Electronic Supplementary Material (ESI) for Dalton Transactions.

Supporting Information for

Synthesis, Characterization and Antiparasitic Activity of Organometallic Derivatives of the Anti-helminthic Drug Albendazole

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Materials

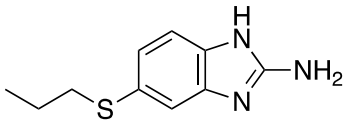
All chemicals were either commercially available or were prepared following standard literature procedures. Solvents were used as received or distilled using standard procedures. All preparations were carried out using standard Schlenk techniques. Albendazole-amine,[1] ruthenocene carboxylic acid,[2] trimethylamoniomethylruthenocene iodide[3] and ferrocenylvinyl) methy-trimethylammonium iodide[4] were synthesized as previously reported.

Instrumentation and methods

^{1}H and ^{13}C NMR spectra were recorded in deuterated solvents on Bruker 400 or 500 MHz spectrometer at room temperature. The chemical shifts, δ, are reported in ppm (parts per million). The residual solvent peaks have been used as internal references. The abbreviations for the peak multiplicities are as follows: s (singlet), d (doublet), t (triplet), m (multiplet). ESI mass spectrometry was performed using a LTQ-Orbitrap XL from Thermo Scientific. Elemental analysis was performed at Science Centre, London Metropolitan University using Thermo Fisher (Carlo Erba) Flash 2000 Elemental Analyser, configured for %CHN. IR spectra were recorded with SpectrumTwo FTIR Spectrometer (Perkin-Elmer) equipped with a Specac Golden GateTM ATR (attenuated total reflection) accessory; applied as neat samples; 1/λ in cm–1. Analytical HPLC measurement was performed using a 1260 Infinity HPLC System (Agilent Technology) comprising: 2 x Agilent G1361 1260 Prep Pump system with Agilent G7115A 1260 DAD WR Detector equipped with an Agilent Pursuit XRs 5C18 (100Å, C18 5 µm 250 x 4.6 mm) Column and an Agilent G1364B 1260-FC fraction collector. The solvents were acetonitrile (HPLC grade) and purified water (Pacific TII). The flow rate was 1 mL/min. Detection was performed at 215nm, 250nm, 350nm, 450nm, 550nm and 650nm with a slit of 4nm.

Synthesis and compound characterization

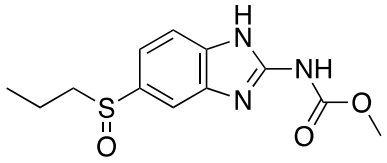
Albendazole-amine **ABZ-NH_2**



ABZ-NH_2

Albendazole-amine was prepared following the procedure reported by Noshita *et al.*[1]The spectroscopy data matched those reported by Noshita *et al.*[1] **^{1}H NMR** (500 MHz, DMSO-d_6) δ 10.69 (s, 1H, NH), 7.14 (dd, *J* = 1.8, 0.6 Hz, 1H, arom), 7.03 (dd, *J* = 8.1, 0.6 Hz, 1H, arom), 6.91 (d, *J* = 8.5 Hz, 1H, arom), 6.22 (s, 2H, NH_2), 2.78 (t, *J* = 7.1, 2H, $CH_3CH_2CH_2S$), 1.54-1.47 (m, *J* = 7.3 Hz, 2H, $CH_3CH_2CH_2S$), 0.93 (t, *J* = 7.3 Hz, 3H, $CH_3CH_2CH_2S$). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 156.5, 124.4, 123.0, 38.0, 22.7, 13.6. Some peaks extrapolated by HMBC. **ESI-MS**: *m/z* (%) = 208.3 ($[M+H]^+$, 100). **Elemental Analysis**: calc. For $C_{10}H_{13}N_3S$ = C, 57.94; H, 6.32; N, 20.27. Found = C, 57.91; H, 6.40; N, 20.22.

Albendazole-sulfoxide **ABZ-Ox** ***(ricobendazole)***

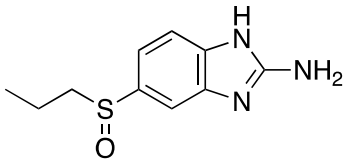


ABZ-Ox

Albendazole sulfoxide was prepared following the procedure reported by Mahler *et al.*[5] The spectroscopy data matched those reported by Mahler *et al.*[5] **^{1}H NMR** (400 MHz, DMSO-d6) δ 12.05 (s, 2H, NH), 7.76 (dd, *J* = 1.7, 0.6 Hz, 1H, arom), 7.59 (dd, *J* = 8.3, 0.6 Hz, 1H, arom), 7.34 (dd, *J* = 8.3, 1.7 Hz, 1H, arom), 3.82 (s, 3H, CH_3), 2.94 – 2.66 (m, 2H, $CH_3CH_2\mathbf{CH_2}$), 1.67-1.54 (m, 1H, $CH_3\mathbf{CH_2}CH_2$), 1.53-1.40 (m, 1H, $CH_3\mathbf{CH_2}CH_2$), 0.94 (t, *J* = 7.4 Hz, 3H, $\mathbf{CH_3}CH_2CH_2$). **^{13}C NMR** (101 MHz, DMSO-d6) δ

154.8, 149.1, 136.7, 117.3, 114.7, 110.5, 58.7, 53.1, 15.9, 13.4. **ESI-MS**: m/z calcd. for $C_{12}H_{16}N_3O_3S^+$, $[M+H]^+$ 282.0907, found 282.0908.

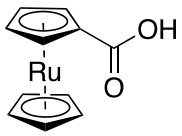
5-(propylsulfinyl)-1H-benzo[d]imidazol-2-amine **ABZ-NH_2-Ox (Ricobendazole amine)**



ABZ-NH_2-Ox

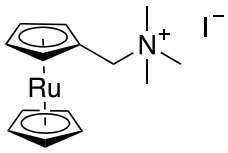
To a 25 mL round-bottom flask with a magnetic stir bar were added albendazole sulfoxide (1.4 g, 5 mmol) and diethylenetriamine (2.2 mL, 20 mmol) under air, and the RBF was sealed with rubber plug. The mixture was stirred at 130 °C overnight. The crude mixture was directly purified by column chromatography on silica with DCM: MeOH (20:1 → 10:1) as the eluent (Rf = 0.32, DCM: MeOH (10:1)) to afford compound **ABZ-NH_2-Ox** as a white powder. Yield: 40% (0.45 g, 2 mmol). **^{1}H NMR** (400 MHz, DMSO-d6) δ 7.39 (d, *J* = 1.7 Hz, 1H, arom), 7.24 (d, *J* = 8.1 Hz, 1H, arom), 7.13 (dd, *J* = 8.1, 1.7 Hz, 1H, arom), 6.50 (s, 2H, NH_2), 2.83 – 2.64 (m, 2H, CH_3CH_2**CH_2**), 1.67 – 1.36 (m, 2H, CH_3**CH_2**CH_2), 0.94 (t, *J* = 7.4 Hz, 3H, **CH_3**CH_2CH_2). **^{13}C NMR** (101 MHz, DMSO-d6) δ 156.8, 141.3, 139.0, 133.6, 115.4, 111.7, 107.2, 58.3, 15.6, 13.0. **ESI-MS**: m/z calcd. for $C_{10}H_{14}N_3OS^+$, $[M+H]^+$ 224.0852, found 224.0849.

Ruthenocene carboxylic acid



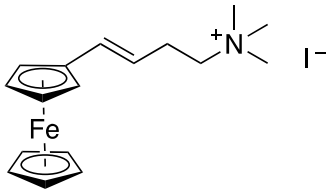
Ruthenocene carboxylic acid was prepared following the procedure reported by Peters *et al.*[2] The spectroscopy data matched those reported by Peters *et al.*[2] **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 5.11 – 5.08 (m, 2H, C_5H_4), 4.70 – 4.66 (m, 2H, C_5H_4), 4.56 (s, 5H, C_5H_5).

(Ruthenocyl)trimethylammonium iodide



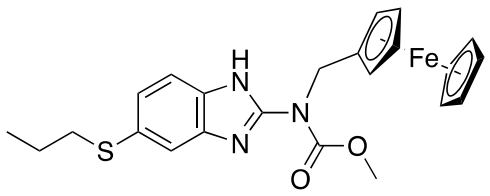
(Ruthenocyl)trimethylammonium iodide was prepared following the procedure reported by Hess *et al.*[3] The spectroscopy data matched those reported by Hess *et al.*[3] **^{1}H NMR** (400 MHz, Chloroform-d) δ 4.91 (t, *J* = 1.7 Hz, 2H), 4.71 – 4.70 (m, 2H), 4.67 (m, 5H), 4.56 (s, 2H), 3.38 (s, 9H).

[(2-Ferrocenylvinyl)methyl]trimethylammonium iodide

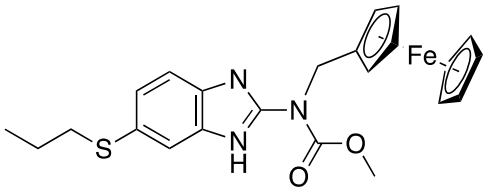


[(2-Ferrocenylvinyl)methyl]trimethylammonium iodide was kindly given by Eric Manoury. The spectroscopy data matched those report by Bouchene *et al.*[6] **^{1}H NMR** (400 MHz, DMSO-d6) δ 6.68 (d, *J* = 15.4 Hz, 1H, **CH**CHCH$_2$), 5.98 (dt, *J* = 15.4, 7.6 Hz, 1H, CH**CH**CH$_2$), 4.59 (t, *J* = 1.9 Hz, 2H, C_4H_4), 4.36 (t, *J* = 1.8 Hz, 2H, C_4H_4), 4.17 (s, 5H, C_4H_5), 3.95 (d, *J* = 7.5 Hz, 2H, CHCH**CH$_2$**), 3.04 (s, 9H, N(**CH$_3$**)$_3^+$).

