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Radical-scavenging properties of ferrocenyl chalcones

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ABSTRACT

The radical-scavenging capacities of ferrocenyl group and phenolic hydroxyl group in ferrocenyl chalcone were identified in this work. 1,1′-Diacetylferrocene was applied to condense with benzaldehyde, vanillin, and protocatechualdehyde to produce ferrocenyl chalcones, which were employed to interact with 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonate) cationic radical (ABTS$^{+\cdot}$), 2,2′-diphenyl-1-picrylhydrazyl radical (DPPH), and galvinoxyl radical, respectively. It was found that ferrocenyl chalcones as well as diacetylferrocene can trap these radicals effectively, and thus, concluded that both iron atom in ferrocene and phenolic hydroxyl group played the radical-scavenging role, and the radical-scavenging capacity of iron atom in ferrocene was even higher than that of phenolic hydroxyl group.

Ferrocene moiety is widely applied in biological systems[1] and in the design of novel drugs[2] because of being readily recognized by amino acids, proteins, DNA, and carbohydrates in vivo.[3] Ferrocene-related organometallic compounds are active to inhibit the proliferation of many kinds of tumor cells.[4,5] In the case of the application of ferrocene, it may be combined with organic moieties to form conjugation and non-conjugation systems. For example, one benzene ring in tamoxifen is replaced by ferrocenyl group to produce ferrocifen, in which the cyclopentadienyl ring (Cp) forms a conjugation system with other benzene rings.[6,7] On the other hand, cyclopentadienyl ring in ferrocene can connect with the carbon chain in chloroquine to generate ferroquine, in which the ferrocenyl moiety forms a non-conjugation system in ferroquine.[8,9] Moreover, acetylferrocene condenses with aromatic aldehyde to form chalcones by Claisen–Schmidt reaction. It has been found that ferrocenyl chalcones deriving from acetylferrocene possess higher antiplasmodial activity than chalcones resulting from ferrocenecarboxyaldehyde.[10] Chalcone attracts much research attention because of the radical-scavenging properties,[11] the molecular probe for the measurement of β-amyloid plaques,[12] the induction of monofunctional phase II enzymes,[13] and anticancer capacities.[14] Thus, it is reasonable to explore the radical-scavenging properties of hydroxyl derivatives of ferrocenyl chalcone. As shown in Scheme 1, 1,1′-diacetylferrocene (DAF) is applied to condense with benzaldehyde, vanillin, and protocatechualdehyde, respectively, to produce 1,1′-dicinnamoylferrocene (DCF), 1-acetyl-1′-(*m*-methoxyl-*p*-hydroxyl) cinnamoylferrocene (VAN-1), 1,1′-bis(*m*-methoxy-*p*-hydroxy)cinnamoylferrocene (VAN-2), and 1-acetyl-1′-(*m*,*p*-dihydroxy)cinnamoylferrocene (PCA-1). Presented here is a study on the reactivity of these ferrocenyl chalcones towards 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonate) cationic radical (ABTS$^{+\cdot}$),[15] 2,2′-diphenyl-1-picrylhydrazyl radical (DPPH), and galvinoxyl radical.

Ethanol (70 mL 95%) was saturated by HCl gas at 0 °C, and then, DAF (4.0 mmol) was added. The aromatic benzaldehyde (>8.0 mmol, dissolved in 15 mL of ethanol) was added dropwisely at 0 °C under stirring. The reaction was followed by TLC until DAF was undetected. The mixture was added to ice-cooled water under stirring. The precipitate was filtered and dissolved in ethyl acetate, and the filtrate was extracted by dichloromethane. The combined organic phase was washed in turn by brine, saturated aqueous solution of $NaHSO_3$, and brine, and dried over $MgSO_4$. After the organic solvent was evaporated under vacuum, the product was purified by silica chromatography with petroleum ether/ethyl acetate (1:1) being eluent when vanillin acted as the reactant, and with chloroform/methanol (9:1) being eluent when protocatechualdehyde acted as the reactant to obtain pure products for the structural characterization[16] and radical-scavenging test.[17]

Low values of EC_{50} and TEC_{50} imply low concentration and rapid rate of the antioxidant to trap the radical, and indicate high ability of the antioxidant to trap the radical. Consequently, EC_{50} and TEC_{50} lead to the antiradical efficiency (AE) expressed by Eq. 1.

$$AE = 1/(EC_{50} \times TEC_{50}) \qquad (1)$$

and the number of radicals trapped by the antioxidant (n) expressed by Eq. 2.

$$n = 1/(EC_{50} \times 2) \qquad (2)$$

High values of AE and n represent high antioxidant effectiveness. The values of EC_{50}, TEC_{50}, AE, and n of the obtained compounds in trapping three radicals are listed in Table 1.

