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Synthesis, structure and enantiomeric resolution of ferrocenylalkyl mercaptoazoles. Antitumor activity *in vivo*

Alexey N. Rodionov [a, *], Kira Ya. Zherebker [a], Lubov′ V. Snegur [a], Alexander A. Korlyukov [a], Dmitry E. Arhipov [a], Alexander S. Peregudov [a], Mikhail M. Ilyin [a], Mikhail M. Ilyin Jr. [a], Oleg M. Nikitin [a, b], Nataliya B. Morozova [c], Alexander A. Simenel [a, d]

[a] A.N. Nesmeyanov Institute of OrganoElement Compounds, Russian Academy of Sciences, 28 Vavilov St., 119991 Moscow, Russian Federation
[b] Chemistry Department, M.V. Lomonosov Moscow State University, Leninskie Gory, 1/3, 119991 Moscow, Russian Federation
[c] P.A. Herzen Research Institute of Oncology, 3, 2nd Botkinskiy pass, 125284 Moscow, Russian Federation
[d] National University of Science and Technology "MISIS", Chemistry Department, 4 Leninskiy prospekt, 119049 Moscow, Russian Federation

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ABSTRACT

Ferrocenylalkyl 2-mercaptobenzimidazoles **3 (a–e)** and 2-mercaptobenzo[d]thiazole-2(3H)-thiones **5 (a–e)** were prepared *via* the reaction of the α-(hydroxy)alkyl ferrocenes, FcCHR(OH) (**1a–e**; Fc = ferrocenyl; R = H, Me, Et, i-Pr, Ph), either with thiobenzimidazole in acetone at room temperature in the presence of TFA (catalytic amounts), in yields of 55–74%, or with thiobenzothiazole in methylendicloride in presence of aqueous HBF_4 (equimolar amounts) at r.t., in yields of 41–58%. The structures, electrochemical properties and enantiomeric resolution **3a–e** and **5a–e** (using HPLC on modified amylose as chiral selector) were investigated. In cyclic voltammetry all studied compounds exhibited a reversible one-electron oxidation–reduction wave owing to the ferrocene–ferricenium redox couple with a positive shift (0.56–0.80 V) compared with that of ferrocene (0.50 V). X-ray determinations of molecular structures of 3-ferrocenylmethylbenzo[d]thiazole-2(3H)-thione (**5a**) 3-ferrocenylethylbenzo[d]thiazole-2(3H)-thione (**5b**) and 3-ferrocenylphenylmethylbenzo[d]thiazole-2(3H)-thione (**5d**) were carried out. The toxicity and antitumor activity of *N*-(ferrocenylethyl)-2-thiobenzimidazole (**3b**) were evaluated *in vivo*. Maximum tolerated dose (MTD) value for the compound **3b** was found to be equal to 800 mg kg^{-1}. The effectiveness of compound under investigation against murine solid tumor system, carcinoma Ca755 (Ca755), was studied in a wide range of doses and significant antitumor effects were found. The index of tumor growth inhibition (TGI) on Ca755 equaled 87% in comparison with control.

Introduction

The search for new agents for the treatment of cancer is an important activity in medicinal chemistry. Many chemical classes of heterocyclic and fused heterocyclic compounds have been identified through molecular biology, empirical screening and rational drug development for evaluation as anticancer drug candidates during the past decade [1]. It could be considered that the benzimidazole heterocycles are of great importance in their biological as well as synthetic roles in medicinal chemistry. From the reported literature, the various substituted derivatives of benzimidazole nucleus showed remarkable biological activities: antitumor including antiproliferative activity [2], antimicrobial including anti-HIV [3], antioxidant [4] and cysticidal activities [5]. The other compound with remarkable biological activity is benzothiazole, a heterocyclic aromatic molecule with electron rich sulfur and nitrogen atoms, used as a pharmacological agent with a wide variety of biological activities, such as immunomodulatory, immunosuppressive, antitumor, and antiviral properties [6]. The benzothiazole skeleton constitutes an important template for a wide variety of biologically active compounds. This molecule and its derivatives are known to be powerful antitumor agents [7], calmodulin (CaM) antagonists [8], neurotransmission blocker [9], and neuroprotective agents [10]. Benzothiazole-type compounds attracted considerable attention in anticancer drug development [11]. Modified benzothiazole derivatives with additional functional groups can likely improve the biological potential of these compounds [12].

* Corresponding author.
E-mail address: rodalex@ineos.ac.ru (A.N. Rodionov).

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However, some negative toxic side-effects of these compounds were found (mainly hemato- and hepato-toxicities) [13]. Thus, the search for new active, antitumor drugs with lower toxicity against normal cells and tissues remains one of the most significant problems of modern antitumor chemotherapy.

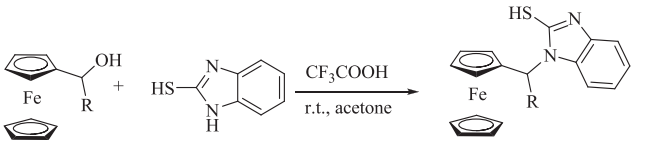
It was found that ferrocene units incorporated into some organic molecules [14] or drugs [15] and vitamins [16] significantly decreased their toxicity. Moreover, the antitumor activities of ferrocene containing compounds themselves were extensively studied *in vitro* and *in vivo* [14c,17,18]. It was demonstrated in experiments *in vivo* that ferrocene compounds with heterocyclic systems are effective against some solid tumors in mice [14c,19] and human tumors [14c]. Ferricenium salts, besides their antiproliferative activity [20], also display DNA-cleaving activity [21] and DNA synthesis inhibitory effect [22]. Recently therapeutic synergism of the antitumor activity of a combination of ferrocenylmethyl thymine with the well known antitumor drug cyclophosphamide against Ca755 was demonstrated [19]. Moreover treatment of *S*-(ferrocenylethyl)-2-thiopyrimidine against carcinoma 755 and Lewis lung carcinoma solid tumors *in vivo* led to 95% and 65% tumor growth inhibition, respectfully [13]. All these results are important for the further investigation of ferrocene compounds as prospective drugs for antitumor polychemotherapy.

In this paper we report an approach to ferrocene derivatives of 2-thiobenzimidazole (**3a**–**e**) (Scheme 1) and 2-thiobenzothiazole (**5a**–**e**) (Scheme 2). Ferrocene containing enantiomers with central chirality were resolved using HPLC on modified amylose as chiral selector. X-ray structure determination for **5a**, **5b** and **5d** was also carried out. The strong antitumor effects of N-ferrocenylethyl-2-thio-benzoimidazole (**3b**) were evaluated in experiments *in vivo*.

