SYNTHESIS OF FERROCENYL SUBSTITUTED PYRAZOLES

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Approval of the Graduate School of Natural and Applied Sciences

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I certify that this thesis satisfies all the requirements as a thesis for the degree of Master of Science.

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This is to certify that we have read this thesis and in our opinion it is full adequate, in scope and quality, as a thesis for the degree of Master of Science.

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ABSTRACT

SYNTHESIS OF FERROCENYL SUBSTITUTED PYRAZOLES

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July 2005, 86 pages

Pyrazoles have been studied for over a century as an important class of heterocyclic compounds and continue to attract considerable interest due to the broad range of biological activities they possess. The incorporation of the essential structural features of pyrazoles with a ferrocene moiety could provide new derivatives with unexpected and/or enhanced biological activities since several ferrocene derivatives have already been shown to be active against a number of tumors. For this reason, we investigated the synthesis of ferrocenyl-substituted pyrazoles, such as 1-alkyl/aryl-5-ferrocenylpyrazoles, by employing the reaction between (2-formyl-1-chlorovinyl)ferrocene and hydrazine derivatives. Although this reaction is known, it was not studied in much detail and the low yields of ferrocenyl pyrazoles were obtained. Thus, we have reinvestigated this reaction and improved the yields of pyrazoles by optimizing the reaction conditions. (2-Formyl-1-chloro vinyl)ferrocene was first reacted with the excess amount (3 equivalents) of hydrazine derivative at 25 °C in dioxane under argon for 2 hours, and the resulting mixture was then heated at 100 °C for 6 hours in the same solvent. Under our optimized conditions, these reactions afforded 1-alkyl/aryl-5-ferrocenylpyrazole derivatives in moderate to good yields as a single or major product of the reaction.

In some cases, 1-alkyl/aryl-3-ferrocenylpyrazole derivatives resulted from these reactions as very minor products.

Keywords: Ferrocene, pyrazole, ferrocenyl pyrazole derivatives, 1-alkyl/aryl-5-ferrocenylpyrazoles, 1-alkyl /aryl-3-ferrocenylpyrazoles, hydrazines

ÖZ

FERROSENİL SÜBSTİTÜE PİRAZOLLERİN SENTEZİ

Görmen, Meral
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Doç. Dr. Metin Zora

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Heterosiklik bileşiklerin önemli bir sınıfını oluşturan pirazoller, bu yüzyılın başından beri birçok çalışmaya konu olmuş ve geniş alana yayılmış biyolojik aktivitelerinden dolayı da bu bileşiklere olan ilgi günümüzde artarak devam etmektedir. Bazı ferrosen türevlerinin antitümör aktiviteye sahip olduğu bilindiğinden, ferrosen ve pirazol yapılarının birleştirilmesi beklenmedik biyolojik aktivitelere sahip yeni türevler oluşturabilir. Bu yüzden, ferrosenil sübstitüe pirazollerin "1-alkil/aril-5-ferrosenilpirazollerin" sentezini (2-formil-1-klorvinil) ferrosen ve farklı hidrazin türevlerini kullanarak gerçekleştirdik. Bu metot önceden bilinse de çok detaylı olarak çalışılmamış ve pirazol türevleri düşük verimlerle elde edilmiştir. Bu yüzden, biz bu tepkimeyi reaksiyon koşullarını yeniden optimize ederek inceledik ve yüksek verimlerle pirazol türevlerini sentezlemeyi başardık. İlk olarak, (2-formil-1-klorvinil)ferrosen ortamda aşırı miktarda bulunan (3 ekivalent) farklı hidrazin türevleri ile 25 °C de dioksan içinde argon atmosferi altında 2 saat boyunca reaksiyona sokulmuş ve bu karışım daha sonra 100 °C de 6 saat boyunca aynı çözücü içerisinde ısıtılmıştır. Bizim optimize ettiğimiz koşullarda, bu tepkimeler 1-alkil/aril-5-ferrosenilpirazolleri oldukça iyi verimlerle tek ürün ya da ana ürün olarak vermiştir. Bazı hidrazin türevleri ile olan tepkimelerde 1-alkil/aril-3-ferrosenilpirazol türevleri de elde edilmiş ancak çok düşük verimler alınmıştır.

Anahtar Kelimeler: Ferrosen, pirazol, ferrosenil pirazol türevleri, 1-alkil/aril-5-ferrosenilpirazol, 1-alkil/aril-3-ferrosenilpirazol, hidrazin

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Aileme,

To My Family,

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LIST OF ABBREVIATIONS

bp	boiling point
br	broad (spectral)
°C	degrees Celcius
Cp	cyclopentadienyl ligand
δ	chemical shift in parts per million downfield from tetramethylsilane
d	doublet (spectral)
Et	ethyl
Fc	ferrocenium ion
FT	fourier transform
g	gram(s)
h	hour(s)
Hz	hertz
IR	infrared
J	coupling constant
m	multiplet (spectral)
mL	milliliter(s)
MHz	megahertz
min	minutes
mmol	millimole(s)
mp	melting point
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million (in NMR)
q	quartet (spectral)
R_f	retention factor (in chromatography)
rt	room temperature

s	singlet (spectral)
t	triplet (spectral)
THF	tetrahydrofuran
TLC	thin layer chromatography
DMF	Dimethylformamide

CHAPTER 1

INTRODUCTION

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

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

Presumably any atom which can form two covalent bonds is capable forming a heterocyclic compound. However, with a few exceptions (e.g., mercury, iodine), all the known heterocyclic compounds involve an element from group IVB, VB or group VIB of the periodic table [2]. The most important “heteroatoms” are nitrogen, oxygen and sulfur.

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

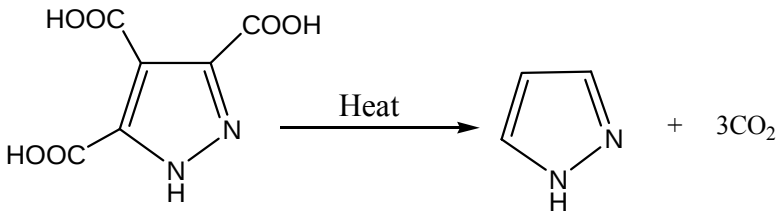

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Figure 1. First synthesis of pyrazole by the decarboxylation of pyrazole-3,4,5-tricarboxylic acid (**1**)

Much of the basic information obtained about the chemistry of the pyrazole moiety was its aromatic properties compared to those of benzene derivatives. Since then the studies of the pyrazoles have centered principally about structural problems arising from the tautomerism existing in the *N*-substituted types and the isomerism of the *N*-substituted derivatives [1]. To illustrate, pyrazole ring, like other nitrogen containing heterocycles, can be represented by different tautomeric structures. Three tautomeric forms can be written for unsubstituted pyrazole (Figure 2) [1].

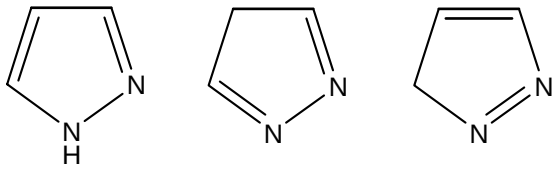

Figure 2. Tautomeric structures of the unsubstituted pyrazole ring

Until recently, the pyrazole ring was believed to be unknown in nature. In 1954, however, the first natural pyrazole derivative was isolated by Japanese workers who isolated 3-*n*-nonypyrazole **2** from Houttuynia Cordata which is a plant of the "*piperaceae*" family from tropical Asia. They observed its antimicrobal activity. Another naturally occuring pyrazole derivative is *levo*-β-(1-pyrazolyl)alanine **3** (Figure 3). This pyrazolic amino acid has been isolated from watermelon seeds (Citrullus Vulgaris). These are the only naturally occuring pyrazole derivatives known at present [1].

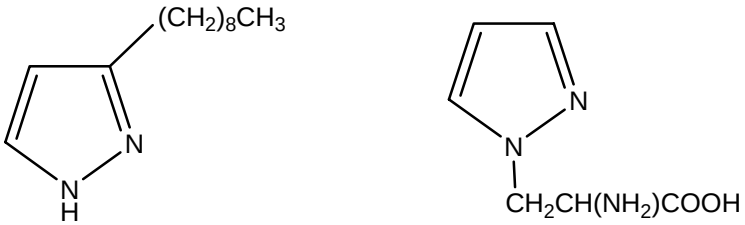

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Figure 3. Examples of naturally occuring pyrazoles

1.1. Synthesis of Pyrazole Derivatives.

The wide range of biological activities of pyrazoles has made them popular synthetic targets. There are many methods to synthesize the pyrazole derivatives. The synthesis of pyrazole derivatives from β-dicarbonyl compounds and hydrazines is the most widely used and the most general method for pyrazole synthesis [1]. In order to the use of β-dicarbonyl compounds (1,3-dicarbonyl compounds), β-aminoenones and halovinylaldehydes have been employed in literature [3].

A single pyrazole is obtained with a symmetrical β-dicarbonyl compound or with hydrazine itself. With other reactants two isomeric pyrazoles can theoretically arise and sometimes both can be isolated from the reaction mixture [1,3]. Many structural and experimental factors are involved in selective formation of one of the two isomeric compounds but at present the controlling influence of such factors is not fully understood [1].

The reaction of methylhydrazine with the sodium salt of formylacetone gives a mixture of two isomeric pyrazoles (Figure 4):

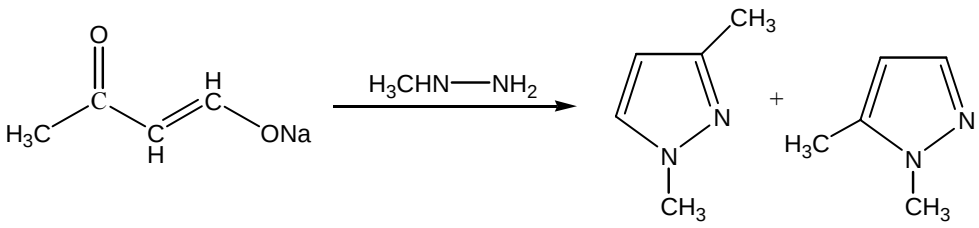


Figure 4. Synthesis of pyrazoles from the salt of formylacetone

Nugiel and co-workers [4] have prepared indenopyrazoles (Figure 5) by starting with 1,3-dicarbonyl compound and hydrazine. 1,3-dicarbonyl compound and hydrazine are refluxed to generate indenopyrazole. Then, removal of the acetamide group by concentrated HCl takes place to form indenopyrazole (Figure 5) [4].

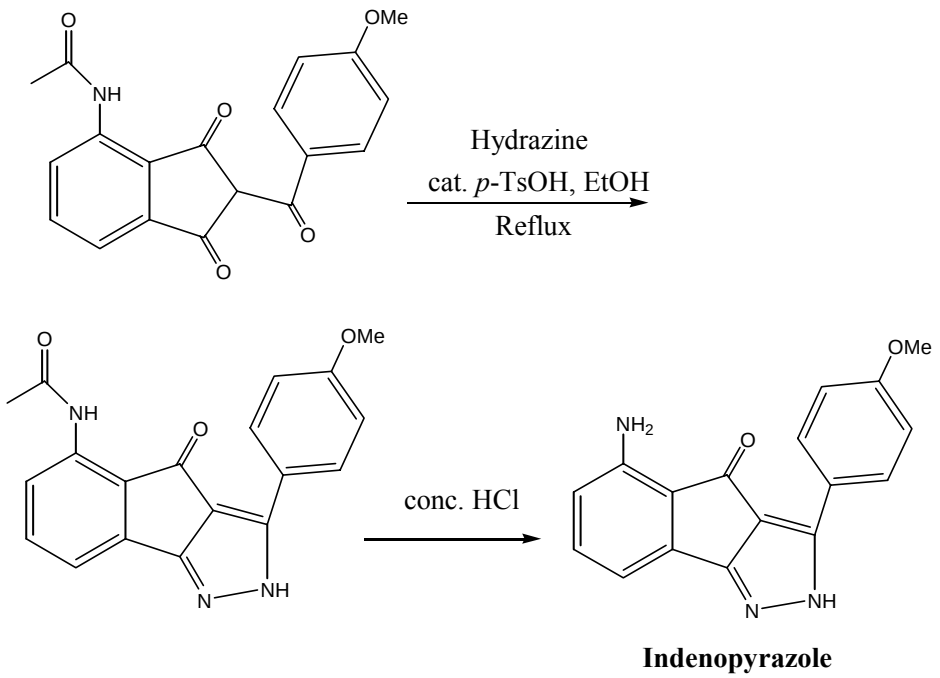


Figure 5. Synthesis of pyrazoles from 1,3-dicarbonyl compounds

An alternative strategy to employ masked 1,3-dicarbonyl compounds such as β-aminoenones has been described by Gonzalez-Ortega and co-workers [5] and also by Dominguez et al [3,6]. β-aminoenones react with hydrazine derivatives to afford regioselectively 1,3,5-trisubstituted pyrazoles as shown in Figure 6 [5]:

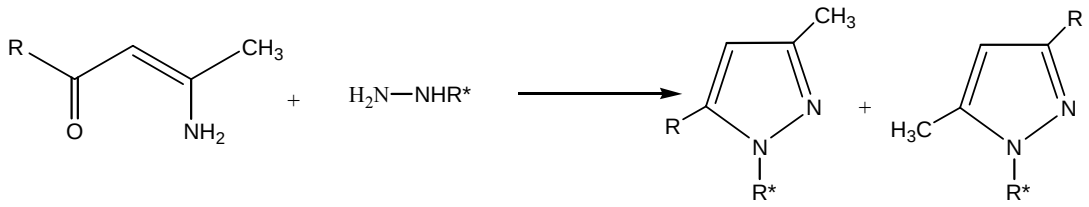


Figure 6. Synthesis of pyrazoles from β-aminoenones

In the reaction between the β-aminoenones and alkyl hydrazines, there is a competition between the predictable mechanisms which lead to mixtures of regioisomeric pyrazoles as depicted in Figure 7.

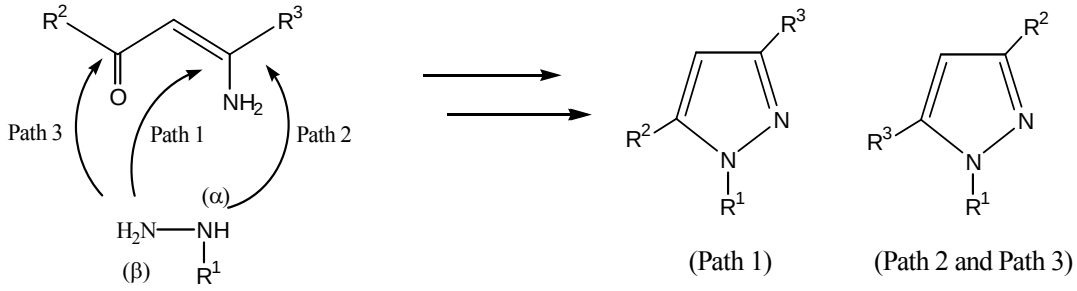


Figure 7. Predictable mechanistic paths for synthesis of pyrazoles

The regioselectivity of the process is conditioned by the catalysis of acetic or hydrochloric acid, which is normally employed to accelerate the reaction. In acetic acid/ethanol, the protonation of the hydrazine nitrogens does not happen and the N_α atom would act as an initial nucleophile (Path 2, Figure 7), which possesses a reduced steric hindrance. In hydrochloric acid/ethanol, the more basic N_α is protonated and N_β would act as a nucleophile in the initial conjugated addition (Path 1, Figure 7). The participation of path 2 in acetic acid medium decreases rapidly with the size and with the withdrawing character of R^1. Thus, it is only observed in low proportion when R_1 = Et or Bn and it is inexistent in bulky alkylhydrazines (*e.g.* R_1 = *t*-Bu) or arylhydrazines (R_1 = aryl) which evolved preferably *via* Path 1 (Figure 7) in hydrochloric or acetic acid medium [5].

In addition, β-aminoenones also known as vinylogous amides can be used in solid- phase organic synthesis in order to construct a pyrazole library [7].

Sekhar and co-workers [8] have recently reviewed the construction of the fused pyrazole derivatives by using β-halovinylaldehydes and β-halovinylketones. Although recent publications disclosed a variety of applications of β-halovinylaldehydes to the field of heterocyclic chemistry, only a few examples have been reported on the introduction of pyrazole moiety to five, six and seven membered heterocycles. Recently, a versatile synthesis of fused heterocycles such as pyrazolothiazole (X = NH, NPh) and thiazoloisoxazole (X = O) has been successfully prepared by the condensation of chloroaldehyde with hydrazine, phenylhydrazine and hydroxyamine (Figure 8) [8].

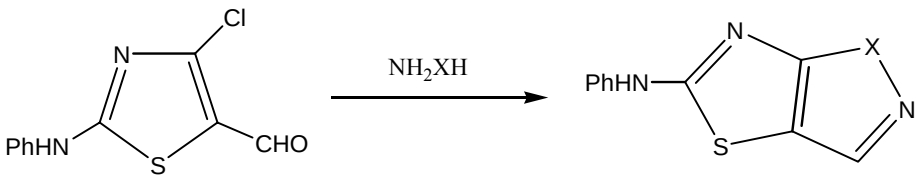


Figure 8. Synthesis of fused pyrazole derivatives by using β-halovinylaldehydes

β-Chlorovinylenones are found to be suitable substrates for synthesis of pyrazole derivatives. For example, very recently pyrazolylpropenone, prepared by condensation of 5-chloro-1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde with RCOMe followed by bromination of the resulting ketones gave dibromo derivatives which in turn on reaction with R^1NHNH_2 furnished pyrazolylpyrazole derivatives (R^1 = Ph) (Figure 9) [8].

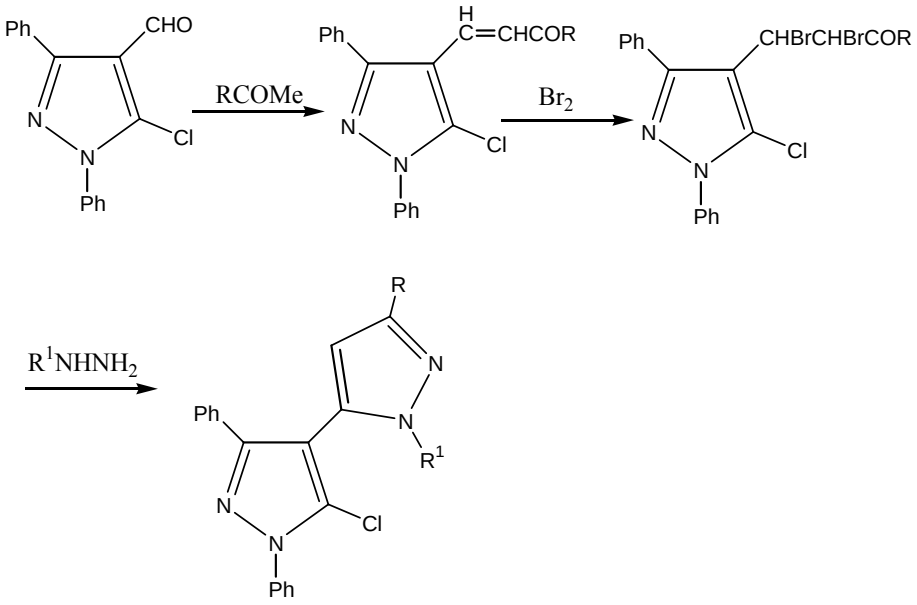


Figure 9. Synthesis of pyrazoylpyrazole derivatives from β-Chlorovinylenones

A somewhat different approach to pyrazole synthesis relies on the reaction of hydrazines with α,β-unsaturated ketones, which contain an α-benzotriazole group, such that an addition-elimination sequence results in the desired pyrazole (Figure 10) [9].

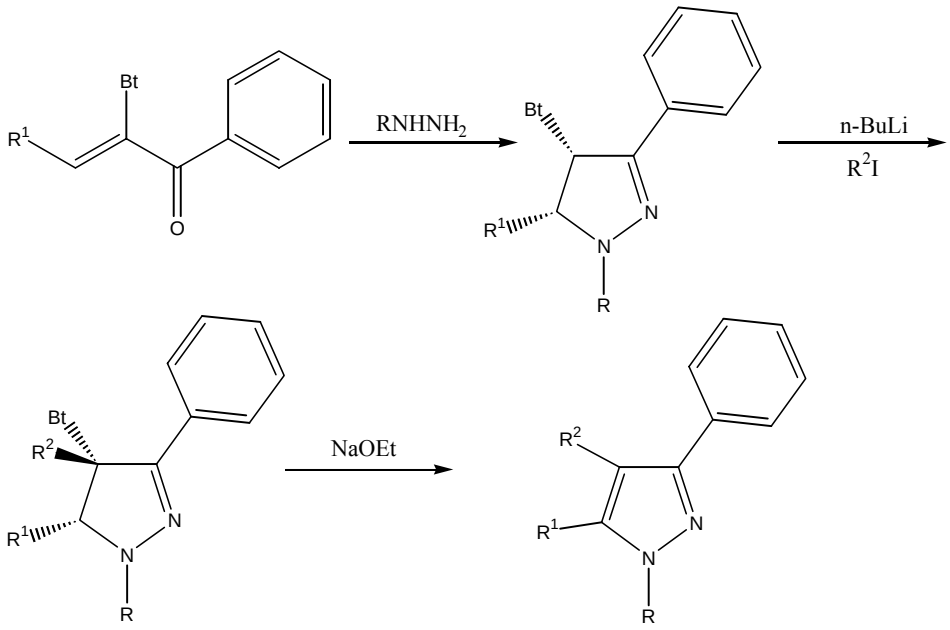


Figure 10. Synthesis of pyrazole derivatives from α, β-unsaturated ketones containing an α-benzotriazole group

In addition to the synthesis of pyrazole derivatives from β-dicarbonyl compounds, there is also a method for synthesis of pyrazole derivatives from the acetylenic carbonyl compounds but the synthesis of pyrazoles from acetylenic carbonyl compounds has not been widely employed because the starting materials have not been readily available (Figure 11) [1].

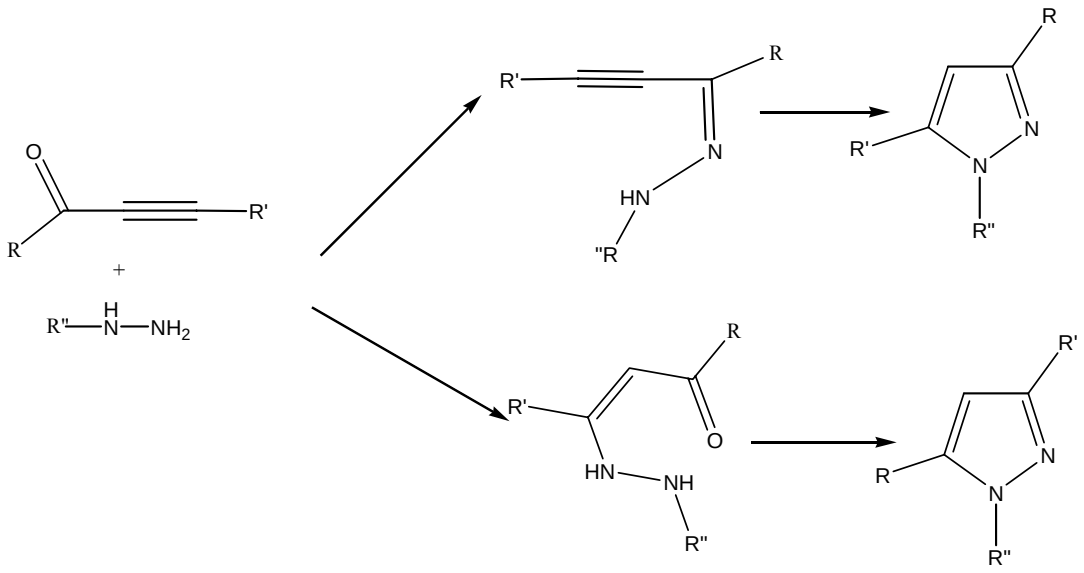


Figure 11. Synthesis of pyrazole derivatives from acetylenic carbonyl compounds

Another method for the synthesis of pyrazoles is the synthesis by ring closure at the 4,5-positions. The synthesis of pyrazoles from acylhydrazones of β-dicarbonyl compounds is of interest in that it involves ring closure between carbon atoms 4 and 5 of the pyrazole ring (Figure 12).

