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Antimicrobial Activities of Ferrocenyl Complexes: A Review

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ABSTRACT

Bioorganometallic chemistry was devoted to the synthesis of new organometallic compounds and their biological and medicinal activities. Ferrocenyl complexes display various pharmacological interests such as antibacterial and antifungal activities. This review article will focus on antimicrobial activities of ferrocenyl complexes (Cu, Co, Ni, and Zn).

INTRODUCTION

Organometallic chemistry is of growing interest especially in the recent decades due to its wide applications in the biological and medicinal field, this application leads to a new area called bioorganometallic chemistry. Ferrocene moiety is used in bioorganometallic chemistry due to its stability, biological activity and application in organic synthesis to prepare new compounds. Also, metal complexes are used in bioorganometallic chemistry since they exhibit a wide range of biological activities against various diseases.

Since the discovery of ferrocene **1** in 1951 (Kealy and Pauson, 1951), ferrocene and its derivatives have attracted the attention of many researchers in the field of organometallic chemistry for using in various applications such as materials science (Kadkin *et al.*, 2007; Ochi *et al.*, 2010), bio-organometallic and biological chemistry (Sudhir *et al.*, 2010; Molina *et al.*, 1999; Patra *et al.*, 2010), nonlinear optics (Morales-Espinoza *et al.*, 2010), asymmetric catalysis (Sondenecker *et al.*, 2011), polymer science as redox active polymers (Hudson, 2001), electrochemistry (Zheng *et al.*, 2013; Qiao *et al.*, 2009), corrosion inhibition (Gupta *et al.*, 2014) and molecular recognition as biosensors (Beer *et al.*, 1992; Beer and Smith, 1998; Moore *et al.*, 1993).

Many ferrocene compounds display interesting antibacterial (Kazemizadeha *et al.*, 2016), antifungal (Dou *et al.*, 2008), antimalarial (Itoh *et al.*, 2000; Kumar *et al.*, 2014), antitumor (Hafez *et al.*, 2013; Long *et al.*, 2009), antioxidant (Hussain *et al.*, 2013) and cytotoxic (Hassan *et al.*, 2015a; Abd El-All *et al.*, 2016) activities. Also, ferrocene compounds appeared promising in biological activities. For example, ferroquine **2** (FQ, SR97193), is a new antimalarial (Dive and Biot, 2008). Compound **3** is a potent antifungal agent and showed 100% inhibitory ratios against *S. sclerotiorum, P. oryzae* and *C. cucumerinum* (Liu *et al.*, 2008). Compound **4**, 3-ferrocenoyl-1-(4-trifluoromethoxyphenyl) urea, shows a potential *in vitro* antitumor activity using reported method (Skehan *et al.*, 1990) against cervical carcinoma cells (KB cells) (Chen *et al.*, 2005) and compound **5**, 1-(4-chlorophenyl)-3-ferrocenylurea, showed potential anti-HIV protease activity (Liu *et al.*, 2012) (Figure 1).

On the other hand, the biological activities of metal complexes have gained attention during the last two decades due to their diverse biomedical applications like antibacterial (Osman *et al.*, 2012; Sakthilatha *et al.*, 2015; Wakil *et al.*, 2017), antifungal (Ran *et al.*, 2011; El-Tabl *et al.*, 2012), cytotoxicity (Osman *et*

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al., 2014; El-Seidy *et al*., 2013), antitumor (Chang *et al.*, 2015; Rubino *et al*., 2016), antiviral (Abou-Melha *et al.*, 2015), DNA cleavage (Kokare *et al.*, 2017; Subbaraj *et al*., 2014), antimalarial (Hubin *et al.*, 2014), antioxidant (Abdel-Monem *et al.*, 2017; Lakshmi *et al*., 2011), analgesic and anti-inflammatory (Hoonur *et al*., 2010; 2011) activities.

