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Ferrocenyl Benzimidazole: A Promising Molecule

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ABSTRACT

Organometallic compound ferrocene formation was a serendipity and due to its "barrel-shape" which grants 3D geometry of the organometallic compound it has an optimal spatial design for better fitting and connection inside the pockets of the dynamic site in natural targets and receptors. The benzimidazole motif has developed to be a significant privileged heterocyclic platform. Ferrocenyl benzimidazole is a complex organic compound having ferrocene an organometallic compound attached to the 2-position of benzimidazole an aromatic heterocyclic compound. Ferrocene benzimidazole derivatives have attracted lots of attention for the construction of new compounds due to their wide applications. By combining ferrocene and benzimidazole produce a vast range of pharmacological actions. Synthetic method and pharmacological effects of various ferrocenyl benzimidazole derivatives were examined. This review gives the medicinal activities of 2- ferrocenyl benzimidazole derivatives like cytotoxic activity, anti-malarial, anti-microbial, anti-fungal etc. were furnished.

KEYWORDS: ferrocene, benzimidazole, cyclopentadiene, 2-ferrocenyl benzimidazole, cytotoxic, anti-malarial.

INTRODUCTION

Ferrocene compounds have been the subject of bioorganometallic chemistry research, which has recently received much greater attention. Organometallic compounds having one metal atom between 2 planar polyhapto ligand, they are commonly called as metallocene and also informally known as sandwich compounds. The structure of ferrocene was introduced by Kealy and Pauson and ferrocene is a complex organometallic compound and it have 2 cyclopentadienyl rings bounded to a central iron atom.(1) The anti-cancer, anti-bacterial, anti-fungal, and antiparasitic properties of ferrocene derivatives have garnered considerable interest. Heterocyclic organic compound benzimidazole derivatives which displayed the potent biological properties in medicinal chemistry. A wide range of heterocyclic compounds were synthesised with the building block benzimidazole. Heterocyclic aromatic organic compound benzimidazole was emerged as a probable nucleus with wide verity of activity. Bicyclic compound by fusing aromatic rings of the compound benzene and imidazole having properties of both acids and bases. Ferrocenyl benzimidazole is a complex organic compound having ferrocene an organometallic compound attached to the 2-position of benzimidazole an aromatic heterocyclic compound. (6) Ferrocene benzimidazole derivatives have attracted lots of attention for the construction of new compounds due to their wide applications. By combining ferrocene and benzimidazole

produce a vast range of pharmacological actions. Synthetic method and pharmacological effects of various ferrocenyl benzimidazole derivatives were reviewed. (18,24,29)

ORGANOMETALLIC COMPOUND: ORGIN OF FERROCENE

Organometallic compounds having one metal atom between 2 planar polyhapto ligand, they are commonly called as metallocene and also informally known as sandwich compounds. The most studied metallocene are the complex of cyclopentadienyl (pentahapto) ligand with transition metals. The first metallocene was reported in 1951 and it was ferrocene $(C_5H_5)_2Fe$. In this molecule iron is sandwiched between two parallel planar rings of cyclopentadiene. Those metallocene has a general formula of Cp_2M, where Cp is the planar cyclopentadiene which is a five-electron donor and M is the transition metal. Other polyhapto ligand having metallocene are chromocene, manganocene etc. The formation of ferrocene was a serendipity and independently by 2 different group of workers. In 1951, kealy and pauson condected an experiment for the synthesis of the fulvalene by reaction of ferric chloride with cyclopentadienyl Grignard reagent but accidently an unexpected product of orange coloured was formed instead of fulvalene. [1] That compound was stable and sublime in air without decomposition, later this compound was identified as ferrocene. on oxidation reaction of cyclopentadienyl Grignard reagent with ferric chloride, the fe^{3+} ion reduced to fe^{2+} ion and this ferrous ion react with the cyclopentadiene compound to form ferrocene.

$$Fe^{2+} + C_5H_5MgX \longrightarrow Fe(C_5H_5)_2 + 2Mg + 2X^-$$

Ferrocene was independently developed by direct reaction between reduced iron and cyclopentadiene at 575k temperature. Here the amines like bases were used which facilitate the reaction by removal of acidic hydrogen of cyclopentadiene so that ferrocene were obtained at comparatively lower temperatures. [2,3]

$$Fe + 2C_5H_6 \longrightarrow Fe(C_5H_5)_2 + H_2$$

PROPERTIES AND STRUCTURE OF FERROCENE

Since the 1960s, ferrocene compounds have been the subject of bioorganometallic chemistry research, which has recently received much greater attention. First reported by Kealy and Pauson in 1951. The structure contains an iron atom with two single bonds connected to two carbon atoms on cyclopentadiene rings. Ferrocene is an organometallic substance with the chemical formula $Fe(C_5H_5)_2$. The anti-cancer, anti-bacterial, anti-fungal, and antiparasitic properties of ferrocene derivatives have garnered considerable interest. Apart from medicinal action ferrocene and its derivatives have various other uses like catalyst in industry, in organic synthesis, ligand scaffold, fuel additives, solid rocket propellant etc.[1,2]

Ferrocene is a complex organometallic compound and it have 2 cyclopentadienyl rings bounded to the central iron atom which is equally bound to all 10 carbon atoms. It is orange solid with camphor like order which sublimes at 373 k. It is also described as iron (II)bis(cyclopentadiene) which is soluble in organic solvents like benzene, ether, alcohol etc and insoluble in water. Having a melting point of 172.5 °C and a boils at 249 °C. It is not affected by air, water, strong bases, and can heated to 400 °C without decomposition. [4]

Iron centre in ferrocene have a +2-oxidation state and the cyclopentadienyl ring have one single negative charge. Thus, the molecular formula is $Fe_2^+(C_5H_5)_2^-$. The Π electrons in the ring were shared with the metal by covalent bonding making the sandwich model of ferrocene. In ferrocene Fe is considered as zero valent and the cyclopentadiene as five electron donor and if Fe is bivalent then $C_5H_5^-$ anion is cyclopentadiene. Is diamagnetic in nature and has no unpaired electrons and thermally stable up to 775k in absence of air.

