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Exploring the Versatility of Ferrocene and Its Derivatives: A Comprehensive Review

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Ferrocene is a remarkable organometallic compound with an iron ion sandwiched between two cyclopentadienyl rings. This unique molecular structure and diverse characteristics such as improved solubility, altered reactivity, and enhanced biological activity make them potential candidates for drug development and diverse applications including cancer therapy. Additionally, ferrocene-based compounds exhibit a lower tendency to induce severe side effects, making them a safer option for cancer treatment. They also have shown potential in overcoming resistance encountered by platinum compounds in treating certain types of cancer. The three primary metabolic pathways for ferrocene include oxidation, cyclization catalyzed by acid, and hydroxylation, forming quinone methide, cyclic indene, and allylic alcohol, respectively. Building on this foundation, researchers have delved deeper into synthesizing and assessing novel ferrocene derivatives to enhance their effectiveness in addressing cancer and other illnesses. This review comprehensively examines potential derivative reactions, highlighting the possibilities for tailoring these compounds to achieve specific therapeutic objectives.

Keywords: Cholesterol; Ferrocene; Ferrocene derivatives; Organometallics; Steroid.

Organometallics are the metallic complexes of organic compounds. Organometallics have a greater diversity of stereochemistry than organic compounds, ranging from linear to octahedral and even beyond (30 stereoisomers exist for an octahedral complex with six different ligands). Kinetic properties of the organometallics can be controlled using rational ligand design. Additionally, their metal atoms have a low oxidation state, without any charges, are kinetically stable, and are highly lipophilic. Organometallic compounds offer abundant opportunities for creating innovative categories of pharmaceutical compounds, potentially showcasing distinctive mechanisms of action specific to metals. This arises from their fundamental distinctions compared to traditional coordination metal complexes[1].

Organometallics employed for medical applications contain Fe, Ru, Co, Zr, Pt, Ti, V, Nb, and Mo. Among them, platinum compounds are most commonly employed. Despite enormous success, platinum compounds have two major side effects: they are ineffective against platinum-resistant tumors and have serious adverse effects,

such as nephrotoxicity. The latter drawback arises from the medication's focal point being DNA, a ubiquitous component in all cells. Furthermore, due to the particular chemical structure of platinum complexes, there are few opportunities for rational improvements that could increase its tumor specificity and lower undesirable side effects[2]. In contrast, ferrocene has fewer side effects and can be used to prevent platinum-resistant tumors. Historically, ferrocene's therapeutic potential has been studied because it was the first organometallic substance for which anti-proliferative effects were noted[2,3].

Ferrocene

Ferrocene (Figure 1) was first identified in 1951[4,5]. Later, Wilkinson and co-workers, and Goermen and co-workers determined its precise structure[6,7]. Woodward and co-workers named these novel iron compounds ferrocene because of their similarity with benzene[8]. Modern organometallic chemistry was founded as a result of the elucidation of the ferrocene molecule's structure, which was a significant discovery in the history of chemistry. Today, the words "sandwich compound" and "metallocene" describe a considerably wider variety of compounds containing various metals in addition to ferrocene and its derivatives[9]. Due to its intriguing chemistry, ferrocene immediately caught the interest of the scientific and technical world[9,10]. Without delay, chemists began to develop synthetic approaches that developed ferrocene derivatives and explored their uses in various scientific fields[11]. Ferrocene has several applications in materials science, including sensors[12-21], catalysts[19,22-27], electroactive materials[28-33], and aerospace materials[34-35], because of its advantageous electrical characteristics and ease of functionalization. Ferrocenes are well-liked molecules for biological applications due to their stability in aqueous and aerobic media and their variety of possible derivatives[35-42].

There are ongoing studies on the uses of ferrocenes in pharmaceutical applications. Numerous studies have demonstrated that some ferrocene derivatives are highly effective both in vitro and in vivo against a variety of diseases, including bacterial and fungal infections[43-44], malaria[40, 45-47], human immunodeficiency virus (HIV) infection[48], and cancer[36-42]. The anticancer efficacy of ferrocene compounds having amine or amide groups against lymphocytic leukemia P-388.48 led Brynes and coworkers[49] to report the anticancer potential of ferrocene derivatives in the late 1970s. Since then, different ferrocene compounds have been synthesized and their anticancer abilities were evaluated. Ge X and coworkers[50] studied ferrocene appended iridium (III) complexes for anticancer activity. Shen-Zhen Ren and coworkers synthesized and evaluated COX-2 inhibition activity of ferrocene-pyrazole derivatives[51]. Ferrocene-modified analogs such as ferrocene phenol hybrid[52], Imatinib and Nilitinib[53] have been studied for anticancer activity.

