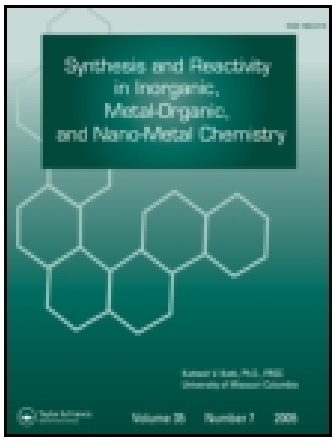

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Synthesis and Evaluation of Novel Ferrocenyl Thiazole Derivatives as Anticancer Agents

Ling Shao [a], Xin Zhou [a], Yan Hu [a], Zhong Jin [a], Jianbing Liu [a] & Jian-xin Fang [a]
[a] State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin, P. R. China
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Ling Shao, Xin Zhou, Yan Hu, Zhong Jin, Jianbing Liu, and Jian-xin Fang
State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin, P. R. China

Novel ferrocenyl-containing thiazole derivatives have been synthesized from 2-amino-4-ferrocenyl-5-(1*H*-1,2,4-triazole-1-yl)-1,3-thiazole and substituted benzoyl chloride. The structures of these compounds have been characterized by ^{1}H NMR, elemental analysis and X-ray diffraction analysis. Evaluation of anticancer activities showed that some of them possessed some degree of anticancer activity.

Keywords 1,3-thiazole, ferrocenyl, anticancer activity

INTRODUCTION

Every year, millions of people die of cancer in our world. First-line drugs, such as fluorouracil (5-FU), doxorubicin and camptothecines, are effective against these cancer cells. These drugs, however, result in irreversible damage to both normal and tumorous cells, and bring toxicity and side-effects. So, we want to provide some compounds that are useful as antitumor agents, but without the drawbacks of the currently available anticancer drugs.

Several 2-amino-1,3-thiazole derivatives are known as synthetic intermediates and therapeutic agents. For example, 5-alkyl-2-phenylalkylcarbonylamino-1,3-thiazoles are known as protein kinase C inhibitors,[1] 5-arylthio-2-acylamino-1,3-thiazoles are known as antitumor agents,[2] phenylacetamido-thiazole derivatives are known as anticancer agents,[3] and 2-(arylmethyl-carbonylamino)-1,3-thiazole derivatives are known as cyclin-dependent kinase inhibitors.[4]

Meanwhile, ferrocenyl units have been invoked as a bonus in the designing of new biologically active molecular, since it is a neutral, chemically stable and non-toxic molecule, and is able to cross cell membranes.[5] For example, ferrocifen, which is a ferrocene derivative of tamoxifen, has been prepared as an estradiol receptor site-directed cytotoxic agent and was tested against a human breast cancer cell line, and looks set to enter clinical trials in the near future.[6] Furthermore, if a molecule of an organic compound is incorporated into a ferrocenyl moiety, it often obtains unexpected biological activity, such as a new ferrocene-chloroquine analogue[7] and novel ferrocenic artemisinin derivatives.[8]

As a continuation of our studies on ferrocenyl-containing derivatives[9–12] and our interest in 1,3-thiazole derivatives,[13,14] and in a search for novel potent anticancer compounds, we herein report the synthesis and structure of a series of novel N-[4-ferrocenyl-5-(1*H*-1,2,4-triazol-1-yl)-1,3-thiazol-2-yl] substituted benzamide. New compounds have been characterized by spectral data, elemental analysis and crystal X-ray diffraction analysis. The anticancer effects of the compounds from this series were investigated in vitro.

