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Synthesis, characterization and antitumor activity of novel amide derivatives containing ferrocenyl pyrazol-moiety

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ABSTRACT

A series of novel 2-(5-ferrocenyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)-*N*-amide derivatives (**1**–**38**) were prepared. The compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, mass spectroscopy and element analysis. Compounds **19** and **30** were also gave crystals suitable for X-ray structural analysis. Biological evaluation of all the compounds were performed in the human prostatic carcinoma cell line (PC-3) and human mammary carcinoma cell line (Bcap-37) using the MTT method. Among them, compound **10** exhibited comparable *in vitro* antitumor activity to the positive control 5-Fluorouracil (5-FU) and cisplatin.

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1. Introduction

Prompted by the initial success of platinum chemotherapeutic metallopharmaceuticals, attention was first shifted to non-platinum chemotherapeutics starting from the basic cisplatin framework, with the aim to optimize the efficiency of such drugs and to avoid serious side-effects caused by platinum chemotherapeutics [1–4]. Among these, organometallic compounds, which are defined as metal complexes containing at least one direct, covalent metal-carbon bond, have attracted special attention recently and been found to be promising anticancer drug candidates [5–7]. Organometallic medicinal chemistry is becoming one of the most promising developments in bioorganometallic chemistry [8].

As the first organometallic compound for which antiproliferative properties were reported [9], the antitumor activities of ferrocene-containing compounds themselves were extensively studied *in vitro* and *in vivo* [10–12]. Unique properties such as the similarities in aromaticity, lipophilicity, stability, low toxicity and unusual redox activity recommend ferrocene for incorporation in drug molecules [13]. Several structural modification of established drugs with ferrocenyl moiety have been reported, such as ferrocene fluconazole [14], ferrocene aspirin [15], the antimalarial drugs chloroquine (termed ferroquine) [16], mefloquine [17], and artemisinin [18]. The ferrocenyl moiety in ferrocifen, which is a ferrocene conjugated tamoxifen, significantly augments the anticancer activity of tamoxifen [19]. Ferricenium salts, besides their antiproliferative activity also display DNA-cleaving activity and DNA synthesis inhibitory effect [20]. Recently therapeutic synergism of the antitumor activity of a combination of ferrocenylmethyl thymine with the well known antitumor drug cyclophosphamide against Ca755 was demonstrated [21]. Accordingly, using ferrocenyl-containing derivatives as medicines and other chemotherapeutants has long been recognized as an attractive way [22,23].

Recently, a ferrocene-containing derivative 3-trifluoromethyl-5-ferrocenyl -pyrazol-1-yl-acetic acid (LCOOH) and three organotin(IV) carboxylate derivatives $[Ph_4Sn_2O(OCH_3)(OOCL)]_2$, $[BuSnO(OOCL)]_6$ and $[Bu_4Sn_2O(OOCL_2)_2]$ had been synthesized in our lab [24]. Their antitumor activities were also evaluated against three cancer cell lines. In continuation with our recent studies on ferrocene derivatives, we have focused our attention to synthesize a series of novel amide derivatives (**1**–**38**) using the same ferrocene-containing acetic acid to extend the structure–activity relationships (SAR) study. We also describe the crystal structures of compounds **19** and **30** featuring the amide derivatives that derived from primary and secondary amines, respectively.

2. Experimental

2.1. General

All the NMR spectra were recorded on a Bruker DRX 400 model Spectrometer in $CDCl_3$. Chemical shifts (δ) for ^{1}H NMR and

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^{13}C NMR spectra were reported in parts per million to residual solvent protons. Melting points were measured on a Boetius micro melting point apparatus. The ESI–MS spectra were recorded on a Mariner System 5304 Mass spectrometer. Carbon, hydrogen and nitrogen assays were carried out with a CHN-O-Rapid instrument and were within ±0.4% of the theoretical values. TLC was run on the silica gel coated aluminum sheets (Silica Gel 60 GF254, E. Merk, Germany) and visualized in UV light (254 nm).

2.2. Synthesis

Acetylferrocene, ethyl trifluoroacetate, ethyl bromoacetate, EDC.HCl, HOBt, primary amines and secondary amines were purchased from Sigma–Aldrich. The synthesis of all the compounds (**1**–**38**) was performed in a manner as outlined in Scheme 1. The intermediates 4,4,4-trifluoro-1-ferrocenylbutane-1,3-dione (**B**), 5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazole(**C**) and 2-(5-ferrocenyl -3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid (**D**) were synthesized according to the established methods [24,25].

A solution of **D** (0.454 mg, 1.2 mmol), EDC·HCl (0.216 g, 1.2 mmol) and HOBt (0.135 g, 1 mmol) in 25 mL of CH_2Cl_2 was stirred at room temperature for 0.5 h. Then, a CH_2Cl_2 solution (25 mL) of substituted primary or secondary amines (1 mmol) was added dropwise, respectively. The reaction mixture was stirred overnight at room temperature and the solvent was evaporated. Column chromatography of the crude mixture on silica gel using petroleum ether/ethyl acetate as eluent to afford the target compounds **1**–**38**, see Table 1 and Table 2.

2.2.1. N-Phenyl-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acet-amide (*1*)

Brown solid (0.408 g, 90.2% yield). Mp.: 151–153 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.18 (s, 5H), 4.42 (s, 2H), 4.55 (s, 2H), 5.17 (s, 2H), 6.63 (s, 1H), 7.12–7.15 (m, 1H), 7.31–7.35 (m, 2H), 7.47 (d, J = 8.4 Hz, 2H), 8.16 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 54.1, 68.7, 69.8, 70.1, 72.1, 104.6, 104.7, 120.0, 125.1, 129.2, 136.8, 145.7, 164.4. MS (ESI): m/z 454 ($[M + H]^+$). Anal. Calc for $C_{22}H_{18}F_3FeN_3O$: C, 58.30; H, 4.00; O, 3.53%. Found: C, 58.12; H, 4.02; O, 3.54%. IR (KBr, cm^{-1}): ν = 3270(m), 1679(s), 1604(s), 1549(s), 1508(m), 1439(s), 1412(s), 1367(m), 1312(m), 1247(s), 1218(s), 1147(s), 1120(s), 976(s), 808(m), 756(m).

2.2.2. N-(4-methoxyphenyl)-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (*2*)

Brown solid (0.450 g, 93.1% yield). Mp.: 121–123 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.81 (s, 3H), 4.21 (s, 5H), 4.44 (s, 2H), 4.58 (s, 2H), 5.18 (s, 2H), 6.66 (s, 1H), 6.88 (d, 2H, J = 9.0 Hz), 7.39 (d, 2H, J = 9.0 Hz), 7.95 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 54.0, 55.5, 68.7, 69.8, 70.0, 72.2, 104.6, 104.6, 114.3, 121.9, 129.9, 145.4, 157.0, 164.3. MS (ESI): m/z 484 ($[M + H]^+$). Anal. Calc for $C_{23}H_{20}F_3FeN_3O_2$: C, 57.16; H, 4.17; O, 6.62%. Found: C, 58.38; H, 4.16; O, 6.64%. IR (KBr, cm^{-1}): ν = 3279(m), 1662(s), 1552(s), 1504(s), 1408(m), 1233(s), 1130(s), 965(m), 825(s), 715(m).

2.2.3. N-(3-methoxyphenyl)-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (*3*)

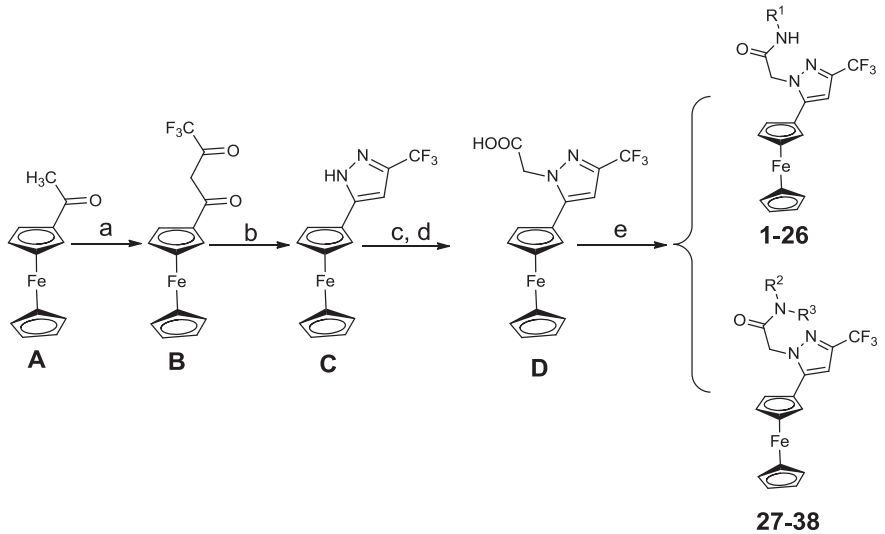
Brown solid (0.398 g, 82.4% yield). Mp.: 136–138 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.82 (s, 3H), 4.21 (s, 5H), 4.45 (s, 2H), 4.57 (s, 2H), 5.18 (s, 2H), 6.66 (s, 1H), 6.71 (d, 1H, J = 8.4 Hz), 6.94 (d, 1H, J = 8.0 Hz), 7.23 (d, 1H, J = 8.0 Hz), 7.26 (s, 1H), 8.14 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 54.0, 55.3, 68.7, 69.8, 70.0, 72.2, 104.6, 104.6, 105.8, 110.8, 112.1, 129.8, 138.1, 145.5, 160.1, 164.4. MS (ESI): m/z 484 ($[M + H]^+$). Anal. Calc for $C_{23}H_{20}F_3FeN_3O_2$: C, 57.16; H, 4.17; O, 6.62%. Found: C, 57.02; H, 4.18; O, 6.61%. IR (KBr, cm^{-1}): ν = 3276(s), 3060(m), 1682(s), 1604(s), 1528(s), 1466(s), 1412(m), 1315(m), 1237(s), 1185(s), 1137(s), 1024(s), 973(s), 858(s), 753(s).

