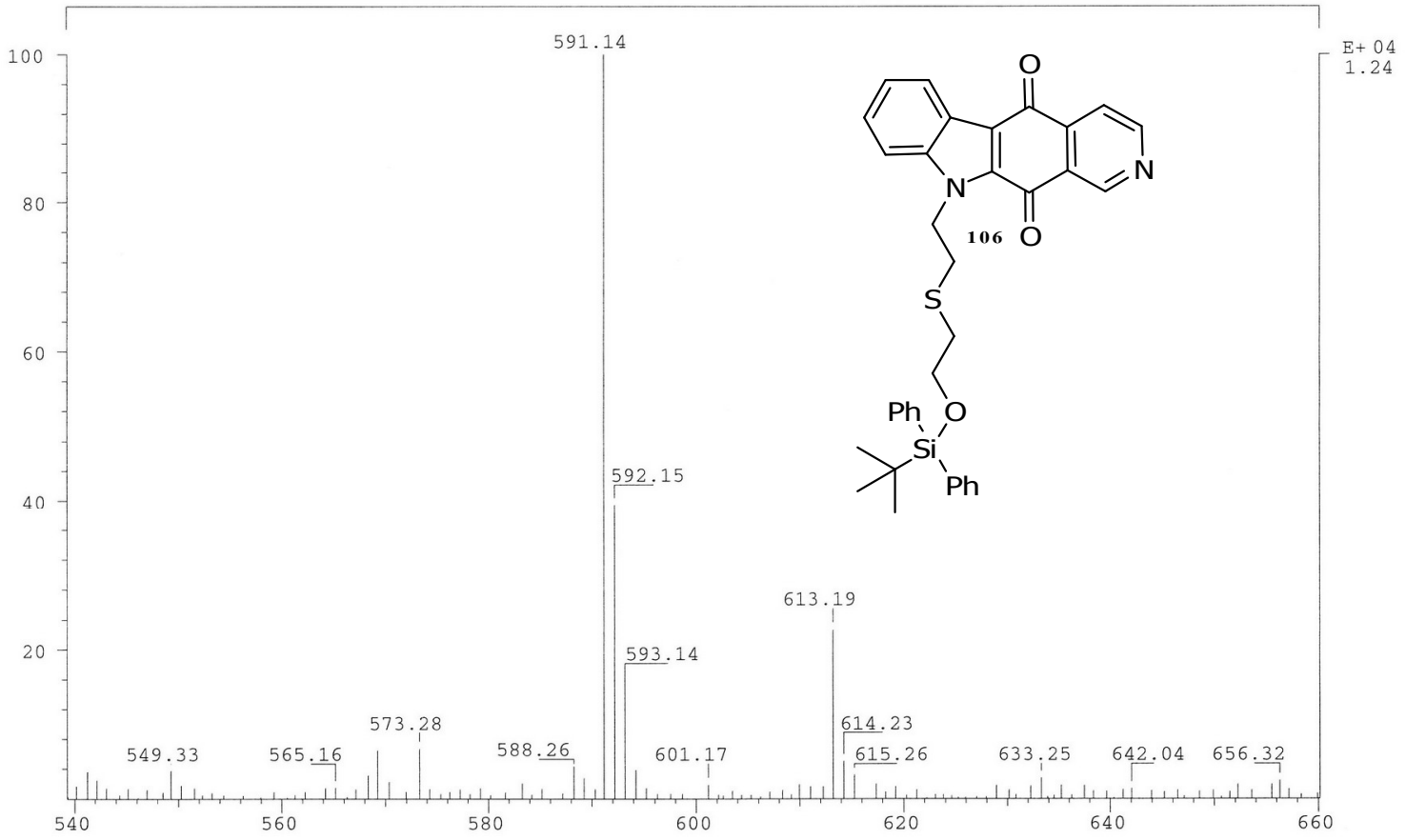


IR spectrum of **106** (KBr).

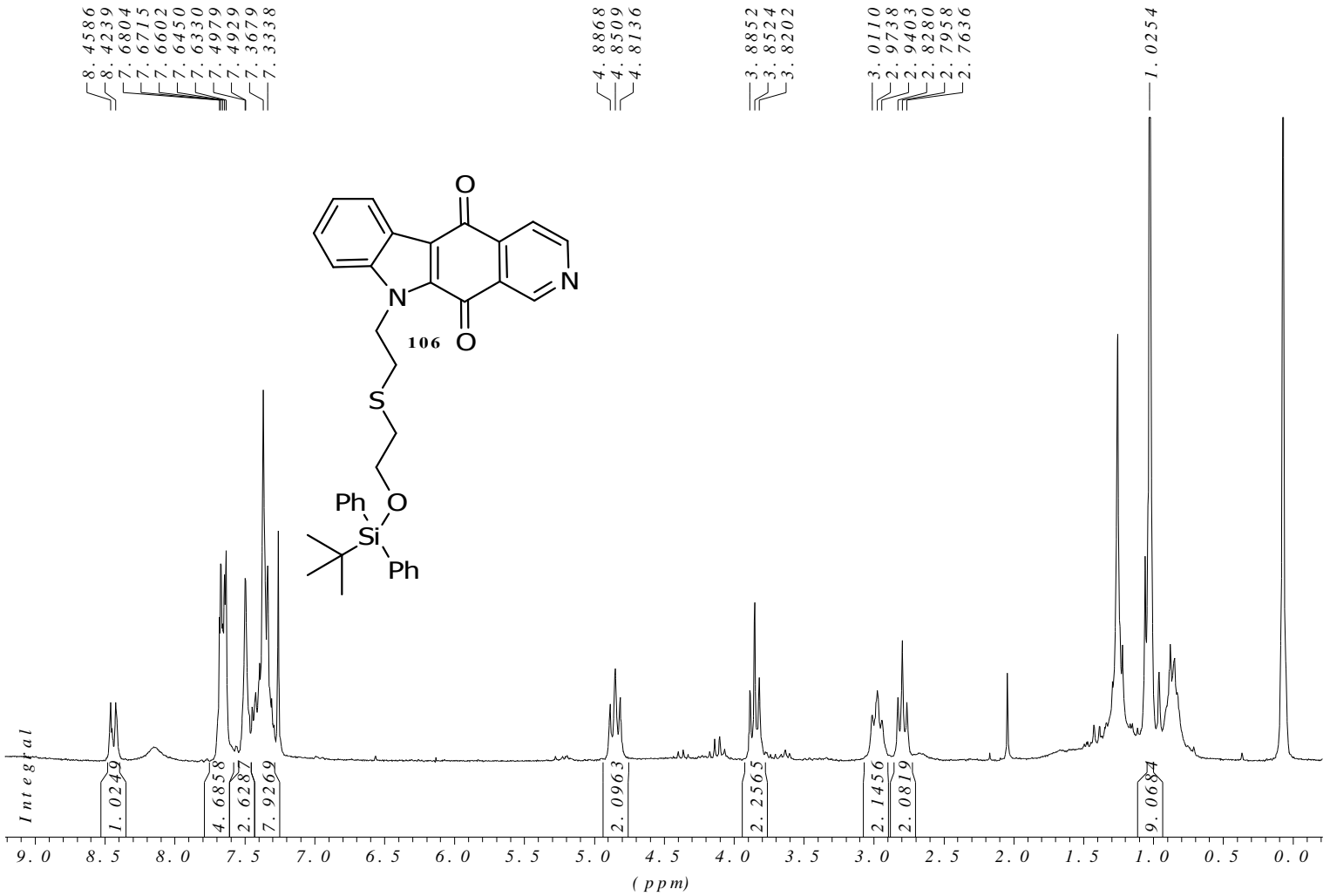


Mass spectrum of **106**.

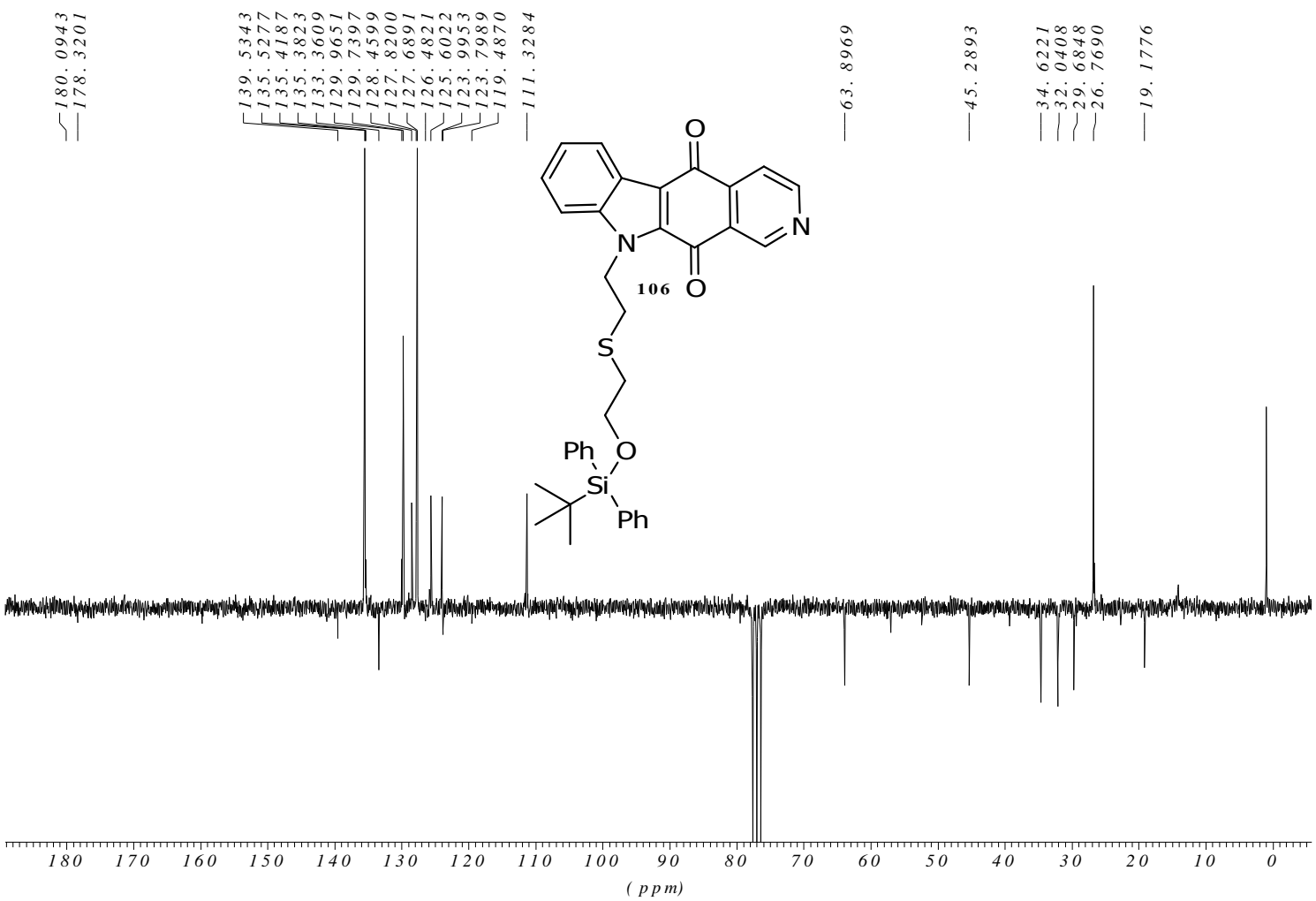
```
SPEC:  00000000000000000000000000000000     02-Apr-95   Elapse:   00:12.7        1
Samp:  MS 590                                            Start :   13:19:45       1
Comm:  4kV 3uA    MeOH/ACN
Mode:  ESI +VE +LMR  BSCAN (EXP) UP LR NRM               Study :   ESI
Oper:  phu           Client:  Theerachart/Holzer/        Inlet :
Base:  591.1                 Inten :  12370              Masses:   101 > 998
Norm:  591.1                 RIC   :  170153             #peaks:   781
Peak:  1000.00  mmu
Data:  AVER : Scans All from /usr/users/finnigan/data/34472_1.dat
```



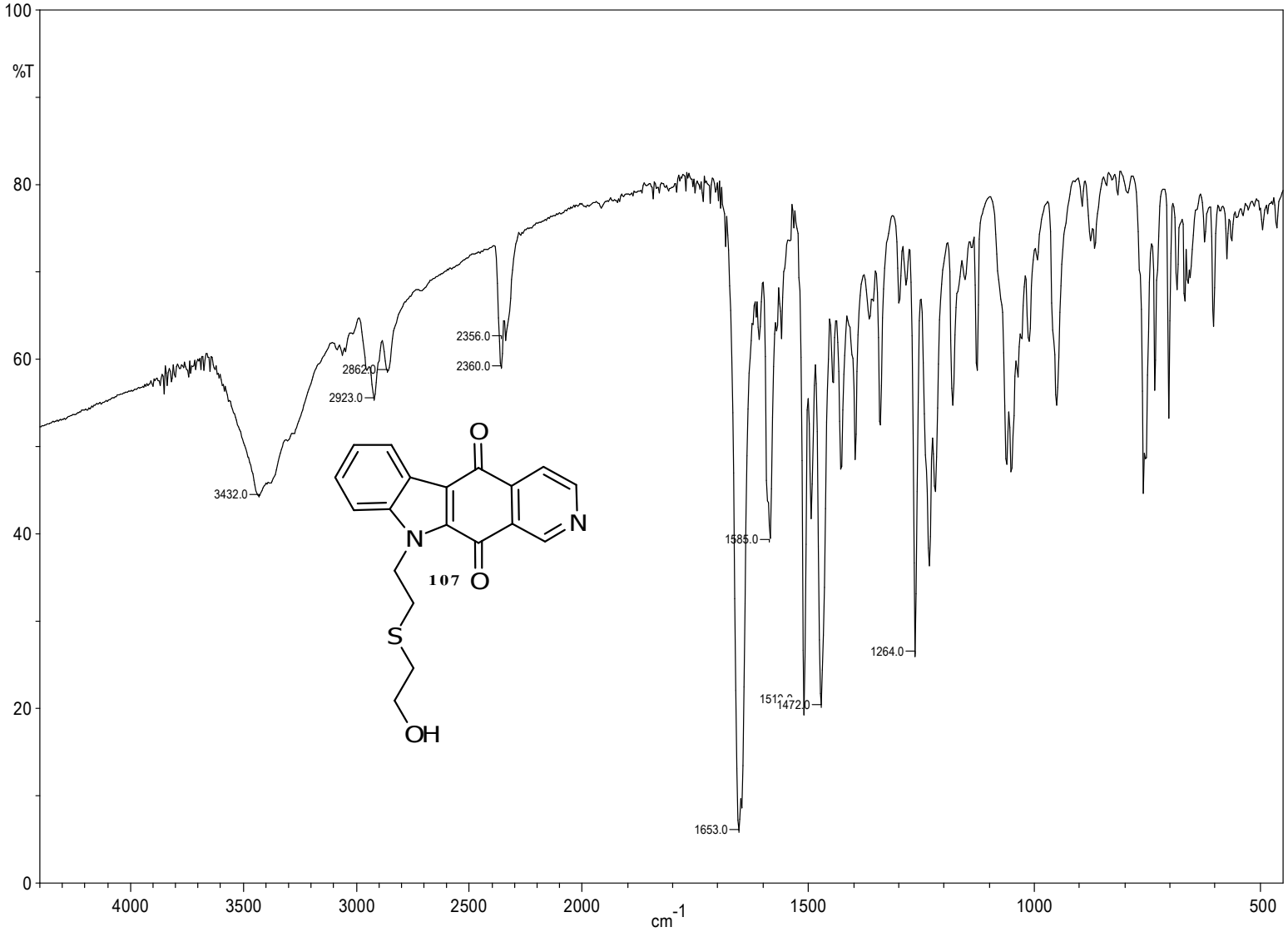
^{1}H NMR spectrum of **106** in $CDCl_3$.



^{13}C NMR spectrum of **106** in $CDCl_3$.

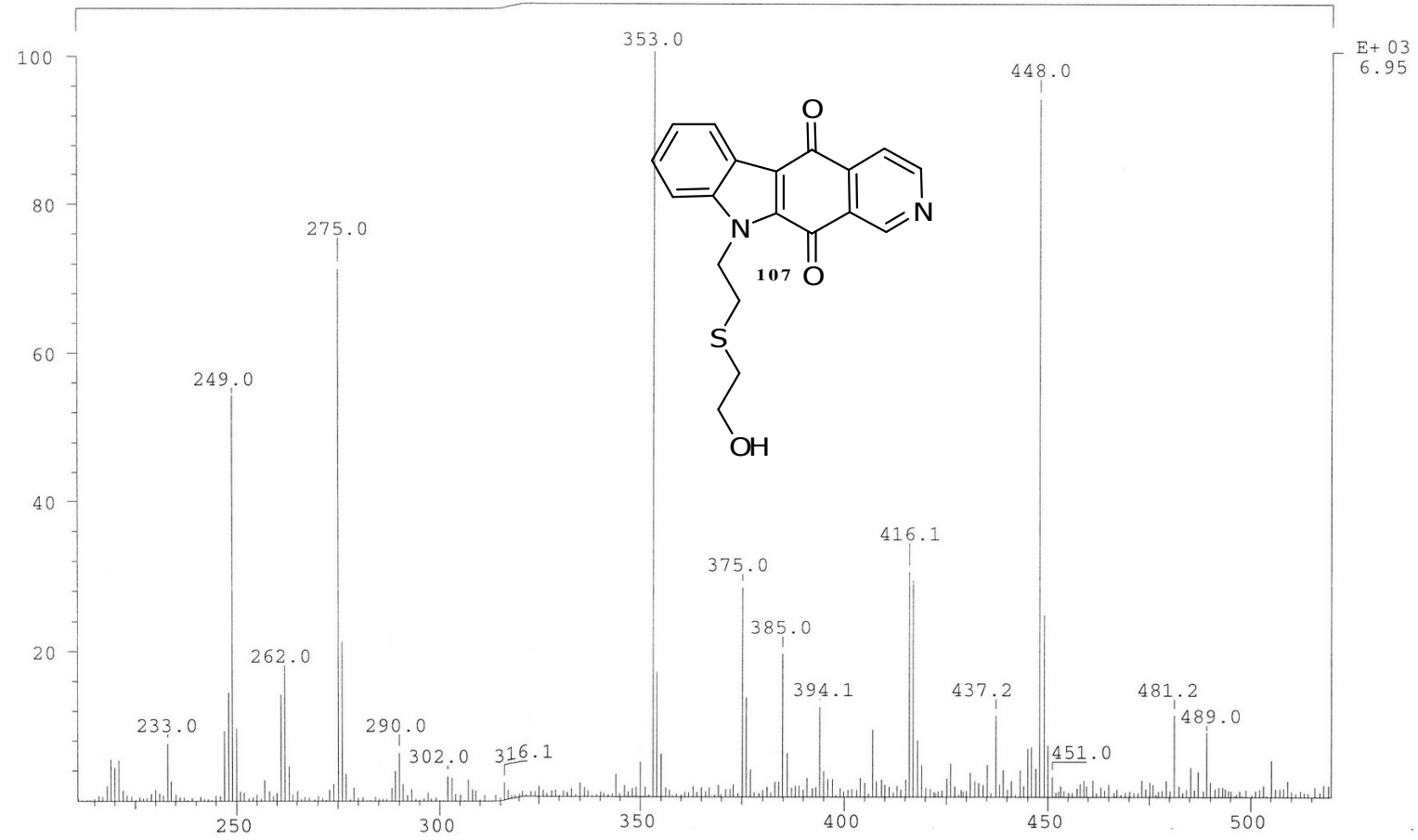


IR spectrum of **107** (KBr).

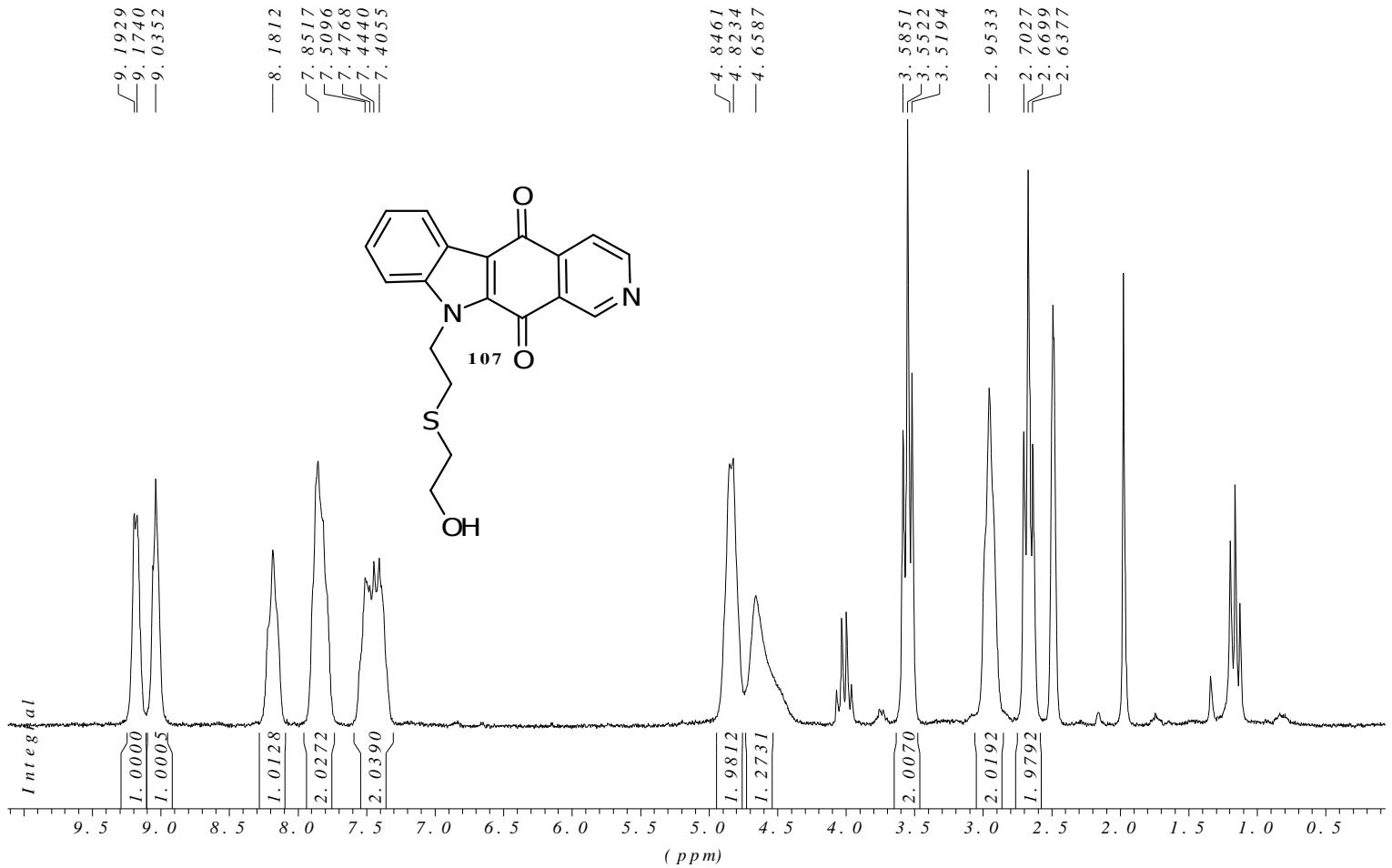


Mass spectrum of **107**.

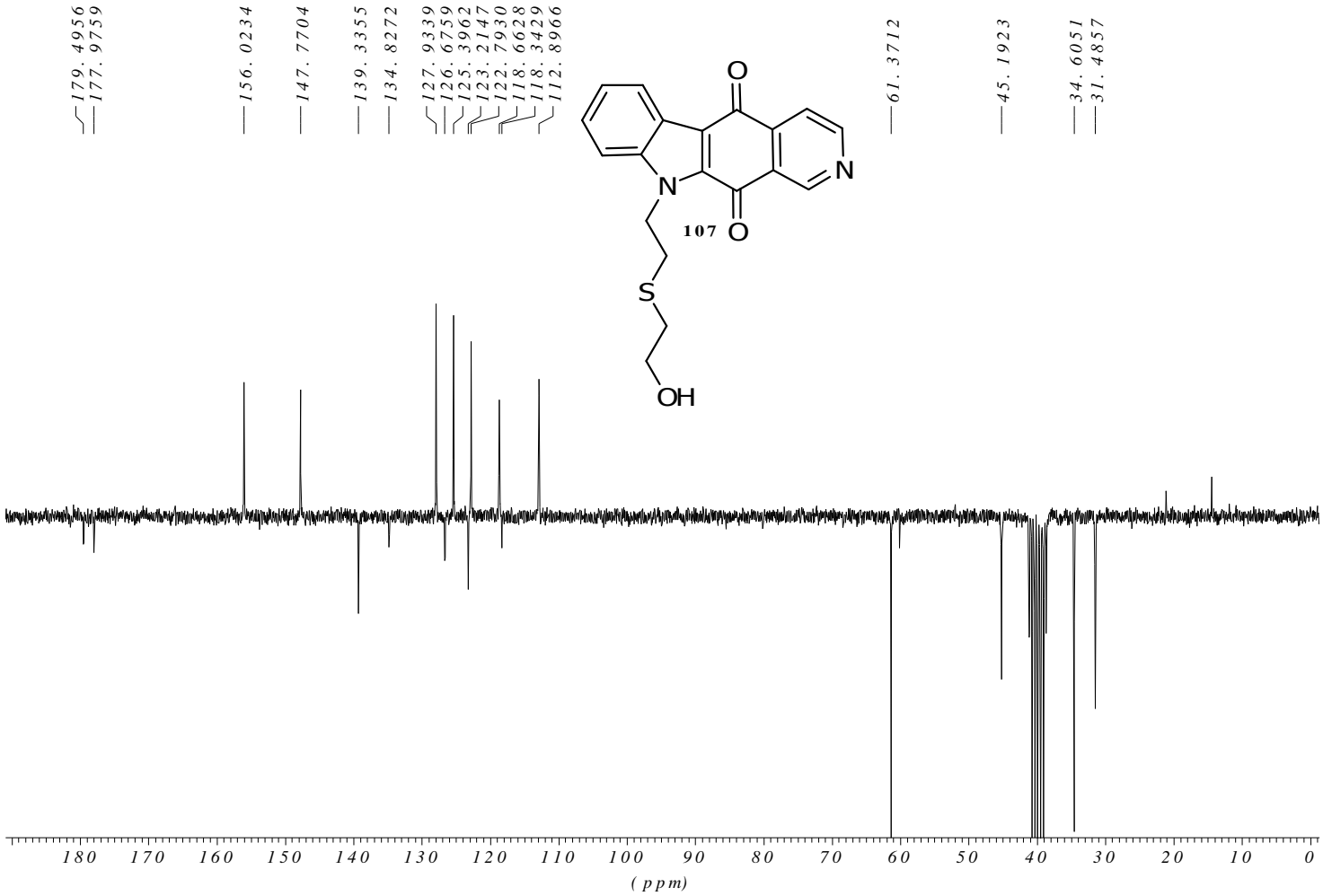
```
SPEC:  00000000000000000000000000000000      24-Mar-95  Elapse:  00:25.3      1
Samp:  MS352                                            Start :  16:31:55      1
Comm:  4kV 3uA   MeOH/ACN
Mode:  ESI +VE +APICID LMR  BSCAN (EXP) UP LR NRM
Oper:  phu           Client:  Theerachart/Holzer/       Inlet :
Base:  353.0               Inten :  6950                Masses:  100 > 999
Norm:  353.0               RIC   :  137142              #peaks:  914
Peak:  1000.00  mmu
Data:  AVER : Scans All from /usr/users/finnigan/data/34448_1.dat
```



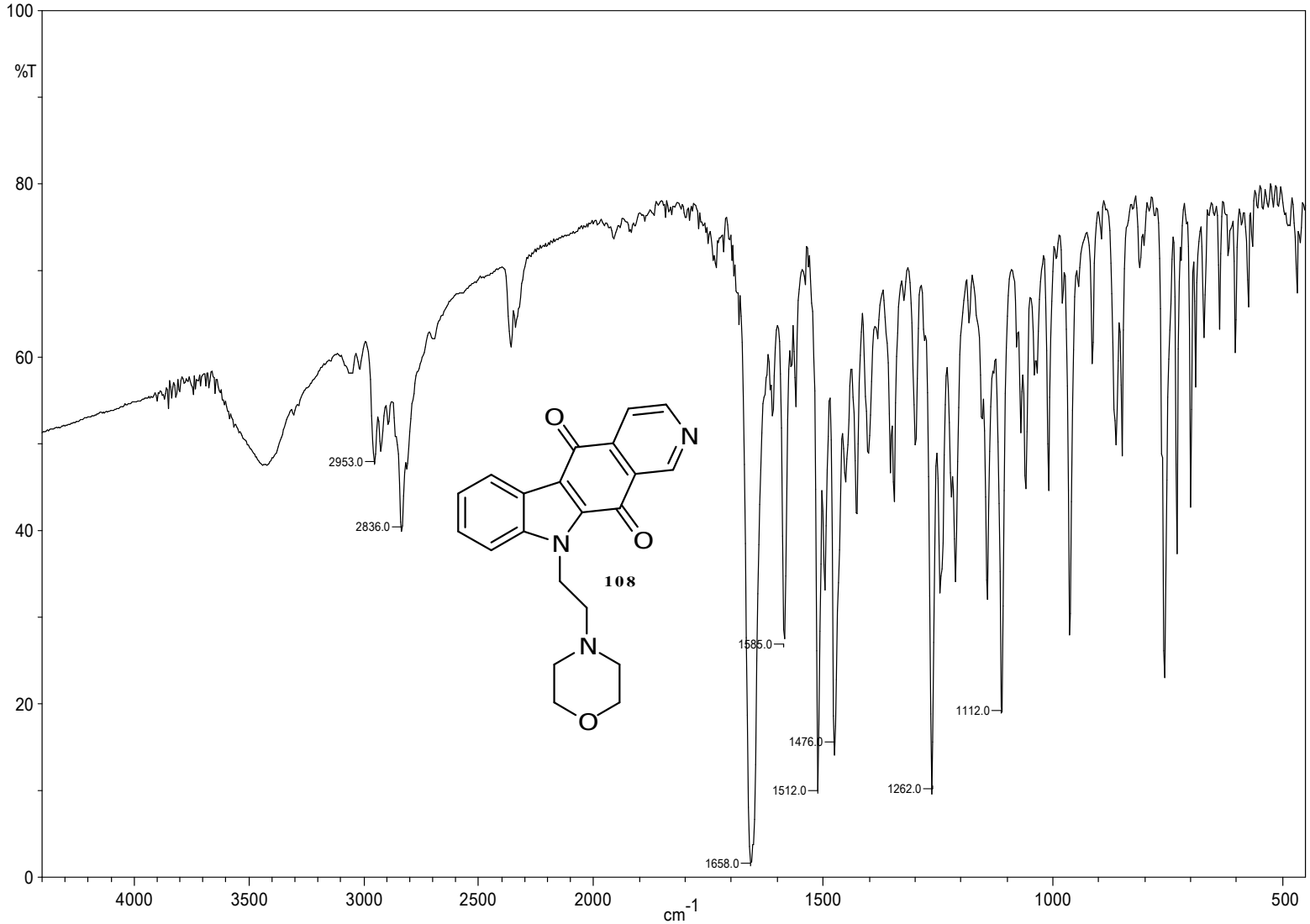
^{1}H NMR spectrum of **107** in DMSO-d_6.



^{13}C NMR spectrum of **107** in DMSO-d_6.

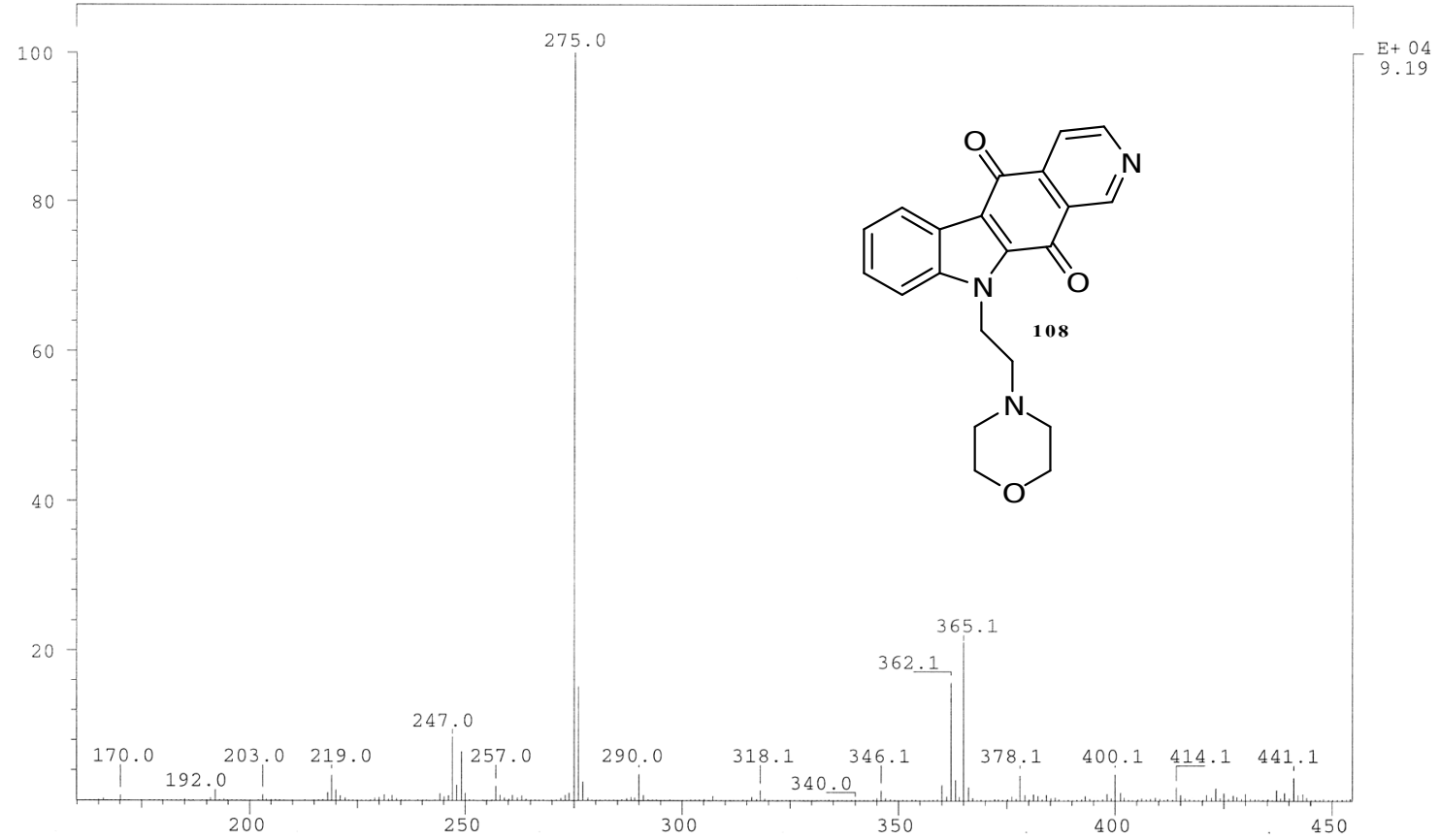


IR spectrum of **108** (KBr).

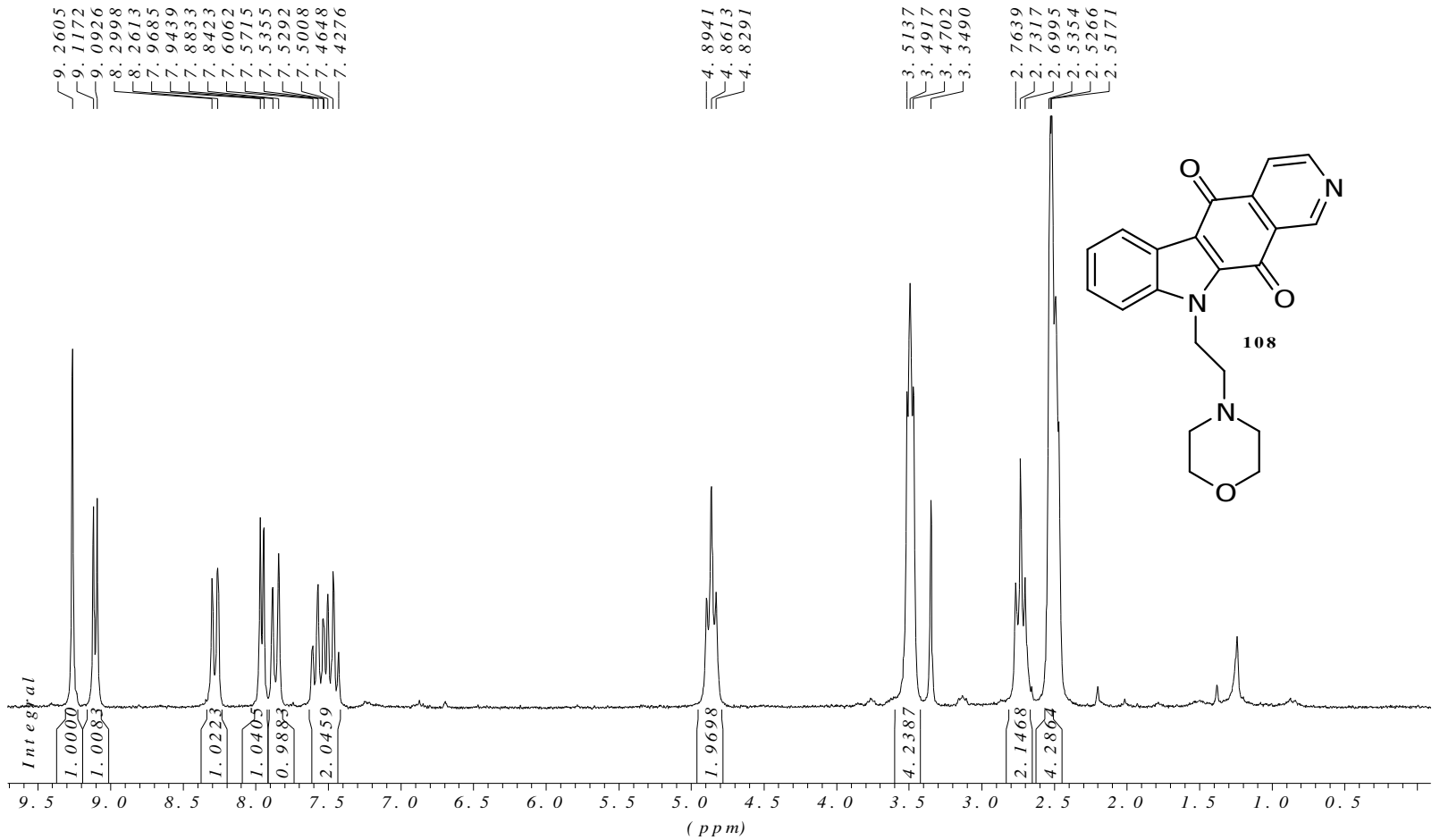


Mass spectrum of **108**.

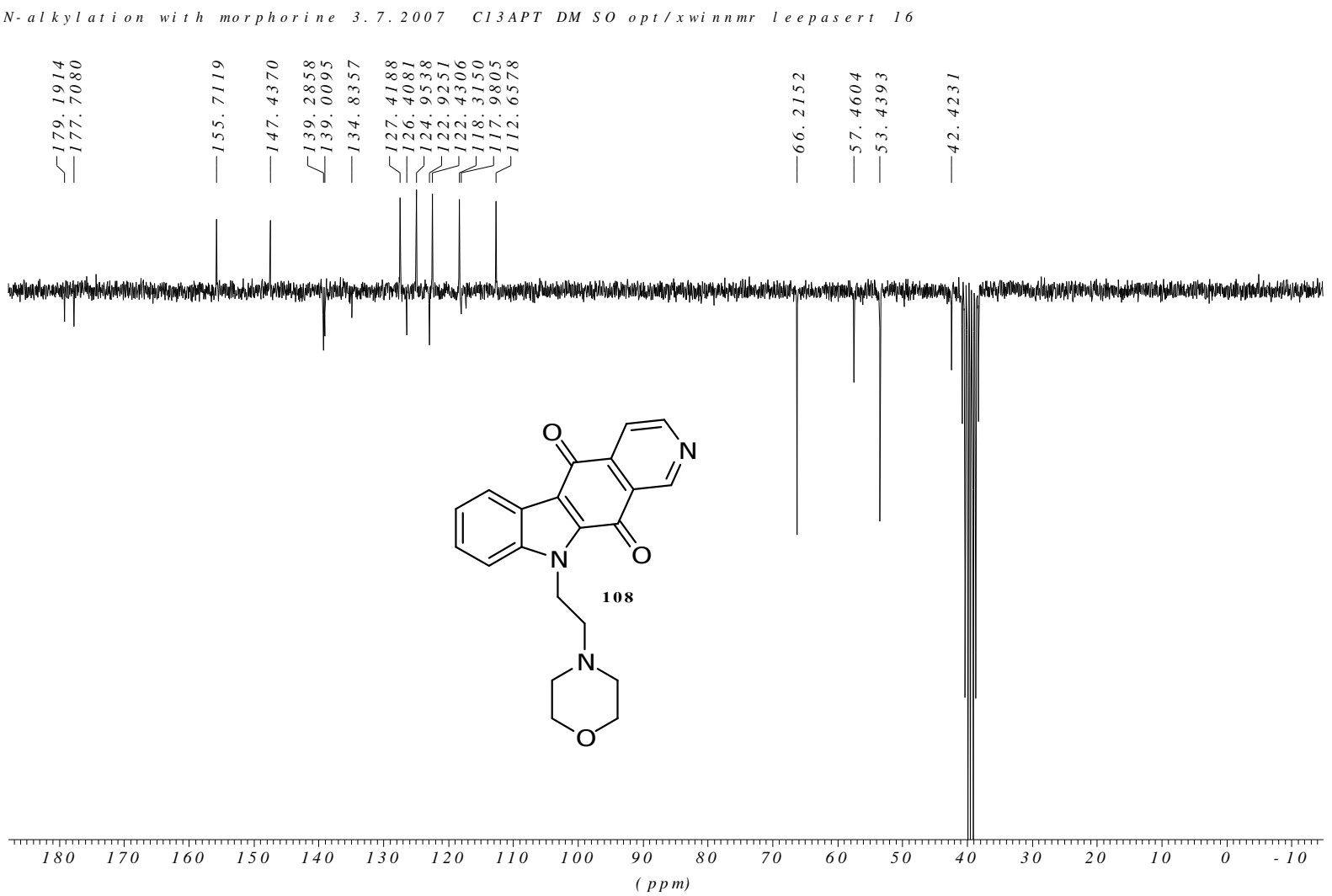
```
SPEC:  00000000000000000000000000000000     24-Mar-95   Elapse:   00:28.0        1
Samp:  MS361                                             Start :   16:44:21       1
Comm:  4kV 3uA    MeOH/ACN
Mode:  ESI +VE +APICID LMR  BSCAN (EXP) UP LR NRM
Oper:  phu            Client:   Theerachart/Holzer/      Inlet :
Base:  275.0                 Inten :   91933             Masses:   101 > 999
Norm:  275.0                 RIC   :   369182            #peaks:   908
Peak:  1000.00  mmu
Data:  AVER : Scans All from /usr/users/finnigan/data/34450_1.dat
```



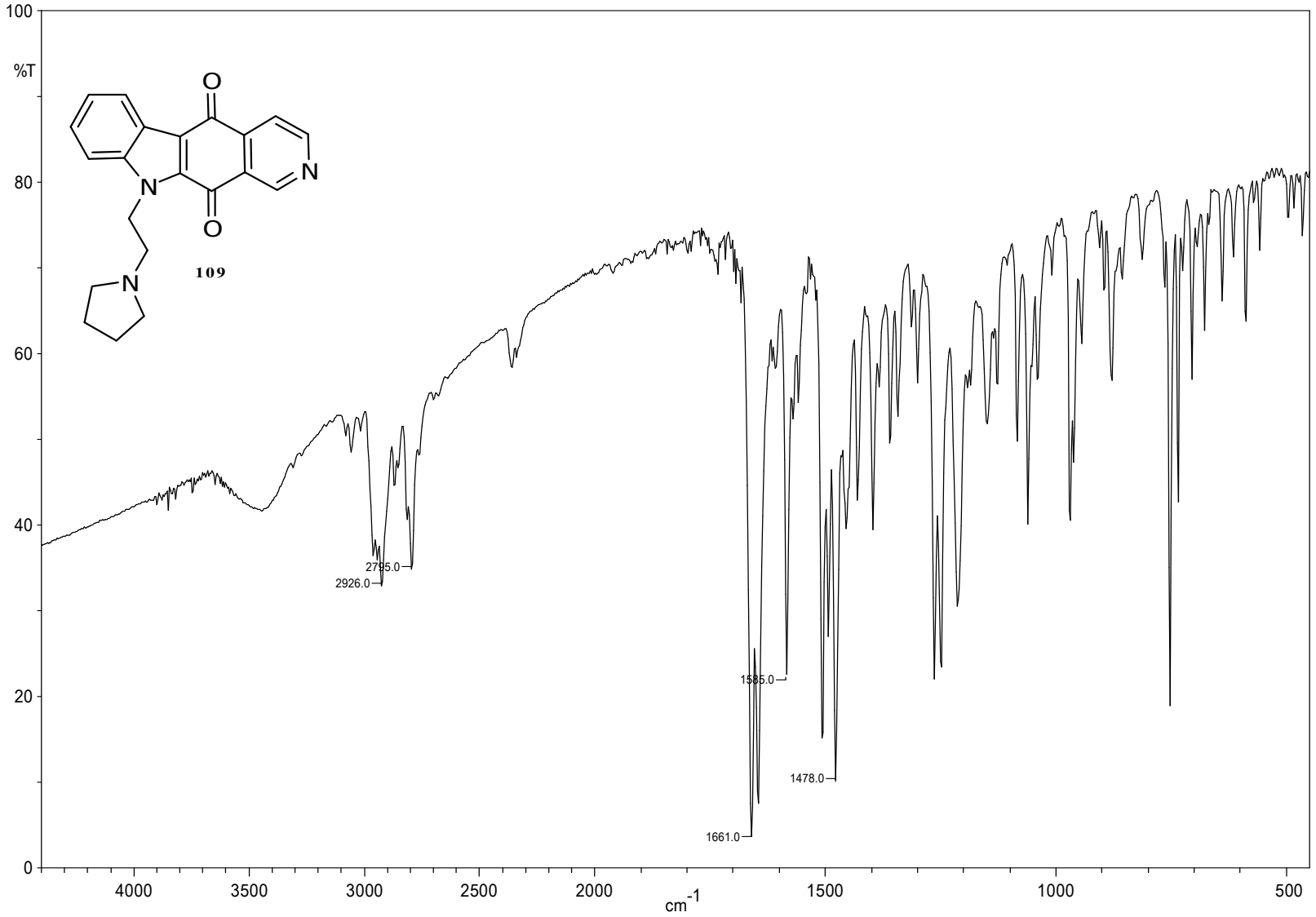
^{1}H NMR spectrum of **108** in DMSO-d_6.



^{13}C NMR spectrum of **108** in DMSO-d_6.

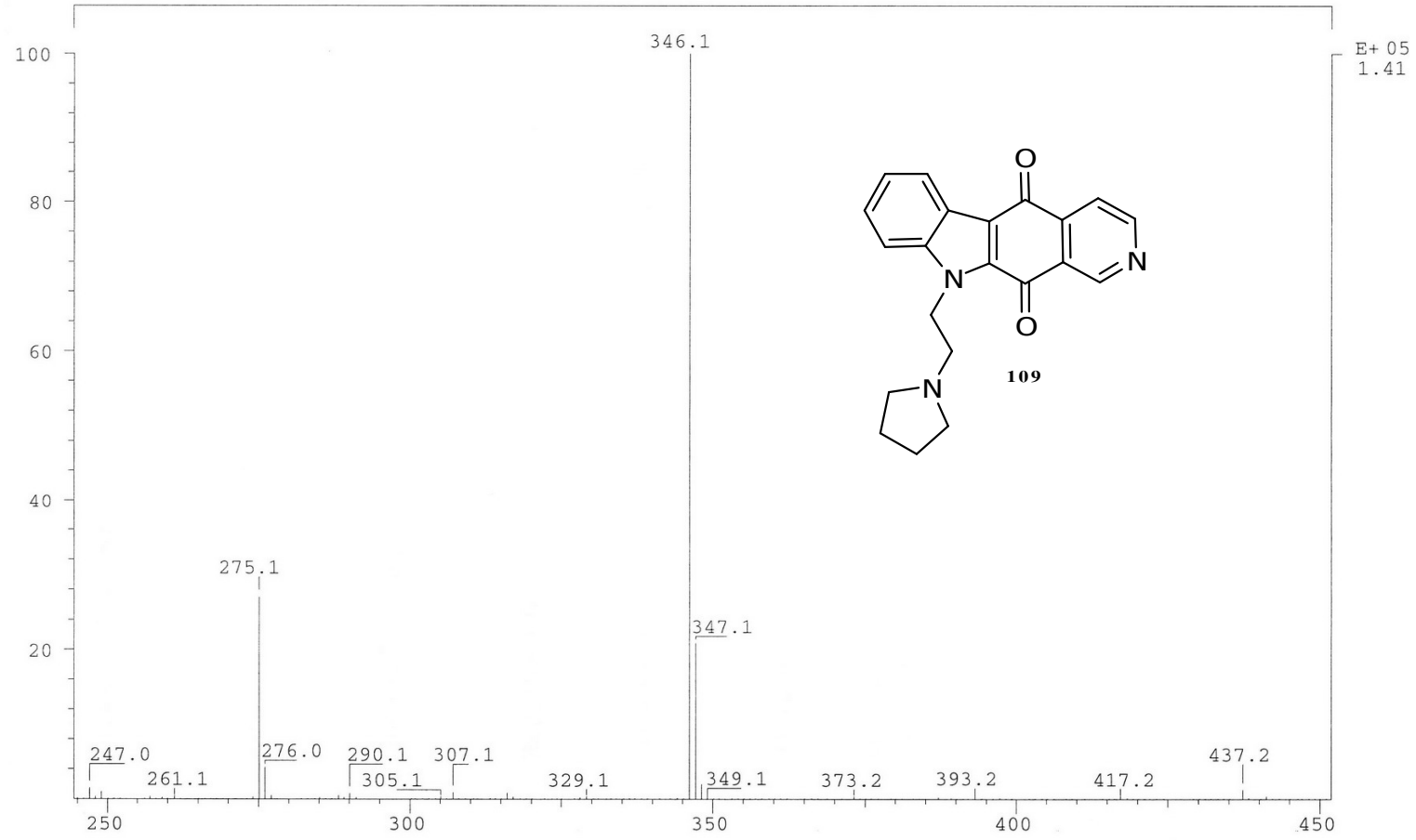


IR spectrum of **109** (KBr).

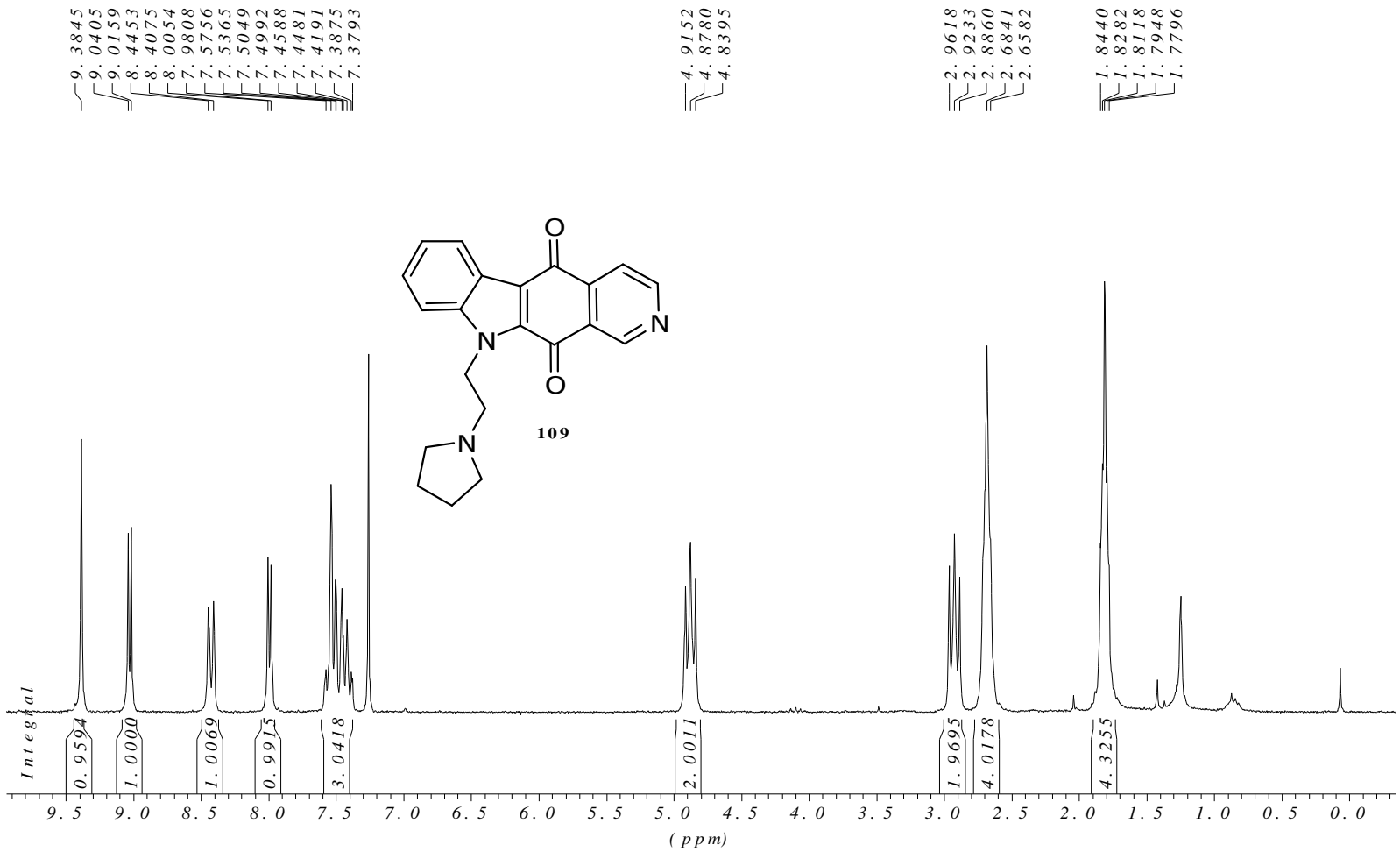


Mass spectrum of **109**.

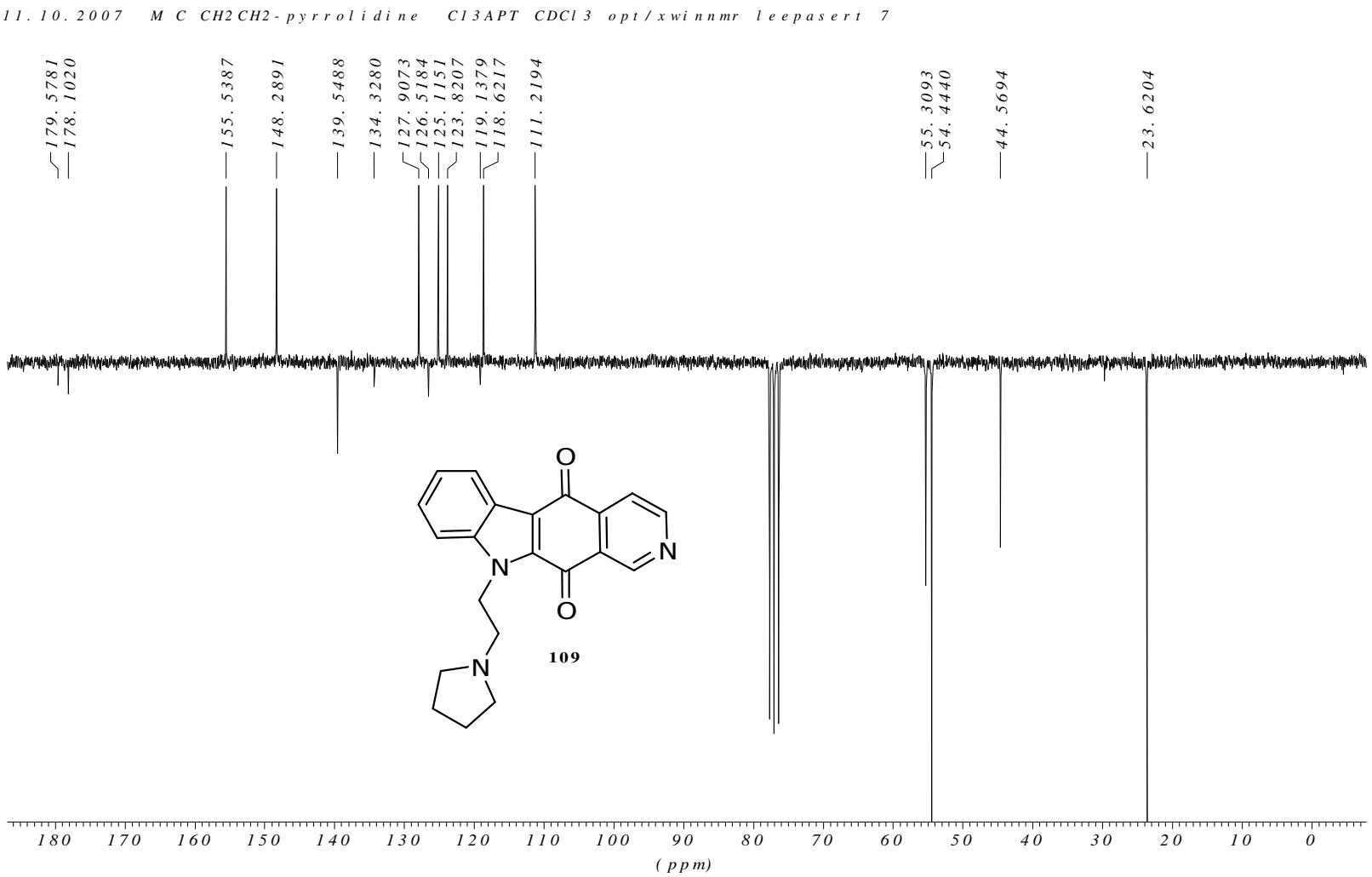
```
SPEC:  00000000000000000000000000000av     24-Mar-95   Elapse:   00:26.9        1
Samp:  MS345                                           Start :   14:40:43       1
Comm:  4kV 3uA    MeOH/ACN
Mode:  ESI +VE +LMR  BSCAN (EXP) UP LR NRM             Study :   ESI
Oper:  phu           Client:  Theerachart/Holzer/      Inlet :
Base:  346.1                 Inten :   140728          Masses:   101 > 999
Norm:  346.1                 RIC   :   302787          #peaks:   735
Peak:  1000.00  mmu
Data:  AVER : Scans All from /usr/users/finnigan/data/34442_2.dat
```



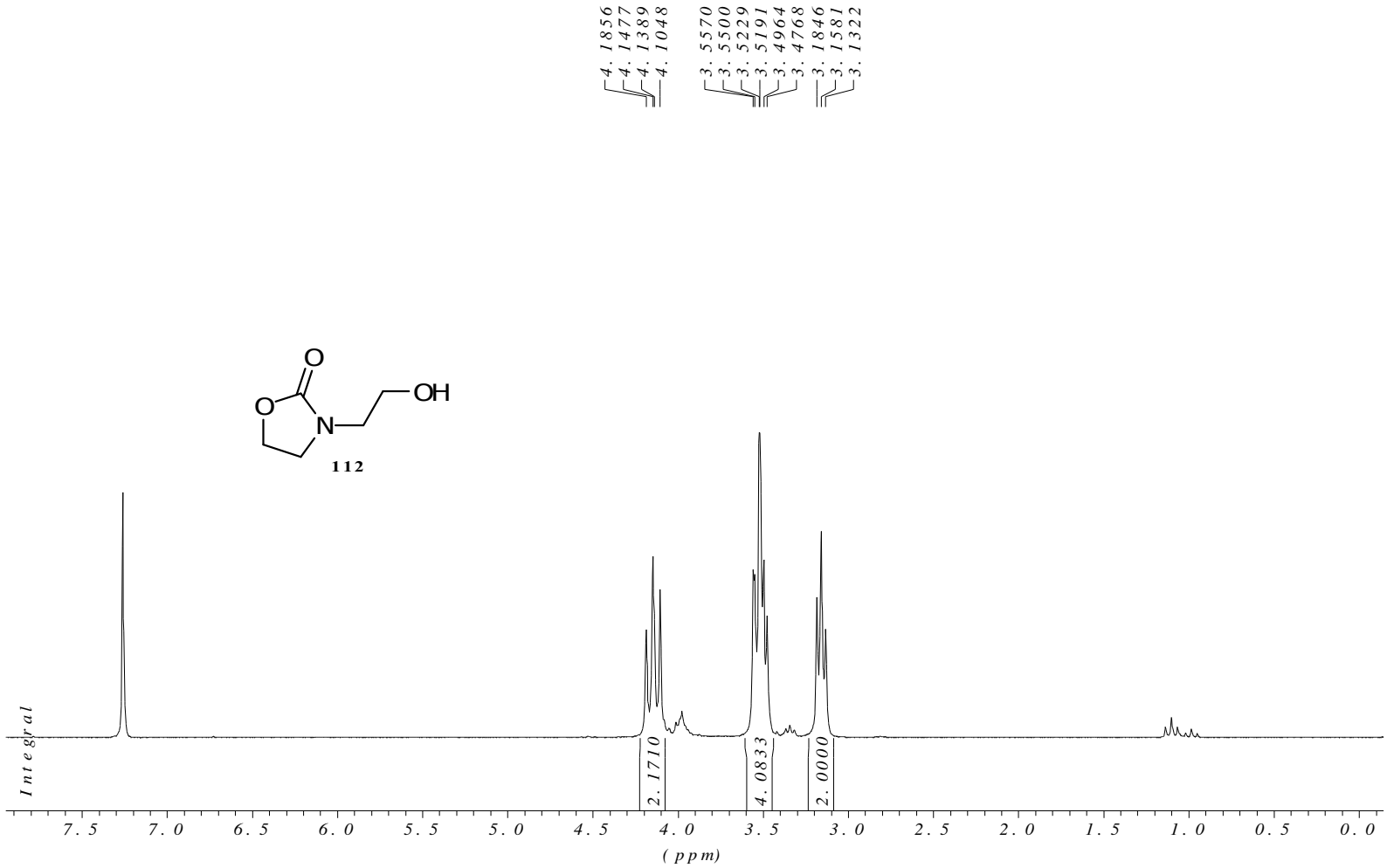
^{1}H NMR spectrum of **109** in $CDCl_3$.



