# SYNTHESIS OF FERROCENYL SUBSTITUTED QUINOLINES

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**SYNTHESIS OF FERROCENYL SUBSTITUTED QUINOLINES**

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## ABSTRACT

SYNTHESIS OF FERROCENYL SUBSTITUTED QUINOLINES

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Quinolines 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 quinolines 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 quinolines, such as 2-ferrocenylquinoline, by employing the molecular iodine catalyzed reaction between enolizable aldehydes and ferrocenyl imines, which were prepared by the condensation reactions of ferrocenecarboxaldehyde with aniline derivatives. As anticipated, these reactions produced 2-ferrocenylquinoline derivatives. By employing this methodology, we synthesized 2-ferrocenylquinoline, 6-chloro-2-ferrocenylquinoline, 6-bromo-2-ferrocenyl-quinoline, 2-ferrocenyl-7-methylquinoline and 2-ferrocenyl-3,7-dimethylquinoline.

Due to the ready availability of ferrocenylimines and aldehydes, this practical one-pot method represents a versatile synthesis of ferrocenyl-substituted quinolines.

Keywords: Ferrocene, ferrocenyl imine, ferrocenyl quinoline, iodine, quinoline.

# ÖZ

FERROSENİL SÜBSTİTÜE KİNOLİNLERİN SENTEZİ

Velioğlu, Özlem
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Prof.Dr. Metin Zora

Ağustos 2008, 61sayfa

Heterosiklik bileşiklerin önemli bir sınıfını oluşturan kinolinler, 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 kinolin yapılarının birleştirilmesi beklenmedik biyolojik aktivitelere sahip yeni türevler oluşturabilir. Bu yüzden, 2-ferrosenilkinolin gibi ferrosenil sübstitüe kinolinlerin sentezi iyot varlığında ferrosenkarboksialdehit ile anilin türevlerinin tepkimesi sonunda elde edilen ferrosen sübstitüe imin ve enolize olabilen aldehitlerin ısıtılması ile gerçekleştirilmiştir. Beklenildiği üzere, bu tepkimeler sonucunda 2-ferrosenilkinolin türevleri elde edilmiştir. Bu metodoloji uygulanarak, 2-ferrosenilkinolin, 6-klor-2-ferrosenilkinolin, 6-brom-2-ferrosenil-kinolin, 2-ferrosenil-7-metilkinolin ve 2-ferrosenil-3,7-dimetilkinolin sentez-lenmiştir. Ferroseniminlerin ve aldehitlerin kolay elde edilir olması sebebiyle bu tek basamak metodoloji birçok ferrosenil substitue kinolinlerin sentezi için uygulanabilir.

Anahtar Kelimeler: Ferrosen, ferrosenil imine, ferrosenil kinolin, iyot, kinolin.

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To Mustafa & Asuman Velioğlu

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| | |
|---|---|
| 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) |
| DMF | Dimethylformamide |
| 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

# CHAPTER 1

# INTRODUCTION

Organic chemistry is the most commonly and simply defined as the chemistry of carbon compounds [1]. Humans have used organic compounds and their reactions for thousands of years. Their first deliberate experience with an organic reaction probably dates from the discovery of fire. But as a science, organic chemistry is less than 200 years old [2].

Comparatively early in the history of chemistry, an interest began to be taken in the noteworthy variety of carbon compounds which could be prepared from plant and animal sources. This led eventually to systematic investigations on their origin and the manner in which they could be transformed one into another [3].

In the beginning of the nineteenth century, organic chemistry was considered as a separate branch of chemical science [4]. Today organic chemistry is a broad field, which intersects with such diverse areas as biology, medicine and pharmacology, polymer technology, agriculture and petroleum engineering.

Virtually all plastics, synthetic and natural fibers, dyes and drugs, insecticides and herbicides, ingredients in perfumes and flavoring agents and all petroleum products are organic compounds. All the foods we eat consist primarily of organic compounds in the families of the carbohydrates, fats and oils, proteins, and vitamins. The substances that make up furs and feathers, hides and skins, and all membranes are also organic [5].

Heterocyclic compounds are cyclic organic substances in which one or more of the ring carbons are replaced by a heteroatom such as nitrogen, oxygen and sulfur.

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 associated with the processes of life [6,7].

Quinoline and isoquinoline (Figure 1) are the two heterocycles in which a benzene ring and a pyridine ring are fused through carbon.


**1**
Quinoline

**2**
Isoquinoline

**Figure 1.** Structure of quinoline (**1**) and isoquinoline (**2**).

In fact, they are two analogs of naphthalene which can result from the fusion of a benzene ring to a pyridine ring. The numbering system and some of the principal resonance forms are shown in Figure 2 [7].

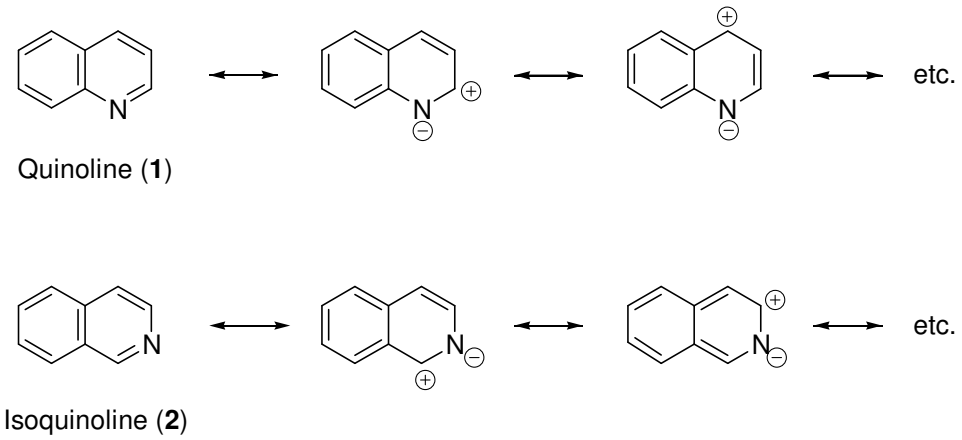



**Figure 2.** Some resonance structures of quinoline (**1**) and isoquinoline (**2**).

An impure quinoline was first obtained from coal tar by Runge in 1834 [8]. Coal tar also contains isoquinoline as well as several alkylquinolines and alkylisoquinolines.

Pure quinoline, or benzo[b]pyridine, is a colorless hygroscopic liquid, with $pK_a$ 4.85 in water at 20 $^{o}$C [9]. It darkens on exposure to light. Otherwise it is very stable and is often used as a high-boiling solvent (b.p. 237 $^{o}$C). It is particularly useful as a solvent for the decarboxylation of aromatic carboxylic acids with copper bronze. Quinoline is not easily oxidized, but with potassium permanganate it gives pyridine-2,3-dicarboxylic acid, where benzene ring is preferentially destroyed [7].


Quinoline (**1**) pyridine-2,3-dicarboxylic acid (**3**)

**Figure 3.** Oxidation of quinoline (**1**).

Like naphthaline, it is a resonance hybrid, but 1,2-, 3,4-, 5,6-, and 7,8-bonds have greater double bond character than 2,3- and 6,7-bonds. For this reason and because the nitrogen atom deactivates the heterocyclic ring, ozonolysis of quinoline occurs more rapidly at 5,6- and 7,8-bonds. Glyoxal and pyridine-2,3-dialdehyde are obtained from quinoline while glyoxal and 2,3-diacetylpyridine form from 5,8-dimethylquinoline. Similarly, 2,3-dimethylquinoline produces glyoxal and dimethylglyoxal when subjected to ozonolysis reaction.

Reduced quinolines are also known. In particular, 1,2,3,4-tetrahydro-quinolines are very important, and they are often prepared by the direct reduction of corresponding quinolines [7]. Quinoline itself is easily reduced 1,2,3,4-tetrahydro-quinoline by tin and hydrochloric acid. Therefore, quinoline is more readily reduced than naphthalene. This is not unexpected for pyridine since it is more readily reduced than benzene. The nitrogen lone pair of electrons tends to make quinoline a mild catalyst poison (quinoline-poisoned palladium has been recommended as a catalyst for the selective hydrogenation of acetylenes to olefins). Catalytic hydrogenation of quinoline also gives 1,2,3,4-tetrahydroquinoline, which is a stronger base than quinoline and behaves like a secondary *N*-alkylaniline. Its *N*-methyl derivative is also known as kairolin [7].

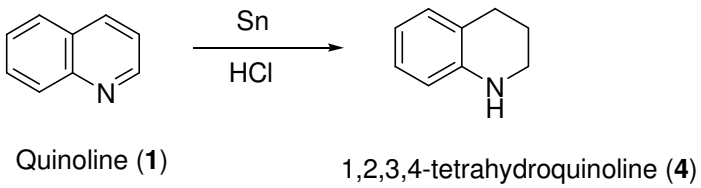



**Figure 4.** Reduction of quinoline

1,2-Dihyroquinoline (**5**) is a colorless solid (Figure 5), which is easily oxidized to the aromatic structure. It has been obtained by reduction of quinoline (**1**) with lithium aluminum hydride or with sodium in liquid ammonia [10]. 1,2-Dihydroquinolines (**5**) are formed as intermediates in the Skraup synthesis.

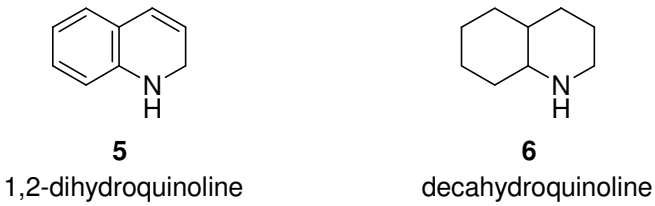



**Figure 5.** Structures of 1,2-dihydroquinoline and decahydroquinoline.

Decahydroquinolines (**6**) are also known (Figure 5) and can be prepared by direct hydrogenation. Catalytic hydrogenation of quinoline (**1**) in glacial acetic acid solution, over platinum, gives mainly *trans*-decahydroquinoline with some of the *cis*-isomer. However, in hydrochloric acid solution, *cis*-decahydroquinoline is obtained predominantly. Decahydroquinolines (**6**) have also been prepared by synthesis [11].

## 1.1. Synthesis of quinoline derivatives

There are many methods to synthesize quinoline ring system. The classical method is the cyclization process in which substituted benzene derivative is the starting material and the heterocyclic ring is constructed during the course of the reaction. In the recent syntheses, however, a carbocyclic ring has been built up onto a substituted pyridine [11,12]. Those derived from a benzenoid starting material are of two types. The more important type is that in which a side chain is constructed and cyclized onto a free *ortho* position of the benzene ring. Such reactions include the Skraup, Friedlander, Doebner-von Miller and Combes syntheses.

The *Skraup synthesis* is a chemical reaction used to synthesize quinolines (Figure 6). It is named after the Czech chemist Zdenko Hans Skraup. In the Skraup, aniline is heated with sulfuric acid, glycerol, and an oxidizing agent to yield quinoline [13,14].

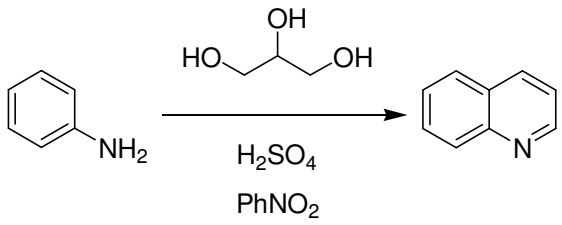



**Figure 6.** Skraup synthesis of quinolines.

In this example, nitrobenzene serves as both the solvent and the oxidizing agent. The reaction, which otherwise has a reputation for being violent, is typically conducted in the presence of ferrous sulfate [15]. Although the details of the reaction sequence have not all been established, it seems most likely that glycerol is

dehydrated to acrolein, which reacts with aniline by conjugate addition. The resulting intermediate is then cyclized, oxidized, and dehydrated to give the quinoline.

In the *Doebner-Von Miller* variation (Figure 7), instead of glycerol, α,β-unsaturated aldehydes or ketones are used, and this creates many possibilities in the substitution pattern. Hydrochloric acid or zinc chloride is generally used as the catalyst. Crotonaldehyde gives 2-methylquinoline and not 4-methylquinoline as the final product (Figure 7). This clearly implies that the ring formation takes place by the conjugate addition of the amine and not by the direct attack on the carbonyl group. In these reactions, it is also possible that Schiff base of the carbonyl compound can undergo conjugate addition [16].

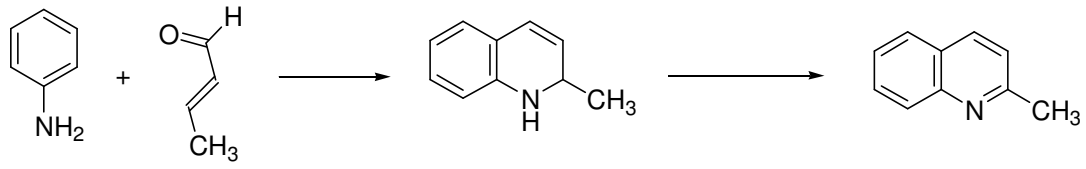



**Figure 7.** Doebner-Von Miller synthesis of quinolines.

In the *Combes* synthesis, the aniline reacts with a 1,3-diketone in the presence of acid to form a Schiff base. Cyclization then takes place via a diprotonated intermediate, which is finally dehydrated to afford the quinoline derivative, as illustrated in Figure 8 [17].

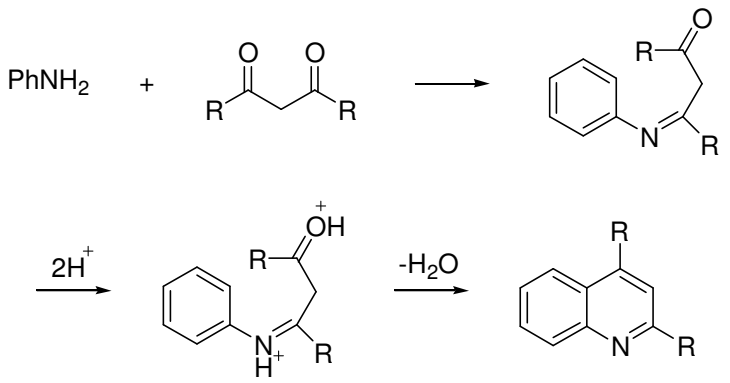



**Figure 8.** Combes synthesis of quinolines.

When a β-ketoester is used in place of a 1,3-diketone, two products can be obtained [24]. For instance, ethyl acetoacetate can give 2-methyl-4-quinoline (**7**) or 4-methyl-2-quinolone (**8**) (Figure 9). Attack on the ketone carbonyl, which is kinetically favored, happens by carrying out the initial reaction at room temperature, followed by thermal cyclization. Attack on the ester function, which is thermodynamically favored, occurs when the reaction is carried out at 110-140 $^{o}$C [18].