RESULTS AND DISCUSSION

Synthesis of 2-amino-4-ferrocenyl-5-(1*H*-1,2,4-triazol-1-yl)-1,3-thiazole

First, α-bromoacetylferrocene was prepared according to the methodology as described by Tárraga and co-workers.[15] Acetylferrocene with LDA at -78°C, followed by a sequential treatment with trimethylchlorosilane and an excess of NBS provided the α-bromoacetylferrocene in 80% yield, along with a small amount of α,α-dibromoacetylferrocene. The α-bromoacetylferrocene was then reacted with 1*H*-1,2,4-triazole by using anhydrous potassium carbonate as a base in acetone achieving α-triazolylacetylferrocene in good yield[9] (Scheme 1). α-Bromo-α-1*H*-1,2,4-triazol-1-yl-acetylferroene (**1**) was obtained by the same method as that of the α-bromoacetylferrocene with a 73% yield and no by-products were found. Sequentially, compound **1** was heated with thiourea in ethanol under

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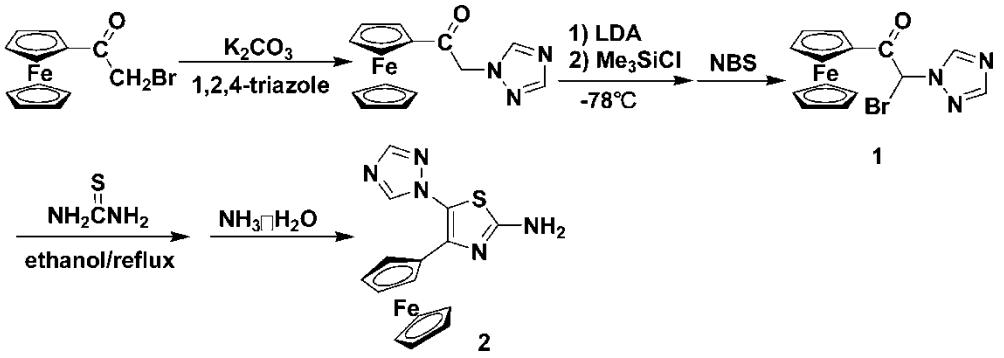
Address correspondence to Jian-xin Fang, Institute and State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. China. E-mail: fjx@nankai.edu.cn



SCH. 1.

reflux and a nitrogen atmosphere for 8 hours; the reaction mixture was then alkalified by ammonia solution (5%) and 2-amino-4-ferrocenyl-5-(1*H*-1,2,4-triazol-1-yl)-1,3-thiazole (**2**) was obtained in 72% yield. This reaction was investigated under various conditions, including solution (methanol, ethanol, isopropanol, acetone, acetonitrile) and ratio of reagents. The best yield was attained when compound **1** and thiourea (1 : 2 mole ratio) was reacted in ethanol at reflux under a nitrogen atmosphere.

The structure of compound **2** was confirmed by ^{1}H NMR, elemental analysis and X-ray diffraction analysis. Figure 1 shows the structure of compound 2, which we have reported on in a previous paper.[14]

Synthesis of N-[4-Ferrocenyl-5-(1*H*-1,2,4-triazol-1-yl)-1,3-thiazol-2-yl] Substituted Benzamide

Because the amino of 2-amino-4-ferrocenyl-5-(1*H*-1,2,4-triazol-1-yl)-1,3-thiazole (**2**) is not active and the solubility of **2** is small in general solvent, the reaction of compound **2** and **3** could not afford **4** when triethylamine was used as the base and the solvent was benzene, toluene or dioxane. Then we chose pyridine, which possesses alkalescency and is a strong solvent, and used magnetic stirring at room temperature for 8 hours. Most of the substituted benzoyl chloride **3** could react with **2** to give **4**, but the yields were relatively low. When compound **2** was suspended in chloroform and pyridine, compound **3** was added in dropwise and heated under reflux and in a nitrogen atmosphere, we obtained **4** in a good yield (Scheme 2). While the solvent was pyridine and benzoyl chloride was in excess, diacylation would occur and afford N-[4-ferrocenyl-5-(1*H*-1,2,4-triazol-1-yl)-1,3-thiazol-2-yl]-N-benzoylbenzamide (**5**) (Scheme 2).

