

SYNTHESIS OF 4-IODOPYRAZOLE DERIVATIVES

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**SYNTHESIS OF 4-IODOPYRAZOLE DERIVATIVES**

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## ABSTRACT

### SYNTHESIS OF 4-IODOPYRAZOLE DERIVATIVES

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Pyrazoles have been studied for over a century as an important class of heterocyclic compounds and continue to attract considerable interest due to the broad range of biological activities they possess. The electrophilic cyclization of the acetylenic hydrazones initiated by molecular iodine could provide new ways of synthesizing biologically active 4-iodopyrazole derivatives, which are important precursors for the synthesis of highly substituted pyrazole derivatives. For this reason, we investigated the synthesis of 4-iodopyrazole derivatives, such as 1-aryl-5-alkyl/aryl-4-iodopyrazoles, starting from phenylhydrazine and  $\alpha,\beta$ -acetylenic aldehyde derivatives. Initially,  $\alpha,\beta$ -acetylenic aldehydes were synthesized by formylation reaction of corresponding alkynes with DMF. Then, hydrazone derivatives of these aldehydes were prepared by heating them with phenylhydrazine in a neat manner at 55 °C for 5 h. Finally, acetylenic phenyl hydrazone derivatives were subjected to electrophilic cyclization by treating with excess molecular iodine at 80 °C for 3 h. Although electrophilic cyclization is commonly used in organic chemistry, it has not been employed for the cyclization of acetylenic phenyl hydrazones to pyrazole derivatives. Under optimized conditions, these reactions afforded 1-aryl-5-alkyl/aryl-4-iodopyrazole derivatives

in moderate to good yields as the single or the major product of the reactions. In some cases, 1-aryl-5-alkyl/arylpyrazole derivatives resulted from these reactions as minor products. In conclusion, 4-iodopyrazole derivatives were synthesized for the first time directly from acyclic starting materials,  $\alpha,\beta$ -acetylenic phenylhydrazones and iodine, via electrophilic cyclization.

Keywords: Acetylenic hydrazone, Electrophilic cyclization, Iodine, 4-Iodopyrazole, Pyrazole.

## ÖZ

### 4-İYOTPİRAZOL TÜREVLERİNİN SENTEZİ

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Heterosiklik bileşiklerin önemli bir sınıfını oluşturan pirazoller, bu yüzyılın başından beri birçok çalışmaya konu olmuş ve geniş alana yayılmış biyolojik aktivitelerinden dolayı da bu bileşiklere olan ilgi günümüzde artarak devam etmektedir. Asetilenik hidrazonların moleküler iyot ile gerçekleştirilen elektrofilik halkalaşma reaksiyonları 4-iyotpirazol türevlerinin sentezi için yeni bir metot olmuştur. 4-İyotpirazol türevleri daha çok süstitüent içeren pirazol türevlerinin sentezinde çok önemli rol oynamaktadır. Bu sebepten dolayı fenilhidrazin ve  $\alpha$ - $\beta$ -asetilenik aldehit türevlerinden başlayarak 1-aril-5-alkil/aril-4-iyotpirazol yapısındaki 4-iyotpirazol türevlerinin sentezi araştırılmıştır. İlk olarak ilgili alkin türevlerinden DMF ile formilasyon tepkimeleri ile  $\alpha$ - $\beta$ -asetilenik aldehit türevleri sentezlenmiştir. Daha sonra aldehit türevleri fenilhidrazin ile 55 °C de 5 saat birlikte ısıtılarak hidrazon türevleri elde edilmiştir. Son olarak, asetilenik fenil hidrazon türevleri fazla miktardaki iyot molekülü ile 80 °C de 3 saat elektrofilik halkalaşma reaksiyonuna sokulmuştur. Elektrofilik halkalaşma reaksiyonları organik kimyada çok yaygın olarak kullanılsada asetilenik fenil hidrazonlardan pirazol türevlerini sentezlemek amacıyla kullanılmamıştır. Optimize edilmiş reaksiyon koşullarında bu tepkimeler 1-aril-5-alkil/aril-4-iyotpirazolleri oldukça iyi

verimlerle tek ürün ya da ana ürün olarak üretmiştir. Bazı tepkimelerde 1-aril-5-alkil/arilpirazol türevleri yan ürün olarak çok düşük verimlerle alınmıştır. Sonuç olarak, ilk kez asiklik başlangıç maddeleri  $\alpha$ - $\beta$ -asetilenik aldehit türevleri ve iyottan başlanarak elektrofilik halkalaşma tepkimesi ile 4-iyotpirazol türevlerinin sentezi gerçekleştirilmiştir.

Anahtar Kelimeler: Asetilenik hidrazon, Elektrofilik halkalaşma, İyot, 4-İyotpirazol, Pirazol.

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Aileme,

To My Family,

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## LIST OF ABBREVIATIONS

br	Broad (spectral)
°C	Degrees Celcius
$\delta$	Chemical shift in parts per million downfield from tetramethylsilane
d	Doublet (spectral)
Et	Ethyl
FT	Fourier transform
g	Gram(s)
h	Hour(s)
Hz	Hertz
IR	Infrared
<i>J</i>	Joupling constant
m	Multiplet (spectral)
mL	Milliliter(s)
MHz	Megahertz
min	Minutes
mmol	Millimole(s)
mp	Melting point
NMR	Nuclear magnetic resonance
Ph	Phenyl
ppm	Parts per million (in NMR)
q	Quartet (spectral)
rt	Room temperature
s	Singlet (spectral)
t	Triplet (spectral)
THF	tetrahydrofuran
TLC	Thin layer chromatography

DMF Dimethylformamide

DCM Dichloromethane

## CHAPTER 1

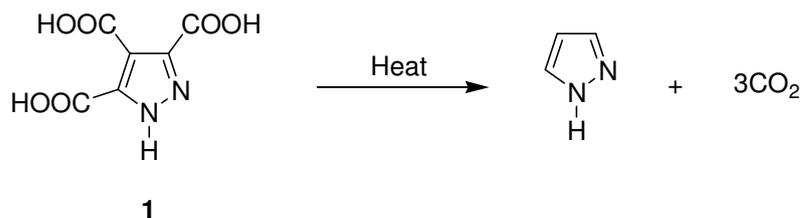
### INTRODUCTION

Organic chemistry is a branch of chemistry that involves the study of organic carbon compounds in all aspects. It encompasses the structures, composition and synthesis of carbon containing compounds. The compounds of carbon are central to life on the planet. They display extremely large variety and their applications are enormous. From the foods to plastics, drugs and paints, which are the origin of life, are derived from organic compounds. In summary, in order to improve the standard of human life the structure, properties and reactions of carbon containing compounds are studied.

The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds [1]. In particular, the heterocyclic compounds have been extensively studied not only for their intrinsic interest, but also because many natural products, many drugs and medicines, and many dyestuffs belong to this group [2].

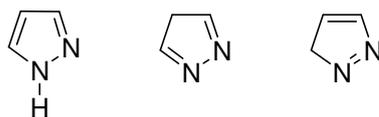
Heterocyclic compounds are cyclic organic substances which contain in the ring system at least one atom other than carbon. The most important “heteroatoms” are nitrogen, oxygen and sulfur. It seems likely that more than a third of the known organic compounds are heterocyclic. Many alkaloids, vitamins, antibiotics and many synthetic medicines and dyestuffs are heterocyclic, and so also are many substances (such as the nucleic acids) which are most intimately connected with the processes of life [1,2].

One of heterocyclic compounds is pyrazole. Pyrazole was described for the first time by Buchner, who obtained it by the decarboxylation of pyrazole-3,4,5-tricarboxylic acid (**1**) in 1889 (Figure 1) [1].



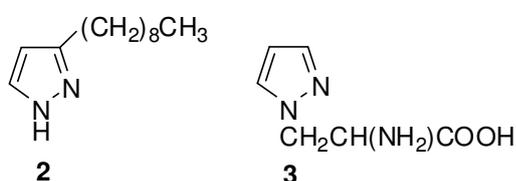
**Figure 1.** First synthesis of pyrazole by the decarboxylation of pyrazole-3,4,5-tricarboxylic acid (**1**).

Much of the basic information about the pyrazole moiety was obtained by the comparison of aromatic property with that of benzene. There is no doubt that pyrazole is aromatic since it contains a conjugated planar ring with delocalized six  $\pi$ -electrons. Importantly, the unsubstituted pyrazole ring exists in tautomeric forms like other nitrogen compounds [1]. As shown in Figure 2, three tautomeric forms are available for the unsubstituted pyrazole ring [1].



**Figure 2.** Tautomeric forms of the unsubstituted pyrazole ring.

Pyrazole ring was believed to be unknown in nature but, in 1954, first natural pyrazole derivative, namely 3-*n*-nonylpyrazole (**2**), was isolated by Japanese workers from *Houttuynia Cordata*, a plant of the “*piperaceae*” family from tropical Asia. Antimicrobial activity of **2** was also examined [3]. Another naturally occurring pyrazole derivative is *levo*- $\beta$ -(1-pyrazolyl)alanine (**3**) (Figure 3). This pyrazolic amino acid has been isolated from watermelon seeds (*Citrullus Vulgaris*) [4].



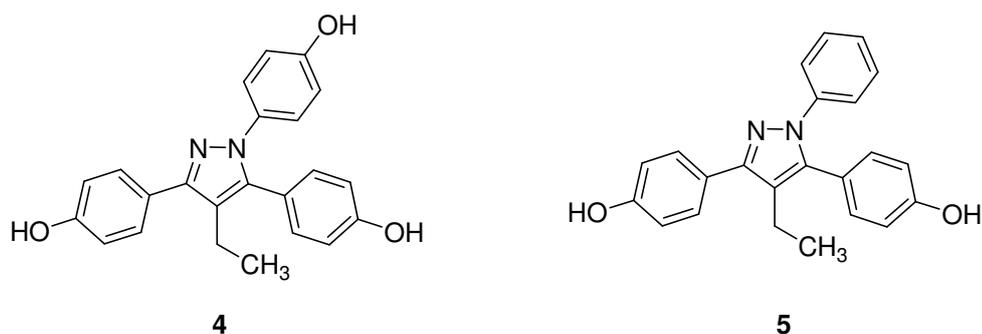
**Figure 3.** Examples of naturally occurring pyrazoles.

### 1.1 Biologically active pyrazole derivatives.

The incorporation of heterocyclic rings into prospective pharmaceutical candidates is a major tactic to gain activity and safety advantages [5]. Although scarcely found in nature, pyrazoles are known not only as potent insecticides, herbicides, and monomers for the preparation of electroluminescent and thermo resistant materials, but also as antitumor, anti-inflammatory, antimicrobial, antipsychotic, or analgesic agents [6]. Thus, due to their wide range of pharmacological and technological applications, pyrazoles have been the focus of much synthetic effort in the past decades [6,7].

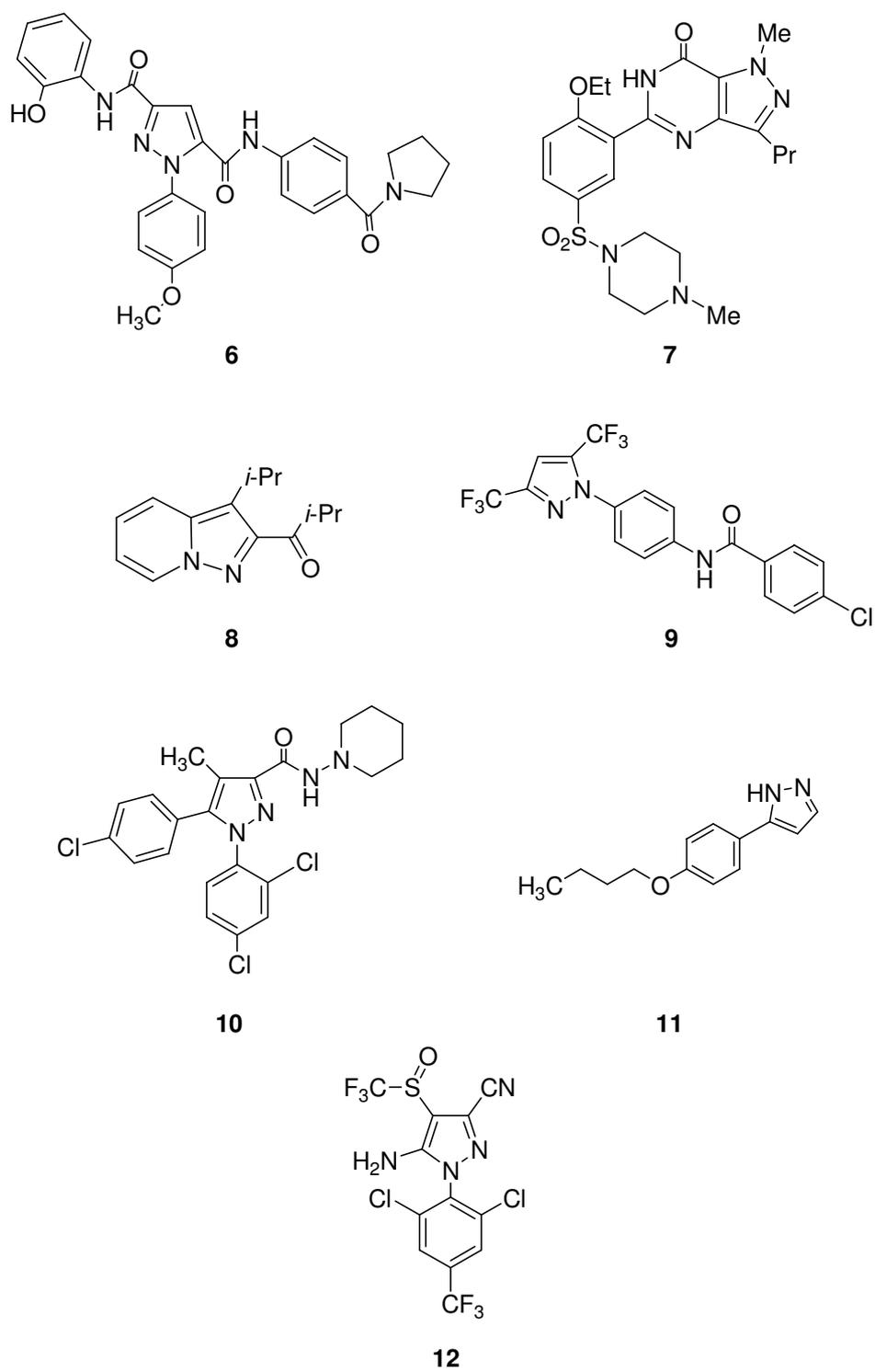
Novel ligands for the estrogen receptor (ER) that might act as selective estrogen receptor have been investigated and founded that 1,3,5-triaryl-4-alkylpyrazoles

such as **4** and **5** were good ligands for ER (Figure 4), demonstrating high binding affinities and transcriptional efficacy that in some cases were very selective for the ER  $\alpha$  subtype (ER $\alpha$ ) [8].



**Figure 4.** Structures of biologically active pyrazole derivatives **4** and **5**.

Helicobacter pylori dehydroorotate dehydrogenase (DHODase) (**6**) is a pyrazole-based inhibitor (Figure 5). Helicobacter pylorus is a gram-negative microaerophilic bacterium that infects up to 50% of the world population and it resides in the acidic medium of the stomach, utilizing a high urease enzyme activity to provide a locally alkaline environment. It has been implicated in numerous gastrointestinal disorders and is associated with gastric ulcers, gastritis and gastric cancer [9]. Other example is Sildenafil (**7**) that is a selective inhibitor of phosphodiesterase 5 (PDE5) and it is the first agent with this mode of action for the treatment of male erectile dysfunction that is a disease more commonly known as male impotence [10]. In addition, pyrazolo[1,5]pyridines, pyrazolo[1,5]quinolines, pyrazolo[1,5]phenanthridines show some biological activity [11]. The phosphodiesterase inhibitor ibudilast (**8**) is a drug of choice for the treatment of diseases involving blood cells and vascular wall disorders. Other common uses of the pyrazole heterocycles are to act as antiviruses for herpes virus infection and also, to treat of Alzheimer's and Parkinson's diseases and dementia [12] (Figure 5).



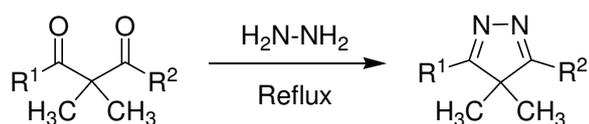
**Figure 5.** Structures of biologically active pyrazole derivatives **9-12**.

A series of bis(trifluoromethyl) pyrazoles (BTPs) (**9**) has been found to be a novel inhibitor of cytokine production. BTPs identified initially as inhibitors of IL-2, show inhibition of IL-4, IL-5, IL-8, and eotaxin production (Figure 5) [13]. Another pyrazole origin compound is Cannabinoid Receptor Antagonist (CB1) (**10**). Cannabinoid, which was reported in 1994 by Sanofi Recherche as a potent selective and orally active antagonist of the brain cannabinoid receptor, is the major psychoactive constituent of marijuana [14]. Cannabinoids have long been the focus of study due to their effects on the central nervous system. Early pharmacological testing has shown that cannabinoids possess analgesic, antiemetic, psychotropic, and anti-inflammatory properties and has also suggested their potential therapeutic utility for the treatment of asthma and glaucoma. However, widespread use of cannabinoids as therapeutic agents has been limited by their psychotropic properties [15]. There are also pyrazole derivatives as new, potent and selective 20-hydroxy-5,8,11,14-eicosatetraenoic acid (20-HETE) (**11**) synthase inhibitors shown in Figure 5. 20-HETE, which is a major metabolite of arachidonic acid produced in the kidney, plays an important role in the regulation of renal vascular and tubular functions and contributes to the control of arterial blood pressure. It is also produced in the brain, where it regulates vascular tone and contributes to the regulation of the cerebral blood flow [16]. The last example to biologically active pyrazole derivative is Fipronil (**12**). Fipronil is the most important example of the phenylpyrazole or fiprole insecticides. It is a major insecticide acting as a non-competitive blocker of the  $\gamma$ -aminobutyric acid (GABA) receptor/chloride channel (Figure 5) [17].

## **1.2. Synthesis of pyrazole derivatives.**

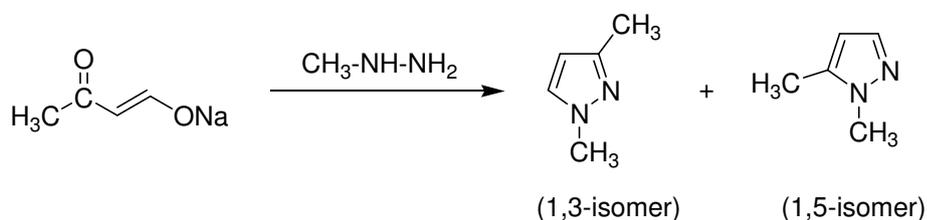
The synthesis of pyrazoles has received considerable attention due to their applications in pharmaceutical and agrochemical industries as a result of their antipyretic, anti-inflammatory, herbicidal, insecticidal and fungicidal properties [18]. Among the available methods, the most commonly used strategy is the

condensation of hydrazines with  $\beta$ -dicarbonyl compounds (i.e., 1,3-dicarbonyl compounds) (Figure 6) [18].



**Figure 6.** Synthesis of pyrazoles from  $\beta$ -dicarbonyl compounds and hydrazines.

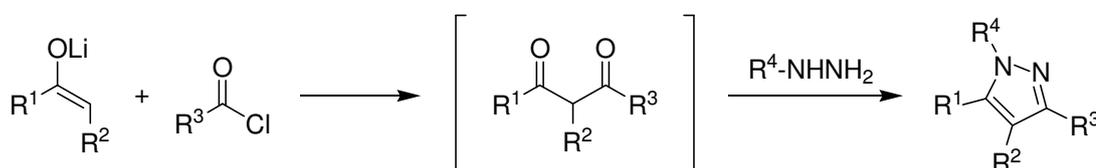
When a symmetrical  $\beta$ -dicarbonyl compound or hydrazine itself is used, a single pyrazole derivative is obtained. However, with other reactants, two isomeric pyrazoles can theoretically arise and sometimes both can be isolated from the reaction mixture [1,19]. Many structural and experimental factors are involved in the selective formation of one of the two isomeric compounds but at present the controlling influence of such factors is not fully understood [1]. For instance, the reaction of methylhydrazine with the sodium salt of formylacetone gives a mixture of two isomeric pyrazoles, which are commonly called 1,3- and 1,5-pyrazole isomers (Figure 7).



**Figure 7.** Synthesis of pyrazoles from the salt of formylacetone.

As noted above, the most prevalent method of obtaining pyrazoles is by the reaction of 1,3-diketones with hydrazine and hydrazine derivatives. However, if a diversity-oriented synthesis of pyrazoles is desired, this method becomes cumbersome since 1,3-diketone is often obtained as a mixture of condensation products and it must be purified. Furthermore, most electrophilic functional groups such as aldehydes, nitriles, esters, and alkyl halides do not survive during the course of the reaction. In the light of these observations, it is clear that using 1,3-diketones as an intermediate is the broadest and most efficient route to pyrazoles [20].

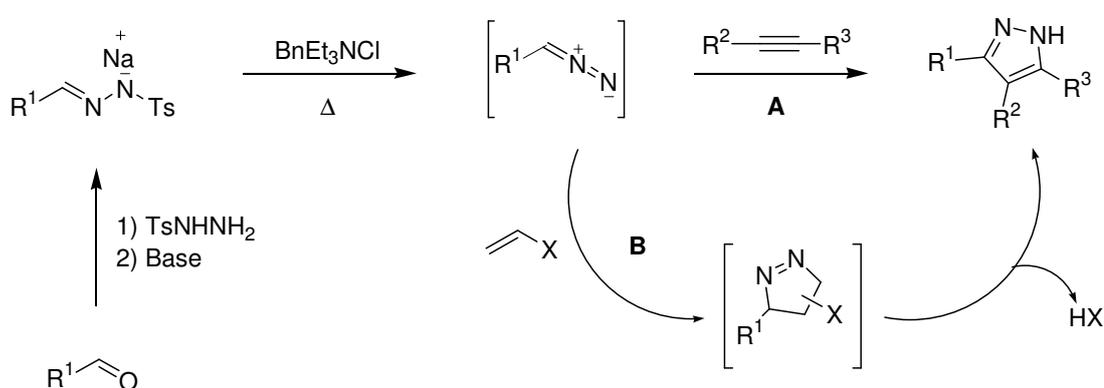
Heller and Natarajan have prepared pyrazoles in one pot synthesis by employing ketones and acid chlorides (Figure 8). This method alleviates the problem of using esters, and in the right conditions, it would be selective, particularly in the presence of other weaker electrophiles such as nitriles [20].



**Figure 8.** Synthesis of pyrazoles from ketones and acid chlorides.

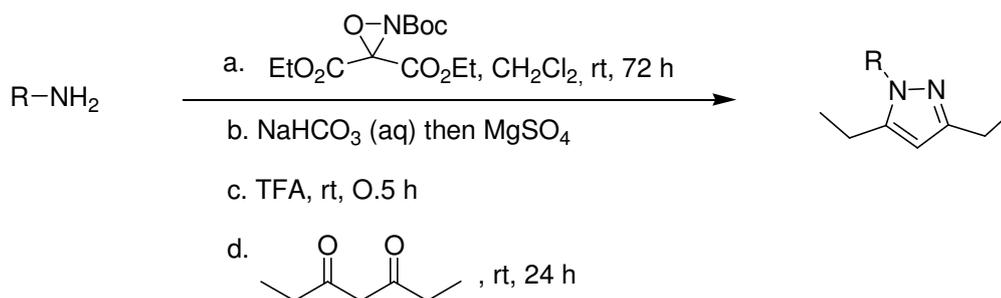
An alternative strategy for the synthesis of pyrazoles is 1,3-dipolar cycloaddition of diazo compounds with alkynes or alkenes, as shown by Aggarwal, and co-workers [21]. Diazo compounds derived from aldehydes were reacted with terminal alkynes to furnish regioselectively 3,5-disubstituted pyrazoles (Figure 9, Route A). Alternatively, the reaction between diazo compounds and olefins such as *N*-

vinylimidazole gave exclusively 3-substituted pyrazoles in a one-pot process (Figure 8, Route B) [21]. The reaction first produces an intermediate cycloadduct, which then affords pyrazoles upon elimination and followed by aromatization. The diazo compounds involved in these [3 + 2] approaches to pyrazoles were generated in situ from tosylhydrazone salts [21].



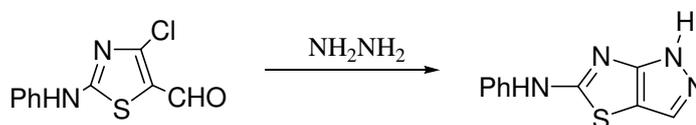
**Figure 9.** Synthesis of pyrazoles from diazo compounds.

An interesting approach to pyrazoles was demonstrated by Armstrong and co-workers [22]. They synthesized pyrazoles by electrophilic amination of primary amines, as shown in Figure 10 [22]. It should be mentioned that this method allows a one-pot synthesis of pyrazoles from primary amines.



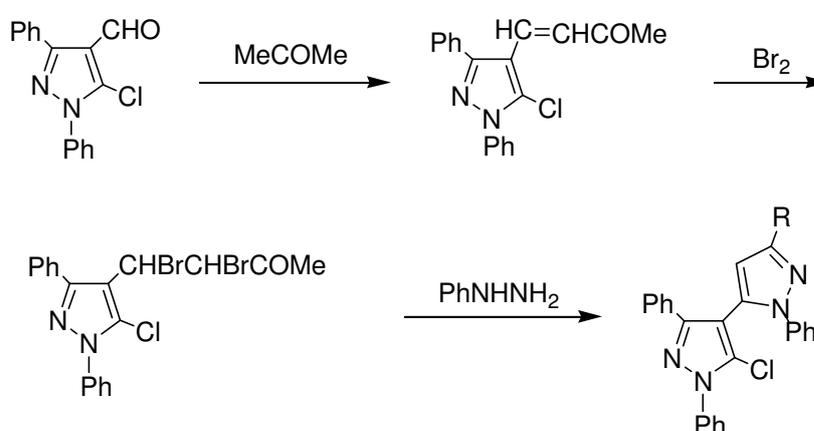
**Figure 10.** Synthesis of pyrazole derivatives from primary aliphatic and aromatic amines.

Sekhar and co-workers have recently reviewed the construction of the fused pyrazole derivatives by using  $\beta$ -halovinylaldehydes and  $\beta$ -halovinylketones [23]. Although recent publications disclosed a variety of applications of  $\beta$ -halovinylaldehydes to the field of heterocyclic chemistry [23], only a few examples have been reported on the introduction of pyrazole moiety to five, six and seven-membered heterocycles. Recently, a versatile synthesis of fused heterocycles such as pyrazolothiazole has been successfully achieved by the condensation of chloroaldehyde with hydrazine and phenylhydrazine (Figure 11) [23].



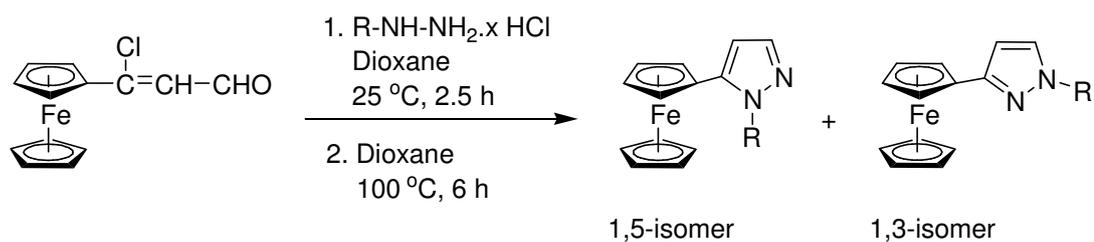
**Figure 11.** Synthesis of fused pyrazole derivatives by using  $\beta$ -halovinylaldehydes.

On the other hand,  $\beta$ -chlorovinylenones are also valuable substrates for synthesis of pyrazole derivatives. For example, pyrazolylpropenone, prepared by condensation of 5-chloro-1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde with acetone, reacted with bromine to afford dibromo compound, which furnished pyrazoles upon reaction with phenylhydrazine (Figure 12) [23].



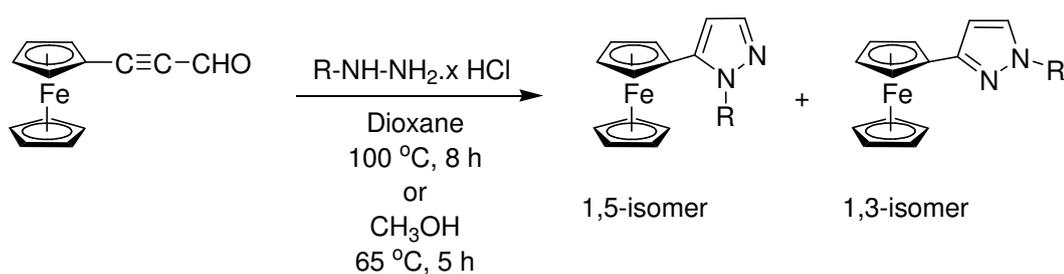
**Figure 12.** Synthesis of pyrazolylpyrazole derivatives.

Recent studies have shown that the integration of a ferrocenyl group into heterocyclic structures such as pyrazoles may enhance their biological activities or generate new medicinal properties. Recently, for this purpose, Zora research group has investigated the reaction between (2-formyl-1-chlorovinyl)ferrocene and hydrazines, which yielded ferrocenyl-substituted 1,5- and 1,3-isomers of pyrazole derivatives [24] (Figure 13). (2-Formyl-1-chlorovinyl)ferrocene was synthesized from acetylferrocene, which is readily available in large quantities according to well known literature procedure [24].



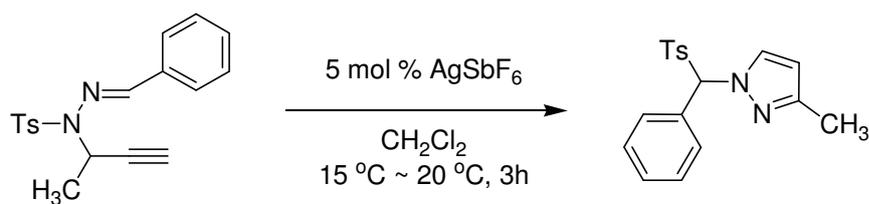
**Figure 13.** Reaction of (2-formyl-1-chlorovinyl)ferrocene with hydrazines.

