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# Synthesis, structure and redox potentials of biologically active ferrocenylalkyl azoles

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**Abstract**

The syntheses, structures, electrochemical properties of the series of ferrocenylalkyl azoles, FcAlkAz, as well as the antitumor activity of ferrocenylmethyl benzimidazole (**8**) have been studied. Above mentioned compounds were investigated by the method of cyclic voltametry. All of them exhibited a reversible one-electron oxidation–reduction wave owing to the ferrocene–ferrocenium redox couple with a positive shift (0.50–0.65 V) compared with that of ferrocene (0.42 V). The X-ray determination of molecular structures of 1-(ferrocenylmethyl)imidazole (**4**), 1-(ferrocenylbenzyl)imidazole (**7**) and 1-(ferrocenylmethyl)bezimidazole (**8**) was carried out. Compound **4** with imidazolyl substituent was found to be present in *N*-protonated form. Antitumor activity of 1-(ferrocenylmethyl)benzimidazole (**8**) against some solid tumor models such as adenocarcinoma 755 (Ca755), melanoma B16 (B16) and Lewis lung carcinoma was studied. The antitumor activity of compound **8** was compared with cisplatin effectiveness against some experimental tumor systems.


*Keywords:* Ferrocenylalkyl azoles; Ferrocene derivatives; Electrochemistry (cyclic voltametry); X-ray crystal structure; Antitumor activity; Experimental tumor systems

## 1. Introduction

The modern investigation of biologically active compounds involves the study of their pharmacokinetics and mechanisms of action that may be responsible for the specific pharmacological effects of tested subjects. This requires the knowledge of what occurs in the first stages of interaction of the compounds with biological objects and what target organs and cell structures are affected by the compounds.

The study of biological activity of ferrocene compounds began since 1960s [1]. The presence of the iron atom in the ferrocene molecule defined in the certain extent the direction of these investigations. The biologically active ferrocene derivatives with the antianaemic properties were among compounds that attracted the great attention of various research groups [1–5]. Ferrocene compounds with N-heterocycle moieties, ferrocenylalkyl azoles, FcAlkAz, are of our current interest due to their antitumor activity combined with low toxicity [6–9]. While discussing possible mechanisms of

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action of these compounds on tumors and metabolic transformation routes in organisms one can assume one-electron oxidation of the ferrocene nuclei to the fericenium forms $Fc^+(Alk)Az$ [8]. Actually fericenium salts $Fc^+X^-$ ($X^- = CCl_3CO_2$, $C_6H_2(NO_2)_3$, $FeCl_4 \cdot 2CH_3COOH$) were the first compounds in the ferrocene series that demonstrated antitumor activity [10,11]. These salts have relatively low reduction potentials [12] suitable for biological processes to occur. The oxidation potentials for substituted ferrocene compounds depend to a marked degree on electron-donating or electron-accepting properties of the lateral substituents and can change in large range [12]. The value of this potential, we believe, may serve as a measure of ease of FcAlkAz metabolic transformations in organism. On the other hand, ferrocenylalkyl azoles as cationoid molecules can be simply protonated to give positively charged particles $Fc(Alk)AzH^+$. Thus neutral FcAlkAz can be easily transformed into the positive particles by means of either oxidation of the ferrocene nucleus or protonation of azole.

Here we report on the synthesis, structures and electrochemical behavior of a series of ferrocenylalkyl azoles. The antitumor effect of the compound from these series, 1-(ferrocenylmethyl)benzimidazole (**8**), was investigated in vivo. The oxidation processes are one-electronic and reversible. The oxidation potential values for the studied compounds ($E_p^{ox} = 0.50$–$0.65$ V) are more positive than that for ferrocene (0.42 V). The reduction potentials were determined for complexes **3**, **6** only (Table 1). The X-ray structure data for 1-(ferrocenylmethyl)imidazole (**4**), 1-(ferrocenylbenzyl)imidazole (**7**) and 1-(ferrocenylmethyl)benzimidazole (**8**) are presented (Figs. 2–4. For compound **4** in the crystals only the *N*-hydrated forms $FcCH_2Im \cdot 0.5H_2O$ were found. The possible routes of biological conversion of ferrocenylalkyl azoles are discussed taking into consideration the electrochemical and structural data, chemical transformations routes and the results of the antitumor activity tests.