2.2.4. N-(2-methoxyphenyl)-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (*4*)

Brown solid (0.365 g, 75.6% yield). Mp.: 131–133 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.72 (s, 3H), 4.06 (s, 5H), 4.33 (s, 2H), 4.48 (s, 2H), 5.11 (s, 2H), 6.58 (s, 1H), 6.77 (d, 1H, J = 8.0 Hz), 6.86–6.91 (m, 1H), 6.96–7.00 (m, 1H), 8.32 (d, 1H, J = 8.0 Hz), 8.52 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 54.5, 55.4, 68.6, 69.9, 70.1, 72.1, 104.5, 104.5, 115.0, 119.4, 121.1, 124.5, 126.9, 145.3, 148.0, 164.4. MS (ESI): m/z 484 ($[M + H]^+$). Anal. Calc for $C_{23}H_{20}F_3FeN_3O_2$: C, 57.16; H, 4.17; O, 6.62%. Found: C, 57.34; H, 4.06; O, 6.64%. IR (KBr, cm^{-1}): ν = 3268(m), 1682(s), 1607(m), 1538(s), 1460(m), 1322(m), 1230(s), 1134(s), 1027(s), 979(m), 828(m), 756(s).

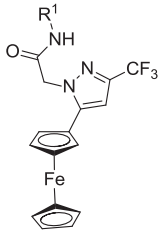
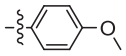
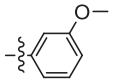
2.2.5. N-(3,5-methoxyphenyl)-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (*5*)

Brown solid (0.372 g, 72.4% yield). Mp.: 96–97 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.79 (s, 6H), 4.21 (s, 5H), 4.44 (s, 2H),



Scheme 1. Synthesis of compounds **1**–**38**. (a) EtOH/Na, $CF_3COOC_2H_5$; (b) EtOH, $NH_2NH_2.H_2O$; (c) $BrCH_2COOC_2H_5$, *t*-BuOK, CH_3CN; (d) KOH, EtOH, H_2O; (e) EDC·HCl, HOBt, CH_2Cl_2.
Figure(s)

Table 1
Structures for compounds **1**–**26**.

Structure	Comp. no.	R^1
	**1**	
	2	
	3	
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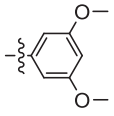
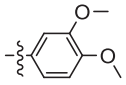
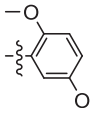
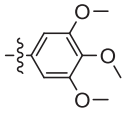
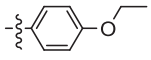
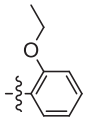
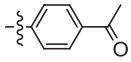
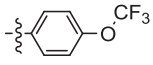
	5	
	6	
	7	
	8	
	9	
	10	
	11	
	12	
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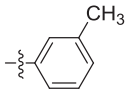
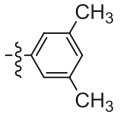
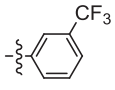
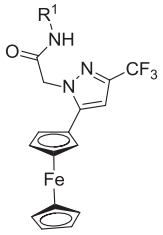
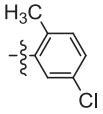
	14	
	15	
	16	

Table 1 (*continued*)

Structure	Comp. no.	R^1
	**17**	
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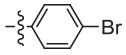
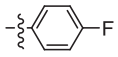
	20	
	21	
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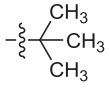
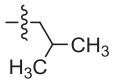
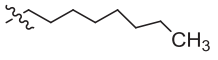
	24	
	25	
	26	

4.57 (s, 2H), 5.16 (s, 2H), 6.27 (s, 1H), 6.66 (s, 1H), 6.72(s, 2H), 8.14 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 54.1, 55.4, 68.7, 69.8, 70.1, 72.1, 97.3, 98.2, 104.6, 104.7, 138.5, 145.6, 161.1, 164.2. MS (ESI): *m*/*z* 514 ($[M + H]^+$). Anal. Calc for $C_{24}H_{22}F_3FeN_3O_3$: C, 56.16; H, 4.32; O, 9.35%. Found: C, 56.03; H, 4.33; O, 9.34%. IR (KBr, cm^{-1}): ν = 3284(m), 1682(s), 1607(s), 1549(m), 1456(s), 1422(m), 1233(s), 1158(s), 1127(s), 1061(m), 825(m).

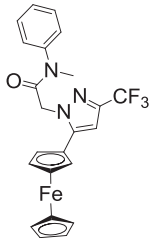
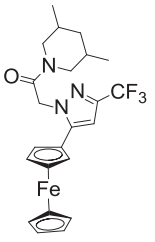
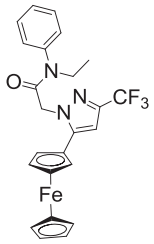
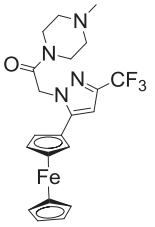
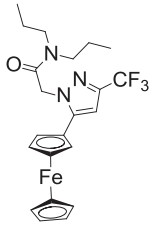
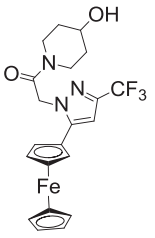
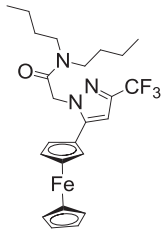
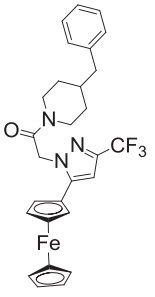
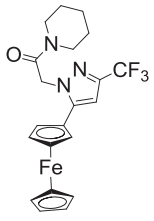
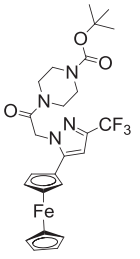
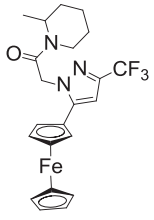
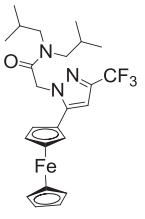
2.2.6. *N-(3,4-methoxyphenyl)-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (**6**)*

Brown solid (0.345 g, 67.3% yield). Mp.: 136–138 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.87 (s, 3H), 3.90 (s, 3H), 4.21 (s, 5H), 4.45 (s, 2H), 4.58 (s, 2H), 5.19 (s, 2H), 6.66 (s, 1H), 6.84(d, 2H, J = 8.8 Hz), 7.28 (s, 1H), 8.04 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 54.1, 56.0, 56.1, 68.7, 69.8, 70.0, 72.1, 104.6, 104.6, 104.8, 111.3, 112.1, 130.4, 145.5, 146.4, 149.2, 164.2. MS (ESI): *m*/*z* 514 ($[M + H]^+$). Anal. Calc for $C_{24}H_{22}F_3FeN_3O_3$: C, 56.16; H, 4.32; O, 9.35%. Found: C, 56.36; H, 4.31; O, 9.38%. IR (KBr, cm^{-1}): ν = 3261(m), 1679(s), 1556(m), 1511(s), 1415(m), 1247(s), 1113(s), 1024(m), 969(s), 797(m).

2.2.7. *N-(2,5-methoxyphenyl)-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (**7**)*

Brown solid (0.357 g, 69.5% yield). Mp.: 114–116 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.77 (s, 3H), 3.81 (s, 3H), 4.15 (s, 5H),

Table 2
Structures for compounds **27**–**38**.

Comp. no.	Structure	Comp. no.	Structure
27		**33**	
28		**34**	
29		**35**	
30		**36**	
31		**37**	
32		**38**	

4.43 (s, 2H), 4.57 (s, 2H), 5.19 (s, 2H), 6.60 (d, 1H, $J = 8.4$ Hz), 6.67 (s, 1H), 6.77 (d, 1H, $J = 8.4$ Hz), 8.14 (s, 1H), 8.59 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 54.5, 55.8, 56.1, 68.5, 69.8, 70.0, 71.9, 104.4, 104.5, 105.9, 109.1, 110.8, 127.5, 142.2, 145.3, 153.8, 164.4. MS (ESI): m/z 514 ($[M + H]^+$). Anal. Calc for $C_{24}H_{22}F_3FeN_3O_3$: C, 56.16; H, 4.32; O, 9.35%. Found: C, 56.32; H, 4.26; O, 9.33%. IR (KBr, cm^{-1}): ν = 3308(m), 3080(m), 1658(s), 1604(s), 1549(s), 1494(s), 1432(m), 1233(s), 1127(s), 973(s), 815(s), 739(m).

*2.2.8. 2-(5-Ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(3,4,5-trimethoxyphenyl)acetamide (**8**)*

Brown solid (0.357 g, 83.5% yield). Mp.: 164–166 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.83 (s, 3H), 3.87 (s, 6H), 4.29 (s, 5H), 4.52 (s, 2H), 4.64 (s, 2H), 5.16 (s, 2H), 6.61 (s, 1H), 6.77 (s, 2H), 8.12 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 53.9, 56.0, 60.9, 68.8, 69.8, 70.0, 72.3, 97.5, 104.6, 104.6, 133.2, 135.0, 145.6, 153.3, 164.2. MS (ESI): m/z 544 ($[M + H]^+$). Anal. Calc for $C_{25}H_{24}F_3FeN_3O_4$: C, 55.27; H, 4.45; O, 11.78%. Found: C, 55.44; H, 4.44; O, 11.76%. IR (KBr, cm^{-1}): ν = 3297(m), 1676(m), 1611(m), 1549(m), 1504(s), 1446(m), 1417(m), 1232(s), 1129(s), 969(m), 816(m).