Molecule is symmetrical with zero dipole moment. The cyclopentadienyl ring is aromatic in nature so that it undergoes most of the reaction shown by the benzene. Ferrocene undergoes electrophilic substitution reactions like acylation, alkylation, sulphonation and metalation etc. ferrocene is high resistive to hydrogenation reaction than benzene because of the coordination of Π electron density of the ring to the metal ion but the electrons are readily available for electrophilic reactions than benzene.[2]

Due to lack of experimental techniques the structure of ferrocene was controversial at olden days, later the structure was confirmed by X ray crystallographic and various spectroscopic techniques like NMR and IR. The structure was explained as a single sigma bonded one like C_5H_5-Fe-C_5H_5, but this structure couldn't explain the properties of ferrocene. In 1956, the structure was confirmed by the X ray Crystallographic study as a sandwich structure in which iron atom placed between 2 planar rings of cyclopentadiene. Initially studied that the 2 cyclopentadienyl rings were in pentagonal antiprismatic arrangement that is in staggered configuration with D_{5d} symmetry. In gaseous phase the electron diffraction has an eclipsed configuration with D_{5h} symmetry. The studies confirmed that in the solid phase ferrocene has a staggered configuration and in gaseous phase it has eclipsed configuration. The Fe in ferrocene have an equidistance from all the carbon atoms of cyclopentadiene. The carbon-carbon bond length in the cyclopentadiene is 0.1389 nm and the Fe-C bond length is 0.204 nm. The length between the 2 rings is 2.35 nm and many theories were put forward for studying the nature of bond between Fe and 2 cyclopentadiene rings. The valance bond theory is used for explain the bond nature and it predicts the involvement of the metal orbital to bonding with the cyclopentadienyl ring. Fisher and fritz consider the ferrocene is similar to the low spin octahedral complex. Iron in the complex is in Fe^{2+} state and the cyclopentadiene as $(C5H5)^-$ and each C_5H_5 supposed to bring 3 electron pairs for bonding so that Fe2+ have 3d6 outer electronic configuration that is, 6 electron pairs for bonding.

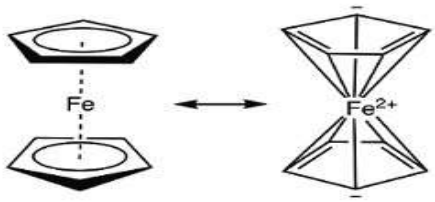


Fig:1 Structure of Ferrocene

The stability of the ferrocenyl group in aqueous and aerobic media, the accessibility of a large number of derivatives, and with its favourable electrochemical properties make ferrocene and its derivatives very famous molecules for biological applications and for conjugation with biomolecules.[3,5,6]

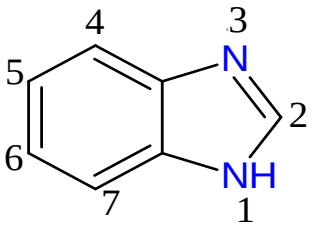
Incorporation of a ferrocene fragment into an organic compound often produces biological activity. Ferrocenic analogues of chloroquine, mefloquine and quinine, synthesized by various researchers, have manifested enhanced antimalarial activities. Replacing the aromatic ring of the well-known anticancer drug tamoxifen with ferrocene (called ferrocifen) produced a compound that exhibited a strong effect against breast cancer cells that were resistant to tamoxifen. Similarly, the antibiotic activity of penicillin and cephalosporin was enhanced many times upon the introduction of ferrocene moiety in these drugs.[7]

AN OVERVIEW OF BENZIMIDAZOLE

Benzimidazole was emerged as a probable nucleus in 1944, from a report it is suggested that it can act like purines due to the structural homology and can exhibit some biological responses. Benzimidazole is an aromatic heterocyclic organic compound having wide medicinal activities. Bicyclic compound by fusing rings of an

aromatic compound benzene with imidazole. It has a colourless nature having melting point 170 to 172 °C. It has a molecular weight of 118.14.[8] Its IUPAC name is 1H-benzimidazole and molecular formula of $C_7H_6N_2$. This moiety shows promising pharmacological properties extensively explored with a potent inhibitor of various enzymes involved in a wide range of therapeutic uses which are antidiabetic, anticancer, antimicrobial, antiparasitic, analgesics, antiviral, and antihistamine etc.[9] They possess excellent properties, like increased stability, bioavailability, and significant biological activity. From 1990 onwards large number of benzimidazole analogues were synthesised and reported, with an increased stability, bioavailability, and significant biological activity and there are a lot of benzimidazole derivatives having a potential activity which have great activity drugs with benzimidazole ring like omeprazole, bendamustine, albendazole, and mebendazole. Most come method of synthesis of benzimidazole were done by reacting orthophenylene diamine with an aldehyde. [10]

