Potential Applications of Ferrocene as a Structural Feature in Antioxidants

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Abstract: Comparing with the wide usage of ferrocene in novel materials, ferrocene was unusually applied to be a structural feature in designing drugs even though some researchers pointed out that ferrocene and its derivatives possessed potential pharmacological applications. This was due to that low polarity limited bioavailability of ferrocene *in vivo*. Since ferrocene was inert to the oxidation at atmosphere, it was deduced that synthetic derivatives of ferrocene may be a novel kind of antioxidant, in which other organic groups may enhance the bioavailability of ferrocene, or large conjugated system formed among ferrocenyl and other organic groups may increase the antioxidant effectiveness. Thus, synthetic derivatives of ferrocene were divided into nonconjugated and conjugated ones in this review. For nonconjugated ferrocenyl derivatives, carbon chain or simple group attached one or two cyclopentadienyl rings in ferrocene to form a novel molecule with ferrocenyl group. The aim of synthesis of nonconjugated ferrocenyl compounds was to increase the bioavailability of ferrocene *in vivo*. On the other hand, the conjugated ferrocenyl derivatives referred to introduce other group to form a conjugated system with the cyclopentadienyl ring in ferrocene. The large conjugated system was beneficial for the single electron to dispense among the whole molecule while forming radicals, and enhanced the antioxidant capacity of the whole molecule. This review summarized the potential usage of ferrocene in antioxidants.

Keywords: Ferrocene, antioxidant, oxidation, free radical, drug design.

INTRODUCTION

The deterioration of the environment played an important role in generating reactive oxygen species (ROS) *in vivo*. Lipid, DNA and protein were targets to be oxidized when a healthy organism was subjected to the oxidative stress for a long period, called environmental-induced carcinogenesis [1]. Even the bad custom in every life such as smoking and overdrinking may also be an initiator of oxidative stress, accelerating ageing consequently [2]. In addition to the regulation for some incretion in metabolism to hinder the oxidative stress [3], most concern has been focused on the functions of polyphenols as antioxidants, which protected human organism against oxidative stress [4]. Furthermore, the antioxidant effectiveness of phenylpropanoids [5] and flavonoids [6] in some plants has been investigated in detail [7], and some novel methods have been developed to screen the effectiveness of antioxidants promptly [8]. Because of the importance of antioxidants to maintain health and to cure ROS-induced diseases, designing antioxidants with novel structures was an attractive research field in organic and medicinal chemistry.

Ferrocene (dicyclopentadienyl iron, Fc) was widely used to modify the electrode in the research of electroanalysis, to synthesize organometallic compounds, and to prepare optical materials. For the physiological research, ferrocenium salt has been found to have antineoplastic activity because the ionic form enhanced the bioavailability of ferrocene *in vivo* [9]. However, recent research indicated that ferrocene was able to enhance hepatic malondialdehyde (MDA) in mice, implicating that ferrocene could induce lipid peroxidation in hepatocyte [10]. Indeed, as shown as equation (1), an *in vitro* oxidation of cyclopentadienyl ring and iron atom may help us to understand the cytotoxic role of the oxidative products from ferrocene [11].

Equation (1) indicated that ferrocene can be oxidized, and thus, it may be oxidized before other substrates were oxidized. If ferrocene was connected with other organic antioxidant molecules, the obtained ferrocenyl compounds were polar molecules, and may possess higher antioxidant capacities. These antioxidants with ferrocenyl structural feature may be the candidates of novel drugs to treat ROS-induced diseases. This paper introduced some findings on the pharmacology of ferrocene firstly, and then summarized the synthetic ferrocenyl compounds by assorting them as nonconjugated and conjugated derivatives. In addition, the potent antioxidative effectiveness was deduced on the basis of structure-activity relationship of antioxidant.

1. NONCONJUGATED FERROCENYL DERIVATIVES

1.1. Ferrocene with Alkyl Substituent

The early investigation on the physiological effect of ferrocene was performed by supplementing ferrocene to experimental rats on a diet for a few months. It was found that non-heme iron and lipid hydroperoxides in ferrocene-treated rats increased significantly, indicating that ferrocene caused liver injury [12]. Moreover, hepatic lipid peroxides and 8-hydroxydeoxyguanosine increased significantly when Wistar albino rats were supplemented by ferrocene and ethanol.

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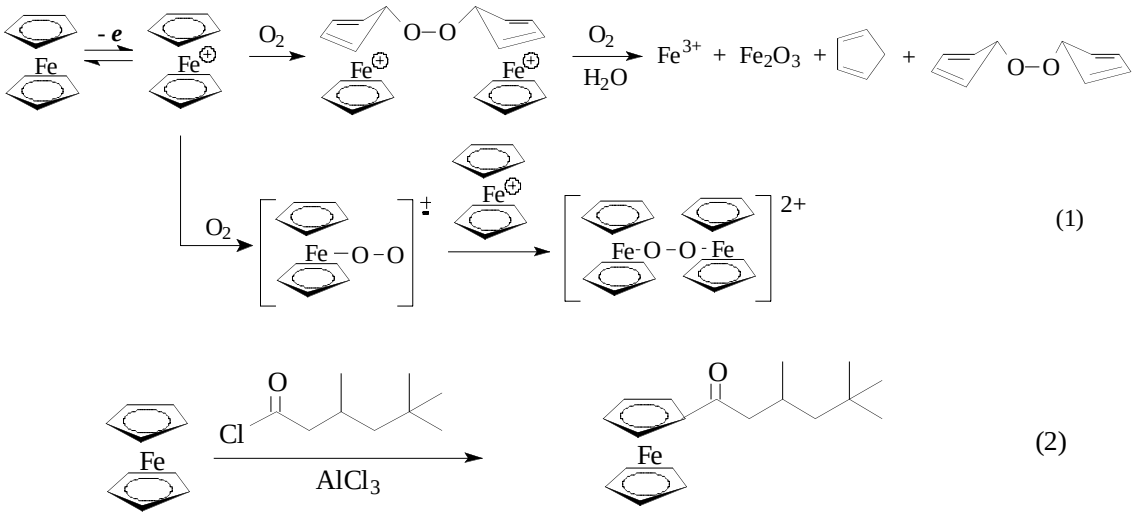


3,5,5-trimethylhexanoyl ferrocene (TMH-ferrocene)

This *in vivo* experimental result revealed that ferrocene and alcohol acted as hepatocarcinogen by generating hydroxyl radicals [13]. Therefore, it was necessary to modify ferrocene in order to decrease the side-effect of ferrocene employed directly. Acyl halide linked with cyclopentadienyl ring to form an alkyl ferrocenyl ketone by Friedel-Crafts reaction as shown as equation (2).

An *in vitro* model was established to analyze the oxidative death of astrocytes isolated from primary mouse, in which *tert*-butyl hydroperoxide acted as an exogenous peroxide to initiate the oxidation, and lactate dehydrogenase was measured to be the index of astrocytes losing viability. While astrocytes were treated by 3,5,5-trimethylhexanoyl ferrocene (TMH-ferrocene) in advance, they were more sensitive to the attack from *tert*-butyl hydroperoxide because TMH-ferrocene decreased the ability of mitochondria to response the oxidative stress [14]. In addition, when Fischer 344 rats were supplemented by TMH-ferrocene dietary, oxidative damage took place in liver because the iron concentration in the liver was found to increase markedly even though the endogenous antioxidant defense system including α-tocopherol (TOH) and glutathione (GSH) were still maintained perfectly [15].

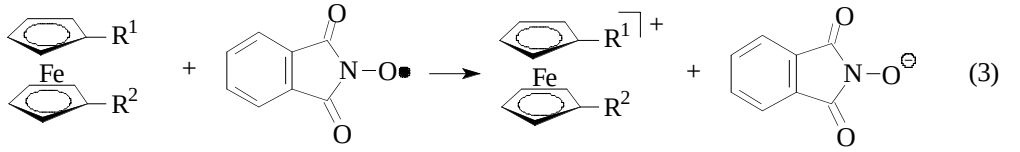
A recent report based on the interaction between simple-substituted ferrocene and phthalimide-*N*-oxyl radical may help us to explain the side-effect of ferrocene *in vivo*. As shown as equation (3), an electron in ferrocene derivative transfered to phthalimide-*N*-oxyl radical, forming ferrocenium cation. The rate constant for the electron transfer was related to the oxidation potential of substituted ferrocene [16]. Thus, it may safely assume that radicals generated from the metabolism had possibility to oxidize ferrocene *in vivo*. Then, the oxidative products derived from the decomposition of ferrocenium cation accumulated in organism, and did harm to health eventually.