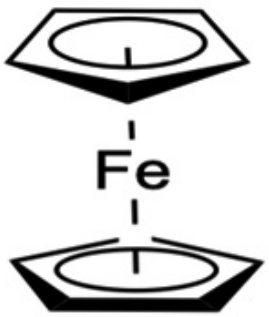
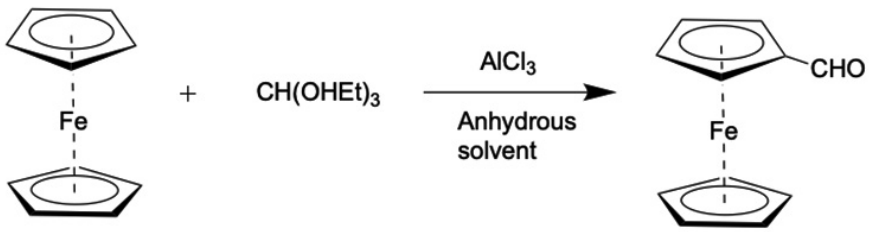
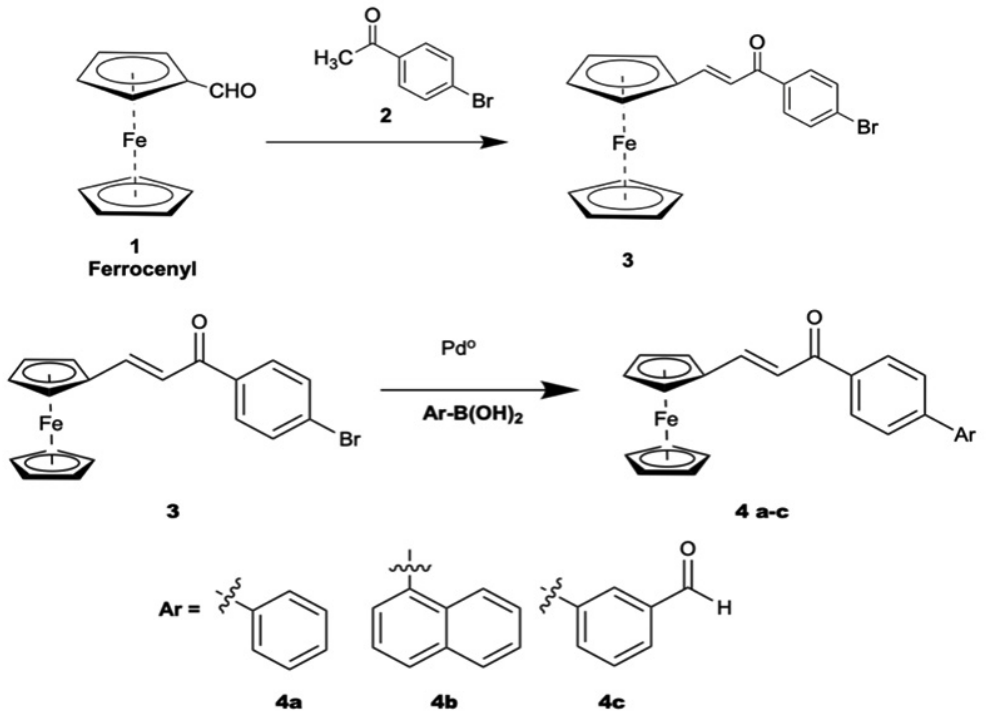


