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# *o*-Carboxybenzoylferrocene. Bioactivity and chemical Modifications

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**The antitumor activity of *o*-carboxybenzoylferrocene sodium salt (1) was studied *in vivo*. Interaction between *o*-carboxybenzoylferrocene (2) and *N,N*′-carbonyldiimidazole in boiling methylene dichloride leads to 3-(*N*-imidazolyl)-3-ferrocenylisobenzofuran-1(3*H*)-one (5). The structure of compound 5 was established by X-ray analysis. Aminolysis of compound 5 in toluene gave rise to ferrocenoylbenzamides (6a–d) – derivatives of dimethylamine, piperidine, pyrrolidine and morpholine. Copyright © 2008 John Wiley & Sons, Ltd.**

**Keywords:** ferrocene; *o*-carboxybenzoylferrocene; *N,N*′-carbonyldiimidazole; antitumor activity; crystal structure

## Introduction

The biological activity of ferrocene compounds is closely related to their unique properties: lipophilicity and membrane permeability, low toxicity, planar chirality, redox activity and bulky structure. During the two decades after the discovery of ferrocene, investigation of their antianemic properties attracted the attention of various research groups. As a result, one compound belonging to the ferrocene series, namely, *o*-carboxybenzoylferrocene sodium salt (**1**), $FcC(O)C_6H_4CO_2Na\cdot 4H_2O$, has been recommended for use in clinical practice.[1,2] This drug (trade marks ferroceron and eritrostimulin) is intended for treating diseases caused by iron-deficient anomalies such as anemia of various etiologies, ozena and parodontosis.[1c,2] In the 1980s, when the antineoplastic effects of ferricenium salts were found,[3] an intensive search for ferrocene-containing compounds with antitumor activity began.[4–12] It can be assumed that the presence or possibility of acquisition of a positive charge is necessary for manifestation of the antitumor effects of ferrocene compounds.[6,13] Thus, positive-charged ferricenium salts with different substituents[3,4,8] – polyferrocenylenemethylene ologomer with ferrocene and ferricenium moieties,[8] *bis*-(ferrocenylmethyl)imidazolium salt[8] and *bis*-(ferrocenylalkyl) benzotriazolium salts[8] – in *in vivo* experiments inhibited tumor growth. It was found that uncharged ferrocene conjugates of polyaspartatamides (*in vitro*)[12] and ferrocenylethyl benzimidazole (*in vivo*)[11] demonstrated the inhibition effect as well. Moreover, potentially anionogenic acids such as ferrocenylacetic $FcCH_2COOH$ and ferrocenylmethylthiomalic $FcCH_2S\text{-}CHCOOH\text{-}CH_2COOH$ in clonogenic *in vitro* tests inhibited a formation of colonies of cells of human lung cancer and cultures of lung carcinoma PC-9,[6] to even a greater degree than do ferricenium salts. This effect does not develop immediately after incubation; a certain prolonged period is needed. It was proposed[6] that a stage of metabolic activation is necessary, possibly the formation of the ferricenium cations of the mentioned acids.

Here we report on the antitumor effect of *o*-carboxybenzoylferrocene sodium salt (**1**). In this compound the ferrocene-containing part of the molecule carries a negative charge. The syntheses of *o*-carboxybenzoylferrocene derivatives including imidazole-containing compound **5** and ferrocenoylbenzamides **6a–d** are studied. The X-ray structure data for 3-(*N*-imidazolyl)-3-ferrocenylisobenzofuran-1(3*H*)-one (**5**) are presented (Fig. 1).

## Results and Discussion

### Antitumor activity tests

In 1984 Köpf-Maier *et al*. published the results of antitumor activity of ferricenium salts.[3] It was established that the ferrocene compounds should be positively charged in order to display antitumor activity. However, later the antitumor activity of uncharged ferrocene compounds – ferrocenylalkyl azoles,[11,14] ferrocene-modified complexes of platinum(II)[15] and ferrocene-conjugates of polyaspartatamides[12] – was shown. The authors[13] believed that these originally uncharged compounds may acquire the charges during their transportation in biological systems (via oxidation to ferricenium salts or protonation of nitrogen-containing heterocyclic moieties). It is of interest to study the activity of *o*-carboxybenzoylferrocene sodium salt (**1**), the antianemic drug that in contrast to positively charged ferricenium salts bears the negative charge on the ferrocene moiety (exactly on the carboxylic substituent).