Methyl ferrocenylmethyl(5-(propylthio)-1H-benzo[d]imidazol-2-yl)carbamate 1a



1a

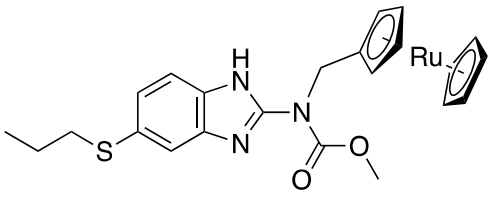


1a'

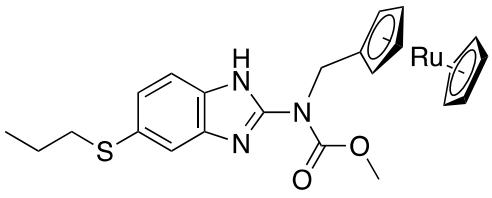
Albendazole (0.26 g, 1.0 mmol), (Ferrocenylmethyl)-trimethylammonium iodide (0.385 g, 1.0 mmol) and K_2CO_3 (0.27 g, 2.0 mmol) were dissolved in dry acetonitrile (50 mL). The orange reaction mixture was refluxed overnight. After 22 h the reaction was allowed to cool to room temperature and filtered through a cotton plug. The solvent was evaporated and the crude product was purified by

column chromatography on silica with hexane: ethyl acetate (5:1 → 3:1) as the eluent (R_f = 0.26, hexane: ethyl acetate (5:1)) to afford **1a** as a yellow solid. Yield: 20% (0.094g, 0.20 mmol). **IR** (Neat, cm^{-1}): 2960w, 1706m, 1533s, 1451s, 1383w, 1252s, 1210s, 1080m, 800s, 770m. *Note: Because of the equilibrium between isomers **1a** and **1a'** the signals for the NH and most signals in the aromatic region are doubled in both ^1H and ^{13}C spectra.* **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.01 (s, 0.5H, NH),11.95 (s, 0.5H, NH) 7.58 – 7.36 (m, 2H, arom), 7.14 (ddd, *J* = 8.3, 4.6, 1.8 Hz, 1H, arom), 4.99 (s, 2H, NCH_2), 4.33 (d, *J* = 1.9 Hz, 2H, C_5H_4), 4.17 (s, 5H, C_5H_5), 4.08 (t, *J* = 1.8 Hz, 2H, C_5H_4), 3.87 (s, 3H, OCH_3), 2.88 (dt, *J* = 13.1, 7.1 Hz, 2H, CH_2), 1.55 (dq, *J* = 1.3 Hz, 7.2, 2H, CH_2), 0.96 (dt, *J* = 3.6 Hz, 7.3, 3H, CH_3). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 154.3, 148.8, 148.6, 141.8, 140.1, 134.4, 132.9, 127.75, 127.70, 124.6, 119.7, 118.2, 113.6, 112.2, 83.5, 69.9, 68.8, 68.2, 54.1, 46.0, 37.0, 36.9, 22.6, 22.5, 13.6. **ESI-MS**: *m/z* (%) = 462.0 ([M-H]$^-$, 100). **Elemental Analysis**: calc. For $C_{23}H_{25}FeN_3O_2S$ = C, 59.62; H, 5.44; N, 9.07. Found = C, 59.46; H, 5.55; N, 9.13.

Methyl ruthenocenylmethyl(5-(propylthio)-1H-benzo[d]imidazol-2-yl)carbamate 1b



1b

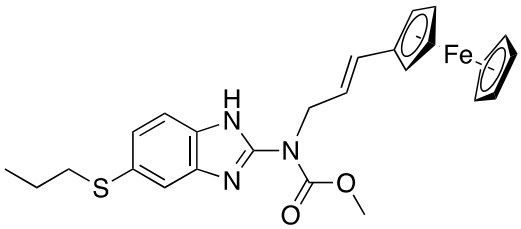


1b'

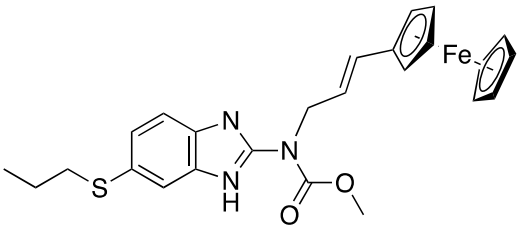
Albendazole (0.18 g, 0.68 mmol), Trimethylammoniomethylruthenocene iodide (0.26 g, 0.62 mmol) and K_2CO_3 (0.17 g, 1.24 mmol) were dissolved in dry acetonitrile (30 mL). The reaction mixture was refluxed overnight. After 22 h the reaction was allowed to cool to room temperature and filtered through a cotton plug. The solvent was evaporated and the crude product was purified by column chromatography on silica with hexane: ethyl acetate (5:1) as the eluent (R_f = 0.40, hexane: ethyl

acetate (3:1)) to afford **1b** as a white solid. Yield: 41% (0.13 g, 0.25 mmol). **IR** (Neat, cm^{-1}): 3399w, 2921w, 1691s, 1621m, 1529s, 1451s, 1380s, 1273s, 1227s, 1203s, 1116s, 1081s, 806s, 770s. *Note: Because of the equilibrium between isomers **1b** and **1b'** the signals for most signals in the aromatic region are doubled in both ^{1}H and ^{13}C spectra.* **^{1}H NMR** (400 MHz, Methylene Chloride-d_2) δ 10.80 (s, 1H, NH), 7.61 – 7.35 (m, 1H, arom), 7.35 – 7.06 (m, 2H, arom), 4.88 – 4.73 (m, 4H, C_5H_4), 4.45 (s, 5H, C_5H_5), 4.39 – 4.26 (m, 2H, CH_2), 3.84 (s, 3H, OCH_3), 2.79 (dt, *J* = 9.2, 7.2 Hz, 2H, CH_2), 1.55 (dq, *J* = 14.6, 7.6 Hz, 2H, CH_2), 0.91 (q, *J* = 7.0 Hz, 3H, CH_3). **^{13}C NMR** (101 MHz, Methylene Chloride-d_2) δ 155.3, 149.3, 149.1, 141.7, 140.1, 133.0, 131.5, 128.7, 128.5, 125.3, 124.9, 120.4, 117.9, 112.9, 110.5, 86.9, 72.5, 70.6, 70.0, 44.8, 37.8, 37.7, 22.7, 22.7, 13.1.**ESI-MS**: *m/z* (%) = 508.6 ([M-H]$^-$, 100). **Elemental Analysis**: calc. For $C_{23}H_{25}N_3O_2RuS$ = C, 54.32; H, 4.95; N, 8.26. Found = C, 54.62; H, 4.74; N, 8.15.

Methyl (2-Ferrocenylvinyl)-methyl-(5-(propylthio)-1H-benzo[d]imidazol-2-yl)carbamate 1c



1c

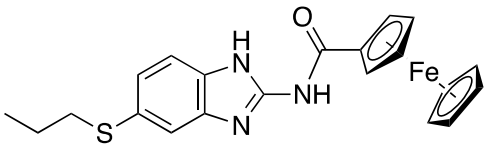


1c'

Albendazole (0.39 g, 1.5 mmol), (2-Ferrocenylvinyl)methyl-trimethylammonium iodide (0.62 g, 1.5 mmol) and K_2CO_3 (0.41 g, 3.0 mmol) were dissolved in dry acetonitrile (50 mL). The orange reaction mixture was refluxed overnight. After 22 h the reaction was allowed to cool to room temperature and filtered through a cotton plug. The solvent was evaporated and the crude product was purified by column chromatography on silica with hexane: ethyl acetate (5:1) as the eluent (R_f = 0.4, hexane: ethyl acetate (3:1)) to afford **1c** as an orange solid. Yield: 10% (0.072g, 0.15 mmol). **IR** (Neat, cm^{-1}):

3404m, 2959w, 1688s, 1622m, 1532s, 1457s, 1382s, 1241s, 1131m, 1043w, 955m, 802s, 762m. *Note: Because of the equilibrium between isomers **1c** and **1c'** the signals for the NH and most signals in the aromatic region are doubled in both ^{1}H and ^{13}C spectra.* **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.12 (S, 0.5H, NH), 12.06 (S, 0.5H, NH), 7.55 – 7.48 (m, 1H, arom), 7.43 (t, *J* = 7.6 Hz, 1H, arom), 7.14 (dt, *J* = 8.3, 2.1 Hz, 1H, arom), 6.30 (d, *J* = 15.7 Hz, 1H, CH), 5.88 (dt, *J* = 15.8, 6.0 Hz, 1H, CH), 4.69 – 4.62 (m, 2H, C_5H_4), 4.38 (t, *J* = 1.9 Hz, 2H, C_5H_4), 4.18 (t, *J* = 1.9 Hz, 2H, CH_2), 3.98 (s, 5H, C_5H_5), 3.88 (s, 3H, OCH_3), 2.85 (dt, *J* = 7.2, 1.9 Hz, 2H, CH_2), 1.51 (dq, *J* = 12.8, 7.2 Hz, 2H, CH_2), 0.93 (dt, *J* = 9.9, 7.3 Hz, 3H, CH_3). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 154.4, 148.8, 148.6, 141.9, 140.2, 134.5, 132.9, 130.5, 127.7, 127.6, 124.8, 124.7, 121.2, 119.9, 118.2, 113.8, 112.2, 82.4, 69.3, 69.0, 67.1, 54.2, 49.0, 37.0, 22.5, 13.5. **ESI-MS**: *m/z* (%) = 488.3 ([M-H]$^-$, 100). **Elemental Analysis**: calc. For $C_{25}H_{27}FeN_3O_2S$ = C, 61.35; H, 5.56; N, 8.59. Found = C, 61.41; H, 5.62; N, 8.62.

