SYNTHESIS AND CHARACTERIZATION OF FERROCENE CONTAINING ORGANOMETALLIC COMPOUNDS

By

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CERTIFICATE

This is to certify that the dissertation entitled" **SYNTHESIS AND CHARACTERIZATION OF FERROCENE CONTAINING ORGANOMETALLIC COMPOUNDS**" being submitted by *NISHIBANYA BEHERA* to the Department of Chemistry, National Institute of Technology, Rourkela, Orissa, for the award of the degree of Master of Science is a record of bonafide research carried out by her under my supervision and guidance. To the best of my knowledge, the matter embodied in the dissertation has not been submitted to any other University / Institute for the award of any Degree or Diploma.

N.I.T. Rourkela.

Date: *Dr. Saurav Chatterjee*

(Supervisor)

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Rourkela

Date: (Nishibanya Behera)

Abstract

Ferrocene based chalcones [(η^5-$C_5H_4)_2$Fe {COCH=CHC_6H_5}] were prepared from the reaction of 1,1'- Diacetylferrocene with Benzaldehyde. The ferrocenyl pyrazolines are synthesized from the reaction of [(η5-$C_5H_4)_2$Fe {COCH=CHC_6H_5}] and Hydrazine Hydrate and Phenyl Hydrazine . Characterization of these organometallic compounds was carried out using FTIR and ^{1}HNMR. The results indicate that these compounds are successfully formed and can be explored in future research work especially as biologically active agents and molecular sensors .

CHAPTER - 1

INTRODUCTION

1.1 Ferrocene

Ferrocene or di(η5-cyclopentadienyl) iron(II) was accidentally discovered by Peter L. Pauson and his graduate student Tom Kealy in 1951 when they attempted the reductive coupling of the Grignard reagent cyclopentadienyl magnesium bromide in the presence of ferric chloride[1]. The unique sandwich structure of ferrocene was first predicted by infrared and nuclear magnetic resonance spectroscopies and later confirmed by X-ray crystallography in 1954[1].

According to the literature survey in 1954, ferrocene comprises a ferrous ion (Fe^{2+}) coordinated to two cyclopentadienyl (Cp) rings. The *d* orbitals on Fe^{2+} are coordinated into the π orbitals on the two cyclopentadienyl radicals to form a unique sandwich structure. It was stable to high temperatures and unaffected by water, strong acids and alkalis. The unique stability of ferrocene is attributed to the distribution of 18 π electrons in the e B2gB and a B1gB non bonding molecular orbitals (Fig. 1).

Ferrocene behaves like an aromatic compound. It is susceptible to direct electrophilic substitution reactions, giving rise to a variety of substituted ferrocenes. Ferrocene has provided a very rich chemistry as a super aromatic compound and had led to multiple applications in the field of materials and molecular engineering, molecular ferromagnets [2], modified electrodes for redox catalysis (titration of glucose in blood), polymers and dendritic electrochemical sensors for molecular recognition and antitumor drugs due to its interesting redox properties. At room temperature ferrocene is an air stable orange colored solid and it can be oxidized to blue-green ferrocenium cation, $[(C_5H_5)_2Fe]^+$. The inter-ring spacing in ferrocene is 332 pm and the distance between the Fe—C bond is 204 pm. The inter-ring spacing in ferrocene is 332 pm and the distance between the Fe—C bond is 204 pm. Ferrocene at room temperature crystallizes in a monoclinic form, at T<164K in a triclinic form and in an orthorhombic modification at T<110K. In the monoclinic form disorder phenomena feign a staggered conformation (D_5d) of individual sandwich molecules. In the triclinic form, the molecules deviate from the eclipsed conformation (D_5d) by 9° while in the orthorhombic form the rings are fully eclipsed (D_5h). In the gas phase ferrocene also adopts an eclipsed conformation, the rotational barrier being small.