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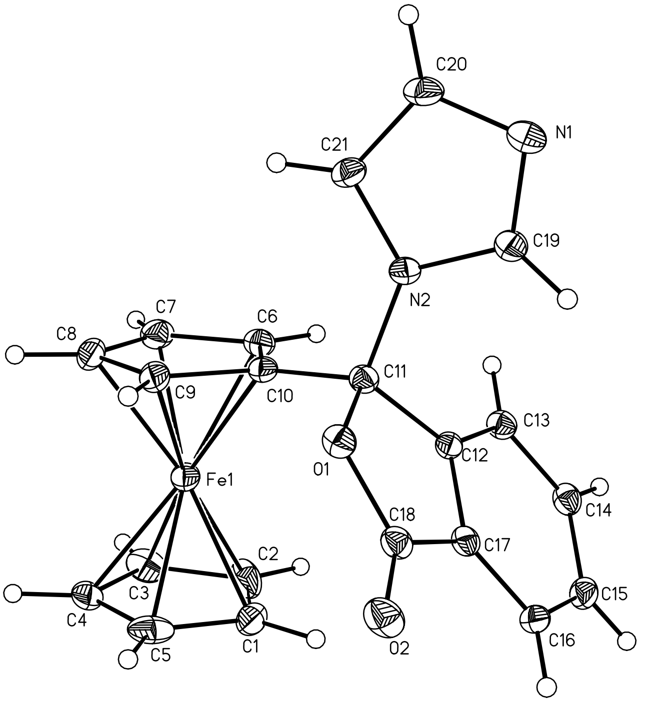


**Figure 1.** Molecular structure of (**5**). Some bond lengths (Å) and angles (deg): average(Fe1–C1–5) = 2.047(2), average(Fe1–C6–10) = 2.045(2), O1–C11 = 1.461(2), N2–C11 = 1.457(2), C10–C11 = 1.505(2), C6–C10–C11 = 126.0(2), C10–C11–O1 = 108.1(1), N2–C11–C12 = 111.6(1), C13–C12–C11 = 130.3(2), C6–C10–C11–N2 = 77.7(2), C6–C10–C11–O1 = −164.3(2), N2–C11–C12–C13 = −59.4(2). Only the major component of the disordered C1–C5 ring is shown for clarity.

**Table 1.** The results of antitumor effect of *o*-carboxybenzoylferrocene sodium salt (**1**) against solid tumor models – carcinoma 755, melanoma B-16 and Lewis lung carcinoma *in vivo*

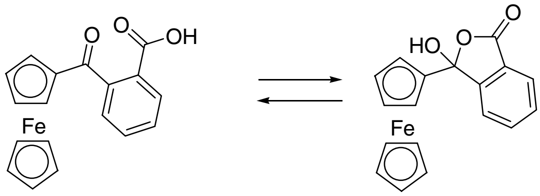
| | | Tumor strains | | |
|---|---|---|---|---|
| | | Ca755 (12th day) | B16 (14th day) | Lewis lung carcinoma |
| Compound | Daily dose, mg kg$^{-1}$ | Tumor growth inhibition, % | | |
| (**1**) | 10.0 | 25 | 50 | 15 |
| (**1**) | 5.0 | 35 | 25 | 10 |
| (**1**) | 2.5 | 70 | 70 | – |

Solvent, water; drug administration, intraperitoneal.

The antitumor activity of *o*-carboxybenzoylferrocene sodium salt (**1**) against some solid tumor models such as carcinoma 755 (Ca755), melanoma B16 (B16) and Lewis lung carcinoma (LLC) transplanted in BDF$_1$ mice was studied.