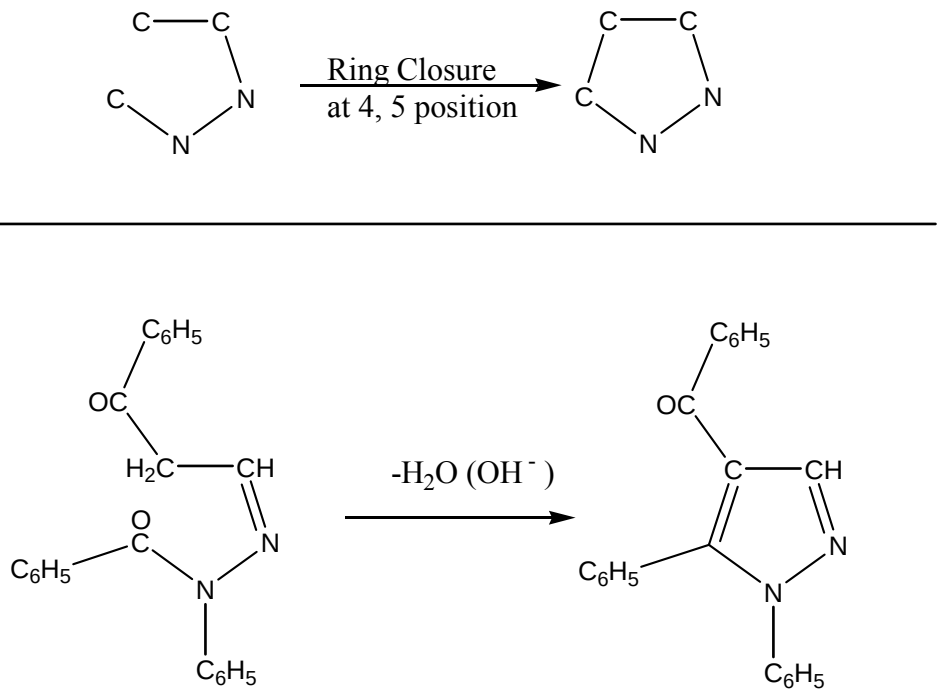


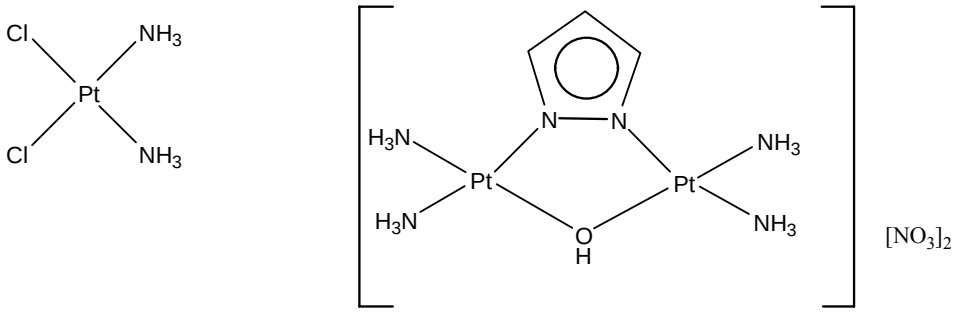
Figure 12. Synthesis of pyrazoles by ring closure at the 4,5-positions

There are also many methods for the synthesis of pyrazole derivatives in addition to these mentioned above such as synthesis from 1,2,3-tricarbonyl compounds with hydrazine, synthesis from α-halocarbonyl compounds with mono- and dithiocarbohydrazines, synthesis from aldehyde arylhydrazones with β-ketoesters, synthesis from aliphatic diazo compounds with acetylene derivatives or with halo- or nitro-vinyl derivatives etc. [1].

1.2. Biologically Active Pyrazole Derivatives.

The incorporation of heterocyclic rings into prospective pharmaceutical candidates is a major tactic to gain activity and safety advantages [10]. Although scarcely found in nature, pyrazoles are known not only as potent insecticides, herbicides, and monomers for the preparation of electroluminiscent and thermo resistant materials, but also as antitumor, anti-inflammatory, antimicrobial, antipsychotic, or analgesic agents. Thus, due to their wide range of pharmacological and technological applications, pyrazoles have been the focus of much synthetic effort in the past decades [3, 6].

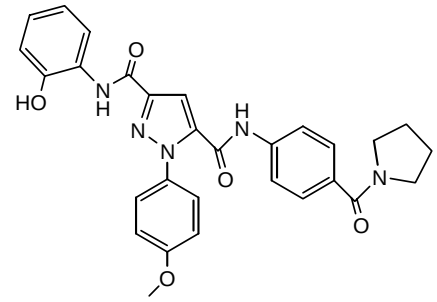
Since the discovery of cisplatin (**4**) as an anticancer agent [11-13], numerous platinum complexes have been prepared in order to improve the clinical inconvenience such as nephrotoxicity and drug resistance [14]. It is generally accepted that cisplatin's cytotoxic effect originates from the interaction with DNA [14] but the applicability of cisplatin is still limited [15]. To overcome intrinsic and acquired resistance, a rational approach would be to prepare platinum complexes that react with DNA in mechanisms distinct from cisplatin and its analogues and some classes of platinum(II) complexes with two or three platinum-amine units linked by a variable length diamine chain are shown to be successful approaches lacking cross-resistance [16, 17]. Cytotoxicity assay of azole-bridged dinuclear platinum (II) complex $[(cis\text{-}Pt(NH_3)_2)_2(\mu\text{-}OH)(\mu\text{-}pz)](NO_3)_2$ (**5**) shown in Figure 13 has been found greater than cytotoxicity of cisplatin [14,15].



4 **5**

Figure 13. Examples of some antitumor agents

One example to the pyrazole-based inhibitor is Helicobacter Pylori Dehydroorotate dehydrogenase (DHODase) **6** (Figure 14). Helicobacter pylori is a gram-negative microaerophilic bacterium that infects up to 50% of the world population and it resides in the acidic medium of the stomach, utilizing a high urease enzyme activity to provide a locally alkaline environment. It has been implicated in numerous gastrointestinal disorders and is associated with gastric ulsers, gastritis and gastric cancer [18]. Other example is Sildenafil **7** that is a selective inhibitor of phophodiesterase5 (PDE5) and it is the first agent with this mode of action for the treatment of male erectile dysfunction that is a disease more commonly known as male impotence [19]. In addition, pyrazolo[1,5]pyridines, pyrazolo[1,5](iso)-quinolines, pyrazolo[1,5]phenanthridines show some biological activity [20]. Besides the phosphodiesterase inhibitor ibudilast **8**, a prostacyclin-mediated vasodilator and antiplatelet drug of choice for the treatment of diseases involving blood cells and vascular wall disorders, other common uses of the above cited pyrazole heterocycles include virucides for herpes virus infection or drugs for the treatment of Alzheimer's and Parkinson's diseases and dementia [21] (Figure 14).



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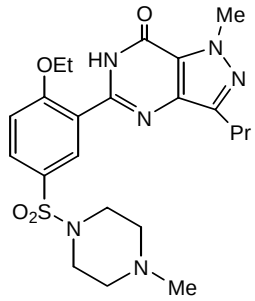

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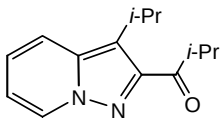

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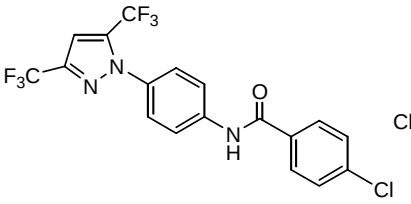

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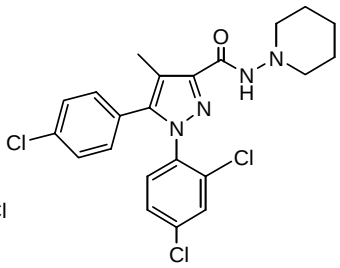

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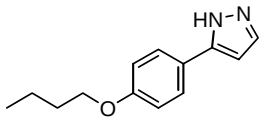

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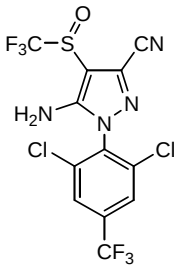

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Figure 14. Biologically active pyrazole derivatives

A series of bis(trifluoromethyl) pyrazoles (BTPs) **9** has been found to be a novel inhibitor of cytokine production. BTPs identified initially as inhibitors of IL-2, show inhibition of IL-4, IL-5, IL-8, and eotaxin production (Figure 14) [22]. Another pyrazole origin compound is Cannabinoid Receptor Antagonist (CB1) **10**. Cannabinoid, which was reported in 1994 by Sanofi Recherche as a potent selective and orally active antagonist of the brain cannabinoid receptor, is the major psychoactive constituent of marijuana [23]. Cannabinoids have long been the focus of study due to their effects on the central nervous system. Early pharmacological testing has shown that cannabinoids possess analgesic, antiemetic, psychotropic, and anti-inflammatory properties and has also suggested their potential therapeutic utility for the treatment of asthma and glaucoma. However, widespread use of cannabinoids as therapeutic agents has been limited by their psychotropic properties [24]. There are also pyrazole derivatives as new, potent and selective 20-hydroxy-5,8,11,14-eicosatetraenoic acid (20-HETE) **11** synthase inhibitors shown in Figure 14. 20-HETE, which is a major metabolite of arachidonic acid produced in the kidney, plays an important role in the regulation of renal vascular and tubular functions and contributes to the control of arterial blood pressure. It is also produced in the brain, where it regulates vascular tone and contributes to the regulation of the cerebral blood flow [25]. The last example to biologically active pyrazole derivative is Fipronil **12**. Fipronil is the most important example of the phenylpyrazole or fiprole insecticides. It is a major insecticide acting as a non-competitive blocker of the γ-aminobutyric acid (GABA) receptor/chloride channel [26] (Figure 14).

1.3. Ferrocene Derivatives and Their Biological Activities.

Organometallic compounds are substances containing metal-carbon bonds; these are generally covalent but may occasionally be ionic as in some of the alkali metal compounds. The field of organometallic chemistry combines aspects of organic chemistry and inorganic chemistry and has led to many important applications in organic synthesis [27]. The pace development of organometallic chemistry initiated by the discovery of ferrocene was spurred by another unexpected discovery by Ziegler [28, 29].

Metallocenes are organometallic compounds which consist of a metal between two planar polyhapto rings [30]. They are informally called "sandwich compounds". One of the ligands encountered in metallocenes is cyclopentadienyl. The cyclopentadienyl ligand (C_5H_5) has played a major role in the development of organometallic chemistry and a huge number of metal cyclopentadienyl compounds are known today. These compounds belong to the most commonly organometallic derivatives and utilized in various areas of chemistry and technology [31].

Ferrocene (**13**) is one of the most important metallocene (Figure 15). During the more than 50 years since the discovery of the first sandwich complex in the early 1950's [32], it has attracted the interest of many scientists and research groups worldwide because its applications in material science [33], and asymmetric synthesis [34], and ferrocenyl derivatives have found numerous uses in various fields of science from biology to materials chemistry [35]. The sandwich structure of Cp_2Fe was discovered in 1951 by G. Wilkinson, R. B. Woodward and E. O. Fischer independently [36]. They suggested a "double cone" structure with all five carbon atom of a cyclopentadienyl ligand interacting with the metal center. Wilkinson and Fischer were awarded the Nobel Prize for the subsequent synthesis of ferrocene (**13**) and further complexes in 1973.

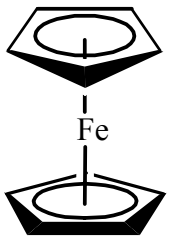

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Figure 15. Structure of ferrocene

Ferrocene (**13**), an orange crystalline and diamagnetic solid, has high stability and reversible redox characteristics so it has been extensively used as starting materials in the synthesis of versatile ferrocenyl derivatives [37]. Ferrocene (**13**), with 18 valence electrons, is the most stable member in the metallocene series. It sublimes readily and is not attacked by air or water, but can be oxidized reversibly [38]. It has been found that ferrocene (**13**) behaves in many respects like an aromatic electron-rich organic compound, which is activated towards electrophilic reactions almost like phenyl. As a consequence, the organometallic moiety is treated like a simple phenyl group [35]. It undergoes Friedel-Crafts acylation and alkylation, Vilsmeier formylation and mercuration [39]. Ferrocene derivatives containing asymmetric substituents are used as ligands for asymmetric hydrogenation catalysts [40]. Some of the basic reactions of ferrocene are shown in Figure 16.

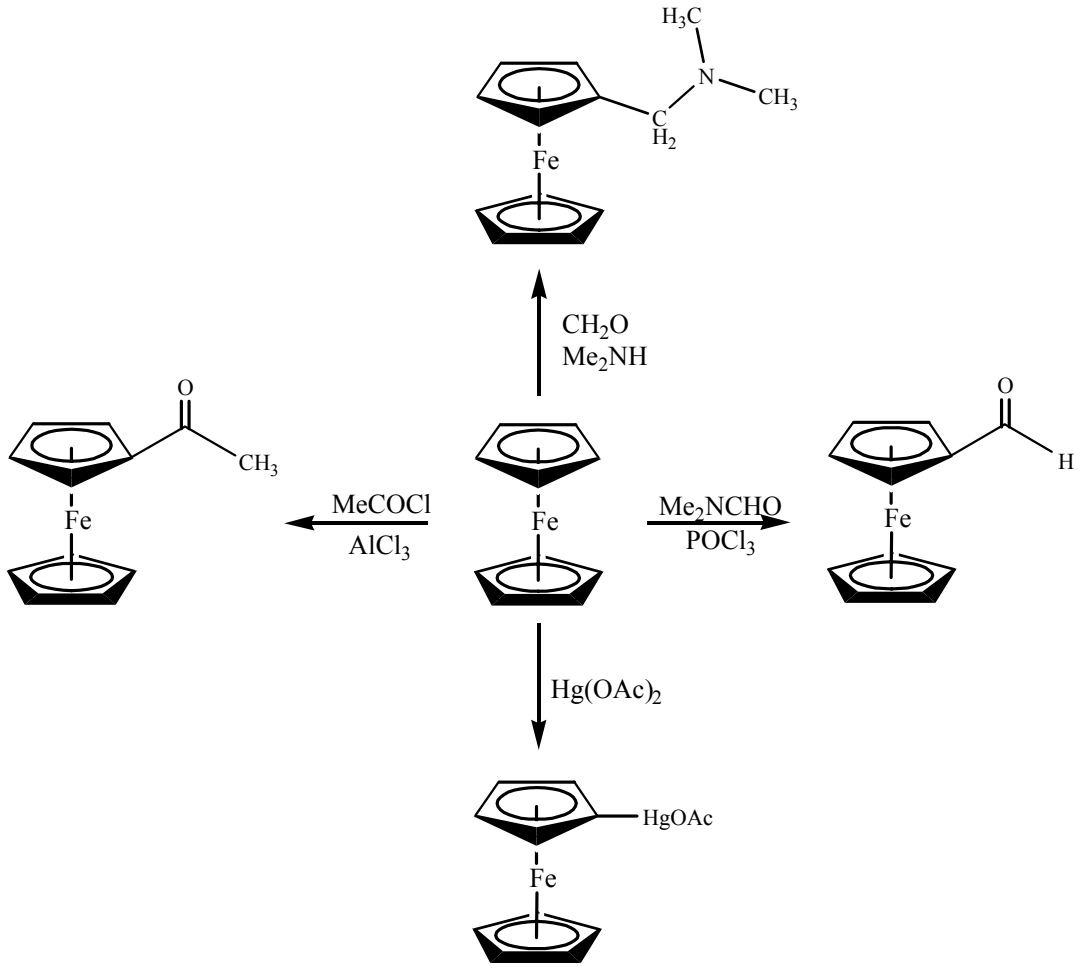
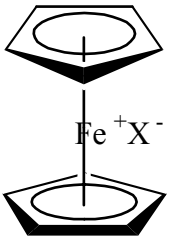


Figure 16. Typical electrophilic substitution reactions of ferrocene

Ferrocenium compounds play an important role in the inhibition of the tumor cell growth. Ferrocene (**13**) is not water soluble compound and it does not show any biological activity even if it is solubilized in water. There are some methods in the literature to overcome this problem. One of them is to create a salt form on the organic residue of ferrocene moiety and other method is to form salt through oxidation of central iron atom. It has been reported that ferrocenium salts such as **14** (Figure 17) are exhibiting antitumor activity against number of tumors [41]. Although they have high solubility in water their tumor inhibitory effect is not related to the water solubility. Their antitumor activity is shown to be related to the oxidation state of the central iron atom of the ferrocene moiety. It has been reported

that only the ferrocenium salts **14** in which the central iron atoms have the oxidation state of +3 exhibit antitumor activity [42].

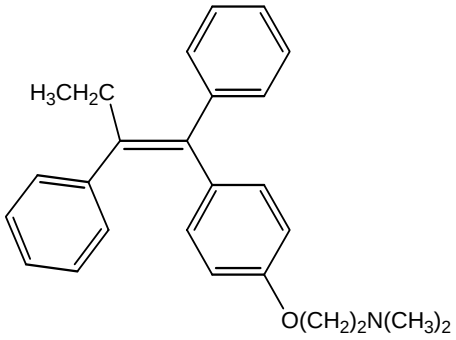


X = (PF_6, $FeCl_4$, 2,4,6-$(NO_2)_3C_6H_2O$, $Cl_3CCO_2.2Cl_3CCO_2H$)

14

Figure 17. Some examples of the ferrocenium salts

Tamoxifen (**15**) is the drug used against breast cancer cells that are mediated by ER_α estrogen reseptors (Figure 18) [43]. There are two types of breast cancer cells: one of them is breast cancer cells that are mediated by ER_α estrogen receptors and the other is breast cancer cells that are mediated by ER_β estrogen receptors. Tamoxifen (**15**) is not effective on breast cancer cells that are mediated by ER_β estrogen receptors. In 2002, Jaouen and co-workers have investigated the tamoxifen analogs that contain an organometallic moiety by replacing the phenyl group with ferrocenyl group. The resulting compound called ferrocifen (**16**) showed a strong effect against breast cancer cells that are mediated by both ER_α and ER_β estrogen receptors (Figure 18) [44].



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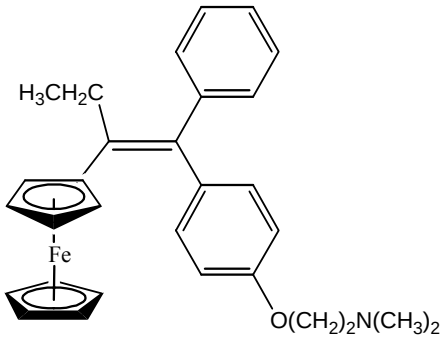

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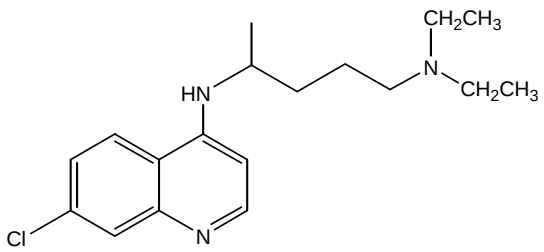
Figure 18. Biologically active compounds as antitumor agents

Ferrocene has also an anti-tumor effect in mice bearing established lung metastases of B-16 melanoma. It has been postulated that the anti-tumor activity of ferrocene is mediated by immune stimulation. Maximal anti-tumor effect has been attained at doses of 0.05– 0.2 mg/kg and it has been found that lower or higher doses are not effective. Ferrocene is a stable, small molecule that exhibits immune stimulatory and anti-tumor properties by a distinct mechanism and is effective at low doses upon i.p. (administration) and oral administration. It has been reported that it may offer therapeutic advantages over some immune stimulatory agents [45].

Another biologically active ferrocenyl compound is ferroquine (**18**), a hybrid compound of chloroquine (**17**) (Figure 19). Several drugs, such as chloroquine (**17**), are used against malaria parasite. Unfortunately resistance to these drugs is increasing [46]. Brocard and co-workers inserted a ferrocenyl group into the side chain of the chloroquine (**17**) and it has been reported that the resulting compound ferroquine (**18**) is much more safe and effective in mice, as well as non-mutagenic [47].



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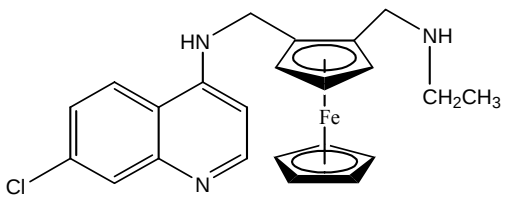

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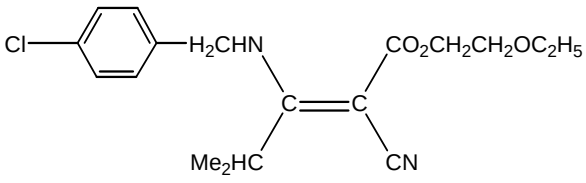
Figure 19. Biologically active compounds as malaria parasite drugs

Cyanoacrylates have been the subject of intense interest for the past decades as one kind of herbicides by disrupting photosynthetic electron transport. Among these cyanoacrylates, (*Z*)-ethoxyethyl-2-cyano-3-(4-chlorophenyl)methylamino-3-isopropylacrylate (**19**, CPNPE) has been a representative compound because of its excellent herbicidal activity (Figure 20). Qingmin and co-workers tried to synthesize a new compound by replacing phenyl group with ferrocenyl moiety and they observed that ferrocenyl cyanoacrylates **20** still retained excellent herbicidal activities [48].



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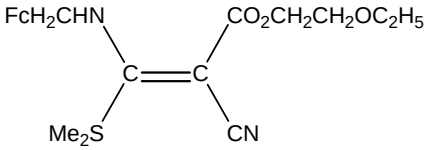

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Figure 20. Herbicidally active compounds

1.4. The Aim of This Study.

The goal of this work is to synthesize the ferrocenyl-substituted pyrazole derivatives since the incorporation of the essential structural features of pyrazoles with a ferrocene moiety could provide new derivatives with enhanced antitumor and biological activities. Although pyrazoles are among the most thoroughly studied compounds, we were surprised that there has been very limited study of the ferrocenyl-substituted pyrazoles. As part of our general involvement in ferrocene containing potential pharmaceuticals, we have investigated the synthesis of ferrocenyl pyrazoles. In particular, although there are numerous methods for the synthesis of pyrazoles, the reaction of (2-formyl-1-chlorovinyl)ferrocene (**21**) with hydrazines can provide a rapid entry to ferrocenyl pyrazoles. In fact, the reaction of (2-formyl-1-chlorovinyl)ferrocene (**21**) with hydrazine and phenyl hydrazine was carried out by Terent'ev and his coworkers for the first time (Figure 21) [49], but the low yield of products were obtained since these reactions were not investigated in much detail. We have restudied this reaction under a variety of condition and improved the yields of pyrazoles by optimizing reaction conditions. Moreover, we have examined this reaction with 7 hydrazine derivatives.