Table 1
The redox potentials for ferrocenylalkyl imidazoles and related compounds

| Compound number | Formula | $E_p^{ox}$ (V) | $E_p^{red}$ (V) |
|---|---|---|---|
| **1** | FcH | 0.42 | – |
| **2** | $FcCH(CH_3)OH$ | 0.42 | – |
| **3** | $FcCH(CH_3)BTr$ | 0.52 | −2.43 |
| **4** | $FcCH_2Im$ | 0.53 | – |
| **5** | $FcC(CH_3)_2Im$ | 0.56 | – |
| **6** | $FcCH(C_3H_7)Im$ | 0.65 | −2.34 |
| **7** | $FcCH(C_6H_5)Im$ | 0.53 | |
| **8** | $FcCH_2BIm$ | 0.50 | |

In $CH_3CN$ solution with 0.1 M $[(n\text{-}Bu)_4N]BF_4$, $c = 2 \times 10^{-3}$ M; Fc – ferrocenyl, BTr – benzotriazolyl ($C_6H_4N_3$), Im – imidazolyl ($C_3H_3N_2$), BIm – benzimidazolyl ($C_7H_5N_2$).

## 2. Results and discussion

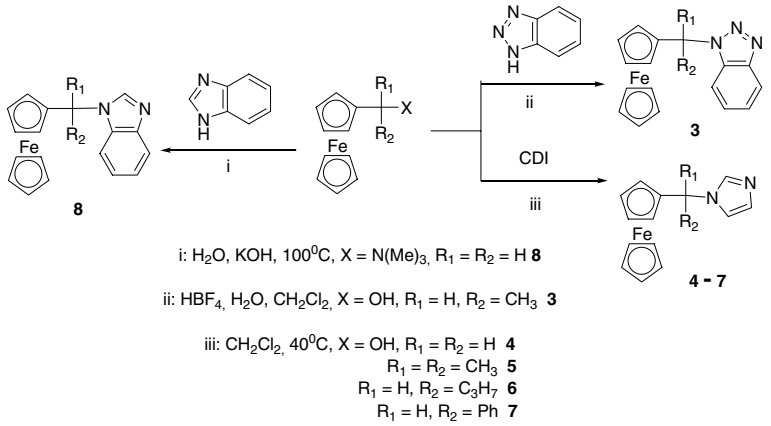
### 2.1. Synthesis

Ferrocenylalkyl azoles were synthesized accordingly to three synthetic approaches (Scheme 1). 1-(α-Ferrocenylethyl)benzotriazole $FcCH(CH_3)BTr$ (**3**) was prepared from 1-ferrocenylethanol (**2**) via the reaction with benzotriazole in $CH_2Cl_2$ in the presence of 45% aqueous fluoroboric acid at room temperature within several minutes [13–15a]. The molecular structure of compound **3** was determined by Starikova [15b]. Since imidazole is a relatively strong base (basic $pK_a$ 7.00) it does not undergo *N*-ferrocenylalkylation under the acidic conditions readily forming a salt $ImH \cdot HBF_4$ instead [15a]. Therefore ferrocenylalkyl imidazoles **4**–**7** were synthesized by a simple recently published route excluding acidic conditions from *N*,*N*′-carbonyldiimidazole (CDI, ImC(O)Im) and appropriate ferrocenylcarbinoles in boiling $CH_2Cl_2$ [16a]. Finally, ferrocenylmethyl benzimidazole $FcCH_2BIm$ (**8**) was prepared according to a classic method from (ferrocenylmethyl)three methylammonium iodide $FcCH_2N(CH_3)_3I$ [17a] and benzimidazole [17b] in boiling water with catalytic amount of potassium hydroxide [17c]. Compound **8** was also prepared by a just published procedure from thionyldibenzimidazole BImS(O)BIm and ferrocenylmethanol in methylene dichloride [16b].

### 2.2. Electrochemistry

It is well known that ferrocene is easily oxidized to the ferricenium cation by one-electron oxidants [12]. The redox-potentials for the ferrocene–ferricenium couple range from 0.3 to 0.4 V. The redox potentials for ferrocene derivatives change within wider limits. The potential depends on the electron-donating or electron-withdrawing ability of the substituents. Thus, the redox properties can be rather strongly affected by altering the substituent nature.

