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Reactions of ferrocenyl chalcones with hydrazines and active methylene compounds

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Abstract: Claisen-Schmidt condensation of ferrocenecarboxaldehyde (**2b**) with 2-acetylfuran (**4**) yielded *(E)*-3-ferrocenyl-1-(2-furyl)prop-2-en-1-one (*E*-**5**) together with 1,5-di(2-furyl)-3-ferrocenylpentane-1,5-dione (**6**). Reactions of the ferrocenyl chalcones **3a,b** and **5** with hydrazine hydrate, phenyl hydrazine, ethyl acetoacetate, ethyl cyanoacetate and malononitrile, were also studied. Possible reaction mechanisms were discussed and structures of the new products were unambiguously characterized by common analytical and spectroscopic methods.

Keywords: active methylenes; ferrocenyl chalcones; hydrazines; preparation.

Introduction

The bioorganometallic chemistry of ferrocene has aroused great interest and its study has been encouraged by potential biological applications [1]. The ferrocenyl moiety has been incorporated into the structure of a number of biologically active molecules such as antibiotic [2], anticancer [3] and antimalarial drugs [4]; resulting in an increase of activity. These compounds can be used for synthesizing an array of pharmacologically active derivatives [5], particularly against human immuno-deficiency virus (HIV) [6] and microbes [7]. In addition, ferrocene derivatives possess numerous applications in chemical sensing, asymmetric catalysis, material science and industrial chemistry [8]. From another side, 1,3-diaryl-2-propen-1-ones (chalcones) have been reported to possess a broad range of biological activities such as antimalarial, antimicrobial, antitumor, antioxidant, antihyperglycemic and anti-HIV properties [9–11]. Replacement of one of the two aryl groups by a ferrocenyl moiety has been reported [11–13]. The resulting ferrocenyl chalcones are dramatically more effective than the original organic molecules [11, 14] which, in particular, is due to their excellent stability in aqueous aerobic media and favorable electrochemical properties [11, 15]. In the present communication, we have studied the reactivity of ferrocenyl chalcones **3a,b** and **5** towards hydrazines and active methylene compounds. The presence of a furyl or a benzofuranyl moiety in the reacting chalcones (**3b** or **5**) or in the reaction products would boost the biological activity [16–19].

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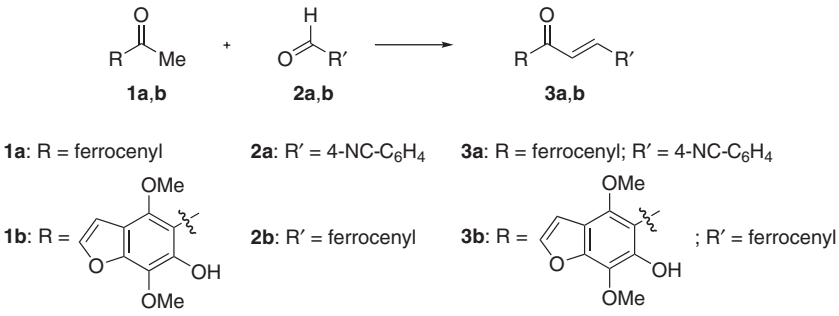
Results and discussion

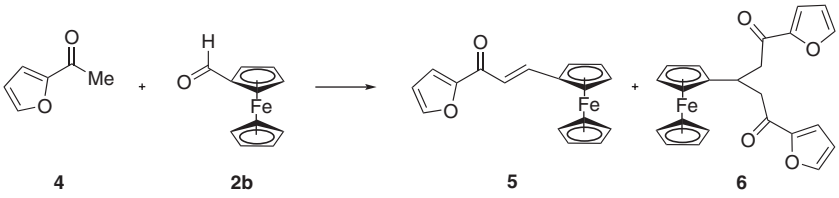
The general plan employed to prepare the ferrocenyl chalcones **3a,b** (Scheme 1) and **5** (Scheme 2) called for the Claisen-Schmidt condensation [20] between the appropriate aldehyde and an acetyl substrate. The resulting chalcones **3a** [21], **3b** and **5** [22, 23] were purified by crystallization.

Claisen-Schmidt condensation of ferrocenecarboxaldehyde (**2b**) with 2-acetylfuran (**4**) has been reported to proceed in aqueous NaOH [22], or under solvent-free conditions [23] yielding chalcone **5** as the sole reaction product. In the present investigation, condensation of **2b** with **4** in ethanol in the presence of 10% NaOH gave a mixture of two products which were separated by column chromatography (Scheme 2).

The first eluted product (40%) was (*E*)-3-ferrocenyl-1-(2-furyl)prop-2-en-1-one, (*E*-**5**). A characteristic feature of the ^{1}H NMR spectrum of **5** is the pair of doublets at 7.16 ppm and 7.60 ppm (J = 15.3 Hz) consistent with the presence of the chalcone moiety with the *E*-configuration [24]. No trace for the *Z*-isomer was detected by NMR. The second eluted product (30%) was 1,5-di(2-furyl)-3-ferrocenylpentane-1,5-dione (**6**). The structure of **6**, in addition to spectral analysis, was established by X-ray crystallographic analysis (Figure 1, Tables 1–3). Apparently, the initially formed chalcone **5** undergoes the addition reaction with another molecule of **4** to afford compound **6**.