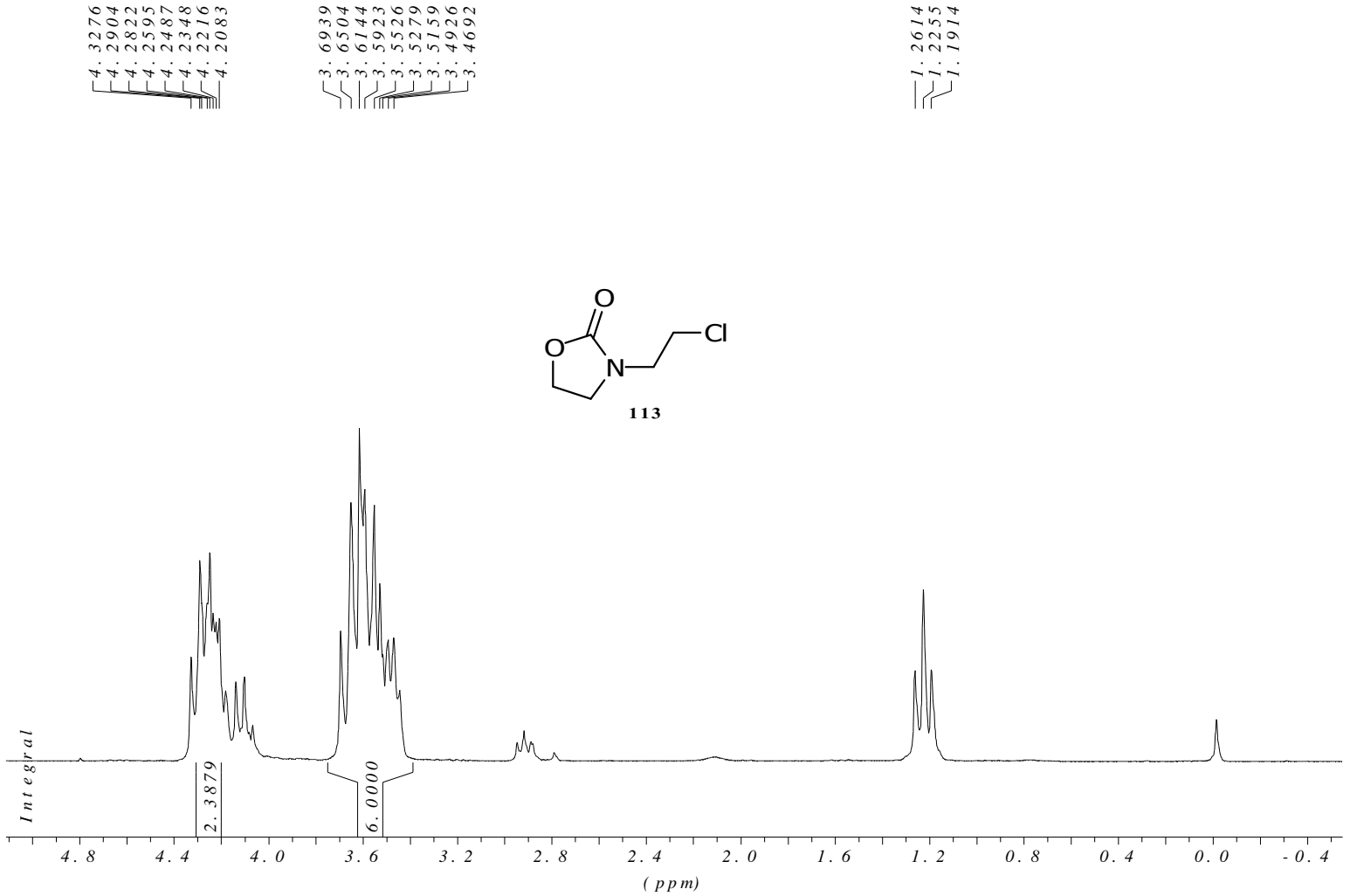
^{13}C NMR spectrum of **109** in $CDCl_3$.



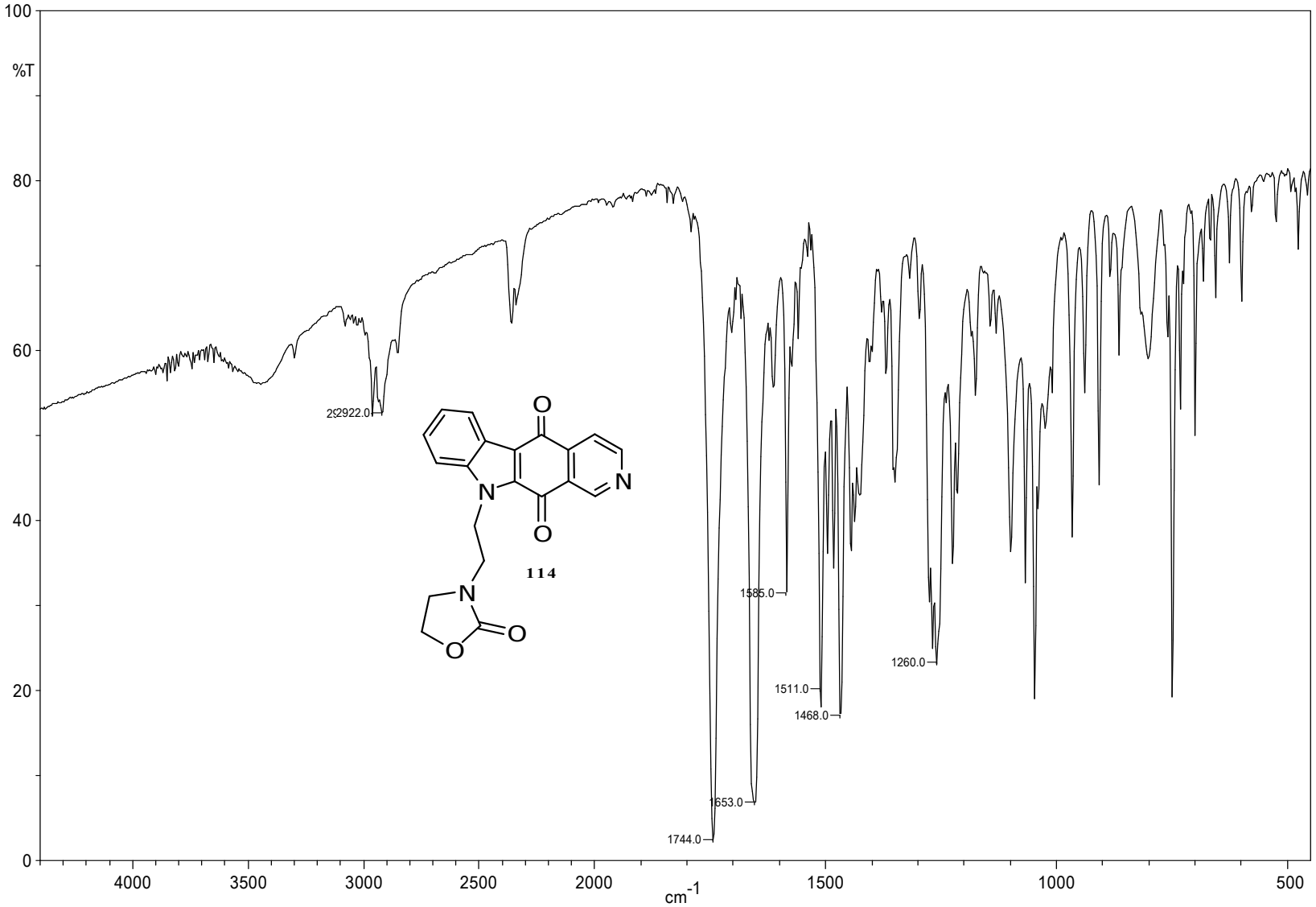
^{1}H NMR spectrum of **112** in $CDCl_3$.



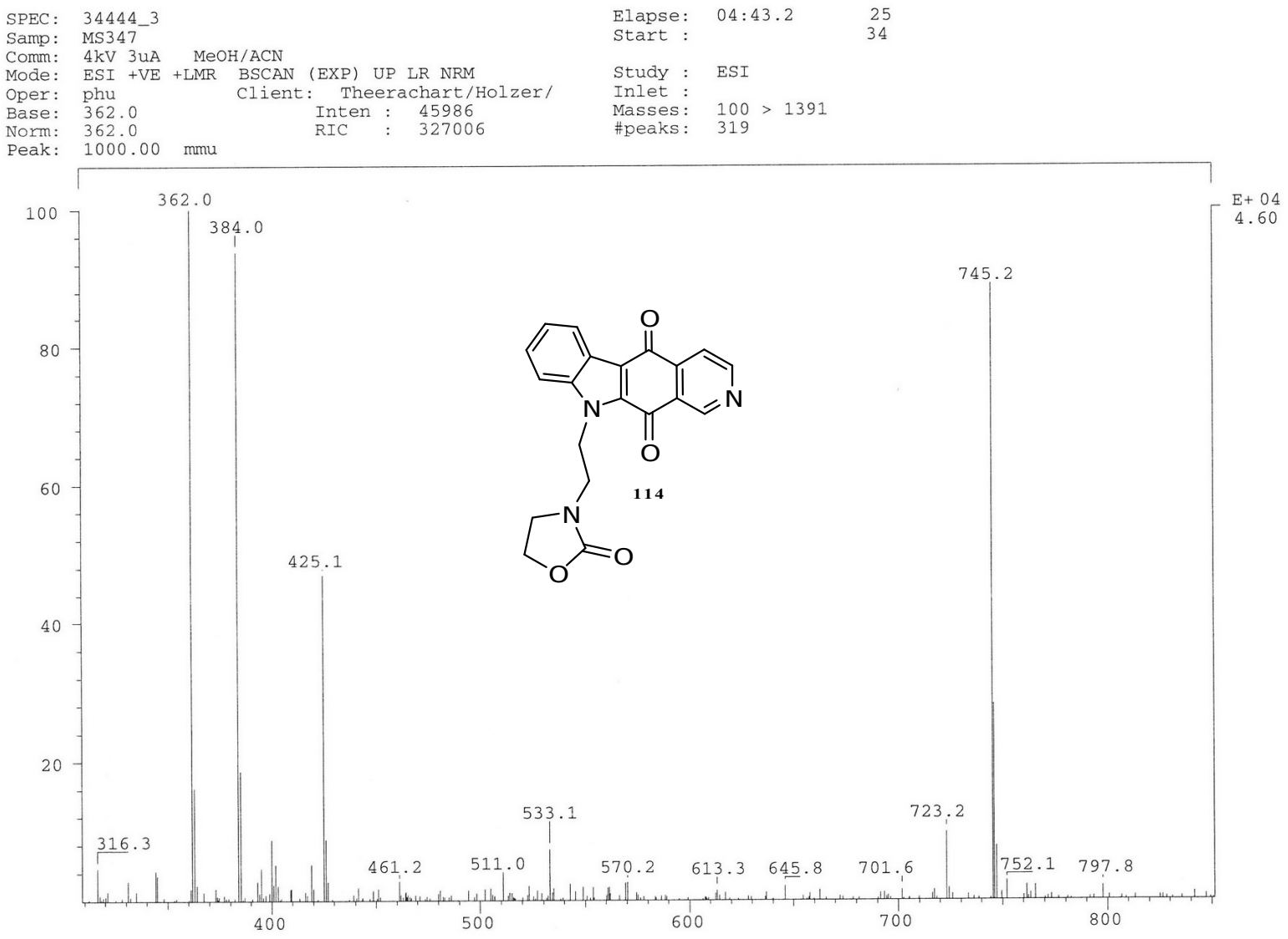
^{1}H NMR spectrum of **113** in $CDCl_3$.



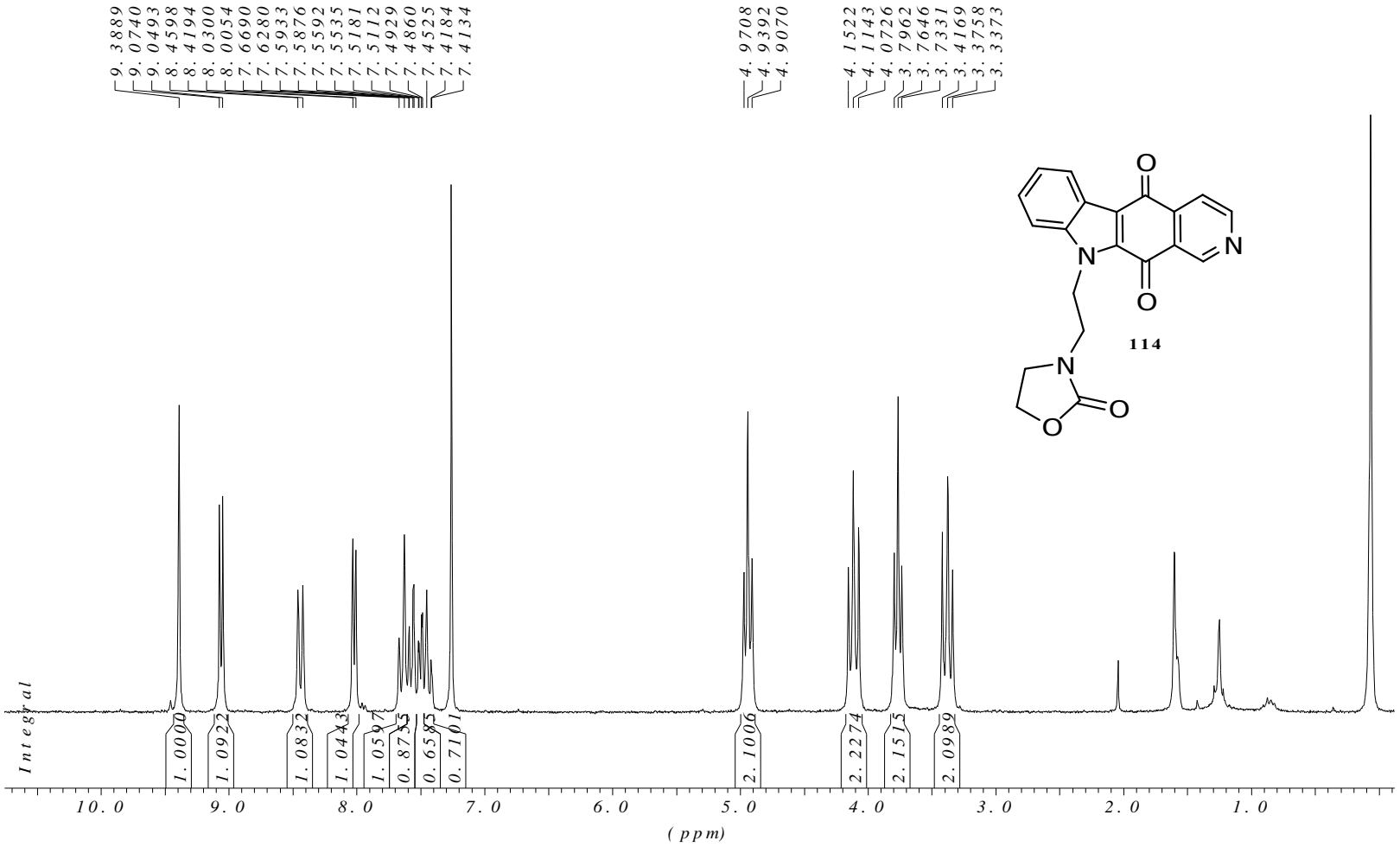
IR spectrum of **114** (KBr).



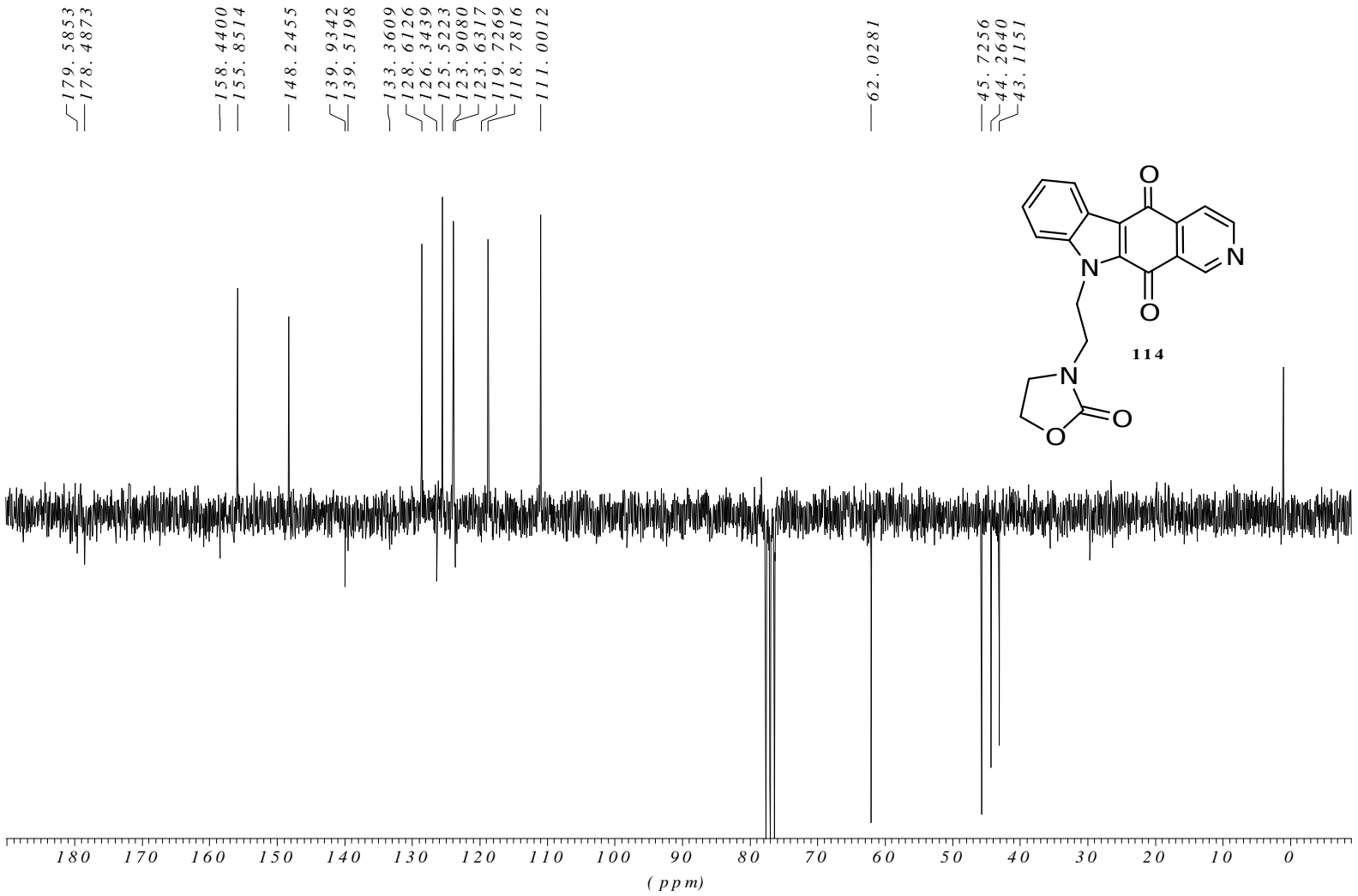
Mass spectrum of **114**.



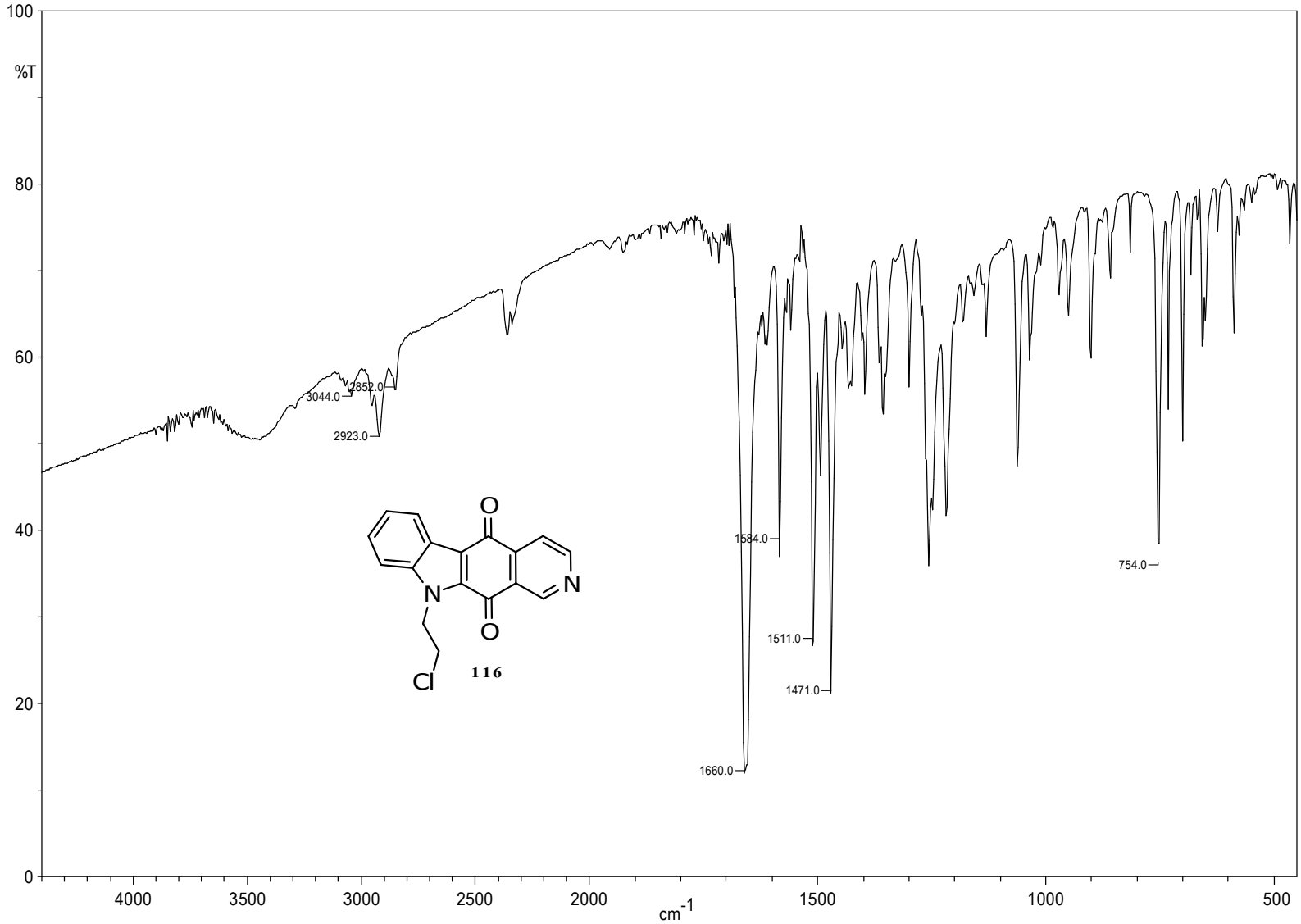
^{1}H NMR spectrum of **114** in $CDCl_3$.



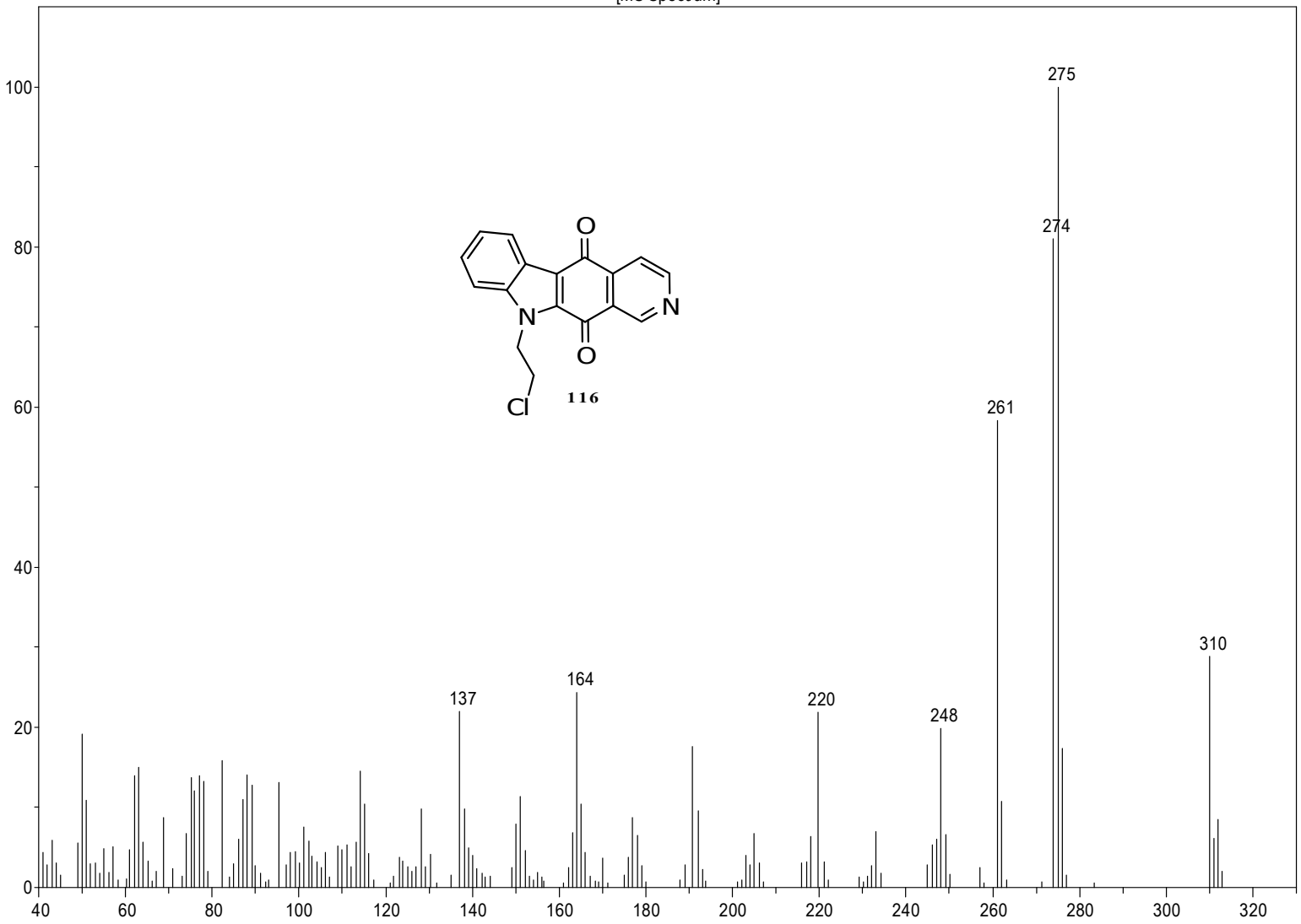
^{13}C NMR spectrum of **114** in $CDCl_3$.



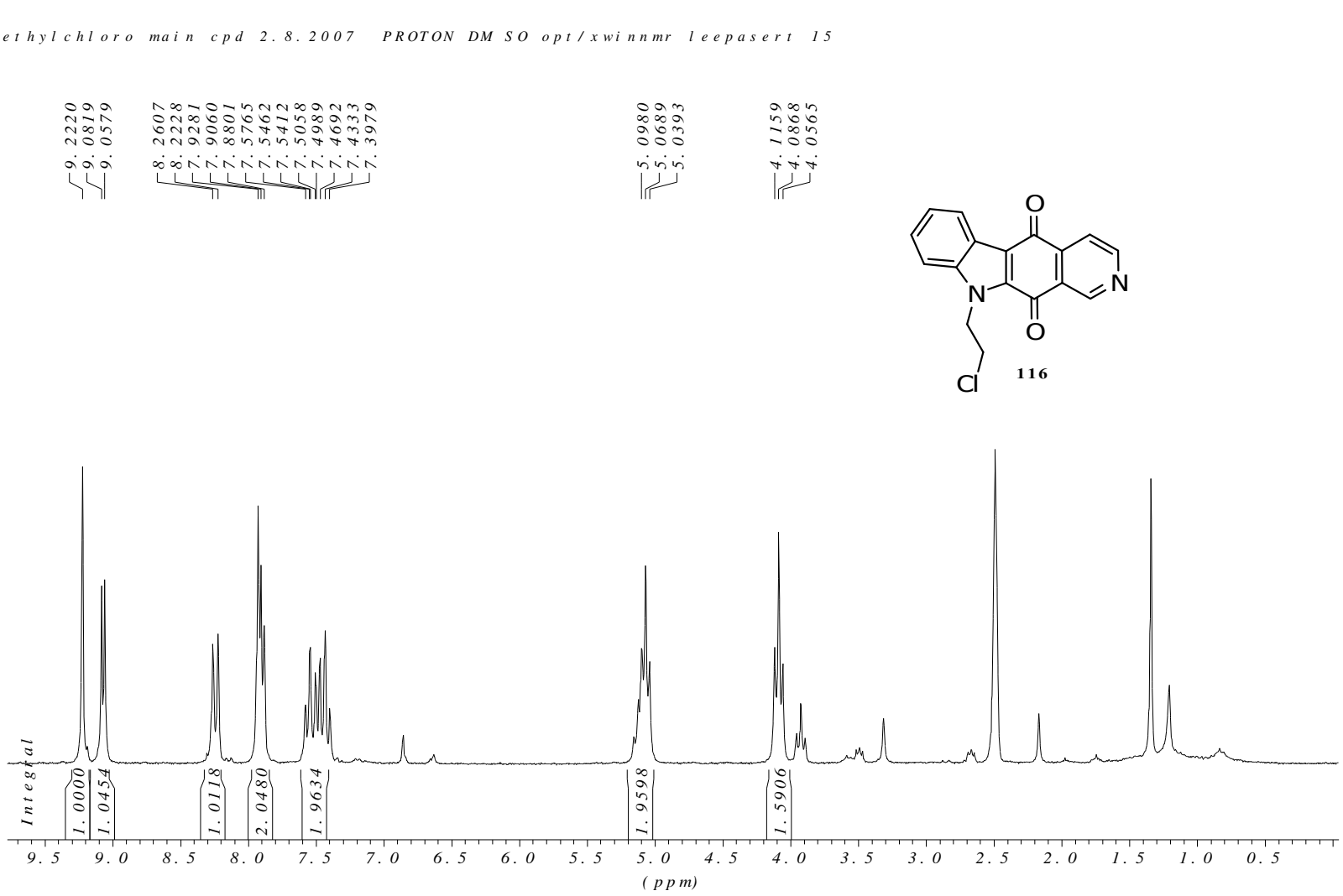
IR spectrum of **116** (KBr).



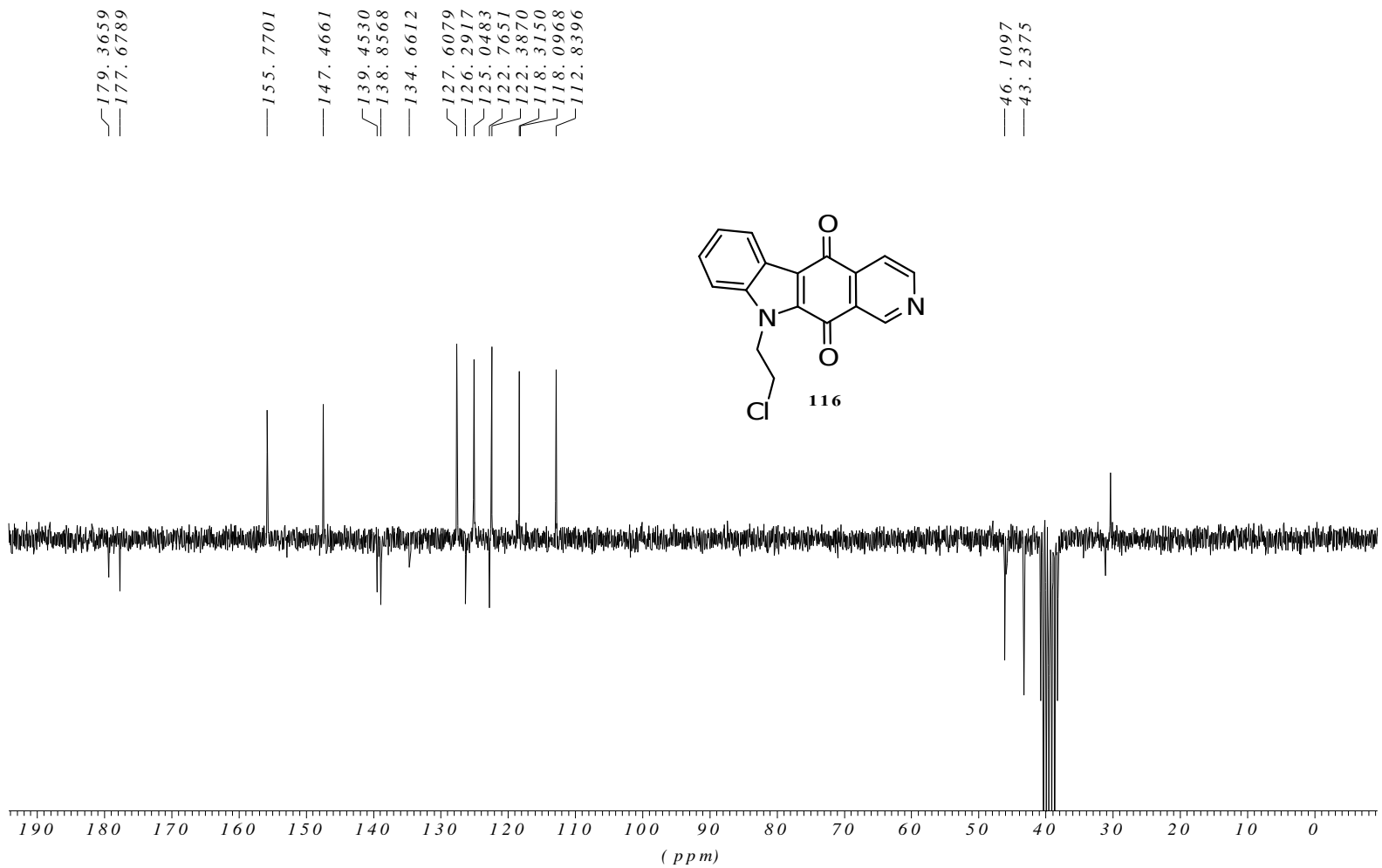
Mass spectrum of **116**.



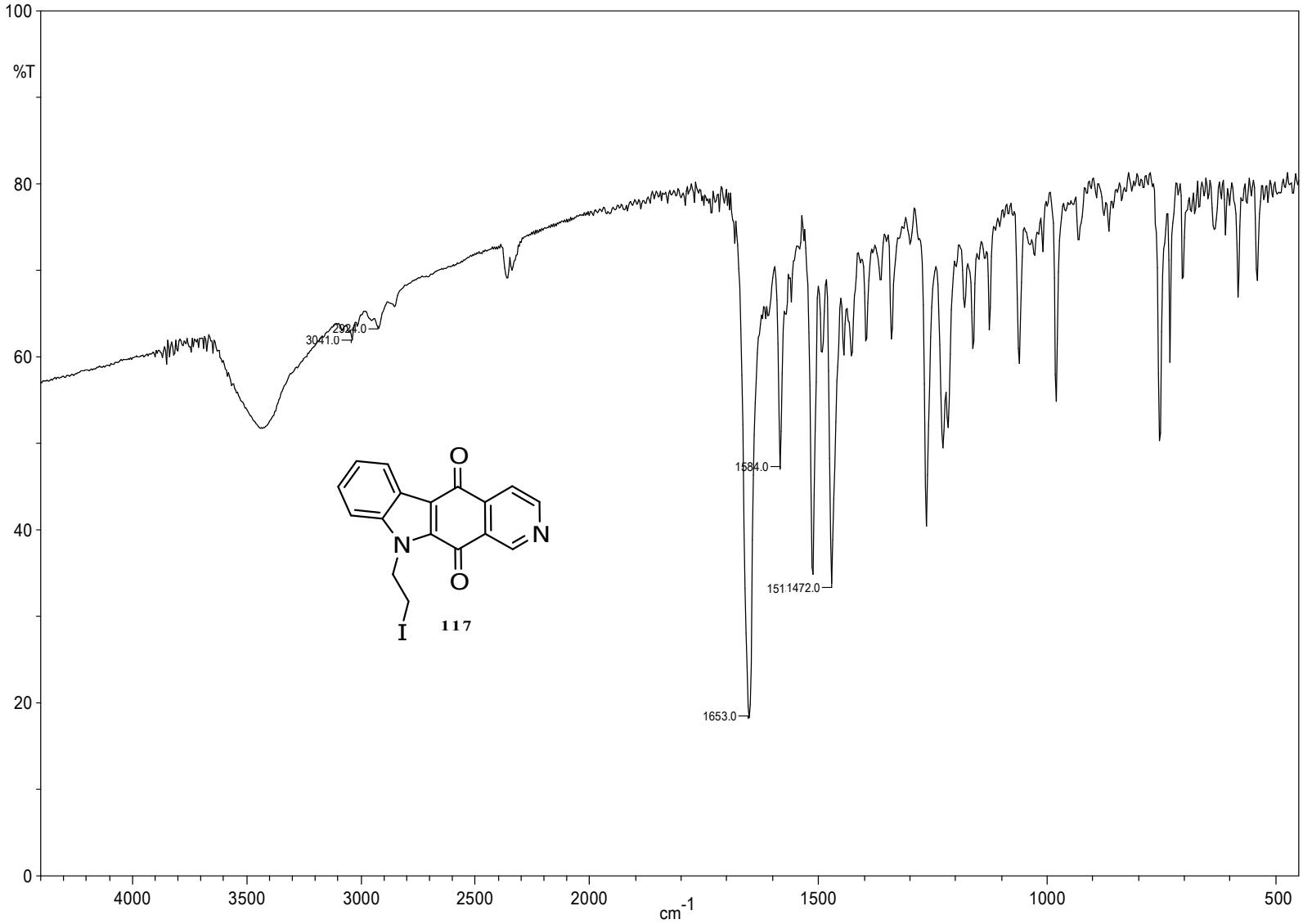
^{1}H NMR of spectrum of **116** in DMSO-d$_6$.



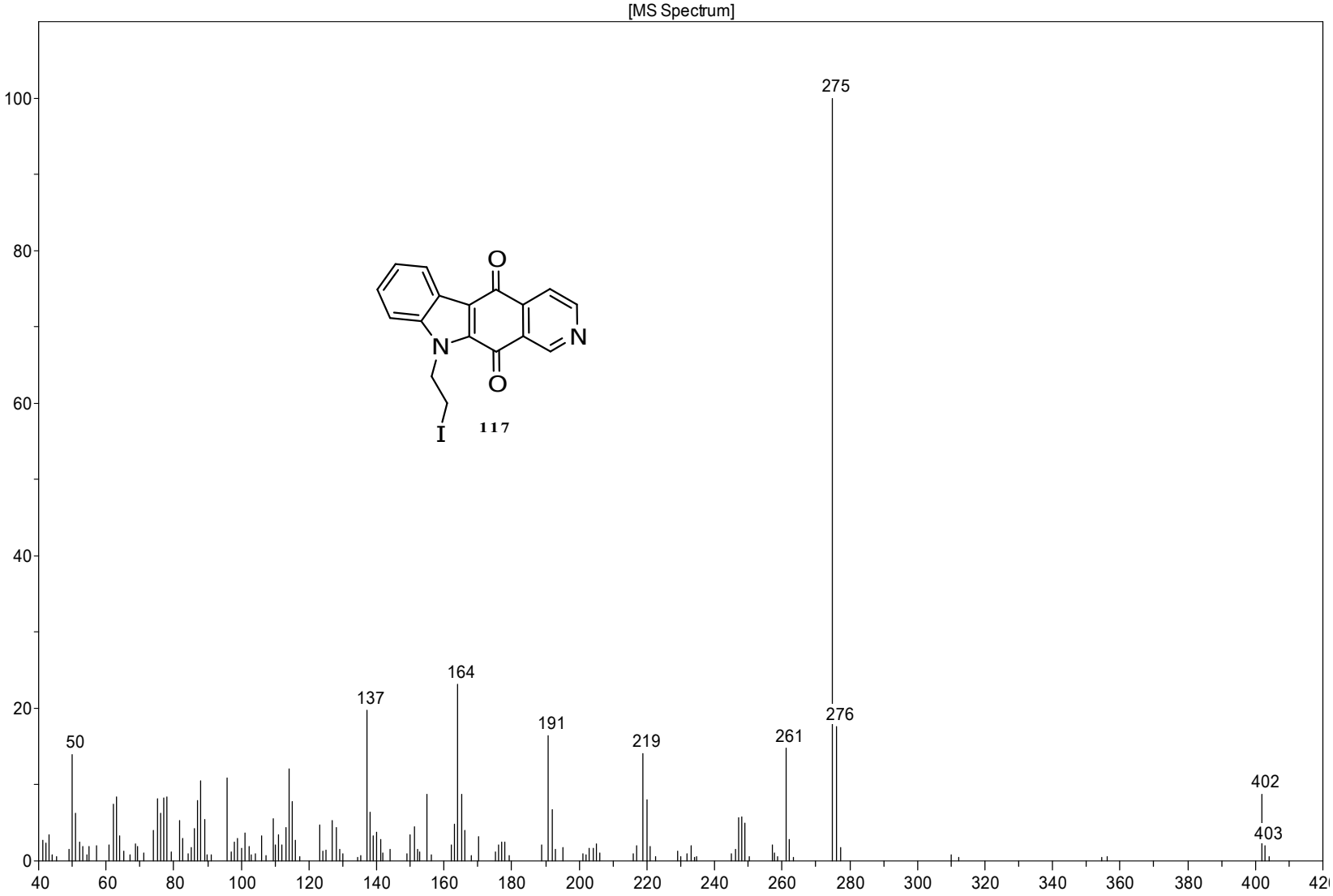
^{13}C NMR of spectrum of **116** in DMSO-d_6.



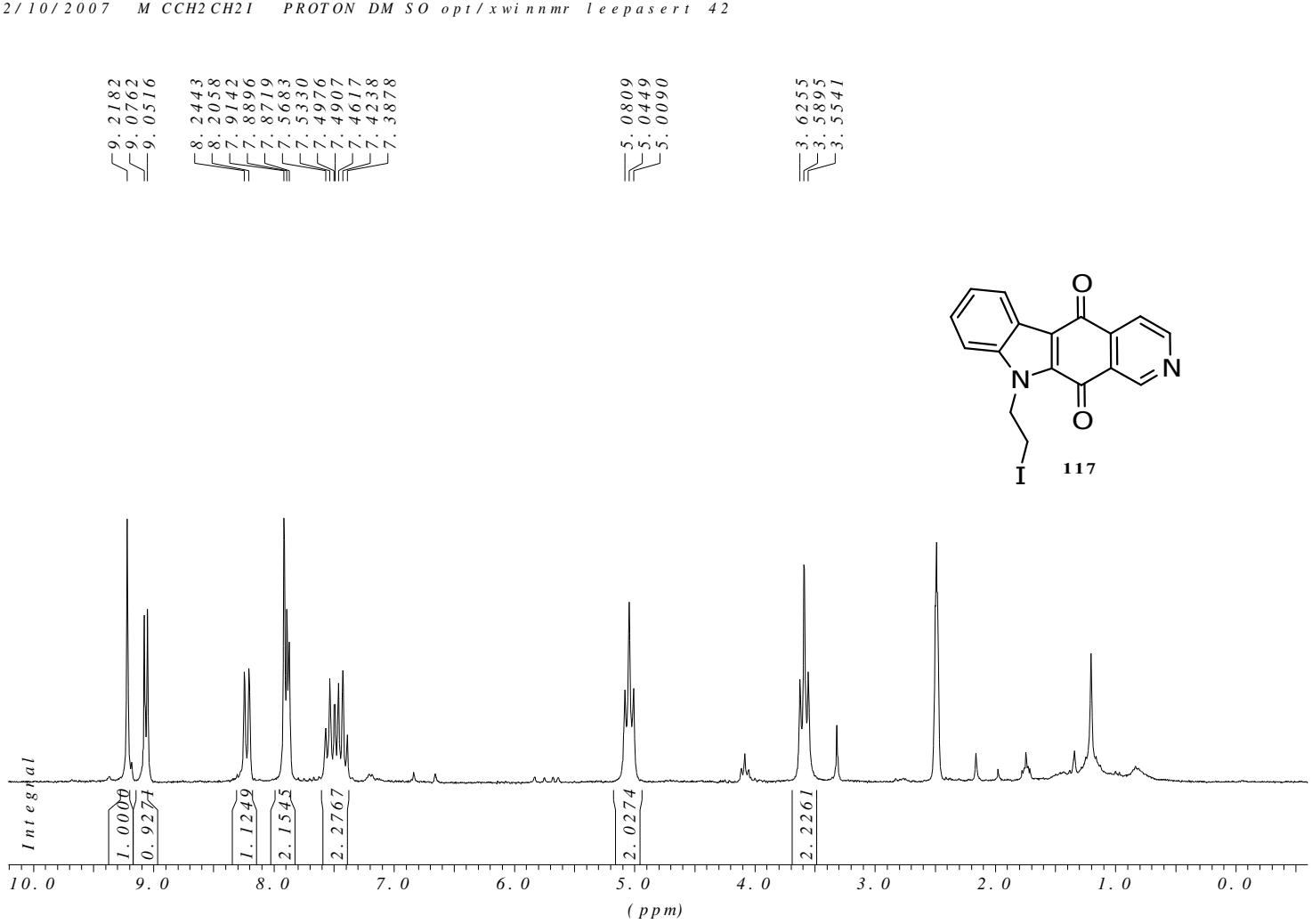
IR spectrum of **117** (KBr).



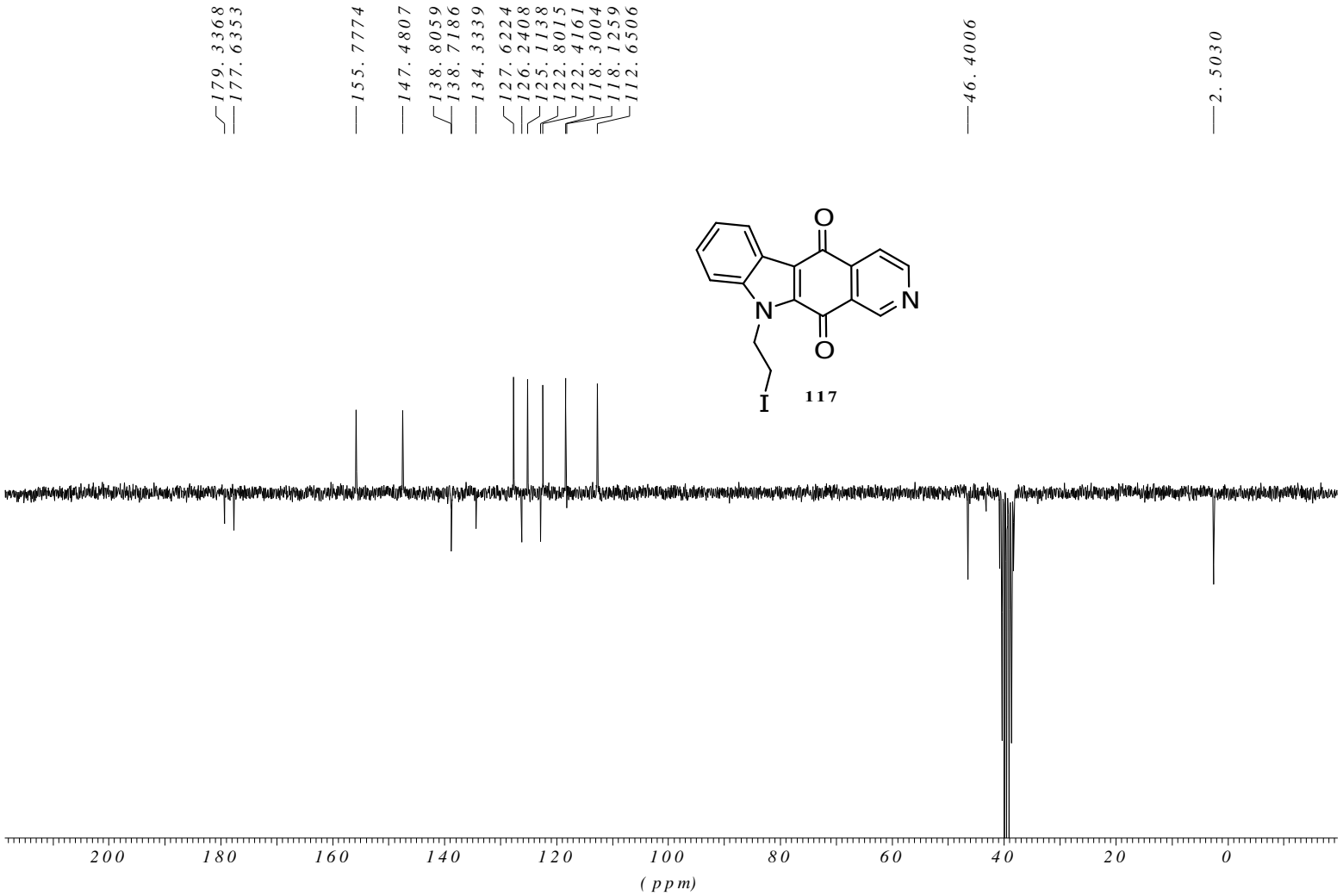
Mass spectrum of **117**.



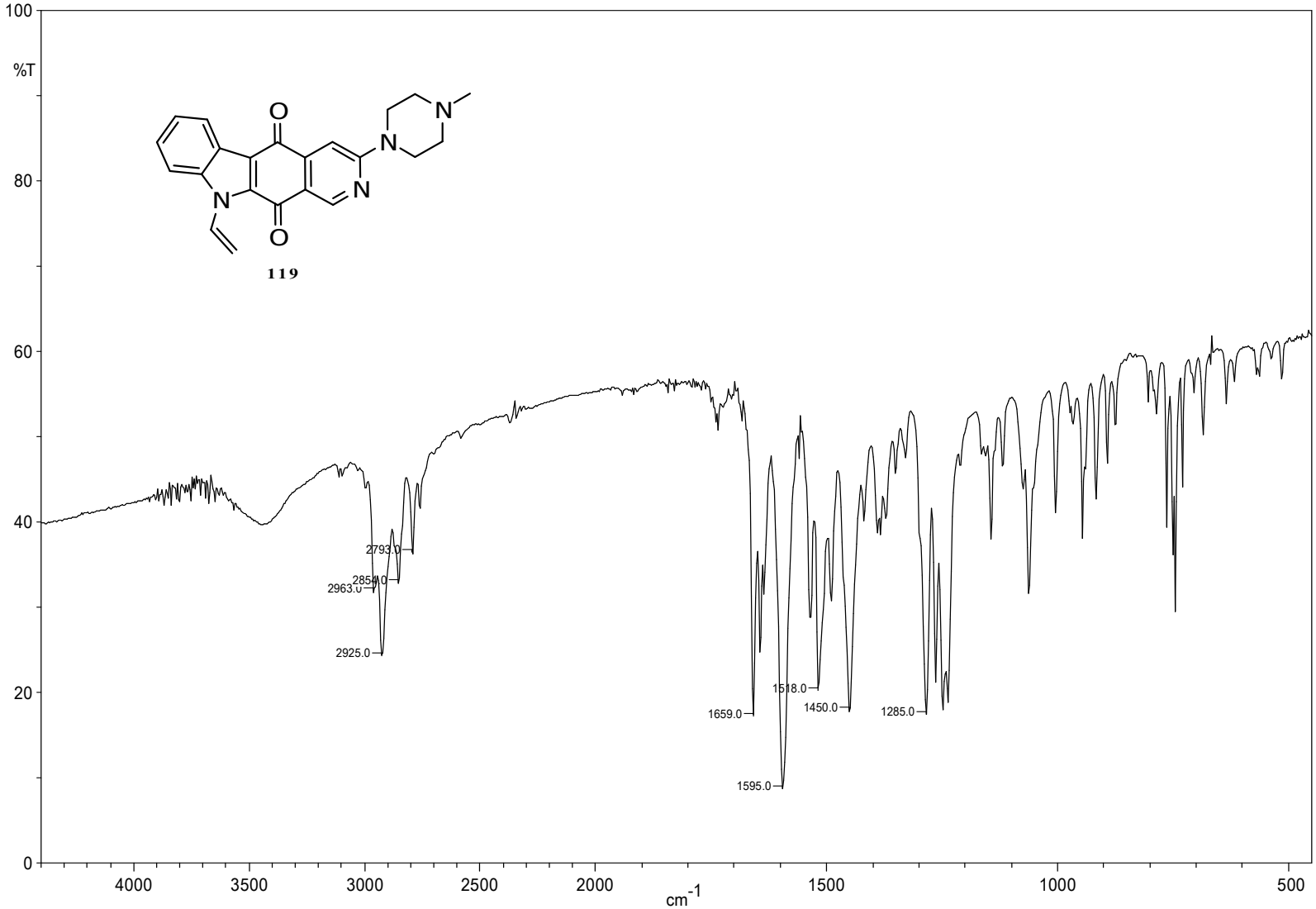
^{1}H NMR of spectrum of **117** in DMSO-d_6



^{13}C NMR of spectrum of **117** in DMSO-d_6.



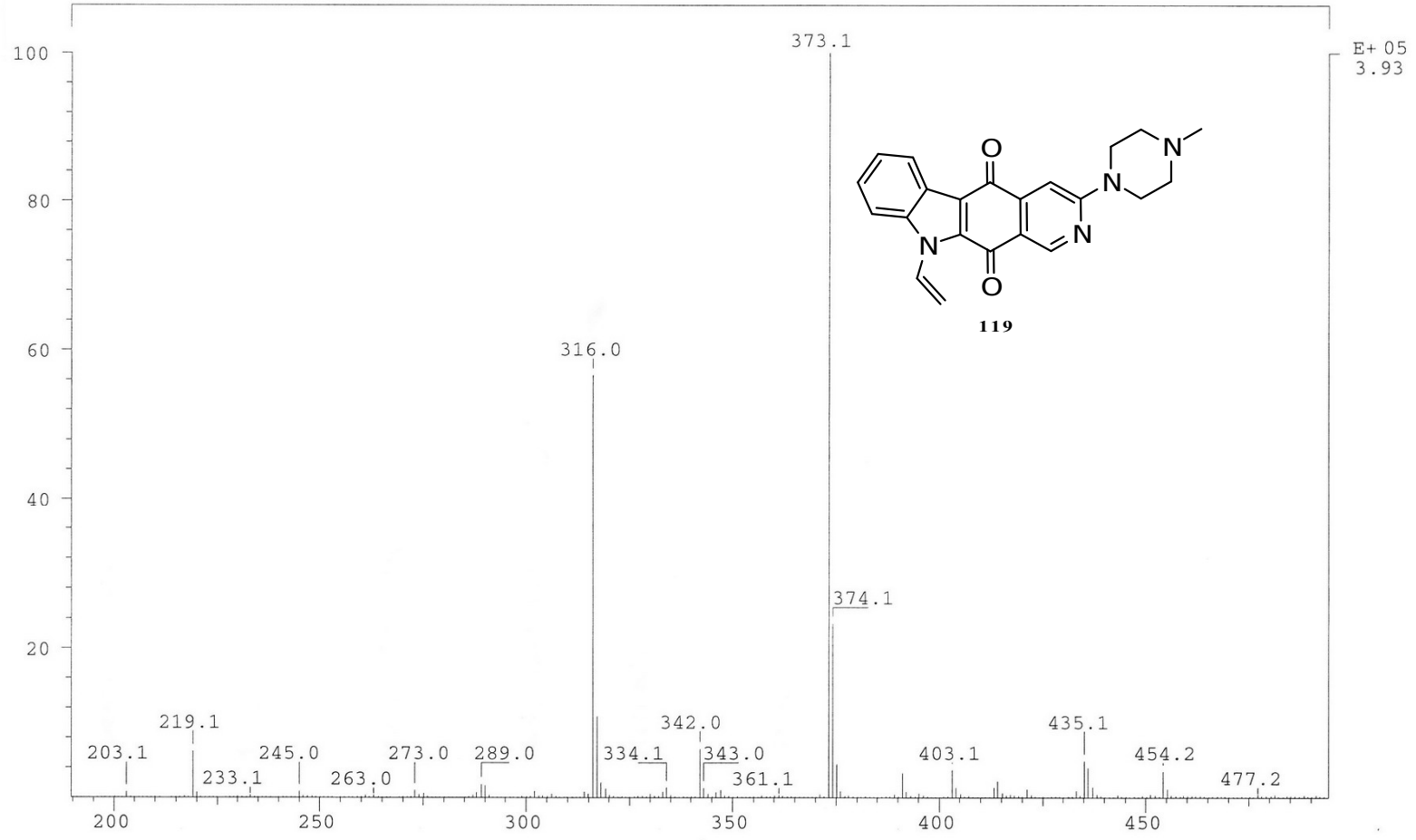
IR spectrum of **119** (KBr).



