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REVIEW ARTICLE

Advances in the Synthesis and Biological Applications of Ferrocene–Conjugated Amino Acids, Carbohydrates, Cholesterol and Nucleobases: A Review

Anija Mol T Philip, Mayur V Khedkar, Shoeb R Khan, Shibin Chacko *

ABSTRACT: Ferrocene, known for its aromaticity, lipophilicity, and stable redox properties, has emerged as a cornerstone in the design of functional molecules due to its unique chemical characteristics. Despite its classification as an organometallic compound, ferrocene and its derivatives exhibit remarkable stability under aqueous and aerobic conditions. Industrially, ferrocene finds applications in diverse sectors including petroleum, plastics, textiles, metallurgy, and catalysis. Medicinally, its derivatives are recognized for their cytotoxic, antitumor, antimalarial, and antianemic properties, which position ferrocene-conjugated biomolecules as promising candidates for therapeutic exploration. One strategy to enhance the water solubility and biocompatibility of ferrocene involves covalent conjugation with biomolecules such as amino acids, carbohydrates, cholesterol, and nucleic acids. These conjugates display unique structural, electrochemical, and biological properties that underpin their potential applications in medicinal and material sciences. However, limited synthetic methodologies have been reported for such conjugates. This review delves into recent advancements in the synthesis of ferrocene-conjugated carbohydrates, amino acids, cholesterol, and nucleobases, with an emphasis on strategies such as thioalkylation, click chemistry, and amide bond formation. Overall, the versatility of ferrocene derivatives, both in terms of chemical reactivity and biological activity, underscores their potential to drive innovations in therapeutic development and material science. Future research promises to uncover novel applications and expand the synthetic repertoire of ferrocene-based biomolecular conjugates.

Keywords: Ferrocene, Antibacterial, Antimalarial, Organometallic, Amino Acids, Carbohydrates, Cholesterol, Nucleobases

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1. INTRODUCTION

Ferrocene with its aromaticity, relative lipophilicity, facile redox properties and the possibility of easy chemical modifications is an attractive moiety to be incorporated into functional molecules. Although an organometallic compound, ferrocene and some of its derivatives are stable in aqueous and aerobic media [1-5]. Ferrocene derived compounds have widespread applications in industries like petroleum, plastic, textiles, metallurgy and in catalysis [2-10]. Medicinal applications of ferrocene are well explored and ferrocene itself shows cytotoxic and antianemic properties, while many of its derivatives exhibit antitumor and antimalarial activities [11-21]. Due to these significant chemical and biological applications, ferrocene linked biomolecules are of particular interest. One of the explicit ways to enhance water solubility and biocompatibility of ferrocene is to make bioconjugates of ferrocene by covalent attachment to biomolecules like amino acids, carbohydrates and nucleic acids [22-23]. Ferrocene containing amino acids, peptides, ligands and carbohydrates have received increased attention because of their structural, electrochemical and biological properties [24]. Incorporation of a ferrocenyl group to carbohydrates

Department of Chemistry, Hislop College, Maharashtra, 440001, India.

*Author to whom correspondence should be addressed: shibinchacko@gmail.com (Shibin Chacko)

provides opportunities to make useful chiral auxiliaries, which combines the advantages of the presence of multiple chiral centers in the carbohydrate part and the lipophilicity of ferrocene (Figure 1). Ferrocenyl carbohydrates and imino sugars are known to have antimalarial, antibacterial and anticancer properties. Available reports for the synthesis of ferrocenyl carbohydrates relies on attaching a sugar derivative with the cyclopentadienyl ring of ferrocene through carboxylate [25], thiol [22], triazole [22], ether [23], boronate [26] and various less common methods [27-30]. There are very few reports are available in literature regarding the synthesis of Ferrocenyl Amino acids, Sugar and Nucleic acids. Derivatives and here we are discussing the most of the reports which is available in literature.

Berenguel and co-workers reported that ferrocene carbohydrate conjugates show sensing properties towards concanavalin A (Con A), a mannose-binding enzyme. The studies are based on comparing the change in enthalpy during the binding of Con A with α-D-mannopyaranoside and Ferrocene-carbohydrate conjugates. Ferrocene carbohydrate conjugates show more binding affinity towards Con A than α-D-mannopyaranoside (Figure 2). Monovalent ferrocene conjugates show 1.3 to 2.1 times more affinity and divalent ferrocene conjugates shows 21 to 33 times more affinity than α-D-mannopyaranoside [31-32]. There are very few reports available in literature regarding the synthesis of ferrocenyl amino acids and carbohydrates conjugates and this limiting the scope of various biological studies of the same. These compounds can be designed and synthesis for various biological studies such as anticancer, antibacterial and diagnosis purposes [33]. Following is a brief discussion of recently reported methods towards the synthesis of ferrocenyl carbohydrates and amino acids.

2. SYNTHESIS OF FERROCENYL CONJUGATES

2.1. Ferrocenyl amino acids

Ferrocene amino acids (FAAs) are a fascinating class of compounds that bridge the gap between organometallic and biomolecular chemistry. Derived from ferrocene, a metallocene with exceptional chemical stability and redox activity, these amino acid analogs exhibit unique structural and functional properties. The ferrocene moiety imparts robustness and redox functionality, making FAAs promising candidates in medicinal chemistry, catalysis, and materials science. The synthesis of FAAs typically involves incorporating the ferrocene scaffold into the amino acid backbone or side chain. Ferrocene amino acids conjugates were prepared by using acid chloride, active ester, oxazolone, click chemistry and Umpolung chemistry (Figure 3).

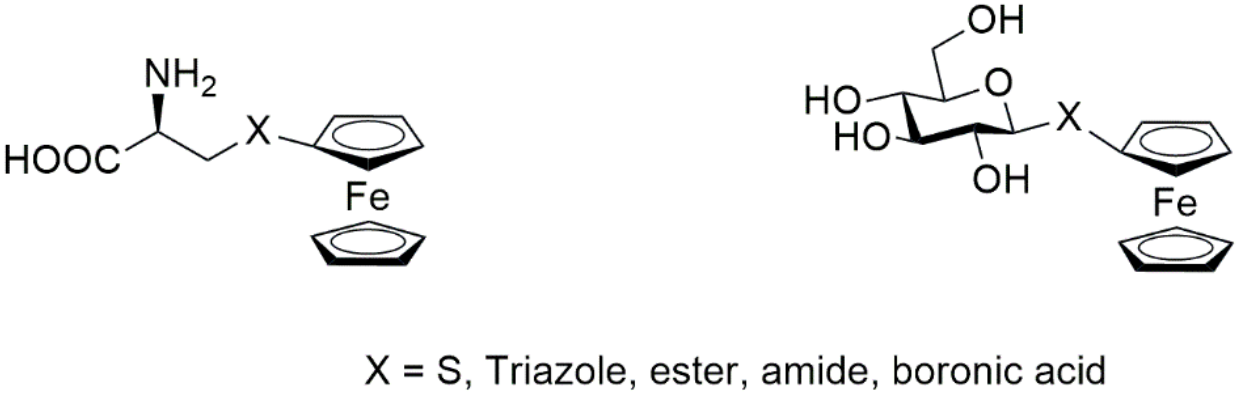


Fig. 1. Ferrocenyl amino acids and carbohydrates conjugates.

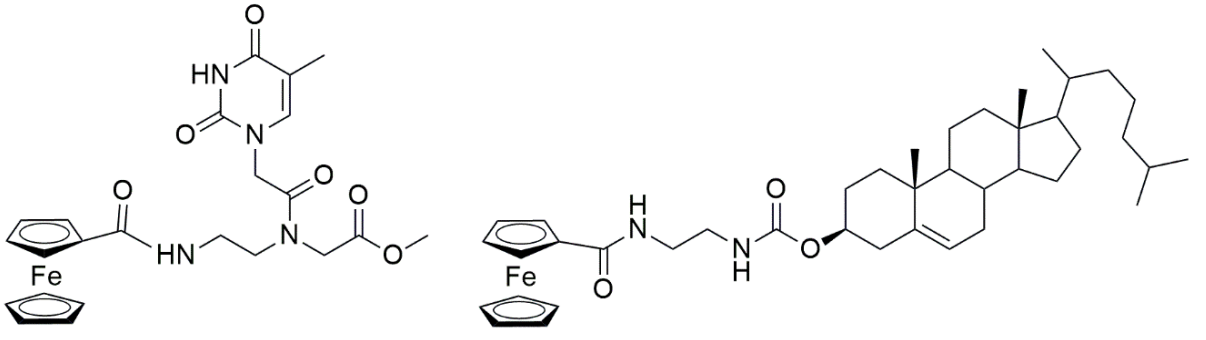


Fig. 2. Ferrocenyl nucleobases and cholesterol conjugates.

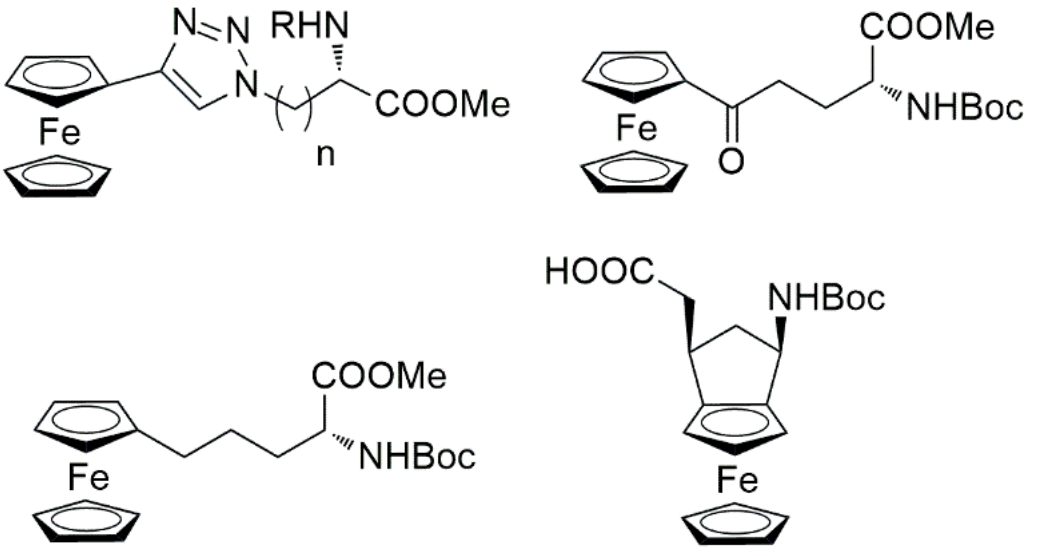
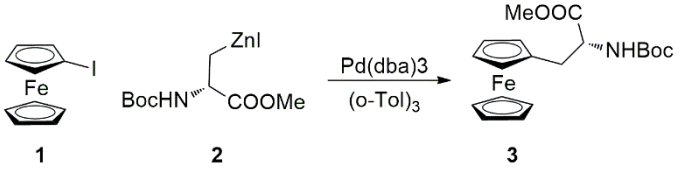


Fig. 3. Ferrocenyl amino acids.

Ferrocenyl amino acids were incorporated in the peptides and explored for various biological studies. The versatility of ferrocene chemistry allows for the generation of diverse derivatives with tailored properties. The ferrocenyl group acts as a redox-active center, enabling their use in electrochemical sensors and as electron donors in molecular electronics. Furthermore, the hydrophobic nature of ferrocene influences the structural and functional behaviour of proteins when incorporated into peptides, potentially stabilizing unique conformations. These properties make FAAs valuable tools in studying protein structure and function. In medicinal chemistry, FAAs have shown promise as antitumor agents, enzyme inhibitors, and antimicrobial agents. The ability of ferrocene to undergo reversible oxidation-reduction reactions contributes to its potential as a redox-modulating therapeutic agent. Furthermore, the incorporation of FAAs in peptide-based drugs can enhance their stability and bioactivity.

Ferrocene-containing α-amino acids were first reported in 1957 by Schlögl et al. and Graham et al., who independently synthesized ferrocenyl glycine. Later, in 1996, Jackson et al. synthesized 1,1'-ferrocenylene-alanine from 1-iodoferrocene and 1,1'-diiodoferrocene using a Pd(0)-catalyzed coupling reaction with a serine-derived zinc reagent (Scheme 1).

