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PhD Course in Chemical Sciences- XXVIII cycle

SYNTHESIS OF NITROGEN HETEROCYCLES BY INTRAMOLECULAR CYCLIZATION OF α,β-UNSATURATED NITRO COMPOUNDS, CATALYZED BY PALLADIUM COMPLEXES AND WITH CARBON MONOXIDE AS THE REDUCTANT

PhD Thesis of:

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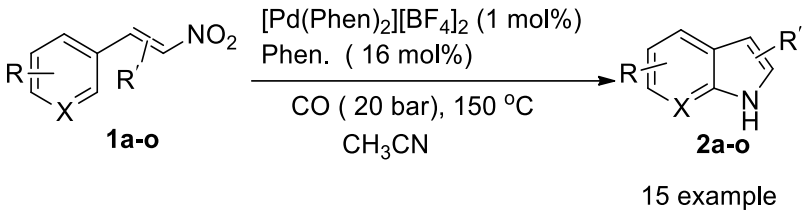
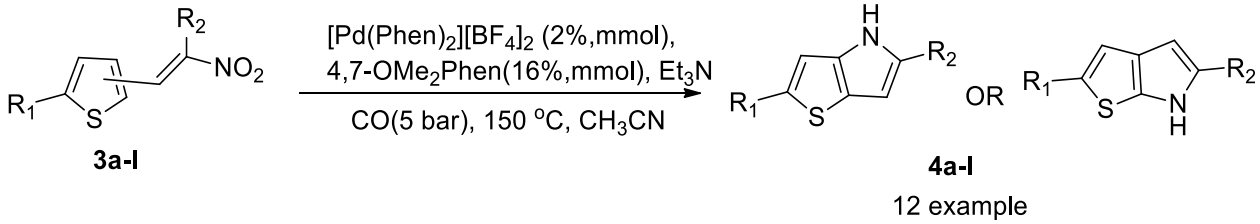
Abstract

The work presented in this thesis was performed in the laboratory of professor Fabio Ragaini, Department of Chemistry, Milan University (UNIMI), in the period of January 2013 to October 2015. Ragaini's research group are interested in using the power of transition metal catalysis, that can economically and efficiently transform readily available substrate and simple reagents (such as nitro compounds, carbon monoxide) into valuable products (such as heterocycles). My thesis describes our continual effort to achieve this goal. This work consists of four main parts.

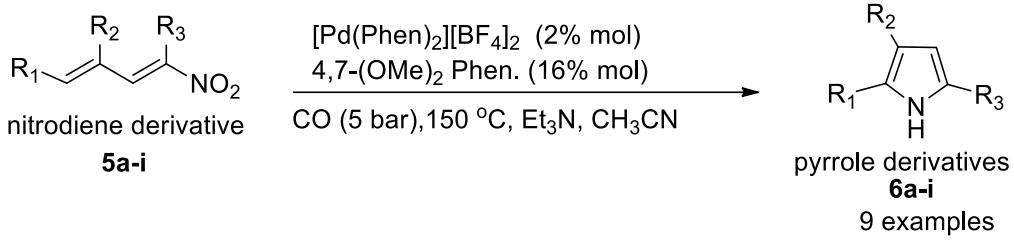
Part I describes the synthesis of medicinally relevant indoles by palladium-catalyzed reductive cyclization of readily obtainable β-nitrostyrenes using carbon monoxide as the reductant and in acetonitrile as a solvent.



Part II describe a new route to synthesize thieno[2,3-b]pyrrole or thieno[3,2-b]pyrrole by intramolecular reductive cyclization of α,β-unsaturated nitro compounds using carbon monoxide as the reductant and catalyzed by palladium complexes.



Part III presents our work on palladium catalyzed intramolecular reductive cyclization of nitro-dienes with carbon monoxide, which provides a novel and efficient method for synthesis of 2,5-disubstituted or 2,3,5-trisubstituted pyrroles



Part IV presents our efforts towards using palladium complexes for allylic amination of cyclohexene by nitroarenes and carbon monoxide. We got a promising results for the catalytic activity of the palladium complex. However, the system does not appear to be competitive with respect to previously reported results with ruthenium complexes.

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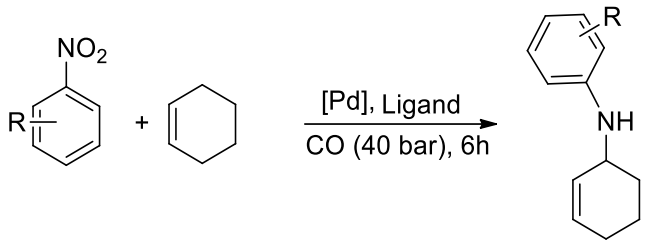

Acknowledgments

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mohamed elatawy

20 october 2015
Milan, Italy

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CHAPTER IV: **APPENDICES**

List of abbreviations

Ac	Acetyl
Ar	Aryl
Ar-BIAN	bis(arylimino)acenaphthene
Atm	atmosphere
Benz.	benzene
Bn	Benzyl
br	broad
^{t}Bu	*tert*-butyl
Bz	benzoyl
°C	degrees Celsius
cat.	Catalytic or catalyst
Conv.	Conversion
Cy	Cyclohexyl
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dd	doublet of doublets
DCM	dicholromethane
DME	1,2-dimethoxyethane
DMEGqu	N-(1,3 dimethylimidazolidin-2-ylidene)quinolin-8-amine
DMF	N,N-dimethylsulfoxide
DMAP	4-dimethylaminopyridine
DMSO	Dimethylsulfoxide
dppp	1,3-bis(diphenylphosphino)propane
EDG	electron-donating group
e.g.	for example or example given
Equiv.	equivalent
Et	ethyl
EWG	electron-withdrawing group

g	gram
GC	gas chromatography
GC/MS	gas chromatography – mass spectrometry
h	hours
J or J	spin-spin coupling constant
K	degree Kelvin
KDR	Kinase insert domain receptor
KO^{t}Bu	potassium tertiary butoxide
Lig.	Ligand
m	multiplet
m-	*meta*-
MDI	4,4'methylene diphenyl diisocyanate
Me	methyl
MeCN	acetonitrile
mg	milligram
MHz	megahertz
ml	milliliter
mmol	millimole
nd	not detected
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
Nuc	nucleophile
n-Bu	n-butyl
o-	*ortho*-
OFET	organic field-effect transistors
OLED	organic light-emitting diodes
OMe	methoxy
OLET	organic light emitting transistors
OPV	Organic photovoltaics
OSCs	organic solar cells
OTFT	organic thin film transistors
p-	*para*-

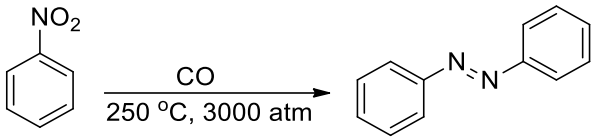
PEG	polyethylene glycol
Ph	phenyl
phen	phenanthroline
ppm	parts per million
Py	pridine
q	quartet
rt	room temperature
s	singlet
Sel.	selectivity
t	triplet
TDI	toluenediisocyanate
TEA	triethylamine
Temp.	temperature
THF	tetrahydrofuran
Thioph.	thiophene
TLC	thin layer chromatography
TMB	2,4,6-trimethylbenzoate
TMBH	2,4,6-Trimethylbenzoic acid
TMphen	3,4,7,8-tetramethyl-1,10-phenanthroline
TPD	thieno[3,4-c]pyrrole-4,6-dione
UNIMI	Università degli Studi di Milano
Δ	heat or thermal
δ	chemical shift

Introduction

1.1 Historical Background

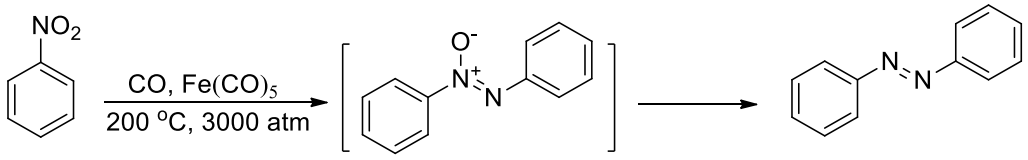
Reductive carbonylation processes constitute industrial core technologies for converting bulk chemicals to a variety of useful products for our daily lives. This powerful technology uses the reductive ability of carbon monoxide to transform nitro compounds into valuable nitrogen functionalities. Such as amines, isocyanates, carbamates and ureas. Recently the scope of reductive carbonylation has been extended to include intramolecular C–H bond amination in the preparation of important nitrogen heterocycles such as indole, carbazole, benzimidazole, etc.

The first example of reductive carbonylation of nitro compounds was reported in 1949 by Buckley and Ray.[1] (Scheme 1.1)



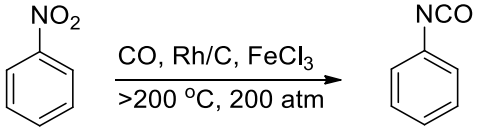
Scheme 1.1

In 1965, Kmiecik introduced the first metal catalyzed reductive carbonylation of nitrobenzene, using iron pentacarbonyl $Fe(CO)_5$ as a catalyst, affording the corresponding azo derivatives.[2] Azoxybenzene was isolated as an intermediate in this transformation. Scheme 1.2



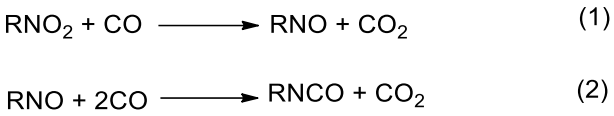
Scheme 1.2

The first reduction of nitro aromatic compounds to isocyanates by carbon monoxide was reported by Hardy and Bennett in 1967.[3] this reaction appeared to be interesting since it is a single step and phosgene-free route to isocyanates. Scheme 1.3



Scheme 1.3

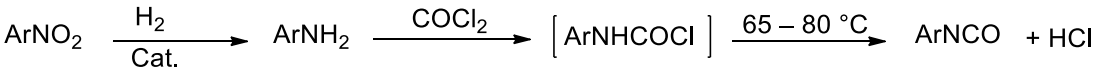
Probable intermediates in this carbonylation reaction are the corresponding nitroso compounds. (eq 1 and 2)



(1)

(2)

The industrial synthesis of isocyanates is carried out from the nitro compounds in two steps with very high yields and selectivities. (eq 3)



(3)

However, highly toxic phosgene is used and large amounts of corrosive HCl are produced as a byproduct in this industrial transformation,[4] So the phosgene free approach has found a widespread acceptance, and since this discovery, research in this area of reductive carbonylation has greatly increased. Many catalytic systems for the carbonylation of nitro compounds were developed in the last years to afford other targets including isocyanates, carbamates, dicarbamates, ureas, and amines[5] (Figure 1.1)

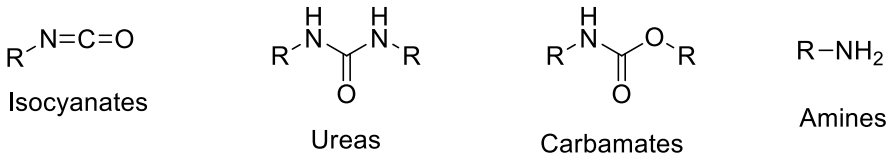


Figure 1.1

Isocyanates are commodity chemicals mostly employed in polyurethane synthesis but also intermediate in the production of carbamates and ureas. Polyurethanes are widely applied in almost every part of modern life in the form of plastic foams, coatings, adhesives, sealants and elastomers and binders. Moreover carbamates and urea are important final products themselves in agrochemical and pharmaceutical industry. The annual world production of these chemicals is several millions metric tons and it is steadily increasing. Among the chemicals cited above, the most widely employed are aromatic isocyanates, especially toluenediisocyanate (TDI) and 4,4'methylene diphenyl diisocyanate (MDI) that account for more than seven million metric tons per year. (Figure 1.2) The industrial interest for these two compounds is evident from the recent investment on new plants by the major producers both in Europe and in Asia.[4]

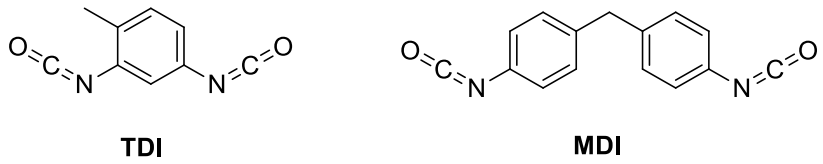


Figure 1.2

An often proposed mechanism for the reaction catalyzed in the homogeneous phase is based on the following steps. Initially, in the presence of the catalyst and CO, the nitro compound generates a metallacycle. This intermediate undergoes decarboxylation, leaving the nitroso group bound to the metal. The subsequent insertion of CO followed by decarboxylation gives a nitrene species as key intermediate, which can be carbonylated to give the isocyanate[5a] (Figure 1.3).

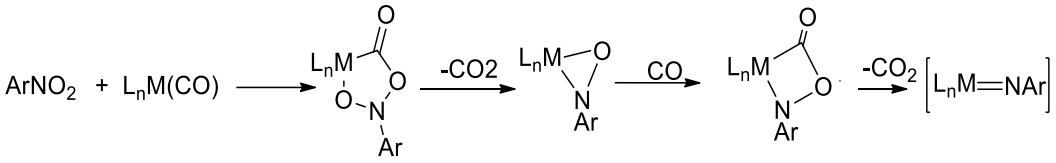


Figure 1.3

The nitrene species can also react with a nitroso compound or another nitrene intermediate, yielding azoxy or azo compounds as side products[5a, 6] (Figure 1.4).

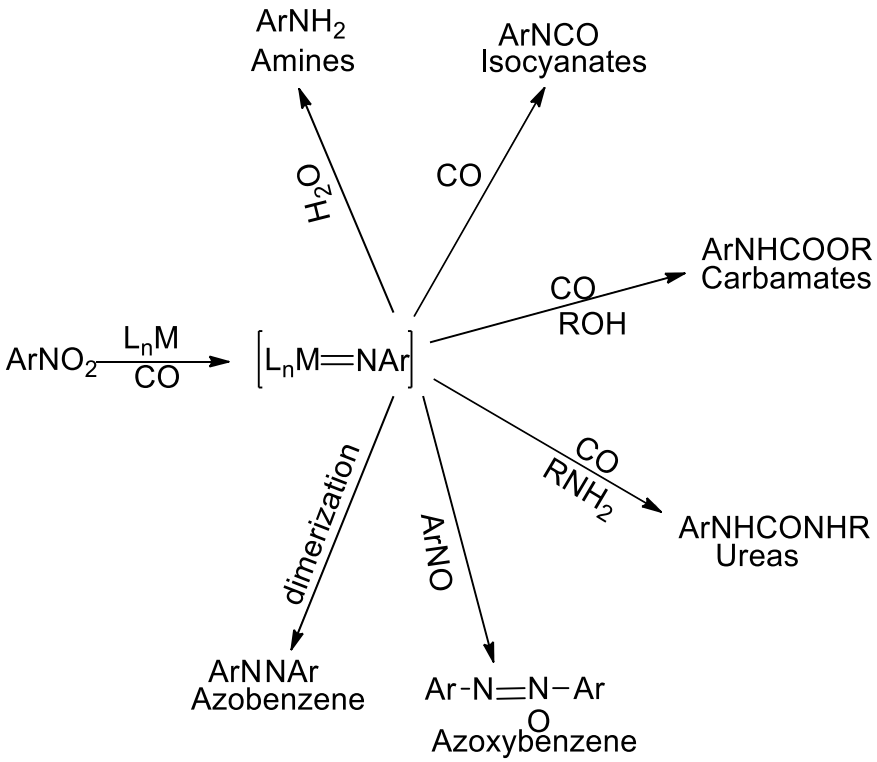


Figure 1.4

1.2 Synthesis of heterocycles by Reductive carbonylation

Heterocyclic molecules play a significant role in life processes and have played a major role in industrial developments of the last century, for instance in the field of pharmaceuticals, dyes, polymers and agrochemicals as well as in commodity and fine chemicals. They comprise not only some of the most interesting and biologically important natural products like alkaloids, carbohydrates, nucleic acids, and antibiotics but include many practical drugs and a large segment of known synthetic organic compounds. Scientists have devoted a great amount of effort to find optimal synthetic approaches to a variety of heterocyclic compounds. Different heterocycles such as indoles, indazoles, carbazoles, benzimidazoles, triazoles, and quinazolinone have been synthesized by reductive cyclization of nitroarenes bearing in the ortho position a suitable functional group.[5-6] (Figure 1.5), The utility of this method arises from the availability of nitroarenes.

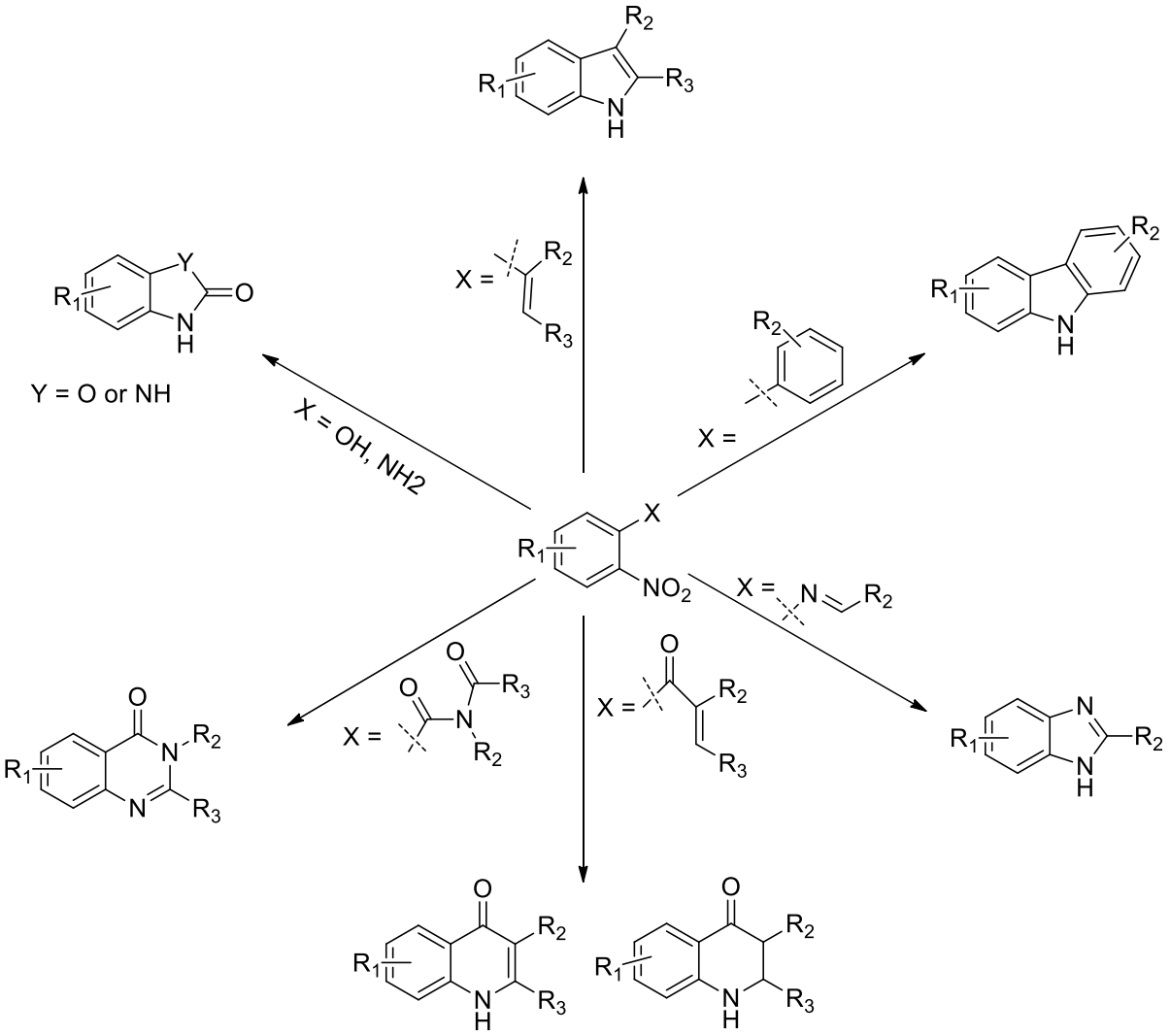
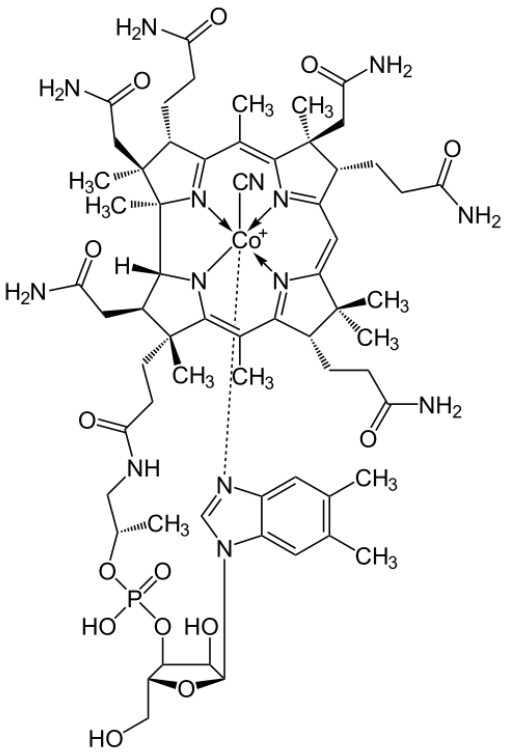


Figure 1.5

The first example of reductive cyclization of nitroarenes for the synthesis of heterocycles was reported by Cadogan in the early 60s.[7] In this reaction a phosphite, usually triethylphosphite, is used as the reductant, thus a stoichiometric amount of phosphate is produced. Despite the use of relatively cheap materials, a serious drawback is represented by the difficulty of removing the stoichiometric by-product from the reaction mixture. This makes this reaction of little interest for an industrial and academic use.

1.2.1 Synthesis of Benzimidazoles

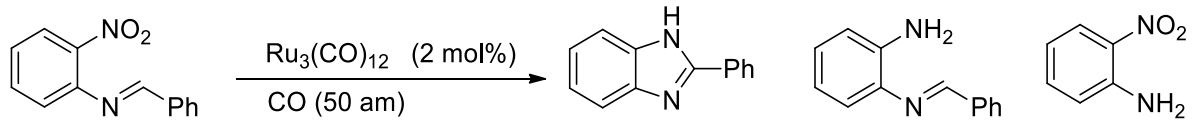
Benzimidazole derivatives play important role in medical field, many of benzimdazole derivatives exhibit many pharmacological activities such as antimicrobial,[8] antiviral,[9] antidiabetic[10] and anticancer activity.[11] In nature the most prominent benzimidazole compound is *N*-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B_{12}.[12] Benzimidazole has been used as carbon skeletons for N-heterocyclic carbenes. The NHCs are usually used as ligands for transition metal complexes. They are usually prepared by deprotonating an N,N'-disubstituted benzimidazolium salts at the 2-position with a base.[13]



Vit B_{12}

It has been shown that different transition metal complexes (Ru, Pd, Se) act as catalysts for affording benzimidazoles by reductive cyclization of various nitroarenes using carbon monoxide as a reductant. Herein some examples, Cenini and coworkers in 1992, reported a synthesis of benzimidazole by

reductive N-heterocyclization of benzylidene (2-nitroaryl)amines with carbon monoxide and using triruthenium dodecacarbonyl $Ru_3(CO)_{12}$ as a catalyst.[14] However, the main disadvantage of this method is the limited number of stable imine, which can be overcome by preparing the imine in situ. Thus reductive carbonylation of *o*-nitroanilines in the presence of aldehydes affords also benzimidazoles by condensation of the aldehyde with the amino group, followed by cyclization[14-15] (Scheme 1.4)

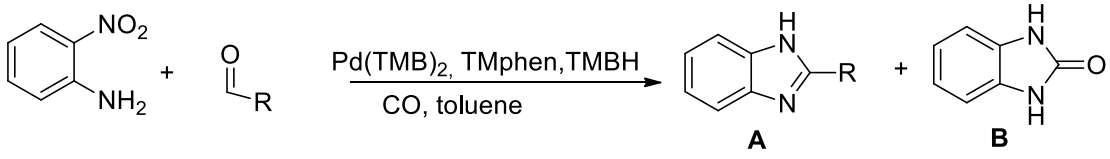


Benzene	220 °C	86%	4%	0 %
Benzene	170 °C	34%	trace	47%
Acetonitrile	170 °C	82%	0%	4%

Scheme 1.4

The most probable mechanism should be based on the metal-assisted deoxygenation of the nitro group by CO, to give an intermediate nitrene bound to the metal center. Subsequent insertion of the nitrene into the C-H bond of the Schiff base should lead to the final product. The formation of the by-product amine would derive from hydrogen-atom abstraction by the intermediate nitrene from the solvent or from the traces of water present in the reaction medium. The formation of o-nitroaniline is due to the partial hydrolysis of the starting material by the moisture in the solvent.[16]

In 1994, Cenini group demonstrated that catalytic system based on palladium can also be used for this reaction[15](Scheme 1.5)

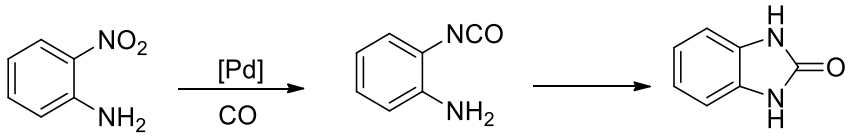


Scheme 1.5

R	T (°C)	t (h)	P_{CO} (atm)	Conv. %	A %	B %
Ph	180	5	40	100	83	trace
Ph	160	3	40	80	55	15
Ph	180	5	20	100	81	17
p-ClC_6H_4	180	2	40	80	55	45
P-$MeOC_6H_4$	180	3	40	100	80	10

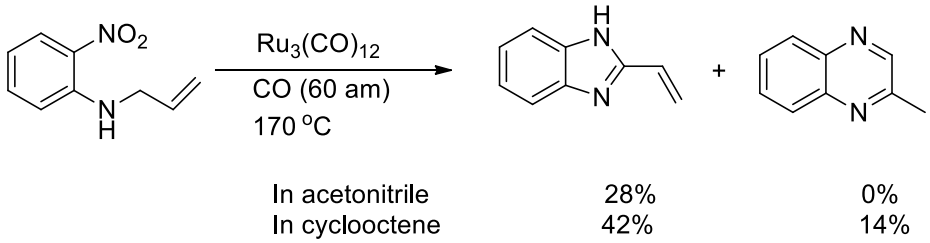
2-C_5H_4N	180	3	40	100	22	trace

2,4,6-Trimethylbenzoic acid (TMBH) is required to catalyse the formation of the Schiff base or else, no reaction occur. The acid was not necessary if the reaction is conducted on the preformed Schiff base. The imidazolone by product is probably formed by carbonylation of *o*-nitroaniline to o-isocyanatoaniline followed by ring closure. (Scheme 1.6)



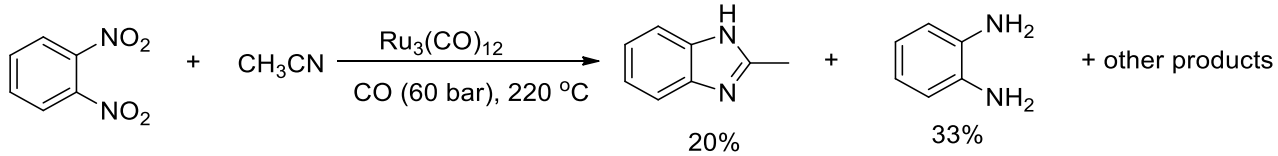
Scheme 1.6

In the same year, Bassoli explored the reductive annulation of N-allyl-2-nitroaniline as the substrate to form a benzimidazole. The reaction of the substrate with (7 mol %) $Ru_3(CO)_{12}$ catalyst at elevated temperature and carbon monoxide pressure gave 2-vinylbenzimidazole (Scheme 7). It is interesting to note that both a higher yield of benzimidazole and the formation of 2-methylquinoxaline were observed using cyclooctene as the solvent.[17] (Scheme 1.7)



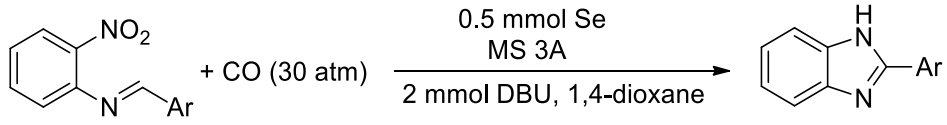
Scheme 1.7

Two years later, Rindone and co-workers reported that *o*-dinitrobenzene can also be employed as substrate in the presence of nitriles and $Ru_3(CO)_{12}$ as catalyst [18](Scheme 1.8). However, yields are low (20%) and the most abundant product is *o*-phenylendiamine. Hydrogenation prevails at least in part because the acetonitrile employed as solvent was not dried and it had been previously reported by Ragaini's group that ruthenium carbonyls are very effective catalysts for the reduction of nitroarenes to anilines by CO/H_2O.[19]



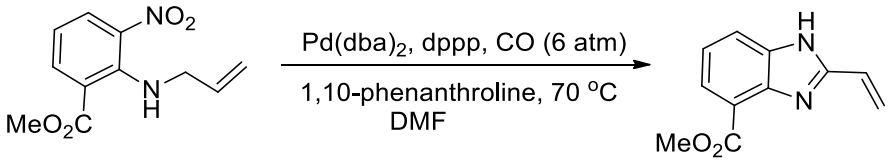
Scheme 1.8

In 2006, Nishiyama introduced selenium as efficient catalyst in the reductive N-heterocyclization of benzylidene(2-nitroaryl)amines with carbon monoxide to afford 2-aryl-1*H*-benzimidazoles.[20] (Scheme 1.9)



Scheme 1.9

In 2007, Soderberg's group reported a mild condition in their study of the palladium-catalyzed synthesis of 2-alkenyl or 2-arylsubstituted benzimidazoles starting from readily available N-allyl- or N-benzyl-2-nitrobenzenamines. The reaction involves, at least formally, an unusual insertion into a sp^3 hybridized carbon–hydrogen bond. The reaction sequence is flexible and a variety of functional groups are tolerated.[21] (Scheme 1.10)



Scheme 1.10

1.2.2 Synthesis of carbazole

The carbazole framework is found in many pharmaceuticals and bioactive natural products. Some of the carbazole-containing molecules show antiviral,[22] antimalarial,[23] and antitumor activity.[24] Some of them are currently being used as lead compounds for drug development.[25] (Figure 1.7) Carbazoles are also used as building blocks for the synthesis of functional materials, such as organic light-emitting diodes (OLED), because of their wide band gap, high luminescence efficiency, and allowing flexible modification of the parent skeleton.[26] Owing to the importance and usefulness of these carbazole based compounds, various approaches for their synthesis have been developed.

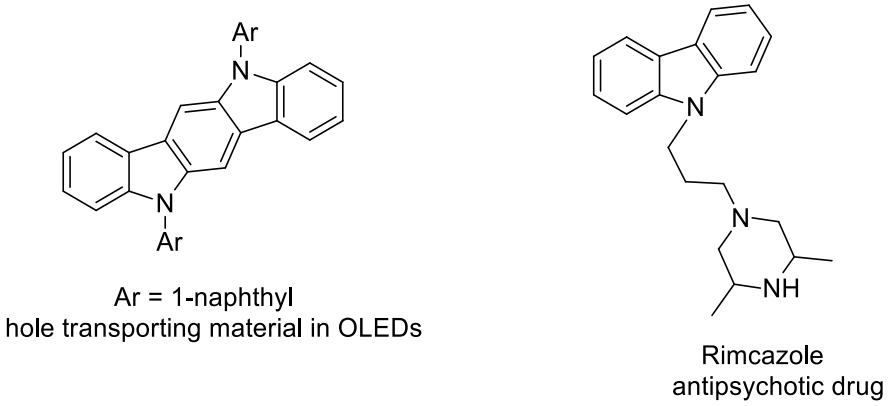
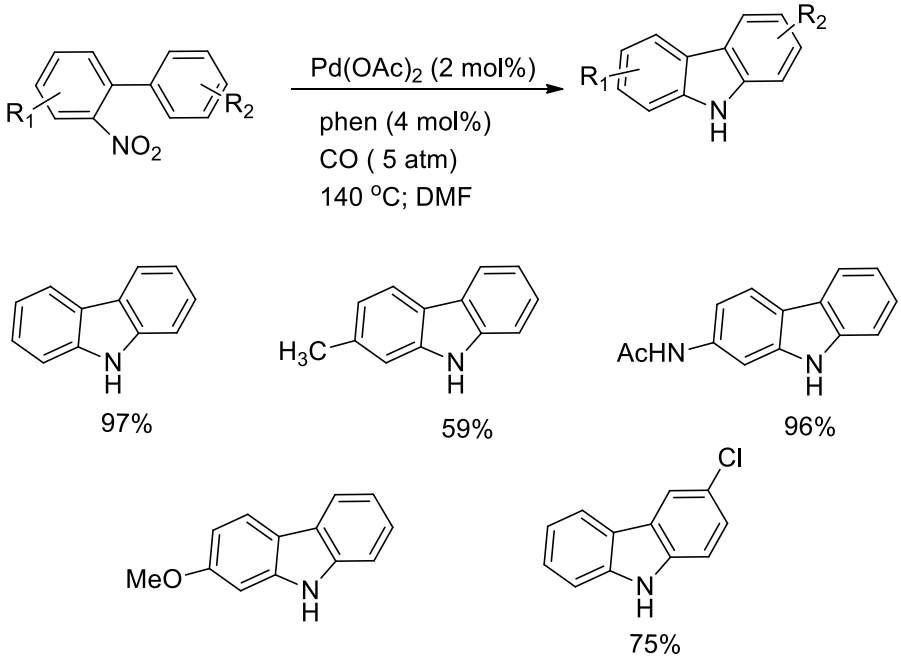


Figure 1.7

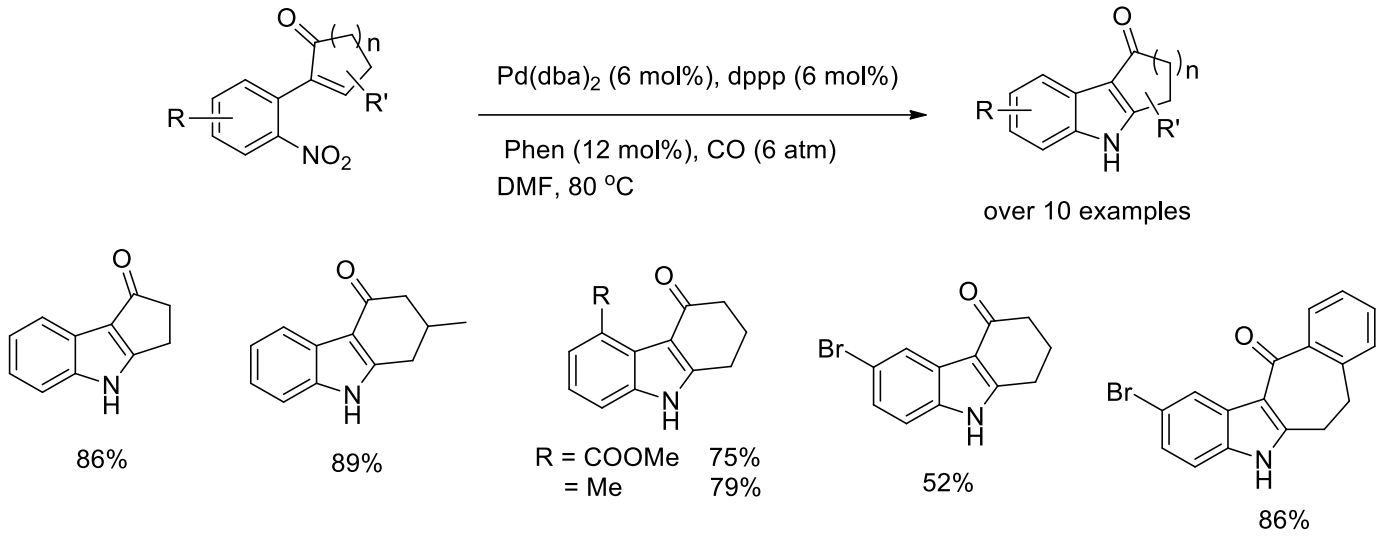
In 2004 Smitrovich and Davies, reported that cyclization of *o*-nitrobiphenyls using (2 mol %) of palladium acetate as a catalyst and (4 mol %) of phenanthroline under (~5 bar absolute pressure) CO at 140 °C in DMF for 16 h gave a 97% isolated yield of carbazole.[27] The reaction was also successfully applied to the synthesis of other carbazoles.

Earlier attempts reported for cyclization of *o*-nitrobiphenyls to carbazole using iron pentacarbonyl[2] $Fe(CO)_5$ or triruthenium dodecacarbonyl $Ru_3(CO)_{12}$ as catalyst gave a low yield of carbazole and also require a harsh conditions[6](Scheme 1.11)



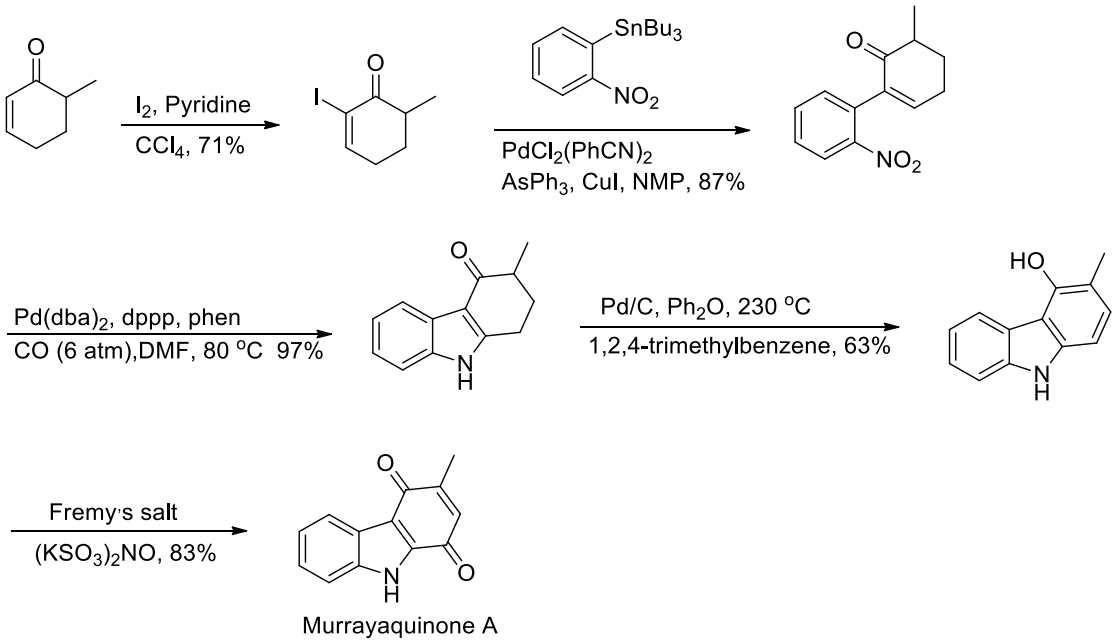
Scheme 1.11

In 2002, Söderberg[28] and coworkers studied cyclic enones as the pendent olefin in the C–H bond amination, using a Pd(0) source with a mixture of bidentate ligands, phenanthroline and dppp, in DMF at 80 °C and 6 atm CO pressure, resulted in carbazolone formation with yields up to 97% (Scheme 1.12).



Scheme 1.12

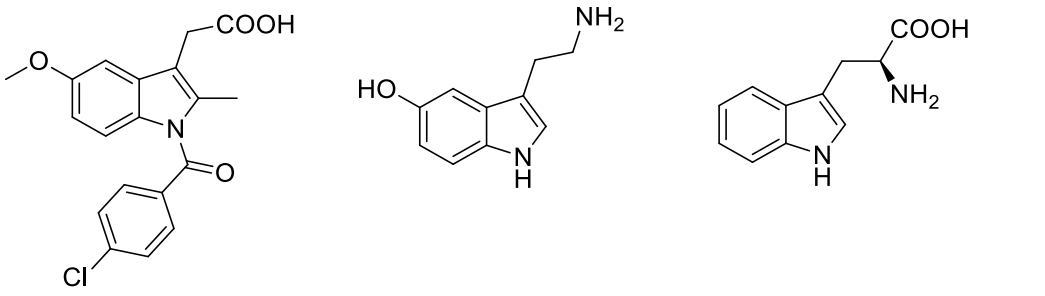
The power of the method was displayed in the formal synthesis of Murrayaquinone A, a carbazole alkaloid isolated from the root bark of *Murraya euchrestifolia* which possess cytotoxic properties against human tumor cells.[29] (Scheme 1.13)



Scheme 1.13

1.2.3 Synthesis of indole

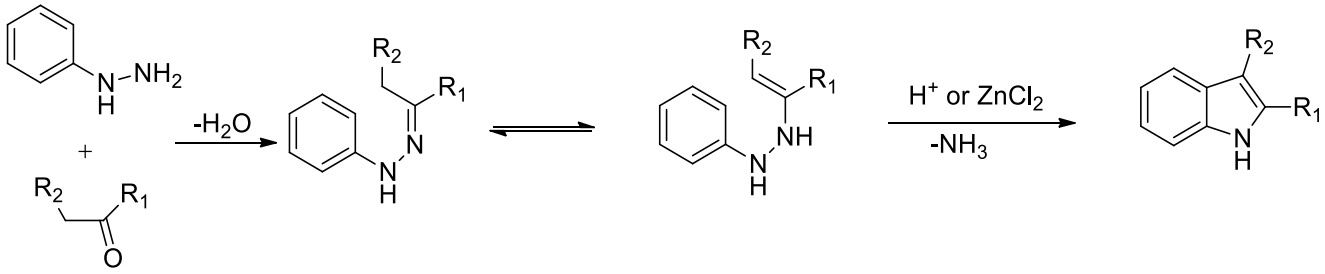
Indole was first isolated in 1869 by treatment of the natural indigo dye with oleum. The name ***indole*** is a combination of the words ***ind****igo* and ***ole****um,*[30] Indole skeleton is the parent substance of a large number of important compounds that occur in nature. Bulk of literature evidence revealed wide spectrum of biological activities of indole and its analogs[31] as e.g. antifungal[32], anticancer,[33] CNS depressant,[34] antiviral,[35] antitumor,[31] antibacterial,[36] anticonvulsant,[37] cardiovascular activity,[38] antihypertensive activity,[39] anti-inflammatory and analgesic.[40] (Figure 1.8)



Indomethacin (anti-inflammatory drug) | Serotonin (neurotransmitter) | Tryptophan (essential alpha amino acid)

Figure 1.8

The synthesis and reactivity of indole derivatives have been a topic of research interest for well over a century and a variety of well-established classical methods are available (*i.e.*: the Fisher indole synthesis, Madelung cyclization of *N*-acyl-*o*-toluidines, the Bischler-Möhlau condensation of anilines and α-bromoacetophenone, etc.). For almost one century the Fisher indole synthesis has remained one of the most used methodologies for the synthesis of indole derivatives. This approach involves transformation of enolizable *N*-arylhydrazones into indoles (Scheme 1.14). The reaction proceed via condensation of an arylhydrazine with a ketone under acid catalysis, followed by a [3,3]-sigmatropic rearrangement, ammonia elimination and aromatization. One of the main advantage of the Fischer reaction is the tolerance to a wide range of functional groups on the aromatic ring.[41]



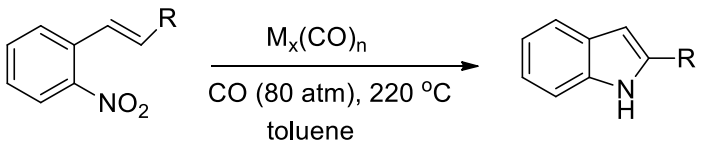
Scheme 1.14

Beside the "classical" organic synthetic methodologies, many transition-metal catalyzed synthetic strategies were developed in the last fifty years. Herein we focus on the metal catalyzed reductive cyclization of nitroarenes to indoles by CO, which could be either intramolecular (as for *o*-nitrostyrenes) or intermolecular (nitroarenes and olefins or alkynes).

1.2.3.1 Intramolecular reductive cyclization of nitroarenes

a- From *o*-nitrostyrenes

The reductive cyclization of *o*-nitrostyrenes has been known since 1965 when Sundberg developed a reductive cyclization reaction of *o*-nitrostyrenes to indoles by trivalent phosphorus as ligand.[42] The disadvantage of this reaction is the production of large amounts of organic phosphorus-containing coproducts. Years later Cenini and coworkers employing the same substrates obtained the catalytic deoxygenation of the nitro group using carbon monoxide and transition metal carbonyls in harsh conditions (220 °C under 80 atm of CO).[43] These severe conditions limit the synthetic utility of this system. (Scheme 1.15)

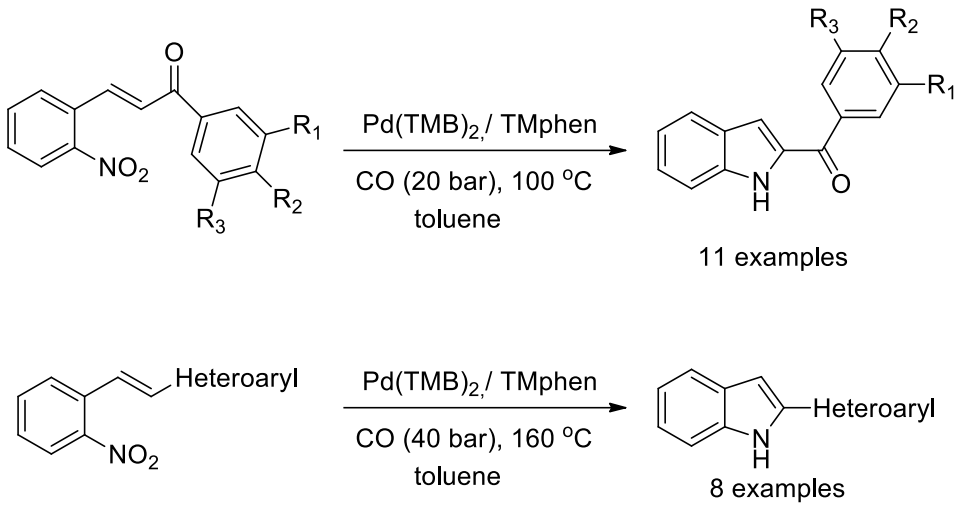


Scheme 1.15

$M_x(CO)_n$	Substrate/cat. ratio	R	Yield %
$Rh_6(CO)_{16}$	50	COOMe	59
$Fe(CO)_5$	10	COOMe	75
$Ru_3(CO)_{12}$	25	Ph	72

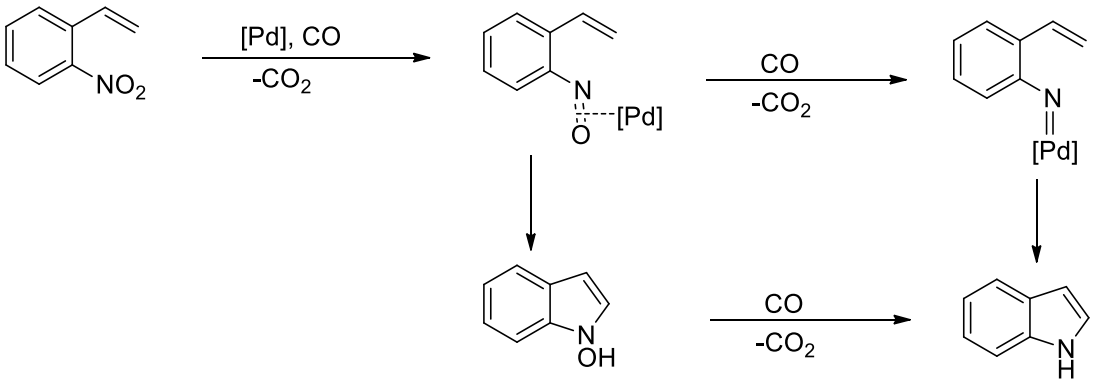
Milder and less harsh conditions (100 °C under 20 bar of CO) were reported by Watanabe and coworkers if $PdCl_2(PPh_3)_2$ and $SnCl_2$ as additive were employed[44] for reductive cyclization of *o*-nitrostyrene. Cenini group also reported a less drastic condition but using nitrogen ligand[15] rather than phosphine one [$Pd(TMP)_2$, TMphen, 40 atm CO and 140 °C].

Cenini and coworkers continued to study this Pd-catalytic system and extended the scope of the reaction to include the synthesis of 2-acyl indoles from 2-nitrochalcones[45] and synthesis of 2-heteroaryl indoles.[46] (Scheme 1.16)



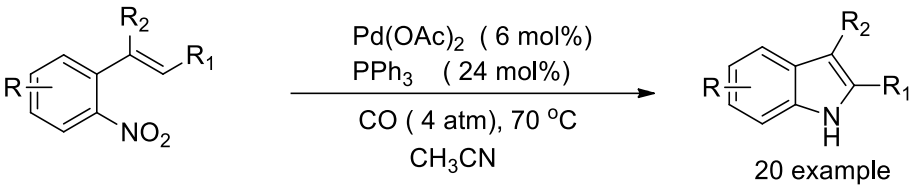
Scheme 1.16

Interestingly, the choice of solvent played a role in these transformations. When toluene is replaced with THF, a significant amounts of *N*-hydroxyindoles and small amounts of anilines (< 8%) formed during the cyclization reaction;[47] yields as high as 60% for the *N* hydroxyindoles have been found at short reaction times (3 h vs. 6 h) and lower temperatures (130 °C vs. 170°C). This result suggests the intermediacy of hydroxyindole and that the nitro functionality is not fully deoxygenated to the nitrenoid prior to cyclization. In fact, when hydroxyindole is subjected to the reaction conditions, indole is formed. Presumably, the hydroxyindole intermediate is longer-lived in a polar solvent (THF) whereas in a nonpolar solvent (toluene), hydroxyindole is rapidly converted to the desired indole product. (Scheme 1.17)



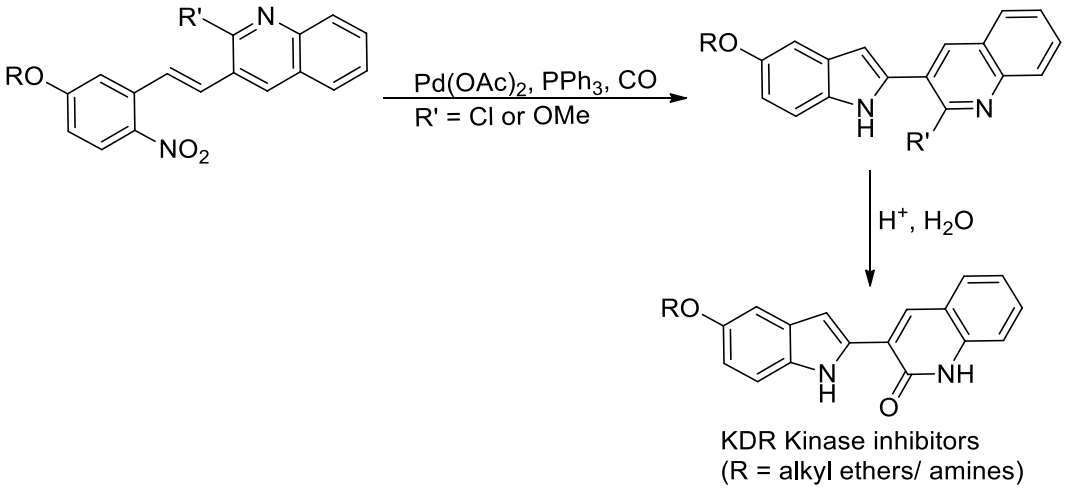
Scheme 1.17

In 1997 Söderberg and coworkers were the first who showed that high temperature and high CO pressures are not required to efficiently reduce nitroarenes.[48] With $Pd(OAc)_2$ various indoles were formed in moderate to excellent yields (40–100%) at 70 °C and 4 atm of CO pressure in MeCN with long reaction times (15–24 h). As well, the use of bidentate ligand, dppp and polar solvent, DMF allowed cyclization to occur (Scheme 1.18). Both electron-donating and electron-withdrawing substituents are tolerated with the latter requiring longer reaction times. Also, sensitive functional groups such as phenol, triflate, and ester did not inhibit catalysis whereas a bromo substituent did (0%). Interestingly, 2,6-dinitrostyrene efficiently cyclized (89%) but only one of the nitro groups was reduced, i.e., 4-nitroindole was obtained rather than 4-aminoindole.



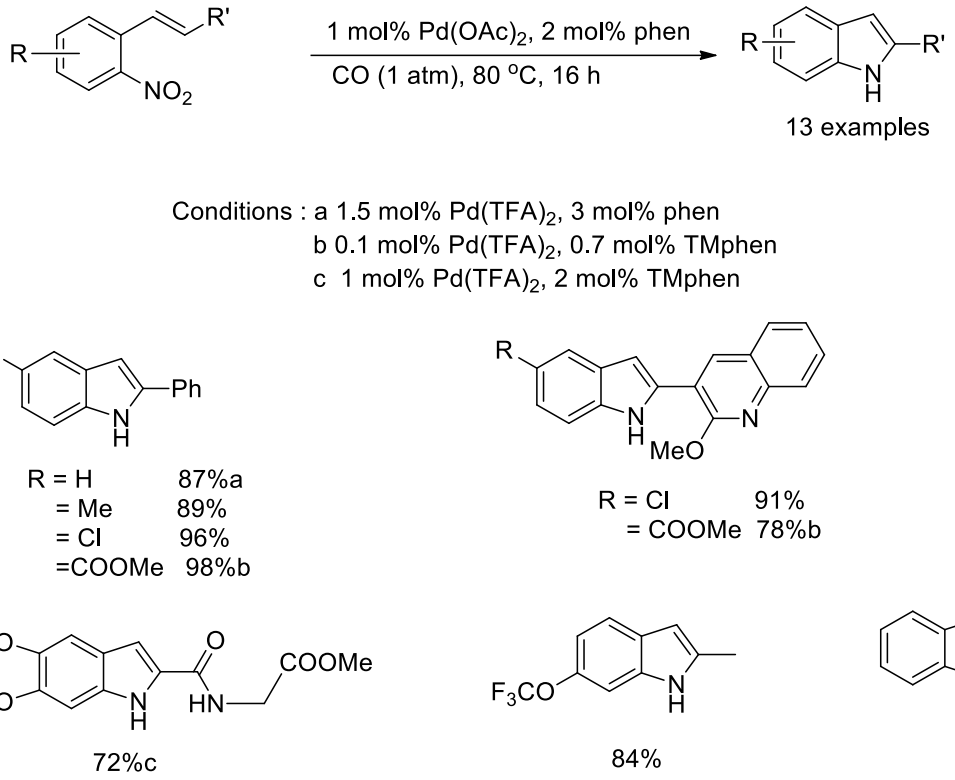
Scheme 1.18

In 2003, the scientists at Merck company applied the Söderberg's reaction conditions [$Pd(OAc)_2$ (6 mol %), PPh_3 (24 mol %), CO (4 atm)]. to the synthesis of some indolylquinolinone derivatives which are selective KDR kinase inhibitors (Figure 1).[49] Although high conversions of cyclization were obtained and indole produced in high assay yield (95%,), crystallization from the reaction mixture resulted in a disappointing isolated yield (45%) due to the presence of triphenylphosphine and triphenylphosphine oxide by products. (Scheme 1.19)



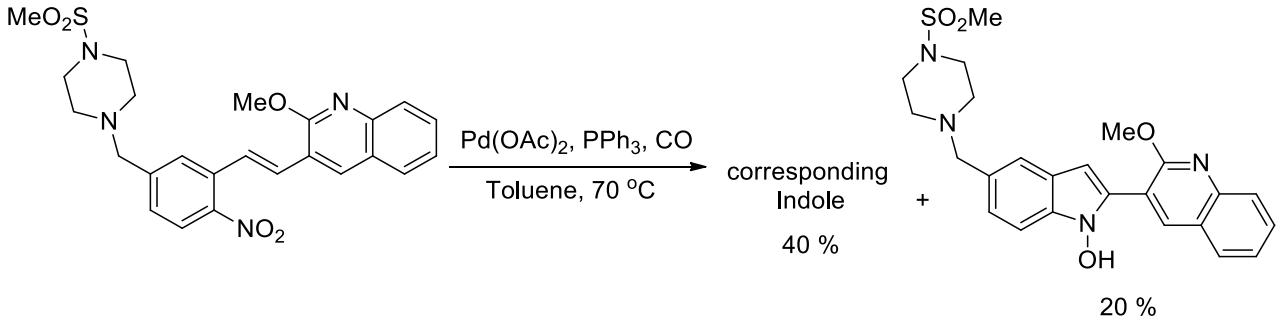
Scheme 1.19

As such, the Merck scientists found alternative reaction conditions with different Pd(II) sources and phenanthroline-based ligands.[50] With these milder conditions, excellent yields were obtained even without the need for phosphine ligands as previous studies suggested. Using 1 mol % Pd(II), 2 mol % phen, atmospheric pressure of CO at 80 °C in DMF, various 2-aryl, heteroaryl, acyl, and alkyl indoles were obtained in yields up to 98% (Scheme 1.20). For certain substrates, Pd loadings as low as 0.1 mol % still efficiently facilitated the cyclization. They found that electron-deficient substrates are easier to cyclize as compared to the electron-rich counterparts where higher catalyst loadings are required.



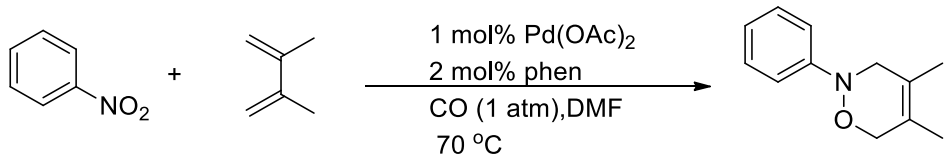
Scheme 1.20

The Merck research group contributed some mechanistic insights by experiments and computation. Using toluene as the solvent, *N*-hydroxyindole was observed. When N-hydroxyindole was resubjected to the standard reductive cylization conditions in DMF, indole was formed quantitatively. This result suggests the intermediacy of hydroxyindole and that the nitro functionality is not fully deoxygenated to the nitrenoid prior to cyclization and nitroso group not nitrene act as the aminating species in this cyclization reaction.[50] (Scheme 1.21)



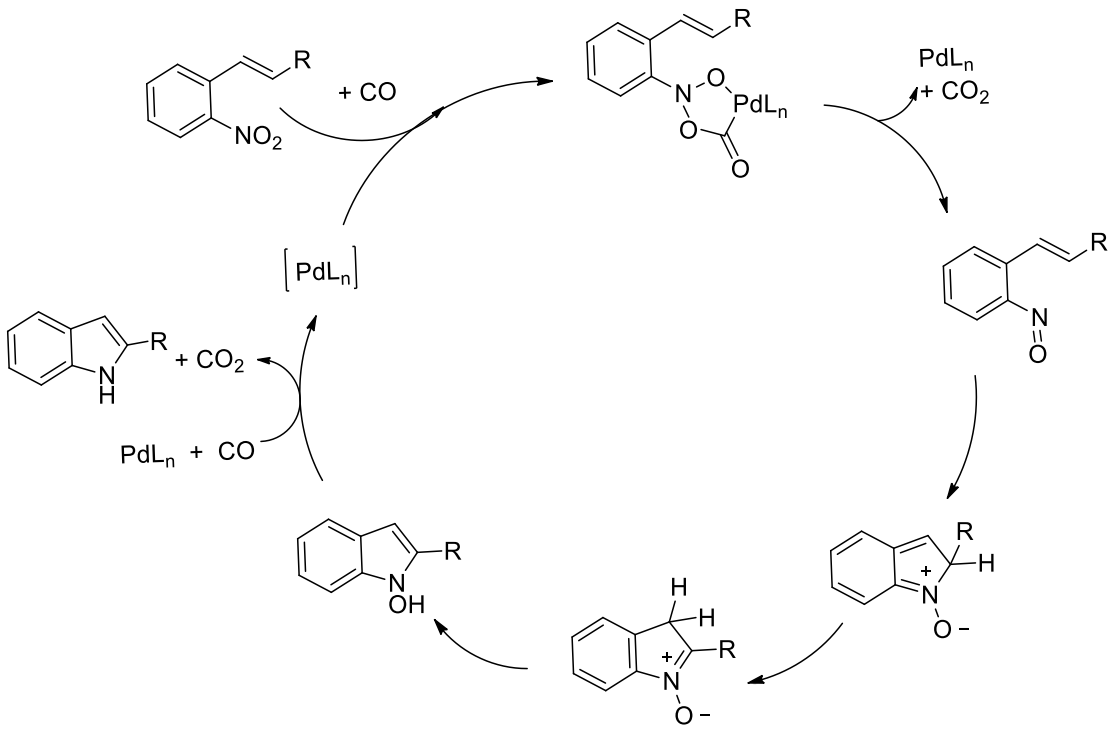
Scheme 1.21

Although, trapping of nitroso intermediate were successful when 2,3-dimethylbutadiene was added to nitrobenzene under the reductive carbonylation conditions and an oxazine adduct was formed, Diels-Alder adducts could not be obtained for the *o*-nitrostyrene with added 2,3-dimethylbutadiene, (Scheme 1.22). This result shows that aromatic nitro groups are indeed reduced to nitroso species under these conditions and that intramolecular cyclization of *o*-nitrostyrenes may be faster than intermolecular cycloaddition with dienes. [50]



Scheme 1.22

According to the above results they proposed the following reaction mechanism. (Scheme 1.23), The catalytic cycle involves the reaction of a nitro compound with the Pd catalyst and CO to give the palladacycle which undergoes the elimination of CO while releasing the nitrosostyrene. This intermediate reacts to give nitrone**,** in an intramolecular electrocyclic reaction. Subsequent 1,5-hydrogen shift and isomerization afford N-hydroxyindole that reacting with a second equivalent of CO converts the hydroxyindole into indole.



Scheme 1.23

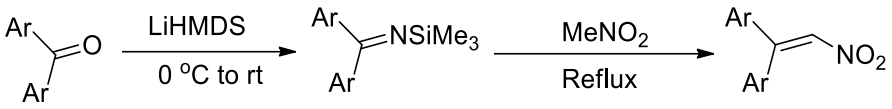
Finally, Hammett correlation studies revealed a □□value of +1.77 which is indicative of negative charge build-up in the rate/turnover limiting step of the cyclization. Also, a linear correlation was obtained in a plot of the log of the rate ratio (*k*X/*k*H) vs. the reduction potential of the substituted nitrostyrenes. These two pieces of data suggests that the rate/turnover limiting step is likely the initial reduction of the substrate which involves an electron transfer to the nitroarene.[50]

b- Using nitroalkene (β-nitrostyrene)

In 1991, Russel and co-workers have reported the reductive cyclization of nitroalkenes to form indoles by using phosphites as a stoichiometric reductant.[51] later in 2009, the group of Dong reported the palladium catalyzed reductive cyclization of α-aryl-β-nitrostyrenes to 3-arylindoles under mild reaction conditions (Scheme) with very good yields.[52]

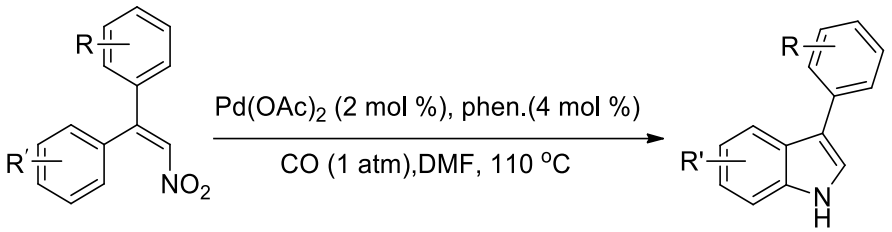
The substrate used for the reaction optimization was 1,1-diphenyl-2-nitroethene and the best reaction conditions were found to be 110 °C, 1 bar overpressure of CO in dimethylformamide (DMF) for 3 h using $Pd(OAc)_2$ as the catalyst and phenanthroline (Phen) as the ligand. The molar ratio of catalyst/Phen/substrate was 1:2:50. In their study, they report the use of these reaction conditions only on diaryl-substituted nitroalkenes, which are non-commercial substrates. So they developed a new

strategy for the synthesis of nitroalkenes from their corresponding benzophenone derivatives via a straightforward two-step sequence as shown in (Scheme 1.24)



Scheme 1.24

Dong's group studied the scope of the reductive cyclization reaction for diaryl nitroalkenes bearing various substituents to afford 3-arylindoles (Table). It was found that the reaction is tolerant of both electron-rich and electron-poor substituents (10 examples, 58–98%) (Scheme 1.25)



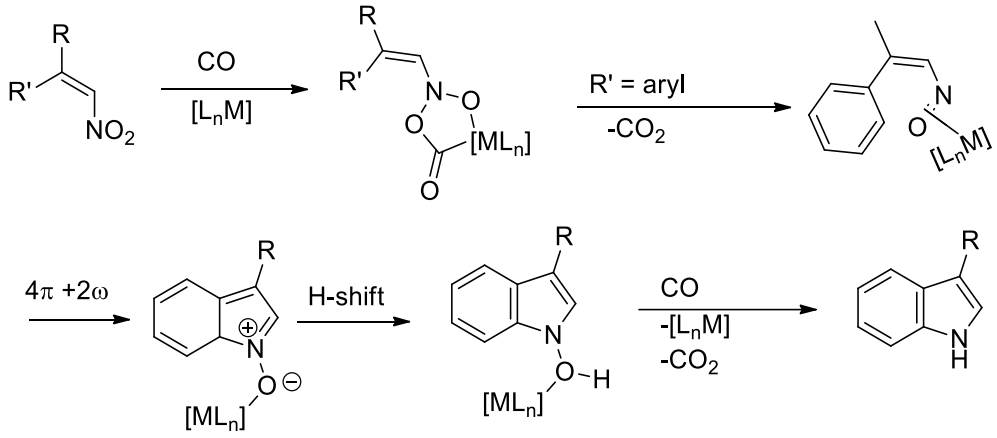
Scheme 1.25

Entry	R, Nitroalkene	T(h)	R', Product	Isolated yield%
1	H	3	H	97
2	*p*-Me	3	6-Me	87
3	*p*-tBu	3	6-tBu	92
4	*p*-MeO	3	6-MeO	93
5	*m*-MeO	3	5-MeO, 7-MeO	91 (53:47)[a]
6	*m*-Cl	6	5-Cl, 7-Cl	91 (42:58)[a]
7	*p*-Cl	6	6-Cl	98
8	*m*-CF*3*	8	5-CF3, 7-CF3	86 (51:49)[a]
9	*p*-CF_3	16	6-CF3	58[b]

a Regioselectivity (based on ^{1}H NMR integrations), *b* the moderate yield is attributed to significant amount of the benzophenone by product formation due to competing hydrolysis at long reaction time.

Based on previous experimental and theoretical mechanistic studies involving nitroarenes systems, Dong's group proposed that the reductive cyclization of nitroalkene would form a five-membered metallacycle. Decarboxylation of metallacycle would generate an η^2-bound nitrosoalkene complex,[53]

which could then undergo intramolecular 4π+2w five-atom electrocyclization to form nitronate. Subsequent hydrogen shift and re-aromatization would generate N-hydroxyindole, which is then reduced to the desired indole product by a second equivalent of CO.[52, 54] (Scheme 1.26)

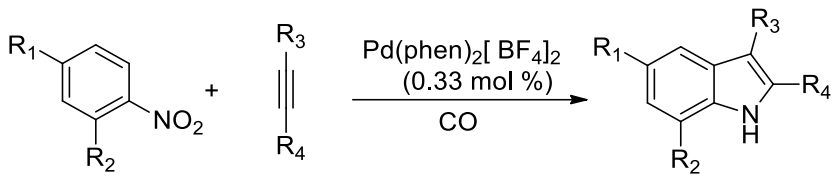


Scheme 1.26

Also they studied the scope of transition-metal catalysts for 1,1-diphenyl-2-nitroethene reductive cyclization and found that a versatile methodology for making indoles can be done using Fe, Rh, Pt and Pd catalysts, also using bidentate N- and P-based ligands.

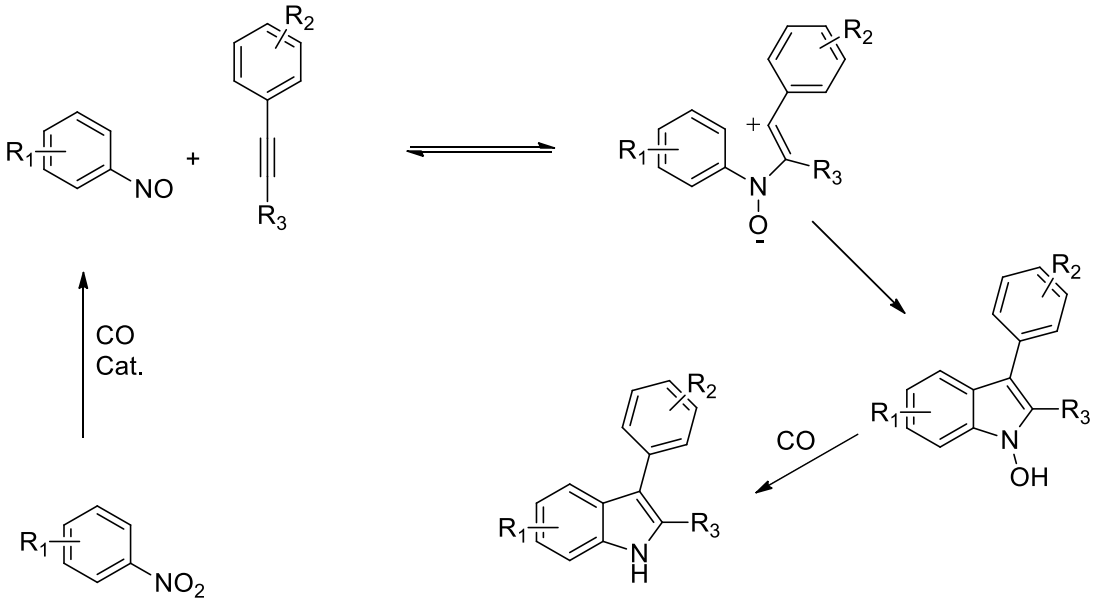
1.2.3.2 Intermolecular reductive cyclization of nitroarene

In 2002 Nicholas' group showed that ruthenium-cyclopentadienyl catalyst $[RuCp^*(CO)_2]_2$ catalyzes the reaction of nitroarenes with alkynes to give indoles.[55] but the application of that reaction is severely limited by the low activity of the catalyst. (substrate/Ru ratio 10:1, 170 ^oC, 48 h). Few years later Ragaini et.al. demonstrated that the intermolecular condensation of nitroarenes and arylalkynes using palladium/phenanthroline complex under CO pressure affording 3-arylindole. They showed that the palladium catalyst $[Pd(Phen)_2][BF_4]_2$ gave a much higher activity (*c.a.* 500 fold) with respect to the ruthenium-cyclopentadienyl catalyst originally reported by Nicholas for the same reaction, but the selectivity remained moderate. The reaction is completely regioselective; no 2-arylindole was detected.[56] (Scheme 1.27)



Scheme 1.27

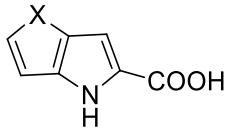
Ragaini's group attempted to improve the selectivity of the palladium/phenanthroline catalytic system for the synthesis of 3-arylindoles, by adding a ruthenium catalyst $Ru_3(CO)_{12}$ together with the palladium catalyst and/or adding dimethylcarbonate as a methylating agent. Using these two approaches together showed that the improvements are additive. The new approach is especially important in the synthesis of 3-(4-fluorophenyl)indole, the scaffold of several pharmaceutically important drugs, for which it allowed an almost doubling of the yield.[57] Moreover, concerning the mechanism of this reaction, catalytic reduction of nitroarene with CO, initially produces nitrosoarene, which further react reversibly with the alkyne to intiate the cyclization to give the corresponding *N*-hydroxyindole which is reduced in a last step to the indole in the presence of CO and the catalyst (Scheme 1.28).



Scheme 1.28

1.2.4 Synthesis of thienopyrrole

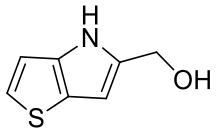
Thienopyrroles are common isosteric and isoelectronic replacements of indoles.[58] Due to their unique stereoelectronic properties, thienopyrroles find numerous applications in the areas of medicinal chemistry and molecular electronics[59] (Figure 1.9). For example, thienopyrrole carboxylic acid act as inhibitors of D- amino acid oxidase[60] (DAAO), which represent potential treatment options for schizophrenia,[61] depression[62] and pain[63], as well as neurodegenerative disorders[64] such as Parkinson's and Alzheimer's disease.[65] Moreover, thienopyrrole are of great importance in the development of organic electronic devices, for example, thieno[3,4-c]pyrrole-4,6-dione (TPD) is widely used as efficient building blocks for organic thin film transistors[66] (OTFT), organic solar cells[67] (OSCs) or organic photovoltaics (OPV), organic light emitting transistors[68] (OLET) and organic field-effect transistors[69] (OFET). In addition thienopyrroles can also be used in the field of fluorescent dyes.[70] Thienopyrrole can exist in different positional isomers according to the position of the fusion between the two rings, e.g. thieno[2,3-b], thieno[3,2-b], thieno[2,3-C], thieno[3,4-b], thieno[4,3-b], and thieno[3,4-C] pyrroles. In this thesis we focus only on thieno[2,3-b] and, thieno[3,2-b]pyrrole.



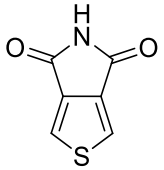
X = O, S

Human D-Amino Acid Oxidase (DAAO) inhibitors

[Useful in the prevention and treatment of a variety of diseases and/or conditions including neurological disorders, pain, ataxia, and convulsion.]



(4H-thieno[3,2-b]pyrrol-5-yl)-methanol
Treatment of cancer

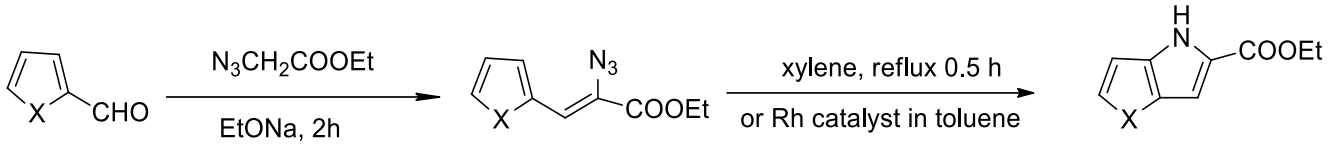


4H-thieno[3,4-c]pyrrole-4,6-dione (TPD)
Biulding block for organic electronic devices

Figure 1.9

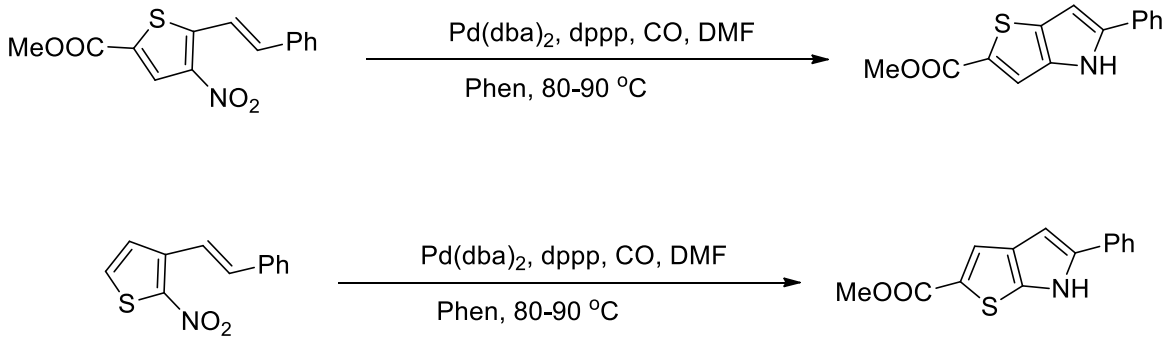
Accordingly, a variety of methods have been developed for the synthesis of thienopyrrole derivative. Synthetic methods for thienopyrroles include FriedelCrafts acylation followed by aromatization,[71] reductive ketone amine condensation,[72] and aldol condensation,[73] nitrene C-H insertion cyclization

using azides[74]or nitrothiophene,[75] intramolecular Heck reaction,[75] and a Rh(II)-mediated-Wolff rearrangement-cyclization sequence.[76]In the literature, nitrene C-H insertion is widely used for synthesis of thieno[2,3-b], thieno[3,2-b]pyrrole carboxylic acid. This method involve condensation of thiophenecarboxaldehyde with ethyl azidoacetate followed by thermal[77] or metal[78] catalyzed cyclization. The utility of this method was enhanced through the availability of many aldehydes which allowed the standard route to be used to generate acids; on the other hand, the major limitation of this method is the use of sodium azide and the potentially explosive intermediate. (Scheme 1.29)



Scheme 1.29

Few years ago, Soderberg extended the work of Davies for reductive cyclization of *o*-nitrostyrene[50] to *o*-alkenylnitroheterocycles owing to afford bicyclic pyrrole fused heteroaromatic compounds.[79] He used carbon monoxide (6 atm) as a reductant in the presence of either a palladium acetate–triphenyl phosphine catalyst system in acetonitrile at 80–90 ^{o}C or using a bis(dibenzylideneacetone) palladium-1,10-phenanthroline catalyst system in DMF at 120 ^{o}C. The latter conditions gave in most cases a higher yield of cyclized product. Among the substrate tested in that work was *o*-styrylnitrothiophene derivative, which afforded the cyclized thieno[3,2-b]pyrrole derivative in 71% yield using palladium acetate–triphenyl phosphine for 40 h. Moreover, thieno[2,3-b]pyrrole obtained in 94 % yield by cyclization of 2-nitro-3-styrylthiophene using the same reaction conditions for 16 h. (Scheme 1.30)



Scheme 1.30

1.2.5 Synthesis of pyrrole

pyrrole nucleus is one of the most important heterocycle abundantly found in bioactive natural molecules, forming the characteristic subunit of heme[80], chlorophyll,[81] vitamin B12[82] as well as in melanin pigments.[83] 1,2,5-Trisubstituted pyrroles display interesting biological properties, such as anti-inflammatory,[84] antipsychotic,[85] spasmolytic,[86] and radioprotective.[87] Two clinical examples of pyrroles displaying this pattern of substitution are amtolmetin and tolmetin.[88](nonsteroidal anti-inflammatory agents) (Figure 10). Generally pharmaceuticals containing pyrroles are of high value as biological agents such as sunitinib [89] (anti-tumour), keterolac [90] (analgesic) and the highly successful cholesterol-lowering drug atorvastatin calcium (Lipitor), which is notable as the first drug to earn in excess of $1 billion of sales in its first year.[91] The electronic properties of pyrrole are important in the context of conducting polymers, where polypyrroles have found many useful applications.[92] (Figure 1.10)

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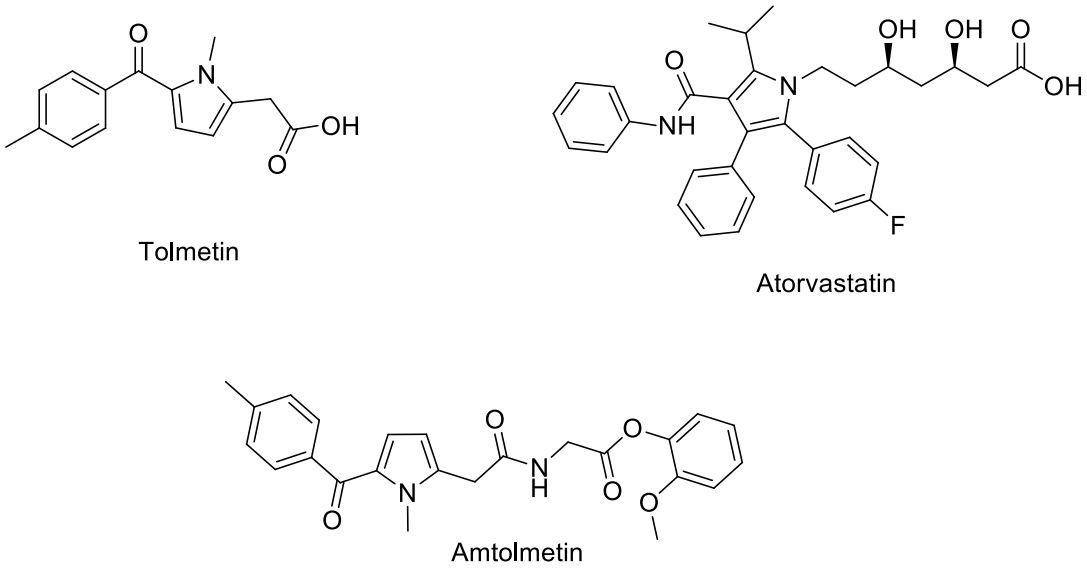


Figure 1.10

Accordingly, investigations on the development of synthetic methodologies for pyrrole derivatives have continuously attracted the attention of organic chemists. The known methods for the construction of the pyrrole rings proceed either by traditional methods via various types of cycloaddition or cycloisomerization of acyclic precursors or by transition-metal-catalyzed reactions.[93]

.

But still a novel and highly efficient chemical reaction that can be used to construct the skeleton of pyrroles with readily accessible substrates and few steps remains an attractive goal.

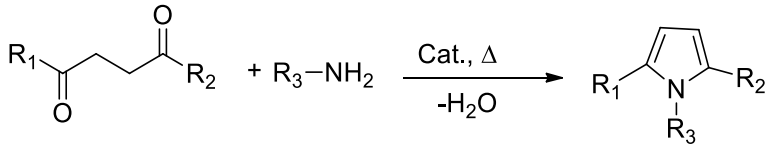
Traditional methods for synthesis of pyrrole

Traditional methods for the synthesis of substituted pyrroles include the classical Paal−Knorr condensation reaction, the Hantzsch reaction, and the Knorr reaction

a- Paal–Knorr synthesis

One of the most classical and common approaches for the synthesis of pyrrole derivatives is the Paal–Knorr synthesis[94] which consists of the condensation of a primary amine with a 1,4 dicarbonyl compound (Scheme 1.31). It is especially well suited for the synthesis of a 1,2,5- trisubstituted pyrroles. The 1,4-diketone component is often obtained by the Stetter reaction,[95] which typically is an addition of an aldehyde to an α,β-unsaturated ketone under cyanide or thiazolium salt catalysis. The Stetter reaction gives only best yields with straight-chain aliphatic, aryl, and heteroaryl aldehydes, and chromatography is usually required to obtain suitably pure 1,4-dicarbonyl compounds.[95a] The combined Stetter-Paal-Knorr sequence give a wide scope for the diversity of pyrroles using both solid/solution phase[94d, 96] and microwave assisted[97] synthesis. The synthesis of pyrroles unsubstituted at nitrogen requires the use of ammonia or magnesium nitride as a source of ammonia.[98]

The Paal–Knorr reaction suffers from limitations such as drastic reaction conditions, high cost, poor yields, tedious workup and long reaction times.



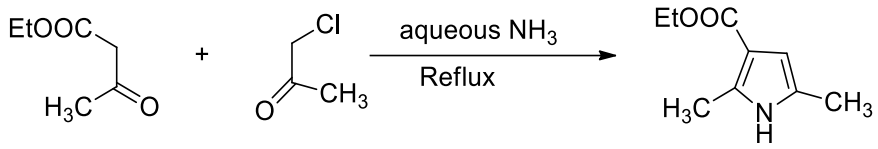
Scheme 1.31

b- Hantzsch cyclocondensation

In 1890 Hantzsch published a cyclocondensation[99] between ‘‘an equimolecular mixture of chloroacetone and aceto-acetic ester under reflux in concentrated aqueous ammonia’’ (Scheme 1.32).

In spite of its named reaction status, the Hantzsch synthesis has received little attention in the literature. Thus, a study by Roomi and MacDonald published in 1970[100] concluded that only nine pyrrole derivatives had been prepared by this method in the 80 years elapsed since the initial Hantzsch publication. While the original Hantzsch method was restricted to the use of ethyl β-aminocrotonate,

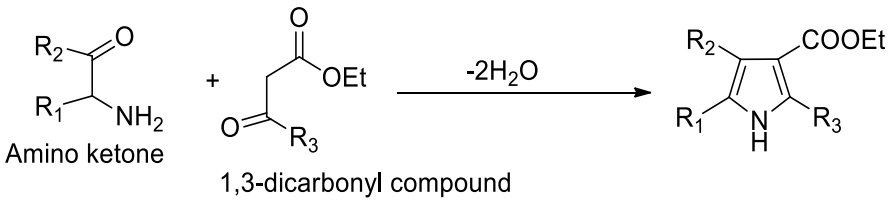
Roomi and MacDonald extended its scope to include substituent's other than methyl. The yields for these reactions were normally below 50%, and this problem has also been found by more recent authors using the Hantzsch pyrrole synthesis.[101]

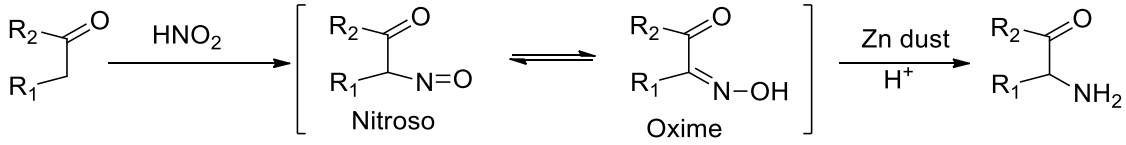


Scheme 1.32

c- Knorr condensation reaction

Another traditional approach for the synthesis of pyrrole derivatives is the Knorr condensation reaction which is achieved through the condensation reaction of 1,3-dicarbonyl compounds with α-amino ketones.[102] Because α-amino-ketones self-condense very easily, they must be prepared *in situ*. by the nitrosation of the ketone to give α-nitroso compound which can tautomerize to α-oxime and then by subsequent reduction using zinc powder under weak acidic conditions afford the desired amino ketone. Eventually, the condensation reaction of α-amino carbonyl compounds with 1,3-dicarbonyl compounds was carried out in glacial acetic acid under reflux conditions or in lactic acid under ultrasonic radiation[103] to give pyrrole derivatives. The reaction of traditional Knorr condensation reaction is shown in (Scheme 1.33).



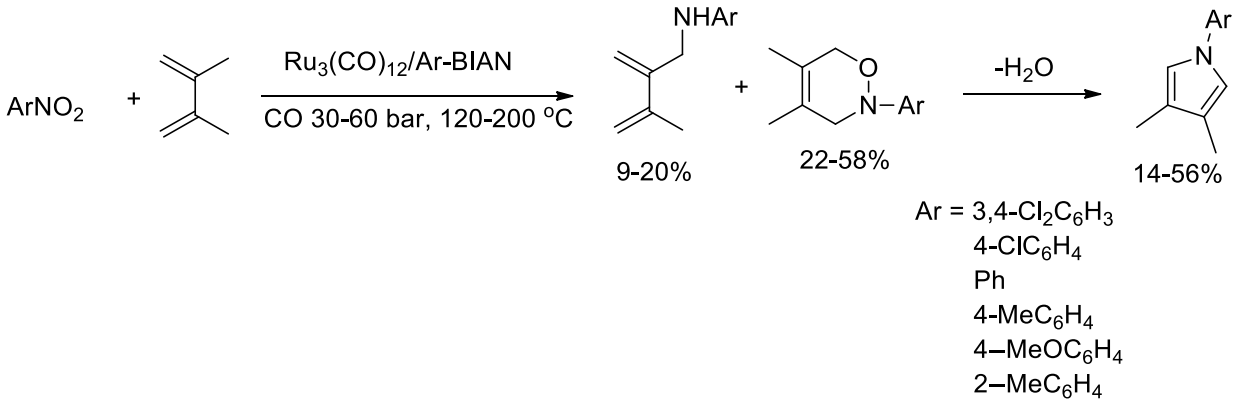


Scheme 1.33

Although these classical methods are very useful for the synthesis of pyrrole derivatives, they have significant drawbacks such as availability of the starting materials, multisteps synthetic operations,

functional group compatibility, regiospecificity, and harsh reaction conditions, which limit their scope. To overcome these limitations, various new efficient strategies such as transition metal catalyzed reactions have recently been developed in the last fifty years.[93d, 104]

As we focus on reductive carbonylation of nitroarenes, in 2001 Ragaini's research group demonstrated that when the $Ru_3(CO)_{12}$/Ar-BIAN system is employed to catalyze the reaction of nitroarenes with conjugated dienes, mixtures of allylic amines, oxazines and *N*-aryl-pyrroles are obtained in different ratios depending on the experimental conditions.[105] (Scheme 1.34)



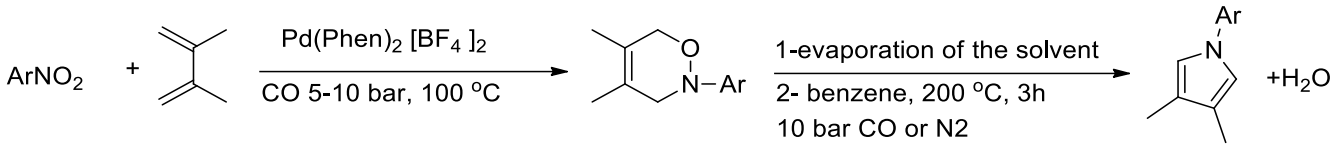
Scheme 1.34

Pyrroles are not primary products of the reaction, but derive from a thermal dehydration of oxazines. The selectivity in the oxazine and pyrrole is completely shifted on either side by a proper choice of the reaction temperature. At 120 °C the oxazines are stable under the reaction conditions and no pyrrole was obtained. Conversely, at 200 °C the oxazines were completely converted into pyrroles. One year later Ragaini group obtained a better results concerning oxazine and pyrrole with a palladium catalyst.[106]

With respect to the ruthenium catalyzed reaction: (a) The selectivity in oxazine is improved from 40-60 % to 80-90 %. (b) A much lower metal loading (0.08 % instead of 3 %) can be used. (c) CO Pressure can be lowered from 40 to 5 bar, thus allowing for the use of a glass autoclave. (d) A moderate steric hindrance on the nitroarene is tolerated, whereas it was not in the case of the ruthenium catalyzed reaction. (e) A lower molar excess of diene is required with respect to the nitroarene.[5b]

As mentioned before, with $Ru_3(CO)_{12}$/ArBIAN as the catalytic system, simply increasing the reaction temperature to 200 °C allowed the synthesis of pyrroles in one step. However, when the same

temperature was applied to the palladium-catalyzed reaction, pyrrole formation was accompanied by extensive oligo- and polymerization of the diene, which rendered product separation problematic. The problem was solved by applying a two-steps one pot procedure (Scheme 1.35). The reaction was first performed at 100 °C; then the autoclave was vented and the solution evaporated in vacuo. At this point toluene (or benzene) was added as solvent and the reaction mixture was placed again in the autoclave and heated at 200 °C for 3 h. Pressure had to be applied even in this second stage to avoid boiling of the solvent, but it is indifferent to apply a CO or a dinitrogen pressure. Since the excess diene had been eliminated in the evaporation step, no oligomers were obtained[5b]



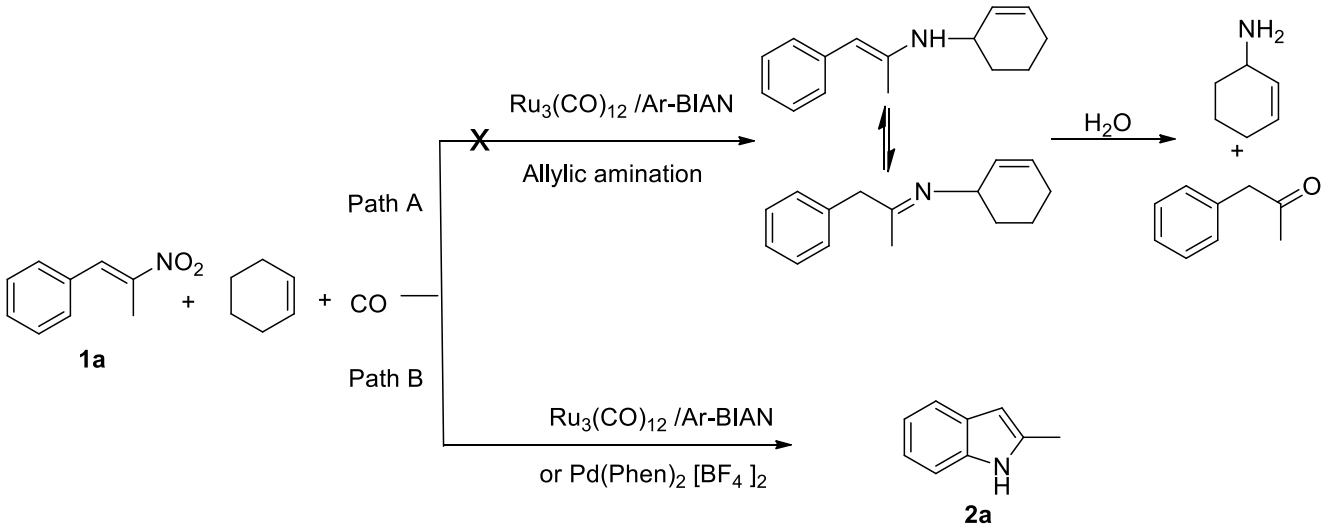
Scheme 1.35

Despite the good yields obtained, the Pd-catalyzed reaction still presents drawbacks when applied to the synthesis of pyrrole such as, the availability of different substituted diene, which limit their scope. Herein in this thesis, we developed a novel synthesis for 2,5-disubstituted and 2,3,5-trisubstituted pyrrole by palladium catalyzed intramolecular reductive cyclization of nitro-dienes and with carbon monoxide as a reductant.