Table 1 gives the electrode potentials for ferrocenylalkyl azoles and the related compounds, namely, 1-(ferrocenylmethyl)imidazole and 1-(ferrocenylmethyl)benzimidazole in which the ferrocenyl moiety is connected to 1-N atom of the azole ring via a methylene bridge (compounds **4**, **8**) or substituted methylene ones: Me (compounds **3**, **5**), *n*-Pr (compound **6**) and Ph (compound **7**). All the compounds exhibit reversible one-electron waves. The electrode potentials for compounds **3**–**8** (0.52, 0.53, 0.56, 0.65, 0.53, and 0.50 V accordingly) showed a positive shift compared to that of ferrocene (0.42 V) indicative of the electron withdrawing effect of the N-heterocycle. The introduction of alkyl groups decreases potential. As to compounds **5** the slight increase of potential compared to that for compound **4** may be attributed to the different alkyl bridge. In contrast with value $E^0 = 0.172$ V (in ethanol) for ferroce-




Scheme 1.

nylbutanoic acide $Fc(CH_2)_3CO_2H$ earlier reported by Professor Neuse [18,19], the oxidation potential for compound **6** with the imidazolyl fragment connected ferrocene by the CH-group bearing *n*-propyl substituent is significantly harder and amounts to 0.65 V. This fact is obviously connected with the intramolecular interaction between the $C_3H_7$-function and the iron atom. However, the presence of the condensed benzene rings in the benzotriazole derivative **3** ($E^0 = 0.52$ V) and benzimidazole one **8** ($E^0 = 0.50$ V) results in the minimum electron withdrawal from the ferrocenyl groups. A similar electrode potential of +0.53 V was obtained for compound **7**. Complex **8** ($E^0 = 0.50$ V) is more easily oxidized than all the complexes investigated (see Fig. 1).

### 2.3. Structures of ferrocenylmethyl imidazole (4), ferrocenylbenzyl imidazole (7) and ferrocenylmethyl benzimidazole (8)

$FcCH_2Im$ (**4**) is formed as a result of the substitution of the N-bonded hydrogen atom in the 1*N*-position of imidazole by the ferrocenylmethyl fragment (Fig. 2). The same substitution site was found in both the corresponding ferrocenylbenzyl derivative **7**, and ferrocenylmethyl benzimidazole (**8**) (Figs. 3 and 4).

The 1*N*-ferrocenylalkyl substituted molecules in all three crystal structures **4**, **7** and **8** are very similar with respect to geometrical characteristics of both imidazole and ferrocenyl moieties. In all three cases the Cp-rings of ferrocenyl group are in the eclipsed conformations (Table 2). The dihedral angles between the imidazole planes and Cp-rings are equal to 111.0°, 108.5° and 115.5° for molecules **4**, **7** and **8**, respectively. The steric effects associated with the presence of the phenyl substituent at the C(6) atom cause slight changes in the bond angles C(1)–C(6)–N(1), that is minimal for **7**.

The heterocycle-ferrocenyl bonds are realized by means of the triad of atoms: N(heterocycle)–C(bridge)–C(ferrocenyl). The exocyclic bonds N(1)–C(6) in molecules **4** and **7** exceed the standard statistical value (1.469 Å) for any bond between C($sp^3$) and a three-coordinated nitrogen atom [20]. The variation of bond lengths N(heterocycle)–C(bridge) correlates with electronic properties of heterocycles and its substituents

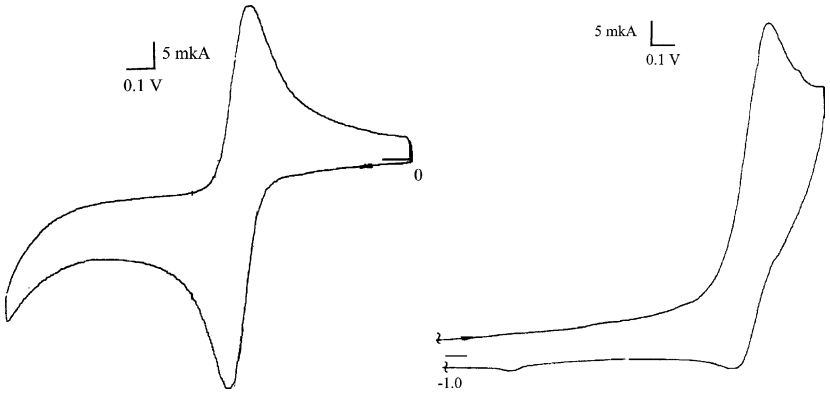



Fig. 1. Cyclic voltamogramms of ferrocenylbutyl imidazole (**6**) ($c = 2\times10^{-3}$ M, with $[(n\text{-}Bu)_4N]BF_4$ in acetonitrile and glassy carbon electrode; the scan rate was 200 $mV\,s^{-1}$).