Scheme 1



Scheme 2

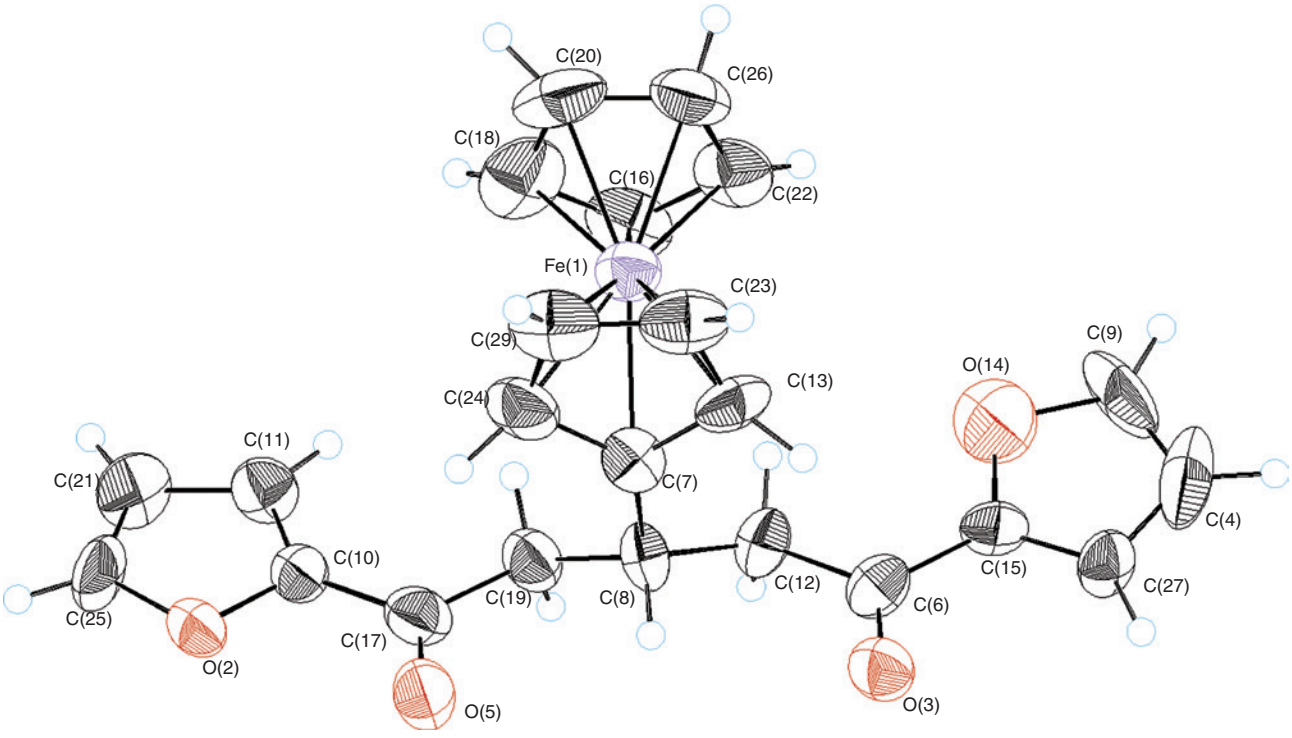


Figure 1 An ORTEP overview of compound **6**.

Reaction of ferrocenyl chalcones 3a, 3b and 5 with hydrazine

Chalcone **3a** was allowed to react with hydrazine hydrate in boiling acetic acid to give a crystalline substance formulated as 4-(1-acetyl-4,5-dihydro-3-ferrocenyl-1*H*-pyrazol-5-yl)-benzonitrile (**7a**). In a similar way, the reaction of chalcone **3b** furnished pyrazoline derivative **7b**.

The reaction of chalcone **5** under similar conditions (Scheme 3) furnished a crystalline substance formulated as 1-(3-(2-furyl)-4,5-dihydro-5-ferrocenylpyrazol-1-yl)ethanone (**7c**). The expected hydrazones **8a–c** were not found

Table 1 Crystal structure and data refinement parameters of compound **6**.

Empirical formula	$C_{23}H_{20}FeO_4$
Formula weight	416.256
Crystal system/space group	Monoclinic/$P2_1/n$
a/Å	10.6264 (5)
b/Å	7.7745 (3)
c/Å	23.0193 (13)
α/°	90.00
β/°	95.886 (2)
γ/°	90.00
V/Å^3	1891.7 (2)
Z	4
D_{calc} (g/cm^3)	1.462
μ (mm^{-1})	0.82
Color/shape	Yellow/Prismatic
θ range for collection/°	0.00–31.42
Reflections collected	5423
Independent reflections	5090
Data/restraints/parameters	5090/0/253
Goodness of fit on F2	0.580
Final R indices [$I > 2\sigma(I)$]	0.0589
R indices (all data)	0.3391
Largest difference peak/Hole	0.328/-0.451

Table 2 Selected bond lengths (Å) of compound **6**.

O2–C25	1.363 (7)	C11–C21	1.424 (9)
O2–C10	1.377 (7)	C13–C23	1.415 (9)
O3–C6	1.225 (7)	O14–C15	1.383 (8)
C4–C9	1.286 (11)	C15–C27	1.308 (8)
C4–C27	1.411 (10)	C16–C22	1.423 (9)
O5–C17	1.215 (7)	C16–C18	1.421 (10)
C6–C15	1.464 (9)	C17–C19	1.507 (8)
C6–C12	1.496 (8)	C18–C20	1.408 (11)
C7–C13	1.425 (9)	C20–C26	1.418 (10)
C7–C24	1.434 (9)	C21–C25	1.332 (9)
C7–C8	1.508 (9)	C22–C26	1.404 (9)
C8–C12	1.527 (8)	C23–C29	1.419 (10)
C8–C19	1.536 (8)	C24–C29	1.412 (10)
C9–O14	1.401 (9)	Fe1–C(Cp) avg	2.031
C10–C11	1.342 (8)	Fe1–C(Cp′) avg	2.030
C10–C17	1.459 (9)		

(Scheme 3). Interestingly, products seven are structural analogs of a known antitubercular drug [25].

Reaction of ferrocenyl chalcones 3a and 3b with phenylhydrazine

Heating chalcone **3a** with phenylhydrazine in ethanol gave a mixture of two products which were separated by column chromatography. The first product (25%) is 4-(3-ferrocenyl-1-phenyl-1*H*-pyrazol-5-yl)benzonitrile (**9a**) and the second product (45%) is 4-(4,5-dihydro-3-ferrocenyl-1-phenyl-1*H*-pyrazol-5-yl)benzonitrile (**10a**) (Scheme 4).

Similarly, reaction of the ferrocenyl chalcone **3b** with phenylhydrazine in ethanol at room temperature gave two products **9b** and **10b** which were separated by column chromatography. Again, the expected hydrazones **11a,b** were not found in the crude mixtures. It appears that compounds **10a,b** undergo dehydrogenation [26] to give **9a,b**.