Results and discussion

2.1 Synthesis of Indoles by Palladium-Catalyzed Reductive Cyclization of β-Nitrostyrenes with Carbon Monoxide as the Reductant

The indole skeleton is central to many biologically active pharmaceutical drugs and natural alkaloids as discussed in the introduction. Indole synthesis continues to attract the attention of many researchers. Many syntheses of indoles are catalyzed by transition metals, but in most cases, they require substrates bearing two suitable functional groups *ortho* to each other, and the preparation of these starting materials often requires several synthetic steps. Several years ago, our group investigated the possibility of using β-nitrostyrenes as aminating agents for olefins by employing a protocol previously devised for nitroarenes[107] and based on the use of a ruthenium/ bis(aryl)acenaphthenequinonediimine (Ru/Ar-BIAN) catalyst. The aim was to obtain a vinylic amine that, after tautomerization, could be easily hydrolyzed to result in the overall introduction of an NH_2 group in the allylic position of cyclohexene.(Scheme 2.1, Path A)



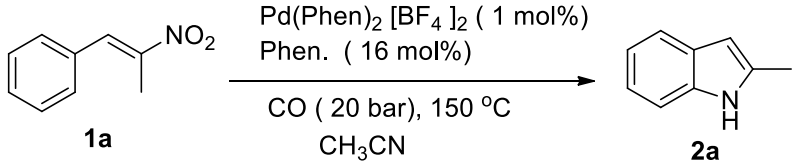
Scheme 2.1

Despite some efforts, formation of the allylic amine was never observed. A mixture of products was obtained, among which 2-methylindole was always present (Scheme 2.1, Path B).

The reductive cyclization reaction of β-nitrostyrenes to indoles has been reported to occur with $P(OEt)_3$ as the reducing agent only if the *α*-position of the styrene bears a substituent, most commonly a second aryl group. [51a, 51b, 108]The reaction is only of little interest owing to the need for a very large excess amount of the trialkylphosphite and the consequent difficulty in its elimination from the product. No method has been reported for the efficient deoxygenative cyclization of **1a** or related β-nitrostyrenes lacking additional substituents in the α-position.[51b] The possibility of conducting the reaction under catalytic conditions intrigued us, as the use of β-nitrostyrenes as substrates in indole

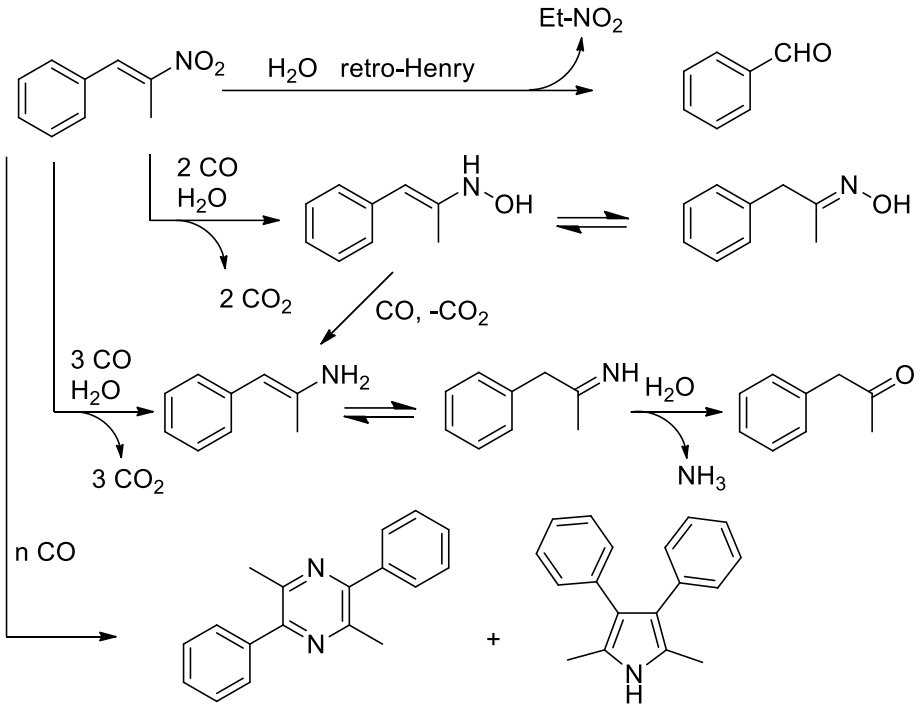
synthesis is very interesting. In fact, in most cases, they can be easily prepared from an aldehyde and a nitroalkane by the Henry reaction, which overcomes problems associated with the complex preparation of the substrates. The indole yield was low with the use of a catalytic system based on ruthenium, but better results were obtained by employing $[Pd(Phen)_2][BF_4]_2$ in the presence of an excess amount of 1,10-phenanthroline (Phen). This system was previously reported to give very good results in other carbonylation reactions, such as the reductive carbonylation of nitroarenes[109] and several types of inter- and intramolecular reductive cyclization reactions of nitroarenes.[56-57, 106]

2.1.1 Optimization of the reaction conditions



Scheme 2.2

The reaction conditions have been previously optimized in our research group and reported before in the M.sc thesis of (Stefania Muto). By summing up the data of the optimization, the best result were obtained at 150 °C, 20 bar of CO, for 2.5 h in acetonitrile as the solvent. With the use of the optimized conditions, we were able to completely convert **1a** into **2a** with 86% isolated yield. (Scheme 2.2). During the optimization study, our research group was able to identify by GC–MS some of the side products of the reaction. Under the optimized conditions, their amount was very low and it was not possible to quantify them. The likely pathways for the formation of these side products are reported in (Scheme 2.3).

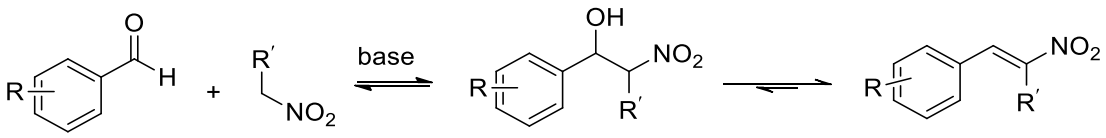


Scheme 2.3

3,6-dimethyl-2,5-diphenylpyrazine and 2,5-dimethyl-3,4-diphenylpyrrole may be derived from dimerization of a radical anionic intermediate; [110] the dimer is then further reduced by carbon monoxide. The formation of 2,5-dimethyl-3,4-diphenylpyrrole was previously reported to occur by reduction of the β-nitrostyrene with aqueous $TiCl_3$[110] Even if the formation of the above-mentioned side products can be almost suppressed under the optimized conditions, some unidentified high-boiling side products still form to some extent.

2.1.2 Synthesis of the substrate

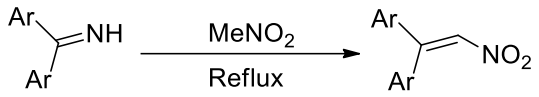
A variety of substituted β-nitrosyrenes were synthesized by the nitroaldol reaction (Henry reaction), which consists in a base catalyzed coupling reaction between an aldehyde or a ketone and a nitroalkane bearing at least one α-hydrogen (Scheme 2.3). If acidic protons are available, the product tends to eliminate water to give nitroalkenes in particular when the formed double bond is conjugated to an aromatic ring. [111] (Scheme 2.4)



Scheme 2.4

The Henry reaction is a classical name reaction known from more than one century. The extensive studies performed by organic chemists and commercial availability of the relatively low cost starting materials make it a versatile and widespread used reaction, indeed Henry reaction is one of the most simple and economical set of reaction conditions reported in the literature.[112]

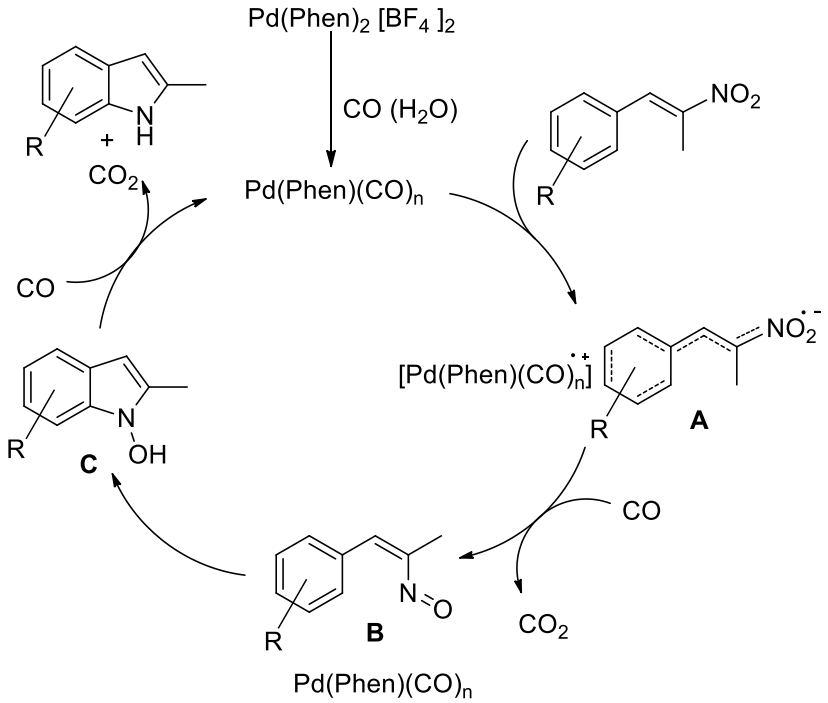
The substituted β-methyl-β-nitrostyrenes were synthesized by heating a mixture of the aldehyde and ammonium acetate in neat nitroethane. We obtained from fair to good yields. A different approach was needed for the synthesis of 1,1-diphenyl-2-nitroethene since the condensation of the ketone is more difficult. The strategy consists in the condensation of the commercial benzophenone imine with nitromethane[113] (Scheme 2.5).



Scheme 2.5

2.1.3 Scope of the reaction

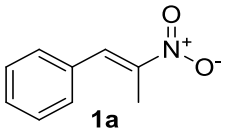
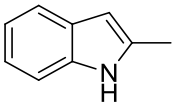
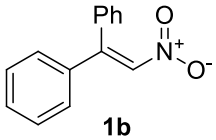
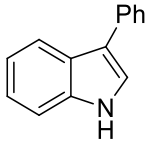
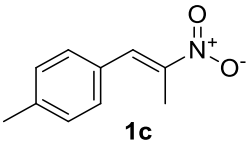
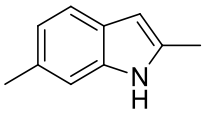
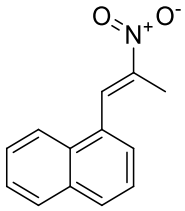
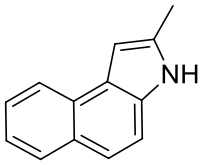
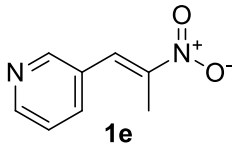
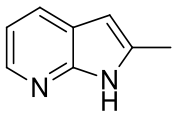
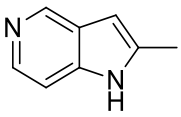
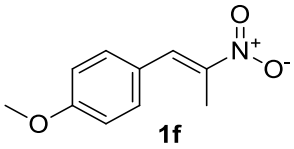
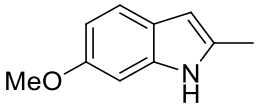
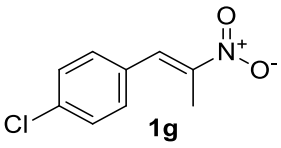
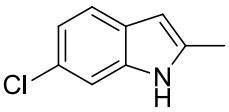
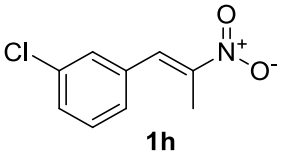
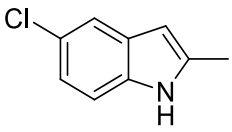
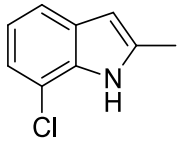
The scope of the reaction has been explored, the optimized conditions were applied to some different substituted β-nitrostyrenes. By using our optimized conditions, excellent results were obtained with both substrates **1a** and **1b**. (Table 2.1). The difference in reactivity between substrates **1a** and **1b** is due to two reasons: the higher reduction potential of β-substituted-β-nitrostyrenes relative to β-nitrostyrene[114] (**1i**) owing to tilting of the nitro group out the olefin plane, and the presence of a more extended π system in **1b**. In fact, given that reduction of the nitro group should involve initial single-electron transfer from the metal to the nitroalkene with the formation of a radical anion[115] (**A** in Scheme 2.5), a high degree of conjugation of the π system should favor radical delocalization and thus the subsequent formation of nitroso compound **B**, which is proposed to be the aminating species, by analogy with what occurs in the cyclization of *o*-nitrostyrenes.[116] Eventually, hydroxyindole **C**, formed by amination, is reduced to the indole by carbon monoxide. (Scheme 2.6). The formation of the radical anion allows easy rotation around the double bond and explains why good selectivities in indole could be obtained even upon employing *trans*-β-nitrostyrenes that are selectively formed by the Henry reaction. The presence of a second aryl group in **1b** is expected to favor the cyclization step, because it maximizes the chances of proper orientation of the nitroso and phenyl groups, in accord with the observation that **1b** gave the highest selectivity among all tested nitrostyrenes



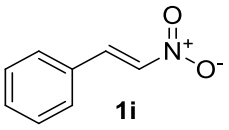
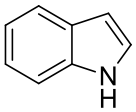
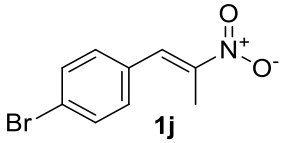
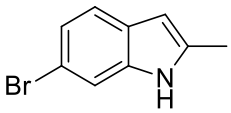
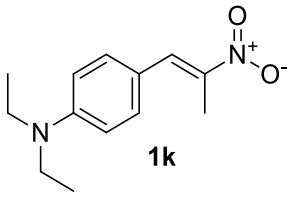
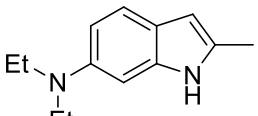
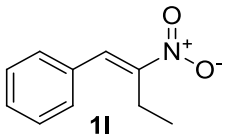
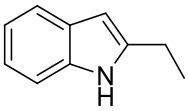
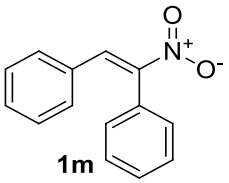
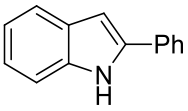
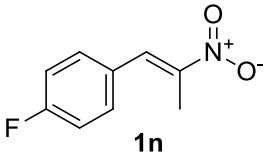
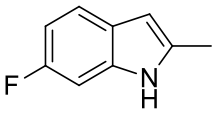
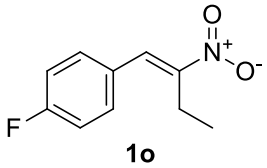
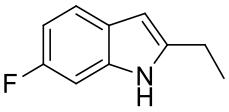
Scheme 2.6

So the best results were obtained for substrate **1b** owing to the presence of the phenyl ring, asmentioned above. For other substrates lacking an aryl group in the α- position, the presence of a substituent in the β-position was fundamental for indole formation and its absence (i.e., for **1i**) resulted in low reactivity and the formation of palladium black. In this case, an insoluble solid derived from the polymerization of the starting β-nitrostyrene[117] was found as the main product of the reaction, whereas 3,4-diphenylpyrrole was detected by GC–MS as the major product in solution. Both electron withdrawing and electron-donating substituents can be present in the *para* position of the aryl ring. However, as expected, the presence of strongly electron-releasing groups, such as methoxy (i.e., compound **1f**) and even more diethylamino (i.e., compound **1k**), led to reduced reactivity because of slower reduction of the nitro group.[56] It is especially notable that good results were obtained with substrate **1e**. Indeed, azaindoles are very important molecules.[118] Cyclization of the nitroso intermediate is an electrophilic process, and attack on the electron-poor 2- or 4-position of the pyridine ring should be disfavored. The 80% regioselectivity in 2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (**2e**), the most disfavored product from an electronic point of view, may be ascribed to partial coordination of the substrate to the metal center. On the contrary, reductive cyclization of chloro derivative **1h** is not regioselective.

Table 2.1. Scope of the reaction.[a]

Entry	Substrate	Conv. (%)[b]	Product (yield %)[c]
1	 **1a**	100	 **2a** (86)
2	 **1b**	100	 **2b** (93)
3	 **1c**	>99	 **2c** (70)
4	 **1d**	>99	 **2d** (75)
5	 **1e**	95	 **2e** (50)  **2e′** (11)[d]
6	 **1f**	94	 **2f** (59)
7	 **1g**	100	 **2g** (51)
8	 **1h**	100	 **2h** (21)  **2h′** (20)

(Continued on next page)

Entry	Substrate	Conv. (%)[b]	Product
9	 **1i**	64	 **2i** (3)[b]
10	 **1j**	100	 **2j** (50)
11	 **1k**	16	 **2k** (-)
12	 **1l**	96	 **2l** (47)
13	 **1m**	93	 **2m** (47)
14	 **1n**	100	 **2n** (57)
15	 **1o**	100	 **2o** (61)

[a]Reaction conditions: $[Pd(Phen)_2][BF_4]_2$= 1.10 x10 $^{-2}$ mmol, mol ratio substrate/Phen/$[Pd(Phen)_2][BF_4]_2$= 100:16:1, 150 °C, 20 bar of CO, $[Et_3N]$ = 0.17 m,CH_3CN (15 mL), 2.5 h. [b] Determined by GC analysis. [c]Isolated yield of the product. [d]Determined by ^{1}H NMR spectroscopy by using anisole as an internal standard.

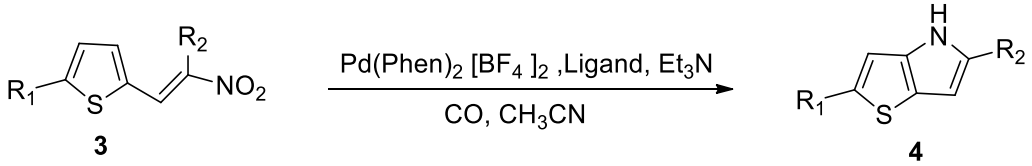
Conclusions

The reaction described herein enables the synthesis of awide range of indoles from easily accessible and often commercially available aldehydes and nitroalkanes. Given that nitroalkanes are much more difficult to reduce than nitroalkenes, it is conceivable that the Henry condensation and the following cyclization could be performed in one pot. Preliminary results showed that this is indeed the case, but selectivities were poor because of difficulties in finding a solvent mixture that was suitable for both the

Henry condensation and the following cyclization. Further efforts will be done in this direction in the future.

2.2 Synthesis of thieno[2,3-b],[3,2-b]pyrrole by intramolecular cyclization of nitro-olefins, catalyzed by palladium complexes and with carbon monoxide as the reductant

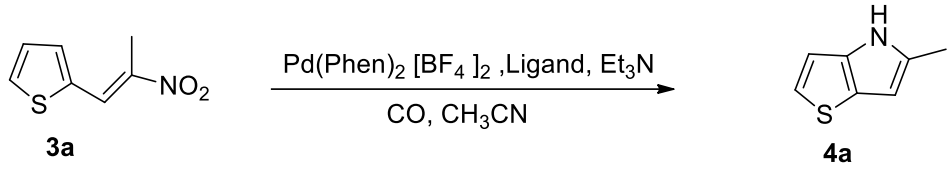
The bicyclic pyrrolo-fused aromatic or heteroaromatic rings are important heteroaromatic compounds. Thienopyrrole derivatives have attracted the attention of organic chemists because they are present in a vast number of pharmaceutical and, in general, biologically active molecules and are also of interest in the field of organic electronic devices. As mentioned in the introduction chapter. A well established method in the literature for synthesis of the medicinally important thieno[2,3- b], [3,2- b]pyrrole-5-carboxyalate is based on thermally assisted or metal catalyzed nitrene C-H insersion.[63] Despite the route to the target was very convergent and atom-economical, the use of azido functionality (to generate nitrene) in large-scale, presented serious safety concerns. Moreover, this methodology is limited to carboxylate substituent at position 5. An alternative method for the synthesis of such bicyclic compounds, using palladium catalyzed reductive cyclization of 3-alkenyl-2-nitrothiophenes, was published few years ago.[52] Despite the mild conditions and the good yields obtained, the major limitation of this method is the requirement for a prefunctionalized thiophene with two suitable adjacent functional groups in the 2 and 3 positions. The preparation of these starting materials often requires several synthetic steps. Moreover, the reactions times is long, ranging from 14 h to 7.5 days. The reductive cyclization of aromatic β-nitroalkenes is an extremely powerful method for the construction of the indole ring. Having an important practical advantage, namely, ready availability of the starting compounds. We recently showed that reductive cyclization of β-nitrostyrenes catalyzed by palladium/phenanthroline complexes and with CO as a reductant affords indoles in good yields.[119] The reaction proceeds by the activation of an aryl C-H bond. We decided to extend such cyclization reaction to other heterocyclic systems, although it is known that the activation of a C-H bond of electron-rich five membered heterocycles is a more difficult reaction. (Scheme 2.7)



Scheme 2.7

2.2.1 Optimization of the reaction conditions

Compound **3a** was chosen as a model compound for the optimization of the experimental conditions. $[Pd(Phen)_2][BF_4]_2$ was chosen as the catalyst for the optimization reactions. This complex showed to be the best choice in the reductive carbonylation of nitroarenes and reductive intermolecular cyclization of alkynes and nitroarenes studied in our group due to the noncoordinating nature of BF_4^- (Scheme 2.8)



3a **4a**

Scheme 2.8

We initially set catalyst/Phen/substrate (3a) molar ratio to 1:8:50. The cyclized bicyclic product 4a was successfully isolated from the reaction mixture and its structure has been fully identified by NMR, and mass spectroscopy and elemental analysis. The optimization of the nature of the ligand, CO pressure, temperature, base and solvent have been done. Results obtained are reported in (Tables 2.2-2.7).

A- Ligand

Nitrogen ligands such as phenanthroline or its derivatives have advantages over phosphines since the latter form stoichiometric amount of phosphine oxide coproducts which make isolation of the desired product difficult. The nitrogen ligands tested in the reductive cyclization reaction of our system are shown in Figure 2.1

Synthesis of the Ligands

We followed a well established procedure in the literature for the synthesis of symmetrically 4,7-disubstituted phenanthroline. This involves condensation between Meldrum acid ,trimethylorthoformate and *o*- phenylenediamine affording a bis-diamine intermediate that, on subsequent heating in diphenyl ether, afforded 4,7-dihydroxy phenanthroline. Then by functional group interconversion the other 4,7-disubstituted phenanthroline have been prepared. (Scheme 2.9)

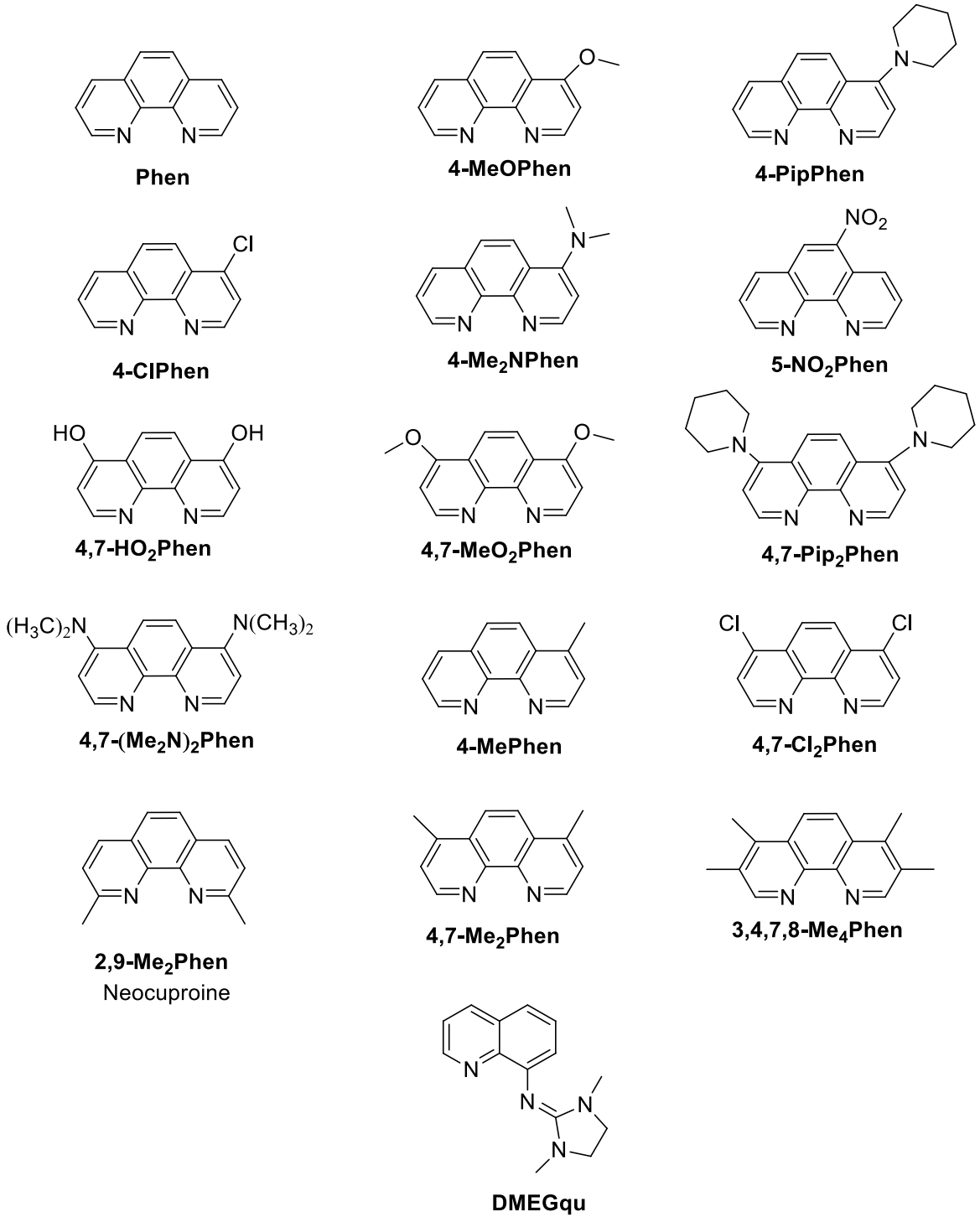
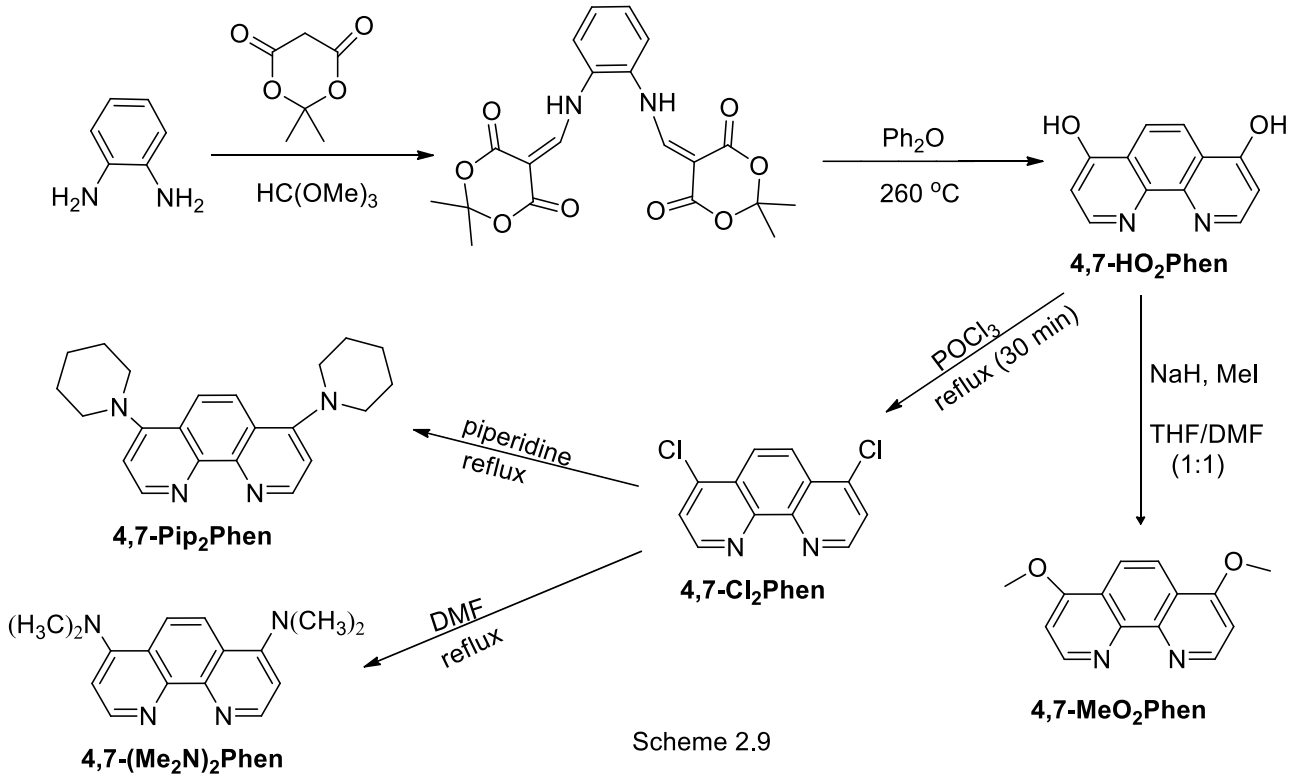
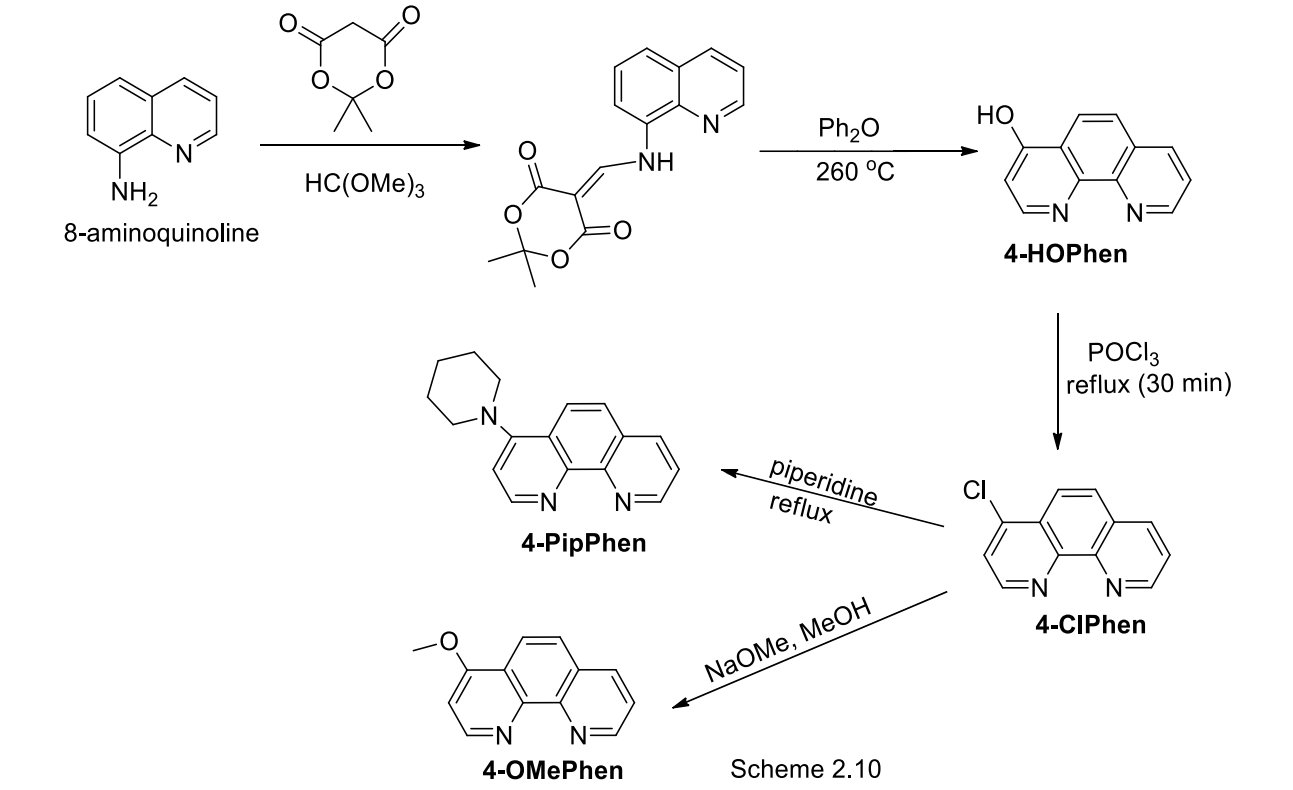

Phen
4-MeOPhen
4-PipPhen
4-ClPhen
4-Me2NPhen
5-NO2Phen
4,7-HO2Phen
4,7-MeO2Phen
4,7-Pip2Phen
4,7-(Me2N)2Phen
4-MePhen
4,7-Cl2Phen
2,9-Me2Phen
Neocuproine
4,7-Me2Phen
3,4,7,8-Me4Phen
DMEGqu

Figure 2.1



Scheme 2.9

The monosubstituted phenanthrolines were synthesized using 8-aminoquinoline instead of *o*-phenylenediamine (Scheme 2.10). 5-Nitro, and 3,4,7,8-tetramethyl-1,10-phanathrolines are commercially available.



Scheme 2.10

In the screening of ligands, sixteen ligands have been tested (Table 2.2). Both the substrate conversion rate and the cyclized product selectivity turned out to be strongly dependent on the nature of the ligand. The unsubstituted 1,10-phenanthroline gave a good catalytic activity but moderate selectivity for the bicyclic product. Electron poor phenanthrolines such as (5-NO_2Phen, 4,7-Cl_2Phen and 4-ClPhen) negatively affect the activity of the catalytic system compared to the unsubstituted phenanthroline. This could be attributed to the following reasons: 1) the reduction of the nitro group should involve initial single-electron transfer from the metal to the nitroalkene with the formation of a radical anion. From electronic point of view, electron rich ligands not the poor ones could enhance and assist the metal for such process. 2) The nitro group of 5-nitrophenanthroline could interfere with the reduction of the nitroolefin. 3) Oxidative addition of carbon halogen bond to the metal in the case of 4,7-Cl_2Phen and 4-ClPhen would compete with the complexation of the ligand to the metal. Phenanthroline substituted with weak to moderate electron donating group such as (4-MePhen, 4,7-Me_2Phen, 4-MeOPhen, 4,7-$(MeO)_2$Phen) gave almost complete conversion moreover, the selectivity increased with respect to the unsubstituted phenanthroline. Among all the tested ligands (4,7-$(MeO)_2$Phen) gave the best catalytic activity and selectivity to the bicyclic product. Phenanthroline substituted with strong electron donating group such as (4,7-$(NMe_2)_2$Phen, 4-(NHMe)Phen, 4,7-$(Pip)_2$-Phen, 4-Pip-Phen, 4,7-$(OH)_2$Phen), not as expected, decreased both catalytic activity and product selectivity. The reasons for this behavior is not well understood yet. Only the negative effect of dihydroxy phenanthroline could be explained on the basis of its low solubility in the reaction medium. Phenanthroline substituted at positions 2 and 9 such as neocuproine (2,9-Me_2Phen) showed poor catalytic activity and lower selectivity relative to the unsubstituted phenanthroline, owing to hindered coordination to the metal by the two bulky methyl groups. Moreover, *N*-(1,3-dimethylimidazolidin-2-ylidene)quinolin-8-amine (DMEGqu) has been tested as a ligand and showed good conversion and moderate selectivity.

Table 2.2 Reductive cyclization of 1- (thien-2yl)-2-nitropropene (**3a**) to 4H-5-methyl thieno[3,2-b]pyrrole (**4a**) by CO, catalyzed by $[Pd(Phen)_2][BF_4]_2$: optimization of the ligand[a].

Entry	**Lig.**	**Conv. (%)[b]**	**Sel. (%)[b]**
1	**5-NO_2Phen**	27.1	34.8
2	**4,7-Cl_2Phen**	33.7	49.7
3	**4-ClPhen**	**75.2**	**60.0**

4	**Phen**	94.8	57.2
5	**4-MePhen**	100	66.0
6	**4,7-Me_2Phen**	96.0	62
7	**4-MeOPhen**	100	68.7
8	**4,7-$(MeO)_2$Phen**	100	81.6
9	**4,7-$(OH)_2$Phen**	4.4	48.6
10	**4-Pip-Phen**	98.1	65.5
11	**4,7-$(Pip)_2$-Phen**	49.7	47.4
12	**4-(NHMe)Phen**	68.2	54.6
13	**2,9-Me_2Phen**	19.3	42.7
14	**DMEGqu**	95.3	42.4
15	**4,7-$(NMe_2)_2$Phen**	39.9	39.8
16	**3,4,7,8-$(Me)_4$Phen**	92.6	61.8

[a]Experimental conditions: catalyst $[Pd(Phen)_2][BF_4]_2$ = 6.4 mg, 1 x 10^{-2} mmol; mol ratio Pd/Ligand/Sub = 1:8:50, T = 150 °C, P_{CO} = 5 bar Et_3N = 400 µl, in CH_3CN (15 ml), Reaction time = 3h. [b] Determined by GC analysis.

B- Carbon monoxide Pressure

The model reaction was then carried out at different pressures of carbon monoxide ranging from 1 to 70 bar (table 2.3). Both substrate conversion and product selectivity were slightly decreased with increasing the carbon monoxide pressure ranging from 5 to 70 bars. (table 4, entry 24-31). A maximum of catalytic activity was reached using 5 bar of carbon monoxide with complete conversion and good selectivity. Further reduction of carbon monoxide pressure to 1 bar, results in strong drop of both substrate conversion and product selectivity. It is worthy to note that; acetonitrile was replaced by DMF when the catalytic reaction was operated at 1 bar of carbon monoxide, to avoid boiling and exhaustive evaporation of the solvent during the reaction. So the drop of catalytic activity at that pressure may depend on both the low pressure of carbon monoxide and the change in the solvent.

Table 2.3 Reductive cyclization of 1- (thien-2yl)-2-nitropropene (**3a**) to 4H-5-methyl thieno[3,2-b]pyrrole (**4a**) by CO, catalyzed by $[Pd(Phen)_2][BF_4]_2$: optimization of Carbon monoxide pressure.[a]

Entry	P_{CO} (bar)	Conv. (%)[b]	Sel. (%)[b]
17	**70**	89.2	72.1
18	**60**	92.5	74.8
19	**50**	91.0	76.5
20	**40**	93.2	78.0
21	**30**	96.4	80.0
22	**20**	98.1	77.0
23	**10**	99.9	78.4
24	**5**	99.8	81.0
25[b]	**1**	50.3	20.6
26[c]	**1**	73	7.2

[a]Experimental conditions: catalyst $[Pd(Phen)_2][BF_4]_2$ = 6.4mg, 1 x 10^{-2} mmole; ligand = 4,7-dimethoxyphenanthroline, mol ratio Pd/Lig/Sub = 1:8:50, T = 150 °C, Et_3N = 400 µl, in CH_3CN (15 ml), Reaction time = 3 h, [b] DMF is used as solvent instead of acetonitrile, Reaction time = 3 h, [c] DMF is used as solvent, Reaction time = 12 h. [b] Determined by GC analysis.

C- Temperature

To investigate the effect of the operating temperature on the catalytic reaction, the model reaction was carried out at different temperature ranging from 100 to 160 °C (Table 2.4). At low temperature, the catalytic activity of the system gave poor results for both conversion and selectivity. With increasing the reaction temperature the substrate conversion strongly increased till 140 °C, at which temperature the conversion become almost complete and remained constant at higher temperatures. On the other hand, the product selectivity reaches a maximum at 150 °C.

Table 2.4 Reductive cyclization of 1- (thien-2yl)-2-nitropropene (**3a**) to 4H-5-methyl thieno[3,2-b]pyrrole (**4a**) by CO, catalyzed by $[Pd(Phen)_2][BF_4]_2$: optimization of reaction temperature[a].

Entry	T (ºC)	Conv.[b] (%)	Sel.[b] (%)
27	**160**	100	79.5
28	**150**	99.8	81.0
29	**140**	99.9	76.0
30	**130**	90.5	72.3
31	**120**	68.7	67.0
32	**100**	32.0	49.7

[a]Experimental conditions: catalyst $[Pd(Phen)_2][BF_4]_2$ = 6.4mg, 1 x 10^{-2} mmol; ligand = 4,7-dimethoxyphenanthroline, mol ratio Pd/L/Sub = 1:8:50, P_{CO} = 5 bar,Et_3N = 400 µl, in CH_3CN (15 ml), Reaction time = 3 h. [b] Determined by GC analysis.

D- Nature of base

In the screening of the base, seven bases were tested including organic and inorganic bases. (Table 2.5) Poor catalytic activity was found for the inorganic ones, which was initially attributed to the low solubility of those bases in the organic solvent. However, the catalytic results did not improved even by adding PEG to enhance their solubility. Moreover, using alkoxide as organic base gave almost no selectivity to our desired cyclized product. A good catalytic activity was obtained when other organic nitrogen bases were tested. The use of a strong base as 1,4-diazabicyclo[2.2.2]octane (DABCO) gave a good conversion but a moderate selectivity, on the other hand, dimethylaminopyridine (DMAP) gave the best results for selectivity but with incomplete conversion. Pyridine and triethylamine gave a comparable results but triethylamine has the advantage of its low cost and lower toxicity.

Table 2.5 Reductive cyclization of 1- (thien-2yl)-2-nitropropene (**3a**) to 4H-5-methyl thieno[3,2-b]pyrrole (**4a**) by CO, catalyzed by $[Pd(Phen)_2][BF_4]_2$: optimization of the nature of the base.[a]

Entry	Base	Additive	Conv.[b] (%)	Sel.[b] (%)
33	**DABCO**	-	81.8	63.5
34	**Py**	-	96.8	76.0

35	**DMAP**	-	93.1	86.1
36	**TEA**	-	99.9	77.4
37	**KO^{t}Bu**	-	100	<1
38	**K_2CO_3**	-	100	11.9
39	**K_2CO_3**	**PEG[c]**	99.7	11.5
40	**Na_2HPO_4**	-	68.0	51.0
41	**Na_2HPO_4**	**PEG[b]**	60.6	57.2

[a]Experimental conditions: catalyst $[Pd(Phen)_2][BF_4]_2$ = 6.4mg, 1 x 10^{-2} mmol; ligand = 4,7-dimethoxyphenanthroline, mol ratio Pd/Lig./Sub = 1:8:50, P_{CO} = 5 bar, T = 150 °C, in CH_3CN (15 ml), Reaction time = 3 h using 1.43 mmole of base, [b] Determined by GC analysis. [c]PEG is polyethylene glycol 1000 dimethyl ether

E-Amount of base

In optimization of the amount of triethylamine (Table 2.6) we found that the reaction does not require a base to occur, but the addition of a base influences positively both the system activity and the selectivity in the cyclized bicyclic product. The conversion seems to be insensitive to the added amount of the base; on the other side selectivity increases slightly with increasing the amount of the base till reaching a maximum when 400 μl is added of triethylamine. Further addition of the base decreases the selectivity.

Table 2.6 Reductive cyclization of 1- (thien-2yl)-2-nitropropene (**3a**) to 4H-5-methyl thieno[3,2-b]pyrrole (**4a**) by CO, catalyzed by $[Pd(Phen)_2][BF_4]_2$: optimization of the amount of the base[a].

Entry	**Et_3N** μl	**Conv.[b] (%)**	**Sel.[b] (%)**
42	**Zero**	94.3	73.5
43	**50**	100	75.0
44	**100**	100	73.1
45	**200**	99.9	77.4
46	**300**	99.9	78.9

47	**400**	99.8	81.0
48	**500**	100	76.2

[a]Experimental conditions: catalyst $[Pd(Phen)_2][BF_4]_2$ = 6.4mg, 1 x 10^{-2} mmol; ligand = 4,7-dimethoxyphenanthroline, mol ratio Pd/L/Sub = 1:8:50, P_{CO} = 5 bar, T = 150 °C, in CH_3CN (15 ml), Reaction time = 3 h. [b] Determined by GC analysis.

E- Nature of Solvent

In the screening of the solvents, (Table 2.7), different types of solvents were tested, including nonpolar, polar protic and aprotic solvent. The nonpolar solvent (toluene) gave the worst catalytic results obtained. This could be attributed to the destablization of the charged intermediate during the course of the reaction. A polar protic solvent (methanol) showed a good conversion but a very poor selectivity to the desired cyclized product. Based on the known carbonylation chemistry of nitroarenes in the presence of alcohols, it can be advanced that be formation of other products like carbamate may be much more favorable in the presence of an alcohol.[109b, 109d] The other four tested solvents are polar and aprotic. Dimethoxy ethane (DME) and tetrahydrofuran (THF) showed a poor convertion and a moderate selectivity. The catalytic results obtained in dimethyl formamide (DMF) and acetonitrile were not so different, both gave almost complete conversion and a good selectivity for the bicyclic product. We select acetonitrile as it gives the best result and it is also much easier to remove at the end of the reaction.

Table 2.7 Reductive cyclization of 1- (thien-2yl)-2-nitropropene (**3a**) to 4H-5-methylthieno[3,2-b]pyrrole (**4a**) by CO, catalyzed by $[Pd(Phen)_2][BF_4]_2$: effect of the solvent[a].

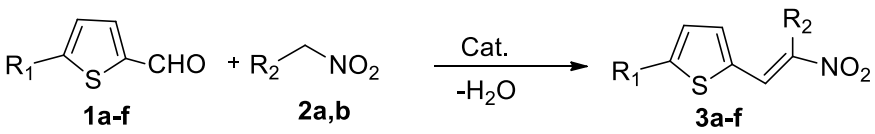
Entry	Solvent	**Conv.[b] (%)**	**Sel.[b] (%)**
49	**DMF**	99.8	70.5
50	**DME**	32.5	47.2
51	**Toluene**	1.0	---
52	**THF**	25.2	55.3
53	**MeOH**	81.4	13.0
54	**CH_3CN**	99.8	81.0

[a]Experimental conditions: catalyst $[Pd(Phen)_2][BF_4]_2$ = 6.4mg, 1 x 10^{-2} mmol; ligand = 4,7-dimethoxyphenanthroline, mol ratio Pd/L/Sub = 1:8:50, P_{CO} = 5 bar, T = 150 ^oC, Et_3N = 400 µl and Reaction time = 3 h. [b] Determined by GC analysis.

By summing up the data of the optimization, the best result were obtained by employing $[Pd(Phen)_2][BF_4]_2$ (2 mol%), 4,7-dimethoxy-1,10-phenanthroline (16 mol%) as ligand, at 150 °C, 5 bar of CO, for 3 h, Et_3N (400 µl) in acetonitrile as the solvent

2.2.2 Synthesis of the substrate

In order to explore the scope of the reaction, we synthesized a variety of substituted 1- (thienyl)-2-nitroethene, which are easily prepared from commercially available thiophenecarboxaldehyde and nitroalkane in one step by the nitroaldol reaction (Henry reaction). (Scheme 2.10), we obtained from fair to good yields.



1a-f **2a,b** **3a-f**

Scheme 2.10

2.2.3 Scope of the reaction

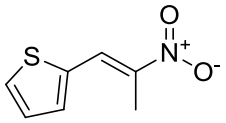
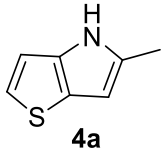
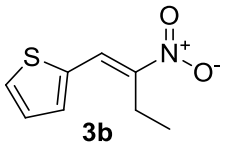
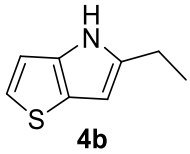
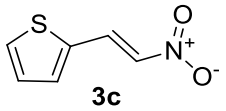
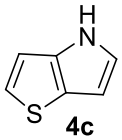
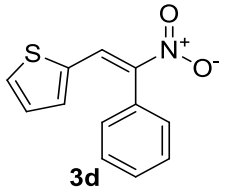
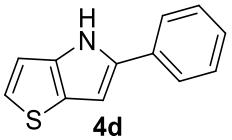
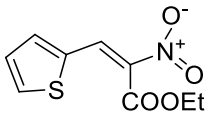
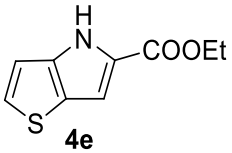
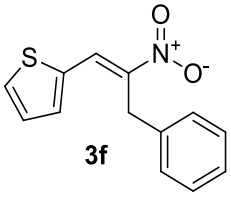
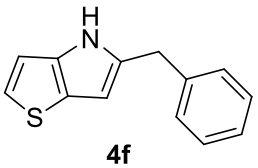
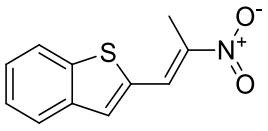
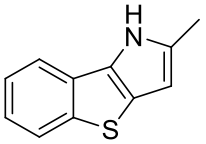
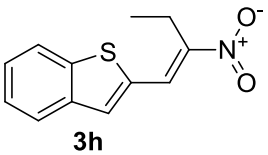
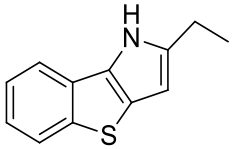
The scope of the reaction has been explored, (Table 2.8). Our optimized conditions were applied to a variety of different substituted 1-(thienyl)-2-nitroethenes (**3a-3l**). Using our optimized conditions, it is interesting to note that both thieno[2,3-b] pyrrole and thieno [3,2-b] pyrrole can be obtained in yield ranging from 40-98%. Excellent results with over 80 % isolated yield were obtained with substrates **3a, 3b, 3f, 3k** and **3l** (Table 2.2). Reductive cyclization of compound **3d**, afforded 5-phenyl-4H-thieno [3,2-b] pyrrole in 62 % yield. Our catalytic system for reductive cyclization tolerates a wide range of substituent at β-position of 1-(thienyl)-2-nitroethene, for example methyl, ethyl, phenyl, and benzyl. Which allowed us to obtain different groups at 5-position of thieno[3,2-b] pyrrole or thieno [2,3-b] pyrrole. To best of our knowledge, no previous method has been reported in the literature for the preparation of most of these compounds.

Moreover, reductive cyclization of compounds **3g** and **3h** afforded the tricyclic compounds 2- methyl and 2-ethyl-1H-[1]benzothieno[3,2-b]pyrroles in 32 and 37 % yield respectively. It is worthy to note that reductive cyclization of compounds **3i** and **3j** were regiospecific to thieno [2,3-b]pyrrole and no thieno [4,3-b]pyrrole was formed. This can be attributed to the higher electron density at α.-postion of

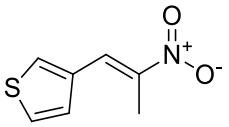
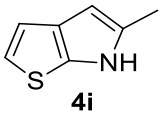
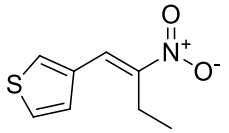
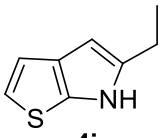
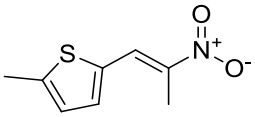
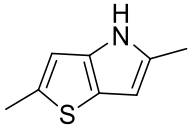
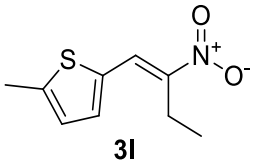
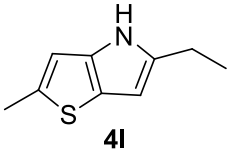
thiophene relative to β-positions,[120] leading to preferential amination at the 2-postion rather than the 3-position and affording the wall [2,3-b].

No cyclization product was observed in case of compound **3c**, which lacks a susbstituent at β- position. We observed formation of palladium black and about 50 % of the substrate has been recovered indicating low catalytic activity. (See Table 1). By analogy to β- nitrostyrene, initially we referred that behavior to the possibility of faster rate of polymerization [117] of **3c** relative to reductive cyclization reaction. Several attempts were done to slightly modify our reaction conditions, to avoid homocoupling, but were not successful. This result confirms that the presence of a substituent in the β-position is fundamental for product formation. In the case of compound **3e,** the starting material was completely consumed leading to a complex mixture containing the desired bicylic product as detected from GC/MS. However, we were not able to isolate it in a pure form. In conclusion, we reported herein a new and efficient catalytic system for the reductive cyclization of some substituted 1-(thienyl)-2-nitroethenes, which are readily available from commercial starting material in one step. Yields in the range of 32–94% were obtained from twelve of the starting materials examined.

Table 2.8: Scope of the reaction[a]

Entry	Substrate	Product	Yield (%)[b]
1	 3a	 4a	82
2	 3b	 4b	90
3	 3c	 4c	nd[c]
4	 3d	 4d	62
5	 3e	 4e	Complex mixture
6	 3f	 4f	98
7	 3g	 4g	32
8	 3h	 4h	37

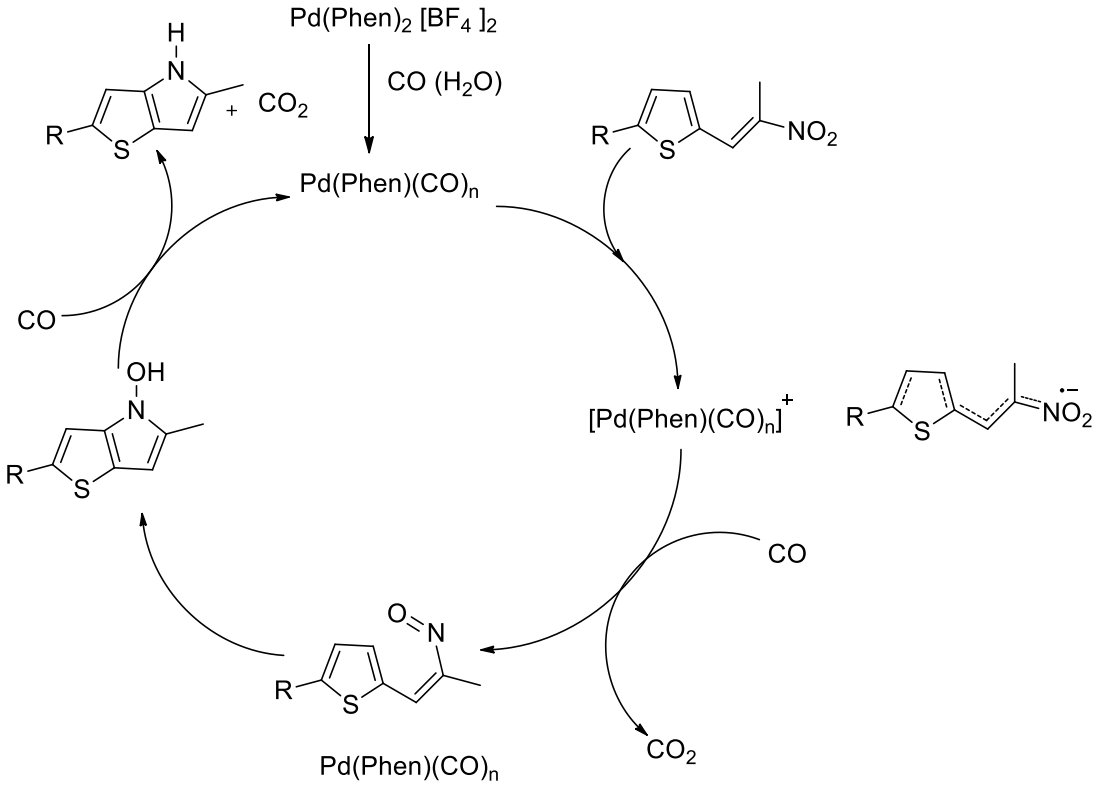
(Continued on next page)

Entry	Substrate	Product	Yield (%)[b]
9	 3i	 4i	78
10	 3j	 4j	40
11	 3k	 4k	89
12	 3l	 4l	93

[a]Experimental conditions: catalyst $[Pd(Phen)_2][BF_4]_2$ = 6.4mg, 1 x 10^{-2} mmol; ligand = 4,7-dimethoxyphenanthroline, mol ratio Pd/L/Sub = 1:8:50, P_{CO} = 5 bar, T = 150 °C, Et_3N = 400 µl, CH_3CN (15 mL), and Reaction time = 3 h. [b] Isolated yield after chromatography. [c]Not detected.

2.2.4 Proposed Mechanism

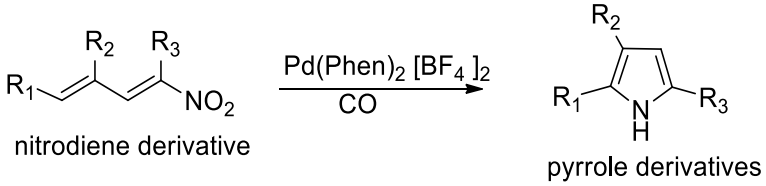
A mechanistic proposal (Scheme 2.11), for reductive cyclization of nitroalkenylthiophene based on previous experimental[116b] and theoretical work[54], involves an initial activation of the nitro compound due to a single-electron transfer from the metal to the nitroalkene and following the formation of an intermediate nitrosoalkene, which is proposed to be the aminating species. Rotation of the double bond in the nitro radical anion intermediate explains why good selectivities are obtained even from *trans*-β-nitroalkenylthiophene. Eventually the N-hydroxy pyrrole ring formed by amination, is reduced to Pyrrole by carbon monoxide.


Pd(Phen)2 [BF4]2
CO (H2O)
Pd(Phen)(CO)n
[Pd(Phen)(CO)n]+
Pd(Phen)(CO)n
CO2
CO
CO
CO2
NO2
NO2
R
S
N
H
OH
O
N

Scheme 2.11

2.3 Palladium catalyzed synthesis of 2,5-disubstituted or 2,3,5-trisubstituted pyrroles by intramolecular reductive cyclization of nitro-dienes

Pyrrole is one of the most important simple heterocycles, which is found in a broad range of natural products and drug molecules. It was first isolated in 1857 from the products of bone pyrolysis, and identified as biologically relevant when it was recognized as a structural fragment of heme,[80] and chlorophyll.[81] It is present also as subunits of bile pigments[121] and vitamin B12.[82] In addition pyrrole derivatives are of interest because of their potential biological activity such as antibacterial,[122] antiinflammatory,[123] antioxidant,[124] antitumor,[125] antifungal[126] and immune suppressant activities.[127] Pyrrole and its derivatives are utilized as intermediates in the synthesis of drugs, biologically active substances, conductive polymers,[128] sensors,[129] optoelectronic materials,[130] solar cells,[131] etc. as it has been mentioned in the introduction chapter. Consequently, many new synthetic methods have been developed for the construction of pyrroles and their derivatives. Classical methods for the synthesis of substituted pyrroles include the classical Knorr reaction,[94b] the Hantzsch reaction,[99] and the Paal-Knorr condensation reaction.[94c] However, these methods have some limitations with respect to the regioselectivity, substitution patterns that can be introduced, multisteps synthetic operations and harsh reaction conditions. Despite recent advances, particularly in transition metal-catalyzed,[132] multicomponent processes[133] and domino reactions,[134]a more flexible and general approach is still of critical importance. Over the past several years ago, metal catalyzed reductive condensation of a nitro and an olefin group for the construction of heterocyclic rings has been shown to be an effective, promising, extremely powerful method. It has the advantage to use cheap and commercially available nitroarenes, converting them into valuable heterocycles. As a contribution in this field, our research group used this methodology to prepare some derivatives of many heterocycles such as indole,[119] carbazole, imidazole, indazole, etc. Inspired by the importance of pyrrole derivatives and as continuation to our previous work, we developed a new, facile and efficient synthesis for some pyrrole derivatives by reductive cyclization of nitrodienes, using palladium/phenanthroline as the catalyst and carbon monoxide as the reductant. The reaction proceeds through the activation of a diene C-H bond in delta position relative to the nitro group. (Scheme 2.11)

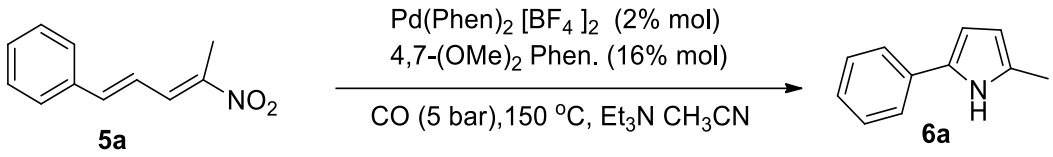


nitrodiene derivative — pyrrole derivatives

Scheme 2.11

2.3.1 Optimization of the reaction conditions

We did an extensive work for the optimization of the Pd catalytic system, used for reductive cyclization of 1-(thien-2yl)-2-nitropropene to 4H-5-methyl thieno[3,2-b]pyrrole. We tried to employ these optimized parameters for the Pd-catalyzed reductive cyclization of diene, as starting point to test the new catalytic pyrrole synthesis. These parameters are $[Pd(Phen)_2][BF_4]_2$ (2 mol%), 4,7-dimethoxy-1,10-phenanthroline (16 mol%) as ligand, at 150 °C, 5 bar of CO, for 3 h, Et_3N (400 µl) in acetonitrile as the solvent. Fortunately, with the use of the optimized conditions, we were able to completely convert **5a** into **6a** with 76% isolated yield (Scheme 2.12)

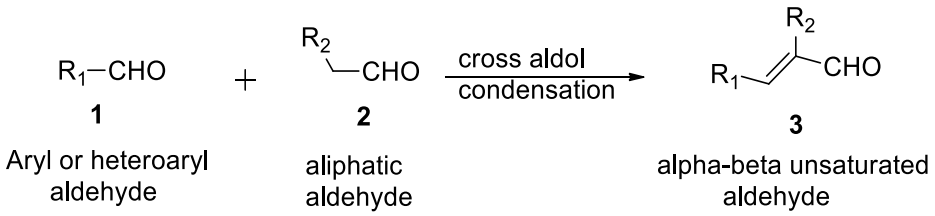


Scheme 2.12

The obtained yield is good but not excellent, so further optimization for this catalytic system, may be done in the future.

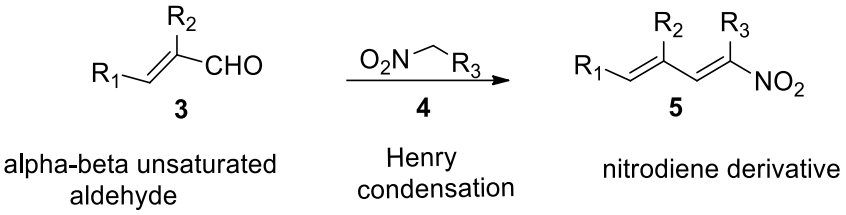
2.3.2 Synthesis of the substrates

The nitrodienes were easily accessible by a two step synthesis: 1) cross aldol condensation between two aldehydes only one of them containing alpha hydrogens, to give an alpha-beta unsaturated aldehyde, (Scheme 2.13)



Scheme 2.13

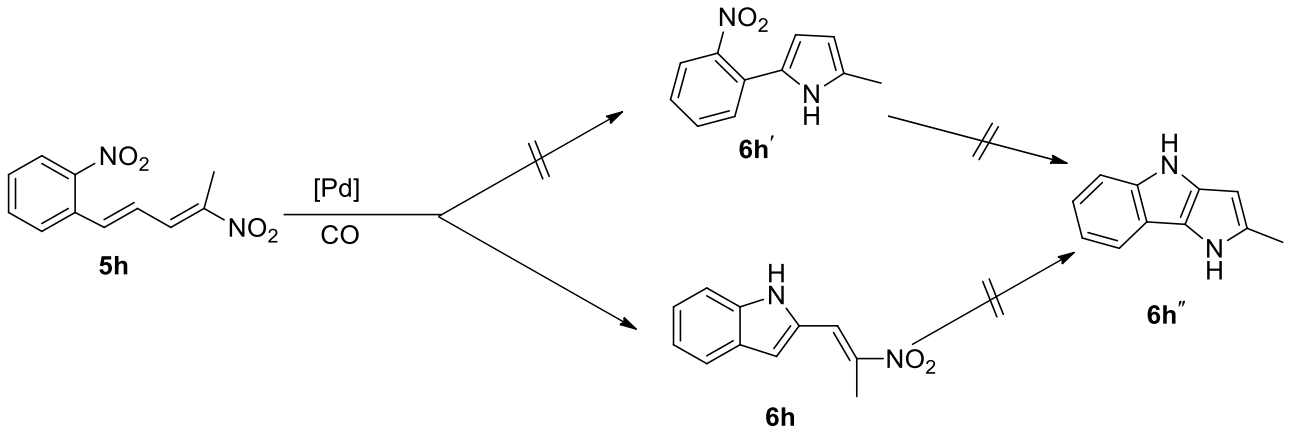
2) Henry condensation of the so obtained unsaturated aldehyde with nitroalkane to give corresponding nitrodiene. (Scheme 2.14)



Scheme 2.14

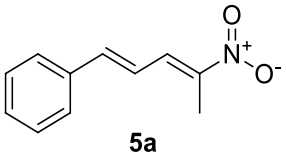
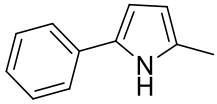
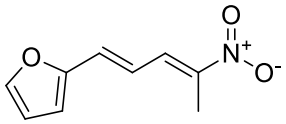
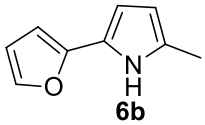
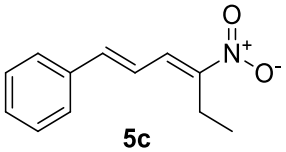
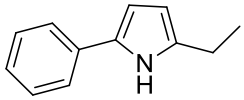
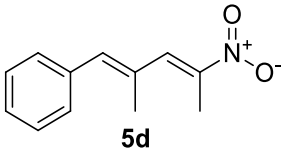
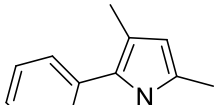
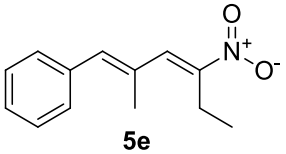
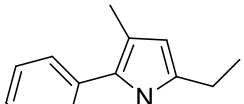
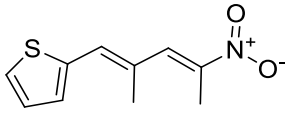
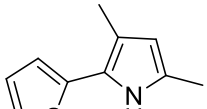
2.3.3 Scope of the reaction

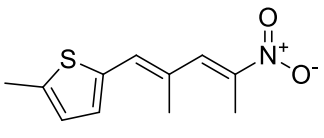
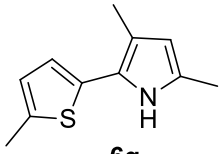
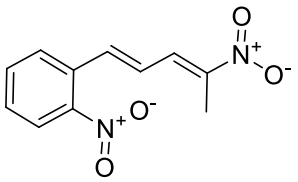
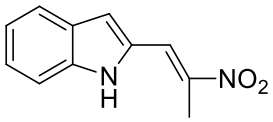
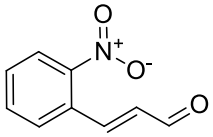
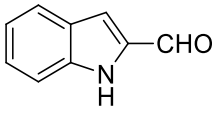
The scope of the reaction has been explored, (Table 2.8). Our optimized conditions were applied to a variety of differently substituted 1-nitro-1,3-butadienes (**5a**-**5h**). Using our optimized conditions, it is especially notable that 2,5-disubstituted or 2,3,5-trisubstituted pyrrole can be obtained in moderate to good yield ranging from 43-76%. The best result was obtained for the reductive cyclization of **5a** to **6a** (Table 2.3). Reductive cyclization of compounds **5a, 5b, 5c** afforded disubstituted pyrrole in a good yield, whereas cyclization to trisubstituted pyrrole **6d**, **6e, 6f** and **6g** gave lower and moderate yield. That can be correlated to the steric hindrance of the three substituents in the latter case, which hinders the cyclization step. It is interesting to note that reductive cyclization of **5h** did not gave the expected disubstituted pyrrole **6h´** (Scheme 2.15); instead it gave the indole derivative **6h.** Moreover double reductive cyclization of the two nitro groups would gave pyrroloindole **6h˝**, but it was not detected in the reactin mixture. Compound **6h** derived from reduction of the nitro group directly attached to benzene ring to nitroso intermediate followed by amination of the C-H present at γ-position relative to the nitro group attached to the diene. This imply, faster rate of reduction of nitroarene relative to nitrodiene under our reaction conditions. To confirm that our optimized conditions are also suitable for reductive cyclization of nitroarenes, the same reaction conditions were reapplied to compound **5i,** from which we obtained the indole **6i** in 72%. Yield. This confirms our proposal.



Scheme 2.15

Table 2.9 Scope of the reaction[a]

Entry	Substrate	Product	Yield (%)[b]
1	 **5a**	 **6a**	**76**
2	 **5b**	 **6b**	**72**
3	 **5c**	 **6c**	**69**
4	 **5d**	 **6d**	**52**
5	 **5e**	 **6e**	**43**
6	 **5f**	 **6f**	**46**

7	 **5g**	 **6g**	**53**
8	 **5h**	 **6h**	**56**
9	 **5i**	 **6i**	**72**

[a]Experimental conditions: catalyst $[Pd(Phen)_2][BF_4]_2$ = 6.4mg, 1 x 10^{-2} mmole; ligand = 4,7-dimethoxyphenanthroline, mol ratio Pd/Lig./Sub = 1:8:50, P_{CO} = 5 bar, T = 150 ^{o}C, in CH_3CN (15 ml), Reaction time = 3 h. [b] Isolated yield after chromatography.

2.4 Allylic Amination of cyclohexene by Nitroarenes and carbon monoxide, Catalyzed by Palladium Complexes.

Several years ago, our research group showed that ruthenium carbonyl complexes with nitrogen ligands catalyze the *inter*-molecular reaction of aromatic nitro compounds with olefins and CO to give allylic amines. Selectivities were high, but the activity of the catalyst was moderate, resulting in the need for relatively large amounts of ruthenium (mol ratio $ArNO_2$/Ru =33).[107c] In the same work, it was shown that a palladium/phenanthroline catalyst only afforded trace amounts of the desired allylic amine. Since palladium complexes are usually more active than ruthenium ones in a series of nitroarene reductive carbonylation reactions, the poor activity in this particular reaction was surprising. It can be speculated that the allylic amination under investigation may require three coordination sites on the metal and, unlikely the ruthenium catalyst, a palladium complex with a chelating ligand may only have two coordination sites available both when in the 0 and in the +2 oxidation states. The solution may be employing a monodentate ligand in place of a chelating one.

In the preliminary experiments done, as shown in table 2.10, different nitroarenes with different Palladium complex and a number of monodentate ligands have been examined. Among the variety of conditions explored only $Pd(OAc)_2$/Pyridine system showed a catalytic activity towards allylic amination. Acridine has been tested because it is a monodentate ligand with a more extended π system with respect to pyridine. This was deemed to facilitate the initial activation of the nitroarene, which proceed by an electron transfer from the metal complex. Unfortunately, acridine was not effective at a low ligand/Pd ratio and the use of high ratios is prevented by its solid nature, in contrast to pyridine that may even be uses as a cosolvent.

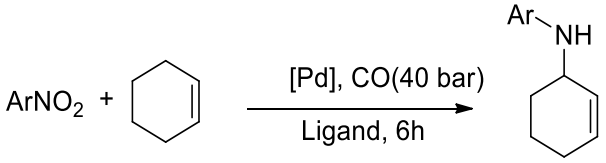


Table 2.10 Preliminary experiments for allylic amination of cyclohexene[a]

Entry	Nitroarene	[Pd]	Ligand	Mol. Ratio Pd/Lig./Sub.	Detection of allyl amine by GC
1	$PhNO_2$	$Pd(Py)_2Cl_2$	DMAP	1:10:50	nd[b]
2	$PhNO_2$	$Pd(OAc)_2$	Py	1:6000:50	nd
3	$PhNO_2$	$Pd(Phen)_2(BF_4)_2$	Acridine	1:3:50	nd

4	4-$ClC_6H_4NO_2$	$Pd(Phen)_2(BF_4)_2$	Acridine	1:10:50	nd
5	3,5-$(CF_3)_2C_6H_3NO_2$	$Pd(OAc)_2$	Acridine	1:50:50	nd
6	3,5-$(CF_3)_2C_6H_3NO_2$	$Pd(OAc)_2$	Py	1:6000:50	detected

[a]Experimental conditions: P_{CO} = 40 bar, cyclohexene (10 ml), Reaction time = 6 h. [b] Not detected

Encouraged by the previous last result, we started trials for optimizing the reaction conditions. 3,4-dichloronitrobenzene was chosen as a model compound for the optimization of the experimental conditions. $Pd(OAc)_2$ was chosen as the catalyst for the optimization reactions (Table 2.11). Chelating ligands were now tested to have a comparison with monodentate ones.

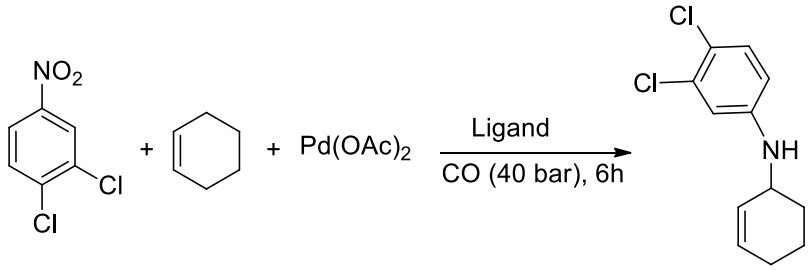
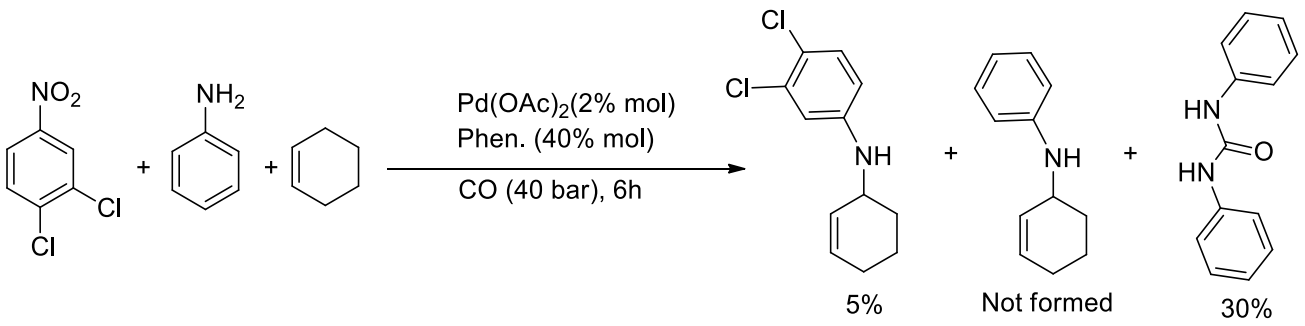


Table 2.11 Trials for optimizing of the reaction conditions[a]

Entry	Ligand	Mol. Ratio Pd/Lig./Sub.	T (ºC)	Conv. %	Sel. %
1	**Py**	1:6000:50	160	49	9
2	**Py**	1:1000:50	160	0	0
3	**DMAP**	1:1000:50	160	100	7
4	**DMAP**	1:200:50	160	56	11
5	**Acridine**	1:200:50	160	0	0
6	**Bipyridine**	1:100:50	160	13	17
7	**Phen**	1:20:50	160	100	20
8	**Phen**	1:20:50	120	74.1	7
9	**Phen**	1:20:50	170	100	23
10	**Phen[b]**	1:20:50	160	100	5
11	**4-OMePhen**	1:20:50	160	100	18
12	**4,7-OMe_2Phen**	1:8:50	160	100	14

[a]Experimental conditions: P_{CO} = 40 bar, cyclohexene (10 ml), Reaction time = 6 h. [b] aniline (96 mg) was added to the reaction mixture

Three nitrogen monodentate ligands have been tested, namely, pyridine, 4-dimethylaminopyridine (DMAP) and acridine. Employing pyridine as a ligand and solvent at the same time, gave a moderate conversion of the nitroarene and revealed formation of the desired allyic amine with low selectivity. In addition, unquantified amounts of 3,4-dichloroaniline have been detected. However, pyridine must be used in a very high ratio with respect to $Pd(OAc)_2$, otherwise no catalytic activity is observed. Complete conversion of the starting nitroarene with a low selectivity for allylic amine and no formation of aniline had been observed using DMAP in high ratio. Decreasing the loading of DMAP leaded to decrease of the conversion to its half without effective change to the selectivity of the allyic amine and appearance of a little amount of aniline. On the other hand no catalytic activity at all was observed for Pd/acridine system. Moreover, other four nitrogen bidentate ligands were also tested, namely, bipyridine, phenantroline, 4-methoxyphenanthroline and 4,7-dimethoxy phenanthroline. Bipyridine showed the least catalytic activity. However, phenanthroline ligand showed a complete conversion of the nitroarene and 20% selectivity of the desired allylic amine and very small amount of 3,4-dichloroaniline. Attempts to improve the selectivity by decreasing the reaction temperature from 160 to 120 ^oC, leaded to lowering both conversion and selectivity. On the other hand, increasing the reaction temperature from 160 to 170 ^oC, leaded to insignificant improvement of the allyl amine selectivity. To ascertain if the aniline is only a byproduct or an intermediate of the reaction reported still here, one experiment was carried out by using 3,4-$Cl_2C_6H_3NO_2$ as substrate, but also adding unsubstituted aniline to the reaction mixture. Only the allylamine containing the substituted aryl ring and no allylamine derived from aniline was detected among the products. Moreover, diphenylurea was formed and isolated from the reaction mixture. Thus aniline is clearly not an intermediate in the reaction leading to the allylamine, although the lower selectivity when the aniline is also added indicates that it may be an intermediate in the synthesis of one or more of the byproducts.

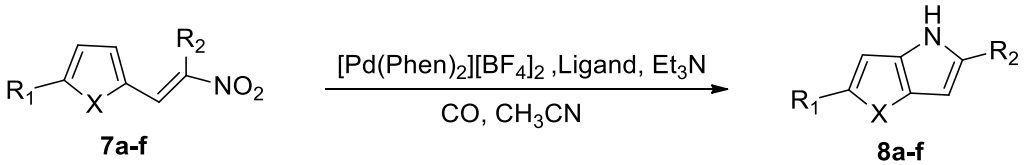


Employing electron rich phenanthrolines such as 4-methoxyphenanthroline and 4,7-dimethoxyphenanthroline gave a complete conversion and selectivities to the allylamine were 18% and 14% respectively. However, it is especially notable that using these ligands leaded to appearance of tetrachloro azobenzene as byproduct.

As a conclusion, the idea that a monodentate ligand may afford better results than phenanthroline has not been confirmed. Phenanthroline and it substituted analogues remain the best ligands. The optimization of the reaction conditions allowed to partially increasing the yield of the reaction, but results are still over 80% for the same reaction by far inferior to those obtainable with a ruthenium catalyst, which afforded selectivities up.

2.5 Preliminary attempts to synthesize pyrrolo[3,2-b]pyrrole and furo[3,2-b]pyrrole using palladium catalyst and carbon monoxide as a reductant

In continuation to our previous work of reductive cyclization of α,β-unsaturated nitro compounds and encouraged by results of reductive cyclization of nitroalkenylthiophenes to thienopyrroles, we decided to extend the scope of the reaction to amination of pyrrole and furan, in order to prepare pyrrolopyrrole and furopyrrole respectively Scheme 2.



a, X = NH, R_1 = H, R_2 = CH_3
b, X = NCH_3, R_1 = H, R_2 = CH_3
c, X = NAc, R_1= H, R_2 = CH_3
d, X = O, R_1 = H, R_2 = CH_3
e, X = O, R_1 = H, R_2 = COOEt
f, X = O, R_1 = CH_3 , R_2 = CH_3

Table 2.12 Preliminary experiments for reductive cyclization of compounds **2a-f** catalyzed by $[Pd(Phen)_2][BF_4]_2$ and with carbon monoxide as a reductant[a]

Entry	Sub.	Lig.	Mol. Ratio Pd/L/Sub.	Et_3N (ml)	T (°C)	P_{CO} (bar)	t (h)	Conv (%)	Detection of bicyclic product by GC/MS
1	**7a**	4,7-OMe_2Phen	1:8:50	0.400	150	5	3	-	nd[b]
2	**7b**	4,7-OMe_2Phen	1:8:50	0.400	150	5	3	52	nd
3	**7b**	Phen	1:16:100	0.356	150	20	2.5	6.8	nd
4	**7b**	Phen	1:8:50	0.356	170	20	7	57.5	nd
5	**7b**	Phen	1:8:50	0.356	150	20	7	98.1	nd
6	**7b**	Phen	1:8:50	0	120	60	4	48	nd
7	**7c**	Phen.	1:8:50	0.356	150	60	4	66.3	detected
8	**7c**	Phen.	1:8:50	0.500	150	60	6	80	detected

9[c]	**7c**	Phen	1:8:50	0.180	150	80	4	52	detected
10	**7c**	4,7-OMe_2Phen	1:8:50	0.356	150	60	4	98	detected
11	**7c**	4,7-OMe_2Phen	1:8:50	0.400	150	5	3	-	detected
12	**7d**	4,7-OMe_2Phen	1:8:50	0.356	155	60	3	-	detected
13	**7d**	4,7-OMe_2Phen	1:8:50	0.400	150	5	3	-	detected
14	**7e**	4,7-OMe_2Phen	1:8:50	0.400	150	5	3	-	Complex mixture
15	**7f**	4,7-OMe_2Phen	1:8:50	0.400	150	5	3	-	detected

[a]Experimental conditions: catalyst $[Pd(Phen)_2][BF_4]_2$ = 6.4mg, 1 x 10^{-2} mmol; CH_3CN (15 ml). [b] nd = Not detected.[c] 2,2-dimethoxypropane (0.050 ml) was added to the reaction. mixture

Unfortunately, all the attempts to reductively cyclize compounds **7a** or **7b** failed. Even if we used the optimized reaction parameters for the Pd catalytic system reported before to give very good results in indole or thienopyrrole synthesis. In all cases, we obtained moderate to complete conversion without detection of the bicyclic product. This behavior could be attributed to the electron rich property of pyrrole containing NH (**7a**) or NCH_3 (**7b**), which inhibits or slows down the initial electron transfer from palladium complex to the nitro group. To overcome this problem, we tried to decrease the electron density of the pyrrole ring. This was done by introducing electron withdrawing group on the ring. By acetylation of **7a**, we obtained the corresponding N-acetylated product **7c.** As expected, catalytic reductive cyclization of **7c** afforded the corresponding pyrrolopyrrole **8c,** as proven from the GC/MS data. That confirmed our idea. Addition of dimethoxypropane as dehydrating agent to the reaction mixture did not improve the selectivity. Employing 4,7-dimethoxy-1,10-phenanthroline as a ligand instead of phenanthroline, enhances both conversion and selectivity. This can be attributed to the higher σ-donating ability of that ligand. Encouraged by these results, we tried also reductive cyclization of nitroalkenylfurans **7d-f**. We obtained promising results with detection of the corresponding bicyclic product, except for the case of **7e,** which gave a complex mixture.

Although the acetylated pyrrolopyrrole and the furopyrrole derivatives were clearly observed by GC-MS, at the mement we failed to isolate them in a pure form and cannot give exact yields. More work will be required in the future to fully exploit this synthetic strategy.

Experimental

Experimental work

3.1 General Procedure.

Unless otherwise stated, all reactions were conducted under a dinitrogen atmosphere. All the solvents used in catalytic reactions, were dried by distillation over CaH_2 or Na and stored under a dinitrogen atmosphere. All glassware and magnetic stirring bars were kept in an oven at 125 °C for at least two hours and let to cool under vacuum before use. 1,10-Phenanthroline (Phen), purchased as hydrate, was dried over Na_2SO_4 after dissolution in CH_2Cl_2 followed by filtration under dinitrogen atmosphere and evaporation in vacuo. Then, it was stored under dinitrogen. Phenanthroline can be weighed in the air, but must be stored in an inert atmosphere to avoid water uptake. $[Pd(Phen)_2][BF_4]_2$, was synthesized following the procedure reported in the literature.[135] If not otherwise stated, all the other reagents were purchased from Aldrich or Alfa-Aesar and used without further purification. ^1H NMR spectra were recorded on a Bruker Avance DRX 300 or on a Bruker Avance DRX 400, operating at 300 and 400 MHz respectively. Mass spectra were obtained by GC mass spectrometry (Shimadzu GC - 17A / QP5050, equipped with SUPELCO SLB TM -5ms capillary column). Quantitative analyses of catalytic reactions were performed using fast gas chromatography (Shimadzu GC – 2010, equipped with SUPELCO EQUITY TM -5ms capillary column).

3.2 Typical Catalytic Reaction

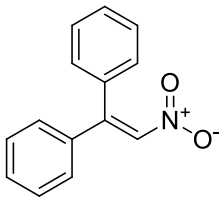
The catalyst, the ligand and the nitro-olefin or nitrodiene were weighed in the air in a glass liner and then placed inside a Schlenk tube with a wide mouth under a dinitrogen atmosphere. The solvent and triethylamine (Et_3N) were added by volume and the liner was closed with a screw cap having a glass wool-filled open mouth which allows gaseous reagents to exchange. The resulting solution was stirred for 10 minutes and then the Schlenk tube was immersed in liquid nitrogen until the solvent froze and evacuated and filled with dinitrogen for three times. The liner was rapidly transferred to a 200 mL stainless steel autoclave equipped with magnetic stirring. The autoclave was then evacuated and filled with dinitrogen three times. CO was charged at room temperature at the required pressure and the autoclave was immersed in a preheated oil bath. The experimental conditions are reported in the captions to the tables in the text. At the end of the reaction the autoclave was quickly cooled with an ice bath, and vented.

3.3 Analysis method for catalytic reactions.

Quantitative analyses of reaction mixtures were carried out by fast gas chromatography using naphthalene as the internal standard (1/4 by weight with respect to the initial substrate). Qualitative

analyses to assess the identity of the obtained indoles were performed on GC-MS. All the conversions were assessed by GC analysis. The yields were obtained by isolation of the products by column chromatography (gradient elution from hexane to hexane/AcOEt 9:1 with the addition of 1% of Et_3N.

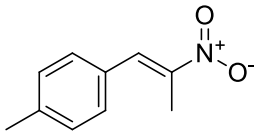
3.4 Synthesis and characterization of substituted β-nitrostyrenes.



1,1-Diphenyl-2-nitroethene (**1b**)

was synthesized following a procedure previously reported in the literature.[113] In a Schlenk flask equipped with a bubble condenser, benzophenone imine (1.0 mL, 6.0 mmol) was dissolved in nitromethane (3.0 mL, 55.5 mmol) and the solution was stirred at reflux for 43 h. The yellow mixture was allowed to cool and the excess nitromethane was evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2 / Hexane = 6:4) affording 0.95 g of the product as a yellow solid (4.20 mmol, 70 %). ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ = 7.48-7.35 (m, 7H), 7.31-7.27 (m, 2H), 7.25-7.19 (m, 2H), ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): δ = 150.6 (*C*), 137.23 (*C*), 135.7 (*C*), 134.5 (*C*H), 131.0 (*C*H), 129.4 (*C*H), 129.03 (*C*H), 129.02 (*C*H), 128.9 (*C*H), 128.6 (*C*H) ppm.

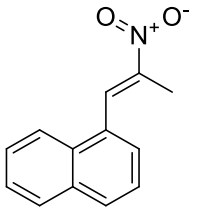
General synthesis of β-Alkyl-β-nitrostyrenes. These substrates were synthesized using a reported standard procedure.[112] All the products were previously reported in the literature. Even if compound **1d** was previously reported,[136] a complete NMR characterization was lacking.



(*E*)-1-Methyl-4-(2-nitroprop-1-enyl)benzene (**1c**).

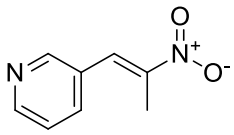
^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ = 8.07 (s, 1H, CH alkenyl), 7.34 (d, *J* = 8.1 Hz, 2H, 3-H, 5-H), 7.26 (d, *J* = 8.1 Hz, 2H, 2-H, 6-H), 2.46 (d, *J* = 0.9 Hz, 3H, -C(NO_2)CH_3), 2.40 (s, 3H, CH_3aromatic) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 300 K): δ = 140.6 (-*C*(NO_2)CH_3), 133.8 (C1), 130.2 (*C*H alkenyl),

129.8 (*C*H aromatic), 129.6 (*C*H aromatic), 21.5 (*C*H_3aromatic), 14.2 (-C(NO_2)*C*H_3) ppm. Spectral data of the compound are in accordance with those reported in the literature.[137]



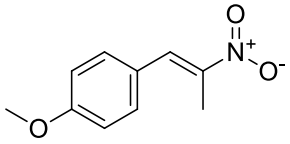
(*E*)-1-(2-Nitroprop-1-enyl)naphthalene(**1d**).

