Synthesis of Fluoro-Isoxazolidine and Fluoro-Pyrrolidine via [3+2] Cycloaddition Reaction of Diethyl (*E*)-Fluoromaleate

by Mehrdad Shadmehr, Bachelor of Science

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ABSTRACT

SYTHESIS OF FLUORO-ISOXAZOLIDINE AND FLUORO-PYRROLIDINE VIA [3+2] CYCLOADDITION REACTION OF Diethyl (*E*)-2-FLUOROMALEATE

by

MEHRDAD SHADMEHR

Chair Person: Professor. Timothy B. Patrick

Imine, and nitrone-olefine [3+2] cycloaddition reactions are processes that display promise for the synthesis of heterocyclic five member rings. Nitrogen-containing heterocycle rings have attracted widespread attention in the field of synthetic and medicinal chemistry. We have investigated the synthesis of diethyl (*E*)-fluoromaleate **(1)** and studied its reactions with different kind of imines and nitrones that have potential biological activities. Diethyl (*E*)-fluoromaleate **(1)** was prepared by the Horner-Wardsworth-Emmons reaction using triethyl 2-fluoro-2-phosphoethanoate with a yield of 89% . The aromatic α-iminoesters **(2-3)** were prepared from aromatic aldehydes, glycine (methyl or ethyl) ester hydrochloride, and NE_3t resulting in yields that range between 65-77%. A series of aromatic nitrones **(4-7)** was prepared from N-methylhydroxylamine and a series of aromatic aldehydes with a yield of 73-80%. The (3+2) reaction between diethyl (*E*)-2-fluoromaleate **(1)**, the dipolarophile, and nitrones **(4-7)**, the dipole, was initiated by refluxing to form the isoxozolidine adduct **(10-13)**. Pyrrolidine adduct was prepared by the catalyzed (3+2) cyloaddition reaction of diethyl (*E*)-fluoromaleate **(1)**, the dipolarophile, aromatic imines **(2-3)**, the dipole, and, AgOAc as acatalyst. Silica gel column chromatoghraphy was used to purify the (3+2) cycloaddition products **(8-9)**.

ACKNOWLEDGEMENTS

Special thanks to Dr. Timothy B. Patrick for accepting me in his lab and for his guidance and invaluable contributions to my research. I would also like to thank the Chemistry Department and Graduate School of SIUE for accepting me into this program. To all other faculty members of the Chemistry Department, I would like to thank you for your continued support and assistance. I am grateful to my lab mates and friends for helping me to survive this program. I would also like to thank to my mom, Shahla Mojaver, and my dad Reza Shadmehr, I would like to thank you for your continued support and words of encouragement. Without all of your guidance, assistance, love, support, and words of encouragement, this research would not have been possible.

DEDICATION

To my mother (Shahla Mojaver), Father (Reza Shadmehr), and brother (Mehdi Shadmehr).

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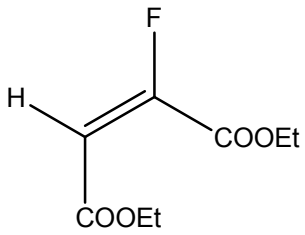

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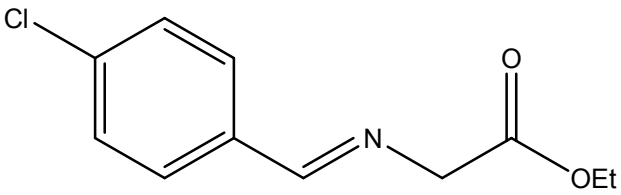

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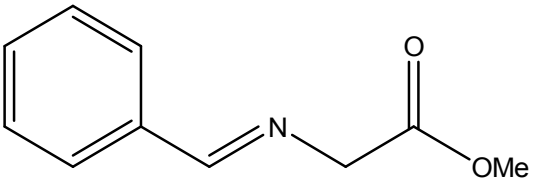

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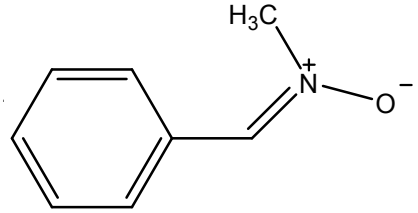

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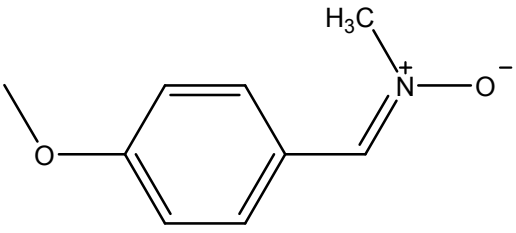

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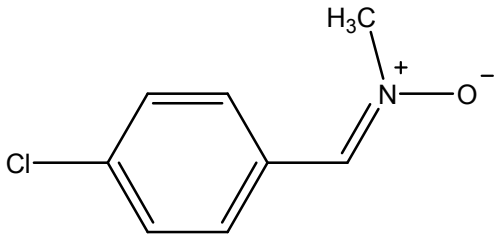

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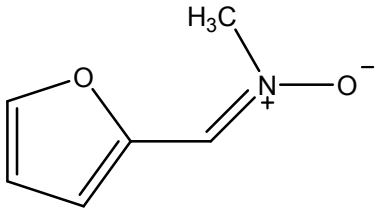

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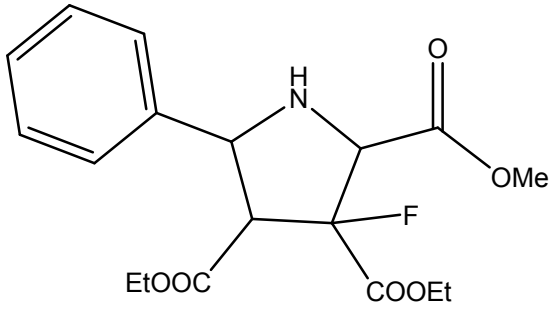

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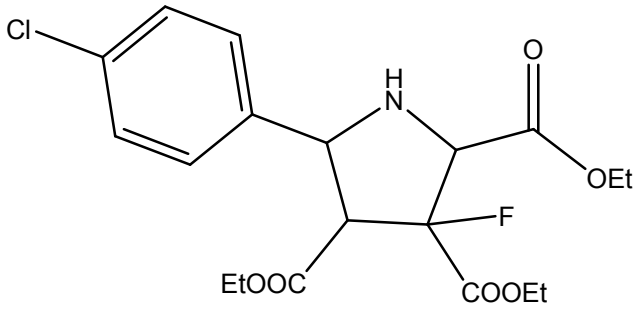

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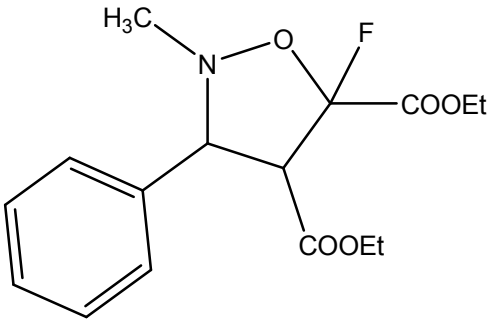

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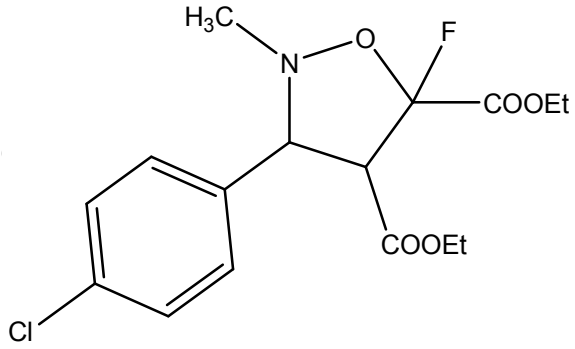

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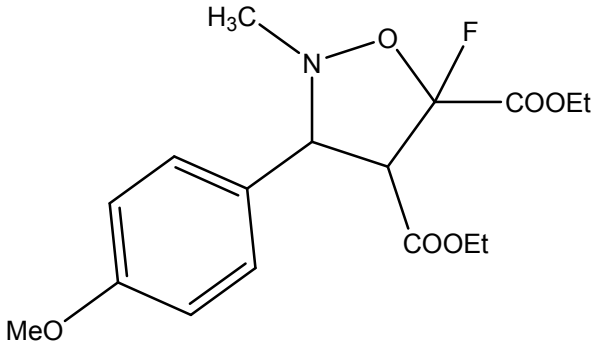

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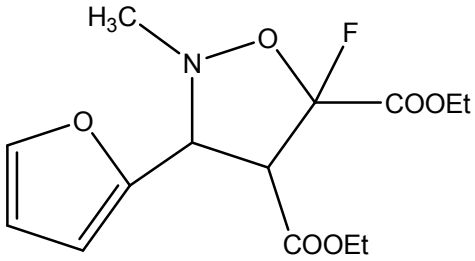

.....Compound **13**

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CHAPTER I

INTRODUCTION

Importance of Fluorinated Compounds

The name of fluorine came after *le fluor,* the French scientist who discovered fluorine natural resource fluorspar in 1812. Although elemental fluorine was isolated by Henri Moissan in 1886[1], synthesis of organofluorine compounds did not make important breakthrough in organic chemistry until the 1930s[2]. Midgely's discovery of cholorofluorocarbons "Freons" for the purpose of refrigeration in 1930[3], can be considered as the beginning of significant and highly technological development into fluorine chemistry. Many useful fluorocarbon products have been produced in the field of material science, fluoropolymer industries, agrochemicals, and medicinal chemistry.[4] In the early 1940s, uniquely suitable fluorinated compounds were used during Manhattan Project to separate uranium isotopes through gas diffusion of their corrosive hexafluorides.[5] The Importance of fluorine in modern organic chemistry is also indicated in the field of medicinal chemistry. There were 44 fluorinated drug candidates under active investigation in phase III clinical trials, and 115 in phase II studies as of Jun 2007.[6] Fluorine is known as the most reactive and most electronegative element in the periodic table. That means it has a high electronic effect on adjacent carbons[7]. Though van der waals radius of fluorine is the smallest one after the hydrogen, its volume and electronegativity are more similar to that of oxygen (Table 1).[8] As a result, fluorine is able to be suitable substituent of oxygen or hydrogen without a major distortion in the geometry of many organic compounds.[9] Due to the strong electron withdrawing nature of fluorine, when fluorine is substituted with another atom (like

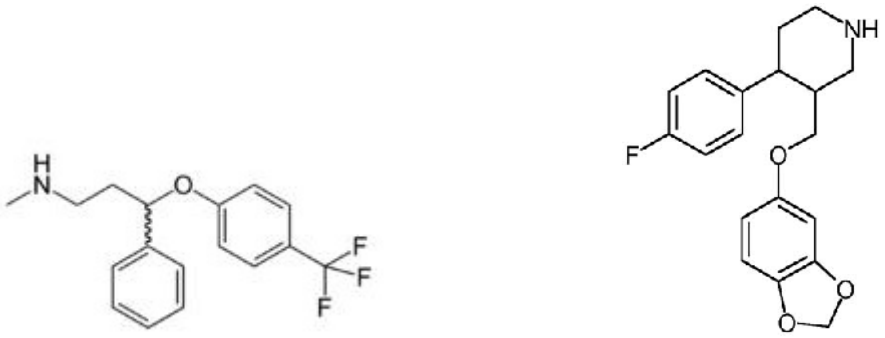
hydrogen or oxygen), there is an effect on the acidity of neighboring functional groups. Basic compounds like amines have their pK_a values lowered when there is fluorine present, making them less basic. Alcohols, carboxylic acids, heterocycles, and phenols become more acidic with adjacent fluorine substitution.[10]

Table 1 Van der Waals Radii and Pauling's Electronegativity.[8]

Atom	Van Der Waals Radii (Å)	Pauling's Electronegativity χ_p
H	1.20	2.20
F	1.47	3.98
Cl	1.75	3.16
Br	1.85	2.96
I	1.98	2.66
C	1.70	2.55
N	1.55	3.04
O	1.52	3.44

Fluorine is a common feature in synthetic active molecules for both pharmaceuticals and agrochemicals. Recent progress in organofluorine chemistry has contributed significantly to the great advances in modern medicinal treatment. With the aid of the known influence of a fluorine atom on physical, chemical, and biological phenomena, therapeutic efficacy has been increased and pharmacological properties improved.[11] Various effective fluoromedicines have been developed and put into the pharmaceutical market place, including anticancer and antiviral agents, anti-inflammatory agents, anti hypertensive agents, and central nervous system drugs like anti-depressants.[12]

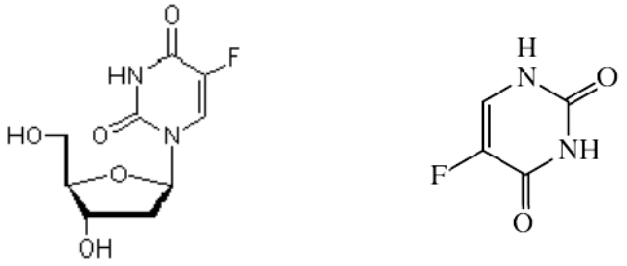
A great success in the development of new fluorine-containing agents is highlighted in the treatment of disorders of the central nervous system. As the lipid solubility of fluorinated aromatic compounds is significantly improved, the rate of absorption and transport of a drug across the blood-brain barrier is greatly enhanced by fluorine substitution.[13] For instance, Fluoxetine was launched in 1986 as an efficient and successful antidepresant (Figure. 1).[14] Paroxetine introduced in 1991, exhibits activity similar to fluoxetine (Figure. 1) with a shorter duration of action.[15]



fluxetine paroxetine

Figure 1. Example of Organofluorine Compounds as Central Nervous System Medicine.[14, 15]

Organofluorine compounds have also significant roles in the treatment of different kind of cancer. Presently, 5-fluorouracil and, 2'-Deoxy-5-fluorouridine (FdUR) are applied as antitumor agents in the treatment of leukemia and solid tumors (Figure. 2).[16]



2-Deoxy-5-fluorouridin 5-fluorouracil

Figure 2. Example of Organofluorine Compounds as Anticancer Agents.[16]

Organofluorine compounds have made a revolution in antibacterial and antifungal agents. Fluoroquinolone carboxylic acids exhibit a superior antibacterial activity to traditional antibacterials like penicillin and tetracycline (Figure. 3). For example, Levofloxacin is especially effective in lowering respiratory, urinary tract and prostate infections.[17]

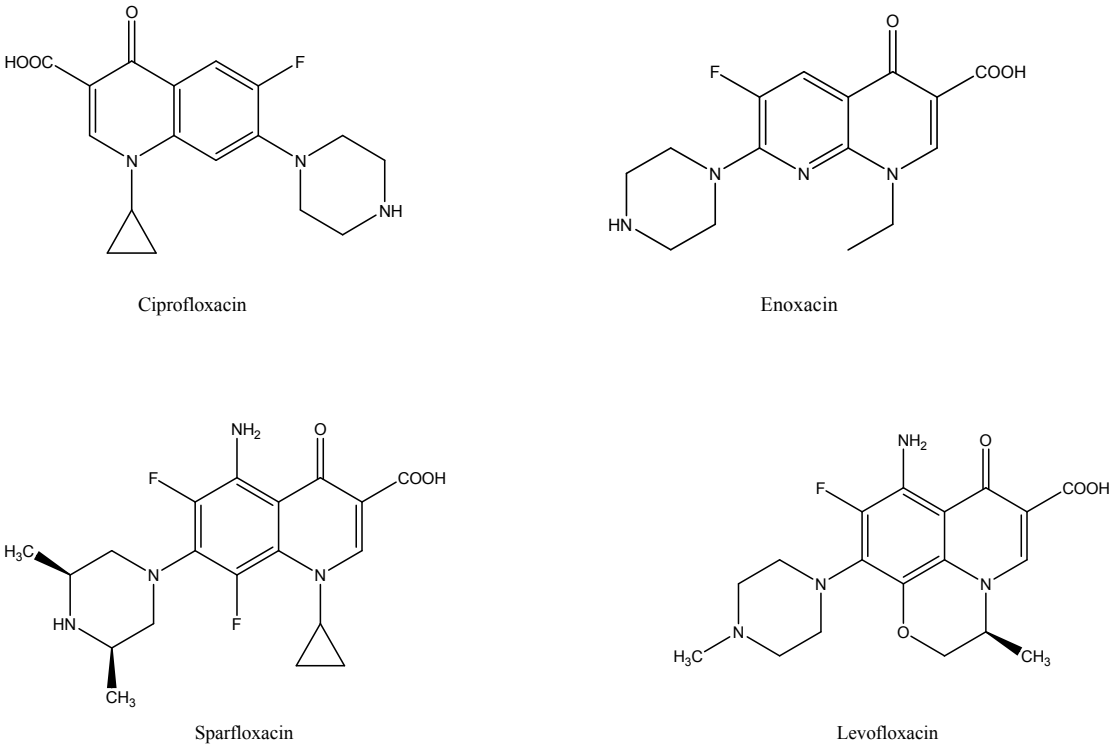
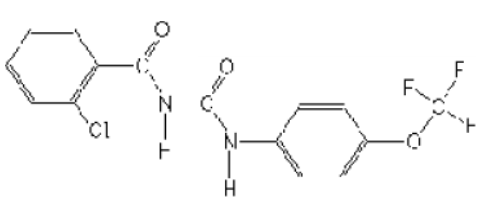


Figure 3. Antibacterial Organofluoro Compounds.[17]

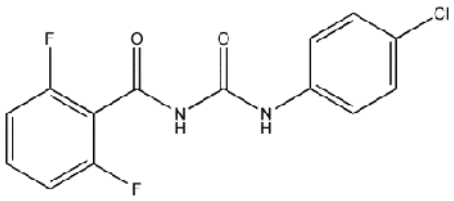
Nowadays, agrochemicals are essential for large-scale production of high quality crops. Because use of large amounts of chemicals may cause problems related with safety and the environment, use of small amount of highly potent, selective and negligibly toxic agents are desirable that are effective only for certain period of time and then will be decomposed rapidly to total nontoxic compounds. Fluorine has played a key role in the design of novel

highly potent agrochemicals.[18]Three main classes of agrochemicals are insecticides, herbicides, and fungicides, that all have examples of molecules containing fluorine.

A typical class of fluorine-containing insecticides is N-2,6-difluorobenzoyl-N'-arylurea and its derivatives that inhibit chitin biosynthesis and are often called insect growth regulators. The insecticides are selective to specific kinds of insects. They are also nontoxic to mammals and have much less influential against their natural enemies and honey bees (Figure. 4).[19]



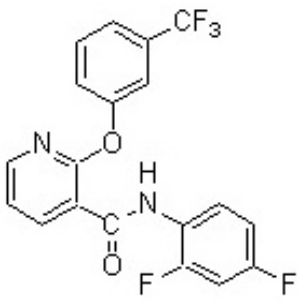
Triflumuron



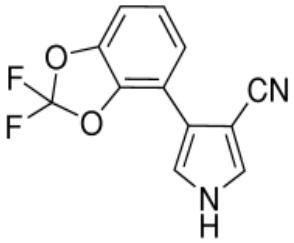
diflubenzuron

Figure 4. Fluorinated Insecticide Products.[19]

The herbicide, Diflufenican, which is a nicotinanilide and inhibits carotenoid biosynthesis, has five fluorines- two as phenyl substituents and a trifluoromethyl group. Fludioxonil, that contains a difluoromethylene unit connecting two oxygen atoms on a benzene ring, is a fungicides that is genrally used as a seed treatment (Figure. 5).[20]



diflufenican



fludioxonil

Figure 5. Fluorinated Herbicide and Fungicide Products.[20]

Fluorine has become popular in drugs and agrochemical fields because of its influence on molecular properties. This discovery process is often done by taking a molecule that has some activity and modifying it to alter its properties like, increasing its binding at a receptor or to increase its bioavailability.[20] Nature rarely uses fluorine and in order to create bioactive compounds, it requires new synthetic routes and compounds. Moreover, the addition of fluorine onto chiral centers, which is essential in synthesis of fluorinated-bioactive compounds, is not as straightforward as one might expect.[21] The ultimate solution is to use sources of fluorine such as alkyl groups that contain fluorine.

[3+2] Cycloaddition Reaction

Efficient methods for the synthesis of fluorine-containing heterocycles have been an interesting subject due to their increasing importance in the field of biology and medicinal chemistry.[22] Among many well developed methods for the construction of 5-membered heterocycle rings, [3+2] cycloaddition, also known as Huisgen cycloaddition, has proven to be one of the most versatile.[23] [3+2] cyloaddtion is an organic chemical reaction of a

dipolarophile (e.g. alkenes, alkynes, ect.) with a 1,3-dipolar compound (e.g. azides, nitones, ect.) to form a cyclic 5-memebered product (Figure 6).[24]

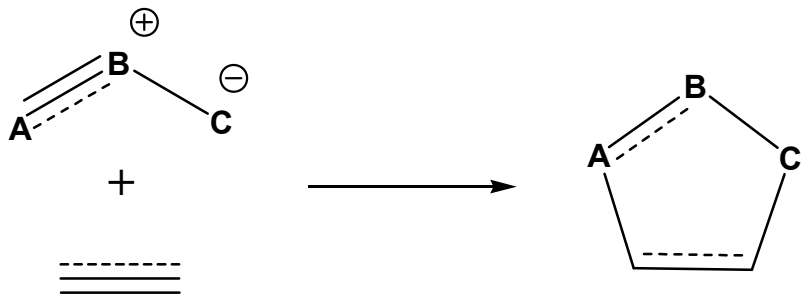


Figure 6. [3+2] Cycloaddtion Reaction.[24]

The first general application of 1,3-dipoles in organic chemistry was launched via systematic studies by Rolf Huisgen[24], that led to many new predicted and discovered reactions in 1960s.[25] In the late 1950s, Huisgen figured out that many apparently unrelated reactions could be integrated under a single pattern[24], that he named as [3+2] cycloaddition. Huisgen's 1963 review about the concept of [3+2] cycloaadtion reaction in *Angewandte Chemie* [26] has been cited around 1000 times in literature and is considered to be one of the most influencial papers of the 20th century.[24]

A 1,3-dipole is designated as an a-b-c structure that goes through [3+2] cycloaddtion reactions (Figure. 7).[27] 1,3-Dipoles are divided into two different types, allyl anion type and the allenyl/propargyl anion type. The allyl anion contain four electrons in three P_z orbitals arranged perpendicularly to the plane of the dipole and the 1,3-dipole is bent (Figure. 7).The allenyl/propargyl anion has an extra π orbital located in the plane orthogonal to molecular orbital of the allenyl anion type, which does not allow the former orbital to be directly

involved in the resonance structures and reactions of dipole. The allenyl/propargyl anion type is linear and the central atom *b* of the dipole is limited to nitrogen.[28]

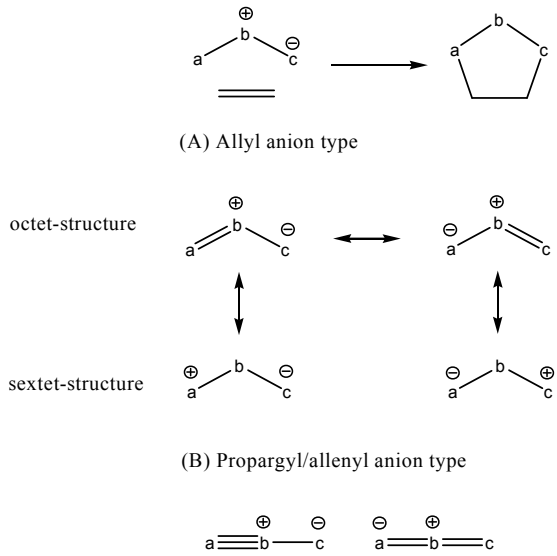


Figure 7. Structure of 1,3-Dipoles.[27]

Mechanism of [3+2] Cycloaddition Reaction

The [3+2] cycloaddition mechanism involves four electrons of the dipolar compound and two π-electrons of the dipolarophile participating in concerted, pericyclic shift. The addition is stereoselective, and as a result it represent a [4_s+2_s] cycloaddition same as that of a Diels-Alder reaction.[28] In 1961, Roth and Doering[29] described a four center, concerted path, for the mechanism of [3+2] cycloaddition reaction, but also urged that it was impossible to obtain direct mechanistic proof. Firestone[30] proposed a stepwise mechanism with diradical intermediate as an alternative pathway for [3+2] cycloaddition based on thermochemical and regiochemical grounds in the late 1960s that made a challenging debate between Firestone and Huisgen, who strongly supported the concerted mechanism.[31] Huigen's mechanism

finally was accepted as the only mechanism that explains all the experimental observations, especially the strict stereospecificity that as a rule characterizes these reactions (Figure 8).[32]

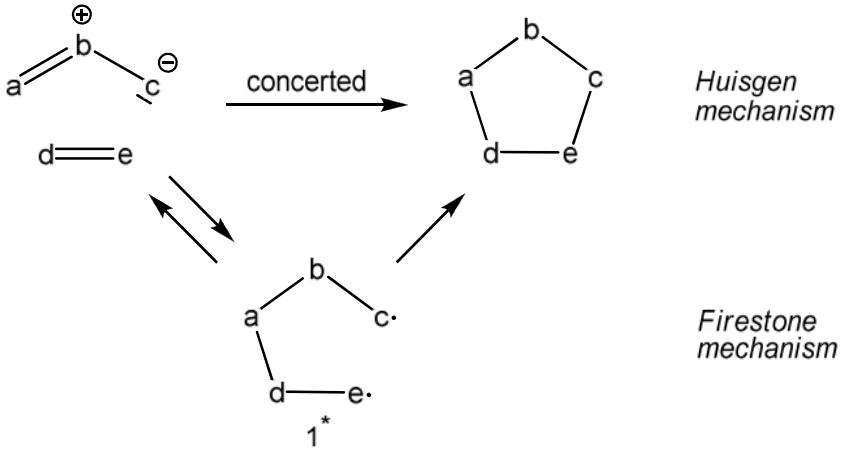


Figure 8. Huisgen Concerted Path and Firestone Diradical Path.[33]

The concerted reaction pathway is explained with the Frontier Molecular Orbital, which states that the highest occupied molecular orbital (HOMO) of one species will interact withthe lowest unoccupied molecular orbital (LUMO) of the other species. According to molecular orbital theory, there are three main patterns of interaction between HOMO and LUMO of reactant based on the different molecular structures of the dipoles (Figure 9).[34]

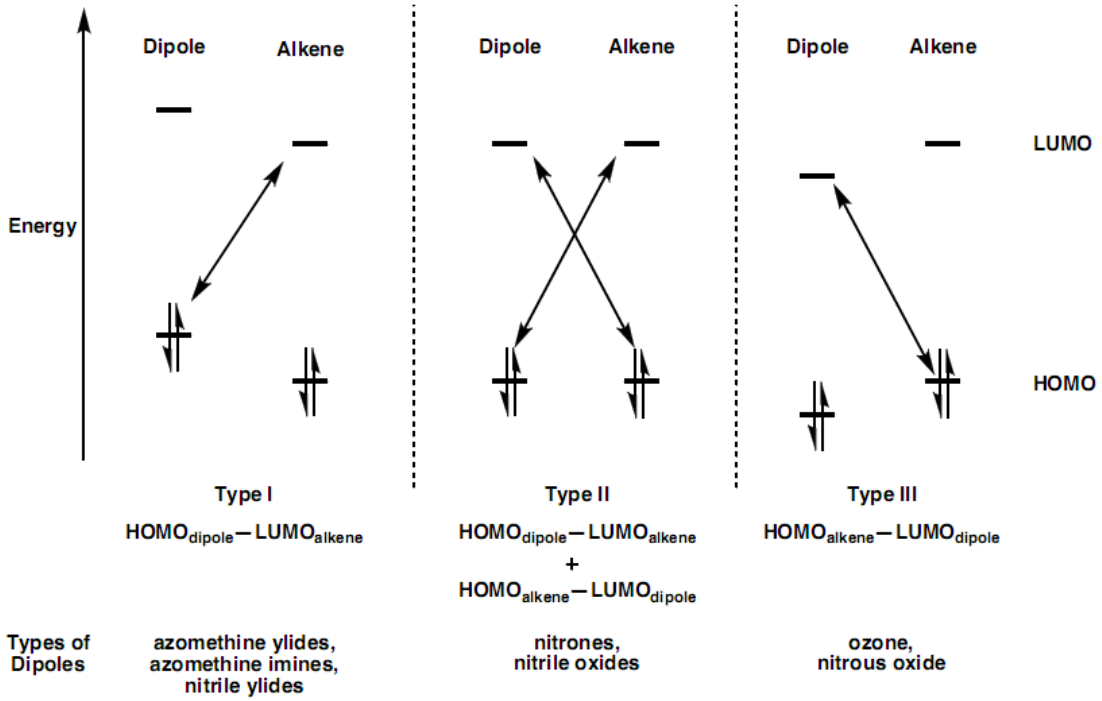


Figure 9. Different Type of Interaction between HOMO and LUMO in [3+2] Cycloadditio Reaction.[34]

Moreover, coordination of lewis acid to either dipole or alkene results in lowering the energy of LUMO, and a faster reaction rate (Figure.10).[34]

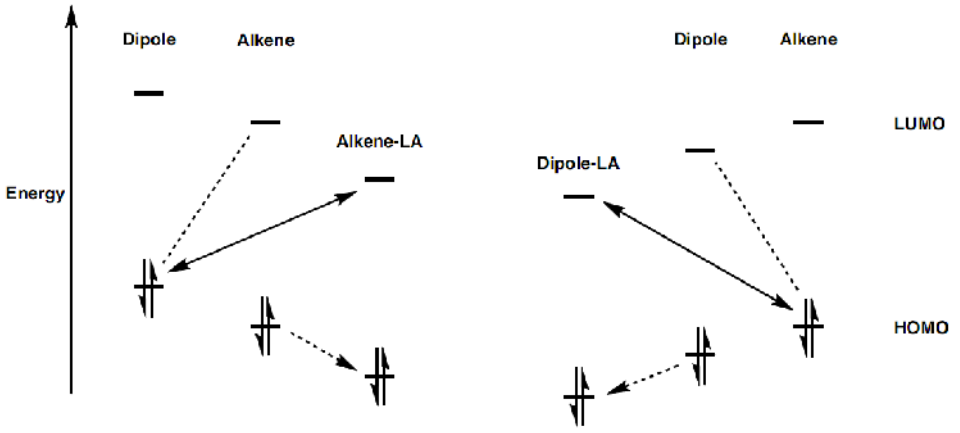


Figure 10. Effect of Lewis Acid on Energy of LUMO in [3+2] Cycloaddition Reaction.[34]

Catalyzed [3+2] Cycloaddition Reaction

Recently, [3+2] cycloaddition reactions were synthesized using N-alkylidene2-amino esters, which are known as azomethine yields. Various types of catalysts such as Fe(II), Ag(I), Li(I), organo catalysts, and composite catalysts have been used in [3+2] cycloaddition reaction of Azomrthine yields and polarized double bond in a stereoselective and regioselective manner. This methodology has been provided organic chemists with the tools necessary to synthesize opitcaly active pyrrolydines and proline derivatives.[35]In the first part of this research we applied Ag(I) as a catalyst to synthesise Fluoro- Pyrrolidine rings which has fluorine atom directly attached on the pyrrolidine rings.

Nitrone-Olefine [3+2] Cycloaddtion

The nitrone-olefine [3+2] cycloaddition reaction was done by Beckman in1890, when he reacted arly isocyanates with nitrones[36]. This first reaction was ignored till Huisgen began to do [3+2] cycloaddition in the 1960s. Nitrone-olefine cycloaddition almost follows the same guide lines as other [3+2] cycloaddition reactions in which 1,3 dipole (nitrone in this case) undergoes the concerted reaction with dipolarophile (alkene, alkyne, ect.) to form a five member ring product.

The presence of substituents plays a significant role on the regioselectivity of the cycloadditon reaction. The presence of an electron withdrawing group on the olefine will increase the dominance of $HOMO_{nitorne}/LUMO_{olefin}$ which will result in carbon five substittuted isooxazolidine. However, the presence of electron donating group will increase the dominance of the $LUMO_{nitrone}/HOMO_{olefine}$ which results in the carbon five substituted

isooxazolidine (Figure 11).[36] In the second part of this research we applied different kind of nitrones to synthesize fluoro-isoxazolidine rings which have the fluorine atom directly on the isoxazolidine rings.