Since pyrazoles and ferrocenes are both valuable compounds for the synthesis of biologically active compounds, the synthesis of ferrocenyl-substituted pyrazoles has gained importance as noted by Zora and coworkers [25]. A recent synthesis of ferrocenyl-substituted pyrazoles was based on the reaction between 3-ferrocenylpropynal and hydrazinium salts. Depending upon the substitution pattern of hydrazine derivative, the reaction affords 1-alkyl/aryl-5-ferrocenylpyrazoles and /or 1-alkyl/aryl-3-ferrocenylpyrazoles (Figure 14) [25].



**Figure 14.** Reaction of 3-ferrocenylpropynal with hydrazinium salts.

Very recently, silver(I)-catalyzed formation of pyrazoles has been reported from propargyl *N*-sulfonylhydrazones (Figure 15). After coordination of Ag<sup>+</sup> ion with triple bond, enhanced electrophilicity of the alkyne gives rise to a subsequent nucleophilic attack of the imine nitrogen atom on the electron deficient alkyne to yield the cyclized silver(I) intermediate. Deprotonation leads to the generation of ion pairs of N atom, followed by an attack of the tosyl anion to the electron deficient imine carbon. Finally, protonation gives pyrazoles. This methodology allows for the efficient and regioselective synthesis of pyrazole derivatives (Figure 15)[26].

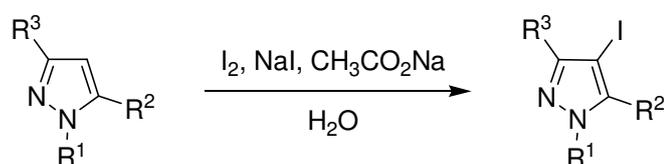


**Figure 15.** AgSbF<sub>6</sub> catalyzed synthesis of substituted pyrazoles.

### 1.3. Synthesis of 4-iodopyrazole derivatives.

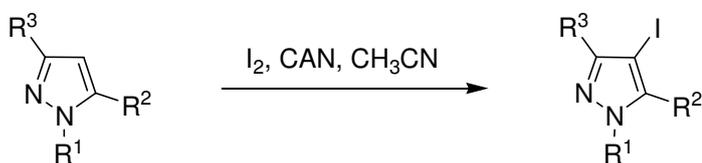
Haloheteroaromatics are valuable synthetic intermediates in the course of drug discovery because of the ease of functionalization [27]. In particular, 4-iodopyrazoles are key substrates in a large variety of compounds of important biological activities [28]. 4-Iodopyrazole derivatives possess a useful halogen atom at the 4-position, which can be used for the further functionalization of corresponding pyrazoles [29].

Rodriguez-Franco and co-workers have applied the classical iodine-iodide method ( $I_2$ , KI) to synthesize 4-iodopyrazole derivatives (Figure 16). The results have shown that the classical iodine-iodide method afforded good yields only with activated pyrazoles, but it provided poor yields with pyrazoles with electron-withdrawing substituents [30].



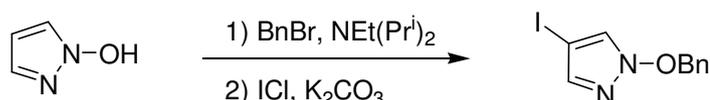
**Figure 16.** Synthesis of 4-iodopyrazoles by classical iodine-iodide method.

It has been reported that the oxidative iodination of *N*-H or *N*-substituted pyrazoles using elemental iodine in the presence of ceric ammonium nitrate (CAN) as the in situ oxidant afforded the corresponding 4-iodopyrazoles in good yields, even with electron-withdrawing substituents in the pyrazolic nucleus (Figure 17) [30].



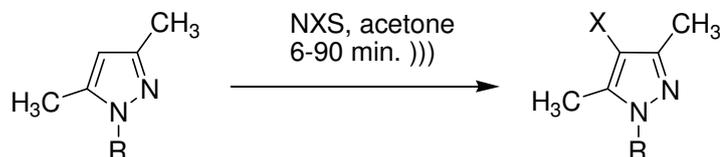
**Figure 17.** CAN-mediated iodination of pyrazoles.

The more reactive iodine monochloride (ICl) have also been used to obtain 4-iodopyrazoles with alkyl- or electron-donating groups (Figure 18) [30,31].



**Figure 18.** Synthesis of 4-iodopyrazole derivatives by monoiodination.

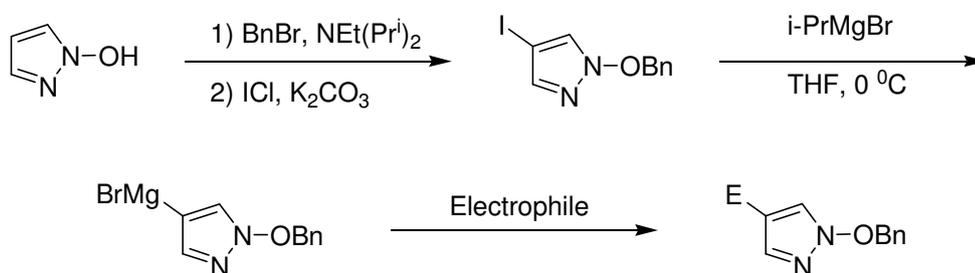
Ultrasound has increasingly been used in organic synthesis in the last three decades. Compared with traditional methods, this technique is more convenient and easily controlled. A large number of organic reactions can be achieved under ultrasound irradiation in high yields and shorter reaction times, and milder conditions. Stefani and co-workers have recently reported the synthesis of 4-halo-3,5-dimethylpyrazoles with good yields in short reaction times in the absence of a catalyst with *N*-halosuccinimides (NXS = NBS, NCS and NIS) under ultrasound irradiation (Figure 19) [28].



**Figure 19.** Synthesis of 4-halopyrazoles by ultrasound irradiation.

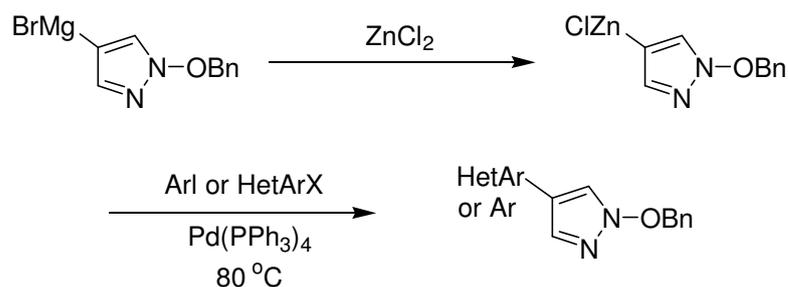
As noted before, 4-iodopyrazoles are valuable starting products in the synthesis of biologically active compounds. They have been used in cross-coupling reactions with terminal acetylenes, organotin aryl derivatives, or aryl boronic acids [32]. In addition, halogen-metal exchange is an attractive route to introduce electrophiles to fourth position of pyrazolic nucleus, not always accessible by conventional methods [30].

Recently, iodine-magnesium exchange with alkylmagnesium bromide has been described as a mild and efficient method for the generation of positionally stable aryl and heteroaryl magnesium halides. Felding and coworkers [31] have used this approach and reported a protocol for the preparation of 4-substituted 1-(benzyloxy)pyrazoles. Regiospecific monoiodination of 1-(benzyloxy)pyrazole followed by iodine-magnesium exchange and reaction with electrophiles produced the corresponding 4-substituted 1-(benzyloxy)pyrazoles (Figure 20) [31].



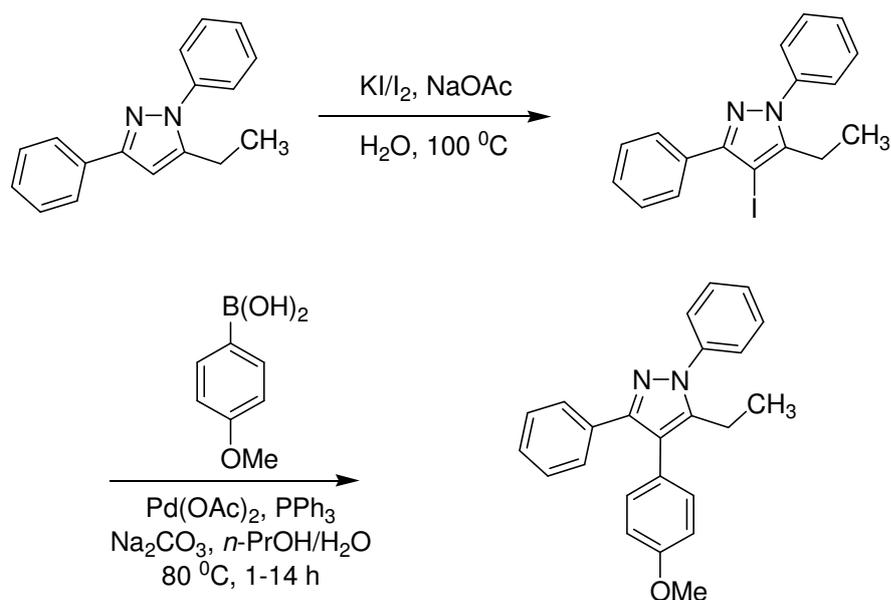
**Figure 20.** Functionalization of pyrazoles by introducing electrophiles via iodine-magnesium exchange.

This method was extended to the synthesis of 4-aryl- and 4-heteroaryl-substituted 1-benzyloxy-pyrazoles by combining iodine-magnesium exchange, transmetalation with zinc chloride ( $\text{ZnCl}_2$ ), and palladium-catalyzed Negishi cross-coupling (Figure 21) [31].



**Figure 21.** Functionalization of pyrazoles by Negishi type of cross coupling.

Suzuki coupling is another type of reaction used to introduce substituents to the 4-iodopyrazoles. Katzenellenbogen and coworkers [33] have first iodinated tri-substituted pyrazoles by treatment with a solution of KI and  $\text{I}_2$ , which is the classical iodine-iodide method, and then subjected to Suzuki coupling conditions with either phenylboronic acid or *p*-methoxyphenylboronic acid (Figure 22) [33].



**Figure 22.** Functionalization of pyrazoles by Suzuki type of cross coupling.

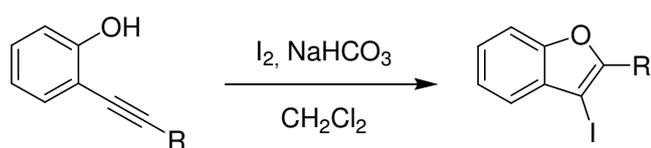
#### 1.4. The Aim of This Study.

The goal of this work is to develop a new methodology to synthesize 4-iodopyrazole derivatives directly from acyclic starting material. Although 4-iodopyrazoles are known compounds, all are synthesized from pyrazoles by an iodination reagent. In other words, pyrazoles are first synthesized, and then they are subjected to iodination. To the best of our knowledge, there is no any example of that 4-iodopyrazoles are synthesized during the construction step of pyrazoles.

We have recently synthesized pyrazoles by the reaction of acetylenic aldehydes with hydrazinium salts (Figure 13) [25]. The results have shown that these reactions require relatively acidic conditions. For instance, when hydrazines are employed in these reactions instead of hydrazinium salts, these reactions produces exclusively corresponding hydrazone derivatives and pyrazoles are obtained in

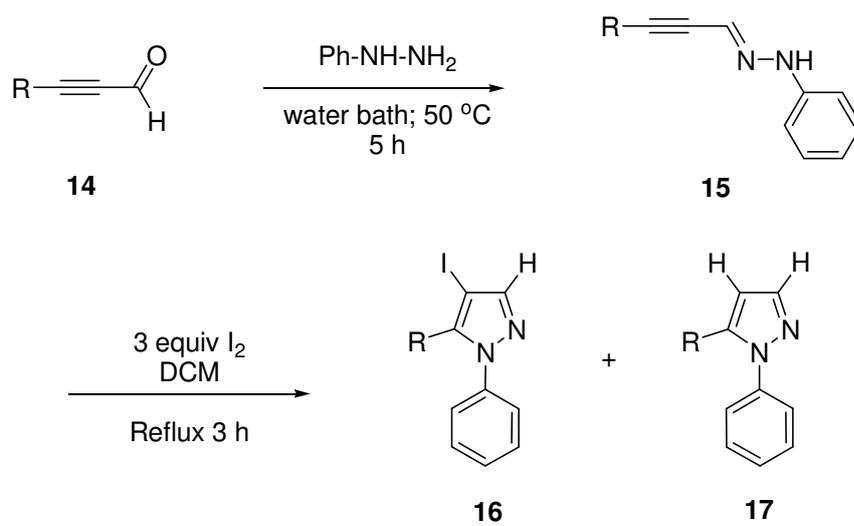
very low yields from these reactions. Moreover, these reactions provide a mixture of 1,5- and 1,3-pyrazole isomers (Figure 13).

Recently molecular iodine ( $I_2$ ) has gained considerable importance as a mild and nontoxic Lewis acid catalyst since it catalyzed various organic reactions with high efficiency and selectivity [34]. Owing to alkyne activating property, molecular iodine was successfully used in the synthesis of benzofurans [35]. Electrophilic cyclization reaction initiated by iodine was successfully carried out by the Larock research group for the synthesis of benzo[*b*]furans (Figure 23) [35].



**Figure 23.** Synthesis of benzo[*b*]furan by electrophilic cyclization.

In the light of these studies, we have proposed that when treated with molecular iodine, acetylenic hydrazone derivatives, obtained from acetylenic aldehydes and hydrazines, should produce corresponding 4-iodopyrazole derivatives as a single or the major product of the reaction (Figure 24). As anticipated, these reactions afforded expected 4-iodopyrazoles in good yields. In this study, the scope, limitations and the mechanism of these reactions will be discussed in detail.



**Figure 24.** Synthesis of 4-iodopyrazole derivatives.

## CHAPTER 2

### RESULTS AND DISCUSSION

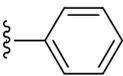
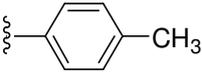
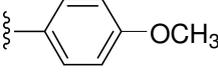
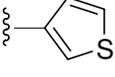
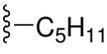
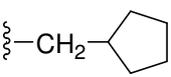
In this study, a new synthetic methodology was developed for the synthesis of 4-iodopyrazole derivatives by employing the reaction of acetylenic phenylhydrazones with molecular iodine ( $I_2$ ). First of all, the starting materials of the reaction,  $\alpha,\beta$ -acetylenic aldehydes (**14**) and acetylenic phenylhydrazones (**15**), were prepared according to well known literature procedures [36].

#### 2.1. Synthesis of $\alpha,\beta$ -acetylenic aldehydes (**14**).

In the first phase of the study, the synthesis of  $\alpha,\beta$ -acetylenic aldehydes (**14**) was achieved starting from mono-substituted acetylene derivatives (**13**), as shown in Table 1, according to a standard protocol [36].

For this reason, mono-substituted acetylene derivative (**13**) was first treated with a solution of *n*-butyllithium at  $-40\text{ }^\circ\text{C}$  in THF. After the generation of lithium alkynide intermediate, anhydrous *N,N*-dimethylformamide (DMF) has been added to the reaction medium. Finally, the extraction of the resulting reaction mixture with methyl *tert*-butyl ether (MTBE) and  $\text{KH}_2\text{PO}_4$  gave exclusively the expected  $\alpha,\beta$ -acetylenic aldehyde derivatives (**14**) [36]. The results are summarized in Table 1.

**Table 1.** Synthesis of  $\alpha,\beta$ -acetylenic aldehyde derivatives (**14**).

$\text{R}-\text{C}\equiv\text{C}-\text{H} \xrightarrow[\text{3. 10\% aq. KH}_2\text{PO}_4 \text{ (4 equiv); MTBE; 5 }^\circ\text{C}]{\begin{array}{l} \text{1. 1 equiv n-BuLi; THF; -40 }^\circ\text{C} \\ \text{2. 2 equiv DMF; -40 }^\circ\text{C to r.t.; 0.5h} \end{array}} \text{R}-\text{C}\equiv\text{C}-\text{C}(=\text{O})\text{H}$ <p style="text-align: center;"><b>13</b> <span style="margin-left: 200px;"></span> <b>14</b></p>		
Entry	R	Yield % of $\alpha,\beta$ -acetylenic aldehydes ( <b>14</b> )
A		87
B		81
C		94
D		52
E		60
F		60

The mechanism first involves the attack of *n*-butyllithium to the most acidic proton of alkyne derivative (**13**), which affords lithium alkynide. Direct formylation of this lithium alkynide with DMF gave  $\alpha,\beta$ -acetylenic aldehyde (**14**). In order to obtain an effective, high-yielding preparation of  $\alpha,\beta$ -acetylenic aldehydes (**14**), an appropriate hydrolysis is needed with an efficient trapping of dimethylamine that

would circumvent side reactions. This has been accomplished by a reverse addition of the reaction mixture into a phosphate buffer (10% aqueous  $\text{KH}_2\text{PO}_4$ , 4.0 equiv.), affording  $\alpha,\beta$ -acetylenic aldehydes (**14**) without any trace amounts of Michael adducts [36].

As illustrated in Table 6, six different derivatives of  $\alpha,\beta$ -acetylenic aldehydes (**14**) were prepared, the overall yields of which range from 52 to 94%. The best yield (94%) was observed for (4-methoxyphenyl)propynal (**14C**) while the lowest yield (52%) was obtained for thiophen-3-ylpropynal (**14D**).

## 2.2. Synthesis of acetylenic phenylhydrazone derivatives (**15**).

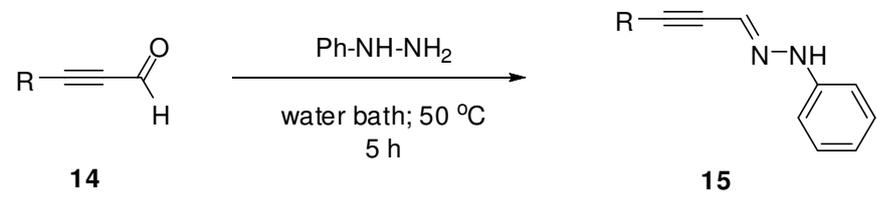
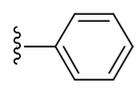
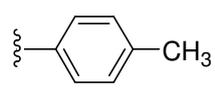
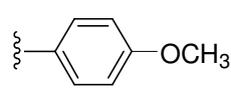
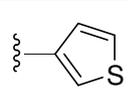
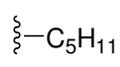
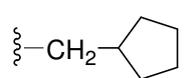
Initially, yield optimization studies were carried out for the synthesis of phenylhydrazones. First, the reaction of phenylhydrazine with  $\alpha,\beta$ -acetylenic aldehydes **14A** and **14C** was investigated in a solvent system. For this reason, a dioxane solution of phenylhydrazine and  $\alpha,\beta$ -acetylenic aldehyde (**14**) was heated at reflux (100 °C) for 5 h to afford the acetylenic phenylhydrazone derivatives (**15**). The results are summarized in Table 2. The yield for the formation of *N*-phenyl-*N'*-(3-phenylprop-2-ynylidene)hydrazine (**15A**) was 61% while it was 57% for *N*-[3-(4-methoxyphenyl)prop-2-ynylidene]-*N'*-phenylhydrazine (**15C**).

**Table 2.** Synthesis of acetylenic phenylhydrazones (**15**) in refluxing dioxane.

Entry	R	Yield % of phenylhydrazone derivatives ( <b>15</b> )
A		61
C		57

Subsequently, the same reactions were performed in a solvent-free manner. Accordingly, phenylhydrazine was reacted neat with propargyl aldehydes **14A** and **14C**, respectively, at 50 °C in a water bath for 5 h. As depicted in Table 3, the reactions carried out in a solvent-free system provided higher yields of acetylenic phenylhydrazones **15A** and **15C** (81 and 64%, respectively), even at relatively lower temperature, as compared to those in refluxing dioxane (Table 2). Thus, the other acetylenic phenylhydrazones were prepared without using any solvent. The highest yield (85%) was obtained for the formation of *N*-phenyl-*N'*-(3-*p*-tolylprop-2-ynylidene)hydrazine (**15B**) while the lowest yield (54%) was observed for *N*-phenyl-*N'*-(3-thiophen-3-ylprop-2-ynylidene)hydrazine (**15D**) (Table 3).

**Table 3.** Synthesis of acetylenic phenylhydrazones (**15**) in a solvent-free manner.

		
Entry	R	Yield % of phenylhydrazone derivatives ( <b>15</b> )
A		81
B		85
C		64
D		54
E		81
F		60

It should be mentioned that due to steric effects, *E* (or anti) isomers of hydrazones were obtained exclusively or they were obtained as the single product of the reactions.

### **2.3. Synthesis of 4-iodopyrazole derivatives (16).**

The reactions were initially examined under a variety of conditions with varying amounts of molecular iodine catalyst. The best results were obtained as follows: Acetylenic phenylhydrazone **15** (1.0 equiv.) was heated in the presence of molecular iodine (3.0 equiv.) at 35 °C for 3 h in dichloromethane (DCM), and the products were isolated by flash chromatography. The results from a systematic study are summarized in Table 4. It should be mentioned that reactions were generally completed in 3 h, since longer reaction times did not improve the yields.

**Table 4.** Synthesis of 4-iodopyrazoles (**16**) and non-iodinated pyrazoles (**17**).

Entry	R	Yield % of 4-iodo-pyrazoles ( <b>16</b> )	Yield % of pyrazoles ( <b>17</b> )
<b>A</b>		78	7
<b>B</b>		64	9
<b>C</b>		84	16
<b>D</b>		75	15
<b>E</b>		15	-
<b>F</b>		23	-

As anticipated, these reactions afforded the expected 4-iodopyrazole derivatives (**16**) as the major or single product of the reactions. The reaction appears to be

general for alkyl and aryl-substituted acetylenic phenylhydrazones (**15**). Notably, aryl-substituted acetylenic phenylhydrazones (i.e., R = aryl) participated well in these reactions and produced 4-iodopyrazoles in good yields (64-84%) (Table 1, Entries A-D). However, the reaction of alkyl-substituted acetylenic phenylhydrazones (i.e., R = alkyl) with molecular iodine produced corresponding 4-iodopyrazole derivatives (**16**) in low yields (Table 1, Entries E and F). A complication in these reactions was the formation of 1-phenyl-5-alkyl/aryl-pyrazoles (**17**) as the minor product of the reactions (7-16%) (Table 1, Entries A-D). However, these minor products were not observed in the reactions with alkyl-substituted acetylenic phenylhydrazones (Table 1, Entries E and F).

We have also carried out the same reactions with iodine monochloride (ICl), which is alternative to the molecular iodine. However, these reactions afforded corresponding 4-iodopyrazole derivatives in very low yields. Moreover, iodine monochloride is difficult to be handled, since it melts near room temperature.

As mentioned above, non-halogenated pyrazole derivatives (**17**) were also observed in these reactions (Table 1, Entries A-D), the formation of which should be mechanistically very important. For this purpose, we have also examined thermolysis reactions of acetylenic phenylhydrazones **15A** and **15C** in the absence of molecular iodine. For this reason, acetylenic phenylhydrazones **15A** and **15C** were separately heated at reflux (100 °C) for 5 h in dioxane. However, these reactions did not produce any pyrazole derivatives, which are consistent with the early findings of Zora research group using similar systems [25], and the starting acetylenic phenyl-hydrazones were recovered.

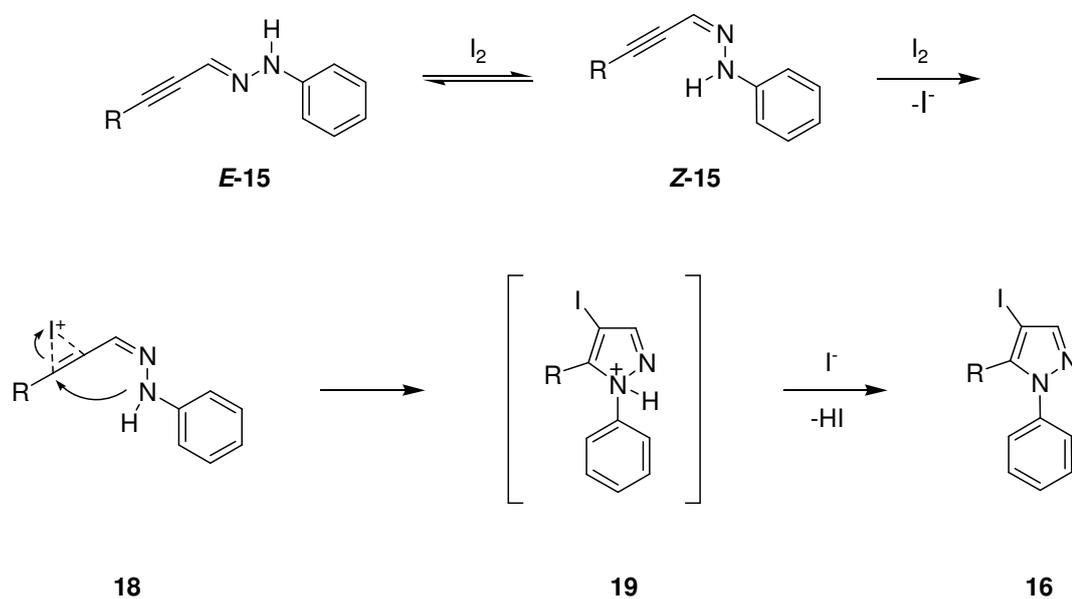
As a second study, we have investigated one-pot synthesis of 4-iodopyrazole derivatives. For this reason, 3-phenylpropionaldehyde (**14C**) was dissolved in dioxane, and to the resulting solution, 1 equivalent of phenylhydrazine and 3 equivalents of iodine were added. The resulting reaction mixture was then heated in dioxane at 100 °C for 5 h (Figure 25). This one-pot reaction afforded 4-iodo-1,5-



On the other hand, the signal at 107.8 ppm in the  $^{13}\text{C}$  NMR spectrum of compound **17A**, which belongs to the carbon at 4<sup>th</sup> position, shifts to 62.3 ppm in the pyrazole **16A**, as a result of iodo substitution.

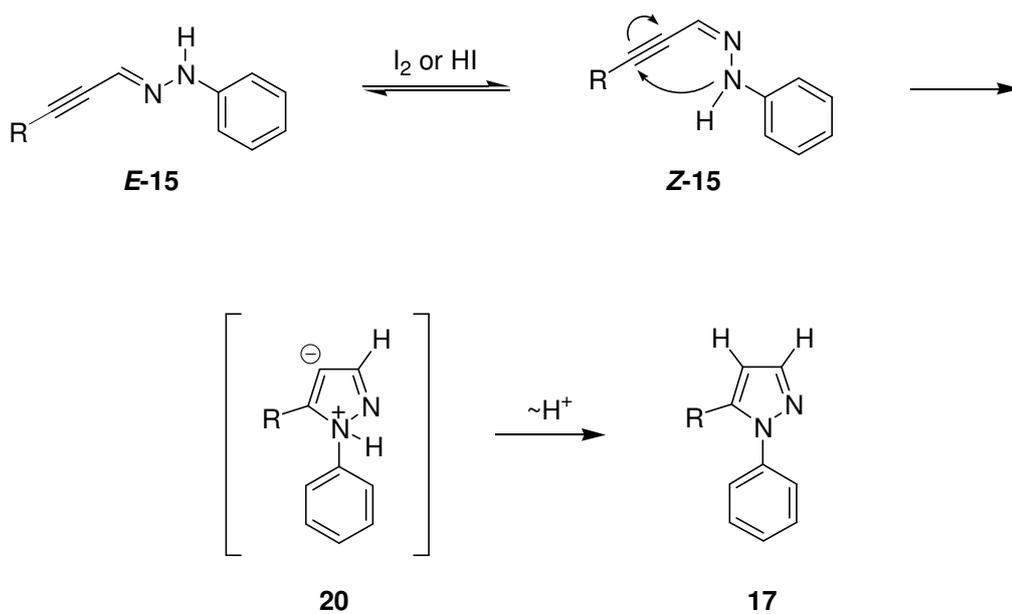
#### 2.4. Mechanism for the formation of pyrazole derivatives.

The mechanism proposed for the formation of 4-iodopyrazole derivatives (**16**) is illustrated in Figure 26. In the presence of iodine, *E* isomer of phenylhydrazone (**E-15**) isomerizes to *Z* isomer (**Z-15**). Then, alkyne functionality of **Z-15** reacts with iodine, yielding iodonium ion **18**. Subsequent nucleophilic attack of secondary nitrogen atom affords the intermediate **19**. Finally, loss of hydrogen produces 4-iodopyrazole derivatives (Figure 26).



**Figure 26.** Proposed mechanism for the formation of 4-iodopyrazoles (**16**).

As noted before, pyrazole derivatives **17** were also resulted from these reactions. The mechanism proposed for the formation of pyrazoles **17** is depicted in Figure 27. As tested before, the thermolysis of *E*-**15** do not produce the expected pyrazole derivatives **17** because the pyrazole forming reaction goes through *Z* isomer of acetylenic phenylhydrazone **Z-15**. As shown in Figure 30, in the presence of iodine or hydrogen iodide, *E* isomer of phenylhydrazone (*E*-**15**) isomerizes to *Z* isomer (**Z-15**). Then, nucleophilic attack of secondary nitrogen atom to alkyne functionality affords the intermediate **20**. Finally, hydrogen exchange affords pyrazole derivatives **17** (Figure 27).



**Figure 27.** Proposed mechanism for the formation of pyrazoles **17**.

## CHAPTER 3

### CONCLUSION

In summary, we have developed a new methodology for the synthesis of 4-iodopyrazoles from acyclic precursors. For this purpose, we have investigated the reaction of acetylenic phenylhydrazone derivatives (**15**) with iodine ( $I_2$ ). As expected, these reactions produced the expected 4-iodopyrazole derivatives (**16**) as the major or single product of the reactions through electrophilic cyclization. The reaction appears to be general for alkyl and aryl-substituted acetylenic phenylhydrazones (**15**). Importantly, aryl-substituted acetylenic phenylhydrazones participated well in these reactions and produced 4-iodopyrazoles in good yields. However, the reactions of alkyl-substituted acetylenic phenylhydrazones with molecular iodine produced corresponding 4-iodopyrazole derivatives (**16**) in low yields.

A complication in these reactions was the formation of 1-phenyl-5-alkyl/aryl-pyrazoles (**17**) as the minor product of the reactions. However, these minor products were not observed in the reactions with alkyl-substituted acetylenic phenylhydrazones, presumably due to the low yields.

These reactions were also carried out in a one-pot manner but these one-pot reactions produced 4-iodopyrazole derivatives (**16**) in relatively low yields. For this reason,  $\alpha,\beta$ -acetylenic phenylhydrazones (**15**) were first prepared from  $\alpha,\beta$ -acetylenic aldehydes (**14**) and phenylhydrazine, and then subjected to electrophilic cyclization with molecular iodine to afford 4-iodopyrazole derivatives (**16**).

