SYNTHESIS OF FERROCENYL SUBSTITUTED PYRAZOLES BY SONOGASHIRA AND SUZUKI-MIYAURA CROSS-COUPLING REACTIONS

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SYNTHESIS OF FERROCENYL SUBSTITUTED PYRAZOLES BY SONOGASHIRA AND SUZUKI-MIYAURA CROSS-COUPLING REACTIONS

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ABSTRACT

SYNTHESIS OF FERROCENYL SUBSTITUTED PYRAZOLES BY SONOGASHIRA AND SUZUKI-MIYAURA CROSS-COUPLING REACTIONS

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Pyrazoles constitute one of the most important classes of heterocyclic compounds due to their interesting chemical and biochemical features. Researchers have studied many pyrazole containing structures for almost over a century in order to investigate the various biological activities possessed by these molecules. A new and important trend in these studies is to produce ferrocenyl substituted pyrazoles since ferrocene attracts considerable interest in the research field of organometallic and bioorganometallic chemistry because of its valuable chemical characteristics like high stability, low toxicity and enhanced redox properties. Moreover, the results of the studies focusing on ferrocenyl compounds have been quite promising. Therefore, the scope of this project involves the combination of the essential structural features of pyrazoles with a ferrocene moiety, which could provide new derivatives with enhanced biological activities. In the course of the project the synthesis of new pyrazole derivatives was performed through Sonogashira and Suzuki-Miyaura cross-coupling reactions of 5-ferrocenyl-4-iodo-1-phenyl-1*H*-pyrazole with terminal alkynes and boronic acids respectively in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$. Although Sonogashira and Suzuki-Miyaura coupling reactions are well known in literature, they were not studied in much detail with multi-substituted

pyrazoles. This also revealed the requirement of the reinvestigation of the reactions and improvement of the yields of pyrazoles by optimizing the reaction conditions.

Keywords: Pyrazole, Ferrocene, Coupling Reactions, Electrophilic Cyclization

ÖZ

SONOGASHİRA VE SUZUKİ-MİYAURA ÇAPRAZ KENETLENME TEPKİMELERİ İLE FERROSENİL SÜBSTİTÜYE PİRAZOLLERİN SENTEZİ

Karabıyıkoğlu, Sedef
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Tez Yöneticisi: Prof. Dr. Metin Zora

Temmuz 2010, 97 sayfa

İlginç kimyasal ve biyokimyasal özelliklerinden dolayı pirazoller heterosiklik bileşiklerin en önemli sınıflarından birini teşkil etmektedir. Sahip oldukları çeşitli biyolojik aktiviteleri incelemek amacıyla araştırmacılar yaklaşık bir yüzyıldır pirazol içeren yapılar üzerinde çalışmaktadır. Bu çalışmalardaki yeni ve önemli bir eğilim ise ferrosenil sübstitüye pirazoller üretmektir çünkü ferrosen yüksek kararlılık, düşük toksisite ve gelişmiş indirgenme-yükseltgenme özellikleri gibi nitelikleriyle organometalik ve biyoorganometalik kimya alanında yoğun bir ilgiyi üzerine çekmektedir. Ayrıca ferrosenil bileşiklere odaklı çalışmalardan şu ana kadar elde edilen sonuçlar oldukça gelecek vadedicidir. Bu nedenle bu proje pirazollerin temel yapısal özellileri ile ferrosen biriminin biraraya gelmesi sonucu potansiyel biyolojik aktivitelere sahip yeni türevlerin oluşturulmasını kapsamaktadır. Proje süresince 1-fenil-5-ferrosenil-4-iodo-1*H*-pirazol'ün terminal alkinler ve boronik asitler ile $PdCl_2(PPh_3)_2$ katalizörlüğünde Sonogashira ve Suzuki-Miyaura çapraz kenetlenme tepkimelerine girmesiyle yeni pirazol türevleri sentezlenmiştir. Bu kenetlenme tepkimeleri literatürde iyi bilinen tepkimeler olmalarına rağmen çoklu-sübstitüye pirazoller ile ayrıntılı olarak çalışılmamışlardır. Bu da tepkimelerin tekrar

incelenmesinin ve ürün verimlerini arttırmak için deney koşullarının optimize edilmesinin gerekliliğini ortaya çıkarmıştır.

Anahtar Kelimeler: Pirazol, Ferrosen, Kenetlenme Tepkimeleri, Elektrofilik Halkalaşma

To My Parents and Sister,

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TABLE OF CONTENTS

LIST OF TABLES

TABLES

LIST OF FIGURES

FIGURES

ABBREVIATIONS

bn	billion
br	broad (spectral)
^{o}C	degrees Celcius
δ	chemical shift in parts per million downfield from
d	doublet (spectral)
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)
min	minutes
mmole	millimole
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million (in NMR)
q	quartet (spectral)
r.t.	room temperature
s	singlet (spectral)
t	triplet (spectral)
THF	tetrahydrofuran
TLC	thin layer chromatography
DCM	dicholoromethane
DMAc	dimethylacetamide
DMF	dimethylformamide

CHAPTER 1

INTRODUCTION

Organic chemistry is the science dealing with compounds of carbon which are central to life on the earth. These compounds provide the proteins that catalyze vital reactions in living organisms and that form the essential parts of our blood, tissue, muscle and skin [1]. Moreover, organic molecules constitute nucleic acids, RNA and DNA that control our genetic structure and the fundamental processes in the cells. In addition to these, the foods we consume everyday, chemicals used for treatments of diseases, gasoline propelling our cars and many other materials that have an important role in our life are composed of organic compounds [2].

Many organic compounds adopt ring systems as components in their structures. When the ring system is built up by carbon and at least one other element (e.g. oxygen, nitrogen, sulfur) the molecule is classified as *heterocyclic*. Heterocyclic chemistry is one of the most important branches in organic chemistry since about half of the organic compounds known today have at least one heterocyclic moiety [3].

It is possible to find many heterocyclic compounds in nature and the functions of these compounds are generally of fundamental importance to biological systems. For instance, nucleic acid bases are very crucial to the mechanism of replication and they are the derivatives of purine and pyrimidine heterocyclic systems. Tryptophan and histidine, two of the essential amino acids, are heterocyclic structures. Chlorophyll is the essential component of photosynthesis and heme is a necessary unit for the oxygen transport process in higher plants. Both of these molecules are derivatives of heterocyclic porphyrin ring system. Vitamins that we need for our diet like vitamin B_1, B_2, B_3, B_6 and C are heterocyclic [3].

Besides their occurrences in natural substances, heterocycles find wide applications in industrial and medicinal chemistry, agriculture, and in many technological fields. For example, melamine (2,4,6-triamino-1,3,5-triazine), when treated with formaldehyde, produces a widely used plastic known as *Formica* which has good heat resistance and used mostly for manufacture of house wares. Polybenzimidazole which is an example of heterocyclic polymers forms fibers which are used to weave one of the most fire resistant fabrics [4].

Heterocycles also compose a large number of agrochemicals. For example, a widely used fungicide is davicil, a pyridine derivative. Moreover, triazoles, like cyproconazole, are good plant fungicides. Other triazoles, such as paclobutrazol, do not have that effective antifungal activity, but they are utilized as plant-growth regulators (Figure 1) [4].

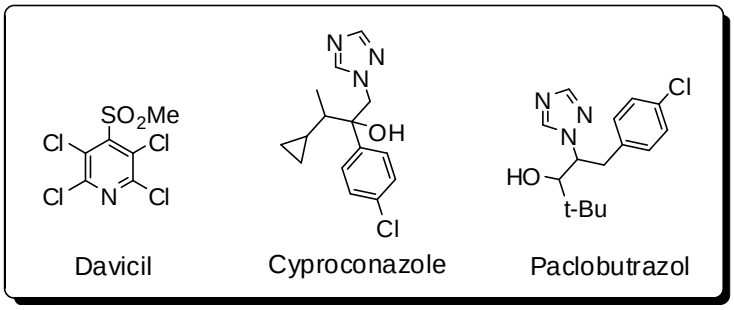


Figure 1. Examples of heterocyclic compounds used as agrochemicals.

The drugs designed for medicinal applications include a broad spectrum of different chemical structures, but there is no doubt that a large group of these structures are heterocyclic small molecules or they have heterocyclic structural components. For example, many antibiotics are heterocyclic. Moreover, even before the development of modern chemistry heterocyclic alkaloids were the active ingredients in many natural remedies and some are still used today, such as morphine derivatives [4,5].

In order to emphasize the importance of heterocycles in medicinal chemistry, it should be noted that seven of the top 10 best selling prescription drugs by amount in the year June 2006-June 2007, were small heterocyclic molecules [6]. These are atorvastatin (Lipitor; \$13.5bn; a statin for cholesterol reduction), esomeprazole (Nexium; \$6.9bn; a proton-pump inhibitor for reduction of gastric acid), clopidogrel (Plavix; \$5.8bn; an anti-platelet agent to prevent blood clots), olenzapine (Zyprexa; \$4.9bn; an anti-schizophrenic), risperidone (Risperdal; \$4.8bn; an anti-schizophrenic), amlodipine (Norvasc; \$4.5bn; an anti-hypertensive agent) and quetiapine (Seroquel; \$4.2bn; for treatment of schizophrenia and bipolar disorder) (Figure 2) [4].

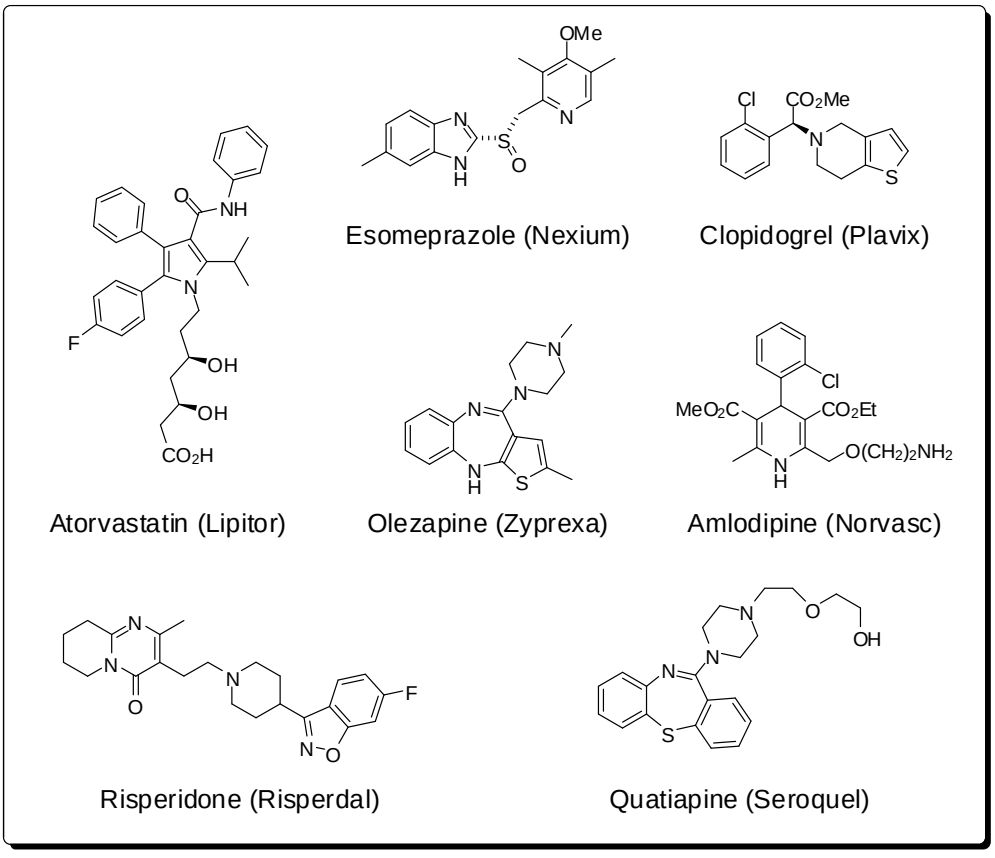


Figure 2. Structures of the heterocyclic molecules reported as the seven of the ten best selling prescription drugs in the year 2006-2007.

According to all the facts mentioned previously it can be concluded that heterocyclic chemistry has a very crucial role in research field, industrial developments and human life. Therefore, every study and project dealing with these compounds may have a great contribution to science and technology.

1.1 Pyrazoles

Even though pyrazoles are rarely found in nature [7], they have practical importance in many fields of study. Due to their extensive applications in pharmacology and technology, pyrazole ring systems have been the basis of numerous projects [5,7].

The term *pyrazole* expresses both the unsubstituted parent compound and the class of simple aromatic organic molecules of the heterocyclic series characterized by a 5-membered cyclic structure made up of three carbon atoms and two nitrogen atoms connected to each other adjacently [8]. In 1889, Buchner described pyrazole for the first time after a decarboxylation reaction he performed with pyrazole-3,4,5-tricarboxylic acid (**1**) and obtained the pyrazole (Figure 3) [9].

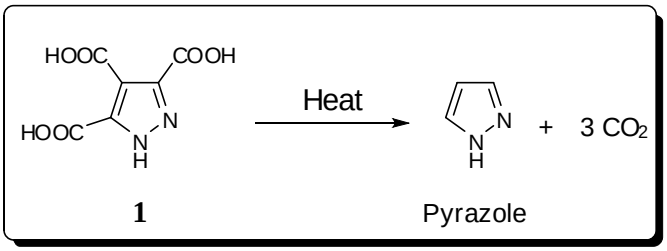


Figure 3. Decarboxylation of pyrazole-3,4,5-tricarboxylic acid (**1**) to pyrazole.

Until 1950s, pyrazole was believed to be obtained only synthetically. However, in 1954, the first natural pyrazole derivative, 3-*n*-nonylpyrazole (**2**), was extracted from a plant called *Houttuynia Cordata* by the Japanese workers and they discovered that

the molecule shows antimicrobial activity. After this event, another natural pyrazole derivative, *levo-β*-(1-pyrazolyl)alanine (**3**) which is a pyrazolic amino acid, was isolated from the seeds of watermelon (Figure 4) [9].

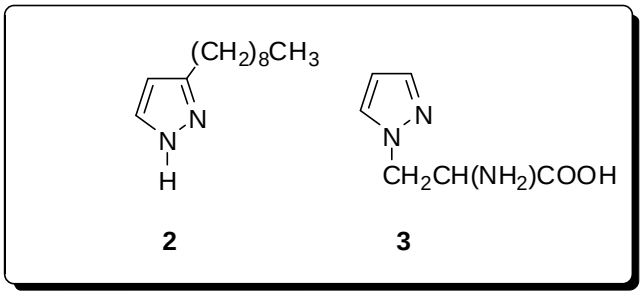


Figure 4. First isolated natural pyrazole derivatives.

Pyrazoles are aromatic molecules due to their planar conjugated ring structure with six delocalized π-electrons. Therefore, many important properties of these molecules were analyzed by comparing them with the properties of benzene derivatives [10]. Like many other nitrogen involving heterocycles, different tautomeric structures can be written for pyrazole. Unsubstituted pyrazoles can be represented in three tautomeric forms (Figure 5) [9].

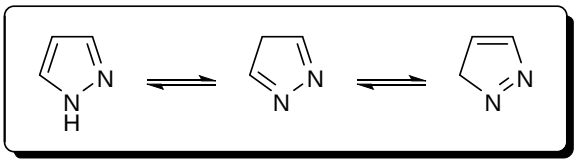


Figure 5. Three tautomeric forms of unsubstituted pyrazole.

For the pyrazole compounds in which two carbon atoms neighboring the nitrogen atoms in the ring have different substituents five tautomeric structures are possible (Figure 6) [9].

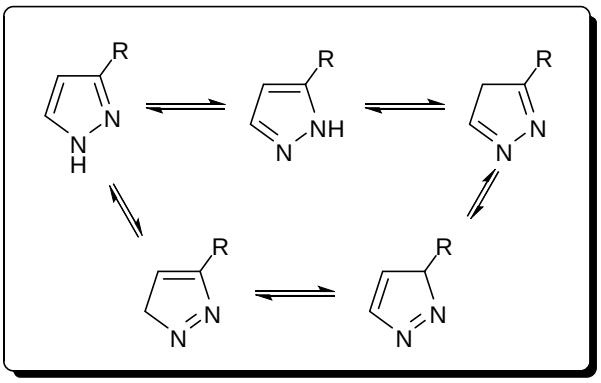


Figure 6. Five tautomeric forms of substituted pyrazole derivative.

The imido group located in the structure of pyrazole provides some interesting properties through hydrogen bonding. For example, pyrazole has a high boiling point which is nearly 187 ^{o}C but its *N*-methyl derivative boils at lower temperature (127 ^{o}C). In addition, pyrazole has a normal behavior in vapor phase but, when dissolved in some organic solvents like benzene or cyclohexane, association occurs due to the hydrogen bonding [5].

1.1.1 Synthesis of Pyrazoles

There are many different methods in literature designed to synthesize pyrazole derivatives. These methodologies include various reactions, transformations and synthetic routes depending on the substitution pattern and number of substituents in the synthesized pyrazole structures [11]. Due to the large variety of studies conducted, only some of the main methodologies were covered in the content of this text.

The most common method to synthesize pyrazoles is the cyclocondensation of hydrazines with carbonyl compounds having two electrophilic carbons in 1,3 locations. In these reactions, hydrazines behave like a bidentate nucleophile and react

with 1,3-dicarbonyl compounds **4** or *α,β*-unsaturated aldehydes or ketones **5-7** (Figure 7) [3,11].

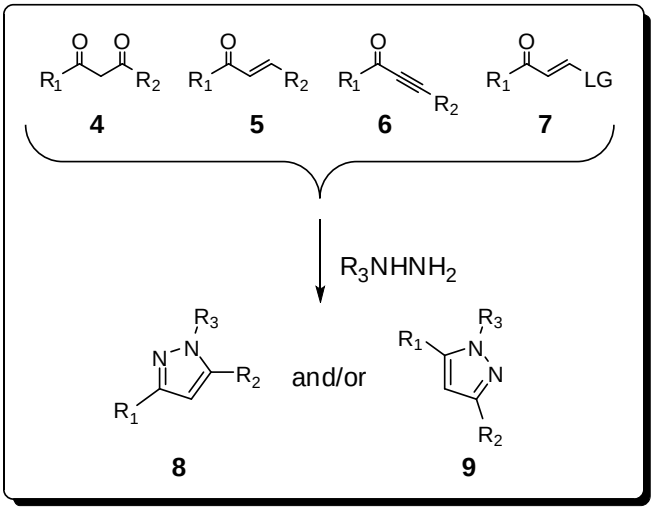


Figure 7. Synthesis of pyrazoles by the reactions of hydrazines with 1,3-dicarbonyl compounds **4** and *α,β*-unsaturated aldehydes or ketones **5**, **6**, **7**.

These reactions often involve different regioselectivities depending upon reaction conditions and substrates. For example, if an unsymmetrical reagent is used in the reaction, mixtures of isomers **8** and **9** are usually produced when the reaction is performed with substituted hydrazines but if hydrazine is unsubstituted then the formation of isomer **9** is hindered by the prototropic tautomerism of pyrazoles (Figure 7) [11]. An important example for this common methodology was reported by Gosselin research group. The group studied the reactions of 1-arylbutane-1,3-diones (**10**) with arylhydrazine hydrochlorides **11** under acidic conditions, which afforded a mixture of pyrazoles **12** and **13** (Figure 8) [12].

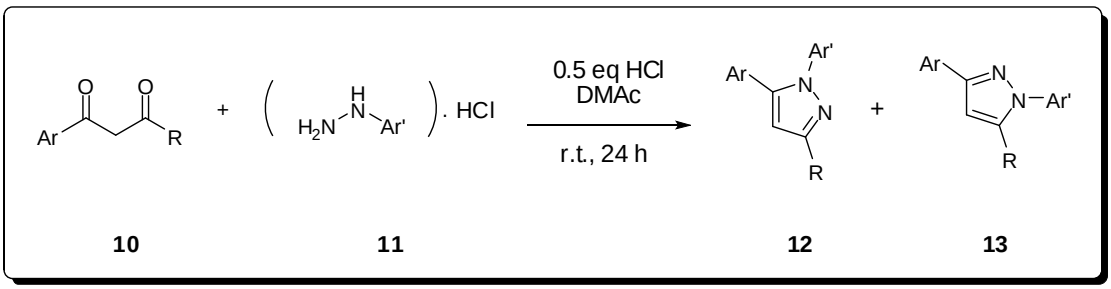


Figure 8. Synthesis of pyrazoles by the reaction of 1-arylbutane-1,3-diones **10** with arylhydrazine hydrochlorides **11**.

Another important study on this matter was conducted by Katritzky and co-workers. This research group synthesized 1-methyl(aryl)-3-phenyl-5-alkyl(aryl)pyrazoles **16** by the regioselective reaction of *α*-benzotriazolyl-*α,β*-unsaturated ketones **14** with hydrazines through pyrazoline intermediates **15** (Figure 9) [13].

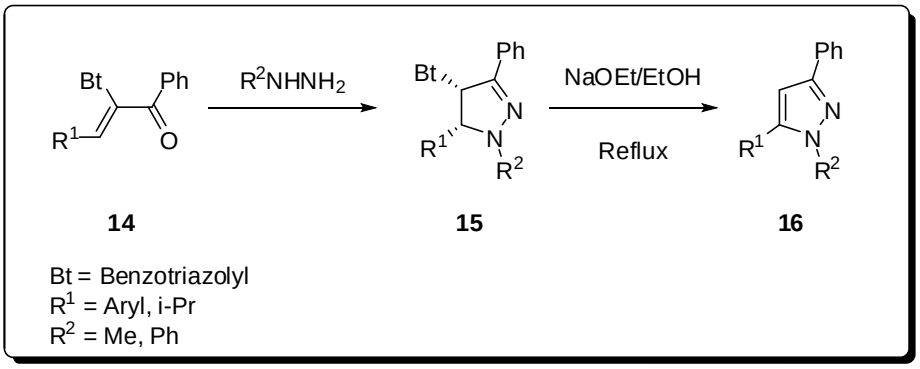


Figure 9. Synthesis of 1-methyl(aryl)-3-phenyl-5-alkyl(aryl)pyrazoles **16** by the regioselective reaction of *α*-benzotriazolyl-*α,β*-unsaturated ketones **14**.

The second widely used synthetic methodology for the synthesis of pyrazoles involves 1,3-dipolar cycloaddition of diazoalkanes or nitrilimines with alkenes or alkynes. The former pathway is especially common for the synthesis of dihydropyrazoles. These compounds can be synthesized by the cycloaddition of diazoalkanes to *α,β*-unsaturated ketones [11,14].

As mentioned, 1,3-dipolar cycloaddition reaction of diazo compounds with triple bonds is often utilized in the synthesis of pyrazoles. A procedure for this type of synthesis starts with the in situ generation of diazo compounds **18** from tosylhydrazones of aldehydes **17** by the treatment with base. Then the intermediate **18** reacts with alkyne and generates the corresponding pyrazole (**19**) (Figure 10) [15].

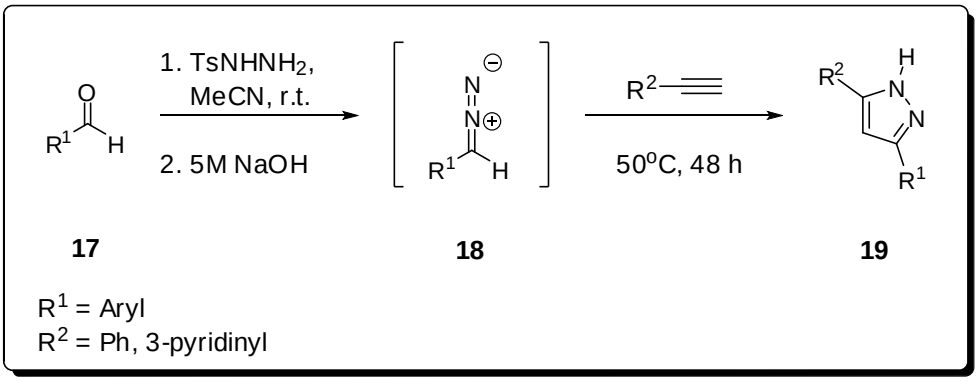


Figure 10. Synthesis of pyrazole derivatives by 1,3-dipolar cycloaddition of diazo compounds **18** with acetylenes.

Pyrazoles can also be prepared by a [1 + 4] approach. A procedure based on this approach involves the reaction of enolizable as well as unsaturated or aromatic aldehydes **17** with diethoxyphosphorylacetaldehyde tosylhydrazone (**20**). The intermediate for this reaction is *α,β*-unsaturated tosylhydrazones **21** (Figure 11) [16]. Lastly, substituted pyrazoles can also be generated by the functionalization of less substituted pyrazoles. These procedures are generally based on multi-step reaction pathways with special reagents [17].

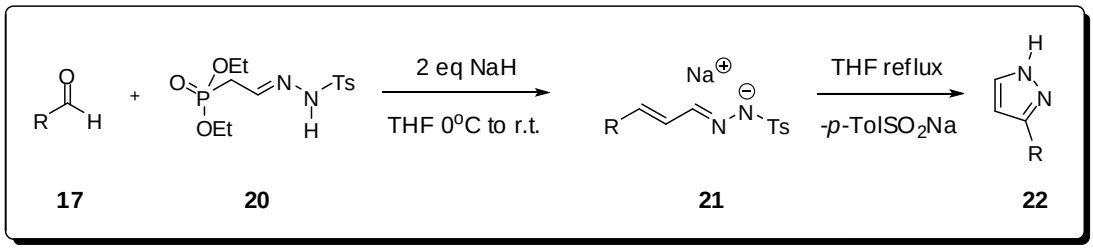


Figure 11. Synthesis of 3-(5)-substituted pyrazoles **22** by a [1 + 4] approach from aldehydes **17** and diethoxyphosphorylacetaldehyde tosylhydrazone (**20**).

Consequently, the synthesis of pyrazoles has been studied by many research groups and the regioselective properties of these reactions have been examined. Chemists devised a wide range of methods affording pyrazole derivatives and recently more studies are being conducted [11]. However, the design of regiospecific pyrazole formation reactions is still a compelling study topic.

1.1.2 Biologically Important Pyrazole Derivatives

Pyrazole ring structure provides the core of many biologically valuable compounds which are potential insecticides [18], herbicides [19], monomers of important polymers with improved chemical and/or physical properties [20] or they are the active molecules of widely used medicines [7]. Moreover, many pyrazolic molecules act as analgesic, antimicrobial, antiinflamatory, antitumor and antipsychotic agents [21]. All the fascinating characteristics of pyrazoles made them one of the most popular research topics among the chemists for the last decades and a large number of new derivatives have been synthesized [7].

Fipronil (**23A**) (Figure 11) is one of the most important insecticides which works effectively by blocking the γ-aminobutric acid (GABA) receptor/chloride channel in the neurologic system [22,23]. A more effective insecticide is the photoaffinity probe of fipronil (**23B**) (Figure 12) [24].

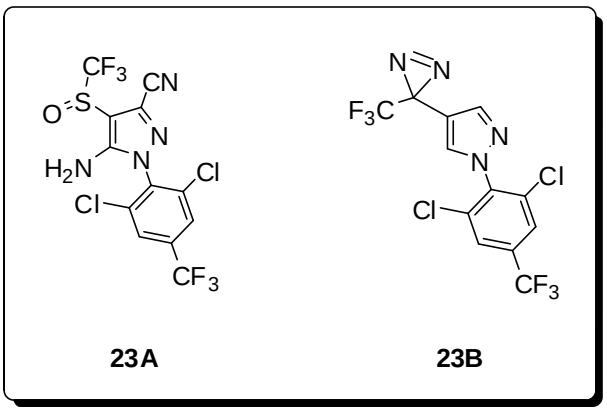


Figure 12. Structures of Fipronil (**23A**) and fipronil based probe (**23B**).

Other important examples of biologically active pyrazole derivatives are the pyrazole inhibitors **24** for the DHODase (Dihydroorotate dehydrogenase) enzyme of the bacterium Helicobacter pyroli that causes many gastrointestinal disorders including ulcer and gastric cancer [25,26] (Figure 13). DHODase enzyme is an essential unit in the biosynthesis of pyrimidine and inhibition of this enzyme results in the termination of cells. This fact is the working pattern of pyrazole inhibitors in Helicobacter pyroli [26]. There are other pyrazole based inhibitors; for example, Celecoxib (**25**) is basically a selective pyrazole inhibitor and it is used for the treatment of arthritis symptoms and relief of pain (Figure 13) [27]. In addition to Celecoxib, DPC 423 (**26**) is a pyrazolic inhibitor active on blood coagulation factor Xa (Figure 13) [27].

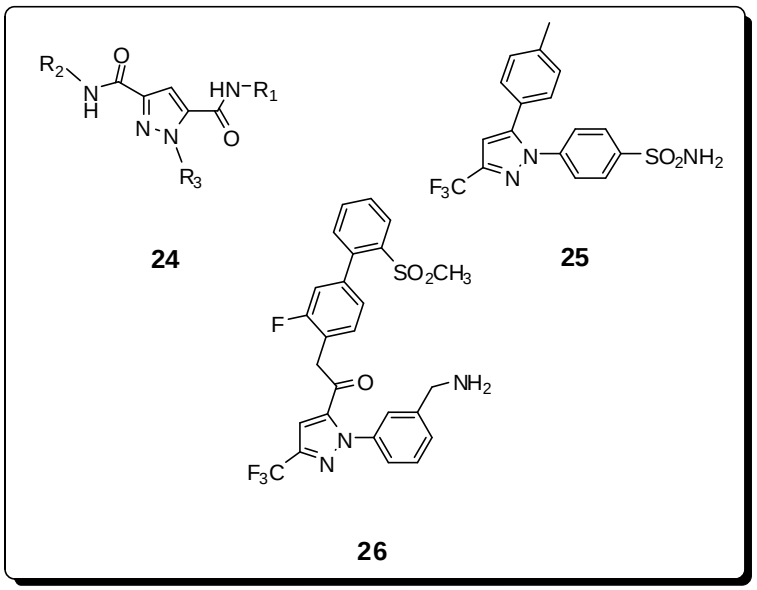


Figure 13. Structures of DHODase pyrazole inhibitors **24**, Celecoxib (**25**) and DPC-423 (**26**).

The sodium hydrogen exchangers (NHEs) are proteins which transport extra Na^+ ions from outside the cell membrane in place of H^+ ions inside the cell. One of the six isoforms of NHEs is NHE-1 and this isoform is essential for mediating myocardial damage during reperfusion and ischemia. However, due to its very high activity, NHE-1 can be harmful for the heart in the course of reperfusion. Therefore, an effective inhibitor is necessary since NHE-1 is the only isoform in the heart [28]. Zoniporide (**27**) having a pyrazole core structure is the selective inhibitor with desired properties (Figure 14) [29].

Viagra is the first oral drug active in the treatment of male impotance and the active molecule for this medicine is the pyrazole derivative Sildenafil (**28**) (Figure 14). This molecule inhibits the phosphodiesterase enzyme located in human corpus cavernosum [30].

PNU-32945 (**29**) (Figure 14), a polysubstituted pyrazole derivative, is a very important compound since it inhibits the reverse transcriptase enzyme of HIV-1, a

class of HIV (Human Immunodeficiency Virus). In other words, this pyrazole structure prevents the virus from reproducing itself [31].

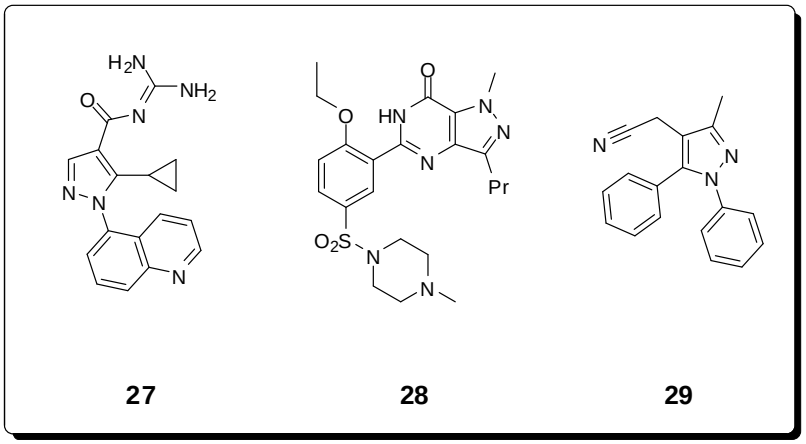
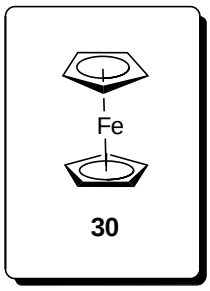


Figure 14. Structures of Zoniporide (**27**), Sildenafil (**28**) and PNU-32945 (**29**).

1.2 Ferrocene and biologically active ferrocene derivatives

Ferrocene (**30**) has been studied widely in organometallic and bioorganometallic chemistry since its discovery (Figure 15). It was first prepared unintentionally in 1951 separately by the research groups of Miller, Tebboth and Tremaine, and of Kealy and Pauson. However, the interesting double-cone sandwich structure was proposed by E. O. Fischer, G. Wilkinson and R. B. Woodward in 1952 [32].

Ferrocene is a crystalline diamagnetic solid with a structure involving iron as the metal center and two cyclopentadienyl rings located around this center. In general, such compounds with this specific structure are called as *metallocenes* [33]. The cyclopentadienyl rings in ferrocene are η^5 type ligands and they are aromatic [34]. Moreover, having 18 valence electrons, ferrocene is one of the most stable organometallic compounds [35].



30

Figure 15. Structure of ferrocene (**30**).

It is possible to synthesize many ferrocenyl substituted compounds starting from ferrocene itself since it is a quite stable substance under various conditions [36]. The most common way of ferrocene synthesis is the deprotonation of cyclopentadiene with KOH and treating with $FeCl_2$ in DMSO (Figure 16) [34].

Figure 16. Preparation of ferrocene.

After the preparation of ferrocene, many important and practical reactions such as Friedel-Crafts acylation/alkylation, Vilsmeier formylation, dimethylamino-methylation and mercuration can be performed with this metallocene because it shows chemical properties of an electron rich aromatic compound (Figure 17) [37].

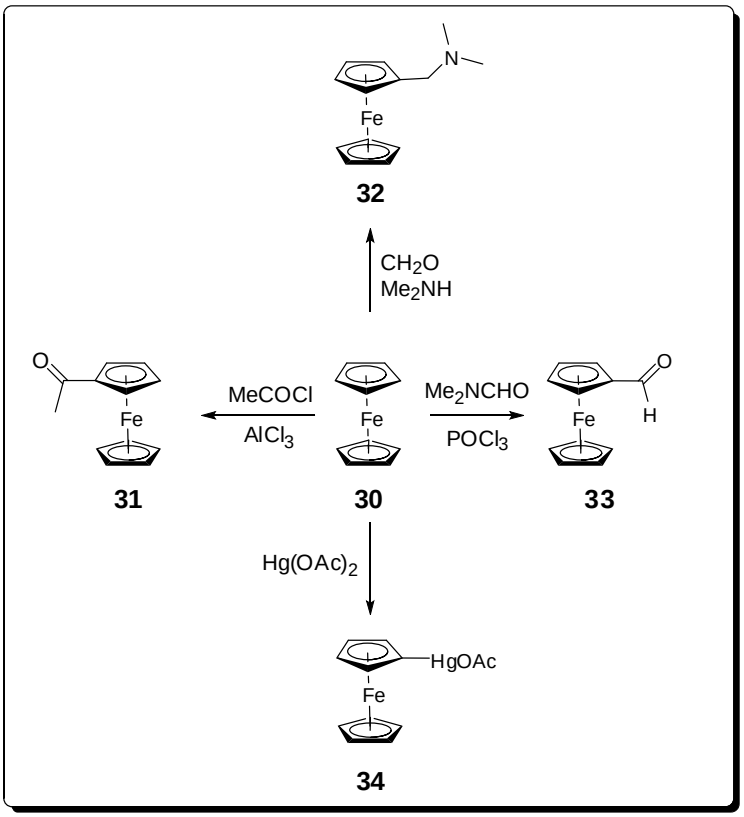


Figure 17. Typical substitution reactions of ferrocene (**30**).

Ferrocene has numerous favorable chemical features that make it one of the most appealing compounds for the researchers during the last decades. It is neutral, highly stable and non-toxic [38], and also it carries many biochemically valuable properties like membrane permeation, solubility in a large array of solvents and enhanced redox abilities [39]. Due to all these characteristics, chemists decided to attach ferrocene unit to biologically active molecules in order to increase the potency of the parent structures [38]. For instance, Jaouen and his co-workers synthesized ferrocenyl analogues of tamoxifen (**35**) and hydroxytamoxifen (**36**), which are the compounds used in the treatment of hormone-independent breast cancer [40]. They observed that ferrocifens, the ferrocenyl analogues, **37** are more active [41]; moreover, they work successfully in the treatment of both hormone-dependent and independent breast cancer (Figure 18) [42]. Later in 2009 Jaouen research group reported that the ferrocenophane derivatives **38** of ferrocifens are even more toxic against breast cancer cell lines (Figure 18) [43].

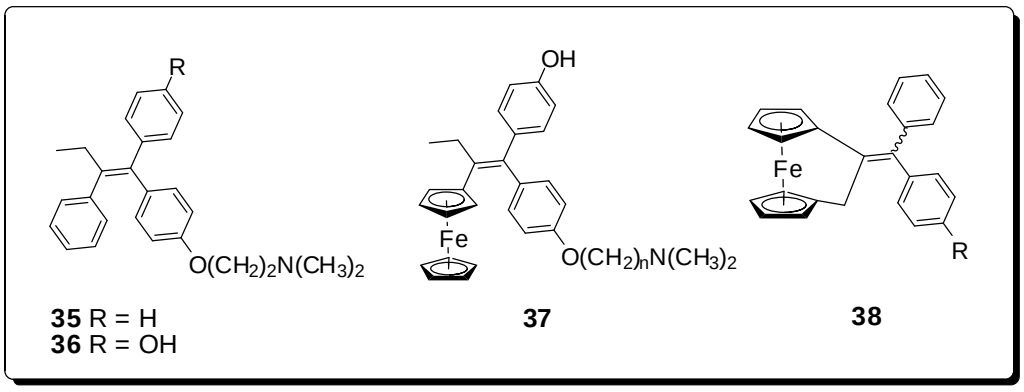


Figure 18. Structures of tamoxifen (**35**), hydroxytamoxifen (**36**), ferrocifens **37** and ferrocenophanes **38**.