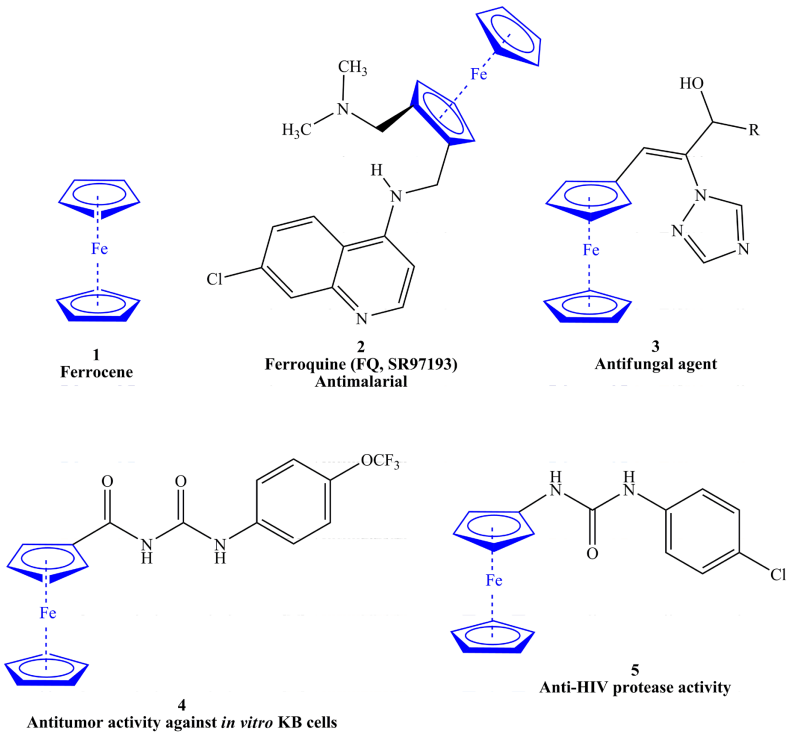


Fig. 1: Structure of ferrocene **1** and its derivatives with biological activities **2-5**.

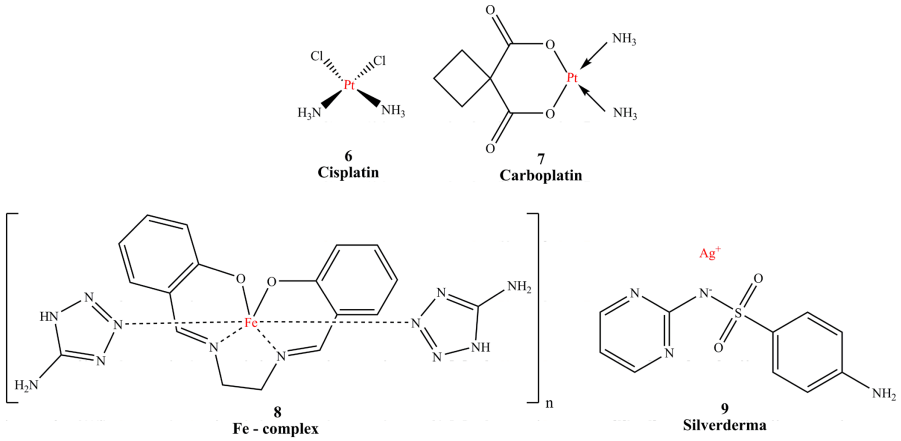


Fig. 2: Structure of some metal complexes with biological activities **6-9**.

Cisplatin (**6**), *cis*-$[PtCl_2(NH_3)_2]$, is the most famous and the best-known example of a small molecule-metal complex that has been used in the chemotherapy for various cancer diseases (Ott and Gust, 2007). Carboplatin (**7**) entered the clinic in 1998; it is a chemotherapy drug that is used against human cancer cell lines (mainly, ovarian carcinoma, lung, head, and neck cancers). Complex (**8**) was the most active against leukemia (K562) and breast (MCF-7) cells with IC_{50} = 6.4 ± 1.2 and 13.1 ± 2.1 µM, respectively, it was more active than the standard drug, oxaliplatin (IC_{50} = 9.0 and 18.0 µM) (Herchel *et al.*, 2009). Also, silverderma (silver complex of sulfadiazine) (**9**) was used as an antifungal drug (Figure 2).

Vitamin Bl2 (cobalamin) (**10**) (Figure 3) has been proved to be an essential complex with various health benefits. Among its benefits are (i) supporting the formation of red blood cells, (ii) maintaining healthy and properly functioning nerve tissues, (iii) treatment of cyanide poisoning and hereditary deficiency of transcobalamin II, and (iv) protect against brain atrophy. For the treatment of cyanide poisoning, sufficiently large amounts of hydroxocobalamin may be administered intravenously. Hydroxocobalamin can also be provided together with sodium thiosulfate (Hall and Rumack, 1987) to deliver a similar effect. The toxic cyanide ion replaces the hydroxycobalamin hydroxide ligand, and the resulting

benign B12 complex is passed with urine. This treatment was approved in fact by the US Food and Drug Administration (FDA) in 2006 to address acute treatment of cyanide poisoning (Dart, 2006). It was also noted (Vogiatzoglou *et al.*, 2008) that high vitamin B12 level in the elderly could provide protection against negative effects of Alzheimer's disease on the brain (including atrophy or shrinkage associated with and impaired cognitive function).