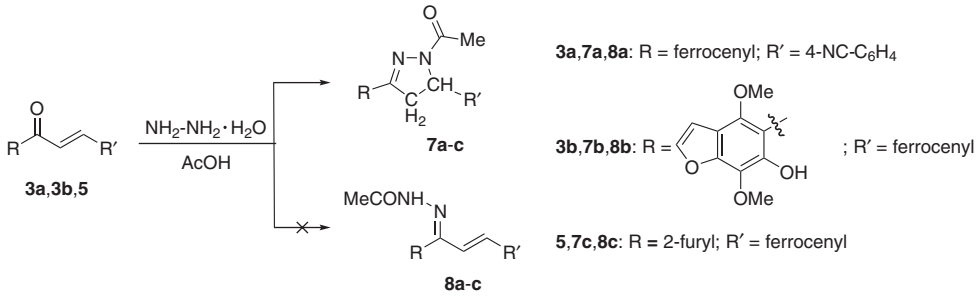
Table 3 Selected bond angles (°) of compound **6**.

C25–O2–C10	105.3 (5)	C27–C15–O14	111.0 (6)
C9–C4–C27	108.3 (7)	C27–C15–C6	128.2 (6)
O3–C6–C15	118.2 (6)	O14–C15–C6	120.8 (7)
O3–C6–C12	124.0 (6)	C22–C16–C18	107.8 (7)
C15–C6–C12	117.8 (6)	O5–C17–C10	121.0 (6)
C13–C7–C24	106.3 (6)	O5–C17–C19	121.8 (7)
C13–C7–C8	125.9 (6)	C10–C17–C19	117.1 (6)
C24–C7–C8	127.8 (7)	C20–C18–C16	108.1 (8)
C7–C8–C12	112.7 (6)	C17–C19–C8	114.8 (5)
C7–C8–C19	112.2 (6)	C18–C20–C26	107.7 (8)
C12–C8–C19	110.3 (5)	C25–C21–C11	104.8 (6)
C4–C9–O14	110.4 (8)	C26–C22–C16	107.6 (7)
C11–C10–O2	109.4 (6)	C13–C23–C29	107.8 (8)
C11–C10–C17	134.3 (7)	C29–C24–C7	108.9 (7)
O2–C10–C17	116.3 (6)	C21–C25–O2	112.4 (6)
C10–C11–C21	108.0 (6)	C22–C26–C20	108.8 (8)
C6–C12–C8	115.4 (5)	C15–C27–C4	106.6 (6)
C23–C13–C7	109.1 (7)	C24–C29–C23	107.9 (7)
C15–O14–C9	103.6 (6)		

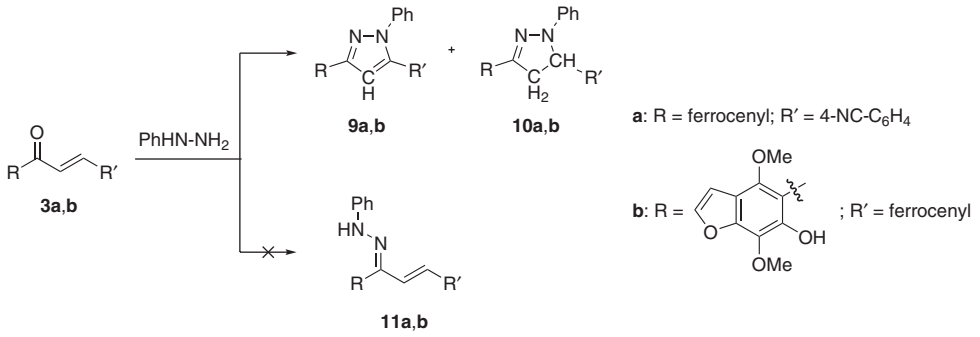
Reaction of ferrocenyl chalcones 3a and 3b with ethyl acetoacetate

Chalcone **3a** was allowed to react with ethyl acetoacetate in boiling ethanol in the presence of a few drops of piperidine to give a crystalline product for which structure **12** was assigned (Scheme 5). Two products were obtained upon refluxing chalcone **3b** with ethyl acetoacetate.

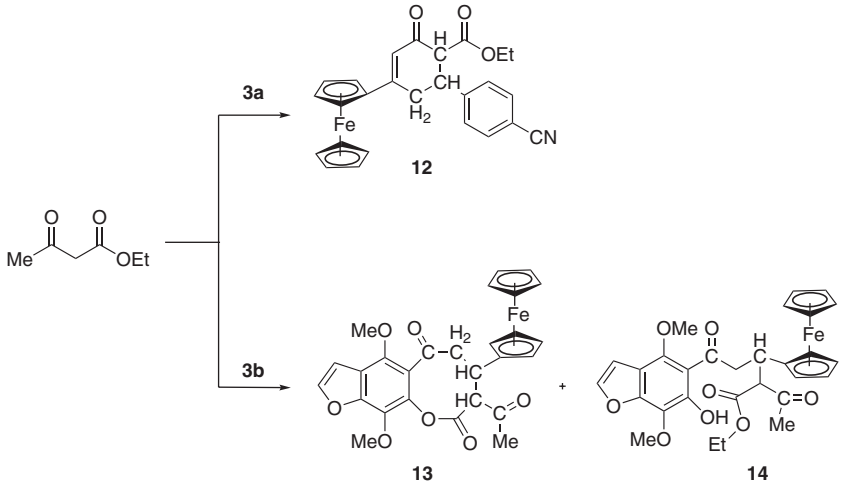
The first compound (20%) was formulated as 8-acetyl-7-ferrocenyl-4,11-dimethoxy-7,8-dihydro-5H-benzofuro[6,5-b]oxocine-5,9(6H)-dione (**13**). The second compound (35%) was ethyl 2-acetyl-3-ferrocenyl-5-(6-hydroxy-4,7-dimethoxybenzofuran-5-yl)-5-oxo-pentanoate (**14**). Apparently, the initially formed 1:1 adduct **14** undergoes intramolecular cyclization via loss of ethanol molecule to give compound **13**.