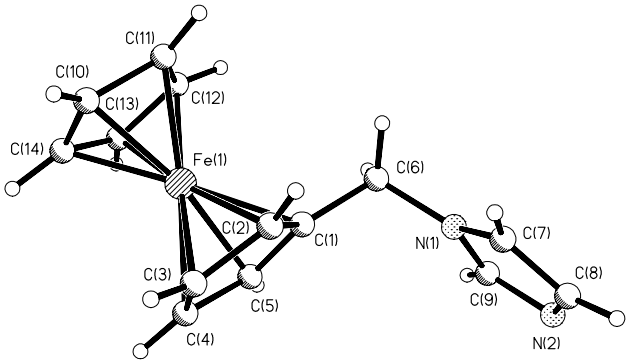



Fig. 2. Molecular structure of ferrocenylmethyl imidazole (**4**). Selected bond lengths (Å) and bond angles (°): C(1)–C(6)=1.500(4), C(6)–N(1)=1.474(4), N(1)–C(7)=1.367(4), N(1)–C(9)=1.357(4), N(2)···H=2.27(4); C(1)–C(6)–N(1)=111.0(2), C(7)–N(1)–C(9)=106.7(3), C(6)–N(1)–C(7)=126.3(3), C(6)–N(1)–C(9)=126.6(3).

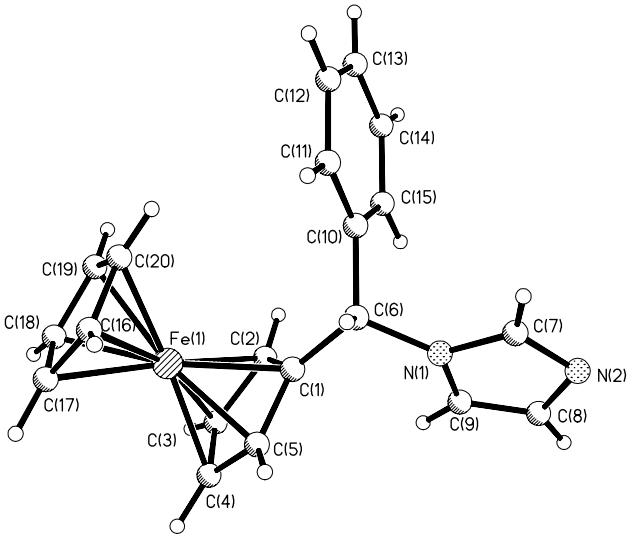



Fig. 3. Molecular structure of ferrocenylbenzyl imidazole (**7**). Selected bond lengths (Å) and bond angles (°): C(1)–C(6)=1.499(5), C(6)–N(1)=1.487(4), C(6)–C(10)=1.521(5), N(1)–C(7)=1.356(5), N(1)–C(9)=1.360(5); C(1)–C(6)–N(1)=108.5(3), C(1)–C(6)–C(10)=115.8(3), N(1)–C(6)–C(10)=109.6(3), C(7)–N(1)–C(9)=105.7(3), C(6)–N(1)–C(7)=124.8(3), C(6)–N(1)–C(9)=129.1(3).

(see also X-ray studies of ferrocenylalkyl nucleobases [21,22]). The bond lengths C(bridge)–C(ferrocenyl) for compounds **4**, **7** and **8** are virtually similar (Table 2).

The other nitrogen atom (of pyridine type) in the imidazole nucleus, being a potential hydrogen acceptor, either does not participate in hydrogen bonding at all (compounds **7** and **8**) or forms the H-bond with water molecule (compound **4**).