N-(5-(propylthio)-1H-benzo[d]imidazol-2-yl)ferrocenamide 2a

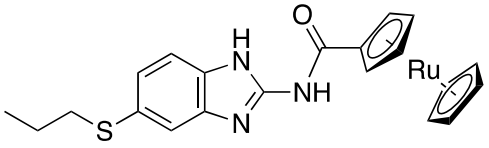


2a

In a round bottom flask, ferrocenecarboxylic acid (0.60 g, 2.6 mmol) was dissolved in 15 mL of dry DMF. To this, TBTU (0.83 g, 2.6 mmol) and N,N-Diisopropylethylamine (0.98 mL, 6.0mmol) were added and stirred for 30 min at room temperature under nitrogen atmosphere. After 30min, the solution of ABZ-NH_2 (0.41 g, 2 mmol) in 10 mL of dry DMF was added to the mixture. Then the reaction stirred at room temperature for 12h. As it finished, the crude materials were extracted with chloroform and washed with brine solution. Organic layer was separated and dried over anhydrous sodium sulfate. The crude product was purified by column chromatography on silica with

dichloromethane: ethyl acetate (5:1) as the eluent (R_f = 0.27, hexane: ethyl acetate (1:1)). Then evaporation of solvent and appropriate recrystallization in ethyl acetate to afford **2a** as an orange solid. Yield: 18% (0.150g, 0.36 mmol). **IR** (Neat, cm^{-1}): 3287w, 1645s, 1626m, 1551s, 1509m, 1453m, 1274s, 1141m, 1009m, 827s, 755m. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.19 (s, 1H, NH), 11.35 (s, 1H, NH), 7.72 – 7.26 (m, 2H, arom), 7.15 (dd, *J* = 8.3, 1.8 Hz, 1H, arom), 5.18 (t, *J* = 1.9 Hz, 2H, C_5H_4), 4.60 – 4.49 (m, 2H, C_5H_4), 4.24 (s, 5H, C_5H_5), 2.87 (t, *J* = 7.1 Hz, 2H, CH_2), 1.56 (q, *J* = 7.2 Hz, 2H, CH_2), 0.96 (t, *J* = 7.3 Hz, 3H, CH_3). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 170.2, 148.2, 127.2, 124.7, 74.6, 71.9, 70.2, 69.6, 37.2, 22.6, 13.6. **ESI-MS**: *m/z* (%) = 420.3 ($[M+H]^+$, 100). **Elemental Analysis**: calc. For $C_{21}H_{21}FeN_3OS$ = C, 60.15; H, 5.05; N, 10.02. Found = C, 60.09; H, 4.96; N, 9.94.

N-(5-(propylthio)-1H-benzo[d]imidazol-2-yl)ruthenocenamide 2b

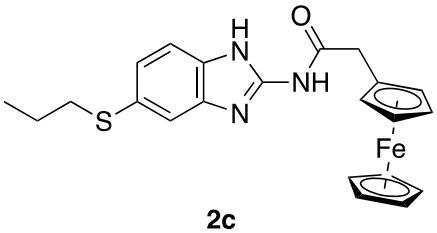


2b

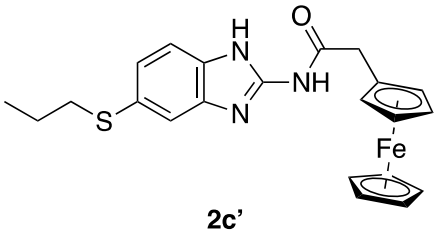
In a round bottom flask, Ruthenocenecarboxylic acid (0.72 g, 2.6 mmol) was dissolved in 20 mL of dry DMF. To this, TBTU (0.83 g, 2.6 mmol) and N,N-Diisopropylethylamine (0.98 ml, 6.0mmol) were added and stirred for 30 min at room temperature under nitrogen atmosphere. After 30 min, the solution of ABZ-NH_2 (0.41 g, 2 mmol) in 10 mL of dry DMF was added to the mixture. Then the reaction stirred at room temperature for 12 h. As it finished, the crude materials were extracted with chloroform and washed with brine solution. Organic layer was separated and dried over anhydrous sodium sulfate. The crude product was purified by column chromatography on silica with dichloromethane: ethyl acetate (3:1) as the eluent (R_f = 0.34, hexane: ethyl acetate (1:1)) to afford **2b** as an yellow solid. Yield: 16% (0.15g, 0.32 mmol). **IR** (Neat, cm^{-1}): 3298w, 2926w, 1648s, 1627s,

1553s, 1511m, 1454s, 1409m, 1376w, 1274s, 1228m, 1130s, 1101s, 817s, 752s, 687s. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.11 (s, 1H, NH), 11.24 (s, 1H, NH), 7.60 – 7.30 (m, 2H, arom), 7.24 – 7.07 (m, 1H, arom), 5.51 (s, 2H, C_5H_4), 4.83 (s, 2H, C_5H_4), 4.62 (s, 5H, C_5H_5), 2.86 (t, *J* = 7.0 Hz, 2H, CH_2), 1.54 (q, *J* = 6.9 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 168.6, 148.1, 127.3, 124.7, 79.2, 73.5, 72.3, 71.3, 37.2, 22.6, 13.6. **ESI-MS**: *m/z* (%) = 466.3 ($[M+H]^+$, 100). **Elemental Analysis**: calc. For $C_{21}H_{21}N_3ORuS$ = C, 54.30; H, 4.56; N, 9.05. Found = C, 54.29; H, 4.56; N, 8.98.

2-Ferrocenyl-N-(5-(propylthio)-1H-benzo[d]imidazol-2-yl)acetamide 2c



2c

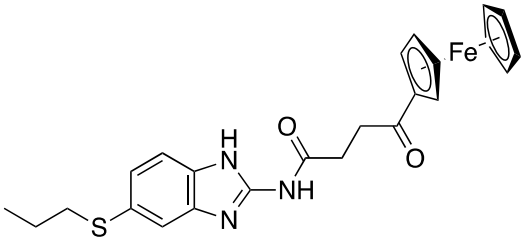


2c'

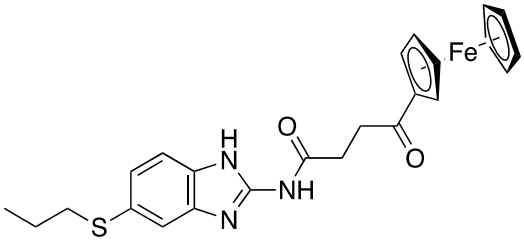
In a round bottom flask, ferrocenacetic acid (0.63 g, 2.6 mmol) was dissolved in 15 mL of dry DMF. To this, TBTU (0.83 g, 2.6 mmol) and N,N-Diisopropylethylamine (0.98 ml, 6.0mmol) were added and stirred for 30 min at room temperature under nitrogen atmosphere. After 30min, the solution of ABZ-NH_2 (0.41 g, 2 mmol) in 10 mL of dry DMF was added to the mixture. Then the reaction stirred at room temperature for 12h. As it finished, the crude materials were extracted with chloroform and washed with brine solution. Organic layer was separated and dried over anhydrous sodium sulfate. The crude product was purified by column chromatography on silica with dichloromethane: ethyl acetate (5:1) as the eluent (R_f = 0.34, hexane: ethyl acetate (2:1)). Then evaporation of solvent and recrystallization in ethyl acetate afforded **2c** as a pale brown solid. Yield: 22% (0.20g, 0.45 mmol). **IR** (Neat, cm^{-1}): 3333w, 2957w, 1686s, 1637s, 1587s, 1517m, 1457m, 1422m, 1363w, 1260m, 1216m, 1106s, 1032s, 805s, 760m, 684s. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.02 (bs, 1H, NH), 11.57 (s, 1H,

NH), 7.61 – 7.22 (m, 2H, arom), 7.05 (d, *J* = 8.2 Hz, 1H, arom), 4.21 (s, 2H, C_5H_4), 4.07 (s, 5H, C_5H_5), 4.05 (s, 2H, C_5H_4), 3.38 (s, 2H, CH_2), 2.78 (t, *J* = 7.1 Hz, 2H, CH_2), 1.47 (q, *J* = 7.2 Hz, 2H, CH_2), 0.88 (t, *J* = 7.3 Hz, 3H, CH_3). *Note: Because of the equilibrium between isomers **2c** and **2c'** the signals for most signals in the aromatic region are doubled in the ^{13}C spectrum.* **^{13}C NMR** (101 MHz, DMSO-d_6) δ 170.5, 147.5, 141.7, 140.2, 133.7, 127.6, 124.7, 119.5, 117.8, 114.1, 112.5, 82.0, 69.1, 69.0, 67.9, 37.1, 36.9, 22.6, 13.5. **ESI-MS**: *m/z* (%) = 434.3 ([M+H]$^+$, 100). **Elemental Analysis**: calc. For $C_{22}H_{23}FeN_3OS$ = C, 60.98; H, 5.35; N, 9.70. Found = C, 60.87; H, 5.38; N, 9.59.