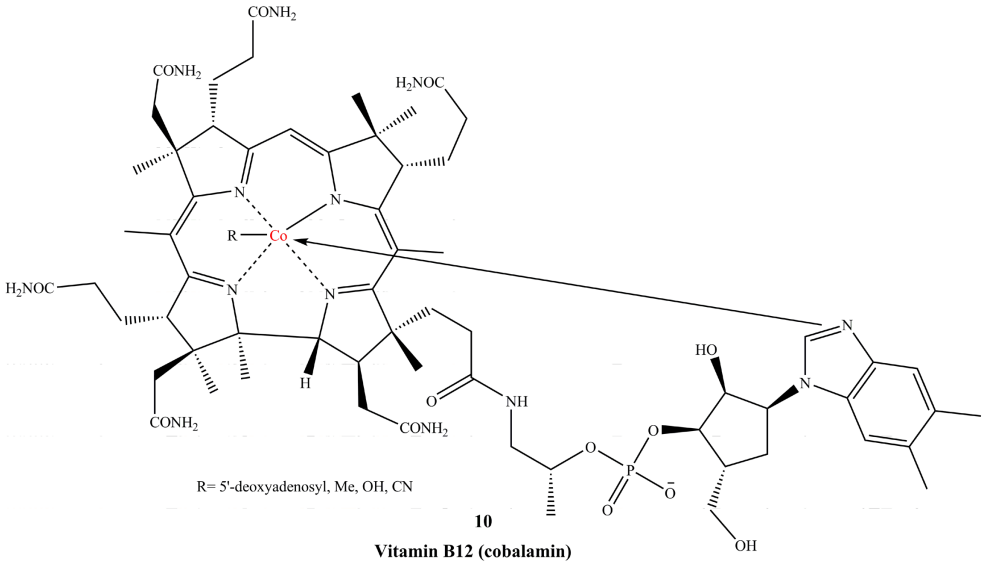


Fig. 3: Structure of vitamin B12 (cobalamin) **10**.

From the previous biological effectiveness of ferrocene compounds and metal complexes as well as our research program to display the biological activities of compounds (Hassan *et al*., 2015b; 2015c; 2016; 2017a; 2017b; 2017c; Elgemeie *et al*., 2008). The main objective of this review is to display the antimicrobial activities of ferrocenyl complexes.

The effectiveness of ferrocenyl complexes (Cu, Co, Ni, Zn) as antimicrobial agents

Antimicrobial drugs have been successfully used for treating patients with micro-organism diseases, but, the major problem is that the microbes have become resistant to these drugs. Therefore, it is too important to design and synthesize new drugs or develop the used drugs by introducing and/or omitting different atoms to change the chemical structure for matching these transformations.

Many drugs that are based on biologically active compounds possess modified pharmacological and toxicological characteristics, compared to their original characteristics, when administered as metal-based compounds. Commonly used ions include cobalt, copper, nickel and zinc {Cu, Co, Ni, Zn}. These metal complexes have low molecular weight with better effect against several diseases. Some ferrocenyl complexes possess antimicrobial characteristics and can be used as new drugs.

Chohan and Praveen in 2000 and 2001 have synthesized Co(II), Ni(II), Zn(II) and Cu(II) complexes of symmetric and asymmetric 1,1'-ferrocene derived Schiff-bases for their evaluation as antibacterial agents against different microbes e.g. *E. coli, S. aureus, P. aeruginosa* and *K. pneumonae*. From the results of antibacterial activity, it was found that [Ni(L^1)(Cl_2)] and [Co(L^3)(Cl_2)] complexes were more active than the other prepared complexes against *E. coli*, while, [Co(L^1)(Cl_2)] and [Co(L^3)(Cl_2)] complexes were more active than the remaining prepared complexes against *K. pneumonae* and *E. coli*, respectively. In comparison with the ligands, the metal complexes were found to be more biologically active (Chohan and Praveen, 2000; 2001) (Figure 4**)**.

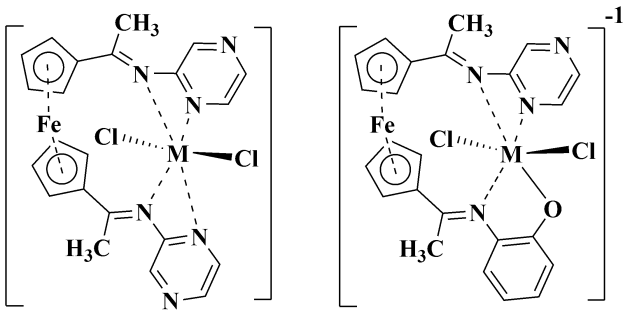


Fig. 4: Metal complexes of symmetric and asymmetric 1,1'-ferrocene derived Schiff-bases.