Fig. 1. Ferrocene

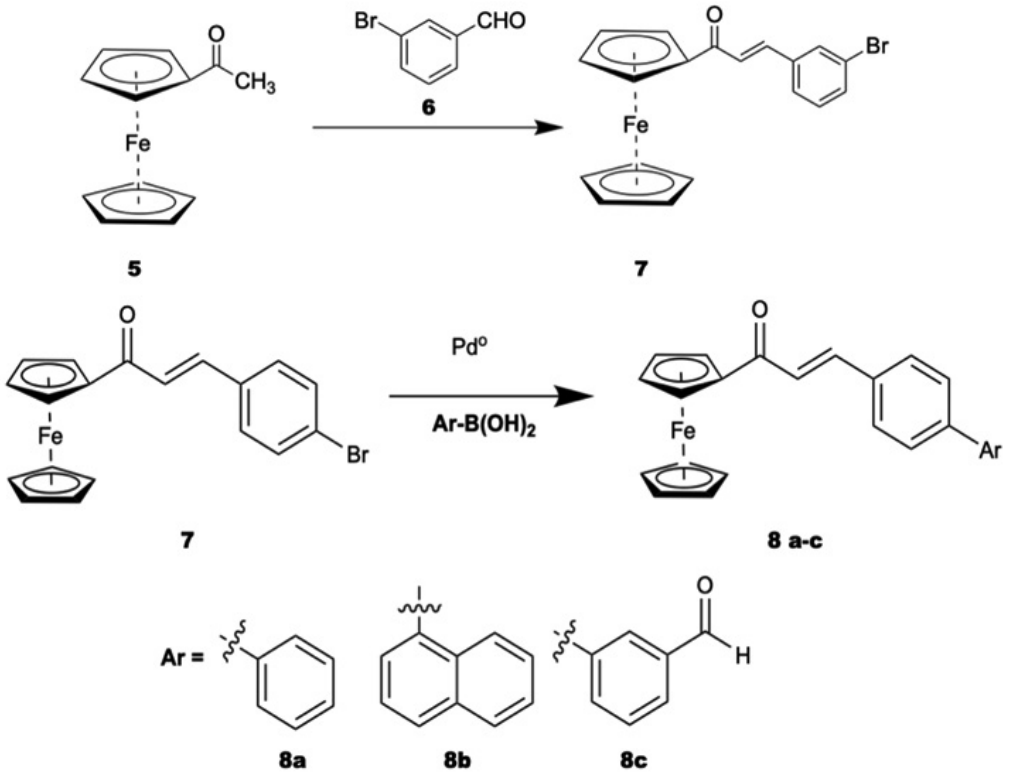


anhydrous solvent (anhydrous $AlCl_3$), followed by stirring to obtain the desired product.

Scheme 1. Synthesis of Formyl Ferrocene

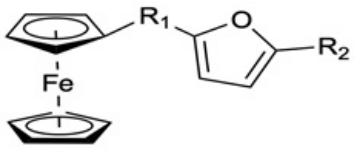


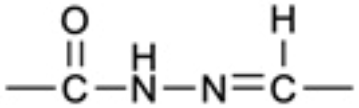
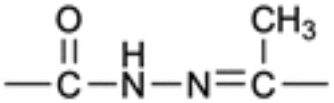
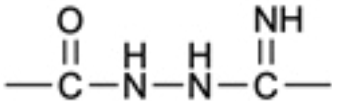
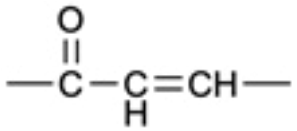
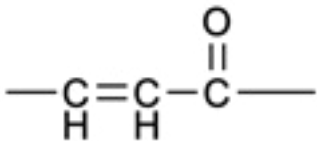
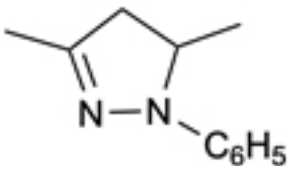
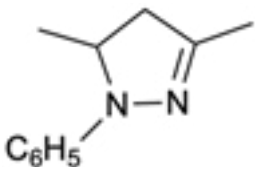
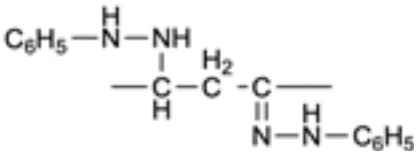
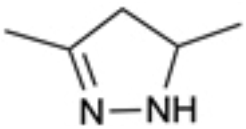
Scheme 2. Synthesis of Chalcone derivatives of Formyl Ferrocene

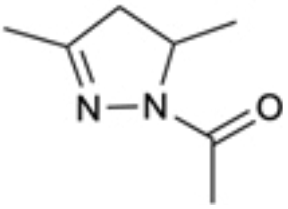
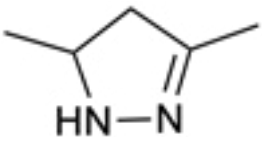


