Supporting Information

A Green Synthesis and Antibacterial Activity of Ferrocene-based Thiazole Derivatives in Choline chloride/Glycerol Eutectic Solvent

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1. General information

The chemicals used in this work were obtained from Energy Chemical and were used without purification. Melting points were determined by use of a WRS-1B melting-point apparatus and were uncorrected. The ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on an Agilent 400-MR spectrometer using $CDCl_3$ or DMSO-d_6 as solvent. The reported chemical shifts (δ values) are given in parts per million downfield from tetramethylsilane (TMS) as the internal standard (NMR abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, *J* = coupling constant). The mass spectra were determined using a MSD VL ESI1 spectrometer. HRMS (ESI) data were acquired on an Bruker Customer micrOTOF-Q 125 high-resolution mass spectrometer. The mass spectra (MS) were determined using a MSD VL ESI1 spectrometer. Elemental analyses were carried out on an EA 2400II elemental analyzer (PerkinElmer, Waltham, MA). The progress of reactions was monitored by TLC on silica gel GF254 using ethyl acetate/petroleum ether (1:2) as the eluent.

2. General procedure for the preparation of the substrates 2l-u

These compounds **2l-u** were synthesized by Friedel–Crafts thioamidation reaction according to the literature method[1]: The respective 1-alkylindole or 9-alkylcarbazole (10.0 mmol) was added to methanesulfonic acid (15 mL) under ice-cooling bath. To the solution was then added potassium thiocyanate (1.12 g, 11.5 mmol) slowly with stirring. The resulting reaction mixture was stirred at room temperature for about 5 h. After the completion of the reaction (TLC eluent for reaction monitorization), the mixture was poured into cold water (30 mL). The resulting precipitate was collected by filtration and recrystallized from ethyl acetate to give the corresponding products of carbothioamides **2l-u** with analytically pure.

3. Preparation of the DES ChCl/Gly

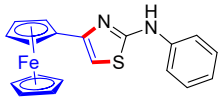
The procedure for the preparation of the DES ChCl/Gly based on the method of literature[2]: A mixture of choline chloride (14.0 g, 0.1 mol) and glycerol (18.4 g, 0.2 mol) was heated up to 100 ^{o}C in a flask with stirring for 2h until a clear solution was produced. After cooling to room temperature and vacuum drying for 5 h, the resulting DES ChCl/Gly was sealed for later use.

4. General procedure for the synthesis of the targeted products 3a-u

Bromoacetylferrocene **1** (0.5 mmol, 0.154 g) and respective thioureas (**2a-k**), 1-alkylindole-3- (**2l-p**) or 9-alkylcarbazole-3-carbothioamides (**2q-u**) (0.55 mmol) was mixed in 6 mL of the ChCl/Gly (1 : 2 mol/mol). The resulting reaction mixture was stirred at 85 ^{o}C for 6~8 hours (as monitored by TLC). After the reaction was completed, the mixture was diluted with an equal volume of water and extracted using dichloromethane (DCM) (3 x 5 mL). The deep eutectic solvent could be easily isolated after removing H_2O from the aqueous layer under vacuum, and could be further used for the next run reaction. The combined DCM layer was dried over Na_2SO_4 followed by evaporation of the solvent under reduced vacuum to afford a crude solid product, which was further purified by recrystallization from ethanol to give the corresponding pure compounds **3a-u**.

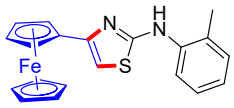
5. Characterization data of products 3a-u

N-Phenyl-4-ferrocenylthiazol-2-amine (3a)



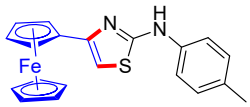
Orange solid, yield 82%, mp 161.1-162.0 °C; IR (KBr): ν 3102, 3074, 1621, 1578, 1525, 1493, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 4.32 (s, 5H, Fc-H), 4.44 (s, 2H, Fc-H), 4.81 (s, 2H, Fc-H), 6.25 (s, 1H, ArH), 7.34 (t, J = 8.0 Hz, 1H, ArH), 7.40 (d, J = 8.0 Hz, 2H, ArH), 7.49 (t, J = 8.0 Hz, 2H, ArH), 11.68 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 67.12, 70.37, 70.58, 71.67, 94.48, 121.04, 127.40, 130.22, 136.51, 141.29, 167.33. MS (ESI, *m/z*): 361.2 $[M + H]^+$. HRMS (ESI, *m/z*) calcd for $C_{19}H_{16}FeN_2NaS$ $[M + Na]^+$: 383.0276, found 383.0269. Anal. Calcd for $C_{19}H_{16}FeN_2S$: C, 63.35; H, 4.48; N, 7.78. Found: C, 63.52; H, 4.54; N, 7.61.

4-Ferrocenyl-N-(*o*-tolyl)thiazol-2-amine (3b)



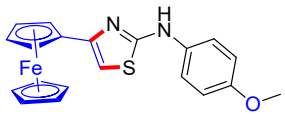
Yellow solid, yield 79%, mp 167.1-168.5 °C; IR (KBr): ν 3200, 2879, 1619, 1585, 1549, 1404, 1300, 1057 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 2.44 (s, 3H, Me), 4.37 (s, 5H, Fc-H), 4.45 (s, 2H, Fc-H), 4.76 (s, 2H, Fc-H), 6.14 (s, 1H, ArH), 7.20-7.25 (m, 2H, ArH), 7.29 (d, J = 7.6 Hz, 1H, ArH), 7.35 (d, J = 7.6 Hz, 1H, ArH), 11.03 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 18.84, 67.48, 70.60, 70.65, 71.92, 95.00, 109.99, 122.60, 127.61, 128.60, 132.09, 133.37, 135.54, 141.44. MS (ESI, *m/z*): 375.1 $[M + H]^+$. HRMS (ESI, *m/z*) calcd for $C_{20}H_{18}FeN_2NaS$ $[M + Na]^+$: 397.0432, found 397.0423. Anal. Calcd for $C_{20}H_{18}FeN_2S$: C, 64.18; H, 4.85; N, 7.48. Found: C, 64.31; H, 4.77; N, 7.23.

4-Ferrocenyl-N-(*p*-tolyl)thiazol-2-amine (3c)



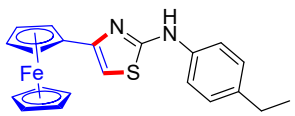
Yellow solid, yield 87%, mp 159.3-160.1 °C; IR (KBr): ν 3109, 2924, 1627, 1599, 1541, 1454, 1326, 1115 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 2.36 (s, 3H, Me), 4.30 (s, 5H, Fc-H), 4.40 (s, 2H, Fc-H), 4.79 (s, 2H, Fc-H), 6.23 (s, 1H, ArH), 7.24 (d, J = 7.6 Hz, 2H, ArH), 7.26 (d, J = 7.6 Hz, 2H, ArH), 11.40 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ :21.25, 67.60, 70.65, 71.82, 95.65, 121.67, 130.87, 133.94, 137.73, 141.13, 168.07. MS (ESI, *m/z*): 375.2 $[M + H]^+$. HRMS (ESI, *m/z*) calcd for $C_{20}H_{18}FeN_2NaS$ $[M + Na]^+$: 397.0432, found 397.0437. Anal. Calcd for $C_{20}H_{18}FeN_2S$: C, 64.18; H, 4.85; N, 7.48. Found: C, 64.01; H, 4.88; N, 7.65.

N-(4-Methoxyphenyl)-4-Ferrocenylthiazol-2-amine (3d)



Yellow solid, yield 91%, mp 168.3-169.1 °C; IR (KBr): ν 3071, 2735, 1616, 1575, 1526, 1509, 1474, 1328, 1128 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 3.82 (s, 3H, OMe), 4.29 (s, 5H, Fc-H), 4.40 (s, 2H, Fc-H), 4.76 (s, 2H, Fc-H), 6.17 (s, 1H, ArH), 6.95 (d, J = 7.6 Hz, 2H, ArH), 7.30 (d, J = 7.6 Hz, 2H, ArH), 11.19 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 55.73, 67.14, 70.41, 71.88, 94.58, 115.40, 124.29, 129.37, 141.16, 159.05, 169.02. MS (ESI, *m/z*): 391.1 $[M + H]^+$. HRMS (ESI, *m/z*) calcd for $C_{20}H_{18}FeN_2NaOS$ $[M + Na]^+$: 413.0382, found 413.0374. Anal. Calcd for $C_{20}H_{18}FeN_2OS$: C, 61.55; H, 4.65; N, 7.18. Found: C, 61.68; H, 4.60; N, 7.29.

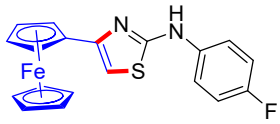
N-(4-Ethylphenyl)-4-ferrocenylthiazol-2-amine (3e)



Yellow solid, yield 85%, mp 139.5-141.2 °C; IR (KBr): ν 3073, 2964, 2817, 1619, 1576, 1258, 1119 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 1.24 (t, J = 7.6 Hz, 3H, $CH_2C\underline{H}_3$), 2.68 (q, J = 7.6 Hz, 2H, $C\underline{H}_2CH_3$), 4.31 (s, 5H, Fc-H), 4.42 (s, 2H, Fc-H), 4.80 (s, 2H, Fc-H), 6.21 (s, 1H, ArH), 7.27 (d, J = 8.0 Hz, 2H, ArH),

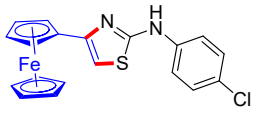
7.30 (d, J = 8.0 Hz, 2H, ArH), 11.44 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 15.42, 28.45, 67.48, 70.62, 70.69, 71.87, 94.93, 121.65, 129.63, 134.11, 141.20, 143.97, 167.89. MS (ESI, *m/z*): 389.2 [M + H]$^+$. HRMS (ESI, *m/z*) calcd for $C_{21}H_{20}FeN_2NaS$ [M + Na]$^+$: 411.0589, found 411.0597. Anal. Calcd for $C_{21}H_{20}FeN_2S$: C, 64.95; H, 5.19; N, 7.21. Found: C, 65.09; H, 5.39; N, 7.06.

N-(4-Fluorophenyl)-4-Ferrocenylthiazol-2-amine (3f)



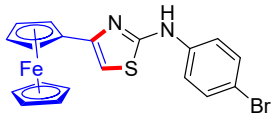
Yellow solid, yield 76%, mp 145.3-145.7 °C; IR (KBr): ν 3073, 2911, 1618, 1544, 1504, 1214, 1164 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ : 4.32 (s, 5H, Fc-H), 4.43 (s, 2H, Fc-H), 4.79 (s, 2H, Fc-H), 6.22 (s, 1H, ArH), 7.17 (d, J = 8.0 Hz, 2H, ArH), 7.39 (d, J = 8.0 Hz, 2H, ArH), 11.52 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 62.83, 66.00, 66.99, 90.22, 112.83 (J = 92.0 Hz), 119.74 (J = 34.4 Hz), 127.80, 136.80, 155.39, 157.87, 163.69. MS (ESI, *m/z*): 379.2 [M + H]$^+$. HRMS (ESI, *m/z*) calcd for $C_{19}H_{15}FFeN_2NaS$ [M + Na]$^+$: 401.0182, found 401.0185. Anal. Calcd for $C_{19}H_{15}FFeN_2S$: C, 60.33; H, 4.00; N, 7.41. Found: C, 60.14; H, 4.15; N, 7.37.

N-(4-Chlorophenyl)-4-Ferrocenylthiazol-2-amine (3g)



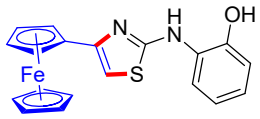
Orange solid, yield 80%, mp 177.3-177.8 °C; IR (KBr): ν 3330, 2850, 1596, 1559, 1520, 1307, 1263, 1213 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ : 4.16 (s, 5H, Fc-H), 4.41 (s, 2H, Fc-H), 4.90 (s, 2H, Fc-H), 7.09 (s, 1H, ArH), 8.02 (d, J = 8.0 Hz, 2H, ArH), 8.36 (d, J = 8.4 Hz, 2H, ArH), 11.10 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 67.19, 68.93, 69.63, 102.50, 110.81, 116.45, 126.08, 140.45, 147.54, 161.40. MS (ESI, *m/z*): 395.1, 397.0 [M + H]$^+$. HRMS (ESI, *m/z*) calcd for $C_{19}H_{15}{}^{35}ClFeN_2NaS$ [M + Na]$^+$: 416.9887, found 416.9895. Anal. Calcd for $C_{19}H_{15}ClFeN_2S$: C, 57.82; H, 3.83; N, 7.10. Found: C, 57.64; H, 3.75; N, 6.91.

N-(4-Bromophenyl)-4-Ferrocenylthiazol-2-amine (3h)



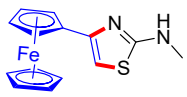
Yellow solid, yield 83%, mp 162.7- 164.2 °C; IR (KBr): ν 3073, 2713, 1618, 1551, 1521, 1487, 1072 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ : 4.20 (s, 5H, Fc-H), 4.31 (s, 2H, Fc-H), 4.69 (s, 2H, Fc-H), 6.06 (s, 1H, ArH), 7.14 (d, J = 8.0 Hz, 2H, ArH), 7.42 (d, J = 8.0 Hz, 2H, ArH), 11.51 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 68.57, 71.31, 71.48, 95.61, 109.99, 120.68, 123.57, 133.57, 135.46, 141.76, 167.26. MS (ESI, *m/z*): 438.9, 441.1 [M + H]$^+$. HRMS (ESI, *m/z*) calcd for $C_{19}H_{15}{}^{79}BrFeN_2NaS$ [M + Na]$^+$: 460.9381, found 460.9372. Anal. Calcd for $C_{19}H_{15}BrFeN_2S$: C, 51.96; H, 3.44; N, 6.38. Found: C, 51.74; H, 3.56; N, 6.19.

2-((4-Ferrocenylthiazol-2-yl)amino)phenol (3i)



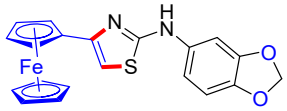
Yellow solid, yield 74%, mp 188.6-189.6 °C; IR (KBr): ν 3074, 2968, 1612, 1523, 1392, 1143 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ : 4.20 (s, 5H, Fc-H), 4.42 (s, 2H, Fc-H), 4.86 (s, 2H, Fc-H), 5.69 (s, 1H, OH), 6.92 (s, 1H, ArH) 6.94-6.98 (m, 1H, ArH), 7.07 (d, J = 7.6 Hz, 1H, ArH), 7.18 (t, J = 7.6 Hz, 1H, ArH), 7.59 (d, J = 7.6 Hz, 1H, ArH), 10.53 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ : 67.16, 69.84, 70.02, 75.27, 100.19, 117.07, 120.12, 123.64, 126.05, 127.88, 141.55, 150.34, 168.15. MS (ESI, *m/z*): 376.8 [M + H]$^+$. HRMS (ESI, *m/z*) calcd for $C_{19}H_{16}FeN_2NaOS$ [M + Na]$^+$: 399.0225, found 399.0217. Anal. Calcd for $C_{19}H_{16}FeN_2OS$: C, 60.65; H, 4.29; N, 7.45. Found: C, 60.89; H, 4.25; N, 7.57.

N-Methyl-4-ferrocenylthiazol-2-amine (3j)



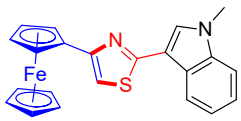
Red solid, yield 76%, mp 144.0-144.7 °C; IR (KBr): ν 3200, 2879, 1585, 1549, 1404, 1300, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 2.91 (s, 3H, Me), 4.02 (s, 5H, Fc-H), 4.17 (s, 2H, Fc-H), 4.57 (s, 2H, Fc-H), 5.65 (s, 1H, NH), 6.28 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 32.39, 66.71, 68.46, 69.45, 80.67, 98.14, 109.99, 150.85. MS (ESI, *m/z*): 299.1 $[M + H]^+$. HRMS (ESI, *m/z*) calcd for $C_{14}H_{14}FeN_2NaS$ $[M + Na]^+$: 321.0120, found 321.0113. Anal. Calcd for $C_{14}H_{14}FeN_2S$: C, 56.39; H, 4.73; N, 9.39. Found: C, 56.51; H, 4.66; N, 9.57.

N-(Benzo[d][1,3]dioxol-5-yl)-4-ferrocenylthiazol-2-amine (3k)



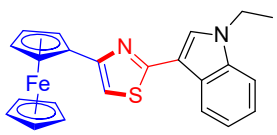
Yellow solid, yield 81%, mp 175.2-175.8 °C; IR (KBr): ν 3083, 1995, 1612, 1523, 1392, 1143 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ : 4.26 (s, 5H, Fc-H), 4.39 (s, 2H, Fc-H), 4.75 (s, 2H, Fc-H), 6.03 (s, 2H, OCH_2O), 6.20 (s, 1H, ArH) 6.81-6.84 (m, 3H, ArH), 11.25 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 66.99, 70.29, 70.48, 71.77, 94.56, 102.19, 104.09, 109.01, 116.08, 130.45, 141.20, 147.29, 148.90, 168.78. MS (ESI, *m/z*): 405.2 $[M + H]^+$. HRMS (ESI, *m/z*) calcd for $C_{20}H_{16}FeN_2O_2NaS$ $[M + Na]^+$: 427.0175, found 427.0167. Anal. Calcd for $C_{20}H_{16}FeN_2O_2S$: C, 59.42; H, 3.99; N, 6.93. Found: C, 59.67; H, 4.13; N, 7.12.

2-(1-Methyl-1H-indol-3-yl)-4-ferrocenylhiazole (3l)



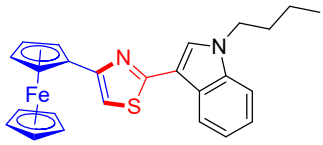
Yellow solid, yield 74%, mp 122.0-122.8 °C; IR (KBr): ν 3107, 2934, 1618, 1545, 1467, 1373, 1358, 1179; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.76 (s, 3H, CH_3), 4.04 (s, 5H, Fc-H), 4.24 (s, 2H, Fc-H), 4.80 (s, 2H, Fc-H), 6.86 (s, 1H, ArH), 7.24-7.30 (m, 3H, ArH), 7.75 (s, 1H, ArH), 8.29 (d, *J* = 8.4 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 33.21, 67.29, 68.75, 69.57, 106.84, 109.70, 109.98, 121.14, 122.73, 125.41, 125.47, 129.12, 137.29, 154.48, 161.94. MS (ESI, *m/z*): 399.1 $[M + H]^+$. HRMS (ESI, *m/z*) calcd for $C_{22}H_{18}FeN_2NaS$ $[M + Na]^+$: 421.0438, found 421.0422. Anal. Calcd for $C_{22}H_{18}FeN_2S$: C, 66.34; H, 4.56; N, 7.03. Found: C, 66.56; H, 4.37; N, 7.21.