In this study, the scope, limitations and the mechanism of the reaction is discussed in more detail as well as product distributions between 1,5- vs 1,3-isomers.

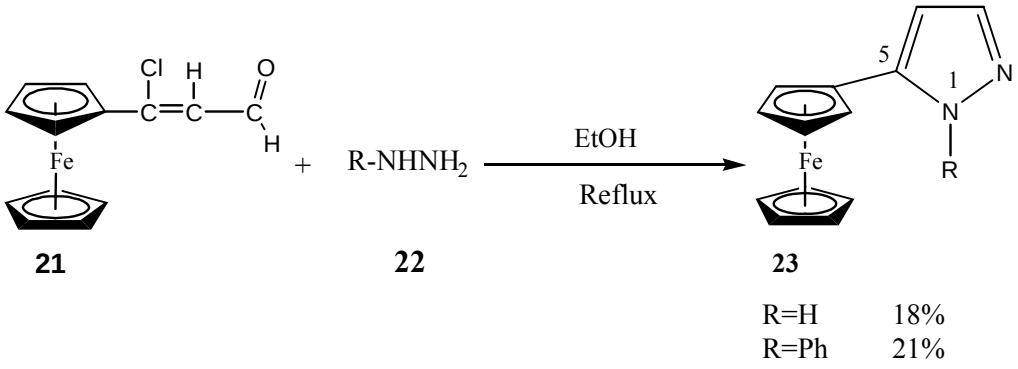


Figure 21. Synthesis of 1-alkyl(aryl)-5-ferrocenyl pyrazole from (2-formyl-1-chlorovinyl)ferrocene

CHAPTER 2

SYNTHESIS OF FERROCENYL SUBSTITUTED PYRAZOLES

2.1. Synthesis of (2-formyl-1-chlorovinyl)ferrocene.

In the first phase of this study, acetyl ferrocene was synthesized from ferrocene. Ferrocene (**13**) behaves as an aromatic compound and easily undergoes Friedel-Crafts Acylation reaction to form acetyl ferrocene (**24**) in 80 % yield according to a known literature [50]. The reaction was performed by using $AlCl_3$ under argon condition (Figure 22).

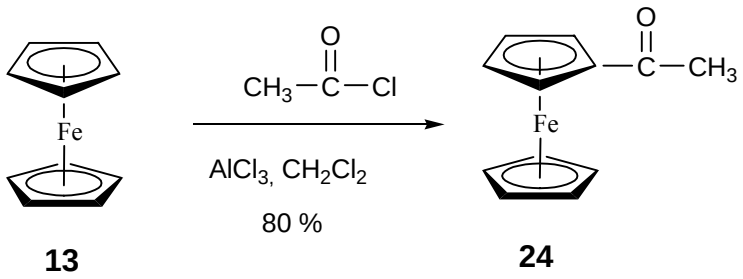


Figure 22. Synthesis of acetyl ferrocene

Subsequently, (2-formyl-1-chlorovinyl)ferrocene (**21**) has been prepared from acetyl ferrocene (**24**) in 93% yield according to known literature (Figure 23) [50]. Treatment of acetyl ferrocene with phosphorus oxychloride in dimethyl formamide (DMF) leads to a mixture of (2-formyl-1-chlorovinyl)ferrocene (**21**) and (1-chlorovinyl)ferrocene with the different product ratio depending on the stoichiometry. However, the formation of (1-chlorovinyl)ferrocene can be effectively suppressed by employing an excess of phosphorus oxychloride. Using DMF as solvent leads to satisfactory results only for small-scale preparations. However, modification of the stoichiometry and experimental conditions led to the above described procedure which is useful for large-scale preparations.

Use of conditions employing a comparatively small excess of DMF and phosphorus oxychloride resulting in a heterogeneous reaction mixture, as well as use of solid sodium acetate trihydrate surmount the problems of scale up and enable the removal of organic impurities. The purity and yield of (2-formyl-1-chlorovinyl)ferrocene (**21**) are substantially improved using the present procedure, and this intermediate is obtained in pure form without need of chromatography [51].

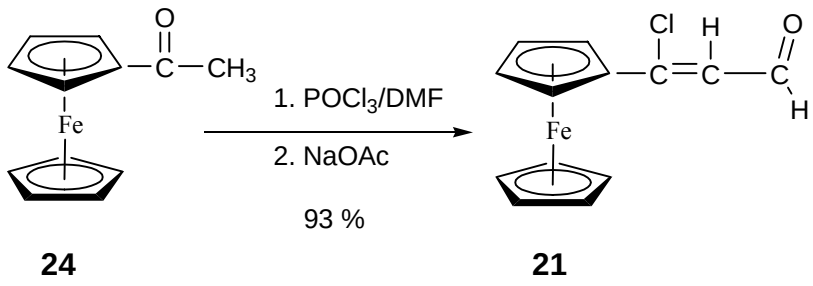
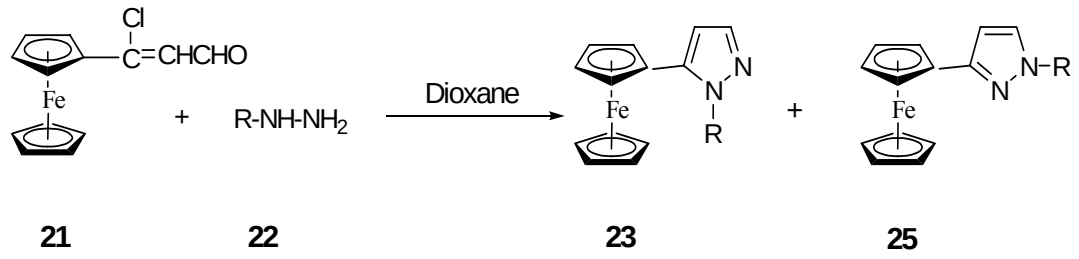


Figure 23. Synthesis of (2-formyl-1-chlorovinyl)ferrocene from acetyl ferrocene.

2.2. Scope and Limitations.

In general, the reaction of (2-formyl-1-chlorovinyl)ferrocene (**21**) with hydrazine derivatives (**22**) have produced two isomers of the expected pyrazole, i.e. 1-alkyl/aryl-5-ferrocenylpyrazole (**23**) and 1-alkyl/aryl-3-ferrocenylpyrazole (**25**) (Figure 24). In order to obtain only 1-alkyl/aryl-5-ferrocenylpyrazole derivatives (**23**), some conditions have been employed as will be discussed below.



21 **22** **23** **25**

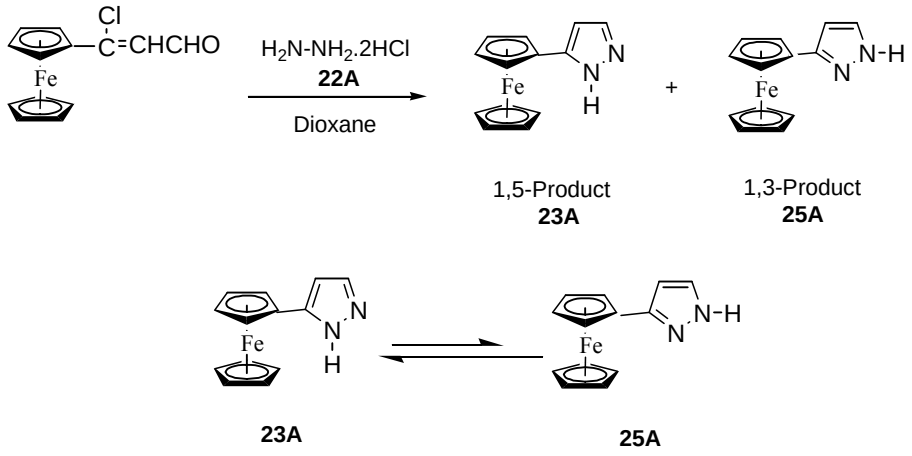
Figure 24. The reaction of (2-formyl-1-chlorovinyl)ferrocene with hydrazine derivatives

Initially, the reaction between hydrazine salt **22A** and (2-formyl-1-chlorovinyl) ferrocene (**21**) was examined in different conditions. Results are summarized in Table 1.

In the first case, the reaction mixture was stirred at room temperature for 2.5 h and then refluxed for 2 h (Table 1). From this reaction, both pyrazole isomers were obtained. 1,3-Pyrazole product **25A** was obtained as major product (31% yield) while 1,5-pyrazole product **23A** was formed as minor product (15% yield). In the second case, reflux time was increased to 4 hours. In this case, both pyrazole isomers were also isolated but 1,5-pyrazole product **23A** was major in 31% yield. 1,3-pyrazole

product **25A** was obtained in 11% yield. In the last case, reflux time was increased to 6 hours, where only 1,5-pyrazole product **23A** was obtained in 51% yield (Table 1). Possibly, 1,3-pyrazole converts to 1,5-pyrazole isomer by increasing the reflux time. Therefore, it can be said that 1,5-pyrazole isomer is more stable than 1,3-pyrazole and it is the thermodynamic product of the reaction. PM3 calculations has also shown that 1,5-pyrazole **23A** isomer is more stable than 1,3-pyrazole isomer **25A** by 3.0 kcal/mol [52].

Table 1. Reactions of (2-formyl-1-chlorovinyl)ferrocene with hydrazine dihydrochloride.

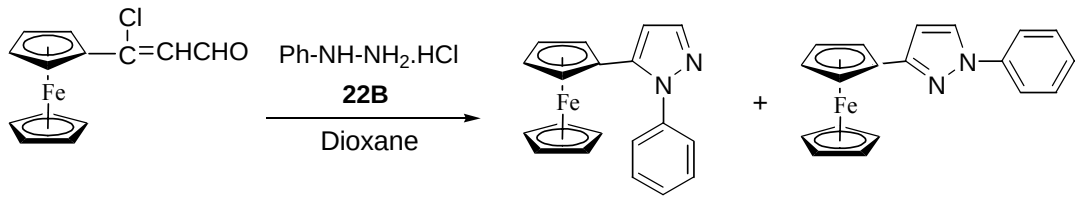


Condition	Yield % of 23A	Yield % of 25A
1. 1. 25 °C, 2.5 h 2. 100 °C, 2 h	15	31
2. 1. 25 °C, 2.5 h 2. 100 °C, 4 h	31	11
3. 1. 25 °C, 2.5h 2. 100 °C, 6 h	51	-

Next, the reaction between phenyl hydrazine salt (**22B**) and (2-formyl-1-chlorovinyl)ferrocene (**21**) was investigated. Four different conditions were employed as summarized in Table 2.

In the first three conditions, the mixture of phenyl hydrazine hydrochloride (**22B**) and (2-formyl-1-chlorovinyl)ferrocene (**21**) was stirred at the room temperature for 2.5 h, then refluxed in dioxane at 100 ^{o}C for 2, 4 or 6 h (Table 2). In the first two case, 1-phenyl-5-ferrocenylpyrazole (**23B**) was formed as a major product while 1-phenyl-3-ferrocenylpyrazole (**25B**) was obtained as a minor product. However, in the third case, 1,5-pyrazole isomer **23B** formed as a single product. In the fourth and the last case, 1,5-pyrazole isomer **23B** and 1,3-pyrazole isomer **25B** were both obtained but **23B** was major.

Table 2. Reaction of (2-formyl-1-chlorovinyl)ferrocene with phenylhydrazine hydrochloride.

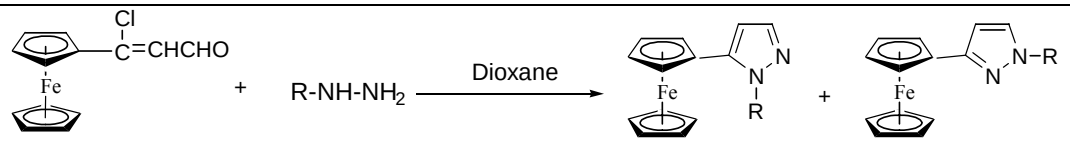


21 1,5-Product **23B** 1,3-Product **25B**

Condition	Yield% of 23B	Yield% of 25B
1. 1. 25 °C, 2.5 h 2. 100 °C, 2 h	41	15
2. 1. 25 °C, 2.5 h 2. 100 °C, 4 h	41	14
3. 1. 25 °C, 2.5 h 2. 100 °C, 6 h	67	-
4. 100 °C, 6 h	50	4

In order to have only 1-alkyl/aryl-5-ferrocenylpyrazole derivatives **23A-G**, the reaction condition with 2.5 h stirring at room temperature and then refluxing for 6 h was chosen. The reaction was performed with 7 different hydrazine derivatives and the results are summarized in Table 3.

Table 3. Reactions of (2-formyl-1-chlorovinyl)ferrocene **21** with hydrazine derivatives **22.**



21 **22** **23** **25**

Entry[a]	**R**	**Products**	**Yield (%)**
A	-H	23A	51
B	-C_6H_5	23B	67
C	-CH_2-C_6H_5	23C	55
D	-CH_2-CH_2-OH	23D 25D	34 3
E	-CO-C_6H_4-OH	23E 23A	43 50
F	-C_6H_4-COOH	23F	47
G	-NC_5H_4	23G	60

[a]Entry Letters define R group for compounds **22**, **23** and **25**.

First, we examined the reaction between (2-formyl-1-chlorovinyl)ferrocene (**21**) with hydrazine salt (**22A**). When the (2-formyl-1-chlorovinyl)ferrocene (**21**) was stirred with hydrazine salt (**22A**) in dioxane at room temperature for 2.5 h and then refluxed for 6 h, the reaction produced **23A** in 51% yield (Table 3, Entry A). Compound **25A** was not obtained in this condition. We suggest that all **25A** produced is converted to **23A** by increasing the reflux time since the latter is more stable, being thermodynamic product of the reaction.

Similarly, the reaction of (2-formyl-1-chlorovinyl)ferrocene (**21**) with phenylhydrazine hydrochloride (**22B**) afforded 1-phenyl-5-ferrocenylpyrazole (**23B**) as a single product in 67% yield (Table 3, Entry B). If the reaction were stopped after 2.5 h stirring at the room temperature, the corresponding hydrazone would be isolated without formation of any pyrazole isomers. This finding implies that the first step is the hydrazone formation, subsequently Michael addition or conjugate addition takes place. As expected, if the hydrazone is thermolyzed, it provides the corresponding pyrazole isomer.

A similar trend was observed when we carried out reaction with (2-formyl-1-chlorovinyl)ferrocene (**21**) and benzylhydrazine dihydrochloride (**22C**), which provided only 1-benzyl-5-ferrocenylpyrazole (**23C**) in 55% yield (Table 3, Entry C).

When the same reaction was performed with (2-formyl-1-chlorovinyl)ferrocene (**21**) and 2-hydroxyethylhydrazine dihydrochloride (**22D**) in the same condition, and both isomers, 1-(2-hydroxyethyl)-5-ferrocenylpyrazole (**23D**) in 34% yield and 1-(2-hydroxyethyl)-3-ferrocenylpyrazole (**25D**) in 3% yield, were obtained (Table3, Entry D). In this case, although the polarity of products are very close to each other and both very polar, 1-(2-hydroxyethyl)-3-ferrocenylpyrazole (**25D**) is slightly less polar than 1-(2-hydroxyethyl)-5-ferrocenylpyrazole (**23D**).

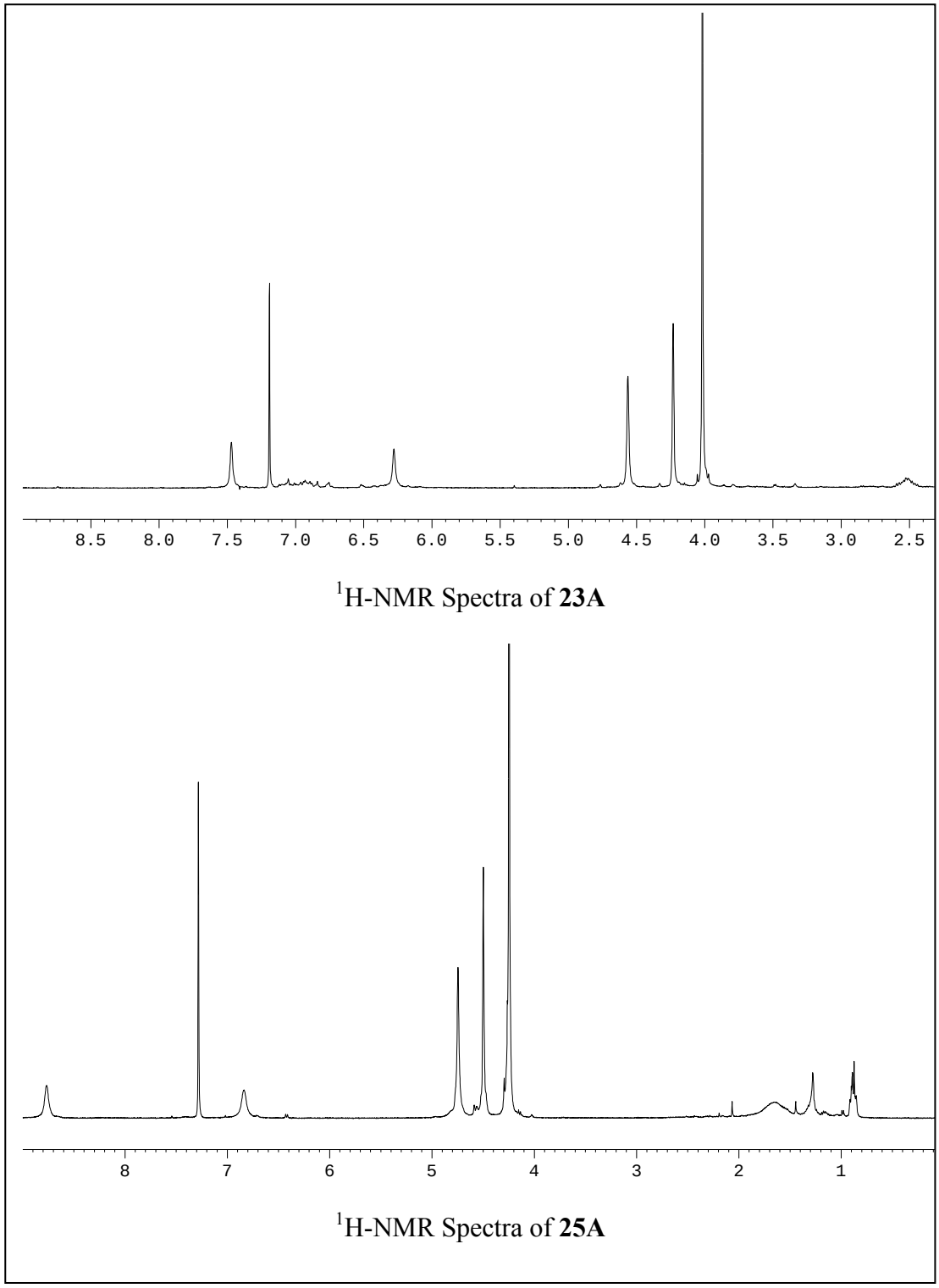
The reaction of (2-formyl-1-chlorovinyl)ferrocene (**21**) with **22E** afforded **23E** in 43% yield and **23A** in 50% yield (Table 3, Entry E). In this case, the formation of **23A** is presumably due to the further reaction of **23E**. The side chain of *p*-hydroxyphenylpyrazolylketone (**23E**) shows amide character and nucleophilic attack by water or other nucleophiles in reaction medium to the carbonyl group ends up with the removal of amine group which produces pyrazole **23A**.

(2-Formyl-1-chlorovinyl)ferrocene (**21**) reacted with **22F** to form **23F** in 47% yield (Table 3, Entry F). This carboxylic acid derivative (**23F**) was the only product obtained. This 1,5-pyrazole product was not very polar but it was difficult to separate it from the reaction mixture due to its acidic character.

In the last case, the reaction of (2-formyl-1-chlorovinyl)ferrocene (**21**) with 2-hydrazinylpyridine (**22G**) in the same condition was examined. The resultant product of this reaction was 1-pyridinyl-5-ferrocenylpyrazole (**23G**) in 60% yield (Table 3, Entry G). This 1, 5-pyrazole product was the only product.

In general, 1,5-pyrazole products (**23**) and 1,3-pyrazole products (**25**) can be differentiated by their ^{1}H-NMR spectra and polarity. The characteristic olefinic proton peaks for 1,3-pyrazole product **25** shift lower fields than those for 1,5-pyrazole product **23**. As an comparison, the ^{1}H-NMR spectra of **23A** and **25A** are illustrated in Figure 25. This is in agreement with those in literature [3].

Another way to differentiate these isomers from each other is to use polarity difference between them. 1,5-pyrazole product **23A** has higher polarity than 1,3-pyrazole product **25A** as concluded from their thin layer chromatography (TLC) analysis. For instance, for **23A** R_f value is 0.094 in 4:1 hexane/ethyl acetate while for **25A** it is 0.36 in 9:1 hexane/ethyl acetate.



^{1}H-NMR Spectra of **23A**

^{1}H-NMR Spectra of **25A**

Figure 25. ^{1}H-NMR Spectra of **23A** and **25A**

As can be seen in Table 3, products were isolated in moderate to good yields. For all cases, 1,5-pyrazole products were obtained as a single product except the case of 2-hydroxyethylhydrazine dihydrochloride (**22D**), where both isomers were obtained, 1-(2-hydoxyethyl)-3-ferrocenylpyrazole (**25D**) and 1-(2-hydoxyethyl)-5-ferrocenylpyrazole (**23D**), but 1-(2-hydoxyethyl)-5-ferrocenylpyrazole (**23D**) was the major product. Overall, we synthesized 10 ferrocenylpyrazole derivatives, and eight of them were synthesized for the first time in literature. 1-Phenyl-5-ferrocenylpyrazole (**23B**) and 5-ferrocenyl-1*H*-pyrazole (**23A**) were synthesized previouly by Russian researchers in 21% yield and 18% yields, respectively [49]. However using our reaction conditions, we achieved the synthesis of these pyrazole derivatives in 67% and 51% yields. Also, for the case of **23E**, **23A** have been obtained due to decomposition of **23E** by attack of H_2O or other nucleophiles in the reaction medium.

2.3. X-Ray Single Crystal Diffraction Analysis.

The structures of 1-phenyl-5-ferrocenylpyrazole (**23B**) and 1-(2-hydroxy-ethyl)-3-ferrocenylpyrazole (**25D**) were further identified by X-ray diffraction analysis. The crystal structures for these compounds are given in Figures 26 and 27. X-Ray crystallographic data for them are given in Table 4 [53].