The structures of all new compounds were characterized by ^{1}H NMR, elemental analysis and X-ray diffraction analysis. Figure 2 shows the molecular structure of **4o**, on which we have recently reported.[16]

Anticancer Evaluation

2-Aminothiazole containing ferrocenyl moiety derivatives (**4, 5**) were evaluated for their potential anticancer activity in vitro on three human cancer cell lines including HL-60 leukemia, BGC-823 gastric carcinoma cells and Hep-2 laryngic carcinoma cells. Using SRB (sulforhodamin B) and MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium

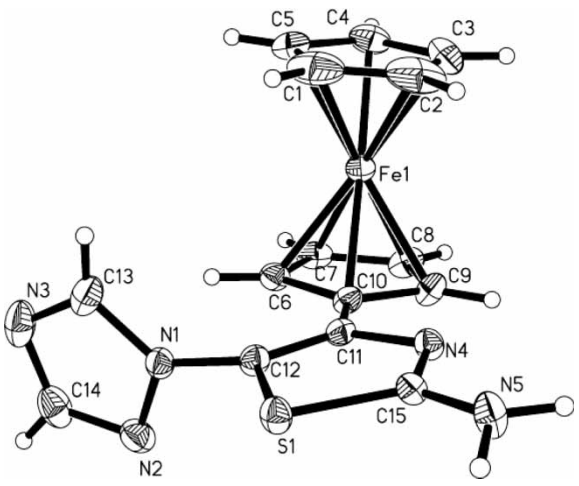
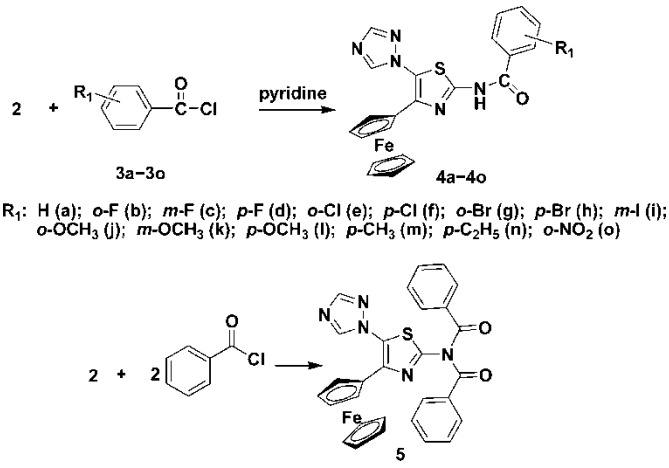


FIG. 1. Molecular structure and atom labeling for compound **2**; 30% thermal ellipsoid is shown.



SCH. 2.

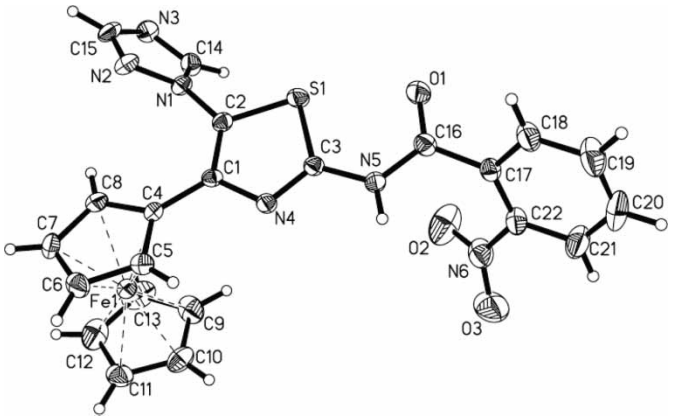


FIG 2. Molecular structure and atom labeling for compound **4o**; 30% thermal ellipsoid is shown.

bromide] assay, the result of inhibition percentages of human tumor cell lines in the presence of selected compounds **4** and **5** in DMSO are presented in Table 1. Some compounds were found to have good activity against these three human tumor cell lines on tested concentrations (10 μM). Compound **4j** showed good cytotoxic activities on HL-60 leukemia, BGC-823 gastric carcinoma cells and Hep-2 laryngic carcinoma cells with 81.40, 63.41, and 53.11% inhibition percentages, respectively, on the tested concentration (10 μM).

Compound **4** had similar structure and differed only in the substitution on the phenyl ring. The results strongly suggest that these differences influenced the activities of compounds. Thiazole **4f** with an electron-withdrawing *para*-chloro substituent on phenyl ring showed increased efficacy over the electron-donating *para*-methoxyl thiazole **4l** in all human cell lines. Methoxyl substitution at the *ortho*-, *meta*- and *para*-positions on phenyl ring was also investigated with compounds **4j**, **4k** and **4l**. The best activity was achieved by methoxyl substitution at the *ortho*-position. Substitution at the *para*-position showed a decrease in activity in all cell lines. Although the *meta*- and *para*-methoxyl on phenyl ring were less active than the *ortho*-methoxyl compounds, methoxyl substitution at both the *meta*- and *ortho*-position provided the most active compound in this series.