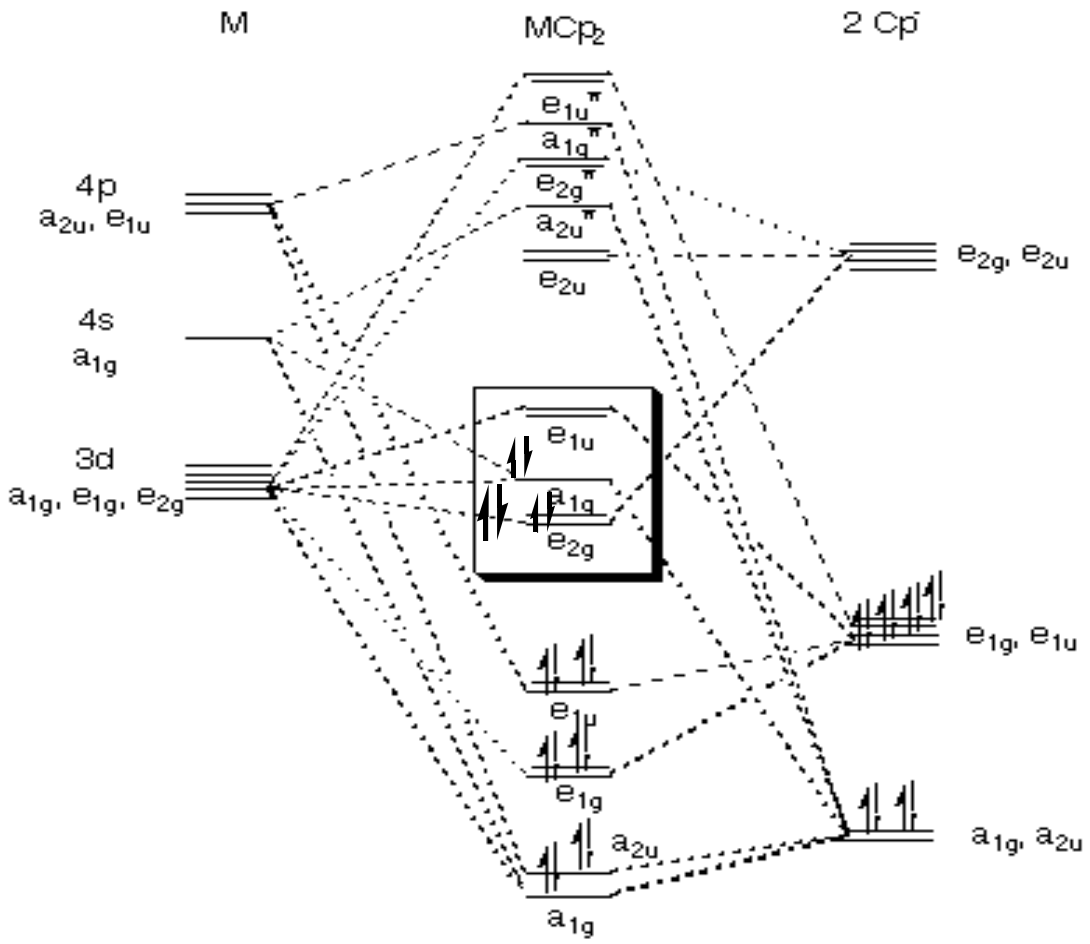


Fig 1

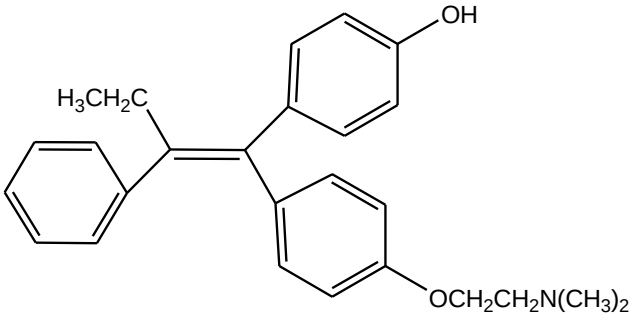
Ferrocene can act as a one electron donor undergoing oxidation to the ferrocenium ion. This has led to the use of ferrocene as a model for sensors and non-linear optical materials[2]. Compared to other metallocenes, ferrocene is more widely employed in drug design. This is prompted by several factors, foremost of which is the reputation of ferrocene as a "safe" metallocene. Acute and chronic tests of ferrocene and several of its derivatives attested to the relative safety of these compounds in many mammalian species (dogs, rats, mice, monkeys)[3,4,5].

1.2 Medicinal chemistry of ferrocene

Medicinal chemists are also open to the inclusion of ferrocene into their drug design strategies because of the novelty introduced by its presence. Ferrocene is a stable, nontoxic compound and haveing good redox properties. Now research is going on to design new compounds which are active against a wide range of cancers and have lesser side effects. Ferrocenes are also known to exhibit a wide range of biological activity and also ferrocene has

attracted special attention since it is a neutral chemically stable and non-toxic molecule. Many ferrocenyl compounds display interesting, cytotoxic, antitumor, antimalarial, anti-fungal and DNA cleaving activities. There are many examples in the literature citing the use of ferrocene in drug design strategies. In one study on some non-steroidal anti-inflammatory agents, the replacement of the aromatic ring by ferrocene did not improve anti-arthritic or platelet aggregatory activities in the resulting compounds[6]. Investigations with ferrocene-containing penicillins, cephalosporins and rifamycins showed that the inclusion of ferrocene did not confer any special advantage [7, 8]. On the other hand, significant changes in activity profiles had been recorded when ferrocene was introduced into established drugs like tamoxifen and chloroquine.

Ferrocenyl derivatives are among the most potential compounds which can be used in cancer research. Cancer is a class of disease characterized by uncontrolled cell proliferation and the ability of these cells to invade other tissues. Cancer can be treated by several methods including chemotherapy, which is one of the main weapons in the fight of cancer. Chemotherapy is the treatment of cancer with drugs (anticancer drugs) that destroy the cancerous cells. In the last decade a revolution in the cancer treatment has been enacted by the organometallic chemists. Many ferrocenyl derivatives show good results as antitumor agents and some of them are now in clinical trials. Ferrocifens are the first molecules shown to be active against both hormone dependent and hormone independent breast cancer cells.



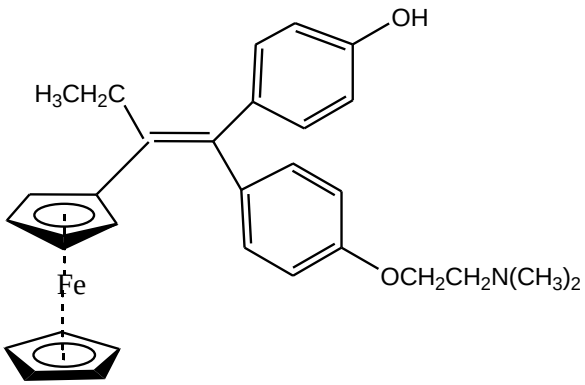


Fig.2 (a) Ferrocenyl derivative of tamoxifen **Fig.2 (b) Tamoxifen**

Ferrocene containing compounds has recently been reported to have antitumor activity due to metabolic formation of ferrocenium ions. Water soluble ferrocenyl derivatives can also be used as anti-cancer agents [9-10] (Figure-3a,3b). These compounds are more potent as an anticancer drug than water insoluble molecule.

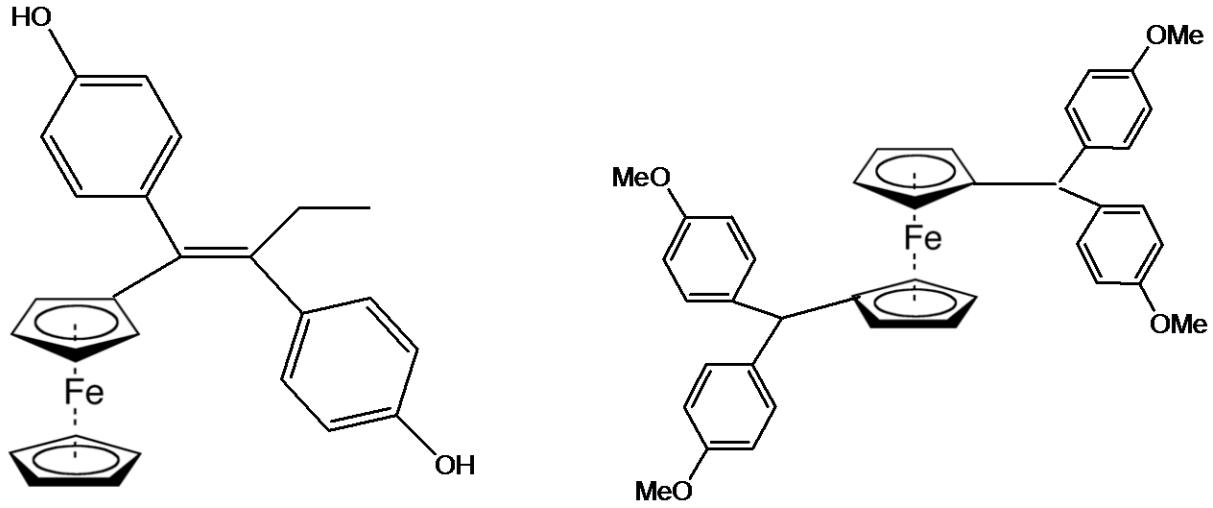


Fig.3a & 3b: Water soluble ferrocenyl derivatives as anti cancer agent.

Some examples of the most important ferrocenyl compounds that have a good activity as anti cancer agents are ferrocenium tetrafluoroborate salt[11] and ferrocenium iodate [12] as shown in Fig 4(a) & Fig 4(b).