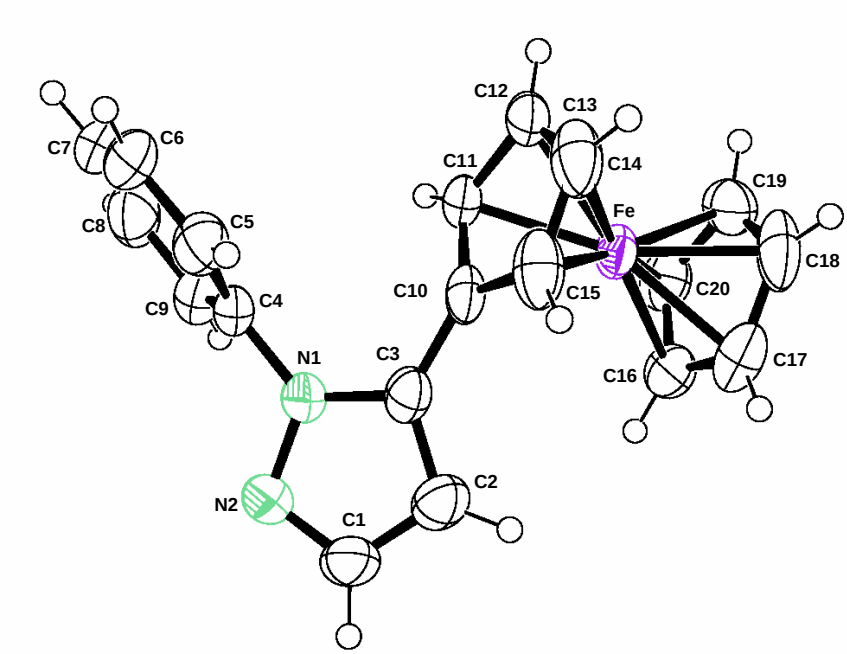


Figure 26. X-Ray Structure of 1-phenyl-5-ferrocenylpyrazole (**23B**).

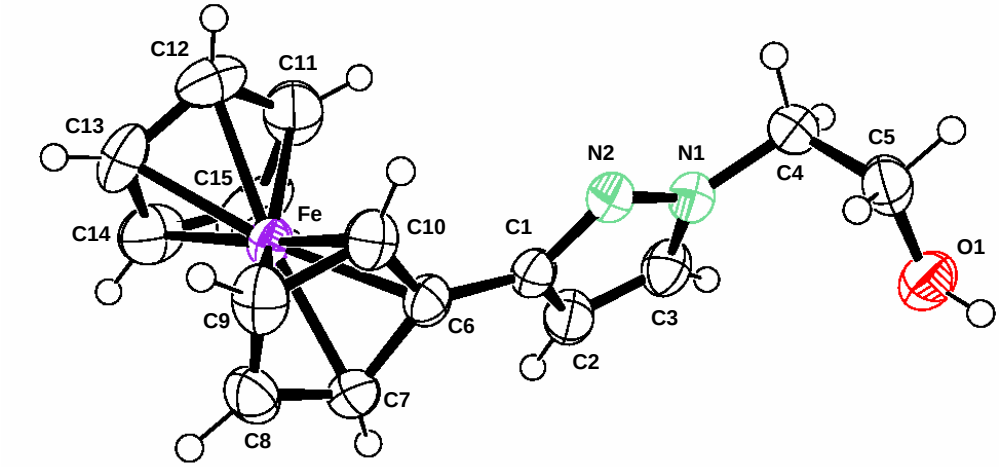


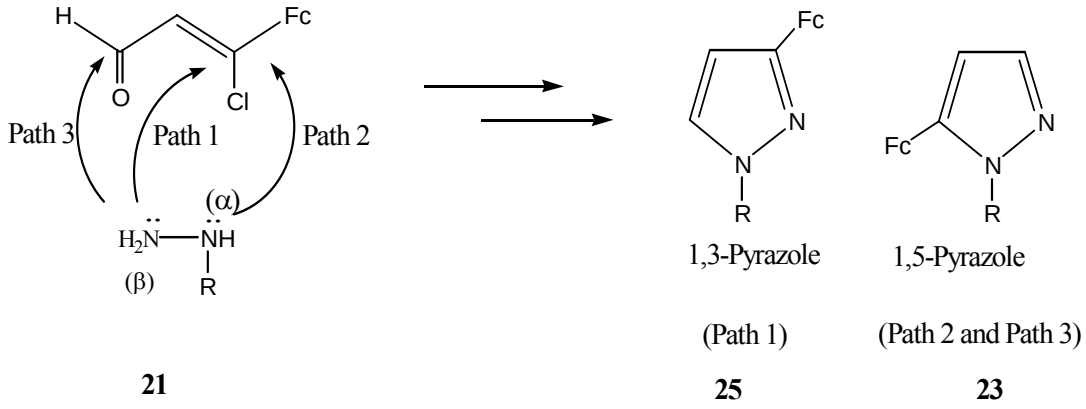
Figure 27. X-Ray Structure of 1-(2-hydroxyethyl)-3-ferrocenylpyrazole (**25D**).

Table 4. X-Ray crystallographic data for compounds **23B** and **25D**.

	Product 23B	**Product 25D**
Chemical formula	$C_{19}H_{16}N_2Fe$	$C_{15}H_{16}N_2OFe$
Molecular weight	328.196	296.15
Crstal system	monoclinic	monoclinic
Space group	'P c'	'P 21/c'
Unit cell dimensions		
a	11.4051(9) Å	9.3078 (6) Å
b	5.9827(6) Å	14.0352 (10) Å
c	21.9993(20) Å	10.6468 (7) Å
α	90.00 °	90.00 °
β	89.984 (7) °	110.484 (5) °
γ	90.00 °	90.00 °
Cell volume	1501.08 (0.23) ($Å^3$)	1302.93 (16) ($Å^3$)
Z (Molecule number in unit cell)	4	4
Density (calculated)	1.452 Mg/m**3	1.510 Mg/m**3
F_{000}	680.0	616
Cell measurement temperature	293	296
Cell measurement reflns used	14905	33304
Cell measurement theta min	1.78	2.04
Cell measurement theta max	27.19	27.95
$S(F^2)$	0.781	0.764
R, R_W	0.026	0.035

2.4 Mechanism.

Three possible mechanisms have been proposed for the formation of pyrazoles as shown in Figure 28. Paths 1 and 2 indicate the conjugate addition to α,β-unsaturated carbonyl compound, (2-formyl-1-chlorovinyl)ferrocene (**21**), or the Michael Addition. Lone pair of the nitrogen attacks to the β position of the (2-formyl-1-chlorovinyl)ferrocene (**21**). In Path 1, attack occurs by the lone pair of NH_2 group. In path 2, lone pair of the NHR group attacks to the (2-formyl-1-chlorovinyl)ferrocene. In Path 3, hydrazone formation first takes place between the carbonyl group of (2-formyl-1-chlorovinyl)ferrocene (**21**) and NH_2 group of hydrazine derivatives **22A-G**. The resultant product of Path 1 is 1-alkyl/aryl-3-ferrocenyl pyrazole (**25**) while those of Paths 2 and 3 are 1-alkyl/aryl-5-ferrocenyl pyrazole (**23**) (Figure 28).



Figere 28. The proposed mechanistic paths.

Path 1. First of all, Michael Addition to (2-formyl-1-chlorovinyl)ferrocene (**21**) occurs with lone pair of NH_2 group to form **26**. Then removal of chloride ion takes place and results in the formation of **27**. This chloride ion attacks to the proton of the positively charged aminium ion to produce **28**. Due to the excess use of hydrazine derivatives (**22A-G**), amine salts can form in place of HCl. Then, lone pair of NHR group attacks to carbonyl group and leads to cyclization to afford **29**. The H migration in **29** forms **30**. Proton abstraction by oxygen occurs to form **31** and then removal of water takes place to give **32**. Finally, water attacks to the proton of positively charged imino group and 1,3- pyrazole product **25** forms (Figure 29).

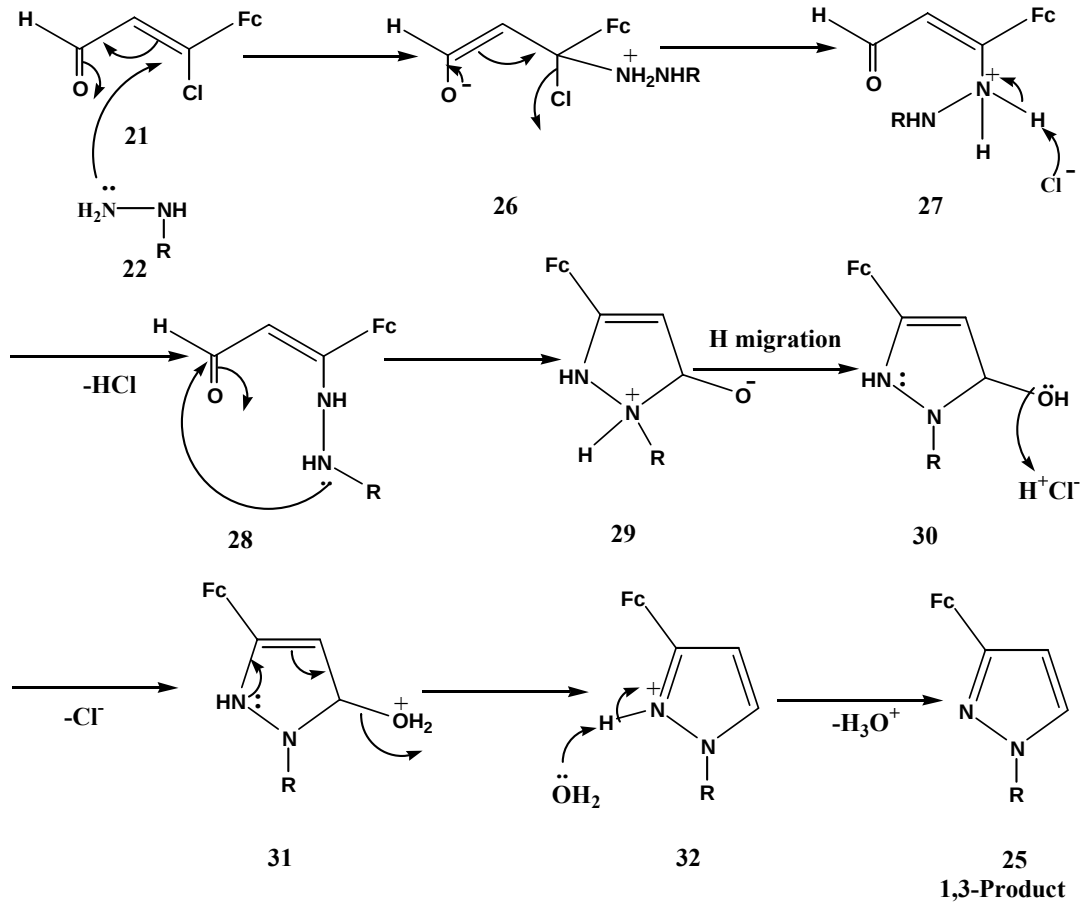


Figure 29. The proposed mechanism for the formation of 1,3-pyrazole product through Path 1.

Path 2. Conjugate addition to α,β unsaturated carbonyl compound (2-formyl-1-chlorovinyl)ferrocene (**21**) or Michael Addition takes place like in path 1. In this case, however, Michael Addition to (2-formyl-1-chlorovinyl)ferrocene occurs with lone pair of NHR group to produce **33**. Here again, removal of chloride ion in **33** followed by proton abstraction in **34** take place to provide **35**. Then, cyclization occurs by hydrazone formation to produce 1,5-pyrazole product **23** (Figure 30).

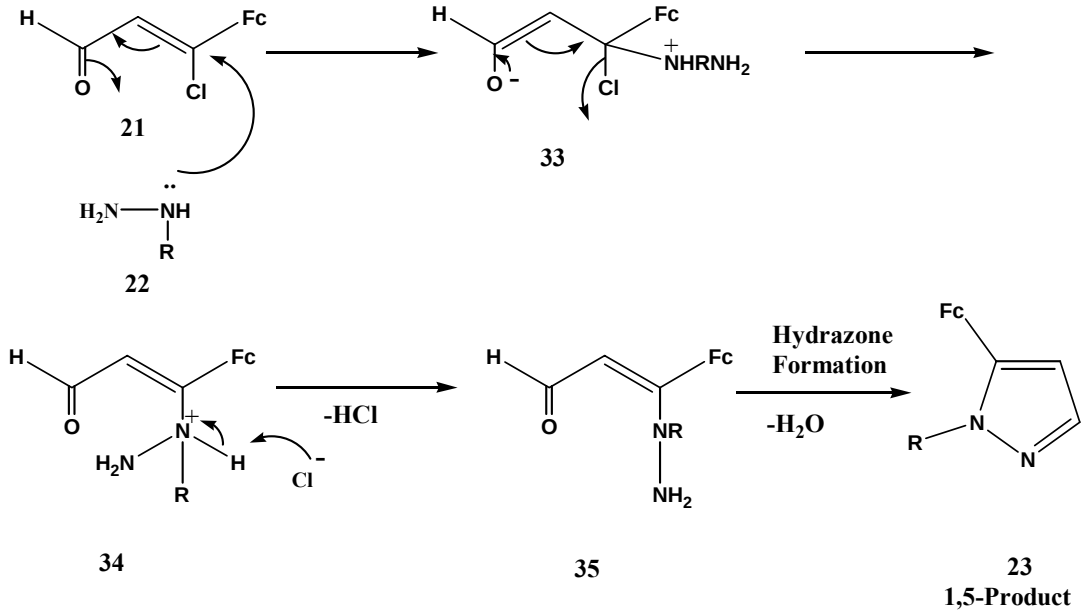


Figure 30. The proposed mechanism for the formation of 1,5-pyrazole product through Path 2.

Path 3. Firstly, hydrazone formation takes place between the carbonyl group of (2-formyl-1-chlorovinyl)ferrocene (**21**) and NH_2 group of hydrazine derivatives (**22A-G**), giving intermediate **36** (Figure 29). Then, cyclization takes place by the attack of lone pair of other N group to double bond to form **37**. After that, negatively charged N attacks to form double bond, which leads to removal of chloride and results in the formation of **38**. Then, proton abstraction by chloride ion produces 1,5- pyrazole product **23** (Figure 31).

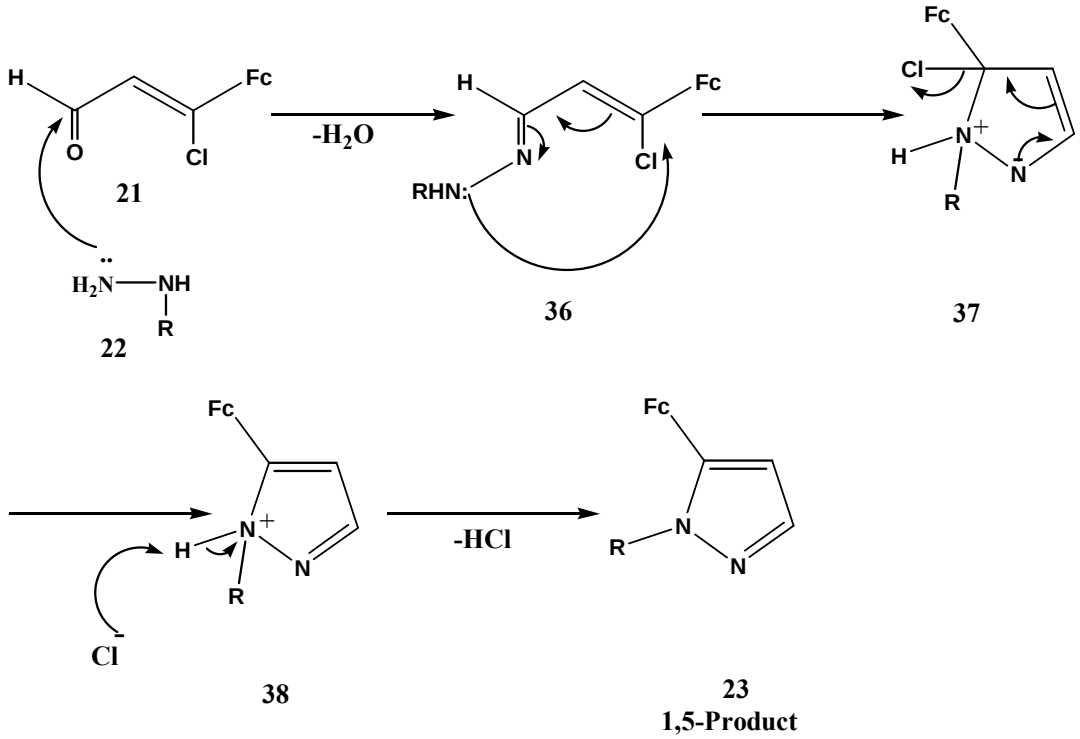


Figure 31. The proposed mechanism for the formation of 1,5-pyrazole product through Path 3.

Conjugate addition (Michael Addition) to α,β-unsaturated carbonyl compounds needs relatively high temperature. On the other hand, hydrazone formation can take place at room temperature. Due to the reaction condition of stirring at room temperature for 2.5 h followed by refluxing the resulting mixture for 6 h, first hydrazone formation is expected. For that reason, the possibility of Path 3 for this study is highly relevant, and as a result, 1-alkyl/aryl-5-ferrocenylpyrazole derivatives have been isolated exclusively.

CHAPTER 3

CONCLUSION

We investigated the synthesis of ferrocenyl substituted pyrazole derivatives **23** starting from (2-formyl-1-chlorovinyl)ferrocene **21** and hydrazine derivatives **22**.

The reaction between (2-formyl-1-chlorovinyl)ferrocene **21** and hydrazine derivatives **22** produced 1-alkyl/aryl-5-ferrocenylpyrazoles **23** as a single or the major product and/or 1-alkyl/aryl-3-ferrocenylpyrazoles **25** as byproducts. After optimizing the reaction conditions we carried out this reaction with seven different hydrazine derivatives **22**. Importantly, 1,3-pyrazole products and 1,5-pyrazole products can be differentiated by their ^{1}H-NMR spectra and polarity in TLC. In addition, the expected molecular formula of these isomers were proved by high resolution mass spectroscopy (HRMS).

For the formation of 1-alkyl/aryl-5-ferrocenylpyrazoles (**23**) and 1-alkyl/aryl-3-ferrocenylpyrazoles (**25**)**,** three mechanisms were proposed involving hydrazone formation followed Michael addition to α,β-unsaturated carbonyl compound, or vice versa. Under our reaction condition, Path 3 seems to be operating.

In conclusion, new ferrocenyl-substituted pyrazole derivatives were synthesized, which are expected to be biologically active compounds. Their biological activities will be tested by collaborative work.

CHAPTER 4

EXPERIMENTAL

General Consideration. Nuclear Magnetic Resonance (^{1}H and ^{13}C) spectra were recorded on a Bruker Spectrospin Avance DPX400 Ultrashield (400 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane reference. Coupling constants (*J* values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). DEPT ^{13}C-NMR information is given in parenthesis as C, CH, CH_2 and CH_3. Infrared spectra were recorded on a Perkin Elmer 1600 Series FT-IR spectrometer. Band positions are reported in reciprocal centimeters (cm^{-1}). Band intensities are reported relative to the most intense band and are listed as: br (broad), vs (very strong), s (strong), m (medium), w (weak), vw (very weak). Mass spectra (MS) were obtained on a Micromass UK Platform-II spectrometer using electron impact (EI); *m/e* values are reported. Flash column chromatography was performed using thick-walled glass columns and "flash grade" silica (Merck 230-400 mesh). Routin thin layer chromatography (TLC) was effected by using precoated 0.25 mm silica gel plates purchased from Merck. The relative proportions of solvents in mixed chromatography solvents refers to the volume:volume ratio. X-Ray Spectra were obtained on a Stoe IPDS- II diffractometer. All commercially available reagents and reactants were obtained in reagent grade and used without purification. All reaction solvents were distilled for purity. Diethylether, THF and dioxane were distilled from sodium/benzophenone kettle. Dichloromethane was distilled from calcium hydride kettle. The inert atmosphere created by slight positive pressure (ca. 0.1 psi) of argon.

4.1 Synthesis of acetylferrocene (24). In a dry flask, ferrocene **(13)** (2 g, 0, 0108 mol) was added and it was dissolved with stirring in dry dichloromethane (15 ml) under argon. To the resultant dark orange/red solution acetyl chloride (1, 03 ml, 0, 0118 mol) was added and then flask was immersed in an ice water bath at 0-5 ^{o}C. Anhydrous aluminium chloride (1, 44 g, 0, 0108 mol) was added in 10 portions (2min. between each addition). The reaction mixture darkened. It was stirred for 2 h allowing the ice-water warm to room temperature. Solution was recooled and hydrolyzed with water by slow addition of 4 x 0, 5 ml of cold water. Then, 3 ml of cold water was added more rapidly. The mixture was transferred to a separating funnel and extracted with dichloromethane then organic extracts were combined and washed with 5% sodium hydroxide solution. Red/ orange solution was dried over magnesium sulfate for 10 min, then filtered off. Solvent was removed on a rotary evaporator to give a red/orange solid. This solid was purified by flash chromatography on silica gel using hexane as the eluent. The red/orange fraction (R_f = 0.1 in 9:1 hexane/ethyl acetate) was collected to give acetyl ferrocene **(24)** (1, 96 g, 80%).

24: ^{1}H-NMR ($CDCl_3$): δ 4.60 (s, 2H), 4.32 (s, 2H), 4.02 (s, 5H), 2.17 (s, 3H); ^{13}C-NMR ($CDCl_3$): δ 79.2 (C), 72.3 (CH), 69.8 (CH), 69.5 (CH), 27.3 (CH_3). The spectral data is in agreement with those reported previously for this compound [49].

4.2. Synthesis of (2-Formyl-1-chlorovinyl)ferrocene (21). To a two necked flask, acetylferrocene **(24)** (2 g, 8.8 mmol) was placed and addition funnel was connected. *N,N*-dimethylformamide (DMF) (2.17 ml, 28.2 mmol) was added on it. The system was flushed with argon, cooled to 0 ^{o}C by means of an ice bath, and the brown reaction mixture was stirred for several minutes. Seperately, in a flask joined with argon, DMF (2.17 ml, 28.2 mmol) was added and cooled to 0 ^{o}C, with good stirring phosphorus oxychloride (2.21 ml, 24 mmol) was added. The resulting viscous, red complex was transferred to the dropping funnel and added to the magnetically stirred mixture of acetylferrocene and DMF dropwise over 30 min. Complete addition was assured by washing the addition funnel and walls of the flask

with small amount of DMF. The mixture was stirred at 0 ^{o}C for 2 hr during which time the color of the reaction mixture changed from dark brown to olive and ultimately to deep blue. Prior to neutralization, 20 ml portion of diethyl ether was added and viscous mixture was stirred vigorously for several minutes. At 0 ^{o}C, (10.18 g, 74.6 mmol) sodium acetate trihydrate was cautiously added to the reaction mixture in one portion followed by addition of 2 ml water with vigorous stirring. The ice bath was removed whereupon the organic layer undergoes a striking color change from blue to ruby red indicating the formation of the formyl derivative. After 1 hr, an additional 2 ml of diethyl ether was added and stirring was continued for 3 hr at room temperature to ensure complete quenching. The reaction mixture was transferred to a seperatory funnel with ether and water and mixed thoroughly, and the organic phase was separated. The aqueous phase was extracted several times with ether. The combined organic phases were carefully washed with 20 ml of saturated aqueous sodium bicarbonate solution. The organic phase was dried over magnesium sulfate, filtered and concentrated using a rotary evaporator. The resulting (2-formyl-1-chlorovinyl)ferrocene **(21)** was obtained as an only product (2.25 g, 93%).

(21): ^{1}H-NMR ($CDCl_3$): δ 10.06 (d, 1H, J = 7.1 Hz), 6.38 (d, 1H, J = 7.1 Hz), 4.73 (t, 2H, J = 1.68 Hz), 4.54 (t, 2H, J = 1.68 Hz), 4.22 (s, 5H). The spectral data is in agreement with those reported previously for this compound [50].