As seen from Table 1, the administration of compound **1** in the dose 2.5 mg kg$^{-1}$, the lowest dose studied, resulted in the inhibition of the growth of carcinoma 755 as well as melanoma B-16 by up to 70% as compared with controls. Carcinoma 755, as noted earlier,[11] is the most sensitive model to the action of the ferrocene compounds in comparison with the other tested tumor systems.

The toxicity of *o*-carboxybenzoylferrocene sodium salt (**1**) was characterized earlier by the level of LD$_{50}$, the dose lethal to 50% of treated animals, which was equal to 60 mg kg$^{-1}$,[16] and the level of the MTD, the maximum tolerated dose, which was equal to 50 mg kg$^{-1}$.



**2** **3**

**Scheme 1.** Equilibration of compound **2** and his cyclic tautomer **3**.

The therapeutic index (TI) for compound **1** was determined as the ratio between the LD$_{50}$ and the most effective ED$_{70}$ dose, as follows: TI = LD$_{50}$/ED$_{70}$. The therapeutic index was found to be equal to 24 (TI = 60/2.5 = 24) for the both testing systems, carcinoma 755 and melanoma B-16. For cisplatin, TI = 2.

It was also found that the mean life-span of tumor-bearing animals with carcinoma 755 as well as with melanoma B-16 treated by compound **1** was increased by 30% in comparison with the control.

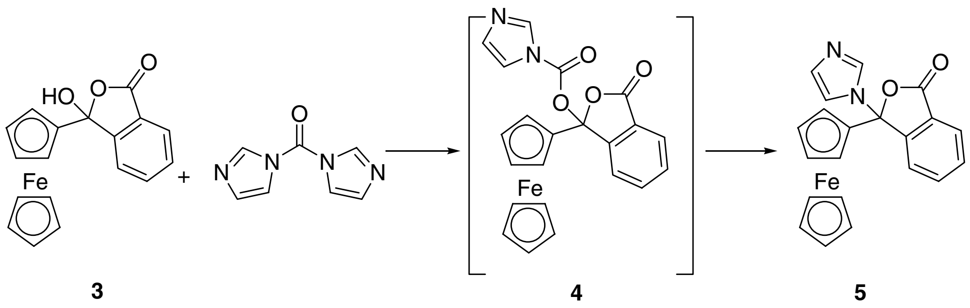
## Synthesis

Interaction of organic acids with *N,N′*-carbonyldiimidazole (CDI) provides a convenient method for the synthesis of amides and peptides[17] not requiring the preliminary preparation of the corresponding acyl chlorides or esters. The application of this method to *o*-carboxybenzoylferrocene (**2**) (the reaction of **2** with CDI in boiling methylene dichloride) furnished orange crystals as a single isolated product **5** that was stable in air and to hydrolysis. The X-ray diffraction analysis showed that compound **5** has the structure presented in Fig. 1 where imidazole is directly bonded to the $\alpha$-carbon atom with respect to the ferrocene moiety. EI-MS and $^1$H NMR spectra were recorded for the compound **5**. Thus, EI-MS displayed the molecular ion at *m/z* 384 and $^1$H NMR spectrum showed signals from the ferrocene nucleus protons (3.76–4.71 ppm, a set of five singlet from substituted and unsubstituted Cp-rings) and phenylene group in the form of two doublets and two triplets in the region of 7.62–7.89 ppm and a set of singlet from the imidazole ring protons in the region of 6.61–7.24 ppm.

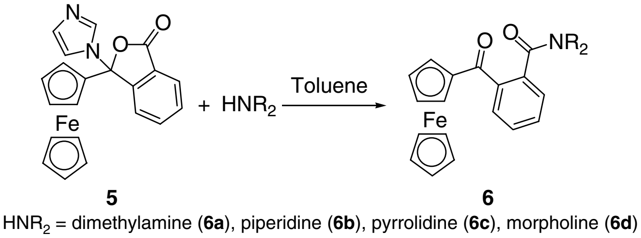
Usually the reaction of organic acids and CDI gives amides[17] and on the basis of EI-MS and $^1$H NMR spectral data it can be assumed that compound **5** my have a structure of *o*-carboxy benzoylferrocene imidazolide, FcC(O)PhC(O)Im. In spite of the X-ray determination results still being outstanding, Fig. 1 shows the cyclic laktame and imidazole in the $\alpha$-position to ferrocene.

