

RECENT ADVANCES ON PHARMACOLOGICAL ACTIVITIES WITH ELECTROCHEMICAL, OPTICAL, CRYSTALLINE AND THERMAL PROPERTIES OF SCHIFF BASES CONTAINING FERROCENE AND THEIR METAL COMPLEXES – AN OVERVIEW

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Abstract. Bioorganometallic chemistry was appointed to the synthesis of new organometallic compounds and their biological and medicinal activities. The attendance of ferrocene (Fc) with Schiff bases has revolutionized bioorganometallic chemistry and is now providing applications in variant areas and sometimes initially unforeseen as nonlinear optical and redox devices together with electrostatic effects, electrochemical and other materials, sensing, liquid crystals, thermal, molecular docking and nanoparticles (NPs). Schiff bases containing ferrocene (Fc) and its complexes exhibit various pharmacological increments such as antibacterial, antifungal, DNA binding, antioxidative, antimalarial, anticancer and antitumor activities. This review article will focus on mentioned activities of ferrocenyl complexes specially containing B(I), Cu(II), Co(II), Ni(II), Zn(II), Si(IV), Sn(II), Pt(II), Pd(II), Pr(III) and other ions.

Keywords: Ferrocene, Ferrocenyl Complexes, Anticancer, Anti-tumor and Crystalline Properties.

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1. Introduction

There has been a great deal of interest in the synthesis of Schiff base complexes of ferrocene due to their conducting properties attempted under various conditions. Formally, a Schiff base (SB) is introduced as a nitrogen analogue of an aldehyde or ketone in which the carbonyl group ($>C=O$) is substituted by an imine or azomethine group (Lee *et al.*, 1996). The ferrocenyl Schiff bases are supposed to be the most remarkable matrix in bioorganometallic chemistry due to their enacting receptivity and structural multiplicity (Yang *et al.*, 2012). Schiff base metal complexes which structurally contain nitrogen, oxygen or sulphur as ligand atoms have become gradually important because these SB can bind with different metal centers involving different coordination sites and consent the target synthesis of metal complexes (Ali *et al.*, 2012). Ferrocene and its derivatives have allowed the outlook of many researches in the sphere of organometallic chemistry for using in various applications such as antibacterial, antifungal and anticancer activities (Sayed *et al.*, 2019). Moreover, Schiff base metal complexes are used in bioorganometallic chemistry where they exhibit an immense range of biological activities against various diseases. Poly(azomethine)esters, that contain C=N linkage in their structure have attracted substantial attention based on their peculiar properties like antitumor and DNA binding activities (Gul *et al.*, 2012; Haque *et al.*, 2006). One of the areas of organometallic chemistry that has attracted vast

advantages during the last decade is the chemistry of ferrocene especially the derivatives containing heteroatoms with good electron donating abilities. Ferrocene and its derivatives can potentially act as electronic mediators in biosensors and electrochemical devices because of their facile electron transferability and π -conjugation system (Abd-Elzaher, 2004). Ferrocene metallomesogens not only have the properties of metal-organic compounds (color, magnetism, electron density and polarizability) but also have the property of non-linear optical materials. Ferrocene derivatives have shown rich liquid crystalline mesophases: nematic phase, smectic phase, and even columnar phase (Yan *et al.*, 2010; Seshadri, 1998; Reddy & Brown, 1992). Currently, the availability of ferrocene cation sensors based in purely optical detection are an emerging area. The preface of a metal center as a donor or acceptor subunit has led to the improvement of new nonlinear optical materials based on Schiff base complexes with regard to the unique optical properties (Trujillo *et al.*, 2010; Uahengo, *et al.*, 2014; Liu *et al.*, 2017). An excellent survey revealed that the literature on the biological evaluation and molecular docking of ferrocene-poly(azomethine)ester is very inaccessible (Gul *et al.*, 2015). Ferrocene (Fc) and its derivatives are well recognized as suitable materials for amperometric sensing due to their splendid high mechanical strength and electrocatalytic properties (Kumar & Menon, 2009).

This review focuses on the biological activities and electrochemical, optical, crytalline and thermal behavior of Schiff bases containing ferrocene and their metal complexes.

2. Biological activity

2.1 Antibacterial and antifungal activity

Three Schiff-base ligands **1-3** (Fig. 1) derived from the condensation of 1,1'-diacetylferrocene with 2-aminopyrazine, 2-aminopyridine and 2-aminothiazole were synthesized by Zahid H. Chohan (2002). Also, metal complexes of all three ligands were synthesized from the different salts of Cu(II) ion. All the synthesized compounds were evaluated for their antibacterial activities at a concentration of 30 $\mu\text{g}/0.01\text{mL}$ in DMF solution against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia*. The result showed that all the Schiff base ligands and their metal complexes possessed the potential inhibitory properties against the tested organism (Chohan, 2002).

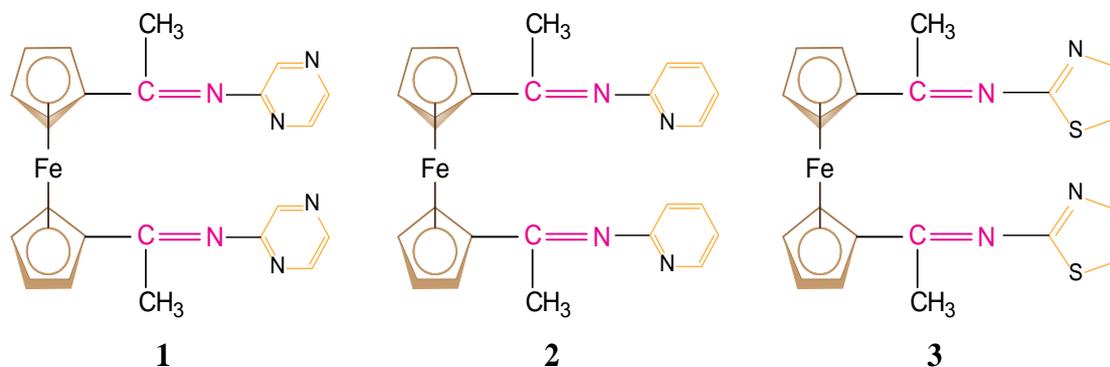


Figure 1. Structure of the Schiff-base ligands **1-3**.

A class of Schiff bases derived from the condensation of various ferrocene-based chalcones with S-benzyl dithiocarbamate were synthesized by Yu-Ting Liu et al (2012). All the synthesized compounds appraised for their in vitro antibacterial activity against two Gram-positive bacteria *Staphylococcus aureus* and *Bacillus cereus* and two Gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa* with two reference standard kanamycin and penicillin. Furthermore, their antifungal activity was studied against *Aspergillus niger* and *Aspergillus fumigatus* with ketoconazole standard. The results revealed that **4**, **5** and **6** show the better antibacterial activity while most of the compounds perform the significant antifungal activity against the tested organisms, whereas **7** and **8** were found to be inactive against all the bacterial strains (Fig. 2) (Liu et al., 2012).

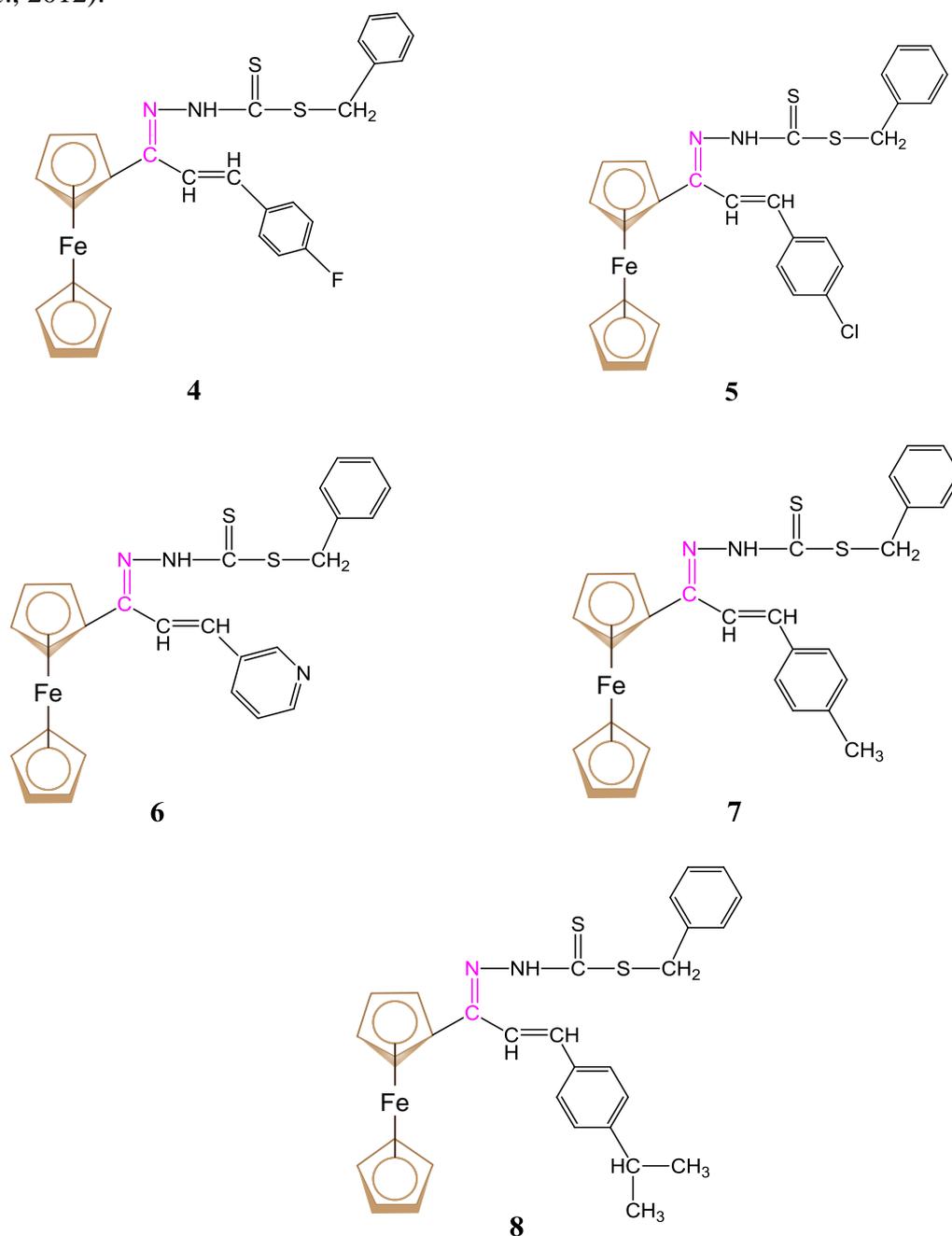


Figure 2. Structure of ferrocene-based Schiff bases 4-8.

M. Zaheer et al (2011) prepared ferrocenyl Schiff bases (Fig. 3) condensing 4-ferrocenyl aniline with aromatic aldehydes and acetyl acetone. The synthesized Schiff bases were not tested for antibacterial activities due to the hydrophobic character of Schiff bases that have adverse impact on bacterial membranes. But compounds **9** and **10** (Fig. 3) showed the appreciable antifungal potential against *Mucor* species (Zaheer *et al.*, 2011).

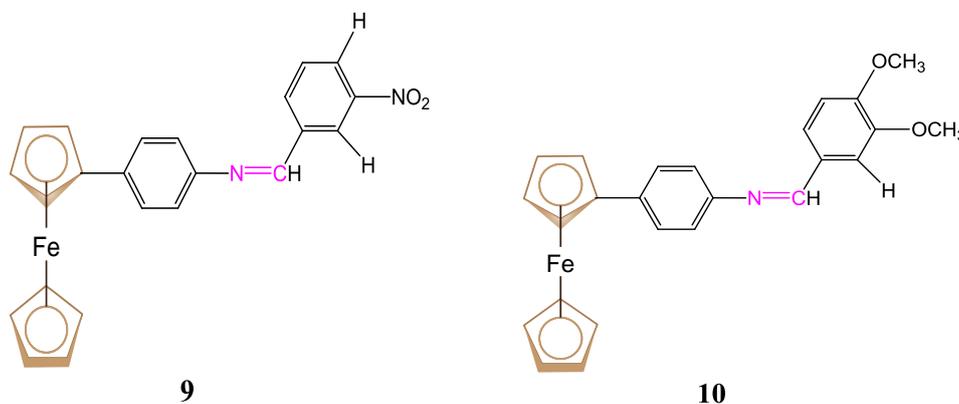


Figure 3. Structure of ferrocenyl Schiff bases **9-10**.