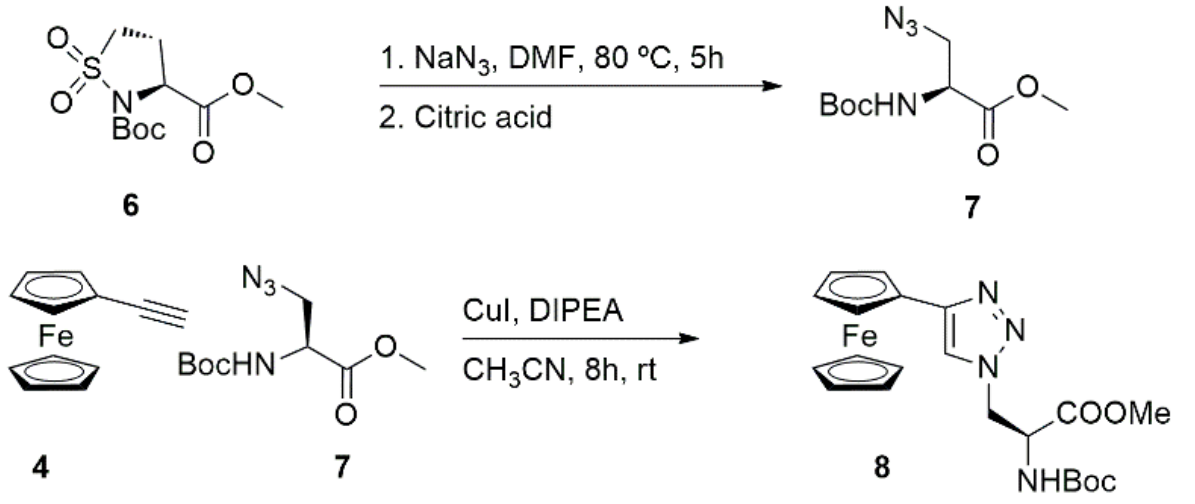


Scheme 1. Palladium catalyzed coupling process

The Iodoferrocenes were prepared using Kovar's methods and subsequently subjected to palladium-catalyzed coupling with an excess of serine-derived zinc reagent (3 equivalents), yielding ferrocenyl alanine in 60% yield [34].

Chandrasekaran et al reported a click chemistry approach for the synthesis of ferrocenyl α-amino acids using ethynyl ferrocene **4** and ferrocene derived azides **5**. To synthesize ferrocene amino acids, amino acids containing an azido group were required, as these could undergo a click reaction with ethynyl ferrocene. To achieve this, sulfamidates **6** were synthesized from the commercially available Serine and these sulfamidates were treated with sodium azide in dimethylformamide to get the required azide **7** in good yield. When azide was treated with ethynyl ferrocene in CH_3CN with CuI as catalyst and DIPEA as base(rt,7–8h) the corresponding protected ferrocene α-amino acid **8** in excellent yield (Scheme 2) [35].

This approach allows them to make different ferrocene amino acids by using azides derived from threonine, lysine, (Figure 4) [35]. The Umpolung reaction has been widely explored in the synthesis of various natural products and bioactive molecules. Recently, Chacko et al. utilized this reaction for synthesizing unnatural amino acids from serine and aromatic aldehydes. Building on this strategy, Philip et al. developed a similar approach for synthesizing ferrocene amino acids using ferrocene carboxaldehyde and alkyl iodides derived from aspartic and glutamic acids. Aspartic acid or glutamic acid was first subjected to esterification with thionyl chloride and methanol, yielding diesters **11a** and **11b**. The free amino group was subsequently protected as NHBoc using di-tert-butyl dicarbonate and $NaHCO_3$ in THF. To achieve selective reduction, the amino group was further treated with an excess of di-tert-butyl dicarbonate in dichloromethane for an extended time in the presence of a catalytic amount of DMAP. The dual Boc-protected amino group provided steric bulk, enabling regioselective reduction with DIBAL-H to form alcohols **13a** and **13b**. These alcohols were then converted to iodides **14a** and **14b** using triphenylphosphine and iodine in THF.



Scheme 2. Copper catalyzed click chemistry approach

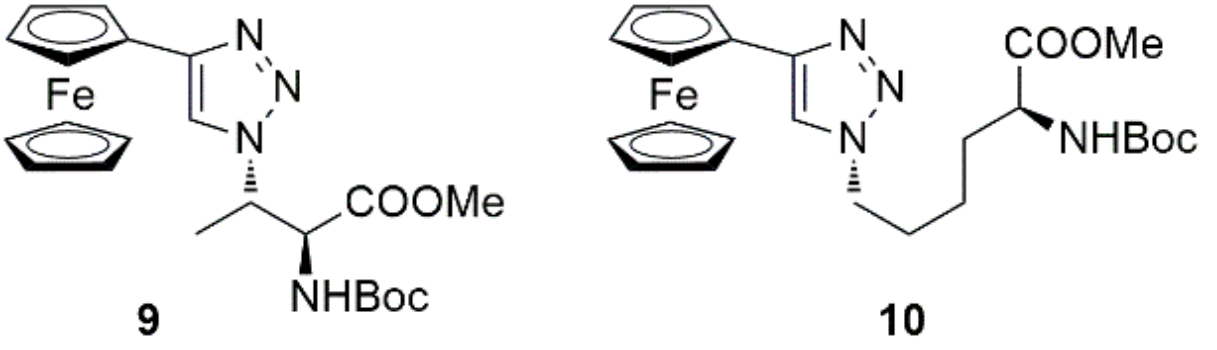


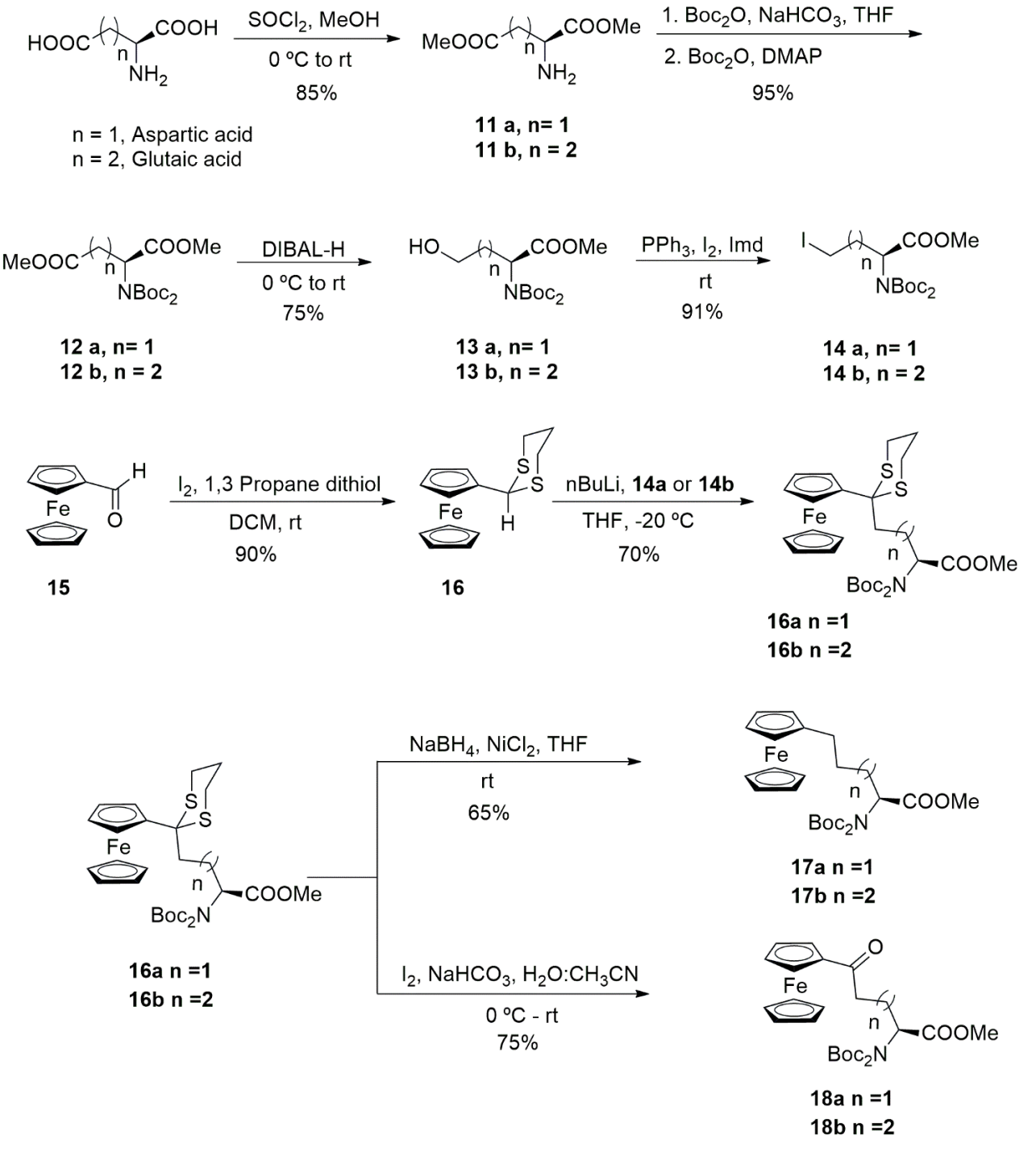
Fig. 4. Ferrocene α-amino acids from threonine and lysine.

Ferrocene aldehyde (**15**) was transformed into ferrocenyl dithiane (**16**), which was subsequently treated with n-BuLi and alkyl iodides (**14a**/**14b**) to synthesize ferrocenyl amino acid derivatives (Scheme 3). The dithiane group could be removed under appropriate conditions to yield either alkane or carbonyl derivatives. Ferrocene-conjugated amino acids (**14a**/**14b**) were treated with nickel chloride and sodium borohydride in THF to produce alkyl derivatives **17a** and **17b**. Alternatively, treatment with iodine and $NaHCO_3$ in a mixture of acetonitrile and water yielded the corresponding oxo derivatives of ferrocenyl amino acids, **18a** and **18b** [36].

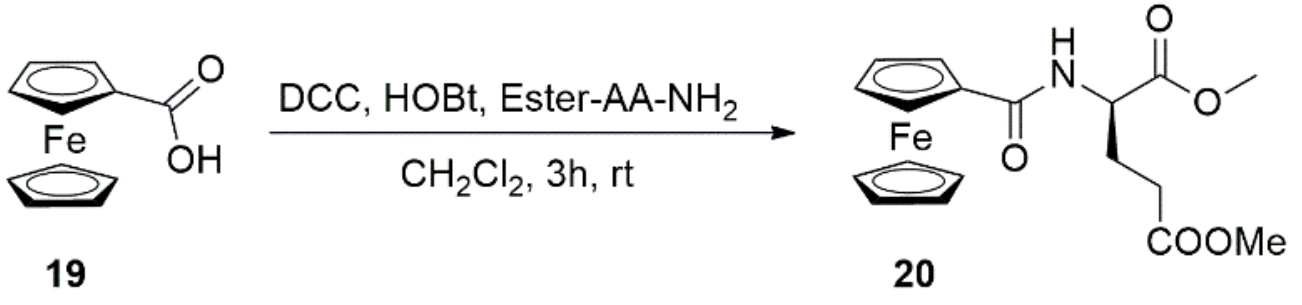
Kraatz et al reported a straight forward synthesis of series of ester protected ferrocenyl amino acids [37]. Synthesis initiated from the ferrocene carboxylic acid **19**, which is coupled with various C-protected amino acids using DCC/HOBt. During the reaction conditions byproducts urea were easily separated by filtration methods and excess reagents were separated by treating with aqueous saturated $KHCO_3$ solution and 5% citric acid. All ferrocenyl amino acid esters were soluble in diethyl ether and the pure product were recrystallized from ether (Scheme 4).

Using the similar strategies, they were able to make compounds from **21** to **26** (Figure 5) from ferrocene carboxylic acids [37]. In 1957, Schlogl et al. reported the asymmetric synthesis of a racemic ferrocene amino acid derived from ferrocene (Scheme 5). The synthesis began with the acetylation of ferrocene using acetic anhydride to yield acetylferrocene **27**, which was subsequently converted into ferrocene carboxylic acid **28** via treatment with iodine and sodium hydroxide [38].