Ferrocifens are not the sole ferrocenyl anticancer agents. For example, the molecule **39** is active against the colon cancer cell line, Colo 205 (Figure 19) [44,45]. It was proved that not only the neutral ferrocene derivatives are anti carcinogenic, but also the salts of ferrocene such as ferrocenium tetrafluoroborate (**40**) (Figure 19) have good activity as anticancer agents [46].

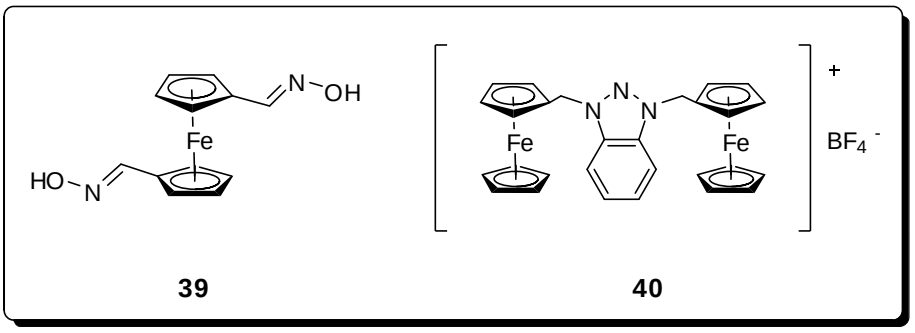


Figure 19. Structures of ferrocenyl derivatives with anticancer activity.

Besides their crucial role in cancer treatments, ferrocenyl compounds are utilized for many biological applications. The most dangerous malaria parasite *Plasmodium falciparum* was found to be resistant to effective anti malaria drugs chloroquine,

mefloquine and quinine and researchers decided to find a solution for this problem [47]. The results of the studies showed that ferroquine derivatives **41** act as anti malarial agents against this parasite (Figure 20) [48]. Another important outcome of studies on ferrocene chemistry was reported by Fang research group. They showed that ferrocene-triadimenol analouges **42** effectively regulate the plant growth (Figure 20) [39].

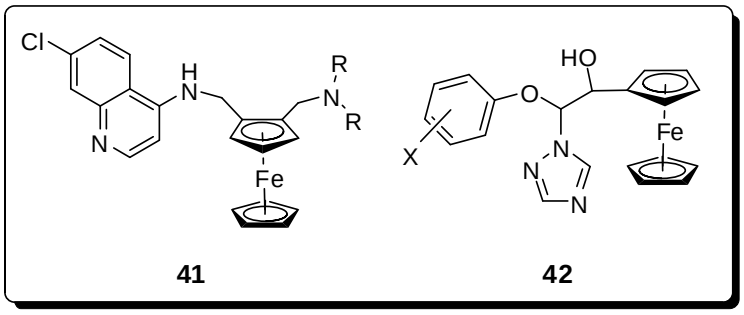


Figure 20. Structures of ferroquine **41** and ferrocene-triadimenol derivatives **42**.

1.3 Ferrocenyl Pyrazoles

It is obvious that both pyrazole and ferrocene chemistries are important research topics because of their wide and efficient applications in many areas. Due to all fascinating properties of these two chemical units, it is inevitable to wonder the results of a study based on the combination of them. However, it is quite surprising that the study of ferrocenyl-substituted pyrazoles was in limited scale. In recent years, more effort has been spent on this subject. Especially, Zora research group has focused on the synthesis of ferrocenyl pyrazole derivatives and provided unignorable contributions [49,50,51].

It was investigated that the synthesis of ferrocenyl pyrazoles can be performed through the reaction of (2-formyl-1-chlorovinyl)ferrocene (**43**) with hydrazines. The reaction produces two isomers of pyrazoles; 1-alkyl/aryl-5-ferrocenylpyrazoles (**44**)

and/or 1-alkyl/aryl-3-ferrocenylpyrazoles (**45**), the former being the single or the major product of the reaction in most cases. The outcome of reaction is affected by the substitution pattern of hydrazines used (Figure 21) [49].

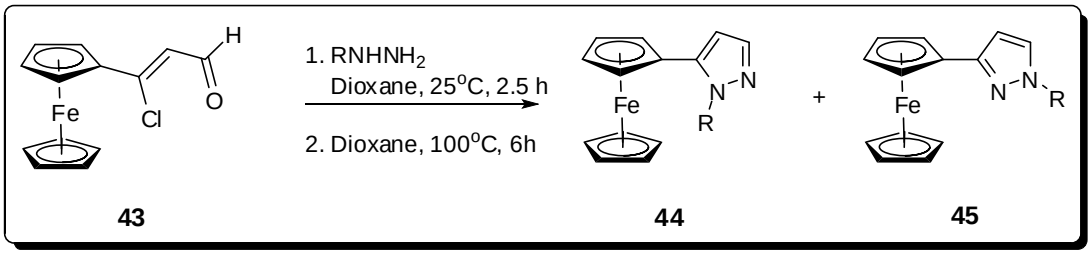


Figure 21. Synthesis of ferrocenyl pyrazoles by the reaction of (2-formyl-1-chlorovinyl)ferrocene (**43**) with hydrazines.

In connection with this study, Zora research group synthesized pyrazoles **44** and **45** by the reaction of 3-ferrocenylpropynal (**46**) with hydrazinium salts, as well (Figure 22) [50]. These reactions afforded pyrazoles **44** and/or **45** in relatively higher yields but, in most cases, the proportion of pyrazole isomer **45** increased at the expense of pyrazole isomer **44**.

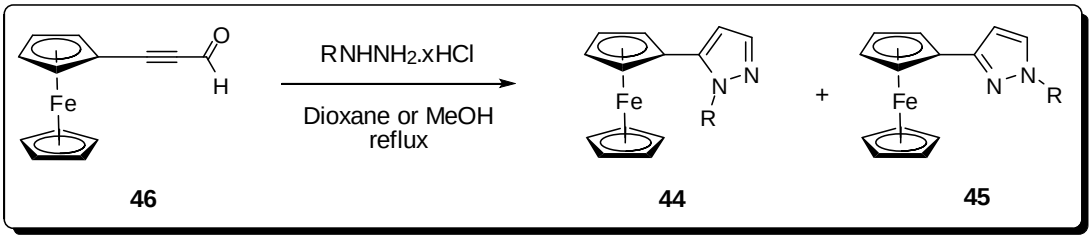


Figure 22. Synthesis of ferrocenyl pyrazoles by the reactions of 3-ferrocenylpropynal (**46**) with hydrazinium salts.

From the synthetic point of view, it is important to develop a regioselective reaction, yielding exclusively or only one pyrazole isomer. This has been achived by

electrophilic cyclization, which generally occurs in very mild reaction conditions and in regioselective manner. When treated with molecular iodine, 3-ferrocenylpropynal hydrazones (**47**), prepared from hydrazines and 3-ferrocenylpropynal (**46**), have undergone electrophilic cyclization to yield 4-iodopyrazole derivatives **48** in good to excellent yields (Figure 23) [52]. These 4-iodopyrazole derivatives **48** are important precursors for the further functionalization of such pyrazoles via metal-catalyzed cross-coupling reactions.

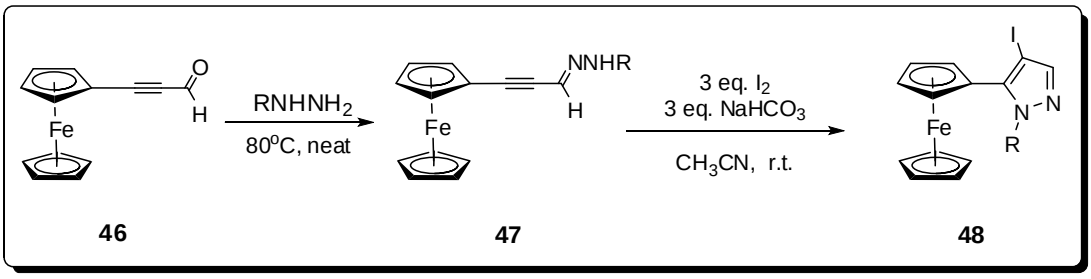


Figure 23. Synthesis of 5-ferrocenyl-4-iodo pyrazoles **48**.

1.4 Sonogashira and Suzuki-Miyaura Cross-coupling Reactions

In organic chemistry, coupling reactions represent a group of procedures in which two hydrocarbons bound each other via the carbon-carbon bond formation with the catalytic effect of metal bearing compounds. When these two molecules are different from each other, the reaction is called cross-coupling reaction. The first laboratory construction of a carbon-carbon bond was achieved by Kolbe in 1845 by the synthesis of acetic acid. Since then carbon-carbon bond-forming reactions have become one of the most important events in the development of chemical synthesis. In the last quarter of the 20th century, especially during 1970s, with the improvements in transition-metal catalysis studies, new methods to combine complex hydrocarbon fragments were designed and these methods created new opportunities in medicinal and process chemistry as well as in total synthesis,

chemical biology and nanotechnology. Among these methods, palladium catalyzed coupling reactions are considered as the most crucial [53,54].

Sonogashira coupling is the reaction of palladium-catalyzed coupling between terminal alkynes and halides [53,55,56]. Actually, this process was first reported independently and at nearly the same time by the groups of Cassar [57] and Heck [58] in 1975. After few months, Sonogashira and co-workers proved that, in many cases, this cross-coupling reaction can work more efficiently if it is accompanied by copper salts (Figure 24) [53,55,56]. Many other procedures for the palladium-catalyzed coupling of terminal acetylenes with sp^2-C halides have been investigated but the Sonogashira pathway with cocatalytic copper salts has been used most widely [53] and provided many conjugated acetylenic compounds, ranging from natural products and pharmaceuticals to nanomaterials [59].

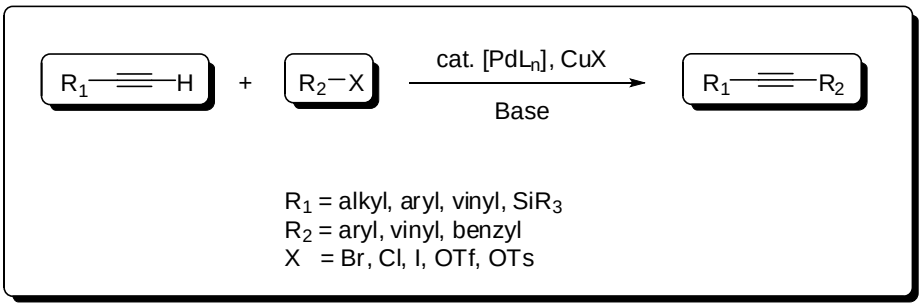


Figure 24. General scheme of Sonogashira coupling reaction.

Another quite practical and efficient palladium-catalyzed coupling reaction is the palladium-mediated C-C bond formation between organoboron compounds and organic electrophiles, like aryl or alkenyl halides and triflates (Figure 25) [53,60]. Today this reaction is known as Suzuki or Suzuki-Miyaura Coupling reaction and it was first reported by the Suzuki research group in 1979 [61,62].

Suzuki-Miyaura reaction is one of the most versatile methods in synthetic chemistry due to availability of the reagents and the mild reaction conditions. Moreover, the

reaction is mostly unaffected by the presence of water, works with a broad range of functional groups, and generally provides high regioselectivity and stereoselectivity [63]. Suzuki coupling is not only suitable for laboratory studies but also it can be used in industry since the inorganic by-product is non-toxic and it can be easily removed from the reaction mixture [63,64].

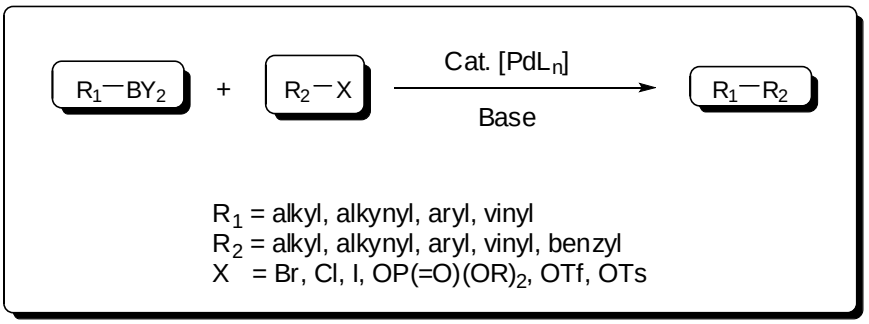


Figure 25. General scheme of Suzuki-Miyaura coupling reaction.

1.5 The aim of the study

Since their discovery, pyrazoles and ferrocenes drove the attention of many researchers due to their interesting chemical characteristics. Assembling the structural features of these two moieties would result compounds with enhanced chemical and biological activities. So it is very important to synthesize new ferrocenyl substituted pyrazole derivatives [49,50]. Therefore, as mentioned before, our research group has investigated the synthesis of ferrocenyl substituted pyrazoles and showed that 1-alkyl/aryl-5-ferrocenylpyrazoles (**44**) and 1-alkyl/aryl-3-ferrocenylpyrazoles (**45**) can be synthesized from (2-formyl-1-chlorovinyl)ferrocene (**43**) and 3-ferrocenylpropynal (**46**) (Figures 21 and 22) [49,50]. Moreover, 5-ferrocenyl-4-iodo pyrazoles (**48**) have been synthesized from corresponding hydrazones derivatives (**47**) in a regioselective manner via electrophilic cyclization reaction initiated with molecular iodine (Figure 23) [52].

The aim of this study is to synthesize a library of ferrocenyl and phenyl substituted pyrazoles via Sonogashira and Suzuki-Miyaura cross coupling reactions of 4-iodopyrazoles with terminal acetylenes and boronic acids, respectively. In the first phase of the study, 5-ferrocenyl-4-iodo-1-phenyl-1*H*-pyrazole (**48**) and 4-iodo-1,5-diphenyl-1*H*-pyrazole (**51**) will be synthesized from 3-ferrocenylpropynal (**46**) and 3-phenylpropynal (**49**) as depicted in Figure 26 [52,65].

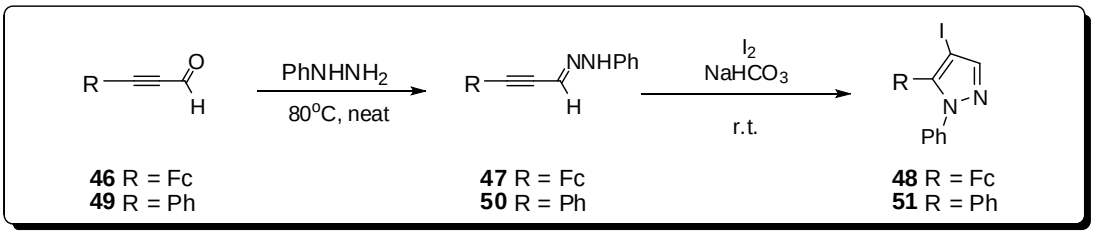


Figure 26. Synthesis of 5-ferrocenyl-4-iodo-1-phenyl-1*H*-pyrazole (**48**) and 4-iodo-1,5-diphenyl-1*H*-pyrazole (**51**).

After preparing 4-iodopyrazoles **48** and **51** as the starting materials, the optimization studies of Sonogashira cross coupling reactions of these compounds with terminal acetylenes (**52**) will be conducted, and with the optimized reaction condition, 4-alkynyl-5-ferrocenyl-1-phenyl-1*H*-pyrazoles (**53**) and 4-alkynyl-1,5-diphenyl-1*H*-pyrazoles (**54**) will be synthesized by using a wide range of terminal alkynes (**52**) (Figure 27) [65].

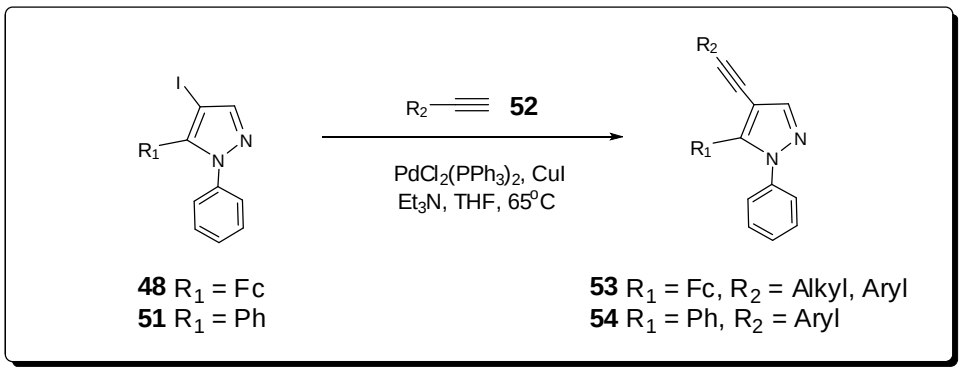


Figure 27. Synthesis of 4-alkynyl-5-ferrocenyl-1-phenyl-1*H*-pyrazoles (**53**) and 4-alkynyl-1,5-diphenyl-1*H*-pyrazoles (**54**).

At the final stage, Suzuki-Miyaura cross coupling reactions of 5-ferrocenyl-4-iodo-1-phenyl-1*H*-pyrazole (**48**) with aryl boronic acids (**55)** will be carried out and a variety of 4-aryl-5-ferrocenyl-1-phenyl-1*H*-pyrazole derivatives (**56**) will be synthesized (Figure 28) [65].

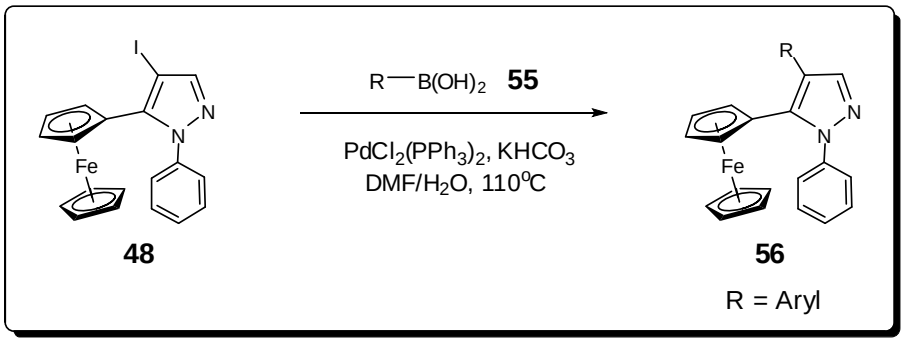


Figure 28. Synthesis of 4-aryl-5-ferrocenyl-1-phenyl-1*H*-pyrazoles (**56**).

In summary, in this thesis, the scope, limitations and mechanisms of Sonogashira and Suzuki-Miyaura cross coupling reactions of 4-iodopyrazoles **48** and **51** with terminal acetylenes and boronic acids will be discussed in detail.

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of 4-alkynyl-5-ferrocenyl-1-phenyl-1*H*-pyrazoles (53)

2.1.1 Synthesis of 5-ferrocenyl-4-iodo-1-phenyl-1*H*-pyrazole (48)

At the first stage of the study, we synthesized 5-ferrocenyl-4-iodo-1-phenyl-1*H*-pyrazole (**48**) starting from commercially available ferrocene (**30**) (Figures 29-32).

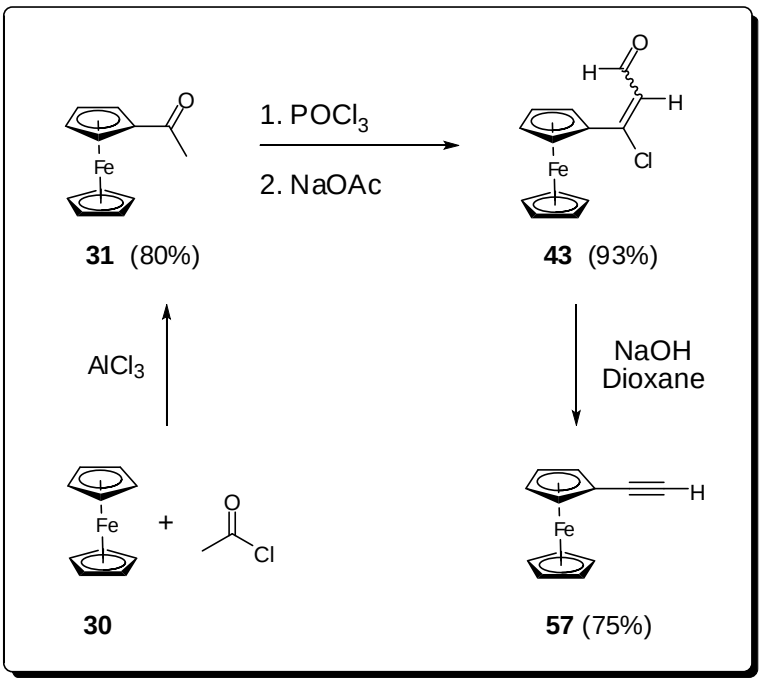


Figure 29. Synthesis of acetylferrocene (**31**), (2-formyl-1-chlorovinyl)ferrocene (**43**) and ethynylferrocene (**57**).

First step of the synthesis was the preparation of acetylferrocene (**31**) through Friedel-Crafts acylation reaction (Figure 29) [66]. Acetylferrocene (**31**) was then treated subsequently with $POCl_3$ and NaOAc to yield (2-formyl-1-chlorovinyl)ferrocene (**43**) [67]. When compound **43** was refluxed with sodium hydroxide in dioxane, ethynylferrocene (**57**) was obtained as the product with 75% yield [67] (Figure 29).

For the synthesis of 3-ferrocenylpropynal (**46**), ethynylferrocene (**57**) was first treated with *n*-butyllithium in THF at -40 ^{o}C under Ar. Then the resulting intermediate, (ferrocenylethynyl)lithium (**58**), was allowed to react with DMF at room temperature. The reaction mixture was extracted with aqueous KH_2PO_4 solution and diethyl ether. Finally, 3-ferrocenylpropynal (**46**) was obtained in 82% yield (Figure 30) [68].

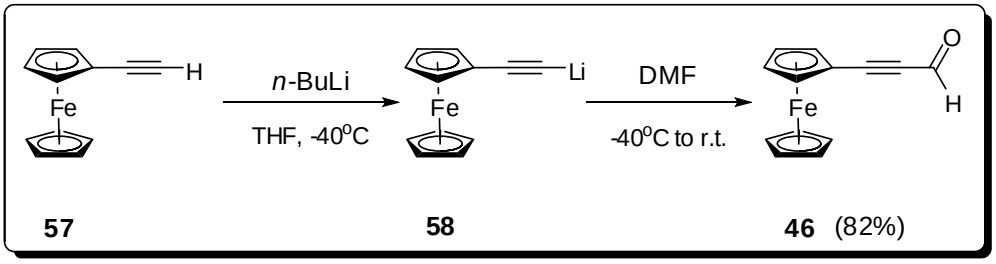


Figure 30. Synthesis of 3-ferrocenylpropynal (**46**).

As stated before, the synthesis of 4-iodopyrazoles was explored and studied in detail by Zora research group. As a part of this previously conducted study, the reaction between 3-ferrocenylpropynal (**46**) with phenylhydrazine was investigated. It was revealed that the reaction produced *E* and *Z* isomers of corresponding hydrazones (**47-*E*** and **47-*Z***) with 36 and 54% yields, respectively, by performing the reaction at 80 ^{o}C in a solvent-free medium (Figure 31) [52]. Two alkynic hydrazone isomers **47-*E*** and **47-*Z*** were easily separated and isolated by column chromatography. Assignments of the isomers were done by the analyses of ^{13}C NMR spectral data, which were supported by literature studies [69]. Moreover, our computational studies

on selected model compounds showed that *Z* isomers of alkynic hydrazones are relatively more stable than corresponding *E* isomers.

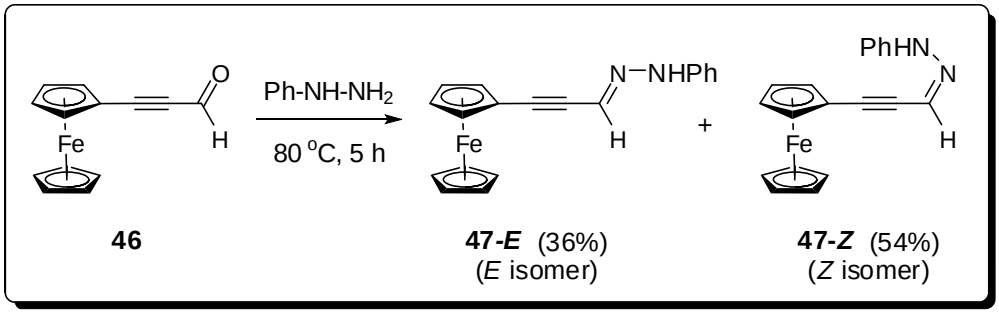


Figure 31. Synthesis of ferrocenyl hydrazones **47-*E*** and **47-*Z***.

At the final stage, the synthesis of 5-ferrocenyl-4-iodo-1-phenyl-1*H*-pyrazole (**48**) was investigated. The reaction of alkynic hydrazones (**47-*E*** or **47-*Z***) with molecular iodine and $NaHCO_3$ in acetonitrile at room temperature resulted in the formation of 4-iodopyrazole **48** in high yields (Figure 32). The reaction mixture was extracted with aqueous sodium thiosulfate solution in order to remove the unreacted iodine and the product was purified by column chromatography [52].

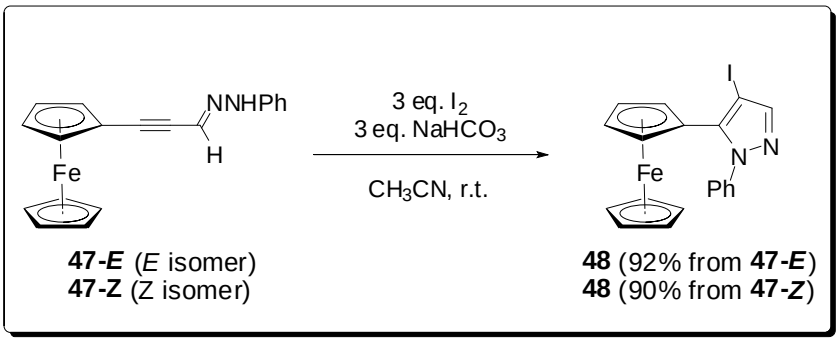


Figure 32. Synthesis of 5-ferrocenyl-4-iodo-1-phenyl-1*H*-pyrazole (**48**).

As stated before, 5-ferrocenyl-4-iodo-1-phenyl-1*H*-pyrazole (**48**) is a convenient precursor for the synthesis of new highly-substituted ferrocenyl pyrazole derivatives through metal-catalyzed cross-coupling reactions. The details of coupling reactions of 4-iodopyrazoles will be discussed in the following sections.

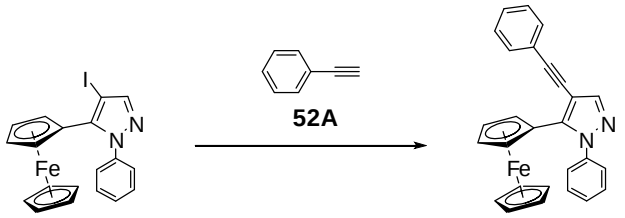
2.1.2 Synthesis of 4-alkynyl-5-ferrocenyl-1-phenyl-1*H*-pyrazole derivatives (53) via Sonogashira Cross-coupling Reaction

In this study, a library of 4-alkynyl-5-ferrocenyl-1-phenyl-1*H*-pyrazoles (**53**) was synthesized by Sonogashira cross-coupling reaction. In fact, Sonogashira reaction is one of the most widely used methods in synthetic chemistry, so there are many possibilities for the choice of catalyst, solvent and base. Therefore, we performed a detailed literature search to narrow down the options and found that Sonogashira coupling reactions of pyrazoles work most effectively with palladium catalysts containing triphenylphosphine (PPh_3) ligands and among these catalysts, bis(triphenylphosphine)palladium(II) dichloride, $PdCl_2(PPh_3)_2$, provides the best results. Moreover, triethylamine (Et_3N) is the most widely used base and the obtained yields of the reactions performed with Et_3N are considerably good [70].

Under the light of these search results, we chose $PdCl_2(PPh_3)_2$ as catalyst, Et_3N as base and CuI as co-catalyst, the latter of which is an essential reagent for Sonogashira coupling reactions. The effect of solvent and temperature was first examined by performing various parallel reactions of 5-ferrocenyl-4-iodo-1-phenyl-1*H*-pyrazole (**48**) with phenylacetylene (ethynylbenzene) (**52A**), yielding 5-ferrocenyl-1-phenyl-4-(phenylethynyl)-1*H*-pyrazole (**53A**). As indicated in Table 1, the reactions performed at room temperature with three different solvents did not produce the desired product **53A** (Entries 1-3 in Table 1). In these experiments, nearly 95% of the starting compound was recovered. Increasing the temperature to 65 ^{o}C and refluxing in THF provided a successful result and **53A** was obtained in 66% yield (Entry 4 in Table 1). In order to improve the yield, the reaction was

carried out at a relatively higher temperature in DMF (Entry 5 in Table 1) but the product formation was not observed and 85% of compound **48** was recovered.

Table 1. Effect of temperature and solvent on the reaction of 5-ferrocenyl-4-iodo-1-phenyl-1*H*-pyrazole (48) with phenylacetylene (52A)[a,b].



48 **53A**

Entry	*Temperature (^{o}C)*	*Solvent*	*% Yield of 53A*
1[c]	25	Et_3N	-
2	25	DMF	-
3	25	THF	-
4	65	THF	66
5	110	DMF	-

[a]All reactions were performed with 1.0 eq. 4-iodopyrazole **48**, 1.2 eq. phenylacetylene, 5% $PdCl_2(PPh_3)_2$, 5% CuI and 1.6 ml Et_3N. [b]Reactions were carried out for approximately 12 hours. [c]Et_3N was used as solvent and base.

We also examined the effect of reaction time on the product yields. The reaction between 5-ferrocenyl-4-iodo-1-phenyl-1*H*-pyrazole (**48**) and phenylacetylene (**52A**) was carried out with different reaction durations and the yields of **53A** were compared. The results are summarized in Table 2. We observed that increasing the reaction time from 4 to 6 hours increased the yield considerably. However, increasing the time from 6 to 12 hours provided a small amount of change in yield while performing the reaction at 27 hours did not even change the previously

observed yield (Table 2). This indicates that the reaction reaches to the optimum time in approximately 12 hours and further refluxing does not stimulates product formation even though the remaining starting reagents are still present in the medium. In summary, the optimum time for the reaction has been found to be approximately 12 hours, which was also supported by TLC (Thin Layer Chromatography) analyses with frequent time intervals during the course of reactions. However, as will be discussed later, some reactions took longer than 12 hours. For such reactions, reaction times were determined by TLC analyses.

Table 2. Effect of reaction time on the product yield[a].

Entry	*Reaction Time*	*% Yield of 53A*
1	4 h	55
2	6 h	64
3	12 h	66
4	27 h	66

[a]All reactions were performed with 1.0 eq. 4-iodo-pyrazole **48**, 1.2 eq. phenylacetylene, 5% $PdCl_2(PPh_3)_2$, 5% CuI and 1.6 ml Et_3N in THF at 65 ^oC.

After these studies, we applied the optimized reaction condition to synthesize a variety of 4-alkynyl-5-ferrocenyl-1-phenyl-1*H*-pyrazole derivatives (**53**). In the reactions, a diverse array of commercially available terminal alkynes (**52**) was employed as illustrated in Figure 33.

The sub-library depicted in Figure 33 was chosen to contain alkynes with various chemical properties. Ethynylbenzene derivatives with different functional groups attached to the aromatic ring (**52A**, **52B**, **52C**, **52G**), acetylenes with aliphatic structural units (**52D**, **52E**, **52H**, **52I**) and alkynes that could participate in hydrogen

bonding as donor and/or acceptors (**52C**, **52D**, **52E**, **52G**) were used in the reactions. Terminal alkyne derivatives involving heterocyclic (**52F**) and organometallic (**57**) moieties were also employed in the reactions (Figure 33). Among the Sonogashira cross-coupling reactions attempted, only two failed. We could not observe any product formation in the reactions carried out with alkyl substituted terminal acetylenes **52H** and **52I** even after 48 hours.

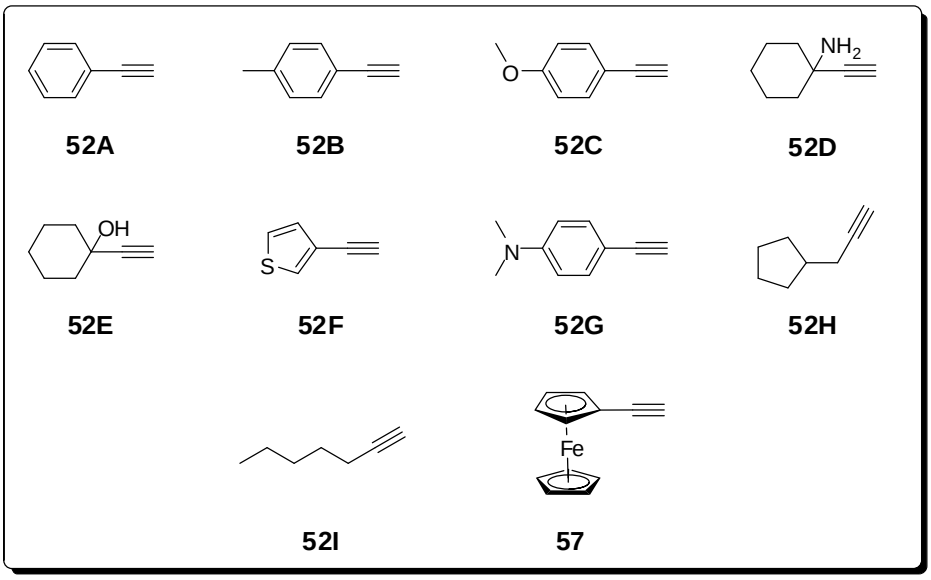


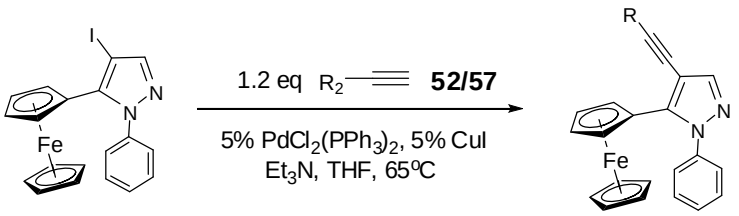
Figure 33. Terminal alkyne sub-library.

An important point to mention here is that contrary to its very important catalytic effect, the existence of copper salts as co-catalyst in Sonogashira reactions may sometimes cause disadvantages. For instance, the in situ generation of copper acetylides often produces homocoupling products of terminal alkynes when exposed to oxidative agents or air. This kind of coupling is called as *Glaser Coupling* [54,71]. It was reported that reductive atmosphere created with hydrogen gas generally prevents homocoupling, but this is a difficult and unpractical method [54,72]. Alternatively, adding terminal alkynes slowly to the reaction medium can eliminate homocoupling [73]. Therefore, in this study, acetylenes were added slowly to the

reaction flask in small portions. Moreover, coupling reactions were done under Ar atmosphere to provide an oxygen free medium.

Table 3 shows the results obtained from reactions of 4-iodopyrazole **48** with terminal alkynes **52A-G** and **57**. As shown in Table 3, reaction times changed from 8 to 25 hours while the yields of products were ranged from moderate to good (37 to 78%). It should be noted that extraction of the reaction mixture with an aqueous phase was avoided in order to eliminate any possible decomposition of products upon exposure to water. In order to prevent the substance loss, the concentrated crude products were directly subjected to flash chromatography.

Table 3. Synthesis of 4-alkynyl-5-ferrocenyl-1-phenyl-1*H*-pyrazoles (**53A-H**).



48 **53**

Entry	***R***	***Product***	***Time (h)***	***Yield (%)***
1	phenyl	**53A**	12	66
2	*p*-tolyl	**53B**	25	37
3	4-methoxyphenyl	**53C**	8	78
4	1-amino-1-cyclohexyl	**53D**	20	68
5	1-hydroxy-1-cyclohexyl	**53E**	14	70
6	3-thiophenyl	**53F**	18	62
7	4-$(CH_3)_2NC_6H_4$	**53G**	15	44
8	ferrocenyl	**53H**	12	68

Figure **34** presents the structures of 4-alkynyl-5-ferrocenyl-1-phenyl-1*H*-pyrazole derivatives **53A-H**.

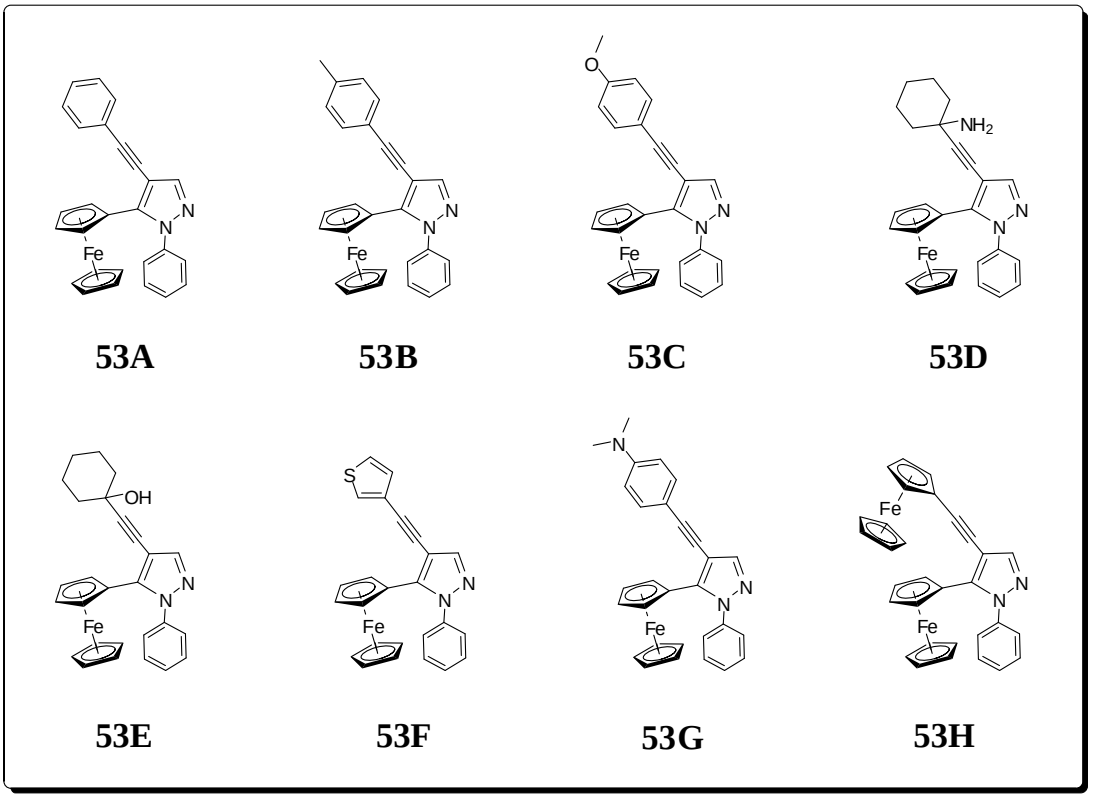


Figure 34. Structures of the synthesized 4-alkynyl-5-ferrocenyl-1-phenyl-1*H*-pyrazoles **53A-H**.