Ferrocene-based azomethines derived from sodium salt of tranexamic acid with 4-amino butanoic acid & phenyl alanine and organotin (IV) ferrocenyl Schiff bases condensed from trialkyl organotin complexes with formyl ferrocene were synthesized by Khira Tahira et al (2011). The synthesized compounds were tested for their antibacterial activity under such bacteria e.g., *Escherichia coli*, *Bacillus subtilis*, *Shigella flexenari*, *Salmonella typhi*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* & *Salmonella typhi*. The tested compounds showed no inhibitory action (Tahira *et al.*, 2011). Bakir J.A. Jeragh et al (2005) prepared ferrocenyl Schiff bases derived from the condensation of 1-acetylferrocene thiosemicarbazone with 1,1'-diacetylferrocene dithiosemicarbazone and the complexes with copper (II). The *in vitro* biological activities were performed at 37°C against two gram positive bacteria: *Bacillus subtilis* & *Staphylococcus* and two gram negative bacteria: *Escherichia coli* & *Salmonella typhi* with one fungal: *Candida albicans*. The biological screening exposed that **11** exhibits more antimicrobial significance than **12** against the tested organisms due to structural features (Fig. 4) (Jeragh & El-Dissouky, 2005).

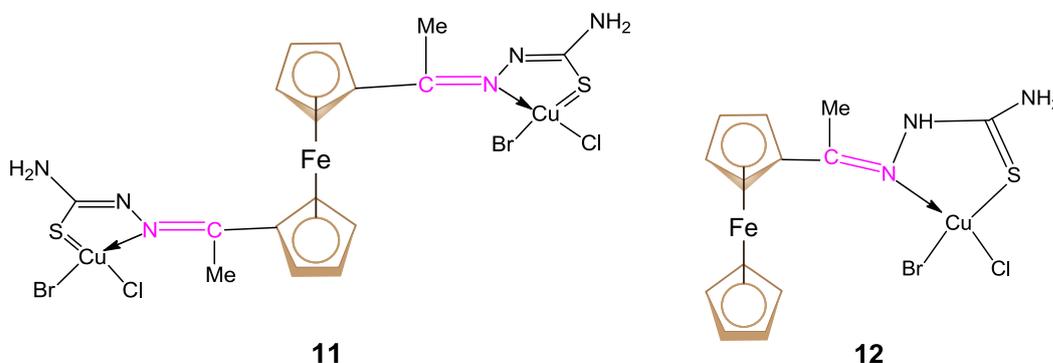


Figure 4. Proposed structures of HL^1 and H_2L^2 copper (II) complexes **11-12**.

Three Schiff-base ligands derived from the condensation of acetylferrocene with hydrazinehydrochloride & S-benzylthiocarbamate were synthesized by Sunita Yadav et al (2011). Also, metal complexes of all three ligands were synthesized from different acetylferrocene coordinated to boron (III). All the synthesized compounds were evaluated for their antimicrobial properties by Paper Disc Plate technique against two bacteria: *Staphylococcus aureus* & *Xanthomonas compestris* and two fungi: *Alternaria alternata* & *Fusarium oxysporum*. The result showed that **13**, **14** and **15** (Fig. 5) with the better fungicidal activity than bactericidal activity (Yadav & Singh, 2011).

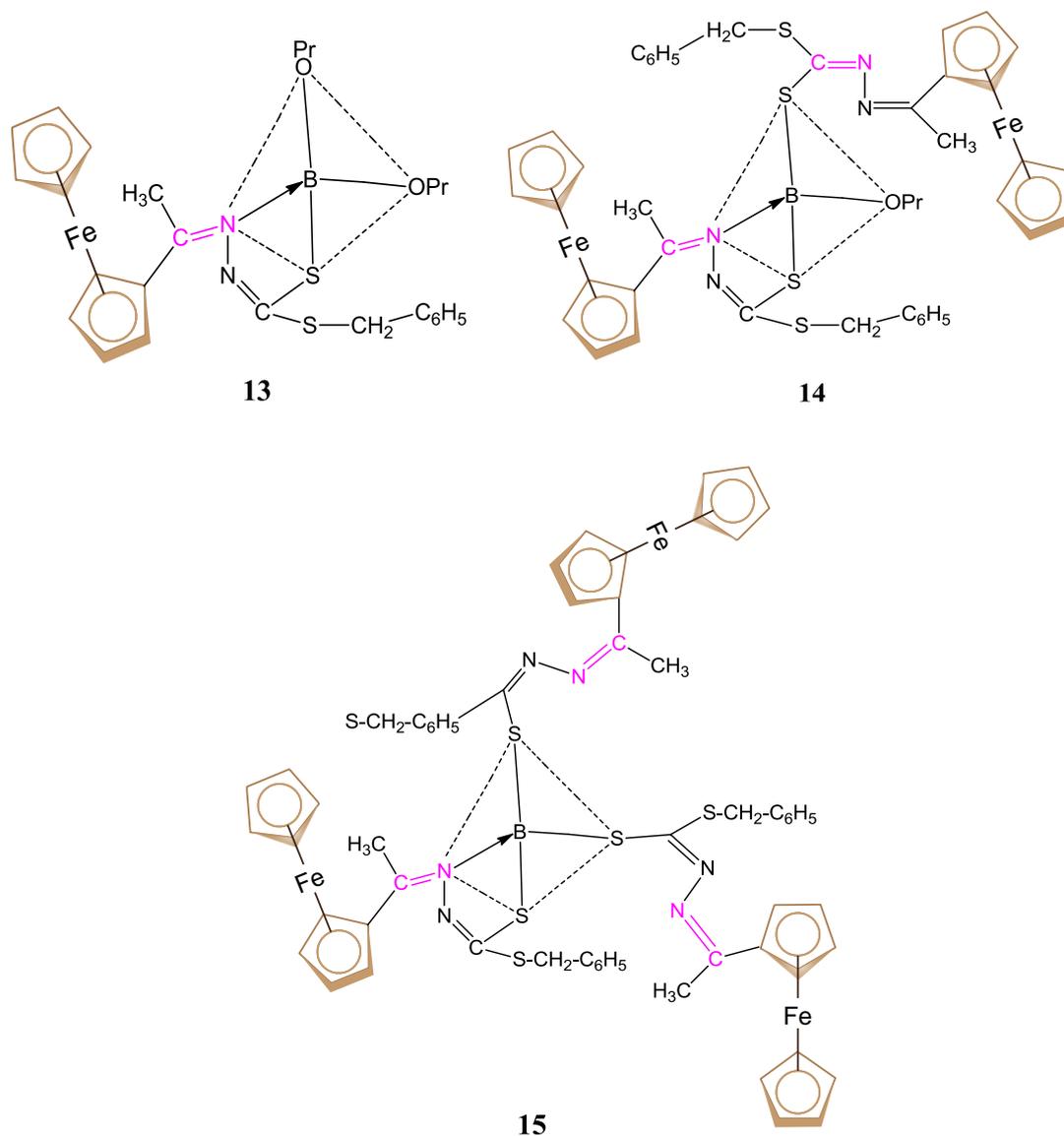


Figure 5. Structure of the complexes **13-15**.

Yin et al (2012) prepared ferrocenyl Schiff bases from the reaction of ferrocenecarboxaldehyde with thiadiazole. The synthesized compounds showed antibacterial activity against three Gram-negative bacteria: *Escherichia coli*, *Pseudomonas aeruginosa*, & *Salmonella typhi* and two Gram-positive bacteria *Bacillus subtilis* & *Staphylococcus aureus* where Amoxicillin was as standard. The results

showed that **16** and **17** (Fig. 6) have the higher antimicrobial activity against *Salmonella typhi* and *Bacillus subtilis* (Yin *et al.*, 2012).

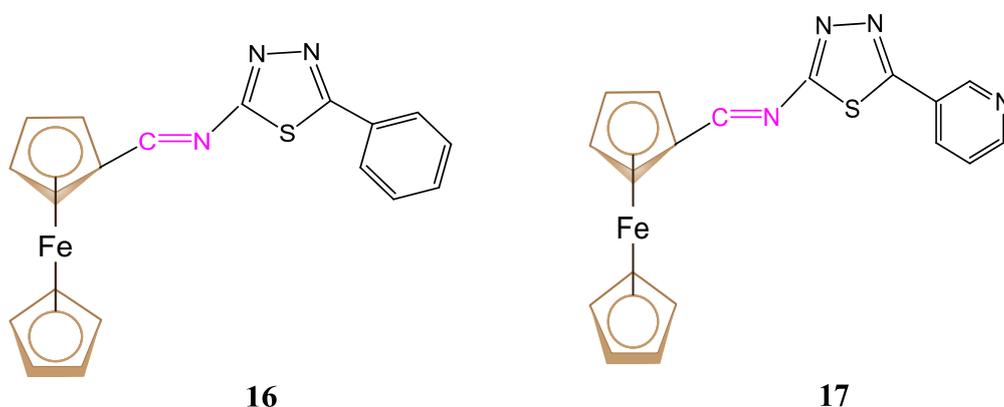
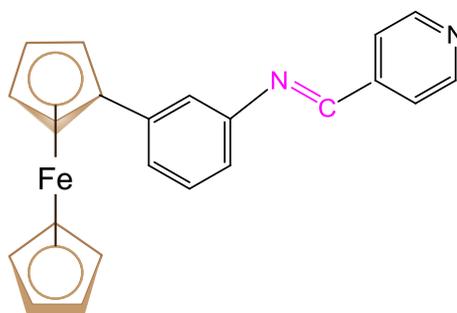


Figure 6. Structure of Ferrocenyl-2-Amino-5-Substituent-[1,3,4]-Thiadiazole **16-17**.

Eric M. Njogu *et al* (2016) prepared ferrocenyl Schiff bases from the condensation of 3- or 4-ferrocenylaniline with either 2-, 3-, or 4 pyridinecarboxaldehyde under solvent-free medium. The antibacterial activities of the synthesized compounds were tested at a concentration of 20 $\mu\text{g}/0.02\text{ mL}$ in DMSO solution against two Gram-negative bacteria *Escherichia coli* & *Salmonella typhimurium*, one Gram-positive bacterium *Staphylococcus aureus* and one fungal *Candida albicans*. The result indicated that **18** (Fig. 7) possesses the larger potential against all tested organisms, whereas most of the compounds showed no activity against *Candida albicans* (Njogu *et al.*, 2016).



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Figure 7. Structure of ferrocenyl Schiff base **18**.

W.H. Hegazy *et al* (2012) prepared asymmetric ferrocenyl Schiff base derivatives (Fig. 8) from the condensation of 1,1'-Diacetyl-ferrocene with 2-aminopyrazine, 2-aminopyridine, 2-aminothiazole & 2-hydroxyaniline and their complexes with Pd and Pt. The antimicrobial potentials were checked against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhi*, *Aspergillus niger* & *Fusarium solani*. The result showed that the metal complexes **19** and **20** (Fig. 8) possess the higher antimicrobial activities than the ligands (Hegazy *et al.*, 2012).

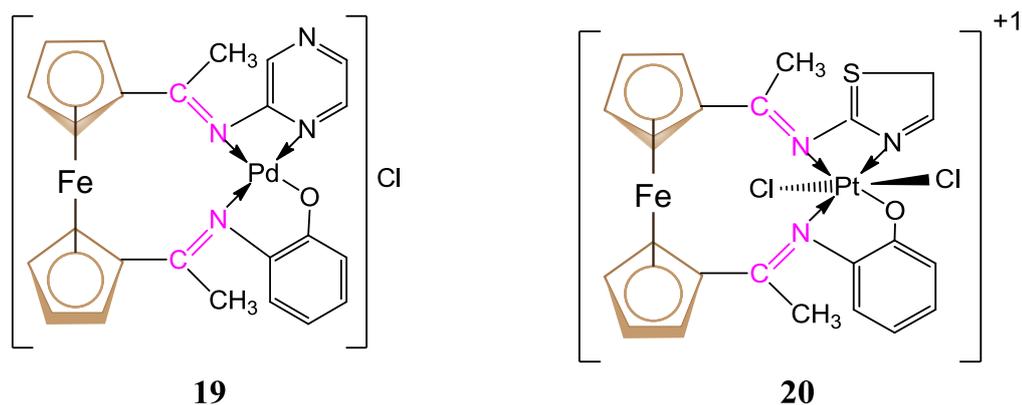


Figure 8. Suggested structure for Pd (II) and octahedral Pt (IV) chelates **19-20**.

A series of ferrocene-based Schiff base ligands derived from the condensation of S-benzyl dithiocarbazate with 1-ferrocenyl-3-(4-methyl benzene) acrylketone & 1-ferrocenyl-3-(4-chlorobenzene)acrylketone were synthesized by Yu-Ting Liu et al (2013). All the synthesized complexes of Ni(II), Cu(II), Co(II), Hg(II), Cd(II), Zn(II) and Pb(II) with the ligands were evaluated for their antimicrobial potential against two Gram-positive bacteria: *Staphylococcus aureus* & *Bacillus cereus*, two Gram-negative bacteria: *Escherichia coli* & *Pseudomonas aeruginosa* and two fungi: *Aspergillus niger* & *Aspergillus fumigatus*. They found that **21**, **22** and **23** (Fig. 9) were the most active against all bacterial strains (Liu et al., 2013).