4-Oxo-4-ferrocenyl-N-(5-(propylthio)-1H-benzo[d]imidazol-2-yl)butanamide 2d



2d

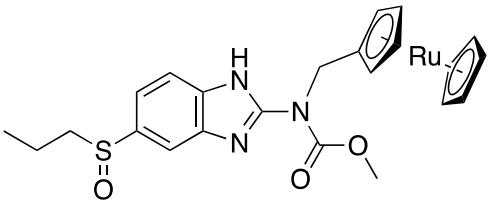


2d'

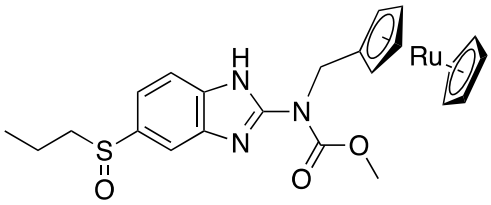
In a round bottom flask, 3-Ferrocenoylpropionic acid (0.74 g, 2.6 mmol) was dissolved in 20 mL of dry DMF. To this, TBTU (0.83 g, 2.6 mmol) and N,N-Diisopropylethylamine (0.98 ml, 6.0mmol) were added and stirred for 30 min at room temperature under nitrogen atmosphere. After 30min, the solution of ABZ-NH_2 (0.41 g, 2 mmol) in 10 mL of dry DMF was added to the mixture. Then the reaction stirred at room temperature for 12h. As it finished, the crude materials were extracted with chloroform and washed with brine solution. Organic layer was separated and dried over anhydrous sodium sulfate. The crude product was purified by column chromatography on silica with dichloromethane: ethyl acetate (5:1→2:1) as the eluent (R_f = 0.16, hexane: ethyl acetate (1:1)). Then evaporation of solvent and recrystallization in ethyl acetate afforded **2d** as an orange solid. Yield: 28% (0.27g, 0.56 mmol). **IR** (Neat, cm^{-1}): 3316w, 2917w, 1662s, 1636s, 1580s, 1518m, 1455s, 1413m, 1353w, 1260m, 1201m, 1166s, 1040s, 817s, 746m, 675s. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.00 (s,

1H, NH), 11.64 (s, 1H, NH), 7.60 – 7.29 (m, 2H, arom), 7.12 (d, *J* = 8.2 Hz, 1H, arom), 4.84 (s, 2H, C_5H_4), 4.57 (s, 2H, C_5H_4), 4.31 (s, 5H, C_5H_5), 3.17 (t, *J* = 6.2 Hz, 2H, CH_2), 2.86 (t, *J* = 7.0 Hz, 2H, CH_2), 2.77 (t, *J* = 6.3 Hz, 2H, CH_2), 1.54 (q, *J* = 7.2 Hz, 2H, CH_2), 0.95 (t, *J* = 7.2 Hz, 3H, CH_3). *Note: Because of the equilibrium between isomers **2d** and **2d'** the signals for most signals in the aromatic region are doubled in the ^{13}C spectrum.* **^{13}C NMR** (126 MHz, DMSO-d_6) δ 201.9, 172.0, 147.2, 141.3, 139.7, 133.1, 131.6, 127.1, 126.5, 124.2, 123.7, 119.0, 117.3, 113.6, 111.9, 78.5, 72.0, 69.7, 69.0, 36.6, 33.5, 29.4, 22.1, 13.1. **ESI-MS**: *m/z* (%) = 476.4 ([M+H]$^+$, 100). **Elemental Analysis**: calc. For $C_{24}H_{25}FeN_3O_2S$ = C, 60.64; H, 5.30; N, 8.84. Found = C, 60.46; H, 5.39; N, 8.77.

Methyl ruthenocenylmethyl(5-(propylsulfinyl)-1H-benzo[d]imidazol-2-yl)carbamate 1b-Ox



1b-Ox

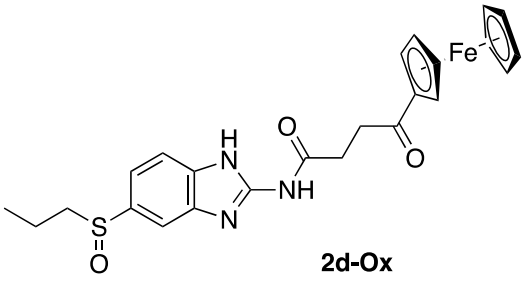


1b-Ox'

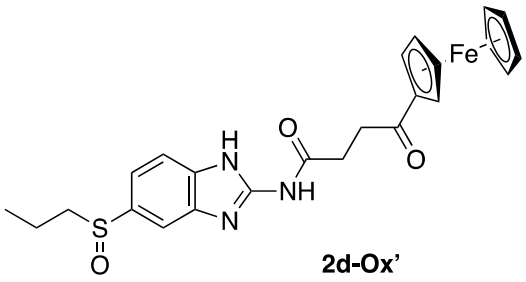
Albendazole sulfoxide (0.2 g, 0.71 mmol), Trimethylammoniomethylruthenocene iodide (0.31 g, 0.71 mmol) and K_2CO_3 (0.2 g, 1.42 mmol) were dissolved in dry acetonitrile (50 mL). The reaction mixture was refluxed overnight. After 22 h the reaction was allowed to cool to room temperature and filtered through a cotton plug. The solvent was evaporated and the crude product was purified by column chromatography on silica with DCM: MeOH (20:1) as the eluent (R_f = 0.33, DCM: MeOH (20:1)) to afford **1b-Ox** as a white solid. Yield: 45% (0.17 g, 0.32 mmol). *Note: Because of the equilibrium between isomers **1b-Ox** and **1b-Ox'** the signals for most signals in the aromatic region are doubled in both ^1H and ^{13}C spectra.* **^{1}H NMR** (400 MHz, Methylene Chloride-d2) δ 11.04 (s, 1H, NH), 7.69 (ddd, *J* = 51.0, 1.7, 0.7 Hz, 1H, arom), 7.63 – 7.37 (m, 1H, arom), 7.30 (ddd, *J* = 16.1, 8.3, 1.7 Hz, 1H, arom), 4.83 (s, 2H, CH_2), 4.78 (dt, *J* = 3.4, 1.7 Hz, 2H, C_5H_4), 4.46 (s, 5H, C_5H_5), 4.37 (t, *J* =

1.7 Hz, 2H, C_5H_4), 3.87 (d, *J* = 1.5 Hz, 3H, CH_3), 2.82 – 2.56 (m, 2H, CH_3CH_2**CH_2**), 1.69 – 1.41 (m, 2H, CH_3**CH_2**CH_2), 0.93 (td, *J* = 7.4, 4.9 Hz, 3H, **CH_3**CH_2CH_2). **^{13}C NMR** (101 MHz, Methylene Chloride-d2) δ 155.3, 150.4, 150.2, 143.3, 141.3, 137.5, 136.9, 134.6, 132.8, 118.1, 117.6, 117.2, 114.1, 111.0, 106.8, 86.7, 72.5, 70.6, 70.1, 59.8, 44.9, 16.1, 16.0, 13.1, 13.0. **ESI-MS**: m/z calcd. for $C_{23}H_{26}FeN_3O_3S^+$, $[M+H]^+$ 526.0733, found 526.0731.

4-Oxo-4-ferrocenyl-N-(5-(propylsulfinyl)-1H-benzo[d]imidazol-2-yl)butanamide 2d-Ox



2d-Ox



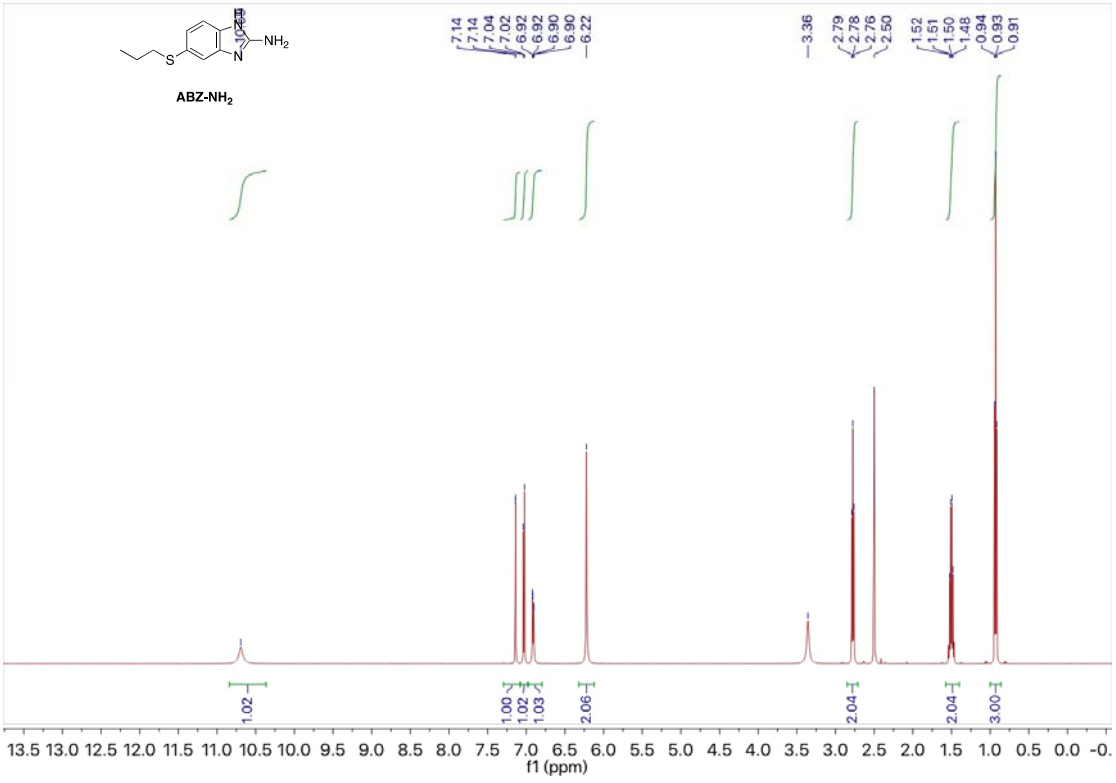
2d-Ox'