2-(1-Ethyl-1H-indol-3-yl)-4-ferrocenylthiazole (3m)



Yellow solid, yield 71%, mp 116.4-118.2 °C; IR (KBr): ν 3104, 2969, 1611, 1541, 1468, 1395, 1335, 1195; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.54 (t, J = 7.2 Hz, 3H, $CH_2C\underline{H}_3$), 4.11 (s, 5H, Fc-H), 4.25 (q, J = 6.8 Hz, 2H, $C\underline{H}_2CH_3$), 4.31 (s, 2H, Fc-H), 4.87 (s, 2H, Fc-H), 6.96 (s, 1H, ArH), 7.29-7.33 (m, 2H, ArH), 7.39 (t, *J* = 7.6 Hz, 1H, ArH), 7.82 (s, 1H, ArH), 8.39 (d, *J* = 8.4 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.39, 41.39, 67.26, 68.69, 69.54, 106.82, 109.74, 109.96, 121.06, 121.25, 122.58, 125.58, 127.37, 136.34, 154.48, 161.98. MS (ESI, *m/z*): 413.0 $[M + H]^+$. HRMS (ESI, *m/z*) calcd for $C_{23}H_{20}FeN_2NaS$ $[M + Na]^+$: 435.0594, found 435.0609. Anal. Calcd for $C_{23}H_{20}FeN_2S$: C, 67.00; H, 4.89; N, 6.79. Found: C, 66.84; H, 5.04; N, 6.65

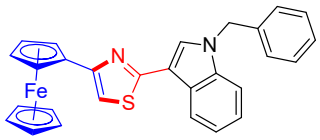
2-(1-Butyl-1H-indol-3-yl)-4-ferrocenylthiazole (3n)



Yellow solid, yield 68%, mp 94.6-96.2 °C; IR (KBr): ν 3117, 2974, 1615, 1543, 1469, 1395, 1356, 1175; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, *J* = 7.2 Hz, 3H, CH_3), 1.32 (sext, *J* = 7.2 Hz, 2H, CH_2), 1.82 (quint, *J* = 7.2 Hz, 2H, CH_2), 4.06 (s, 5H, Fc-H), 4.10 (t, *J* = 7.2 Hz,

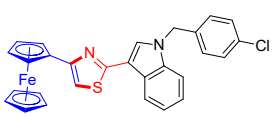
2H, CH_2), 4.26 (s, 2H, Fc-H), 4.82 (s, 2H, Fc-H), 6.85 (s, 1H, ArH), 7.22-7.25 (m, 2H, ArH), 7.31 (d, *J* = 7.6 Hz, 1H, ArH), 7.69 (s, 1H, ArH), 8.32 (d, *J* = 8.0 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 11.70, 18.16, 30.18, 44.49, 65.29, 66.74, 67.62, 104.86, 107.83, 107.96, 118.97, 119.24, 120.52, 123.48, 125.99, 134.61, 152.49, 159.94. MS (ESI, *m/z*): 441.3 $[M + H]^+$. HRMS (ESI, *m/z*) calcd for $C_{25}H_{24}FeN_2NaS$ $[M + Na]^+$: 463.0907, found 463.0893. Anal. Calcd for $C_{25}H_{24}FeN_2S$: C, 68.18; H, 5.49; N, 6.36. Found: C, 68.29; H, 5.64; N, 6.11.

2-(1-Benzyl-1H-indol-3-yl)-4-ferrocenylthiazole (3o)



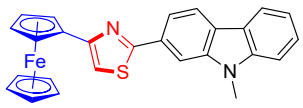
Yellow solid, yield 76%, mp 167.5-168.4 °C; IR (KBr): ν 3115, 2970, 1618, 1543, 1470, 1396, 1352, 1172; ^{1}H NMR (400 MHz, DMSO-d6) *δ*: 4.08 (s, 5H, Fc-H), 4.35 (s, 2H, Fc-H), 4.90 (s, 2H, Fc-H), 5.54 (s, 2H, $ArCH_2$), 7.23-7.32 (m, 5H, ArH), 7.35 (d, *J* = 8.0 Hz, 2H, ArH), 7.44 (s, 1H, ArH), 7.58 (d, *J* = 8.0 Hz, 1H, ArH), 8.33 (s, 1H, ArH), 8.36 (d, *J* = 8.4 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d6) *δ*: 49.79, 67.38, 68.96, 69.65, 80.86, 108.22, 110.78, 111.45, 121.26, 121.56, 123.07, 125.43, 127.61, 127.99, 129.07, 130.08, 136.77, 138.02, 154.32, 161.78. MS (ESI, *m/z*): 475.1 $[M + H]^+$. HRMS (ESI, *m/z*) calcd for $C_{28}H_{22}FeN_2NaS$ $[M + Na]^+$: 497.0751, found 497.0768. Anal. Calcd for $C_{28}H_{22}FeN_2S$: C, 70.89; H, 4.67; N, 5.91. Found: C, 71.10; H, 4.53; N, 6.15.

2-(1-(4-Chlorobenzyl)-1H-indol-3-yl)-4-ferrocenylthiazole (3p)



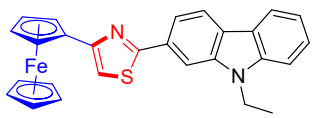
Yellow solid, yield 73%, mp 177.7-179.5 °C; IR (KBr): ν 3114, 2968, 1617, 1541, 1474, 1393, 1337, 1174; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 4.05 (s, 5H, Fc-H), 4.25 (s, 2H, Fc-H), 4.81 (s, 2H, Fc-H), 5.28 (s, 2H, $ArCH_2$), 6.91 (d, *J* = 8.4 Hz, 1H, ArH), 7.03 (d, *J* = 8.4 Hz, 2H, ArH), 7.19 (d, *J* = 8.4 Hz, 2H, ArH), 7.22-7.27 (m, 3H, ArH), 7.78 (s, 1H, ArH), 8.35 (d, *J* = 7.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 49.88, 67.30, 68.79, 69.56, 107.04, 109.99, 110.12, 121.39, 121.52, 123.12, 125.71, 128.12, 128.18, 129.09, 133.79, 135.01, 136.73, 154.49, 158.27. MS (ESI, *m/z*): 509.1, 511.0 $[M + H]^+$. HRMS (ESI, *m/z*) calcd for $C_{28}H_{21}{}^{35}ClFeN_2NaS$ $[M + Na]^+$: 531.0361, found 531.0383. Anal. Calcd for $C_{28}H_{21}ClFeN_2S$: C, 66.09; H, 4.16; N, 5.51. Found: C, 66.19; H, 4.34; N, 5.28.

2-(9-Methyl-9H-carbazol-2-yl)-4-ferrocenylthiazole (3q)



Yellow solid, yield 72%, mp 163.2-164.1 °C; IR (KBr): ν 3052, 2961, 1611, 1596, 1541, 1452, 1382, 1234, 1153; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* : 8.60 (s, 1H, ArH), 8.12 (d, *J* = 7.6 Hz, 1H, ArH), 8.03 (d, *J* = 7.6 Hz, 1H, ArH), 7.44 (t, *J* = 7.6 Hz, 1H, ArH), 7.34 (d, *J* = 7.6 Hz, 2H, ArH), 7.23 (t, *J* = 8.4 Hz, 1H, ArH), 6.81 (s, 1H, ArH), 5.02 (s, 2H, Fc-H), 4.49 (s, 2H, Fc-H), 4.24 (s, 5H, Fc-H), 3.80 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* : 29.37, 68.39, 70.42, 71.42, 108.63, 108.77, 110.22, 118.82, 119.46, 120.72, 122.82, 123.00, 124.76, 125.25, 126.22, 141.51, 141.91, 155.53, 168.41. MS (ESI, *m/z*): 449.2 $[M + H]^+$. HRMS (ESI, *m/z*) calcd for $C_{26}H_{20}FeN_2NaS$ $[M + Na]^+$: 471.0594, found 471.0611. Anal. Calcd for $C_{26}H_{20}FeN_2S$: C, 69.65; H, 4.50; N, 6.25. Found: C, 69.49; H, 4.37; N, 6.42.

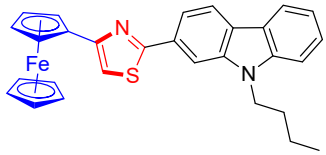
2-(9-Ethyl-9H-carbazol-2-yl)-4-ferrocenylthiazole (3r)



Yellow solid, yield 68%, mp 149.2-150.3°C; IR (KBr): ν 3103, 2966, 1619, 1598, 1545, 1455, 1376, 1233, 1157; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.49 (t, J = 6.8 Hz, 3H, $CH_2C\underline{H}_3$), 4.40 (s, 5H, Fc-H), 4.43 (q, J = 6.8

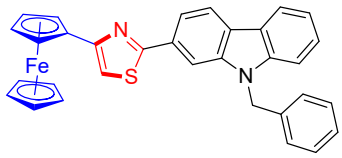
Hz, 2H, $C\underline{H}_2CH_3$), 4.45 (d, J=2.0 Hz, 2H, Fc-H), 4.98 (d, J=2.0 Hz, 2H, Fc-H), 7.02 (s, 1H, ArH), 7.31 (t, *J* = 7.6 Hz, 1H, ArH), 7.44-7.48 (m, 2H, ArH), 7.53 (t, *J* = 7.6 Hz, 1H, ArH), 8.15 (d, *J* = 7.6 Hz, 1H, ArH), 8.23 (d, *J* = 7.2 Hz, 1H, ArH), 8.74 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.13, 38.01, 68.17, 68.56, 69.97, 70.91, 108.84, 109.00, 109.97, 119.16, 121.07, 123.25, 123.44, 124.94, 125.52, 126.38, 140.72, 141.13, 155.79, 168.60. MS (ESI, *m/z*): 463.0 $[M + H]^+$. HRMS (ESI, *m/z*) calcd for $C_{27}H_{22}FeN_2NaS$ $[M + Na]^+$: 485.0751, found 485.0739. Anal. Calcd for $C_{27}H_{22}FeN_2S$: C, 70.13; H, 4.80; N, 6.06. Found: C, 69.94; H, 4.71; N, 6.17.

2-(9-Butyl-9H-carbazol-2-yl)-4-ferrocenylthiazole (3s)



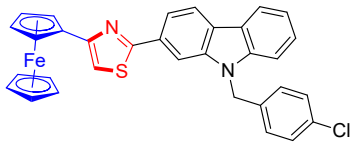
Orange solid, yield 65%, mp 107.8-108.7 °C; IR (KBr): ν 3118, 2959, 1610, 1594, 1541, 1458, 1366, 1237, 1161; ^{1}H NMR (400 MHz, $CDCl_3$) δ : 0.88 (t, *J* = 7.2 Hz, 3H, CH_3), 1.30-1.38 (sext, J= 7.2 Hz, 2H, CH_2), 1.81 (quint, J= 7.2 Hz, 2H, CH_2), 4.16 (s, 5H, Fc-H), 4.26 (t, *J* = 7.2 Hz, 2H, CH_2), 4.39 (s, 2H, Fc-H), 4.94 (s, 2H, Fc-H), 6.88 (s, 1H, ArH), 7.22 (t, *J* = 8.0 Hz, 1H, ArH), 7.34-7.37 (m, 2H, ArH), 7.42 (t, *J* = 8.0 Hz, 1H, ArH), 8.03 (d, *J* = 8.0 Hz, 1H, ArH), 8.12 (d, *J* = 7.6 Hz, 1H, ArH), 8.62 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 13.92, 20.57, 31.13, 43.06, 67.94, 69.72, 70.64, 82.19, 108.92, 109.03, 109.78, 118.91, 119.35, 120.79, 122.90, 123.06, 124.71, 125.14, 126.12, 140.96, 141.44, 155.52, 168.42. MS (ESI, *m/z*): 491.1 $[M + H]^+$. HRMS (ESI, *m/z*) calcd for $C_{29}H_{26}FeN_2NaS$ $[M + Na]^+$: 513.1064 , found 513.1078. Anal. Calcd for $C_{29}H_{26}FeN_2S$: C, 71.02; H, 5.34; N, 5.71. Found: C, 71.19; H, 5.28; N, 5.53.

2-(9-Benzyl-9H-carbazol-2-yl)-4-ferrocenylthiazole (3t)



Yellow solid, yield 70%, mp 161.4-161.9 °C; IR (KBr): ν 3109, 2924, 1621, 1599, 1541, 1454, 1385, 1238, 1161; ^{1}H NMR (400 MHz, $CDCl_3$) δ : 4.09 (s, 5H, Fc-H), 4.32 (s, 2H, Fc-H), 4.88 (s, 2H, Fc-H), 5.49 (s, 2H, CH_2), 6.96 (s, 1H, ArH), 7.08 (d, *J* = 8.4 Hz, 1H, ArH), 7.18-7.26 (m, 3H, ArH), 7.34 (t, *J* = 7.6 Hz, 2H, ArH), 7.40 (t, *J* = 7.6 Hz, 1H, ArH), 8.04 (d, *J* = 8.0 Hz, 1H, ArH), 8.71 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 42.54, 66.63, 66.69, 68.28, 68.88, 107.55, 107.59, 109.70, 117.76, 118.01, 119.72, 122.15, 122.21, 123.51, 124.60, 124.81, 125.69, 127.92, 129.00, 132.70, 138.91, 139.37, 156.14, 166.77. MS (ESI, *m/z*): 525.2 $[M + H]^+$. HRMS (ESI, *m/z*) calcd for $C_{32}H_{24}FeN_2NaS$ $[M + Na]^+$: 547.0907, found 547.0896. Anal. Calcd for $C_{32}H_{24}FeN_2S$: C, 73.28; H, 4.61; N, 5.34. Found: C, 73.51; H, 4.70; N, 5.13.

2-(9-(4-Chlorobenzyl)-9H-carbazol-2-yl)-4-ferrocenylthiazole (3u)



Yellow solid, yield 66%, mp 178.0-178.7 °C; IR (KBr): ν 3120, 2955, 1617, 1597, 1549, 1450, 1378, 1235, 1163; ^{1}H NMR (400 MHz, DMSO-d_6) δ : 4.08 (s, 5H, Fc-H), 4.36 (s, 2H, Fc-H), 4.93 (s, 2H, Fc-H), 5.74 (s, 2H, CH_2), 7.21 (d, *J* = 8.4 Hz, 2H, ArH), 7.31 (d, *J* = 8.4 Hz, 1H, ArH), 7.36 (d, *J* = 7.6 Hz, 2H, ArH), 7.50 (t, *J* = 7.6 Hz, 1H, ArH), 7.60 (s, 1H, ArH), 7.69 (d, *J* = 8.0 Hz, 1H, ArH), 7.79 (d, *J* = 8.4 Hz, 1H, ArH), 8.11 (d, *J* = 8.0 Hz, 1H, ArH), 8.38 (d, *J* = 8.4 Hz, 1H, ArH), 8.82 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ : 45.48, 67.43, 69.02, 69.70, 80.61, 110.37, 110.55, 111.03, 118.92, 120.25, 121.45, 122.70, 123.11, 124.94, 125.48, 127.03, 129.04, 132.36, 136.97, 141.09, 141.47, 155.38, 167.64. MS (ESI, *m/z*): 559.0, 561.1 $[M + H]^+$. HRMS (ESI, *m/z*) calcd for $C_{32}H_{23}{}^{35}ClFeN_2NaS$ $[M + Na]^+$: 581.0518, found 581.0531. Anal. Calcd for

$C_{32}H_{23}ClFeN_2S$: C, 68.77; H, 4.15; N, 5.01. Found: : C, 68.92; H, 4.24; N, 4.89.