^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ = 8.63 (s, 1H, CH alkenyl), 8.03 - 7.85 (m, 3H, CH aromatic), 7.64 - 7.55 (m, 2H, CH aromatic), 7.52 (d, *J* = 8.1 Hz, 1H, CH aromatic), 7.44 (d, *J* = 7.1 Hz, 1H, CH aromatic), 2.37 (d, *J* = 1.0 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): δ = 149.4 (*C*) 133.6 (*C*), 132.1 (*C*H alkenyl), 131.5 (*C*), 130.3 (*C*H), 129.9 (*C*), 128.9 (*C*H), 127.33 (*C*H), 127.28 (*C*H), 126.8 (*C*H), 125.3 (*C*H), 124.3 (CH), 14.3 (*C*H_3) ppm.



(*E*)-3-(2-Nitroprop-1-enyl)pyridine(**1e**).

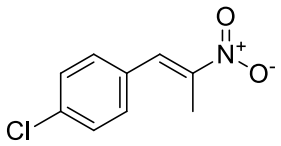
^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ =8.69 (s, 1H, 2-H), 8.65 (d, *J* = 3.8 Hz, 1H, 6-H), 8.04 (s, 1H, CH alkenyl), 7.75 (d, *J* =7.9 Hz, 1H, 4-H), 7.40 (dd, *J* = 4.8 Hz and *J* = 7.9 Hz, 1H, 5-H), 2.45 (d, *J* = 1.0 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): δ = 150.5 (*C*H overlapped with onequaternary carbon), 149.5 (*C*), 137.0 (*C*H), 129.8 (*C*H), 128.8 (*C*), 123.8 (*C*H), 14.2 (*C*H_3) ppm. Spectral data of the compound are in accordance with those reported in the literature.[138]



(*E*)-1-Methoxy-4-(2-nitroprop-1-enyl)benzene(**1f**).

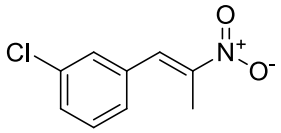
^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ = 8.07 (s, 1H, CH alkenyl), 7.43 (d, *J* = 8.9 Hz, 2H, 3-H, 5-H), 6.98 (d, *J* = 8.9 Hz, 2H, 2-H, 6-H), 3.86 (s, 3H, -OCH_3), 2.47 (s, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): 161.2 (*C*), 145.9 (*C*), 133.8 (*C*H), 132.2 (*C*H), 124.9 (*C*), 114.6 (*C*H), 55.6 (O*C*H_3),

14.3 (*C*H_3) ppm. Spectral data of the compound are in accordance with those reported in the literature.[137]



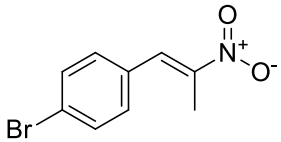
(*E*)-1-Chloro-4-(2-nitroprop-1-enyl)benzene (**1g**).

^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ = 8.03 (s, 1H, CH alkenyl), 7.44 (d, *J* = 8.5 Hz, 2H, CH aromatic), 7.37 (d, *J* = 8.4 Hz, 2H, CH aromatic), 2.44 (s, 3H, CH_3).ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): 148.2 (*C*), 136.2 (*C*), 132.4 (*C*H), 131.3 (*C*H), 131.0 (*C*), 129.4 (*C*H), 14.2 (*C*H_3) ppm. Spectral data of the compound are in accordance with those reported in the literature.[139]



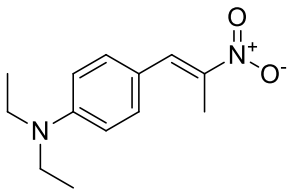
(*E*)-1-Chloro-3-(2-nitroprop-1-enyl)benzene (**1h**).

^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ = 7.99 (s, 1H, CH alkenyl), 7.40 (m, 3H, CH aromatic), 7.34-7.24 (m, 1H, CH aromatic), 2.44 (d, *J* = 0.9 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): 148.9 (*C*), 135.0 (*C*), 134.3 (*C*), 132.0 (*C*H), 130.3 (*C*H), 130.0 (*C*H), 129.7 (*C*H), 128.1 (*C*H), 14.1 (*C*H_3) ppm. Spectral data of the compound are in accordance with those reported in the literature.[140]



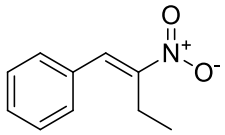
(*E*)-1-Bromo-4-(2-nitroprop-1-enyl)benzene (**1j**).

^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ = 8.01 (s, 1H, CH alkenyl), 7.60 (d, *J* = 8.5 Hz, 2H,CH aromatic), 7.30 (d, *J* = 8.4 Hz, 2H, CH aromatic), 2.43 (s, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 328 K): 148.6 (*C*), 132.5 (*C*H), 132.2 (*C*H), 131.7 (*C*), 131.4 (*C*H), 124.6 (*C*), 14.1 (*C*H_3) ppm. Spectral data of the compound are in accordance with those reported in the literature.[140]



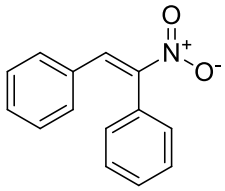
(*E*)-*N*,*N*-diethyl-4-(2-nitroprop-1-enyl)aniline (**1k**).

^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ = 8.09 (s, 1H, CH alkenyl), 7.40 (d, *J* = 9.0 Hz, 2H,3-H, 5-H), 6.69 (d, *J* = 9.1 Hz, 2H,2-H, 6-H), 3.42 (q, *J* = 7.1 Hz, 4H,C*H*$_2$CH$_3$), 2.51 (s, 3H, CH_3), 1.21 (t, *J* = 7.1 Hz, 6H,CH_2C*H*$_3$)ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 300 K): 149.3 (*C*), 142.1 (*C*), 135.2 (*C*H), 133.0 (*C*H), 118.7 (*C*), 111.3 (*C*H), 44.5 (*C*H_2), 14.3 (*C*H_3), 12.5 (CH_2*C*H_3) ppm. Spectral data of the compound are in accordance with those reported in the literature.[141]



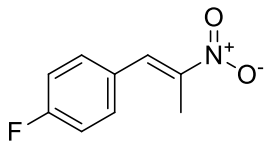
(E)-(2-Nitrobut-1-en-1-yl)benzene (1l).

^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ = 8.02 (s, 1H, CH alkenyl), 7.50 – 7.35 (m, 5H, CH aromatic), 2.87 (q, *J* = 7.4 Hz, 2H, C*H*$_2$CH$_3$), 1.28 (t, *J* = 7.4 Hz, 3H, CH_2C*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): δ = 153.8 (*C*), 133.5 (*C*), 132.8 (*C*H), 130.4 (*C*H), 130.0 (*C*H), 129.4 (*C*H), 21.1 (*C*H_2), 12.9 (*C*H_3) ppm. Spectral data of the compound are in accordance with those reported in the literature.[142]



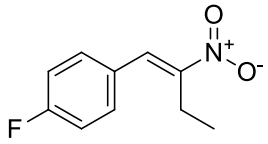
(E)-(2-Nitro-2-phenylethene-1-yl)benzene (1m).

The synthesis was performed starting from phenylnitromethane as previously reported in the literature.[143]^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ = 8.25 (s, 1H, CH alkenyl), 7.58 – 7.45 (m, 3H, CH aromatic), 7.40 – 7.29 (m, 3H CH aromatic), 7.23 (d, *J* = 7.2 Hz, 2H, CH aromatic), 7.12 (d, *J* = 7.4 Hz, 2H, CH aromatic) ppm.^{13}C NMR (75 MHz, $CDCl_3$, 300 K): δ = 150.1 (*C*), 135.2 (*C*H), 131.6 (*C*), 131.5 (*C*H), 131.2 (*C*H), 131.0 (*C*H), 130.4 (*C*H), 129.6 (*C*H), 129.1 (*C*H) ppm. Spectral data of the compound are in accordance with those reported in the literature.



(*E*)-1-Fluoro-4-(2-nitroprop-1-enyl)benzene (1n).

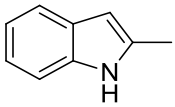
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.05 (s, 1H), 7.43 (dd, $^{3}J_{H,H}$ = 8.6 and $^{4}J_{H,F}$ =5.3 Hz, 2H), 7.15 (pst, $^{3}J_{H,H}$ and $^{3}J_{H,F}$= 8.6 Hz, 2H), 2.44 (s, 3H)ppm.^{13}C NMR (75 MHz, $CDCl_3$) δ163.8 (d, $^{1}J_{C,F}$ =252.1 Hz, *C*F), 147.9 (*C*), 132.8 (*C*H), 132.4 (d, $^{3}J_{C,F}$ =8.4 Hz, *C*H), 128.9 (*C*), 116.6 (d, $^{2}J_{C,F}$ =21.9 Hz, *C*H), 14.34(CH_3) ppm. $C_9H_8FNO_2$ requires: C, 59.67; H, 4.45; N, 7.73 %.Found C, 60.03; H, 4.45; N, 7.71 %. Spectral data of the compound are in accordance with those reported in the literature.[144]



(E)-1-fluoro-4-(2-nitrobut-1-en-1-yl)benzene (1o).

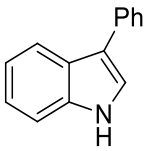
^{1}H NMR (300 MHz, $CDCl_3$) δ =7.99 (s, 1H), 7.44 (dd, $^{3}J_{H,H}$ = 8.6 and $^{4}J_{H,F}$ =5.3 Hz, 2H), 7.16 (pst, $^{3}J_{H,H}$ and $^{3}J_{H,F}$ = 8.6 Hz, 2H), 2.86 (q, *J* = 7.4 Hz, 2H), 1.28 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): 163.9 (d, $^{1}J_{C,F}$ =252.0 Hz, *C*F), 153.5 (*C*), 132.3 (*C*H), 132.1 (d, $^{3}J_{C,F}$= 8.5 Hz,*C*H), 128.85 (*C*), 116.64 (d, $^{2}J_{C,F}$= 21.9 Hz, *C*H), 21.04 (CH_2), 12.76 (CH_3)ppm. $C_{10}H_{10}FNO_2$ requires: C, 61.53; H, 5.16; N, 7.18%.Found C, 61.60; H, 5.21; N, 7.19%. Spectral data of the compound are in accordance with those reported in the literature.[145]

3.5 Characterization of indoles



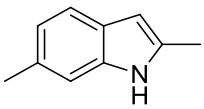
2-Methyl-1*H*-indole (2a):[146]

white solid, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): □ = 7.76 (br, 1H,NH), 7.50 (d, *J* = 7.1 Hz, 1H, 4-H), 7.25 (dd, *J* = 8.0 Hz, 1H, 7-H), 7.13 - 7.01 (m, 2H, 5-H and 6-H), 6.24 – 6.08 (m, 1H, 3-H), 2.42 (d, *J* = 0.6 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): 136.1 (*C*), 135.3 (*C*), 129.1 (*C*), 120.9 (*C*H), 119.7 (*C*H), 110.4 (*C*H), 100.3 (*C*H), 13.5 (CH_3) ppm.



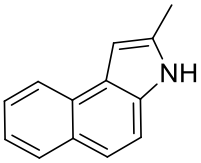
3-Phenyl-1*H*-indole (2b):[147]

white solid,^{1}H NMR (300 MHz, $CDCl_3$, 300 K): □ = 8.15 (br, 1H, NH), 7.95 (d, *J* = 7.5 Hz, 1H), 7.68 (dd, *J* = 5.2, 2.9 Hz, 2H), 7.53 – 7.36 (m, 3H), 7.36 – 7.13 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): 136.8 (*C*), 135.7 (*C*), 128.9 (*C*H), 127.7 (*C*H), 126.1 (*C*H), 125.9 (*C*), 122.6(*C*H), 121.9 (*C*H), 120.5, 120.0 (*C*H), 118.5 (*C*), 111.5 (*C*H) ppm.



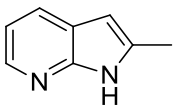
2,6-Dimethyl-1*H*-indole (2c):[148]

white solid,^{1}H NMR (300 MHz, $CDCl_3$, 300 K): □ = 7.65 (br, 1H, NH), 7.40 (d, *J* = 8.0 Hz, 1H, 4-H or 5-H), 7.07 (s, 1H, 7-H), 6.92 (d, *J* = 8.0 Hz, 1H, 4-H or 5-H), 6.17 (d, *J* = 0.9 Hz, 1H 3-H), 2.46 (s, 3H, CH_3), 2.42 (s, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): □ = 136.7 (*C*), 134.4 (*C*), 130.7 (*C*), 127.0 (*C*), 121.4 (*C*H), 119.4 (*C*H), 110.4 (*C*H), 100.3 (*C*H), 21.8 (*C*H_3), 13.8 (*C*H_3) ppm.



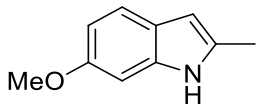
2-Methyl-3*H*-benzo[e]indole (2d):[149]

colorlessoil,^{1}H NMR (300 MHz, $CDCl_3$, 300 K):□□= 8.26 (d, *J* = 8.2 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.85 (br, 1H, NH), 7.65 – 7.55 (m, 2H), 7.55 – 7.45 (m, 1H), 7.36 (d, *J* = 8.7 Hz, 1H), 6.81 (d, *J* = 0.8 Hz, 1H), 2.44 (s, 3H, CH_3) ppm.^{13}C NMR (75 MHz, $CDCl_3$, 300 K): □ = 133.2 (*C*), 132.1(*C*), 129.2(*C*), 128.6(*C*H), 127.8 (*C*H), 125.6 (*C*H), 123.7 (*C*), 123.2 (*C*H), 123.1 (*C*H), 121.7 (*C*H), 112.5 (*C*H), 99.8 (*C*H), 13.7 (*C*H_3) ppm.



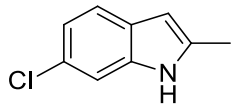
2-Methyl-1*H*-pyrrolo[2,3-b]pyridine (2e):[150]

white solid, ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): □=12.57 (br, 1H, NH), 8.25 (d, *J* = 4.8 Hz, 1H, 6-H), 7.85 (d, *J* = 7.7 Hz, 1H, 4-H), 7.06 (dd, *J* = 7.7 and 4.8 Hz, 1H, 5-H), 6.20 (s, 1H, 3-H), 2.59 (s, 3H, CH_3).ppm.^{13}C NMR (100 MHz, $CDCl_3$, 300 K): □ =149.5 (*C*), 140.1(*C*H), 137.1(*C*), 127.6 (*C*H), 122.3(*C*), 115.5 (*C*H), 98.0 (*C*H), 14.1(*C*H_3).ppm.



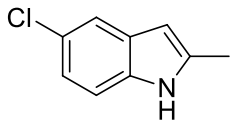
6-Methoxy-2-methyl-1*H*-indole (2f):[151]

Off-white solid, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K):□□= 7.68 (br, 1H, NH), 7.40 (d, *J* = 9.2 Hz, 1H), 6.85 – 6.70 (m, 2H), 6.15 (s, 1H, 3-H), 3.84 (s, 3H, OCH_3), 2.40 (s, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): □ = 155.8 (*C*), 136.9 (*C*), 134.0 (*C*), 123.5 (*C*), 120.2 (*C*H), 109.1 (*C*H), 100.1 (*C*H), 94.7 (*C*H), 55.9 (O*C*H_3), 13.7 (*C*H_3) ppm.



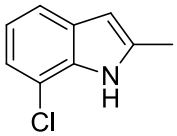
6-Chloro-2-methyl-1*H*-indole (2g):[152]

white solid, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): □ =7.75 (br, 1H, NH), 7.41 (d, *J* = 8.4 Hz, 1H, 4-H), 7.23 (s, 1H, 7-H), 7.05 (dd, *J* = 8.4 and 1.7 Hz, 1H, 5-H), 6.20 (s, 1H, H-3), 2.42 (s, 3H, CH_3) ppm.^{13}C NMR (75 MHz, $CDCl_3$, 300 K): □ = 136.5 (*C*), 136.0 (*C*), 127.8 (*C*), 126.8 (*C*), 120.5(*C*H), 120.4 (*C*H), 110.3(*C*H), 100.6 (*C*H), 13.8 (*C*H_3) ppm.



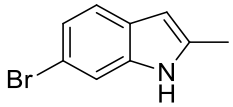
5-Chloro-2-methyl-1*H*-indole (2h):[153]

white solid, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): □= 7.80 (br, 1H, NH), 7.49 (d, *J* = 1.8 Hz, 1H, 4-H), 7.16 (d, *J* = 8.5 Hz, 1H, 7-H), 7.07 (dd, *J* = 8.6 and 1.8 Hz, 1H, 6-H), 6.18 (s, 1H, 3-H), 2.42 (s, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): □ =136.8(*C*), 134.5(*C*), 130.3(*C*), 125.3(*C*), 121.2 (*C*H), 119.1(*C*H), 111.2 (*C*H), 100.3(*C*H), 13.8 (*C*H_3) ppm.



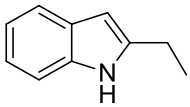
7-Chloro-2-methyl-1*H*-indole (2h'):[154]

off-white solid,^{1}H NMR (400 MHz, $CDCl_3$, 300 K): □ = 8.03 (br, 1H, NH), 7.37 (d, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.96 (t, *J* = 7.7 Hz, 1H, 5-H), 6.25 – 6.14 (m, 1H, 3-H), 2.39 (s, 3H, CH_3) ppm.^{13}C NMR (75 MHz, $CDCl_3$, 300 K): □□= 136.0(*C*), 133.4 (*C*), 130.6 (*C*), 120.5 (*C*H), 120.4 (*C*H), 118.4 (*C*H), 115.8(*C*), 101.6 (*C*H), 13.8 (CH_3) ppm.



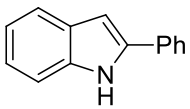
6-Bromo-2-methyl-1*H*-indole (2j):[155]

white solid,^{1}H NMR (300 MHz, $CDCl_3$, 300 K): □ = 7.70 (br, 1H, NH), 7.38 (d, *J* = 8.4 Hz, 1H, 4-H), 7.35 (s, 1H, 7-H), 7.19 (dd, *J* = 8.4 and 1.6 Hz, 1H, 5-H), 6.20 (s, 1H, 3-H), 2.41 (s, 3H, CH_3) ppm.^{13}C NMR (75 MHz, $CDCl_3$, 300 K): □□= 136.9 (*C*), 136.0 (*C*), 128.1 (*C*), 122.9 (*C*H), 120.9(*C*H), 114.3 (*C*), 113.3 (*C*H), 100.7 (*C*H), 13.8 (CH_3) ppm.



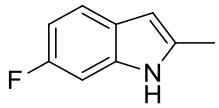
2-Ethyl-1*H*-indole (2l):[156]

white solid,^{1}H NMR (300 MHz, $CDCl_3$, 300 K): □ = 7.80 (br, 1H, NH), 7.58 (d, *J* = 7.3 Hz, 1H, 4-H), 7.30 (d, *J* = 7.9 Hz, 1H, 7-H), 7.20 -7.07 (m, 2H, 5-H and 6-H), 6.30 - 6.27 (m, 1H, 3-H), 2.80 (q, *J* = 7.6 Hz, 2H, CH_2CH_3), 1.37 (t, *J* = 7.6 Hz, 3H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): □ = 141.51 (*C*), 135.97 (*C*), 128.94 (*C*), 121.08 (*C*H), 119.90 (*C*H), 119.70 (*C*H), 110.41 (*C*H), 98.79 (*C*H), 21.5 (CH_2), 13.4 (CH_3) ppm.



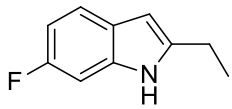
2-Phenyl-1*H*-indole (2m):[157]

white solid,[1]H NMR (400 MHz, $CDCl_3$, 300 K): □ = 8.34 (br, 1H, NH), 7.68 (d, *J* = 7.4 Hz, 2H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.49 - 7.38 (m, 3H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.13 (t, *J* = 7.4 Hz, 1H), 6.83 (s, 1H, 3-H) ppm. [13]C NMR (100 MHz, $CDCl_3$, 300 K): □ = 138.0 (*C*), 137.0 (*C*), 132.5 (*C*), 129.4 (*C*), 129.1 (*C*H), 127.8 (*C*H), 125.3 (*C*H), 122.5 (*C*H), 120.8 (*C*H), 120.4 (*C*H), 111.0 (*C*H), 100.1 (*C*H) ppm.



6-Fluoro-2-methyl-1*H*-indole (2n):

white solid,[1]H NMR (400 MHz, $CDCl_3$, 300 K): □ = 7.73 (br, 1H, NH), 7.43 (dd, *J* = 8.6 and 5.4 Hz, 1H, 4-H), 6.95 (dd, *J* = 9.6 and 2.1 Hz, 1H, 7-H), 6.87 (ddd, *J* = 9.8, 8.6 and 2.3 Hz, 1H, 5-H), 6.23 - 6.19 (m, 1H, 3-H), 2.41 (s, 3H, CH_3) ppm.[13]C NMR (100 MHz, $CDCl_3$, 300 K): □ =159.4 (d, $^1Jc_{,F}$ = 236.2 Hz, *C*F), 136.0 (d, $^3Jc_{,F}$ = 12.1 Hz, *C*), 135.6(*C*), 125.6(*C*), 120.2 (d, $^3Jc_{,F}$ = 9.9 Hz, *C*H), 108.2 (d, $^2Jc_{,F}$ = 24.0 Hz,*C*H), 100.4 (*C*H), 96.9 (d, $^2Jc_{,F}$ = 26.1 Hz, *C*H), 13.7 (CH_3) ppm.



6-Fluoro-2-ethyl-1*H*-indole (2o):[158]

white solid, [1]H NMR (400 MHz, $CDCl_3$, 300 K): □ = 7.76 (br, 1H, NH), 7.47 (dd, *J* = 8.6 and 5.4 Hz, 1H, 4-H), 6.96 (dd, *J* = 9.7, 1.8 Hz, 1H, 7-H), 6.90 (ddd, *J* = 10.1, 8.9 and 2.2 Hz, 1H, 5-H), 6.25 (s, *J* = 0.9 Hz, 1H, 3-H), 2.77 (q, *J* = 7.6 Hz, 2H, CH_2), 1.36 (t, *J* = 7.6 Hz, 3H, CH_3) ppm.[13]C NMR (75 MHz, $CDCl_3$, 300 K): □ = 159.4 (d, $^1Jc_{,F}$= 236.1 Hz, *C*F), 142.0(*C*), 135.83 (d, $^3Jc_{,F}$= 13.1 Hz, *C*), 125.38 (*C*), 120.37 (d, $^3Jc_{,F}$= 9.7 Hz, *C*H), 108.11 (d, $^2Jc_{,F}$= 24.1 Hz, *C*H), 98.64 (*C*H), 96.95 (d, $^2Jc_{,F}$= 25.6 Hz, *C*H), 21.44 (CH_2), 13.20 (CH_3) ppm.

3.6 Synthesis and characterization of substituted nitroalkenylthiophenes

Nitroalkenylthiophenes were prepared by Henry condensation of the corresponding aldehyde and nitroalkane using different methods for the Henry reaction.

Method A

In a Schlenk flask, aldehyde (10 mmol) and ammonium acetate (5 mmol) were dissolved in nitroethane (5 ml) The mixture was stirred at reflux for 5 hours and the conversion of the aldehyde checked by TLC on silica. The solvent was evaporated and the residue was taken up with methylene chloride and washed with water. The organic layer was dried and finally purification over a short silica column with EtOAc: hexane as eluent afforded the olefin.[112, 159]

Method B

A solution of nitroethane (1.6 ml, 22.4 mmol) or (nitropropane), n-butylamine (0.9 ml, 9.1 mmol) and the aldehyde (7.9 mmol) in glacial acetic acid (4 ml) was heated at 80 C for 2h. the crude product that separate on cooling was filtered, recrystallized from methanol and finally purified using a short column of silica.[160]

Method C

A mixture of ethyl nitroacetate (2g, 15 mmol), aldehyde (10 mmol), a catalytic amount of phenyl alanine (0.03g) and 1 ml of glacial acetic acid in 10 ml of anhydrous benzene was refluxed for 2 h under Dean-Stark conditions. After cooling the reaction mixture was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was then removed with a rotary evaporator. Finally the residue was washed with ethanol.[161]

Method D

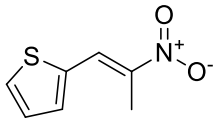
Aldehyde (10 mmol), nitroalkane (60 mmol) and piperidine (1 mmol) were added sequentially to around-bottomed flask containing toluene. To this mixture anhydrous ferric chloride (1 mmol) was added, and the mixture was slowly heated to reflux. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature, the excess solvent was removed under reduced pressure and the residue was purified by column chromatography on silica to afford the nitroalkene product as a yellow solid.[144]

Method E

Methanol (5 ml), phenylnitromethane (11 mmol), methylamine hydrochloride (1 mmol), sodium hydrogen carbonate (0.2 mmol), and aldehyde (10 mmol), were stirred at 18–20°C for 72 h. The resulting precipitate was collected by filtration and washed with methanol.[143]

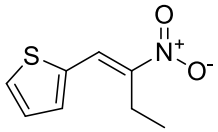
Method F

A mixture of sodium acetate, methylamine hydrochloride, nitroethane and aldehyde in absolute ethanol was stirred for 5h. the mixture was diluted with water and extracted with dichloromethane. The combined extracts were washed with water and evaporated. Finlly the crude product was filtered over short column of silica using (hexane/EtOAc 7:3)



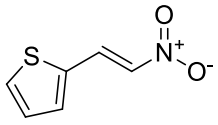
(E)-2-(2-nitroprop-1-en-1-yl)thiophene (**3a**)[160]

Method B; Yellow solid, Yield 95%, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K), δ = 8.33 (s, 1H, alkenyl H), 7.67 (d, *J* = 5.1 Hz, 1H, H_5), 7.46 (d, *J* = 3.6 Hz, 1H, H_3), 7.25 – 7.18 (m, 1H, H_4), 2.59 (s, 3H, CH_3). ^{13}C NMR (75MHz, $CDCl_3$, 300 K) δ 144.39, 135.23, 134.76, 131.77, 128.21, 127.22, 14.24. MS (M = 169). $C_7H_7NO_2S$: requires: C, 49.69; H, 4.17; N, 8.28 %.Found: C, 49.43; H 4.13; N 8.22 %.



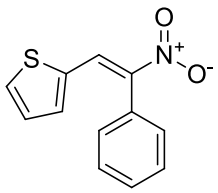
(E)-2-(2-nitrobut-1-en-1-yl)thiophene (3b)

Method B; Yellow oil, Yield 69%, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ = 8.25 (s, 1H, alkenyl H), 7.64 (d, *J* = 5.1 Hz, 1H, H_5), 7.43 (d, *J* = 3.6 Hz, 1H, H_3), 7.19 (dd, *J* = 5.1, 3.6 Hz, 1H, H_4), 3.04 (q, *J* = 7.4 Hz, 2H, CH_2), 1.28 (t, *J* = 7.4 Hz, 3H, CH_3).^{13}C NMR (75MHz, $CDCl_3$, 300 K) δ 150.35, 135.26, 135.10, 132.07, 128.59, 127.03, 21.79, 11.98.



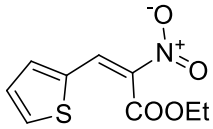
(E)-2-(2-nitrovinyl)thiophene (**3c**)[144]

Method D; Yellow solid. Yield 57 %, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ 8.18 (d, *J* = 13.4 Hz, 1H, alkenyl H), 7.58 (d, *J* = 5.0 Hz, 1H, H_5), 7.50 (d, *J* = 13.4 Hz, 1H, alkenyl H), 7.48 (d, *J* = 3.1 Hz, 1H, H_3), 7.21 – 7.13 (m, 1H, H_4). ^{13}C NMR (75 MHz, CDCl3, 300 K) δ 128.7, 131.5, 132.0, 133.5, 134.4, 135.2 $C_6H_5NO_2S$ requires: C, 46.44; H, 3.25; N, 9.03% Found: C,46.25 ; H 3.02 ; N 8.84%.



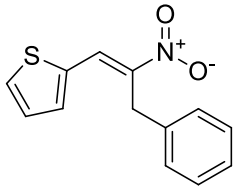
(E)-2-(2-nitro-2-phenylvinyl)thiophene (**3d**)[162]

Method E ; Yellow solid, Yield 85%, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ= 8.51 (s, 1H, alkenyl H), 7.66 – 7.53 (m, 3H, Phenyl H), 7.43 – 7.40 (m, 2H, Phenyl H), 7.39 (d, *J* = 5.0 Hz, 1H, H_5), 7.34 (d, *J* = 3.6 Hz, 1H, H_3), 7.05 (dd, *J* = 5.0, 3.5 Hz, 1H, H_4). ^{13}C NMR (75 MHz, CDCl3, 300 K) δ =147.07, 136.46, 135.54, 133.61, 131.31, 130.99, 130.16, 129.98, 129.55, 127.96. $C_{12}H_9NO_2S$ requires: C, 62.32; H, 3.92; N, 6.06% Found: C, 62.31; H, 3.86; N, 6.08%.



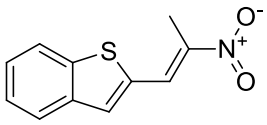
(E)-ethyl 2-nitro-3-(thiophen-2-yl)acrylate (3e)[161]

Method C; Yellow solid, Yield 58 %, ^{1}H NMR (400 MHz, $CDCl_3$, 300 K), δ = 7.73 (s, 1H, alkenyl H), 7.71 (d, *J* = 5.0 Hz, 1H, H_5), 7.49 (d, *J* = 3.8 Hz, 1H, H_3), 7.18 (dd, *J* = 5.0, 3.9 Hz, 1H, H_4), 4.39 (q, *J* = 7.2 Hz, 2H, CH_2), 1.40 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl3, 300 K) δ = 159.50, 135.69, 134.28, 131.80, 128.52, 126.73, 62.94, 14.11. MS (M = 227).



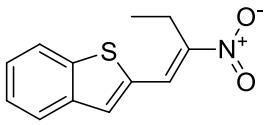
(E)-2-(2-nitro-3-phenylprop-1-en-1-yl)thiophene(3f)

Method B; Yellow oil, Yield 47 %, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ= 8.51 (s, 1H, alkenyl H), 7.62 (d, *J* = 5.1 Hz, 1H, H_5), 7.49 (d, *J* = 3.5 Hz, 1H, H_3), 7.38 – 7.22 (m, 5H, Phenyl H), 7.19 (dd, *J* = 5.1, 3.5 Hz, 1H, H_4), 4.44 (s, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ = 147.12, 135.74, 134.86, 132.39, 129.18, 129.00, 128.72, 128.32, 127.40, 33.84.



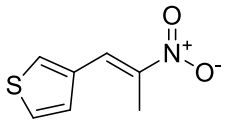
(E)-2-(2-nitroprop-1-en-1-yl)benzo[b]thiophene (3g)[163]

Method A; Yellow solid, Yield 82 %, ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 8.37 (s, 1H, alkenyl H), 7.88 (d, *J* = 7.5 Hz, 2H, Phenyl H), 7.68 (s, 1H, $H_{Thioph.}$), 7.46 (dd, *J* = 7.5, 3.9 Hz, 2H, Phenyl H), 2.66 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 300 K) δ = 146.18, 143.11, 138.61, 134.89, 132.00, 127.73, 126.82, 125.41, 124.74, 122.34, 14.26. $C_{11}H_9NO_2S$ requires: C, 60.26; H, 4.14; N, 6.39%. Found: C, 60.52; H, 4.18; N, 6.15 %.



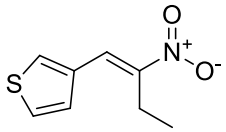
(E)-2-(2-nitrobut-1-en-1-yl)benzo[b]thiophene (3h)

Method A; Yellow solid, Yield 78 %, ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ= 8.31 (s, 1H, alkenyl H), 7.88 (d, *J* = 6.9 Hz, 2H, Phenyl H), 7.66 (s, 1H, $H_{Thioph.}$), 7.46 (t, *J* = 5.0 Hz, 2H, Phenyl H), 3.12 (q, *J* = 7.4 Hz, 2H, CH_2), 1.34 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 300 K) δ = 151.69, 142.05, 138.48, 134.50, 132.28, 127.21, 126.72, 125.26, 124.74, 122.49, 21.60, 12.25. $C_{12}H_{11}NO_2S$ requires: C, 61.78; H, 4.75; N, 6.00%. Found: C 61.77; H 4.64; N 5.69%.



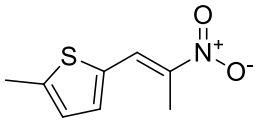
(E)-3-(2-nitroprop-1-en-1-yl)thiophene (3i)[164]

Method A; Yellow solid, Yield 72%, ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 8.09 (s, 1H, alkenyl H), 7.62 (d, *J* = 2.5 Hz, 1H, H_2), 7.46 (dd, *J* = 5.1, 2.9 Hz, 1H, H_4), 7.30 (d, *J* = 5.1 Hz, 1H, H_5), 2.51 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 300 K) δ = 146.41, 133.78, 129.92, 128.19, 127.56, 127.01, 14.18. $C_7H_7NO_2S$ requires: C, 49.69; H, 4.17; N, 8.28%. Found: C 49.94; H 4.14; N 8.20%.



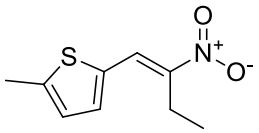
(E)-3-(2-nitrobut-1-en-1-yl)thiophene (3j)

Method A; Yellow oil, Yield 80%, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ = 7.97 (s, 1H), 7.57 (d, *J* = 2.2 Hz, 1H, H_2), 7.41 (dd, *J* = 5.0, 3.0 Hz, 1H, H_4), 7.23 (dd, *J* = 5.0, 0.7 Hz, 1H, H_5), 2.88 (q, *J* = 7.4 Hz, 2H, CH_2), 1.23 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ 151.94, 133.77, 130.56, 128.30, 127.66, 127.48, 21.41, 12.45. $C_8H_9NO_2S$ requires: C, 52.44; H, 4.95; N, 7.64%. Found: C 52.18; H 4.79; N 7.46%.



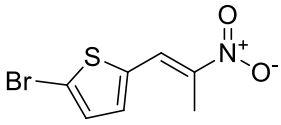
(E)-2-methyl-5-(2-nitroprop-1-en-1-yl)thiophene (3k)[165]

Method A; Yellow solid, Yield 72%, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ = 8.22 (s, 1H, alkenyl H), 7.26 (d, *J* = 3.3 Hz, 1H, Thioph. H), 6.86 (d, *J* = 3.6 Hz, 1H, Thioph. H), 2.58 (s, 3H, CH_3), 2.52 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ 148.25, 143.44, 136.07, 133.67, 128.22, 127.21, 16.16, 14.62. $C_8H_9NO_2S$ requires: C, 52.44; H, 4.95; N, 7.64% Found: C 52.54; H 4.90; N 7.56%.



(E)-2-methyl-5-(2-nitrobut-1-en-1-yl)thiophene (3l)

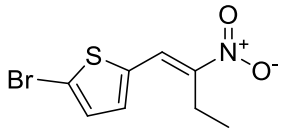
Method A; Yellow solid, Yield 72%, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ = 8.15 (s, 1H, alkenyl H), 7.24 (d, *J* = 3.6 Hz, 1H, $H_{Thioph.}$), 6.84 (d, *J* = 3.6 Hz, 1H, H_{Thioph}), 2.97 (q, *J* = 7.4 Hz, 2H, CH_2), 2.56 (s, 3H, CH_3), 1.24 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ 149.06, 148.38, 136.41, 133.10, 128.13, 127.18, 21.70, 16.14, 12.04. $C_9H_{11}NO_2S$ requires: C, 54.80; H, 5.62; N, 7.10% Found: C 54.72; H 5.63; N 7.09%.



(E)-2-bromo-5-(2-nitroprop-1-en-1-yl)thiophene (3m)[160]

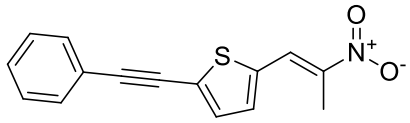
Method A; Yellow solid, Yield 66%, ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ 8.18 (s, 1H, alkenylH), 7.20 (d, *J* = 4.0 Hz, 1H, H_{thioph}), 7.17 (d, *J* = 4.0 Hz, 1H, H_{thioph}), 2.51 (s, 3H, CH_3). ^{13}C NMR (100

MHz, $CDCl_3$, 300 K) δ 144.59, 136.87, 134.95, 131.12, 126.59, 119.91, 14.28. $C_7H_6BrNO_2S$ requires: C, 33.89; H, 2.44; N, 5.65%. Found: C, 34.00; H, 2.32; N, 5.56%.



(E)-2-bromo-5-(2-nitrobut-1-en-1-yl)thiophene (3n)

Method A; Yellow solid, Yield 68%, ^1H NMR (400 MHz, $CDCl_3$, 300 K) δ 8.13 (s, 1H, alkenyl H), 7.19 (d, *J* = 4.0 Hz, 1H, H_{thioph}), 7.17 (d, *J* = 4.0 Hz, 1H, H_{thioph}), 2.96 (q, *J* = 7.4 Hz, 2H, CH_2), 1.28 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 300 K) δ 150.13, 136.29, 135.29, 131.33, 126.08, 119.92, 21.70, 11.48. $C_8H_8BrNO_2S$ requires: C, 36.66; H, 3.08; N, 5.34% Found: C, 36.32; H, 3.23; N, 5.18%

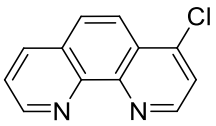


(E)-2-(2-nitroprop-1-en-1-yl)-5-(phenylethynyl)thiophene (3o)

Method A; Yellow solid, Yield 41%, ^1H NMR (400 MHz, $CDCl_3$, 300 K) δ 8.25 (s, 1H, alkenyl H), 7.58 – 7.53 (m, 2H, Phenyl H), 7.43 – 7.38 (m, 3H, Phenyl H), 7.35 (d, *J* = 3.9 Hz, 1H, H_{thioph}), 7.32 (d, *J* = 3.9 Hz, 1H, H_{thioph}), 2.59 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 300 K) δ 136.22, 134.85, 134.70, 132.46, 131.55, 129.71, 129.15, 128.53, 126.82, 122.24, 97.31, 82.09, 14.49.

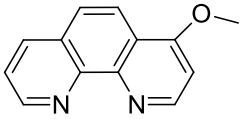
3.7 Synthesis and characterization of ligands

All the tested ligands are either commercially available or were prepared according to a reported standard procedure in the literature.[166] Herein the characterizations of the prepared ones.



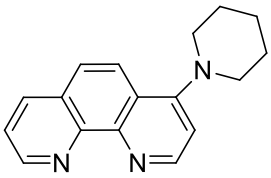
4-Chloro-1,10-Phenanthroline (4-ClPhen)[166]

^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ = 9.24 (dd, *J* = 4.3, 1.7 Hz ,1H), 9.08 (d, *J* = 4.8 Hz, 1H), 8.31 (dd, *J* = 8.1, 1.7 Hz ,1H) , 8.28 (d, *J* = 9.1 Hz, 1H), 7.93 (d, *J* = 9.1 Hz, 1H), 7,75 (d, *J* = 4.8 Hz ,1H), 7,70 (dd, *J* = 8.11, 4.3 Hz ,1H). Spectral data of the compound are in accordance with those reported in the literature



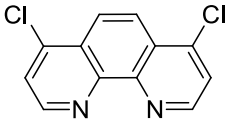
4-Methoxy-1,10-Phenanthroline (4-MeOPhen)[166]

^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ = 9.17 (dd, *J* = 4.3, 1.7 Hz ,1H), 9.03 (d, *J* = 5.3 Hz, 1H), 8.22 (dd, *J* = 8.1, 1.7 Hz ,1H) , 8.20 (d, *J* = 9 Hz, 1H), 7.74 (d, *J* = 9 Hz, 1H), 7,60 (dd, *J* = 8.1,4.3 Hz ,1H), 7,00 (d, *J* = 5.3 Hz ,1H), 4.08 (s, 3H, CH_3). Spectral data of the compound are in accordance with those reported in the literature



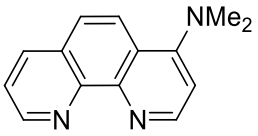
4-Piperidino-1,10-Phenanthroline (4-PipPhen)[167]

^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ = 9.16 (dd, *J* = 4.3, 1.8 Hz ,1H), 8.98 (d, *J* = 5.1 Hz, 1H), 8.21 (dd, *J* = 8.1, 1.8 Hz ,1H) , 8.03 (d, *J* = 9.1 Hz, 1H), 7.72 (d, *J* = 9.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 4.3 Hz ,1H), 7.09 (d, *J* = 5.1 Hz ,1H), 3.27 (t, *J* = 5.3 Hz ,4H), 1.87 (m, 4H), 1.74 (m, 2H). Spectral data of the compound are in accordance with those reported in the literature



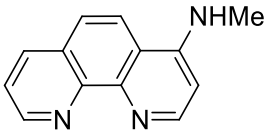
4,7-dichloro-1,10-Phenanthroline (4,7-Cl_2Phen)[168]

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.13 (d, *J* = 4.7 Hz, 2H), 8.40 (s, 2H), 7.81 (d, *J* = 4.7 Hz, 2H). Spectral data of the compound are in accordance with those reported in the literature



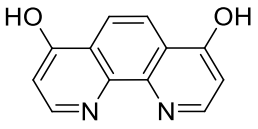
4-dimethylamino-1,10-Phenanthroline (4-Me_2NPhen)

Prepared by heating a mixture of 4-chlorophenanthroline (1 mmol) and DMF (9 ml) in a pressure tube at 160 ^{o}C for 10 h. the DMF was removed under reduced pressure, the product was extracted with chloroform and dried over anhydrous sodium sulfate and concentrated to afford the product. Further purification over short column of silica gel is required to obtain pure product. ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ 9.11 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.90 (d, *J* = 5.2 Hz, 1H), 8.15 (d, *J* = 9.6 Hz, 1H), 8.02 (d, *J* = 9.1 Hz, 1H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.53 (dd, *J* = 8.0, 4.3 Hz, 1H), 6.99 (d, *J* = 5.2 Hz, 1H), 3.00 (s, 6H).



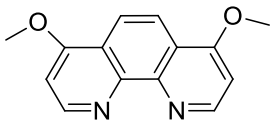
N-methyl-1,10-phenanthrolin-4-amine (4-MeNHPhen)

Prepared by heating a mixture of 4- chlorophenanthroline (1 mmol) and DMF (9 ml) in a pressure tube at 200 ^{o}C for 24 h. DMF was removed under reduced pressure, the product was extracted with chloroform and dried over anhydrous sodium sulfate and concentrated to afford the product. Further purification over short column of silica gel is required to obtain pure product. ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ 9.02 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.60 (d, *J* = 5.3 Hz, 1H), 8.39 (d, *J* = 6.6 Hz, 1H), 8.20 (d, *J* = 9.1 Hz, 1H), 7.81 (d, *J* = 9.1 Hz, 1H), 7.68 (dd, *J* = 8.0, 4.2 Hz, 1H), 7.37 (br s, exchangeable, 1H), 6.68 (d, *J* = 5.4 Hz, 1H), 2.94 (d, *J* = 4.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, 300 K) δ 151.66, 150.42, 149.86, 146.46, 146.20, 136.17, 128.49, 123.82, 123.16, 120.67, 117.91, 101.67, 29.94.



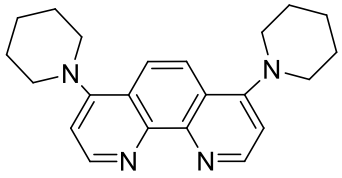
4,7-hydroxy-1,10-Phenanthroline (4,7-$(HO)_2$Phen)[168]

^{1}H NMR (D_2O, NaOH, 400 MHz) δ 8.17 (d, 2H, *J* = 5.6 Hz), 7.75 (s, 2H), 6.43 (d, 2H *J* = 5.6 Hz). Spectral data of the compound are in accordance with those reported in the literature



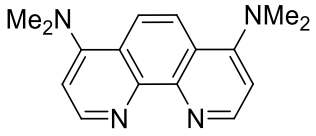
4,7-dimethoxy-1,10-Phenanthroline (4,7-$(MeO)_2$Phen)[169]

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.03 (d, *J* = 5.3 Hz, 2H), 8.20 (s, 2H), 7.02 (d, *J* = 5.3 Hz, 2H), 4.12 (s, 6H). $C_{14}H_{12}N_2O_2$ requires: C, 69.99; H, 5.03; N, 11.66% Found : C, 69.65; H, 5.40; N, 11.56%. Spectral data of the compound are in accordance with those reported in the literature



4,7-dipiperidino-1,10-Phenanthroline (4,7-$(Pip)_2$Phen)[170]

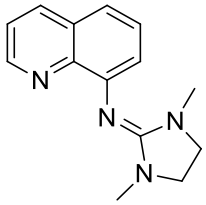
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, *J* = 5.1 Hz, 2H), 7.92 (s, 2H), 7.03 (d, *J* = 5.1 Hz, 2H), 3.44 – 3.02 (m, 8H), 1.94-1.82 (m, 8H), 1.77 – 1.62 (m, 4H). $C_{22}H_{26}N_4$ requires: C, 76.27; H, 7.56; N, 16.17% Found : C, 75.90; H, 7.45; N, 16.25%. Spectral data of the compound are in accordance with those reported in the literature



4,7-bis-(dimethylamino)-1,10-Phenanthroline (4,7-$(Me_2N)_2$Phen)

Prepared by heating a mixture of 4,7-dichlorophenanthroline (3 mmol) and DMF (15 ml) in a pressure tube at 160 ^oC for 12 h. the DMF was removed under reduced pressure, the product was extracted with chloroform and dried over anhydrous sodium sulfate and concentrated to afford the product. Further purification over short column of silica gel is required to obtain pure product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.93 (d, *J* = 5.3 Hz, 2H), 7.97 (s, 2H), 7.02 (d, *J* = 5.3 Hz, 2H), 3.11 (s, 12H). $C_{16}H_{18}N_4$

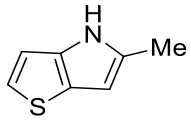
requires: C, 72.15; H, 6.81; N, 21.04% Found : C, 72.07; H, 6.93; N, 21.15%. Spectral data of the compound are in accordance with those reported in the literature.[171]



N- (1,3-dimethylimidazolidin-2-yllidene) quinolin-8-amine (DMEGqu)[167]

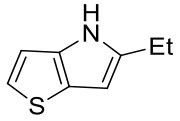
^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ = 8.92 (dd, *J* = 4.1, 1.8 Hz ,1H), 8.09 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.40 (dd, *J* = 8.0, 7.4 Hz ,1H) , 7.33 (m, 2H), 7.19 (dd, *J* = 7.4, 1.2 Hz, 1H), 3.40 (s, 4H), 2.68 (s, 6H). Spectral data of the compound are in accordance with those reported in the literature

3.8 Characterization of thienopyrroles



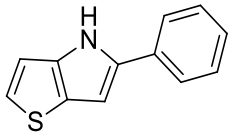
5-methyl-4*H*-thieno[3,2-*b*]pyrrole (4a):[172]

Colorless solid, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ = 7.96 (br s, 1H; exchangeable, NH), 7.00 (d, *J* = 5.2 Hz, 1H, H_{Thioph}), 6.90 (d, *J* = 5.2 Hz, 1H, H_{Thioph}), 6.17 (s,1H, $H_{Pyrrole}$), 2.43(s, 3H, CH_3). ^{13}C NMR (100 MHz, $(CD_3)_2SO$, 300 K): δ = 138.19, 133.78, 122.98, 121.02, 111.91, 98.60, 14.16. C_7H_7NS requires: C, 61.28; H, 5.14; N, 10.21%. Found: C, 60.91; H, 5.07; N, 9.96%.



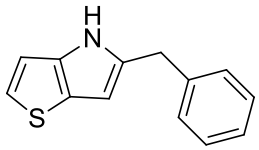
5-ethyl-4H-thieno[3,2-b]pyrrole(4b):

Colorless solid, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ = 7.96 (br s, exchangeable, 1H, NH), 7.02 (d, *J* = 5.2 Hz, 1H, H_{Thioph}), 6.92 (dd, *J* = 5.2, 0.7 Hz, 1H, H_{Thioph}), 6.22 (s, 1H, $H_{Pyrrole}$), 2.78 (q, *J* = 7.6 Hz, 2H, CH_2), 1.34 (t, *J* = 7.6 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ = 140.43, 138.13, 124.48, 122.18, 111.25, 98.33, 21.73, 14.47. C_8H_9NS : requires: C, 63.54; H, 6.00; N, 9.26%. Found: C, 63.22; H, 6.05; N, 8.97%.



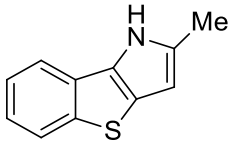
5-phenyl-4H-thieno[3,2-b]pyrrole(4d):[75]

Colorless solid, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ = 8.45 (br s, exchangeable,1H, NH), 7.62 – 7.51 (m, 2H, Phenyl H), 7.43 (t, *J* = 7.7 Hz, 2H, Phenyl H), 7.34 – 7.27 (m, 1H, Phenyl H), 7.12 (d, *J* = 5.2 Hz, 1H, $H_{Thioph.}$), 7.00 (d, *J* = 5.0 Hz, 1H, H_{Thioph}), 6.79 (d, *J* = 1.4 Hz, 1H, $H_{Pyrrole}$). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ = 139.86, 137.76, 133.37, 129.43, 127.24, 126.08, 124.66, 124.33, 111.46, 99.51. $C_{12}H_9NS$ requires: C, 72.33; H, 4.55; N, 7.03%. Found: C, 72.27; H, 4.35; N, 7.22%.



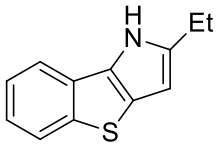
5-benzyl-4H-thieno[3,2-b]pyrrole (4f):

Colorless solid, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ = 7.85 (br s, exchangeable,1H, NH), 7.31 (m, 5H, Phenyl H), 7.02 (d, *J* = 5.2 Hz, 1H, $H_{Thioph.}$), 6.87 (d, *J* = 5.2 Hz, 1H, $H_{Thioph.}$), 6.30 (s, 1H, $H_{pyrrole}$), 4.11 (s, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ = 139.38,139.37, 138.57, 136.81, 129.17, 129.13, 127.08, 122.60, 111.40, 100.40, 35.47. $C_{13}H_{11}NS$: requires: C, 73.20; H, 5.20; N, 6.57%. Found: C, 73.21; H, 4.93; N, 6.48%.



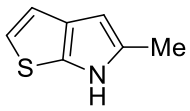
2-methyl-1H[1]benzothieno[3,2-b]pyrrole (4g):

Colorless solid, ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 8.37 (br s, exchangeable,1H, NH), 7.79 (d, *J* = 8.1 Hz, 1H, H_{Benz}), 7.63 (d, *J* = 7.9 Hz, 1H, H_{Benz}), 7.33 (dd, *J* = 7.9, 1.0 Hz, 1H, H_{Benz}), 7.21 (dd, *J* = 8.1, 1.1 Hz, 1H, H_{Benz}), 6.24 (s, 1H, $H_{Pyrrole}$), 2.49 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 300 K) δ = 141.28, 133.69, 131.18, 127.04, 124.11, 123.93, 123.18, 122.04, 117.45, 100.54, 14.18. $C_{11}H_9NS$ requires: C, 70.55; H, 4.84; N, 7.48 %. Found: C, 70.27; H, 5.13; N, 7.69 %.



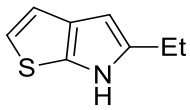
2-ethyl-1H[1]benzothieno[3,2-b]pyrrole (4h):

Colorless solid, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ = 8.38 (br s, exchangeable,1H, NH), 7.80 (d, *J* = 8.0 Hz, 1H, H_{Benz}), 7.64 (d, *J* = 7.9 Hz, 1H, H_{Benz}), 7.37-7.33 (m, 1H, H_{Benz}), 7.23 – 7.19 (m, 1H, H_{Benz}), 6.27 (s, 1H, $H_{Pyrrole}$), 2.83 (q, *J* = 7.6 Hz, 2H, CH_2), 1.38 (t, *J* = 7.6 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ = 141.69, 140.69, 131.39, 127.45, 124.48, 124.31, 123.40, 122.43, 117.88, 99.34, 22.33, 14.17. $C_{12}H_{11}NS$: requires: C, 71.60; H, 5.51; N, 6.96 %. Found: C, 71.32; H, 5.48; N, 6.59 %.



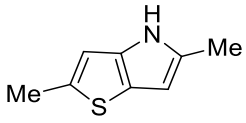
5-methyl-6H-thieno[2,3-b]pyrrole (4i):[173]

Colorless solid, ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 7.82 (br s, *exchangeable*, 1H, NH), 6.99 (d, *J* = 5.2 Hz ,1H, H_{Thioph}), 6.84 (d, *J* = 5.2 Hz, 1H, H_{Thioph}),) 6.19 (s, 1H, $H_{Pyrrole}$), 2.40 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 300 K) δ = 134.61, 132.04, 131.33, 117.47, 117.10, 99.44, 14.00.



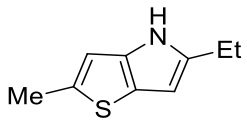
5-ethyl-6H-thieno[2,3-b]pyrrole (4j)

Colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ = 7.99 (br s, *exchangeable*, 1H, NH), 6.97 (d, *J* = 5.2 Hz ,1H, H_{Thioph}), 6.81 (d, *J* = 5.2 Hz, 1H, H_{Thioph}),) 6.19 (s, 1H, $H_{Pyrrole}$), 2.76 (q, *J* = 7.6 Hz, 2H, CH_2), 1.33 (t, *J* = 7.6 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ = 141.60, 132.34, 131.54, 117.92, 117.41, 98.24, 22.25, 14.17.



2,5-dimethyl-4H-thieno[3,2-b]pyrrole (4k)

Colorless solid, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ = 7.78 (br s, *exchangeable*, 1H, NH), 6.59 (s, 1H, H_{Thioph}), 6.08 (s, 1H, $H_{Pyrrole}$) 2.54 (s, 3H, CH_3), 2.39 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ 137.14, 136.82, 131.84, 122.43, 109.71, 99.57, 16.82, 14.25.



5-ethyl-2-methyl-4H-thieno[3,2-b]pyrrole (4l)

Colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ = 7.76 (br s, *exchangeable*, 1H, NH), 6.62 (s, 1H, $H_{Thioph.}$), 6.18 (s, 1H, $H_{Pyrrole}$),) 2.75 (q, *J* = 7.6 Hz, 2H, CH_2), 2.60 (s, 3H, CH_3), 1.35 (t, *J* = 7.6 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ 138.66, 137.10, 136.89, 122.23, 109.94, 98.10, 22.14, 16.91, 14.25.

3.9 Synthesis and characterization of α,β-unsaturated aldehyde

Non commercially available α,β-unsaturated aldehydes were prepared using cross aldol condensation as follows:

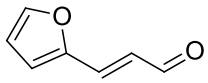
Method G

To a solution of aromatic or heteroaromatic aldehyde (10 mmol) was added 10 ml of H_2O and sodium hydroxide (25 mmol) at room temperature; propionaldehyde (50 mmol) was added at last. The reaction mixture was stirred at 45 ^{o}C for 12 h. the mixture was washed with ethyl acetate (3 x 350 ml), and the combined washings were evaporated to dryness under reduced pressure to give the crude unsaturated aldehyde as yellow oil, then it was purified over a column of silica gel (gradient elution from hexane to hexane/AcOEt 9:1) [174]

Method H

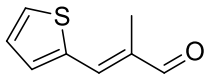
A mixture of vinyl acetate (12 mmol) as acetaldyhyde equivalent and aromatic or heteroaromatic aldehyde (10 mmol) in THF (10 ml) was added slowely to a stirred suspension of $Ba(OH)_2$ (12 mmol) in THF (20 ml). the reaction mixture was refluxed for 7h until all the aldehyde has been consumed (as indicated by TLC). The reaction mixture after cooling was poured into cold water and filtered to remove the insoluble barium salt. The filterate was extracted with DCM and the organic layer was

washed with water, dried (anhyd. Na_2SO_4) and evaporated to give crude aldehyde which was puriefied by column chromatography (silica gel)[175]



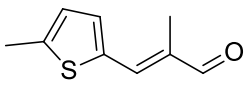
(E)-3-(fur-2-yl)acrylaldehyde[175]

Method H; off white solid, Yield 56 %, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ 9.61 (d, *J* = 7.9 Hz, 1H, CHO), 7.56 (s, 1H, H_{furan}), 7.22 (d, *J* = 15.7 Hz, 1H, alkenyl H), 6.77 (d, *J* = 3.4 Hz, 1H, H_{furan}), 6.58 (dd, *J* = 14.8, 7.0 Hz, 1H, alkenyl H), 6.53 (d, *J* = 3.3 Hz, 1H, H_{furan}). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ 193.22, 151.00, 146.30, 138.16, 126.39, 117.09, 113.26, 77.89, 77.47, 77.05.



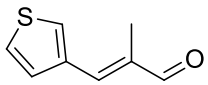
(E)-2-methyl-3-(thiophen-2-yl)acrylaldehyde[176]

Method G; yellow oil, Yield 53 %, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ 9.49 (s, 1H, CHO), 7.58 (d, *J* = 5.1 Hz, 1H, H_{Thioph}), 7.40 (s, 1H, alkenyl H), 7.37 (d, *J* = 3.6 Hz, 1H, H_{Thioph}), 7.14 (dd, *J* = 5.1, 3.7 Hz, 1H, H_{Thioph}), 2.06 (s, 3H, CH_3).



(E)-2-methyl-3-(5-methylthiophen-2-yl)acrylaldehyde

Method G; yellow solid, Yield 44 %, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ 9.50 (s, 1H, CHO), 7.34 (s, 1H, alkenyl H), 7.22 (d, *J* = 3.6 Hz, 1H, H_{Thioph}), 6.85 (d, *J* = 3.5 Hz, 1H, H_{Thioph}), 2.57 (s, 3H, CH_3), 2.07 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, , 300 K) δ 194.66, 147.49, 142.82, 137.50, 134.30, 133.76, 126.80, 16.16, 11.14. $C_9H_{10}OS$ requires: C, 65.02; H, 6.06%.Found: C, 65.27; H, 6.16%. Spectral data are provided in the appendix.

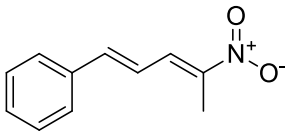


(E)-2-methyl-3-(thien-3-yl)acrylaldehyde[177]

Method G; yellow oil, Yield 46 %, ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ 9.55 (s, 1H, CHO), 7.65 (d, *J* = 2.5 Hz, 1H, H_{Thioph}), 7.43 (dd, *J* = 5.1, 2.9 Hz, 1H, H_{Thioph}), 7.37 (dd, *J* = 5.0, 0.9 Hz, 1H, H_{Thioph}), 7.27 (s, 1H, alkenyl H), 2.09 (s, 3H, CH_3).

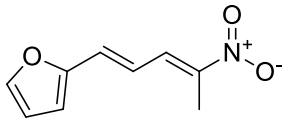
3.10 Synthesis and characterization of substituted nitrodiene

Nitrodienes were prepared by Henry condensation between their corresponding α,β-unsaturated aldehyde and appropriate nitroalkane.



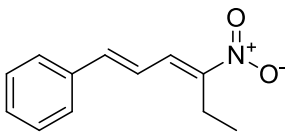
(*1E,3E*)-4-Nitro-1-phenylpenta-1, 3-diene (5a)[172]

Method A for Henry condensation between cinnamaldehyde and nitroethane; Yellow solid, Yield 67 %, ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ 7.80 (d, *J* = 11.5 Hz, 1H, H_{diene}), 7.57 – 7.52 (m, 2H, Phenyl H), 7.46 – 7.35 (m, 3H, Phenyl H), 7.12 (d, *J* = 15.4 Hz, 1H, H_{diene}), 6.92 (dd, *J* = 15.4, 11.5 Hz, 1H, H_{diene}), 2.39 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$, 300 K) δ 146.35, 143.93, 135.71, 133.68, 129.87, 128.99, 127.54, 121.28, 13.03.



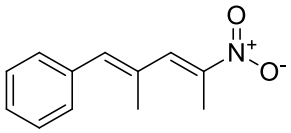
(1E,3E) 4-nitro-1-fur-2-ylpenta-1,3-diene (5b)

method A; Yellow solid, Yield 70%, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ 7.72 (d, *J* = 9.8 Hz, 1H, H_{diene}), 7.50 (d, *J* = 0.9 Hz, 1H, H_{furan}), 6.91 – 6.71 (m, 2H, H_{diene}), 6.57 (d, *J* = 3.4 Hz, 1H, H_{furan}), 6.50 (dd, *J* = 3.4, 1.8 Hz, 1H, H_{furan}), 2.35 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ 152.42, 146.61, 144.89, 133.81, 130.31, 119.96, 113.92, 113.02, 13.42. $C_9H_9NO_3$ requires: C, 60.33; H, 5.06; N, 7.82%.Found: C, 60.56; H, 4.93; N, 7.86%.



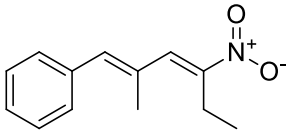
(*1E,3E*)-4-Nitro-1-phenylhexa-1,3-diene (5c)[178]

Method A, for Henry condensation between cinnamaldehyde and nitropropane; Yellow solid, Yield 53 %, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ 7.73 (d, *J* = 11.4 Hz, 1H, H_{diene}), 7.59 – 7.30 (m, 5H, Phenyl H), 7.12 (d, *J* = 15.5 Hz, 1H, H_{diene}), 6.92 (dd, *J* = 15.4, 11.5 Hz, 1H, H_{diene}), 2.84 (q, *J* = 7.4 Hz, 2H, CH_2), 1.24 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ 210.02, 152.59, 144.43, 136.12, 133.55, 130.26, 129.38, 127.94, 121.36, 20.84, 13.41. $C_{12}H_{13}NO_2$ requires: C, 70.92; H, 6.45; N, 6.89%.Found: C 70.64; H 6.43; N 6.97 %



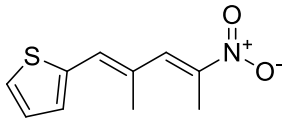
(1E,3E)-2-methyl-4-nitro-1-phenylpenta-1,3-diene (5d)

Method A for Henry condensation between trans- α-methylcinnamaldehyde and nitroethane. Yellow solid, Yield 52%, ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ 7.77 (s, 1H, H_{diene}), 7.49 – 7.31 (m, 5H, Phenyl H), 6.85 (s, 1H, H_{diene}), 2.47 (s, 3H, CH_3), 2.20 (d, *J* = 1.3 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 300 K) δ 146.43, 139.27, 138.34, 136.18, 131.29, 129.49, 128.48, 128.14, 17.80, 14.34. $C_{12}H_{13}NO_2$ requires: C, 70.92; H, 6.45; N, 6.89%. Found: C, 71.16; H, 6.33; N, 6.83%.



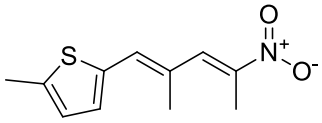
(1E,3E)-2-methyl-4-nitro-1-phenylhexa-1,3-diene (5e)

Method A for Henry condensation between α-methylcinnamaldehyde and nitropropane. Yellow oil, Yield 44 %, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ 7.71 (s, 1H, H_{diene}), 7.51 – 7.32 (m, 5H, Phenyl H), 6.86 (s, 1H, H_{diene}), 2.92 (q, *J* = 7.4 Hz, 2H, CH_2), 2.18 (s, 3H, CH_3), 1.25 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ 152.35, 139.07, 138.27, 136.69, 131.62, 129.79, 128.84, 128.47, 21.55, 17.85, 13.71.



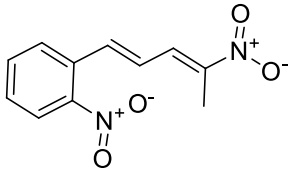
(1E,3E)-2-methyl-4-nitro-1-thien-2-ylpenta-1,3-diene(5f)

Method A for Henry condensation; Yellow oil, Yield = 53%, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ 7.79 (s, 1H, H_{diene}), 7.48 (d, *J* = 5.0 Hz, 1H, H_4), 7.22 (d, *J* = 3.6 Hz, 1H, H_{thioph}), 7.12 (dd, *J* = 5.0, 3.6 Hz, 1H, H_4), 7.01 (s, 1H, H_{diene}), 2.47 (s, 3H, CH_3), 2.30 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.30, 140.04, 138.92, 132.75, 131.09, 129.09, 128.86, 127.99, 18.47, 14.93.



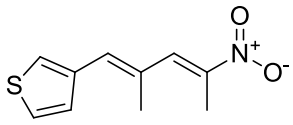
(1E,3E)-2-methyl-4-nitro-1-(5-methylthien-2-yl)penta-1,3-diene(5g)

Method A, for Henry condensation. Orange solid, Yield = 32 %,^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ 7.79 (s, 1H, H_{diene}), 7.02 (d, *J* = 3.6 Hz, 1H, H_{thioph}), 6.94 (s, 1H, H_{diene}), 6.79 (dd, *J* = 3.8, 0.7 Hz, 1H, H_{thioph}), 2.55 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.27 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ 145.66, 144.44, 139.48, 137.92, 133.84, 131.69, 127.45, 126.21, 18.16, 15.92, 14.75. $C_{11}H_{13}NO_2S$ requires: C, 59.17; H, 5.87; N, 6.27%.Found: C, 59.21; H, 5.86; N, 6.20%.



(1E,3E)-4-nitro-1-(2-nitrophenyl)penta-1,3-diene (5h)

Method A for Henry condensation between *o*-nitrocinnamaldehyde and nitroethane. Yellow solid, Yield = 92% ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ 8.06 (d, *J* = 8.1 Hz, 1H, H_{diene}), 7.80 (d, *J* = 11.6 Hz, 1H, H_{diene}), 7.67 – 7.50 (m, 4H, Phenyl H), 6.86 (dd, *J* = 15.2, 11.6 Hz, 1H, H_{diene}), 2.40 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ 158.62, 148.47, 138.62, 133.80, 132.65, 131.85, 130.15, 128.96, 126.36, 125.61, 13.60. $C_{11}H_{10}N_2O_4$ requires: C, 56.41; H, 4.30; N, 11.96%.Found: C, 56.52; H, 4.23; N, 12.00%.

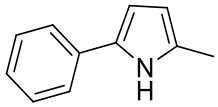


(1E,3E)-2-methyl-4-nitro-1-thien-3-ylpenta-1,3-diene(5j)

Method A for Henry condensation; yellow oil, Yield = 24 %,^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H, H_{diene}), 7.43 – 7.35 (m, 2H, H_{thioph}), 7.21 (dd, *J* = 4.8, 1.3 Hz, 1H, H_{thioph}), 6.82 (s, 1H, H_{diene}), 2.46

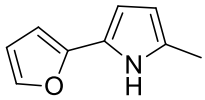
(s, 3H, CH_3), 2.24 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.11, 138.56, 137.70, 133.37, 130.10, 128.74, 125.99, 125.77, 18.11, 14.39.

3.11 Characterization of pyrroles



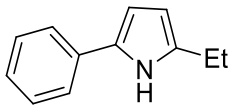
2-methyl-5-phenyl-1H-pyrrole (**6a**)[179]

Colorless solid, ^1H NMR (300 MHz, $CDCl_3$, 300 K) δ 8.12 (br s, *exchangeable,* 1H, NH), 7.46 (d, *J* = 7.9 Hz, 2H, Phenyl H), 7.37 (t, *J* = 7.7 Hz, 2H, Phenyl H), 7.19 (t, *J* = 7.3 Hz, 1H, Phenyl H), 6.43 (t, *J* = 3.0 Hz, 1H, $H_{Pyrrole}$), 5.99 (s, 1H, $H_{Pyrrole}$), 2.37 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ 133.37, 131.19, 129.42, 129.21, 126.05, 123.74, 108.36, 106.61, 13.58. $C_{11}H_{11}N$ requires: C, 84.04; H, 7.05; N, 8.91%. Found: C, 84.18; H, 6.69; N, 8.60%.



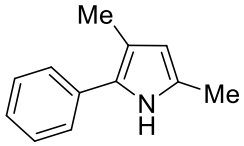
2-(fur-2-yl)-5-methyl-1H-pyrrole(**6b**)[180]

Colorless oil, ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (br s, exchangeable, 1H, NH), 7.35 (d, *J* = 1.4 Hz, 1H), 6.44 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.34 (t, *J* = 2.9 Hz, 1H), 6.30 (d, *J* = 3.3 Hz, 1H), 5.95 (dd, *J* = 3.9, 1.8 Hz, 1H), 2.34 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 300 K) δ 148.58, 139.92, 128.40, 122.73, 111.42, 107.56, 105.63, 101.32, 13.05.



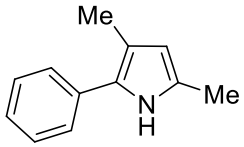
2-ethyl-5-phenyl-1H-pyrrole (**6c**)[181]

Colorless solid, ^1H NMR (400 MHz, $CDCl_3$, 300 K) δ 8.15 (br s, exchangeable, 1H, NH), 7.47 (d, *J* = 7.9 Hz, 2H, Phenyl H), 7.37 (t, *J* = 7.7 Hz, 2H, Phenyl H), 7.19 (t, *J* = 7.3 Hz, 1H, Phenyl H), 6.45 (s, 1H, $H_{Pyrrole}$), 6.02 (s, 1H, $H_{Pyrrole}$). 2.72 (q, *J* = 7.6 Hz, 2H, CH_2), 1.33 (t, *J* = 7.6 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 300 K) δ 135.63, 133.00, 130.62, 128.83, 125.69, 123.42, 106.25, 106.00, 21.03, 13.62. $C_{12}H_{13}N$: requires: C, 84.17; H, 7.65; N, 8.18%. Found: C, 84.11; H, 7.76; N, 8.05%.



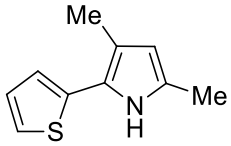
3,5-dimethyl-2-phenyl-1H-pyrrole (6d)[182]

Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ 7.83 (br s, exchangeable, 1H, NH), 7.43 (s, 4H, Phenyl H), 7.23 (m, 1H, Phenyl H), 5.87 (s, 1H, $H_{Pyrrole}$), 2.33 (s, 3H, CH_3), 2.28 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$, 300 K) δ 133.96, 128.65, 127.49, 126.75, 125.92, 125.46, 116.49, 110.30, 12.98, 12.49.



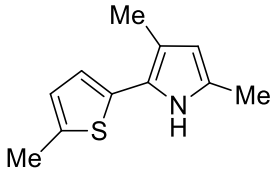
5-ethyl-3-methyl-2-phenyl-1H-pyrrole (6e)[181]

Colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ = 7.85 (br s, exchangeable, 1H, NH), 7.55 – 7.34 (m, 4H, Phenyl H), 7.34 – 7.20 (m, 1H, Phenyl H), 5.91 (s, 1H, $H_{Pyrrole}$), 2.69 (q, *J* = 7.6 Hz, 2H, CH_2), 2.29 (s, 3H, CH_3), 1.32 (t, *J* = 7.6 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ 134.59, 134.46, 129.04, 126.67, 126.37, 125.87, 116.66, 108.99, 21.26, 14.00, 12.95.



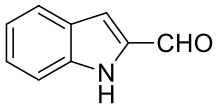
3,5-dimethyl-2-(thien-2-yl)-1H-pyrrole (6f)

Colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ = 7.79 (br s, exchangeable, 1H, NH) 7.17 (dd, *J* = 5.1, 1.2 Hz, 1H, $H_{Thioph.}$), 7.05 (dd, *J* = 5.1, 3.6 Hz, 1H, H_{Thioph}), 6.95 (dd, *J* = 3.6, 1.1 Hz, 1H, H_{Thioph}).5.81 (s, 1H, $H_{Pyrrole}$), 2.29 (s, 3H, CH_3), 2.21 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ 131.70, 128.02, 127.75, 122.48, 122.22, 121.44, 117.66, 110.66, 13.48, 12.76.



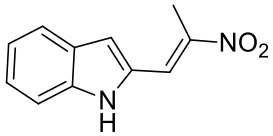
3,5-dimethyl-2-(5-methylthien-2-yl)-1H-pyrrole (6g)

Yellow oil,[1]H NMR (400 MHz, $CDCl_3$, 300 K) δ 7.73 (br s, exchangeable, 1H, NH), 6.74 (d, *J* = 3.5 Hz, 1H, $H_{thioph.}$), 6.70 (m, 1H, $H_{thioph.}$), 5.80 (s, 1H, $H_{pyrrole}$), 2.51 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.22 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 300 K) δ 136.86, 134.14, 127.60, 125.79, 121.20, 119.90, 116.56, 110.10, 15.20, 13.09, 12.44.



1H-indole-2-carbaldehyde (6h)[183]

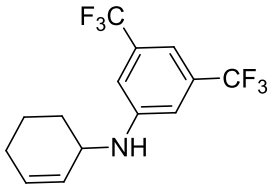
Colorless solid, [1]H NMR (400 MHz, $CDCl_3$, 300 K) δ =9.89 (s, 1H, CHO), 9.78 (s, exchangeable, 1H, NH), 7.78 (d, *J* = 8.1 Hz, 1H, Phenyl H), 7.53 (d, *J* = 8.4 Hz, 1H, Phenyl H), 7.43 (t, *J* = 7.7 Hz, 1H, Phenyl H), 7.32 (d, *J* = 0.9 Hz, 1H, $H_{Pyrrole}$), 7.21 (t, *J* = 7.5 Hz, 1H, Phenyl H). ^{13}C NMR (100 MHz, $CDCl_3$, 300 K) δ 182.40, 138.38, 136.88, 127.40, 127.34, 123.42, 121.26, 115.25, 112.70. C_9H_7NO : requires: C, 74.47; H, 4.86; N, 9.65%. Found: C, 74.47; H, 4.80; N, 9.28%.



(E)-2-(2-nitroprop-1-en-1-yl)-1H-indole

Yellow solid, [1]H NMR (300 MHz, $CDCl_3$, 300 K) δ 8.37 (br s, exchangeable, 1H, NH), 8.13 (s, 1H, alkenyl H), 7.71(d, *J* = 8.0 Hz, 1H, Phenyl H), 7.45 (d, *J* = 8.2 Hz, 1H, Phenyl H), 7.34 (t, *J* = 7,6 Hz, 1H, Phenyl H), 7.20 (t, *J* = 7.5 Hz, 1H, Phenyl H), 6.99 (s, 1H, $H_{Pyrrole}$), 2.66 (s, 3H, CH_3).

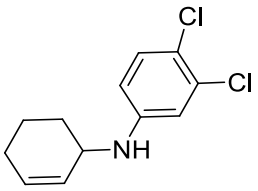
3.12 Synthesis and characterization of allylamine



N-(cyclohex-2-en-1-yl)-3,5-bis(trifluoromethyl)aniline[107b]

Prepared according to previously reported procedure[107b] with a modification of the work up. The product was isolated using short column of silica gel (hexane/ AcOEt 9:1) . Colorless liquid, [1]H NMR

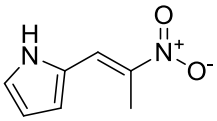
(300 MHz, $CDCl_3$, 300 K) δ 7.14 (s, 1H), 6.96 (s, 2H), 5.91 (m, 1H), 5.73 (dd, *J* = 10.0, 2.1 Hz, 1H), 4.14 (br s, exchangeable, 1H, NH), 4.05 (s, 1H), 2.09 (m, 2H), 2.02 – 1.90 (m, 1H), 1.83 – 1.59 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ 148.03, 132.63 (q, $J_{C–F}$ = 32.8 Hz), 131.95, 127.48, 122.18 (q, $J_{C–F}$ = 272.5 Hz), 112.49, 110.30, 48.18, 28.98, 25.45, 19.91.



3,4-dichloro-N-(cyclohex-2-en-1-yl)aniline[107a]

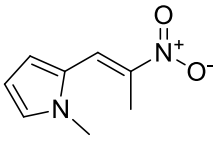
Prepared according to previously reported procedure.[107a] The product was isolated using short column of silica gel (hexane/ AcOEt 9:1) . Colorless liquid, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ 7.18 (d, *J* = 8.7 Hz, 1H), 6.70 (d, *J* = 2.7 Hz, 1H), 6.45 (dd, *J* = 8.8, 2.7 Hz, 1H), 5.90 (dt, *J* = 7.1, 2.6 Hz, 1H), 5.71 (dd, *J* = 10.0, 2.3 Hz, 1H), 3.93 (s, 1H), 3.75 (br s,exchangeable, 1H), 2.17 – 1.52 (m, 6H). ^{13}C NMR (75 MHz, CDCl3, 300 K) δ 147.18, 133.31, 131.25, 131.03,, 127.93, 119.94, 114.49, 113.36, 48.52, 29.04, 25.61, 20.00.

3.13 Synthesis and characterization of nitroalkenylpyrrole and nitroalkenylfuran



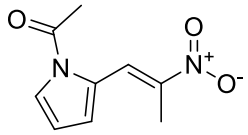
(E)-2-nitro-1-pyrrol-2-ylpropene (7a)[138]

Method A; Yellow solid, Yield 64%, ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 8.64 (br s, 1H, NH), δ 8.06 (s, 1H, alkenyl H), 7.13 (m, 1H, $H_{pyrrole}$), 6.75 (m, 1H, $H_{pyrrole}$), 6.46 (dd, *J* = 4.2, 2.7 Hz,1H, $H_{pyrrole}$), 2.53 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 141.64, 125.67, 124.25, 123.97, 116.34, 112.45, 14.13. MS (M = 152). $C_7H_8N_2O_2$: requires: C, 55.26; H, 5.30; N, 18.41%.Found: C, 55.48; H 5.30; N 18.68%.



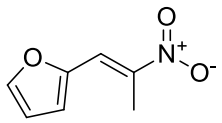
(E)-2-nitro-1-(N-methylpyrrol-2-yl)propene (7b)

Method F; Yellow solid, Yield 76 %, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K), δ 8.14 (s, 1H, alkenyl H), 6.95 (m, 1H, $H_{pyrrole}$), 6.69 (d, *J* = 4.0, 1H, $H_{pyrrole}$), 6.34 (dd, *J* = 4.0, 2.6 Hz, 1H, $H_{pyrrole}$), 3.78 (s, 3H, NCH_3), 2.50 (s, 3H, CH_3). MS (M = 166). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 144.22, 129.03, 126.52, 122.39, 116.56, 110.87, 34.86, 14.60. MS (M = 166). $C_8H_{10}N_2O_2$: requires: C, 57.82; H, 6.07; N, 16.86 %. Found: C, 58.06; H, 6.15; N, 16.59 %.



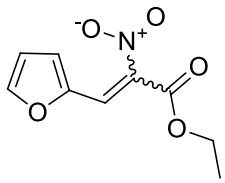
(E)-2-nitro-1-(N-acetylpyrrol-2-yl)propene (7c)

Prepared by acetylation of compound **(7a)** as follows: to a solution of the pyrrole derivative **(7a)** (3 mmol) in DCM (6 ml) at room temperatue was added DMAP (0.3 mmol), Et_3N (3.6 mmol), and acetic anhydride (3.6 mmol) in a schlenk flask. The reaction was stirred under nitrogen for 24h, then the reaction mixture was diluted with DCM, washed with water, dried over anhydrous sodium sulfate and finally the organic phase was evaporated to give the desired product;[184] Yellow solid, Yield 71 %, 1H NMR (300 MHz, CDCl3, 300 K), δ 8.64 (s, 1H, alkenyl H), 7.33 (d, J = 4.1 Hz, 1H, $H_{pyrrole}$), 6.60 (d, *J* = 3.4 Hz, 1H, $H_{pyrrole}$), 6.43 (t, *J* = 3.5 Hz, 1H, $H_{pyrrole}$), 2.64 (s, 3H, NAc), 2.46 (s, 3H, CH_3). MS (M = 194). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K), δ 169.48, 145.96, 128.33, 125.79, 124.84, 119.75, 113.52, 24.46, 14.71. MS (M = 194). $C_9H_{10}N_2O_3$: requires: C, 55.67; H, 5.19; N, 14.43%. Found: C, 55.28; H 5.10; N 14.43 %.



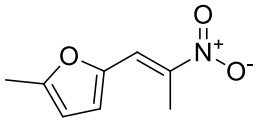
(E)-2-nitro-1-(fur-2-yl)propene (7d)[185]

Method B; Yellow solid, Yield 46%, ^{1}H NMR (400 MHz, $CDCl_3$, 300 K), δ 7.88 (s, 1H, alkenyl H), 7.66 (d, *J* = 1.4 Hz, 1H, H_5), 6.83 (d, *J* = 3.3 Hz, 1H, H_3), 6.60 (dd, 3.4, 1.8 Hz, 1H, H_4), 2.62 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K), δ 150.93, 146.57, 145.65, 120.97, 119.51, 113.22, 14.41. MS (M = 153). $C_7H_7NO_3$: requires: C, 54.90; H, 4.61; N, 9.15%. Found: C, 54.85; H 4.39; N 8.95 %.



ethyl 3-(fur-2-yl)-2-nitroacrylate (7e)[186]

Method C, Yellow solid, total yield 62% (72% Z-isomer, 28% E isomer), the two isomers were isolated using flash chromatography (silica gel). ^{1}H NMR for the major isomer (300 MHz, $CDCl_3$, 300 K), δ 7.64 (d, *J* = 1.3 Hz, 1H, H_{furan}), 7.37 (s, 1H, alkenyl H), 6.94 (d, *J* = 3.6 Hz, 1H, H_{furan}), 6.58 (dd, *J* = 3.5, 1.7 Hz, 1H, H_{furan}), 4.38 (q, *J* = 7.1 Hz, 2H, CH_2), 1.37 (t, *J* = 7.1 Hz, 3H, CH_3). ^{1}H NMR of the minor isomer (300 MHz, $CDCl_3$, , 300 K) δ 7.87 (s, 1H, alkenyl H), 7.66 (d, *J* = 1.3 Hz, 1H, H_{furan}), 7.08 (d, *J* = 3.6 Hz, 1H, H_{furan}), 6.64 (dd, *J* = 3.5, 1.8 Hz, 1H, H_{furan}) 4.50 (q, *J* = 7.1 Hz, 1H), 1.43 (t, *J* = 7.1 Hz, 1H).

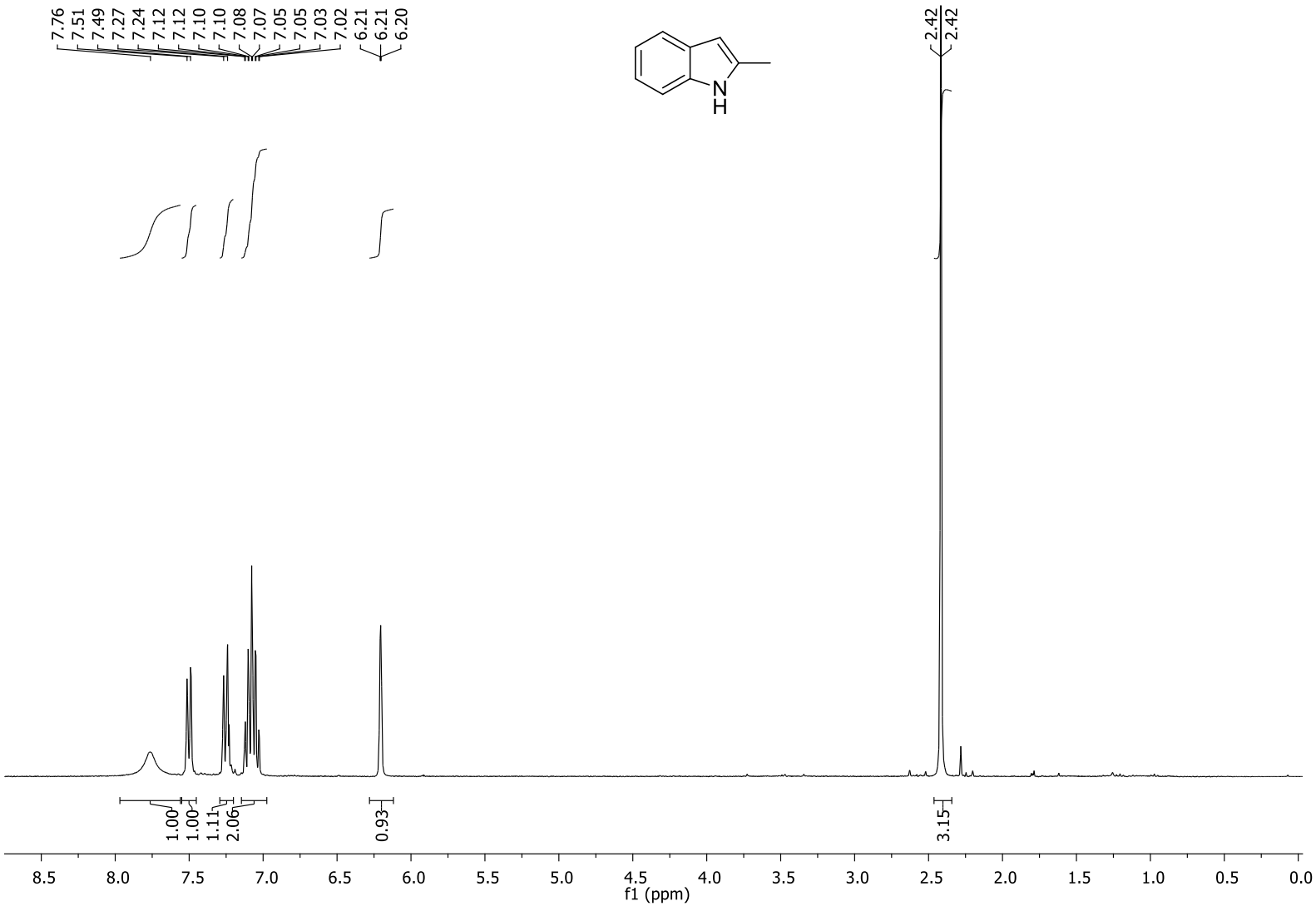


(E)-2-methyl-5-(2-nitroprop-1-en-1-yl)furan (7f)[165]

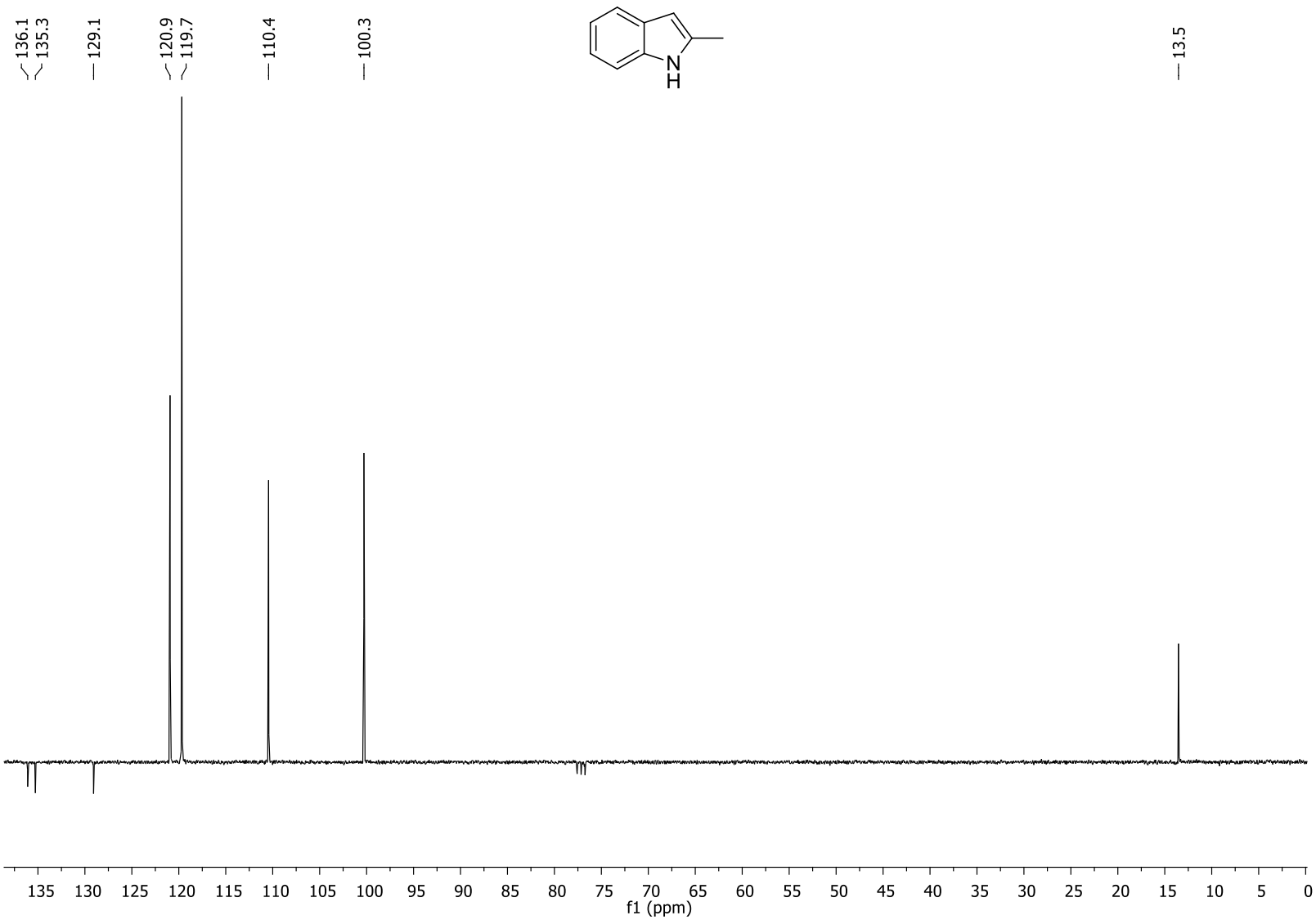
Method B; Yellow solid, Yield 87%, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K), δ 7.82 (s, 1H, alkenyl H), 6.75 (d, *J* = 3.3 Hz, 1H, H_{furan}), 6.21 (d, *J* = 2.7 Hz, 1H, H_{furan}), 2.59 (s, 3H, CH_3), 2.42 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ 157.79, 146.97, 143.29, 121.60, 121.21, 110.04, 14.50, 14.42. MS (M = 167). $C_8H_9NO_3$: requires: C, 57.48; H, 5.43; N, 8.38 %. Found: C, 57.67; H 5.24; N 8.31 %.

