Synthesis and antioxidant activity of novel vanillin-based ferrocenyl chalcones

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Abstract: A small series of new ferrocenyl chalcones was prepared, starting from the corresponding aldehydes and monoacetyl ferrocene. Di-derivatives of vanillin and ethylvanillin were prepared and used as aldehydes for this synthesis. All new compounds were characterized by IR and NMR spectroscopy and physical data. The antioxidant potential of new compounds was evaluated using the DPPH test and the results showed moderate activity *in vitro*.

Keywords: antioxidant activity, chalcones, ferrocene, synthesis, vanillin

1. Introduction

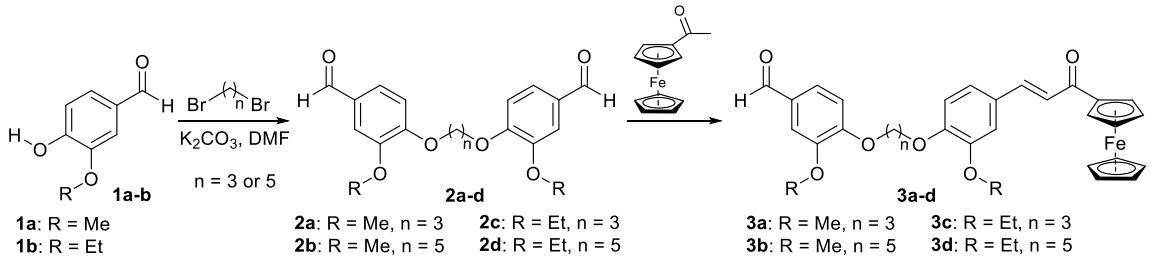
Chalcones are the core of many biologically interesting compounds from natural sources. They are used as an effective template in medicinal chemistry, and a high percentage of synthesized chalcones showed biological activities, such as anti-inflammatory [1], antitumor [2], antiviral [3], antioxidant [4], and many others.
On the other hand, ferrocene chemistry has revived in recent years. The ferrocenyl group has been incorporated into the structure of many biologically active molecules, such as flavones [5], chalcones [6], quinolinones [7], resulting in increased activities [8]. Different studies have demonstrated an important role for the ferrocene moiety as a structural motif for the enhancement of antioxidant activity [9].
Taking into account our earlier results in the synthesis of bioactive ferrocene chalcones [10], we decided to prepare new chalcones containing ferrocene and vanillin pharmacophores and investigate their antioxidant activity.

2. Results and discussion

2.1. Chemistry synthesis

The novel ferrocenyl chalcones were synthesized in two steps (Scheme 1). For the synthesis of starting aldehydes, the alkylation of the OH group of vanillin **1a** and

ethylvanillin **1b** was performed using corresponding dibromoalkanes in the presence of K_2CO_3 in DMF. The intermediate di-vanillins and di-ethylvanillins (**2a-d**) were obtained in excellent yields. Then, the Claisen-Schmidt condensation of **2a-d** with monoacetylferrocene in the presence of NaOH in ethanol resulted in the formation of ferrocenyl chalcones (**3a-d**).



Scheme 1. Synthesis of vanillin-based ferrocenyl chalcones, **3a-d.**

The new ferrocenyl chalcones were obtained in a crystal form and characterized by their spectral data (IR, ^{1}H and ^{13}C NMR).

2.2. Antioxidant activity

The DPPH radical scavenging activity of **3a-d** is presented in Table 1. The tested ferrocenyl derivatives exhibited moderate activity, with IC_{50} values ranging from 21.36 to 50.51 μM. Compounds that contain a longer linker in their structure (**3b** and **3d**) possess better activity. Additionally, vanillin-derived compounds showed stronger antioxidant capacity than their corresponding ethyl vanillin analogues. Compound **3b** showed the most promising activity (IC_{50} = 21.36 μM), comparable to reference, ascorbic acid. Further derivatization of these compounds, featuring the incorporation of catechol-containing moieties, may lead to the enhancement of their antioxidant activity.

Table 1. DPPH scavenging activity of compounds 3a-d.[a]

Compound	IC_{50} ± SD (μM)
3a	43.13 ± 0.61
3b	21.36 ± 0.79
3c	50.51 ± 0.84
3d	30.47 ± 0.17
Ascorbic acid	18.70 ± 0.86

[a] Results are mean values ± SD from three independent measurements.

3. Material and methods

3.1. Chemistry

All starting chemicals were commercially available and used as received, and the solvents were purified by distillation. IR spectra: PerkinElmer Spectrum One FT-IR

spectrometer with a KBr disc (cm^{-1}); NMR spectra: Varian Gemini 200 MHz spectrometer, using $CDCl_3$ as the solvent and TMS as the internal standard. ^1H and ^{13}C NMR chemical shifts were reported in parts per million (ppm). The melting points: MelTemp1000 apparatus. UV spectra: Agilent Technologies, Cary 300 Series UV-Vis Spectrophotometer.

3.1.1. General procedure for the synthesis of di-vanillins and di-ethylvanillins

The corresponding aldehyde was dissolved in DMF (36 ml) followed by the addition of anhydrous K_2CO_3 (46 mmol). The resulting suspension was stirred for a few minutes, and to this dibromopropane or dibromopentane was added, and the reaction mixture was allowed to stir at 50-60°C overnight. After that, the reaction mixture was heated to reflux for 2h. Then the reaction mixture was poured slowly into ice-cold water with constant stirring and kept in a refrigerator overnight. The precipitate obtained was filtered, washed, and dried. The obtained aldehydes were isolated as white to yellow powder.

3.1.2. General procedure for the synthesis of ferrocenyl chalcones

To a stirred solution of monoacetyl ferrocene (1.5 mmol) in absolute ethanol (20 ml) NaOH was added (340 mg) slowly. The resulting mixture was stirred at 50-60°C for 30 min. The corresponding aldehyde (1 mmol) was added, and the mixture was heated to reflux 4h. After reaction completion (monitored by TLC), the reaction mixture was poured slowly into ice-cold water and kept in a refrigerator overnight. The precipitate obtained was filtered, washed, dried, and chromatographed on a silica gel column using a dichloromethane-acetone (9:1) mixture as eluent (**3a-d**). All compounds were isolated as red crystalline molecules.

3.2. Antioxidant activity

The DPPH free radical scavenging activity of the studied compounds was determined according to the method described previously [11]. IC_{50} values represent the concentration necessary to obtain 50% of maximum scavenging activity. The results are presented as mean ± standard deviation (SD) calculated from the independent experiments performed in triplicate using Microsoft Excel software.

4. Conclusions

In this study, four new ferrocenyl chalcones were synthesized in very good yields, and their structures were characterized by spectral data (IR, ^1H NMR, and ^{13}C NMR). Antioxidant activity was evaluated, and the results showed that chalcones containing longer linkers, between two vanillin **3b** or ethylvanillin **3d** fragments, have more prominent *in vitro* activities. These compounds can be a good basis for further derivatization and investigation.

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