REACTION OF PROPARGYL ALDEHYDES WITH HYDRAZINIUM SALTS: SYNTHESIS OF FERROCENYL AND PHENYL SUBSTITUTED PYRAZOLES

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REACTION OF PROPARGYL ALDEHYDES WITH HYDRAZINIUM SALTS: SYNTHESIS OF FERROCENYL AND PHENYL SUBSTITUTED PYRAZOLES

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ABSTRACT

REACTION OF PROPARGYL ALDEHYDES WITH HYDRAZINIUM SALTS: SYNTHESIS OF FERROCENYL AND PHENYL SUBSTITUTED PYRAZOLES

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Pyrazoles have been focus of a large number of investigations in the design and synthesis of novel biologically active agents that show remarkable medicinal activities. Although pyrazoles have been studied for over a century as an important class of heterocyclic compounds, they still continue to attract considerable attention due to the wide range of medicinal activities they possess. Recent studies have shown that combination of a ferrocenyl unit with structural features of pyrazoles can lead to products with enhanced or/and unexpected biological activity since several ferrocene derivatives have already been shown to be active against a number of tumors. As a result, we have investigated the reaction of 3-ferrocenylpropynal with hydrazinium salts. As anticipated, these reactions afforded two kinds of pyrazoles, namely 1-alkyl/aryl-5-ferrocenylpyrazoles (1,5-isomer) and 1-alkyl/aryl-3-ferrocenylpyrazoles (1,3-isomer). In most cases, 1,5-pyrazole isomers have resulted from these reactions as the single or the major product of the reactions. The structures of 1-benzyl-5-ferrocenylpyrazole, 1-phenyl-5-ferrocenyl-pyrazole and 1-(2-hydroxy-ethyl)-3-ferrocenylpyrazole were identified by X-ray single crystal analysis. The analogous reactions between 3-phenylpropynal and hydrazinium salts were also studied, which afforded 1-alkyl/aryl-5-phenylpyrazoles (1,5-isomer) and/or

1-alkyl/aryl-3-phenylpyrazoles (1,3-isomer). The regioselectivity of the reactions is mainly governed by the nature of the substituents in hydrazine derivative.

Keywords: Alkynal, Cyclization, Ferrocene, Hydrazine, Pyrazole

ÖZ

PROPARJİL ALDEHİTLERİN HYDRAZİNYUM TUZLARI İLE TEPKİMELERİ: FERROSENİL VE FENİL SÜBSTİTÜYE PİRAZOLLERİN SENTEZİ

Pinar, Ayşe Nur
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Önemli tıbbi aktiviteler gösteren biyolojik olarak aktif maddelerin tasarım ve sentezinde pirazoller birçok araştırmanın odak noktası olmuştur. Heterosiklik bileşiklerin önemli bir sınıfını oluşturan pirazoller, yüzyıldan beri birçok çalışmaya konu olmasına rağmen geniş alana yayılmış tıbbi etkilerinden dolayı bu bileşiklere olan ilgi günümüzde artarak devam etmektedir. Birçok ferrosen türevlerinin antitümör aktiviteye sahip olduğu bilindiğinden, son çalışmalar göstermiştir ki, ferrosen biriminin pirazol bileşiklerinin yapısal özellikleri ile birleştirilmesi sonucu elde edilen bileşiklerin biyolojik aktiviteleri daha da artmakta ve/veya çok daha farklı beklenmeyen biyolojik aktiviteler göstermelerine sebep olmaktadır. Bu nedenle, 3-ferrosenilpropinal bileşiğinin hidrazinyum tuzları ile tepkimelerini araştırdık. Beklenildiği gibi, bu reaksiyonlar iki çeşit pirazol ürünü oluşturmuştur, 1-alkil/aril-5-ferrosenilpirazol'leri (1,5-izomer) ve 1-alkil/aril-3-ferrosenilpirazol'leri (1,3-izomer). Birçok durumda, 1,5-pirazol izomerleri bu tepkimelerden tek ürün veya ana ürün olarak elde edilmiştir. 1-Benzil-5-ferrosenilpirazol, 1-fenil-5-ferrosenil-pirazol ve 1-(2-hidroksietil)-3-ferrosenilpirazol bileşiklerinin yapıları X-ray tek kristal analizi ile tanımlanmıştır. Benzer olarak 3-fenilpropinal bileşiğinin hidrazinyum tuzları ile tepkimeleride çalışılmış ve bu tepkimelerden 1-alkil/aril-5-fenilpirazol ve/veya 1-

alkil/aril-3-fenilpirazol türevleri alınmıştır. Reaksiyonların bölgesel seçiciliğinin hidrazinyum tuzlarının substitüentleri tarafından yönlendirildiği gözlenmiştir.

Anahtar sözcükler: Alkinal, Halkalaşma, Hidrazin, Ferrosen, Pirazol

TO DEAR MY FATHER AND MOTHER

ACKNOWLEDGMENTS

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ABBREVIATIONS

bp	boiling point
br	broad (spectral)
°C	degrees Celcius
Cp	cyclopentadienyl ligand
δ	chemical shift in parts per million downfield from
d	doublet (spectral)
Et	ethyl
Fc	ferrocenium ion
FT	fourier transform
g	gram(s)
h	hour(s)
Hz	hertz
IR	infrared
J	coupling 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)
R_f	retention factor (in chromatography)
rt	room temperature
s	singlet (spectral)
t	triplet (spectral)

THF tetrahydrofuran

TLC thin layer chromatography

DMF Dimethylformamide

DMAc Dimethylacetamide

CHAPTER 1

INTRODUCTION

Organic chemistry can be defined as the study of carbon compounds. The proteins of our hair, skin and the muscles, nucleic acids, RNA and DNA that control our genetic heritage are all organic compounds. Beside these, the foods (fats, proteins, and carbohydrates) we eat daily are organic compounds. Every living organism is made of organic chemicals.[1] Medicines that heal us, gasoline that propels our cars and many materials that go into our houses are all organic. The clothing (wool, cotton or polyester) we wear is also made of carbon compounds.[1] In conclusion, not only are we composed largely of organic compounds, not only are we derived from and nourished by them, we also live in an age of organic chemistry since there is a good relationship between the standard of living and the investment in the research of organic chemistry.[2]

Until near future, there was a common belief that the source of the organic compounds are living organisms, but chemists discovered that in laboratory conditions, organic compounds can be synthesized and also from inorganic compounds. Over the years, the original distinction between compound obtained from living and nonliving source was lost.[3]

Most of the organic compounds contain ring system. When the ring systems contain at least one atom other than carbon (such as N, O, S) these organic substances are called heterocyclic compounds. Nearly half of the known organic compounds contain at least one heterocyclic component.[4] Heterocyclic compounds are important branch of organic chemistry. For instances, many antibiotics, vitamins, dyestuffs and nucleic acids are heterocyclic. Presumably, any atom which can form two covalent bonds is capable of forming a heterocyclic compound.[5]

Pyrazoles have been studied for over a century as an important class of heterocyclic compounds and still continue to attract considerable attention due to the wide range of medicinal activities they posses. Pyrazole (**2**) was described by Bucher in 1889 for the first time by the decarboxylation of pyrazole-3,4,5-tricarboxylic acid (**1**) (Figure 1).[6]

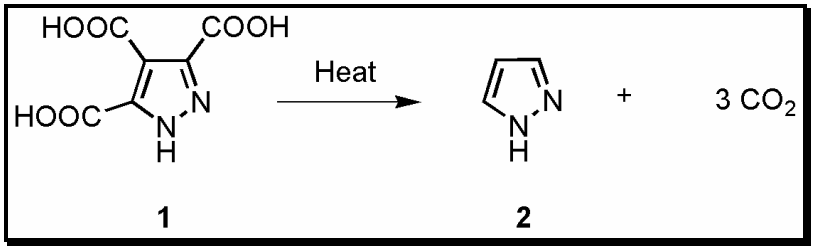


Figure 1. First synthesis of pyrazole (**2**) by the decarboxylation of pyrazole-3,4,5-tricarboxylic acid (**1**).

Much of the information about the pyrazoles was obtained by the comparison of its aromatic properties with those of benzene derivatives. There is no doubt that pyrazole is aromatic because pyrazole consists of a conjugated planar ring system with delocalized six π-electrons.[7] Since then the studies of the pyrazoles have centered principally about structural problems arising from the tautomerism existing in the *N*-substituted types and the isomerism of the *N*-substituted derivatives. For example, three tautomeric forms are available for the unsubstituted pyrazole ring (Figure 2).[6]

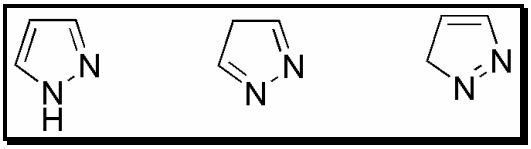


Figure 2. Tautomeric forms of the unsubstituted pyrazole ring.

Until 1954, it was believed that pyrazole ring is unknown in nature. Japanese workers isolated the first natural pyrazole, 3-*n*-nonylpyrazole (**2**), from a plant of piperaceae grown in tropical Asia, and examined its antimicrobial activity. [6] Another naturally occuring pyrazole derivative is levo-ß-(1-pyrazolyl)alanine (**3**) (Figure 3). This pyrazolic amino acid has been isolated from watermelon seeds (Citrullus Vulgaris). [6]

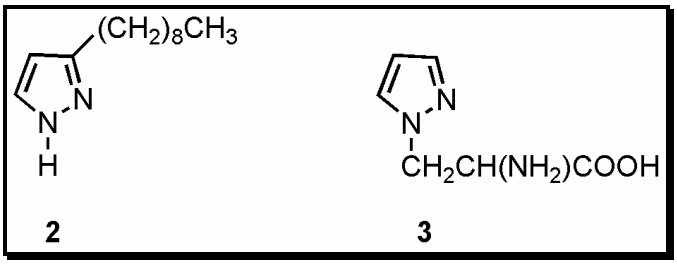


Figure 3. Examples of naturally occuring pyrazoles.

1.1 Biologically active pyrazole derivatives

Compounds which contain the pyrazole ring as a core structure have important biological activities such as antitumor, anti-inflammatory, antimicrobial, antipsychotic and analgesic agents and also have insecticides, herbicides properties.[8] For example, the identification of celecoxib (**4**) has an important advance for the relief of pain and the treatment of the symptoms of arthritis and related diseases

(Figure 4). Another significant application of pyrazole chemistry has resulted from the discovery that highly functionalized pyrazoles (such as DPC 423 (**5**)) can act as orally, bioavailable inhibitors of blood coagulation factor Xa (Figure 4).[9]

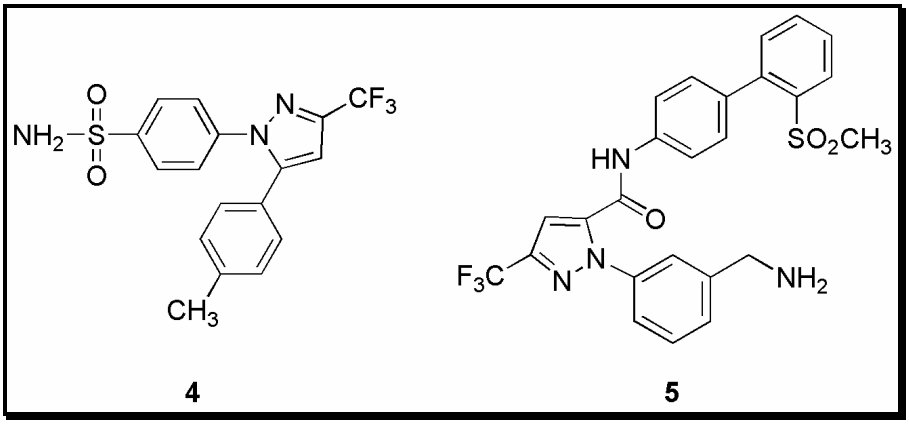


Figure 4. Structures of celecoxib (**4**) and DPC 423 (**5**).

Dehydroorotate dehydrogenase (DHODase) (**6**) (Figure5), which has a pyrazole as a core structure, was identified as a Helicobacter Pylori inhibitor. Helicobacter Pylori is a bacterium that resides in the acidic surroundings of stomach, using a high urease enzyme activity to provide a locally alkaline environment, which causes gastric ulcers, gastritis, and gastric cancer.[10]

Pyrazofurin (**7**) has received considerable attention as a result of its various biological effects including potent antimicrobial and broad spectrum antiviral activities against many RNA and DNA viruses. As has been also noted, pyrazofurin has been evaluated against several tumour cell lines; consequently, it has only been used clinically as an anticancer agent (Figure 5).[11]

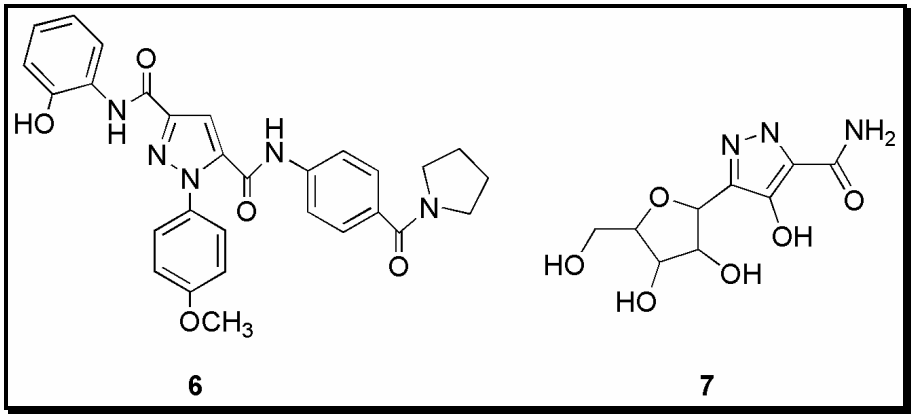


Figure 5. Structures of dehydroorotate dehydrogenase (**6**) and pyrazofurin (**7**).

Bekhit and coworkers, who study in the field of anti-inflammatory and antimicrobial agent synthesis, reported pyrazole derivatives **8**[12], **9**[13] and **10**[14,15] that have anti-inflammatory and antimicrobial activities (Figure 6).

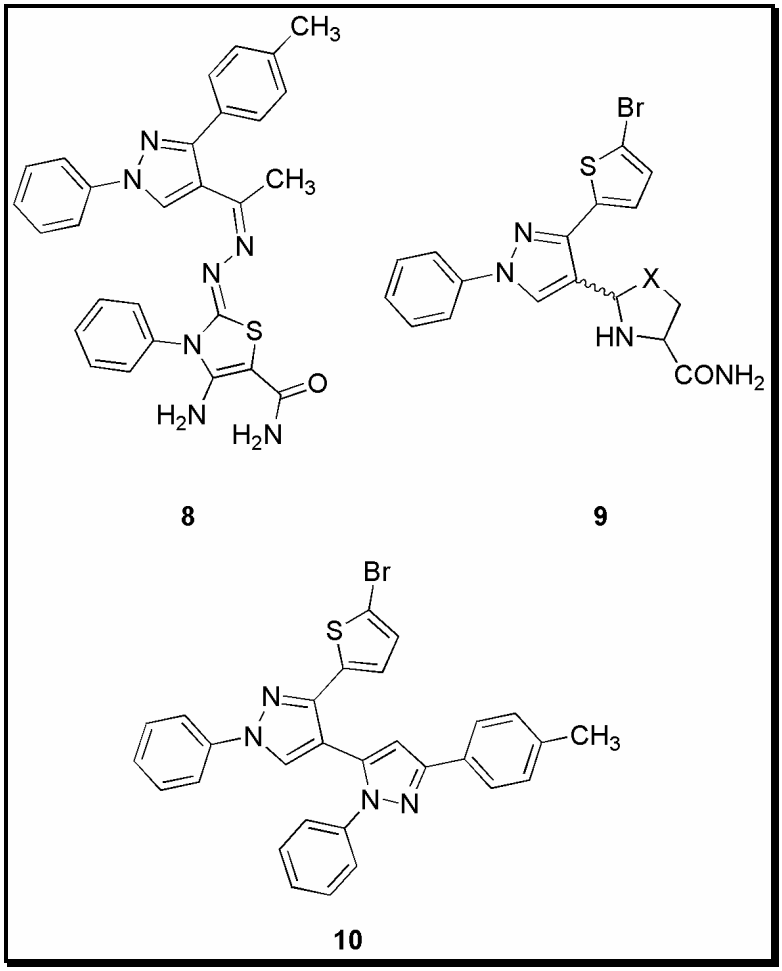


Figure 6. Biologically active pyrazole derivatives reported by Bekhit and coworkers.

One other example of biologically active pyrazole derivatives is Cannabinoid Receptor Antagonist **11** (Figure 7), which was reported in 1994 as an orally active antagonist of brain cannabinoid receptor (CBI). Cannabinoids have effects on the central nervous system and the major psychoactive constituent of marijuana. Cannabinoids have analgesic, antiemetic, psychotropic, and anti-inflammatory properties, and also they are used for the treatment of asthma and glaucoma.[16]

Zoniporide (**12**)[17] and PNU-32945 (**13**)[18], which contain pyrazole moieties in their structures, have also useful biological activities (Figure 7). Zoniporide is a sodium

hydrogen ion exchanger while PNU-32945 is HIV-1 reverse transcriptase inhibitor. There are also other compounds which bear a pyrazole unit acting as an insecticides, pesticides and acaricides such as fenpyroximate (**14**) (Figure 7).[19]

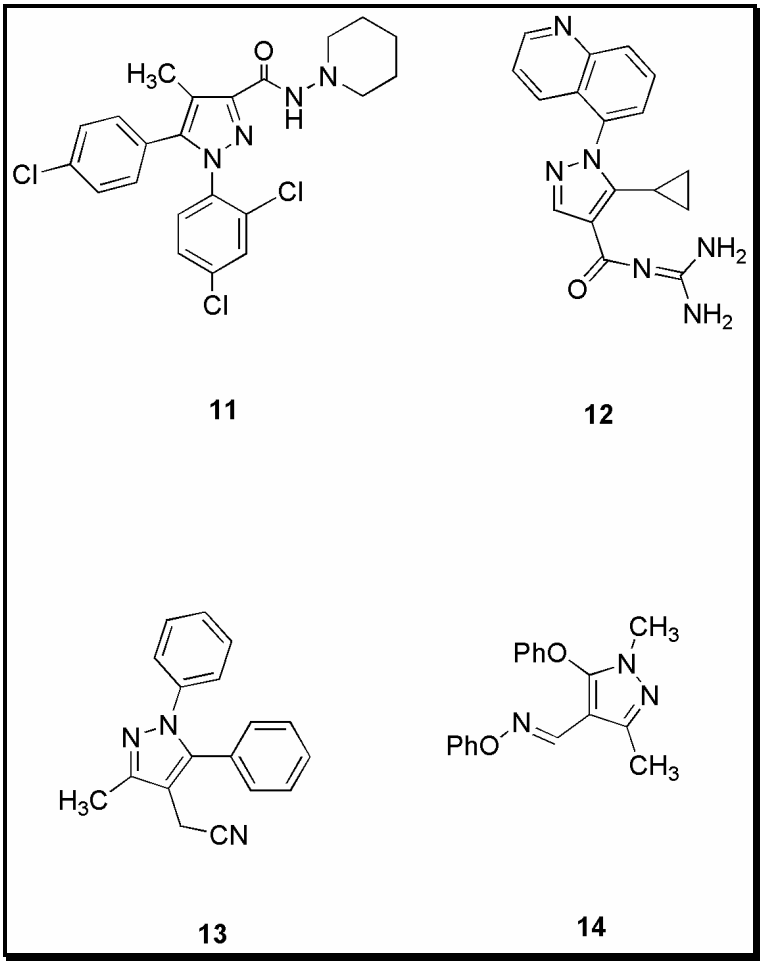


Figure 7. Structures of Cannabinoid Receptor Antagonist (**11**), Zoniporide (**12**), PNU-32945 (**13**) and Fenpyroximate (**14**).

1.2 Synthesis of pyrazole derivatives

Since pyrazoles have many biological activities many methods have arised to synthesize pyrazole derivatives. Pyrazoles are most commonly synthesized by the

reaction of hydrazine with a 1,3-dicarbonyl compound. A highly regioselective synthesis of trisubstituted pyrazoles **17** and **18** based on the condensation of 1,3-diketones **15** with arylhydrazines **16** proceeds at room temperature in *N,N*-dimethylacetamide, yielding pyrazoles in good yields (Figure 8).[20]

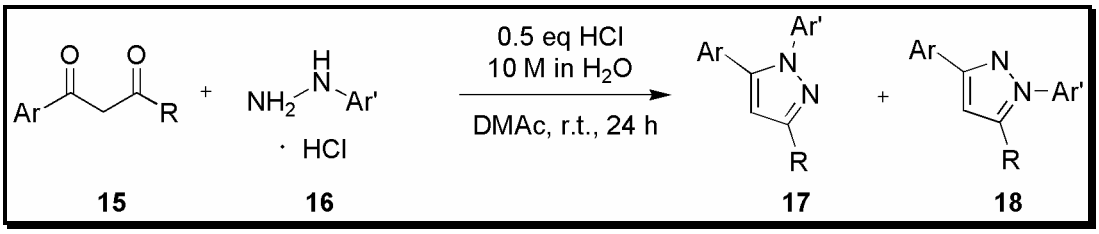


Figure 8. Pyrazole synthesis from 1,3-diketones and arylhydrazines.

Pyrazoles can also be obtained from the reactions of β-amino enones with hydrazine derivatives. Gonzalez-Ortega and coworkers studied the reaction of β-amino enones **19** and hydrazine derivatives **20** to give 1,3,5-trisubstituted pyrazoles (Figure 9).[21] However, these reactions produced a mixture of two pyrazole derivatives, **21** and **22**.

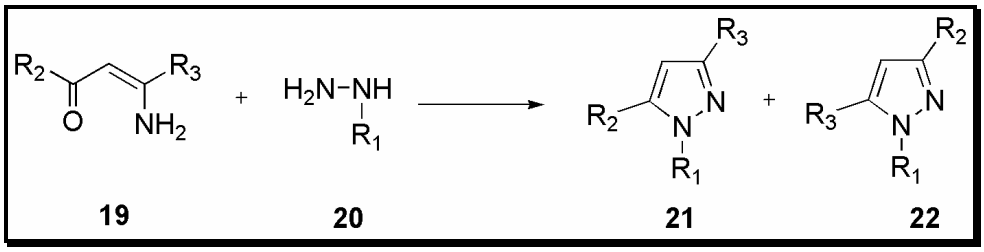


Figure 9. Synthesis of pyrazoles from β-amino enones and hydrazines.

Calle Research Group used this methodology to synthesize silylpyrazoles **25** and **26** by employing silyl-substituted β-amino enones **23** and hydrazine **24** (Figure 10).[22]

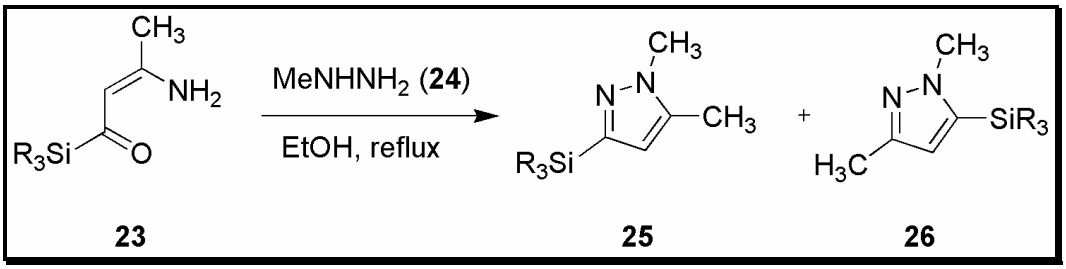


Figure 10. Synthesis of silyl-substituted pyrazoles.

Recently, Zora research group has reported the synthesis of ferrocenyl-substituted pyrazoles derivatives,[23] which are not often found in literature. The reaction between (2-formyl-1-chlorovinyl)ferrocene (**27**) and hydrazinium salts produced 1-alkyl/aryl-5-ferrocenylpyrazoles (1,5-isomer) (**28**) and 1-alkyl/aryl-3-ferrocenylpyrazoles (1,3-isomer) (**29**), the former being the single or major product of the reaction (Figure 11)

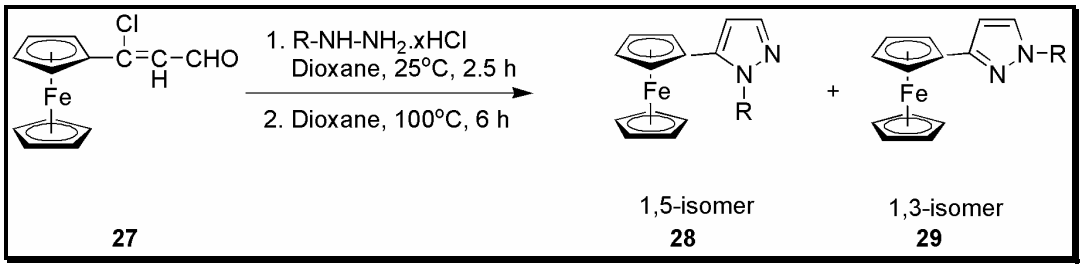


Figure 11. Synthesis of ferrocenyl-substituted pyrazole derivatives.

A regioselective synthesis of substituted pyrazoles **33** from *N*-substituted hydrazones **32** and nitroolefins was also described. The reaction was performed in a one-pot manner and the yields changed from moderate to excellent (Figure 12).[24]

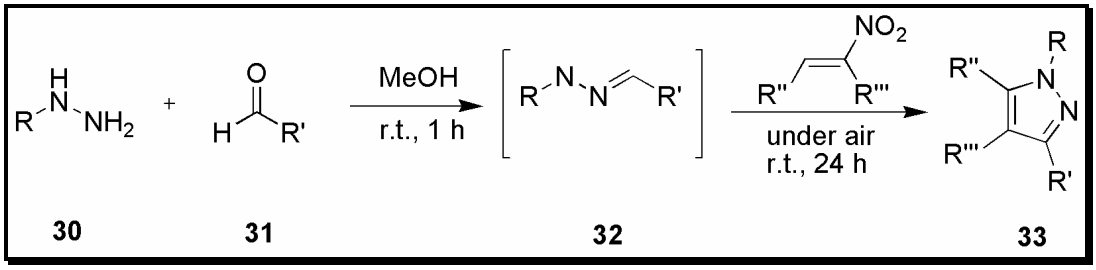


Figure 12. Synthesis of pyrazoles from nitroolefins and hydrazines.

3-Amino-2*H*-pyrazoles **36** have many biological activities as well as industrial applications. So, several methods have been reported for the preparation of 3-amino-2*H*-pyrazoles. An efficient and clean synthesis of such pyrazoles has been achieved by the reaction between α-keto nitriles **34** and hydrazines **35** in the presence of methanesulphonic acid (Figure 13).[25]

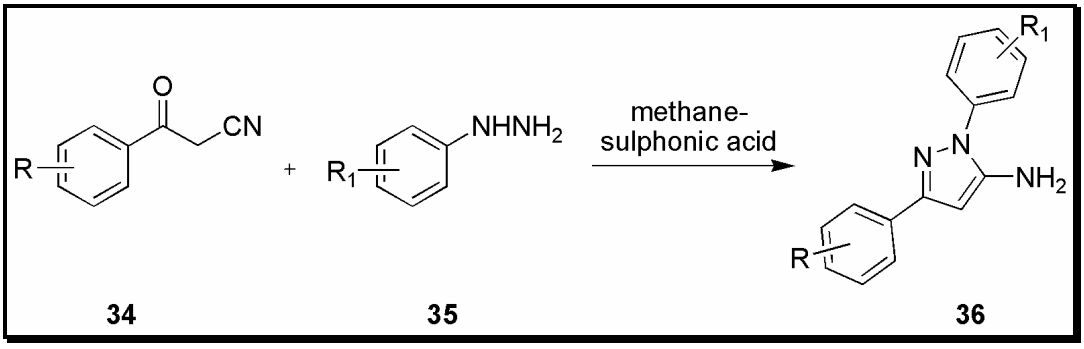


Figure 13. Synthesis of 3-amino-2*H*-pyrazoles.