1.2. Ferrocene with Complicated Substituent

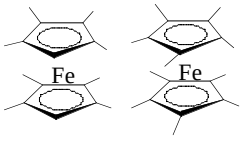
The negative results derived from ferrocene did not retard researchers to explore the function of ferrocene derivatives on various models of pharmacological experiments. So, researchers synthesized much more ferrocene derivatives with more complicated substituents. It was found that ferrocenyl group can decrease cytotoxicity of some drugs. For example, retinoids and retinoic acids were toxic at high dosage when they were employed to prevent cancer in mammals. As shown as equation (4), ferrocenyl alcohol was connected with 13-*cis*-retinoic acid by Mitsunobu reaction, leading to a stronger antiproliferative activities than that of retinoic acid [17].

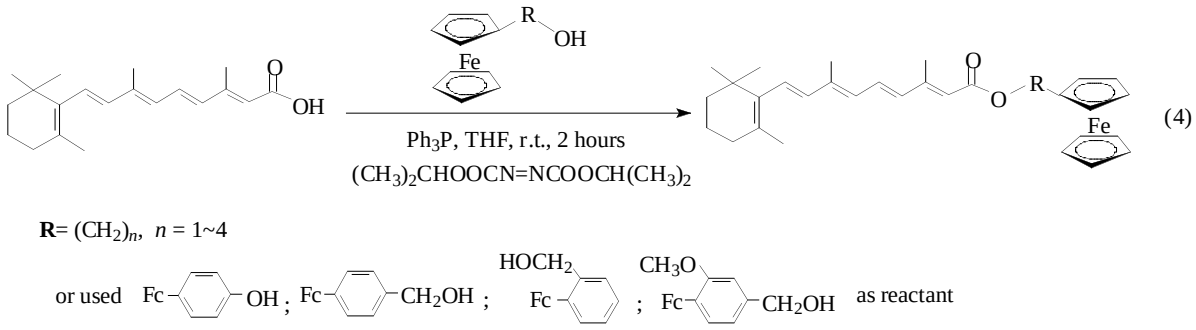
Ferrochloroquine (structure shown in Scheme **1**), a ferrocene analog of chloroquine, was found to be active against resistant strains of *Plasmodium* [18].

Acetyl ferrocene can form chalcones with a variety of aromatic aldehyde by the reaction of Claisen-Schmidt con-

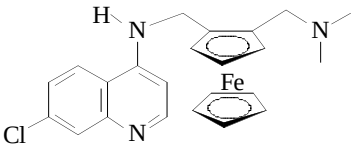


R¹ = **R²** = H
R¹ = C_2H_5 ; **R²** = H
R¹ = $COOC_2H_5$; **R²** = H
R¹ = $CONH_2$; **R²** = H
R¹ = **R²** = CH_3
R¹ = CH_2CN ; **R²** = H
R¹ = CH_2OH ; **R²** = H





densation as shown as equation (5), while ferrocenecarboxyaldehyde can also form chalcones with acetyl-substituted aromatic compounds by the same reaction. The obtained chalcones were found to influence antiplasmodial activity, among which chalcones derived from acetyl ferrocene behaved more selective and potent antiplasmodial activities than those from ferrocenecarboxyaldehyde. This was due to the polar carbonyl linkages attenuated lipophilicities of these chalcones, and increased the affinity to biological tissues. In particular, the half concentration (IC_{50}) of 1-ferrocenyl-3-(4-nitrophenyl)prop-2-en-1-one against KB3-1 cells was as low as 4.6 μM. Moreover, the free-radical-scavenging activities of ferrocene-related chalcones were explained by interacting these chalcones with 2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonate) cation radical ($ABTS^{+\cdot}$), and by measuring the rate of them to trap α-phenyl-tert-butylnitrone (PBN) and 5,5-dimethylpyrroline-*N*-oxide (DMPO) by means of electron paramagnetic resonance (EPR). It was concluded that the incorporation of ferrocene enhanced the abilities of chalcones to quench free radicals [19].

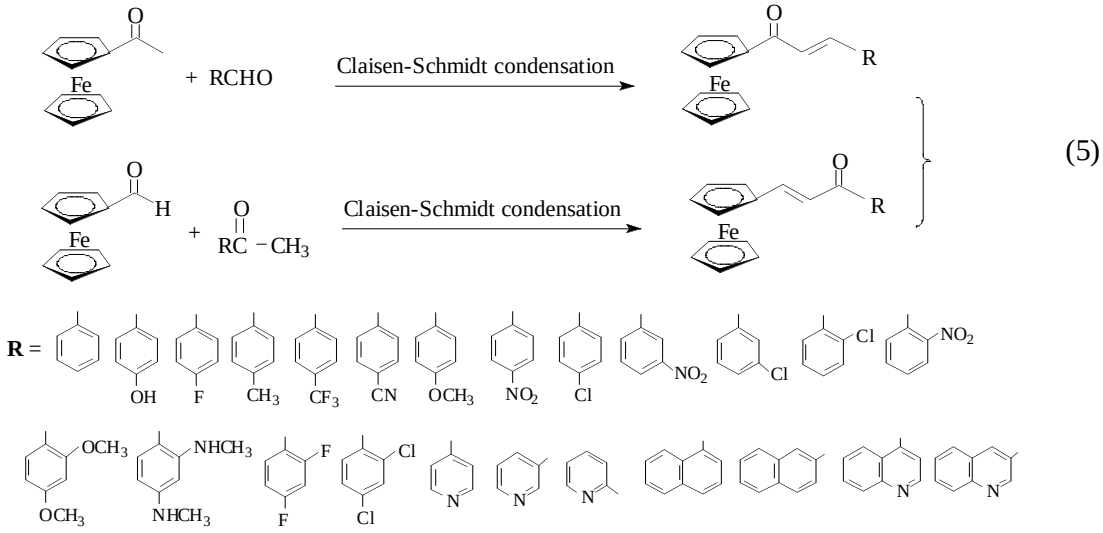


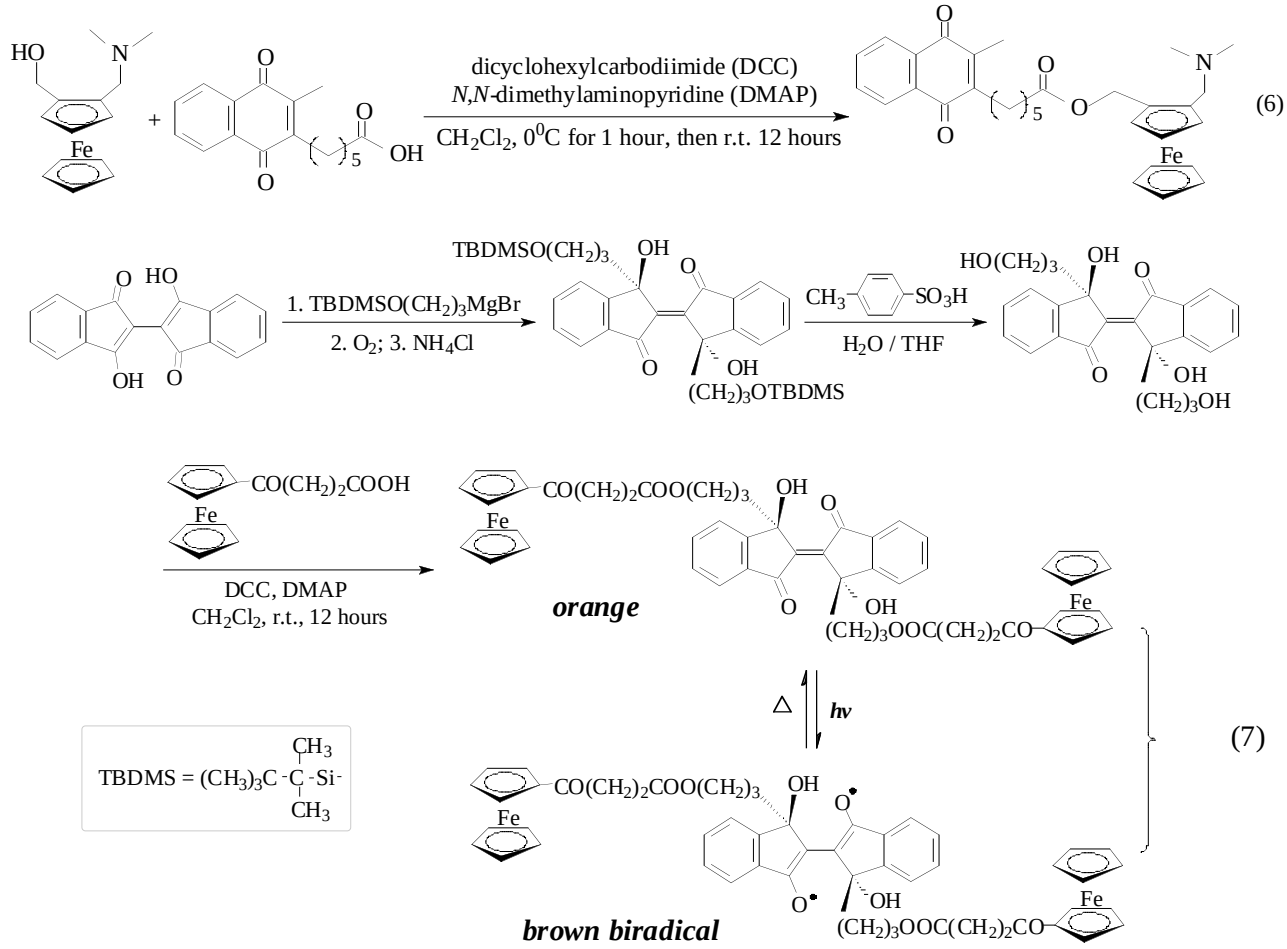
Scheme 1. Structure of ferrochloroquine.