In 2003, Chohan *et al*., have prepared metal complexes of symmetrically 1,1'-disubstituted ferrocene derived from Schiff-bases for their evaluation as antibacterial agents against *E. coli, S. aureus, P. aeruginosa* and *K. pneumoniae.* From the results of the antibacterial activity, it was found that $[Co(L^1)(Cl_2)]$, $[Zn(L^1)(Cl_2)]$ and $[Co(L^3)(Cl_2)]$ complexes were more active than the other prepared complexes against *E. coli*. $[Cu(L^1)(Cl_2)]$, $[Cu(L^3)(Cl_2)]$ and $[Zn(L^3)(Cl_2)]$ complexes were more active than the remaining prepared complexes against *S. aureus*. Complexes of $[Ni(L^1)(Cl_2)]$ and $[Ni(L^3)(Cl_2)]$ were active against *P. aeruginosa.* Complexes of $[Co(L^1)(Cl_2)]$, $[Co(L^2)(Cl_2)]$, $[Ni(L^2)(Cl_2)]$ and $[Co(L^3)(Cl_2)]$ were active against *K. pneumonia* (Chohan *et al*., 2003) (Figure 5**)**.

Abd-Elzaher in 2004, synthesized and evaluated the antimicrobial activities of Co(II), Cu(II), Ni(II) and Zn(II) complexes of ferrocenyl Schiff bases bearing a phenol moiety against *E. coli*, *B.subtilus* and *C. albicans*. From the results of antimicrobial evaluation, the prepared complexes of $Cu(L1)_2$, $Zn(L1)_2{\cdot}2H_2O$, $Co(L2)_2{\cdot}2H_2O$, $Ni(L2)_2{\cdot}2H_2O$, $Cu(L2)_2$ and $Zn(L2)_2{\cdot}2H_2O$ showed significant antimicrobial activity against *C. albicans* (Abd-Elzaher, 2004) (Figure 6).

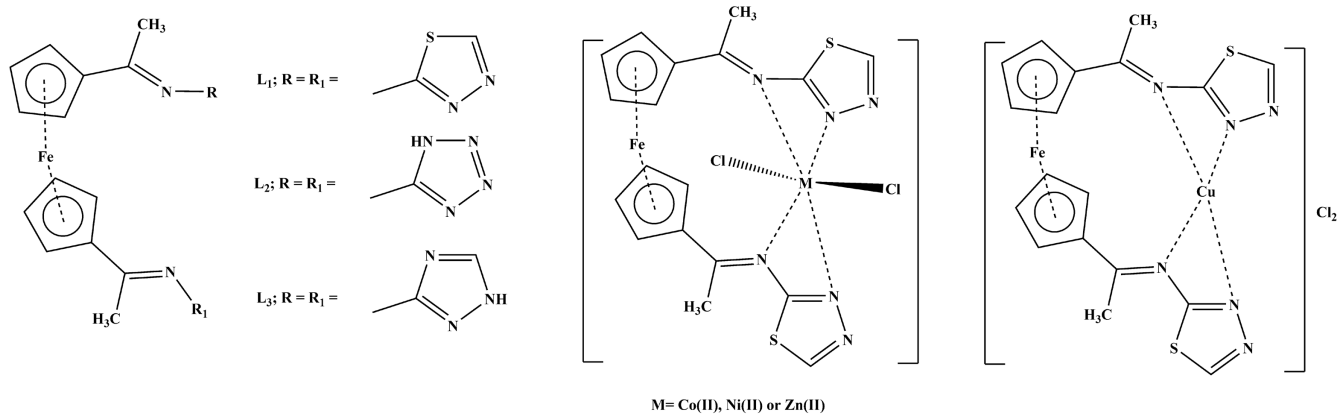


Fig. 5: Metal complexes of symmetrically 1,1'-disubstituted ferrocene derived Schiff-bases.

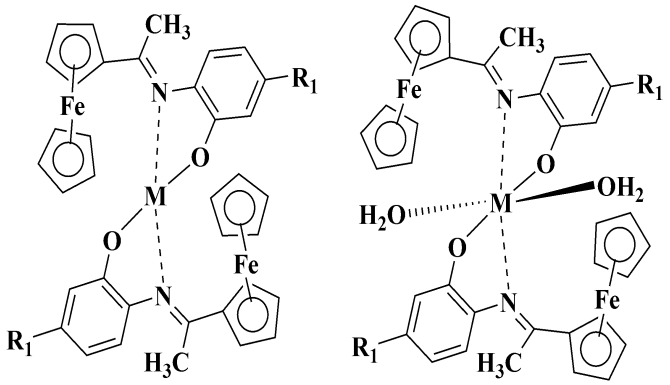


Fig. 6: Metal complexes of ferrocenyl Schiff bases containing a phenol moiety.