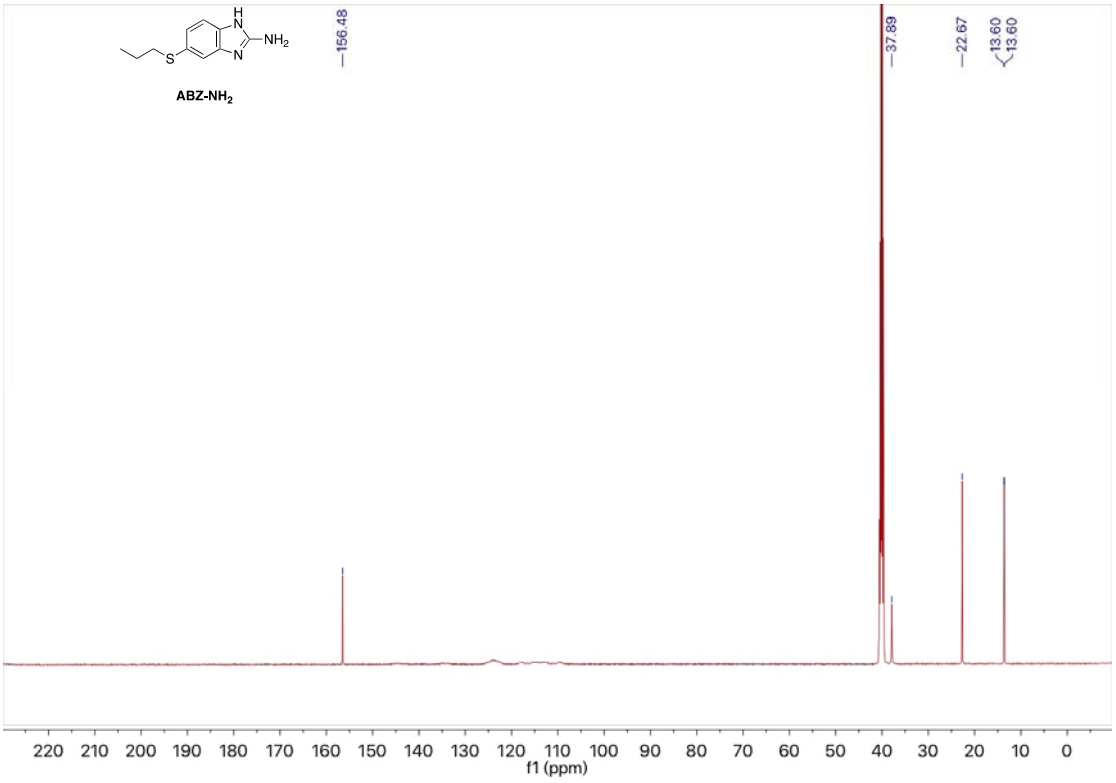
In a round bottom flask, 3-Ferrocenoylpropionic acid (1.08 g, 3.8 mmol) was dissolved in 20 mL of dry DMF. To this, TBTU (1.2 g, 3.8 mmol) and N,N-Diisopropylethylamine (1.48 ml, 8.7 mmol) were added and stirred for 30 min at room temperature under nitrogen atmosphere After 30 min, the solution of ABZ-NH_2-Ox (0.65 g, 2.9 mmol) in 10 mL of dry DMF was added to the mixture. Then the reaction stirred at room temperature for 24 h. As it finished, the crude materials were extracted with chloroform and washed with brine solution. Organic layer was separated and dried over anhydrous sodium sulfate. The crude product was purified by column chromatography on silica with dichloromethane: methanol (30:1) as the eluent (R_f = 0.3, dichloromethane: methanol (20:1)) to afford **2d-Ox** as an orange solid. Yield: 40% (0.57 g, 1.2 mmol). *Note: Because of the equilibrium between isomers **2d-Ox** and **2d-Ox'** the signals for most signals in the aromatic region are doubled in both ^{1}H and ^{13}C spectra.* **^{1}H NMR** (400 MHz, DMSO-d6) δ 12.29 (d, *J* = 3.3 Hz, 1H, NH), 11.78 (s, 1H, NH), 7.93 – 7.68 (m, 1H, arom), 7.60 (dd, *J* = 21.4, 8.3 Hz, 1H, arom), 7.34 (dd, *J* = 8.3, 1.7 Hz, 1H,

arom), 4.84 (t, *J* = 1.9 Hz, 2H, C_5H_4), 4.58 (t, *J* = 1.9 Hz, 2H, C_5H_4), 4.32 (s, 5H, C_5H_5), 3.23 – 3.09 (m, 2H, $CH_3CH_2\mathbf{CH_2}$), 2.79 (t, *J* = 6.4 Hz, 4H, CH_2CH_2), 1.73 – 1.33 (m, 2H, $CH_3\mathbf{CH_2}CH_2$), 0.95 (t, *J* = 7.4 Hz, 3H, $\mathbf{CH_3}CH_2CH_2$). **^{13}C NMR** (101 MHz, DMSO-d6) δ 202.4, 172.7, 148.7, 143.2, 141.3, 137.0, 136.1, 135.0, 133.2, 117.8, 117.6, 116.8, 113.3, 112.6, 108.3, 79.0, 72.5, 70.2, 69.5, 58.6, 34.0, 29.9, 15.9, 13.4. **ESI-MS**: m/z calcd. for $C_{24}H_{25}FeN_3O_3SNa^+$, $[M+Na]^+$ 514.0858, found 514.0857.