119

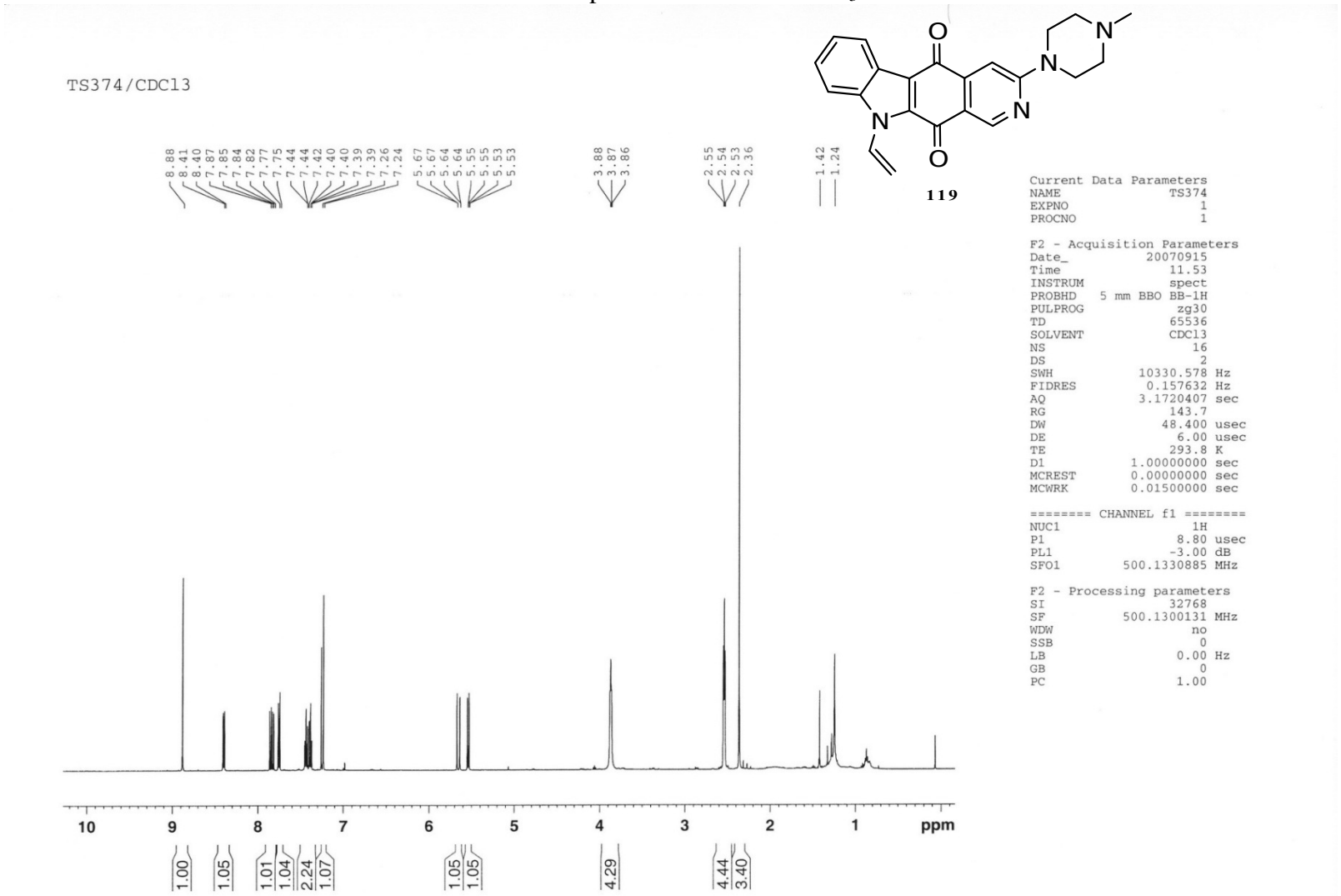
Mass spectrum of **119**.

```
SPEC:  00000000000000000000000000000000     24-Mar-95   Elapse:   00:27.9        1
Samp:  MS372                                             Start :   16:58:57       2
Comm:  4kV 3uA   MeOH/ACN
Mode:  ESI +VE +APICID LMR  BSCAN (EXP) UP LR NRM
Oper:  phu           Client:  Theerachart/Holzer/        Inlet :
Base:  373.1                 Inten :  393228             Masses:   101 > 999
Norm:  373.1                 RIC   :  1551520            #peaks:   905
Peak:  1000.00  mmu
Data:  AVER : Scans All from /usr/users/finnigan/data/34452_1.dat
```



119

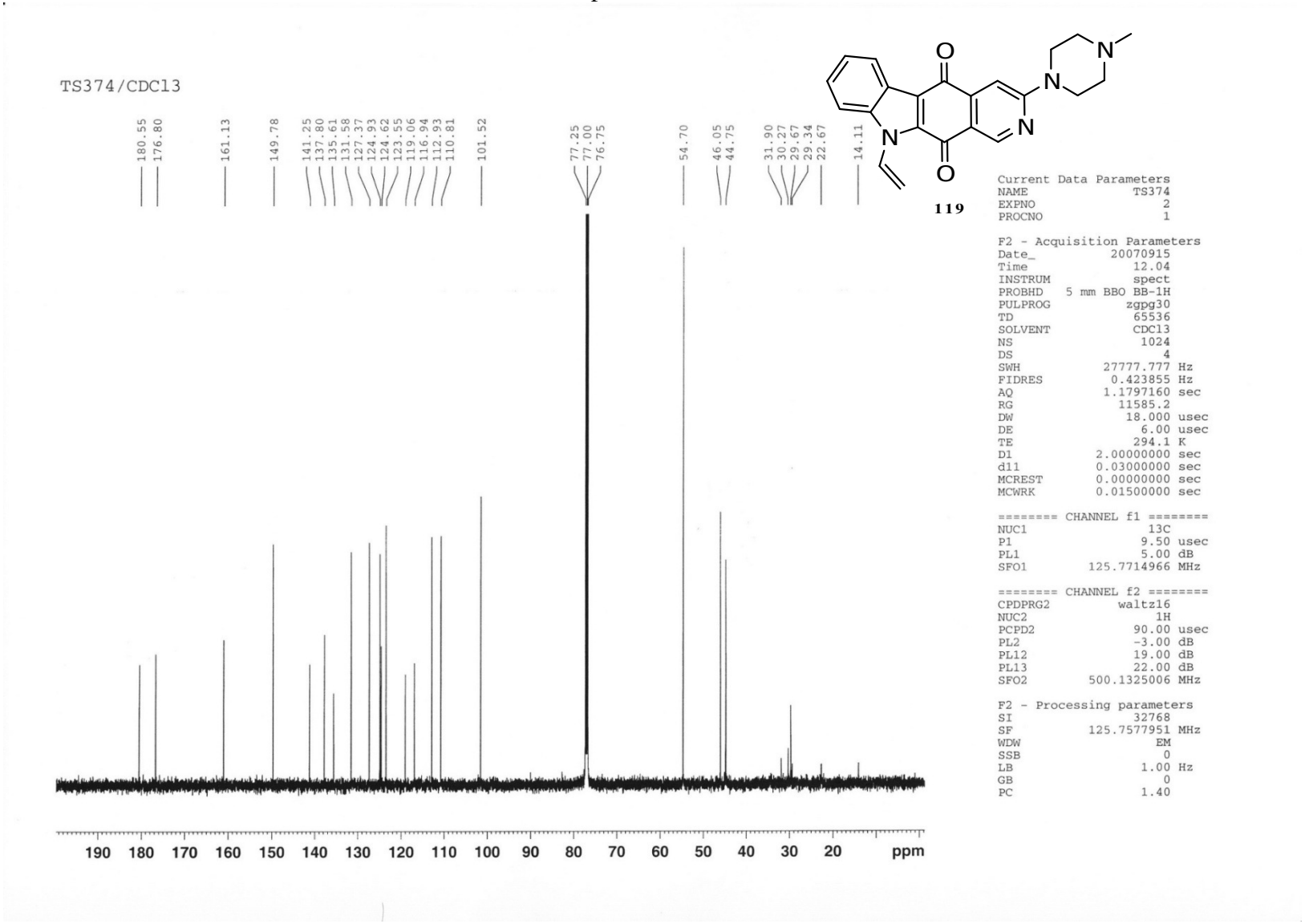
^{1}H NMR spectrum of **119** in $CDCl_3$.



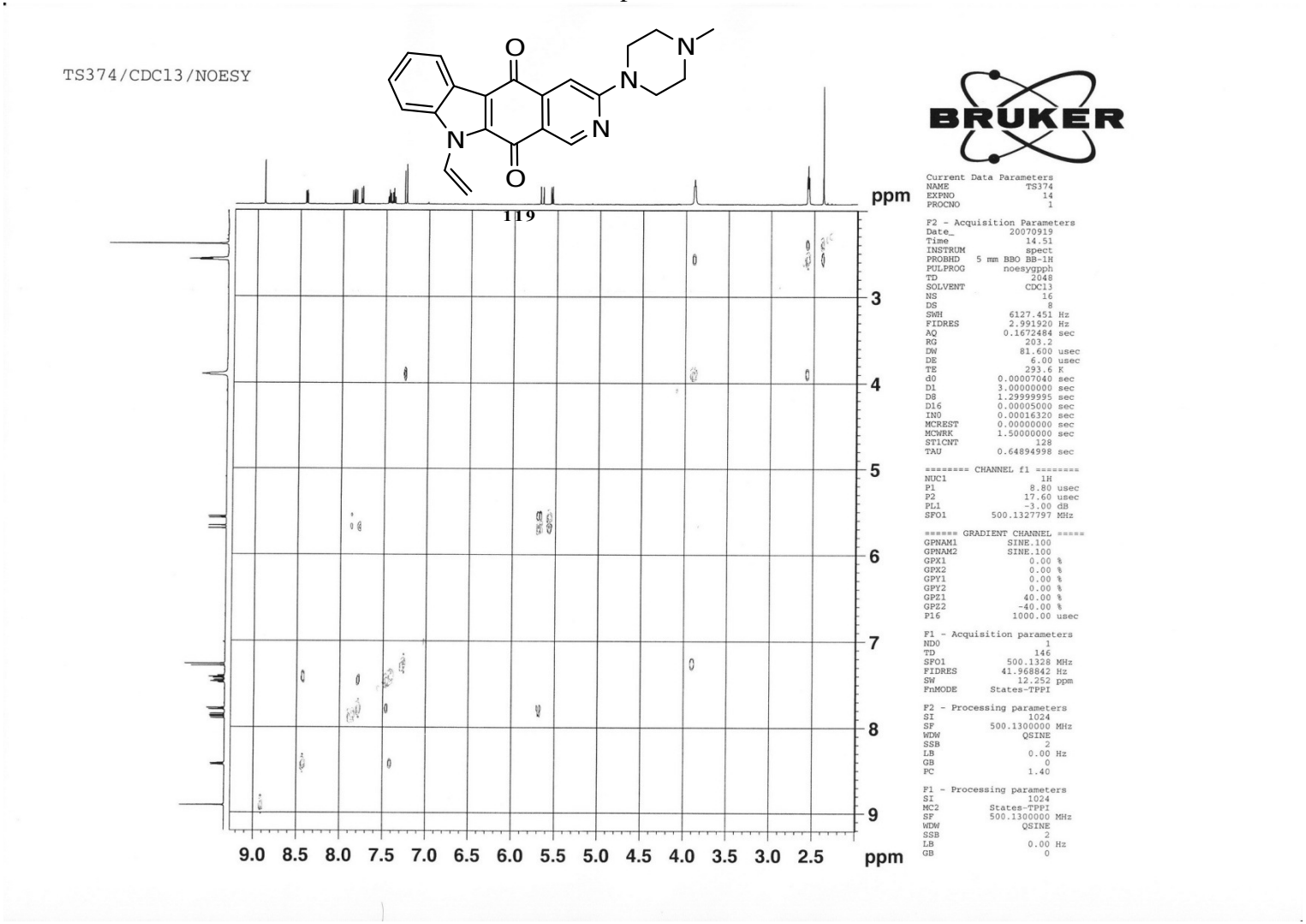
119

```
Current Data Parameters
NAME                  TS374
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20070915
Time                 11.53
INSTRUM              spect
PROBHD    5 mm BBO BB-1H
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH             10330.578 Hz
FIDRES          0.157632 Hz
AQ              3.1720407 sec
RG                   143.7
DW                48.400 usec
DE                 6.00 usec
TE                 293.8 K
D1             1.00000000 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                   8.80 usec
PL1                 -3.00 dB
SFO1         500.1330885 MHz

F2 - Processing parameters
SI                   32768
SF           500.1300131 MHz
WDW                    no
SSB                     0
LB                   0.00 Hz
GB                      0
PC                   1.00
```

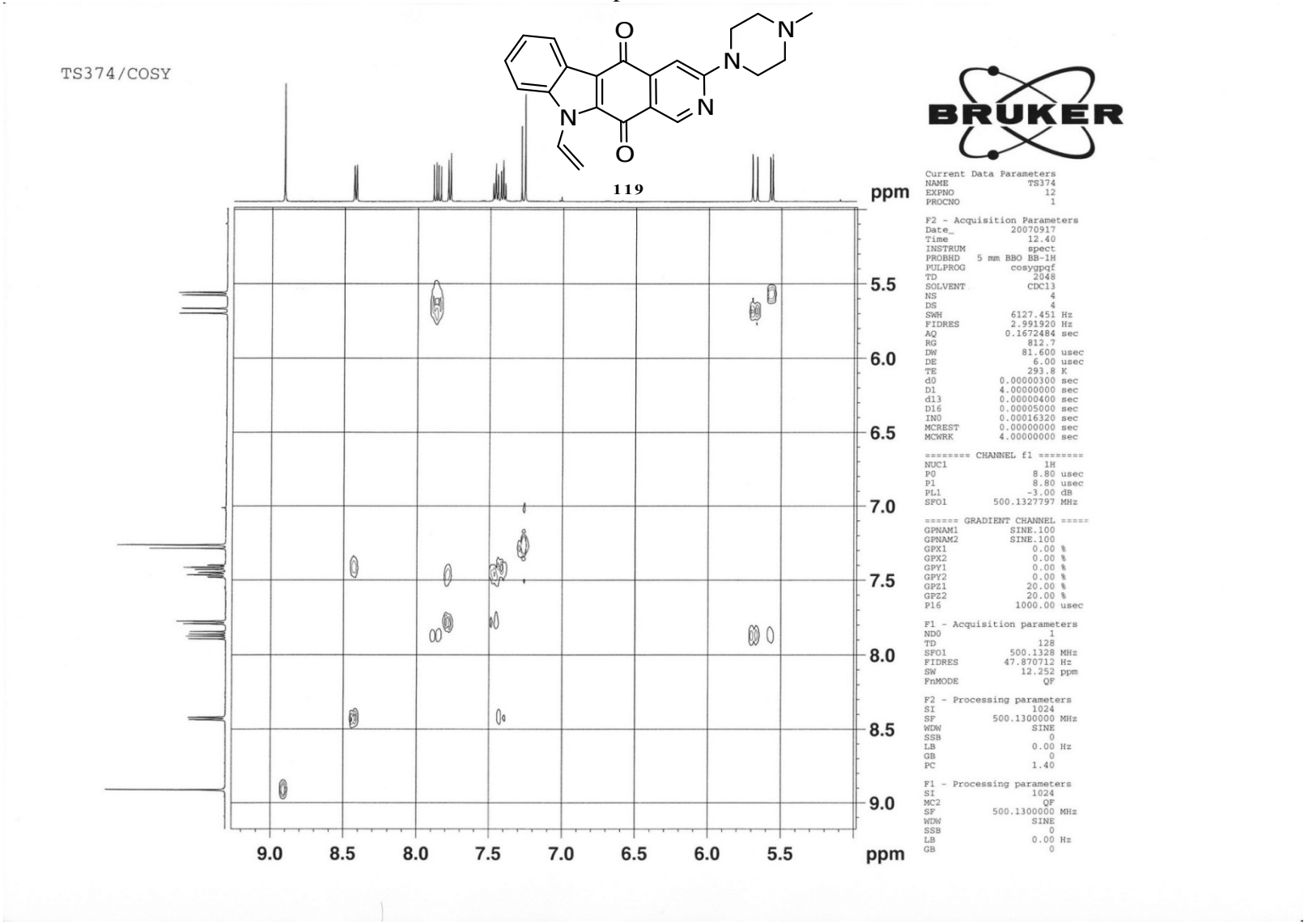
^{13}C NMR spectrum of **1** in $CDCl_3$.



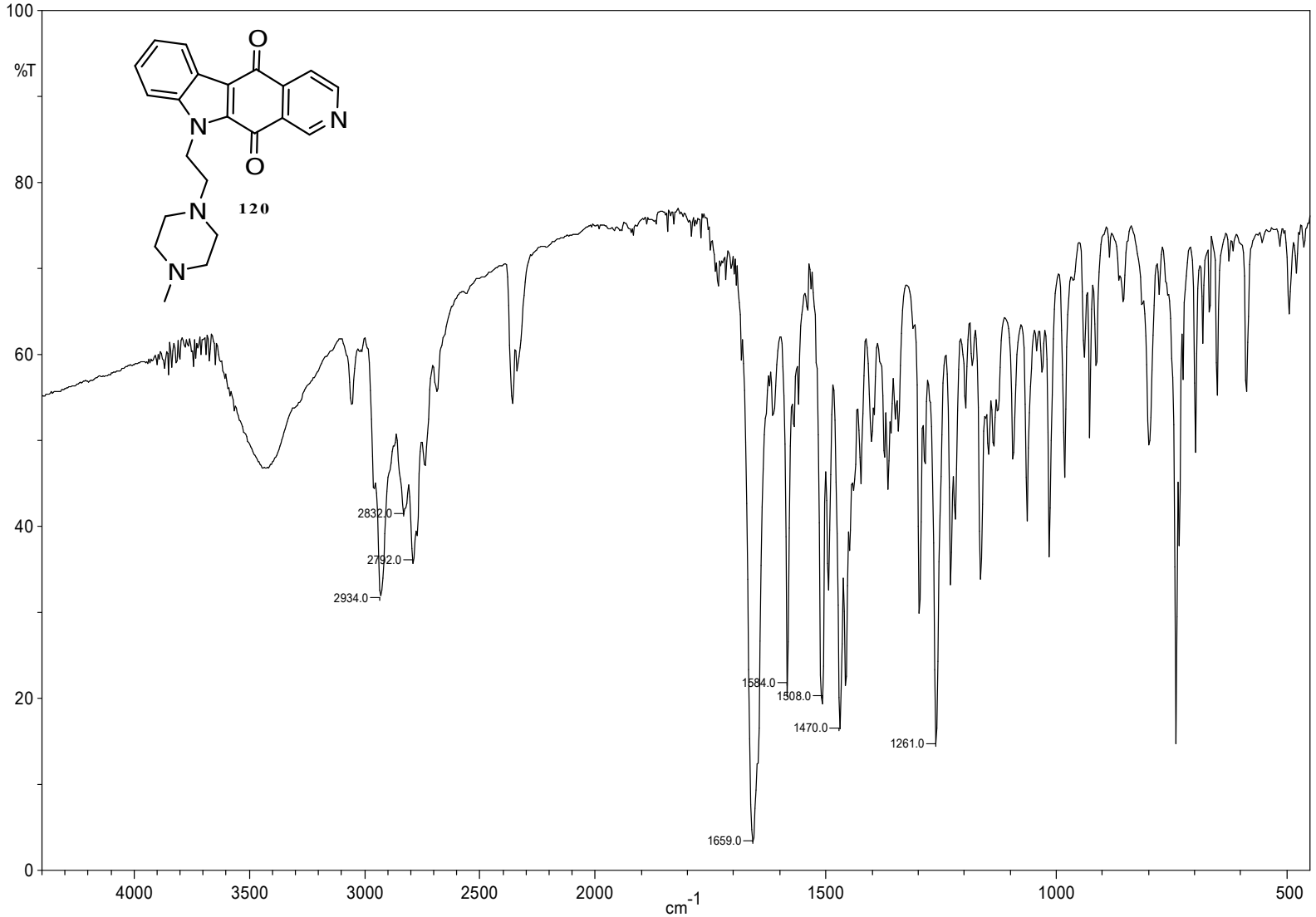
NOESY spectrum of **119**.



COSY spectrum of **119**.

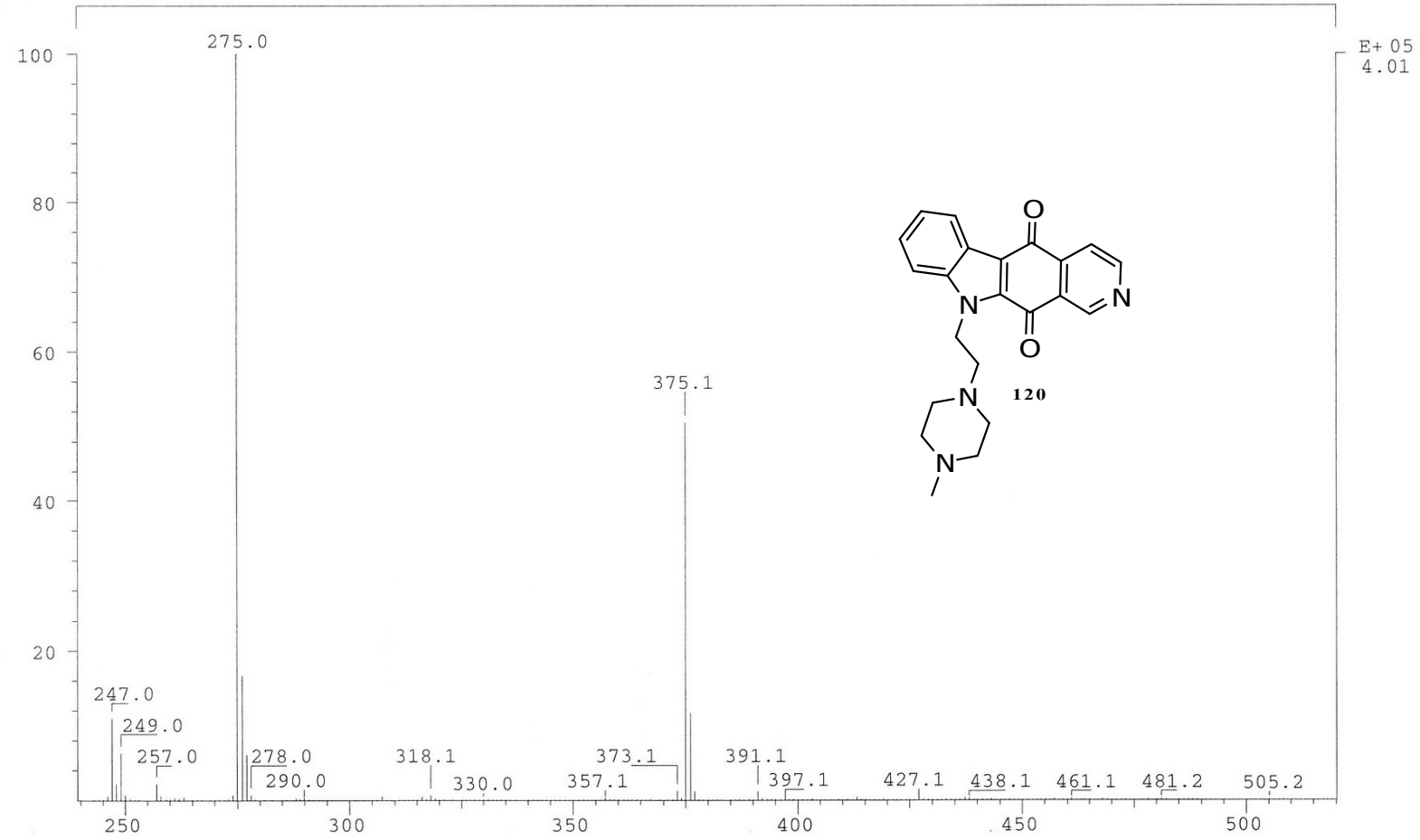


IR spectrum of **120** (KBr).

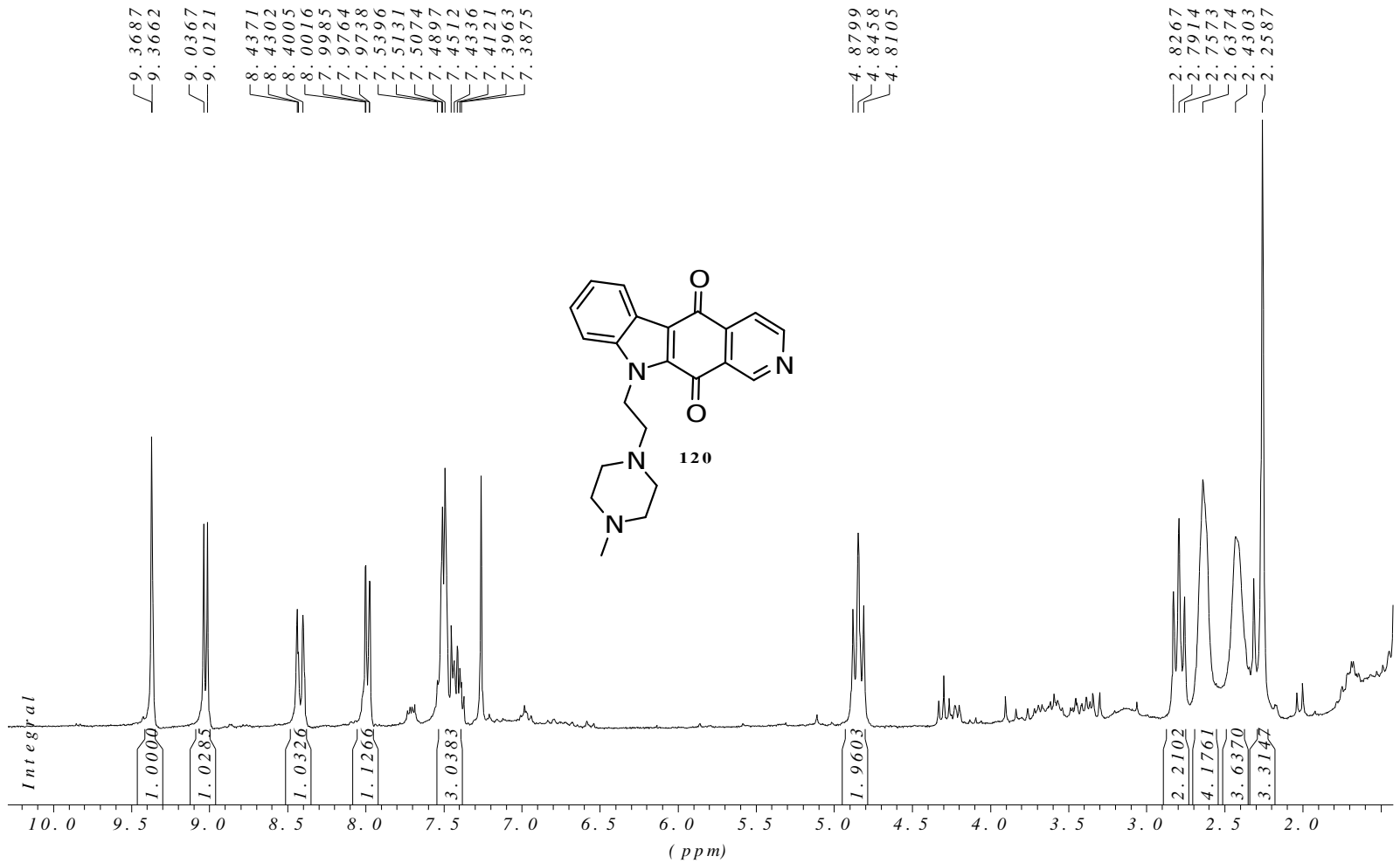


Mass spectrum of **120**.

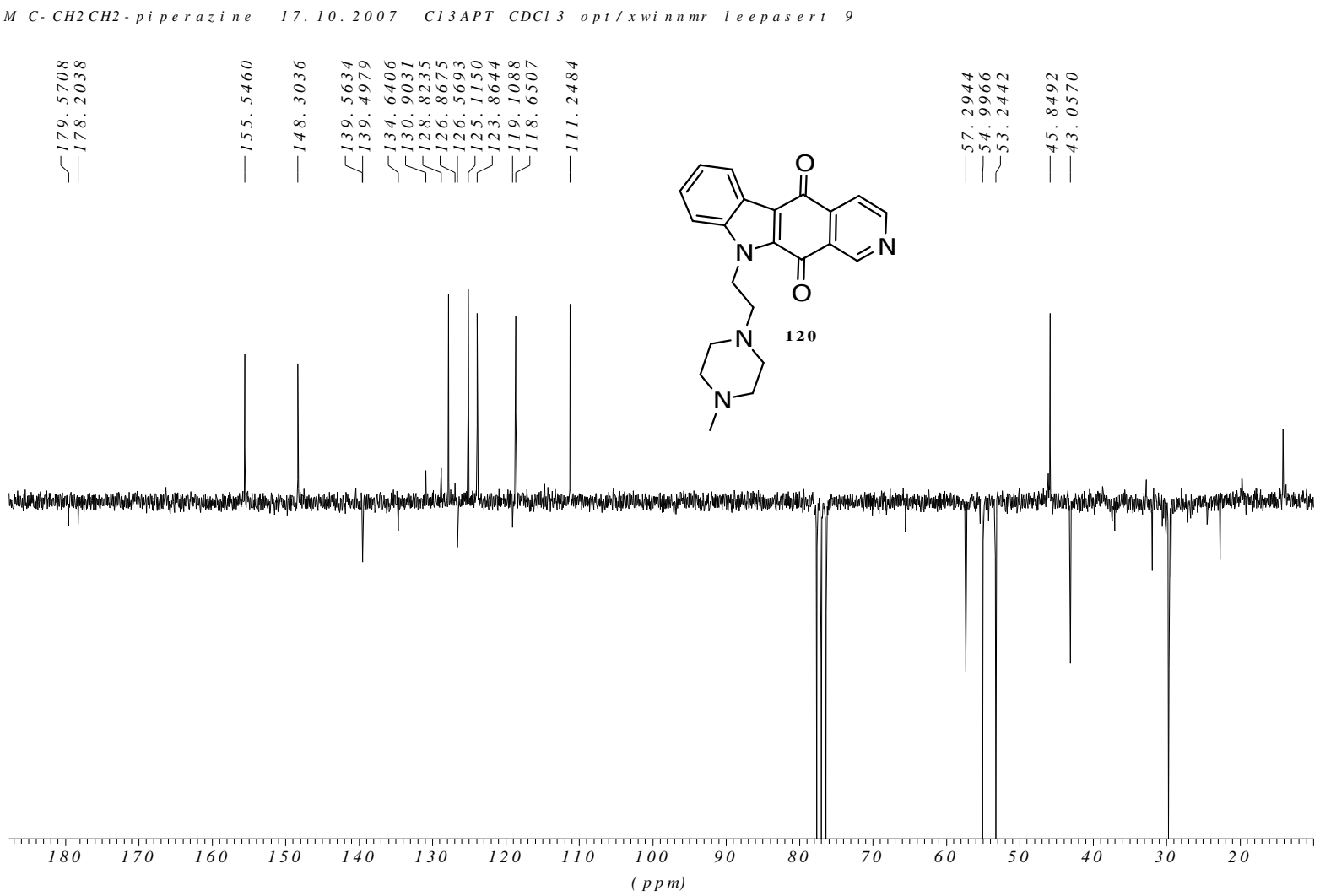
```
SPEC:  00000000000000000000000000000000     24-Mar-95   Elapse:   00:24.4        1
Samp:  MS374                                             Start :   17:09:12       1
Comm:  4kV 3uA   MeOH/ACN
Mode:  ESI +VE +APICID LMR  BSCAN (EXP) UP LR NRM
Oper:  phu           Client:  Theerachart/Holzer/        Inlet :
Base:  275.0                 Inten :  400851             Masses:   101 > 999
Norm:  275.0                 RIC   :  1092899            #peaks:   909
Peak:  1000.00  mmu
Data:  AVER : Scans All from /usr/users/finnigan/data/34454_1.dat
```



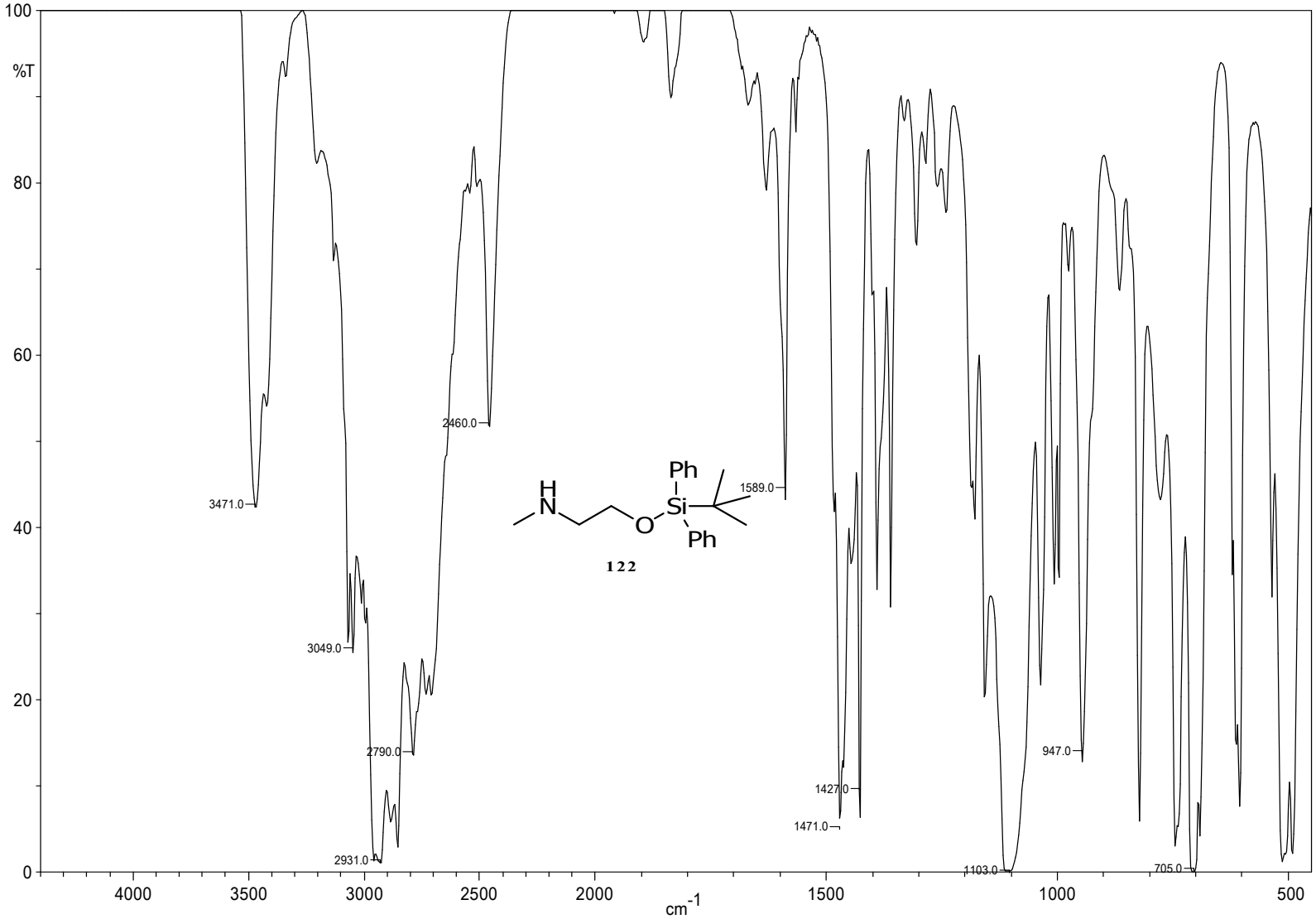
^{1}H NMR spectrum of **120** in $CDCl_3$.



^{13}C NMR spectrum of **120** in $CDCl_3$.

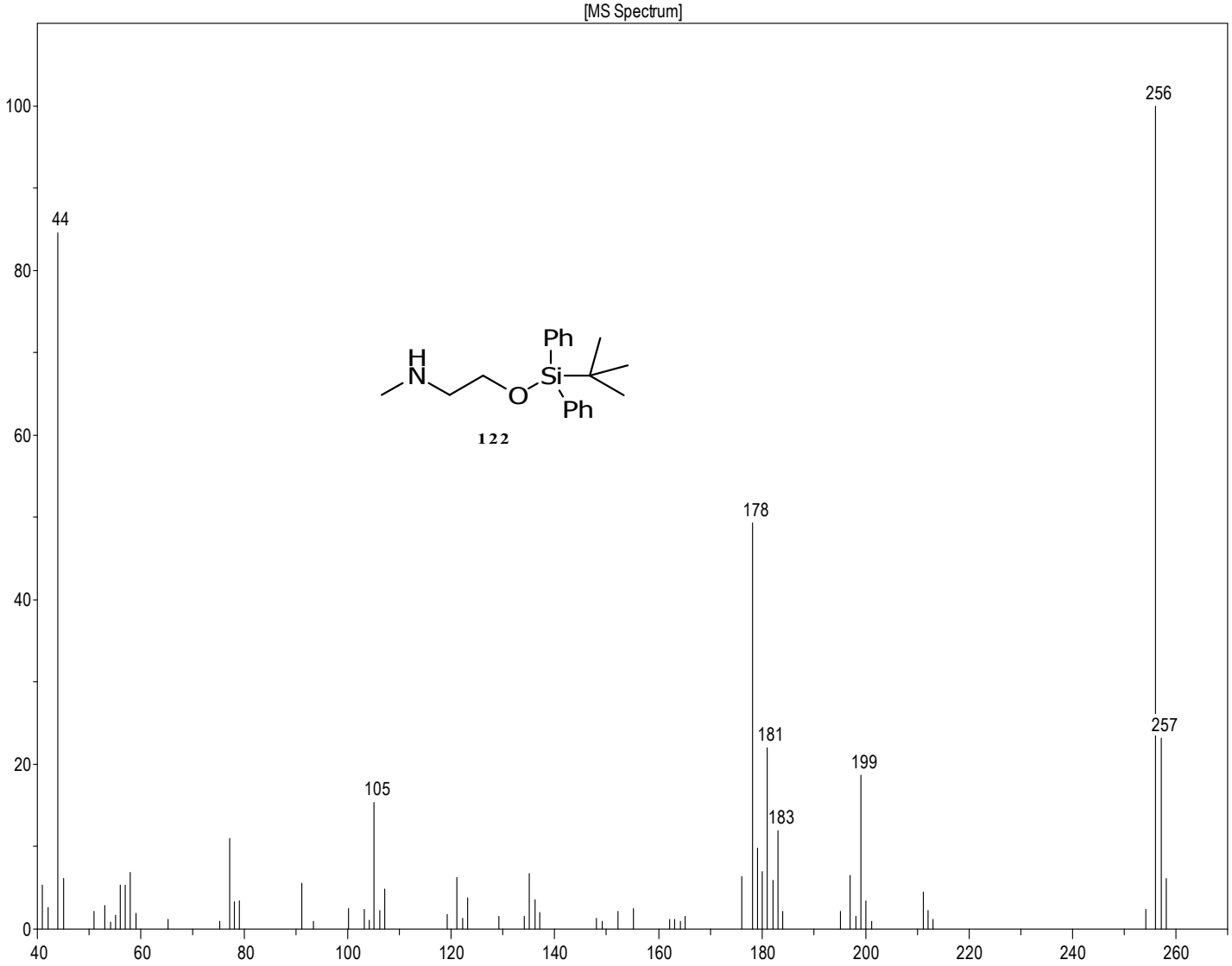


IR spectrum of **122** (NaCl).

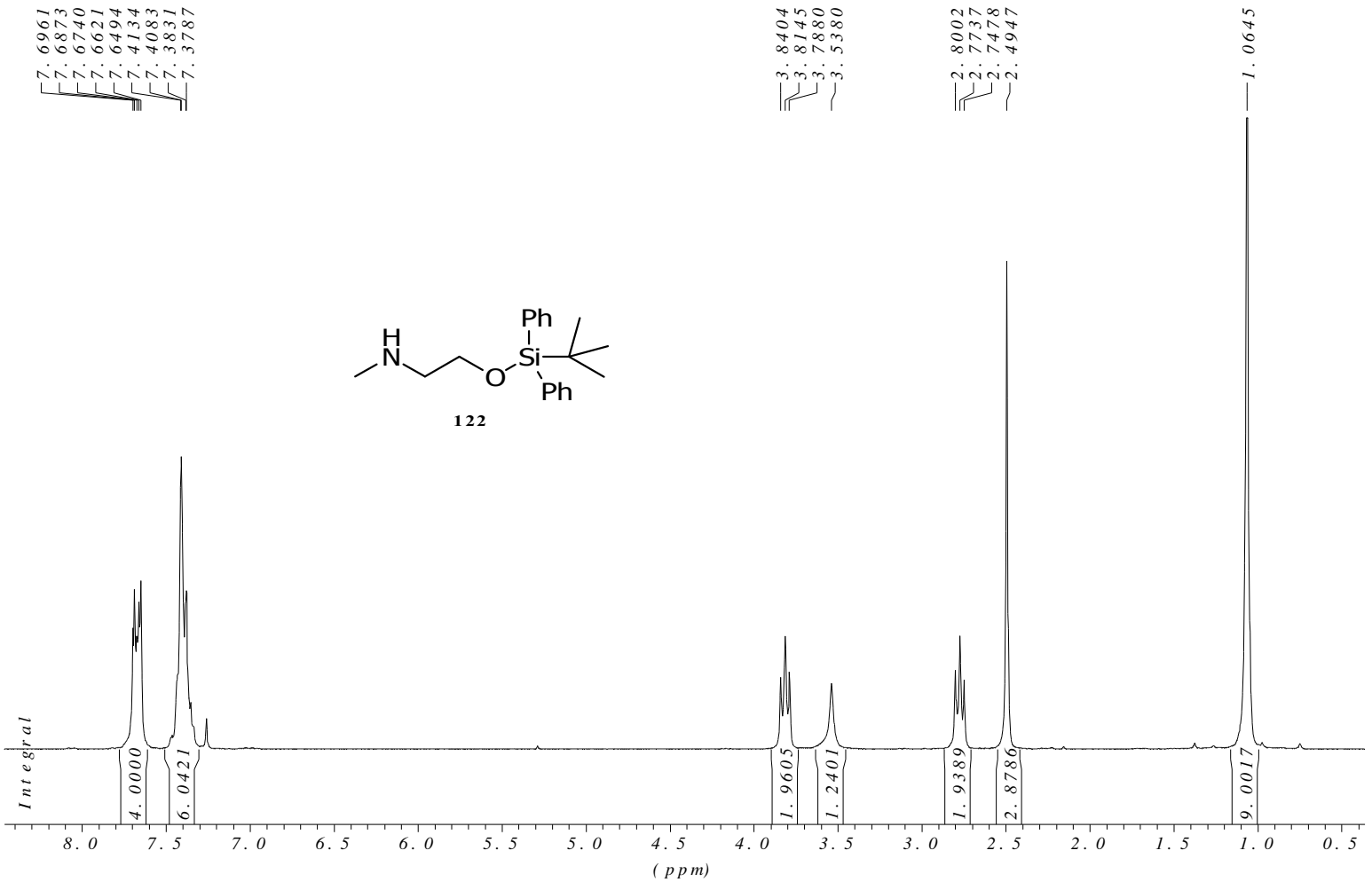


122

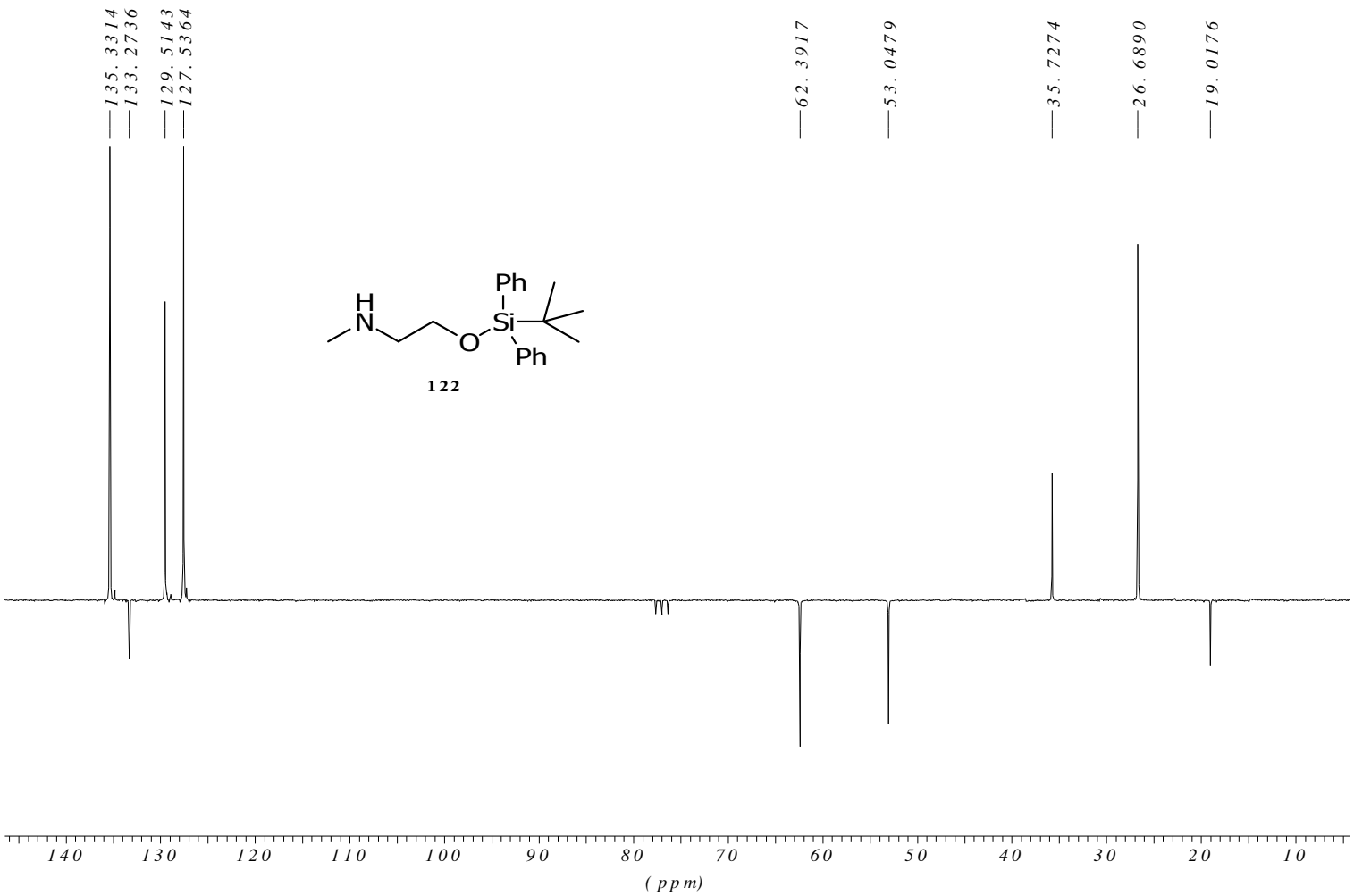
Mass spectrum of **122**.



^{1}H NMR spectrum of **122** in $CDCl_3$.

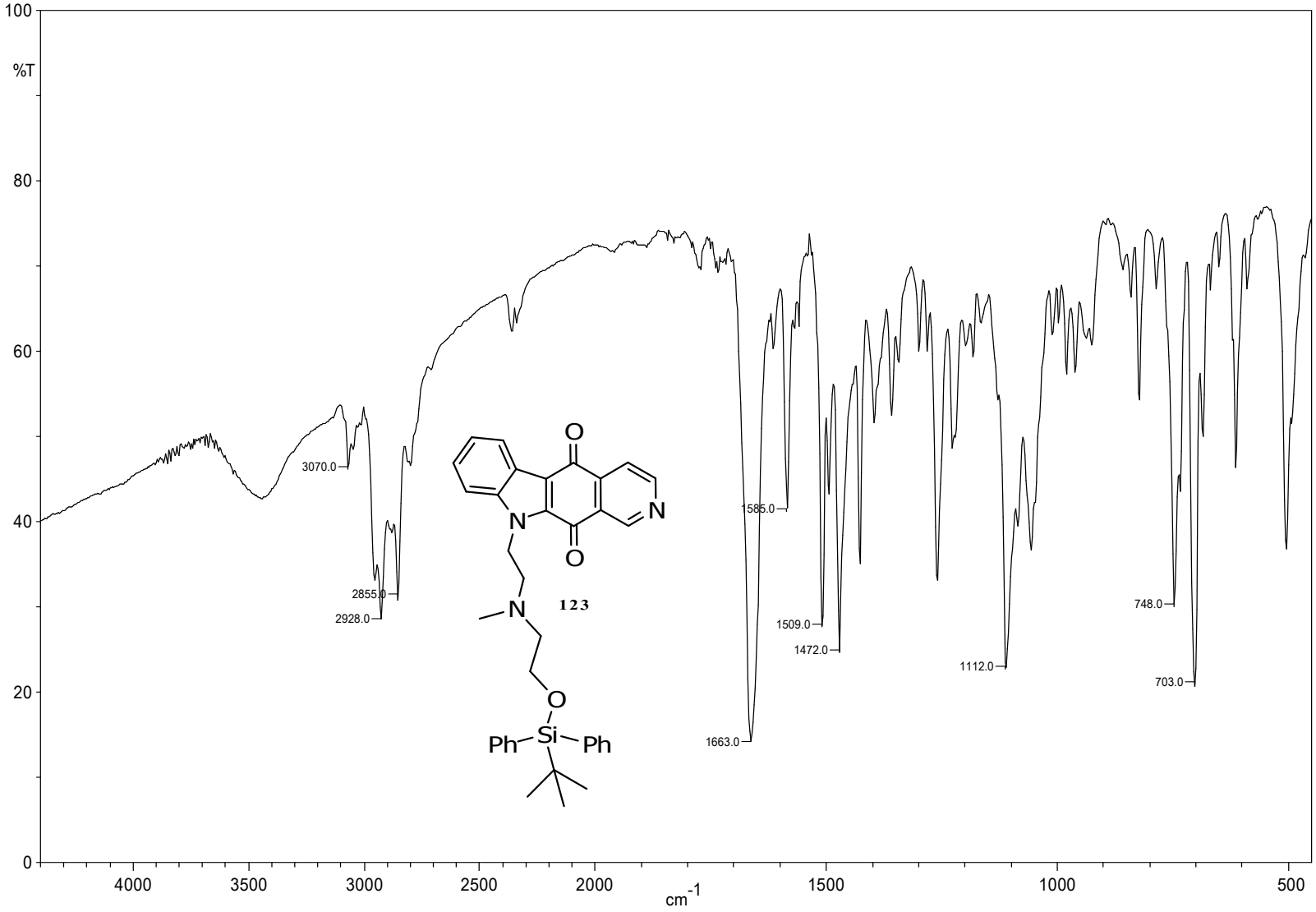


^{13}C NMR spectrum of **122** in $CDCl_3$.



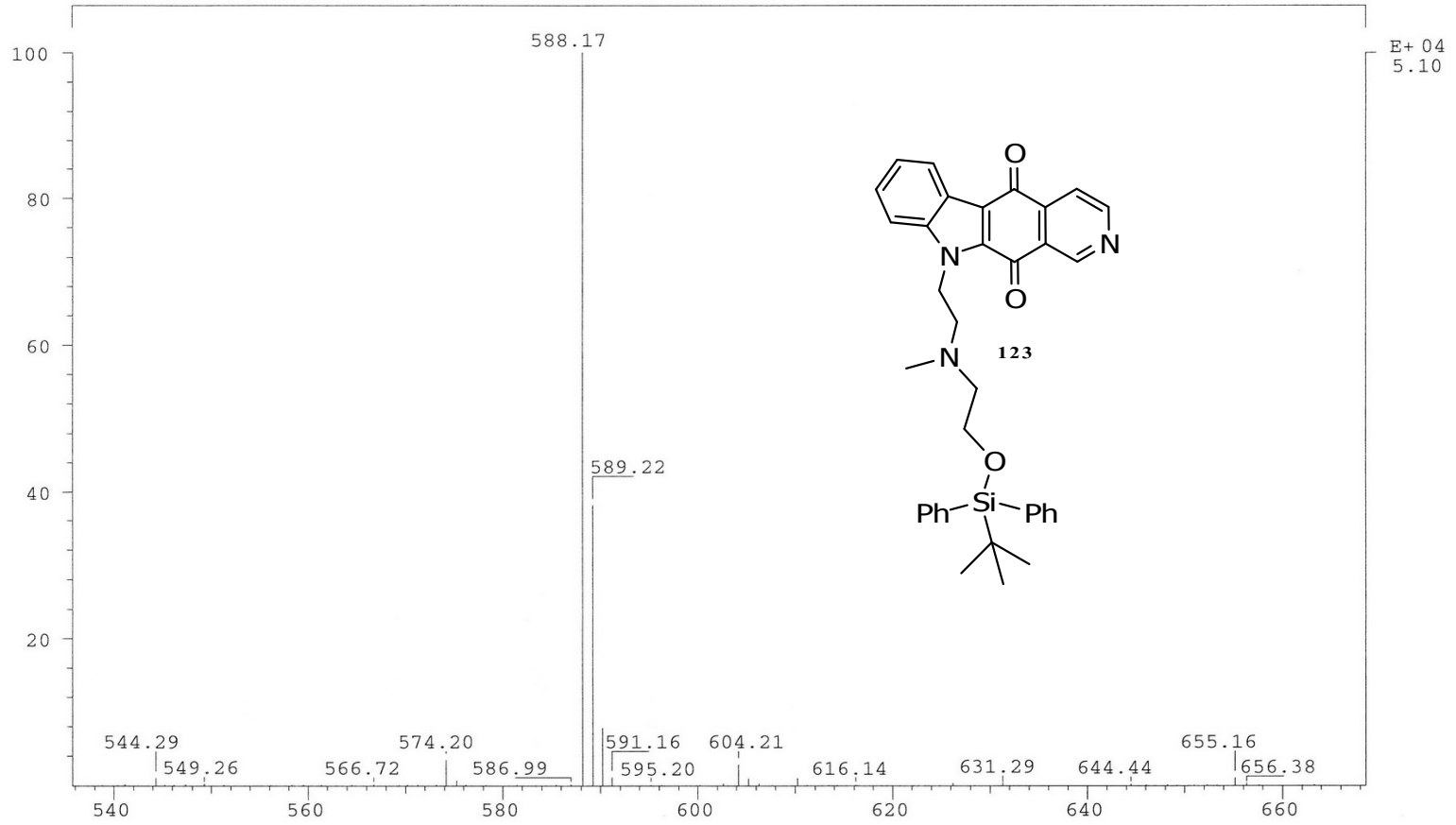
122

IR spectrum of **123** (KBr).

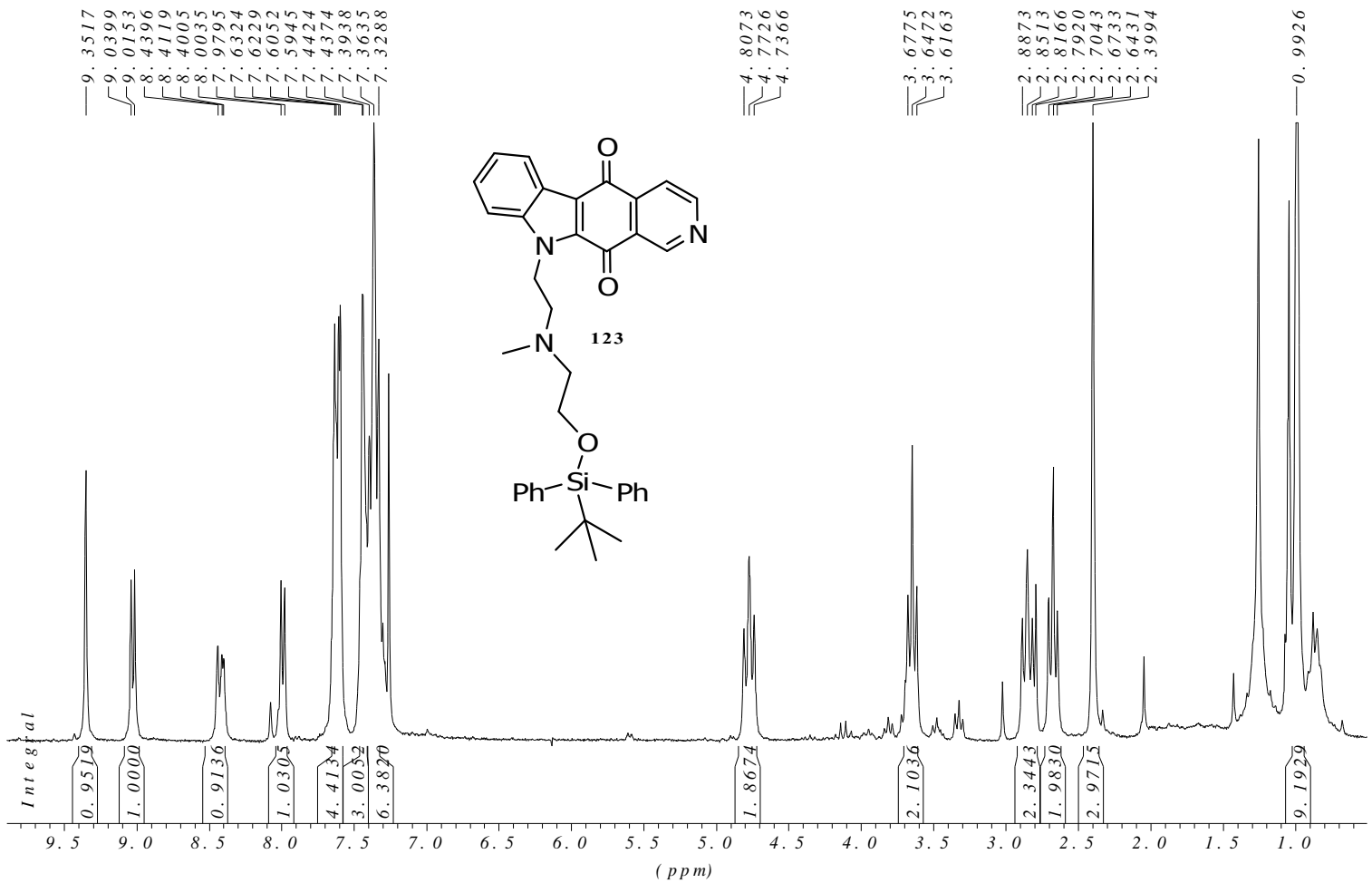


Mass spectrum of **123**.