The structures of products have been analyzed by NMR spectroscopy. As an example, ^{1}H NMR spectrum of 5-ferrocenyl-1-phenyl-4-(phenylethynyl)-1*H*-pyrazole (**53A**) is demonstrated in Figure 35. As noted, typical ferrocene H peaks appear at 4.0-4.5 ppm region of the spectrum. Two pseudo triplet peaks at 4.14 and 4.40 ppm represent four protons of substituted cyclopentadienyl ring while the singlet peak at 4.04 ppm belongs to five protons of unsubstituted cyclopentadienyl ring. The proton attached to C3 of pyrazole ring resonates as a singlet at 7.73 ppm (see Figure 35 for atom numbering). The peaks of ten phenyl protons are observed at around 7.25 to 7.56 ppm (Figure 35).

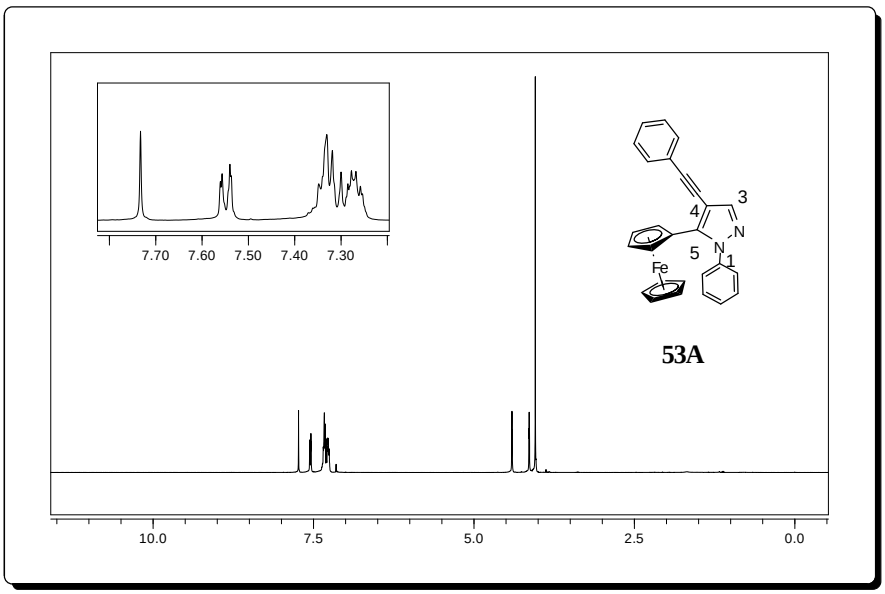


Figure 35. ^{1}H NMR spectrum of pyrazole **53A**.

^{13}C NMR spectra of 4-iodopyrazole derivative **48** and 4-(phenylethynyl)pyrazole derivative **53A** are shown in Figure 36. The C4 of 4-iodopyrazole **48** resonates at around 59.6 ppm (shown by an arrow) but, when the coupling occurs and the iodide is replaced by the terminal alkyne, the peak shifts to downfield and appears around 102.5 ppm (depicted by an arrow). Furthermore, as seen in the spectrum of **53A,** two acetylenic C peaks appear at 83.0-94.0 ppm region while they do not exist in the ^{13}C spectrum of **48**, implying that coupling reaction has occurred and the alkyne functionality has been introduced into the structure (Figure 36).

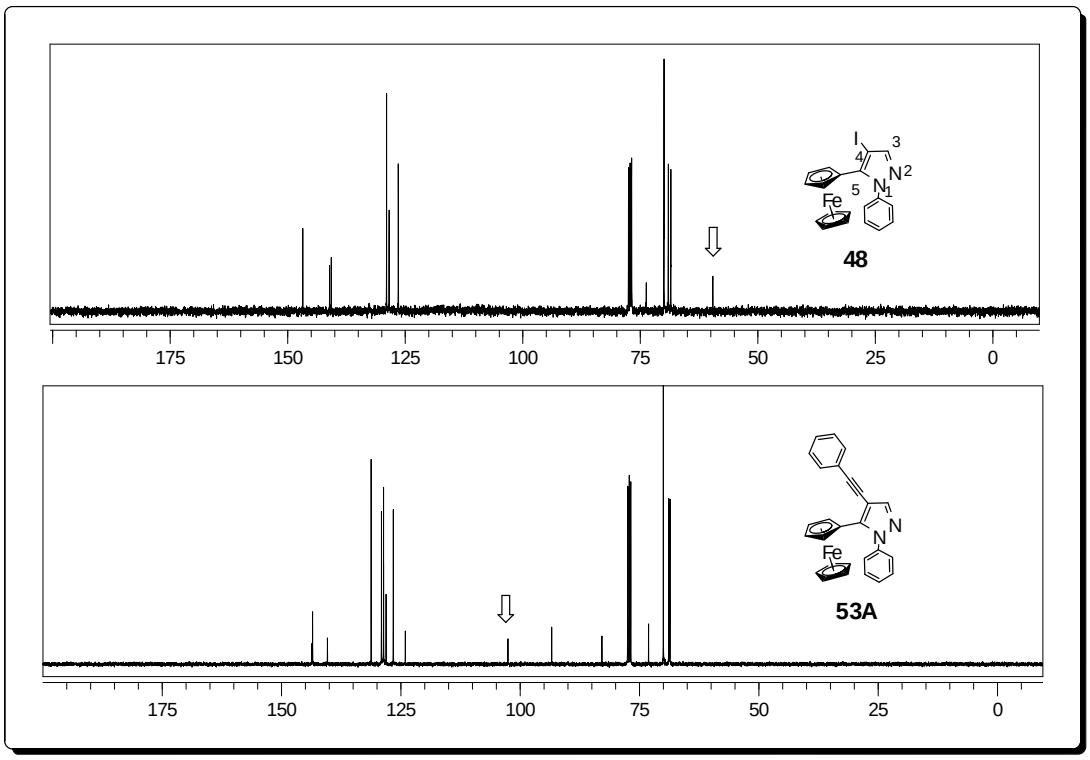


Figure 36. ^{13}C NMR spectra of 5-ferrocenyl-4-iodo-1-phenyl-1*H*-pyrazole (**48**) and 5-ferrocenyl-1-phenyl-4-(phenylethynyl)-1*H*-pyrazole (**53A**).

2.2 Synthesis of 4-alkynyl-1,5-diphenyl-1*H*-pyrazoles (54)

2.2.1 Synthesis of 4-iodo-1,5-diphenyl-1*H*-pyrazole (51)

4-Iodo-1,5-diphenyl-1*H*-pyrazole (**51**) was synthesized from 3-phenylpropynal (**52A**), the preparation of which was achieved from phenylacetylene (**52A**) by the treatment with *n*-BuLi followed by formylation of the resulting lithium alkynide **59** by DMF (Figure 37) [68].

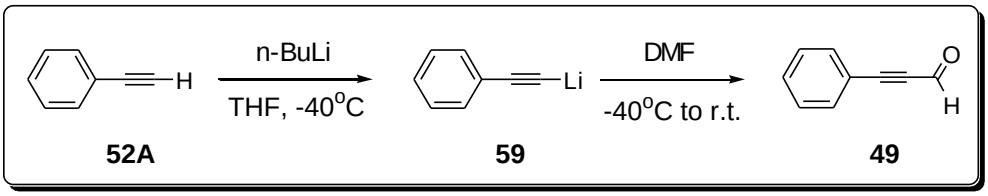


Figure 37. Synthesis of 3-phenylpropynal (**49**).

3-Phenylpropynal (**49**) was then heated with phenylhydrazine in neat condition, which afforded mainly *Z* isomer of corresponding acetylenic hydrazone (**50-*Z*)** (Figure 38) [52]. It should be mentioned that this reaction also produced *E* isomer of corresponding acetylenic hydrazone (**50-*E*)** in minor amount as indicated by TLC analysis, but *E* isomer was found not to be so stable that it slowly started to convert into *Z* isomer, especially during column chromatography. For this reason, afford was not spent to isolate *E* isomer. Moreover, keeping the reaction time relatively longer minimized the formation of *E* isomer [52].

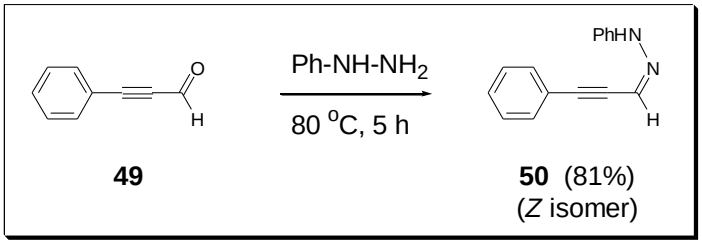


Figure 38. Synthesis of phenyl substituted hydrazone **50**.

For the synthesis of 4-iodo-1,5-diphenyl-1*H*-pyrazole (**51**), a similar procedure applied for the preparation of 5-ferrocenyl-4-iodopyrazoles **48** was utilized except that in this procedure, DCM was used instead of acetonitrile. Phenyl substituted acetylenic hydrazone (**50-*Z***) was stirred with excess molecular iodine and $NaHCO_3$ in DCM at room temperature for 2 hours. The reaction produced the desired pyrazole **51** in 80% yield (Figure 39) [52]. The work up was completed by the extraction of

reaction mixture with aqueous sodium thiosulfate solution and diethyl ether to eliminate unreacted iodine. Final purification of crude pyrazole **51** was performed by column chromatography.

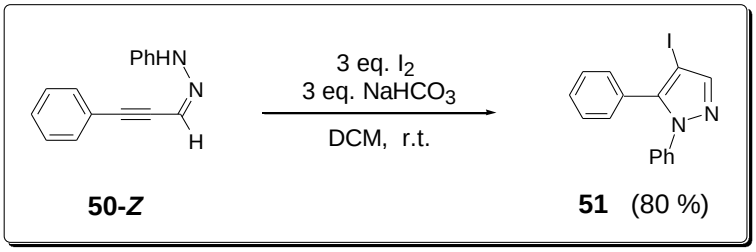


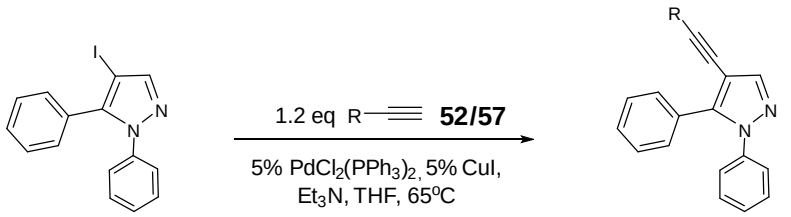
Figure 39. Synthesis of 4-iodo-1,5-diphenyl-1*H*-pyrazole (**51**).

2.2.2 Synthesis of 4-alkynyl-1,5-diphenyl-1*H*-pyrazole derivatives (54) via Sonogashira Cross-coupling Reaction

During the course of the study, we have synthesized 4-alkynyl-1,5-diphenyl-1*H*-pyrazoles (**54**), as well. A sub-library of terminal alkynes **52** have been reacted with 4-iodopyrazole **51** under previously optimized reaction condition. The results are given in Table 4.

As indicated in Table 4, the reaction times altered from 7 to 24 hours while the yields of pyrazoles (**54**) ranged from moderate to good (36 to 85%). It should be noted that in general, the yields of 4-alkynyl-1,5-diphenyl-1*H*-pyrazoles (**54**) (Table 4) are relatively lower as compared to those of 4-alkynyl-5-ferrocenyl-1-phenyl-1*H*-pyrazoles (**53**) (Table 3), except that the yield (85%) of 1,5-diphenyl-4-(thiophen-3-ylethynyl)-1*H*-pyrazole (**54D**) was higher than that (62%) of 5-ferrocenyl-1-phenyl-4-(thiophen-3-ylethynyl)-1*H*-pyrazole (**53F**). In addition, the reaction for the formation of pyrazole **54D** went to completion in 7 hours (Table 4) while that for pyrazole **53D** led to completion in 18 hours (Table 3).

Table 4. Synthesis of 4-alkynyl-1,5-diphenyl-1*H*-pyrazoles (**54A-E**).



51 **54**

Entry	*R*	*Product*	*Time (h)*	*Yield (%)*
1	phenyl	**54A**	15	42
2	*p*-tolyl	**54B**	24	36
3	4-methoxyphenyl	**54C**	16	76
4	3-thiophenyl	**54D**	7	85
5	ferrocenyl	**54E**	13	54

Structures of 4-alkynyl-1,5-diphenyl-1H-pyrazoles (**53A-H**) are present in Figure 40, which contain different functional groups including heterocyclic (**54D**) and organometallic (**54E**) moities.

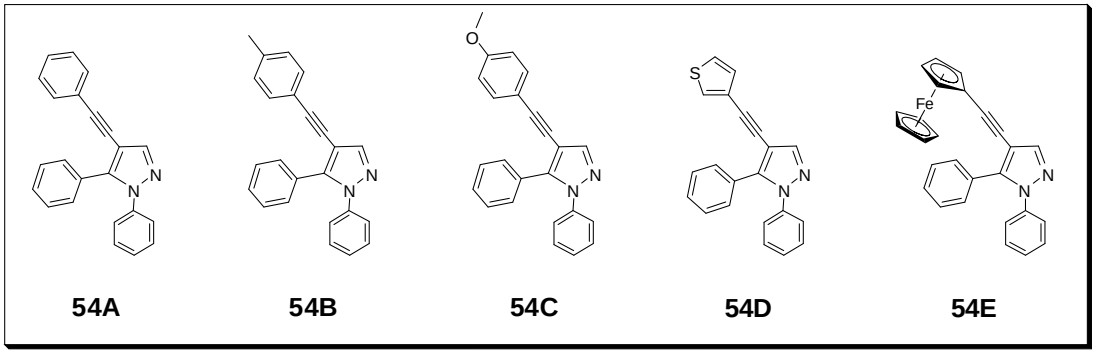
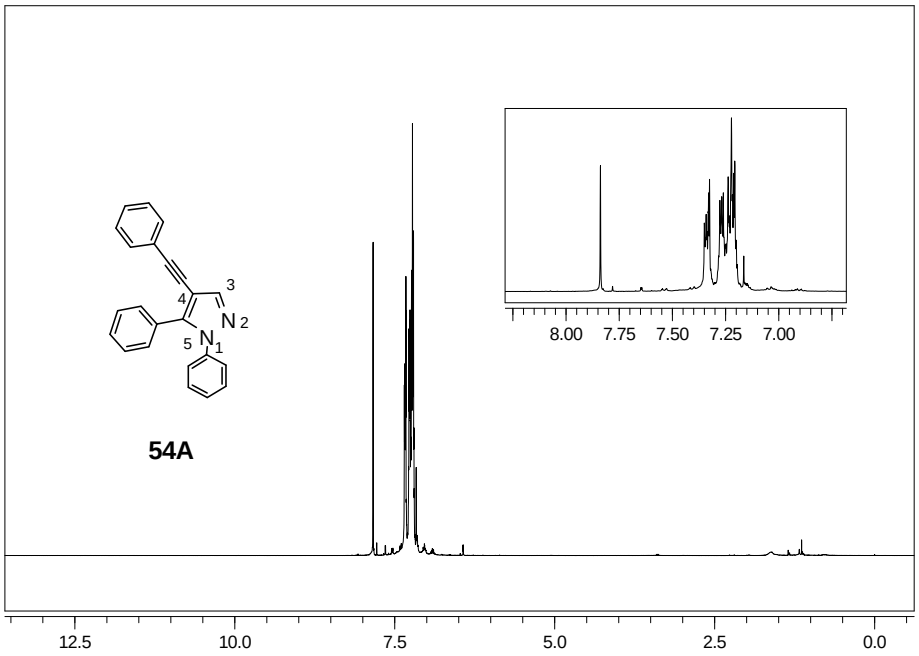
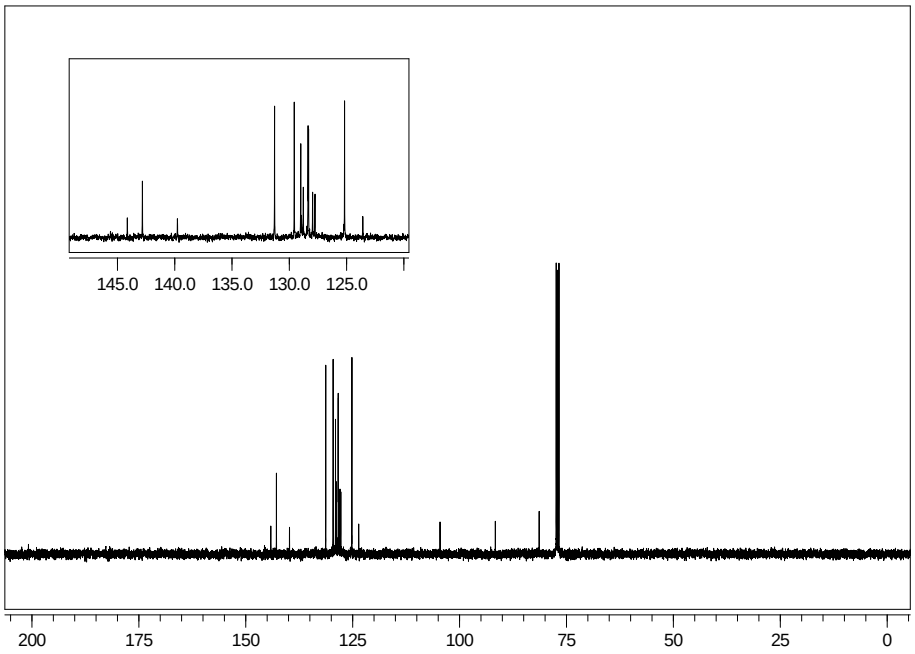


Figure 40. Structures of 4-alkynyl-1,5-diphenylpyrazoles (**54A-E**).

Structural assignments of 4-alkynyl-1,5-diphenyl-1*H*-pyrazoles were determined by ^{1}H and ^{13}C NMR spectroscopy. As a representative example, ^{1}H and ^{13}C NMR spectra of 1,5-diphenyl-4-(phenylethynyl)-1*H*-pyrazole (**54A**) were given in Figure 41. As expected, in ^{1}H NMR spectrum, phenyl protons resonates at aromatic region (δ 7.10-7.40 ppm) while pyrazole proton peak at C3 appears around 7.84 ppm. On the other hand, in ^{13}C NMR spectrum, two acetylenic carbons resonate at 81.4 and 91.6 ppm. Moreover, it is apparent that due to the absence of iodine, C4 peak (see Figure 41 for atom numbering) shifts to downfield and appears around at 104 ppm. Overall, all NMR data supports the indicated structure of pyrazole **54A** (Figure 41).



^{1}H NMR spectrum of **54A**



^{13}C NMR spectrum of **54A**

Figure 41. ^{1}H and ^{13}C NMR spectra of 1,5-diphenyl-4-(phenylethynyl)-1*H*-pyrazole (**54A**).

2.3 Synthesis of 4-aryl-5-ferrocenyl-1-phenyl-1H-pyrazoles (56) via Suzuki-Miyaura Cross-Coupling Reaction

At the second stage of this study, we synthesized a large library of ferrocenyl substituted pyrazoles **56** by employing Suzuki-Miyaura cross-coupling reaction of 5-ferrocenyl-4-iodo-1-phenyl-1*H*-pyrazole (**48**) with arylboronic acids **55**. The preparation of 4-iodopyrazole **48** was described in earlier sections. Suzuki-Miyaura coupling reactions have also been tested with a large number of different solvents, bases and palladium catalysts by researchers. Our literature search revealed that bases in bicarbonate salt form and palladium catalysts with triphenylphosphine ligands, especially $PdCl_2(PPh_3)_2$, work quite effectively in these reactions. In addition, DMF/H_2O combination is one of the most widely used solvent systems in such reactions [74]. Under the light of this knowledge, the condition involving $PdCl_2(PPh_3)_2$, $KHCO_3$ and DMF/H_2O was adapted for Suzuki-Miyaura coupling reaction.

In Suzuki-Miyaura cross-coupling reactions, we employed eleven boronic acids (**55A-K**) and one boronic acid ester derivative (**55L**), including a broad range of functionalities (Figure 42). The boronic acid derivatives involving heterocycles and important substituents could enhance current biological properties or bring in new biological activities to the resulted products. For instance, 5-indoleboronic acid (**55I**) was employed since the synthesized pyrazole product could contain favorable physicochemical properties due to indole moiety. Moreover, in order to synthesize organofluorine derivatives of ferrocenyl pyrazoles which could have versatile utility in medicine and industry, boronic acids **55F** and **55J** were employed [74a].

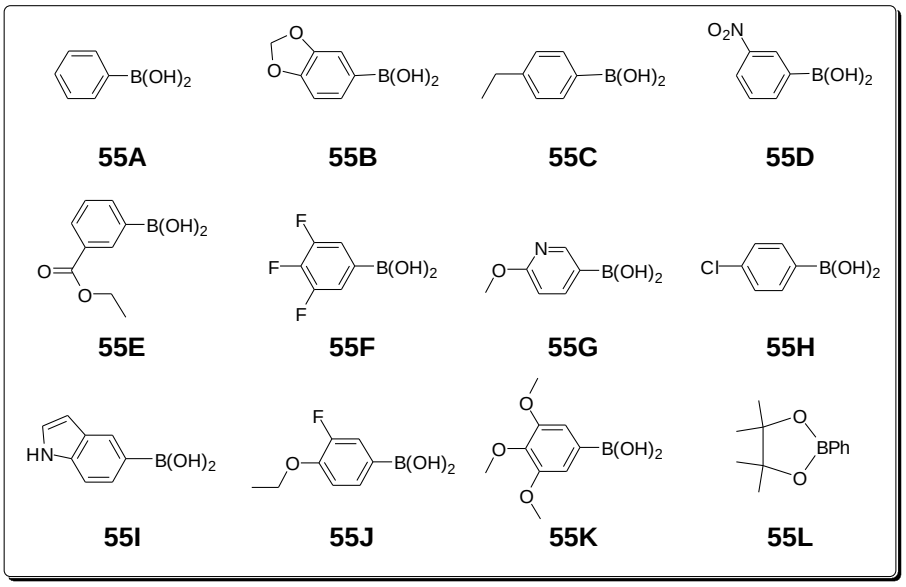
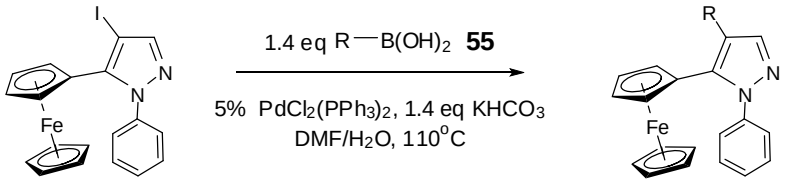


Figure 42. Structures of boronic acids **55A-K** and boronic acid ester derivative **55L** used in Suzuki-Miyaura cross-couplings.

As previously stated, $PdCl_2(PPh_3)_2$ was used as catalyst, $KHCO_3$ was employed as base and DMF/H_2O solution in 4/1 ratio was chosen as the solvent system during the reactions. The coupling reactions of 5-ferrocenyl-4-iodo-1-phenyl-1*H*-pyrazole (**48**) with the boronic acids (**55**) were carried out at 110 ^oC (Table 5). As shown in Table 5, all coupling reactions were quite successful and, as a result, eleven new derivatives of 4-aryl-5-ferrocenyl-1-phenyl-1*H*-pyrazole (**56**) were synthesized. Reaction times for the completion of reactions were determined by the frequent TLC analyses. It was revealed that Suzuki-Miyaura coupling reactions proceed in shorter time intervals than the Sonogashira coupling reactions. In order to minimize the substance loss, extraction was avoided and the reaction solvent (DMF/H_2O) was evaporated under high pressure vacuum. Finally the products were purified by column chromatography. Importantly, as summarized in Table 5, pyrazole derivatives **56** were synthesized in considerable high yields. Particularly, it should be pointed out that pyrazole **56D** was obtained in 99% yield.

Table 5. Synthesis of 4-aryl-5-ferrocenyl-1-phenyl-1*H*-pyrazoles (**56A-K**).



48 **56**

Entry	*R*	*Product*	*Time (h)*	*Yield (%)*
1	Ph	**56A**	4	72
2[a]	Ph	**56A**	6	80
3	3,4-(OCH_2CH_2O)C_6H_3	**56B**	7	52
4	4-ethylphenyl	**56C**	5	65
5	3-nitrophenyl	**56D**	6	99
6	3-(EtO_2C)C_6H_4	**56E**	5	93
7	3,4,5-$F_3C_6H_2$	**56F**	5	95
8	6-methoxy-3-pyridinyl	**56G**	4	94
9	4-chlorophenyl	**56H**	6	91
10	5-indolyl	**56I**	13	42
11	4-EtO-3-FC_6H_3	**56J**	4	80
12	3,4,5-$(MeO)_3C_6H_2$	**56K**	5 h	78

. [a]The reaction was carried out by boronic acid ester derivative **55L**.

Figure 43 illustrates the structures of 4-aryl-5-ferrocenyl-1-phenyl-1*H*-pyrazoles (**56A-K**), including different functional groups such as aryl, heterocyclic and organometallic functionalities.

Suzuki-Miyaura coupling of 5-ferrocenyl-4-iodo-1-phenyl-1*H*-pyrazole (**48**) with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (**55L**) was also investigated. The reaction was performed with the same Suzuki-Miyaura coupling condition. This reaction produced 5-ferrocenyl-1,4-diphenyl-1*H*-pyrazole (**56A**) in 6 hours with 80% yield (Enrty 2 in Table 5).

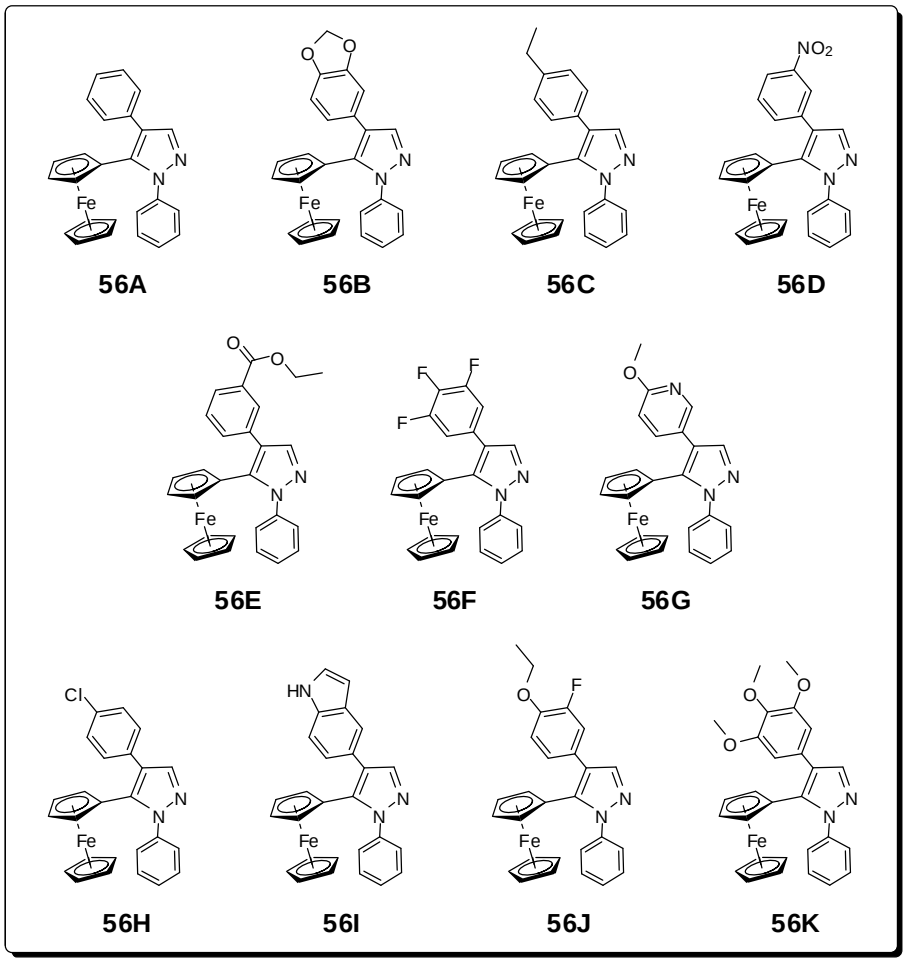


Figure 43. Structures of 4-aryl-5-ferrocenyl-1-phenyl-1*H*-pyrazoles (**56A-K**).

It is noteworthy to mention that homocoupling of arylboronic acids was not observed during the course of reactions. In order to prevent the oxidative homocoupling of boronic acids experiments were carried out under Ar atmosphere. Moreover, using a palladium catalyst with triphenylphosphine ligand instead of palladium salts such as $PdCl_2$ could cause an inhibiting effect on the intermolecular reaction of boronic acids [75].

The structures of pyrazoles **56** were determined by ^{1}H and ^{13}C NMR spectroscopy. As an illustration, ^{1}H NMR spectrum of 5-ferrocenyl-1,4-diphenyl-1*H*-pyrazole (**56A**) is shown in Figure 44. As noted previously, ferrocenyl H peaks are apparent at

around 4.00-3.60 ppm and the proton attached to C3 resonates at nearly 7.58 ppm. The remaining phenyl hydrogens show up between 7.25 and 7.50 ppm (Figure 44).

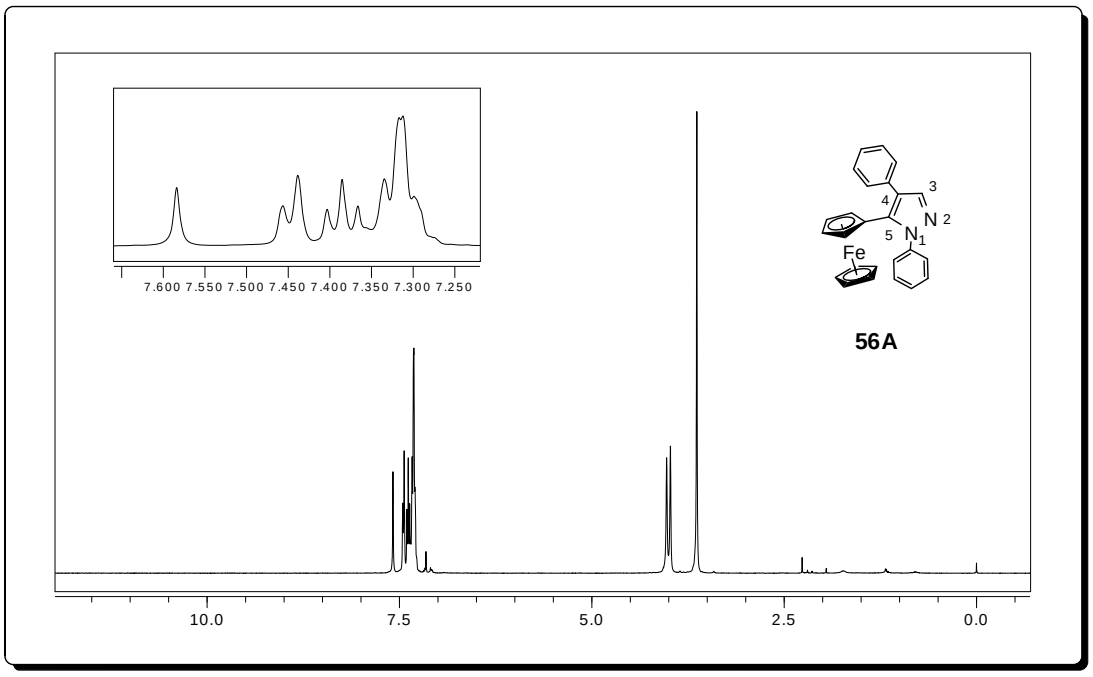


Figure 44. ^{1}H NMR spectrum of 5-ferrocenyl-1,4-diphenyl-1*H*-pyrazole (**56A**).

^{13}C NMR spectra of 4-iodo-5-ferrocenyl-1-phenyl-1*H*-pyrazole (**48**) and 5-ferrocenyl-1,4-diphenyl-1*H*-pyrazole (**56A**) are given for comparison in Figure 45. As it can be seen, the peak of carbon (shown by an arrow) bearing the iodide in compound **48** shifts to downfield with the substitution of phenyl group through Suzuki-Miyaura coupling and appear at 123.3 ppm (depicted with an arrow) in pyrazole **56A**. Furthermore, in the spectrum of compound **56A**, the existence of four new C peaks in the aromatic region proves the formation of targeted product (Figure 45).

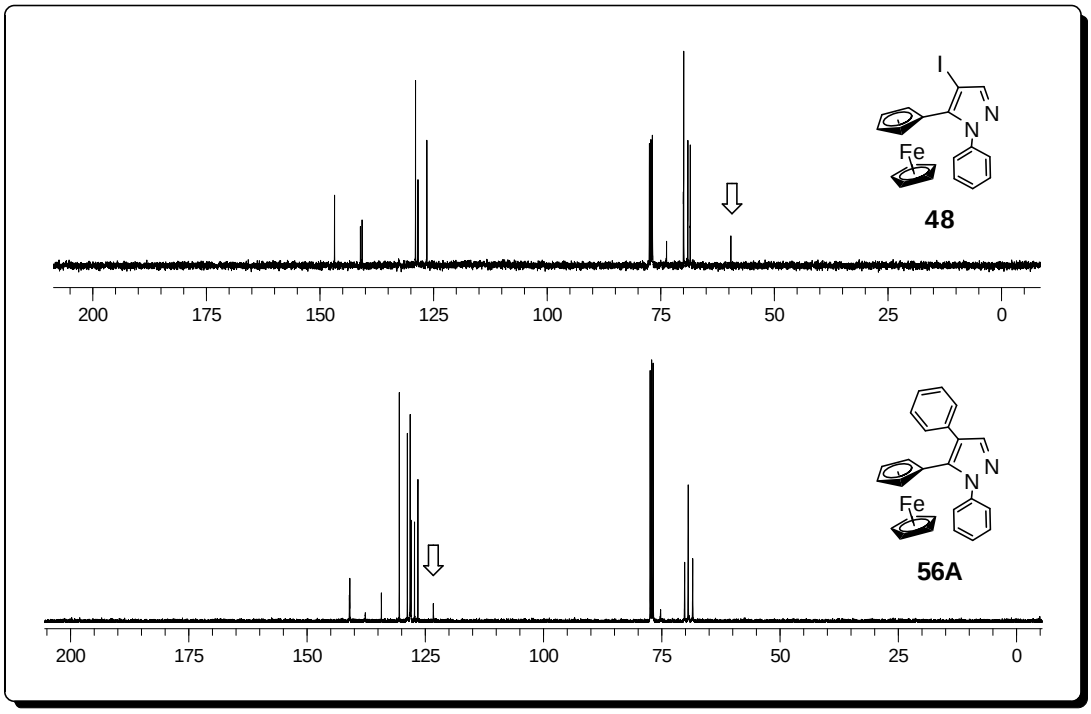


Figure 45. ^{13}C NMR spectra of 4-iodo-5-ferrocenyl-1-phenyl-1*H*-pyrazole (**48**) and 5-ferrocenyl-1,4-diphenyl-1*H*-pyrazole (**56A**).

2.4 Mechanisms

The mechanism for the formation of 4-iodo-5-ferrocenyl-1-phenyl-1*H*-pyrazole (**48**) and 4-iodo-1,5-diphenyl-1*H*-pyrazole (**51**) is shown in Figure 46. The electrophillic cyclization reaction starts with the formation of iodonium ion (**60**/**61**) by the coordination of iodine to the triple bond of hydrazone (**47**/**50**). Then the attack of secondary nitrogen to the carbon atom attached to R group forms the protonated pyrazole (**62**/**63)**. In this step, it is predicted that the hydrazone **47**/**50** is in *Z* form. It was also observed that *E* isomer of **47** can also go through this reaction pathway but in the presence of I_2 and $NaHCO_3$, this isomer is converted to Z isomer and then the cyclization can occur. Finally the abstraction of proton by the base $NaHCO_3$ results in the formation of 4-iodopyrazole products **48**/**51** and as anticipated, H_2CO_3 formed is released as H_2O and CO_2 (Figure 46) [52].

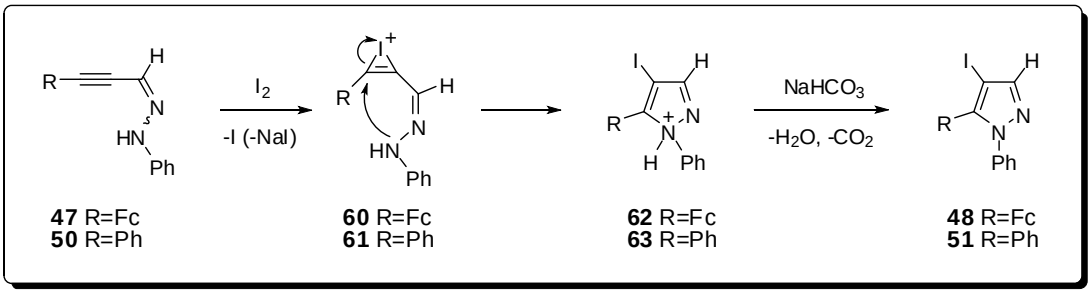


Figure 46. The mechanism for the formation of 4-iodo-5-ferrocenyl-1-phenyl-1*H*-pyrazole (**48**) and 4-iodo-1,5-diphenyl-1*H*-pyrazole (**51**).