TABLE 1
Inhibition percentages of three human tumor cell lines in the presence of selected compounds **4** (%)

Comp. (10 μM)	HL-60 (leukemia) (MTT)	BGC-823 (gastric) (SRB)	Hep-2 (laryngic) (SRB)
4a	23.40	−0.74	4.01
4b	30.51	9.85	7.65
4d	21.53	5.24	21.38
4e	27.66	−5.96	9.63
4f	24.32	−7.43	2.04
4g	8.22	1.15	−1.22
4j	81.40	63.41	53.11
4k	62.00	30.15	31.56
4l	12.03	−3.08	−0.70
4m	15.88	−7.52	12.31
5	76.14	27.18	32.90

Comparison of the results of compounds **4a** and **5**, the inhibition percentage of **5** are higher than that of **4a** on all cancer cell lines. It is suggested that introducing a big unit on the side chain of the amino group could enhance anticancer activity.

Summary

In summary, we have synthesized a series of N-[4-ferrocenyl-5-(1*H*-1,2,4-trizaol-1-yl)-1,3-thiazol-2-yl] substituted benzamide, **4a**–**4o**, and their structures were established on the basis of ^{1}H NMR spectral data and elemental analysis. Finally, the structures of compounds **2** and **4o** were confirmed by X-ray crystallographic studies. These novel ferrocenyl-containing thiazole derivatives have also been screened for their anticancer activity against three human cancer cell lines. Thiazole **4j**, **4k** and **5** all showed good inhibition percentages against human cancer cell lines. These compounds represent promising lead compounds for the development of thiazole-containing anticancer agents and are candidates for further studies.

EXPERIMENT

All melting points were determined on a Yanaco-241 apparatus and the thermometer was uncorrected. The ^{1}H NMR spectra were measured on a Brucker AC-300 spectrometer in DMSO-d_6 or $CDCl_3$ solution with TMS as the internal standard. Elemental analyses were determined on a Yanaco CHN CORDER MT-3 elemental analyser. X-ray diffraction data were recorded at 293 K on a Bruker Smart1000 diffractometer (graphite-monochromatized Mo Kα radiation, $\lambda = 0.71073$ Å).

Synthesis of α-Bromo-α-1*H*-1,2,4-triazol-1-yl-acetylferrocene (1)

A solution of α-1*H*-1,2,4-triazol-1-yl-acetylferrocene (12.3 g, 43.8 mmol) in anhydrous THF (150 ml) was added in dropwise to a solution of LDA (72.3 mmol) in anhydrous THF (20 ml) at −78°C and under a nitrogen atmosphere. The reaction mixture was stirred at −78°C for 2 hr and then trimethylchlorosilane (57 mmol) was added. After 4 hr under these reaction conditions, NBS (9.92 g, 57 mmol) was added and the solution was stirred until the reaction reached room temperature (8 h). The reaction mixture was filtered through a silica gel layer, and the resulting solution was evaporated to dryness and chromatographed on a silica gel column using ethyl acetate/petroleum ether (V/V = 1/3) as eluent to give compound **1** 11.96 g in 73% yield; m.p. 114–116°C.

Synthesis of 2-amino-4-ferrocenyl-5-(1*H*-1,2,4-triazol-1-yl)-1,3-thizole (2)

A mixture of α-bromo-α-1*H*-1,2,4-triazol-1-yl-acetylferrocene (**1**) (10.85 g, 29 mmol) and thiourea (4.41 g, 58 mmol) in anhydrous ethanol was refluxed for 8 hr under a nitrogen atmosphere. Then the mixture was alkalified by ammonia solution (5%). Allowed to cool overnight, the precipitated product was collected by filtration, washed with water and dried. Recrystallization from methanol afforded the desired 2-amino-4-ferrocenyl-5-(1*H*-1,2,4-triazol-1-yl)-1,3-thiazole 7.33 g, in 72% yield; m.p. 248–250°C. Anal. (%) C, 51.30; H, 3.73; N, 19.94; Calc. for $C_{15}H_{13}FeN_5S$: C, 51.35; H, 3.61; N, 19.72; ^{1}H NMR δ (DMSO-d_6): 8.88 (s, 1H, Tr-H), 8.34 (s, 1H, Tr-H), 7.44 (s, 2H, NH_2), 4.07 (s, 5H, Fc-H), 4.22–4.20 (t, 2H, Fc-H), 3.93–3.91 (t, 2H, Fc-H).