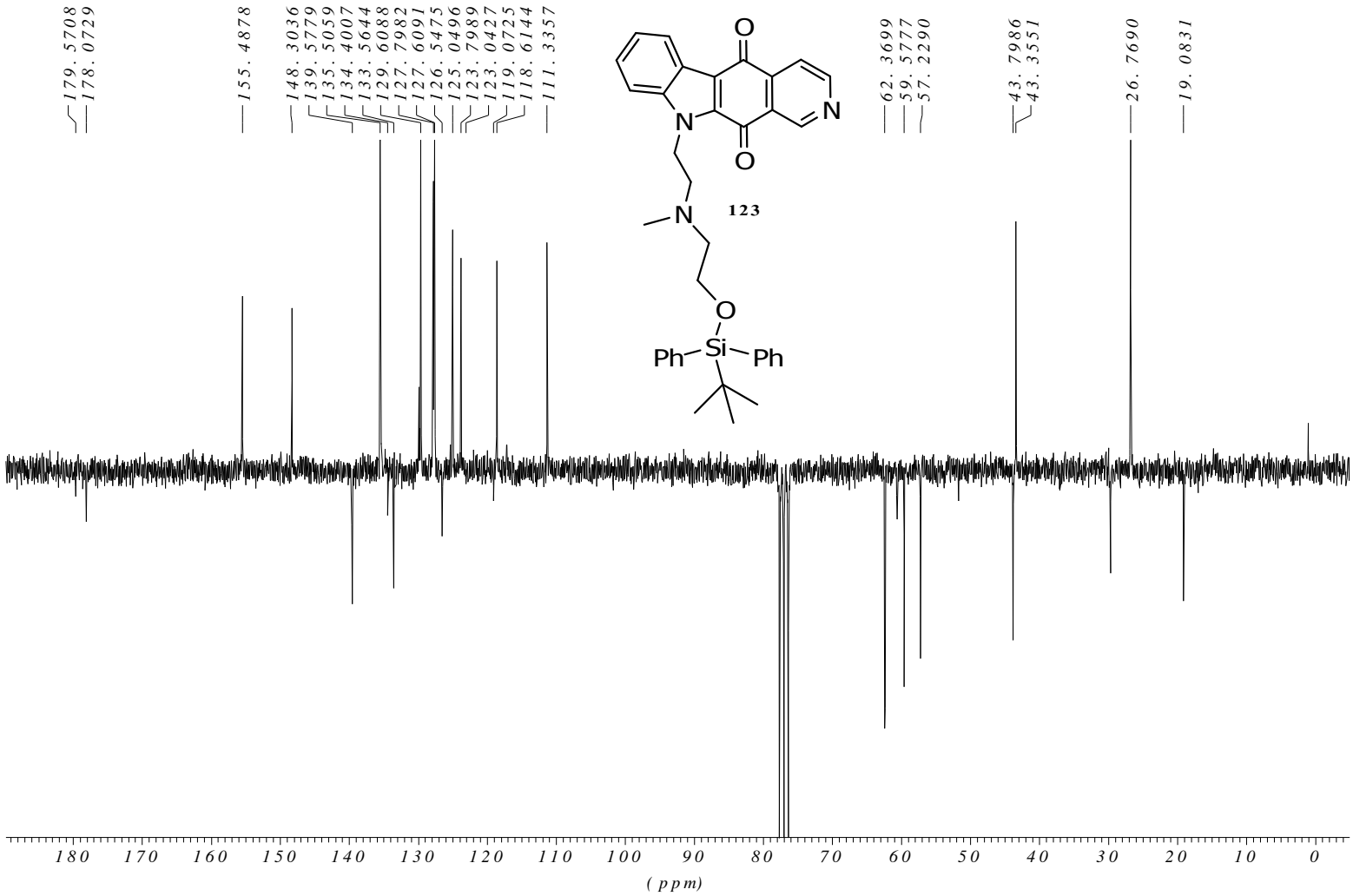
```
SPEC:  00000000000000000000000000000000     02-Apr-95   Elapse:   00:12.1        1
Samp:  MS 587                                            Start :   13:09:00       1
Comm:  4kV 3uA    MeOH/ACN
Mode:  ESI +VE +LMR  BSCAN (EXP) UP LR NRM               Study :   ESI
Oper:  phu           Client:  Theerachart/Holzer/        Inlet :
Base:  428.2                 Inten :  63973              Masses:   102 > 998
Norm:  588.2                 RIC   :  298518             #peaks:   334
Peak:  1000.00  mmu
Data:  AVER : Scans All from /usr/users/finnigan/data/34470_1.dat
```



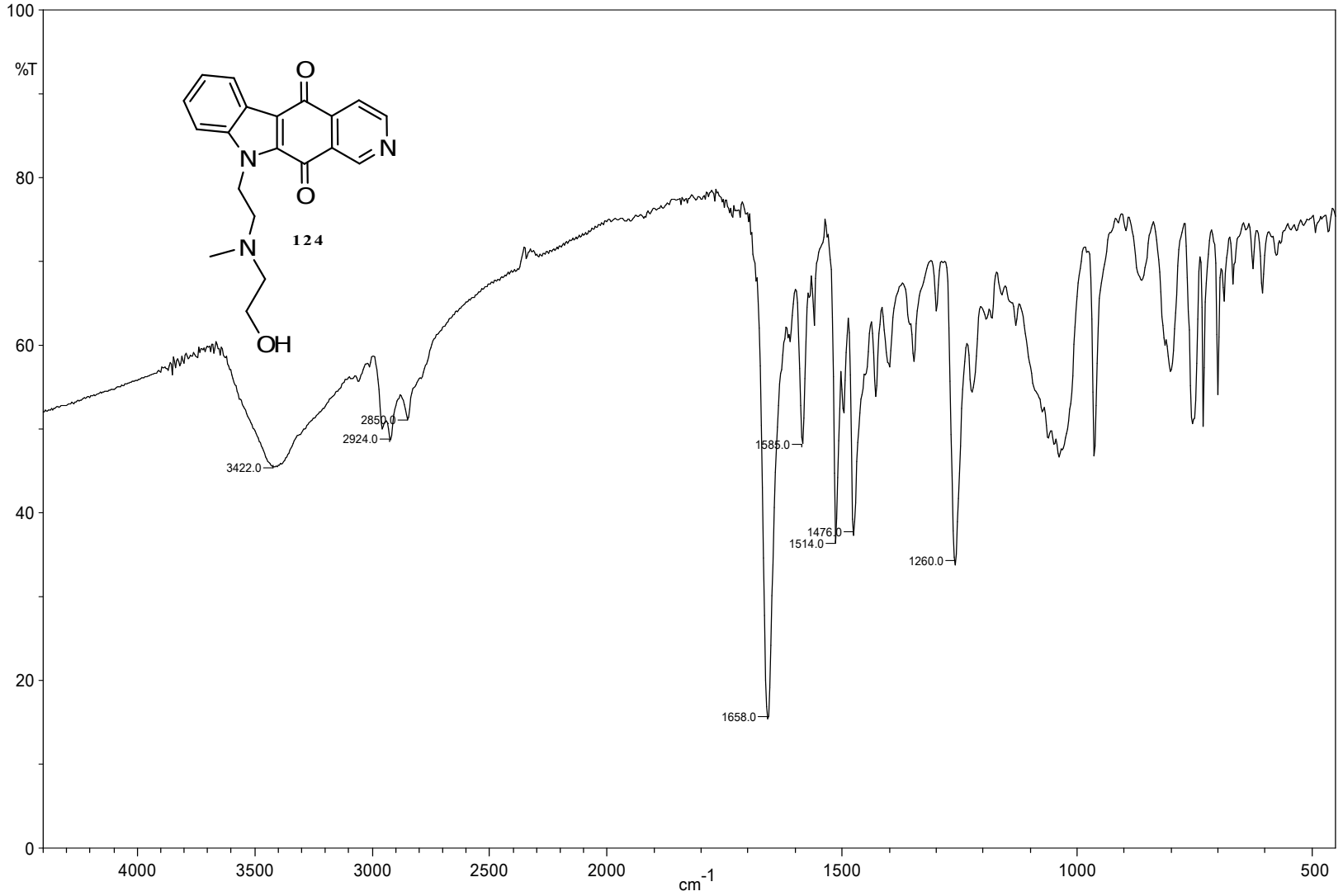
^{1}H NMR spectrum of **123** in $CDCl_3$.



^{13}C NMR spectrum of **123** in $CDCl_3$.

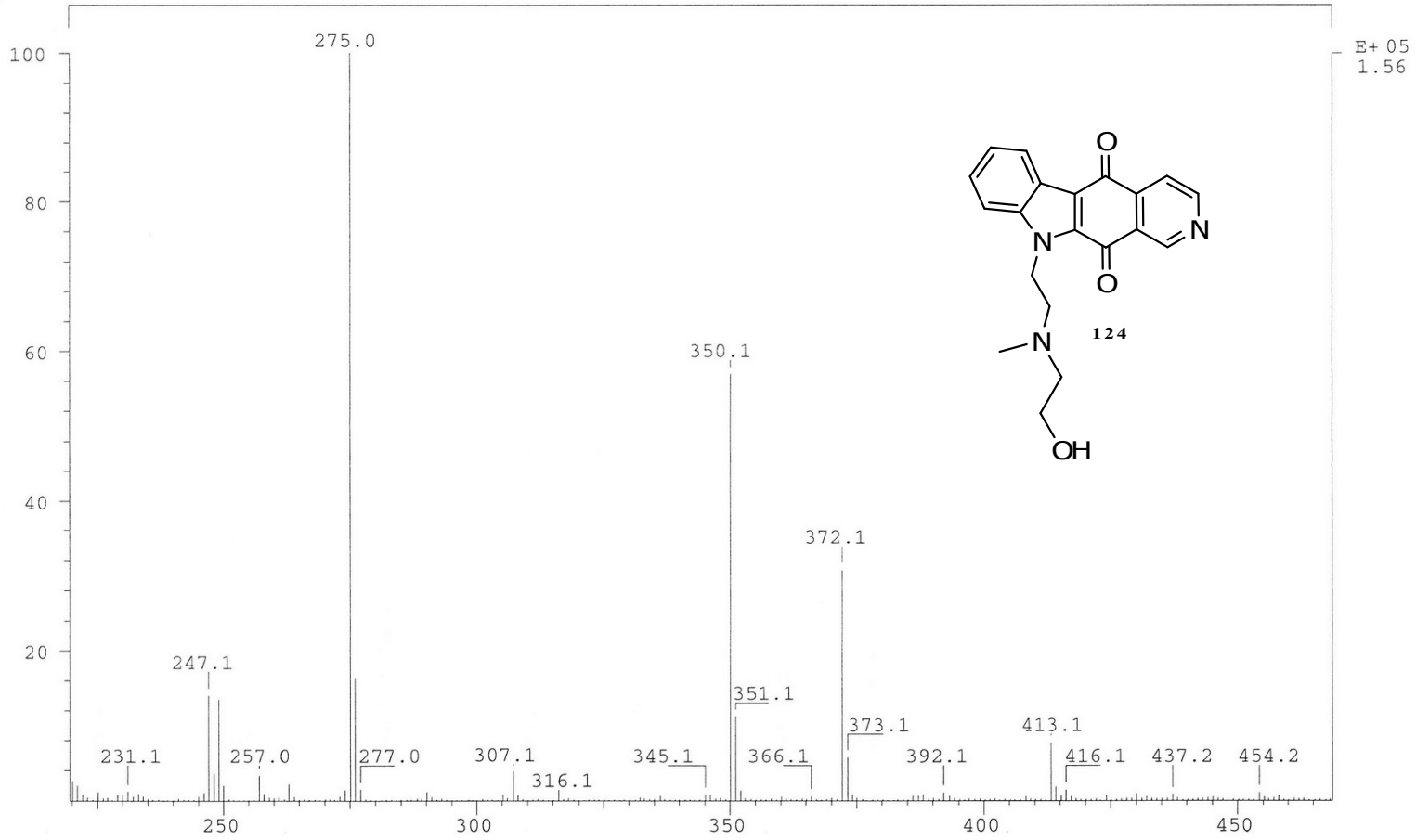


IR spectrum of **124** (KBr).



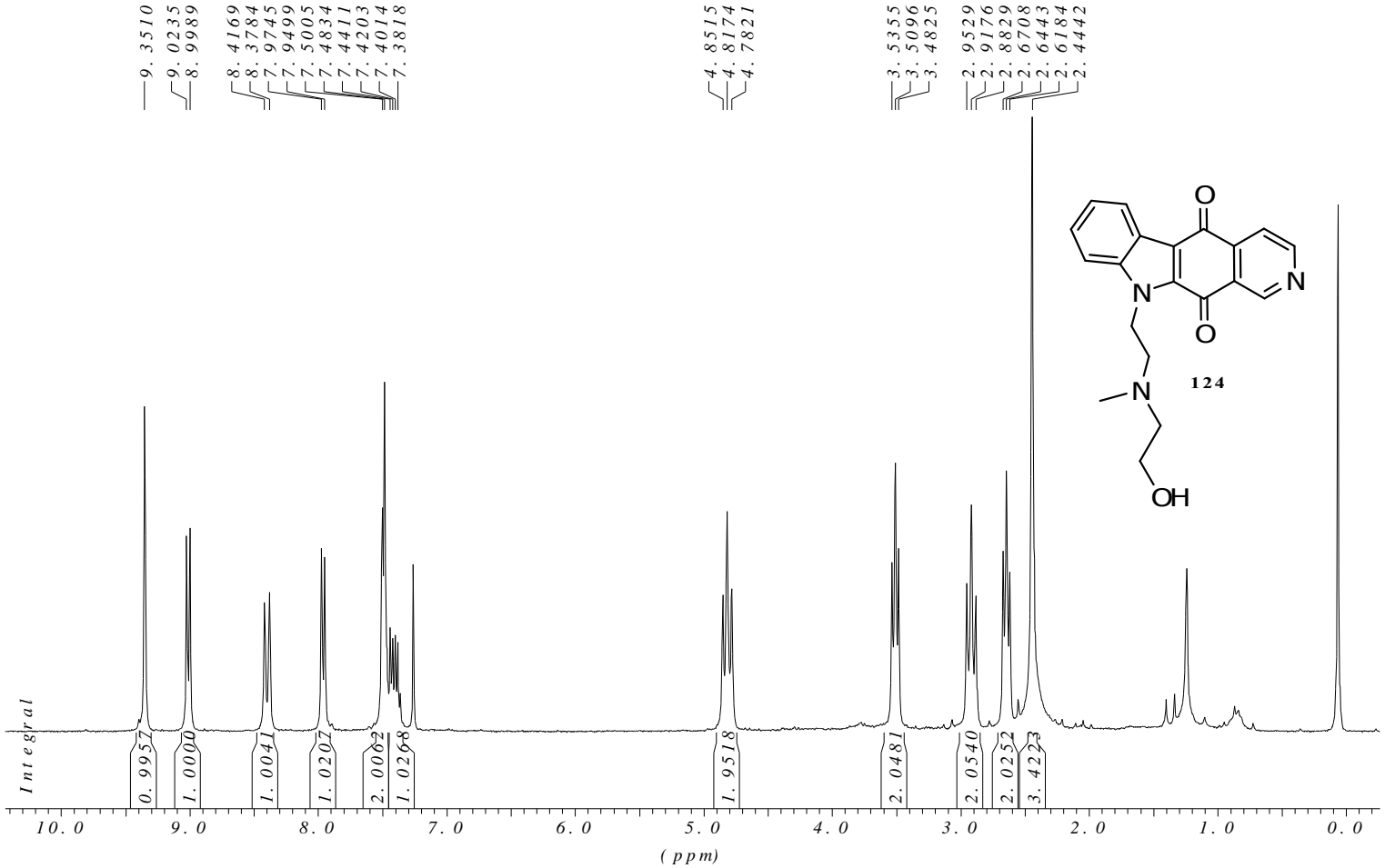
Mass spectrum of **124**.

```
SPEC:  00000000000000000000000000000000     24-Mar-95  Elapse:   00:22.3        1
Samp:  MS349                                            Start :   16:15:38       1
Comm:  4kV 3uA   MeOH/ACN
Mode:  ESI +VE +APICID LMR  BSCAN (EXP) UP LR NRM
Oper:  phu           Client:  Theerachart/Holzer/       Inlet :
Base:  275.0                 Inten :  156045            Masses:  101 > 999
Norm:  275.0                 RIC   :  768125            #peaks:  926
Peak:  1000.00  mmu
Data:  AVER : Scans All from /usr/users/finnigan/data/34446_1.dat
```

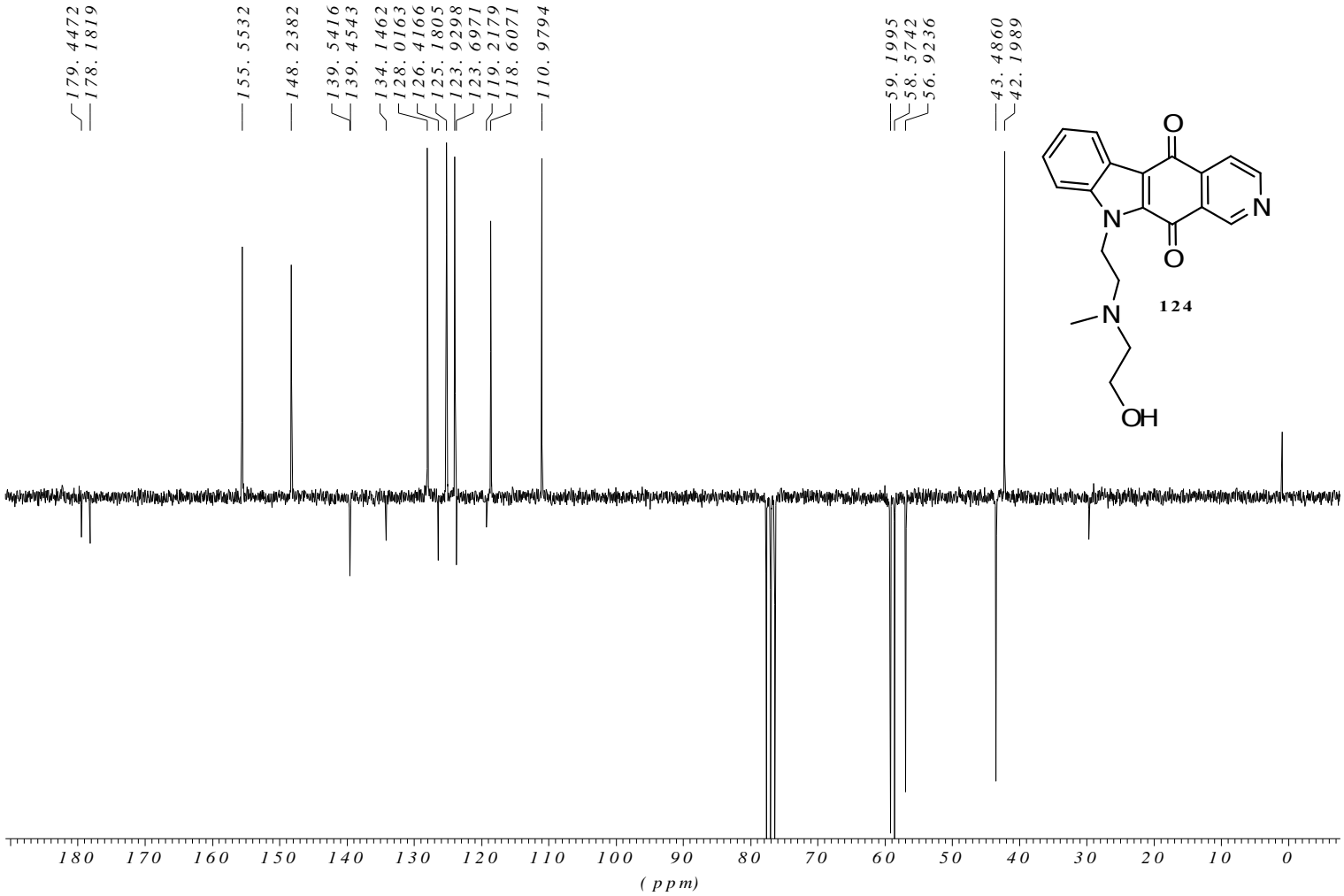


124

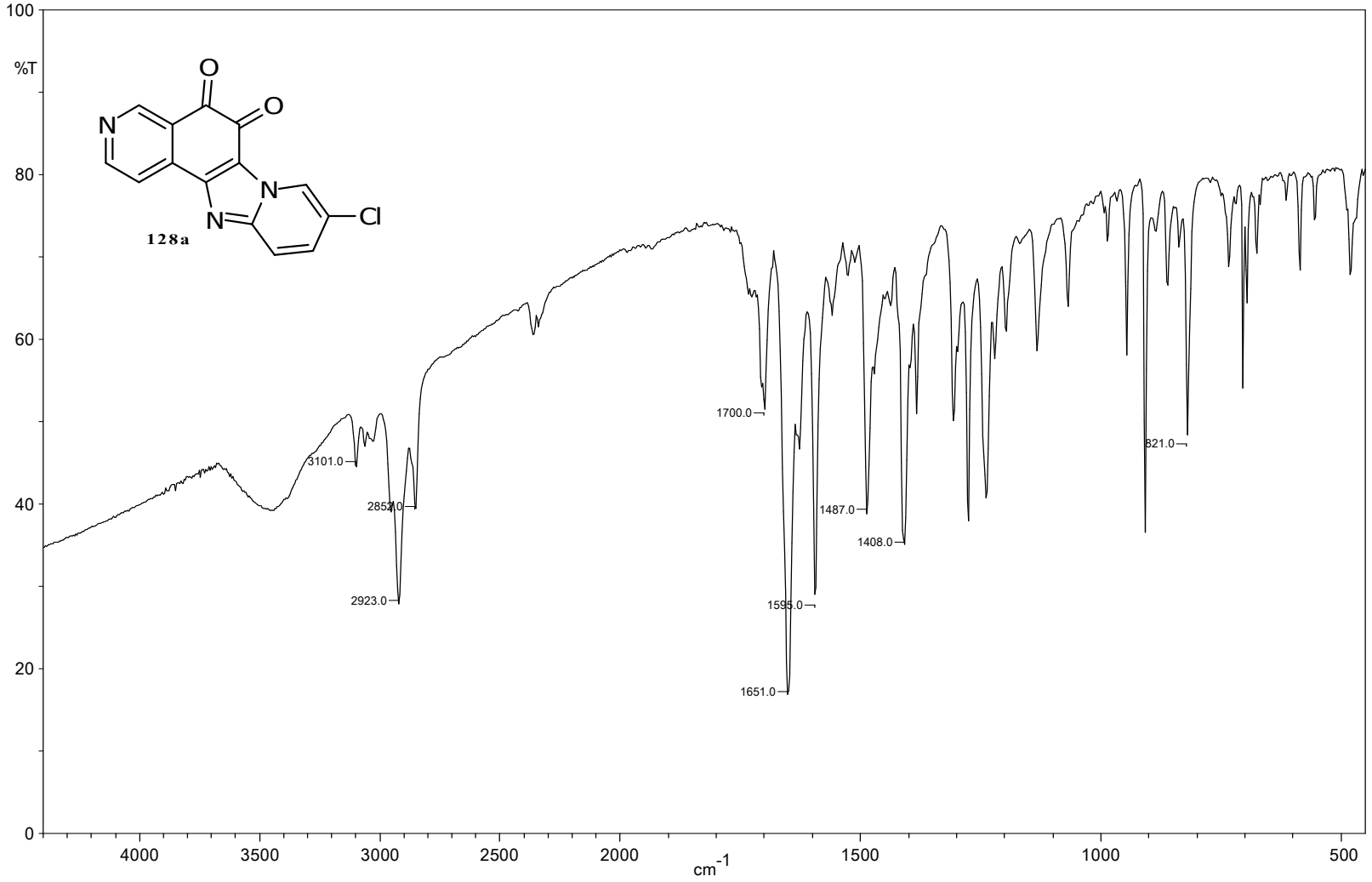
^{1}H NMR spectrum of **124** in $CDCl_3$.



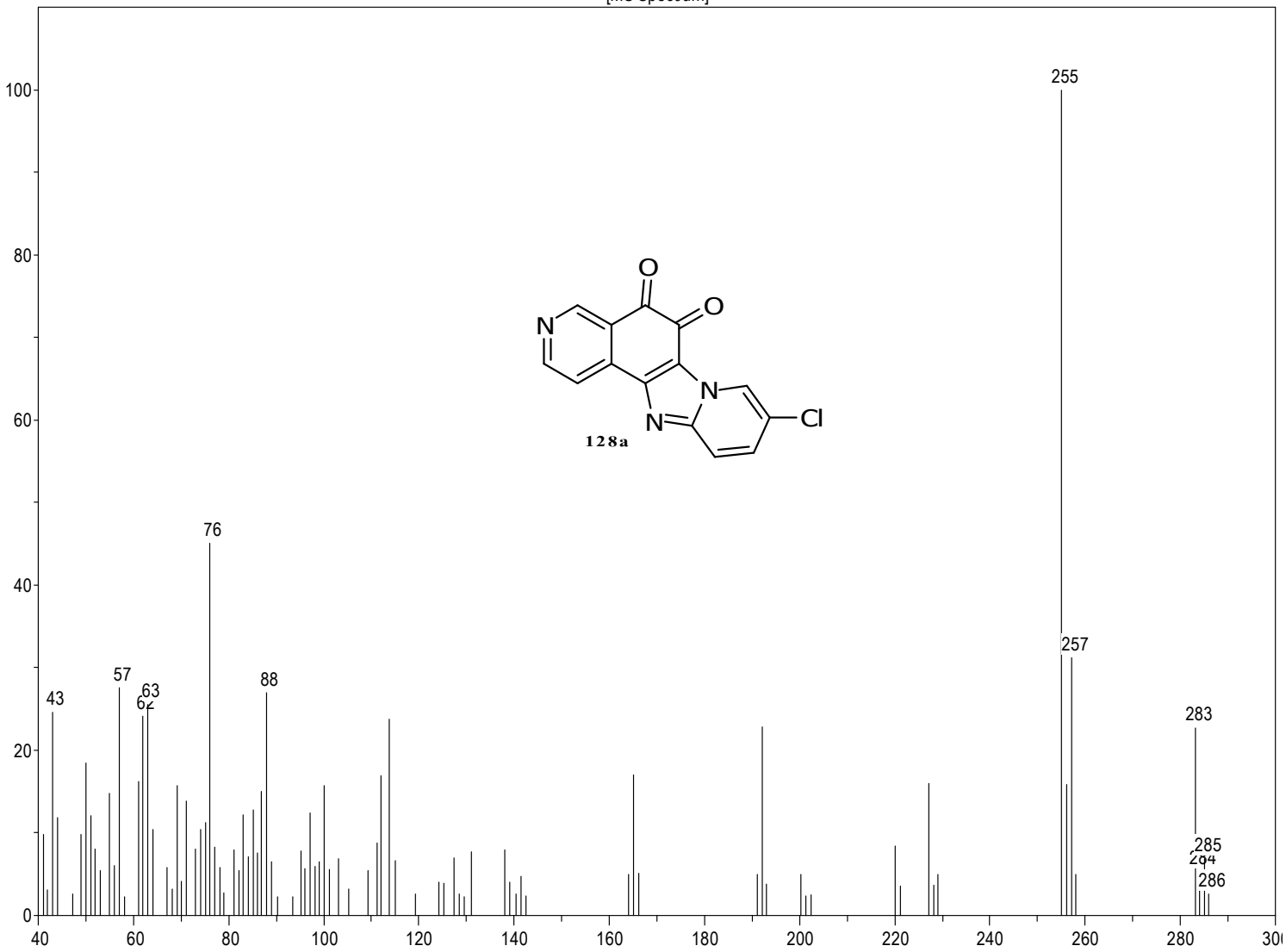
^{13}C NMR spectrum of **124** in $CDCl_3$.



IR spectrum of **128a** (KBr).



Mass spectrum of **128a**.

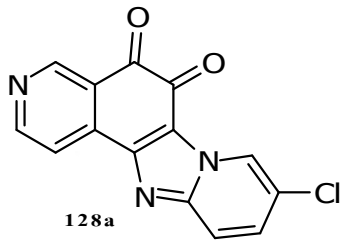


^{1}H NMR of spectrum of **128a** in DMSO-d_6.

TM283/DMSO

expl stdlh

SAMPLE		DEC. & VT	
date	Mar 28 09	dfrq	299.951
solvent	DMSO	dn	H1
file	exp	dpwr	30
ACQUISITION		dof	1196.9
sfrq	299.950	dm	nnn
tn	H1	dmm	c
at	4.998	dmf	200
np	59968	dseq	undefined
sw	5999.7	dres	undefined
fb	3400	homo	n
bs	4	temp	28.0
tpwr	57	PROCESSING	
pw	6.0	lb	not used
dl	5.000	gf	not used
tof	600.0	gfs	not used
nt	128	wtfile	
ct	100	proc	ft
alock	n	fn	65536
gain	52	math	f
FLAGS			
il	n	werr	
in	n	wexp	
dp	y	wbs	
hs	nn	wnt	
DISPLAY			
sp	2318.3		
wp	491.3		
vs	3392		
sc	0		
wc	180		
hzmm	2.73		
is	17899.21		
rfl	2081.0		
rfp	746.9		
th	18		
ins	15.048		
ai	ph		



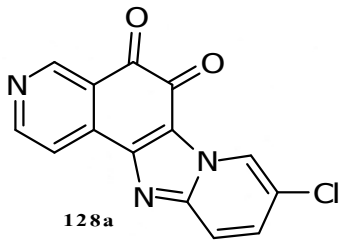
128a

^{13}C NMR of spectrum of **128a** in DMSO-d_6.

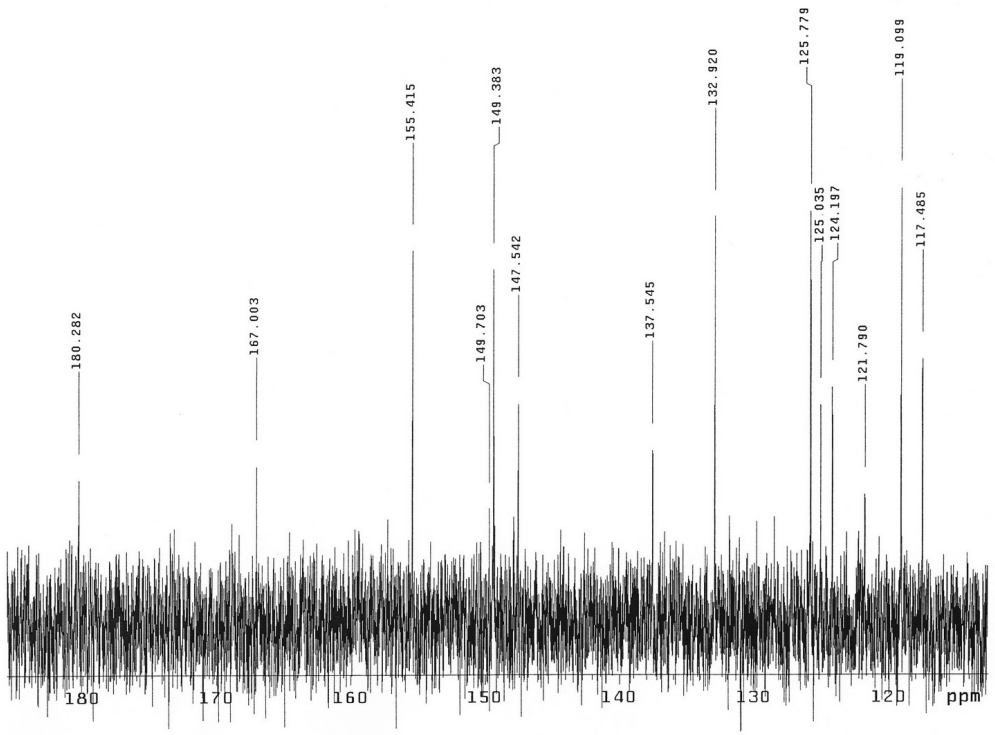
TM283/DMSO

exp3 stdl3c

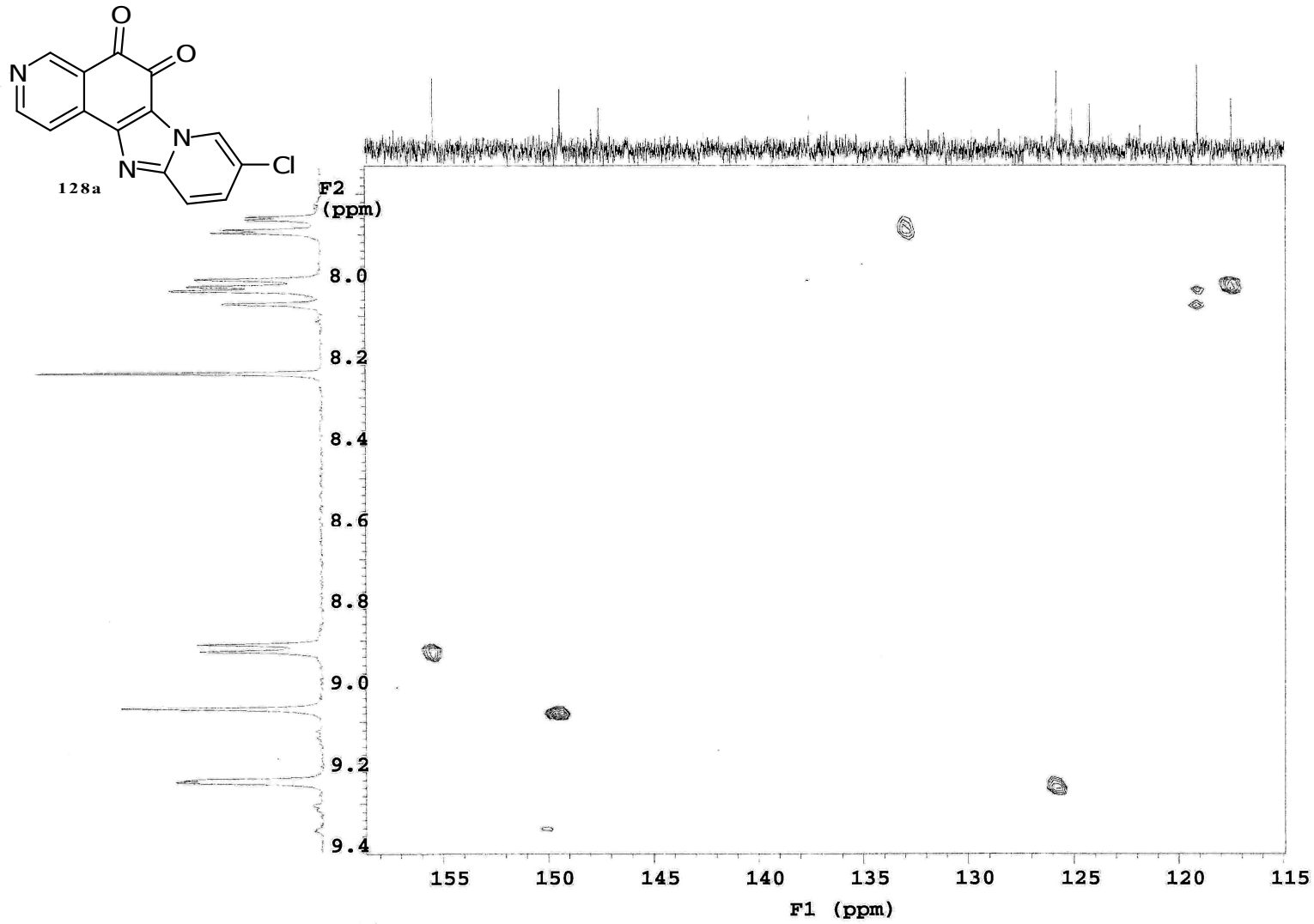
SAMPLE		DEC. & VT	
date	Mar 28 09	dfrq	299.951
solvent	DMSO	dn	H1
file	exp	dpwr	41
ACQUISITION		dof	1500.0
sfrq	75.429	dm	yyy
tn	C13	dmm	w
at	2.000	dmf	12000
np	80000	dseq	undefined
sw	20000.0	dres	undefined
fb	11000	homo	n
bs	8	temp	28.0
ss	4	PROCESSING	
tpwr	53	lb	0.60
pw	7.0	wtfile	
dl	2.500	proc	ft
tof	-191.6	fn	131072
nt	25600	math	f
ct	0		
alock	n	werr	
gain	not used	wexp	
FLAGS		wbs	
il	n	wnt	
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	8491.3		
wp	5510.3		
vs	5669		
sc	0		
wc	180		
hzmm	30.61		
is	500.00		
rfl	5780.1		
rfp	2979.5		
th	25		
ins	1.000		
nm	ph		



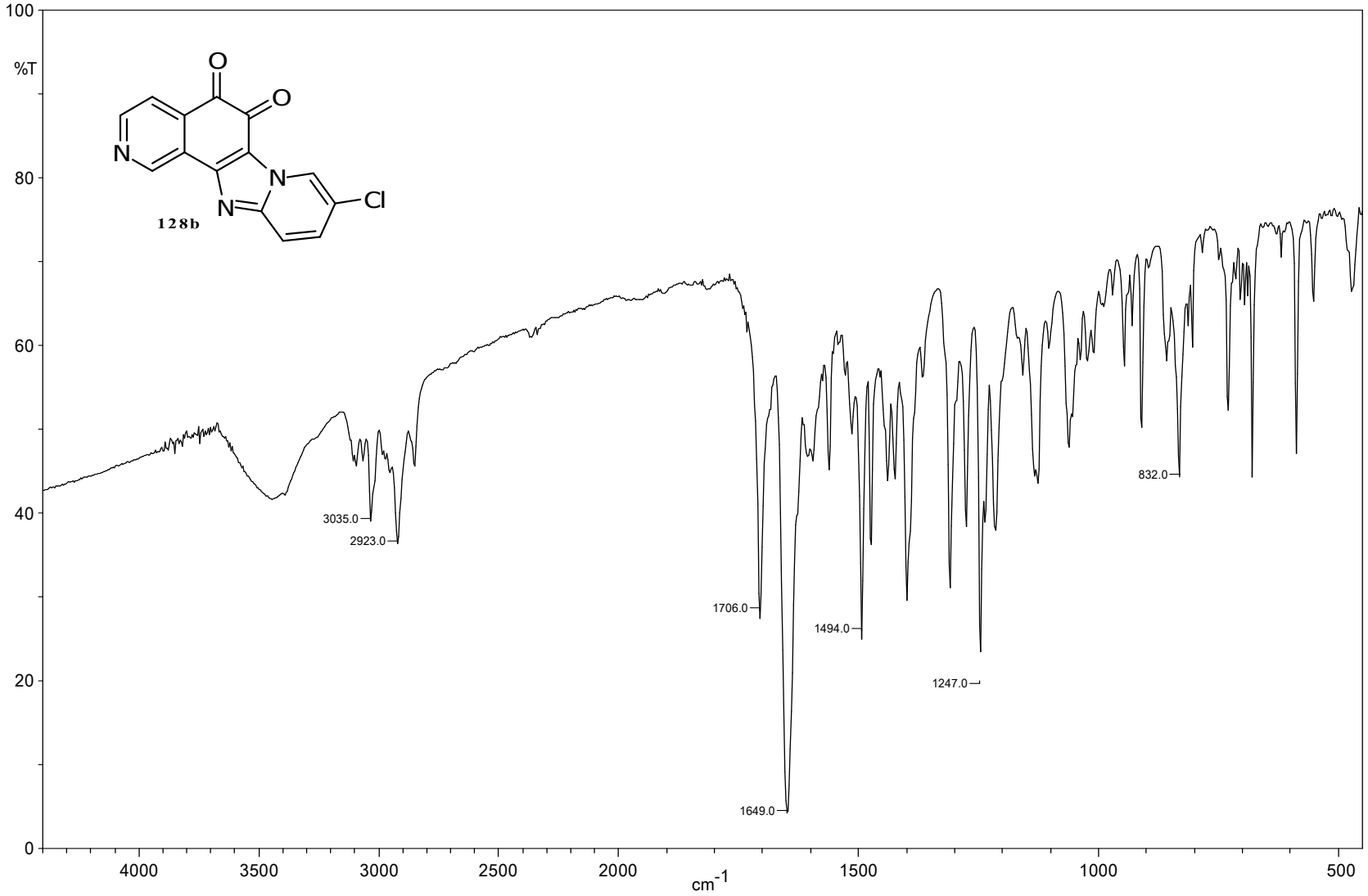
128a



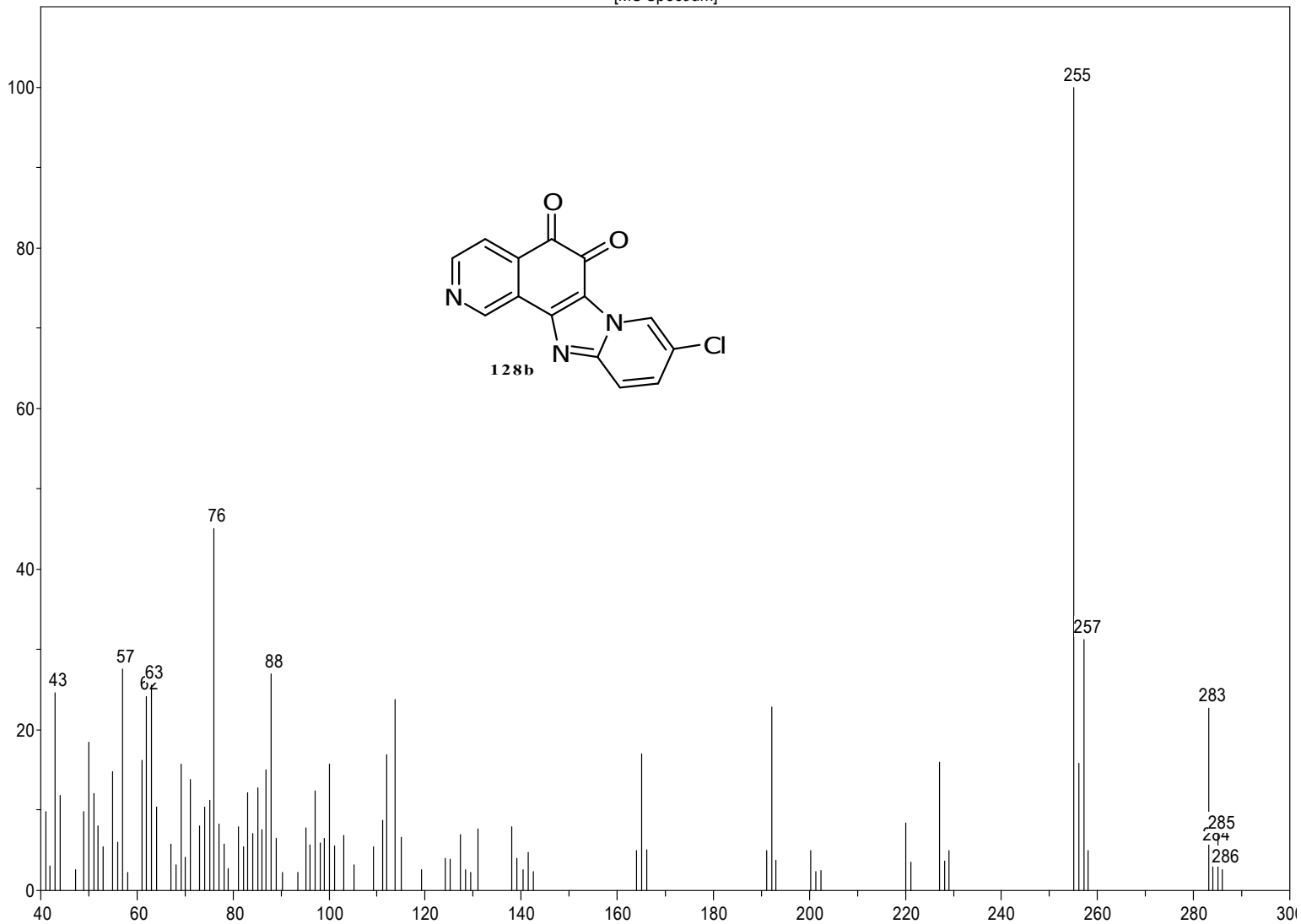
HMBC spectrum of **128a**.



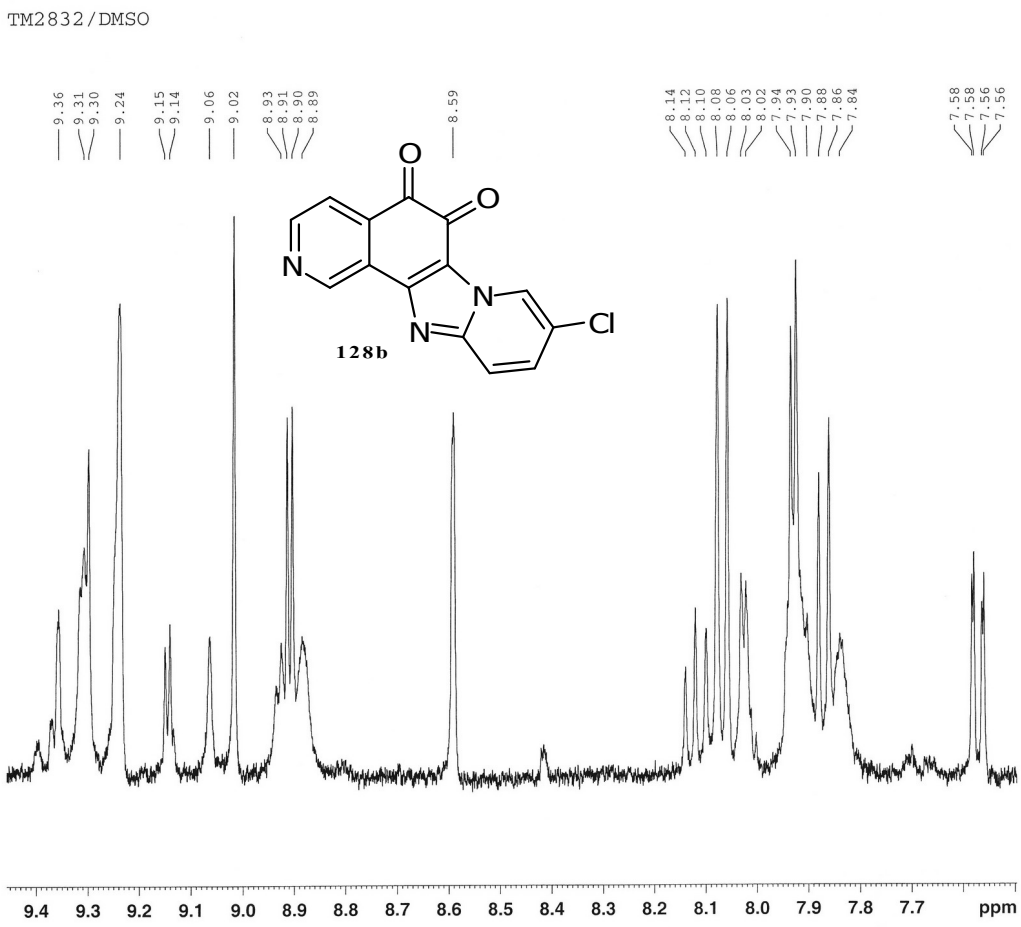
IR spectrum of **128b** (KBr).



Mass spectrum of **128b**.

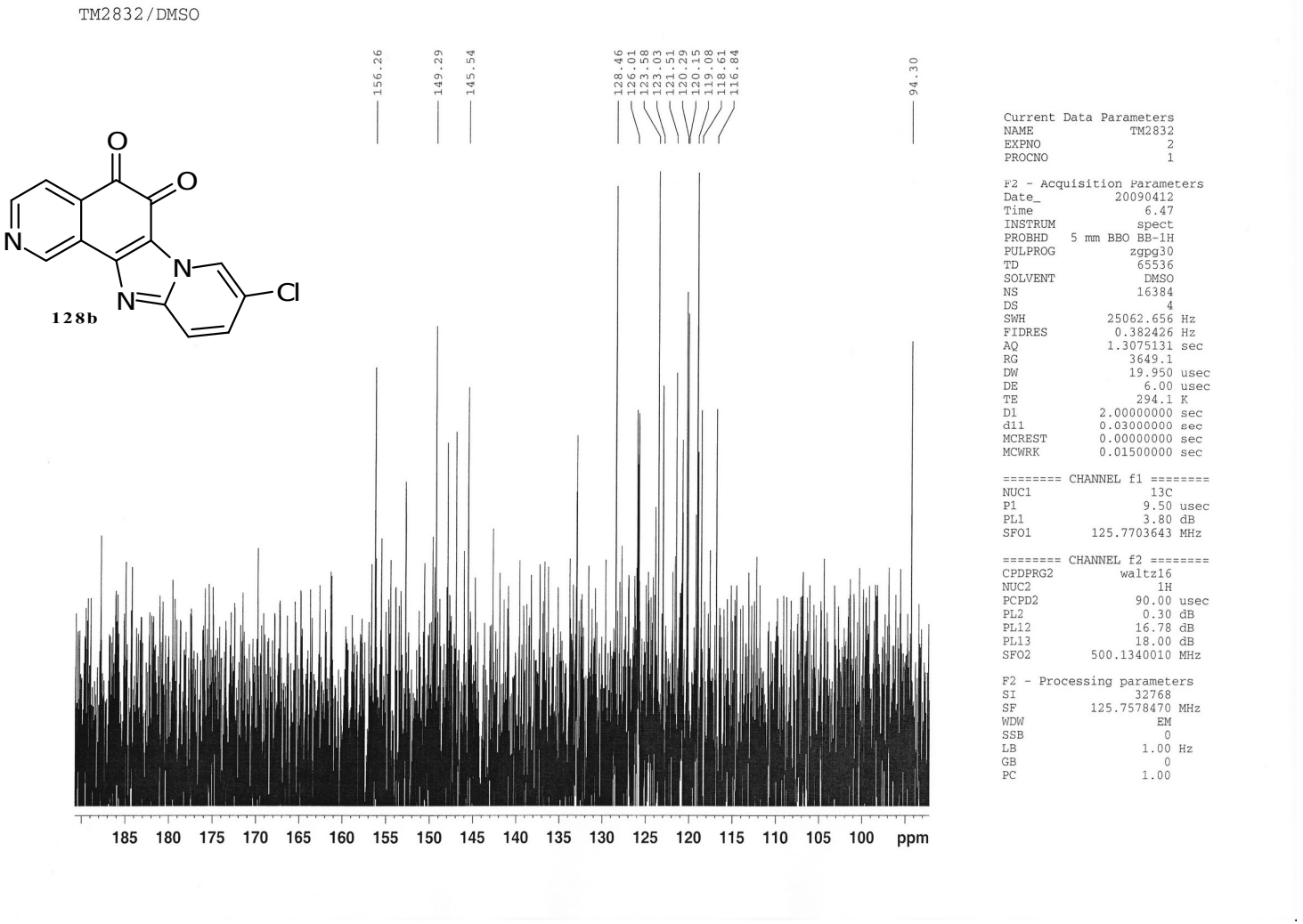


^{1}H NMR of spectrum of **128b** in DMSO-d_6.



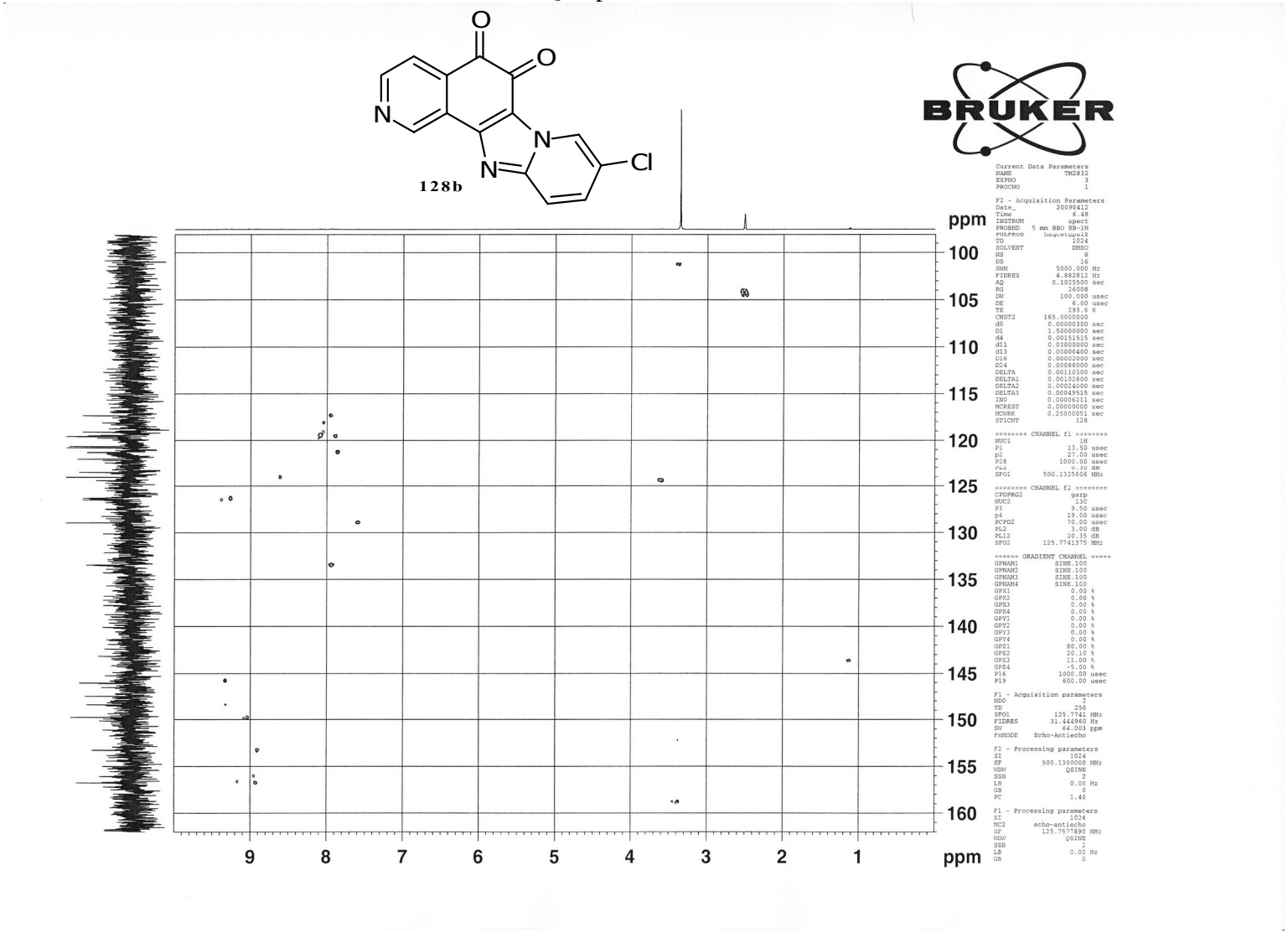

```
Current Data Parameters
NAME                  TM2832
EXPNO                      1
PROCNO                     1

F2 - Acquisition Parameters
Date_              20090411
Time                  15.28
INSTRUM               spect
PROBHD   5 mm BBO BB-1H
PULPROG                zg30
TD                    82642
SOLVENT                DMSO
NS                        32
DS                         2
SWH                8012.820 Hz
FIDRES                0.096958 Hz
AQ                 5.1569734 sec
RG                       256
DW                    62.400 usec
DE                     6.00 usec
TE                    293.0 K
D1                 5.00000000 sec
MCREST             0.00000000 sec
MCWRK              0.01500000 sec

======== CHANNEL f1 ========
NUC1                       1H
P1                    13.50 usec
PL1                    0.30 dB
SFO1             500.1330885 MHz

F2 - Processing parameters
SI                       131072
SF               500.1300099 MHz
WDW                        EM
SSB                         0
LB                     0.20 Hz
GB                          0
PC                      1.00
```

^{13}C NMR of spectrum of **128b** in DMSO-d_6.

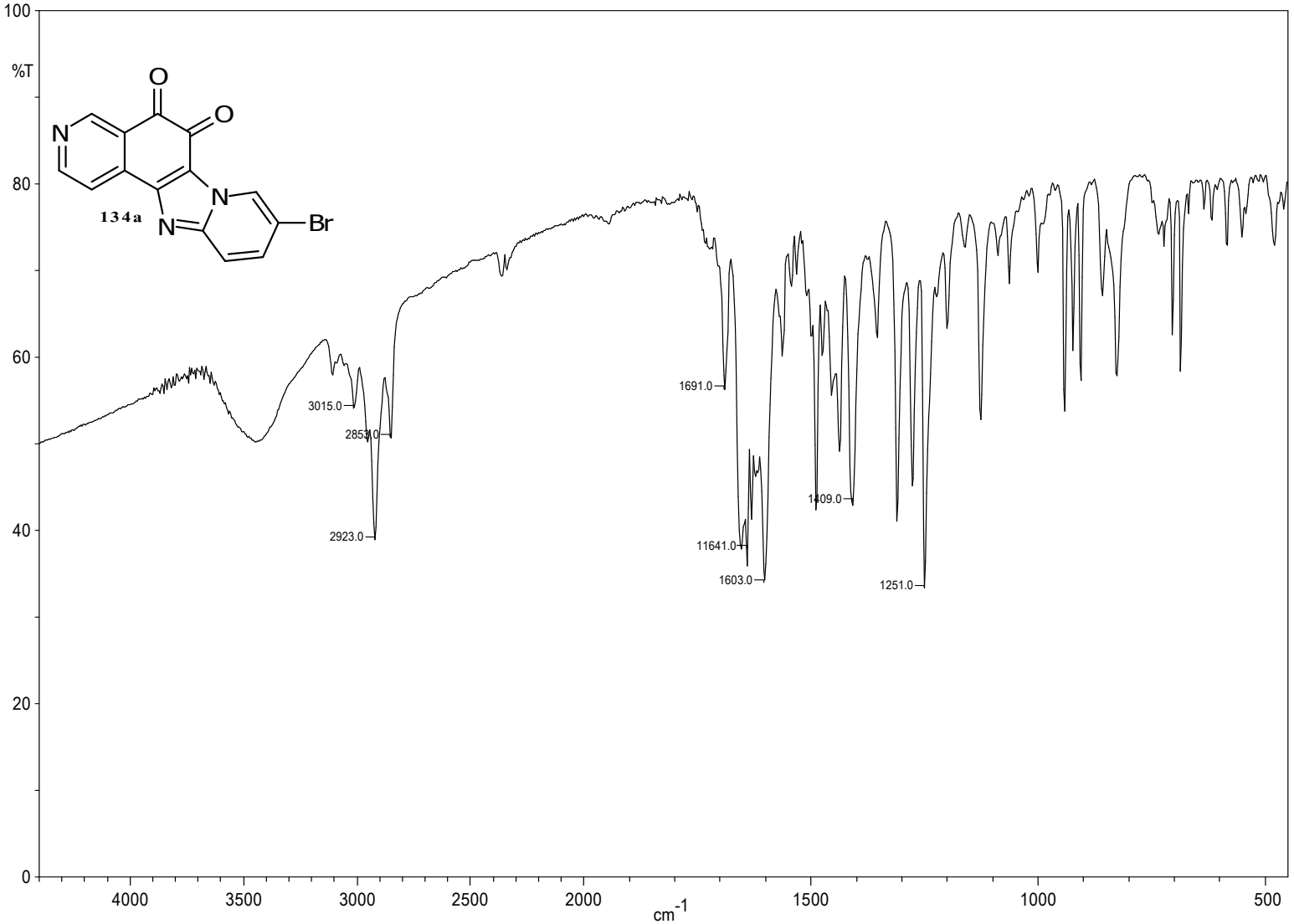



```
Current Data Parameters
NAME                 TM2832
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
Date_              20090412
Time                   6.47
INSTRUM               spect
PROBHD   5 mm BBO BB-1H
PULPROG             zgpg30
TD                    65536
SOLVENT                DMSO
NS                    16384
DS                        4
SWH               25062.656 Hz
FIDRES                0.382426 Hz
AQ                1.3075131 sec
RG                    3649.1
DW                   19.950 usec
DE                    6.00 usec
TE                    294.1 K
D1               2.00000000 sec
d11              0.03000000 sec
MCREST           0.00000000 sec
MCWRK            0.01500000 sec

======== CHANNEL f1 ========
NUC1                    13C
P1                    9.50 usec
PL1                   3.80 dB
SFO1           125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                    1H
PCPD2                90.00 usec
PL2                   0.30 dB
PL12                 16.78 dB
PL13                 18.00 dB
SFO2           500.1340010 MHz

F2 - Processing parameters
SI                    32768
SF             125.7578470 MHz
WDW                      EM
SSB                       0
LB                    1.00 Hz
GB                        0
PC                    1.00
```

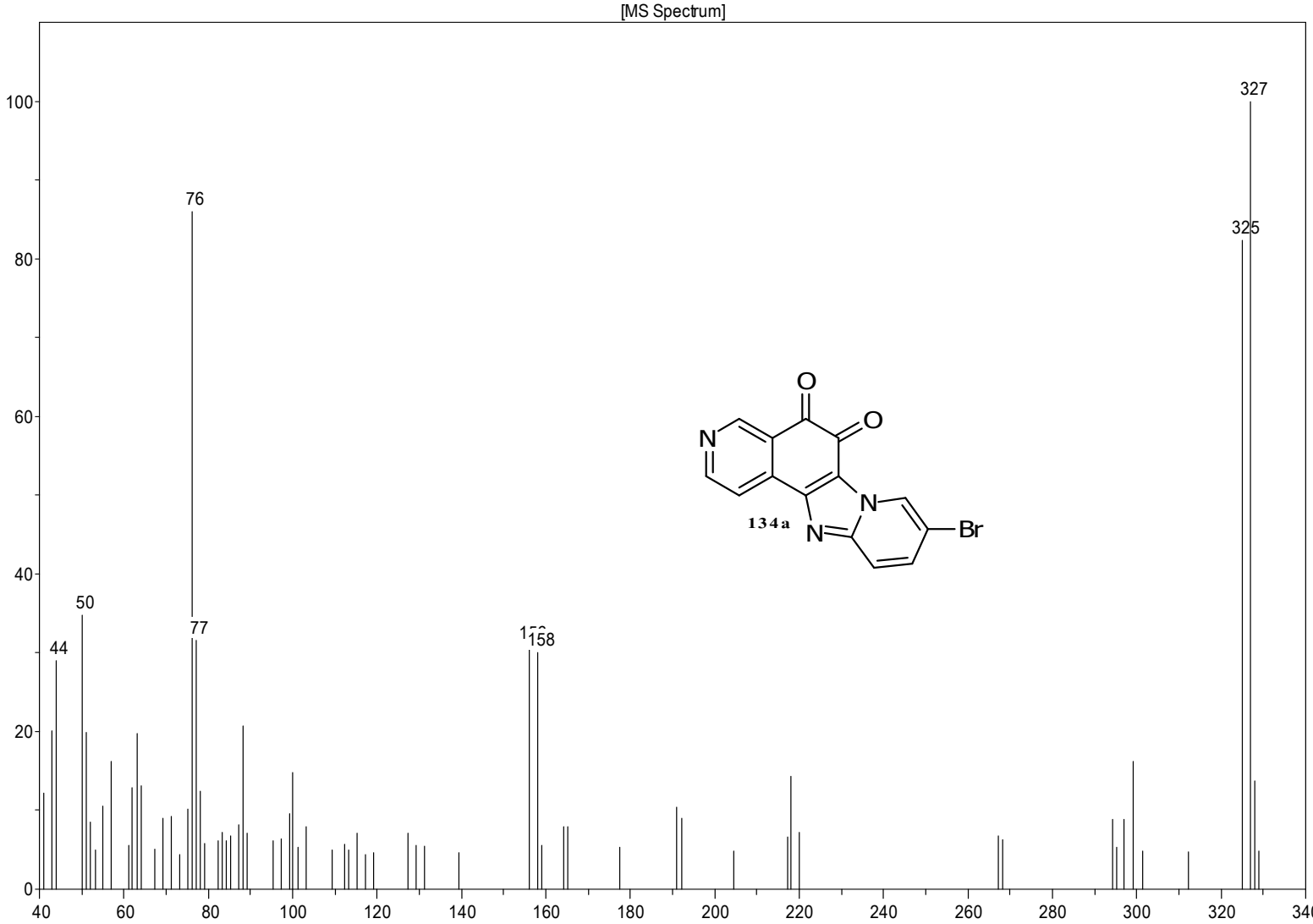
HSQC spectrum of **128b**.



IR spectrum of **134a** (KBr).