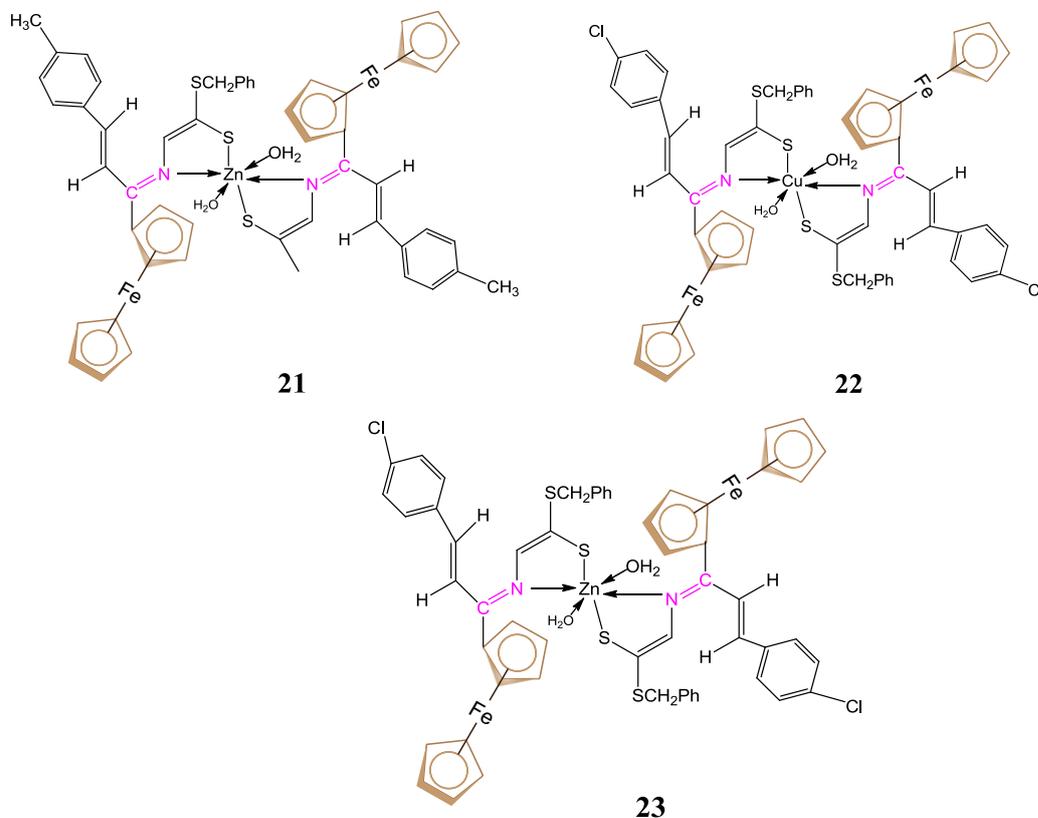


Figure 9. Structure of the metal complexes **21-23**.

A symmetric series of Schiff base ligands derived from the condensation of 1,1'-diacetylferrocene with 2-aminopyrazine, 2-aminopyridine and 2-aminothiazole. The Co(II), Cu(II), Ni(II) and Zn(II) complexes of these ligands were synthesized by Zahid H. Chohan et al (2000). The antibacterial properties of the ligands and their metal complexes were studied in DMF solution against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Klebsiella pneumoniae*. The result showed that the metal compounds were strong inhibitors than the ligands against the tested organisms. Again, **24** and **25** (Fig. 10) possess significant inhibition zone against *Escherichia coli* (Chohan & Praveen, 2000).

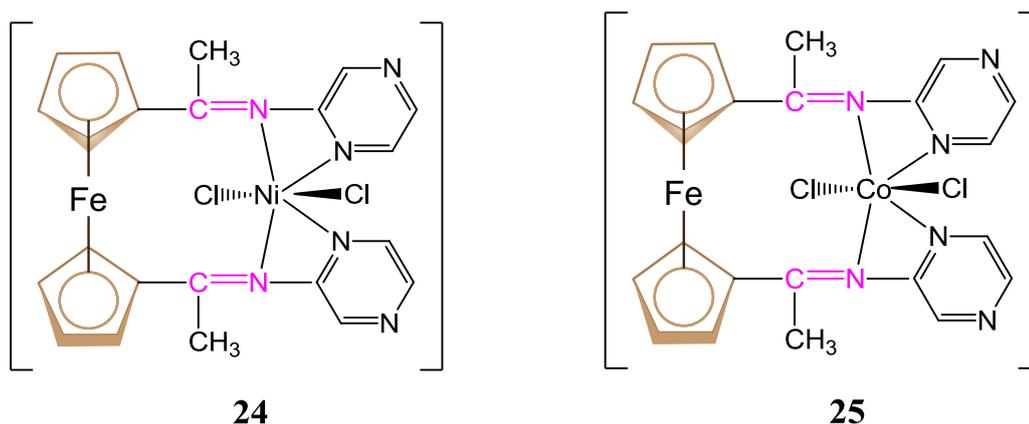


Figure 10. Proposed structures for the metal chelates **24-25**.

Ferrocenyl Schiff base ligands obtained from the condensation of ferrocenecarboxaldehyde with 2-aminophenol by Ahmed Mourtada Elseman et al (2017). Also, metal complexes of all ligands were synthesized from the metal Co(II), Ni(II), Cu(II), and Pd(II) ions. The synthesized compounds were investigated for their antimicrobial activities against three gram-negative bacteria: *Escherichia coli*, *Pseudomonas aeruginosa* & *Klebsiella pneumonia* and three gram-positive bacteria: *Staphylococcus aureus*, *Bacillus subtilis* & *Streptococcus pyogenes* with ampicillin and gentamicin as standard and three fungi: *Aspergillus fumigatus*, *Geotrichum candidum* & *Candida albicans* with amphotericin as standard. The complex **26** (Fig. 11) exhibited the highest potential against *Aspergillus fumigatus* and *Geotrichum candidum* (Elseman et al., 2017).

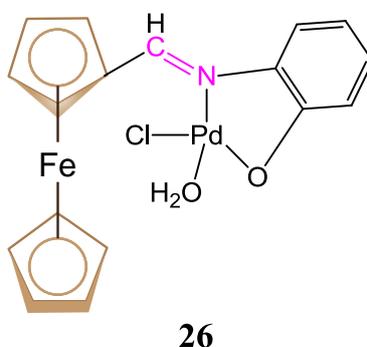


Figure 11. Structure of the most reactive ferrocenyl Schiff base **26**.

The ferrocenyl Schiff base derivatives were derived from the condensation of N-benzoyl-N'-phenylthioureas & p-ferrocenylaniline with triethylamine in DMF solution by Rukhsana Gul et al (2014). The synthesized compounds were evaluated for their antimicrobial activities against two gram-positive bacteria: *Staphylococcus aureus* & *Bacillus subtilis*; three gram-negative bacteria: *Escherichia coli*, *Pseudomonas aeruginosa* & *Klebsiella pneumonia* and three fungi: *Fusarium moniliforme*, *Aspergillus fumigatus* & *Aspergillus flavus*. The result revealed that **27** and **28** (Fig. 12) showed good antimicrobial potential against the tested organisms (Gul et al., 2014).

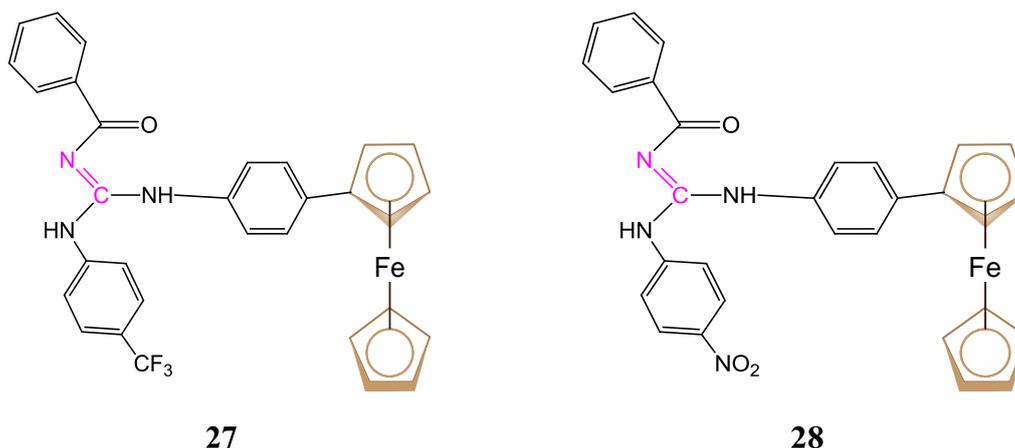
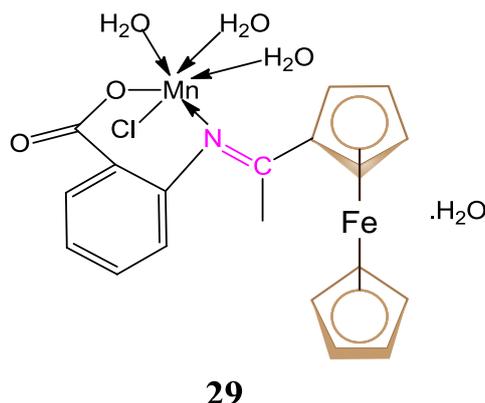


Figure 12. Structures for ferrocenyl guanidines **27-28**.

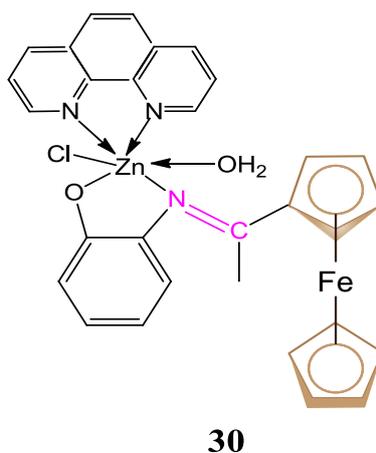
R.V. Singh et al (2002) prepared Schiff base ligand (Fig. 13) from the condensation of 1-acetylferrocene with thiosemicarbazide. Also, the metal complexes of the ligand were synthesized from the different salts of Sn(IV) and Si(IV) ions. All the synthesized compounds were investigated for their antimicrobial activities against bacteria: *Escherichia coli*, *Klebsiella aerogenus*, *Pseudomonas cepacicola* & *Staphylococcus aureus* with streptomycin as standard and fungi: *Fusarium oxysporium*, *Aspergillus niger* & *Macrophomina phaseolina* with Bavistin as standard. The results confirmed that sulfur-containing tin complexes were the most active than silicon complexes against the tested organisms ((Singh et al., 2002).

2.2 DNA binding activity

A class of ferrocenyl Schiff bases derived from the condensation of (Z)-(4-(1-((2-carboxycyclohexa-2,4-dien-1-yl)imino)ethyl)[bis(η^5 cyclopenta-1,3-dien-1-yl)] iron separately with Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II) & Cd(II) were prepared by W.H. Mahmoud et al (2017). Molecular docking studies with all the compounds confirmed that all the compounds had attractive binding modes against DNA with human proteins. The result revealed that **29** (Fig.13) was with the larger binding potential with human-DNA-Topo I complex and even with *Escherichia coli* (Mahmoud et al., 2017).

**29****Figure 13.** Structure of ferrocenyl derivatives bearing transition metal complex **29**.

The Schiff base ligand prepared from the reaction of 2-acetylferrocene with 2-aminophenol and 1,10-phenanthroline by W.H. Mahmoud et al (2018). Also, metal complexes (Fig. 15) of the ligand were synthesized from the different metal ions Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II). All the synthesized compounds were evaluated for their molecular operations against acetylcholinesterase, DNA dodecamer and virus protein of HIV-1. The complex **30** (Fig. 14) provided the larger binding activities with minimum binding energy through electrostatic, hydrogen acceptor and donor capacities (Mahmoud *et al.*, 2018).

**30****Figure 14.** Structure of HL Schiff base metal complex **30**.

The Schiff bases were synthesized from the condensation of ferrocenyl aldehydes and 2,4-butadione by M. Zaheer et al (2014). The synthesized compounds were demonstrated their DNA binding activities attributed to H_2O_2 observed in chicken blood. The experiment results that **6** and **7** (Fig. 3) possess the significant DNA-protecting potentials only at higher concentrations through electrostatic interactions using cyclic voltammetry (Zaheer *et al.*, 2011). Rukhsana Gul et al (2014) prepared ferrocenyl Schiff bases from the reaction of N-benzoyl-N'-phenylthioureas & p-ferrocenylaniline with triethylamine in DMF solution. The synthesized compounds were evaluated for their DNA binding activities. The result showed that compounds **24** (Fig. 12) and **31** (Fig. 15) combined with DNA intercalation accomplish more readily the oxidation process (Gul *et al.*, 2014).