The proposed mechanism for the formation of 4-iodopyrazole derivatives (**16**) first involves the isomerization of *E* isomer of phenylhydrazone (***E*-15**) into the *Z* isomer (***Z*-15**). Then, alkyne functionality of ***Z*-15** reacts with iodine, giving an iodonium ion **18**. Subsequent nucleophilic attack of secondary nitrogen atom affords a heterocyclic intermediate **19**, in which the loss of hydrogen produces 4-iodopyrazoles (**16**).

In conclusion, we synthesized 4-iodopyrazole derivatives for the first time directly from acyclic starting materials,  $\alpha,\beta$ -acetylenic phenylhydrazones (**15**) and iodine, via electrophilic cyclization. In other words, 4-iodopyrazoles were synthesized during the construction step of pyrazoles.

## CHAPTER 4

### EXPERIMENTAL

**General Consideration.** Nuclear Magnetic Resonance ( $^1\text{H}$  and  $^{13}\text{C}$ ) spectra were recorded on a Bruker Spectrospin Avance DPX400 Ultrashield (400 MHz) spectrometer. Chemical shifts are reported in parts per million ( $\delta$ ) downfield from an internal tetramethylsilane reference. Coupling constants ( $J$  values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). DEPT  $^{13}\text{C}$ -NMR information is given in parenthesis as C, CH,  $\text{CH}_2$  and  $\text{CH}_3$ . Infrared spectra were recorded on a Bruker Vertex 70 Spectrometer using attenuated total reflection (ATR). Band positions are reported in reciprocal centimeters ( $\text{cm}^{-1}$ ). Band intensities are reported relative to the most intense band and are listed as: br (broad), vs (very strong), s (strong), m (medium), w (weak), vw (very weak). Mass spectra (MS) were obtained on a Bruker Daltonics spectrometer using Electrospray Ionization (ESI) with Micro-Tof;  $m/z$  values are reported (For each measurement, the mass scale was recalibrated with sodium formate clusters, and samples were dissolved and measured in MeOH). Flash column chromatography was performed using thick-walled glass columns and “flash grade” silica (Merck 230-400 mesh). Routine thin layer chromatography (TLC) was effected by using precoated 0.25 mm silica gel plates purchased from Merck. The relative proportions of solvents in mixed chromatography solvents refers to the volume:volume ratio. All commercially available reagents and reactants were obtained in reagent grade and used without purification. All reaction solvents were distilled for purity. Diethylether, THF and dioxane were distilled from sodium/benzophenone kettle.

Dichloromethane was distilled from calcium hydride kettle. The inert atmosphere created by slight positive pressure (ca. 0.1 psi) of argon.

**4.1 General Procedure 1. Synthesis of  $\alpha,\beta$ -acetylenic aldehydes 14A-F (Table 1).** The corresponding alkyne (50 mmol) was dissolved in dry THF (125 ml) and the solution was cooled to -40 °C under argon. *n*-Butyllithium (1.53 M in hexanes, 32.7 ml, 50 mmol) was added dropwise over 2 minutes maintaining the temperature between -35 and -40 °C. After completion of the addition, anhydrous DMF (7.75 ml, 100 mmol) was added in one portion and the cold bath was removed. The reaction mixture was allowed to warm to room temperature and aged for 30 minutes. The THF solution was poured into a vigorously stirred biphasic solution prepared from a 10% aqueous solution of  $\text{KH}_2\text{PO}_4$  (270 ml, 200 mmol) and MTBE (250 ml) cooled over ice to +5 °C. Layers were separated and the organic extract was washed with water (2 x 200 ml). Combined aqueous layers were back extracted with MTBE (150 ml). Combined organic layers were dried over  $\text{MgSO}_4$ , filtered and concentrated to give the crude acetylenic aldehyde as an oil which was filtered through a pad of silica gel (40 g) using a 9:1 mixture of hexanes/ethylacetate as the eluent.

**4.1.1. 3-Phenylpropionaldehyde (14A).** General Procedure 1 was followed by using 1-ethynylbenzene (**13A**) (500 mg, 3.88 mmol), *n*-BuLi (2.4 ml, 3.88 mmol), and DMF (0.62 ml, 7.76 mmol). After chromatographic purification using 9:1 hexane-ethylacetate as the eluent, the product was assigned as 3-phenylpropionaldehyde (**14A**) (435 mg, 87%).

**14A:**  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  9.47 (s, 1H), 7.52 (m, 2H), 7.44 (m, 1H), 7.36 (m, 2H);  $^{13}\text{C}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  176.7, 133.2, 131.3, 128.8, 119.4, 95.0, 88.5. The spectral data were in agreement with those reported previously for this compound [37].

**4.1.2. 3-*p*-Tolylpropionaldehyde (14B).** General Procedure 1 was followed by using 1-ethynyl-4-methylbenzene (**13B**) (500 mg, 4.3 mmol), *n*-BuLi (3.0 ml, 4.3 mmol), and DMF (0.67 ml, 8.6 mmol). After chromatographic purification using

9:1 hexane-ethylacetate as the eluent, the product was identified as 3-*p*-tolylpropionaldehyde (**11B**) (502 mg, 81%).

**14B:**  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  9.41 (s, 1H), 7.49 (d,  $J = 8.06$  Hz, 2H), 7.20 (d,  $J = 8.06$  Hz, 2H), 2.39 (s, 3H);  $^{13}\text{C}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  176.7, 142.1, 133.3, 129.5, 116.3, 95.9, 88.5, 21.7. The spectral data were in agreement with those reported previously for this compound [37].

**4.1.3. 3-(4-Methoxyphenyl)propionaldehyde (14C).** General Procedure 1 was followed by using 1-ethynyl-4-methoxybenzene (**13C**) (500 mg, 3.78 mmol), *n*-BuLi (2.3 ml, 3.78 mmol), and DMF (0.60 ml, 7.56 mmol). After chromatographic purification using 9:1 hexane-ethylacetate as the eluent, the product was assigned as 3-(4-methoxyphenyl)propionaldehyde (**14C**) (570 mg, 94%).

**14C:**  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  9.28 (s, 1H), 7.42 (d,  $J = 9.0$  Hz, 2H), 6.80 (d,  $J = 9.0$  Hz, 2H), 3.78 (s, 3H);  $^{13}\text{C}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  176.6, 162.2, 135.4, 114.5, 111.2, 96.5, 88.7, 55.5. The spectral data were in agreement with those reported previously for this compound [38].

**4.1.4. 3-(Thiophen-3-yl)propionaldehyde (14D).** General Procedure 1 was followed by using 3-ethynylthiophene (**13D**) (500 mg, 4.62 mmol), *n*-BuLi (2.8 ml, 4.62 mmol), and DMF (0.73 ml, 9.24 mmol). After chromatographic purification using 9:1 hexane-ethylacetate as the eluent, the product was identified as 3-(thiophen-3-yl)propionaldehyde (**14D**) (303 mg, 52%).

**14D:**  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  9.42 (s, 1H), 7.83 (s, 1H), 7.37 (m, 1H); 7.26 (m, 1H);  $^{13}\text{C}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  176.6, 134.8, 130.3, 126.4, 118.8, 90.5, 88.9.

**4.1.5. Oct-2-ynal (14E).** General Procedure 1 was followed by using hept-1-yne (**13E**) (500 mg, 5.21 mmol), *n*-BuLi (3.2 ml, 5.21 mmol), and DMF (0.82 ml, 10.42 mmol). After chromatographic purification using 9:1 hexane-ethylacetate as the eluent, the product was assigned as oct-2-ynal (**14E**) (388 mg, 60%).

**14E:** <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): δ 9.16 (s, 1H), 2.40 (t, *J* = 7.1 Hz, 3H), 1.55 (m, 2H); 1.31 (m, 4H); 0.90 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (400MHz, CDCl<sub>3</sub>): δ 177.2, 99.3, 81.7, 30.9, 27.2, 22.1, 19.1, 13.8.

**4.1.6. 4-Cyclopentylbut-2-ynal (14F).** General Procedure 1 was followed by using (prop-2-ynyl)cyclopentane (**13F**) (500 mg, 4.62 mmol), *n*-BuLi (2.8 ml, 4.62 mmol), and DMF (0.73 ml, 9.24 mmol). After chromatographic purification using 9:1 hexane-ethylacetate as the eluent, the product was identified as 4-cyclopentylbut-2-ynal (**14F**) (377 mg, 60%).

**14F:** <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): δ 9.18 (s, 1H), 2.42 (d, *J* = 6.8 Hz, 2H), 2.09 (m, 1H), 1.80 (m, 2H), 1.53 (m, 4H), 1.20 (m, 2H); <sup>13</sup>C NMR (400MHz, CDCl<sub>3</sub>): δ 143.8, 129.3, 128.3, 120.7, 115.8, 113.1, 104.3, 71.9, 31.2, 28.2, 22.2, 19.7, 14.0.

## **4.2 General Procedure 2. Synthesis of phenylhydrazones 15A-F (Table 3).**

Phenylhydrazine (1.00 mmol) was put in a round bottom flask equipped with condenser and the reflux system was placed into water bath. Then,  $\alpha,\beta$ -acetylenic aldehyde (**14**) (1.00 mmol) was added into flask. The reaction mixture was heated for 5 h at 55 °C in water bath. The product was purified by flash chromatography on silica gel using a 9:1 mixture of hexane/ethylacetate as the eluent.

**4.2.1. Reaction of 3-phenylpropionaldehyde (14A) with phenylhydrazine (Table 3, Entry A).** General Procedure 2 was followed by using 3-phenylpropionaldehyde (**14A**) (200 mg, 1.55 mmol), phenylhydrazine (167 mg, 1.55 mmol). After chromatographic purification using 9:1 hexane-ethyl acetate as eluent, one fraction was isolated. The product was assigned as 2-phenyl-1-(3-phenylprop-2-ynylidene)hydrazine (**15A**) (275 mg, 81%).

**15A:** <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): δ 8.67 (br s, 1H), 7.53 (m, 2H), 7.40 (m, 3H), 7.29 (m, 2H), 7.10 (m, 2H), 6.92 (m, 1H), 6.62 (s, 1H); <sup>13</sup>C NMR (400MHz, CDCl<sub>3</sub>): δ 143.5, 131.8, 129.5, 129.4, 128.6, 121.6, 121.2, 114.7, 113.3, 101.9, 79.6; IR (neat): 3307, 3051, 3028, 2185, 1596, 1523, 1500, 1438, 1342, 1309,

1255, 1124, 1068, 764, 682  $\text{cm}^{-1}$ ; MS (ESI,  $m/z$ ): 243.09  $[\text{M}+\text{Na}]^+$ ; HRMS (ESI): calcd. for  $\text{C}_{15}\text{H}_{12}\text{N}_2\text{Na}$ : 243.0897  $[\text{M}+\text{Na}]^+$ . Found: 243.0893.

**4.2.2. Reaction of 3-*p*-tolylpropionaldehyde (14B) with phenylhydrazine (Table 3, Entry B).** General Procedure 2 was followed by using 3-*p*-tolylpropionaldehyde (**14B**) (200 mg, 1.39 mmol) and phenylhydrazine (150 mg, 1.39 mmol). After chromatographic purification using 9:1 hexane-ethyl acetate as eluent, one fraction was isolated. The product was identified as 2-phenyl-1-(3-*p*-tolylprop-2-ynylidene)hydrazine (**15B**) (276 mg, 85%).

**15B:**  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  8.68 (b s, 1H), 7.45 (d,  $J = 7.99$  Hz, 2H), 7.31 (t,  $J = 7.7$  Hz, 2H), 7.22 (d,  $J = 7.9$  Hz, 2H), 7.13 (d,  $J = 8.2$  Hz, 2H), 6.94 (t,  $J = 7.2$  Hz, 1H), 2.41 (s, 3H);  $^{13}\text{C}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  143.6 (C), 139.9 (C), 131.7 (CH), 129.4 (CH), 129.3 (CH), 121.0 (CH), 118.5 (C), 114.9 (CH), 113.3 (CH), 102.3 (C), 79.1 (C), 21.6 ( $\text{CH}_3$ ); IR (neat): 3317, 3053, 3029, 2918, 2189, 1598, 1531, 1508, 1348, 1253, 1122, 1068, 885, 810, 750, 688  $\text{cm}^{-1}$ ; MS (ESI,  $m/z$ ): 257.11  $[\text{M}+\text{Na}]^+$ ; HRMS (ESI): calcd. for  $\text{C}_{16}\text{H}_{14}\text{N}_2\text{Na}$ : 257.1054  $[\text{M}+\text{Na}]^+$ . Found: 257.1049.

**4.2.3. Reaction of 3-(4-methoxyphenyl)propionaldehyde (14C) with phenylhydrazine (Table 3, Entry C).** General Procedure 2 was followed by using 3-(4-methoxyphenyl)propionaldehyde (**14C**) (200 mg, 1.25 mmol) and phenylhydrazine (136 mg, 1.25 mmol). After chromatographic purification using 9:1 hexane-ethyl acetate as eluent, one fraction was isolated. The product was assigned as 1-(3-(4-methoxyphenyl)prop-2-ynylidene)-2-phenylhydrazine (**15C**) (188 mg, 64%).

**15C:**  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  8.64 (b s, 1H, NH), 7.48 (d,  $J = 8.7$  Hz, 2H), 7.29 (t,  $J = 7.5$  Hz, 2H), 7.11 (d,  $J = 8.2$  Hz, 2H), 6.93 (m, 3H), 6.62 (s, 1H), 3.86 (s, 3H);  $^{13}\text{C}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  160.6 (C), 143.6 (C), 133.4 (CH), 129.3 (CH), 121.0 (CH), 115.2 (C), 114.3 (CH), 113.6 (C), 113.2 (C), 102.2 (C), 78.6 (C), 55.4 ( $\text{CH}_3$ ); IR (neat): 3290, 3055, 2839, 2192, 1598, 1542, 1504, 1346, 1290, 1240, 1172, 1105, 1026, 885, 827, 748, 690  $\text{cm}^{-1}$ ; MS (ESI,  $m/z$ ): 273.10

[M+Na]<sup>+</sup>; HRMS (ESI): calcd. for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>ONa: 273.1003 [M+Na]<sup>+</sup>. Found: 273.0998.

**4.2.4. Reaction of 3-(thiophen-3-yl)propionaldehyde (14D) with phenylhydrazine (Table 3, Entry D).** General Procedure 2 was followed by using 3-(thiophen-3-yl)propionaldehyde (**14D**) (200 mg, 1.58 mmol) and phenylhydrazine (171 mg, 1.58 mmol). After chromatographic purification using 9:1 hexane-ethyl acetate as eluent, one fraction was isolated. The product was identified as 2-phenyl-1-(3-(thiophen-3-yl)prop-2-ynylidene)hydrazine (**15D**) (157 mg, 54%).

**15D:** <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): δ 8.55 (br s, 1H, NH), 7.51 (d, *J* = 1.9 Hz, 1H), 7.26 (m, 1H), 7.20 (m, 2H), 7.12 (d, *J* = 5.4 Hz, 1H), 7.02 (d, *J* = 8.3 Hz, 2H), 6.84 (t, *J* = 7.2 Hz, 1H), 6.51 (s, 1H); IR (neat): 3305, 3105, 3053, 2181, 1598, 1498, 1342, 1521, 1120, 1068, 856, 779, 748, 688 cm<sup>-1</sup>; MS (ESI, *m/z*): 249.05 [M+Na]<sup>+</sup>; HRMS (ESI): calcd. for C<sub>13</sub>H<sub>10</sub>N<sub>2</sub>SNa: 249.0462 [M+Na]<sup>+</sup>. Found: 249.0457.

**4.2.5. Reaction of oct-2-ynal (14E) with phenylhydrazine (Table 3, Entry E).** General Procedure 2 was followed by using oct-2-ynal (**14E**) (200 mg, 1.76 mmol) and phenylhydrazine (193 mg, 1.76 mmol). After chromatographic purification using 9:1 hexane-ethyl acetate as eluent, one fraction was isolated. The product was assigned as 1-(oct-2-ynylidene)-2-phenylhydrazine (**15E**) (300 mg, 81%).

**15E:** <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): δ 8.46 (b s, 1H, NH), 7.19 (t, *J* = 7.68 Hz, 2H), 7.03 (d, *J* = 7.88 Hz, 2H), 6.81 (t, *J* = 7.20 Hz, 1H), 6.32 (s, 1H), 2.40 (t, *J* = 6.93 Hz, 2H), 1.55 (p, *J* = 7.15 Hz, 2H), 1.33 (m, 4H), 0.87 (t, *J* = 7.0 Hz, 3H); <sup>13</sup>C NMR (400MHz, CDCl<sub>3</sub>): δ 143.8 (C), 129.3 (CH), 120.8 (CH), 115.8 (CH), 113.1 (CH), 104.3 (C), 71.9 (C), 31.2 (CH<sub>2</sub>), 28.2 (CH<sub>2</sub>), 22.2 (CH<sub>2</sub>), 19.7 (CH<sub>2</sub>), 14.0 (CH<sub>3</sub>); IR (neat): 3307, 2954, 2929, 2858, 2196, 1600, 1535, 1502, 1344, 1253, 1151, 1114, 1066, 883, 810, 746, 690 cm<sup>-1</sup>; MS (ESI, *m/z*): 237.14 [M+Na]<sup>+</sup>; HRMS (ESI): calcd. for C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>Na: 237.1367 [M+Na]<sup>+</sup>. Found: 237.1362.

**4.2.6. Reaction of 4-cyclopentylbut-2-ynal (14F) with phenylhydrazine (Table 3, Entry F).** General Procedure 2 was followed by using 4-cyclopentylbut-2-ynal (**14F**) (200 mg, 1.47 mmol) and phenylhydrazine (160 mg, 1.47 mmol). After chromatographic purification using 9:1 hexane-ethyl acetate as eluent, one fraction was isolated. The product was identified as 1-(4-cyclopentylbut-2-ynylidene)-2-phenylhydrazine (**15F**) (200 mg, 60%).

**15F:**  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ): 8.58 (s, 1H), 7.31 (m, 2H), 7.08 (d,  $J = 7.50$ , 2H), 7.0 (t,  $J = 7.26$ , 1H), 6.43 (s, 1H), 2.55 (d,  $J = 6.80$ , 2H), 2.16-2.27 (m, 1H), 1.95-1.88 (m, 2H), 1.77-1.61 (m, 4H), 1.43-1.35 (m, 2H); IR (neat): 3307, 2947, 2864, 2194, 1600, 1533, 1502, 1344, 1307, 1523, 1151, 114, 1066, 810, 764, 690  $\text{cm}^{-1}$ ; MS (ESI,  $m/z$ ): 249.14  $[\text{M}+\text{Na}]^+$ ; HRMS (ESI): calcd. for  $\text{C}_{15}\text{H}_{18}\text{N}_2\text{Na}$ : 249.1367  $[\text{M}+\text{Na}]^+$ . Found: 249.1362.

**4.3 General Procedure 3. Synthesis of 4-iodopyrazoles 16A-F and 17A-D (Table 4).** The phenylhydrazone (**15**) (1.00 mmol) was put in a two necked round bottom flask equipped with condenser and the system was flushed with argon. It was dissolved with 10 ml dichloromethane and  $\text{I}_2$  (3.00 mmol) was then added. The mixture was refluxed under argon for 3 h. The progress of the reaction was monitored by routine TLC for the disappearance of phenylhydrazone. The mixture was then cooled to room temperature and the excess  $\text{I}_2$  was removed by washing with a aqueous solution of 10%  $\text{Na}_2\text{S}_2\text{O}_3$ . The aqueous solution was then extracted with chloroform (3 x 10 ml). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure to yield the crude product. The crude product was purified by flash chromatography on silica gel using a hexane/ethylacetate mixture as the eluent.

**4.3.1. Reaction of 2-phenyl-1-(3-phenylprop-2-ynylidene)hydrazine (15A) with iodine (Table 4, Entry A).** General Procedure 3 was followed by using 2-phenyl-1-(3-phenylprop-2-ynylidene)hydrazine (**15A**) (390 mg, 1.78 mmol) and iodine (1376 mg, 5.34 mmol). After chromatographic purification using 9:1 hexane-ethyl acetate as the eluent, two fractions were collected. The product in the

first fraction was assigned as 4-iodo-1,5-diphenyl-1*H*-pyrazole (**16A**) (477 mg, 78%). The product in the second fraction was identified as 1,5-diphenyl-1*H*-pyrazole (**17A**) (27 mg, 7%).

**16A:** <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): δ 7.71 (s, 1H), 7.29 (m, 3H), 7.19 (m, 5H), 7.13 (m, 2H); <sup>13</sup>C NMR (400MHz, CDCl<sub>3</sub>): δ 145.5, 143.5, 139.9, 130.3, 129.6, 129.0, 128.8, 128.5, 127.6, 124.7, 62.3; IR (neat): 3029, 2923, 2852, 1595, 1492, 1444, 1377, 1066, 943, 844, 758 cm<sup>-1</sup>; MS (ESI, *m/z*): 368.99 [M+Na]<sup>+</sup>, 347.00 [M+H]<sup>+</sup>; HRMS (ESI): calcd. for C<sub>15</sub>H<sub>11</sub>IN<sub>2</sub>Na: 368.9865 [M+Na]<sup>+</sup>. Found: 368.9859.

**17A:** <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): δ 7.75 (d, *J* = 1.6 Hz, 1H), 7.32 (m, 8H), 7.27 (m, 2H), 6.53 (d, *J* = 1.6 Hz, 1H); <sup>13</sup>C NMR (400MHz, CDCl<sub>3</sub>): δ 143.0, 140.3, 140.2, 130.6, 128.9, 128.8, 128.4, 128.2, 127.4, 125.2, 107.8.

**4.3.2. Reaction of 2-phenyl-1-(3-*p*-tolylprop-2-ynylidene)hydrazine (**15B**) with iodine (Table 4, Entry B).** General Procedure 3 was followed by using 2-phenyl-1-(3-*p*-tolylprop-2-ynylidene)hydrazine (**15B**) (245mg, 1.05 mmol) and iodine (804 mg, 3.14 mmol). After chromatographic purification using 9:1 hexane-ethyl acetate as the eluent, two fractions were collected. The product in the first fraction was assigned as 4-iodo-1-phenyl-5-*p*-tolyl-1*H*-pyrazole (**16B**) (251 mg, 64%). The product in the second fraction was identified as 1-phenyl-5-*p*-tolyl-1*H*-pyrazole (**17B**) (22 mg, 9%).

**16B:** <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): δ 7.72 (s, 1H), 7.23 (m, 3H), 7.14 (m, 4H), 6.83 (d, *J* = 8.3 Hz, 2H), 3.77 (s, 3H); <sup>13</sup>C NMR (400MHz, CDCl<sub>3</sub>): δ 159.9 (C), 145.3 (CH), 143.4 (C), 140.0 (C), 131.6 (CH), 128.8 (CH), 127.5 (CH), 124.7 (CH), 121.7 (C), 113.9 (CH), 62.2 (C), 55.2 (CH<sub>3</sub>); IR (neat): 3101, 2914, 2852, 1595, 1496, 1434, 1380, 1315, 1068, 943, 914, 858, 815, 761 cm<sup>-1</sup>; MS (ESI, *m/z*): 383.00 [M+Na]<sup>+</sup>, 361.02 [M+H]<sup>+</sup>; HRMS (ESI): calcd. for C<sub>16</sub>H<sub>13</sub>IN<sub>2</sub>Na: 383.0021 [M+Na]<sup>+</sup>. Found: 383.0016.

**17B:** <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): δ 7.74 (d, *J* = 1.4 Hz, 1H), 7.35 (m, 5H), 7.15 (m, 4H), 6.51 (d, *J* = 1.5 Hz, 1H), 2.37 (s, 3H); <sup>13</sup>C NMR (400MHz, CDCl<sub>3</sub>): δ 143.1 (C), 140.3 (C), 140.2 (CH), 138.1 (C), 129.2 (CH), 128.9 (CH), 128.7 (CH),

127.8 (C), 127.3 (CH), 125.2 (CH), 107.6 (CH), 21.2 (CH<sub>3</sub>); IR (neat): 3124, 2979, 2869, 1596, 1496, 1446, 1382, 1128, 1072, 1022, 960, 923, 821, 785, 759 cm<sup>-1</sup>; MS (ESI, *m/z*): 257.11 [M+Na]<sup>+</sup>, 235.12 [M+H]<sup>+</sup>; HRMS (ESI): calcd. for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>Na: 257.1054 [M+Na]<sup>+</sup>. Found: 257.1049; calcd. for C<sub>16</sub>H<sub>15</sub>N<sub>2</sub>: 235.1236 [M+H]<sup>+</sup>. Found: 235.1230.

**4.3.3. Reaction of 1-(3-(4-methoxyphenyl)prop-2-ynylidene)-2-phenylhydrazine (15C) with iodine (Table 4, Entry C).** General Procedure 3 was followed by using 1-(3-(4-methoxyphenyl)prop-2-ynylidene)-2-phenylhydrazine (**15C**) (248 mg, 0.99 mmol) and iodine (762 mg, 2.98 mmol). After chromatographic purification using 9:1 hexane-ethyl acetate as the eluent, two fractions were collected. The product in the first fraction was assigned as 4-iodo-5-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole (**16C**) (312 mg, 84%). The product in the second fraction was identified as 5-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole (**17C**) (45 mg, 16%).

**16C:** <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): δ 7.72 (s, 1H), 7.23 (m, 3H), 7.14 (m, 4H), 6.83 (d, *J* = 8.3 Hz, 2H), 3.77 (s, 3H); <sup>13</sup>C NMR (400MHz, CDCl<sub>3</sub>): δ 159.9 (C), 145.3 (CH), 143.4 (C), 140.0 (C), 131.6 (CH), 128.8 (CH), 127.5 (CH), 124.7 (CH), 121.7 (C), 113.9 (CH), 62.2 (C), 55.2 (CH<sub>3</sub>); IR (neat): 2912, 1595, 1496, 1434, 1380, 1315, 1068, 943, 914, 858, 815, 761 cm<sup>-1</sup>; MS (ESI, *m/z*): 399.00 [M+Na]<sup>+</sup>, 377.02 [M+H]<sup>+</sup>; HRMS (ESI): calcd. for C<sub>16</sub>H<sub>14</sub>IN<sub>2</sub>NaO: 398.9970 [M+Na]<sup>+</sup>. Found: 398.9968.

**17C:** <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): δ 7.68 (d, *J* = 1.0 Hz, 1H), 7.30 (m, 5H), 7.14 (d, *J* = 8.67 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 6.43 (d, *J* = 1.0 Hz, 1H), 3.78 (s, 3H); <sup>13</sup>C NMR (400MHz, CDCl<sub>3</sub>): δ 159.6 (C), 142.87 (C), 140.3 (C), 140.2 (CH), 130.0 (CH), 128.9 (CH), 127.3 (CH), 125.2 (CH), 123.0 (C), 113.9 (CH), 107.3 (CH), 55.3 (CH<sub>3</sub>); IR (neat): 3134, 2929, 2835, 1598, 1496, 1442, 1384, 1288, 1245, 1178, 1130, 1029, 960, 925, 835, 786, 759, 692 cm<sup>-1</sup>.

**4.3.4. Reaction of 2-phenyl-1-(3-(thiophen-3-yl)prop-2-ynylidene)hydrazine (15D) with iodine (Table 4, Entry D).** General Procedure 3 was followed by using 2-phenyl-1-(3-(thiophen-3-yl)prop-2-ynylidene)hydrazine (**15D**) (66 mg, 0.31 mmol) and iodine (234 mg, 0.92 mmol). After chromatographic purification using 9:1 hexane-ethyl acetate as the eluent, two fractions were collected. The product in the first fraction was assigned as 4-iodo-1-phenyl-5-(thiophen-2-yl)-1*H*-pyrazole (**16D**) (78 mg, 75%). The product in the second fraction was identified as 1-phenyl-5-(thiophen-2-yl)-1*H*-pyrazole (**17D**) (10 mg, 15%).

**16D:** <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): δ 7.67 (s, 1H), 7.29 (dd, *J* = 1.0 Hz, *J* = 2.9 Hz, 1H), 7.22 (m, 2H), 7.19 (m, 2H), 7.16 (d, *J* = 1.7 Hz, 1H), 7.14 (m, 1H), 6.79 (d, *J* = 4.5 Hz, 1H); <sup>13</sup>C NMR (400MHz, CDCl<sub>3</sub>): δ 145.6 (CH), 139.9 (C), 139.4 (C), 129.3 (C), 128.9 (CH), 128.2 (CH), 127.9 (CH), 126.8 (CH), 125.8 (CH), 124.8 (CH), 62.2 (C); IR (neat): 3091, 2954, 2921, 2852, 1593, 1498, 1444, 1375, 1182, 1066, 943, 854, 786, 761 cm<sup>-1</sup>; MS (ESI, *m/z*): 374.94 [M+Na]<sup>+</sup>, 352.96 [M+H]<sup>+</sup>; HRMS (ESI): calcd. for C<sub>13</sub>H<sub>10</sub>IN<sub>2</sub>NaS: 374.9429 [M+Na]<sup>+</sup>. Found: 374.9423.

**17D:** <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): δ 7.62 (s, 1H), 7.27 (m, 5H), 7.17 (m, 1H), 7.00 (s, 1H), 6.82 (s, *J* = 6.82, 1H), 6.45 (s, 1H); <sup>13</sup>C NMR (400MHz, CDCl<sub>3</sub>): δ 140.3, 140.2, 138.5, 130.8, 129.0, 127.9, 127.6, 125.7, 125.6, 123.6, 107.1.

**4.3.5. Reaction of 1-(oct-2-ynylidene)-2-phenylhydrazine (15E) with iodine (Table 4, Entry E).** General Procedure 3 was followed by using 1-(oct-2-ynylidene)-2-phenylhydrazine (**15E**) (100 mg, 0.47 mmol) and iodine (360 mg, 1.41 mmol). After chromatographic purification using 9:1 hexane-ethyl acetate as the eluent, one fraction was isolated. The product was assigned as 4-iodo-5-pentyl-1-phenyl-1*H*-pyrazole (**16E**) (24 mg, 15%).

**16E:** <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): δ 7.59 (s, 1H), 7.44 (m, 3H), 7.35 (d, *J* = 7.6 Hz, 2H), 2.67 (t, *J* = 8 Hz, 2H), 1.44 (p, *J* = 7.39 Hz, 2H), 1.23 (m, 4H), 0.8 (t, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (400MHz, CDCl<sub>3</sub>): δ 144.6 (C), 144.5 (CH), 139.9 (C), 129.2 (CH), 128.5 (CH), 125.5 (CH), 60.6 (C), 31.2 (CH<sub>2</sub>), 28.2 (CH<sub>2</sub>), 25.7 (CH<sub>2</sub>), 22.0 (CH<sub>2</sub>), 13.8 (CH<sub>3</sub>); IR (neat): 2954, 2925, 2858, 1596, 1500, 1456, 1390,

1174, 933, 846, 761  $\text{cm}^{-1}$ ; MS (ESI,  $m/z$ ): 363.03  $[\text{M}+\text{Na}]^+$ , 341.05  $[\text{M}+\text{H}]^+$  ; HRMS (ESI): calcd. for  $\text{C}_{14}\text{H}_{17}\text{IN}_2\text{Na}$ : 363.0334  $[\text{M}+\text{Na}]^+$ . Found: 363.0329.