Heterocyclic organic compound benzimidazole derivatives which displayed the potent biological properties in medicinal chemistry. A wide range of heterocyclic compounds were synthesised with the building block benzimidazole. Benzimidazole moiety has a structural characteristic feature having a combination of benzene with the 4th and 5th position of imidazole ring system. They possess both acidic and basic actions. The amino group in the benzimidazole is highly acidic and which also possess some basic nature. It has the ability to form salt. The benzimidazole moiety have a wide range of use in the development of new medicinal compounds in pharmaceutical field. A key role for different natural activities were shown by the vital benzimidazole pharmacophore sub structure. When changing various groups in the core structure benzimidazole-based drugs shows a wide range of various pharmacological activities. In several natural products like histidine, purines, and vitamin B12, benzimidazole is the one common scaffold found. The hetero-aromatic bicyclic ring act as a pharmacophore for various therapeutic interest with the broad spectrum of action. Antimicrobial, antiviral, anticancer, anti-inflammatory, analgesic properties were shown by the benzimidazole derivatives. [11,12]



1*H*-benzimidazole

Fig 2: structure of benzimidazole

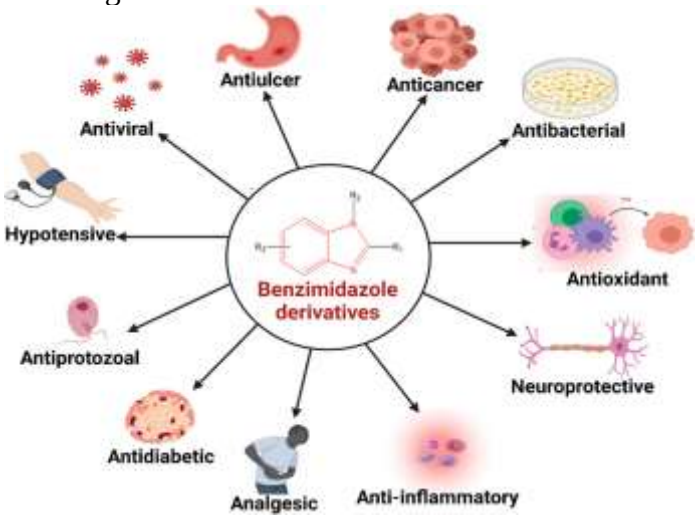


Fig 3: Activities of Benzimidazole

Substitutions in the 2nd and 3rd position increases the medicinal activities and also the substitution of alkyl groups or bulky groups in the benzene ring of benzimidazole also increases the pharmacological actions. The members of this group of molecules are well-known building blocks for biopolymers, such as adenine and guanine, two of the five nucleic acid bases, uric acid, and caffeine etc. In modern drug discovery benzimidazole nucleus containing pharmacophore were extensively applied in the biological and clinical studies. The biological profiles of the benzimidazole derivatives possess a fruitful matrix for further development of better medicinal agents.[13]

FERROCENYL BENZIMIDAZOLE SCAFFOLD

A series of ferrocene benzimidazole derivatives have attracted lots of attention for the construction of new compounds due to their wide applications. By combining ferrocene and benzimidazole produce a wide range of pharmacological actions.[6]

2-ferrocenyl benzimidazole is a complex organic compound having ferrocene an organometallic compound attached to the 2-position of benzimidazole an aromatic heterocyclic compound. Which have a molecular formula of $C_{17}H_{16}FeN_2$ with a molecular weight of 304.17g/mol. The cyclopenta-1,3-diene-1,3-dien-1-yl-1h benzimidazole, iron with 1 hydrogen bond donor and one hydrogen bond acceptor has developed for studies involved in drug discovery. There is one rotatable bond with an extra mass of 304.066284. the topological polar surface area is 24. 1 A°2 having a heavy atom count of 20. Its complexity is 248.

Several strategies were employed in the development of harmacologically active ferrocene containing organometallic compound. Ferrocene derivatives achieved high hit rates against biological targets. Ferrocene consist of its bulky 'barrel shaped' structure which impart a 3D geometry of organometallic compound relative to its flat aryl bioisosteric form. This confers an ideal spatial configuration for better fitting and interaction within the pockets of the sites of biological targets and receptors.

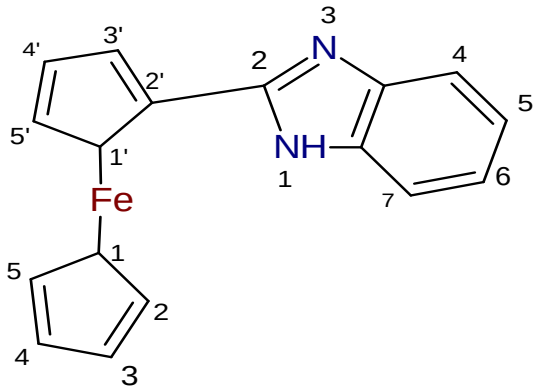


Fig 4: 2-ferrocenyl-dihydro-1h-benzimidazole

The modification of 2nd and 5th position of the benzimidazole yield a variety of biologically active compounds. Chloro, bromo, and fluro substitution exhibit most potent activity. presence of nitro group in the 5th position of organometallic-benzimidazole increases the anti-malarial activity.

Synthetic method of 2-ferrocenyl benzimidazole: To a solution of 1,2-diamino compound (2.37 mmol) in nitrobenzene (5ml) was added to the corresponding ferrocene carboxaldehyde (2.37 mmol) or ferrocene dicarboxaldehyde (1.19mmol) and the acetic acid was introduced and the mixture was stirred at 60°c for 15 hrs. An orange solid was obtained and the resulting solid was filtered, washed with diethyl ether (10ml), chromatographed on a silica gel column using (CH_2CL_2/MeOH) in the ratio 9:1 as eluent, and finally crystallized from acetonitrile to give as crystalline solid.