Armstrong research group has reported one pot synthesis of pyrazoles **38** from primary amines **37**. They used ketone-derived *N*-Boc-oxaziridine and diethyl ketomalonate to convert amines to the corresponding protected hydrazines. Protected alkyl hydrazines are highly useful for the construction of a large range of valuable heterocycles (Figure 14).[26]

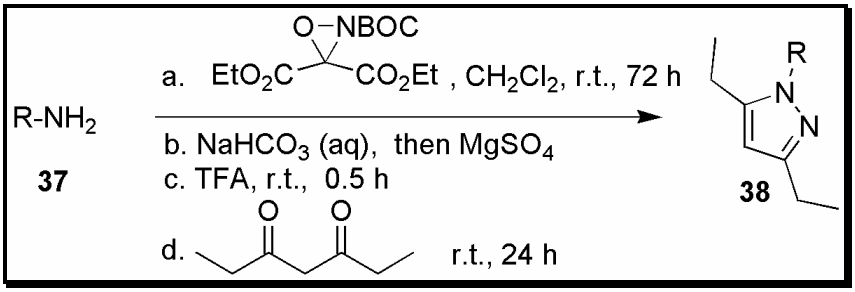


Figure 14. One pot synthesis of pyrazoles.

One pot construction of heterocycles from simple organic molecules is a always simple and practical method. Treatment of phenylethyne (**39**), aqueous hydrazine (**40**), carbon monoxide (**41**) and iodobenzene (**42**) in the presence of $PdCl_2(PPh_3)_2$ afforded 3,5-diphenylpyrazole (**43**). Formation of the ring structure took place in one pot manner, and with readily available reagents and substrates, and also reaction was carried out at room temperature with an ambient pressure of carbon monoxide (Figure 15).[27]

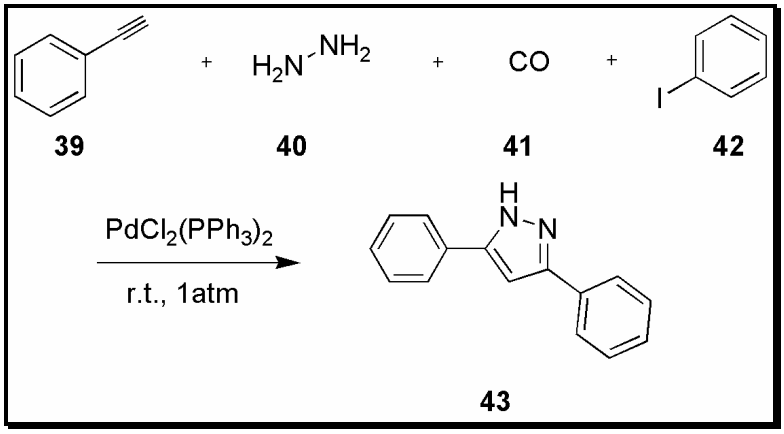


Figure 15. One-pot construction of pyrazoles with palladium-catalyzed four component coupling.

In the presence of activated carbon, 1,3,5-trisubstituted pyrazolines **44** were aromatized with molecular oxygen to the corresponding pyrazoles **45** in excellent yields (Figure16).[28]

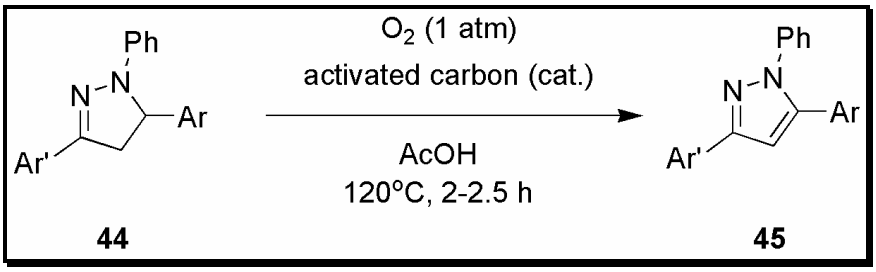


Figure 16. Synthesis of pyrazoles from pyrazolines.

Pyrazole-3-carboxylic acid derivatives represent important pharmacological properties. Langer and coworkers reported a new and convenient approach to pyrazole- 3-carboxylates (**48**) by one pot cyclization of hydrazone (**46**) with diethyl oxalate (**47**) (Figure 17).[29]

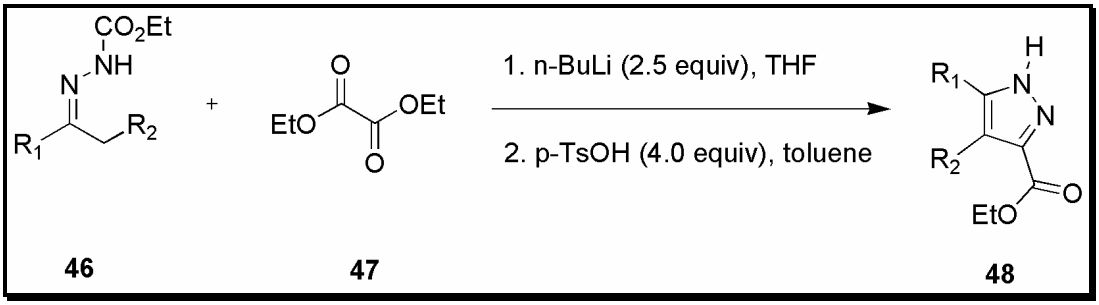


Figure 17. Synthesis of pyrazole-3-carboxylates (**48**).

1.3 Ferrocene derivatives and their biological activities

Ferrocene (**49**) was discovered in the 1950s by G. Wilkinson, R. B. Woodward and E. O. Fischer.[30] Structural properties of ferrocene and its derivatives have been the subject of increasing interest in all fields of organometallic chemistry.

Ferrocene, an orange crystalline diamagnetic solid, is one of the most common and well known organometallic compounds.[31] Ferrocene has a sandwich structure which is a simple complex consisting of an iron center and two cyclopentadienyl (Cp) rings surrounding the metal. Ferrocene, with its 18 valence electrons, is also one of the most stable member of the metallocenes and thermally stable and tolerant to oxygen and moisture.[32]

Ferrocene (**49**) is easily transformed to the blue, paramagnetic, ferrocenium ion (**50**) by the mild one-electron oxidizing agents such as ferric salts, silver salts, halogens, nitric acid, and even sulfuric acid (Figure 18).[33]

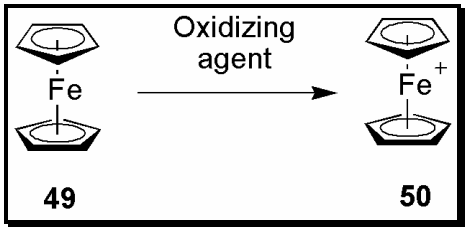


Figure 18. Oxidation of ferrocene to ferrocenium ion.

Because of its high stability towards air and water and also reversible redox characteristics, ferrocene has been extensively used as starting materials in the synthesis of ferrocenyl derivatives. For example, such derivatives are very important electron-transfer systems for molecular electronics owing to its characteristic redox behaviors.[34] It has been found that ferrocene behaves in many aspects like an aromatic electron-rich organic compound almost like phenyl. As a consequence, the cyclopentadienyl moiety of ferrocene is treated like a simple phenyl group.[35] It undergoes Friedel-Crafts acylation and alkylation, Vilsmeier formylation, dimethylaminomethylation and mercuration,[36] which are shown in Figure 19.

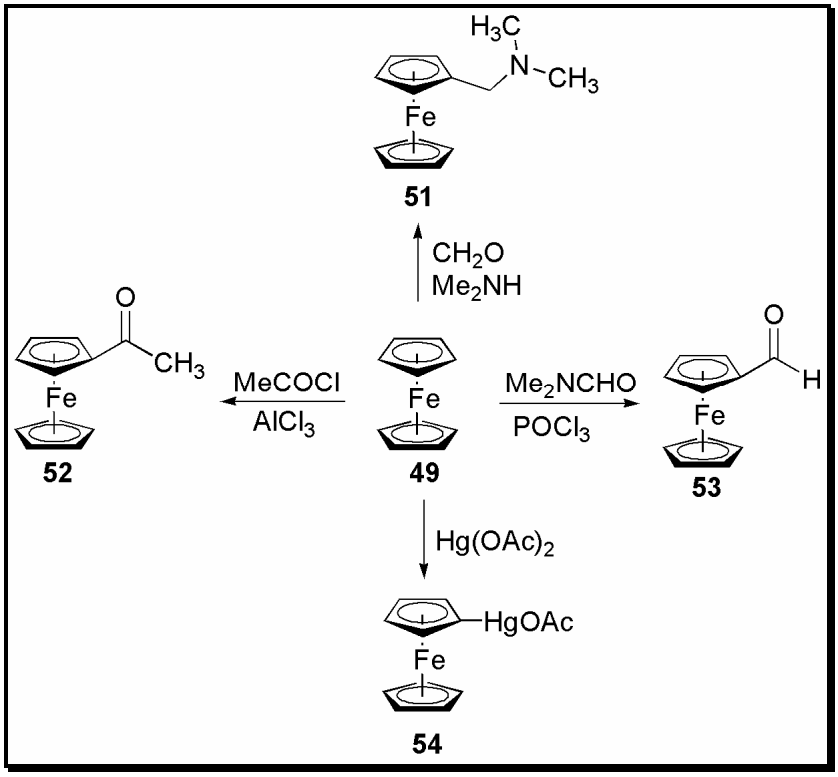


Figure 19. Typical electrophilic substitution reactions of ferrocene.

Ferrocenes have wide applications in a variety of areas. They are used in supramolecular chemistry, as magnetic materials and liquid crystals, in asymmetric catalysis,[34] and as oil additives.[37] Ferrocenyl compounds function as enzyme inhibitors and can act as cancer therapeutic agents.[38,39] Ferrocene is neutral, chemically stable, non-toxic and able to cross cell membranes.[40] In addition, ferrocenyl and multiferrocenyl systems have been used as redox sensors for molecular recognition, as in building blocks in polymers or as coatings to modify electrode surfaces.[41] Some ferrocene derivatives such as 1,1-diformylferrocene, 1,1-diacetylferrocene, 2-benzimidazolylthioacetylferrocene are inhibitors for mild corrosion in both HCl and H_2SO_4 solutions.[42]

Ferrocene (**49**) is not water soluble compound and it does not show any biological activity. On the other hand, it has been reported that ferrocenium salts are exhibiting

antitumor activity against a number of tumors. In 1984, Köpf-Maier reported on the antineoplastic activity of some ferrocenium salts against Ehrlich ascites tumor (EAT) cell line.[43,44] Ferrocene and ferrocenium salts had been tested *in vivo* for their inhibitory activity towards the EAT cell line. Studies showed that only the ferrocenium salts, in which the central iron atoms have the oxidation state +3 (as in ferrocenium cations) exhibit tumor inhibitory effects.[45] However, when intercalated into cells, ferrocene is biologically oxidized to ferrocenium ion and shows biological activity. Due to its unique structure, different membrane-permeation behavior and anomalous metabolism, ferrocene is frequently integrated into an organic compound in order to have enhanced or unexpected biological activities.

Tamoxifen (**55**) is the drug used against breast cancer cells (Figure 20). It has inhibitory effect against breast cancer cells which are hormone dependent.[46] It does not have any effects on hormone independent cancer lines. Jaouen and coworkers replaced phenyl group of tamoxifen with ferrocenyl moiety. Resulting ferrocifen (**56**) have shown to be active against both hormone dependent and hormone independent breast cancer cells (Figure 20).[47]

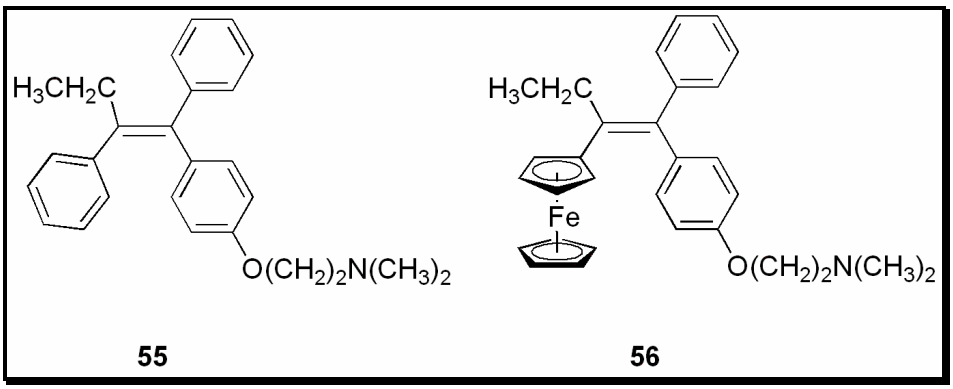


Figure 20. Structures of tamoxifen (**55**) and ferrocifen (**56**).

Chloroquine (**57**) is a drug which is used for the treatment of malaria (Figure 20). But unfortunately, malaria parasite gained resistance to this drug.[48] Brocard and coworkers inserted a ferrocenyl group into the side chain of the chloroquine (**57**), thus producing a hybrid compound called ferroquine (**58**).[49] It has been reported that the resulted ferroquine (**58**) is much more safe and effective in mice, as well as non-mutagenic (Figure 21).[50]

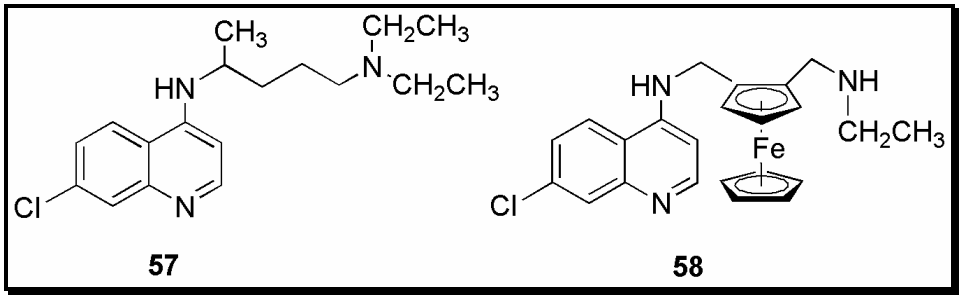


Figure 21. Structures of chloroquine (**57**) and ferroquine (**58**).

One other example to structural variations of established drugs with the ferrocenyl moiety is ferrocenyl aspirin.[51]

1.4 The aim of this study

As mentioned previously, pyrazoles are important heterocycles due to their biological activity. Recent studies have shown that substitution of an aromatic nucleus with a ferrocene unit can lead to products with enhanced or unexpected biological activity which is absent or less manifest in the parent molecule.[52,53] In other words, if the structural features of pyrazoles are combined with a ferrocenyl moiety, current biological activities may be enhanced.

Although pyrazoles are among the most thoroughly studied compounds, we were surprised that there has been very limited study of the ferrocenyl-substituted

pyrazoles. In this regard, the reactions of acetylenic ketones with hydrazines have been frequently used to synthesize pyrazole derivatives. However, analogous reactions between acetylenic aldehydes and hydrazines are almost unknown since, to the best of our knowledge, there is only one example of such reaction. It has been reported that the microwave assisted reaction of 3-phenylpropynal and phenylhydrazine provided 1,3-and 1,5-diphenypyrazoles in 58% and 28% yields, respectively.[54] As a part of our general involvement in ferrocene chemistry, we have investigated the reaction of 3-ferrocenylpropynal (**59**) with hydrazinium salts (**60**) (Figure 22).[55] As anticipated, these reactions afforded two kinds of pyrazoles, namely 1-alkyl/aryl-5-ferrocenylpyrazoles and 1-alkyl/aryl-3-ferrocenylpyrazoles, which we will refer to as 1,5- and 1,3-isomers, respectively.

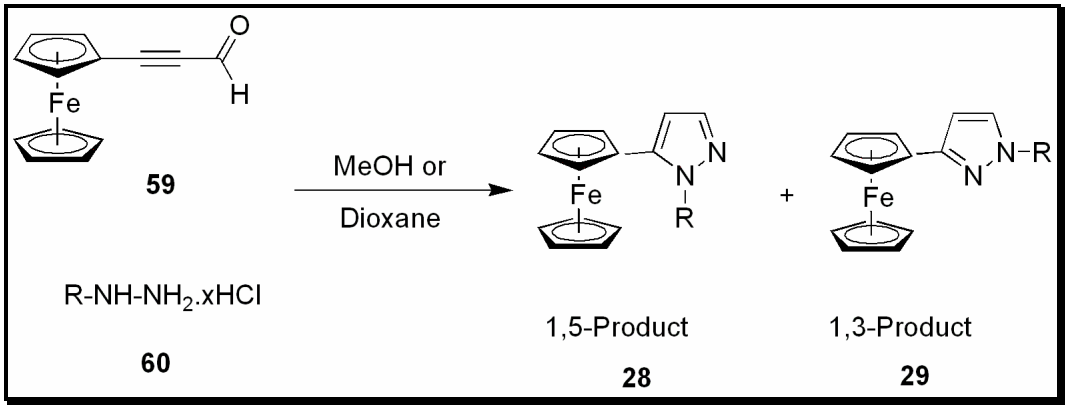


Figure 22. Reaction of 3-ferrocenylpropynal (**59**) with hydrazinium salts (**60**).

We realized that analogous thermal reactions between 3-phenylpropynal and hydrazine derivatives were not studied in detail. For this reason, we also studied the reactions of 3-phenylpropynal (**61**) with hydrazinium salts (**60**) (Figure 23). From this reactions, 1-alkyl/aryl-5-phenylpyrazoles and/or 1-alkyl/aryl-3-phenylpyrazoles were isolated.

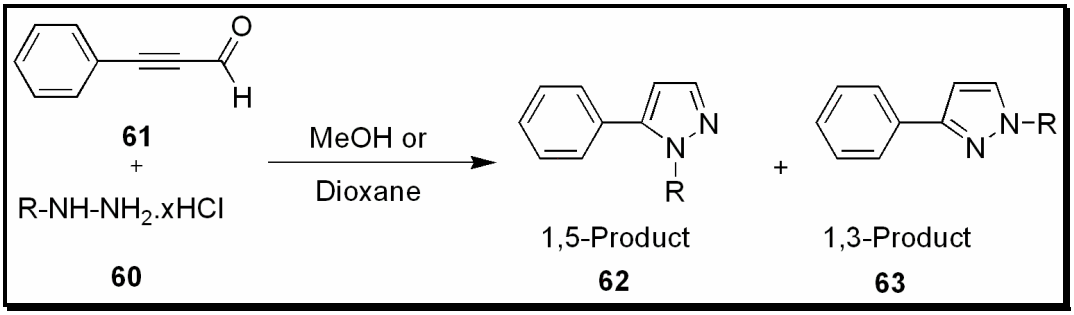


Figure 23. Reaction of 3-phenylpropynal (**61**) with hydrazinium salts (**60**).

In this thesis, the scope, limitations and mechanisms of these reactions will be discussed.

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of ferrocenyl-substituted pyrazoles

2.1.1 Synthesis of 3-ferrocenylpropynal

In the first part of this study, acetyl ferrocene (**52**) was synthesized from ferrocene (**49**). Ferrocene (**49**) behaves as an aromatic compound and easily undergoes Friedel-Crafts acylation reaction to form acetyl ferrocene (**52**) in 80 % yield according to a well known literature procedure.[56] The reaction was performed by using $AlCl_3$ as catalyst under argon. Subsequently, (2-formyl-1-chlorovinyl)-ferrocene (**27**) has been prepared from acetyl ferrocene (**52**) in 93% yield according to a standard protocol (Figure 24).[57] Treatment of acetylferrocene with phosphorus oxychloride in *N*,*N*-dimethylformamide (DMF) leads to formation of (2-formyl-1-chlorovinyl)ferrocene (**27**). Then, (2-formyl-1-chlorovinyl)ferrocene (**27**), was refluxed in dioxane in the presence of sodium hydroxide to afford ethynylferrocene (**64**) in 75% yield (Figure 24).[57]

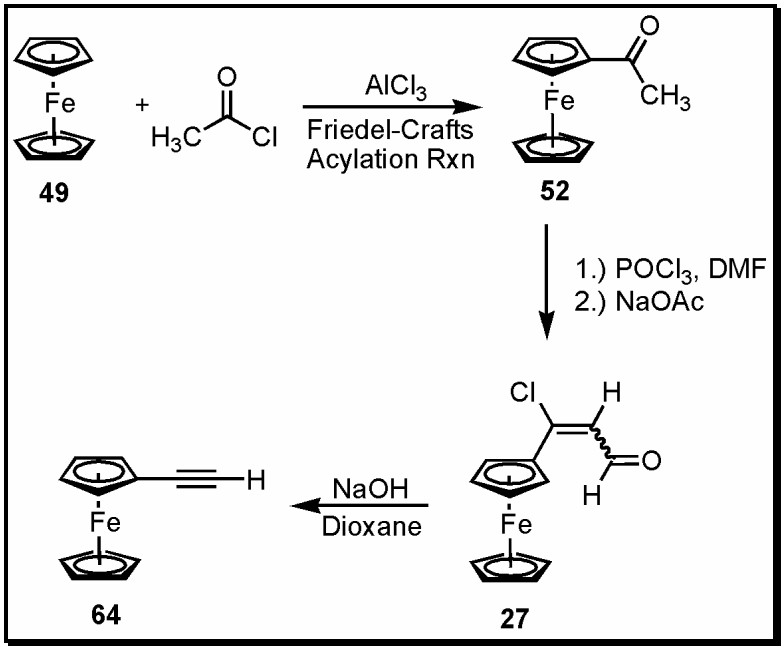


Figure 24. Synthesis of ethynylferrocene (**64**)

Finally, ethynylferrocene (**64**) was treated with *n*-butyllithium (*n*-BuLi) in dry THF at –40 °C under argon. After the addition of DMF, it was allowed to room temperature and stirred for 30 min. Then the reaction mixture was poured into vigorously stirred biphasic solution prepared from a 10% aq. solution of KH_2PO_4 and methyl tertiary butyl ether (MTBE) to afford 3-ferrocenylpropynal (**59**) in 82% yield (Figure 25).[58]

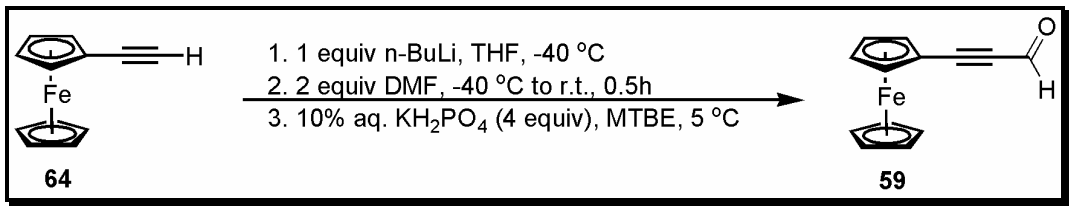


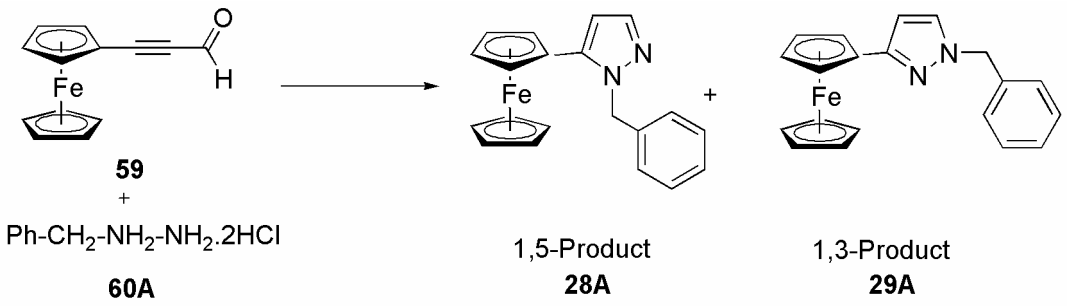
Figure 25. Synthesis of 3-ferrocenylpropynal (**59**)

2.1.2 Scope and limitations.

After synthesizing 3-ferrocenylpropynal (**59**), we have investigated its reactions with hydrazinium salts (**60**), which were all commercially available, except that (2-hydroxyethyl)hydrazinium dichloride was prepared according to a standard procedure.[59] The reactions between 3-ferrocenylpropynal (**59**) and hydrazinium salts (**60**) were examined in a variety of conditions and it was found that the optimal conditions require heating a 1:1.5 mole ratio of 3-ferrocenylpropynal (**59**) with hydrazinium salt (**60**) in MeOH or Dioxane as it will be discussed below. The reaction products were isolated from these reactions by flash column chromatography and characterized by means of ^{1}H- and ^{13}C-NMR, IR, MS and HRMS spectroscopy.

Initially, the reaction between 3-ferrocenylpropynal (**59**) and benzylhydrazine dihydrochloride (**60A**) was examined in different conditions. Results are summarized in Table 1. In the first case, the reaction mixture was refluxed in methyl alcohol for 5 h, which yielded 1,5- and 1,3-pyrazole isomers. 1,5-pyrazole product **28A** was obtained in 46% yield while 1,3-pyrazole product **29A** was formed in 30% yield. Then, reflux time was increased to 8 h but longer reaction time did not improve the yields of the products and the partial decomposition of the products was observed as well. Reaction solvent was then changed to dioxane. As seen in Table 1, the reaction in refluxing dioxane afforded only 1,5-product **28A** with 63% yield.

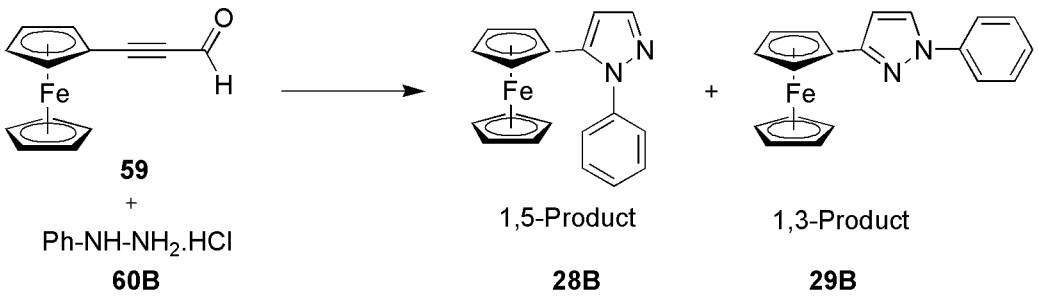
Table 1. Reactions of 3-ferrocenylpropynal (**59**) with benzylhydrazine dihydrochloride (**60A**).



Solvent	Condition	Yield of 1,5-product, %	Yield of 1,3-product, %
MeOH	65 ^{o}C, 5 h	46	30
MeOH	65 ^{o}C, 8 h	36	33
Dioxane	100 ^{o}C, 8 h	63	-

Next, the reaction between phenylhydrazine dihydrochloride (**60B**) and 3-ferrocenylpropynal (**59**) was investigated (Table 2). In the first two conditions, the reaction mixture was refluxed in methyl alcohol for 5 h and 8 h, respectively. In the last condition, the reaction was refluxed in dioxane for 8 h. In all cases, 1-phenyl-5-ferrocenylpyrazole (**28B**) was formed as a major product while 1-phenyl-3-ferrocenylpyrazole (**29B**) was obtained as a minor product. Results are summarized in Table 2.

