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Synthesis of isoxazole moiety containing ferrocene derivatives and preliminarily *in vitro* anticancer activity

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Seven new structures of an isoxazole moiety containing ferrocene derivatives (**3a–3g**) were firstly synthesized and characterized by ^{1}H NMR, ^{13}C NMR, ESI-MS. Subsequently, their *in vitro* anticancer activity against A549, HCT116 and MCF-7 cell lines was preliminarily evaluated using the MTT method. Among them, **3d** exhibited a wide spectrum and the most potent anticancer activity against A549 and HCT116 cell lines (IC_{50}s: 0.747 and 3.65 nM, respectively) as compared with the reference drug gefitinib (IC_{50}s: 17.90 and 21.55 μM, respectively). **3d** can be seen as the best candidate for development of anticancer drugs.

1. Introduction

Cancer is the second most lethal disease with abnormal cellular proliferation and metastasis, second only to cardiovascular and cerebrovascular disease worldwide. Cancer types include lung cancer, gastric cancer, liver cancer, colon cancer and breast cancer, non-small cell lung cancer (NSCLC), *etc.* lung cancer causes a fifth of all cancer-related deaths; moreover, NSCLC accounts for most cases of lung cancer and is usually diagnosed in advanced stages. Cancer is a great threat to human survival, and there is an urgent need to discover new anticancer drugs.

Ferrocene has attracted significant interest, mainly due to its aromaticity, chemical stability and low toxicity; it has been used as the most attractive pharmacophore for drug design and discovery. Edwards *et al.*[1] synthesized ferrocenyl-penicillin (Fig. 1) and tested it against penicillin-resistant bacteria. The results showed that ferrocenyl-penicillin can increase the antibacterial activity and it is more active than penicillin. Ferroquine (FQ, SSR97193, Fig. 1) is another ferrocene core containing quinoline derivative, which exhibits a higher antimalarial activity than chloroquine (CQ, Fig. 1); it is also more active against chloroquine-resistant malaria. FQ may be useful as an alternative drug for treating chloroquine-resistant malaria[2,3] and it is about to complete phase-II clinical trials. To date, different kinds of ferrocene derivatives, together with different biological activities, especially anticancer activity, have been reported.[4–19]

The isoxazole moiety, as a potential functional group, is usually introduced into drug molecules to improve their biological activities. In our previous work, we introduced the isoxazole moiety at the C-30 position of glycyrrhetinic acid and 11-deoxyglycyrrhetinic acid, and synthesized a series of isoxazole-moiety-containing glycyrrhetinic acid amide derivatives. The biological evaluation results showed that most compounds exhibit higher activities of anti-inflammatory, analgesic, cough prevention and liver protection than those of glycyrrhetinic acid, but what is most important is that some isoxazole rings containing glycyrrhetinic acid derivatives greatly reduced the pseudoaldosteronism caused by glycyrrhetinic acid. Deoxyglycychloxazol (TY501, Fig. 2) is the most potent compound among these glycyrrhetinic acid derivatives and it is in preclinical studies for the development of an anti-inflammatory drug.[20–22]

In recent years we have been devoted to the design and synthesis of anticancer drugs based on the epidermal growth factor receptor (EGFR) target, and we have achieved remarkable results.[23–25] Based on our previous results,[20,23,24] in this current work we have introduced the isoxazole moiety to the ferrocene core and first of all synthesized seven novel structures of isoxazole moiety containing ferrocene derivatives (**3a–3g**) (Scheme 1). Furthermore, their *in vitro* anticancer activity against the breast cancer cell line MCF-7, lung cancer cell line A549 and colorectal cancer cell line HCT116 was evaluated.

2. Experimental

2.1 Materials and apparatus

All melting points were determined on a X-4 micro melting point apparatus, and values are uncorrected; ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a 400 MHz Bruker AVANCE III spectrometer in $CDCl_3$, with the chemical shifts expressed in ppm relative to tetramethylsilane (TMS) as the internal standard; ESI-MS was performed on a DECAX-30000 LCQ Deca XP(70 Ev); column chromatography was performed

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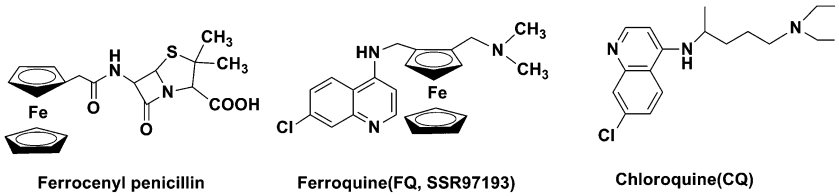


Fig. 1 Chemical structures of ferrocenyl-penicillin, FQ and CQ.