**4.3.6. Reaction of 1-(4-cyclopentylbut-2-ynylidene)-2-phenylhydrazine (15F) with iodine (Table 4, Entry F).** General Procedure 3 was followed by using 1-(4-cyclopentylbut-2-ynylidene)-2-phenylhydrazine (**15F**) (148 mg, 0.66 mmol) and iodine (509 mg, 1.99 mmol). After chromatographic purification using 9:1 hexane-ethyl acetate as the eluent, one fraction was isolated. The product was identified as 5-(cyclopentylmethyl)-4-iodo-1-phenyl-1*H*-pyrazole (**16F**) (54 mg, 23%).

**16F:**  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  7.59 (s, 1H), 7.43 (m, 3H), 7.36 (m, 2H), 2.74 (d,  $J = 7.6$  Hz, 2H), 1.91 (p, 1H), 1.49 (m, 4H), 1.38 (m, 2H), 1.01 (m, 2H);  $^{13}\text{C}$  NMR (400MHz,  $\text{CDCl}_3$ ):  $\delta$  144.6 (CH), 144.3 (C), 140.2 (C), 129.2 (CH), 128.9 (CH), 125.8 (CH), 61.3 (C), 39.6 (CH), 32.7  $\text{CH}_2$ , 31.0 ( $\text{CH}_2$ ), 24.6 ( $\text{CH}_2$ ); MS (ESI,  $m/z$ ): 375.03  $[\text{M}+\text{Na}]^+$ , 353.05  $[\text{M}+\text{H}]^+$  ; HRMS (ESI): calcd. for  $\text{C}_{15}\text{H}_{17}\text{IN}_2\text{Na}$ : 375.0334  $[\text{M}+\text{Na}]^+$ . Found: 375.0329.

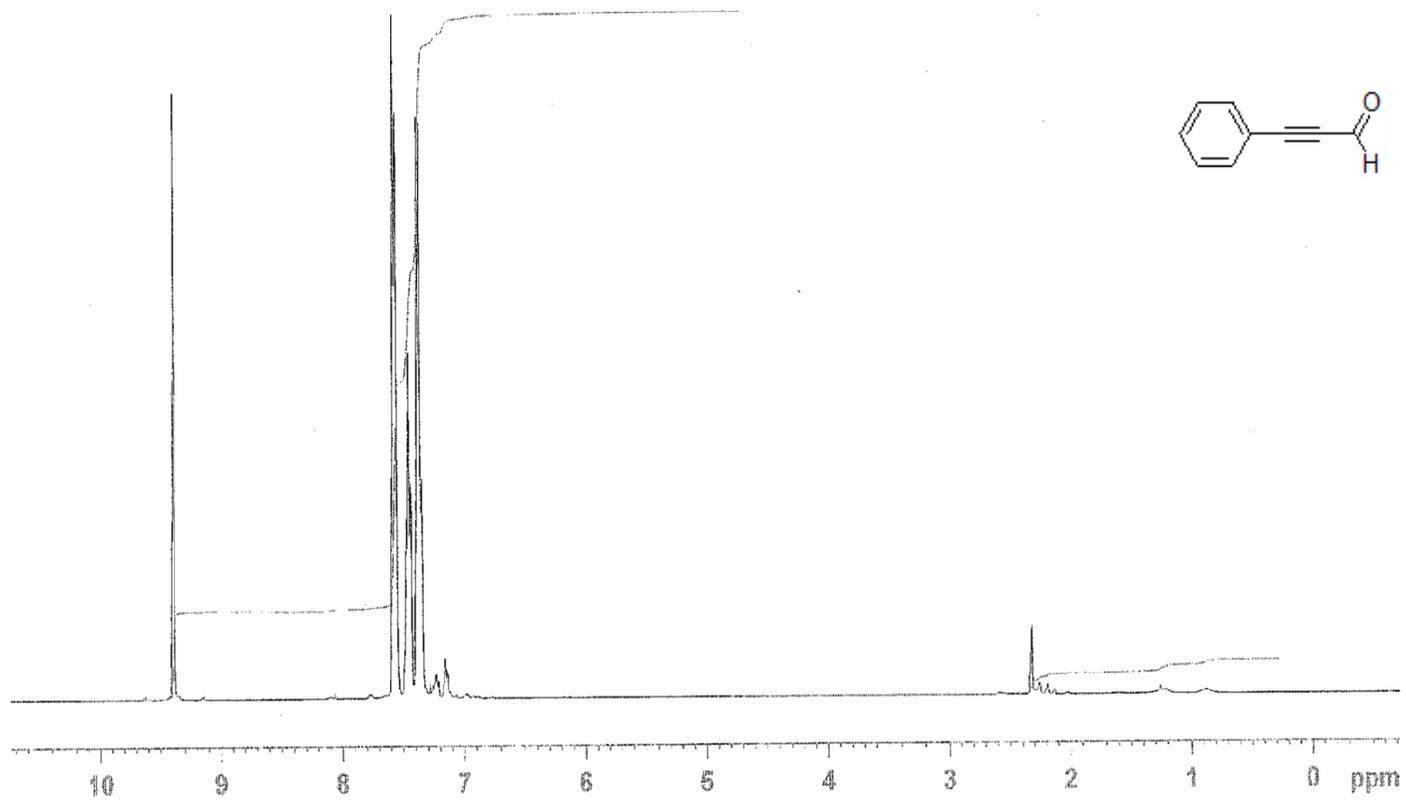
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(b) Togo, S.; Lida, S., *Synlett*, **2006**, 2159.
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**Figure A1.**  $^1\text{H}$  NMR Spectrum of **14A**.

SPECTRUMS

APPENDIX A

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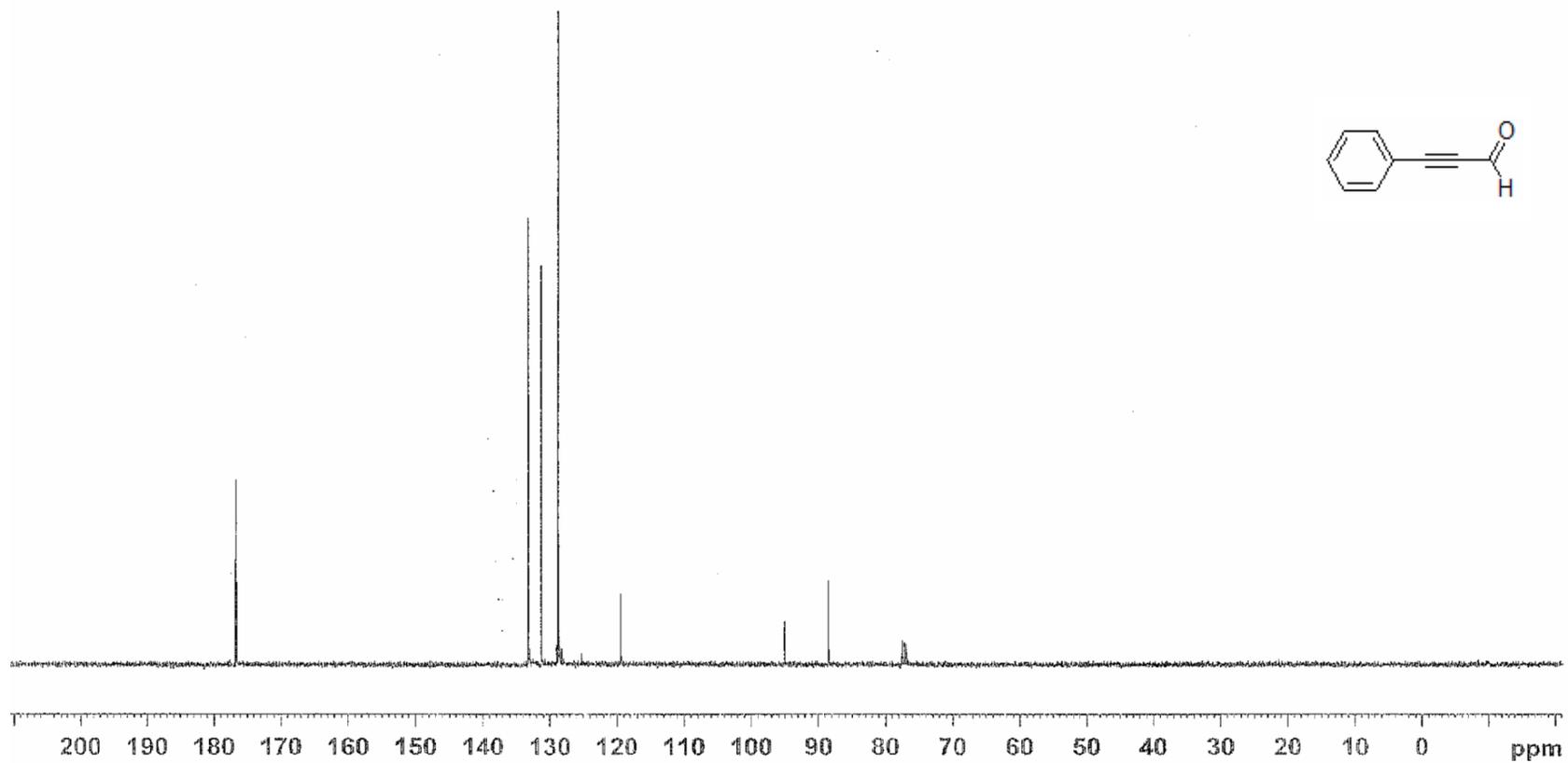
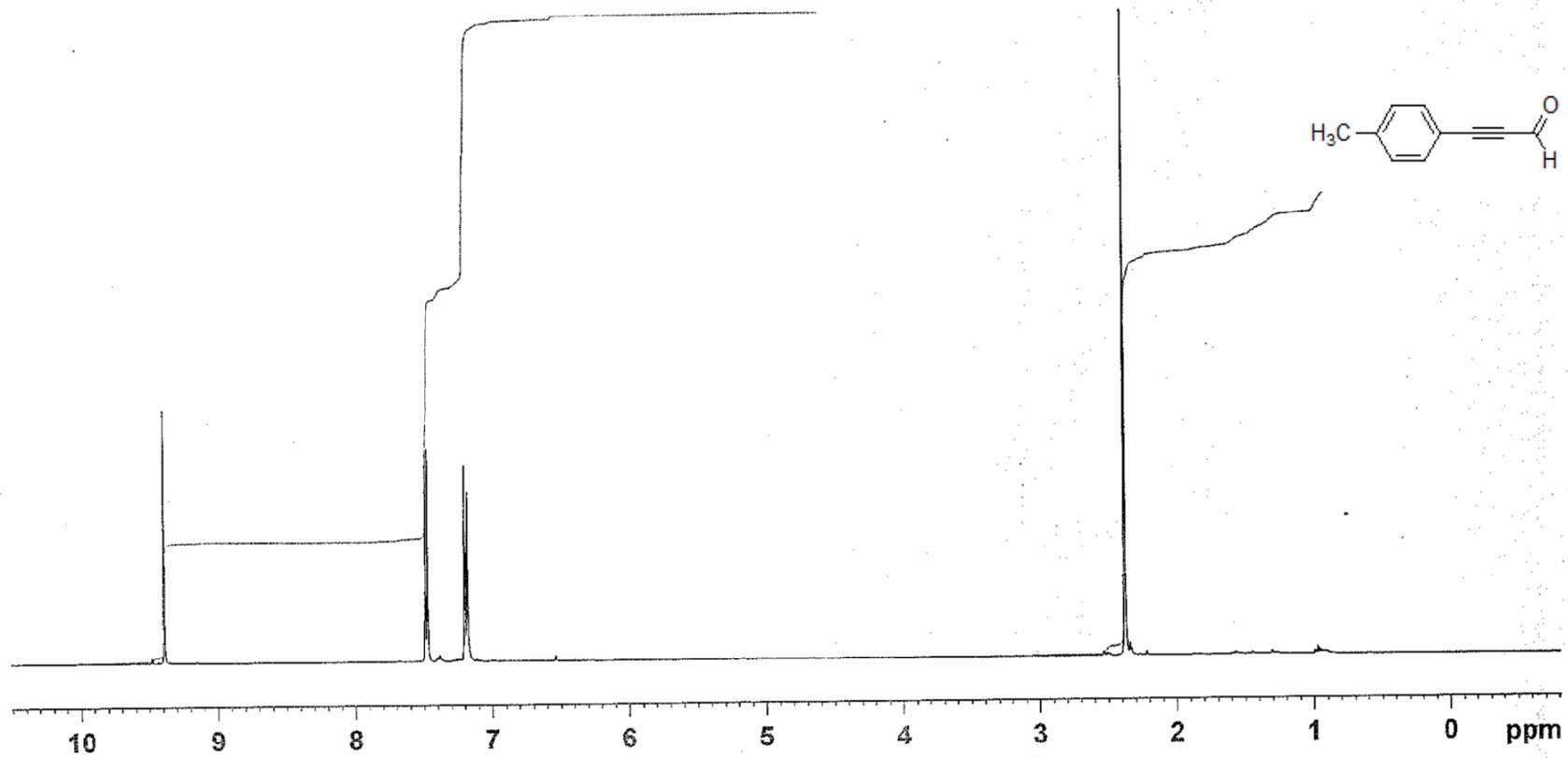


Figure A2.  $^{13}\text{C}$  NMR Spectrum of 14A.



**Figure A3.**  $^1\text{H}$  NMR Spectrum of **14B**.

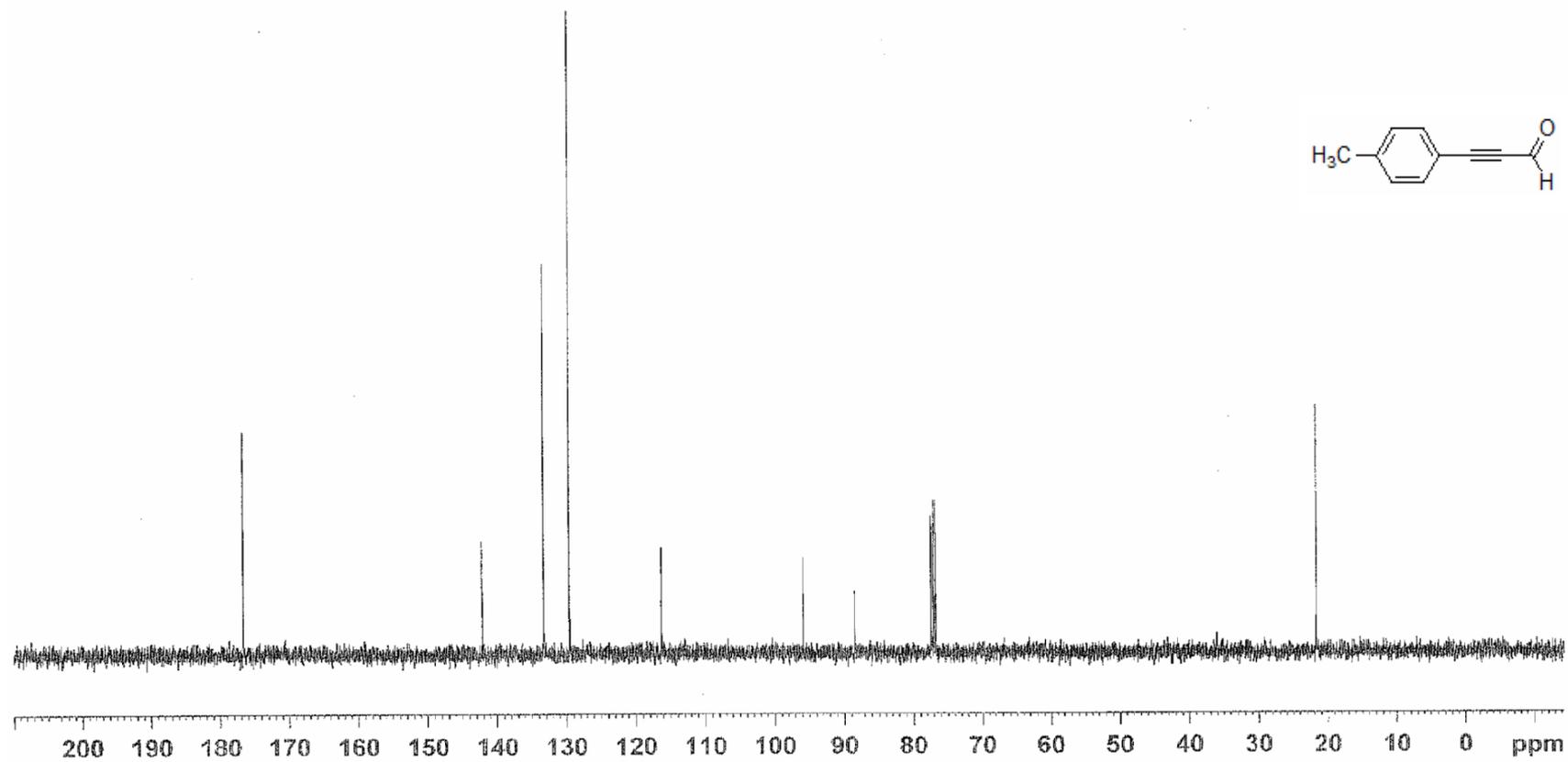


Figure A4.  $^{13}\text{C}$  NMR Spectrum of 14B.

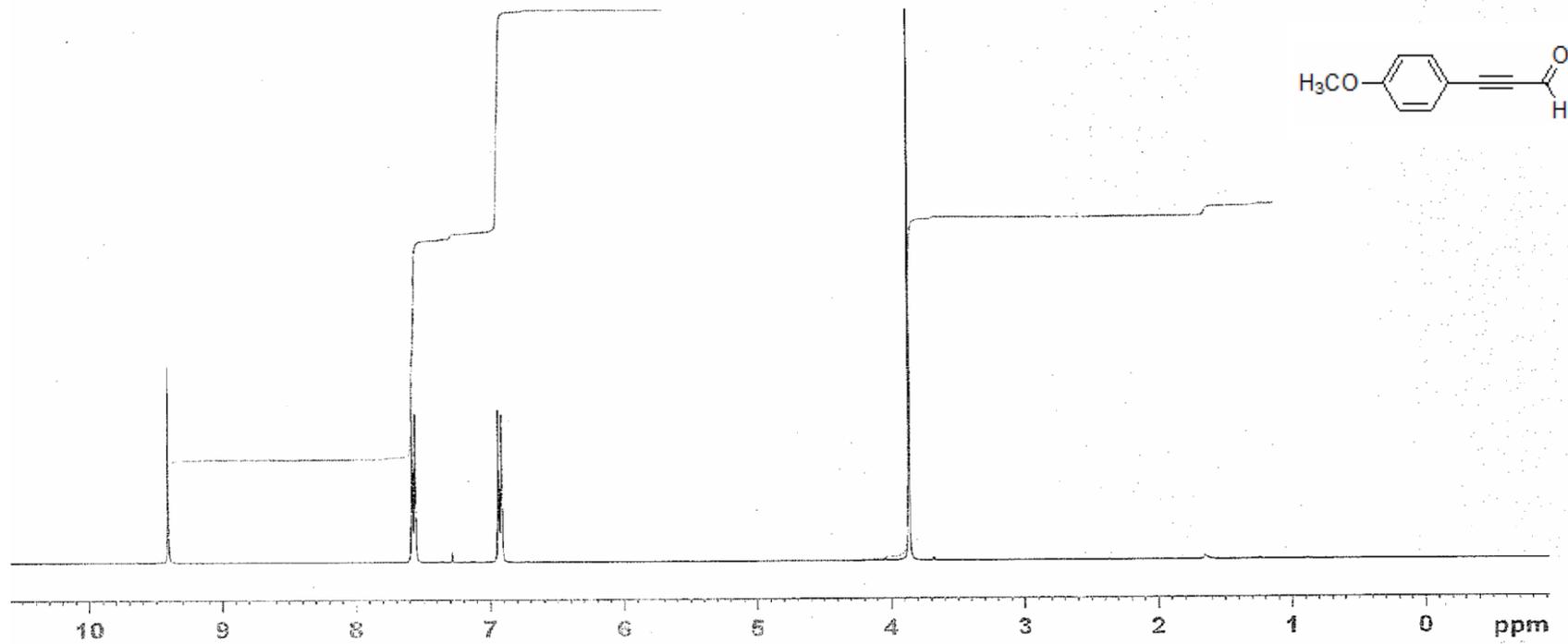
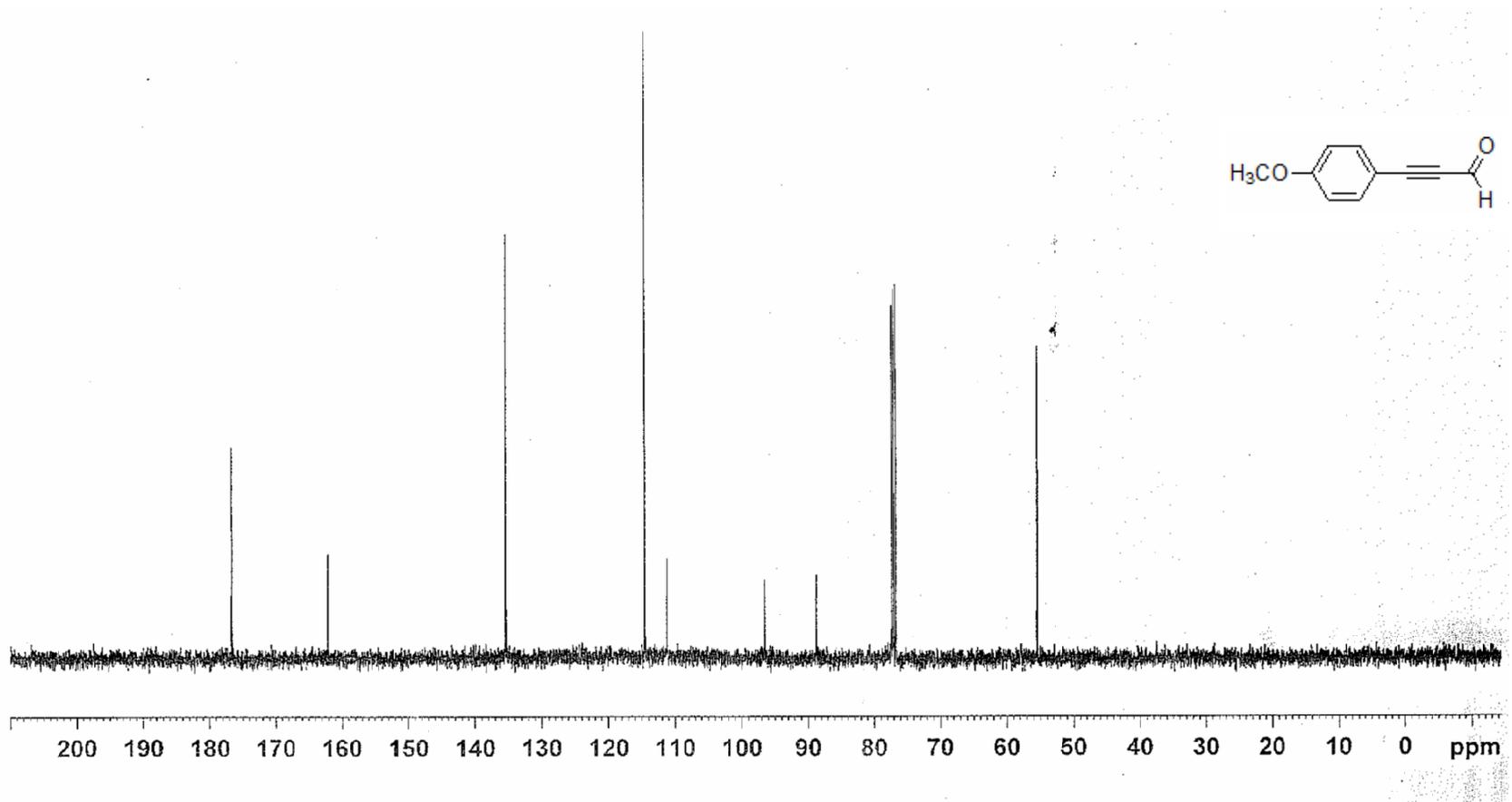


Figure A5.  $^1\text{H}$  NMR Spectrum of 14C.



**Figure A6.**  $^{13}\text{C}$  NMR Spectrum of **14C**.

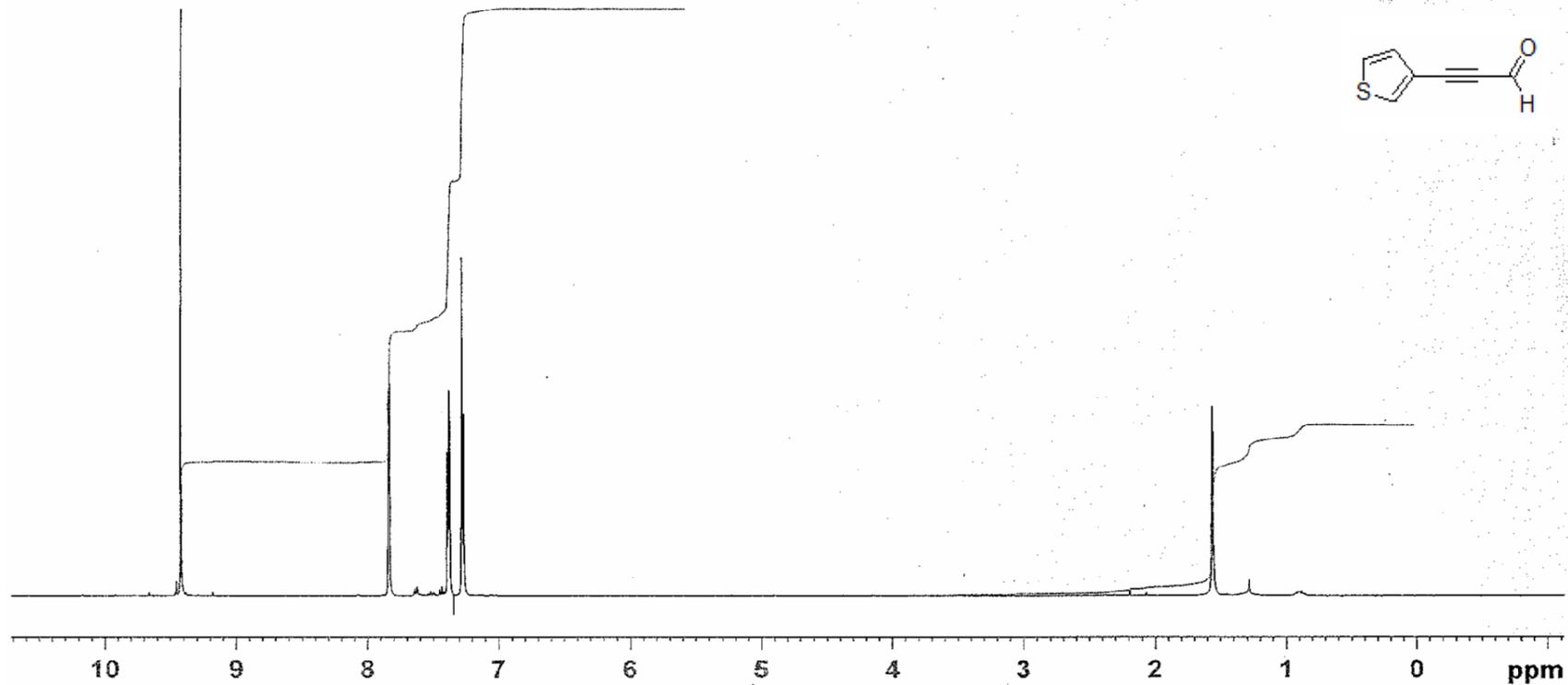


Figure A7.  $^1\text{H}$  NMR Spectrum of 14D.

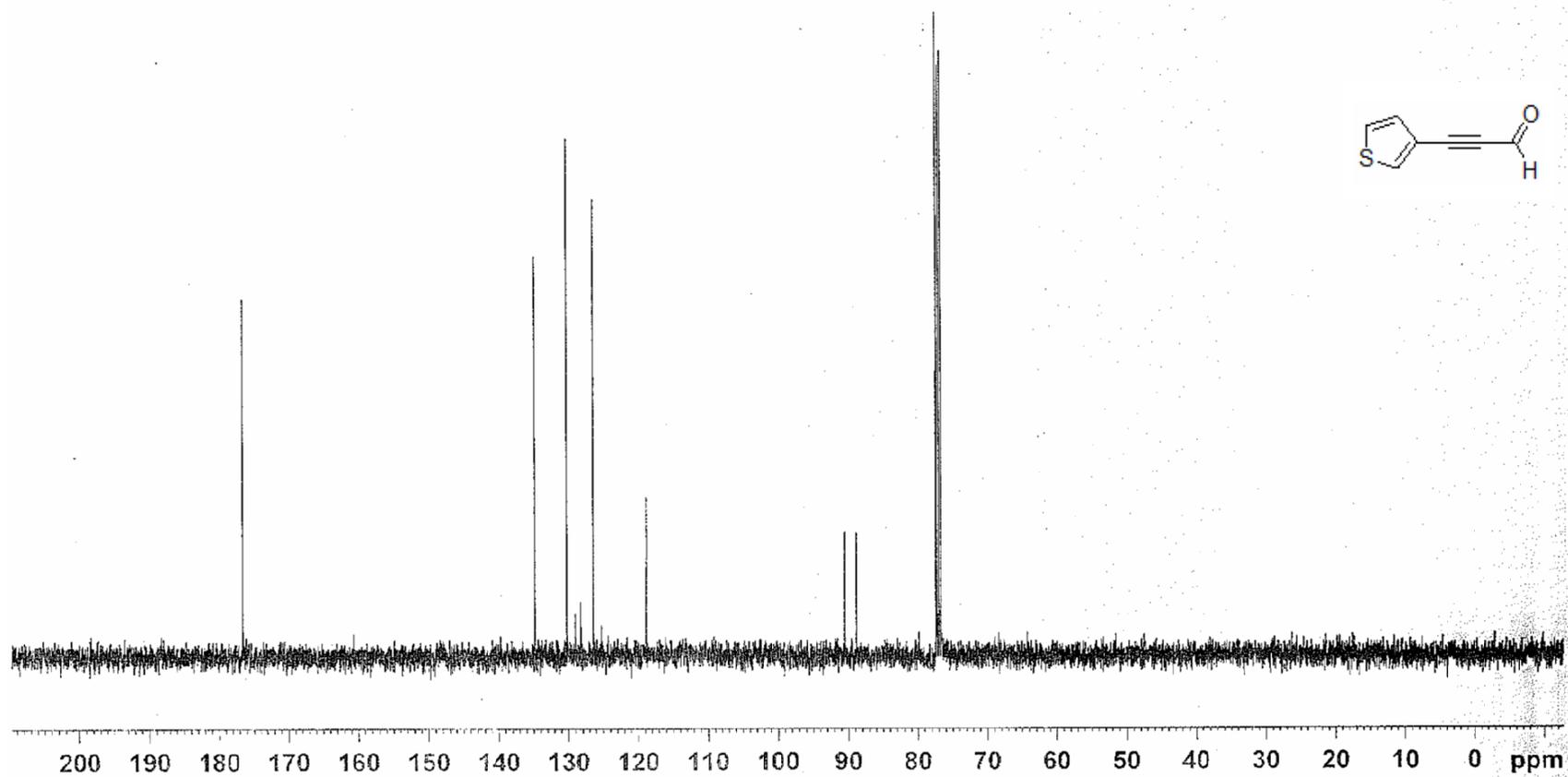


Figure A8.  $^{13}\text{C}$  NMR Spectrum of 14D.