Appendices

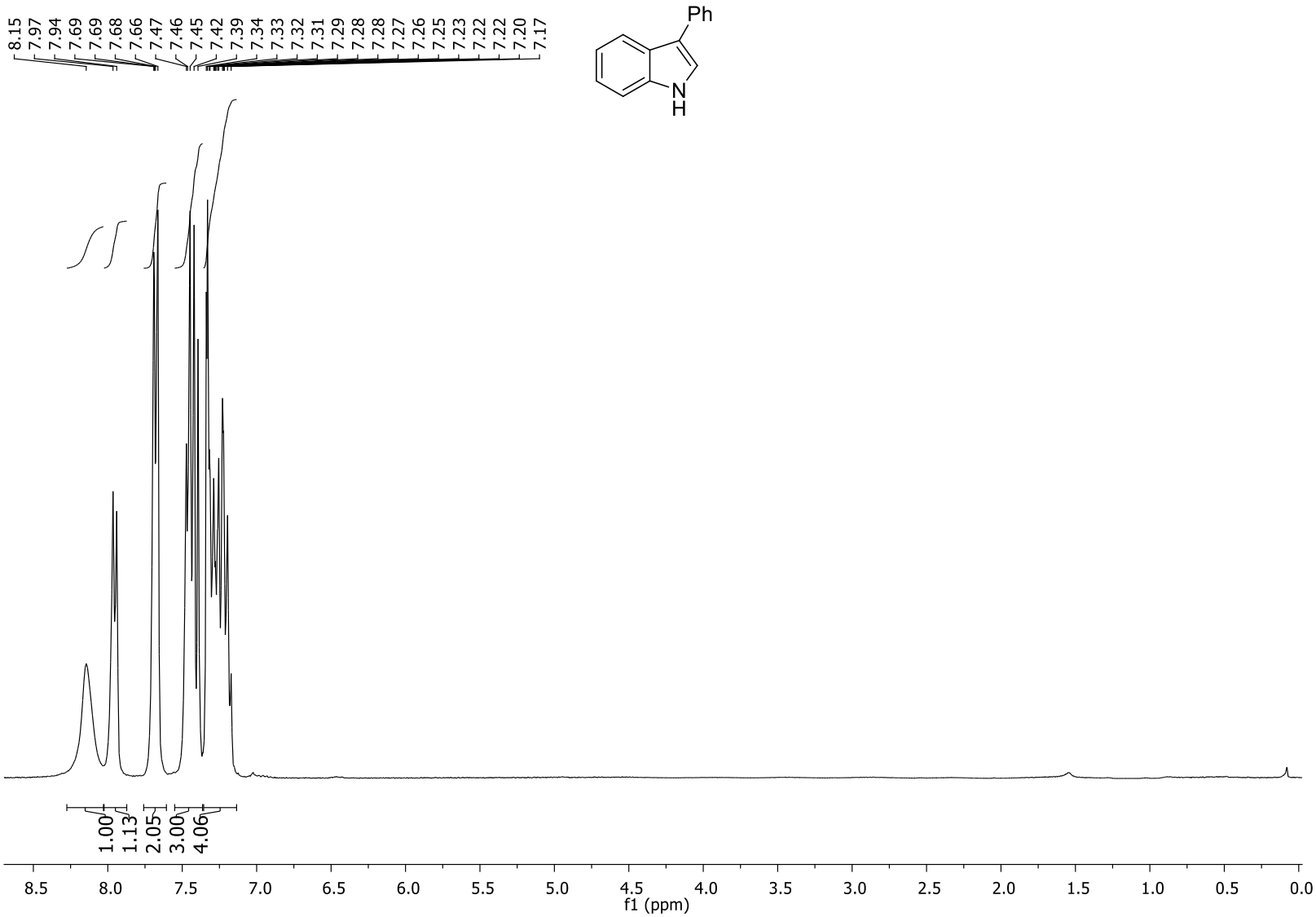
4.1 Appendix A: NMR spectra for indoles synthesis



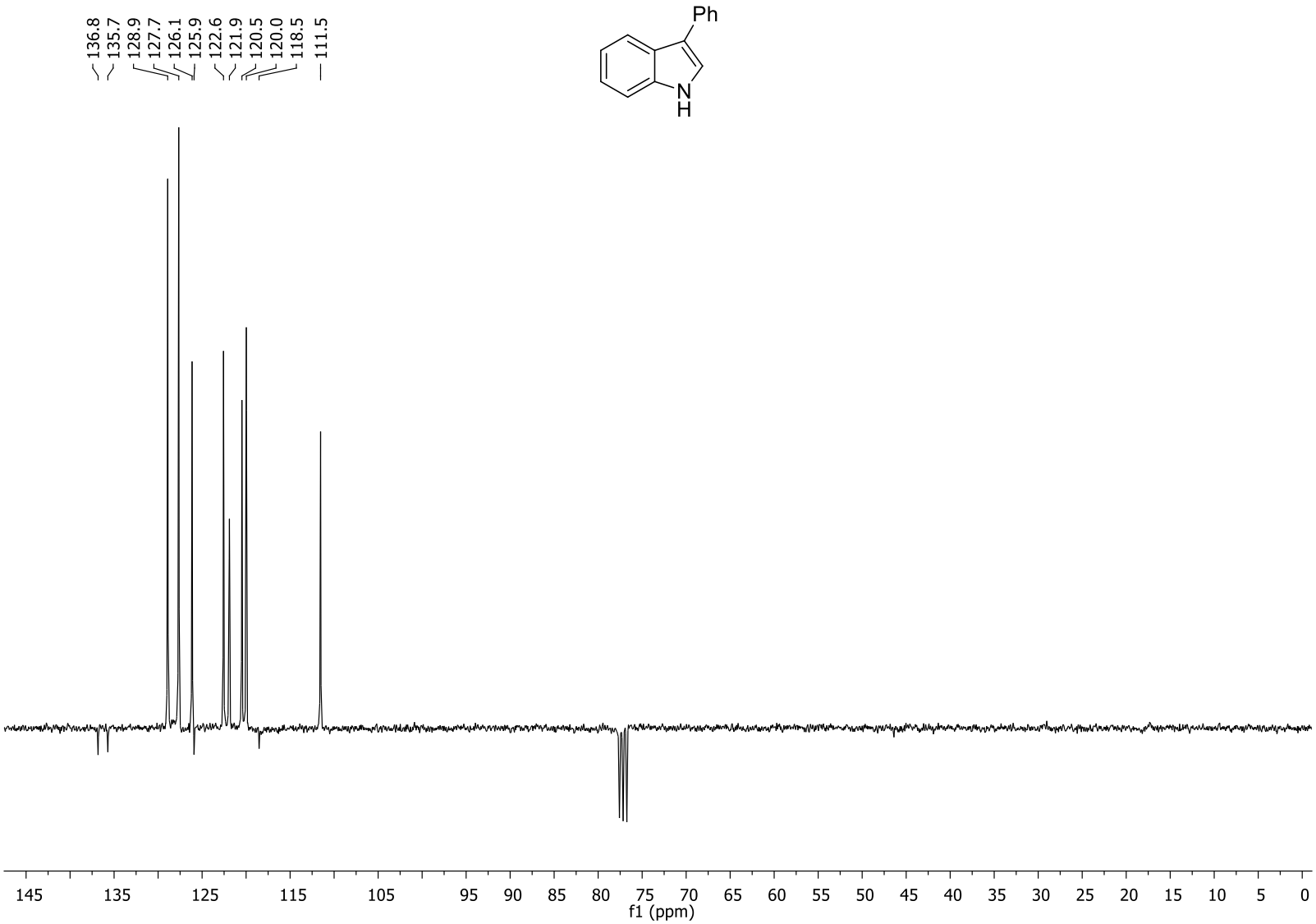
^{1}H NMR of 2-methyl-1*H*-indole (**2a**)



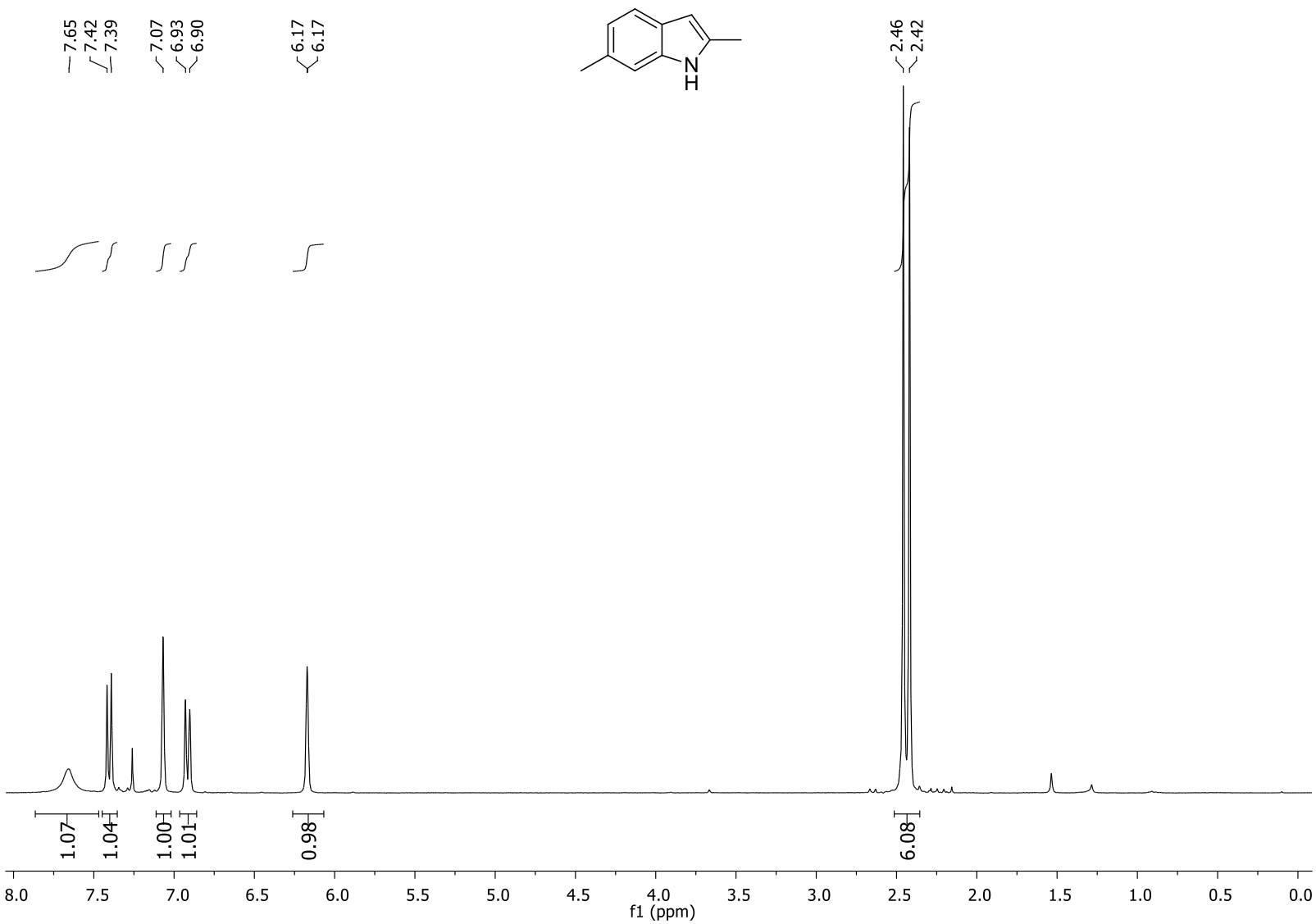
^{13}C APT NMR of 2-methyl-1*H*-indole (**2a**).



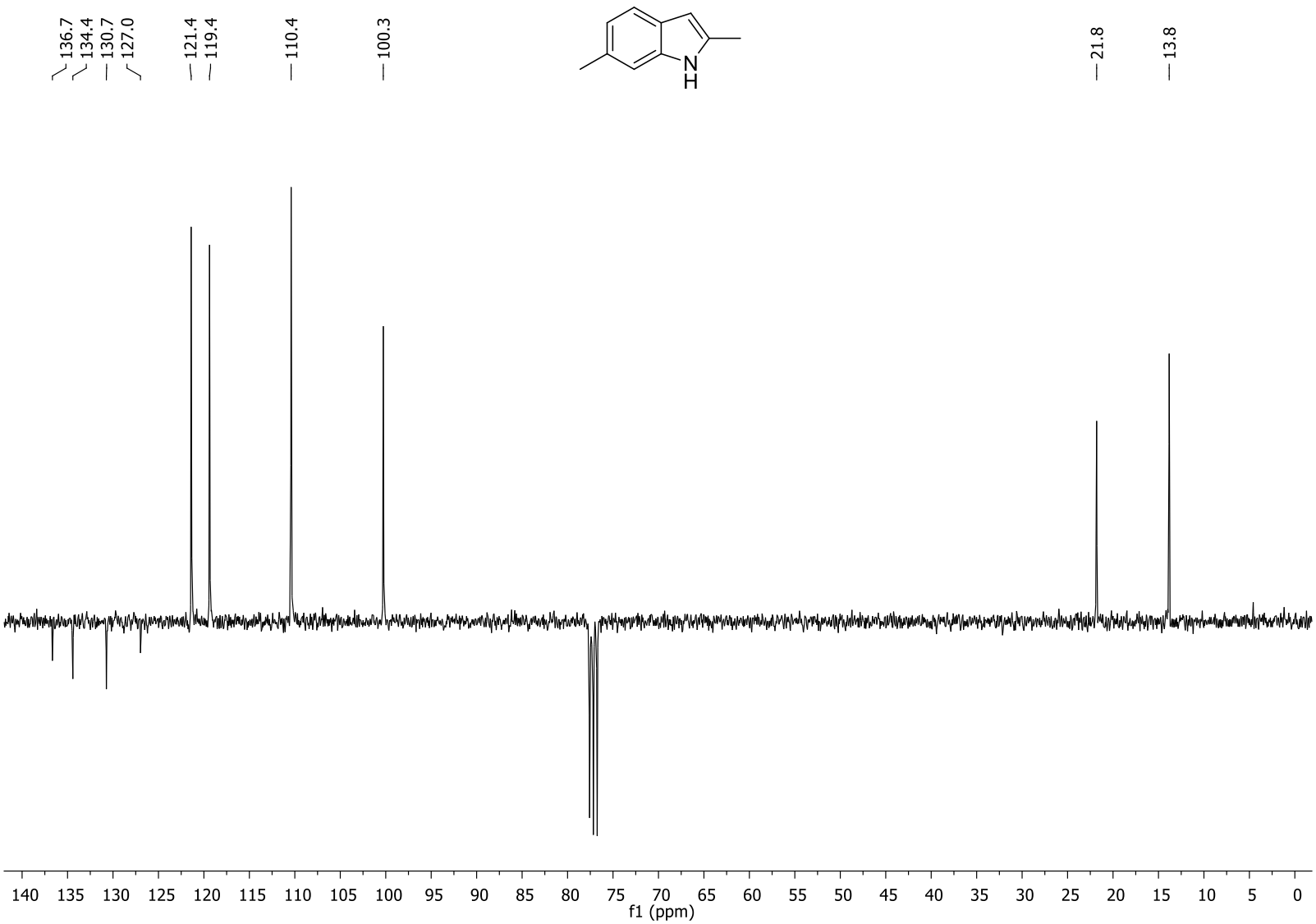
^{1}H NMR of 3-phenyl-1*H*-indole (**2b**)



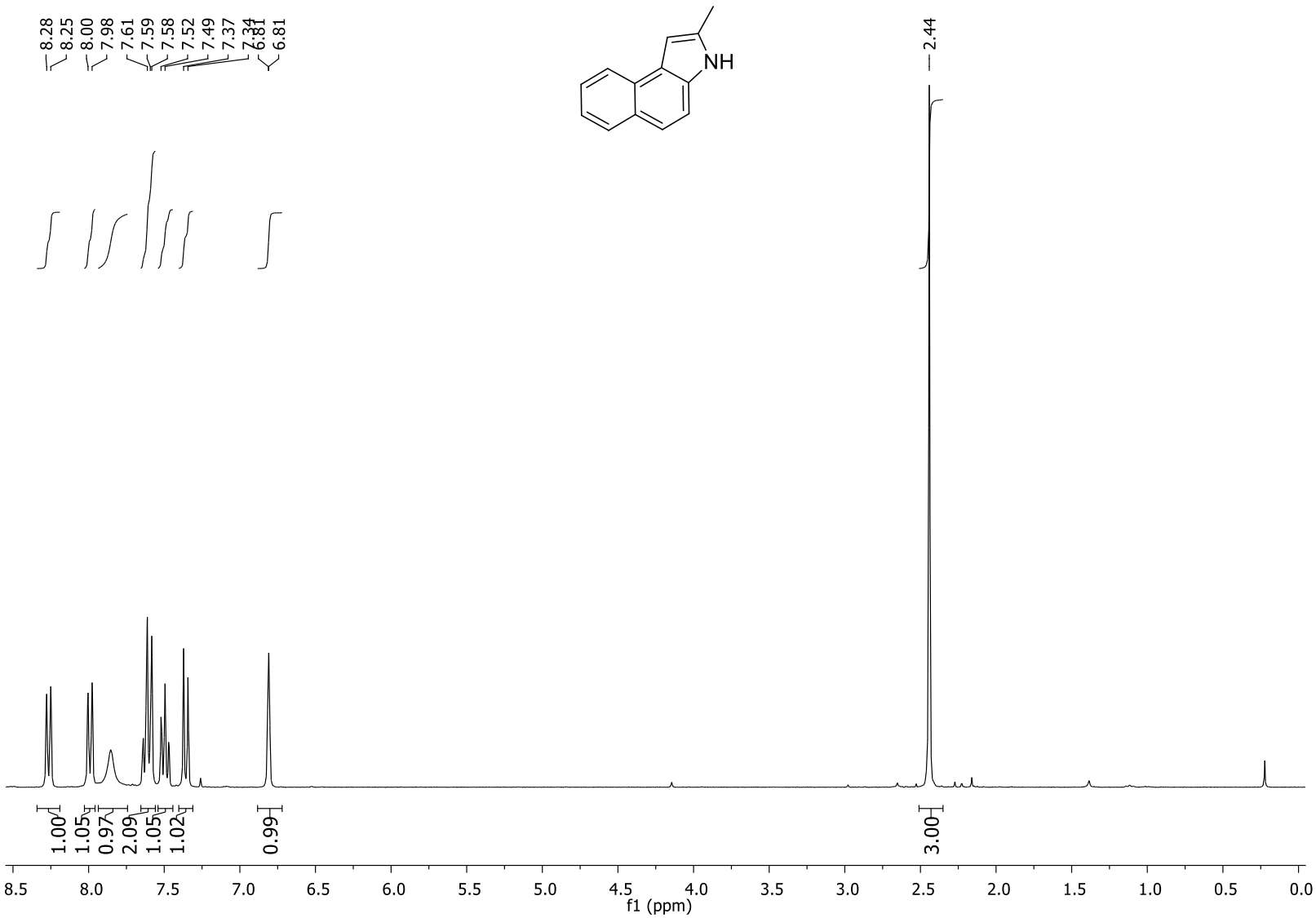
^{13}C APT NMR of 3-phenyl-1*H*-indole (**2b**).



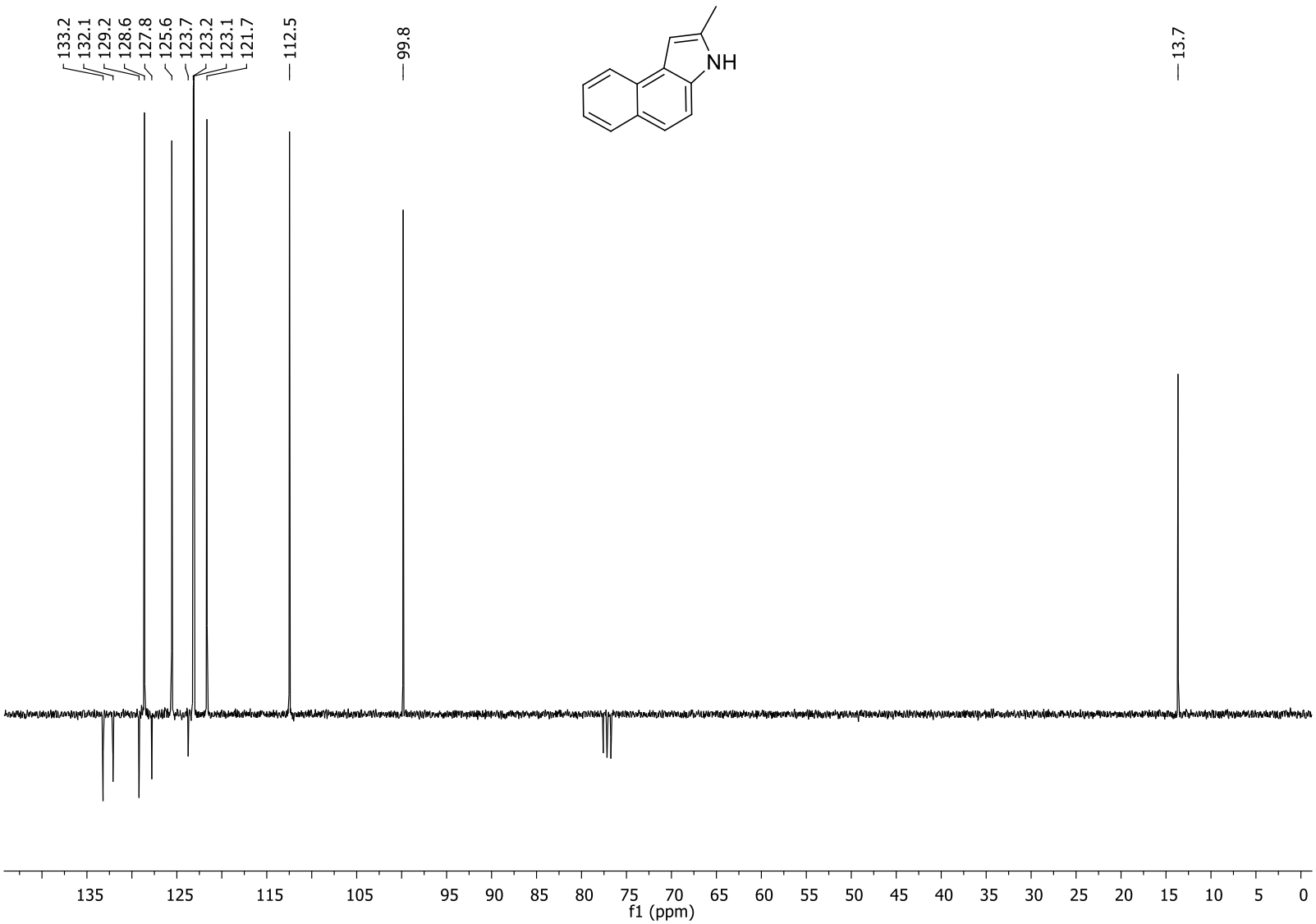
^{1}H NMR of 2,6-dimethyl-1*H*-indole (**2c**).



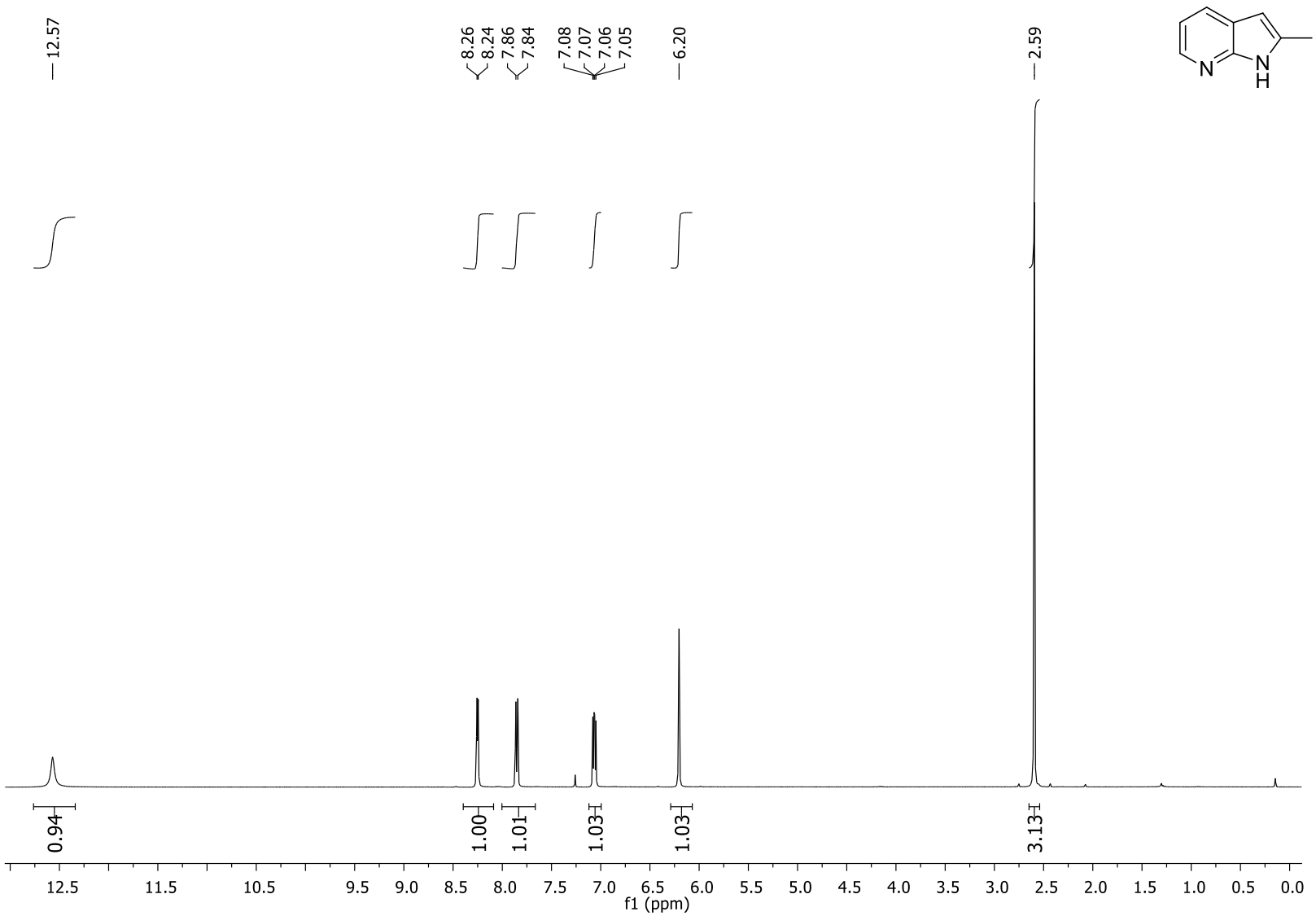
^{13}C APT NMR of 2,6-dimethyl-1*H*-indole (**2c**).



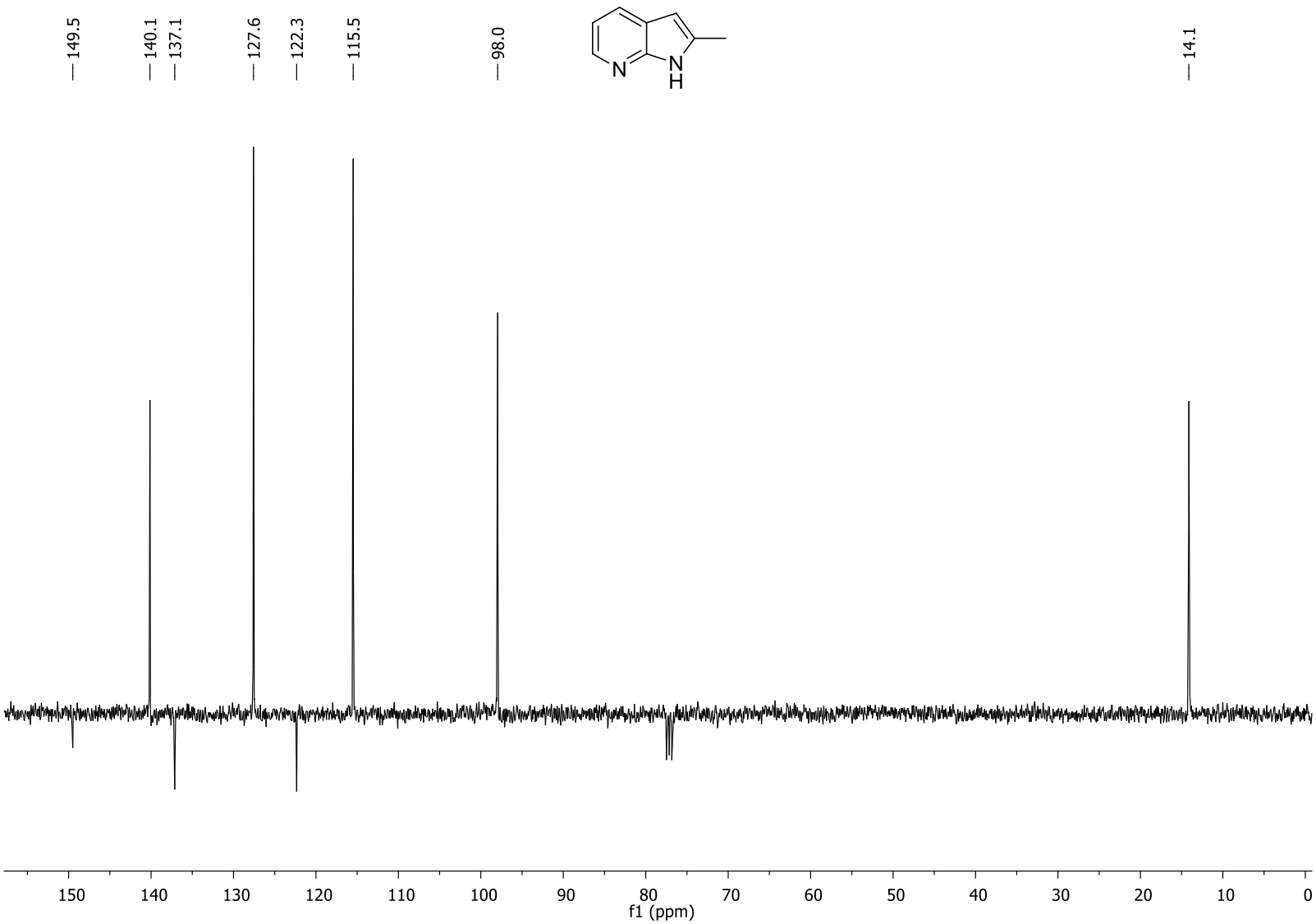
^{1}H NMR of 2-methyl-3*H*-benzo[e]indole (**2d**).



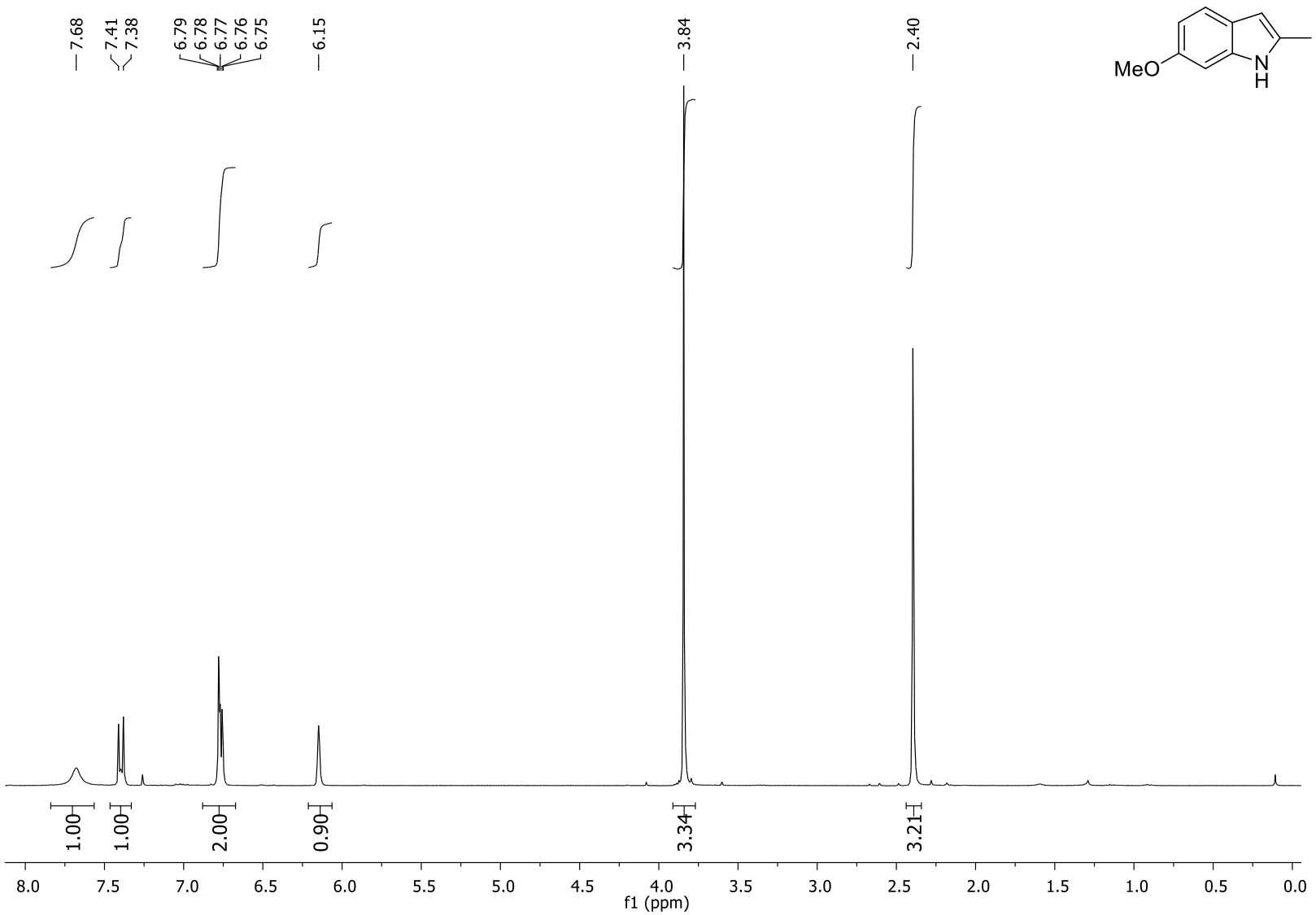
^{13}C APT NMR of 2-methyl-3*H*-benzo[e]indole (**2d**).



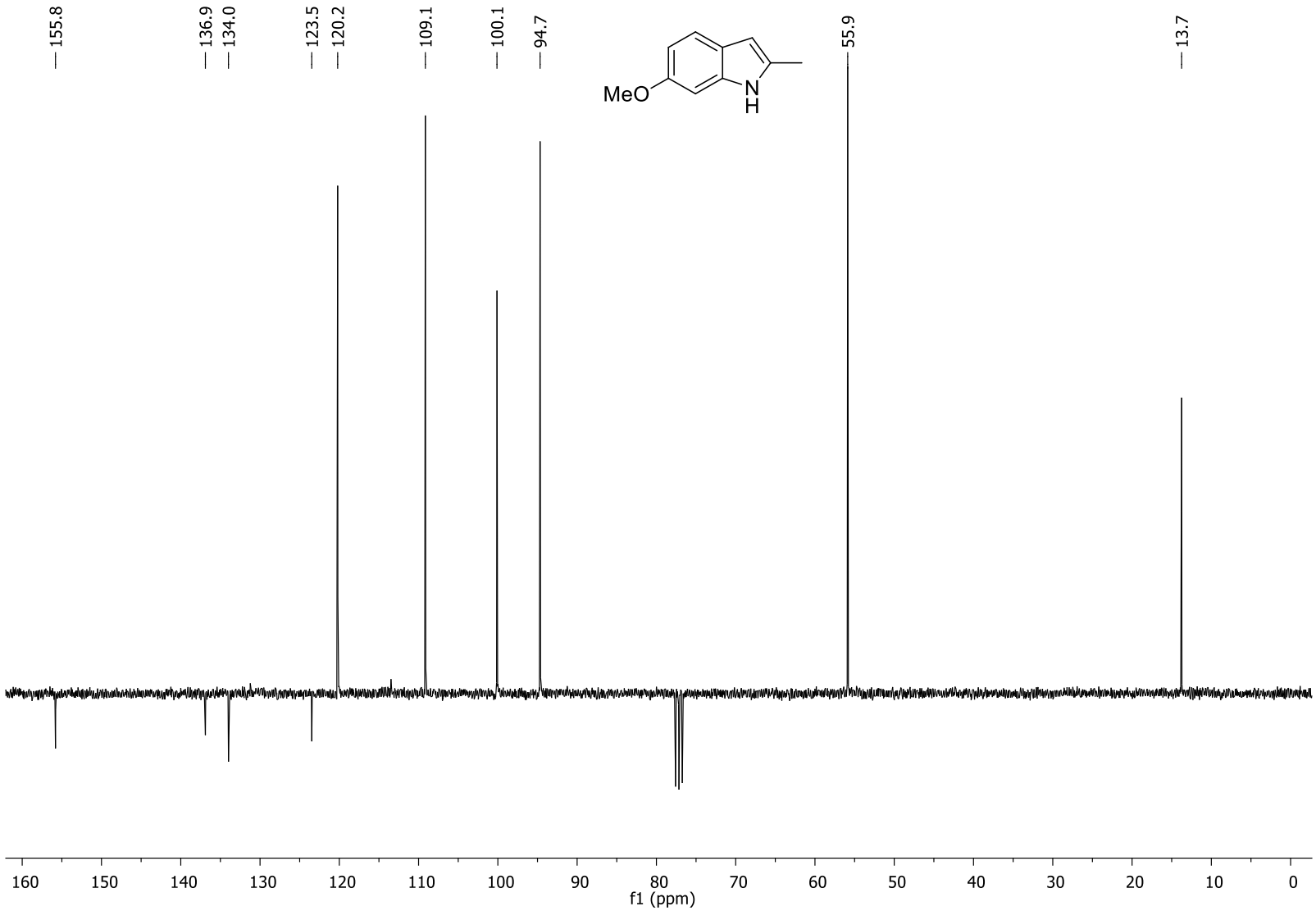
^{1}H NMR of 2-methyl-1*H*-pyrrolo[2,3-b]pyridine (**2e**).



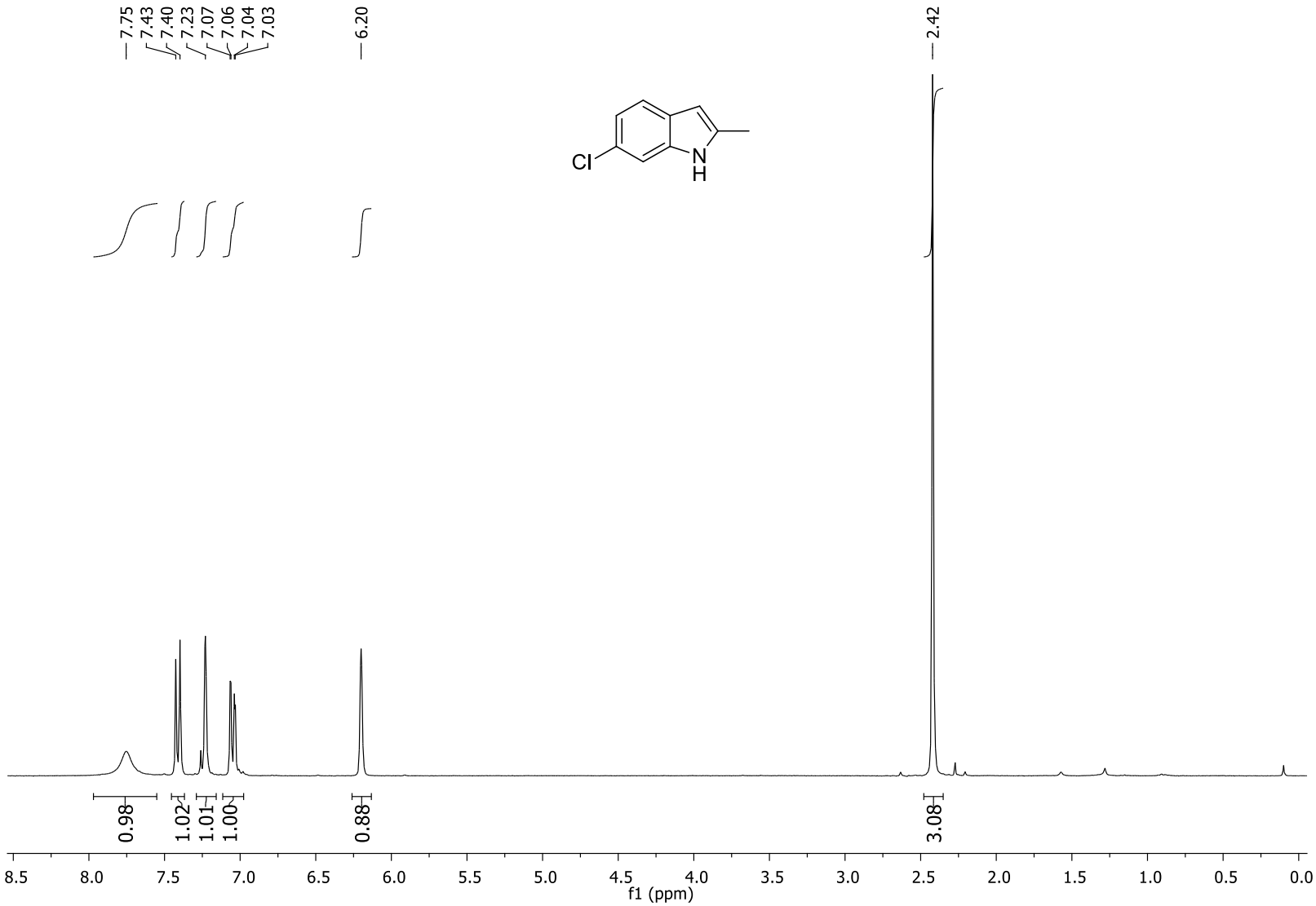
^{13}C APT NMR of 2-methyl-1*H*-pyrrolo[2,3-b]pyridine (**2e**).



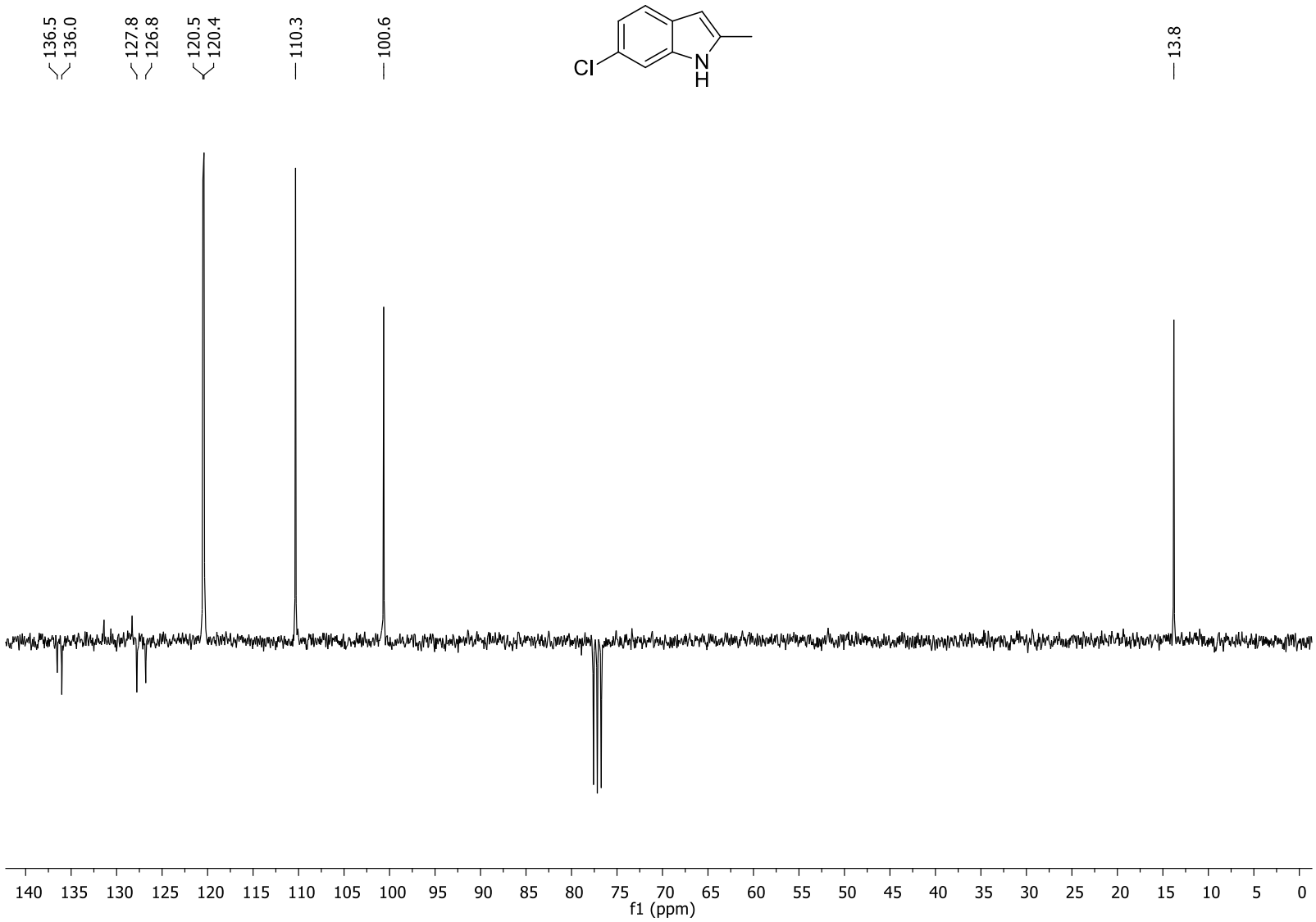
^{1}H NMR of 6-methoxy-2-methyl-1*H*-indole (**2f**).



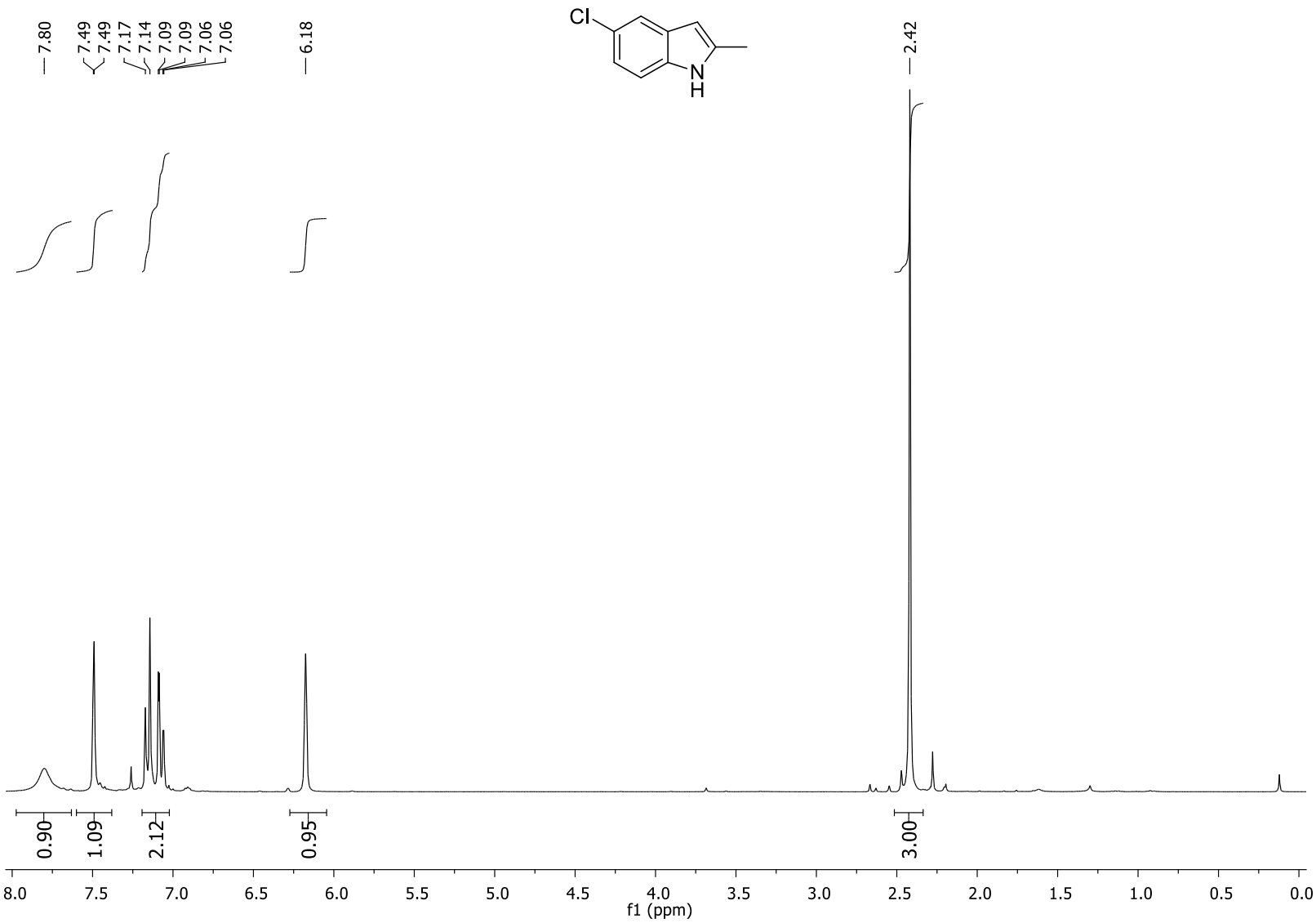
^{13}C APT NMR of 6-methoxy-2-methyl-1*H*-indole (**2f**).



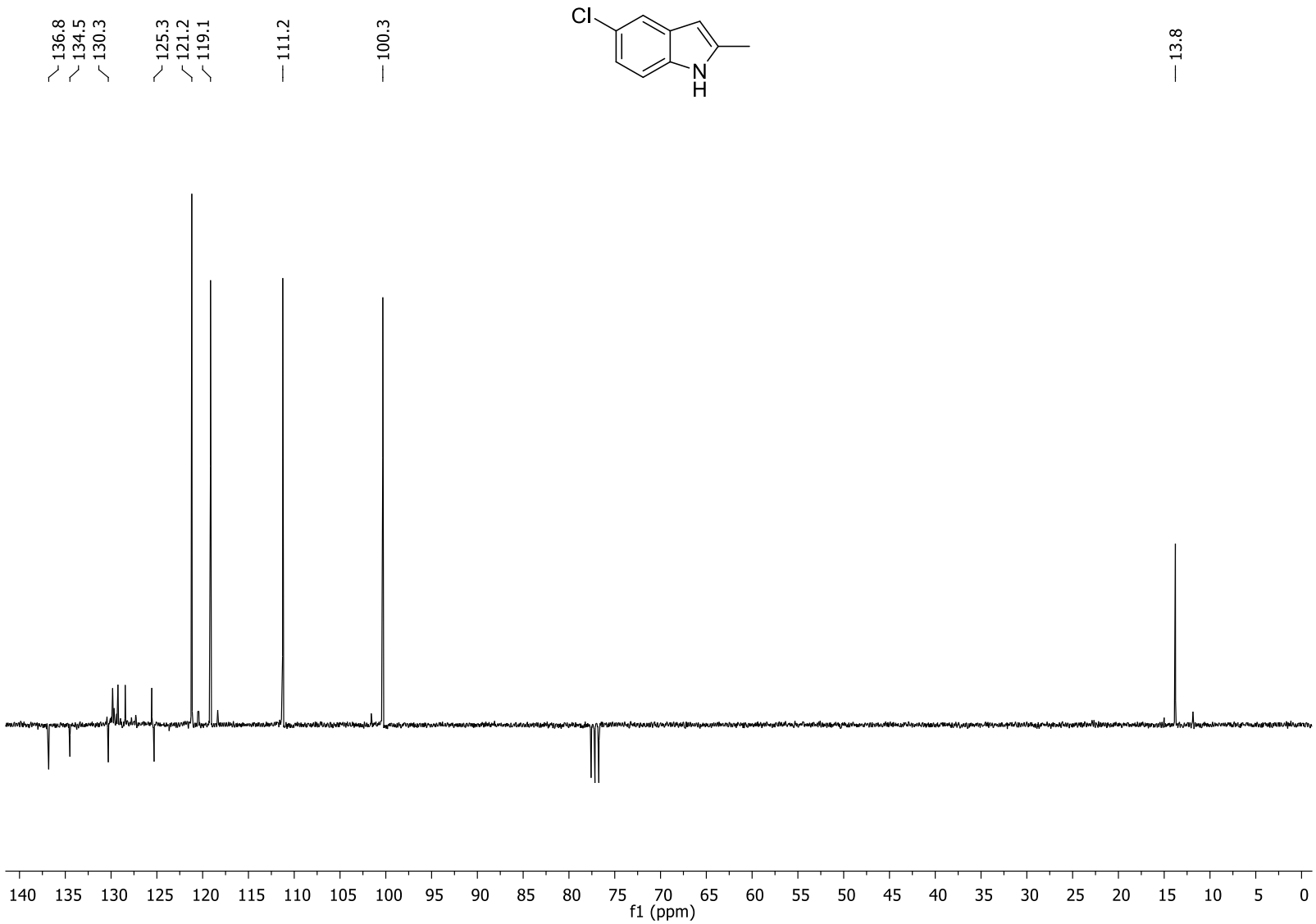
^{1}H NMR of 6-chloro-2-methyl-1*H*-indole (**2g**).



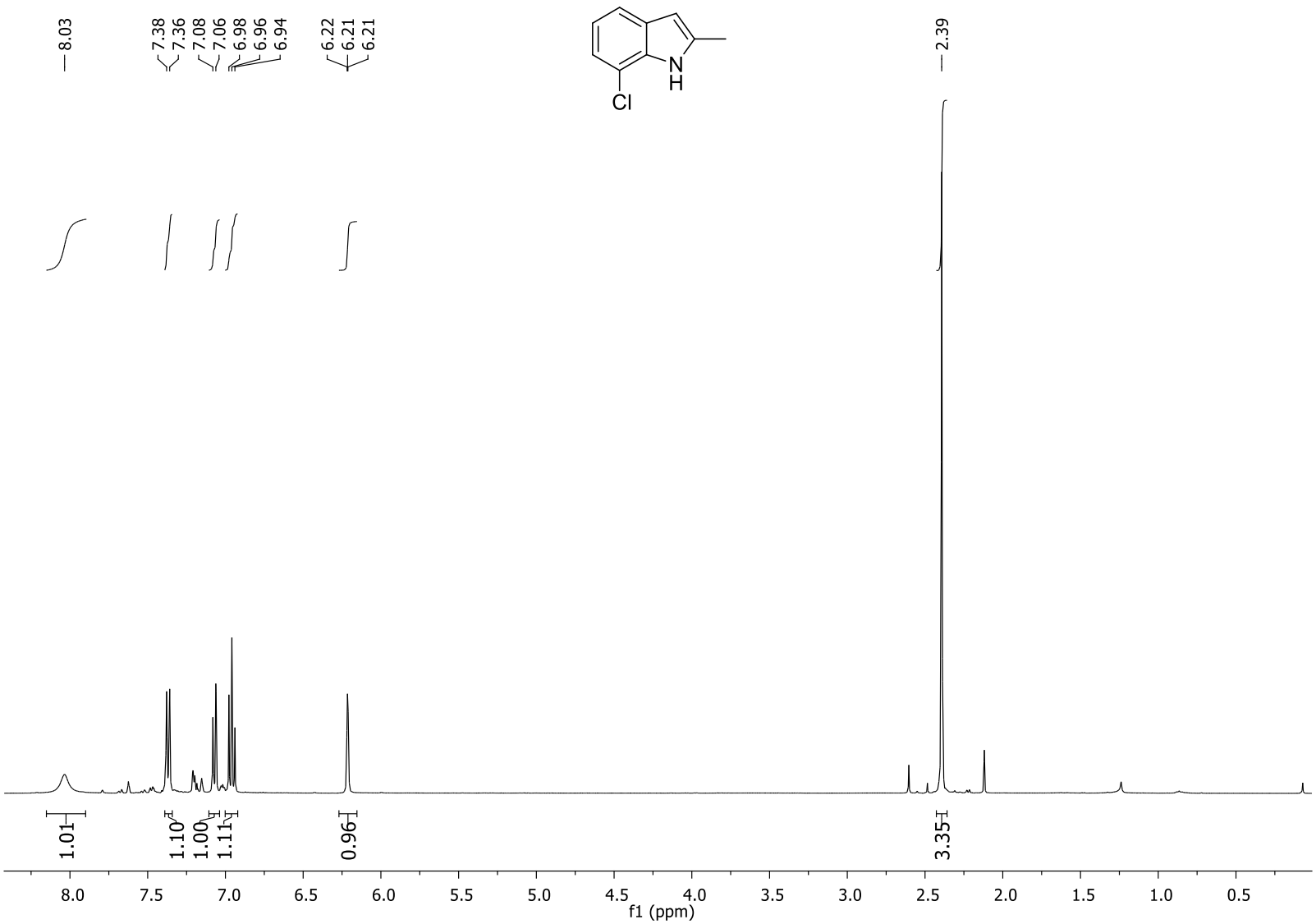
^{13}C APT NMR of 6-chloro-2-methyl-1*H*-indole (**2g**).



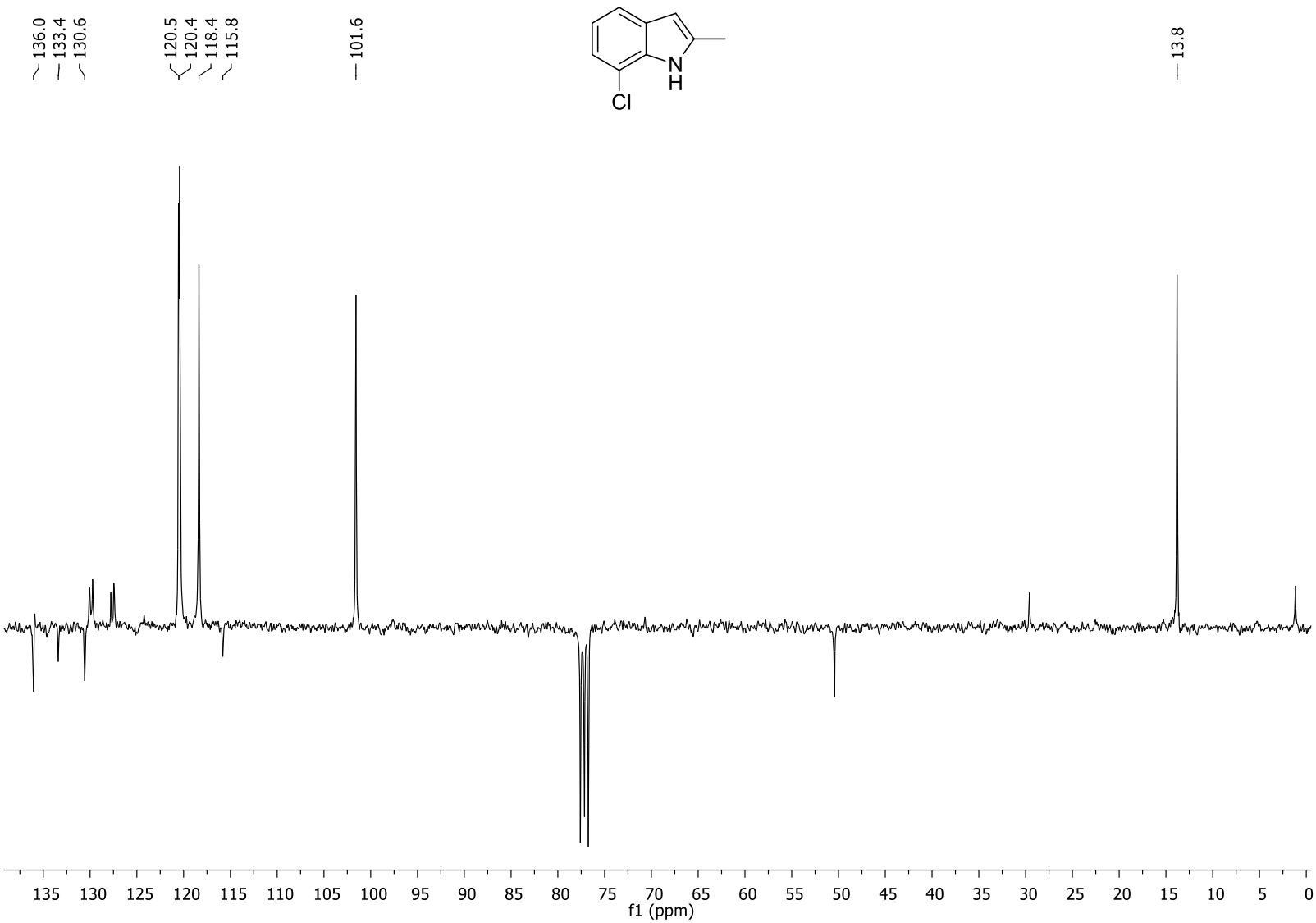
^{1}H NMR of 5-Chloro-2-methyl-1*H*-indole (**2h**).



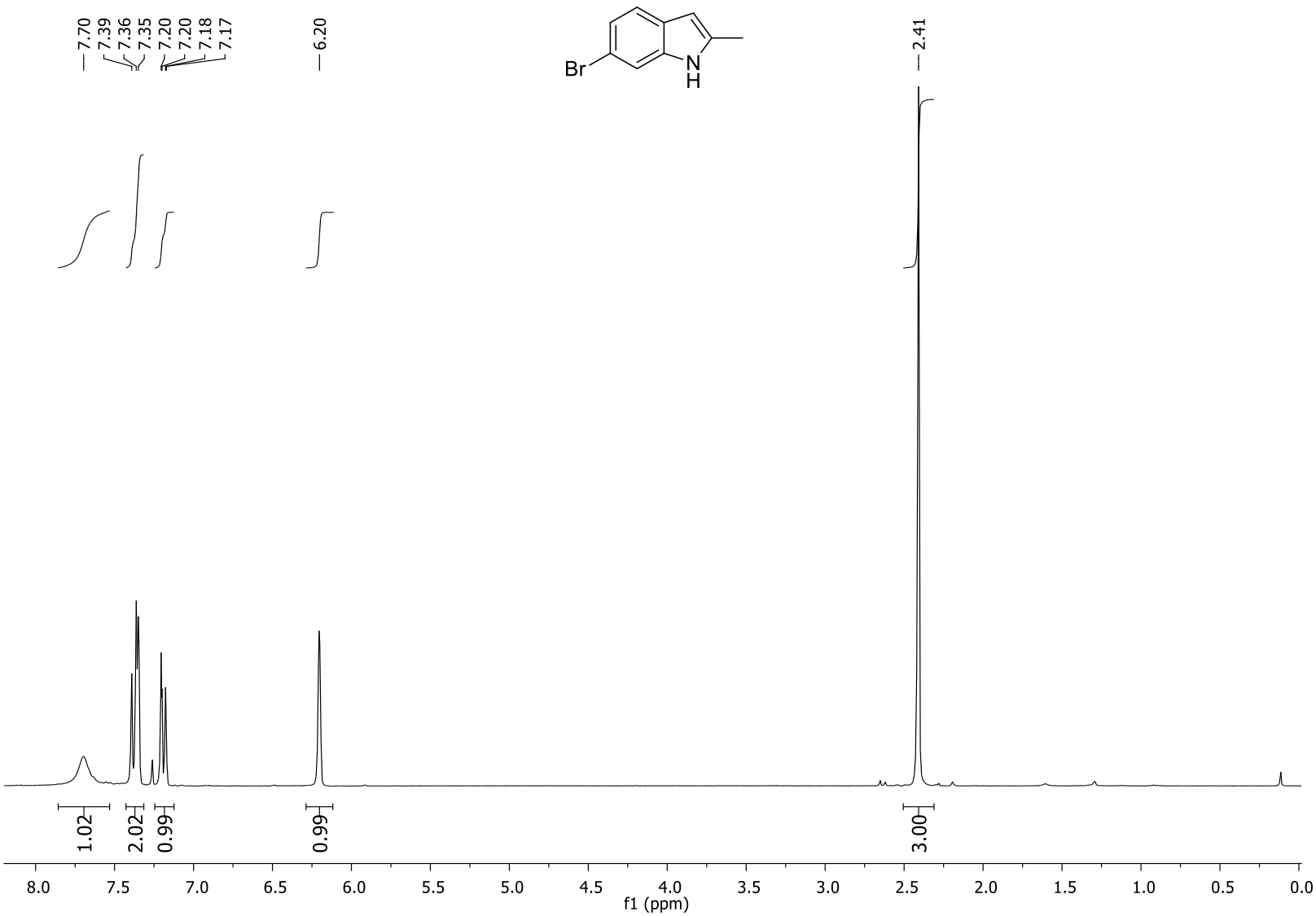
^{13}C APT NMR of 5-Chloro-2-methyl-1*H*-indole(**2h**).



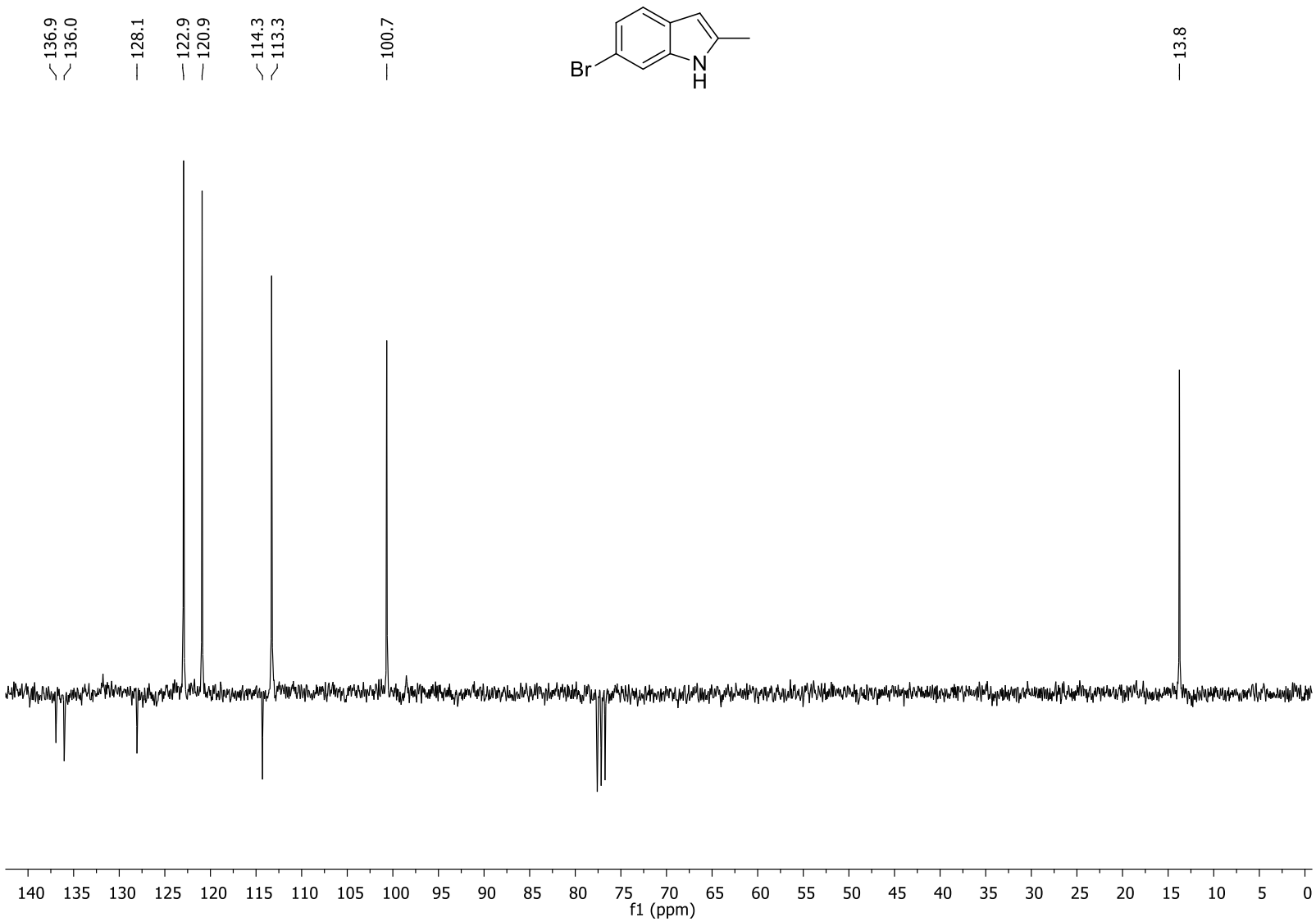
^{1}H NMR of 7-Chloro-2-methyl-1*H*-indole(**2h'**).



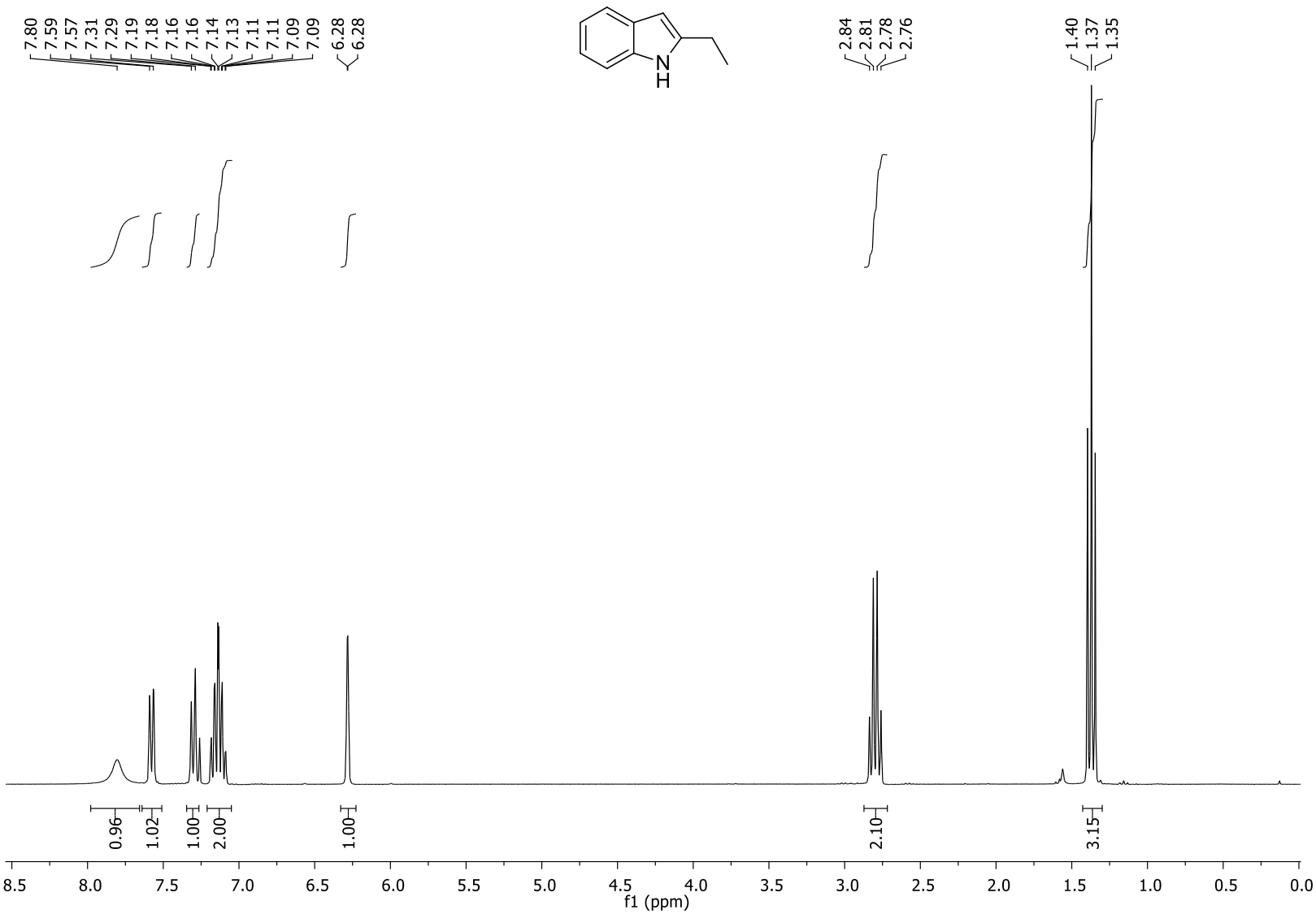
^{13}C APT NMR of 7-Chloro-2-methyl-1*H*-indole (**2h'**).



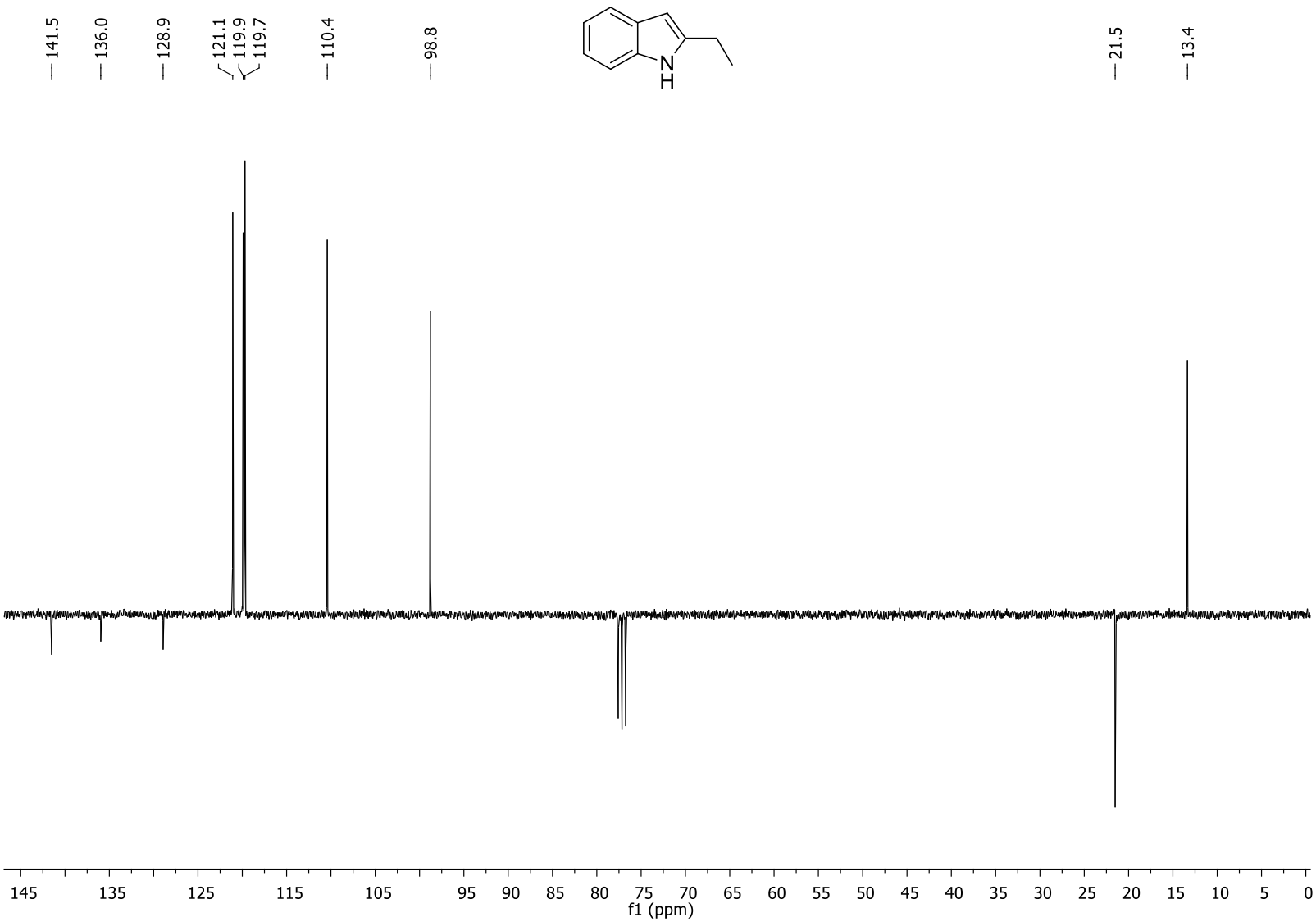
^{1}H NMR of 6-bromo-2-methyl-1*H*-indole (**2j**).



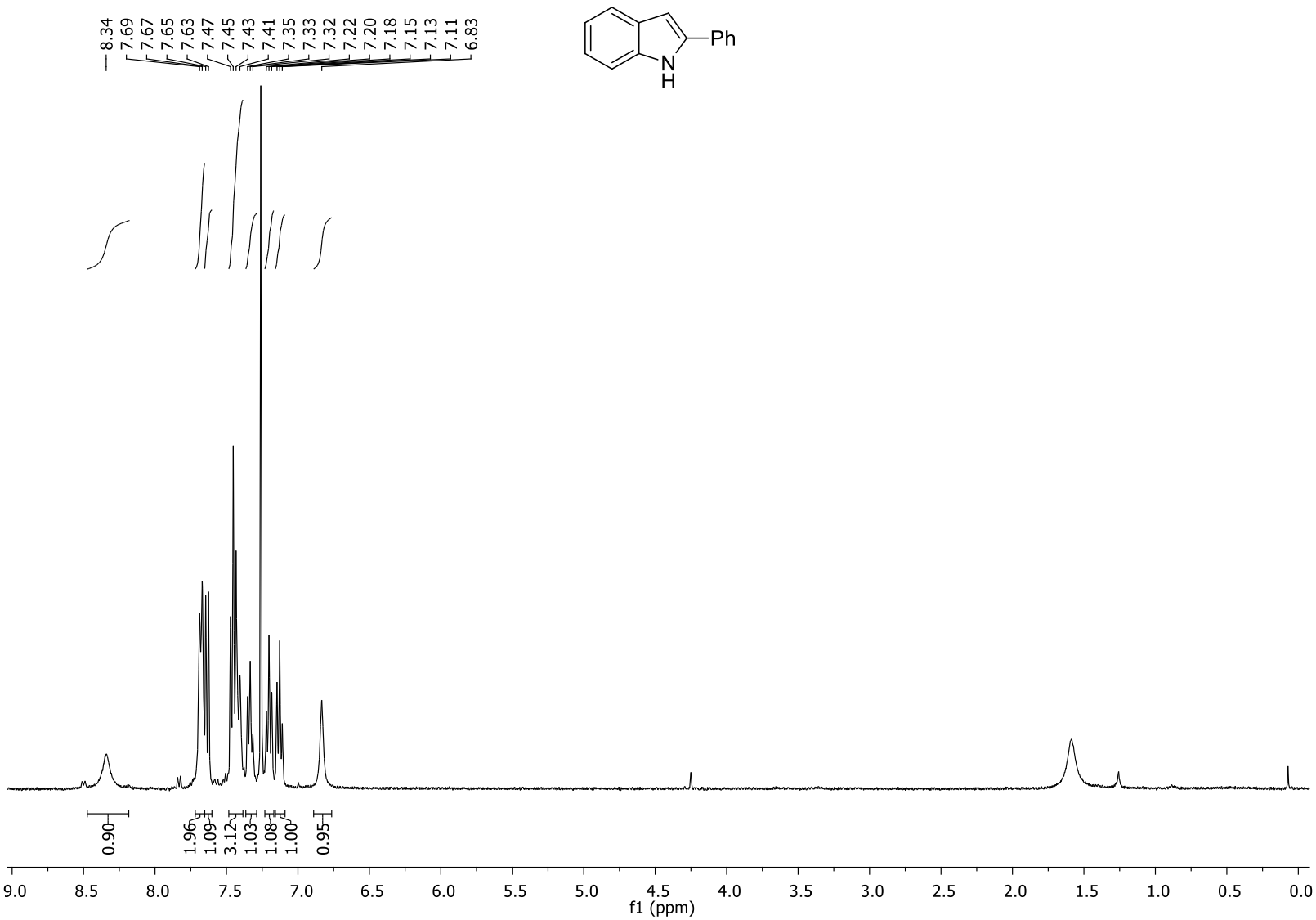
^{13}C APT NMR of 6-bromo-2-methyl-1*H*-indole (**2j**).



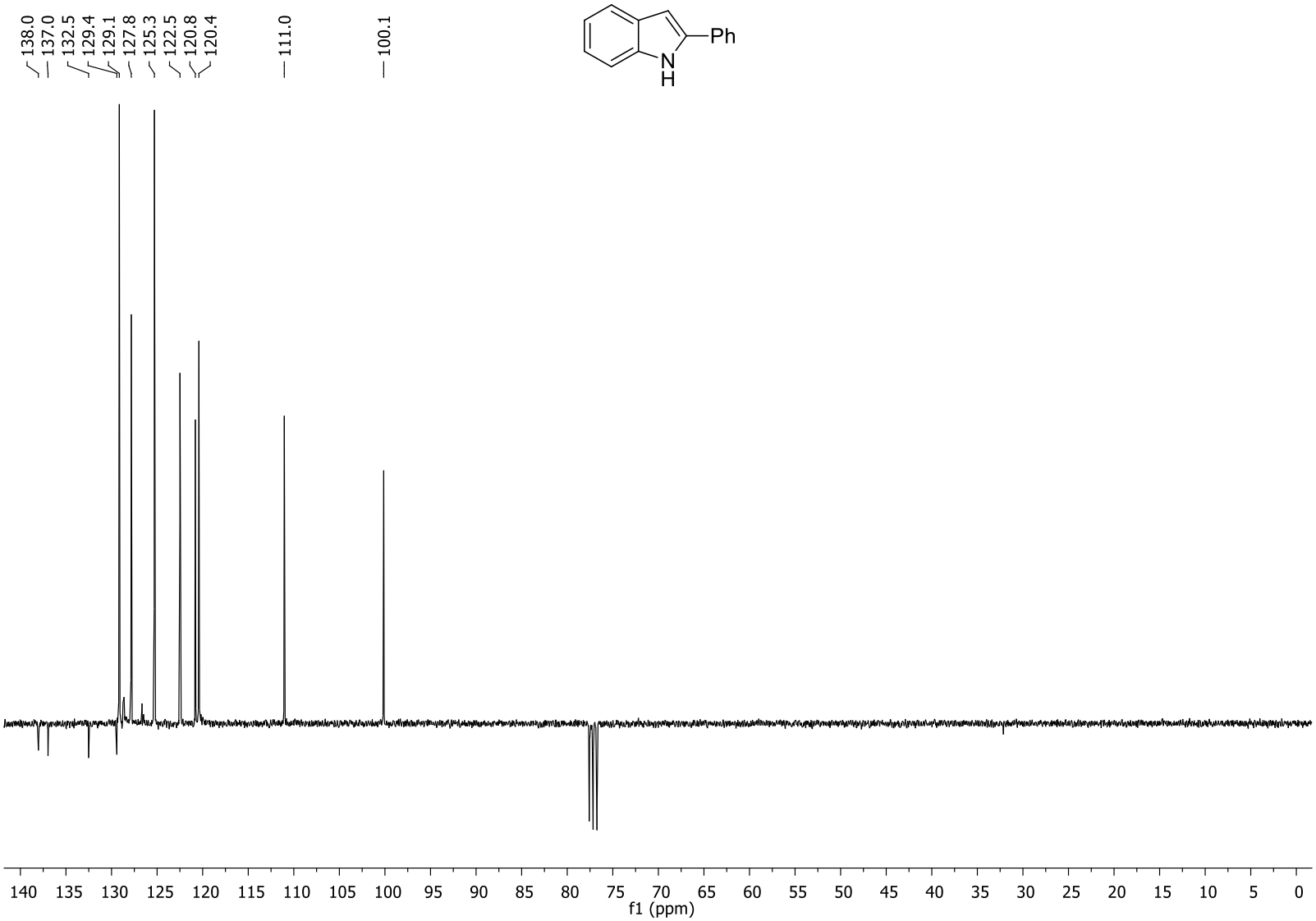
^{1}H NMR of 2-ethyl-1*H*-indole (**2l**).



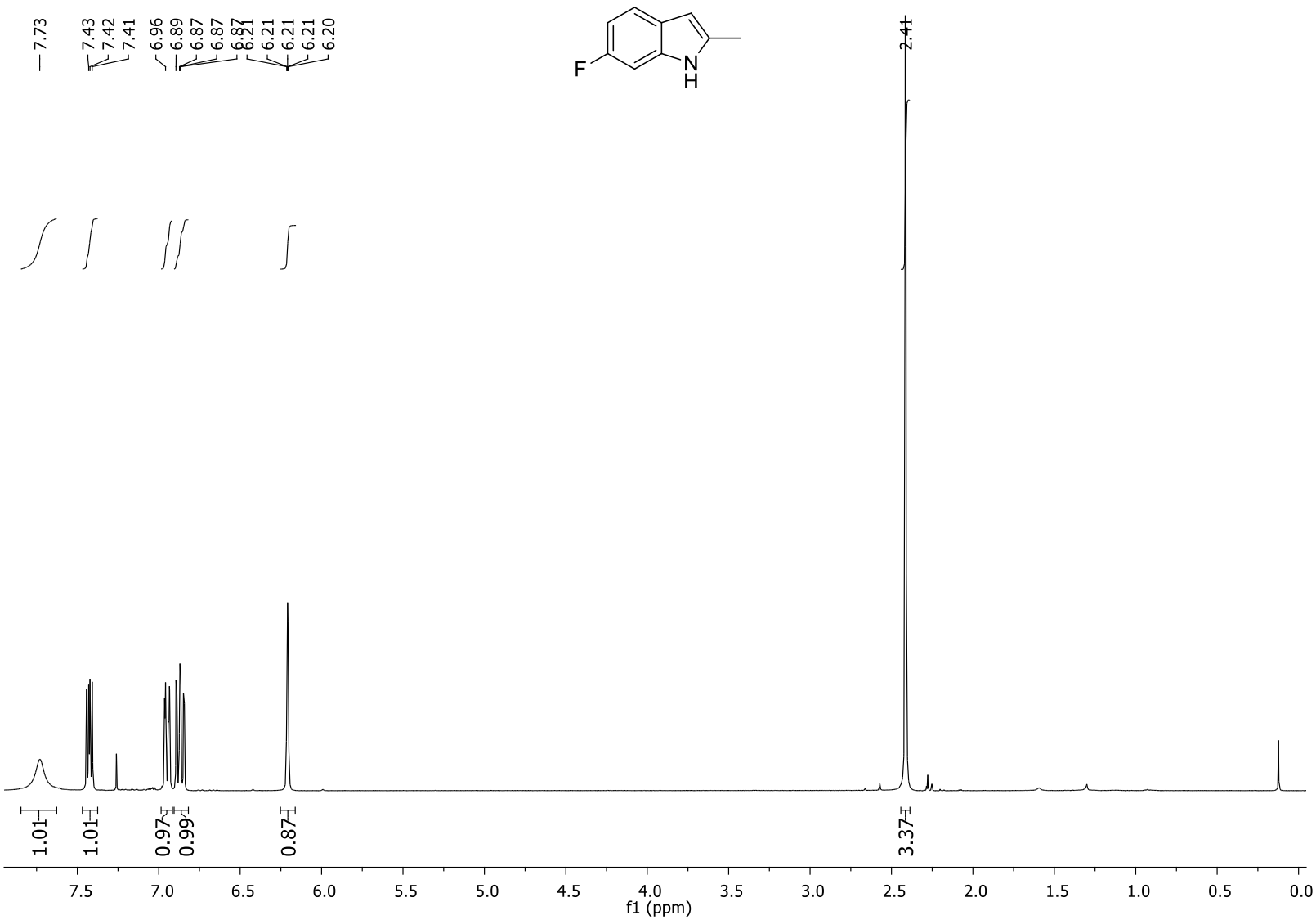
^{13}C APT NMR of 2-ethylindole (**2l**).



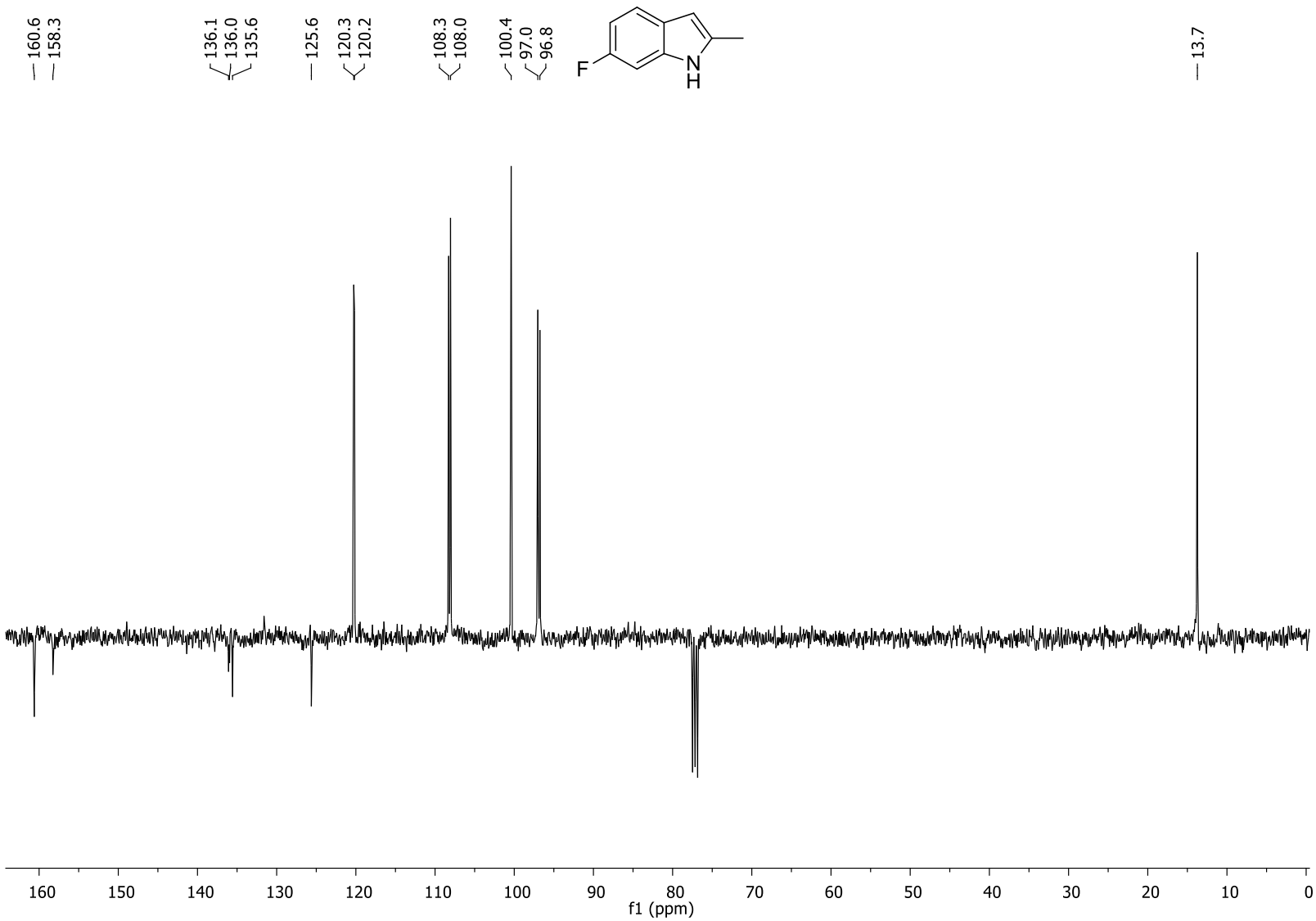
^{1}H NMR of 2-phenyl-1*H*-indole (**2m**).