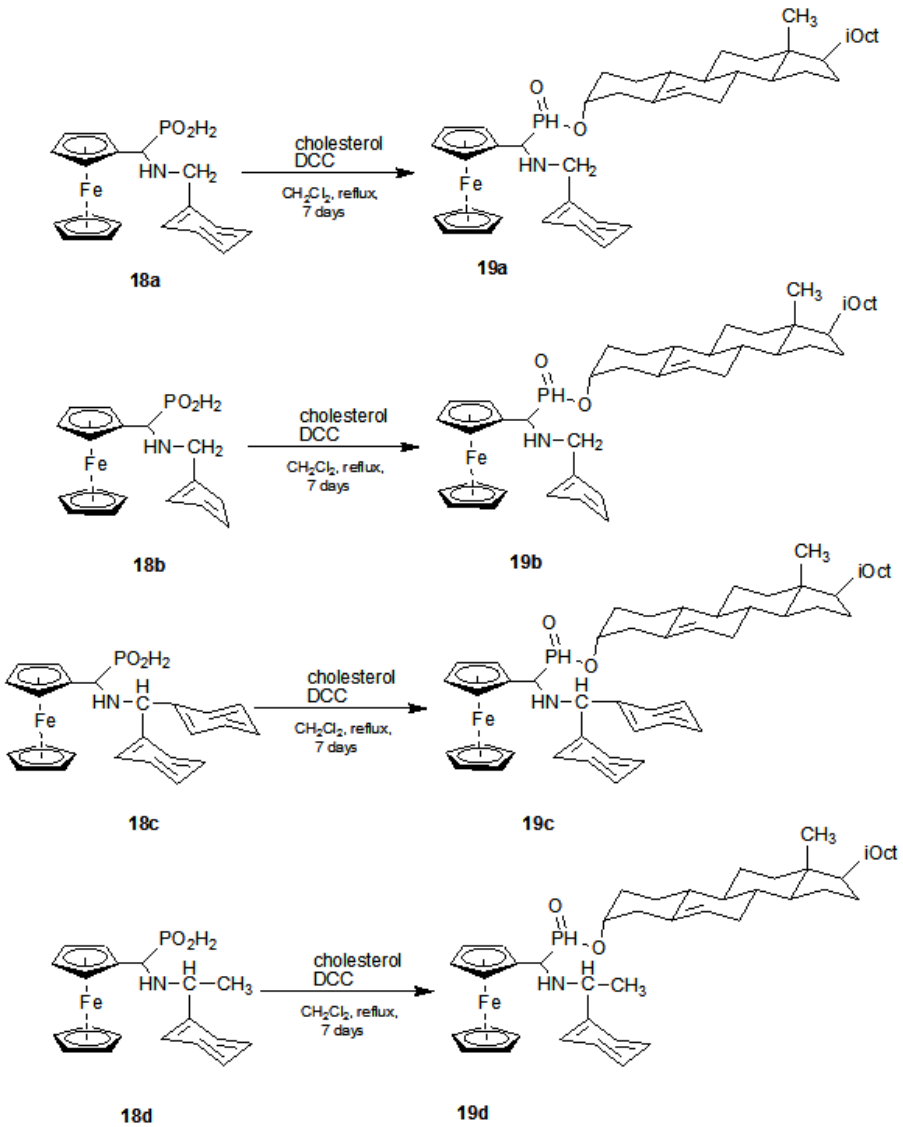
Scheme 3. Synthesis of Chalcone derivatives of Acetyl Ferrocene