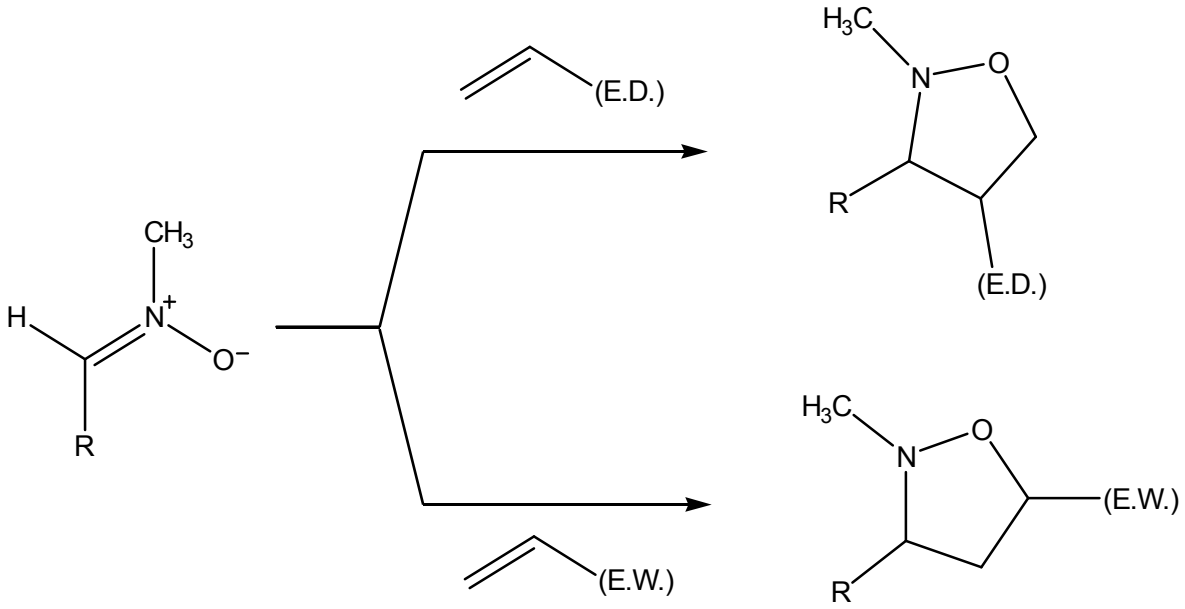


Figure 11. Effect of Different Substituted Olefin on Regioselectivity of the Product.

Importance of Pyrrolidine and Isoxazolidine

Pyrrolidine, tetrahydropyrrole, is a cyclic amine with five-member heterocycle made up of four carbon atoms and one nitrogen atom, which can be extracted from tobacco or carrot leaf.[37]. Proline and hydroxyproline are two amino acids that both have pyrrolindine ring as the central structure. Proline is applied for the production of cartilage and collagen in human body. Proline plays a significant role in maintaining muscle and joint flexibility and help to reduce sagging and wrinkling that accompany UV exposure and normal aging of the skin (Figure. 12).[38]

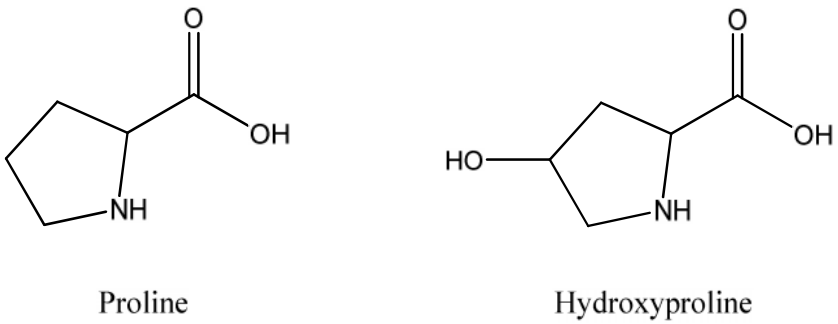


Figure 12. Amino Acids Containing Pyrrolidine.[42]

Pyrrolidines is in use as an intermediate for the production of various types of compounds like pharmaceuticals, pestiside, plasticizers, photo graphic chemicals, and crop protection agents. As an example, Pyrrolidine-1,2-dicarboxamides, known as novel series of orally bioavailable factor Xa inhibitors, that are used as anti-coagulate agents (Figure. 13).[39]

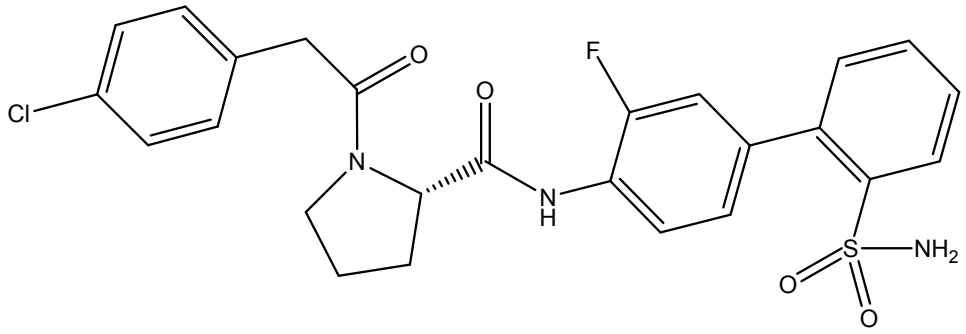


Figure 13. Example of Anti-coagulate Agents of Pyrrolidine.[39]

Isoxozalidine is a five membered heterocycle ring that made up of three carbons, one nitrogen atom, and one oxygen atom in the ring (Figure. 14).

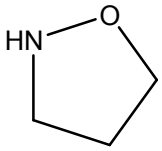
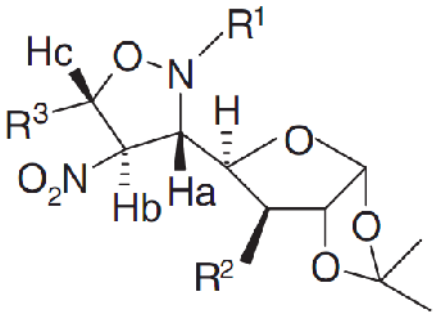


Figure 14. Structure of Isoxazolidine.

The isoxazolidine compound has a wide range of applications. It can be applied as building block molecules for synthesis of bioactive compounds such as antibiotics, antiviral, anticancer, and antifungal agents.[44] As an example, D-glucose that contains isoxazolidine ring in its alpha position has recently been introduced as a potent antibacterial agent (Figure 15).[40]



$R_{1=}$ Ph, $R_{2=}$ *p*-Br-Ph-CH-O, $R_{3=}$ Ar

Figure 15. Isoxazolidine as a Potent Antibacterial Agent[40].

CHAPTER II

EXPERIMENTAL

General

All glassware were cleaned with detergent, rinsed with water and acetone, and allowed to dry before use. N,N-diisopropylethylamine, triethyl 2-fluoro-2-phosphoethanoate, ethyl glyoxylate, glycine methyl ester hydrochloride, glycine ethyl ester hydrochloride, triethylamine, 4-cholorobenzaldehyde, 4-methoxybenzaldehyde, 2-furanaldehyde, benzaldehyde, N-methylhydroxylamine, N-butyllithium, and silver acetate, were commercially available and obtained from Sigma-Aldrich. Ethyl acetate, toluene, methylene chloride, ethylether anhydrous, tetrahydrofuran, and magnesium sulfate anhydrous were commercially available and obtained from Fisher Scientific. All acquired chemicals were used without further purification unless otherwise stated. Chromatographic silica gel (230-400 mesh) was also obtained from Fisher Scientific.

The ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Varian-PLUS 300 MHz spectrometer. The chemical shifts were reported as parts per million (ppm) downfield of tetramethylsilane (TMS) in δ units. The ^{1}H NMR spectra were recorded at 300.0 MHz with TMS (δ= 0 ppm) as the internal standard. The ^{13}C NMR spectra were recorded at 75.5 MHz with deuterated choloroform ($CDCl_3$, δ=77.0 ppm) as the internal standard. The ^{19}F NMR spectra were recorded at 282 MHz with trifluoroacetic acid (TFA) as the internal standard. Splitting patterns are Designed as ‘s’ for singlet, ‘d’ for doublet, ‘t’ for triplet, ‘q’ as quartet and ‘m’ for multiplet.

Coupling constant are reported in Hertz (Hz). All samples were dissolved in deuterated chloroform for NMR determination.

Procedure for Column Chromatography

A small piece of cotton is added to the bottom of a column, followed by a small layer of sand (1cm). Silica gel was added to the mobile phase and poured into the column and packed by blowing nitrogen gas until it reached near top of the column and finished with another layer of sand (1cm) on top of the silica. The sample to be chromatographed was then added to the top of the column and allowed to enter through the layer of sand. The liquid solvent (eluent) was then passed through the column by application of nitrogen gas under pressure. Equilibrium is established between the solute adsorbed in the adsorbent and the eluting solvent flowing down through the column. The individual components were collected as the solvent drips from the bottom of the column. Thus 100 mL fractions containing 100% hexane, and 5%, 10%, 15%, 20%, 25%, etc. ethyl acetate in hexane, respectively, were obtained.The solvents were evaporated under reduced pressure on a rotary evaporator and NMR spectra of the compound were recorded.

Preparation of Diethyl (*E*)-2- fluoromaleate **(1)**

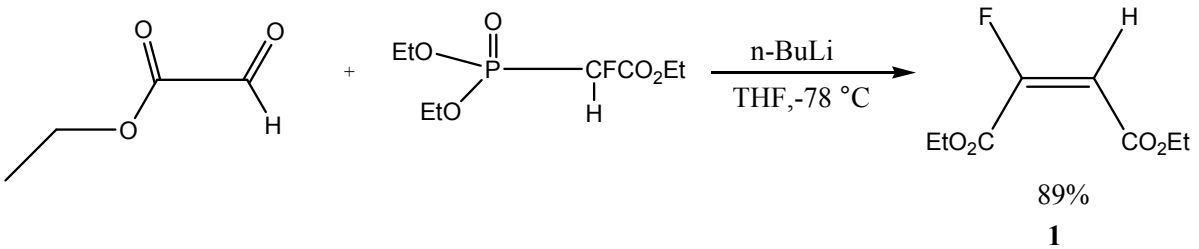


Figure 16. Reaction Scheme for the Synthesis of Fluoromaleate.

A three necked rubber capped 100 mL round bottom flask equipped with a magnetic stir ar was flamed dried. With a syringe triethyl-2-fluoro-2-phosphoethanoate (4.56 g, 16.8 m mol) in 20 mL of anhydrous tetrahydrofuran (THF) was added to the dried flask. Under nitrogen gas, the solution was cooled to -78 $^{\circ}$C which was obtained by adding dry ice and acetone together. After stirring for 20 minutes, 12.5 mL of 1.6 M n-butyllithium in hexane was gradually injected into the flask. Upon this injection, the solution turned to light yellow color. After 20 minutes of stirring, 5 mL of ethyl glyoxylate (5.15g, 50 mmol) was added with the syringe.

The mixture was allowed to stir at -78 $^{\circ}$C under an inert atmosphere. After one hour, the solution was allowed to stir overnight to warm to the ambient temperature. This solution was quenched with 80 mL of chilled deionized water and then was poured into a 250 mL separatory funnel. The extraction was done three times with ethyl ether (3× 20 mL). Finally, the solution was filtered through $MgSO_4$. The solvent was removed by evaporation on the rotovapor to give 3.18 g (89% yield) of diethyl (*E*)-2-fluoromaleate **(1)**.

Diethyl (*E*) -2-fluoromaleate (1): ^{1}H NMR ($CDCl_3$, TMS) δ 1.2-1.3 (m, CH_3), 4.2-4.3 (m, CH_2), 6.1 (d, J=16 Hz, CH);^{13}C NMR ($CDCl_3$, TMS): δ 14.1 (d, J=6.5 Hz, CH_3), δ 61.8 (d, J=0.3 Hz CH_2), δ 108.8 (d, J=0.3, <u>C</u>CF), δ 153.7 (d, J=3.6, CF), δ 160.7 (d, J=0.3 Hz <u>C</u>OOEt), δ 163.5 (d, J=0.3 Hz, F<u>C</u>OOEt); ^{19}F NMR: (TFA= 0, 76.6 relative to $CDCl_3$) δ=-35.4 (d, J=5.3 Hz)

General Procedure for the Synthesis of Aromatic α-Iminoester

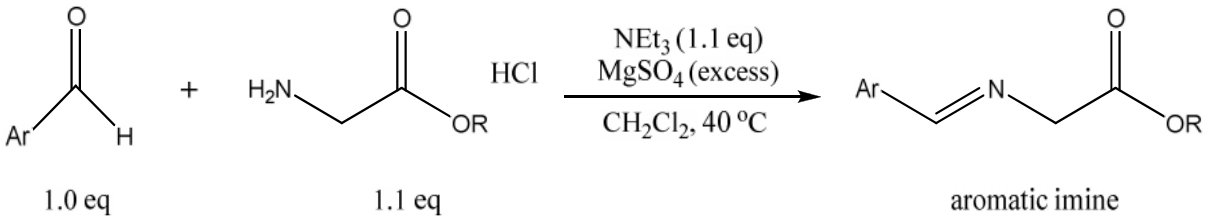
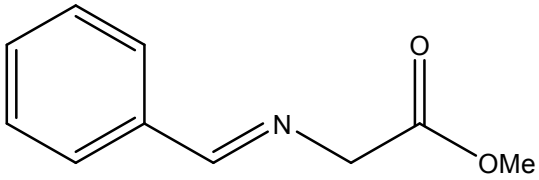
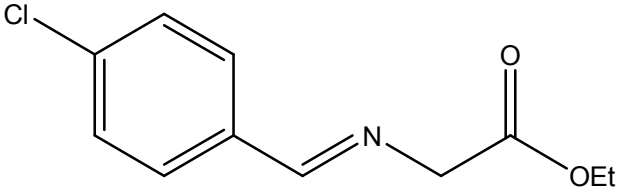


Figure 17. Reaction Scheme for the Synthesis of Aromatic Imines.

Table 2. Time Required to Synthesize the α-imines **(2-3)** and Yields Obtained.

Ar	**Time (hrs)**	**Imine Substrate**	**Yield (%)**
Ph	20	 **2**	77
4-Cl-Ph	24	 **3**	65

The α-iminoesters were prepared following the Longmire et al.[41] literature procedure as a guideline.

A suspension of glycine methyl ester hydrochloride (1.84 g, 1.1 eq) or glycine ethyl ester hydrochloride (2.05 g, 1.1 eq), NEt_3 (1.1 eq) and excess $MgSO_4$ in CH_2Cl_2 was stirred at

25°C for 1 hour. An aromatic aldehyde (1.0 eq) was added and the reaction stirred and refluxed at 40 ºC for a duration that varied (see Table 2). $MgSO_4$ was removed by filtration and the filtrate was washed once with H_2O. The aqueous phase was extracted once with CH_2Cl_2 and the combined organic layers were washed with brine. The organic phase was dried over $MgSO_4$, filtered and then concentrated via rotary evaporator (rotovap) to afford the imine substrates (**2-3)**.

(Benzylidene-amino)-acetic acid methyl ester (2): ^{1}H NMR: ($CDCl_3$, TMS) δ 3.74 (s, 3H, CH_3), δ 4.38 (d, J=1.2 Hz, 2H, CH_2), δ 7.38-7.76 (m, 5H, C_6H_5), δ 8.25 (s, 1H, CH); ^{13}C NMR ($CDCl_3$, TMS) δ 52.33 (m, OCH_3), δ 62.24 (t, CH_2), δ 127.88-140.08 (m, C_6H_5), δ 165.72 (d, J=14.65 Hz, CH), δ 170.82 (s, CO).

[(4-Chloro-benzylidene)-amino]-acetic acid ethyl ester (3): ^{1}H NMR: ($CDCl_3$, TMS) δ 1.95 (t, 3H, CH_3), δ 4.24 (m, 2H, CH_2N) δ 4.38 (d, J=1.5 Hz, 2H, CH_2N), δ 7.20-7.83 (m, 5H, C_6H_4), δ 8.24 (s, 1H, CH); ^{13}C NMR: ($CDCl_3$, TMS) δ 14.39 (m, CH_3), δ 61.27 (s, O<u>C</u>H_2CH_3), δ 62.00 (t, CH_2N), δ 127.90-139.65 (m, C_6H_4), δ 164.19 (d, J=19.18 Hz, CH), δ 170.14 (s, CO).

<u>Preparation of Aromatic Nitrones</u>

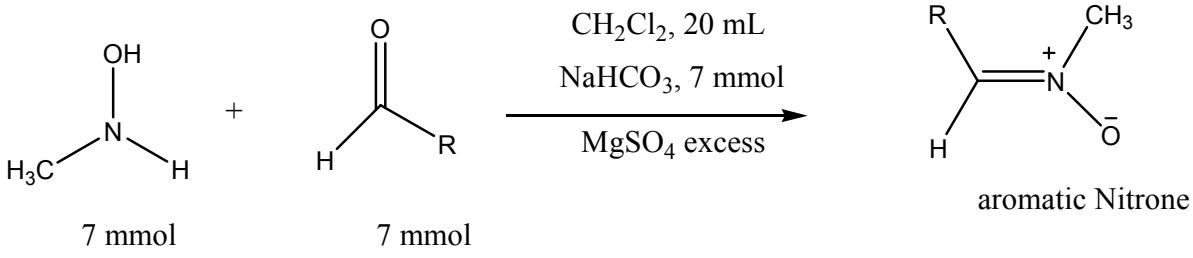
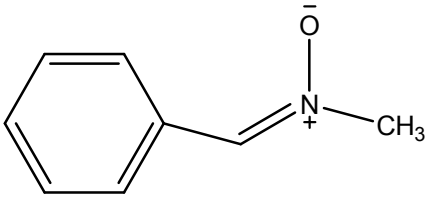
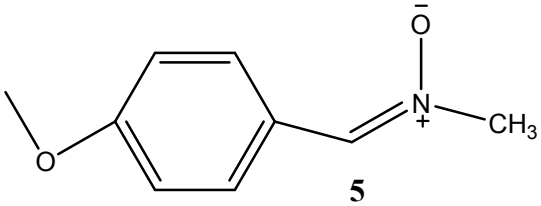
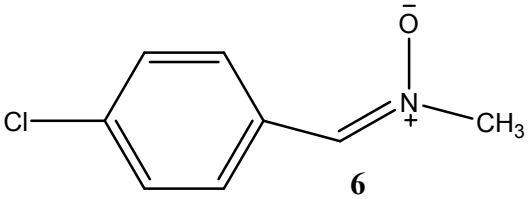
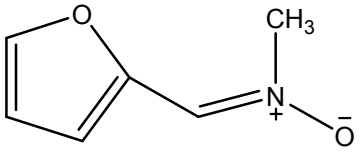


Figure 18. Reaction Scheme for the Synthesis of Nitrones.

Table 3. Time Reaction to Synthesis the Nitrones **(4-7)** and Percent Yields.

R	**Time (hrs)**	**Aromatic Nitrones**	**Yield (%)**
Ph	18	 **4**	77
4-OMe-Ph	18	 **5**	73
4-Cl-Ph	18	 **6**	80
Furyl	18	 **7**	85

A suspension of N-methylhydroxylamine (7 mmole), anhydrous sodium bicarbonate (7 mmol), anhydrous magnesium sulfate (excess), freshly distilled methylene chloride (20 mL), and respective aldhyde (7 mmol) poured in a clean100 mL round bottle flask. The reaction is refluxed overnight for 18 hrs. Magnesium sulfate was then filtered off by gravity filtration and washed two times with distilled methylene chloride (30 mL). The filtrate was evaporated

under reduced pressure by means of a rotoevaporator resulting in the crude product. Nitrones **(4-7)** were purified via flash chromatography (Table 3).

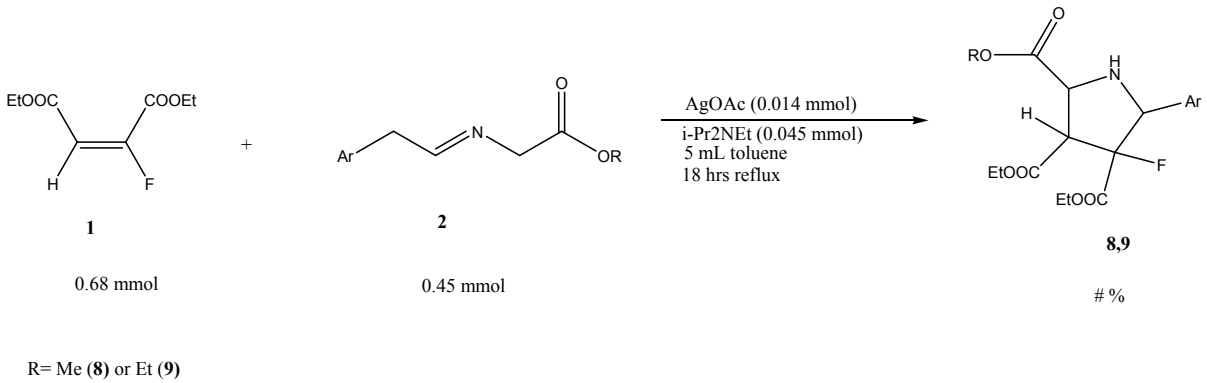
Phenyl-N-methylnitrone (4): ^{1}H NMR: ($CDCl_3$, TMS) δ 3.8 (s, 3H, CH_3), δ 7.3-8.1 (m, 5H, C_6H_5); ^{13}C NMR: ($CDCl_3$, TMS) δ 54.1 (s, CH_3), δ 128.9 (s, 4 (CH)), δ129.4 (s, CH)δ 131.5 s, C=N).

4-Methosyphenyl-N-methylnitrone (5): ^{1}H NMR: ($CDCl_3$, TMS) δ 3.8 (s, 3H, CH_3), δ 3.9 (s, H, CHN), δ 6.9-7.3(m, 5H, C_6H_5); ^{13}C NMR: ($CDCl_3$, TMS) δ 53.6 (s, 3H, OCH_3), δ 55.3 (s, CH_3), δ 114.3 (s, CH, meta-C_6H_5), δ 130.4 (s, CH, ortho-C_6H_5), δ 131.5 (s, C=N), δ 160.5 (s, C-O).

4-Cholorophenyl-N-methylnitrone (6): ^{1}H NMR: ($CDCl_3$, TMS) δ 3.8 (s, 3H, CH_3), δ 7.4-8.3 (m, 5H, C_6H_5); ^{13}C NMR: ($CDCl_3$, TMS) δ 54.1 (s, CH_3), δ 128.9 (s, 4 (CH)), δ120.4 (s, CCl) δ 131.5 (s, C=N).

Furan-2-yl-N-methylnitrone (7): ^{1}H NMR: ($CDCl_3$, TMS) δ 3.8 (s, 3H, CH_3), δ 6.5, δ 7.4-7.7 (m, 3H, Furan), δ 7.2 (s, 1H, CH); ^{13}C NMR: ($CDCl_3$, TMS) δ 52.7 (s, CH_3), δ 112.3, δ 115.3, δ 126.3, δ 143.6 (m, Furan), 146.6 (s, OCH).

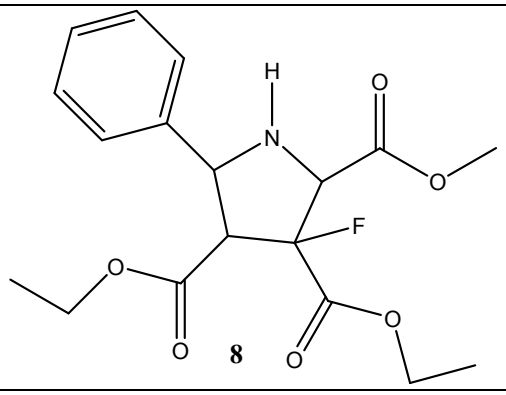
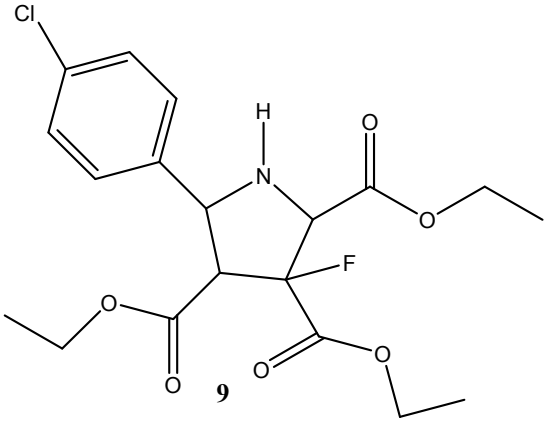
Preparation of Fluorinated Pyrrolidines **(8-9)**



R= Me (**8**) or Et (**9**)

Figure 19. Reaction Scheme for Synthesis of Fluorinated Pyrrolydines (**8-9).**

Table 4. Time for Preparation of Pyrrolidines (**8-9)** and Percent Yields.

Ar	**Time (hrs)**	**Pyrrolidine**	**Yield (%)**
Ph	20	 **8**	65
4-Cl-Ph	72	 **9**	77

The [3+2] cycloaddition product was prepared following the Longmire et al[41]. literature procedure as a guideline.The catalyst was prepared by stirring AgOAc (2.3 mg, 0.014 mmol) in distilled toluene (2 mL) for 1h. The imine substrate (**2-3**) (87.84 mg, 0.45 mmol) was added as a solution in distilled toluene (3mL) followed by diethyl (*E*) 2-fluoromaleate (**1**) (90 mg, 0.68 mmol) and i-Pr_2Net (8 µL, 0.045 mmol). The reaction was refluxed using a heating mantle (110 °C) for 20 hours. The volume of toluene was reduced via rotovap and the product was isolated by silica gel chromatography (Hexanes/EtOAc, 3:1)

3,4-diethyl 2-methyl 3-fluoro-5phenylpyrrolidine-2,3,4-tricarboxylate (8): ^{1}H NMR: ($CDCl_3$, TMS), δ 1.2 (m, 6H, $CH_2C\underline{H}_3$**),** δ 2.0 (s, H, N<u>H</u>), δ 3.7 (s, 3H, $OC\underline{H}_3$), δ 3.8-4.0 (m, H, C-3<u>H</u> pyrrolidine), δ 4.2 (m, 4H, $OC\underline{H}_2CH_3$), δ 4.6 (d, H, C-5<u>H</u> pyrrolidine), δ 7.2-7.5 (m, 5H, C_6H_5); ^{13}C NMR: ($CDCl_3$, TMS),δ 13.8 (d, J=0.7, $OCH_2\ \underline{C}H_3$), δ 53.2 (m, C-3 pyrrolidine), δ 58.5 (d, C-2 pyrrolidine), δ 61.0 (d, C-4 pyrrolidine), δ 62.0 ($O\underline{C}H_2\ CH_3$), δ 128.0-140.0 (m, $\underline{C}_6H_5$), δ164.0 (d, $CF\underline{C}OOCH_2CH_3$), δ171.3 (d,C-3 $COOCH_2CH_3$), δ 171.7 (d, C-4, $COOCH_3$); ^{19}F NMR: (TFA= 0, 76.6 relative to $CDCl_3$) δ -78.2 (d,d, CF), δ -83.5 (d,d, CF)

Triethyl 5-(4-cholorophenyl)-3-fluoropyrrolidine-2,3,4-tricarboxylate (9): ^{1}H NMR: ($CDCl_3$, TMS), δ 1.3 (m, 6H, $CH_2C\underline{H}_3$**)**, δ 3.8-4.0 (m,3H, C-3<u>H</u> pyrrolidine), δ 4.2 (m, 6H, $OC\underline{H}_2CH_3$), δ 4.6 (d, H, C-5<u>H</u> pyrrolidine), δ 7.2-7.9 (m, 5H, C_6H_5); ^{13}C NMR: ($CDCl_3$, TMS), δ 14.8 (d, J=0.7, $OCH_2\ \underline{C}H_3$), δ 54.3 (m, C-3 pyrrolidine), δ 59.5 (d, C-2 pyrrolidine), δ 62.0 (d, C-4 pyrrolidine), δ 128.0-140.0 (m, $\underline{C}_6H_5$), δ168.0 (d, $CF\underline{C}OOCH_2$), δ172.4 (d, C-3 $COOCH_2CH_3$), δ 172.7 (d, C-4, $COOCH_3$); ^{19}F NMR: (TFA= 0, 76.6 relative to $CDCl_3$) δ -79.2 (d,d, J=27.8 Hz, CF)

Preparation of Fluorinate Isoxazolidines (**10-13)**

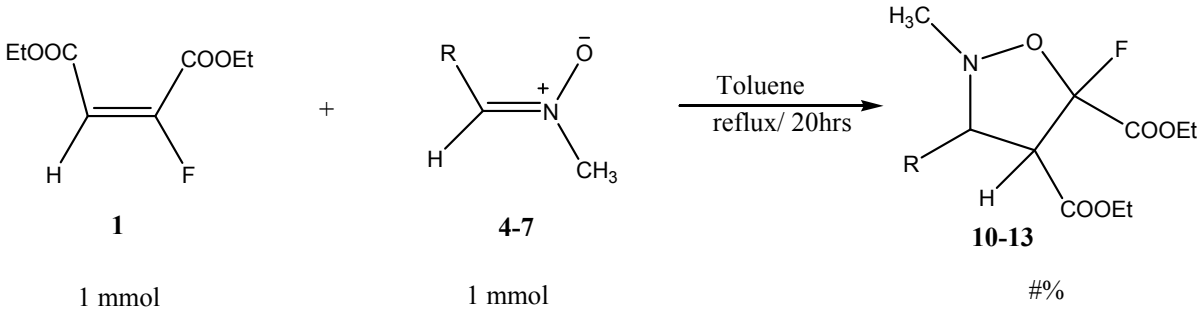
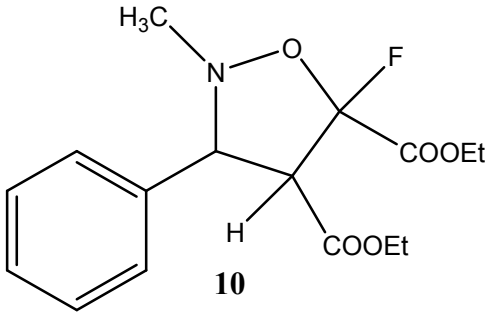
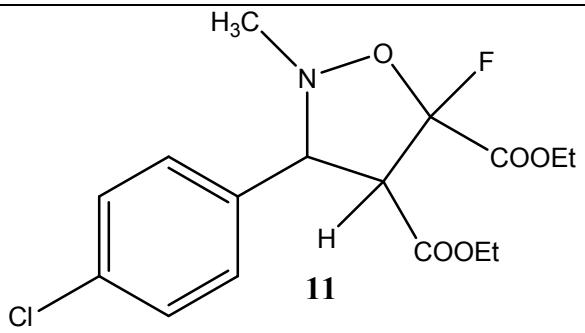
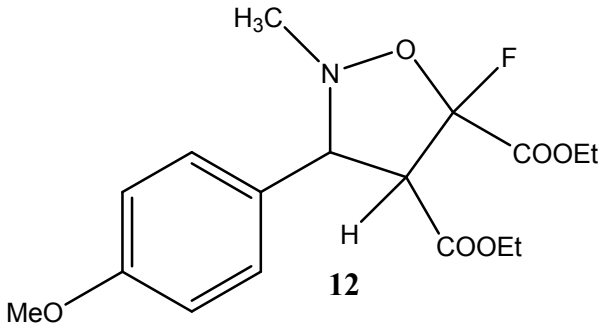
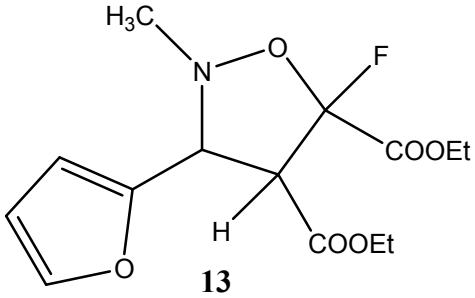


Figure 20. Reaction Scheme for the Synthesis of Fluorinated Isoxazolidines **(10-13).**

Table 5. Time for Preparation of Isoxazolidine (**10-13**) and Percent Yields.

Ar	**Time (hrs)**	**Isoxazolidine**	**Yield (%)**
Ph	20	 **10**	76
4-Cl-Ph	20	 **11**	78

4-OMe-Ph	20	 **12**	70
Furano	20	 **13**	70

To a 25 mL round bottom flask was added a stir bar, nitrone (**3-7**) (1 mmol), diethyl (*E*) -fluoromaleate (**1**) (1mmol), and 4 mL of toluene. The reaction was refluxed for 20 hours at 110 $^{\circ}$C and the solvent was evaporated off under reduced pressure by use of a rotary evaporator. The fluorinated isoxazolidine (**10-13**) was purified via flash chromatography (Hexanes/EtOAc, 3:1).