The formation of the compound **5** allowed us to suggest Scheme 2. *o*-Carboxybenzoylferrocene is known to exist in solution in the form of two isomers[18] due to its capability of ring-chain tautomerism (Scheme 1). Only one of them is active in some transformations. In organic solvents, the less polar ring tautomer **3** is predominant and it is the one that reacts with CDI (Scheme 2). Most likely, the nucleophilic attack of carbinol **3** at the carbonyl carbon atom of CDI occurs in the first step and intermediate **4** forms after elimination of imidazole.

As shown earlier,[19] the ImC(O)O-group at the $\alpha$-position relative to the ferrocenyl fragment is rather labile and can be easily removed. This occurs due to the nucleophilic action of



**Scheme 2.** The 3-(*N*-imidazolyl)-3-ferrocenylisobenzofuran-1(3*H*)-one formation.



**Scheme 3.** Amides formation of the *o*-carboxybenzoylferrocene.

imidazole evolved earlier, furnishing product **5** in high yield (89%). Compound **5** represents itself a cyclic ester on the one hand and *N*-alkylated imidazole on the other.

Aminolysis of compound **5** in a solvent with higher b.p. than that of methylene dichloride, such as toluene, gave rise to amides **6** (Scheme 3). The structures of amides **6a–d** are non-cyclic since IR spectra have absorption bands corresponding to carbonyl and amide groups.

## Experimental

### Antitumor activity tests

Adenocarcinoma 755 (Ca755), melanoma B16 (B16), Lewis lung carcinoma (LLC) were transplanted subcutaneously to the inbred mice $f_1$ ($C_{57}Bl_6 \times DBA_2$), males with the weight 18–20 g. The water solution of compound **1** was administered in several doses, 2.5, 5.0 and 10.0 mg $kg^{-1}$ $day^{-1}$, intraperitoneally seven times every day starting from the next day after tumor transplantation. Each group comprised five to seven animals including control group of animals

The index of tumor growth inhibition was calculated as $(C - T)/C$, %, where $C$ and $T$ are the average sizes of tumors in groups of control and treated animals, respectively. The mean life-span of treated animals ($\tau_{exp}$) was compared with that of untreated ones in control group ($\tau_k$) and was expressed as the ratio $\tau = (\tau_{exp} - \tau_k)/\tau_k$, %, where $\tau$ is the index that characterizes the increase in mean life-span of treated mice compared with controls.

### Synthesis

$^1$H NMR spectra were obtained on a BruAVANCE instrument at 300 MHz. EI mass spectra were taken on a Kratos MS-890 spectrometer at 70 eV, IR spectra were recorded on an UR-20 spectrophotometer (Karl Zeiss). Methylene dichloride was dried over $CaCl_2$. CDI and amines were purchased from Acros Organics and used without purification. *o*-Carboxybenzoylferrocene was synthesized by acylation of ferrocene with phthalic anhydride.[1] *o*-Carboxybenzoylferrocene sodium salt (**1**) is commercially available and can be prepared according to patents.[1]