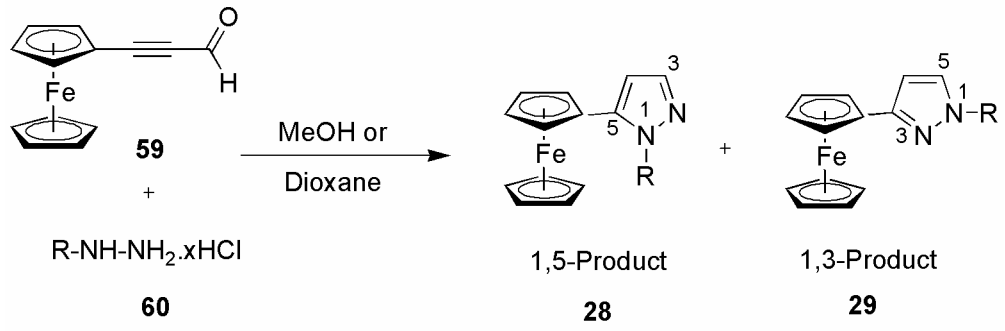
Table 2. Reactions of 3-ferrocenylpropynal (**59**) with phenylhydrazine hydrochloride (**60B**).



Solvent	Condition	Yield of 1.5-product, %	Yield of 1.3-product, %
MeOH	65 ^{o}C, 5 h	70	20
MeOH	65 ^{o}C, 8 h	63	18
Dioxane	100 ^{o}C, 8 h	45	14

After these results, two conditions were adopted for optimum yield. One is refluxing 3-ferrocenylpropynal (**59**) with hydrazinium salt (**60**) in MeOH for 5 h and the other is refluxing the starting compounds in dioxane for 8 h. Overall, the reaction was performed with four different hydrazinium salts and the results are summarized in Table 3.

Table 3 Reactions of 3-ferrocenylpropynal (**59**) with hydrazinium salts **60.**



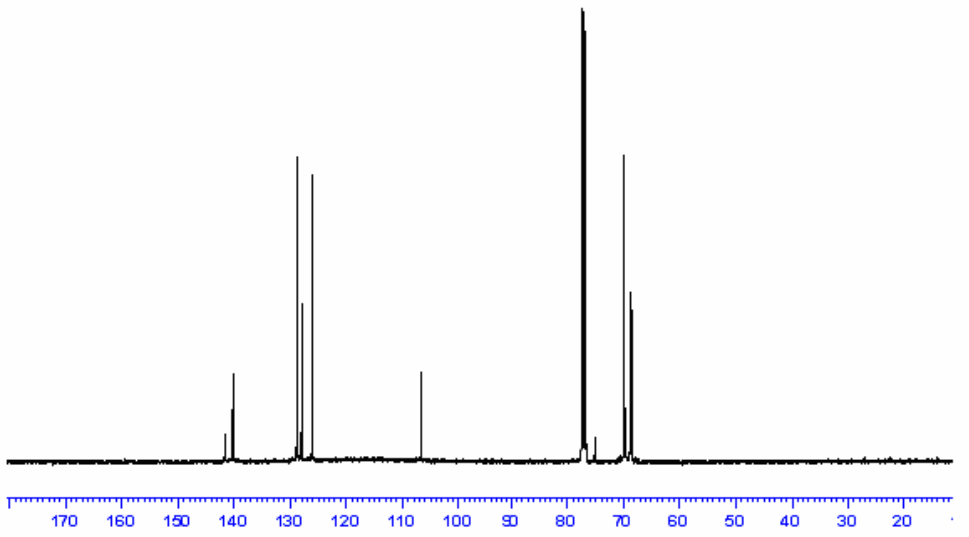
Entry[a]	R	x	Products (isolated yields, %)	
			Condition A[b]	Condition B[c]
A	$-CH_2-C_6H_5$	2	**28A** (63)	**28A** (46) + **29A** (30)
B	$-C_6H_5$	1	**28B** (45) + **29B** (14)	**28B** (70) + **29B** (20)
C	-H	2	**28C** (47)	**28C** (70)
D	$-CH_2-CH_2-OH$	2	**28D** (6) + **29D** (19)	**28D** (31) + **29D** (25)

[a]Entry Letters define R group for compounds **28**, **29** and **60**.

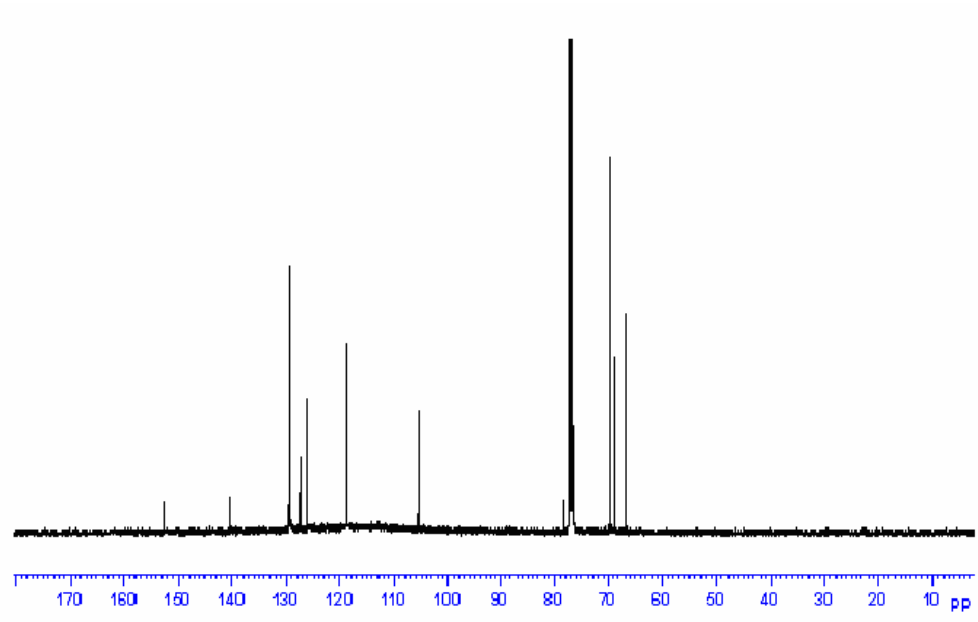
[b]Condition A: dioxane, 100 ^oC, 8h.

[c]Condition B: CH_3OH, 65 ^oC, 5h.

It should be noted that 1,5- and 1,3-isomers of these types of pyrazoles can easily be identified on the basis of their ^{13}C-NMR spectra.[23] In general, the C5 peak in 1,5-isomer is relatively upfield and resonates near 140 ppm while the corresponding C3 peak in 1,3-isomer is comparatively downfield and appears around 150 ppm (see Table 3 for atom numbering), as seen in the ^{13}C-NMR spectra of pyrazole isomers **28B** and **29C** (Figure 26). Furthermore, in 1,5-isomer, the absolute value of chemical



^{13}C-NMR Spectrum of **28B**



^{13}C-NMR Spectrum of **29B**

Figure 26. ^{13}C-NMR Spectra of **28B** and **29B**

shift difference between C5 and C3 carbons is generally smaller than that between respective C3 and C5 carbons in 1,3-isomer,[23] i.e. $|\Delta\delta(C5–C3)_{1,5\text{-isomer}}| < |\Delta\delta(C3–C5)_{1,3\text{-isomer}}|$.

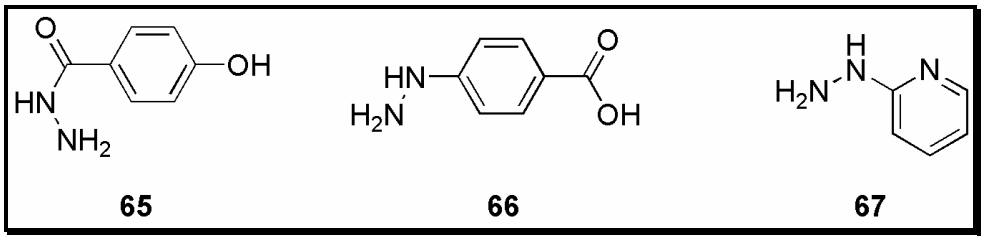
Subsequently, the reaction of 3-ferrocenylpropynal (**59**) and hydrazine dihydrochloride (**60C**) was examined. The reaction mixture was refluxed for 8 h in dioxane at 100 ^{o}C (condition A) and in MeOH for 5 h at 65^{o} C (condition B). Under both conditions, the reaction led to formation of a pyrazole derivative, which was tentatively identified as 5-ferrocenylpyrazole (**28C**). It is noteworthy to mention that owing to annular tautomerism, pyrazoles can exist in two tautomeric forms such as **28C** and **29C**.[60] Proton transfer in pyrazoles is a formal [1,5]-hydrogen shift and the barriers for such processes in both solid state and solution are about 10–14 kcal/mol.[60c] As we noted previously,[23] we were unable to get a well-resolved ^{13}C-NMR spectrum from this compound at both 25 and -15 ^{o}C to determine its tautomeric identity. In fact, pyrazole **28C** is a known compound,[61] but specific spectroscopic data (such as ^{13}C-NMR data) to distinguish it from its tautomer **29C** has not been reported. At present, our efforts to differentiate these tautomers spectroscopically from each other have been failed.

Importantly, in a previous study,[23] the relative energies of pyrazoles **28C** and **29C** was calculated at the density functional theory (DFT) level (B3LYP/6-31G*) and it was found that **29C** is more stable than **28C** by 0.3 kcal/mol. Note that, in gas phase (DFT calculations), **29C** is the more stable while, in solution and solid state, it might correspond to a metastable structure, which requires further study. As shown by Elguero and co-workers,[60d] pyrazoles can exist in different tautomeric forms depending upon their physical phase or state. For instance, in gas phase and solution, 3-phenylpyrazole is more stable than its tautomer, 5-phenylpyrazole. However, in solid state, crystals of 3-phenylpyrazole evolved to be 5-phenylpyrazole.[60d]

Finally, the reaction between 3-ferrocenylpropynal (**59**) and (2-hydroxyethyl)-hydrazinium dichloride (**60D**)[59] led to formation of 2-(5-ferrocenylpyrazol-1-

yl)ethanol (**28D**) and 2-(3-ferrocenylpyrazol-1-yl)ethanol (**29D**) in varying yields under both conditions (Table 3). Interestingly, in condition A, pyrazole **29D** was obtained as the major product of the reaction while, in condition B, pyrazole **28D** was the major one.

After the reactions between 3-ferrocenylpropynal (**59**) and hydrazinium salts **60A-D,** we examined the reactions of 3-ferrocenylpropynal (**59**) with 4-hydroxy-benzhydrazide (**65**), 4-hydrazinobenzoic acid (**66**), 2-pyridiniohydrazinium dichloride (**67**), the structures of which are given in Figure 27. Unfortunately, the reactions carried out with these hydrazine derivatives did not afford the corresponding pyrazole derivatives or they produced the expected pyrazoles in very low yields, the isolation and characterization of which were not possible.



65 **66** **67**

Figure 27. Structures of some hydrazine derivatives.

As can be concluded from the results in Table 3, in refluxing dioxane (condition A), pyrazole derivatives were obtained in relatively low yields. However, refluxing methanol (Condition B) was found to shorten the reaction time and gave the higher yields of pyrazoles. In the latter case, however, mostly a mixture of 1,5- and 1,3-pyrazole derivatives was obtained (Table 3).

2.2 Synthesis of phenyl-substituted pyrazoles

2.2.1 Synthesis of 3-phenylpropynal

Phenyl acetylene (ethynylbenzene) (**68**) was first treated with *n*-BuLi in THF at –40 °C under argon. After the addition of DMF, the resulting mixture was allowed to come to room temperature and then was poured into vigorously stirred biphasic solution, prepared from a 10% aq. solution of KH_2PO_4 and MTBE cooled over ice, to afford 3-phenylpropynal (**69**), as depicted in Figure 28.[62]

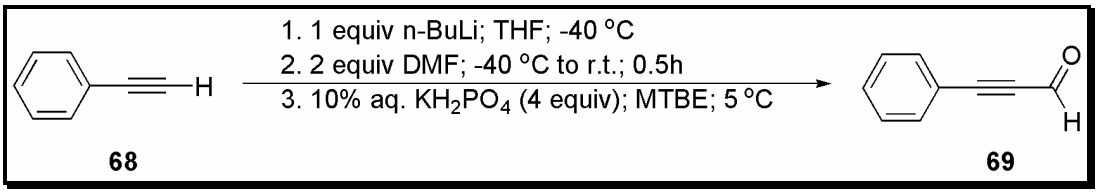
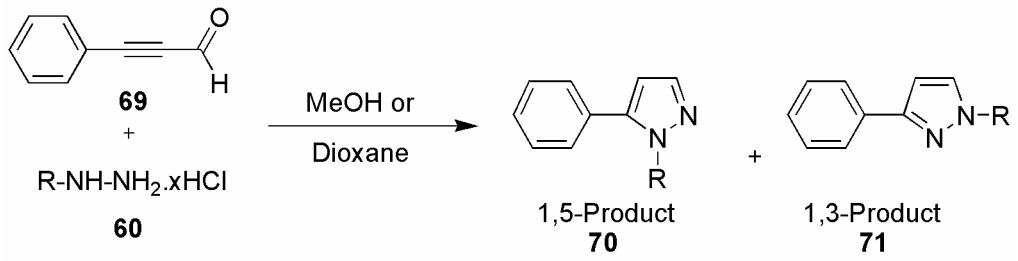


Figure 28. Synthesis of 3-phenylpropynal (**68**).

2.2.2 Scope and limitations

In the second phase of the study, we investigated the reactions of 3-phenylpropynal (**69**) with the hydrazinium salts (**60**) by using the same conditions. The results are collected in Table 4.

Table 4. Reactions of 3-phenylpropynal (**59**) with hydrazinium salts (**60**).



Entry[a]	R	x	Products (isolated yields, %)	
			Condition A[b]	Condition B[c]
A	$-CH_2-C_6H_5$	2	**70A** (22) + **71A** (7)	**70A** (27) + **71A** (11)
B	$-C_6H_5$	1	*d*	**70B** (20)
C	-H	2	**71C** (66)	**71C** (74)
D	$-CH_2-CH_2-OH$	2	**70D** (24)	**70D** (10) + **71D** (7)

[a]Entry Letters define R group for compounds **60**, **70** and **71**.

[b]Condition A: dioxane, 100 ^oC, 8h.

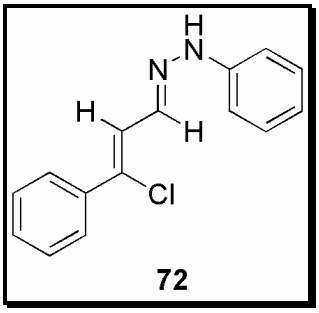
[c]Condition B: CH_3OH, 65 ^oC, 5h.

[d]No any pyrazole product was obtained.

Firstly, the reaction of 3-phenylpropynal (**69**) with benzylhydrazine dihydrochloride (**60A**) was examined. In both conditions, isomeric pyrazole derivatives were obtained. The reaction in condition B afforded 1,5- and 1,3-pyrazole products **70A** and **71A** in 27 and 11% yields, respectively. Similarly, in condition A, the same reaction yielded 1,5- and 1,3-pyrazoles **70A** and **71A** in 22 and 7% yields, respectively. In both conditions, 1,5-isomer **70A** formed as the major product of the

reaction. It should be noted that this product was previously synthesized by others with 24% yield.[63]

Next, the reaction of 3-phenylpropynal (**69**) with phenylhydrazine dihydrochloride (**60B**) was carried out. In refluxing MeOH (condition A), only 1,5- diphenylpyrazole was isolated in 20% yield (Table 4). However, in refluxing dioxane (condition B), no any pyrazole derivatives were obtained. Instead, the reaction produced *N*-(3-chloro-3-phenylallylidene)-*N*'-phenylhydrazine (**72**), the structure of which is shown in Figure 29. Possibly, during the course of the reaction, HCl is added to the alkyne functionality of the starting propargyl aldehyde **69B**, then corresponding hydrazone derivative **72** forms. At present, the reason for this is not fully clear.



72

Figure 29. Structure of compound (*N*-(3-chloro-3-phenylallylidene)-*N*'-phenyl-hydrazine, **72**) obtained from the reaction of 3-phenylpropynal (**69**) with phenylhydrazine dihydrochloride (**60B**).

On the other hand, the reaction 3-phenylpropynal (**69**) with hydrazine dihydrochloride (**60C**) afforded 1,3-product **71C** as a single product of the reaction in both conditions. In dioxane, it formed in 66% yield while, in MeOH, it was obtained in 74% yield, which has been the highest yield observed in the reactions of 3-phenylpropynal (**69**) with hydrazine salts (**60**). It should be mentioned that 1,3-tautomer **71C** is more stable than 1,5-isomer **70C** by 2.0 kcal/mol in solution (NMR)

and in the gas phase (ab initio calculations).[60d] However, in the solid state (C-CPMAS-NMR), the chemical shifts correspond to the 1,5-tautomer **70C.**[60d]

Finally, the reaction 3-phenylpropynal (**69**) with (2-hydroxyethyl)-hydrazinium dichloride (**60D**)[59] was examined (Table 4). In condition A, only 1,5-product **70D** was obtained in 24% yield. However, in condition B, a mixture of 1,5- and 1,3-pyrazole isomers **70D** and **71D** was isolated from the reaction. Full separation of these isomers from each other was not successful because their polarity was too close to each other.

2.3 X-Ray single crystal diffraction analysis

The structures of 1-benzyl-5-ferrocenylpyrazole (**28A**) 1-phenyl-5-ferrocenyl-pyrazole (**28B**), 1-(2-hydroxy-ethyl)-3-ferrocenylpyrazole (**29D**) were also identified by X-ray diffraction analysis. ORTEP diagrams of **28A**, **28B** and **29D** are shown in Figures 30, 31 and 32, respectively. X-Ray crystallographic data for them are given in Table 5.

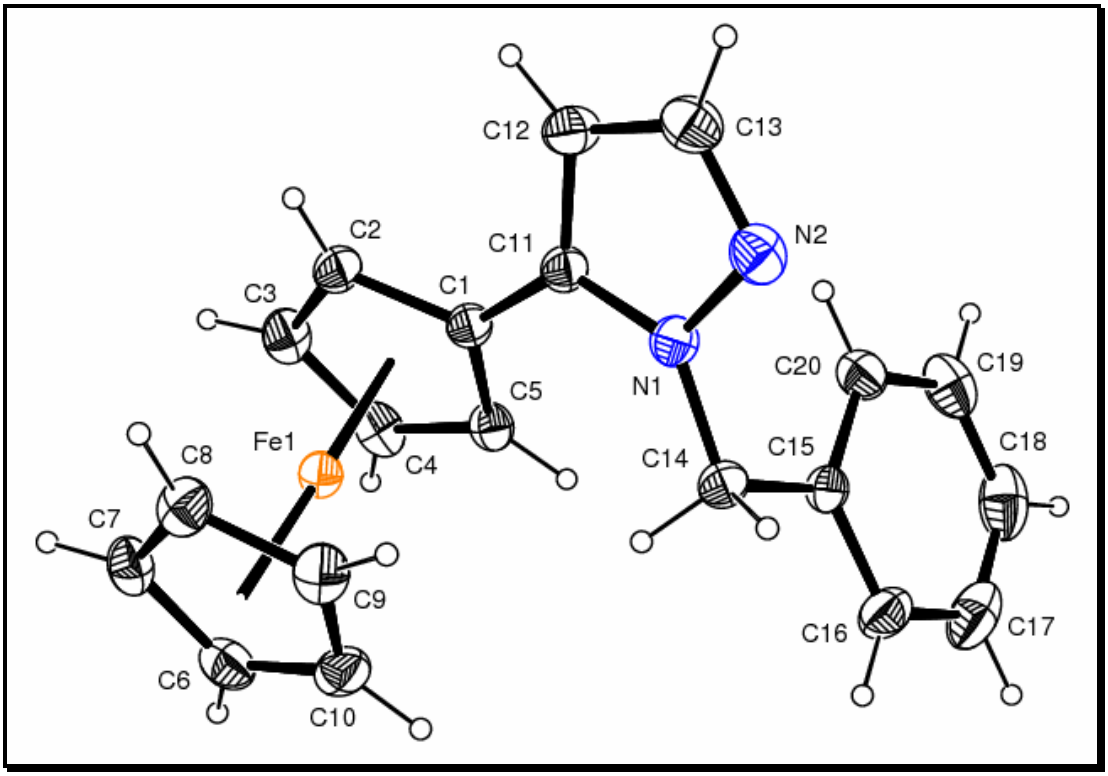


Figure 30. ORTEP diagram of 1-benzyl-5-ferrocenylpyrazole (**28A**). Ellipsoids are drawn at 20% probability**.**

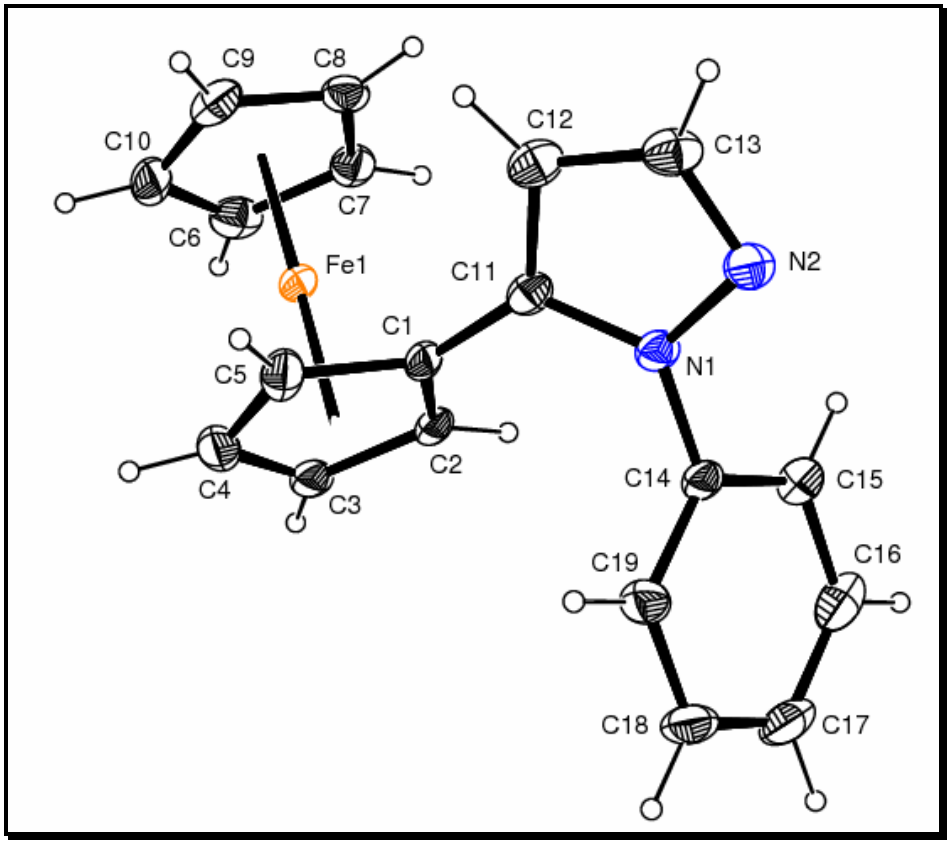


Figure 31. ORTEP diagram of 1-phenyl-5-ferrocenylpyrazole (**28B**), Ellipsoids are drawn at 20% probability.

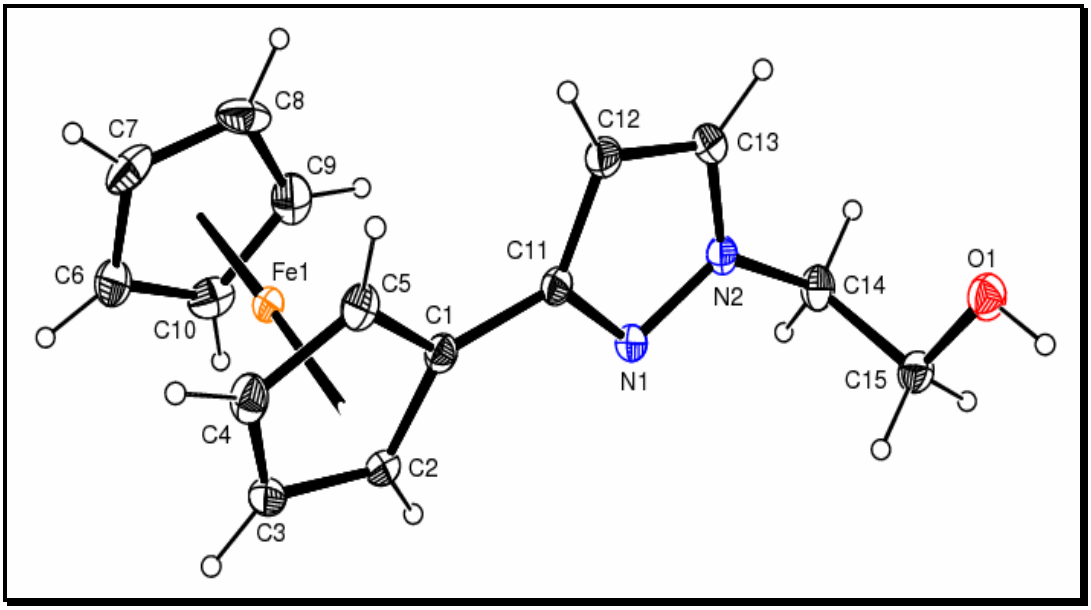


Figure 32. ORTEP diagram of 1-(2-hydroxy-ethyl)-3-ferrocenylpyrazole (**29D**). Ellipsoids are drawn at 20% probability

Table 5. Crystallographic data and structure refinement parameters for **28A**, **28B** and **29D**.

	28A	**28B**	**29D**
Empirical formula	$C_{20}H_{18}FeN_2$	$C_{19}H_{16}FeN_2$	$C_{15}H_{16}FeN_2O$
Formula weight	342.21	328.19	296.15
Crystal size (mm)	0.640 x 0.570 x 0.440	0.470 x 0.380 x 0.260	0.780 x 0.423 x 0.210
Temperature (K)	293(2)	293(2)	296(2)
Crystal system	Triclinic	Orthorhombic	Monoclinic
Space group	P -1	P c a 21	P 21/c
a (Å)	9.2923(5)	21.999(2)	9.3038(17)
b (Å)	10.7911(6)	5.9827(6)	14.0340(3)
c (Å)	16.9299(9)	11.4051(9)	10.6563(16)
α (°)	75.493(4)	90.000(0)	90.000(0)
β (°)	89.605(4)	90.000(0)	110.482(13)
γ (°)	75.870(4)	90.000(0)	90.000(0)
V (Å^3)	1591.12(15)	1501.1(2)	1303.4(4)
Z	4	4	4
D_x (g cm^{-3})	1.429	1.452	1.509
μ (Mo K_α) (mm^{-1})	0.948	1.001	1.149
Radiation/wavelength (Å)	Mo K_α/0.71073	Mo K_α/0.71073	Mo K_α/0.71073
θ_{max} (°)	27.90	27.06	26.00
Index range (*hkl*)	-12/12, -14/14, -22/22	-22/27, -7/7, -14/14	-11/11, -17/17, -13/13
Reflections measured	30561	7738	15701
Independent reflections (R_{int})	7544	3217	2563
Reflections with $I > 2\sigma(I)$	6232	2645	2270
Number of parameters	415	199	172
Number of restraints	0	1	0
$R[F^2 > 2\sigma(F^2)]$	0.028	0.0399	0.0251
$wR(F^2)$	0.0759	0.1236	0.0660
Goodness-of-fit (F^2)	1.050	1.201	1.046
Max, min $\Delta\rho$ (e/Å^3)	0.198, -0.351	0.882, -0.750	0.217, -0.268

2.4 Mechanism

Three mechanistic pathways are possible for the synthesis of pyrazoles from acetylenic aldehydes and hydrazinium salts, as shown in Figure 33. Paths 1 and 2 start with Michael addition to acetylenic carbon while, in path 3, primary NH_2 group attacks at the carbonyl. The resultant product of path 1 is 1-alkyl/aryl-3-ferrocenyl/phenyl-substituted pyrazole while those of paths 2 and 3 are 1-alkyl/aryl-5-ferrocenyl/phenyl-substituted pyrazole (Figure 33).