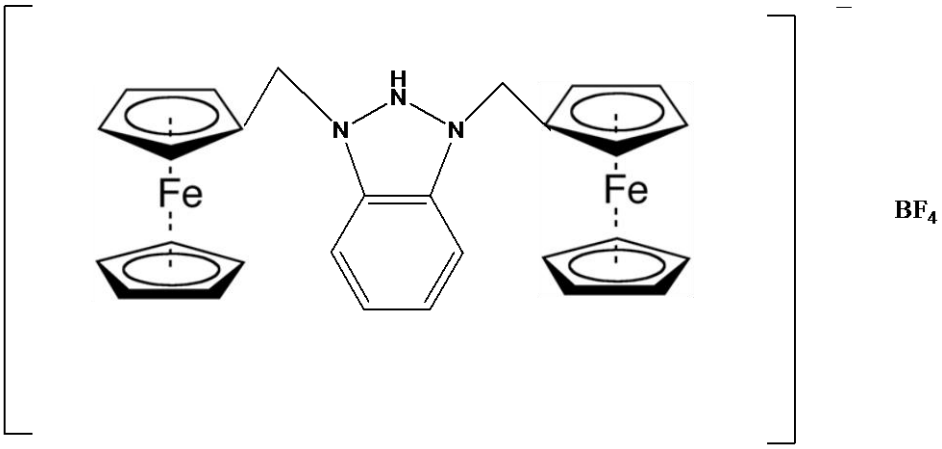


Fig.4(a):Ferrocenium tetrafluoro borate salt

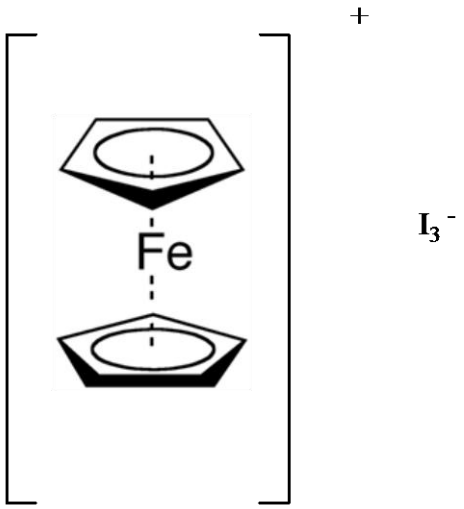
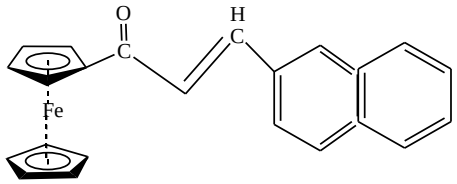


Fig.4(b) Ferrocenium tri iodate

1.3. Ferrocenyl derivatives

1.3.1 Ferrocenyl chalcones

Chalcones are a family of aromatic ketones with two aromatic groups bridged by an enone linkage (Ar–COCH=CH–Ar') [13]. The term chalcone is given to the 1,3-diphenylprop-2-en-1-one framework. Chalcones occur in nature as precursors of flavonoids. They are also readily synthesized in the laboratory and structural modifications of the chalcone template are readily achieved. The biological activities of chalcones are equally wide ranging[14,15]. Not many structural templates can claim association with such diverse pharmacological activities, of which cytotoxicity, anti-tumors, anti inflammatory, antiplasmodial, antileishmanial, antioxidant, immunosuppression are some examples. In this regard, chalcones can be regarded as a privileged structure, a term used to describe selected structural motifs capable of binding to multiple, unrelated classes of receptors or enzymes with high affinity [16] . They have a wide range of applications covering from materials with various biological activities [17–20] to non-linear optical (NLO) [21–24] and electroactive fluorescent [25,26] materials .The synthesis of chalcones is generally able to be achieved by base-catalyzed aldol condensation [27]. Ferrocenyl chalcones belong to a chalcone family in which one aromatic group (Ar or Ar') is substituted by the ferrocenyl group.

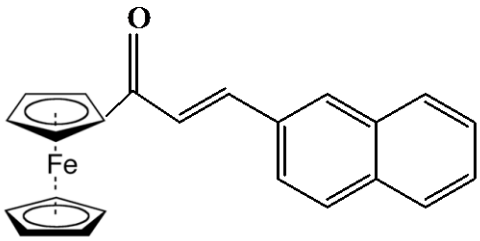


Fc-Naph

Fig.5

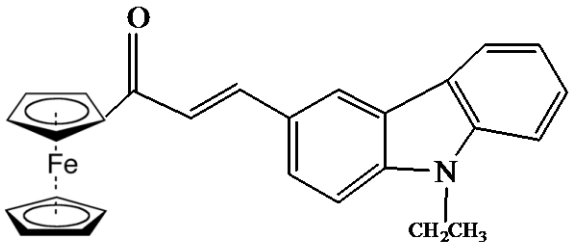
Dong-Young Noh in 2009 reported some ferrocenyl chalcones which are designed to modulate the electrochemical and optical properties of the polycyclic moieties by the electron donating ferrocenyl group through the enone linkage. They show antimalarial activity due to lipophillicity, electronic effects and size of the ferrocene ring associated with the chalcone.

Recently a series of ferrocenyl chalcones linked with aromatic and polycyclic compounds such as ferrocene,[28] naphthalene[29] and anthracene (Fig. 6a & 6b).[30] are studied because these systems were designed in order to modulate the electrochemical and optical properties of the polycyclic moieties by the electron donating ferrocenyl group through the enone linkage. The optical properties of the naphthalene and anthracene moieties were quenched by the ferrocenyl moiety which acts as a quencher.



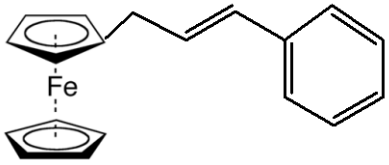
Fc-Naph

Fig 6(a)



Fc-Etcb$_2$

Fig 6(b)



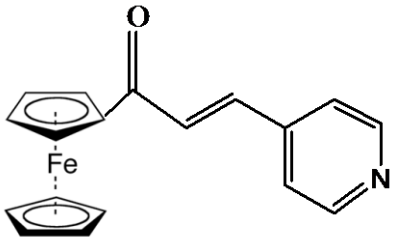
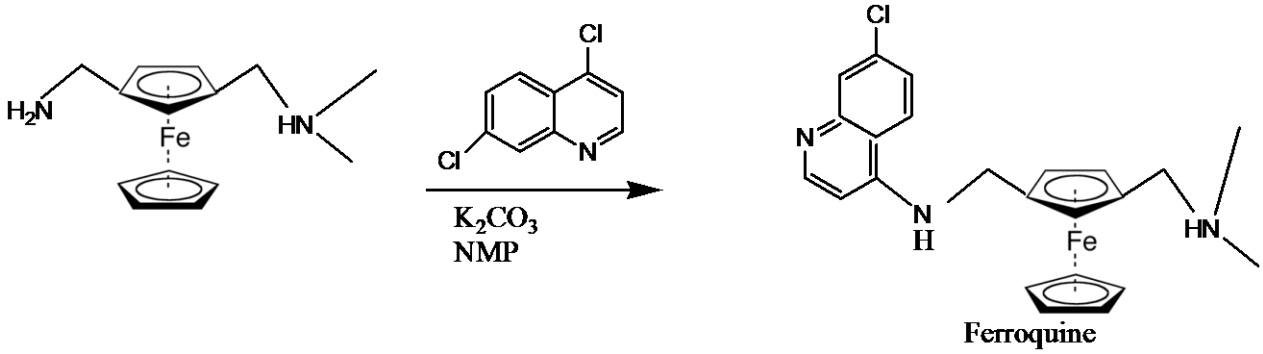