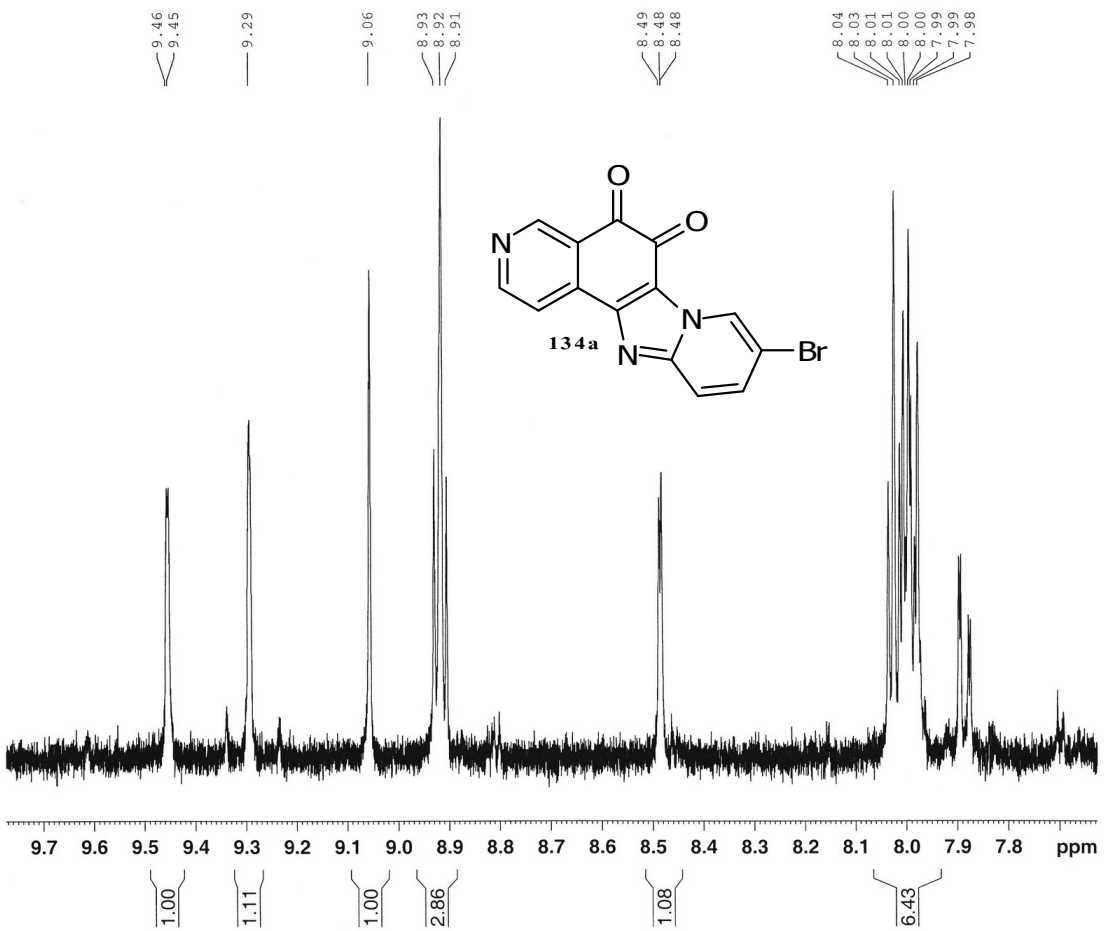


Mass spectrum of **134a**.



^{1}H NMR of spectrum of **134a** in DMSO-d_6.

TM3271/DMSO



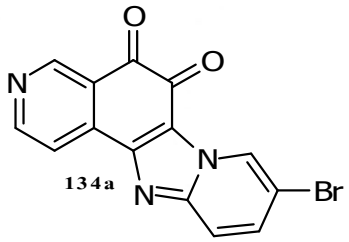

```
Current Data Parameters
NAME                 TM3271
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20090403
Time                 11.45
INSTRUM              spect
PROBHD    5 mm BBO BB-1H
PULPROG              zg30
TD                  82642
SOLVENT              DMSO
NS                     16
DS                      2
SWH               8012.820 Hz
FIDRES               0.096958 Hz
AQ                5.1569734 sec
RG                     128
DW                  62.400 usec
DE                   6.00 usec
TE                  293.6 K
D1             5.00000000 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  13.50 usec
PL1                  0.30 dB
SFO1          500.1330885 MHz

F2 - Processing parameters
SI                  131072
SF            500.1300099 MHz
WDW                    no
SSB                     0
LB                   0.00 Hz
GB                      0
PC                   1.00
```

^{13}C NMR of spectrum of **134a** in DMSO-d_6.

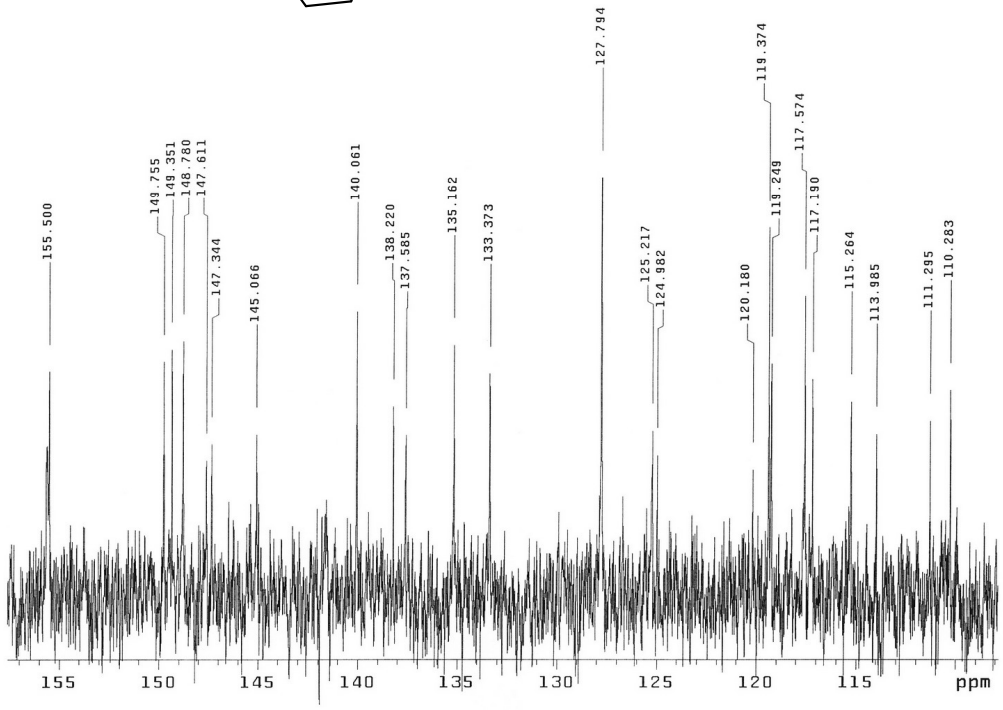
TM3271/DMSO

exp3 stdl3c

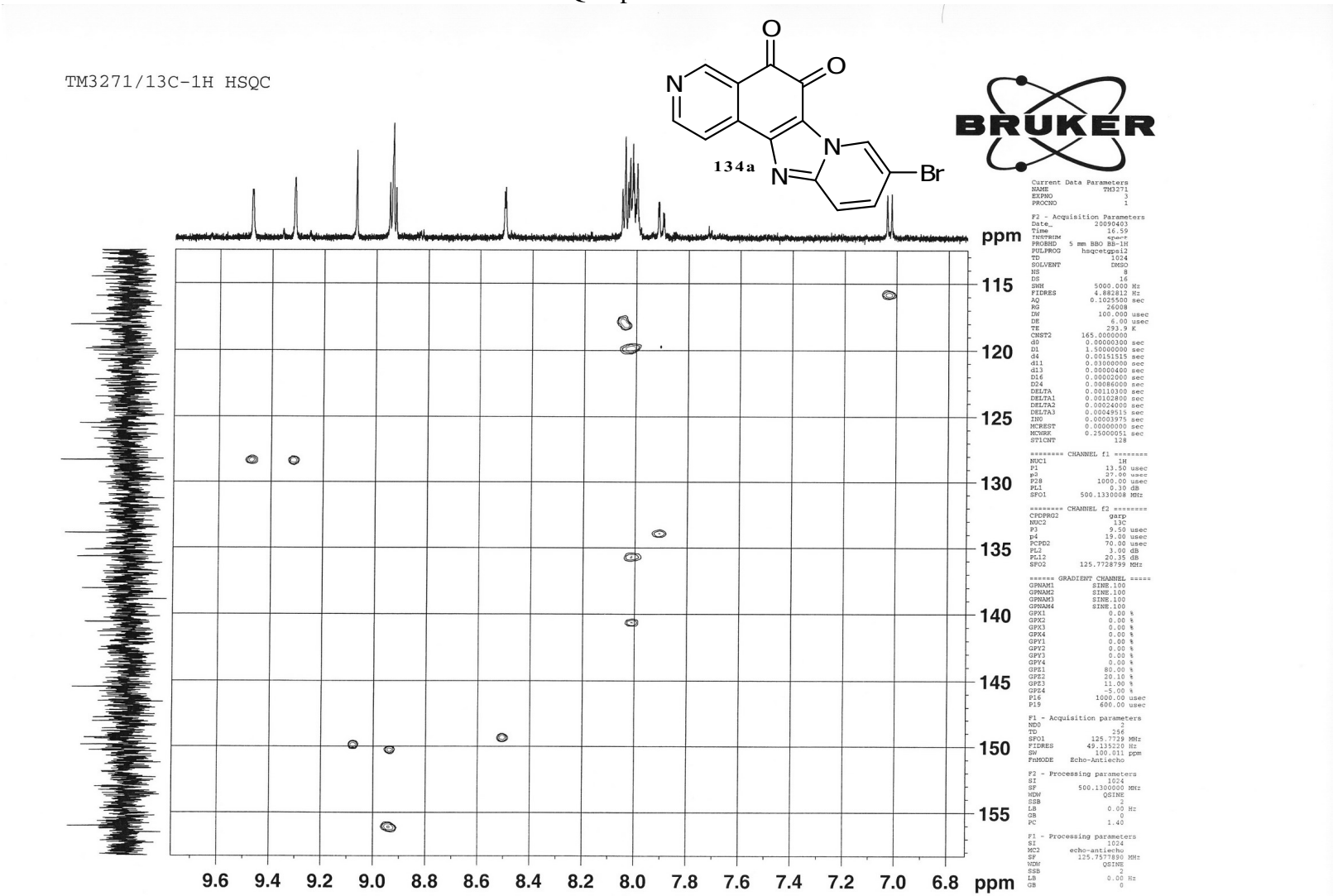
SAMPLE		DEC. & VT	
date	Apr 7 09	dfrq	299.951
solvent	DMSO	dn	H1
file	exp	dpwr	41
ACQUISITION		dof	1500.0
sfrq	75.429	dm	yyy
tn	C13	dmm	w
at	2.000	dmf	12000
np	80000	dseq	undefined
sw	20000.0	dres	undefined
fb	11000	homo	n
bs	8	PROCESSING	
ss	4	lb	1.20
tpwr	53	wtfile	
pw	7.0	proc	ft
dl	2.500	fn	131072
tof	-191.6	math	f
nt	32768		
ct	0	werr	
alock	n	wexp	
gain	not used	wbs	
FLAGS		wnt	
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	8134.9		
wp	3751.9		
vs	17056		
sc	0		
wc	180		
hzmm	20.84		
is	500.00		
rfl	5776.5		
rfp	2979.5		
th	28		
ins	1.000		
nm	ph		



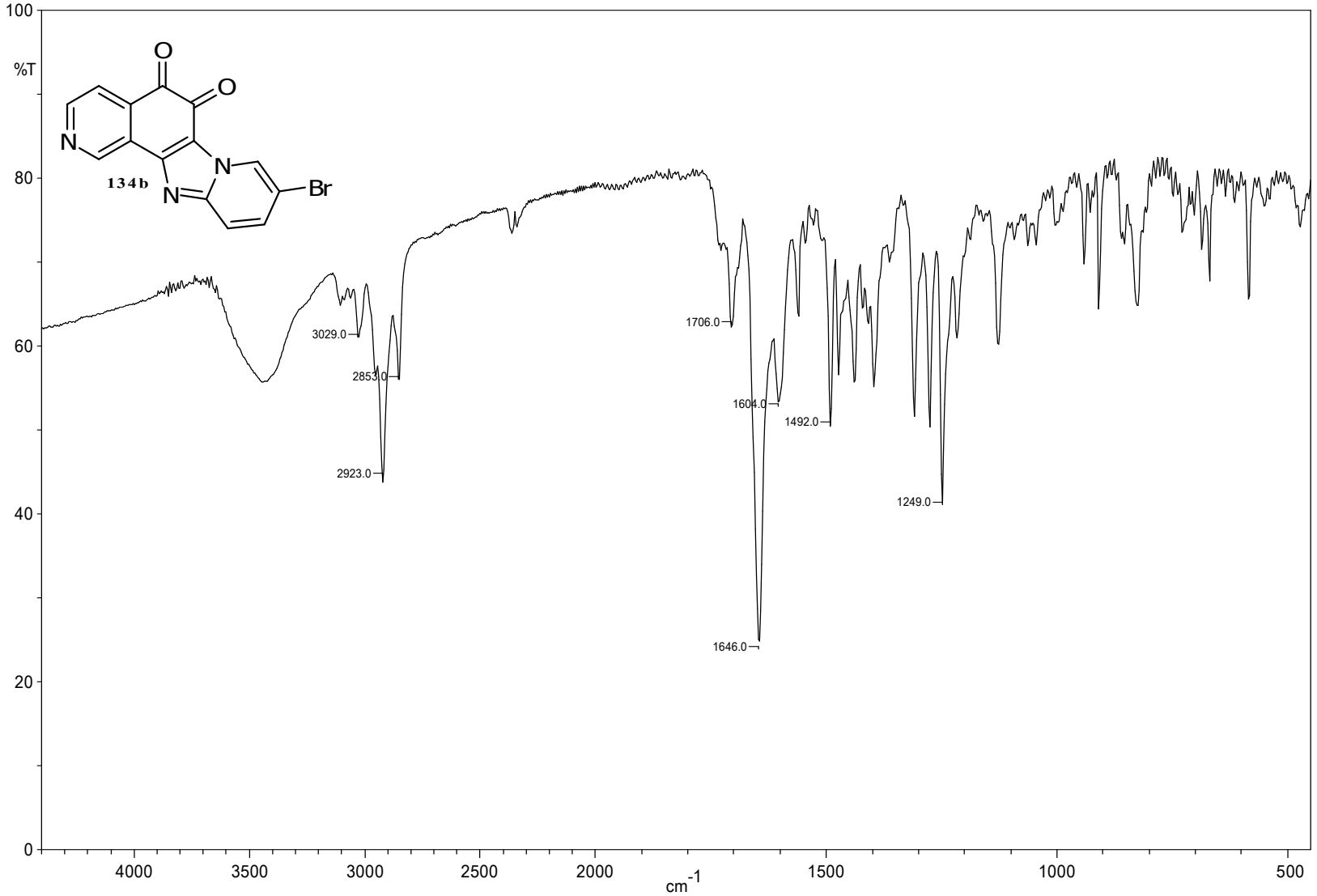
134a



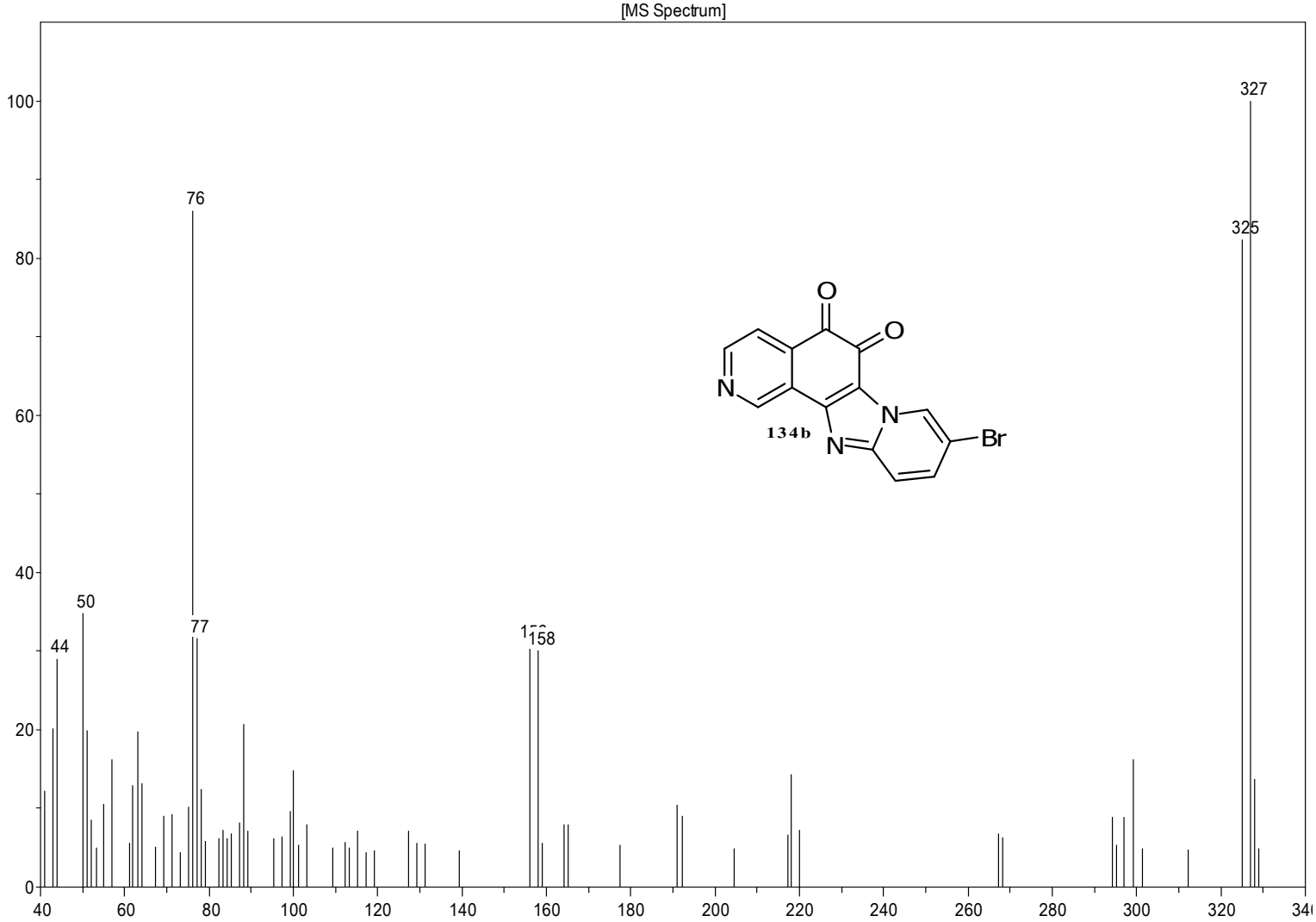
HSQC spectrum of **134a**.



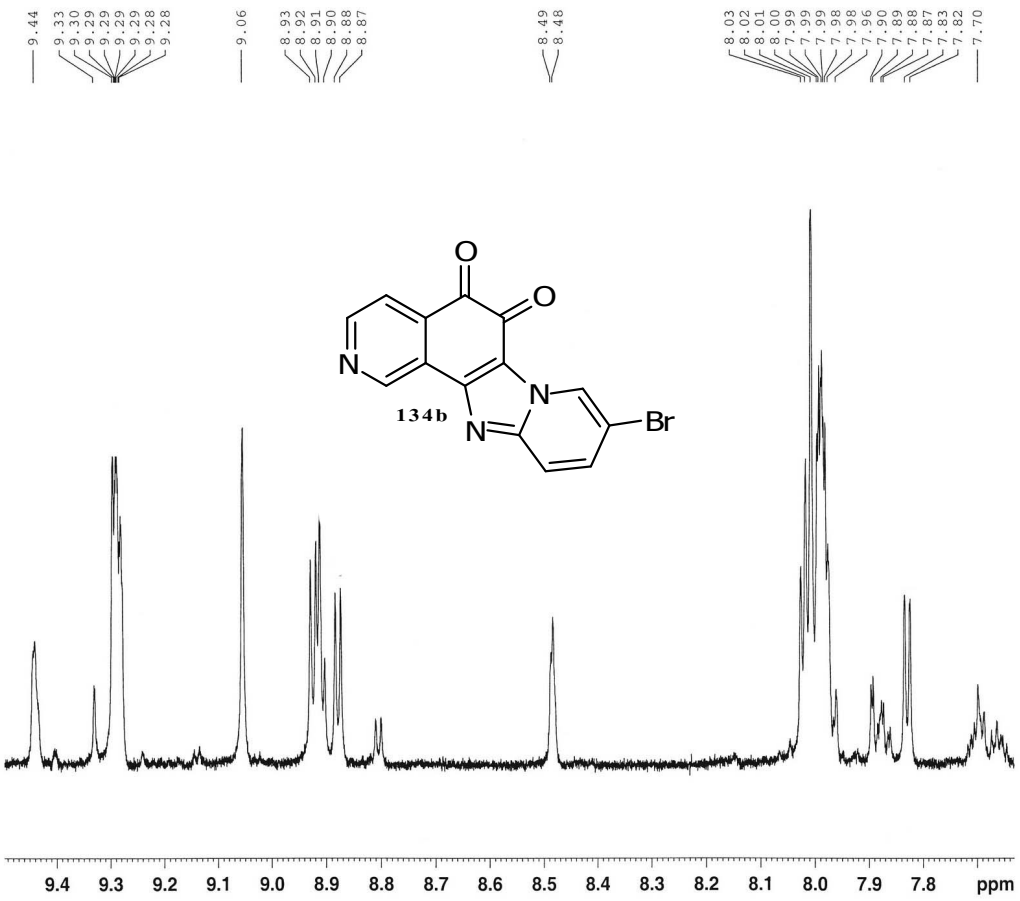
IR spectrum of **134b** (KBr).



Mass spectrum of **134b**.

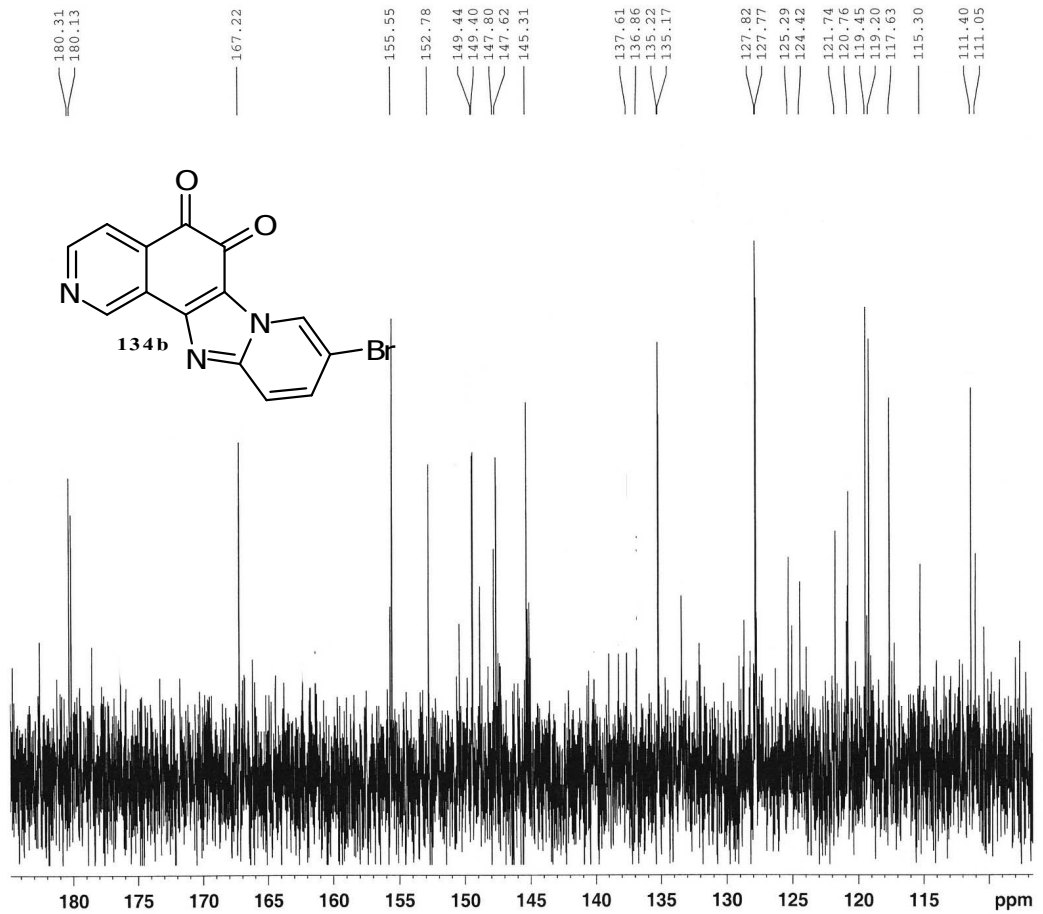


^{1}H NMR of spectrum of **134b** in DMSO-d_6.



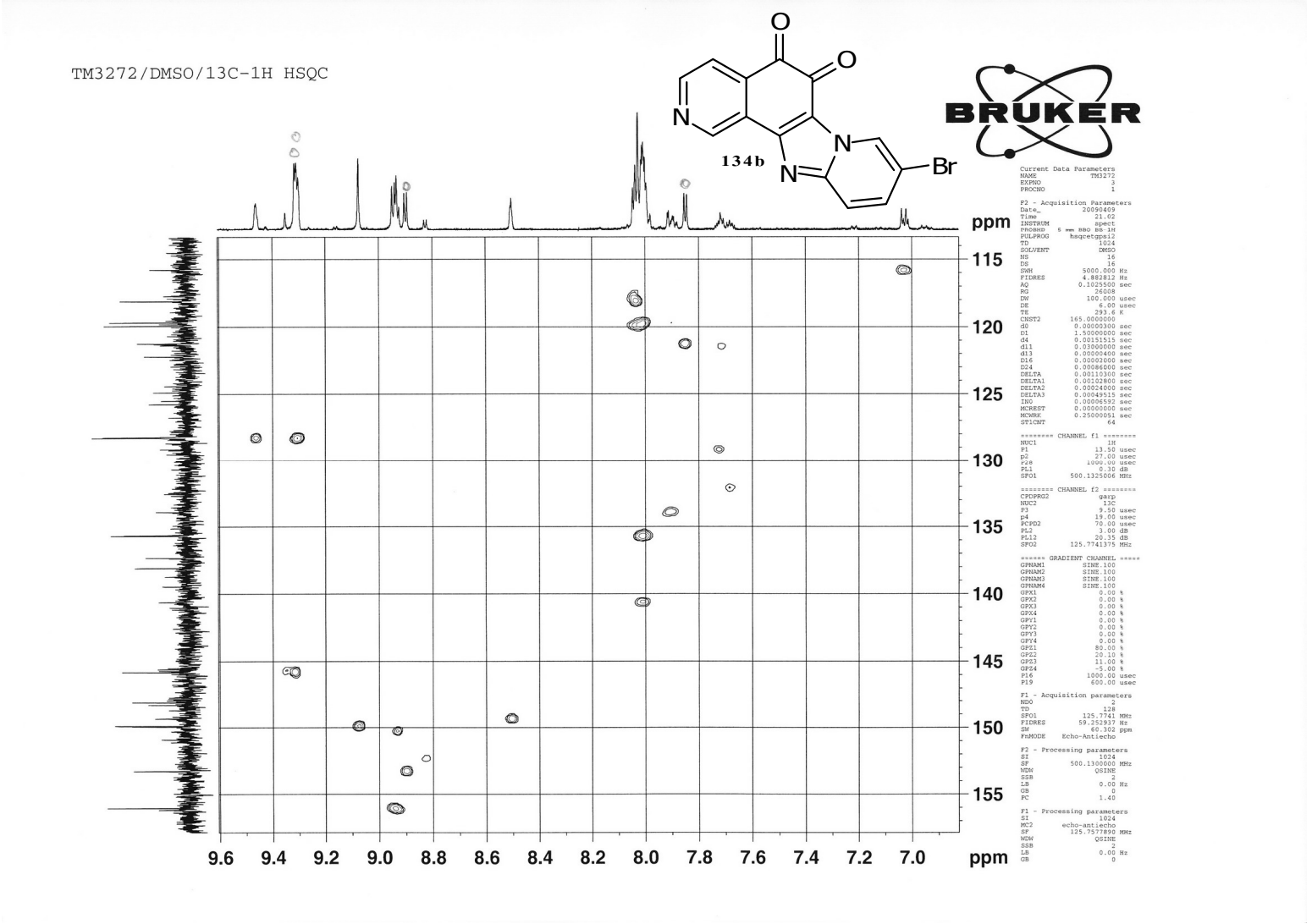

```
Current Data Parameters
NAME                 TM3272
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20090409
Time                 11.47
INSTRUM              spect
PROBHD    5 mm BBO BB-1H
PULPROG              zg30
TD                  65536
SOLVENT              DMSO
NS                     16
DS                      2
SWH               8012.820 Hz
FIDRES               0.122266 Hz
AQ                4.0895586 sec
RG                   228.1
DW                  62.400 usec
DE                   6.00 usec
TE                  293.2 K
D1                5.00000000 sec
MCREST            0.00000000 sec
MCWRK             0.01500000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                   13.50 usec
PL1                   0.30 dB
SFO1           500.1330885 MHz

F2 - Processing parameters
SI                    65536
SF             500.1300098 MHz
WDW                     no
SSB                      0
LB                    0.00 Hz
GB                       0
PC                    1.00
```

.^{13}C NMR of spectrum of **134b** in DMSO-d_6.

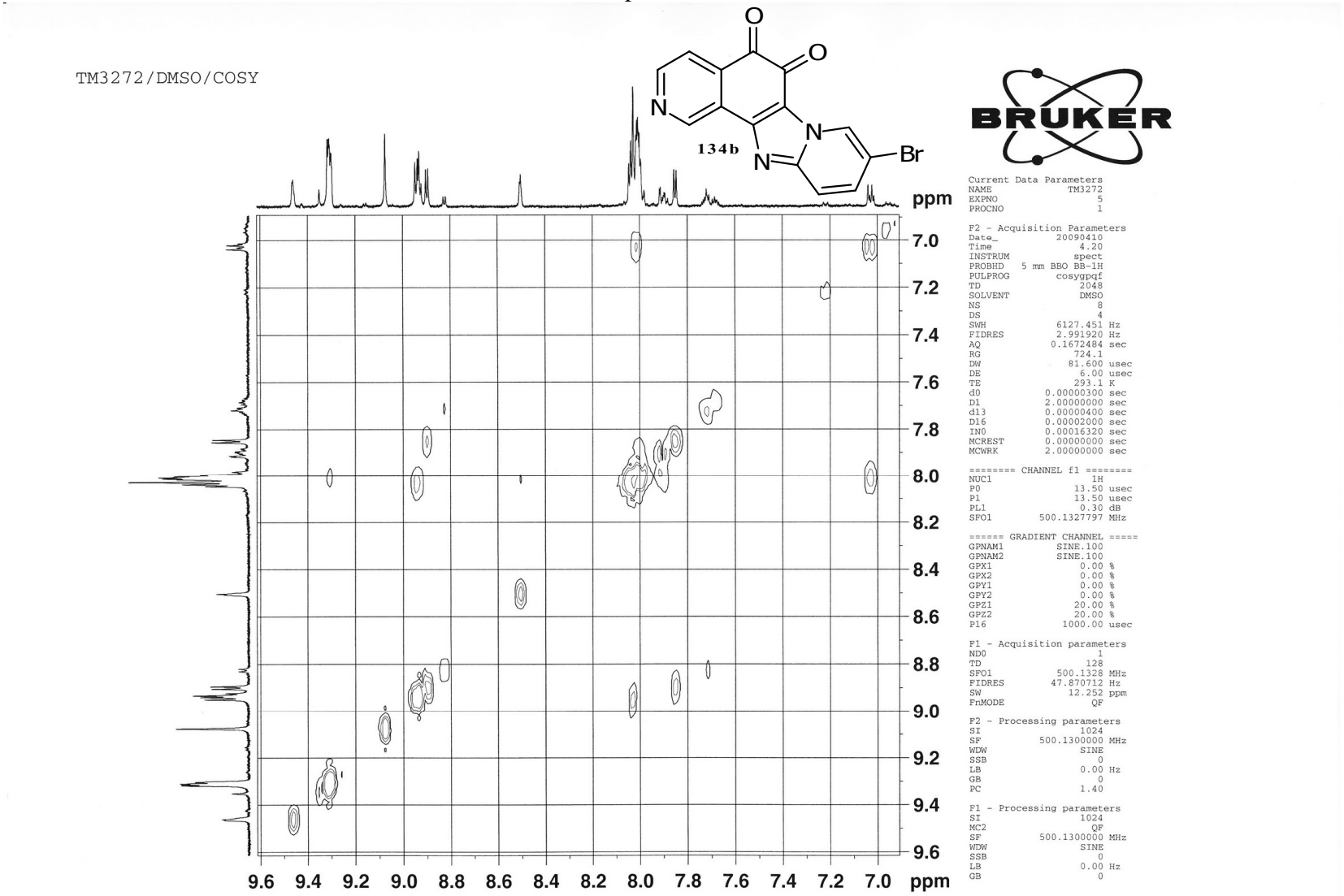



```
Current Data Parameters
NAME                 TM3272
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
Date_              20090409
Time                 12.06
INSTRUM              spect
PROBHD    5 mm BBO BB-1H
PULPROG             zgpg30
TD                  105816
SOLVENT               DMSO
NS                    8192
DS                       4
SWH              26455.027 Hz
FIDRES           0.250010 Hz
AQ               1.9999913 sec
RG                  3649.1
DW                  18.900 usec
DE                   6.00 usec
TE                  294.3 K
D1              2.00000000 sec
d11             0.03000000 sec
MCREST          0.00000000 sec
MCWRK           0.01500000 sec

======== CHANNEL f1 ========
NUC1                  13C
P1                   9.50 usec
PL1                  3.80 dB
SFO1          125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                  1H
PCPD2               90.00 usec
PL2                  0.30 dB
PL12                16.78 dB
PL13                18.00 dB
SFO2          500.1337510 MHz

F2 - Processing parameters
SI                   32768
SF            125.7578474 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.00
```

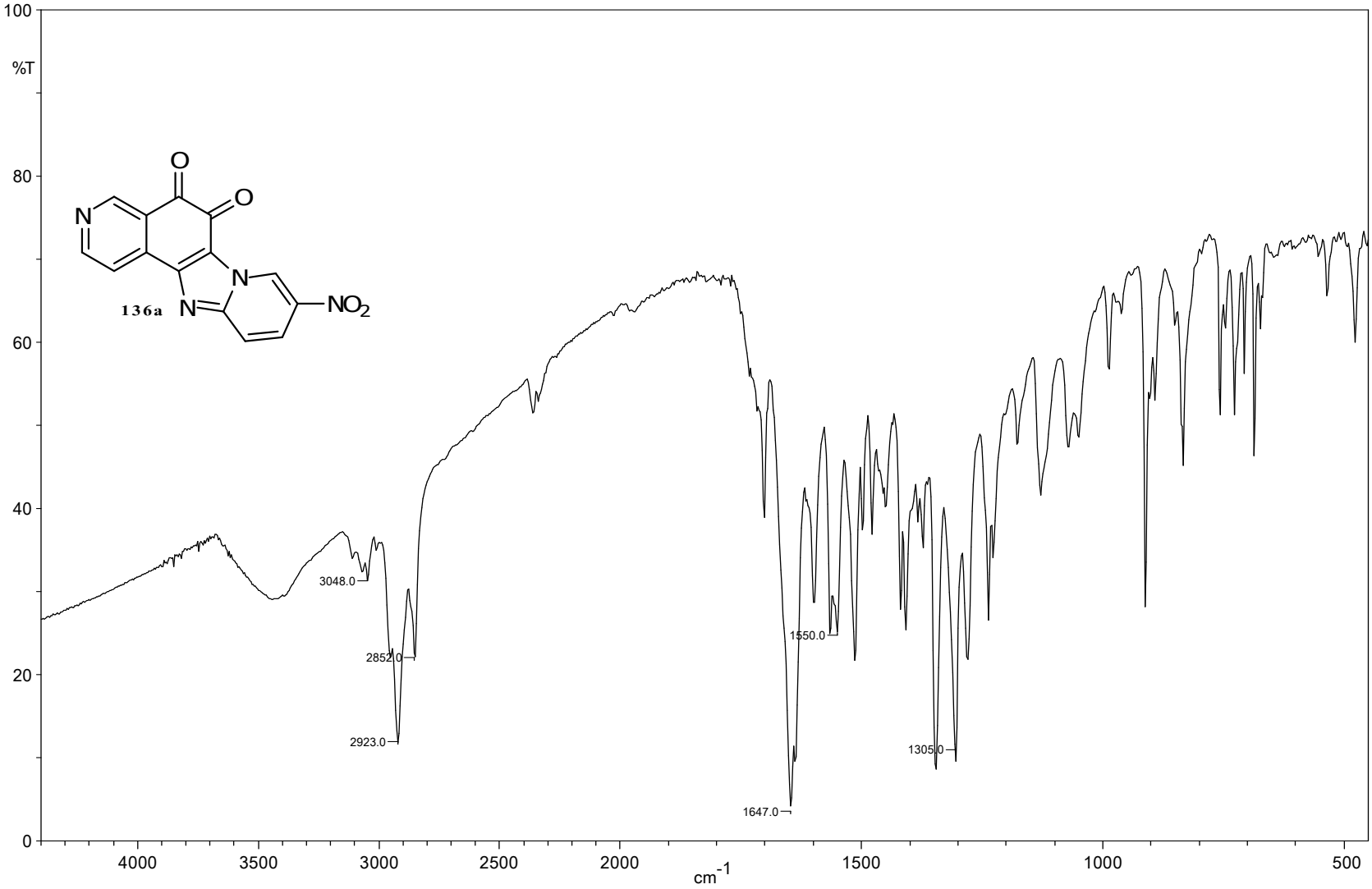
HSQC spectrum of **134b**.



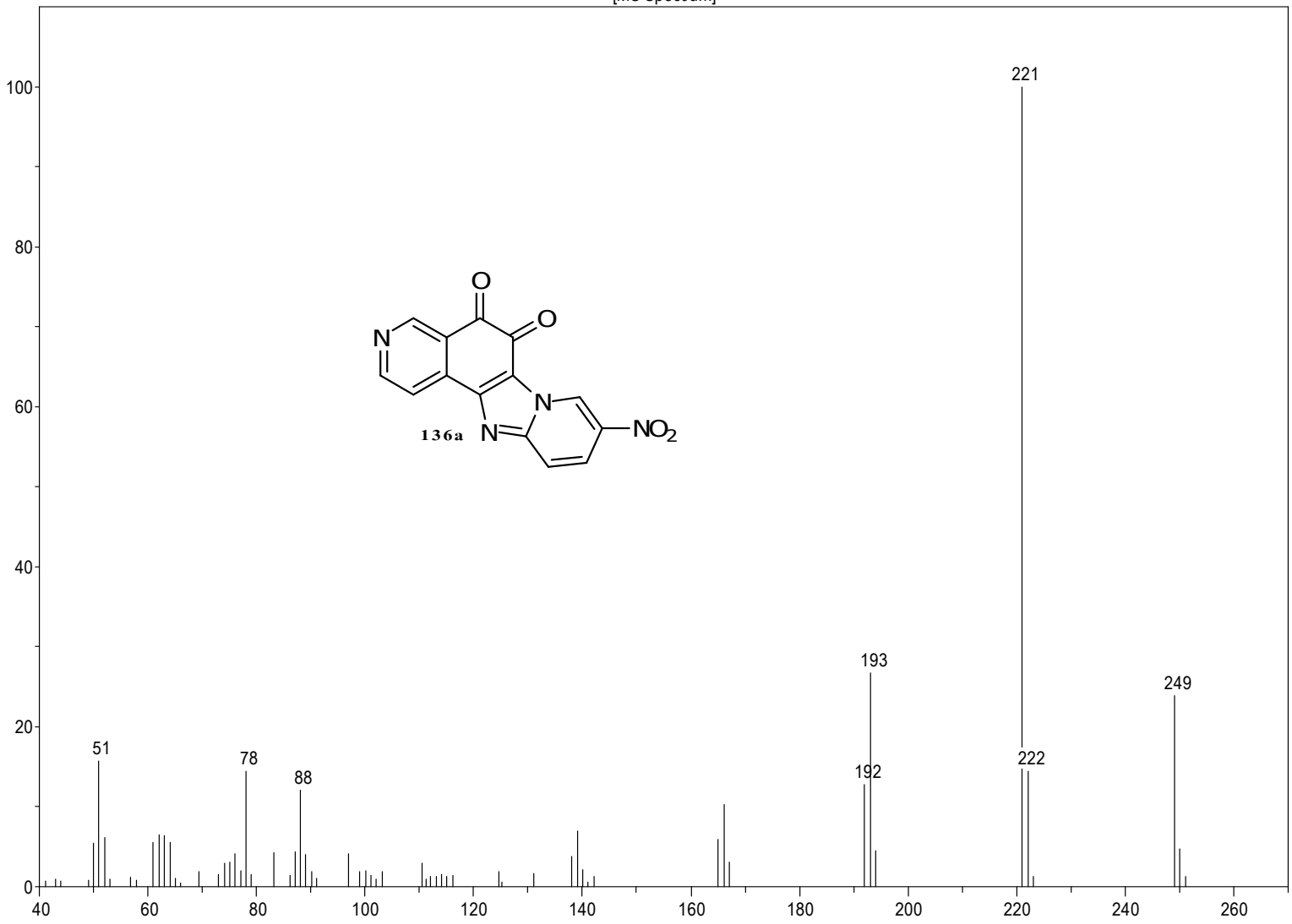
COSY spectrum of **134b**.



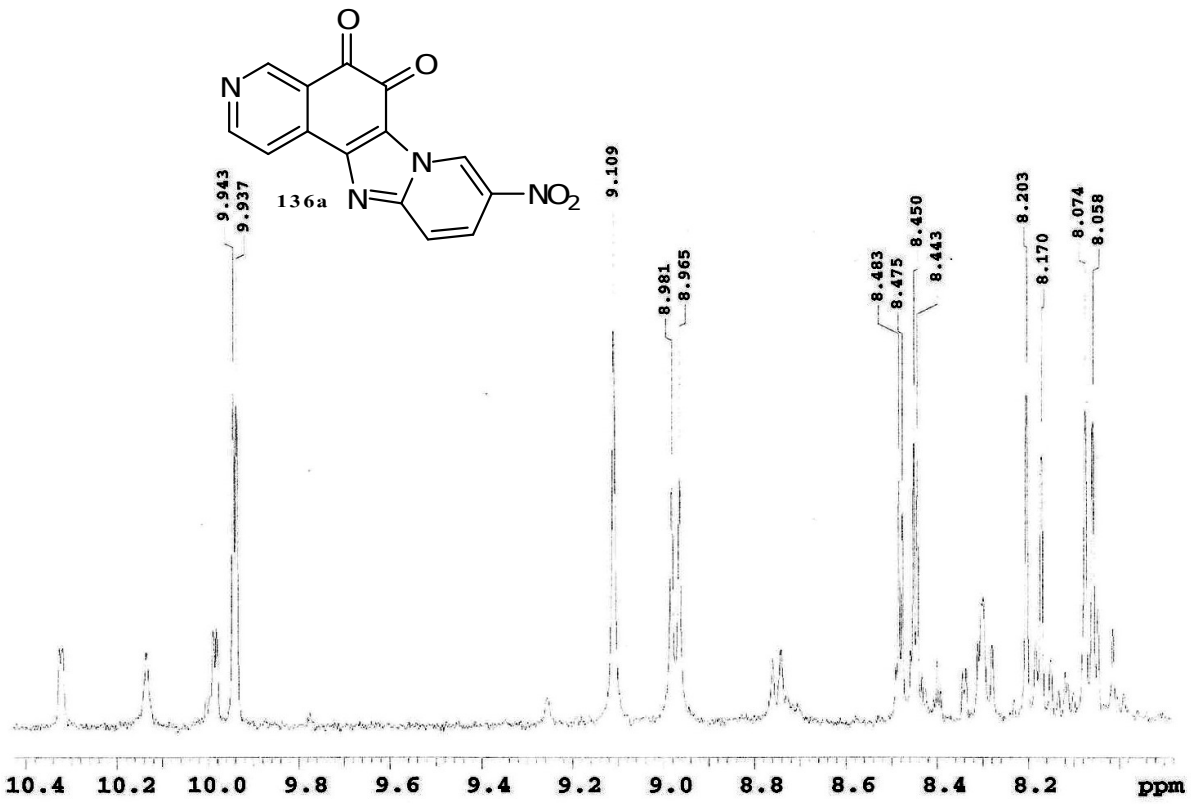
IR spectrum of **136a** (KBr).



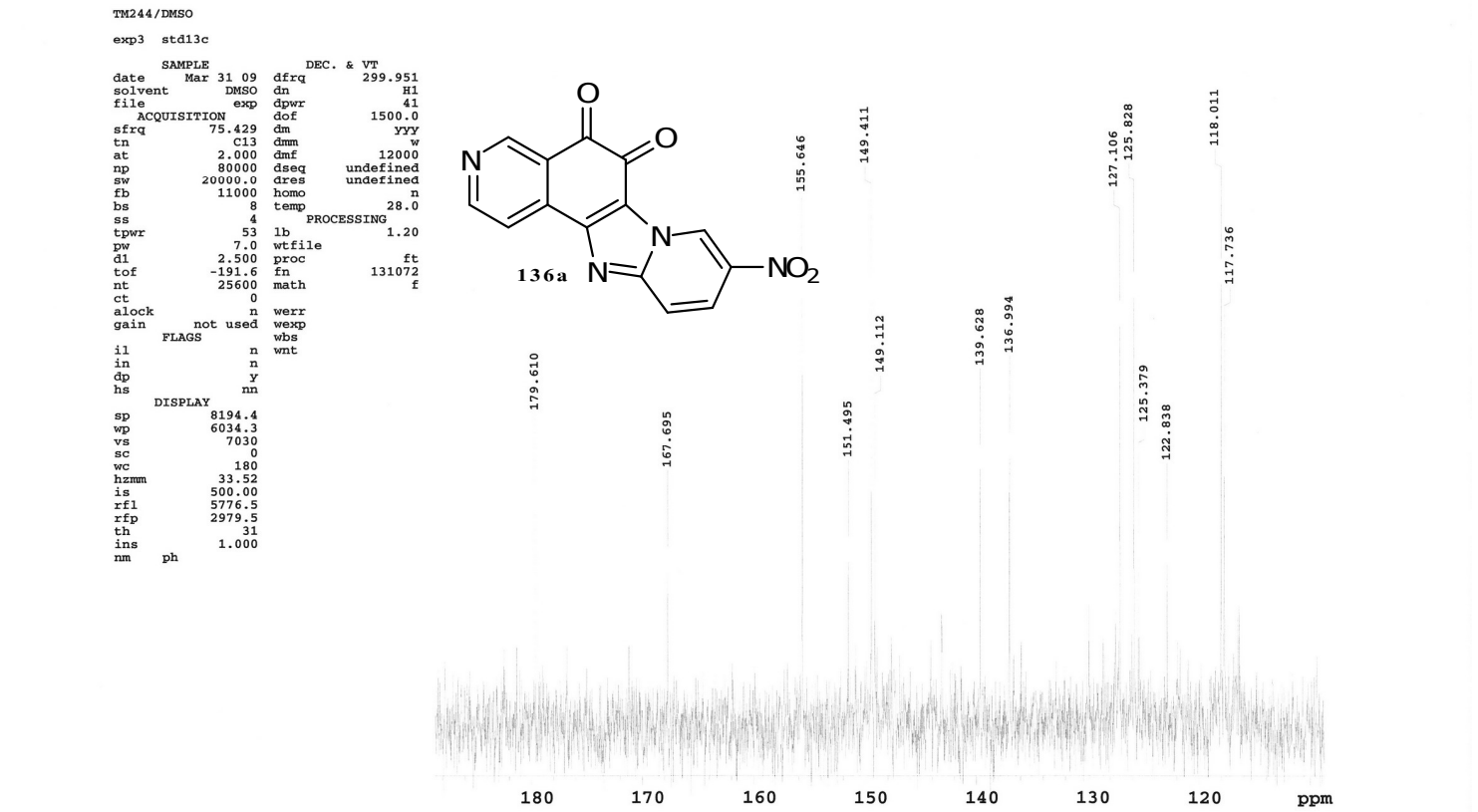
Mass spectrum **136a**.



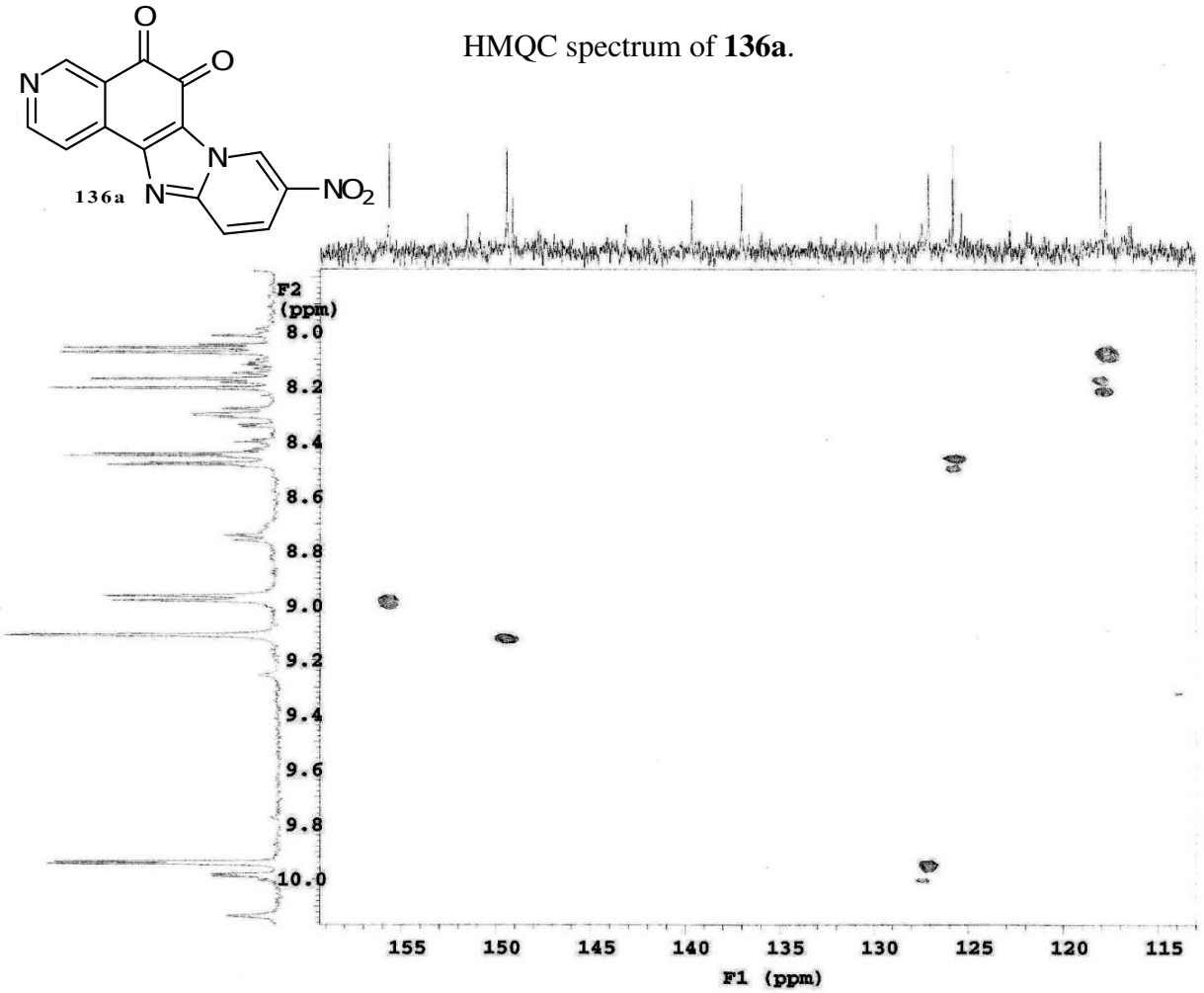
^{1}H NMR of spectrum of **136a** in DMSO-d_6.



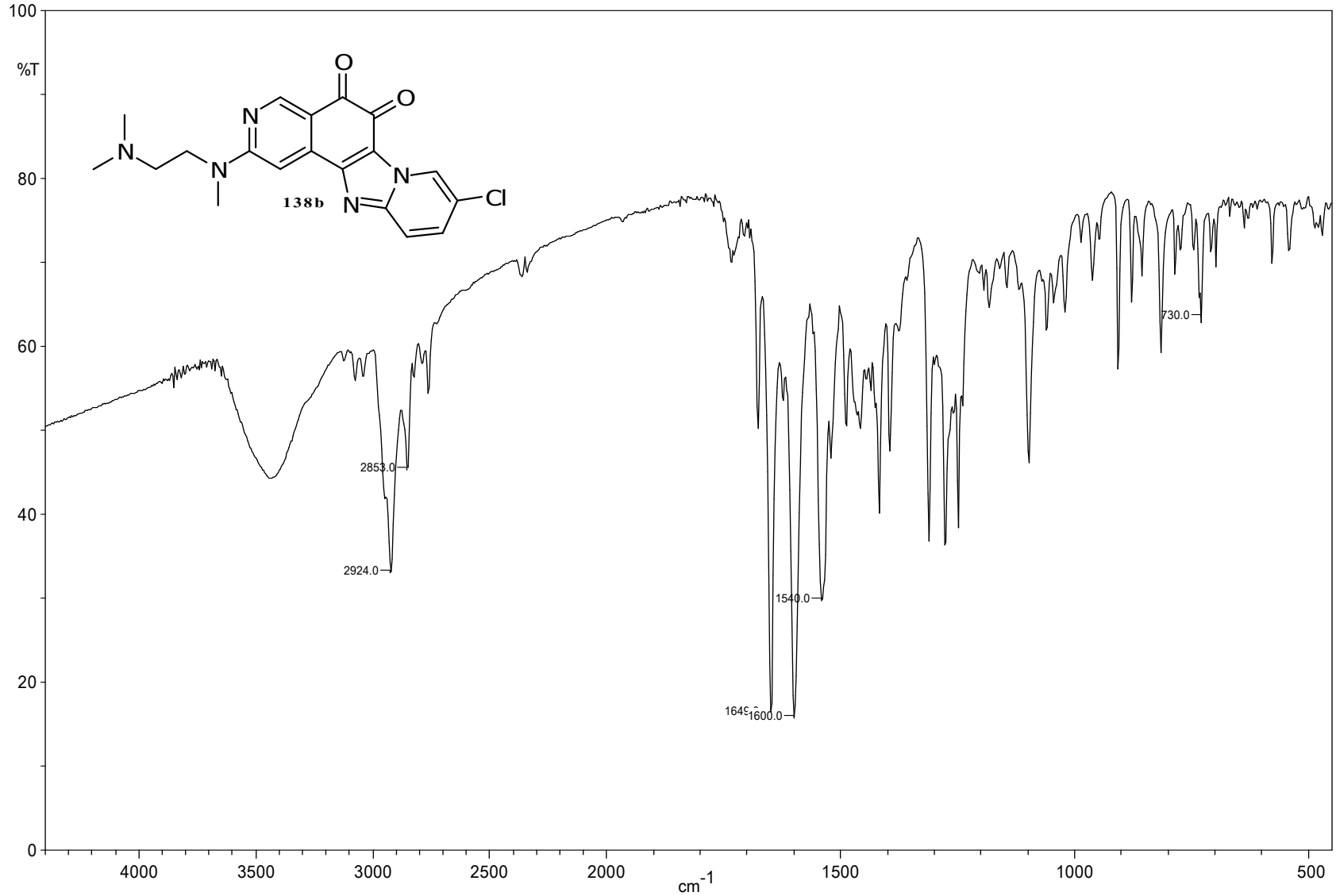
^{13}C NMR of spectrum of **136a** in DMSO-d_6.



HMQC spectrum of **136a**.

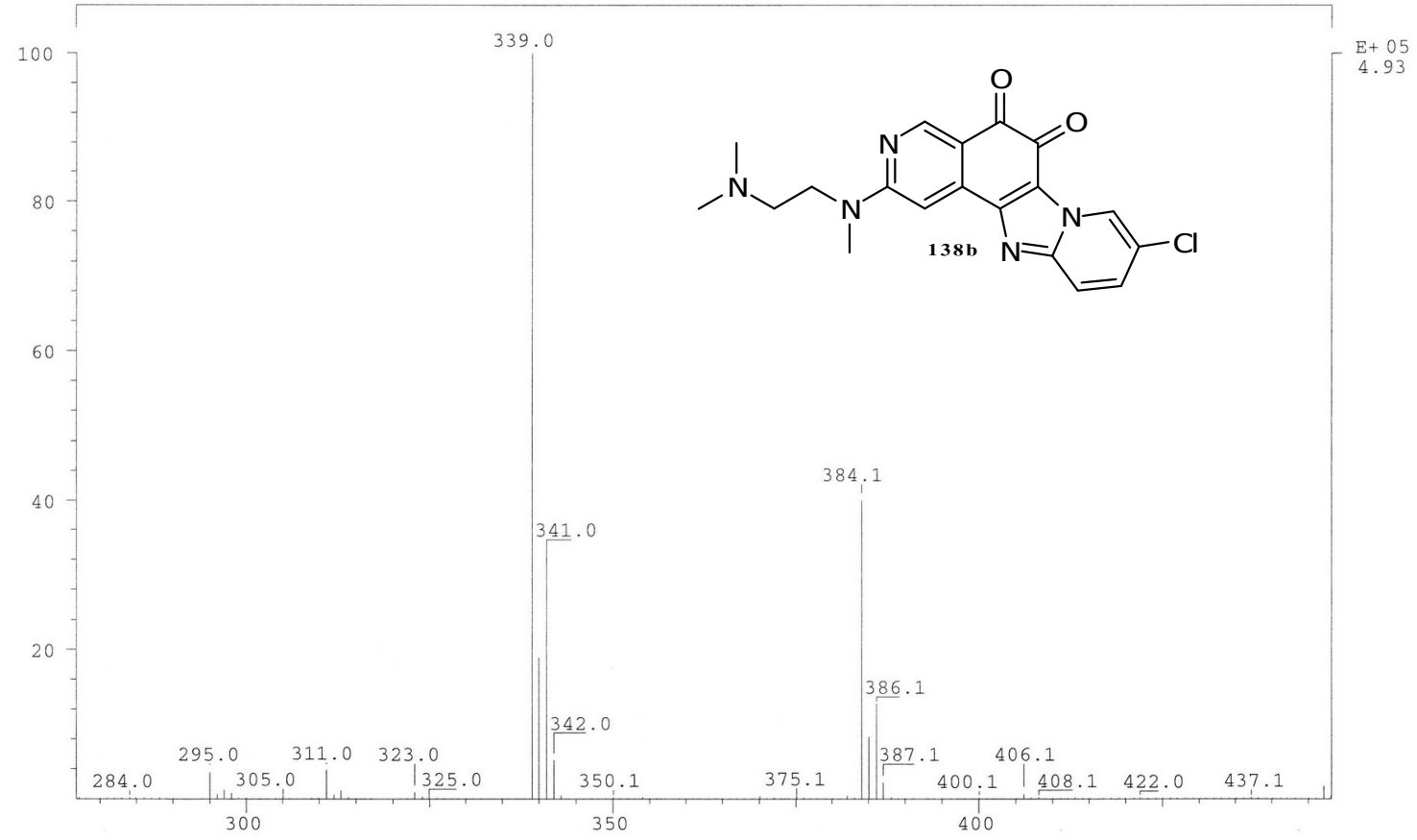


IR spectrum of **138b** (KBr).