Diethyl 5-fluoro-2-methyl-3phenylisoxazolidine-4,5-dicarboxylate (10): ^{1}H NMR: ($CDCl_3$, TMS) δ 1.3 (t, 6H, CH_3), δ 2.7 (s, 3H, $NC\underline{H}_3$), 3.84-3.96 (m, H, C-4 isoxazolidine), 4.0-4.1 (m, 4H, $OC\underline{H}_2CH_3$), δ 4.2-4.3 (d,d J=3 C-3 isoxazolidine), δ7.3-7.5 (m, 5H, C_6H_5); ^{13}C NMR: ($CDCl_3$, TMS) δ 14 (d, $OCH_2\underline{C}H_3$), δ 43.4 (s, $N\underline{C}H_3$), δ 61.8 (d, C-4 isoxazolidine), δ 63.2 (d, $O\underline{C}H_2CH_3$), δ 76.1 (d, C-3 isoxazolidine), δ 117 (d, $\underline{C}F$), δ 128.4 (m, Ph), δ 135 (m C-1 Ph), δ 164 (d, $CF\underline{C}OOCH_2CH_3$), δ 167 (d, $CH\underline{C}OOCH_2CH_3$); ^{19}F NMR: (TFA= 0, 76.6 relative to $CDCl_3$) δ -20.6 (d, J=22.6 Hz, $C\underline{F}$).

Diethyl 3-(4-cholorophenyl)-5-fluoro-2-methylisoxazolidine-4,5-dicarboxylate (11):

^{1}H NMR: ($CDCl_3$, TMS) δ 1.4 (t, 6H, CH_3), δ 2.7 (s, 3H, $NC\underline{H}_3$), 3.84-3.96 (m, H, C-4 isoxazolidine), 4.1-4.2 (m, 4H, $OC\underline{H}_2CH_3$), δ 4.2-4.3 (d,d J=3 C-3 isoxazolidine), δ7.4-7.5 (m, 5H, C_6H_5); ^{13}C, NMR: ($CDCl_3$, TMS) δ 14 (d, $OCH_2\underline{C}H_3$), δ 43.4 (s, $N\underline{C}H_3$), δ 61.8 (d, C-4isoxazolidine), δ 63.2 (d, $O\underline{C}H_2CH_3$), δ 76.1 (d, C-3 isoxazolidine), δ 120 (d, $\underline{C}F$), δ 128.4 (m, Ph), δ 135 (m C-1 Ph), δ 135 (m $\underline{C}$C-Ph), δ 164 (d, $CF\underline{C}OOCH_2CH_3$), δ 167 (d, $CH\underline{C}OOCH_2CH_3$); ^{19}F NMR: (TFA= 0, 76.6 relative to $CDCl_3$) δ -20.9 (d, J=20.9 Hz, $C\underline{F}$).

Diethyl 3-(4-methoxyphenyl)-5-fluoro-2-methylisoxazolidine-4,5-dicarboxylate (12):

^{1}H NMR: ($CDCl_3$, TMS) δ 1.4 (t, 6H, CH_3), δ 2.7 (s, 3H, $NC\underline{H}_3$),δ 3.8 (s, 3H, $OC\underline{H}_3$) 3.84-3.96 (m, H, C-4 isoxazolidine), 4.1-4.2 (m, 4H, $OC\underline{H}_2CH_3$), δ 4.2-4.3 (d,d J=3 C-3 isoxazolidine), δ7.0-7.3 (m, 5H, C_6H_5); ^{13}C NMR: ($CDCl_3$, TMS) δ 14.1 (d, $OCH_2\underline{C}H_3$), δ 43.5 (s, $N\underline{C}H_3$),δ 55.5 (s, $O\underline{C}H_3$), δ 61.9 (d, C-4isoxazolidine), δ 63.3 (d, $O\underline{C}H_2CH_3$), δ 76.8 (d, C-3 isoxazolidine), δ 114.4 (m, metha- C- Ph), δ 120 (d, $\underline{C}F$), δ 130 (m ortho-C-Ph), δ 136 (m $\underline{C}$1-Ph), δ 160 (s, $\underline{C}OCH_3$), δ 164 (d,$CF\underline{C}OOCH_2CH_3$), δ 167 (d, $CH\underline{C}OOCH_2CH_3$); ^{19}F NMR: (TFA= 0, 76.6 relative to $CDCl_3$) δ -20.5 (d, J=20.9 Hz, $C\underline{F}$).

Diethyl 5-fluoro-3-(furan-2-yl)-2-methylisoxazolidine-4,5-dicarboxylate (13):

^{1}H NMR: ($CDCl_3$, TMS) δ 1.4 (t, 6H, CH_3), δ 2.8 (s, 3H, $NC\underline{H}_3$), 4.1 (m, H, C-4 isoxazolidine), 4.1-4.2 (m, 4H, $OC\underline{H}_2CH_3$), δ 4.4-4.5 (d,d J=3 C-3 isoxazolidine), δ 6.29 (m, 2H, CH), δ 7.3(d, H, CH); ^{13}C NMR: ($CDCl_3$, TMS) δ 14.1 (d, $OCH_2\underline{C}H_3$), δ 43.5 (s, $N\underline{C}H_3$),δ 55.5 (s, $O\underline{C}H_3$), δ 62 (d, C-4isoxazolidine), δ 63.5 (d, $O\underline{C}H_2CH_3$), δ 70 (d, C-3 isoxazolidine), δ 110.4,δ 143,δ 144 (s, Furan), δ 164 (d,$CF\underline{C}OOCH_2CH_3$), δ 164 (d, $CH\underline{C}OOCH_2CH_3$); ^{19}F NMR: (TFA= 0, 76.6 relative to $CDCl_3$) δ -20.9 (d, J=20.5 Hz, $C\underline{F}$)

CHAPTER III

RESULTS AND DISCUSSION

Sythesis of Diethyl (*E*)-fluoro maleate **(1)**

Diethyl (*E*)-fluoromaleate compound **(1)** was prepared by applying the Horner-Wardsworth-Emmons reaction with a good yield of 89%. The compound **(1)** was prepared by reacting ethyl glyoxylate with tri-ethyl-2-fluoro-2-phosphoethanoate in the presence of n-butyl lithium and anhydrous THF. The reaction condition required completely dry in order to avoid side reactions. From the NMR data, it was concluded that this reaction gives only E isomer (Figure 21).

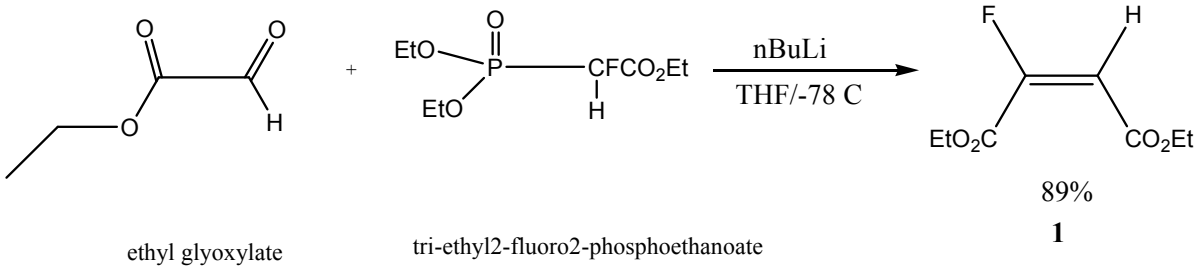


Figure 21. Reaction Scheme for Synthesis of Diethyl (*E*)-flouromaleate

The proposed mechanism for synthesis of compound **(1)** is based on Hornor-Wardsworth-Emmons reaction that is described in (Fugure.22).

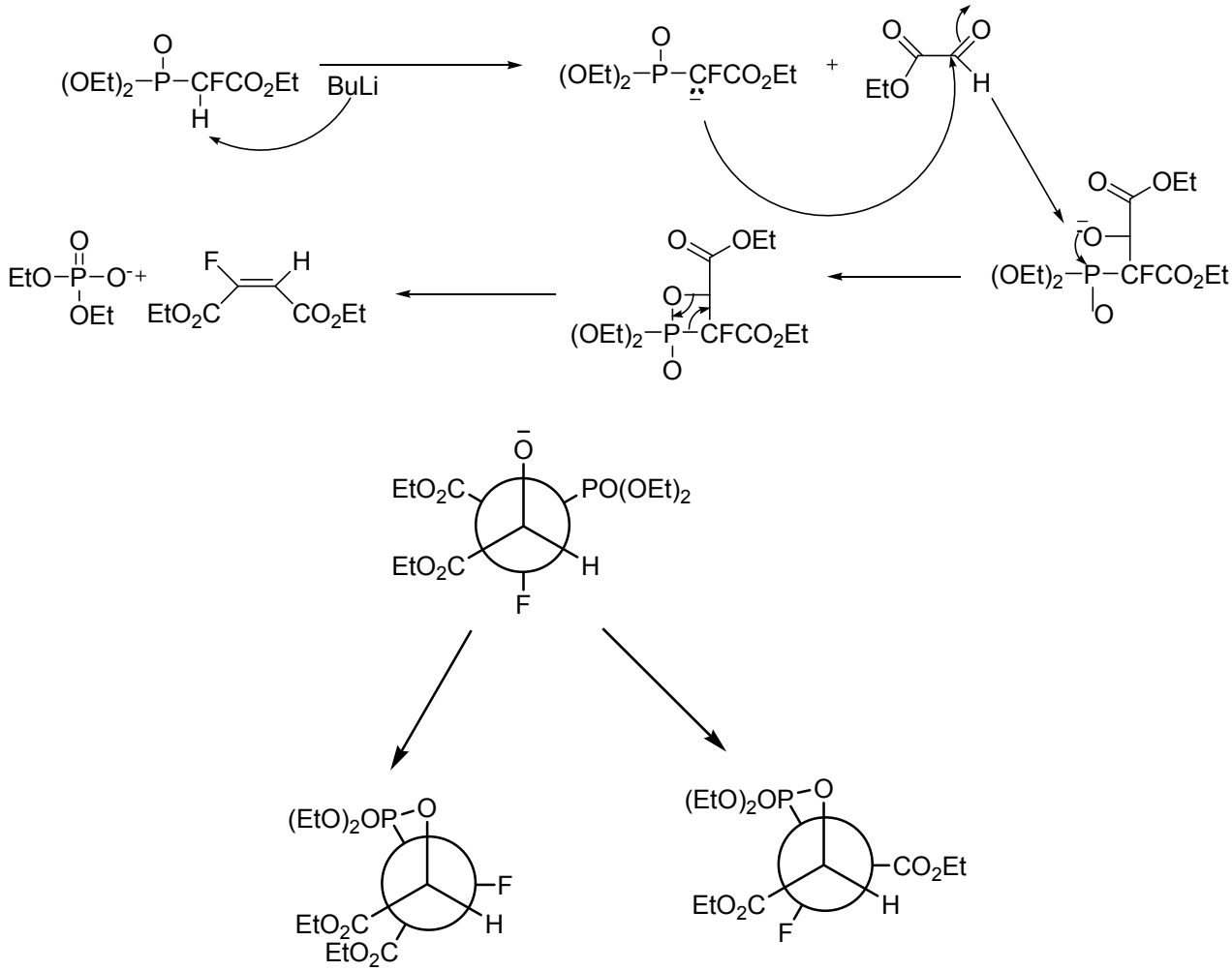


Figure 22. Proposed Mechanism for Synthesis of Diethyl (*E*)-fluoromaleate.

Synthesis of Aromatic α-Iminoesters **(2-3)**

The aromatic imines **(2-3)** were synthesized from the refluxing of glycine-ethyl or methyl-ester hydrochloride with a mixture of an aromatic aldehyde, tri-ethylamine, and $MgSO_4$ in methylencholoride. The yields were between 65-77% (Figure 23).

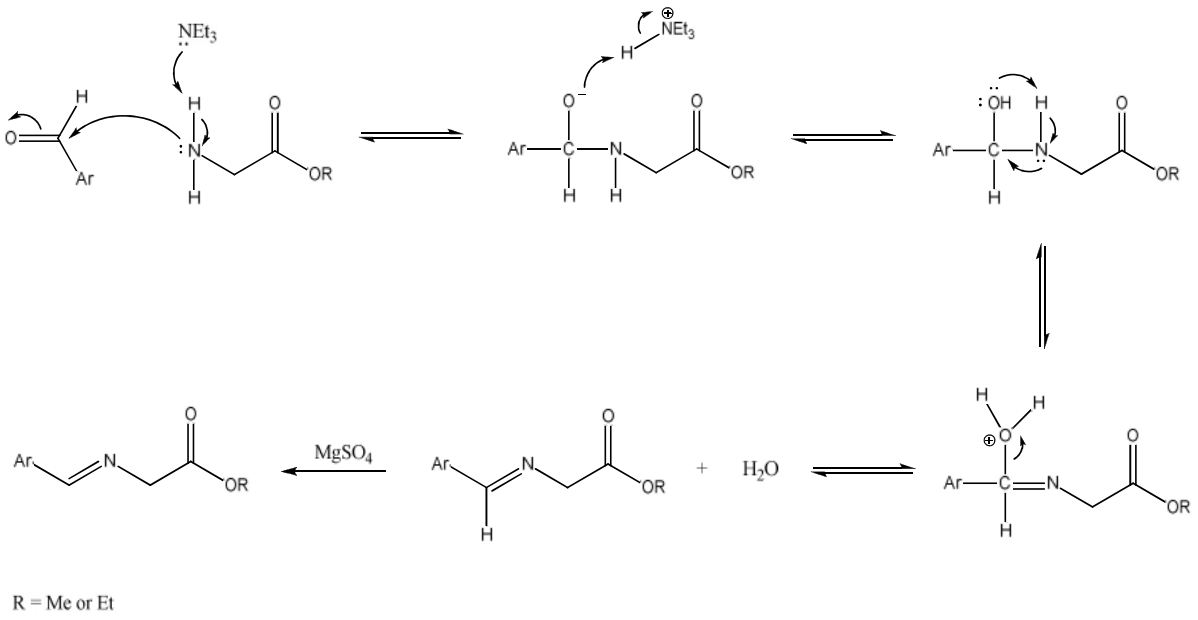


Figure 23. Proposed Mechanism for Synthesis of Aromatic Imines.

Imines are very sensitive to the moisture and hydrolysis, and sometimes it is difficult to isolate and purify them due to their sensitivity to moisture. Imine hydrolysis is the reverse of the process of its formation[45]. First, the synthesis of imines was attempted at room temperature. It was discovered that the reaction, despite the presence of excess $MgSO_4$, as a water absorbent, was not being driven to completion at that temperature, Although several attempts were made to purify the product by applying flash chromatography, a large amount of starting material remained. Purer and higher yield of products were obtained by refluxing the reaction at 40 °C. After obtaining an ^1H NMR spectrum on a once purified and stored at 0 °C sample of imine **2,** the effects of hydrolysis on an imine were witnessed for the second time.

Synthesis of Aromatic N-Methylnitrones **(4-7)**

The production of the series of aromatic N-methylnitrones is achieved by the condensation reaction of a range of substituted aldehydes with N-methylhydroxylamine. N-methylhydroxylamine is stored as a hydrochloride salt and must be activated with the addition of a weak base, $NHCO_3$, to let the condensation reaction to occur. Magnesium solfate is also added as a water absorbent. The reaction mixture is refluxed at 40 °C for 20 hours. The production of aromatic N-methylnitrones **(4-7)** are recorded with a yields of 77-85% (Figure 24).

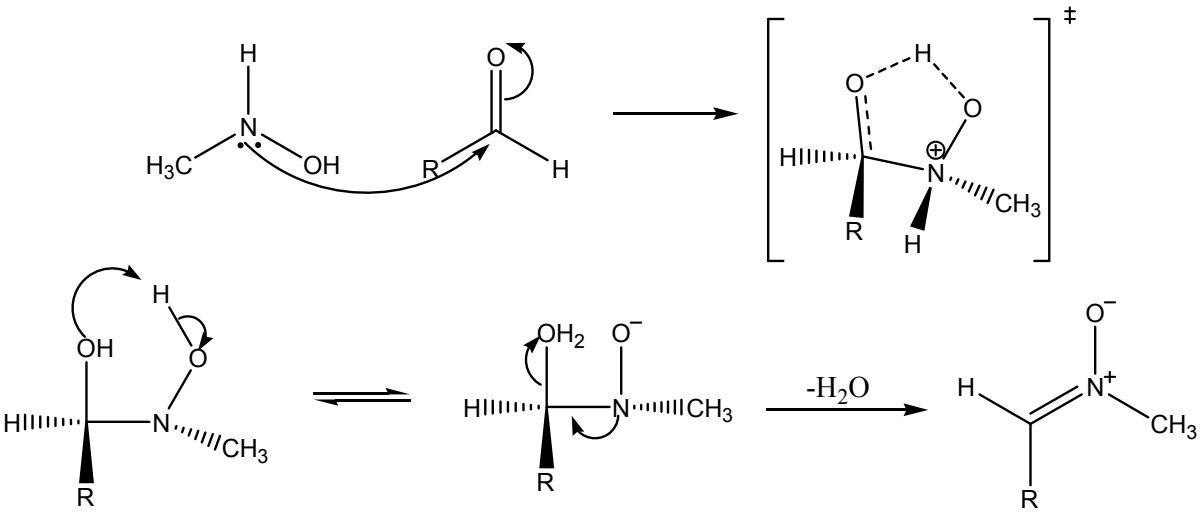


Figure 24. Proposed Mechanism for Synthesis of Aromatic N-methylnitrones **(4-7)**.

Nitrones are unstable at room temperature. All nitrones must be stored below 0 °C. The concentration of N-methylhydroxylamine in methylencholoride, plays an important role for the reaction. Since most hydroxylamine decomposition pathways are bimolecular so the concentration must be high enough to undergo the desired intermolecular reaction but not so

high as to undergo bimolecular isomerization. The presence of water can result in inhibition of the reaction to go to completion.

(3+2) Cycloaddition Reaction of Diethyl (*E*)-fluoromaleate with Aromatic α-Iminoesters

The (3+2) cycloaddition adducts **(8-9)** were synthesized from refluxing of diethyl (*E*)-fluoromaleate **(1)** and a series of aromatic imines **(2-3)** in a solution mixture of AgOAc, toluene, and iPr_2Net. The reactions were achieved with the products yields between 65-77%.

According to the results, it seems that products with an electron withdrawing group on the phenyl part of the imine leads to higher yields. The (3+2) cycloaddition products might be generated as shown in (Figure 25).

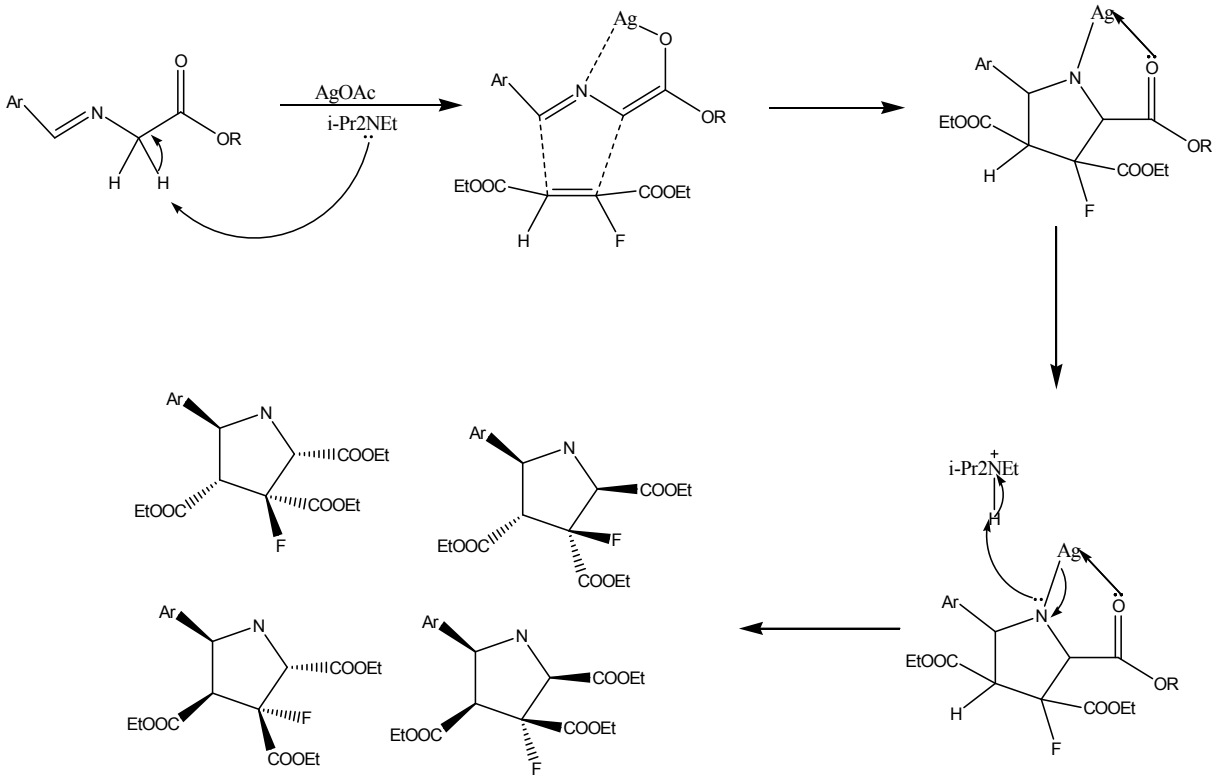


Figure 25. Proposed Mechanism for Synthesis of Fluoro-pyrrolidine.

The proposed mechanism, shown in (Figure 25), suggests that cycloaddition process between the dipole, aromatic imines, and the dipolarophile, diethyl (*E*)-fluoromaleate **(1)**, occurs according to the principles of Michael addition. The dipole would attack the carbon of the dipolarophile that attached to the fluorine atom which is more positive based on high electronegativity of fluorine. This concept was confirmed using COSY NMR (Figure 27).

The synthesis of triethyl 3-fluoro-5-phenylpyrrolidine-2,3,4-tricarboxylate **(8)** was achieved with a 65% yield, containing the mixture of cis, and trans isomers. The ^{19}F NMR spectrum showed two fluorine products are present (Figure 26). The ^{19}F NMR results shows two different sets of peaks of major product (-83.5 ppm, -84.0ppm). In the first set of peaks the hydrogen atom on C-1 and the hydrogen on C-3 are coupled with the fluorine atom on C-2 into doublet. The J coupling value for fluorine is 26.08 in both cases that confirms the fluorine atom is cis to these two hydrogen atoms. However, there is no coupling between fluorine and the hydrogen on C-4 that confirms that the hydrogen atom on C-4 and fluorine on C-2 are trans to each other. There is also another set of peaks (-78.2 ppm) which are related to the minor product.

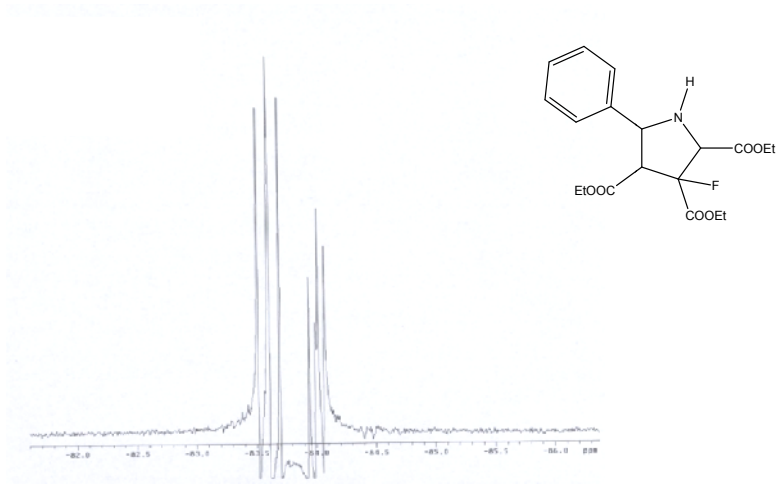


Figure 26. ^{19}F NMR Spectra of Compound **(8)**.

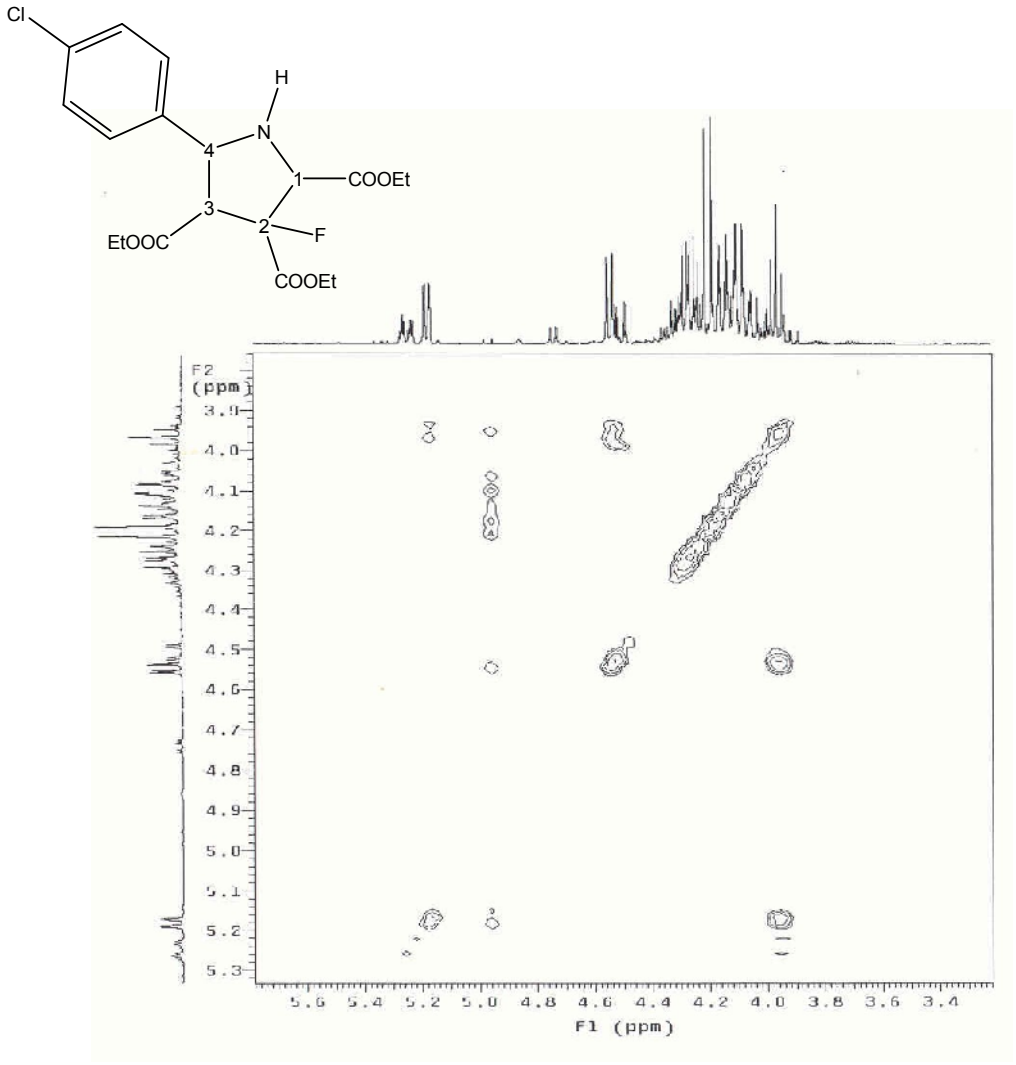


Figure 27. COSY NMR Confirming Regioselectivity of **(9)**.

Figure 27 shows a COSY of triethyl 5-(4-chlorophenyl)-3-fluoropyrrolidine-2,3,4-tricarboxylate **(9)** that reveals the correlation between hydrogens on the pyrrolidine derivative. It can be seen that C-3 hydrogen (3.90-4.00 ppm) correlate with the C-4 hydrogen (4.56-4.58 ppm), which support the validity of the proposed mechanism.

The synthesis of Triethyl 5-(4-chlorophenyl)-3-fluoropyrrolidine-2,3,4-tricaboxylate **(9)** was achieved with a 77% yield, that contain only one isomer. The ^{19}F NMR results shows that the hydrogen atom on C-1 and the hydrogen on C-3 are coupled with the fluorine atom

on C-2 in to doublet. The J coupling value for fluorine is 27.82 Hz in both cases that confirms the fluorine atom is cis to these hydrogen. However, there is no coupling between fluorine and the hydrogen on C-4 that confirms the hydrogen atom on C-4 and fluorine on C-2 are trans to each other (Figure 28).

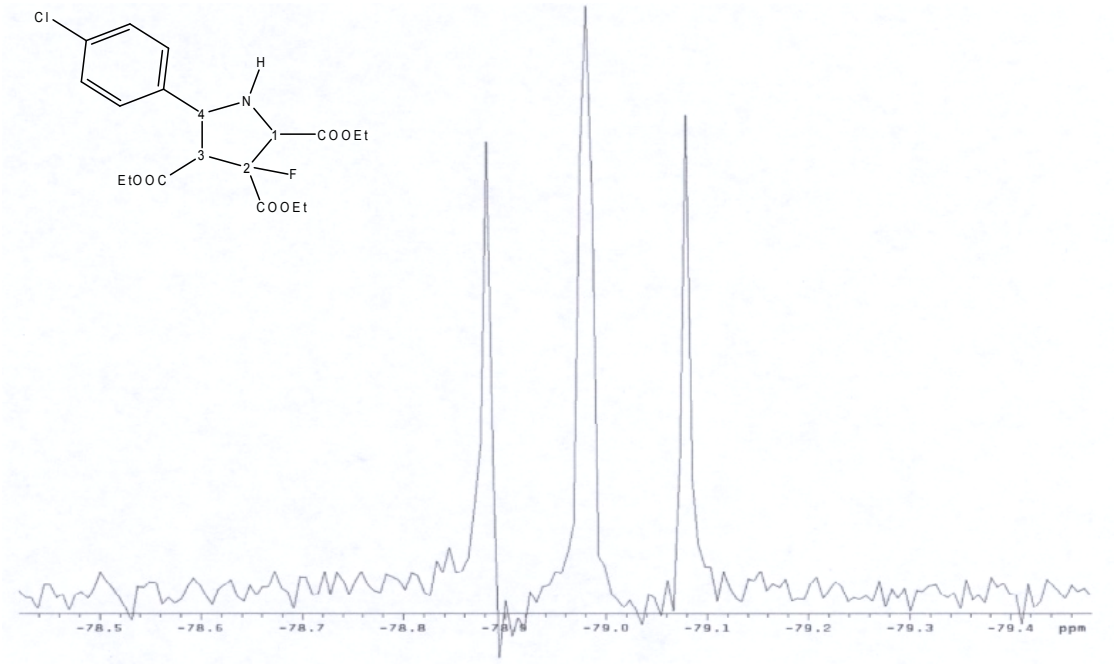


Figure 28. ^{19}F NMR Spectra of Compound **(9)**.

Synthesis of Fluorinated Isoxazolidine Derivatives **(10-13)**

The [3+2] adducts **(10-13)** were synthesized from refluxing of diethyl (*E*)- fluoromaleate and substituted N-methylnitornes **(4-7)** in toluene for 20 hours. The reaction were achieved with the products having yields between 70-78% (Figure. 29).

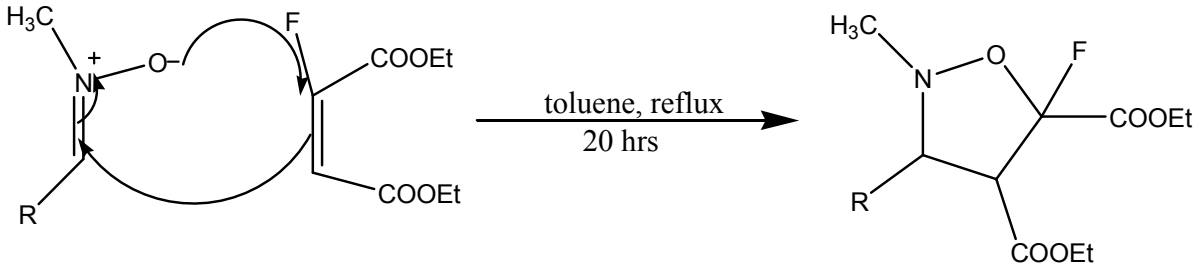


Figure 29. Proposed Mechanism for Synthesis of Fluoroisoxazolidines **(10-13)**.