6. ^{1}H NMR and ^{13}C NMR spectra of products 3a-u

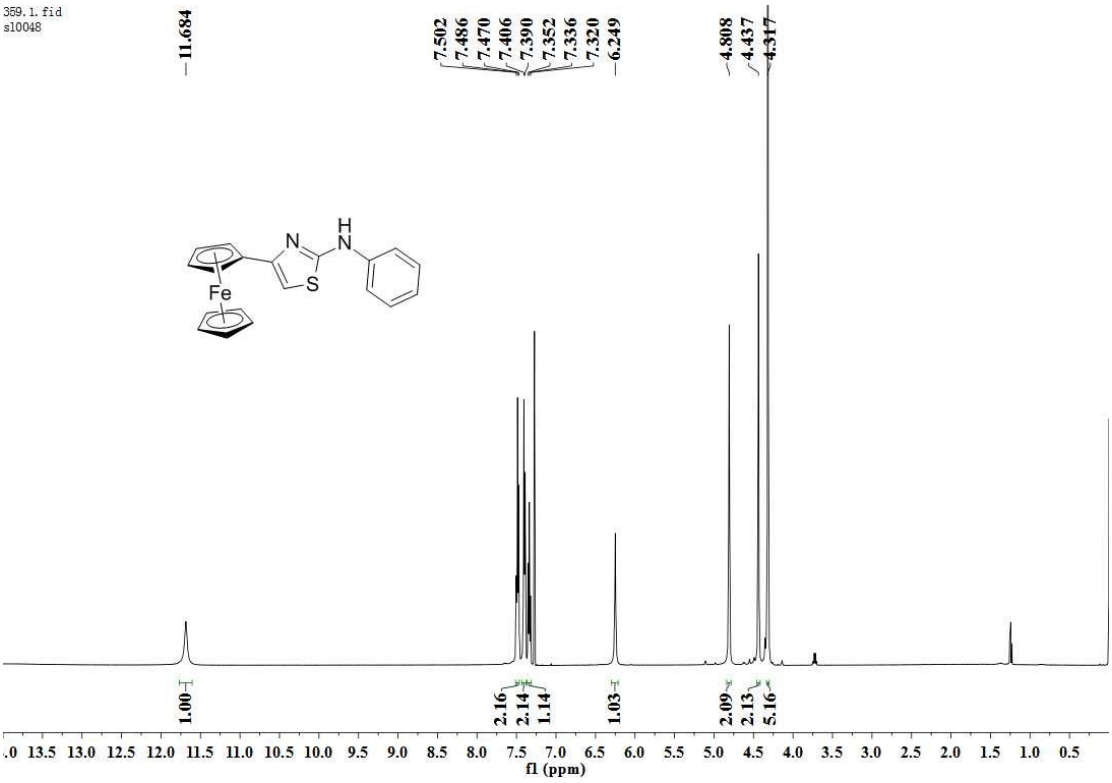


Fig. S1 ^{1}H NMR spectrum of **3a**

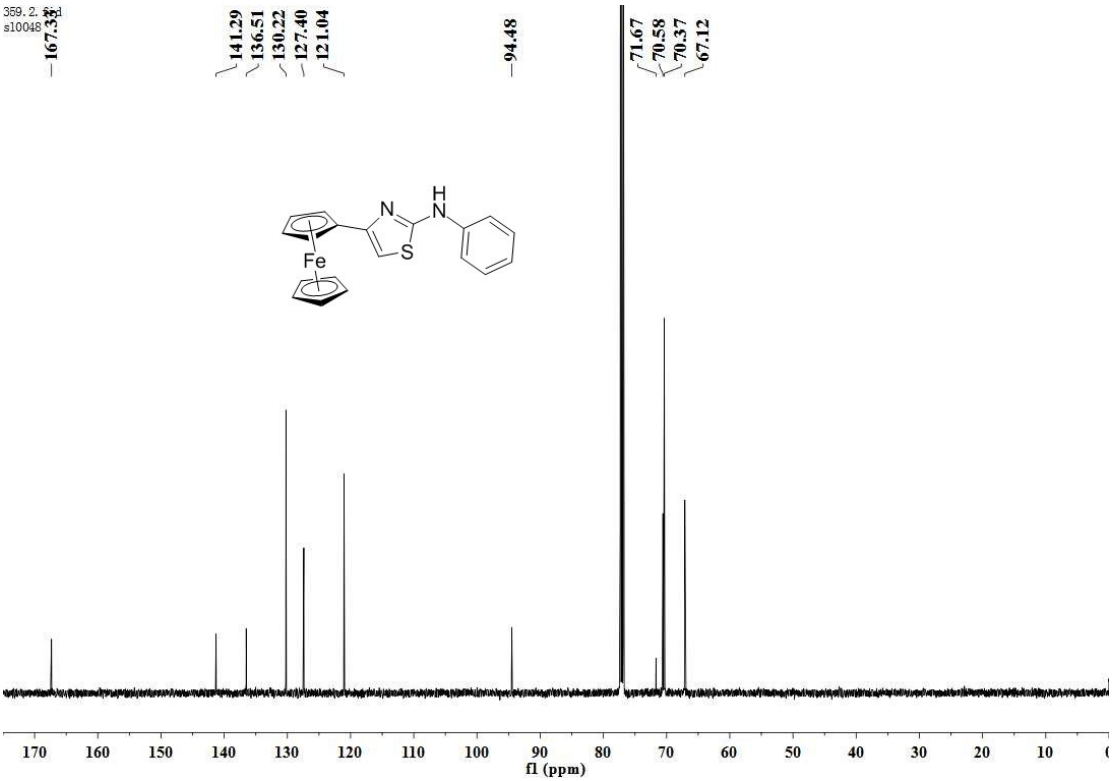


Fig. S2 ^{13}C NMR spectrum of **3a**

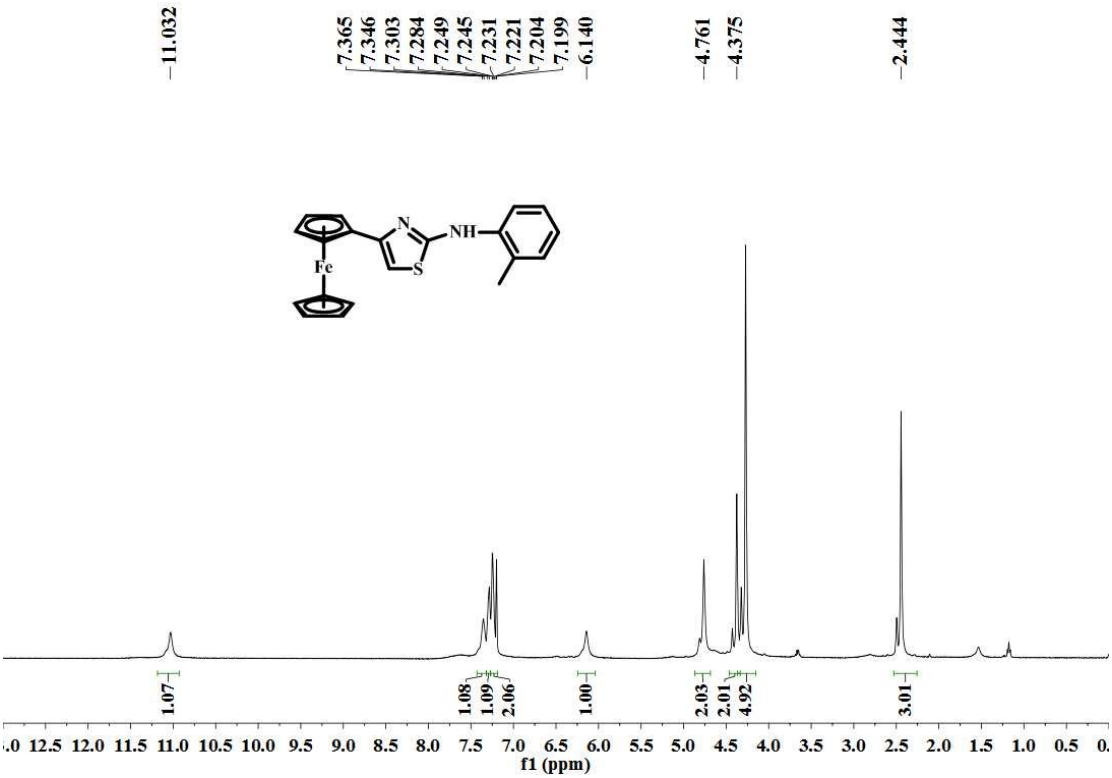


Fig. S3 ^{1}H NMR spectrum of **3b**

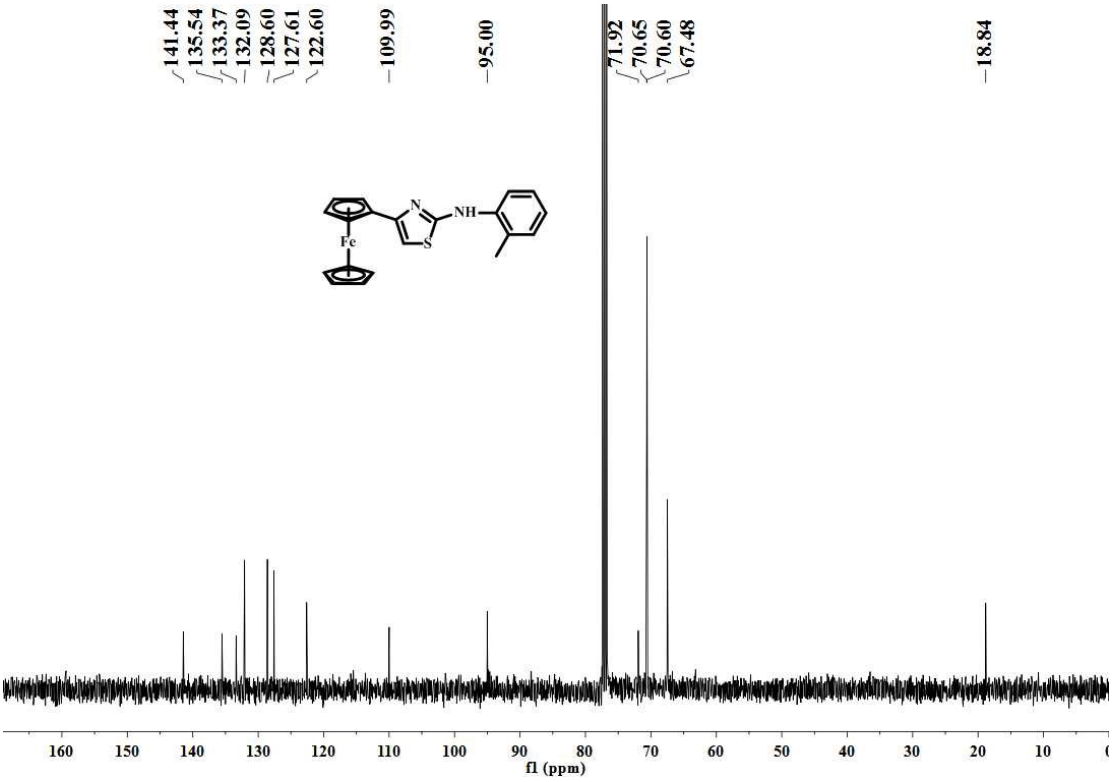


Fig. S4 ^{1}H NMR spectrum of **3b**

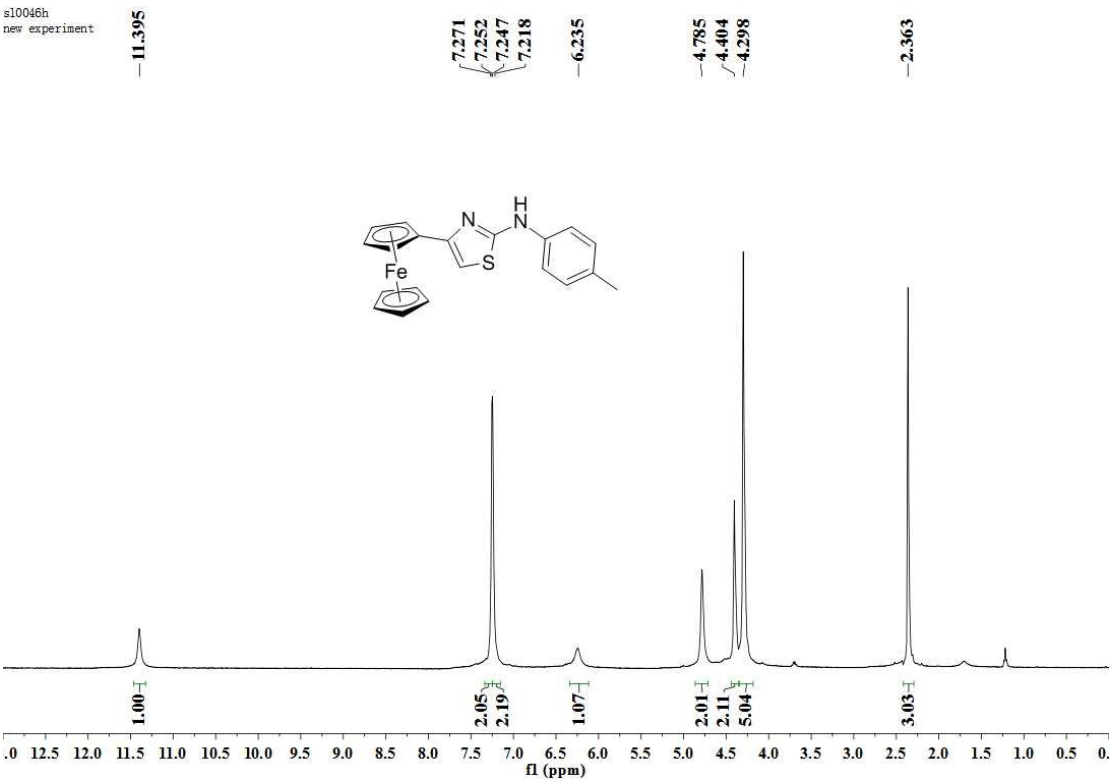


Fig. S5 ^{1}H NMR spectrum of **3c**

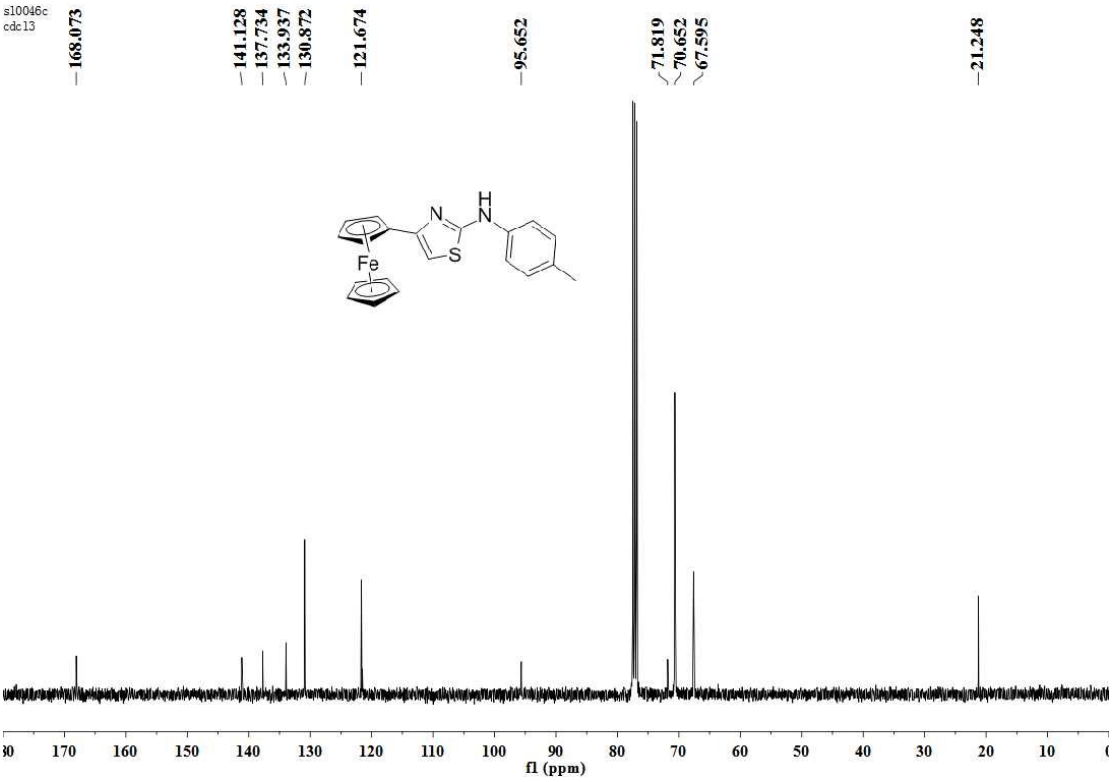


Fig. S6 ^{13}C NMR spectrum of **3c**

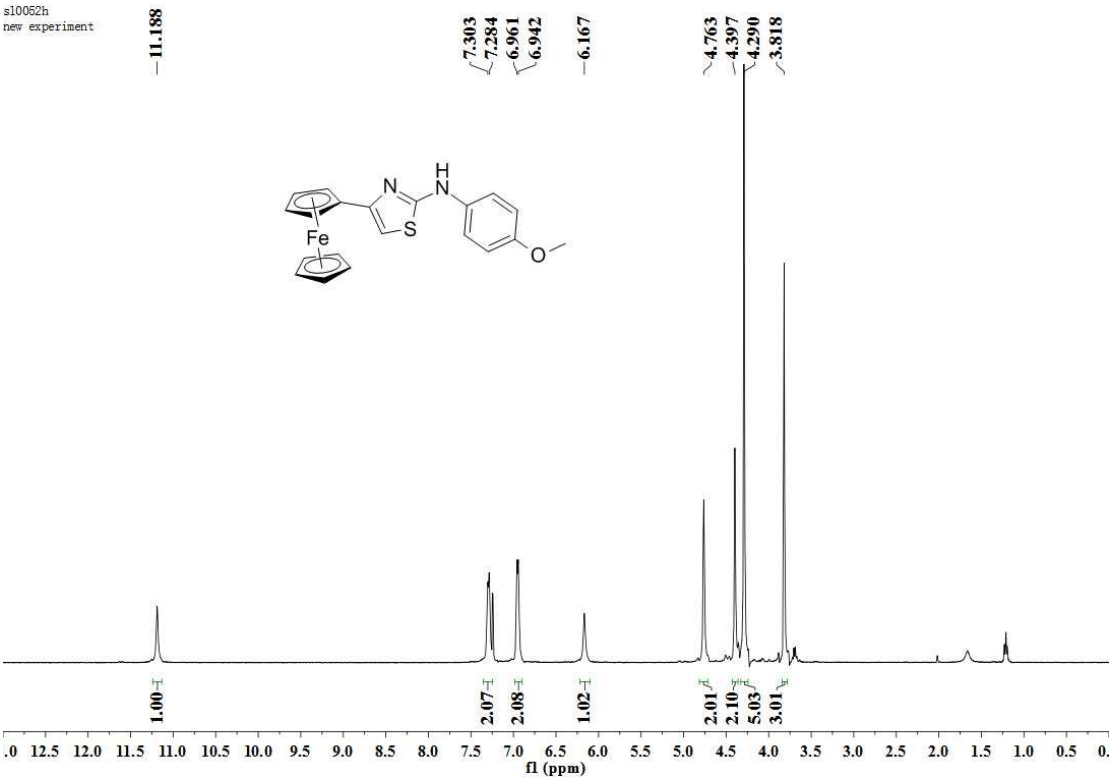


Fig. S7 ^{1}H NMR spectrum of **3d**

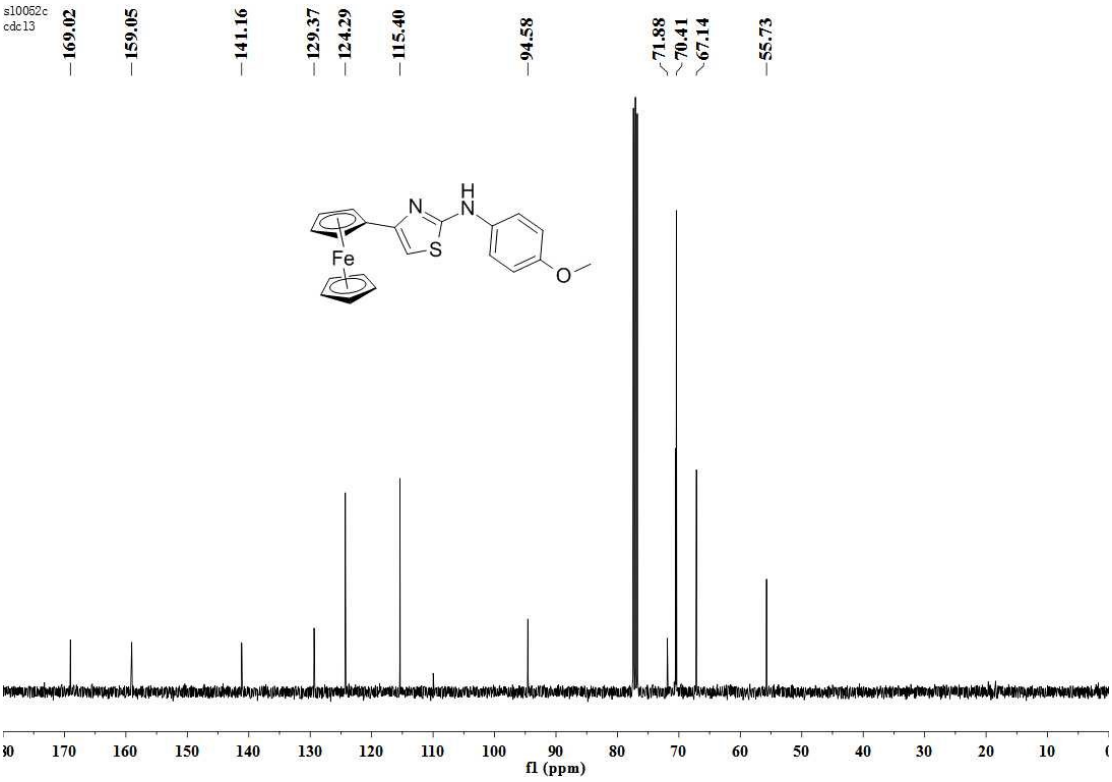


Fig. S8 ^{13}C NMR spectrum of **3d**

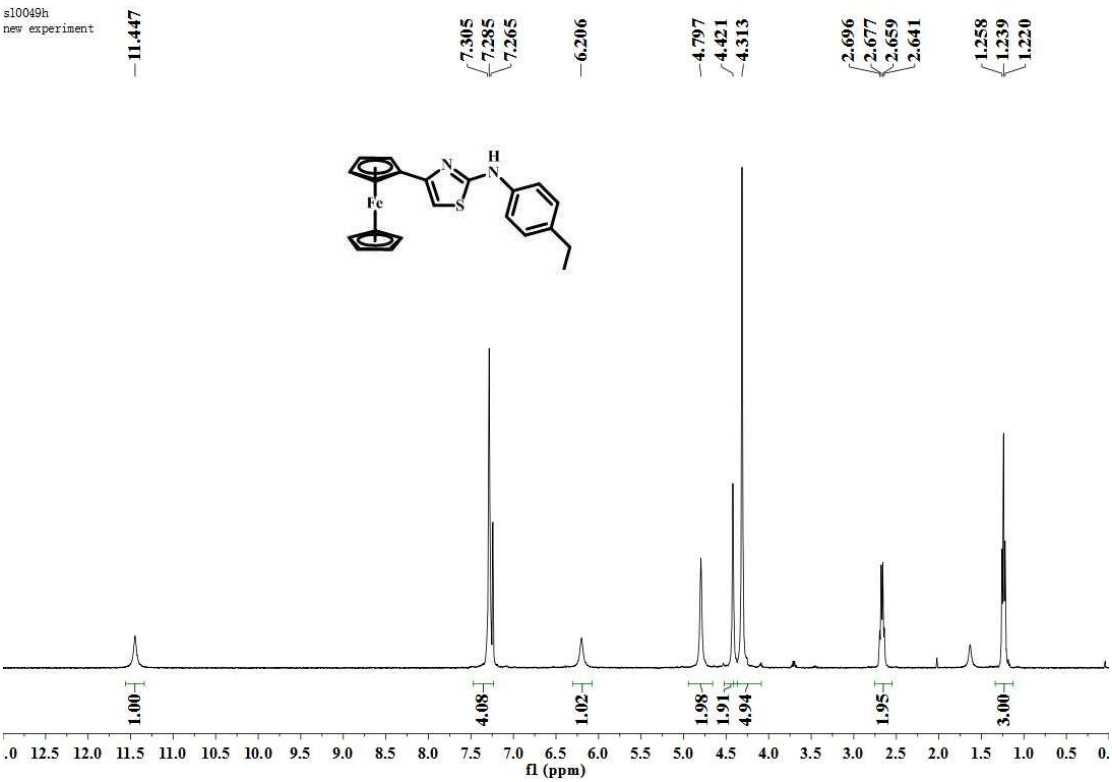