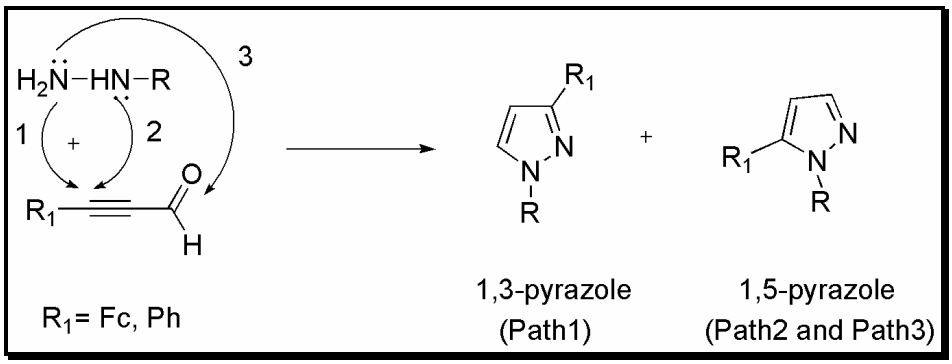


Figure 33. Proposed mechanistic paths for the synthesis of pyrazole derivatives

Path 1. In the first step, Michael addition of NH_2 group of hydrazine derivative occurs at the 3-ferrocenyl/phenyl-substituted propynal (**59/69**) (Figure 34). After H migration, keto-enol tautomerization happens. Then, the attack of NHR group at the carbonyl group forms 5-membered ring intermediate **76**, in which hydrogen migration gives **77**. The proton capture followed by the removal of water generates 1,3- pyrazole product **29/71** (Figure 34).

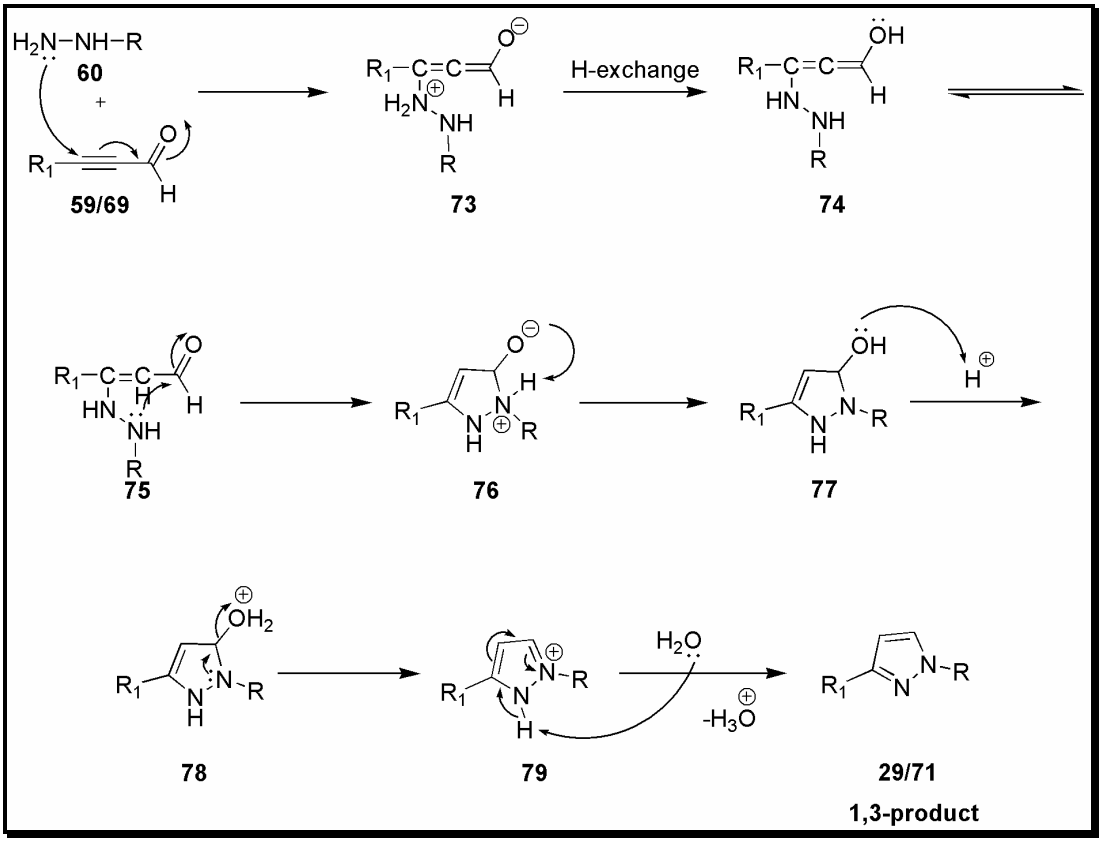


Figure 34. The proposed mechanism for the formation of 1,3-pyrazole derivatives through pathway 1.

Path 2. Michael addition of secondary NHR group of hydrazine to acetylenic aldehyde takes place first to produce intermediate **80** (Figure 35). After hydrogen migration followed by keto-enol tautomerisation, the condensation of primary NH_2 group with carbonyl initiates the cyclization to afford 5-membered ring intermediate **83**, which, upon hydrogen exchange, generates **84**. Finally, the removal of water from **84** through the intermediates **85** and **86** produces 1,5-pyrazole product **28/70** (Figure 35).

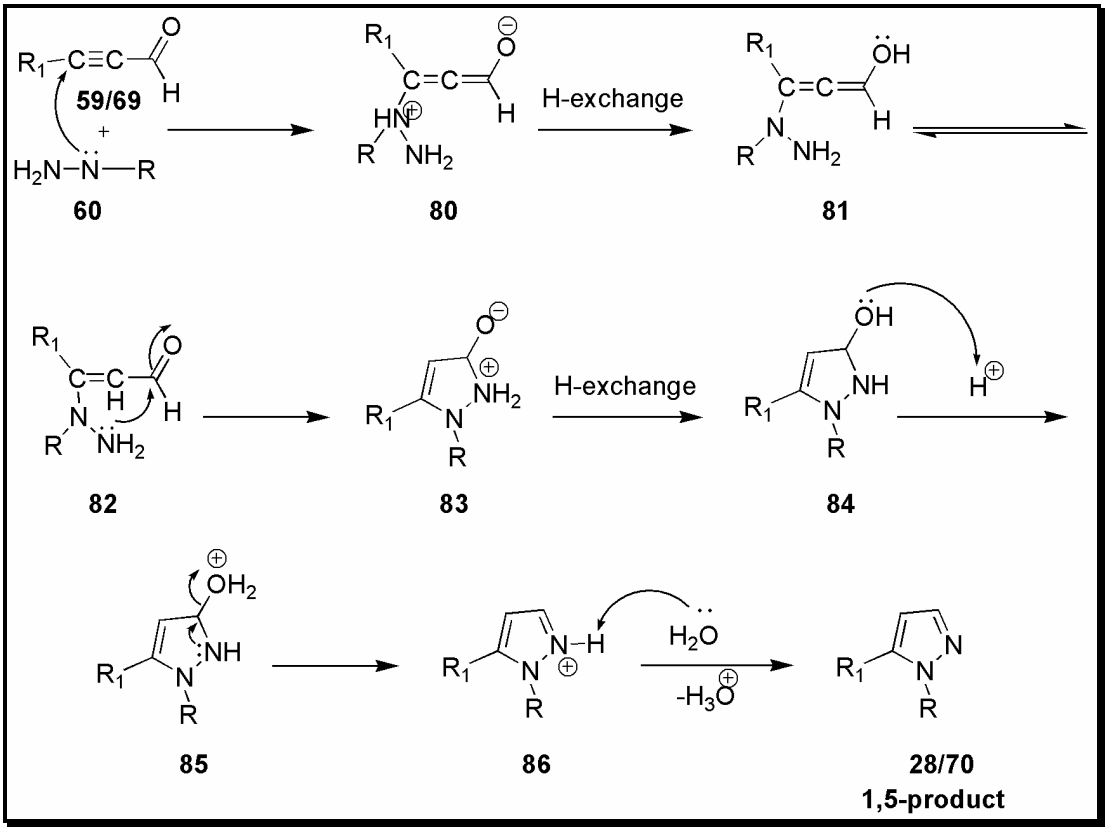


Figure 35. The proposed mechanism for the formation of 1,5-pyrazole derivatives through pathway 2.

Path 3. The condensation of primary amino group of hydrazine with carbonyl group of acetylenic aldehyde leads to formation of hydrazone **91** with removal of water through the intermediates **87**-**90** (Figure 36). Then, addition of secondary NHR group to alkyne functionality produces 5-membered ring intermediates **92**, which, upon hydrogen exchange, gives 1,5-pyrazole product **28/70**.

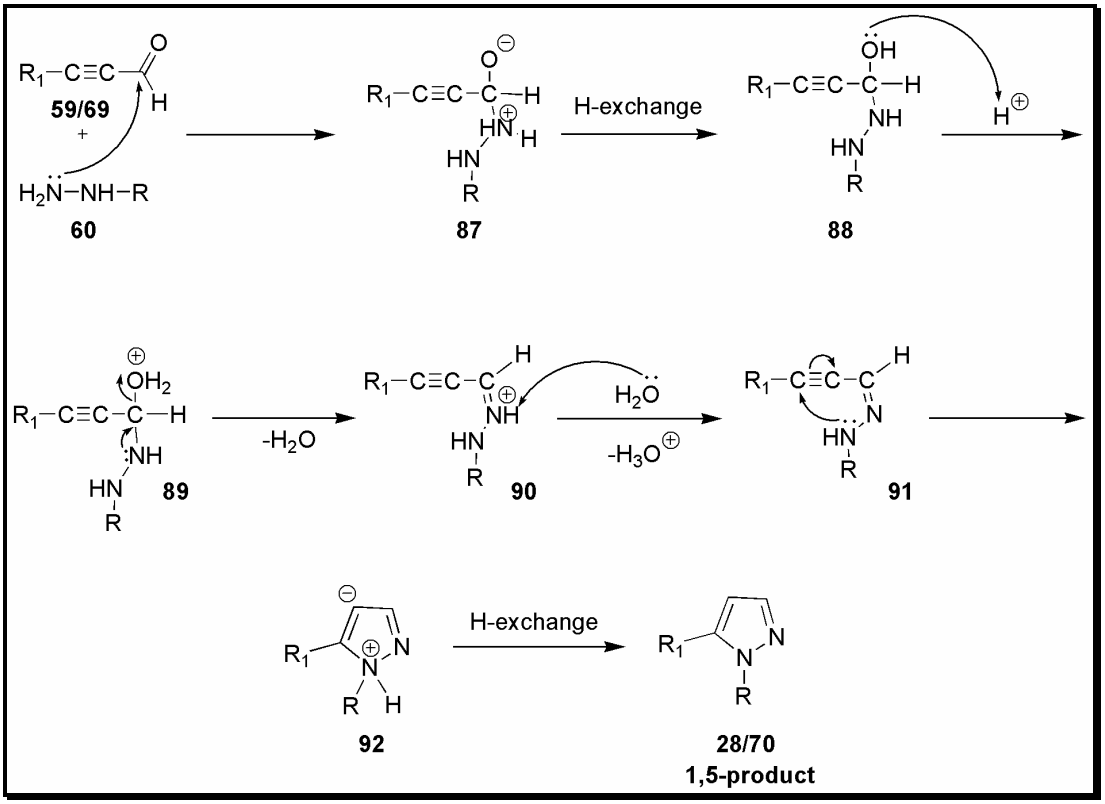


Figure 36. The proposed mechanism for the formation of 1,5-pyrazole derivatives through pathway 3.

CHAPTER 3

CONCLUSION

In summary, we have investigated the reactions of 3-ferrocenylpropynal (**59**) and 3-phenylpropynal (**69**) with hydrazinium salts (**60**) to synthesize the corresponding pyrazole derivatives. Pyrazoles are among the most commonly studied compounds but ferrocenyl-substituted pyrazoles are not often found in literature. In this regard, the reactions of acetylenic ketones with hydrazines have been frequently used to synthesize pyrazole derivatives, but analogous reactions between acetylenic aldehydes and hydrazines are almost unknown since, to the best of our knowledge, there is only one example of such reaction.

In the first phase of the study, the starting materials of the reactions, i.e. acetylenic aldehydes, were prepared according to well known formylation procedures.

Initially, the reactions between 3-ferrocenylpropynal and hydrazinium salts were examined. The reactions were carried out in refluxing dioxane at 100 ^{o}C for 8 h (condition A) or in refluxing methanol for 5 h at 65 ^{o}C (condition B). These reactions afforded 1-alkyl/aryl-5-ferrocenylpyrazoles (1,5-isomer) and/or 1-alkyl/aryl-3-ferrocenylpyrazoles (1,3-isomer). In most cases, 1,5-pyrazole isomers have resulted from these reactions as the single or the major products. In methanol, the reactions gives higher yields of products and go to completion in shorter times. The structures of 1-benzyl-5-ferrocenylpyrazole (**28A**), 1-phenyl-5-ferrocenyl-pyrazole (**28B**) and 1-(2-hydroxy-ethyl)-3-ferrocenylpyrazole (**29D**) were also identified by X-ray single crystal analysis. The regioselectivity of the reactions is mainly governed by the nature of the substituents in hydrazine derivative.

Then, the reactions between 3-phenylpropynal (**69**) and hydrazinium salts (**60**) were investigated. Similarly, from these reactions, 1-alkyl/aryl-5-phenylpyrazoles (1,5-isomer) and/or 1-alkyl/aryl-3-phenylpyrazoles (1,3-isomer) were obtained.

In conclusion, we have demonstrated that, when treated with hydrazinium salts, acetylenic aldehydes, i.e. alkynals, afford pyrazoles, as in the case of acetylenic ketones or alkynones. The synthesized pyrazoles are expected to have some potential biological activities, which will be tested by collaborative work. Additionally, these studies will be of value in the development of new synthetic pathways for the synthesis of new pyrazole derivatives.

CHAPTER 4

EXPERIMENTAL

General. Nuclear Magnetic Resonance (^{1}H and ^{13}C) spectra were recorded on a Brucker Spectrospin Avance DPX400 Ultrashield (400 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) 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), br s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet). DEPT ^{13}C-NMR information is given in parenthesis as C, CH, CH_2 and CH_3. Infrared spectra were recorded on a Varian 5000 FT-IR spectrometer. Band positions are reported in reciprocal centimeters (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 an Agilent 1100 Series LC MSD spectrometer, using electrospray ionization (ESI) (Fragmentor 100 eV, positive polarity). Elemental analyses were carried out on a LECO CHNS-932 instrument. 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 proportion 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. Diethyl ether, THF and dioxane were distilled from sodium/benzophenone kettle. The inert atmosphere is created by slight positive pressure (ca. 0.1 psi) of argon.

4.1 Synthesis of acetylferrocene (52)

Ferrocene (**49**) (10 g, 54 mmol) was dissolved with stirring in dry dichloromethane (45 mL) under argon. To the resultant dark orange/red solution, acetyl chloride (4.6 mL, 59 mmol) was added and then flask was immersed in an ice water bath at 0-5 ^{o}C. Anhydrous aluminium chloride (7,2 g, 54 mmol) was added in approximately 10 portions to the reaction mixture, allowing approximately 2 min between each addition for heat exchange. After stirring the reaction mixture at room temperature for 2 h, it was recooled by placing it in a fresh ice-water bath. The reaction mixture was hydrolyzed by the slow addition of 4 x 2.5 mL portions of cold water. Then a further 15 mL of cold water was added more rapidly. The mixture was extracted with CH_2Cl_2, and organic extracts were washed with 5% sodium hydroxide solution followed by saturated aqueous sodium chloride solution. Then organic phase was dried over magnesium sulfate. Final purification was achieved by flash chromatography on silica gel using hexane:ethyl acetate (9:1) as the eluent. The product was isolated as an orange fraction with 80% (1, 96 g) yield and assigned as acetylferrocene (**52**)**.**

52: ^{1}H-NMR ($CDCl_3$): δ 4.60 (s, 2H), 4.32 (s, 2H), 4.02 (s, 5H), 2.17 (s, 3H); ^{13}C-NMR ($CDCl_3$): δ 79.2 (C), 72.3 (CH), 69.8 (CH), 69.5 (CH), 27.3 (CH_3). The spectral data is in agreement with those reported previously for this compound.[56]

4.2 Synthesis of (2-formyl-1-chlorovinyl)ferrocene (27)

Acetylferrocene (**52**) (2.3 g, 10 mmol) and DMF (2.5 mL, 32 mmol) were added into a two-necked, round-bottom flask equipped with a dropping funnel, and cooled to 0 °C by means of an ice bath under argon. The brown reaction mixture was stirred well for several minutes. Separately, into a small round-bottom flask, DMF (2.5 mL, 32 mmol) was added and cooled in crushed ice and agitated by hand during the cautious addition of phosphorus oxychloride (2.5 mL, 27 mmol). The resulting viscous complex was transferred to the dropping funnel and added to the reaction mixture of acetylferrocene (**52**) and DMF dropwise over 30 min. After the completion of addition, the mixture was stirred at 0 °C for 2 h during which time the color of the

reaction mixture changed from dark brown to olive and ultimately to deep blue. Then, a 7.5 mL portion of diethyl ether was added, and the viscous mixture was stirred vigorously for several minutes. With continued ice cooling, sodium acetate trihydrate (11.6 g, 85 mmol) was cautiously added to the reaction mixture in one portion followed by cautious addition of 1 mL of water with vigorous stirring. The ice bath was removed whereupon the organic layer undergone a striking color change from colorless to ruby red indicating the formation of the formyl derivative. After 1 h, an additional 1 mL of ether was added, and stirring was continued for 3 h at room temperature to ensure complete quenching. The reaction mixture was extracted with ether, and the combined organic layers were washed with saturated aqueous sodium bicarbonate solution. The organic phase was dried over magnesium sulfate. Removing solvent using a rotary evaporator afforded (2-formyl-1-chlorovinyl)ferrocene (**27**) with 93% yield (2.5 g) as deep purple crystals after drying under high vacuum.

27: ^{1}H-NMR ($CDCl_3$): δ 10.06 (d, 1H, *J* = 7.1 Hz), 6.38 (d, 1H, *J* = 7.1 Hz), 4.73 (t, 2H, *J* = 1.68 Hz), 4.54 (t, 2H, *J* = 1.68 Hz), 4.22 (s, 5H). The spectral data is in agreement with those reported previously for this compound.[57]

4.3 Synthesis of ethynylferrocene (**64**)

To (2-formyl-1-chlorovinyl)ferrocene (**27**) (2.6 g, 9.5 mmol), anhydrous 1,4-dioxane (30 mL) was added after flushing it with argon. The reaction mixture was heated to reflux and after 5 min at reflux, a boiling 1 N solution of NaOH (25 mL) was added as rapidly as possible in one portion, and the mixture was heated at reflux for another 25 min. Then, the reaction mixture was allowed to cool to room temperature and it was cautiously poured into ice and neutralized with 1 N HCl. The aqueous mixture was extracted with hexane (5 x 10 mL). Combined organic extracts were washed with 10 mL portions of saturated aqueous sodium bicarbonate solution and water, respectively. The organic phase was dried over $MgSO_4$, and the solvent was removed on a rotary evaporator affording an orange residue of crude ethynylferrocene (**64**). The crude product was purified by flash chromatography on silica gel with elution by

hexane giving 1.48-1.50 g (74-75%) of pure ethynylferrocene which crystallized as an orange solid.

64: ^{1}H-NMR ($CDCl_3$): δ 4.46 (s, 2H), 4.21 (s, 5H), 4.19 (s, 2H), 2.71 (s, 1H). The spectral data is in agreement with those reported previously for this compound.[57]

4.4 General Procedure I. Synthesis of acetylenic aldehydes (59/69)

Corresponding alkyne (50 mmol) was dissolved in dry THF (12.5 mL) and the solution was cooled to - 40 ^{o}C under argon. *n*-BuLi (1,53 M in hexane, 32.7 mL, 50 mmol) was added dropwise over 2 min maintaining the temperature between -35 ^{o}C and - 40 ^{o}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 stirred for 30 min. The reaction mixture was poured into a vigorously stirred biphasic solution prepared from a %10 aq. solution of KH_2PO_4 (270 mL, 200 mmol) and MTBE (250 mL) cooled over ice. Layers are separated and organic extract was washed with water (2 x 200mL). Combined aqueous layers were back extracted with MTBE (150 mL). Combined organic layers were dried over $MgSO_4$, filtered and crude product was purified by flash chromatography on silica gel with elution by hexane:ethylacetate.

4.4.1 Synthesis of 3-ferrocenylpropynal (59)

General Procedure I was followed by using ethynylferrocene (**64**) (645 mg, 3.06 mmol), *n*-BuLi (1.53 M in hexane, 2 mL, 3.06 mmol) and anhydrous DMF (0.486 mL, 6.12 mmol). After the purification of crude product by flash chromatography on silica gel with elution by a 19:1 hexane/ethyl acetate solution, 3-ferrocenylpropynal (**59**) was isolated as a red fraction with 82% yield (600 mg).

59: ^{1}H-NMR ($CDCl_3$): δ 9.27 (s, 1H), 4.60 (s, 2H), 4.41 (s, 2H), 4.25 (s, 5H). The spectral data is in agreement with those reported previously for this compound.[57,64]

4.4.2 Synthesis 3-phenylpropynal (69)

General Procedure I was followed by using ethynylbenzene (**68**) (2.2 mL,20 mmol), n-BuLi (1.6 M in hexane, 12.2 mL, 20mmol) and anhydrous DMF (3.08 mL, 40 mmol). After the purification of crude product by flash chromatography on silica gel with elution by a 19:1 hexane/ethyl acetate solution, 3-phenylpropynal (**69**) was isolated as a red fraction with 97% yield (2.47 g).

22: ^{1}H-NMR ($CDCl_3$): δ 9.45 (s, 1H), 7.52–7.64 (m, 2H), 7.44–7.49 (m, 1H), 7.36–7.40 (m, 2H); ^{13}C-NMR ($CDCl_3$): δ 176.9 (CH), 133.4 (CH), 131.4 (CH), 128.8 (CH), 119.6 (C), 95.3 (C), 88.9 (C).The spectral data is in agreement with those reported previously for this compound.[65]

4.5 General Procedure 2. Synthesis of ferrocenyl-substituted pyrazoles 28A-D and/or 29A-D (Table 3)

3-Ferrocenylpropynal (**59**) (0.420 mmol) was placed in a round bottom flask equipped with condenser and the system was flushed with argon. Then, it was dissolved in 10 mL MeOH (condition A) or 10 mL dioxane (condition B), and corresponding hydrazinium salt (**60**) was added. The mixture was heated at reflux for 5 h at 65 ^{o}C (condition A) or 8 h at 100 ^{o}C (condition B). After the reaction was complete, the mixture was cooled to room temperature and the solvent was removed on a rotary evaporator. The obtained residue was washed with water (20 mL) and extracted with chloroform (3 x 30 mL). After drying over $MgSO_4$, the solvent was removed on a rotary evaporator. This mixture was purified by flash chromatography on silica gel using hexane/ethyl acetate as the eluent.

4.5.1 Reaction of 3-ferrocenylpropynal (59) with benzylhydrazine dihydrochloride (60A) (Table 3, Entry A)

General Procedure 2 was followed by using 3-ferrocenylpropynal (**59**) (100 mg, 0.420 mmol) and benzylhydrazine dihydrochloride (**60A**) (95.09 mg, 0.630 mmol). After chromatographic purification, two orange colored fractions were collected.

First fraction (R_f = 0.17 in 9:1 hexane/ethyl acetate) was assigned as 1-benzyl-5-ferrocenylpyrazole (**28A**) (90 mg, 63% yield for condition A and 66 mg, 46% yield for condition B). Second fraction fraction (R_f = 0.15 in 9:1 hexane/ethyl acetate) was identified as 1-benzyl-3-ferrocenylpyrazole (**29A**) (44 mg, 30% yield for condition B).

28A: ^{1}H-NMR ($CDCl_3$): δ 7.56 (s, 1H), 7.36 (t, 2H, *J* = 7.20 Hz), 7.29 (t, 1H, *J* = 7.20 Hz), 7.08 (d, 2H, *J* = 7.20 Hz), 6.44 (s, 1H), 5.54 (s, 2H), 4.39 (s, 2H), 4.28 (s, 2H), 4.12 (s, 5H); ^{13}C-NMR ($CDCl_3$): δ 141.4 (C), 139.1 (C), 137.9 (CH), 128.7 (CH), 127.4 (CH), 126.3 (CH), 106.0 (CH), 74.9 (C), 69.6 (CH), 68.8 (CH), 68.5 (CH), 53.3 (CH_2); IR (neat): 3142, 3109, 2950 , 2896 , 1556 , 1502, 1409, 1321, 1231, 1071, 873, 825, 765 cm^{-1}. The spectral data is in agreement with those reported previously for this compound.[23]

29A: ^{1}H-NMR ($CDCl_3$): δ 7.40-7.31 (m, 3H), 7.28 (s, 1H), 7.23 (d, 2H, *J* = 7.2 Hz), 6.32 (s, 1H,), 5.34 (s, 2H), 4.77 (s, 2H), 4.34 (s, 2H), 4.14 (s, 5H; ^{13}C-NMR ($CDCl_3$): δ 150.8 (C), 137.0 (C), 130.1 (CH), 128.7 (CH), 127.9 (CH), 127.5 (CH), 103.7 (CH), 79.0 (C), 69.6 (CH), 68.5 (CH), 66.7 (CH), 55.8 (CH_2); IR (neat): 3108 , 3079, 3030, 2941, 1556, 1497, 1435, 1404, 1303, 1230, 1102, 1060 , 1000, 874, 833, 813, 761, 716 cm^{-1}; MS (EI): 343.1 $(M+H)^+$, 252.0; Anal. Calc. for $C_{20}H_{18}FeN_2$ with 0.263 mol $CHCl_3$ incorporation: C, 65.14; H, 4.93; N, 7.50. Found: C, 65.14; H, 5.62; N, 7.50%.[66]

4.5.2 Reaction of 3-ferrocenylpropynal (59) with phenylhydrazine hydrochloride (60B) (Table 3, Entry B)

General Procedure 2 was followed by using 3-ferrocenylpropynal (**59**) (100 mg, 0.420 mmol) and phenylhydrazine hydrochloride (**60B**) (90.69 mg, 0.630 mmol). After chromatographic purification, two fractions were collected. First fraction in orange color (R_f = 0.21 in 9:1 hexane/ethyl acetate) was assigned as 1-phenyl-5-ferrocenylpyrazole (**28B**) (62 mg, 45% yield for condition A and 97 mg, 70% yield for condition B). Second fraction in purple color (R_f = 0.43 in 9:1 hexane/ethyl

acetate) was identified as 1-phenyl-3-ferrocenylpyrazole (**29B**) (20 mg, 14% yield for condition A and 28 mg, 20% yield for condition A).