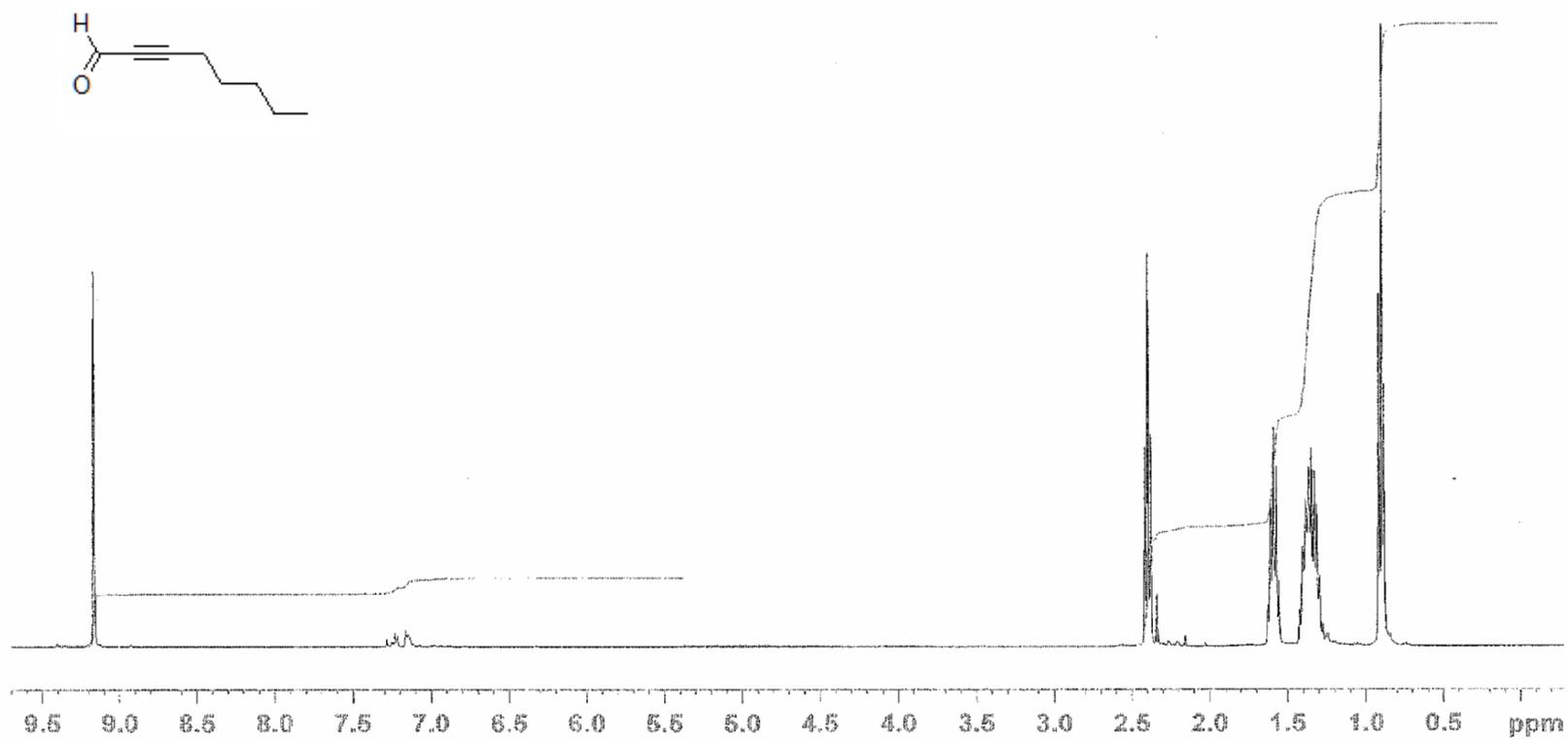
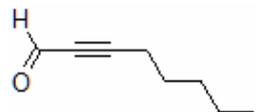


Figure A9.  $^1\text{H}$  NMR Spectrum of 14E.



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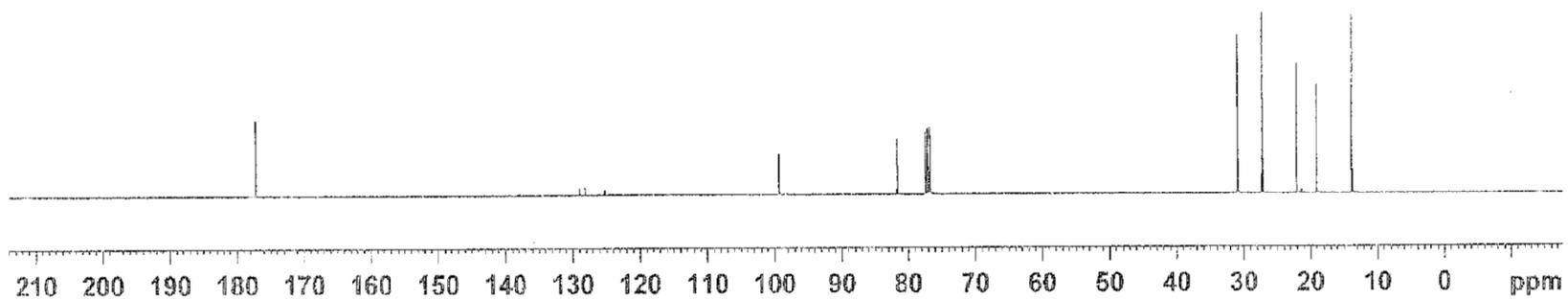


Figure A10.  $^{13}\text{C}$  NMR Spectrum of 14E.

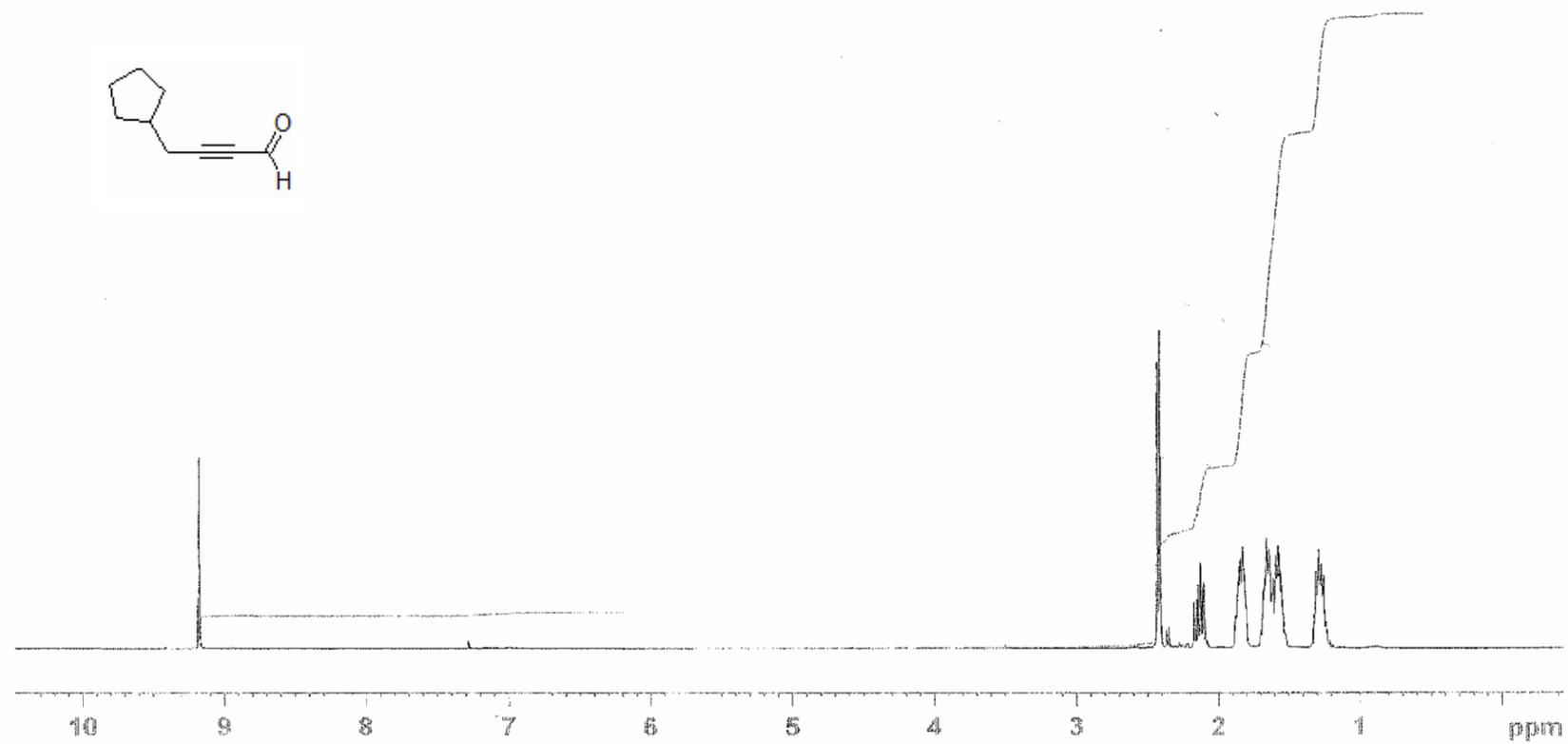
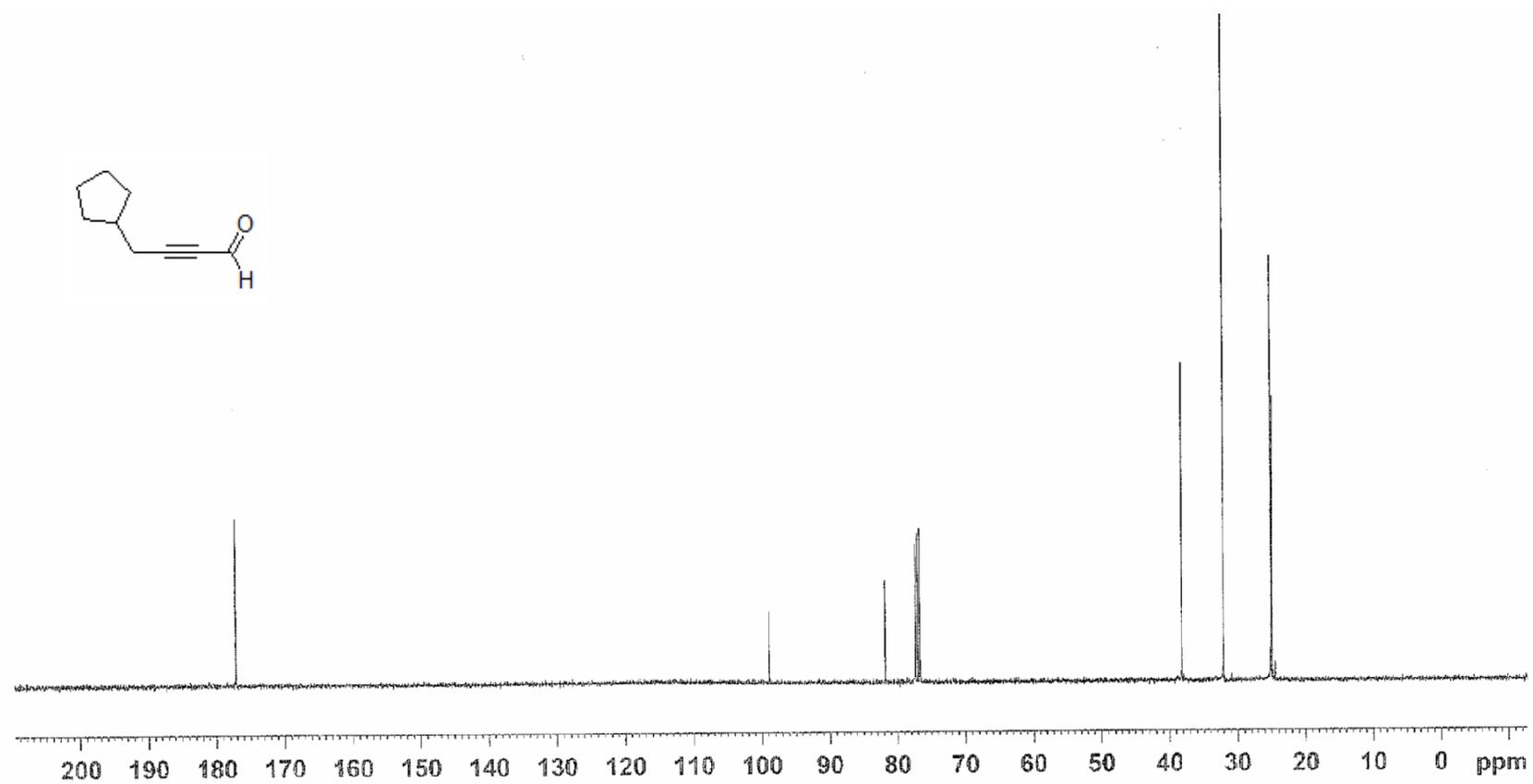


Figure A11.  $^1\text{H}$  NMR Spectrum of **14F**.



**Figure A12.**  $^{13}\text{C}$  NMR Spectrum of **14F**.

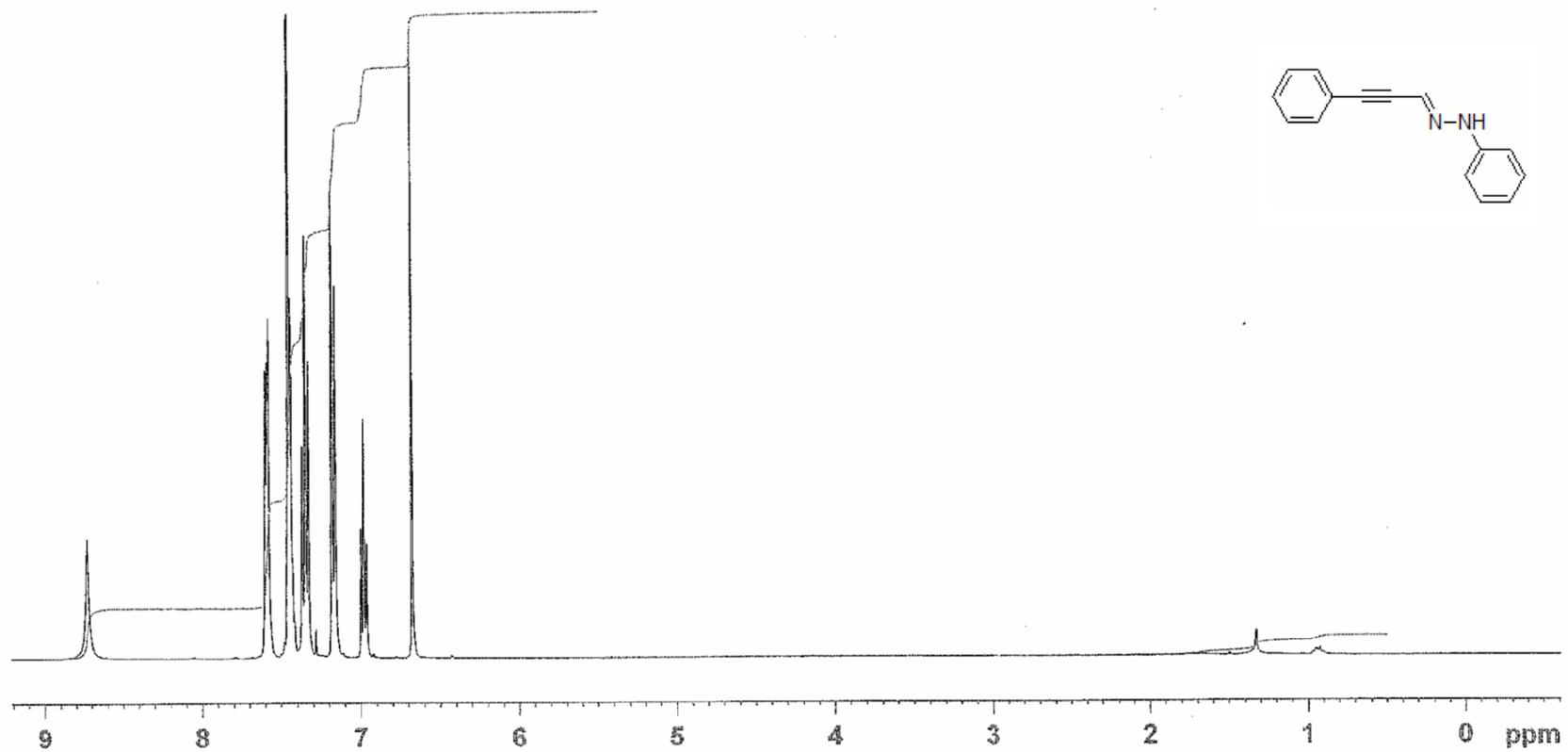


Figure A13.  $^1\text{H}$  NMR Spectrum of 15A.

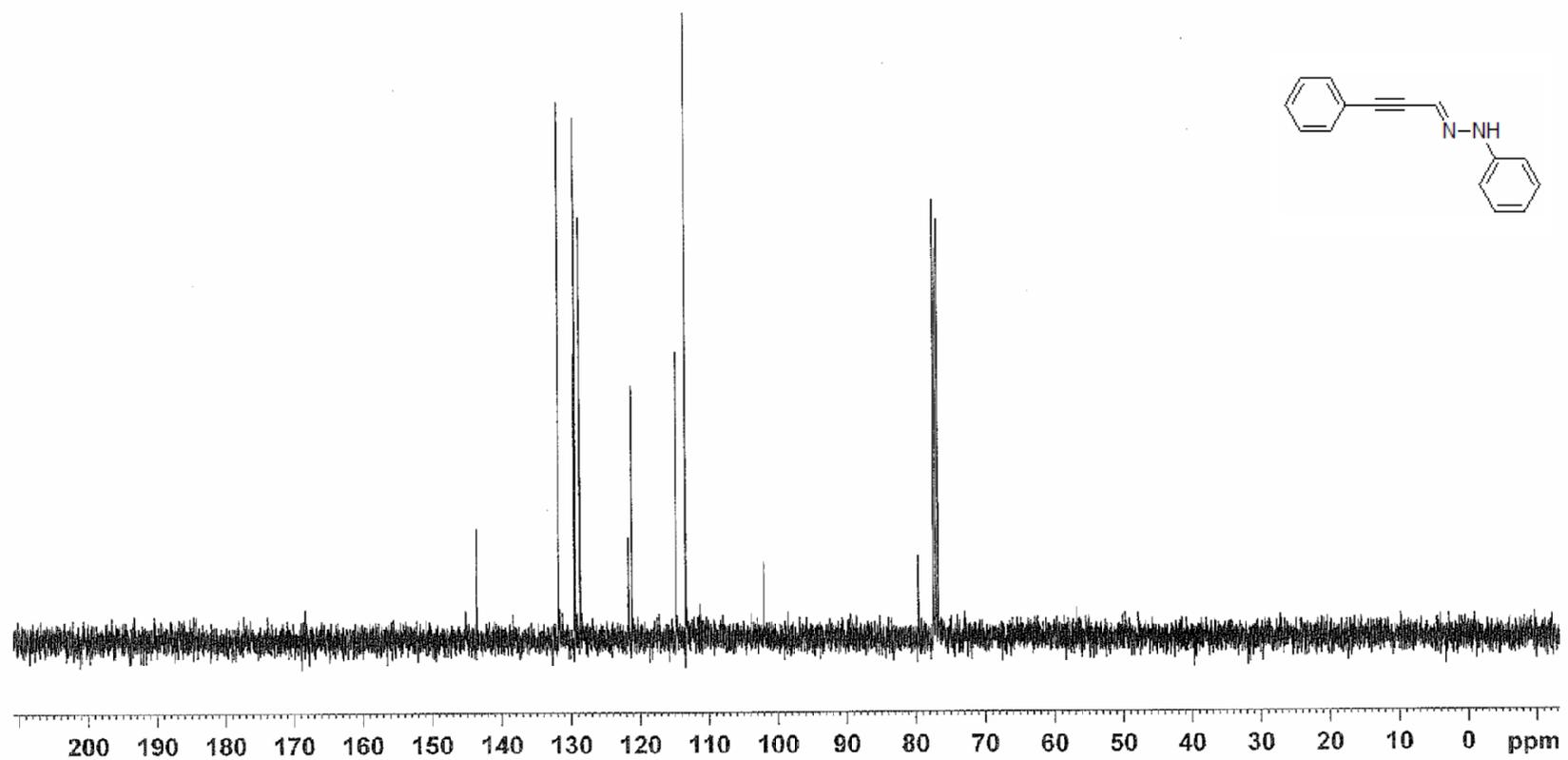
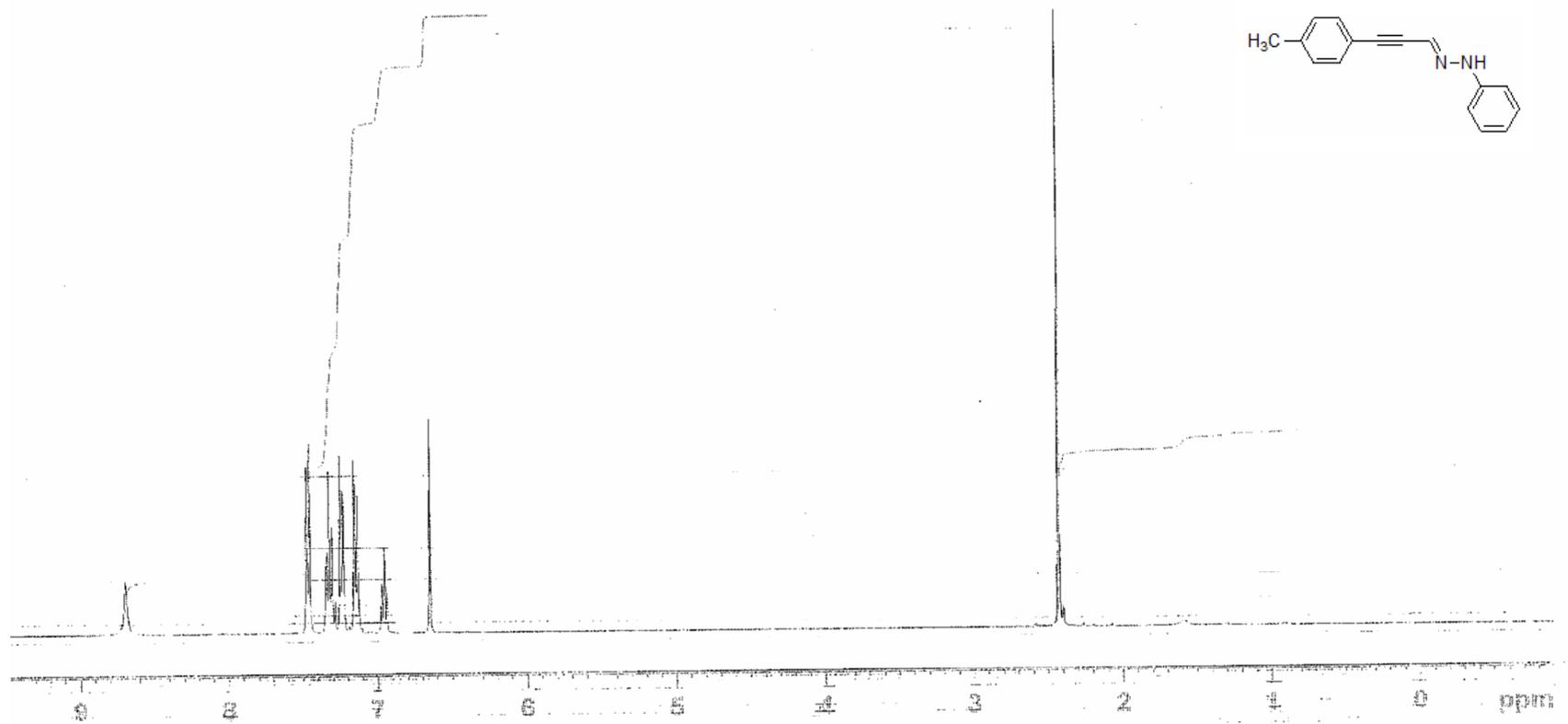


Figure A14.  $^{13}\text{C}$  NMR Spectrum of 15A.



**Figure A15.**  $^1\text{H}$  NMR Spectrum of **15B**.

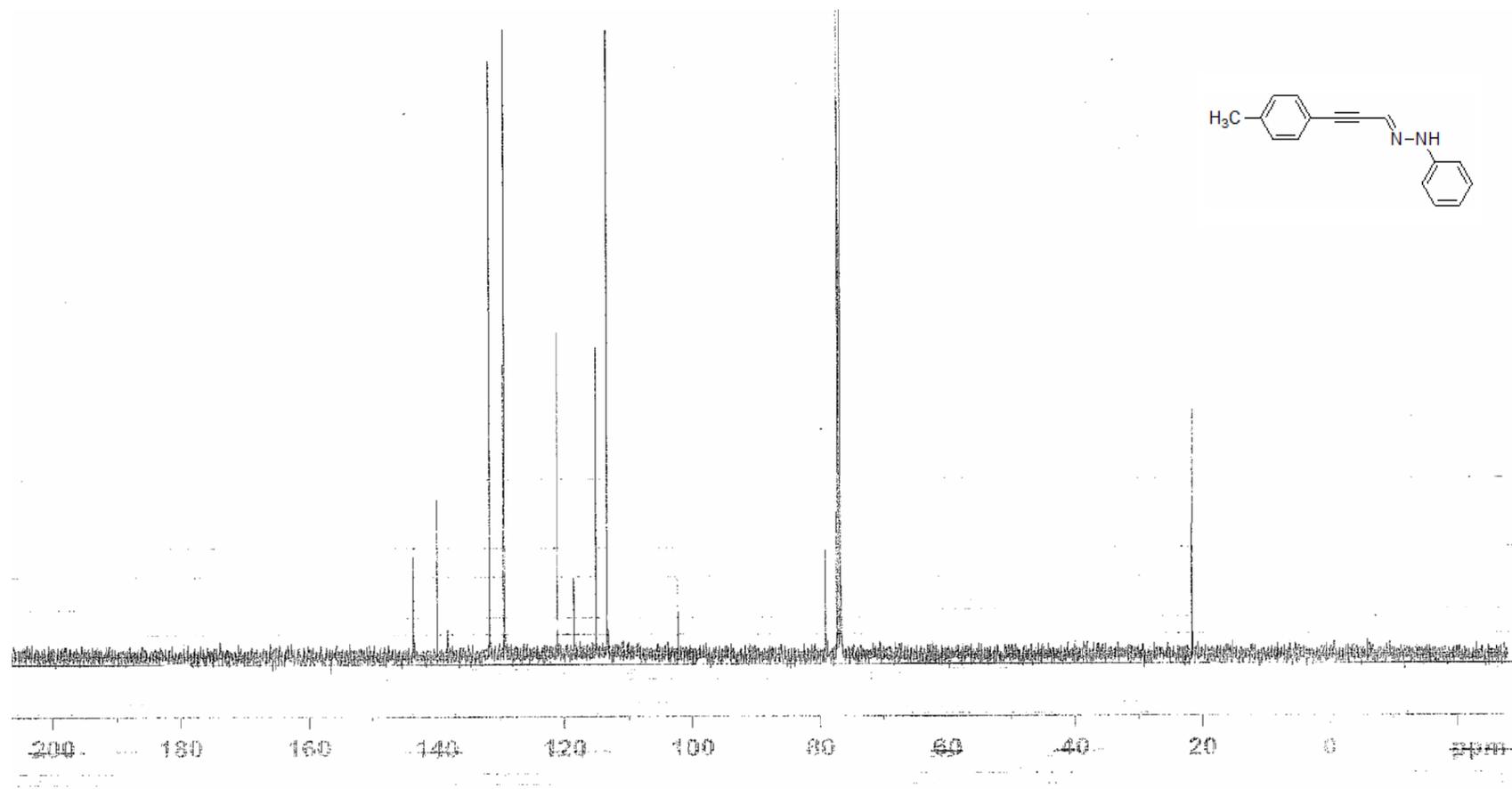


Figure A16.  $^{13}\text{C}$  NMR Spectrum of 15B.