The mechanism of the Sonogashira coupling reaction is still not known exactly. In fact, various physical and thermochemical methods were devised to identify the transient molecules and the results of these studies suggested a possible mechanism (Figure 47) [54]. According to this mechanism, copper-cocatalyzed coupling reactions of 4-iodopyrazoles **48**/**51** can occur through two independent catalytic cycles. The main cycle is the Pd-cycle. The first step of this cycle is the oxidative addition of 4-iodopyrazoles **48**/**51** to $Pd(PPh_3)_2$ complex which is formed by the reduction of palladium-(II) catalyst ($PdCl_2(PPh_3)_2$). The second step in the Pd-cycle intercepts with Cu-cycle. During this stage, the formed copper acetylide **64** goes through a transmetallation reaction leading to the attachment of acetylide ligand to the palladium complex **65** to afford complex **66**. After a possible *trans*/*cis*-isomerization (**66** to **67**), reductive elimination happens. At this last step, final coupling product (**53**/**54**) is obtained and the catalyst is regenerated (Figure 47).

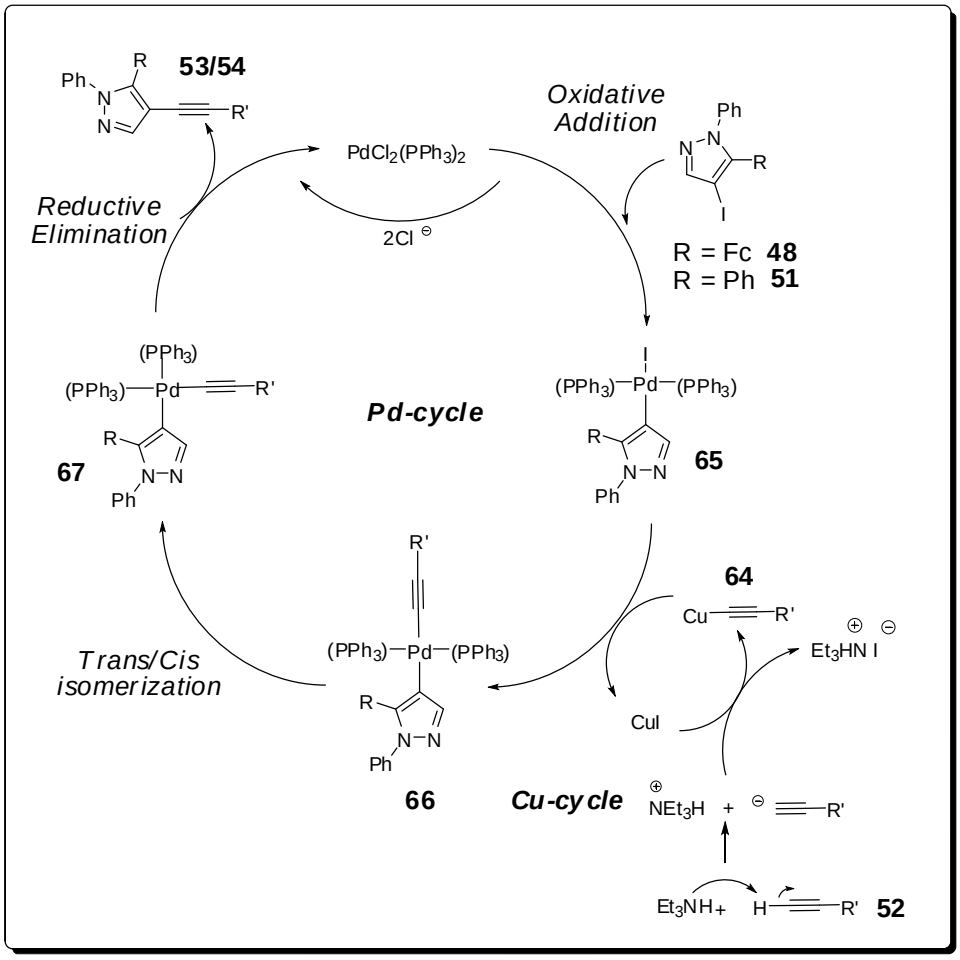


Figure 47. Mechanism of Sonogashira coupling reaction.

The mechanistic pathway of Suzuki-Miyaura reaction is quite similar to Sonogashira coupling mechanism (Figure 48). First, at the main Pd-cycle, the oxidative addition of 4-iodo-5-ferrocenyl-1-phenyl-1*H*-pyrazole (**48**) to the generated Pd^0 complex occurs. The formed palladium intermediate (**68**) then reacts with $KHCO_3$ and, as a result, I^- is replaced by HCO_3^- in the organo-palladium species **68,** forming complex **69**. At the side step of the mechanism, aryl boronic acid **55** reacts with base ($KHCO_3$) to produce a boronate complex **70** and this complex goes through a transmetallation reaction with the organo-palladium species **69**. As a result, aryl group is introduced into the palladium complex **69**, forming **71**. At the last step of cyclic mechanism, reductive elimination occurs with retention of stereochemistry

and final coupling product **56** is formed while the catalyst $PdCl_2(PPh_3)_2$ is regenerated (Figure 48) [63,76].

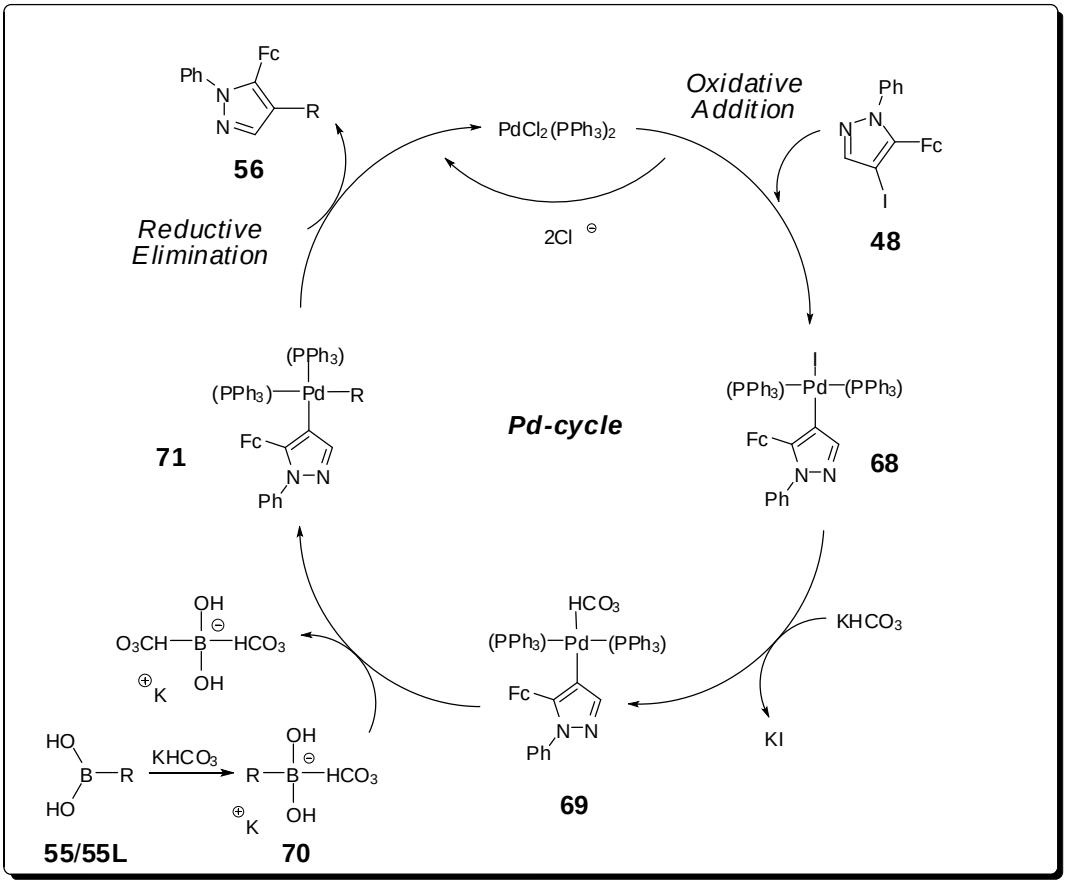


Figure 48. Mechanism of Suzuki-Miyaura coupling reaction with boronic acids.

CHAPTER 3

CONCLUSION

In summary, we have investigated the synthesis of 4-alkynyl-5-ferrocenyl-1-phenyl-1*H*-pyrazoles (**53**), 4-alkynyl-1,5-diphenyl-1*H*-pyrazoles (**54**) and 4-aryl-5-ferrocenyl-1-phenyl-1*H*-pyrazoles (**56**) through palladium catalyzed Sonogashira and Suzuki-Miyaura coupling reactions of 4-iodopyrazoles (**48** and **51**) with terminal alkynes (**52**) and boronic acids (**55**), respectively. Owing to the importance of ferrocene and pyrazole molecules in chemistry, biology, biochemistry and medicinal chemistry, the synthesis of multi-substituted pyrazoles and ferrocenylpyrazoles has been crucial. Therefore, we have focused on the synthesis of new pyrazole derivatives substituted with various functional groups, particularly with ferrocenyl groups, having potential biological activities.

In the first phase of the study, ferrocenyl and phenyl substituted acetylenic hydrazones (**47** and **50**) have been prepared and subjected to electrophillic cyclization to afford 4-iodopyrazoles (**48** and **51**). In the second phase, a large variety of new 4-alkynyl-5-ferrocenyl-1-phenyl-1*H*-pyrazole derivatives (**53**) have been synthesized from 5-ferrocenyl-4-iodopyrazole (**48**) and terminal alkynes (**52** and **57**) by employing the optimized Sonogashira coupling condition. Furthermore, using the same Sonogashira coupling condition, 4-alkynyl-1,5-diphenyl-1*H*-pyrazole derivatives (**54**) have been synthesized from 4-iodo-5-phenylpyrazole (**51**) and terminal alkynes (**52** and **57**).

At the final stage, Suzuki-Miyaura coupling reactions of 5-ferrocenyl-4-iodo-1-phenyl-1*H*-pyrazole (**48**) with boronic acids (**55**) have been explored and 4-aryl-5-ferrocenyl-1-phenyl-1*H*-pyrazoles (**56**) have been synthesized in good to excellent yields.

In conclusion, we have achieved the synthesis of a large library of new multi-substituted ferrocenylpyrazole derivatives (**53** and **56**) as well as phenylpyrazole derivatives (**54**). The biological activity tests of these derivatives will be carried out by collaborative work.

CHAPTER 4

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Spectrospin Avance DPX400 Ultrashield (400 MHz) spectrometer. The chemical shifts are reported in parts per million (ppm) downfield from an internal TMS (trimethylsilane) reference. Coupling constants (*J*) are reported in hertz (Hz), and the spin multiplicities are presented 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 parentheses as C, CH, CH_2 and CH_3. Infrared spectra (IR) were recorded on a NICOLET IS10 FTIR Spectrometer using attenuated total reflection (ATR). Band positions are reported in reciprocal centimeters (cm^{-1}). Band intensities are indicated 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 MicroTof (Bruker Daltonics) and TRITON TI spectrometer, using electrospray ionization (ESI). Flash chromatography was performed using thick-walled glass columns and ‘’flash grade’’ silica (Merck 230-400 mesh). Thin layer chromatography (TLC) was performed by using commercially prepared 0.25 mm silica gel plates and visualization was effected with short wavelength UV lamp. The relative proportions of solvents in chromatography solvent mixtures refer to the volume:volume ratio. All commercially available reagents were used directly without purification unless otherwise stated. All the solvents used in reactions distilled for purity. THF, dioxane and diethyl ether were distilled from sodium/benzophenone in glass kettle. The inert atmosphere was created by slight positive pressure (ca. 0.1 psi) of argon. All glassware was dried in oven prior to use.

4.1 Synthesis of acetylferrocene (31)

Ferrocene (**30**) (2g, 10.8 mmol) was dissolved in dry DCM (9ml) by constant stirring under argon. Then acetyl chloride (0.92ml, 11.8 mmol) was added to the resultant orange/red solution. The flask was immersed in a 0-5 ^{o}C ice-water bath. Anhydrous aluminum chloride (1.44 g, 10.8 mmol) was slowly added in small portions to the reaction flask. The reaction mixture was stirred at room temperature for 2 h and then it was recooled to 0-5 ^{o}C by a fresh ice-water bath. By the slow addition of cold water (4 x 0.5 ml), the reaction mixture was hydrolyzed. Then a further 3 ml of cold water was added more rapidly. The hydrolyzed reaction mixture was extracted with DCM and collected organic extracts were washed with 5% NaOH solution followed by brine solution. The organic phase was dried over magnesium sulfate and filtered off. An orange/red solid was obtained after solvent was removed on rotary evaporator. The resultant solid was purified by flash column chromatography on silica gel using 9:1 hexane/ethylacetate as the eluent to give acetylferrocene (**31**) (1.96 g, 80%).

31: ^{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 are in agreement with those reported previously for this compound [66].

4.2 Synthesis of (2-formyl-1-chlorovinyl)ferrocene (43)

In a two necked flask, acetylferrocene (**31**) (2 g, 8.8 mmol) and DMF (2.17 ml, 28.2 mmol) were added under argon. The flask was cooled to 0 ^{o}C by ice-water bath and the brown reaction mixture was stirred for 10 minutes. Separately, in a round-bottom flask, DMF (2.17 ml, 28.2 mmol) was added and cooled to 0 ^{o}C under argon. Then cautiously phosphorus oxychloride (2.21 ml, 28.2 mmol) was added to DMF with good stirring. The resultant viscous red complex was slowly (over 30 minutes) transferred to the two necked flask containing acetylferrocene (**31**) and DMF by a dropping funnel. After the addition was completed, the contents of the flask were

stirred at 0 ^{o}C for approximately 2 h until the color of reaction mixture changed from dark brown to olive green and then to dark blue. A 20 ml portion of diethyl ether was added, and the mixture was stirred vigorously. Then with continued cooling with ice-water bath, sodium acetate trihydrate (10.18 g, 74.6 mmol) was carefully added to the reaction flask in one portion followed by addition of water (2 ml). The ice water bath is removed and a color change in organic layer from colorless to ruby red, indicating the formation of formyl derivative, was observed. After 1 h, additional ether (2 ml) was added and the stirring was continued for 3 h at room temperature for complete quenching. The reaction mixture was extracted with diethyl ether. The organic extracts were combined and washed with saturated sodium bicarbonate solution. After dried by magnesium sulfate and filtered, organic phase was concentrated on rotary evaporator, yielding (2-formyl-1-chlorovinyl)ferrocene (**43**) (2.25 g, 93%).

43: ^{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 are in agreement with those reported previously for this compound [67].

4.3 Synthesis of ethynylferrocene (57)

In a dry flask, (2-formyl-1-chlorovinyl)ferrocene (**43**) (1.3 g, 4.75 mmol) was dissolved in anhydrous dioxane (15 ml) by flashing with argon and heated to reflux. After approximately 5 minutes a boiling 1 N solution of sodium hydroxide (12.5 ml) was added rapidly in one portion and the reflux continued for another 25 minutes. Then refluxing was stopped and the mixture was allowed to cool to room temperature. The contents of the flask were poured directly into ice and neutralized with 1 N hydrochloric acid solution. The resultant mixture was extracted with hexane (5 x 5 ml). The organic phase was washed with sodium bicarbonate solution and water. The combined organic parts were dried over magnesium sulfate, filtered and the solvent was removed on rotary evaporator. The crude ethynylferrocene **(57)** was purified by flash chromatography on silica gel by using hexane as the eluent and the clear product was obtained as orange crystals (750 mg, 75%).

57: ^{1}H NMR ($CDCl_3$): δ 4.46 (s, 2H), 4.21 (s, 5H), 4.19 (s, 2H), 2.71 (s, 1H); ^{13}C ($CDCl_3$): δ 82.6 (C), 73.6 (C), 71.7 (CH), 70.0 (CH), 68.7 (CH), 63.9 (CH). The spectral data are in agreement with those reported previously for this compound [67].

4.4 General Procedure 1. Synthesis of propargyl aldehydes (46 and 49)

In approximately 25 ml of dry THF, corresponding alkyne (0.1 mol) was dissolved. The solution was cooled to -40 ^{o}C under argon by using a dewar flask equipped with a thermometer and containing ethyl acetate/liquid nitrogen mixture. By flashing with argon, *n*-butyllithium (1.6 M in hexane, 65.4 ml, 0.1 mol) was cautiously added by a glass syringe slowly over 5 minutes, keeping the temperature between -35 and -40 ^{o}C. After the addition was completed, dry *N*,*N*-dimethylformamide (15.5 ml, 0.2 mol) was rapidly added in one portion and the cooling progress was stopped. The mixture was allowed to warm to room temperature. The contents of the reaction flask were poured into a cold mixture prepared from 10% aqueous KH_2PO_4 solution (540 ml, 0.4 mol) and diethylether (500 ml). Layers were separated by extraction. The organic phase was washed with water (4 x 200 ml) and the collected aqueous phase was further extracted with ether. The combined organic extracts were dried over $MgSO_4$ and filtered. The flash chromatography on silica gel by using hexane/ethyl acetate as the eluent afforded the corresponding propargyl aldehyde.

4.4.1 Synthesis of 3-ferrocenylpropynal (46)

General Procedure 1 was followed by using ethynylferrocene (**57**) (1 g, 4.74 mmol), *n*-butyllithium (1.6 M in hexane, 3.1 ml, 4.74 mmol) and dry *N*,*N*-dimethyl-formamide (0.75 ml, 9.5 mmol). The product was purified by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent (930 mg, 82%).

46: ^{1}H NMR ($CDCl_3$): δ 9.27 (s, 1H), 4.60 (s, 2H), 4.41 (s, 2H), 4.25 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 176.2 (C), 99.5 (C), 87.7 (C), 73.3 (CH), 71.3 (CH), 70.6 (CH),

59.2 (C). The spectral data are in agreement with those reported previously for this compound [68,77].

4.4.2 Synthesis of 3-phenylpropynal (49)

General Procedure 1 was followed by using phenylacetylene (**52A**) (1.1 ml, 10 mmol), *n*-butyllithium (1.6 M in hexane, 6.1 ml, 10 mmol) and dry *N*,*N*-dimethylformamide (1.54 ml, 20 mmol). The product was purified by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent (1.24 g, 97%).

49: ^{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 ($CDCl_3$): 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 are in agreement with those reported previously for this compound [78].

4.5 General Procedure 2. Synthesis of acetylenic hydrazones (47 and 50)

The corresponding propargyl aldehyde (0.1 mol) and phenylhydrazine (0.1 mol) were added into a dry test tube. The neat reaction mixture was heated at 80 ^{o}C under argon with continues stirring for 3 to 5 h. The resultant viscous crude product was purified by flash chromatography on silica gel by using hexane/ethyl acetate as the eluent.

4.5.1 Synthesis of (*E*)- and (*Z*)-1-(3-ferrocenylprop-2-ynylidene)-2-phenylhydrazines (47-*E* and 47-*Z*)

General Procedure 2 was followed by using 3-ferrocenylpropynal (**46**) (500 mg, 2.10 mmol) and phenylhydrazine (0.21 ml, 2.10 mmol). The resultant mixture of isomers was separated by flash chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent, yielding hydrazones **47-*E*** (*E* isomer, 248 mg, 36%) and **47-*Z*** (*Z* isomer, 372 mg, 54%).

47-*E* (*E* isomer): ^{1}H NMR ($CDCl_3$): δ 7.95 (br, s, 1H, NH), 7.27 (t, 2H, *J* = 7.9 Hz), 7.08 (d, 2H, *J* = 7.9 Hz), 7.03 (s, 1H), 6.90 (t, 1H, *J* = 7.3 Hz), 4.51 (s, 2H), 4.27 (s, 2H), 4.25 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 143.7 (CH), 129.3 (CH), 120.8 (CH), 120.4 (C), 113.1 (CH), 92.2 (C), 82.0 (C), 71.6 (CH), 70.1 (CH), 69.2 (CH), 64.3 (C). The spectral data are in agreement with those reported previously for this compound [52].

47-*Z* (*Z* isomer): ^{1}H NMR ($CDCl_3$): δ 8.64 (br, s, 1H, NH), 7.32 (t, 2H, *J* = 7.3 Hz), 7.13 (d, 2H, *J* = 7.6 Hz), 6.94 (t, 1H, *J* = 7.3 Hz), 6.55 (s, 1H), 4.57 (s, 2H), 4.35 (s, 2H), 4.29 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 143.7 (CH), 129.4 (CH), 120.4 (CH), 115.7 (CH), 113.2 (CH), 102.4 (C), 76.5 (C), 71.8 (CH), 70.3 (CH), 69.7 (CH), 62.9 (C). The spectral data are in agreement with those reported previously for this compound [52].

4.5.2 Synthesis of (*Z*)-1-phenyl-2-(3-phenylprop-2-ynylidene)hydrazine (50-*Z*)

General Procedure 2 was followed by using 3-phenylpropynal (**49**) (500 mg, 3.85 mmol) and phenylhydrazine (0.38 ml, 3.85 mmol). The resultant crude product was purified by flash chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent, yielding hydrazone **50-*Z*** (*Z* isomer, 687 mg, 81%).

50-*Z* (*Z* isomer): ^{1}H NMR ($CDCl_3$): δ 8.67 (br, s, 1H, NH), 7.52-7.54 (m, 2H), 7.38-7.42 (m, 3H), 7.28-7.30 (m, 2H), 7.08-7.12 (m, 2H), 6.90-6.93 (m, 1H), 6.62 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 143.5 (CH), 131.8 (CH), 129.5 (CH), 129.4 (CH),

128.6 (CH), 121.6 (C), 121.2 (CH), 114.7 (CH), 113.3 (CH), 101.9 (C), 79.6(C). The spectral data are in agreement with those reported previously for this compound [52].

4.6 General Procedure 3. Synthesis of 4-iodo-1-phenyl-1H-pyrazoles (48 and 51)

In a dry round-bottom flask, molecular iodine (3 equiv) and sodium bicarbonate (3 equiv) were added and dissolved in acetonitrile or DCM by flashing with argon. Then separately in a dry flask, hydrazone **47-*E*** (*E* isomer), **47-*Z*** (*Z* isomer) or **50-*Z*** (*Z* isomer) (1 equiv) was added and dissolved in acetonitrile or DCM. The resulting solution was added dropwise to the solution including I_2 and $NaHCO_3$. The reaction mixture was allowed to stir for 1 h at room temperature. After the completion of the reaction (controlled by TLC), solvent was removed on a rotary evaporator. Then contents of the reaction flask was transferred to separatory funnel including diethyl ether and washed with saturated aqueous sodium thiosulfate solution followed by water. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated on rotary evaporator. The crude product was purified by flash chromatography on silica gel with 19:1 hexane/ethyl acetate as the eluent, affording corresponding 4-iodopyrazole (**48** or **51**).

4.6.1 Synthesis of 5-ferrocenyl-4-iodo-1-phenyl-1*H*-pyrazole (48)

General Procedure 3 was followed by using molecular iodine (320 mg, 1.26 mmol), sodium bicarbonate (106 mg, 1.26 mmol) and hydrazone **47-*E*** (*E* isomer) or **47-*Z*** (*Z* isomer) (138 mg, 0.42 mmol) and acetonitrile (20 ml) as solvent. The resultant crude product was purified by flash chromatography on silica gel with 19:1 hexane/ethyl acetate as the eluent, affording 5-ferrocenyl-4-iodo-1-phenyl-1*H*-pyrazole (**48**) as orange solid (176 mg, 92% from **47-*E***; 172 mg, 90% from **47-*Z***).

48: ^{1}H NMR ($CDCl_3$): δ 7.73 (s, 1H), 7.39-7.43 (m, 3H), 7.27-7.29 (m, 2H), 4.41 (s, 2H), 4.25 (s, 2H), 4.21 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 146.7 (CH), 141.1 (C),

140.8 (C), 128.9 (CH), 128.4 (CH), 126.4 (CH), 74.1 (C), 70.2 (CH), 69.2 (CH), 68.7 (CH), 59.6 (C). The spectral data are in agreement with those reported previously for this compound [52].

4.6.2 Synthesis of 4-iodo-1,5-diphenyl-1*H*-pyrazole (51)

General Procedure 3 was followed by using molecular iodine (692 mg, 2.72 mmol), sodium bicarbonate (229 mg, 2.72 mmol), hydrazone **50-*Z*** (*Z* isomer) (200 mg, 0.90 mmol) and dichloromethane (25 ml) as solvent. The resultant crude product was purified by flash chromatography on silica gel with 19:1 hexane/ethyl acetate as the eluent, affording 4-iodo-1,5-diphenyl-1*H*-pyrazole (**51**) (249 mg, 80%).

51: ^{1}H NMR ($CDCl_3$): δ 7.71 (s, 1H), 7.24-7.28 (m, 3H), 7.15-7.19 (m, 5H), 7.10-7.13 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 145.5 (CH), 143.5 (C), 139.9(C), 130.3 (CH), 129.6 (C), 129.0 (CH), 128.8 (CH), 128.5 (CH), 127.6 (CH), 124.7 (CH), 62.3 (C). The spectral data are in agreement with those reported previously for this compound [52].

4.7 General Procedure 4. Synthesis of 4-alkynyl-5-ferrocenyl/phenyl-1-phenyl-1*H*-pyrazoles (53 and 54) via Sonogashira coupling reaction (Tables 3 and 4)

In a dry flask, 4-iodopyrazole (**48** or **51**) (0.22 mmol), $PdCl_2(PPh_3)_2$ (7.73 mg, 0.011 mmol) and CuI (2.09 mg, 0.011 mmol) were dissolved in a mixture of triethylamine (1.6 ml) and THF (1 ml) by vigorous stirring under argon. Meanwhile, separately in a flask, corresponding terminal alkyne (**52** or **57**) (0.264 mmol) was dissolved in THF (1 ml) and added slowly to the first reaction flask over 1 h. Then the resulting reaction mixture was heated to reflux (65 ^{o}C). After the completion of the reaction (controlled by TLC), the mixture was concentrated on a rotary evaporator and

purified by flash chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent.

4.7.1 Synthesis of 4-alkynyl-5-ferrocenyl-1-phenyl-1*H*-pyrazoles (53) (Table 3)

General Procedure 4 was followed by using 5-ferrocenyl-4-iodo-1-phenyl-1*H*-pyrazole (**48**) (100 mg, 0.22 mmol), corresponding terminal alkyne (**52** or **57**) (0.264 mmol), $PdCl_2(PPh_3)_2$ (7.73 mg, 0.011 mmol), CuI (2.09 mg, 0.011 mmol), Et_3N (1.6 ml) and THF (2 ml). After chromatographic purification, 4-alkynyl-5-ferrocenyl-1-phenyl-1*H*-pyrazoles (**53**) given in Table 3 were isolated with the indicated yields, the spectroscopic data for which are provided below.

53A: Yield: 66%; ^{1}H NMR ($CDCl_3$): δ 7.73 (s, 1H), 7.54-7.56 (m, 2H), 7.25-7.35 (m, 8H), 4.40 (pseudo t, 2H), 4.14 (pseudo t, 2H), 4.04 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 143.6 (C), 143.5 (CH), 140.4 (C), 131.2 (CH), 129.0 (CH), 128.6 (CH), 128.5 (CH), 128.0 (CH), 126.6 (CH), 124.0 (C), 102.5 (C), 93.4 (C), 82.9 (C), 73.1 (C), 70.0 (CH), 68.9 (CH), 68.6 (CH); IR (neat): 3729 (m), 3698 (m), 3054 (w), 2228 (vw), 1554 (m), 1495 (s), 1398 (m), 859 (m), 762 (s), 693 (s) cm^{-1}; MS (ESI, *m/z*): 451.09 $[M + Na]^+$, 428.09 $[M]^+$; HRMS (ESI): calc. for $C_{27}H_{20}FeN_2Na$: 451.0874 $[M + Na]^+$. Found: 451.0868; calc. for $C_{27}H_{20}FeN_2$: 428.0976 $[M]^+$. Found: 428.0971.

53B: Yield: 37%; ^{1}H NMR ($CDCl_3$): δ 7.84 (s, 1H), 7.55 (d, 2H, *J* = 7.9 Hz), 7.46-7.48 (m, 3H), 7.39-7.41 (m, 2H), 7.25 (d, 2H, *J* = 7.9 Hz), 4.56 (s, 2H), 4.29 (s, 2H), 4.20 (s, 5H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 143.4 (C), 143.3 (CH), 140.4 (C), 138.2 (C), 131.1 (CH), 129.3 (CH), 129.0 (CH), 128.5 (CH), 126.5 (CH), 121.0 (C), 102.8 (C), 93.5 (C), 82.0 (C), 73.5 (C), 70.2 (CH) 69.0 (CH), 68.8 (CH), 21.6 (CH_3); IR (neat): 3733 (m), 3698 (w), 3059 (vw), 2988 (br), 2916 (br), 1500 (s), 1398 (m), 1078 (w), 815 (m), 767 (m), 694 (m) cm^{-1}; MS (ESI, *m/z*): 465.10 $[M + Na]^+$, 442.11 $[M]^+$; HRMS (ESI): calc. for $C_{28}H_{22}FeN_2Na$: 465.1030 $[M + Na]^+$. Found: 465.1025; calc. for $C_{28}H_{22}FeN_2$: 442.1132 $[M]^+$. Found: 442.1127.

53C: Yield: 78%; ^{1}H NMR ($CDCl_3$): δ 7.72 (s, 1H), 7.49 (d, 2H, *J* = 8.7 Hz), 7.35-7.36 (m, 3H), 7.27-7.29 (m, 2H), 6.87 (d, 2H, *J* = 8.7 Hz), 4.41 (s, 2H), 4.16 (s, 2H), 4.06 (s, 5H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 159.5 (C), 143.4 (CH), 143.3 (C), 140.4 (C), 132.7 (CH), 129.0 (CH), 128.5 (CH), 126.5 (CH), 116.2 (C), 114.3

(CH), 102.9 (C), 93.2 (C), 81.2 (C), 73.3 (C), 70.0 (CH), 68.7 (CH), 68.6 (CH), 55.4 (CH_3); IR (neat): 3057(w), 2969 (w), 2839 (w), 1896 (vw), 1603 (s), 1498 (vs), 1398 (s), 1286 (s), 1245 (vs), 1175 (s), 1027 (s), 966 (s), 878 (m) cm^{-1}; MS (ESI, *m/z*): 481.09 $[M + Na]^+$, 458.10 $[M]^+$; HRMS (ESI): calc. for $C_{28}H_{22}FeN_2ONa$: 481.0979 $[M + Na]^+$. Found: 481.0974; calc. for $C_{28}H_{22}FeN_2O$: 458.1082 $[M]^+$. Found: 458.1076.

53D: Yield: 68%; ^1H NMR ($CDCl_3$): δ 7.63 (s, 1H), 7.36-7.38 (m, 3H), 7.26-7.29 (m, 2H), 4.38 (s, 2H), 4.12 (s, 2H), 4.03 (s, 5H), 1.96-2.00 (m, 2H, NH_2), 1.52-1.70 (m, 8H), 1.15-1.28 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 143.9 (CH), 142.8 (C), 140.6 (C), 129.1 (CH), 128.7 (CH), 126.8 (CH), 102.2 (C), 75.8 (C), 73.1 (C), 70.0 (CH), 68.8 (CH), 68.2 (CH), 60.4 (C), 40.6 (C); 25.5 (CH_2), 23.5 (CH_2), 14.2 (CH_2); IR (neat): 3284 (w), 3090 (w), 2927 (vs), 2852 (s), 2222 (w), 1596 (s), 1504 (s), 1381 (m), 1105 (m), 1001 (m), 967 (m), 817 (s), 766 (s), 693 (s) cm^{-1}.

53E: Yield: 70%; ^1H NMR ($CDCl_3$): δ 7.65 (s, 1H), 7.37-7.38 (m, 3H), 7.27-7.29 (m, 2H), 4.40 (s, 2H), 4.16 (s, 2H), 4.08 (s, 5H), 2.24 (br s, OH), 2.02-2.07 (m, 2H), 1.53-1.74 (m, 6H), 1.55-1.56 (m, 1H), 1.25-1.35 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 143.8 (CH), 143.4 (C), 140.5 (C), 129.1 (CH), 128.7 (CH), 126.8 (CH), 101.8 (C), 97.1 (C), 73.2 (C), 70.2 (CH), 69.3 (C), 69.0 (CH), 68.5 (CH), 40.1 (CH_2), 25.3 (CH_2), 23.3 (CH_2) (one carbon peak missing due to overlap); IR (neat): 3725 (w), 3354 (br), 3095 (w), 2930 (vs), 2854 (m), 2218 (w), 1736 (m), 1596 (m), 1505 (s), 1402 (s), 1381 (s), 1255 (m), 1067 (s), 966 (s), 767 (s), 693 (s) cm^{-1}.

53F: Yield: 62%; ^1H NMR ($CDCl_3$): δ 7.72 (s, 1H), 7.50 (d, 1H, *J* = 2.3 Hz), 7.34-7.36 (m, 3H), 7.26-7.29 (m, 3H), 7.20 (d, 1H, *J* = 4.8 Hz), 4.40 (s, 2H), 4.16 (s, 2H), 4.07 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 143.6 (C), 143.4 (CH), 140.3 (C), 129.7 (CH), 129.0 (CH), 128.5 (CH), 127.9 (CH), 126.5 (CH), 125.7 (CH), 123.0 (C), 102.5 (C), 88.5 (C), 82.1 (C), 73.3 (C), 70.1 (CH), 69.0 (CH), 68.7 (CH); IR (neat): 3725 (m), 3691 (m), 2988 (s), 2921 (s), 1489 (s), 1399 (m), 1063 (w), 867 (w), 777 (m), 753 (m), 687 (m) cm^{-1}; MS (ESI, *m/z*): 457.04 $[M + Na]^+$, 434.05 $[M]^+$; HRMS (ESI): calc. for $C_{25}H_{18}FeN_2SNa$: 457.0438 $[M + Na]^+$. Found: 457.0433; calc. for $C_{25}H_{18}FeN_2S$: 434.0540 $[M]^+$. Found: 434.0535.

53G: Yield: 44%; ^1H NMR ($CDCl_3$): δ 7.82 (s, 1H), 7.54 (d, 2H, *J* = 8.7 Hz), 7.44-7.47 (m, 3H), 7.37-7.39 (m, 2H), 6.77 (d, 2H, *J* = 8.7 Hz), 4.54 (s, 2H), 4.25 (s, 2H), 4.18 (s, 5H), 3.05 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 150 (C), 143.3 (CH), 142.9 (C),

140.5 (C), 132.4 (CH), 129.0 (CH), 128.4 (C), 126.5 (CH), 112.1 (CH), 103.4 (C), 94.2 (C), 80.2 (C), 73.6 (C), 70.0 (CH), 68.7 (CH), 68.6 (CH), 40.3 (CH_3) (one carbon peak missing due to overlap); IR (neat): 3831 (w), 3722 (s), 3698 (m), 2988 (s), 2922 (s), 1744 (vw), 1599 (vw), 1219 (vw), 1066 (m), 796 (vw), 668 (m) cm^{-1}; MS (ESI, *m/z*): 472.14 $[M + H]^+$, 471.13 $[M]^+$; HRMS (ESI): calc. for $C_{29}H_{26}FeN_3$: 472.1476 $[M + H]^+$. Found: 472.1443; calc. for $C_{29}H_{26}FeN_3$: 471.1398 $[M]^+$. Found: 471.1389.

53H: Yield: 68%; ^1H NMR ($CDCl_3$): δ 7.69 (s, 1H), 7.27-7.35 (m, 5H), 4.54 (s, 2H), 4.44 (s, 2H), 4.28 (s, 5H), 4.25 (s, 2H), 4.17 (s, 2H), 4.13 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 143.4 (CH), 143.2 (C), 140.4 (C), 129.0 (CH), 128.5 (CH), 126.6 (CH), 103.2 (C), 92.0 (C), 78.8 (C), 73.6 (C), 71.2 (CH), 70.2 (CH), 70.0 (CH), 69.0 (CH), 68.9 (CH), 68.7 (CH), 66.7 (C); IR (neat): 3725 (m), 3599 (w), 3099 (m), 2988 (m), 2903 (m), 2231 (w), 1595 (s), 1497 (s), 1398 (s), 1105 (s), 1000 (s), 965 (s), 816 (s), 767 (s), 695 (s) cm^{-1}; MS (ESI, *m/z*): 559.05 $[M + Na]^+$, 536.06 $[M]^+$; HRMS (ESI): calc. for $C_{31}H_{24}Fe_2N_2Na$: 559.0536 $[M + Na]^+$. Found: 559.0531; calc. for $C_{31}H_{24}Fe_2N_2$: 536.0638 $[M]^+$. Found: 536.0634.

4.7.2 Synthesis of 4-alkynyl-1,5-diphenyl-1*H*-pyrazoles (54) (Table 4)

General Procedure 4 was followed by using 4-iodo-1,5-diphenyl-1*H*-pyrazole (**51**) (100 mg, 0.22 mmol), corresponding terminal alkyne (**52** or **57**) (0.264 mmol), $PdCl_2(PPh_3)_2$ (7.73 mg, 0.011 mmol), CuI (2.09 mg, 0.011 mmol), Et_3N (1.6 ml) and THF (2 ml). After chromatographic purification, 4-alkynyl-1,5-diphenyl-1*H*-pyrazoles (**54**) given in Table 4 were isolated with the indicated yields, the spectroscopic data for which are provided below.

54A: Yield: 42%; ^1H NMR ($CDCl_3$): δ 7.84 (s, 1H), 7.33-7.35 (m, 5H), 7.20-7.28 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 144.1 (C), 142.8 (CH), 139.8 (C), 131.3 (CH), 129.6 (CH), 129.0 (CH), 128.9 (CH), 128.7 (C), 128.4 (CH), 128.3 (CH), 128.0 (CH), 127.7 (CH), 125.1 (CH), 123.6 (C), 104.5 (C), 91.6 (C). 81.4 (C); IR (neat): 3693 (w), 3058 (m), 2929 (w), 2223 (m), 1967 (w), 1596 (s), 1495 (s) 1441 (s), 1387 (s), 1063 (m), 962 (m), 907 (s),751 (s), 730 (s), 688 (s) cm^{-1}.