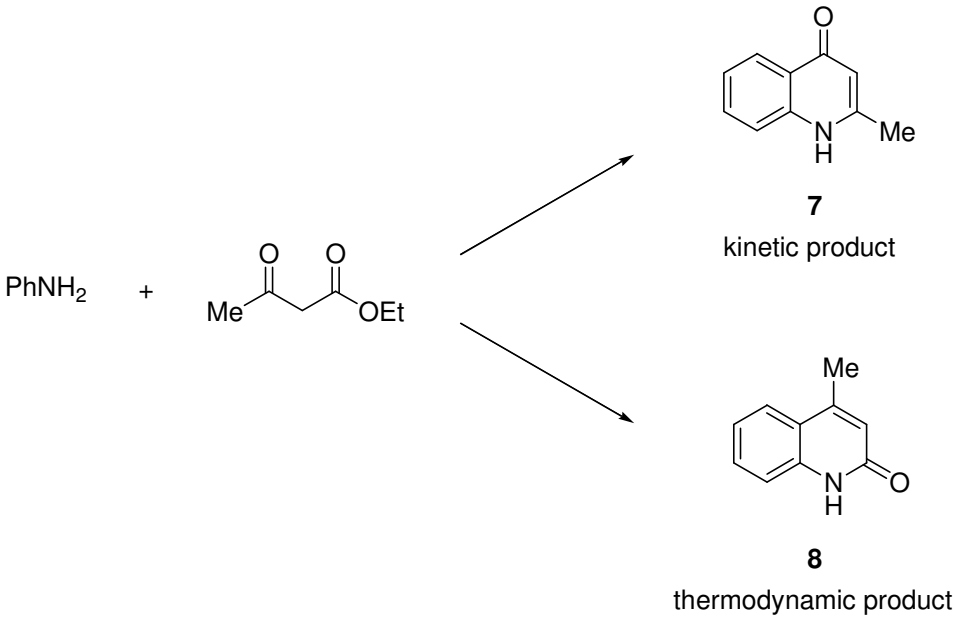



**Figure 9.** Reaction of a β-ketoester with aniline.

All these methods suffer from the disadvantage that if the aniline bears a meta-substituent, there are two different ortho positions available for cyclization. In some cases, the ratio of products favors one isomer (for example, 3-methoxyaniline gives mainly 7-methoxyquinoline rather than 5-methoxyquinoline in the *Skraup* synthesis) but often both possible isomers are formed. However, if an *o*-disubstituted benzene is used as the starting material for the synthesis of quinoline ring, this problem is avoided [18].

The *Friedländer synthesis* is the chemical reaction of 2-aminobenzaldehydes [19] with ketones to form quinoline derivatives [20] (Figure 10), which is named by its discoverer's name, Paul Friedländer. This reaction has been catalyzed by trifluoroacetic acid [21], toluenesulfonic acid [22], iodine [23] and Lewis acids [24].

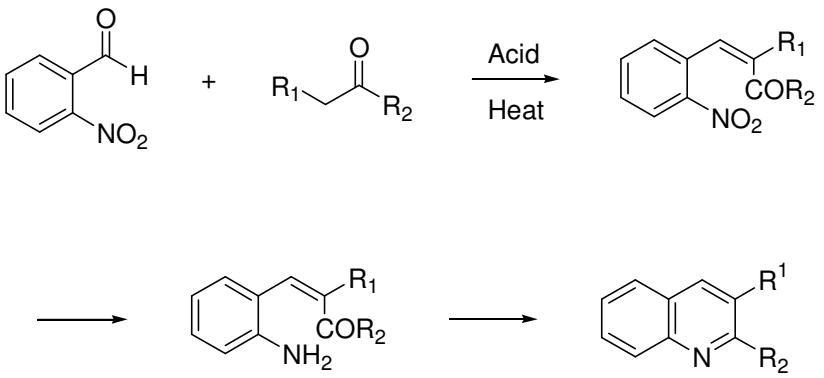



**Figure 10.** Friedlander synthesis of quinolines.

The *Povarov reaction* is generally described as a formal cycloaddition between an aromatic imine and an alkene (Figure 11). The imine in this organic reaction is a condensation reaction product from an aniline type compound and a benzaldehyde type compound [25]. The alkene must be electron rich which means that functional groups attached to the alkene must be able to donate electrons. Such alkenes are enol ethers and enamines. The reaction product in the original Povarov reaction is a quinoline. Because the reactions can be carried out with the three components premixed in one reactor it is an example of a multi-component reaction.

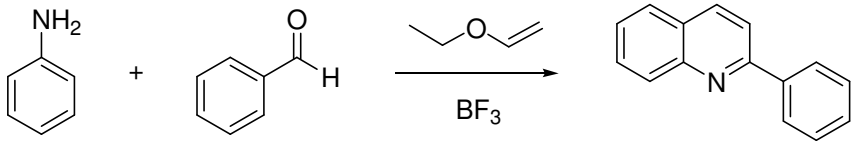



**Figure 11.** Pavarov synthesis of quinolines.

The *Pfitzinger reaction* (also known as the Pfitzinger-Borsche reaction) is the chemical reaction of isatin with base and a carbonyl compound to give substituted quinoline-4-carboxylic acids [26] (Figure 12).

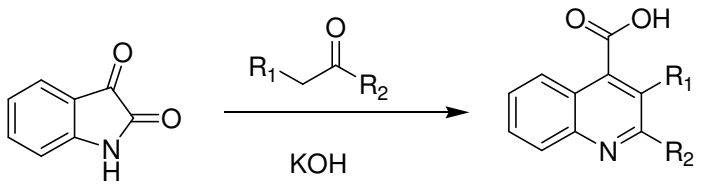



**Figure 12.** Pfitzinger synthesis of quinolines.

The *Camps quinoline synthesis* (also known as the Camps cyclization) is a chemical reaction whereby an *o*-acylaminoacetophenone is transformed into two different hydroxyquinolines, products (**9**) and (**10**), using base [27] (Figure 13).

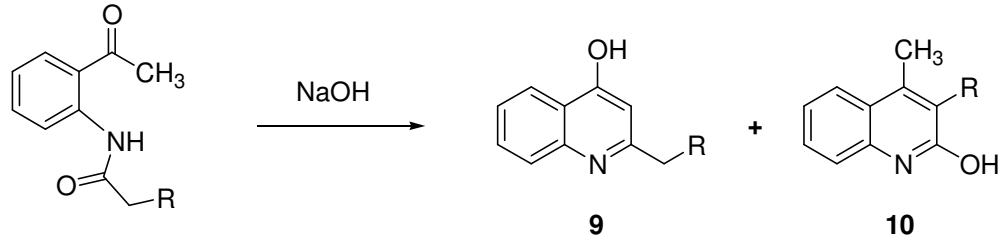



**Figure 13.** Camps synthesis of quinolines.

The relative proportions of the hydroxyquinolines **9** and **10** are dependent upon the reaction conditions and structure of the starting material. Although the reaction product is commonly depicted as a quinoline (the enol form), it is believed that the keto form predominates in both the solid state and solution, making the compound a quinolone [28].

The *Conrad-Limpach synthesis* is known as the reaction of anilines (**11**) with β-ketoesters (**12**) to form 4-hydroxyquinolines (**14**) via a Schiff base (**13**) [29,30] (Figure 14).

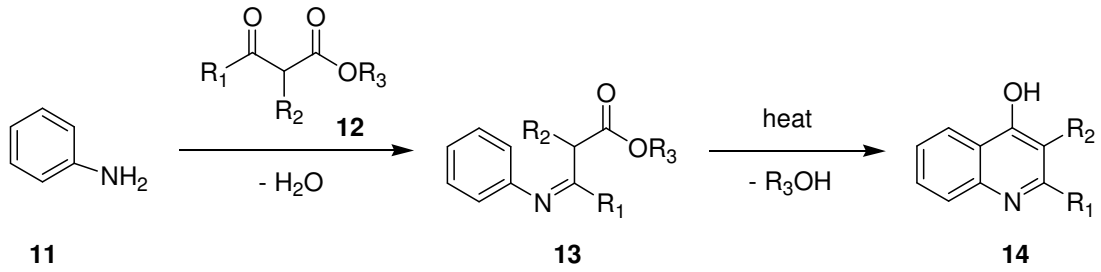



**Figure 14.** Conrad-Limpach synthesis of quinolines.

## 1.2. Biologically active quinoline derivatives.

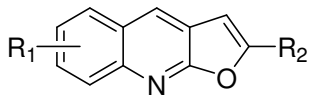
Quinoline moiety is present in many classes of biologically active compounds. A number of them have been clinically used as antifungal, antibacterial and antiprozoic drugs as well as antineoplastics [31].

The quinoline ring system is found in a variety of compounds including dyes, organic materials, and pharmaceuticals. Among the pharmaceuticals, quinoline derivatives have been commonly used for the treatment of parasitic infections such

as malaria [32] and leishmaniasis [33] as well as being present in antitumor agents such as streptonigrin [34], luotonin A [35], dynemicin A [36] and camptothecin [37]. In addition, natural product isolations and biological activity assays continue to identify new, potentially useful quinoline alkaloids from both plant and marine animal sources [38].

Quinoline derivatives have been well known not only in medicinal chemistry, because of their wide occurrence in natural products [39] and drugs [40] but also in polymer chemistry, electronics and optoelectronics for their excellent mechanical properties [41].

Furoquinoline (**15**), shown in Figure 15, and pyranoquinoline derivatives are alkaloids isolated mainly from rutaceous plants [42]. Many efforts are still being made in order to isolate new family members due to their broad biological properties, which include antiplatelet aggregation, antifungal, insecticide, antibacterial, antimicrobial, analgesic, antipyretic and also cytotoxic properties [42].



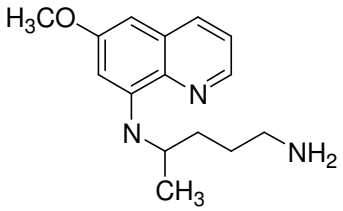

**15**

**Figure 15.** Structure of furoquinolines (**15**).

Tuberculosis (TB), one of the most common infectious diseases, which is a major cause of morbidity and mortality all over the world [43,44]. Therefore, in order to control the rapid spread of tuberculosis, there is an urgent need for new anti-TB drugs with unique modes of action and improved properties such as enhanced

activity against MDR strains, reduced toxicity and shortened duration of therapy [45]. During the past decade, several of the fluoroquinoline antibacterial drugs (such as 4-amino substituted 2,8-bis(trifluoromethyl)quinoline derivatives) have been examined as potential chemotherapeutics for *M. tb* (Mycobacterium tuberculosis) infection [46,47]. Styrylquinoline derivatives have gained strong attention because of their activity as perspective HIV integrase inhibitors [48].

Several 8-aminoquinoline compounds, for instance Primaquine (**16**) (Figure 16)**,** have been applied as chemotherapeutics for treatment of malaria diseases [49,50].




**16**

**Figure 16.** Structure of primaquine.

In fact, the quinoline skeleton has been used as the basis for the design of many synthetic antimalarial compounds. The alkoloid quinine (**17**) is a traditional antimalarial drug (Figure 17), which is also used in tonics [51]. Chloroquine (**18**) has long been used in the treatment and prevention of malaria [51]. It is also used in some autoimmune disorders (rheumatoid arthritis and lupus erythematosus) since it gently suppresses the immune system.

The cyanine dyes are also important commercial quinolines. The tetrahydro-quinoline derivative oxamniquine (**19**) is used to eradicate blood flukes (schistosoma mansoni) (Figure 17), which is a major cause of disease in tropical regions [51].

Papaverine (**20**) is an opium alkaloid, which is a nonspecific smooth muscle relaxant and a vasodilator [64] (Figure 17). The morphine alkaloids can also be considered as isoquinoline derivatives. There are several other families of isoquinoline alkaloids, which occur widely in the plant kingdom; all of which are derived in nature from the amino acid tyrosine [51].

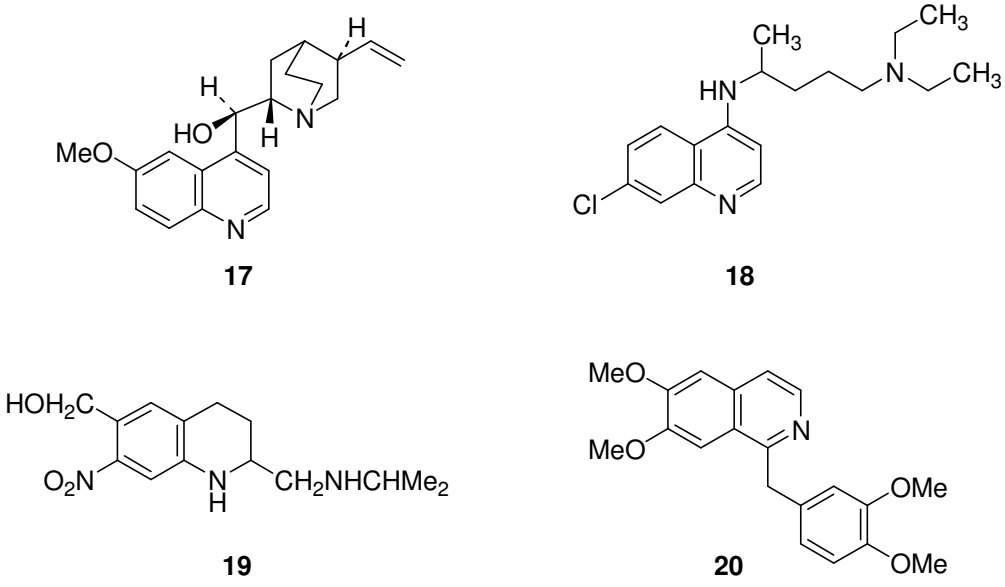


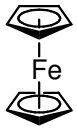

**Figure 17.** Examples of biologically active quinoline and isoquinoline derivatives.

## 1.3. Ferrocene derivatives and their biological activities.

Organometallic chemistry is the study of chemical compounds containing bonds between carbon and a metal [52]. In other words, organometallic compounds can be defined as the substances containing metal-carbon bonds. These bonds are mostly 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 [53]. The pace development of organometallic chemistry initiated by the discovery of ferrocene was spurred by another unexpected discovery by Ziegler [54,55].

A metallocene is a compound with the general formula $(R)_2M$ consisting of a metal center in the oxidation state II between two planar polyhapto rings. Metallocenes are a subset of a broader class of organometallic compounds called sandwich compounds. One of the ligands encountered in metallocenes is cyclopentadienyl ($C_5H_5$). These complexes, which belong to the most commonly organometallic derivatives, are utilized in various areas of chemistry and technology [56].

Ferrocene (**21**) is the chemical compound with the formula $Fe(C_5H_5)_2$ (Figure 18). Ferrocene (**21**) is the prototypical metallocene, a type of organometallic chemical compound consisting of two cyclopentadienyl rings bound on opposite sides of a central metal atom [57].




**21**
Ferrocene

**Figure 18.** Structure of ferrocene.

Ferrocene (**21**), like many chemical compounds, was first prepared unintentionally. In 1951, Pauson and Kealy reported the reaction of cyclopentadienyl magnesium bromide and ferric chloride with the goal of oxidatively coupling the diene. Instead, they obtained a light orange powder of "remarkable stability" [58]. This stability was due to the aromatic character of the negatively charged cyclopentadienyl groups, but the sandwich structure [$\eta^5$ (pentahapto)] of ferrocene was recognized later by others.

Woodward and Wilkinson deduced the structure based on its reactivity [59]. Independently, Fisher also came to the conclusion of the sandwich structure and started to synthesize other metallocenes such as nickelocene and cobaltocene [60]. The structure of ferrocene was confirmed by NMR spectroscopy and X-Ray crystallography [61,62]. Its distinctive "sandwich" structure led to an explosion of interest in compounds of d-block metals with hydrocarbons and initiated the development of the now flourishing study of organometallic chemistry.

In 1973, Fisher and Wilkinson shared a Nobel Prize for their work on organometallic chemistry, specifically sandwich type complexes.