Results and discussion

Synthesis

The ferrocenylalkylation method for introduction of ferrocenylalkyl groups into various nucleophilic substrates was based on the reaction of α-(hydroxy)ferrocenes or ferrocenylalkyl amines with nucleophiles [23]. This reaction can occur in neutral [23b] and acidic [23c] media in or under the catalysis by transition metal salts [23d,e]. Ferrocenylalkyl thiobenzimidazoles (**3a**–**e**, Scheme 1) were obtained *via* the reaction of the thiobenzimidazole with five different ferrocenyl carbinols, FcCHR(OH) in acetone at room temperature in the presence of trifluoroacetic acid (TFA) with a mole ratio of ferrocenylcarbinoles (**1a**–**e**) and thiobenzimidazole of about 1: 1. Catalytic amounts of TFA were used for generation of ferrocenylcarbenium ions $FcCH(R)^+$. The products of reactions were isolated by filtration. Thus ferrocenylalkyl thiobenzimidazoles were synthesized in satisfactory to good yields (55–74%). The structures of compounds were assigned on the basis of ^1H and ^{13}C NMR spectra and $^1H/^{13}C$ heteronuclear correlations. Particularly in the HMBC spectrum of 1*N*-ferrocenylphenylmethyl-2-thiobenzimidazole (**3e**),

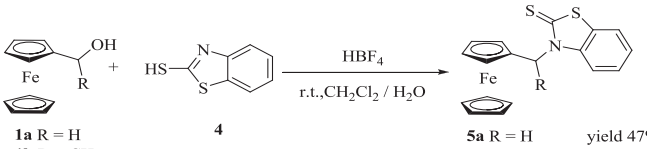


1a R = H
1b R = CH_3
1c R = C_2H_5
1d R = *i*-C_3H_7
1e R = Ph

2

3a R = H yield 74%
3b R = CH_3 70%
3c R = C_2H_5 63%
3d R = *i*-C_3H_7 55%
3e R = Ph 74%

Scheme 1. Synthesis of *N*-ferrocenylalkylthiobenzimidazole.



1a R = H
1b R = CH_3
1c R = C_2H_5
1d R = *i*-C_3H_7
1e R = Ph

4

5a R = H yield 47%
5b R = CH_3 58%
5c R = C_2H_5 40%
5d R = *i*-C_3H_7 45%
5e R = Ph 41%

Scheme 2. Synthesis of ferrocenylalkylbenzo[d]thiazole-2(3H)-thiones.

there are correlations between singlet at 7.63 ppm attributed to the CH linked to the ferrocene residue, and C-2 and C-8 carbon atoms of 2-thiobenzimidazole (168.38 and 131.82 ppm respectively) Thus ferrocenylalkilation proceeds in 1*N*-position of benzimidazole ring. Regioselectivity of alkylation of the other derivatives was proved in the same way. Fc-Alkylation appeared to be regiospecific and *N*-ferrocenylalkyl thiobenzimidazoles were isolated exclusively.

Because of thiobenzothiazole basicity is significantly weaker than thiobenzimidazole we carried out the Fc-alkylation reaction with equimolar ratio of reagents and strong acid avoiding protonation of heterocycle (**5a**–**e**, Scheme 2). As thiobenzimidazole the ferrocenylalkylation of 2-mercaptobenzothiazole proceeds exclusively on the *N*-position, as was confirmed by NMR data of bridge protons shifts (around 8 ppm), which is very different from bridge protons shifts of *S*-ferrocenylalkylthiopyrimidines (5.5–6.5 ppm) [13]. Moreover the IR data of compounds demonstrated presence of intense bands relating to stretching vibrations of the C=S double bond in the range 1200–1050 cm^{-1} [24]. Finally, the structures of 2-mercaptobenzothiazole derivatives **5a**, 5**b** and 5**d** were confirmed by X-ray data. These results contradict with published data [25]. There it was shown that the character of heterocycle significantly affected the regioselectivity of ferrocenylalkylation reactions of mercapto-nitrogen-containig heterocycles (pyrimidines, imidazoles, and benzothiazoles).

X-ray structure determination

X-ray crystallographic studies of **5a**, **5b** and **5d**, Figs. 1–3, show the bond lengths and angles falls in range typical for ferrocene and thioazole derivatives, according to a search of the Cambridge Structural Database (3612 ordered structures with R < 0.05) [26]. The most prominent feature in the compounds studied is the mutual orientation of ferrocene and 2-mercaptobenzothiazole fragments which shows no overlap between π-systems is possible owing to steric repulsion. Indeed, the planes of above mentioned moieties are nearly perpendicular (the interplanar angle is equal to 69.60(5), 75.67(17) and 77.38(17), and 89.2(4)°, respectively). The increase of the volume of R substituent leads to noticeable changes in the Fe1–C6–C11–N1 torsion angle. In **5a** this angle is close to 180° (172.97(9)°). The deviation from 180° increased upon the replacement of H to Me (164.2(3) and 163.9(3)°) and *i*-Pr (145.5(9)°).

In the crystal packing of **5a**, **5b** and **5d** there are no stacking interactions found between ferrocene and 2-mercaptobenzothiazole π-systems. On the other hand, the self-association of molecules **5a** and **5b** in crystal occurs by means of a number of S … S, H … H, C–H … π and H … S interactions. To estimate their contribution to the stability of the crystal structures the Hirshfeld surface analysis (HAS [27]) was applied. This method is based on the calculation of the promolecule (superposition of spherical atoms) both in crystal and in gas phase with subsequent analysis of molecular volume, shape and surface. The molecular surface can be divided into regions correspond to the various types of

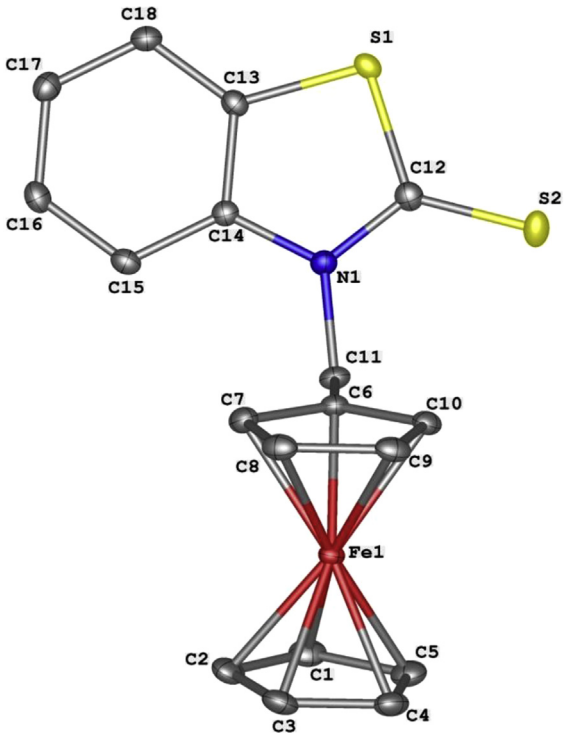


Fig. 1. General view of molecule **5a** presented in anisotropic displacement ellipsoids at 50% probability. Hydrogen atoms are omitted for clarity.