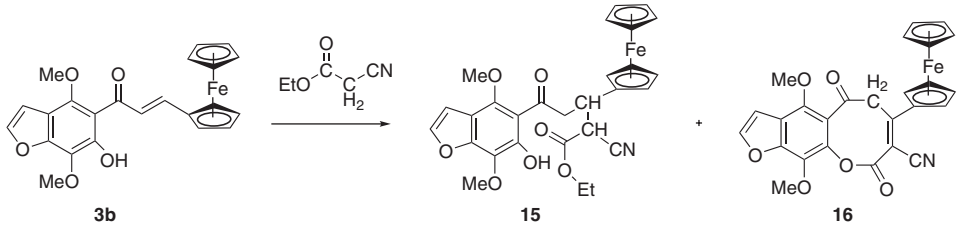
Scheme 3



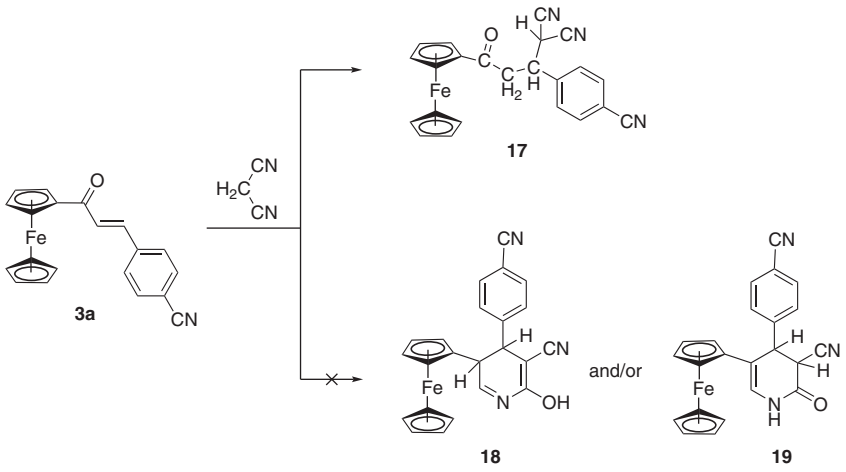
Scheme 4 Heterocyclization reaction of chalcones **3a,b** with phenyl hydrazine.



Scheme 5



Scheme 6



Scheme 7

Reaction of ferrocenyl chalcone 3b with ethyl cyanoacetate

The reaction of chalcone **3b** with ethyl cyanoacetate in boiling ethanol furnished a mixture of two substances which were separated by column chromatography (Scheme 6) These are structures **15** (36%) and **16** (22%).

Reaction of ferrocenyl chalcone 3a with malononitrile

Compound **3a** was allowed to react with malononitrile in boiling ethanol to give crystalline 4-(1,1-dicyano-4-oxo-4-ferrocenylbutan-2-yl)benzonitrile (**17**). On the basis of the experimental data the dihydropyridinyl structures **18** and/or **19** were safely excluded (Scheme 7).

Conclusions

The present work describes simple methods for the preparation of new ferrocene derivatives by the reaction of ferrocenyl chalcones **3a,b** and **5** with hydrazines and active methylene reagents. Of particular interest is the reaction of phenylhydrazine with ferrocenyl chalcones **3a** and **3b** which yields a mixture of pyrazolyl and dihydropyrazolyl products in each case. Generally, the dihydropyrazolyl form is solely isolated in reactions of other chalcones with the same reagent [27–31].

Experimental

Solvents were purified and dried according to the usual procedures. Chalcone **3a** [21] was prepared as previously described. The reactions were monitored (TLC) and purity of the isolated products analyzed by using aluminum sheets coated with silica gel with fluorescent indicator F_{254} [Fluka]. Column chromatography was performed on silica gel with grain size 0.063–0.200 mm (Merck). Uncorrected melting points were determined on an Electrothermal Digital Melting Point Apparatus. Elemental analytical data were obtained at the analytical laboratory of the National Research Centre. The IR spectra were recorded in KBr disks on a Jasco Fourier Transform Infrared Spectrophotometer model FT/IR-300E. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL 500 AS or a Varian Mercury VX-300 spectrometer. Electron-impact mass spectra (EI-MS) were determined at 70 eV on a Finnigan MAT SSQ 7000 spectrometer. X-ray diffraction analysis: The intensity data were performed with a κ-CCD Enraf Nonius FR 590 single crystal diffractometer, temperature 298 K, wavelength Mo *K*α (0.71073 Å). The structure was solved by direct methods using the *SIR*92 program [32] and refined using ma*X*us [33]. The molecular graphics were made with ORTEP [34]. Crystallographic data (CIF) for the structure reported in this article have been deposited in the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication No. CCDC 1425801. Copies of the data can be obtained, free of charge, upon application to the CCDC, 12 Union Road, Cambridge CB 12EZ, UK (FAX: + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk).

Preparation of (*E*)-1-ferrocenyl-3-(4-cyanophenyl)-2-propen-1-one (3a)

A solution of 4-cyanobenzaldehyde (**2a**, 1 mmol) in *N*,*N*-dimethylformamide (5 mL) was added gradually to a solution of acetylferrocene (**1a**, 1 mmol) in alcoholic KOH (2%, 15 mL) and the mixture was stirred at room temperature for 12 h. The separated solid was filtered, washed with water, dried and crystallized from DMF/H_2O to give compound **3a** as deep red crystals, mp 219–221°C [Ref. [21] mp 222°C (ethanol)]; yield 43%; IR: 3080, 3055, 4022, 2235, 1645, 1620 cm^{-1}.

Preparation of (*E*)-3-ferrocenyl-1-(6-hydroxy-4,7-dimethoxybenzofuran-5-yl)prop-2-en-1-one (3b)

A solution of ferrocenealdehyde (**2b**, 1 mmol) in *N*,*N*-dimethylformamide (5 mL) was added gradually to a solution of khellinone (**1b**,

1 mmol) in alcoholic KOH (2%, 15 mL) and the mixture was stirred at room temperature for 12 h. The separated solid was filtered, washed with water, dried and crystallized from DMF/H_2O to give compound **3b** as dark brown crystals; mp 195–197°C; IR: 3435, 3086, 3045, 3025, 2985, 2890, 1635, 1615, 1590 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.88 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.17 (s, 5H, ferrocene), 4,60 (s, 2H, ferrocene), 4.62 (s, 2H, ferrocene), 6.72 (d, J = 14.0 Hz, 1H, O=C–C<u>H</u>=C), 6.96 (d, J = 3.0 Hz, 1H, furyl), 7.13 (d, J = 14.0 Hz, 1H, O=C–C=C<u>H</u>), 7.36 (d, J = 3.0 Hz, 1H, furyl), 9.95 (s, 1H, OH, D_2O exchangeable). Anal. Calcd for $C_{23}H_{20}FeO_5$ (432.25): C, 63.91; H, 4.66; Fe, 12.92. Found: C, 64.02; H, 4.64.