The acid was then esterified using diazomethane to produce methyl ferrocene carboxylate **29** with excellent yields. The ester was reduced using lithium aluminum hydride (LiAlH4) to form the corresponding alcohol **30**. This alcohol was subsequently transformed into ferrocene methyl chloride **31** via reaction with phosphorus trichloride (PCl3). The alkyl halide underwent a nucleophilic substitution reaction to yield the amino ester **32**. Ester group was proceeded to hydrolysis using sodium hydroxide to get the dicarboxylic acid, which is further proceeded to decarboxylation reaction to get the NH-protected carboxylic acid **33**. NH-CHO group were removed by using acidic condition to get the racemic ferrocene carboxylic acid **34**. This synthetic route highlights a series of well-defined transformations, including acetylation, halogenation, esterification, reduction, and nucleophilic substitution, offering a comprehensive approach to obtaining ferrocene-derived amino acids. This is the first reported synthesis of ferrocene amino acids.



Scheme 3. Umpolung approach for the synthesis of ferrocene amino acids.



Scheme 4. Synthesis of ferrocenyl amino acids via peptide coupling agents.

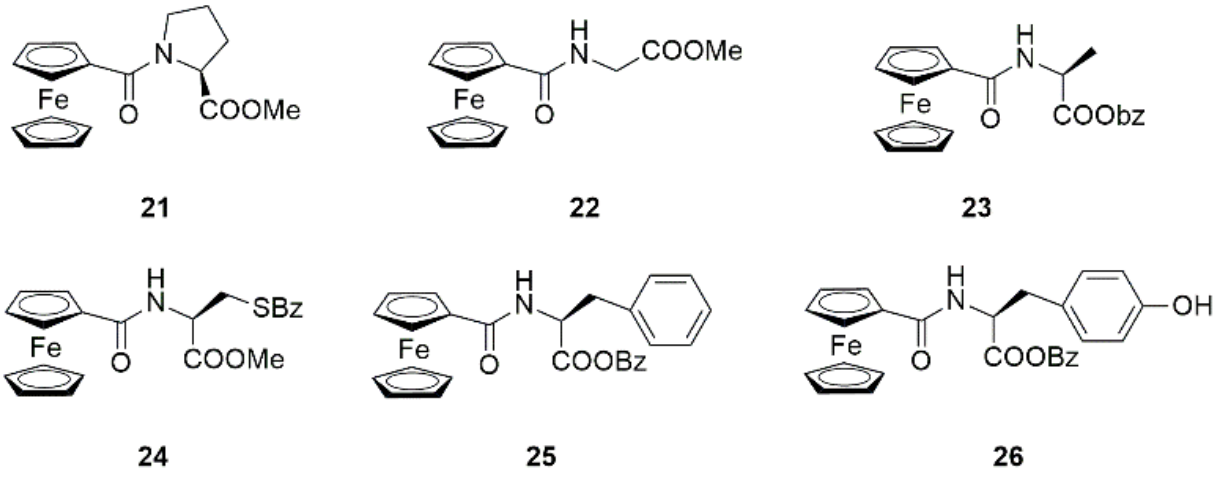
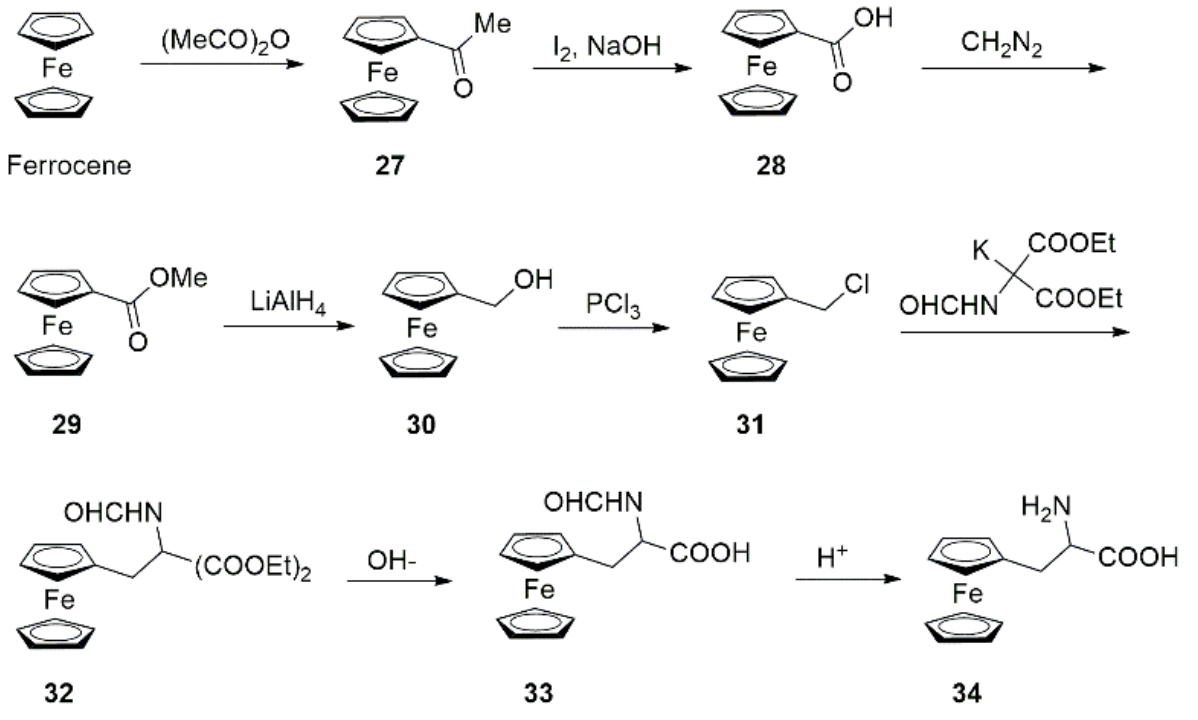
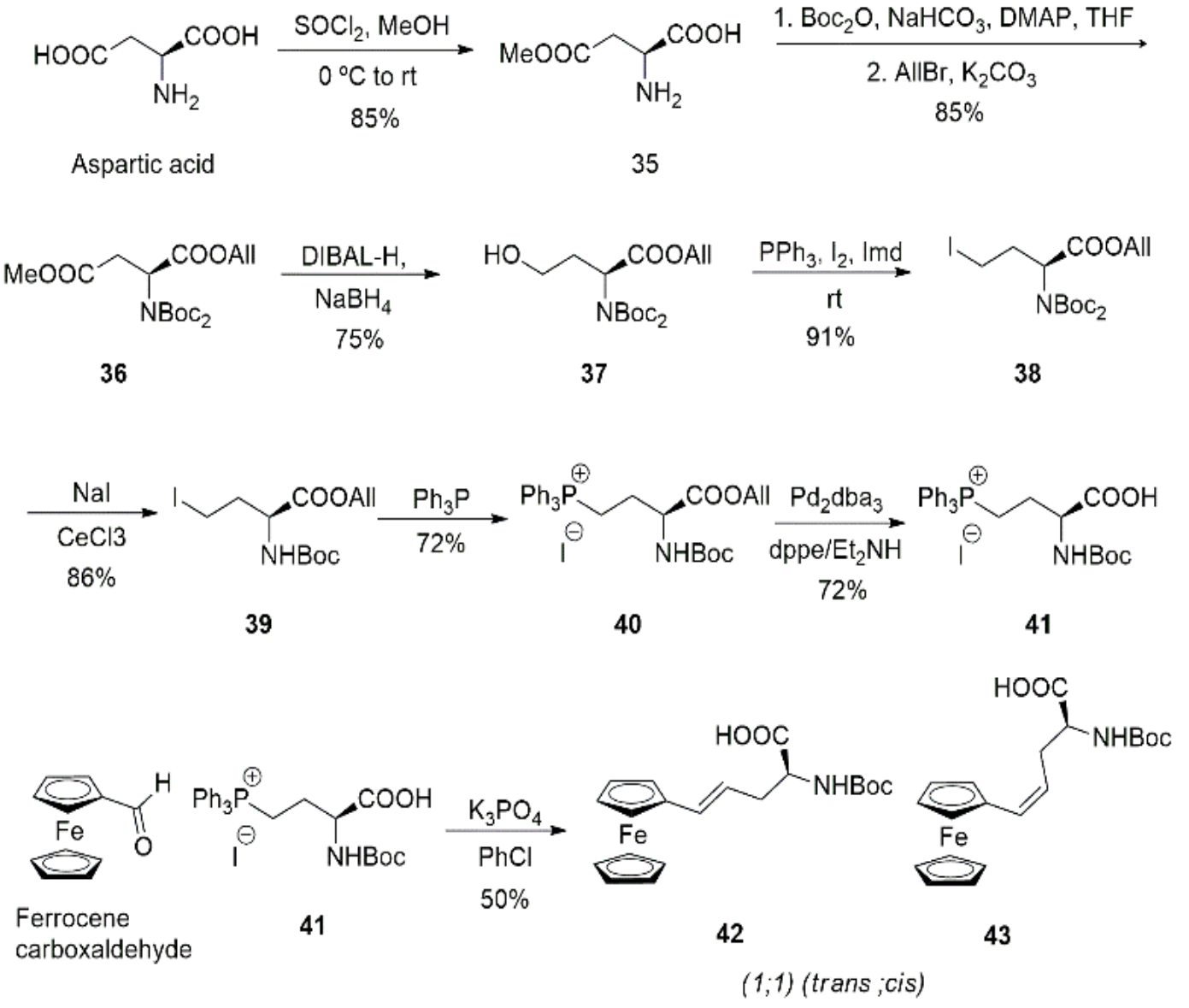


Fig. 5. Various Ferrocenyl amino acids esters



Scheme 5. Schlogl et al synthesis of racemic ferrocenyl amino acids.

Juge and co-workers reported the synthesis of unnatural amino acids from aspartic acid and aldehydes (Scheme 6) [39]. The stereoselective synthesis of a novel amino acid phosphonium salt was achieved through the quaternization of molten triphenylphosphine with a γ-iodo-NHBoc-amino ester, which is synthesized from L-aspartic acid. Synthesis of iodide **38** was carried out using the scheme 3. Iodide **38** further treated with sodium iodide and cerium chloride to deprotect the Boc group which is further treated with triphenyl phosphine to get the Wittig salt **40**. The carboxylic acid functionality was deprotected via a palladium-catalyzed desallylation reaction, yielding the phosphonium salt with a free carboxylic acid group **41**. This phosphonium salt was employed in the Wittig reaction with a variety of aromatic and aliphatic aldehydes, as well as trifluoroacetophenone, under solid–liquid phase-transfer conditions in chlorobenzene, using K_3PO_4 as a weak base. The reaction successfully produced unsaturated amino acids 50% yield with 1:1 ratio of both cis and trans product without any racemization.