Ferrocene (**21**) is an air stable orange solid that readily sublimates in vacuum, especially upon heating. The central iron atom in ferrocene is normally considered to be in the +2 oxidation state. Each cyclopentadienyl ring is then allocated a single negative charge. This extra electron occupies an $\pi$ orbital, bringing the number of $\pi$-electrons on each ring to six and thus making them aromatic. These twelve electrons (six from each ring) are then shared with metal via covalent bonding, which, when combined with the six *d*-electrons on $Fe^{2+}$, results in the complex having an 18-electron, inert gas electron configuration. This configuration makes ferrocene particularly stable [63].

Ferrocene undergoes many reactions characteristic of aromatic compounds, enabling the preparation of derivatives (substituted ferrocenes). It undergoes

Friedel-Crafts acylation and alkylation, Vilsmeier formylation and mercuration [64]. Ferrocene derivatives containing asymmetric substituents are used as ligands for asymmetric hydrogenation catalysts [65]. Some of the basic reactions of ferrocene are shown in Figure 19.

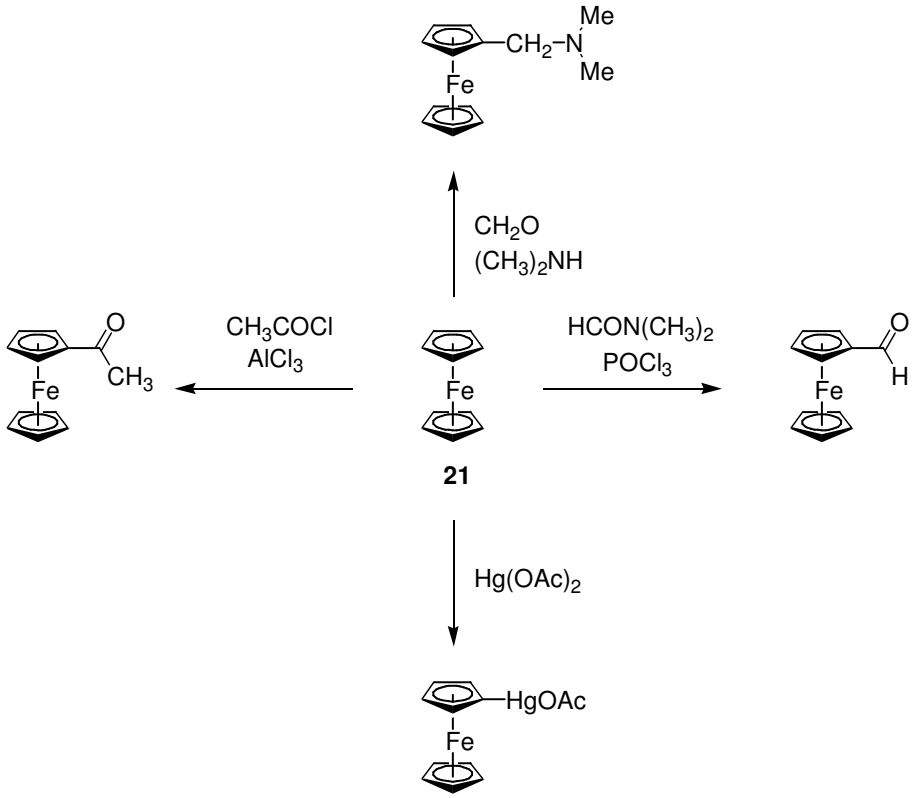



**Figure 19.** Typical electrophilic substitution reactions of ferrocene (**21**).

Ferrocenium salts such as **22** (Figure 20) have been proved to be particularly active against a number of various animal and human tumors [66]. Ferrocene (**21**) itself is insoluble in water and does not display any antitumor activity. Even if it is solubilized in water using heptakis(2,6-di-*O*-methyl)-β-cyclodextrin (dmβ-CD), it

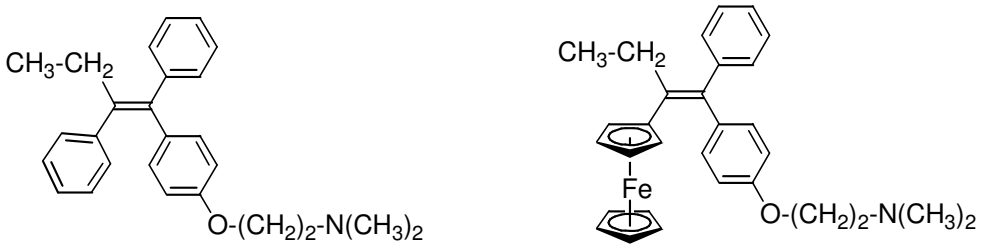
does not show any tumor inhibitory effect [80], but ferrocenium salts (**22**), in which the central iron atom has a +3 charge, have antitumor activity against a number of tumors [66,67]. Although the excellent solubility of salts in water, caused by their ionic character, proves to be propitious for applications in biological systems, the inhibitory activity of ferrocenium salts (**22**) is independent of the water solubility. The only factor that makes these ferrocenium salts active against tumors is the +3 oxidation state of the central iron [67]. Importantly, recent studies have shown that when intercalated into cells, ferrocene can be easily oxidized to corresponding ferrocenium ion by biological oxidation, and it might show biological activity.


**22**
Ferrocenium salt
[X = $PF_6$, $FeCl_4$, 2,4,6-$(NO_2)_3C_6H_2O$, $Cl_3CCO_2 \cdot 2Cl_3CCO_2H$)]

**Figure 20.** Some examples of the ferrocenium salts (**22**).

Some ferrocenium salts exhibit anticancer activity and an experimental drug has been reported which is a ferrocenyl version of tamoxifen (**23**). Tamoxifen (**23**) is the drug used against breast cancer cells that are mediated by $ER_\alpha$ estrogen reseptors (Figure 16) [68]. In facts, there are two types of breast cancer cells: one of them is a breast cancer cell that is mediated by $ER_\alpha$ estrogen receptors and the other is a breast cancer cell that is mediated by $ER_\beta$ estrogen receptors. Tamoxifen (**23**) is not effective on breast cancer cells that are mediated by $ER_\beta$ estrogen receptors. In 2002, Jaouen and coworkers have investigated the tamoxifen analogs that contain an organometallic moiety by replacing the phenyl group with ferrocenyl group. The

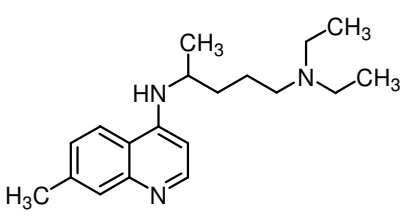
resulting compound called ferrocifen (**24**) showed a strong effect against breast cancer cells that are mediated by both $ER_\alpha$ and $ER_\beta$ estrogen receptors (Figure 17) [69].



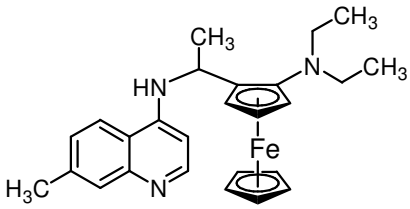

**23** **24**

**Figure 21.** Structures of tamoxifen (**23**) and ferrocifen (**24**).

Another biologically active ferrocenyl compound is ferroquine (**25**) (Figure 22), a hybrid compound of chloroquine (**18**). Several drugs, including chloroquine (**18**), are used against malaria parasite. Unfortunately resistance to these drugs is increasing [70]. Brocard and coworkers inserted a ferrocenyl group into the side chain of the chloroquine (**18**). It has been reported that the resulting compound ferroquine (**25**) is much safer than chloroquine and it is effective in mice, as well as non-mutagenic [71].




**18**




**25**

**Figure 22.** Structures of chloroquine (**18**) and ferroquine (**25**).

## 1.4. The aim of this study

Recent studies have shown that the combination of a ferrocenyl moiety with biologically active structures, such as quinolines, may increase their biological activities or create new medicinal properties [73,74]. It is noteworthy to mention that due to its unique structure, different membrane-permeation behavior and anomalous metabolism, ferrocene is frequently integrated into an organic compound in order to have enhanced or unexpected biological activities [73,74]. Although quinolines are among the most extensively studied heterocyclic compounds [72,75], ferrocenyl-substituted quinolines are not often found in the literature [76]. Therefore, the synthesis of quinoline derivatives directly linked to a ferrocene unit, such as 2-ferrocenylquinolines, is of considerable interest since their properly substituted 2-aryl analogues are biologically active and exist in the structures of various antitumor agents [77].

Recently, as shown by the Shimizu [78], Baba [79] and Wang [80] research groups, the reactions of aromatic imines (in-situ synthesized or isolated) with enolizable aliphatic aldehydes in the presence of metal, Brønsted or Lewis acid catalysts led to formation of quinoline derivatives. In this respect, molecular iodine ($I_2$) has gained considerable importance as a mild and nontoxic Lewis acid catalyst since it

catalyzed various organic reactions with high efficiency and selectivity [81]. Owing to carbonyl activating property [82], molecular iodine was successfully used as a catalyst in the quinoline forming reactions of imines and aldehydes as well [80,83]. However, to the best of our knowledge, such reactions catalyzed by iodine were not used for the synthesis of ferrocenyl-substituted quinolines.

As part of a program to synthesize new ferrocenyl-substituted heterocyclic compounds as potential pharmaceuticals [84], we have recently investigated molecular iodine catalyzed reactions of *in situ* synthesized ferrocenyl imines (**26**) with enolizable aliphatic aldehydes (**27**) to afford 2-ferrocenylquinolines (**28**) (Figure 23) [85].

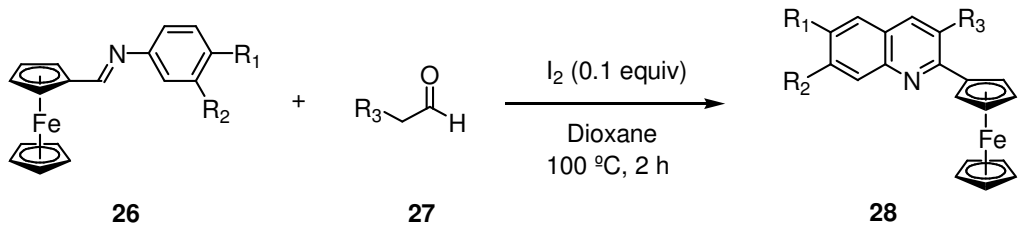



**Figure 23.** Iodine-catalyzed reactions of ferrocenylimines **26** with enolizable aldehydes 27 to afford ferrocenyl-substituted quinolines **28**.

In this thesis, the scope, limitations and mechanisms of these reactions will be discussed [85].

# CHAPTER 2

# RESULTS AND DISCUSSION

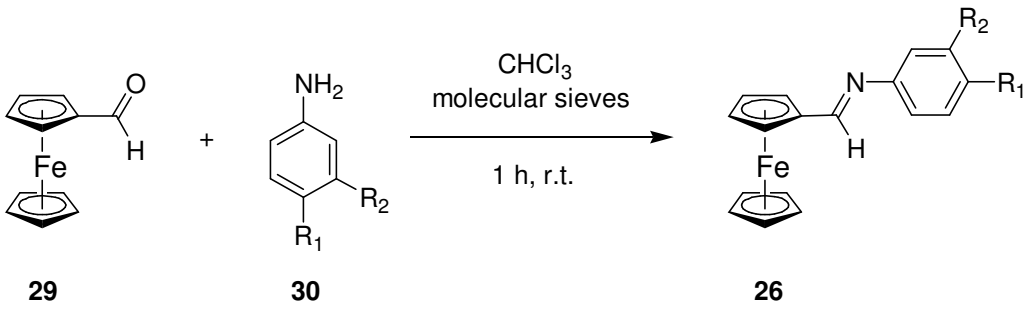
## 2.1. Synthesis of ferrocenyl quinolines.

The main objective of this study is to investigate the reaction between ferrocenyl-substituted imines and different enolizable aliphatic aldehydes to synthesize ferrocenyl-substituted quinolines derivatives, which have some potential biological activities.

### 2.1.1. Synthesis of ferrocenyl-substitued imine derivatives.

For the synthesis of ferrocenyl-substituted quinoline derivatives (**28**), the starting materials, ferrocenyl-substitued imine derivatives (**26**) were first prepared. Synthesis of imines was achieved from ferrocenecarboxaldehyde (**29**) according to known literature procedures. Results are summarized in Table 1. Initially, ferrocenecarboxaldehyde (**29**) was reacted with aniline (**30A**) in chloroform at room temperature for 1 h in the presence of molecular sieves. This reaction produced *N*-(ferrocenylidene)aniline (**26A**) in 59% yield. Then, the same reaction was carried out with *p*-chloroaniline (**30B**), *p*-bromoaniline (**30C**) and *m*-tolylamine (**30D**) to synthesize 4-chloro-*N*-(ferrocenylidene)aniline (**26B**), 4-bromo-*N*-(ferrocenylidene)aniline (**26C**) and *N*-(ferrocenylidene)-3-methylaniline (**26D**), respectively, as depicted in Table 1.

**Tablo 1.** Synthesis of ferrocenyl-substituted imine derivatives (**26**).




**29** **30** **26**

| **Entry**[a] | **$R_1$** | **$R_2$** | **Yield of 26 (%)** |
|---|---|---|---|
| **A** | H | H | 59 |
| **B** | Cl | H | 62 |
| **C** | Br | H | 64 |
| **D** | H | $CH_3$ | 63 |

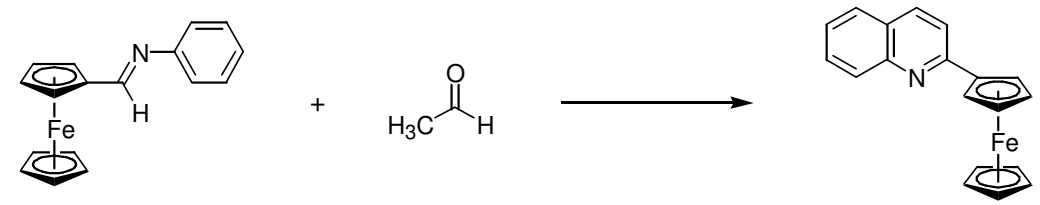
[a] Entry letters define $R_1$ and $R_2$ groups for compound **26** and **30**.

During the course of synthesis, it was observed that imines partially decomposed or hydrolyzed during the separation by flash chromatography as well as on standing for next reaction. For this reason, after the requisite imines were synthesized, they were immediately subjected to the next step.

### 2.1.2. Synthesis of ferrocenyl-substituted quinoline derivatives.

The reactions were initially examined under different conditions, such as refluxing THF, benzene, dioxane and toluene with varying amounts of molecular iodine catalyst, as illustrated in Table 2. The best results were obtained as follows: ferrocenylimine **26A** (1.2 equiv) was reacted with acetaldehyde (**27A**) (1.0 equiv) in the presence of molecular iodine (0.1 equiv) at 100 °C in dioxane for 2 h, and the products were isolated by flash chromatography. It should be noted that longer reaction times did not improve the yields of products. Without using iodine, no any quinoline product was obtained.