Fig 7(a) **Fig 7(b)**

Some ferrocenyl derivative have been reported to show interesting electrochemical and spectroscopic properties (Fig. 7a & 7b).[31,32]



Scheme-1

Scheme 1 shows the reaction to prepare ferroquine which shows antiplasmodial and other biological properties.[33]

1.3.2 Ferrocenyl pyrazolines and pyrazolos

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 also are many nucleic acids which are most intimately connected with the processes of life. Any atom which can form two covalent bonds is capable forming a heterocyclic compound. All the known heterocyclic compounds involve an

element from group IVB, VB or group VIB of the periodic table. The most important "heteroatoms" are nitrogen, oxygen and sulfur.

Any of the group of heterocyclic compounds containing three carbon atoms , two adjacent nitrogen atoms and one double bond in the ring known as pyrazolines. Considerable attention has been focused on pyrazoline derivatives due to their interesting biological activities. They have found to possess a Antifungal[34], antibacterial[35], antidepressant[36], anticonvulsant[37,38] anti-inflammatory[39] , anti-tumor[40] , antidiabetic, anaesthetic and analgesic[41-43]. Pyrazolines and their derivatives have been found to possess antihypertensive [44] antioxidant [45] and anticancer[46,47] activities. Recently Ali et al., have reported 1,3,5-trisubstituted pyrazolines for anti HIV activity involving one additional methyl group on ring A and isoniotinyl group at 1 position of pyrazolyl ring[48].

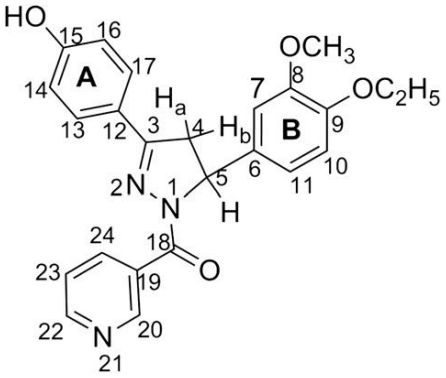
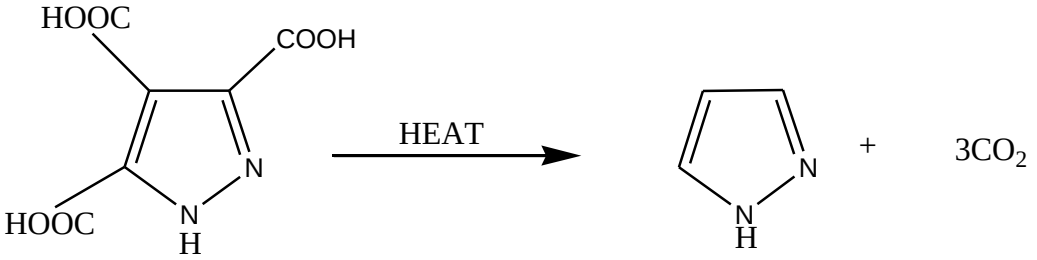


Fig 8

Similar to pyrazoline, another heterocyclic compound, pyrazole also shows interesting biological properties. Pyrazole was described for the first time by Buchner, who obtained it by decarboxylation of pyrazole-3,4,5-tricarboxylic acid in 1889 (Scheme 2) [49].



Scheme-2

Some pyrazole compounds like 3-*n*-nonypyrazole and *levo*-β-(1-pyrazolyl)alanine are the naturally occuring pyrazole derivative (Fig. 10). This pyrazolic amino acid has been isolated from watermelon seeds.[50] .

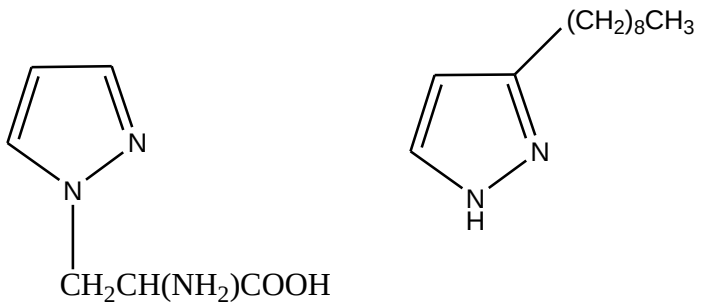


Fig 10.

Combination of a ferrocenyl moiety with heterocyclic structures may increase their biological activities or create new medicinal properties. Ferrocene containing pyrazolo quinoline derivatives that may have significant biological activities. The wide range of biological activities of pyrazoles has made them popular synthetic targets. Some of the pyrazole derivatives which are used as reverse transcriptase inhibiters for HIV disorders and can also be useful for the treatment of Alzheimer's disease (Fig. 11a & 11b).

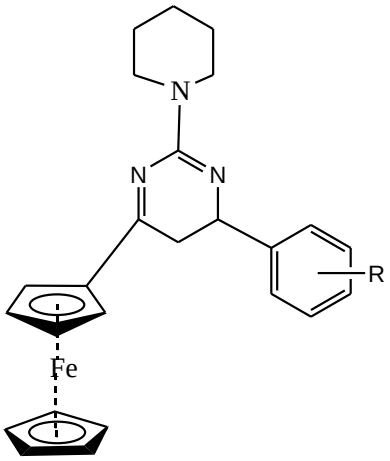


Fig 11(a)

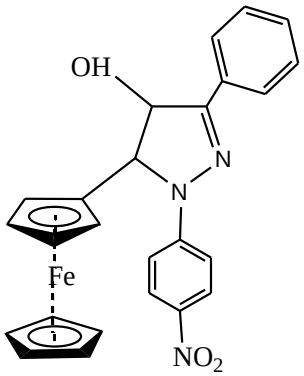


Fig 11(b)