Fig. S9 ^{1}H NMR spectrum of **3e**

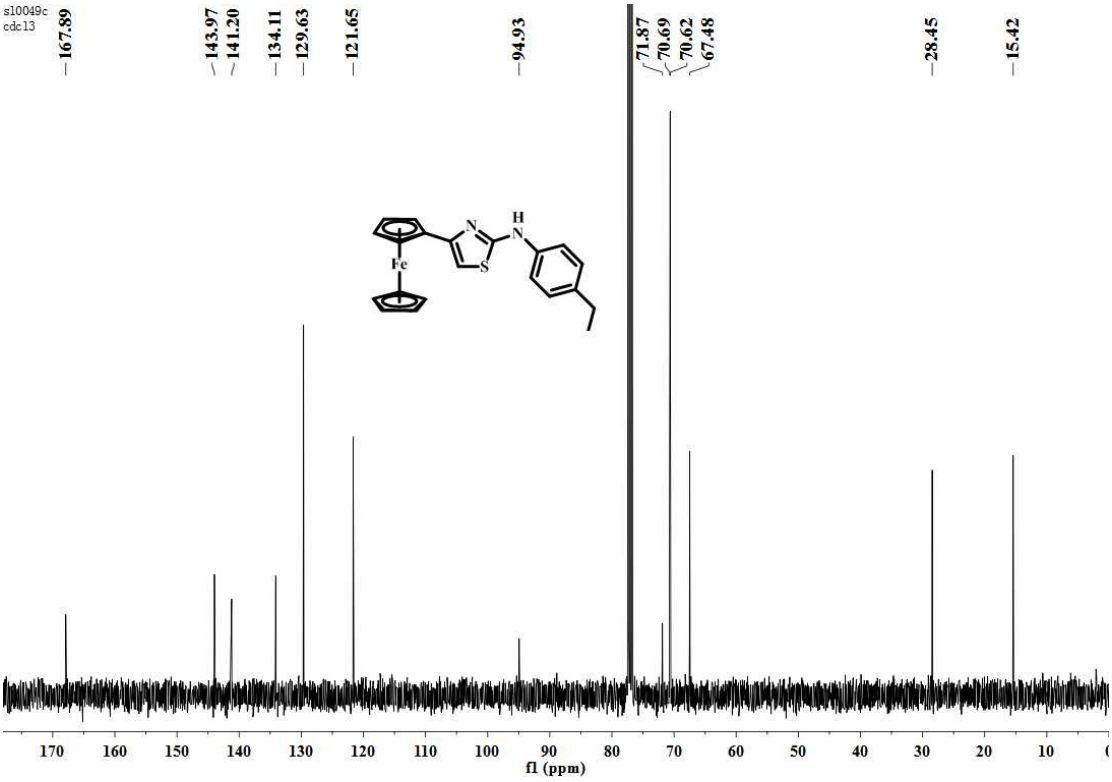


Fig. S10 ^{13}C NMR spectrum of **3e**

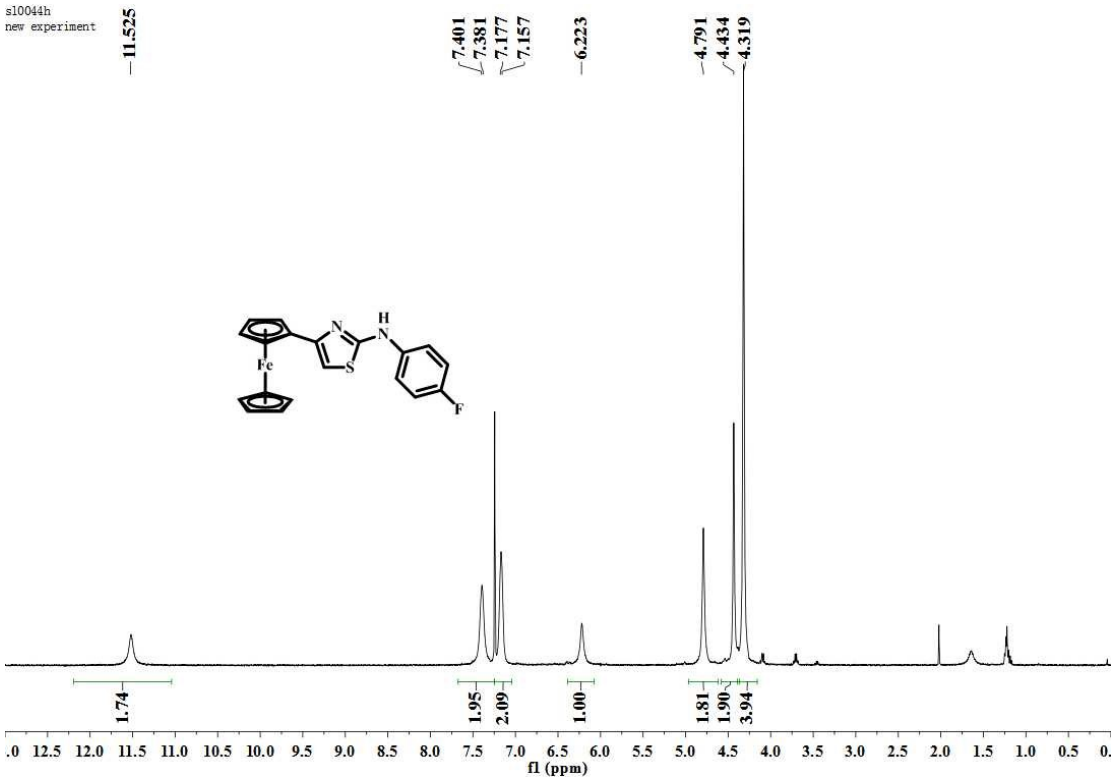


Fig. S11 ^{1}H NMR spectrum of **3f**

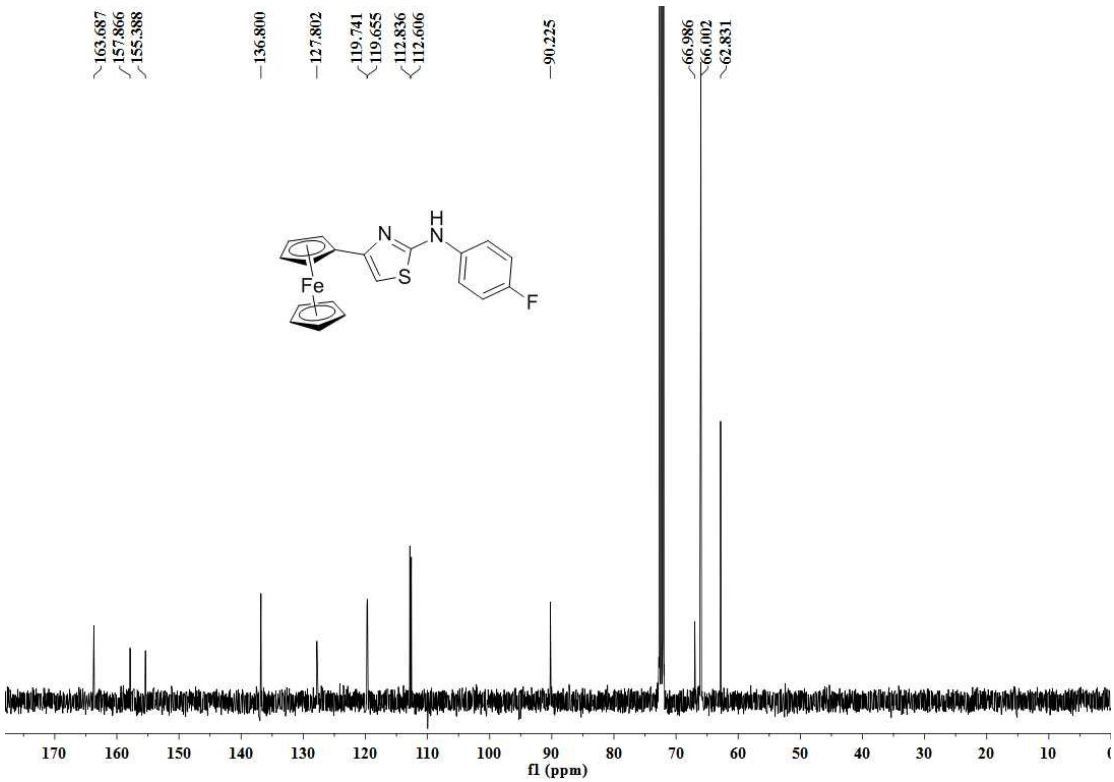


Fig. S12 ^{13}C NMR spectrum of **3f**

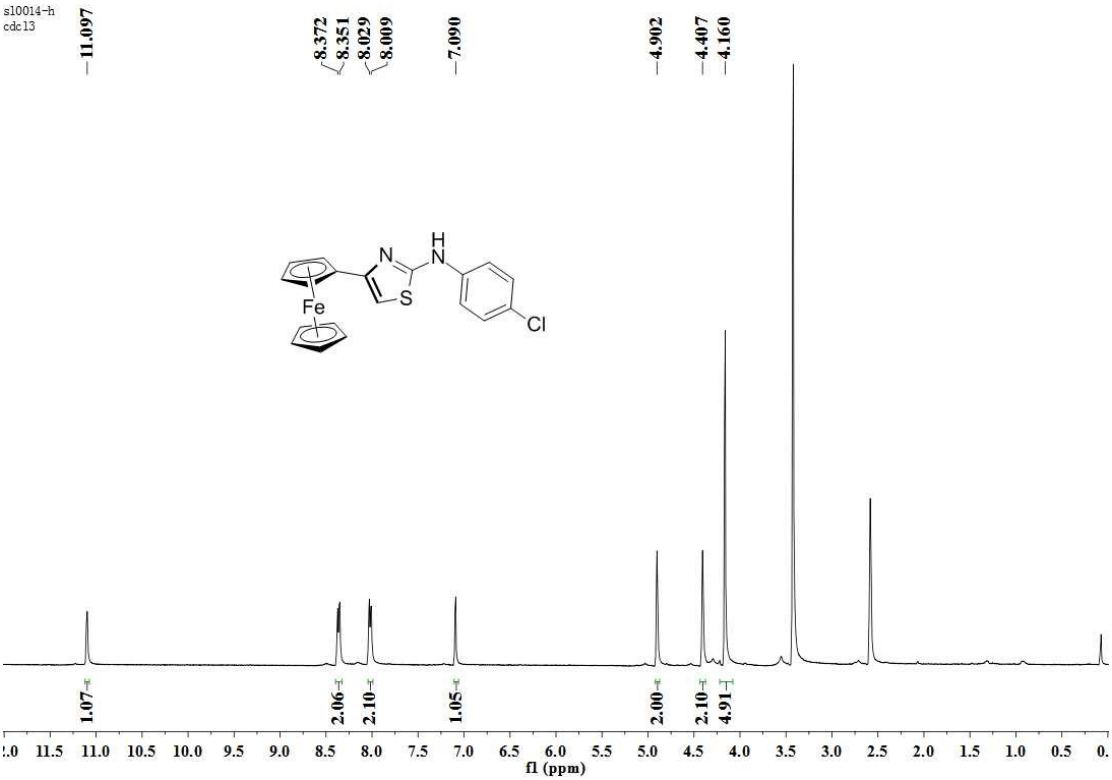


Fig. S13 ^{1}H NMR spectrum of **3g**

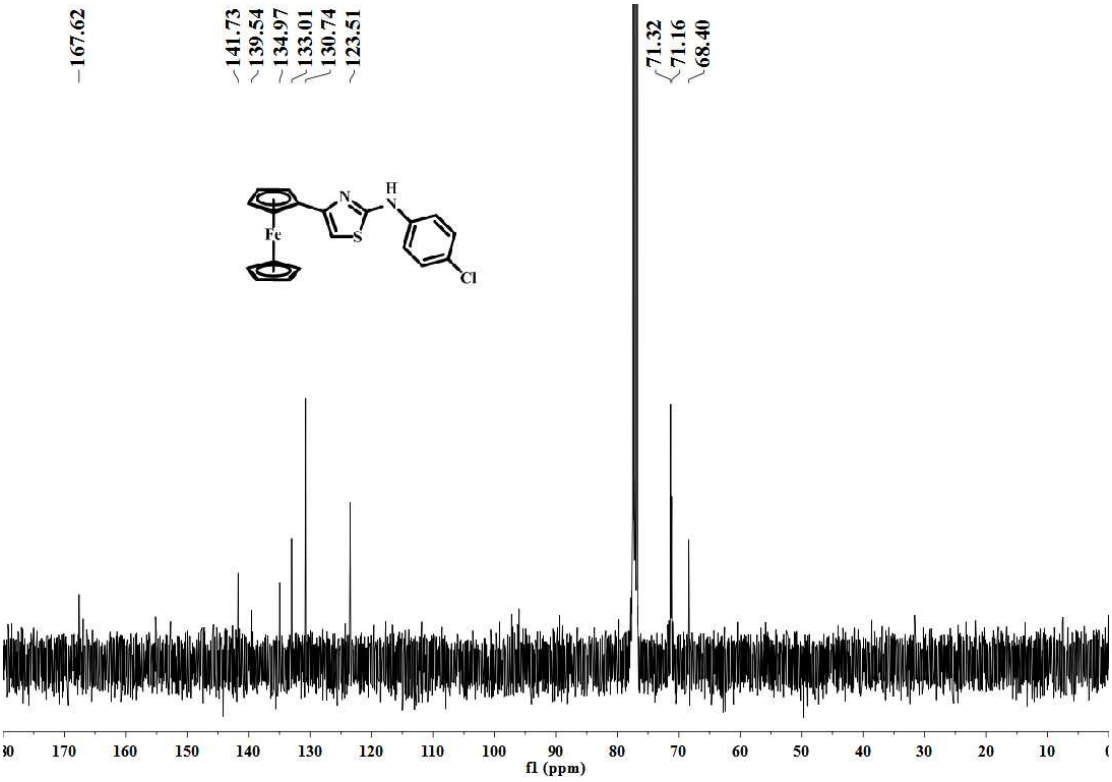


Fig. S14 ^{13}C NMR spectrum of **3g**

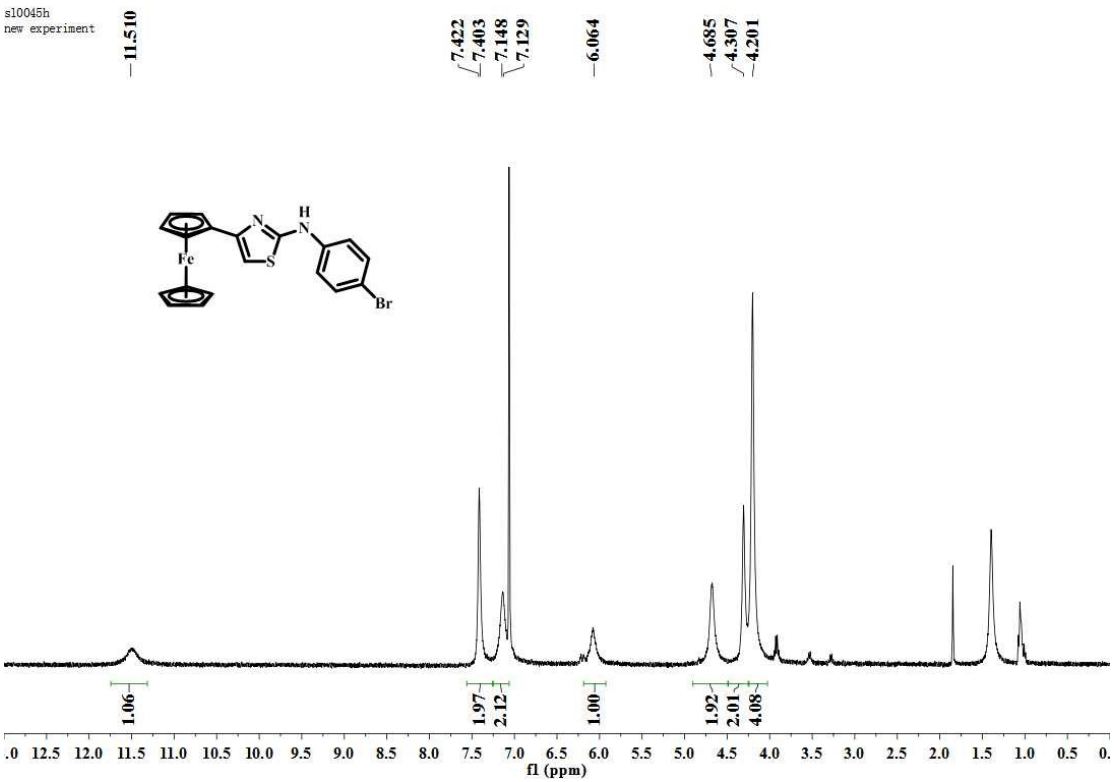


Fig. S15 ^{1}H NMR spectrum of **3h**

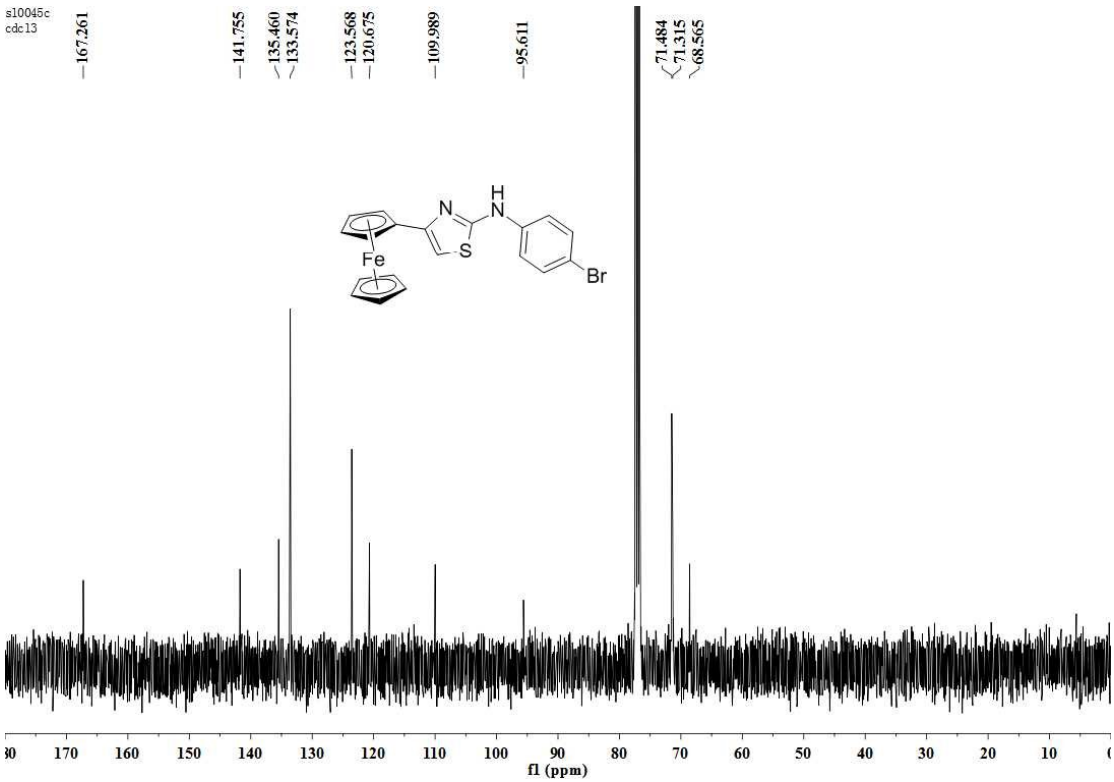


Fig. S16 ^{13}C NMR spectrum of **3h**

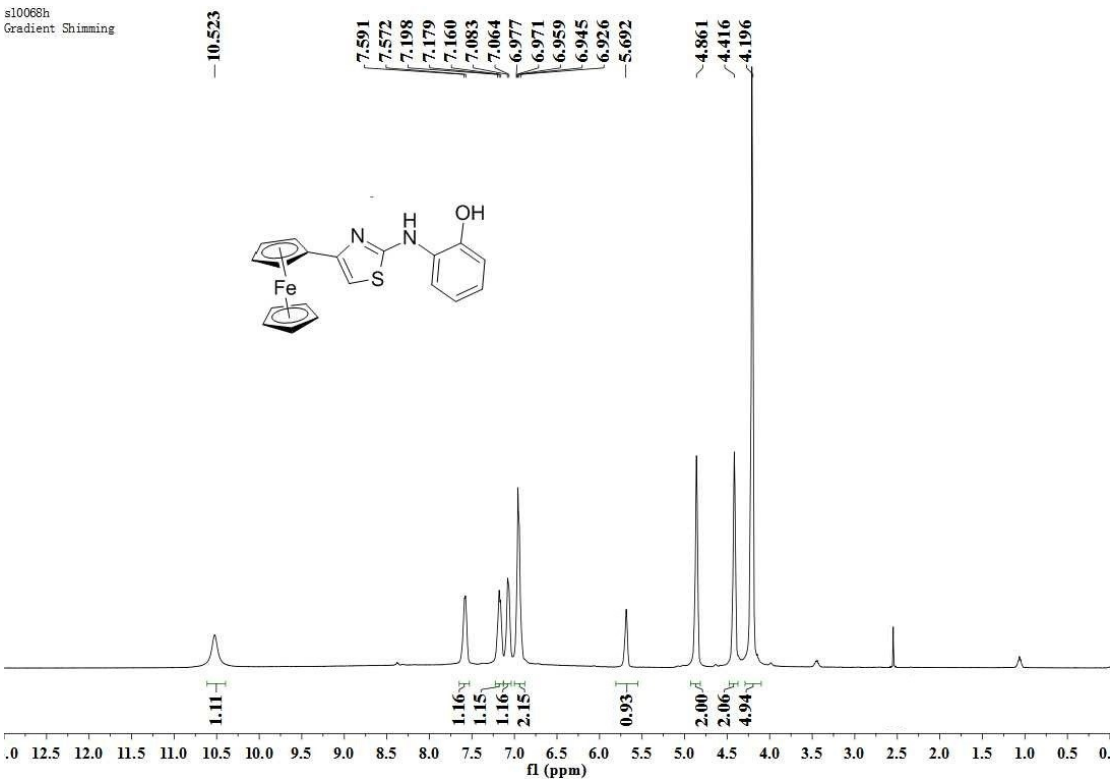


Fig. S17 ^{1}H NMR spectrum of **3i**