intermolecular interactions. Total area accounted for particular type of intermolecular interactions proportional to its contribution in the energy of crystal packing. Also, the information provided by HAS method can useful to understand the mechanism of

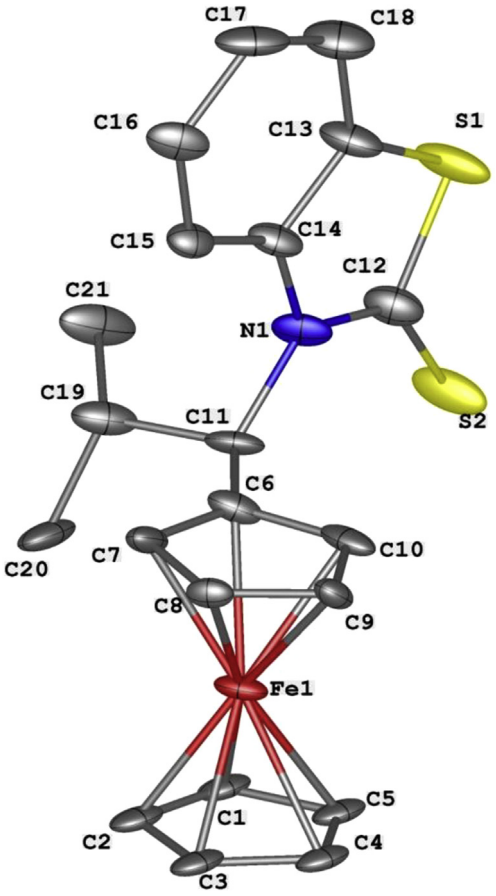


Fig. 3. General view of molecule **5d** (one disordered orientation only) presented in anisotropic displacement ellipsoids at 50% probability. Hydrogen atoms are omitted for clarity.

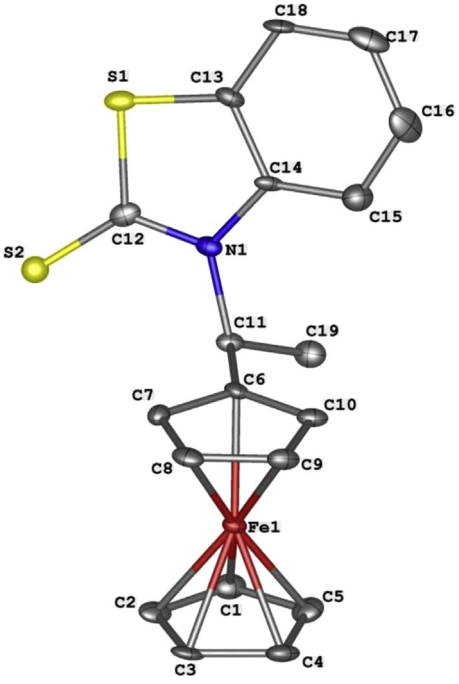


Fig. 2. General view of molecule **5b**-**A** presented in anisotropic displacement ellipsoids at 50% probability. Hydrogen atoms are omitted for clarity. The structure of **5b**-**B** is very similar (see text).

pharmaceutical activity of **5a**, **5b** and **5d** and related compounds. The fingerprint plots [28] for **5a** and **5b** can be found in the Supplementary Material.

One might expect that both the molecular volume and surface area of **5a**, **5b** and **5d** is increased in accord with the increase of the volume of the R substituent. However, in ordered structures **5a** and **5b** the value of molecular volume is depended on crystal environment, as indicated in the crystal structure of **5b** which contains two independent molecules (***A*** and ***B***) with noticeably different volumes (393.2 and 378.5 $Å^3$). These molecules are almost identical with only noticeable difference related to mutual orientation of ferrocene and 2-mercaptobenzothiazole moieties, the value of root mean square deviation is 0.363 Å. The volume of **5a** is almost the same (379.0 $Å^3$) as molecule ***B*** in **5b**. In turn, the surface area of molecule **5a** (334.4 $Å^2$) is less than those for molecules A and B in crystal structure of **5b** (339.4 and 365.7 $Å^2$). An increase of the volume of the R substituent leads to an increase in the contribution of H … S intermolecular interactions to surface area. Indeed, the percentage of H … S intermolecular interactions is 18.5% for **5a**, while analogous values for molecules A and B are equal to 19.9 and 21.8%, respectively. The similar trend is found for the H … C interactions (including C–H … π ones) which cover 14.0, 27.0 and 24.4% of surface area of molecules **5a**, **5b**-***A*** and **5b**-***B***. The role of S … S interactions in crystal packing is negligible (such the interactions cover 1–3% of surface area). Molecules of **5b**-***A*** and **5b**-***B*** also participate in weak C–H … Cl hydrogen bond with solvated molecules of $CHCl_3$ (7.0 and 6.5%). The rest of the surface area is

Table 1
Cyclic voltammetry data for ferrocene containing complexes (1 mM, ACN, 0.05 M Bu_4NBF_4, Pt, 100 mV/s, vs Ag/AgCl/KCl).

Compound number	E^{ox}, mV	Compound number	E^{ox}, mV
5a	620/565, 1790	**3a**	610/540, 1510
5b	605/540, 1750	**3b**	600/525, 1460
5c	825/740, 1860	**3c**	830/740, 1680
5d	860/730, 1880	**3d**	865/735, 1570
5e	740/675, 1830	**3e**	745/675, 1540
4	1090	**2**	990

covered by H … H interactions. The crystal structure of **5d** is the special case. The structure of **5d** in crystal can be described as the superposition of R and S enantiomers in 1:1 ratio (according to the value of Flack parameter, Table 1). Unsubstituted Cp ring and 2-mercaptobenzothiazole moiety disordered over two positions on opposite sides of pseudo-mirror plane passing through C8, Fe1 atoms and the middle point of the C6–C10 bond (Fig. 4).

Electrochemistry

The electrochemical measurements for all ferrocene containing complexes were obtained by cyclic voltammetry (CV) under argon in acetonitrile (ACN) solvent. The results are listed in Table 1.