In 2017, Mahmoud *et al*., synthesized metal complexes of $[M(L)Cl(H_2O)_3]$ {M = Ni(II), Cu(II)} and $[M(L)Cl(H_2O)_3].nH_2O$ {M = Co(II), n = 1 and M = Zn(II), n = 2} of (*Z*)-(4-(1-((2-carboxycyclohexa-2,4-dien-1-yl)imino)ethyl)[*bis*(η5cyclopenta-1,3-dien-1 yl)]iron for their evaluation as antimicrobial agents against some bacteria and fungi. From the results of the antimicrobial evaluation, the prepared ferrocenyl complexes exhibited the highest antibacterial and antifungal activities. The antimicrobial activity of ferrocenyl complex depending on the nature of ferrocene derivative, the total charge of the complex, and the metal center in the complex (Mahmoud *et al.*, 2017) (Figure 7).

In 2005, Abd-Elzaher *et al*., have prepared the complexes of Co(II), Ni(II), Cu(II) and Zn(II) of 1,1'-*bis*[(2-thienylmethylidene)hydrazono-1-ethyl]ferrocene and tested against two Gram-positive, two Gram-negative bacteria, two fungi and one yeast. By comparing the results of antimicrobial activity, it was found that the complexes of Ni(II), Cu(II) and Zn(II) are more active towards *C. albicans* than the Co(II) complex and the Cu(II) complex is more active than the remaining complexes against *S. Typhi* (Abd-Elzaher *et al*., 2005) (Figure 8**)**.

In 2006, Abd-Elzaher *et al*., and El-shiekh *et al.*, have prepared different metal complexes of 1,1'-*bis*[1-methyl-5-phenyl-4*H*-(1,3,4)-thiadiazolo[2,3-*c*](1,2,4)triazin-4-one]ferrocene and

1,1'-*bis*[1,5-methyl-4*H*-(1,3,4)-thiadiazolo[2,3-*c*](1,2,4)triazin-4-one]ferrocene then evaluated their activities against different microbes, e.g., *A. niger, C. herbarum, F. moniliforme, E. coli* and *S. aureus*. The results revealed that the complexes have higher biological activity than the free ligand and the order of inhibition zone diameter (mm) by the complexes is Zn(II) > Cu(II) > Mn(II) > Co(II) > Ni(II) > Fe(III) (Abd-Elzaher *et al*., 2006; El-shiekh *et al*., 2006) (Figure 9).

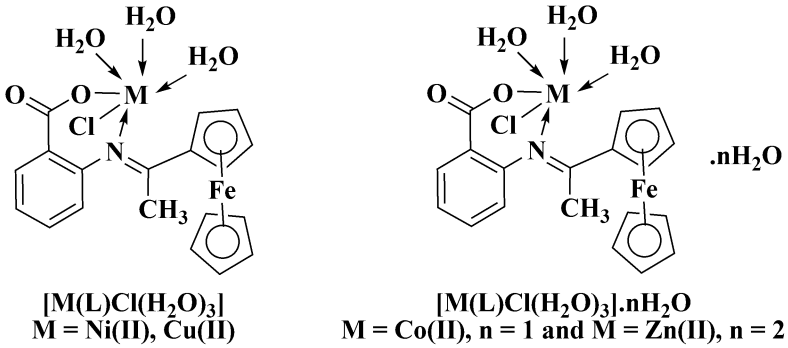


Fig. 7: Metal complexes of ferrocene-based Schiff base ligand.

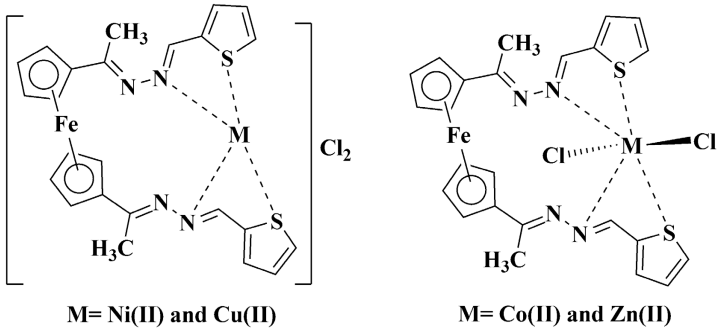


Fig. 8: Metal complexes of 1,1'-bis[(2-thienylmethylidene)hydrazono-1-ethyl]ferrocene.