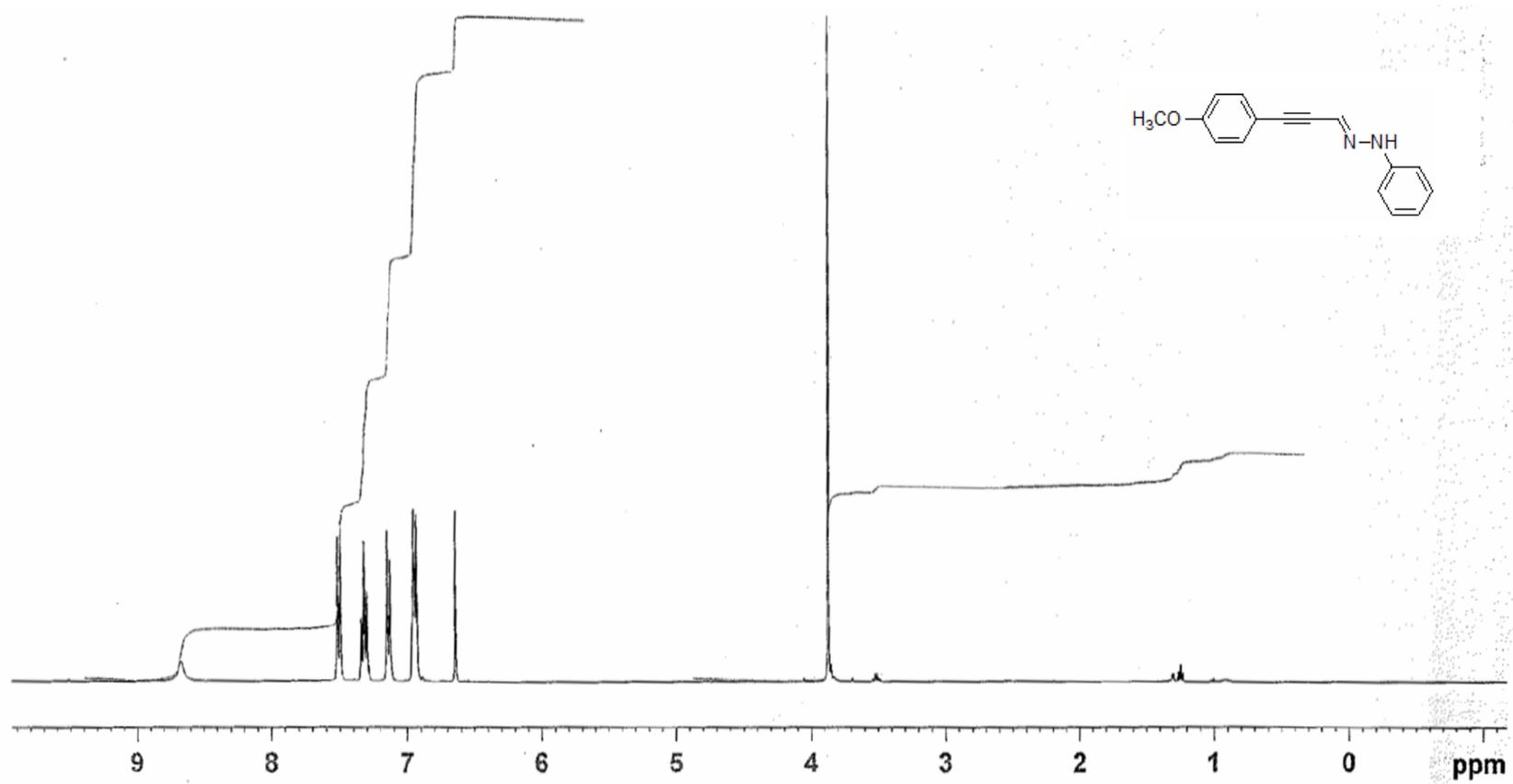


Figure A17.  $^1\text{H}$  NMR Spectrum of **15C**.

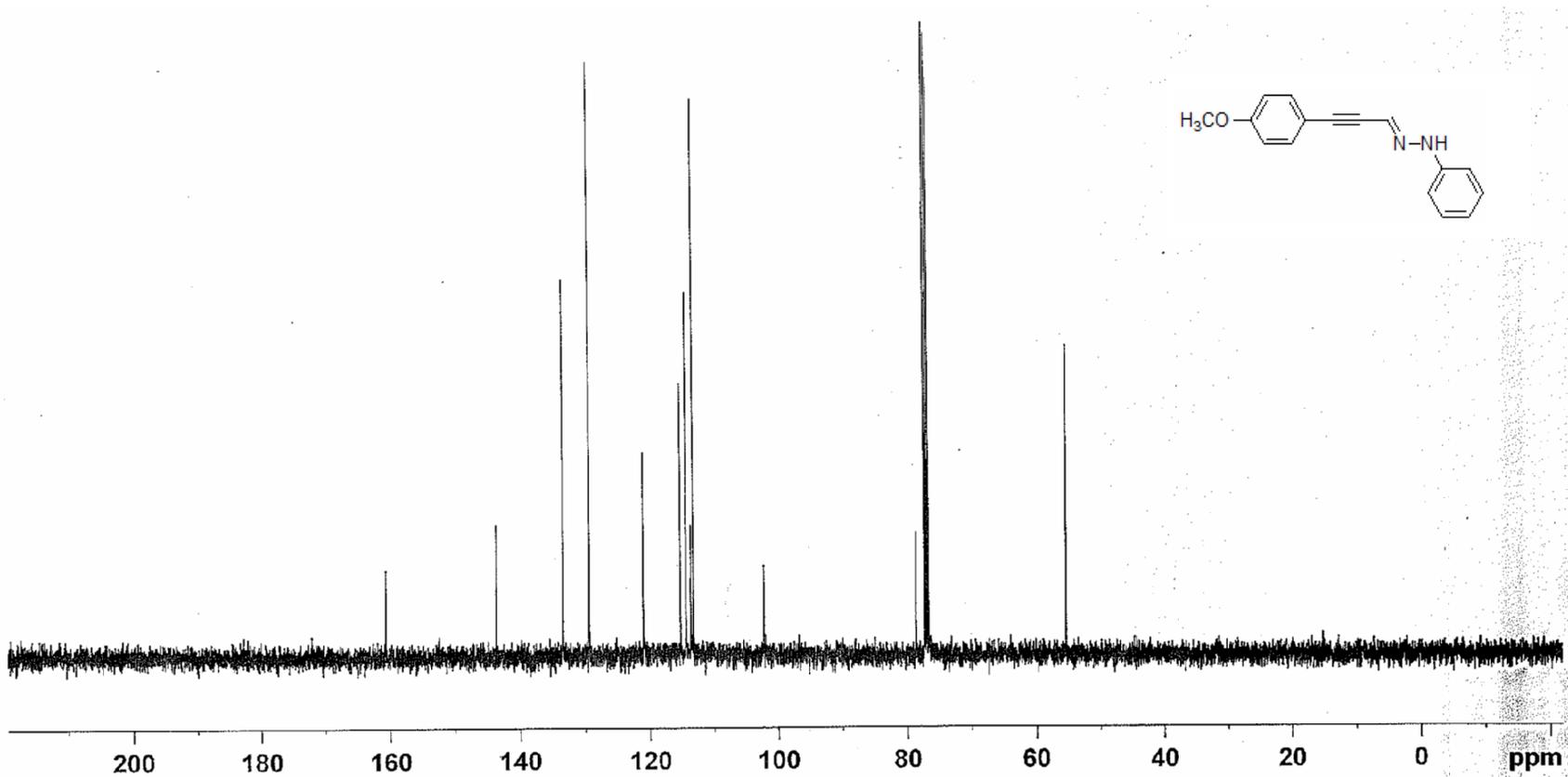


Figure A18.  $^{13}\text{C}$  NMR Spectrum of 15C.

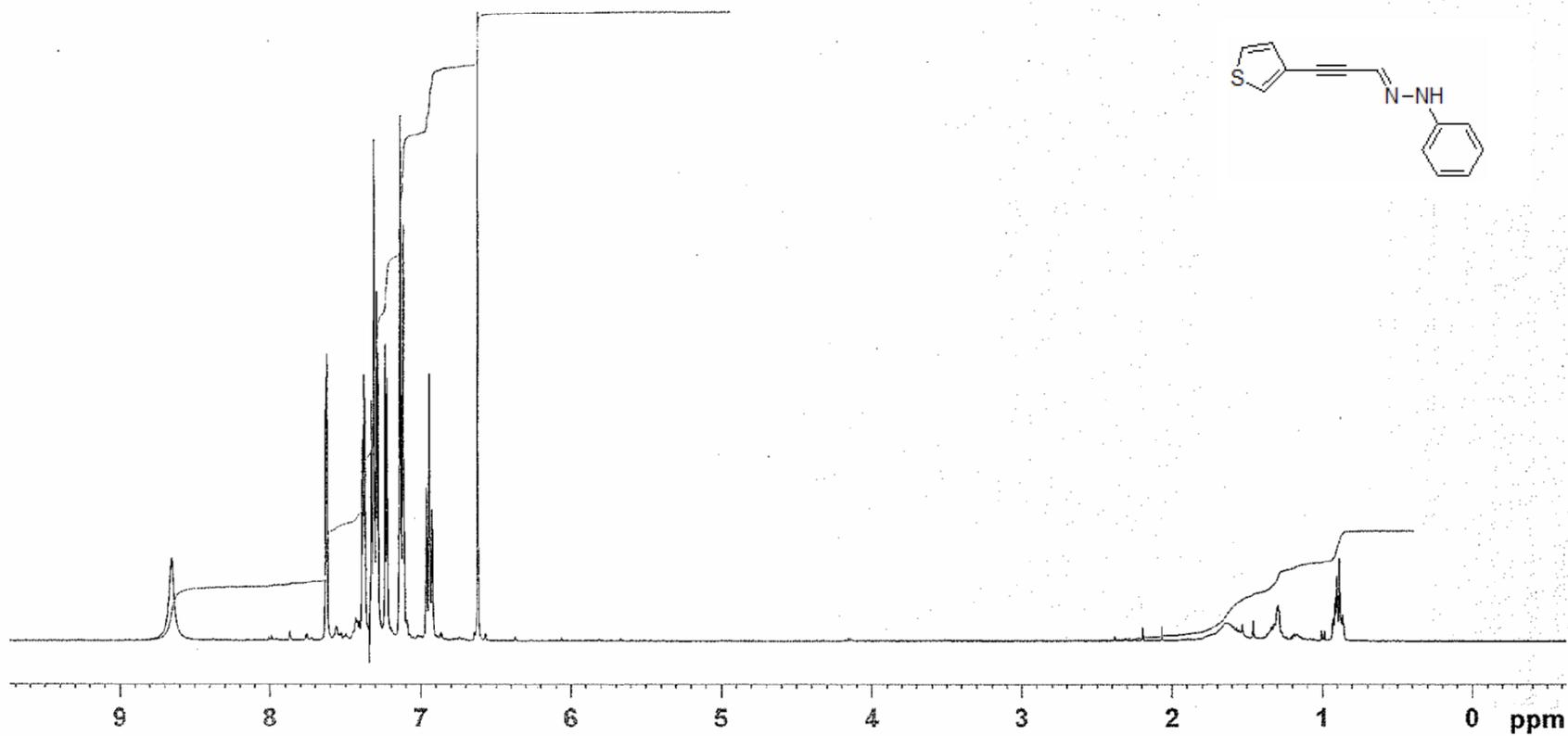


Figure A19.  $^1\text{H}$  NMR Spectrum of 15D.

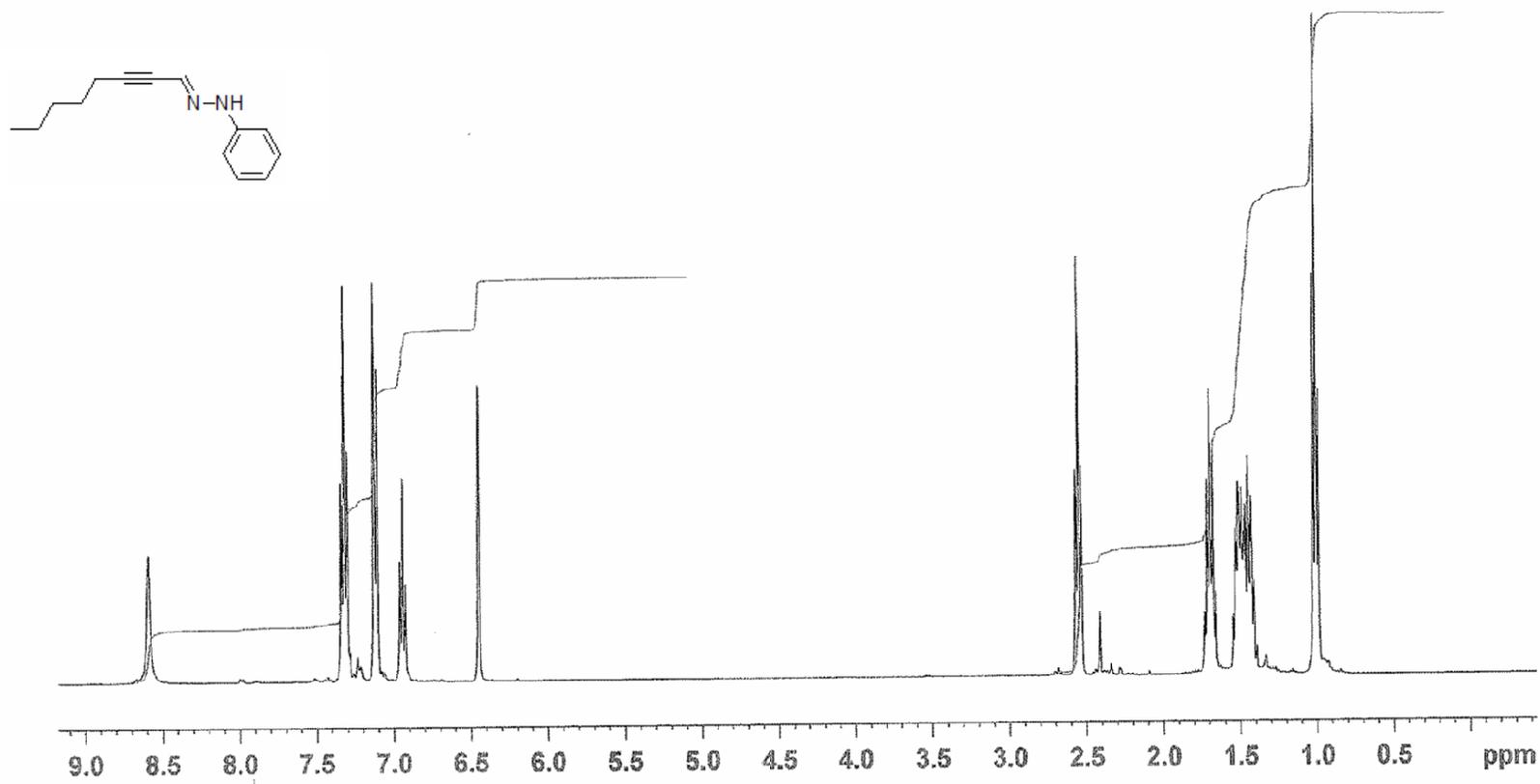


Figure A20.  $^1\text{H}$  NMR Spectrum of **15E**.

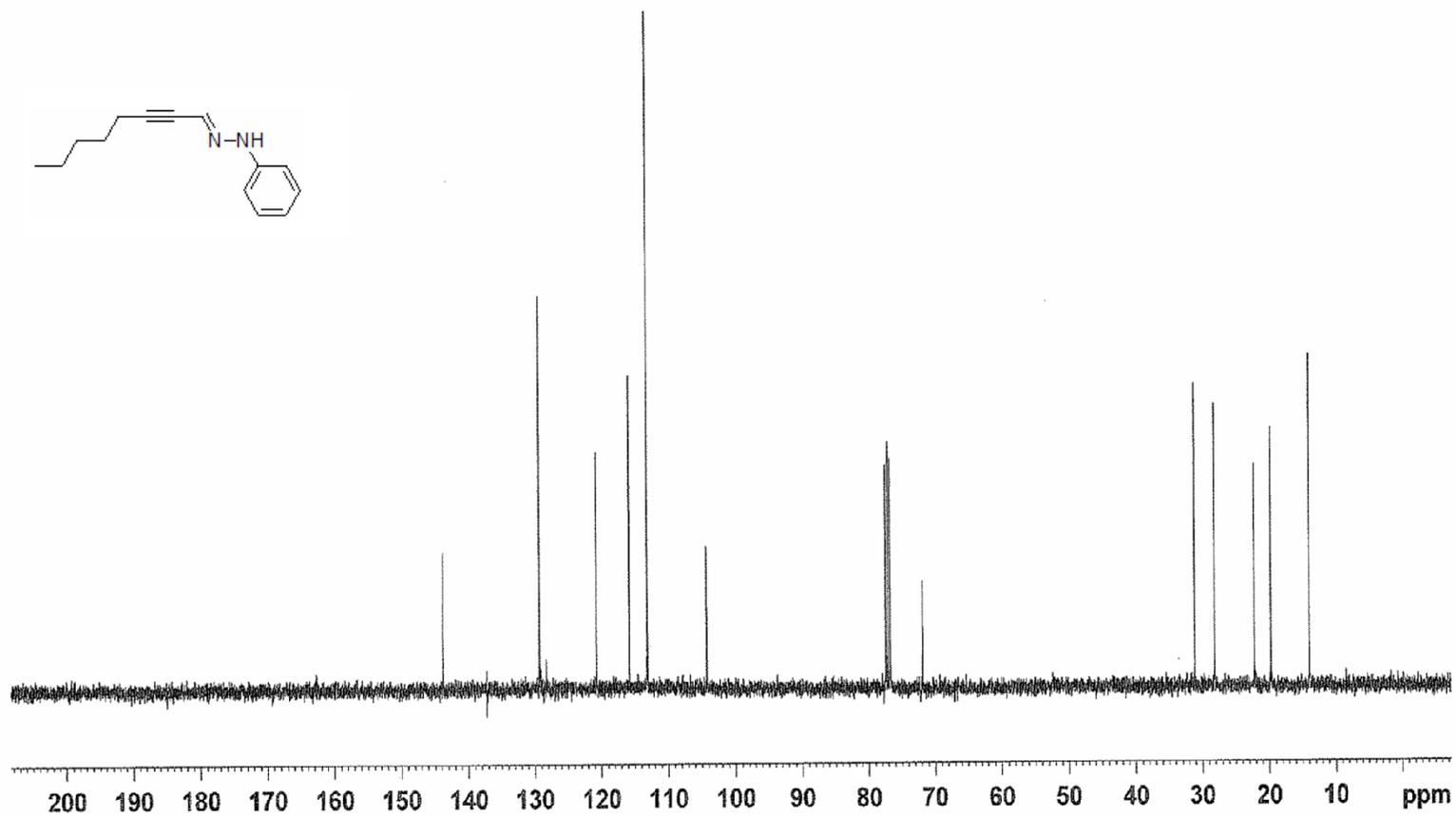


Figure A21.  $^{13}\text{C}$  NMR Spectrum of **15E**.

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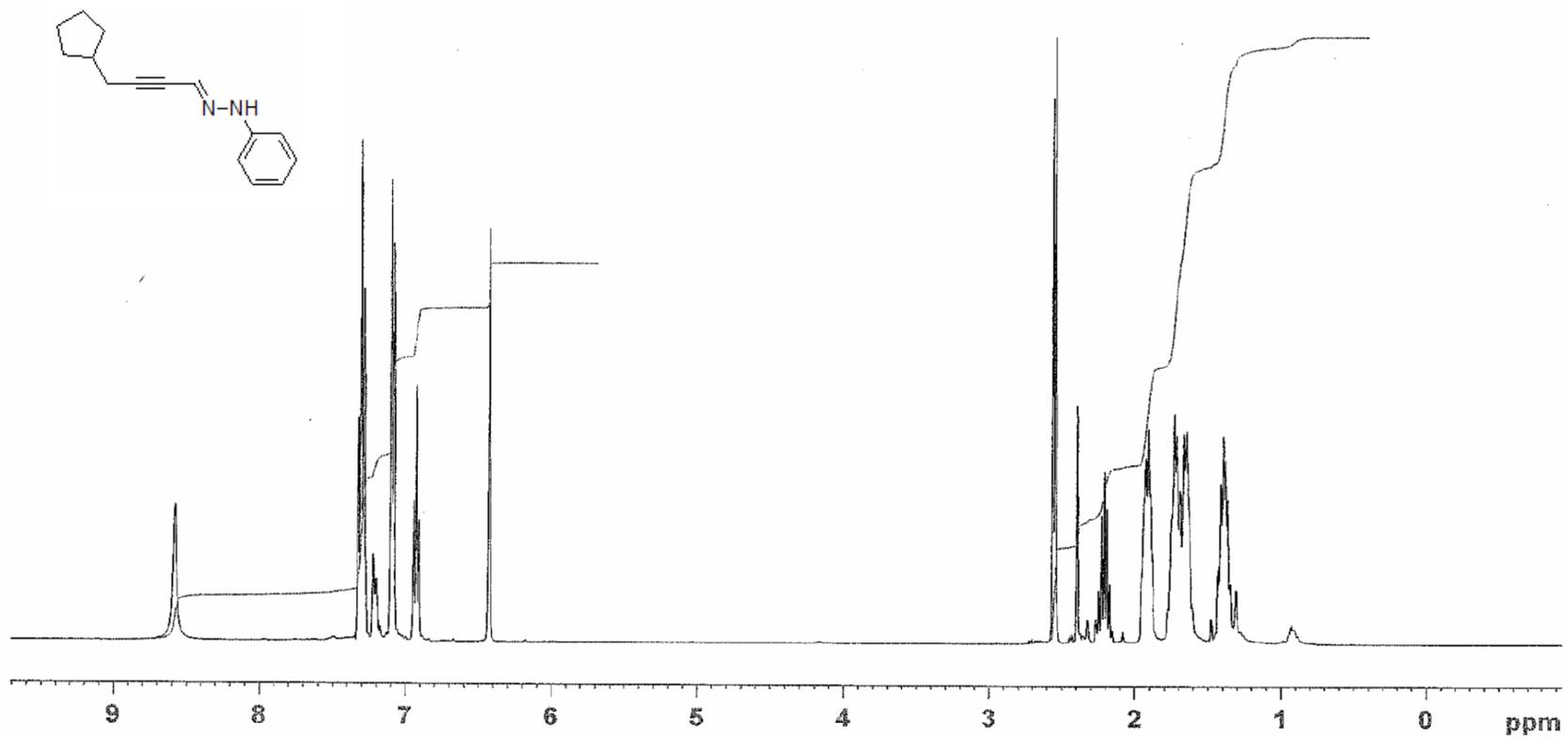


Figure A22.  $^1\text{H}$  NMR Spectrum of 15F.

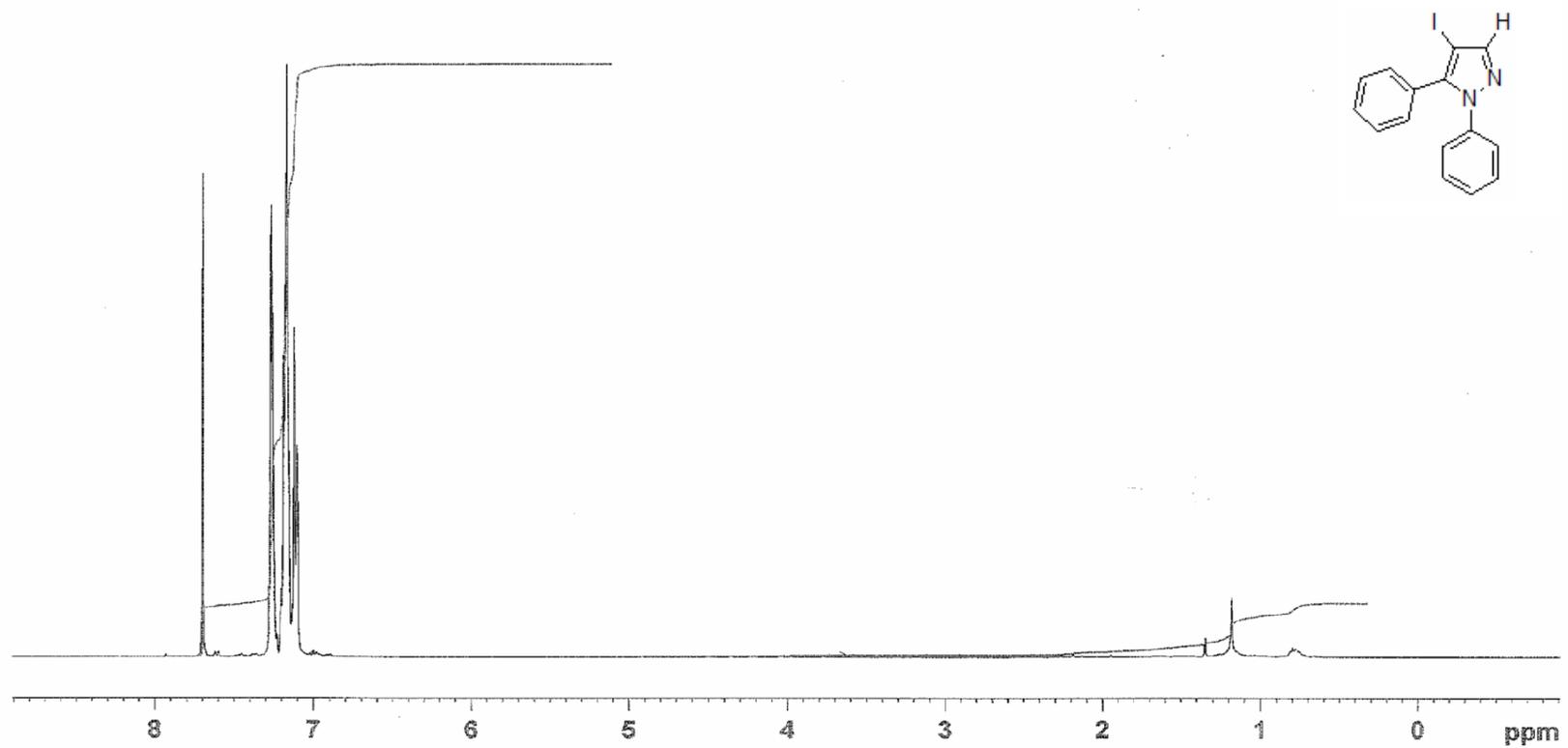


Figure A23.  $^1\text{H}$  NMR Spectrum of 16A.

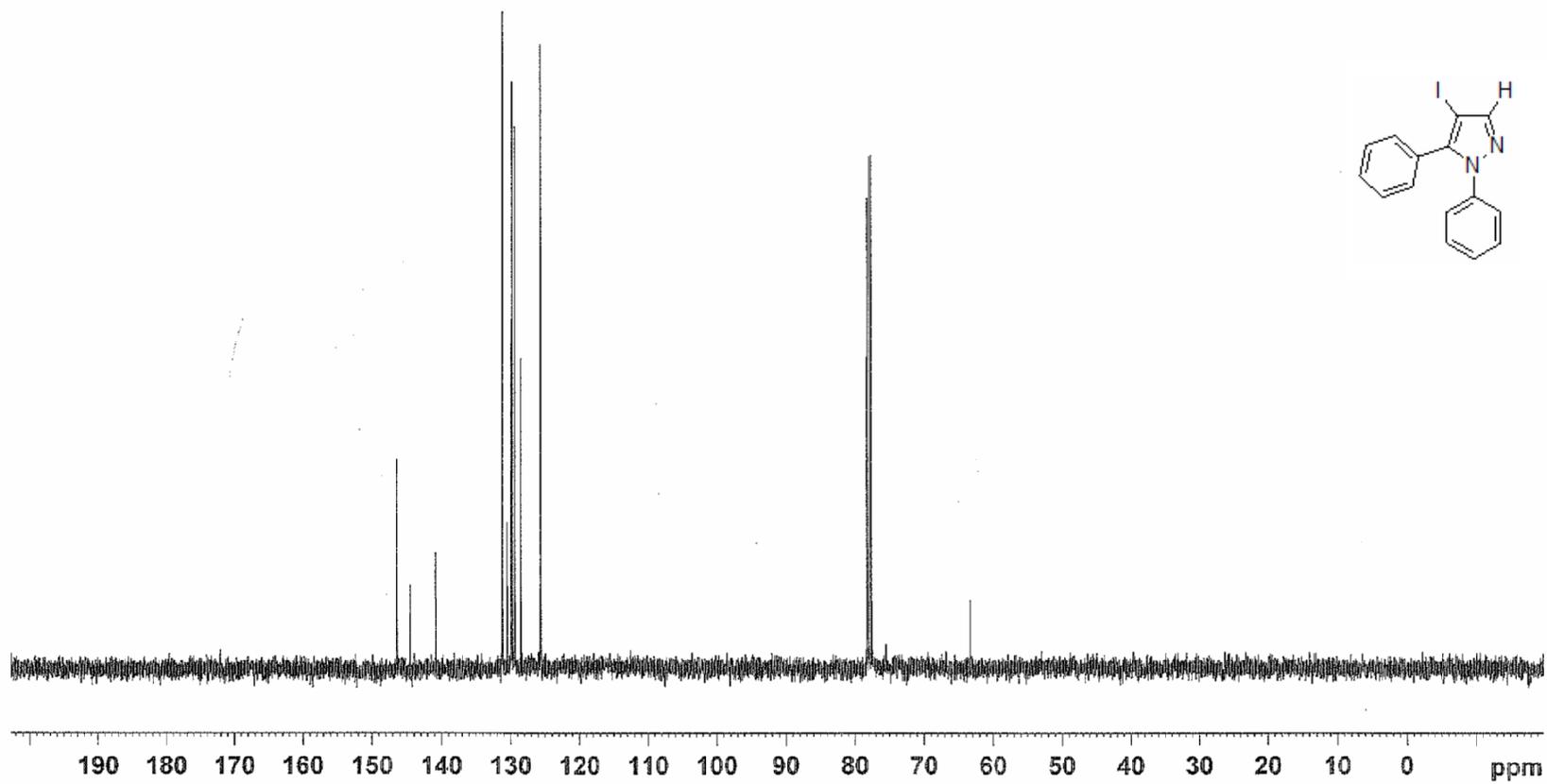


Figure A24.  $^{13}\text{C}$  NMR Spectrum of 16A.