### *2.4. Antitumor activity of 1-(ferrocenylmethyl)benzimidazole (**8**)*

Preliminary investigations showed the low toxicity of such type of ferrocene compounds as **8** [7]. $LD_{50}$ proved to be impossible to determine due to the small solubility

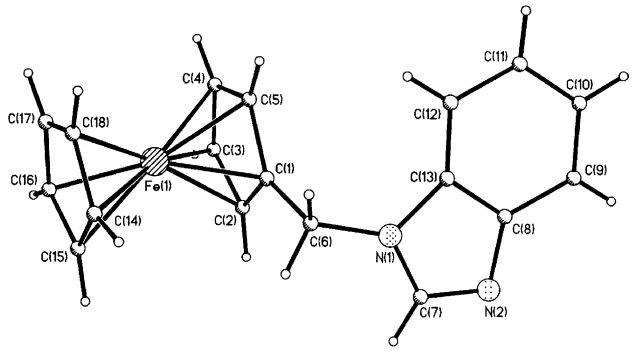



Fig. 4. Molecular structure of ferrocenylmethyl benzimidazole (**8**). Selected bond lengths (Å) and bond angles (°): C(1)–C(6)=1.506(10), C(6)–N(1)=1.450(11), N(1)–C(7)=1.338(11), N(1)–C(13)=1.394(10); C(1)–C(6)–N(1)=113.5(6), C(7)–N(1)–C(13)=106.2(9), C(6)–N(1)–C(7)=128.9(9), C(6)–N(1)–C(13)=124.6(9).

Table 2
Some bond lengths (Å) and selected angles (°) in 1-(ferrocenylmethyl)imidazole (**4**), 1-(ferrocenylbenzyl)imidazole (**7**) and 1-(ferrocenylmethyl)bezimidazole (**8**)

| Compound | $FcCH_2Im$ (**4**) | FcCH(Ph)Im (**7**) | $FcCH_2BIm$ (**8**) |
|---|---|---|---|
| Fe–C(average) | 2.026; 2.043 | 2.030; 2.029 | 2.027; 2.028 |
| $Fe–C_{ipso}$ | 2.031 | 2.036 | 2.021 |
| Fe–(center $C_5H_5$) | 1.637 | 1.652 | 1.643 |
| Fe–(center $C_5H_4$) | 1.642 | 1.633 | 1.629 |
| Angle Cp–Cp eclipse | 1.0 | 4.2 | 1.4 |
| Angle $Cp_{substituted}$–Het | 111.0(2) | 108.6(3) | 113.5(6) |
| $C_{ipso}$–C | 1.500(4) | 1.498(5) | 1.506(10) |
| $C_5H_4CH(R)–N_{Het}$ | 1.474(4) | 1.488(4) | 1.450(11) |

of the neutral ferrocenylmethyl benzimidazole (**8**) in water. The maximal over-come dose (MD) was found to be 400 mg/kg. The antitumor activity of compound **8** against solid tumors was studied. These in vivo investigations were carried out with survival tumors of animals. Adenocarcinoma Ca755, melanoma B16 and Lewis lung carcinoma (LLC) were used as experimental models of solid tumors. The tested doses varied in the interval 5–50 mg/kg. The results are presented in a graphic form (Fig. 5). It was found (in general) that complex **8** provided antitumor effectiveness against all of three tested solid tumors. The inhibition of tumor growth was shown to be up to 70% (LLC, curve D, dose 5 mg/kg), which compared with that of cisplatin (positive control, our data) at the same dose, and also with the inhibition produced by **8** upon Ca755 at the dose of 50 mg/kg (curve B).

With respect to carcinoma 755 (curve B), compound **8** exhibited the approximately direct doze-efficiency dependence. As to the B16 and LLC tumors, the curves have a maximum and a minimum accordingly (doses 25 mg/kg) and are symmetrically disposed towards the horizontal axis, the maximum effectiveness being 60%

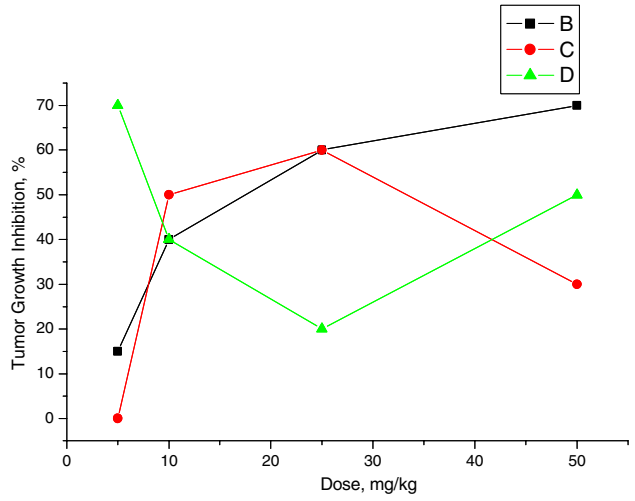



Fig. 5. Dose–antitumor effect of ferrocenylmethyl benzimidazole $FcCH_2BIm$ (**8**) against adenocarcinoma 755 (curve B), melanoma B16 (curve C) and Lewis lung carcinoma (curve D) on the 15th day after treatment.