In ACN, all complexes displayed identical behavior as there are two one-electron peaks in their CV. A typical example of a CV for the complexes is presented in Fig. 5. The first peak is reversible with i_{pc}/i_{pa} close to 1; peak separations were all 60–65 mV at the scan rate of 100 mV/s. This peak corresponds to oxidation of the ferrocene fragment. The second peak is one-electron and irreversible. It

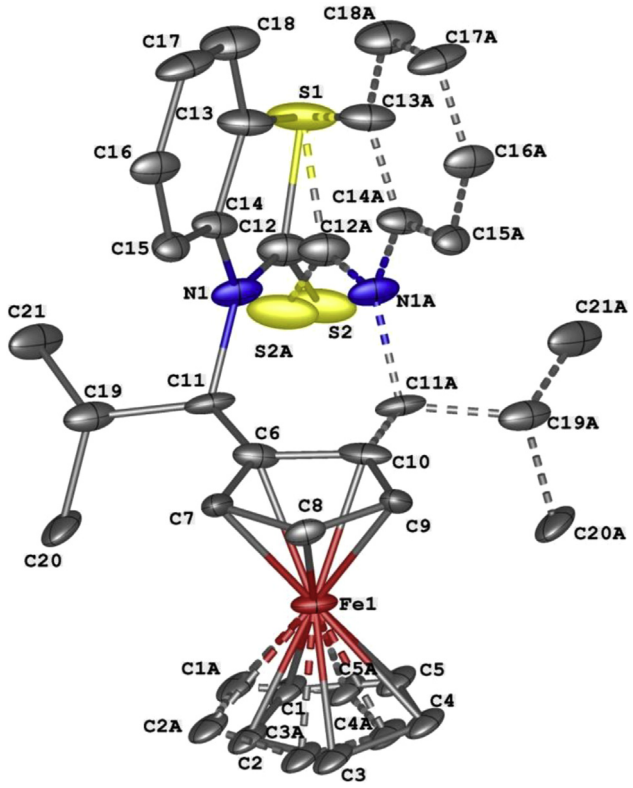


Fig. 4. View of the disorder of molecule **5d** in its crystal structure. The positions of atoms of the *S*-enantiomer are shown by dashed line. Atoms are presented in anisotropic displacement ellipsoids at 50% probability. Hydrogen atoms are omitted for clarity.

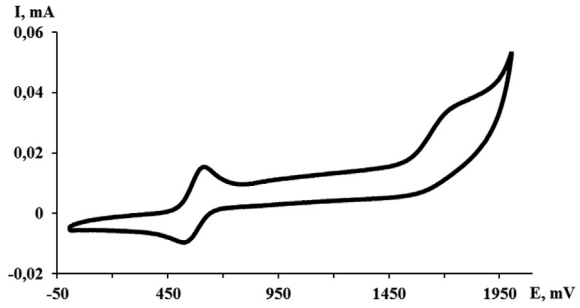


Fig. 5. The Cyclic voltammogram of **5b** (1 mM, ACN, 0.05 M Bu_4NBF_4, Pt, 100 mV/s, vs Ag/AgCl/KCl).

arises from to oxidation of the heterocyclic fragment. The influence of substituents at the C-atom close to the ferrocene fragment on oxidation potential is presented in Table 2 from which it can be seen that the more electron-withdrawing character of the substituent the greater oxidation potential.

It is surprising, that substances with different heterocyclic fragments displayed similar oxidation potentials (compare **5e** and **3e**, **5c** and **3c**, **5b** and **3b**). This is in accord with the observation that there is little or no electronic communication between the ferrocene and 2-thiobenzimidazole and 2-thiobenzothiazole residues as discussed above.

HPLC resolution

The synthesized eight ferrocene derivatives (**3b**–**e** and **5b**–**e**) contain one asymmetric carbon atom in their structures and give racemic mixtures. It is logical to suppose that the two enantiomers may possess different biological activities. So we separated the racemic mixtures into two enantiomers using high-performance liquid chromatography (HPLC). Earlier, this method of separation was successfully used for racemic ferrocene compounds with different simple substituents [29], the chiral sorbents based upon β- and γ-cyclodextrins turned out to be effective in these cases. To separate mixtures of racemic ferrocene derivatives having bulky substituents such as ferrocenylalkyl azoles [14c,30a,b] modified cellulose was used as the chiral stationary phase. The enantiomeric resolution analytical data are summarized in Table 3. We successfully separated all 8 pairs of investigated compounds. The recognition mechanism on amylose is apparently connected, with the formation of specific hydrogen bonds between the strongly basic nitrogen atom of the corresponding heterocyclic fragments and carbamate units on the modified amylose.

Biological tests. Toxicity and antitumor activity

Since the end of the 1990s, increased interest in the biochemistry ferrocenes has emerged, especially in the therapeutic areas of oncology [17e,31,32]. At the end of 2010 we published a review paper devoted to antitumor activities of ferrocene compounds including ferrocene-modified nucleic bases [33]. Soon after, this problem was carefully regarded by Omelas [34] and Metzler-Nolte

Table 2
The potential of oxidation of ferrocene containing alcohols (1 mM, AN, 0.05 M Bu_4NBF_4, Pt, 100 mV/s, vs Ag/AgCl/KCl).

Compound number	1a	1b	1c	1d	1e
E^{ox}, mV	500/430	490/420	470/410	480/410	520/460

Table 3
Enantiomeric resolution of **3 (b–e)** and **5 (b–e)** racemic mixtures on column Kromasil 3-AmyCoat.

Compound number	HPLC data		
	k'_1	k'_2	α
3b	2.80	7.00	2.50
3c	1.90	7.50	3.95
3d	2.50	3.50	1.40
3e	2.75	2.98	1.08
5b	0.70	0.90	1.29
5c	0.50	0.85	1.70
5d	0.35	0.47	1.34
5e	0.55	0.65	1.18

Eluent, hexane–isopropanol 9:1 (v/v).

with colleagues [35]. Such great attention to ferrocenes was caused by their unique properties including membrane permeability, low toxicity, redox ability, chemical stability and, finally, commercial availability. Antitumor effects of several ferrocene derivatives of nucleobases and pyrimidines on some murine tumor systems such as carcinoma 755, melanoma B16 and Lewis lung carcinoma were evaluated *in vivo* [19,13]. The significant antitumor effects of studied compounds, for example, for ferrocenylethyl 2-thiopyrimidine equal to the 95% of tumor growth inhibition, as compared with control, were found [13]. This effectiveness was compared with that of cisplatin. It was marked that just solid tumor models, namely, carcinoma 755 and Lewis lung carcinoma were considerably more sensitive to ferrocene compounds than ascite ones, such as L1210 and P388 leukemia.

Our current interest in this area is due to mechanistic aspects responsible for the specific pharmacological effects of ferrocene compounds, and medicinal applications [13,14c,d,19,33].

The possible mechanisms for ferrocenes in inhibition of tumor growth are considered in literature [33,34,35]. We believed that the introduction of the bulky ferrocene markers into DNA can trigger the activity of the Ca- and Mg-dependent endonucleases, the enzymes playing a critical role at the early stages of apoptosis, i.e. the process of the pre-programmed cell destruction.