Reaction of ferrocenaldehyde with 2-acetylfuran

A solution of NaOH (10%, 10 mL) was added dropwise to a mixture of ferrocenecarboxaldehyde (1 mmol) and 2-acetylfuran (excess) in 20 mL ethanol while cooling and stirring. The mixture was stirred at room temperature for an additional 12 h. The precipitate formed was subjected to column chromatography to give compounds **5** and **6**.

(*E*)-3-Ferrocenyl-1-(2-furyl)prop-2-en-1-one (5) Eluent: petroleum ether/acetone (95/3, v/v); red crystals; yield 40%; mp 107–110°C [Ref. [22] mp 108–110°C]; MS: *m/z* 306 (94%).

1,5-Di(2-furyl)-3-ferrocenylpentane-1,5-dione (6) Eluent: petroleum ether/acetone (95/5, v/v); yellow crystals; yield 30%; mp 134°C; IR: 3124, 2927, 1660, 1564, 1465 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.20 (d, J = 6.1 Hz, 4H, $CH(C\underline{H}_2)_2$), 3.80 (quintet, J = 6.1 Hz, 1H, $C\underline{H}(CH_2)_2$), 4.06 (d, J = 1.5 Hz, 2H, ferrocene), 4.08 (d, J = 1.5 Hz, 2H, ferrocene), 4.12 (s, 5H, ferrocene), 6.52 (dd, J = 3.8, 1.5 Hz, 2H, furyl), 7.22 (d, J = 3.8 Hz, 2H, furyl), 7.56 (d, J = 1.5 Hz, 2H, furyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.7, 40.4, 67.5, 68.8, 68.9, 93.06, 113.1, 119.1, 148.4, 152.6, 187.8; MS: *m/z* 416 (100%) [M^+]. Anal. Calcd for $C_{23}H_{20}FeO_4$ (416.25): C, 66.37; H, 4.84; Fe, 13.42. Found: C, 66.44; H, 4.82.

Reaction of ferrocenyl chalcones 3a, 3b or 5 with hydrazine hydrate

A solution of chalcone **3a, 3b** or **5** (1 mmol) and hydrazine hydrate (1.5 mmol) in acetic acid (20 mL) was heated under reflux for 2–5 h. The mixture was cooled to room temperature, poured onto ice-cooled water and left overnight. The resultant precipitate was collected and purified by chromatography on silica gel to give products **7a** and **7c** for the respective reactions with **3a** and **5**. Product **7b** derived from **3b** was crystallized from cyclohexane.

4-(1-Acetyl-4,5-dihydro-3-ferrocenyl-1*H*-pyrazol-5-yl)benzonitrile (7a) Eluent: petroleum ether/ethyl acetate (80/20, v/v); orange crystals; yield 69%; mp 88–90°C; IR: 3100, 3051, 2923, 2852, 2221, 1658, 1620, 1495 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 3H, $COCH_3$), 2.94 (dd, J_{gem} = 17.7, J_{vic} = 4.8 Hz, 1H, C<u>H</u>$_2$-CH-N pyrazoline, *trans*–H), 3.71 (dd, J_{gem} = 17.7, J_{vic} = 11.7 Hz, 1H, C<u>H</u>$_2$-CH-N pyrazoline, *cis*–H), 4.12 (s, 5H, ferrocene), 4.43 (s, 2H, ferrocene), 4.58 (s, 1H, ferrocene), 4.65 (d, J = 1.5 Hz, 1H, ferrocene), 5.56 (dd, J = 11.7, 4.8 Hz, 1H, CH_2-C<u>H</u>-N pyrazoline), 7.36 and 7.65 (2d, each with J = 8.4 Hz, 4H, aromatic AA′BB′ system); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.0, 43.6 (CH_2), 58.9, 67.6, 68.2, 69.7, 70.7, 70.8, 75.3, 119.18, 126.8, 133.2, 148.3, 156.7, 167.3; MS: *m/z* 355 [M^+ – CH_2=C=O]. Anal. Calcd for $C_{22}H_{19}FeN_3O$ (397.25): C, 66.52; H, 4.82; Fe, 14.06; N, 10.58. Found: C, 66.63; H, 4.79; N, 10.54.

1-(4,5-Dihydro-3-(6-hydroxy-4,7-dimethoxybenzofuran-5-yl)-5-ferrocenylpyrazol-1-yl)ethanone (7b) Yellow crystals; mp 166°C; yield 67%; IR: 3420, 3114, 3080, 2983, 2938, 2842, 1647, 1618, 1568 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 3H, $COCH_3$), 4.00 (dd, J_{gem} = 12.0 Hz, J_{vic} = 6.0 Hz, 1H, C<u>H</u>$_2$CH-N pyrazoline, *trans*–H), 4.07 (dd, J_{gem} = 12.0 Hz, J_{vic} = 9.0 Hz, 1H, C<u>H</u>$_2$CH-N pyrazoline, *cis*–H), 4.11–4.20 (m, 14H, $2OCH_3$, 8H of ferrocene), 4.53 (s, 1H, ferrocene), 5.42 (dd, J = 9.0, 6.0 Hz, 1H, CH_2-C<u>H</u>-N pyrazoline), 6.92 (d, J = 3.0 Hz, 1H, furyl), 7.56 (d, J = 3.0 Hz, 1H, furyl), 11.47 (s, 1H, OH, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.1, 43.8, 53.6, 61.0, 65.5, 68.5, 68.6, 70.5, 77.2, 87.1, 104.9, 105.2, 112.2, 129.5, 143.7, 148.3, 148.7, 150.0, 156.5, 167.5; MS: *m/z* 488 (23%) [M^+]. Anal. Calcd for $C_{25}H_{24}FeN_2O_5$ (488.31): C, 61.49; H, 4.95; Fe, 11.44; N, 5.74. Found: C, 61.40; H, 4.98; N, 5.70.