6-[2'-(3'-Methyl)-1',4'-naphthoquinolyl]hexanoic acid (structure shown in equation (6)) was able to inhibit the malarial parasitic *Plasmodium falciparum*. But this menadione exhibited an uncompetitive inhibition to nicotinamide adenine dinucleotide phosphate (NADPH) and to glutathione disulfide. As shown as equation (6), when the carboxylic group in menadione was esterified by 2-(*N*,*N*-dimethylaminomethyl)ferrocenylmethanol, the polarity of the carboxylic acid of menadione was attenuated, and the IC_{50} even decreased to 1.0 μM against the chloroquine-resistant strain [20].

As shown as equation (7), the carbonyl group in 2,2'-biindanylidene-1,1',3,3'-tetraone reacted with Grignard reagent to increase the length of the carbon chain, and then, the formed hydroxyl was esterified by ferrocenoyl carboxylic acid [21]. The product transformed into a brawn biradical under irradiation, in which the biradical form was identified by electron spin resonance (ESR). Alternatively, the brawn biradical can convert into original orange compound under heating. So, this compound was a photochromic material. Hence, the biradical form of the product may be useful to screen the abilities of antioxidants to scavenge radical because the donation of hydrogen atom from antioxidants to the biradical can alter the color of the compound from brawn to orange.

Hydroxyl-substituted Schiff bases exhibited free-radical-scavenging properties [22] and can protect DNA [23] and





(6)

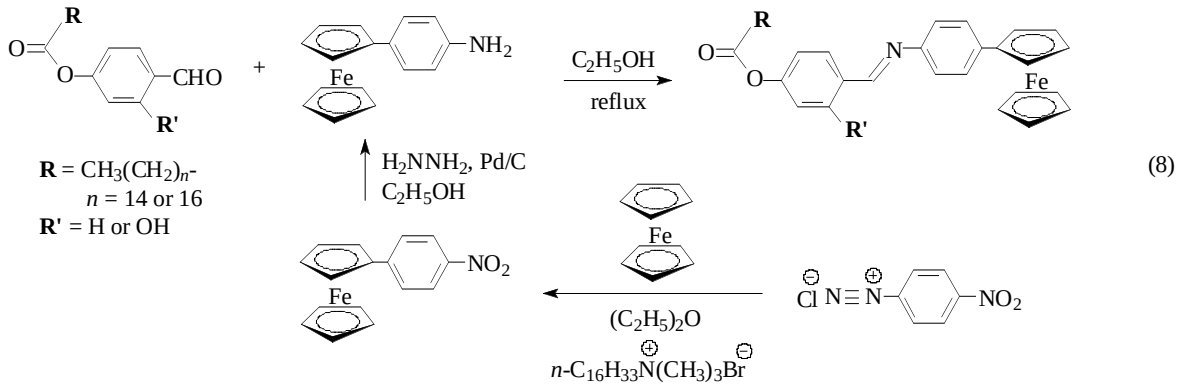
(7)

erythrocytes [24] against peroxyl-radical-induced oxidation. Diazonium salt of 4-nitroaniline reacted with ferrocene to link benzene ring and ferrocene, then ferrocenyl Schiff bases were prepared according to equation (8). The products can trap radicals and can protect DNA against ROS-induced oxidation. Ferrocenyl-related Schiff bases showed high antitumor activities [25].

1.3. Ferrocene-Related Peptide Conjugates

The aim of synthesis of ferrocene-related peptide was to monitor the interaction between organic substrates and the peptide chain, and to make biosensors. As shown as equation (9), ferrocenoyl group linked with glycylcystamine to obtain a ferrocene-related peptide [26].

The hydroxylmethyl attaching to cyclopentadienyl rings of ferrocene was of importance to generate carbocation because the reactivity of ferrocenylmethanol was similar to that of benzyl alcohol. The hydroxyl group in ferrocenylmethanol can be eliminated by trifluoroacetic acid to form a carbocation, which was able to attack –SH in glutathione to form a peptide glutathione containing ferrocene as shown as equation (10) [27]. After the obtained compound ($FcCH_2SG$, SG = glutathione moiety) reacted with a base to form salt, the



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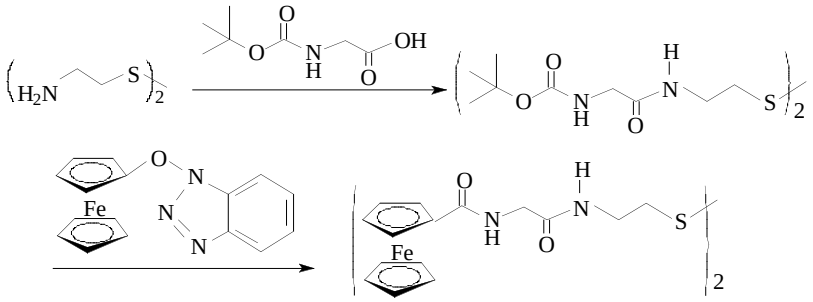

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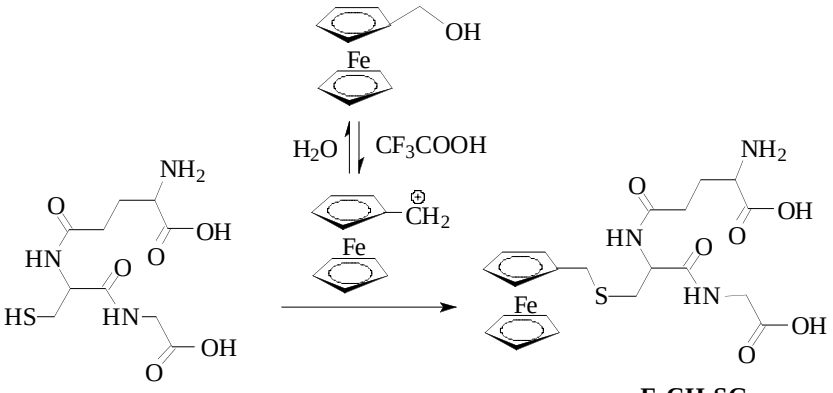


FcCH$_2$SG

(10)

electrooxidation reactions of $FcCH_2SG^-$ exhibited two consecutive steps represented as $FcCH_2SG^- \rightarrow Fc^+CH_2SG^- + e$ and $FcCH_2SG^{2-} \rightarrow Fc^+CH_2SG^{2-} + e$, respectively [28].