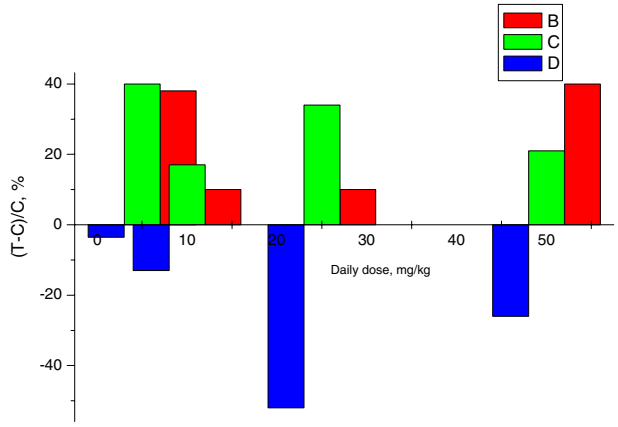



Fig. 6. Dependence of the life span (% to control) of tumor-bearing mice with adenocarcinoma 755 (B) melanome B16 (C) and Lewis lung carcinome (D) from the daily dose of ferrocenylmethyl benzimidazole $FcCH_2BIm$ (**8**).

(B16, dose 25 mg/kg,) and 70% (LLC, dose 5 mg/kg), respectively.

The life span of mice with Ca755 and B16 melanoma, treated with $FcCH_2BIm$ increased in compare to control (Fig. 6). It is note worthy, that compound **8** showed diminishing the life span of animals with LLC.

## 3. Experimental

### 3.1. Synthesis

The starting ferrocenylmethanol was obtained from trimethylferrocenylmethylammonium iodide [17a]. Carbinols $FcCH(CH_3)OH$ (**2**), $FcCH(C_3H_7)OH$, $FcCH(C_6H_5)OH$ were prepared by acylation of ferrocene with corresponding acid chlorides [23] followed by reduction of the acyl derivatives with lithium aluminium hydride in diethyl ether [24,15a]. Dimethylferrocenylcarbinol $FcC(CH_3)_2OH$ was synthesized by the reaction of ferrocene with acetone in the presence of 95% sulfuric acid [25]. Ferrocenylethyl benzotriazole $FcCH(CH_3)BTr$ (**3**) was obtained by the reaction of 1-ferrocenylethanol (**2**) with benzotriazole in methylene dichloride in the presence of 45% fluoroboric acid at r.t. for several minutes [15]. Ferrocenylalkyl imidazoles **4**–**7** were synthesized from carbonyldiimidazole (CDI, ImC(O)Im) and appropriate α-ferrocenylcarbinols [16]. Ferrocenylmethyl benzimidazole $FcCH_2BIm$ (**8**) was prepared both from (ferrocenylmethyl)threemethylammonium iodide $FcCH_2N(CH_3)_3I$ and benzimidazole in boiling water [17c] and thionyldibenzimidazole and ferrocenylmethanol in methylene dichloride [16c].

*α-Ferrocenylethyl benzotriazole* (**3**). Yield: 93%. Yellow crystals, m.p. 131–132 °C. Anal. C, 65.74; H, 5.24; Fe, 16.56; N, 12.06%. Calc. for $C_{18}H_{17}FeN_3$: C, 65.28; H, 5.17; Fe, 16.86; N, 12.69%. EI-MS, *m/z*: 331 (relative intensity 100%) $[M^+]$; 303 $[M–N_2]^+$; 238 $[M–N_2–Cp]^+$; 213 $[M–C_6H_4N_3]^+$; 165.5 $[M]^{2+}$. $^1H$ NMR (acetone-$d_6$, δ, ppm): 1.31 (d, 3H, $CH_3$); 4,19 (s, 2H, $C_5H_4$); 4.23 (s, 5H, $C_5H_5$); 4.43 (s, 2H, $C_5H_4$); 5.60 (s, 2H, $CH_2$); 7.33–8.00 (m, 4H, Ph). IR (KBr, *ν*, $cm^{-1}$): 3090, 2985, 2950, 1500, 1460, 1381, 1320, 1276, 1240, 1170, 1150, 1109, 1008, 994, 825.