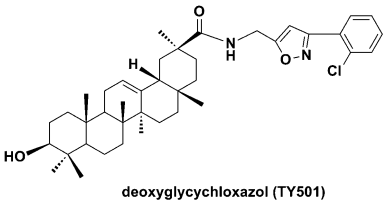


Fig. 2 Chemical structure of deoxyglycychloxazol (TY501).

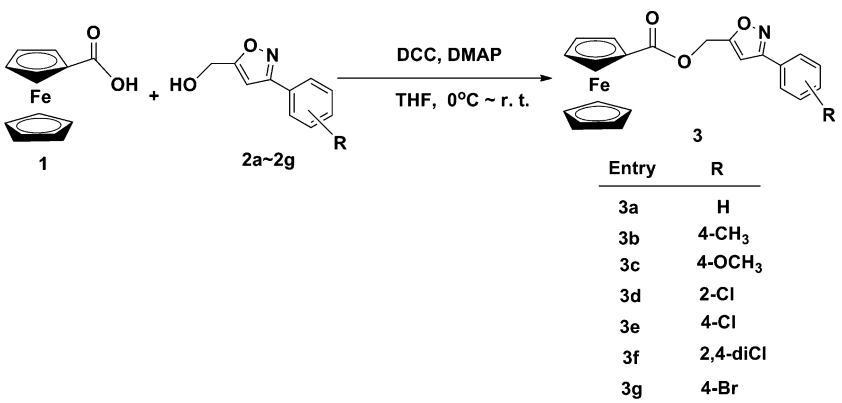
on silica gel (100–200 mesh, Qingdao Haiyang Chemical Co. Ltd); MTT {[3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide], Amresco} and dimethyl sulfoxide (DMSO) were purchased from Sigma; gefitinib was purchased from the Hubei Prosperity Galaxy Chemical Co. Ltd., China; Dulbecco's modified essential medium (DMEM) was purchased from Invitrogen; 10% fetal bovine serum (FBS) and 1% penicillin–streptomycin were purchased from Invitrogen; the intermediates 3-[(*R*)-substituted-phenyl]-isoxazole-5-methanol (**2a–2g**) were prepared according to the published procedures reported by us;[28] other chemicals were commercially available, and used without further purification; tetrahydrofuran (THF) was distilled over sodium and benzophenone before use.

2.2 Synthesis

In the general process for synthesis of **3a**, ferrocene carboxylic acid **1** (0.23 g, 1 mmol) and DCC (0.22 g, 0.55 mmol) were added into a 25 mL one-necked round-bottomed flask with 5 mL dry THF. The mixture was stirred in a cold bath and protected under nitrogen for about 10 min. Then DMAP (0.14 g, 0.11 mmol) in 5 mL dry THF was added to the reaction system using a syringe, and the mixture was stirred in a cold bath for an additional 30 min. Subsequently, 1.0 mmol **2a** in 5 mL THF was added dropwise to the reaction system using a syringe, at which time the temperature rose to room temperature. TLC confirmed the completion of the reaction. The reaction mixture was evaporated under reduced pressure, and the residue was directly purified by column chromatography on silica gel with elution by petroleum ether and ethyl acetate (5 : 1 → 2 : 1). Fractions with similar R_f values were combined to obtain the target compound **3a**. Other ferrocene derivatives, **3b–3g**, were synthesized using the same process as for **3a**.

Ferrocene carboxylic acid 3-phenyl-isoxazol-5-ylmethyl ester (**3a**). Yield 84%. Light yellow solid: mp 138–139 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.19 (s, 5H, C_5H_5), 4.45 (s, 2H, C_5H_4), 4.87 (s, 2H, C_5H_4), 5.38 (s, 2H, isoxazole-CH_2), 6.70 (s, 1H, isoxazole-H), 7.45–7.46 (m, 3H), 7.81–7.83 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 56.09, 69.75, 69.83, 70.39, 71.80, 102.25, 126.88, 126.90, 126.95, 126.98, 128.98, 129.00, 130.18, 130.20, 171.5. ESI-MS (*m*/*z*, 100%) 388 ($[M + 1]^+$, 6). Anal. calcd for $C_{21}H_{17}FeNO_3$: C, 65.11; H, 4.40; N, 3.62. Found: C, 65.04; H, 4.46; N, 3.47%.