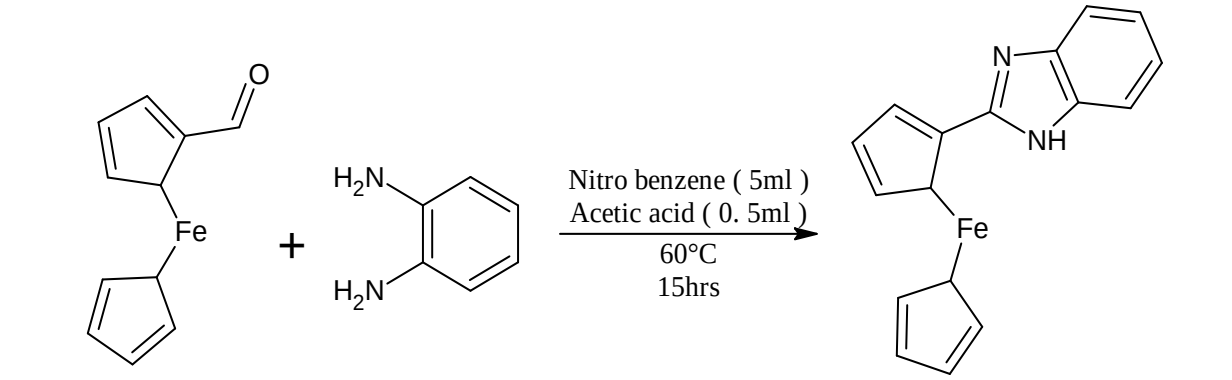


Fig 5: Scheme 1: synthesis of 2-ferrocenyl benzimidazole

Ferrocenium ion produced from ferrocene through one electron reversible oxidation. Substitutes on ferrocene moiety influence the redox behaviour by changing the energy level of highest occupied molecular orbital so that the reversibility may be significantly lowered. Its lipophilicity, low cytotoxicity of ferrocene in biological systems and the pi-conjugated system and the resulting exclusion electron-transfer ability make its derivatives good candidates for the investigation of their biological applications. Those compounds show good antibacterial, antitumor and antifungal activities, the NO2 substitution at the C-7 position increases the activities. The development of mono and multi complexes containing the ferrocene chemotype. Organometallic demonstrated to form favourable binding interactions with protein receptors. Insilico docking simulations of multinuclear ferrocenyl compounds show enhanced binding affinity with potential protein targets for anticancer activity.[14,15] Conjugation of the ferrocene moiety with the benzimidazole motif yields mono and trinuclear based organometallic compounds. The docking interaction of 2- ferrocenyl benzimidazole metallofragments with established oncological protein targets by using computer aided molecular docking. the preliminary cytotoxic evaluation of these compounds in two breast cancer cell line.

PHARMACOLOGICAL ACTIVITIES OF 2- FERROCENYL BENZIMIDAZOLE

ANTIFUNGAL ACTIVITIES

Screening against the Mycobacterium TB H37Rv strain revealed that the hybrid had increased lipophilicity. Fungal infections are steadily increasing in patients with hematologic malignancies undergoing chemotherapy, immunocompromised patients undergoing organ transplantation, and patients with acquired immunodeficiency. There are various infections caused by Candida, Aspergillus, Cryptococcus, etc. Among them, most die of malignant disease, infected with Candida, and one third with Aspergillus. His two newly discovered ferrocinyl-5-fluoro-6-(4-substituted-1-piperazinyl) benzimidazoles have significant antimitotic effects. This compound was synthesized by reacting ferrocene carboxaldehyde with $phNO_2/C_2H_5OH$ at 200 °C for 4 min to generate various derivatives.

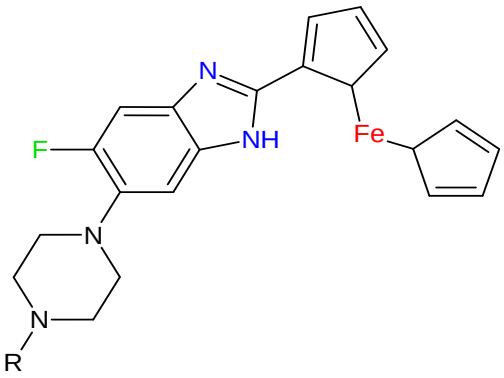


Fig 6: Derivatives of 2-ferrocenyl-5-fluoro-6-(4-substituted-1-pipera-zinyl) benzimidazoles

R: 2a-Me, 2b-phenyl, 2c-p. chlorophenyl, 2d-p. methoxyphenyl, 2e-fluorophenyl.

A series of compounds established and bioassays of those established compounds were performed. Those derivatives show potent antimicrobial activity were selected and subjected to in-depth analysis to find their mode of inhibition on growth concentration. [16]

The minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC) for a number of newly developed derivatives of 2-ferrocenyl-5-fluoro-6-(4-substituted-1-pipera-zinyl) benzimidazoles were determined using a broth macrodilution method study for medically important Candida sp. The study demonstrate that compounds 4-fluoro-5-(4-methyl-1-piperazinyl)-2-nitroaniline, 4-Fluoro-5-(4-phenyl-1-piperazinyl)-2-nitroaniline, 2-ferrocenyl-5-fluoro-6-(4-methyl-1-piperazinyl) benzimidazole, 2-ferrocenyl-5-fluoro-6-(4-phenyl-1-piperazinyl) benzimidazole and 2-ferrocenyl-5-fluoro-6-[4-(4-fluorophenyl)-1-piperazinyl] benzimidazole were found to have potent in vitro antifungal activity with MICs at which 80% of the strains were inhibited (MIC80s) of 15-125 μg mL-1. The active compounds were further screened for establish their mode of action on the basis of inhibitory effects on growth, budding, germ-tube formation and leakage of cytoplasmic content release after treatment. [17]

Compared to control agents such as nystatin, miconazole nitrate, and ketoconazole. Some of 4-fluoro-5-(4-substituted-1-piperazinyl)-2-nitroanilines and 2-ferrocenyl-5-fluoro-6-(4-substituted-1-piperazinyl)-[1H]-benzimidazoles derivatives were found to be more effective at low micromolar concentrations (15-500 μg ml-1). It is clear from the data presented here that further studies on the structure-activity relationship, mechanism of action and clinical potential in vivo efficacy of these compounds were determined.