4.3. General Procedure 1. Synthesis of Pyrazoles 23A-B and 25A-B (Table 1 and Table 2). (2-formyl-1-chlorovinyl)ferrocene **(21)** was placed in a two necked round bottom flask equipped with condenser and the system was flushed with argon. It was dissolved with 25 ml dry dioxane and hydrazine **(22)** was added. The mixture was stirred for 2.5 h at room temperature and then heated at reflux for 2 h. The solvent removed in rotary evaporator and the residue was extracted with chloroform/water. Aqueous phase was extracted with 3x30 ml chloroform and the combined chloroform extracts were dried over anhydrous magnesium sulfate, filtered and concentrated in rotary evaporator. This mixture was purified by flash chromatography on silica gel using hexane/ethylacetate as the eluent.

4.3.1. Reaction of (2-formyl-1-chlorovinyl)ferrocene (21) with hydrazine dihydrochloride salt (22A) (Table 1, Entry 1). General Procedure 1 was followed by using (2-formyl-1-chlorovinyl)ferrocene **(21)** (100 mg, 0.363 mmol), hydrazine dihydrochloride salt **(22A)** (114.34 mg, 1.089 mmol). After chromatographic purification, the purple colored fraction (R_f = 0.36 in 9:1 hexane/ethyl acetate) was collected to give 3-Ferrocenyl-1-*H*-pyrazole **(25A)** (28 mg, 31%) and a yellow fraction (R_f = 0.094 in 4:1 hexane/ethyl acetate) was collected to give 5-Ferrocenyl-1-*H*-pyrazole **(23A)** (14 mg, 15%).

(25A): ^{1}H-NMR ($CDCl_3$): δ 8.71 (s, 1H), 6.79 (s, 1H), 4.70 (s, 2H), 4.45 (s, 2H), 4.20 (s, 5H), 2.25 (m, NH); ^{13}C-NMR ($CDCl_3$): δ 160.3 (CH), 117.9 (CH), 82.2 (C), 71.1 (CH), 70.6 (CH), 68.1 (CH); MS (EI): 252 (M^+), 232, 210, 166, 158, 121, 89, 56; HRMS (EI): Calc. For $C_{13}H_{12}{}^{56}FeN_2$: 252.0350. Found: 252.0348.

(23A): ^{1}H-NMR ($CDCl_3$): δ 7.52 (s, 1H), 6.33 (s, 1H), 4.61 (s, 2H), 4.28 (s, 2H), 4.06 (s, 5H), 2.27 (m, NH); ^{13}C-NMR ($CDCl_3$): δ 134.9 (CH), 108.4 (CH), 75.5 (C), 69.6 (CH), 68.7 (CH), 66.6 (CH); IR (neat): 3439 (s), 3192 (b), 3049 (w), 2958 (m), 2932 (vs), 2854 (w), 1693 (vw), 1559 (s), 1413 (s), 1263 (s), 868 (w), 821 (s); MS (EI): 252 (M^+), 250, 224, 187, 166, 158, 133, 121, 103, 77; HRMS (EI): Calc. For $C_{13}H_{12}{}^{56}FeN_2$: 252.0350. Found: 252.0352.

4.3.2. Reaction of (2-formyl-1-chlorovinyl)ferrocene (21) with phenyl hydrazine hydrochloride salt (22B) (Table 2, Entry 1). General Procedure 1 was followed by using (2-formyl-1-chlorovinyl)ferrocene **(21)** (300 mg, 1.089 mmol), phenyl hydrazine hydrochloride salt **(22B)** (472.4 mg, 3.27 mmol). After chromatographic purification, a purple fraction (R_f = 0.43 in 9:1 hexane/ethyl acetate) was collected to give 1-phenyl-3-ferrocenylpyrazole **(25B)** (18 mg, 15%) and an orange fraction (R_f = 0.21 in 9:1 hexane/ethyl acetate) was collected to give 1-phenyl-5-ferrocenylpyrazole **(23B)** (49 mg, 41%).

(25B): ^{1}H-NMR ($CDCl_3$): δ 7.84 (d, 1H, *J* = 2.4 Hz), 7.71 (d, 2H, *J* = 7.8 Hz), 7.44 (t, 2H, *J* = 7.8 Hz), 7.25 (t, 1H, *J* = 7.8 Hz), 6.48 (d, 1H, *J* = 2.4 Hz), 4.76 (s, 2H), 4.29 (s, 2H), 4.07 (s, 5H); ^{13}C-NMR ($CDCl_3$): δ 152.5 (C), 140.3 (C), 129.4 (CH), 127.4 (CH), 126.0 (CH), 119.0 (CH), 105.6 (CH), 78.4 (C), 69.6 (CH), 68.7 (CH), 66.9 (CH); IR (neat): 3742 (s), 3669 (w), 3030 (vw), 2959 (vs), 2865 (s), 1719 (vs), 1681 (b), 1506 (s), 1257 (vs), 1129 (w), 1043 (m), 868 (w), 820 (m); MS (EI): 328 (M^+), 326, 263, 246, 206, 178, 149, 121, 91, 77, 56; HRMS (EI): Calc. For $C_{19}H_{16}{}^{56}FeN_2$: 328.0663. Found: 328.0665.

(23B): ^{1}H-NMR ($CDCl_3$): δ 7.62 (s, 1H), 7.40 (m, 5H), 6.50 (s, 1H), 4.17 (s, 2H), 4.14 (s, 2H), 4.05 (s, 5H); ^{13}C-NMR ($CDCl_3$): δ 141.5 (C), 140.4 (C), 140.0 (CH), 128.8 (CH), 128.0 (CH), 126.1 (CH), 106.8 (CH), 75.1 (C), 69.9 (CH), 68.8 (CH), 68.6 (CH); IR (neat): 3744 (w), 3098 (m), 3048 (s), 1737 (vw), 1665 (s), 1597 (s), 1498 (vs), 1402 (s), 1312 (vw), 1259 (vs), 1145 (s), 923 (s), 822 (vs); MS (EI): 328 (M^+), 326, 263, 235, 207, 170, 153, 121, 77, 56; HRMS (EI): Calc. For $C_{19}H_{16}{}^{56}FeN_2$: 328.0663. Found: 328.0661.

4.4. General Procedure 2. Synthesis of Pyrazoles 23C-G (Table 3). (2-formyl-1-chlorovinyl)ferrocene **(21)** was placed in a two necked round bottom flask equipped with condenser and the system was flushed with argon. It was dissolved with 25 ml dry dioxane and hydrazine **(22)** was added. The mixture was stirred for 2.5 h at room temperature and then heated at reflux for 6 h. The solvent removed in rotary evaporator and the residue was extracted with chloroform/water. Aqueous phase was extracted with 3x30 ml chloroform and the combined chloroform extracts were dried over anhydrous magnesium sulfate, filtered and concentrated in rotary evaporator. This mixture was purified by flash chromatography on silica gel using hexane/ethylacetate as the eluent.

4.4.1. Reaction of (2-formyl-1-chlorovinyl)ferrocene (21) with benzyl hydrazine dihydrochloride salt (22C) (Table 3, Entry C). General Procedure was followed by using (2-formyl-1-chlorovinyl)ferrocene **(21)** (100 mg, 0.363 mmol), benzyl hydrazine dihydrochloride salt **(22C)** (212.44 mg, 1.089 mmol). After chromatographic purification, the orange colored fraction (R_f = 0.17 in 9:1 hexane/ethyl acetate) was collected to give 1-benzyl-5-ferrocenylpyrazole **(23C)** (68 mg, 55%).

(23C): ^{1}H-NMR ($CDCl_3$): δ 7.44 (s, 1H), 7.23 (t, 2H, *J* = 7.28 Hz), 7.15 (t, 1H, *J* = 7.28 Hz), 6.96 (d, 2H, *J* = 7.28 Hz), 6.35 (s, 1H), 5.42 (s,2H), 4.29 (s, 2H), 4.17 (s, 2H), 4.00 (s, 5H); ^{13}C-NMR ($CDCl_3$): δ 141.7 (C), 139.1 (C), 137.7 (CH), 128.6 (CH), 127.3 (CH), 126.3 (CH), 106.0 (CH), 74.9 (C), 70.0 (CH), 68.8 (CH), 68.4 (CH), 53.3 (CH_2); IR (neat): 3096 (w), 2954 (s), 2930 (s), 2858 (w), 1721 (vs), 1673 (b), 1405 (s), 1281 (vs), 1130 (s), 1076 (s), 928 (s), 822 (s); MS (EI): 342 (M^+), 277, 252, 223, 185, 157, 121, 91, 65, 56; HRMS (EI): Calc. For $C_{20}H_{18}{}^{56}FeN_2$: 342.0819. Found: 342.0817.

4.4.2. Reaction of (2-formyl-1-chlorovinyl)ferrocene (21) with 2-hydroxy ethyl hydrazine dihydrochloride salt (22D) (Table 3, Entry D). General Procedure was followed by using (2-formyl-1-chlorovinyl)ferrocene **(21)** (100 mg, 0.363 mmol), 2-hydroxy ethyl hydrazine dihydrochloride salt **(22D)** (162.25 mg, 1.089 mmol). After chromatographic purification, the bright yellow colored fraction (R_f = 0.107 in 1:1 hexane/ethyl acetate) was collected to give 1-(2-hydroxy ethyl)-3-ferrocenylpyrazole **(25D)** (3 mg, 3%) and yellow/orange colored fraction (R_f = 0.054 in 1:1 hexane/ethyl acetate) was collected to give 1-(2-hydroxy ethyl)-5-ferrocenylpyrazole **(23D)** (36.7 mg, 34%).

(25D): ^{1}H-NMR ($CDCl_3$): δ 7.46 (d, 1H, *J* = 1.8 Hz), 6.30 (d, 1H, *J* = 1.8 Hz), 4.49 (s, 2H), 4.36 (t, 2H, *J* = 4.5 Hz), 4.33 (s, 2H), 4.18 (s, 5H), 4.02 (t, 2H, *J* = 4.5 Hz); ^{13}C-NMR ($CDCl_3$): δ 141.4 (C), 138.7 (CH), 106.0 (CH), 74.9 (C), 69.6 (CH), 68.9 (CH), 68.8 (CH), 61.8 (CH_2), 51.0 (CH_2); IR (neat): 3049 (w), 2925 (vs), 2863 (s), 1724 (s), 1623 (b), 1458 (w), 1285 (s) 1142 (w), 1071 (w), 1034 (vw), 824 (s); MS (EI): 296 (M^+), 294, 265, 252, 231, 200, 187, 146, 121, 103; HRMS (EI): Calc. For $C_{15}H_{16}{}^{56}FeN_2O$: 296.0612. Found: 296.0610.

(23D): ^{1}H-NMR ($CDCl_3$): δ 7.31 (s, 1H), 6.22 (s, 1H), 4.76 (s, 2H), 4.35 (s, 2H), 4.21 (t, 2H, *J* = 4.3 Hz), 4.12 (s, 5H), 3.97 (t, 2H, *J* = 4.3 Hz); ^{13}C-NMR ($CDCl_3$): δ 151.3 (C), 130.8 (CH), 103.0 (CH), 78.3 (C), 69.4 (CH), 68.3 (CH), 66.6 (CH), 62.1 (CH_2), 53.5 (CH_2); IR (neat): 3051 (s), 2926 (s), 2858 (s), 1727 (s), 1461 (vw), 1376 (w), 1261 (vs), 1243 (b), 1070 (vw), 821 (vw); MS (EI): 296 (M^+), 294, 278, 264, 231, 213, 199, 173, 148, 121, 103, 81; HRMS (EI): Calc. For $C_{15}H_{16}{}^{56}FeN_2O$: 296.0612. Found: 296.0614.

4.4.3. Reaction of (2-formyl-1-chlorovinyl)ferrocene (21) with 4-hydroxybenzhydrazide (22E) (Table 3, Entry E). General Procedure was followed by using (2-formyl-1-chlorovinyl)ferrocene **(21)** (100 mg, 0.363 mmol), 4-Hydroxybenzhydrazide **(22E)** (165.68 mg, 1.089 mmol). After chromatographic purification, the orange colored fraction (R_f = 0.283 in 4:1 hexane/ethyl acetate) was collected to give **23E** (58 mg, 43%). Also, 1-*H*-5-ferrocenyl pyrazole **23A** was collected (46 mg, 50%).

(23E): ^{1}H-NMR ($CDCl_3$): δ 8.33 (s, 1H), 8.21 (d, 2H, *J* = 7.95 Hz), 6.89 (d, 2H, *J* = 7.95 Hz), 6.51 (s, 1H), 5.87 (s, OH), 4.81 (s, 2H), 4.40 (s, 2H), 4.14 (s, 5H); ^{13}C-NMR ($CDCl_3$): δ 165.1 (C), 160.3 (C), 156.6 (C), 134.5 (CH), 131.5 (CH), 123.6 (C), 115.3 (CH), 107.9 (CH), 78.2 (C), 71.2 (CH), 71.1 (CH), 68.6 (CH); IR (neat): 3946 (m), 3690 (vw), 3058 (vs), 2981 (s), 2676 (w), 2295 (s), 1418 (vs) 1266 (vs), 1150 (vw), 896 (s), 705 (s); MS (EI): 372 (M^+), 370, 307, 252, 224, 187, 158, 141, 121, 93, 84; HRMS (EI): Calc. For $C_{20}H_{16}{}^{56}FeN_2O_2$: 372.0561. Found: 372.0563.

4.4.4. Reaction of (2-formyl-1-chlorovinyl)ferrocene (21) with 4-hydrazinobenzoic acid (22F) (Table 3, Entry F). General Procedure was followed by using (2-formyl-1-chlorovinyl)ferrocene **(21)** (100 mg, 0.363 mmol), 4-Hydrazinobenzoic acid **(22F)** (165.68 mg, 1.089 mmol). After chromatographic purification, the purple colored fraction (R_f = 0.329 in 1:1 hexane/ethyl acetate) was collected to give **23F** (63 mg, 47%).

(23F): ^{1}H-NMR ($CDCl_3$): δ 10.07 (s, OH), 8.00 (d, 2H, *J* = 7.5 Hz), 7.86 (d, 1H, *J* = 8.5 Hz), 7.05 (d, 2H, *J* = 7.5 Hz), 6.68 (d, 1H, *J* = 8.5 Hz), 4.63 (t, 2H, *J* = 1.7 Hz), 4.37 (t, 2H, *J* = 1.7 Hz), 4.19 (s, 5H); ^{13}C-NMR ($CDCl_3$): δ 170.5 (C), 139.1 (CH), 137.0 (C), 136.0 (C), 132.3 (CH), 120.3 (C), 117.8 (CH), 111.9 (CH), 83.0 (C), 70.2 (CH), 70.1 (CH), 67.4 (CH); IR (neat): 3052 (w), 2920 (s), 2860 (w), 2308 (vw), 1720 (s), 1687 (s), 1603 (s), 1261 (vs), 1163 (s), 849 (vw); MS (EI): 372 (M^+), 370, 329, 307, 251, 234, 205, 178, 137, 120, 65, 56; HRMS (EI): Calc. For $C_{20}H_{16}{}^{56}FeN_2O_2$: 372.0561. Found: 372.0559.

4.4.5. Reaction of (2-formyl-1-chlorovinyl)ferrocene (21) with 2-hydrazino pyridine (22G) (Table 3, Entry G). General Procedure was followed by using (2-formyl-1-chlorovinyl)ferrocene **(21)** (100 mg, 0.363 mmol), 2-hydrazino pyridine **(22G)** (118.83 mg, 1.089 mmol). After chromatographic purification, the orange/red colored fraction (R_f = 0.4 in 1:1 hexane/ethyl acetate) was collected to give 1-pyridinyl-5-ferrocenylpyrazole **(23G)** (71.4 mg, 60%).

(23G): ^{1}H-NMR ($CDCl_3$): δ 8.11 (ddd, 1H, *J* = 8.6, *J* = 6.8, *J* = 1.8 Hz), 7.87 (d, 1H, *J* = 9.0 Hz), 7.58 (ddd, 1H, *J* = 8.6, *J* = 7.5, *J* = 1.8 Hz), 7.22 (d, 1H, *J* = 8.5 Hz), 6.77 (ddd, 1H, *J* = 8.6, *J* = 7.5, *J* = 1.8 Hz), 6.65 (d, 1H, *J* = 9.0 Hz), 4.58 (t, 2H, *J* = 1.9 Hz), 4.35 (t, 2H, *J* = 1.9 Hz), 4.18 (s, 5H); ^{13}C-NMR ($CDCl_3$): δ 155.9 (C), 146.9 (CH), 139.1 (CH), 138.5 (CH), 136.7 (C), 118.1 (CH), 115.8 (CH), 107.6 (CH), 83.4 (C), 70.1 (CH), 70.0 (CH), 67.3 (CH); IR (neat): 3940 (s), 3586 (b), 3058 (vs), 2983 (s), 2682 (s), 1674 (vw), 1604 (w), 1424 (s), 1261 (s), 896 (s), 748 (s); MS (EI): 329 (M^+), 302, 300, 271, 264, 237, 210, 184, 156, 149, 120, 89, 67; HRMS (EI): Calc. For $C_{18}H_{15}{}^{56}FeN_3$: 329.0615. Found: 329.0613.