Table 1. Reactants for furan derivatives of ferrocene

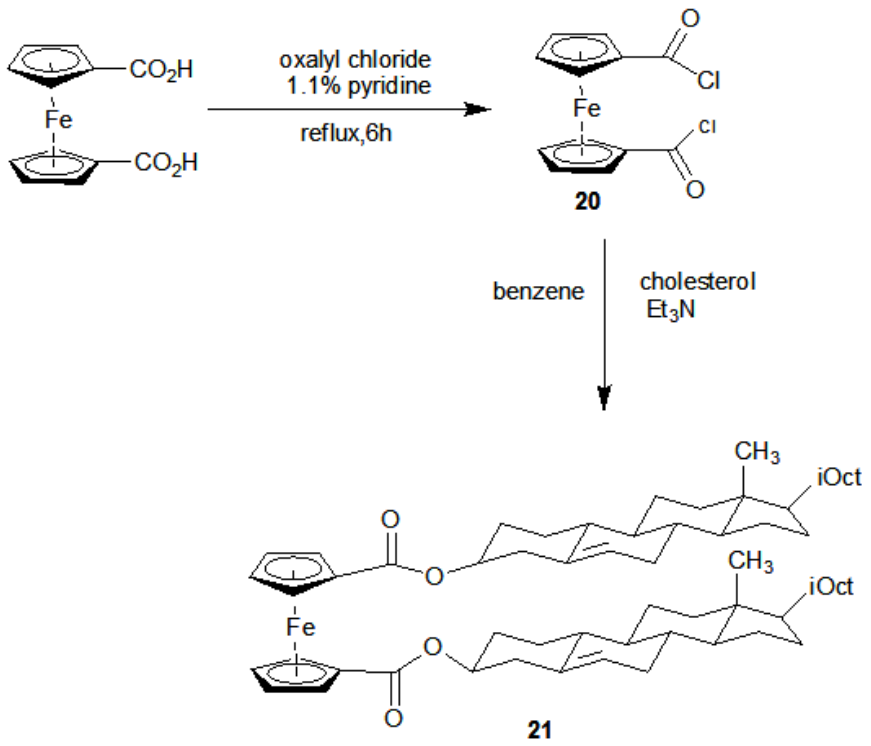


Reactants	R_1	R_2	Product
Ferrocene carboxy hydrazide, 5- Nitrofuranaldehyde		$-NO_2$	9a
Ferrocene carboxy hydrazide, 5- Nitro-2-acetylfuran		$-NO_2$	9b
Ferrocene carboxyhydrazide, 5- Nitro-2-furimidate		$-NO_2$	10
Acetyl ferrocene, furanaldehyde		$-H/-CH_3/-NO_2$	11a/11b/11c
Ferrocene carbaxaldehyde, 2-acetyl furan/2-acetyl-5-nitrofuran		$-H/-NO_2$	12a/12b
11a, phenylhydrazines		-H	13
12a/12b, phenylhydrazines		$-H/-NO_2$	14a/14b
Ferrocene carboxaldehyde, acetyl furan, hydrazine at RT		-H	15
11a, hydrazine		-H	16a

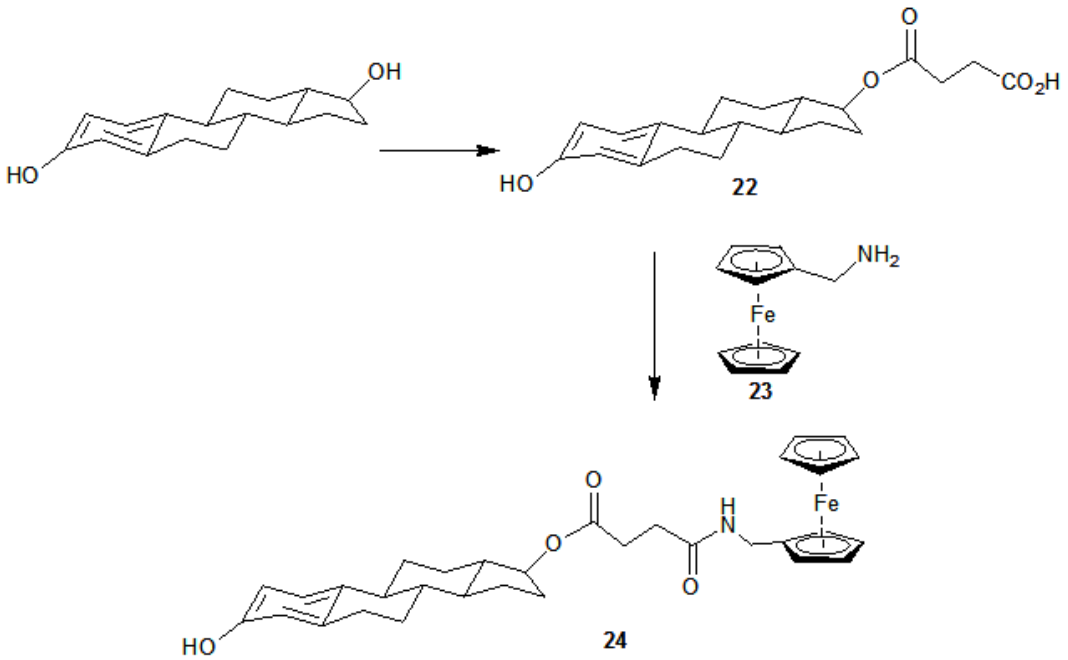
11a, acetylhydrazine		-H	16b
12a/12b, hydrazine		-H/-NO_2	17a /17b