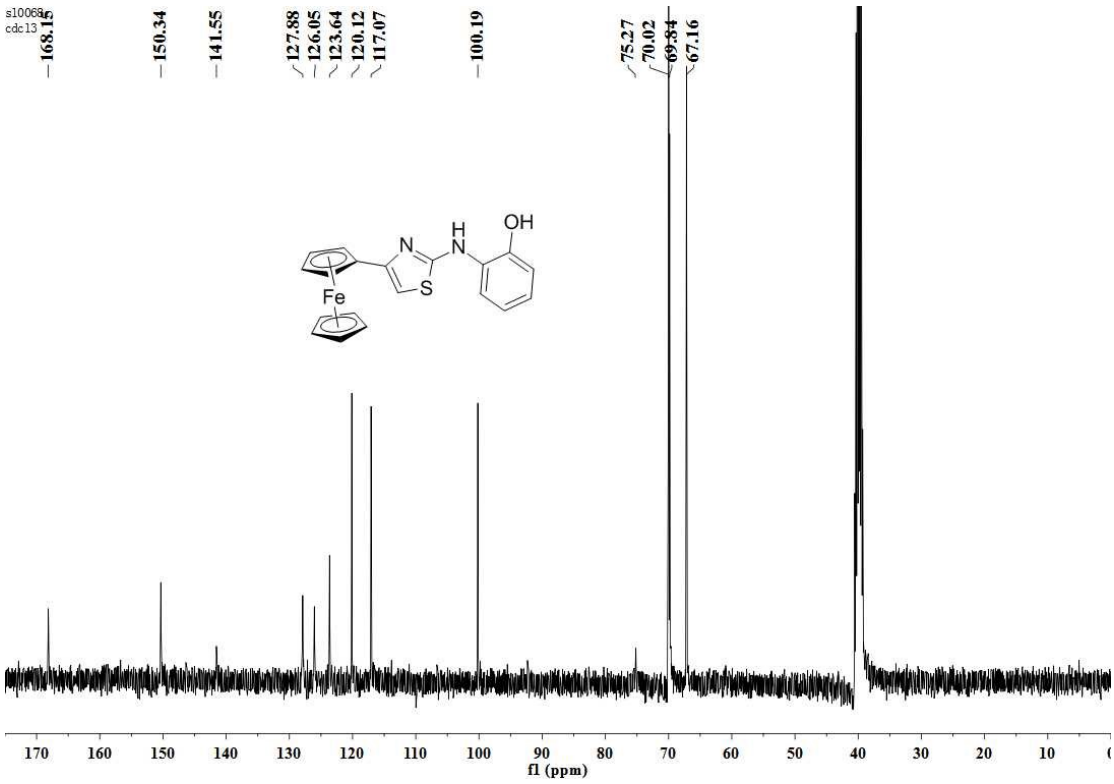


Fig. S18 ^{13}C NMR spectrum of **3i**

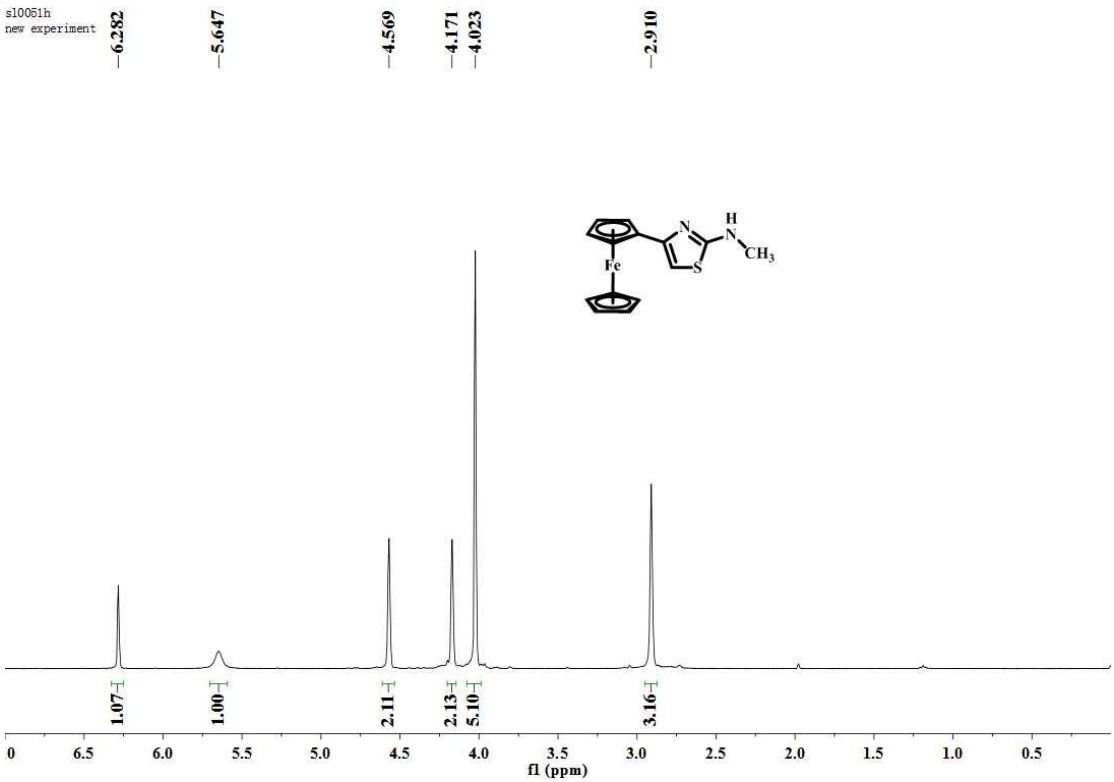


Fig. S19 ^{1}H NMR spectrum of **3j**

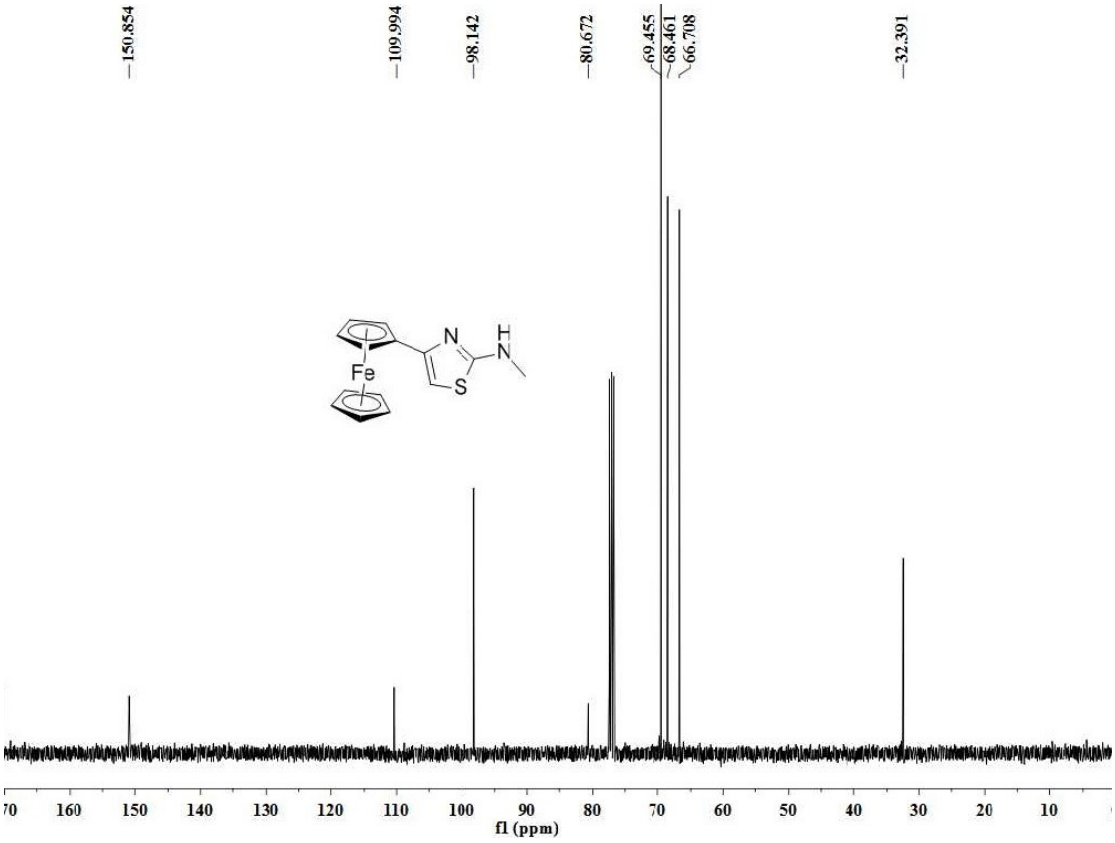


Fig. S20 ^{13}C NMR spectrum of **3j**

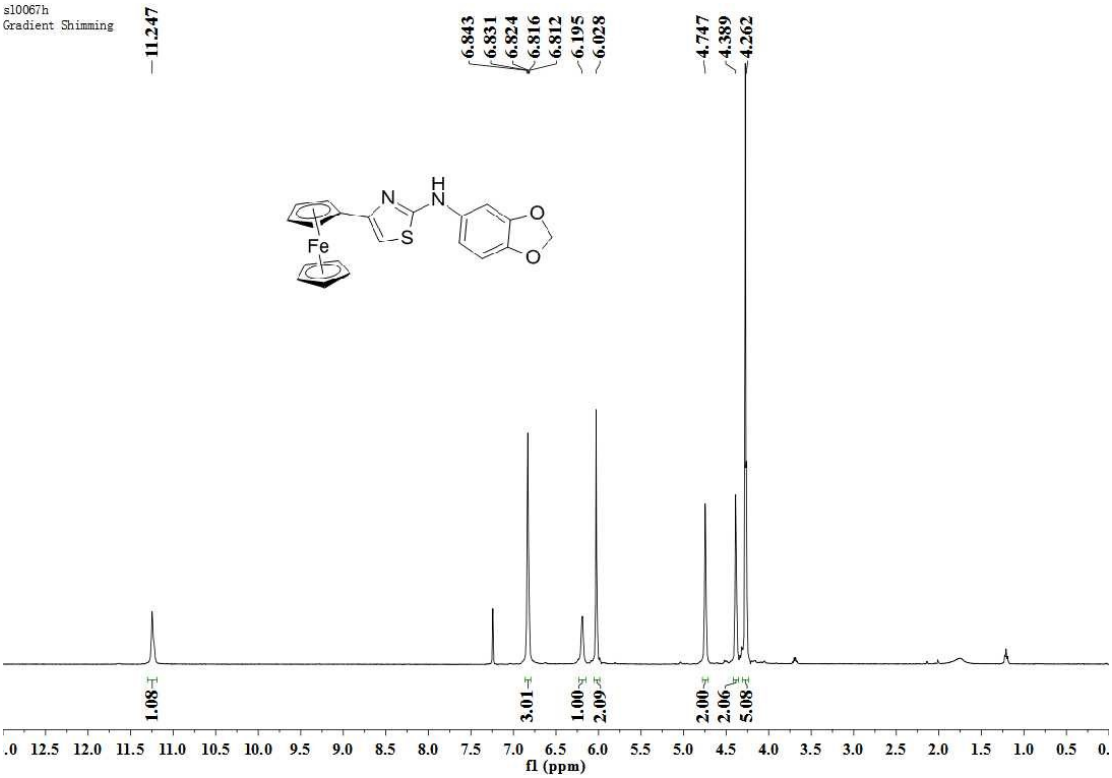


Fig. S21 ^{1}H NMR spectrum of **3k**

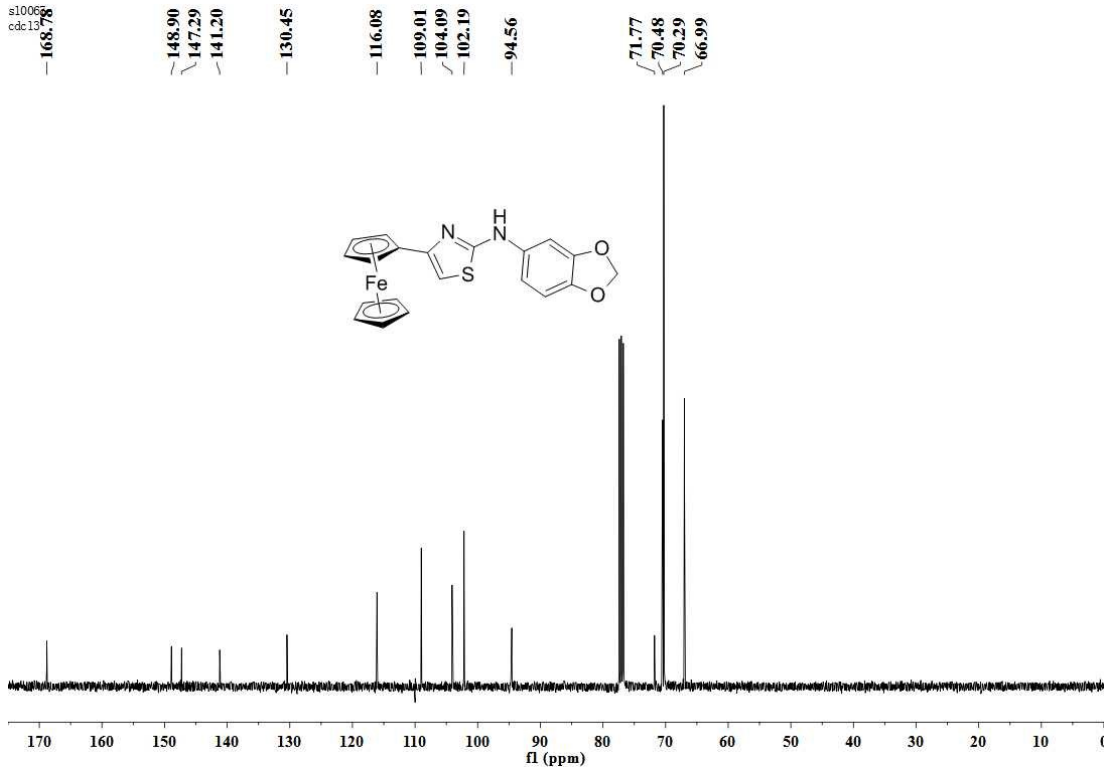


Fig. S22 ^{13}C NMR spectrum of **3k**

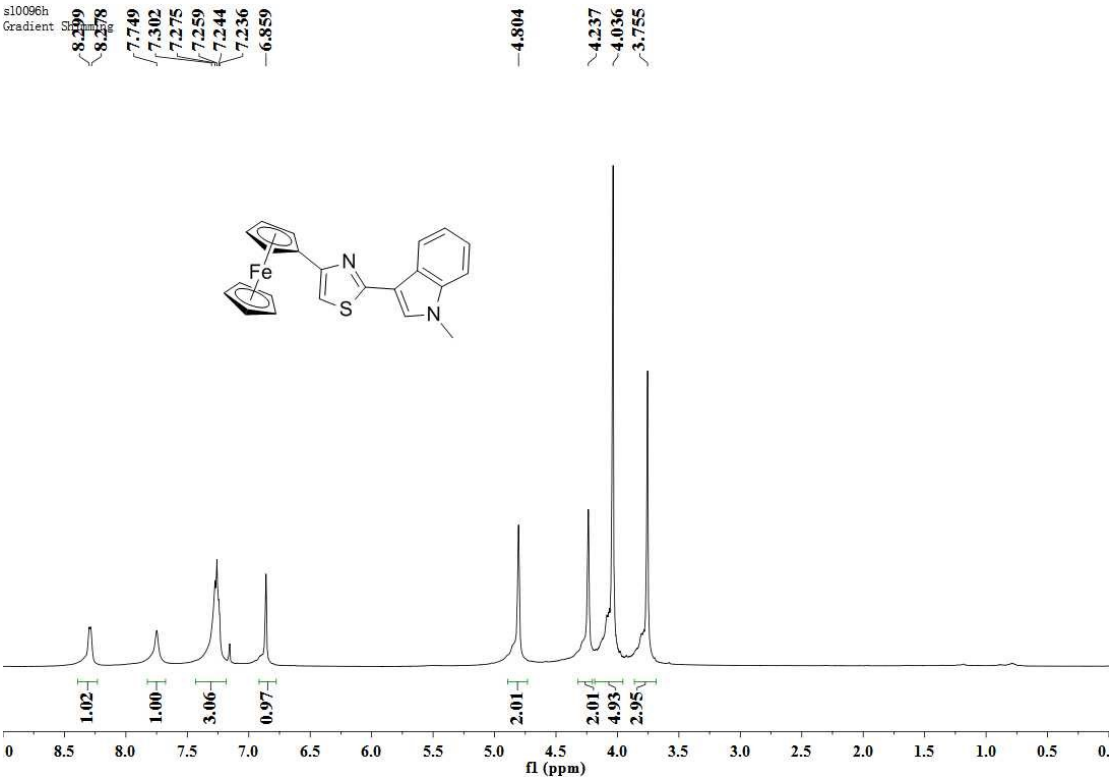


Fig. S23 ^{1}H NMR spectrum of **3l**

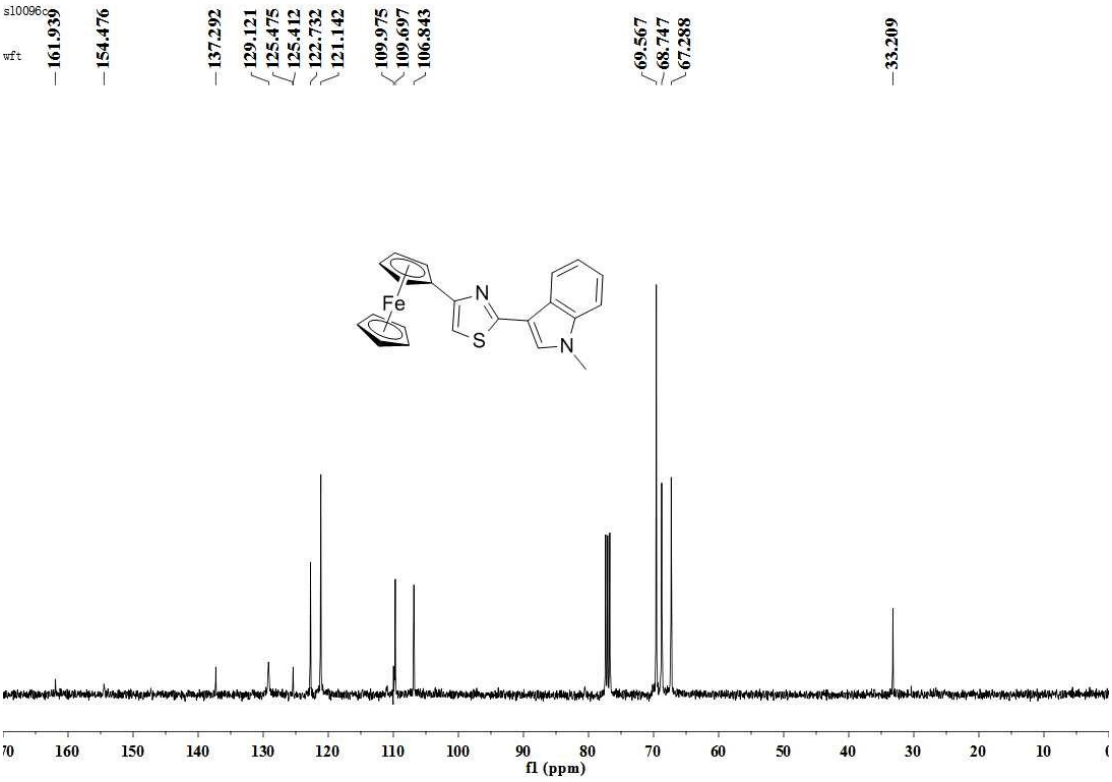


Fig. S24 ^{13}C NMR spectrum of **3l**

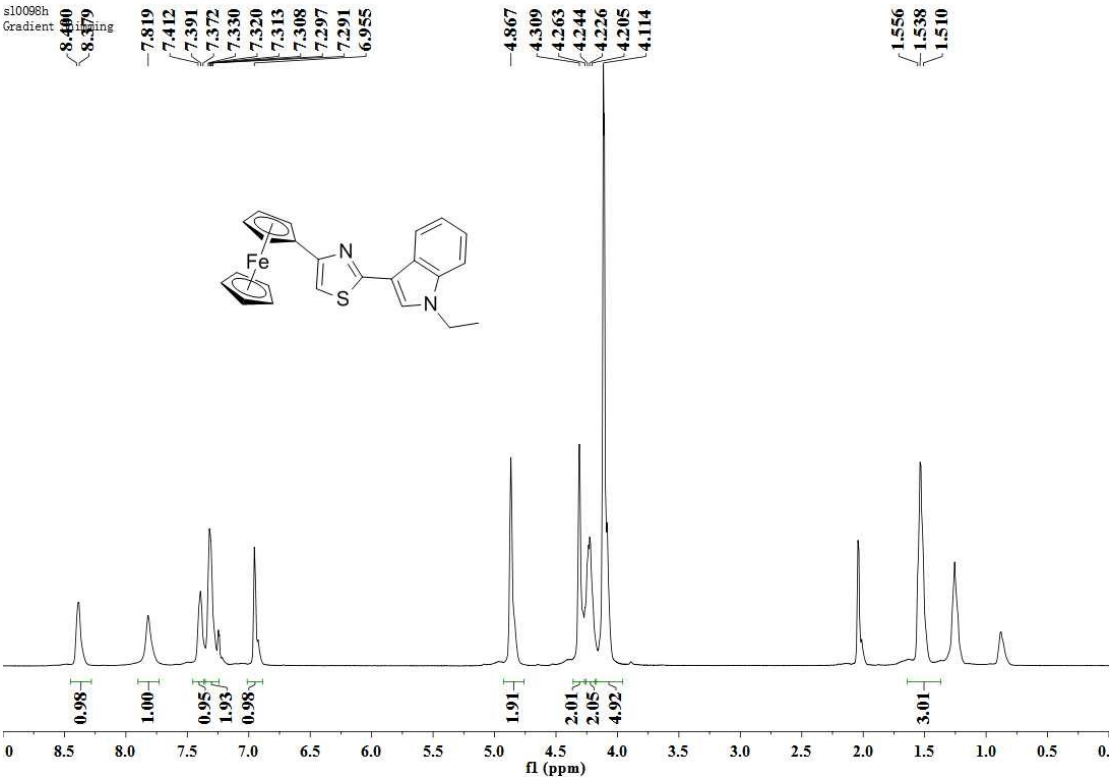


Fig. S25 ^{1}H NMR spectrum of **3m**

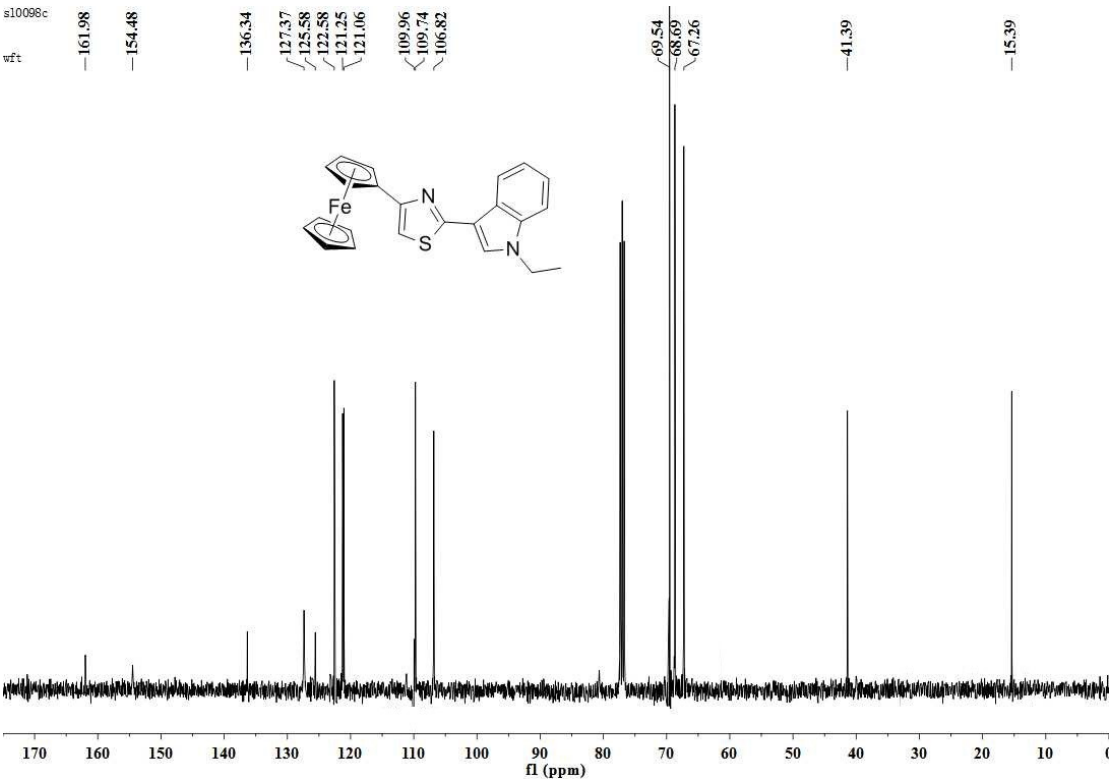


Fig. S26 ^{13}C NMR spectrum of **3m**