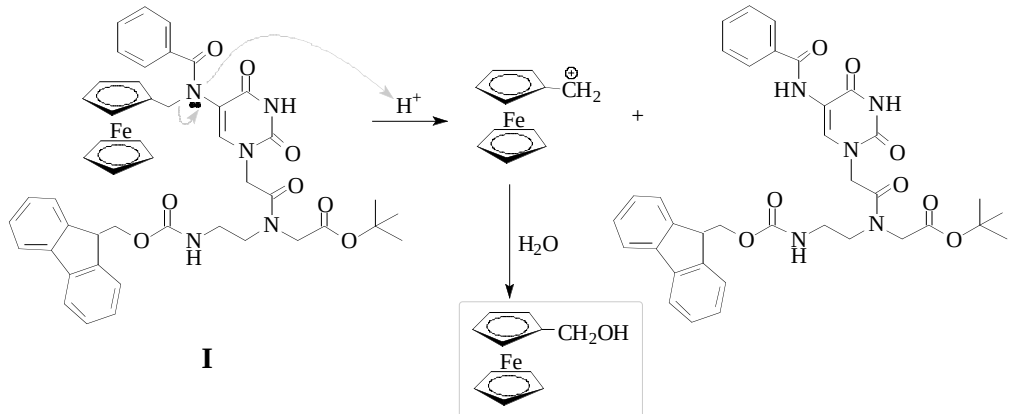
Ferrocenylmethanol was generated as a byproduct in the hydrolysis of ferrocenyl uracil peptide nucleic acid (PNA) monomer (**I**). The formation of ferrocenylmethanol can be deduced by equation (11). Ferrocenylmethyl carbocation was an intermediate formed by the breakage of C-N in the presence of H^+, and then, the carbocation combined with water to form ferrocenylmethanol [29].

Ferrocenecarboxylic acid can be amidated by aminopyridine as shown as equation (12) [30].

Furthermore, when two cyclopentadienyl rings in ferrocene were all amidated, hydrogen atom in N-H bond from one amide chain formed a hydrogen-bond with the oxygen atom from carbonyl group in another amide chain as shown as Scheme **2**, leading to Herrick, van Staveren, and open conformation, respectively [31].

The amides formed in two cyclopentadienyl rings of ferrocene with the different conformations made 1,1'-ferrocene dicarboxylic acid an reagent, which can be applied to isolate amino acid. As shown as equations (13,14), a mixed ester of two amino acids can be isolated after they reacted with 1,1'-ferrocene dicarboxylic acid to form three amides [31].

The linkage of ferrocene and peptide enhanced the bioavailability of ferrocene in protein and in other biological issues. Two amidated ferrocenoyl peptide bioconjugates, Fc-Orn-Orn-Orn and Fc-Tyr-Orn-Orn-Orn (structures shown in Scheme **3**), were prepared by using solid phase peptide synthesis method, and were regarded as the mimics of superoxide



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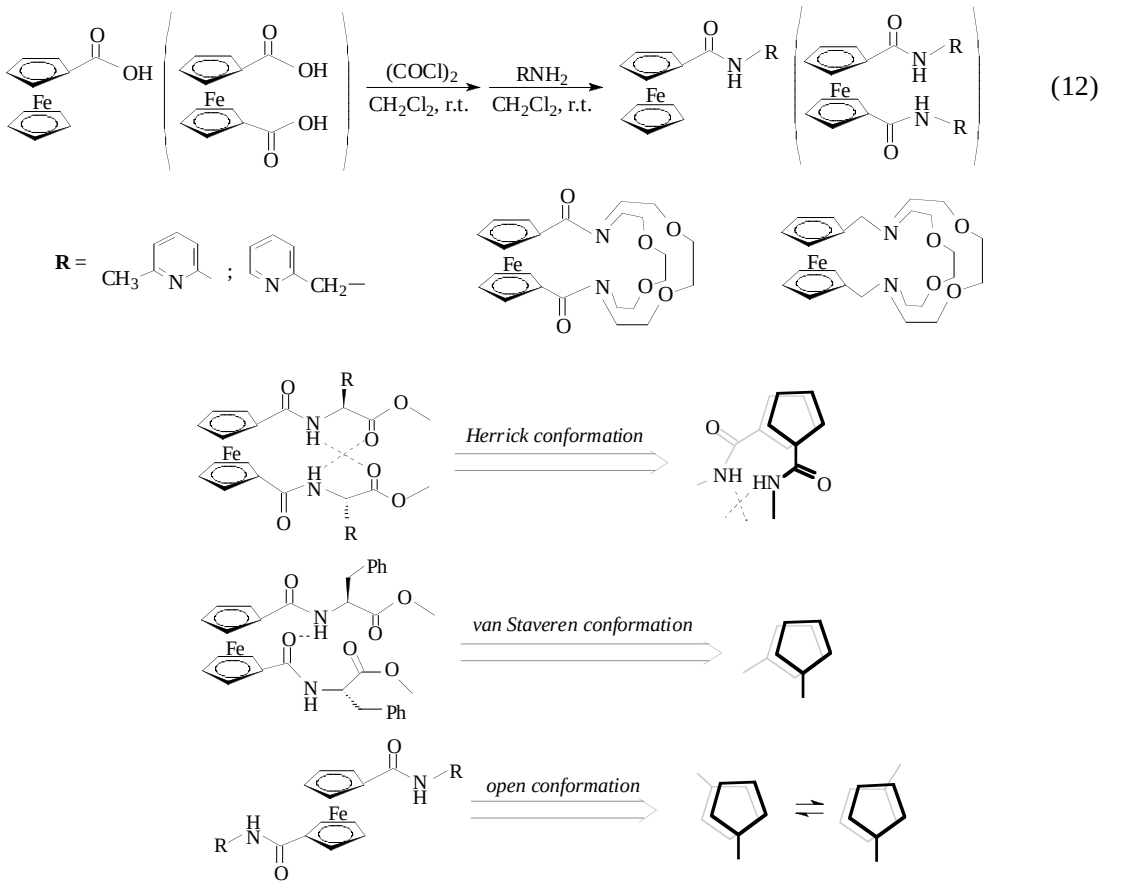
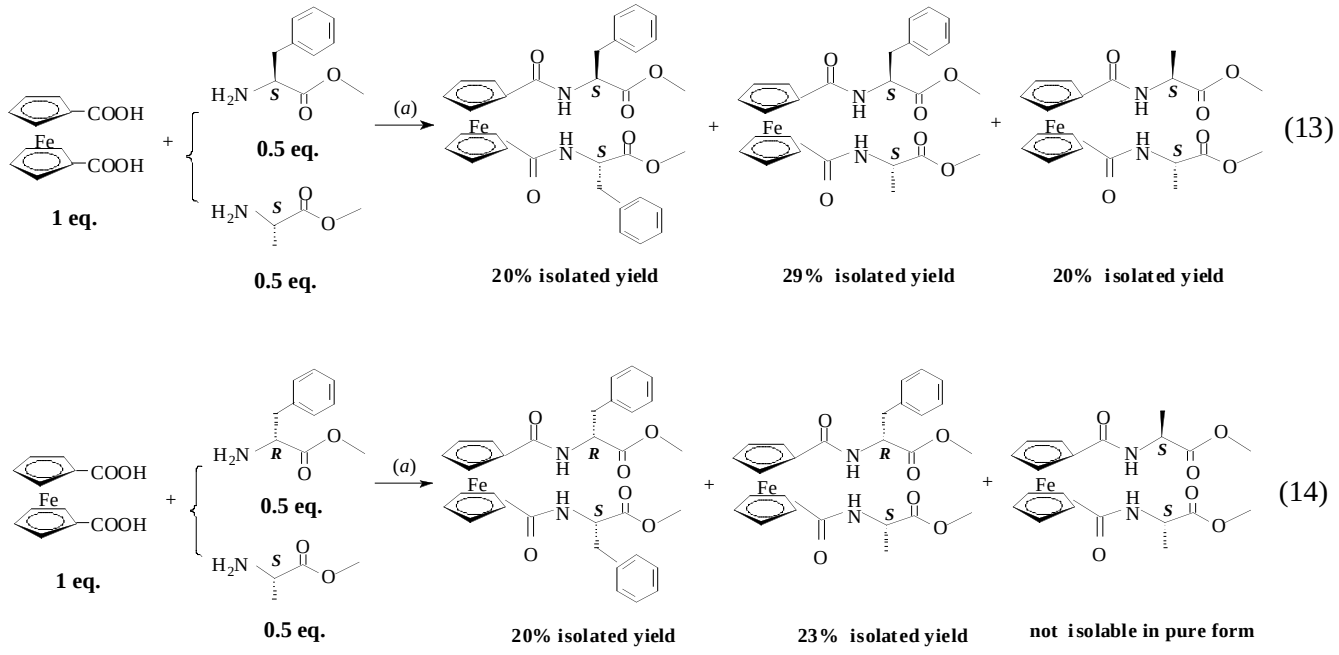
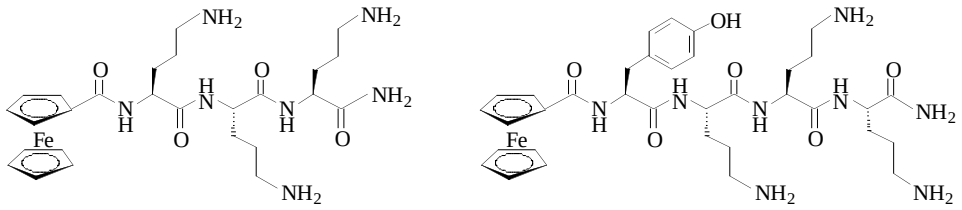


Scheme 2. Herrick, van Staveren, and open conformation of ferrocene-related amides.