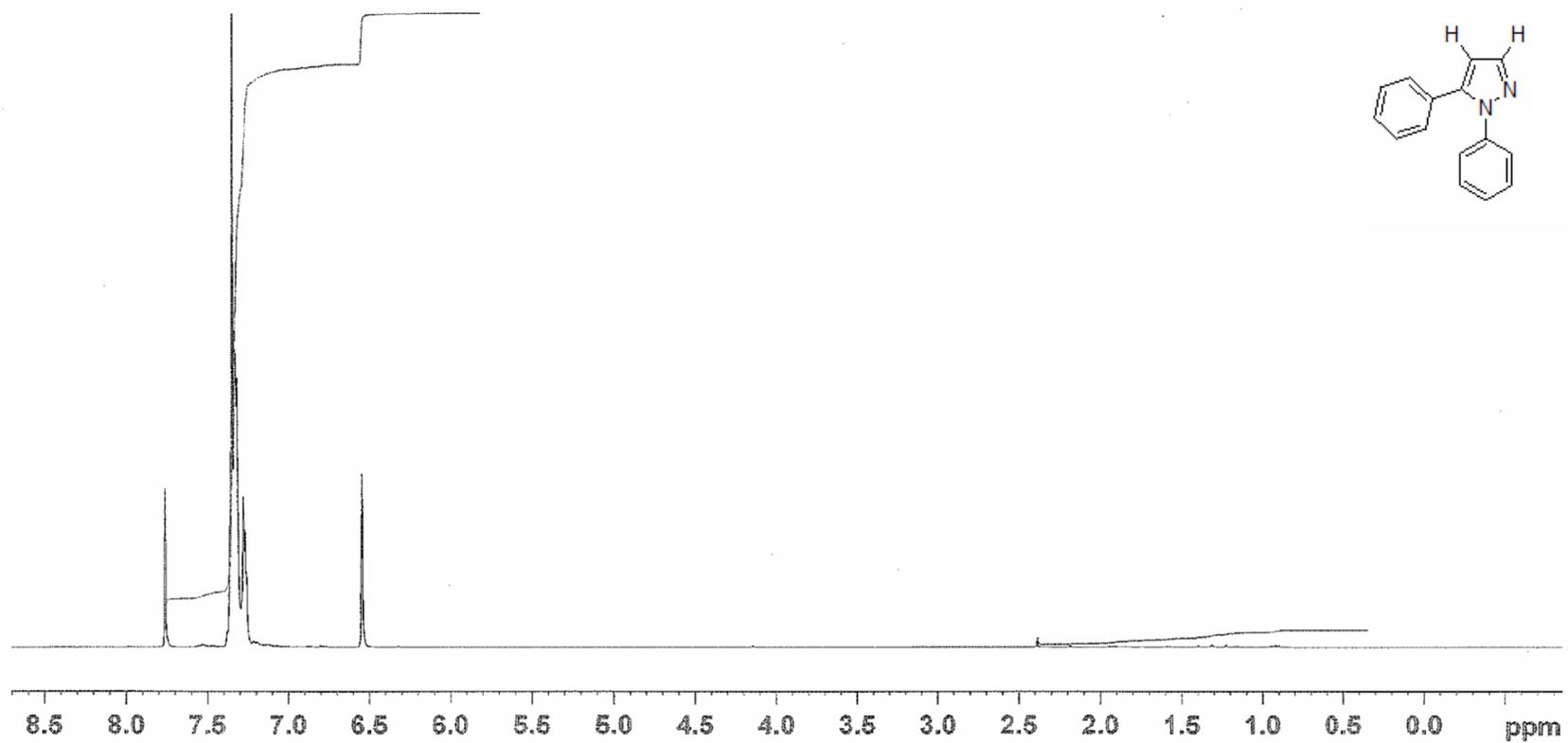


Figure A25.  $^1\text{H}$  NMR Spectrum of 17A.

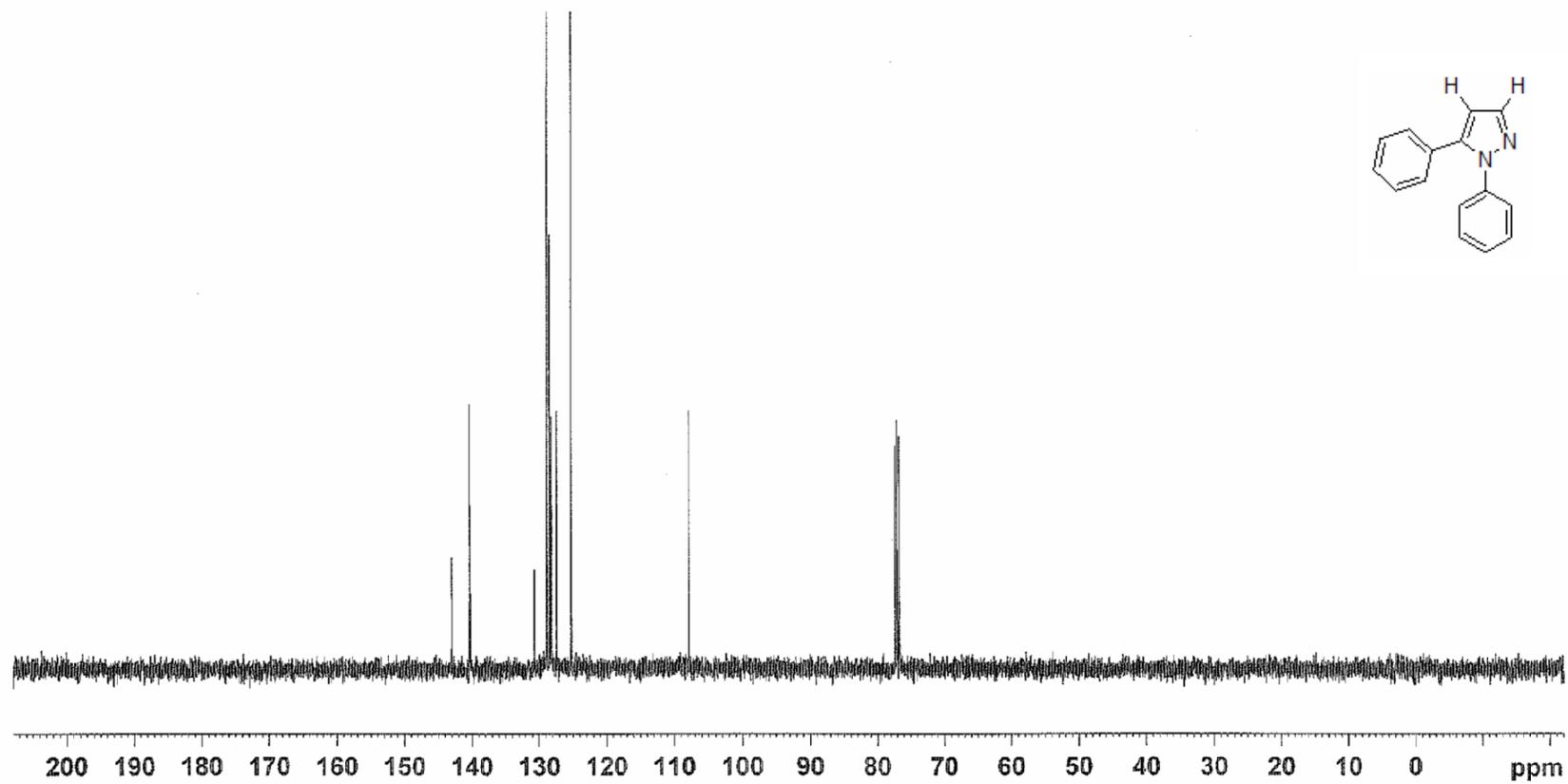


Figure A26.  $^{13}\text{C}$  NMR Spectrum of 17A.

75

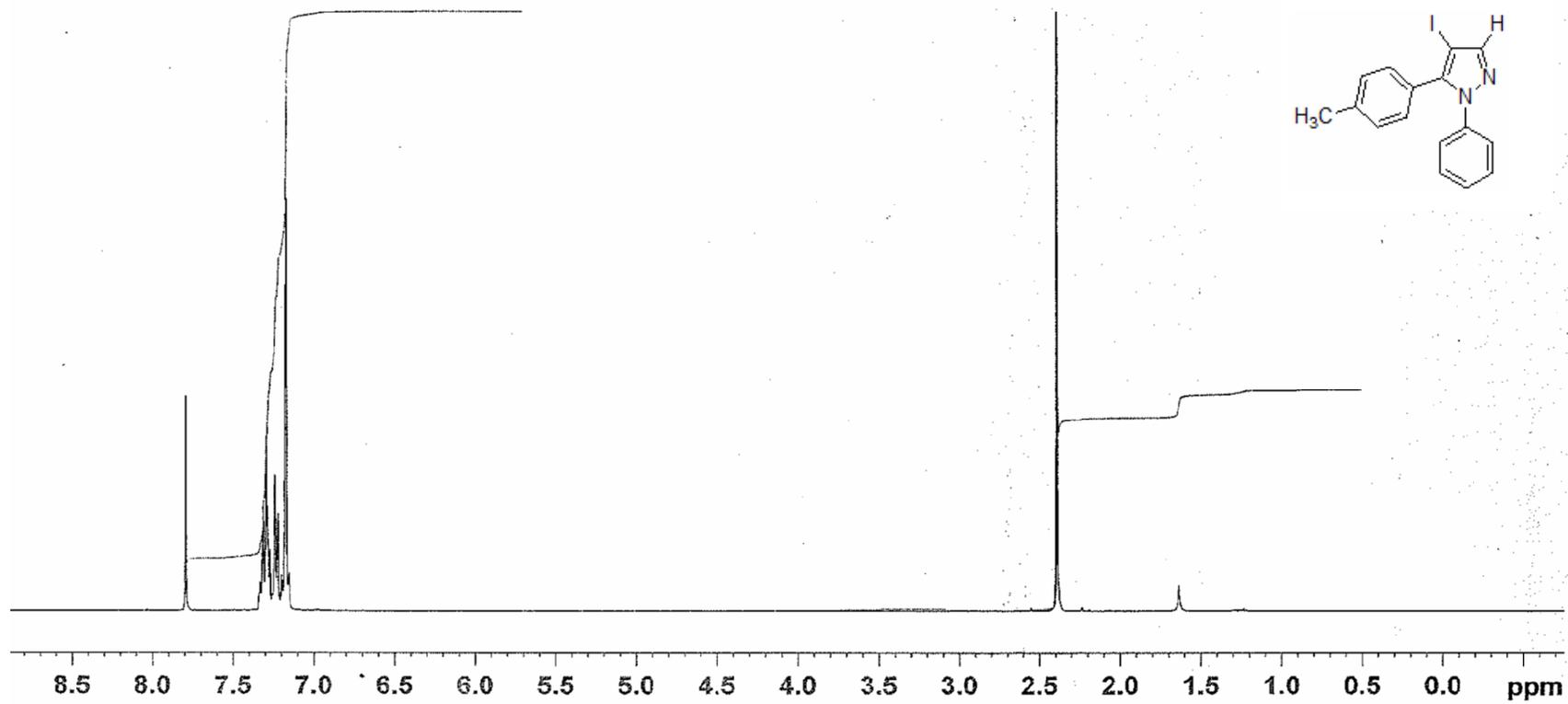


Figure A27.  $^1\text{H}$  NMR Spectrum of 16B.

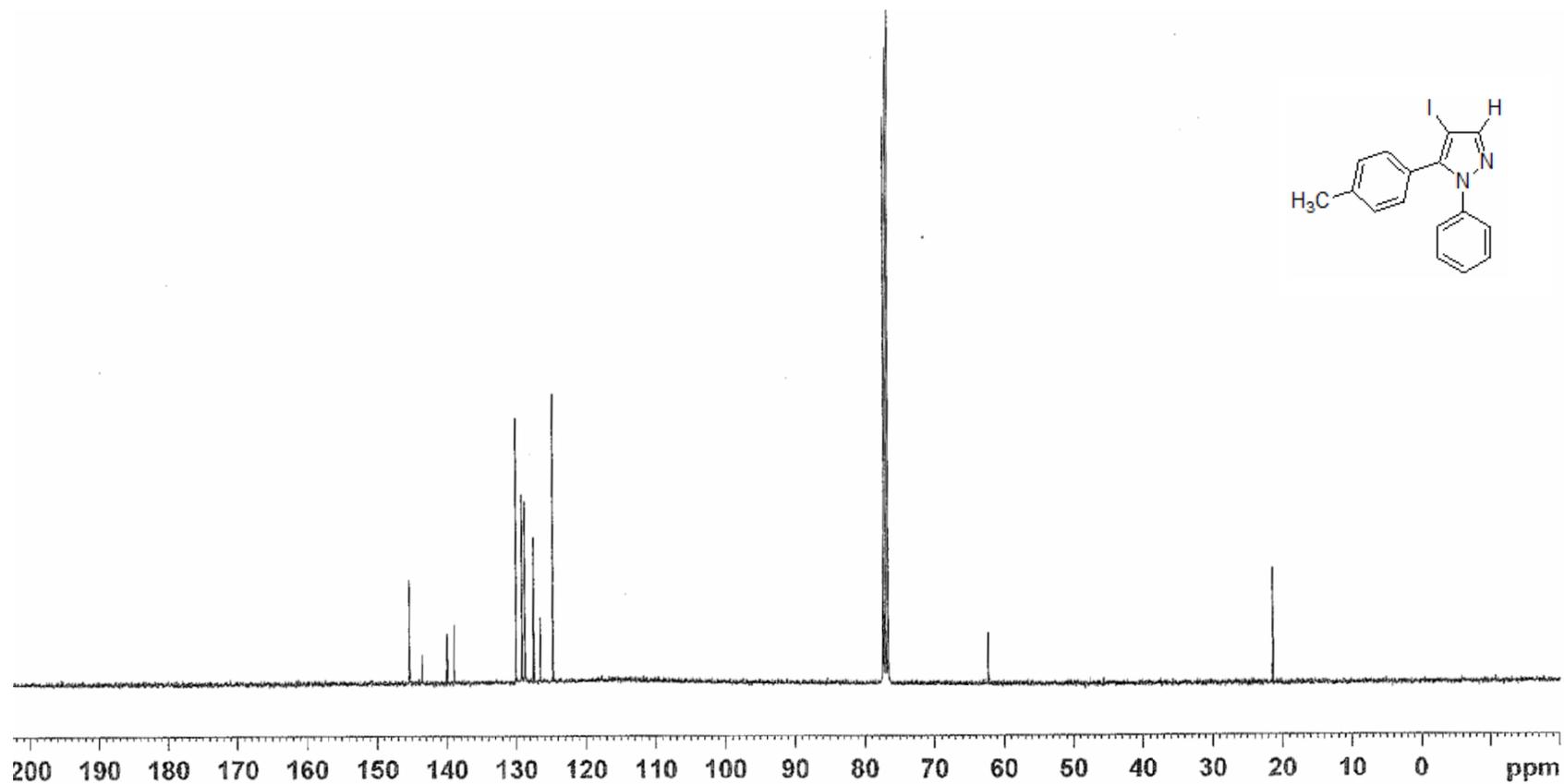


Figure A28.  $^{13}\text{C}$  NMR Spectrum of 16B.

77

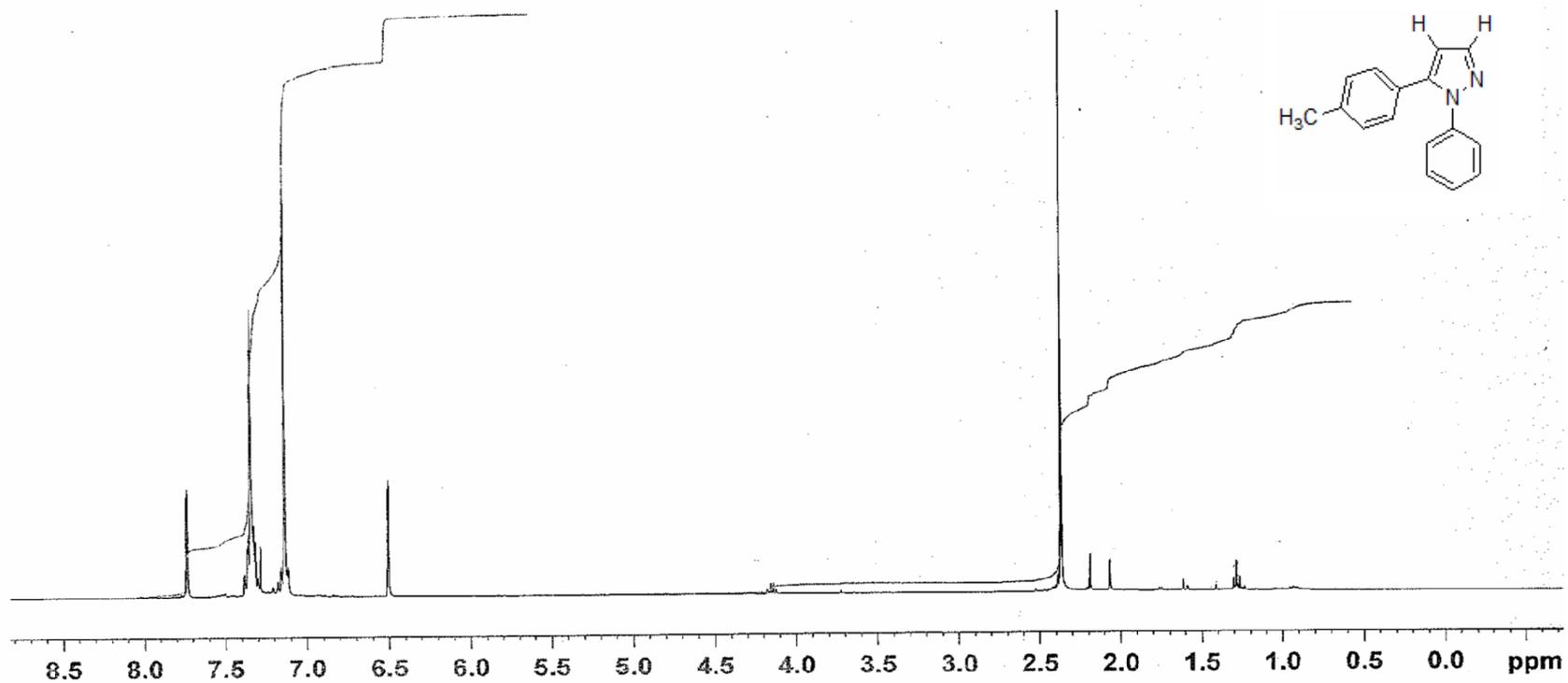


Figure A29.  $^1\text{H}$  NMR Spectrum of 17B.

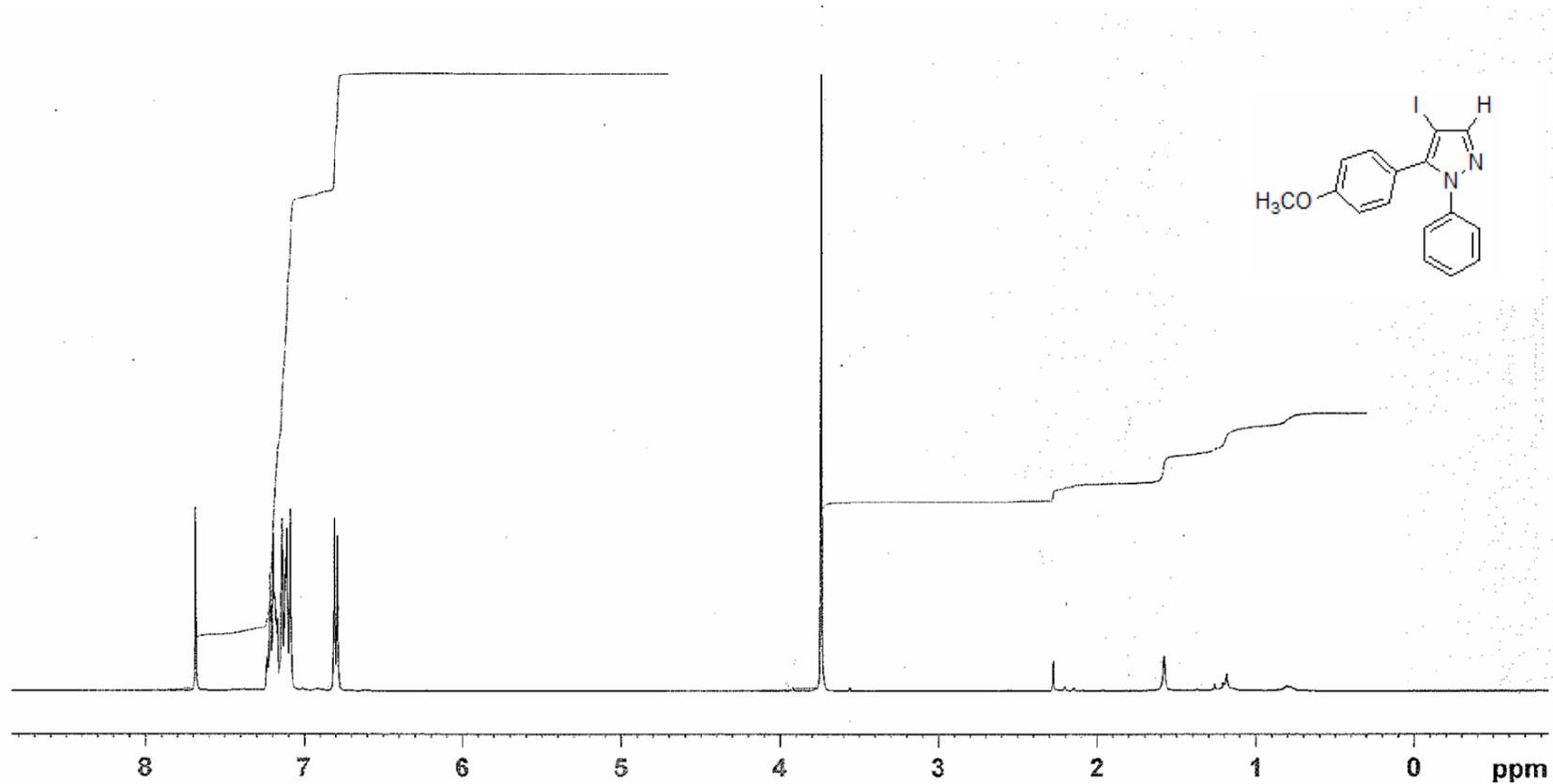


Figure A30.  $^1\text{H}$  NMR Spectrum of 16C.

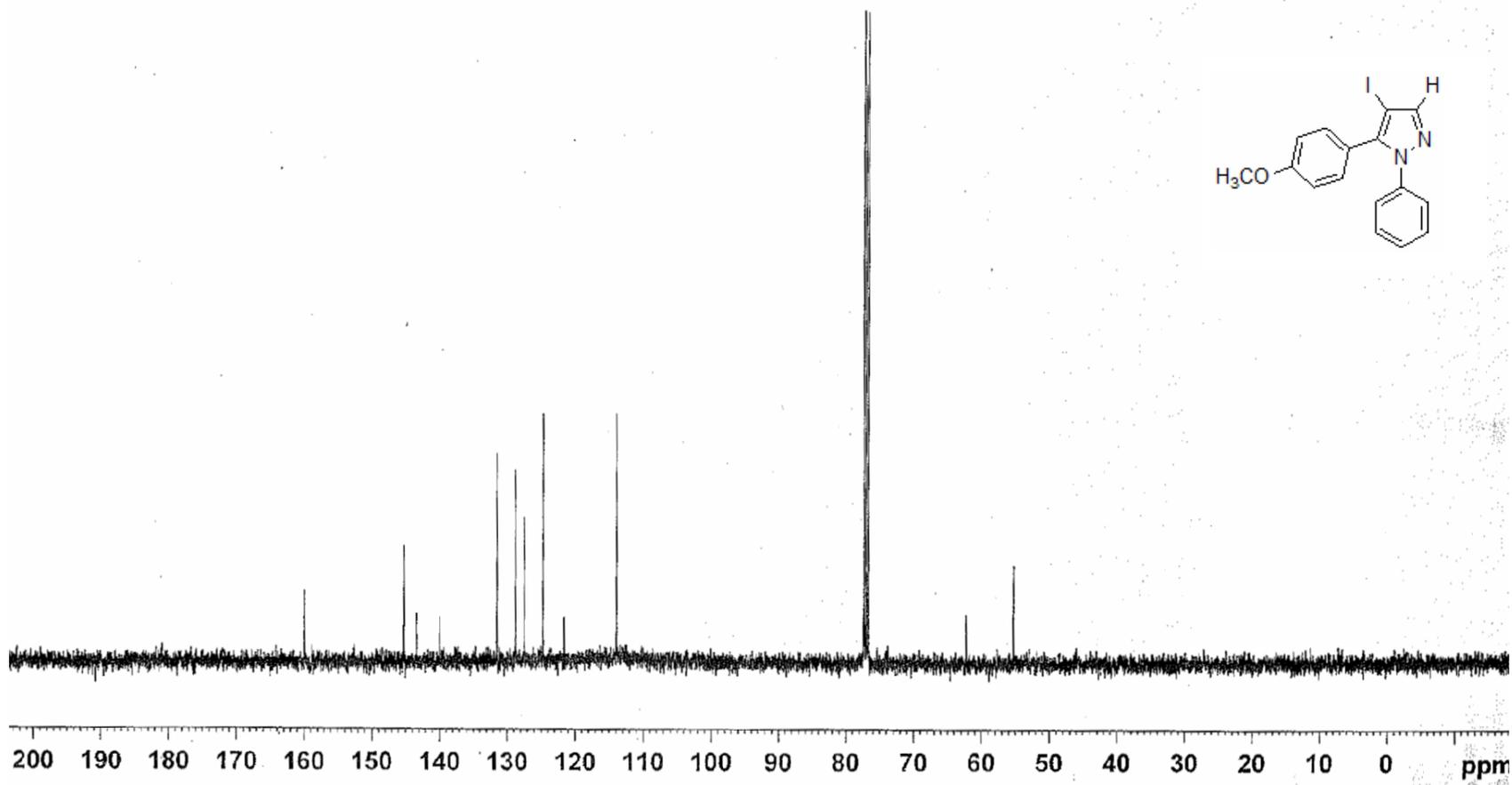


Figure A31.  $^{13}\text{C}$  NMR Spectrum of 16C.

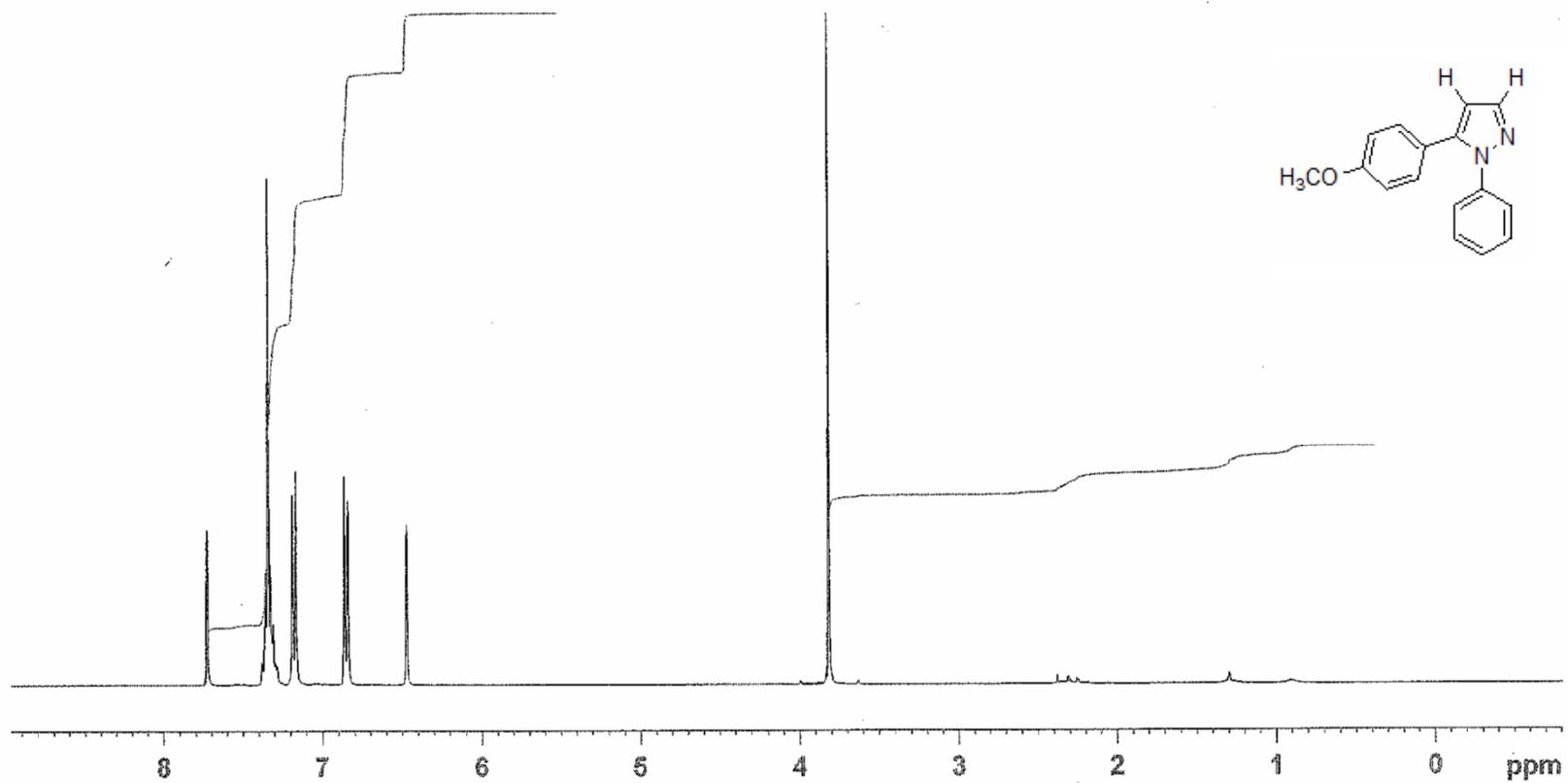


Figure A32.  $^1\text{H}$  NMR Spectrum of 17C.

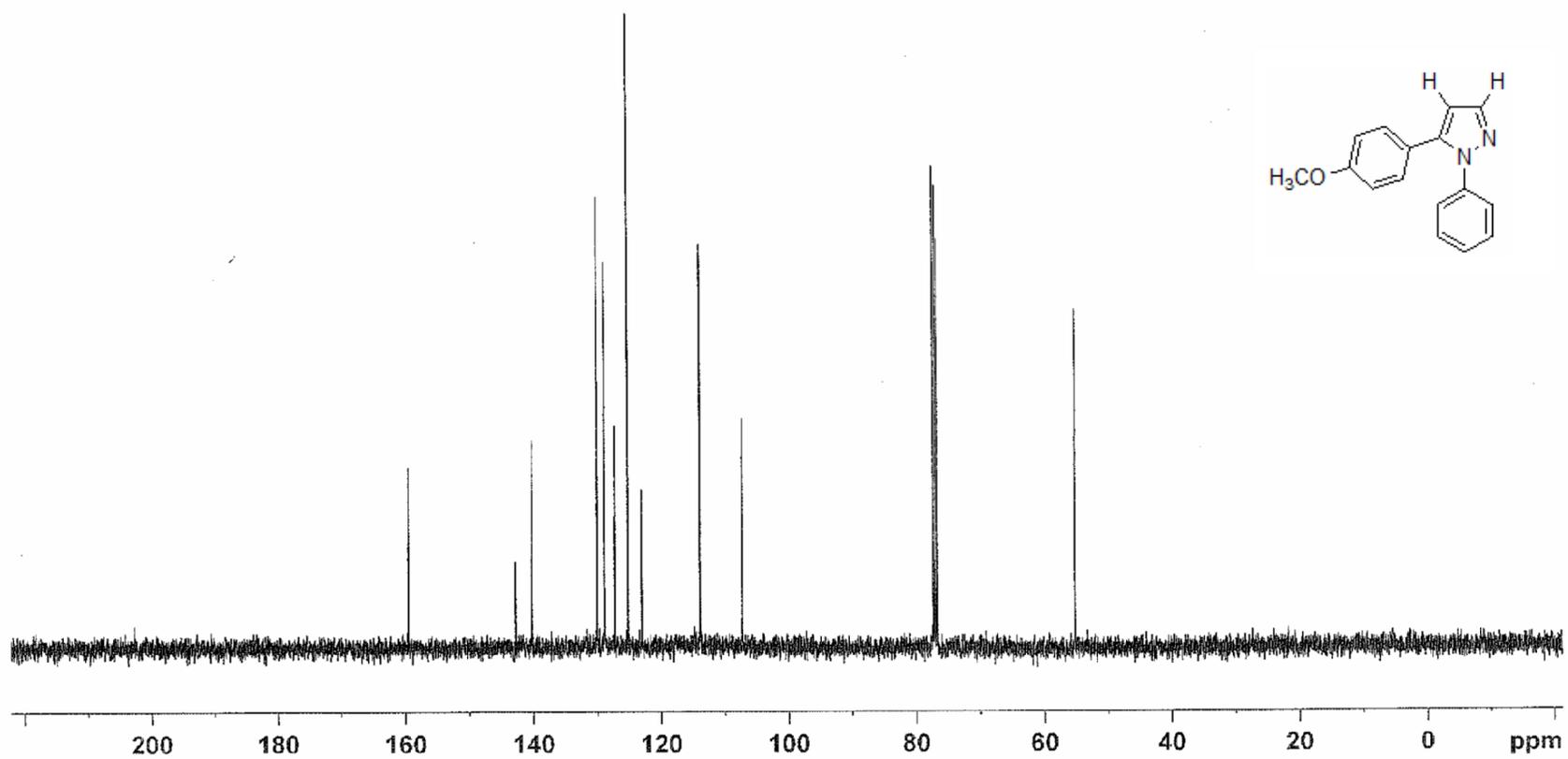


Figure A33.  $^{13}\text{C}$  NMR Spectrum of 17C.