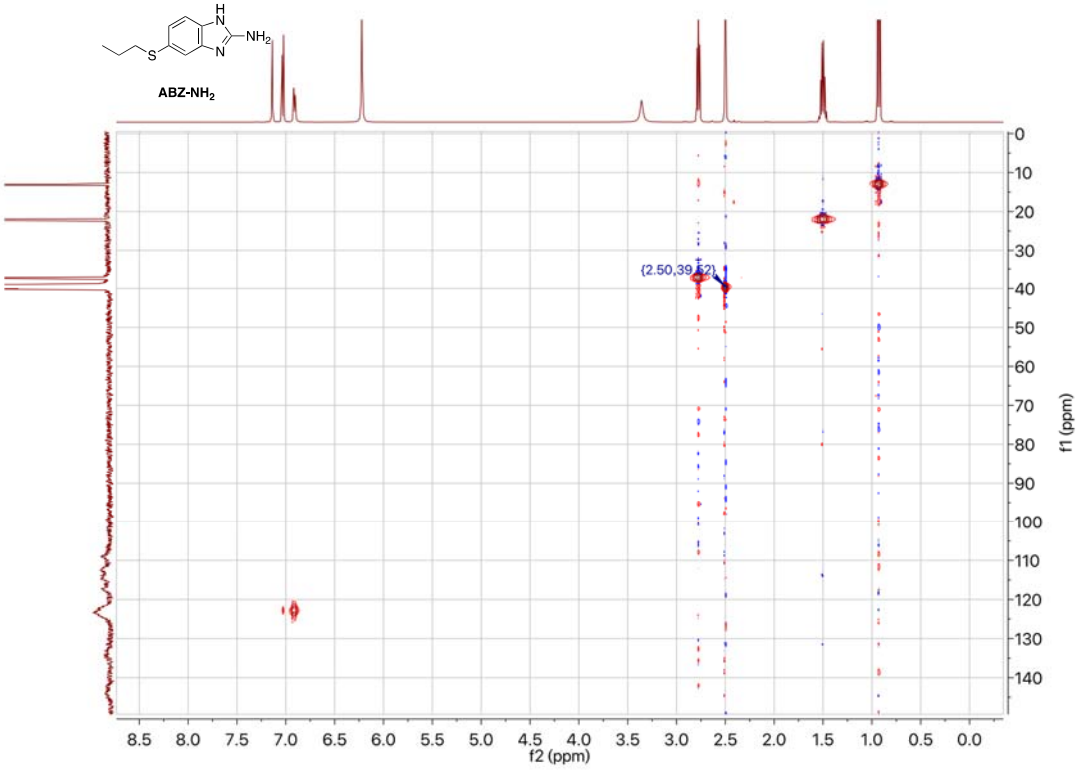
NMR spectra of compounds

Albendazole-amine ABZ-NH_2

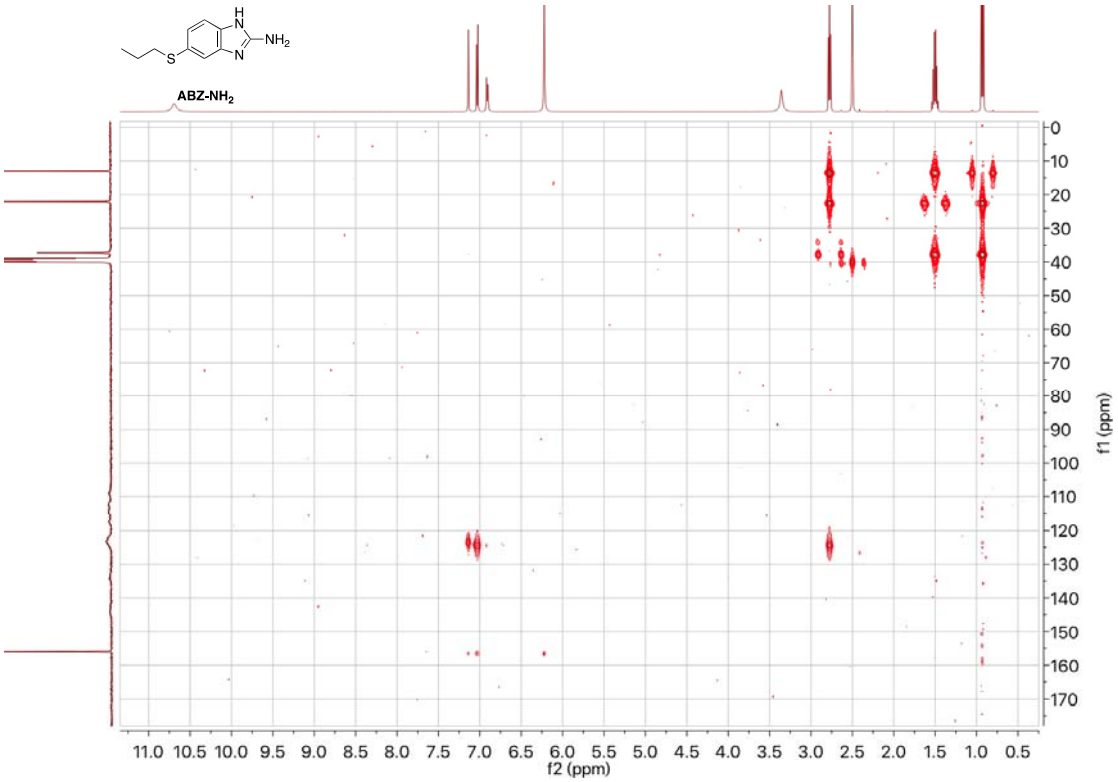




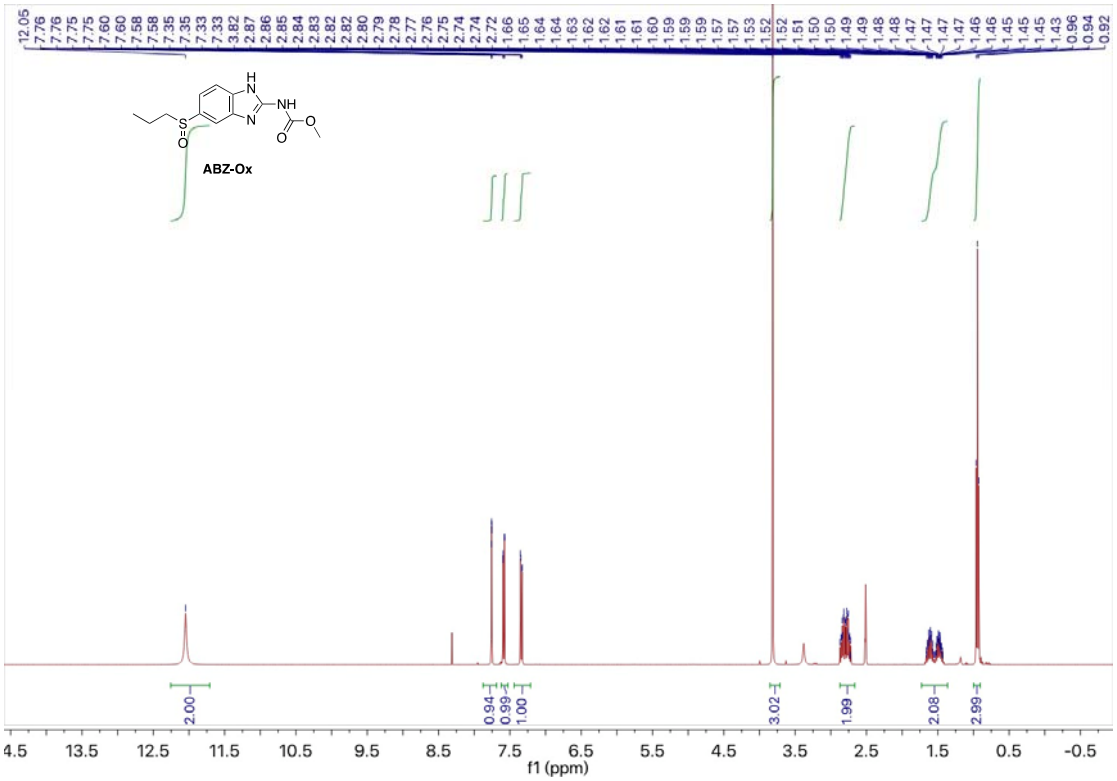
HSQC Spectrum of ***Albendazole-amine*** **ABZ-NH_2** in DMSO-D6