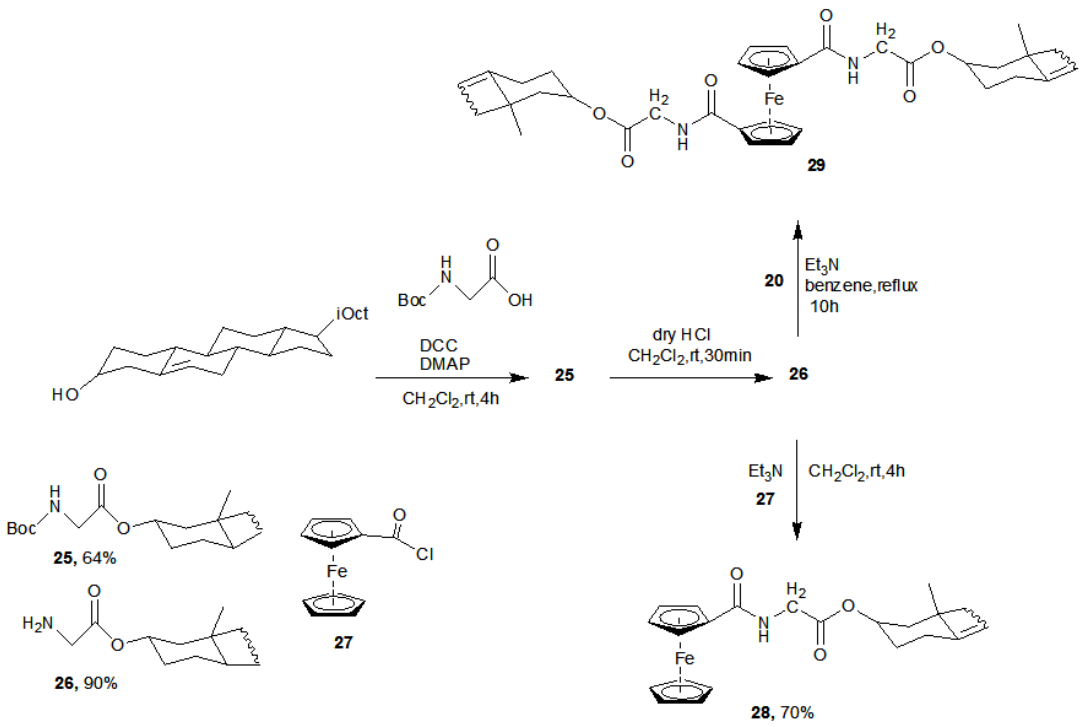
Scheme 4. Synthesis of Cholesterol derivatives of Ferrocene



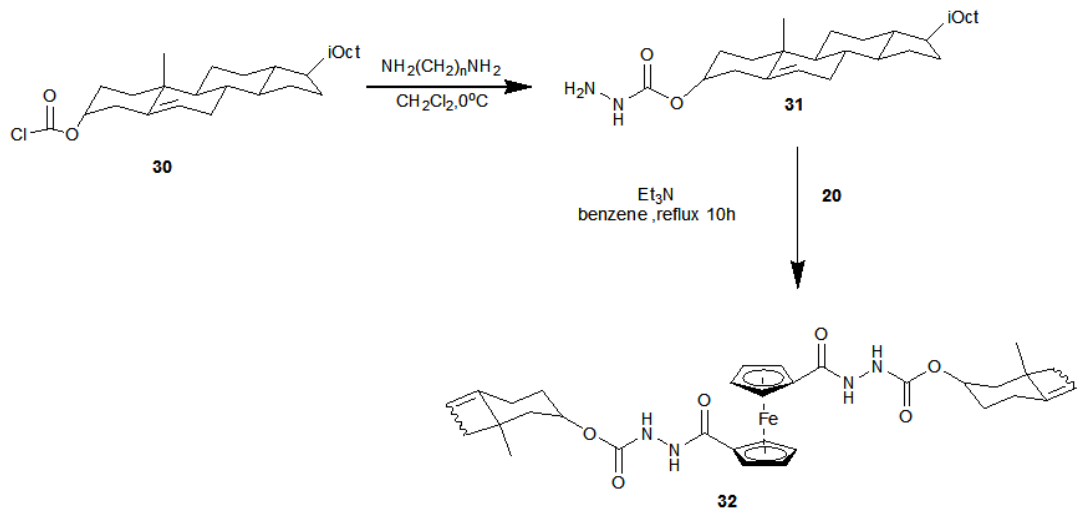
Scheme 5. Synthesis of Diester derivatives of Ferrocene