54B: Yield: 36%; ^{1}H NMR ($CDCl_3$): δ 7.83 (s, 1H), 7.32-7.35 (m, 2H), 7.22-7.27 (m, 10 H), 7.04 (d, 2H, *J* = 7.9 Hz), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 144.0 (C), 142.8 (CH), 139.8 (C), 138.1 (C), 131.2 (CH), 129.5 (CH), 129.0 (CH), 128.9 (CH), 128.7 (C), 128.3 (CH), 127.7 (CH), 125.2 (CH), 120.5 (C), 104.7 (C), 91.7 (C), 80.5 (C), 21.5 (CH_3) (one carbon peak missing due to overlap); IR (neat): 3733 (m), 3703 (m), 2988 (s), 2919 (s), 2237 (vw), 1593 (m), 1498 (s), 1442 (m), 1382 (s), 818 (s), 761 (m), 691 (s) cm^{-1}.

54C: Yield: 76%; ^{1}H NMR ($CDCl_3$): δ 7.81 (s, 1H), 7.31-7.33 (m 2H), 7.20-7.25 (m, 10 H), 6.74 (d, 2H, *J* = 8.7 Hz), 3.70 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 159.4 (C), 143.8 (C), 142.7 (CH); 139.8 (C), 132.7 (CH), 129.6 (CH), 129.0 (CH), 128.9 (CH), 128.7 (C), 128.3 (CH), 127.7 (CH), 125.2 (CH), 116.0 (C), 114.0 (CH), 105.0 (C), 91.5 (C), 79.8 (C), 55.3 (CH_3); IR (neat): 3838 (vw), 3614 (vw), 3055 (w), 2836 (w), 1605 (s), 1496 (s), 1439 (s), 1383 (s), 1251 (s), 1173 (s), 960 (m), 825 (s), 694 (s) cm^{-1}.

54D: Yield: 85%; ^{1}H NMR ($CDCl_3$): δ 7.81 (s, 1H), 7.29-7.32 (m, 3H), 7.20-7.24 (m, 8H), 7.15 (dd, 1H, *J* = 4.0, 3.0), 7.0 (dd, 1H, *J* = 5.0, 1.0 Hz); ^{13}C NMR ($CDCl_3$): δ 144.2 (C), 143.0 (CH), 140.0 (C), 130.0 (CH), 129.7 (CH), 129.2 (CH), 129.1 (C), 128.9 (CH), 128.6 (CH), 128.3 (CH), 127.9 (CH), 125.5 (CH), 125.4 (CH), 122.7 (C), 104.7 (C), 86.9 (C), 80.9 (C); IR (neat): 3614 (vw), 3566 (vw), 3096 (br), 2923 (m), 2851 (m), 2586 (vw), 2215 (vw), 1592 (s), 1498 (vs), 1440 (s), 1386 (s) 960 (s), 771 (s), 761 (s) cm^{-1}.

54E: Yield: 54%; ^{1}H NMR ($CDCl_3$): δ 7.78 (s, 1H), 7.17-7.33 (m, 10H), 4.38 (s, 2H), 4.14 (s, 2H), 4.10 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 143.8 (C), 142.8 (CH), 140.0 (C), 129.6 (CH), 129.2 (C), 129.0 (CH), 128.7 (CH), 128.3 (CH), 127.7 (CH), 125.1 (CH), 105.1 (C), 90.2 (C), 71.5 (CH), 70.1 (CH), 70.0 (CH), 65.8 (C) (one carbon peak missing due to overlap); IR (neat): 3648 (vw), 3069 (m), 2225 (w), 1594 (s), 1494 (vs), 1442 (s), 1384 (vs) 961 (s), 762 (vs), 691 (s) cm^{-1}.

4.8 General Procedure 5. Synthesis of 4-aryl-5-ferrocenyl-1-phenyl-1H-pyrazoles (56) via Suzuki-Miyaura coupling reaction (Table 5)

In a dry flask, 5-ferrocenyl-4-iodo-1-phenyl-1*H*-pyrazole (**48**) (100 mg, 0.22 mmol), corresponding boronic acid or boronic acid ester derivative (**55**) (0.308 mmol), $PdCl_2(PPh_3)_2$ (7.73 mg, 0.011 mmol) and $KHCO_3$ (30.84 mg, 0.308 mmol) were mixed in a mixture of DMF (8 ml) and H_2O (2 ml) by flashing with argon for several minutes. The resulting reaction mixture was heated at 110 ^oC and it was stirred at this temperature until TLC revealed the completion of reaction. The reaction mixture was then concentrated on a high pressure vacuum (ca. -900 mbar) equipped with two serially connected traps immersed in liquid N_2. The crude products were purified by flash chromatography on silica gel using 9:1 hexane/ethylacetate mixture as the eluent. After chromatographic purification, 4-aryl-5-ferrocenyl-1-phenyl-1*H*-pyrazoles (**56**) given in Table 5 were isolated with the indicated yields, the spectroscopic data for which are provided below.

56A: Yield: 72% from **55A** and 80% from **55L**; ^{1}H NMR ($CDCl_3$): δ 7.58 (s. 1H), 7.44-7.46 (m, 2H), 7.37-7.40 (m, 2H), 7.30-7.34 (m, 6H), 4.03 (s, 2H), 4.00 (s, 2H), 3.63 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 141.0 (C), 140.9 (CH), 137.7 (C), 134.3 (C), 130.5 (CH), 128.8 (CH), 128.2 (CH), 128.0 (CH), 127.3 (CH), 126.5 (CH), 123.3 (C), 75.24 (C), 70.2 (CH), 69.4 (CH), 68.4 (CH); IR (neat): 3727 (w), 3627 (w), 3106 (vw), 1597 (w), 1497 (s), 1377 (m), 1106 (m), 999 (m), 863 (m), 818 (m), 754 (s), 690 (s), cm^{-1}.

56B: Yield: 52%; ^{1}H NMR ($CDCl_3$): δ 7.54 (s 1H), 7.29-7.38 (m, 5H), 6.93 (d, 1H, *J* = 1.2 Hz), 6.91 (dd, 1H, *J* = 8.0, 1.6 Hz), 6.85 (d, 1H, *J* = 8.0 Hz), 5.96 (s, 2H), 4.05 (s, 2H), 3.96 (s, 2H), 3.72 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 147.8 (C), 147.3 (C), 141.4 (C), 141.3 (CH), 137.9 (C), 129.2 (CH), 128.5 (CH), 128.4 (C), 127.0 (CH), 124.1 (CH), 123.0 (C), 111.3 (CH), 108.5 (CH), 101.6 (CH_2), 75.5 (C), 70.3 (CH), 69.7 (CH), 68.8 (CH); IR (neat): 3726 (m), 3697 (m), 3627 (m), 2988 (s), 2892 (s), 1596 (w), 1473 (s), 1371 (s), 1230 (s), 1033 (s), 810 (s), 762 (s), 696 (s) cm^{-1}.

56C: Yield: 65%; ^{1}H NMR ($CDCl_3$): δ 7.56 (s, 1H), 7.34 (d, 2H, *J* = 7.6 Hz), 7.30-7.32 (m, 5H), 7.22 (d, 2H, *J* = 7.6 Hz), 4.05 (s, 2H), 4.02 (s, 2H), 3.67 (s, 5H), 2.65 (q, 2H, *J* = 7.6 Hz), 1.22 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$): δ 143.4 (CH), 141.0 (C), 140.9 (C), 137.5 (C), 131.4 (C), 130.4 (CH), 128.7 (CH), 127.9 (CH),

127.6 (CH), 126.5, (CH), 123.3 (C), 75.6 (C), 70.3 (CH), 69.5 (CH), 68.5 (CH), 28.7 (CH_2), 15.7 (CH_3); IR (neat): 3928 (w), 3659 (w), 3094 (m), 2962 (s), 2228 (m), 1596 (s), 1499 (vs), 1374 (s), 1107 (s), 951 (s), 820 (s), 762 (s), 728 (s), 693 (s) cm^{-1}.

56D: Yield: 99%; ^1H NMR ($CDCl_3$): δ 8.34 (s, 1H), 8.18 (d, 1H, *J* = 7.2 Hz), 7.74-7.76 (m, 1H), 7.64-7.69 (m, 1H), 7.55-7.57 (m, 1H) 7.35-7.38 (m, 5H), 4.09 (s, 2H), 3.94 (s, 2H), 3.65 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 148.1 (C), 140.7 (C), 140.4 (CH), 138.5 (C), 136.1 (C), 135.9 (CH), 129.2 (CH), 128.9 (CH), 128.5 (CH), 126.7 (CH), 124.7 (CH), 122.0 (CH), 120.8 (C), 74.2 (C), 70.0 (CH), 69.3 (CH), 68.9 (CH); IR (neat): 8726 (m), 3697 (m), 3628 (m), 3072 (w), 2988 (s), 2900 (s), 1522 (s), 1345 (s), 1081 (m), 809 (m), 768 (m), 683 (m) cm^{-1}.

56E: Yield: 93%; ^1H NMR ($CDCl_3$): δ8.29 (s, 1H), 8.13 (d, 1H, *J* = 7.6 Hz), 7.72-7.74 (m, 2H), 7.55-7.59 (m, 1H), 7.41-7.48 (m, 5H), 4.46 (q, 2H, *J* = 7.2 Hz), 4.14 (s, 2H), 4.04 (s, 2H), 3.75 (s, 5H), 1.45 (t, 3H, *J* = 7.2); ^{13}C NMR ($CDCl_3$): δ 166.5 (C), 140.9 (C), 140.7 (CH), 138.0 (C), 134.6 (C), 134.5 (CH), 131.4 (CH), 130.5 (C), 128.8 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 126.6 (CH), 122.1 (C), 74.7 (C), 69.9 (CH), 69.2 (CH), 68.4 (CH), 61.1 (CH_2), 14.4 (CH_3); IR (neat): 3925 (w), 3726 (w), 3628 (w), 3094 (m), 2978 (s), 2230 (m), 1714 (vs), 1499 (s), 1367 (s), 1257 (vs), 1104 (s), 908 (s), 757 (s), 726 (vs), 691 (s) cm^{-1}.

56F: Yield: 95%; ^1H NMR ($CDCl_3$): δ 7.54 (s, 1H), 7.32-7.38 (m, 5H), 7.05 (br s, 2H), 4.12 (s, 2H), 3.94 (s, 2H), 3.74 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 152.08-152.22 (m, C), 149.60-149.69 (m, C), 140.7 (C), 140.2 (CH), 138.3 (C), 128.9 (CH) 128.6 (CH), 126.9 (CH), 120.2 (C), 113.92-114.13 (m, CH), 74.3 (C), 70.0 (CH), 69.5 (CH), 69.0 (CH) (extra peaks due to C-F splitting); IR (neat): 3726 (m), 3697 (m), 3628 (m), 3090 (w), 2988 (s), 1526 (s), 1408 (s), 1231 (m), 1046 (s), 846 (m), 754 (m), 695 (m) cm^{-1}.

56G: Yield: 94%; ^1H NMR ($CDCl_3$): δ 8.37 (s, 1H), 7.72 (d, 1H, *J* = 7.6 Hz), 7.66 (s, 1H), 7.40-7.43 (m, 5H), 6.88 (d, 1H, *J* = 8.4), 4.14 (2, 2H), 4.04 (br s, 5H), 3.77 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 163.4 (C), 147.5 (CH), 140.8 (CH), 140.4 (C), 138.1 (C), 128.8 (CH), 128.1 (CH), 126.5 (CH), 123.1 (C), 119.1 (C), 110.3 (CH), 74.7 (C), 70.0 (CH), 69.2 (CH), 68.5 (CH), 53.6 (CH_3) (one carbon peak missing due to overlap); IR (neat): 3726 (m), 3698 (m), 3627 (m), 2988 (s), 2900 (m), 1564 (m), 1477 (m9, 1289 (s), 1017 (s), 948 (m), 810 (m), 668 (m) cm^{-1}.

56H: Yield: 91%; ^{1}H NMR ($CDCl_3$): δ 7.54 (s, 1H), 7.32-7.42 (m, 9H), 4.12 (s, 2H), 4.03 (s, 2H), 3.75 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 140.9 (C), 140.7 (CH), 133.1 (C), 132.8 (C), 131.5 (CH), 128.8 (CH), 128.4 (CH), 128.3 (CH), 126.7 (CH), 126.1 (C), 121.9 (C), 74.7 (C), 70.0 (CH), 69.3 (CH), 68.5 (CH); IR (neat): 3929 (vw), 3737 (vw), 3095 (w), 2230 (vw), 1948 (vw), 1595 (s), 1550 (s), 1498 (vs), 1381 (s), 1088 (s), 952 (s), 822 (vs), 765 (s) 694 (s) cm^{-1}.

56I: Yield: 42 %; ^{1}H NMR (DMSO): δ 11.17 (s, NH), 7.71 (br s, 1H), 7.68 (s, 1H), 7.36-7.51 (m, 8H), 7.23-7.26 (m, 1H), 4.14 (t, 2H, *J* = 2.0 Hz), 4.01 (t, 2H, *J* = 2 Hz), 3.65 (s, 5H), 3.35 (s, 3H), 2.5 (t, 3H, *J* = 2.0 Hz); ^{13}C NMR (DMSO): δ 140.7 (C), 140.6 (CH), 136.4 (C), 135.1 (C), 128.7 (CH), 127.8 (CH), 127.6 (CH), 126.3 (CH), 125.8 (CH), 124.2 (C), 124.1 (C), 123.6 (CH), 121.4 (C), 110.9 (CH), 101.2 (CH), 75.2 (C), 69.6 (CH), 68.8 (CH), 67.9 (CH); IR (neat): 3727 (s), 3698 (s), 3627 (s), 3182 (s), 2988 (vs), 2900 (s), 1407 (m), 1309 (m), 1083 (m), 967 (m), 809 (m), 767 (m), 663 (m) cm^{-1}.

56J: Yield: 80%; ^{1}H NMR ($CDCl_3$): δ 7.55 (s, 1H), 7.28-7.37 (m, 5H), 7.20 (dd, 1H, *J* = 10.0, 2.0 Hz), 7.12 (d, 1H, *J* = 8.4 Hz), 6.95-9-6.99 (m, 1H), 4.1 (q, 2H, *J* = 7.2 Hz), 4.04 (pseudo t, 2H), 3.93 (pseudo t, 2H), 3.68 (s, 5H), 1.42 (t, 3H, *J* = 7.2 Hz): ^{13}C NMR ($CDCl_3$): δ 150.36 (d, C, *J* = 976 Hz), 144.37 (d, C, *J* = 44 Hz), 139.2 (C), 138.9 (CH), 135.9 (C), 127.0 (CH), 126.3 (CH), 124.8 (CH), 124.23 (d, CH, *J* = 16 Hz); 119.9 (C), 116.5 (CH), 116.2 (CH), 112.7 (d, C, J = 36 Hz), 73.0 (C), 68.1 (CH), 67.4 (CH), 66.6 (CH), 63.3 (CH_2)13.1 (CH_3) (extra peaks due to C-F splitting); IR (neat): 3726 (m), 2986 (m), 2924 (m), 1566 (m), 1514 (s), 1474 (s), 1262 (s), 1128 (s), 1037 (s), 967 (m), 824 (m), 775 (s), 701 (s), cm^{-1}.

56K: Yield: 78%; ^{1}H NMR ($CDCl_3$): δ 7.68 (s, 1H), 7.42-7.49 (m, 5H), 6.72 (s, 2H), 4.16 (s, 2H), 4.10 (s, 2H), 3.95 (s, 3H), 3.94 (s, 6H), 3.81 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 152.9 (C), 141.0 (CH), 140.6 (C), 137.5 (C), 129.7 (C), 128.8 (CH), 128.2 (CH), 126.7 (CH), 123.2 (C), 107.8 (CH), 75.1 (C), 70.1 (CH), 69.4 (CH), 68.5 (CH), 61.1 (CH_3), 56.3 (CH_3) (one carbon peak missing due to overlap); IR (neat): 3726 (m), 3698 (m), 3627 (m), 2985 (br), 1581 (s), 1409 (s), 1243 (s), 1123 (vs), 1013 (m), 819 (m), 774 (m), 663 (m) cm^{-1}; MS (ESI, *m/z*): 495.13 $[M + H]^+$, 494.12 $[M]^+$; HRMS (ESI): calc. for $C_{28}H_{27}FeN_2O_3$: 495.1371 $[M + H]^+$. Found: 495.1331; calc. for $C_{28}H_{26}FeN_2O_3$: 494.1293 $[M]^+$. Found: 494.1291.

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APPENDIX A

NMR DATA

NMR spectra were recorded on a Bruker Spectrospin Avance DPX400 Ultrashield (400 MHz) spectrometer

^{1}H and ^{13}C NMR spectra of products are given below.

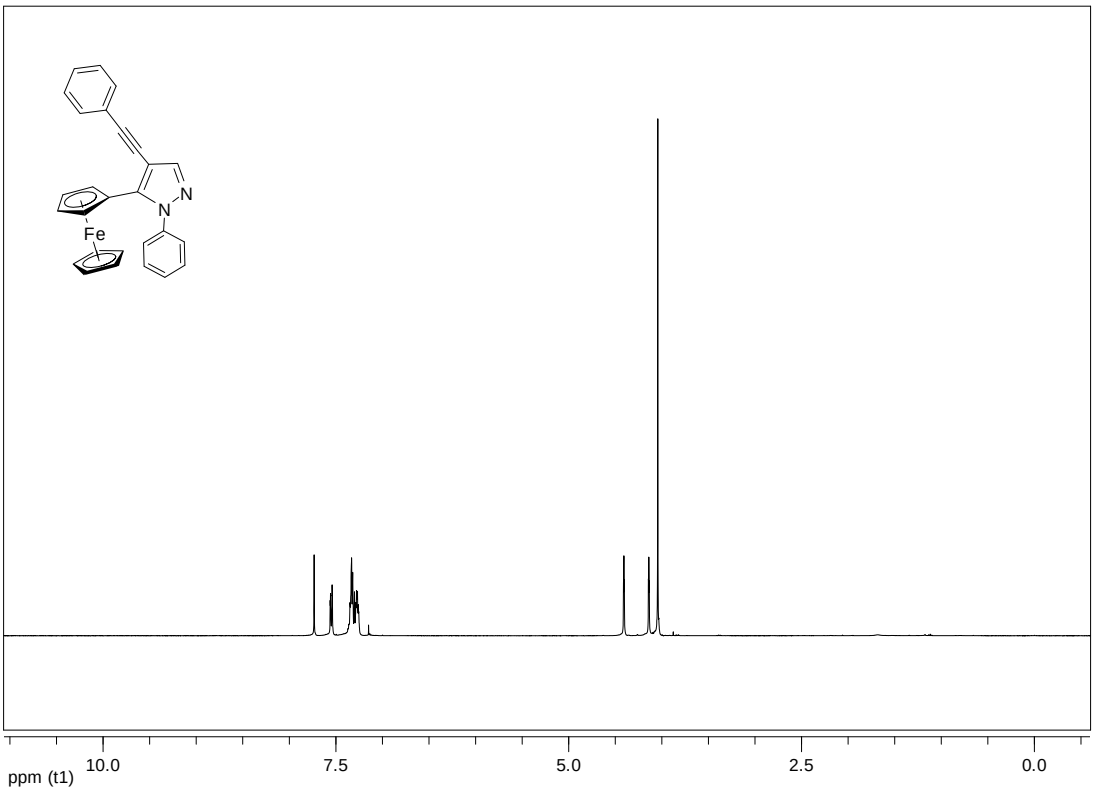

Figure A1. ^{1}H NMR spectra of **53A**.

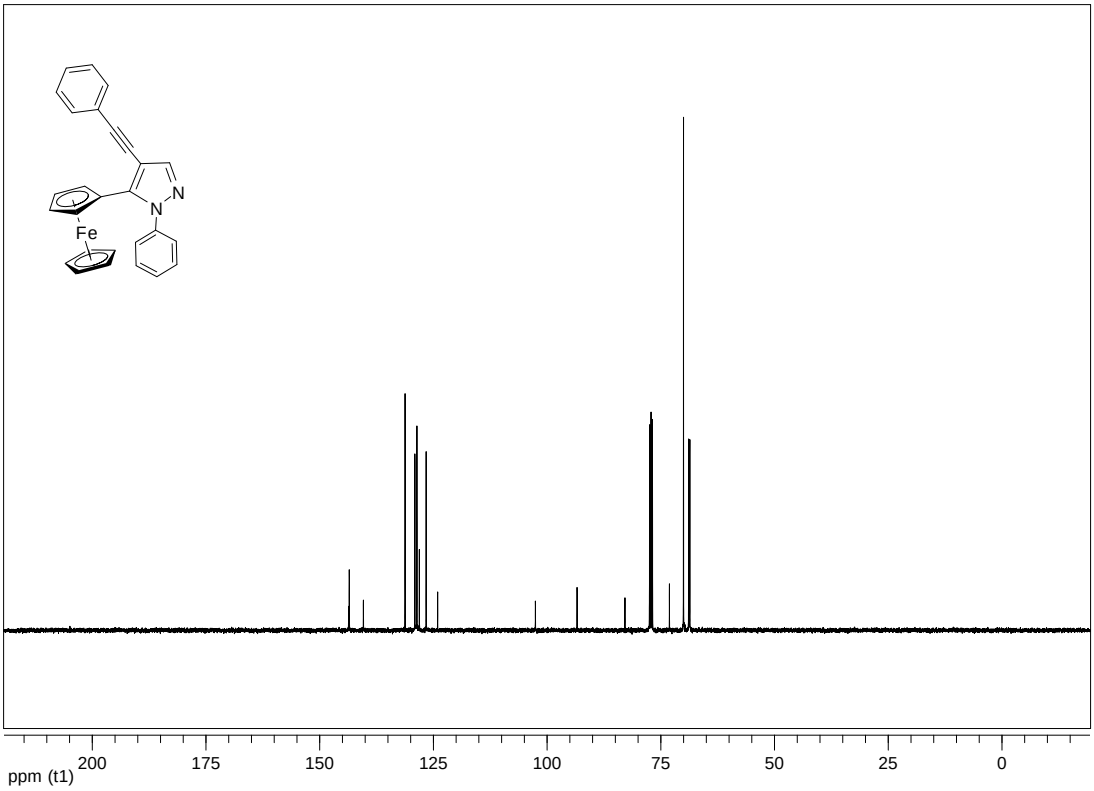

Figure A2. ^{13}C NMR spectra of **53A**.

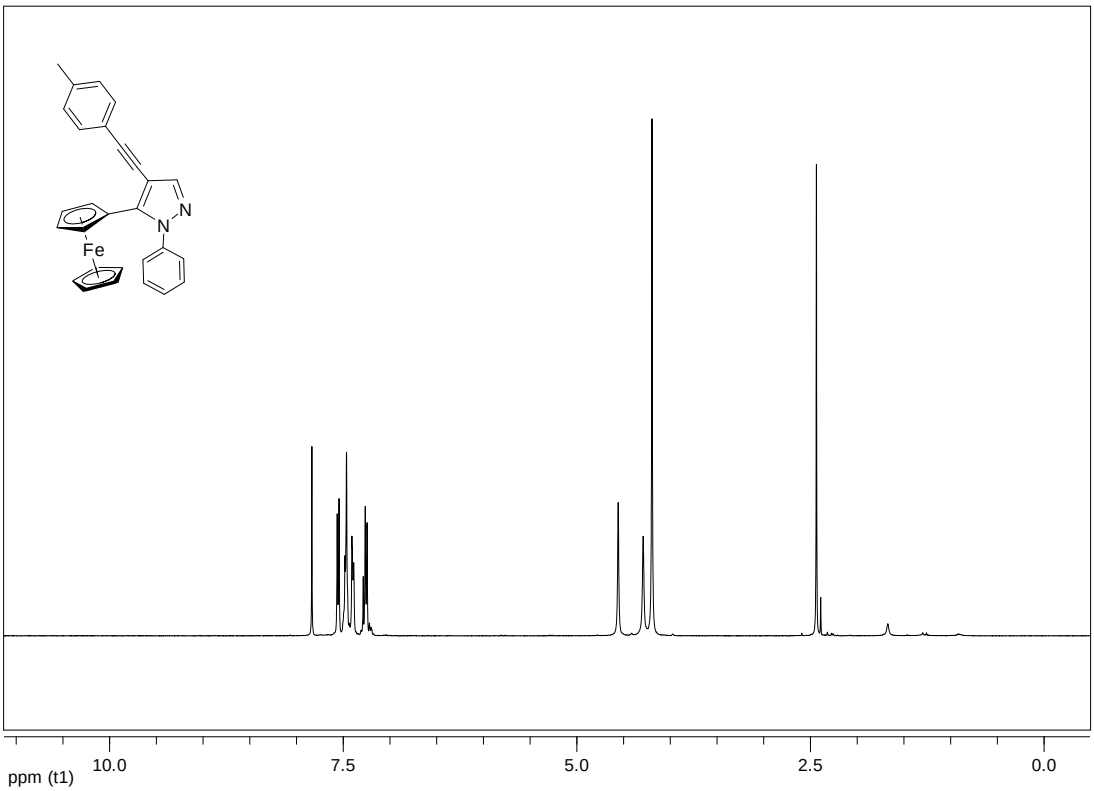

Figure A3. ^{1}H NMR spectra of **53B**.

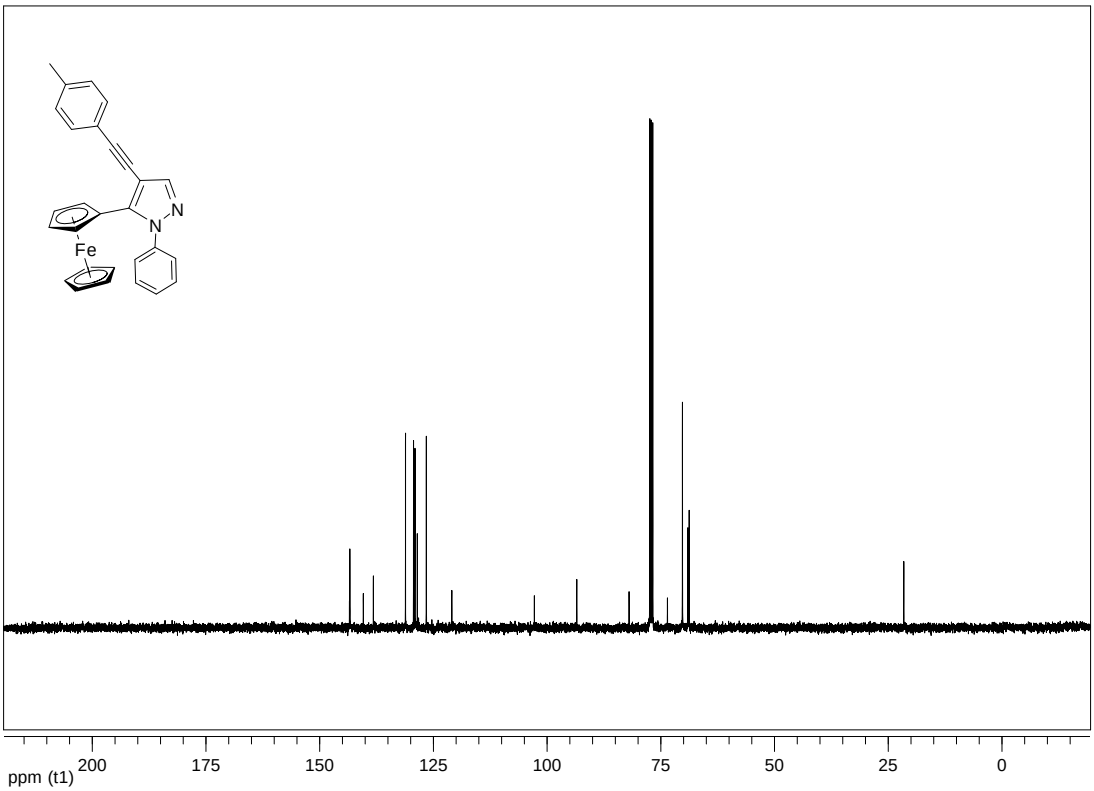

Figure A4. ^{13}C NMR spectra of **53B**.

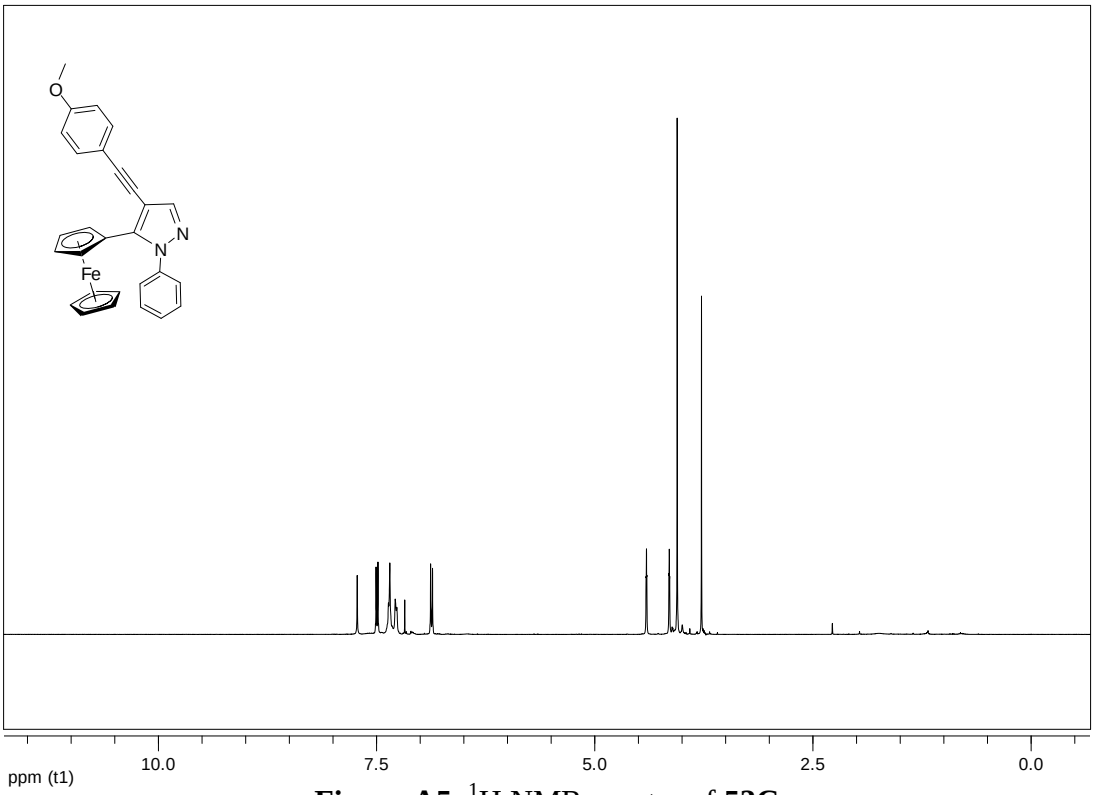

Figure A5. ^{1}H NMR spectra of **53C**.

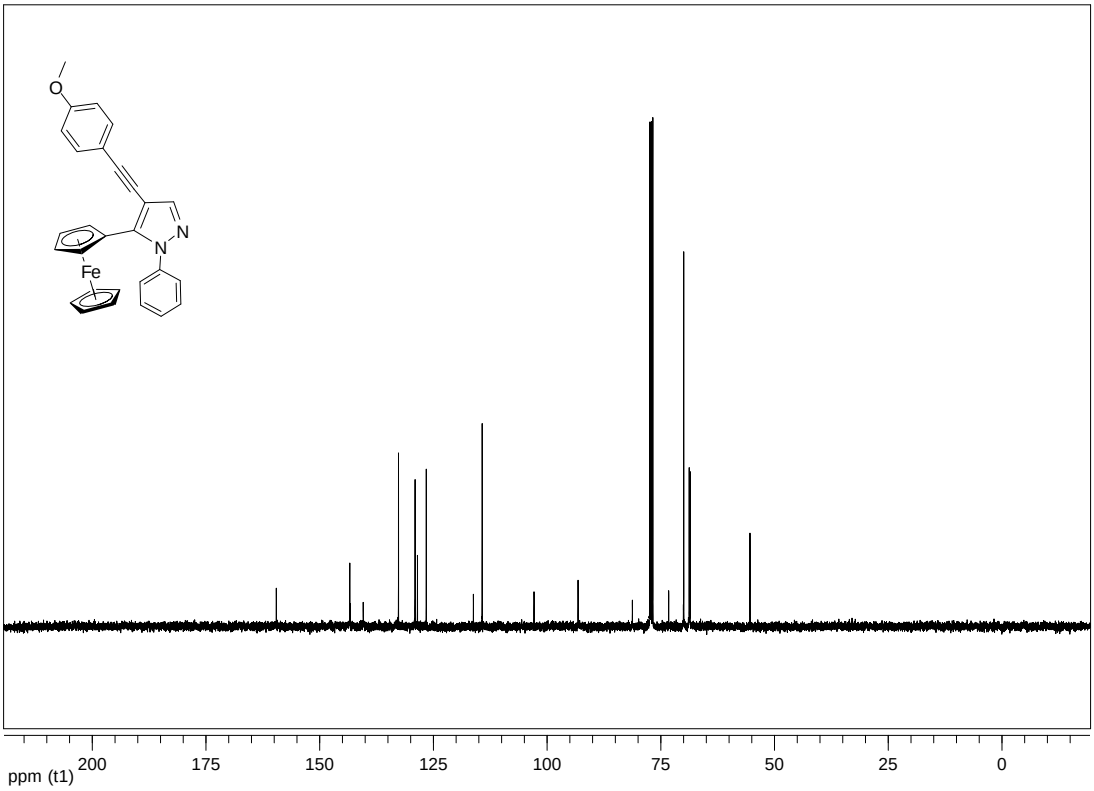

Figure A6. ^{13}NMR spectra of **53C**.

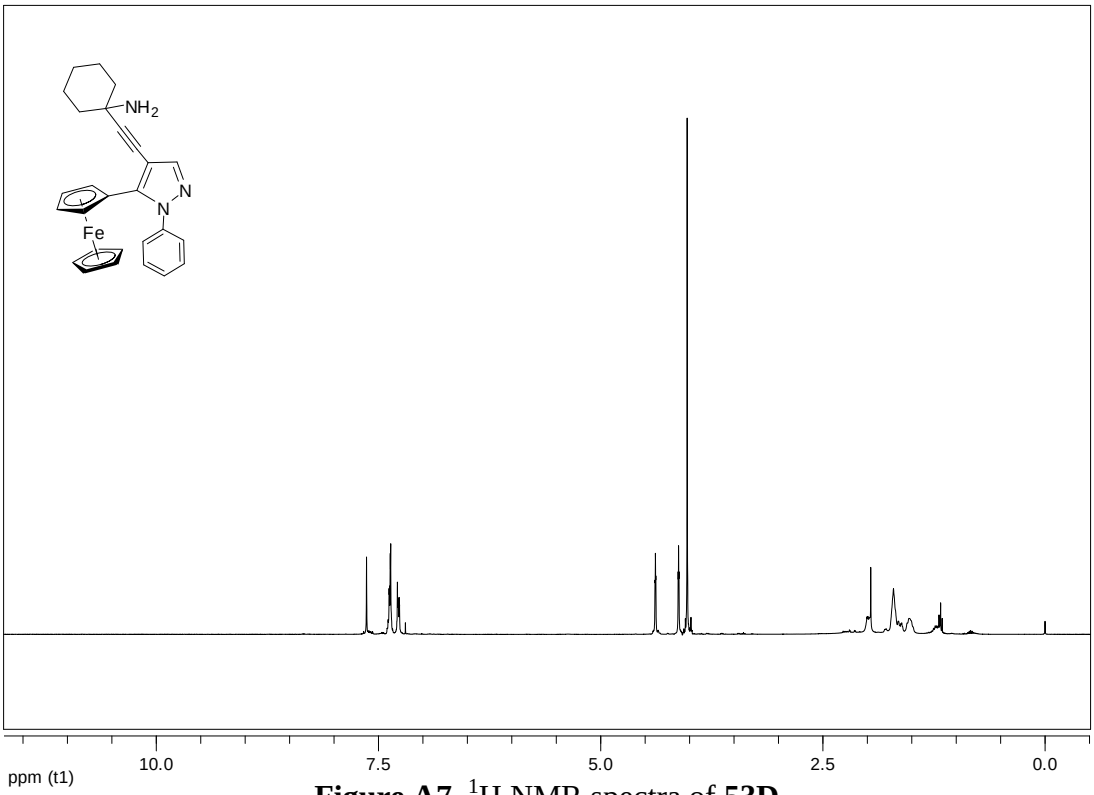

Figure A7. ^{1}H NMR spectra of **53D**.

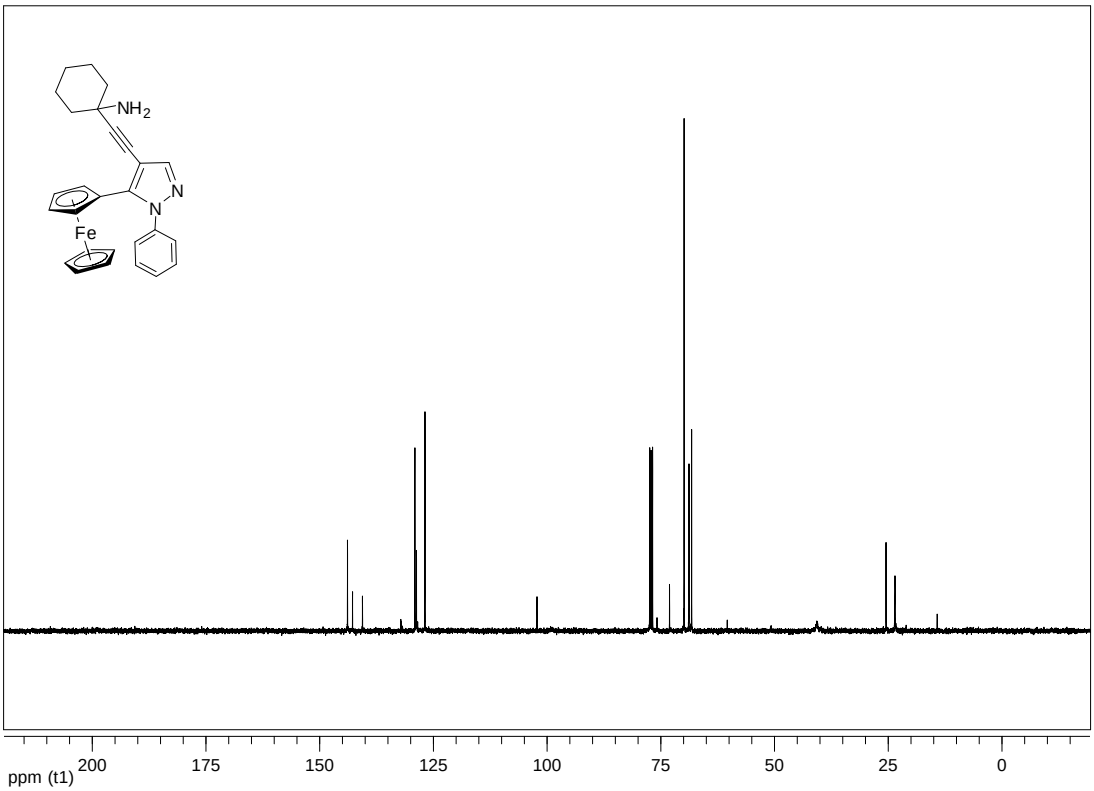

Figure A8. ^{13}C NMR spectra of **53D**.