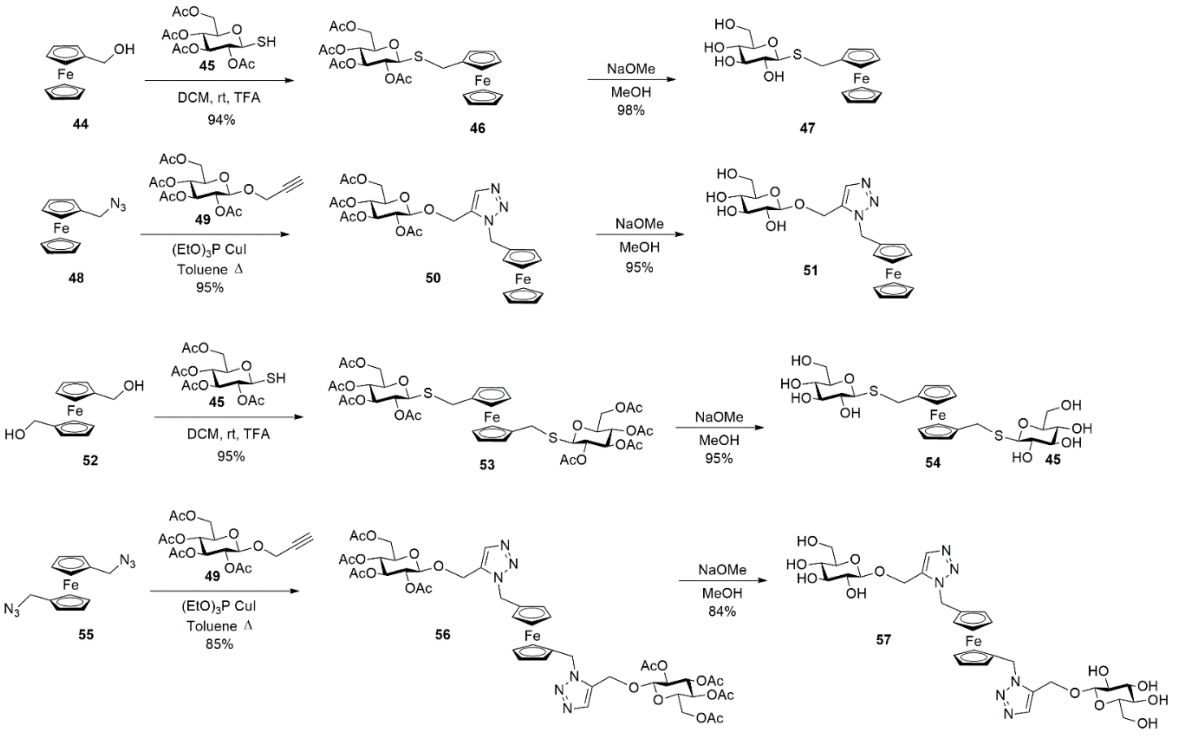


Scheme 6. Ferrocene amino acids synthesis from Aspartic acid derived Chiron.

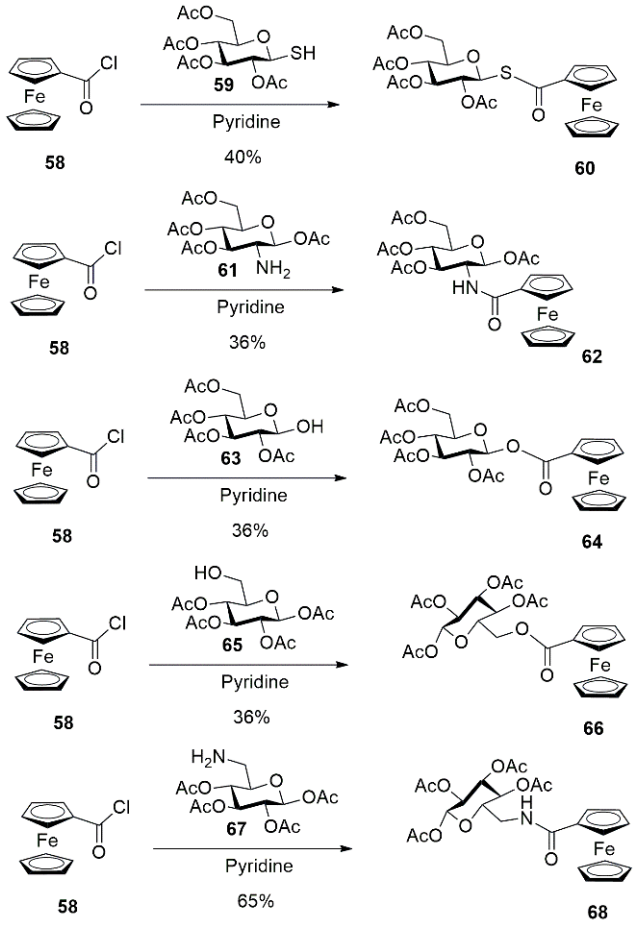
2.2. Ferrocenyl Sugar Derivatives

Gonzales et al reported the synthesis of ferrocene carbohydrates using acid catalyzed thio alkylation as well as copper catalyzed click reaction between an azide and an alkyne (Scheme 7). Hydroxymethyl ferrocene **44** was treated with TFA to get ferrocenylmethyl carbocation which was reacted with various thiols **45** synthesized from carbohydrates to get the ferrocene carbohydrates conjugate **46** in 94% yield. Acetate groups were removed by treating with sodium methoxide in methanol yielded water soluble ferrocene carbohydrate conjugates **47** in an excellent yield. Alkynes derived from carbohydrates **49** subjected to azide-alkyne click chemistry using organo- soluble catalysts such as $(Ph_3P)_3$·CuBr and $(EtO)_3P$·CuI in presence of organic bases such as DIPEA or DBU to get ferrocene carbohydrate conjugates **50** [22]. Using the similar strategies, they were able to make the di-substituted ferrocene carbohydrates conjugates **54** and **57**.

Orvig et al. successfully synthesized a series of seven ferrocene-carbohydrate conjugates utilizing ferrocene carbonyl chloride as a key precursor to establish amide linkages for various carbohydrate derivatives (Scheme 8) [25]. In this work, ferrocenyl acid chloride **58,** was reacted with diverse nucleophiles, including thiols **59**, amines **61**, **67**, and hydroxyl groups **63**, **65**, yielding corresponding thioester **60**, amides **62**, **68**, and esters **64**, **66**, respectively. These reactions were characterized by relatively low yields, attributed to the significant steric hindrance imposed by the bulky ferrocene and cyclohexyl substituents. Subsequent biological evaluations of these compounds revealed promising antimalarial activity, demonstrating their potential for further development as therapeutic agents. The study highlighted the utility of ferrocene conjugates in medicinal chemistry and expanded the scope of bioactive organometallic compounds.



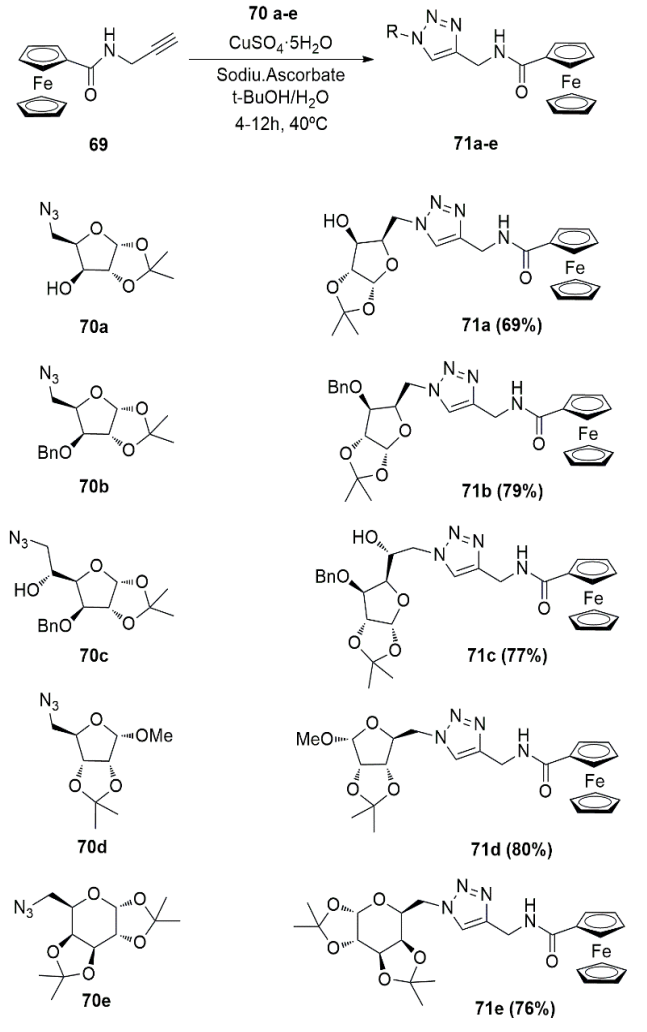
Scheme 7. Synthesis of ferrocene-carbohydrate conjugates via thio-alkylation and azide-alkyne click chemistry.



Scheme 8. Synthesis of ferrocene-carbohydrate conjugates

Trivedi et al reported the synthesis of ferrocene-carbohydrate conjugates using the amide-traizole linkage [29]. Synthesis initited from the ferrocenoyl propargylamide **69**, which was synthesized by using the reported procedure. Ferrocenoyl propargylamide **69** was subjected to the click reaction with and various sugar azides (**70a–e**) in the presence of sodium ascorbate and copper (II) sulfate in a 1:1 mixture of tBuOH and water at 40 °C for 4 h (Scheme 9). This reaction proceeds with 69-80% yield and the lower yiled can be due to the bulkiness of furanose ring and this approach. All these compounds were stable in organic solvents as well as in the buffer system under physiological conditions (pH = 7.0). Compounds derived from xylose and ribose demonstrated cytotoxic effects on both hormone-dependent and hormone-independent breast cancer cell lines. In contrast, those synthesized from glucose and galactose were observed to be non-toxic. Furthermore, none of the compounds exhibited antimicrobial activity against either Gram-positive or Gram-negative pathogens, highlighting their selective biological properties and potential for targeted applications in cancer therapy without antimicrobial interference.

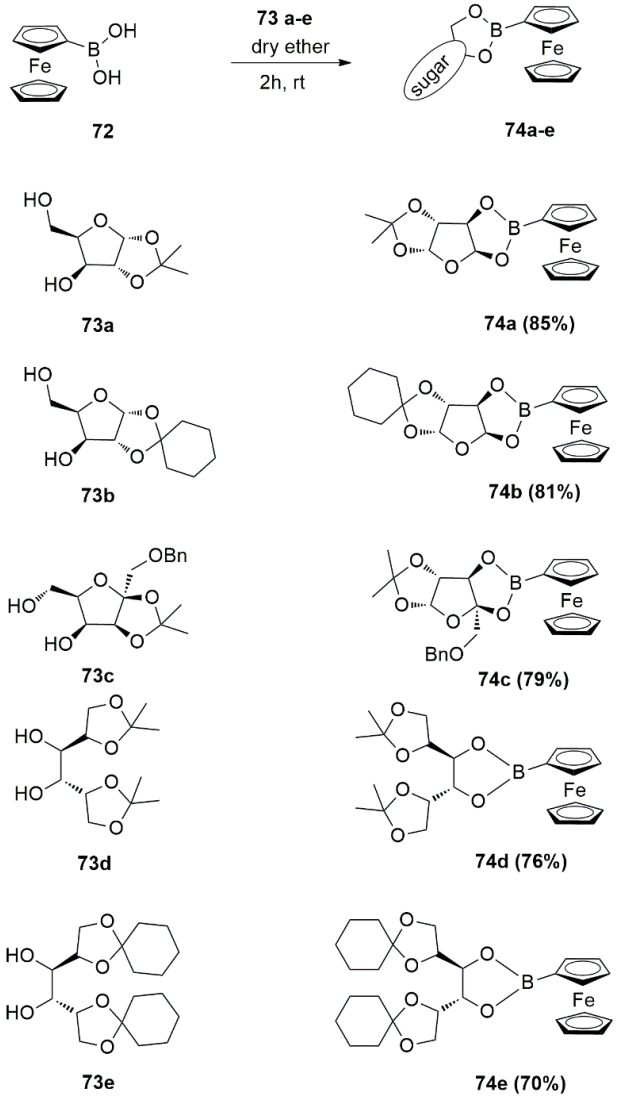
Trivedi and co-workers presented an efficient synthesis of ferrocene-carbohydrate conjugates by employing ferrocene boronic acid **72** as a coupling agent [26]. This methodology involved the reaction of ferrocene boronic acid with a series of diols derived from D-xylose, L-sorbose, and D-mannitol (compounds **73a-e**), showcasing the versatility of this approach (Scheme 10). The coupling reactions were carried out under mild conditions in dry diethyl ether at room temperature for two hours, leading to the formation of ferrocene-carbohydrate conjugates **74a-e** in excellent yields (Scheme 10).



Scheme 9. Synthesis of ferrocene-carbohydrate conjugates via amide and triazole linkages.