In the nitrone-olefine [3+2] cycloaddition reaction, the presence of EWG on the dipolarophile creates a reaction site that favors the attack of the oxygen on the α-carbon, as opposed to the attack on the β-carbon. This creates a regiospecific isoxazolidine structure that is the major isomer of this reaction (Figure. 30).The presence of water was also observed to hinder the the yield of the reaction due to hydrolises of nitrones.

Major Minor

Figure 30. Major and Minor Isoxazolidine Products.

Based on FMO (Frontier Molecular Orbital), that helps to explain the nitrone-olefine [3+2] cycloaddition reaction, the most favorable orientation is the one invovling the frontier orbitals of nitrone and olefine with the closest energies. According to calculation with Spartan 08 , it os believed that LUMO of **(1)** will interact with HOMO of **(4)** resulting in the

C-5 substituted isoxazolidine compounds. This interaction is believed to occur for the reaction of nitrones **(5-7)** with diethyl (*E*)-fluoromaleate **(1)** (Figure. 31).

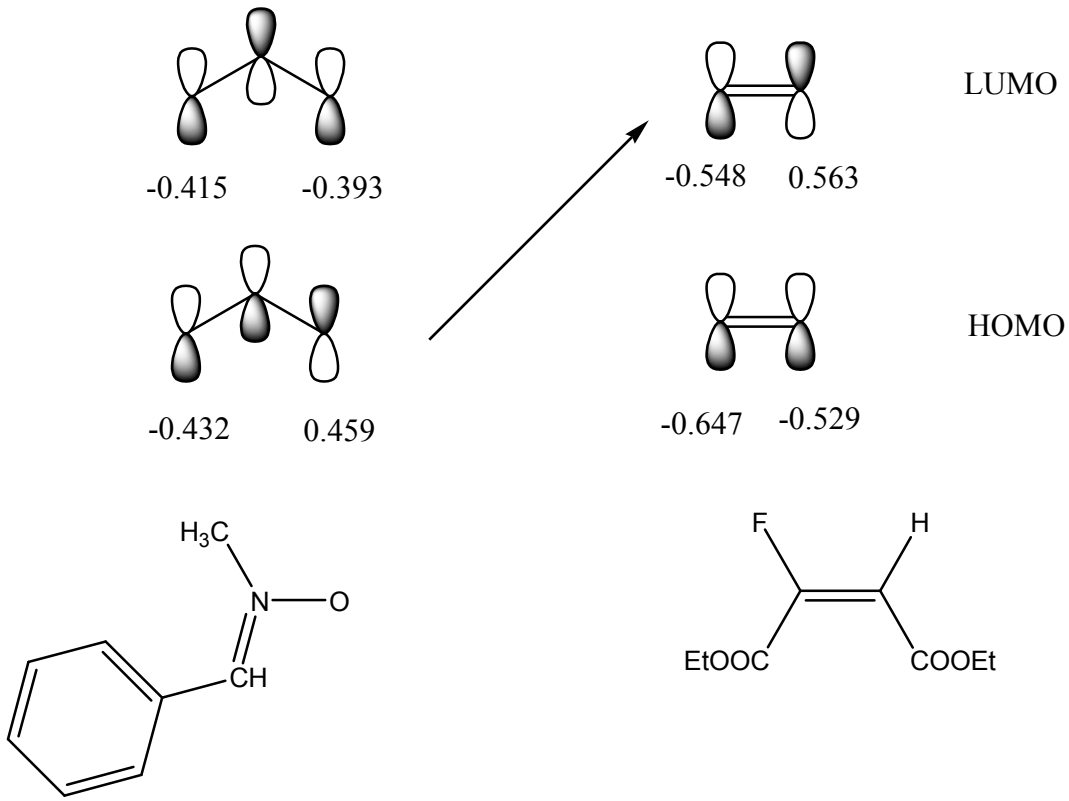


Figure 31. Frontier Orbital Interaction in Nitrone-olefine [3+2] Cycloaddition Reaction.

The orbital interaction that drives he regioselectivity is between the HOMO orbital of the oxygen in the nitrone and the LUMO orbital of the fluorine substituted carbon in the olefin.This interaction has the lower energy change compared to all other orbital interaction that can be possible as shown above.

Beside the major isoxazolidine product, there are two chiral centers in the molecule which allows for the formation of four diastereomers. Sufficient data has not been collected yet to prove which diastereomer is the most stable and dominant structure (Figure 32).

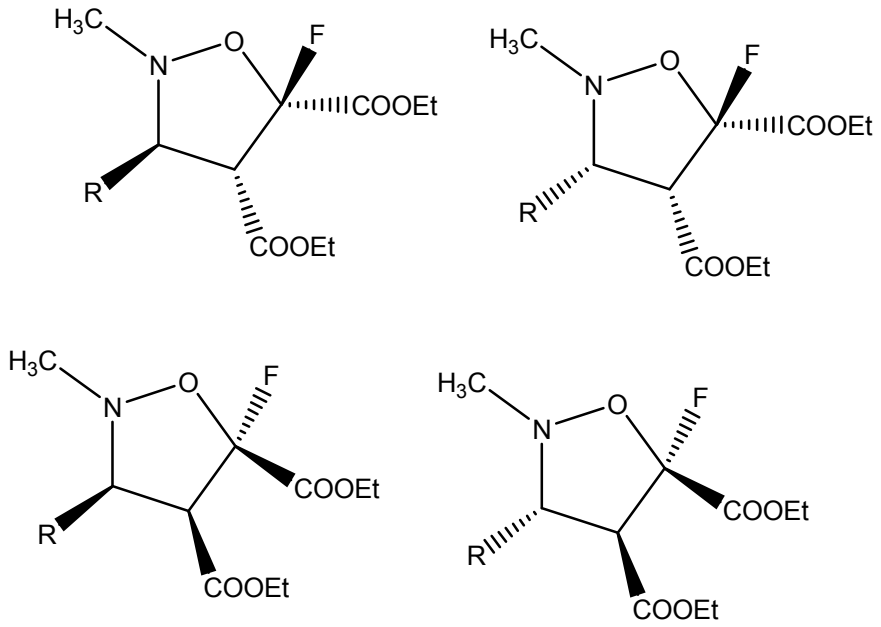


Figure 32. Possible Diasteromers of Fluoro-isoxazolidine Compounds.

The ^{1}H NMR is able to show the splitting of the hydrogen on C-4 with the bonded fluorine on C-5 and the hydrogen on C-3 (3.9 ppm). This splitting is perceived as dublet of dublet. Another close multiplet is that for single hydrogen on the C-3 of the isoxazolidine ring (4.4 ppm). This hydrogen split by the hydrogen on the C-4 and also split by fluorine atom on C-5 This pattern was seen in all isoxazolidine compounds that the presence of hydrogen on C-4 were in close proximity of the fluorine atom (Figure 33).

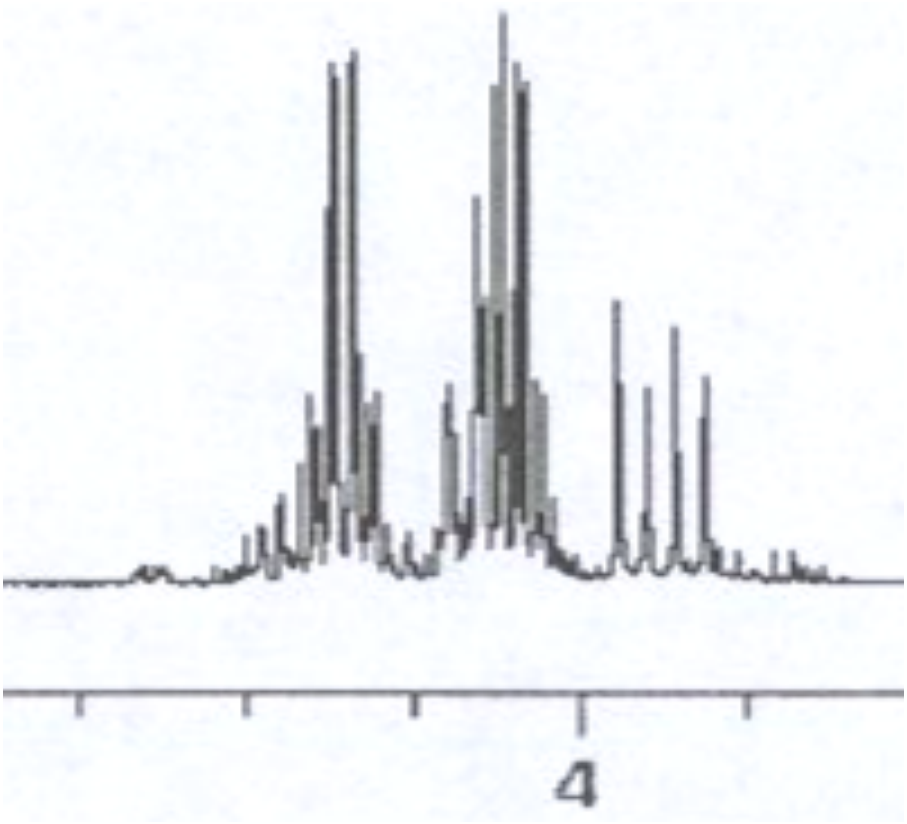


Figure 33. Expanded ^{1}H NMR of C-4 and C-3 Hydrogen Splitting.

The ^{19}F spectra for all isoxazolidine compounds diplay a similar peak that appears to be doublet at (-20.5, -20.9 ppm). Based on this spliting and the value of J coupling (20 Hz), it has perdicted that the fluorine on C-5 is cis to hydrogen on C-4 and trans to hydrogen on C-3. All of the isoxazolidine compounds display the same peak characteristics due to the fluorine being present in the same position (Figure. 34).

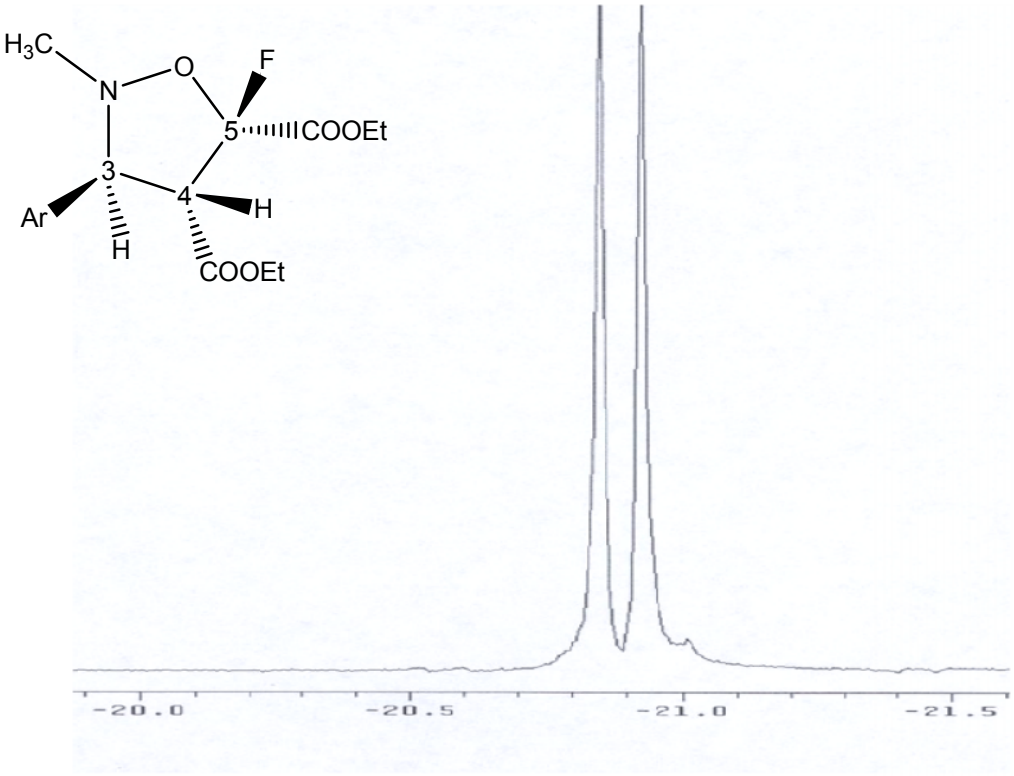
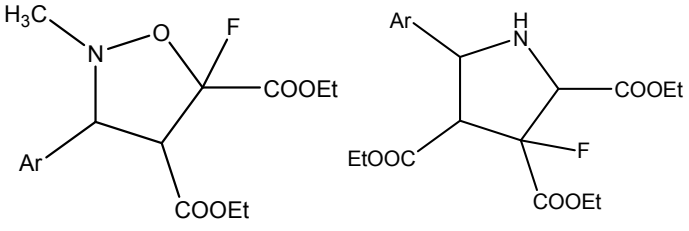


Figure 34. Expanded ^{19}F NMR Spectrum for Isoxazolindine Compounds.

CHAPTER IV

CONCLUSION

The application of [3+2] cycloaddition reactions has been one of the most productive methods of modern sysnthesis in organic chemistry that allows for the synthesis of stereospecific cyclic structures. With this reaction, we synthesized a new series of fluorinated-pyrrolindine compounds and a new series of fluorinated-isoxazolidine compounds have been synthesized. The presence of fluorine atom on these compounds helps to increase possible bioactivity and stability. The reaction of diethyl (*E*)-fluoromaleate **(1)** with aromatic imines **(2-3)** resulted in stereospecific pyrrolidines where fluorine is attached directly to the pyrrolidine rings. The reaction of diethyl(*E*)-fluoromaleate **(1)** with amromatic N-methyl nitornes **(4-7)** resulted in stereospecific isoxazolidine rings where the fluorine is found to favor the C-5 position. The reaction of **(1)** with compounds **(2-3)** in presence of silver acetate has been shown that the catalyzed [3+2] cycloaddition reaction is a potential method for the construction of a chemical library comprised of fluorinated pyrrolidine motifs. Nitrone-olefin [3+2] cycloaddtion reaction also shown as a convienient method for the synthesis of fluorinated-isoxazolidine compounds, which can be applied to develop new pharmacutical compounds (Figure 35).



Fluorinated-Isoxazolidine Fluorinated-Pyrrolidine

Figure 35. General Fluorinated-Isoxazolidine and Fluorinated Pyrrolidine Structures.

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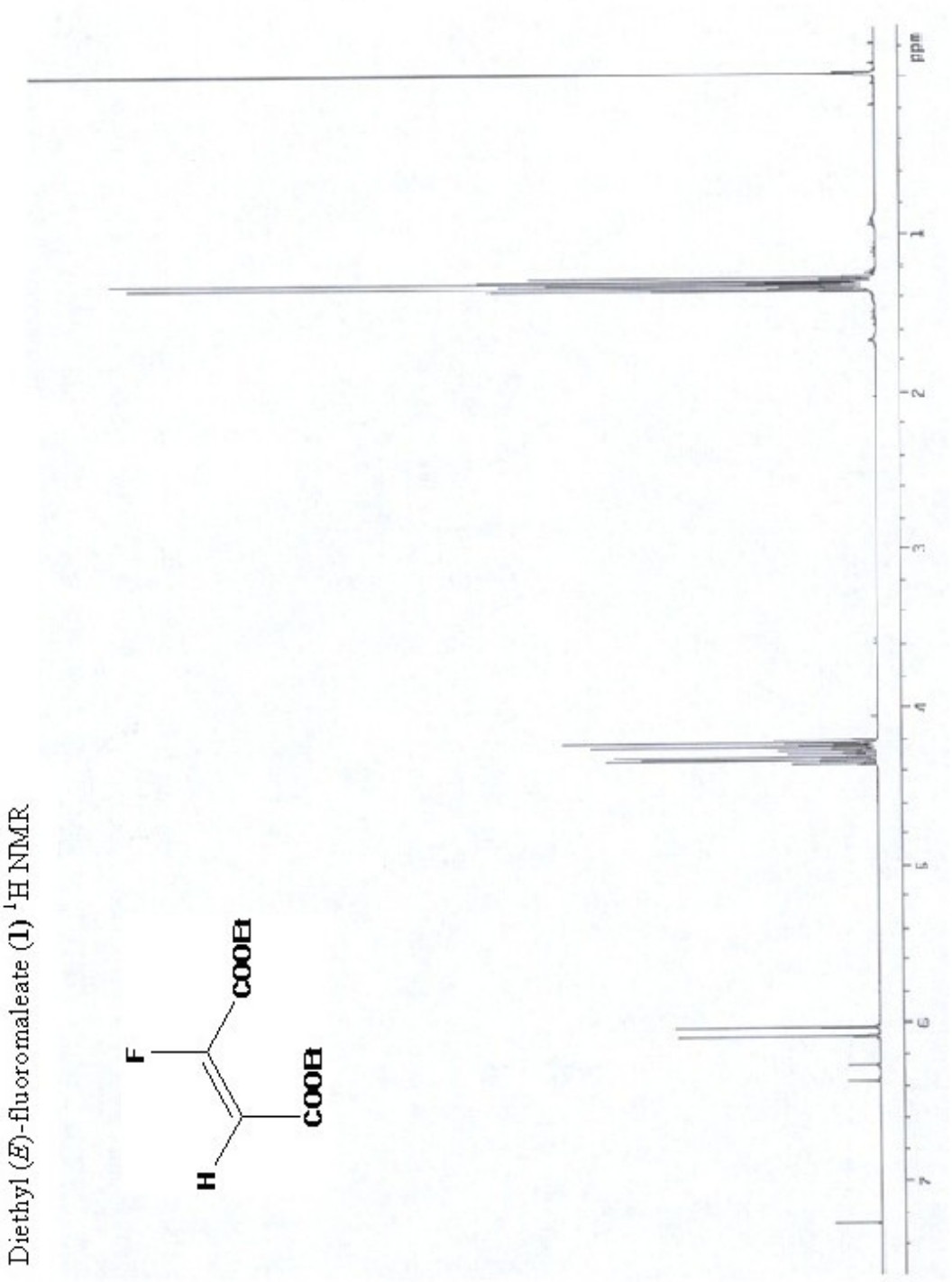
APPENDIX

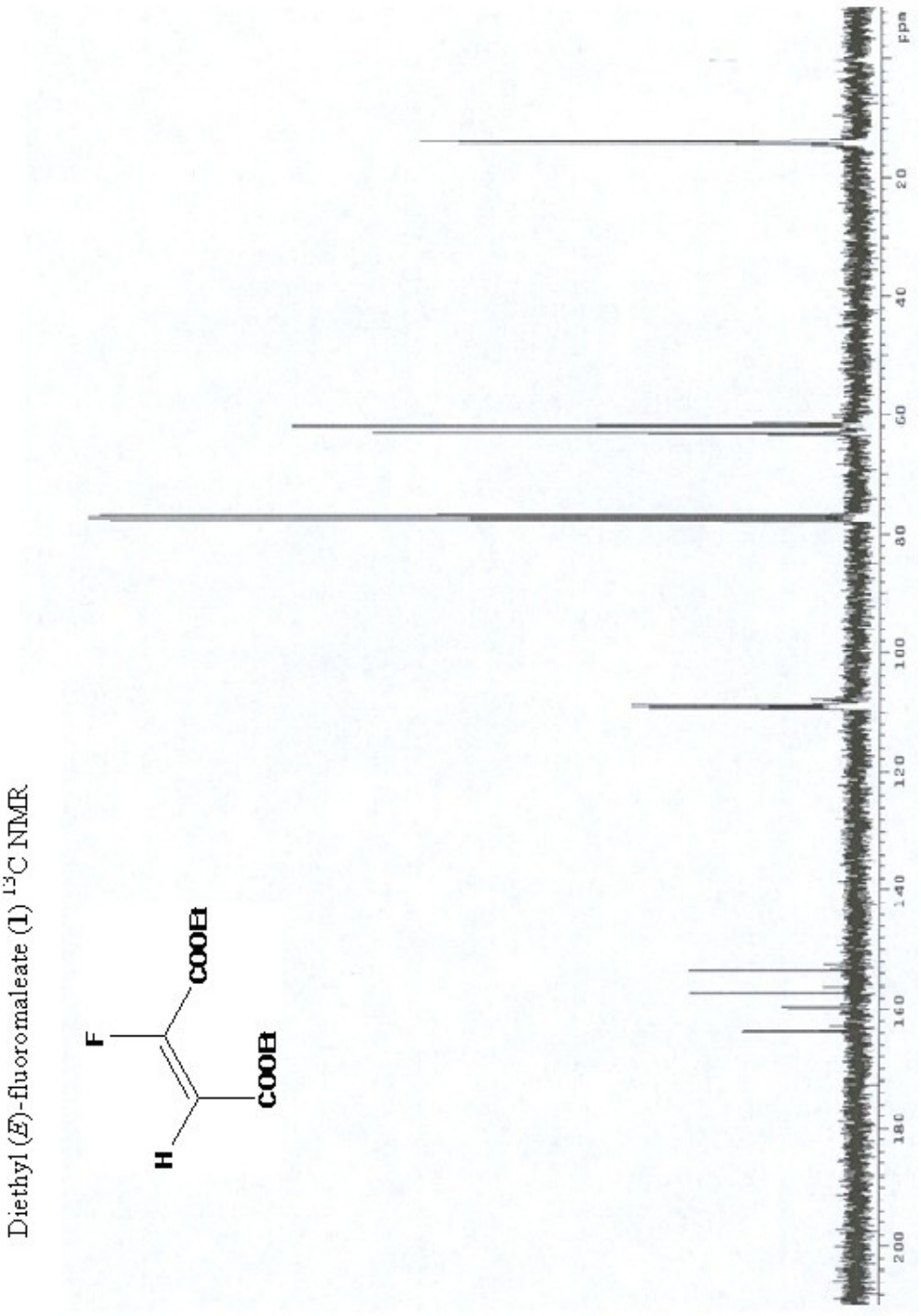
SPECTRAL DATA

Diethyl (*E*)-fluoromaleate (**1**) ^{1}H NMR

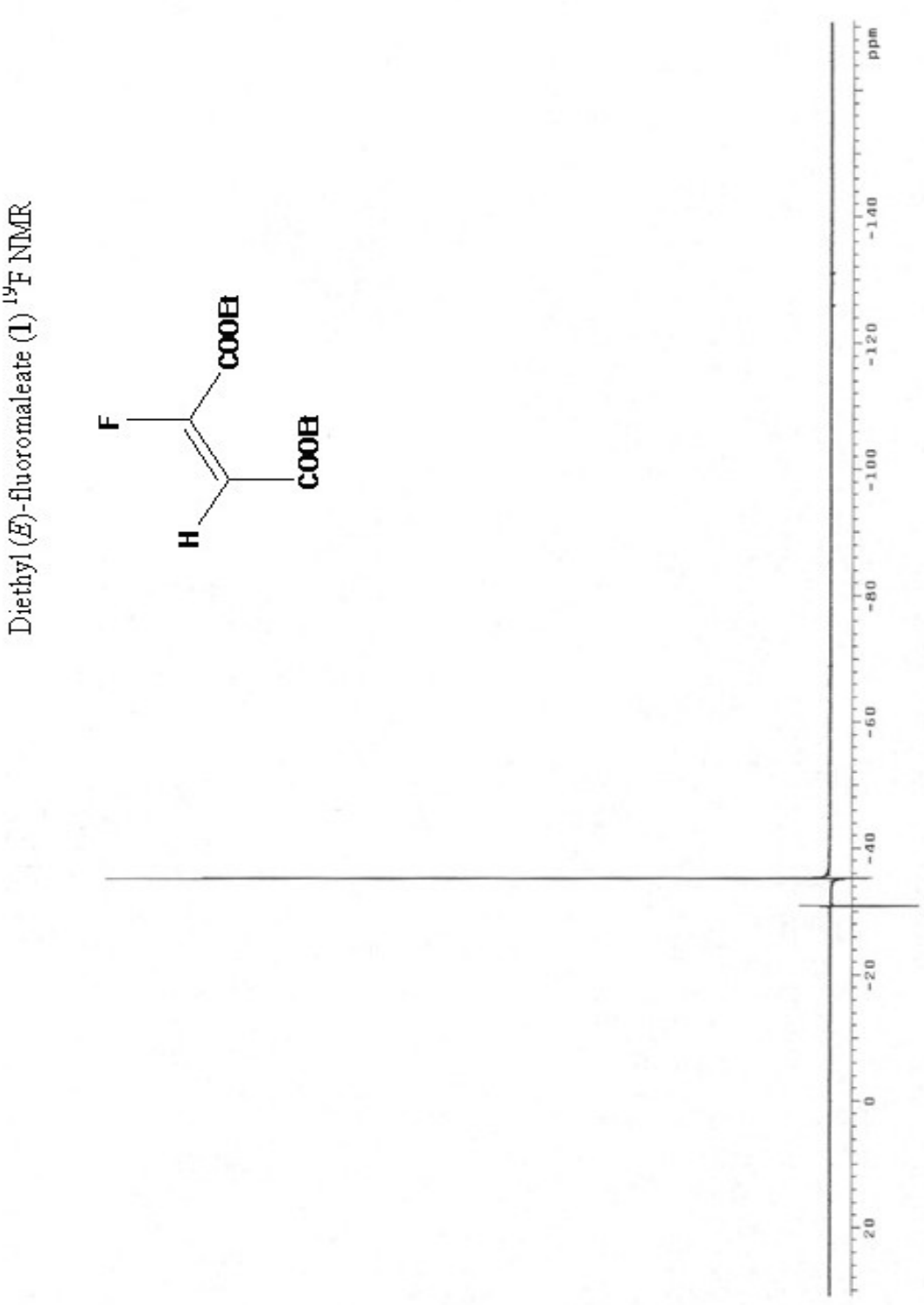


Diethyl (*E*)-fluoromaleate (**1**) ^{1}H NMR

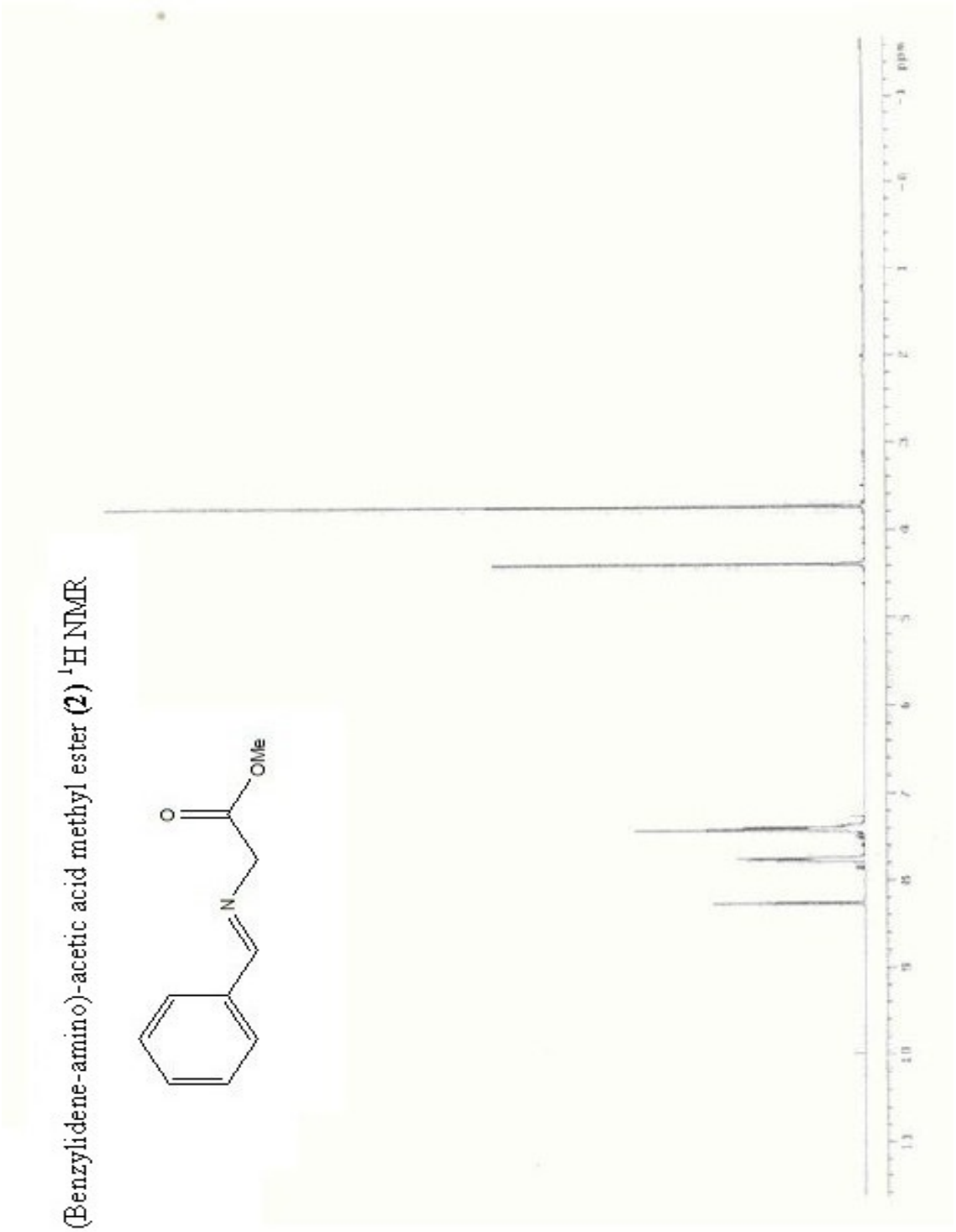
Diethyl (*E*)-fluoromaleate (**1**) ^{13}C NMR



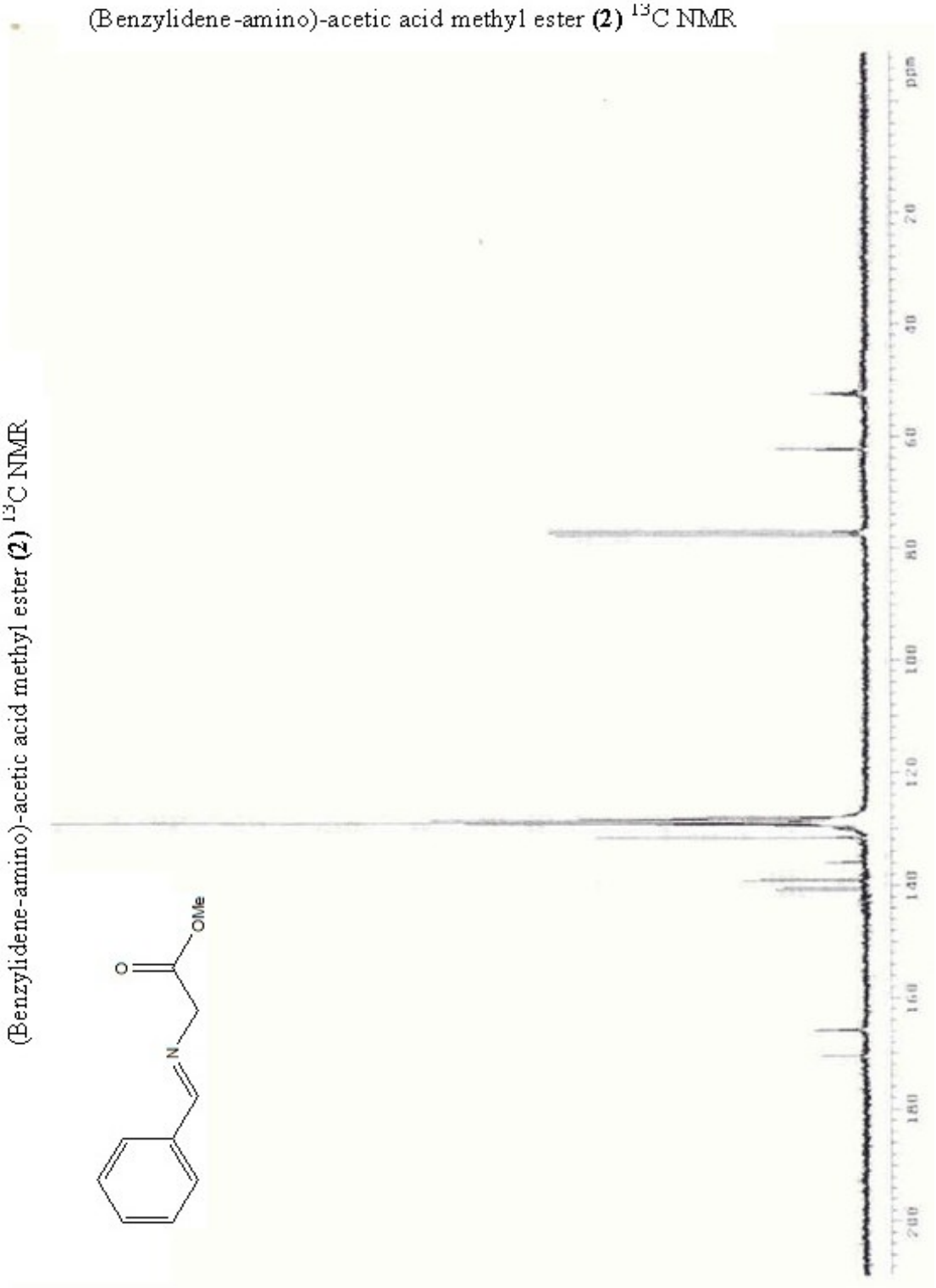
Diethyl (*E*)-fluoromaleate (**1**) ^{19}F NMR