**Tablo 2.** Yield optimization studies for the synthesis of ferrocenylquinolines (**28**).

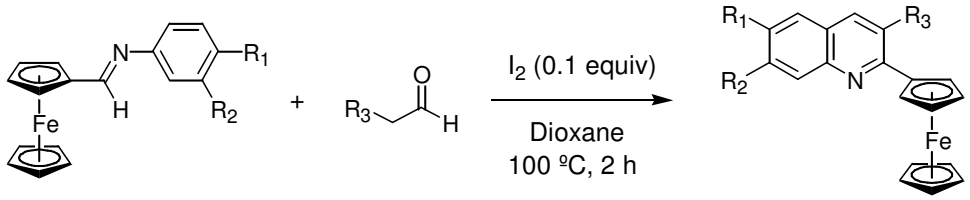



**26A** (1.2 equiv) **27A** (1.0 equiv) **28A**

| Catalyst | Amount of Catalyst | Solvent | Temperature | Time | Yield (%) |
|---|---|---|---|---|---|
| $I_2$ | 0.10 equiv | THF | 65 °C | 2 h | 39 |
| $I_2$ | 0.10 equiv | benzene | 80 °C | 2 h | 51 |
| **$I_2$** | **0.10 equiv** | **dioxane** | **100 °C** | **2 h** | **78** |
| $I_2$ | 0.01 equiv | dioxane | 100 °C | 2 h | 69 |
| $I_2$ | 0.10 equiv | toluene | 111 °C | 2 h | 28 |
| - | - | dioxane | 100 °C | 2 h | - |

Subsequently, we synthesized different quinoline derivatives by employing the optimized conditions. Results are shown in Table 3. The reaction between *N*-(ferrocenylidene)-aniline (**26A**) and acetaldehyde (**27A**) led to the formation of 2-ferrocenylquinoline (**28A**) in 78% yield (Entry A). Similarly, the reaction of acetaldehyde (**27A**) with 4-chloro-*N*-(ferrocenylidene)aniline (**26B**) and 4-bromo-*N*-(ferrocenylidene)aniline (**26C**) produced 6-chloro-2-ferrocenylquinoline (**28B**) and 6-bromo-2-ferrocenyl-quinoline (**28C**) in 63 and 65% yields, respectively (Entries B and C). Interestingly, from the reaction between *N*-(ferrocenylidene)-3-methylaniline (**26D**) and acetaldehyde (**27A**), only one regioisomer, namely 2-ferrocenyl-7-methylquinoline (**28D**), was obtained in 88% yield (Entry D). The reaction of ferrocenylimine **26D** with propionaldehyde (**27B**) gave a complex mixture, from which only 2-ferrocenyl-3,7-dimethylquinoline (**28E**) was isolated even though in low yield (25%) (Entry E). Formation of polymeric by-products as well as the partial hydrolysis of starting imine **26D** apparently lowered the yield of **28E**.

**Tablo 3.** Iodine-catalyzed reactions of ferrocenylimines **26** with enolizable aldehydes **27** to afford ferrocenyl-substituted quinolines **28**.




**26A** ($R_1$=$R_2$=H)
**26B** ($R_1$=Cl, $R_2$=H)
**26C** ($R_1$=Br, $R_2$=H)
**26D** ($R_1$=H, $R_2$=$CH_3$)

**27A** ($R_3$=H)
**27B** ($R_3$=$CH_3$)

**28**

| **Entry**[a] | **Reacting Partners** | **$R_1$** | **$R_2$** | **$R_3$** | **Products (isolated yield, %)** |
|---|---|---|---|---|---|
| **A** | **26A** + **27A** | H | H | H | **28A** (78) |
| **B** | **26B** + **27A** | Cl | H | H | **28B** (63) |
| **C** | **26C** + **27A** | Br | H | H | **28C** (65) |
| **D** | **26D** + **27A** | H | $CH_3$ | H | **28D** (88) |
| **E** | **26D** + **27B** | H | $CH_3$ | $CH_3$ | **28E** (25) |

[a] Entry letters define $R_1$, $R_2$ and $R_3$ groups for compound **28**.

### 2.1.3. Mechanism for the formation of quinolines 28.

The mechanism proposed for the formation of quinoline derivatives **28** is given in Figure 24. It is well known that in the presence of Lewis acids such as iodine, imines such as **26** can be activated. Similarly, in the presence of iodine, aldehydes such as **27** can be easily equilibrated with their corresponding enols **31**. As expected, the reaction between in situ generated enol **31** and iodine-activated imine **32** gives β-anilino-propionaldehyde **33**. The intramolecular Friedel-Crafts reaction of iodine-activated β-anilinopropionaldehyde **34** affords tetrahydroquinolinol derivative **35**. The subsequent dehydration in **35** leads to formation of dihydroquinoline **36**. Finally, the aerobic oxidation of **36** produces the expected quinoline derivative **28**. Alternatively, dihydroquinoline **36** can be oxidized to quinoline **28** by the starting imine **26** to some extent since it was reported that imines can behave as hydrogen acceptor in these types of reactions [78c]. In this case, reaction should also produce a secondary amine, such as (ferrocenylmethyl)aniline derivative **37** (Figure 24). However, the formation of such amines in these reactions was not detected.

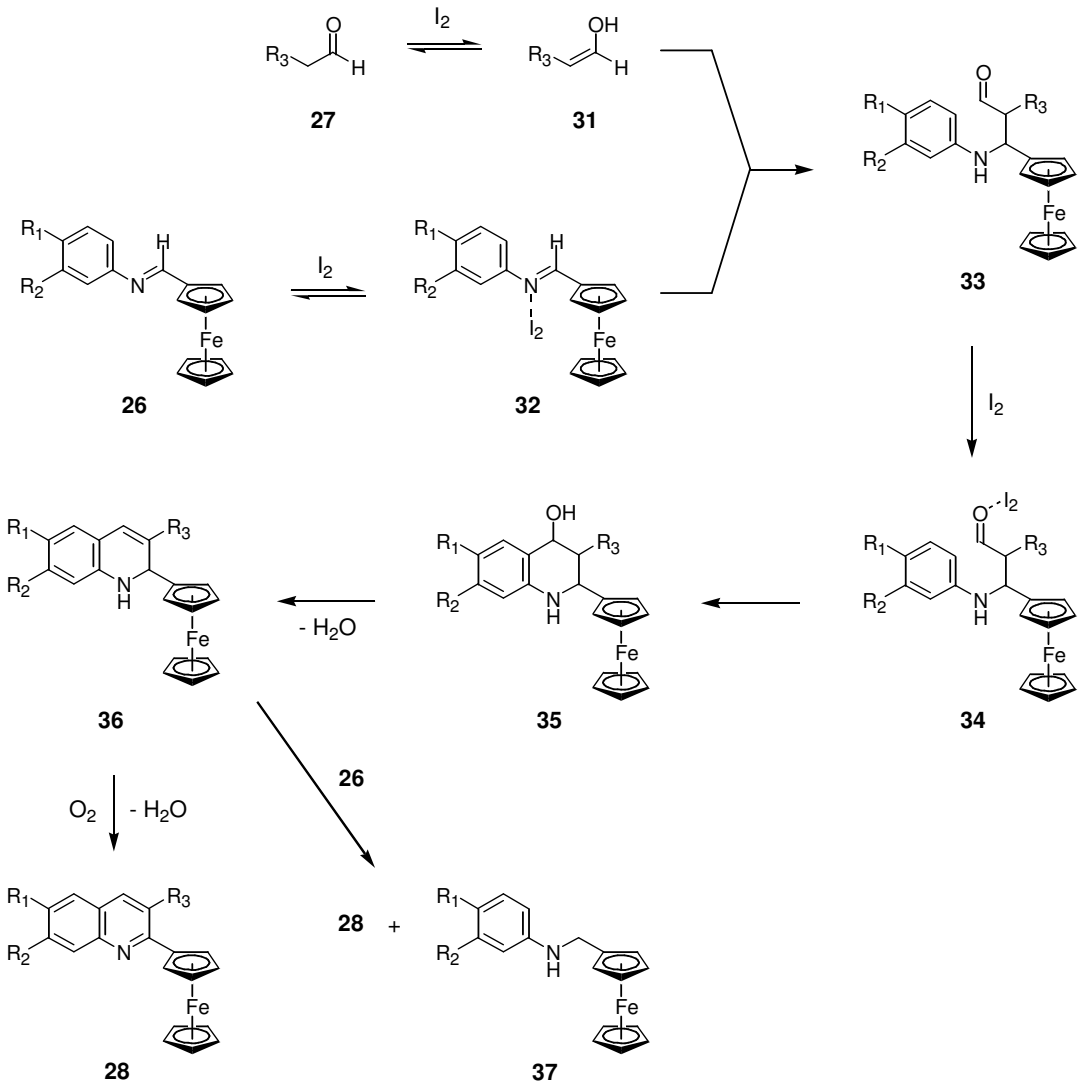



**Figure 24.** Proposed mechanism for the formation of ferrocenyl-substituted quinolines **28**.

# CHAPTER 3

# CONCLUSION

We have investigated the iodine-catalyzed reaction between ferrocenylimines (**26**) and enolizable aldehydes (**27**) to synthesize 2-ferrocenylquinolines (**28**).

First of all, ferrocenyl-substituted imine derivatives (**26**) were prepared by treating ferrocenecarboxaldehyde (**29**) with corresponding aniline derivatives (**30**). Then, these imines (**26**) were subjected to iodine-catalyzed quinoline-forming reactions with corresponding aldehydes.

Reactions were initially examined under a variety of conditions, such as refluxing THF, benzene, dioxane and toluene with varying amounts of molecular iodine catalyst. The best results were obtained with ferrocenylimine (**26**) (1.2 equiv), aldehyde (**27**) (1.0 equiv) in the presence of molecular iodine (0.1 equiv) at 100 °C in dioxane for 2 h. As anticipated, in all cases, the expected 2-ferrocenylquinolines (**28**) were obtained from these reactions.

In summary, we synthesized new ferrocenyl-substituted quinoline derivatives (**28**), which will be of value in the development of new synthetic pathways for the synthesis of new pyrazole derivatives. Due to the ready availability of ferrocenylimines **26** and aldehydes **27**, this practical one-pot method represents a versatile synthesis of ferrocenyl-substituted quinolines **28**.

# 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 Bruker Vertex 70 Spectrometer using attenuated total reflection (ATR). 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 Bruker Daltonics spectrometer using Electrospray Ionization (ESI) with Micro-Tof; m/z values are reported (For each measurement, the mass scale was recalibrated with sodium formiate clusters, and samples were dissolved and measured in MeOH). High resolution mass spectra (HRMS) were also obtained on a Bruker Daltonics spectrometer. 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. All commercially available reagents and reactants were obtained in reagent grade and used without purification. All reaction solvents were distilled for purity. Diethylether, THF and dioxane were distilled from sodium/benzophenone kettle.

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

### 4.1. General Procedure 1. Synthesis of ferrocene substituted imines 26A-D (Table 1).

To the mixture of ferrocenecarboxaldehyde (**29**) (2 mmol) and aniline derivatives (**30**) (4 mmol) under argon was added molecular sieves (0.4 nm) (0.760 mg) and the resulting mixture was dissolved in dichloromethane (8 mL) and stirred at room temperature for 1 h. At the end of the period, the mixture was filtered to separate molecular sieves and the solvent was evaporated in a rotary evaporator. Final purification of the crude product was achieved through flash chromatography on silica gel using hexane/EtOAc (24/1) as eluent.

#### 4.1.1. Synthesis of *N*-(ferrocenylidene)aniline (26A) (Table 1, Entry A).

General Procedure 1 was followed by using ferrocenecarboxaldehyde (**29**) (0.428 g, 2 mmol), aniline (**30A**) (0.365 mL, 4 mmol) and molecular sieves (0.4 nm) (0.760 mg). After chromatographic purification, the brick-red colored fraction was collected to give *N*-(ferrocenylidene)aniline (**26A**) (340 mg, 59% yield).

#### 4.1.2. Synthesis of 4-chloro-*N*-(ferrocenylidene)aniline (26B) (Table 1, Entry B).

General Procedure 1 was followed by using ferrocenecarboxaldehyde (**29**) (0.428 g, 2 mmol), *p*-chloroaniline (**30B**) (0.365 mL, 4 mmol) and molecular sieves (0.4 nm) (0.760 mg). After chromatographic purification, the brick-red colored fraction was collected to give 4-chloro-*N*-(ferrocenylidene)aniline (**26B**) (400 mg, 62% yield).

### 4.1.3. Synthesis of 4-bromo-*N*-(ferrocenylidene)aniline (26C) (Table 1, Entry C).

General Procedure 1 was followed by using ferrocenecarboxaldehyde (**29**) (0.428 g, 2 mmol), *p*-bromoaniline (**30C**) (0.365 mL, 4 mmol) and molecular sieves (0.4 nm) (0.760 mg). After chromatographic purification, the brick-red colored fraction was collected to give 4-bromo-*N*-(ferrocenylidene)aniline (**26C**) (401 mg, 64% yield).

### 4.1.4. Synthesis of *N*-(ferrocenylidene)-3-methylaniline (26D) (Table 1, Entry D).

General Procedure 1 was followed by using ferrocenecarboxaldehyde (**29**) (0.428 g, 2 mmol), *m*-tolylaniline (**30D**) (0.365 mL, 4 mmol) and molecular sieves (0.4 nm) (0.760 mg). After chromatographic purification, the brick-red colored fraction was collected to give *N*-(ferrocenylidene)-3-methylaniline (**26D**) (382 mg, 62% yield).

## 4.2. General Procedure 2. Synthesis of ferrocenyl quinolines 28A-E (Table 3).

To a solution of ferrocenylimine (**26**) (1.2 mmol) and aldehyde (**27**) (1.0 mmol) in 5 mL of dioxane was added iodine (0.1 mmol). The resulting mixture was then heated at reflux for 2 h. After the reaction was complete, the mixture was cooled to 25 $^{o}$C, and the solvent was removed on a rotary evaporator. Final purification of the crude product was achieved through flash chromatography on silica gel using hexane/EtOAc (24/1) as eluent.

### 4.2.1. Synthesis of 2-ferrocenylquinoline [(quinolin-2-yl)ferrocene] (28A) (Table 3, Entry A).

General Procedure 2 was followed by using ferrocenyl imine (**26A**) (225 mg, 0.78 mmol), acetaldehyde (**27A**) (0.036 mL, 0.65 mmol) and iodine (15.3 mg, 0.065

mmol). After chromatographic purification, the red colored fraction was collected to give 2-ferrocenylquinoline (**28A**) (158.6 mg, 78% yield).

**28A:** $^{1}$H NMR ($CDCl_3$): δ 8.06 (d, 1H, *J* = 8.5 Hz), 8.02 (d, 1H, *J* = 8.5 Hz), 7.74 (d, 1H, *J* = 8.0 Hz), 7.66 (pseudo t, 1H, *J* = 7.4 Hz), 7.56 (d, 1H, *J* = 8.5 Hz), 7.45 (pseudo t, 1H, *J* = 7.4 Hz), 5.08 (pseudo t, 2H, *J* = 1.6 Hz), 4.47 (pseudo t, 2H, *J* = 1.6 Hz), 4.05 (s, 5H); $^{13}$C NMR ($CDCl_3$): δ 159.5 (C), 148.3 (C), 135.4 (CH), 129.3 (CH), 129.0 (CH), 127.5 (CH), 126.7 (C), 125.4 (CH), 119.5 (CH), 84.0 (C), 70.4 (CH), 69.7 (CH), 68.0 (CH); IR (neat): 3092, 3061, 2922, 2851, 1614, 1599, 1556, 1510, 1424, 1280, 1129, 1104, 1092, 910, 907, 815, 756 $cm^{-1}$; MS (ESI, *m/z*): 314.06 $[M+H]^+$; HRMS (ESI): calcd. for $C_{19}H_{16}FeN$: 314.0632 $[M+H]^+$. Found: 314.0627. The spectral data are in agreement with those previously reported [76a,b,d].