1-(3-(2-Furyl)-4,5-dihydro-5-ferrocenylpyrazol-1-yl)ethanone (7c) Eluent: petroleum ether/ethyl acetate (60/40, v/v); yellow crystals; mp 179°C; yield 71%; IR: 3080, 2925, 2851, 1644, 1482 cm^{-1} (C=C, C=N); ^1H NMR (300 MHz, DMSO-d_6): δ 2.14 (s, 3H, $COC\underline{H}_3$), 3.46 (dd, J_{gem} = 18.0, J_{vic}=6.0 Hz, 1H, C<u>H</u>$_2$-CH-N pyrazoline, *trans*–H), 3.75 (dd, J_{gem} = 18.0, J_{vic}=12.0 Hz, 1H, C<u>H</u>$_2$-CH-N pyrazoline, *cis*–H), 4.01 (s, 1H, ferrocene), 4.12 (s, 2H, ferrocene), 4.19 (s, 5H, ferrocene), 4.38 (s, 1H, ferrocene), 5.34 (dd, J = 12.0, 6.0 Hz, 1H, CH_2-C<u>H</u>-N pyrazoline), 6.71 (t, J = 3.0 Hz, 1H, furyl), 7.16 (d, J = 3.0 Hz, 1H, furyl), 7.91 (d, J = 3.0 Hz, 1H, O-CH-C, furyl); ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.2, 26.8, 55.0, 66.0, 68.2, 68.3, 68.9, 69.0, 70.4, 87.8, 112.6, 114.4, 145.9, 146.4, 146.8, 167.7; MS: *m/z* 320 (10%) [M^+ – CH_2=C=O]. Anal. Calcd for $C_{19}H_{18}FeN_2O_2$ (362.20): C, 63.00; H, 5.01; Fe, 15.42; N, 7.73. Found: C, 62.90; H, 5.03; N, 7.69.

Reaction of ferrocenyl chalcone 3a with phenylhydrazine

A solution of chalcone **3a** (1 mmol) and phenylhydrazine (1.5 mmol) in absolute ethanol (20 mL) was heated under reflux for 3 h. The volatile materials were removed under reduced pressure and the residue was subjected to chromatography on silica gel using petroleum ether/ethyl acetate as eluent to give products **9a** and **10a**.

4-(3-Ferrocenyl-1-phenyl-1*H*-pyrazol-5-yl)benzonitrile (9a) Eluent: petroleum ether /ethyl acetate (90/10, v/v); yellow crystals; mp146–148°C; yield 25%; IR: 3090, 2220, 1601, 1561, 1494 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.13 (s, 5H, ferrocene) 4.29 (d, 2H, J = 3 Hz, ferrocene), 4.34 (d, J = 3 Hz, 2H, ferrocene), 7.28 (s, 1H, pyrazole), 7.30–7.57 (m, 5H, phenyl), 7.93 and 8.12 (2d, each with J = 9.0 Hz, 4H, aromatic AA′BB′ system); ^{13}C NMR (75 MHz, DMSO-d_6): δ 67.0, 68.6, 69.2, 69.8, 70.1, 74.3, 78.1, 105.1, 107.5, 110.4, 115.6, 119.4, 125.7, 126.3, 126.8, 129.2, 129.7, 132.9, 133.2, 137.8, 140.3, 144.1, 149.3; MS: *m/z* 429 (100%) [M^+]. Anal. Calcd for $C_{26}H_{19}FeN_3$ (429.29): C, 72.74; H, 4.46; Fe, 13.01; N, 9.79. Found: C, 72.67; H, 4.48; Fe, N, 9.78.

4-(4,5-Dihydro-3-ferrocenyl-1-phenyl-1*H*-pyrazol-5-yl)benzonitrile (10a) Eluent: petroleum ether/ethyl acetate (60/40, v/v), yellow crystals, mp 160°C; yield 45%; IR: 3084, 3010, 2914, 2223, 1647 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 2.98 (dd, 1H, J_{gem} = 15.0 Hz, J_{vic} = 6.0 Hz, C<u>H</u>$_2$-CH-N pyrazoline, *trans*–H), 3.86 (dd, 1H, J_{gem} = 15.0 Hz, J_{vic} = 12.0 Hz, C<u>H</u>$_2$-CH-N pyrazoline, *cis*–H), 4.12 (s, 5H, ferrocene), 4.41 (d, 2H, J = 3 Hz, ferrocene), 4.62 (d, 1H, J = 3 Hz, ferrocene), 4.69 (t, 1H, J =

3Hz, ferrocene), 5.50 (dd, J = 12.0, 6.0 Hz, 1H, CH_2-C<u>H</u>-N pyrazoline), 6.69 (t, 1H, J = 9.0 Hz, aromatic), 6.88 (d, 2H, J = 9.0 Hz, aromatic), 7.14 (t, 2H, J = 9.0 Hz, aromatic), 7.49 (d, 2H, J = 6.0 Hz, aromatic), 7.85 (d, 2H, J = 9.0 Hz, aromatic); ^{13}C NMR (75 MHz, DMSO-d_6): δ 44.6, 62.4, 67.0, 67.3, 69.4, 70.0, 77.1, 110.6, 113.0, 118.6, 119.1, 127.4, 128.7, 129.4, 133.4, 144.7, 148.6, 149.3; MS: m/z 431 (100%) [M$^+$]. Anal. Calcd for $C_{26}H_{21}FeN_3$ (431.31): C, 72.40; H, 4.91; Fe, 12.95; N, 9.74. Found: C, 72.49; H, 4.89; Fe, N, 9.70.

Reaction of ferrocenyl chalcone 3b with phenylhydrazine

A mixture of chalcone **3b** (1 mmol) and phenyl hydrazine (1.5 mmol) in absolute ethanol (20 mL) was stirred at room temperature for 12 h. The volatile materials were removed under reduced pressure and the residue was subjected to chromatography on silica gel using petroleum ether/acetone as eluent to give the two products **9b** and **10b**.