One of the most common N-heterocyclic drug components is imidazole and its benzo-derivatives. Therefore compound **3b** was chosen for *in vivo* trials. Moreover, the methyl substituent in the bridge increases the lipophilicity of the system in the whole. Finally, 1-ferrocenyl ethanol, an initial ferrocene alcohol, can be easily synthesized from commercially accessible acetylferrocene. The antitumor activities of **3b** was studied against the murine solid tumor, carcinoma 755 (Ca755), transplanted in mice. Tumor sizes were measured during the whole period of tumor growth. The index of tumor growth inhibition was calculated at the time when the antitumor activity of the drug was maximal. This was after 11 days. The test doses of 100–500 mg kg^{-1} and 5.0–25.0 mg kg^{-1} were chosen. The results of antitumor effects of **3b** are summarized in Tables 4 and 5. As can be seen from Table 4, significant antitumor effects of compound **3b** were shown on carcinoma 755 at large doses. The maximum level of the tumor growth inhibition, 87% as compared with control, was observed on Ca755 after administration of compound **3b** at the dose of 250.0 mg kg^{-1} day^{-1}.

Ferrocenes are known to have low toxicities and **3b** is not an exception. The maximum tolerated dose found to be equal to 800 mg kg^{-1} for **3b** as the determination of LD_{50} was impossible due to the low solubility of the complex in water or physiological solution.

The latent period and life span of mice with Ca755, treated with compound **3b** increased in compare to control (Tables 4 and 5).

Table 4
The results of antitumor activity of *N*-(ferrocenylethyl)-2-thiobenzimidazole (**3b**) on carcinoma 755 *in vivo*.

Daily dose, mg kg^{-1}	Carcinoma 755 (11th day)[a]					
	Mean tumor weight, g	Tumor growth inhibition, %	Latent period		Life span	
			days	%	days	%
500.0	0.70 ± 0.16	56	7.5	29	24.5	4
250.0	0.21 ± 0.10	87	7.6	31	32.6	37
166.0	0.53 ± 0.13	67	6.5	12	21.8	−8
125.0	0.30 ± 0.13	81	6.2	7	29.3	23
100.0	0.65 ± 0.17	59	5.3	−9	33.5	41
Control	1.60 ± 0.35	–	5.8	–	23.8	–

Solvent, physiological solution-DMSO 90:10, percentage by volume; drug administration, intraperitoneal.
[a] Evaluation of the index of tumor growth inhibition (%), day 11 after tumor Ca755 inoculation.

Table 5
The results of antitumor activity of *N*-(ferrocenylethyl)-2-thiobenzimidazole (**3b**) on carcinoma 755 *in vivo*.

Daily dose (total dose), mg kg^{-1}	Carcinoma 755 (11th day)[a]					
	Mean tumor weight, g	Tumor growth inhibition, %	Latent period		Life span	
			days	%	days	%
25.0 (125.0)	1.17 ± 0.21	43	6.33	36	23.8	24
12.5 (52.5)	0.69 ± 0.15	67	6.50	39	21.7	13
8.33 (41.65)	0.90 ± 0.20	57	7.17	54	19.8	3
6.25 (31.25)	0.70 ± 0.19	66	6.67	43	19.2	0
5.0 (25.0)	1.51 ± 0.49	27	6.67	43	23.2	21
Control	2.07 ± 0.51	–	4.67	–	19.2	–

Initial solvent, physiological solution–DMSO, 90:10, percentage by volume; drug administration, intraperitoneal; during five days after tumor inoculation.
[a] Evaluation of the index of tumor growth inhibition (%), day 11 after tumor Ca755 inoculation.

Conclusion

Ferrocenylalkyl 2-mercaptobenzimidazoles and 2-mercaptobenzo[d]thiazole-2(3H)-thiones were prepared *via* the reaction of the α-(hydroxy)alkyl ferrocenes with corresponding heterocycles in acidic media. Under these conditions, the alkylation takes place on the nitrogen heterocycles and not by thiol moiety. The structures, electrochemical properties and enantiomeric resolution were studied. The toxicity and antitumor activity of *N*-(ferrocenylethyl)-2-thiobenzimidazole were evaluated *in vivo*. Systematic *in vivo* investigations of ferrocene compounds antitumor activities demonstrate significant tumor inhibition effects combined with low acute toxicities. These results allow us to say about new class of nontoxic anticancer drug candidates on the basis of ferrocene-based complexes bearing N,S-heterocyclic fragments.

Experimental

General

Melting points were determined with a Boethius microstage and are uncorrected. ^1H and ^{13}C NMR spectra were obtained on a Bruker DRX-500 spectrometer at 500.13 MHz and 125.76 MHz for protons and ^{13}C, respectively, in $CDCl_3$ or CD_3OD at 30 °C. Chemical shifts are given in ppm relative to solvent residual protons. IR spectra were recorded on a Carl Zeiss UR-20 spectrophotometer using a KBr disk. EI mass spectra were taken on a FINNIGAN POLARIS Q spectrometer at 70 eV and the temperature of the ion

chamber 250 °C. The solvents were purified by standards techniques.

Heterocycles were purchased from Acros Organics and used without purification. Ferrocenylmethanol was obtained from trimethylferrocenylmethylammonium iodide according to a well-known procedure [36]. Other ferrocenylcarbinoles were synthesized from the corresponding acyl ferrocenes by reduction with lithium aluminum hydride in THF [37].

Syntheses

To a solution of ferrocenylcarbinol, FcCHR(OH), (1.0 mmol) and 2-thiobenzimidazole (1.0 mmol) in acetone (5.0 ml) two drops of trifluoroacetic acid were added. The reaction mixture was stirred overnight until the residue was formed. Then the residue was filtered, washed with cold ether (2 × 20 ml) and dried in vacuo over $CaCl_2$.

*N-ferrocenylmethyl-2-thio-benzoimidazole (**3a**)*

Yield 74%. Yellow powder, m.p. 198–200°C. Anal.: C 60.81; H 4.77; N 7.81; S 8.76%. Calc. for $C_{18}H_{16}FeN_2S$: C 60.52; H 4.80; N 7.84; S 8.98%. EI-MS, *m/z* (RI, %): 348 $[M]^+$ (83). ^{1}H NMR ($CDCl_3$, *δ*, ppm): 4.11 (s, 2H, Fc); 4.25 (s, 5H, Fc); 4.49 (s, 2H, Fc); 5.28 (s, 2H, CH_2); 7.15-7.22 (m, 4H, Het); 10.43 (s, 1H, SH). ^{13}C NMR ($CDCl_3$, *δ*, ppm): 51.7 (CH_2), 66.3 (C_5H_4), 66.9 (C_5H_4), 69.3 (C_5H_4), 69.7 (C_5H_5), 86.9 (*ipso*-C_5H_4), 109.9 (Het, C-5), 111.7 (Het, C-6), 122.8 (Het, C-4), 123.2 (Het, C-7), 128.9 (Het, C-9), 131.0 (Het, C-8), 166.7 (C–S).