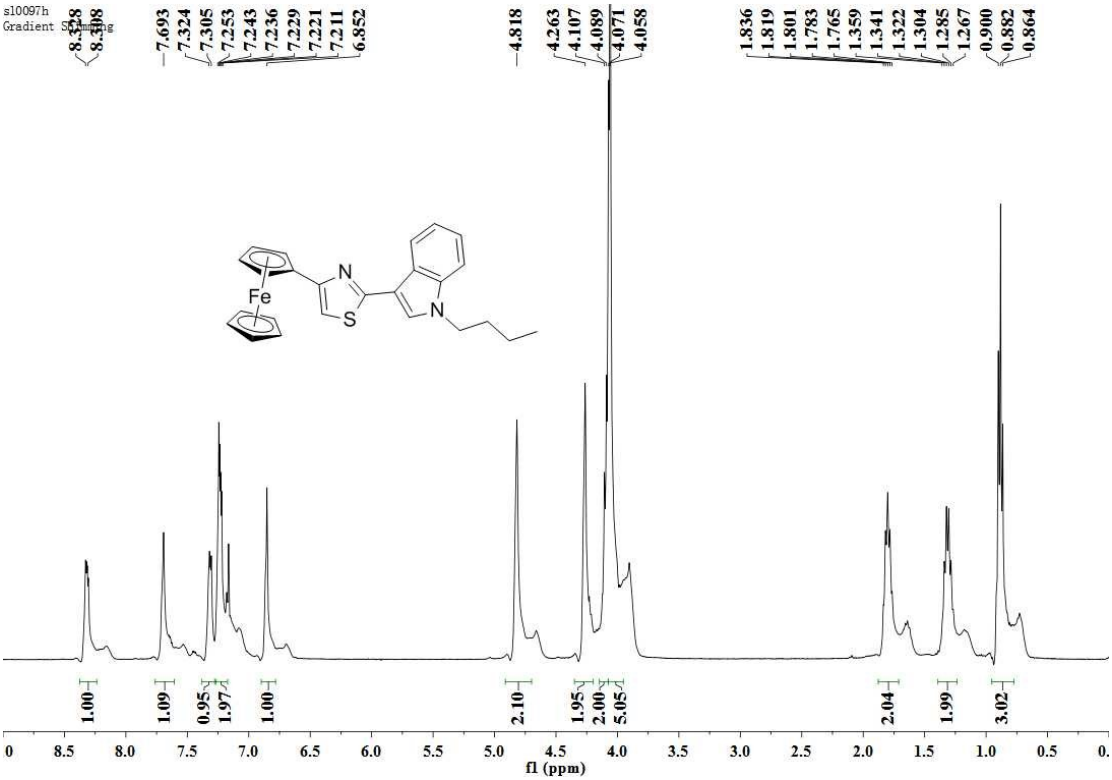


Fig. S27 ^{1}H NMR spectrum of **3n**

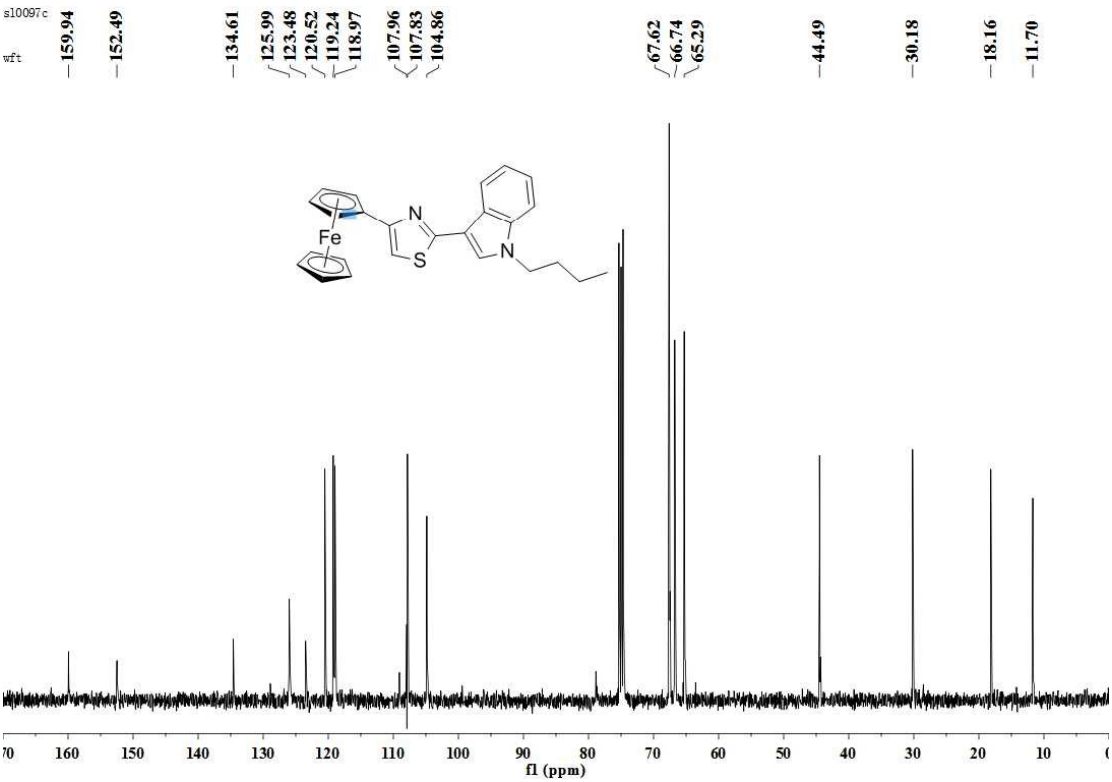


Fig. S28 ^{13}C NMR spectrum of **3n**

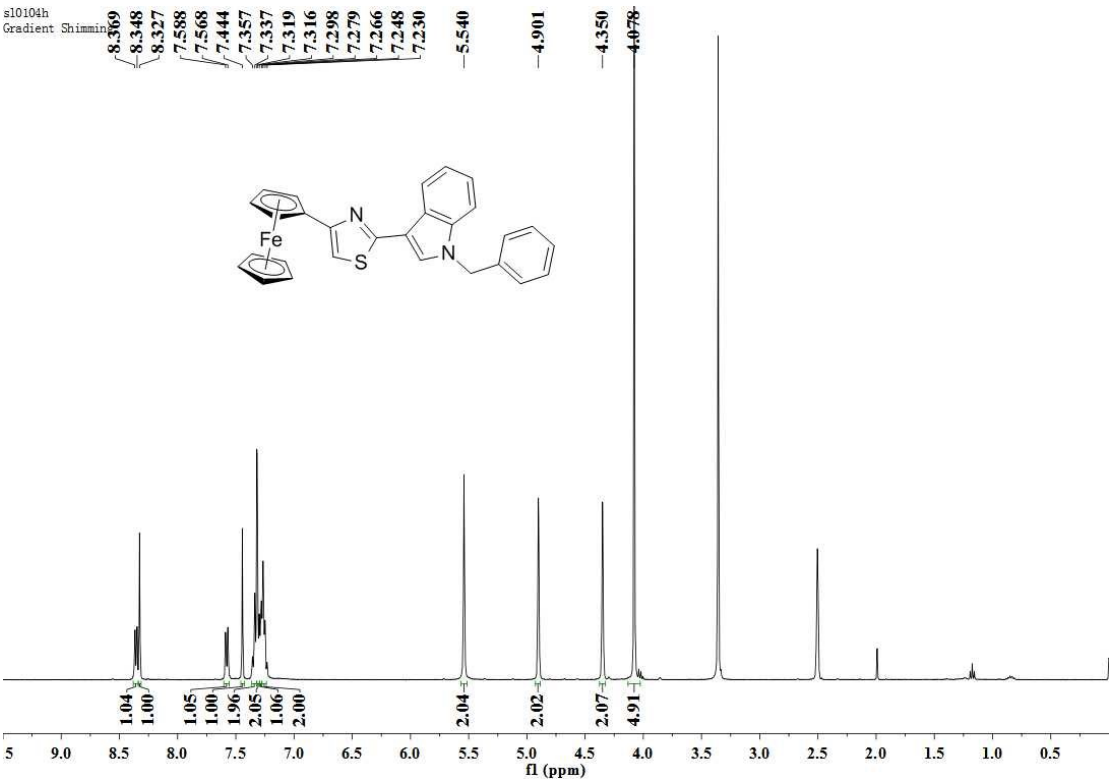


Fig. S29 ^{1}H NMR spectrum of **3o**

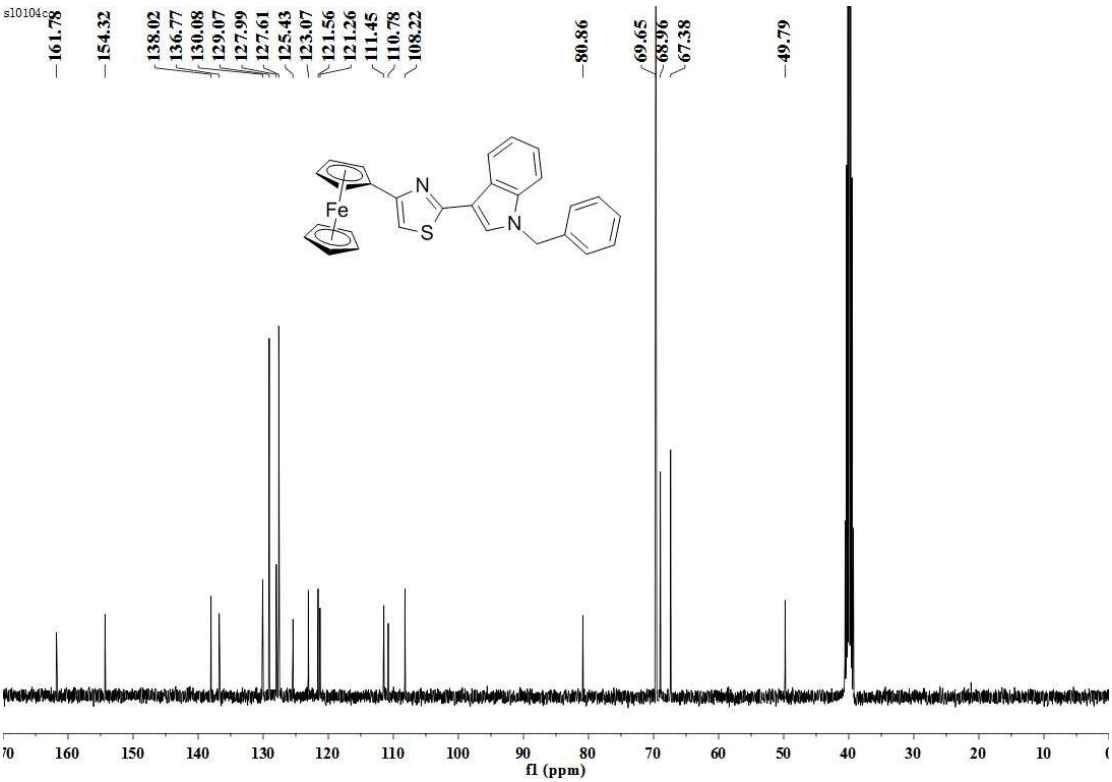


Fig. S30 ^{13}C NMR spectrum of **3o**

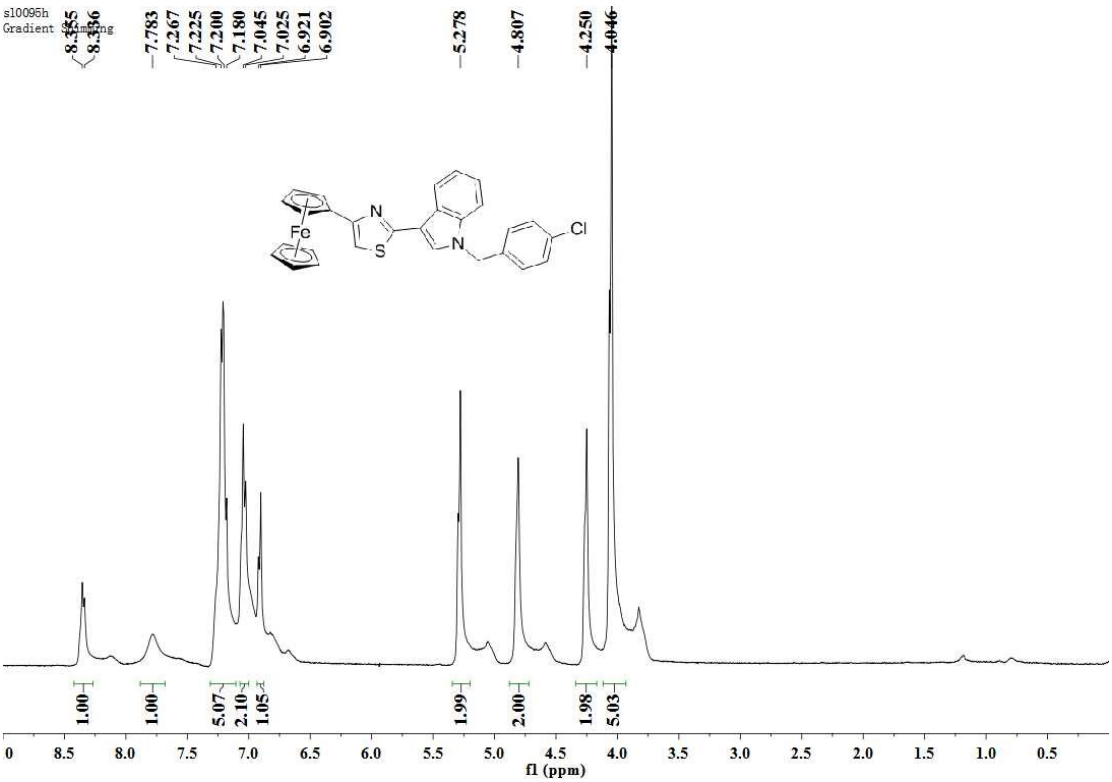


Fig. S31 ^{1}H NMR spectrum of **3p**

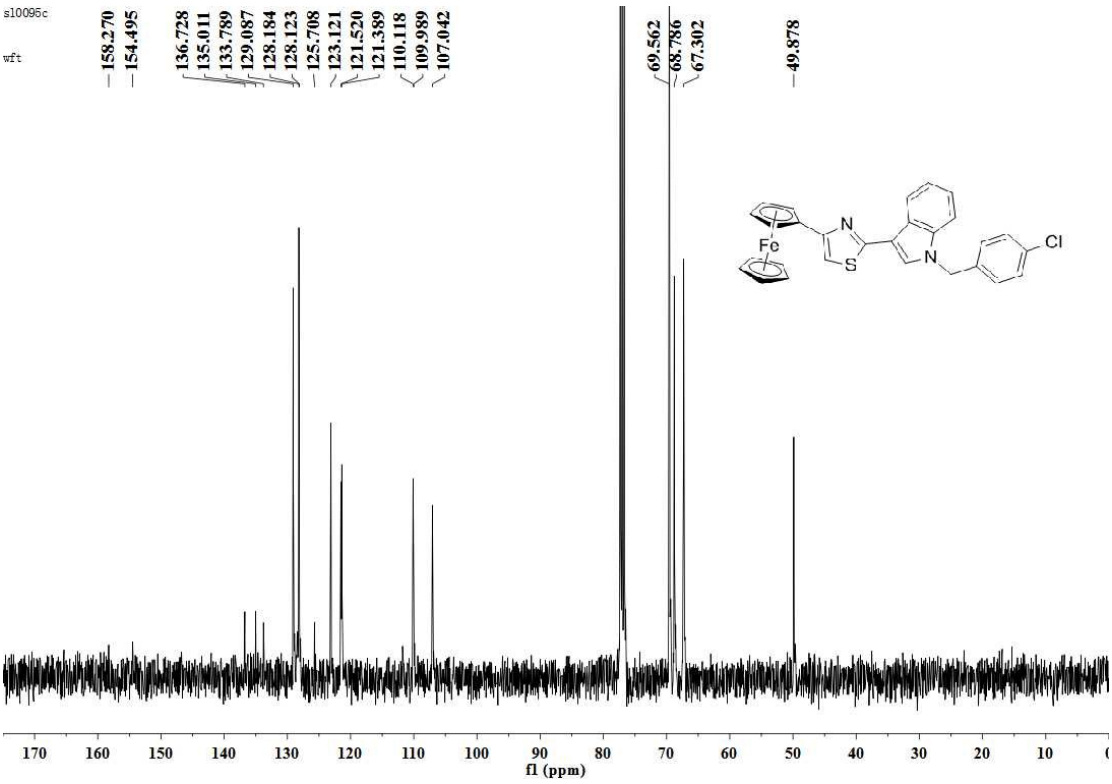


Fig. S32 ^{13}C NMR spectrum of **3p**

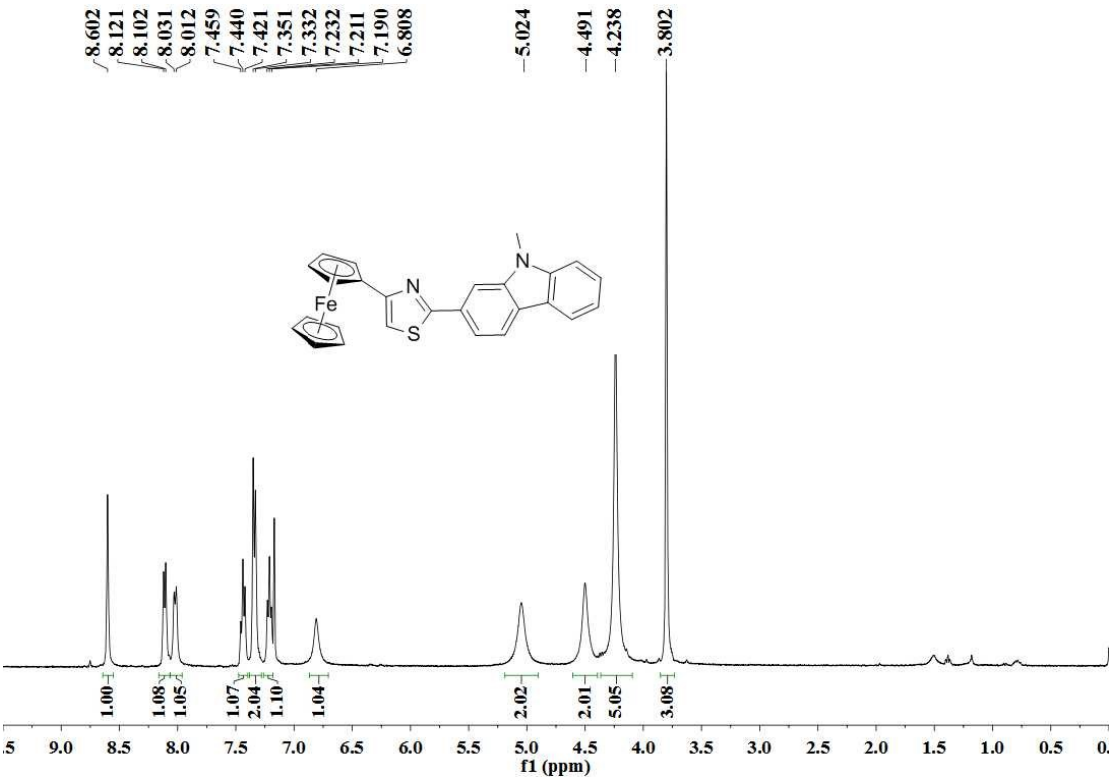


Fig. S33 ^{1}H NMR spectrum of **3q**

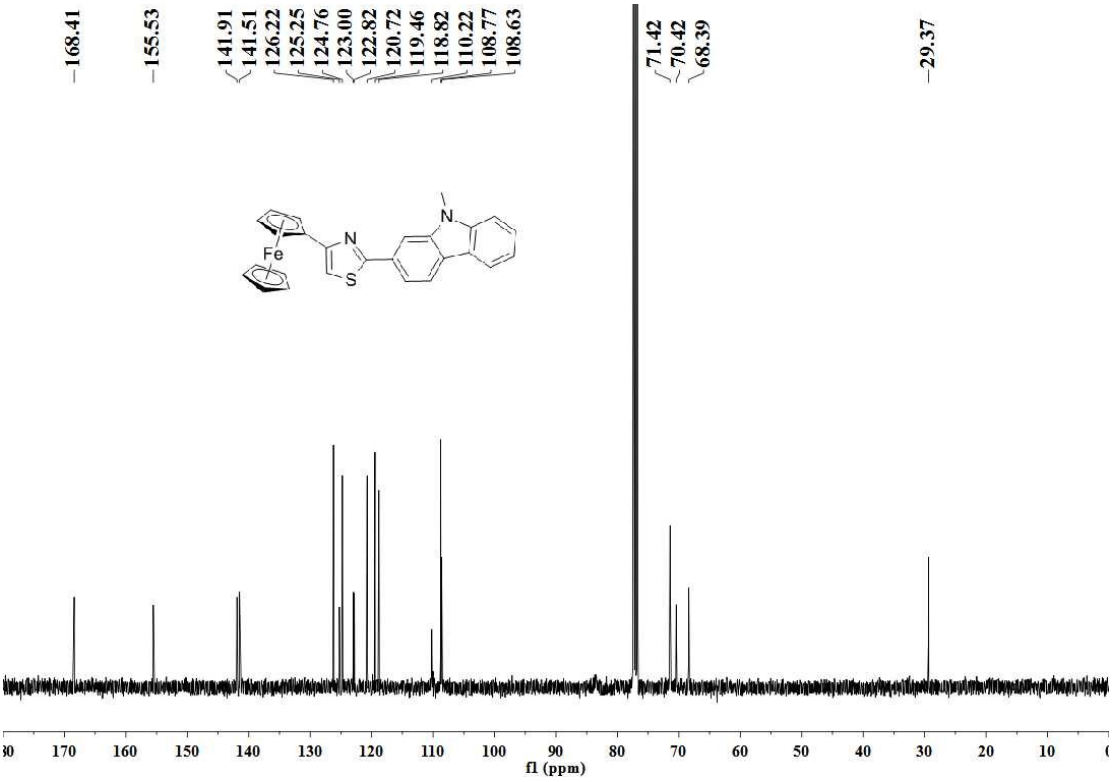


Fig. S34 ^{13}C NMR spectrum of **3q**

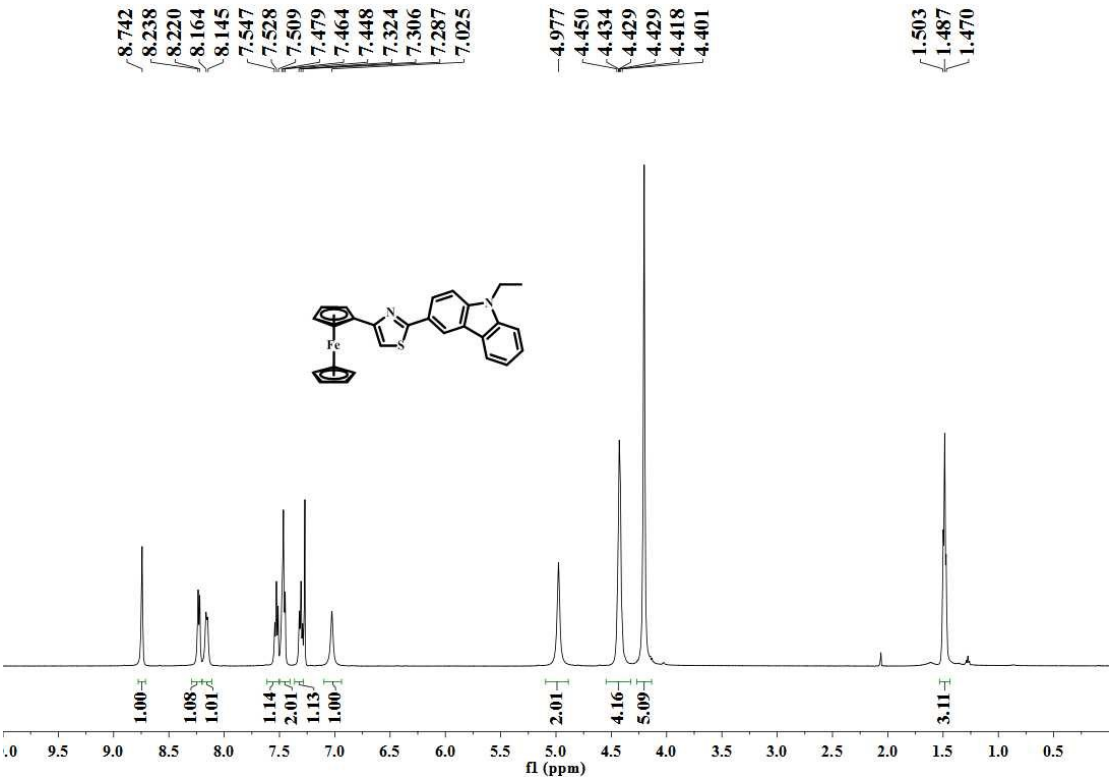


Fig. S35 ^{1}H NMR spectrum of **3r**