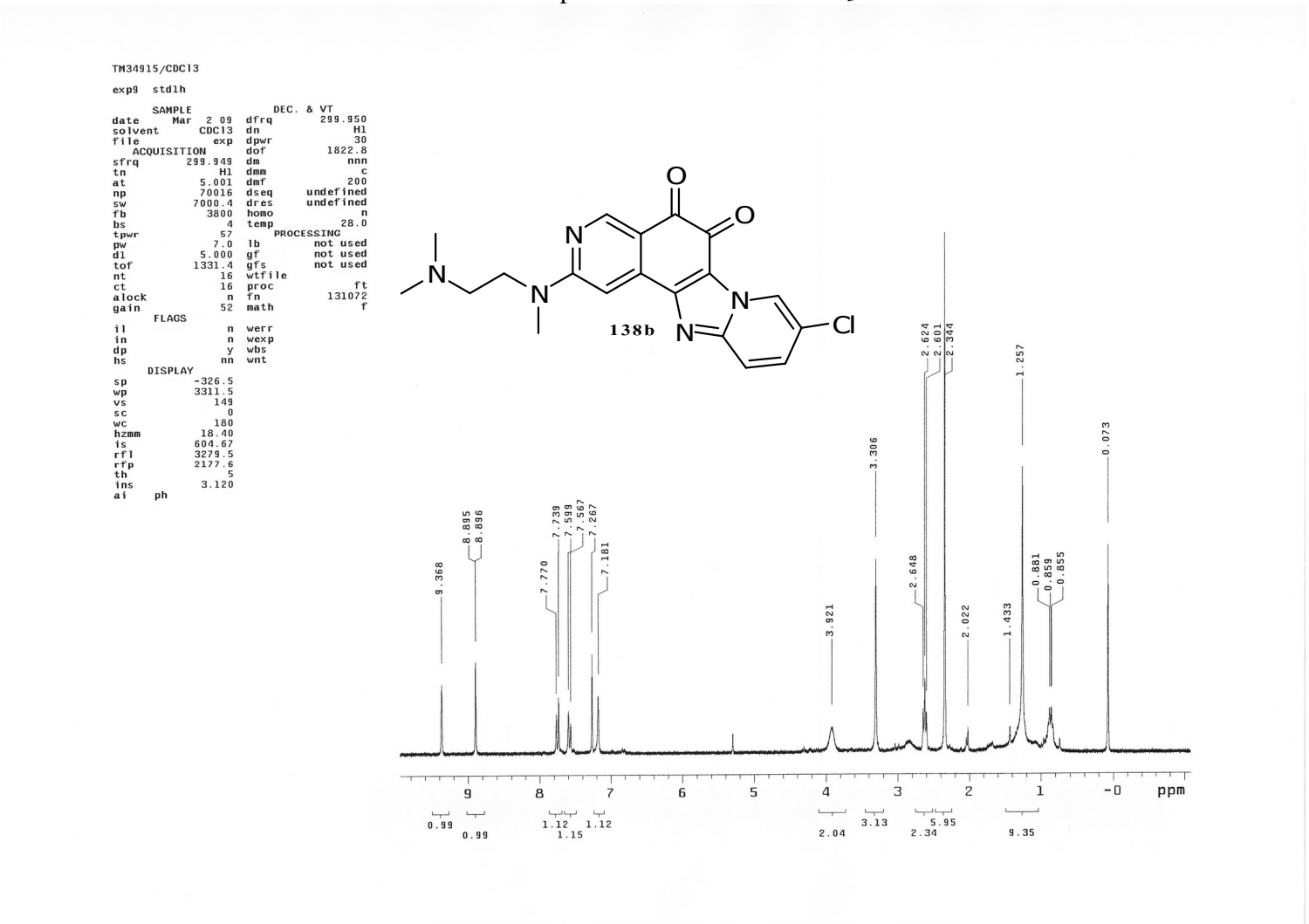


Mass spectrum of **138b**.

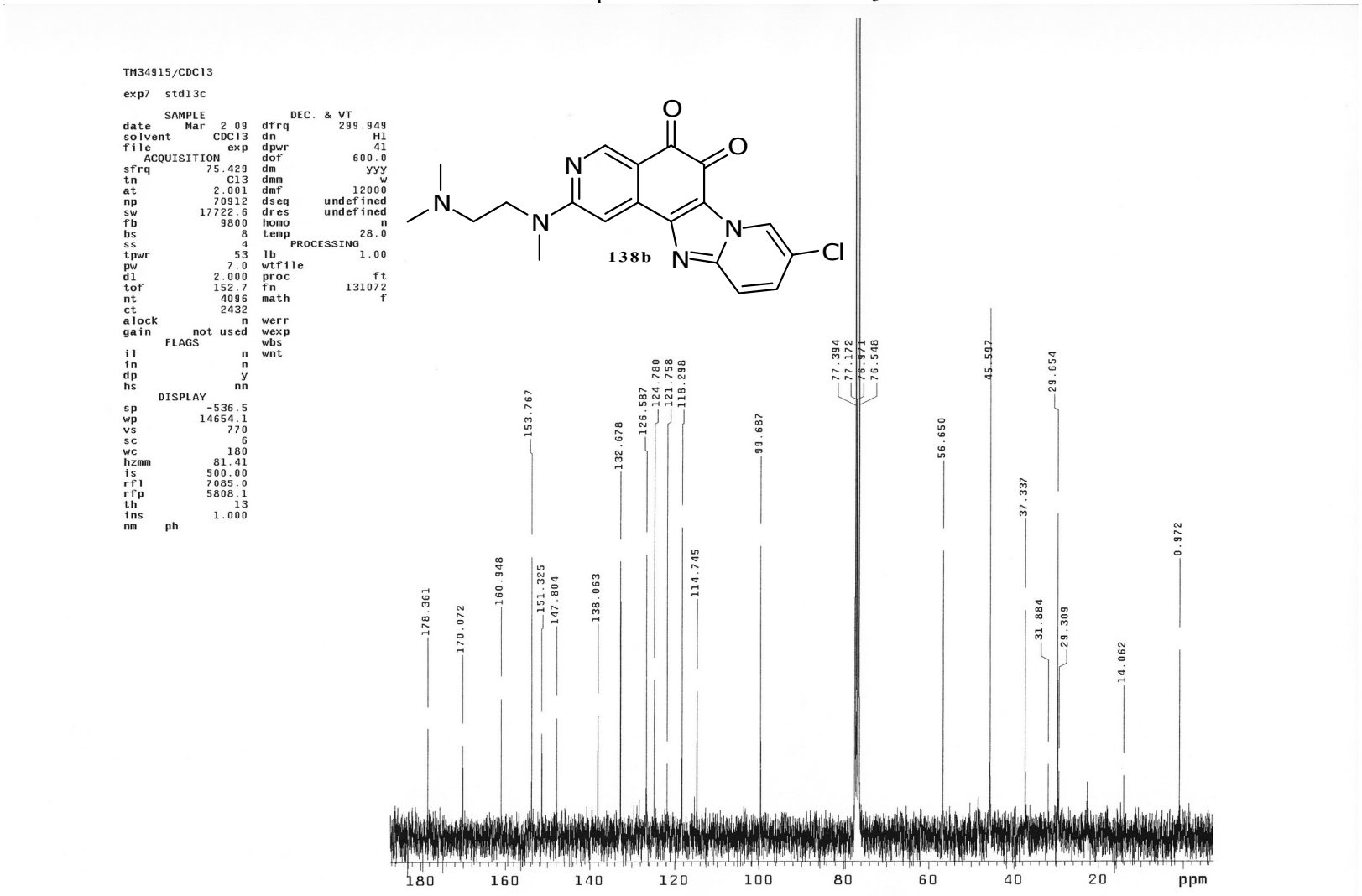
```
SPEC:  00000000000000000000000000000000     24-Mar-95  Elapse:  00:30.9        1
Samp:  MS383                                            Start :  17:18:09       1
Comm:  4kV 3uA   MeOH/ACN
Mode:  ESI +VE +APICID LMR  BSCAN (EXP) UP LR NRM
Oper:  phu           Client:  Theerachart/Holzer/       Inlet :
Base:  339.0                 Inten :  492879            Masses:  102 > 999
Norm:  339.0                 RIC   :  1320803           #peaks:  862
Peak:  1000.00  mmu
Data:  AVER : Scans All from /usr/users/finnigan/data/34456_1.dat
```

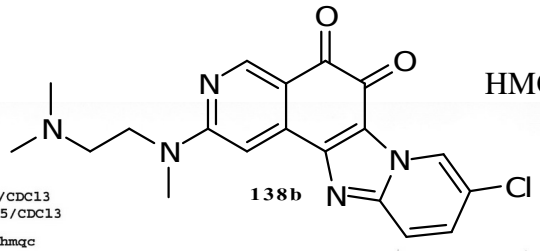


^{1}H NMR spectrum of **138b** in $CDCl_3$.

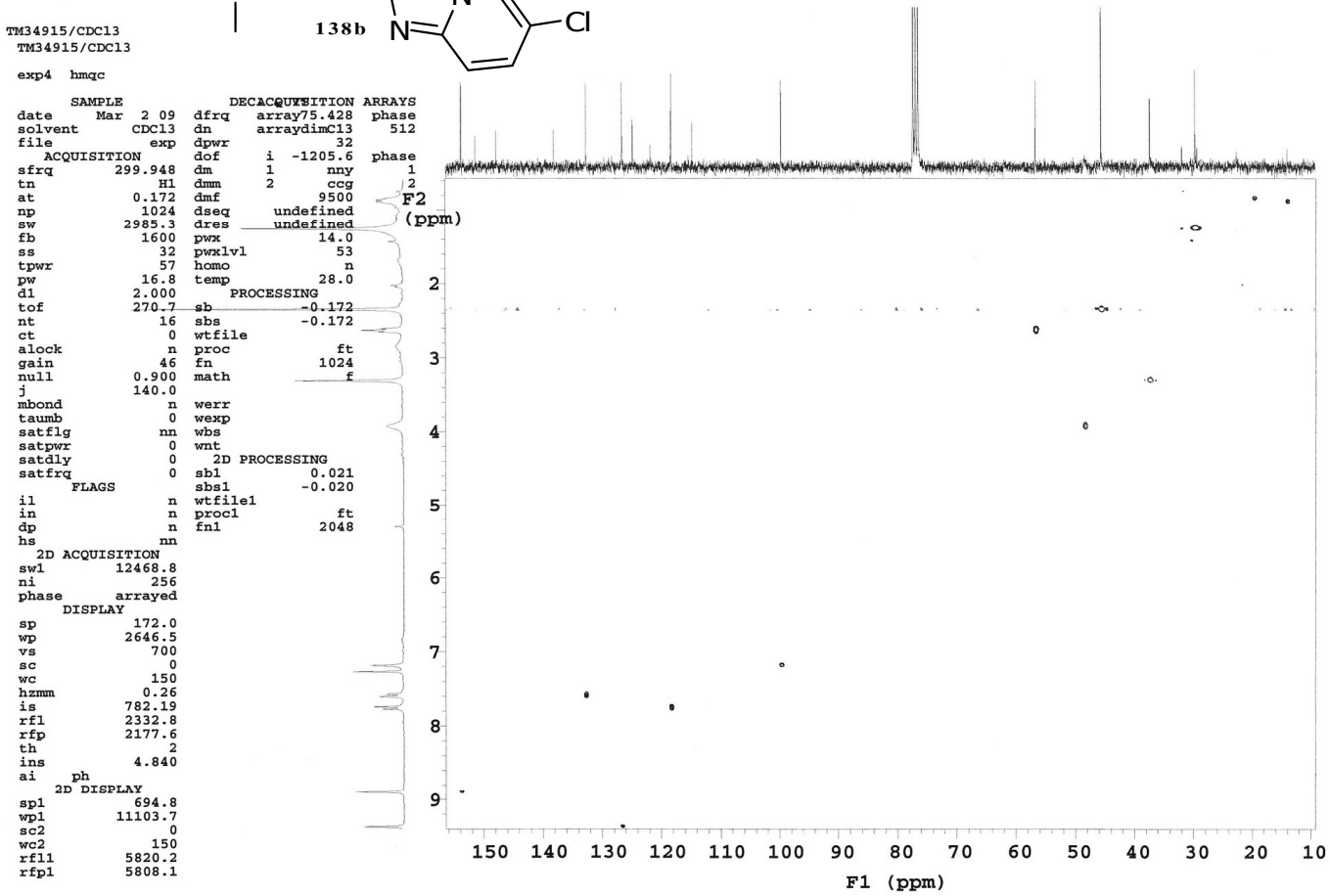


^{13}C NMR spectrum of **138b** in $CDCl_3$.

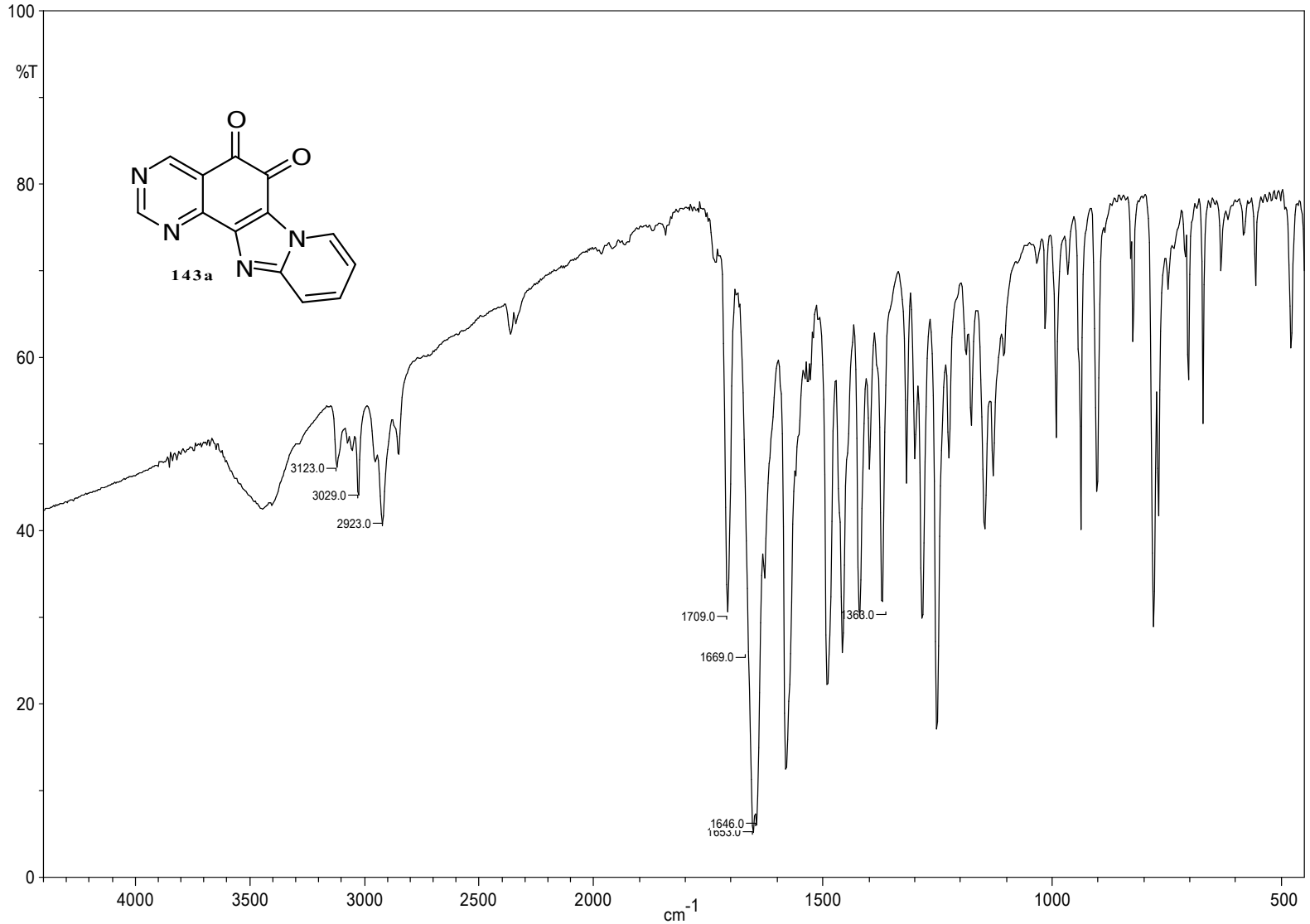




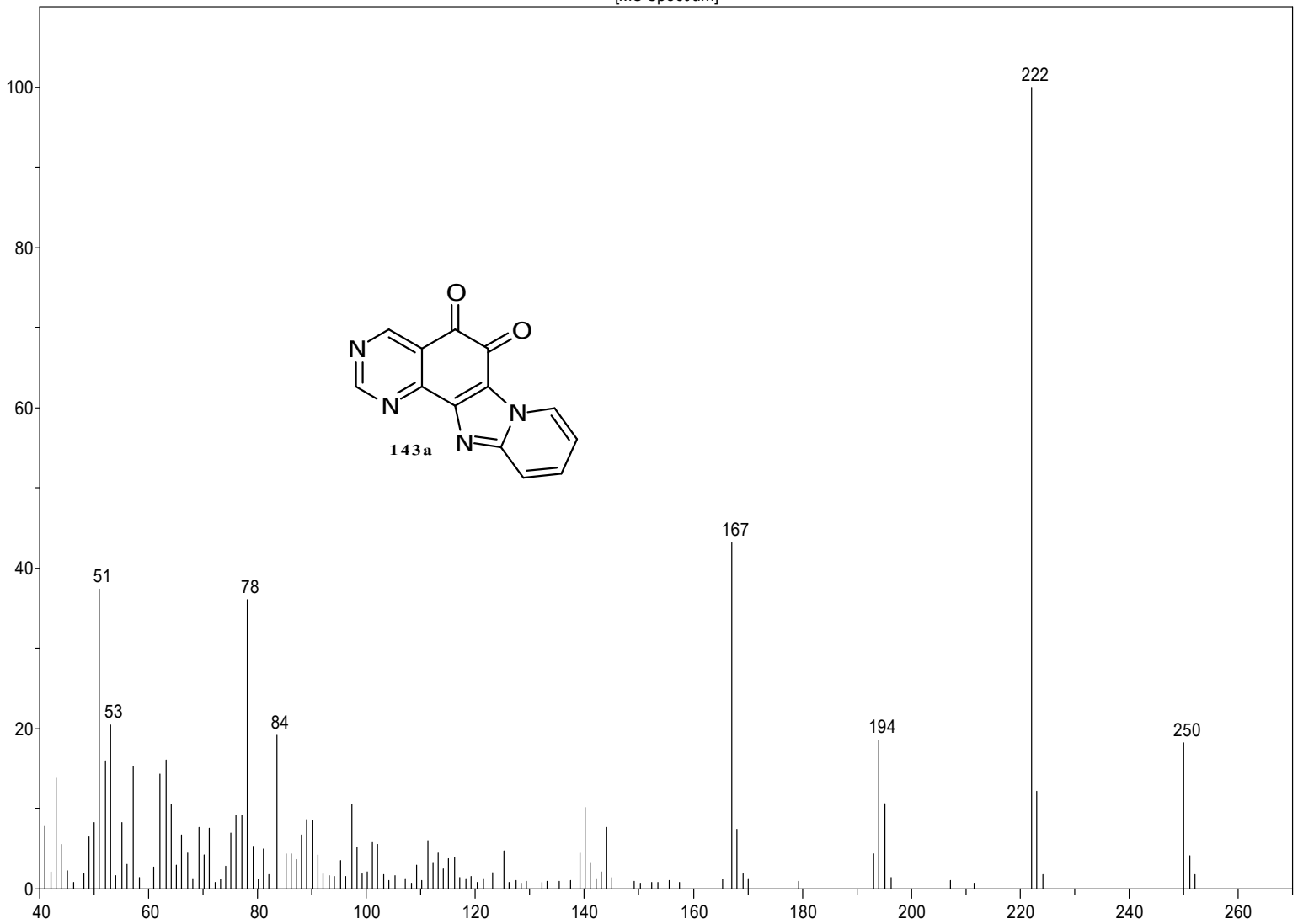
HMQC spectrum of **138b**.



IR spectrum of **143a** (KBr).

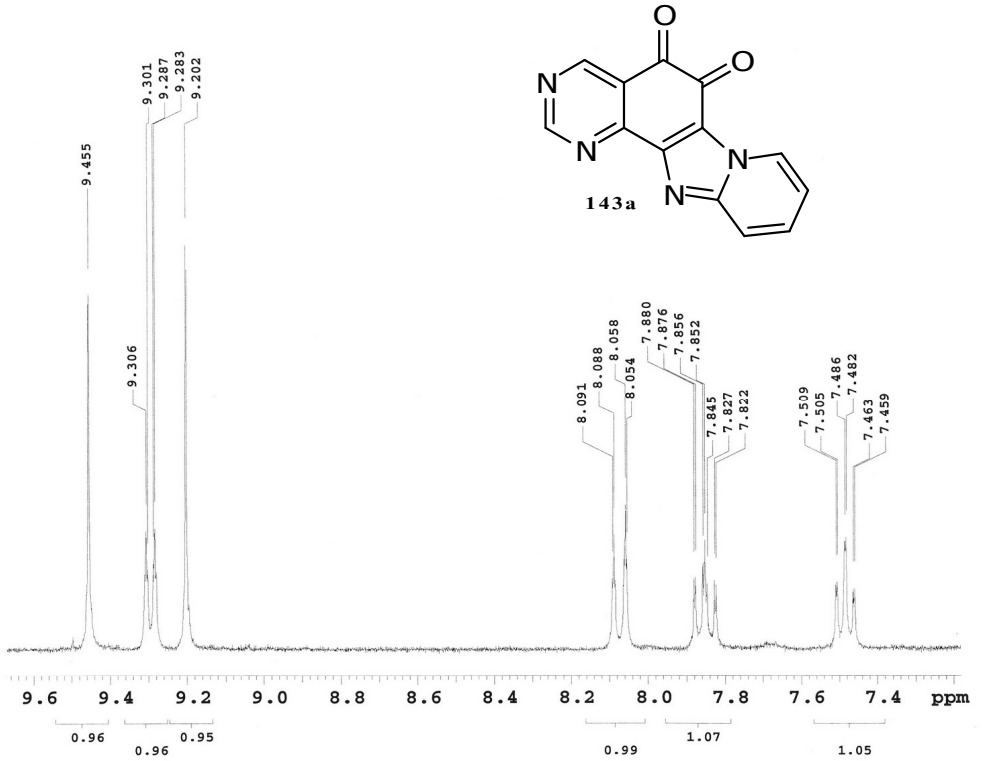


Mass spectrum of **143a**.



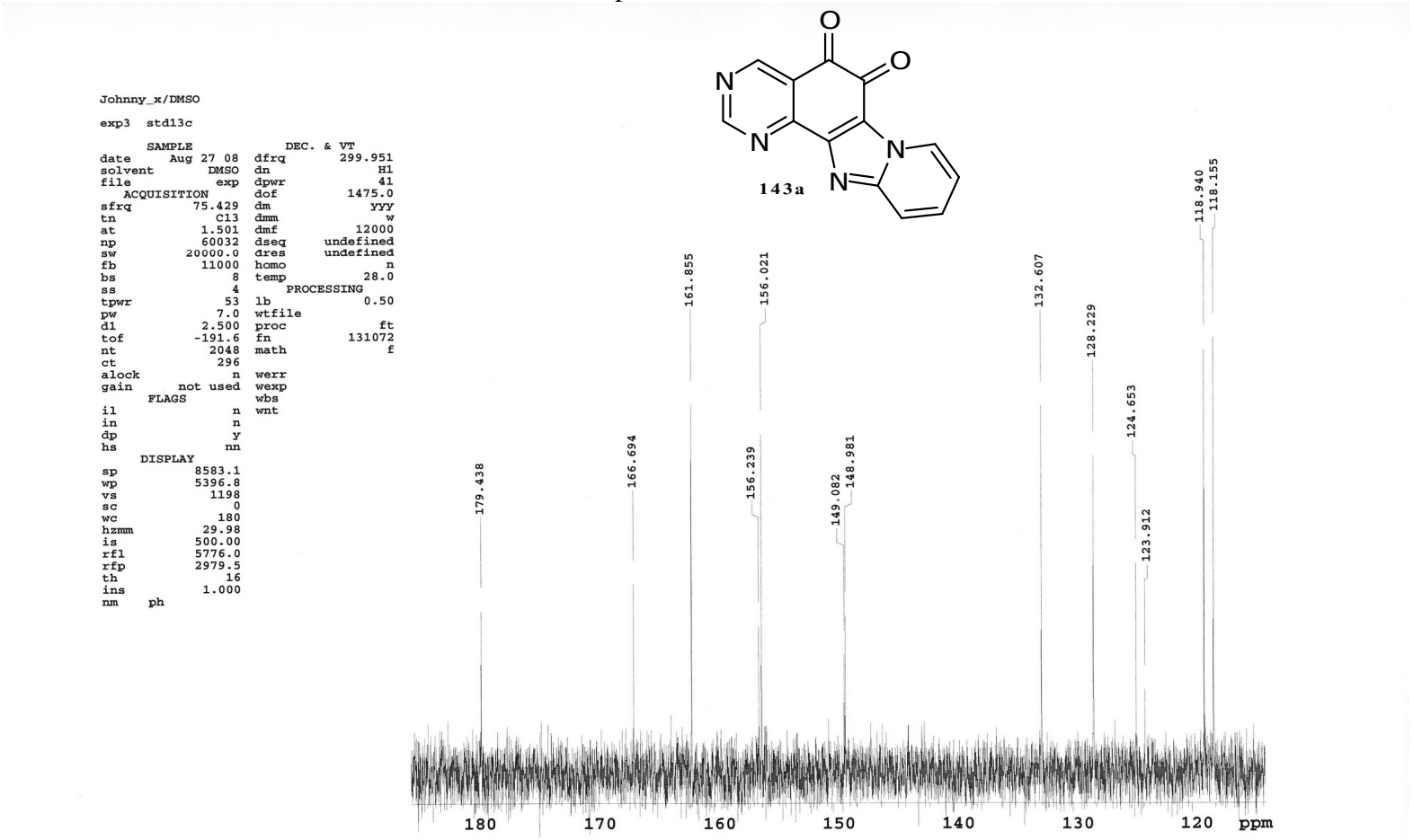
^{1}H NMR of spectrum of **143a** in DMSO-d_6.

```
Johnny_x/DMSO

exp1  std1h

       SAMPLE                    DEC. & VT
date       Aug 27 08  dfrq          299.951
solvent         DMSO  dn                H1
file             exp  dpwr              30
    ACQUISITION       dof           1374.9
sfrq          299.951  dm                nnn
tn                H1  dmm                c
at             4.998  dmf              200
np             59968  dseq       undefined
sw            5999.7  dres       undefined
fb              3400  homo               n
bs                 4  temp            28.0
tpwr              57       PROCESSING
pw               6.0  lb           not used
d1             5.000  gf           not used
tof           1200.0  gfs          not used
nt                16  wtfile
ct                16  proc              ft
alock              n  fn             65536
gain              54  math              f
       FLAGS
il                 n  werr
in                 n  wexp
dp                 y  wbs
hs                nn  wnt
     DISPLAY
sp            2154.0
wp             746.5
vs               333
sc                 0
wc               180
hzmm            4.15
is           2873.06
rfl          1477.6
rfp           746.9
th                10
ins           13.438
ai     ph
```

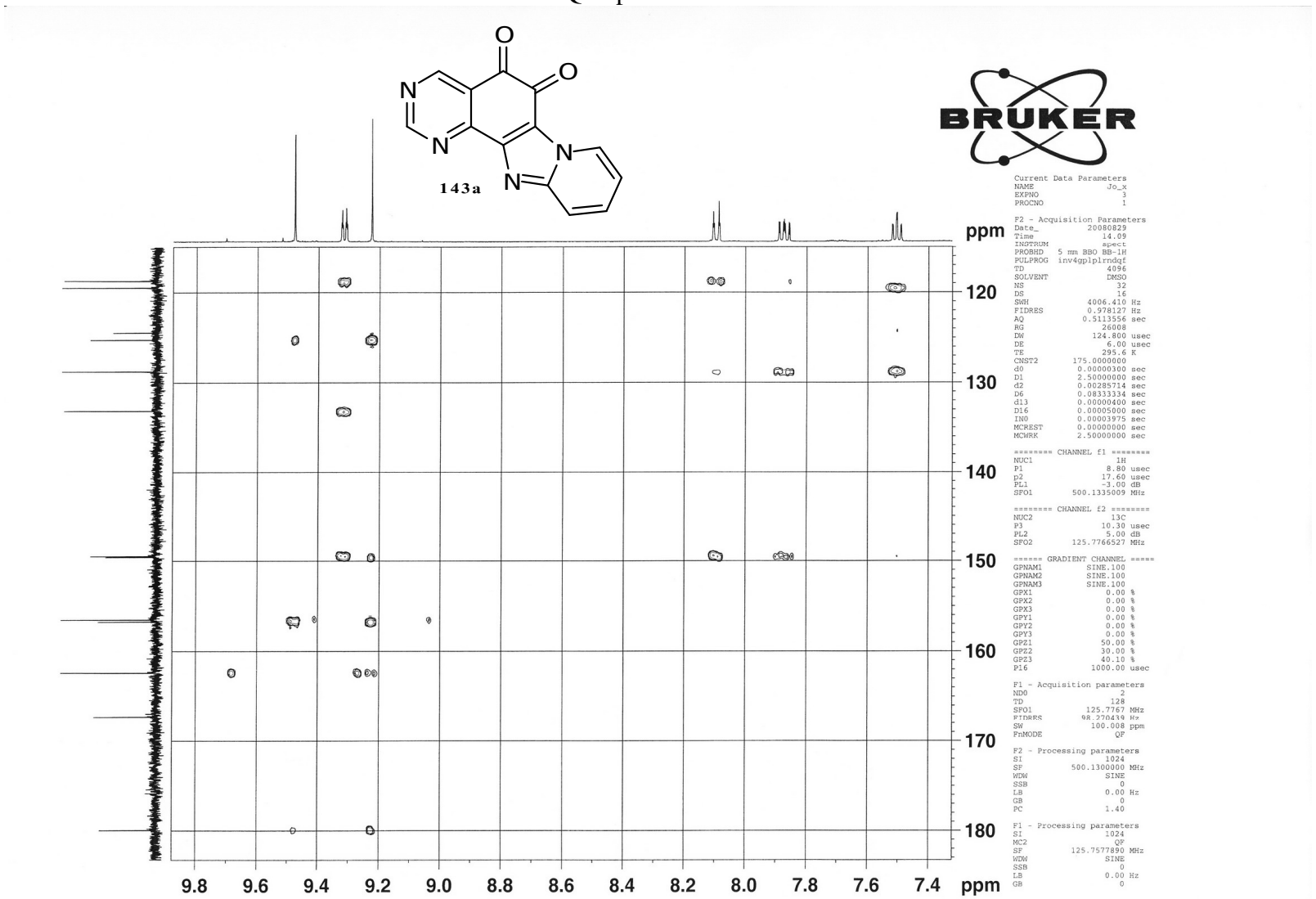


143a

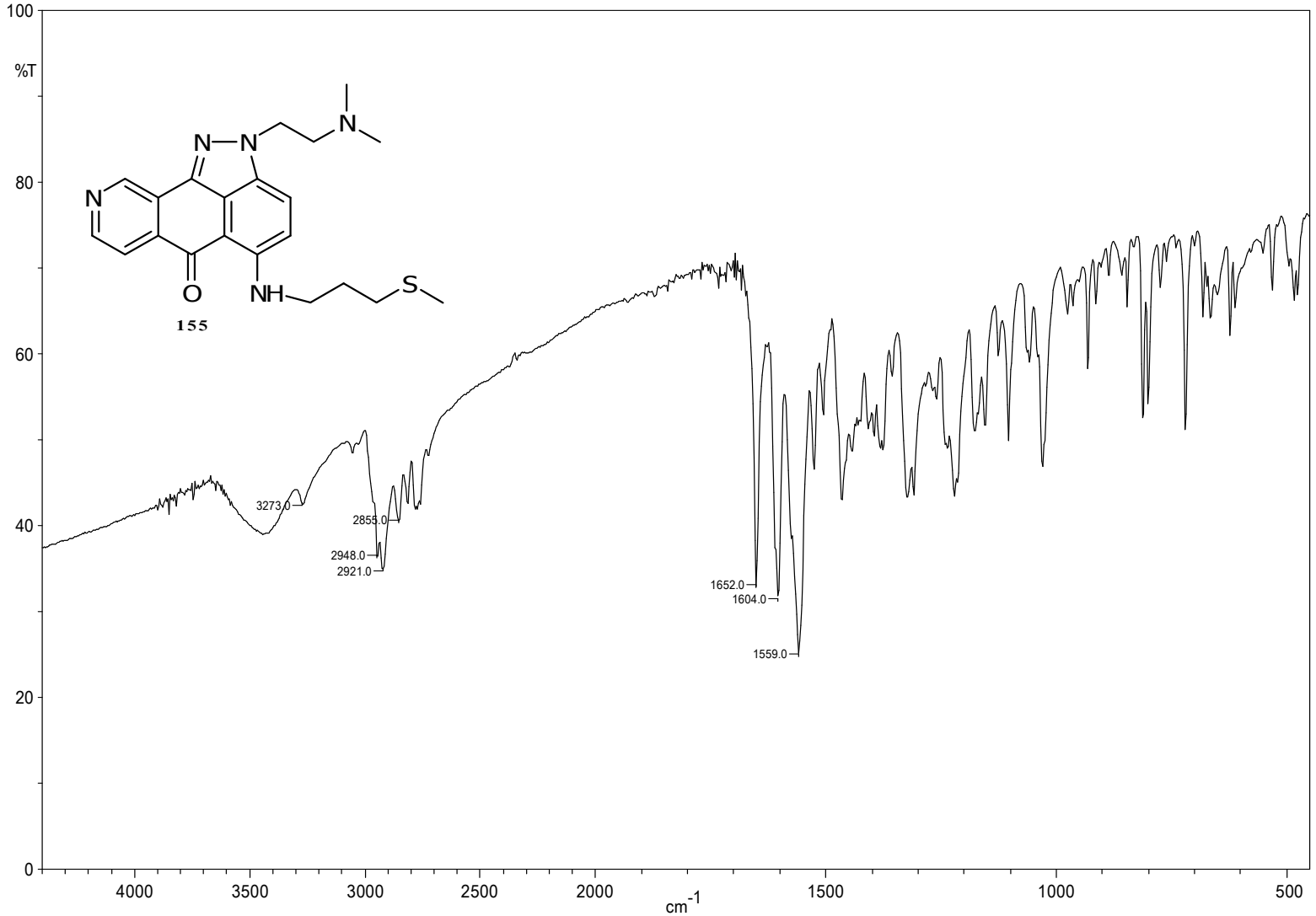
.^{13}C NMR of spectrum of **143a** in DMSO-d_6.



HMQC spectrum of **143a**.



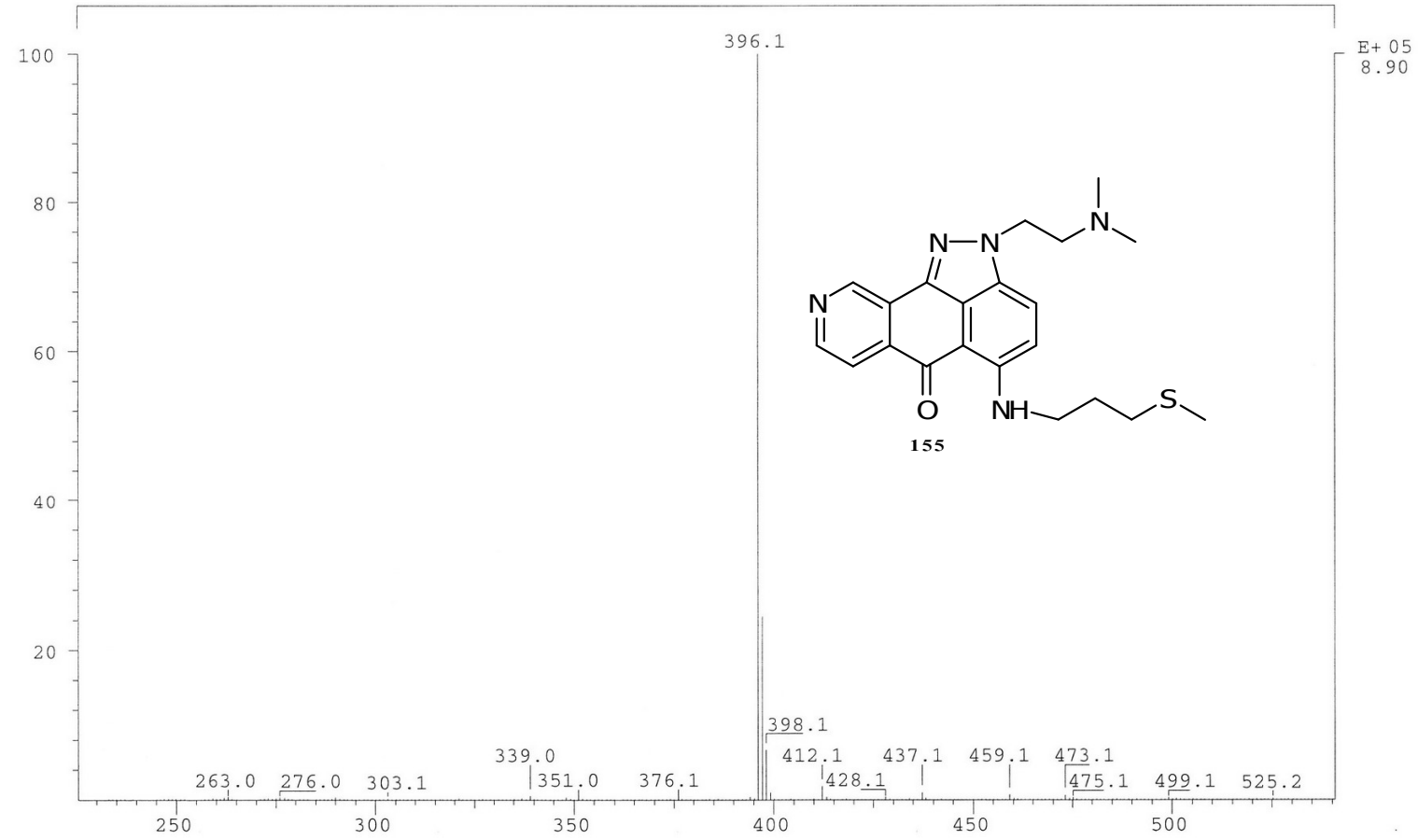
IR spectrum of **155** (KBr).



155

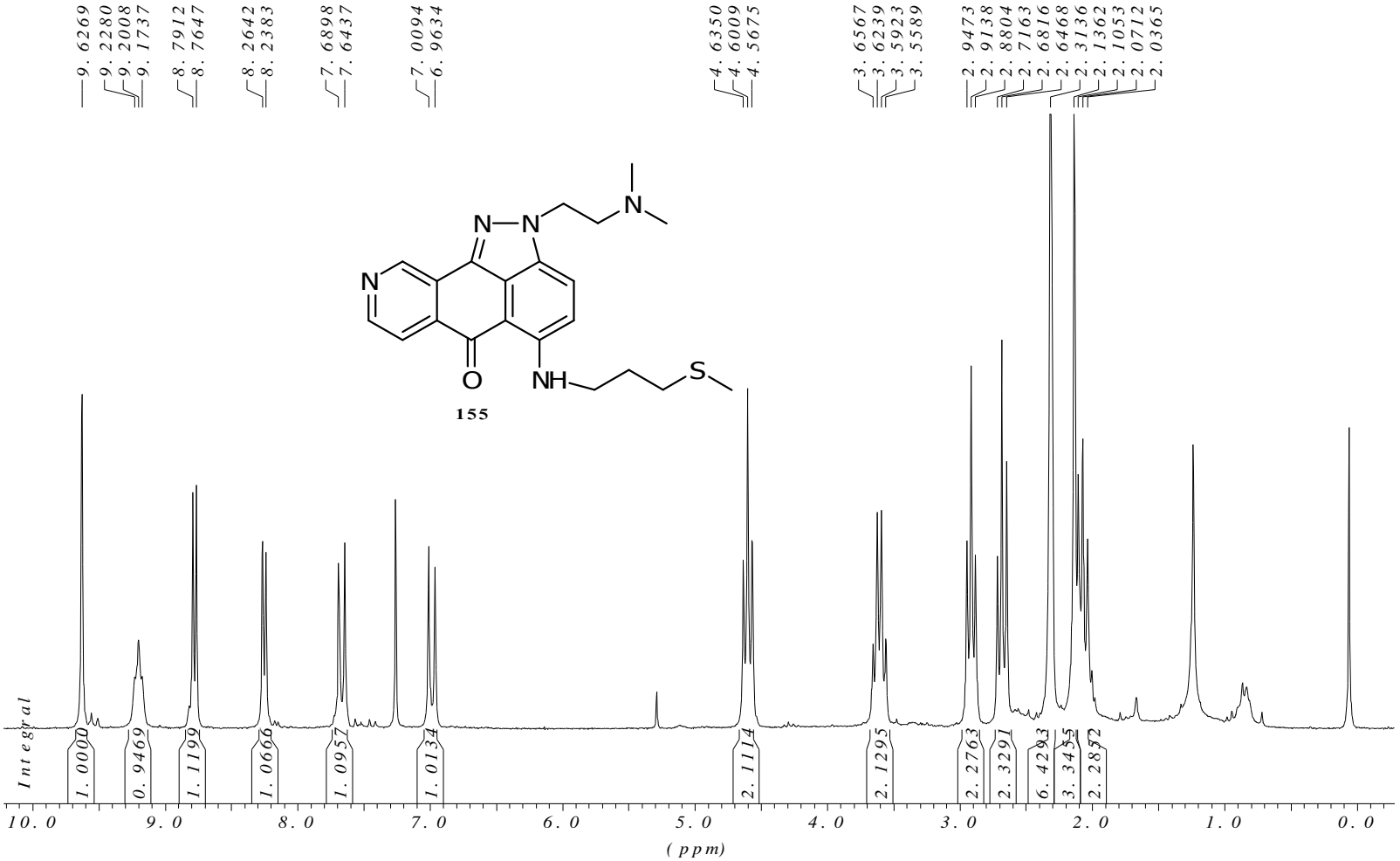
Mass spectrum of **155**.

```
SPEC:  00000000000000000000000000000000     24-Mar-95   Elapse:   00:24.0        1
Samp:  MS395                                             Start :   17:24:52       1
Comm:  4kV 3uA    MeOH/ACN
Mode:  ESI +VE +APICID LMR  BSCAN (EXP) UP LR NRM
Oper:  phu            Client:   Theerachart/Holzer/      Inlet :
Base:  396.1                 Inten :   889566            Masses:   102 > 999
Norm:  396.1                 RIC   :   1614273           #peaks:   869
Peak:  1000.00  mmu
Data:  AVER : Scans All from /usr/users/finnigan/data/34458_1.dat
```

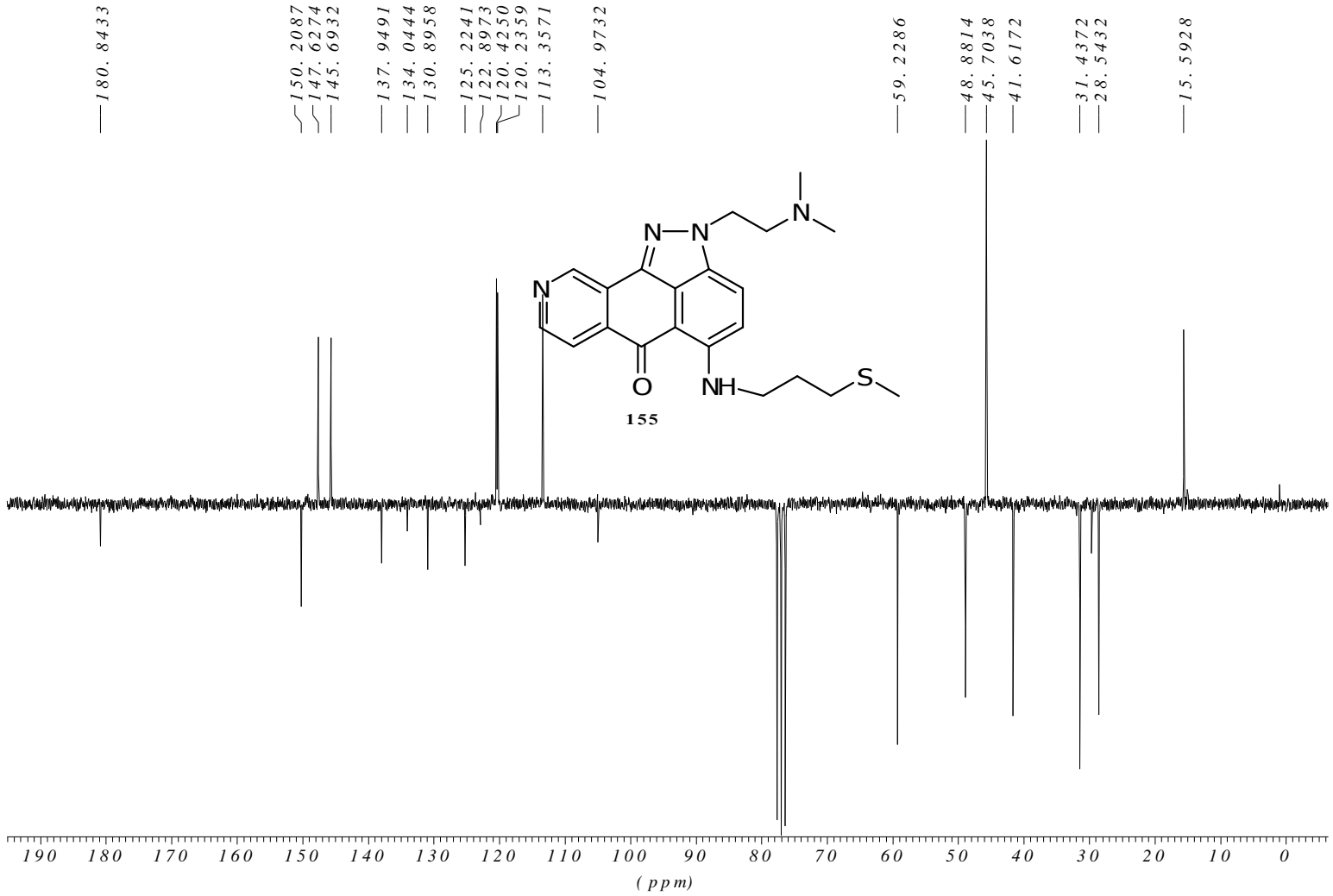


155

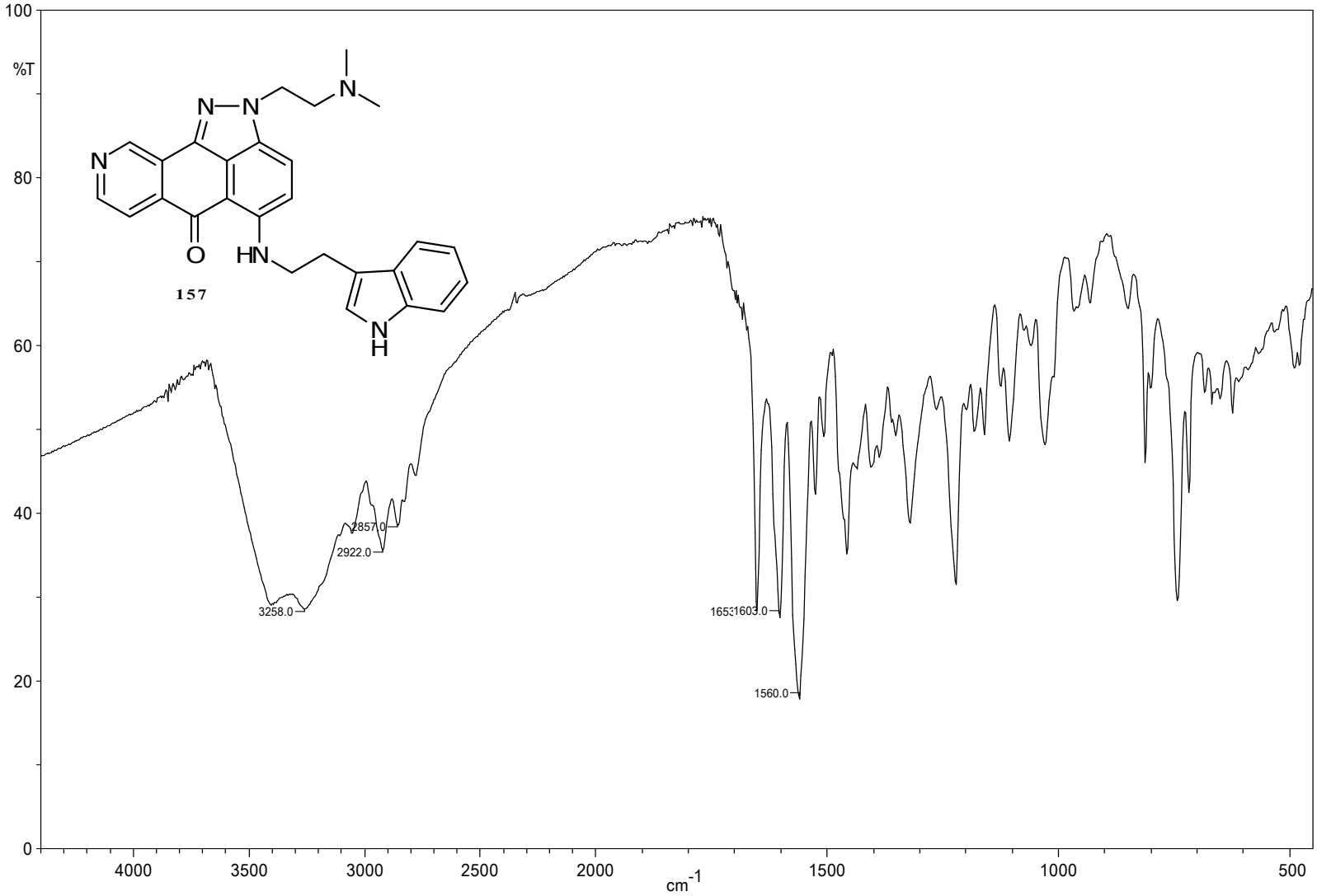
^{1}H NMR spectrum of **155** in $CDCl_3$.



^{13}C NMR spectrum of **155** in $CDCl_3$.

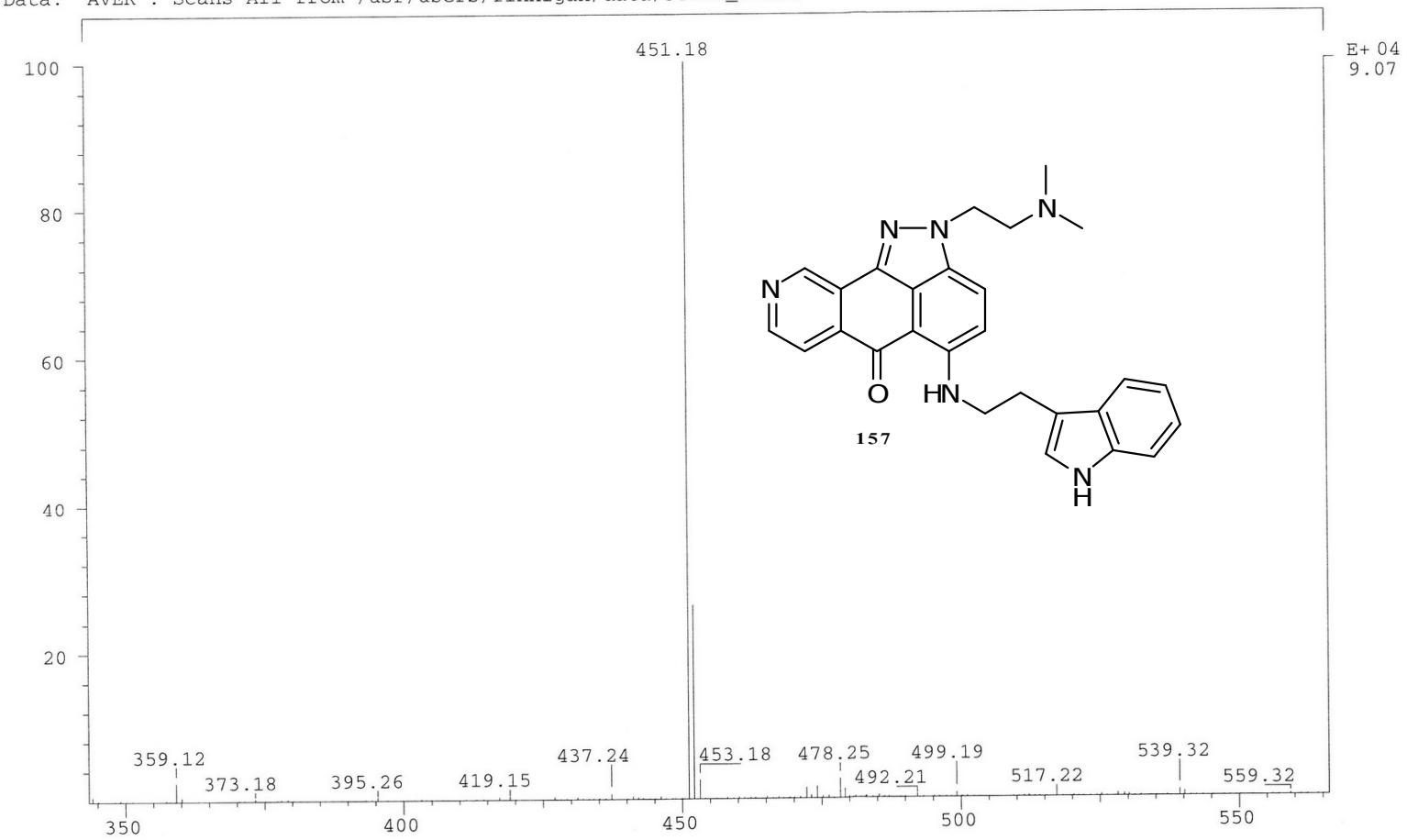


IR spectrum of **157** (KBr).



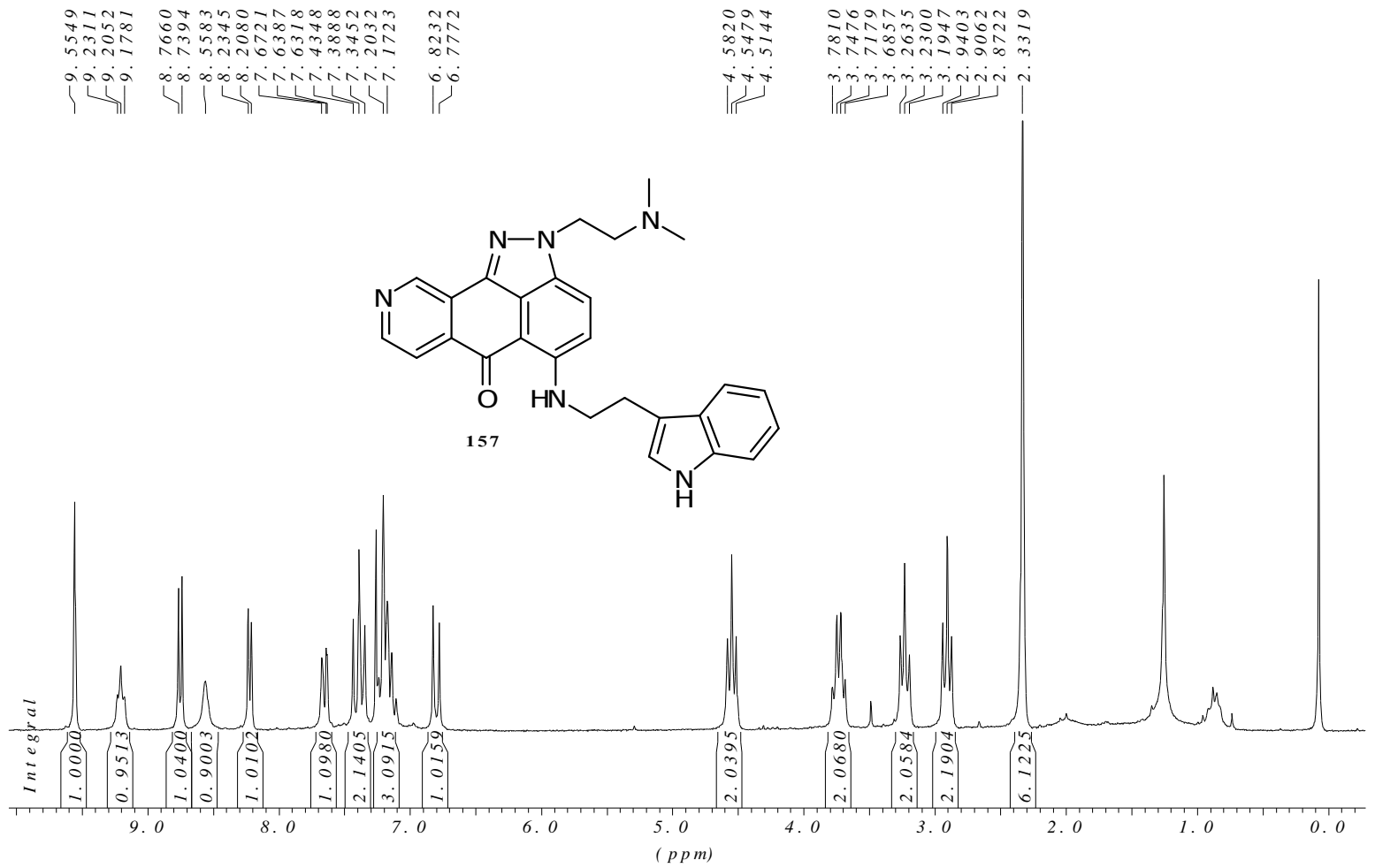
Mass spectrum of **157**.

```
SPEC:  00000000000000000000000000000000     02-Apr-95  Elapse:  00:13.4      1
Samp:  MS 450                                           Start :  12:59:50      1
Comm:  4kV 3uA   MeOH/ACN
Mode:  ESI +VE +LMR  BSCAN (EXP) UP LR NRM              Study :  ESI
Oper:  phu           Client:  Theerachart/Holzer/       Inlet :
Base:  451.2                 Inten :  90707             Masses:  102 > 998
Norm:  451.2                 RIC   :  478121            #peaks:  511
Peak:  1000.00  mmu
Data:  AVER : Scans All from /usr/users/finnigan/data/34468_1.dat
```

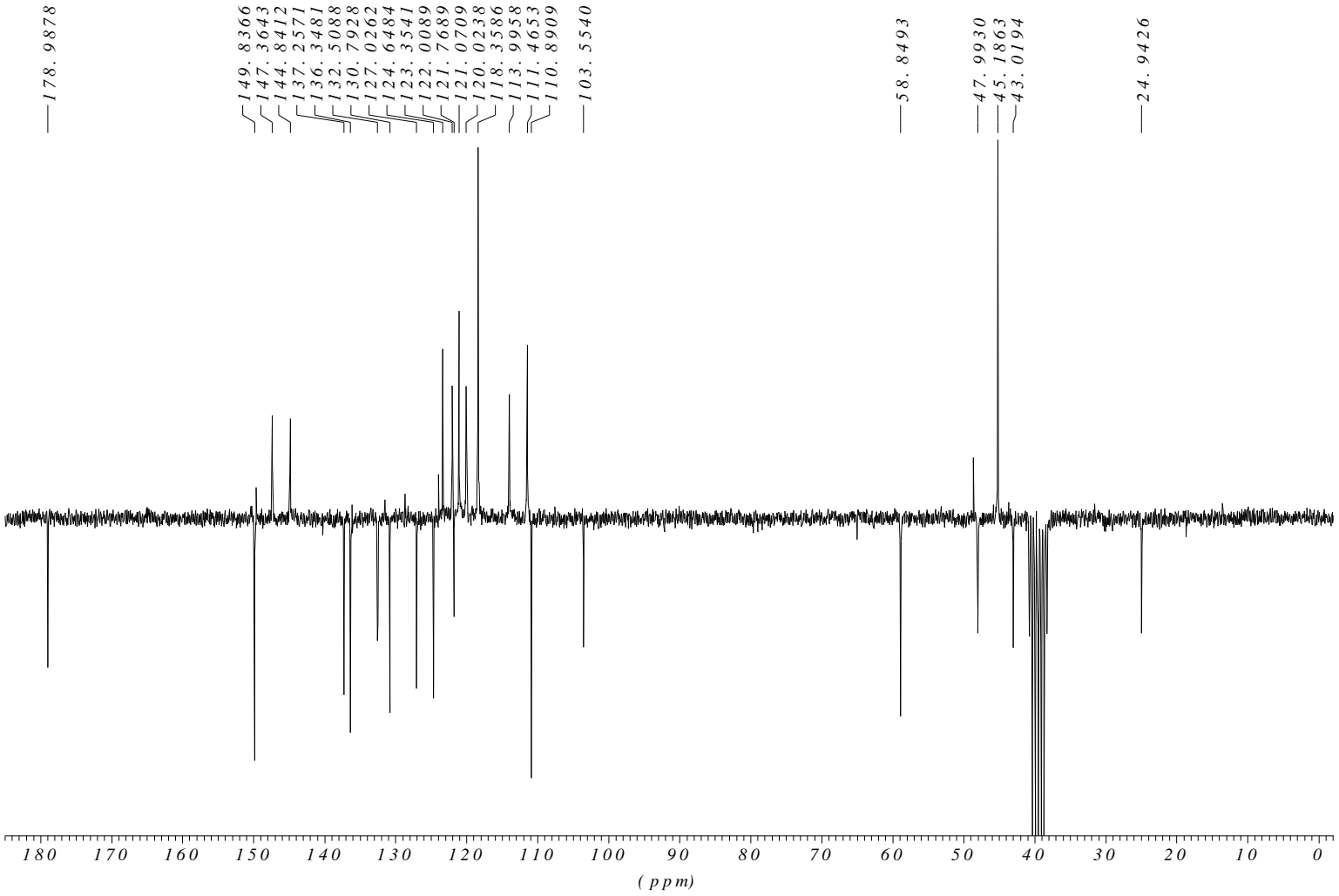


157

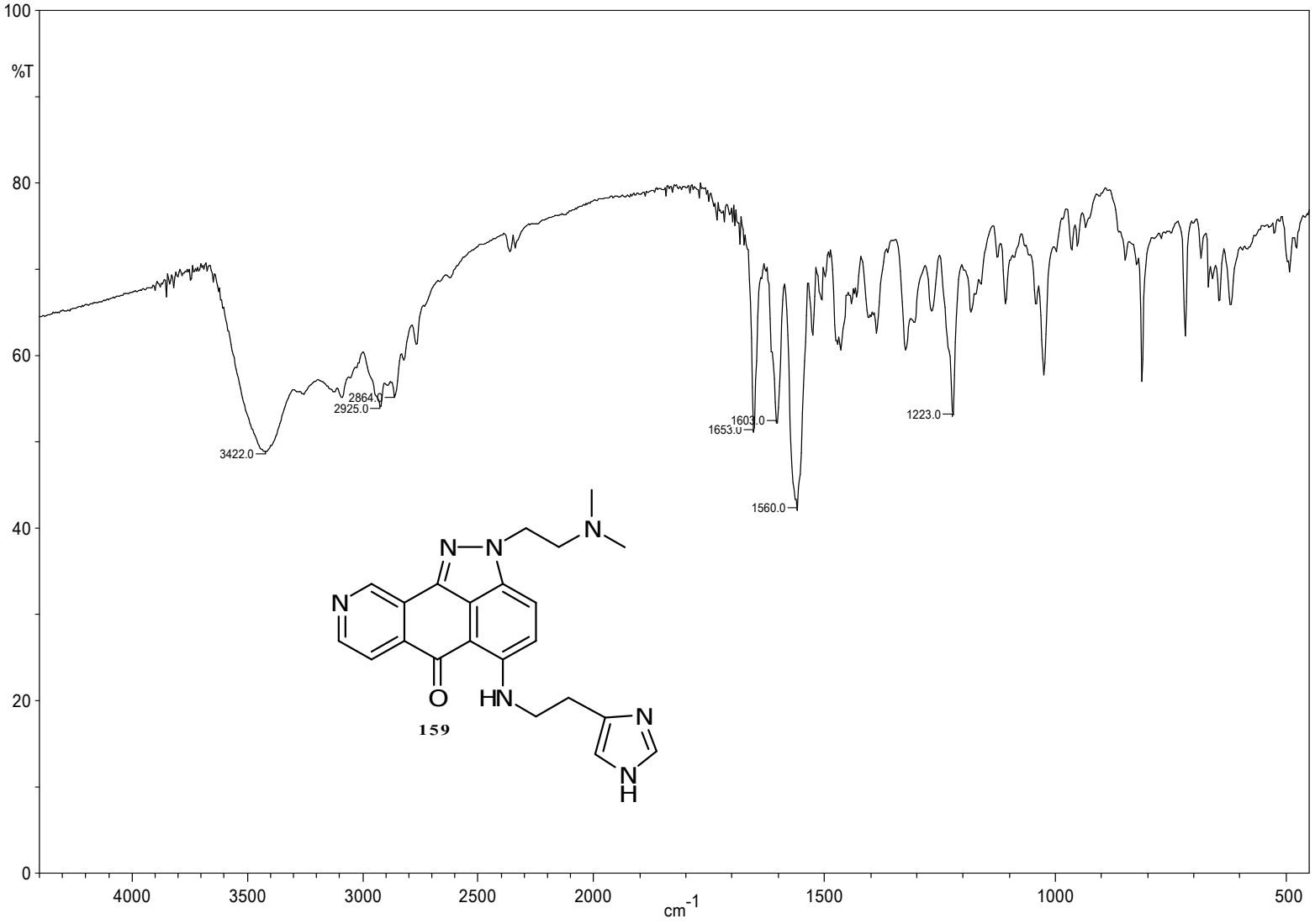
^{1}H NMR spectrum of **157** in DMSO-d_6.