Scheme 6. Synthesis of Steroid derivatives of Ferrocene



Scheme 7. Synthesis of Steroid derivatives of Ferrocene with glycine as a linker group and two cholesteryl groups



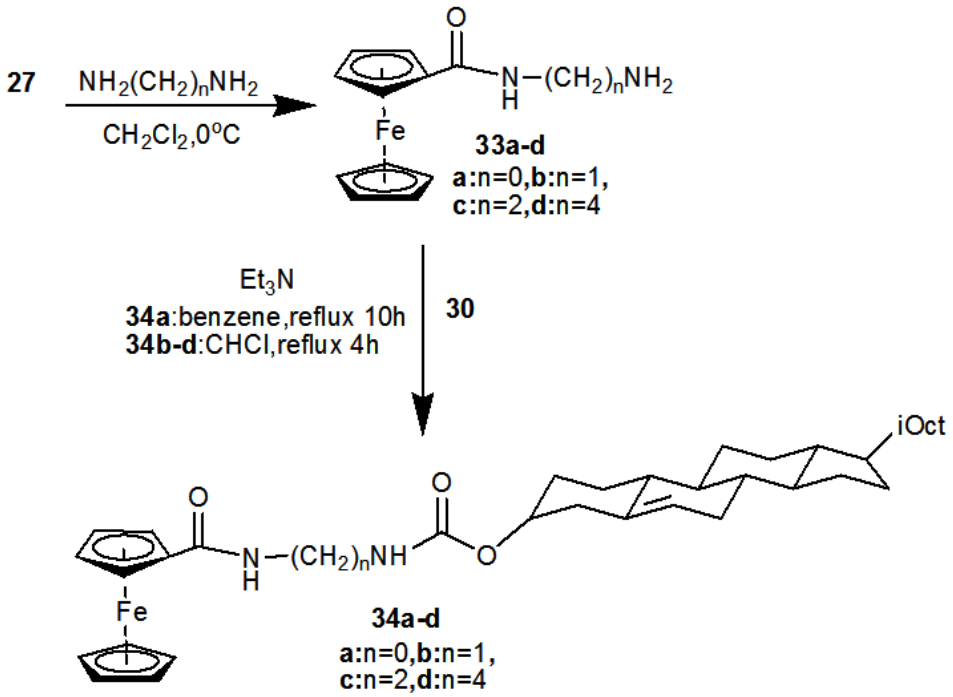
Scheme 8. Synthesis of Steroid derivatives of Ferrocene with two cholesteryl groups

It was significant enough to demonstrate that adding a ferrocene group to the right carrier might increase an agent's antitumor activity.

Ferrocene derivatives

Formyl derivative of ferrocene

Tang J[54] synthesized Formyl ferrocene through the reaction of ferrocene, $CH(OEt)_3$, and



Scheme 9: Synthesis of steroid derivatives of Ferrocene with amino moiety as the linker group

anhydrous solvent (anhydrous $AlCl_3$), followed by stirring to obtain the desired product.

Chalcone derivative of formyl ferrocene

Song QB[55] synthesized ferrocene chalcone derivatives (Scheme 2). To synthesize compound 3, formyl ferrocene underwent a reaction with bromoacetophenone (2). Subsequently, compound 3 was subjected to treatment with Pd (0) and $ArB(OH)_2$, resulting in the formation of compounds 4a-4c. Various derivatives can be synthesized by using substituted Ar.