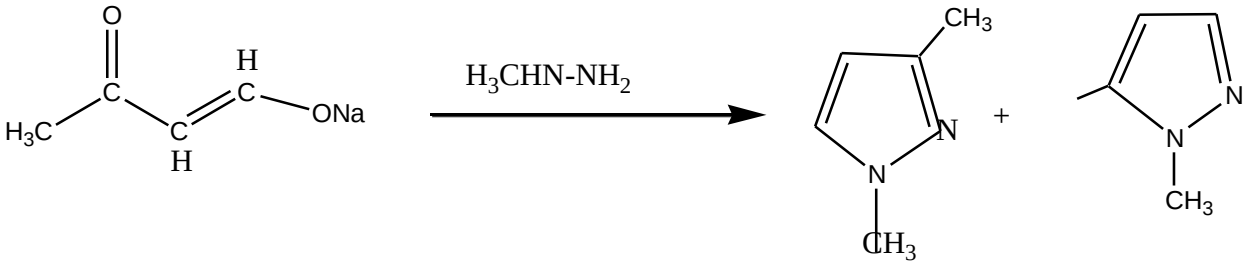
CHAPTER –2

Synthesis and reactivity of ferrocenyl chalcone compounds

2.1. Introduction

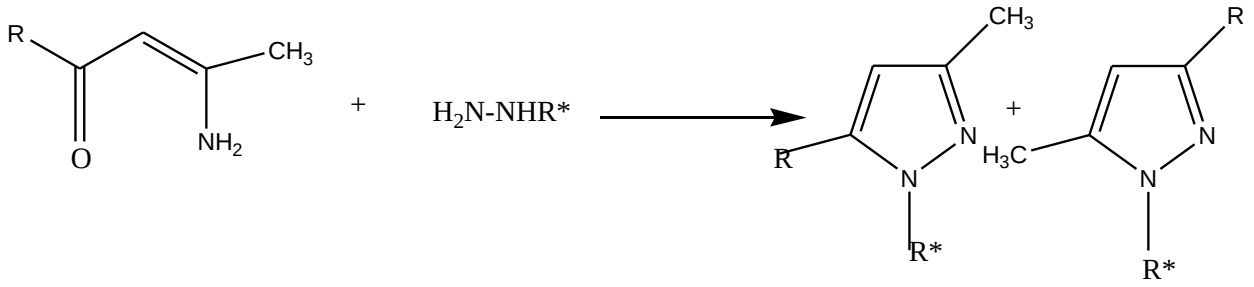
Much of the basic information obtained about the chemistry of the pyrazole moiety was its aromatic properties compared to those of benzene derivatives. The first natural pyrazole derivative was isolated by Japanese workers in 1954 who isolated 3-*n*-nonypyrazole from Houttuynia Cordata which is a plant of the "*piperaceae*" family from tropical Asia. They observed the antimicrobal activity of that compound. Another naturally occuring pyrazole derivative is *levo*-β-(1-pyrazolyl) alanine. This pyrazolic amino acid has been isolated from watermelon seeds (Citrullus Vulgaris). These are the only naturally occuring pyrazole derivatives known at present [50].

There are many methods to synthesize the pyrazole derivatives. Due the wide range of biological activities of pyrazoles has became popular for synthetic targets. The synthesis of pyrazole derivatives from β-dicarbonyl compounds and hydrazines is the most widely used and the most general method for pyrazole synthesis (Scheme 3) [50].



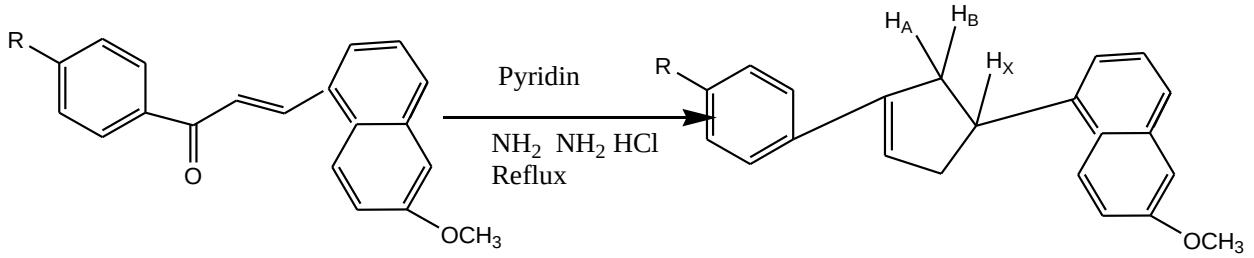
Scheme-3:

An alternative strategy to employ masked 1,3-dicarbonyl compounds such as β-aminoenones has been described by Gonzalez-Ortega and co-workers and also by Dominguez et al β-aminoenones react with hydrazine derivatives to afford regioselectively 1,3,5-trisubstituted pyrazoles as shown in scheme 4 [51,52,53].



Scheme-4

Pyrazoline are prominent nitrogen containing heterocyclic compounds play important role in medicinal chemistry. Considerable attention has been focused on pyrazoline derivatives due to their interesting biological activities. Biological activities of pyrazoline prompted to synthesize various substituted pyrazoline derivatives. Synthesis of novel isoxazoline derivative (scheme-5) remains a main focus of medicinal chemist, due to their diverse pharmacological activity [50].

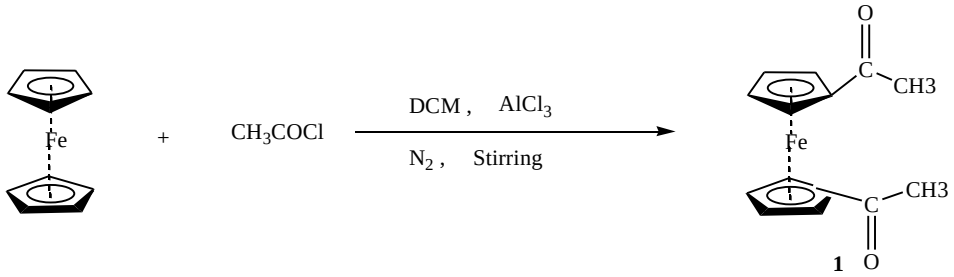


Scheme 5

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. Incorporation of pyrazole pharmacophore into the ferrocene scaffold should have an attracting structural result for development of novel antitumor agent.A series of bis(trifluoromethyl) pyrazoles (BTPs) has been found to be a novel inhibitor of cytokine production. The pyrazole derivatives 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 [50]. The last example to biologically active pyrazole derivative is Fipronil . 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 [51].

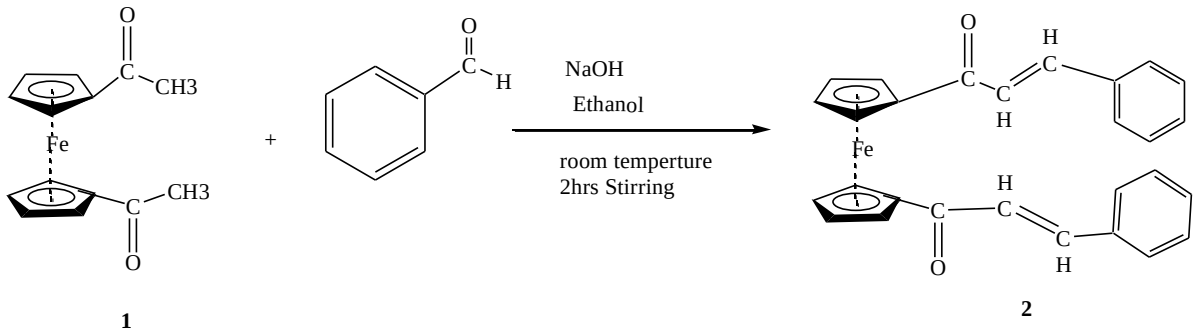
2.2. Results and Discussions

1,1'-Diactylferrocene (**1**) was prepared by taking ferrocene, acetyl chloride and anhydrous $AlCl_3$ in 1:1:2 ratios respectively (Scheme 6)**.** The IR of compounds **1** shows peaks at 1656 cm^{-1} is indicative of its carbonyl group due to $\nu_{C=O}$ stretching vibration.