#### *3-(N-imidazolyl)-3-ferrocenylisobenzofuran-1(3H)-one (**5**)*

A mixture of 1.0 mmol of *o*-carboxybenzoylferrocene (**2**) and 1.3 mmol of CDI in anhydrous $CH_2Cl_2$ was refluxed for 1 h. The resulting mass was cooled and then washed with a 20% solution of phosphoric acid (2 × 50 ml), a 10% solution of KOH (2 × 50 ml) and water (2 × 100 ml). The organic layer was dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*. The resulting product was dried over $CaCl_2$. Yield 89%. Orange crystals, m.p. 165–168 °C, EI-MS: $m/z$ 384 (relative intensity 55%) $[M]^+$. $C_{21}H_{16}FeN_2O_2$. IR (KBr, $\nu$, $cm^{-1}$): 1797, 1667, 1480, 1364, 1288, 1262-1241, 1119, 1105, 1054, 999, 956, 857. $^1$H NMR ($CDCl_3$, $\delta$, ppm): 3.76 (s, 5H, Cp); 4.28 (s, 1H, CH); 4.34 (s, 1H, CH); 4.40 (s, 1H, CH); 4.71 (s, 1H, CH); 6.61 [s, 1H, CH(Im)]; 6.94 [s, 1H, CH(Im)]; 7.24 [s, 1H, CH(Im)]; 7.62 [d, $J$ = 7.4 Hz, 1H, $CH(C_6H_4)$]; 7.77 [dd (Viewed as triplet; the same relates to the other cases.), 1H, $CH(C_6H_4)$]; 7.84 [dd, 1H, $CH(C_6H_4)$]; 7.89 [d, $J$ = 7.4 Hz, 1H, $CH(C_6H_4)$].

### *o*-Ferrocenoylbenzamides (*6a–d*)

As the general procedure, a mixture of 1.0 mmol of *o*-carboxybenzoylferrocene and 1.3 mmol of CDI in toluene was refluxed for 1 h. Then 1.5 mmol of the corresponding amine was added, and the resulting mixture was refluxed for 2 h, cooled, and then washed with a 20% solution of phosphoric acid (2 × 50 ml), a 10% solution of KOH (2 × 50 ml) and brine. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*. The product was dried over $CaCl_2$.

#### *o-Ferrocenoylbenzdimethylamide (**6a**)*

Compound **6a** was synthesized from **2** and dimethylamine. Yield 47%. Brown powder, m.p. 163–164 °C, EI-MS, $m/z$: 361 (91%) $[M]^+$. $C_{20}H_{19}FeNO_2$. IR (KBr, $\nu$, $cm^{-1}$): 3137, 2942, 2869, 1790, 1665, 1524, 1499, 1480, 1427, 1415, 1391, 1364, 1342, 1288, 1260, 1242, 1192, 1120, 1105, 1067, 1046, 994, 955, 923, 840. $^1$H NMR ($CDCl_3$, $\delta$, ppm): 2.61 (s, 6H, $CH_3$); 3.78 (s, 5H, Cp); 4.30 (s, 1H, CH); 4.36 (s, 1H, CH); 4.41 (s, 1H, CH); 4.72 (s, 2H, CH); 7.64 [d, $J$ = 7.4 Hz, 1H, $CH(C_6H_4)$]; 7.78 [dd, 1H, $CH(C_6H_4)$];.7.85 [dd, 1H, $CH(C_6H_4)$]; 8.14 [d, $J$ = 7.4 Hz, 1H, $CH(C_6H_4)$].

### *o*-Ferrocenoylbenzpiperidinide (**6b**)

Compound **6b** was synthesized from **2** and piperidine. Yield 49%. Red-brown powder, m.p. 84–87 °C, EI-MS, *m/z*: 401 (60%) $[M]^+$. $C_{23}H_{23}FeNO_2$. IR (KBr, $\nu$, $cm^{-1}$): 1799, 1655, 1480, 1361, 1288, 1260-1242, 1119, 1103, 1084, 1065, 1045, 993, 956, 921, 844, 764. $^1H$ NMR ($CDCl_3$, $\delta$, ppm): 1.46 (m, 2H, $CH_2$); 1.67 (m, 4H, $CH_2$); 3.24 (m, 4H, $CH_2$); 4.29 (s, 5H, Cp); 4.41 (s, 1H, CH); 4.55 (s, 1H, CH); 4.72 (s, 1H, CH); 4.82 (s, 1H, CH); 7.63 [d, $J = 7.2$ Hz, 1H, $CH(C_6H_4)$]; 7.78 [dd, 1H, $CH(C_6H_4)$]; 7.85 [dd, 1H, $CH(C_6H_4)$]; 7.90 [d, $J = 7.2$ Hz, 1H, $CH(C_6H_4)$].