28B: ^{1}H-NMR ($CDCl_3$): δ 7.66 (d, 1H, *J* = 1.31 Hz), 7.40 (m, 5H), 6.55 (d, 1H, *J* = 1.31 Hz), 4.21 (s, 2H), 4.19 (s, 2H), 4.10 (s, 5H); ^{13}C-NMR ($CDCl_3$): δ 141.5 (C), 140.4 (C), 140.0 (CH), 128.8 (CH), 128.0 (CH), 126.1 (CH), 106.8 (CH), 75.1 (C), 69.9 (CH), 68.8 (CH), 68.6 (CH); IR (neat): 3089, 3036, 1665, 1597, 1557, 1498, 1402, 1259, 1145, 971, 923, 870 cm^{-1}. The spectral data is in agreement with those reported previously for this compound.[23]

29B: ^{1}H-NMR ($CDCl_3$): δ 7.84 (d, 1H, *J* = 2.4 Hz), 7.71 (d, 2H, *J* = 7.8 Hz), 7.44 (t, 2H, *J* = 7.8 Hz), 7.25 (t, 1H, *J* = 7.8 Hz), 6.48 (d, 1H, *J* = 2.4 Hz), 4.76 (s, 2H), 4.29 (s, 2H), 4.07 (s, 5H); ^{13}C-NMR ($CDCl_3$): δ 152.5 (C), 140.3 (C), 129.4 (CH), 127.3 (CH), 126.0 (CH), 118.9 (CH), 105.6 (CH), 78.4 (C), 69.8 (CH), 68.9 (CH), 67.0 (CH); IR (neat): 3090, 3030, 2959, 2865, 1681, 1649, 1598, 1557, 1506, 1458, 1257, 1129, 1043, 868, 820 cm^{-1}. The spectral data is in agreement with those reported previously for this compound.[23]

4.5.3 Reaction of 3-ferrocenylpropynal (59) with hydrazine dihydrochloride (60C) (Table 3, Entry C)

General Procedure 2 was followed by using 3-ferrocenylpropynal (**59**) (100 mg, 0.420 mmol) and hydrazine dihydrochloride (**60C**) (66 mg, 0.630 mmol). After chromatographic purification, a yellow fraction (R_f = 0.094 in 4:1 hexane/ethyl acetate) was collected and tentatively assigned as 5-ferrocenyl-1-*H*-pyrazole (**28C**) (48 mg, 45% yield for condition A and 75 mg, 70% yield for condition A).

28C: ^{1}H-NMR ($CDCl_3$): δ 7.52 (s, 1H), 6.33 (s, 1H), 4.58 (s, 2H), 4.28 (s, 2H), 4.04 (s, 5H), NH peak was not observed due to H/D exchange and/or tautomerism; IR (neat): 3115, 3026, 2875, 2840, 2816, 1598, 1565, 1463, 1415, 1289, 1102, 1053, 999, 937, 810, 764 cm^{-1}. The spectral data is in agreement with those reported previously for this compound.[23]

4.5.4 Reaction of 3-ferrocenylpropynal (59) with 2-hydroxyethylhydrazine dihydrochloride (60D) (Table 3, Entry D)

General Procedure 2 was followed by using 3-ferrocenylpropynal (**59**) (100 mg, 0.420 mmol) and 2-hydroxyethylhydrazine dihydrochloride (**60D**) (93.3 mg, 0.63 mmol). After chromatographic purification, two fractions were collected. First fraction in yellow/orange color (R_f = 0.054 in 1:1 hexane/ethyl acetate) was assigned as 1-(2-hydroxy ethyl)-5-ferrocenylpyrazole (**28D**) (7.5 mg, 6% yield for condition A and 38.6 mg, 31% yield for condition B). Second fraction in bright yellow color (R_f = 0.107 in 1:1 hexane/ethyl acetate) was identified as 1-(2-hydroxyethyl)-3-ferrocenylpyrazole (**29D**) (24 mg, 19% yield for condition A and 31 mg, 25% yield for condition B).

28D: ^{1}H-NMR ($CDCl_3$): δ 7.48 (s, 1H), 6.35 (s, 1H), 4.50 (s, 2H), 4.36 (t, 2H, *J* = 4.5 Hz), 4.34 (s, 2H), 4.19 (s, 5H), 4.05 (t, 2H, *J* = 4.5 Hz); ^{13}C-NMR ($CDCl_3$): δ 141.4 (C), 138.7 (CH), 106.0 (CH), 74.9 (C), 69.6 (CH), 68.9 (CH), 68.8 (CH), 61.8 (CH_2), 51.0 (CH_2); IR (neat): 3331, 2965, 2937, 1562, 1460, 1331, 1070, 1043, 824, 800 cm^{-1}. The spectral data is in agreement with those reported previously for this compound.[23]

29D: ^{1}H-NMR ($CDCl_3$): δ 7.27 (s, 1H), 6.20 (s, 1H), 4.61 (s, 2H), 4.21 (s, 2H), 4.14 (t, 2H, J = 4.3 Hz), 4.00 (s, 5H), 3.92 (t, 2H, J = 4.3 Hz); 13C-NMR ($CDCl_3$): δ 151.3 (C), 130.8 (CH), 103.0 (CH), 78.3 (C), 69.4 (CH), 68.3 (CH), 66.6 (CH), 62.1 (CH_2), 53.5 (CH_2); IR (neat): 3229, 3142, 2950, 2869, 1556, 1502, 1408, 1349, 1230, 1067, 824, 764 cm^{-1}. The spectral data is in agreement with those reported previously for this compound.[23]

4.6 General Procedure 3. Synthesis of phenyl-substituted pyrazoles 70A-D and/or 71A-D (Table 4)

3-Phenylpropynal (**69**) (0.769 mmol) was placed in a round bottom flask equipped with condenser and the system was flushed with argon. Then, it was dissolved in 10 mL MeOH (condition A) or in 10 mL dioxane (condition B) and corresponding hydrazinium salt **60** was added. The mixture was heated at reflux for 5 h at 65 ^{o}C

(condition A) or 8 h at 100 ^{o}C (condition B). After the reaction was complete, the mixture was cooled to room temperature and the solvent was removed on a rotary evaporator. The obtained residue was washed with water (20 mL) and extracted with chloroform (3 x 30 mL). After drying over $MgSO_4$, the solvent was removed on a rotary evaporator. This mixture was purified by flash chromatography on silica gel using hexane/ethylacetate as the eluent.

4.6.1 Reaction of 3-phenylpropynal (69) with benzylhydrazine dihydrochloride (60A) (Table 4, Entry A)

General Procedure 3 was followed by using 3-phenylpropynal (**69**) (100 mg, 0.769 mmol) and benzylhydrazine dihydrochloride **60A** (225mg mg, 1.15 mmol). After chromatographic purification, two fractions were collected. First fraction in yellow/orange color (R_f = 0.36 in 4:1 hexane/ethyl acetate) was assigned as 1-benzyl-5-phenylpyrazole (**70A**) (40 mg, 22% yield for condition A and 48.5 mg, 27% yield for condition B). Second fraction in light brown color (R_f = 0.64 in 4:1 hexane/ethyl acetate) was identified as 1-benzyl-3-phenylpyrazole (**71A**) (12.5 mg, 7% yield for condition A and 19 mg, 11% yield for condition B).

70A: ^{1}H-NMR ($CDCl_3$): δ 7.52 (d, 1H, *J* = 0.83 Hz), 7.33-7.12 (m, 8H), 6.96 (d, 2H, *J* = 7.12 Hz), 6.26 (d, 1H, *J* = 0.83 Hz), 5.27 (s, 2H); ^{13}C-NMR ($CDCl_3$): δ 144.1 (C), 139.2 (CH), 137.6 (C), 130.7 (C), 129.1 (CH), 128.7 (CH), 127.7 (CH), 126.9 (CH), 106.5 (CH), 53.2 (CH_2), two aromatic carbons overlap on each other; IR (neat): 3084, 2928, 1724, 1652, 1454, 1403, 1283, 1127, 1071, 728, 697 cm^{-1}.

71A: ^{1}H-NMR ($CDCl_3$): δ 7.74 (d, 2H, *J* = 7.4 Hz), 7.30 (s, 1H, *J* = 1.57 Hz), 7.27-7.21 (m, 6H,), 7.17 (d, 2H, *J* = 7.4 Hz), 6.48 (d, 1H, *J* = 1.57 Hz), 5.27 (s, 2H); ^{13}C-NMR ($CDCl_3$): δ 151.6 (C), 136.6 (C), 133.5 (C), 130.7 (CH), 128.8 (CH), 128.6 (CH), 128.1 (CH), 127.7 (CH), 127.6 (CH), 125.7 (CH), 103.4 (CH), 56.1 (CH_2); IR (neat): 3126, 3061, 2930, 1719, 1638, 1500, 1455, 1354, 1229, 1075, 761, 718.

4.6.2 Reaction of 3-phenylpropynal (69) with phenylhydrazine hydrochloride (60B) (Table 4, Entry B)

General Procedure 3 was followed by using 3-phenylpropynal (**69**) (100 mg, 0.769 mmol) and phenyl hydrazine hydrochloride (**60B**) (166.7 mg, 1.15 mmol). After chromatographic purification, a yellow fraction (R_f = 0.42 in 4:1 hexane/ethyl acetate) was collected and assigned as 1,5-diphenylpyrazole (**70B**) (35 mg, 20% yield for condition B).

70B: ^{1}H-NMR ($CDCl_3$): δ 7.76 (d, 1H, *J* = 1.4 Hz), 7.36-7.32 (m, 8H), 7.28-7.26 (m, 2H,), 6.55 (d, 1H, *J* = 1.4 Hz); ^{13}C-NMR ($CDCl_3$): δ 143.0 (C), 140.3 (CH), 140.2 (C), 130.7 (C), 129.5 (CH), 128.8 (CH), 128.5 (CH), 128.2 (CH), 127.4 (CH), 125.2 (CH), 107.9 (CH); IR (neat): 3059, 2926, 1600, 1499, 1447, 1385, 1129, 1070, 762, 696 cm^{-1}.

4.6.3 Reaction of 3-phenylpropynal (69) with hydrazine dihydrochloride (60C) (Table 4, Entry C)

General Procedure 3 was followed by using 3-phenylpropynal (**69**) (100 mg, 0.769 mmol) and hydrazine dihydrochloride (**60C**) (66 mg, 0.630 mmol). After chromatographic purification, a dirty yellow fraction (R_f = 0.38 in 1:1 hexane/ethyl acetate) was collected and identified as 3-phenyl-1-*H*-pyrazole (**71C**) (72.5 mg, 66% yield for condition A and 82 mg, 74% yield for condition B).

71C: ^{1}H-NMR ($CDCl_3$): δ 12.25 (br s,1H), 7.82 (d, 2H, *J* = 7.7 Hz), 7.63 (d, 1H, *J* = 1.66 Hz), 7.43 (d, 2H, *J* = 7.7 Hz), 7.37 (t, 1H, *J* = 7.2 Hz), 6,65 (d, 1H, *J* = 1.66 Hz); ^{13}C-NMR ($CDCl_3$): δ 149.1 (C), 133.3 (C), 132.2 (CH), 128.8 (CH), 128.1 (CH), 125.9 (CH), 102.7 (C); IR (neat): 3185, 3107, 2926, 1631, 1452, 1093, 958, 758, 688 cm^{-1}. The spectral data is in agreement with those reported previously for this compound.[60d]

4.6.4 Reaction of 3-phenylpropynal (69) with 2-hydroxyethylhydrazine dihydrochloride (60D) (Table 4, Entry D).

General Procedure 3 was followed by using 3-phenylpropynal (**69**) (100 mg, 0.769 mmol) and 2-hydroxyethylhydrazine dihydrochloride (**60D**) (170.8 mg, 1.15 mmol). After chromatographic purification, two fractions were collected. First fraction in light yellow color (R_f = 0.33 in 9:1 ethyl acetate/hexane) was assigned as 1-(2-hydroxyethyl)-5-phenylpyrazole (**70D**) (34.6 mg, 24% yield for condition A and 14.4 mg, 10% yield for condition B). Second fraction in bright yellow color (R_f = 0.33 in 9:1 ethyl acetate/hexane) was identified as 1-(2-hydroxyethyl)-3-phenylpyrazole (**71D**) (9.6 mg, 7% yield for condition B). Note that if compound **71D** was formed, it was obtained as a mixture with its isomer **70D** from flash column chromatography. The efforts to fully separate **71D** from **70D** were not successful.

70D: ^{1}H-NMR ($CDCl_3$): δ 7.48 (d ,1H, *J* = 1.37 Hz), 7.39-7.32 (m, 5H), 6.25 (d, 1H, *J* = 1.37 Hz), 4.15 (t, 2H, *J* = 4.7 Hz), 3.90 (t, 2H, *J* = 4.7 Hz), 3,59 (br s, 1H); ^{13}C-NMR ($CDCl_3$): δ 144.2 (C), 138.9 (CH), 130.3 (C), 129.1 (CH), 128.8 (CH), 127.7 (CH), 106.1 (CH), 61.9 (CH_2), 50.9 (CH_2); IR (neat): 3237, 3107, 2924, 1633, 1462, 1073, 932, 763, 701 cm^{-1}

71D: ^{1}H-NMR ($CDCl_3$): δ 7.82 (d ,1H, *J* = 2.26 Hz), 7.49-7.28 (m, 5H), 6.60 (d, 1H, *J* = 2.26 Hz), 4.31 (t, 2H, *J* = 4.7 Hz), 4.06 (t, 2H, *J* = 4.7 Hz), 3,37 (br s, 1H).

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[66] Note that solvent correction has been applied since compound **29A** incorporates 0.263 mol $CHCl_3$ solvent as indicated by Solvent Correction CHN Calculator, which is available at http://www.che.hw.ac.uk/research/services/solvent.html.,last accesed date: 01/August/2008