### 4.2.2. Synthesis of 2-ferrocenyl-7-methylquinoline [(7-methylquinolin-2-yl)-ferrocene] (28B) (Table 3, Entry B).

General Procedure 2 was followed by using ferrocenyl imine (**26B**) (261 mg, 0.86 mmol), acetaldehyde (**27A**) (0.04 mL, 0.72 mmol) and iodine (18.4 mg, 0.072 mmol). After chromatographic purification, the red colored fraction was collected to give 2-ferrocenyl-7-methylquinoline (**28B**) (207 mg, 88% yield).

**28B:** $^{1}$H NMR ($CDCl_3$): δ 7.97 (d, 1H, *J* = 8.5 Hz), 7.84 (s, 1H), 7.62 (d, 1H, *J* = 8.2 Hz), 7.49 (d, 1H, *J* = 8.5 Hz), 7.29 (d, 1H, *J* = 8.2 Hz), 5.06 (s, 2H), 4.45 (s, 2H), 4.04 (s, 5H), 2.55 (s, 3H); $^{13}$C NMR ($CDCl_3$): δ 159.4 (C), 148.5 (C), 139.6 (C), 135.1 (CH), 128.2 (CH), 127.6 (CH), 127.2 (CH), 124.7 (C), 118.7 (CH), 84.1 (C), 70.3 (CH), 69.6 (CH), 67.9 (CH), 21.8 ($CH_3$); IR (neat): 3094, 3037, 2914, 2854, 1625, 1595, 1558, 1517, 1435, 1277, 1104, 1091, 1027, 998, 874, 844, 811 $cm^{-1}$; MS (ESI, *m/z*): 350.06 $[M+Na]^+$, 328.08 $[M+H]^+$; HRMS (ESI): calcd. for $C_{20}H_{18}FeN$: 328.0789 $[M+H]^+$. Found: 328.0783.

### 4.2.3. Synthesis of 6-bromo-2-ferrocenylquinoline [(6-bromoquinolin-2-yl)-ferrocene] (28C) (Table 3, Entry C).

General Procedure 2 was followed by using ferrocenyl imine (**26C**) (260 mg, 0.833 mmol), acetaldehyde (**27A**) (0.039 mL, 0.69 mmol) and iodine (17.8 mg, 0.07 mmol). After chromatographic purification, the red colored fraction was collected to give 6-bromo-2-ferrocenylquinoline (**28C**) (176 mg, 65% yield).

**28C:** $^{1}$H NMR ($CDCl_3$): δ 7.91 (d, 1H, *J* = 8.5 Hz), 7.89 (d, 1H, *J* = 8.5 Hz), 7.88 (s, 1H), 7.70 (dd, 1H, *J* = 8.5, 2.0 Hz), 7.54 (d, 1H, *J* = 8.5 Hz), 5.04 (pseudo t, 2H, *J* = 1.6 Hz), 4.47 (pseudo t, 2H, *J* = 1.6 Hz), 4.04 (s, 5H); $^{13}$C NMR ($CDCl_3$): δ 160.1 (C), 146.9 (C), 134.4 (CH), 132.7 (CH), 130.7 (CH), 129.5 (CH), 127.8 (C), 120.2 (CH), 118.9 (C), 83.4 (C), 70.7 (CH), 69.7 (CH), 68.0 (CH); IR (neat): 3094, 3069, 2923, 1593, 1545, 1500, 1381, 1327, 1281, 1188, 1134, 1105, 1062, 1025, 944, 880, 844 $cm^{-1}$; MS (ESI, *m/z*): 413.95 $[M+Na]^+$, 391.97 $[M+H]^+$; HRMS (ESI): calcd. for $C_{19}H_{15}BrFeN$: 391.9737 $[M+H]^+$. Found: 391.9733.

### 4.2.4. Synthesis of 6-chloro-2-ferrocenylquinoline [(6-chloroquinolin-2-yl)-ferrocene] (28D) (Table 3, Entry D).

General Procedure 2 was followed by using ferrocenyl imine **26D** (280 mg, 0.87 mmol), acetaldehyde (**27A**) (0.04 mL, 0.73 mmol) and iodine (18.56 mg, 0.072 mmol). After chromatographic purification, the red colored fraction was collected to give 6-chloro-2-ferrocenylquinoline (**28D**) (160 mg, 63% yield).

**28D:** $^{1}$H NMR ($CDCl_3$): δ 7.94 (m, 2H), 7.70 (s, 1H), 7.56 (m, 2H), 5.05 (s, 2H), 4.47 (s, 2H), 4.04 (s, 5H); $^{13}$C NMR ($CDCl_3$): δ 160.0 (C), 146.6 (C), 134.5 (CH), 130.9 (CH), 130.5 (CH), 130.2 (C), 127.2 (C), 126.2 (CH), 120.3 (CH), 83.3 (C), 70.6 (CH), 69.7 (CH), 68.0 (CH); IR (neat): 3094, 2923, 2853, 1597, 1548, 1503, 1485, 1411, 1379, 1327, 1281, 1189, 1132, 1106, 1094, 1074, 1026, 999, 948, 873, 853, 811 $cm^{-1}$; MS (ESI, *m/z*): 370.00 $[M+Na]^+$, 348.02 $[M+H]^+$; HRMS (ESI):

calcd. for $C_{19}H_{14}ClFeNNa$: 370.0062 $[M+Na]^+$. Found: 370.0057; calcd. for $C_{19}H_{15}ClFeN$: 348.0242 $[M+H]^+$. Found: 348.0237.

### 4.2.5. Synthesis of 2-ferrocenyl-3,7-dimethylquinoline [(3,7-dimethylquinolin-2-yl)ferrocene] (28E) (Table 3, Entry E).

General Procedure 2 was followed by using ferrocenyl imine **26D** (280 mg, 0.93 mmol), propionaldehyde (**27B**) (0.051 mL, 0.773 mmol) and iodine (19.84 mg, 0.078 mmol). After chromatographic purification, the red colored fraction was collected to give 2-ferrocenyl-3,7-dimethylquinoline (**28E**) (66mg, 25% yield).

**28E:** $^1$H NMR ($CDCl_3$): δ 7.83 (s, 1H), 7.79 (s, 1H), 7.58 (d, 1H, *J* = 8.2 Hz), 7.27 (d, 1H, *J* = 8.2 Hz), 5.09 (s, 2H), 4.44 (s, 2H), 4.10 (s, 5H), 2.74 (s, 3H), 2.54 (s, 3H); $^{13}$C NMR ($CDCl_3$): δ 158.3 (C), 146.9 (C), 138.5 (C), 136.4 (CH), 128.3 (C), 127.9 (CH), 127.8 (CH), 126.2 (CH), 124.9 (C), 85.5 (C), 70.0 (CH), 69.8 (CH), 69.5 (CH), 21.8 ($CH_3$), 21.4 ($CH_3$); IR (neat): 3092, 3071, 3051, 2969, 2920, 2854, 1625, 1599, 1502, 1453, 1410, 1383, 1323, 1268, 1140, 1105, 1074, 999, 896, 877, 823, 808, 779 $cm^{-1}$; MS (ESI, *m/z*): 342.09 $[M+H]^+$; HRMS (ESI): calcd. for $C_{21}H_{20}FeN$: 342.0945 $[M+H]^+$. Found: 342.0940.