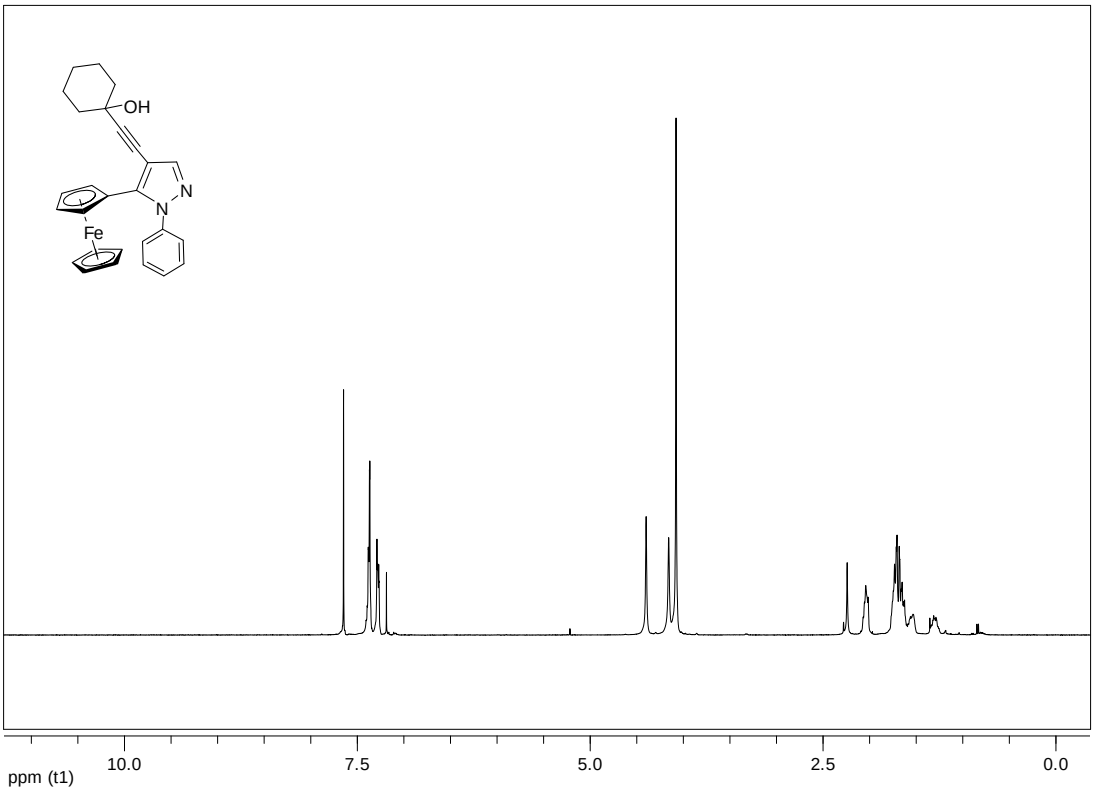

Figure A9. ^{1}H NMR spectra of **53E**.

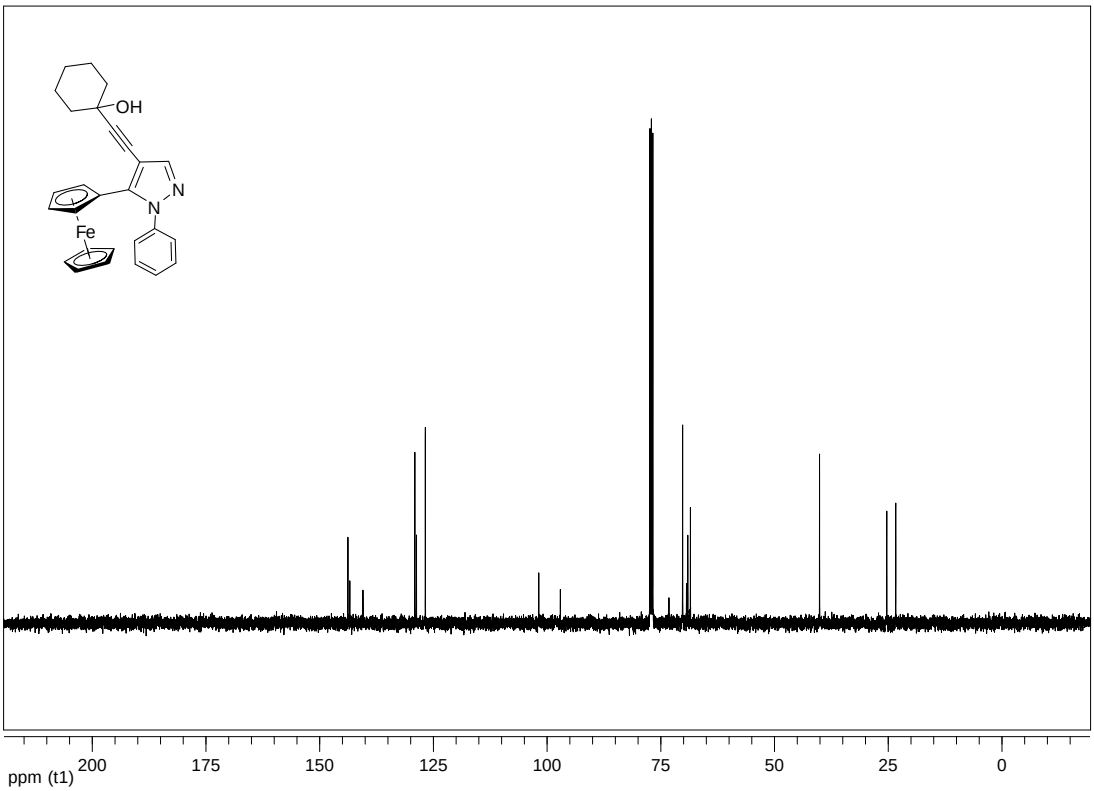

Figure A10. ^{13}C NMR spectra of **53E**.

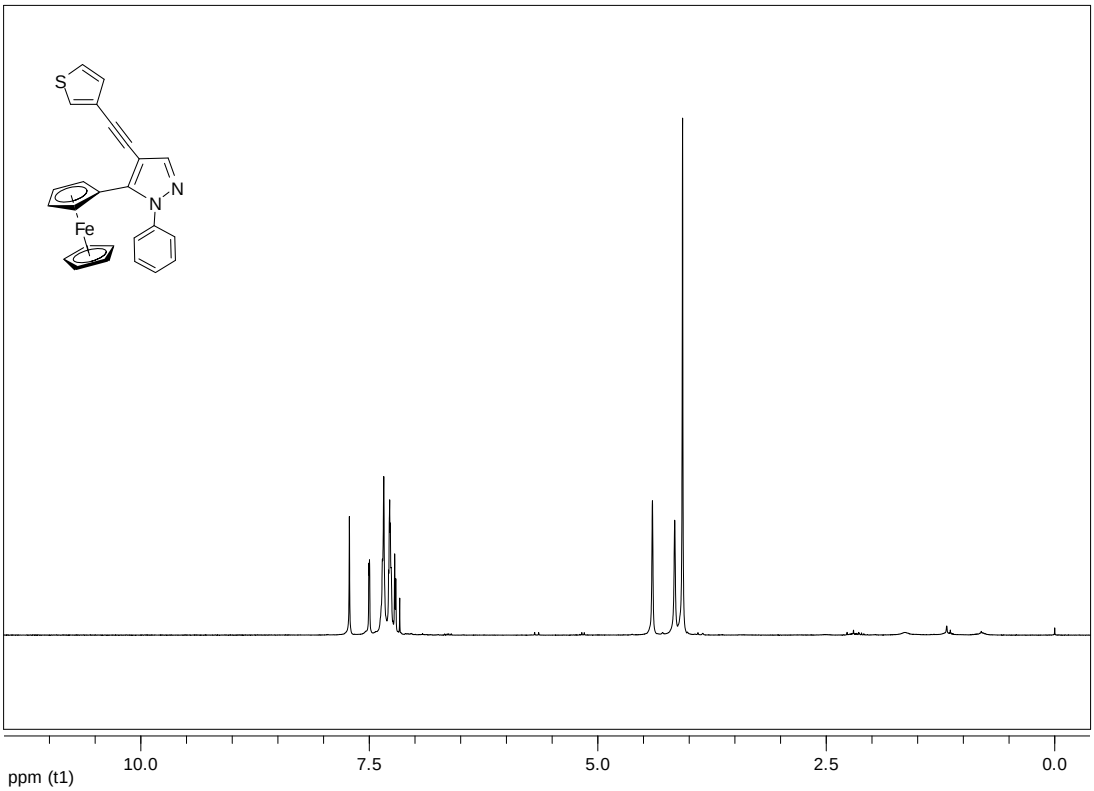

Figure A11. ^{1}H NMR spectra of **53F**.

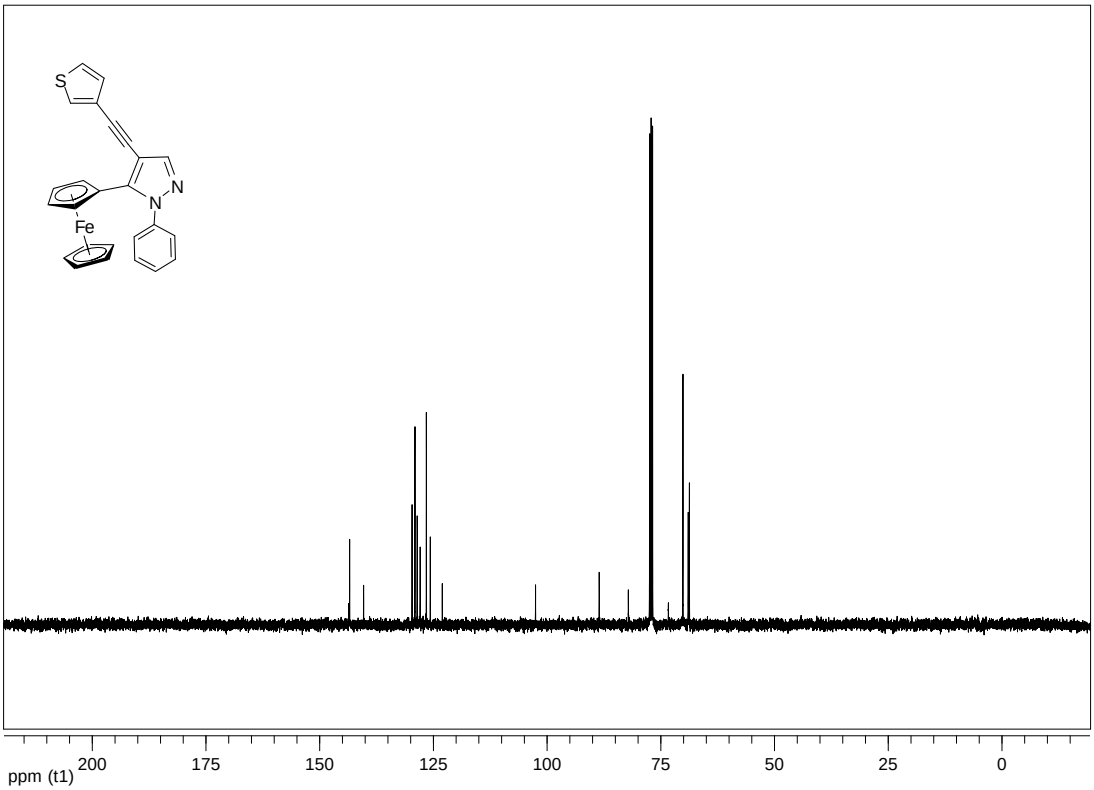

Figure A12. ^{13}C NMR spectra of **53F**.

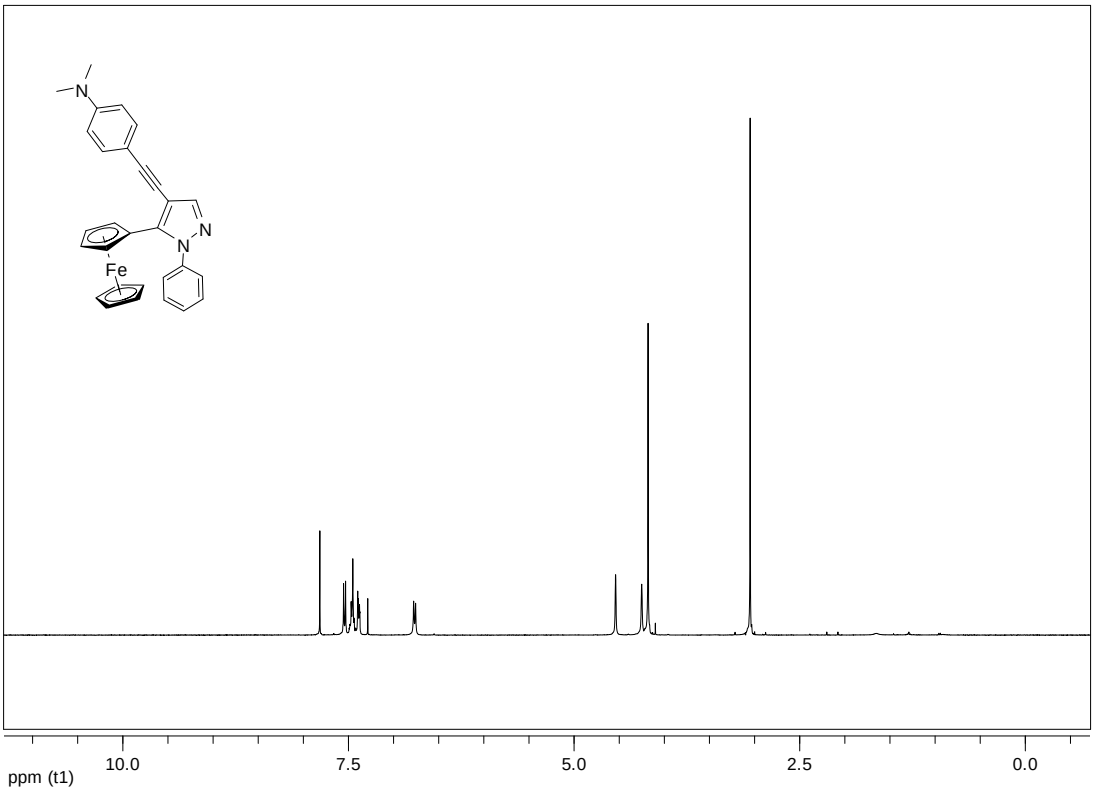

Figure A13. ^{1}H NMR spectra of **53G**.

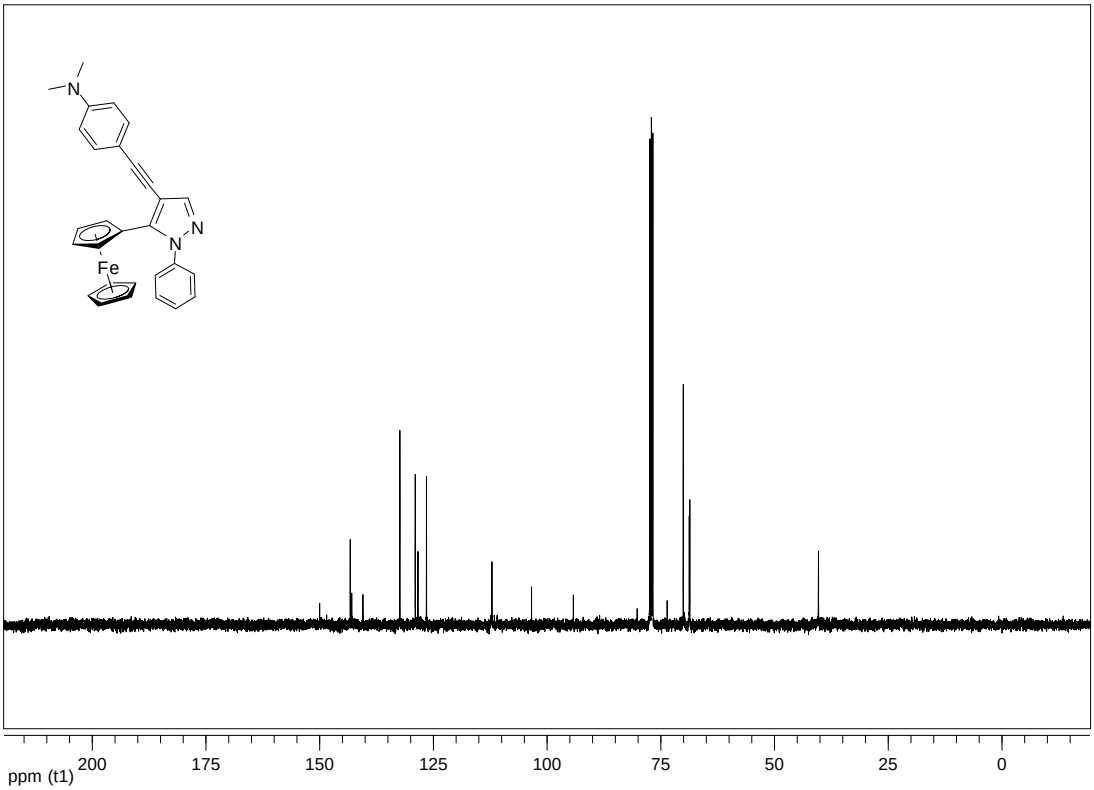

Figure A14. ^{13}C NMR spectra of **53G**.

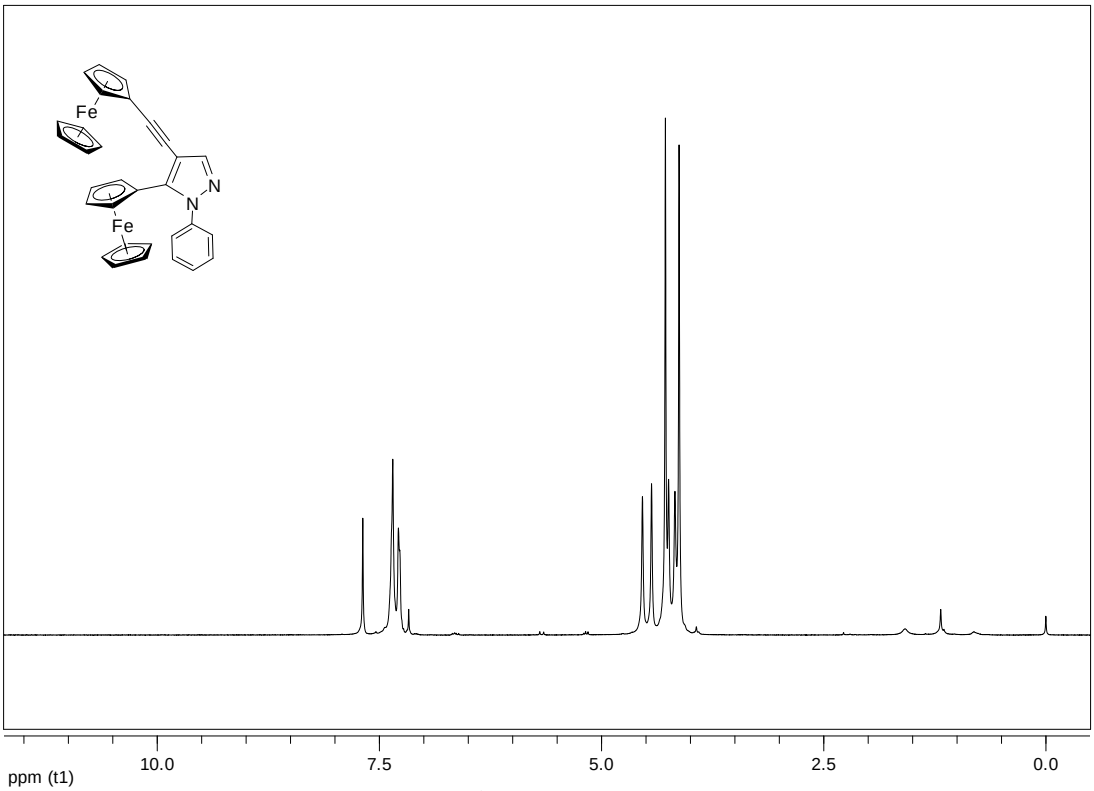

Figure A15. ^{1}H NMR spectra of **53H**.

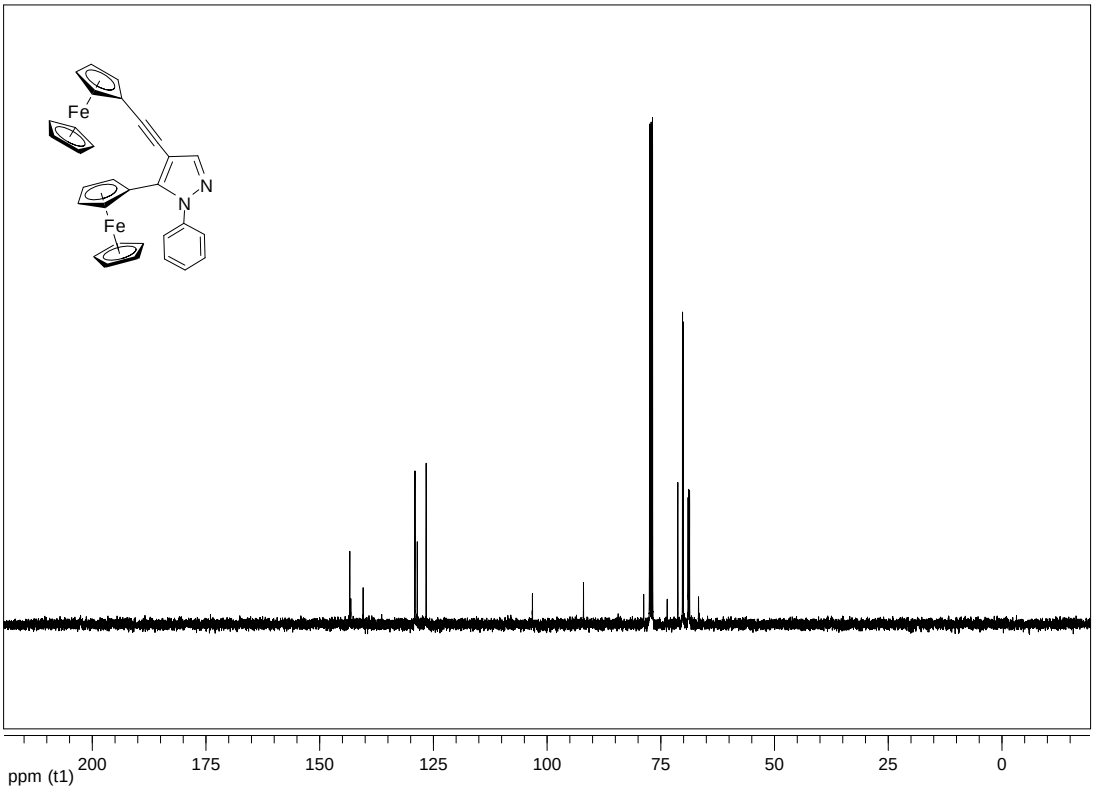

Figure A16. ^{13}C NMR spectra of **53H**.

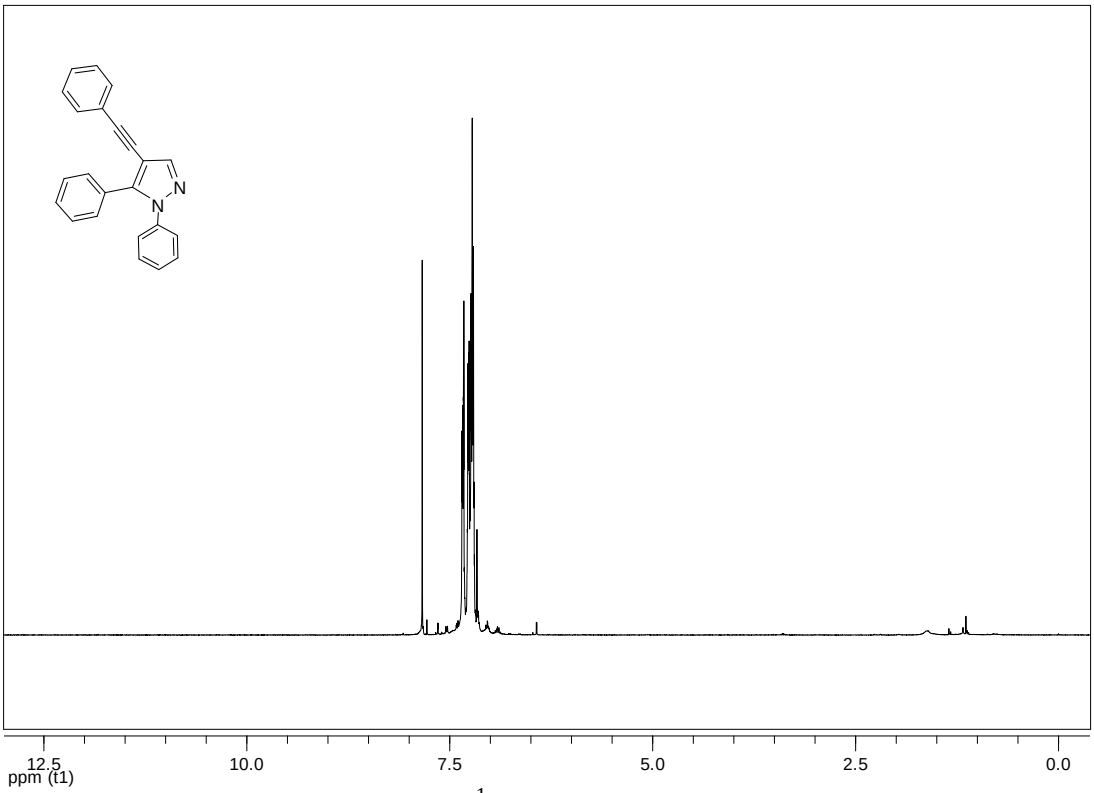

Figure A17. ^{1}H NMR spectra of **54A**.

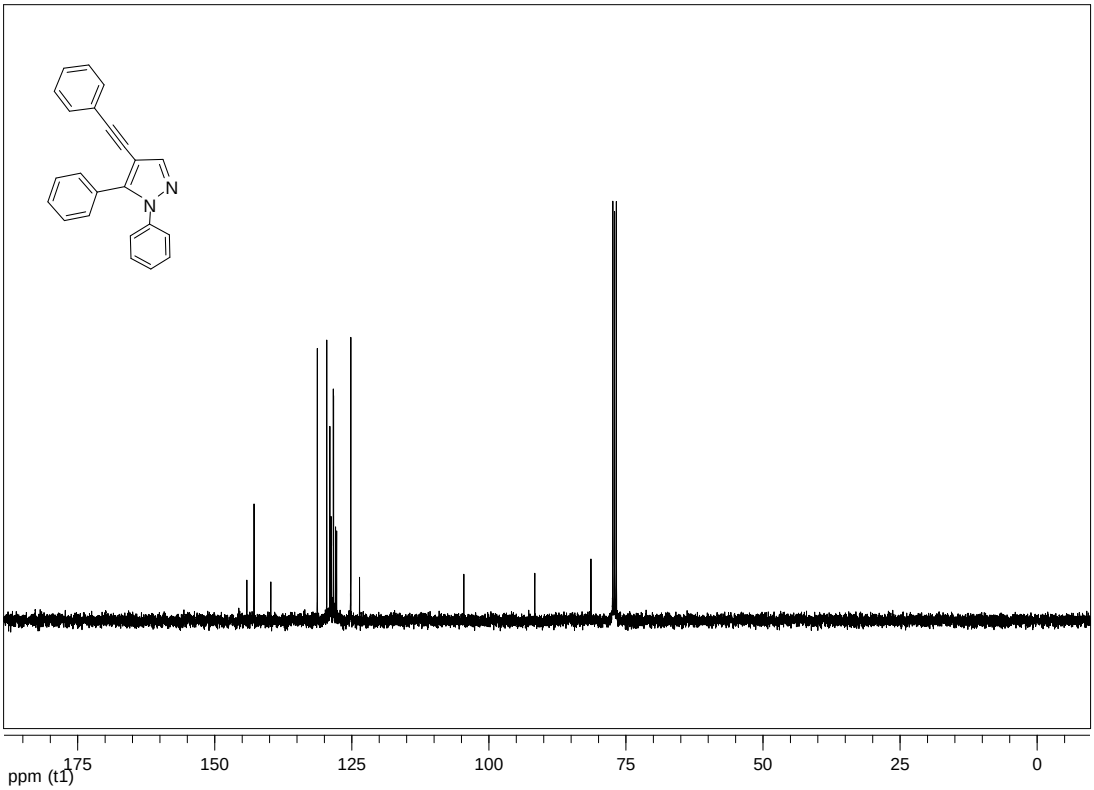

Figure A18. ^{13}C NMR spectra of **54A**.

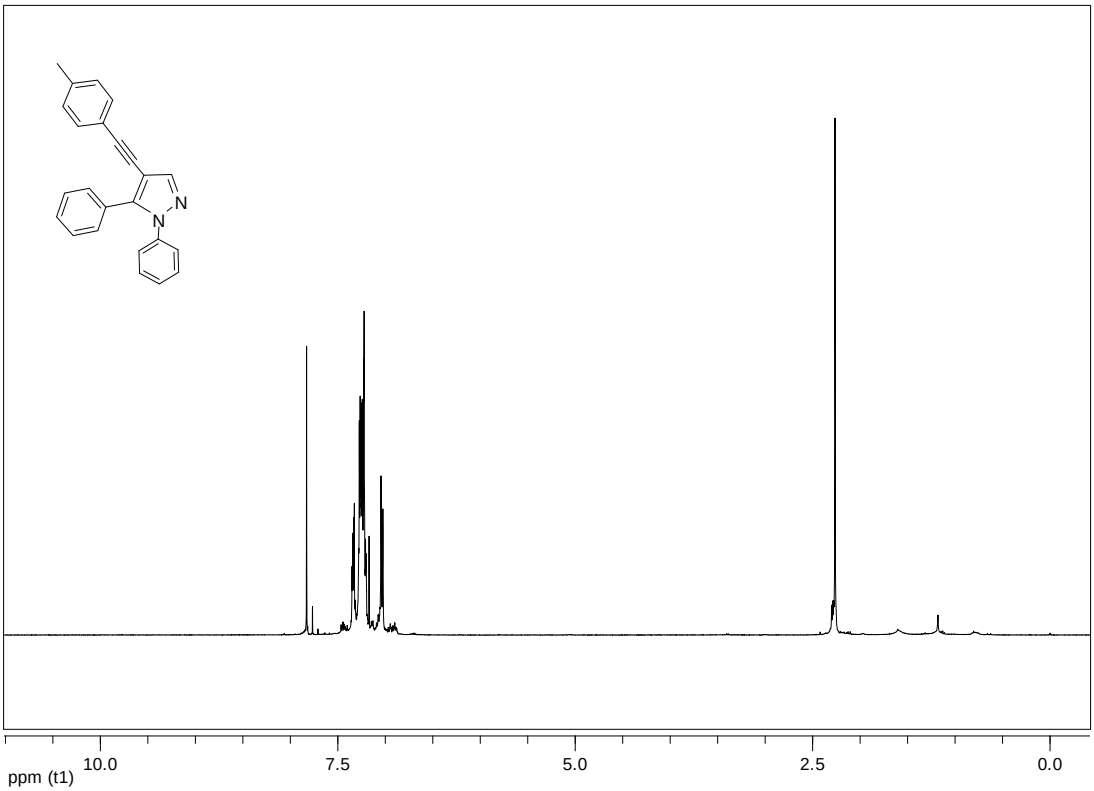

Figure A19. ^{1}H NMR spectra of **54B**.

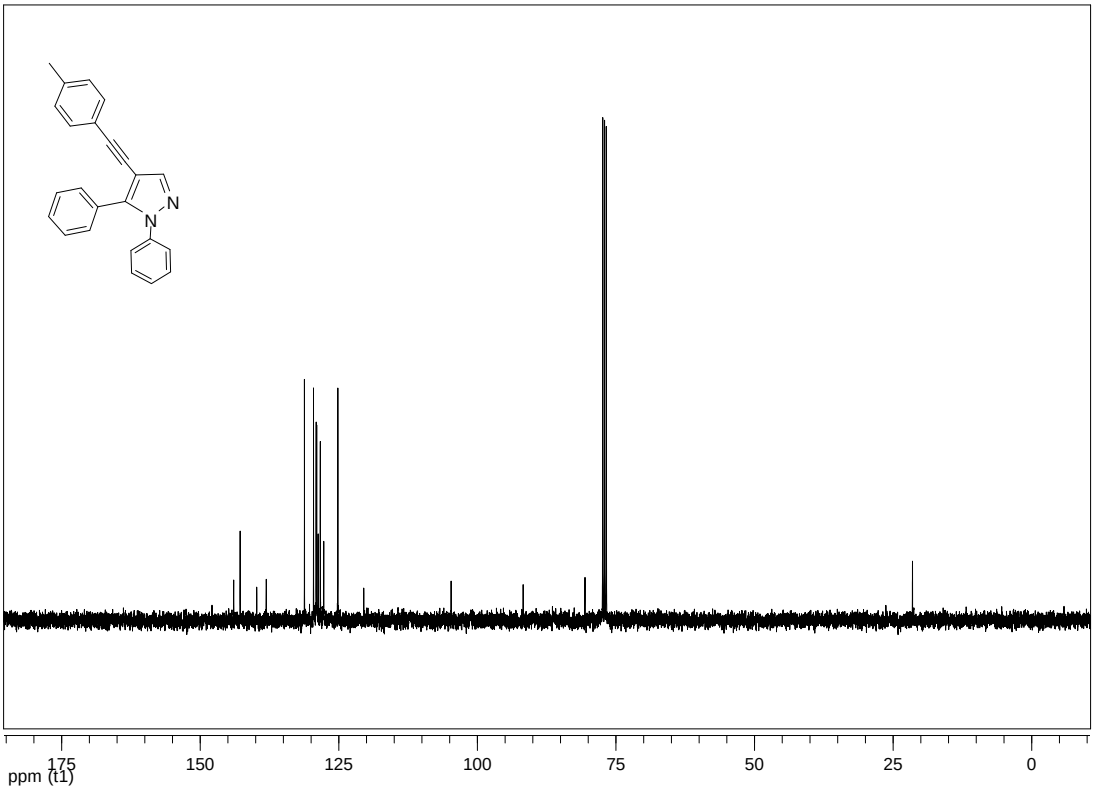

Figure A20. ^{13}C NMR spectra of **54B**.

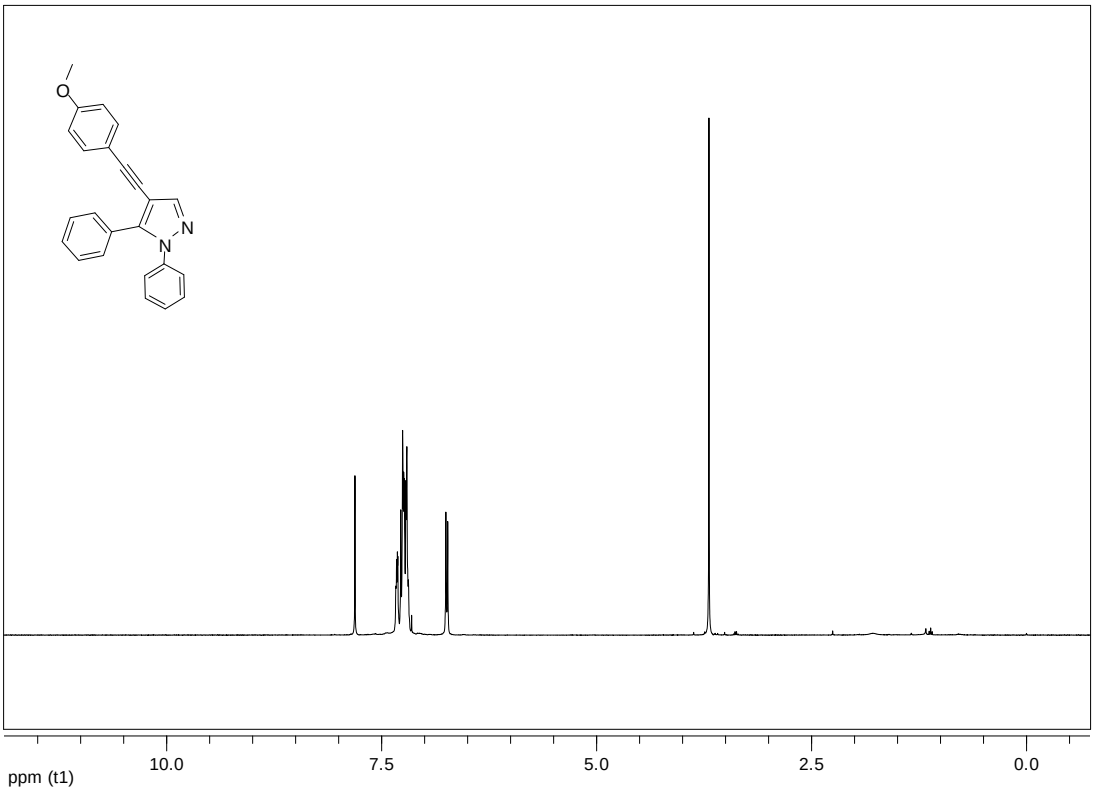

Figure A21. ^{1}H NMR spectra of **54C**.