APPENDIX A

NMR AND FT-IR SPECTRUMS

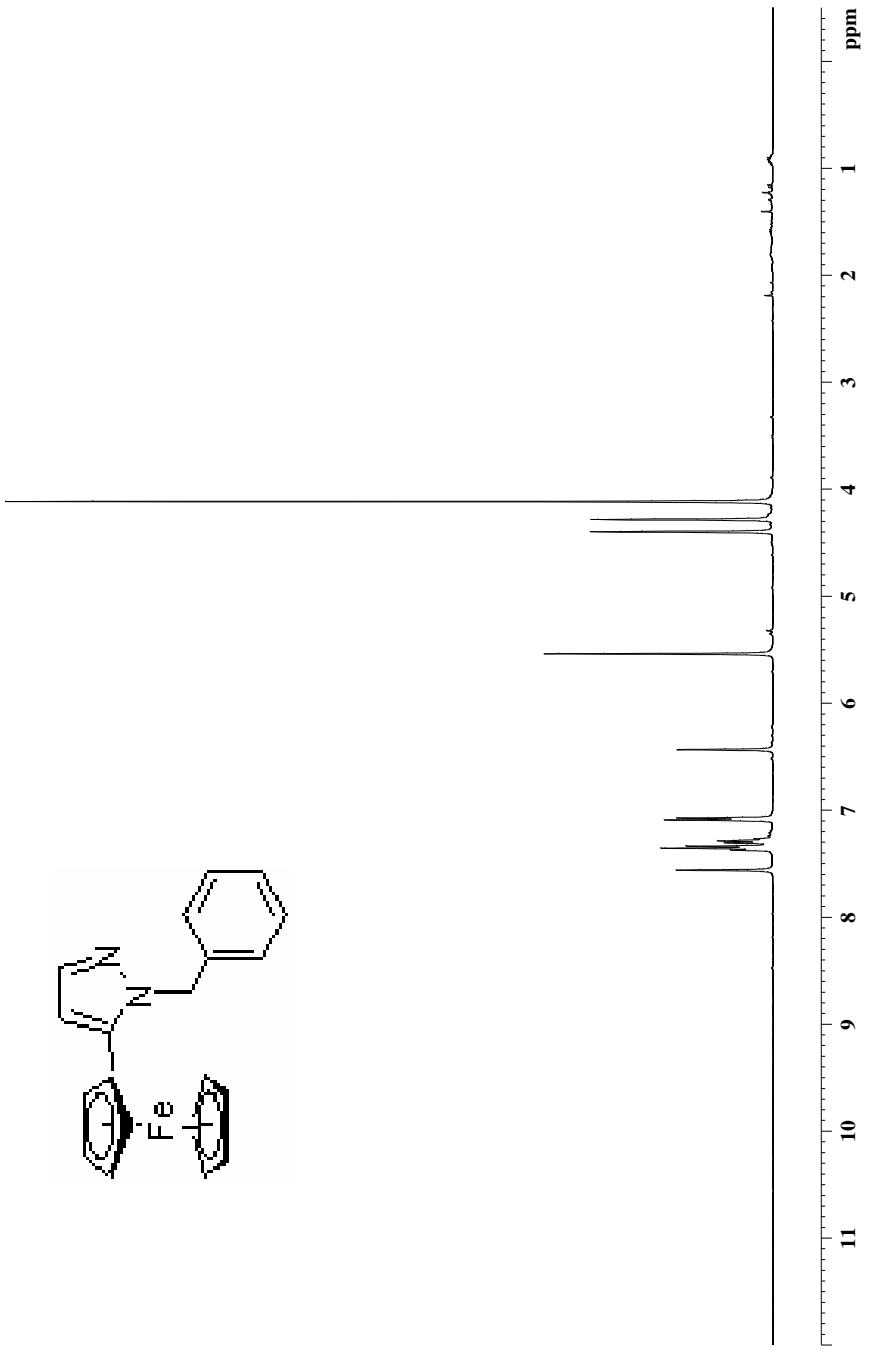

Figure A1. ^{1}H-NMR spectrum of **28A**

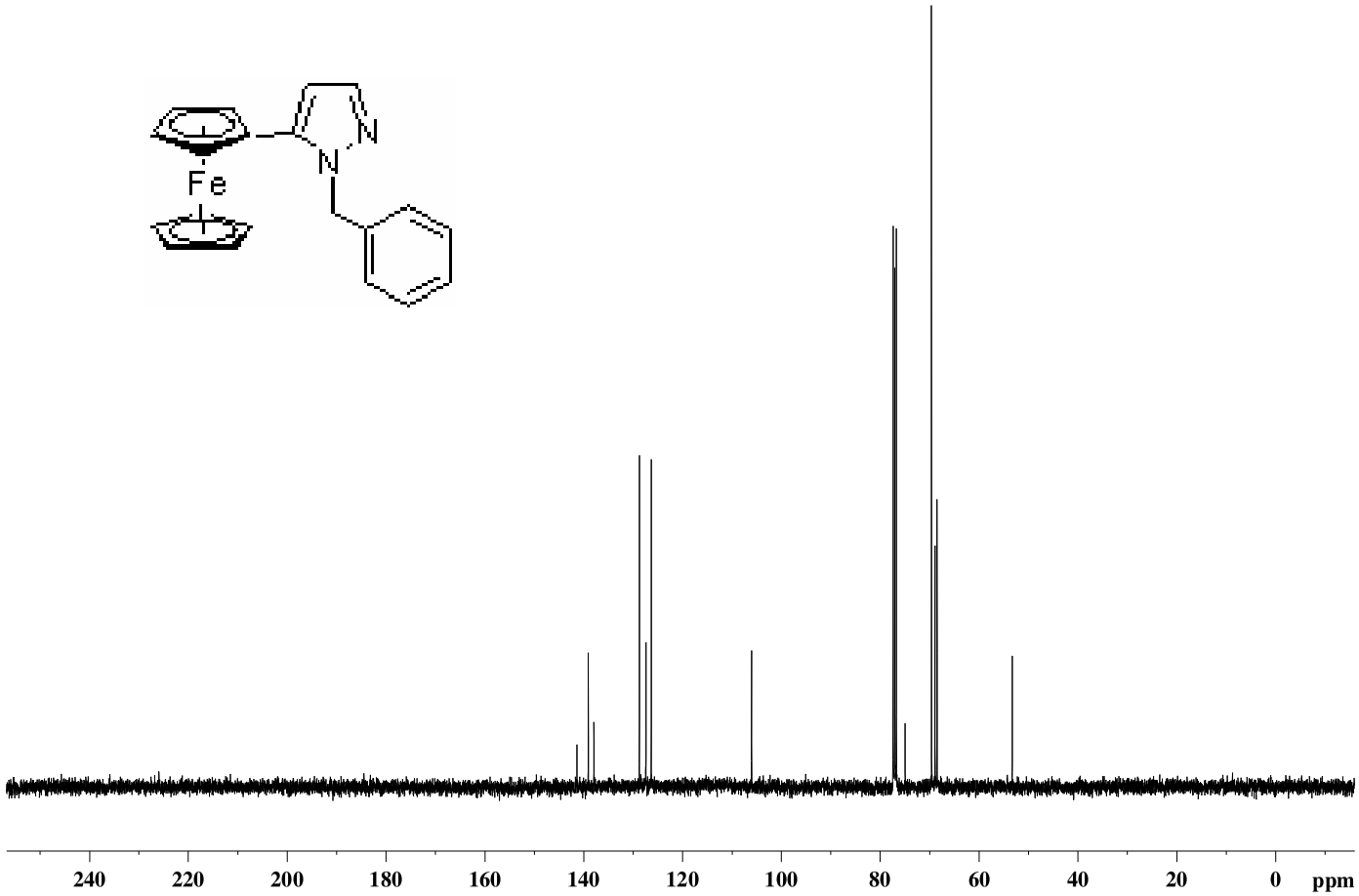

Figure A2. ^{13}C-NMR spectrum of **28A**

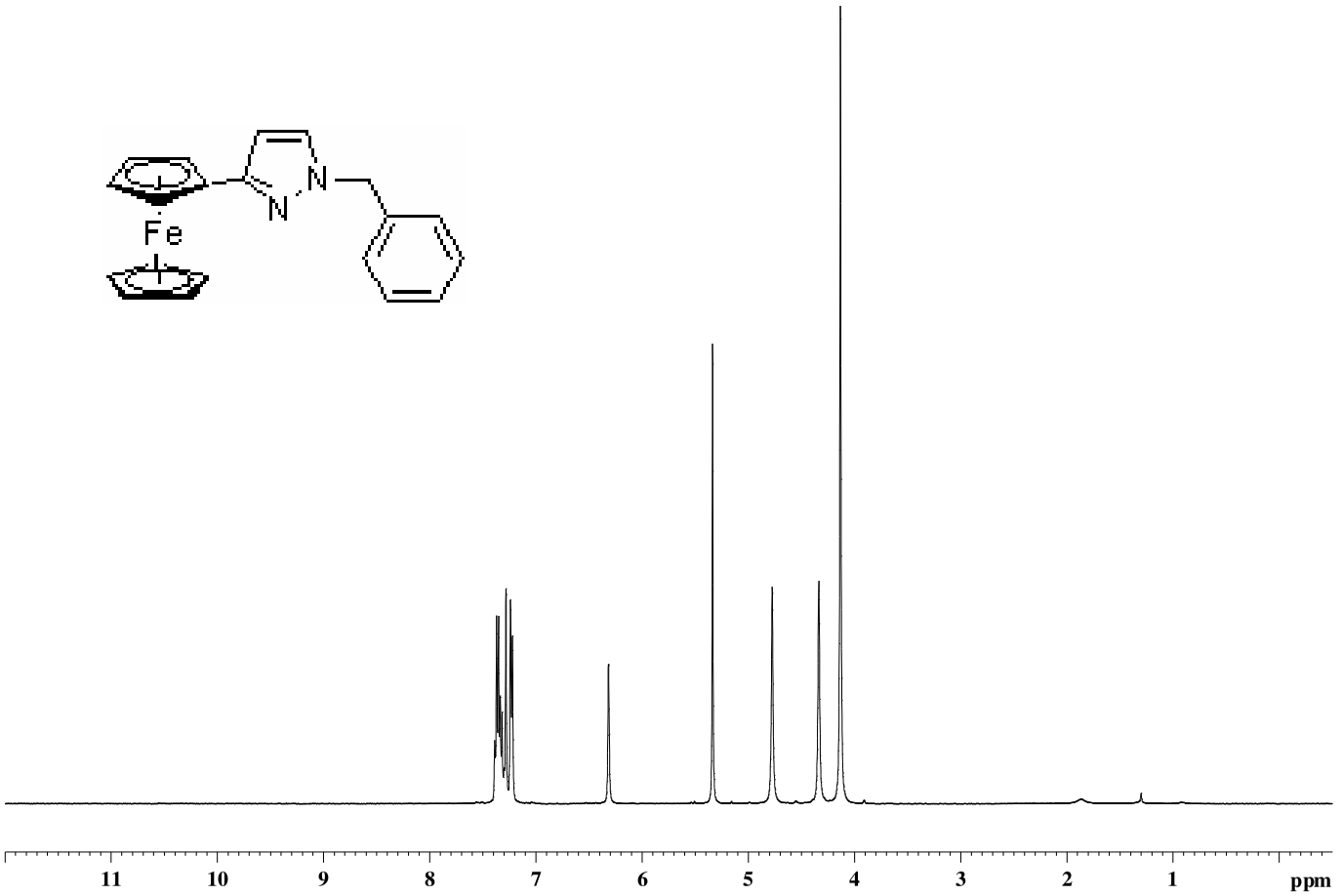

Figure A3. ^{1}H-NMR spectrum of **29A**

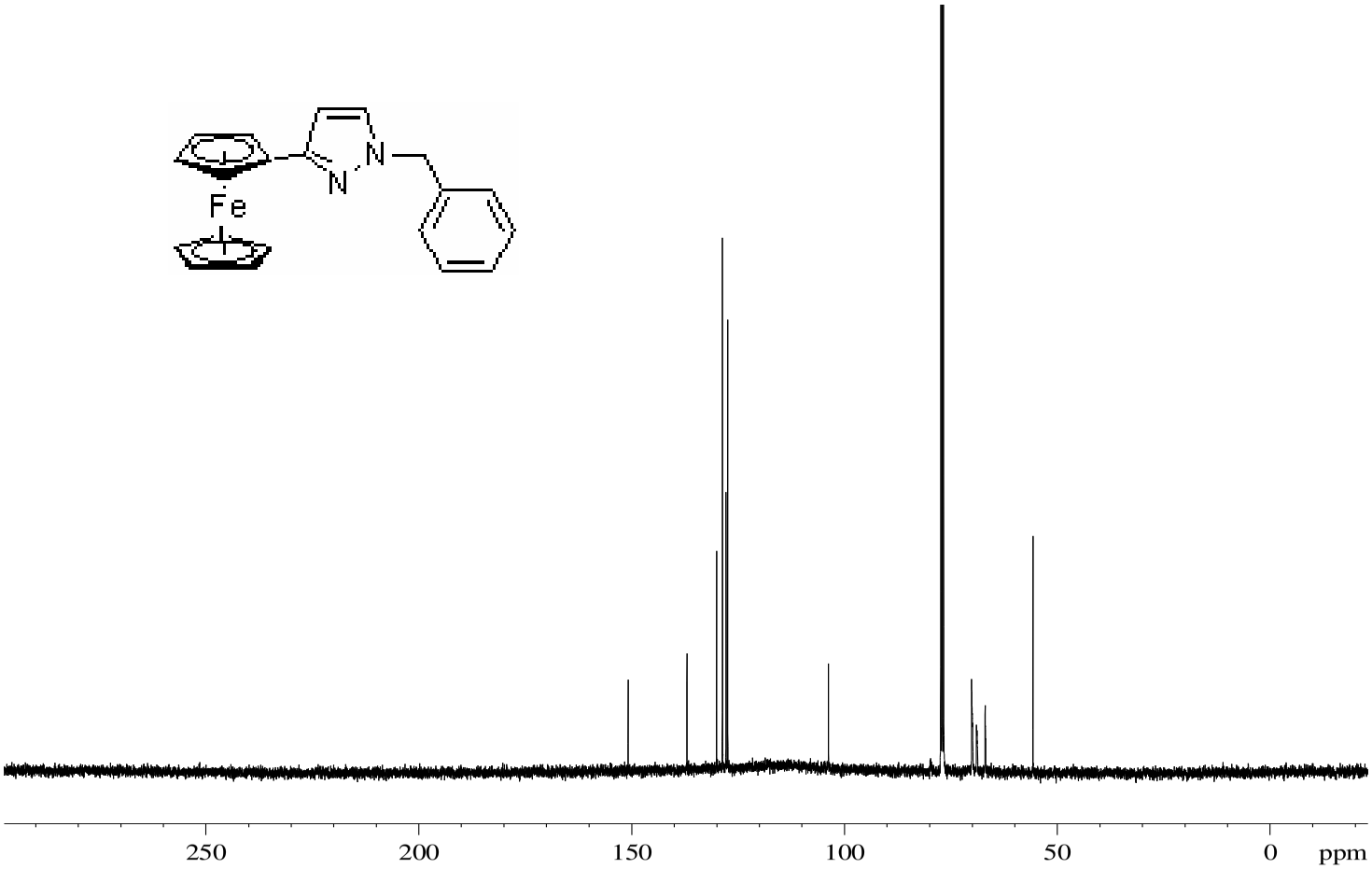

Figure A4. ^{13}C-NMR spectrum of **29A**

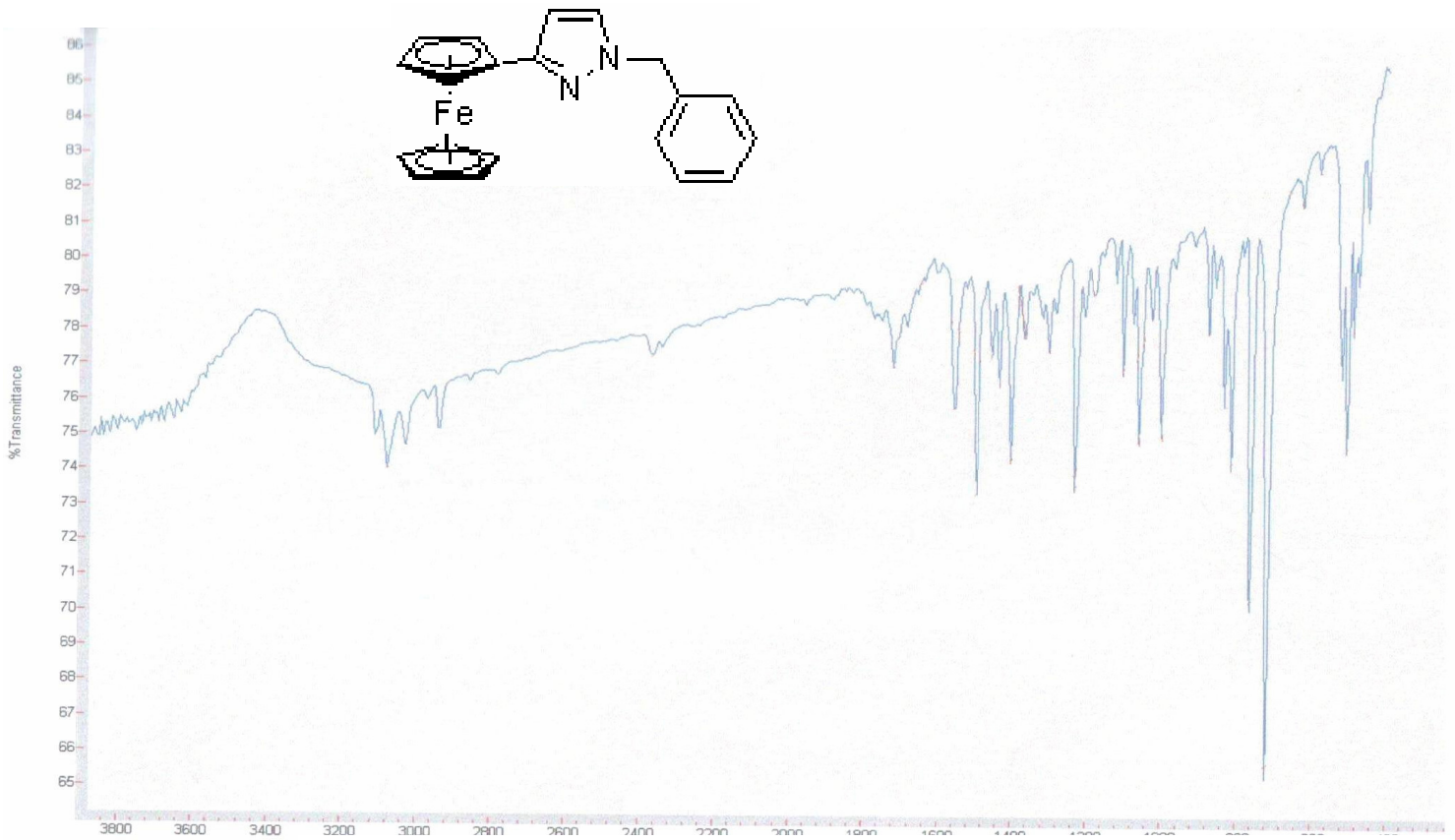

Figure A5.FT-IR spectrum of **29A**

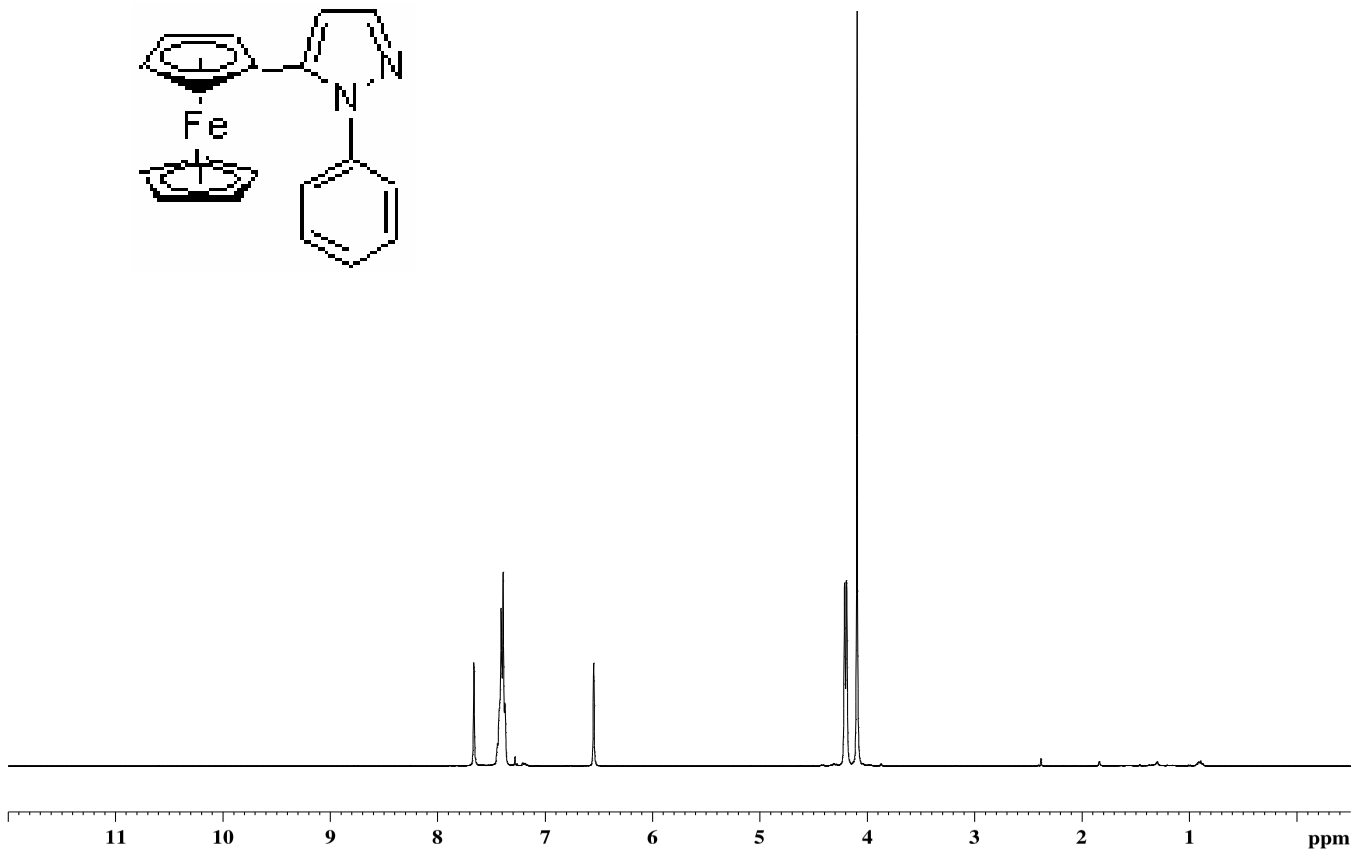

Figure A6. ^{1}H-NMR spectrum of **28B**

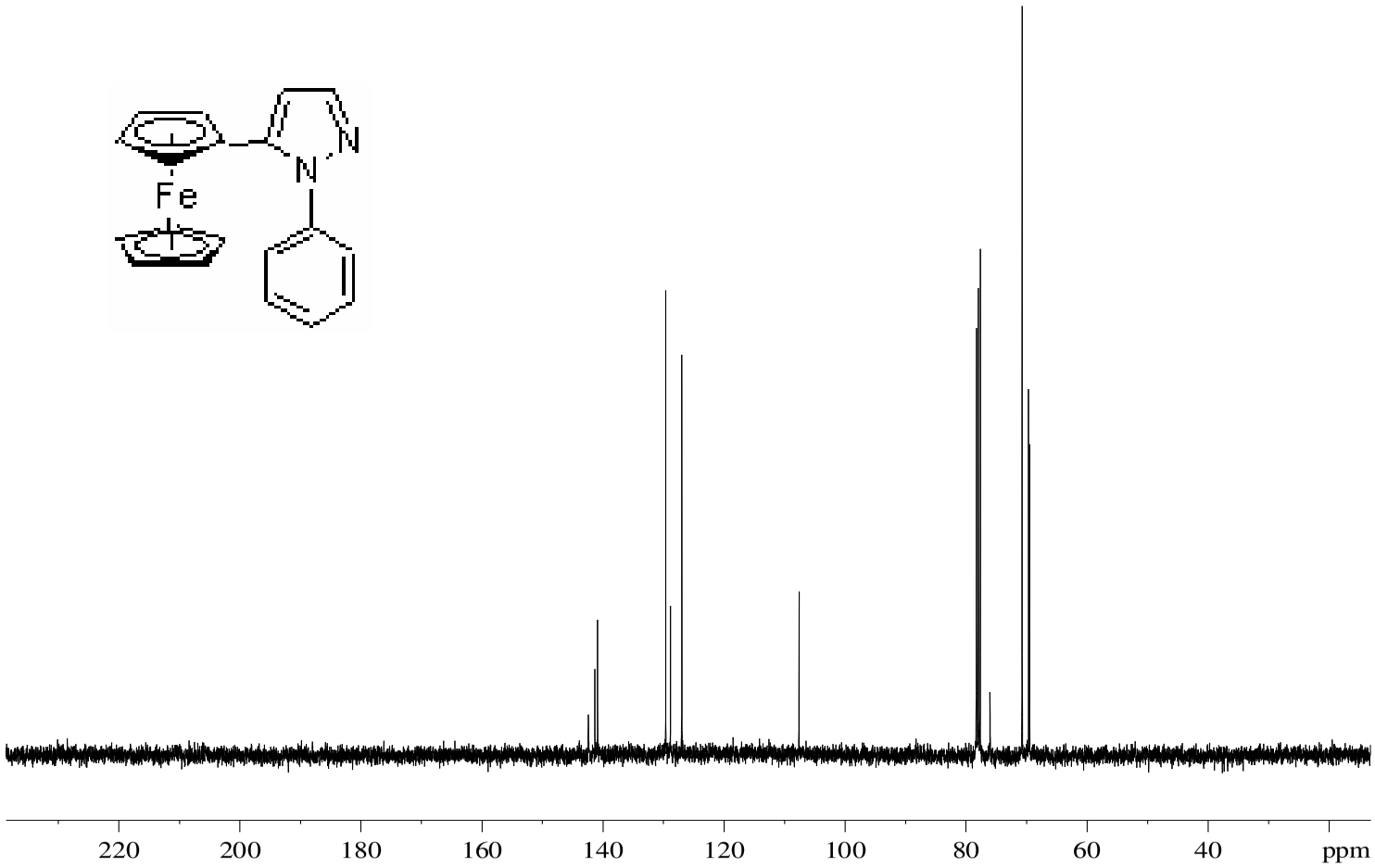

Figure A7. ^{13}C-NMR spectrum of **28B**

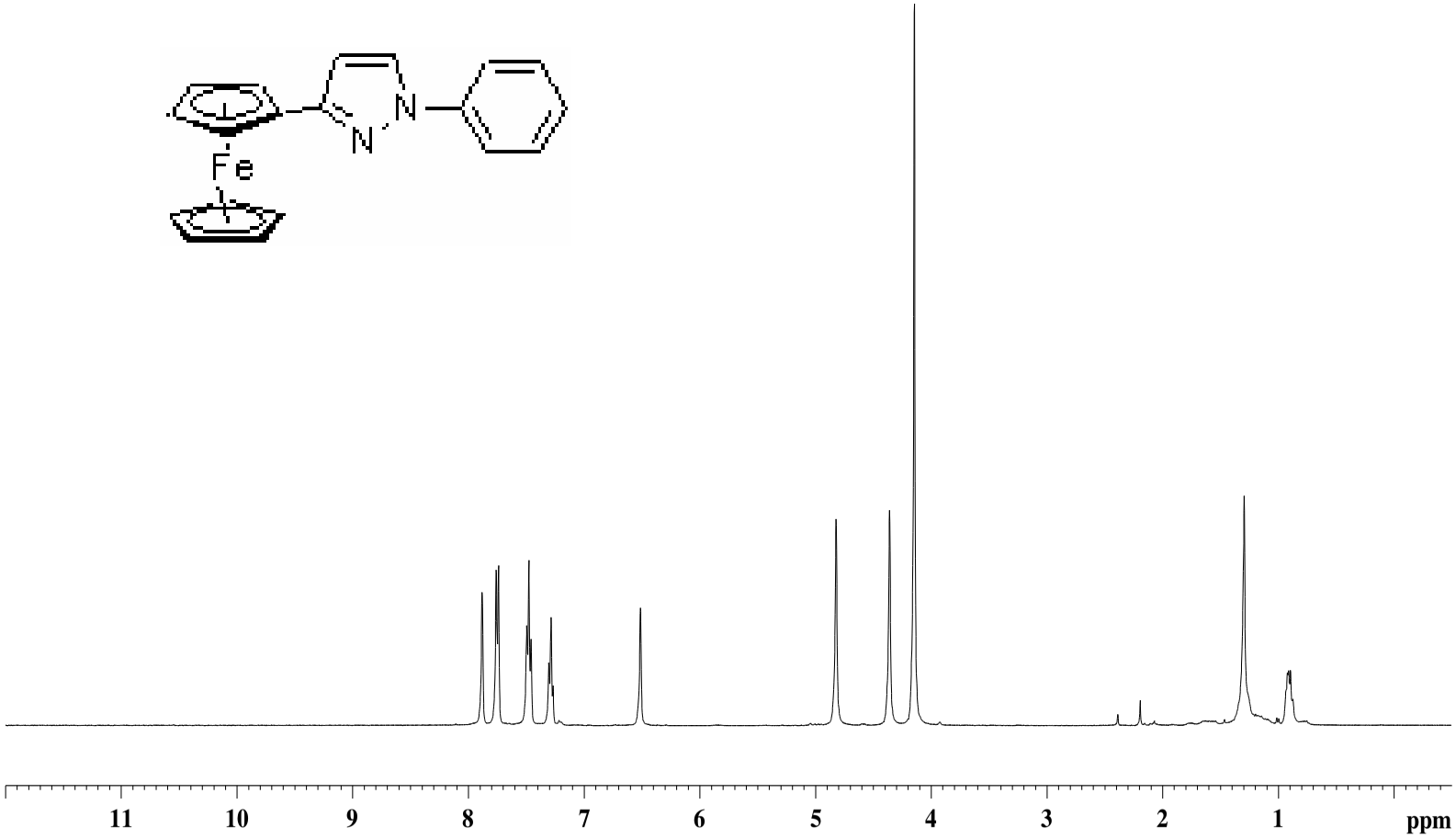

Figure A8. ^{1}H-NMR spectrum of **29B**

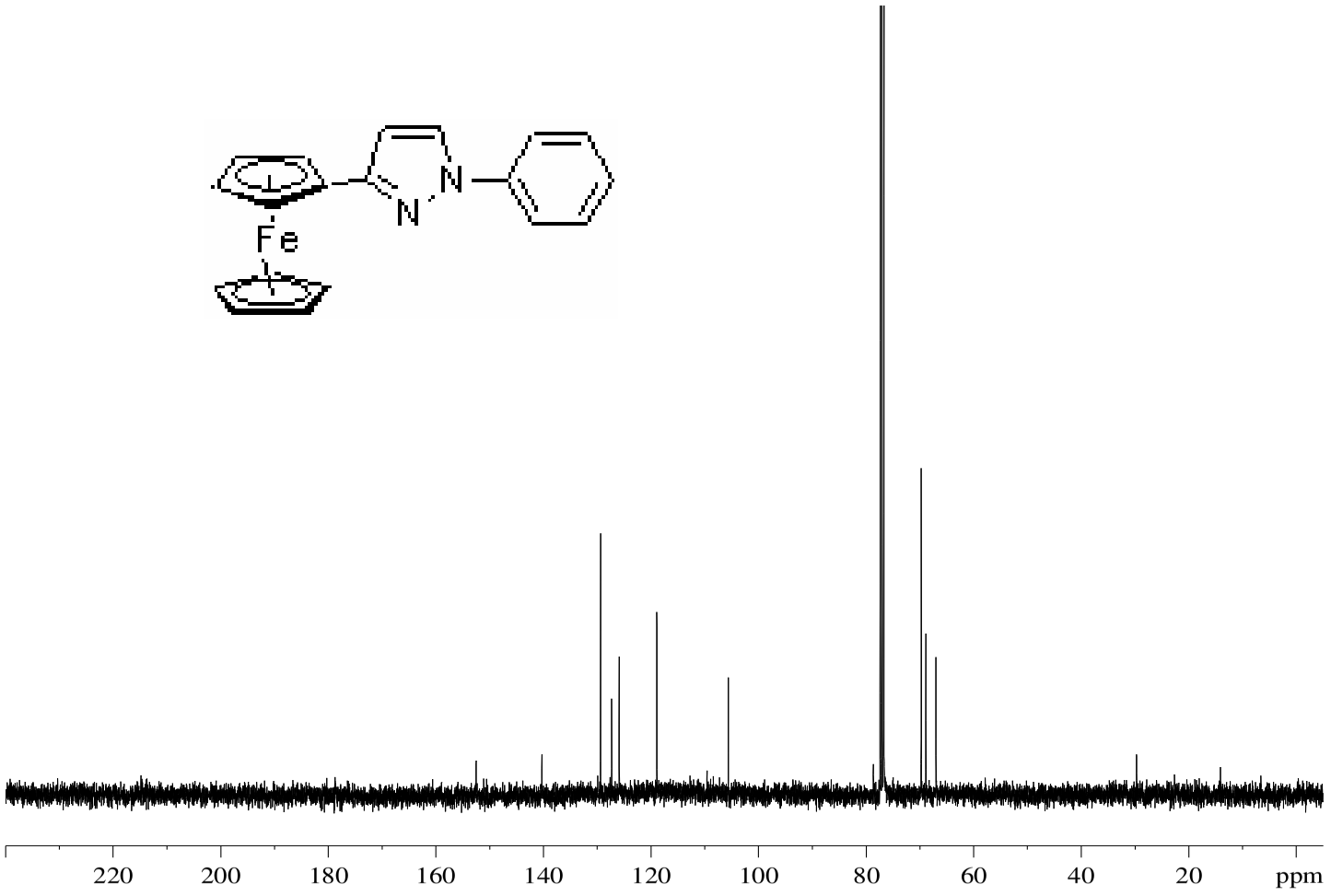