(*a*): *O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HBTU, 1 eq.), 1-hydroxybenzotriazole (HOBt, 1 eq.), *N*,*N*-diisopropylethylamine (DIPEA, 4 eq.).



Fc-Orn-Orn-Orn **Fc-Tyr-Orn-Orn-Orn**

Scheme 3. Structures of ferrocenoyl peptide bioconjugates, Fc-Orn-Orn-Orn and Fc-Tyr-Orn-Orn-Orn.

dismutase (SOD) isolated from *Escherichia coli*. Both of them can inhibit peroxynitrite-mediated tyrosine nitration, during which the IC_{50} of Fc-Orn-Orn-Orn and Fc-Tyr-Orn-Orn-Orn were 575 μM and 310 μM, respectively [32].

The compounds included in equations (11,12,13,14) and Scheme **3** seemed not related to antioxidants. But it has been reported that N-H in phenothiazine [33] and indole [34] together with amidated N-H in lidocaine [35] and melatonin [36] were able to scavenge free radical, thus it is worthy to investigate whether the compounds shown in equations (11,12,13,14) and Scheme **3** are active to scavenge free radicals because these compounds are amides and contain N-H bonds. It is also expected that hydrogen bond formed between two amide chains as shown in equations (12,13,14) may largely change the antioxidant ability.

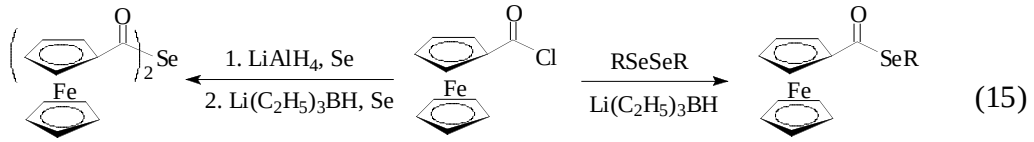
1.4. Ferrocene-Related Organoselenium Compounds

After formate dehydrogenase and glycine reductase were proved to be organoselenium compounds, the *in vivo* biochemical investigations revealed that selenium acted as the active motif of glutathione peroxidase, an antioxidant enzyme. A large body of organoselenium compounds has been synthesized in order to explore the antioxidant capacities, and to explain the antioxidant mechanism [37]. The development of synthetic organoselenium compounds inevitably quested for ferrocene as a structural feature in organoseleniums. The simplest preparation of ferrocene-related selenium was shown in equation (15), in which ferrocenoyl chloride reacted with RSeSeR to form ferrocenoyl organoseleniums in the presence of $Li(C_2H_5)_3BH$, or to bridge two ferrocenoyl groups with Se-Se under reductive conditions. The antioxidant effectiveness of ferrocenoyl organoseleniums was screened by using H_2O_2-induced oxidation of benzenethiol (PhSH) to form PhSSPh (λ_{max} = 305nm; ε_{305} =1.24×10^3 M^{-1}cm^{-1}) as the model reaction. Unfortunately, these ferrocenoyl organoseleniums did not show any antioxidant property on this reaction [38].

The further investigation on ferrocene-related organoseleniums was to link ferrocene and Se atom by C-Se bond. As shown as equation (16), the connection of two ferrocene by Se-Se or Te-Te has been simplified as just treating ferrocene by *n*-butyl lithium and Se or Te powder to form lithium arenetellurolate, which converted into diferrocenyl diselenium (ditelluride) after oxidation in atmosphere [39].

In addition, a simple method was recommended to prepare ferrocenyl selenides as shown as equation (17). The hydrogen atom of cyclopentadienyl ring in *N*,*N*-diisopropyl ferrocenecarboxamide was withdrawn by *n*-butyl lithium to form an arenelithium, which reacted with corresponding organodiselenides (RSeSeR) to yield 35-45% ferrocenyl selenides [40]. In this work, the protective effects of ferrocenyl selenides were characterized on the nitration of 4-hydroxyphenylacetate mediated by peroxynitrite ($ONOO^-$). The IC_{50} for these ferrocenyl selenides to inhibit the nitration of 4-hydroxyphenylacetate were less than 100 μM. However, the IC_{50} were larger than 250 μM while Se atom in ferrocenyl selenides was replaced by S atom, demonstrating that Se atom was of importance to the antioxidant property of ferrocenyl selenides.

Moreover, mercury-related ferrocene was an important reagent to synthesize Te-substituted ferrocene. As shown as



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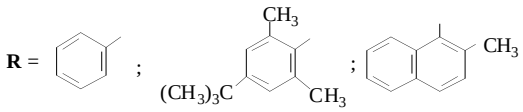

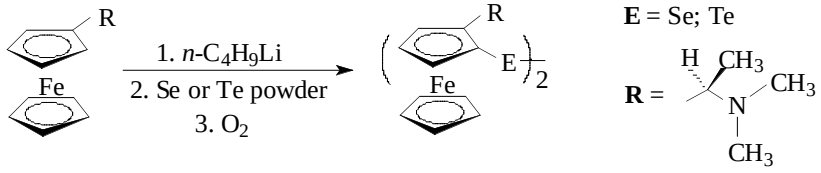

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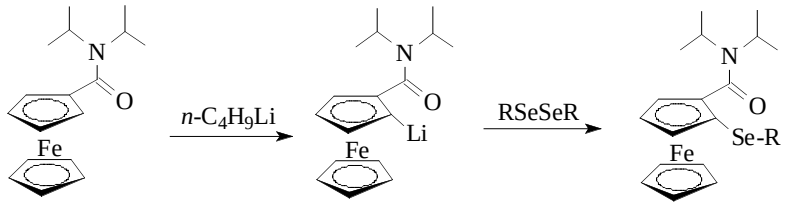

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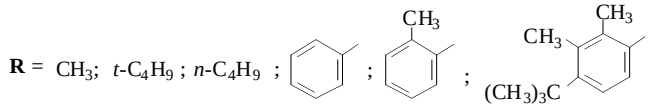
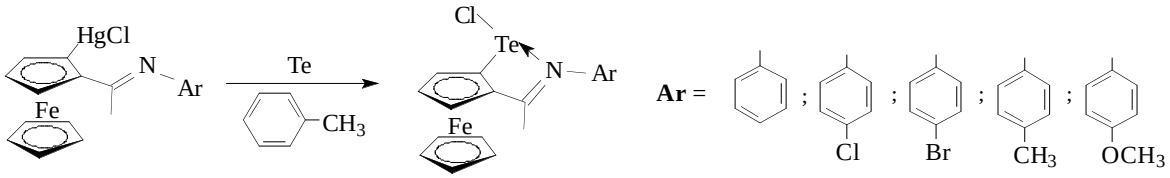




(18)

equation (18), when a mercury-related ferrocene including a Schiff-base group was treated by Te powder, a five-numbered ring was formed by N-Te bond. The CD spectra revealed that both reagent and product have the same configuration [41]. Organotelluriums were potent antioxidants, so, it was worthy to detect the antioxidant property of the obtained ferrocenyl telluride.