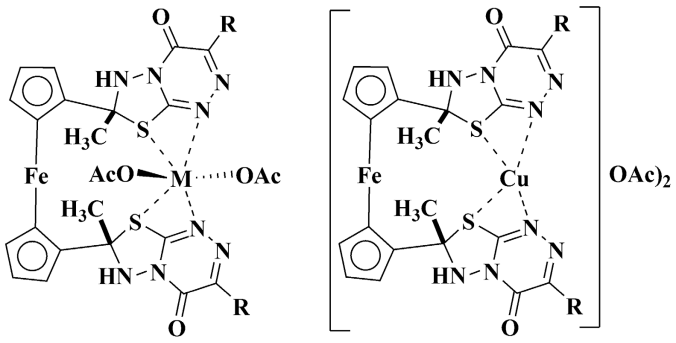


Fig. 9: Metal complexes of 1,1'-*bis*[1-methyl-5-phenyl-4*H*-(1,3,4)-thiadiazolo[2,3-*c*](1,2,4)triazin-4-one]ferrocene and 1,1'-*bis*[1,5-methyl-4*H*-(1,3,4)-thiadiazolo[2,3-*c*](1,2,4)triazin-4-one]ferrocene.

Chohan *et al*., in 2004, have obtained Co(II), Cu(II), Ni(II) and Zn(II) complexes of ferrocenyl hydrazones, *bis*-(1,1'-disubstituted ferrocenyl)thiocarbohydrazone (L1) and *bis*-(1,1'-disubstituted ferrocenyl)carbohydrazone (L2) and tested for antibacterial and antifungal activities. All the prepared complexes showed significant antibacterial and antifungal activities against all the micro-organisms in this study (Chohan *et al*., 2004) (Figure 10).

In 2005, Chohan and Supuran have prepared of Co(II), Cu(II), Ni(II) and Zn(II) complexes of 1,1'-(dicarbohydrazono) ferrocenes and evaluated their activities against bacterial and fungal strains. The inhibition zones (mm) and the minimum inhibitory concentration (MIC) of some selected compounds were determined by using the disc diffusion method (Atta-ur-Rahman *et al*., 2001). The experimental results showed that the ferrocenyl complexes were more active than their ligands in inhibiting the growth of the organisms when tested at 10 µg ml^{-1} concentrations (Chohan and Supuran 2005) (Figure 11).

In 2007, Chohan and Naseer have synthesized and screened for their antibacterial and antifungal properties of Co(II),

Cu(II), Ni(II) and Zn(II) complexes of 1-acetyl, 1'-ethanolamine ferrocene and 1,1'-*di*-ethanolamine ferrocene. All the metal(II) complexes have shown good antibacterial and antifungal activities from moderate to a significant degree (Chohan and Naseer, 2007) (Figure 12).

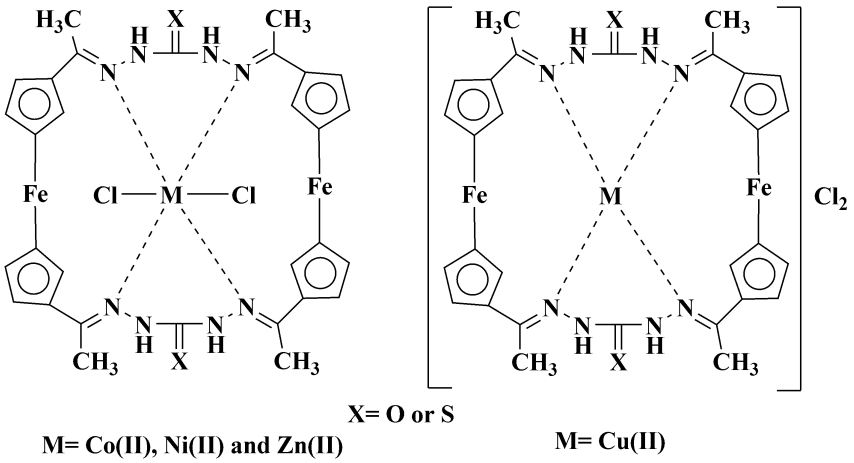


Fig. 10: Metal complexes of new ferrocenyl hydrazones.

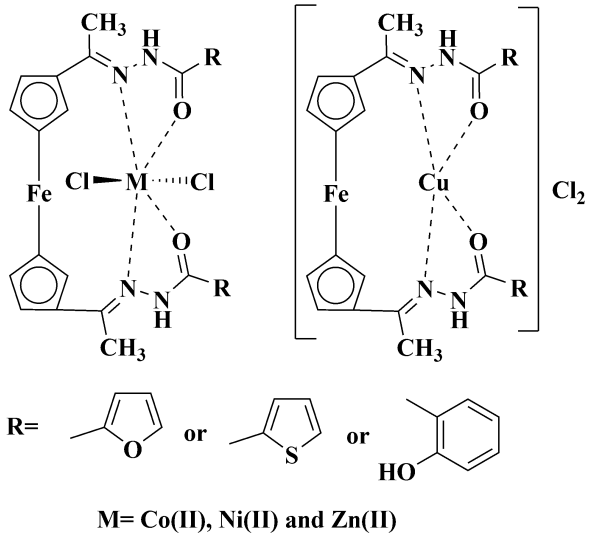


Fig. 11: Metal complexes of 1,1'-(dicarbohydrazono) ferrocenes.