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# APPENDIX A

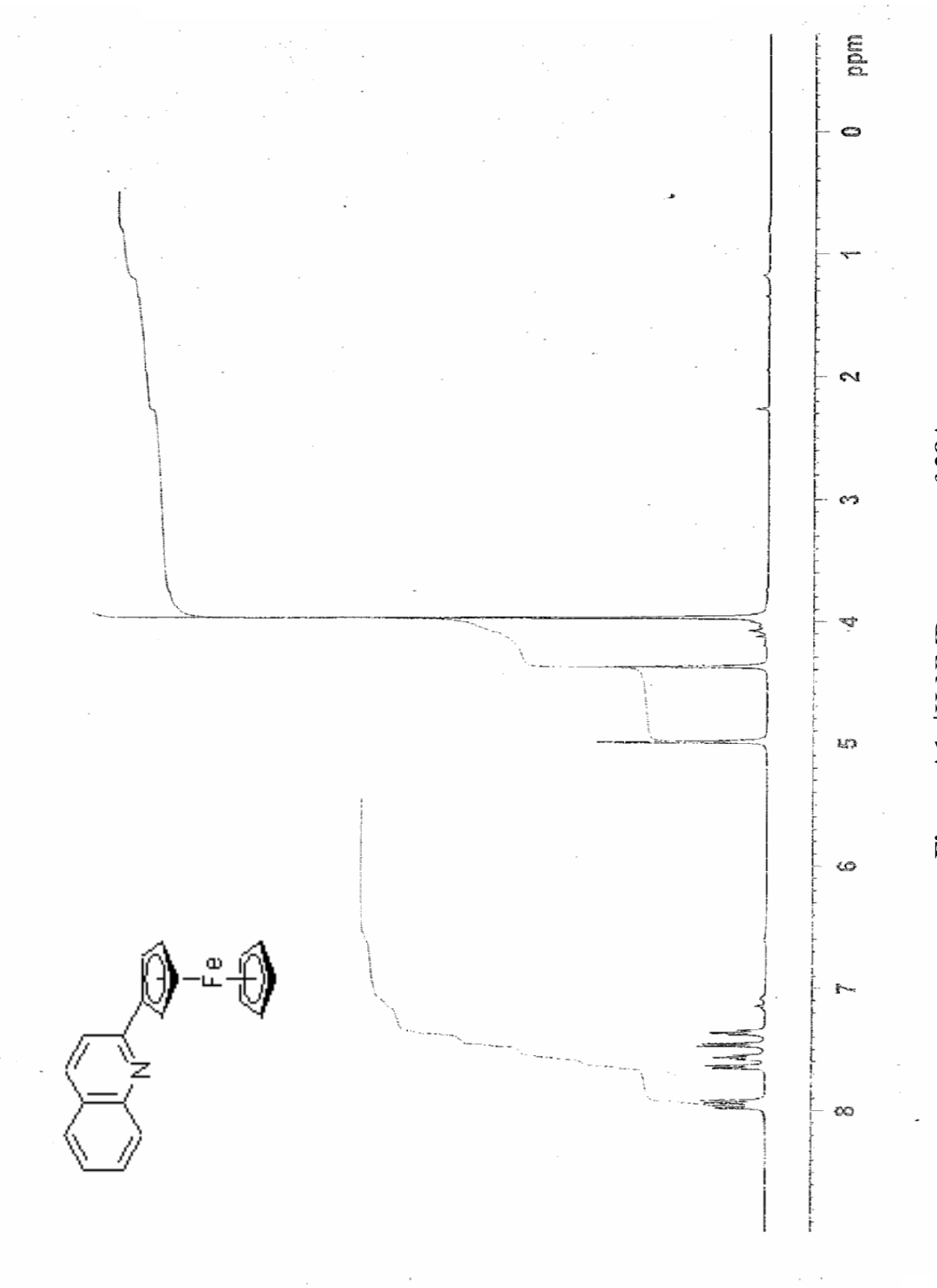


**Figure A1.** $^{1}$H-NMR spectrum of **28A.**

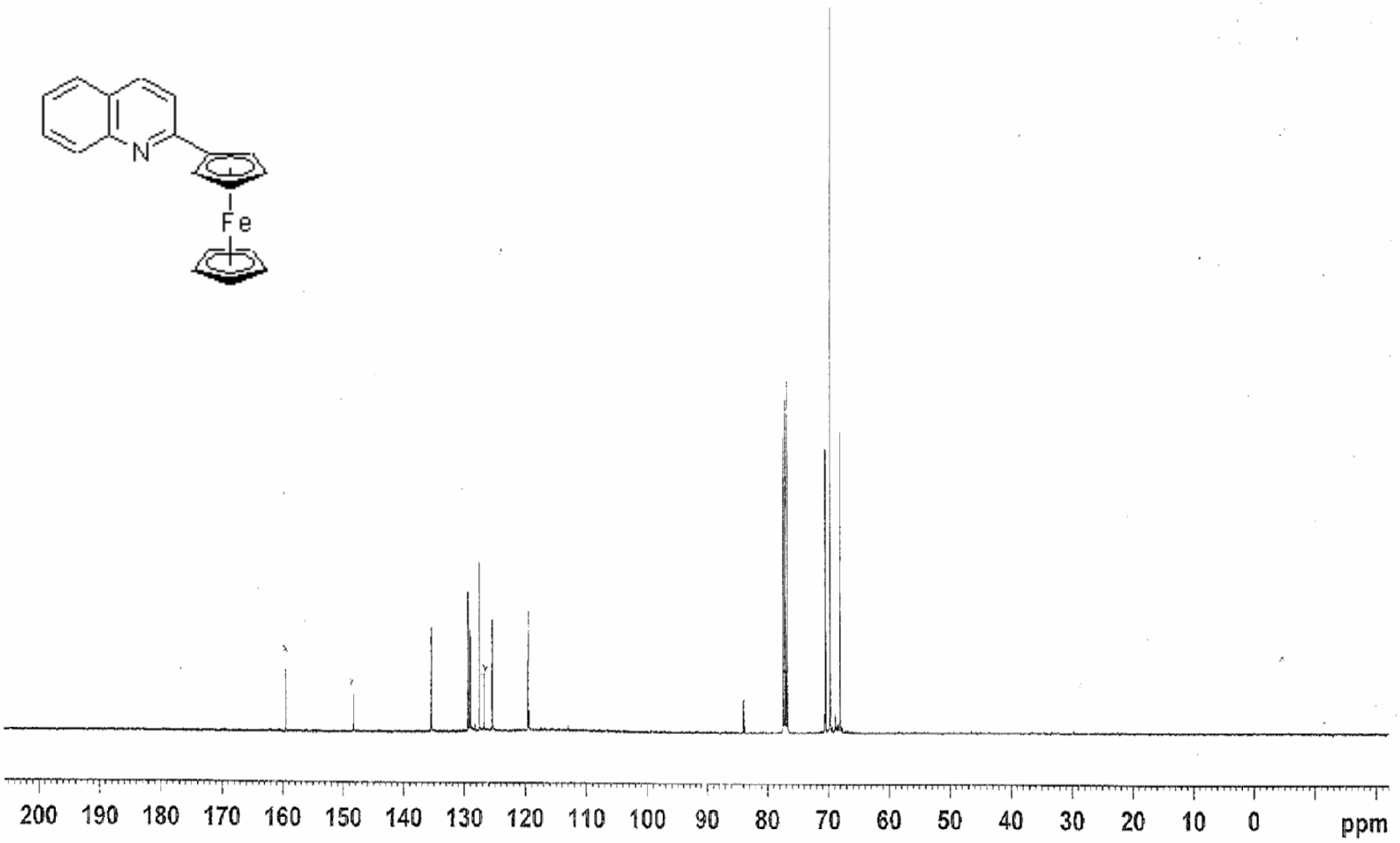


**Figure A2**. $^{13}$C-NMR spectrum of **28A.**

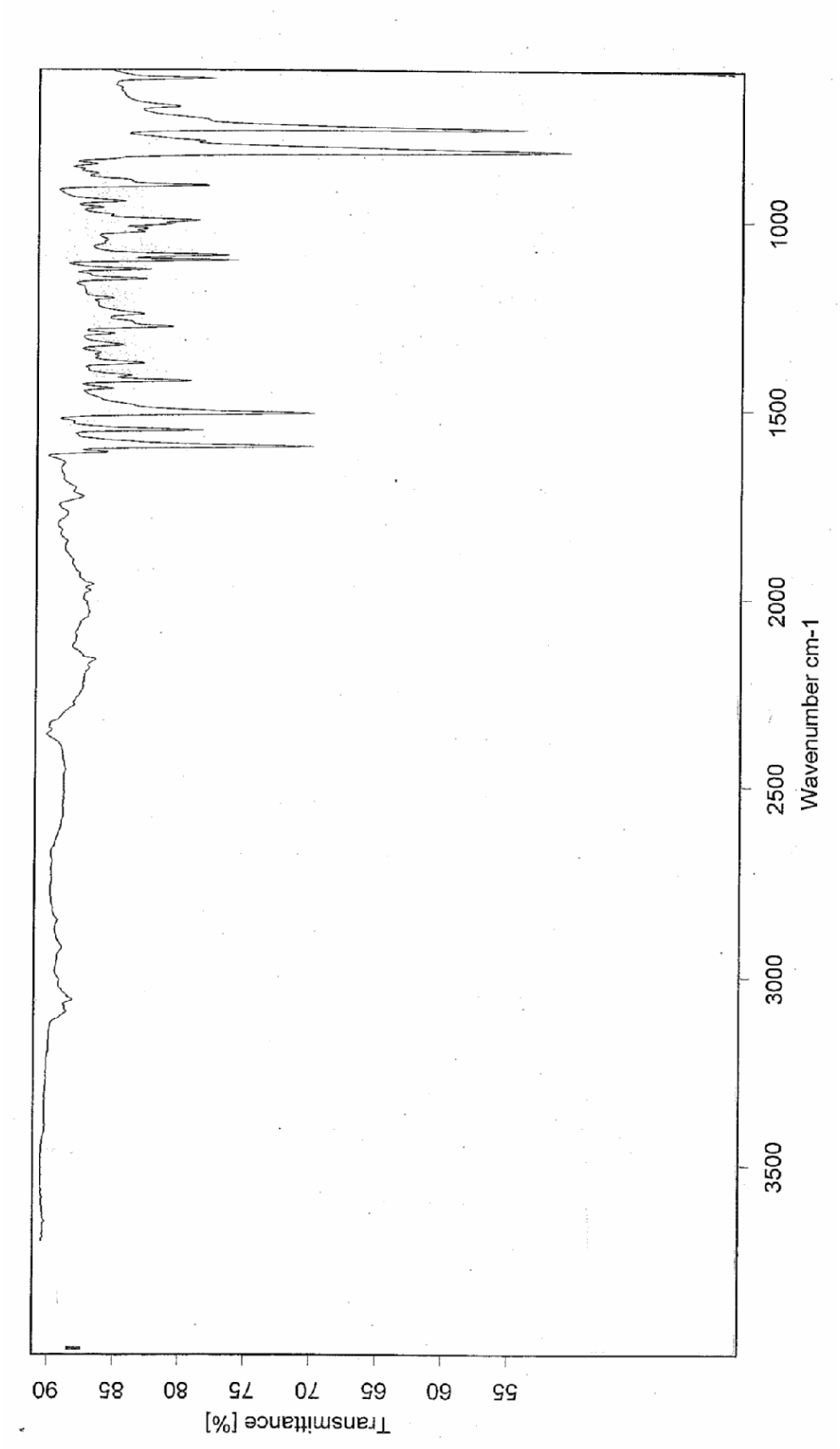


**Figure A3**. IR spectrum of **28A.**

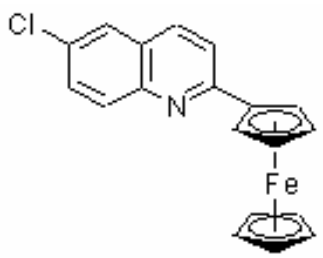


**Figure A4**. $^{1}$H-NMR spectrum of **28B**.

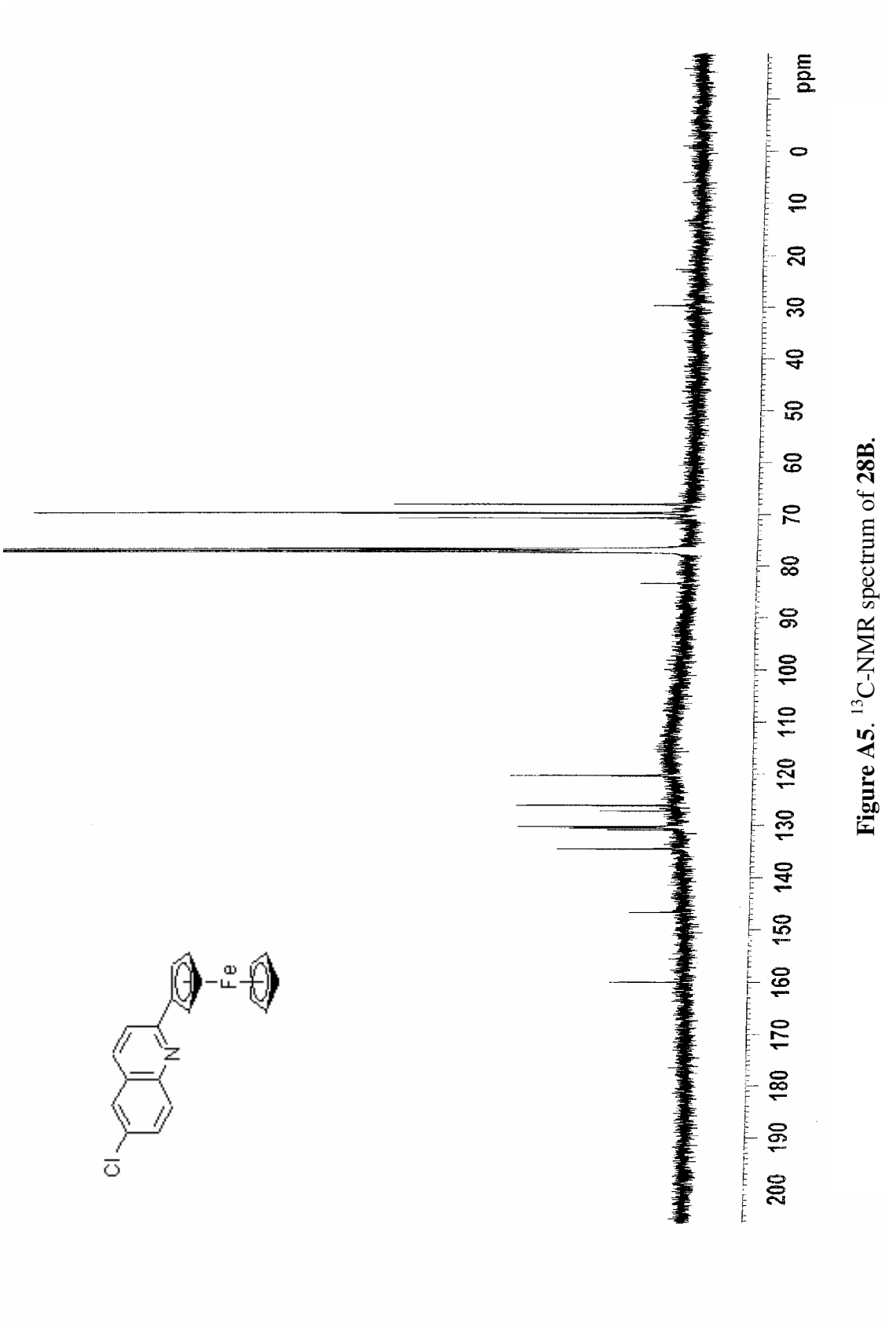