*2.2.9. N-(4-ethoxyphenyl)-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (**9**)*

Brown solid (0.454 g, 91.2% yield). Mp.: 140–142 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.41 (t, 3H, $J = 7.2$ Hz), 4.02 (q, 2H, $J = 6.8$ Hz), 4.21 (s, 5H), 4.45 (s, 2H), 4.58 (s, 2H), 5.17 (s, 2H), 6.65 (s, 1H), 6.87 (d, 2H, $J = 7.8$ Hz), 7.37 (d, 2H, $J = 7.8$ Hz), 7.93 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 14.8, 54.1, 63.7, 68.7, 69.8, 70.0, 71.8, 104.6, 104.6, 114.9, 121.8, 129.7, 145.4, 156.3, 164.2. MS (ESI): m/z 498 ($[M + H]^+$). Anal. Calc for $C_{24}H_{22}F_3FeN_3O_2$: C, 57.97; H, 4.46; O, 6.43%. Found: C, 58.16; H, 4.38; O, 6.45%. IR (KBr, cm^{-1}): ν = 3256(m), 2946(m), 1679(s), 1604(s), 1545(s), 1442(s), 1388(m), 1243(s), 1134(s), 1041(s), 962(s), 917(m), 818(m), 743(s).

*2.2.10. N-(2-ethoxyphenyl)-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (**10**)*

Brown solid (0.352 g, 70.7% yield). Mp.: 136–138 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.34 (t, 3H, $J = 7.2$ Hz), 4.03 (q, 2H, $J = 7.2$ Hz), 4.15 (s, 5H), 4.42 (s, 2H), 4.58 (s, 2H), 5.20 (s, 2H), 6.68 (s, 1H), 6.84 (d, 1H, $J = 8.0$ Hz), 6.92–6.99 (m, 1H), 7.02–7.08 (m, 1H), 8.31 (s, 1H), 8.44 (d, 1H, $J = 7.6$ Hz). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 15.0, 54.9, 64.3, 68.4, 69.8, 70.1, 72.0, 104.2, 104.2, 111.0, 115.1, 118.4, 120.9, 124.6, 145.3, 147.3, 164.5. MS (ESI): m/z 498 ($[M + H]^+$). Anal. Calc for $C_{24}H_{22}F_3FeN_3O_2$: C, 57.97; H, 4.46; O, 6.43%. Found: C, 57.86; H, 4.47; O, 6.46%. IR (KBr, cm^{-1}): ν = 3410(m), 3286(m), 1679(s), 1597(s), 1538(s), 1452(s), 1398(m), 1231(s), 1134(s), 1045(s), 973(s), 828(m), 753(s).

*2.2.11. N-(4-acetylphenyl)-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (**11**)*

Brown solid (0.442 g, 89.2% yield). Mp.: 48–49 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.58 (s, 3H), 4.19 (s, 5H), 4.44 (s, 2H), 4.54 (s, 2H), 5.20 (s, 2H), 6.65 (s, 1H), 7.59 (d, 2H, $J = 8.4$ Hz), 7.94 (d, 2H, $J = 8.4$ Hz), 8.57 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 26.5, 53.9, 68.8, 69.8, 70.1, 72.1, 104.7, 104.7, 119.2, 129.8, 141.3, 145.9, 164.6, 197.0. MS (ESI): m/z: 496 ($[M + H]^+$). Anal. Calc for $C_{24}H_{20}F_3FeN_3O_2$: C, 58.20; H, 4.07; O, 6.46%. Found: C, 58.08; H, 4.08; O, 6.48%. IR (KBr, cm^{-1}): ν = 3296(m), 3102(m), 1682(s), 1600(s), 1535(s), 1412(m), 1257(s), 1137(s), 973(m), 825(s).

*2.2.12. 2-(5-Ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(4-(trifluoromethoxy)phenyl)acetamide (**12**)*

Brown solid (0.455 g, 84.6% yield). Mp.: 93–94 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.19 (s, 5H), 4.44 (s, 2H), 4.54 (s, 2H), 5.17 (s, 2H), 6.64 (s, 1H), 7.00 (d, 1H, $J = 8.0$ Hz), 7.25 (d, 1H, $J = 8.0$ Hz), 7.33 (t, 1H, $J = 8.4$ Hz), 7.60 (s, 1H), 8.40 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 53.8, 68.8, 69.6, 69.8, 70.1, 72.1, 104.7, 104.7, 112.8, 117.9,

130.1, 138.3, 145.7, 149.6, 164.5. MS (ESI): m/z 538.2 ($[M + H]^+$). Anal. Calc for $C_{23}H_{17}F_6FeN_3O_2$: C, 51.42; H, 3.19; O, 5.96%. Found: C, 51.34; H, 3.18; O, 5.97%. IR (KBr, cm^{-1}): ν = 3276(s), 3070(m), 1672(s), 1607(s), 1562(s), 1247(s), 1151(s), 974(m), 804(s), 695(m).

*2.2.13. 2-(5-Ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(o-tolyl)acetamide (**13**)*

Brown solid (0.442 g, 89.2% yield). Mp.: 178–180 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.14 (s, 3H), 4.22 (s, 5H), 4.46 (s, 2H), 4.59 (s, 2H), 5.24 (s, 2H), 6.66 (s, 1H), 7.06–7.10 (m, 1H), 7.18 (d, 1H, J = 7.6 Hz), 7.23–7.26 (m, 1H), 8.07 (d, 1H, J = 8.0 Hz), 8.10 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 17.2, 54.2, 68.7, 69.8, 70.1, 72.0, 104.7, 104.7, 121.4, 125.2, 126.9, 127.7, 130.6, 135.2, 145.5, 164.3. MS (ESI): m/z 468 ($[M + H]^+$). Anal. Calc for $C_{23}H_{20}F_3FeN_3O$: C, 59.12; H, 4.31; O, 3.42%. Found: C, 59.00; H, 4.32; O, 3.44%. IR (KBr, cm^{-1}): ν = 3338(m), 1655 (s), 1607(s), 1552(s), 1480(s), 1408(m), 1302(s), 1227(s), 1117(s), 976(s), 904(m), 821(s).

*2.2.14. 2-(5-Ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(m-tolyl)acetamide (**14**)*

Brown solid (0.442 g, 89.2% yield). Mp.: 158–160 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.36 (s, 3H), 4.24 (s, 5H), 4.47 (s, 2H), 4.61 (s, 2H), 5.17 (s, 2H), 6.63 (s, 1H), 6.97 (d, 1H, J = 6.8 Hz), 7.22 (d, 1H, J = 8.0 Hz), 7.24–7.26 (m, 1H), 7.33 (s, 1H), 8.01 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 20.4, 53.1, 67.7, 68.8, 69.0, 71.1, 103.6, 103.6, 116.1, 119.6, 124.9, 127.9, 135.7, 138.1, 144.4, 163.3. MS (ESI): m/z 468 ($[M + H]^+$). Anal. Calc for $C_{23}H_{20}F_3FeN_3O$: C, 59.12; H, 4.31; O, 3.42%. Found: C, 59.00; H, 4.32; O, 3.44%. IR (KBr, cm^{-1}): ν = 3296(m), 1676(s), 1618(s), 1566(s), 1494(m), 1415(m), 1302(s), 1254(s), 1120(s), 791(s).

*2.2.15. N-(3,5-dimethylphenyl)-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (**15**)*

Brown solid (0.421 g, 87.4% yield). Mp.: 151–153 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.31 (s, 6H), 4.20 (s, 5H), 4.44 (s, 2H), 4.57 (s, 2H), 5.16 (s, 2H), 6.66 (s, 1H), 6.80(s, 1H), 7.11 (s, 2H), 7.93 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 21.3, 54.2, 68.7, 69.8, 70.0, 72.2, 104.6, 104.6, 117.7, 126.8, 136.6, 138.9, 145.4, 164.4. MS (ESI): m/z 482 ($[M + H]^+$). Anal. Calc for $C_{24}H_{22}F_3FeN_3O$: C, 59.89; H, 4.61; O, 3.32%. Found: C, 59.78; H, 4.62; O, 3.34%. IR (KBr, cm^{-1}): ν = 3308(m), 1671(s), 1537(s), 1497(s), 1403(m), 1258(s), 1115(s), 961(s), 785(s), 703(m).

*2.2.16. 2-(5-Ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(3-(trifluoromethyl)phenyl)acetamide (**16**)*

Brown solid (0.350 g, 67.2% yield). Mp.: 96–98 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.22 (s, 5H), 4.46 (s, 2H), 4.59 (s, 2H), 5.20 (s, 2H), 6.66 (s, 1H), 7.02 (d, 1H, J = 8.0 Hz), 7.27 (d, 1H, J = 8.0 Hz), 7.36–7.38 (m, 1H), 7.63 (s, 1H), 8.44 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 53.9, 68.7, 69.8, 70.1, 71.9, 104.8, 104.8, 112.8, 117.1, 117.9, 130.2, 138.3, 144.1, 145.8, 149.6, 164.5. MS (ESI): m/z 522 ($[M + H]^+$). Anal. Calc for $C_{23}H_{17}F_6FeN_3O$: C, 53.00; H, 3.29; O, 3.07%. Found: C, 53.17; H, 3.28; O, 3.08%. IR (KBr, cm^{-1}): ν = 3328(s), 2946(m), 1655(s), 1562(s), 1518(s), 1305(s), 1233(s), 1089(s), 965(s), 890(m), 777(s).