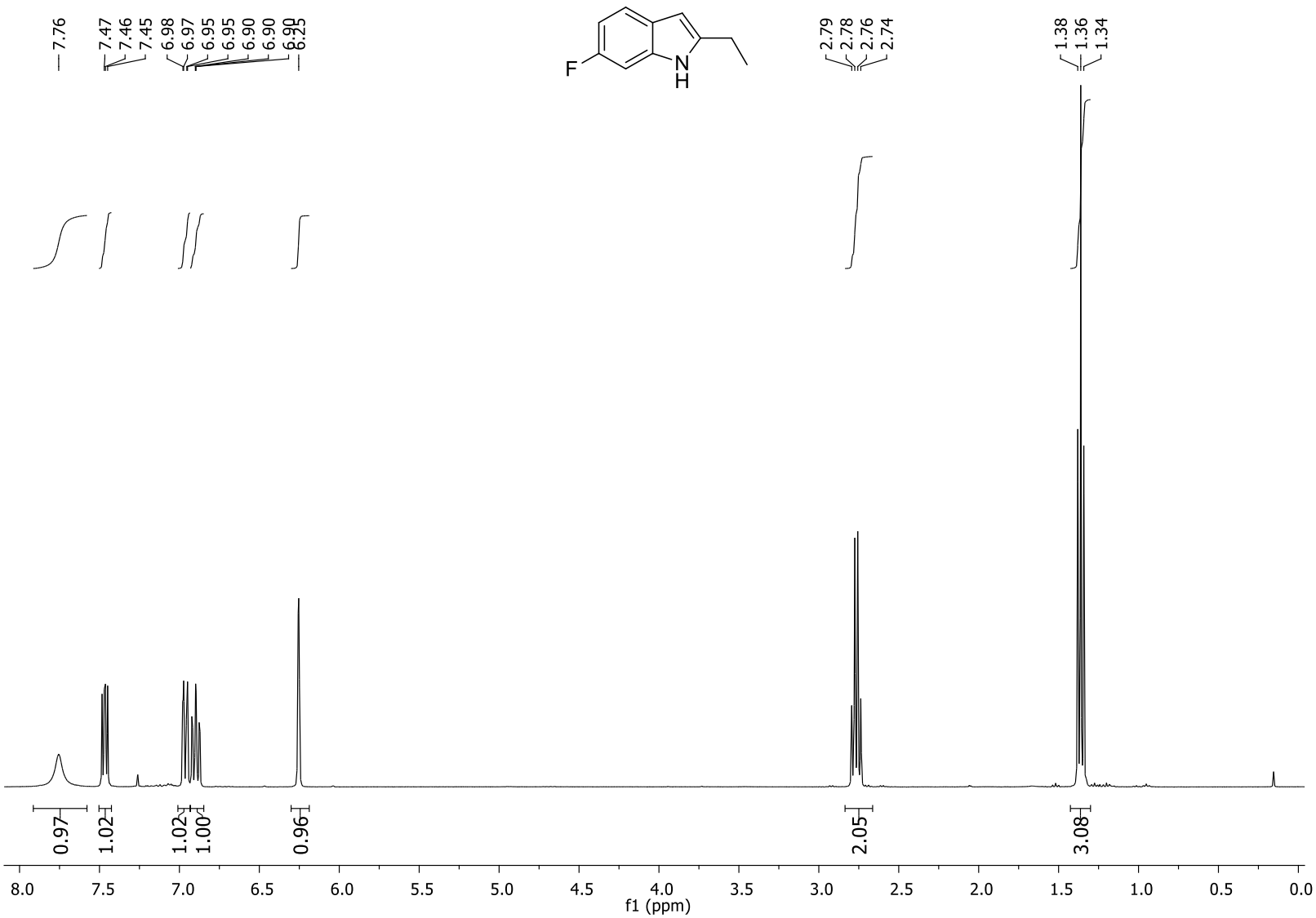
^{13}C APT NMR of 2-phenylindole (**2m**).



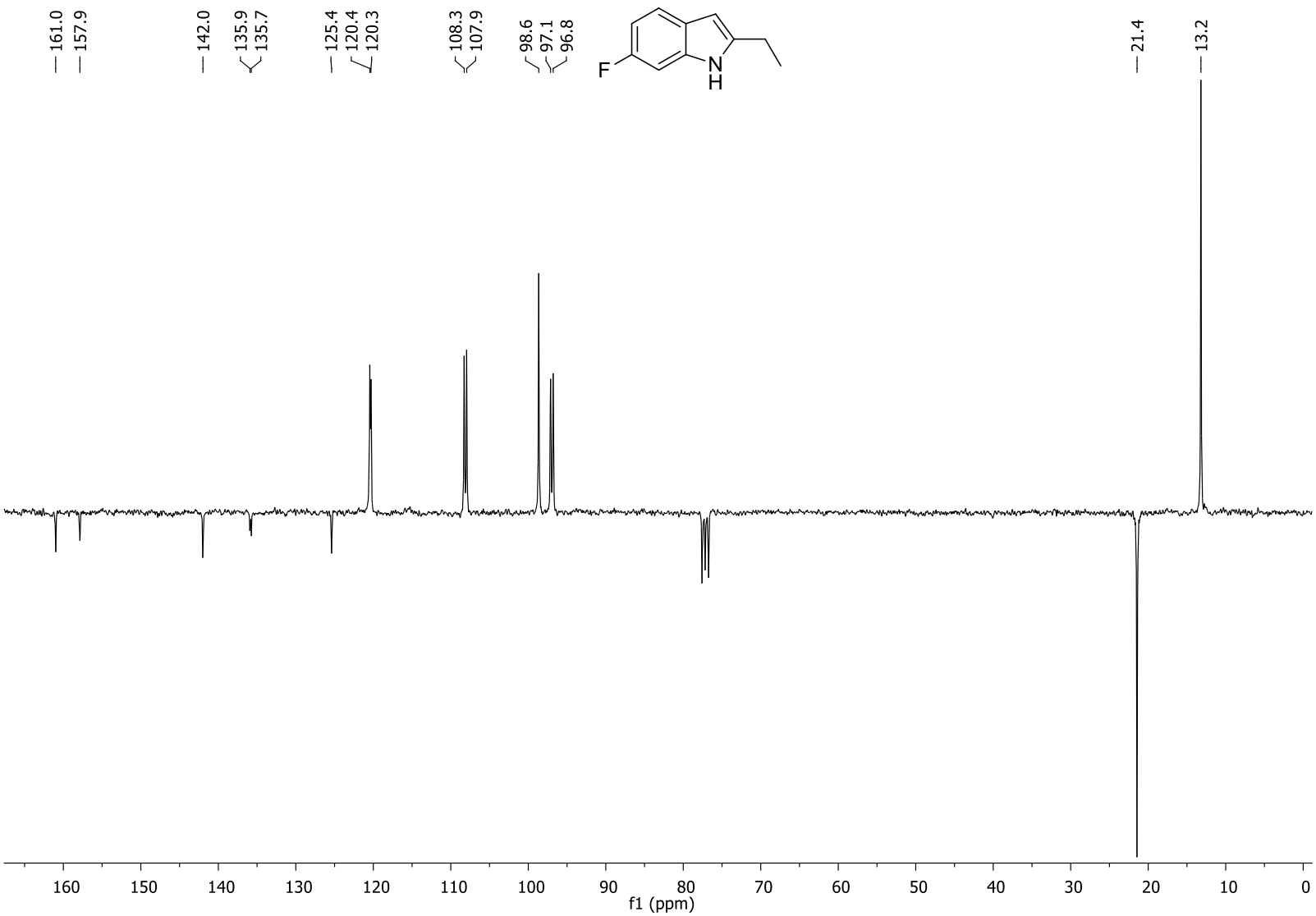
^{1}H NMR of 6-fluoro-2-methyl-1*H*-indole (**2n**).



^{13}C APT NMR of 6-fluoro-2-methyl-1*H*-indole (**2n**).

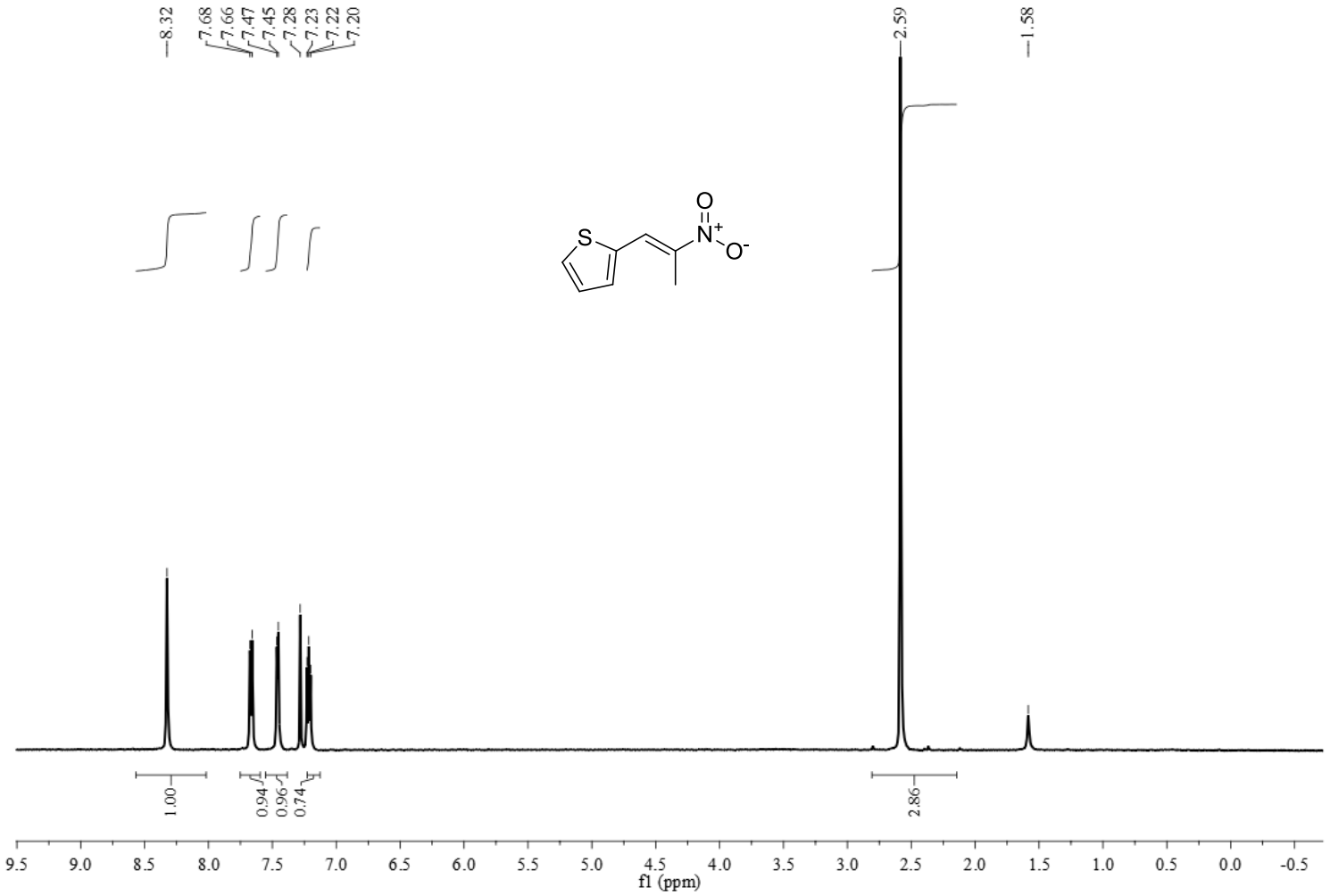


^{1}H NMR of 6-fluoro-2-ethyl-1*H*-indole (**2o**).

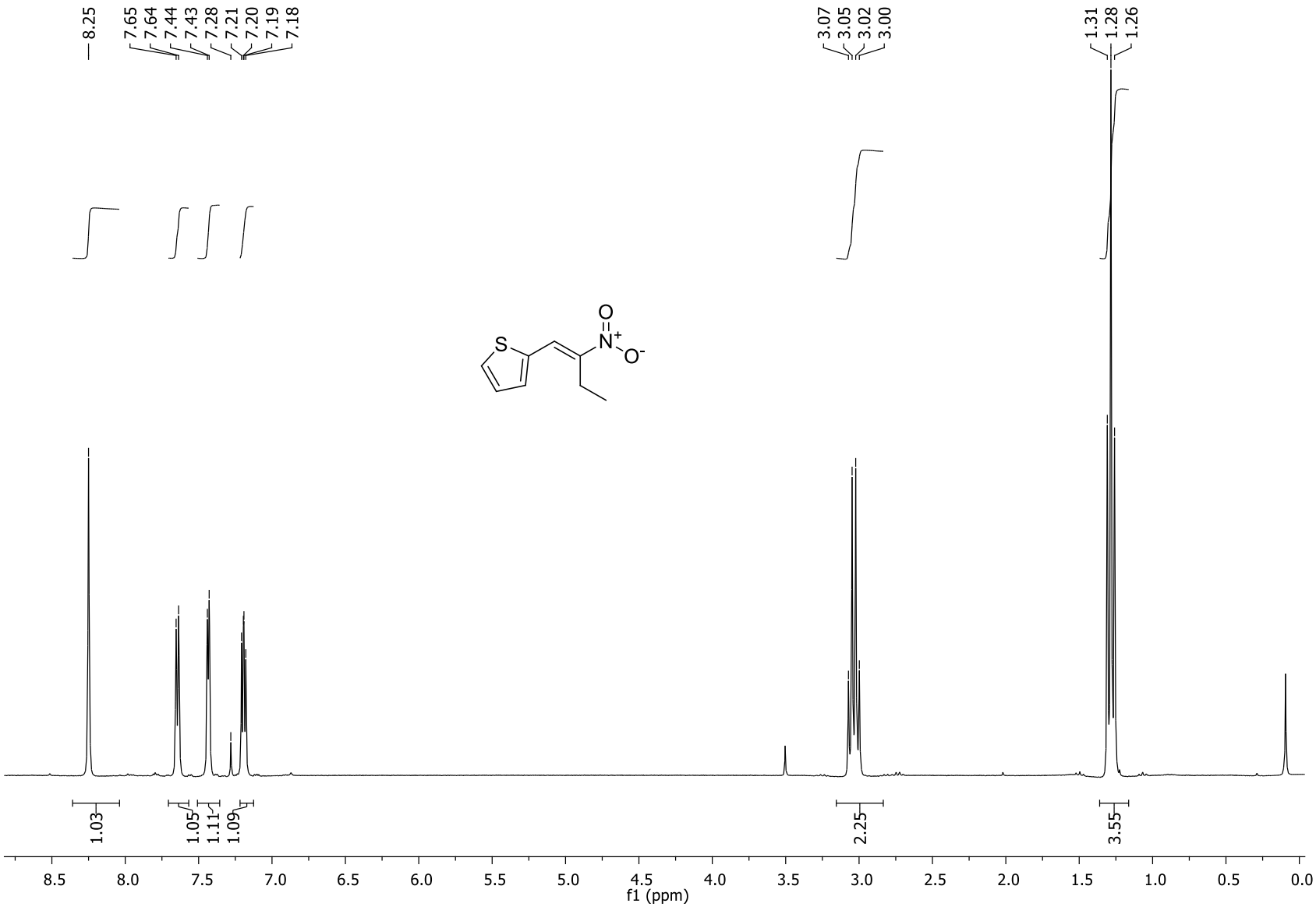


^{13}C APT NMR of 6-fluoro-2-ethyl-1*H*-indole (**2o**).

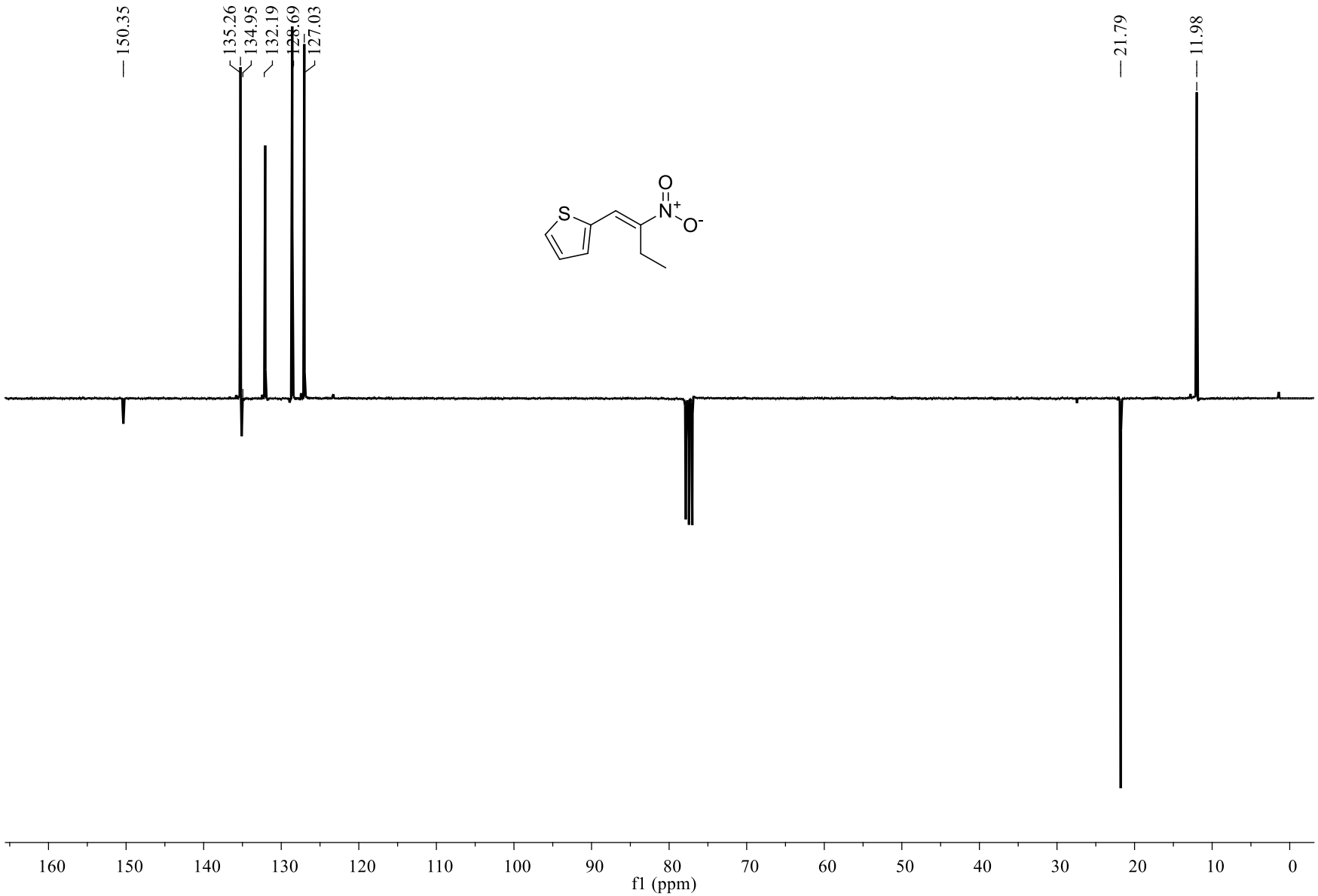
4.2 Appendix B: NMR spectra for thienopyrrole synthesis



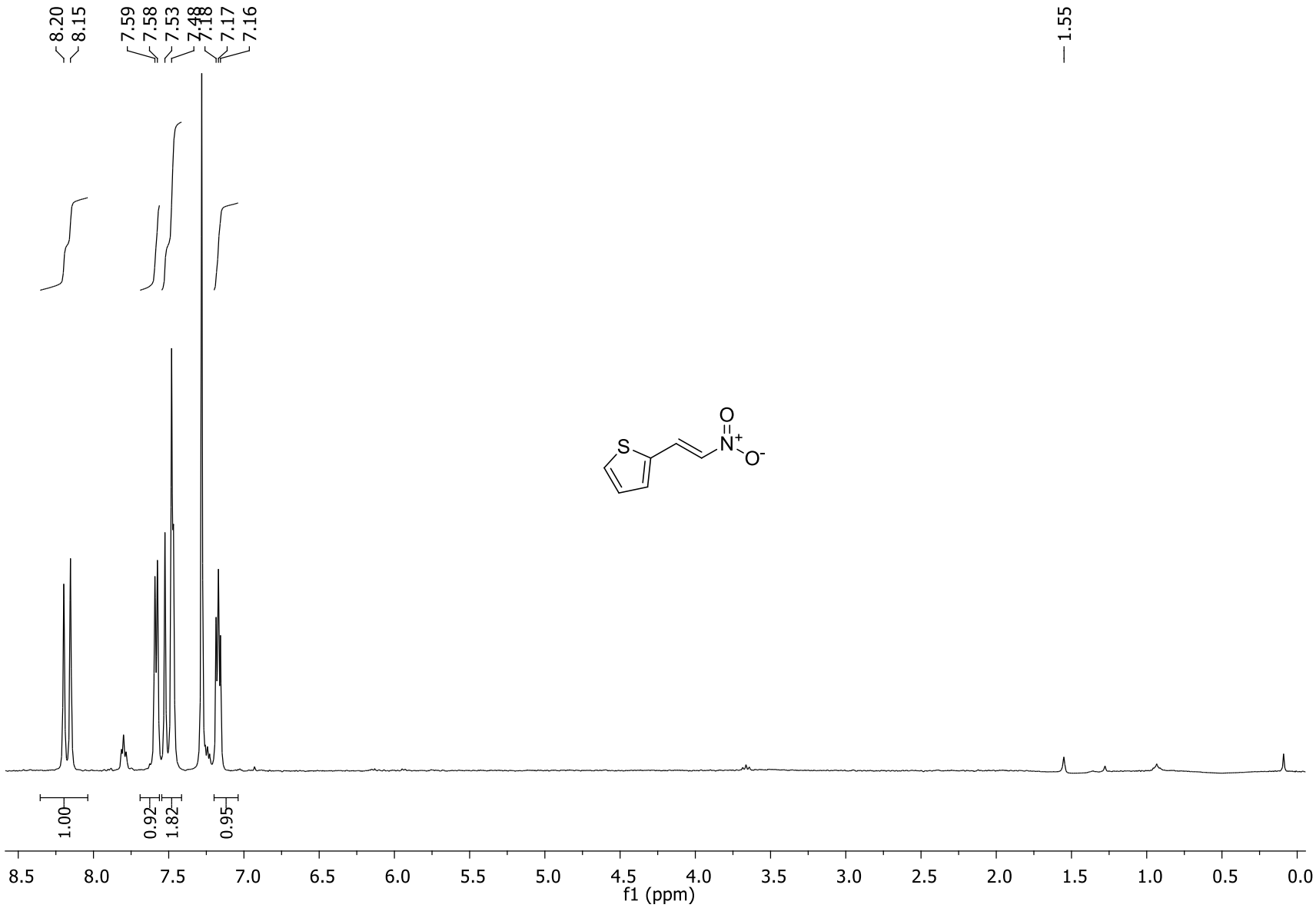
^{1}H NMR of (E)-2-(2-nitroprop-1-en-1-yl)thiophene (**3a**)



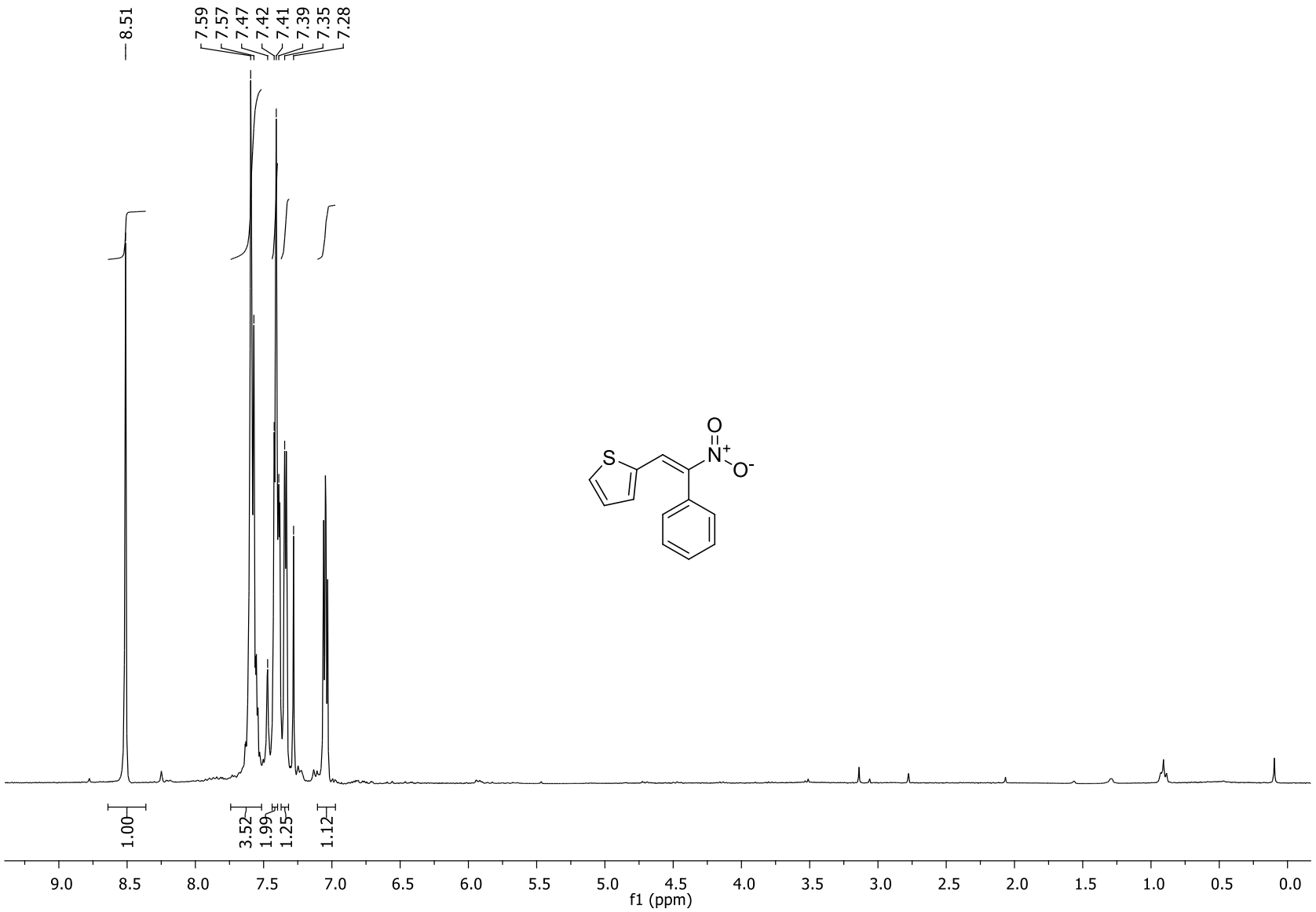
^{1}H NMR of (E)-2-(2-nitrobut-1-en-1-yl)thiophene (**3b**)



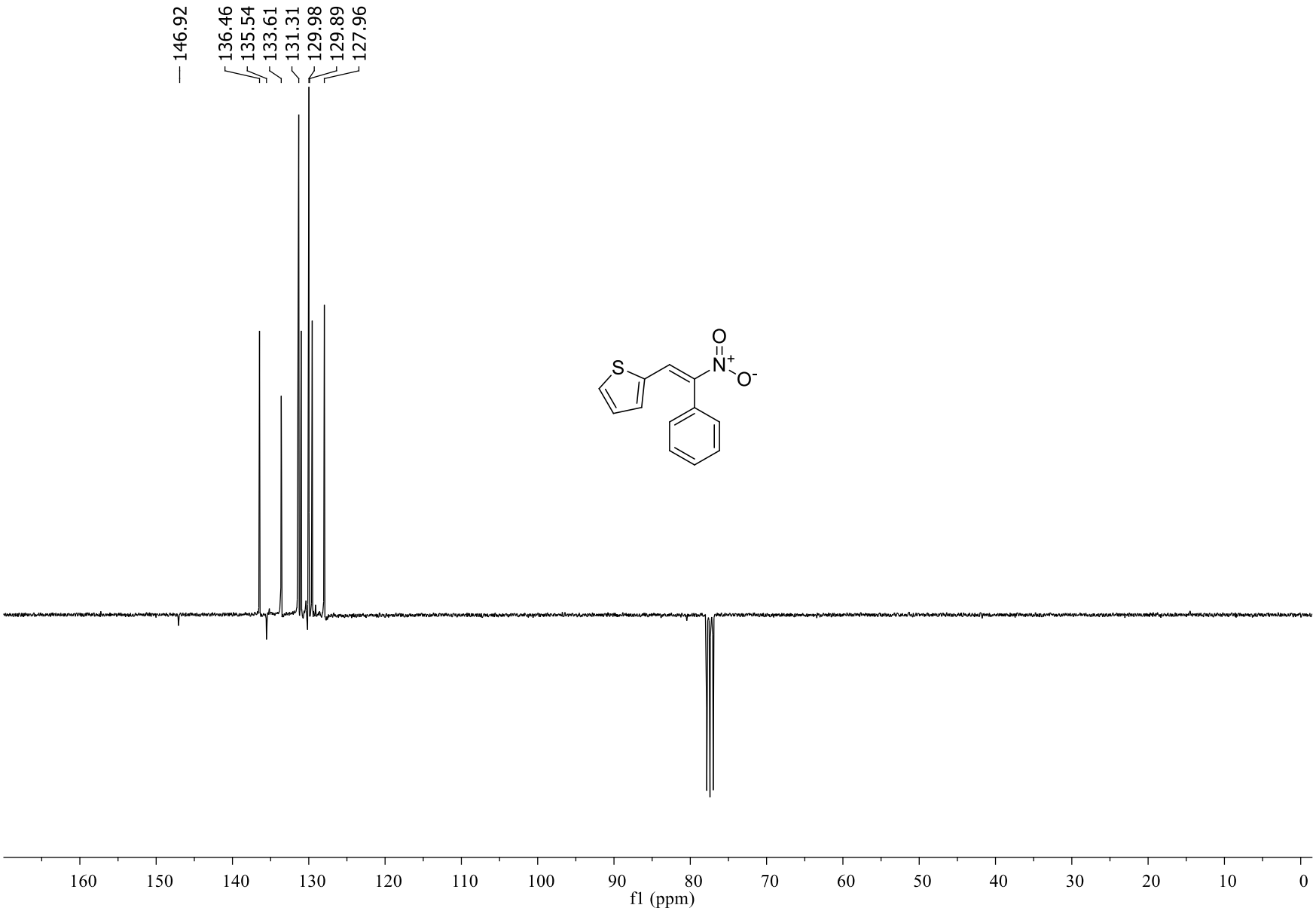
^{13}C APT NMR of (E)-2-(2-nitrobut-1-en-1-yl)thiophene(**3b**)



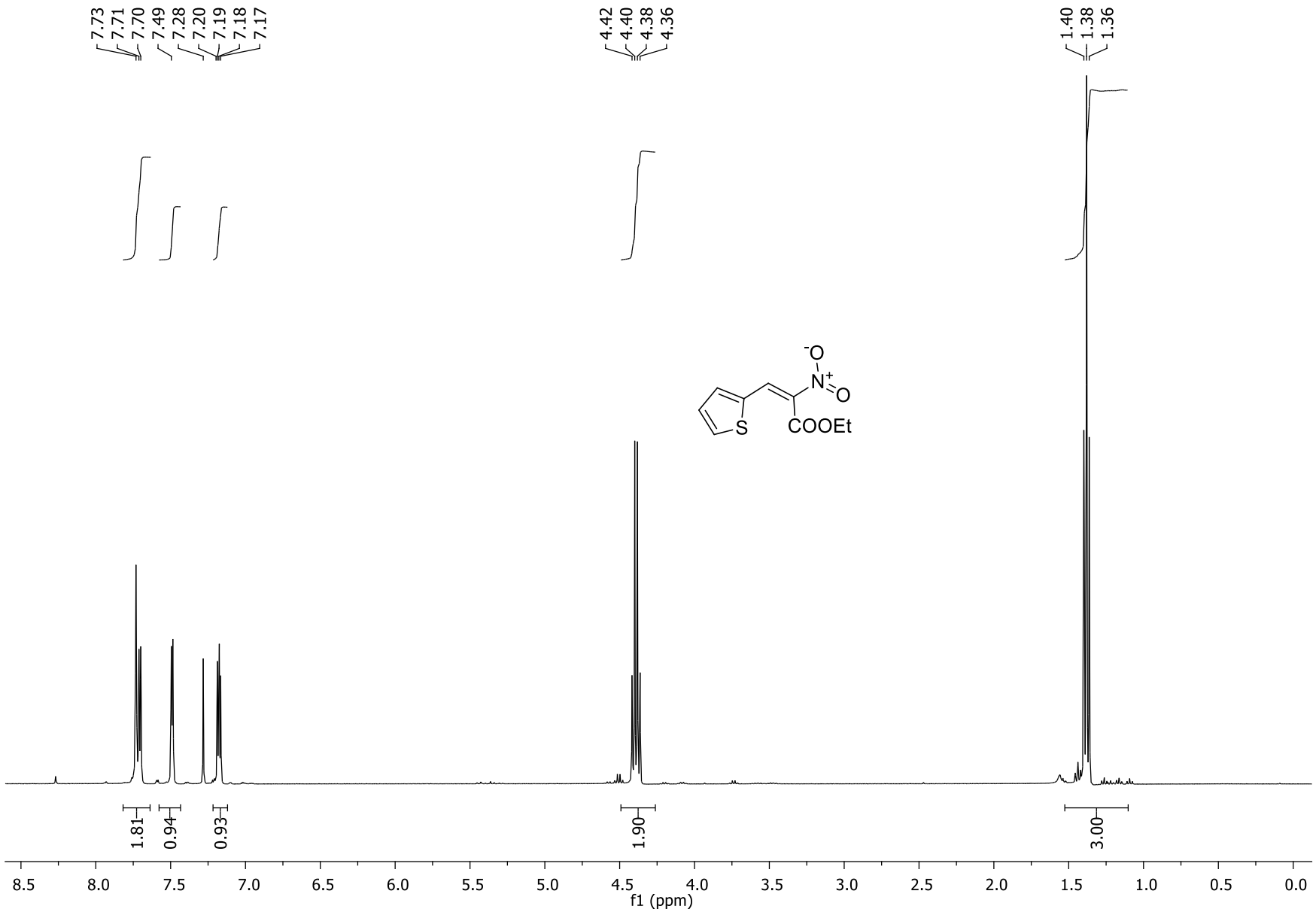
^{1}H NMR of (E)-2-(2-nitrovinyl)thiophene (**3c**)



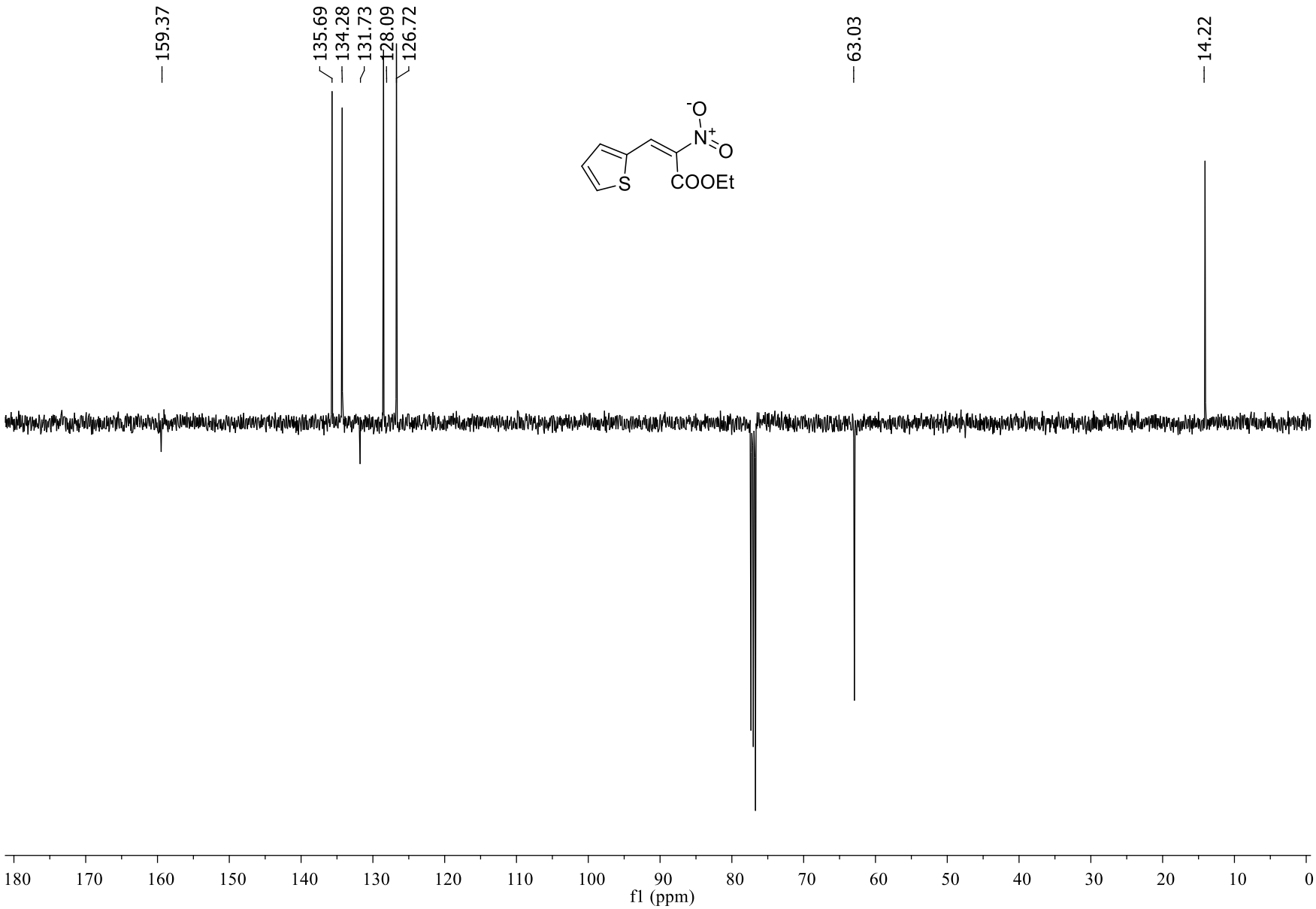
^{1}H NMR of (E)-2-(2-nitro-2-phenylvinyl)thiophene (**3d**)



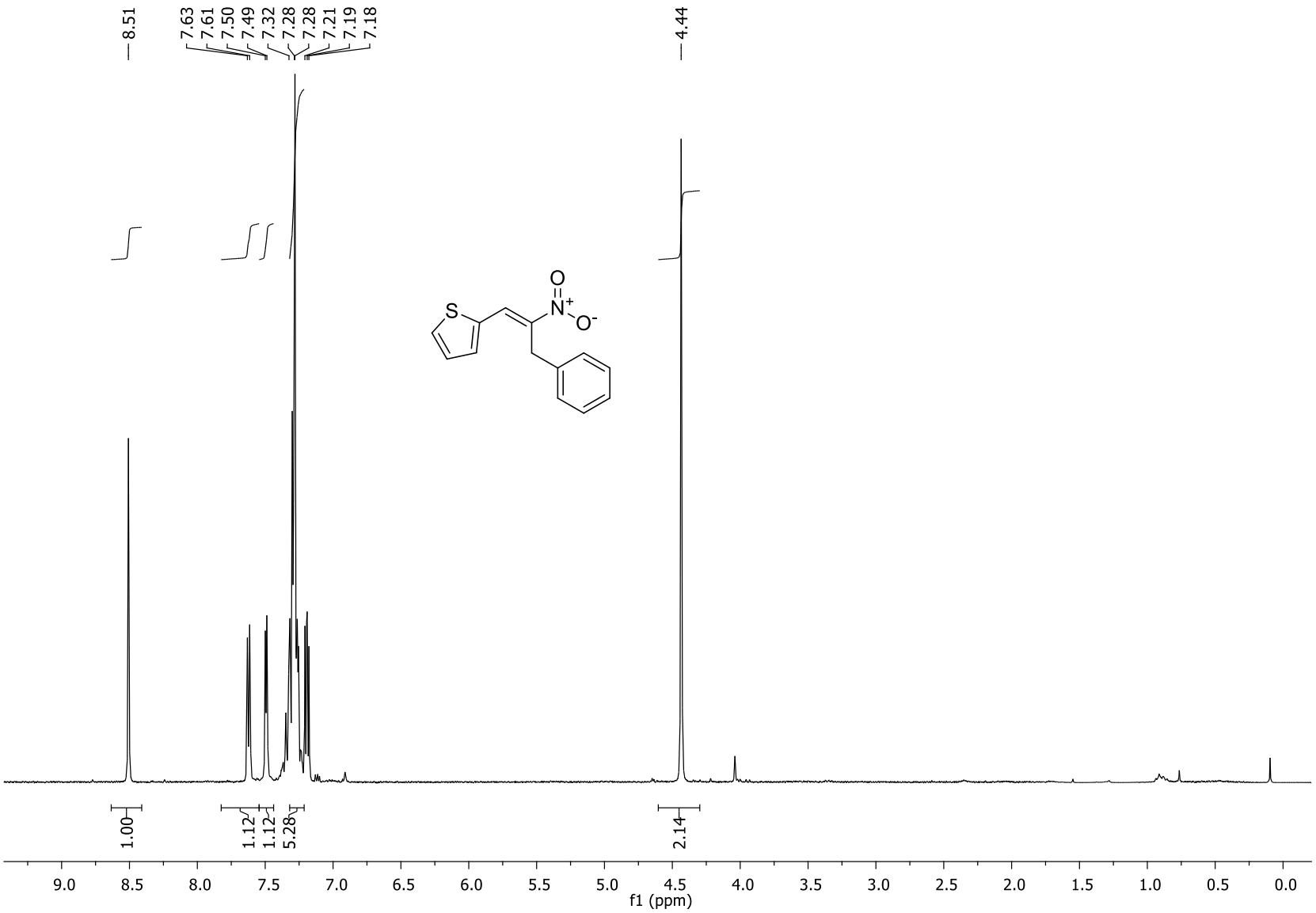
^{13}C APT NMR of (E)-2-(2-nitro-2-phenylvinyl)thiophene (**3d**)



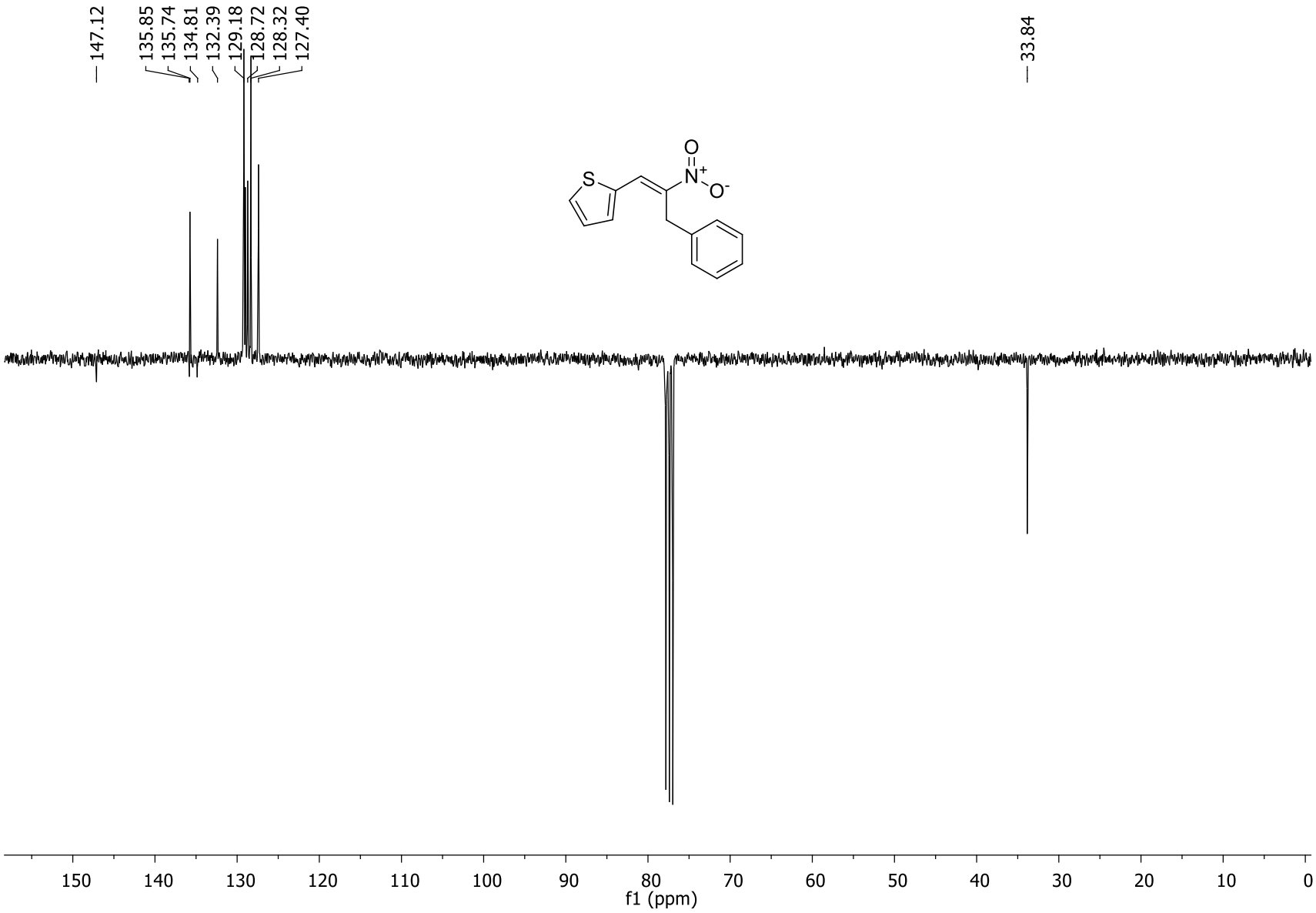
^{1}H NMR of (Z)-ethyl 2-nitro-3-(thiophen-2-yl)acrylate (**3e**)



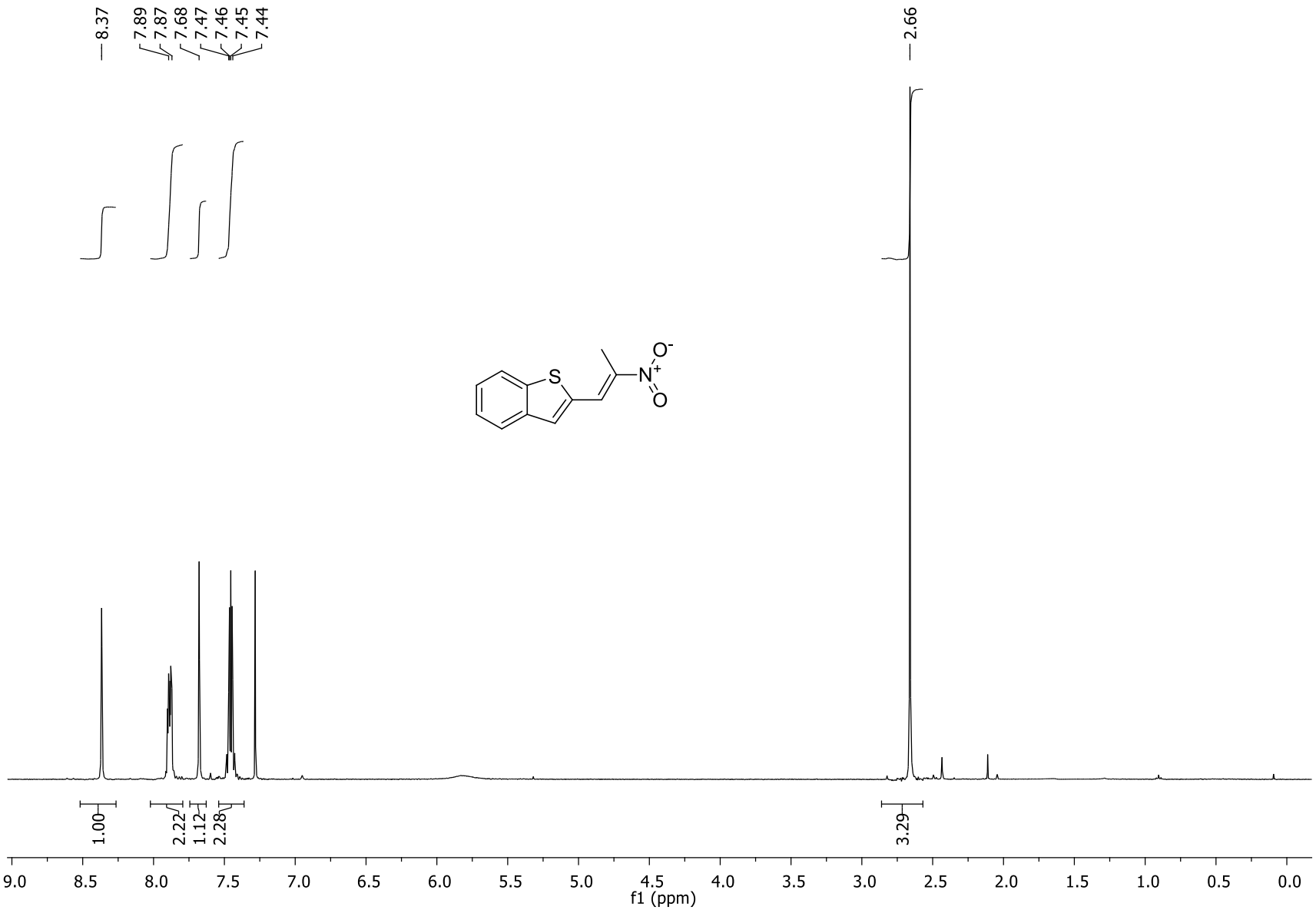
^{13}C APT NMR of (Z)-ethyl 2-nitro-3-(thiophen-2-yl)acrylate (**3e**)



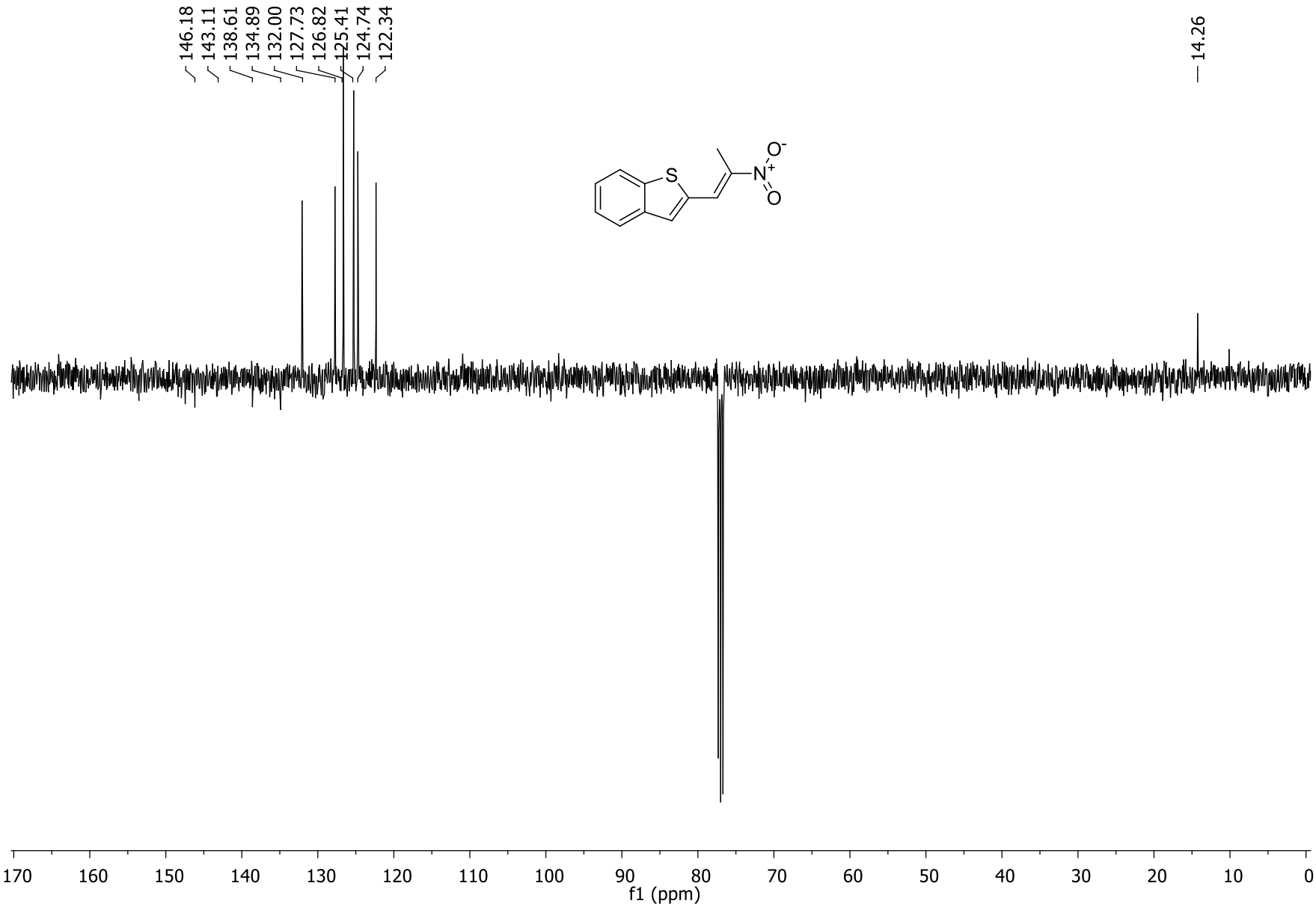
^{1}H NMR of (E)-2-(2-nitro-3-phenylprop-1-en-1-yl)thiophene(**3f**)



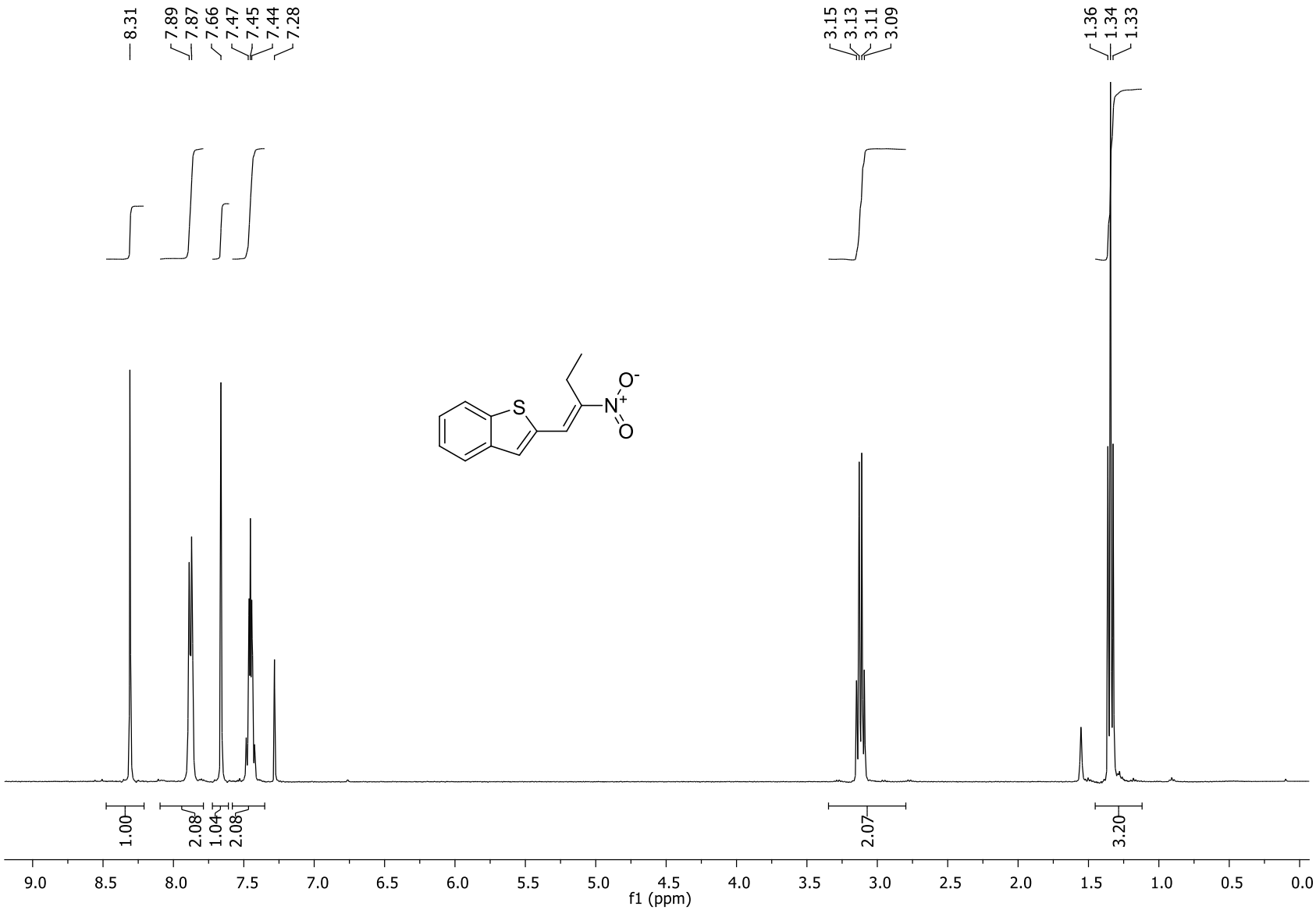
^{13}C APT H NMR of (E)-2-(2-nitro-3-phenylprop-1-en-1-yl)thiophene(**3f**)



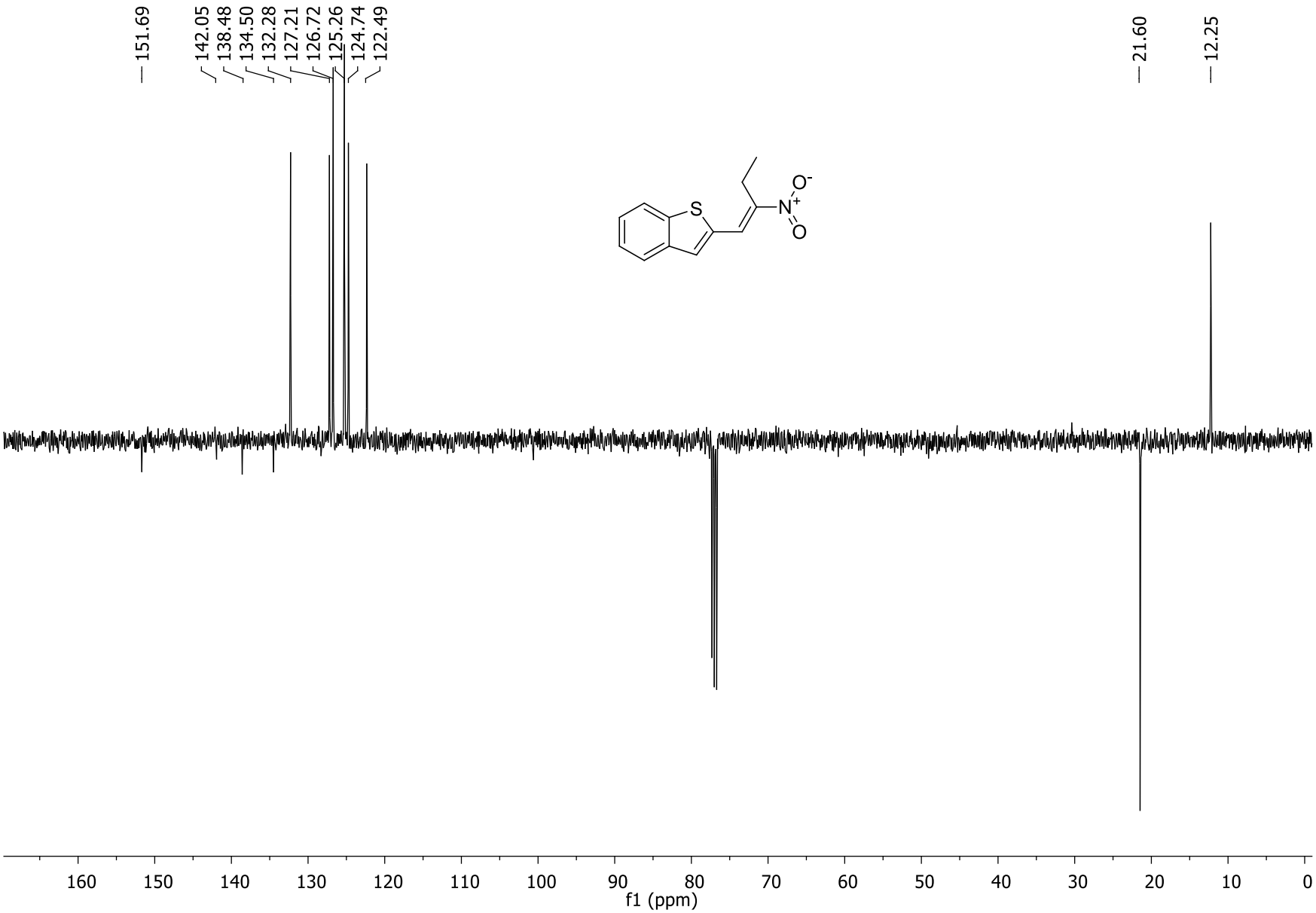
^{1}H NMR of (E)-2-(2-nitroprop-1-en-1-yl)benzo[b]thiophene (**3g**)



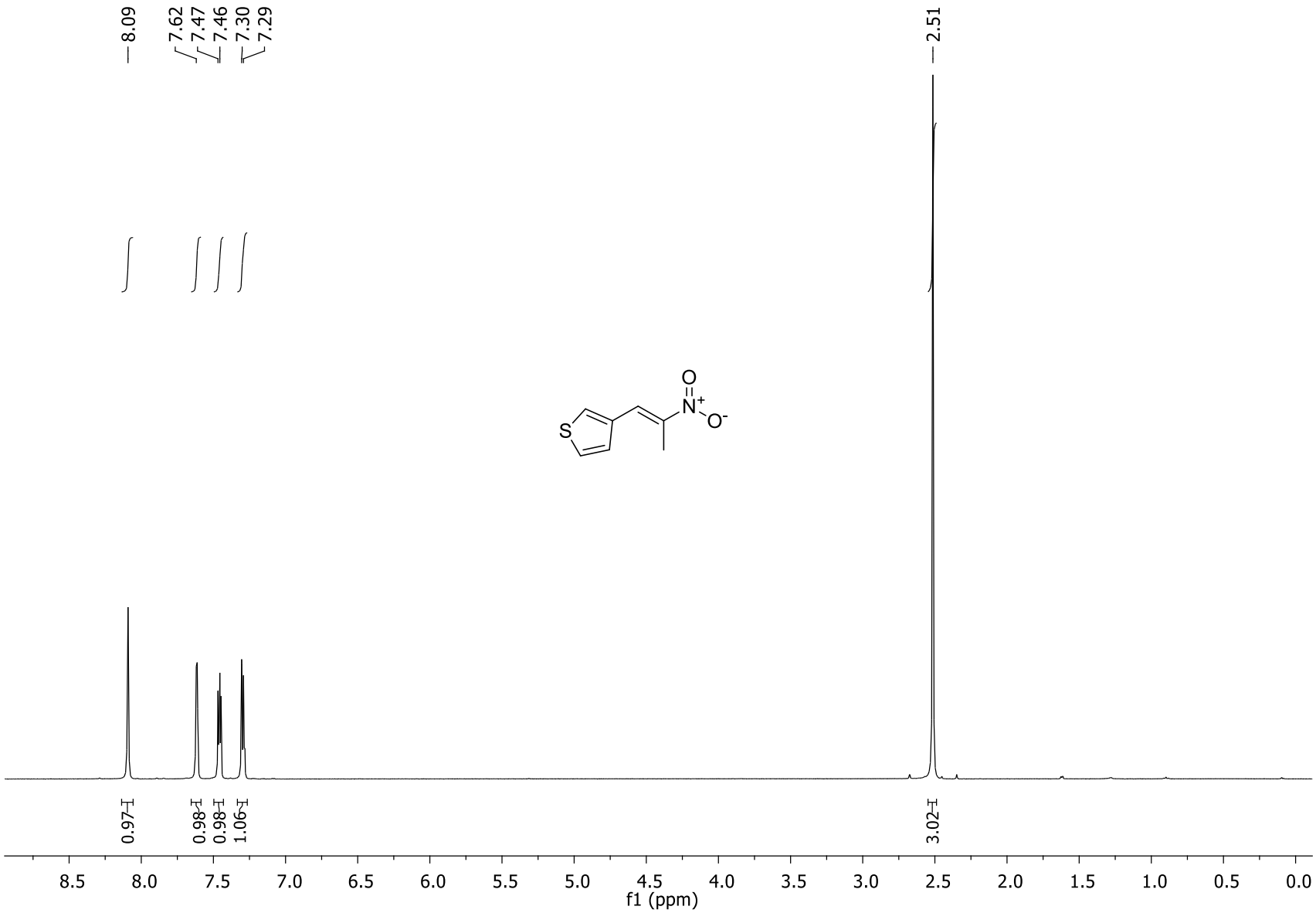
^{13}C APT NMR of (E)-2-(2-nitroprop-1-en-1-yl)benzo[b]thiophene (**3g)**



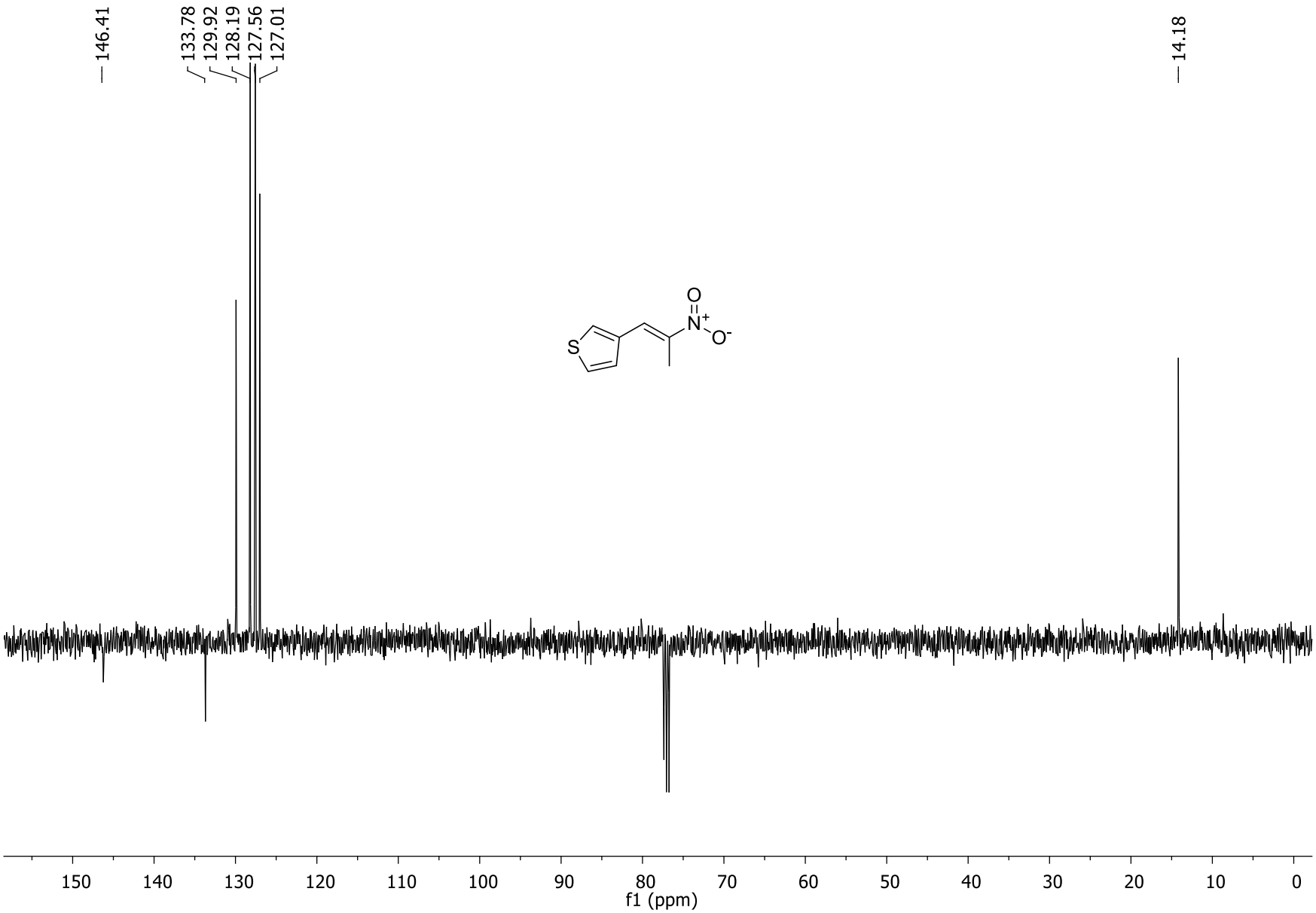
^{1}H NMR of (E)-2-(2-nitrobut-1-en-1-yl)benzo[b]thiophene(**3h**)



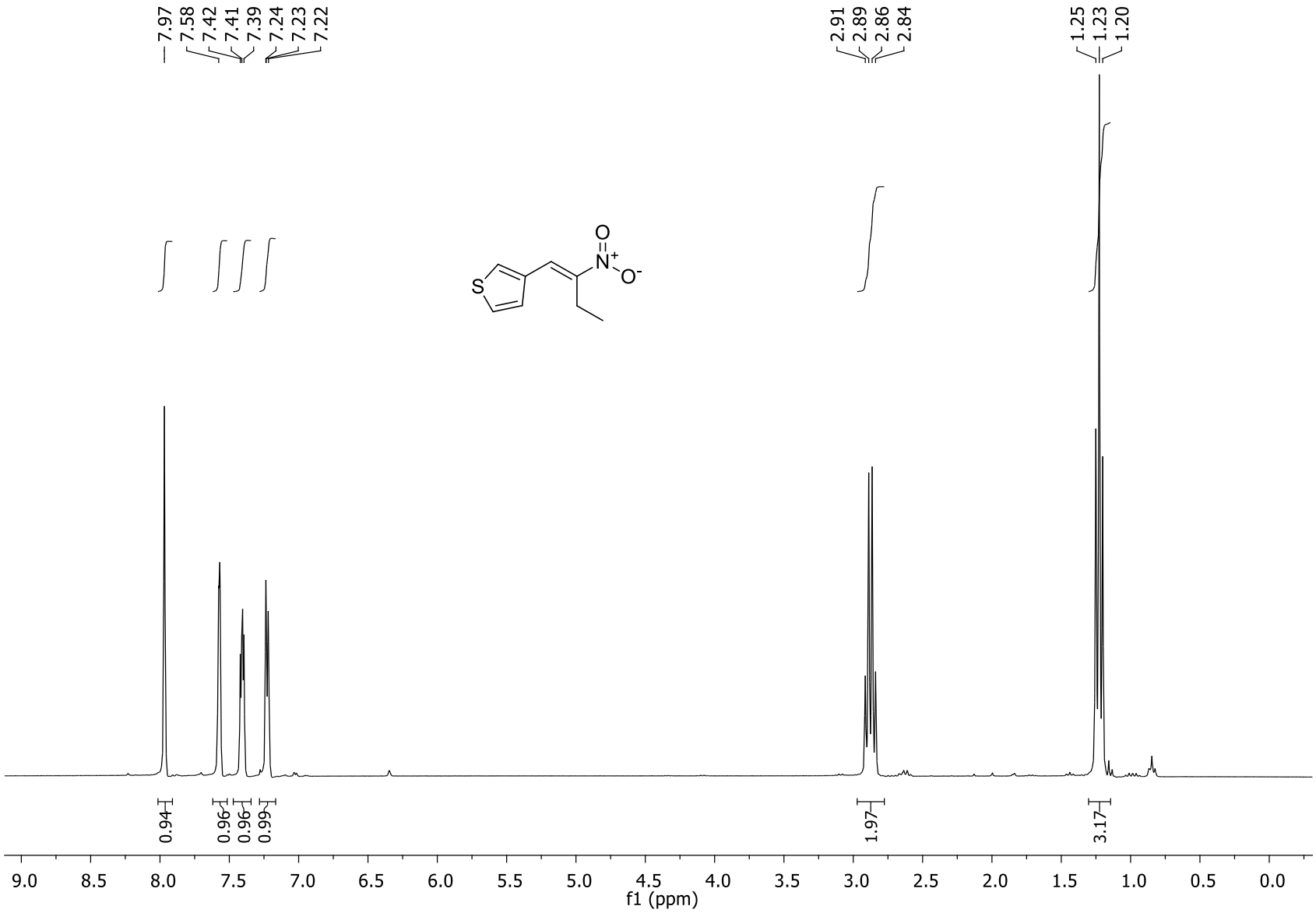
^{13}C APT NMR of (E)-2-(2-nitrobut-1-en-1-yl)benzo[b]thiophene(**3h)**



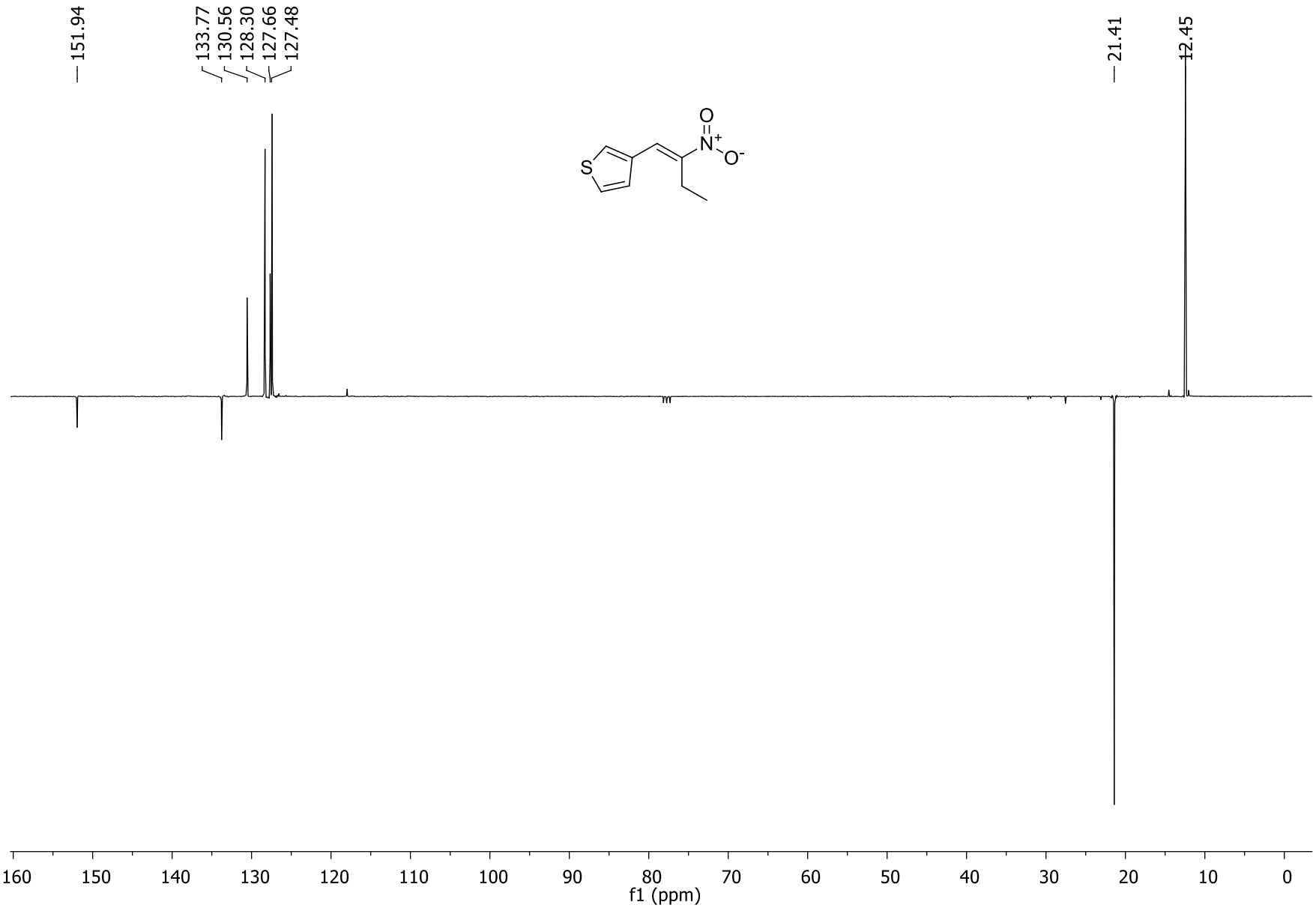
^{1}H NMR of (E)-3-(2-nitroprop-1-en-1-yl)thiophene (**3i**)



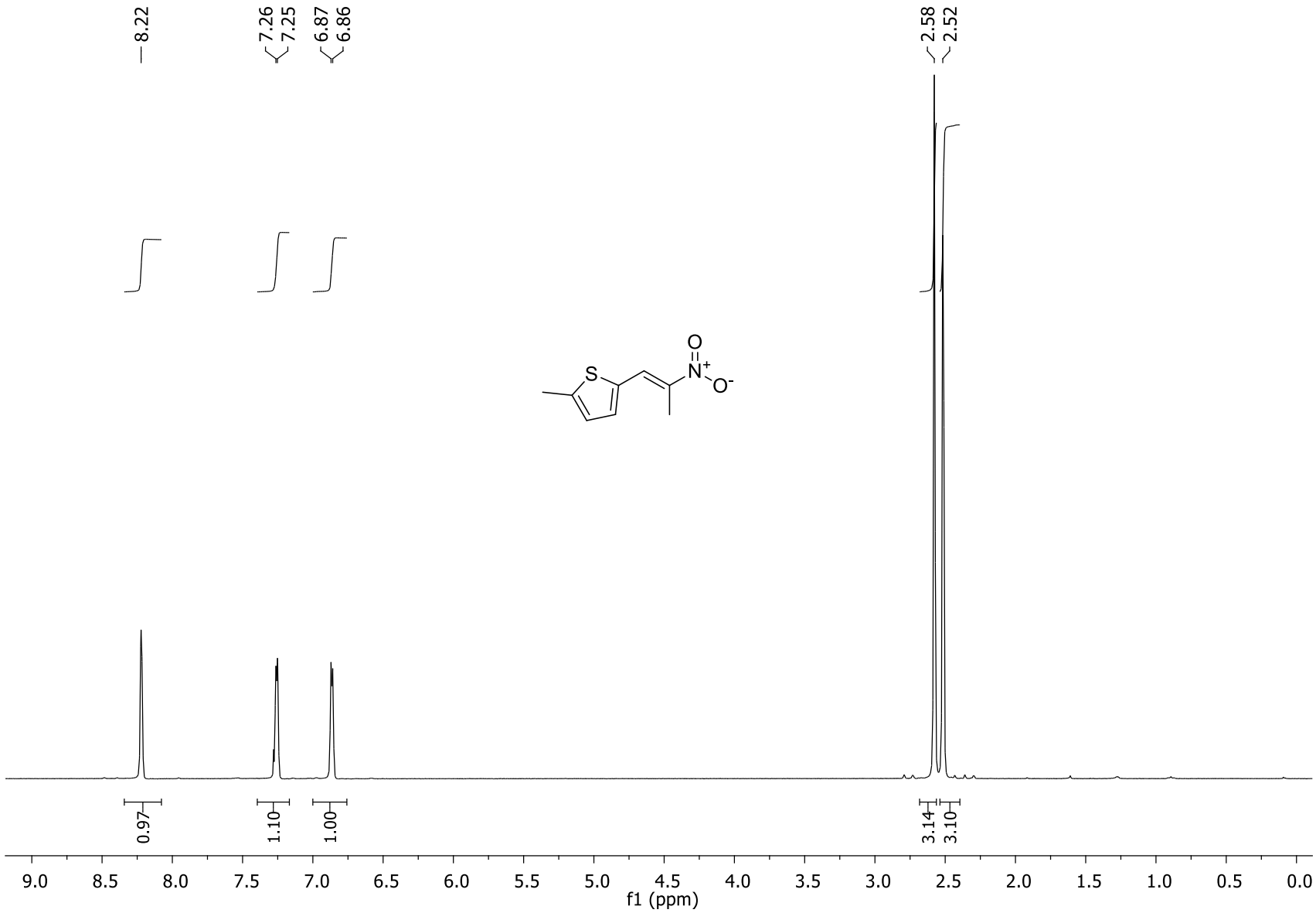
^{13}C APT NMR of (E)-3-(2-nitroprop-1-en-1-yl)thiophene (**3i**)



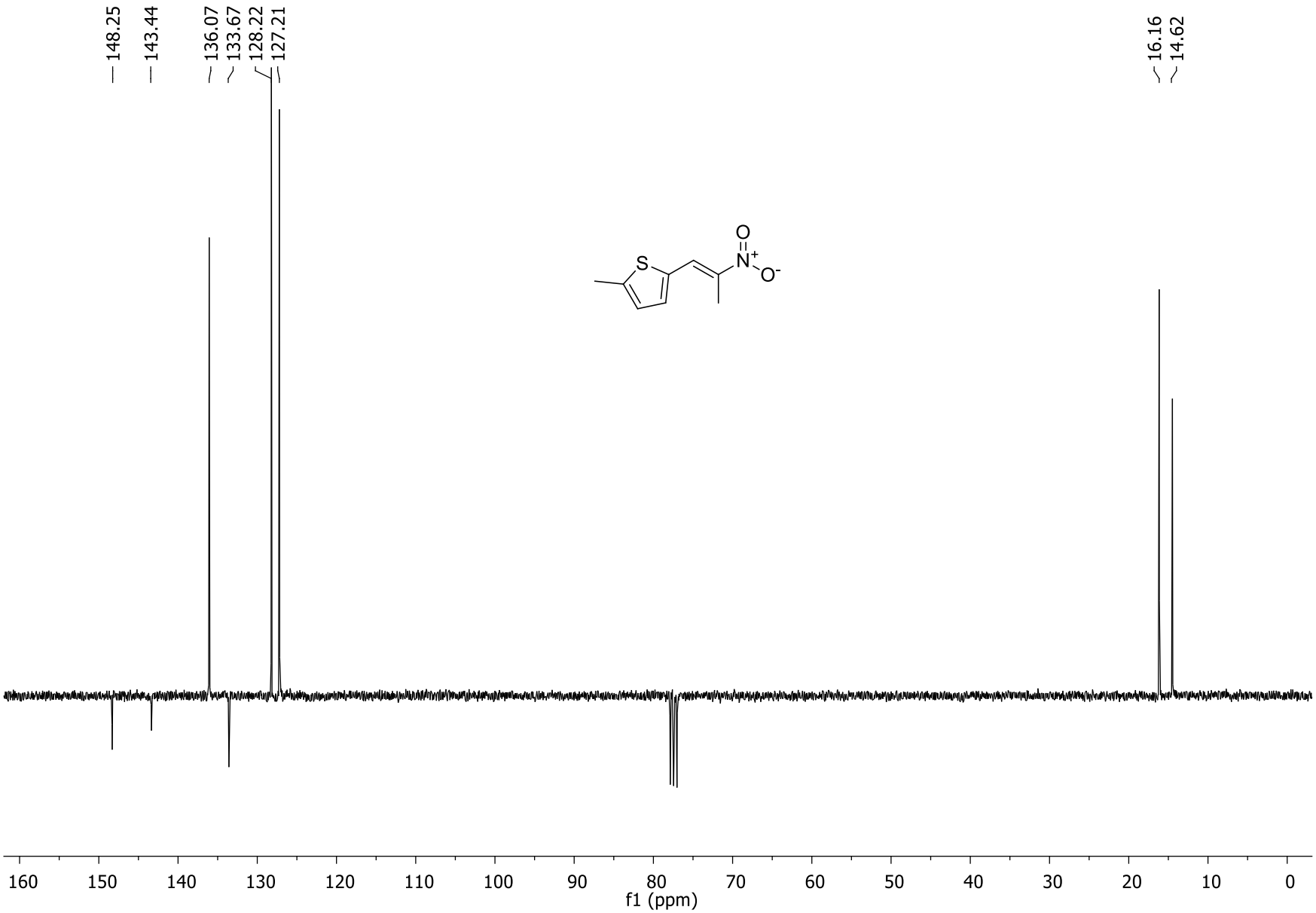
^{1}H NMR of (E)-3-(2-nitrobut-1-en-1-yl)thiophene(**3j**)



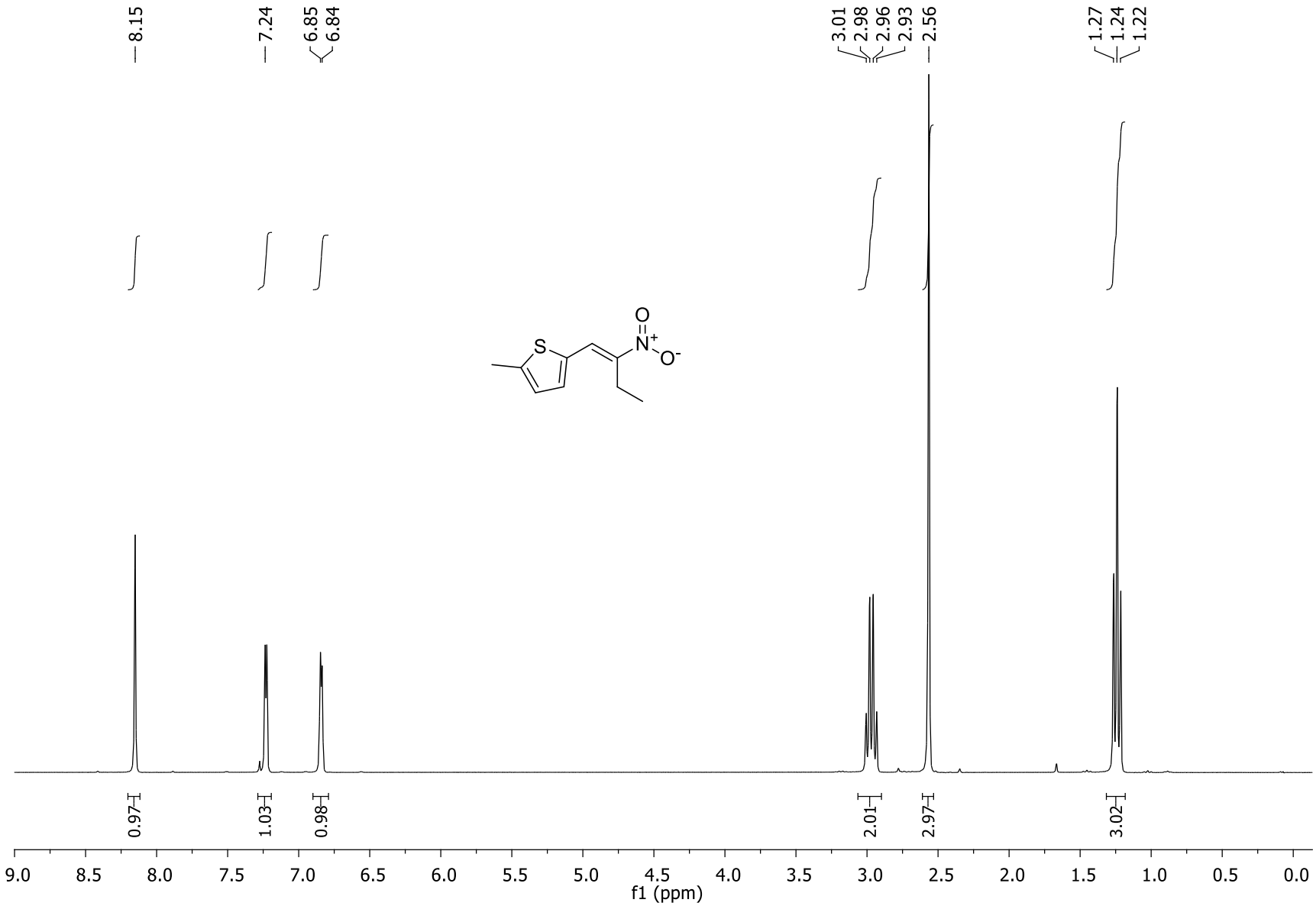
^{13}C APT NMR of (E)-3-(2-nitrobut-1-en-1-yl)thiophene (**3j**)



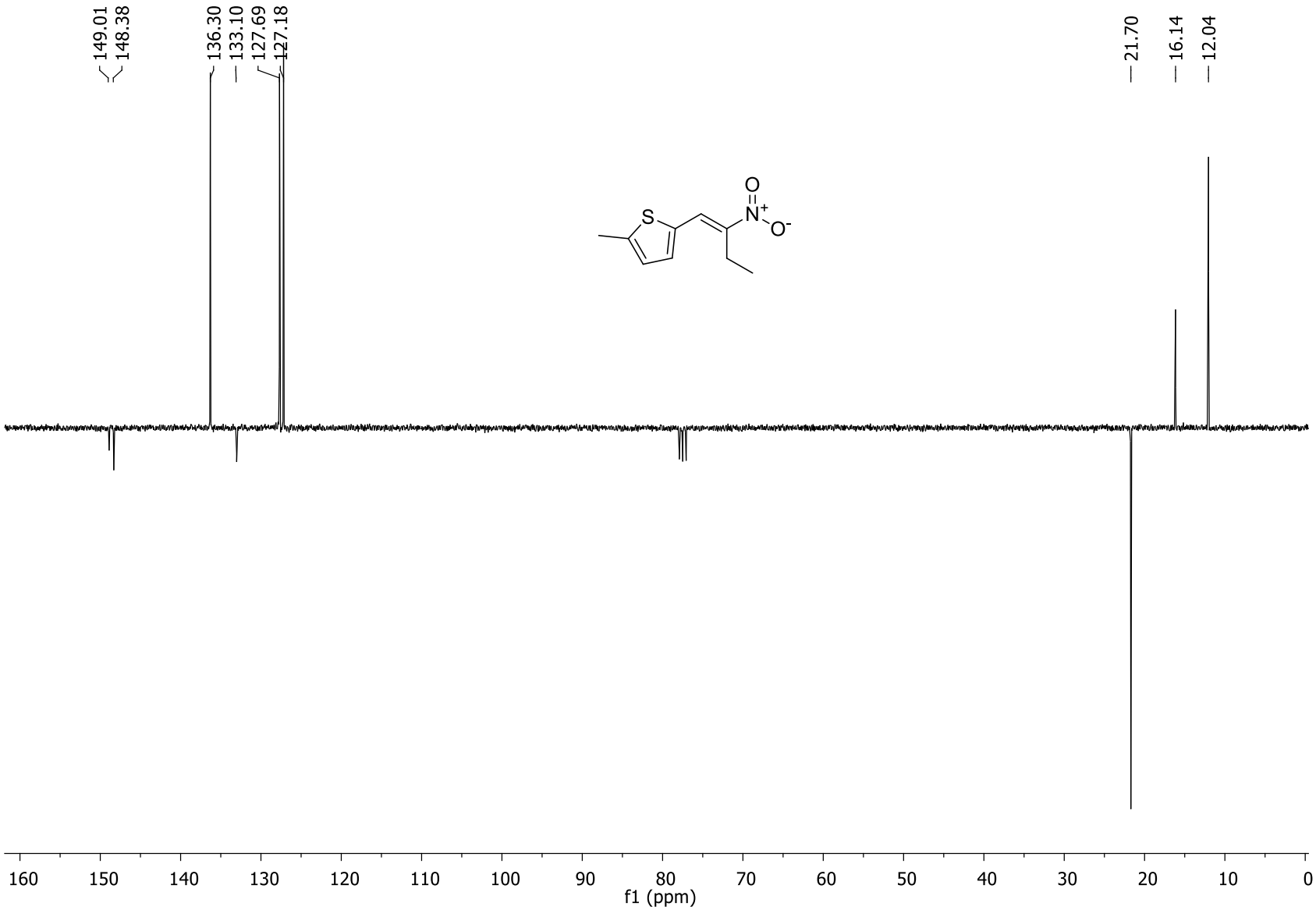
^{1}H NMR of (E)-2-methyl-5-(2-nitroprop-1-en-1-yl)thiophene (**3k**)