### *o*-Ferrocenoylbenzpyrrolidinide (**6c**)

Compound **6c** was synthesized from **2** and pyrrolidine. Yield 77%. Red-brown powder, m.p. 113–115 °C, EI-MS, *m/z*: 387 (60%) $[M]^+$. $C_{22}H_{21}FeNO_2$ (387.25): calcd C 68.23, H 5.47, Fe 14.42, N 3.62%; found C 68.08, H 5.37, Fe 14.17, N 3.41%. IR (KBr, $\nu$, $cm^{-1}$): 1800, 1664, 1460, 1290-1267, 1244, 1121, 959, 849. $^1H$ NMR ($CDCl_3$, $\delta$, ppm): 1.67 (m, 4H, $CH_2$); 3.33 (m, 4H, $CH_2$); 4.30 (s, 5H, Cp); 4.35 (s, 1H, CH); 4.41 (s, 1H, CH); 4.55 (s, 1H, CH); 4.71 (s, 1H, CH); 7.64 [d, $J = 7.4$ Hz, 1H, $CH(C_6H_4)$]; 7.79 [dd, 1H, $CH(C_6H_4)$]; 7.86 [dd, 1H, $CH(C_6H_4)$]; 7.90 [d, $J = 7.4$ Hz, 1H, $CH(C_6H_4)$].

### *o*-Ferrocenoylbenzmorpholinide (**6d**)

Compound **6d** was synthesized from **2** and morpholine. Yield 42%. Red powder, m.p. 168–171 °C, EI-MS, *m/z*: 403 (100%) $[M]^+$. $C_{22}H_{21}FeNO_3$ (403.25): calcd C 65.53, H 5.25, N 3.47%; found C 65.41, H 5.16, N 3.41%. IR (KBr, $\nu$, $cm^{-1}$): 2970, 1660, 1479, 1463, 1300-1277, 1126, 1042, 876, 857, 795. $^1H$ NMR ($CDCl_3$, $\delta$, ppm): 3.37 (m, 4H, $CH_2$); 3.68 (m, 4H, $CH_2$); 4.19 (s, 5H, Cp); 4.38 (s, 2H, CH); 4.44 (s, 2H, CH); 7.36 [d, $J = 7.4$ Hz, 1H, $CH(C_6H_4)$]; 7.45 [dd, 1H, $CH(C_6H_4)$]; 7.47 [dd, 1H, $CH(C_6H_4)$]; 7.84 [d, $J = 7.4$ Hz, 1H, $CH(C_6H_4)$].

## Structure determination

The single-crystal X-ray diffraction experiment for an orange block of **5** (grown from the slow evaporation of an acetone solution of **5** held at room temperature) was carried out with a Bruker Smart 1000 CCD area detector, using graphite monochromated Mo-$K_\alpha$ radiation ($\omega$-scans with a 0.3° step in $\omega$ and 10 s per frame exposure) at 120 K. The temperature was maintained with a Cryostream (Oxford Cryosystems) open-flow $N_2$ gas cryostat, and no absorption correction was applied to the data.

The structure was solved by direct methods and refined by a full-matrix last-squares technique using standard methods. The C1–C5 cyclopentadienyl ring was found to be disordered over two sites with the site occupancy factors, from refinement, of 0.58(2) and 42(2).

*Crystal data for* **5**: formula, $C_{21}H_{16}FeN_2O_2$, $M = 384.21$, triclinic, $P-1$ $a = 8.1248(6)$, $b = 9.5952(7)$, $c = 12.2928(9)$ Å, $\alpha = 104.051(2)$, $\beta = 99.095(2)$, $\gamma = 108.950(2)°$, $V = 849.46(11)$ Å$^3$, $Z = 2$, $D_{calc} = 1.502$ g $cm^{-3}$, $\mu = 0.905$ $mm^{-1}$, $\theta_{max} = 29.0°$, no. of reflections = 8600, no. independent reflections = 4399, no. unique reflections with $I > 2\sigma(I) = 3717$, no. parameters = 281, $R_1 = 0.038$, and $wR_2 = 0.083$.

All calculations were carried out on IBM PC using the SHELXTL program.[20]

## Supplementary material

Atomic coordinates are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; deposition number CCDC-608 061.

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