*2.2.17. N-(5-chloro-2-methylphenyl)-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (**17**)*

Brown solid (0.375 g, 74.8% yield). Mp.: 154–156 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.11 (s, 3H), 4.22 (s, 5H), 4.47 (s, 2H), 4.60 (s, 2H), 5.23 (s, 2H), 6.66 (s, 1H), 7.05 (d, 1H, J = 7.8 Hz), 7.09 (d, 1H, J = 7.8 Hz), 8.23 (s, 1H), 8.26 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 16.8, 54.0, 68.7, 69.8, 70.2, 71.9, 104.8, 104.8, 120.9, 124.9, 125.4, 131.3, 132.3, 136.2, 145.7, 164.3. MS (ESI): m/z 503 ($[M + H]^+$). Anal. Calc for $C_{23}H_{19}ClF_3FeN_3O$: C, 55.06; H, 3.82; O, 3.19%. Found: C, 54.93; H, 3.83; O, 3.20%. IR (KBr, cm^{-1}): ν = 3204(m), 1672(s), 1545(m), 1404(m), 1243(m), 1123(s), 976(m), 794(s).

*2.2.18. N-(2-chlorophenyl)-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (**18**)*

Brown solid (0.371 g, 76.1% yield). Mp.: 123–125 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.18 (s, 5H), 4.44 (s, 2H), 4.56 (s, 2H), 5.23 (s, 2H), 6.88 (s, 1H), 7.06–7.10 (m, 1H), 7.28–7.32 (m, 1H), 7.37 (d, 1H, J = 8.0 Hz), 8.45 (d, 1H, J = 8.0 Hz), 8.58 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 54.3, 68.6, 69.9, 70.1, 71.9, 104.8, 104.8, 119.0, 121.1, 125.4, 127.7, 129.2, 133.9, 145.6, 164.7. MS (ESI): m/z 489 ($[M + H]^+$). Anal. Calc for $C_{22}H_{17}ClF_3FeN_3O$: C, 54.18; H, 3.51; O, 3.28%. Found: C, 54.30; H, 3.50; O, 3.29%. IR (KBr, cm^{-1}): ν = 3266(m), 1672(s), 1542(s), 1439(m), 1415(m), 1158(m), 1123(s), 973(m), 794(m), 739(m).

*2.2.19. N-(3-chlorophenyl)-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (**19**)*

Brown solid (0.392 g, 80.4% yield). Mp.: 162–164 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.22 (s, 5H), 4.46 (s, 2H), 4.56 (s, 2H), 5.19 (s, 2H), 6.66 (s, 1H), 7.12–7.16 (m, 1H), 7.27 (d, 1H, J = 8.0 Hz), 7.69 (s, 1H), 8.27 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 54.0, 68.7, 69.8, 70.1, 71.8, 104.7, 104.7, 117.9, 120.1, 125.1, 130.1, 134.9, 138.0, 145.6, 164.4. MS (ESI): m/z 488 ($[M + H]^+$). Anal. Calc for $C_{22}H_{17}ClF_3FeN_3O$: C, 54.18; H, 3.51; O, 3.28%. Found: C, 54.33; H, 3.52; O, 3.27%. IR (KBr, cm^{-1}): ν = 3214(m), 1669(s), 1590(m), 1528(s), 1398(m), 1298(m), 1195(m), 1127(s), 973(s), 794(m), 743(m).

*2.2.20. N-(4-bromophenyl)-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (**20**)*

Brown solid (0.504 g, 94.7% yield). Mp.: 151–153 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.21 (s, 5H), 4.46 (s, 2H), 4.56 (s, 2H), 5.18 (s, 2H), 6.66 (s, 1H), 7.40 (d, 2H, J = 9.0 Hz), 7.46 (d, 2H, J = 9.0 Hz), 8.24 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 52.9, 67.7, 68.8, 69.1, 71.0, 103.7, 103.7, 116.7, 120.4, 131.1, 134.9, 144.6, 163.3. MS (ESI): m/z 533 ($M + H]^+$). Anal. Calc for $C_{22}H_{17}BrF_3FeN_3O$: C, 49.66; H, 3.22; O, 3.01%. Found: C, 49.58; H, 3.21; O, 3.02%. IR (KBr, cm^{-1}): ν = 3266(m), 3152(m), 1604(s), 1682(s), 1614(s), 1549(s), 1484(s), 1404(s), 1312(s), 1250(s), 1141(s), 973(m), 818(s), 732(m).

*2.2.21. N-(4-fluorophenyl)-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (**21**)*

Brown solid (0.430 g, 91.2% yield). Mp.: 95–97 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.21 (s, 5H), 4.45 (s, 2H), 4.56 (s, 2H), 5.19 (s, 2H), 6.66 (s, 1H), 7.04 (t, 2H, J = 8.4 Hz), 7.46 (dd, 2H, J = 5.2, 8.4 Hz), 8.19 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 53.9, 68.7, 69.8, 70.1, 72.0, 104.7, 104.7, 115.7, 115.9, 121.8, 132.9, 145.6, 164.3. MS (ESI): m/z 472 ($[M + H]^+$). Anal. Calc for $C_{22}H_{17}F_4FeN_3O$: C, 56.07; H, 3.64; O, 3.40%. Found: C, 55.97; H, 3.65; O, 3.41%. IR (KBr, cm^{-1}): ν = 3236(s), 3102(s), 1658(s), 1559(s), 1500(s), 1404(m), 1223(s), 1127(m), 969(s), 828(s), 725(s).

*2.2.22. N-Cyclopropyl-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (**22**)*

Brown solid (0.315 g, 75.4% yield). Mp.: 137–139 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.44–0.48 (m, 2H), 0.77–0.85 (m, 2H), 2.70–2.75 (m, 1H), 4.18 (s, 5H), 4.41 (s, 2H), 4.49 (s, 2H), 5.01 (s, 2H), 6.07 (s, 1H), 6.59 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 6.6, 22.7, 53.7, 68.5, 69.8, 70.0, 72.2, 104.3, 104.4, 145.0, 167.9. MS (ESI): m/z 418 ($[M + H]^+$). Anal. Calc for $C_{19}H_{18}F_3FeN_3O$: C, 50.41; H, 4.01; O, 3.53%. Found: C, 50.31; H, 4.02; O, 3.54%. IR (KBr, cm^{-1}): ν = 3276(s), 3080(m), 1666(s), 1552(s), 1412(m), 1322(m), 1250(s), 1127(m), 969(s), 893(m), 808(s), 735(s).

*2.2.23. N-Cyclohexyl-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (**23**)*

Brown solid (0.334 g, 72.7% yield). Mp.: 139–141 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.13–1.85 (m, 10H), 3.77–3.86 (m, 1H),

4.18 (s, 5H), 4.40 (s, 2H), 4.51 (s, 2H), 5.00 (s, 2H), 5.87 (s, 1H), 6.60 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 24.3, 25.4, 32.5, 48.2, 53.9, 68.6, 69.8, 69.9, 72.3, 104.4, 104.4, 145.0, 165.6. MS (ESI): *m/z* 460 ($[M + H]^+$). Anal. Calc for $C_{22}H_{24}F_3FeN_3O$: C, 57.53; H, 5.27; O, 3.48%. Found: C, 57.39; H, 5.29; O, 3.47%. IR (KBr, cm^{-1}): ν = 3410(s), 2906(s), 1631(s), 1518(s), 1152(s), 1329(m), 1250(s), 1192(s), 1134(s), 1010(s), 976(s), 883(m), 804(s).

2.2.24. N-(tert-butyl)-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (**24**)

Brown solid (0.285 g, 65.8% yield). Mp.: 132–134 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.31 (s, 9H), 4.19 (s, 5H), 4.42 (s, 2H), 4.52 (s, 2H), 4.95 (s, 2H), 5.83 (s, 1H), 6.59 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 28.5, 51.7, 54.4, 68.5, 69.8, 70.0, 72.3, 104.4, 104.4, 145.1, 165.5. MS (ESI): *m/z* 434 ($[M + H]^+$). Anal. Calc for $C_{20}H_{22}F_3FeN_3O$: C, 55.44; H, 5.12; O, 3.69%. Found: C, 55.63; H, 5.11; O, 3.70%. IR (KBr, cm^{-1}): ν = 3050(m), 1762(s), 1676(s), 1487(m), 1439(s), 1360(s), 1237(s), 1134(s), 1086(s), 959(s), 901(m), 815(m), 783(s), 756(s).

2.2.25. N-Isobutyl-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (**25**)

Brown solid (0.363 g, 83.7% yield). Mp.: 117–119 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.83 (d, 6H, *J* = 6.4 Hz), 1.67–1.75 (m, 1H), 3.12 (d, 2H, *J* = 5.6 Hz), 4.18 (s, 5H), 4.41 (s, 2H), 4.52 (s, 2H), 5.05 (s, 2H), 6.09 (s, 1H), 6.61 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 19.8, 28.2, 46.7, 53.7, 68.6, 69.8, 70.0, 72.2, 104.4, 104.4, 145.1, 166.5. MS (ESI): *m/z* 434 ($[M + H]^+$). Anal. Calc for $C_{20}H_{22}F_3FeN_3O$: C, 55.44; H, 5.12; O, 3.69%. Found: C, 55.34; H, 5.14; O, 3.68%. IR (KBr, cm^{-1}): ν = 2896(s), 1676(s), 1508(s), 1452(s), 1384(m), 1237(s), 1203(s), 1111(s), 965(s), 856(m), 818(s), 739(s).