Ferrocene carboxylic acid 3-(4-methyl-phenyl)-isoxazol-5-ylmethyl ester (**3b**). Yield 83%. Light yellow solid: mp 145–146 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.40 (s, 3H, Ph-CH_3), 4.21 (s, 5H, C_5H_5), 4.47 (s, 2H, C_5H_4), 4.88 (s, 2H, C_5H_4), 5.37 (s, 2H, isoxazole-CH_2), 6.69 (s, 1H, isoxazole-H), 7.27 (d, 2H, $J = 8.0$ Hz), 7.71 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 21.44 (Ph–$\underline{C}H_3$), 56.09, 69.83, 69.96, 70.39, 71.81, 102.18, 126.76, 129.67, 140.33, 140.53, 162.56, 167.49, 171.21. ESI-MS (*m*/*z*, 100%) 401 ($[M]^+$, 100). Anal. calcd for $C_{22}H_{19}FeNO_3$: C, 65.83; H, 4.74; N, 3.49. Found: C, 65.89; H, 4.76; N, 3.36%.



Entry	R
3a	H
3b	4-CH_3
3c	4-OCH_3
3d	2-Cl
3e	4-Cl
3f	2,4-diCl
3g	4-Br

Scheme 1 The synthetic route for ferrocene derivatives.

Ferrocene carboxylic acid 3-(4-methoxyl-phenyl)-isoxazol-5-yl-methyl ester (**3c**). Yield 79%. Light yellow solid: mp 128–130 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.85 (s, 3H, Ph–OCH_3), 4.18 (s, 5H, C_5H_5), 4.44 (s, 2H, C_5H_4), 4.85 (s, 2H, C_5H_4), 5.36 (s, 2H, isoxazole-CH_2), 6.64 (s, 1H, isoxazole-H), 6.98 (d, 2H, J = 8.8 Hz), 7.76 (d, 2H, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 26.31 (Ph–O$\underline{C}H_3$), 55.39, 69.76, 69.93, 70.29, 71.18, 102.03, 125.89, 126.81, 129.72, 140.50, 162.63, 167.52, 171.23. ESI-MS (m/z, 100%) 417 ([M]$^+$, 30). Anal. calcd for $C_{22}H_{19}FeNO_4$: C, 63.31; H, 4.56; N, 3.36. Found: C, 63.38; H, 4.52; N, 3.31%.

Ferrocene carboxylic acid 3-(2-chloro-phenyl)-isoxazol-5-yl-methyl ester (**3d**). Yield 70%. Light yellow solid: mp 110–111 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.19 (s, 5H, C_5H_5), 4.45 (s, 2H, C_5H_4), 4.87 (s, 2H, C_5H_4), 5.40 (s, 2H, isoxazole-CH_2), 6.87 (s, 1H, isoxazole-H), 7.33–7.41 (m, 2H), 7.48–7.50 (m, 1H), 7.73–7.75 (m, 1H); ^{13}C NMR($CDCl_3$, 100 MHz) 55.98, 69.78, 69.95, 70.39, 71.81, 105.49, 127.18, 128.08, 130.46, 131.04, 132.97, 161.24, 169.98, 171.12. ESI-MS (m/z, 100%) 421 ([M]$^+$, 10). Anal. calcd for $C_{21}H_{16}FeClNO_3$: C, 59.86; H, 3.80; N, 3.33. Found: C, 60.04; H, 4.06; N, 3.43%.