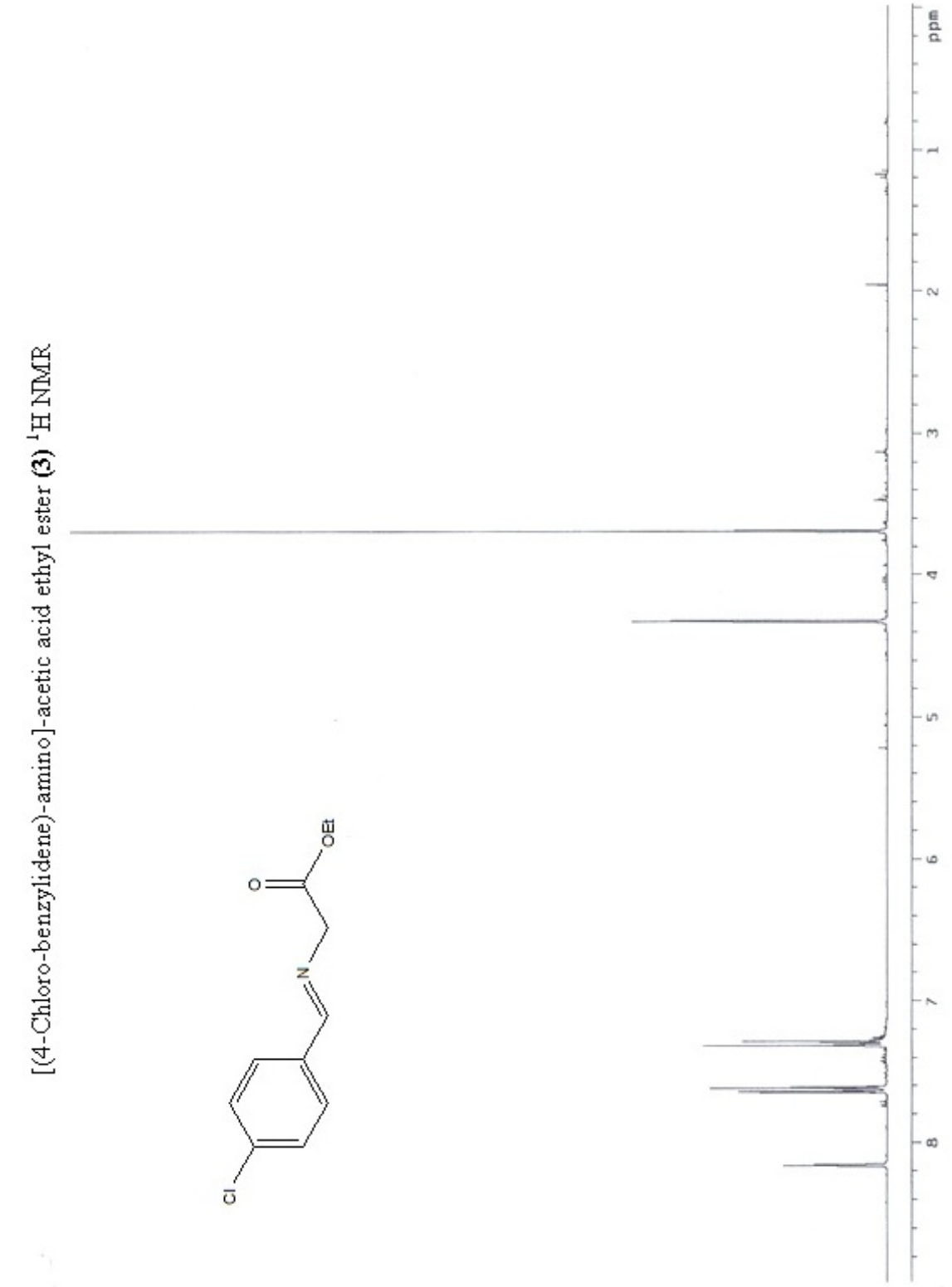
(Benzylidene-amino)-acetic acid methyl ester **(2)** ^{1}H NMR



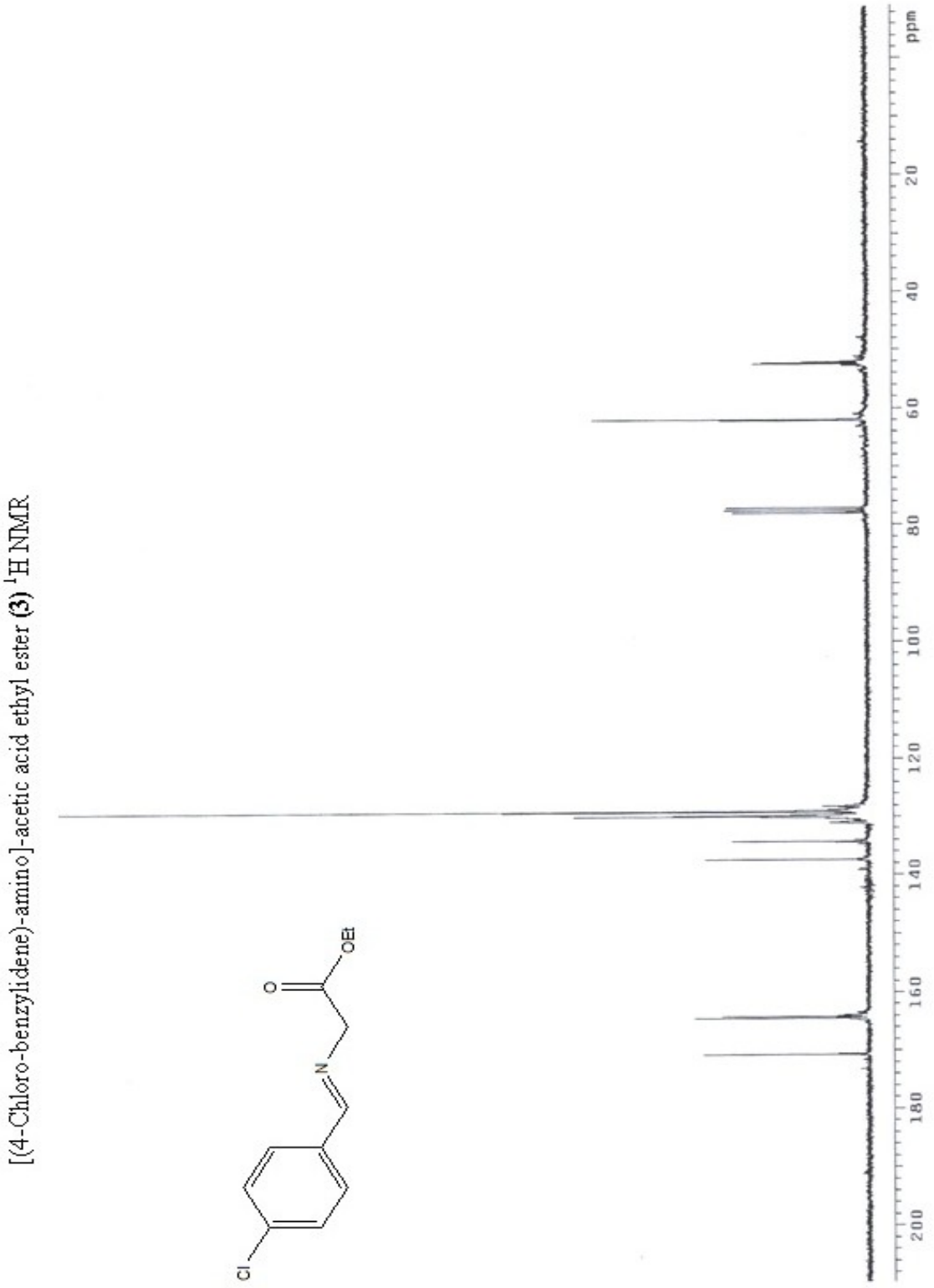
(Benzylidene-amino)-acetic acid methyl ester **(2)** ^{13}C NMR



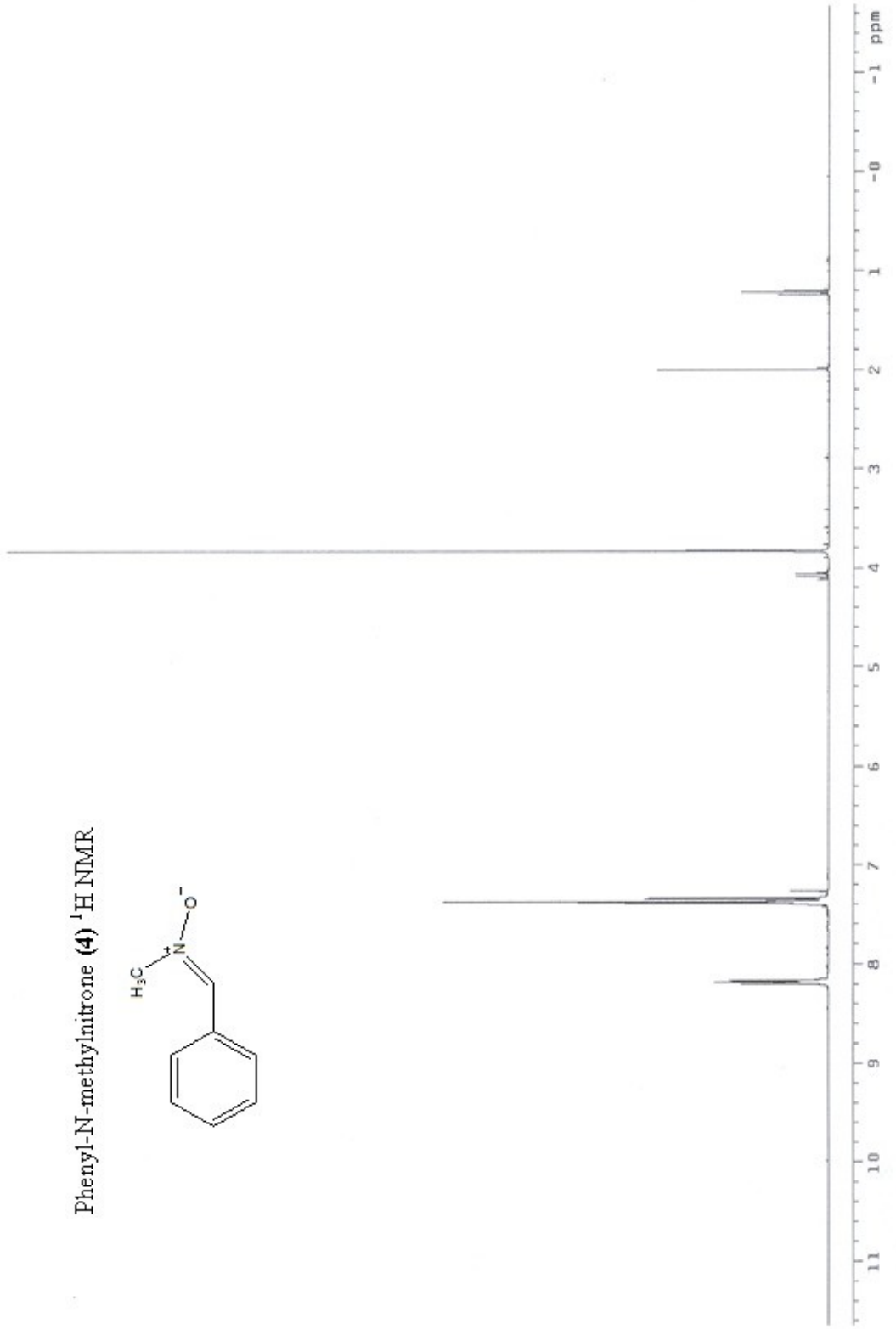
[(4-Chloro-benzylidene)-amino]-acetic acid ethyl ester **(3)** ^{1}H NMR



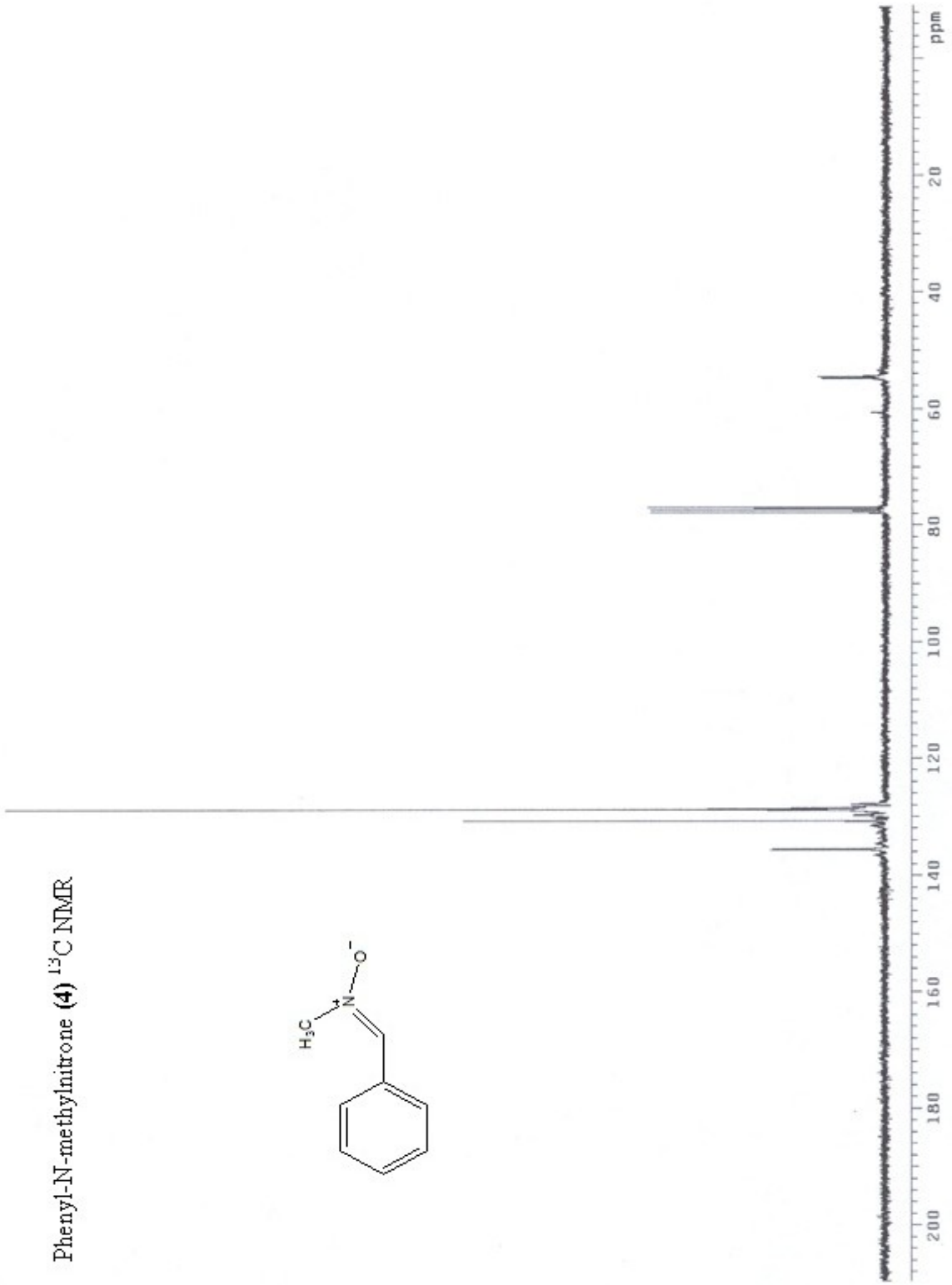
[(4-Chloro-benzylidene)-amino]-acetic acid ethyl ester **(3)** ^{1}H NMR



Phenyl-N-methylnitrone **(4)** ^{1}H NMR

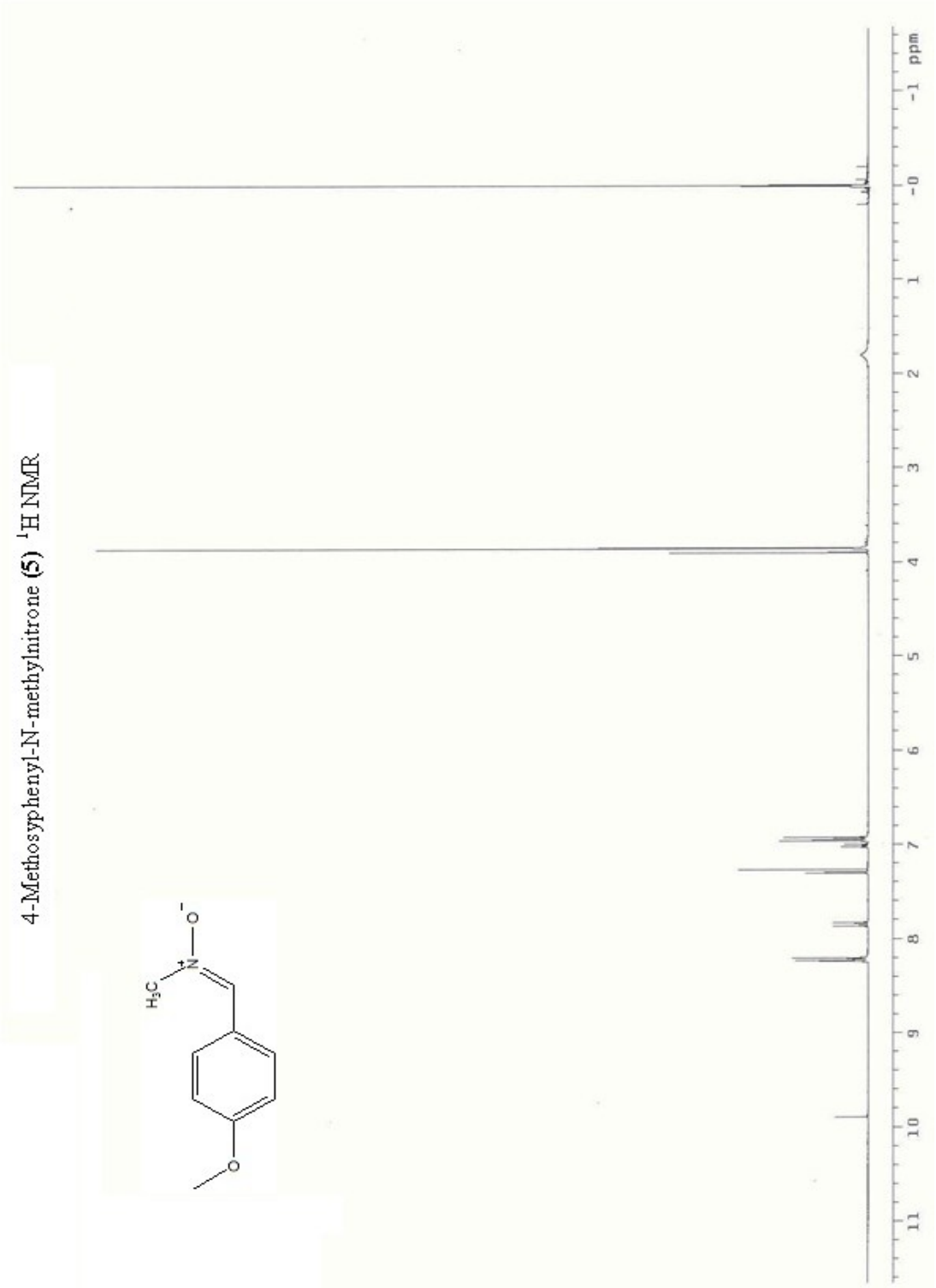


Phenyl-N-methylnitrone **(4)** ^{13}C NMR

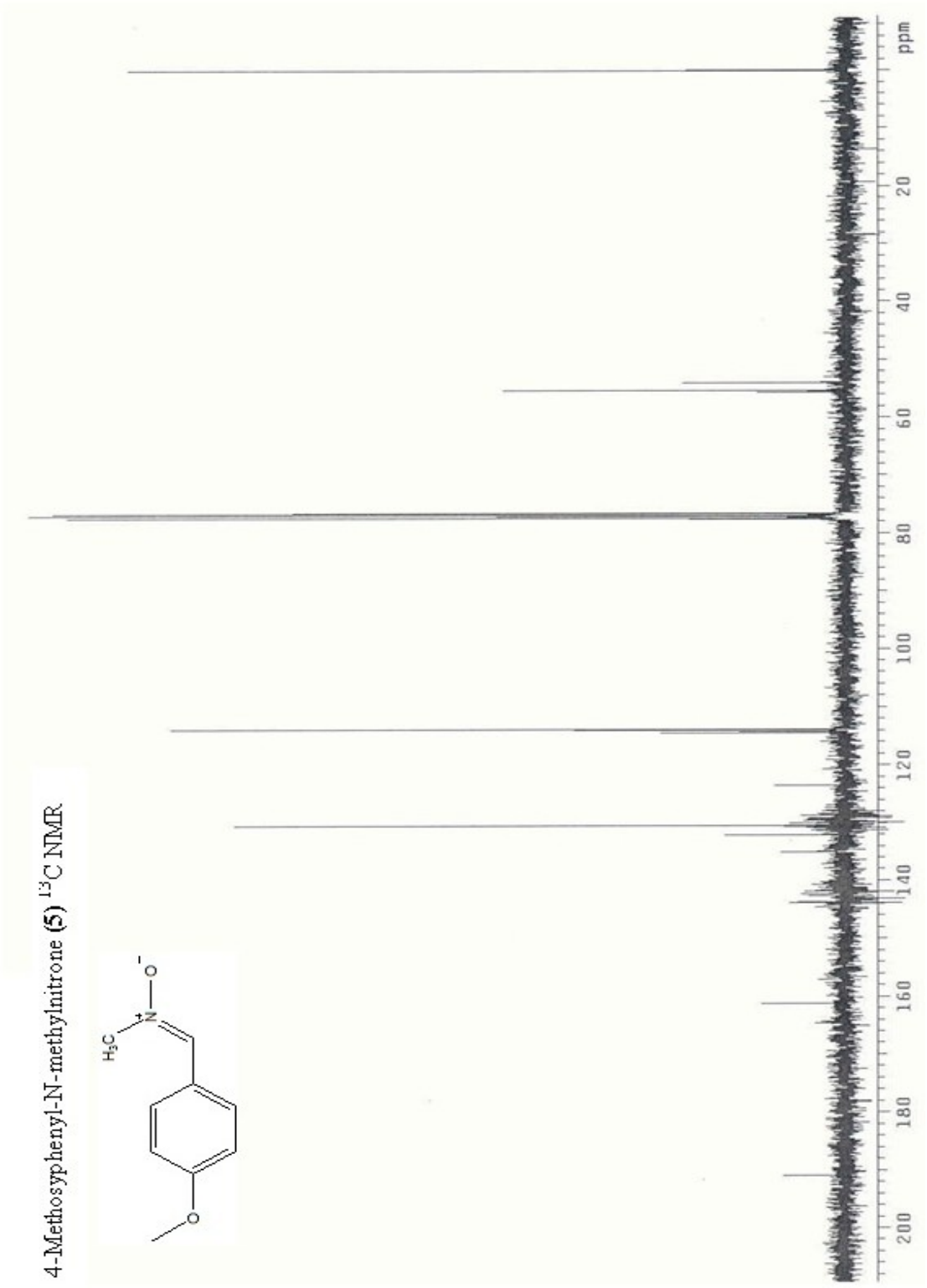


Phenyl-N-methylnitrone **(4)** ^{13}C NMR

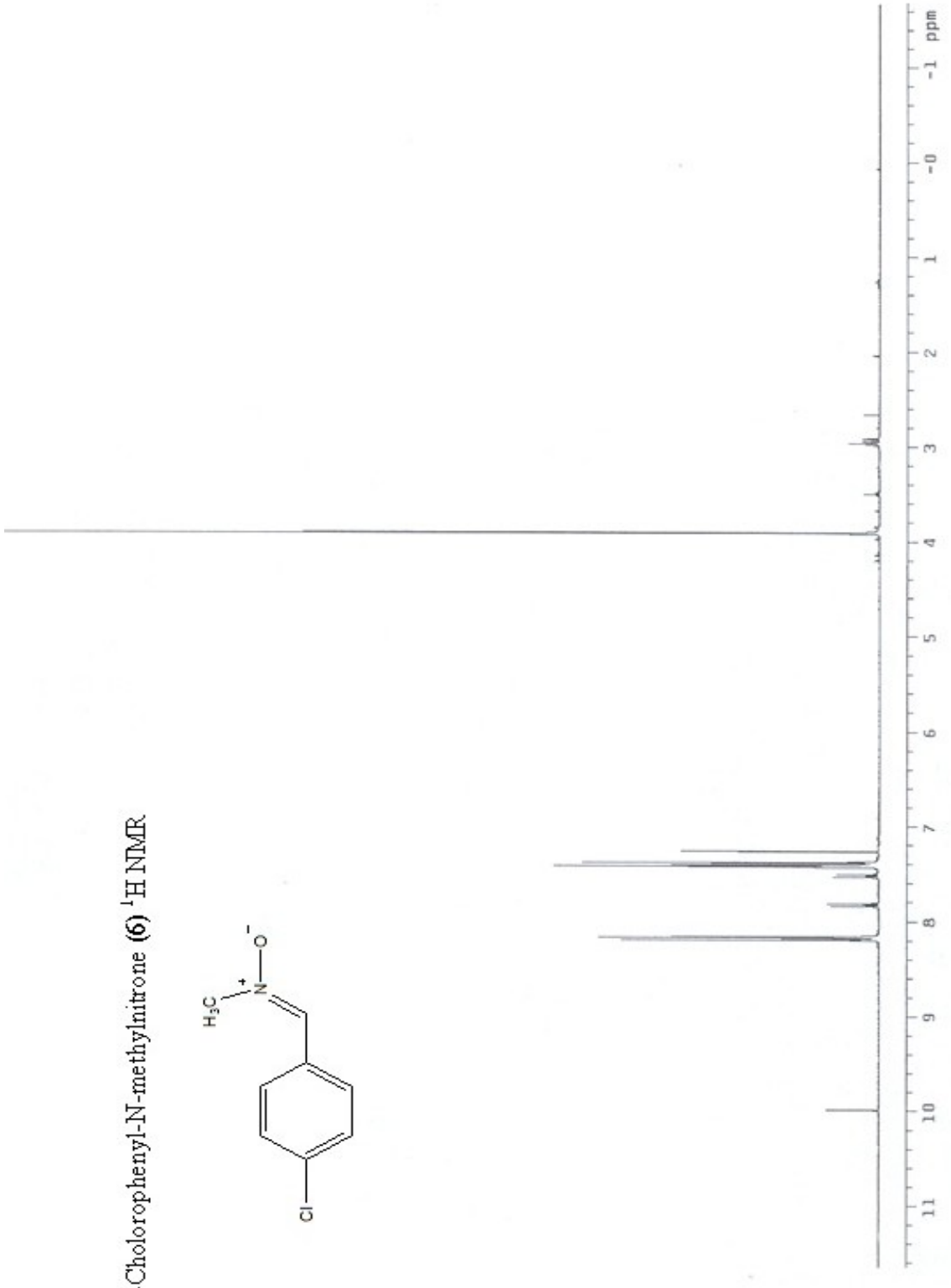
4-Methosyphenyl-N-methylnitrone **(5)** ^{1}HNMR



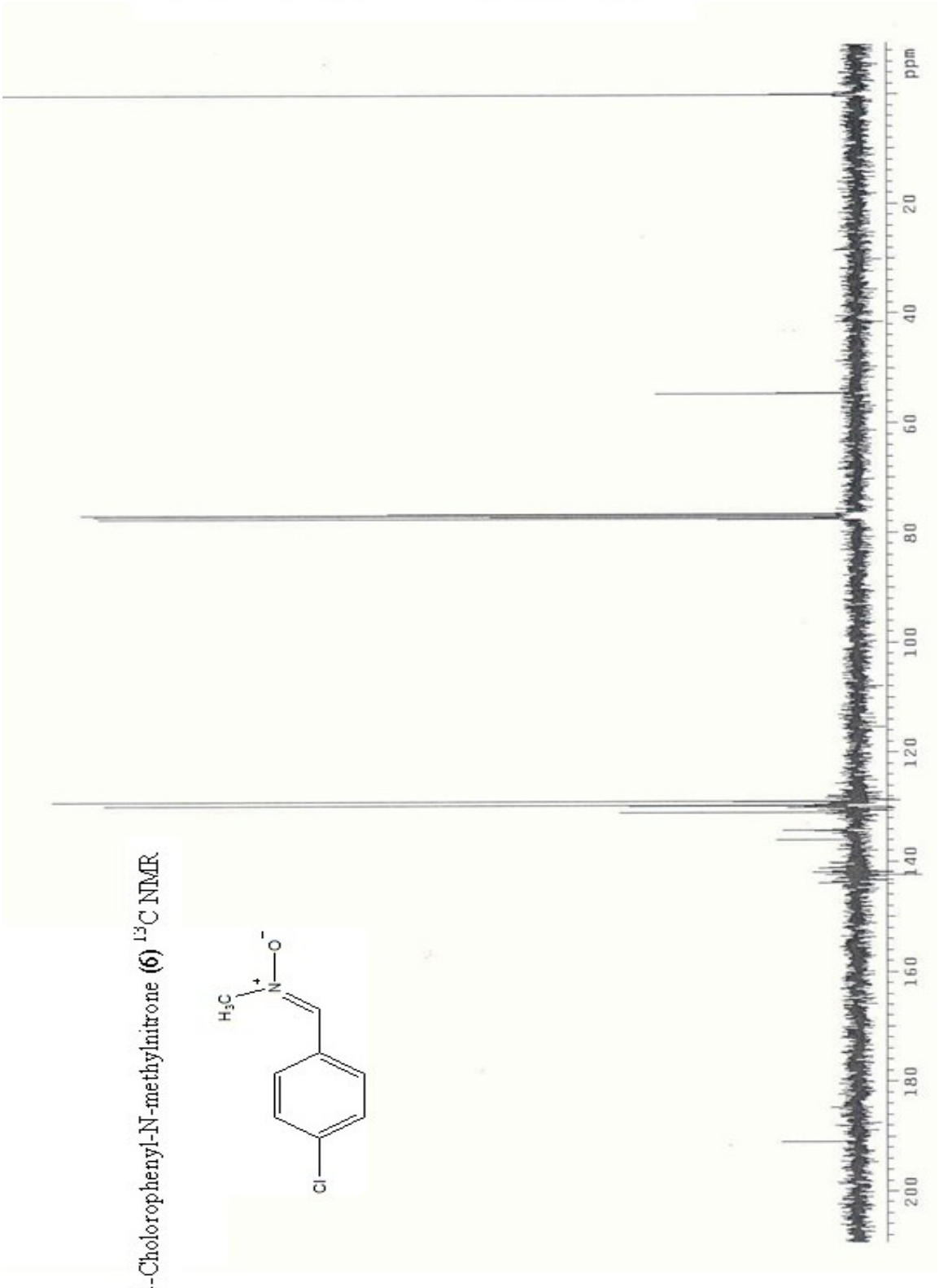
4-Methosyphenyl-N-methylnitrone **(5)** ^{13}C NMR