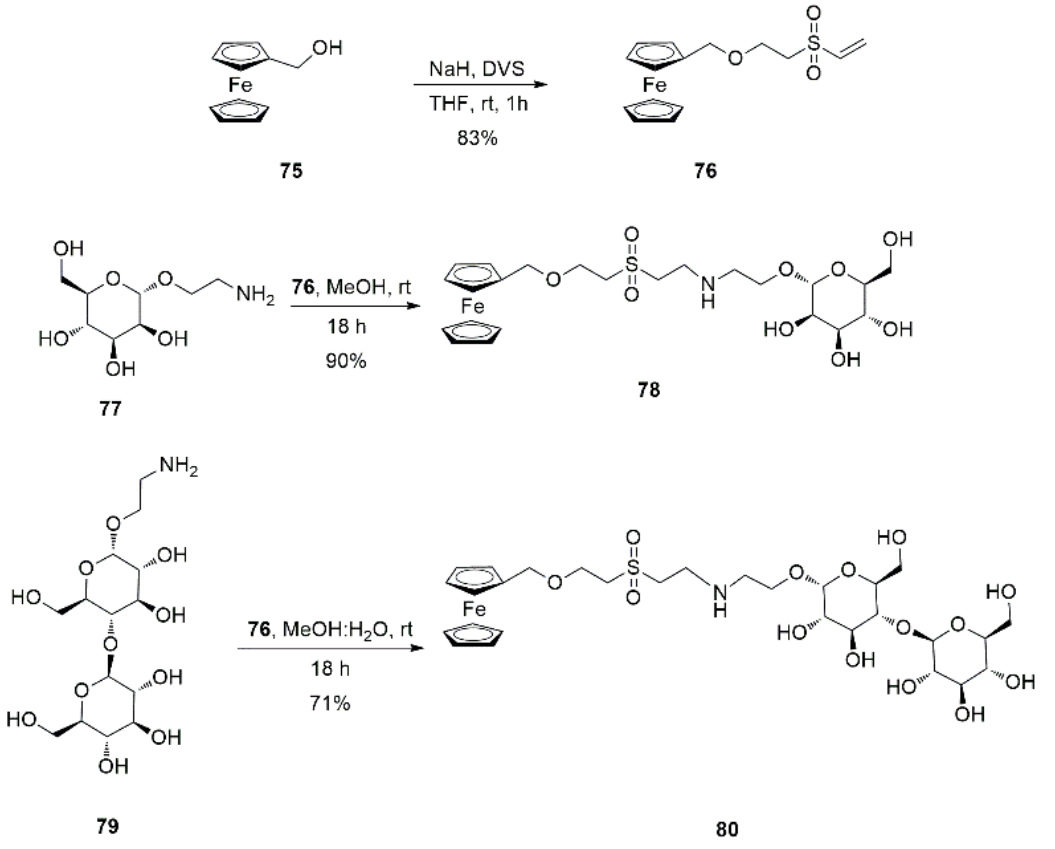
The success of this synthesis highlights the compatibility of ferrocene boronic acid with various diols, providing a straightforward and efficient route to functionalized ferrocene derivatives. Furthermore, the mild reaction conditions and high yield underscore the practicality and reproducibility of this method, making it a valuable strategy for the synthesis of complex ferrocene-based conjugates. The synthesized compounds **74a-e** were evaluated for their in vitro antibacterial activity against a range of Gram-positive and Gram-negative bacterial strains. The results demonstrated that these compounds exhibited moderate to significant inhibitory effects against the tested pathogens, with activity levels comparable to or slightly lower than those of standard antimicrobial agents.

Gonzles and co-workers explored vinyl sulfone containing ferrocene for the synthesis of various ferrocene bioconjugates. These reagents have demonstrated utility in conjugating and bioconjugating amine- and thiol-containing molecules or biomolecules through Michael-type addition reactions under mild conditions, preserving the biological activity of the substrates [40]. This approach has been successfully applied to create a diverse range of conjugates and bioconjugates, including ferrocenyl-terminated dendrimers and conjugates such as ferrocene-sugar, ferrocene-cyclodextrin, ferrocene-peptide, and ferrocene-protein systems. These results highlight the potential of ferrocene derivatives in advancing bioconjugation methodologies and functional material development. Synthesis started from ferrocene alcohol **75**, with sulfone and sodium hydride to get the Michael acceptor **76**. The compound **76** is subsequently reacted with mannose 77 and disaccharide **79**, containing an amino group in methanol for 18 hours to yield ferrocene-conjugated mannose and disaccharide derivatives, respectively (Scheme 11).

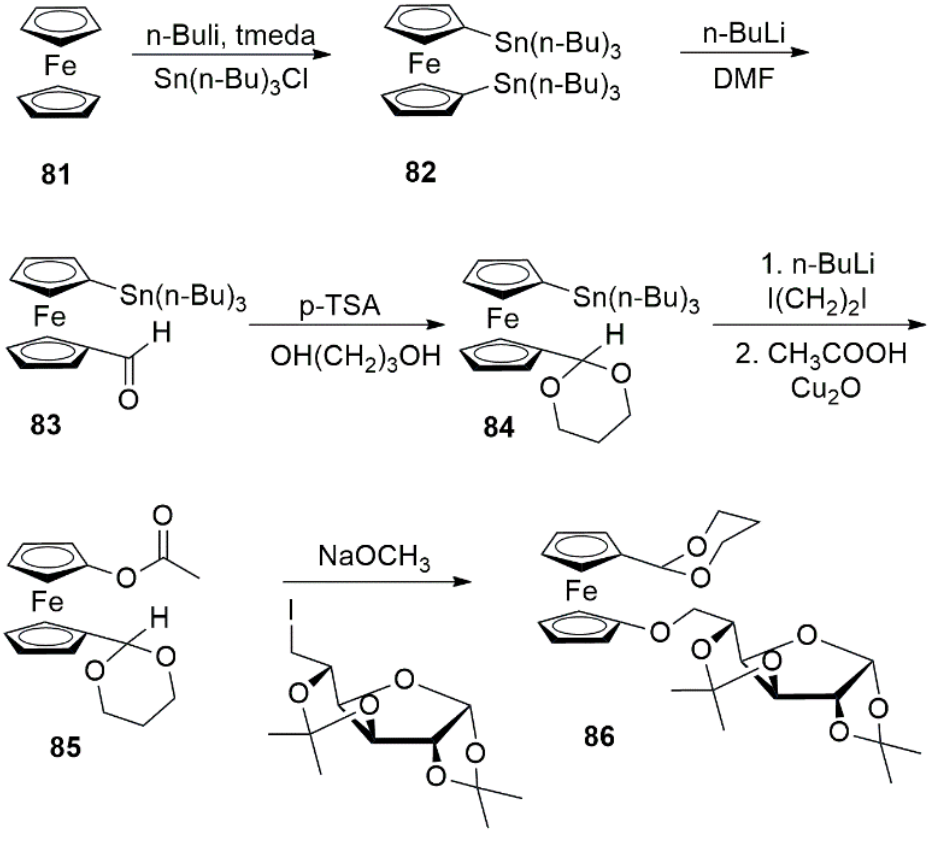


Scheme 10. Synthesis of ferrocene-carbohydrate boronate esters.

Orvig etal reported the synthesis of ferrocene crabohydrates chloroquine conjugates which is having potential antimalarial activity. Herein this ferrocene attached to the carbohydrates through the ether linkage (Scheme 12) [23].



Scheme 11. Synthesis of ferrocene-mannose conjugates via esters Michael-type addition reaction.



Scheme 12. Synthesis of ferrocene-carbohydrates conjugates through ether linkage.

The synthesis began with ferrocene **81**, which was treated with *n*-BuLi in a double deprotonation step, using TMEDA as an auxiliary base. This generated the intermediate 1,1′-dilithium salt. Without isolating the intermediate, transmetalation with tri-*n*-butyltin chloride afforded 1,1′-bis(tri-*n*-butylstannyl)ferrocene **82** with a yield of approximately 90%. Each stannyl group could be selectively substituted by reacting with one equivalent of *n*-BuLi. Subsequent quenching with DMF yielded 1′-(tri-*n*-butylstannyl)ferrocene-1-carboxaldehyde **83**. The labile aldehyde was protected as an acetal by reacting it with 1,3-propanediol, forming 1-(1,3-dioxan-2-yl)-1′-(tri-*n*-butylstannyl)ferrocene. Further treatment with *n*-BuLi followed by acetic acid yielded the ester **85**. Hydrolysis of the acetate produced the corresponding alkoxide ion, which reacted *in situ* with carbohydrate iodides, resulting in ferrocene-carbohydrate conjugates **86**. The compound 86 further proceeded to coupling with chloroquine to get the compound with antimalarial activity.

2.3. Ferrocenyl Cholesterol Derivatives

Ferrocene-cholesterol conjugates represent a unique class of hybrid molecules combining the structural and functional properties of ferrocene, a stable organometallic compound, and cholesterol, a biologically significant steroid. These conjugates are designed to leverage the redox properties of ferrocene alongside the bioactivity and membrane affinity of cholesterol.Recent studies on ferrocene-cholesterol conjugates have explored their ability to integrate into lipid bilayers, disrupting cell membranes or enhancing the delivery of therapeutic agents [41]. Their synthetic versatility and multifaceted biological interactions continue to make them a focus of research in the development of novel bioorganometallic compounds. The synthesis of such conjugates typically involves linking ferrocene to cholesterol through ether, esters or amides (Figure 6). Ferrocene-cholestrol conjugates based organogels are thoruogly studied.

Gokel and co-workers successfully designed and synthesized ferrocene-cholesterol conjugates in 1991, demonstrating that this class of compounds exhibits notable aggregation properties [42-43]. The synthesis began with [(dimethylamino)methyl]ferrocene **87**, which was reacted with cholesterol **88** in the presence of excess methyl iodide and acetone. This reaction yielded the desired conjugates **89.** Their findings highlighted the potential of these hybrid molecules to form aggregates, paving the way for further exploration of their structural and functional properties in bioorganometallic chemistry (Scheme 13).

Fang and co-workers successfully conjugated ferrocene with cholesterol through an amide linkage, exploring their unique sol-gel behavior and properties. The synthesis of these conjugates commenced with ferrocene carboxylic acid, which was treated with phosphorus pentachloride (PCl_5) to form the acid chloride (Scheme 14) [44]. The resulting acid chloride was then reacted with a diamine to yield a terminal amine-containing ferrocene derivative **91**. This intermediate was subsequently treated with cholesterol carbonochloridate **92** to produce the ferrocene-cholesterol conjugate **93**.

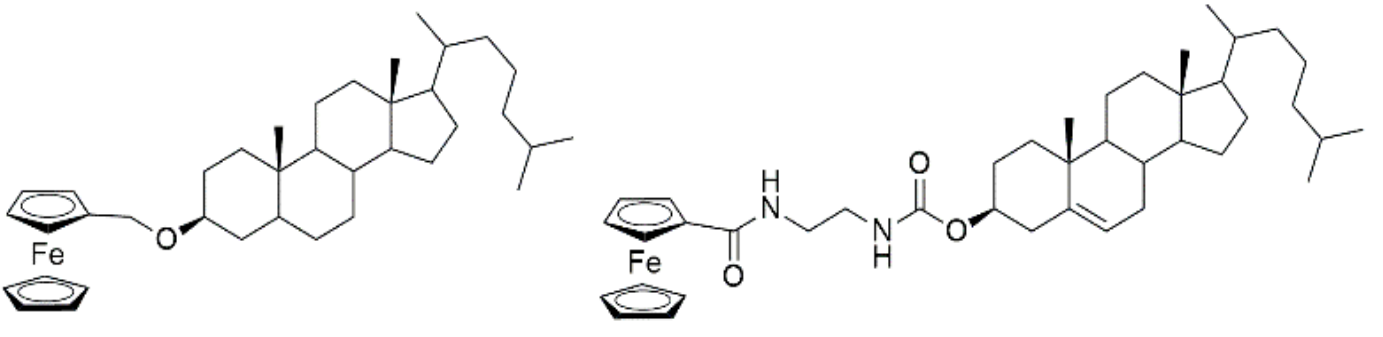
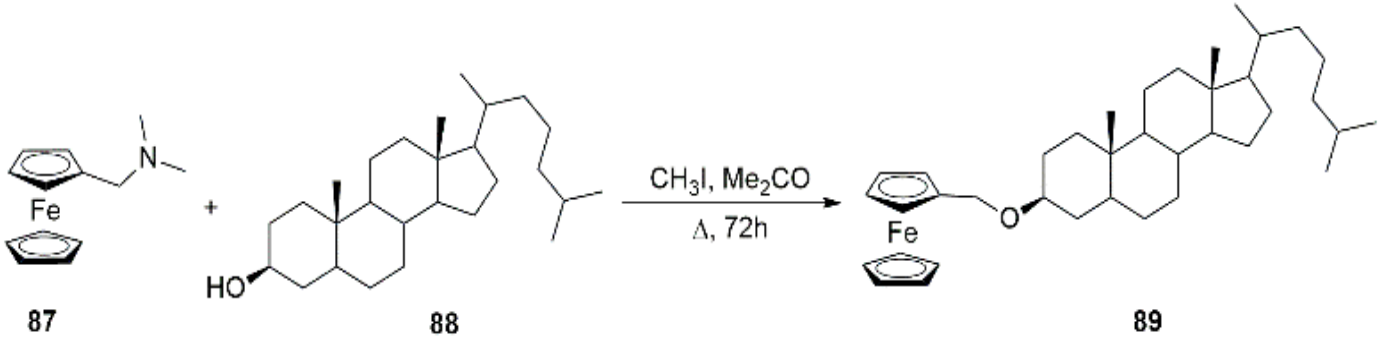


Fig. 6. Ferrocene-Cholesterol Conjugates.