Ferrocene carboxylic acid 3-(4-chloro-phenyl)-isoxazol-5-yl-methyl ester (**3e**). Yield 81%. Light yellow solid: mp 152–153 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.19 (s, 5H, C_5H_5), 4.46 (s, 2H, C_5H_4), 4.87 (s, 2H, C_5H_4), 5.37 (s, 2H, isoxazole-CH_2), 6.67 (s, 1H, isoxazole-H), 7.45 (d, 2H, J = 8.4 Hz), 7.77 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 56.02, 69.73, 69.95, 70.39, 71.86, 102.12, 124.75, 125.85, 127.26, 128.13, 129.29, 168.05, 170.29. ESI-MS (m/z, 100%) 422 ([M + 1]$^+$, 10). Anal. calcd for $C_{21}H_{16}FeClNO_3$: C, 59.86; H, 3.80; N, 3.33. Found: C, 60.24; H, 4.08; N, 3.33%.

Ferrocene carboxylic acid 3-(2,4-dichloro-phenyl)-isoxazol-5-yl-methyl ester (**3f**). Yield 68%. Light yellow solid: mp 100–101 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) 4.18 (s, 5H, C_5H_5), 4.45 (s, 2H, C_5H_4), 4.86 (s, 2H, C_5H_4), 5.40 (s, 2H, isoxazole-CH_2), 6.86 (s, 1H, isoxazole-H), 7.35 (dd, 1H, J = 2.0, 2.0 Hz), 7.52 (d, 1H, J = 1.6 Hz), 7.71 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 55.91, 69.69, 69.93, 70.38, 71.82, 105.27, 126.62, 127.63, 130.33, 131.76, 133.66, 136.52, 160.37, 167.32, 171.11. ESI-MS (m/z, 100%) 457 ([M + 1]$^+$, 20). Anal. calcd for $C_{21}H_{15}FeCl_2NO_3$: C, 55.26; H, 3.29; N, 3.07. Found: C, 55.24; H, 3.30; N, 3.09%.

Ferrocene carboxylic acid 3-(4-bromo-phenyl)-isoxazol-5-yl-methyl ester (**3g**). Yield 82%. Light yellow solid: mp 158–159 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.22 (s, 5H, C_5H_5), 4.48 (s, 2H, C_5H_4), 4.89 (s, 2H, C_5H_4), 5.36 (s, 2H, isoxazole-CH_2), 6.66 (s, 1H, isoxazole-H), 7.61 (d, 2H, J = 8.4 Hz), 7.70 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 56.03, 69.71, 69.93, 70.40, 71.83, 102.10, 124.735, 125.84, 127.25, 128.10, 129.28, 168.04, 170.10. ESI-MS (m/z, 100%) 466 ([M]$^+$, 35). Anal. calcd for $C_{21}H_{16}FeBrNO_3$: C, 54.08; H, 3.43; N, 3.00. Found: C, 54.00; H, 3.45; N, 2.97%.

2.3 Anticancer evaluation

The anticancer activity of **3a–3g** was evaluated against MCF-7, HCT116 and A549 cell lines using the MTT {(3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide)} method. The evaluation process has been described elsewhere, with some modifications.[26,27] Briefly, each compound was dissolved in DMSO at a concentration of 500 μM, then diluted successively with DMSO for eight different concentrations (500 μM, 50 μM, 5 μM, 500 nM, 50 nM, 5 nM, 500 pM and 50 pM, respectively) as stock solution for the experiments described below.

In relation to the procedure for anticancer evaluation, target cancer cell lines were seeded in 96-well plates with 100 μL DMEM supplemented with 10% fetal bovine serum, and cultured at 37 °C in a humidified CO_2 incubator (95% air, 5% CO_2) for 24 h. While the cell lines grew to 90% in logarithmic growth, a 1 μL solution of different concentrations of each compound was added into each well (every concentration was repeated three times), and the plates were incubated for another 18 h at 37 °C. Then, 20 μL of PBS containing 5 mg mL^{-1} of MTT was added to each well. Four hours later, the culture medium was removed from the well, and 150 μL DMSO was added to each well. The optical density was measured at a wavelength of 595 nm on an ELISA microplate reader. DMSO was used as a negative control. The results were expressed as the inhibition calculated as the percentage [(1 − (OD_{595} treated/OD_{595} negative control)) × 100]. Data analysis was performed using GraphPad Prism software, and 50% of cell growth inhibition (IC_{50}) was determined by non-linear regression. The inhibitory potentials of ferrocene derivatives were comparable to that of the reference drug gefitinib.

3. Results and discussion

Chemistry

We used our optimized conditions[28–31] to synthesize ferrocene ester derivatives (**3a–3g**) in high yield, and their structures were confirmed by ^{1}H and ^{13}C NMR mass spectrometry.