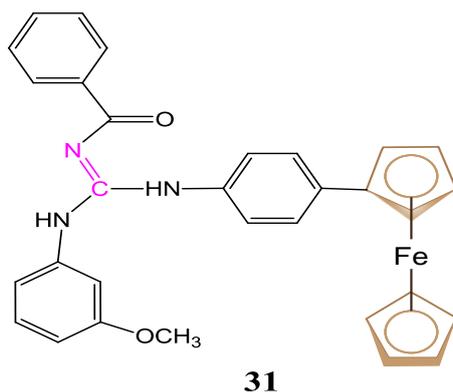


Figure 15. Structure of ferrocenyl guanidine **31**.

The ferrocenyl Schiff bases prepared from the condensation of 1,1'-diacetyl ferrocene with *o*-, *m*- or *p*-aminophenol were synthesized by Yan-Feng Li et al (2011). All the synthesized compounds were appraised for their DNA activities. The result shows that the compound **32** (Fig. 16) strongly binds to DNA against AAPH-induced oxidation (Li & Liu, 2011).

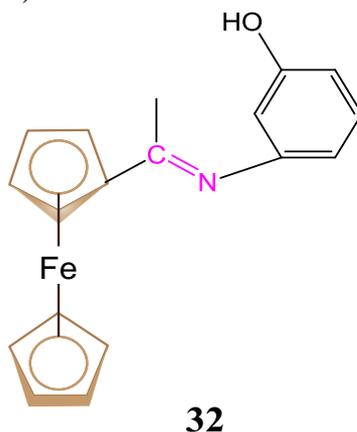


Figure 16. Structure of the ferrocenyl Schiff base **32**.

Haq Nawaz et al (2009) prepared ferrocenyl Schiff base derivatives derived from 4-aminophenyl ferrocene with 4-hydroxy benzaldehyde. DNA binding activities of those compounds were evaluated at concentration 10 μ g/ml by DPPH & OH free radicals scavenging. The procedure occurred that the compound **45** (Fig. 21) shows the larger DNA protective potential than other synthesized compounds (Nawaz *et al.*, 2009).

2.3 Antioxidative activity

Ferrocenyl Schiff base derivatives (Fig. 18) were derived from the condensation of acetylferrocene with *o*-, *m*- or *p*-aminophenol by Yan-Feng Li et al (2011). The synthesized compounds were evaluated for their antioxidant activities in radical based oxidation of DNA than benzene-related Schiff bases. The result revealed that **33** and **34** (Fig. 17) showed the larger antioxidant potentials with significance stabilization (Li & Liu, 2011).

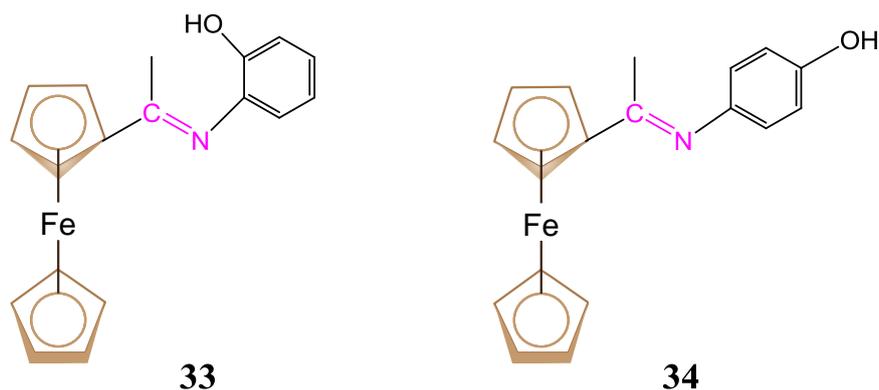


Figure 17. Structures of ferrocenyl Schiff bases **33-34**.

I.V. Smolyaninov et al (2018) prepared ferrocenyl Schiff base derivatives from the condensation of *o*-aminothiophenol with ferrocenecarboxaldehyde and 3,5-di-*tert*butyl- 4-hydroxybenzaldehyde hemihydrate. The synthesized compounds were tested for their antioxidant activities in DPPH radical on lipid peroxidation in vitro rat brain. The result showed that all the compounds possess significant potential against vitamin E & Trolox standard, whereas only **35** (Fig. 18) prefers the less inhibitory protective potential against Trolox standard (Smolyaninov *et al.*, 2018).

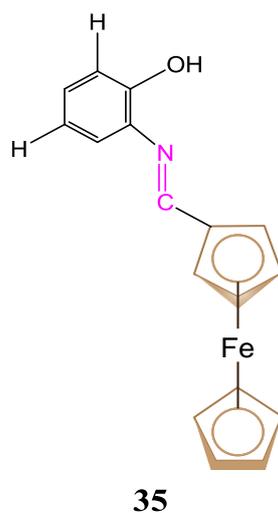


Figure 18. Structure of the synthesized compounds **35**.

2.4 Antimalarial activity

The ferrocenyl Schiff base derivatives **36-43** (Fig. 19) were synthesized from 4-aminophenyl ferrocene with 4-hydroxy benzaldehyde by Monisola I. Ikhile et al (2017). The antimalarial activities were checked at 37°C in RPMI medium against *Plasmodium falciparum* using chloroquine as standard. Although all of the tested compounds having lipophilic character but maintained very low antimalarial activity (Ikhile & Ndinteh, 2017).

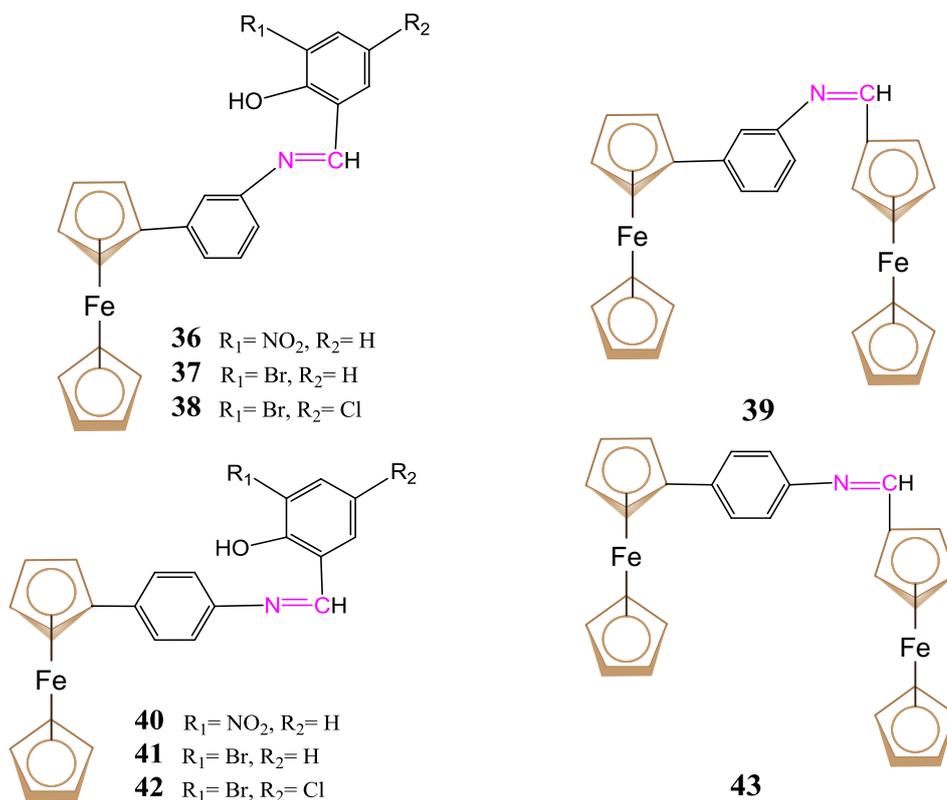


Figure 19. Structures of the tested Ferrocenyl Schiff bases **36-43**.

2.5 Anticancer activity

M.M. Abd-Elzaher et al (2014) prepared the ferrocenyl Schiff base ligand from the condensation of 1,1'-diacetyl ferrocene with 2-amino-5-methylthiazole. Also, metal complexes of the ligand were synthesized from the different salts of La(III), Ce(III), Pr(III) and Gd(III) ions. All the synthesized compounds were tested for their anticancer activities against human hepatocellular carcinoma, breast adenocarcinoma, human colon cancer and human hepatocellular carcinoma. The result showed that the complex **44** (Fig. 20) exhibited the significant anticancer potential against human hepatocellular carcinoma and human lung cancer (Abd-Elzaher *et al.*, 2014).

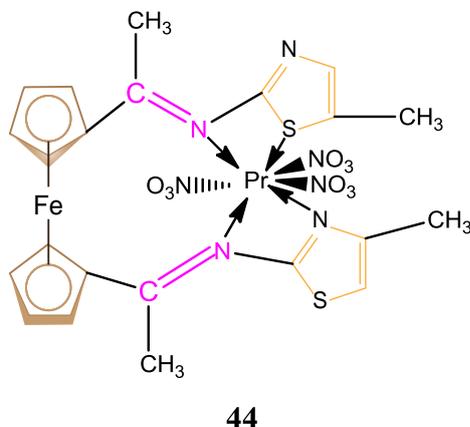
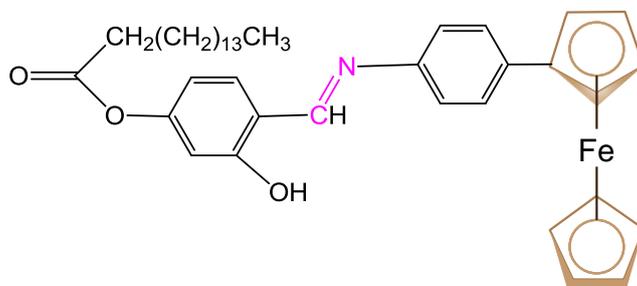


Figure 20. Structure of metal complexes **44**.

2.6 Antitumor activity

Haq Nawaz et al (2009) synthesized ferrocenyl Schiff-base esters from the condensation of 4-hydroxy benzaldehyde with long chain esters. The synthesized Schiff bases were checked for their antitumor activities against *Agrobacterium tumefaciens*. Only **45** (Fig. 21) showed the larger antitumor potential against the tested organism (Nawaz et al., 2009).

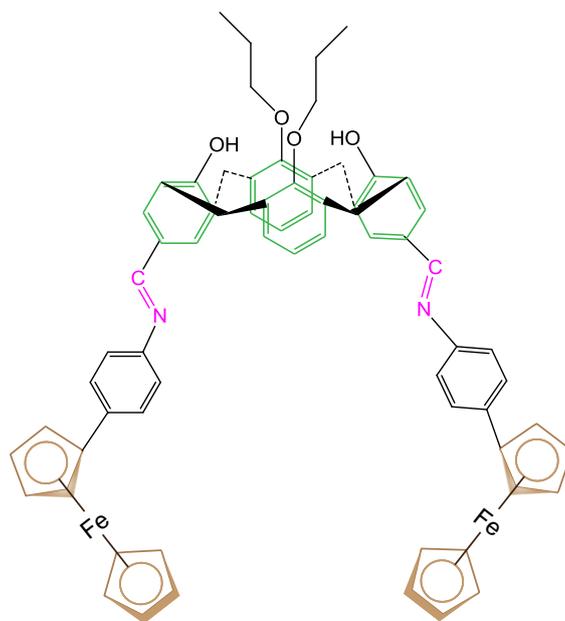


45

Figure 21. Structure of the tested compound **45**.

3. Electrochemical Properties

The ferrocenyl Schiff base derivative were prepared from the condensation of diformyl calix[4]arene with 4-ferrocenylaniline in DMSO solution by Behrouz Shaabani et al (2011). The synthesized compound showed reduction wave & more visibility at fewer positive potentials. The result revealed that the compound **46** (Fig. 22) possesses the larger anodic fluctuation & half wave potential with electrochemical binding stoichiometry 1:1 (Shaabani & Shaghghi, 2011).



46

Figure 22. Structure of the designed receptor **46**.

Mei-Jun Zhu et al (2007) prepared ferrocene functionalized diketoimines from the reaction of acetoacetylferrocene with benzidine & 4,4'-diaminodiphenylmethane. The cyclic voltammograms of all synthesized compounds showed a pair of stable redox waves within a fixed potential. Compounds **47** and **48** (Fig. 23) exhibited the lower oxidation potential due to the effect of electron withdrawing substituents (Zhu *et al.*, 2007).