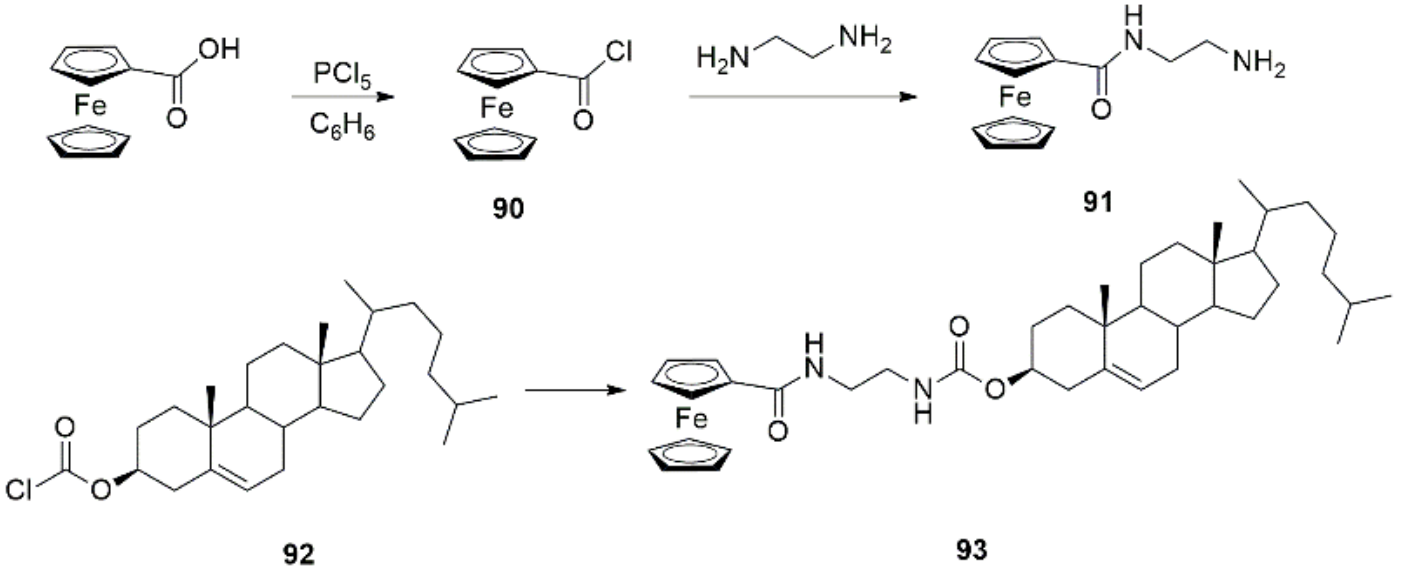


Scheme 13. Synthesis of ferrocene-cholesterol amphiphile precursor.

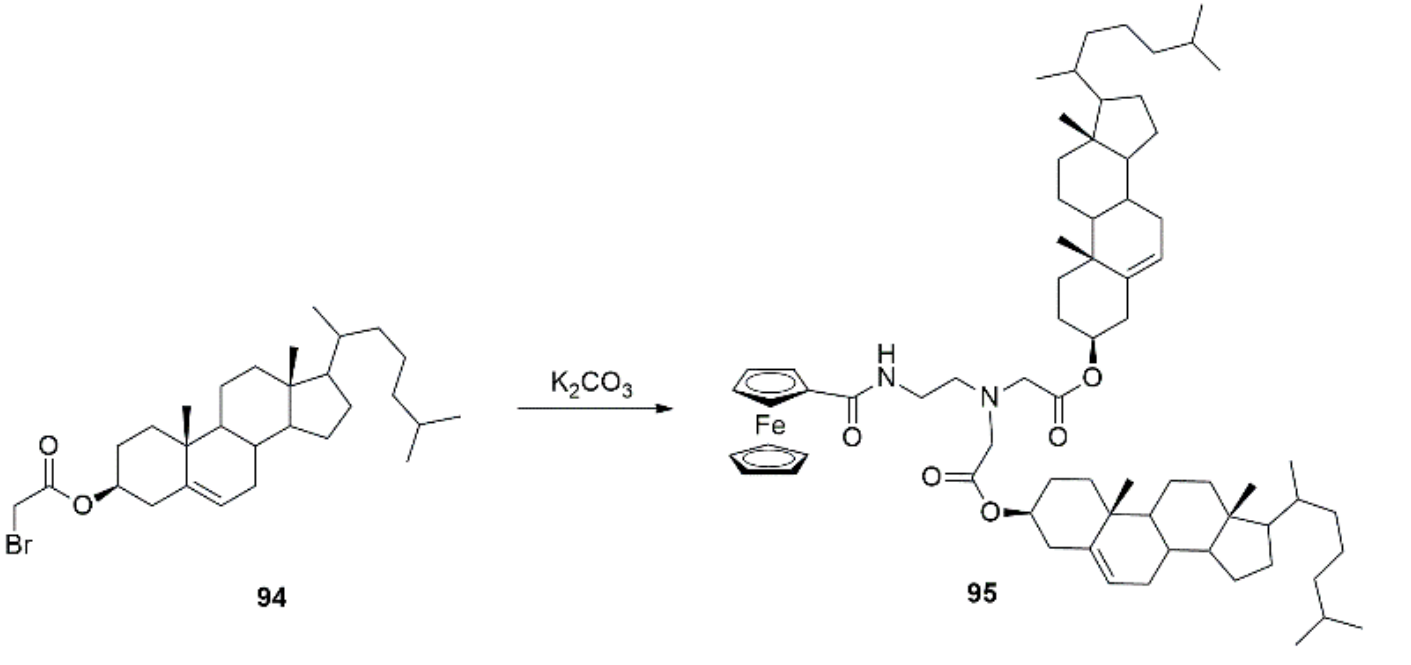
This synthetic strategy effectively integrated the organometallic ferrocene unit with the biologically relevant cholesterol framework, enabling further exploration of their distinct physicochemical and biological properties. In this study, they screened various solvents to identify the gelation properties of these hybrid molecules. They observed that ferrocene-cholesterol compounds exhibit unusual redox-, mechanical-, and ultrasonic-controllable sol–gel phase transition phenomena, highlighting their multifunctional nature and potential applications in material science and biomedicine.

. Fang and co-workers expanded their research by synthesizing ferrocenyl-cholesterol conjugates with an additional cholesterol moiety linked to compound **93** via an amide bond. Synthesis started from compound **91**, which was treated with cholestryl bromide in presence of pottasium carbonate yileded di substituted cholestrol-ferroecene conjugates **95** (Scheme 15) [45].

This modification introduced a second cholesterol unit, further enhancing the structural complexity and enabling detailed investigations into the material properties and biological functionalities of these novel conjugates. The dual cholesterol linkage provided new insights into the gelation behavior, phase transition phenomena, and potential biomedical applications of these ferrocenyl-cholesterol hybrid.



Scheme 14. Synthesis of ferrocene-cholesterol conjugates via amide linkage.



Scheme 15. Synthesis of disubstituted ferrocene-cholesterol conjugates

2.4. Ferrocenyl Nucleobase Conjugates

Ferrocene nucleic acids (FcNAs) combine the biological significance of nucleic acids with the redox activity and stability of ferrocene. These hybrid molecules are of considerable interest due to their potential in applications such as biosensors, electrochemical detection, and targeted drug delivery. The incorporation of ferrocene into nucleic acids can impart enhanced stability, facilitate electron transfer, and enable precise interactions with biomolecules, opening doors to innovations in molecular diagnostics and therapeutics. This area of research has witnessed significant developments, with studies focusing on methods for attaching ferrocene units to nucleobases, sugar-phosphate backbones, or as terminal modifications. Advances in synthetic methodologies have allowed the generation of FcNAs with tailored properties, enabling investigations into their structure-activity relationships, binding efficiencies, and redox-responsive behaviors. Here in this part we are discussing the synthesis of FcNAs conjugates (Figure 7) [46].

Nucleic acid conjugates of ferrocene can be prepared in different two ways: (i) the direct coupling of Fc derivatives, for example an active ester of Fc carboxylic acid, to an end tagged primary amine on the DNA oligonucleotide in solution and (ii) the synthesis of a nucleoside phosphoamidite derivative containing the Fc redox probe and incorporating it at any site during the standard automated DNA solid-phase synthesis or (iii) through coupling metal catalyzed reactions.

Houlton et al explored Sonogashira cross-coupling in the synthesis of ferrocene nucleosides. In this work they reported the synthesis of ferrocenyl-nucleoside, 5-ethynylferrocenyl-2'deoxycytidine has been prepared by Pd-catalyzed cross-coupling between ethynylferrocene and 5-iodo-2'-deoxycytidine **97** (Scheme 16). The alkyne **98** further proceeded to reduction reaction using insitu generated nickel boride to get **100** [47].