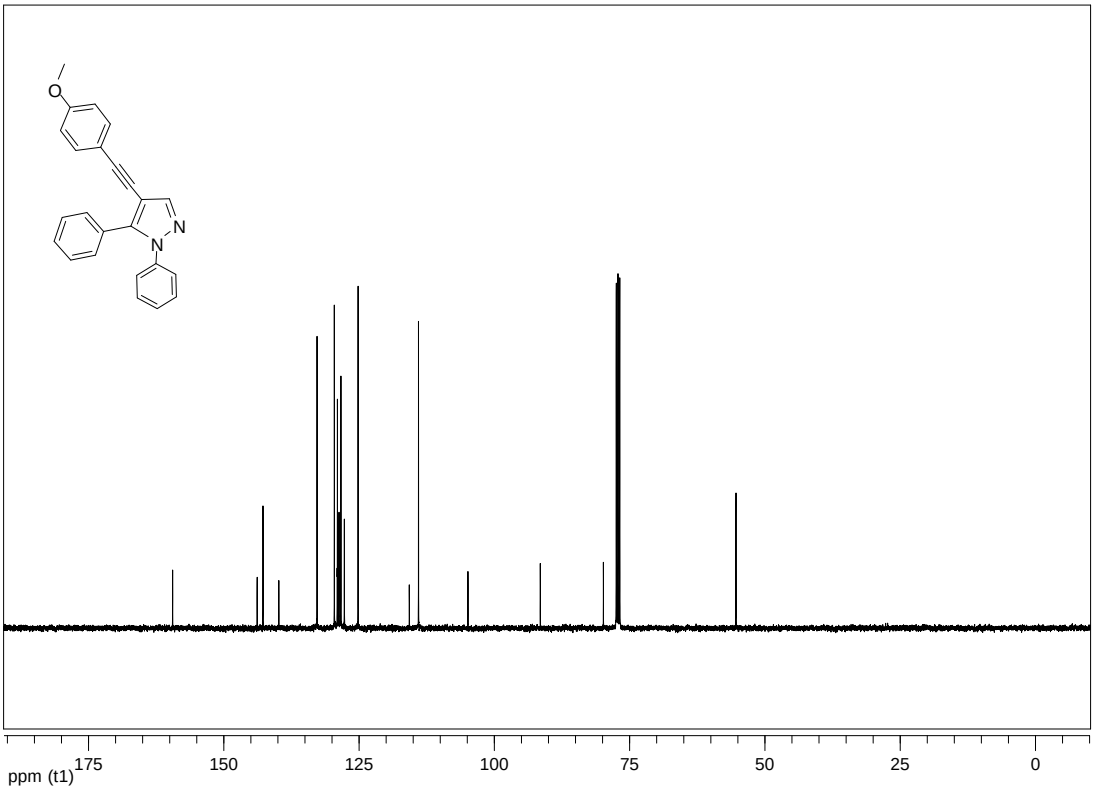

Figure A22. ^{13}C NMR spectra of **54C**.

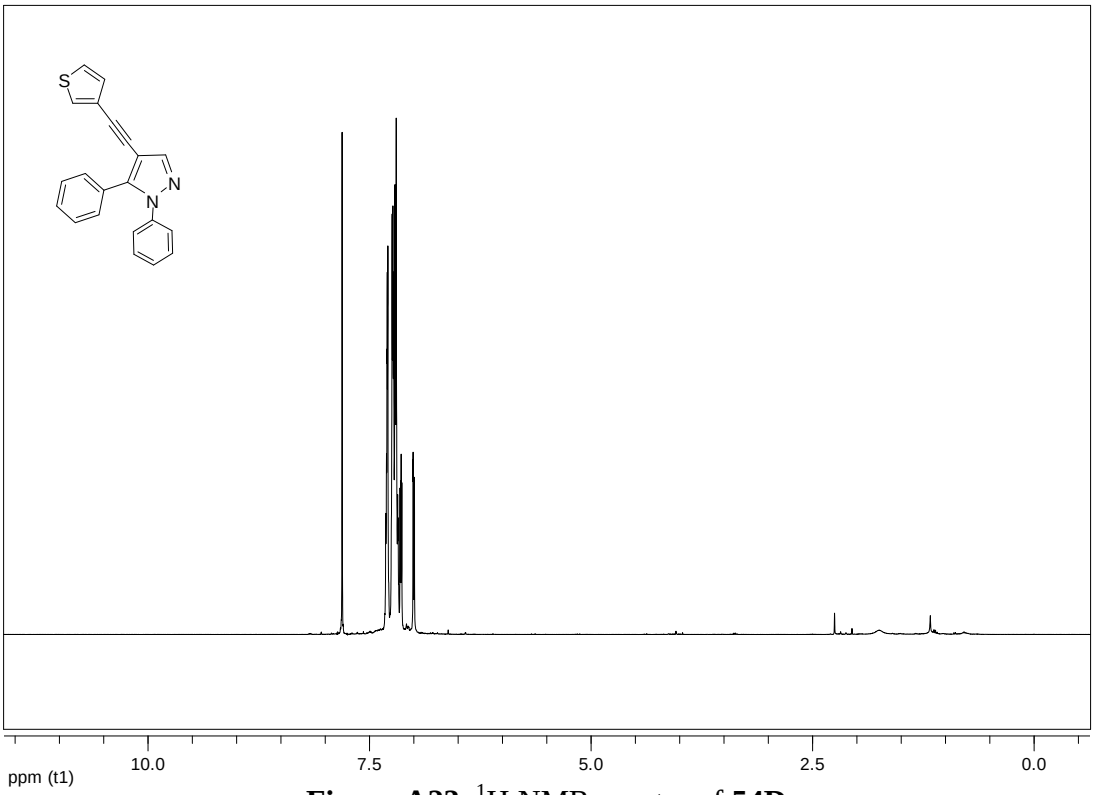

Figure A23. ^{1}H NMR spectra of **54D**.

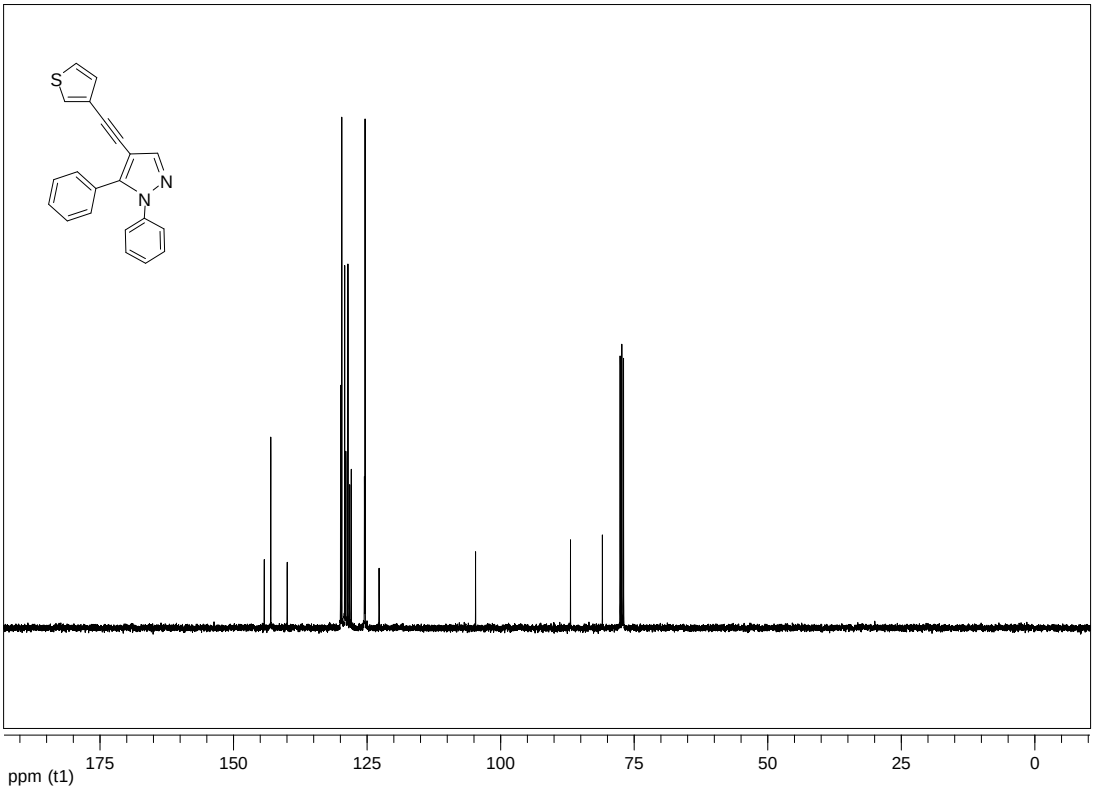

Figure A24. ^{13}C NMR spectra of **54D**.

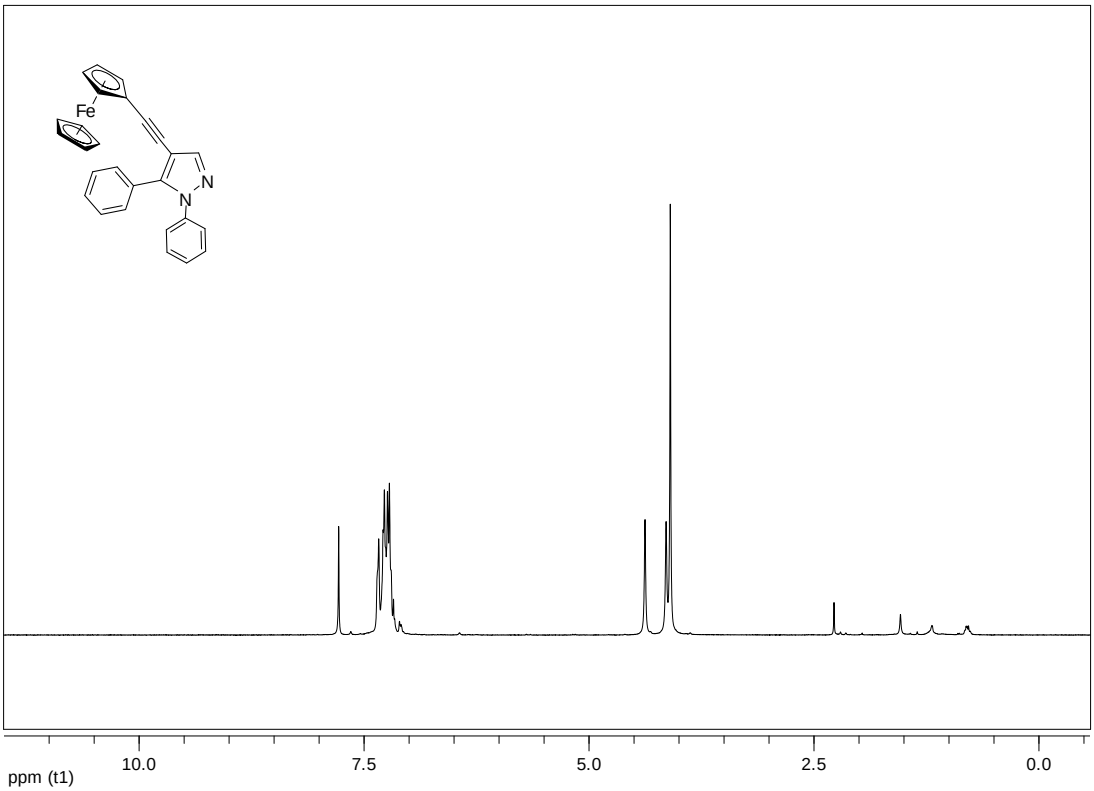

Figure A25. ^{1}H NMR spectra of **54E**.

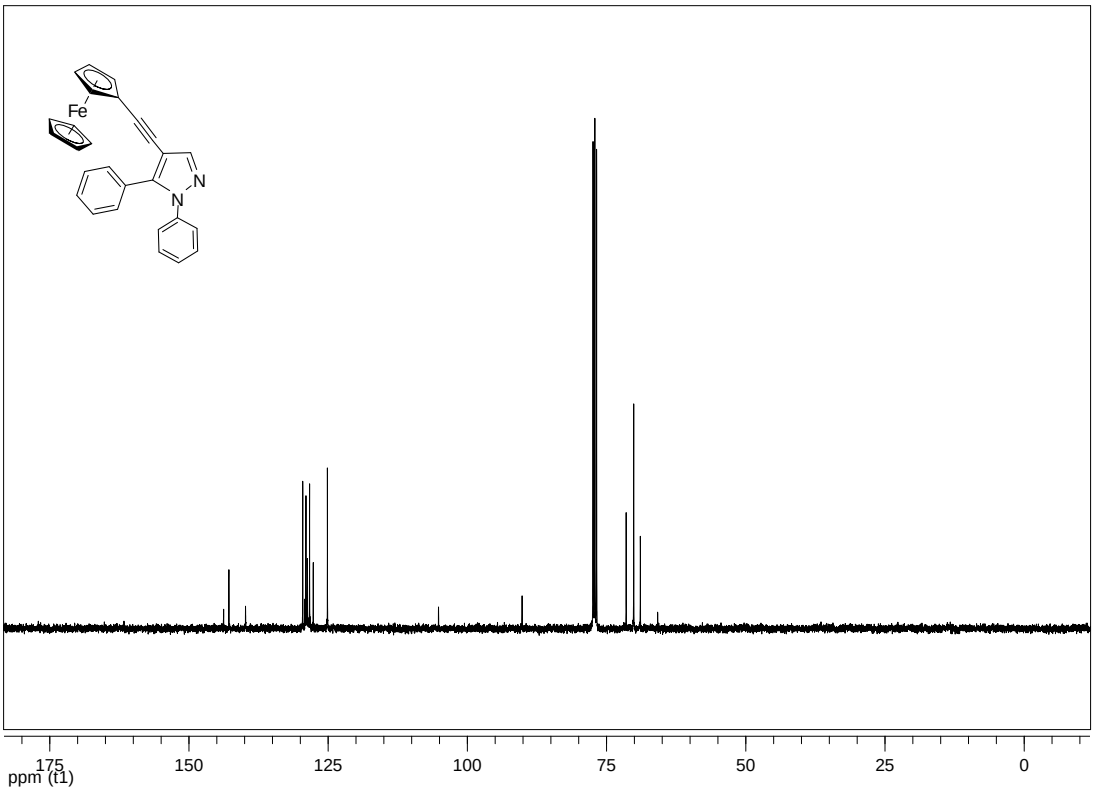

Figure A26. ^{13}C NMR spectra of **54E**.

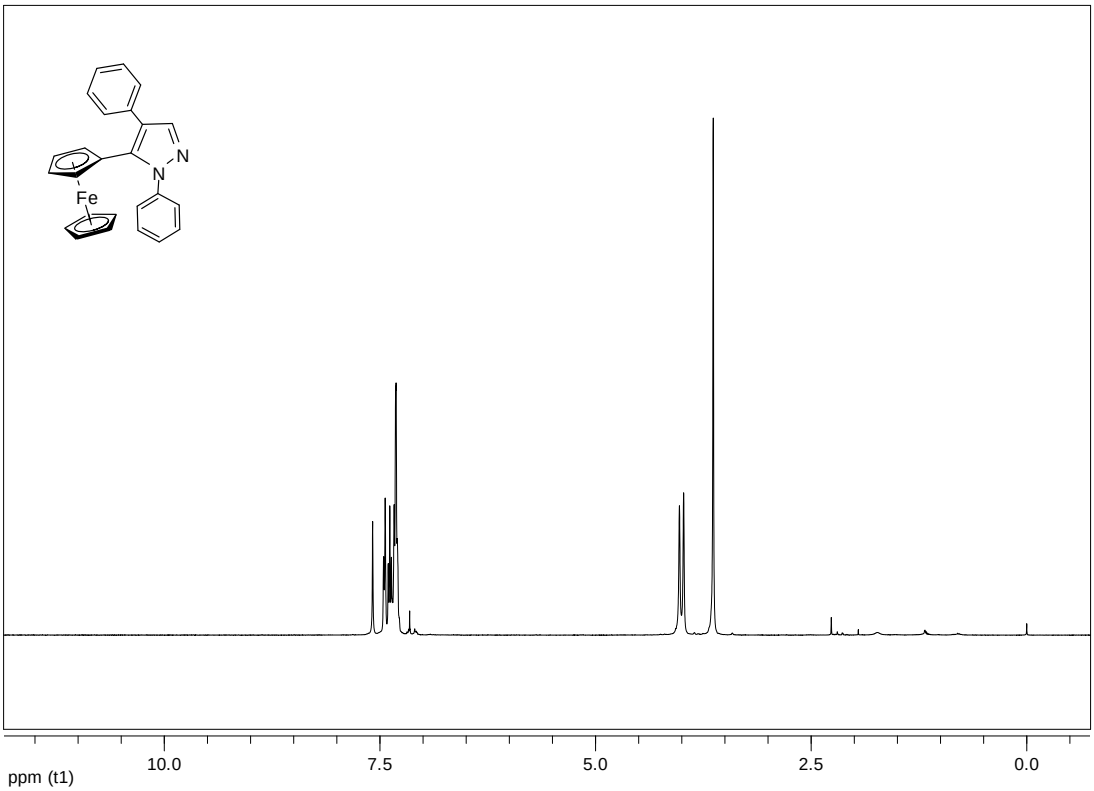

Figure A27. ^{1}H NMR spectra of **56A**.

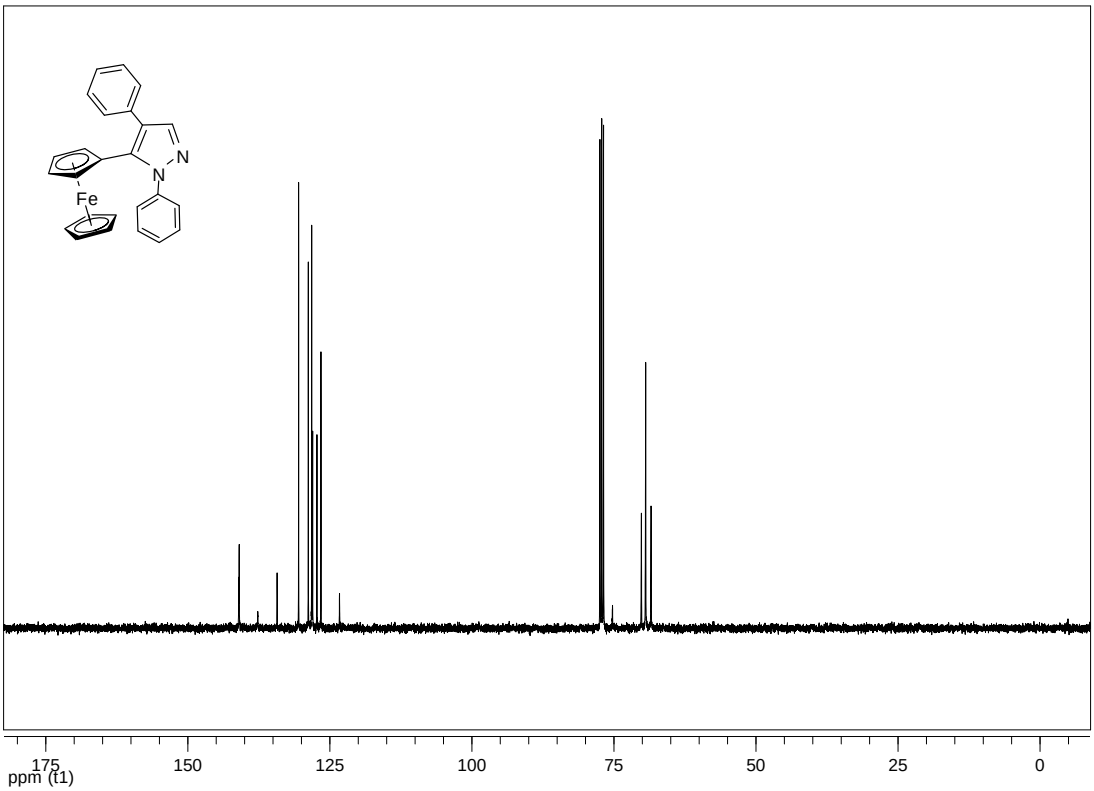

Figure A28. ^{13}C NMR spectra of **56A**.

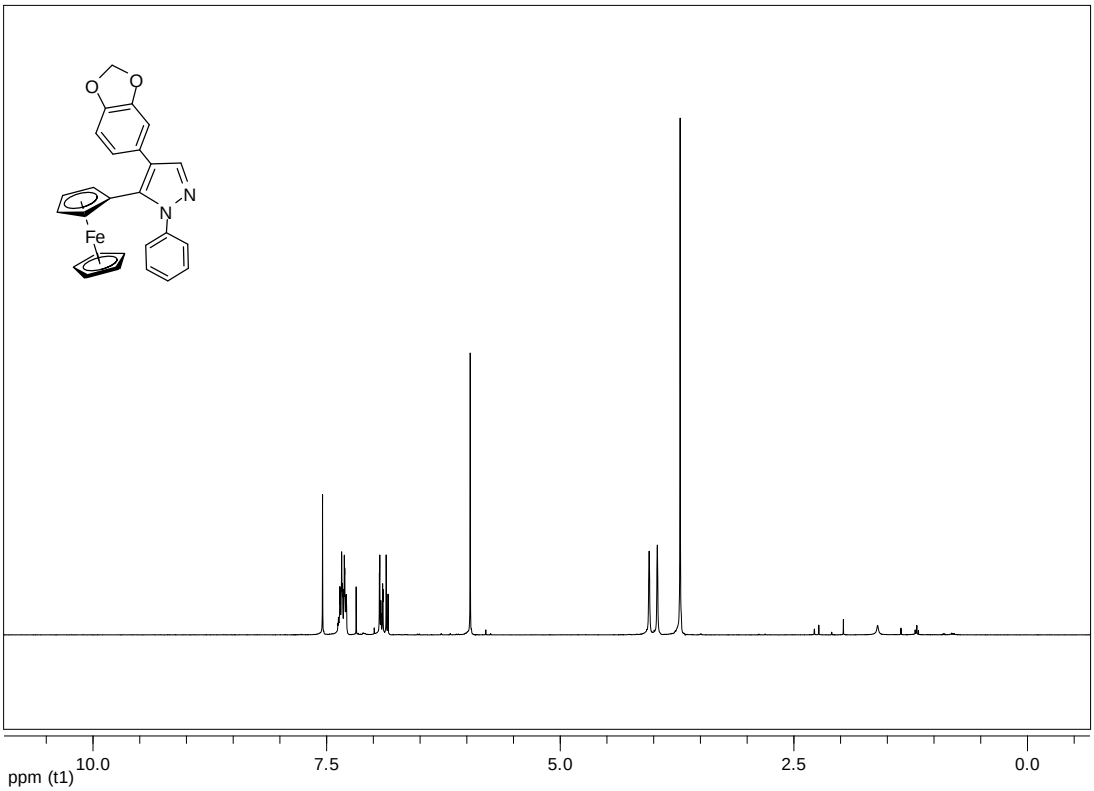

Figure A29. ^{1}H NMR spectra of **56B**.

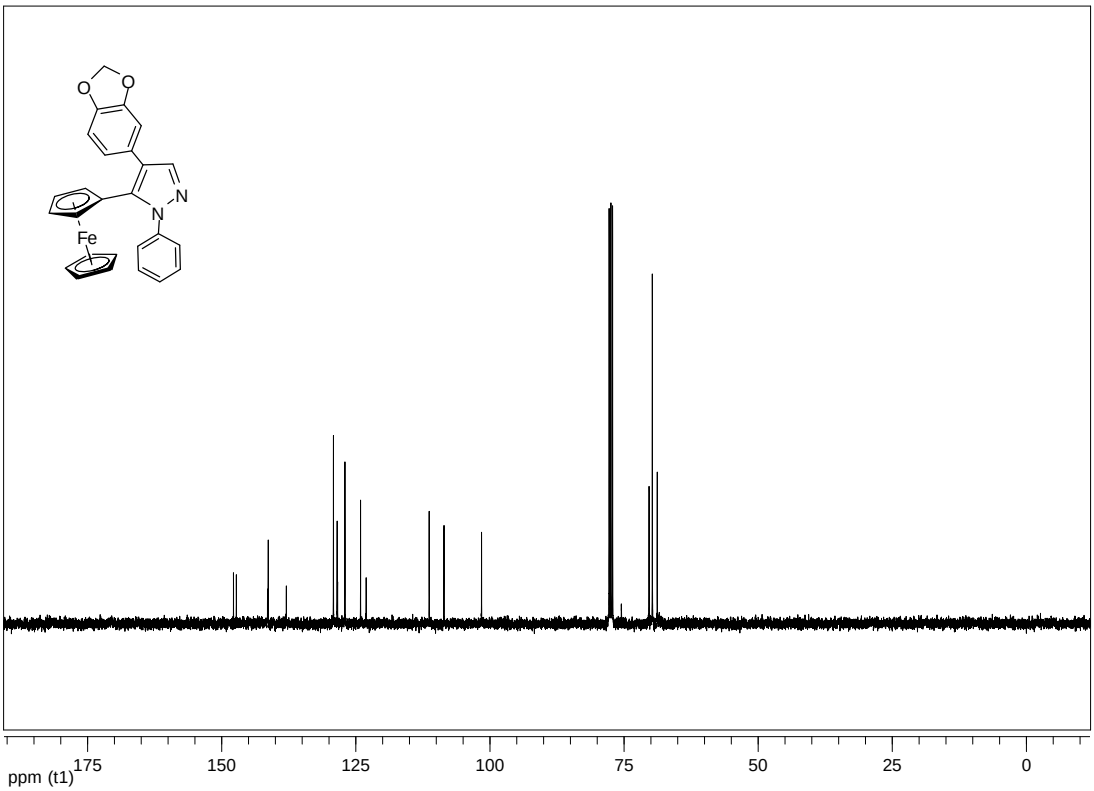

Figure A30. ^{13}C NMR spectra of **56B**.

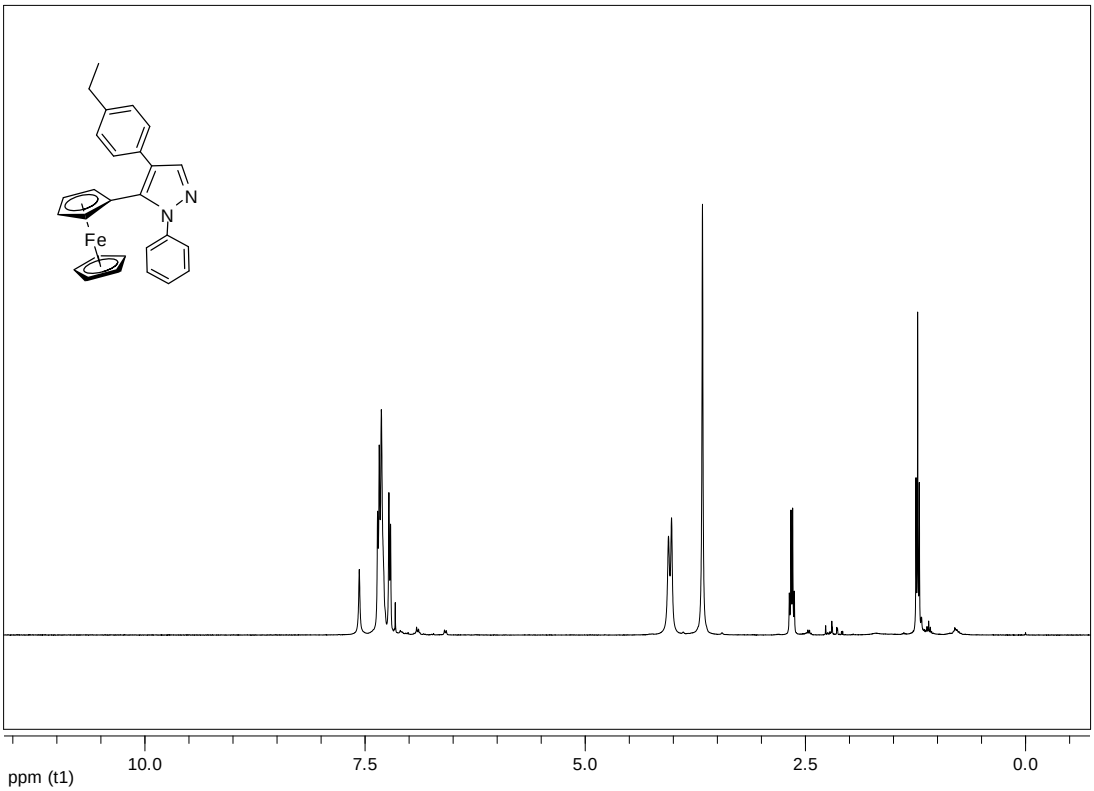

Figure A31. ^{1}H NMR spectra of **56C**.

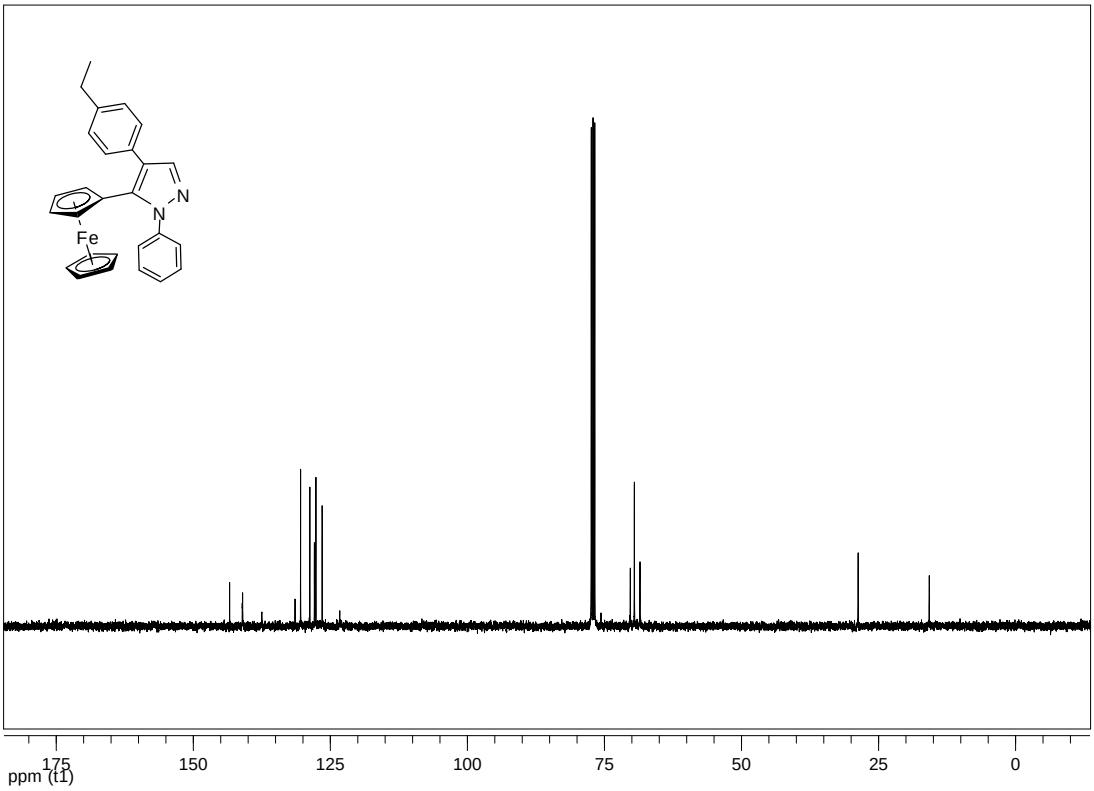

Figure A32. ^{13}C NMR spectra of **56C**.

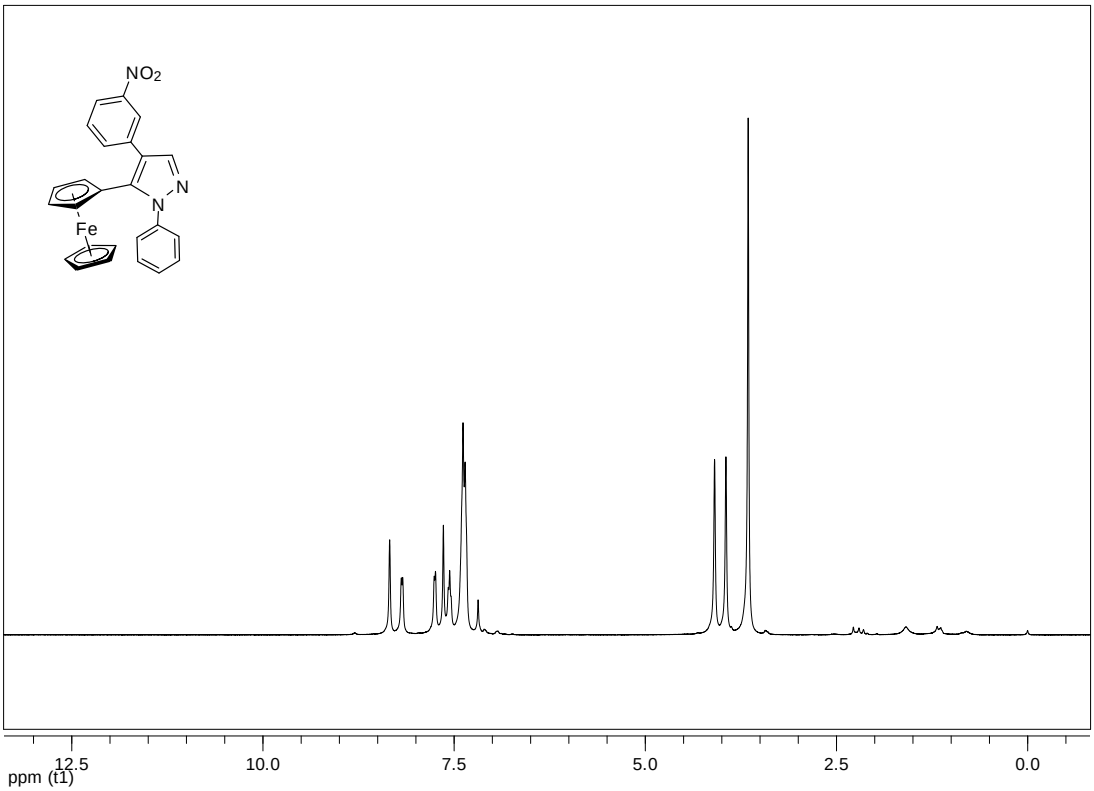

Figure A33. ^{1}H NMR spectra of **56D**.

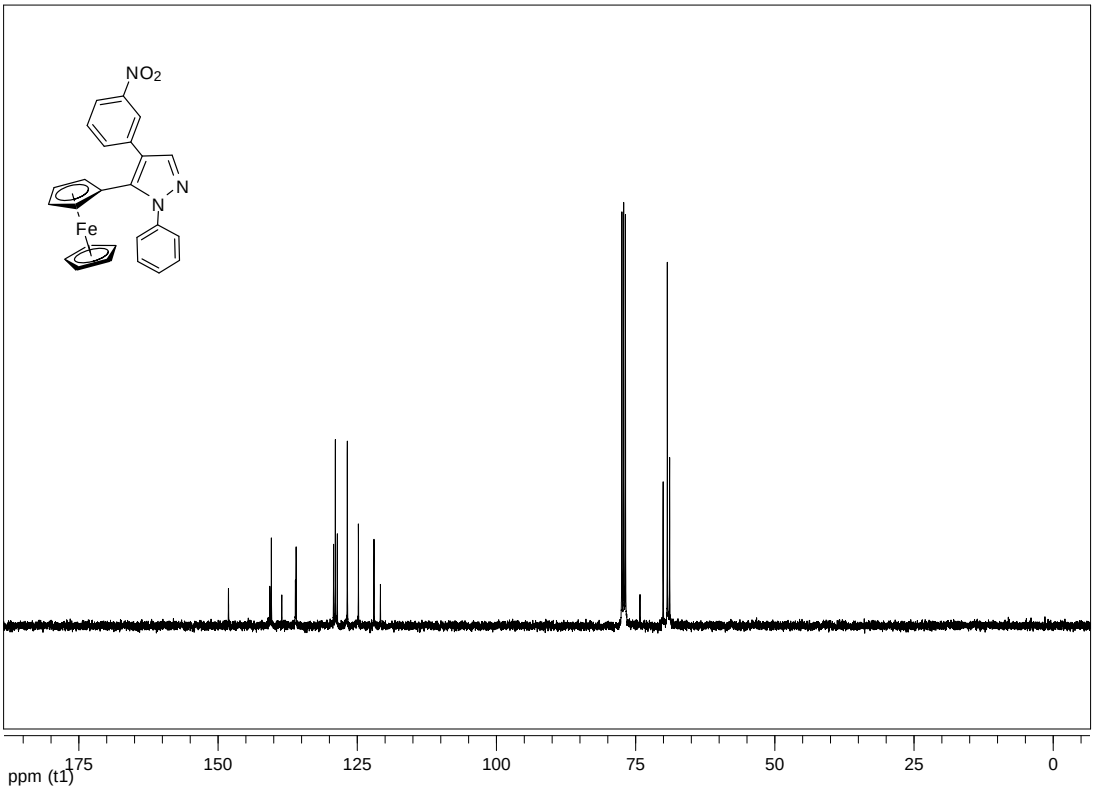

Figure A34. ^{13}C NMR spectra of **56D**.

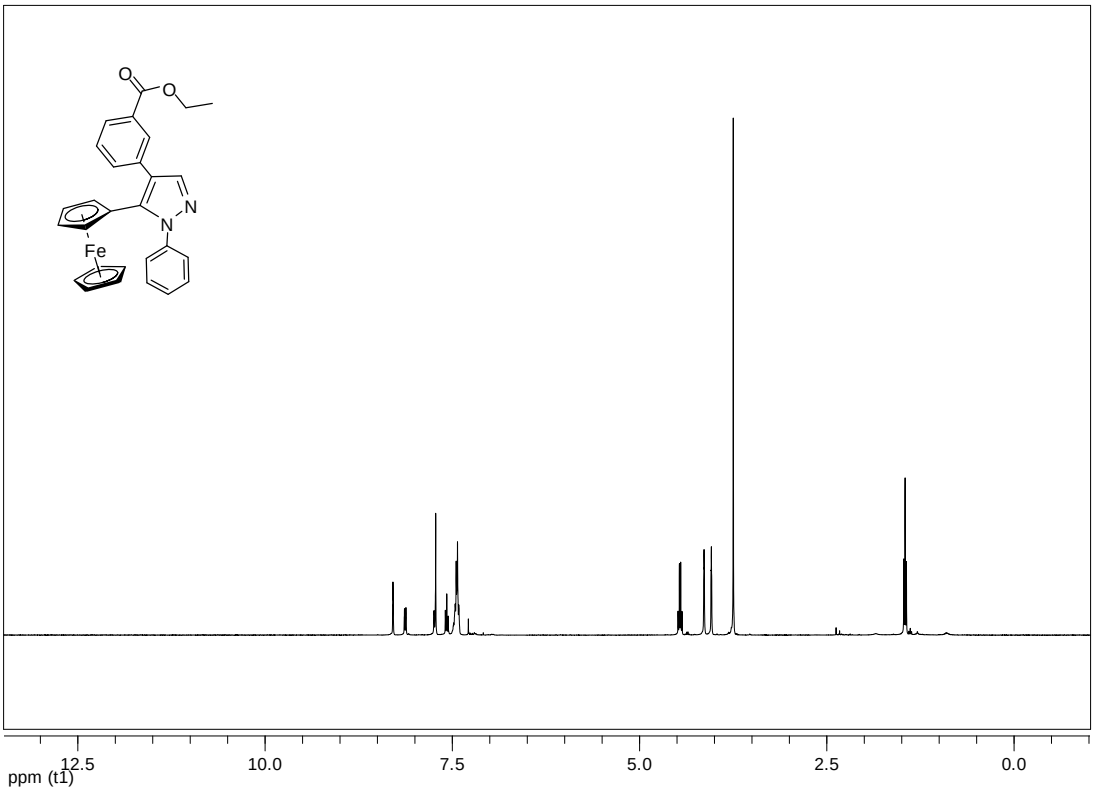

Figure A35. ^{1}H NMR spectra of **56E**.