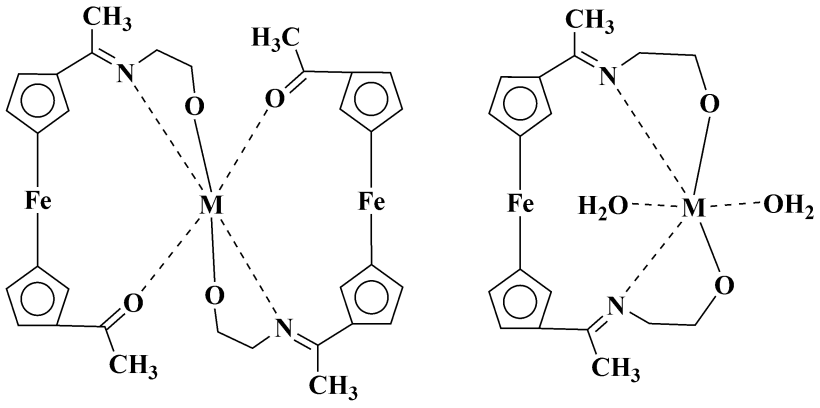
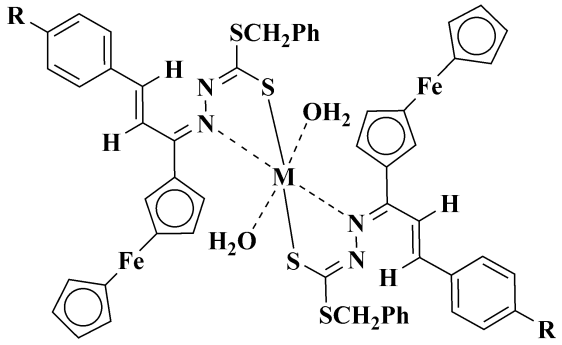


Fig. 12: Metal complexes of 1-acetyl, 1'-ethanolamine ferrocene and 1,1'-*di*-ethanolamine ferrocene.

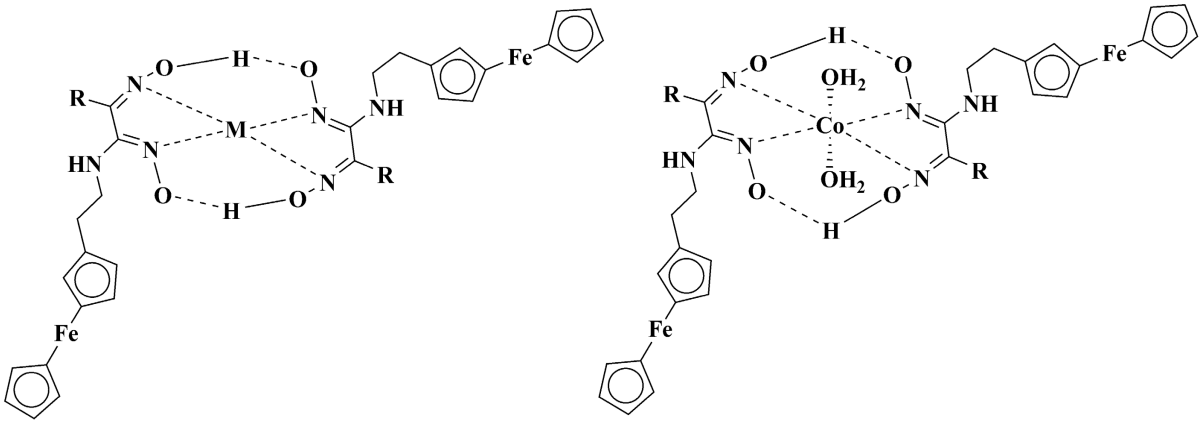
Liu *et al.*, in 2013, have synthesized the metal complexes of *S*-benzyl-*N*-(1-ferrocenyl-3-(4-methylbenzene)acrylketone) dithiocarbazate (**HL1**) and *S*-benzyl-*N*-(1-ferrocenyl-3-(4-chlorobenzene)acrylketone)dithiocarbazate (**HL2**) and tested for their antibacterial and antifungal properties. The results revealed that Zn(II) complexes of both the ligands and Cu(II) complex of the **HL2** were shown to have significant activity against all bacterial strains. The minimum inhibitory concentration (MIC) of Zn(II) and Cu(II) complexes of ligand (**HL2**) was in the range of 1.54×10^{-8} to 3.750×10^{-7} M while Zn(II) complex of (**HL1**) proved to be the most active one and it inhibited the growth of *A. niger* at 1.319×10^{-8} M. The metal(II) complexes showed good antifungal activity against different fungal strains (Liu *et al.*, 2013) (Figure 13).