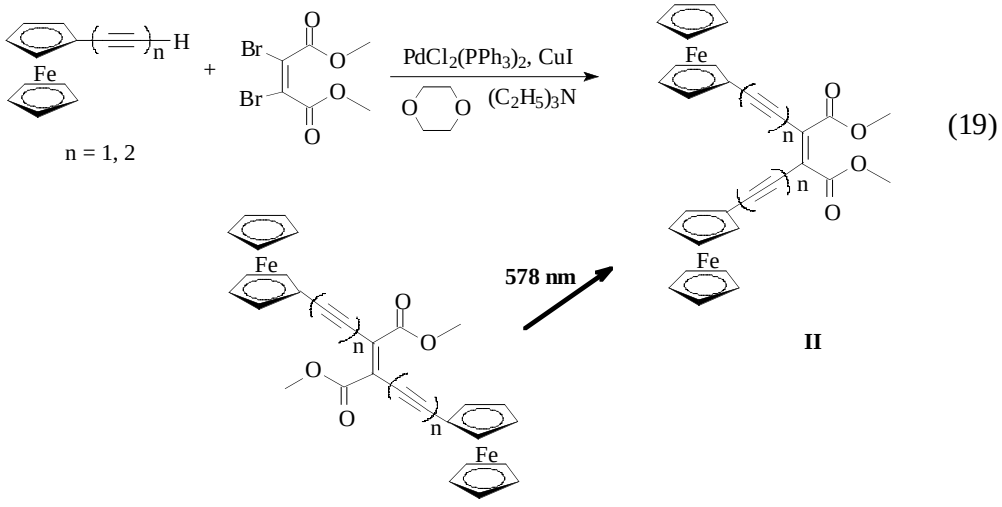
The mutual antioxidant effectiveness of ebselen still attracted much research attention [42], the aforementioned ferrocene-related organoseleniums and organotelluriums may have additional antioxidant abilities and are worthy to be researched in detail.

2. CONJUGATED FERROCENYL DERIVATIVES

2.1. The Connection of Ferrocene with Alkynyl and Aryl Groups

A conjugated system seemed to form between cyclopentadienyl ring and C≡C or aromatic ring when ferrocene moiety bridged with alkynyl or aryl groups by C-C bond. Actually, the cylindrically symmetrical electron orbital in C≡C cannot conjugate with π-bond of cyclopentadienyl ring in ferrocene. Similarly, cyclopentadienyl ring in ferrocene formed a dihedral angle with aromatic ring when ferrocene connected with aromatic ring by a C-C bond. As a result, π-bond of cyclopentadienyl ring in ferrocene cannot conjugate with that of aromatic ring. Nowadays, the investigation on these ferrocene derivatives focused on the photochromic properties. However, these ferrocene derivatives may be used as antioxidants or as probe molecules to characterize antioxidant capacity.

Sonogashira reaction was usually employed to construct C-C bond between C≡CH and alkyl halide. As shown as equation (19), the *trans*- product (**III**) can convert into *cis*-product under the irradiation at 578 nm. The quantum yield of the photochromism did not alter with the increase of the amount of C≡C, that is, the quantum yield cannot be affected by the number of **n** in equation (18) [43]. The transformation from **III** to **II** may be a model reaction to test whether an antioxidant can retard the conversion. If an antioxidant can retard the conversion from **III** to **II**, it will possess the ability to hinder the photo-induced oxidation of biological species.



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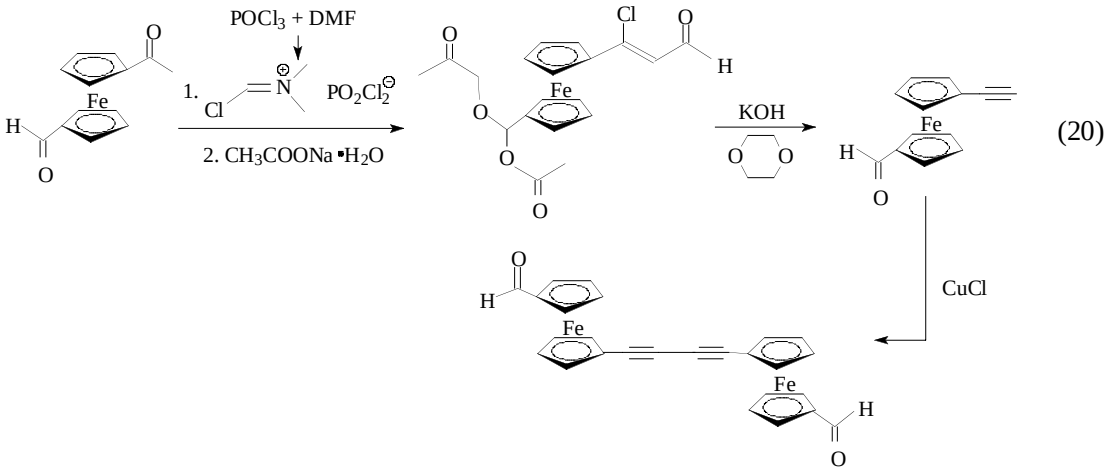

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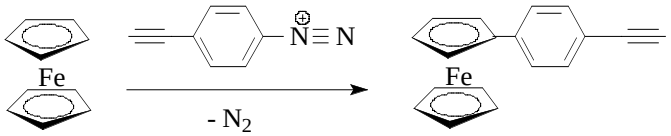


(21)

Another way to link an alkynyl group with ferrocene was to convert acetyl group into alkynyl group by Vilsmeier complex derived from $POCl_3$ and *N*,*N*-dimethylformamide (DMF) as shown as equation (20). In addition, arenediazonium connected with ferrocene by eliminating of N_2 to form a C-C bond as shown as equation (21) [44].

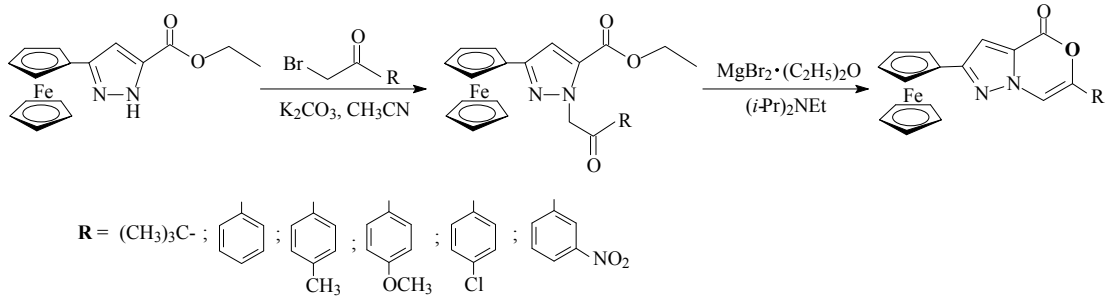
The aforementioned synthesis of organometallic ferrocene did not correlate with antioxidants directly. But the obtained compounds may be reagents to prepare novel antioxidants containing ferrocene motif. For example, some efforts devoted to improve the organic group in ethyl 3-ferrocenyl-*1H*-pyrazole-5-carboxylate as shown as equation (22) [45]. The obtained ferrocenyl pyrazolo[1,5-a]pyrazin-4(5*H*)-one derivatives were able to inhibit the growth of A549 cells in dosage-dependent manners through cell cycle arrest [46], and to induce apoptosis in A549 lung cancer cells effectively [47]. Thus the antioxidant properties of these compounds are worthy to be evaluated by means of chemical kinetics in order to explore the antioxidant mechanisms.

Pyrrole, ferrocenecarboxyaldehyde and 3,5-di-*tert*-butylbenzaldehyde (2:1:1, mole ratio) can form porphyrin-ferrocene by self-assembling reaction in the presence of trifluoroacetic acid as shown as equation (23). The ultrafast electron transfer occurring in the obtained ferrocenyl porphyrin was studied by femtosecond up-conversion and pump-probe techniques [48]. Hence, ferrocenyl porphyrin may be a probe molecule to detect the ability of an antioxidant to affect the electron transfer in biological systems.

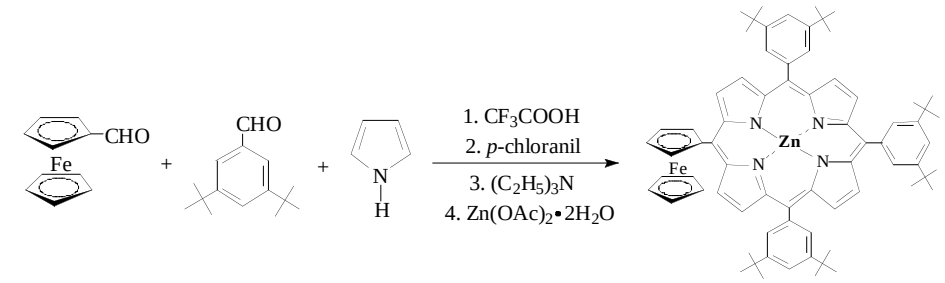
The electrochemical oxidation to a crowded structure, as shown as equation (24), resulted in the formation of cationic radical at both ferrocene and central phosphorous atom [49]. The generated radical may be applied to detect the ability of an antioxidant to quench radicals.