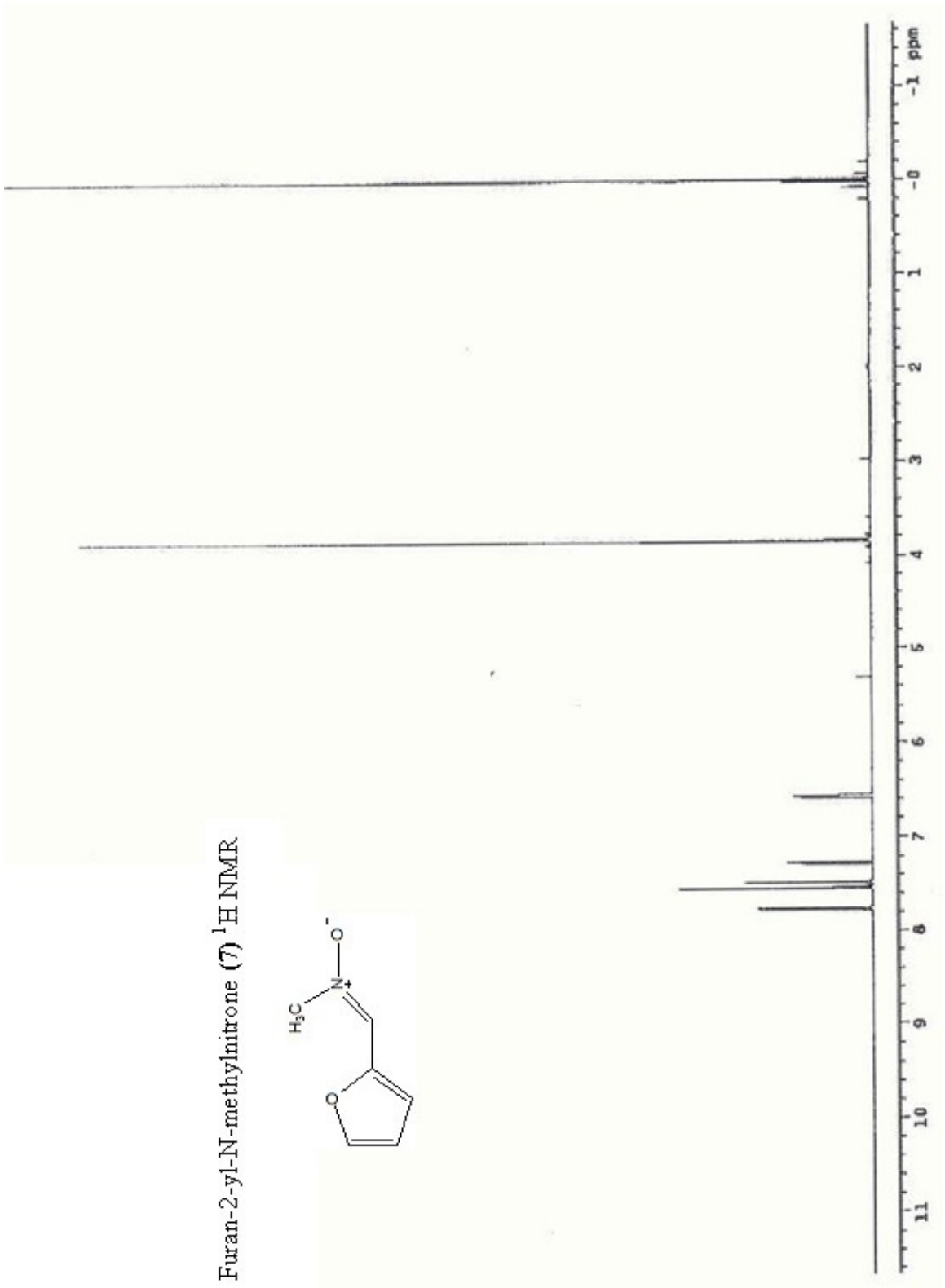
4-Cholorophenyl-N-methylnitrone **(6)** ^{1}H NMR



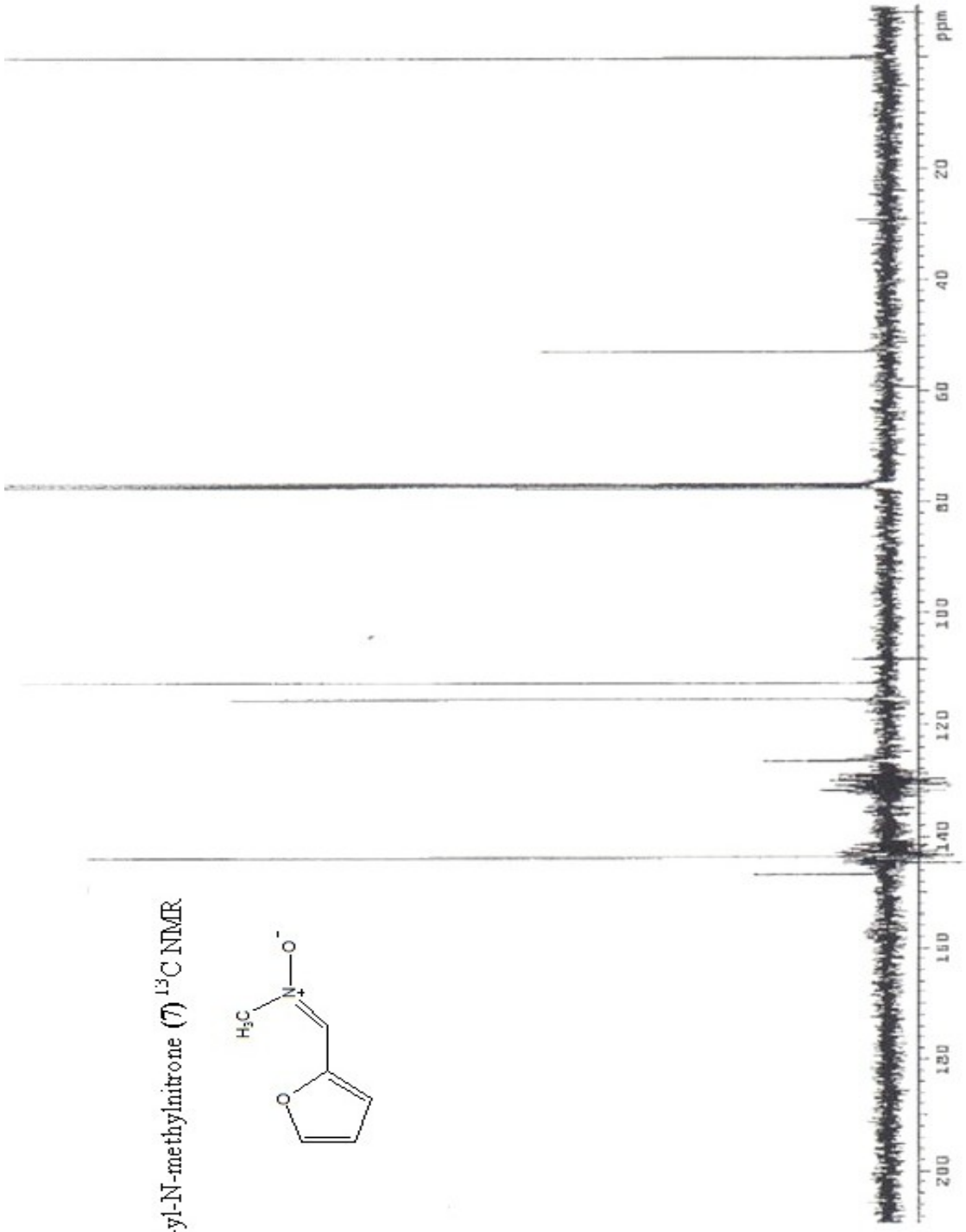
4-Cholorophenyl-N-methylnitrone **(6)** ^{13}C NMR



Furan-2-yl-N-methylnitrone (7) ^{1}H NMR

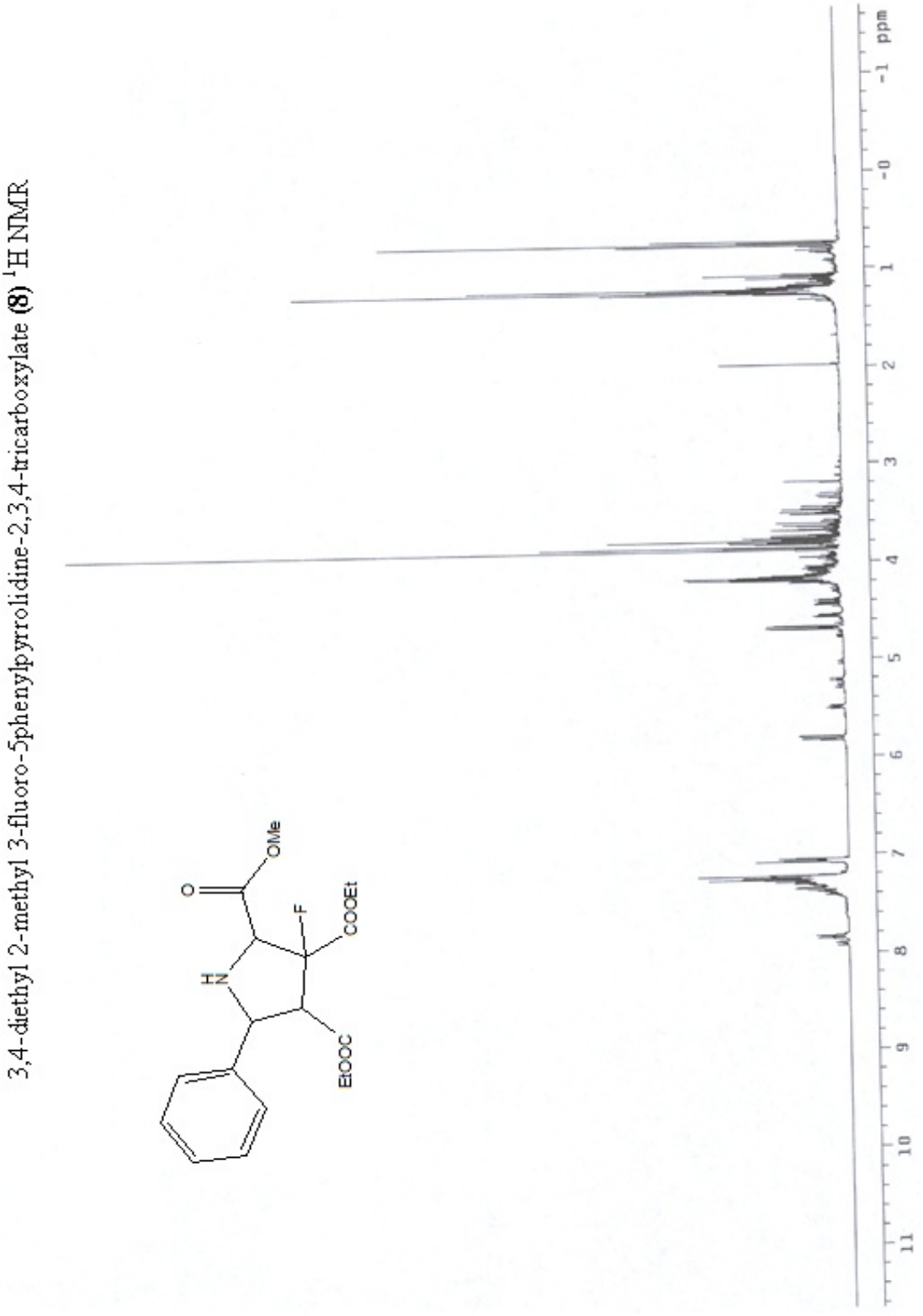


Furan-2-yl-N-methylnitrone **(7)** ^{13}C NMR

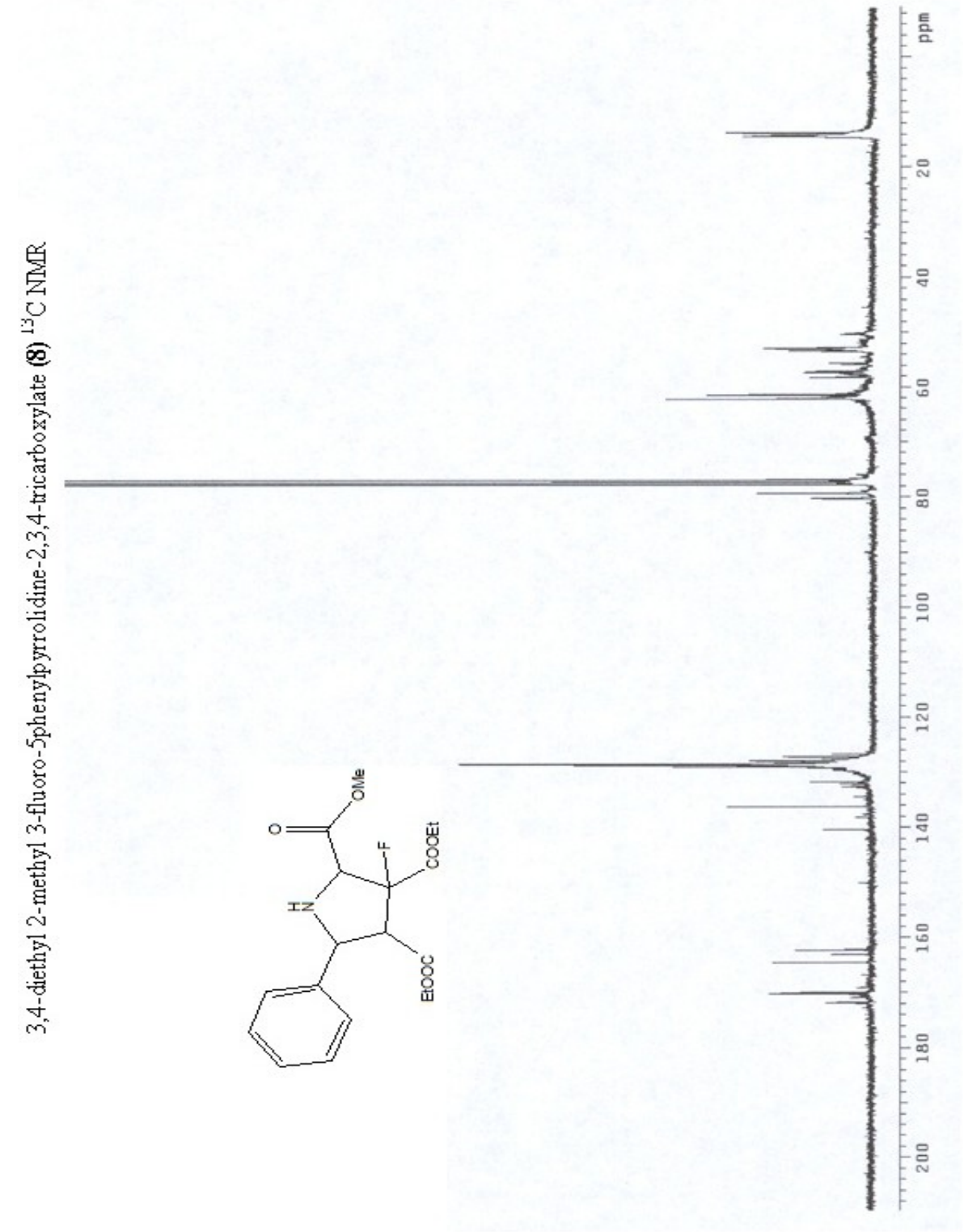


Furan-2-yl-N-methylnitrone **(7)** ^{13}C NMR

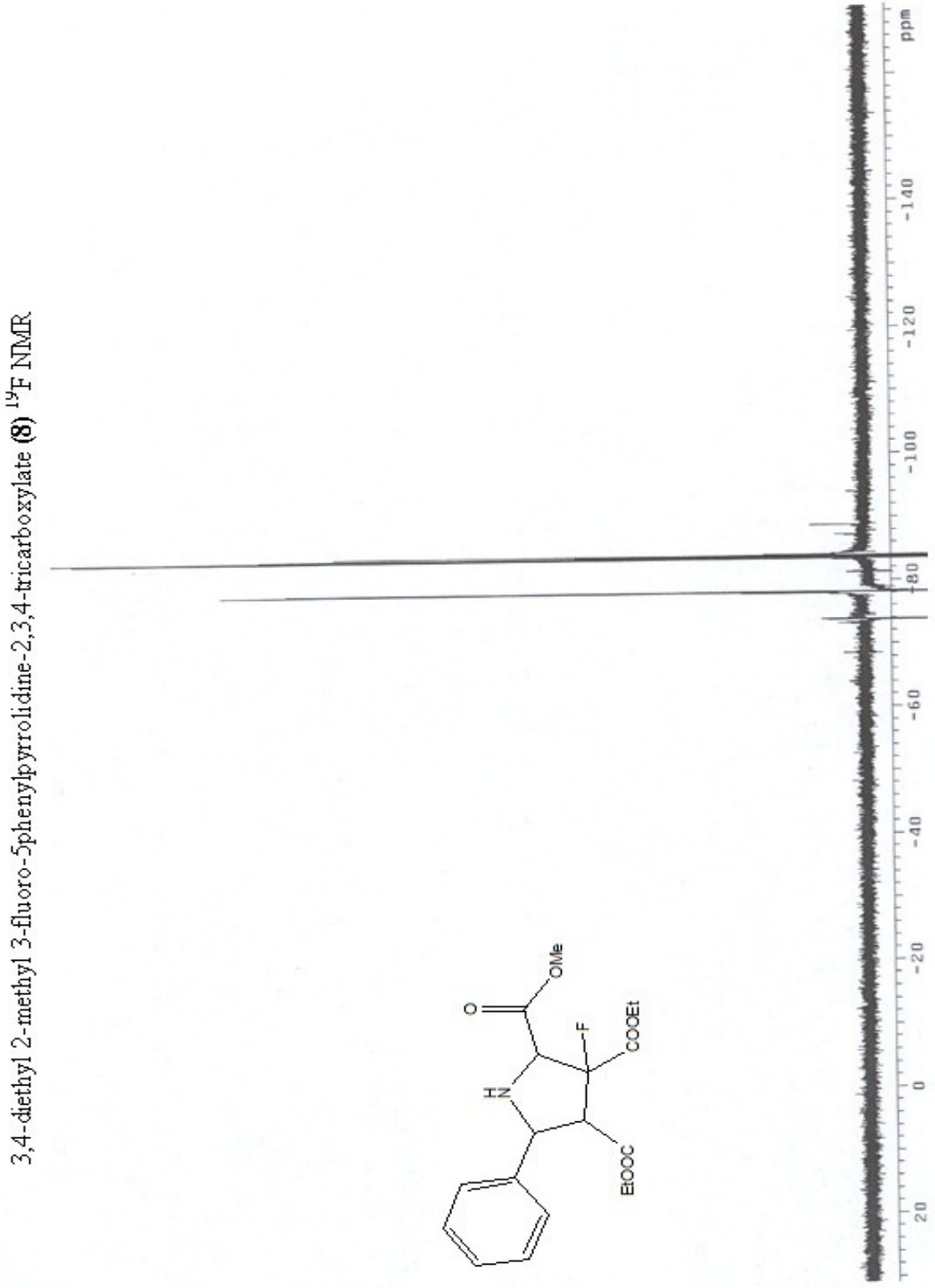
3,4-diethyl 2-methyl 3-fluoro-5phenylpyrrolidine-2,3,4-tricarboxylate **(8)** ^{1}HNMR



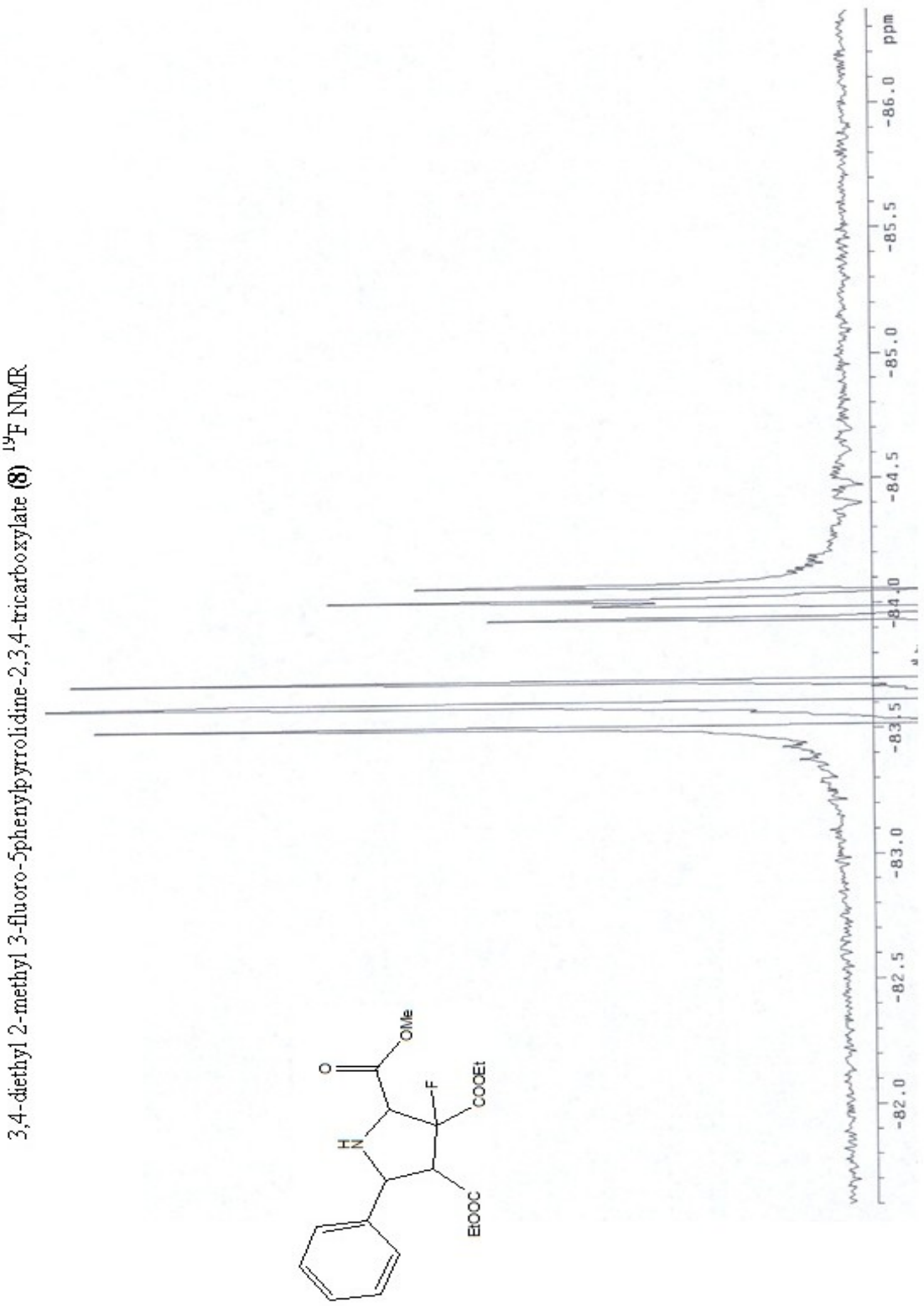
3,4-diethyal 2-methyl 3-fluoro-5phenylpyrrolidine-2,3,4-tricarboxylate **(8)** ^{13}C NMR



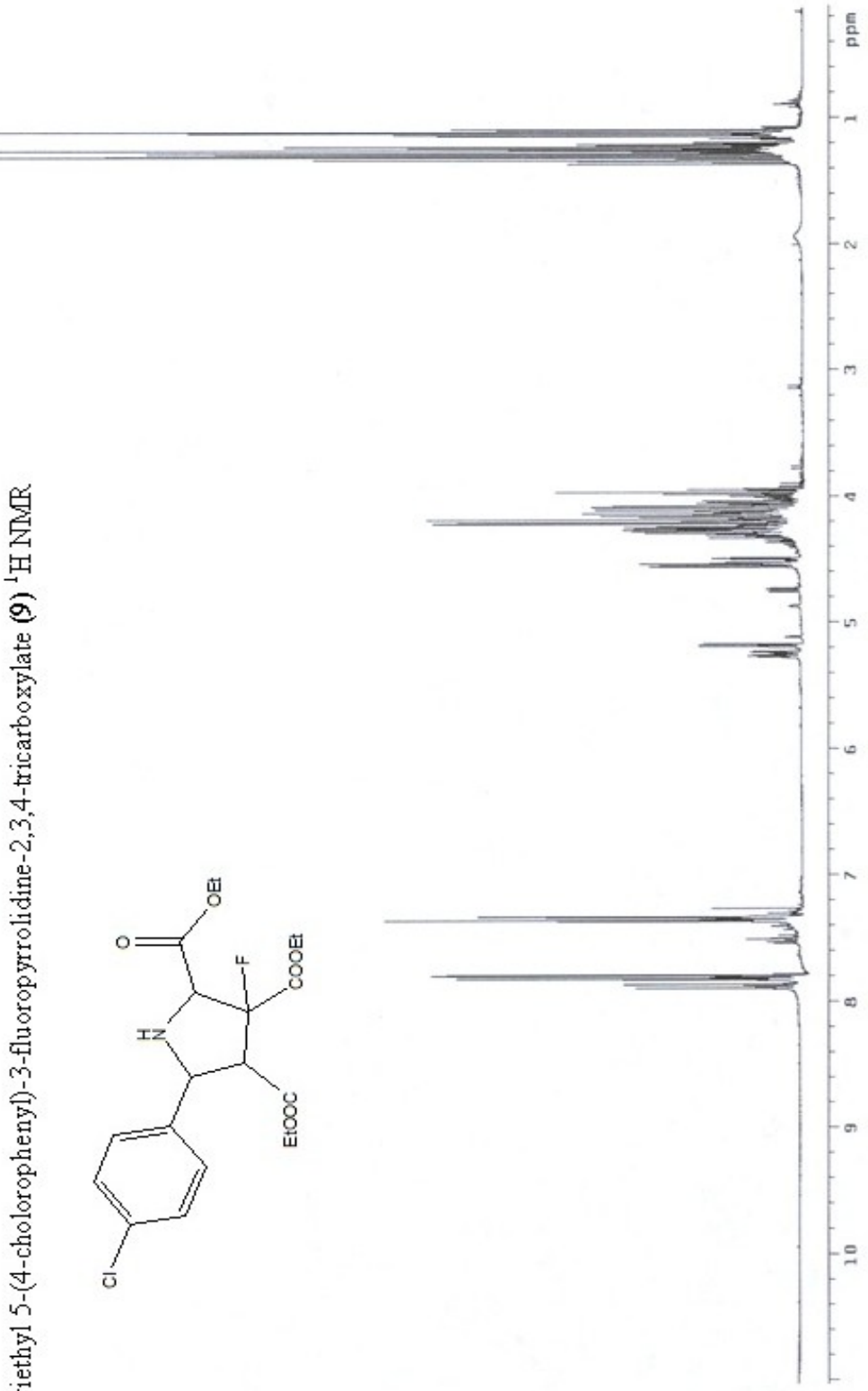
3,4-diethyal 2-methyl 3-fluoro-5phenylpyrrolidine-2,3,4-tricarboxylate **(8)** ^{19}F NMR



3,4-diethyal 2-methyl 3-fluoro-5phenylpyrrolidine-2,3,4-tricarboxylate **(8)** ^{19}F NMR

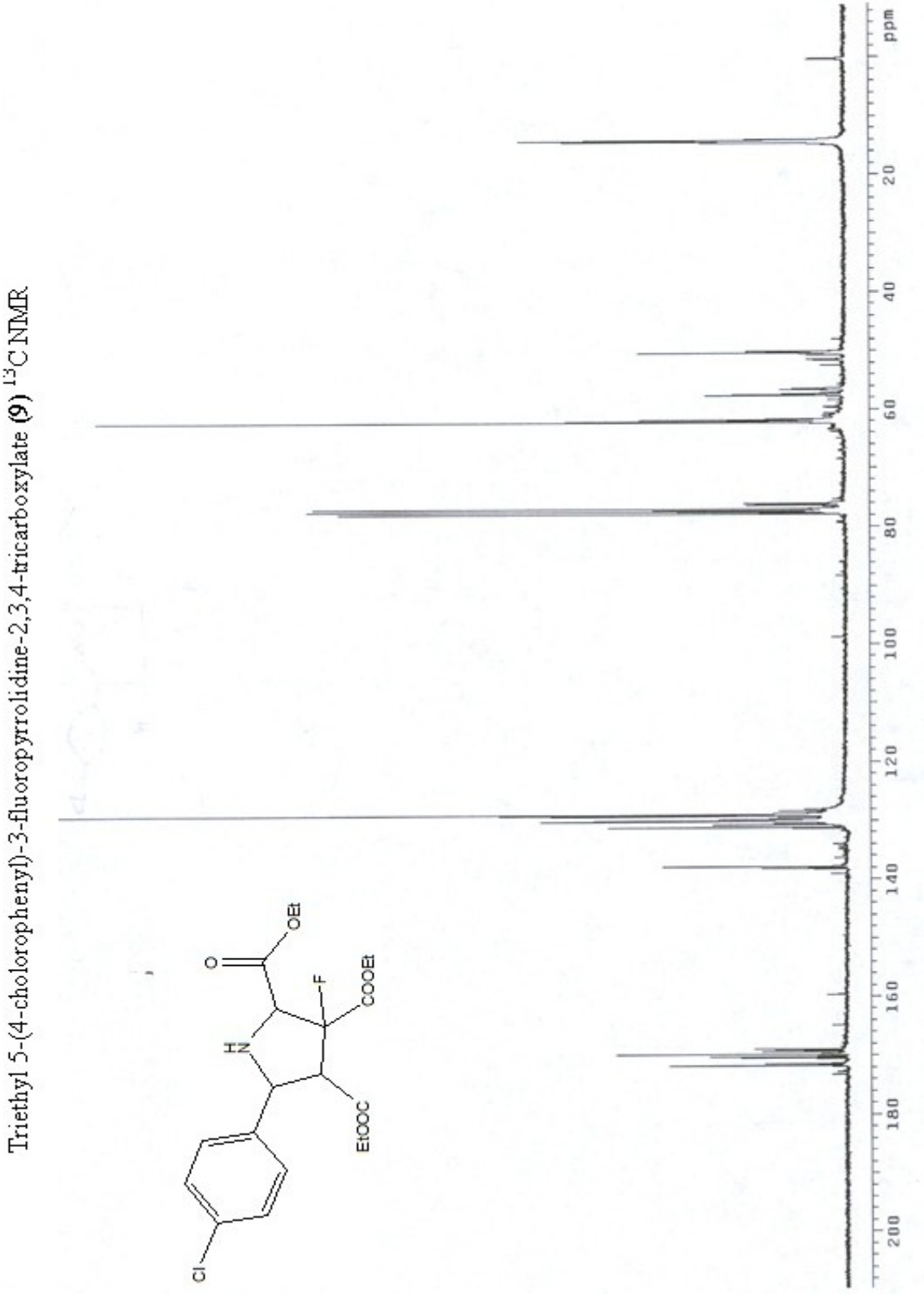


Triethyl 5-(4-cholorophenyl)-3-fluoropyrrolidine-2,3,4-tricarboxylate **(9)**^{1}H NMR



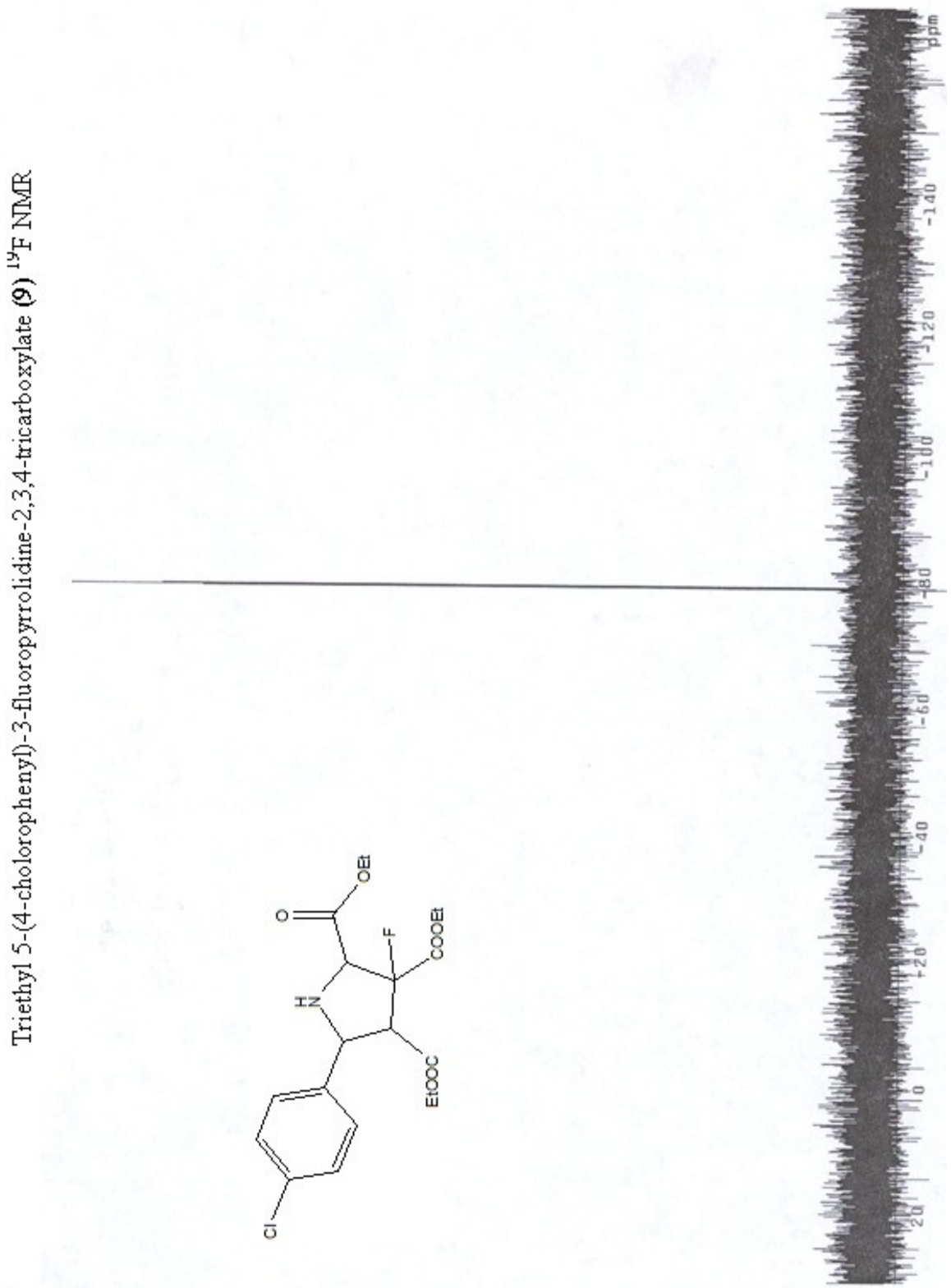
Triethyl 5-(4-cholorophenyl)-3-fluoropyrrolidine-2,3,4-tricarboxylate **(9)** ^{1}H NMR