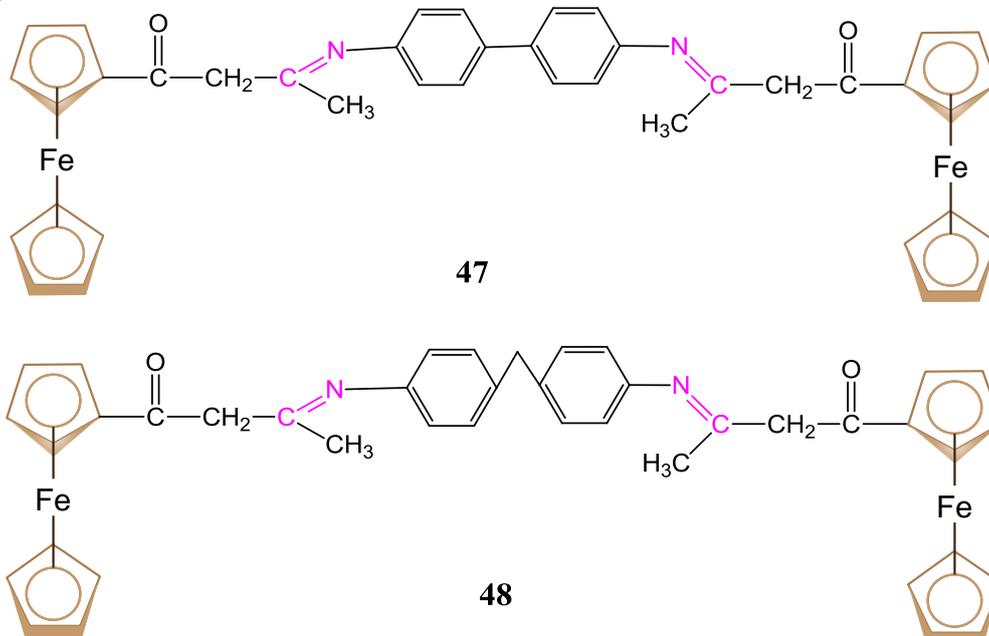


Figure 23. Ferrocene containing diketoimines **47-48**.

The novel ferrocenyl Schiff base derivatives were prepared from the condensation of ferrocenecarbaldehyde and 2-mercaptoaniline by Sonia Perez et al (2004). Moreover, metal compounds of all three ligands were synthesized from the different salts of Pt(II) & Pd(II) ions and scanned at different scan rate. From the polarization curves it was clear that the compound **49** possesses the larger half-wave potential with unique peak current, and another compound **50** exhibited the higher oxidation affinity among all the compounds with *mer*-terdentate ligand (Fig. 24) (Pérez *et al.*, 2004).

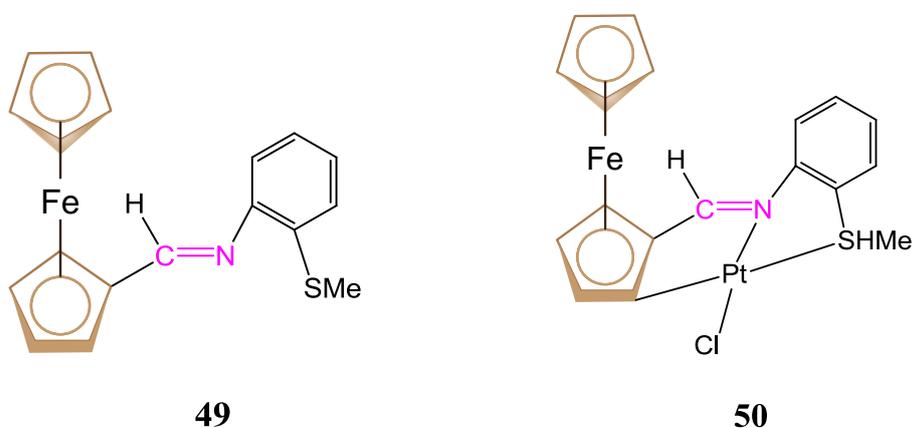


Figure 24. Ferrocene containing diketoimines **49-50**.

R.K. Nagarale et al (2009) synthesized chitosan composite of ferrocenyl polysiloxane from the reaction of 3-aminopropyltrimethoxysilane with ferrocenyl aldehyde. The synthesized compound was evaluated for its spontaneous electrochemical behavior on printed carbon electrode. The result revealed that the composite **51** (Fig. 25) displayed a reversible redox potential with higher diffusion which eased to form biocompatible glucose sensor (Nagarale *et al.*, 2009).

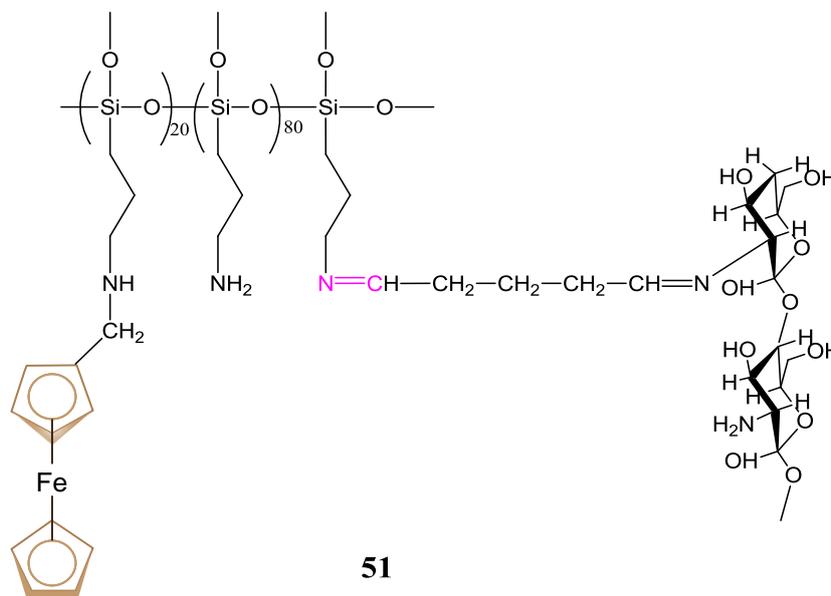


Figure 25. Representation of ferrocene modified polysiloxane/chitosan composite (Fc20/Chi) **51**.

The ferrocenyl Schiff base derivative were obtained from the condensation of 1,1'-diformylferrocene with 2-Aza-1,3-butadiene. The synthesized compound was evaluated for its redox potential among several metal cations accounted for Zn^{2+}/Cd^{2+} selectivity. The oxidation wave potential was found in presence of Fe(II)/Fe(III) electrode by coupling Zn^{2+} ion (Zapata *et al.*, 2007). XUAN Guang-Shan et al (2006) prepared ferrocenyl Schiff base derivative from the condensation of ferrocenecarboxaldehyde with 3-aminopropyltriethoxysilane. The sol-gel based glucose biosensor of the synthesized compound was demonstrated for its electrochemistry especially with higher current potentials. The procedure visualized that the substantiality of *N*-(3-triethoxysilylpropyl)-ferrocenylmethylimine varied linearly with the anodic peak current in absence of glucose (Xuan *et al.*, 2006). J. Razumiene et al (2003) produced bioorganometallic ferrocene derivative from the reaction of 2-amino-4-nitrophenol with 4-ferrocenylaniline & 4-hydroxybenzaldehyde. The derived compound was performed for its electrochemistry at different scanning speeds. The result revealed that the compound **52** (Fig. 26) exhibited larger catalytic current & sensitivity among all mediators (Razumiene *et al.*, 2003).

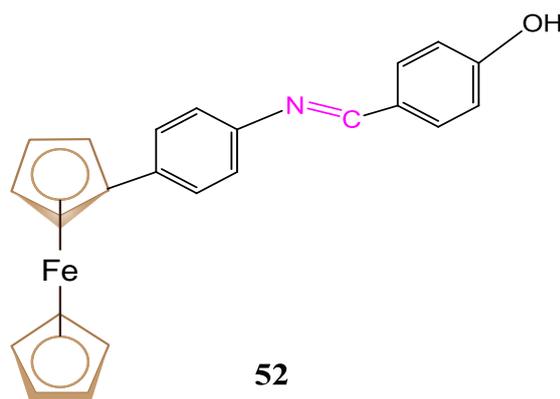


Figure 26. Structure of the derived compound **52**.

A Schiff base derivative of ferrocene was prepared from the condensation of 1,2-(diphenylphosphino) ferrocenyl ethanamine with N-(pyridin-2-aldehyde) by Congxin Xie et al (2018). The synthesized compound was substantially evaluated for its electrochemical behavior in nonaqueous medium at several scanning rates. The result confirmed that **53** (Fig. 27) displayed the sustainable redox peak potentials with reversibility the larger current potential in addition with significant diffusion coefficient (Xie *et al.*, 2018).

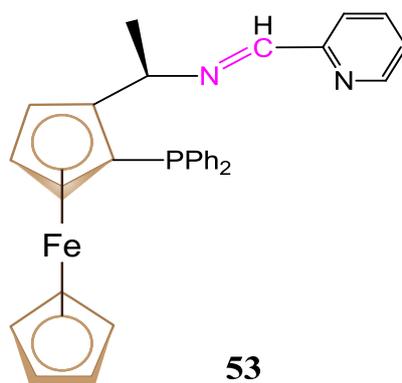


Figure 27. Structure of the derived compound **53**.

The two redox-active ferrocenyl Schiff base ligands were derived one of which was produced from the condensation of 3-formyl-4-methoxyphenylferrocene with 1,2-diaminoethane and the other was from 1,1'-bis(3-formyl diethylacetal-4-methoxyphenyl)ferrocene with 1,2-diaminopropane by C. Dennis Hall et al (1998). Further, the metal complexes of these ligands with Cu^+ & Ag^+ ions were evaluated for their electrochemical properties where cathodic shift promoted a mild electron density for the oxidization of metals (Hall *et al.*, 1998). Scott M. Shepard et al (2016) prepared Schiff base derivatives from the condensation of N,N'-ethylenesalicylimine with N-fluoro-2,4,6-trimethylpyridine tetrafluoroborate. Co and Zn complexes of these derivatives were evaluated for their electrochemical properties. The cyclic voltammetry showed that the redox behavior of **54** was more fascinating than **55** (Fig. 28) (Shepard & Diaconescu, 2016).

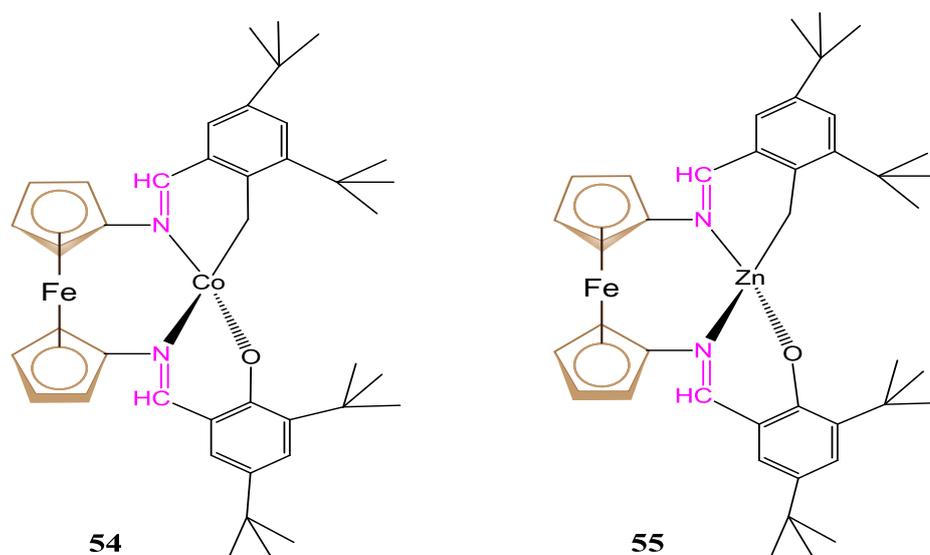


Figure 28. Structures of ferrocene-based metal complexes **54-55**.

Chang Su et al. prepared ferrocene based polytriphenylamine derivative from the reaction of N',N''-diphenylbenzene-1,4-diamine with ferrocenecarboxaldehyde. The derived compound was evaluated in DMF solution for its prospective electrochemical nature according to absolute sensitivity. The cyclic voltammetry of (E)-N-(4-(Diphenylamino)phenyl)formimidoyl ferrocene **56** (Fig. 29) pronounced the comprehensive redox peak potential (Su *et al.*, 2012).