*N-ferrocenylethyl-2-thio-benzoimidazole (**3b**)*

Yield 70%. Yellow powder, m.p. 188–189°C. Anal.: C 63.38; H 5.06; N 7.68; S 8.76%. Calc. for $C_{19}H_{18}FeN_2S$: C 62.99; H 5.01; N 7.73; S 8.85%. EI-MS, *m/z* (RI, %): 362 $[M]^+$ (46). ^{1}H NMR ($CDCl_3$, *δ*, ppm): 1.83 (d, *J* = 7.1 Hz, 3H, CH_3); 4.12 (s, 1H, Fc); 4.21 (s, 1H, Fc); 4.26 (s, 6H, Fc); 4.52 (s, 1H, Fc); 6.45 (q, *J* = 6.8 Hz, 1H, CH); 6.94-7.12 (m, 3H, Het); 7.19 (d, *J* = 7.9 Hz, 1H, Het (C-7)); 10.50 (s, 1H, SH). ^{13}C NMR ($CDCl_3$, *δ*, ppm): 17.1 (CH_3), 51.9 (CH), 66.9 (C_5H_4), 67.5 (C_5H_4), 69.1 (C_5H_4), 69.3 (C_5H_5), 86.6 (*ipso*-C_5H_4), 110.2 (Het, C-5), 111.4 (Het, C-6), 122.3 (Het, C-4), 123.0 (Het, C-7), 128.8 (Het, C-9), 130.8 (Het, C-8), 166.9 (C–S).

*N-Ferrocenylpropyl-2-thio-benzoimidazole (**3c**)*

Yield 63%. Yellow powder, m.p. 197–199°C. Anal.: C 63.92; H 5.39; N 7.44; S 8.60%. Calc. for $C_{20}H_{20}FeN_2S$: C 63.84; H 5.36; N 7.44; S 8.52%. EI-MS, *m/z* (RI, %): 376 $[M]^+$ (51). ^{1}H NMR ($CDCl_3$, *δ*, ppm): 0.93 (t, *J* = 7.3 Hz, 3H, CH_3); 2.34–2.44 (m, 2H, CH_2); 4.09 (s, 1H, Fc); 4.18 (s, 1H, Fc); 4.26 (s, 6H, Fc); 4.48 (s, 1H, Fc); 6.40–6.45 (m, 1H, CH); 7.00–7.12 (m, 3H, Het); 7.19 (d, *J* = 7.7 Hz, 1H, Het (C-7)); 10.50 (s, 1H, SH). ^{13}C NMR ($CDCl_3$, *δ*, ppm): 10.6 (CH_3), 24.5 (CH_2), 57.0 (CH), 66.5 (C_5H_4), 67.1 (C_5H_4), 68.3 (C_5H_4), 68.5 (C_5H_4), 68.9 (C_5H_5), 86.3 (*ipso*-C_5H_4), 109.8 (Het, C-5), 111.0 (Het, C-6), 121.9 (Het, C-4), 122.6 (Het, C-7), 129.1 (Het, C-9), 130.5 (Het, C-8), 168.0 (C–S).

*N-(1-Ferrocenyl)-2-methylpropyl-2-thio-benzoimidazole (**3d**)*

Yield 55%. Yellow powder, m.p. 145–146°C. Anal.: C 67.42; H 6.41; N 4.81; S 7.45%. Calc. for $C_{21}H_{22}FeN_2S$: C 64.62; H 5.68; N 7.18; S 8.21; Fe 14.31%. EI-MS, *m/z* (RI, %): 388 $[M]^+$ (79). ^{1}H NMR ($CDCl_3$, *δ*, ppm): 0.74 (d, J = 6.6 Hz, 3H, CH_3), 1.59 (d, J = 6.4 Hz, 3H, CH_3), 2.64–2.73 (m, 1H, CH) 4.10 (s, 2H, Fc), 4.13 (s, 1H, Fc), 4.22 (s, 5H, Fc), 4.48 (s, 1H, Fc), 6.82 (d, J = 10.8 Hz,1H, CH), 6.92–7.09 (m, 3H, Het); 7.18 (d, *J* = 7.9 Hz, 1H, Het (C-7)); 10.52 (s, 1H, SH).^{13}C NMR ($CDCl_3$, *δ*, ppm): 19.4 (CH_3), 22.3 (CH_3), 31.0 (CH), 63.6 (CH), 67.8 (C_5H_4), 68.3 (C_5H_4), 69.9 (C_5H_5), 84.9 (*ipso*-C_5H_4), 109.4 (Het, C-5), 111.2 (Het, C-6), 121.7 (Het, C-4), 122.8 (Het, C-7), 128.7 (Het, C-9), 130.3 (Het, C-8), 168.2 (C–S).

*N-(Ferrocenyl(phenyl)methyl-2-thio-benzoimidazole (**3e**)*

Yield 74%. Orange powder, m.p. 220°C (dec.). Anal.: C 67.95; H 4.76; N 6.60; S 7.54%. Calc. for $C_{24}H_{20}FeN_2S$: C 67.93; H 4.75; N 6.60; S 7.56%. EI-MS, *m/z* (RI, %): 424 $[M]^+$ (79). ^{1}H NMR (CD_3OD, *δ*, ppm): 4.17–4.24 (m, 9H, Fc); 6.77 (d, *J* = 8.2 Hz, 1H, Het (C-4)); 6.90 (t, *J* = 8.2 Hz, 1H, Het (C-6)); 7.08 (t, *J* = 8.2 Hz, 1H, Het (C-5)); 7.20 (d, *J* = 8.2 Hz, 1H, Het (C-7)); 7.22 (t, *J* = 7.5 Hz, 1H, *p*-Ph); 7.27 (t, *J* = 7.5 Hz, 2H, *m*-Ph); 7.35 (d, *J* = 7.5 Hz, 2H, *o*-Ph); 7.63 (s, 1H, CH); 10.80 (s, *1*H, SH). ^{13}C NMR ($CDCl_3$+CD_3OD, *δ*, ppm): 59.2 (CH), 67.7 (C_5H_4), 68.3 (C_5H_4), 68.6 (C_5H_4), 69.3 (C_5H_4), 69.9 (C_5H_5), 86.1 (*ipso*-C_5H_4), 110.0 (Het, C-5), 112.5 (Het, C-6), 122.1 (Het, C-7), 122.9 (Het, C-4), 127.7 (p-Ph), 128.0 (*o*-Ph), 128.3 (*m*-Ph), 130.8 (Het, C-9), 131.8 (Het, C-8), 138.7 (*ipso*-Ph), 168.3 (C–S)

To a mixture of 1.0 mmol of ferrocenylcarbinol and 1.0 mmol of the corresponding heterocycle in 1.0 ml of methylene dichloride, 0.18 ml of 45% aqueous solution of fluoroboric acid was added under vigorous stirring. The agitation was continued for 5 min then Et_2O (15 ml), the same amount of cold water, and 5–10 mg of ascorbic acid were added to the reaction flask. After vigorous shaking of the mixture the organic solution was separated, washed with cold water (5 × 15 ml), the solvent was removed and the residue was dried over $CaCl_2$.