ANTICANCER ACTIVITIES

A number of substituents in the 5th position of benzimidazole make multinuclear compounds which have potential interaction with protein targets. 2-ferrocenylbenzimidazole metallofragments, having varying substituents in the 5-position of a benzimidazole moiety was described. Those features include long-lived stability in non-oxidizing media, low toxicity, and reversible redox behaviour increases the activity.[18] The first recorded clinical approval of a ferrocene containing compound was ferrocerone, used to treat anaemia in the 1970s Using protein models insilico stimulations were performed for common cancer therapy targets to predict the binding affinity. For the design of new organometallic derivatives as potential biological agents, development of several mono and multimeric complexes with the ferrocene chemotype mono- and trimeric PGM-containing 2-aryl benzimidazoles were introduced and they shows promising antiplasmodial and anticancer activity. Molecular docking has not been extensively explored in the design of biologically active multinuclear organometallic complexes.[19] Organometallic ferrocene fragments have favourable binding interactions with protein receptors was experimentally demonstrated. Using computer-aided molecular docking simulations established oncological protein targets and the preliminary cytotoxic evaluation of these compounds in two breast cancer cell lines was performed. 2-ferrocenyl-1-propyl benzimidazole derivatives were developed and screened for cytotoxic effects against breast cancer cell lines which shows moderate activity. The conjugation of ferrocenyl moiety to the benzimidazole has a significant strategy in the development of organometallic compound for anticancer therapy. Mono and trimetric 2-ferrocenyl benzimidazole complexes were developed comparing both trinuclear complex shows higher affinity with superior binding energies than monomeric conjugates scaffolds that play major role in the pharmacological

functioning of essential molecules and are surprisingly effective with their restraint movement and favourable selectiveness.

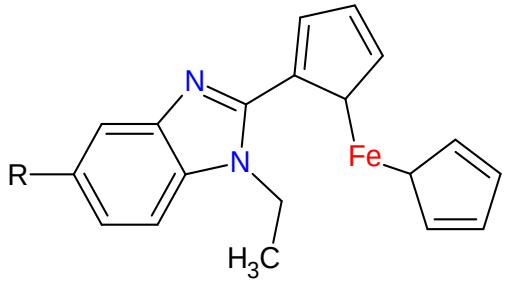


Fig 7: Mono metric 2-ferrocenyl benzimidazole derivatives
Fig 7: R: 3a-H, 3b-CH_3, 3c-CF_3

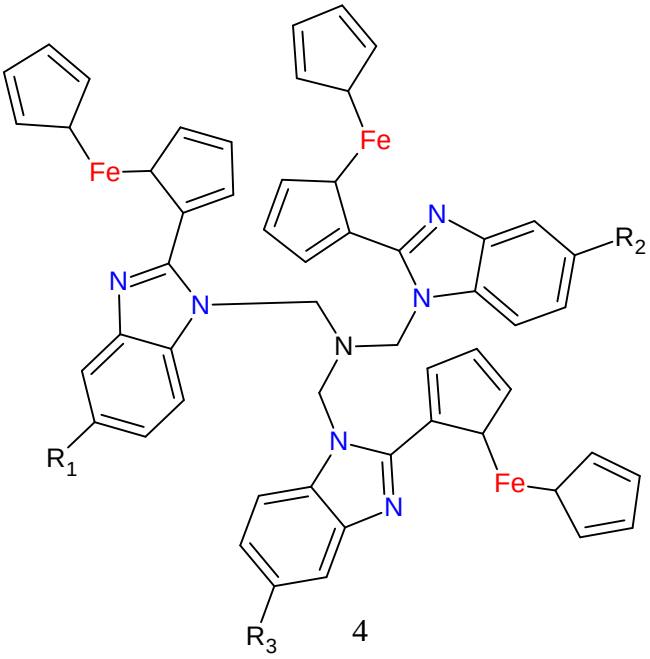


Fig 8: Trimetric 2-ferrocenyl benzimidazole derivatives
Fig 8: R: 4a, 4b, 4c

4a	R=H	R=H	R=H
4b	R=CH3	R=CH3	R=CH3
4c	R= CF3	R=CF3	R=CF3

For development of the mono- and trimeric 2-ferrocenylbenzimidazoles reagents used are ferrocene carboxaldehyde react with ethanol in presence of trifluoracetic acid for 24 hrs. By using the SRB method on the cancer cell line (HCT116), Tahlan et al. discovered a new set of benzimidazole benzamide compounds and established its anticancer efficacy (5-fuorouracil). Compounds produced derivatives demonstrated the significant antitumor activity. Mononuclear (3a, 3b, 3c) and trinuclear 2-ferrocenylbenzimidazoles (4a, 4b, 4c) with possible substituents in the 5^{th} position of the benzimidazole molecule were developed. The interactions of the synthesized complexes with proteins that are generally overexpressed in cancer cells relative to healthy tissues were evaluated using molecular docking studies, as these proteins may serve as potential cellular targets for the treatment of cancer. The results of these in silico studies, which need to be validated experimentally, lend strong support and reveal a general trend in which the trinuclear 2-ferrocenylbenzimidazole complexes (4a, 4b, 4c) bind to target proteins (HSP90, CDK1, PARP-1, EGFR and Cathepsin B) with significantly higher affinity relative to their corresponding mononuclear counterparts (3a, 3b, 3c). Notably, the trinuclear complexes (4a, 4b, 4c) were predicted to bind more favorably with HSP90, CDK1, Cathepsin B and EGFR, relative to reference ligands from the literature with an established affinity for these proteins.