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APPENDIX A

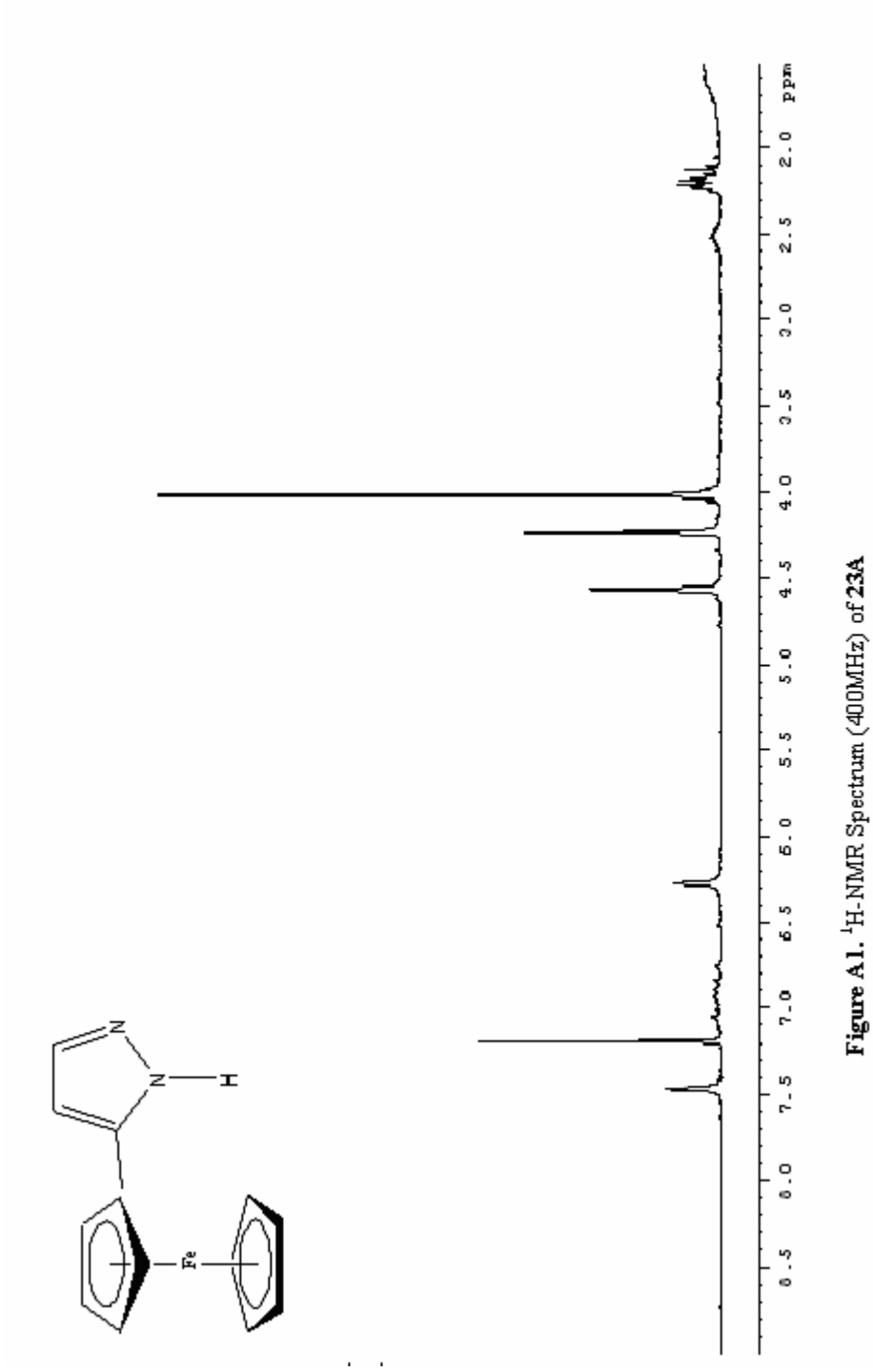

Figure A1. ^{1}H-NMR Spectrum (400MHz) of **23A**

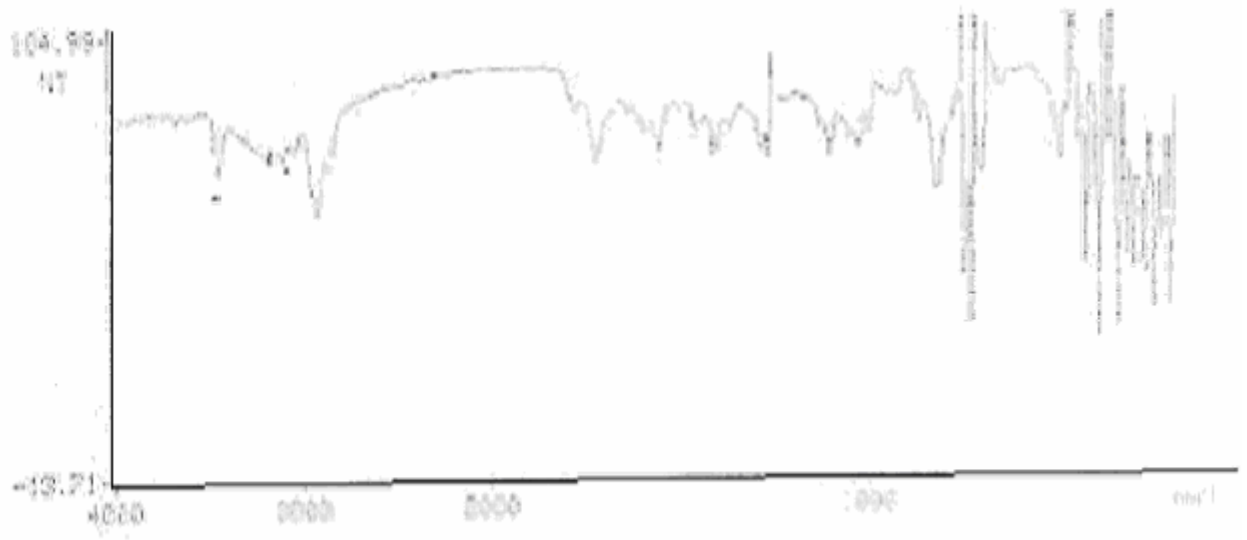

Figure A2. FT-IR Spectrum of **23A**

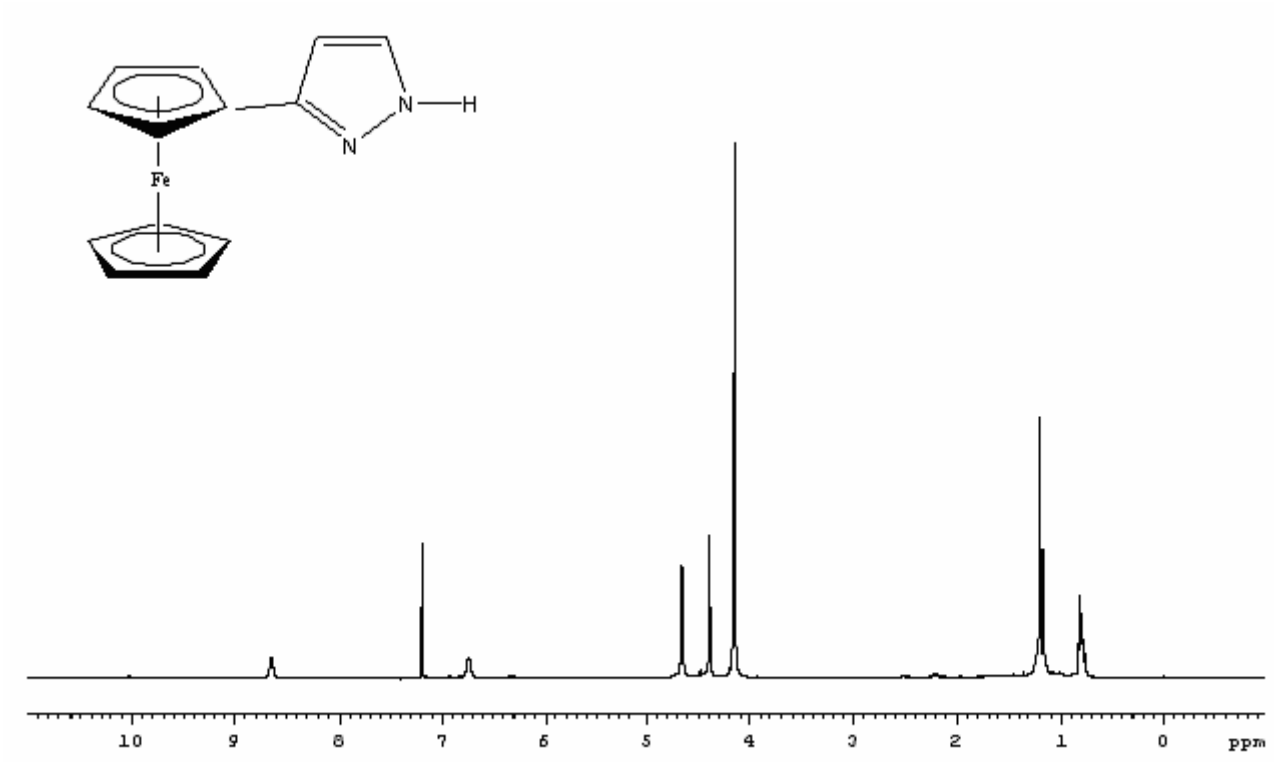

Figure A3. ^{1}H-NMR Spectrum (400 MHz) of **25A**

Figure A4. ^{13}C-NMR Spectrum(100 MHz) of **25A**

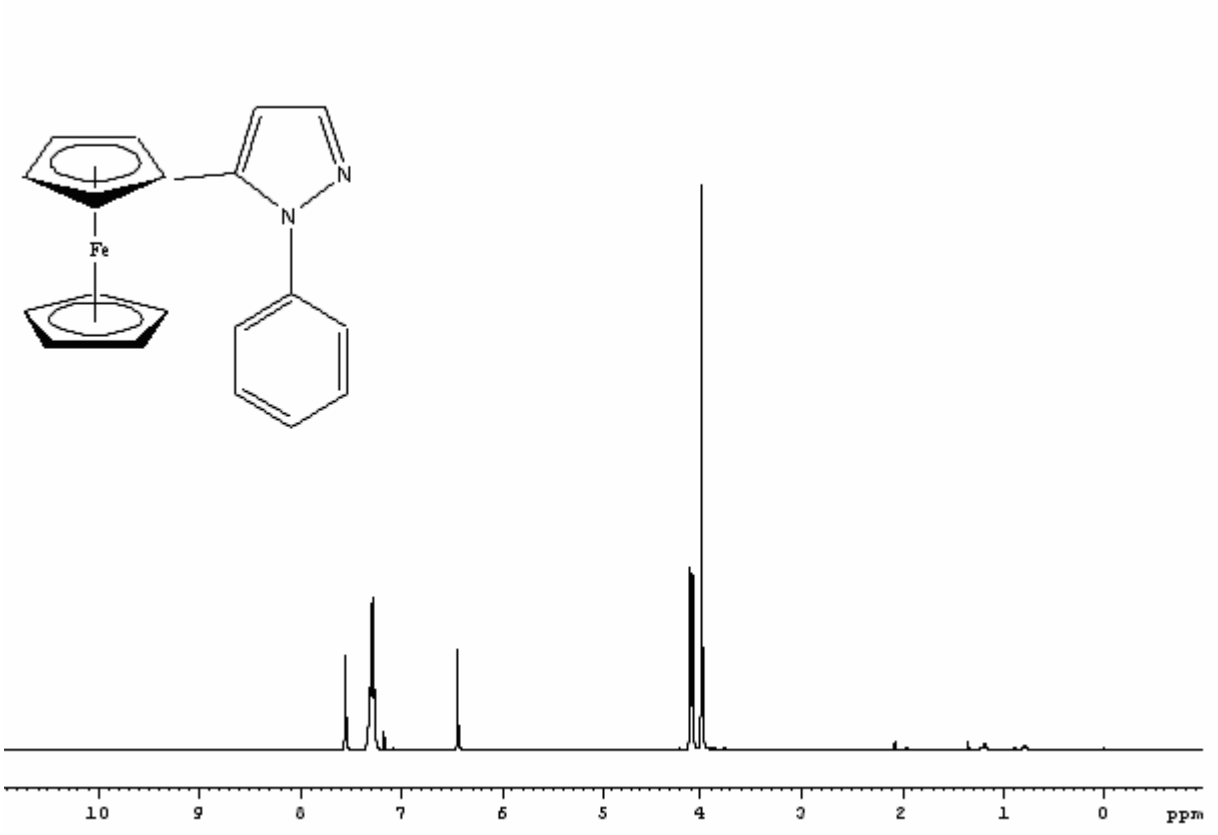

Figure A5. ^{1}H-NMR Spectrum (400 MHz) of **23B**

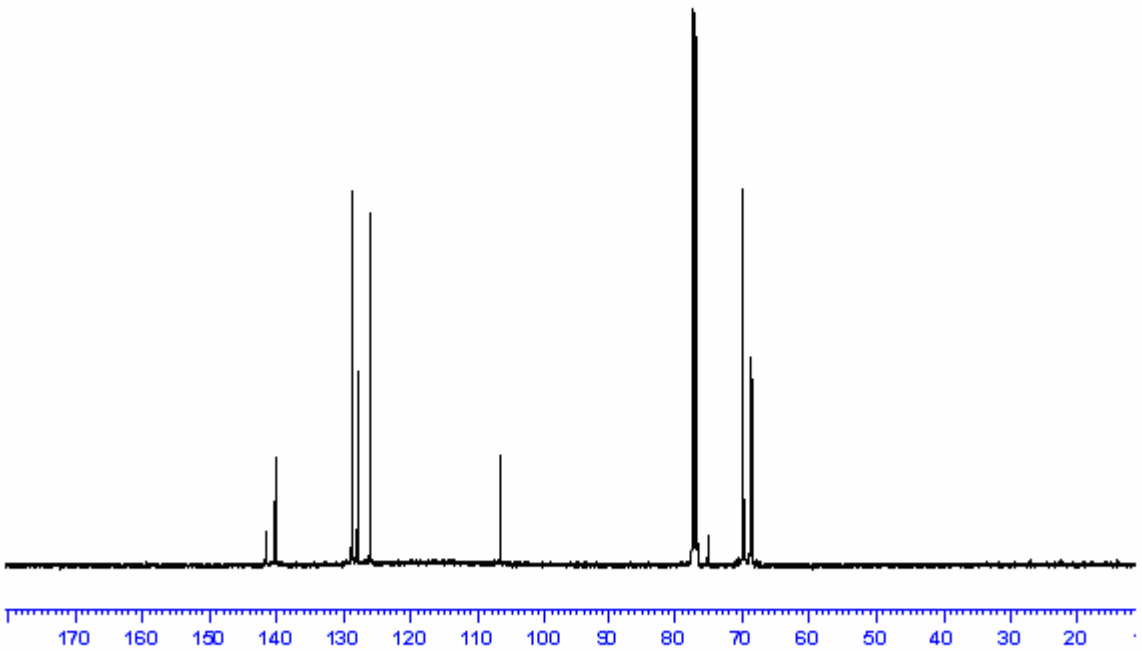

Figure A6. ^{13}C-NMR Spectrum(100 MHz) of **23B**

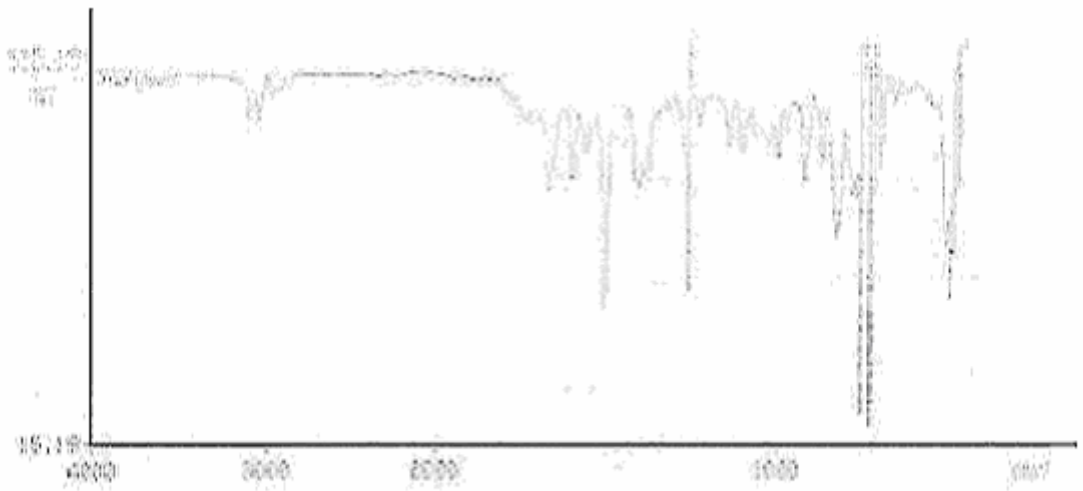

Figure A7. FT-IR Spectrum of **23B**

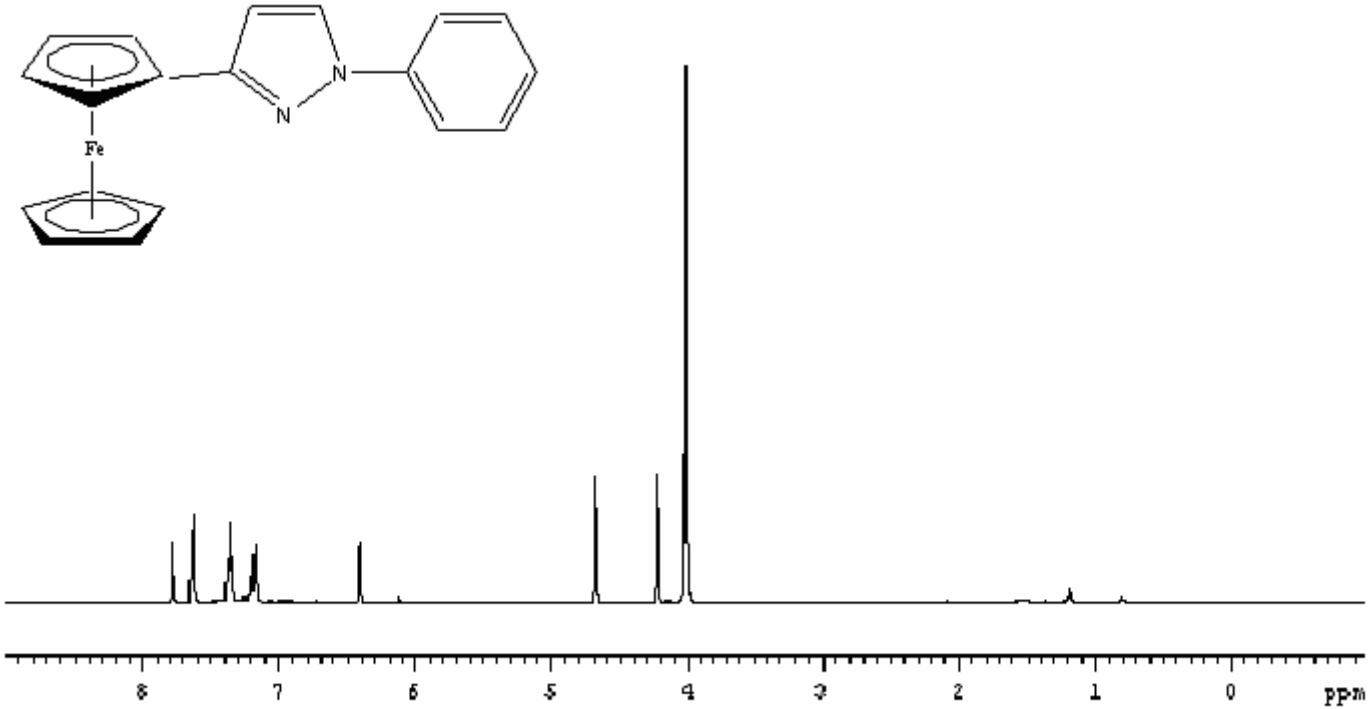

Figure A8. ^{1}H-NMR Spectrum (400 MHz) of **25B**

Figure A9. ^{13}C-NMR Spectrum(100 MHz) of **25B**

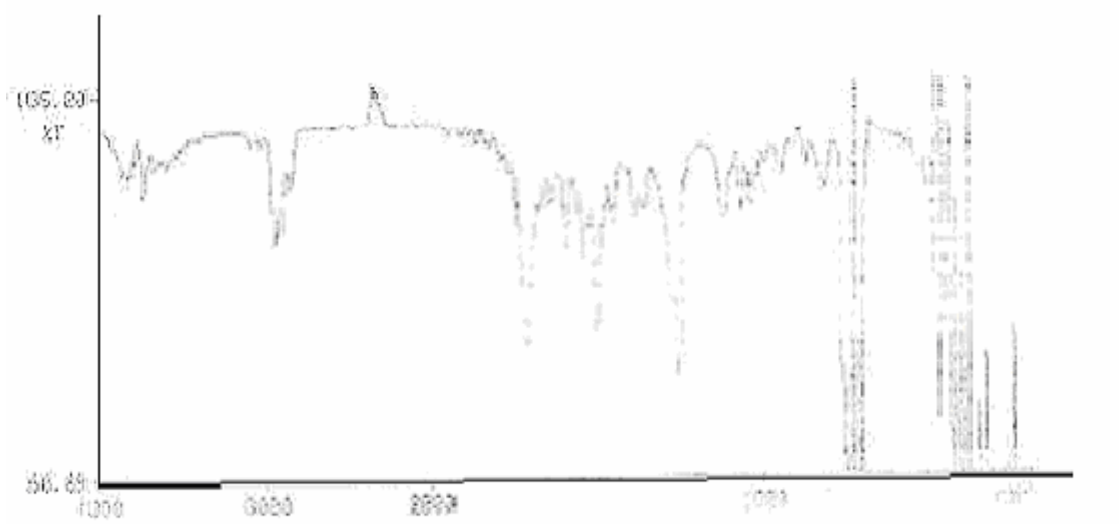