5-(5-Ferrocenyl-1-phenyl-1*H*-pyrazol-3-yl)-4,7-dimethoxybenzofuran-6-ol (9b) Eluent: petroleum ether/acetone (93/7, v/v); yellow crystals; yield 20%; mp 176°C; IR: 3427, 3117, 2932, 1617, 1494 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.90 (s, 1H, ferrocene), 4.09 (s, 3H, OCH_3), 4.21(s, 5H, ferrocene), 4.29 (s, 1H, ferrocene), 4.32 (d, 3H, J = 3 Hz, ferrocene), 7.16 (d, 1H, J = 3 Hz, furyl), 7.22–7.57 (m, 5H aromatic and 1H pyrazole), 7.89 (d, 1H, J = 3 Hz, furyl), 11.58 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 60.8, 60.8, 68.9, 69.0, 69.3, 70.2, 73.9, 105.7, 106.4, 108.0, 112.6, 126.5, 128.7, 129.3, 129.7, 139.6, 142.7, 144.6, 146.8, 147.4, 148.2, 148.4; MS: m/z 520 (43%) [M$^+$]. Anal. Calcd for $C_{29}H_{24}FeN_2O_4$ (520.36): C, 66.94; H, 4.65; Fe, 10.73; N, 5.38. Found: C, 66.88; H, 4.67; N, 5.33.

5-(4,5-Dihydro-5-ferrocenyl-1-phenyl-1*H*-pyrazol-3-yl)-4,7-dimethoxy)benzofuran-6-ol (10b) Eluent: petroleum ether/acetone (85/15, v/v); yellow crystals; yield 40%; mp 55°C; IR: 3420, 3086, 2931, 1677, 1597, 1477 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.83–5.00 (m, 18H, 2 OCH_3, ferrocene, CH_2 and CH pyrazoline), 6.56–7.85 (m, 7H, phenyl, furyl), 11.53 (s, 1H, OH); MS: m/z 522 (10%) [M$^+$]. Anal. Calcd for $C_{29}H_{26}FeN_2O_4$ (522.37): C, 66.68; H, 5.02; Fe, 10.69; N, 5.36. Found: C, 66.77; H, 5.00; Fe, N, 5.32.

Reaction of ferrocenyl chalcone 3a with ethyl acetoacetate

A mixture of chalcone **3a** (1 mmol) and ethyl acetoacetate (1 mmol) in absolute ethanol (20 mL) and a few drops of piperidine was heated under reflux for 8 h. The volatile materials were removed under reduced pressure and the residue was subjected to chromatography on silica gel using *n*-hexane/ethyl acetate as eluent to give compound **12.**

Ethyl 6-(4-cyanophenyl)-4-ferrocenyl-2-oxocyclohex-3-enecarboxylate (12) Eluent: petroleum ether/ethyl acetate (83/17, v/v); red crystals; mp 200°C; yield 64%; IR: 3095, 2976, 2923, 2869, 2226, 1739, 1641 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (t, 3H, J = 6.0 Hz, CH_2-C<u>H</u>$_3$), 1.30 (dt, J = 9.0, 6.0 Hz, 1H, -CH_2-C<u>H</u>-CH), 2.79 (dd, 1H, J_{gem} = 18.0, J_{vic} = 9.0 Hz, -CH_2-, *cis*–H), 3.01 (dd, J = 18.0, 6.0 Hz, 1H, -CH_2-, *trans*–H), 3.72 (q, J = 6.0 Hz, 2H, OC<u>H</u>$_2$$CH_3$), 3.84 (d, J = 9.0 Hz, 1H, OC–C<u>H</u>(CO)–CH), 4.23 (d, J = 3.0 Hz, 1H, ferrocene), 4.17 (s, 5H, ferrocene), 4.55 (s, 2H, ferrocene), 4.60 (s, 1H, ferrocene), 6.37 (s, 1H, C=CH), 7.45 and 7.75 (2d, each with J = 6.0 Hz, 4H, aromatic AA′BB′ system); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.04, 35.25, 43.90, 58.94, 61.27, 67.0, 67.80, 69.4, 70.3, 70.7, 72.0, 79.9, 111.5, 118.5, 119.9, 128.3, 132.2, 146.6, 161.4, 169.0, 191.9; MS: m/z 453 (20%) [M$^+$]. Anal. Calcd for $C_{26}H_{23}FeNO_3$ (453.31): C, 68.89; H, 5.11; Fe, 12.32; N, 3.09. Found: C, 68.92; H, 5.08; N, 3.05.

Reaction of ferrocenyl chalcone 3b with ethyl acetoacetate

A mixture of chalcone **3b** (1 mmol) and ethyl acetoacetate (1 mmol) in absolute ethanol (20 mL) was heated under reflux for 4 h. The volatile materials were removed under reduced pressure and the residue was subjected to chromatography on silica gel to resolve compounds **13** and **14**.

8-Acetyl-7-ferrocenyl-4,11-dimethoxy-7,8-dihydro-5H-benzofuro[6,5-b]oxocine-5,9(6H)-dione (13) Eluent: petroleum ether/acetone (95/5, v/v); yellow crystals; yield 20%; mp 183°C; IR: 3109, 2992, 2937, 1674,1618, 1543 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.2 (m, 1H, CH-C<u>H</u>-CH_2), 2.43 (s, 3H, CH_3CO), 3.02, 3.11 (2d, each with J = 14 Hz, 2H,CH_2), 3.89 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.22 (s, 5H, ferrocene), 4.35 (s, 2H, ferrocene), 4.38 (s, 2H, ferrocene), 5.34 (d, J = 9.0 Hz, 1H, O=C-CH-C=O), 7.13 (d, J = 3.0 Hz, 1H, C<u>H</u>=CH-O, furyl), 7.91 (d, J = 3.0 Hz, 1H, CH=C<u>H</u>-O, furyl); MS: m/z 516 (2%) [M$^+$]. Anal. Calcd for $C_{27}H_{24}FeO_7$ (516.32): C, 62.81; H, 4.69; Fe, 10.82. Found: C, 62.91; H, 4.66.