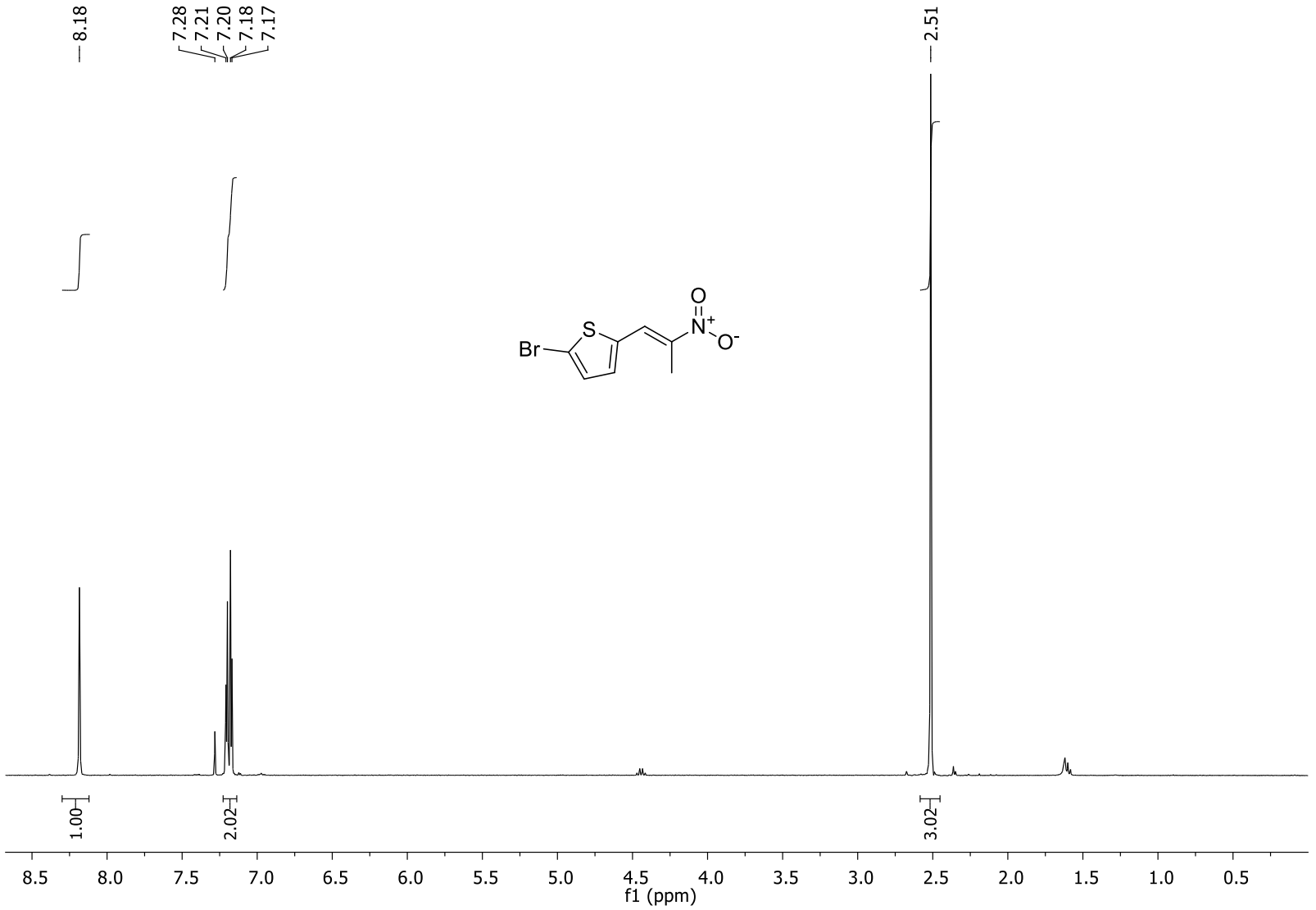
^{13}C APT NMR of (E)-2-methyl-5-(2-nitroprop-1-en-1-yl)thiophene (**3k**)



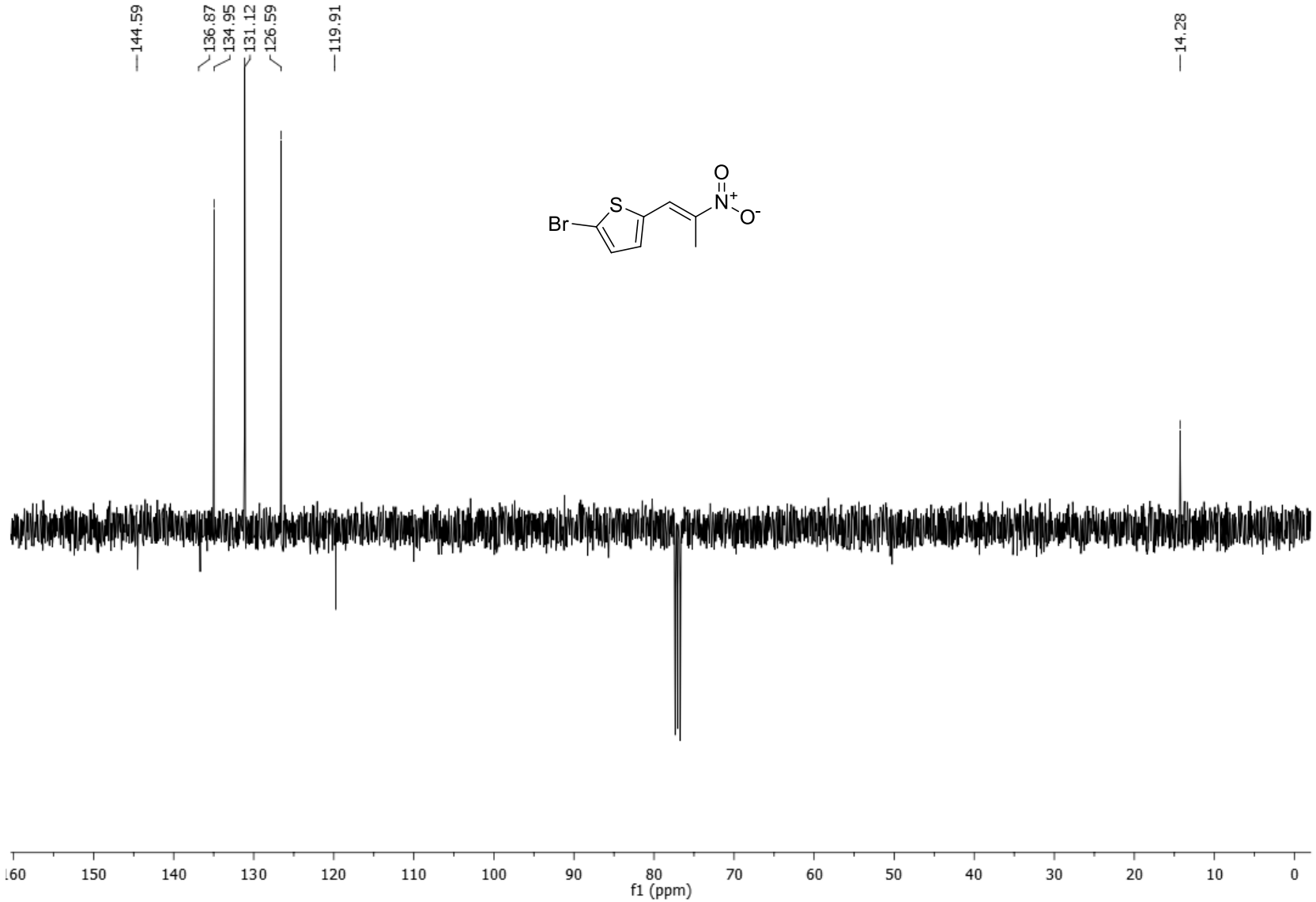
^{1}H NMR of (E)-2-methyl-5-(2-nitrobut-1-en-1-yl)thiophene (**3l**)



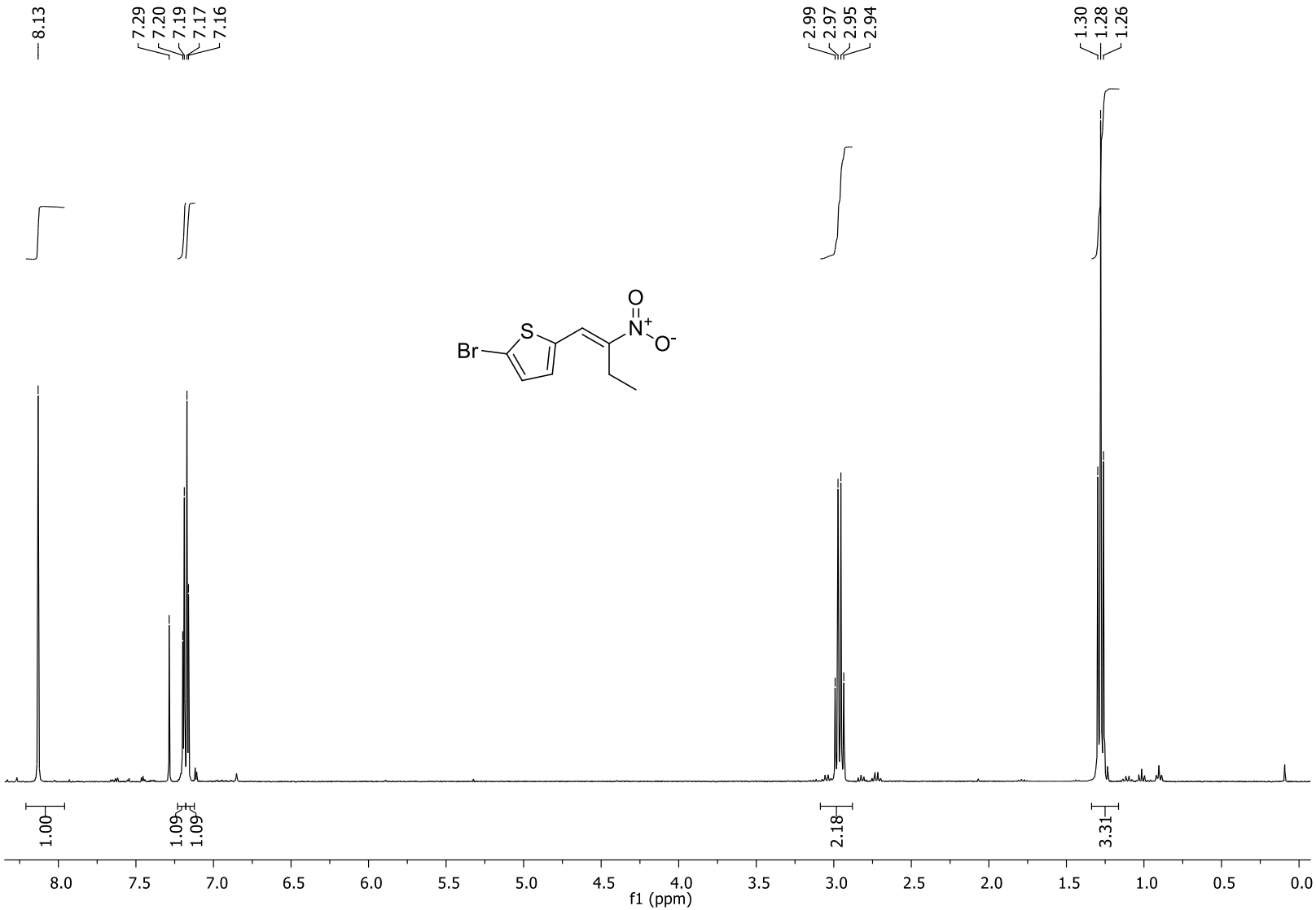
^{13}C APT NMR of (E)-2-methyl-5-(2-nitrobut-1-en-1-yl)thiophene (**3l**)



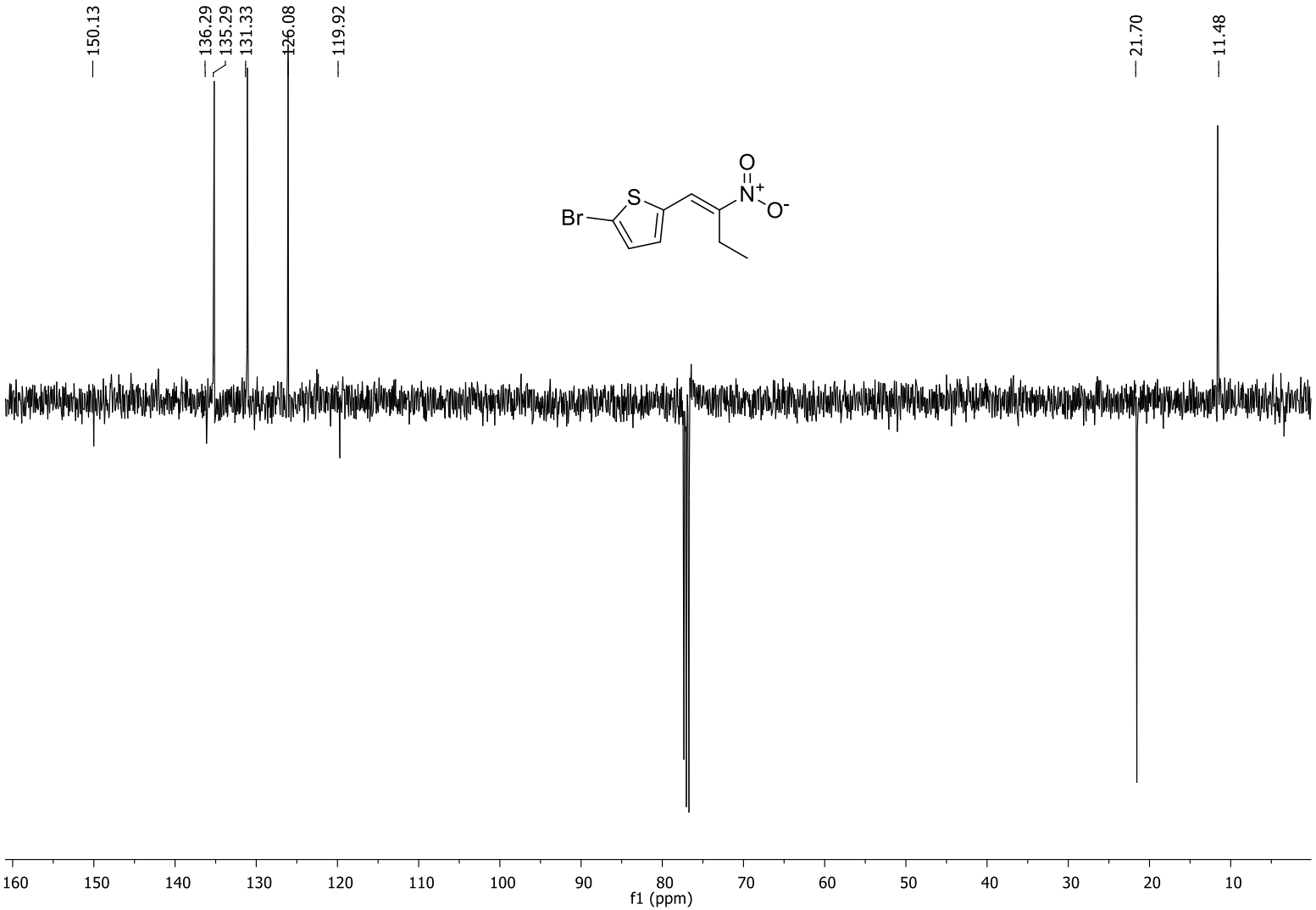
^{1}H NMR of (E)-2-bromo-5-(2-nitroprop-1-en-1-yl)thiophene (**3m**)



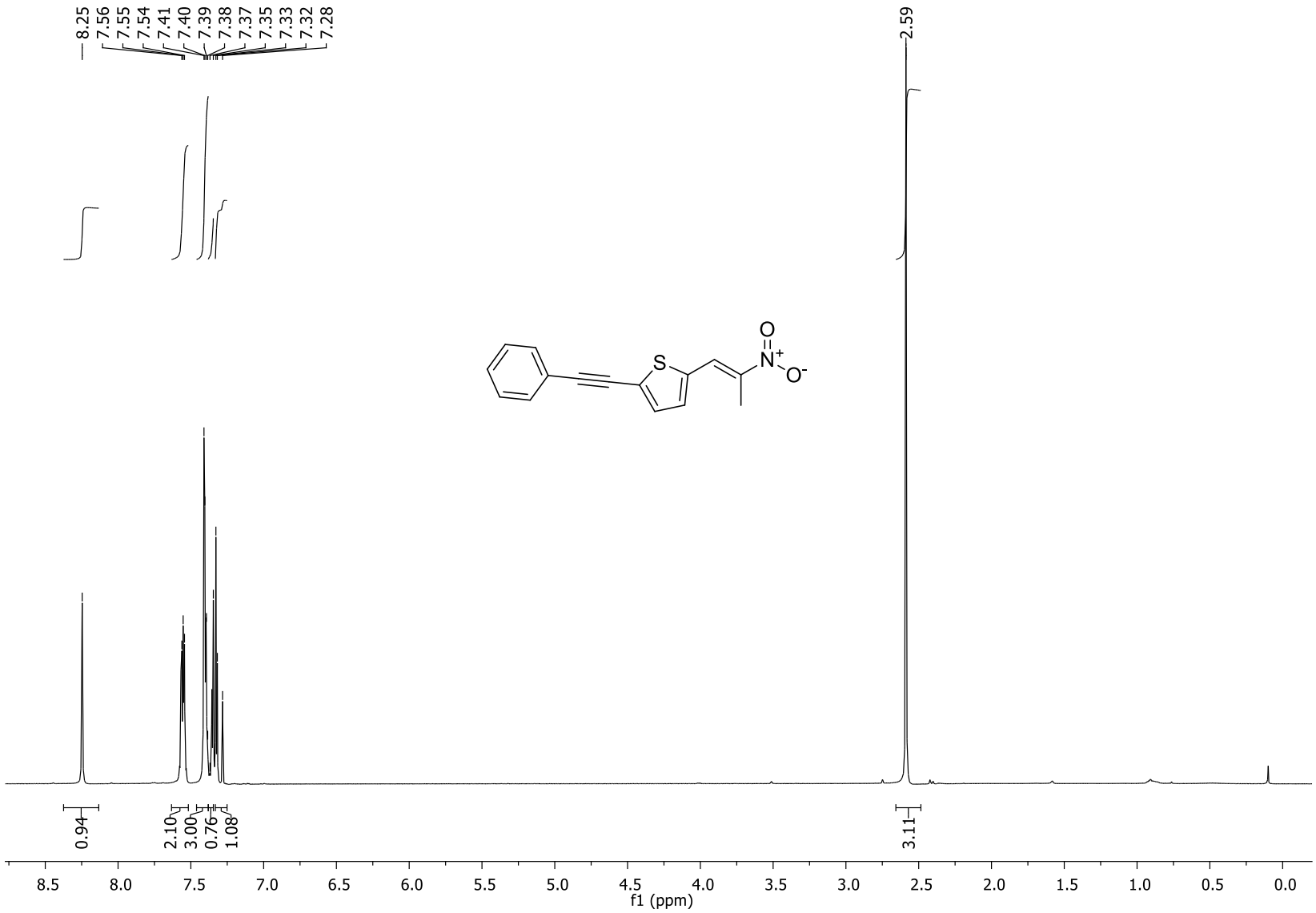
^{13}C APT NMR of (E)-2-bromo-5-(2-nitroprop-1-en-1-yl)thiophene (**3m**)



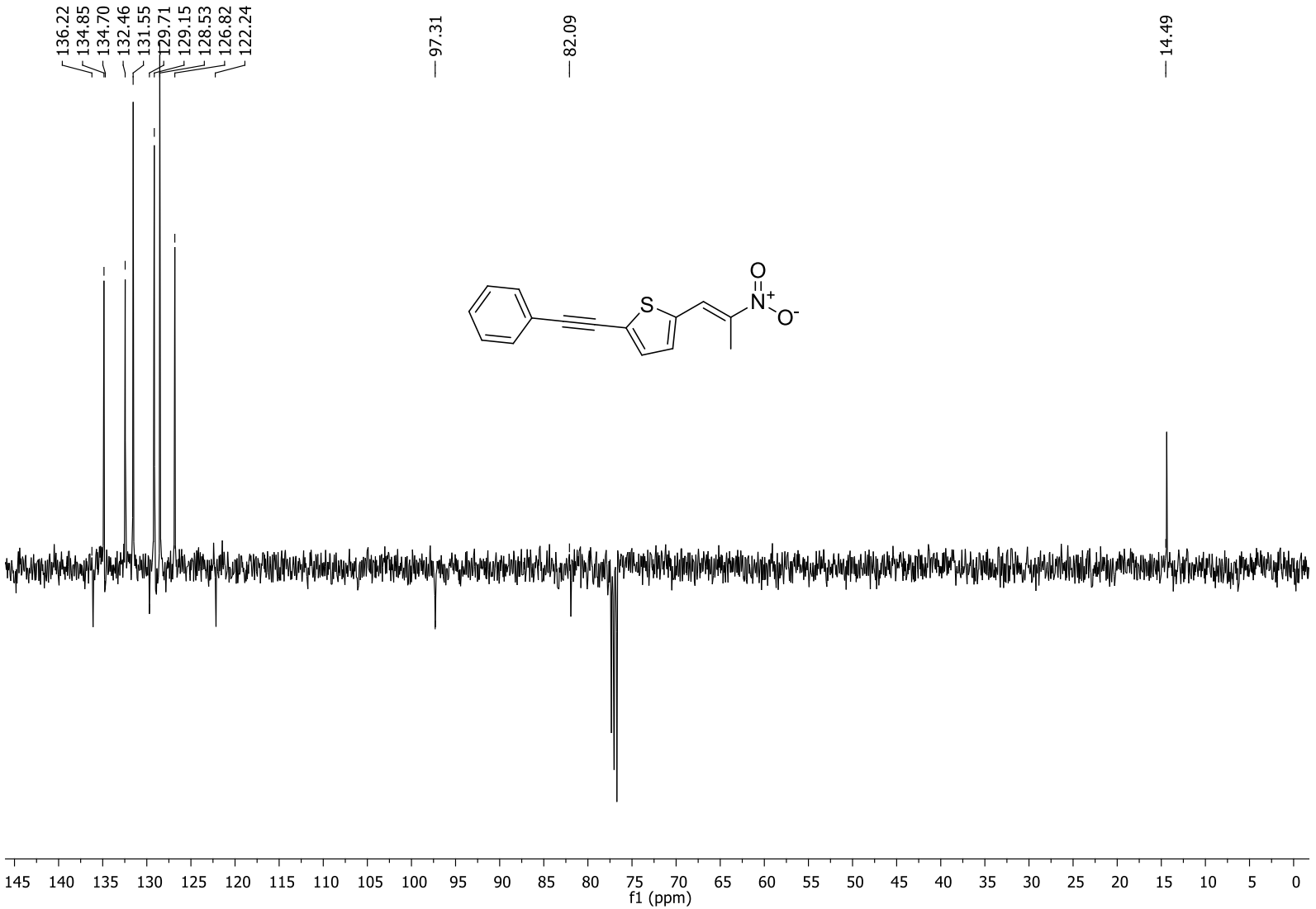
^{1}H NMR of (E)-2-bromo-5-(2-nitrobut-1-en-1-yl)thiophene (**3n**)



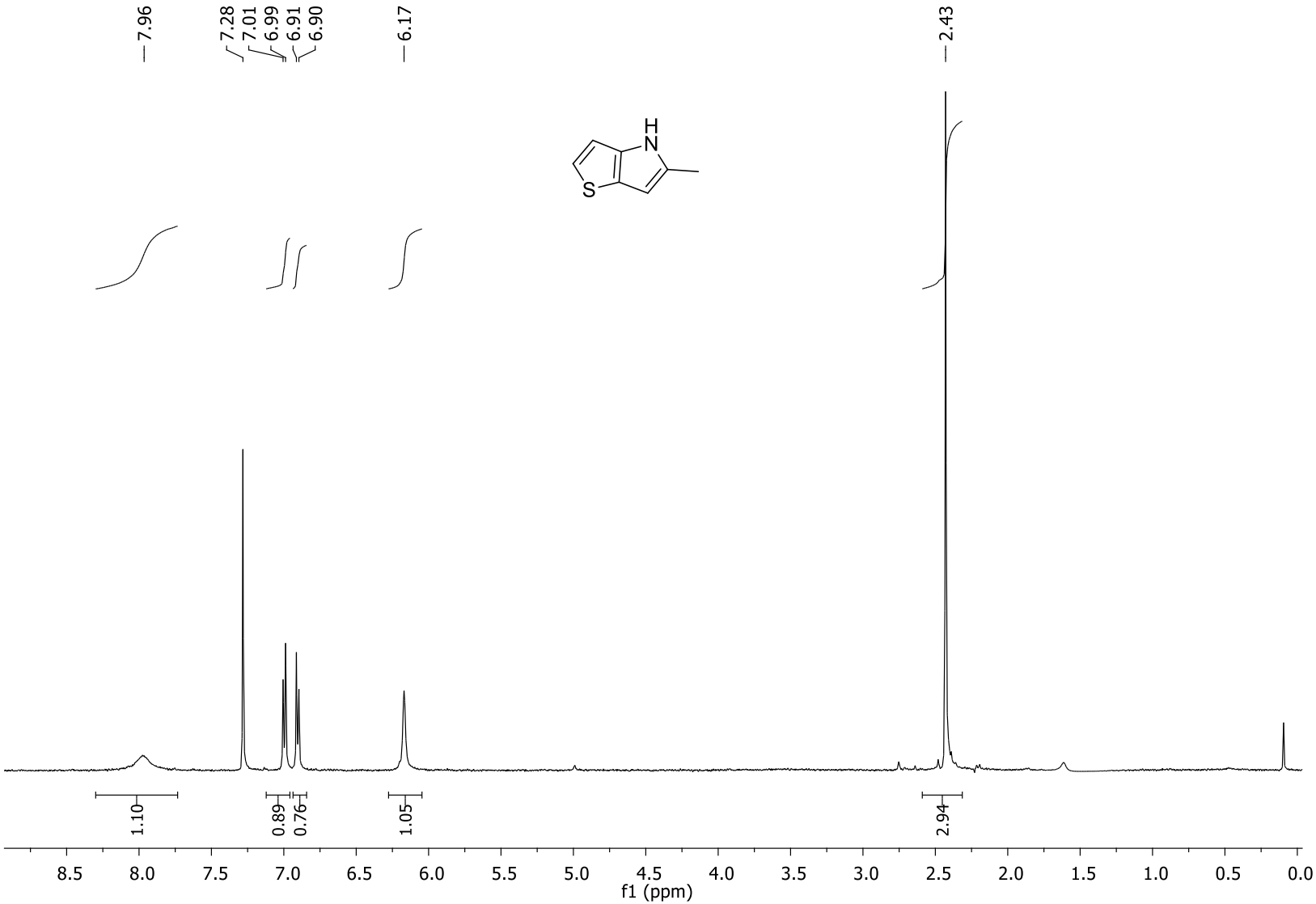
^{13}C APT NMR of (E)-2-bromo-5-(2-nitrobut-1-en-1-yl)thiophene (**3n**)



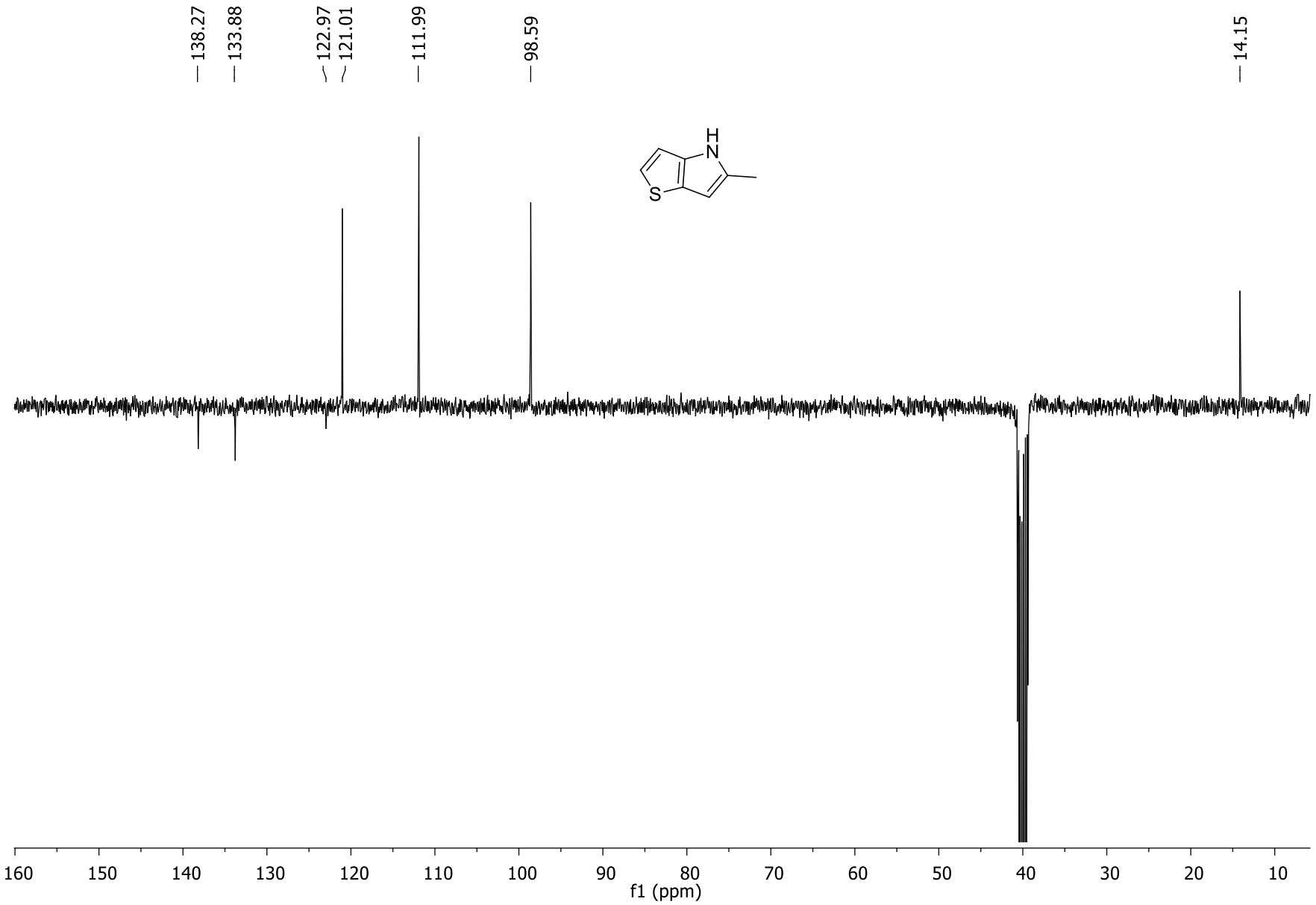
^{1}H NMR of (E)-2-(2-nitroprop-1-en-1-yl)-5-(phenylethynyl)thiophene (**3o**)



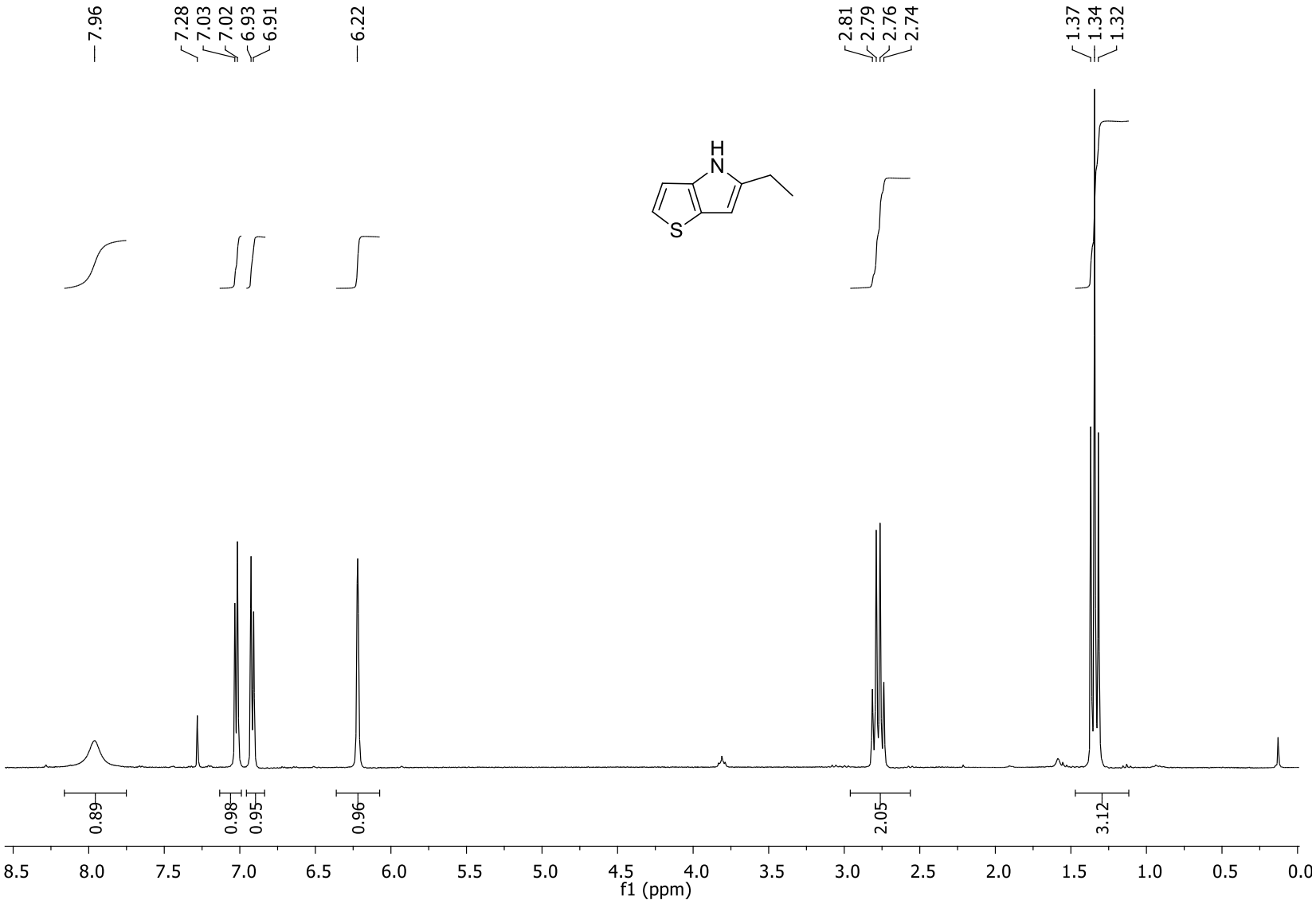
^{13}C APT NMR of (E)-2-(2-nitroprop-1-en-1-yl)-5-(phenylethynyl)thiophene (**3o**)



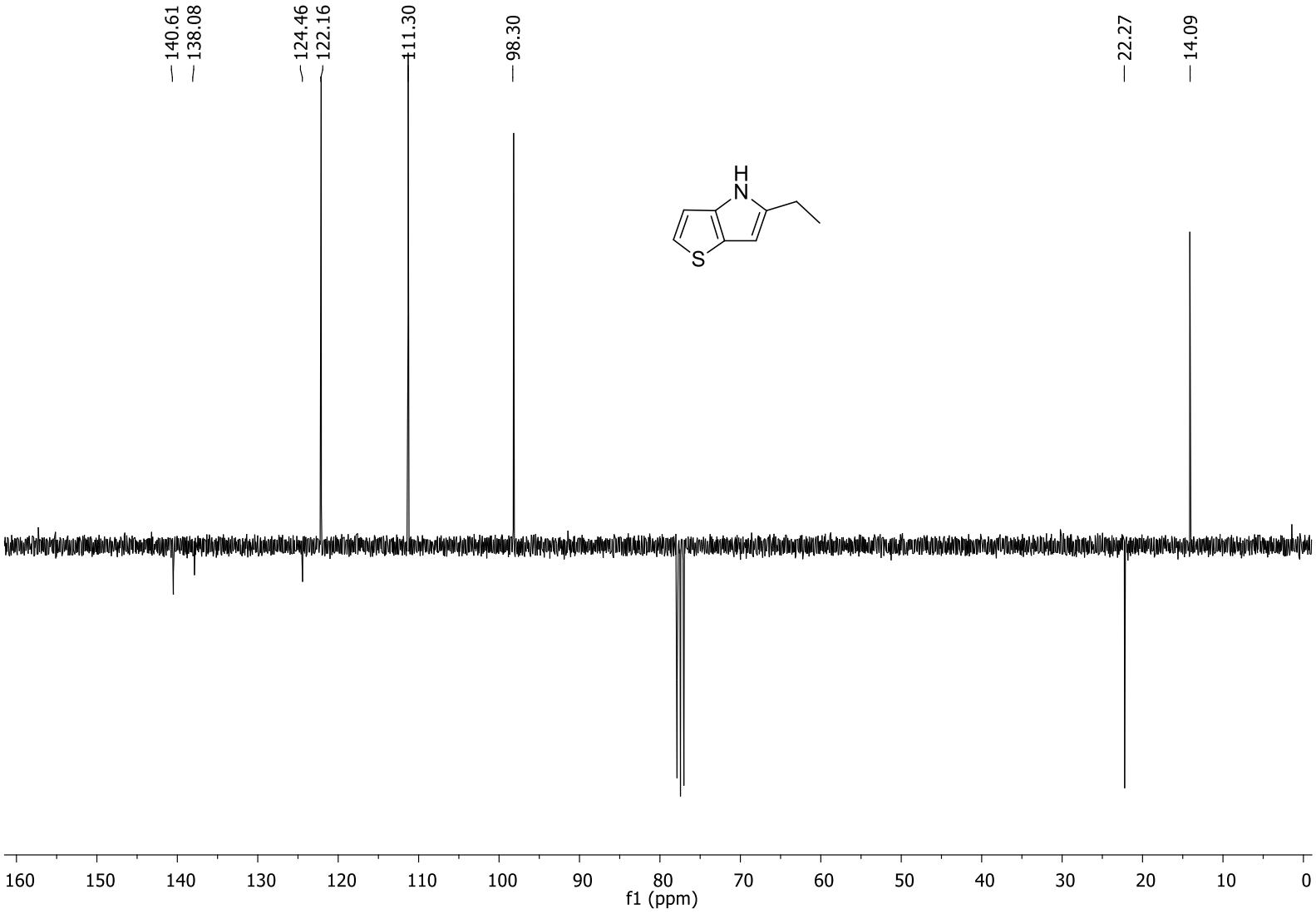
^{1}H NMR of 5-methyl-4H-thieno[3,2-b]pyrrole (**4a**)



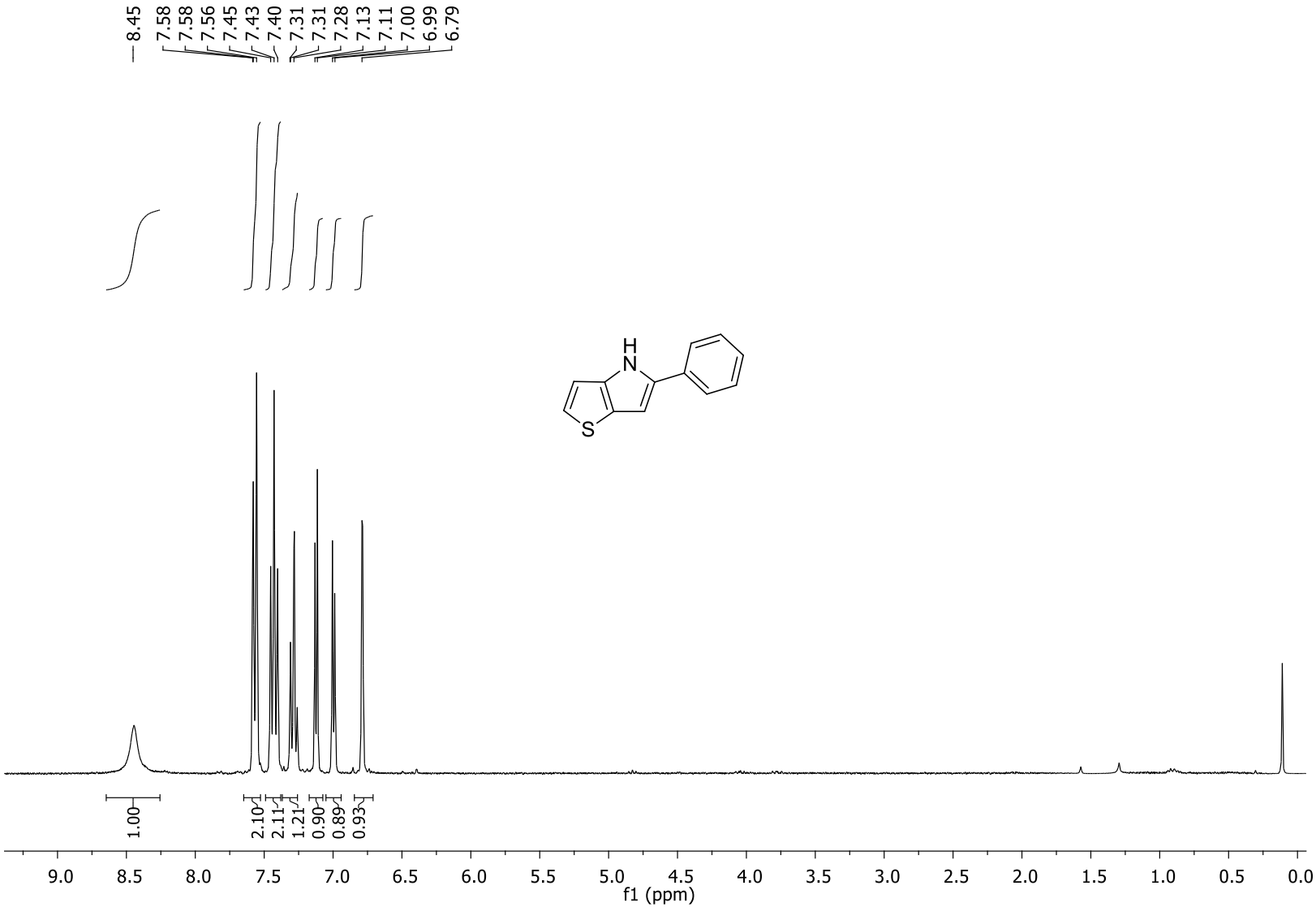
^{13}C APT NMR of 5-methyl-4H-thieno[3,2-b]pyrrole (**4a**)



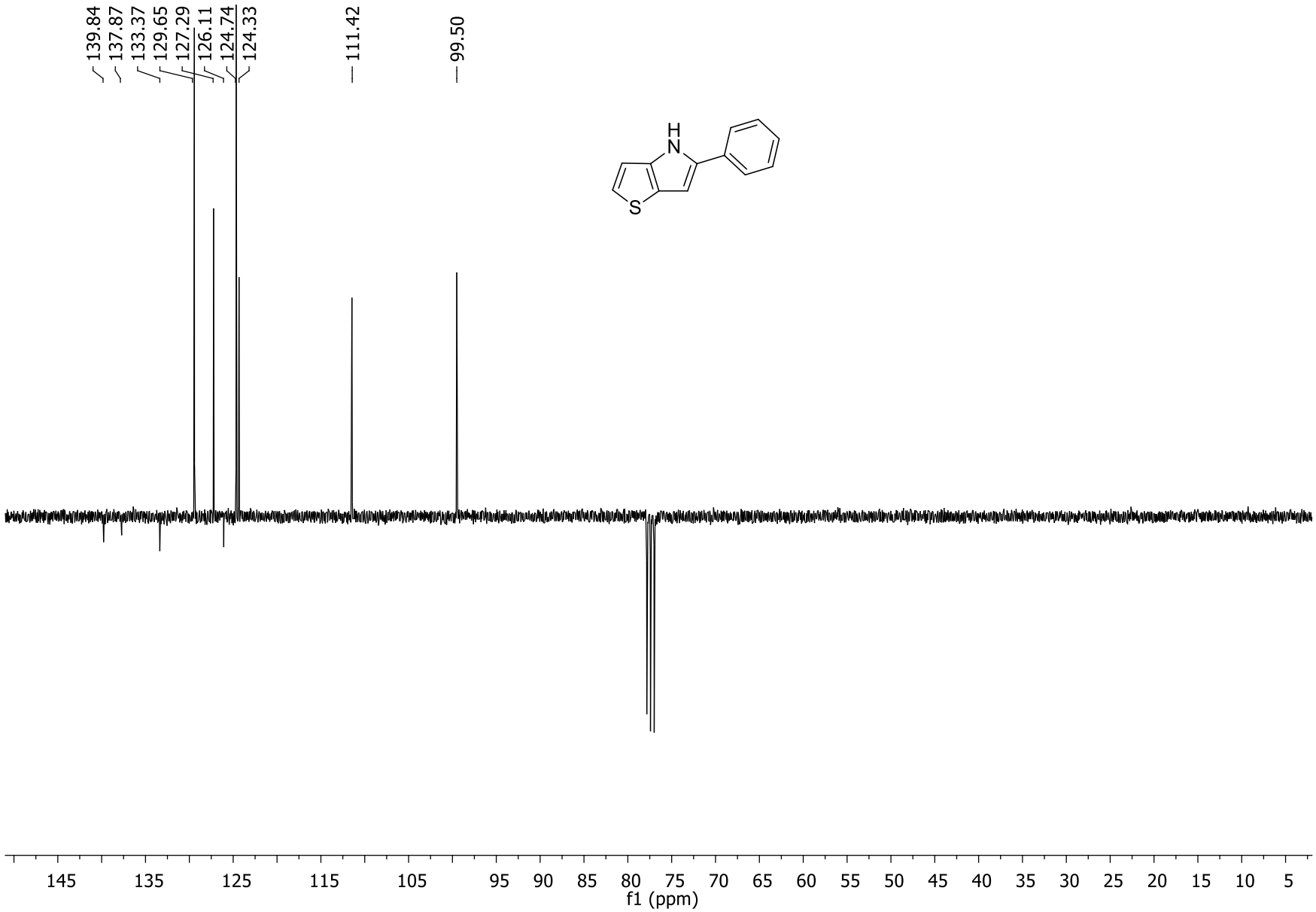
^{1}H NMR of 5-ethyl-4H-thieno[3,2-b]pyrrole (**4b**)



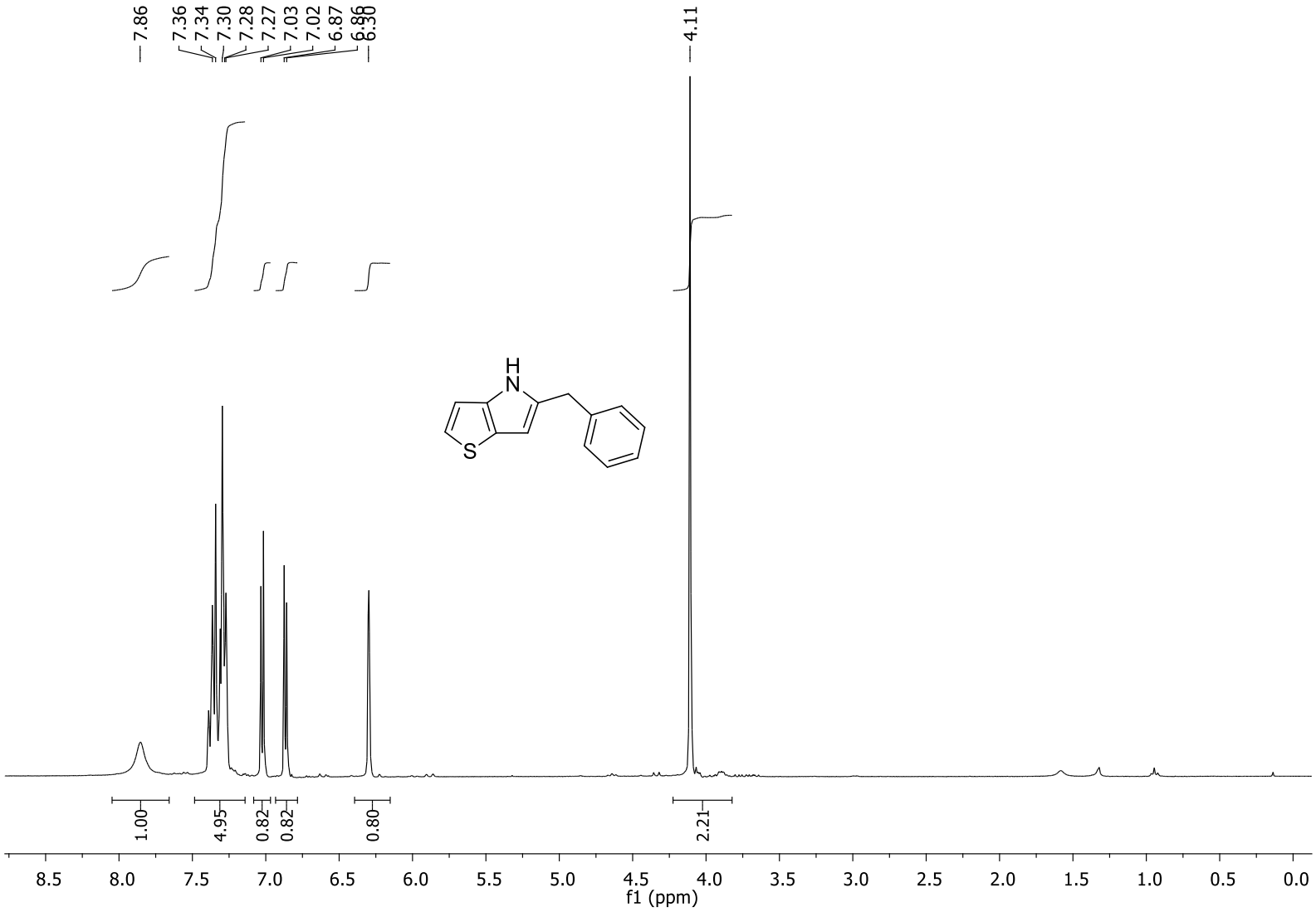
^{13}C APT NMR of 5-ethyl-4H-thieno[3,2-b]pyrrole (**4b**)



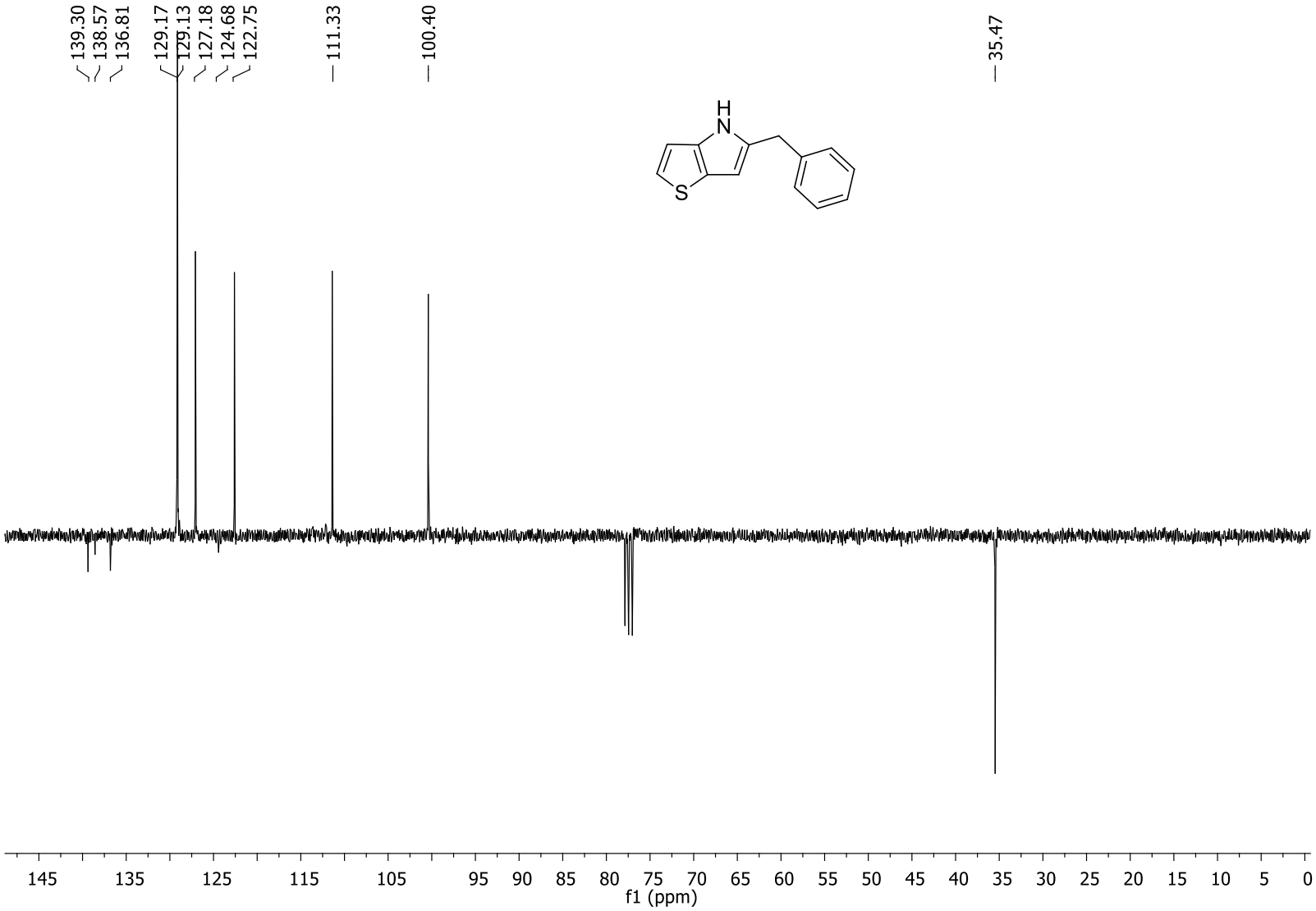
^{1}H NMR of 5-phenyl-4H-thieno[3,2-b]pyrrole (**4d**)



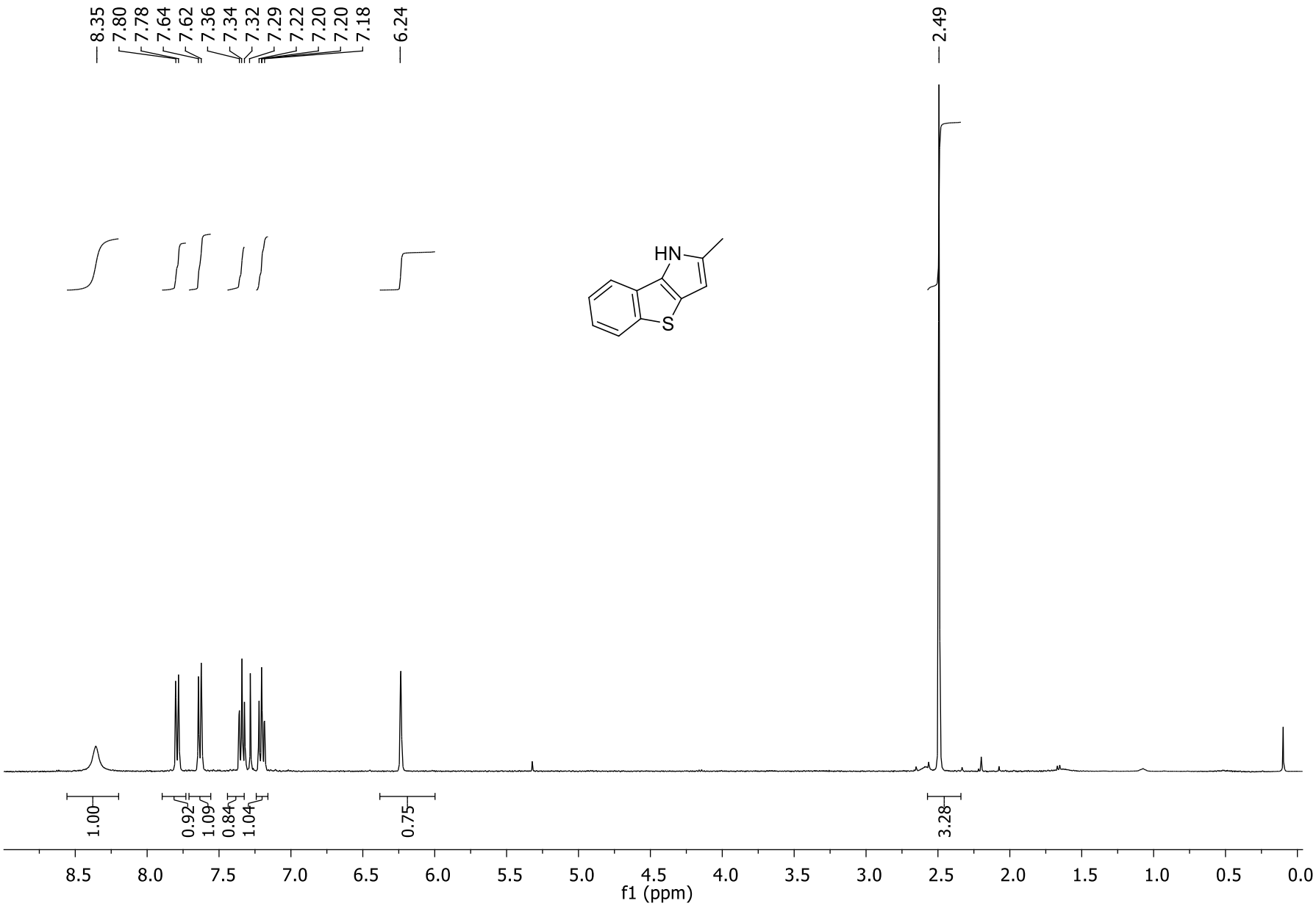
^{13}C APT NMR of 5-phenyl-4H-thieno[3,2-b]pyrrole (**4d**)



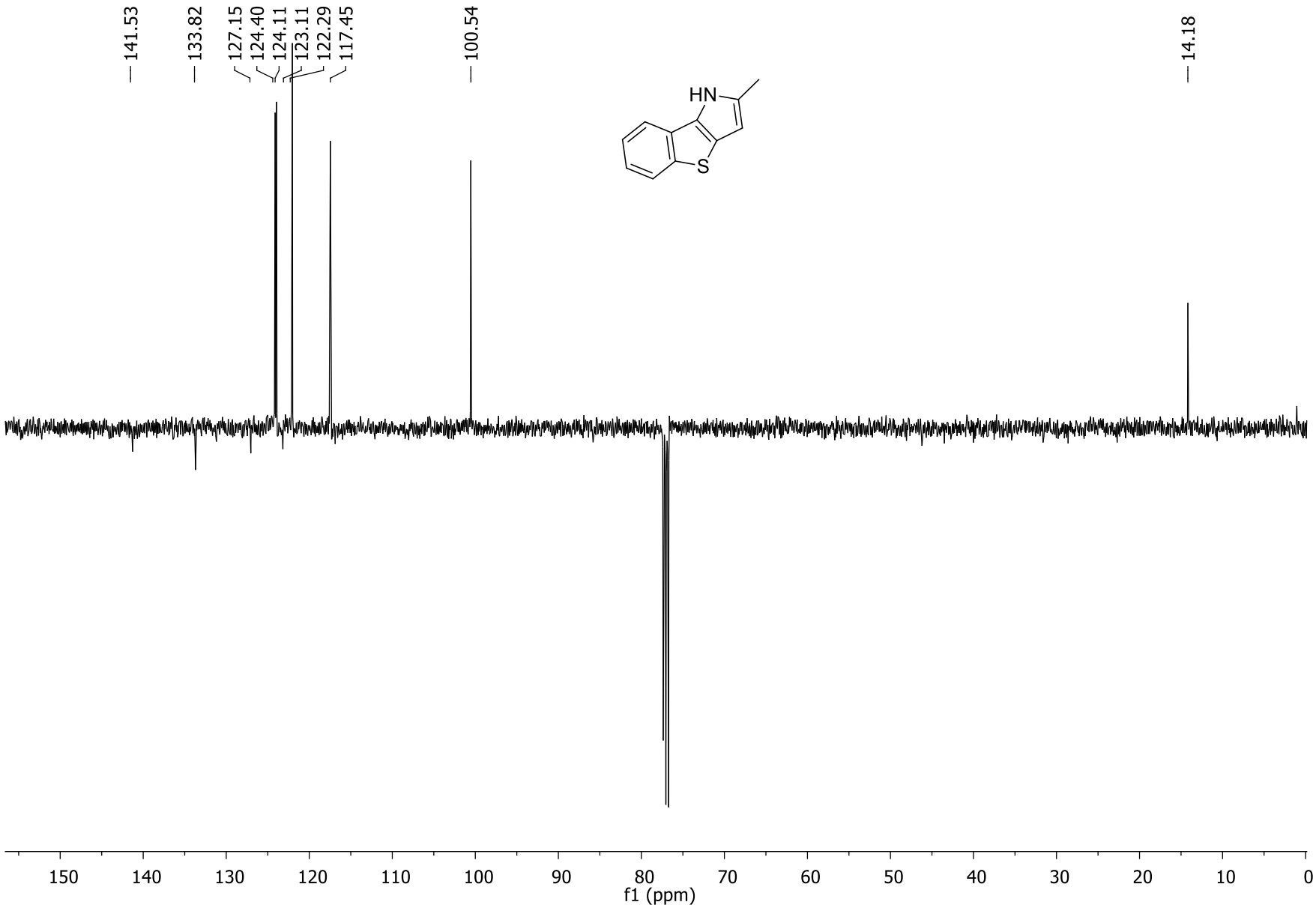
^{1}H NMR of 5-benzyl-4H-thieno[3,2-b]pyrrole (**4f**)



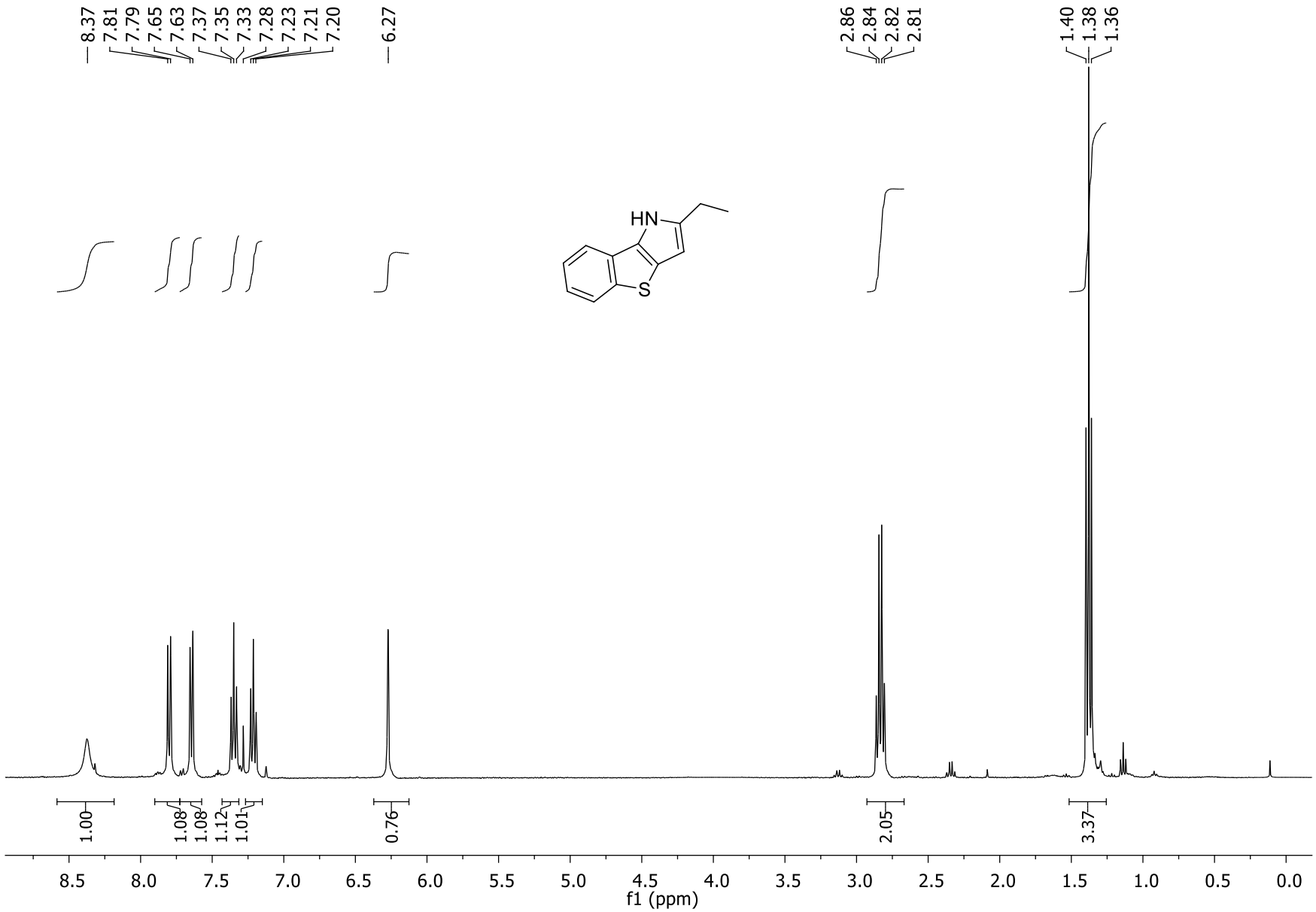
^{13}C APTNMR of 5-benzyl-4H-thieno[3,2-b]pyrrole (**4f**)



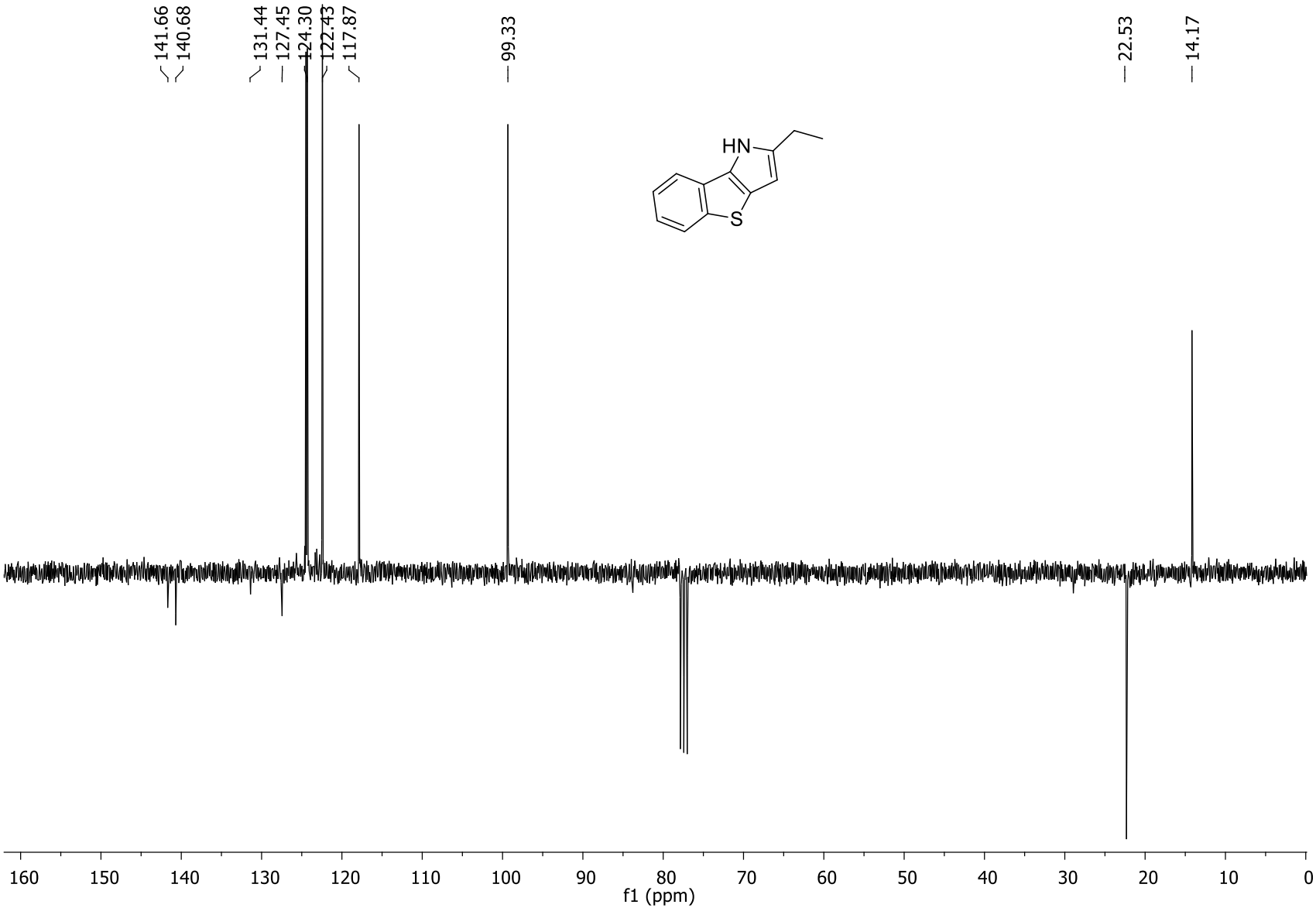
^{1}H NMR of 2-methyl-1H[1]benzothieno[3,2-b]pyrrole (**4g**)



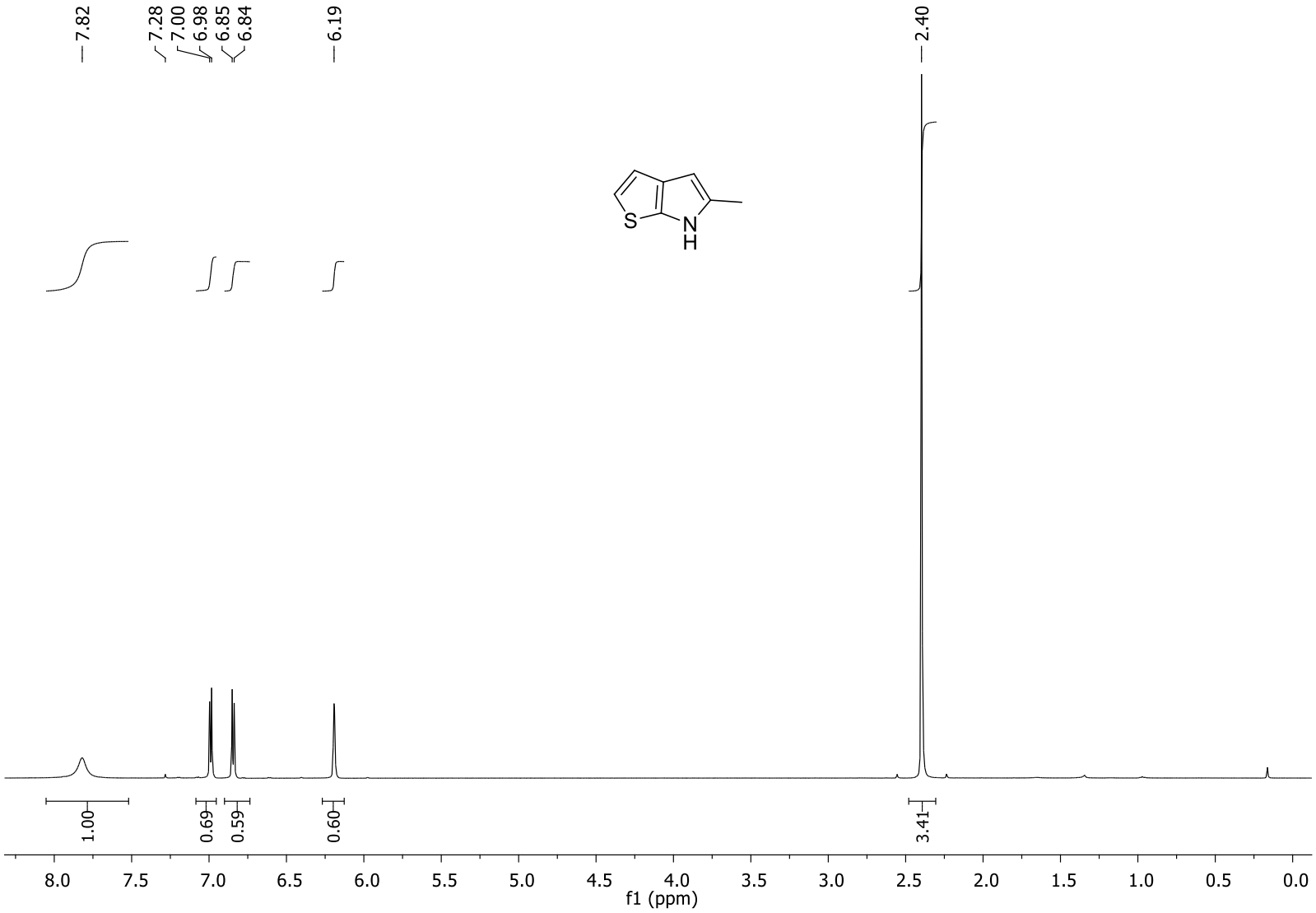
^{13}C APT NMR of 2-methyl-1H[1]benzothieno[3,2-b]pyrrole (**4g**)



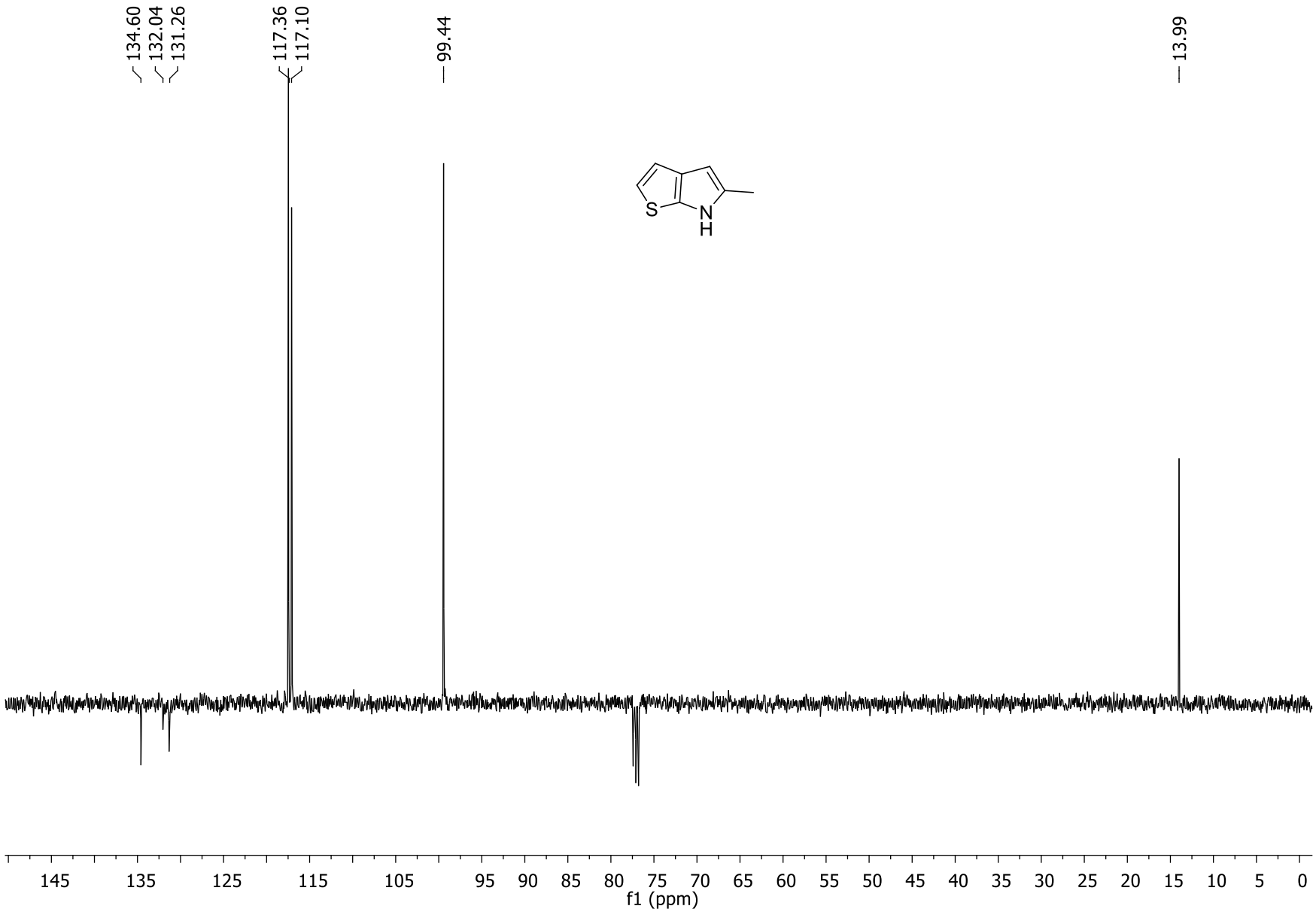
^{1}H NMR of 2-ethyl-1H[1]benzothieno[3,2-b]pyrrole (**4h**)



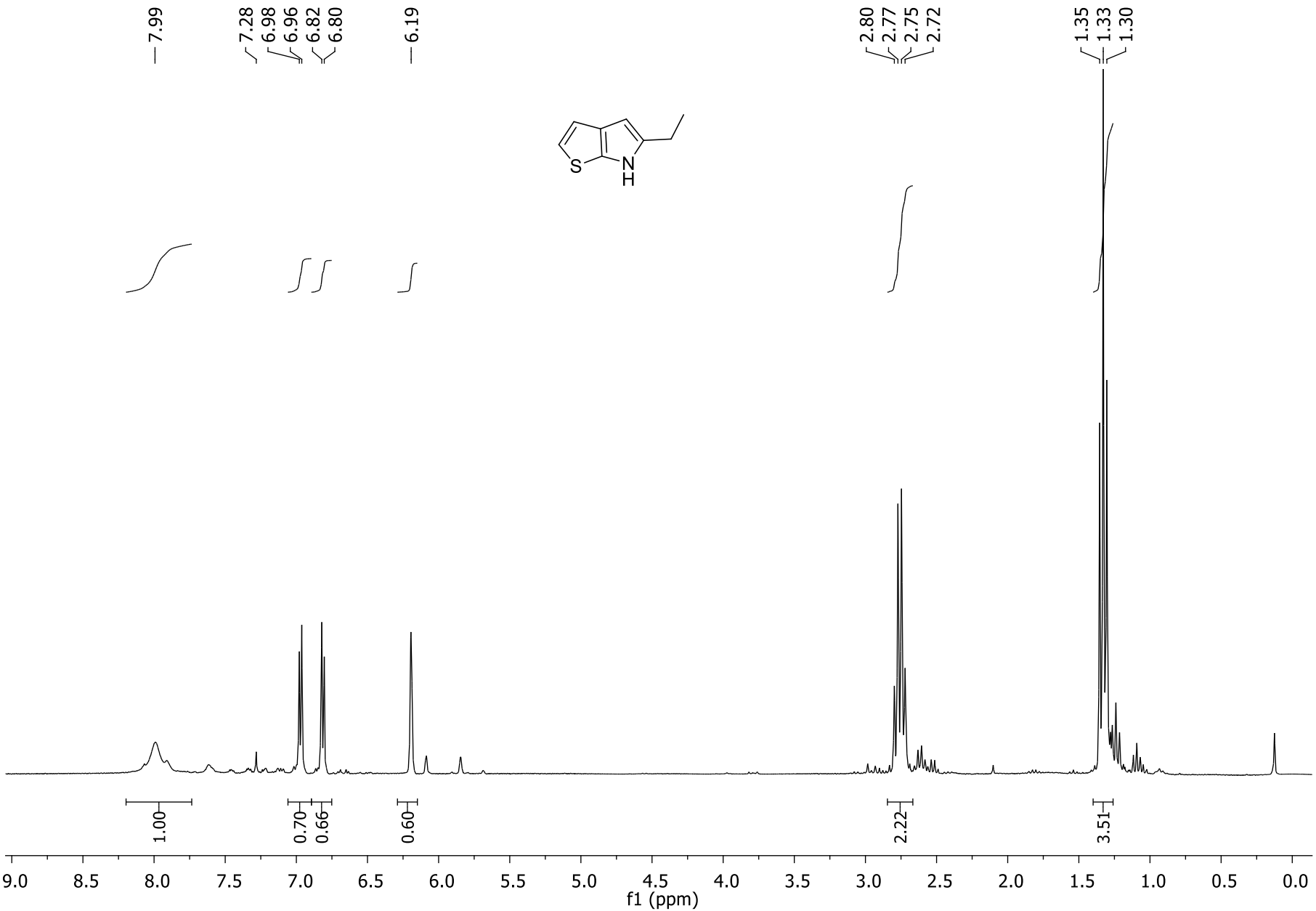
^{13}CNMR of 2-ethyl-1H[1]benzothieno[3,2-b]pyrrole (**4h**)



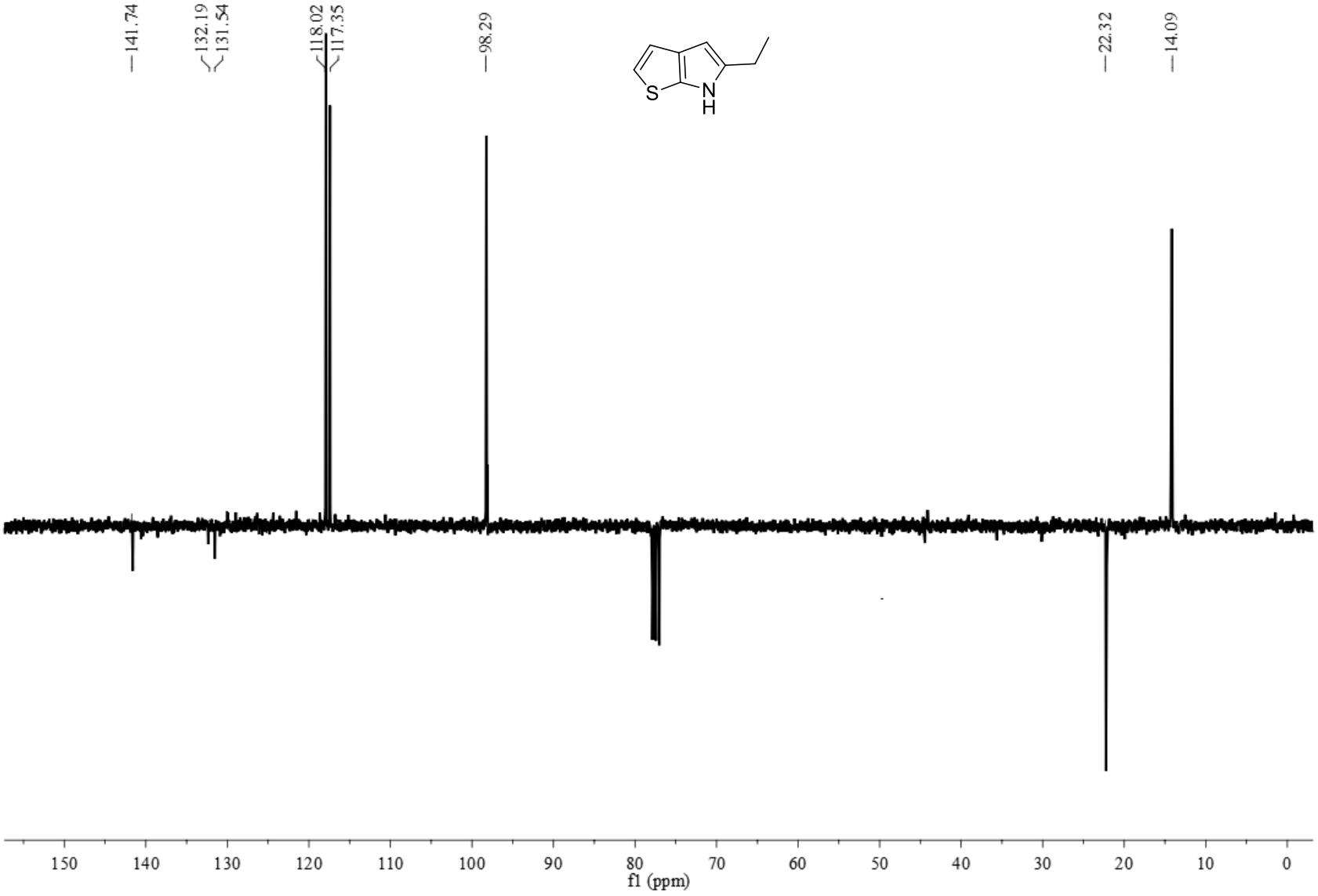
^{1}H NMR of 5-methyl-6*H*-thieno[2,3-b]pyrrole (**4i**)



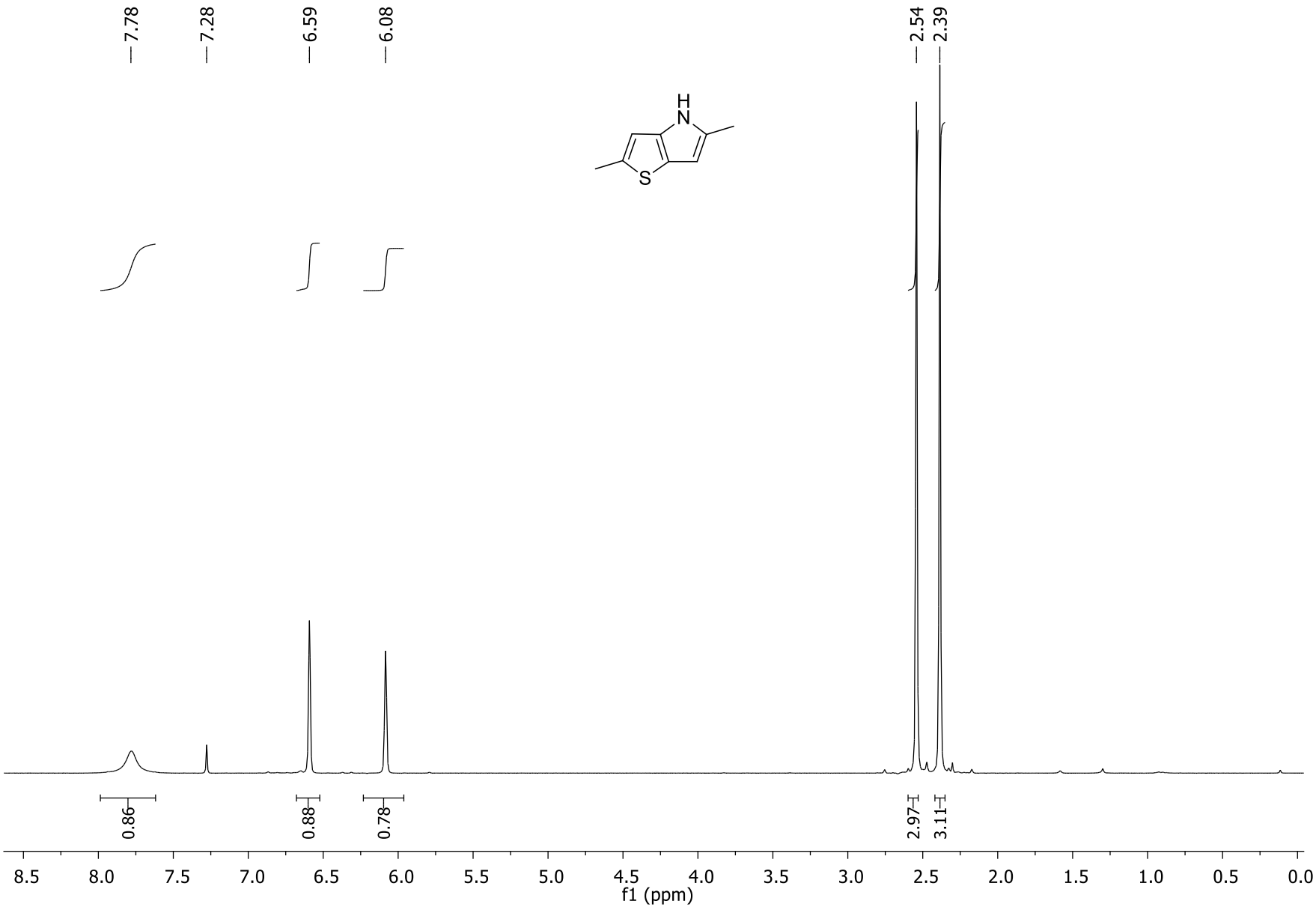
^{13}C APT NMR of 5-methyl-6*H*-thieno[2,3-b]pyrrole (**4i**)



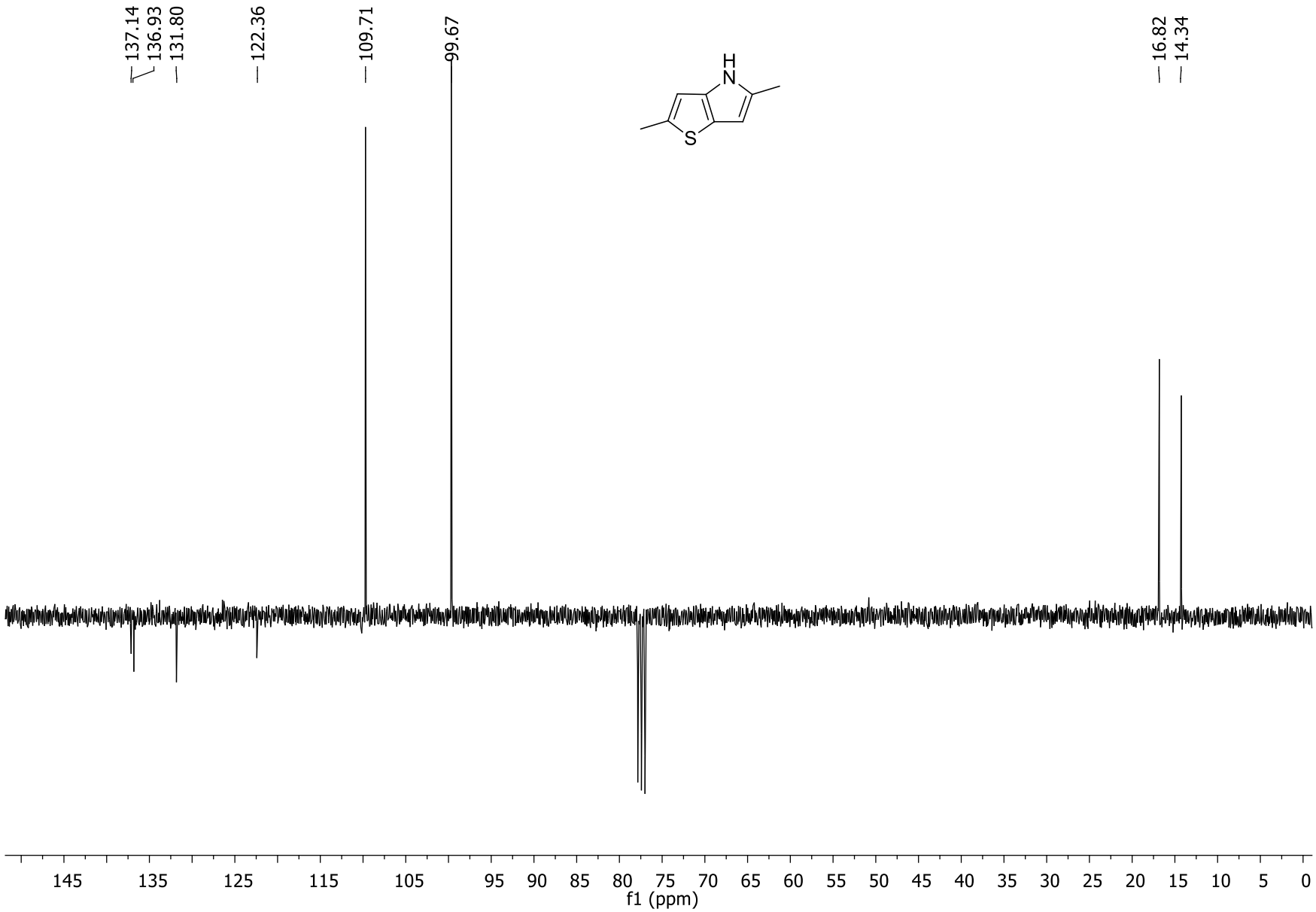
^{1}H NMR of 5-ethyl-6*H*-thieno[2,3-b]pyrrole (**4j**)