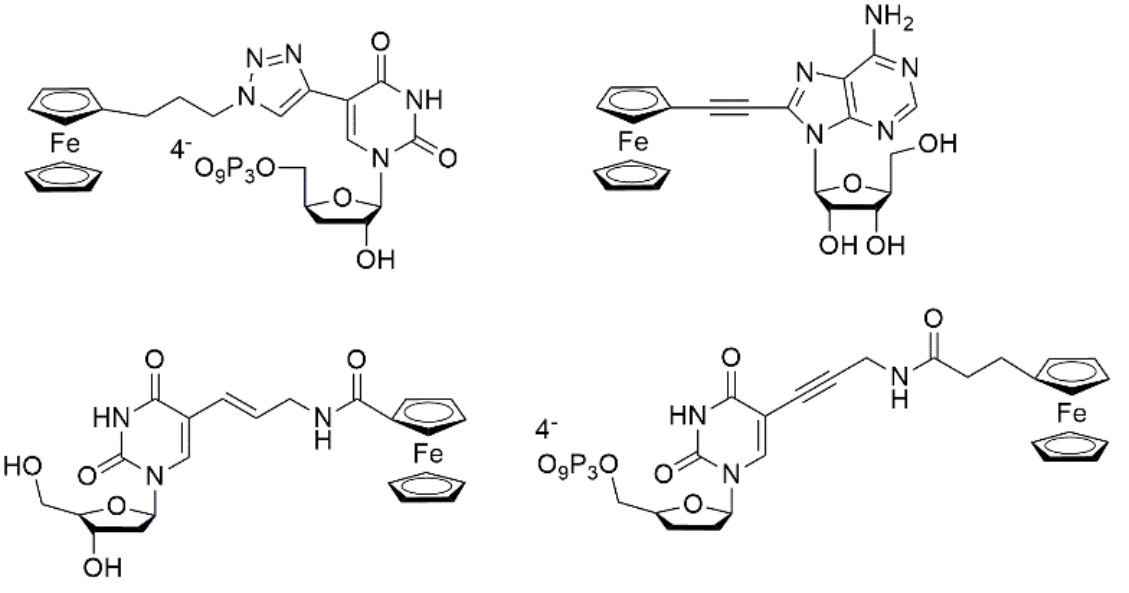
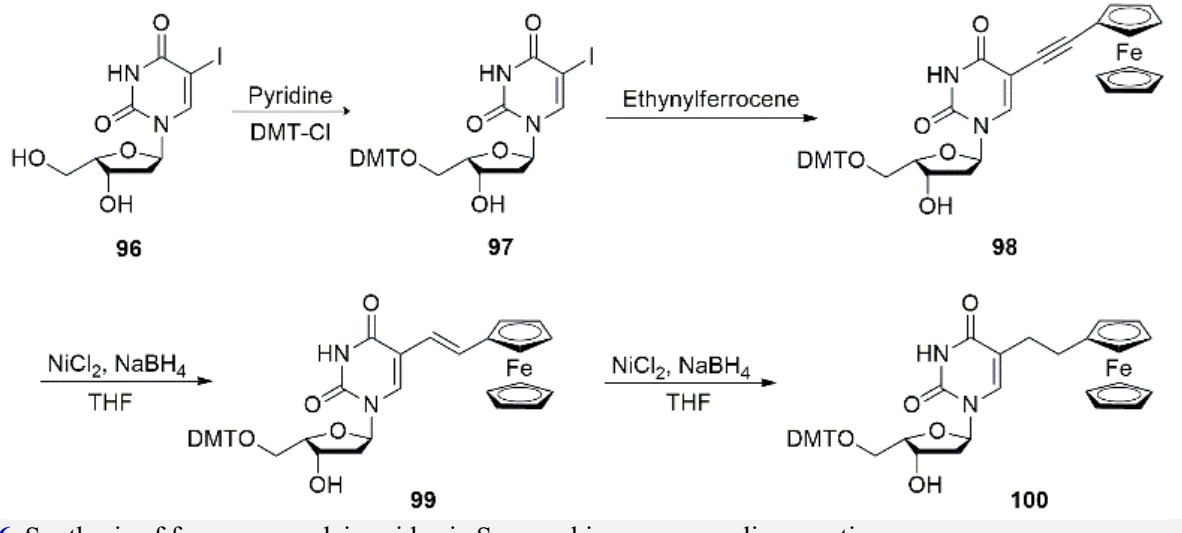


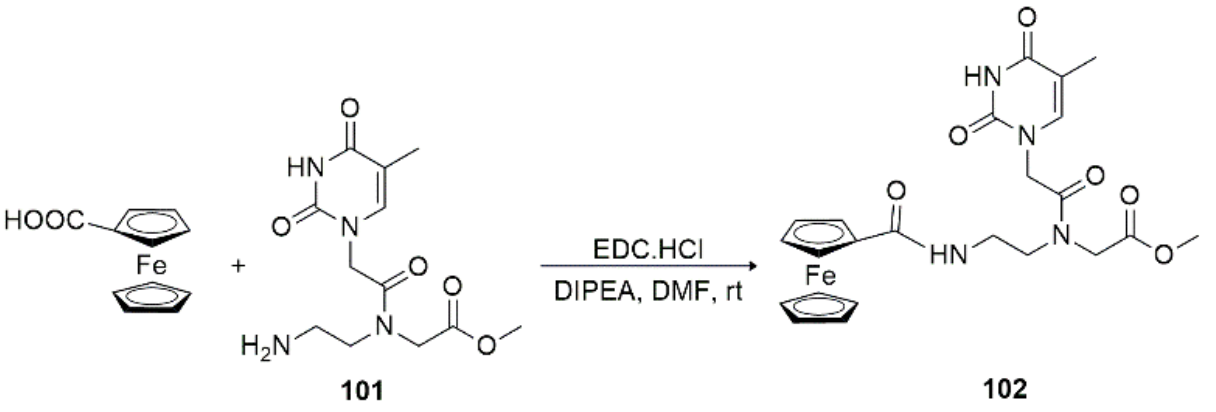
Fig. 7. Ferrocene-Nucleobase Conjugates



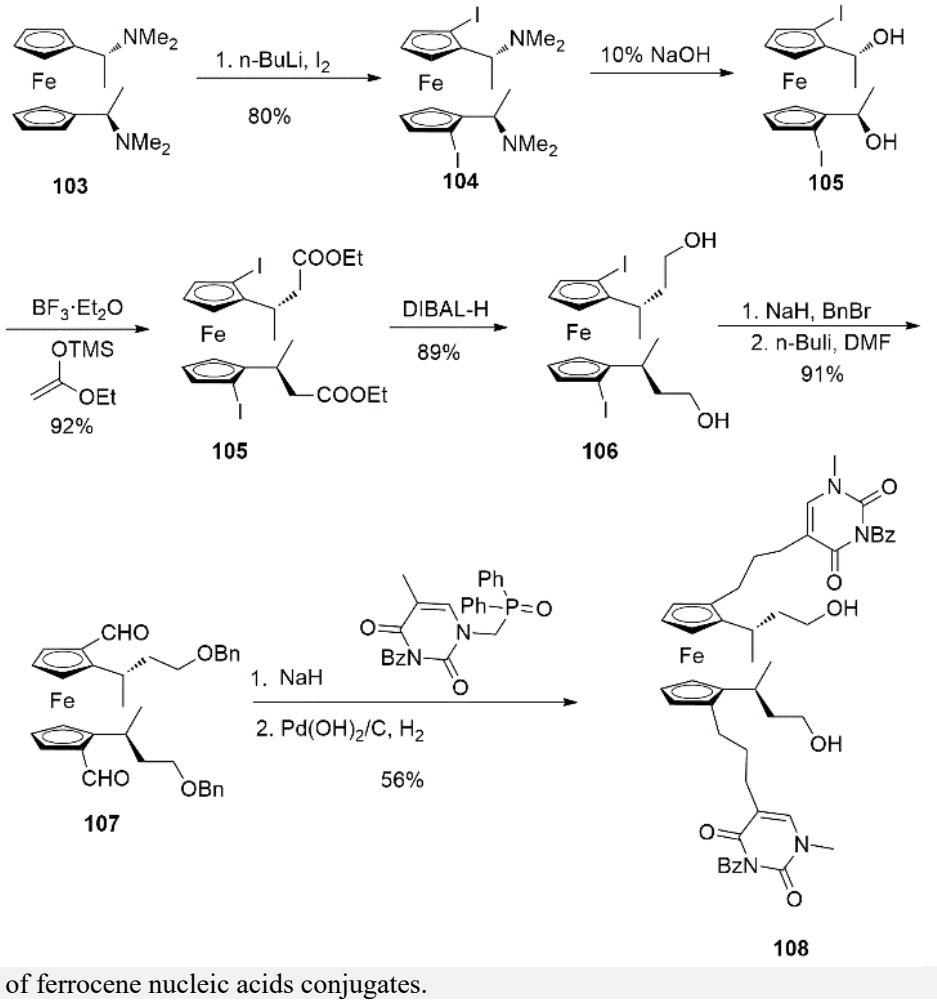
Scheme 16. Synthesis of ferrocene nucleic acids via Sonogashira cross-coupling reaction.

Ferrocene nucleosides **102** were synthesized by conjugating ferrocene carboxylic acid with amine **101** using the coupling reagent EDC·HCl and *Hünig's base* in dimethylformamide (DMF) as the solvent. This approach facilitated efficient amide bond formation, yielding the desired ferrocene-conjugated nucleoside derivatives under mild reaction conditions (Scheme 17) [48].

Tucker A and cowrokers reported the synthesis of ferrocene nucleic acid oligomer as an organo metallic structural mimic of DNA [49] (Scheme 18). Inorder to have the stereochemical control, two centrally chiral stereocenters were introduced into the linker arms, initiating the synthesis with ferrocenyl bis-amine **103**. This modification enabled a diastereoselective ortho-lithiation and iodination process, confirmed through chiral HPLC analysis. Subsequently, the synthesized compound was treated with 10% sodium hydroxide to get the intermediate **104**. This intermediate was further treated with silyl ketene acetal and boron trifluoride etherate, resulting in the formation of the bis-ester **105**.



Scheme 17. Synthesis of ferrocene nucleic acids using acid amine coupling reaction



Scheme 18. Synthesis of ferrocene nucleic acids conjugates.

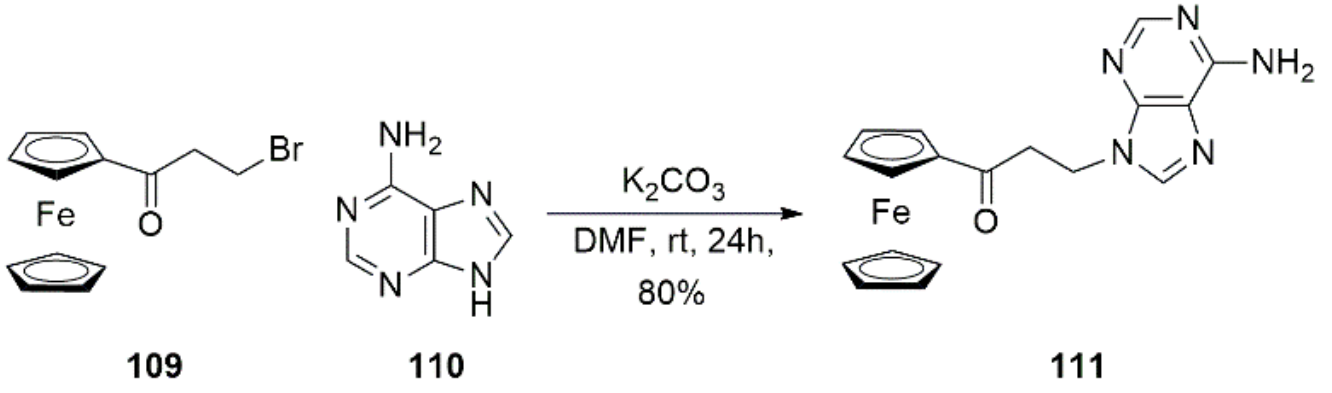
The stereochemistry of the product, encompassing four chiral centers (S, S, Sp, Sp), was conclusively verified via X-ray crystallography. Reduction of the two ester groups produced the bis-alcohol **106**, featuring the intended three-carbon linker arms. To safeguard these groups during further reactions, benzyl protection was employed, leading to the formation of the bis-aldehyde **107**. This compound underwent a Horner–Wittig reaction with benzoyl-protected thymine phosphine oxide, following established protocols. The reaction predominantly yielded olifiene, whose double bonds were subsequently reduced, and the benzyl protective groups were removed through hydrogenation. Finally, in a single-pot process, the thymine groups were deprotected using methylamine to produce the desired diol **108**.

Verma and co-workers reported the synthesis of adenine derivative **111** [50]. The synthesis involved the reaction of easily accessible 3-bromopropionylferrocene **109** with adenine under basic conditions at room temperature (Scheme 19). This alkylation reaction selectively yielded N9-ferrocenylated adenine **111** as the sole product (Scheme 19).