Figure A9. ^{13}C-NMR spectrum of **29B**

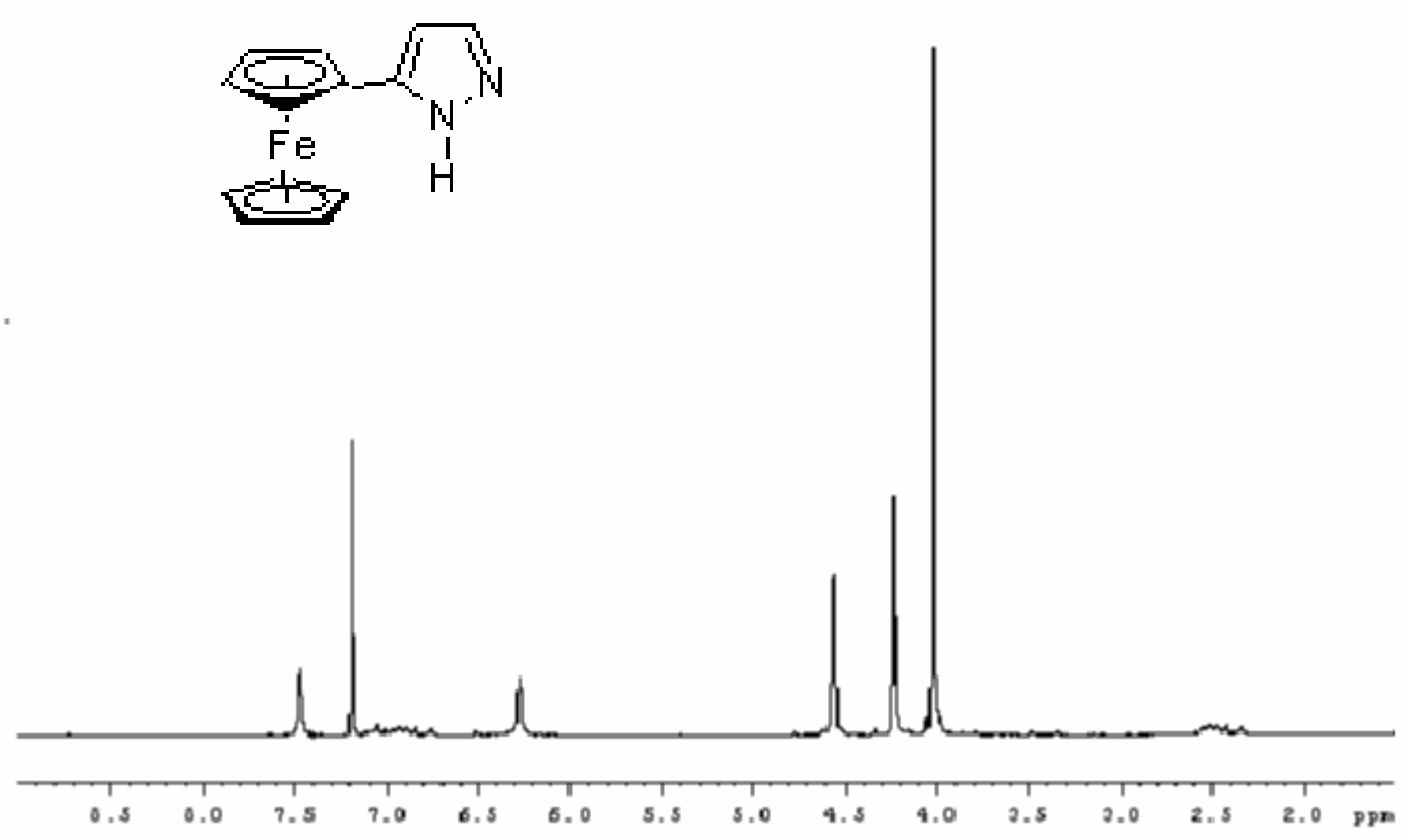

Figure A10. ^{1}H-NMRspectrum of **28C**

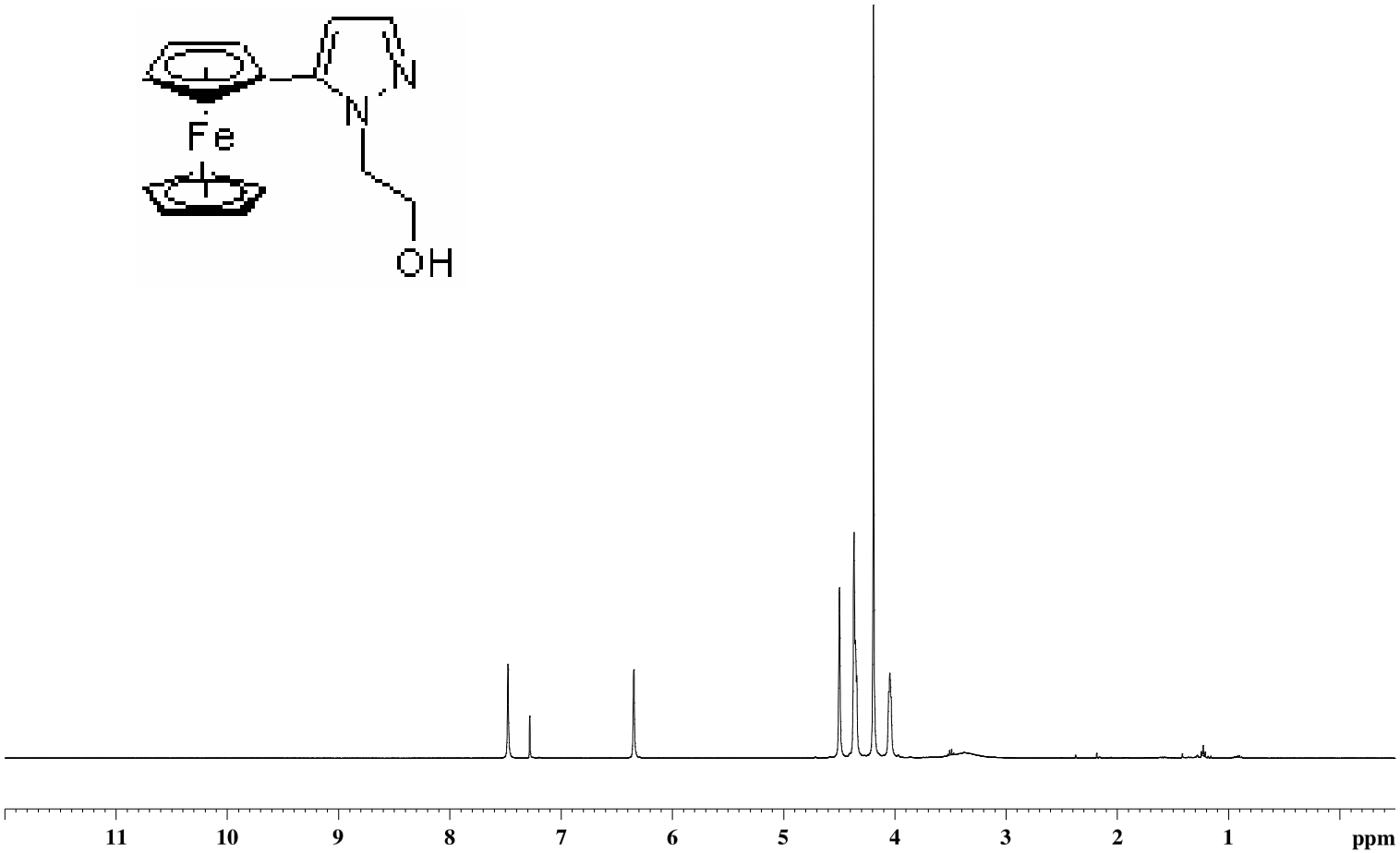

Figure A11. ^{1}H-NMRspectrum of **28D**

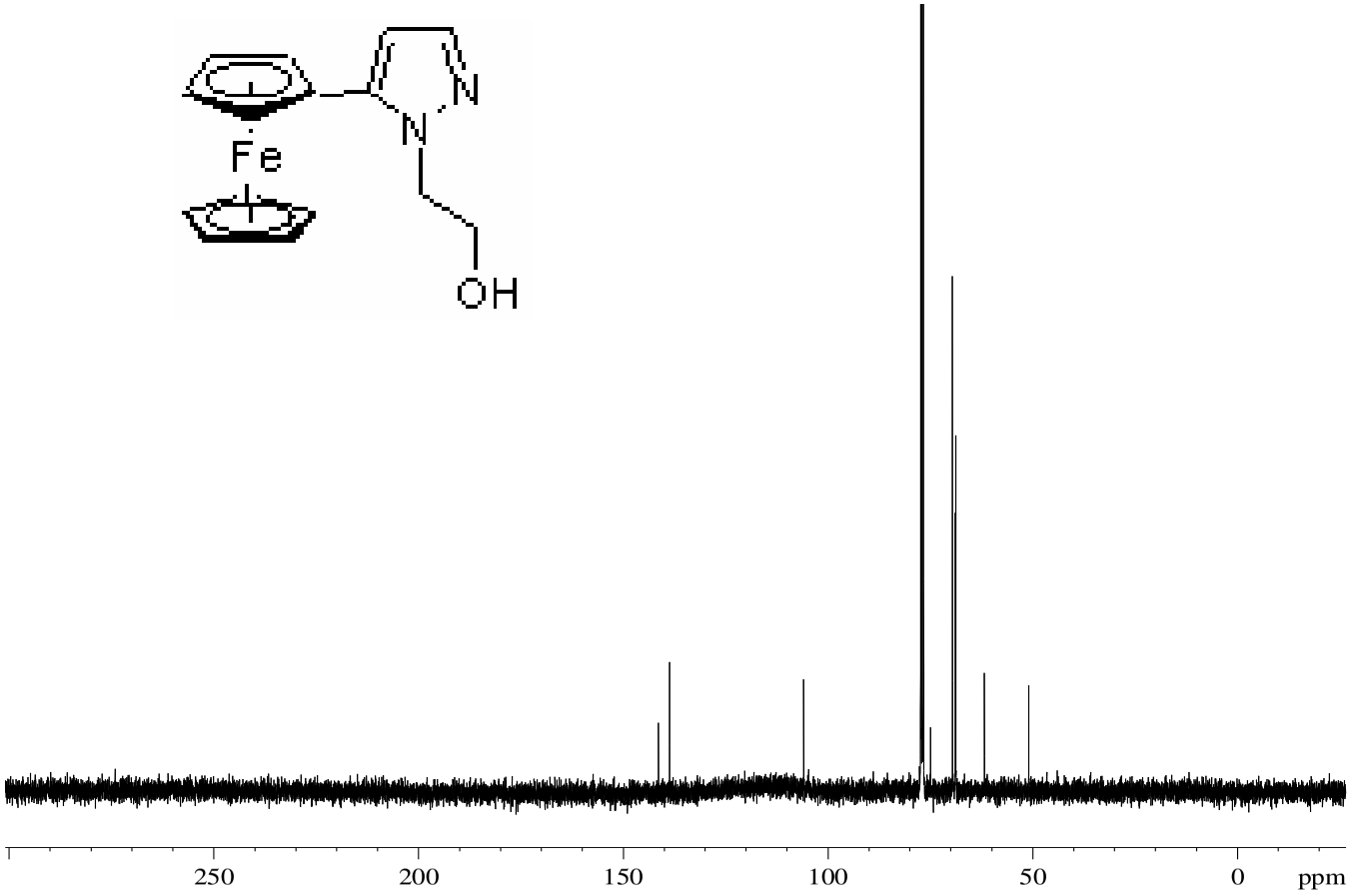

Figure A12. ^{13}C-NMRspectrum of **28D**

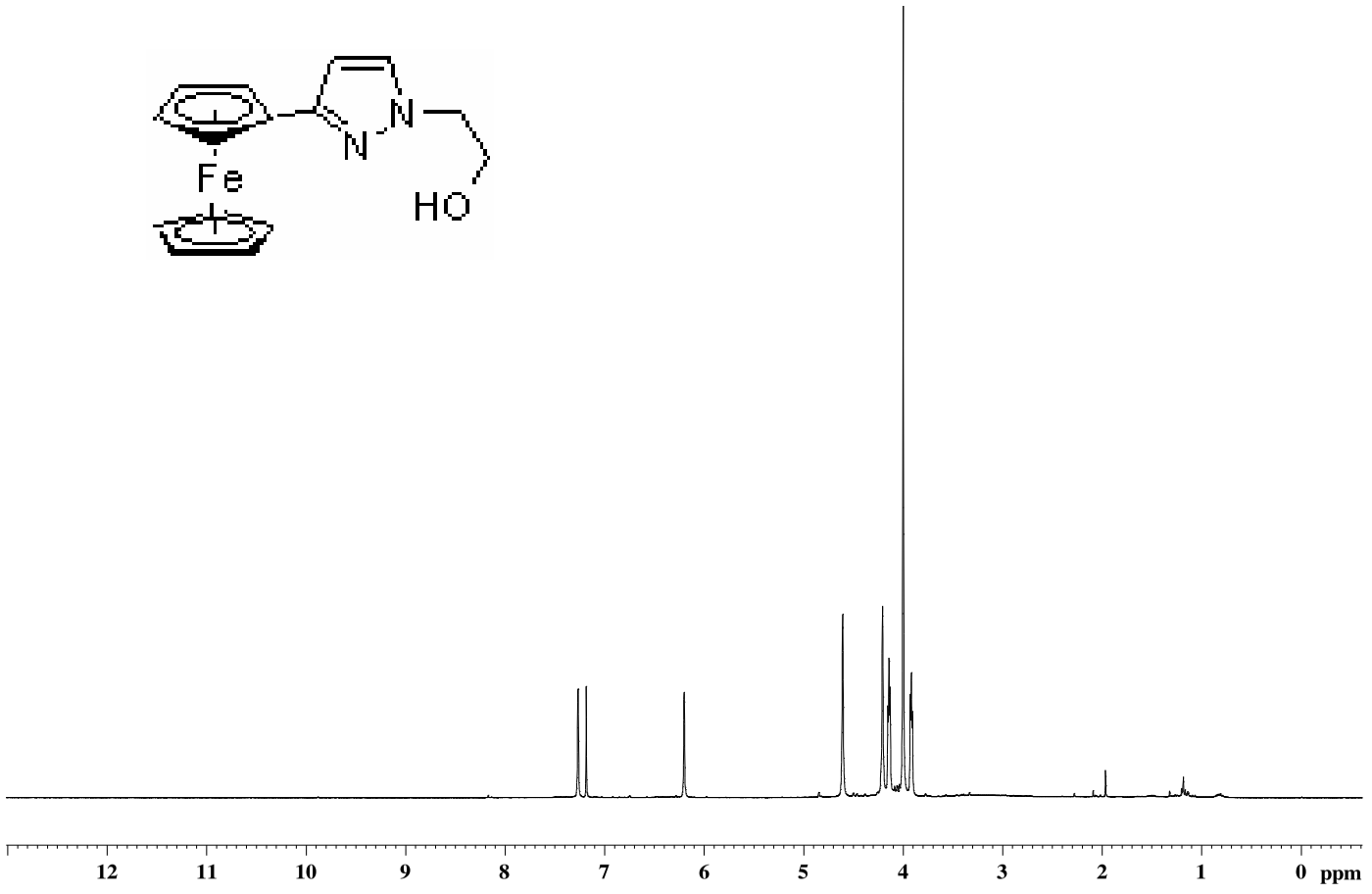

Figure A13. ^{1}H-NMRspectrum of **29D**

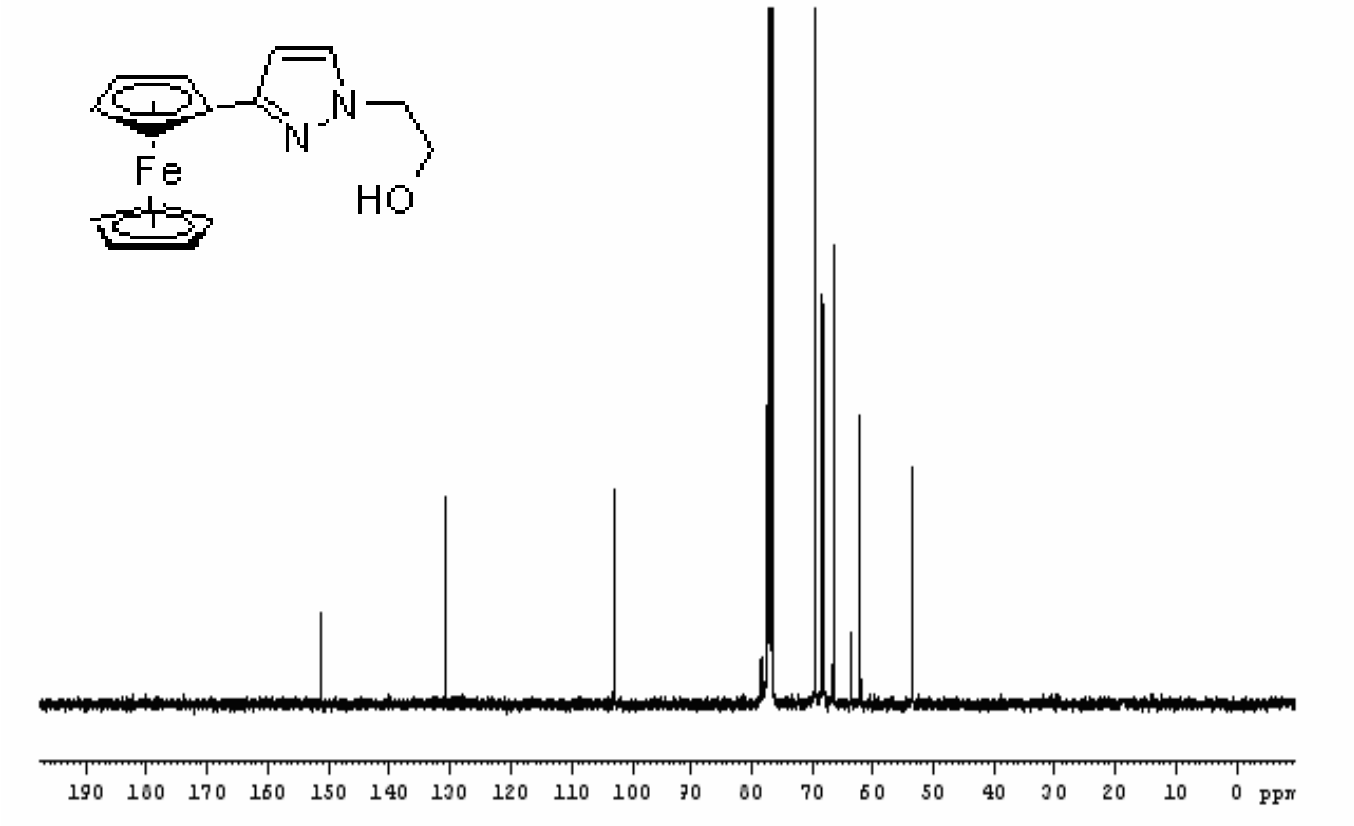

Figure A14. ^{13}C-NMRspectrum of **29D**

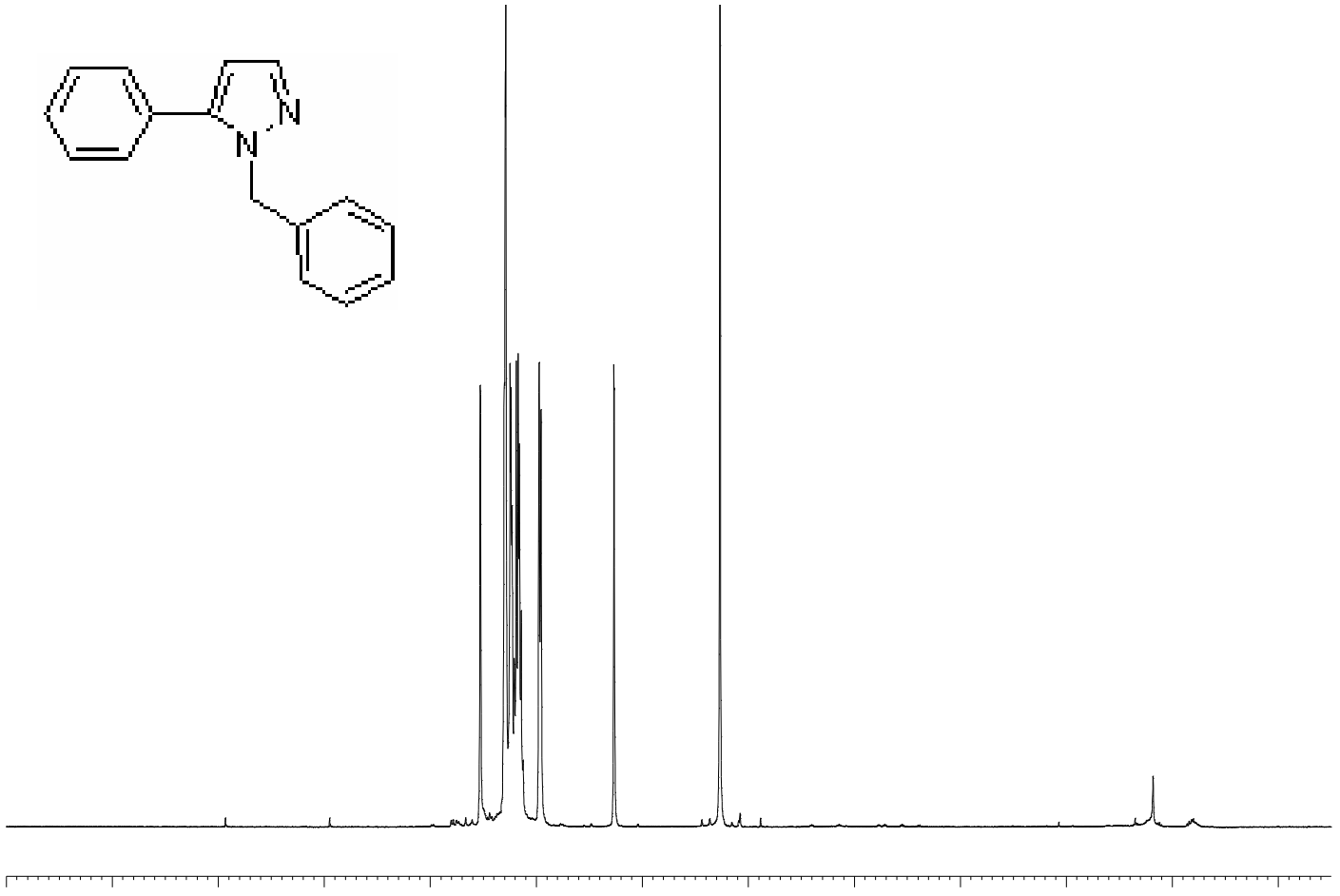

Figure A15. ^{1}H-NMRspectrum of **70A**

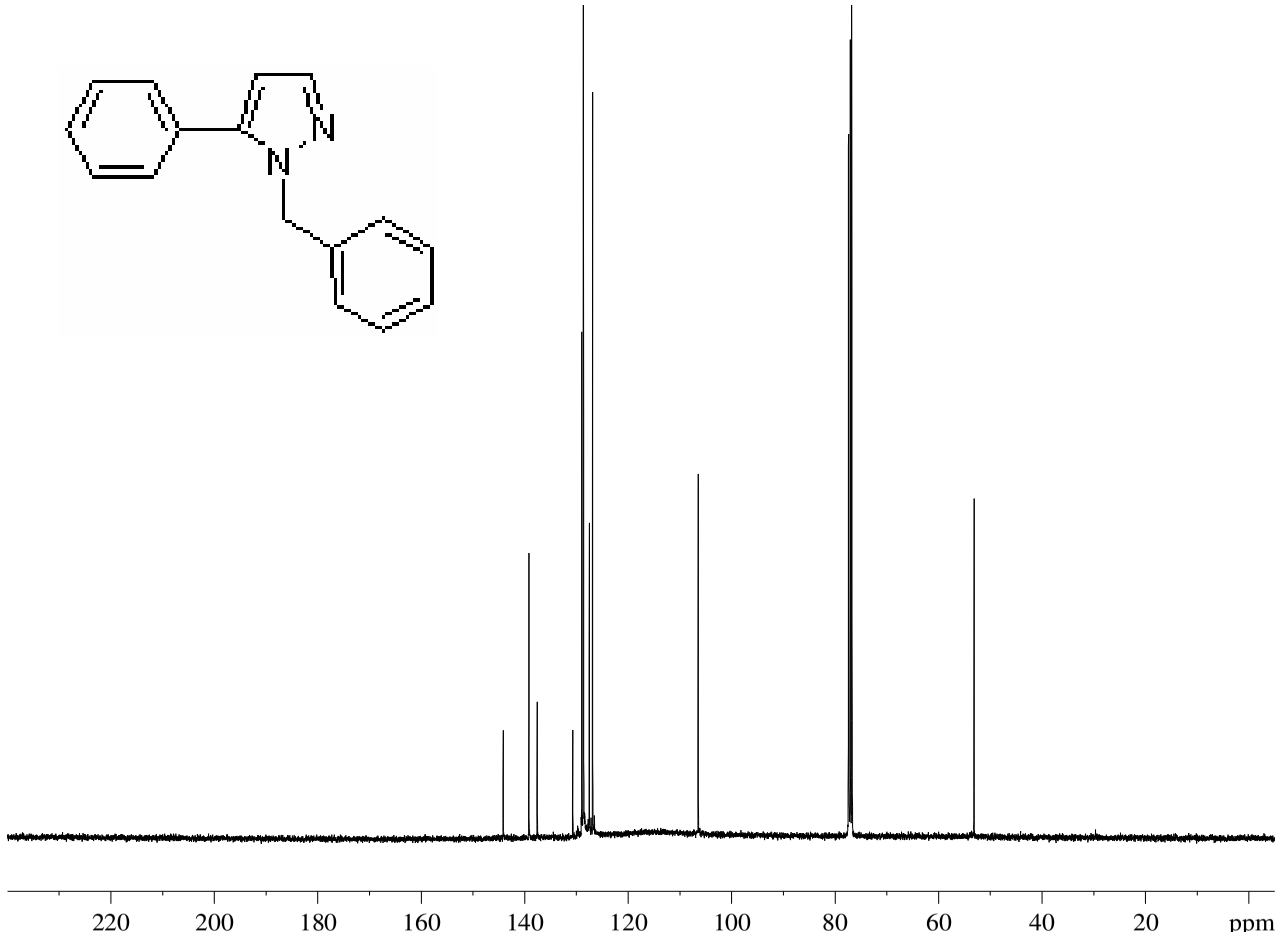

Figure A16. ^{13}C-NMRspectrum of **70A**

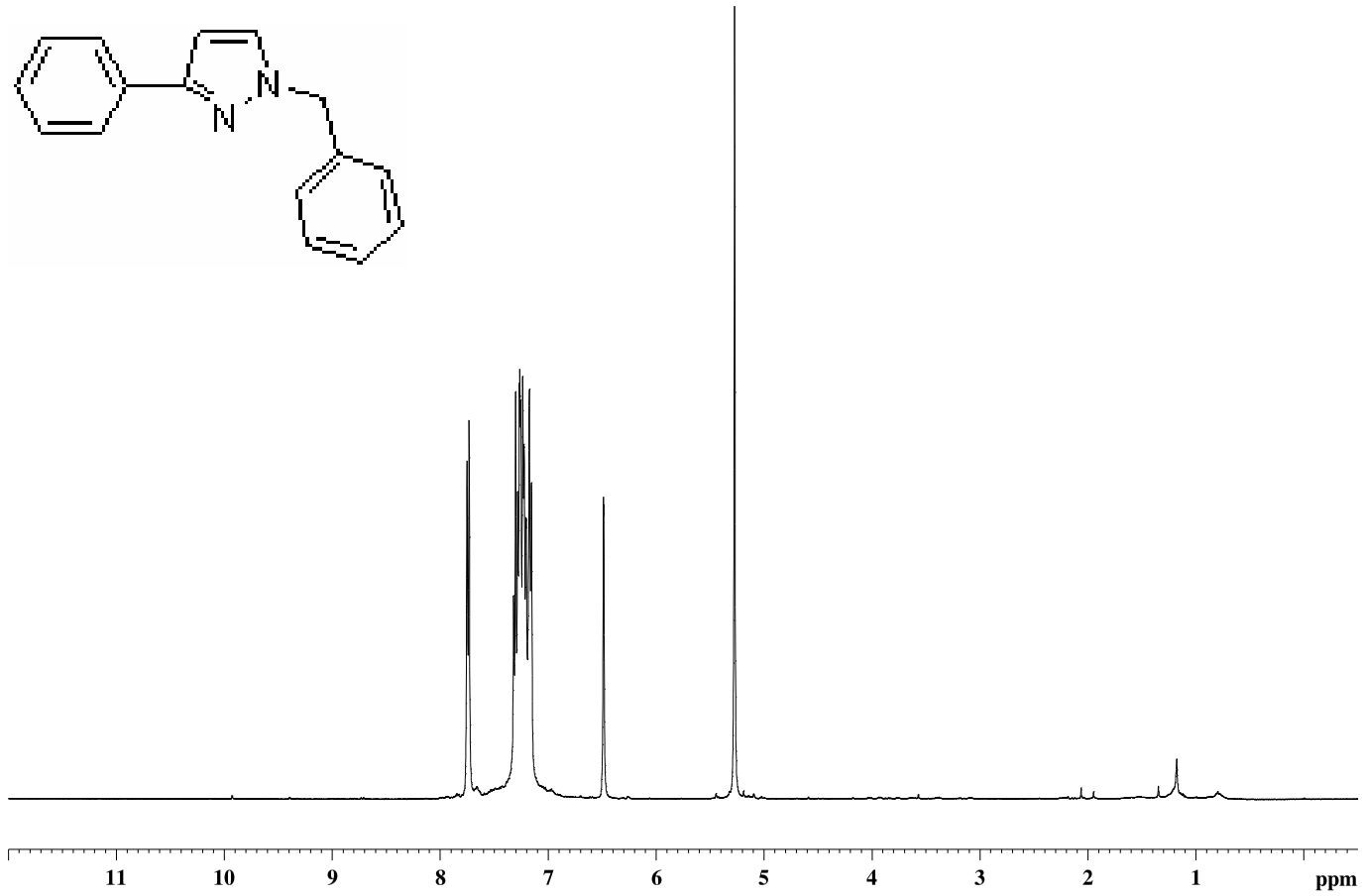

Figure A17. ^{1}H-NMRspectrum of **71A**

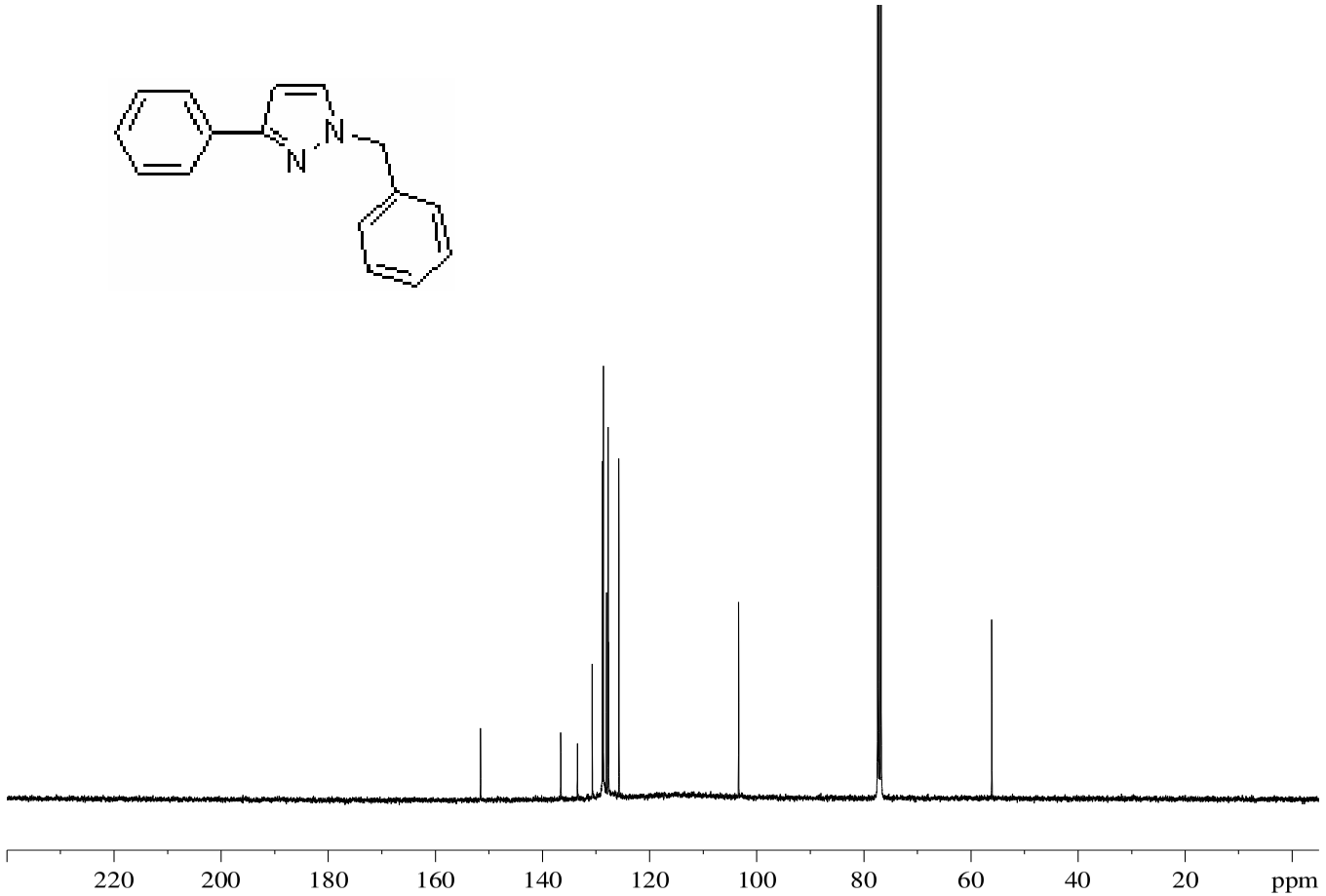