Triethyl 5-(4-cholorophenyl)-3-fluoropyrrolidine-2,3,4-tricarboxylate **(9)** ^{13}C NMR

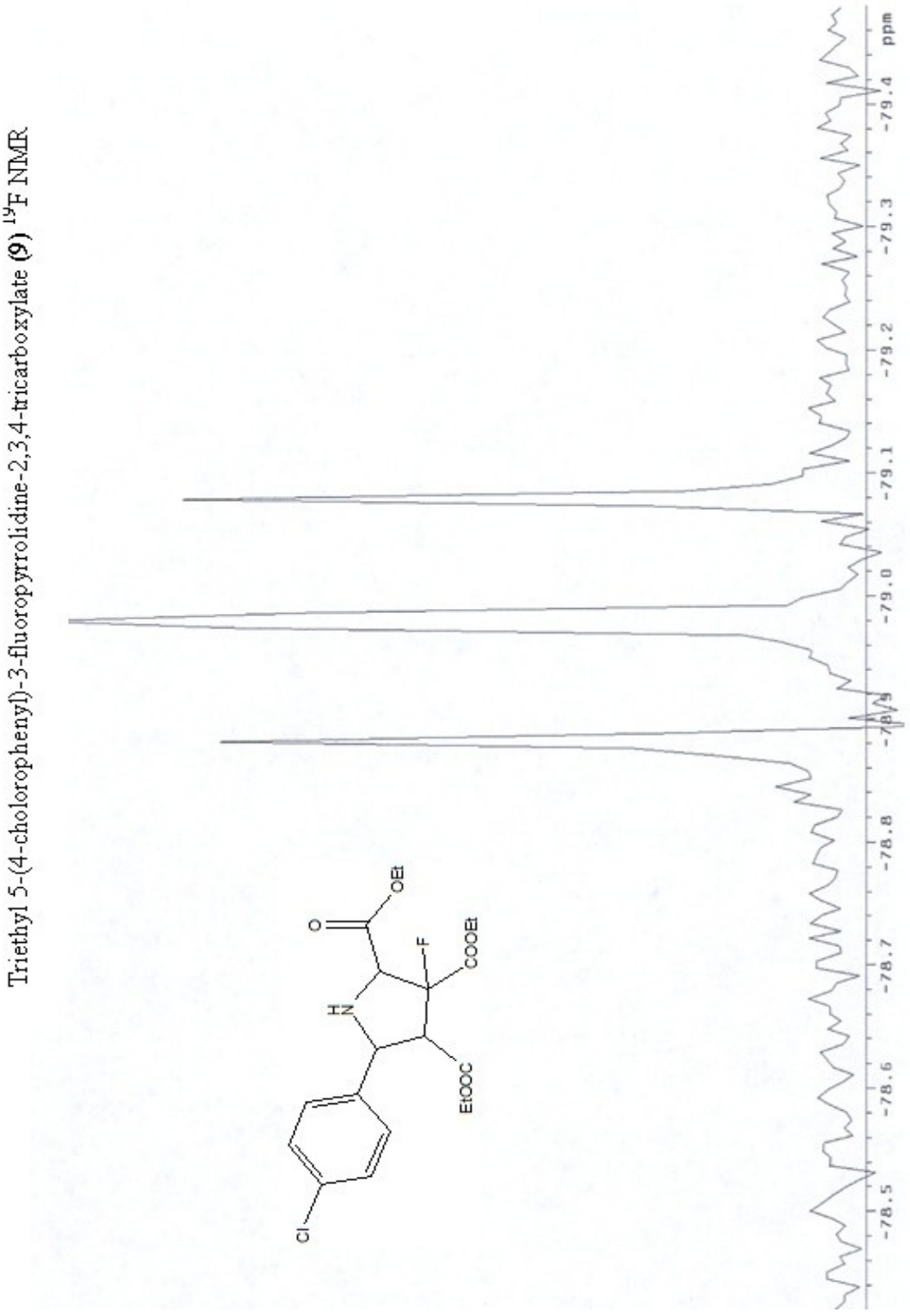


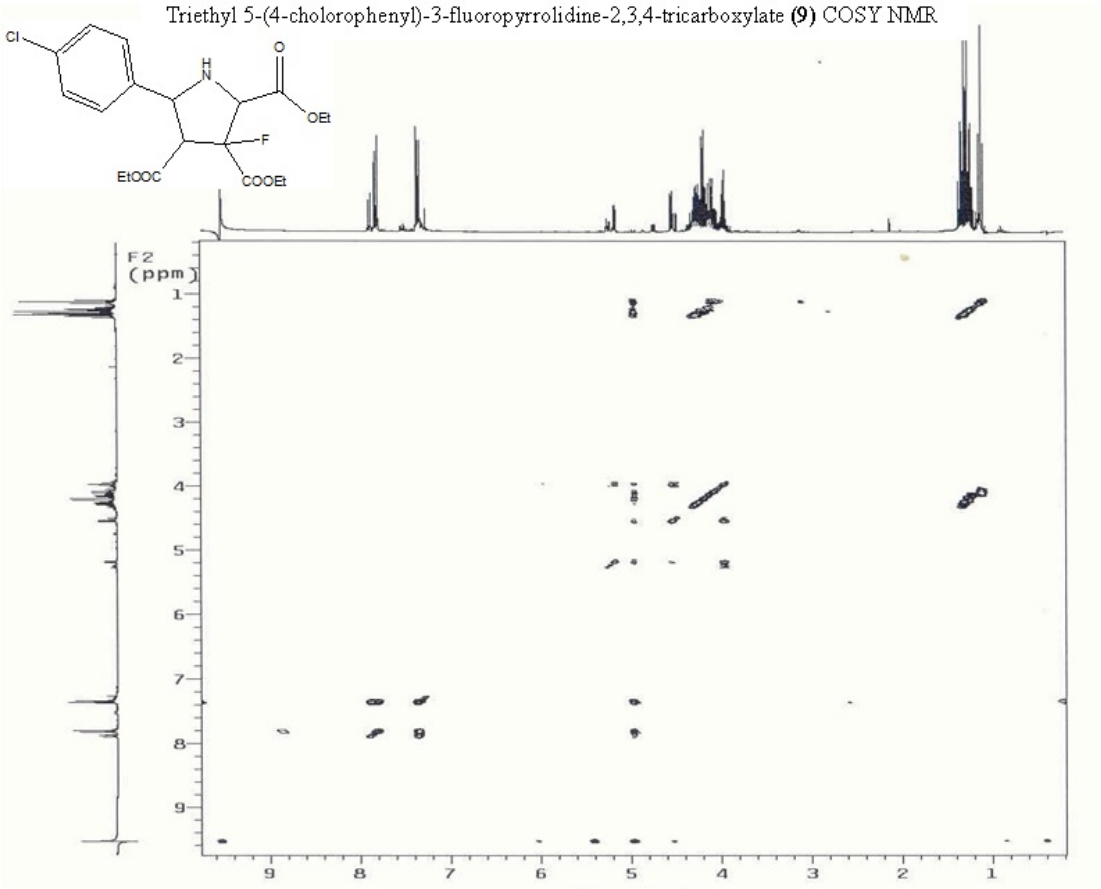
Triethyl 5-(4-cholorophenyl)-3-fluoropyrrolidine-2,3,4-tricarboxylate **(9)** ^{13}C NMR

Triethyl 5-(4-cholorophenyl)-3-fluoropyrrolidine-2,3,4-tricarboxylate **(9)** ^{19}F NMR



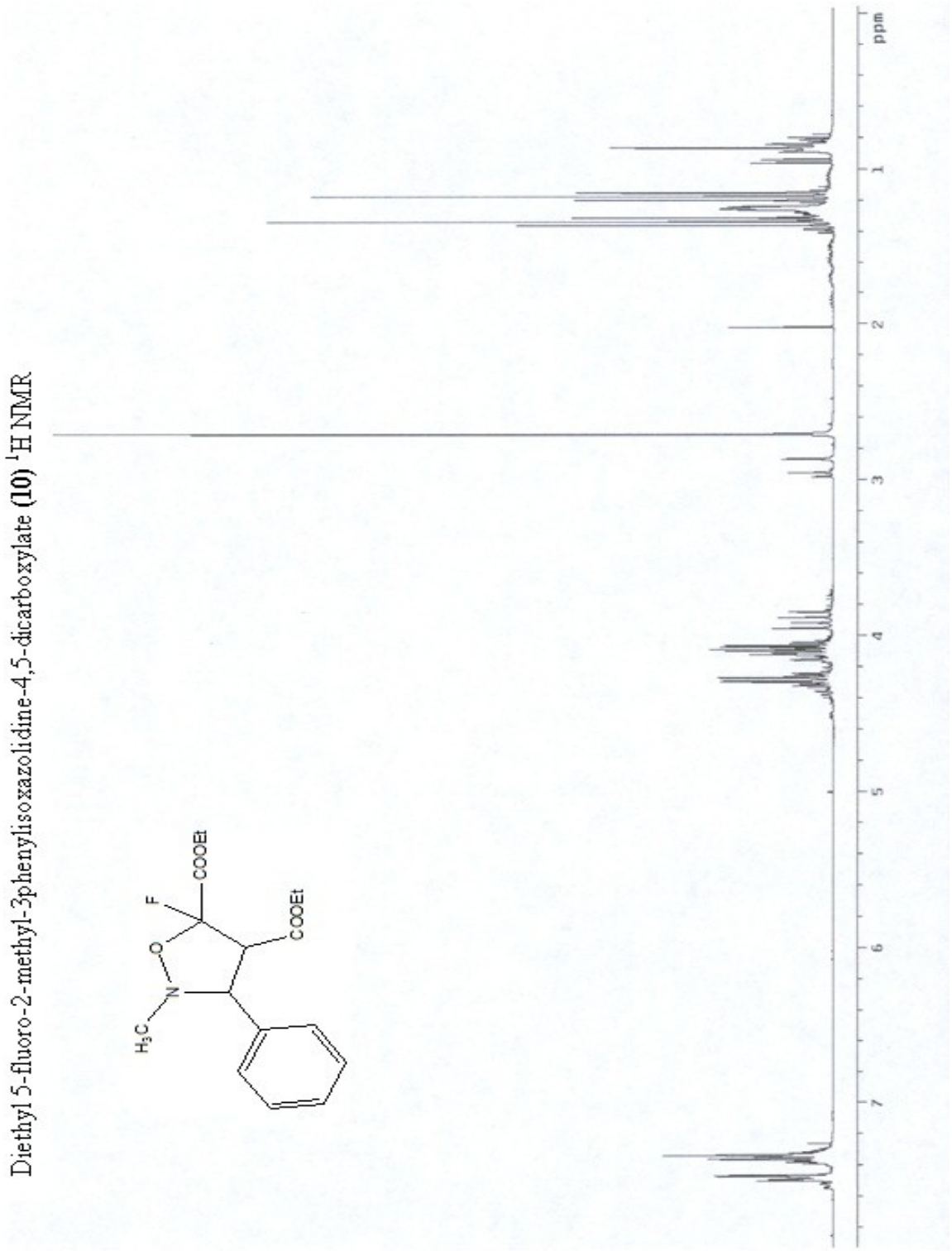
Triethyl 5-(4-cholorophenyl)-3-fluoropyrrolidine-2,3,4-tricarboxylate **(9)** ^{19}F NMR



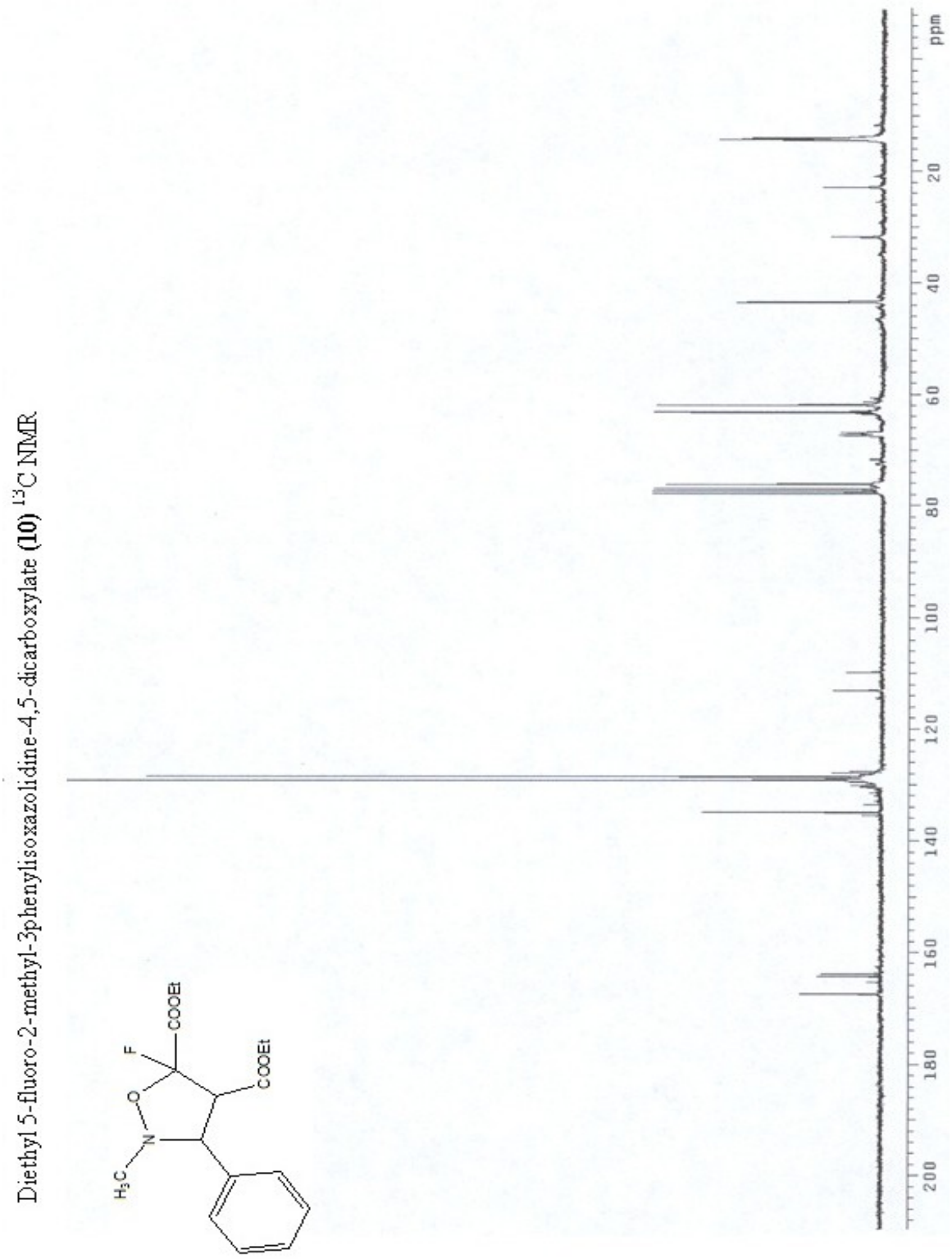


Triethyl 5-(4-cholorophenyl)-3-fluoropyrrolidine-2,3,4-tricarboxylate **(9)** COSY NMR

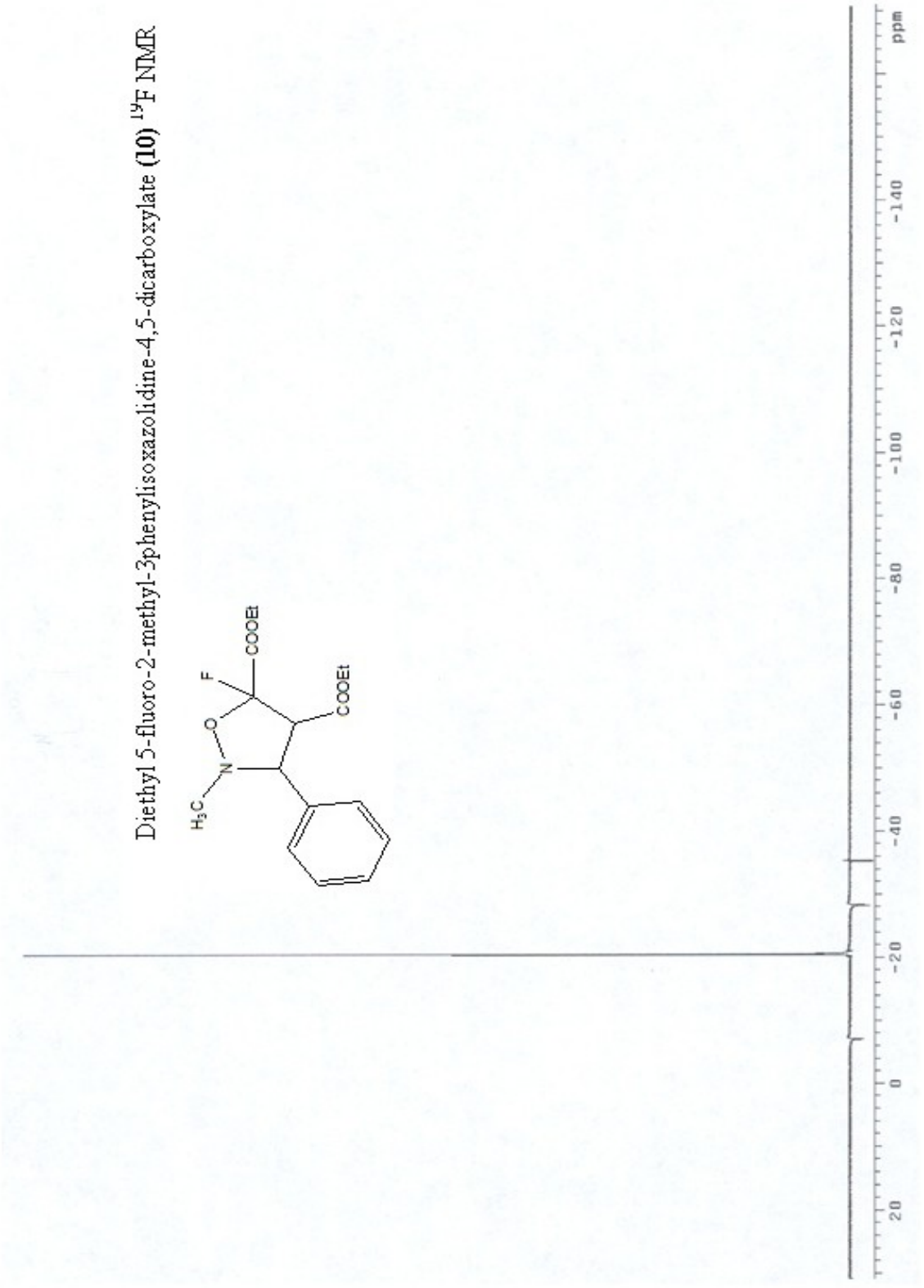
Diethyl 5-fluoro-2-methyl-3phenylisoxazolidine-4,5-dicarboxylate **(10)** ^{1}H NMR



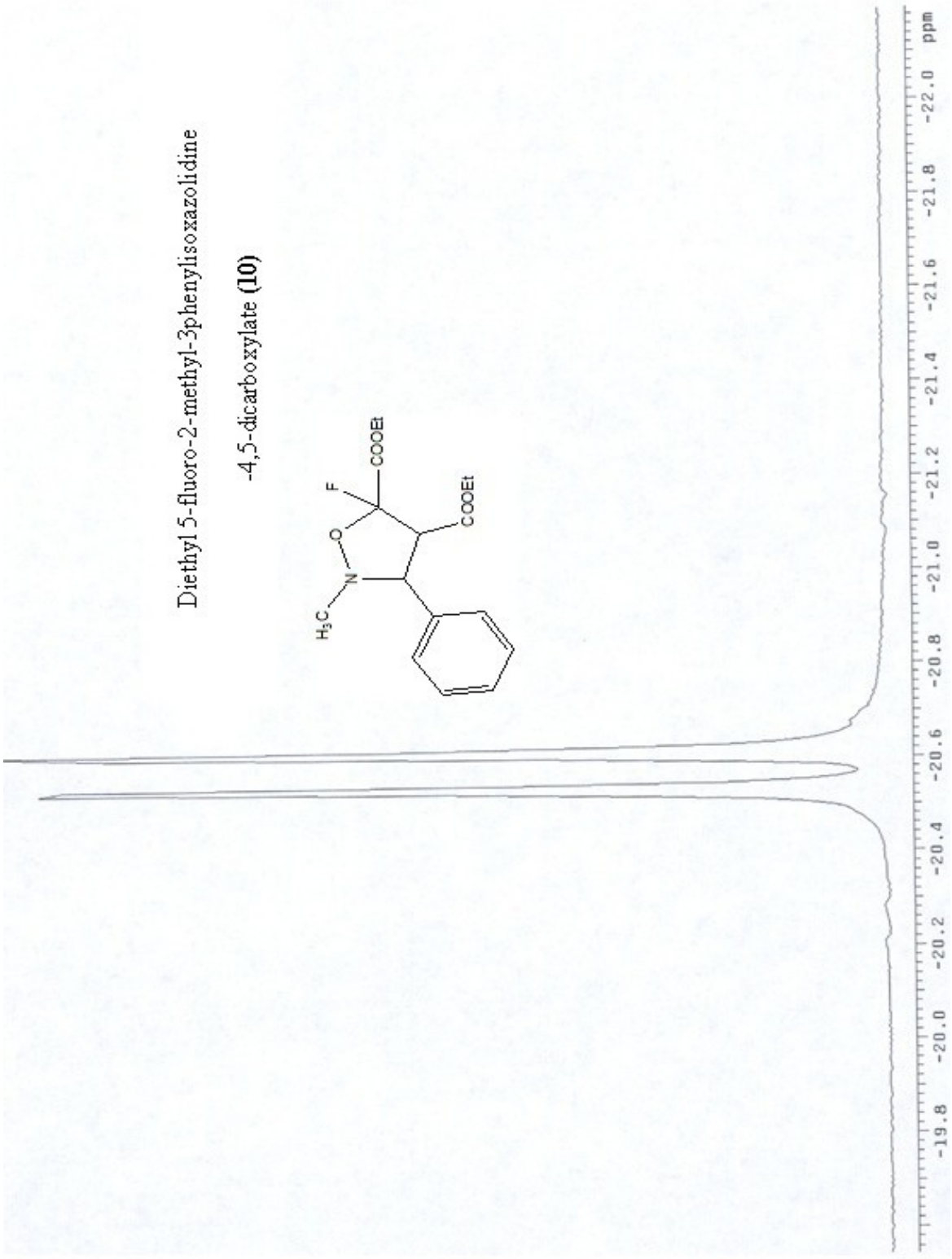
Diethyl 5-fluoro-2-methyl-3phenylisoxazolidine-4,5-dicarboxylate **(10)** ^{13}C NMR



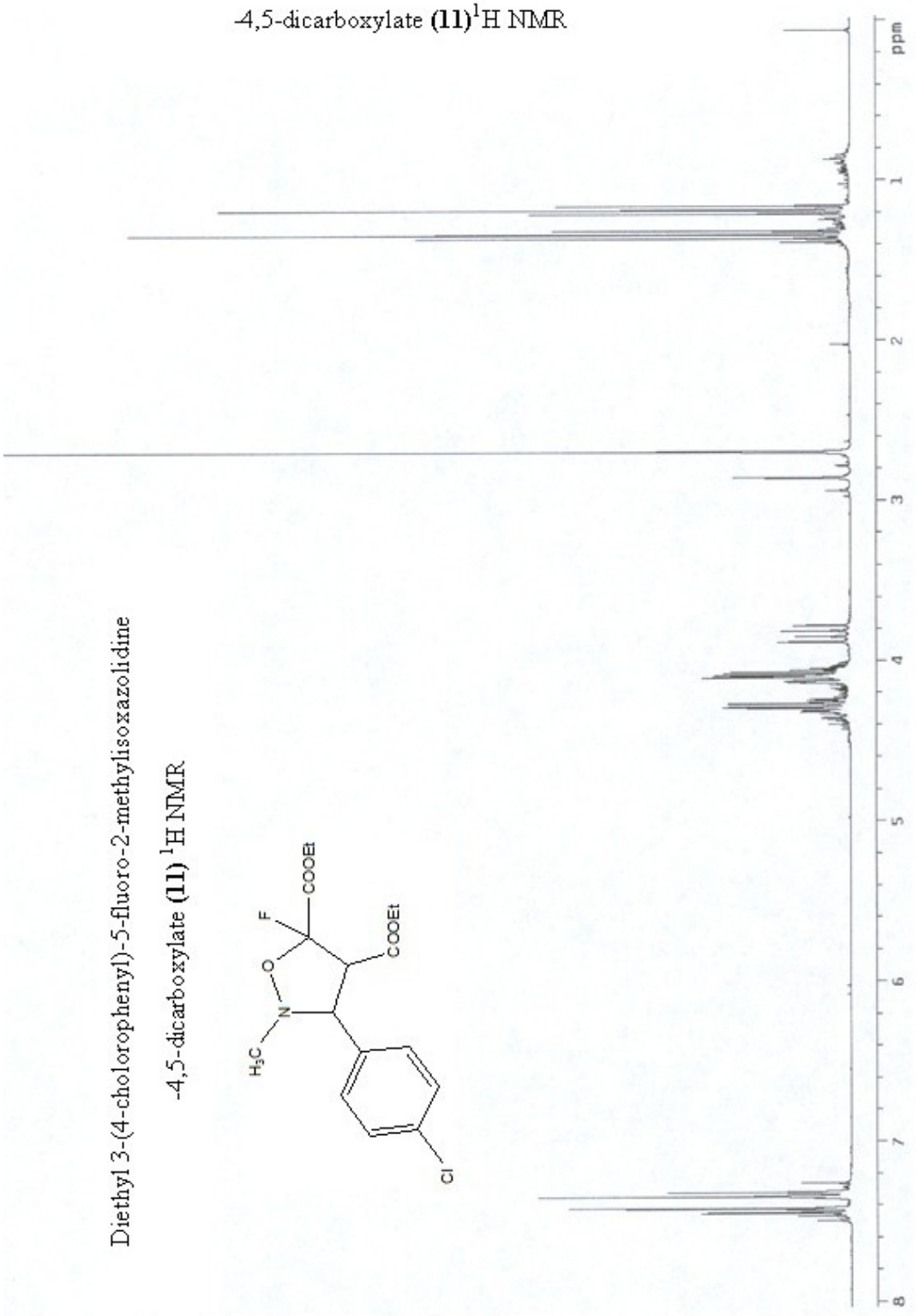
Diethyl 5-fluoro-2-methyl-3phenylisoxazolidine-4,5-dicarboxylate **(10)** ^{19}F NMR



Diethyl 5-fluoro-2-methyl-3phenylisoxazolidine-4,5-dicarboxylate **(10)** ^{19}F NMR

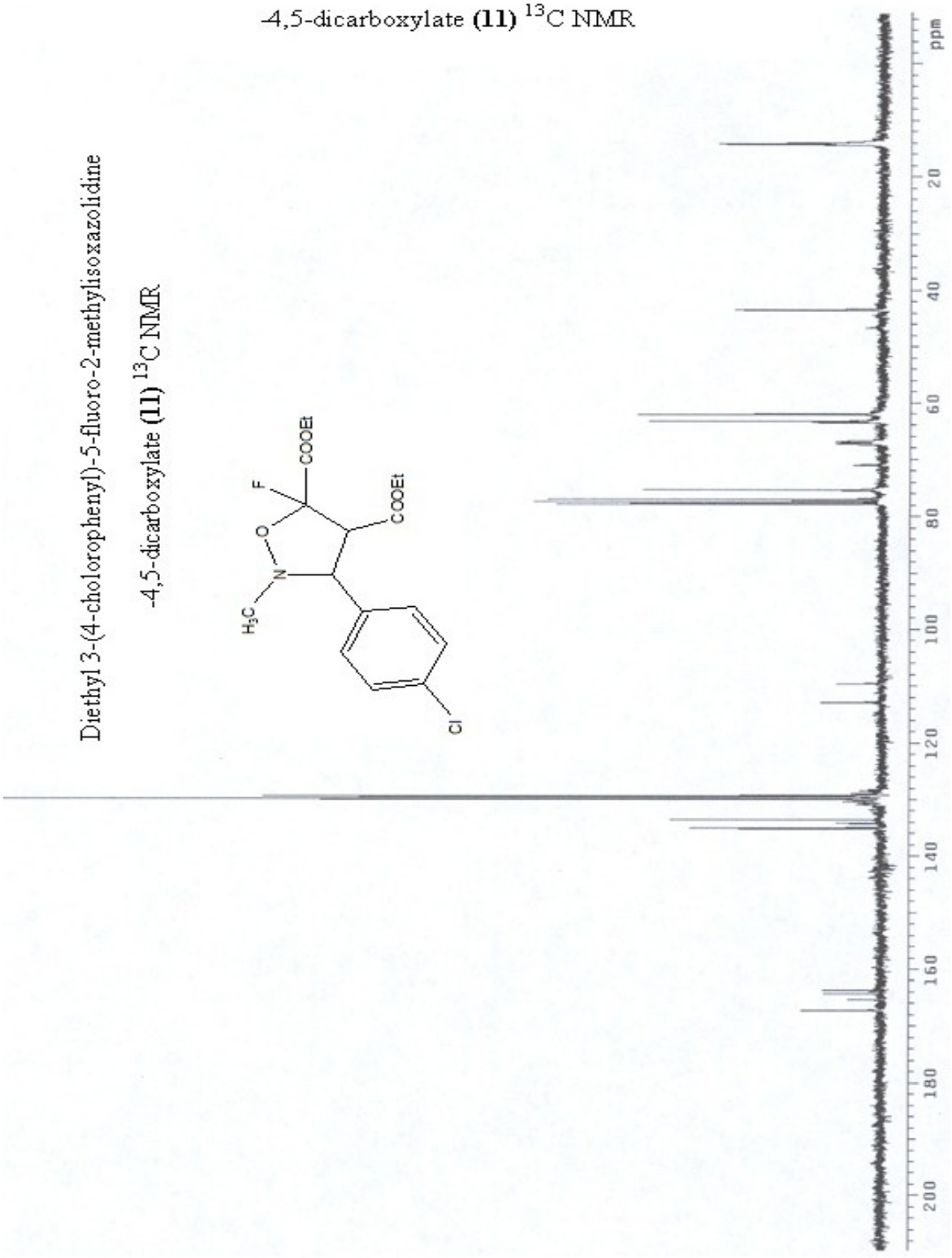


Diethyl 3-(4-cholorophenyl)-5-fluoro-2-methylisoxazolidine -4,5-dicarboxylate **(11)** ^{1}H NMR