2.2.26. 2-(5-Ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-octylacetamide (**26**)

Brown solid (0.360 g, 73.6% yield). Mp.: 61–63 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.88 (t, 3H, *J* = 6.4 Hz), 1.25–1.29 (m, 10H), 1.45–1.48 (m, 2H), 3.28 (m, 2H), 4.20 (s, 5H), 4.43 (s, 2H), 4.53 (s, 2H), 5.05 (s, 2H), 5.99 (s, 1H), 6.62 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 14.0, 22.6, 26.7, 29.1, 29.2, 31.7, 39.6, 53.8, 68.5, 69.8, 70.0, 72.2, 104.3, 104.3, 145.0, 166.4. MS (ESI): *m/z* 490 ($[M + H]^+$). Anal. Calc for $C_{24}H_{30}F_3FeN_3O$: C, 58.91; H, 6.18; O, 3.27%. Found: C, 59.09; H, 6.19; O, 3.26%. IR (KBr, cm^{-1}): ν = 2988(s), 1681(s), 1569(m), 1456(s), 1393(s), 1239(s), 1187(s), 1115(s), 991(s), 879(m), 827(s), 723(m).

2.2.27. N-Methyl-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-phenylacetamide (**27**)

Brown solid (0.407 g, 87.2% yield). Mp.: 95–97 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.35 (s, 3H), 4.15 (s, 5H), 4.38 (s, 2H), 4.44 (s, 2H), 4.82 (s, 2H), 5.32 (s, 1H), 6.58 (s, 1H), 7.31 (d, 2H, *J* = 7.2 Hz), 7.40–7.44 (m, 1H), 7.47–7.51 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 37.7, 52.5, 68.7, 69.3, 69.8, 73.6, 104.1, 104.1, 127.4, 128.8, 130.3, 142.1, 144.1, 165.9. MS (ESI): *m/z* 468 ($[M + H]^+$). Anal. Calc for $C_{23}H_{20}F_3FeN_3O$: C, 59.12; H, 4.31; O, 3.42%. Found: C, 58.99; H, 4.30; O, 3.43%. IR (KBr, cm^{-1}): ν = 3410(m), 1676(s), 1590(m), 1494(m), 1391(s), 1336(m), 1254(m), 1127(s), 959(s), 801(s), 701(s).

2.2.28. N-Ethyl-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-phenylacetamide (**28**)

Brown solid (0.411 g, 85.3% yield). Mp.: 113–115 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.18 (t, 3H, *J* = 7.2 Hz), 3.81 (q, 2H, *J* = 7.2 Hz), 4.14 (s, 5H), 4.38 (s, 2H), 4.43 (s, 2H), 4.76 (s, 2H), 5.32 (s, 1H), 6.57 (s, 1H), 7.27 (d, 2H, *J* = 7.2 Hz), 7.41–7.45 (m, 1H), 7.48–7.52 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 13.0, 44.7, 52.9, 68.6, 69.3, 69.7, 73.6, 104.0, 104.1, 128.4, 128.9, 130.2, 140.4, 144.0, 165.3. MS (ESI): *m/z* 482 ($[M + H]^+$). Anal. Calc for $C_{24}H_{22}F_3FeN_3O$: C, 59.89; H, 4.61; O, 3.32%. Found: C, 60.04; H, 4.60; O, 3.34%. IR (KBr, cm^{-1}): ν = 2958(m), 1676(s), 1586(s), 1497(s), 1398(s), 1326(m), 1257(s), 1195(s), 1141(s), 965(s), 873(m), 815(s), 765(s), 704(s).

2.2.29. 2-(5-Ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N,N-dipropylacetamide (**29**)

Brown solid (0.306 g, 66.4% yield). Mp.: 63–64 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.90 (t, 3H, *J* = 7.2 Hz), 0.94 (t, 3H, *J* = 7.2 Hz), 1.56–1.66 (m, 4H), 3.23 (t, 2H, *J* = 8.0 Hz), 3.32 (t, 2H, *J* = 7.6 Hz), 4.19 (s, 5H), 4.32 (s, 2H), 4.45 (s, 2H), 5.03 (s, 2H), 6.61 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 11.4, 20.8, 48.2, 51.9, 68.9, 69.3, 69.6, 73.7, 104.2, 104.2, 144.3, 165.4. MS (ESI): *m/z* 462 ($[M + H]^+$). Anal. Calc for $C_{22}H_{26}F_3FeN_3O$: C, 57.28; H, 5.68; O, 3.47%. Found: C, 57.12; H, 5.70; O, 3.46%. IR (KBr, cm^{-1}): ν = 3442(m), 2978(s), 1662(s), 1466(s), 1398(m), 1223(s), 1147(s), 965(s), 883(m), 818(s), 743(m).

2.2.30. N,N-dibutyl-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (**30**)

Brown solid (0.307 g, 62.7% yield). Mp.: 66–68 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.96 (t, 6H, *J* = 7.2 Hz), 1.28–1.39 (m, 4H), 1.54–1.62 (m, 4H), 3.27 (t, 2H, *J* = 7.6 Hz), 3.37 (t, 2H, *J* = 7.6 Hz), 4.22 (s, 5H), 4.35 (s, 2H), 4.47 (s, 2H), 5.05 (s, 2H), 6.63 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 13.8, 20.2, 31.1, 47.3, 51.9, 68.9, 69.3, 69.8, 73.7, 104.2, 104.2, 144.3, 165.5. MS (ESI): *m/z* 490 ($[M + H]^+$). Anal. Calc for $C_{24}H_{30}F_3FeN_3O$: C, 58.91; H, 6.18; O, 3.27%. Found: C, 59.11; H, 6.16; O, 3.28%. IR (KBr, cm^{-1}): ν = 3462(m), 2968(s), 1652(s), 1508(m), 1462(s), 1389(m), 1334(m), 1239(s), 1120(s), 953(s), 806(s), 741(m).

2.2.31. 2-(5-Ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)-1-(piperidin-1-yl)ethanone (**31**)

Brown solid (0.283 g, 65.7% yield). Mp.: 132–134 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.84–0.90 (m, 1H), 1.53–1.61 (m, 2H), 1.89–1.92 (m, 2H), 3.28–3.37 (m, 2H), 3.73–3.75 (m, 1H), 3.96–4.02 (m, 2H), 4.19 (s, 5H), 4.35 (s, 2H), 4.47 (s, 2H), 5.09 (s, 2H), 6.60 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 23.3, 25.3, 45.1, 50.8, 67.8, 68.3, 68.8, 72.5, 103.2, 103.2, 143.4, 163.2. MS (ESI): *m/z* 446 ($[M + H]^+$). Anal. Calc for $C_{21}H_{22}F_3FeN_3O$: C, 56.65; H, 4.98; O, 3.59%. Found: C, 56.52; H, 4.97; O, 3.61%. IR (KBr, cm^{-1}): ν = 3482(m), 2936(s), 1648(s), 1511(m), 1456(s), 1340(m), 1237(s), 1134(s), 1007(s), 969(m), 811(s), 732(m).

2.2.32. 2-(5-Ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)-1-(2-methylpiperidin-1-yl)ethanone (**32**)

Brown solid (0.293 g, 63.9% yield). Mp.: 124–125 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.83–0.87 (m, 2H),1.24–1.30 (m, 1H),1.58–1.61 (m, 3H), 1.66–1.68 (m, 2H), 3.43–3.45 (m, 2H), 3.57–3.60 (m, 2H), 4.19 (s, 5H), 4.34 (s, 2H), 4.47 (s, 2H), 5.07 (s, 2H), 6.60 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 16.9, 26.1, 30.6, 40.3, 48.1, 52.3, 53.4, 68.7, 69.4, 69.8, 73.6, 104.1, 104.1, 144.3, 164.2. MS (ESI): *m/z* 460 ($[M + H]^+$). Anal. Calc for $C_{22}H_{24}F_3FeN_3O$: C, 57.53; H, 5.27; O, 3.48%. Found: C, 57.41; H, 5.28; O, 3.50%. IR (KBr, cm^{-1}): ν = 3452(m), 2946(m), 1658(s), 1446(s), 1550(s), 1247(s), 1171(s), 993(s), 818(m), 732(m).

2.2.33. 1-(3,5-Dimethylpiperidin-1-yl)-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)ethanone (**33**)

Brown solid (0.399 g, 84.2% yield). Mp.: 137–139 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.75–0.84 (m, 1H), 0.91 (t, 6H, *J* = 6.4 Hz), 1.26–1.33 (m, 1H), 1.58–1.66 (m, 2H), 1.84–1.87 (m, 1H), 2.08 (t, 1H, *J* = 8.0 Hz), 2.58 (t, 1H, *J* = 8.4 Hz), 3.67–3.71 (m, 1H), 4.19 (s, 5H),

4.34 (s, 2H), 4.48 (s, 2H), 5.08 (s, 2H), 6.60 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 19.0, 32.2, 42.1, 49.4, 52.2, 68.8, 69.4, 69.8, 73.7, 104.1, 104.1, 144.4, 163.9. MS (ESI): *m/z* 474 ($[M + H]^+$). Anal. Calc for $C_{23}H_{26}F_3FeN_3O$: C, 58.36; H, 5.54; O, 3.38%. Found: C, 58.55; H, 5.53; O, 3.39%. IR (KBr, cm^{-1}): ν = 3452(m), 2926(m), 1662(s), 1446(s), 1250(s), 1137(s), 969(s), 828(m).