When the predicted binding energies of the phenyl analogues of complexes 3a and 4a were compared, the 2-ferrocenyl bioisosteres were noted to have superior predicted binding to the EGFR. This again was attributed to the ferrocene moieties in complexes 3a and 4a imparting a geometry that is better suited to fit into the receptor site of the EGFR. Moreover, the ferrocenyl

moieties of 3a and 4a provide multiple points of contact for forming interactions that stabilize the simulated protein-compound adduct. Preliminary evaluation for the cytotoxic activity of the derived compounds at 10 μM revealed that the mononuclear 2- ferrocenylbenzimidazoles (3a, 3b, 3c) to have less activity in the MCF-7 breast cancer cell line, with 3c possess the most active and reducing cell survival by 21%. There was no significant effect on MCF-7 breast cancer cell survival upon increasing the concentration of 3a, 3b, 3c to 20 μM. The trinuclear 2-ferrocenylbenzimidazole compounds (4a, 4b, 4c) were evaluated against the MCF-7 breast cancer cell line, none of the tested trimeric compounds were noted to have any significant activity in the aforementioned cell line. This was attributed to the observed precipitation of 4a, 4b, 4c out of the growth media over time, prompting further investigations to improve solubility. The in-silico studies conducted was reveal that the introduction of the ferrocene substituent in the benzimidazole scaffold plays a key role and has important repercussions for multinuclear complexes as bioactive drug leads. Additionally, the preliminary cytotoxic evaluation suggests that a series of compounds may present a promising class of compounds in the treatment of cancer.[20,21,22, 23]

ANTIMALARIAL ACTIVITIES

A series of ferrocenyl benzimidazole conjugates were synthesized and estimated the antimalarial properties in plasmodium falciparum. ferrocene and cyrhetrene bioconjugates were compared for the antimalarial activity and the benzimidazole conjugated with cyrhetrene gives most potent activities than the ferrocenyl conjugates.[24]

Hybrid compounds of bioisosteric ferrocenyl-aminoquinoline-benzimidazole were synthesised and evaluated for their antiplasmodial activity against the strains chloroquine-sensitive NF54 and multi-drug resistant K1 of the human malaria parasite, Plasmodium falciparum. These ferrocenyl benzimidazole derivatives were shows activity against the two strains, and have enhanced activity in the K1 strain having resistance indices less than 1. Chinese hamster ovarian cells from Chinese hamster were used for cytotoxic studies and shows that the hybrids are non-cytotoxic and produces selective killing of that parasite.[25] Data from In vitro antiplasmodial and cytotoxicity activity were developed and, the most potent phenyl and ferrocenyl hybrids are evaluated in vivo against the mouse model with Plasmodium berghei. With displaying superior activity two compounds caused a reduction in parasitaemia when related to the control. The inhibition of b-haematin formation in a NP-40 detergent-mediated assay which is shown by best active phenyl and ferrocenyl derivatives, that indicate a proper mechanism of antiplasmodial activity.

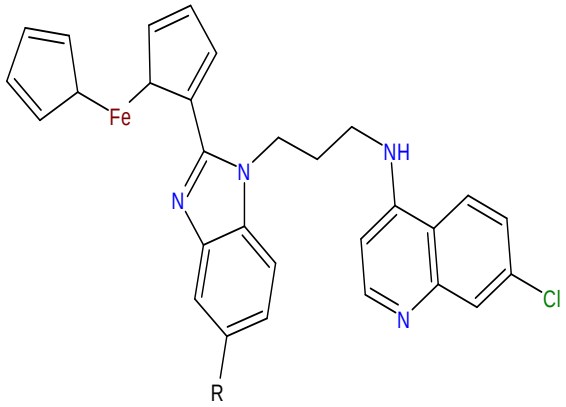


Fig 9: Ferrocenyl-aminoquinoline-benzimidazole derivatives
R :5a = H, 5b = CH_3, 5c = CF_3, 5d = CN, 5e = SO_2CH_3

Among these substitutions the compound 5c have a significant superior activity. This study displaying good in vitro activity against malaria.[26] These derivatives when opposed to the sensitive strain, the resistant strain exhibits greater activity, with resistance indices often less than 1. The non-tumorigenic Chinese hamster ovary (CHO) cell line demonstrated that all hybrids were non-toxic, and selectivity indices suggested that the hybrids were selective for the Plasmodium parasite. A reduction in parasitemia was observed after

treatment with each substance, with the ferrocenyl counterpart 5b showing higher action. Regarding a potential mode of action, a few derivatives inhibited the production of synthetic hemozoin, suggesting that the haemoglobin breakdown pathway may be a potential target for this family of hybrids. Early studies showed that there were few reactive oxygen species (ROS) generated by 5b generated from ferrocenyl. This indicates that it is not ROS-induced parasite damage that likely contributes to the mechanism of action of the ferrocenyl hybrids. Screening against the Mycobacterium TB H37Rv strain showed that hybrids with increased lipophilicity exhibited improved activity. Furthermore, inclusion of the ferrocenyl moiety improved activity compared to the phenyl analogue. These hybrids show promise as potential antibacterial agents.