There were three kinds of proton signals for the ferrocene ring of the ferrocene derivatives (**3a–3g**) in the ^{1}H NMR spectra. The proton of C_5H_5 ring showed a singlet at 4.0 ppm, while the proton of C_5H_4 showed two singlets at 4.45 and 4.87 ppm, respectively. The proton of the isoxazole ring showed a singlet at 6.7 ppm. Three signals of the carbon atoms of the C_5H_4 ring and one singlet of the carbon atom of the C_5H_5 appeared in the ^{13}C NMR spectra, while two carbon signals of the C_5H_4 ring appeared upfield and one carbon signal of the C_5H_4 ring appeared downfield compared with the carbon signal of the C_5H_5 ring. The ^{1}H and ^{13}C chemical shifts of ferrocene ring and isoxazole ring in these isoxazole-moiety-containing ferrocene derivatives are very consistent with those reported in the literature.[32,33]

Anticancer activity

The target compounds were preliminarily screened for their *in vitro* anticancer activity against the breast cancer MCF-7 cell line, lung cancer A549 cell line and colorectal cancer HCT116 cell line. The anticancer efficacy was comparable with that of the reference drug gefitinib, and the results are summarized in Table 1. As evidenced from Table 1, most of the target compounds exhibit a wide spectrum of anticancer activity against MCF-7, HCT116 and A549 cell lines. As to the compounds **3a–3c**, these exhibit higher anticancer activity against MCF-7, HCT116 and A549 cell lines, but the efficacy is not notable. This indicates that introducing the methyl and methoxy groups to the benzene ring of the isoxazole moiety

Table 1 *In vitro* anticancer activity of compounds **3a–3g**

	$IC_{50} \pm SD$ (μM)		
Compd	A549	HCT116	MCF-7
3a	78.11 ± 0.0241	36.22 ± 0.0306	$1.01 \times 10^3 \pm 0.0781$
3b	34.18 ± 0.0431	45.91 ± 0.0290	—[a]
3c	$3.27 \times 10^5 \pm 0.0727$	$6.38 \times 10^5 \pm 0.0178$	274.50 ± 0.0437
3d	$7.47 \times 10^{-4} \pm 0.1221$	$3.65 \times 10^{-3} \pm 0.1103$	698.10 ± 0.1154
3e	—[a]	46.80 ± 0.0232	442.00 ± 0.0587
3f	—[a]	582.70 ± 0.1336	—[a]
3g	—[a]	443.80 ± 0.0629	$1.97 \times 10^5 \pm 0.0024$
Gefitinib	17.90 ± 0.0074	21.55 ± 0.0129	20.68 ± 0.0384

[a] The IC_{50} values cannot be calculated.

cannot greatly improve the anticancer activity. Indeed, introducing the methoxy group to the benzene ring will greatly reduce the anticancer activity against HCT116 and A549 cell lines (for example, **3a** is 4186-fold more active than **3c** against the A549 cell line, and 17 614-fold more active than **3c** against the HCT116 cell line). For **3d–3f** (the benzene ring substituted by Cl), **3d** and **3e** (benzene ring substituted by a single chlorine atom) are more potent than **3f** (benzene ring substituted by two chlorine atoms); however, **3d** (2-position of benzene ring substituted by chlorine) is much more potent than **3e** (4-position of benzene ring substituted by chlorine), and **3d** is the most potent among **3a–3g**. In fact **3d** is 23 962-fold more active than gefitinib against the A549 cell line, and 5904-fold more active than gefitinib against the HCT116 cell line. This trend is consistent with the isoxazole ring containing glycyrrhetinic acid derivatives as anti-inflammatory agents, as studied by us before (for example, TY501 is the most potent among the isoxazole ring containing glycyrrhetinic acid derivatives).[20–22]

In summary, seven isoxazole-ring-containing ferrocene derivatives were first synthesized and their *in vitro* anticancer activity was also evaluated. The results indicate that introducing the isoxazole moiety to the ferrocene core will greatly improve its anticancer activity. **3d** is a promising candidate for the development of anticancer drugs. Further study of the anticancer activity of **3d** is under way. Based on this research, more novel structures of ferrocene derivatives will be designed and synthesized, and their biological activities will also be studied soon.

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