**Figure A5**. $^{13}$C-NMR spectrum of **28B**.

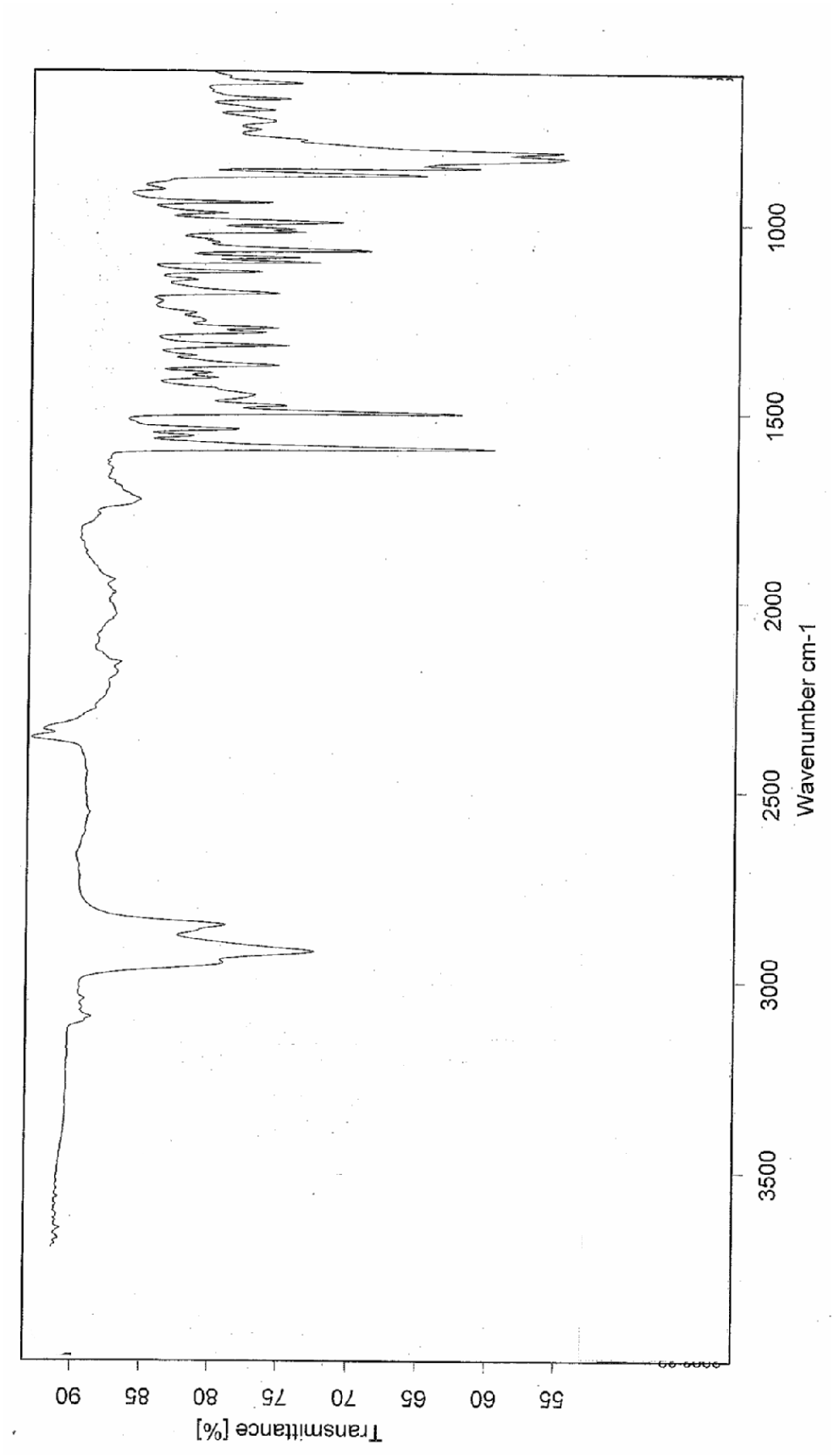


**Figure A6**. IR spectrum of **28B.**

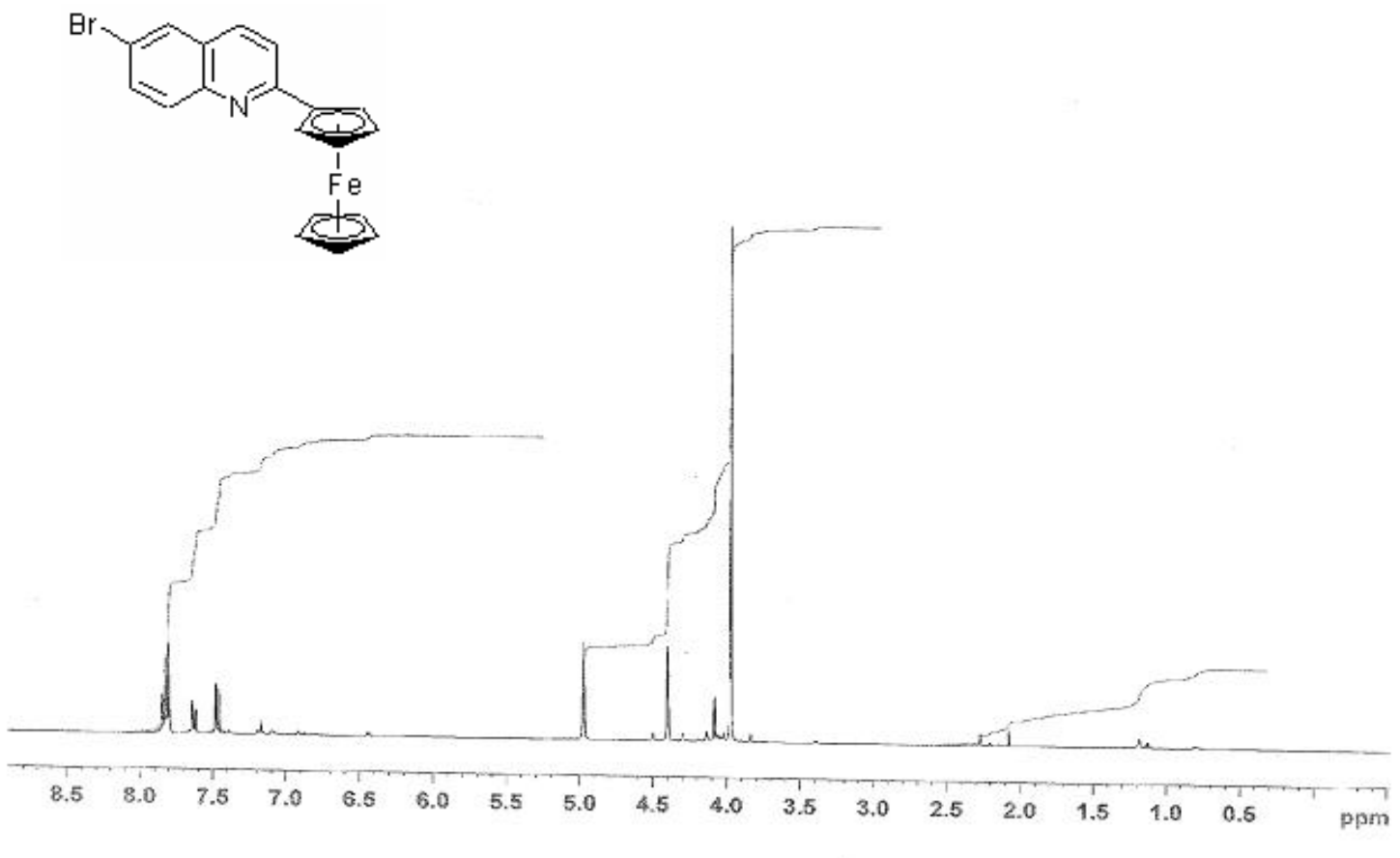


**Figure A7**. $^{1}$H-NMR spectrum of **28C.**

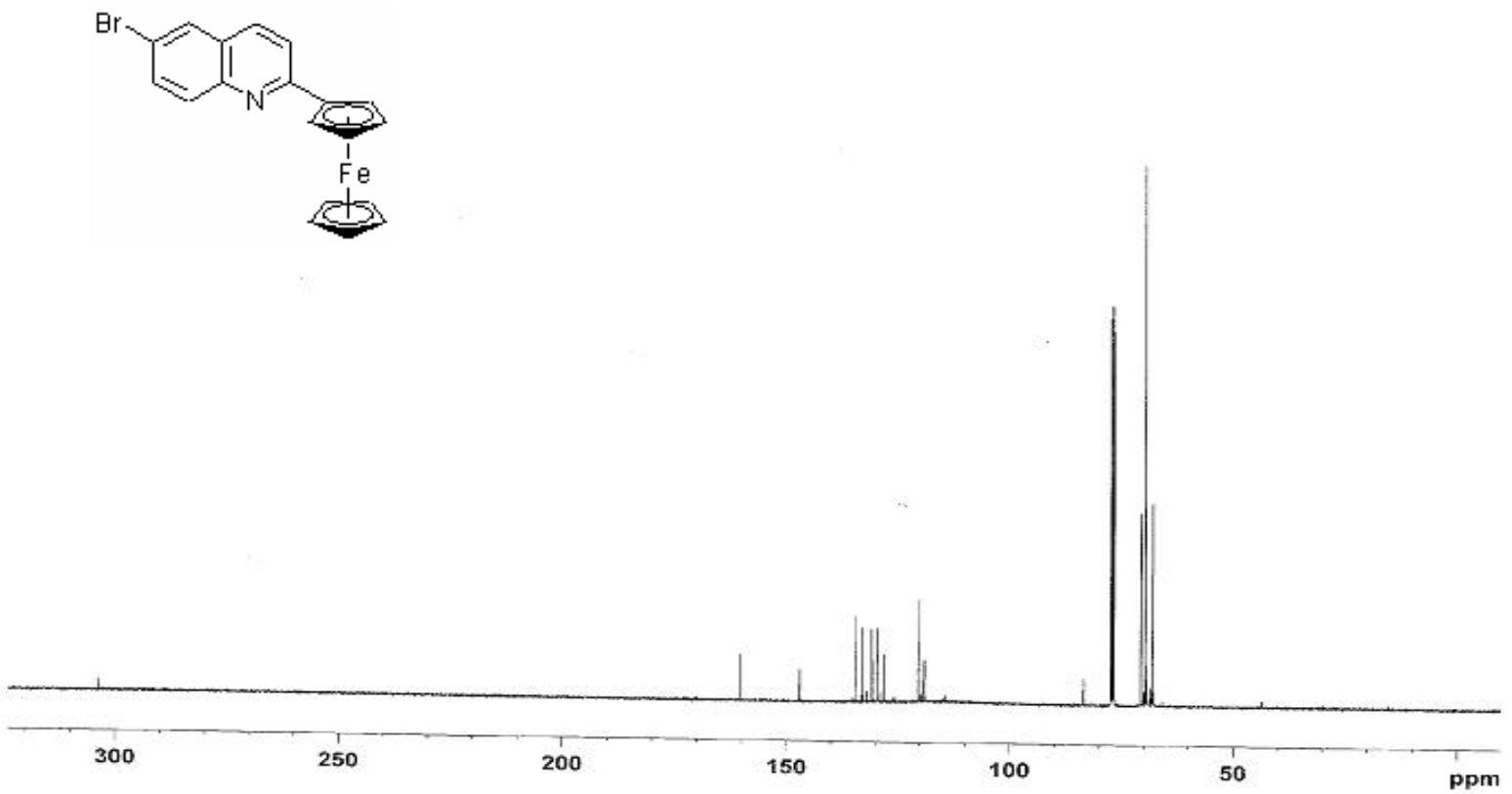


**Figure A8**. $^{13}$C-NMR spectrum of **28C.**

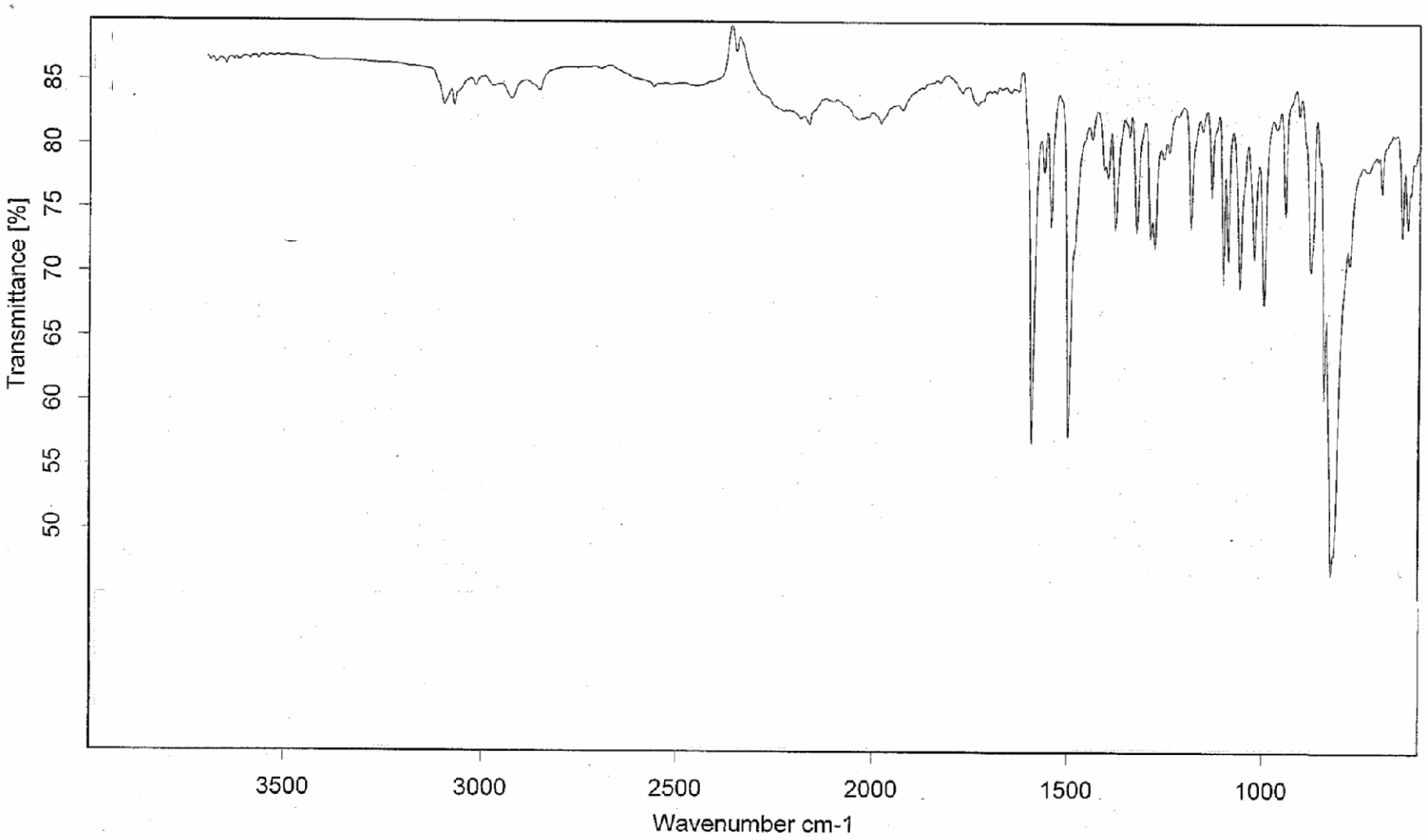


**Figure A9**. IR spectrum of **28C.**

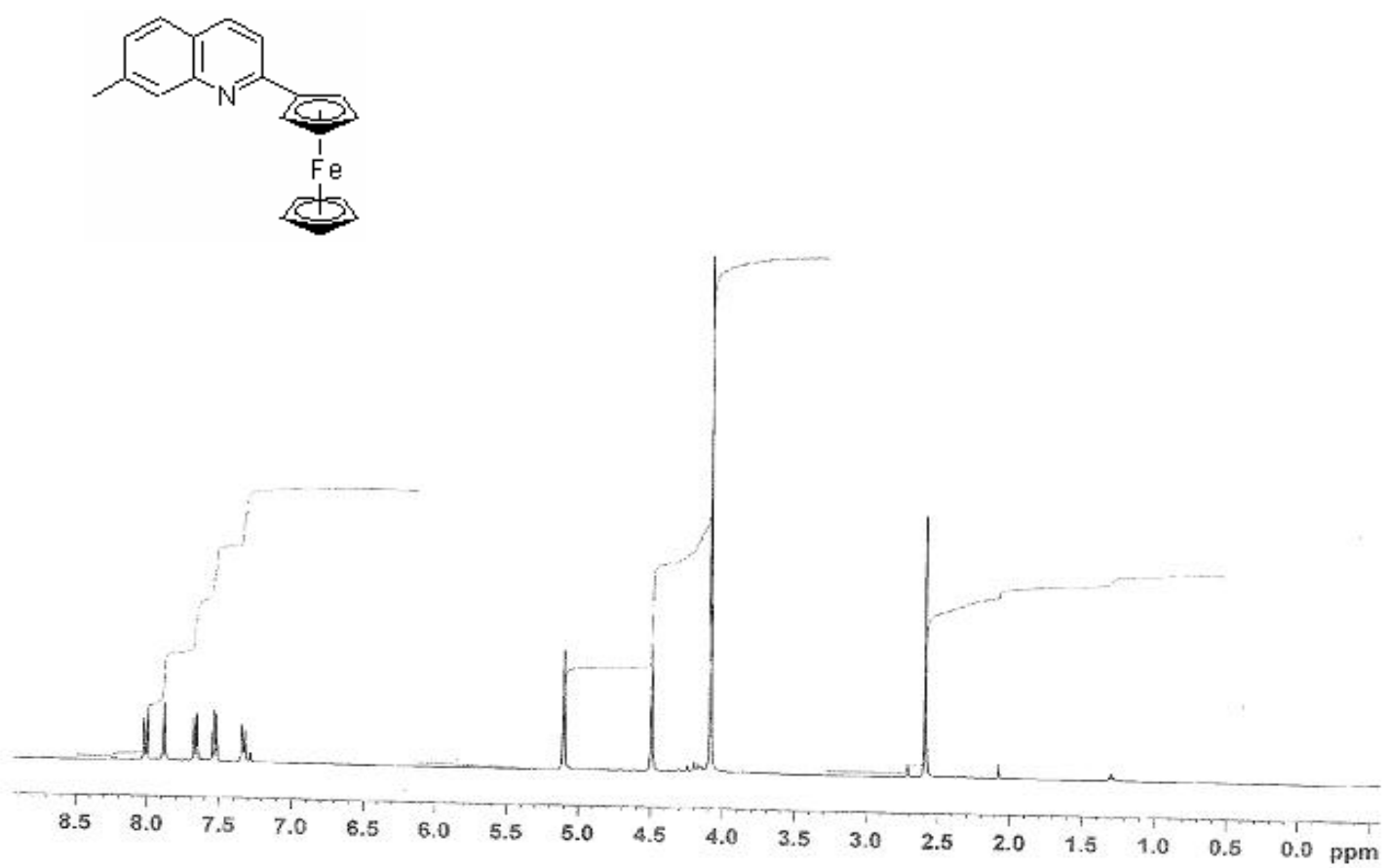