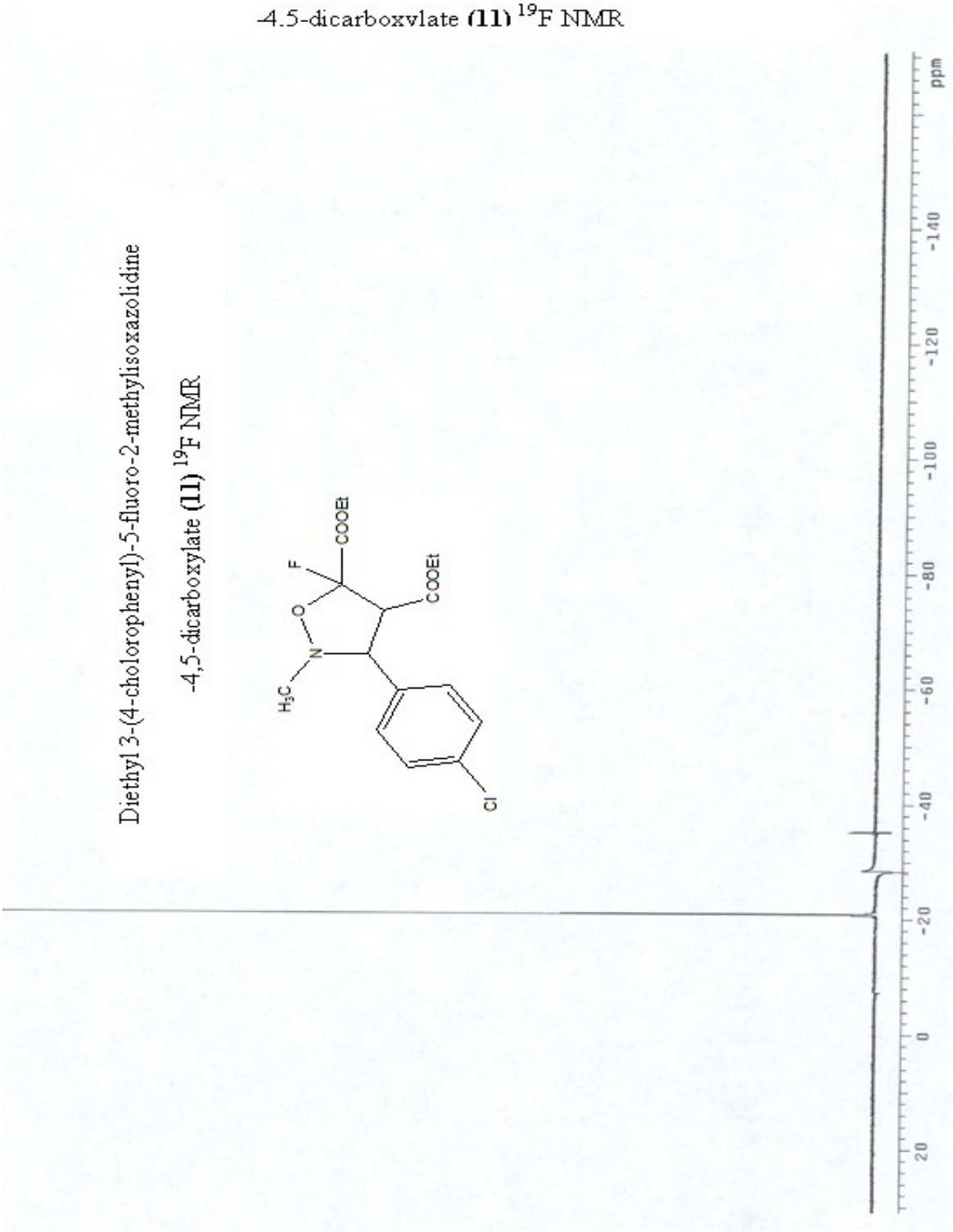
Diethyl 3-(4-cholorophenyl)-5-fluoro-2-methylisoxazolidine -4,5-dicarboxylate **(11)** ^{1}H NMR

Diethyl 3-(4-cholorophenyl)-5-fluoro-2-methylisoxazolidine -4,5-dicarboxylate **(11)** ^{13}C NMR



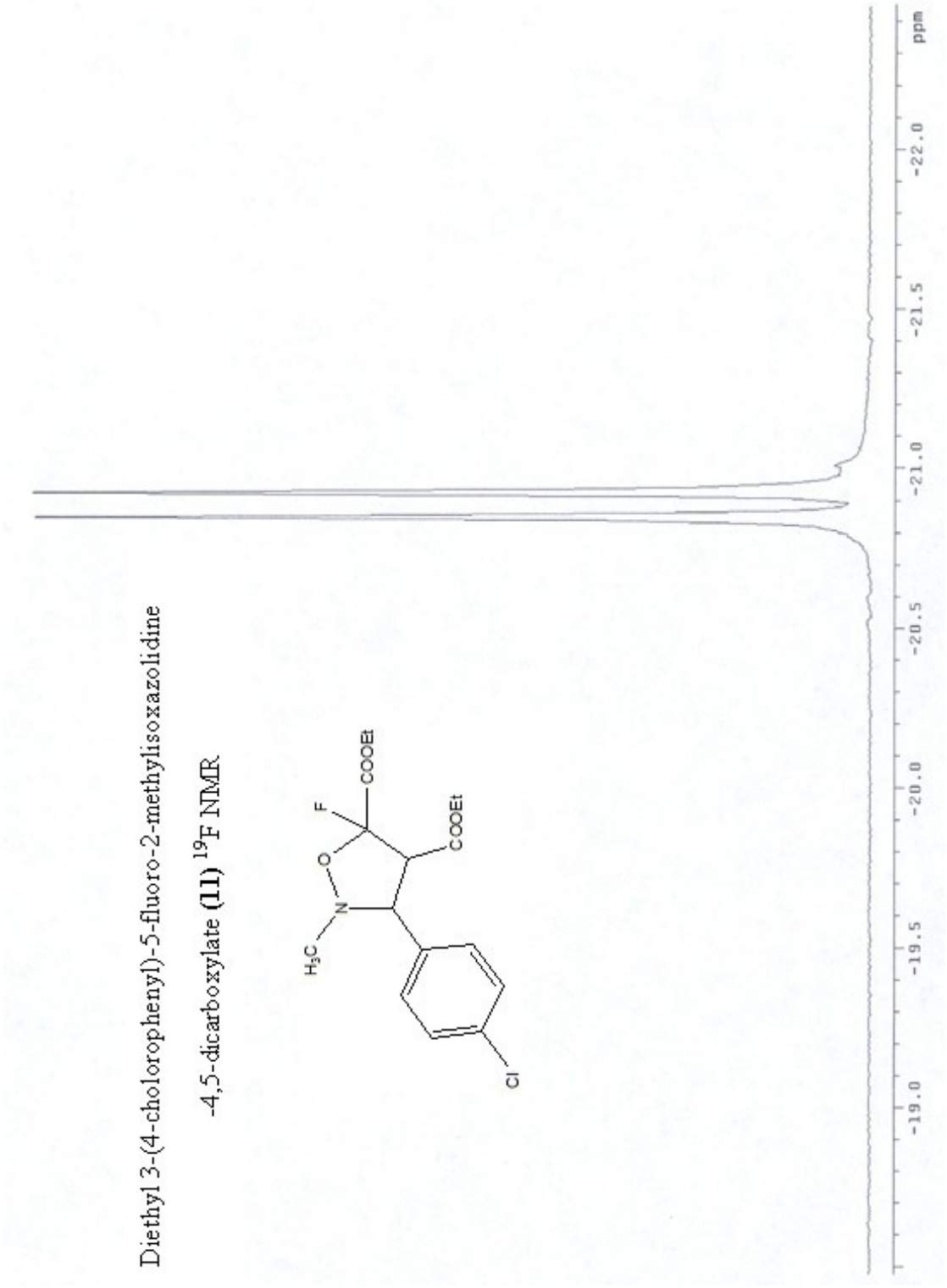
Diethyl 3-(4-cholorophenyl)-5-fluoro-2-methylisoxazolidine

-4.5-dicarboxylate **(11)** ^{19}F NMR

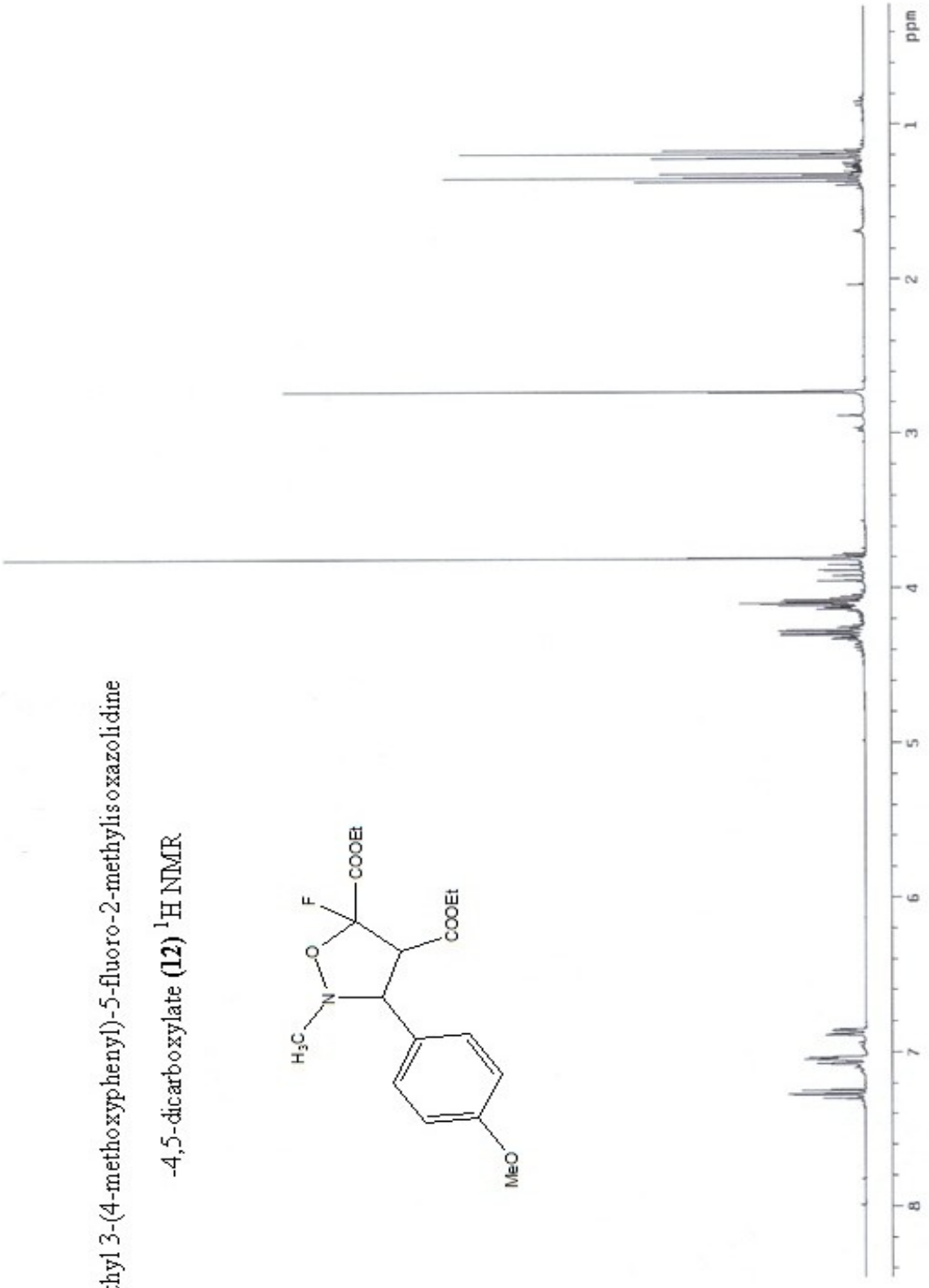


Diethyl 3-(4-cholorophenyl)-5-fluoro-2-methylisoxazolidine

-4.5-dicarboxylate **(11)** ^{19}F NMR

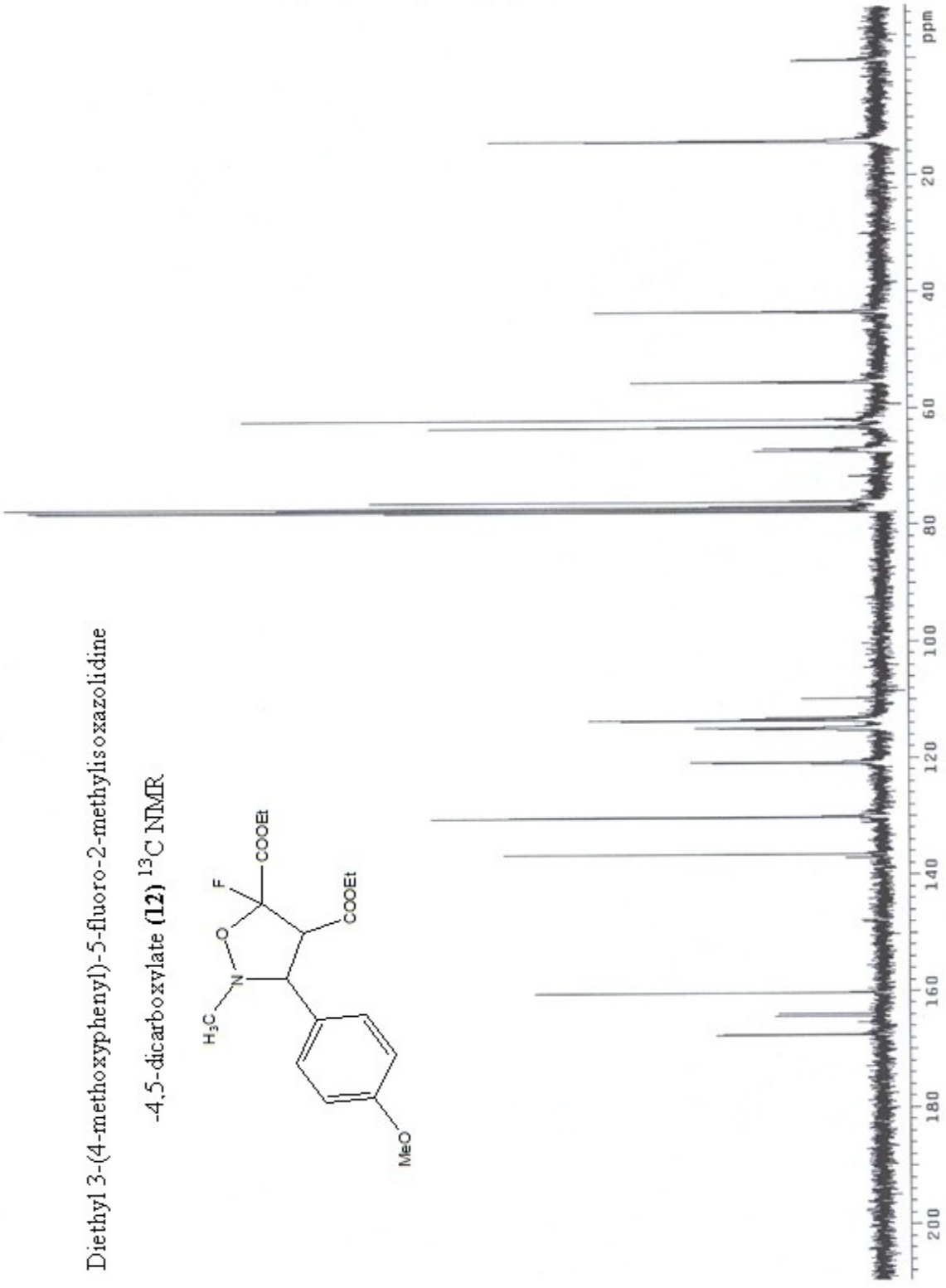


Diethyl 3-(4-methoxyphenyl)-5-fluoro-2-methylisoxazolidine -4,5-dicarboxylate **(12)** ^{1}H NMR



Diethyl 3-(4-methoxyphenyl)-5-fluoro-2-methylisoxazolidine -4,5-dicarboxylate **(12)** ^{1}H NMR

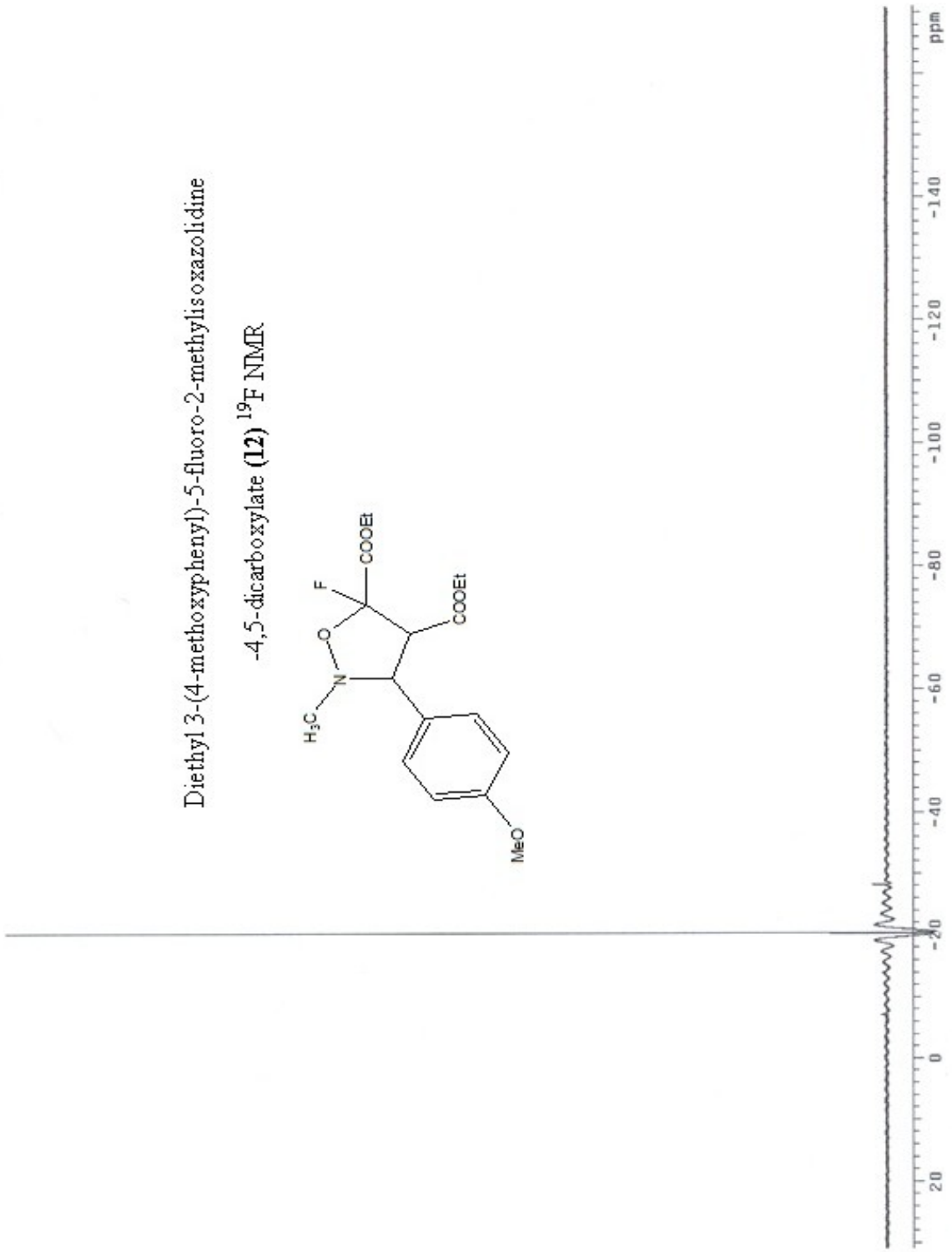
Diethyl 3-(4-methoxyphenyl)-5-fluoro-2-methylisoxazolidine -4,5-dicarboxylate **(12)** ^{13}C NMR



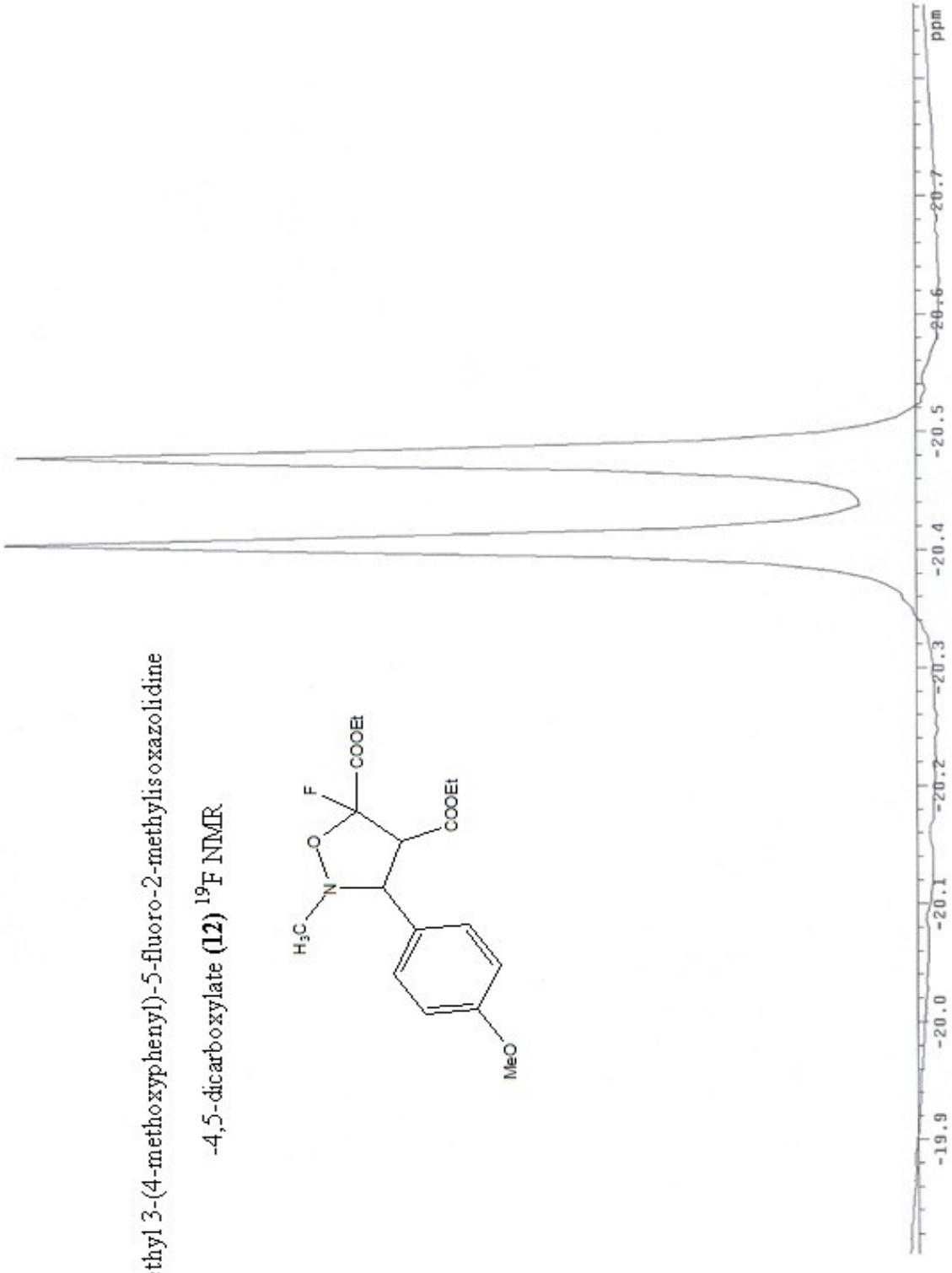
Diethyl 3-(4-methoxyphenyl)-5-fluoro-2-methylisoxazolidine -4,5-dicarboxylate **(12)** ^{13}C NMR

Diethyl 3-(4-methoxyphenyl)-5-fluoro-2-methylisoxazolidine

-4,5-dicarboxylate **(12)** ^{19}F NMR



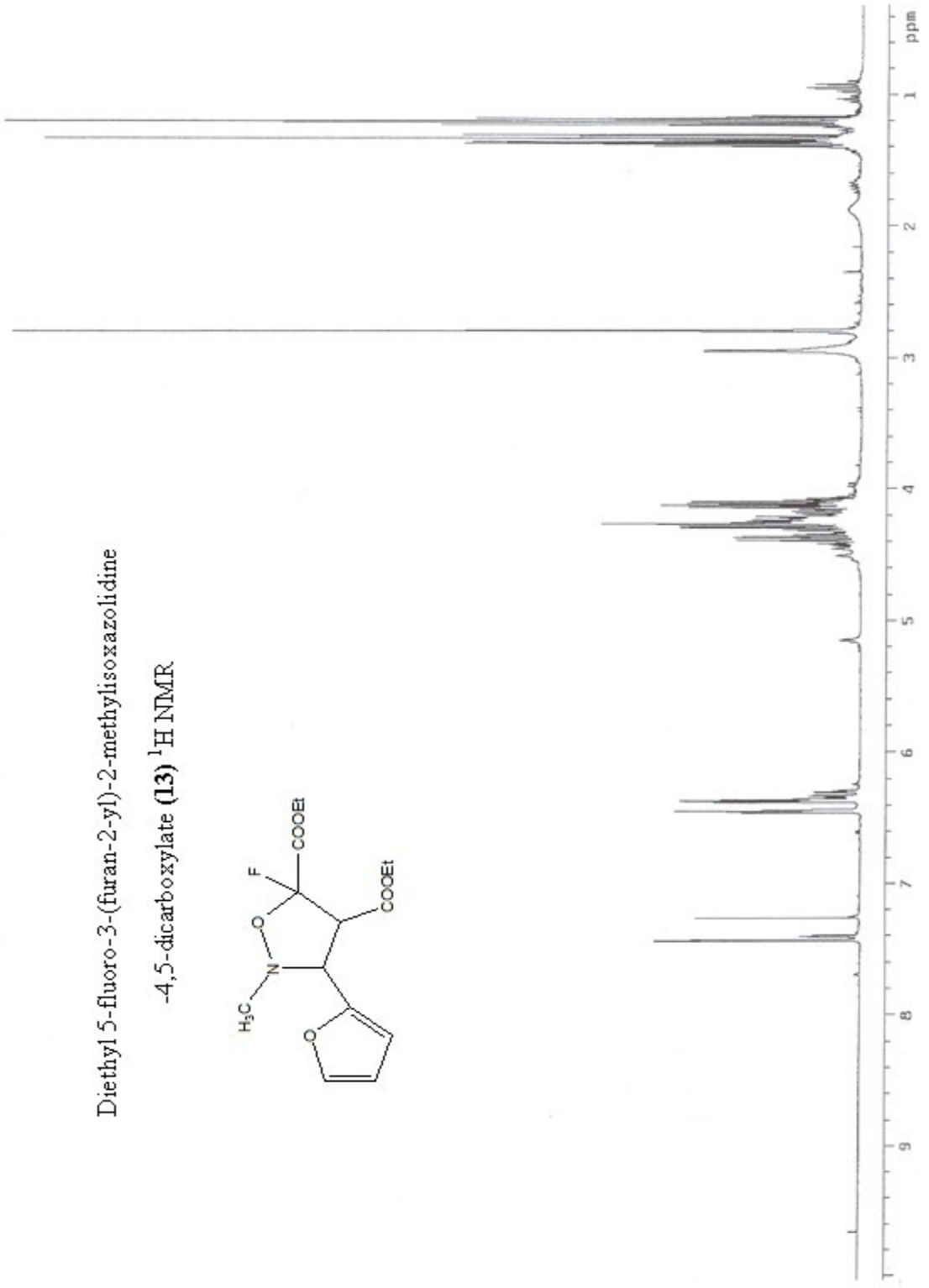
Diethyl 3-(4-methoxyphenyl)-5-fluoro-2-methylisoxazolidine -4,5-dicarboxylate **(12)** ^{19}F NMR



Diethyl 3-(4-methoxyphenyl)-5-fluoro-2-methylisoxazolidine -4,5-dicarboxylate **(12)** ^{19}F NMR

Diethyl 5-fluoro-3-(furan-2-yl)-2-methylisoxazolidine

-4,5-dicarboxylate **(13)** ^{1}H NMR

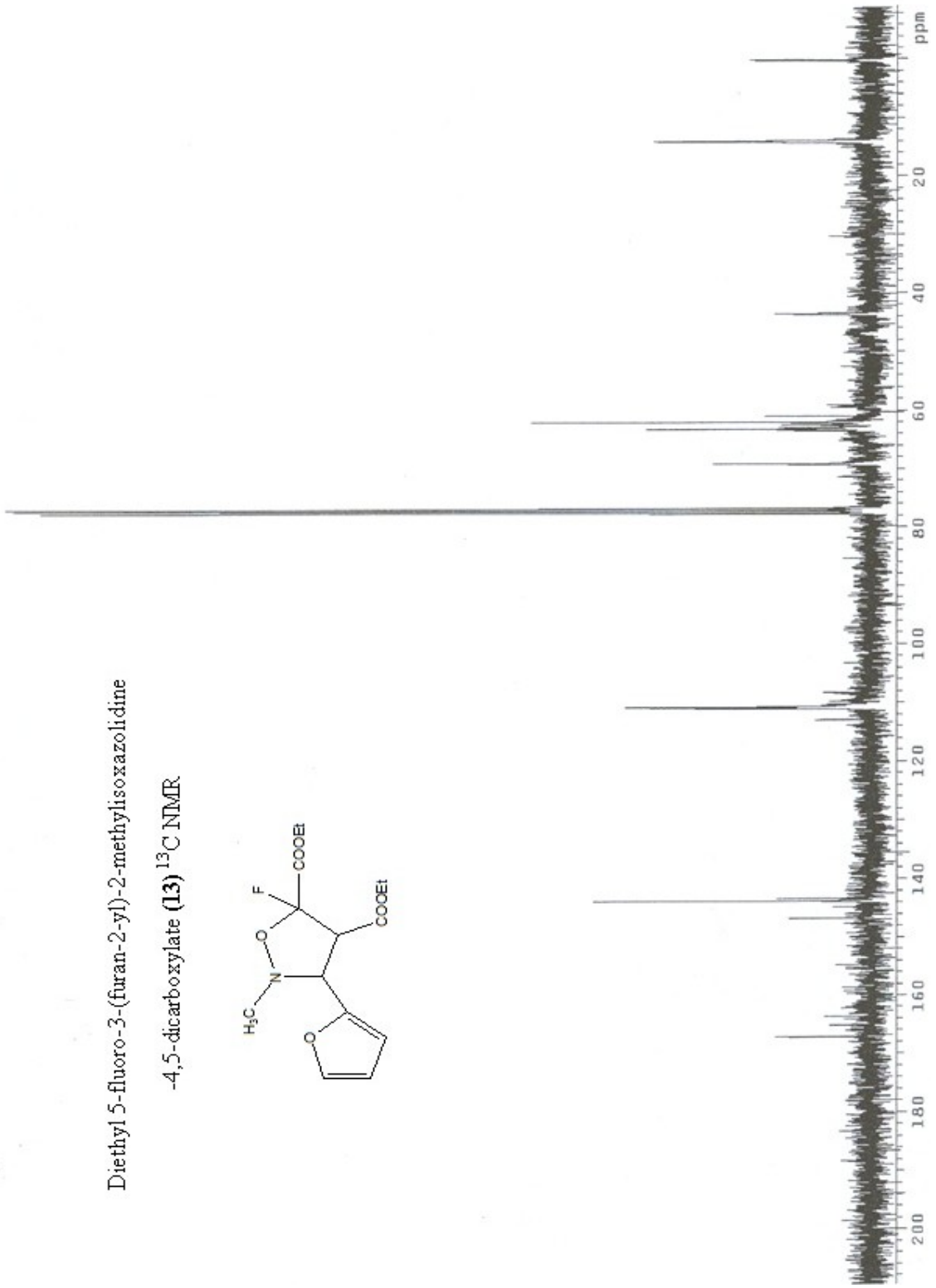


Diethyl 5-fluoro-3-(furan-2-yl)-2-methylisoxazolidine

-4,5-dicarboxylate **(13)** ^{1}H NMR

Diethyl 5-fluoro-3-(furan-2-yl)-2-methylisoxazolidine

-4,5-dicarboxylate **(13)** ^{13}C NMR



Diethyl 5-fluoro-3-(furan-2-yl)-2-methylisoxazolidine

-4,5-dicarboxylate **(13)** ^{13}C NMR

Diethyl 5-fluoro-3-(furan-2-yl)-2-methylisoxazolidine

-4,5-dicarboxylate **(13)** ^{19}F NMR