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Study of Potential applications of Ferrocene functionalized derivatives for its anticancer, antimalarial, antifungal, antiviral and antitubercular properties.

Ajitkumar V. Ingle[1,2], Shrimant V. Rathod[1*], Sheetal Powar[2], Kailas W. Shinde[1]
[1]*Department of Chemistry, Bhavan's Hazarimal Somani College, University of Mumbai, Mumbai, Maharashtra, India*
[2]*Department of Chemistry, VWTCT'S Bhaskar Waman Thakur College of Science, University of Mumbai Virar, Maharashtra, India*

Abstract : *Ferrocene and its derivatives have a wide range of medicinal applications such as anticancer, antitubercular, antifungal, antiviral, antibacterial, analgesics, etc. This study specifically focusses on the discussion of reported potential biological activity applications of Ferrocene functionalized derivatives for its anticancer, antiviral, antifungal, antimalarial and antitubercular properties.*
Keywords – *Applications, Biological activities, Ferrocene derivatives.*

I. INTRODUCTION

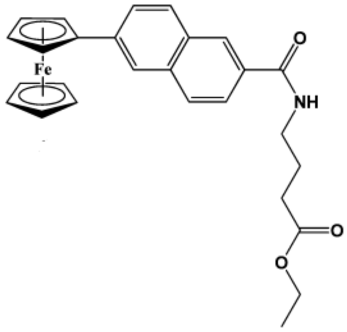
The discovery of ferrocene [1,2] in 1951 has given chemists a new way to carry out various interdisciplinary research activities. Since then, many ferrocene derivatives have been prepared and are found to have various vital applications in diverse fields such as medicinal chemistry [3-5], supramolecular chemistry [6], homogenous catalysis [7], biosensors [8], materials science [9] etc. Ferrocene functionalized organic compounds often show various biological activities due to different membrane permeation properties and anomalous metabolism [10]. Ferrocene is preferred because of its ease in substitution, stability of the ring and significant changes in biological activity which makes it a better compound for designing of drugs. Heterocyclic compounds are also well known for biological activity like pyrazoline and its derivatives have shown antifungal [11], antibacterial [12], antidepressant [13], anticonvulsant [14,15], anti-inflammatory [16], anti-tumor [17], anesthetic and analgesic [18-20], antihypertensive [21], antioxidant [22], anticancer [23,24] properties. The combination of ferrocenyl moiety with heterocyclic structure may increase their biological activities or create new medicinal properties and hence ferrocene heterocycles have become an important pathway for bioactive compounds [25-29].

II. BIOLOGICAL ACTIVITIES

2.1 Ferrocene and its derivatives in cancer research

A lot of research indicates that Ferrocene derivatives have a very good anticancer activity. The anticancer potential of ferrocene derivatives bearing amine or amide groups was first discovered in the late 1970s by Brynes and co-workers against lymphocytic leukemia P-388 [30]. Since then, numerous types of ferrocenyl compounds have been evaluated in for their anticancer properties. Ko¨pf-Maier, Ko¨pf, and Neuse [31] disclosed the anti-tumor activity of ferricenium salts against Ehrlich ascites tumor and Rauscher leukemia virus. In their studies it was observed that the activity of ferricenium salts strongly depends on the counter anion and type of cancer [32]. Ferrocenyl-peptide derivatives were tested in vitro against the human lung carcinoma cell line H1299, and most of them showed IC50 values below 10 mM. In particular, N-(6-ferrocenyl-2- naphthoyl)-g-aminobutyric acid ethyl ester (Fig.1) had an IC50 value of 0.62 mM, and is more active in vitro than the clinical employed anti-cancer drug cisplatin.[33-36]. Kondapi and co-workers reported a series of ferrocenyl derivatives and studied their inhibitory properties against topoisomerase IIa and b. [37,38] in which they discovered that azalactone ferrocene (Fig 2a) and thiomorpholide amido methyl ferrocene (Fig 2b), presented a substantial effect against topoisomerase II activity causing numerous genetic implications that ultimately resulted in neoplastic cell death [37]. Ferrocenes show promising activity against breast cancer. [39,40].

Ferrocifens are found to show promising results for ER+ breast cancer, commonly the non-steroidal selective estrogen receptor modulator (SERM) tamoxifen (Fig.3) [41].