2.2.34. 2-(5-Ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)-1-(4-methylpiperazin-1-yl)ethanone (**34**)

Brown solid (0.303 g, 65.8% yield). Mp.: 95–97 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.27 (s, 3H), 2.36–2.39 (t, 4H, J = 6.0 Hz), 3.48 (t, 2H, J = 4.4 Hz), 3.61 (t, 2H, J = 4.4 Hz), 4.12 (s, 5H), 4.28 (s, 2H), 4.42 (s, 2H), 5.00 (s, 2H), 6.53 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 42.2, 45.1, 46.0, 51.6, 54.5, 54.8, 68.9, 69.4, 69.8, 73.6, 104.3, 104.3, 144.4, 164.5. MS (ESI): *m/z* 461 ($[M + H]^+$). Anal. Calc for $C_{21}H_{23}F_3FeN_4O$: C, 54.80; H, 5.04; O, 3.48%. Found: C, 54.97; H, 5.05; O, 3.49%. IR (KBr, cm^{-1}): ν = 3524(s), 2958(m), 2782(m), 1666(s), 1453(s), 1291(m), 1240(s), 1134(s), 979(m), 804(s).

2.2.35. 1-(4-Hydroxypiperidin-1-yl)-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)ethanone (**35**)

Brown solid (0.256 g, 55.4% yield). Mp.: 193–195 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.79–3.57 (m, 9H), 4.19 (s, 5H), 4.33 (s, 2H), 4.46 (s, 2H), 5.03 (s, 2H), 6.60 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 34.1, 42.2, 51.7, 66.3, 68.8, 69.5, 69.8, 73.5, 104.2, 104.2, 144.5, 164.3. MS (ESI): *m/z* 461 ($[M + H]^+$). Anal. Calc for $C_{21}H_{22}F_3FeN_3O_2$: C, 54.68; H, 4.81; O, 6.94%. Found: C, 54.86; H, 4.80; O, 6.93%. IR (KBr, cm^{-1}): ν = 3430(s), 1658(s), 1466(m), 1364(m), 1223(s), 1137(s), 979(s), 815(s).

2.2.36. 1-(4-Benzylpiperidin-1-yl)-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)ethanone (**36**)

Brown solid (0.262 g, 48.9% yield). Mp.: 109–111 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.82–3.08 (m, 9H), 3.78 (d, 1H, J = 13.6 Hz), 4.19 (s, 5H), 4.33 (s, 2H), 4.46 (s, 2H), 4.56 (d, 1H, J = 13.2 Hz), 5.05 (s, 2H), 6.60 (s, 1H), 7.14 (d, 2H, J = 6.8 Hz), 7.20–7.23 (m, 1H), 7.28–7.32 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 21.8, 22.4, 41.9, 51.7, 53.6, 68.6, 69.7, 69.8, 72.9, 104.9, 104.9, 109.3, 120.3, 125.3, 128.9, 143.5, 165.9. MS (ESI): *m/z* 536 ($[M + H]^+$). Anal. Calc for $C_{28}H_{28}F_3FeN_3O$: C, 62.81; H, 5.27; O, 2.99%. Found: C, 63.00; H, 5.26; O, 3.00%. IR (KBr, cm^{-1}): ν = 2936(s), 1631(s), 1442(s), 1216(s), 1203(m), 1110(s), 1024(m), 965(s), 791(s), 732(m).

2.2.37. tert-Butyl-4-(2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetyl)piperazine-1-carboxylate (**37**)

Brown solid (0.390 g, 71.3% yield). Mp.: 92–93 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.45 (s, 9H), 3.44–3.62 (m, 8H), 4.19 (s, 5H), 4.35 (s, 2H), 4.49 (s, 2H), 5.08 (s, 2H), 6.60 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 28.4, 42.1, 45.1, 51.5, 68.9, 69.5, 69.8, 73.5, 80.5, 104.3, 104.3, 144.6, 154.4, 164.6. MS (ESI): *m/z* 547 ($[M + H]^+$). Anal. Calc for $C_{25}H_{29}F_3FeN_4O_3$: C, 54.96; H, 5.35; O, 8.79%. Found: C, 55.14; H, 5.34; O, 8.81%. IR (KBr, cm^{-1}): ν = 3462(m), 2968(s), 1682(s), 1449(s), 1412(s), 1223(s), 1154(s), 973(m), 818(s).

2.2.38. N,N-diisobutyl-2-(5-ferrocenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (**38**)

Brown solid (0.329 g, 67.3% yield). Mp.: 117–119 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.87 (s, 3H), 0.87 (s, 3H), 0.88 (s, 3H), 0.93 (s, 3H), 0.94 (s, 3H), 1.92–2.06 (m, 2H), 3.10 (d, 2H, J = 7.6 Hz), 3.22 (d, 2H, J = 7.2 Hz), 4.20 (s, 5H), 4.31 (s, 2H), 4.45 (s, 2H), 5.02 (s, 2H), 6.61 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 32.3, 42.9, 45.5, 51.8, 68.9, 69.3, 69.8, 73.8, 104.2, 104.3, 139.7, 164.3. MS (ESI): *m/z* 489.4 ($[M + H]^+$). Anal. Calc for $C_{20}H_{21}F_3FeN_4O$: C, 58.91; H, 6.18; O, 3.27%. Found: C, 58.74; H, 6.20; O, 3.28%. IR (KBr, cm^{-1}): ν = 3430(m), 3040(m), 1765(m), 1658(m), 1442(m), 1364(s), 1257(s), 1144(s), 1082(s), 955(s), 777(s), 746(s).

2.3. Crystal structure determination

Single crystal X-ray diffraction measurements for compounds **19** and **30** were carried out on a Siemens Smart 1000 CCD diffractometer equipped with a graphite crystal monochromator situated in the incident beam for data collection at room temperature. The determination of unit cell parameters and data collections were performed with Mo–Kα radiation (λ = 0.71073 Å). Unit cell dimensions were obtained with least-squares refinements, and all structures were solved by direct methods with SHELXL-97 [26]. All the non-hydrogen atoms were located in successive difference Fourier syntheses. The final refinement was performed by full-matrix least-squares methods with anisotropic thermal parameters for non-hydrogen atoms on F2. The hydrogen atoms were added theoretically and riding on the concerned atoms. The crystal data and structure refinement were listed in Table 3.

2.4. Biological test

The antitumor activity of all the prepared compounds against PC-3 and Bcap-37 cell lines were evaluated as described elsewhere with some modifications [27]. Target tumor cell lines were grown to log phase in RPMI 1640 medium supplemented with 10% fetal bovine serum. After diluting to 2 × 10^4 cells mL^{-1} with the complete medium, 100 μL of the obtained cell suspension was added to each well of 96-well culture plates. The subsequent incubation was permitted at 37 °C, 5% CO_2 atmosphere for 24 h before the cytotoxicity assessments. Tested samples at pre-set concentrations were added to 6 wells with adriamycin coassayed as positive control. After 72 h exposure period, 100 μL of PBS containing 0.5 mg/mL of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was added to each well. 4 h later, 100 μL extraction solution (10% SDS-5% isobutyl alcohol-0.01 M HCl) was added. After an overnight incubation at 37 °C, the optical density was measured at a wavelength of 570 nm on an ELISA microplate reader. In all experiments three replicate wells were

Table 3
Crystallographic data and structure refinements for compounds **19** and **30**.

	19	**30**
Formula	$C_{22}H_{17}ClF_6FeN_3O$	$C_{24}H_{30}F_3FeN_3O$
Mr	487.69	489.36
Crystal system	Triclinic	Monoclinic
Space group	P–1	P2(1)
Crystal size (mm^3)	0.24 × 0.23 × 0.18	0.25 × 0.23 × 0.22
a (Å)	9.4482(17)	10.490(3)
b (Å)	14.457(3)	10.176(3)
c (Å)	16.135(3)	11.552(3)
α (°)	82.827(2)	90.00
β (°)	82.726(2)	94.342(3)
γ (°)	75.941(2)	90.00
Volume ($Å^3$)	2110.6(6)	1229.6(6)
Z	2	2
D_c (g/cm^{-3})	1.535	1.332
μ (mm^{-1})	0.886	0.656
F (000)	992	512
θ rang (°C)	2.37–26.00	2.53–25.50
Reflections collected	8136	4543
Reflections unique	5323	3546
Parameters	617	330
Goodness-of-fit on F^2	0.835	0.697
R_1,wR_2 [$I > 2\sigma(I)$]	0.0462, 0.1068	0.0335, 0.0863
R_1, wR_2	0.0818, 0.1188	0.0488, 0.1004

Table 4
Selected bond lengths (Å) and angles (°) for compounds **19** and **30**.

$C_{22}H_{17}ClF_3FeN_3O$(**19**)			
Bond lengths			
C(17)–N(3)	1.419(6)	C(16)–N(3)	1.330(5)
C(16)–O(1)	1.216(5)	C(15)–N(2)	1.446(5)
N(2)–N(1)	1.356(4)	C(15)–C(16)	1.511(5)
H(31)–F(5)	2.682(5)	H(6)–F(2)	2.784(3)
H(6)–F(3)	2.851(3)	H(6A)–O(1)	2.070(4)
H(3A)–O(2)	2.102(3)		
Bond angles			
C(17)–N(3)–C(16)	122.6(3)	N(3)–C(16)–O(1)	122.2(4)
N(3)–C(16)–C(15)	115.4(3)	O(1)–C(16)–C(15)	122.3(3)
C(16)–C(15)–N(2)	111.5(3)	C(15)–N(2)–N(1)	117.3(3)
C(15)–N(2)–C(11)	129.7(3)	C(31)–H(31)···F(5)	135.5(3)
C(6)–H(6)···F(2)	128.2(3)	C(6)–H(6)···F(3)	169.0(3)
N(6)–H(6A)···O(1)	170.4(2)	N(3)–H(3A)···O(2)	177.7(3)
$C_{24}H_{30}F_3FeN_3O$(**30**)			
Bond lengths			
N(2)–N(3)	1.356(8)	N(2)–C(15)	1.432(8)
C(15)–C(16)	1.529(8)	C(16)–O(1)	1.198(8)
C(16)–N(1)	1.352(8)	N(1)–C(17)	1.471(1)
N(1)–C(21)	1.452(1)	H(18B)–F(3)	2.869(1)
H(20C)–F(2)	2.822(1)		
Bond angles			
N(3)–N(2)–C(15)	118.2(5)	N(2)–C(15)–C(16)	112.0(5)
C(15)–C(16)–O(1)	121.4(5)	O(1)–C(16)–N(1)	123.6(6)
C(15)–C(16)–N(1)	115.0(5)	C(16)–N(1)–C(17)	118.6(5)
C(16)–N(1)–C(21)	124.6(6)	C(21)–N(1)–C(17)	116.7(6)
C(18)–H(18B)···F(3)	123.1(6)	C(20)–H(20C)···F(2)	150.3(1)

used for each drug concentration. Each assay was carried out at least three times. The results were summarized in Table 5.