It can be found in Table 1 that these compounds exhibit different activity towards ABTS$^{+\cdot}$, DPPH and galvinoxyl radical. High values of AE and n of VAN-1 (0.96 and 22.7) in trapping ABTS$^{+\cdot}$

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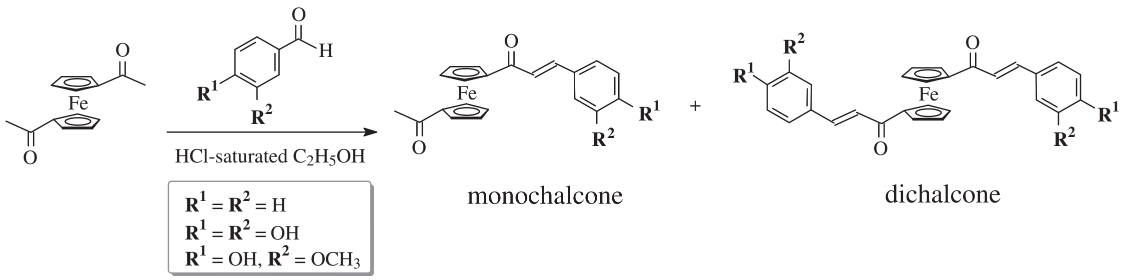

Scheme 1. Synthesis of ferrocenyl chalcones.

indicate that VAN-1 possesses higher reactivity towards $ABTS^{+\cdot}$ than that of VAN-2 (0.48 and 13.2) and PCA-1 (0.23 and 12.2). More hydroxyl groups do not enhance the abilities of VAN-2 and PCA-1 to trap $ABTS^{+\cdot}$. Thus, it is necessary to explore the influence of ferrocenyl group on the reactivity of chalcones. Diacinnamoylferrocene is a ferrocenyl chalcone without hydroxyl attached. The values of AE and *n* of diacinnamoylferrocene are even as high as 0.33 and 9.6, indicating that the skeleton of ferrocenyl chalcone scavenges $ABTS^{+\cdot}$ effectively. Moreover, the value of *n* of DAF (11.6) is close to that of PCA-1 (12.2) and VAN-2 (13.2), but AE of DAF (0.09) is lower than that of PCA-1 (0.23) and VAN-2 (0.48). Hence, the number of electron trapped by DAF is large even though the antiradical efficiency is low. The oxidation potentials of ferrocene, acetylferrocene, and DAF are 0.417, 0.66, and 0.89 V,[18] respectively, while the oxidation potential of $ABTS^{+\cdot}$ (0.68 V) is comparable to these ferrocene-related compounds.[19] It was reported that the oxidation potentials of 4-hydroxyl and 4,4′-dihydroxyl ferrocifen are 0.397 and 0.373 V, respectively, lower than that of ferrocifen without hydroxyl group, 0.421 V.[20] The low oxidation potentials imply that both phenolic hydroxyl group and the redox couple of Fe(II)/Fe(III) in ferrocene are potent radical-scavengers.[21] Therefore, the radical-scavenging capacities of the obtained ferrocenyl chalcone containing phenolic hydroxyl groups or not are owing to the scavenged radicals by phenolic hydroxyl groups and redox couple of Fe(II)/Fe(III) in ferrocene.[22] This phenomenon is also found in trapping DPPH and galvinoxyl radicals by ferrocenyl chalcones.

DPPH is a nitrogen-centered radical[23] that can be quenched by phenolic hydroxyl via sequential proton loss electron transfer (SPLET) and hydrogen atom transfer (HAT) mechanisms.[24] The values of AE and *n* of VAN-2 (6.67 and 13.3) are higher than that of VAN-1 (4.39 and 8.8), indicating that double substitutions by *m*-methoxy-*p*-hydroxyphenyl group increase the ability of ferrocenyl chalcone to trap DPPH. Meanwhile, the values of AE and *n* of PCA-1 (5.56 and 11.1) are also higher than that of VAN-1, revealing a well-known conclusion that two hydroxyl groups at *ortho*-position are beneficial for the radical-scavenging property. Moreover, the values of AE and *n* of DAF (5.43 and 10.9) are higher than that of diacinnamoylferrocene (4.55 and 9.1), revealing that the formation of ferrocenyl chalcones does not increase DPPH-scavenging ability. The values of AE and *n* of diacinnamoylferrocene approach to that of hydroxyl-substituted ferrocenyl chalcones, revealing that hydroxyl groups do not increase DPPH-scavenging capacity of ferrocenyl chalcones.

Table 1
Radical-scavenging parameters for ferrocenyl chalcones to trap $ABTS^{+\cdot}$, DPPH, and galvinoxyl radical

Radical	Compounds	EC_{50}	TEC_{50} (min)	AE	*n*
ABTS	DAF	0.043	81.4	0.09	11.6
	DCF	0.052	58.1	0.33	9.6
	VAN-1	0.022	47.4	0.96	22.7
	VAN-2	0.038	55.4	0.48	13.2
	PCA-1	0.041	105.6	0.23	12.2
DPPH	DAF	0.092	35.0	5.43	10.9
	DCF	0.110	73.8	4.55	9.1
	VAN-1	0.114	88.4	4.39	8.8
	VAN-2	0.075	110.8	6.67	13.3
	PCA-1	0.090	39.5	5.56	11.1
Galvinoxyl	DAF	0.098	70.1	0.15	5.1
	DCF	0.044	69.9	0.33	11.4
	VAN-1	0.266	60.3	0.06	1.9
	VAN-2	0.058	81.4	0.21	8.6
	PCA-1	0.132	143.1	0.05	3.8