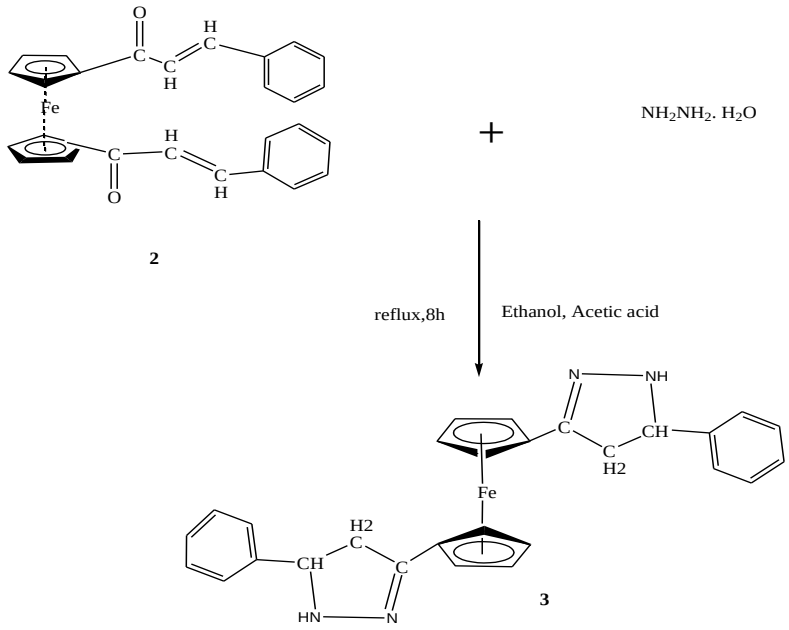
Scheme 6

The ferrocenyl dichalcone, **2** was synthesized by room temperature stirring reaction of diacetyl ferrocene and benzaldehyde at 1:6 ratio (scheme-7). The infra-red spectra (Fig.12) of **2** shows the presence of peak at 1656 cm^{-1}, due to the $\nu_{C=O}$ group of the ferrocenyl moiety and the peak at 1598 cm^{-1}, due to the $\nu_{C=C}$ of the aromatic region. The proton NMR spectroscopy (Fig.13) of **2** shows two singlet at δ 5.081 and δ 4.682, each corresponding to four protons of the cyclopentadiene ring. Peaks at 7.42-7.82ppm (multiplet) corresponds to five protons of the benzene ring. Two doublets at δ 7.62 and δ 7.36 corresponding to the two olefinic protons respectively.



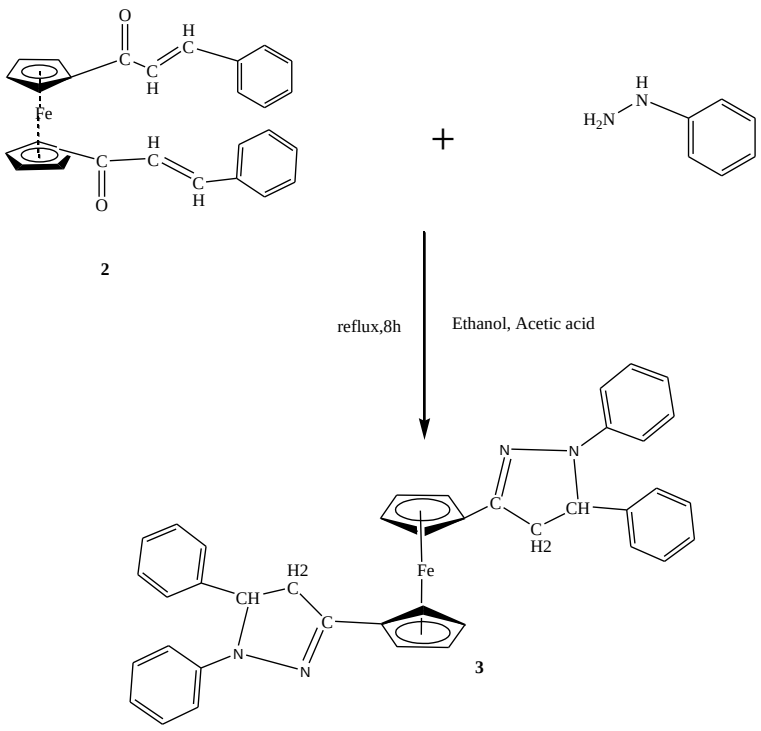
Scheme 7

Room temperature reaction of ferrocenyl dichalcone with hydrazine hydrate for 3 hours results in the formation of orange product as shown in the (scheme-8). The orange compound was isolated and FTIR was performed. Scheme 8 shows the tentative structure of the compound. The IR of compounds **3** shows peaks at 1652 cm^{-1} is indicative of its carbonyl group due to($\nu_{C=O}$) stretching vibration. The peak at 2921 cm^{-1} shows due to the (ν_{N-H}) stretching vibration and the peak at 2357 cm^{-1} shows due to the ($\nu_{C=O}$) stretching vibration.



Scheme 8

Ferrocenyl dichalcone was also reacted with phenyl hydrazine at reflux temperature to obtain orange coloured product as shown in the (scheme-9). Tentative structure has been predicted from the preliminary observation.



Scheme 9

2.3. Experimental Section

2.3.1. General Procedures

All reactions were performed under nitrogen atmosphere and room temperature. Solvents were purified and distilled prior to use. FT-IR spectra as KBr pellets of the samples were recorded on a perkin elmer VX-II spectrometer. NMR spectra was recorded in a 400 MHz bruker NMR instrument in $CDCl_3$ solvent. Ferrocene was procured from Spectrochem and used without purification.