Figure A10. FT-IR Spectrum of **25B**

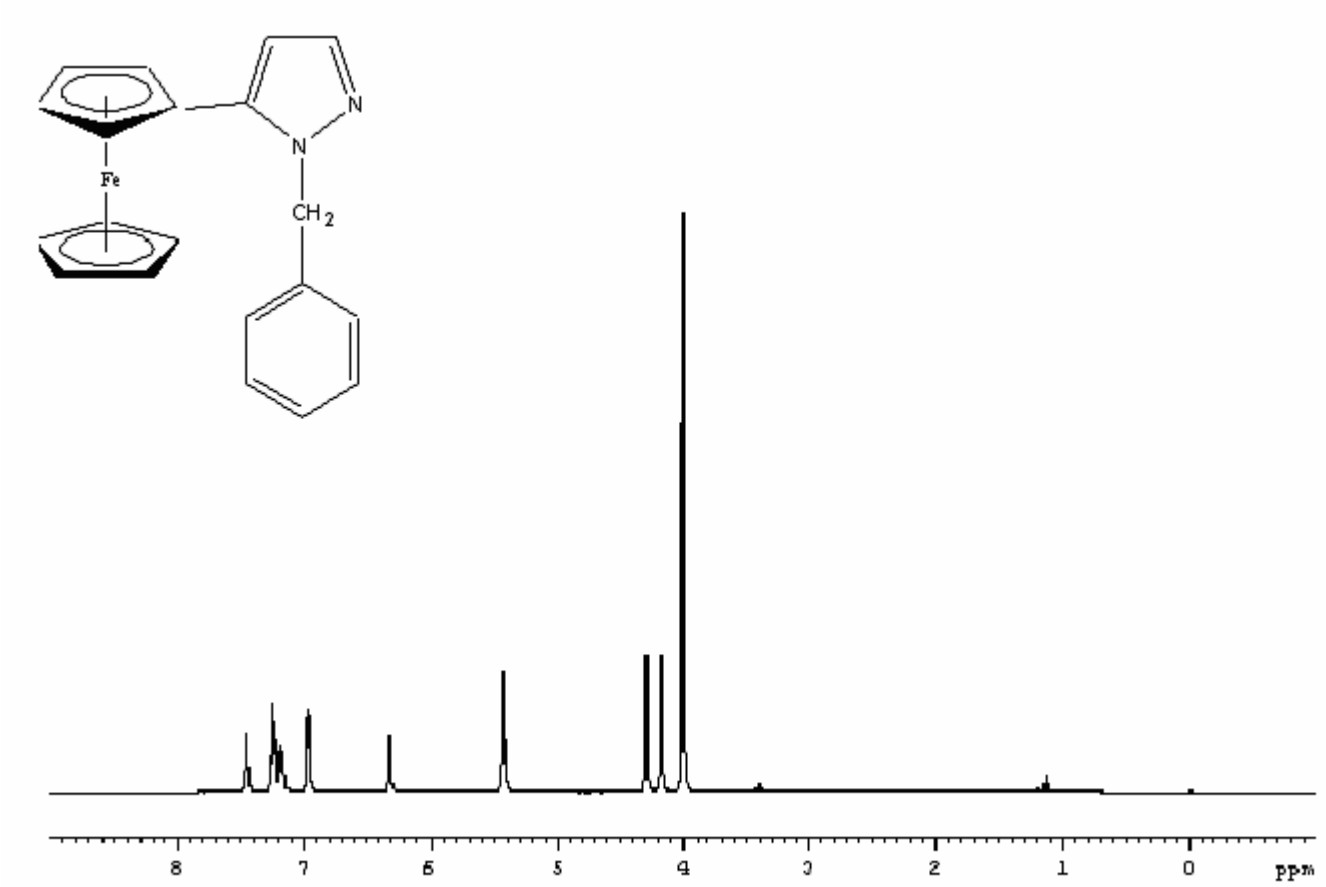

Figure A11. ^{1}H-NMR Spectrum (400 MHz) of **23C**

Figure A12. ^{13}C-NMR Spectrum(100 MHz) of **23C**

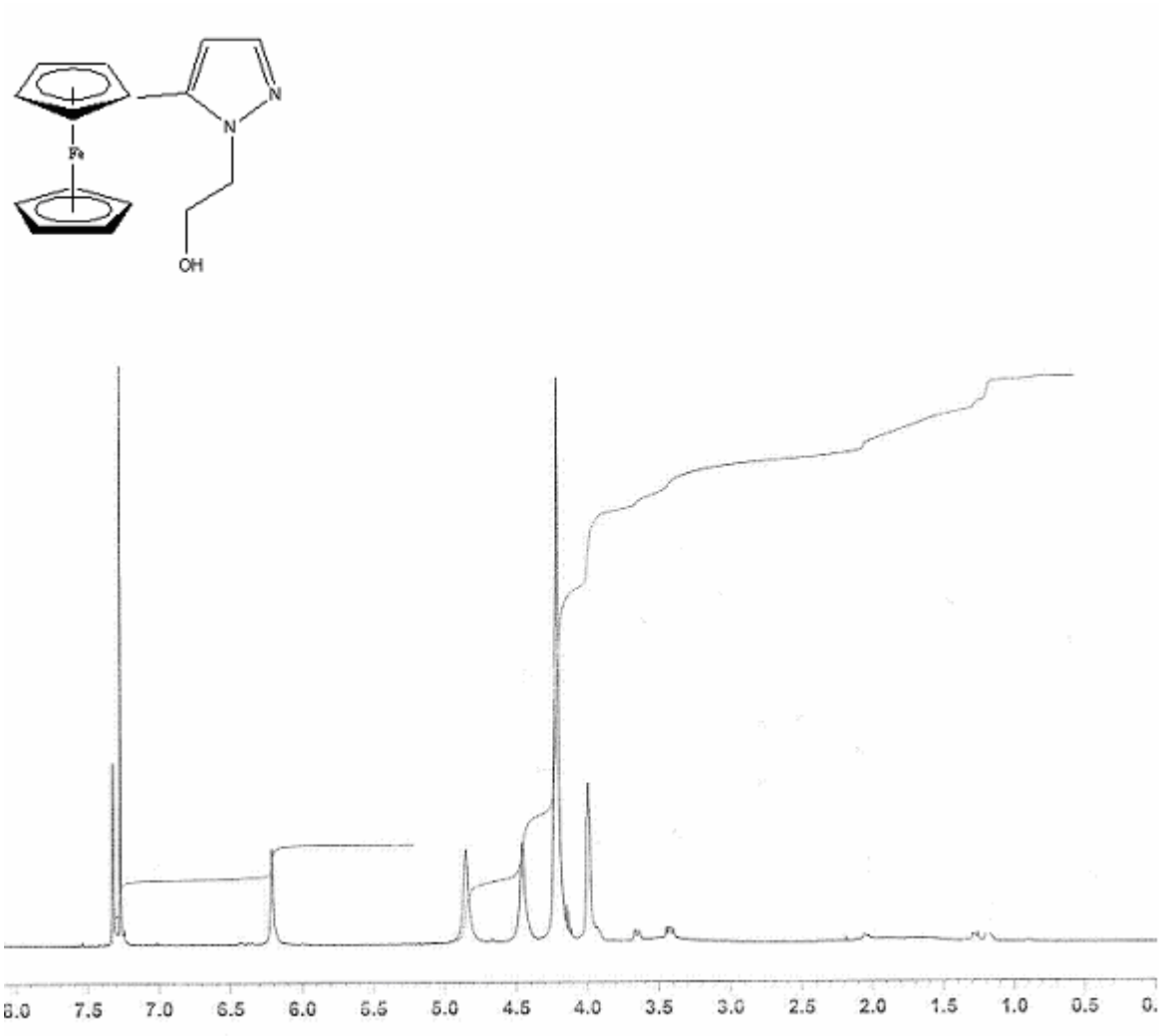

Figure A13. ^{1}H-NMR Spectrum (400 MHz) of **23D**

Figure A14. ^{13}C-NMR Spectrum(100 MHz) of **23D**

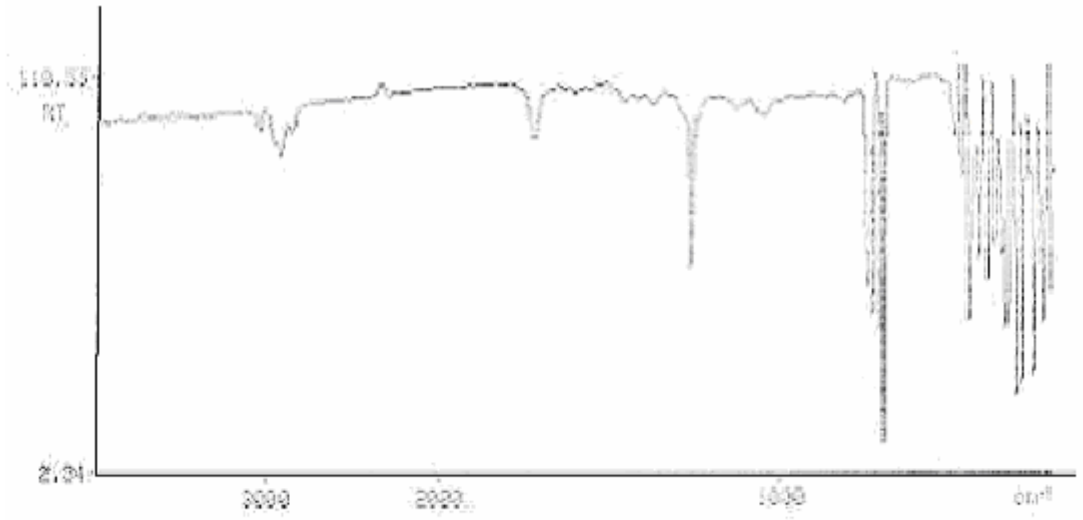

Figure A15. FT-IR Spectrum of 23D

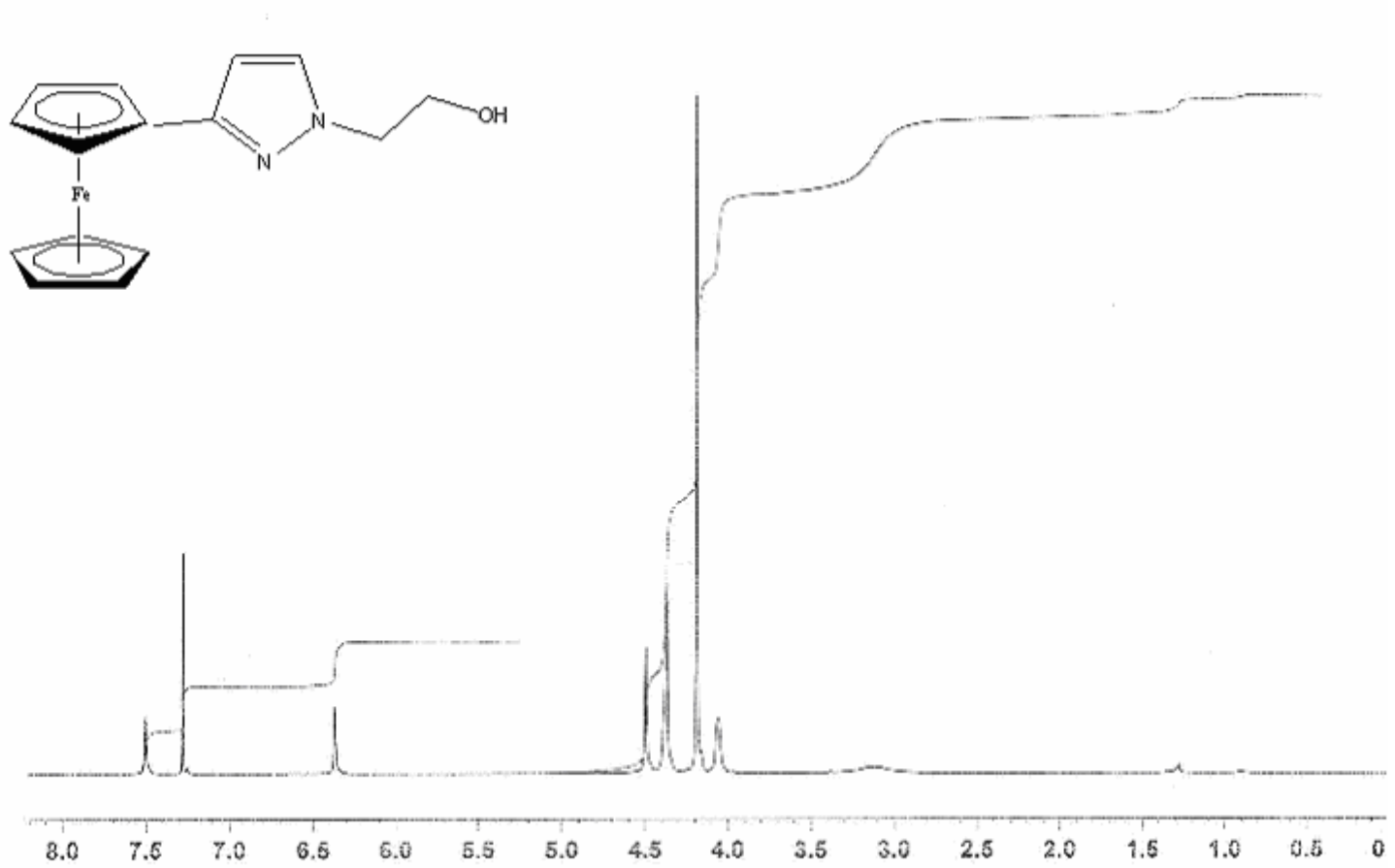

Figure A16. ^{1}H-NMR Spectrum (400 MHz) of **25D**

Figure A17. ^{15}C-NMR Spectrum (100 MHz) of **25D**

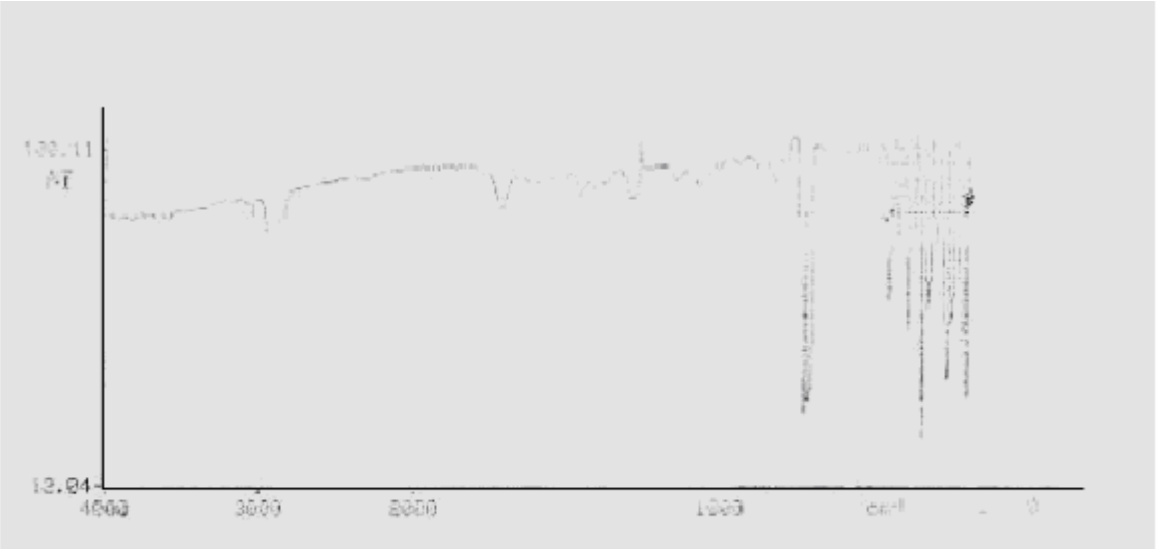

Figure A18. FT-IR Spectrum of **25D**

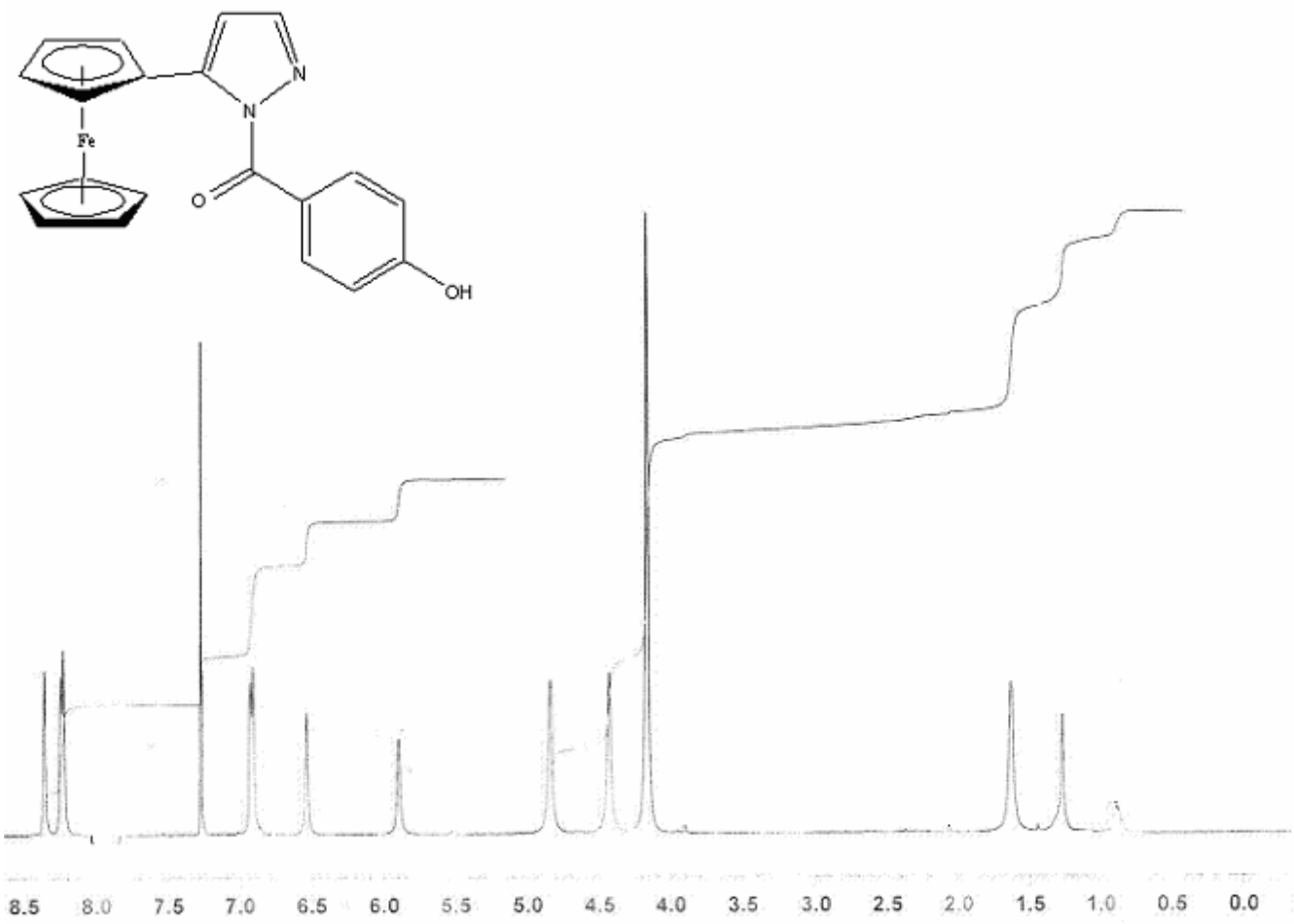

Figure A19. ^{1}H-NMR Spectrum (400 MHz) of **23E**

Figure A20. ^{13}C-NMR Spectrum (100 MHz) of **23E**