*3-Ferrocenylmethylbenzo[d]thiazole-2(3H)-thione (**5a**)*

Yield 47%. Dark brown crystals, m.p. 134–135 °C. Anal.: C 59.27; H 4.09; N 3.80; S 17.50%. Calc. for $C_{18}H_{15}FeNS_2$: C 59.18; H 4.14; N 3.83; S 17.56%. EI/MS, *m/z* (RI%): 365 $[M]^+$ (78). ^{1}H NMR ($CDCl_3$, *δ*, ppm): 4.12 (s, 2H, Fc), 4.24 (s, 5H, Fc), 4.51 (s, 2H, Fc), 5.44 (s, 2H, CH_2), 7.32–7.42 (m, 4H, Het). ^{13}C NMR ($CDCl_3$, *δ*, ppm): 45.5 (CH_2), 68.4 (C_5H_4), 69.0 (C_5H_5), 69.9 (C_5H_4), 81.2 (*ipso*-C_5H_4), 112.8 (C-4, Het), 121.3 (C-7, Het), 124.7 (C-6, Het), 126.8 (C-5, Het), 127.6 (C-8, Het), 141.3 (C-9, Het), 189.1 (C=S).

*3-Ferrocenylethylbenzo[d]thiazole-2(3H)-thione (**5b**)*

Yield 58%. Yellow crystals, m.p. 130 °C. Anal.: C 60.34; H 4.23; N 3.41; S 16.67%. Calc. for $C_{19}H_{17}FeNS_2$: C 60.16; H 4.52; N 3.69; S 16.91%. EI/MS, *m/z* (RI%): 279 $[M]^+$ (20). ^{1}H NMR ($CDCl_3$, *δ*, ppm): 1.84 (d, J = 7.2 Hz, 3H, CH_3), 4.15 (s, 1H, Fc), 4.21 (s, 1H, Fc), 4.24 (s, 1H, Fc), 4.26 (s, 5H, Fc), 4.53 (s, 1H, Fc), 7.10–7.25 (m, 4H, Het + CH), 7.41 (d, J = 7.7 Hz, 1H, Het(C-4)). ^{13}C NMR ($CDCl_3$, *δ*, ppm): 15.7 (CH_3), 53.5 (CH), 66.8 (C_5H_4), 67.4 (C_5H_4), 69.3 (C_5H_5), 85.9 (*ipso*-C_5H_4), 114.2 (C-4, Het), 121.0 (C-7, Het), 124.1 (C-6, Het), 126.1 (C-5, Het), 127.2 (C-8, Het), 139.9 (C-9, Het), 188.9 (C=S).

*3-Ferrocenylpropylbenzo[d]thiazole-2(3H)-thione (**5c**)*

Yield 40%. Yellow crystals, m.p. 140 °C. Anal.: C 60.38; H 4.94; N 3.52; S 16.12%. Calc. for $C_{20}H_{19}FeNS_2$: C 61.07; H 4.87; N 3.56; S 16.30%. EI/MS, *m/z* (RI%): 393 $[M]^+$ (20). ^{1}H NMR ($CDCl_3$, *δ*, ppm): 0.98 (t, J = 7.4 Hz, 3H, CH_3), 2.35–2.48 (m, 2H, CH_2), 4.12 (s, 1H, Fc), 4.18 (s, 1H, Fc), 4.23 (s, 1H, Fc), 4.26 (s, 5H, Fc), 4.49 (s, 1H, Fc), 7.11–7.24 (m, 4H, Het + CH), 7.42 (d, J = 7.7 Hz, 1H, Het(C-4)). ^{13}C NMR ($CDCl_3$, *δ*, ppm): 11.0 (CH_3), 24.1 (CH_2), 59.0 (CH), 66.7 (C_5H_4), 67.5 (C_5H_4), 69.5 (C_5H_5), 85.7 (*ipso*-C_5H_4), 114.1 (C-4, Het), 121.1 (C-7, Het), 124.2 (C-6, Het), 126.2 (C-5, Het), 127.0 (C-8, Het), 139.9 (C-9, Het), 190.2 (C=S).

*3-(2-Methyl-1-ferrocenylpropyl)benzo[d]thiazole-2(3H)-thione (**5d**)*

Yield 45%. Dark brown crystals, m.p. 155–156 °C. Anal.: C 61.24; H 5.26; N 3.40; S 15.57%. Calc. for $C_{21}H_{21}FeNS_2$: C 61.92; H 5.20; N 3.44; S 15.74%. EI/MS, *m/z* (RI%): 407 $[M]^+$ (20). ^{1}H NMR ($CDCl_3$, *δ*, ppm): 0.76 (d, J = 6.6 Hz, 3H, CH_3), 1.58 (d, J = 6.4 Hz, 3H, CH_3), 2.69–2.78 (m, 1H, CH) 4.07 (s, 2H, Fc), 4.17 (s, 1H, Fc), 4.20 (s, 5H, Fc), 4.46 (s, 1H, Fc), 6.83 (d, J = 10.8 Hz,1H, CH), 7.12–7.19 (m, 3H, Het), 7.47 (d, J = 7.6 Hz, 1H, Het(C-4)). ^{13}C NMR ($CDCl_3$, *δ*, ppm): 19.7

(CH_3), 22.8 (CH_3), 30.9 (CH), 63.1 (CH), 67.4 (C_5H_4), 68.4 (C_5H_4), 69.6 (C_5H_5), 85.8 (*ipso*-C_5H_4), 114.1 (C-4, Het), 121.1 (C-7, Het), 124.3 (C-6, Het), 126.2 (C-5, Het), 126.6 (C-8, Het), 140.3 (C-9, Het), 189.7 (C═S).