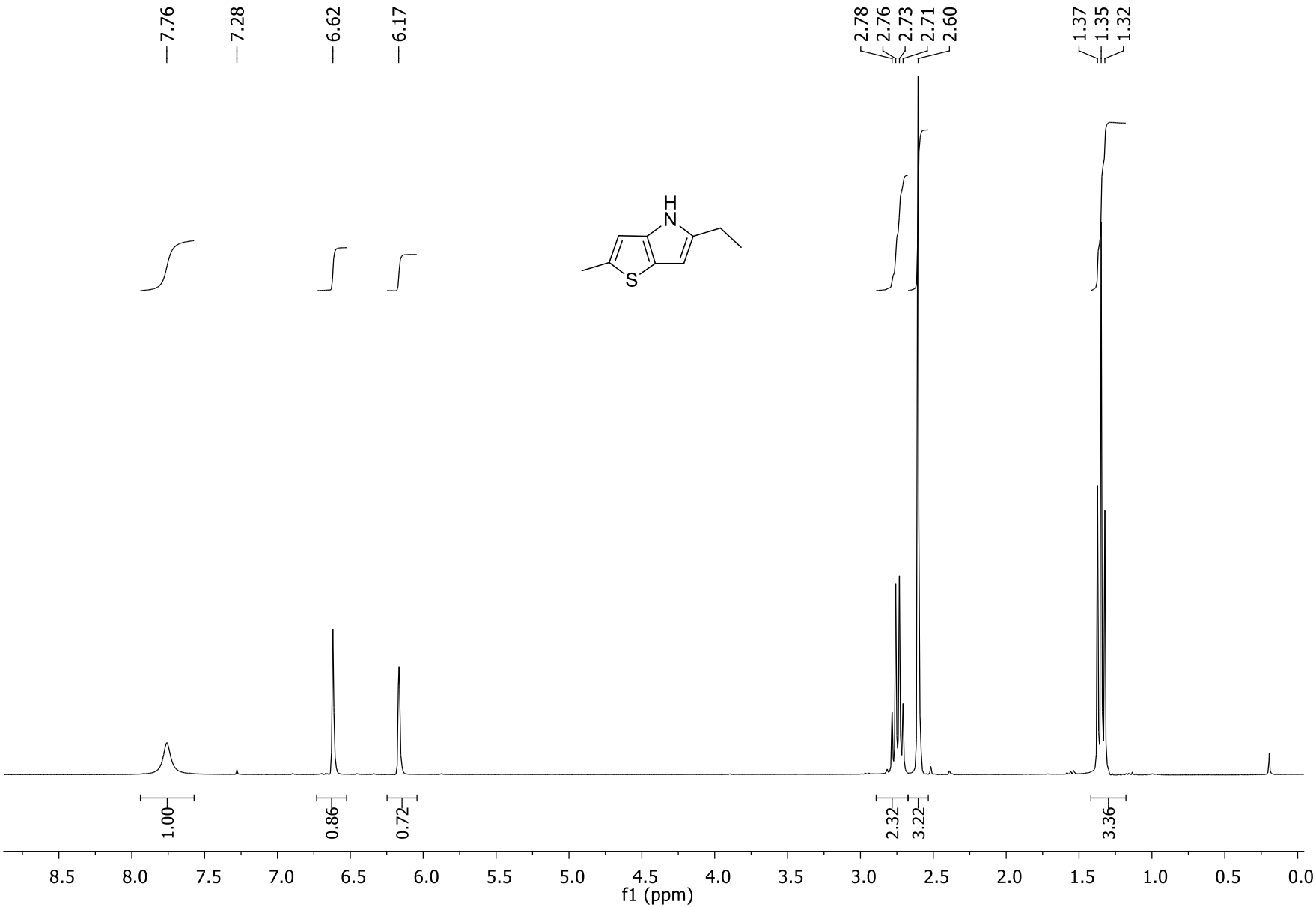
^{13}C APT NMR of 5-ethyl-6*H*-thieno[2,3-b]pyrrole (**4j**)



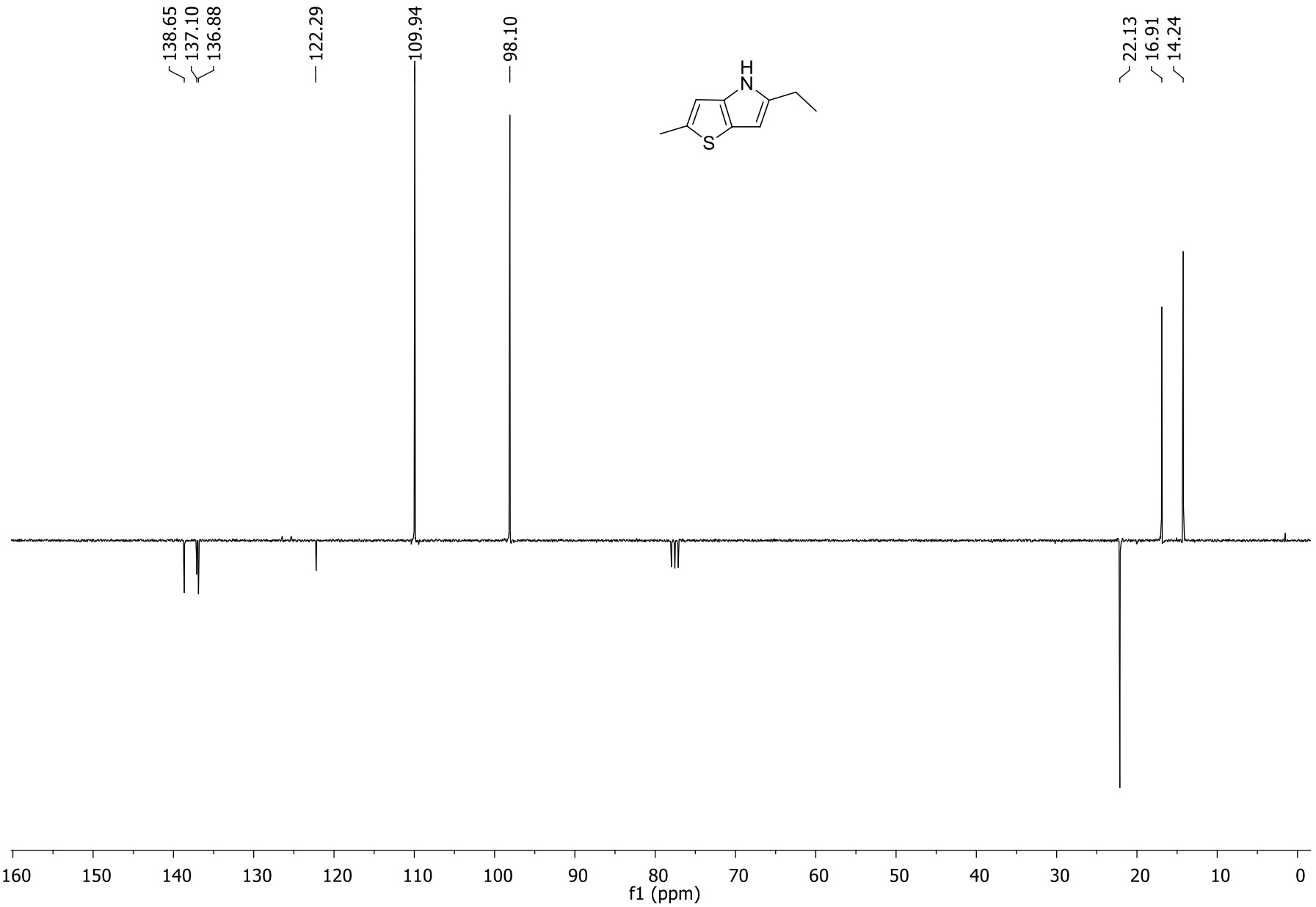
^{1}H NMR of 2,5-dimethyl-4*H*-thieno[3,2-b]pyrrole (**4k**)



^{13}C APT NMR of 2,5-dimethyl-4*H*-thieno[3,2-b]pyrrole (**4k**)

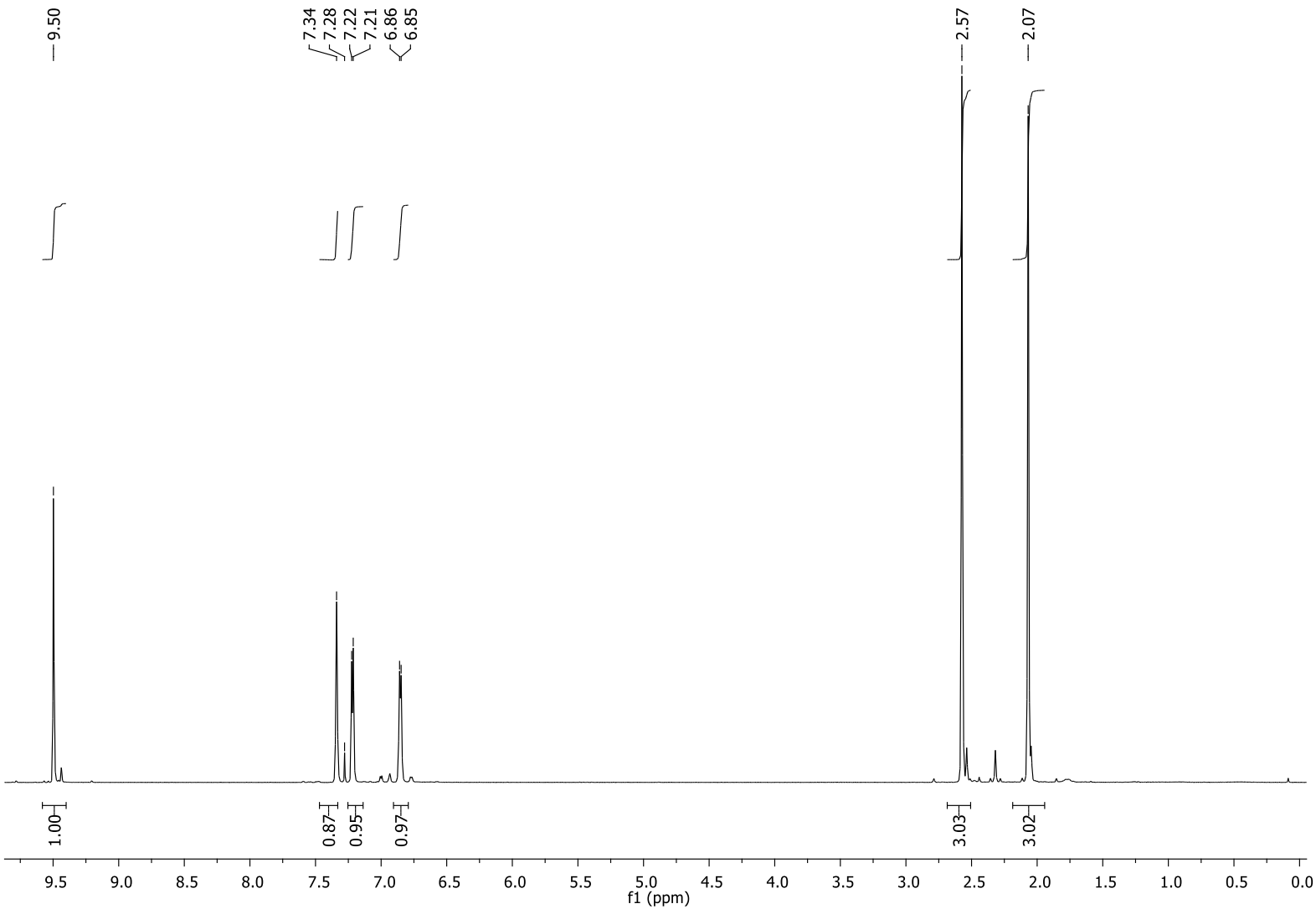


^{1}H NMR of 5-ethyl-2-methyl-4*H*-thieno[3,2-b]pyrrole (**4l**)

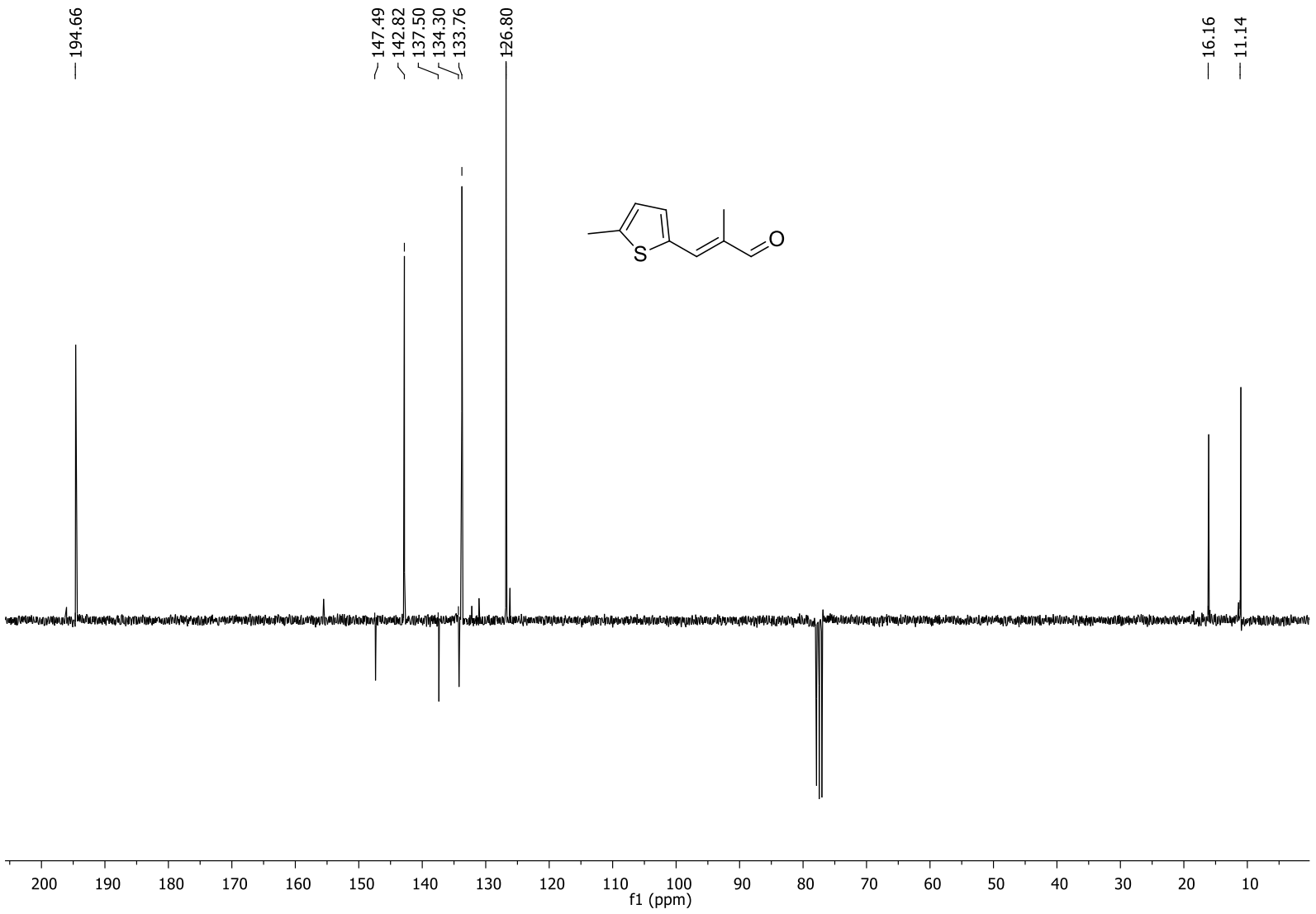


^{13}C APT NMR of 5-ethyl-2-methyl-4*H*-thieno[3,2-b]pyrrole (**4l**)

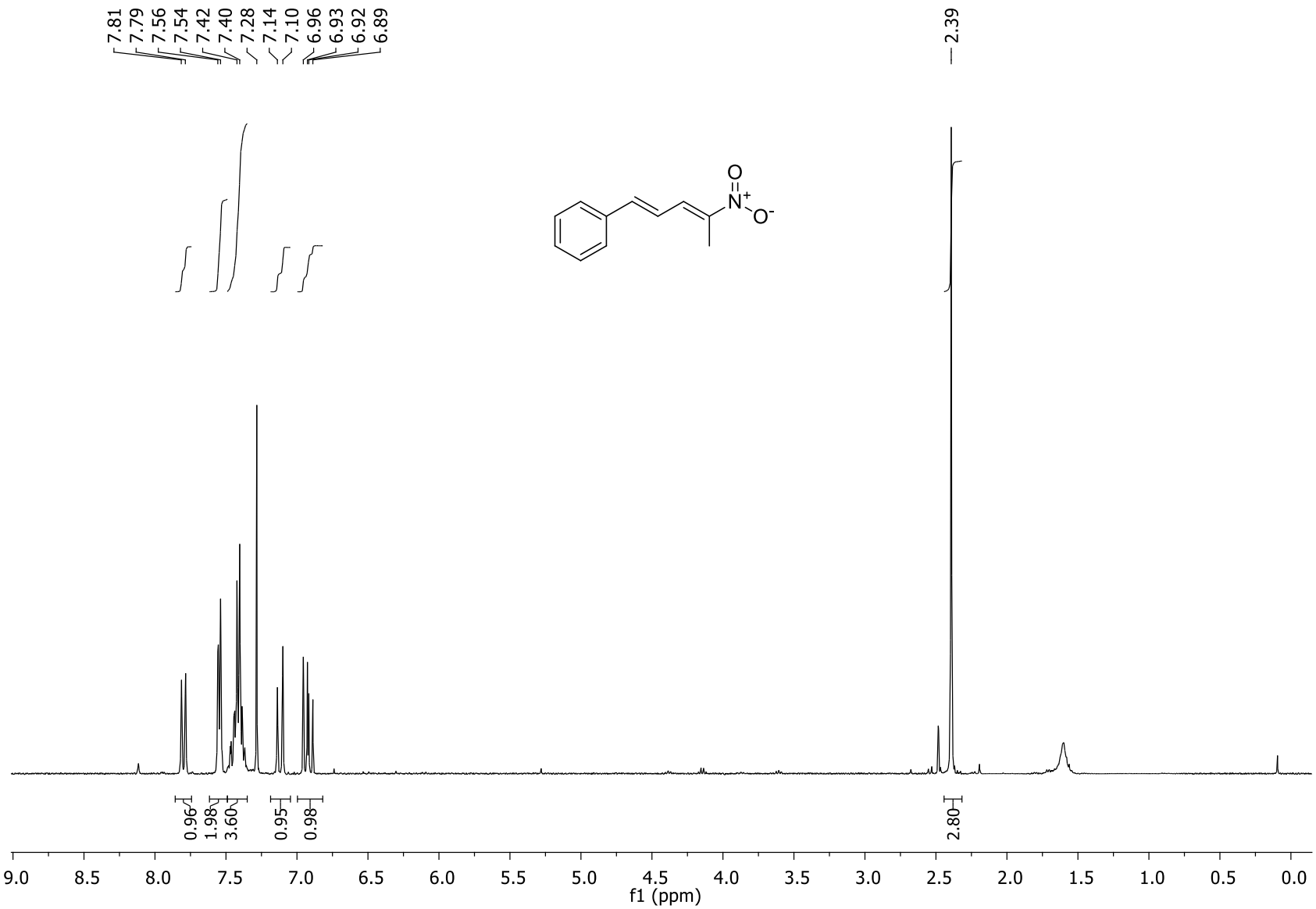
4.3 Appendix C: NMR spectra for pyrrole synthesis



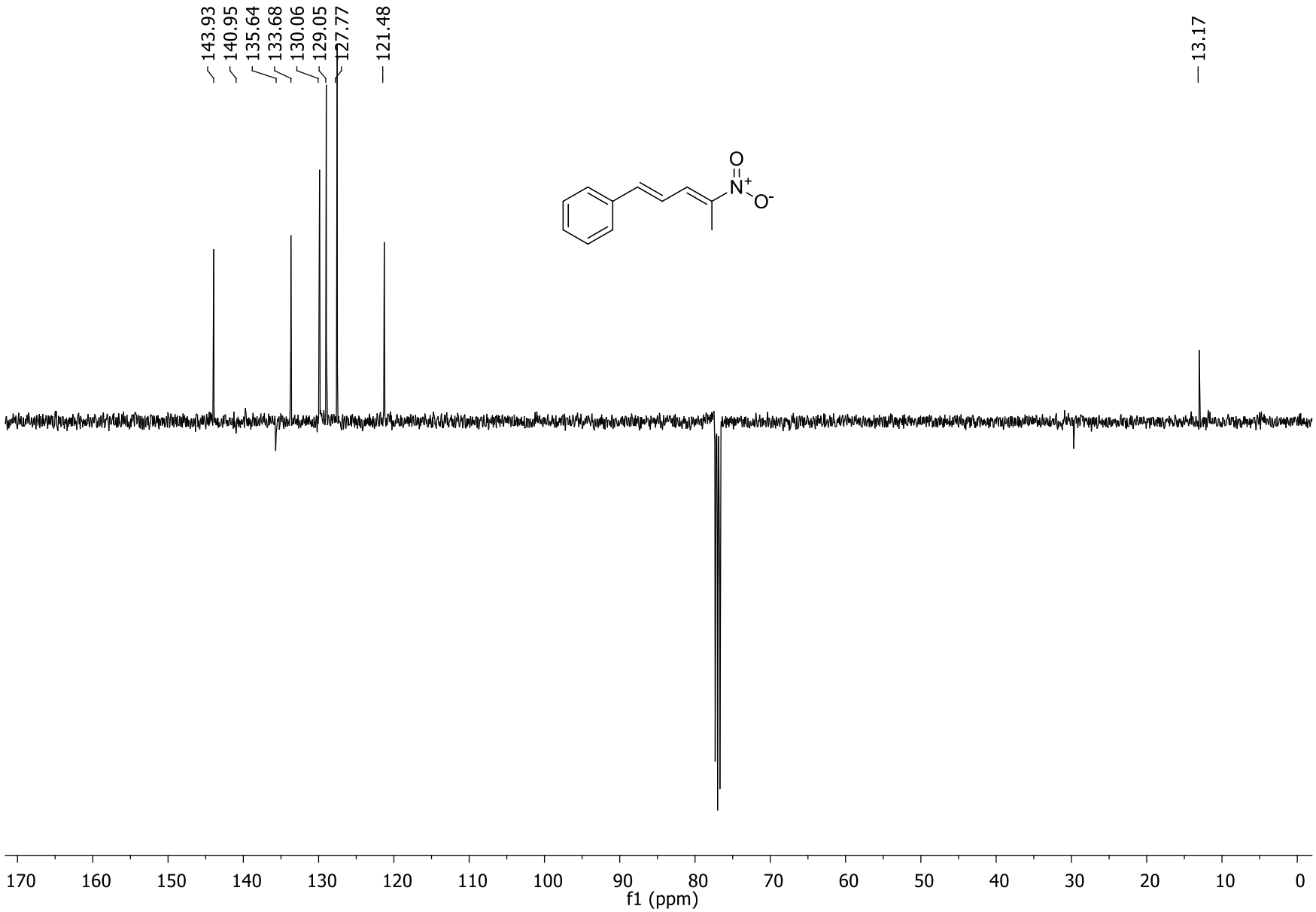
^{1}H NMR of (E)-2-methyl-3-(5-methylthien-2-yl)acrylaldehyde



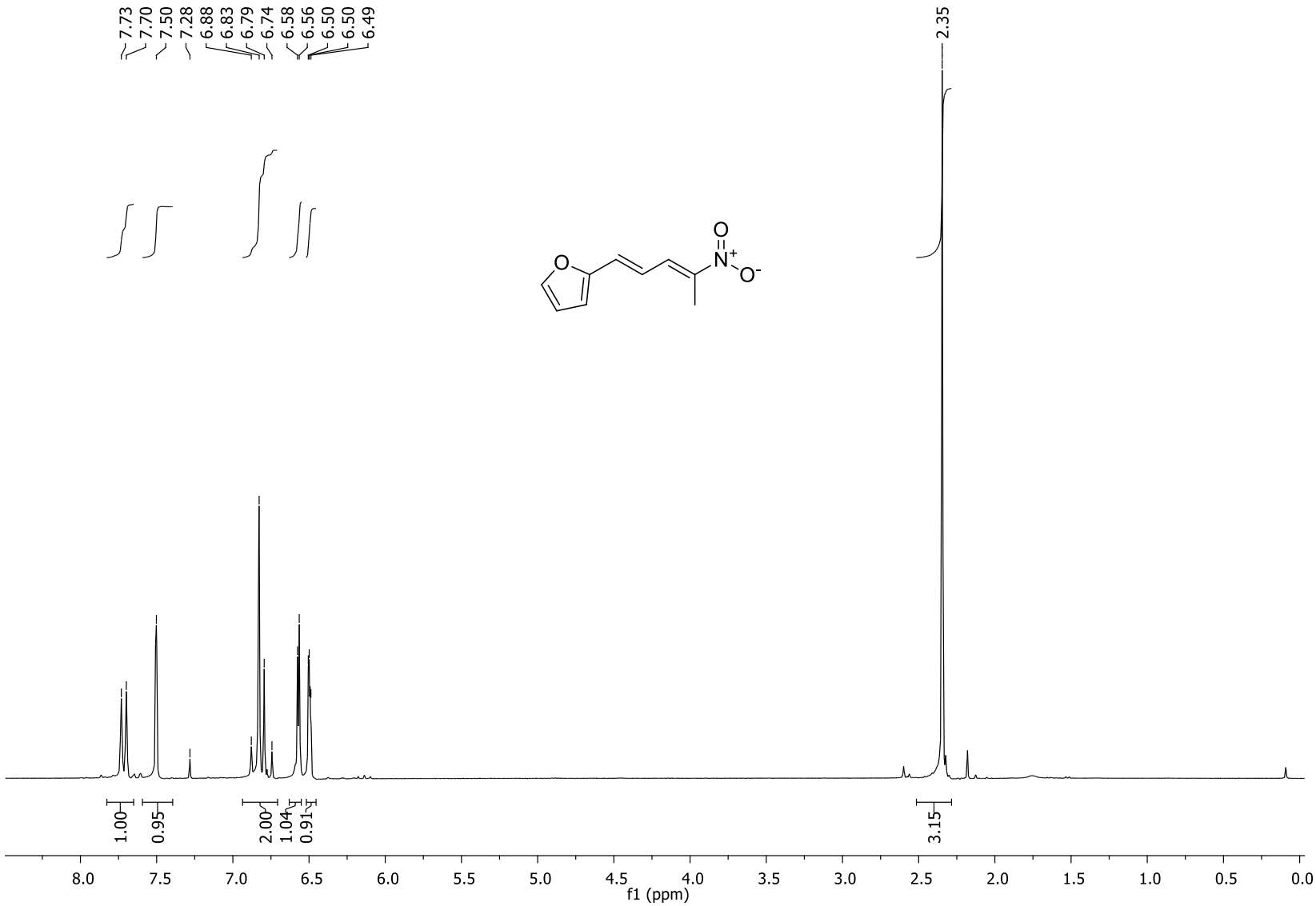
^{13}C APT NMR of (E)-2-methyl-3-(5-methylthien-2-yl)acrylaldehyde



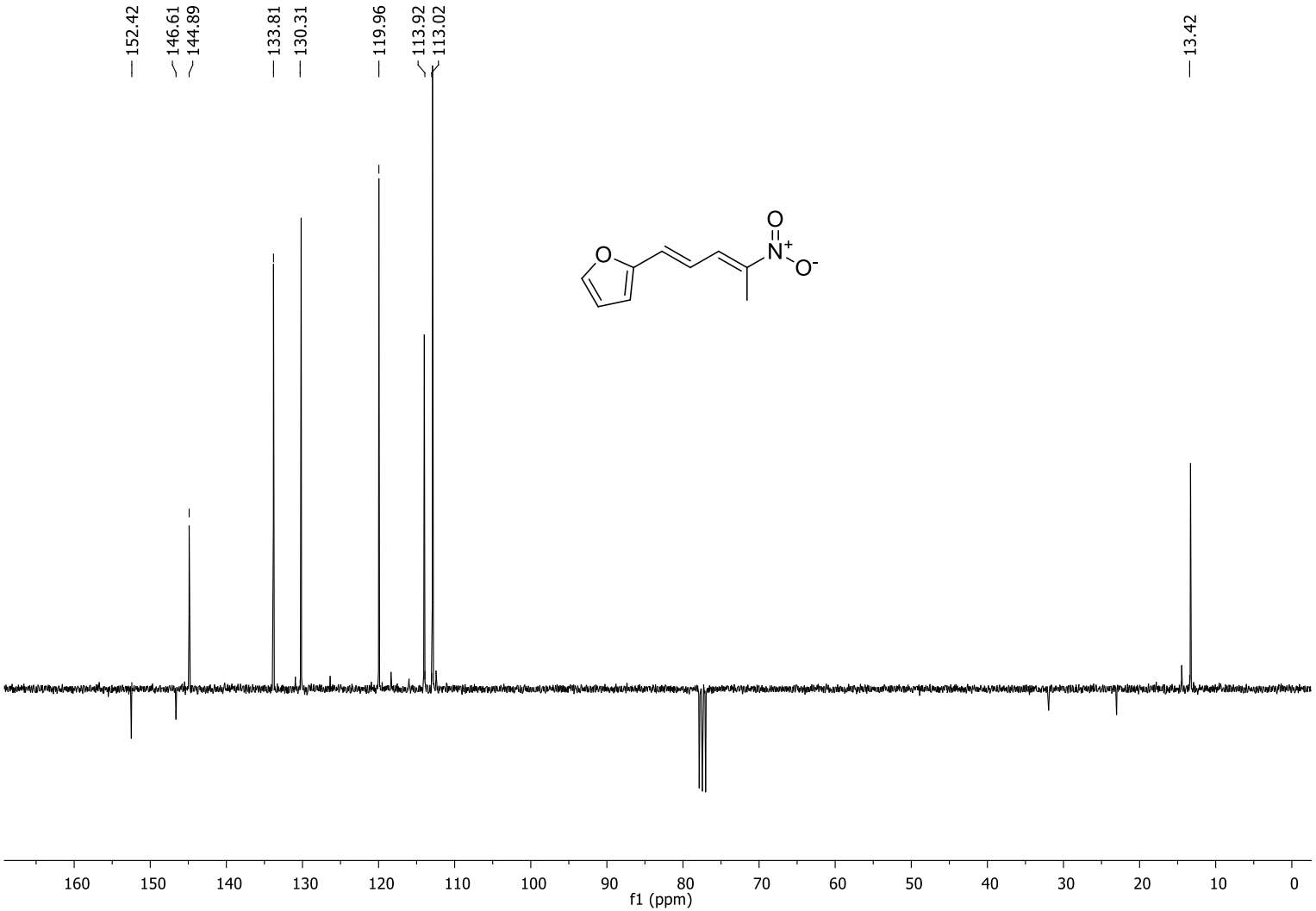
^{1}H NMR of (*1E,3E*)-4-Nitro-1-phenylpenta-1, 3-diene (**5a**)



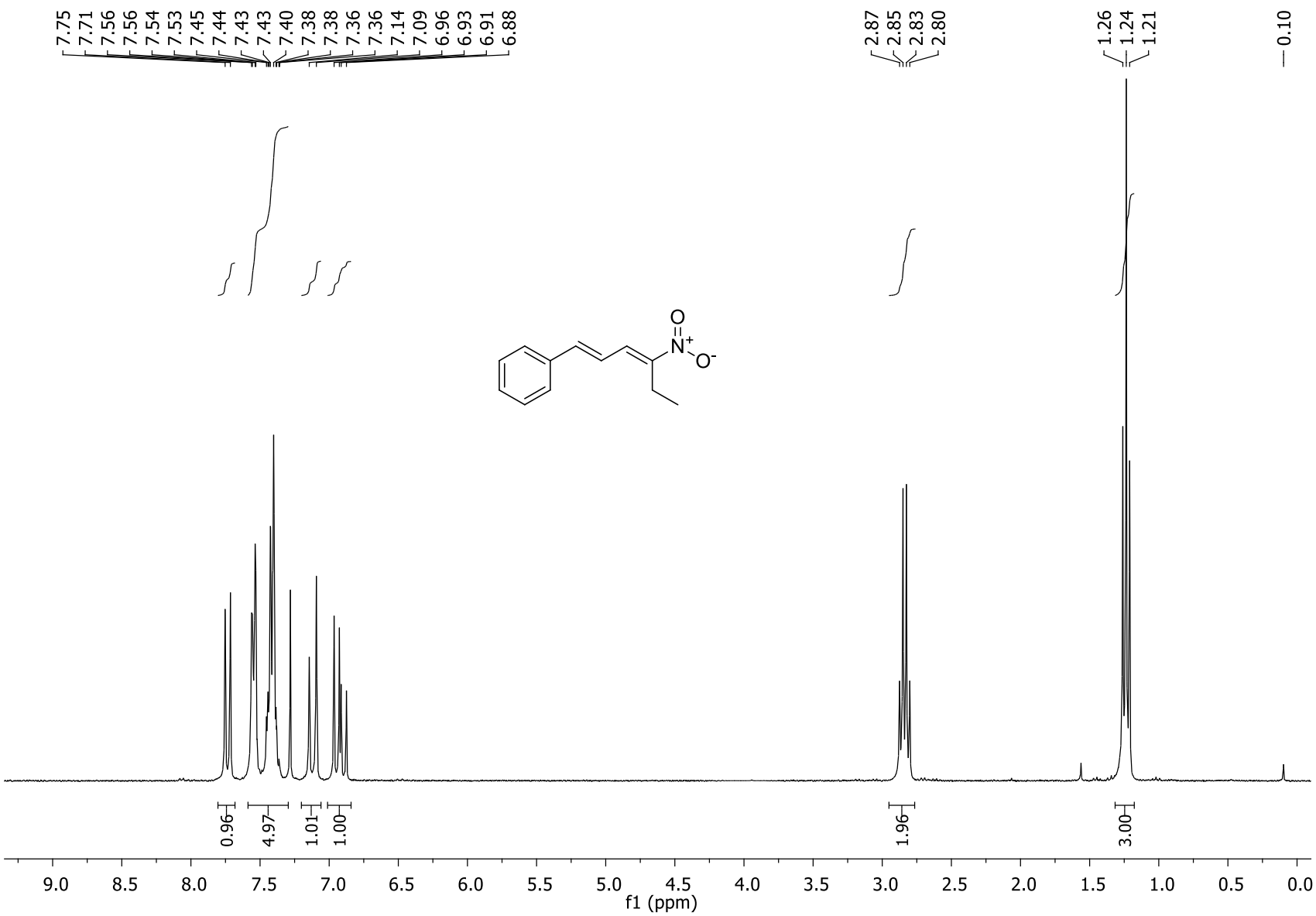
^{13}C APT NMR of (*1E,3E*)-4-Nitro-1-phenylpenta-1, 3-diene (**5a**)



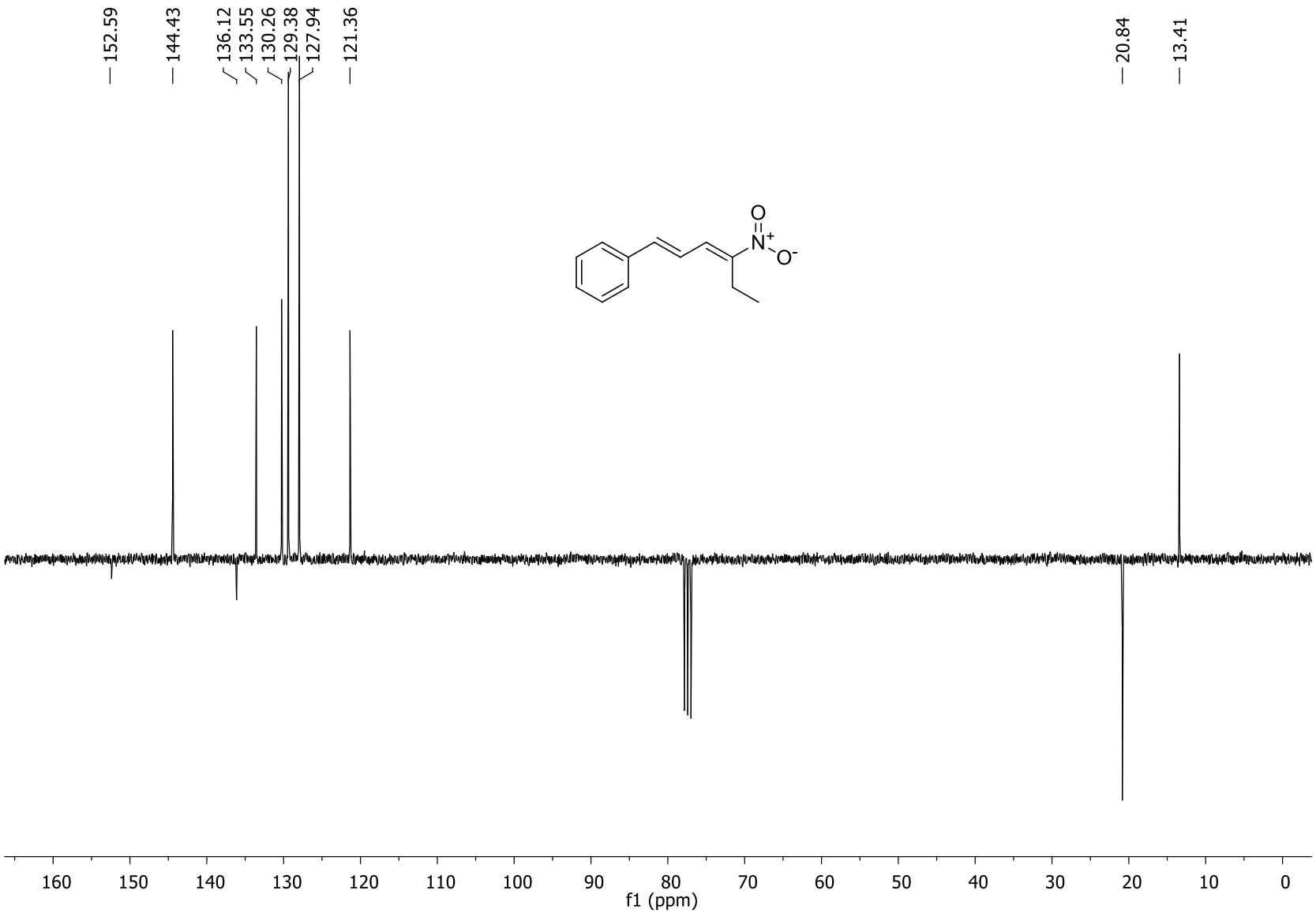
^{1}H NMR of (1E,3E) 4-nitro-1-fur-2-ylpenta-1,3-diene (**5b**)



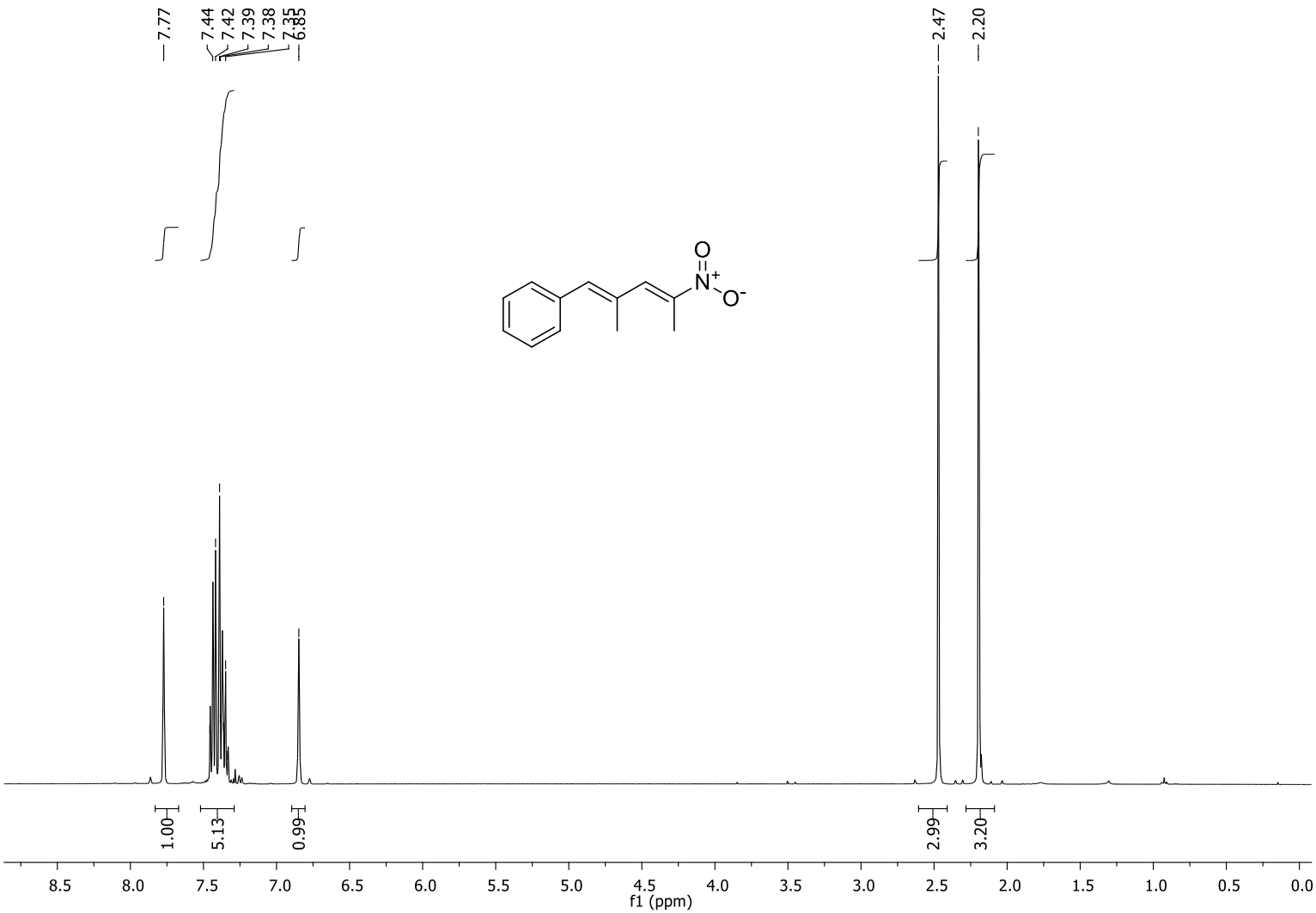
^{13}C APT NMR of (1E,3E) 4-nitro-1-fur-2-ylpenta-1,3-diene (**5b**)



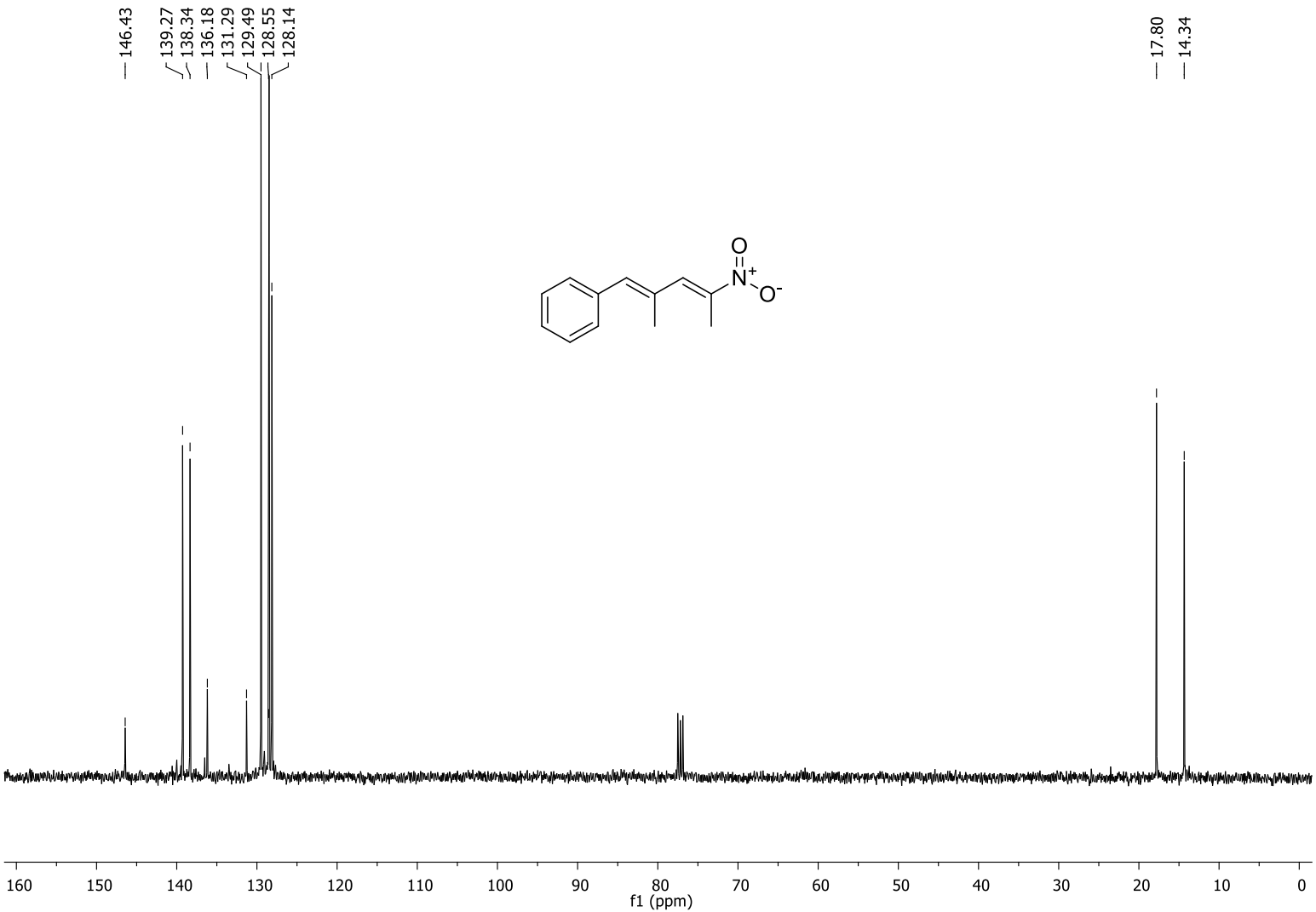
^{1}H NMR of (1E,3E)-4-nitro-1-phenylhexa-1,3-diene (**5c**)



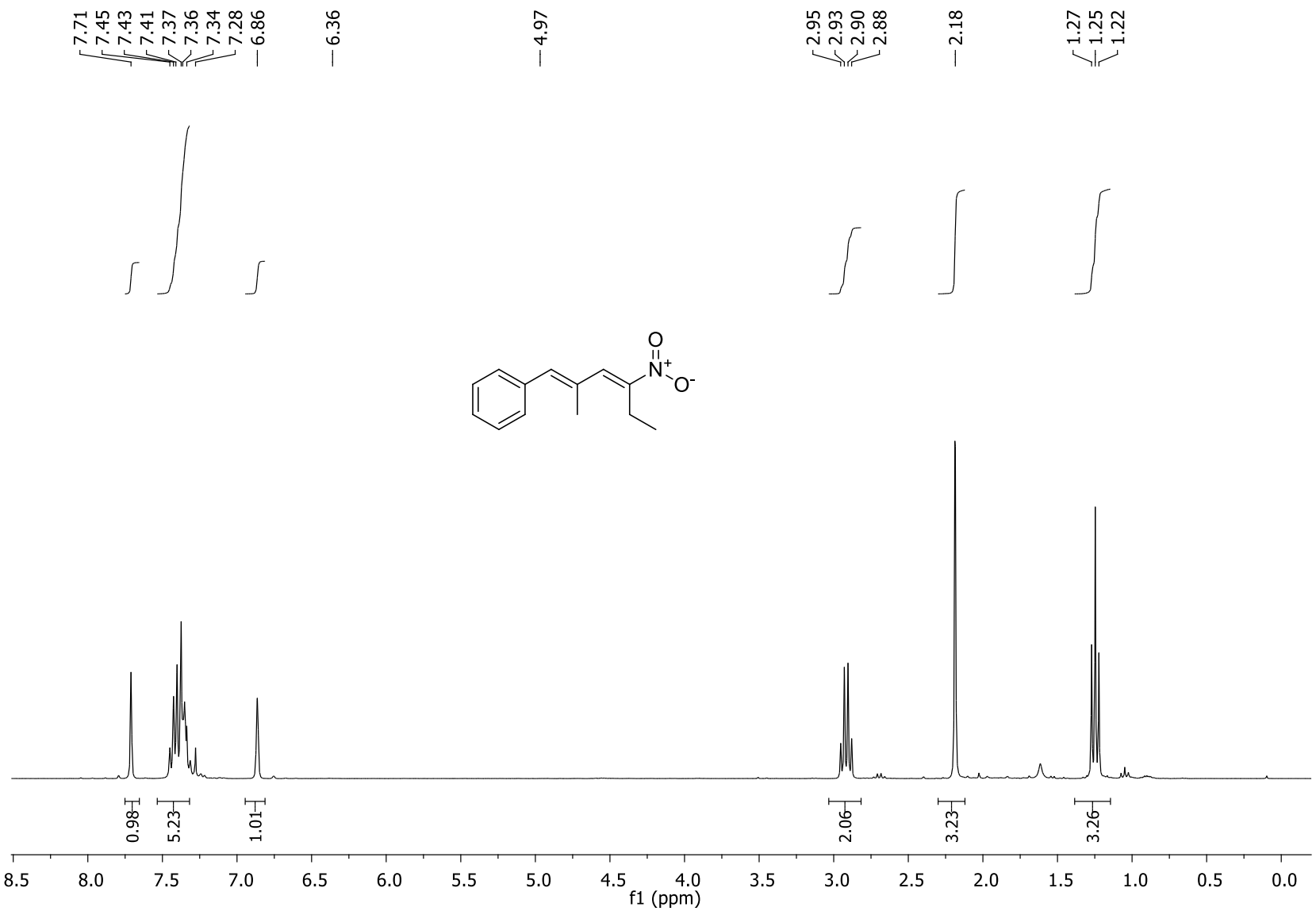
^{13}C APT NMR of (1E,3E)-4-nitro-1-phenylhexa-1,3-diene (**5c**)



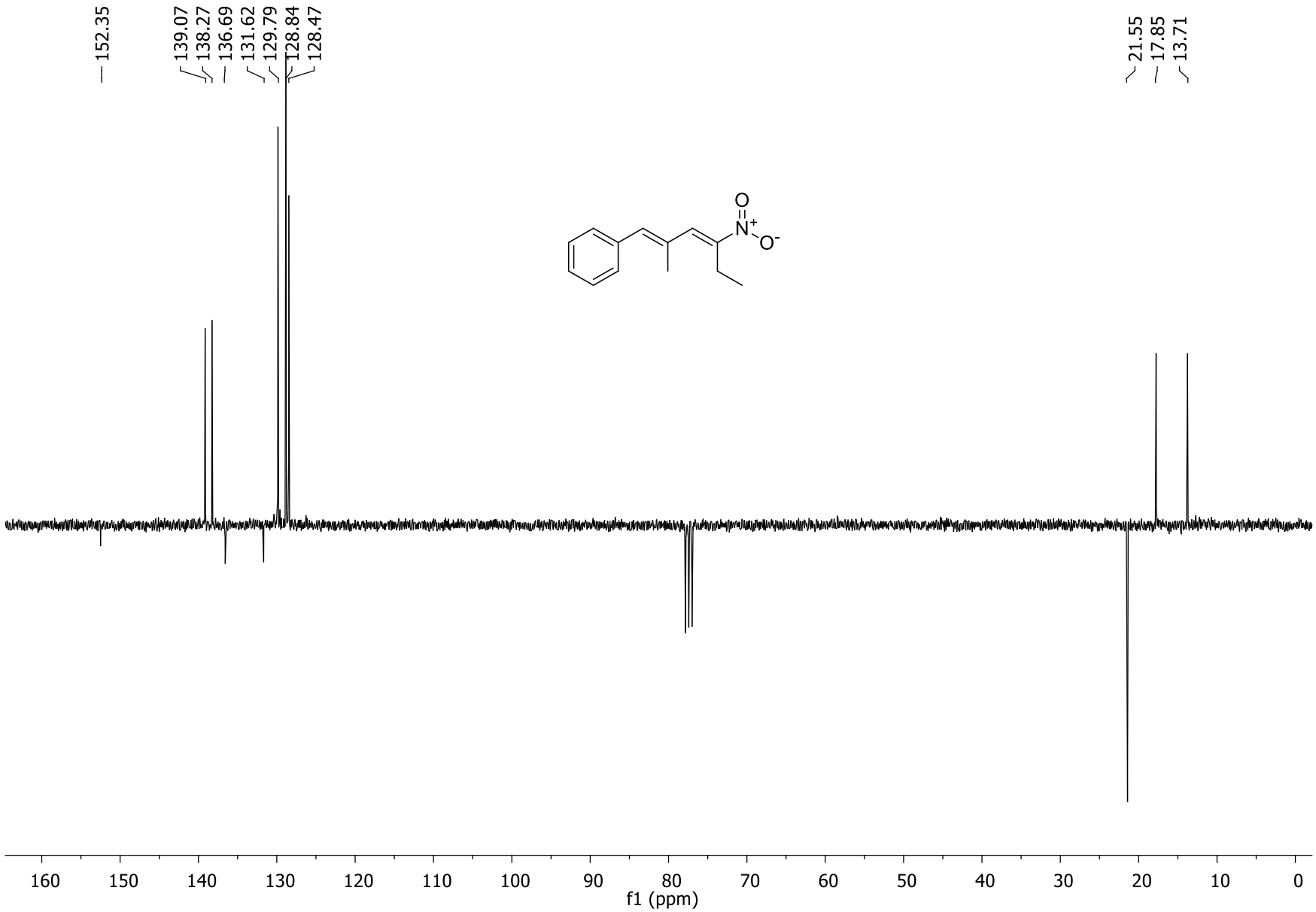
^{1}H NMR of (1E,3E)-2-methyl-4-nitro-1-phenylpenta-1,3-diene (**5d**)



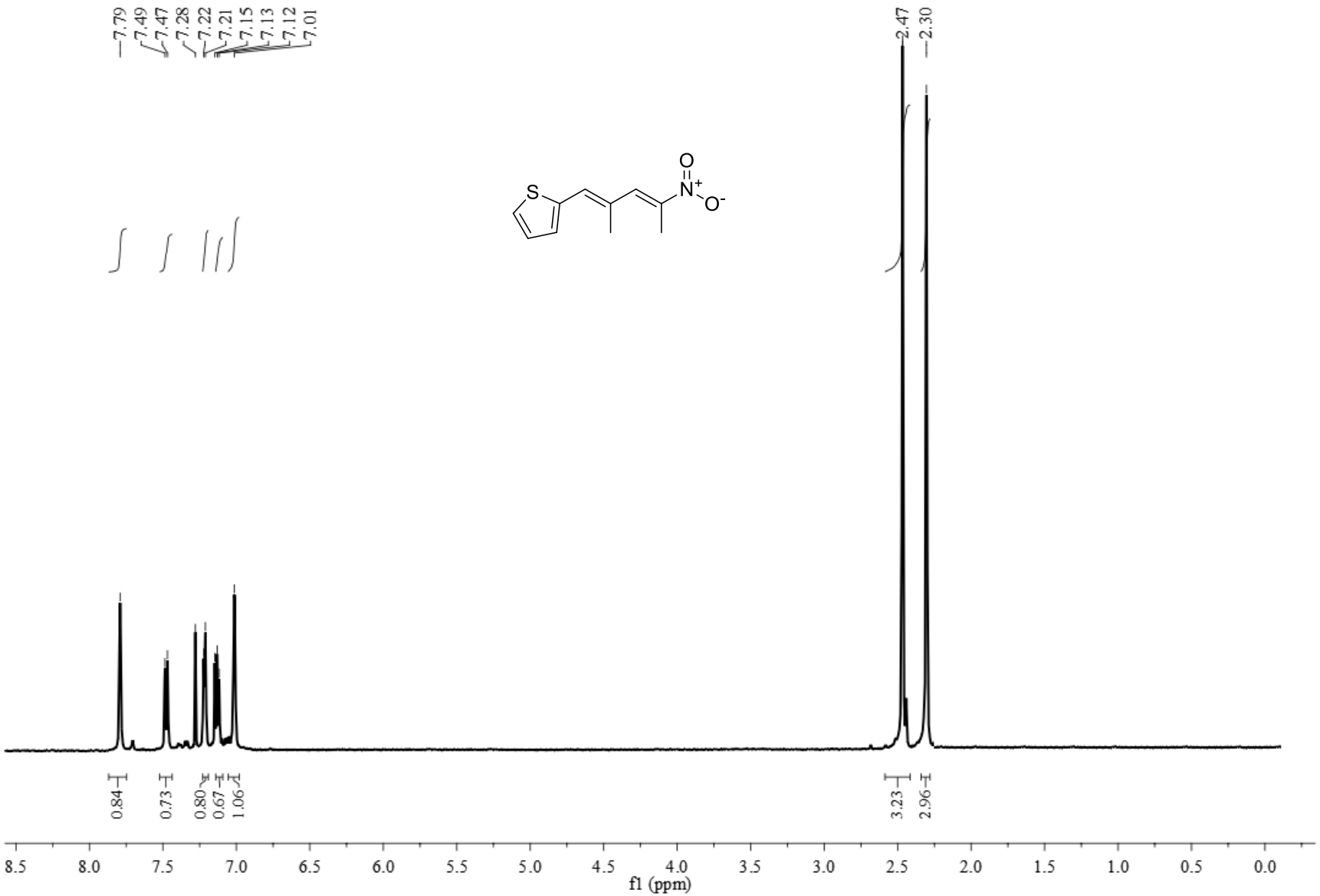
^{13}C ZGDC NMR of (1E,3E)-2-methyl-4-nitro-1-phenylpenta-1,3-diene (**5d**)



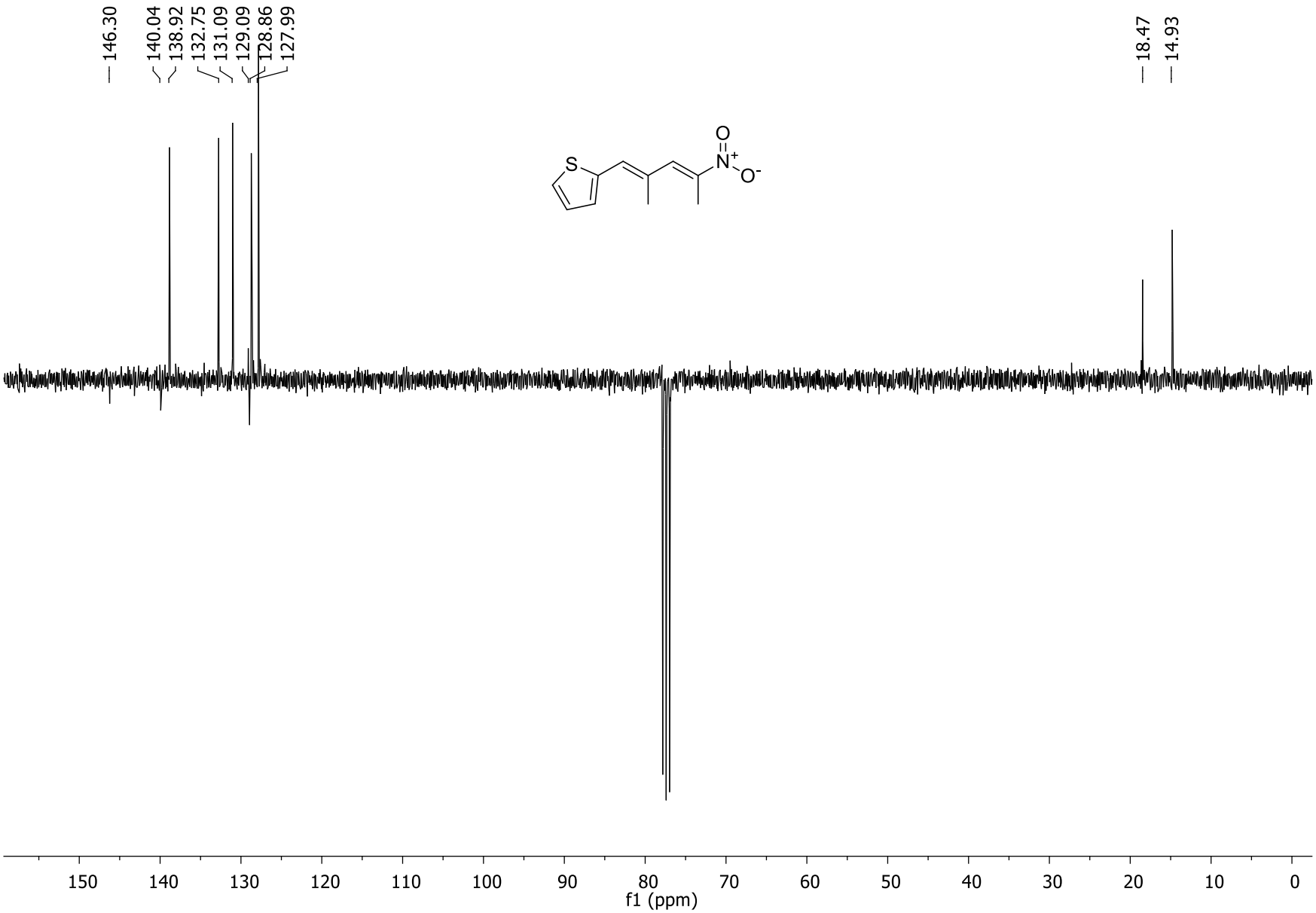
^{1}H NMR of (1E,3E)-2-methyl-4-nitro-1-phenylhexa-1,3-diene (**5e**)



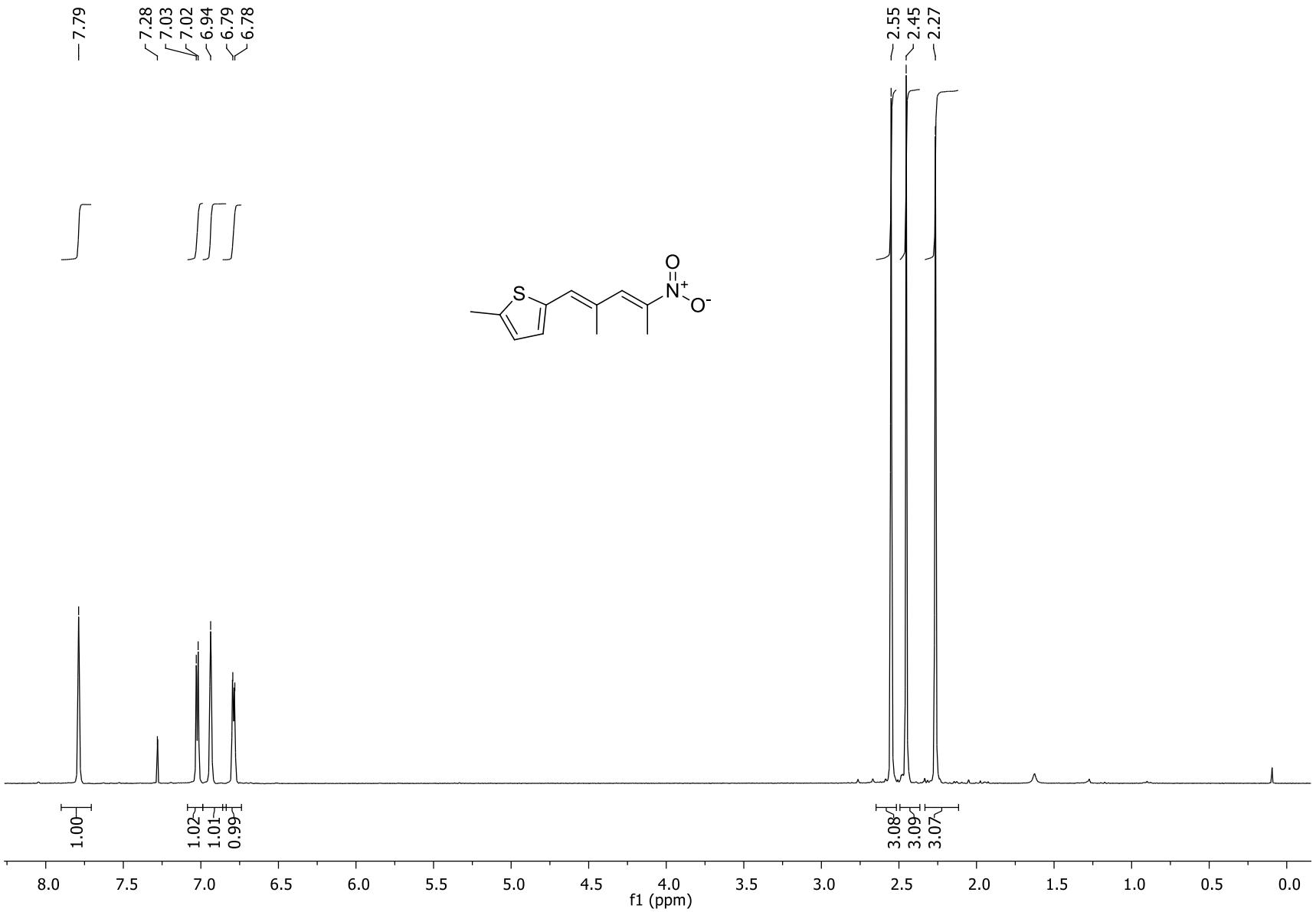
^{13}C APT NMR of (1E,3E)-2-methyl-4-nitro-1-phenylhexa-1,3-diene (**5e**)



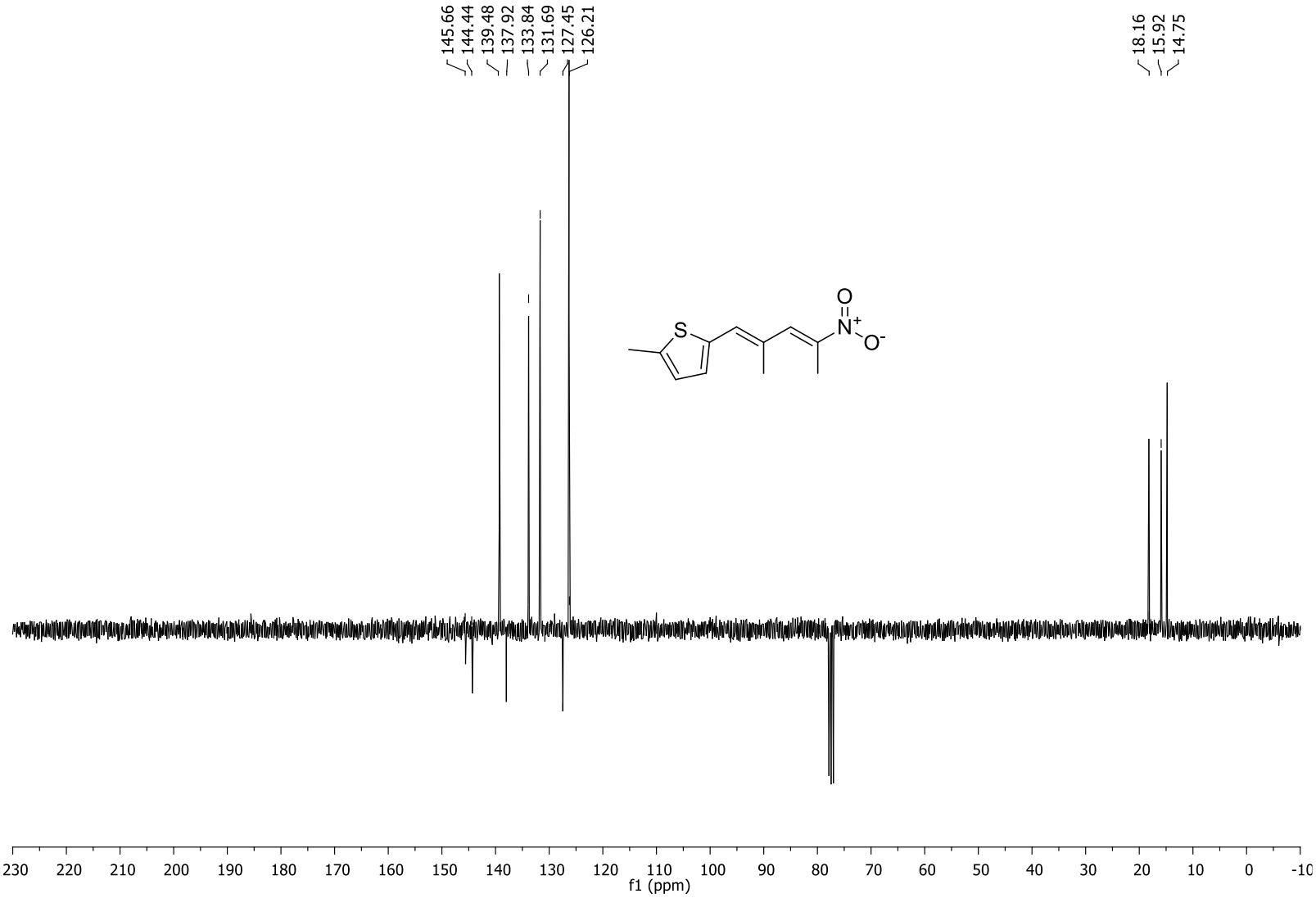
^{1}H NMR of (1E,3E)-2-methyl-4-nitro-1-thien-2-ylpenta-1,3-diene (**5f**)



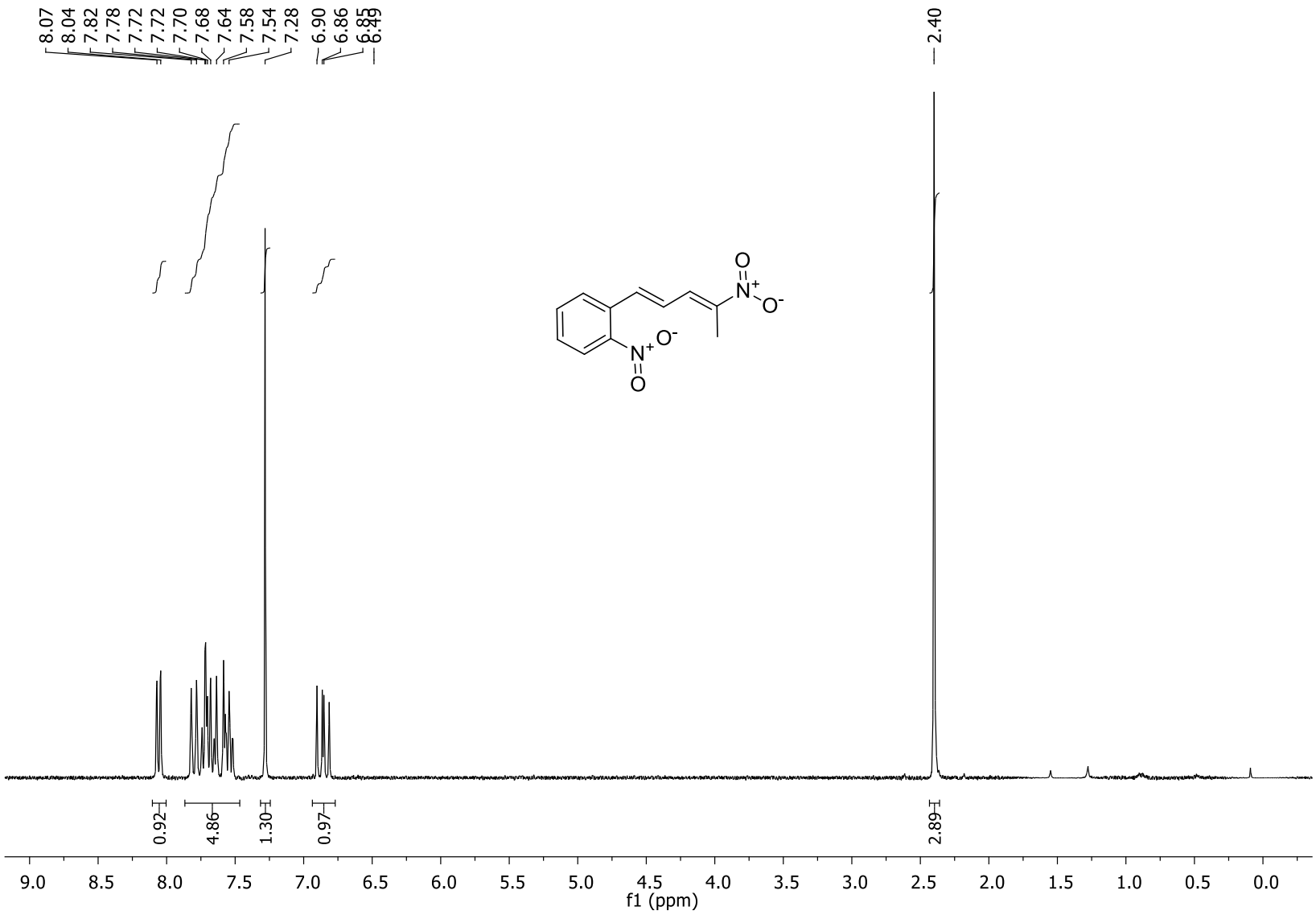
^{13}C APT NMR of (1E,3E)-2-methyl-4-nitro-1-thien-2-ylpenta-1,3-diene (**5f**)



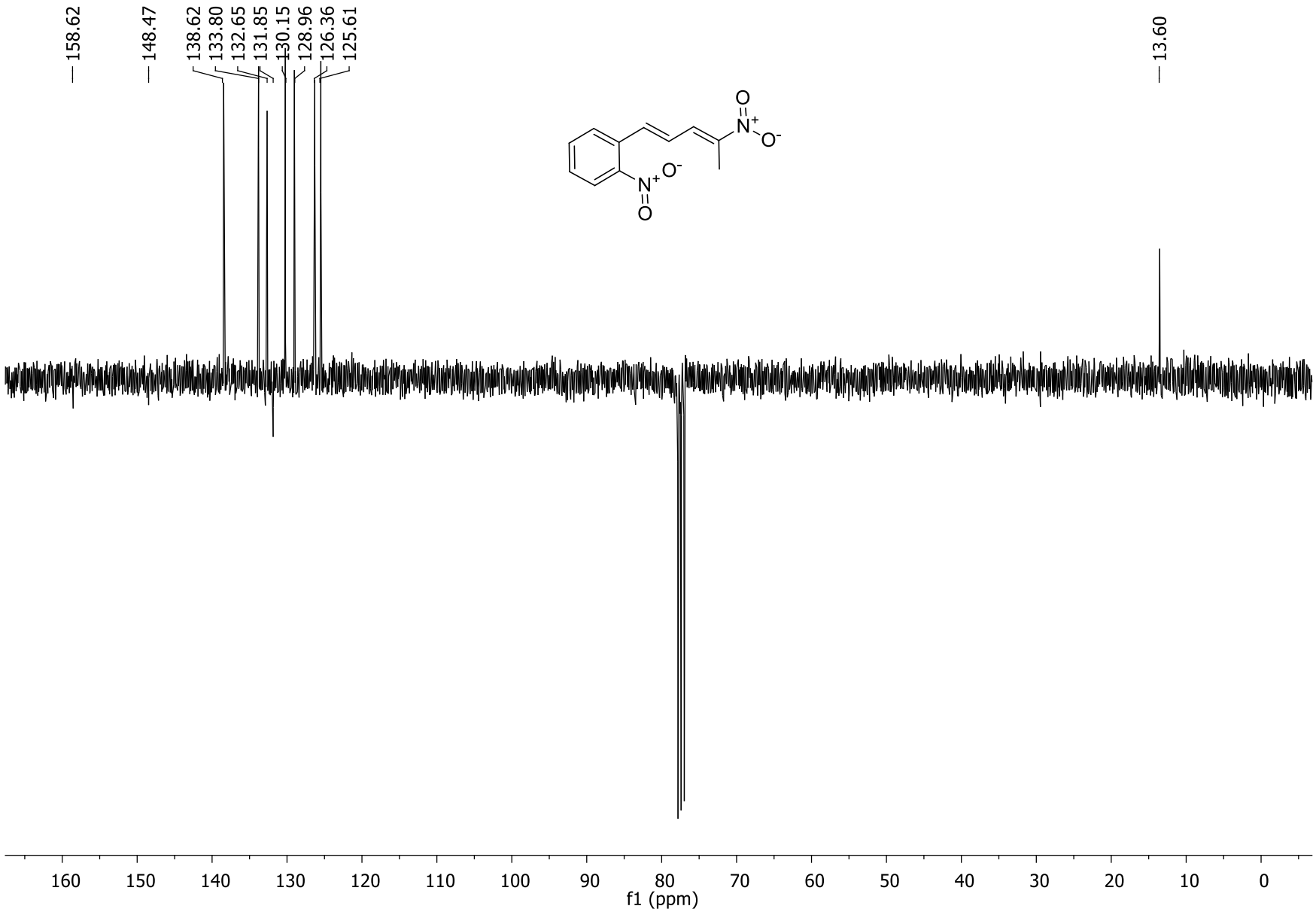
^{1}H NMR of (1E,3E)-2-methyl-4-nitro-1-(5-methylthien-2-yl)penta-1,3-diene (**5g**)



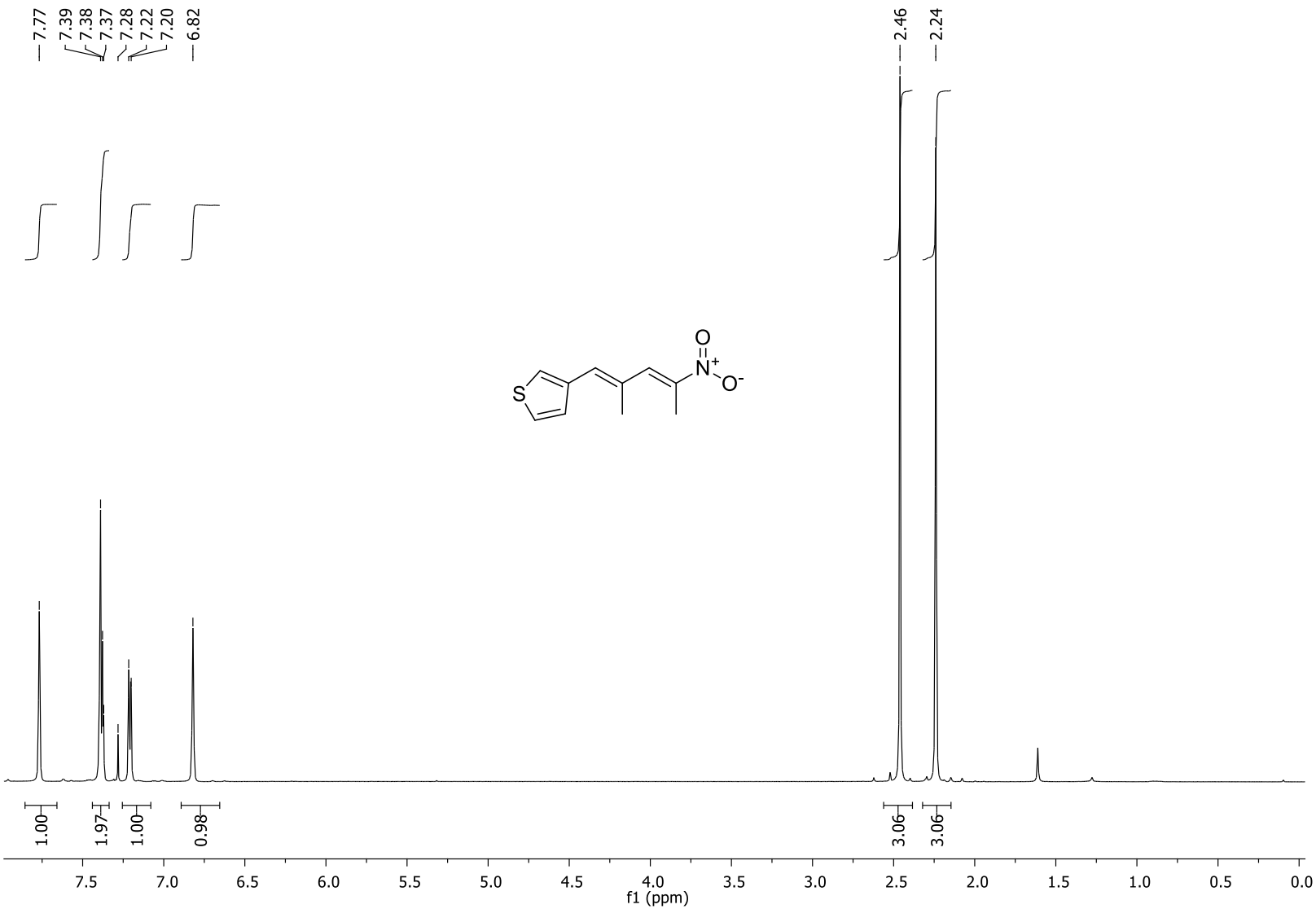
^{13}C APT NMR of (1E,3E)-2-methyl-4-nitro-1-(5-methylthien-2-yl)penta-1,3-diene (**5g**)



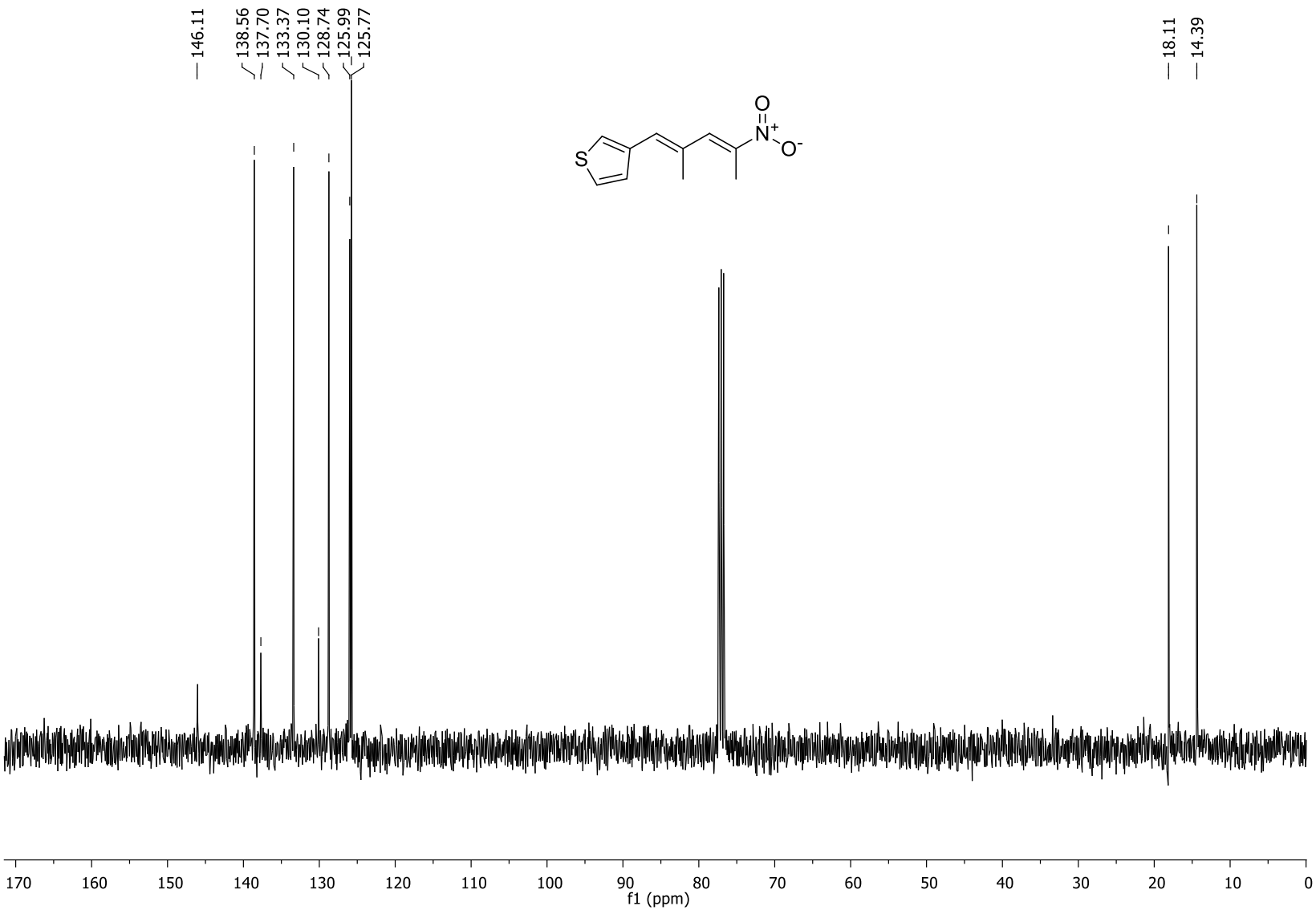
^{1}H NMR of (1E,3E)-4-nitro-1-(2-nitrophenyl)penta-1,3-diene (**5h**)



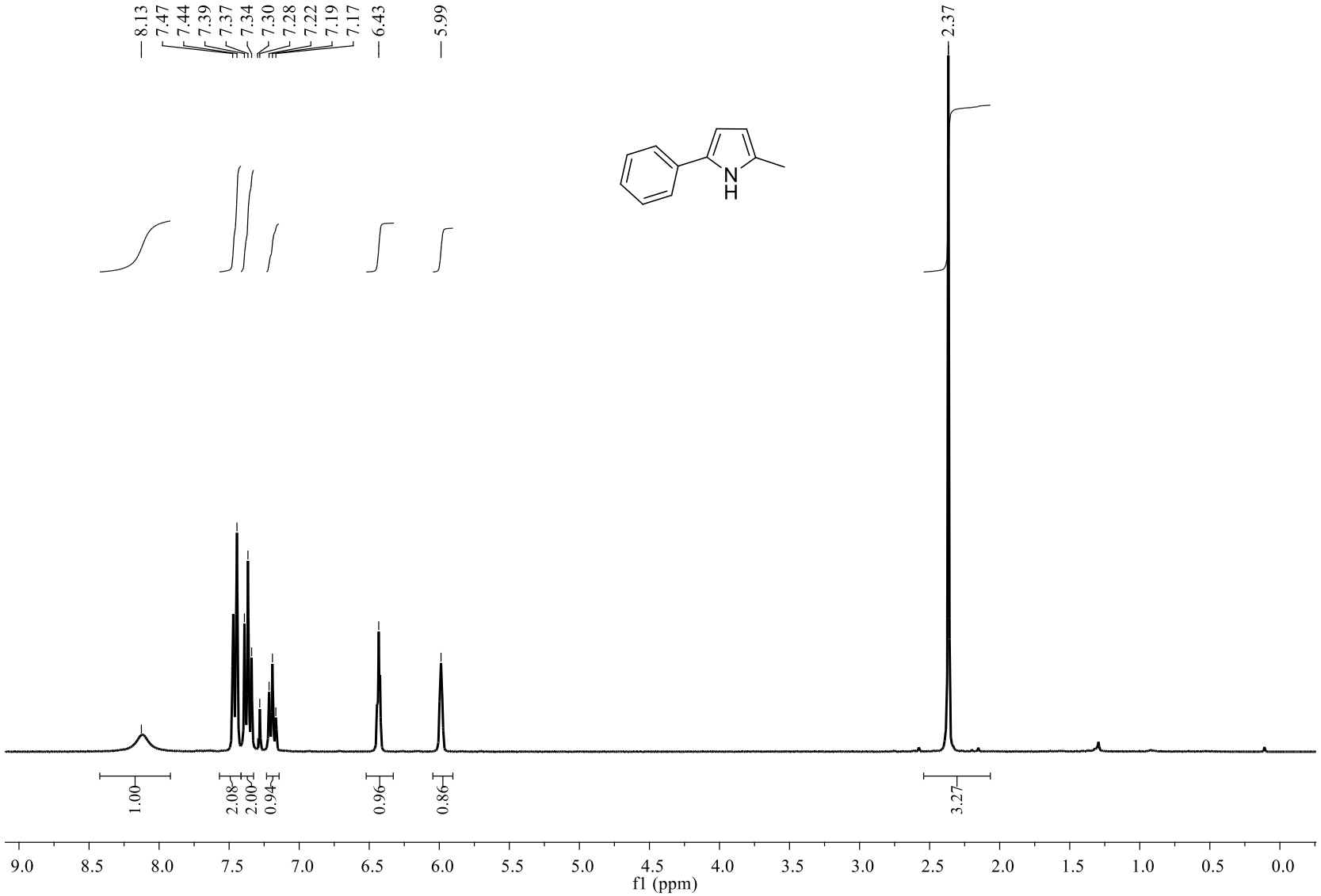
^{13}C APT NMR of (1E,3E)-4-nitro-1-(2-nitrophenyl)penta-1,3-diene (**5h**)