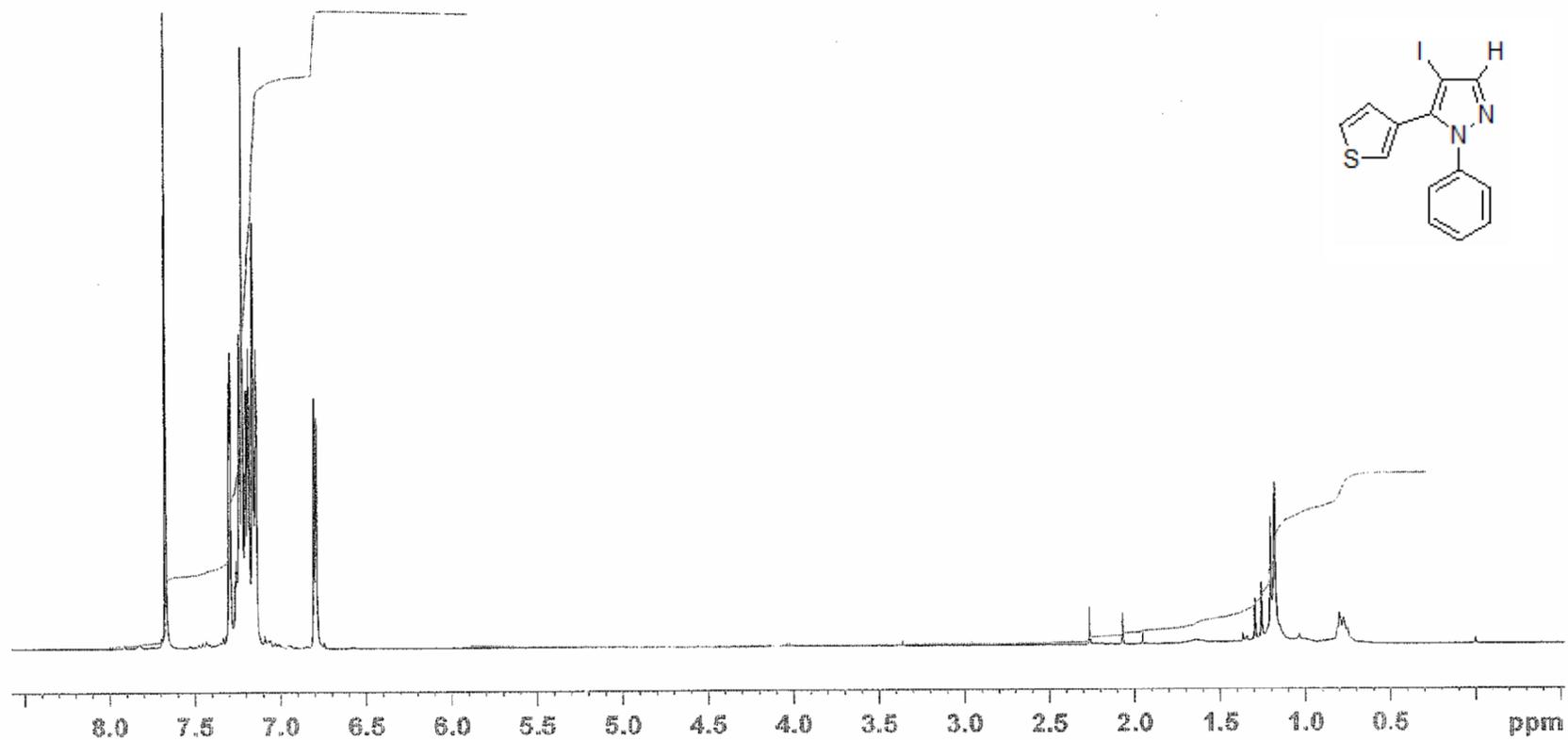


Figure A34.  $^1\text{H}$  NMR Spectrum of 16D.

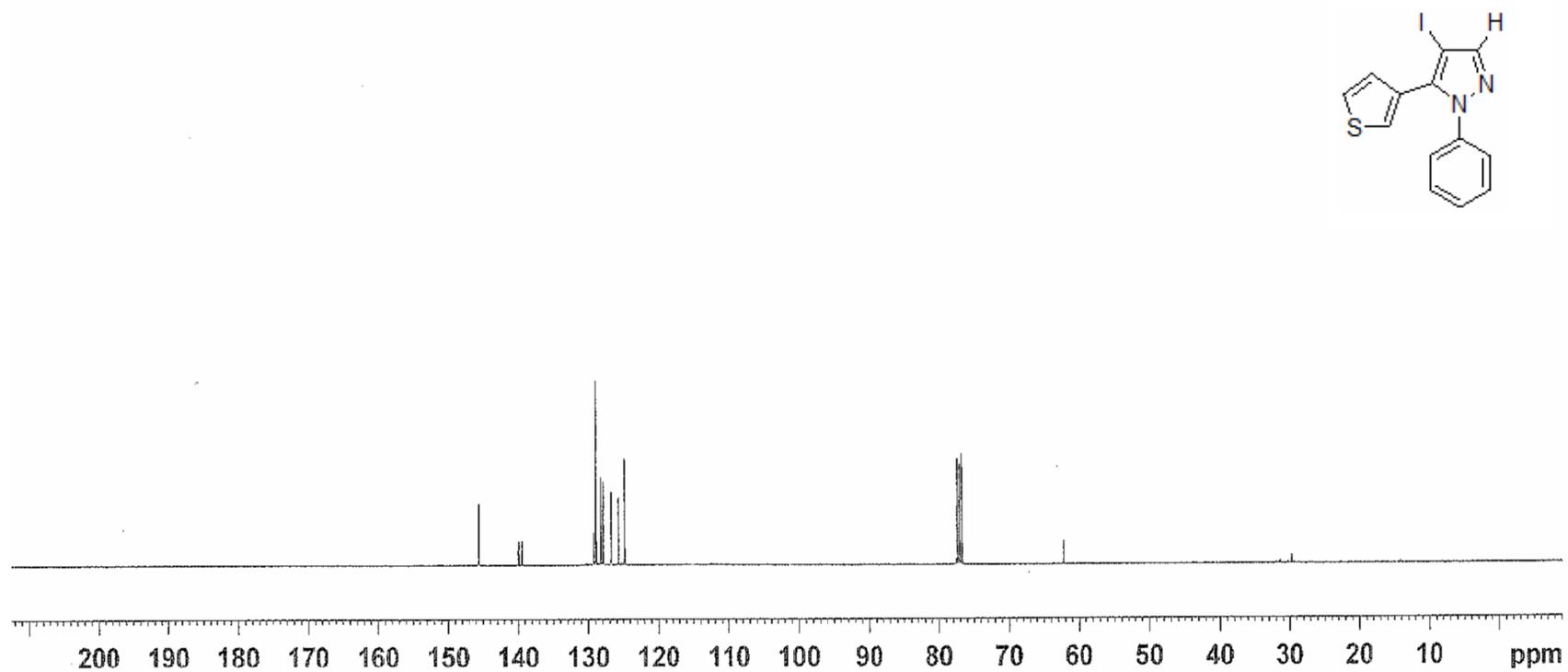
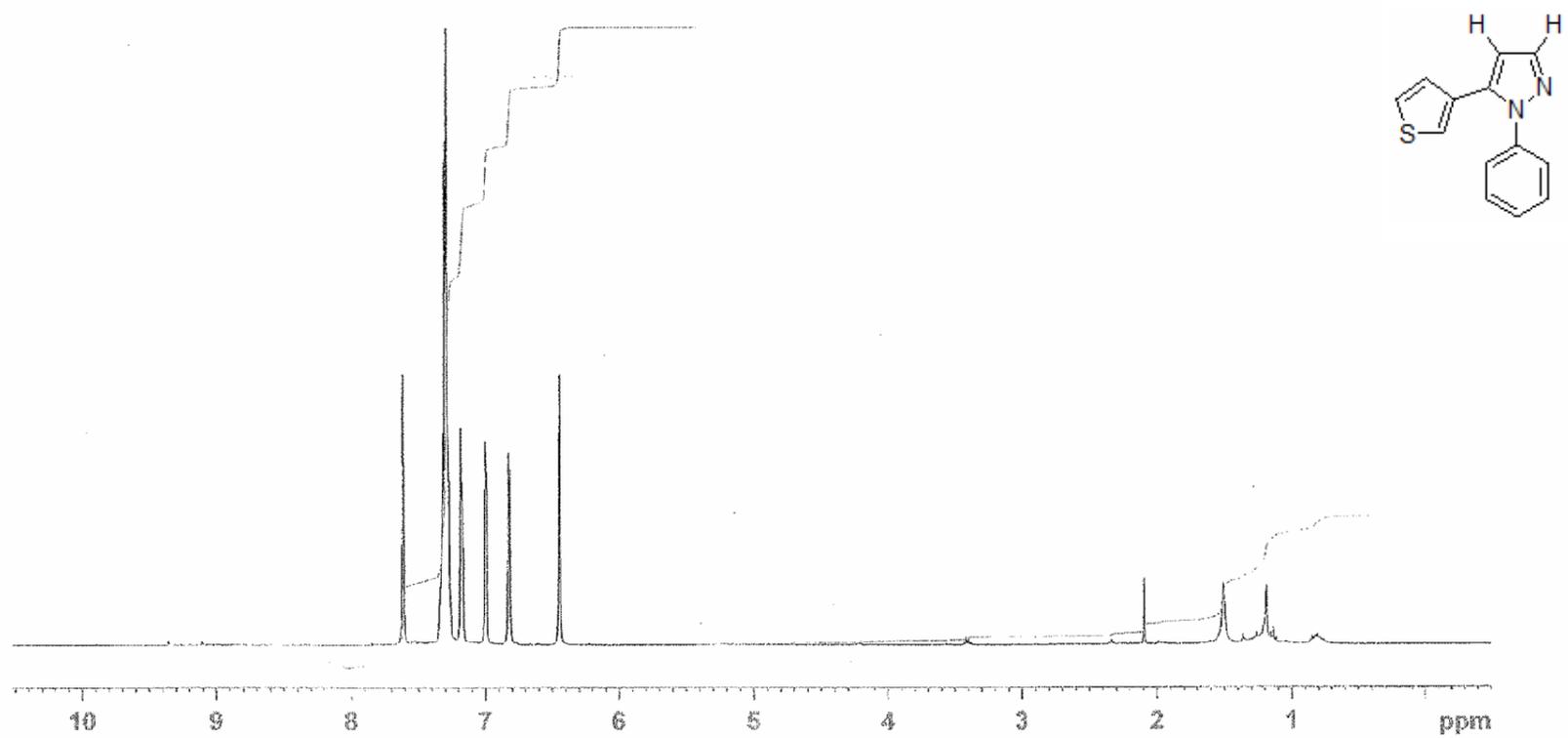


Figure A35.  $^{13}\text{C}$  NMR Spectrum of 16D.



**Figure A36.**  $^1\text{H}$  NMR Spectrum of 17D.

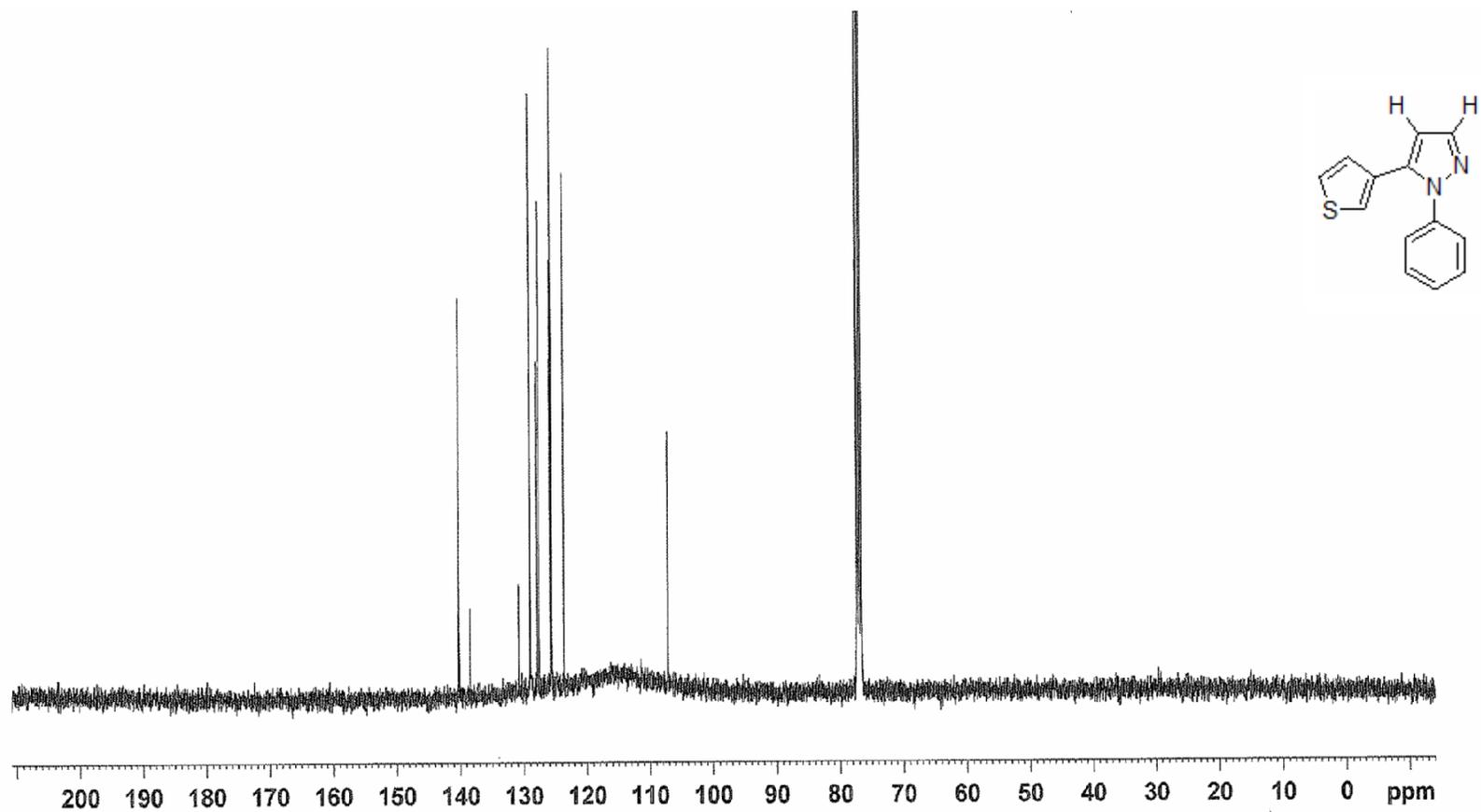


Figure A37.  $^{13}\text{C}$  NMR Spectrum of 17D.

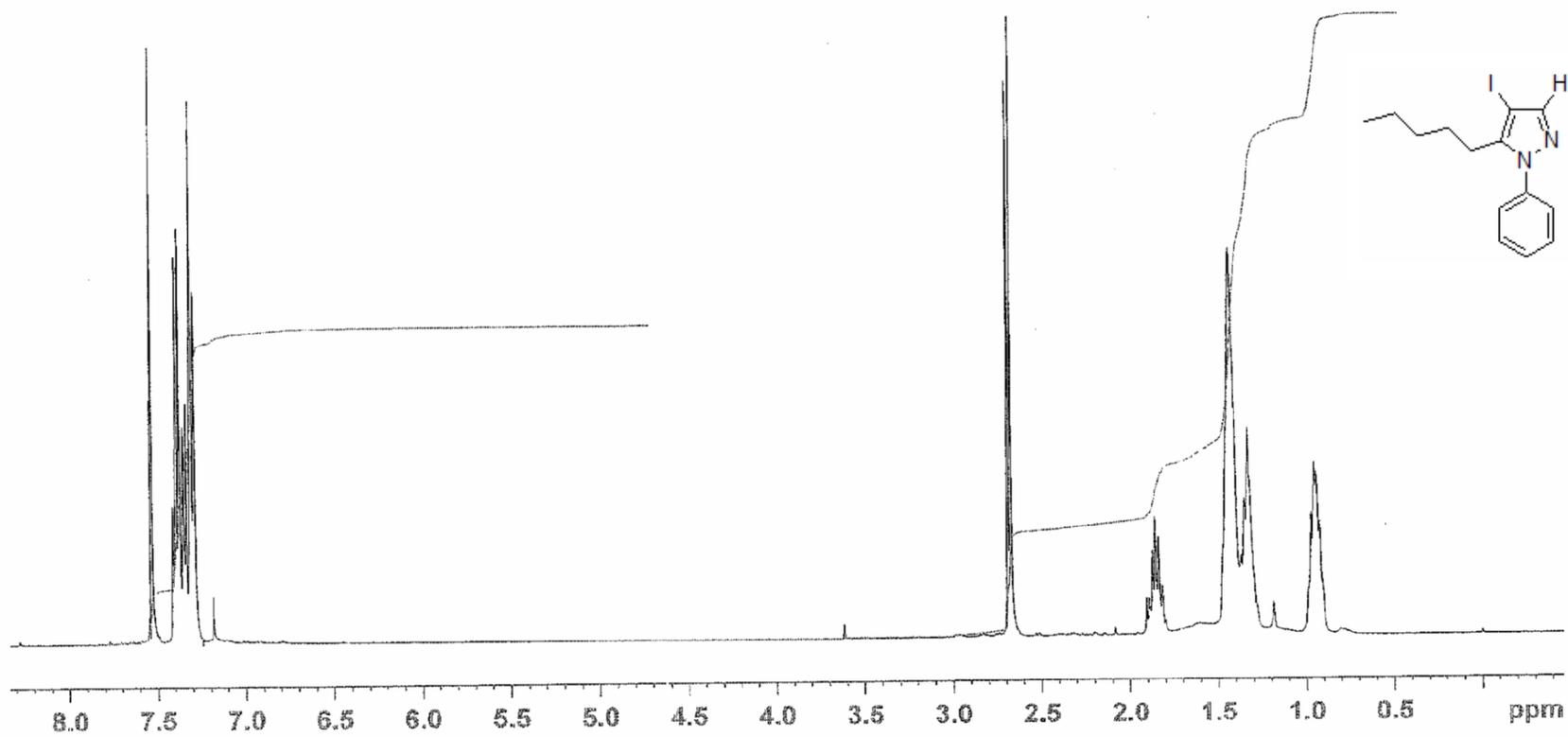
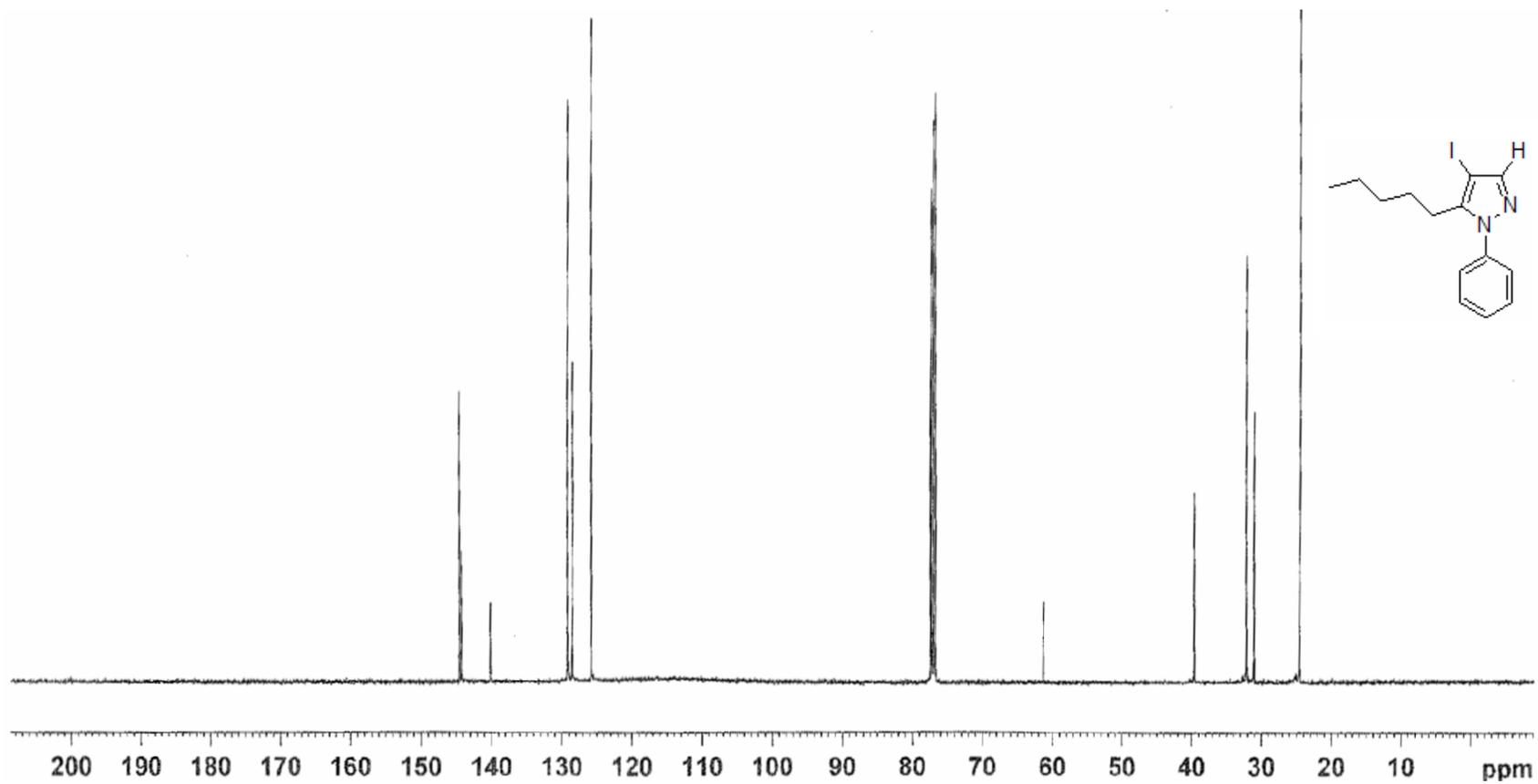


Figure A38.  $^1\text{H}$  NMR Spectrum of 16E.



**Figure A39.**  $^{13}\text{C}$  NMR Spectrum of **16E**.

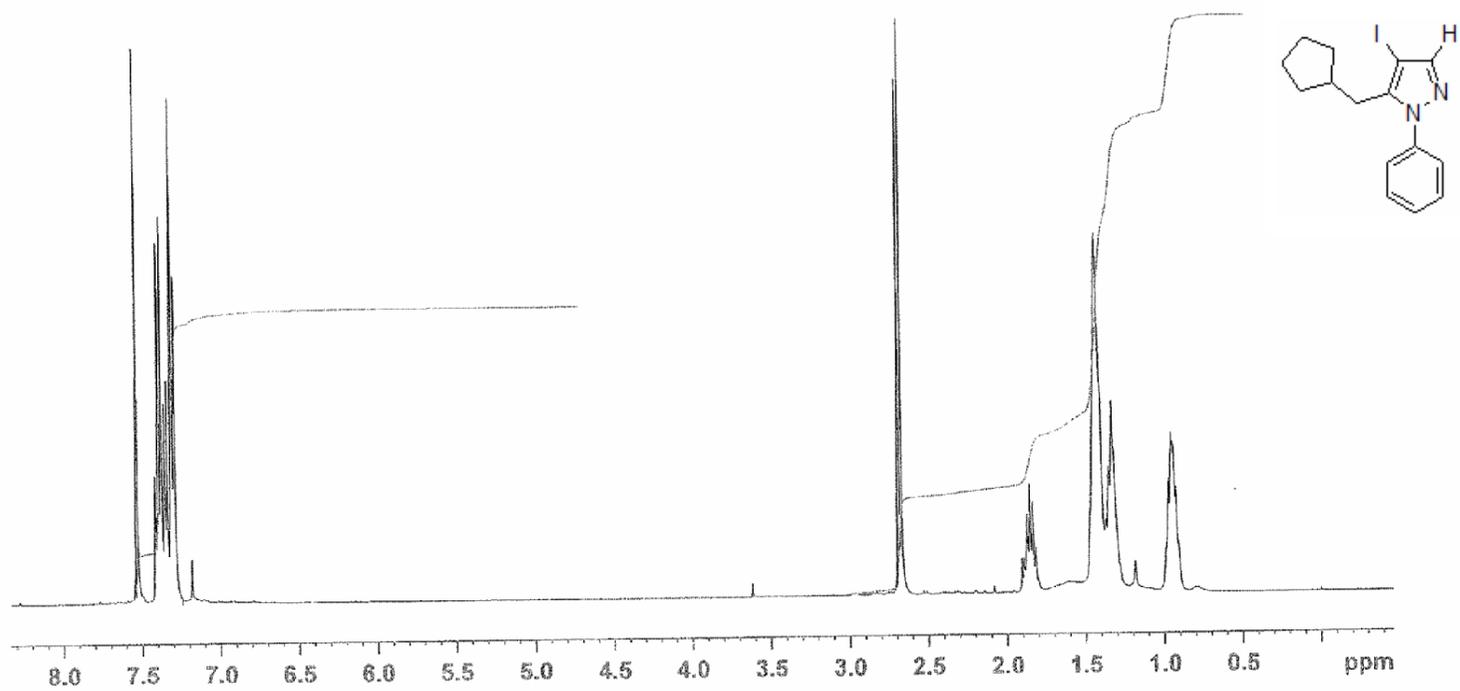


Figure A40.  $^1\text{H}$  NMR Spectrum of 16F.

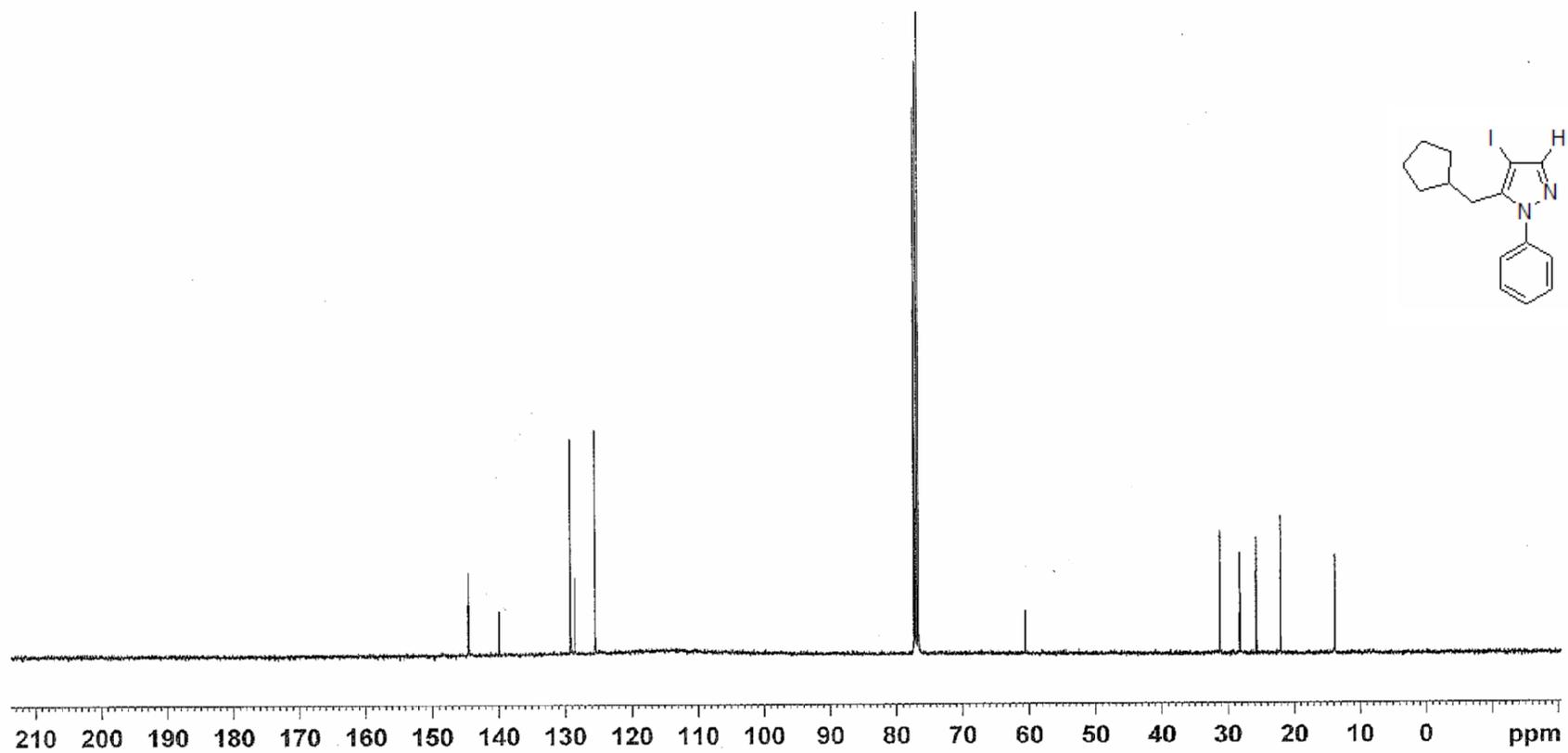


Figure A41.  $^{13}\text{C}$  NMR Spectrum of **16F**.