2.3.2. Preparation of 1,1'- diacetyl ferrocene (1)

A 100 ml two necked flask equipped with glass stoppers, magnetic stirring bar was connected with a schlenk line manifold. To this flask 2 g (0.01 moles) of ferrocene was added and then to it 25 ml of CH_2Cl_2 was poured. To the stirring solution of ferrocene 2.5 ml (0.03 moles) of acetyl chloride was added drop wise with a syringe. The stirred reaction mixture was cooled in the ice bath for 15 minutes and then 4.1 g (0.03 moles) of anhydrous $AlCl_3$ was added

in small portions during 15 minutes. After the addition the ice bath was removed and the reaction mixture was stirred for additional 30 minutes at room temperature. The color of the reaction mixture transformed to dark violet. The formation of the diacetyl derivative of ferrocene was monitored by Thin Layer Chromatography (using CH_2Cl_2 / hexane in 1:1 ratio). The reaction mixture was then poured on 50 g of crashed ice in 50 ml of water in a beaker. The flask was then rinsed with small amount of CH_2Cl_2 and the combined layers were transferred into a separatory funnel. The organic layer contained the desired product of diacetyl ferrocene, $[(\eta^5\text{-}C_5H_4)_2Fe(COCH_3)_2]$ and was extracted with CH_2Cl_2. The combined organic layers were dried to obtain the diacetyl ferrocene for further synthesis. Purification of the compound was done by column chromatography using Pet-ether/dichloromethene as solvent mixture.

1:IR (CH_2Cl_2,cm^{-1}): 1656 (s)

2.3.3. Synthesis of 1,1'-Fc(COCH=CHPh)$_2$ (2)

To the round bottom flask 0.270 gmof diacetyl ferrocene was dissolved in 5ml. ethanol. Then it was stirred for 15mins. Then 0.04gm of NaOH was added.After 20mins.0.636gm of Benzaldehyde with 2ml.ethanol was added in 1:6 ratio. Then the stirring was continued for 3-4 hrs. at room temperature. The color of the reaction mixture transformed orangered to dark orange. The formation of the ferrocenyl dichalcone was monitored by Thin Layer Chromatography (using hexane and ethyl acetate in 1:1 ratio).

2: **IR:**(CH_2Cl_2,cm^{-1}):1656 (s), 1598 (s). **^{1}H NMR(CDCl3, δ):** 4.68 (4H ,s, C_5H_4), 5.082 (4H ,s, C_5H_4), 7.428-7.83 (10H , m, Ph-) 7.6 (2H ,d, =CH) 7.35 (2H, d, =CH).

2.3.4. Reaction of Ferrocenyl-dichalcone (2) with hydrazine hydrate

To 100 ml two necked round bottom flask equipped with glass stoppers, magnetic stirring bar was connected with a nitrogen cylinder. 0.1mm of diacetyl ferrocene was dissolved in 5ml. ethanol.to this flask. After for 15mins. Of stirring 0.04gm of NaOH was added. To it After 20mins.0.636gm of Benzaldehyde with 2ml.ethanol was added in 1:6 ratio.Then stire for 3-4 hrs till the deep orange colour precipitate formed. The product was separated by thin layer chromatography.

3: **IR:**(KBr,cm^{-1}):1652 (s), 2921 (m, br)

2.3.5 Reaction of Ferrocenyl-dichalcone (2) with Phenyl hydrazine

A 100 ml two necked flask equipped with glass stoppers, magnetic stirring bar was connected with a nitrogen cylinder. To this flask 0.1mm of diacetyl ferrocene was dissolved in 5ml. ethanol. Then it was stirred for 15mins.Then 0.04gm of NaOH was added. After 20mins 0.648 Phenyl hydrazine was added followed by 2ml ethanol in1:6 ratio and the stiring was continued for 5-6 hours till the precipitate formed . Initial colour of the reaction mixture was yellowish orange and after stirring the colour changes to red. The product was separated by thin layer chromatography followed by pet ether and ethyl acetate in 1:10 ratio.

4: **IR:**(KBr,cm^{-1}):1657 (s), 2925 (m, br)