ANTIMICROBIAL ACTIVITY

Synthesis of Schiff bases along with 2-(ferrocen-1-yl-methyliden) amino-4-methylphenol (HSB1) and 2-(ferrocen-1-yl-methyliden) amino-4-chloro-5-nitrophenol (HSB2), and their derivatives containing the ferrocene organization with $CoCl_2$) and their complexes with $CoCl_2$ have been synthesized and characterized. Various derivatives benzimidazole derivatives combines with the ferrocene organization 2-[(ferrocen1-yl)-5-x-6-y-1H-benzimidazole (BZ1, BZ2 and BZ3). In addition, antimicrobial sports of the compounds have been examined towards six microorganism and 3 fungi. It changed into discovered that the compounds have a huge variety of antimicrobial sports at the take a look at microorganisms.[27] It changed into located that the non-chelate complexes are extra powerful than the alternative complexes and ligands. The maximum antifungal interest changed into exhibited via way of means of the Co(II) complicated of BZ2 towards C. parapsilosis with a MIC cost of 19.5 µg/mL. BZ1 changed into acquired via way of means of response of ferrocene carboxaldehyde (1.07 g, 5 mmol) with an equal quantity of NaHSO3 (0.52 g, 10 mmol) at room temperature in an ethanol/water aggregate (20 mL / 5mL) for ~3 h. The aggregate changed into handled with 4-methyl-1,2-phenylenediamine (0.61g, 5 mmol) in dimethylformamide (15 mL) and refluxed for 3 h. Then, the response aggregate changed into delivered over 500 mL of water and a precipitate changed into fashioned rapidly after. The precipitate changed into filtered, dried and crystallized from methanol. BZ2 changed into synthesized in a comparable way as BZ1 the usage of 4,5-dimethyl-1,2-benzenediamine (0.68g, 5 mmol). BZ3 changed into synthesized in a comparable way as BZ1 the usage of 4-chloro-5-nitro-1,2-benzenediamine (0.95g, 5mmol).[28]

The antimicrobial activity of the ligands and complexes are in comparison with antibiotic and antifungal properties. The broadest action is proven via way of means of HSB2, while the narrowest activity belongs to BZ2. The maximum activity is exhibited through the Co (II) complex of BZ2 with a MIC value of 19.5 µg/mL towards C. parapsilosis. This complex is also greater active towards the other fungi when in comparison with the alternative compounds. Another crucial end result is that generally, all complexes display excessive activity towards C. parapsilosis according to the ligands. Moreover, all investigated compounds look like lively towards C. tropicalis, and all of them except $[Co(BZ2)Cl_2(H_2O)_2]\cdot 4H_2O$ shows a alternatively vast activity towards S. epidermidis, even though low. Also, all investigated compounds aside from the complexes of BZ2 and BZ3 are powerful towards S. aureus, whether or not reasonably or low. A broad spectrum of activity towards the gram-positive microorganism S. epidermidis and S. aureus was in popular observed via way of means of the investigated compounds.[29]

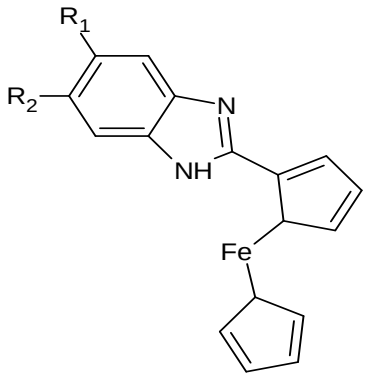


Fig 10: 2- [(ferrocenl-yl)-5-x-6-y-1H- benzimidazole

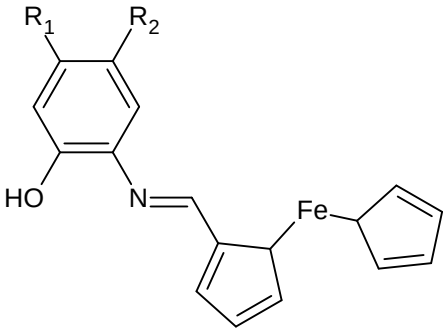


Fig 11: 2- [(ferrocene-1-yl- methylidene) amino-4 methylphenol]

BZ1: R1= CH3, R2=H2
BZ2: R1=R2= CH3
BZ3: R1= NO2, R2 = Cl

HSB1: R1= H, R2= CH3
HSB2: R1= NO2, R2= Cl

It also can be observed that the Co(II) complexes have better interest towards fungi than the ligands. For instance, the MIC value of the Co(II) complex of HSB2 towards S. aureus is 312 µg/mL at the same time as that of HSB2 is 1250 µg/mL. The Co(II) complex of HSB2 indicates activity with a MIC value of 312 µg/mL towards C. albicans, while the ligand itself is inactive. This complex is powerful towards C. parapsilosis with a MIC value of 312 µg/mL; however, the ligand (HSB2) indicates decrease activity than the complex (625 µg/mL). It is interesting that the complexes besides that of HSB2 display antibacterial activity towards P. mirabilis with the equal value (625 µg/mL). Additionally, at the same time as the complexes of BZ1, BZ2 and BZ3 had been discovered to show antimicrobial activity, mainly towards P. mirabilis, C. albicans and C. parapsilosis, the ligands themselves had been now no longer active at all. This behavior may be defined through the non-chelate structure of the complexes. The metal ion of the complexes that do not have a chelate structure binds to the proteins of the bacteria more easily and prevents their activities, as a result increasing the antimicrobial effect. Antimicrobial sports of the compounds had been examined towards six bacteria and 3 fungi. It turned into determined that the ligands and the complexes have a wide range of antimicrobial activity. The Co(II) complex of BZ2 indicates the highest activity towards C. parapsilosis with a MIC cost of 19. µg/mL. It was determined that the complexes with nonchelated structure are greater effective than the alternative complexes and ligands.[27,28,29]