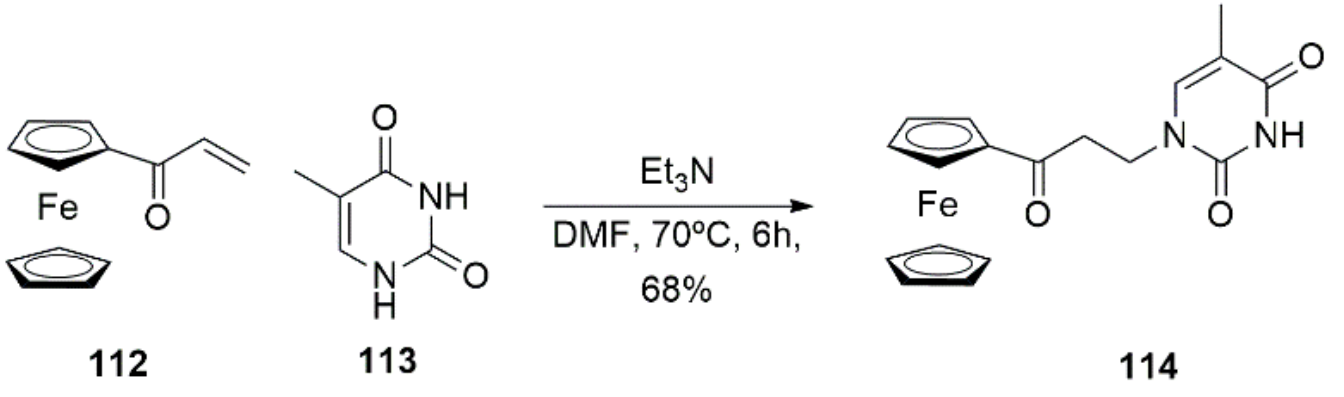
The Michael addition reaction has long been recognized as a versatile synthetic strategy in organic and organometallic chemistry, particularly in the functionalization of nucleobases. In 2012 Kowalski and colleagues were the first to report such a transformation, wherein acryloylferrocene **112**, acting as the Michael acceptor, was reacted with thymine nucleobase **113**, serving as the Michael donor (Scheme 20). This reaction led to the selective formation of an N1-ferrocenylated adduct **114** in a moderate yield of 64%. This study demonstrated the potential of the Michael addition as a synthetic tool for creating novel ferrocenylated nucleobase derivatives, expanding the scope of applications in bioorganometallic chemistry and material science [51].

3. BIOLOGICAL APPLICATIONS OF FERROCENYL CONJUGATES

Ferrocenyl amino acids, carbohydrates, cholesterol, and nucleic acid conjugates have diverse applications in material science. However, our primary focus is on exploring their potential in various biological applications. These conjugates hold promise in areas such as drug delivery, bioimaging, enzyme mimetics, and therapeutic agents due to their unique redox properties, stability, and ability to interact with biological systems. The incorporation of a ferrocenyl group into drug molecules has been shown to significantly influence molecular properties, particularly in terms of reactive oxygen species (ROS) production, redox behaviour, and lipophilicity. Ferrocenyl carbohydrates and imino sugars are known to have antimalarial, antibacterial and anticancer properties.



Scheme 19. Synthesis of ferrocenyl-adenine complex



Scheme 20. Michael addition reaction of acryloyl ferrocene with a thymine nucleobase.

Orvig et al reported the synthesis and biological applications of ferrocene carbohydrates conjugates with chloroquine (Figure 8) [23]. These conjugates show antiplasmodial activity and their strategy was exploring the glucose consumption of parasites' life cycle.

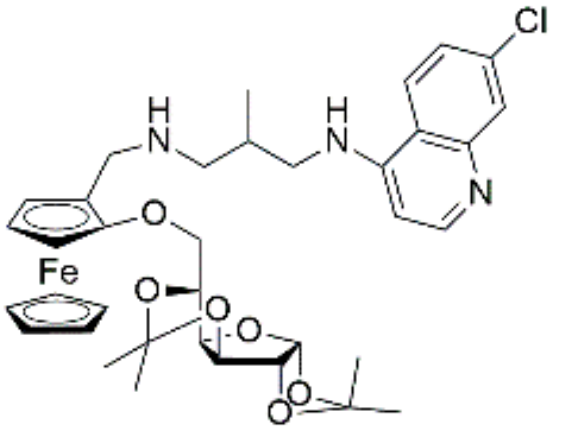


Fig. 8. Ferrocene carbohydrate conjugates with antiplasmodial activity

Orvig et al previously reported that glucose uptake and metabolism are elevated in the parasites life cycle and conjugating with ferrocene can induce the cell death through the inhibiting the detoxification of ferric heme complex, which is toxic for the parasites. Trivedi et al reported the synthesis and biological studies of ferrocenyl boronate esters based on carbohydrates (Figure 9) [22]. Antibacterial activity of these compounds was tested against various bacteria Bacillus subtilis (MTCC 441), Staphylococcus aureus (MTCC 96), and Staphylococcus epidermidis (MTCC 2639) and Gram-negative organisms viz. Escherichia coli (MTCC 443), Pseudomonas aeruginosa (MTCC 741), and Klebsiella pneumoniae (MTCC 618). Compounds were showing very good antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*.

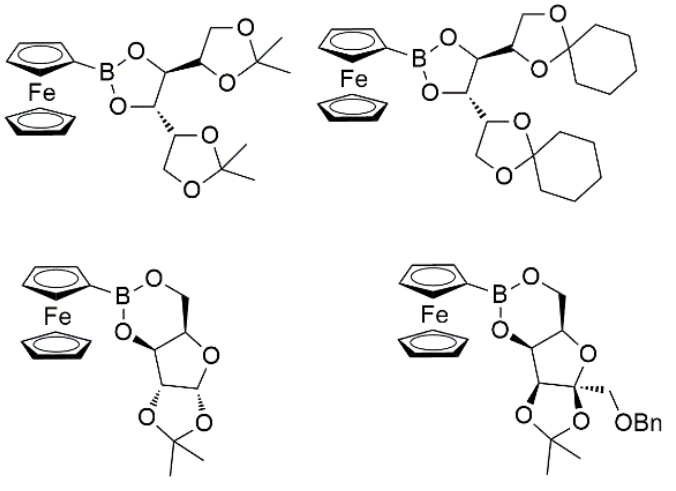


Figure 9: Bioactive ferrocene carbohydrate conjugates

4. CONCLUSION

In conclusion, ferrocene and its derivatives have emerged as versatile and potent moieties due to their unique chemical properties such as aromaticity, lipophilicity, and redox behaviour, making them highly attractive for incorporation into functional molecules. The stability of ferrocene in aqueous and aerobic media, combined with its ability to undergo facile chemical modifications, has led to its wide-ranging applications across industries such as petroleum, textiles, and catalysis. Furthermore, in the realm of medicinal chemistry, ferrocene-based compounds exhibit significant cytotoxic, antianemic, antitumor, and antimalarial properties. Of particular interest are ferrocene-linked biomolecules, such as carbohydrates, amino acids, and nucleic acids, which show promise in enhancing water solubility and biocompatibility while retaining the bioactivity of ferrocene. Recent research has demonstrated the potential of these conjugates in drug development, particularly for antibacterial and anticancer applications. The conjugation of ferrocene with biologically active molecules, such as peptides, nucleic acids, and sugars, continues to be an exciting avenue for future research, offering new possibilities for therapeutic development and advancing our understanding of organometallic biological interfaces.

DECLARATIONS

Ethical Approval

We affirm that this manuscript is an original work, has not been previously published, and is not currently under consideration for publication in any other journal or conference proceedings. All authors have reviewed and approved the manuscript, and the order of authorship has been mutually agreed upon.

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Availability of data and material

All of the data obtained or analyzed during this study is included in the report that was submitted.

Conflicts of Interest

The authors declare that they have no financial or personal interests that could have influenced the research and findings presented in this paper. The authors alone are responsible for the content and writing of this article.

Authors' contributions

All authors contributed equally in the preparation of this manuscript.

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ABOUT THE AUTHORS

Dr. Anija Mol T. Philip is an accomplished academic currently serving as an Assistant Professor in the Department of Chemistry at Hislop College, Nagpur. She earned her Ph.D. in Organic Chemistry from the prestigious Indian Institute of Technology (IIT) Kanpur in 2016. During her academic journey, she qualified for several competitive exams, including UGC-JRF, UGC-NET, and GATE, reflecting her strong academic foundation. Following her doctoral studies, Dr. Philip gained valuable research experience as a Postdoctoral Researcher at the University of Kansas from February 2017 to July 2019. Her diverse research interests span natural product synthesis, organocatalysis, asymmetric synthesis, peptide synthesis, and Alzheimer's drug discovery. She has made significant contributions to the scientific community, publishing seven international articles and two national articles in reputed journals. Dr. Philip's dedication to her field has been recognized with several awards, such as the Best Poster Presentation Award at the Royal Society of Chemistry (RSC) Conference held at IIT Kanpur and the Best Oral Presentation Award at the International E-Conference on Recent Advances in Chemical Sciences (E-ICRACS-21). Additionally, she has successfully secured two minor research projects funded by Nagpur University, highlighting her active involvement in research and innovation. Her work continues to contribute meaningfully to the advancement of chemical sciences.

Dr. Mayur V. Khedkar is an accomplished academic currently serving as an Assistant Professor in the Department of Chemistry at Hislop College, affiliated with Rashtra Sant Tukadoji Maharaj Nagpur University, Nagpur, Maharashtra. He earned his Ph.D. from the prestigious Institute of Chemical Technology (ICT), Matunga, Mumbai. During his master's studies, he successfully cleared the CSIR NET (JRF) and GATE examinations, demonstrating his strong academic credentials.
Dr. Khedkar has a rich teaching and research experience spanning 14 years. He has authored over 15 research papers published in internationally reputed journals, achieving an impressive H-index of 12, which underscores the impact of his work in the scientific community. He actively mentors students for their research projects and doctoral studies, contributing to the development of future scientists and researchers. His excellence in research has been recognized with the Royal Society of Chemistry (RSC) Best Research Paper Award. In addition to his academic and research activities, Dr. Khedkar is passionate about science popularization and participates actively in initiatives to promote scientific awareness. He has also successfully secured one minor research project funded by Nagpur University, further highlighting his commitment to advancing chemical sciences.

Dr. Shoeb R. Khan is an accomplished academic currently serving as an Assistant Professor in the Department of Chemistry at Hislop College, Nagpur. He earned his Ph.D. in Organic Chemistry from the prestigious Institute of Chemical Technology (ICT/UDCT), Mumbai. Dr. Khan has demonstrated his academic prowess by qualifying in various competitive examinations, including CSIR-JRF, UGC-NET, and SET. Dr. Khan has extensive research experience, having worked on projects related to transition metal catalysis and hydroformylation reactions. His scholarly contributions include 10 international publications, two national papers, and one book chapter published by Nova Science Publishers. His impactful research is reflected in his h-index of 9 and over 240 citations. Dr. Khan has been recognized for his research excellence, receiving awards for the best poster and oral presentations at international conferences. As an RTMNU-approved postgraduate teacher and research guide, he currently supervises one Ph.D. student in Chemistry. A dedicated science communicator, Dr. Khan actively organizes sessions titled "Hands-on Activity in Chemistry" for schools and colleges in Nagpur to promote chemical sciences among students. He has also served as a resource person for the India International Science Fair (IISF) from 2016 to 2023 and is a key science expert for Royal Society of Chemistry (RSC) workshops at VNIT, Nagpur. Additionally, he contributes to the India International Science Festival-Student Science Village (IISF-SSV), an initiative of DST, Government of India, and VIBHA, since 2016.

Dr. Shibin Chacko is an accomplished academic and researcher, currently serving as an Assistant Professor in the Department of Chemistry at Hislop College, Nagpur. He holds a Bachelor's degree in Polymer Chemistry from Calicut University, where he excelled academically and was awarded the university gold medal in 2007 for securing the first rank. He subsequently completed his Master's degree from the School of Chemical Sciences, Mahatma Gandhi University, Kottayam. Dr. Chacko demonstrated academic brilliance by qualifying in several competitive examinations, including CSIR-JRF (AIR 105), UGC-NET, and GATE. He earned his Ph.D. in Chemistry from the prestigious Indian Institute of Technology Kanpur (IIT Kanpur), where he worked on cutting-edge

research. Following this, he undertook postdoctoral research in medicinal chemistry at two globally renowned institutions, Brandeis University and the University of Kansas, where he contributed to advancing drug discovery methodologies. Dr. Chacko has made significant contributions to the field of chemistry through his extensive publication record, which includes 23 international and 2 national papers in highly reputed journals. He has also authored five book chapters, reflecting his expertise and thought leadership in the domain. His excellence in research has been recognized through several awards, including the prestigious first prize ($20,000) in the Brandeis SPROUT 2017 competition. Additionally, he has been the recipient of three minor research project grants from RTM Nagpur University. Dr. Chacko has received numerous accolades for presenting his research at international conferences, including six Best Oral Presentation Awards and one Best Poster Presentation Award. His research interests lie in developing chemical tools to address major health challenges, focusing on infectious diseases and cancer.