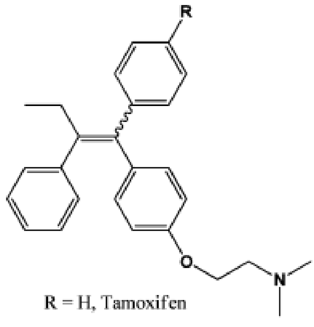


Fig 1

Fig 3

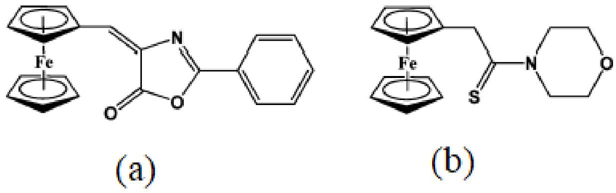


Fig 2

2.2 Ferrocene and its derivatives as Antimalarials

Ferrocene-Quinoline derivative Ferroquine derived from chloroquine by Biot and co-workers (Fig 4a) was found to be more effective against chloroquine resistance P. falciparum and non-toxic in vivo [42]. Ferroquine has low pKa values, however it exhibits a significant inhibition activity against beta-haematin formation compared to chloroquine and it is preferentially localized at the lipid–water interface, making it an effective antimalarial agent when compared to chloroquine [42]. Derivatives of trioxaferroquines were reported by Bellot et al. (Fig 4b). They were effective against chloroquine-resistant strains (FcB1 and FcM29) with IC50 values between 16–43 nM [42]. They exhibited significant antimalarial activity with IC50 values 17 and 29 nM against FcB1 and FcM29, respectively.

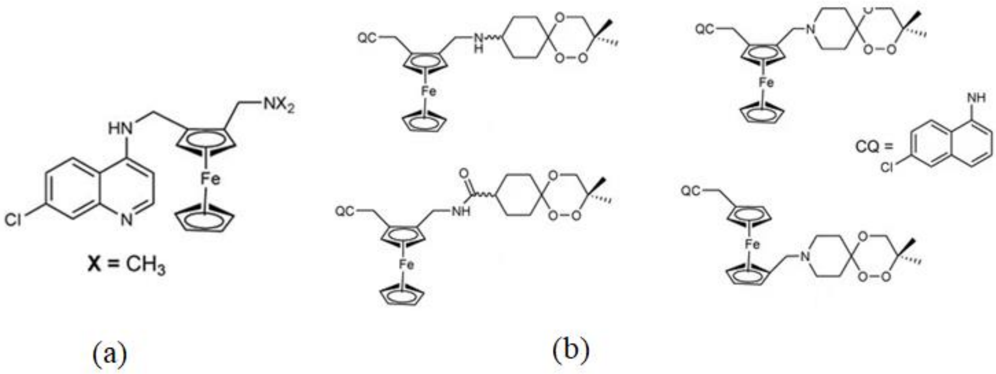


Fig 4

Reiter et al. reported an artemisinin derivative containing ferrocene moiety and egonol. In vitro studies indicated that the derivative formed was the only one exhibiting antimalarial activity among the seven other artemisinin–ferrocenyl derivatives studied, while others exhibited anticancer activity. Its antimalarial activity was enhanced when compared to the parent drug, egonol, with an inhibition value of 88 nM (Fig 5) [43,44].

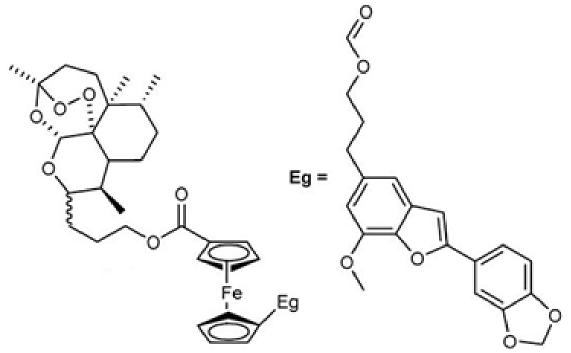


Fig 5

2.3 Antifungal and Antiviral activity of Ferrocene derivatives

Ferrocene-containing fluconazole derivatives were synthesized by Biot and co-workers synthesized exhibited moderate antifungal activity [45]. The dithiothione (Fig 6a) and dithioketone (Fig 6b) derivatives of ferrocene prepared by Chohan [46]. were comparable to the drugs miconazole and amphotericin B in their antifungal activity for fungi like C. albicans and Aspergillus flavus (A. flavus) [46]. The both 6a and 6b compounds showed moderate antibacterial activity as well [46].