*3-(Ferrocenyl(phenyl)methyl)benzo[d]thiazole-2(3H)-thione (**5e**)*

Yield 41%. Yellow crystals, m.p. 153 °C. . Anal.: C 65.31; H 4.34; N 3.17; S 14.53%. Calc. for $C_{24}H_{19}FeNS_2$: C 64.88; H 4.39; N 3.15; S 14.41%. EI/MS, *m*/*z* (RI%): 441 $[M]^+$ (20). ^1H NMR ($CDCl_3$, δ, ppm): 4.13 (s, 1H, Fc), 4.18 (s, 1H, Fc), 4.22 (s, 5H, Fc), 4.24 (s, 1H, Fc), 4.36 (s, 1H, Fc),7.00 (d, J = 7.2 Hz, 1H, Het(C-7)), 7.02 (t, J = 7.2 Hz, 1H, Het(C-6)), 7.14 (t, J = 7.2, 1H, Het(C-5)), 7.24–7.28 (m, 3H, Ph), 7.34 (d, J = 8, 2H, *o*-Ph), 7.41 (d, J = 7.2, 1H, Het(C-4)), 8.20 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, δ, ppm): 60.14 (CH), 67.8 (C_5H_4), 68.0 (C_5H_4), 68.5 (C_5H_4), 69.5 (C_5H_5), 70.2 (C_5H_4), 85.1 (*ipso*-C_5H_4), 115.9 (C-4, Het), 121.0 (C-7, Het), 124.5 (C-6, Het), 125.8 (C-5, Het), 126.9 (C-8, Het), 127.6 (*ipso*-Ph), 127.8 (*o*-Ph), 128.6 (*m*-Ph), 137.5 (*p*-Ph), 140.7 (C-9, Het), 190.1 (C═S).

Electrochemistry

Electrochemical properties of heterocyclic derivatives of ferrocene have been investigated using cyclic voltammetry (CV). The measurements were carried out in acetonitrile solution in the presence of 0.05 M Bu_4NBF_4 at a platinum working electrode versus Ag/AgCl/KCl as reference electrode.

Chromatographic separation of enantiomers

Kromasil 3-AmyCoat chiral column (250, 4.6 mm, 5 μm) was used. The HPLC system, Bruker LC 31 with a UV 254 detector was operated at a flow rate of 1.0 ml^{-1} and ambient temperature.

X-ray crystallography

Single-crystal X-ray diffraction experiments for **5a**, **5b** and **5d** were carried out at 100 K on a Bruker APEX II diffractometer. Crystal data and experimental parameters are summarized in Table 6.

The structures were solved by direct methods and refined by full-matrix last-squares technique for non-hydrogen atoms in the anisotropic approximation. All H-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 methyl groups. In the refinement of **5b**, the carbon atoms of $CHCl_3$ molecules were disordered over a 2-fold axis. Thus the symmetry independent part of $CHCl_3$ molecule is one carbon atom (occupancy value is equal to 0.5) and two chloride atoms (occupancy values are 1.0 and 0.5). Disorder was also resolved in the refinement of **5d** resulting from the superimposition of R- and S-enantiomers.

All calculations were carried out on IBM PC using SHELXTL program [38]. Molecular graphics was produced by OLEX2 program [39]. Hirshfeld surface analysis was performed using Crystal Explorer 3.0 code [40].

Toxicity

FcCH(CH3)-(2-S-BimH) (**3b**). For the assessment of toxicity inbred DBA and C57/Bl mice were used. Compound **3b** was dissolved in DMSO (6.5 mg cm^{-3}, 16.5 mg cm^{-3}) and diluted with physiological solution to give a final range of concentrations. The solutions were administered intraperitoneally. Five groups of animals were used in each experiment, three mice in each group on the dose. The experimental doses ranged from 126.0 to 800 mg kg^{-1}. Maximum tolerated dose (MTD) value was equal to 800 mg kg^{-1}.

Table 6
Crystal data and experimental parameters in **5a**, **5b** and **5d**.

	5a	5b	5d
Chemical formula	$C_{18}H_{15}FeNS_2$	$2(C_{19}H_{17}FeNS_2)\cdot CHCl_3$	$C_{21}H_{21}FeNS_2$
Formula weight	365.28	877.98	407.36
Space group	*P*1	*Pccn*	$P2_12_12_1$
a, (Å)	7.4337 (4)	24.3685 (10)	11.1475 (11)
b, (Å)	7.7823 (4)	24.3722 (10)	12.3742 (12)
c, (Å)	14.8982 (8)	12.3771 (5)	13.6099 (13)
α, (°)	85.031(1)	90	90
β, (°)	80.581 (1)	90	90
γ, (°)	65.483 (1)	90	90
V ($Å^3$)	773.43 (7)	7350.9 (5)	1877.4 (3)
Z	2	8	4
F(000)	376	3600	848
μ (mm^{-1})	1.239	1.268	1.029
Crystal size (mm)	0.29 × 0.23 × 0.21	0.25 × 0.21 × 0.19	0.28 × 0.22 × 0.19
Reflections collected	10396	89146	18010
Independent refelections	4767	9778	3702
Reflections with $[I > 2\sigma(I)]$	4264	8051	3511
R_{int}	0.017	0.097	0.046
θ_{max} (°)	30.6	29.0	26.0
R_1 $[I > 2\sigma(I)]$	0.027	0.055	0.059
wR_2	0.069	0.125	0.152
No. of parameters	199	464	243
$\Delta\rho_{max}$, $\Delta\rho_{min}$ ($e\cdot Å^{-3}$)	0.55, −0.44	0.75, −0.76	0.85, −0.49
Flack parameter	–	–	0.49(4)

Antitumor activity tests

Carcinoma 755 (Ca755) was transplanted subcutaneously to the inbred mice F1, a hybrid line of C57Bl6 females and DBA2 males, with weight 18–20 g, in accordance with the standard procedure. The agent was administered on the next day after tumor inoculation. The tested doses varied in the intervals 100–500 mg kg^{-1}, 5.0–25.0 mg kg^{-1} (total doses 25.0–125.0 mg kg^{-1}). The DMSO-physiological solution (10% by volume) of compound **3b** was administered intraperitoneally in daily doses (Tables 4 and 5) in the last case five times every day starting from the next day after tumor inoculation. Each group comprised five to seven animals, including the control group of animals.

The kinetics of tumor growth was studied by measurement of tumor size during the whole period of tumor development. Two cross-coupling tumor sizes were measured and the volume of the tumor was calculated as $V = ab^2/2$, where a is the length and b is the width and the height of the tumor. As estimated previously, the density of tumor tissue is equal to 1 g cm^{-3}. So it is assumed that the weight of tumor in grams is equal to the volume of tumor in cm^3. The index of tumor growth inhibition (TGI) was calculated as (C − T)/C, %, where C and T are the mean tumor weight in groups of control and treated animals, respectively. The mean life-span of treated animals (τexp) was compared with that of untreated ones in the control group (τc) and was expressed as the ratio $\tau = (\tau exp - \tau c)/\tau c$, where τ is the index that characterizes the increase in mean life-span of treated mice compared with controls.

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Appendix A. Supplementary material

CCDC 939085–939087 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Appendix B. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jorganchem.2015.01.031.

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