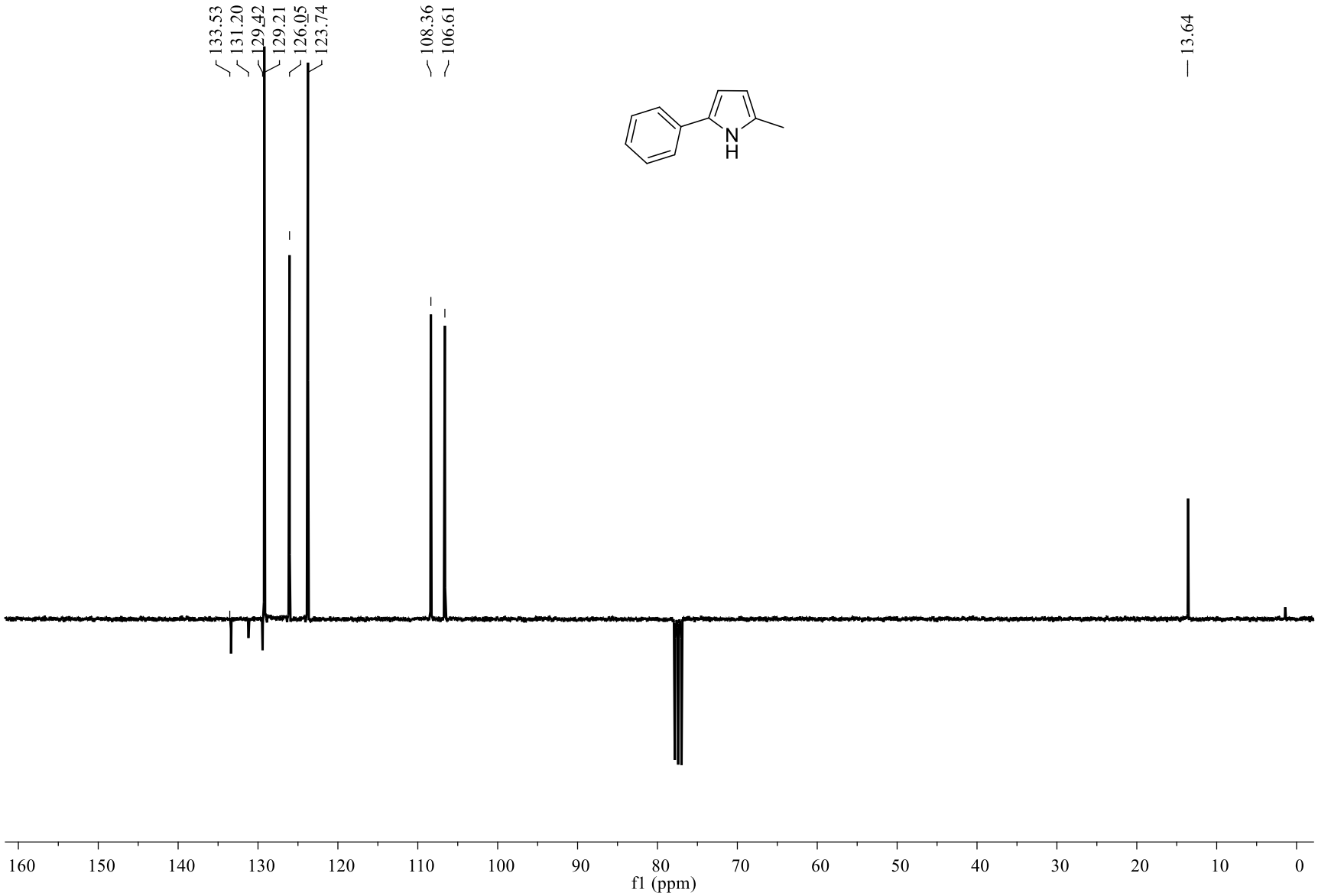
^{1}H NMR of (1E,3E)-2-methyl-4-nitro-1-thien-3-ylpenta-1,3-diene (**5j**)



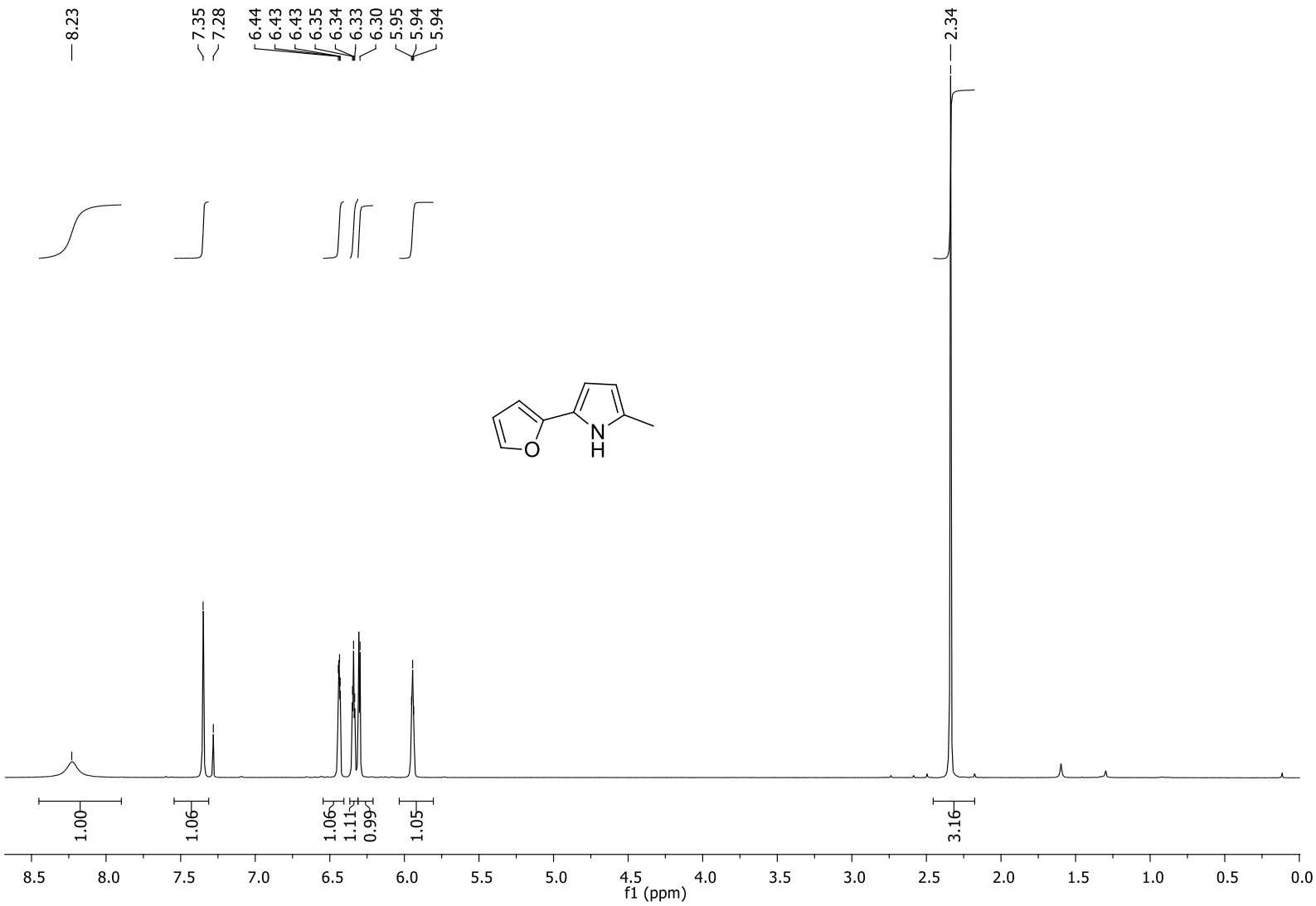
^{13}C ZGDC NMR of (1E,3E)-2-methyl-4-nitro-1-thien-3-ylpenta-1,3-diene (**5j**)



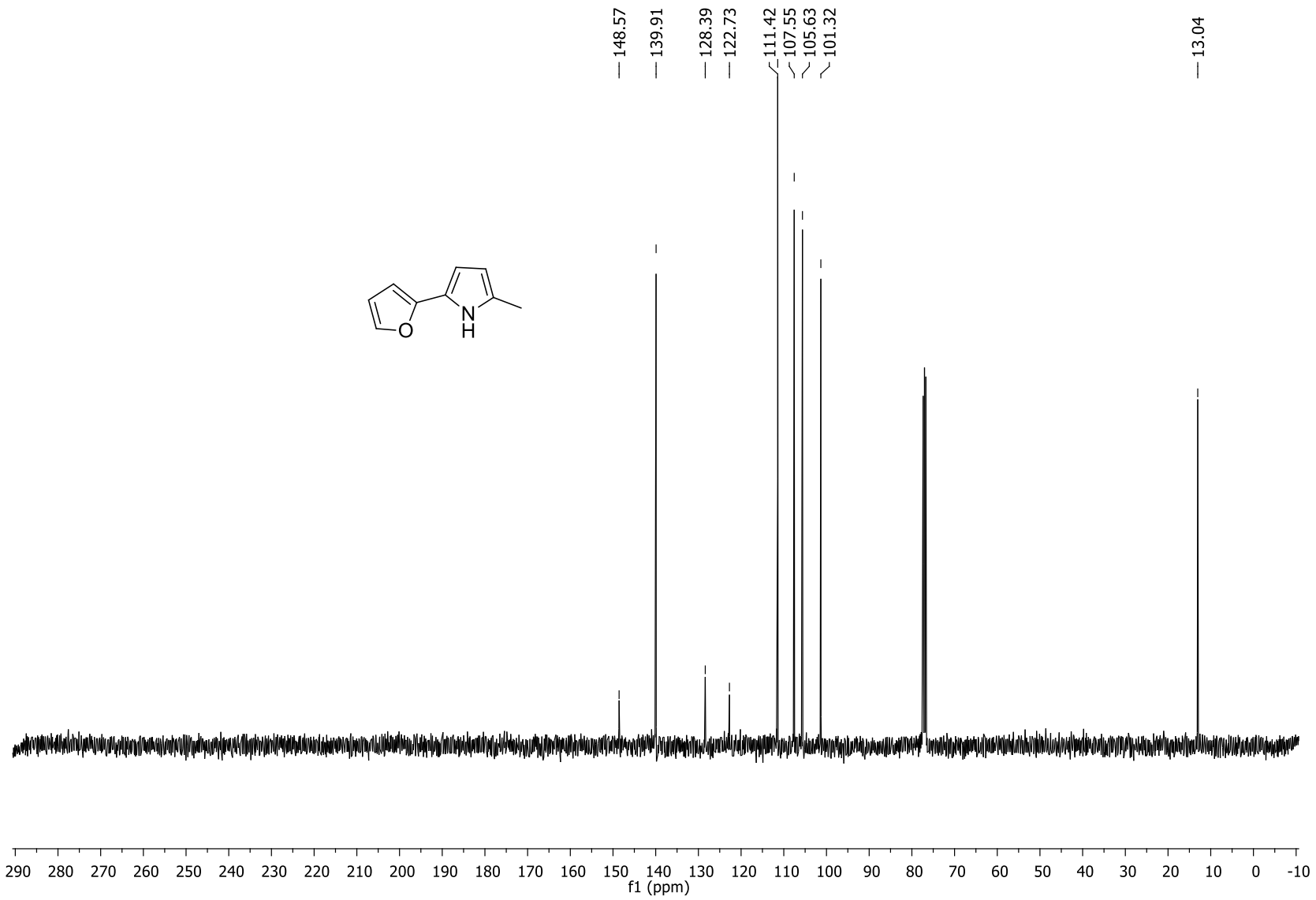
^{1}H NMR of 2-methyl-5-phenyl-1H-pyrrole (**6a**)



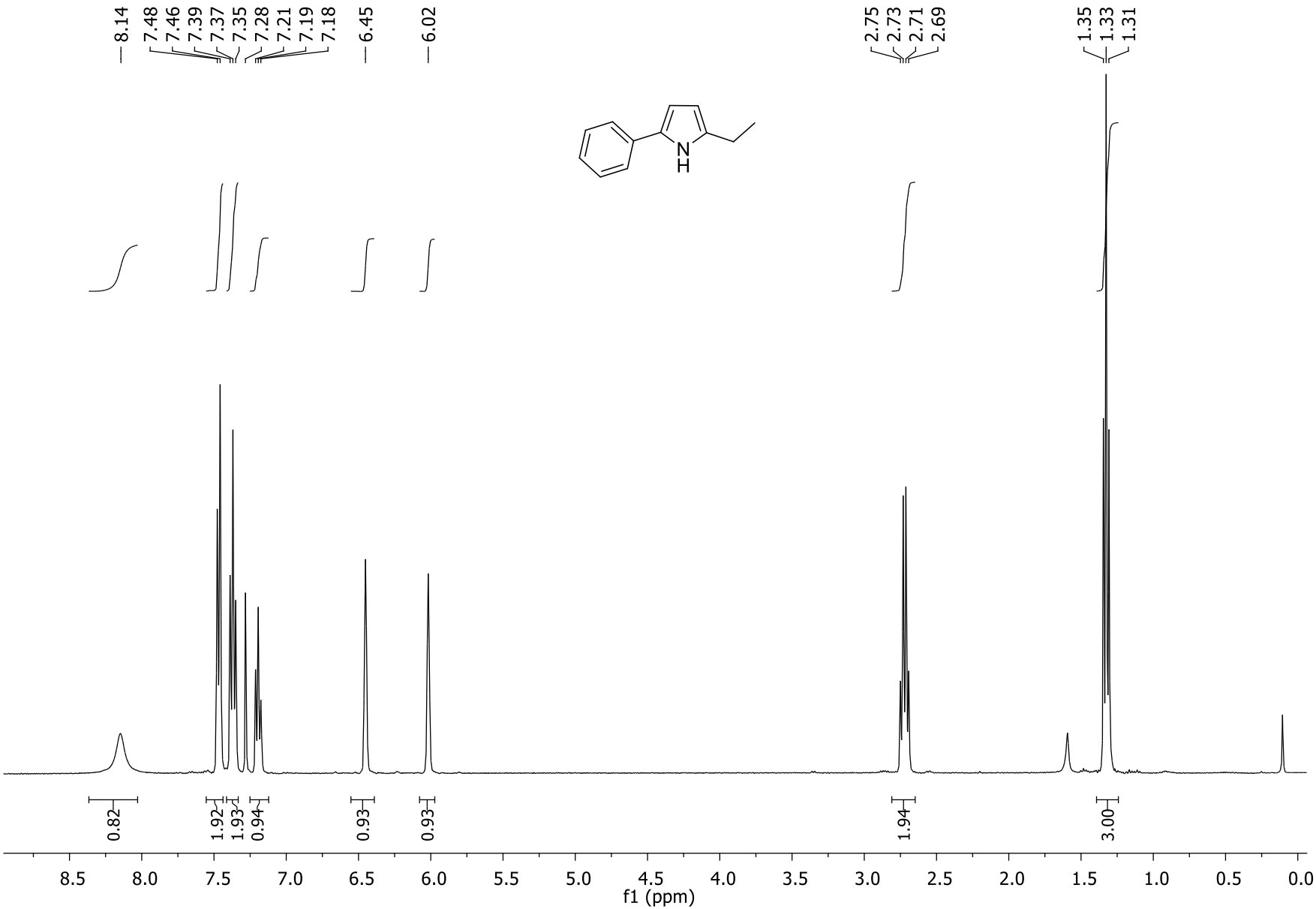
^{13}C APT NMR of 2-methyl-5-phenyl-1H-pyrrole(**6a**)



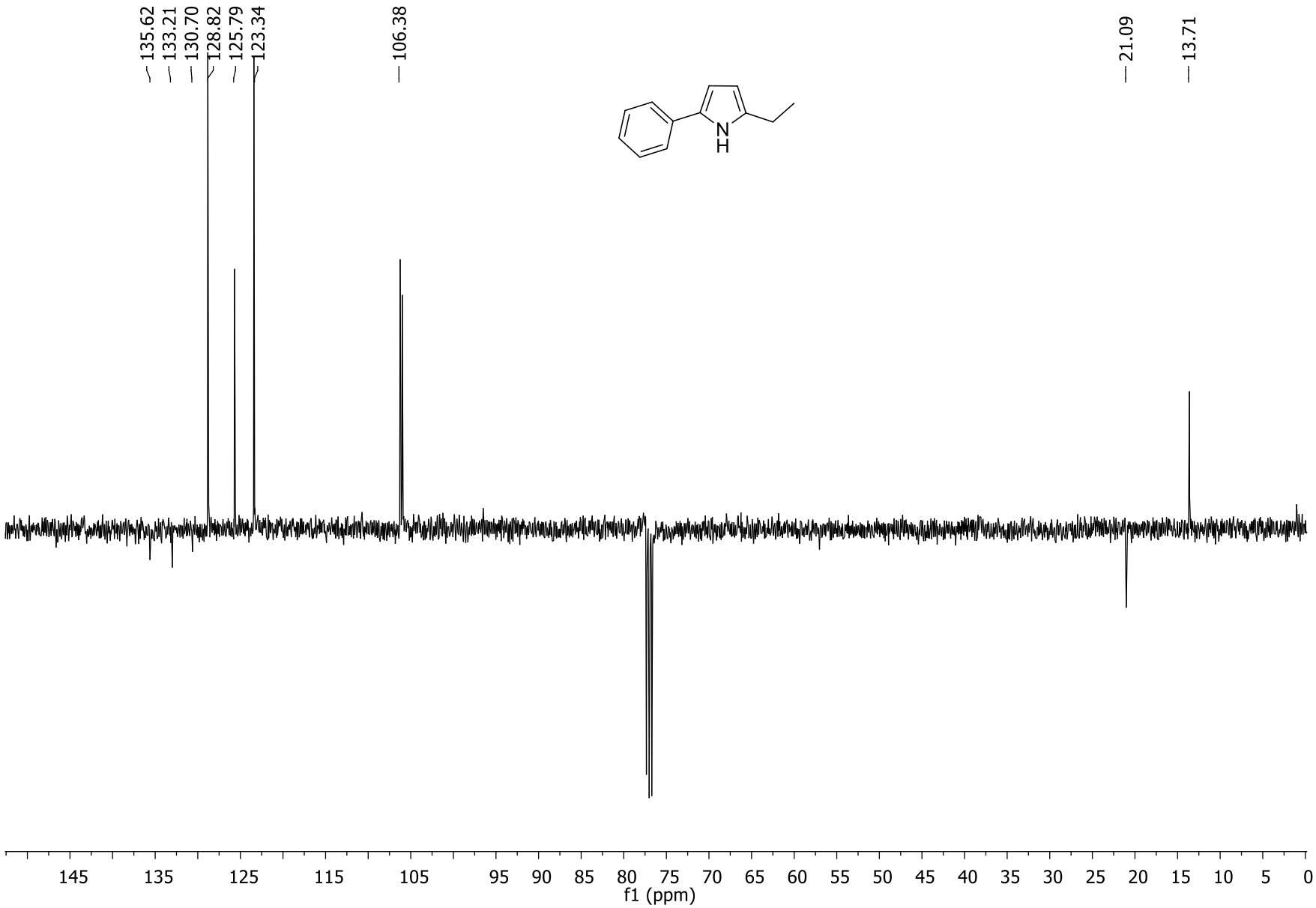
^{1}H NMR 2-(fur-2-yl)-5-methyl-1H-pyrrole (**6b**)



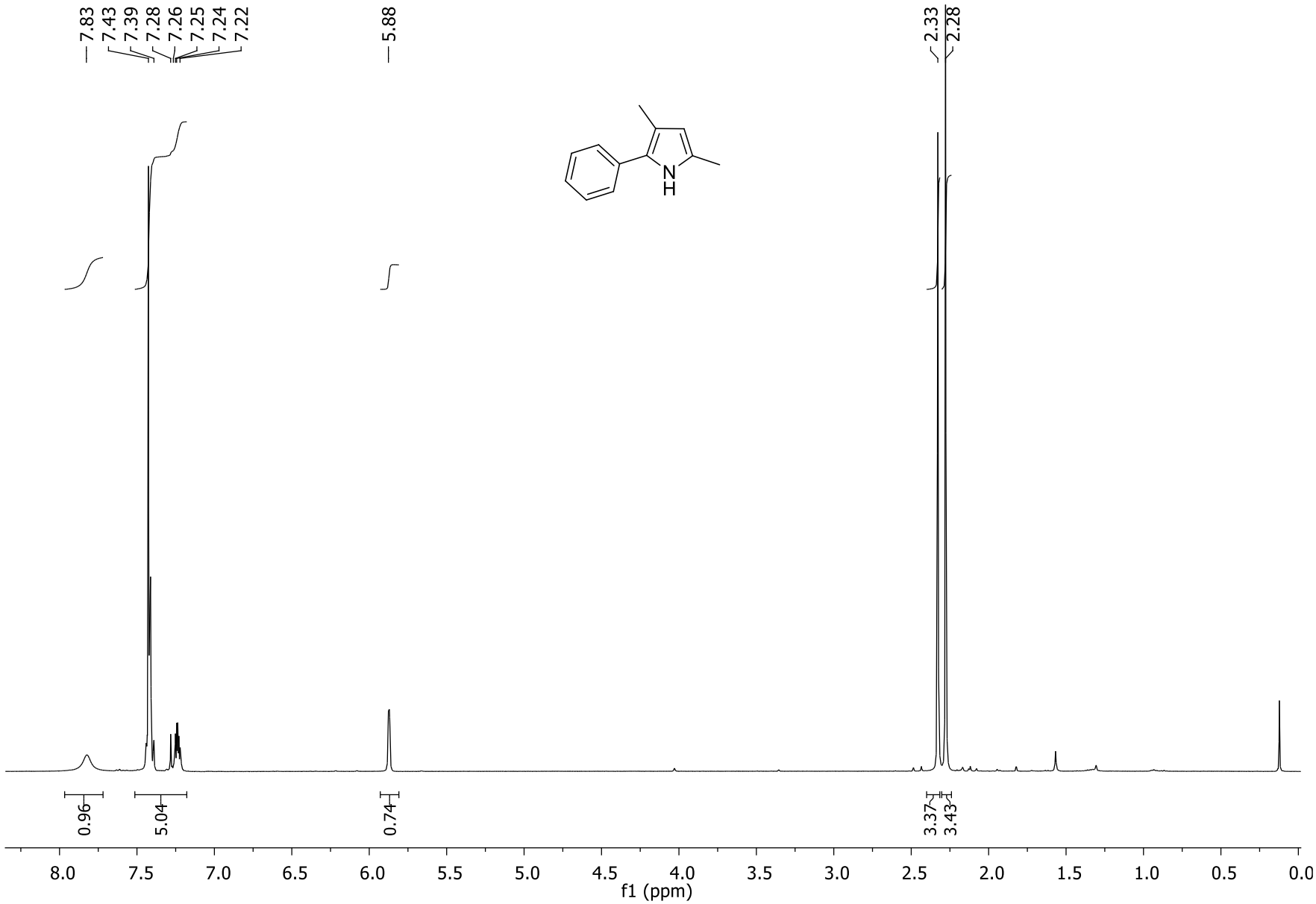
^{13}C ZGDC NMR 2-(fur-2-yl)-5-methyl-1H-pyrrole (**6b**)



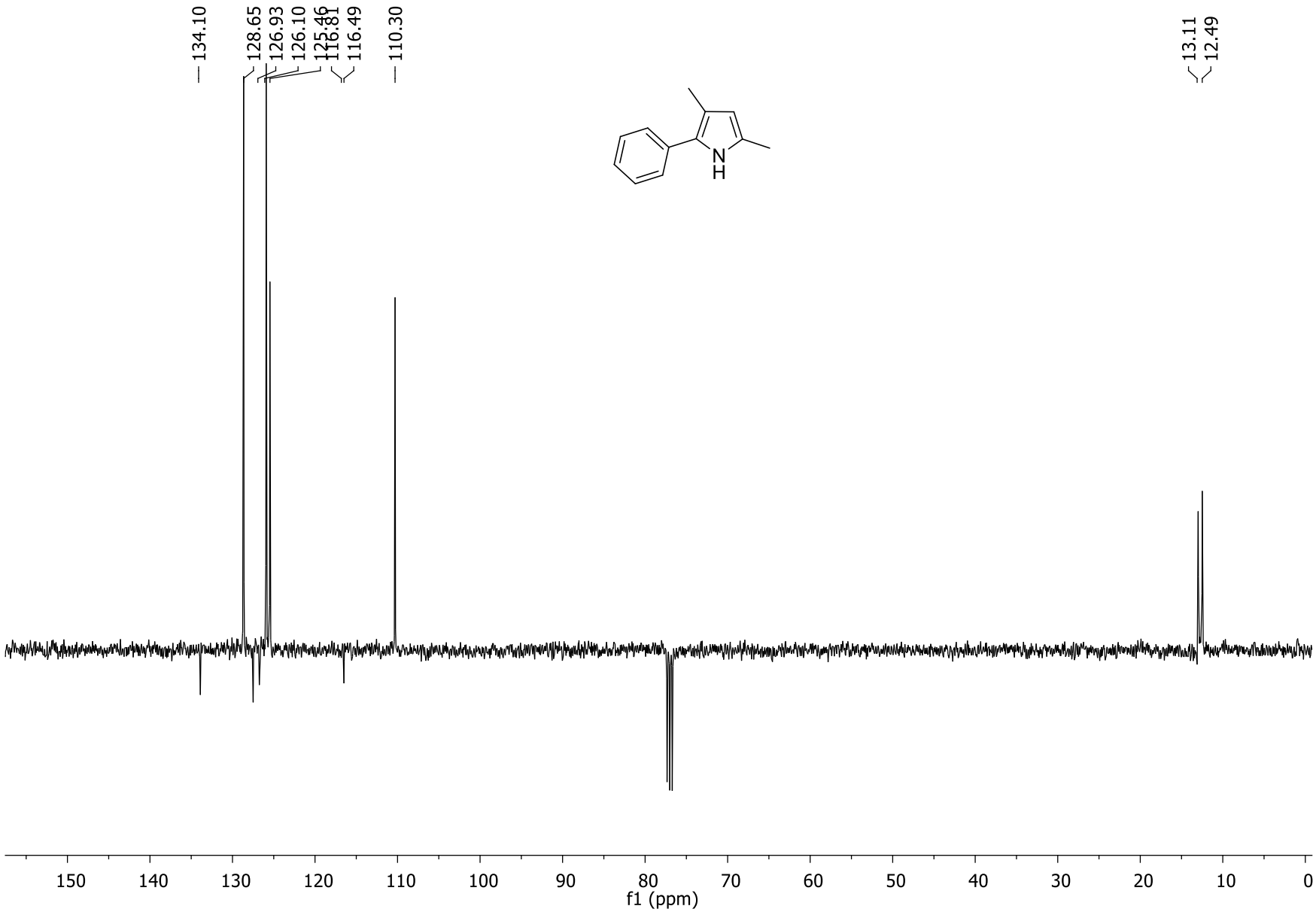
^{1}H NMR of 2-ethyl-5-phenyl-1H-pyrrole (**6c**)



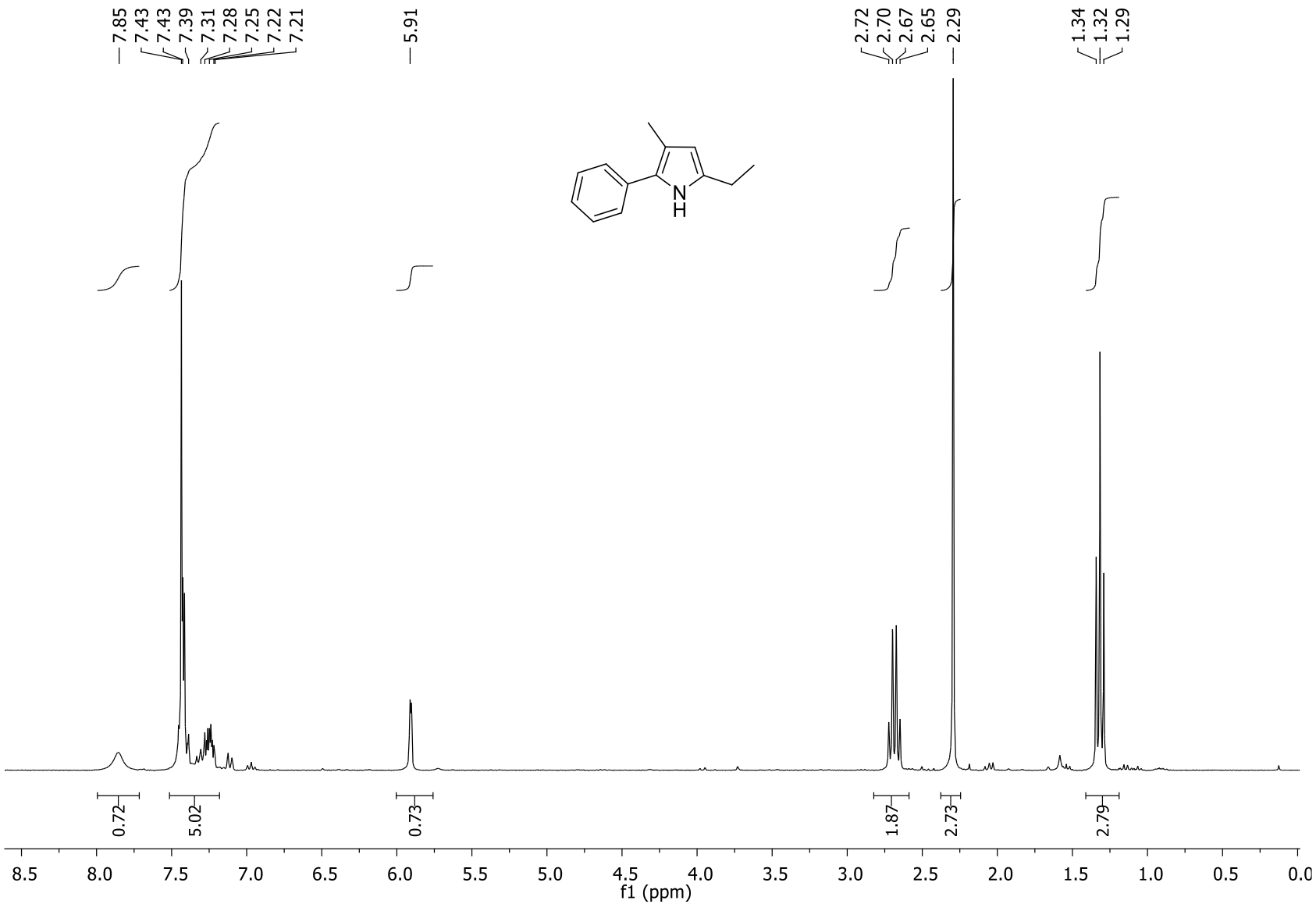
^{13}C APT NMR of 2-ethyl-5-phenyl-1H-pyrrole (**6c**)



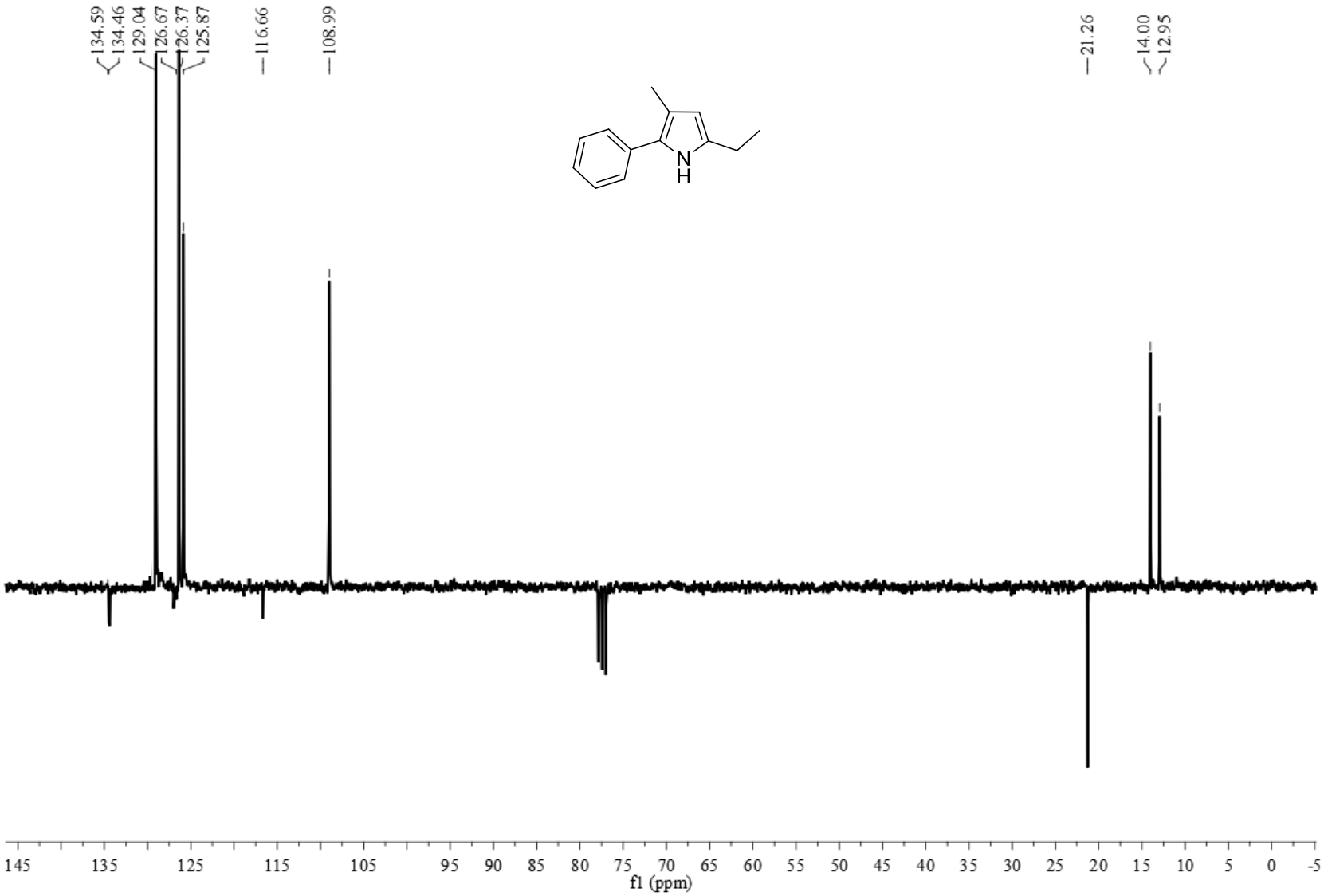
^{1}H NMR of 3,5-dimethyl-2-phenyl-1H-pyrrole(**6d**)



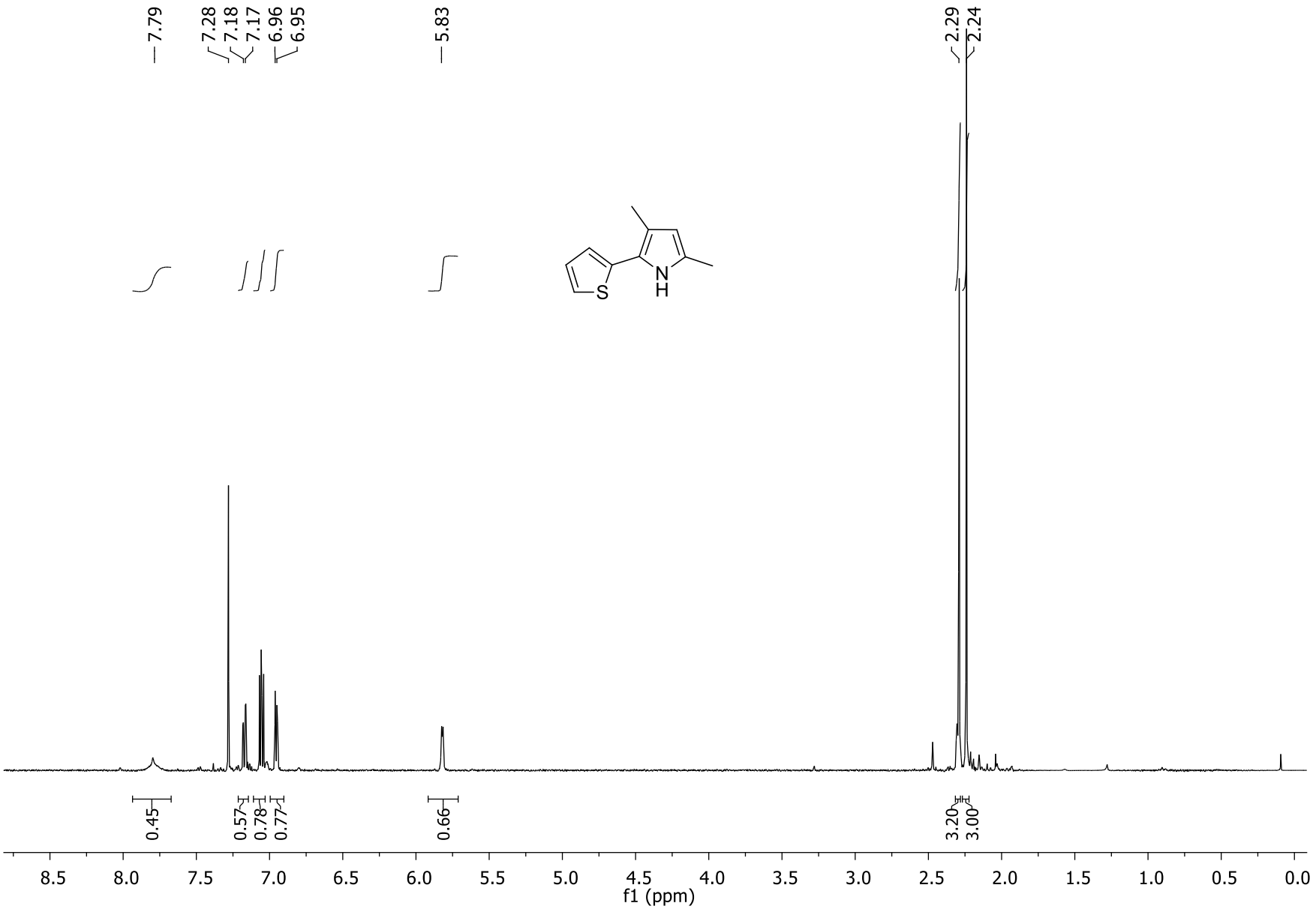
^{13}C APT NMR of 3,5-dimethyl-2-phenyl-1H-pyrrole(**6d**)



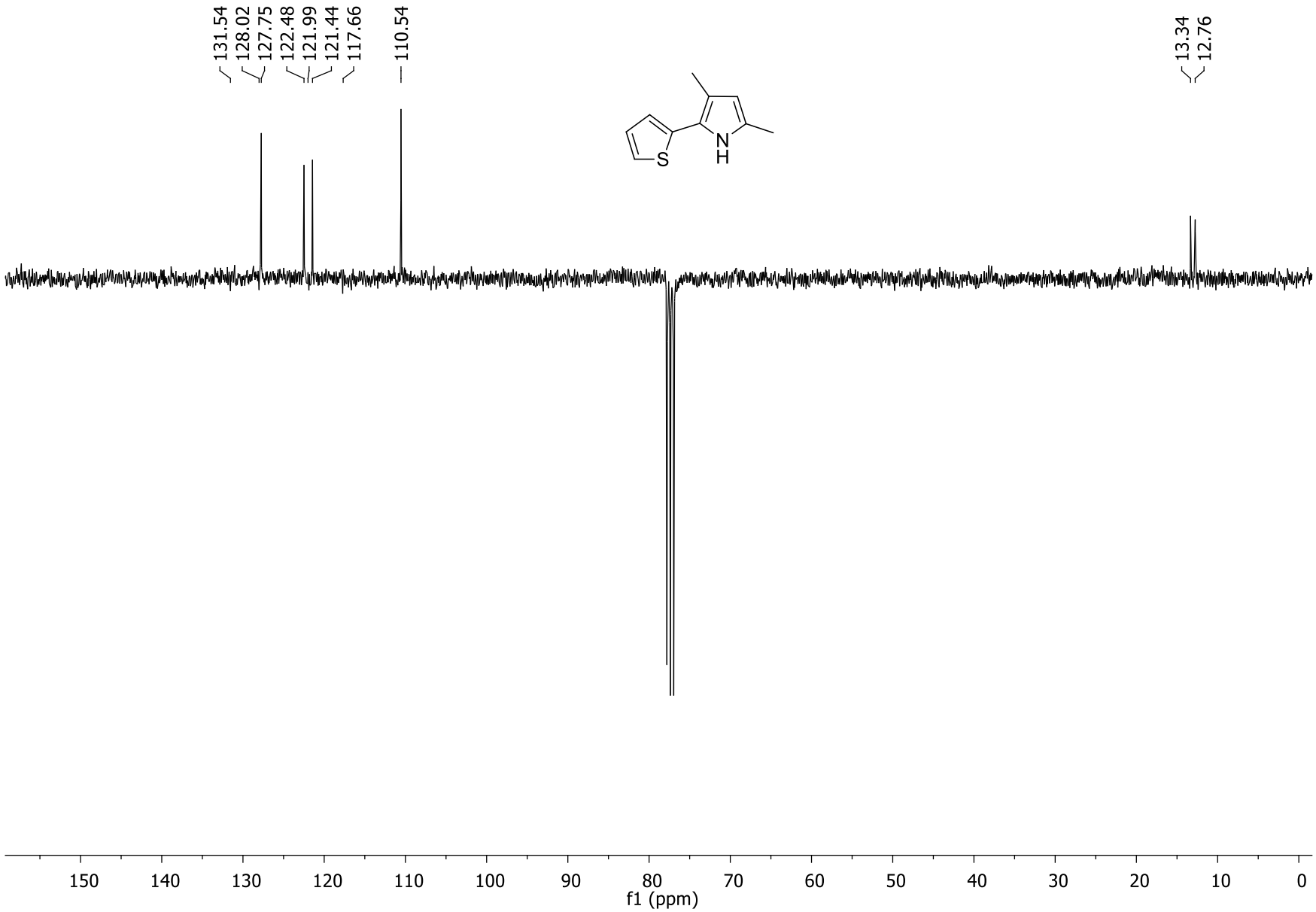
^{1}H NMR of 5-ethyl-3-methyl-2-phenyl-1H-pyrrole (**6e**)



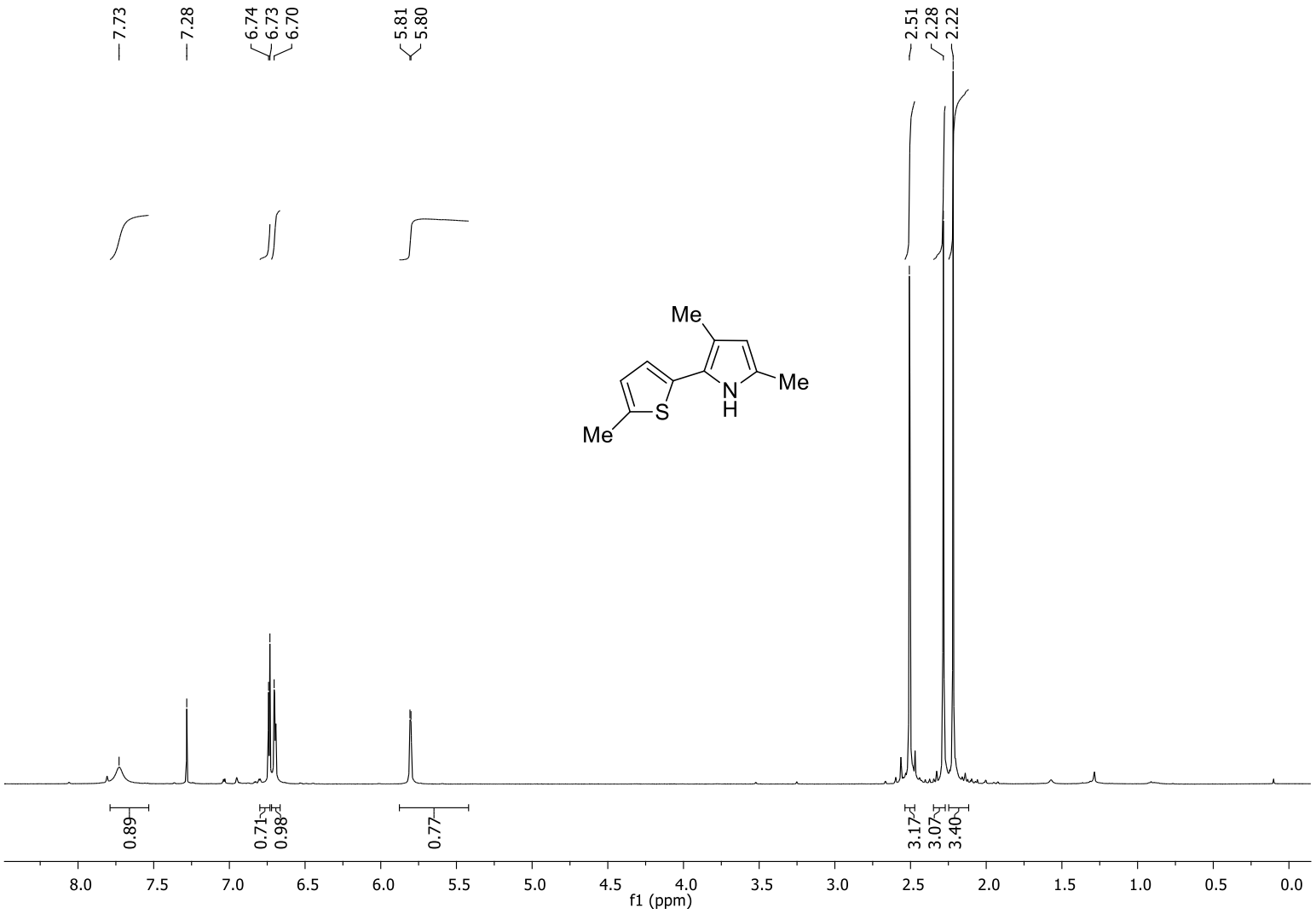
^{13}C APT NMR of 5-ethyl-3-methyl-2-phenyl-1H-pyrrole (**6e**)



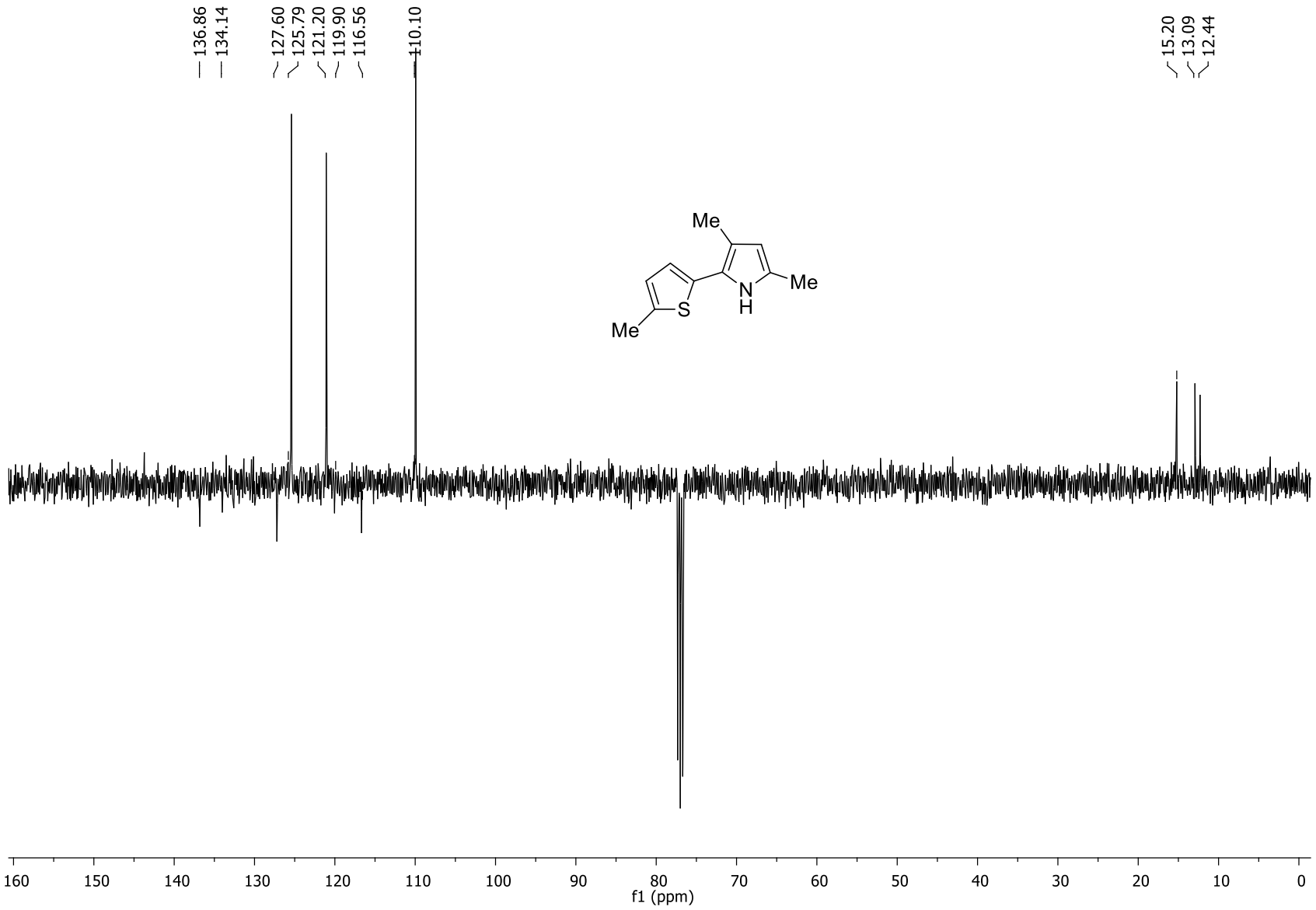
^{1}H NMR of 3,5-dimethyl-2-(thien-2-yl)-1H-pyrrole (**6f**)



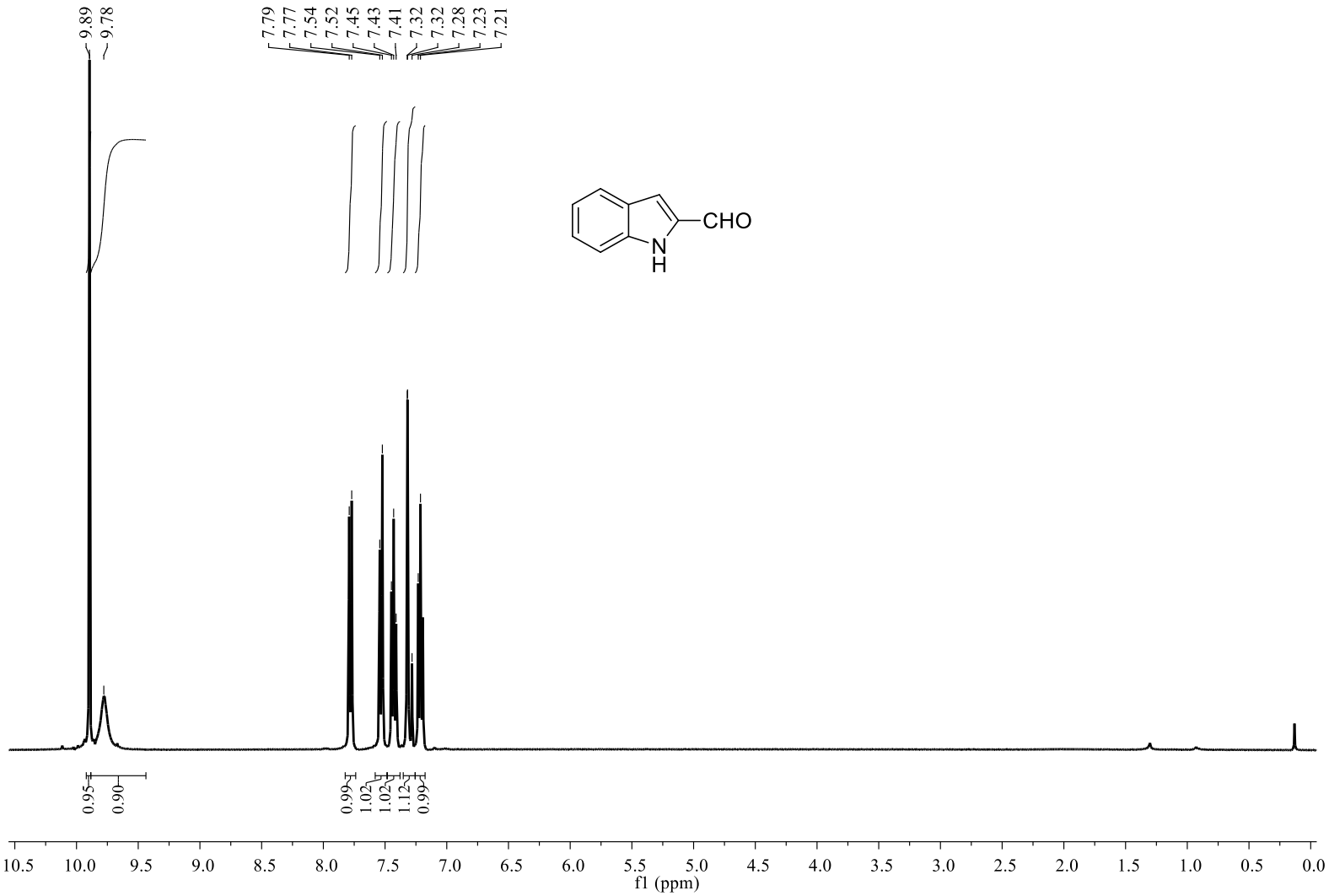
^{13}C APT NMR of 3,5-dimethyl-2-(thien-2-yl)-1H-pyrrole (**6f)**



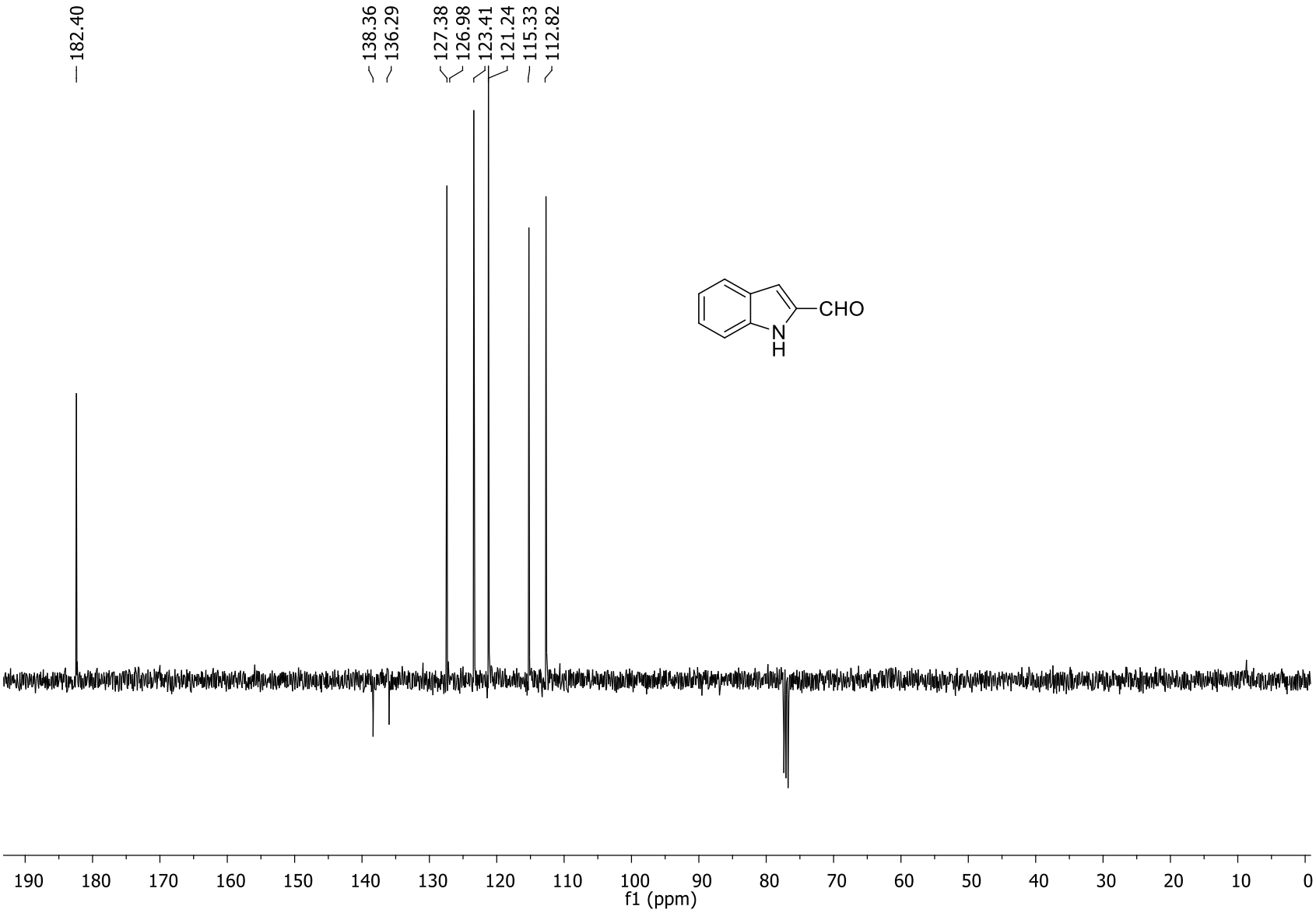
^{1}H NMR of 3,5-dimethyl-2-(5-methylthie-2-yl)-1H-pyrrole (**6g**)



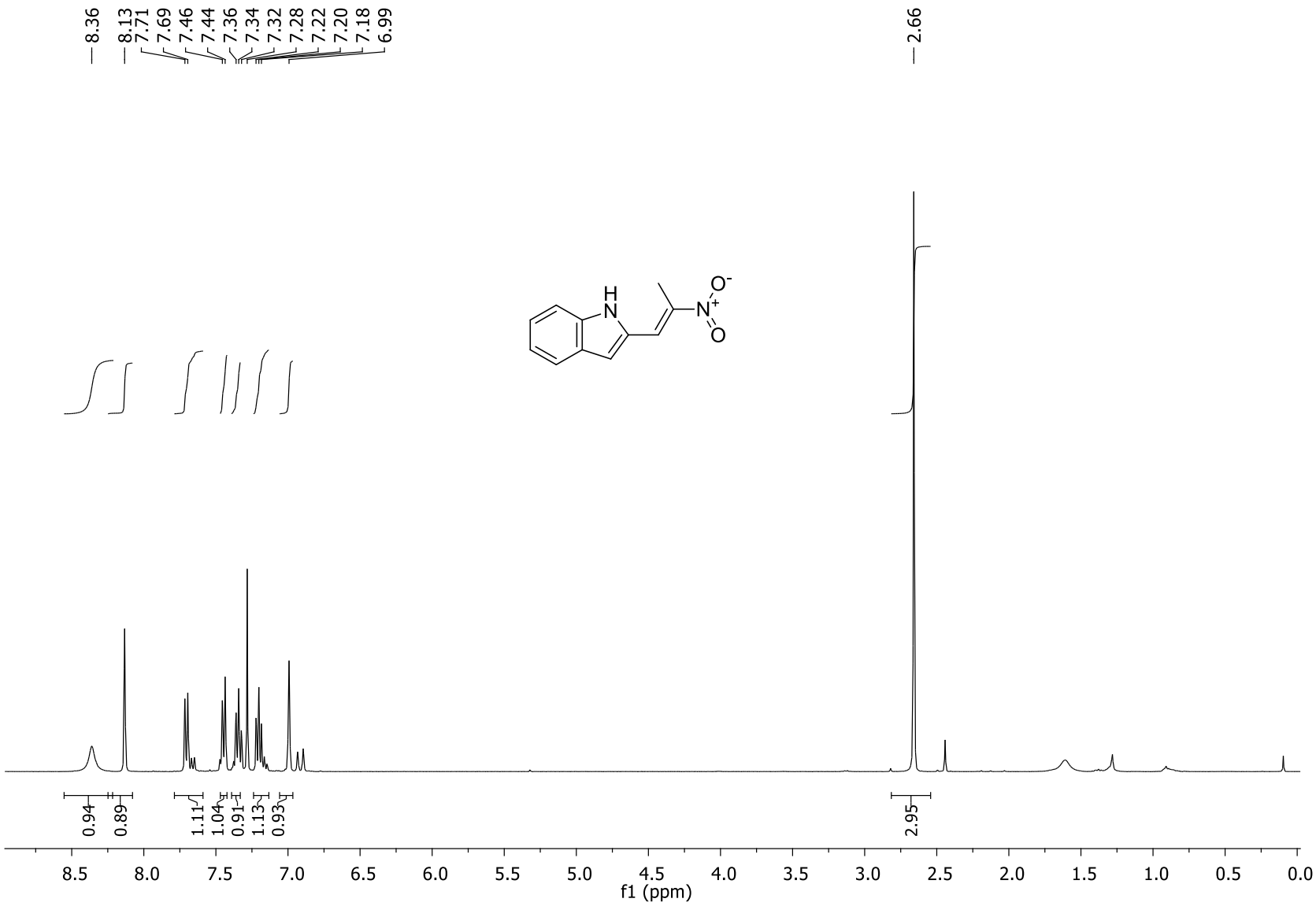
^{13}C APT NMR of 3,5-dimethyl-2-(5-methylthie-2-yl)-1H-pyrrole (**6g**)



^{1}H NMR of 1*H*-indole-2-carbaldehyde (**6i**)

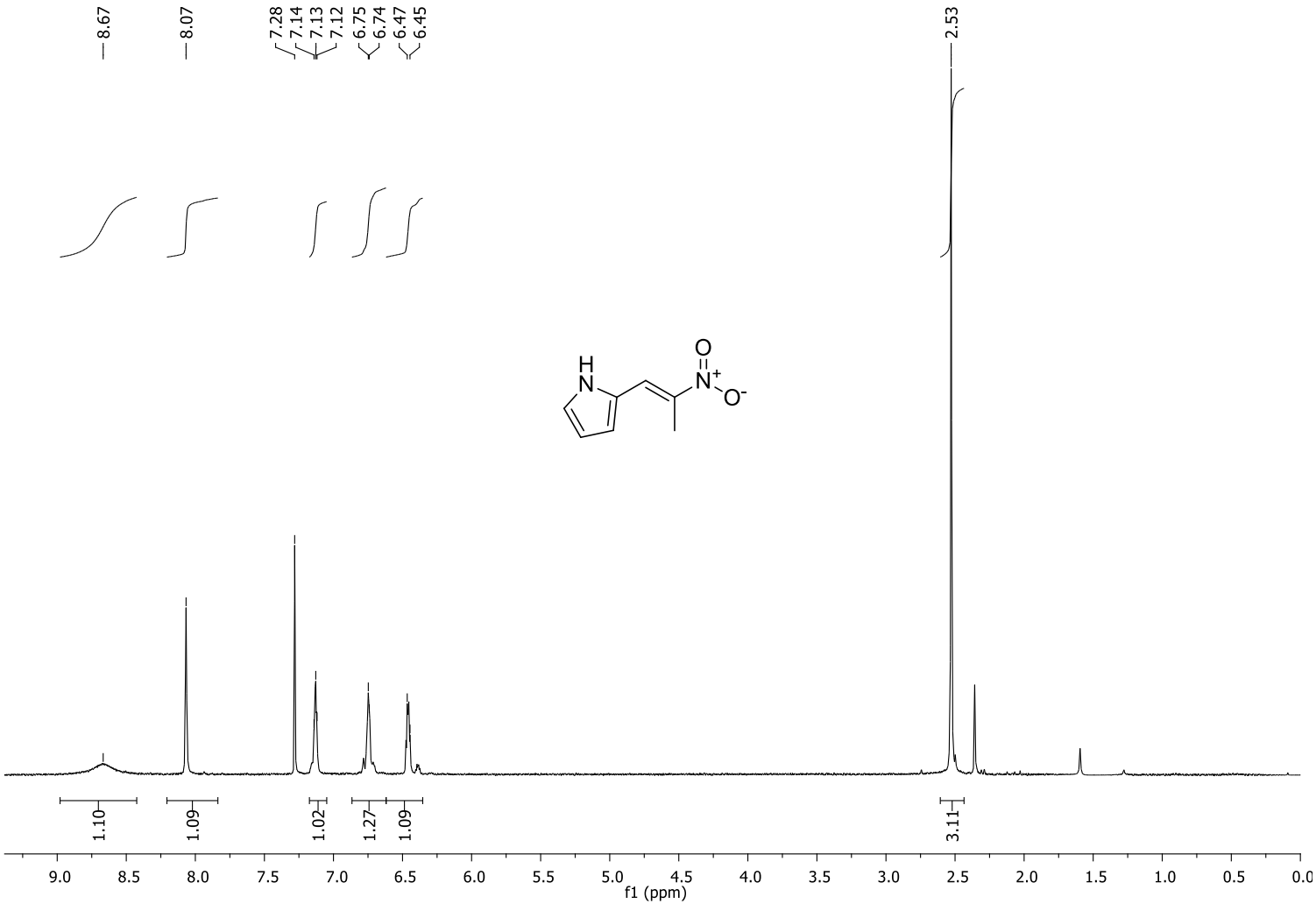


^{13}C APT NMR of 1*H*-indole-2-carbaldehyde (**6i**)

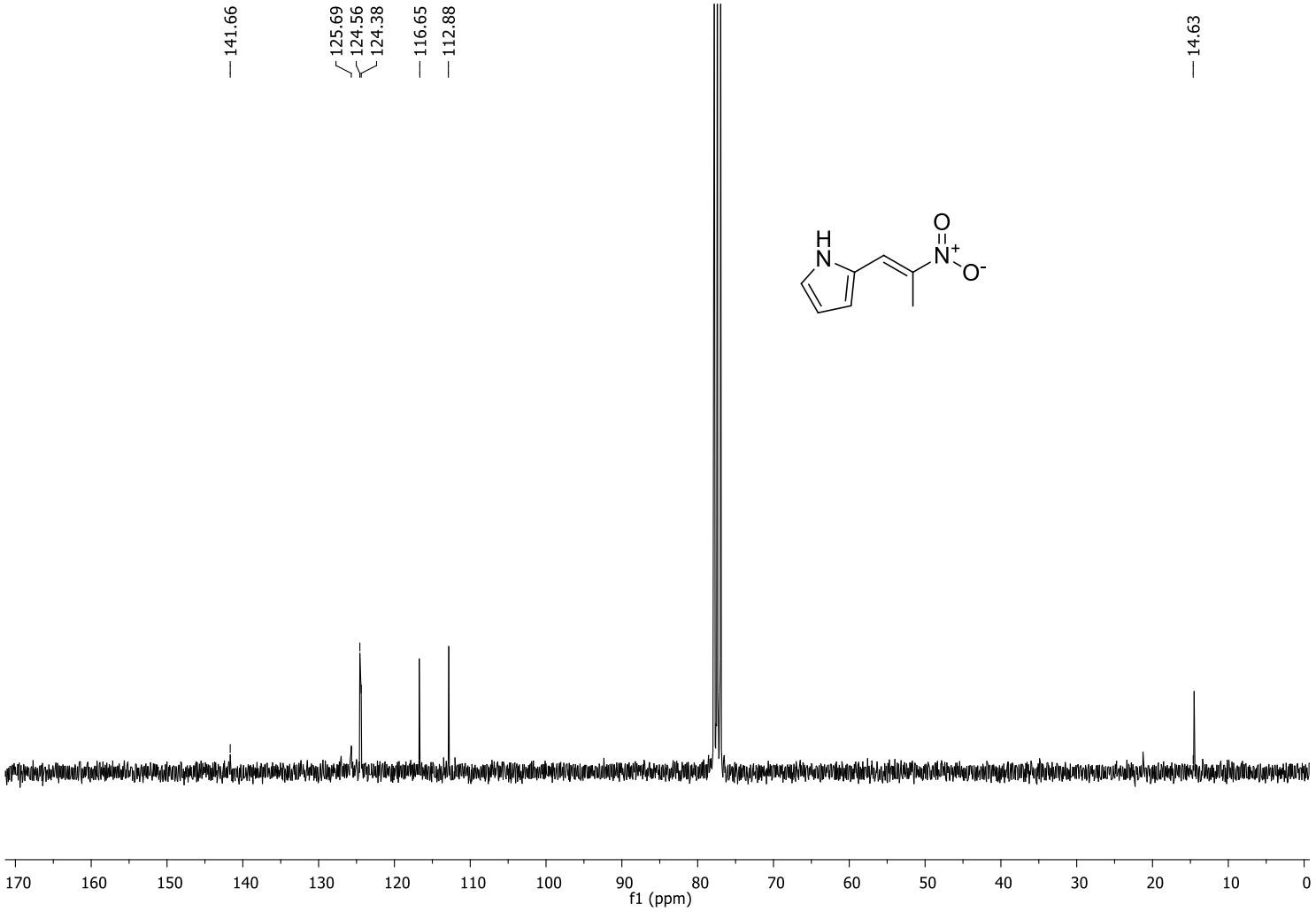


^{1}H NMR of (E)-2-(2-nitroprop-1-en-1-yl)-1H-indole (**6h**)

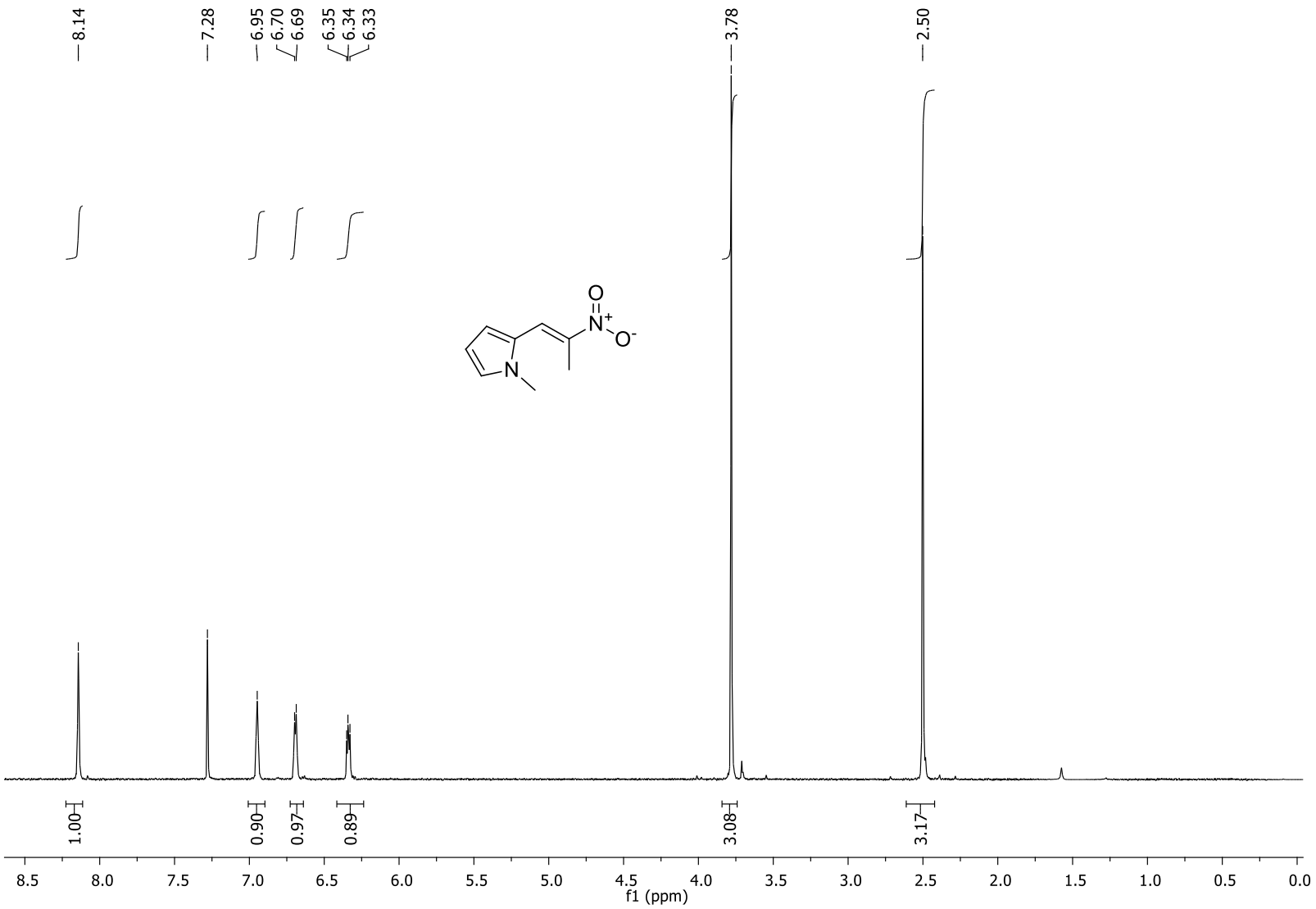
4.4 Appendix D: NMR spectra for nitroalkenylpyrrole and nitroalkenylfuran



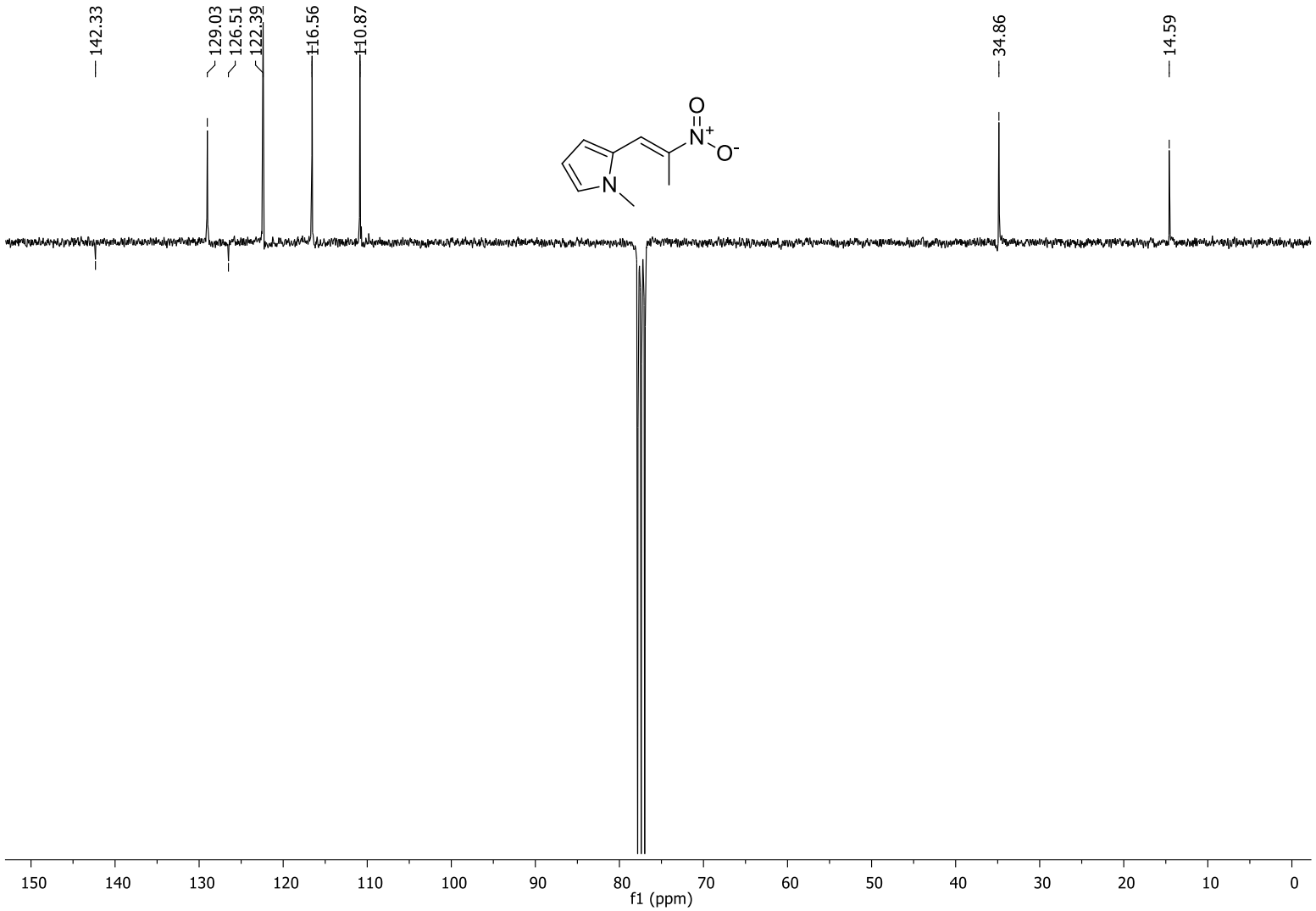
^{1}H NMR of (E)-2-(2-nitroprop-1-en-1-yl)-1H-pyrrole (**7a**)



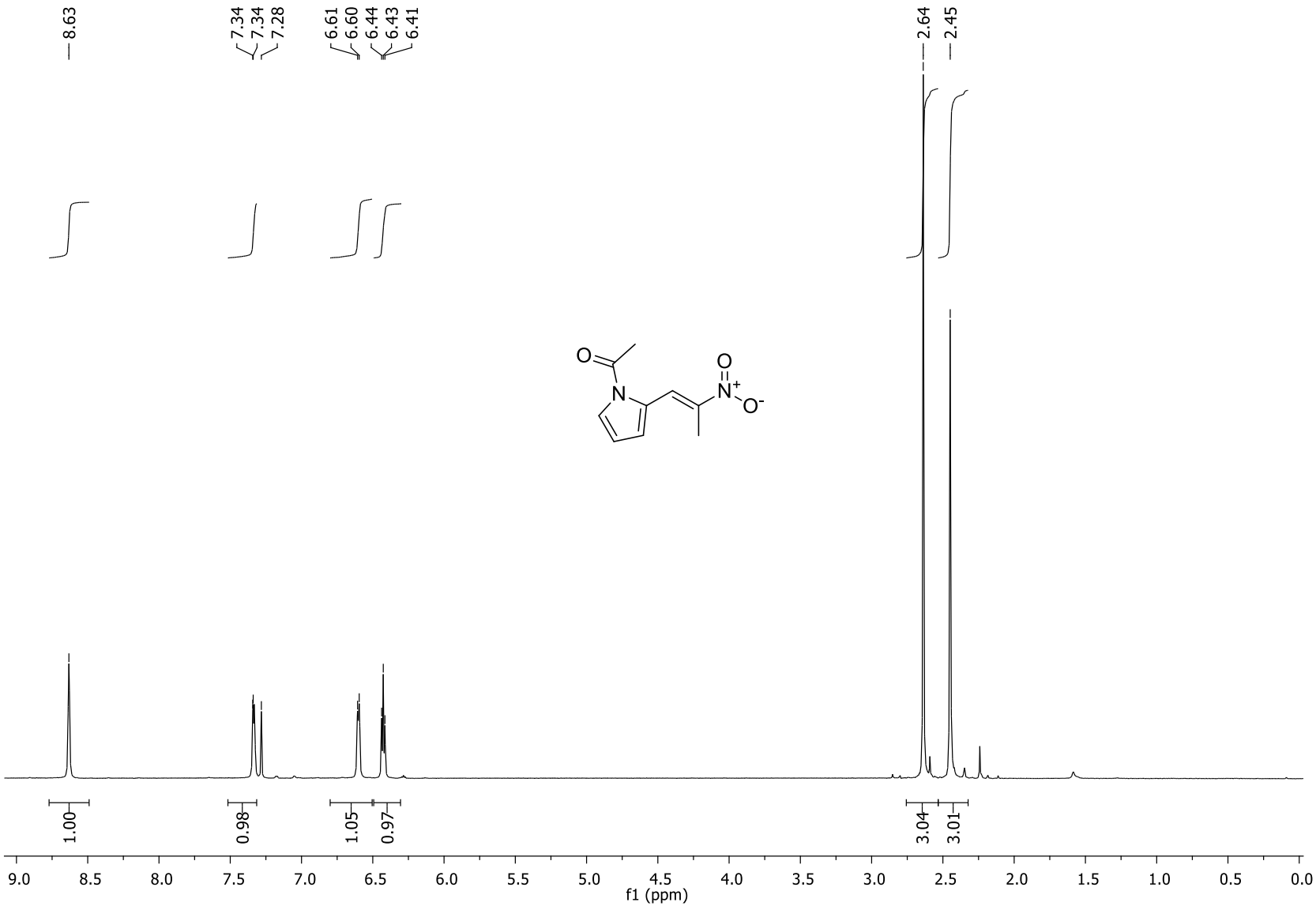
^{13}C ZGDC NMR of (E)-2-(2-nitroprop-1-en-1-yl)-1H-pyrrole (**7a**)



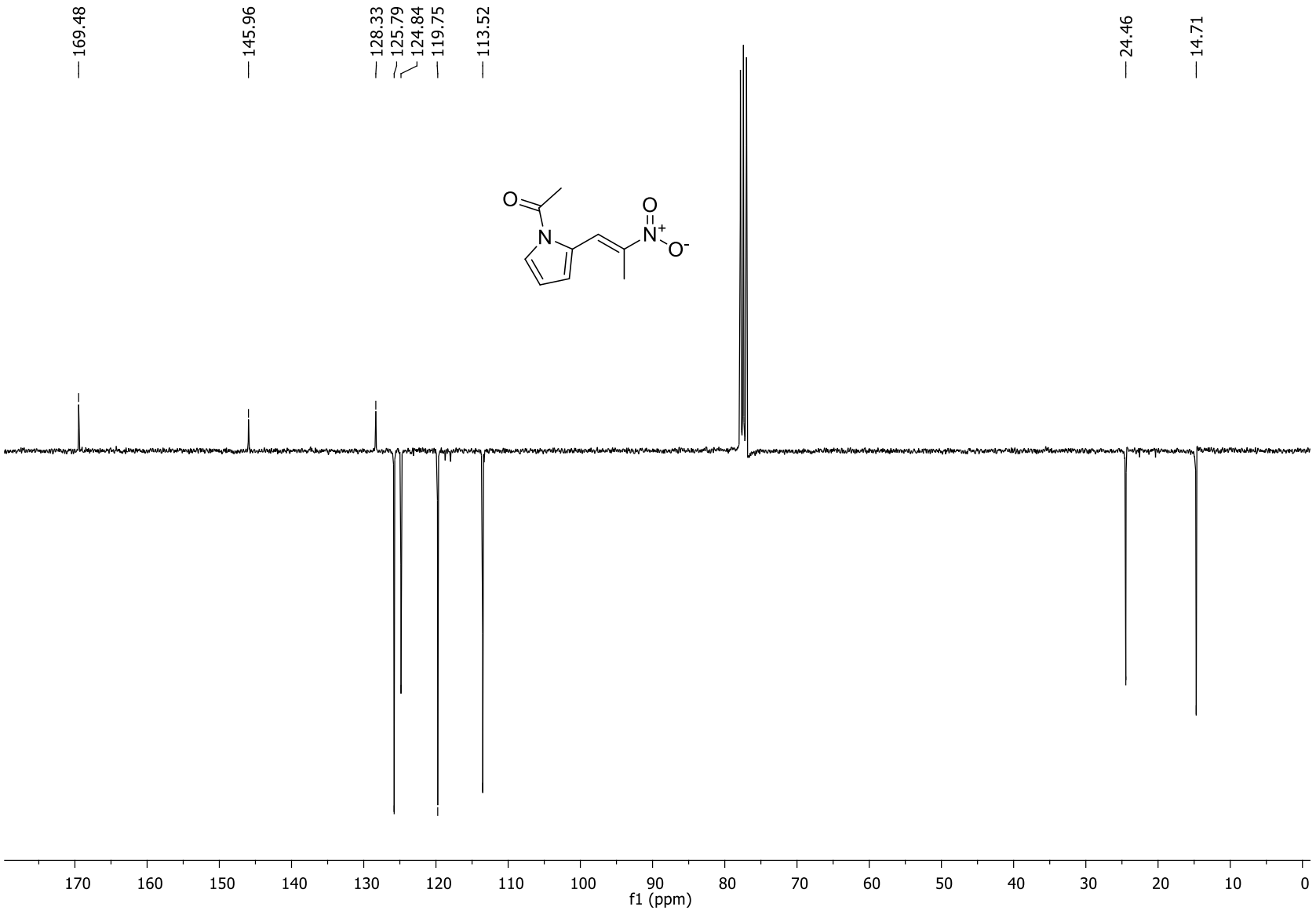
^{1}H NMR of (E)-1-methyl-2-(2-nitroprop-1-en-1-yl)-1H-pyrrole (**7b**)



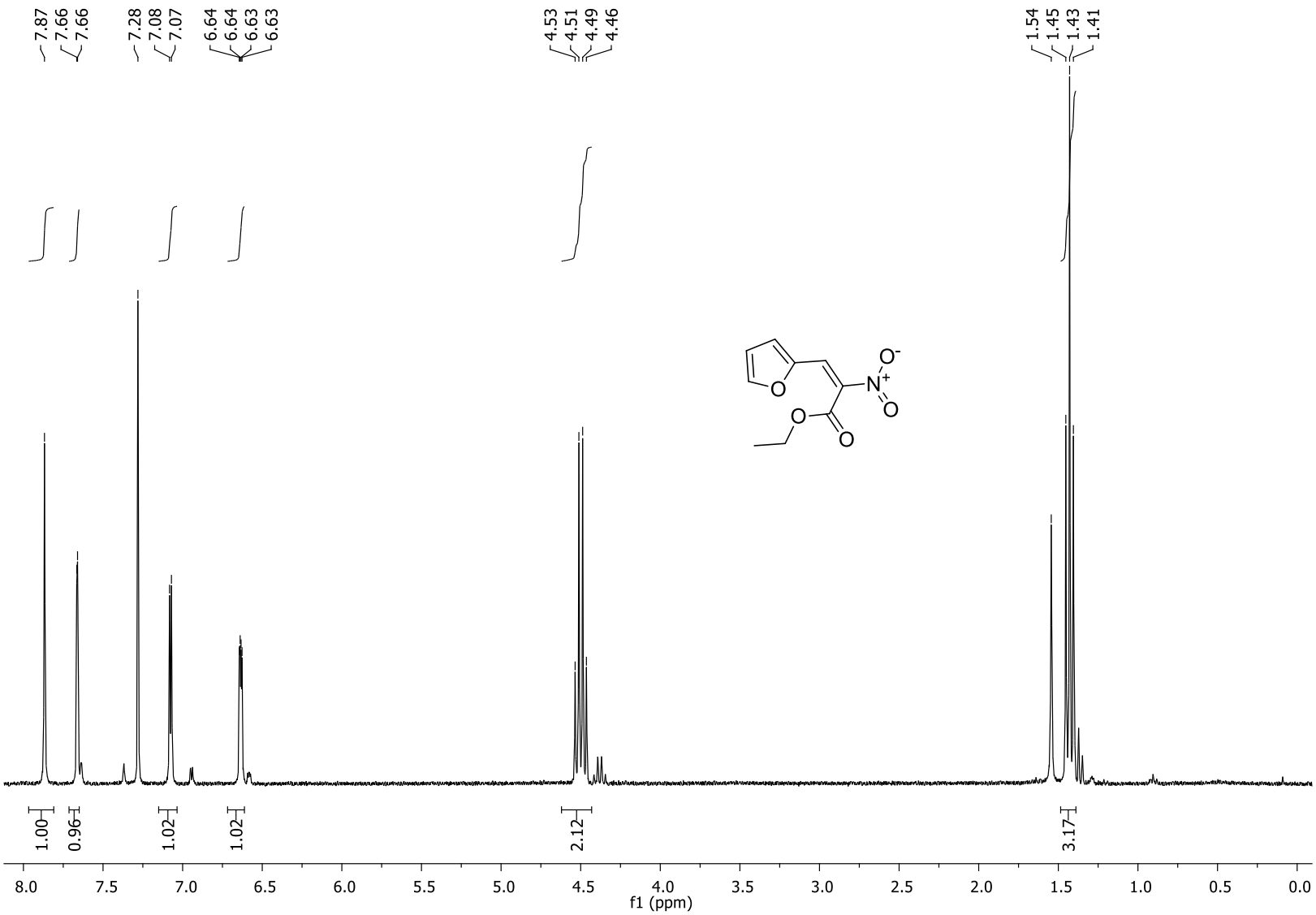
^{13}C APT NMR of (E)-1-methyl-2-(2-nitroprop-1-en-1-yl)-1H-pyrrole (**7b**)



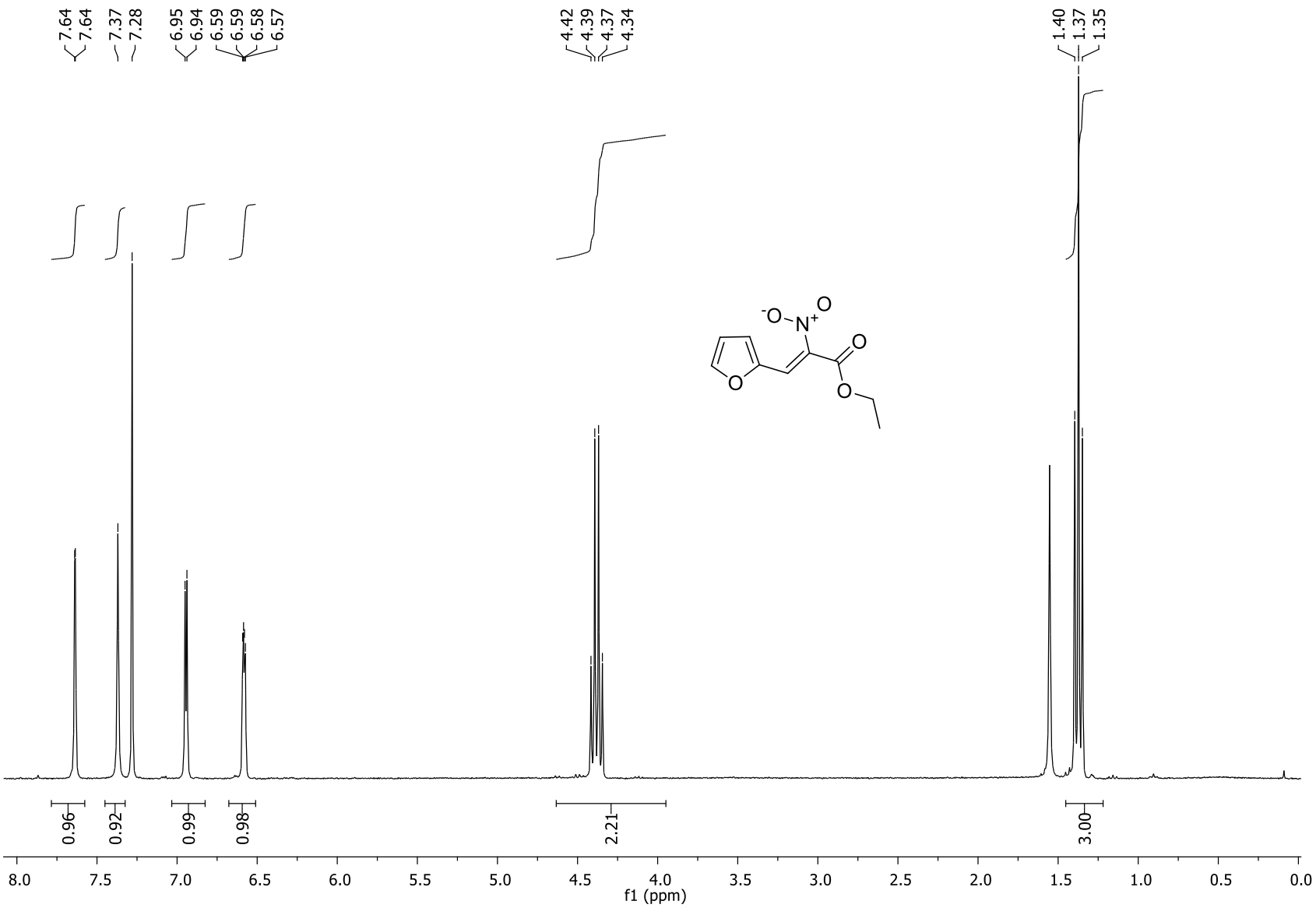
^{1}H NMR of (E)-2-nitro-1-(N-acetylpyrrol-2-yl)propene (**7c**)



^{13}C APT NMR (E)-2-nitro-1-(N-acetylpyrrol-2-yl)propene (**7c**)



^{1}H NMR of (E)-ethyl 3-(furan-2-yl)-2-nitroacrylate (**7e**)



^{1}H NMR of (Z)-ethyl 3-(furan-2-yl)-2-nitroacrylate (**7e**)

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