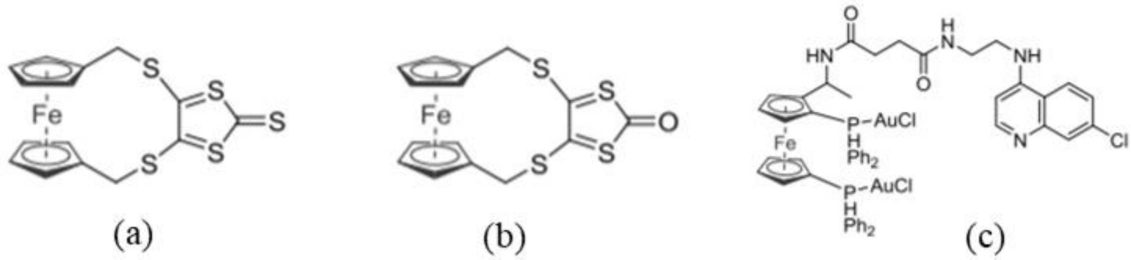


Fig 6

A ferrocene peptide conjugate, HNG-156 was synthesized by Chaiken and co-workers an HIV entry inhibitor, (Fig 6, c), and its activity was studied for its antiviral potency for HIV-1 envelope gp120 [47]. The work demonstrated that 134 acts as a dual receptor site antagonist of virus envelope gp120 [47]. Also HNG-156 showed a low IC50 value (96 nM) for the inhibition of P4-CCR5 MAGI (CD4 expressing HeLa-based cells) cell infection caused by HIV-1 whole virus [47].

Ferrocene conjugates were also analysed for their potential activity against other viruses such as hepatitis C virus (HCV that causes acute and chronic hepatic inflammation (hepatitis), Wiles et al. synthesized a metalorganic compound with a 1,1´ -ferrocenediyl scaffold and a biplanar organic structure (Fig 7) [48,49]. This molecule targets and inhibits nonstructural protein 5A NS5A, a zinc-binding phosphoprotein that plays a key role in the viral RNA replication cycle.

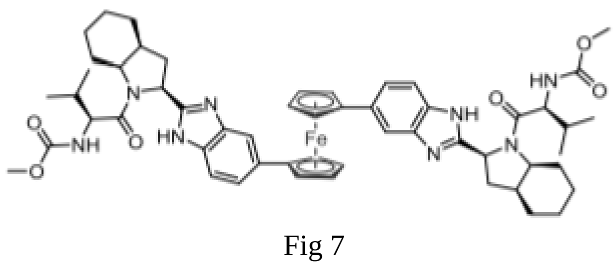


Fig 7

2.4 Antitubercular activity of Ferrocene derivatives

Ferrocene based hydrazone derivative (Fig 8) was found to show excellent activity against *Mycobacterium Tuberculosis.* This quinoline ferrocene hybrid exhibited significant activity against TB with MIC90 of 2.5 – 5 µg/mL as compared to EMB (with MIC of 2.5 µg/mL) used as a reference drug. This activity reported may be due to the presence of the quinoline ring [50]. The newly synthesized quinoline-ferrocene hybrid (Fig 8a) [51] showed potent activity, in a concentration range comparable to the one of EMB, the activity is attributed to the presence of quinoline moiety. Novel ferrocenyl hydrazones ((Fig 8b)) with their cyclodextrin inclusion complexes have been evaluated for their anti-tubercular activities[52]. The cyclodextrin inclusion complexes of the ferrocenyl hydrazones were found to possess higher water solubility, improved hydrolytic stability and greater antitubercular activity.

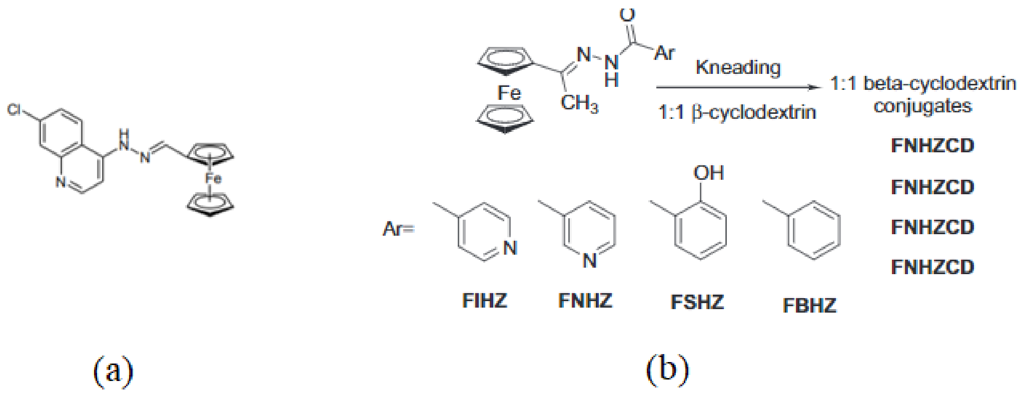


Fig 8

III. Conclusion

Ferrocene derivatives have ever an increasing number of applications in medicinal chemistry, resulting synthesis of new derivatives every time. Ferrocene derivatives are active due to their multiple substitution possibilities at the cyclopentadienyl ring and mode of action. The biological activity and its applications can be seen through the increasing number of publications regarding various antiparasitic, antiviral, anticancer, antitubercular and antifungal ferrocene derivatives. This study clearly indicates that ferrocene conjugates have shown various remarkable potential activities and definitely have a wide scope in exploring more potent and diverse range of applications in medicinal field.

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