Galvinoxyl radical is widely employed to evaluate the ability of antioxidants to contribute the hydrogen atom to oxygen-centered radical.[25] Although the AE of VAN-1 (0.06) is very similar to that of PCA-1 (0.05), the value of *n* of PCA-1 (3.8) is higher than that of VAN-1 (1.9), revealing that two hydroxyl groups at *ortho*-position enhances galvinoxyl-scavenging capacity of ferrocenyl chalcone. Furthermore, double substitutions by *m*-methoxy-*p*-hydroxyphenyl group increase the values of AE and *n* of VAN-2 remarkably. However, diacinnamoylferrocene possesses the highest values of AE and *n* (0.33 and 11.4), revealing that the skeleton of ferrocenyl chalcone as well as DAF show high activities to trap galvinoxyl radical.

To sum up, ferrocenyl chalcones containing hydroxyl group or not are able to trap $ABTS^{+\cdot}$, DPPH, and galvinoxyl radical effectively. DAF exhibits radical-scavenging property as well, demonstrating that both the redox couple of Fe(II)/Fe(III) in ferrocene and phenolic hydroxyl group play the radical-scavenging role. Consequently, the radical-scavenging effectiveness of ferrocenyl chalcone is higher than chalcone itself.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.12.051.

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16. *1,1′-Dicinnamoylferrocene (DCF)*: Orange red needles, and yield 35%. IR (KBr, cm^{-1}): 1654 (C=O), 1572 (C=C). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.60, 4.93 (2s, 8H, two Cps), 7.06, 7.77 (2d, 4H, vinyl protons), 7.37, and 7.39 (2s, 10H, Ph). *1-Acetyl-1′-(m-methoxyl-p-hydroxyl)cinnamoylferrocene*: Red solid, and yield 9%. IR (KBr, cm^{-1}): 3476 (O–H), 1658 and 1648 (two C=O), 1574 (C=C). ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.31 (s, 3H, COCH_3), 3.89 (s, 3H, OCH_3), 4.57–5.08 (m, 8H, Cp), 7.29, 7.57 (d, 2H, vinyl), 6.84, 7.20, 7.47 (d, 1s, 3H, Ph). Elemental analysis: Anal. Calcd for $C_{22}H_{20}FeO_4$: C, 65.37; H, 4.99. Found: C, 64.99; H, 5.12. *1,1′-Bis(m-methoxy-p-hydroxy)cinnamoylferrocene*: Orange red solid, and yield 5%. IR (KBr, cm^{-1}): 3400 (O–H), 1647 (C=O), 1576 (C=C). ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.88 (s, 6H, 2CH_3), 4.03, 5.02 (s, 8H, Cp), 6.82, 7.18, 7.43 (d, 1s, 6H, Ph), 7.24, 7.54 (d, 4H, vinyl). Elemental analysis: Anal. Calcd for $C_{22}H_{20}FeO_4$: C, 66.93; H, 4.87. Found: C, 65.93; H, 5.02. *1-Acetyl-1′-(m, p-dihydroxy)cinnamoylferrocene*: Red solid, and yield 9%. IR (KBr, cm^{-1}): 3432 (O–H), 1643 (C=O), 1572 (C=C). ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, COCH_3), 4.57, 4.67, 4.76, 5.03 (8H, Cp), 6.81, 7.12, 7.26 (d, 3H, Ph), 7.18, 7.50 (d, 2H, vinyl), 9.11, 9.70 (s, 2H, O*H*). Elemental analysis: Anal. Calcd for $C_{21}H_{18}FeO_4$: C, 64.64; H, 4.65. Found: C, 64.38; H, 4.92. The purities of the obtained compounds were analyzed by high performance liquid chromatography (HPLC) and were >98.0%. The measured percentages of carbon in the element analysis of the obtained compounds were a little lower than the calculated data because the iron atom in ferrocene combined with carbon to produce iron carbonate other than to generate CO_2.
17. Two milliliter of 4.0 mM ABTS aqueous solution was oxidized by 1.41 mM $K_2S_2O_8$ for 16 h, then, 100 mL of ethanol was added to make the absorbance (Abs_0) ~ 0.70 at 734 nm ($\varepsilon_{734} = 1.6 \times 10^4\ M^{-1}\ cm^{-1}$). DPPH and galvinoxyl radical were dissolved in ethanol to make the absorbance (Abs_{ref}) around 1.00 at 517 nm ($\varepsilon_{517} = 4.09 \times 10^3\ M^{-1}\ cm^{-1}$) and 428 nm ($\varepsilon_{428} = 1.4 \times 10^5\ M^{-1}\ cm^{-1}$), respectively. The ethanolic solution of five different concentrations of each compound (0.1 mL) was added to 1.9 mL of radical solution. The absorbance (Abs_{detect}) was recorded at a certain intervals, and the percentage of radical trapped by the compound was obtained by (Abs_{detect}/Abs_0) × 100. The presented data were the average value from at least three independent measurements with the experimental error within 10%.
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