3. Results and discussion

3.1. Structural results from single crystal X-ray diffraction

Single crystals of compounds **19** and **30** were obtained by the slow evaporation of dichloromethane/methanol solutions. X-ray crystal structure analysis of compounds **19** and **30** revealed the structures depicted in Figs. 1 and 2, respectively. The selected bond lengths (Å) and angles (°) were listed in Table 4.

Compound **19** crystallizes in the triclinic space group Pī with two independent molecules in the asymmetric unit. There are some differences between the two molecules. The principal dimensions are carboxylate ester C]O (C16 = O1 1.216(5), C38 = O2 1.220(5) Å) and N–C=O with the values of 122.2(4) and 125.0(4)°. The average distances between the Fe center and each carbon atom of its Cp rings in both molecules are 2.03–2.04 Å. This distance is nearly identical to the analogs average distance found in ferrocene. The shortest Fe–C(Cp) separation is to C27, with value of 2.022(4) Å. The three-atom link between the C_5 rings results in close to eclipsed conformation for the C_5 rings (θ = 0.5 and 1.1°) and the Cp^0–Fe–Cp^0 angles (Cp^0 = centroids of Cp rings) both deviate somewhat from linearity (178.6 and 179.2°) [28,29]. In addition, the pyrazole moieties are rotated out the plane of the Cp rings (C1–C2–C3–C4–C5 and C23–C24–25–C26–C27) by approximately 45.7 and 43.4°, respectively.

In the case of compound **30**, it crystallizes in the monoclinic space group P2(1) with one molecules in the asymmetric unit. The principal dimensions are carboxylate ester C=O 1.198(8) Å, N–C=O 123.6(6)° and C–N–C 116.7(6)°. The average distance between the Fe center and each carbon atom of its Cp rings is also 2.04 Å. As is characteristic of other ferrocene compounds the Fe–Cp^0 separations range from 1.6467(6) to 1.6501(1) Å. The shortest Fe–C(Cp) separation is 1.972(1) Å (Fe1–C10). The three-atom link between the C_5 rings also results in close to eclipsed conformation for the C_5 rings (θ = 4.0°) and the Cp^0–Fe–Cp^0 angle deviates somewhat from linearity (175.7°). However, the pyrazole moiety was rotated out the plane of the Cp ring (C4–C5–C6–C7–C8) by approximately 28.0°, which is a little different from that of compound **19**.

Layers of the two complexes are depicted in Fig. 3 and Fig. 4, respectively. Because compound **19** crystallizes with two independent molecules in the asymmetric unit, intermolecular H–F bonds (H31–F5) between adjacent molecules lead to one kind of 1D chains and intermolecular H–F bonds (H6–F2 and H6–F3) between adjacent molecules lead to another 1D chains. Then, N–H···O interactions (N6–H6A···O1 and N3–H3A···O2) between adjacent 1D chains generate a 2D layer, see Fig. 3.

In compound **30**, intermolecular H–F bonds (H18B–F3) between adjacent molecules lead to 1D chains. Then, C–H···F interactions (C20–H20C···F2) between adjacent 1D chains generate a 2D layer, see Fig. 4.

The bond lengths (Å) and angles (°) of the intermolecular interaction were listed in Table 4.

Table 5
Antitumor activity (IC_{50}) against PC-3 and Bcap-37 cell lines of compounds **1**–**38**.

Comp. no	IC_{50} ± SD(μg/mL)	
	PC-3	Bcap-37
1	20.33 ± 1.61	35.25 ± 3.72
2	13.07 ± 3.25	36.25 ± 3.22
3	8.36 ± 1.43	17.34 ± 2.47
4	16.21 ± 2.48	27.34 ± 2.36
5	15.35 ± 3.23	32.05 ± 3.35
6	18.15 ± 3.24	34.09 ± 1.97
7	19.34 ± 3.16	29.09 ± 2.41
8	12.28 ± 2.13	20.34 ± 2.44
9	16.47 ± 1.42	25.23 ± 3.34
10	6.53 ± 1.23	15.01 ± 1.80
11	25.94 ± 4.31	34.25 ± 3.52
12	23.04 ± 3.30	31.27 ± 2.23
13	21.67 ± 3.24	34.42 ± 3.82
14	22.95 ± 2.45	38.23 ± 2.87
15	21.97 ± 2.28	34.75 ± 3.01
16	21.51 ± 3.35	35.53 ± 2.63
17	23.47 ± 3.42	31.15 ± 4.25
18	22.54 ± 2.26	37.72 ± 4.18
19	25.14 ± 2.52	34.03 ± 1.93
20	26.23 ± 2.47	36.49 ± 2.68
21	22.05 ± 2.34	31.15 ± 2.32
22	23.27 ± 1.64	38.39 ± 3.94
23	26.49 ± 4.28	34.46 ± 2.85
24	12.82 ± 2.42	18.34 ± 3.30
25	27.80 ± 0.16	34.49 ± 3.63
26	15.75 ± 1.46	19.31 ± 2.21
27	23.14 ± 2.27	34.36 ± 2.41
28	21.65 ± 2.62	35.69 ± 2.96
29	25.43 ± 3.67	34.65 ± 3.48
30	24.48 ± 3.34	37.47 ± 4.68
31	25.25 ± 1.89	36.49 ± 4.20
32	22.42 ± 1.39	36.06 ± 4.12
33	27.15 ± 4.21	39.16 ± 3.18
34	26.42 ± 3.13	38.16 ± 2.92
35	25.49 ± 3.48	31.49 ± 2.76
36	20.61 ± 2.71	30.42 ± 4.05
37	22.15 ± 3.25	33.15 ± 4.09
38	24.76 ± 3.53	32.15 ± 4.01
D[a]	32.24 ± 4.47	45.73 ± 4.92
5-FU[b]	18.74 ± 1.13	19.43 ± 1.22
Cisplatin[b]	3.26 ± 0.84	4.35 ± 0.87

Each data represents mean ± S. D. from different experiments performed in triplicate.
[a] 3-trifluoromethyl-5-ferrocenyl-pyrazol-1-yl-acetic acid.
[b] Positive control for cytotoxicity.

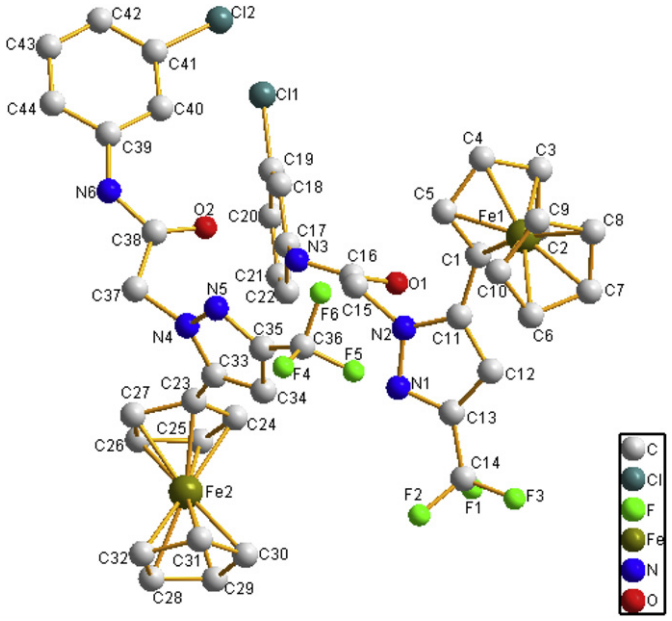


Fig. 1. Molecular structure of compound **19** using Diamond (all hydrogen atoms are omitted for clarity).

3.2. Biological activity

All the synthesized compounds were evaluated for their *in vitro* antitumor activity against two human tumor cell lines: human prostatic carcinoma cell line (PC-3) and human mammary carcinoma cell line (Bcap-37) using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium (MTT) method. 5-Fluorouracil (5-FU) and cisplatin were employed as positive control. The results of the *in vitro* cytotoxic effects of all the compounds were presented in Table 5.