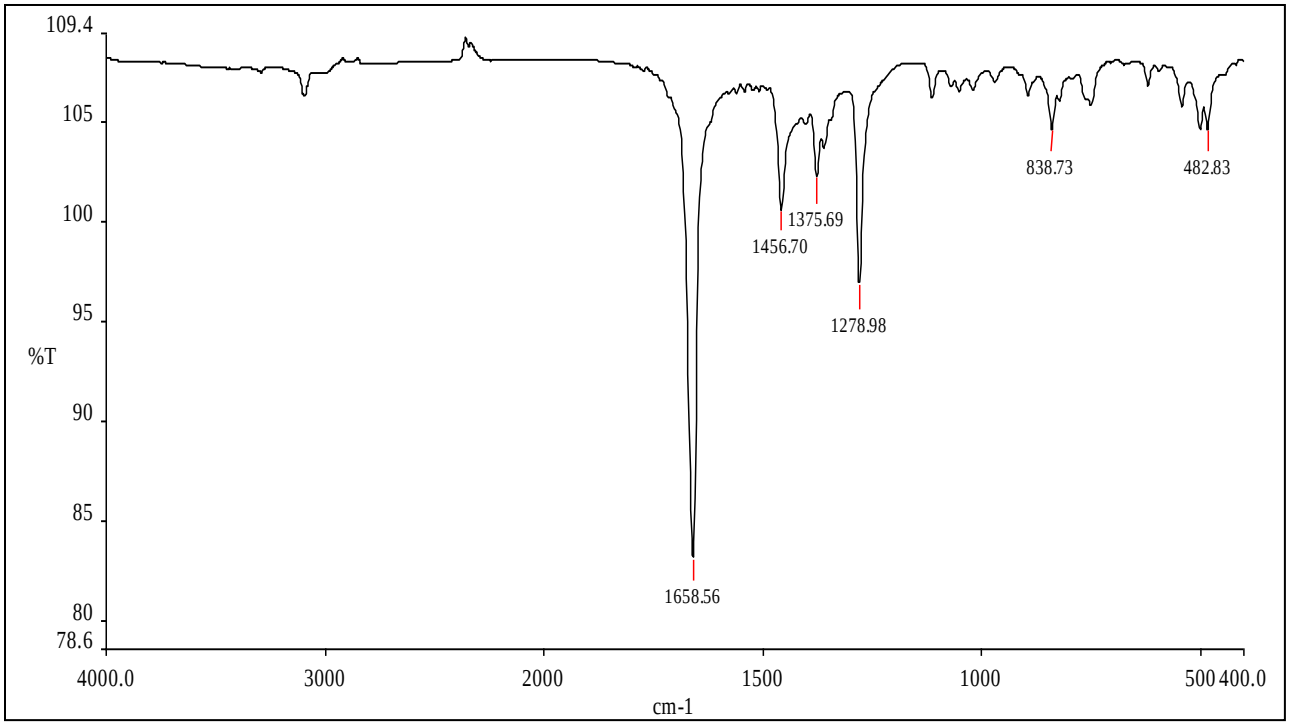


Fig.12 : IR spectra of 1,1'- diacetyl ferrocene

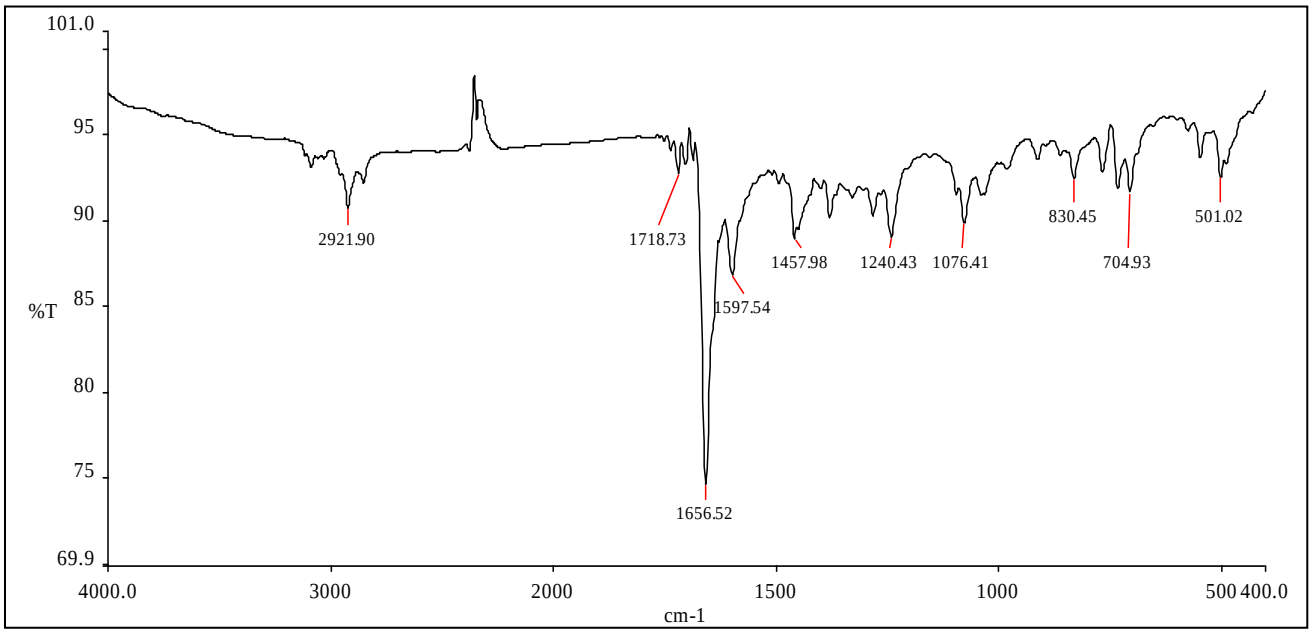


Fig.13: IR spectra of 1,1 '-Fc(COCH=CHPh)$_2$

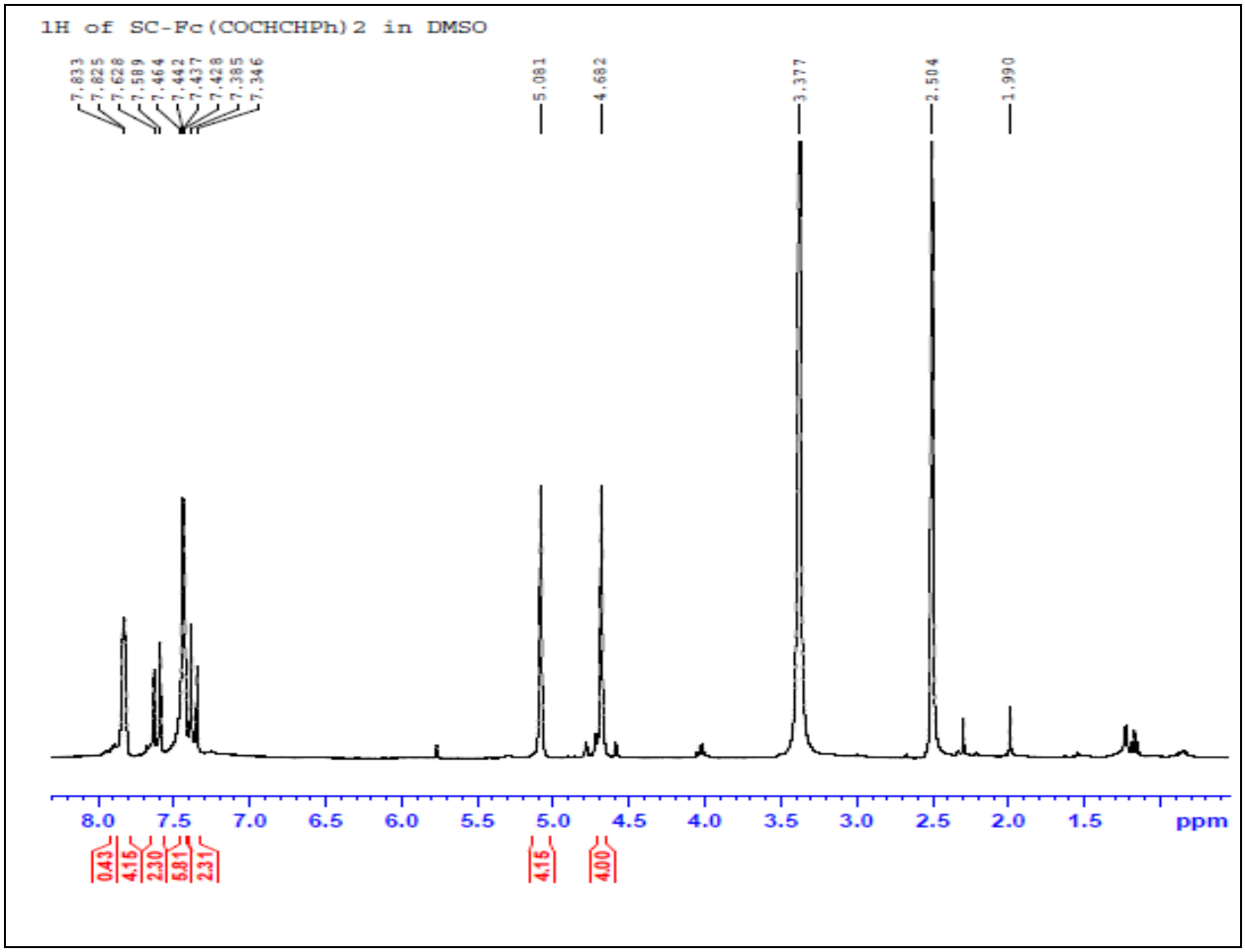


Fig.14 :^{1}H NMR Spectrum of 1,1 '-Fc(COCH=CHPh)$_2$

3 Conclusions

Diactylferrocene was successfully used to prepare 1,1'-ferrocenyl dichalcone (**2**) in high yield. Ferrocenyl-dichalcone has been characterized by FTIR and NMR spectroscopy. Ferrocene containing pyrazoline compound (**3**) has been synthesized by the room temperature reaction of ferrocenyl-dichalcone with hydrazine hydrate and preliminary characterization was performed by spectroscopic techniques. Reaction of Ferrocenyl-dichalcone with phenylhydrazine at higher temperature results in the formation of the phenyl analogue of **3**.

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