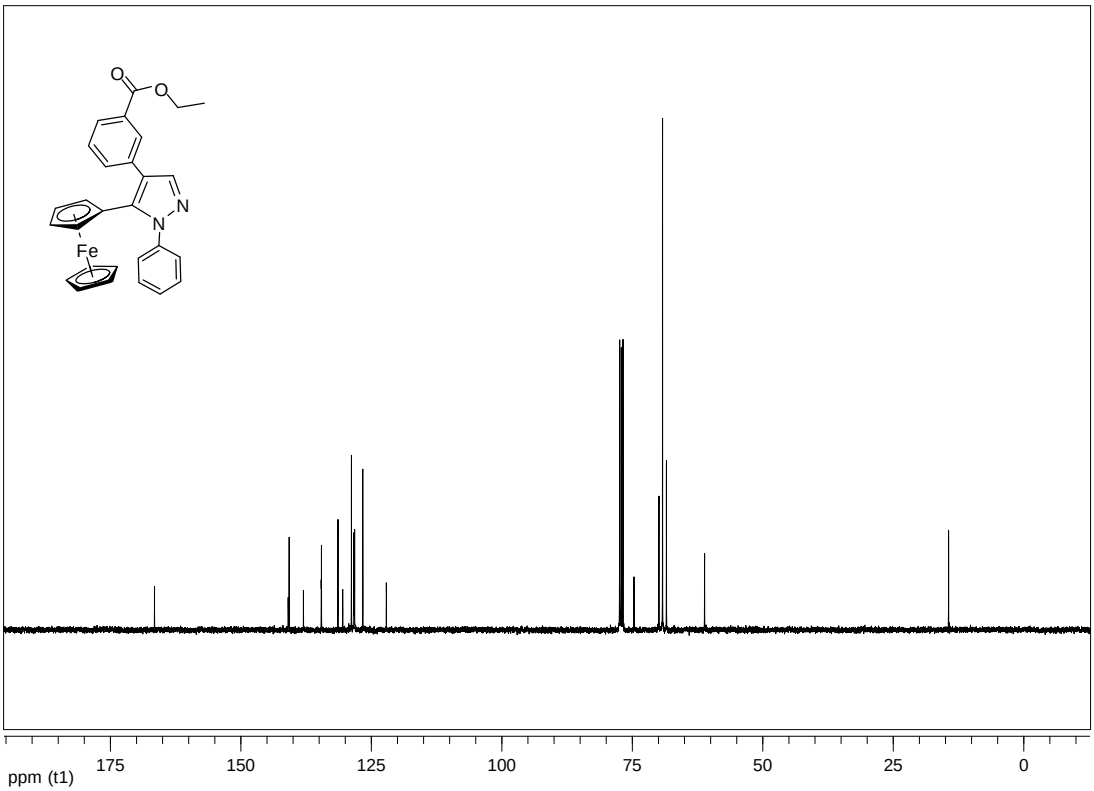

Figure A36. ^{13}C NMR spectra of **56E**.

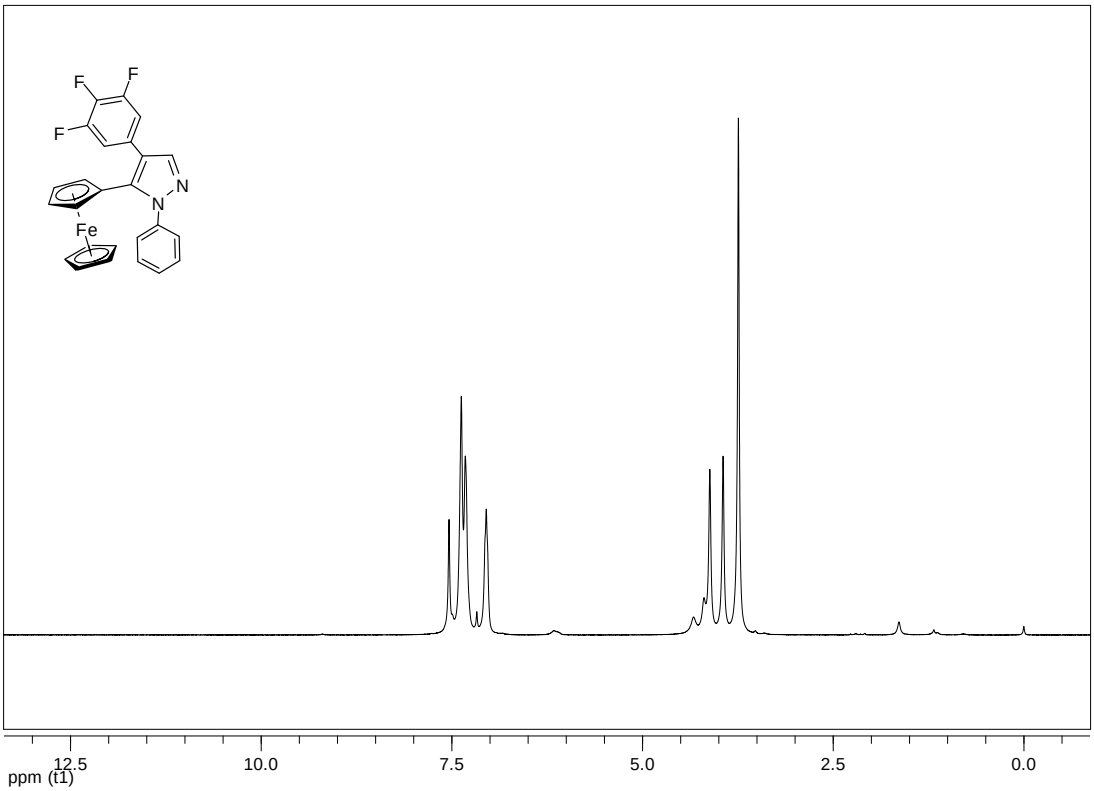

Figure A37. ^{1}H NMR spectra of **56F**.

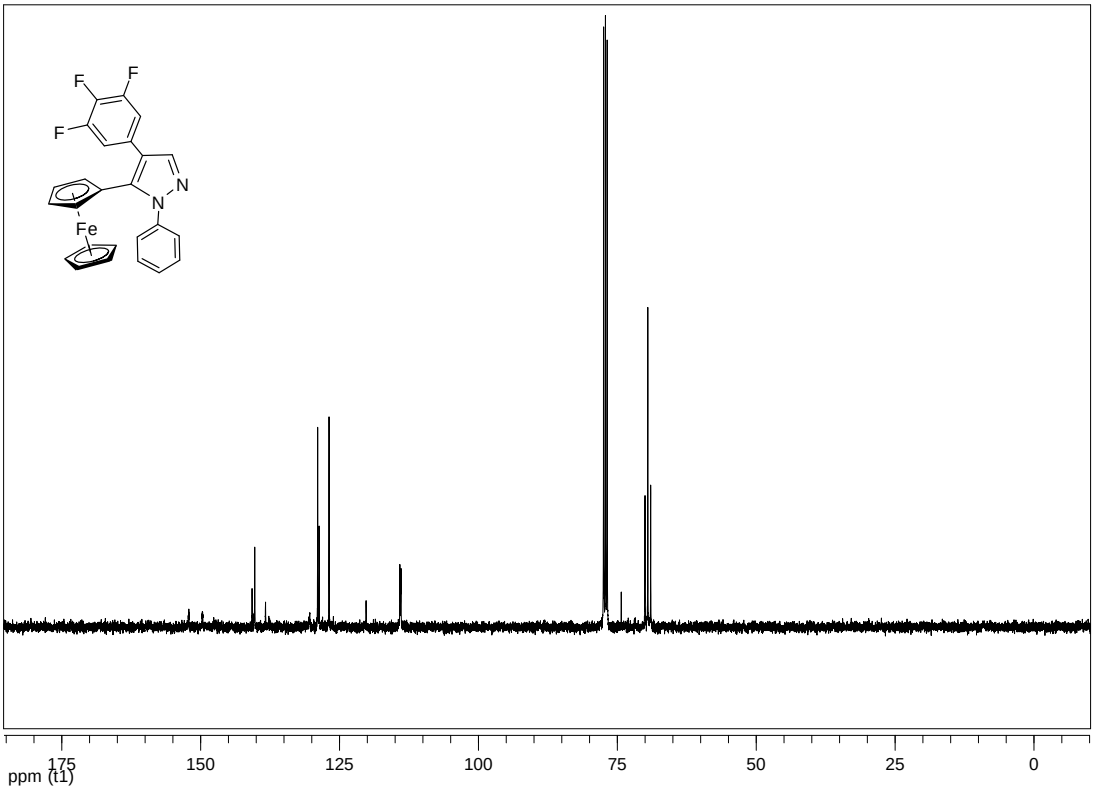

Figure A38. ^{13}C NMR spectra of **56F**.

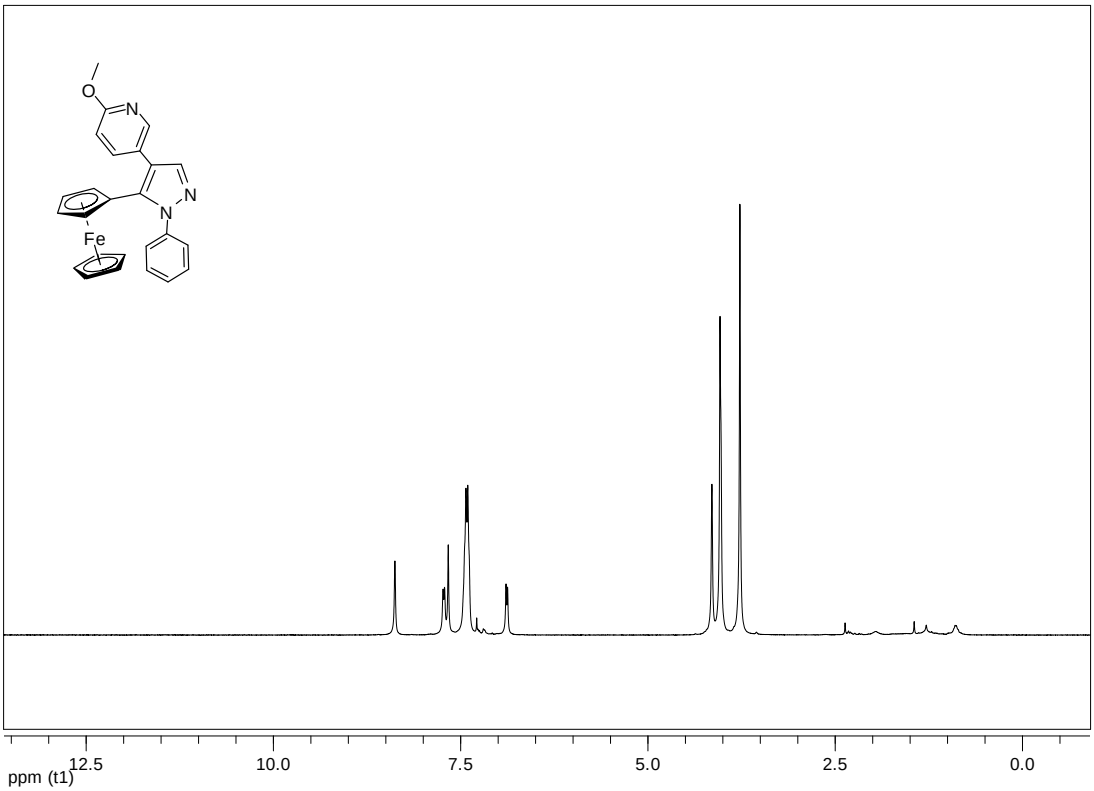

Figure A39. ^{1}H NMR spectra of **56G**.

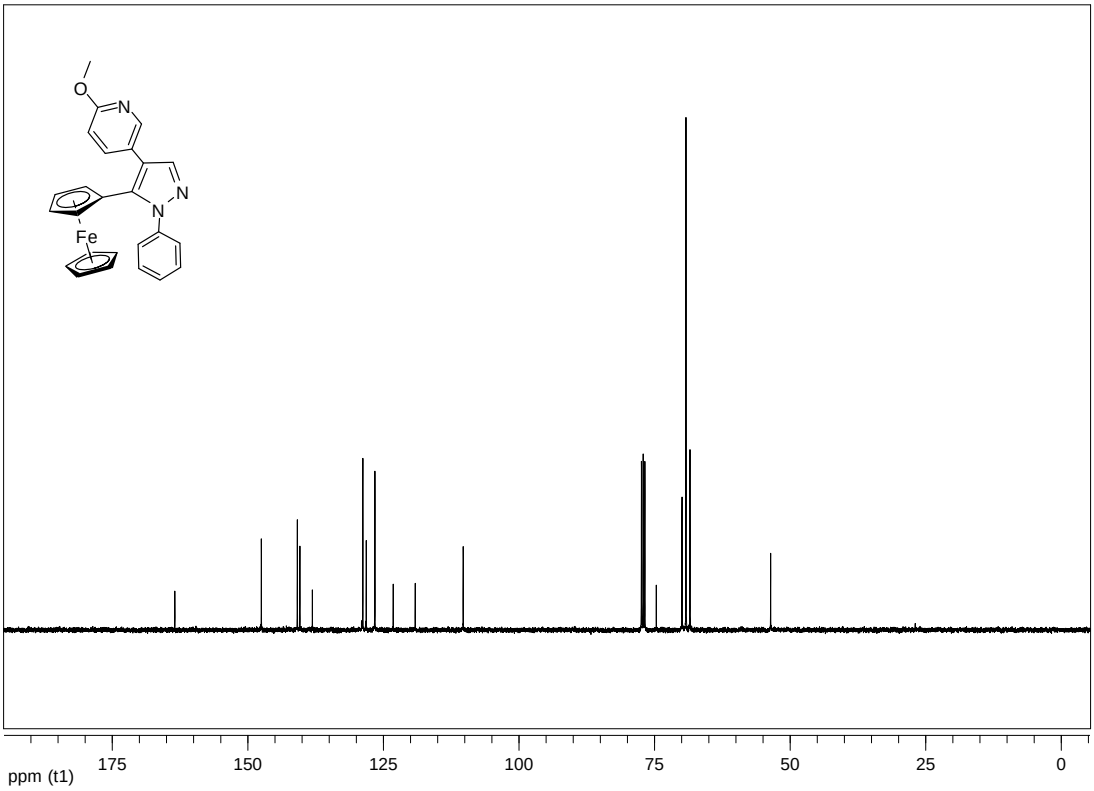

Figure A40. ^{13}C NMR spectra of **56G**.

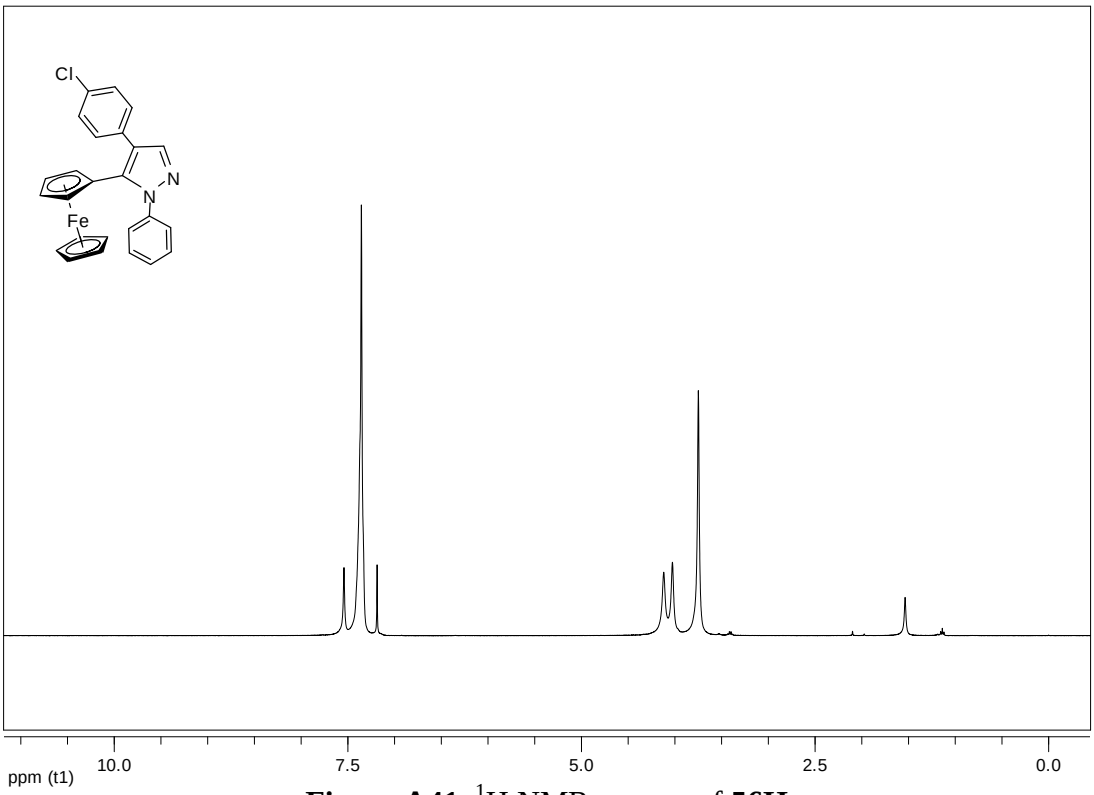

Figure A41. ^{1}H NMR spectra of **56H**.

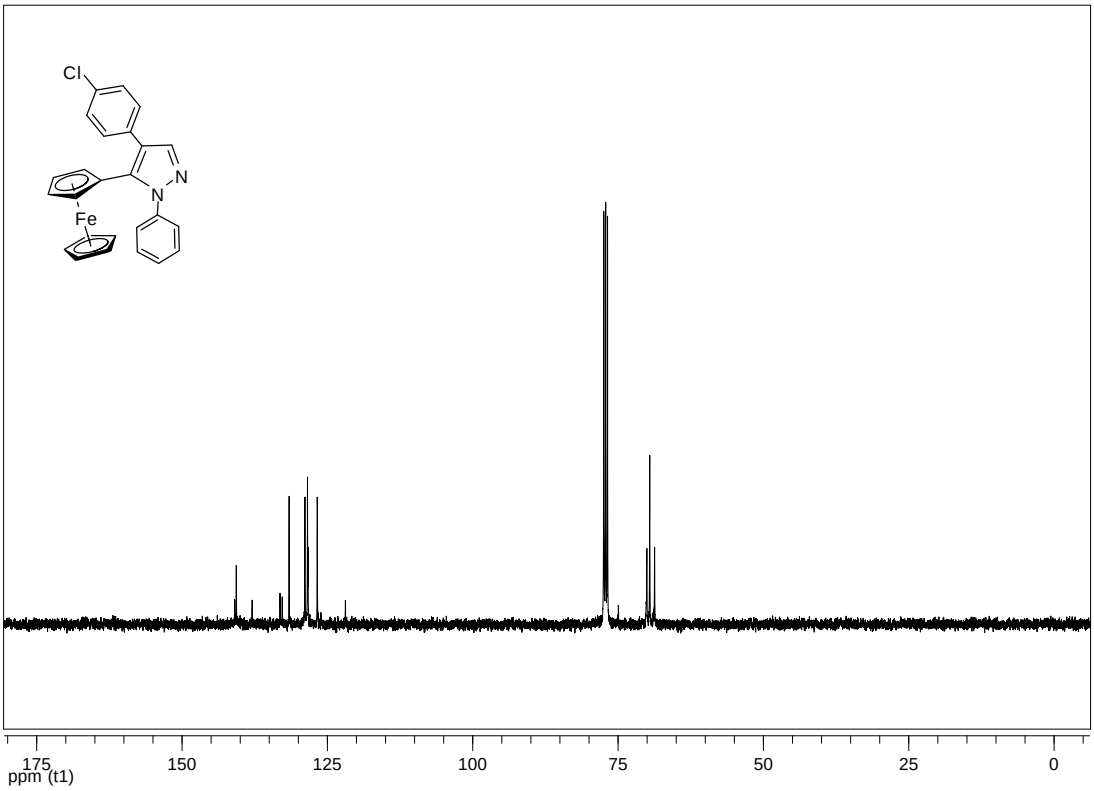

Figure A42. ^{13}C NMR spectra of **56H**.

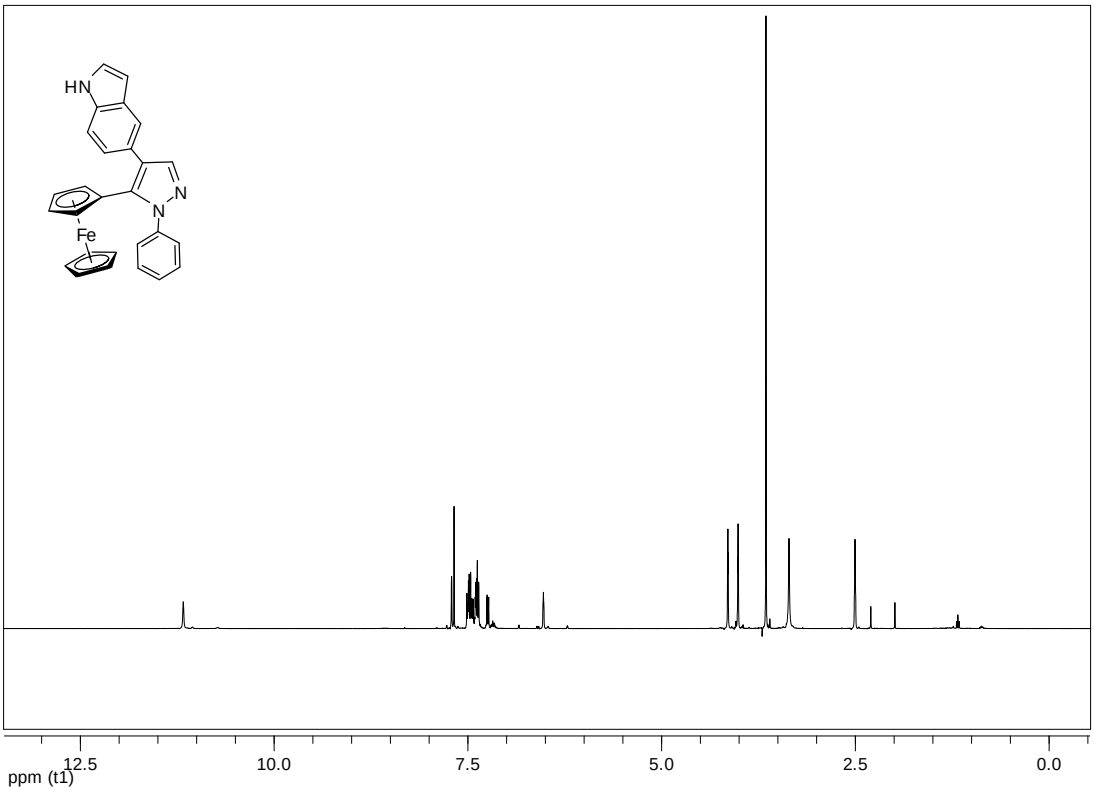

Figure A43. ^{1}H NMR spectra of **56I**.

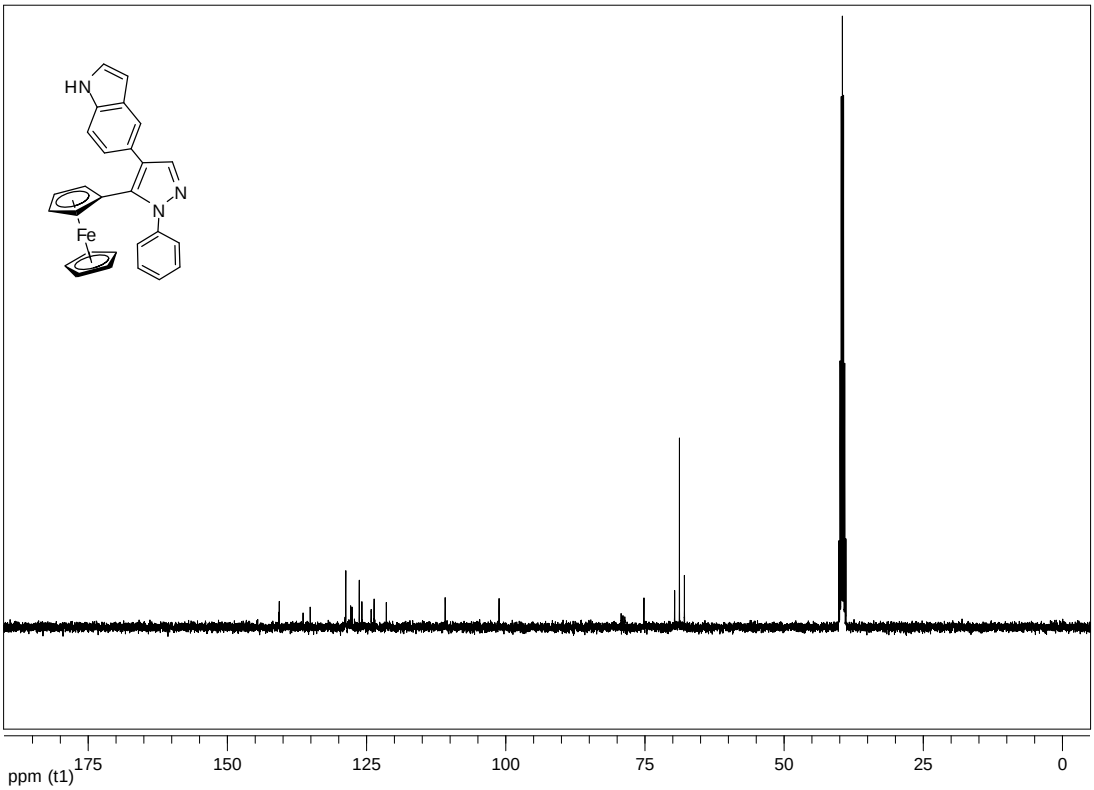

Figure A44. ^{13}C NMR spectra of **56I**.

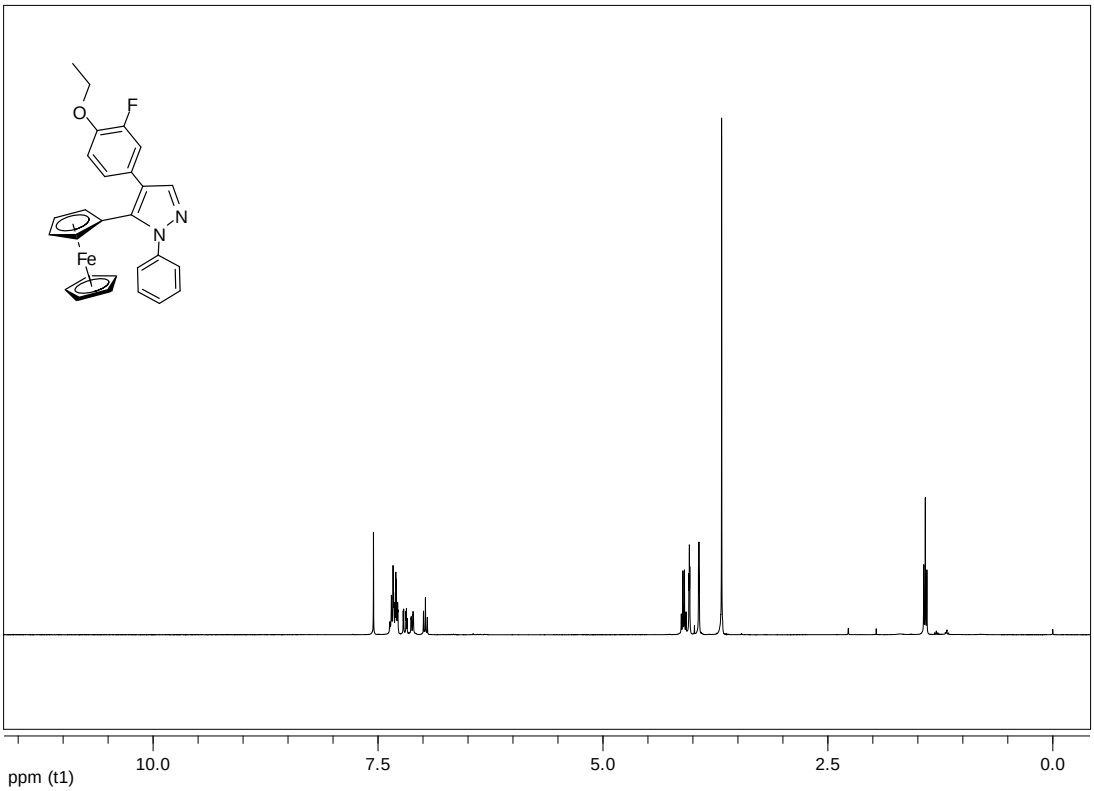

Figure A45. ^{1}H NMR spectra of **56J**.

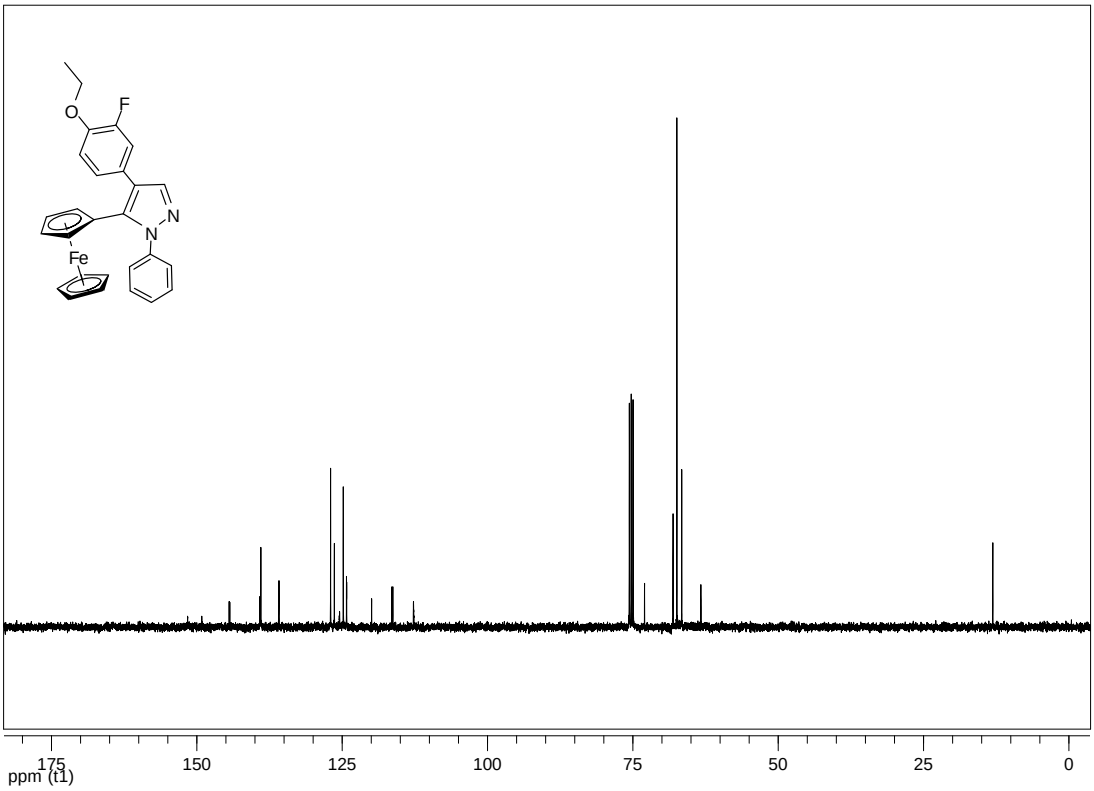

Figure A46. ^{13}C NMR spectra of **56J**.

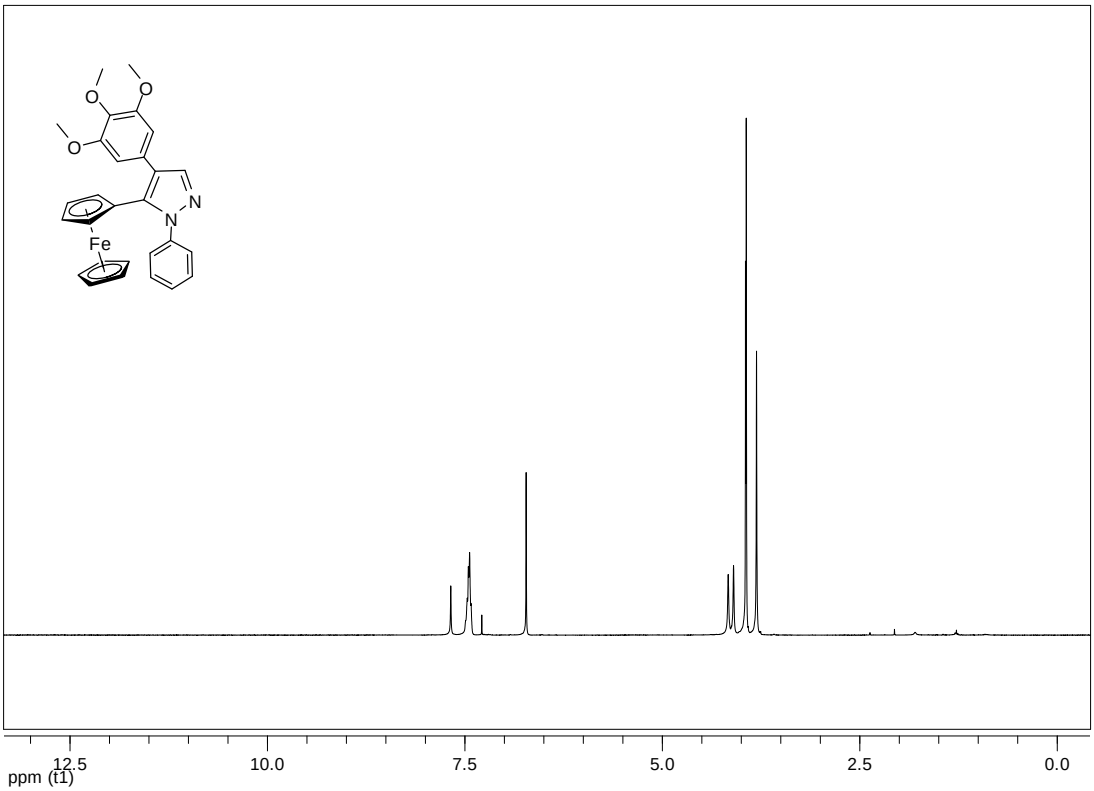

Figure A47. ^{1}H NMR spectra of **56K**.

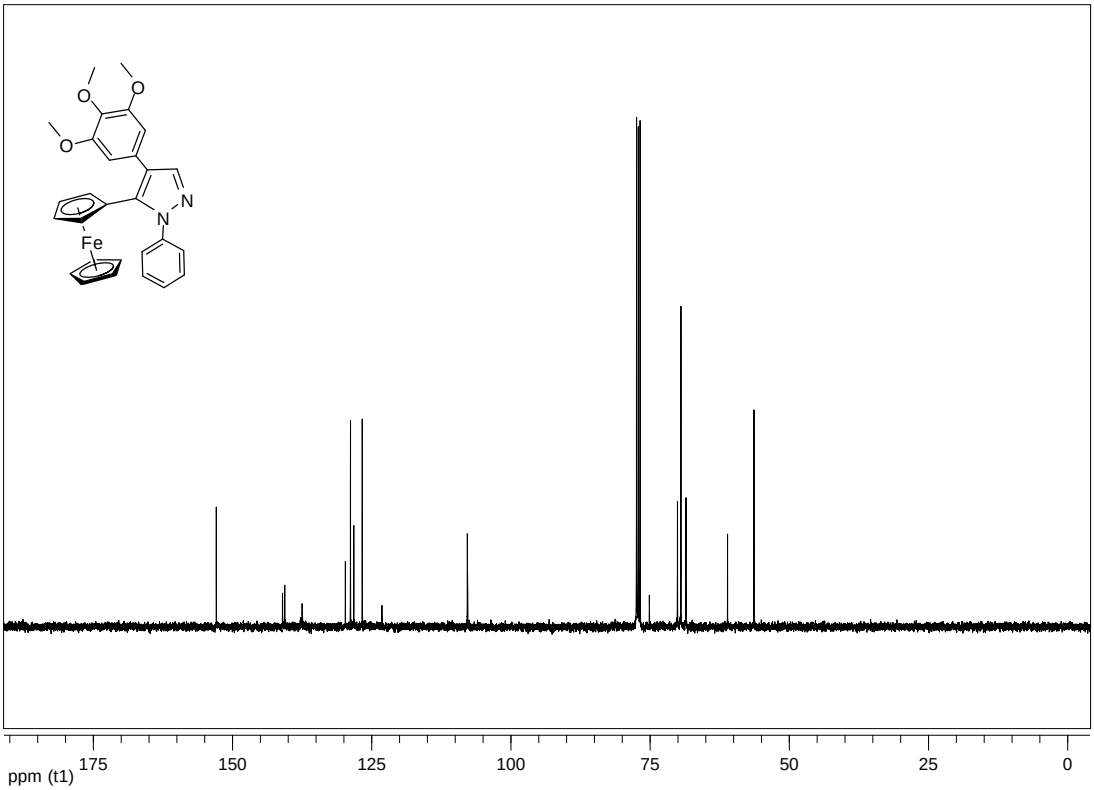

Figure A48. ^{13}C NMR spectra of **56K**.