As shown in Table 5, compounds **1**–**38** exhibited fairly good antitumor activity, which were much better than the starting material (**D**). All the compounds were also exhibited better antitumor activity against PC-3 cell line when compared to the results against Bcap-37 cell line. Compounds **10**, **3**, **24**, **8**, **26** and **9**

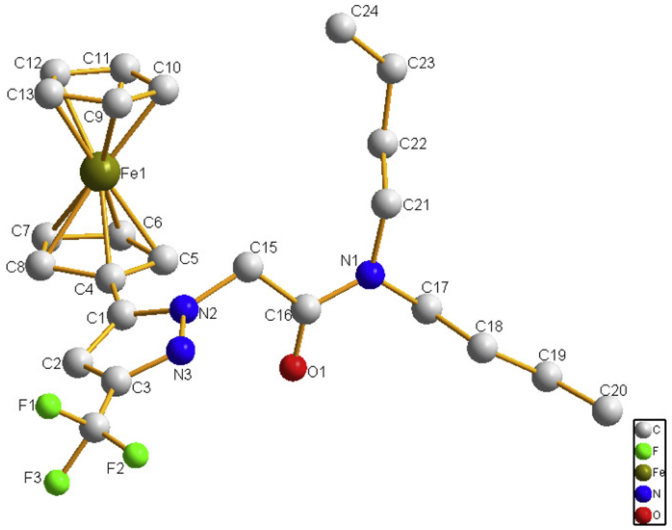


Fig. 2. Molecular structure of compound **30** using Diamond (all hydrogen atoms are omitted for clarity).

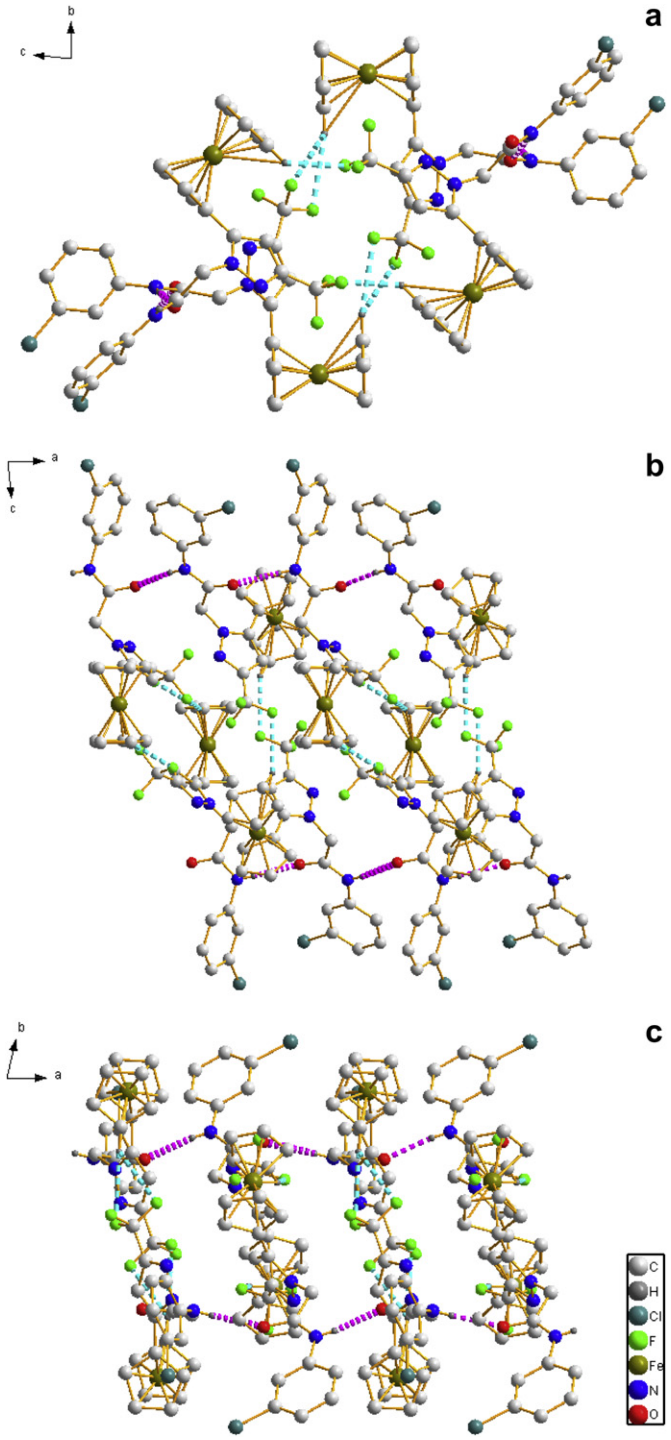


Fig. 3. (a) View of the layers of **19** along the *a*-axis. (b) View of the layers of **19** along the *b*-axis. (c) View of the layers of **19** along the *c*-axis.

displayed relative good antitumor activity against PC-3 cell line. Among them, compound **10** displayed the most potent antitumor activity against PC-3 cell line with the IC_{50} value of 6.53 μg/mL, which was comparable to the positive control cisplatin.

Subsequently SAR studies were performed to determine how the substituents affected the antitumor activity. Compound **1** without any substituent on the phenyl ring showed moderate antitumor activity with the mean IC_{50} value of 20.33 μg/mL when tested against PC-3 cell line. Introducing methoxy group(s) on the

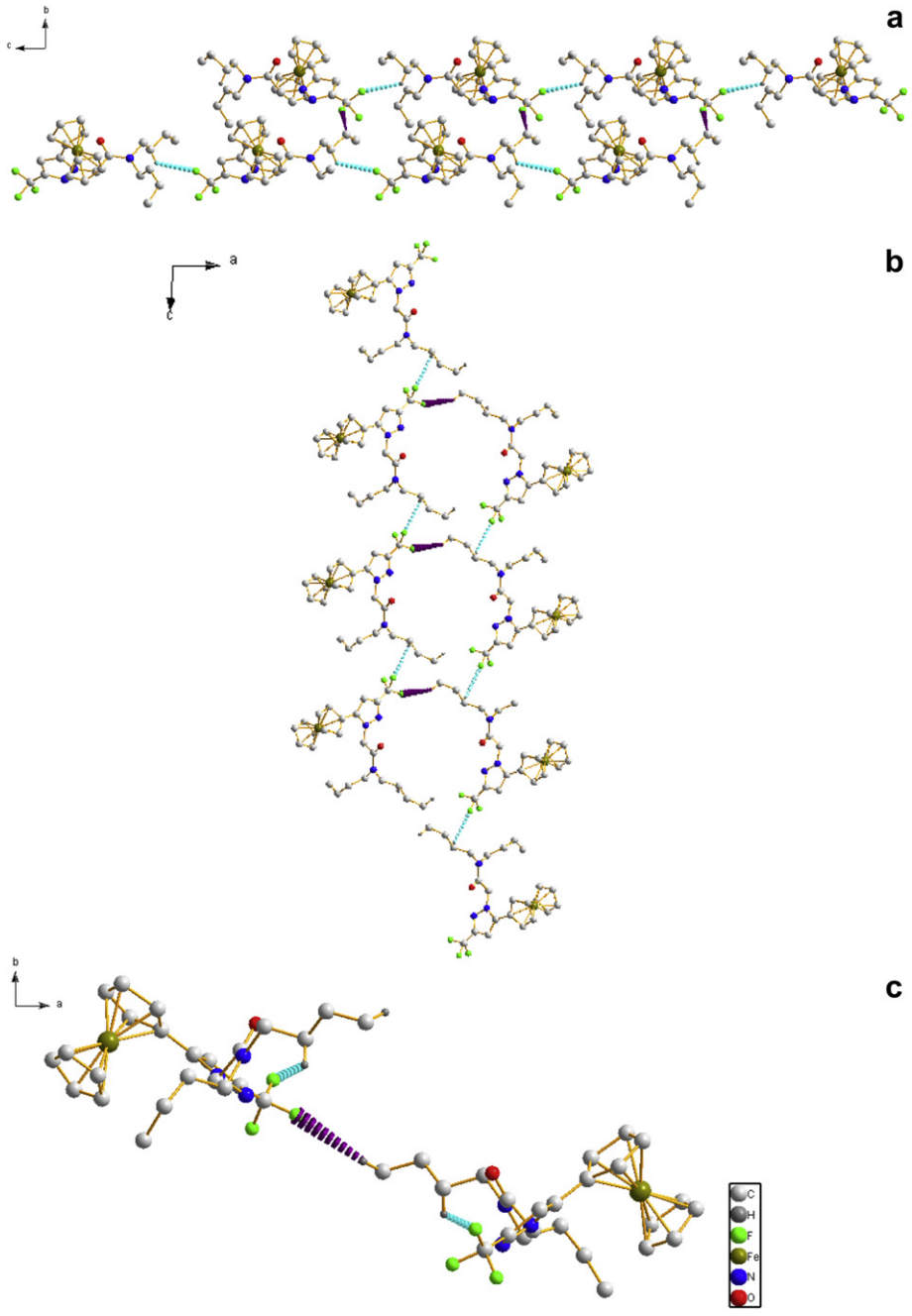


Fig. 4. (a) View of the layers of **30** along the *a*-axis. (b) View of the layers of **30** along the *b*-axis. (c) View of the layers of **30** along the *c*-axis.

phenyl ring in **1** to form a class of compounds greatly increased the antitumor activity against PC-3 cell line (e.g., **3**, $IC_{50} = 8.36$ μg/mL; **2**, $IC_{50} = 13.07$ μg/mL; **8**, $IC_{50} = 12.28$ μg/mL). It can be seen that the number and the position of the methoxy group may affect the antitumor activity.

4. Conclusions

In summary, a series of novel 2-(5-ferrocenyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)-*N*-amide derivatives (**1**–**38**) were prepared and characterized. Among them, compounds **19** and **30** gave crystals suitable for X-ray structural analysis. All the synthesized compounds were evaluated for their antitumor activities. Some of the synthesized compounds exhibited moderate to potent antitumor activities against PC-3 cell line *in vitro*. In particular, compound **10** was the most promising derivative, with the IC_{50} value of 6.53 μg/mL when tested against PC-3 cell line.

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Appendix A. Supplementary material

CCDC 842639 and 842640 contain the supplementary crystallographic data for compounds **19** and **30**. These data can be

obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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