.^{13}C NMR of spectrum of **157** in DMSO-d_6.



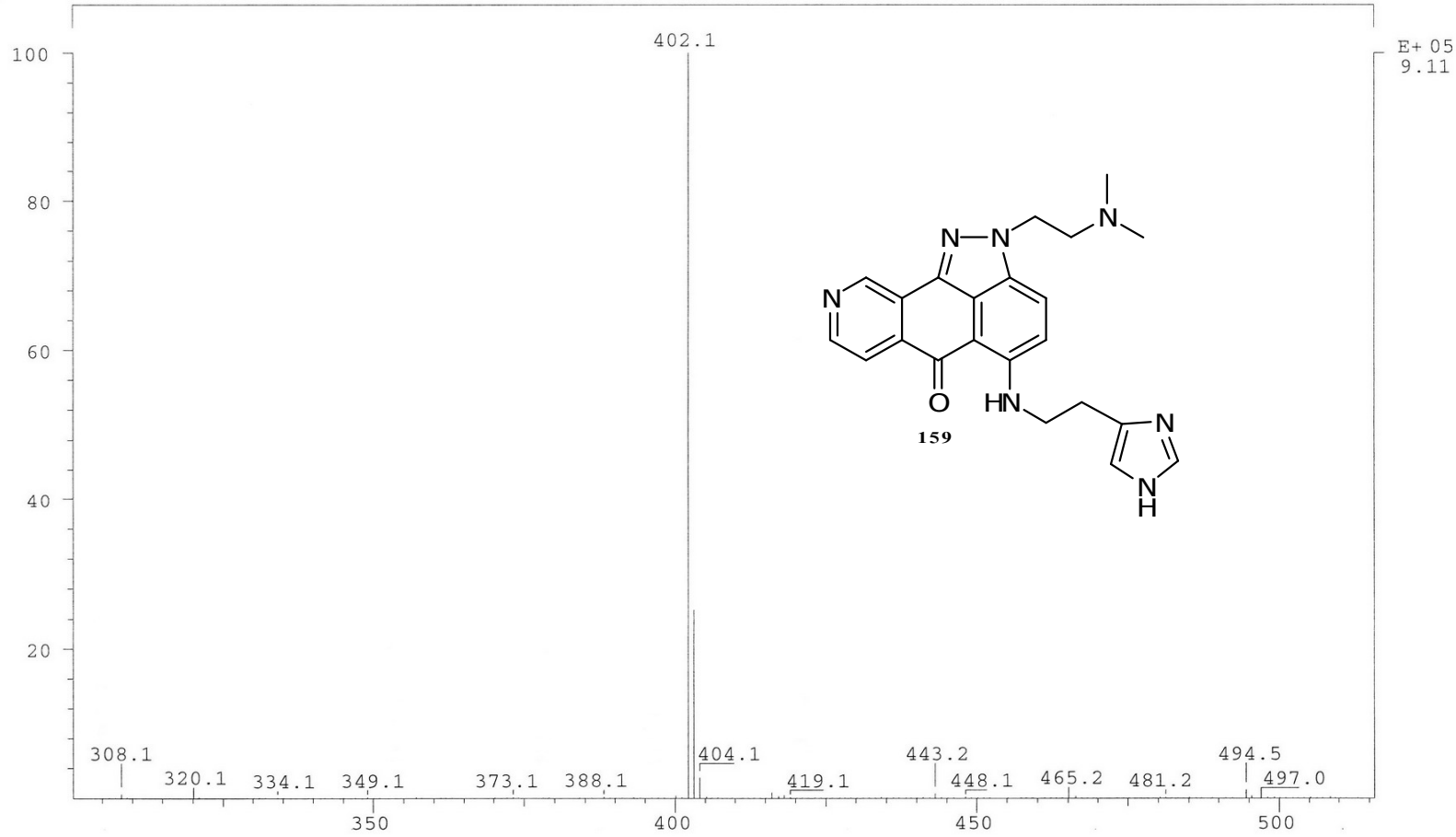
IR spectrum of **159** (KBr).



159

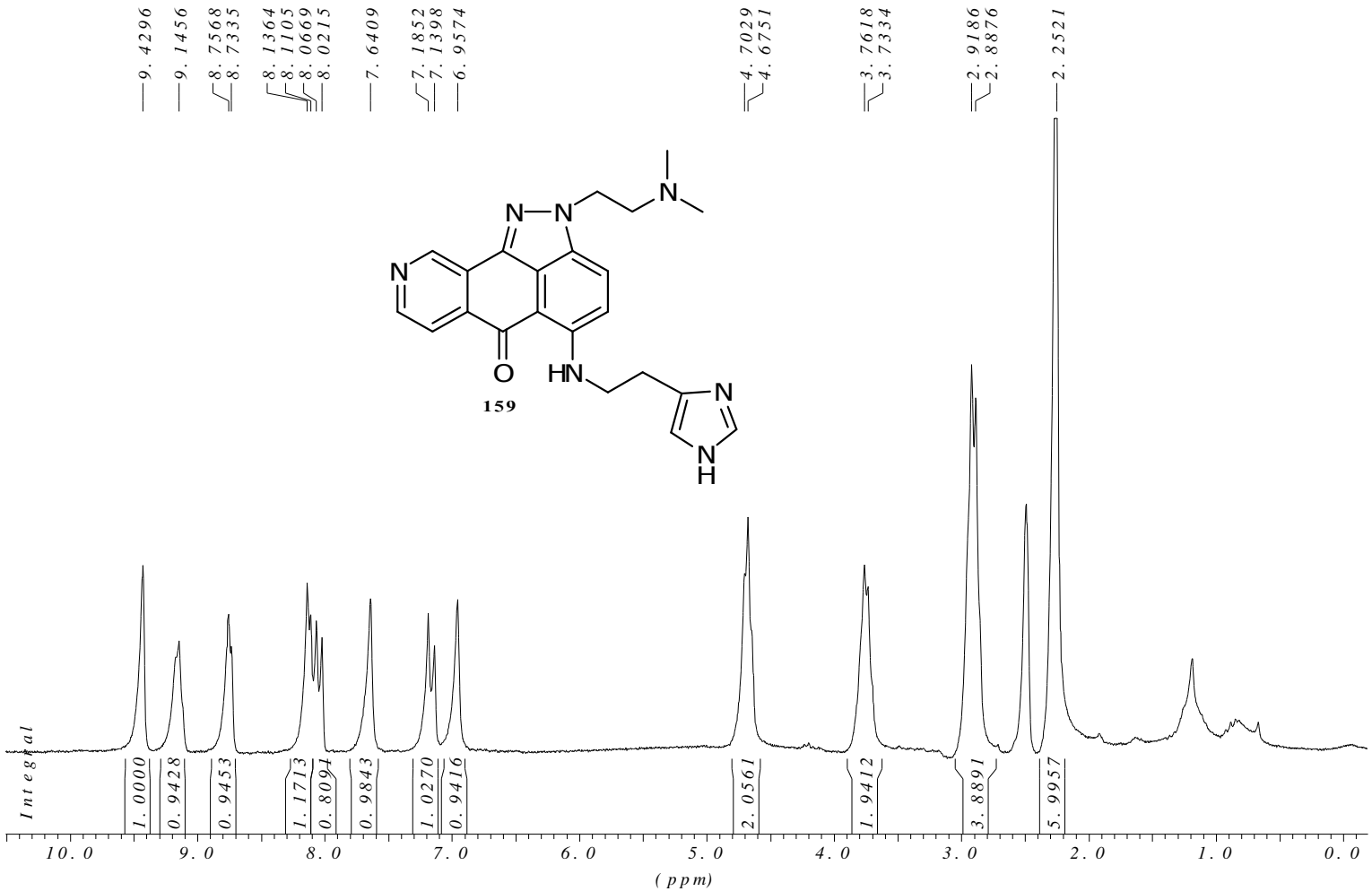
Mass spectrum of **159**.

```
SPEC:  00000000000000000000000000000000     24-Mar-95   Elapse:   00:24.9        1
Samp:  MS401                                             Start :   17:32:32       1
Comm:  4kV 3uA   MeOH/ACN
Mode:  ESI +VE +APICID LMR  BSCAN (EXP) UP LR NRM
Oper:  phu           Client:  Theerachart/Holzer/        Inlet :
Base:  402.1                 Inten :  910764             Masses:   102 > 999
Norm:  402.1                 RIC   :  2130610            #peaks:   786
Peak:  1000.00  mmu
Data:  AVER : Scans All from /usr/users/finnigan/data/34460_1.dat
```

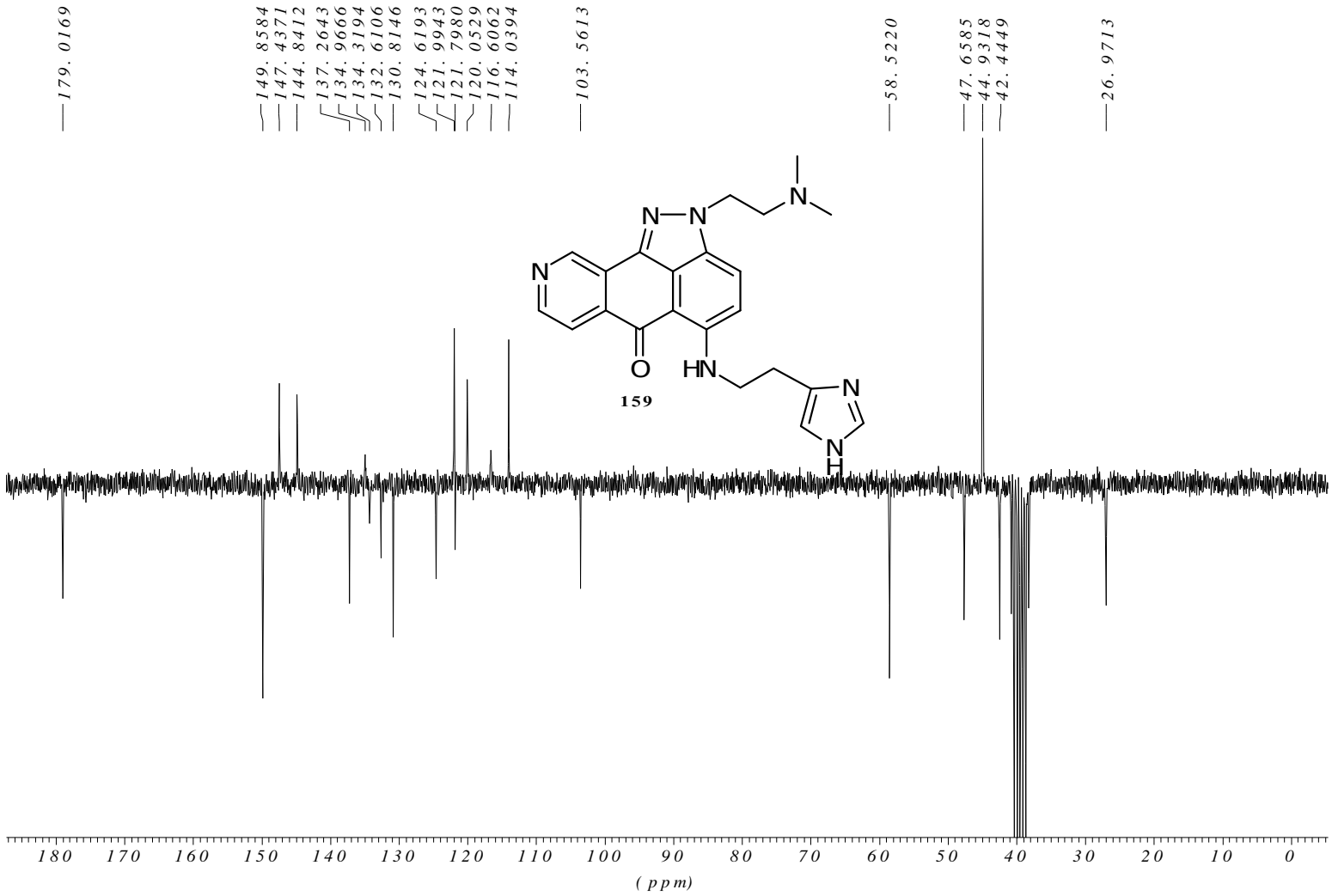


159

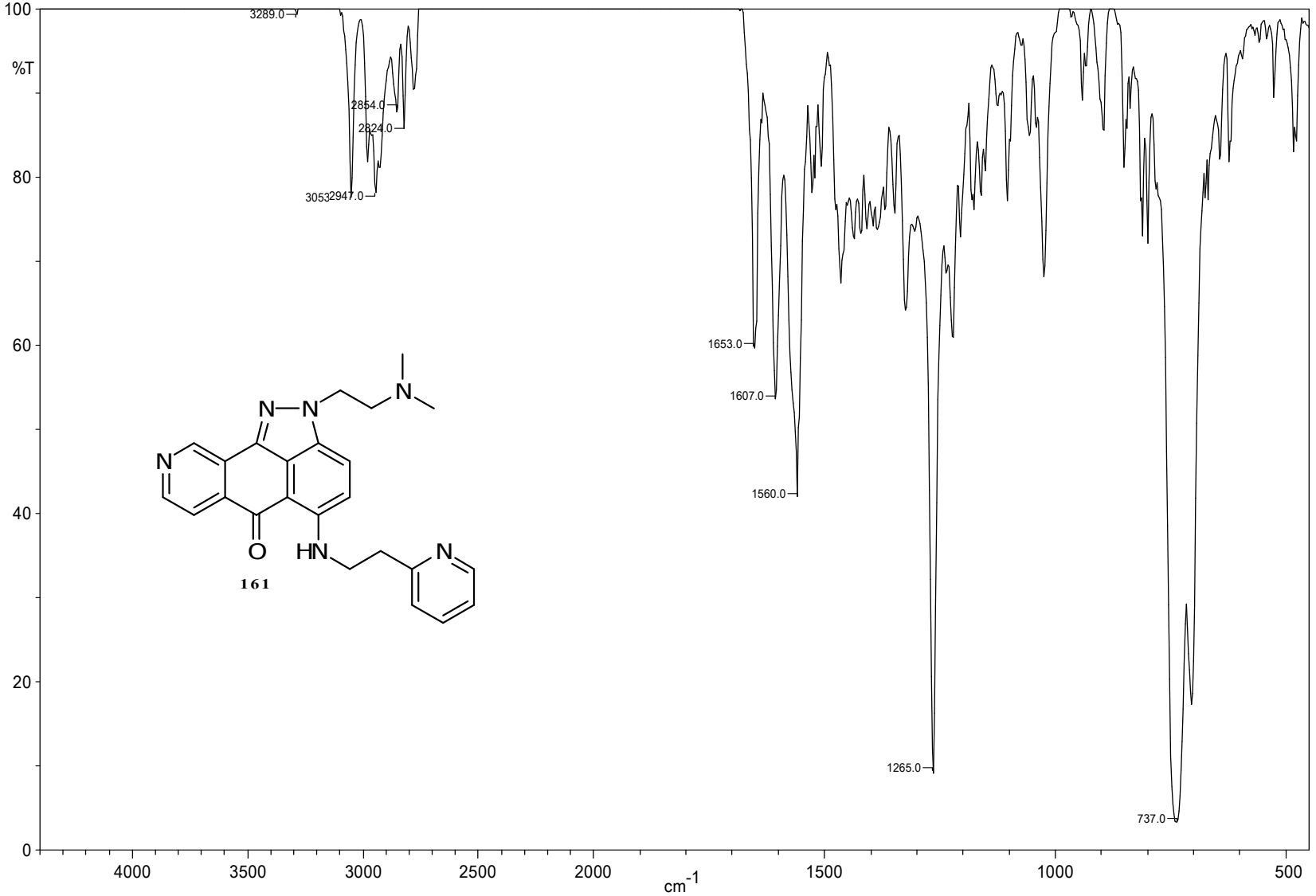
^{1}H NMR of spectrum of **159** in DMSO-d_6.



^{13}C NMR of spectrum of **159** in DMSO-d_6.

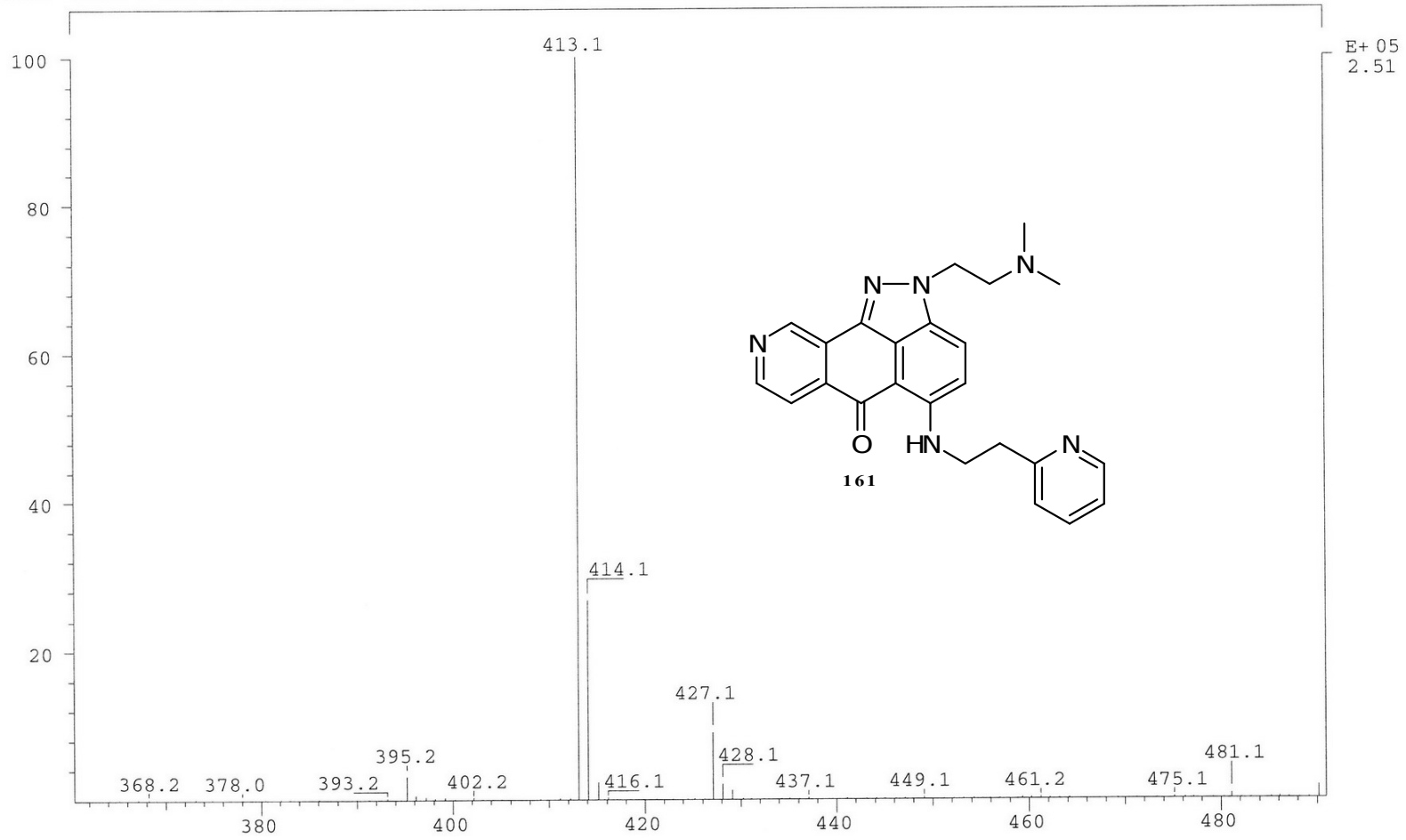


IR spectrum of **161** (NaCl).



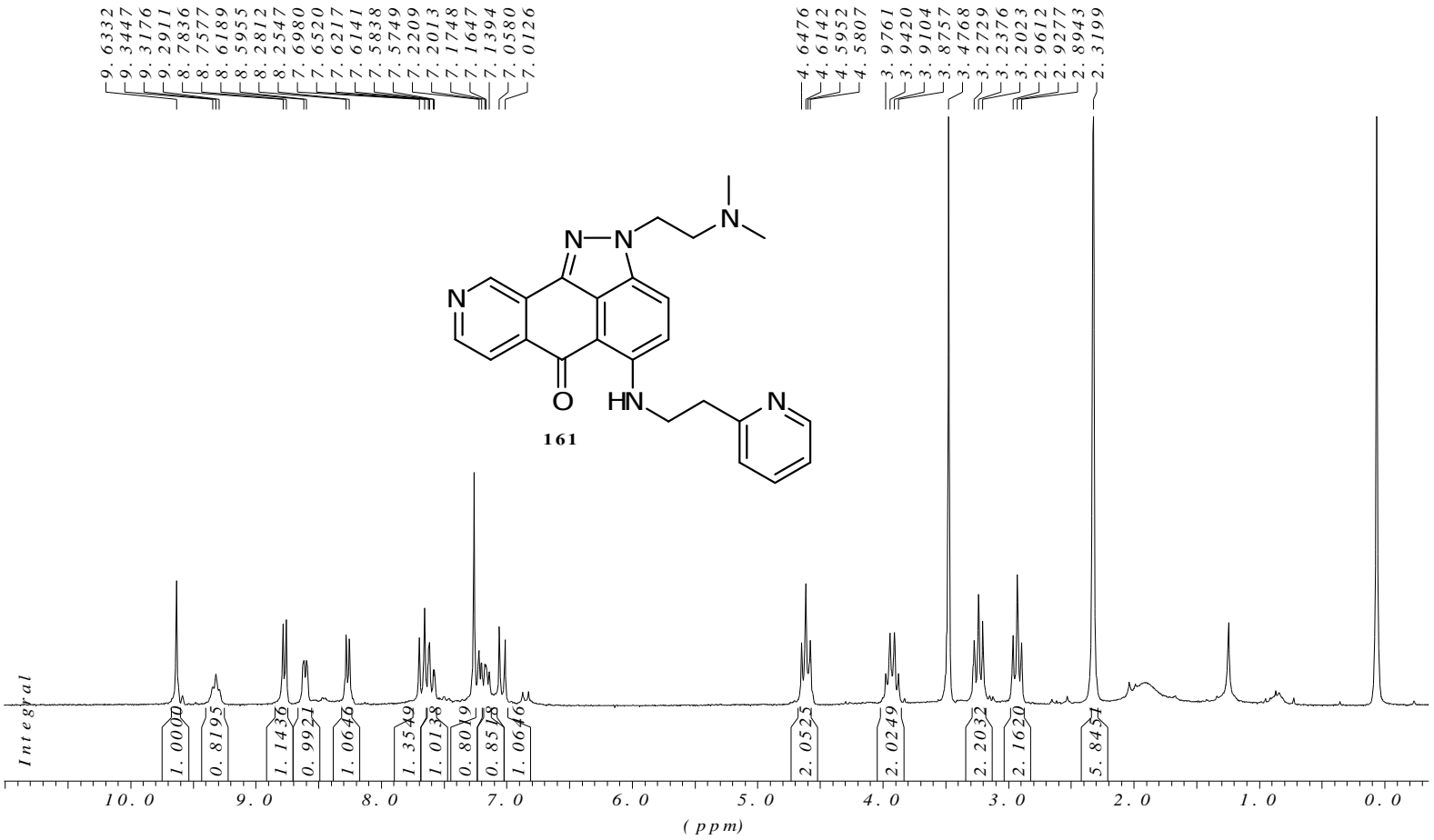
Mass spectrum of **161**.

```
SPEC:  00000000000000000000000000000000     02-Apr-95  Elapse:  00:11.4        1
Samp:  MS 412                                          Start :  12:47:23       1
Comm:  4kV 3uA    MeOH/ACN
Mode:  ESI +VE +LMR  BSCAN (EXP) UP LR NRM             Study :  ESI
Oper:  phu           Client:  Theerachart/Holzer/      Inlet :
Base:  413.1                 Inten :  251239           Masses:  106 > 1000
Norm:  413.1                 RIC   :  605863           #peaks:  495
Peak:  1000.00  mmu
Data:  AVER : Scans All from /usr/users/finnigan/data/34462_1.dat
```

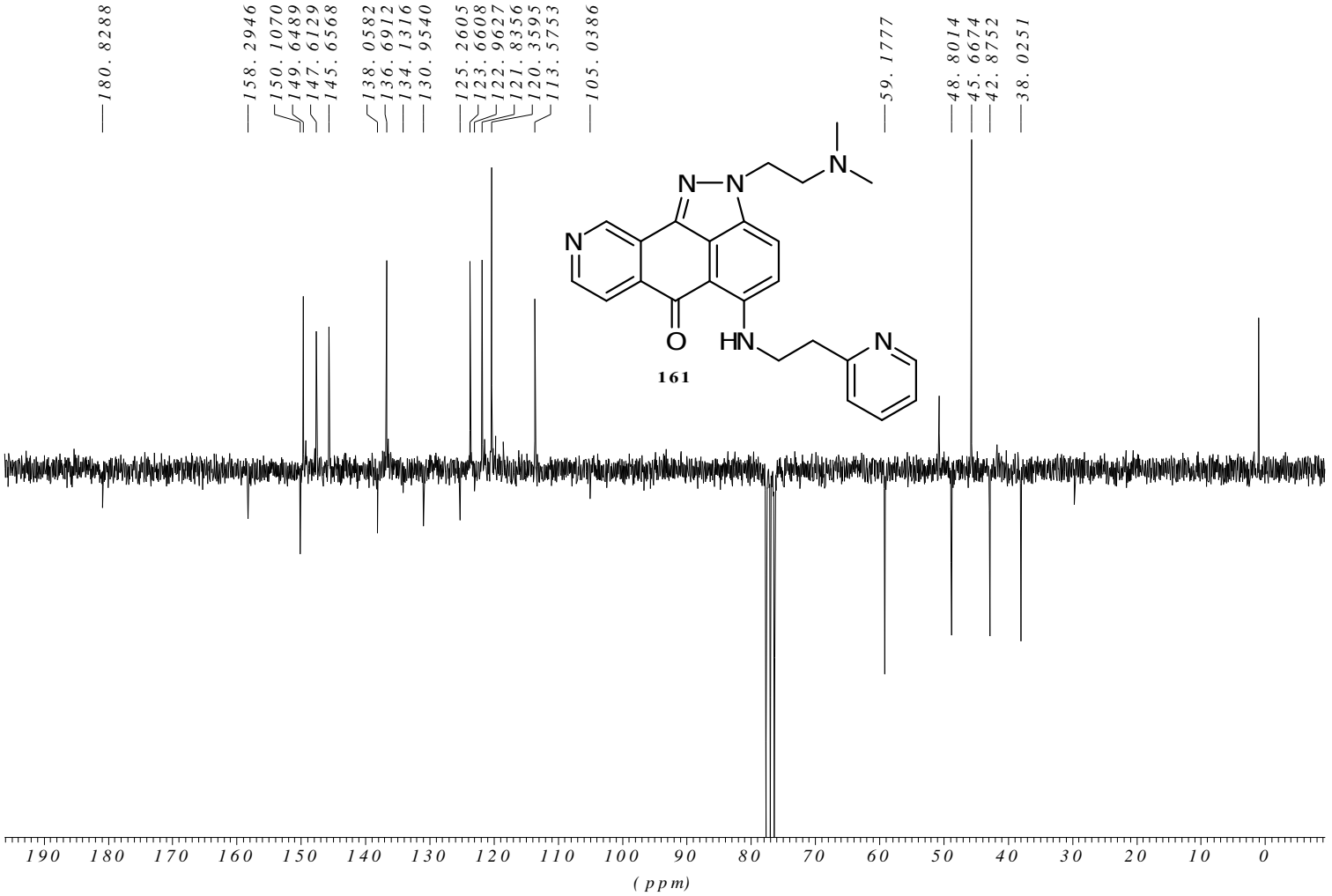


161

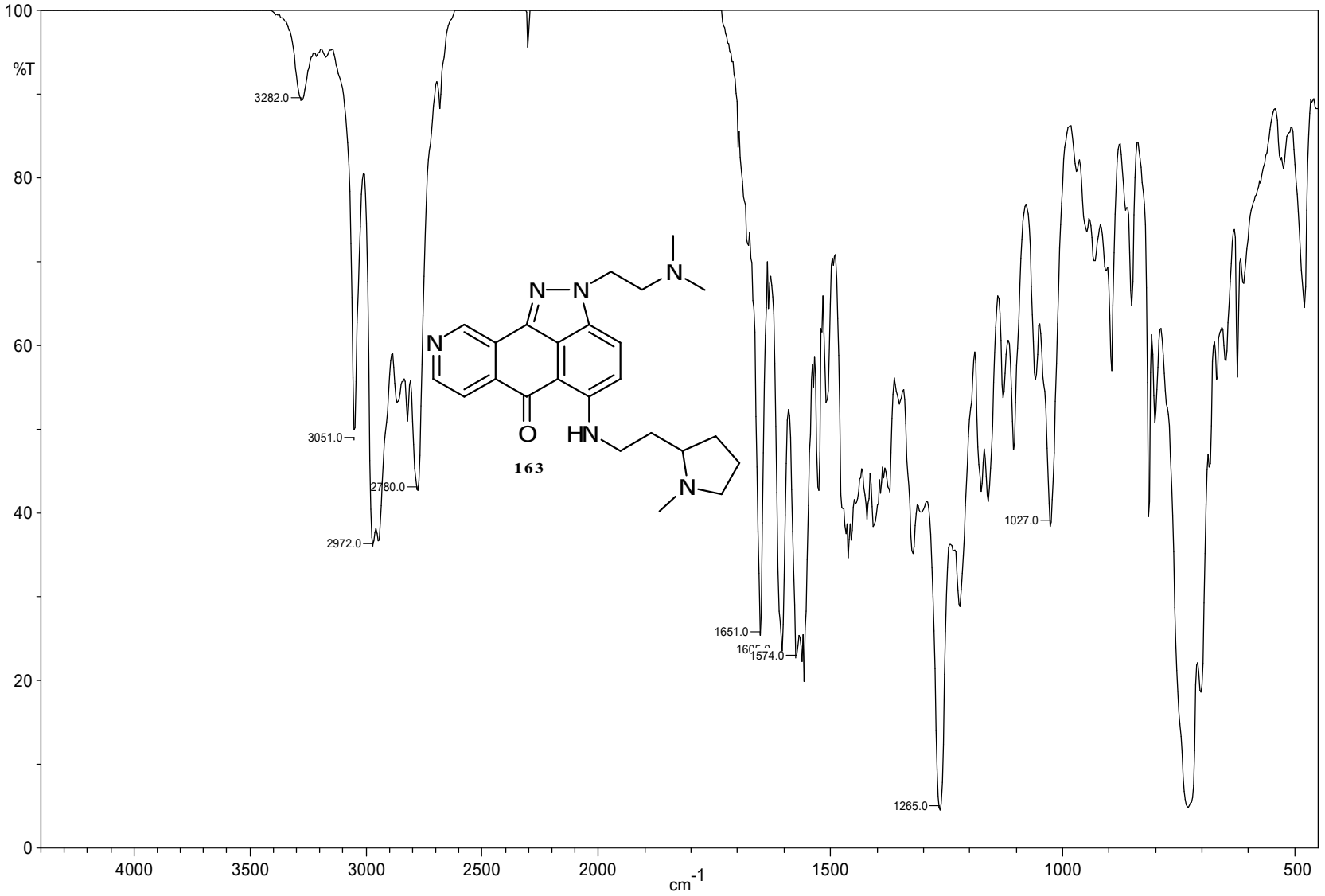
^{1}H NMR spectrum of **161** in $CDCl_3$.



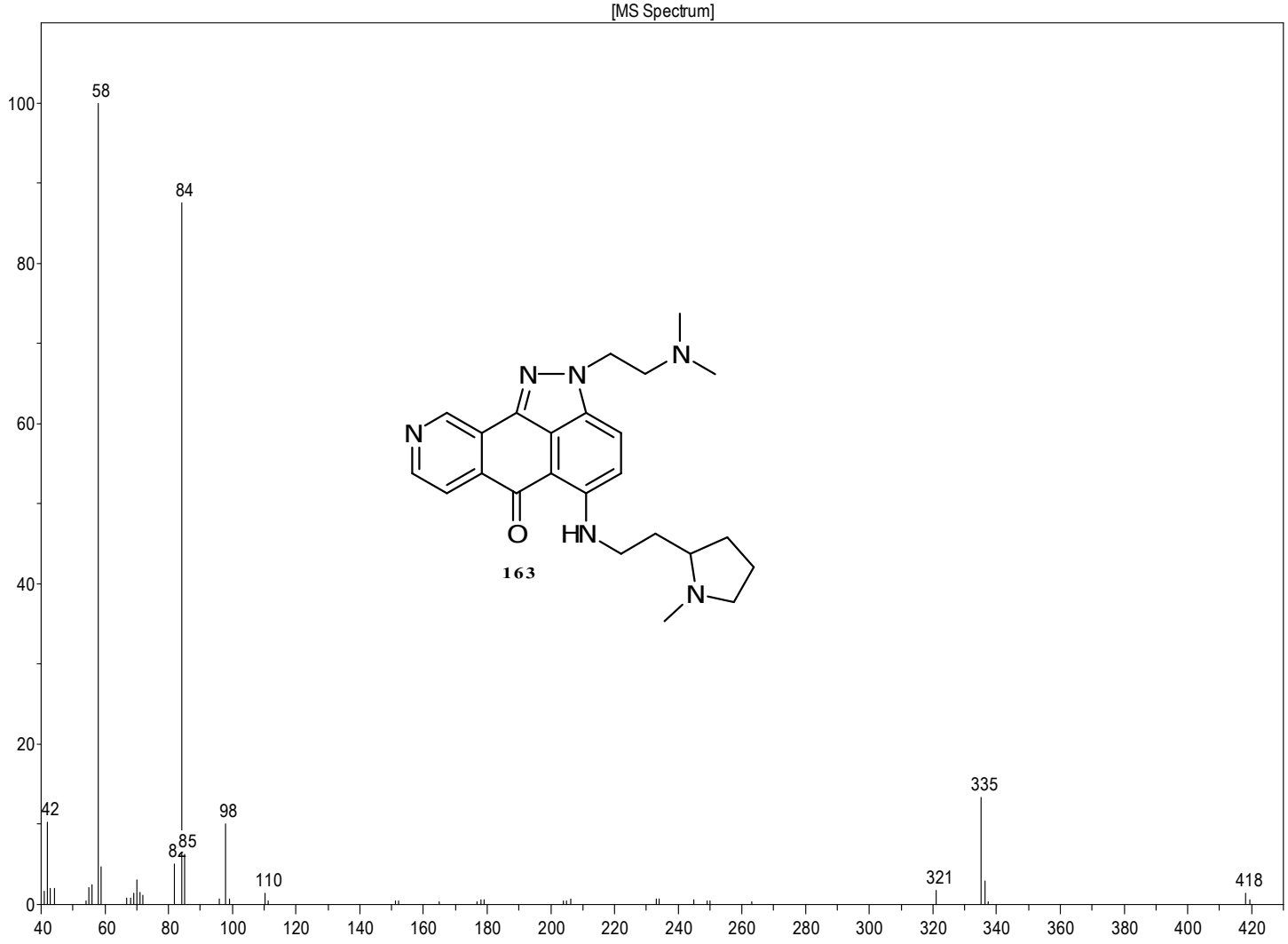
^{13}C NMR spectrum of **161** in $CDCl_3$.



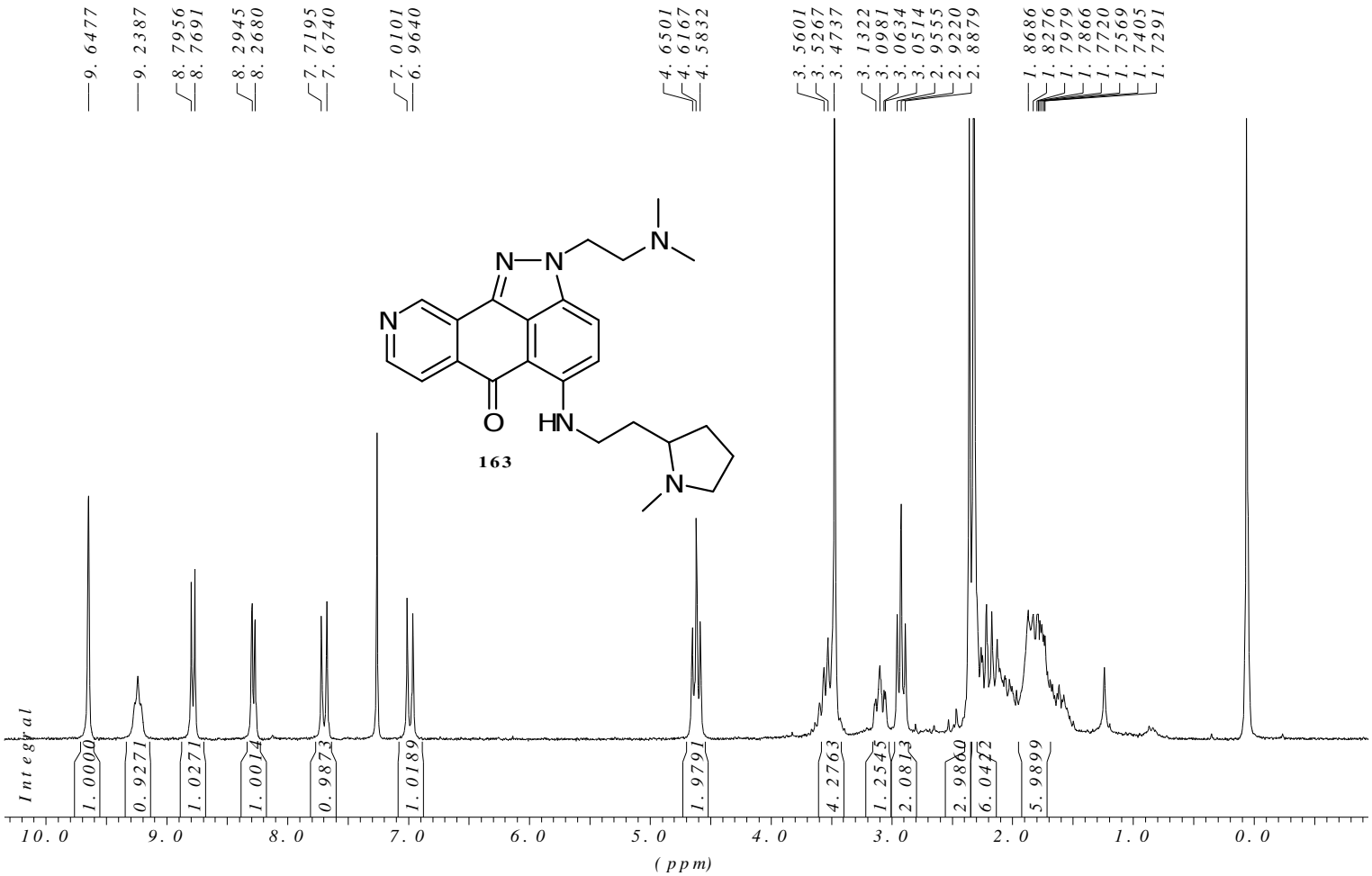
IR spectrum of **163** (NaCl).



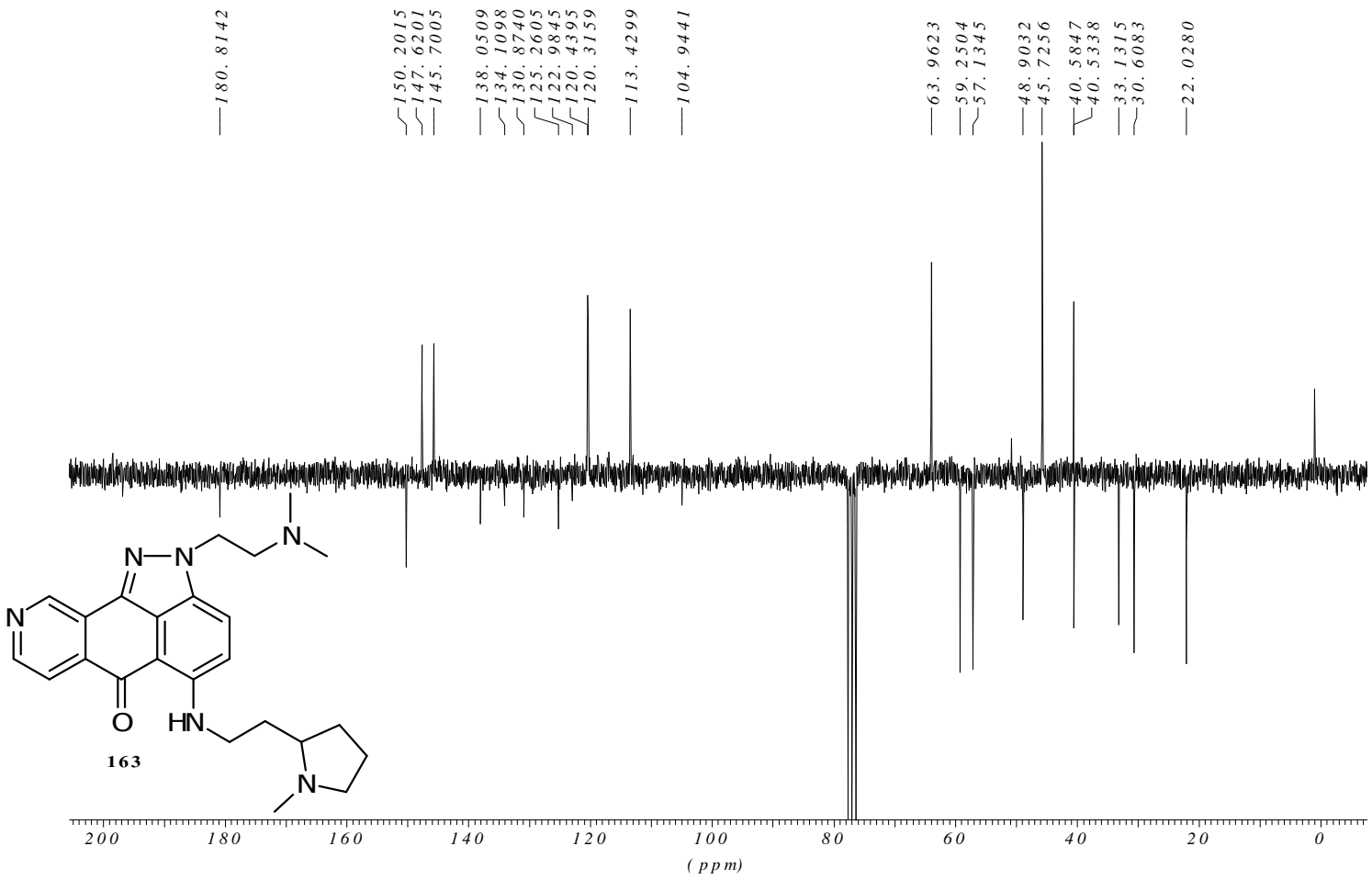
Mass spectrum of **163**.



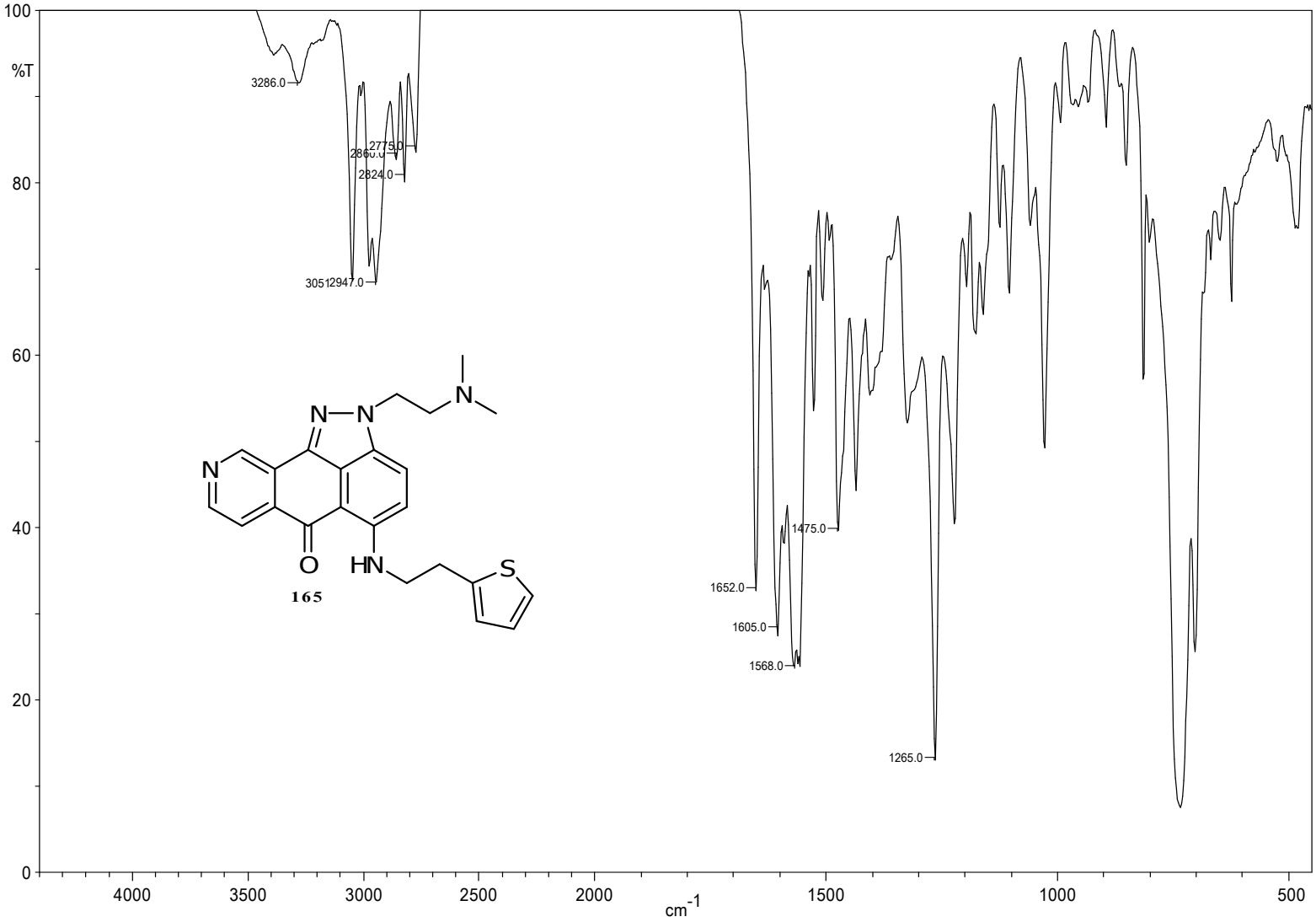
^{1}H NMR spectrum of **163** in $CDCl_3$.



^{13}C NMR spectrum of **163** in $CDCl_3$.

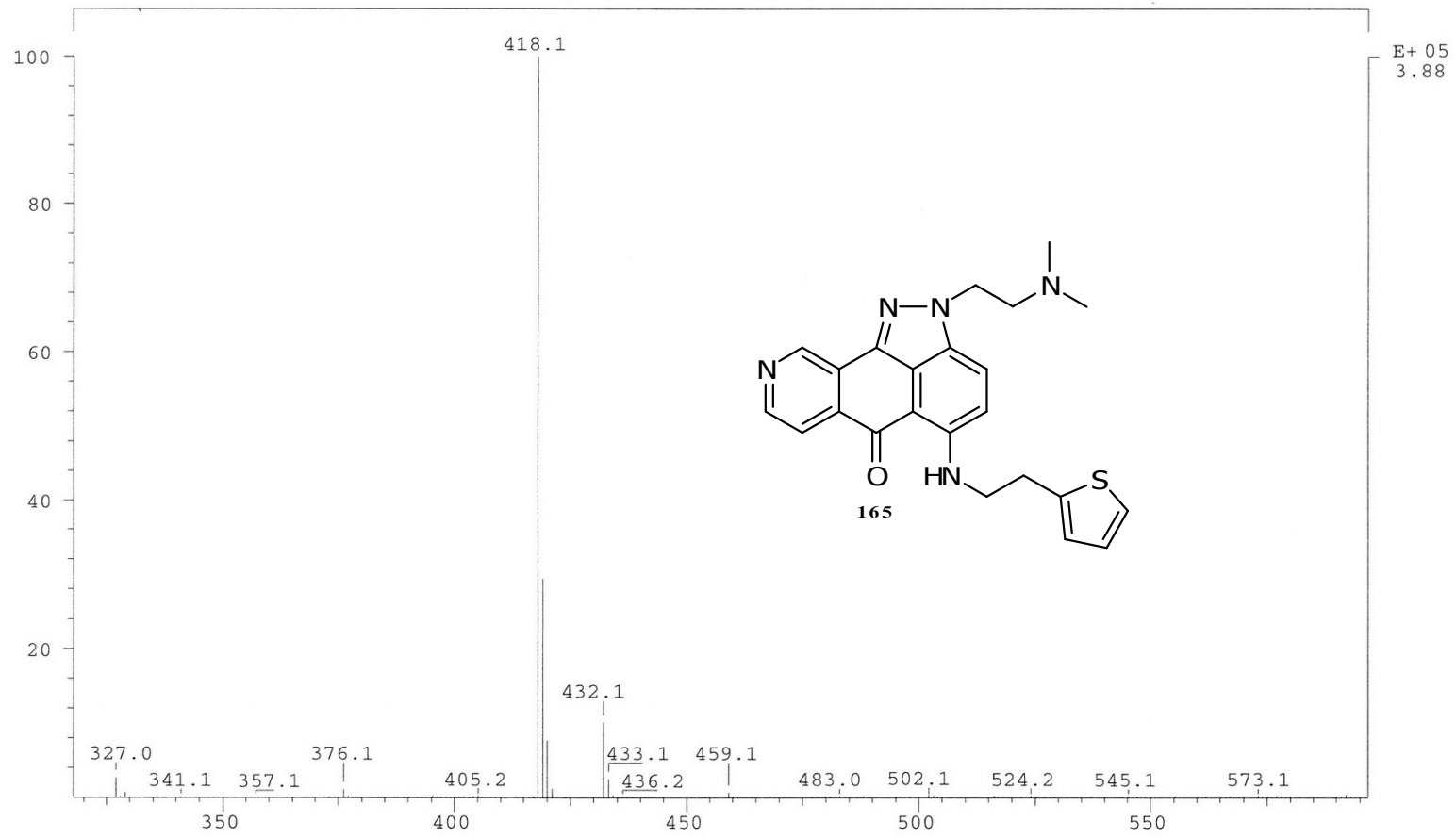


IR spectrum of **165** (NaCl).



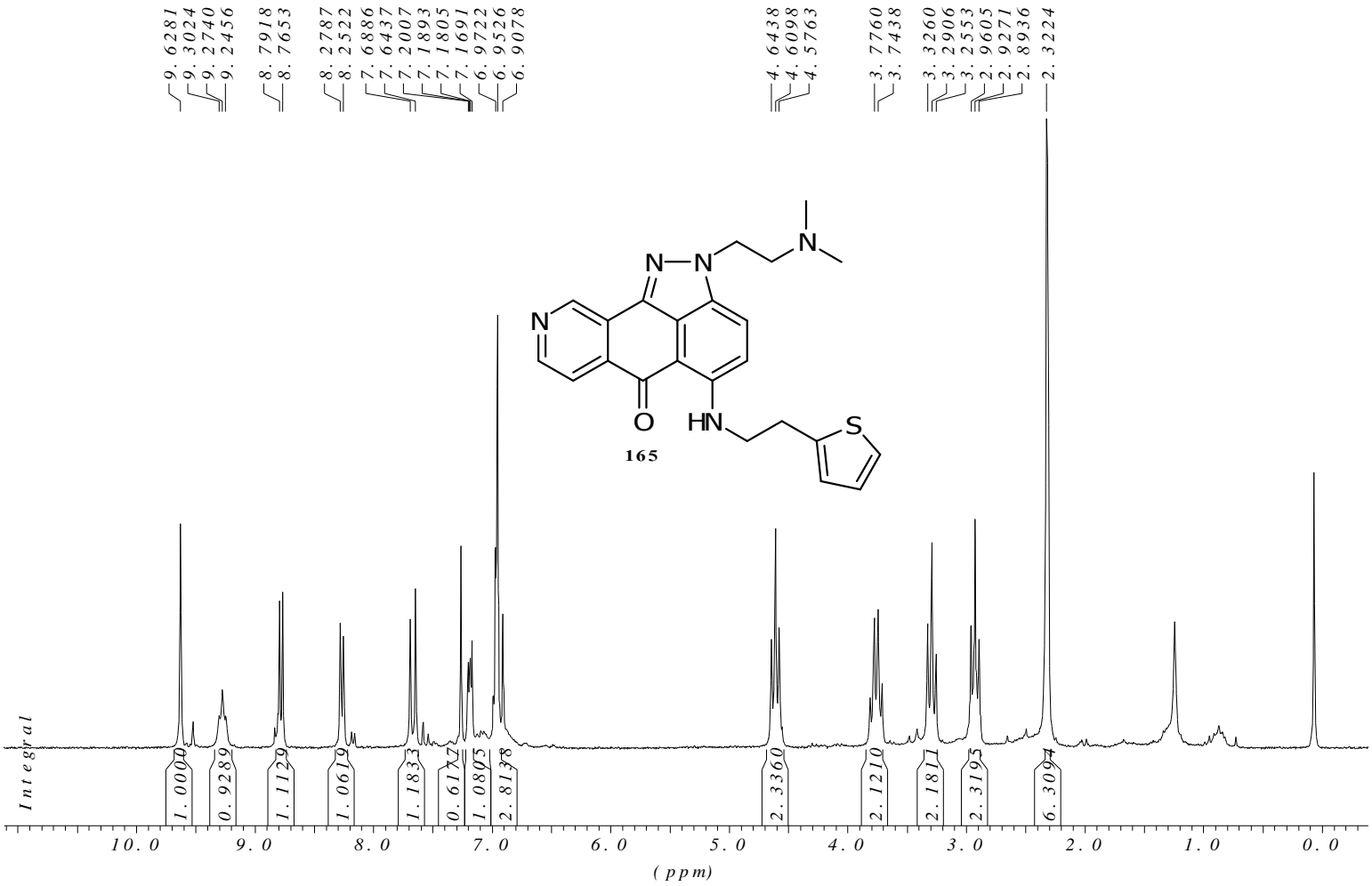
Mass spectrum of **165**.

```
SPEC:  00000000000000000000000000000000     02-Apr-95   Elapse:   00:11.1        1
Samp:  MS 418                                            Start :   12:54:08       1
Comm:  4kV 3uA    MeOH/ACN
Mode:  ESI +VE +LMR  BSCAN (EXP) UP LR NRM               Study :   ESI
Oper:  phu             Client:   Theerachart/Holzer/     Inlet :
Base:  418.1                 Inten :   387676           Masses:   102 > 991
Norm:  418.1                 RIC   :   1269485          #peaks:   548
Peak:  1000.00  mmu
Data:  AVER : Scans All from /usr/users/finnigan/data/34466_1.dat
```

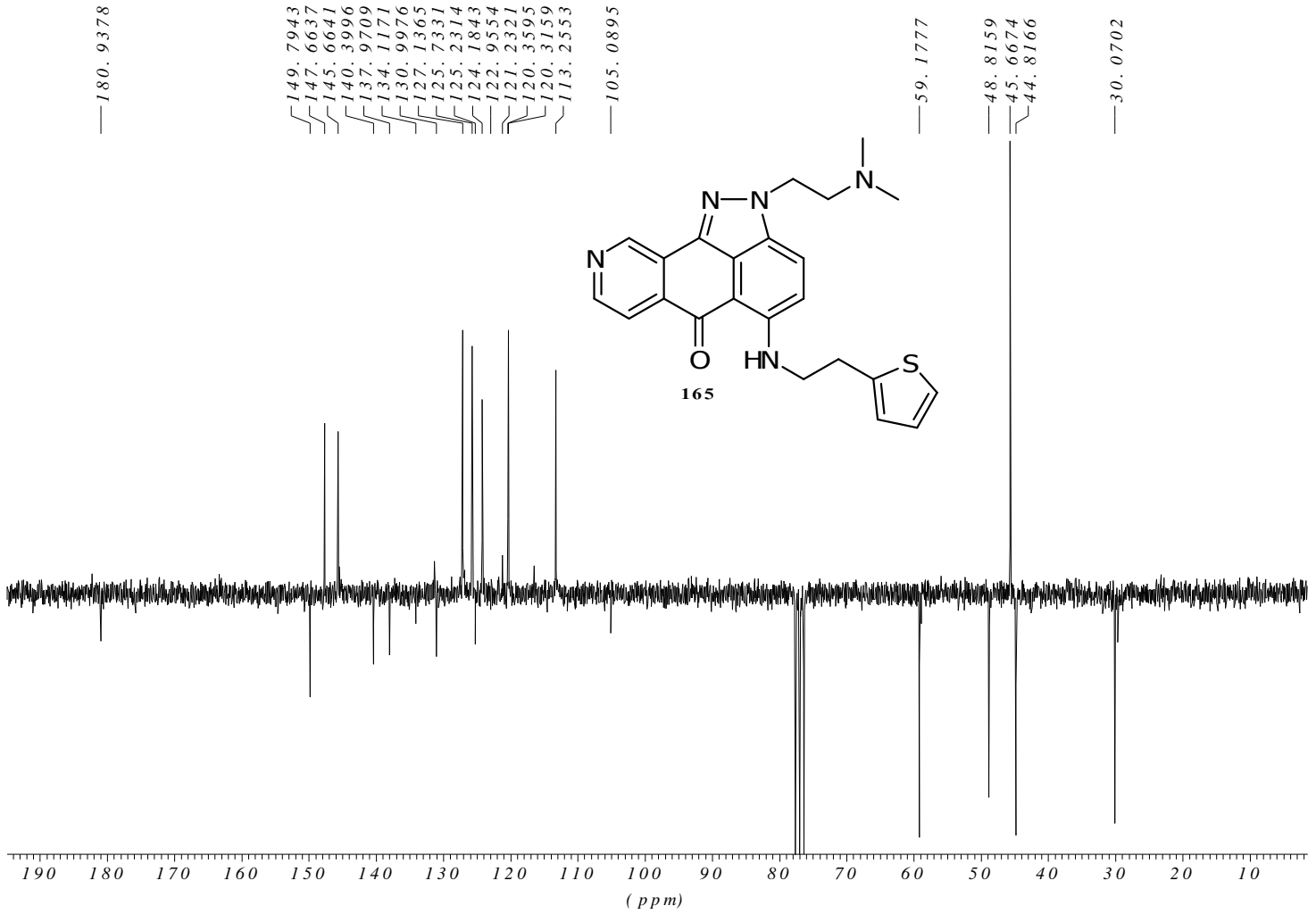


165

^{1}H NMR spectrum of **165** in $CDCl_3$.