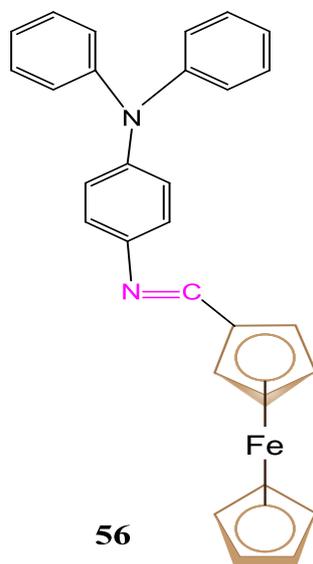


Figure 29. Structure of (E)-N-(4-(Diphenylamino)phenyl)formimidoyl ferrocene **56**.

A series of ferrocenyl calix[4]arene derivatives were yielded from the condensation of 25,27-dihydroxy-26,28-bis[(3-aminopropyl)oxy]calix[4]arene with 25,26,27,28-tetra[(3-aminopropyl)oxy]calix[4]arene and ferrocenecarboxaldehyde by Serkan Erdemir et al (2012). The *cone* and *1,3-alternate* configuration of the synthesized

compounds were checked for their electrochemical behavior in DMSO solution with F^- , Cl^- , Br^- , $H_2PO_4^-$ & CH_3COO^- ions. The electrochemical experiment showed that the quasireversible redox couple in case of anionic species where **57** with chloride ion slightly lowers the peak current than the rested ions in view of Fc/Fc^+ couple. On the contrary, **58** assumed the prosper selectivity with respect to $H_2PO_4^-$ & CH_3COO^- ions (Fig. 30) (Erdemir *et al.*, 2012).

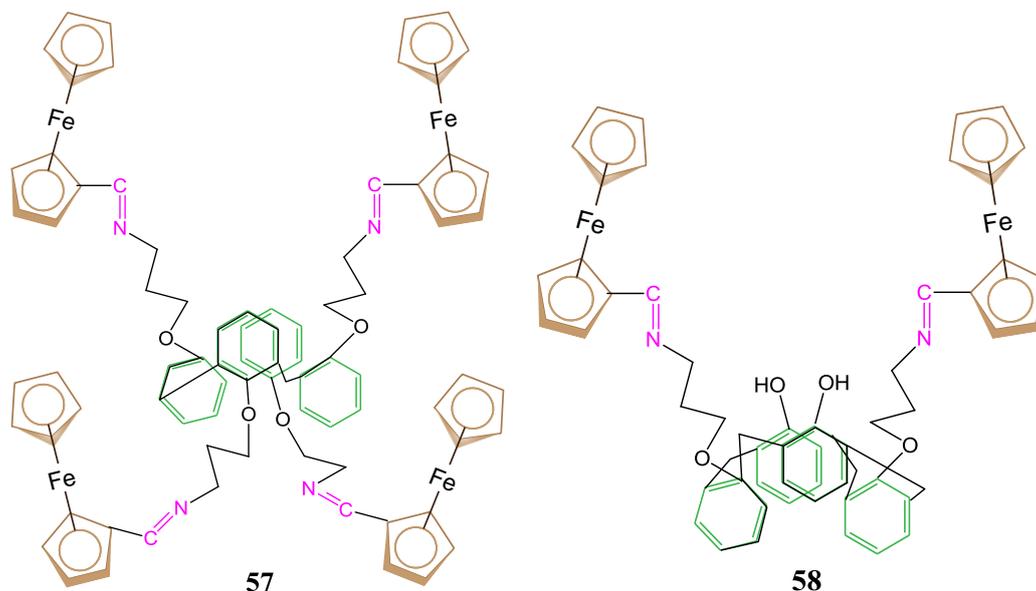


Figure 30. Structure of calix[4]arene derivatives containing ferrocene **57-58**.

The ferrocenyl Schiff bases were prepared from the condensation of ferrocenecarboxaldehyde with 4-amino-2,6-di-tert-butylphenol hydrochloride, 3,5-di-tert-butyl-4-hydroxybenzylamine, aniline & benzylamine by N.N. Meleshonkova et al (2007). The compounds **59** and **60** (Fig. 31) were evaluated for their electrochemistry showed three oxidation peak potentials. Also, all the synthesized compounds with 3,5-di-tert-butyl-4-hydroxyphenyl uphold the multidimensional redox behavior contributed electron transfer to the functional parts among them (Meleshonkova *et al.*, 2007).

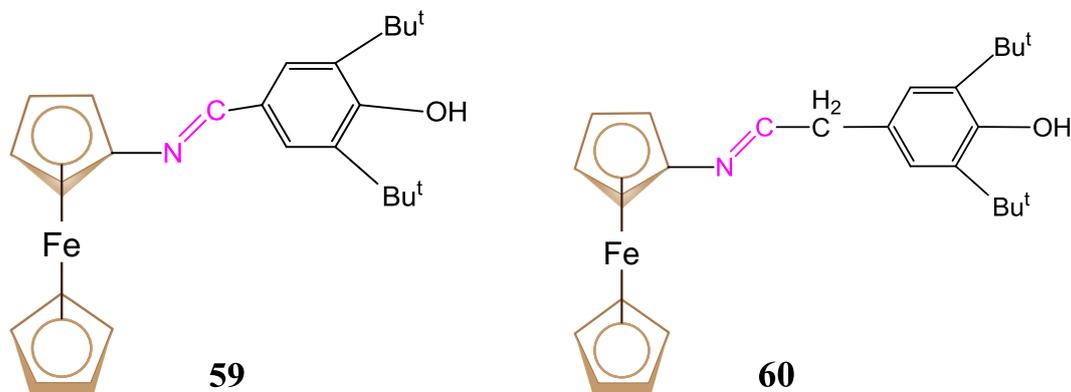


Figure 31. Structure of the redox active ferrocenyl Schiff bases **59-60**.

Taher S. Kassem et al (2002) prepared ferrocenyl hydrazones of Cu (II) ion from the condensation of acetylferrocene with benzoylhydrazine, 4-chlorobenzoylhydrazine, 4-hydroxybenzoylhydrazine and 4-methylhydrazine. The synthesized compounds were screened out for their electrochemical behavior in accordance with quasi reversible process favored for Fc/Fc⁺ couple with several scanning speeds. The cyclic voltammetry showed substituents effected larger negative potentials in which the complex **61** (Fig. 32) disrupts the electrostatic interactions by pushing electrons within a step (Kassem *et al.*, 2002).

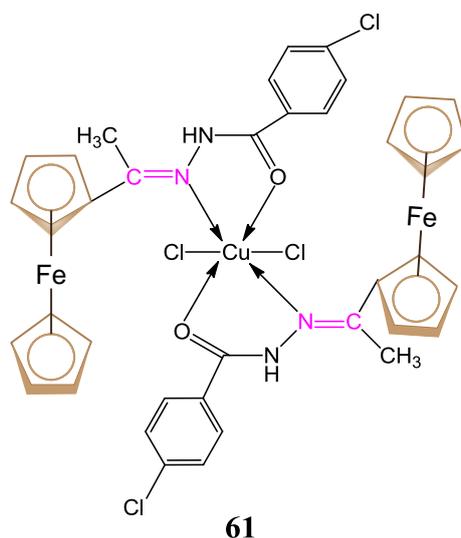


Figure 32. Suggested structure of the metal complexes **61**.

Bao-Xian Ye et al (2005) prepared ferrocenyl Schiff bases from the schema of ferrocenylaniline with 2-hydroxy benzaldehyde. The derived compounds were checked for their permanent redox properties. The procedure narrated that two compounds **62** and **63** (Fig. 33) possess the larger potential attributed to hydroxybenzylidene where passivation occurred on electrode by both hydroxyl & imine groups (Ye *et al.*, 2005).

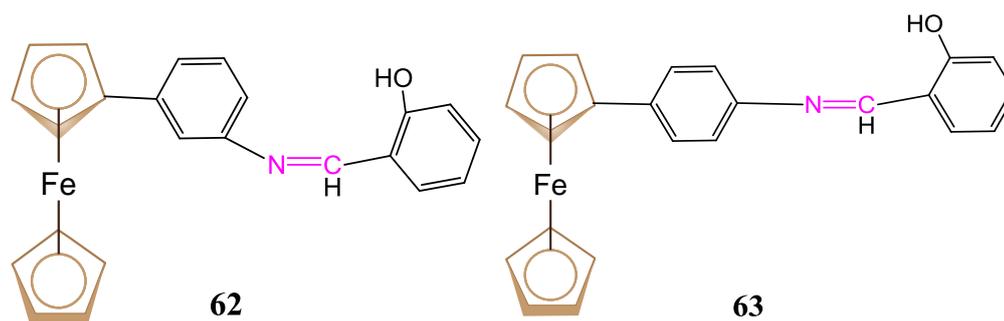


Figure 33. Structure of two experimental compounds **62-63**.

Ferrocenyl Schiff-base derivatives attained from the condensation of *N,N'*-bis(ferrocenylmethylene)ethylenediamine with different salts of Sn(II), Sn(IV), Cd(II), Cu(II) & Ti(IV) ions by Tuğba Akcan Kardaş et al (2017). All the synthesized compounds were evaluated for their electrochemical behavior at 0.1M [(*n*-Bu)₄N]PF₆ electrolytic solution with standard Ag/AgCl. The cyclic voltammetry revealed that most

of the complexes showed only one irreversible oxidation peak preferred to the higher anodic potential (Akcan Kardaş *et al.*, 2017). The ferrocenyl Schiff base prepared from the reaction of ferrocenecarboxaldehyde with (3-aminopropyl)trimethoxysilane on graphene oxide incorporated glassy carbon electrode by Mari Elanchezian et al (2017). The synthesized compound **64** (Fig. 34) evaluated for its nonenzymatic sensitivity and substantial stability with fast charge transfer on tempered electrode. The result produced that the glassy carbon electrode possesses the significant potential valued the structural immobility of the nonenzymatic sensor (Elanchezian *et al.*, 2017).

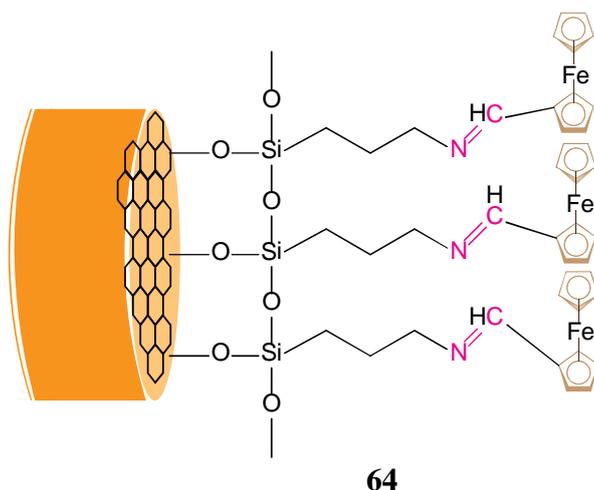
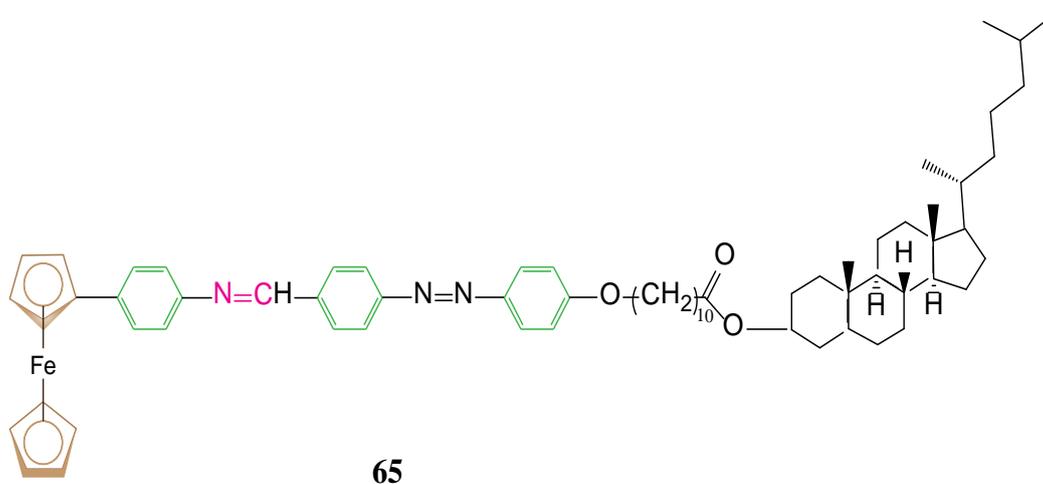


Figure 34. Schematic representation of the fabrication of Fc/APTMS/GO/GCE **64**.