**Figure A107**. $^{1}$H-NMR spectrum of **28D.**

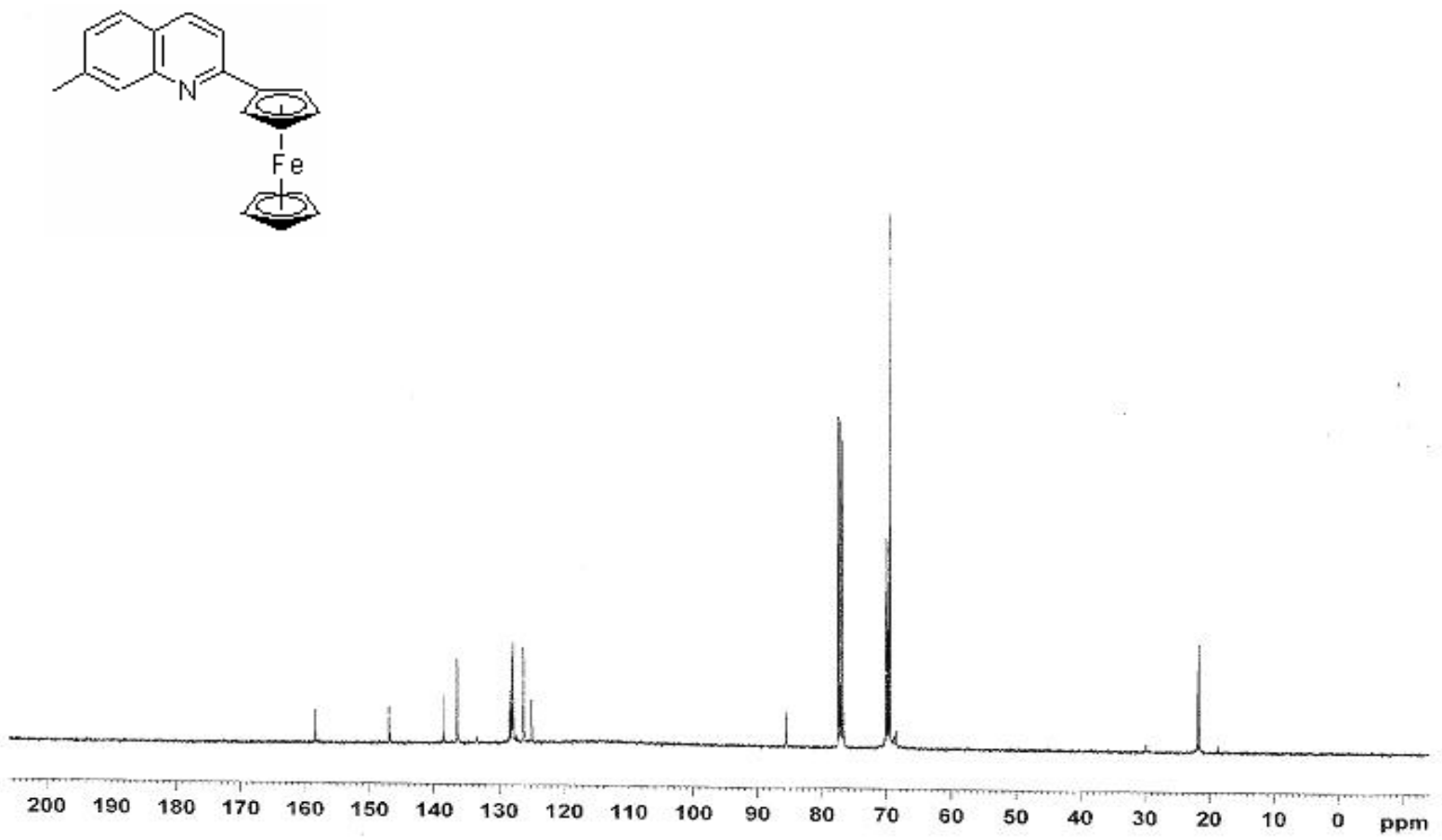


**Figure A11**. $^{13}$C-NMR spectrum of **28D.**

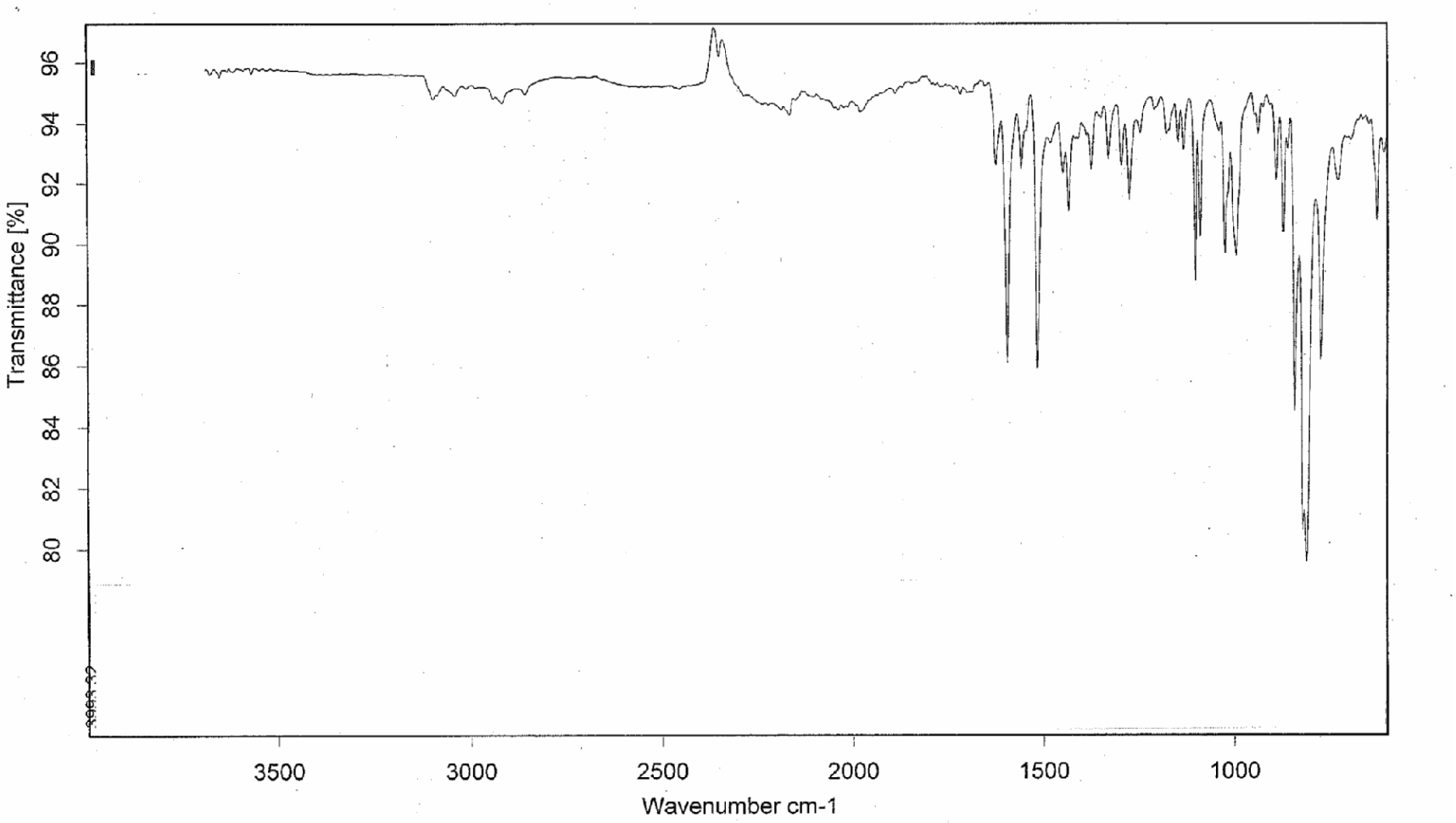


**Figure A12**. IR spectrum of **28D.**

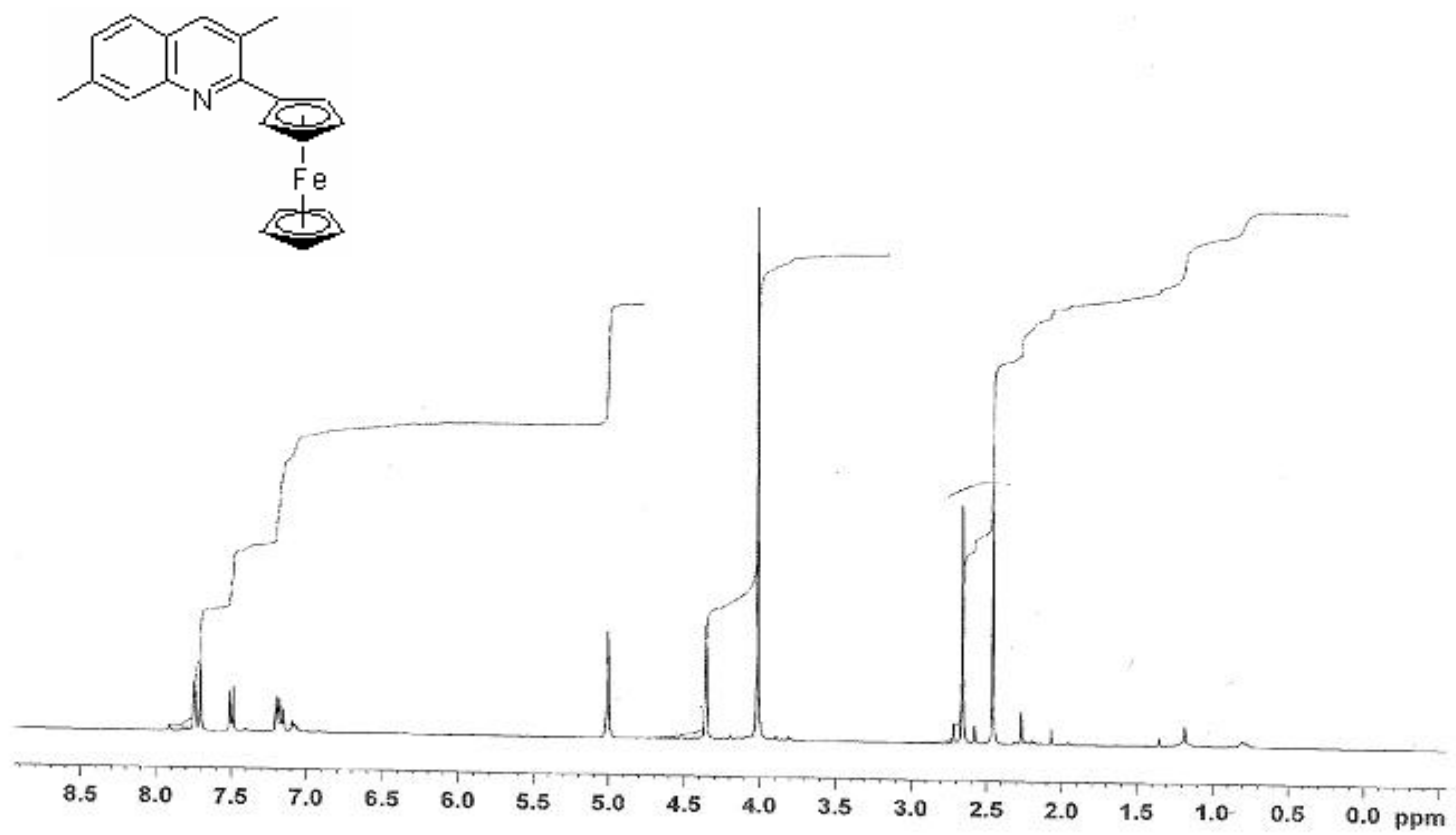


**Figure A13**. $^{1}$H-NMR spectrum of **28E.**

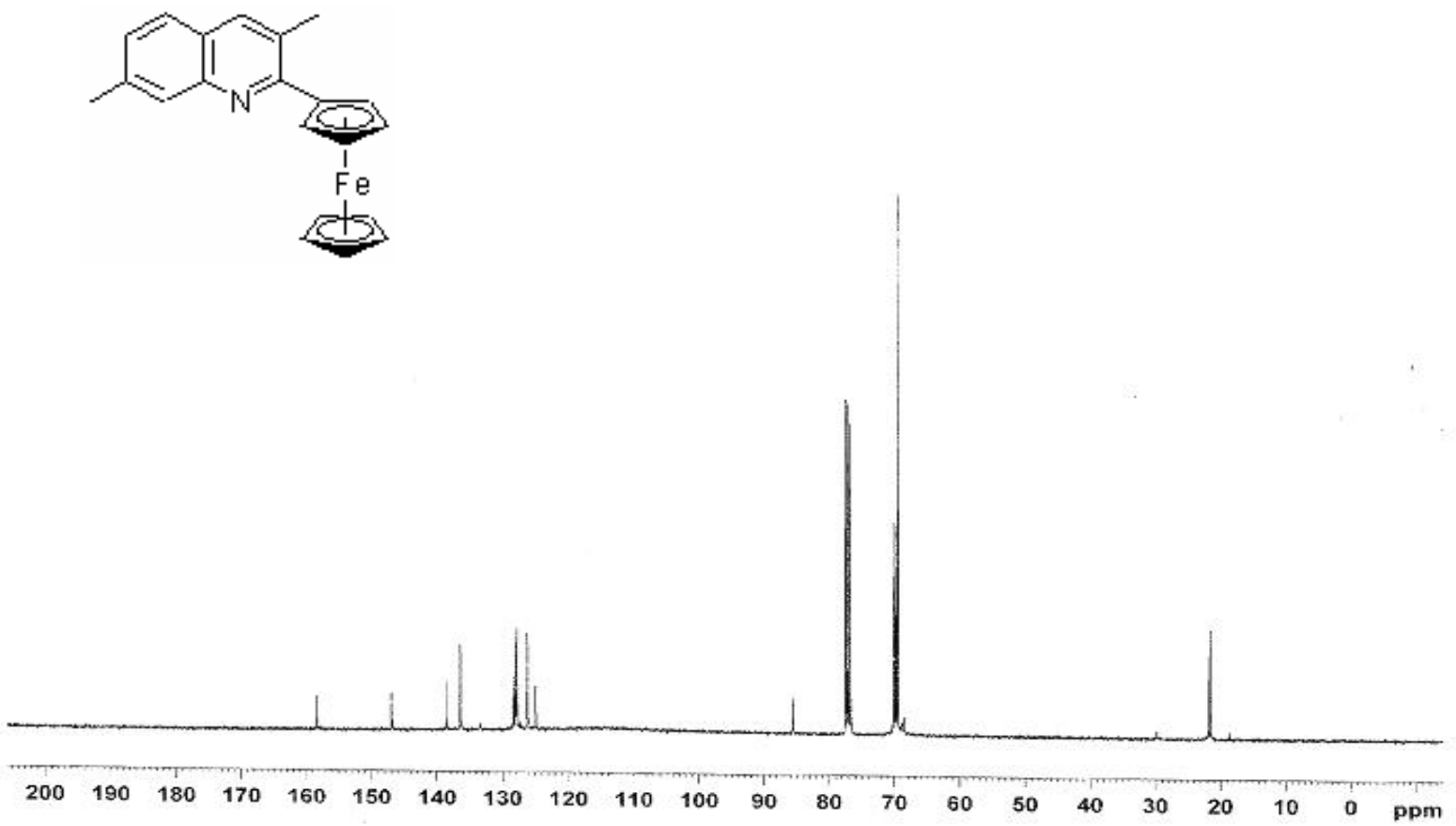


**Figure A14**. $^{13}$C-NMR spectrum of **28E.**

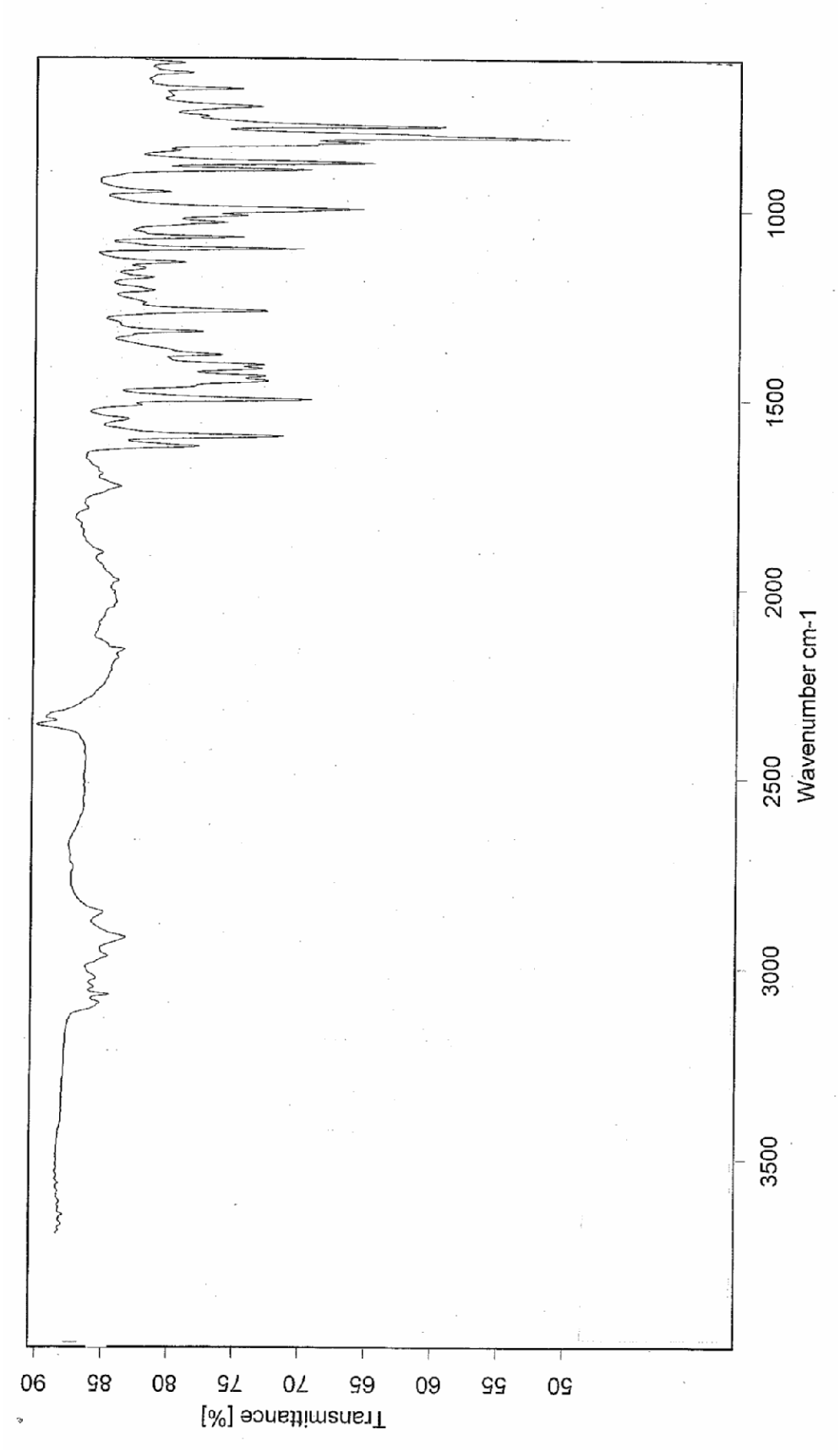


**Figure A15**. IR spectrum of **28E.**