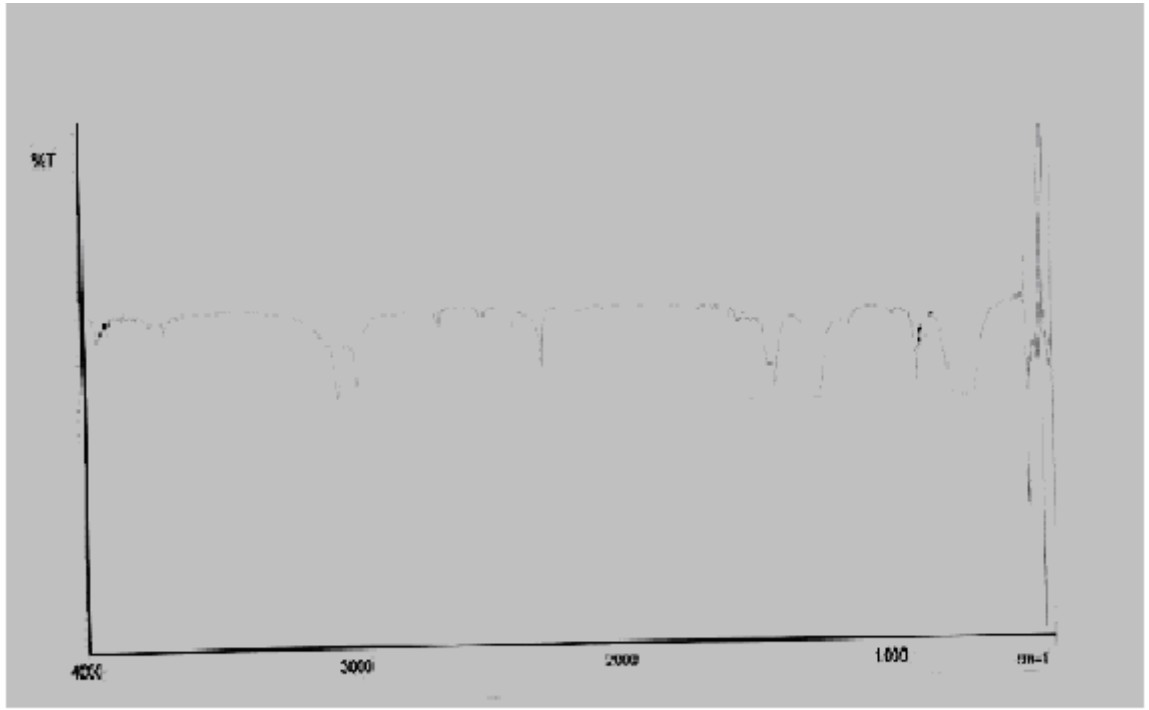

Figure A21. FT-IR Spectrum of **23E**

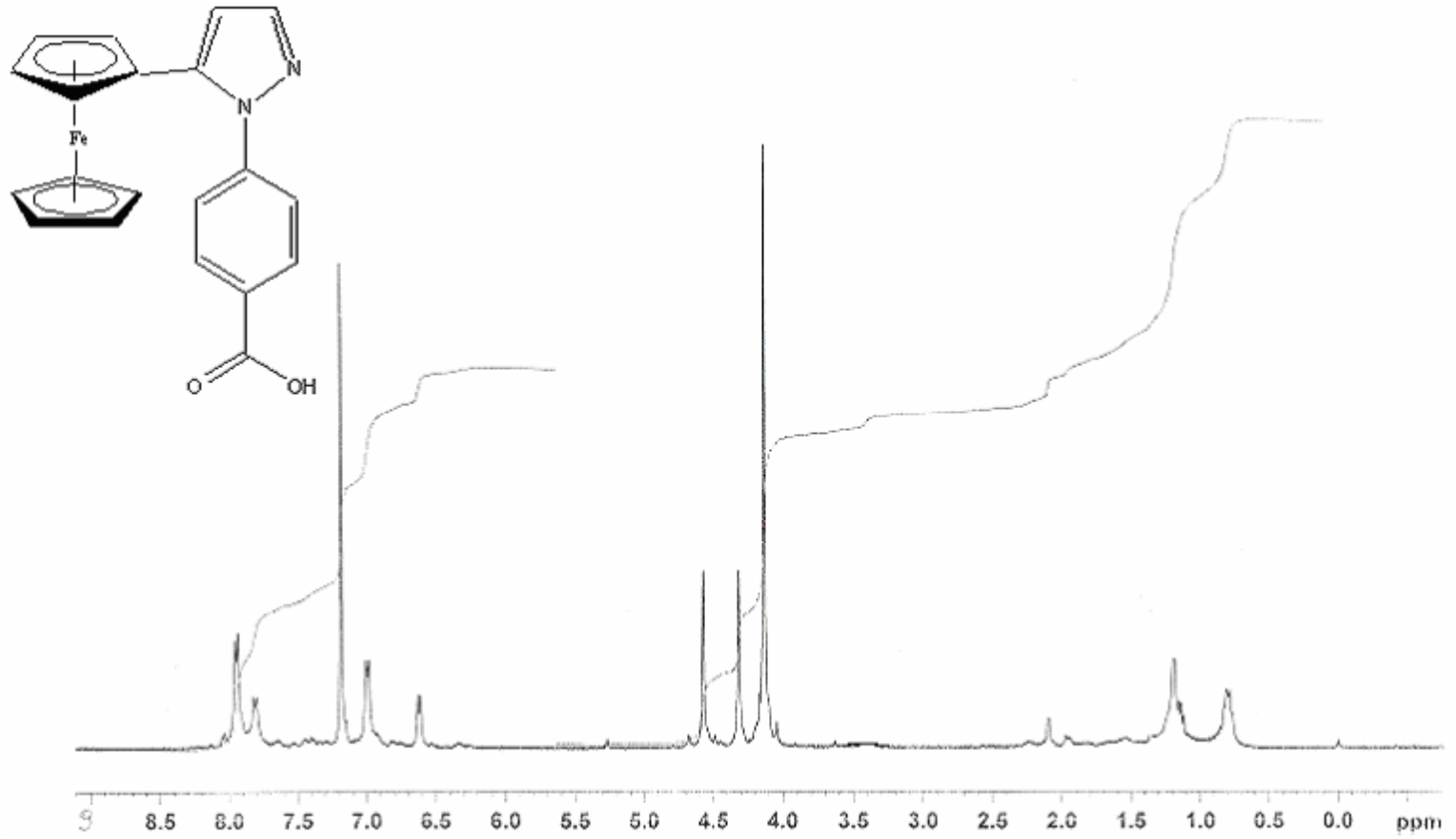

Figure A22. ^{1}H-NMR Spectrum (400 MHz) of **23F**

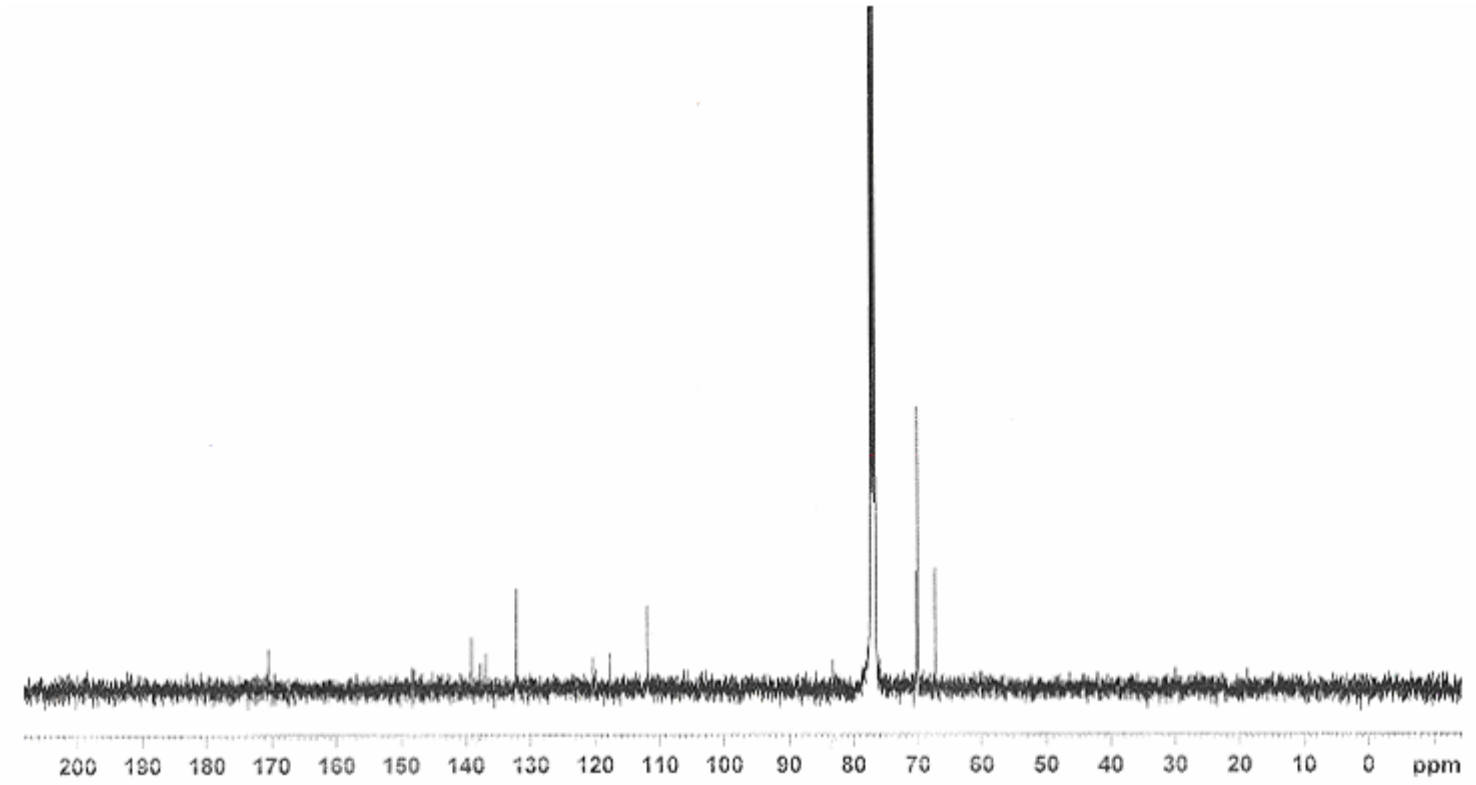

Figure A23. ^{13}C-NMR Spectrum (100 MHz) of **23F**

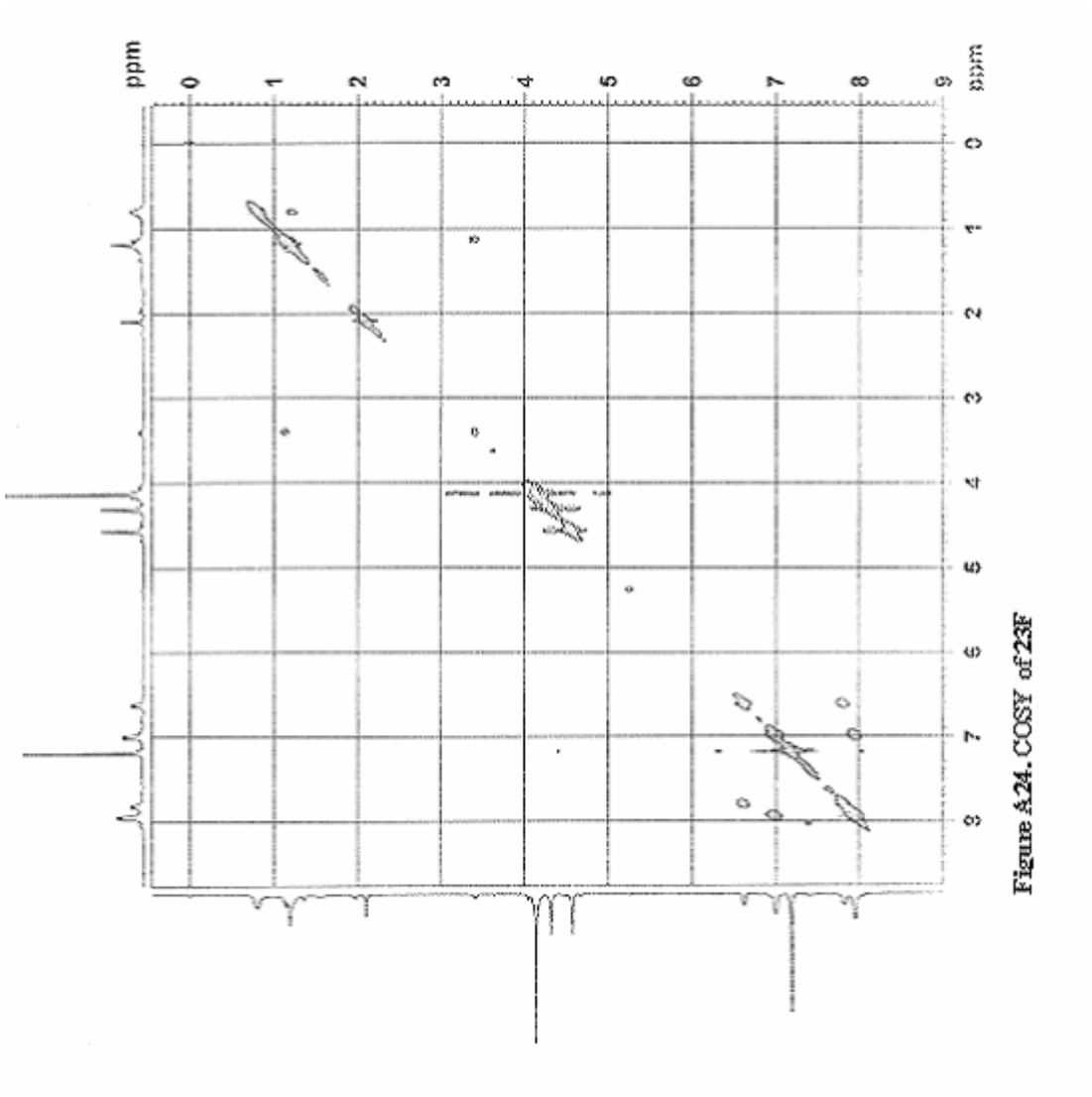

Figure A24. COSY of 23F

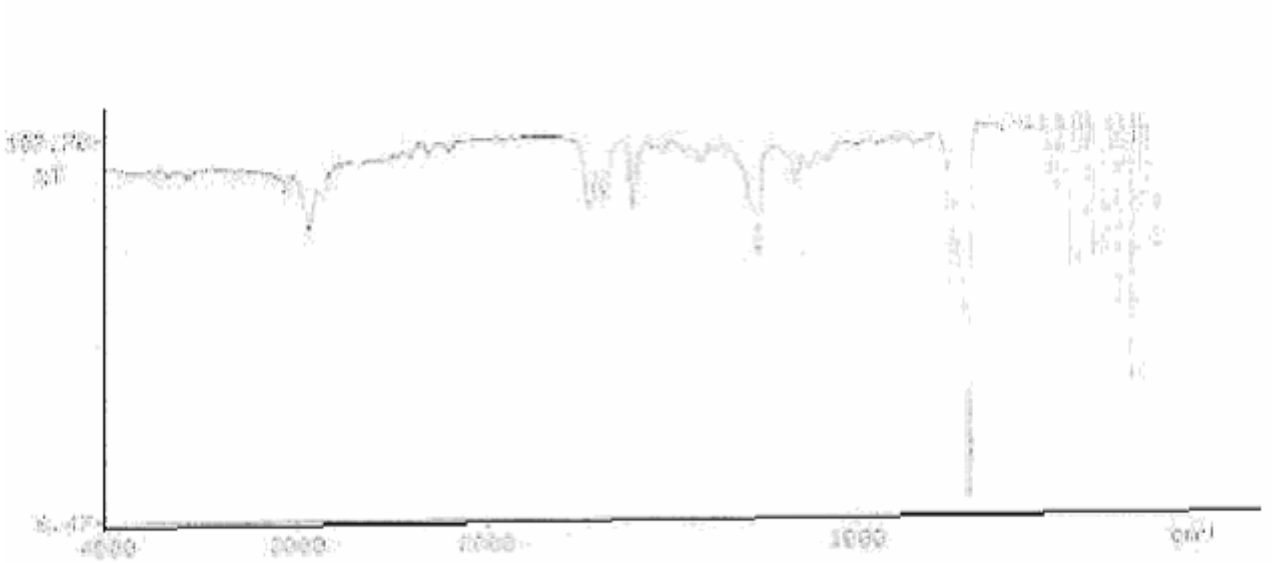

Figure A25. FT-IR Spectrum of **23F**

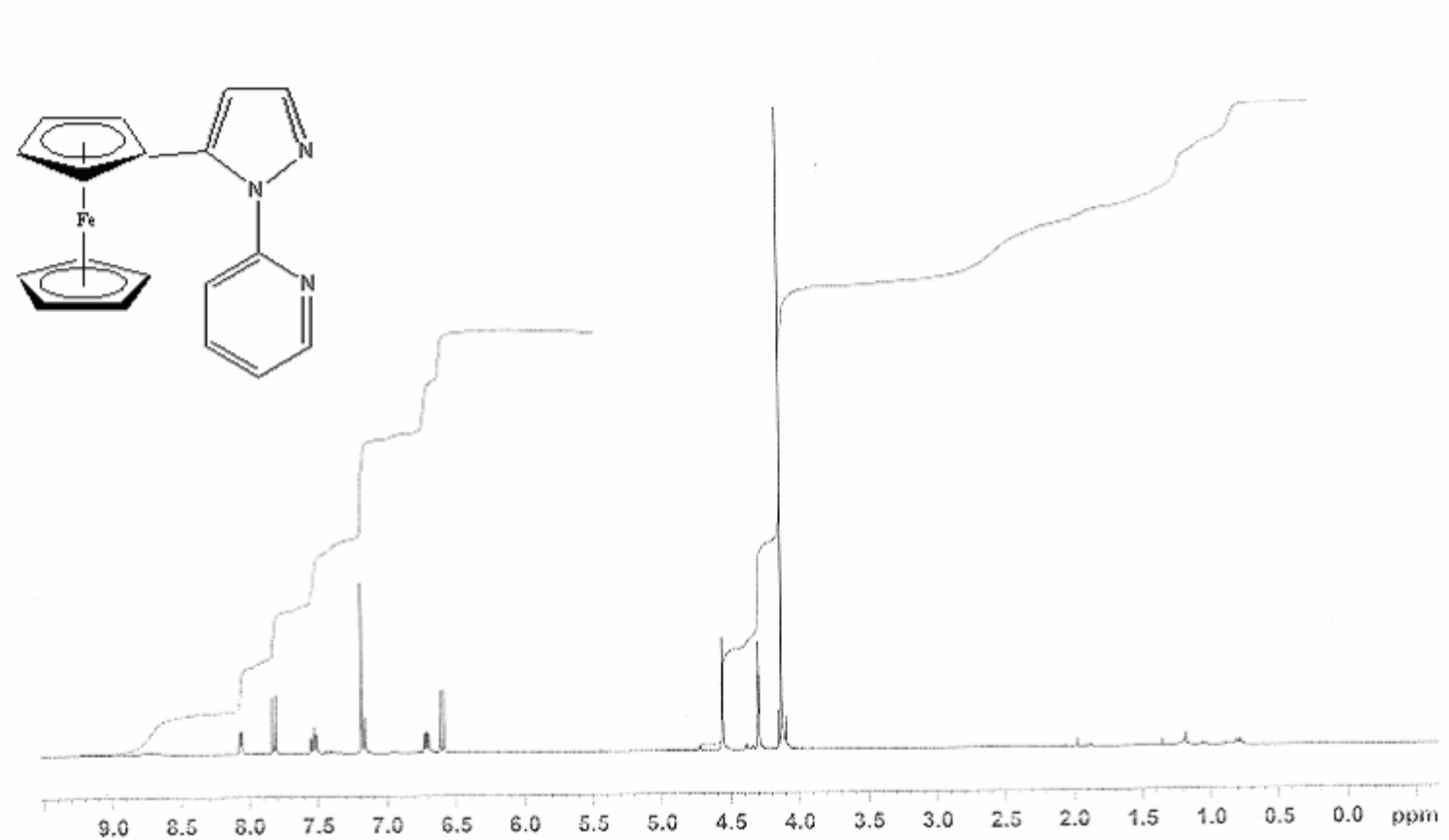

Figure A26. ^{1}H-NMR Spectrum (400 MHz) of **23G**

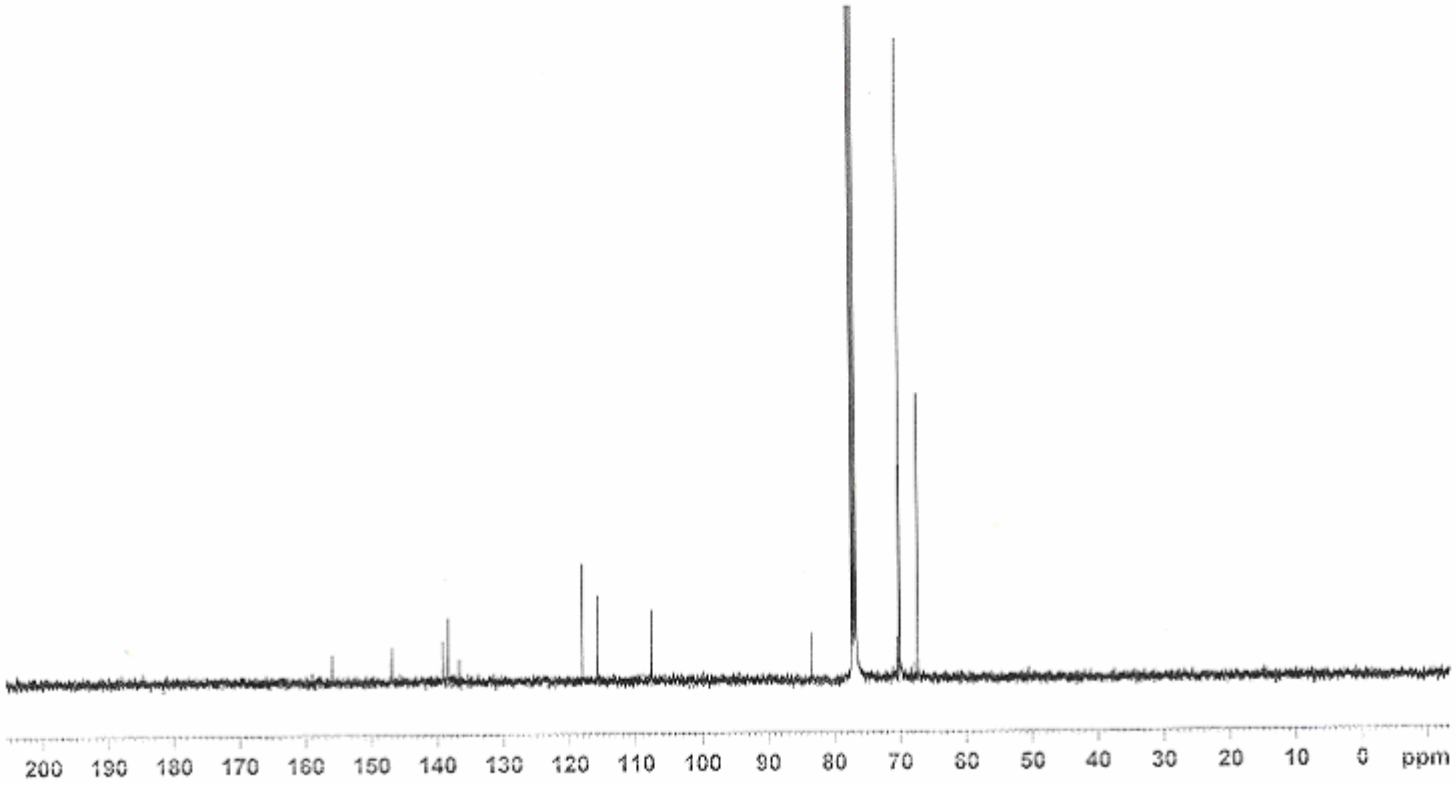

Figure A27. ^{13}C-NMR Spectrum (100 MHz) of **23G**

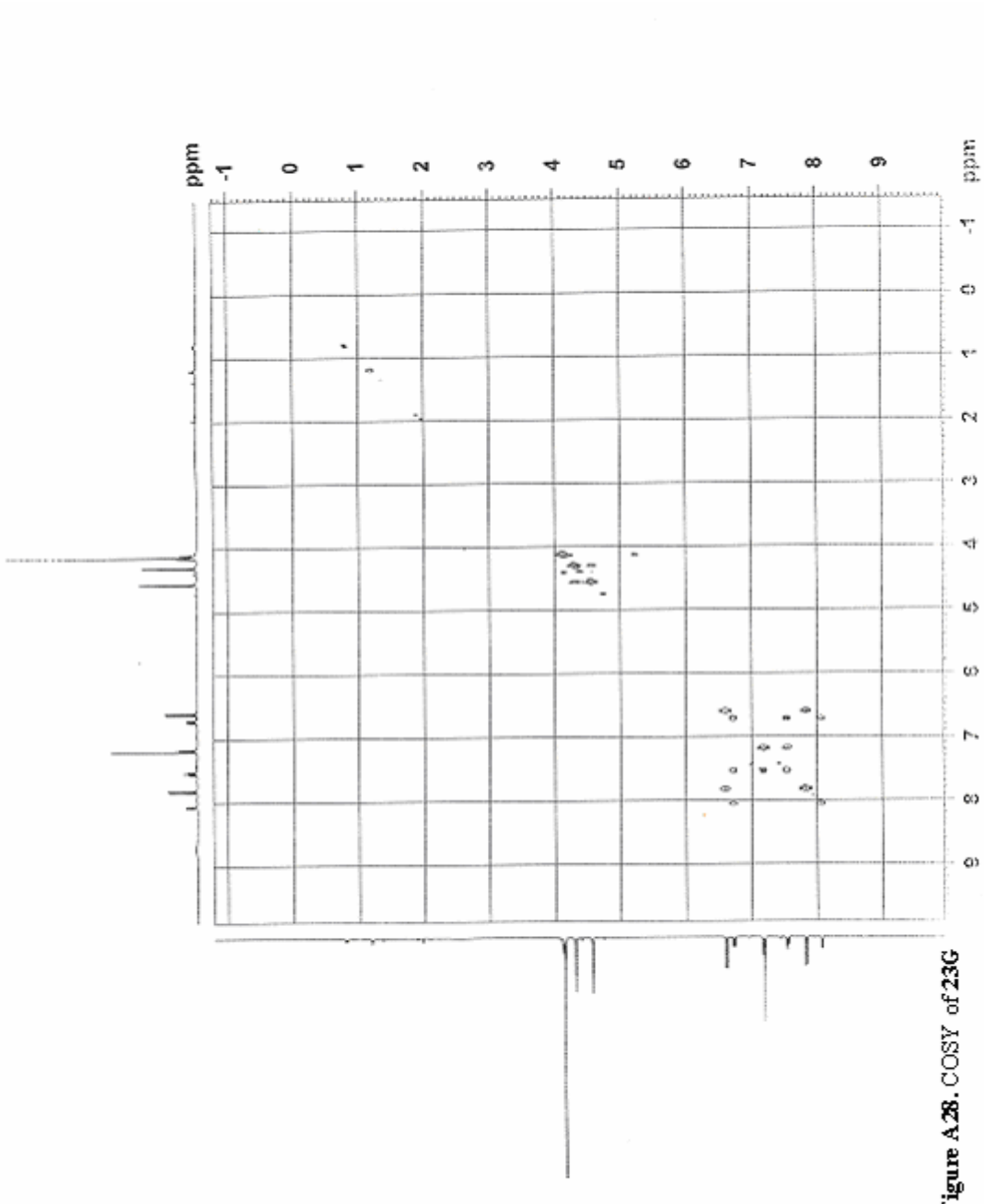

Figure A28. COSY of **23G**

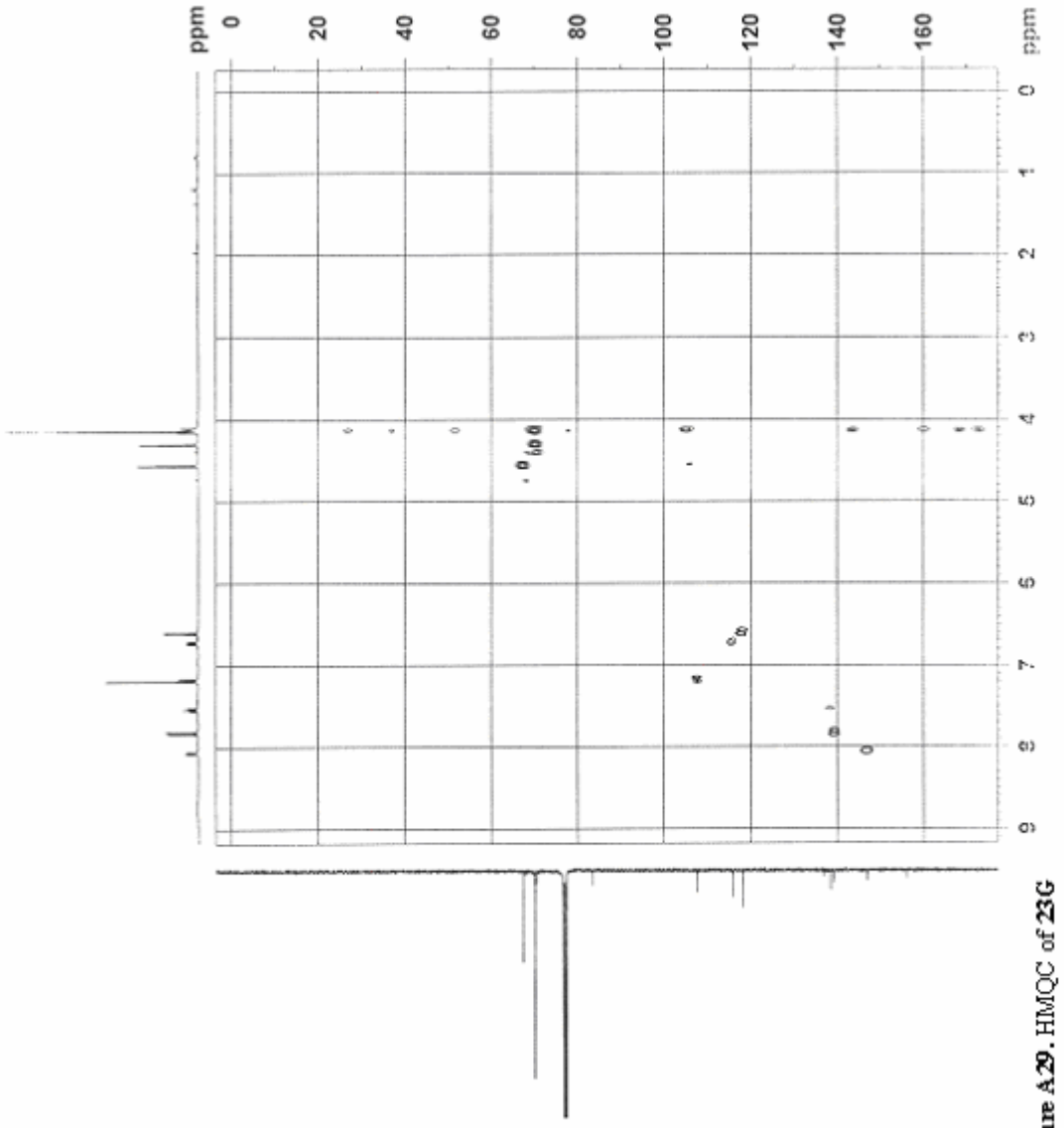

Figure A29. HMQC of **23G**

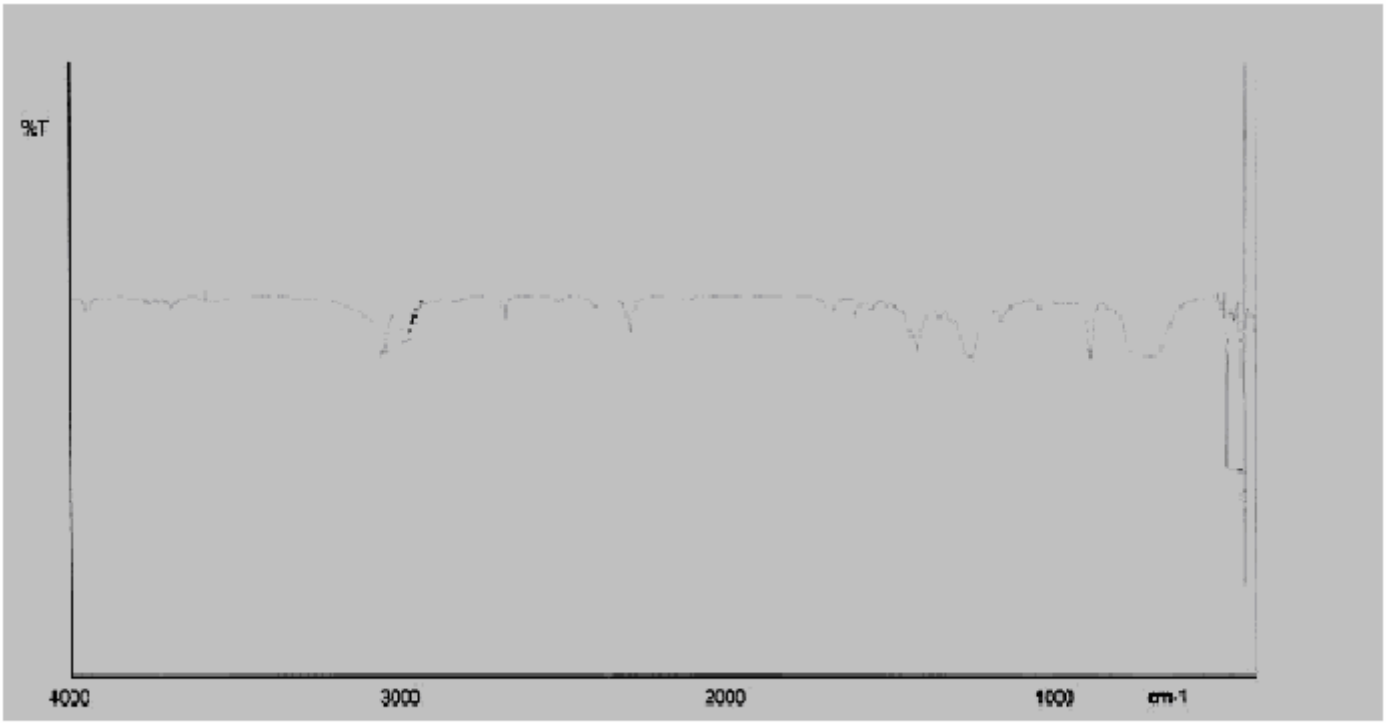

Figure A30. FT-IR Spectrum of **23G**