Ethyl 2-acetyl-3-ferrocenyl-5-(6-hydroxy-4,7-dimethoxybenzofuran-5-yl)-5-oxo-pentanoate (14) Eluent: petroleum ether/acetone (80/20, v/v); yellow crystals; yield 35%; mp 68–70°C; IR: 3427, 3100, 2930, 1734, 1663, 1601; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (q, J = 6.0 Hz, 1H, CH_2-C<u>H</u>-CH), 1.27 (t, J = 9.0 Hz, 3H, C<u>H</u>$_3$$CH_2$O), 2.24 (s, 3H, $COCH_3$), 2.90, 3.40 (2dd, each with J = 18.0, 12.0 Hz, 2H, CH_2), 3.95 (q, J = 9.0 Hz, 2H, CH_3C<u>H</u>$_2$O), 4.35–4.00 (m, 15H, 2OCH_3, ferrocene), 5.88 (d, 1H, J = 6.0 Hz, O=C-C<u>H</u>-C=O), 7.53 (d, J = 3.0 Hz, 1H, CH=C<u>H</u>-O, furyl), 6.20 (s, 1H, OH, D_2O-exchangeable), 6.88 (d, J = 3.0 Hz, 1H, C<u>H</u>=CH-O, furyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 35.8, 37.9, 61.0, 61.2, 62.0, 65.7, 67.6, 68.5, 77.2, 89.7, 104.9, 113.7, 115.4, 128.0, 129.3, 142.1, 143.4, 144.8, 170.2, 194.1; MS: m/z 560 (5%) [M$^+$ – 2H]. Anal. Calcd for $C_{29}H_{30}FeO_8$ (562.39): C, 61.93; H, 5.38; Fe, 9.93. Found: C, 61.84; H, 5.41.

Reaction of ferrocenyl chalcone 3b with ethyl cyanoacetate

A mixture of **3b** (1 mmol) and ethyl cyanoacetate (1 mmol) in absolute ethanol (20 mL) in the presence of a few drops of piperidine was heated under reflux for 6 h. The volatile materials were removed under reduced pressure and the residue was subjected to chromatography on silica gel to give two compounds **15** and **16**.

Ethyl 2-cyano-3-ferrocenyl-5-(6-hydroxy-4,7-dimethoxybenzofuran-5-yl)-5-oxo-pentanoate (15) Eluent: petroleum ether/ethyl acetate (70/30, v/v); yellow crystals; yield 36%; mp 125°C; IR: 3360, 3144, 3093, 2962, 2934, 2835, 2246, 1738, 1628, 1560, 1500 cm^{-1}; ^{1}H NMR

(500 MHz, DMSO-d_6): δ 1.14–1.16 (m, 4H, C<u>H</u>$_3$CH$_2$-O, CH$_2$-C<u>H</u>-CH), 3.40-3.55 (m, 2H, O=C-C<u>H</u>$_2$-CH), 3.84–4.29 (m, 18H, 2OCH$_3$, CH$_3$C<u>H</u>$_2$-O, NC-CH-C=O, ferrocene), 7.18 (d, J = 3.5 Hz, 1H, C<u>H</u>=CH-O, furyl), 7.90 (d, J = 3.5 Hz, 1H, CH=C<u>H</u>-O, furyl), 10.40 (s, 1H, OH, D$_2$O-exchangeable); MS: *m/z* 545 (5%) [M$^+$]. Anal. Calcd for $C_{28}H_{27}FeNO_7$ (545.36): C, 61.67; H, 4.99; Fe, 10.24; N, 2.57. Found: C, 61.57; H, 5.03; N, 2.52.

6,9-Dihydro-4,11-dimethoxy-7-ferrocenyl-5,9-dioxo-5*H*-benzofuro[6,5-b]oxocine-8-carbonitrile (16) Eluent: petroleum ether/ethyl acetate (5/95, v/v); yellow crystals; yield 22%; mp 200°C; IR: 3157, 3134, 3012, 2945, 2848, 2223, 1725, 1602, 1555 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.96 (s, 2H, CH$_2$), 4.11–4.16 (m, 15H, 2OCH$_3$ and ferrocene), 7.02 (d, J = 3.5 Hz, 1H, C<u>H</u>=CH-O, furyl), 7.66 (d, J = 3.5 Hz, 1H, CH=C<u>H</u>-O, furyl). Anal. Calcd for $C_{26}H_{19}FeNO_6$ (497.28): C, 62.80; H, 3.85; Fe, 11.23; N, 2.82. Found: 62.76; H, 3.88; N, 2.80.

Reaction of ferrocenyl chalcone 3a with malononitrile

A mixture of **3a** (1 mmol) and malononitrile (1.5 mmol) in absolute ethanol (20 mL) was heated under reflux for 6 h. The volatile materials were removed under reduced pressure and the residue was subjected to chromatography on silica gel to give compound **17**.

4-(1,1-Dicyano-4-oxo-4-ferrocenylbutan-2-yl)benzonitrile (17) Eluent: petroleum ether/acetone (95/5, v/v); red crystals; mp 175°C; IR: 3100, 2885, 2229, 1656, 1502 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.33 (dd, J = 18.0, 6.0 Hz, 1H, O=C-C<u>H</u>-C), 3.50 (dd, 1H, J = 18.0, 9.0 Hz, O=C-C<u>H</u>-C), 3.97 (q, J = 6.0 Hz, 1H, CH$_2$-C<u>H</u>-CH), 4.82 (d, J = 12.0 Hz, 1H, C<u>H</u>(CN)$_2$), 7.65 and 7.79 (2d, each with J = 9.0 Hz, 4H, aromatic AA′BB′ system); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.0, 40.4, 41.1, 69.3, 70.1, 73.2, 76.9, 77.2, 98.9, 129.0, 133.0, 141.6, 157.3, 172.7 (C=O); MS: *m/z* 407 (78%) [M$^+$]. Anal. Calcd for $C_{23}H_{17}FeN_3O$ (407.25): C, 67.83; H, 4.21; Fe, 13.71; N, 10.32. Found: C, 67.91; H, 4.18; N, 10.28.

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