Synthesis of N-[4-ferrocenyl-5-(1*H*-1,2,4-triazol-1-yl)-1,3-thiazol-2-yl] substituted Benzamide (4)

To a suspended solution of 2-amino-4-ferrocenyl-5-(1*H*-1,2,4-triazol-1-yl)-1,3-thiazole (0.35 g, 1.0 mmol) and pyridine (0.12 g, 1.5 mmol) in chloroform (20 ml), the solution of substituted benzoyl chloride (1.2 mmol) in chloroform (5 ml) was added in dropwise under a nitrogen atmosphere. Then the mixture was heated under reflux for 3–5 hr, cooled and freed from solvent in vacuum. The residue was washed with water and dried. Purification by chromatograph on a silica gel column using ethyl acetate/petroleum ether (V/V = 1/3) as eluent afforded **4a**–**4o** in various yields. The physical properties, elemental analysis data and ^{1}H NMR data of compound **4** thus synthesized are reported in Table 2 and Table 3, respectively.

Synthesis of N-[4-ferrocenyl-5-(1*H*-1,2,4-triazol-1-yl)-1,3-thiazol-2-yl]-N-benzoylbenzamide (5)

Benzoyl chloride (1.4 g, 10 mmol) was added dropwise to a solution of 2-amino-4-ferrocenyl-5-(1*H*-1,2,4-triazol-1-yl)-1,3-thiazole (0.35 g, 1.0 mmol) in dry pyridine (20 ml). After stirring for 8 hr at room temperature, the reaction mixture was poured into water (150 ml). After 2 days the precipitate was collected, washed with water and dried. Recrystallization from ethanol, 0.26 g red crystalloid (**5**) was obtained (yield 46.48%). m.p. 277–279°C. Anal. (%) C, 62.41; H, 3.65; N, 12.47; Calc. for $C_{29}H_{21}FeN_5O_2S$: C, 62.26; H, 3.78; N, 12.52; ^{1}H NMR δ (DMSO-d_6): 9.00 (s, 1H, Tr-H), 8.42 (s, 1H, Tr-H), 7.92–7.56 (m, 10H, phenyl-H), 4.19 (s, 2H, Fc-H), 3.77 (s, 2H, Fc-H), 3.70 (s, 5H, Fc-H).

Supplementary Material

Crystallographic data for the structure **2** and **4o** have been deposited with the Cambridge Crystallographic Data Center,