*Ferrocenylmethyl imidazole* (**4**) [16c]. Yield: 80%. Yellow crystals, m.p. 65 °C, EI-MS *m/z*: 266 (100%) $[M^+]$.

*Ferrocenyl-iso-propyl imidazole* (**5**) [16c]. Yield: 80%. Yellow crystals, m.p. 104–105 °C, EI-MS *m/z*: 294 (23%) $[M^+]$.

*Ferrocenylbutyl imidazole* (**6**) [16c]. Yield: 78%. Dark brown oil, EI-MS *m/z*: 308 (100%) $[M^+]$.

*Ferrocenylbenzyl imidazole* (**7**) [16c]. Yield: 82%. Yellow crystals, m.p. 91–92 °C, EI-MS *m/z*: 342 (75%) $[M^+]$.

*Ferrocenylmethyl benzimidazole* (**8**) [17c]. Yield: 73%. Yellow crystals, m.p. 129–129.5 °C (from hexane), m.p. 119–122 °C [17b]. Anal. C, 68.41; H, 5.11; Fe, 17.68; N, 8.91%. Calc. for $C_{18}H_{16}FeN_2$: C, 68.38; H, 5.10; Fe, 17.66; N, 8.86%. EI-MS, *m/z*: 316 $[M^+]$; 199 $[FcCH_2]^+$; 195 $[C_5H_4CH_2BIm]^+$; 186 $[FcH]^+$; 121 $[FeCp]^+$; 118 $[BzImH]^+$; 78 $[C_5H_4CH_2]^+$; 65$[Cp]^+$; 56 $[Fe]^+$. $^1H$ NMR ($C_6H_6$, δ, ppm): 3.71–3.95 (m, 9H, 2Cp); 4,30 (c, 2H, $CH_2$); 7.10–7.37 (m, 2H, Ph); 7.65 (c, H, Im); 8.13 (m, 2H, Ph). IR (KBr, *ν*, $cm^{-1}$): 3150–3080, 1620, 1500, 1450, 1410, 1385–1520, 1290, 1270, 1240, 1210, 1160, 1110, 1035, 1010, 940, 845, 820, 785, 770, 745.

### 3.2. Electrochemistry

The electrochemical (cyclic voltammetry) measurements were performed on a PI-50-1 potentiostat. The

Table 3
Details of crystal structure determinations

| | $FcCH_2Im$ (**4**) | FcCH(Ph)Im (**7**) | $FcCH_2BIm$ (**8**) |
|---|---|---|---|
| Formula | $C_{14}H_{14}FeN_20.5H_2O$ | $C_{20}H_{18}FeN_2$ | $C_{18}H_{16}FeN_2$ |
| Formula weight | 275.13 | 342.21 | 316.18 |
| Crystal growth | Hexane–acetone 2:1, r.t. | Benzene, r.t. | Hexane–acetone 2:1, +7 °C |
| Crystal appearance | Orange prism | Pale yellow plate | Yellow prism |
| Crystal size ($mm^3$) | 0.50×0.40×0.25 | 0.50×0.40×0.20 | 0.35×0.20×0.15 |
| Crystal system | Tetragonal | Monoclinic | Orthorhombic |
| Space group | $P4_32_12$ | $P2_1/c$ | $P2_12_12_1$ |
| Diffractometer | Bruker SMART | Siemens P3/PC | Siemens P3/PC |
| $T$ (K) | 140 | 293 | 293 |
| $a$ (Å) | 8.9107(8) | 10.188(3) | 9.427(3) |
| $b$ (Å) | 8.9107(8) | 10.917(3) | 9.460(4) |
| $c$ (Å) | 30.742(4) | 14.489(4) | 16.440(7) |
| $\beta$ (°) | 90 | 94.93(2) | 90 |
| $V$ ($Å^3$) | 2440.9(4) | 1605.5(8) | 1466(1) |
| $Z$ | 8 | 4 | 4 |
| $D_{calc}$ ($g cm^{-3}$) | 1.497 | 1.416 | 1.433 |
| $\mu$ ($mm^{-1}$) | 1.218 | 0.939 | 1.022 |
| Absorption correction | SADABS | None | None |
| $T_{min}/T_{max}$ | 0.410/0.746 | – | – |
| $F(000)$ | 1144 | 712 | 656 |
| $\theta_{max}$ (°) | 58 | 50 | 54 |
| Number of reflections | 18906 | 3031 | 1773 |
| Independent reflections | 3218 | 2795 | 1731 |
| $R_{int}$ | 0.0557 | 0.0428 | 0.0446 |
| Number of parameters | 163 | 208 | 254 |
| $R1$ ($I>2\sigma(I)$) | 0.0515 (2517) | 0.0493 (1969) | 0.00658 (622) |
| $wR_2$ | 0.1298 | 0.1220 | 0.1139 |
| Goodness-of-fit | 0.992 | 1.035 | 0.808 |
| $\Delta\rho_{max}$, $\Delta\rho_{min}$ (e $Å^{-3}$) | 1.503/−0.317 | 0.414/−0.248 | 0.290/−0.257 |