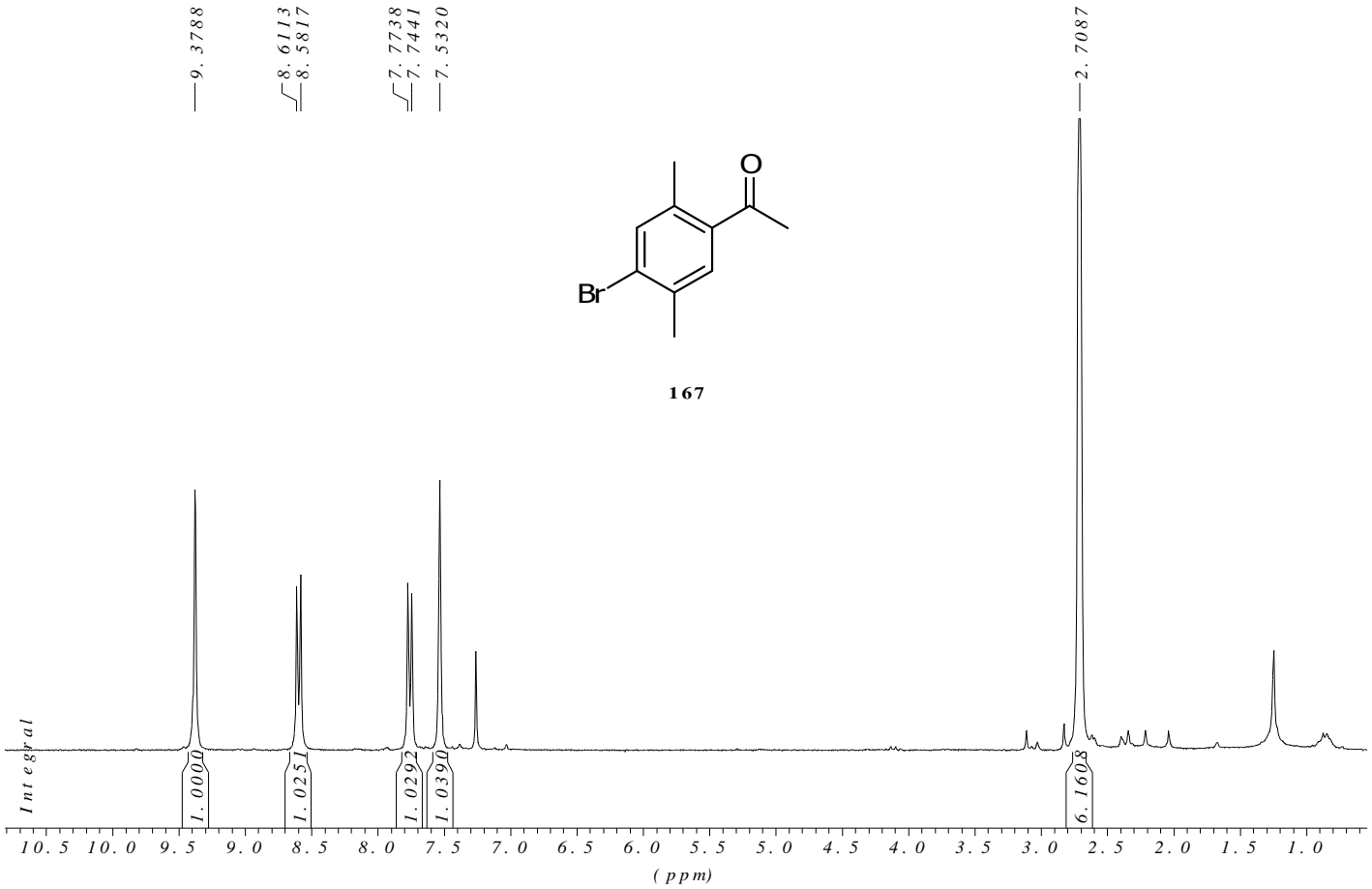


^{13}C NMR spectrum of **165** in $CDCl_3$.

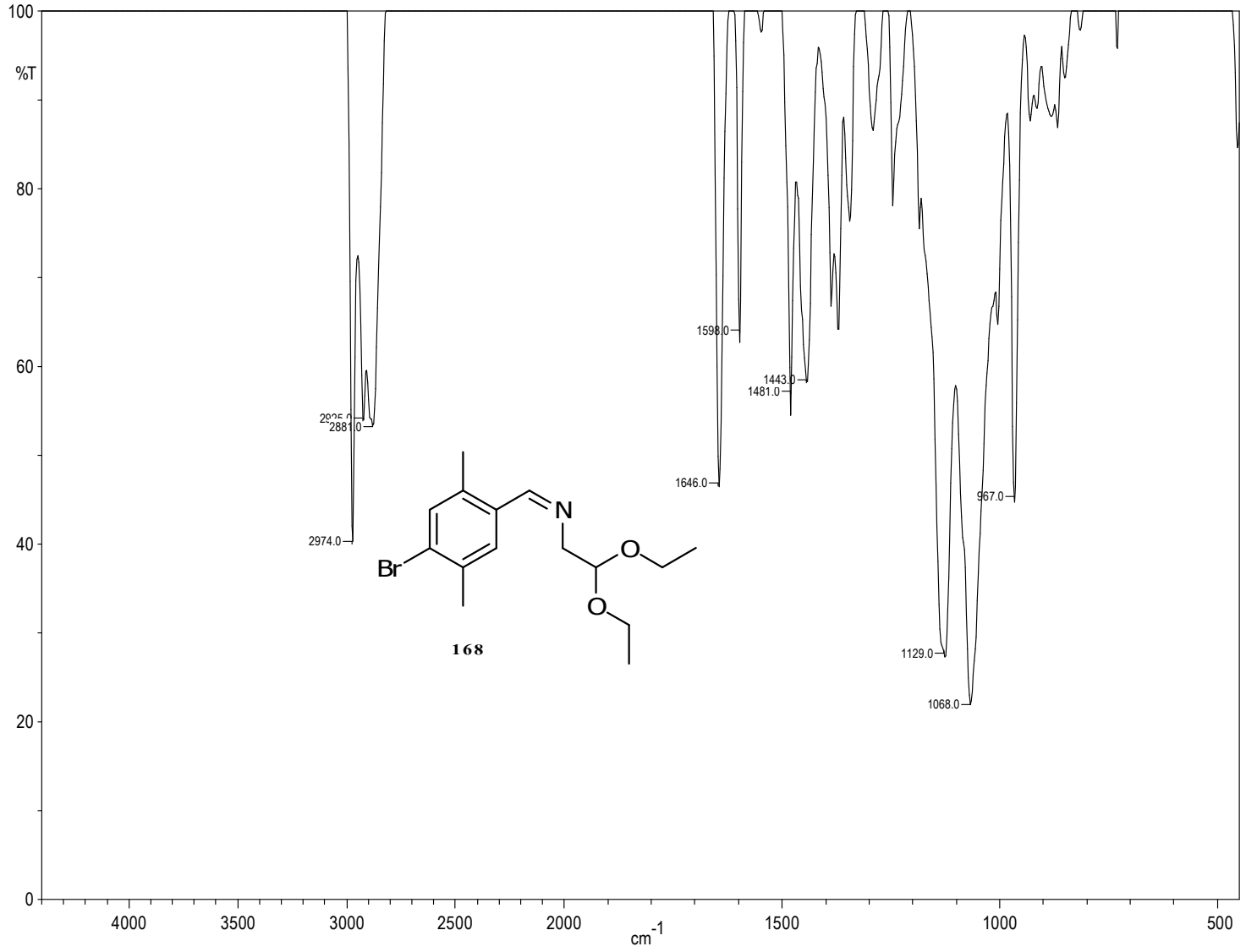


^{1}H NMR spectrum of **167** in $CDCl_3$

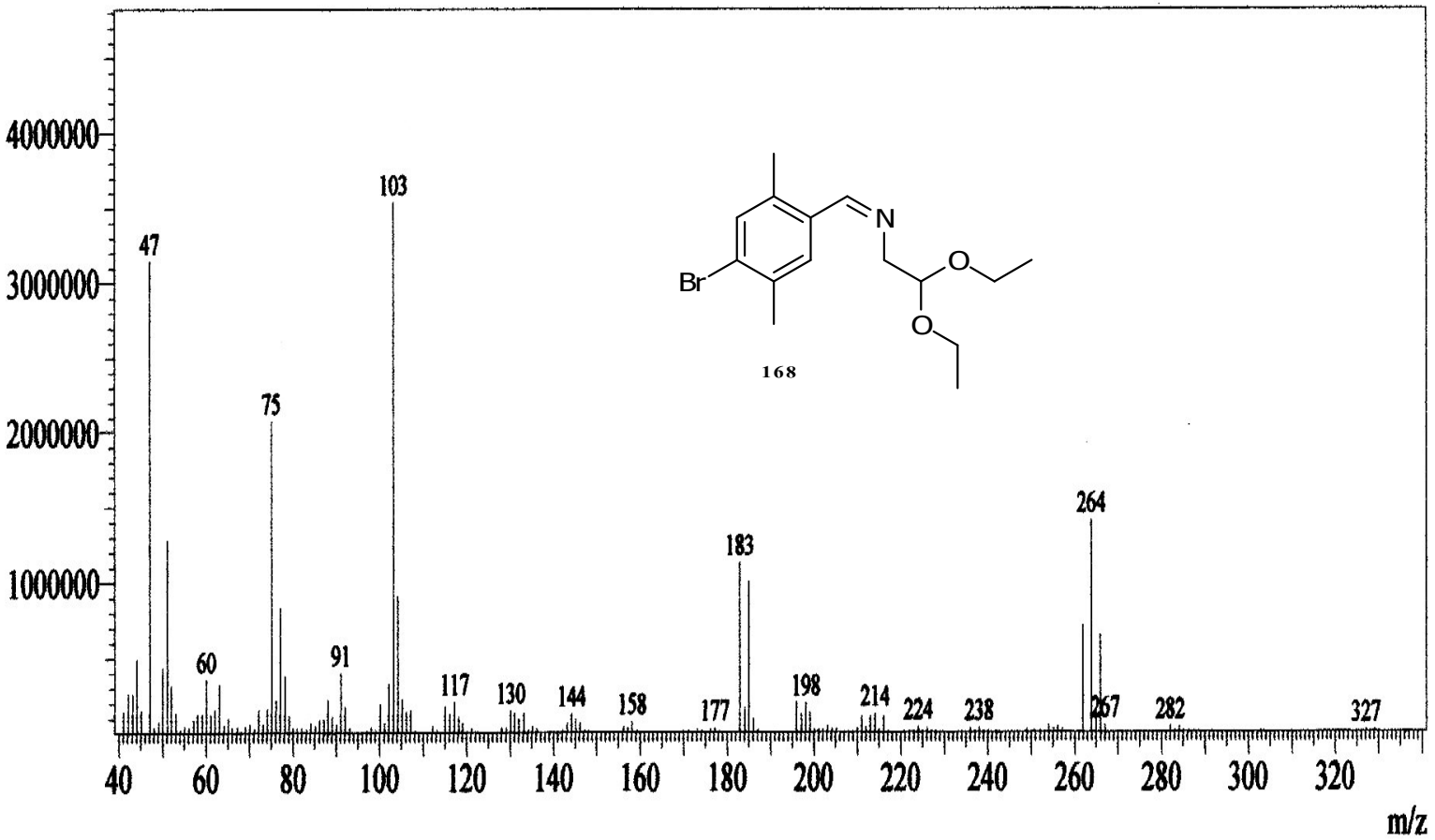
.



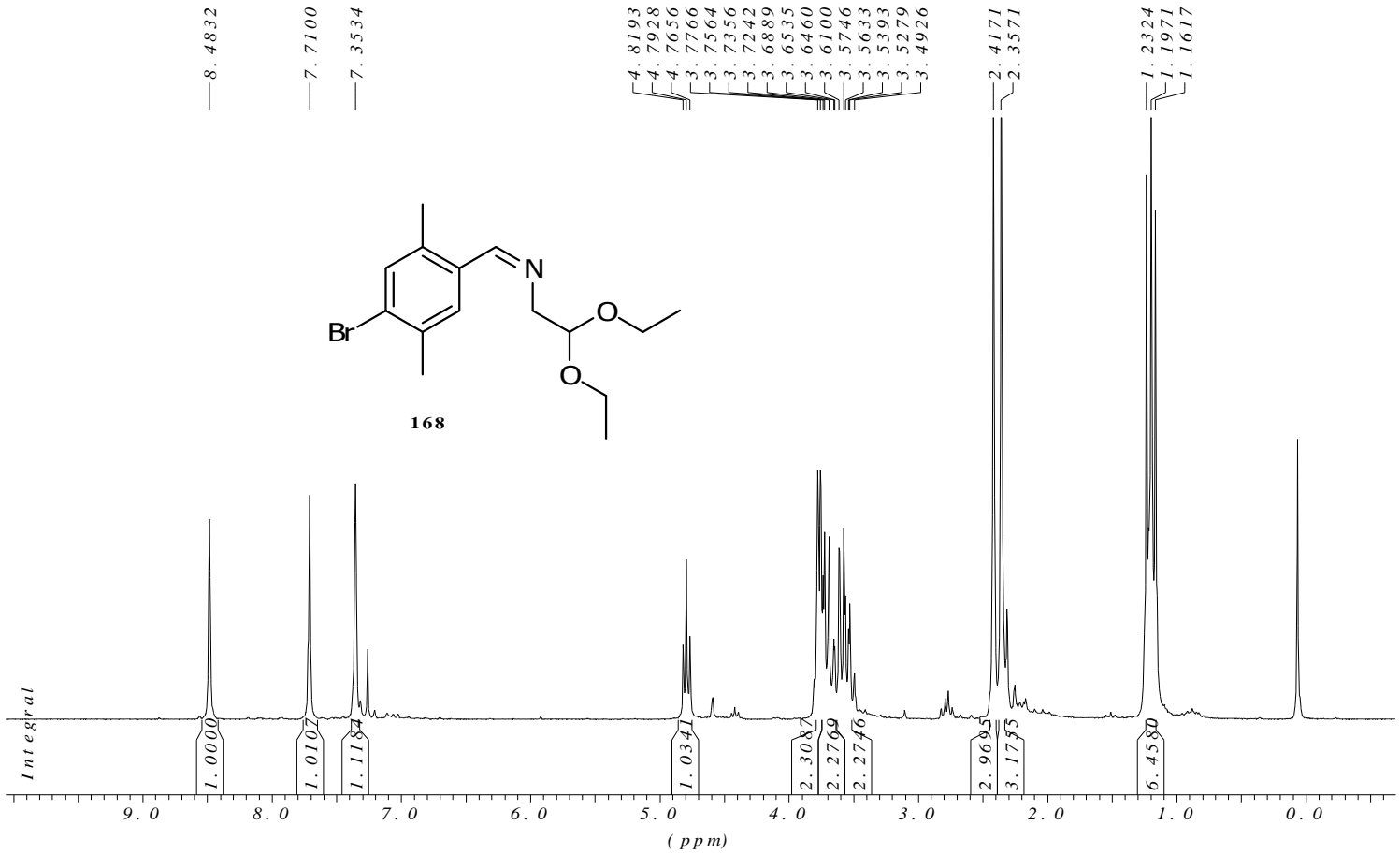
IR spectrum of **168** (NaCl).



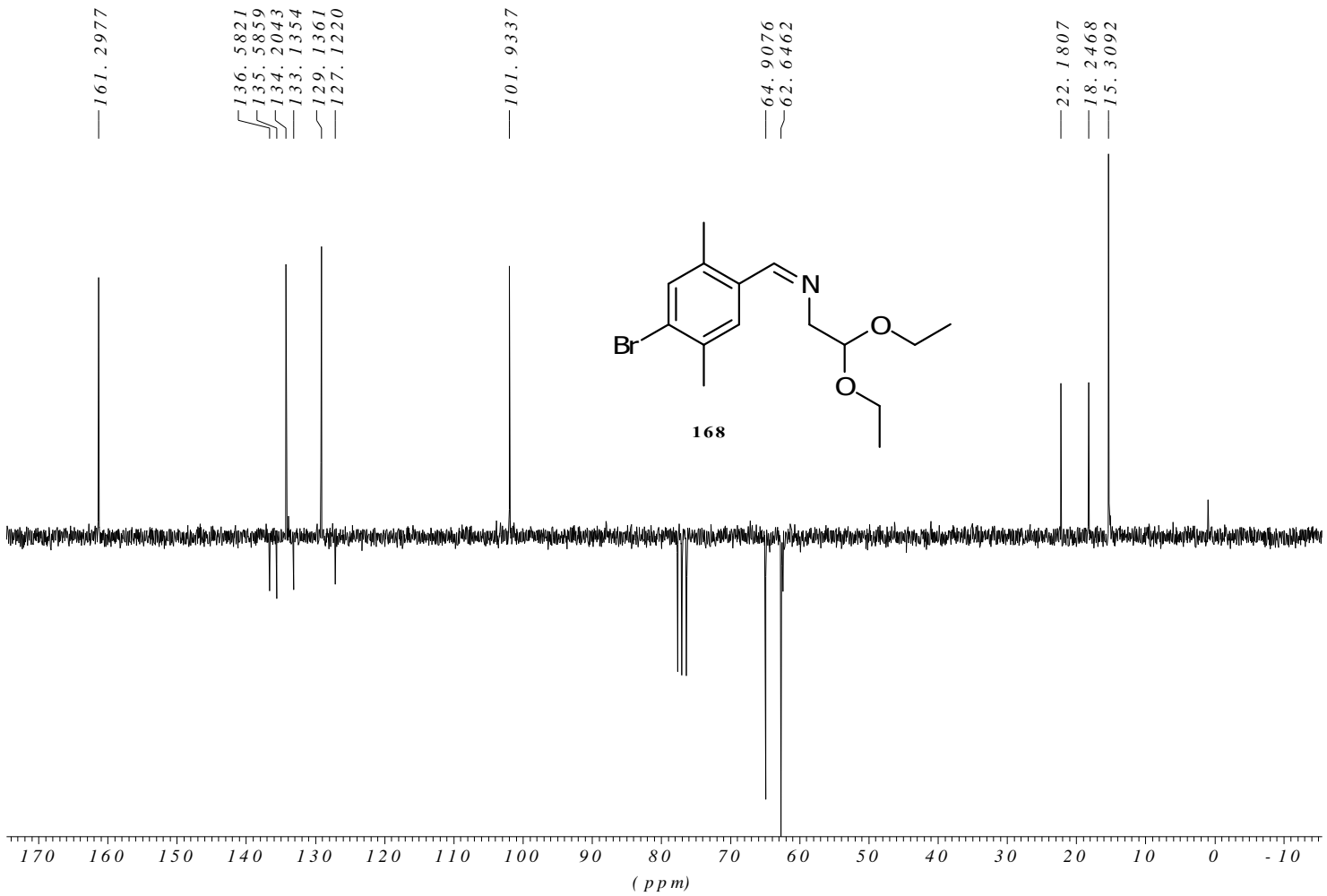
Mass spectrum of **168**.



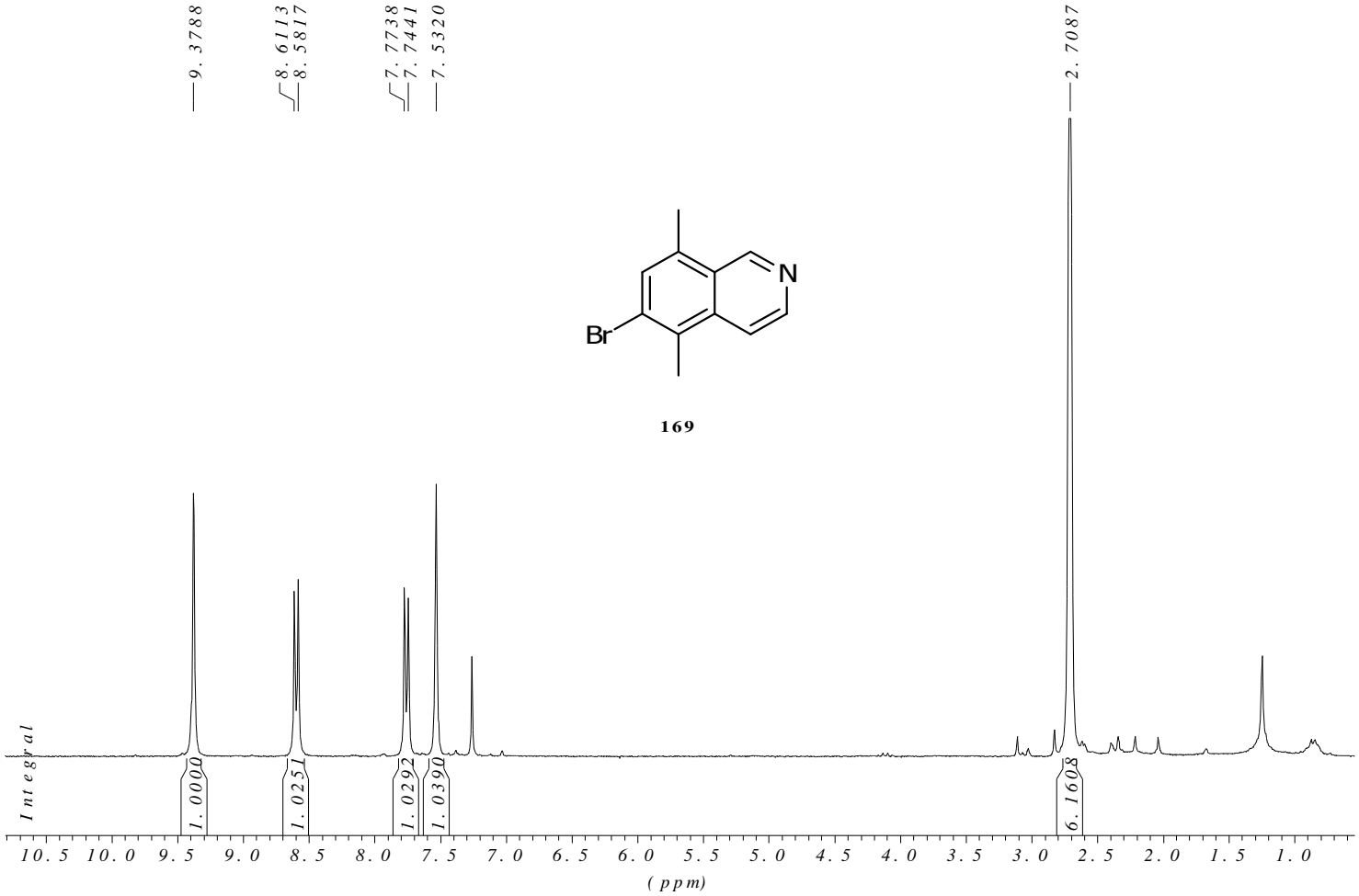
^{1}H NMR spectrum of **168** in $CDCl_3$.



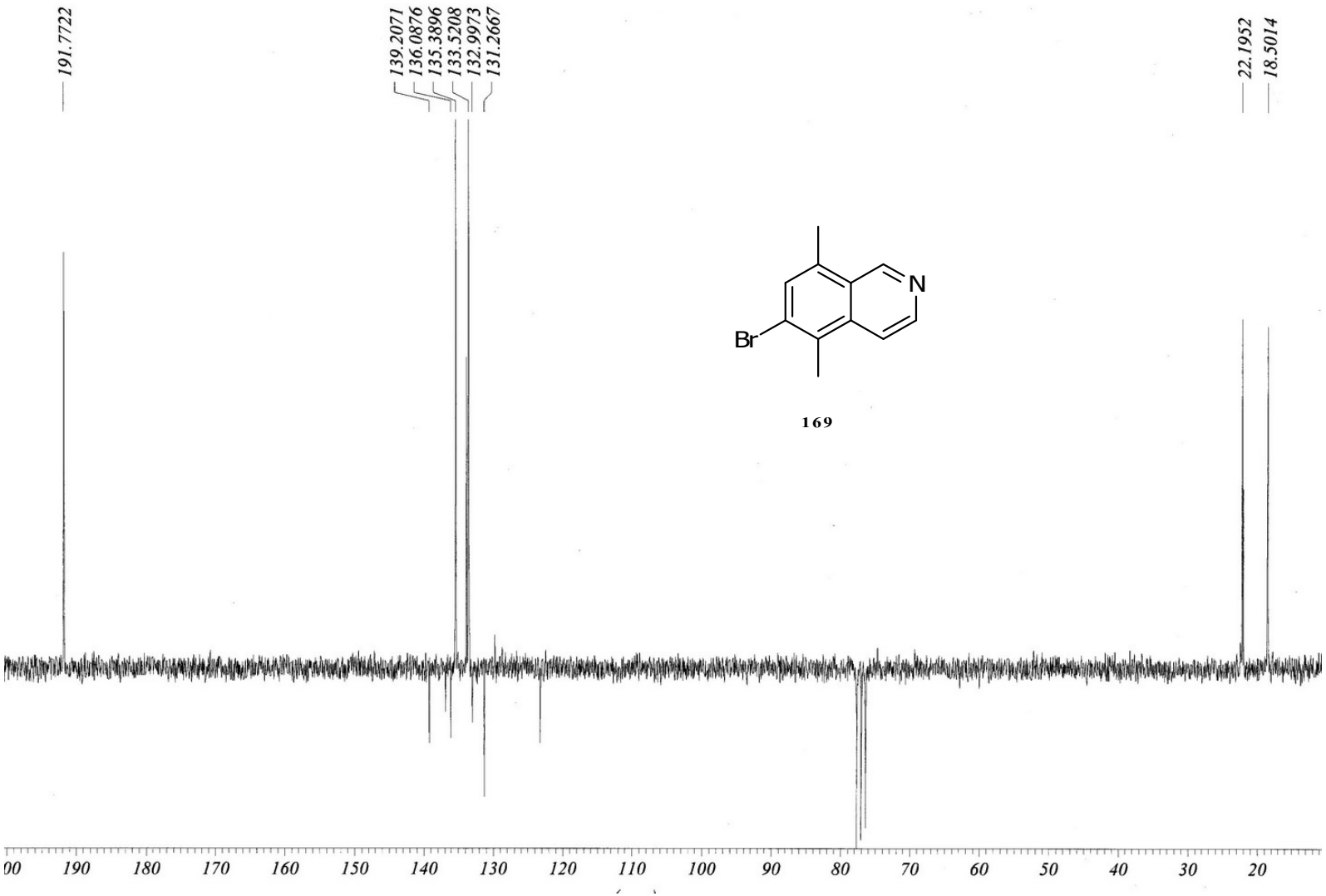
^{13}C NMR spectrum of **168** in $CDCl_3$.



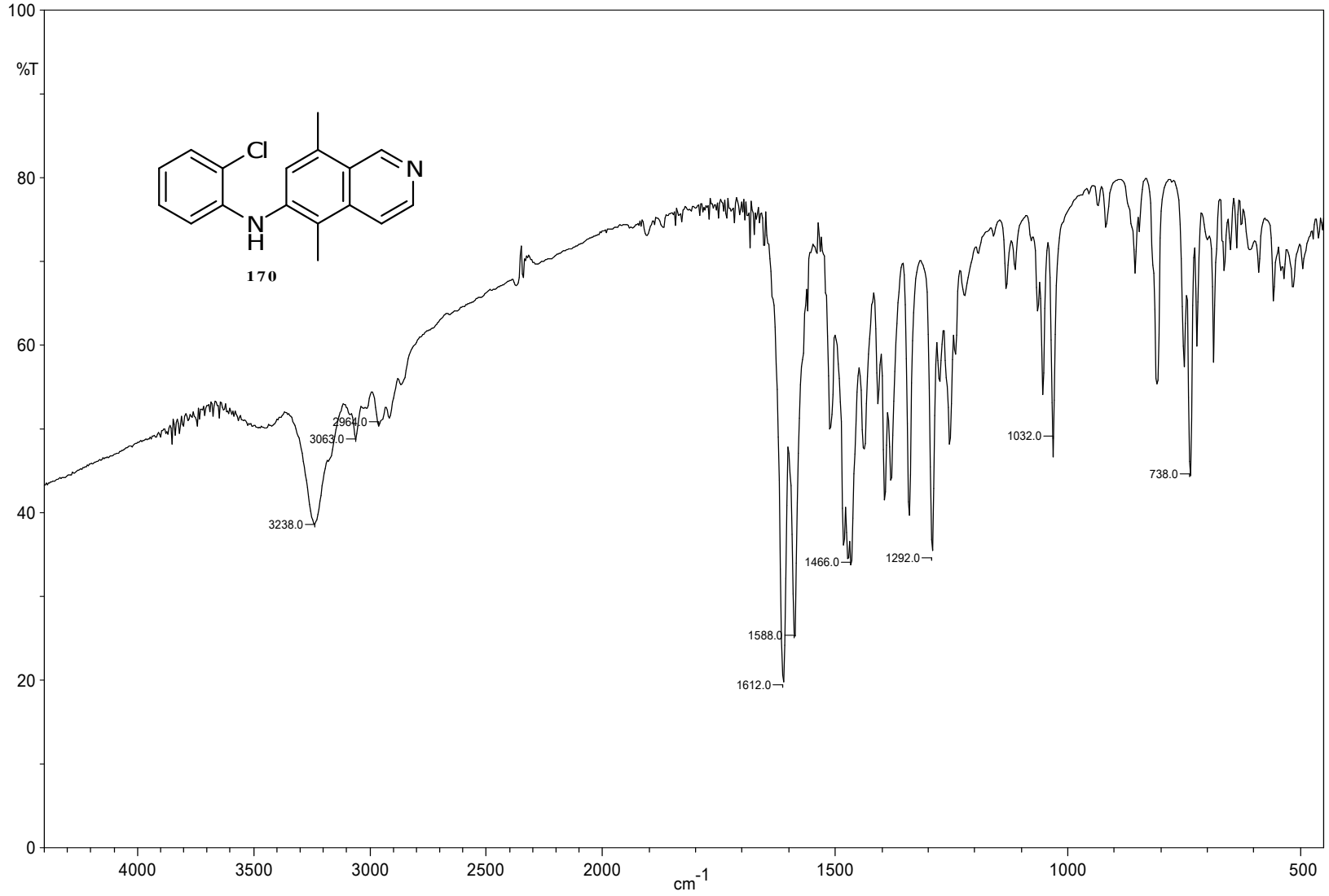
^{1}H NMR spectrum of **169** in $CDCl_3$.



^{13}C NMR spectrum of **169** in $CDCl_3$.

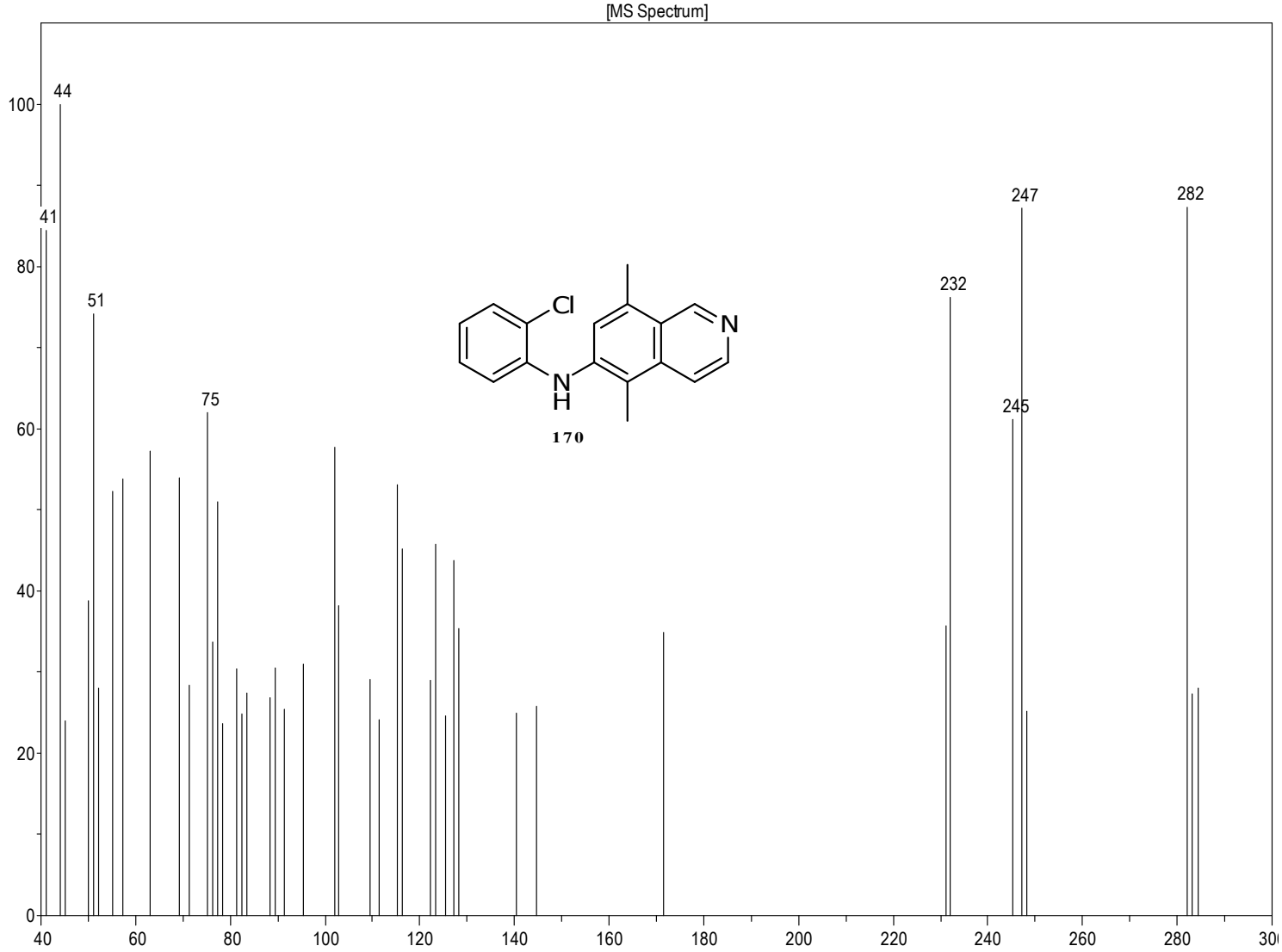


IR spectrum of **170** (KBr).

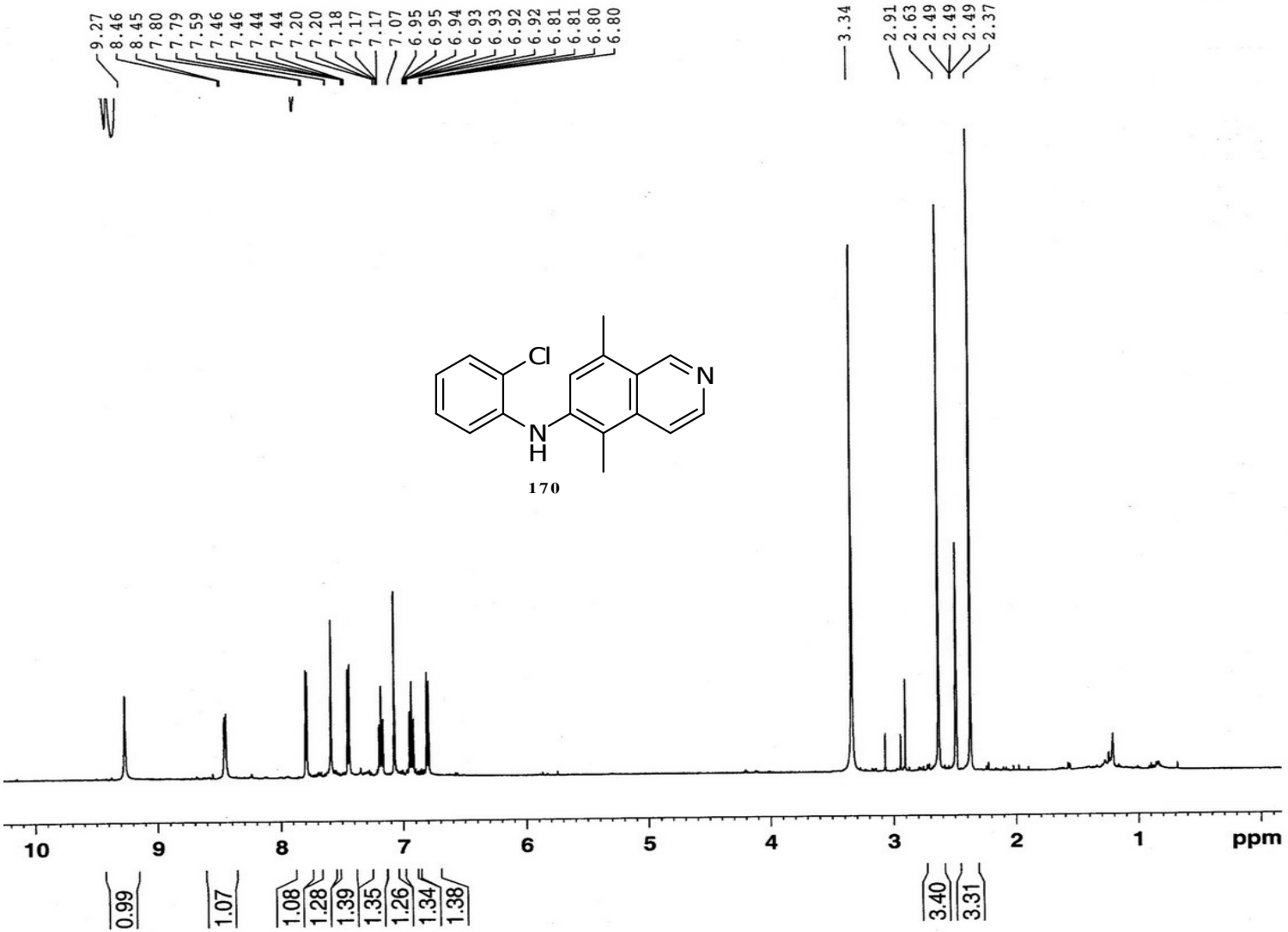


170

Mass spectrum of **170**.

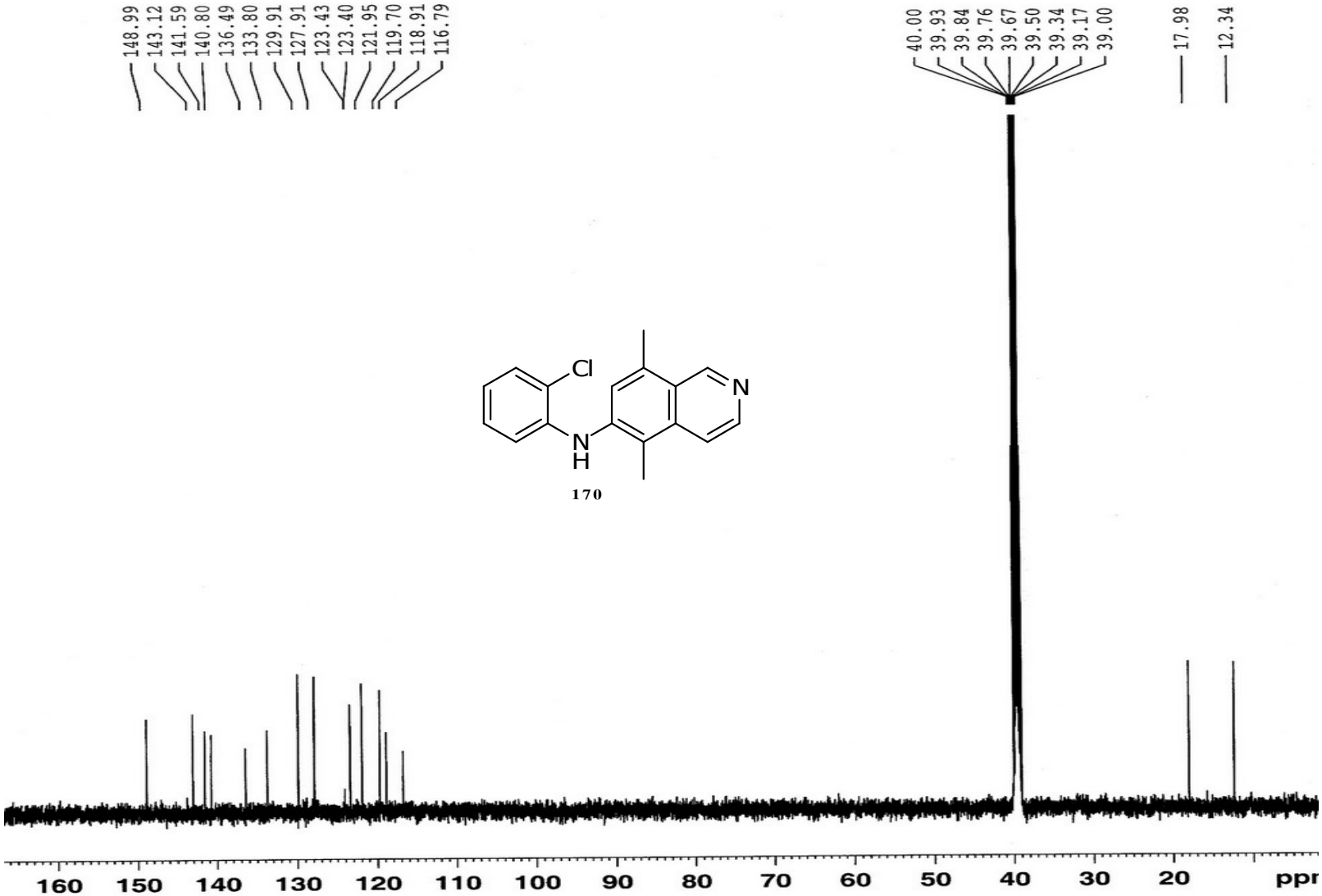


^{1}H NMR of spectrum of **170** in DMSO-d_6.

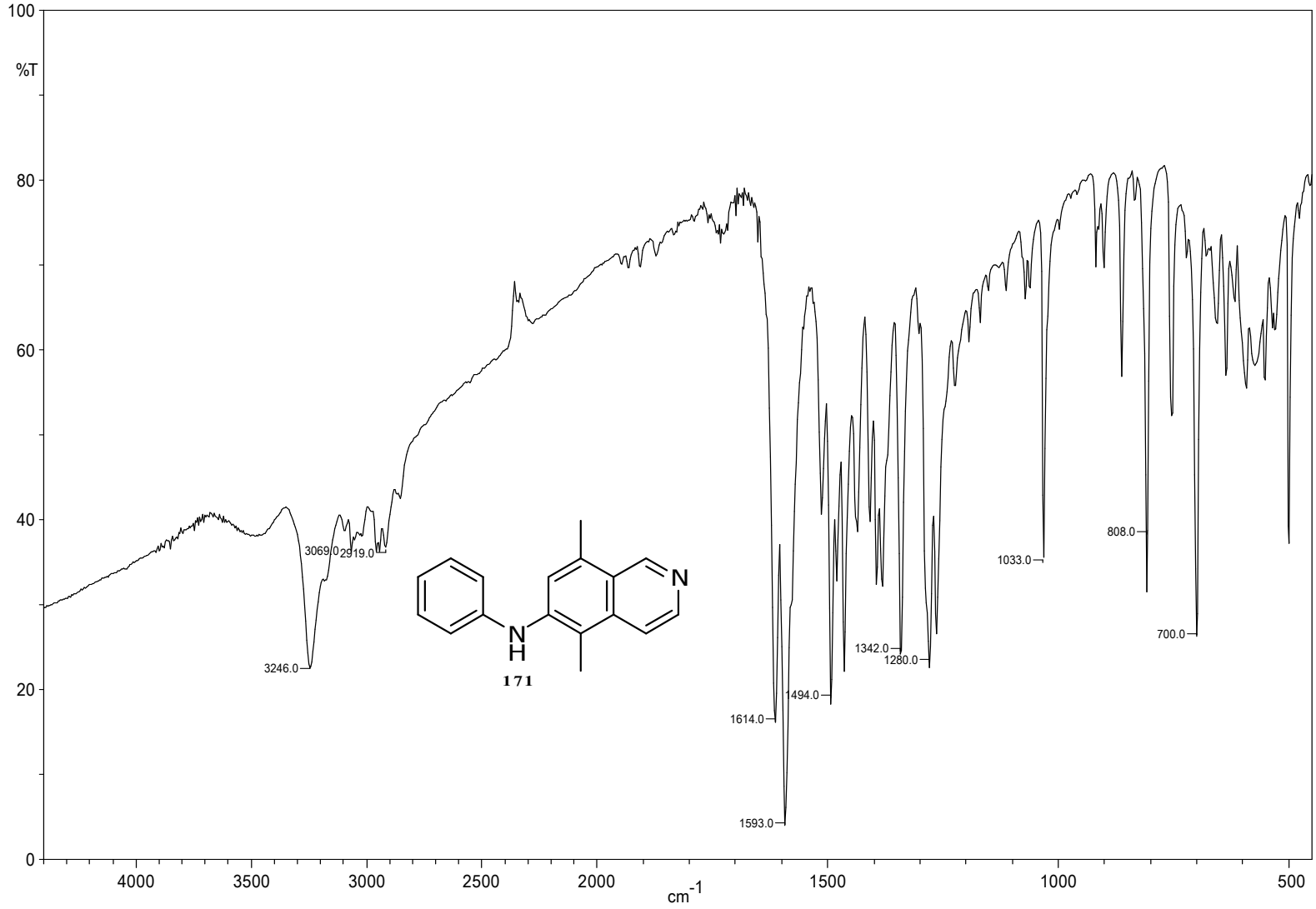


170

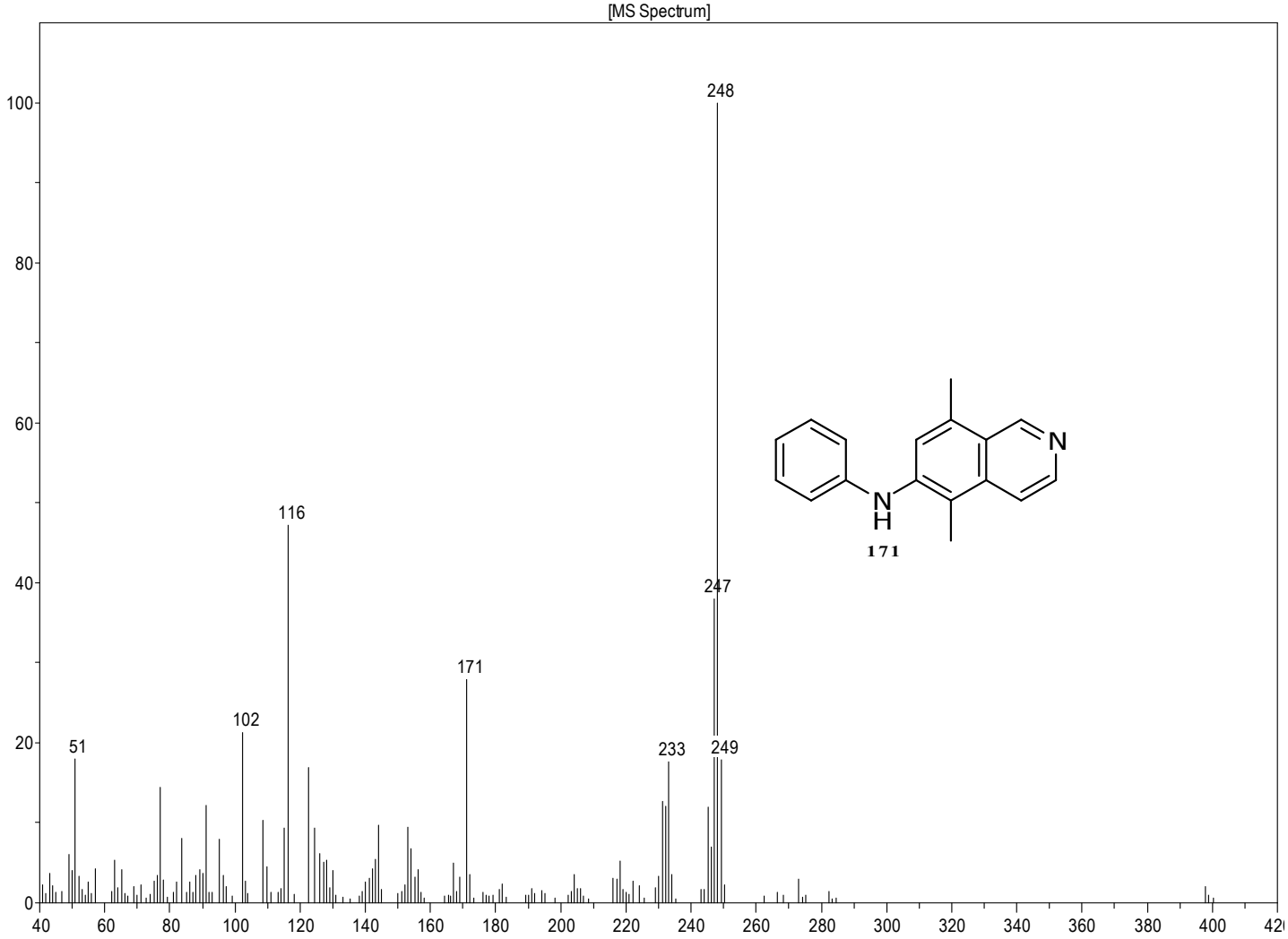
^{13}C NMR of spectrum of **170** in DMSO-d_6.



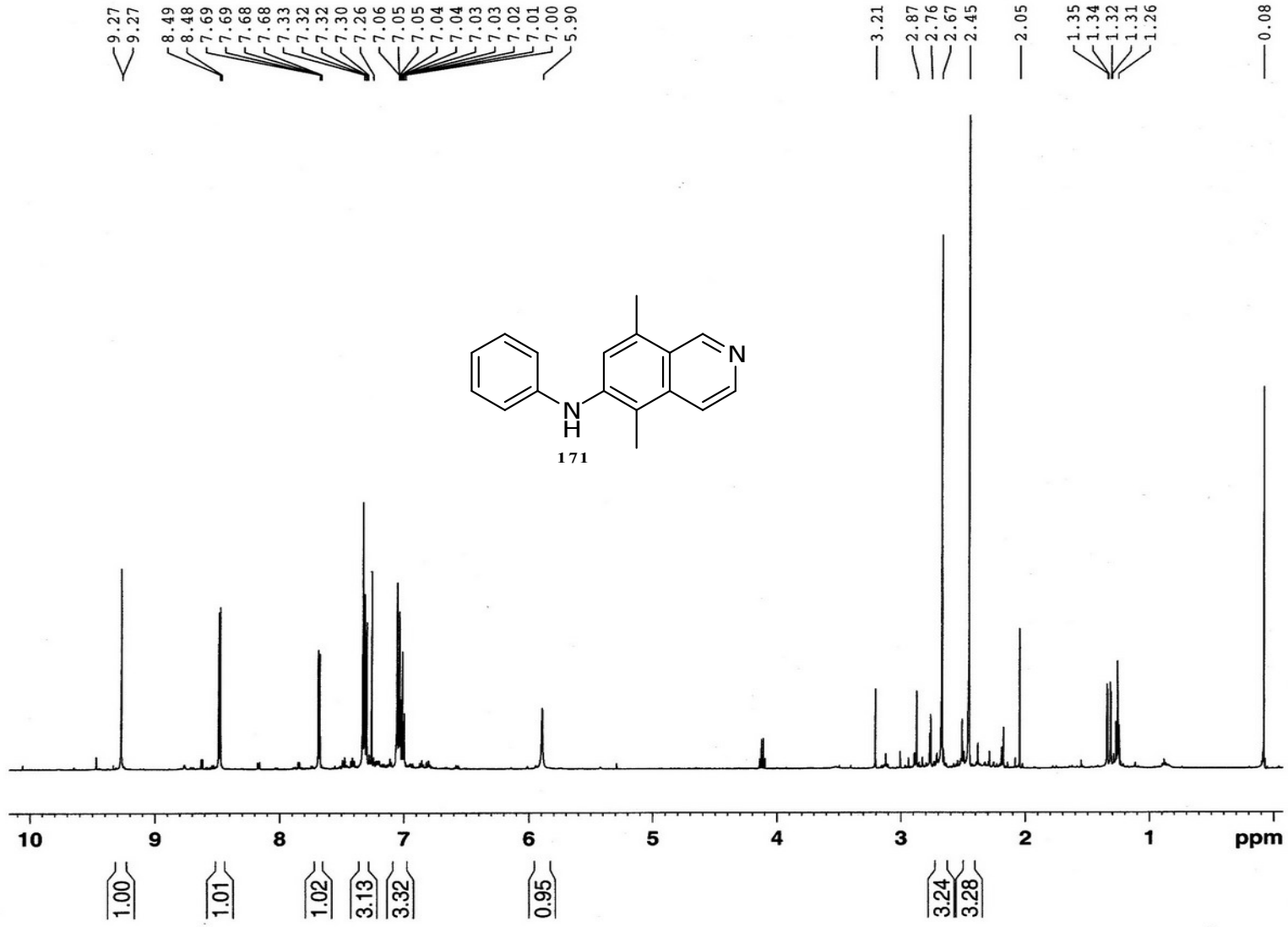
IR spectrum of **171** (KBr).



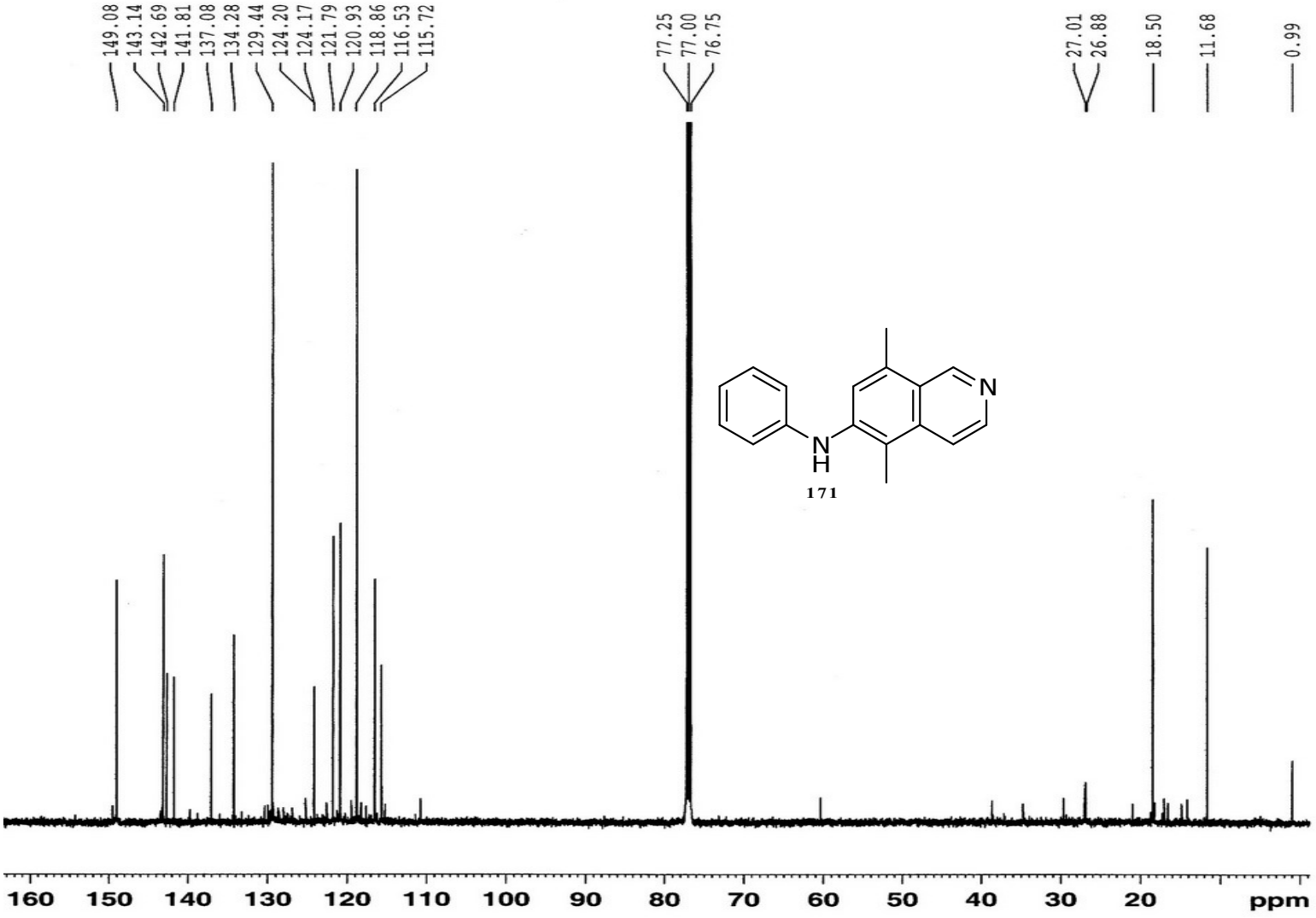
Mass spectrum of **171**.



^{1}H NMR spectrum of **171** in $CDCl_3$.



^{13}C NMR spectrum of **171** in $CDCl_3$.



CURRICULUM VITAE

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Education

1992-1994	High School, Wat Intharam, Bangkok, Thailand
1996-1999	B.Sc. (Chemistry), Kasetsart University, Thailand Research Advisor: Asst. Prof. Supanna Techasakul Thesis: Chemical components in *Solanum torvum Sw*.
2000-2004	M.Sc. (Organic Chemistry), Kasetsert University, Thailand Research Advisor: Asst. Prof. Supanna Techasakul Thesis: Reaction and Synthesis of Dibenz[b,f]azepine Alkaloids for Medical purposes.

My Research Projects

2000-2003	Synthesis of Oxcarbazepine and derivatives for medical purposes funded by Chulabhorn Research Institute (CRI).
2003-2006	Synthesis of Nevirapine and derivatives enhance their activities for inhibiting HIV-reverses transcriptase funded by Thailand Research Fund (TRF) and Commission on Higher Education.
2004-2006	Synthesis of Efavirenz and investigate on HIV-1 Reverse transcriptase-inhibitor interaction funded by Commission on Higher Education.

Experiences

2000-2001	Teaching Assistant in organic chemistry laboratory for representative of Thai Chemistry Olympiad students.
2000-2003	Teaching Assistant in organic chemistry, laboratory, Department of Chemistry, Kasetsart University
2003-2006	Invited lecturer in organic chemistry laboratory, Department of Chemistry, Kasetsart University.

Scientific Contributions

2001	Presentation in 27th Congress on Science and Technology of Thailand (STT2001) "Synthesis of 10,11-Dihydro-10-oxo-5H-dibenz[b,f]azepine; A precursor of oxcarbazepine"
2003	Invited speaker at Government Pharmaceutical Organization of Thailand the topic: Synthesis of Nevirapine

Research Interests Synthesis of anticancer and anti HIV-1