Alternatively, acetyl ferrocene (5) was reacted with bromobenzaldehyde (6). After this, compound 7 was treated with Pd (0) and $ArB(OH)_2$, forming compound 8. Various chalcone derivatives (Scheme 3) can be synthesized by substituting Ar in $ArB(OH)_2$.

Furan containing derivatives of ferrocene

Moynahan EB[56] successfully produced Ferrocene derivatives incorporating a furan ring (Table 1). The condensation of ferrocene carboxy hydrazide with 5-nitro-2-furaldehyde and 5-nitro-2-acetylfuran led to compounds 9a and 9b, respectively. Ferrocene carboxy hydrazide was condensed with ethyl-5-nitro-2-furimidate hydrochloride, resulting in the synthesis of N-ferrocenecarboxamido-5-nitro-2-furamidine, designated as compound 10.

Acetylferrocene readily undergoes condensation with 2-furan aldehyde and 5-methyl-2-furaldehyde, forming compounds 11a and 11b, respectively. However, this reaction failed under various conditions with 5-nitro-2-furanaldehyde to yield 11c. Alternatively, ferrocene carboxaldehyde can be condensed with 2-acetylfuran and 2-acetyl-5-nitrofuran, producing compounds 12a and 12b respectively, which are isomeric to 11a and 11c.

The reaction of compounds 11a, 12a, and 12b with phenylhydrazine resulted in the formation of pyrazolines 13, 14a, and 14b, respectively[55]. However, when chalcone 12a was subjected to a reaction with phenylhydrazine at room temperature, a compound presumed to be 15 was obtained instead of the expected pyrazoline 14a.

The reaction of hydrazine or acetyl hydrazine with 11a led to pyrazoline 16a or 16b formation. Reaction of isomeric chalcones 12a/12b with hydrazine led to pyrazoline 17a/17b[56].

Cholesterol derivative of ferrocene

Cholesterol derivatives of ferrocene were synthesized by Lewkowski J and co-workers[57] in 2004 and then by Váradi M, and Skoda-Földes R[58] in 2022. á-(Ferrocenyl)-amino methane phosphonous acid derivatives (19a-19d) were synthesized by joining the steroid moiety and the ferrocene group with the help of amino phosphonous acid (Scheme 4).

Diester derivative of ferrocene

1,1'-Bis-(chlorocarbonyl)ferrocene (20) derivatives were synthesized by Medina[59]. 20 after reaction with cholesterol in the presence of benzene and triethylamine, resulted in the formation of 1,1'-diester cholesterol derivative (21).

Steroid Derivative of Ferrocene

Estradiol after esterification (22) with dicarboxylic acid (succinic acid) was converted to 17â- hemisuccinate (24). Cais M[60] used amino methyl ferrocene (23) as a conjugating reagent to form an amide bond with the carboxylic acid.

Steroid derivative of ferrocene with glycine as linker group and with two cholesteryl groups

Utilizing an N-protected glycine ester, product 25 was synthesized via the acylation of cholesterol. Subsequently, following the removal of the protecting group, the amino derivative 26 was linked to ferrocene derivatives 1-chlorocarbonyl ferrocene (27) and 1,12 -bis(chlorocarbonyl) ferrocene (20) through an amide bond, resulting in the formation of conjugates 28 and 29, respectively[61].

Similarly, compound 32 containing two cholesteryl moieties was produced starting from 1,12 -bis(chlorocarbonyl)ferrocene 20[62].

1-chlorocarbonyl ferrocene (27) after reaction with diamino alkane gave 33, which after reaction with 30 yielded 34[63].

CONCLUSION

In conclusion, the synthesis and preparation of diverse ferrocene derivatives present a compelling avenue for advancing research in various fields, including materials science, catalysis, and medicinal chemistry. The versatility of ferrocene's structural framework offers immense potential for tailoring properties to suit specific applications. Through innovative synthetic methodologies and strategic functionalization, researchers continue to expand the scope of ferrocene derivatives, unlocking novel properties and applications. As this manuscript highlights, the systematic exploration of ferrocene derivatives contributes significantly to advancing interdisciplinary research and holds promise for addressing complex challenges in diverse scientific domains. Further exploration and refinement of synthetic strategies will undoubtedly lead to the discovery of new ferrocene derivatives with enhanced properties and functionalities, driving progress in both fundamental understanding and practical applications.

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Conflict of interest

The authors do not have any conflict of interest.

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