working electrode was a glassy carbon disk ($s=2$ mm), the auxiliary electrode was a platinum plate. All the potential values are referred to the Saturated Calomel Electrode (SCE). The experiments were carried out at $c=2\times10^{-3}$ M under argon in deoxygenated acetonitrile solution containing 0.1 M $[(n\text{-}Bu)_4N]BF_4$, as a supporting electrolyte. The scan rate was 0.2 $V s^{-1}$.

### 3.3. Structures

Crystal data for compounds **4**, **7** and **8** are in Table 3. Single-crystal X-ray diffraction experiment for ferrocenylmethyl imidazole (**4**) was carried out with a Bruker SMART 1000 CCD area detector, using graphite monochromated Mo Kα radiation ($\omega$-scans with a 0.3° step in $\omega$ and 10 s per frame exposure) at 140 K. Low temperature of the crystals was maintained with a Cryostream (Oxford Cryosystems) open-flow $N_2$ gas cryostat. Reflection intensities were integrated using SAINT software [26] and semi-empirical method SADABS [27]. X-ray diffraction experiments for ferrocenylbenzyl imidazole (**7**) and 1-ferrocenylmethyl benzimidazole (**8**) were carried out with a Siemens P3/PC diffractometer ($T=293$ K, graphite-monochromated Mo Kα radiation), no absorption correction was applied.

The structure was solved by direct method and refined by the full-matrix last-squares technique for non-hydrogen atoms in the anisotropic approximation. All H atoms (except the H(N) and $H(O_w)$ atoms) were placed in the geometrically calculated positions and included in the refinement using the riding model approximation with the $U_{iso}(H)=1.2U_{eq}(C)$ for the methylene and $U_{iso}(H)=1.5U_{eq}(C)$ for methylene and methyl groups, where the $U_{eq}(C)$ is the equivalent isotropic temperature factor of the carbon atom bonded to the corresponding H atom. All calculations were carried out on IBM PC with the help of SHELXTL program [28].

### 3.4. Antitumor activity tests

Adenocarcinoma Ca755, melanoma B16, Lewis lung carcinoma were transplanted subcutaneously with the fragments of tumor tissues to the inbred mice $f_1(C_{57}Bl\times DBA_2)$, males with the weight 18–20 g. The were some groups of treated animals as well as the group of mice served as a control one, and the other one as a positive control (cisplatin). All groups comprised 5–7 animals each. Oil solutions of the ferrocenylmethyl benzimidazole (**8**) were given orally to the each group of treated animals beginning from the next day after

transplantation of the tumors. The index of tumor growth inhibition was calculated as $(C-T)/C$, %, where $C$ and $T$ – the average sizes of tumors in groups of control and treated animals, respectively. The mean survival time of the treated animals ($T$) was compared with that of untreated ones ($C$) and was expressed as the ratio $(T-C)/C$, %.

## 4. Supplementary material

Crystallographic data and refinement parameters for all compounds (**4**, **7** and **8**) are presented in the Table 3. Atomic coordinates are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, deposition numbers: CCDC-232572, CCDC-232573, and CCDC-232574, respectively.

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