Figure A18. ^{13}C-NMRspectrum of **71A**

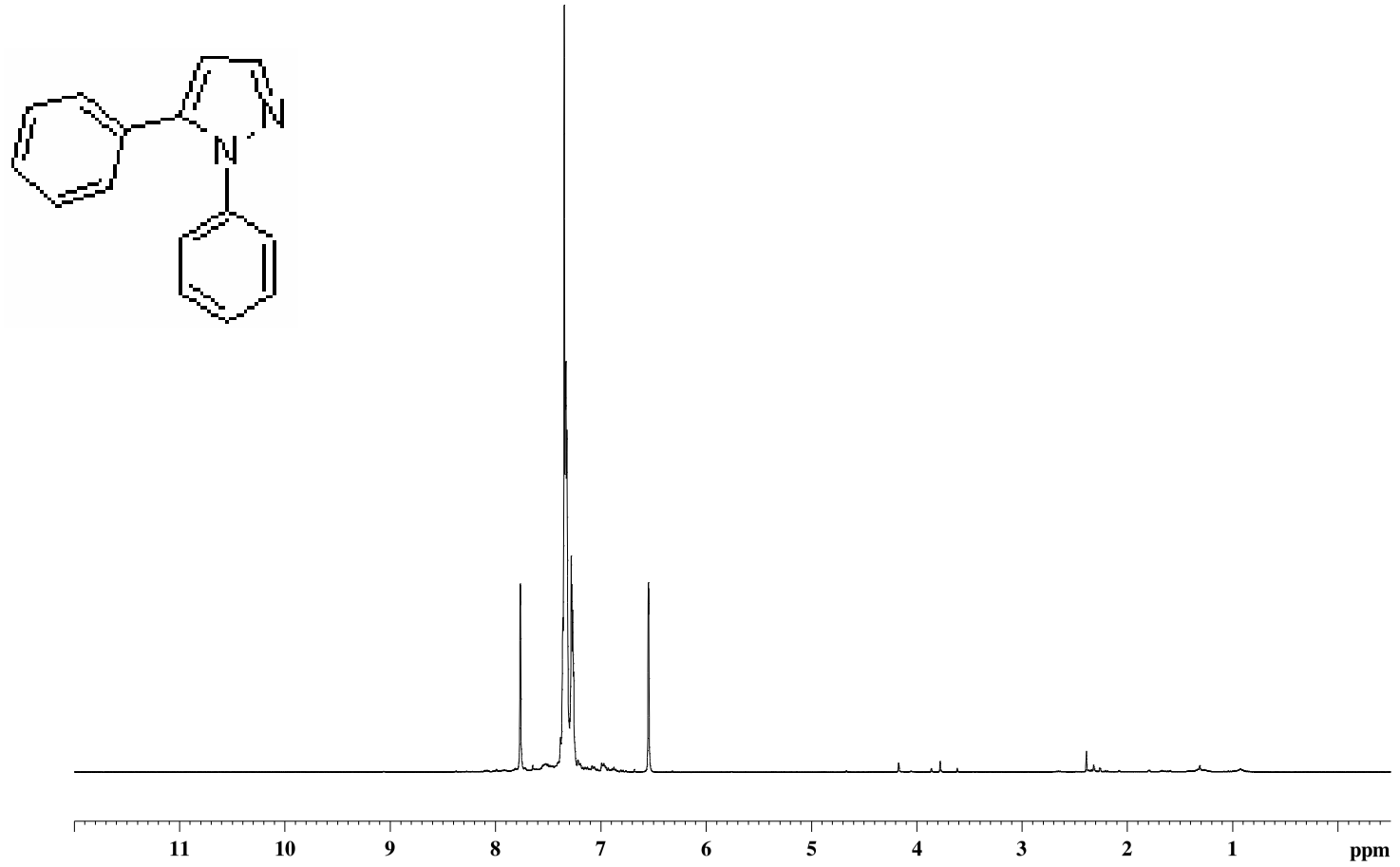

Figure A19. ^{1}H-NMR spectrum of **70B**

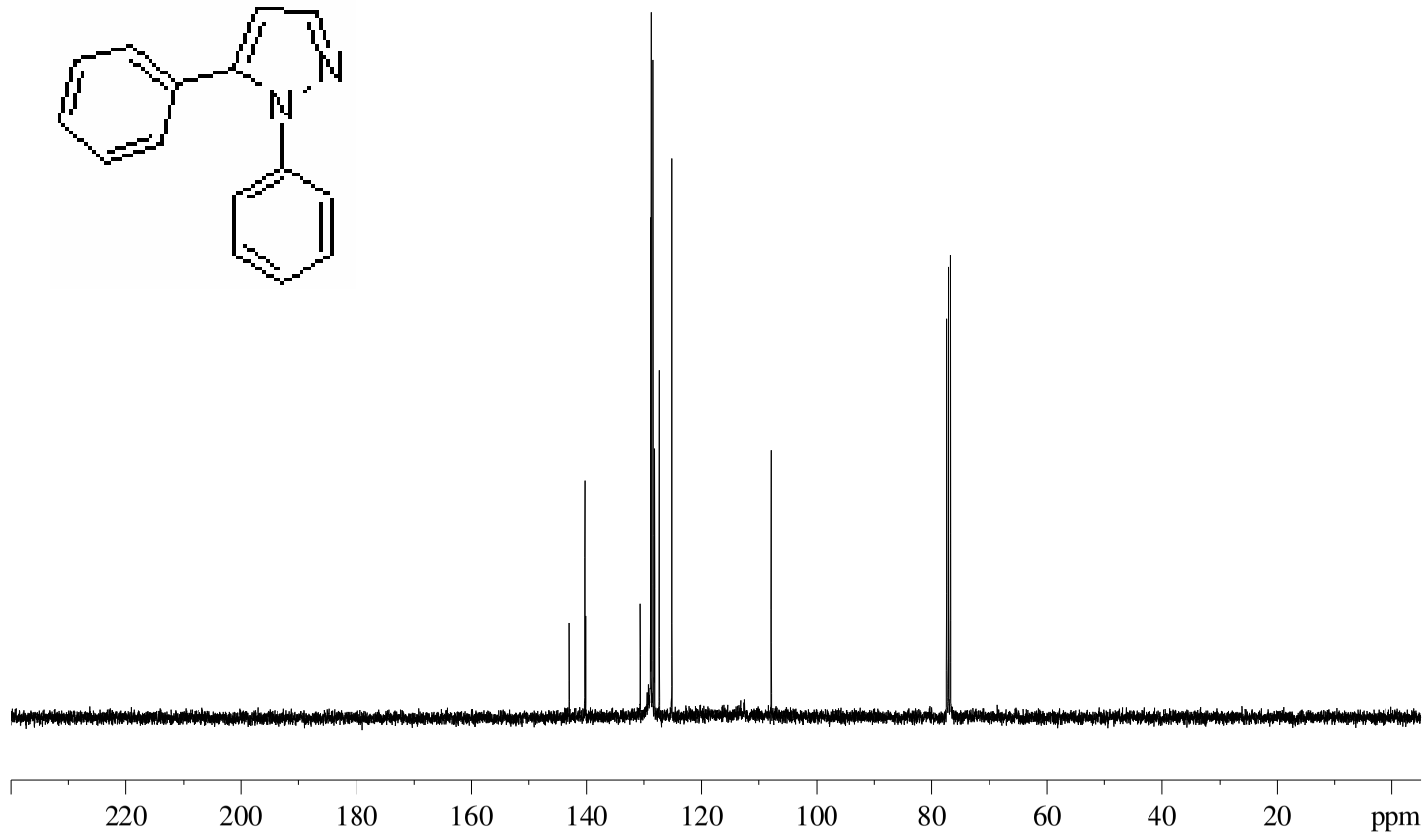

Figure A20. ^{13}C-NMRspectrum of **70B**

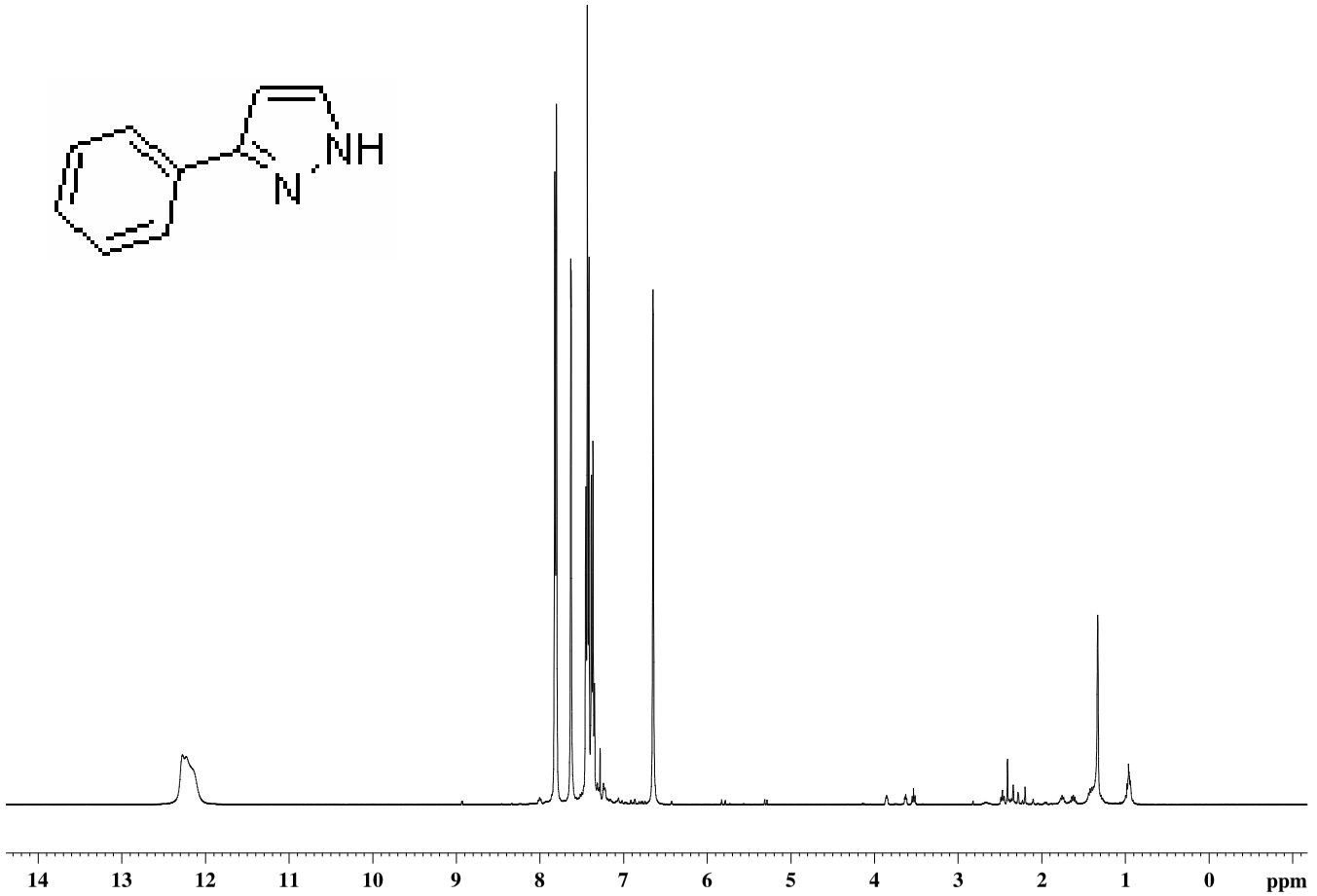

Figure A21. ^{1}H-NMRspectrum of **71C**

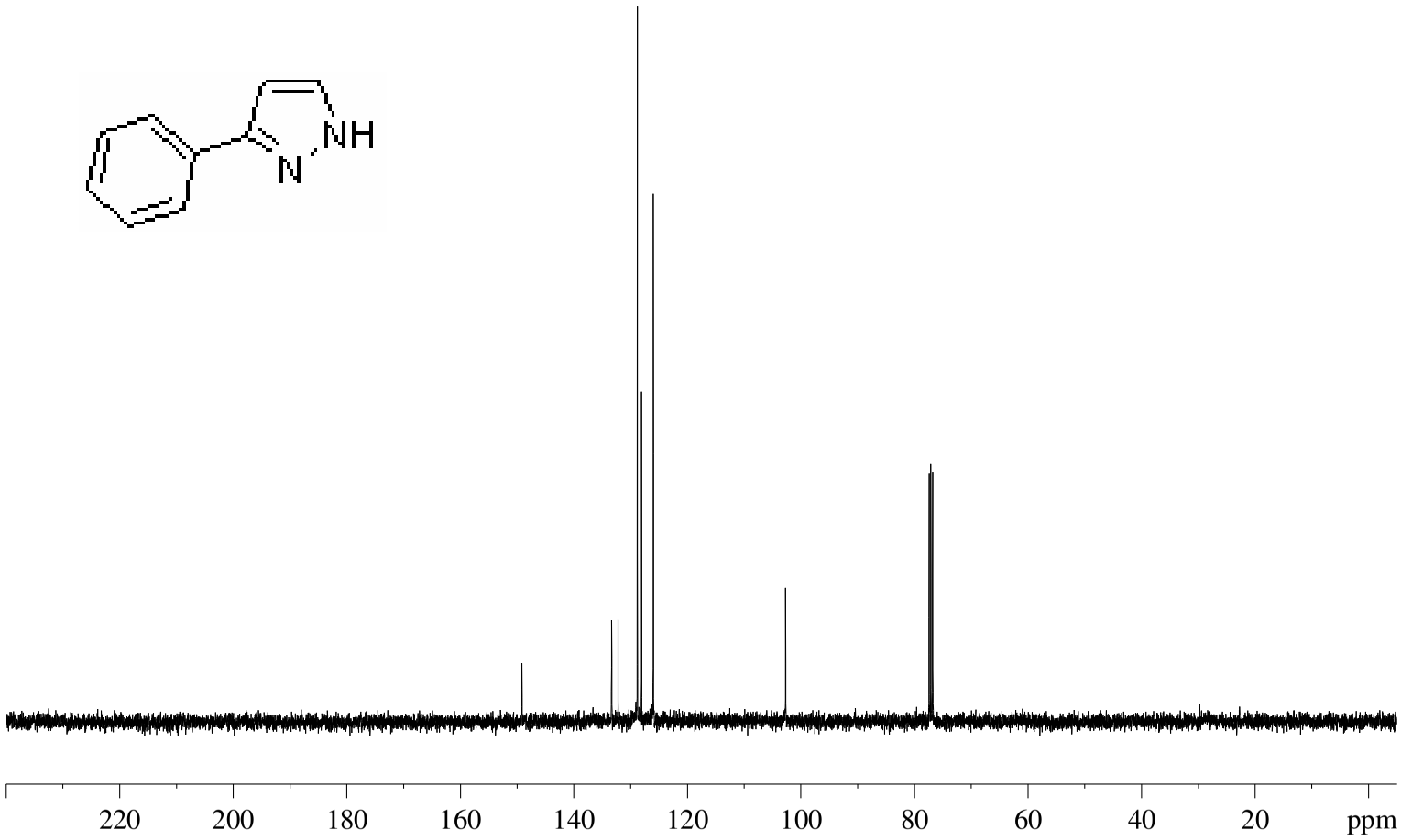

Figure A22. ^{13}C-NMRspectrum of **71C**

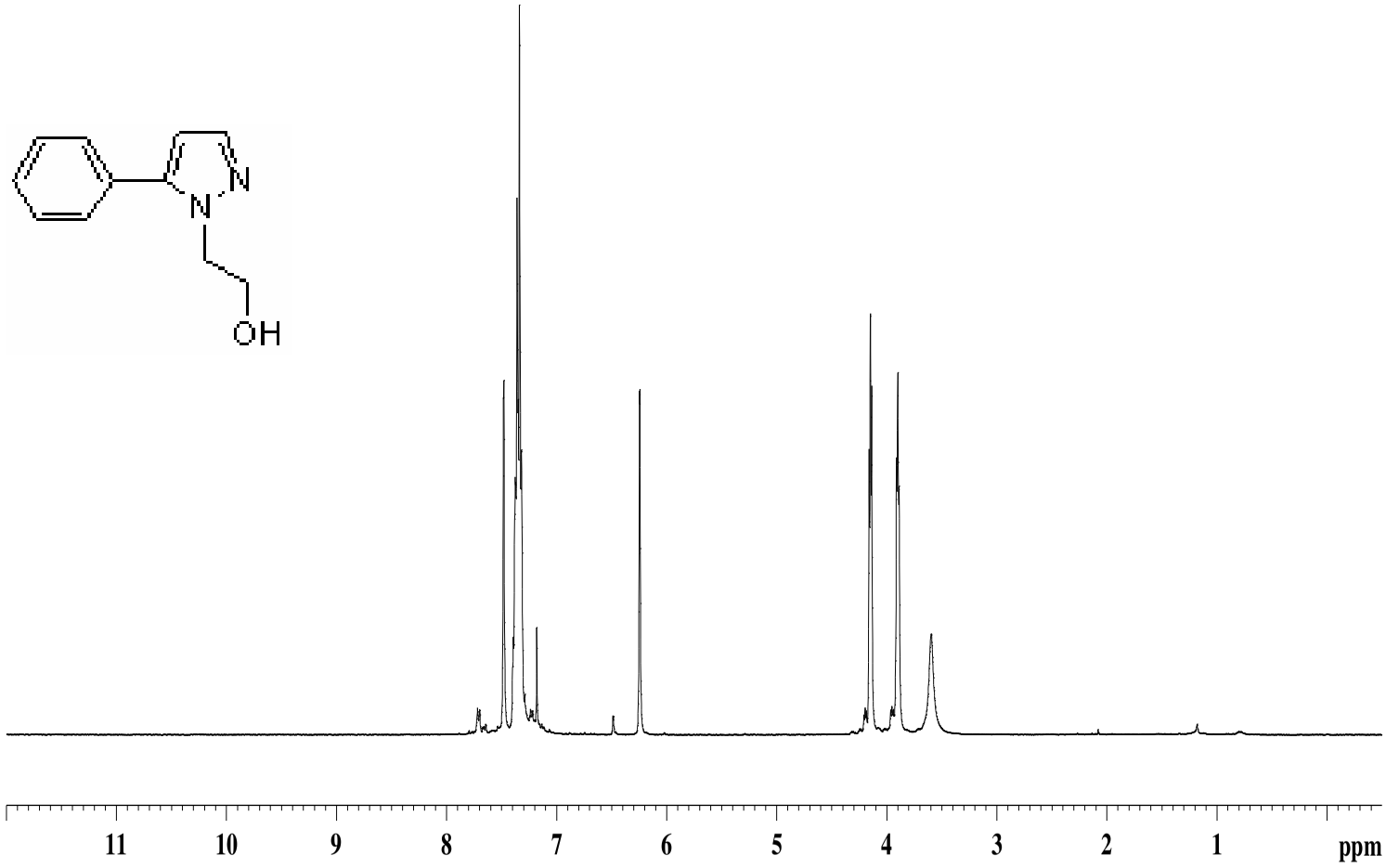

Figure A23. ^{1}H-NMRspectrum of **70D**

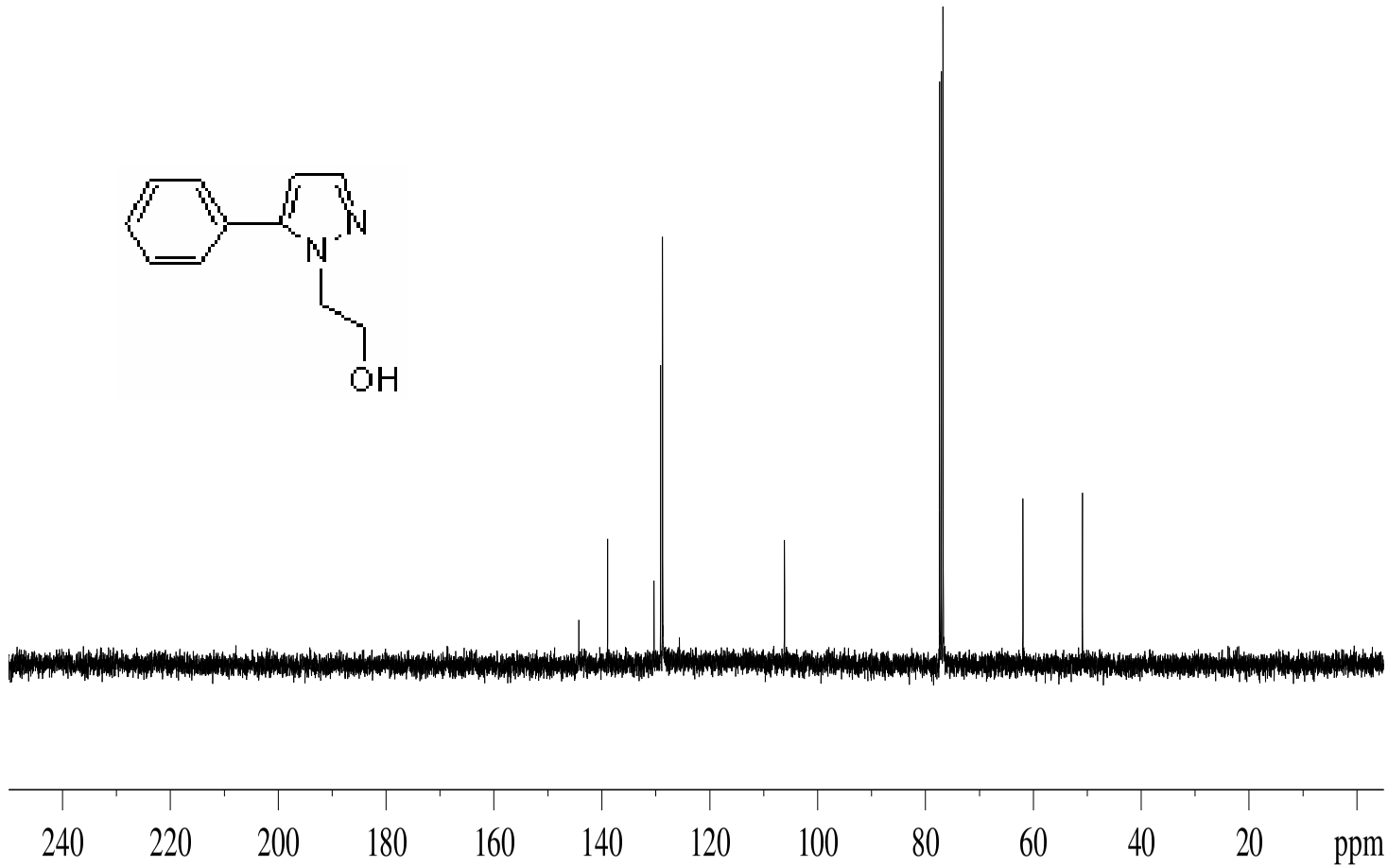

Figure A24. ^{13}C-NMRspectrum of **70D**

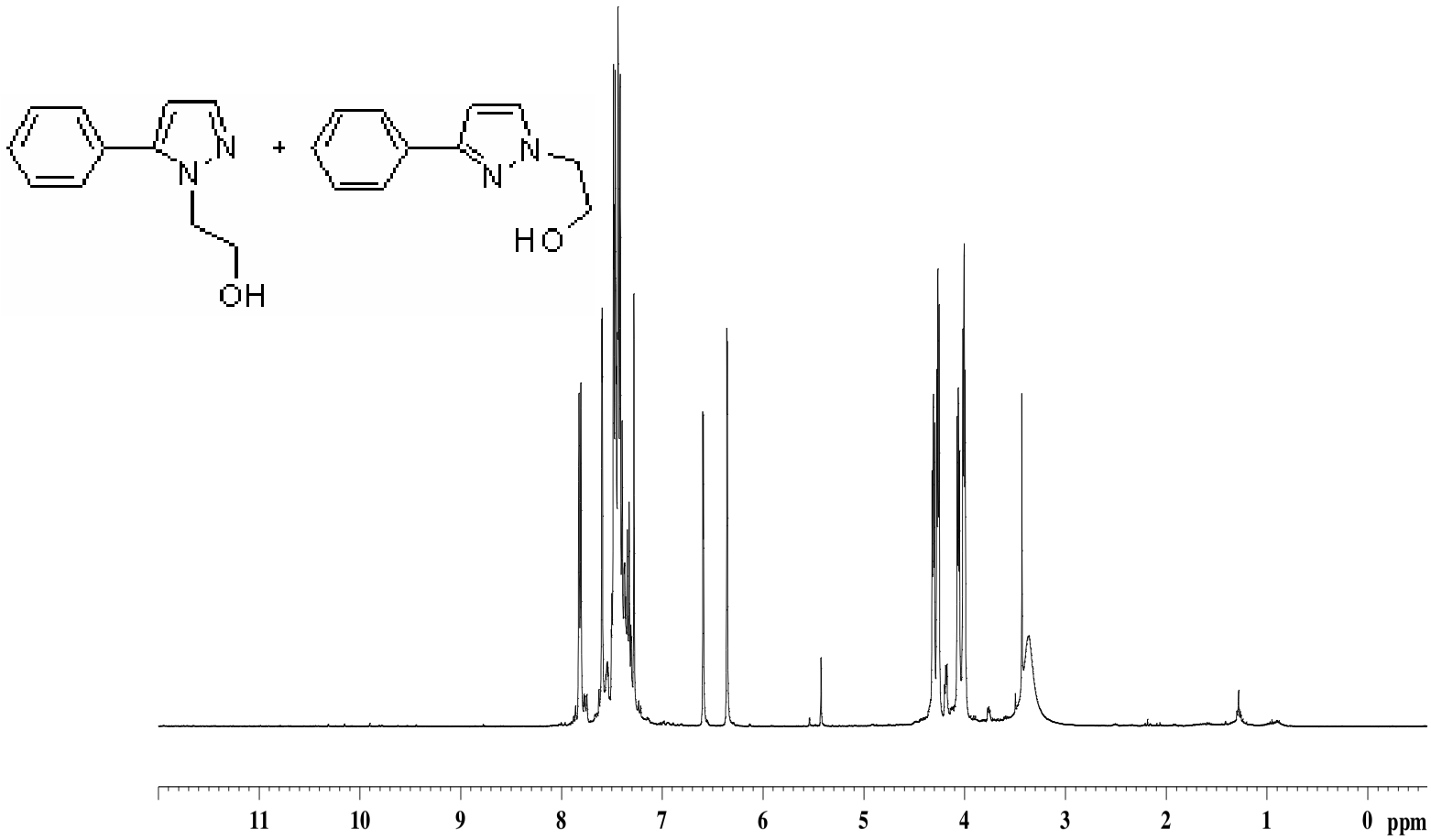

Figure A25. ^{1}H-NMRspectrum of **70D** and **71D**

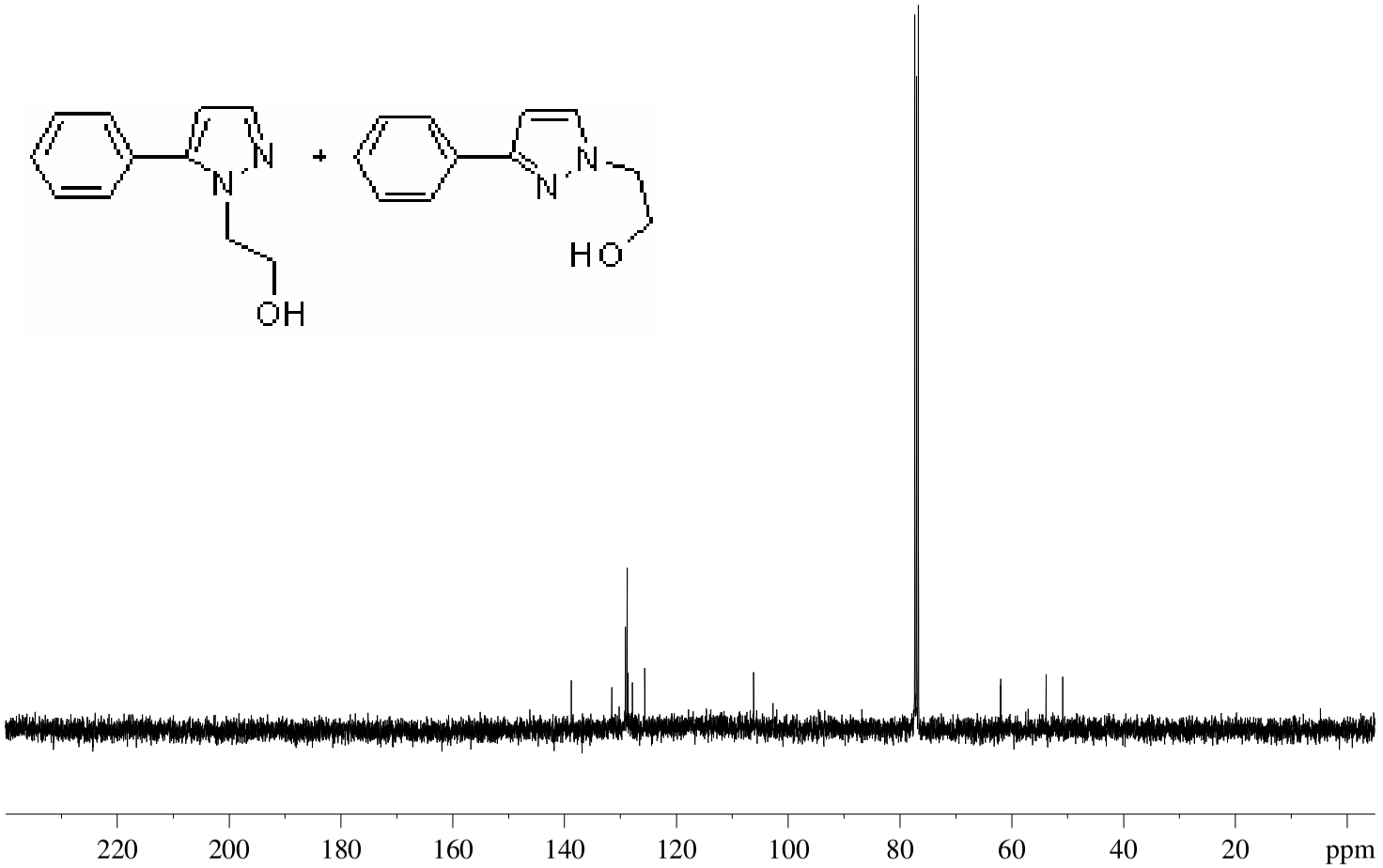

Figure A26. ^{13}C-NMR spectrum of **70D** and **71D**