4. Liquid Crystalline Properties

The ferrocenyl liquid crystalline compounds were derived from the condensation of cholesteryl aldehydes with 4-ferrocenylaniline & 4-Ferrocenylcarboxyaniline by Daniela Apreutesel et al (2007). All the synthesized compounds were characterized for their liquid crystalline properties. The result showed that the derivatives **65-66** (Fig. 35) broadly possess the highest stable mesophases with smectic phase behavior at several transition temperatures (Apreutesei *et al.*, 2007)



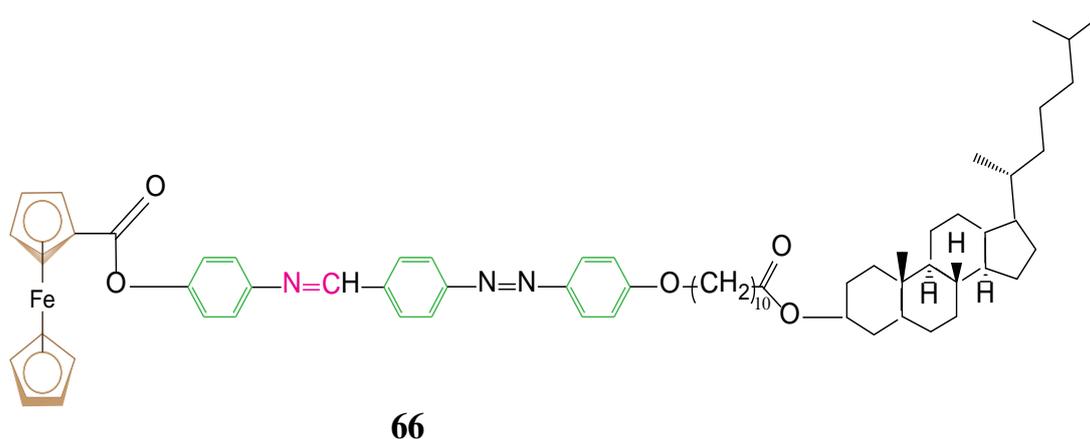
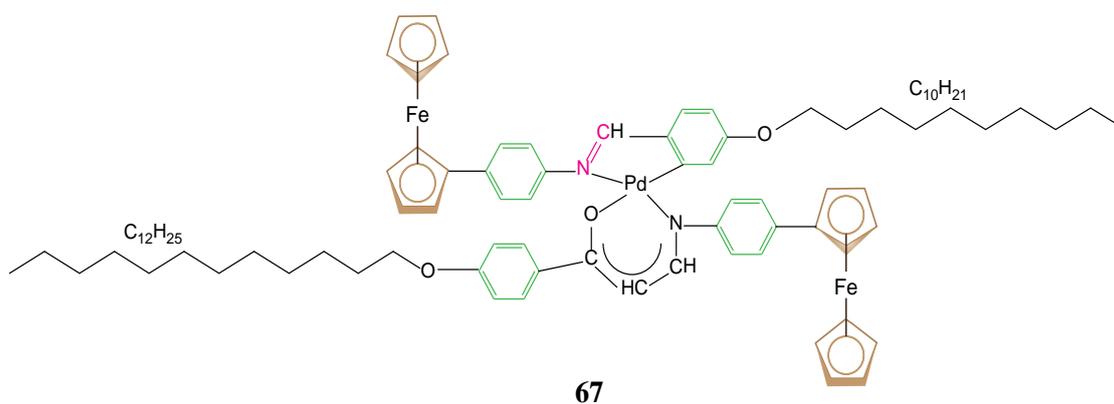


Figure 35. Structures of imine-linked ferrocene derivatives **65-66**.

V.G. Bekeshev et al (1995) derived liquid crystalline compounds of ferrocene from the reaction of 1,1'-bis(alkyloxybenzoyloxy-benzylidene) with *p*-acetylhydrazone. The derived compounds were performed experiment with thermotropic liquid crystals at temperature 25-31K and observed isotropic intramolecular vibrations. The experiment revealed that all the compounds developed nematic phases above 140°C but only 1,1'-bis(alkyloxybenzoyloxybenzylidene)ferrocene preferred both nematic and smectic phases (Bekeshev *et al.*, 1995). Oleg Katkin et al (1999) prepared ferrocenyl Schiff bases of Cu(II) and Pd(II) from the condensation of 4-aminophenylferrocene with 4-dodecyloxybenzaldehyde, 2-(4'-dodecyloxybenzoyl)acetaldehyde, 1-(4'-dodecyloxyphenyl)-3-octadecylamino)-2-propenone-1, N-octadecyl-4-dodecyloxysalicylidene-imine, 4-dodecyloxysalicylidene-4'-imino-2',2',6',6'-tetramethylpiperidinyloxy & 4-dodecyloxysalicylaldehyde. The synthesized compounds were evaluated for their liquid crystalline behavior depended upon transition temperature. The result revealed that the most of the compounds possess smectic phases, whereas mesogenic palladium(II) compounds **67-70** (Fig. 36) required more transition temperatures than copper (II) compounds (Katkin *et al.*, 1999).



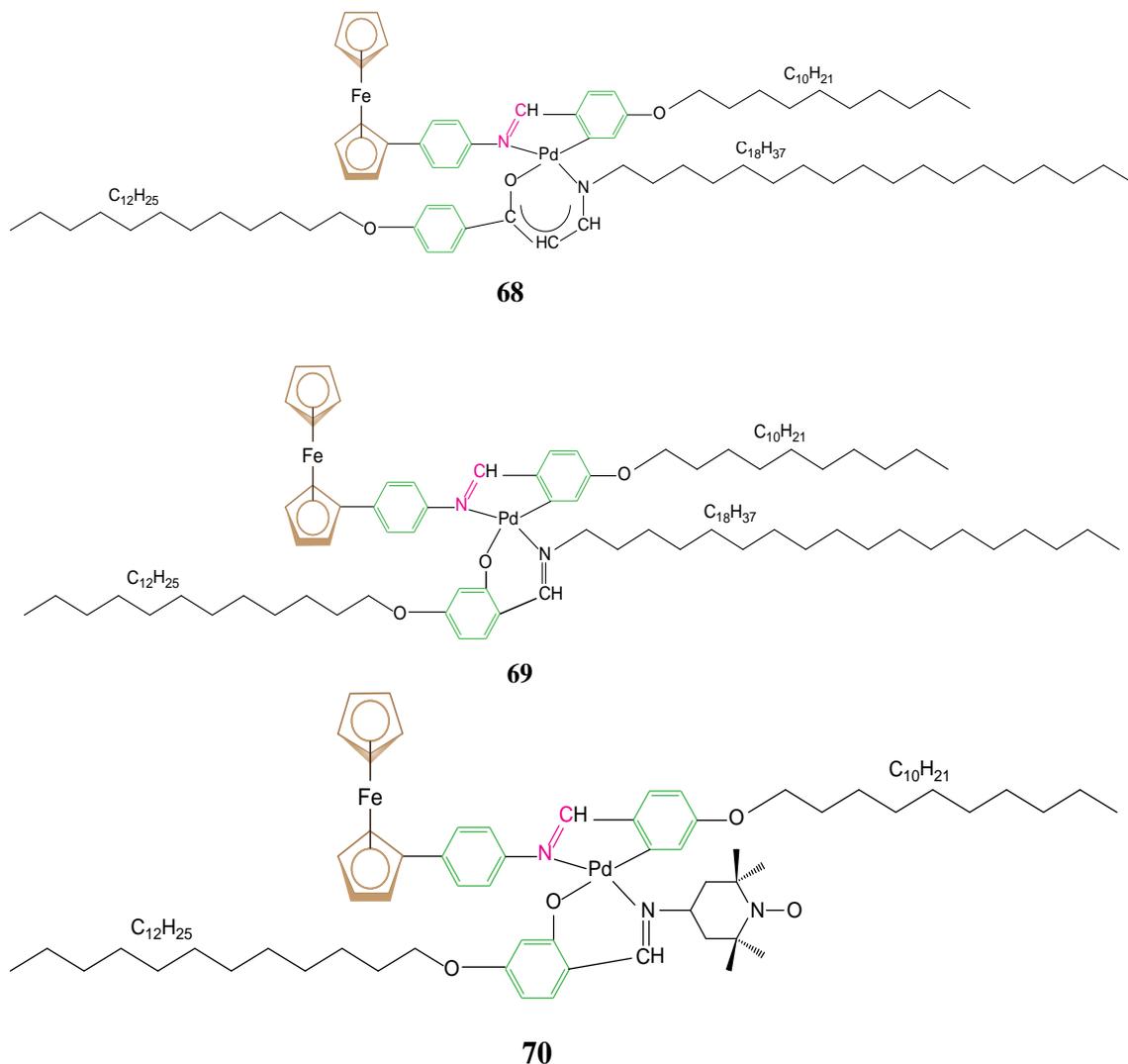


Figure 36. The chemical structures of the mixed ligand heteronuclear complexes **67-70**.

Ferrocene-based Schiff bases compounds were derived from the condensation of Bis{4-ferrocenyl-N-[4-(4-dodecyloxybenzoyloxy) salicylidene]phenyliminato} separately with nickel (II), palladium (II), oxovanadium (IV) & chloroiron (III) and μ -oxo-bis(bis{4-ferrocenyl-N-[4-(4-dodecyloxybenzoyloxy) salicylidene] phenyliminato} with iron (III) by Yu. G. Galyametdinov et al (1994). All the synthesized heterogeneous compounds were checked for their crystalline properties in view of mesomorphism of metallomesogens estimated quasi-planar conformations. The procedure released that most of the compounds clearly showed the paramagnetic liquid crystal behavior (Galyametdinov *et al.*, 1994). Ferrocenyl oxadiazole-based Schiff bases were obtained from the reaction of 6-bromohexanoyl chloride with *p*-hydroxyethylbenzoate, *p*-hydroxybenzaldehyde & 6-bromohexanoylchloride in presence of cholesterol by K.C. Majumdar et al (2012). The synthesized compounds were rationalized by their liquid crystalline properties over temperature provided twist grain boundary phase. The experiment designed that all the synthesized compounds deliver phase trend: twist grain boundary phase having SmC* slabs- chiral nematic (TGBC*-N*) (Majumdar *et al.*, 2012). Ke-Qing Zhao et al (2001) prepared ferrocenyl Schiff bases from the

condensation of p-nitrophenyl ferrocene, cetyltrimethyl ammonium bromide & p-aminophenyl ferrocene. The synthesized compounds possess smectic phase but only **71** (Fig. 37) showed nematic phase (Zhao *et al.*, 2001).

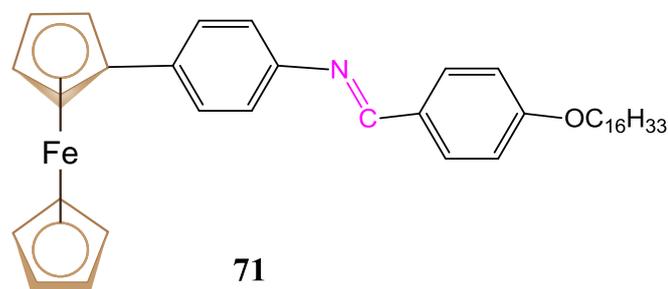
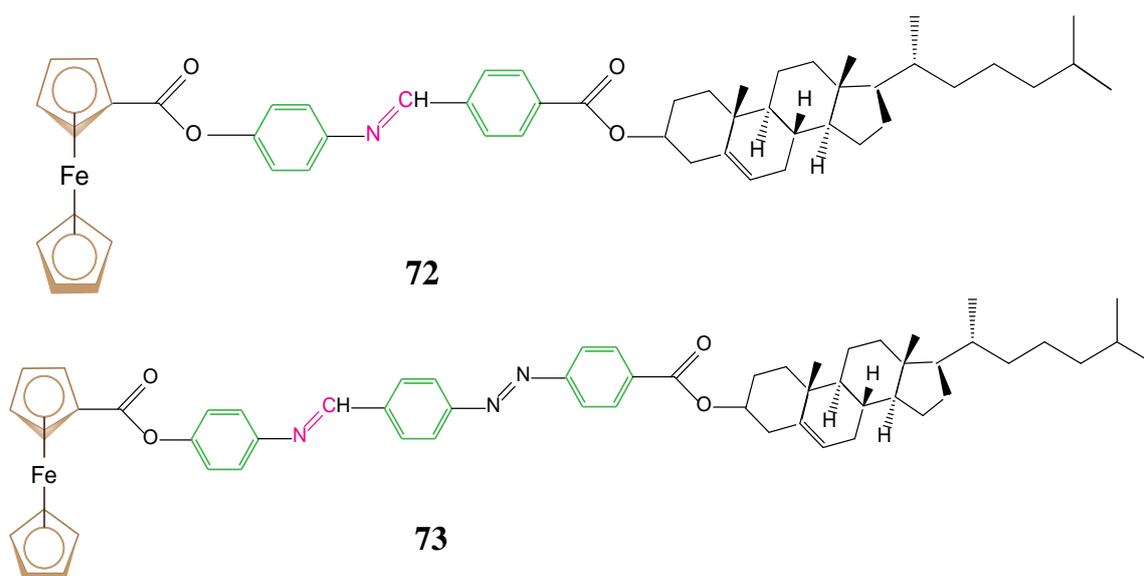


Figure 37. Structure of ferrocene containing liquid crystal **71**.