2.2. The Complete Conjugated System with Ferrocene

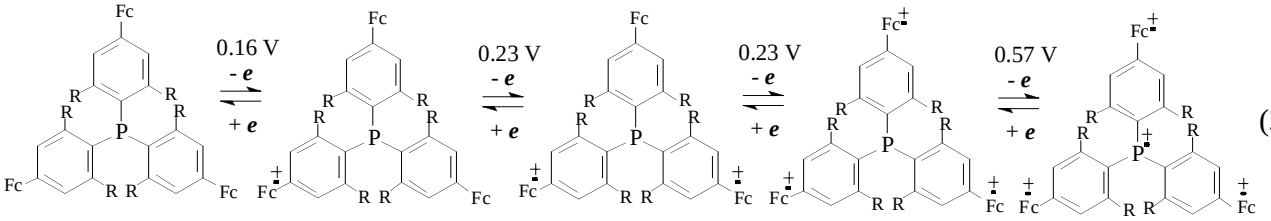
A complete conjugated system between aromatic ring and cyclopentadienyl ring in ferrocene actually bridged π-bond of these two aromatic systems by C=C, and was beneficial for the intramolecular electron transfer. As shown as equation (25), the electron of Fe atom in 3,5-di-*tert*-butyl-4-hydroxyphenyl ferrocene can be withdrawn by oxidant, and the hydrogen atom of hydroxyl group can be abstracted to generate a cationic radical. So, 3,5-di-*tert*-butyl-4-hydroxyphenylferrocene was not only an antioxidant, but also a model compound to study the intramolecular electron transfer between phenolic and ferrocenyl groups [50].



(22)

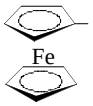


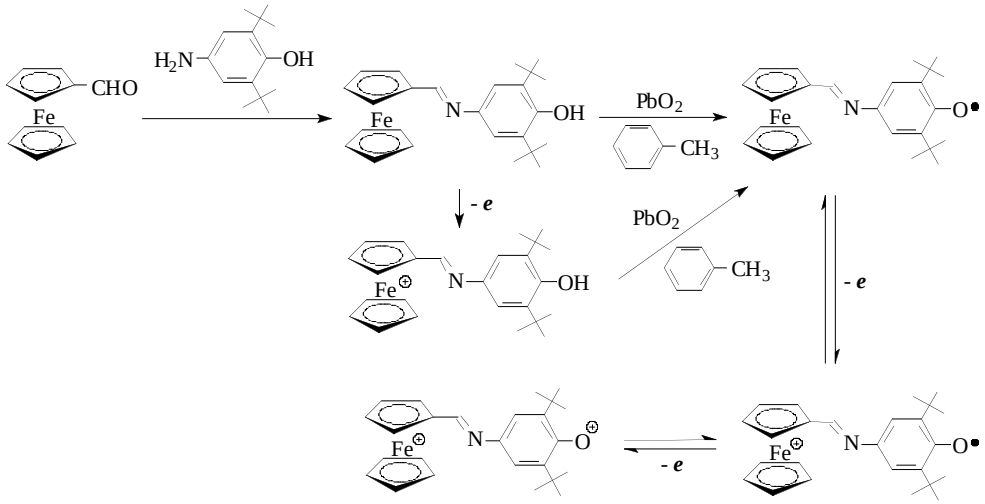
(23)



(24)

R = *i*-C_3H_7- **Fc** =





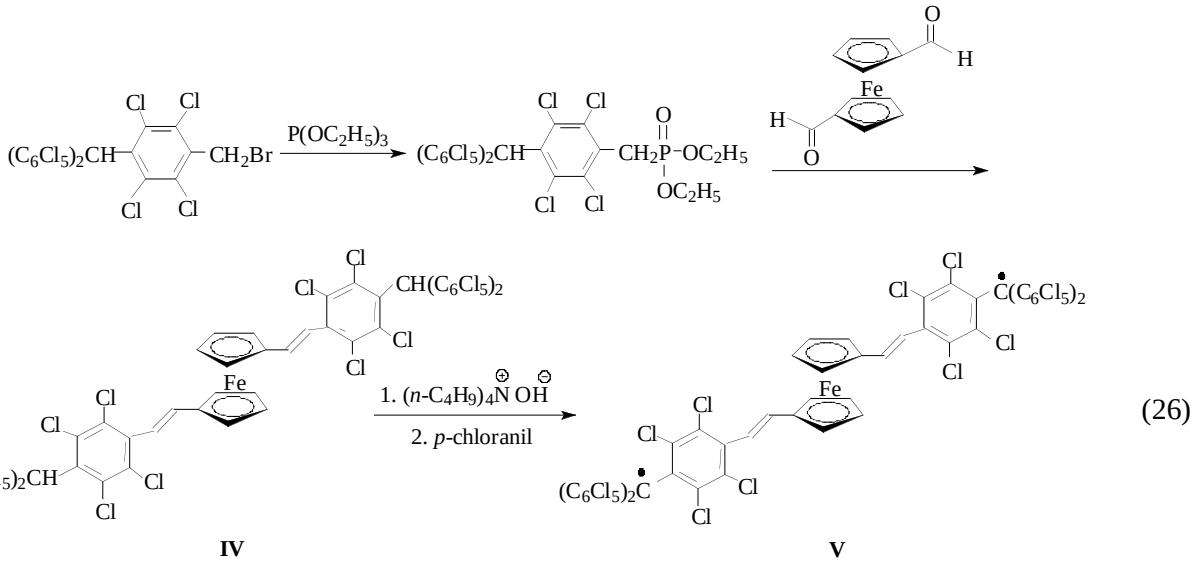
(25)

In addition to the benefit of crowded structure for stabilizing radicals, Fe atom in ferrocene acted as the target site to be oxidized electrochemically as well. A large conjugative system with ferrocene as the central structural feature (**IV**) was prepared by Wittig reaction as shown as equation (26). The hydrogen atom at benzyl position was neutralized by alkaline, and then, was oxidized by *p*-chloranil to form a biradical (**V**), which was stable below 150°C at atmosphere [51].

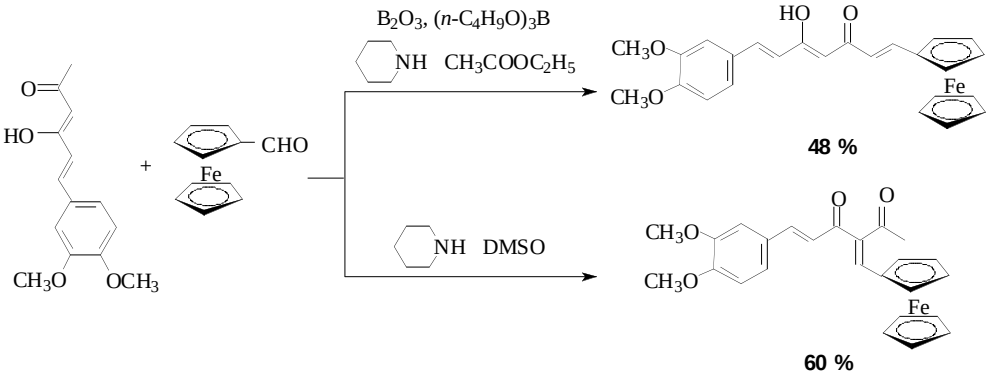
The structure of biradical **V** was identified by X-ray diffraction and NMR spectra, and the magnetic susceptibility was investigated as well [52]. The influence of solvent on the intramolecular electron transfer through the vinylene π-bridge to ferrocene was also clarified [53]. The biradical **V** was stabilized by the crowded structure of three chloro-substituted benzene rings, and may be used to test the ability of an antioxidant to donate its hydrogen atom to carbon-centered radical as an antioxidant interacted with 2,2'-diphenyl-1-picrylhydrazyl (DPPH), galvinoxyl, and $ABTS^{+\cdot}$.