TABLE 2
Physical properties and elemental analysis of compound **4**

Component	R_1	Yield (%)	m.p. (°C)	Formula (g/mol)	Elemental analysis (%); Found (Calcd)		
					C	H	N
4a	H	41.7	271–273	$C_{22}H_{17}FeN_5OS$ 455.31	57.90 (58.03)	3.78 (3.76)	15.11 (15.38)
4b	*o*-F	44.4	174–176	$C_{22}H_{16}FFeN_5OS$ 473.30	55.88 (55.83)	3.59 (3.41)	14.70 (14.80)
4c	*m*-F	42.3	216–218	$C_{22}H_{16}FFeN_5OS$ 473.30	55.63 (55.83)	3.43 (3.41)	14.79 (14.80)
4d	*p*-F	48.6	248–250	$C_{22}H_{16}FFeN_5OS$ 473.30	55.81 (55.83)	3.84 (3.41)	14.79 (14.80)
4e	*o*-Cl	49.0	237–239	$C_{22}H_{16}ClFeN_5OS$ 489.76	53.80 (53.95)	3.33 (3.29)	14.48 (14.30)
4f	*p*-Cl	51.0	223–225	$C_{22}H_{16}ClFeN_5OS$ 489.76	53.96 (53.95)	3.39 (3.29)	14.44 (14.30)
4g	*o*-Br	43.1	254–256	$C_{22}H_{16}BrFeN_5OS$ 534.21	49.33 (49.46)	3.22 (3.02)	12.98 (13.11)
4h	*p*-Br	44.9	246 darkness	$C_{22}H_{16}BrFeN_5OS$ 534.21	49.31 (49.46)	3.19 (3.02)	13.07 (13.11)
4i	*m*-I	53.4	144–147	$C_{22}H_{16}FeIN_5OS$ 581.21	45.46 (45.46)	3.00 (2.77)	11.87 (12.05)
4j	*o*-OCH_3	43.3	190–193	$C_{23}H_{19}FeN_5O_2S$ 485.34	56.78 (56.92)	3.82 (3.95)	14.42 (14.43)
4k	*m*-OCH_3	41.2	188–191	$C_{23}H_{19}FeN_5O_2S$ 485.34	57.09 (56.92)	3.79 (3.95)	14.48 (14.43)
4l	*p*-OCH_3	45.4	275 darkness	$C_{23}H_{19}FeN_5O_2S$ 485.34	56.84 (56.92)	4.01 (3.95)	14.46 (14.92)
4m	*p*-CH_3	46.9	239–242	$C_{23}H_{19}FeN_5OS$ 469.34	58.76 (58.86)	4.04 (4.08)	14.80 (14.92)
4n	*p*-C_2H_5	47.6	233–235	$C_{24}H_{21}FeN_5OS$ 483.37	59.51 (59.64)	4.40 (4.38)	14.24 (14.49)
4o	*o*-NO_2	46.0	231–233	$C_{22}H_{16}FeN_6O_3S$ 500.31	53.68 (53.71)	3.73 (3.53)	16.63 (16.34)