Rhodium(I) Complexes of Ferrocenylbenzimidazol-2-ylidene Ligands Showed Better Performance for the Desired Products Compared to Monodentate NHC Ligands, Bidentate NHC Ligands with a Phosphonyl Group Guarantees significantly higher selectivity. The rhodium complex becomes more soluble in the reaction medium upon the addition of a methyl substituent to the benzene ring of the benzimidazol-2-ylidene ligand. Although the ligands used in this work were achiral, we plan to prepare planar chiral 1,2-disubstituted ferrocenyl ligands using techniques established here for use in asymmetric hydrosilylation.[6,29] The chemistry of benzimidazoles has been extensively studied for important biological effects, including antihypertensive effects. We synthesize and characterize m-acetate-bridged dinuclear Cu(II) complexes with hydrazide ligands containing both benzimidazole and ferrocene moieties. Ferrocenyl-substituted heterocyclic hydrazide ligands and their Cu(II) complexes were characterized by IR, UV, NMR, TG, elemental analysis, and mass spectrometry (MS). The compound exhibits a reversible redox couple that can be

assigned to an Fcþ/Fc couple. Copper(II) complexes act as effective catalysts for the oxidation of 3,5-di-tert-butylcatechol to the corresponding quinone derivatives in O2-saturated DMF. The biological importance of copper, the synthesis of polymetallic copper complexes of benzimidazoles, provides an important avenue for the development of novel models of metalloenzymes.[30]

CONCLUSION

The anticancer, antimalarial, antifungal, and antiparasitic properties of ferrocene derivatives have attracted considerable interest.[18] Metallocenes were investigated with a broad activity spectrum of ferrocene complexes. Benzimidazole, a heterocyclic aromatic organic compound, has been identified as a core that may show broad efficacy. Ferrocenyl benzimidazole is a complex organic compound in which ferrocene, an organometallic compound, is attached to the 2-position of benzimidazole, an aromatic heterocyclic compound.[3] Ferrocene benzimidazole derivatives have attracted much attention for the design of new compounds. The 2-ferrocenyl benzimidazole with a significant pharmacological action was established. The various studies like antifungal, anti-malarial, anticytotoxic effects were reported and this complex have a wide range of interest in the medicinal chemistry. Increased stability, bioavailability of the benzimidazole produces a potent pharmacological effect when combines with the ferrocene moiety. In ferrocene scaffold due to the presence of the iron and the cyclopentadienyl structure make the molecule more potent to the medicinal action. 2-ferrocenylbenzimidazole metallofragments, with varying substituents in the 5-position of a benzimidazole scaffold were described.[14] These features include long-term stability in non-oxidizing media, low toxicity, and reversible redox behavior that enhances activity. Two derived ferrocinyl-5-fluoro-6-(4-substituted-1-piperazinyl) benzimidazoles have significant antimitotic effects. We selected those derivatives that showed potent antibacterial activity and underwent exhaustive analysis to determine their inhibition of growth concentrations of Candida species. When we compared the antimalarial activity of bioconjugates of ferrocene and cyletrene, benzimidazole conjugated with cyletrene showed stronger activity than ferrocenyl conjugate. Ferrocenyl derivatives showed inhibition of b-hematin formation in an NP-40 detergent-mediated assay, indicating a possible contributing mechanism for antiplasmodium activity. Ferrocenylbenzimidazole derivatives were active against the two strains and showed enhanced activity in the K1 strain. Based on favorable in vitro antiplasmodium and cytotoxicity data, the most active phenyl and ferrocenyl hybrids were tested in vivo against the rodent mouse model Plasmodium berghei. Both compounds caused a reduction in parasitemia compared to controls while exhibiting excellent activity. Ferrocene fragments have been experimentally shown to form favorable binding interactions with oncoprotein receptors. A 2-ferrocenyl-1-propylbenzimidazole derivative was developed and screened for cytotoxic effects against moderately active breast cancer cell lines. Monomeric and trimeric 2-ferrocenyl-benzimidazole complexes have been developed. Both trinuclear complexes exhibit higher affinity with superior binding energies than monomeric conjugate scaffolds that play a central role in the biological function of essential molecules. Conjugation of ferrocene moieties to benzimidazoles has a valuable strategy in the development of organometallic compounds for anticancer therapy. In preliminary cytotoxicity evaluations, the panel of compounds has revealed a promising class of compounds for the treatment of cancer. Information obtained from various studies conducted on the molecule ferrocenyl benzimidazole indicates important efficacy in the pharmaceutical field.[24,26]

Declaration by Authors

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List Of Abbreviations

Cp	Cyclopentadiene
NMR	Nuclear Magnetic Resonance
IR	Infra-Red
3D	Three Dimensional
MIC	Minimum Inhibitory Concentration
MFC	Minimum Fungicidal Concentration
TB	Tuberculosis
HSP90	Heat-Shock Protein 90
CDK1	Cyclin-Dependent Kinase 1
PARP-1	Poly-ADP-Ribose Polymerase
EGFR	Epidermal Growth Factor Receptor
ROS	Reactive Oxygen Species
CHO	Chinese Hamster Ovary
HSB1	2-(ferrocen-1-yl-methyliden) amino-4-methylphenol
HSB2	2-(ferrocen-1-yl-methyliden) amino-4-chloro-5-nitrophenol
BZ	2-[(ferrocen1-yl)-5-x-6-y-1H-benzimidazole

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