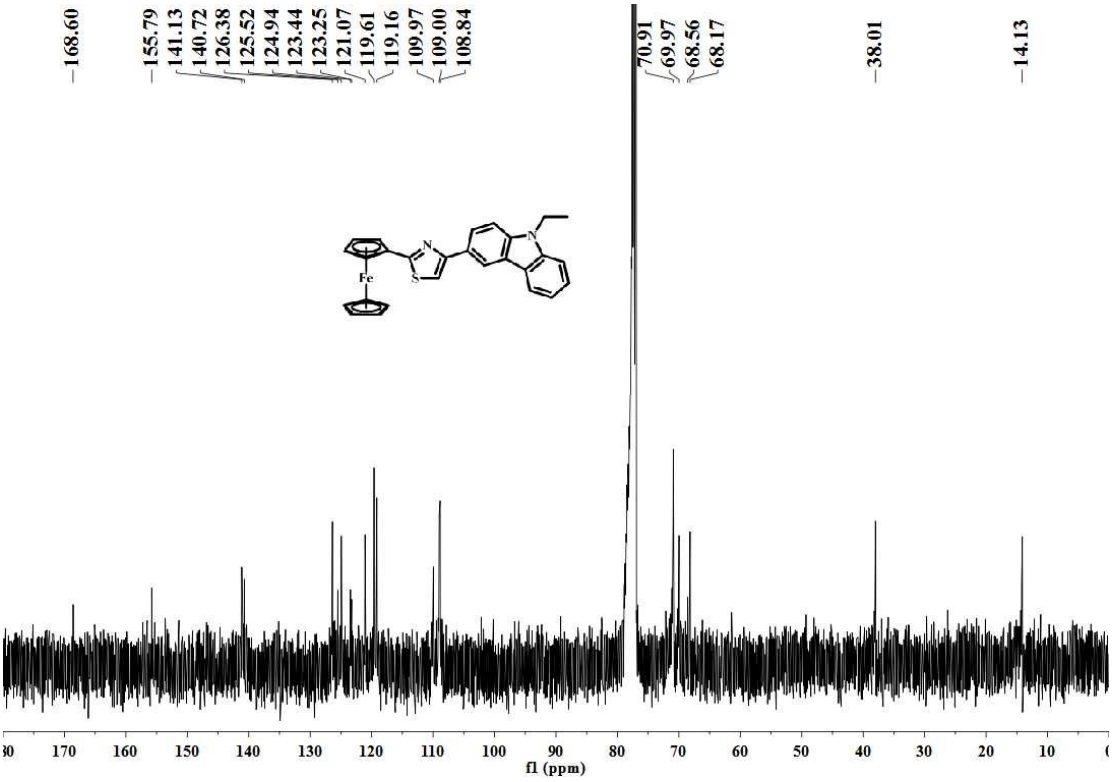


Fig. S36 ^{13}C NMR spectrum of **3r**

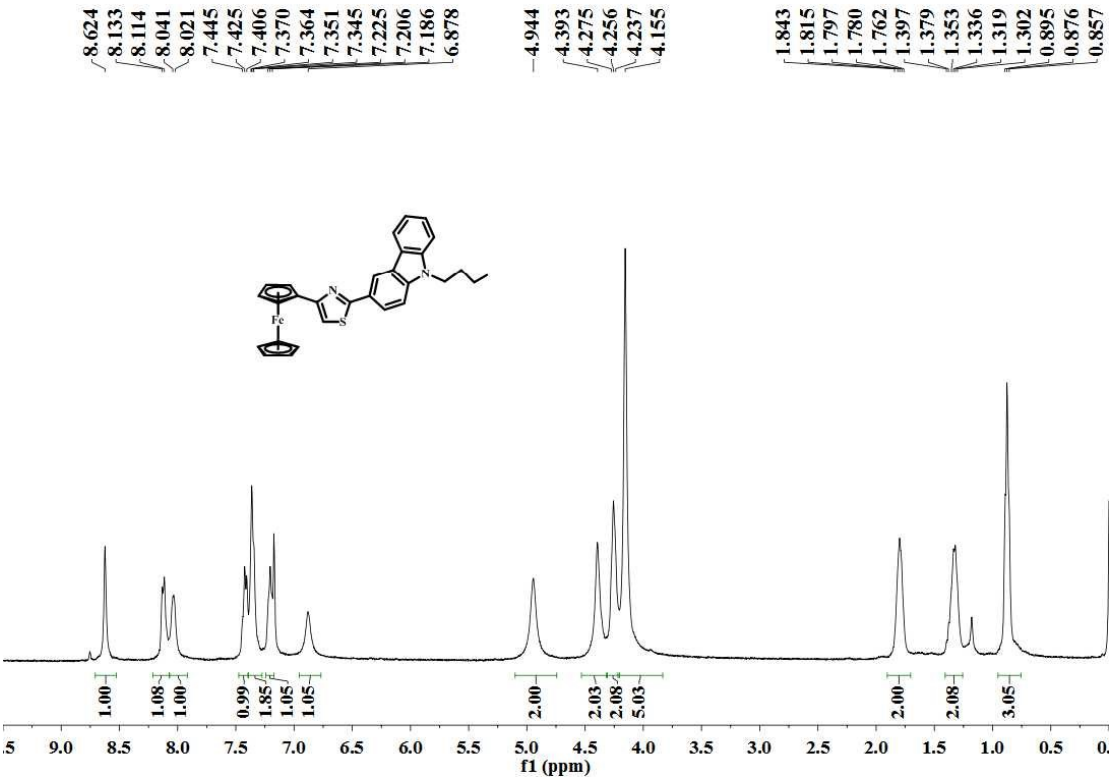


Fig. S37 ^{13}C NMR spectrum of **3s**

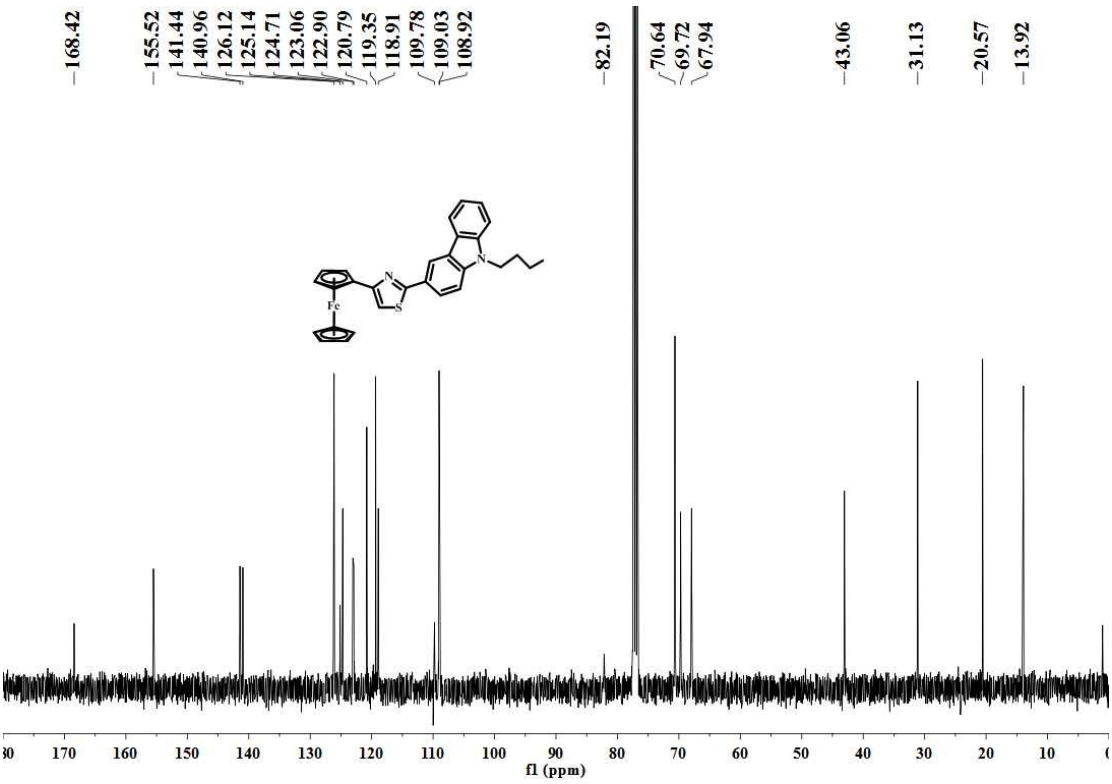


Fig. S38 ^{1}H NMR spectrum of **3s**

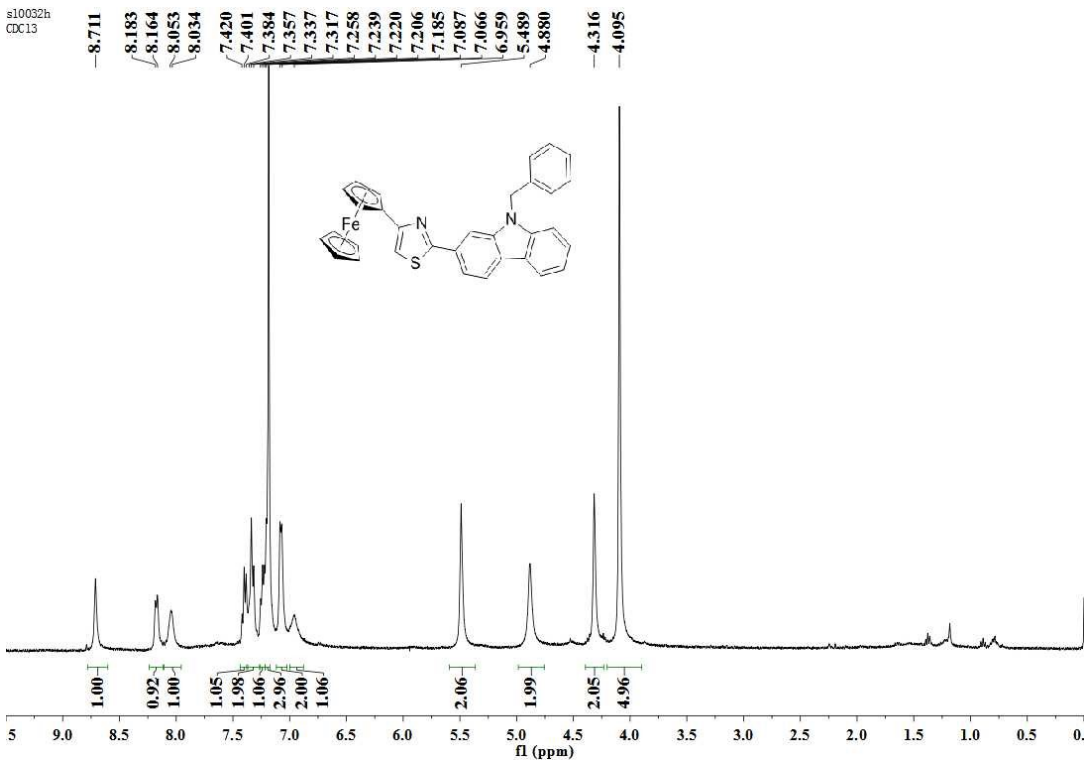


Fig. S39 ^{1}H NMR spectrum of **3t**

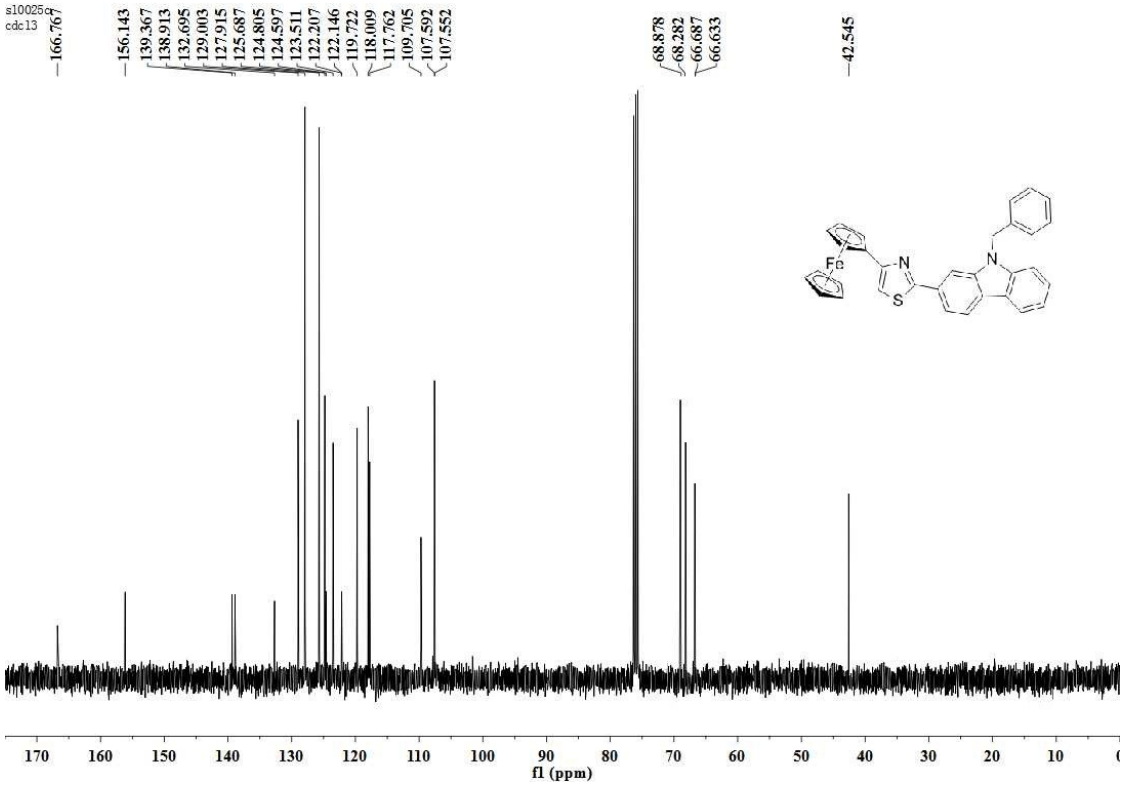


Fig. S40 ^{13}C NMR spectrum of **3t**

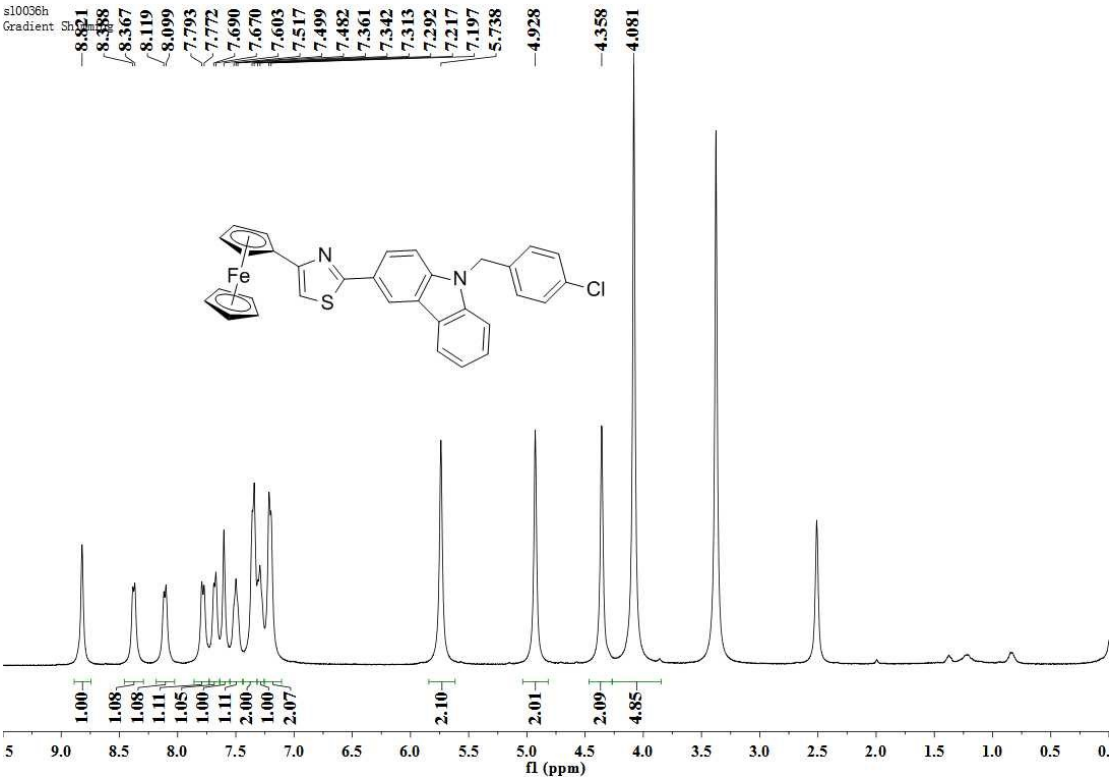


Fig. S41 ^{1}H NMR spectrum of **3u**

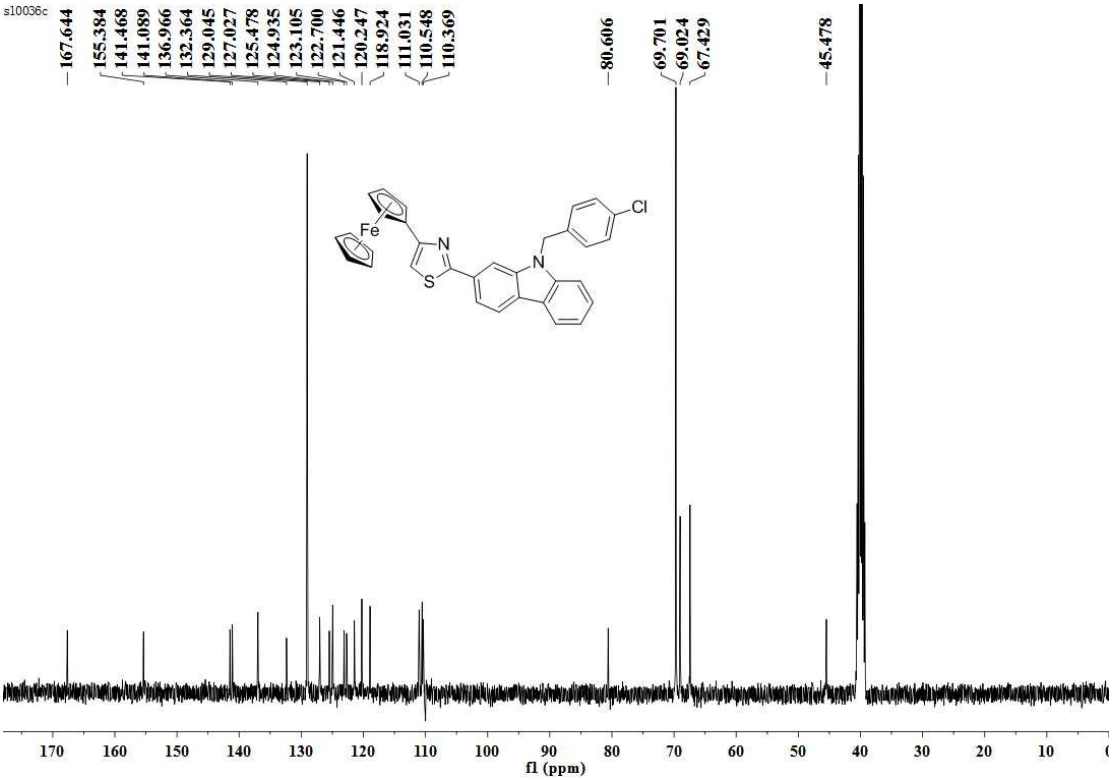


Fig. S42 ^{13}C NMR spectrum of **3u**

7. Antibacterial activity assay

All these newly-synthesized compounds **3a-u** herein were screened for their potential in vitro anti-bacterial activities against *Bacillus subtilis* (*B. subtilis*) [CMCC (B) 63501] , *Staphylococcus aureus* (S. aureus) [CMCC (B) 26003] , *Escherichia coli* (E. coli) [CMCC (B) 44102] and *Pseudomonas aeruginosa* (P. aeruginosa) [CMCC (B) 10104] by the broth microdilution assay. Each of the test compounds was dissolved in DMSO and then was serially diluted in different concentrations at 2-fold dilutions (250, 125, 62.5, 31.25, 15.625, 7.8125 μg/mL) to determine the MICs. Ciprofloxacin was used as the reference standard.

8. References

[1] S. Aki, T. Fujioka, M. Ishigami and J. Minamikawa, Bioorg. Med. Chem. Lett., 2002, **12**, 2317.
[2] S. Perrone, M. Capua, F. Messa, A. Salomone and L. Troisi, *Tetrahedron*, 2017, **73**, 6193.