TABLE 3
^{1}H NMR spectral data of compounds **4**

Component	^{1}H NMR (DMSO or $CDCl_3$/TMS, δ)
4a (DMSO)	9.382 (s, 1H, N-H); 9.024 (s, 1H, Tr-H); 8.439 (s, 1H, Tr-H); 8.180, 8.156 (d, 2H, Ph-H); 7.711–7.560 (m, 3H, Ph-H); 4.324, 4.319, 4.313 (t, 2H, Fc-H); 4.125, 4.119, 4.113 (t, 2H, Fc-H), 4.092 (s, 5H, Fc-H)
4b ($CDCl_3$)	9.929, 9.881 (d, 1H, N-H); 8.281 (s, 1H, Tr-H); 8.246 (s, 1H, Tr-H); 7.687–7.280 (m, 4H, Ph-H); 4.264 (s, 2H, Fc-H); 4.198 (s, 2H, Fc-H); 4.111 (s, 5H, Fc-H)
4c ($CDCl_3$)	9.647 (s, 1H, N-H); 8.290 (s, 1H, Tr-H); 8.259 (s, 1H, Tr-H); 7.792–7.331 (m, 4H, Ph-H); 4.279 (s, 2H, Fc-H); 4.175 (s, 2H, Fc-H); 4.117 (s, 5H, Fc-H)
4d (DMSO)	9.375 (s, 1H, N-H); 9.009 (s, 1H, Tr-H); 8.435 (s, 1H, Tr-H); 8.263–8.215 (q, 2H, Ph-H); 7.453–7.394 (q, 2H, Ph-H); 4.330, 4.324, 4.317 (t, 2H, Fc-H); 4.120, 4.117, 4.107 (t, 2H, Fc-H); 4.091 (s, 5H, Fc-H)
4e (DMSO)	9.375 (s, 1H, N-H); 9.018 (s, 1H, Tr-H); 8.438 (s, 1H, Tr-H); 7.726–7.464 (m, 4H, Ph-H); 4.316, 4.310, 4.304 (t, 2H, Fc-H); 4.087 (s, 7H, Fc -H)
4f (DMSO)	9.375 (s, 1H, N-H); 9.009 (s, 1H, Tr-H); 8.435 (s, 1H, Tr-H); 8.263–8.215 (q, 2H, Ph-H); 7.453–7.394 (q, 2H, Ph-H); 4.330, 4.324, 4.317 (t, 2H, Fc-H); 4.120, 4.117, 4.107 (t, 2H, Fc-H); 4.091 (s, 5H, Fc-H)
4g (DMSO)	9.374 (s, 1H, N-H); 9.016 (s, 1H, Tr-H); 8.439 (s, 1H, Tr-H); 7.779–7.495 (m, 4H, Ph-H); 4.322, 4.316, 4.310 (t, 2H, Fc-H); 4.088 (s, 7H, Fc-H)
4h ($CDCl_3$)	9.749 (s, 1H, N-H); 8.278 (s, 1H, Tr-H); 8.257 (s, 1H, Tr-H); 7.903, 7.875 (d, 2H, Ph-H, $J = 8.4$); 7.733, 7.705 (d, 2H, Ph-H, $J = 8.4$); 4.276 (s, 2H, Fc-H); 4.169 (s, 2H, Fc-H); 4.113 (s, 5H, Fc-H)
4i ($CDCl_3$)	8.341 (s, 1H, N-H); 8.304 (s, 1H, Tr-H); 8.269 (s, 1H, Tr-H); 7.995–7.309 (m, 4H, Ph); 4.281 (s, 2H, Fc); 4.172 (s, 2H, Fc); 4.120 (s, 5H, Fc)
4j ($CDCl_3$)	9.358 (s, 1H, N-H); 9.003 (s, 1H, Tr-H); 8.432 (s, 1H, Tr-H); 7.736–7.090 (m, 4H, Ph-H); 4.316, 4.311 (d, 2H, Fc-H); 4.084, 4.079 (d, 7H, Fc-H); 3.964, 3.930 (d, 3H, OCH_3)
4k ($CDCl_{3)}$	9.371 (s, 1H, N-H); 9.011 (s, 1H, Tr-H); 8.435 (s, 1H, Tr-H); 7.750–7.224 (m, 4H, Ph-H); 4.329, 4.323, 4.317 (t, 2H, Fc-H); 4.125, 4.119, 4.113 (t, 2H, Fc-H); 4.092 (s, 5H, Fc-H); 3.883 (s, 3H, OCH_3)
4l ($CDCl_3$)	9.483 (s, 1H, N-H); 8.280 (s, 1H, Tr-H); 8.256 (s, 1H, Tr-H); 7.984, 7.955 (d, 2H, Ph-H, $J = 8.7$); 7.053, 7.024 (d, 2H, Ph-H, $J = 8.7$); 4.260 (s, 2H, Fc-H); 4.163 (s, 2H, Fc-H); 4.109 (s, 5H, Fc-H); 3.912 (s, 3H, OCH_3)
4m ($CDCl_3$)	9.628 (s, 1H, N-H); 8.269 (s, 1H, Tr-H); 8.247 (s, 1H, Tr-H); 7.924, 7.897 (d, 2H, Ph-H, $J = 8.1$); 7.385, 7.358 (d, 2H, Ph-H, $J = 8.1$); 4.267 (s, 2H, Fc-H); 4.170 (s, 2H, Fc-H); 4.114 (s, 5H, Fc-H); 2.472 (s, 3H, CH_3)
4n ($CDCl_3$)	9.513 (s, 1H, N-H); 8.272 (s, 1H, Tr-H); 8.246 (s, 1H, Tr-H); 7.941, 7.914 (d, 2H, Ph-H, $J = 8.1$); 7.407, 7.380 (d, 2H, Ph-H, $J = 8.1$); 4.272 (s, 2H, Fc-H); 4.176 (s, 2H, Fc-H); 4.119(s, 5H, Fc-H); 2.804–2.727 (q, 4H, CH_2); 1.326, 1.300, 1.275 (t, 3H, CH_3)
4o (DMSO)	9.377 (s, 1H, N-H); 9.019 (s, 1H, Tr-H); 8.433 (s, 1H, Tr-H); 8.245–7.839 (m, 4H, Ph); 4.325, 4.319, 4.312 (t, 2H, Fc); 4.088, 4.078, 4.072 (t, 7H, Fc)

(Tr: triazole; Fc: ferrocenyl).

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