The significant antioxidant effectiveness of curcumin motivated researchers to incorporate ferrocenyl moiety with the framework of curcumin in order to increase the conjugated system of curcumin. As shown as equation (27), Knoevenagel condensation occurred between curcumin and ferrocenecarboxyaldehyde, incorporating ferrocenyl moiety with methyl or methylene position of curcumin according to different experimental conditions. Moreover, as shown as equation (28), 1,4-addition took place between curcumin and ferrocenyl propynone, resulting in a ferrocenoyl curcuminoid [54].

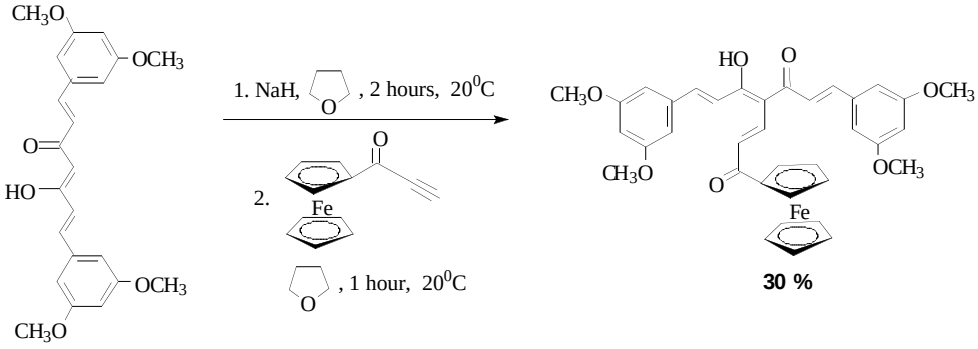
Ferrocenyl propyne can also function as the reagent to incorporate with substituted cyclobutendione, forming 2-ferrocenylidene-4-cyclopentene-1,3-diones as shown as equation (29) [55]. The hydrogen atom in compound **VI** and



(26)



(27)

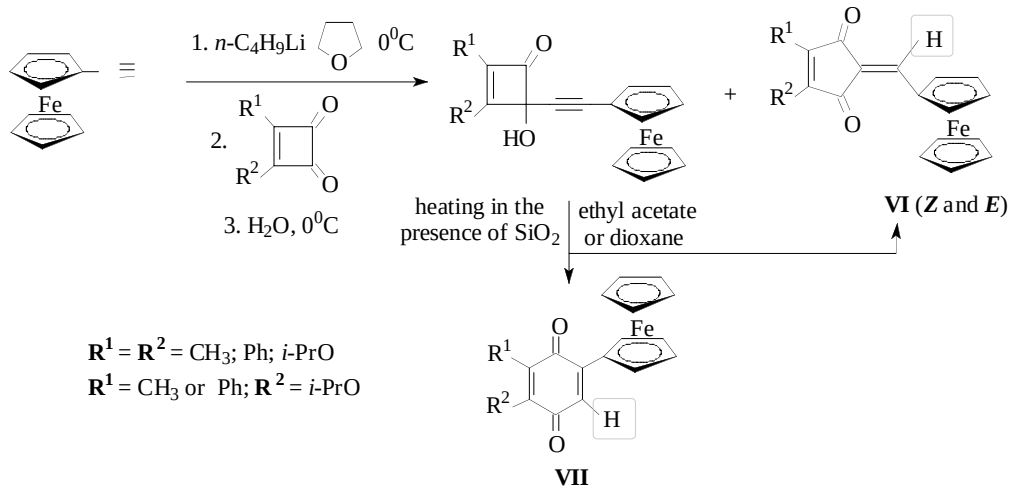


(28)

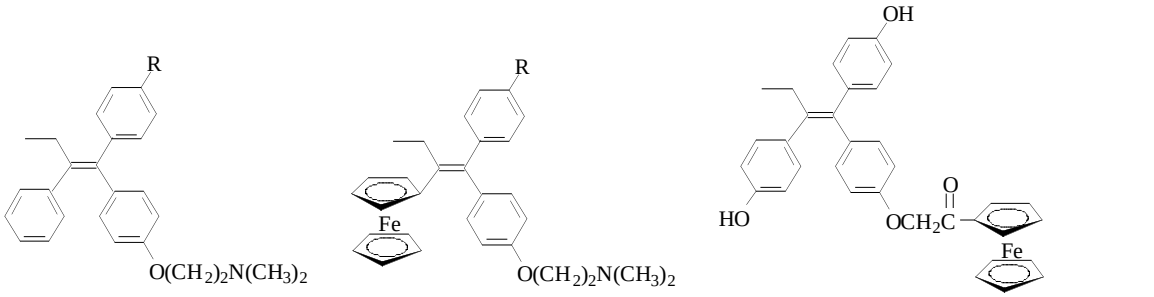
VII (shown in the framework) can be abstracted by radicals, thus, these two compounds were antioxidants.

Since tamoxifen and ferrocifen (structures shown in Scheme **4**) were found to have strong antiproliferative activity in breast cancer cells [56], connecting hydroxyl-substituted diphenyl ketone with acyl ferrocene by McMary reaction to prepare ferrocifen analogues attracted much research attention.

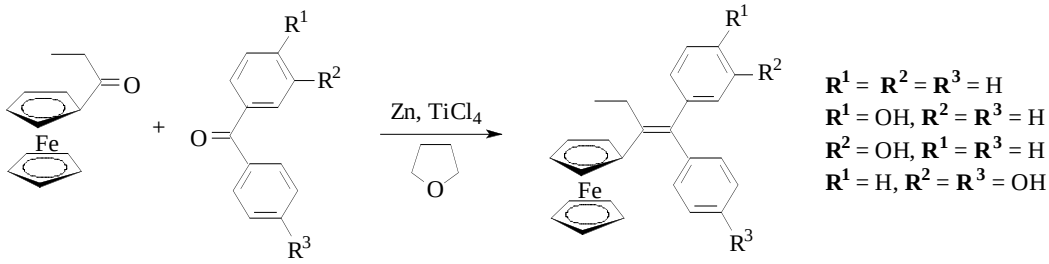
As shown as equations (30,31), one or two ferrocene motif replaced benzene ring in tamoxifen to form novel antioxidants, in which ferrocene motif conjugated with diphenyl ketone by C=C. But the shortcoming of McMary reaction was the formation of byproducts from self-condensation of diphenyl ketone or acyl ferrocene. The similar polarity of the obtained products made the isolation by column chromatography very difficult. So, high performance liquid chromatography (HPLC) was usually employed to obtain the target product. The *in vitro* study revealed that cytotoxic capacity of ferrocifen with a *para*-hydroxyl was superior to that with a *meta*-hydroxyl, and the cytotoxic capacity of ferrocifen with one ferrocenyl group was superior to that with two ferrocenyl groups [57]. These compounds possessed antiproliferative effects on the hormone-dependent (MCF7) and hormone-independent (MDA-MB231) breast cancer cell with the IC_{50} even lower than 1.0 μM [58].



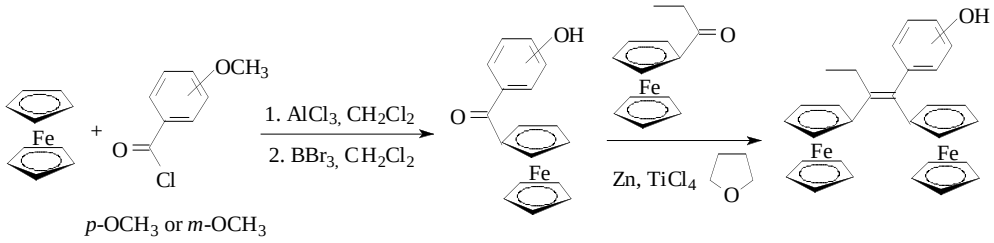
(29)



Scheme 4. Structures of tamoxifens and ferrocifens.



(30)



(31)

3. CONCLUSION AND PERSPECTIVE

Altogether, to be an organometallic compound, ferrocene had a great potential to be employed in designing antioxidants with ferrocenyl motif. A ferrocene-related antioxidant without conjugated system enhanced the bioavailability of ferrocenyl group. While ferrocenyl group formed a conjugated system among with other part of molecule, the conjugated system was beneficial to enhance the antioxidant effectiveness. Therefore, the development of ferrocene-related antioxidants will bring with us a worthwhile topic for designing novel drugs for the treatment of ROS-induced diseases.

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