5. Thermal properties

Mona Ahmed Abdel-Rahman *et al.* (2013) prepared Schiff base derivatives from the reaction of 1-(*m*-formylphenyl)-1'-(5-formyl-2-methoxyphenyl)-ferrocene with several aliphatic and aromatic diamines. The synthesized polyazomethines were assigned for their thermal characteristics. The result showed that ferrocenyl polyazomethines were stable in high T_g values (Abdel-Rahman *et al.*, 2013). R. G. Gamper *et al.* (1971) derived ferrocenyl poly-Schiff bases from the polycondensation of 1,1'-diacetylferrocene with *p*-phenylenediamine in air or inert condition. The result exhibited that the compounds with substantial diamines brought out their thermal behaviors where the initial weight loss stabilized upto 700°C (Gamper *et al.*, 1971). The Schiff bases were obtained from the reaction of ferrocenyl derivatives with cholesterol by Gabriela Lisa *et al.* (2010). Most of the compounds were evaluated for their thermal behavior. The thermal analysis showed that the synthesized ester derivatives **72-77** (Fig. 38) containing the electro withdrawing group decreased the thermo stability than azo-derivatives, whereas cholesterol derivatives partially increased the thermo stability (Lisa *et al.*, 2010).



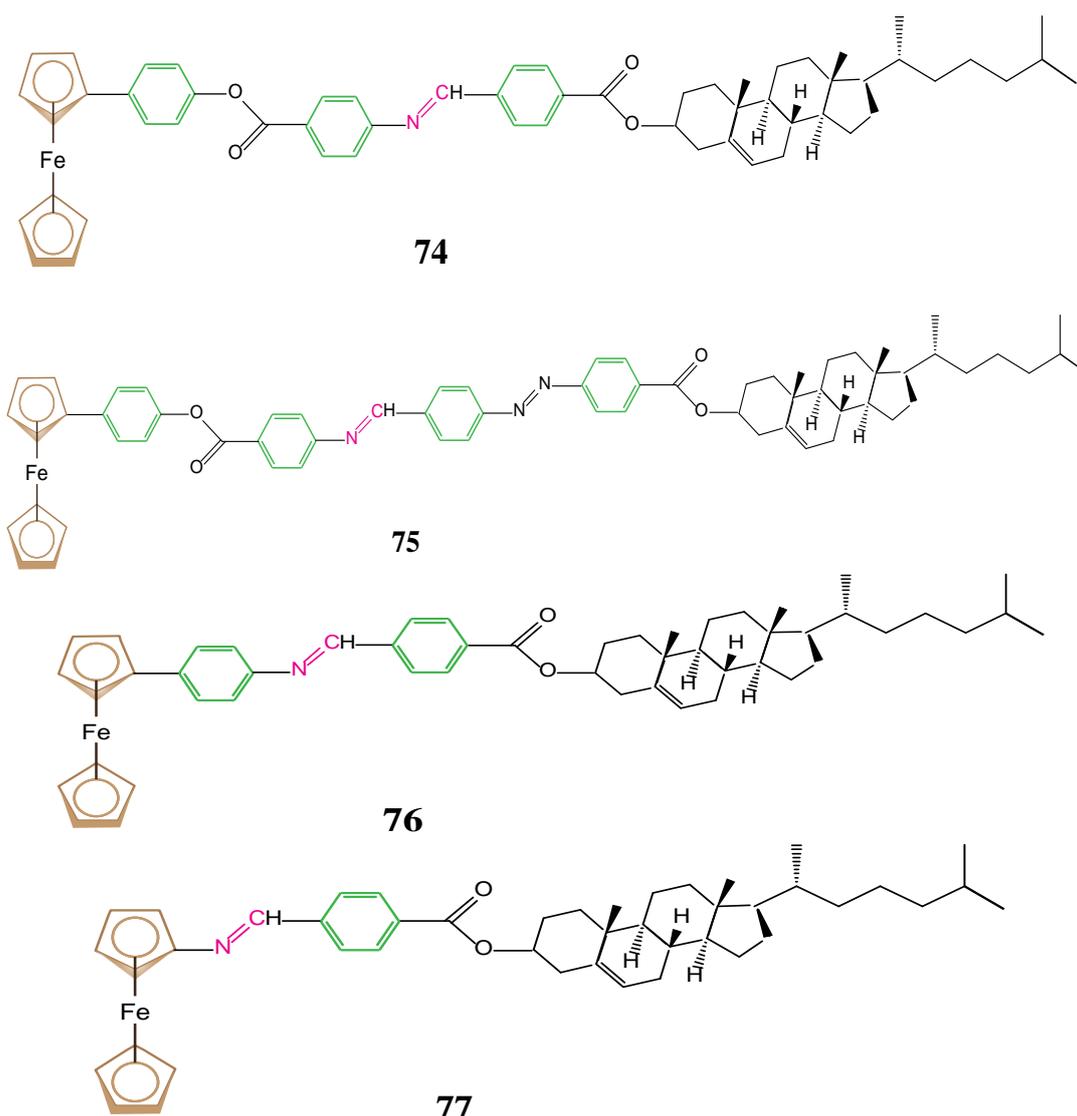


Figure 38. Structure of Schiff bases with cholesteryl unit **72-77**.

The ferrocenyl Schiff base derivatives were prepared from the condensation of ferrocenecarboxaldehyde with N-methylformanilide in presence of phosphorus oxychloride by Lawrence Verbit et al (1975). The synthesized compounds were demonstrated for their thermal properties by differential thermal analysis using polarized light microscopy under transition temperature. All the synthesized compounds showed significant thermo stability (Verbit & Halbert, 1975). Gabriela Lisa et al (2011) synthesized Schiff bases from the reaction of ferrocene derivatives with the cholesteryl unit severely linked to the mesogen part. The synthesized compounds were evaluated for their thermal stabilities in mesophase state. The result showed that the thermostability decreased when the electronic interactions were available in aromatic rings and in the iminic type synthesized compounds having a flexible side chain, whereas the cholesteryl part partially increased the thermo stability (Lisa *et al.*, 2011).

6. Optical properties

Guo-Sheng Huang et al (2003) prepared Schiff base derivatives from the condensation of ferrocenyl amine with aldehyde or an amine at room temperature. The derived compounds were checked for their optical activities by electronic absorption spectra. The experiment revealed that the derived compounds having strong electron-withdrawing group showed the larger nonlinear optical potential against urea standard. Furthermore, *o*-nitro derivatives owned the significant nonlinear optical properties than that of *m*-nitro & *p*-nitro (Huang *et al.*, 2003). A class of ferrocenyl Schiff bases were derived from the condensation of ferrocenecarboxaldehyde with 2,5-diamino anisole, 2-chloro-1,4-phenylenediamine, 2,3,5,6-tetramethyl-1,4-phenylenediamine, formylferrocene and benzidine by Sushanta K. Pal et al (2000). All the synthesized compounds **78-86** (Fig. 39) were evaluated for their second-order nonlinear optical properties according to charge transfer process bridged with electron-withdrawing effect that the compounds where metal to ligand charge transfer is possible showed the larger second order optical potential (Pal *et al.*, 2000).

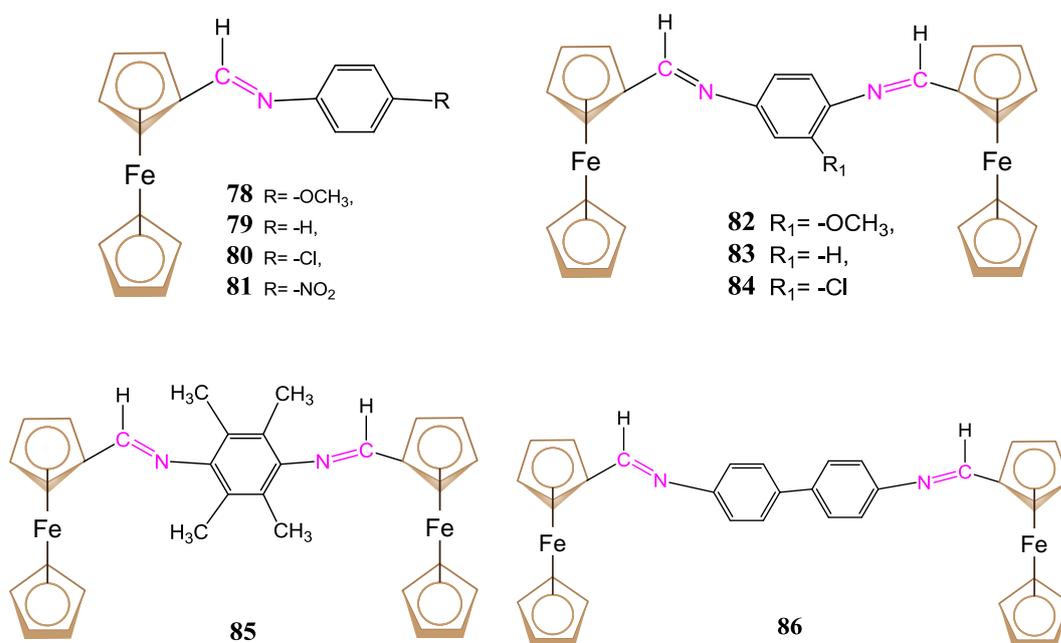


Figure 39. Structure of the synthesized compounds **78-86**.

The ferrocenyl Schiff bases were prepared from the reaction of ferrocenecarboxaldehyde and aromatic amine with base catalyst by Jian-Hong Jia et al (2011). All the derived compounds were demonstrated for their third-order optical characteristics. The optical path of DFWM and UV-Vis absorption spectra informed that all the compounds showed excellent third-order nonlinear optical properties (Jia *et al.*, 2011). Weiguo Yu et al (2015) synthesized symmetrical ferrocenyl Schiff bases from the schema of Ferrocene-1,1'-dicarbaldehyde with aromatic amine in presence of xylene and DMF solution. All the synthesized compounds experimented for their nonlinear optical characteristics based on π -D- π conjugation provided hyperpolarizability with symmetry of the molecule. The result revealed that both **87** and

88 (Fig. 40) showed the significant third-order nonlinear optical potentials with different optical susceptibility and refractive index (Yu *et al.*, 2015).

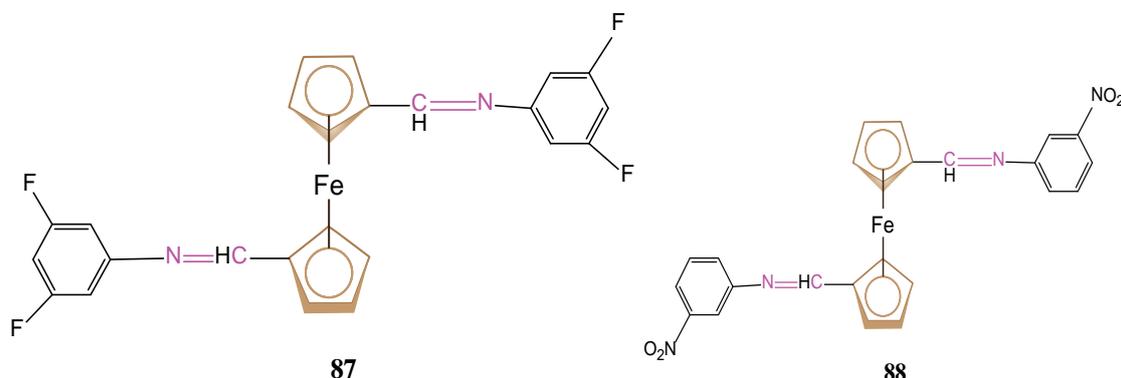


Figure 40. Structure of ferrocenyl Schiff base derivatives **87-88**.

Hongwei Hou et al (2003) prepared ferrocenyl Schiff-base complexes from the condensation of 1,2-Bis[(ferrocen-1-ylmethylene)amino]ethane with AgNO_3 and HgI_2 solution at room temperature. The compounds were evaluated for their optical properties. The result revealed that complexes exhibited very large third order nonlinear optical properties with refractive effects in DMF solution (Hou *et al.*, 2003)

7. Conclusion

From this review, it can be terminated that ferrocenyl Schiff bases and its complexes robustly perform pharmacological and medicinal activities as antimicrobial agents against different microbes. The ferrocenyl complexes are more potential than the free ligands and this activity depends on the metal ion and the tested microbes. Furthermore, their versatile redox properties with key applications make the crucial interest in fields such as nanomedicine, biological sensing, catalysis, and other materials, and other areas involving supramolecular and optoelectronic property aspects. On account of that, ferrocenyl complexes have attracted vulturine attention of the scientists for searching of new potent bioorganometallic activities.

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