HL1, R= CH_3; HL2, R= Cl

M= Cu(II), Co(II), Ni(II) and Zn(II)

Fig. 13: Metal complexes of S-benzyl-N-(1-ferrocenyl-3-(4-methylbenzene)acrylketone) dithiocarbazate **(HL1)** and S-benzyl-N-(1-ferrocenyl-3-(4-chlorobenzene) acrylketone)dithiocarbazate **(HL2)**.



R= CH_3 or Ph

M= Cu(II), Co(II), Ni(II) and Zn(II)

Fig. 14: Metal complexes of *anti*-β-ferrocenylethylaminoglyoxime and *anti*-β-ferrocenylethylaminophenylglyoxime.

Deveci and Arslanb in 2011, have synthesized Ni(II), Cu(II) and Co(II) complexes of *anti*-β-ferrocenylethylaminoglyoxime and *anti*-β-ferrocenylethylami nophenylglyoxime and their antibacterial activity were studied. The results indicated that all the complexes have mild levels of antibacterial activity against gram-negative and gram-positive species and the minimum inhibitory concentrations (MICs) of complexes were found in the range from 32 mg/ml to 128 mg/ml (Deveci and Arslanb, 2011) (Figure 14).

In 2015, Ali *et al.,* have synthesized and screened for their *in vitro* evaluation of antibacterial and antifungal properties Zn(II), Cd(II), Hg(II) and Pd(II) complexes of 1,1'-(4,4'-*di*-ferrocenyl)-*di*-phenyl thiourea. The results indicated that all the complexes are biologically active against Gram-positive, Gram-negative bacteria and yeast (Ali *et al.*, 2015) (Figure 15).

The mode of action

According to the chelation theory, chelation tends to make the ligands act as more powerful and potent bactericidal agents, thus killing the microorganisms. As such a possible explanation of the results may relate to the polarity of a metal ion and its interaction with a ligand, increasing the lipophilic nature of the metal and enhancing its penetration capacity through the lipid layer of the cell membrane of the microorganism. Furthermore,

it was proposed that the presence of heteroatom has an important role in promoting antimicrobial activities, and enhancing the hydrophobic and liposolubility characteristics of the overall structure. Other factors, such as solubility, conductivity and dipole moment (influenced by the presence of metal ions), may also be possible reasons for increasing this activity (Abd-Elzaher 2004; Abd-Elzaher *et al*., 2006).

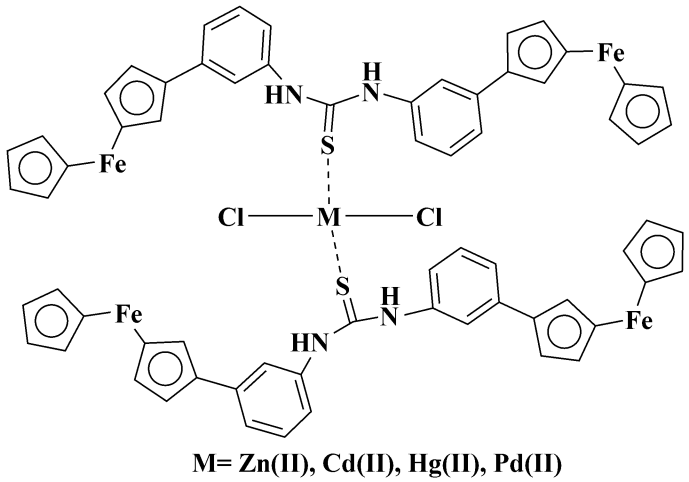


Fig. 15: Metal complexes of 1,1'-(4,4'-di-ferrocenyl)-*di*-phenyl thiourea.

CONCLUSION

From this review, it can be concluded that ferrocenyl complexes display pharmacological and medicinal activities as antimicrobial agents against different microbes. The ferrocenyl complexes are more active than the free ligand and this activity depends on the metal ion and the tested microbes. For that, ferrocenyl complexes have attracted increasing attention of the scientists for searching of new potent pharmacological and medicinal activities.

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