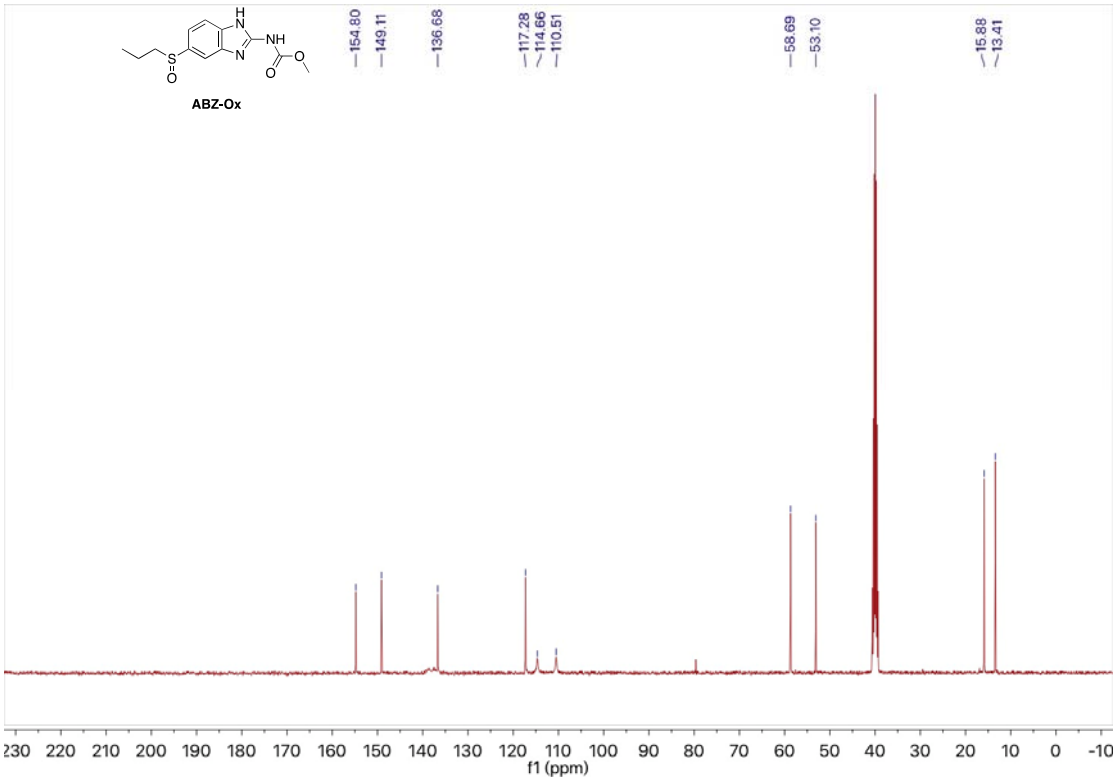


HMBC Spectrum of ***Albendazole-amine*** **ABZ-NH_2** in DMSO-D6

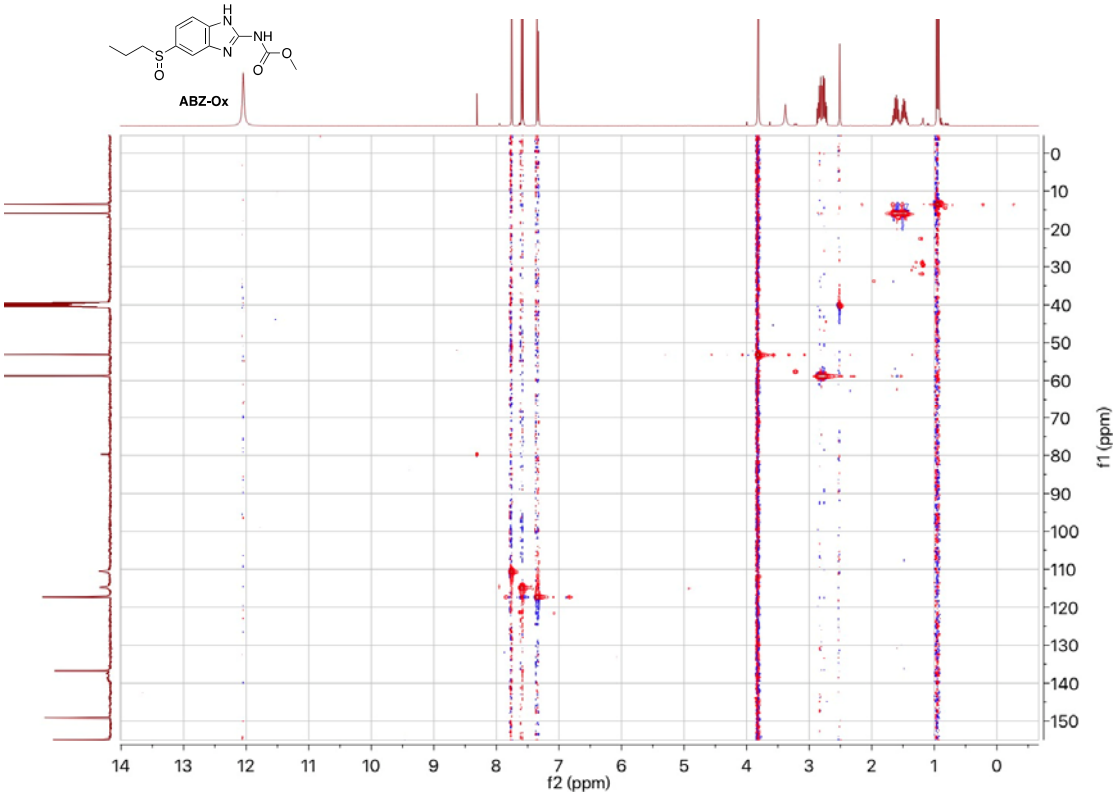


Albendazole-sulfoxide ABZ-Ox *(ricobendazole)*

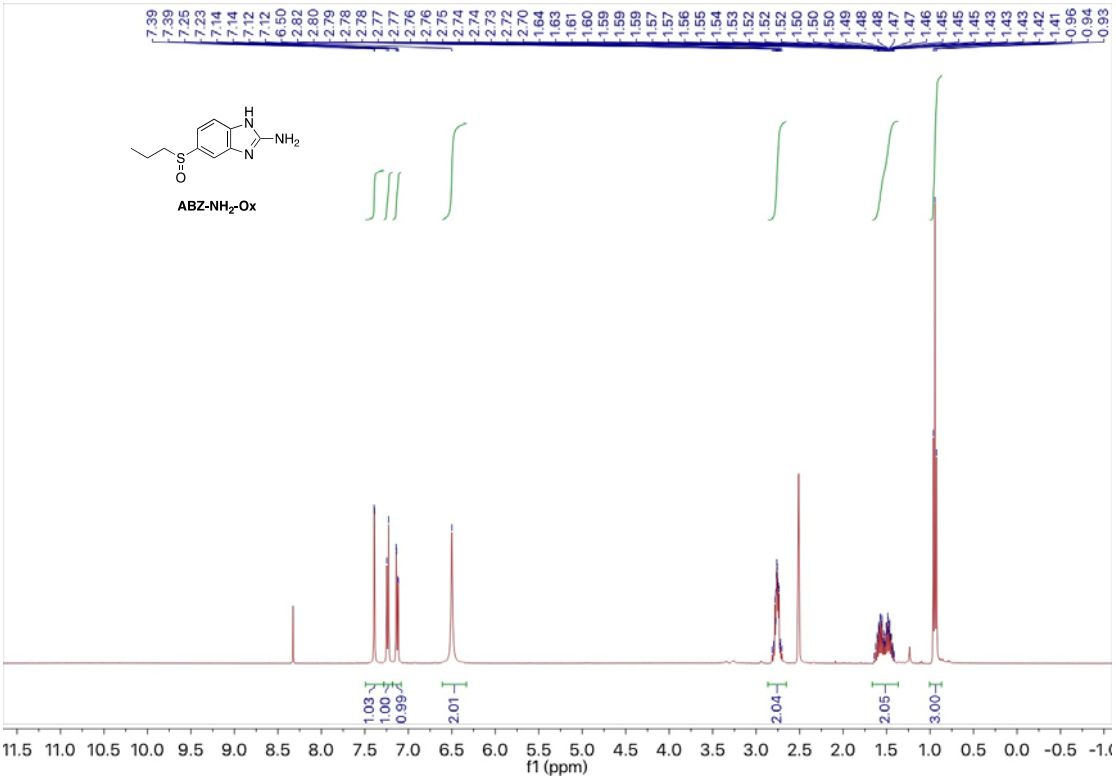


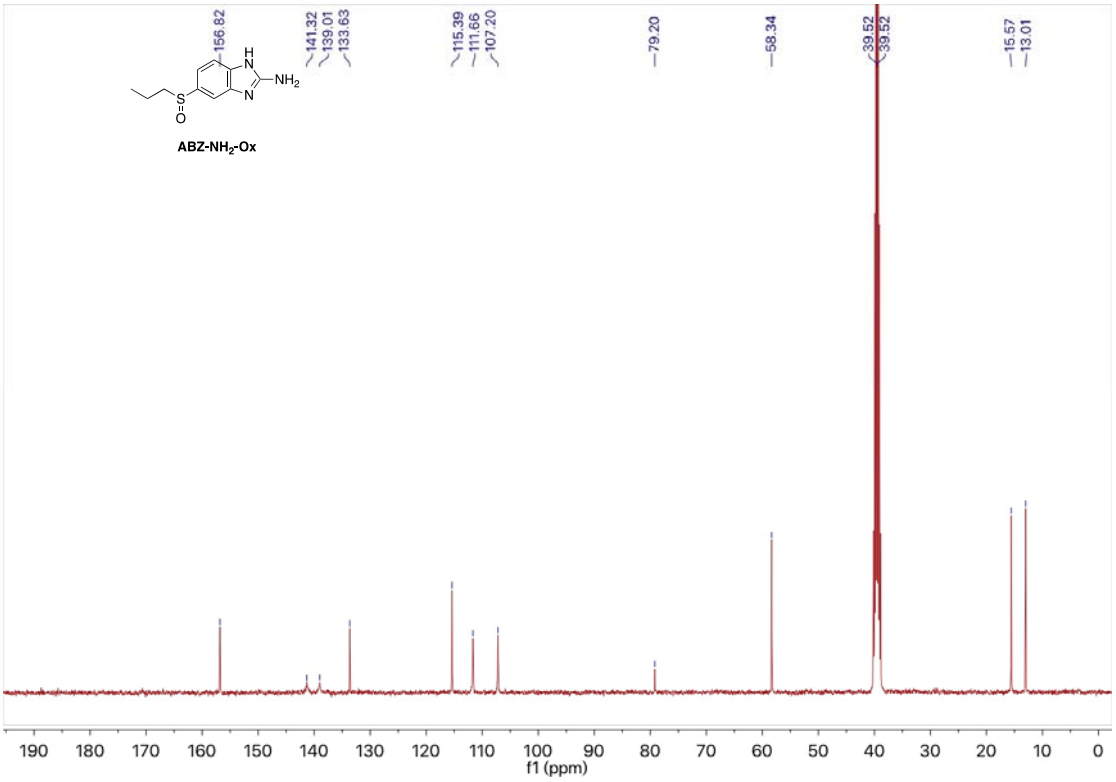


HSQC Spectrum of ***Albendazole-sulfoxide*** **ABZ-Ox** in DMSO-D6

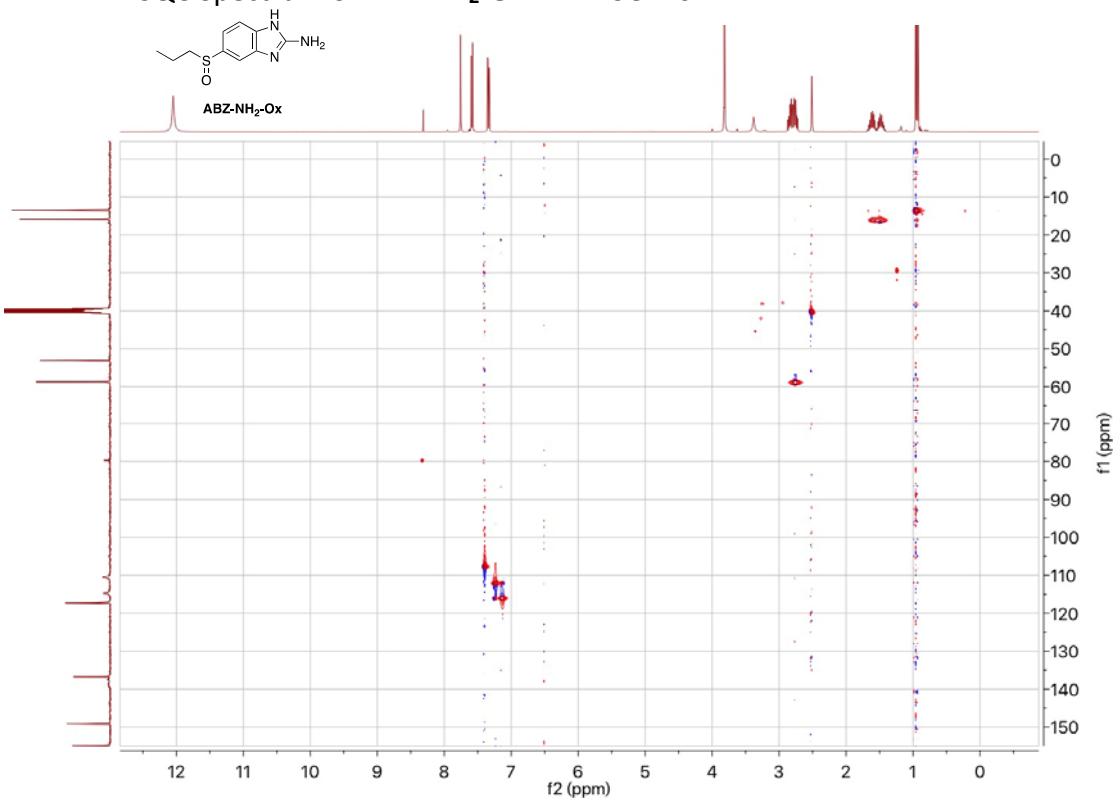


5-(propylsulfinyl)-1H-benzo[d]imidazol-2-amine ABZ-NH_2-Ox (Ricobendazole amine)

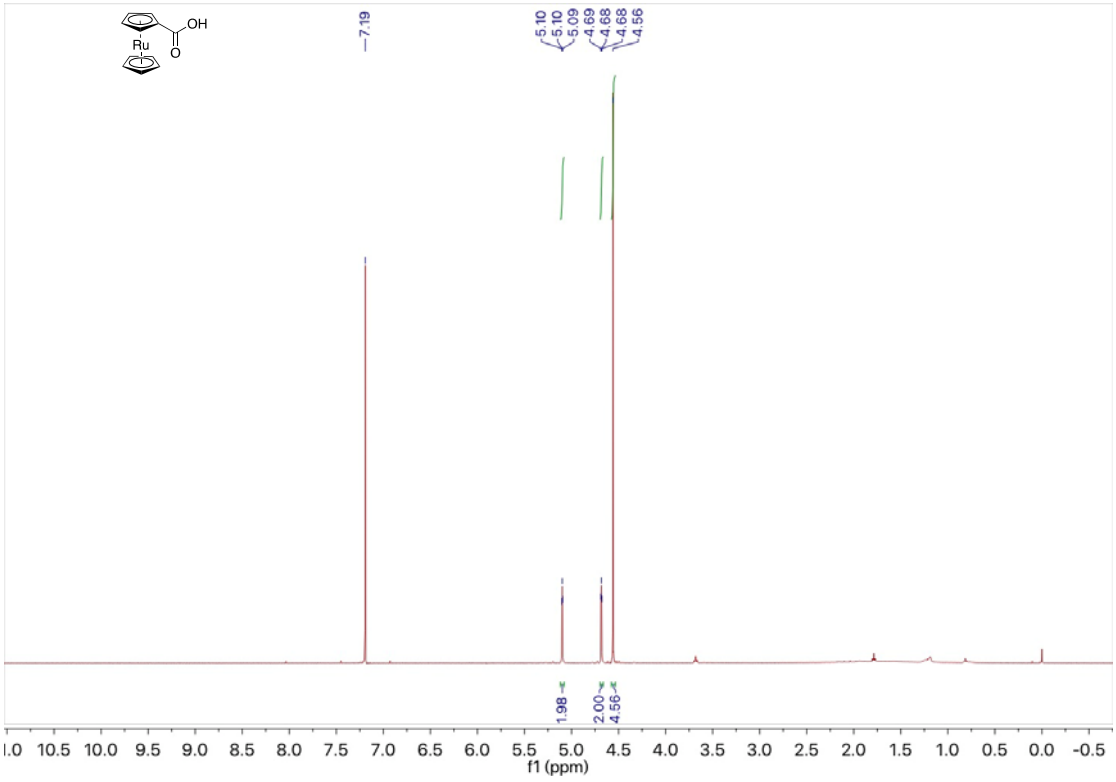




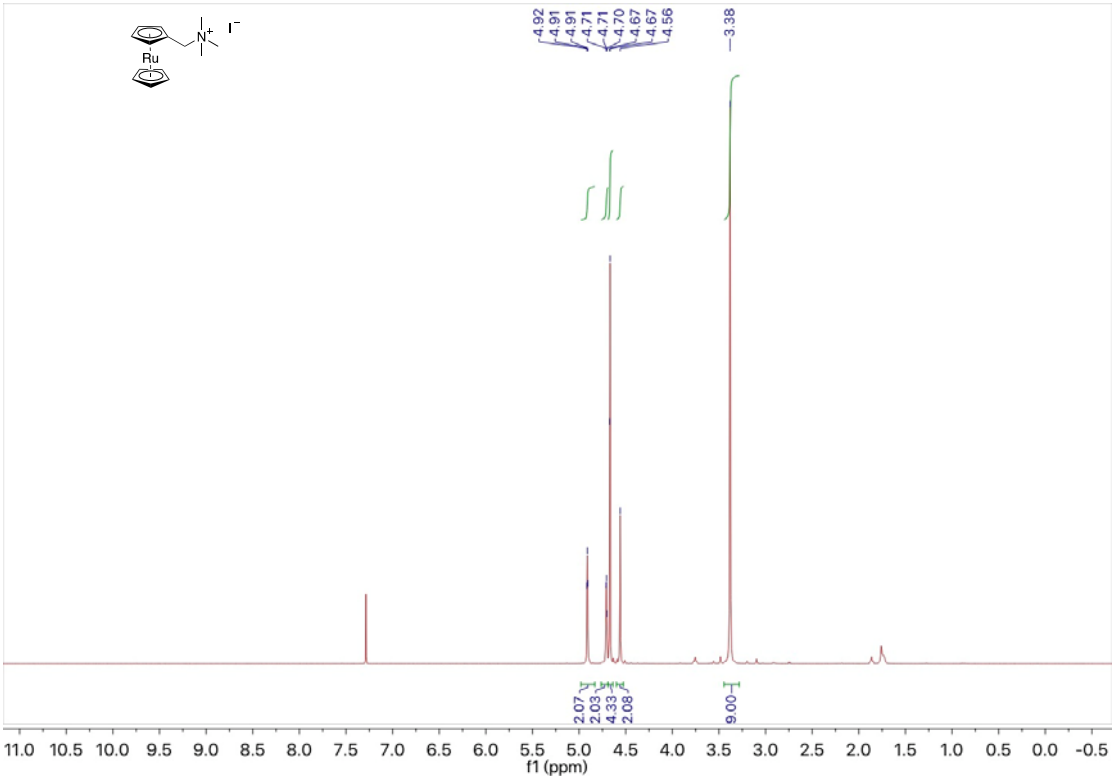
HSQC Spectrum of **ABZ-NH_2-Ox** in DMSO-D6



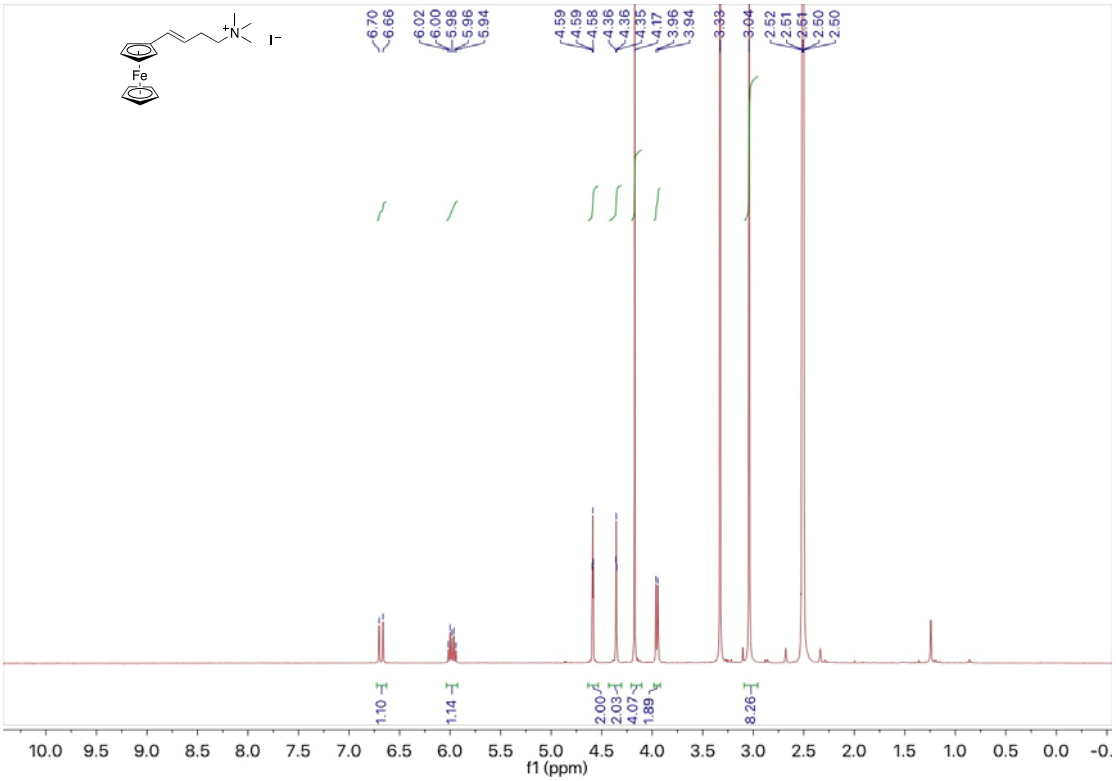
Ruthenocene carboxylic acid



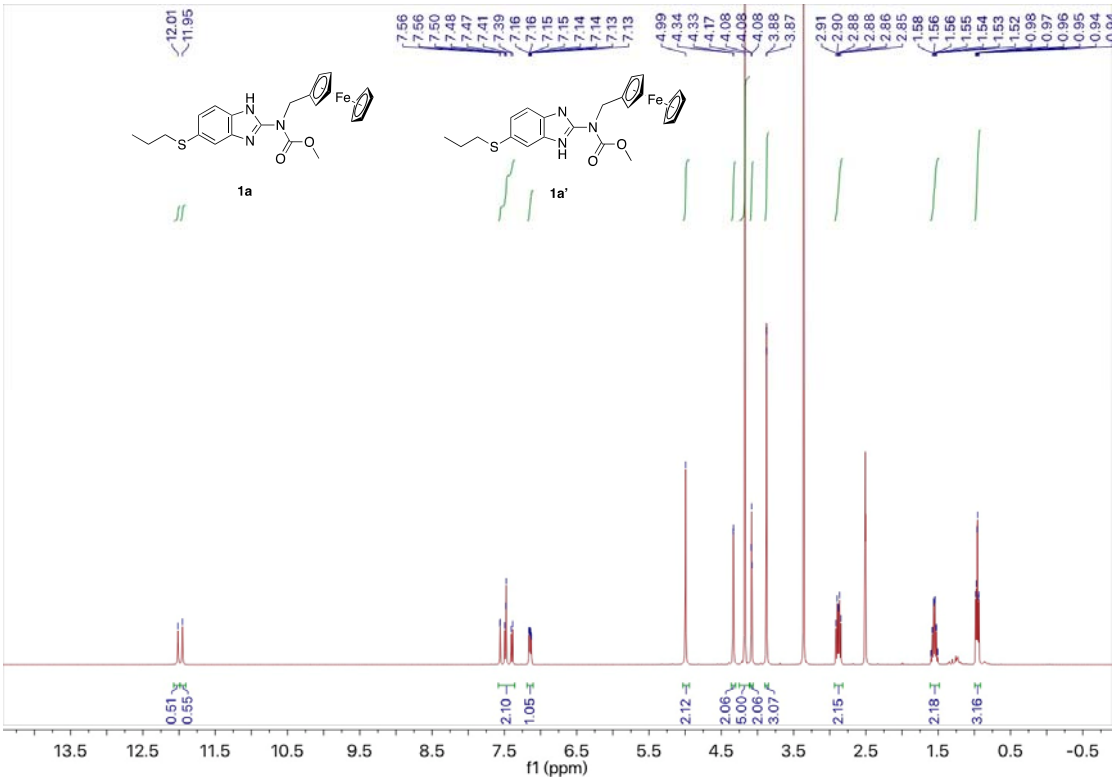
(Ruthenocyl)trimethylammonium iodide

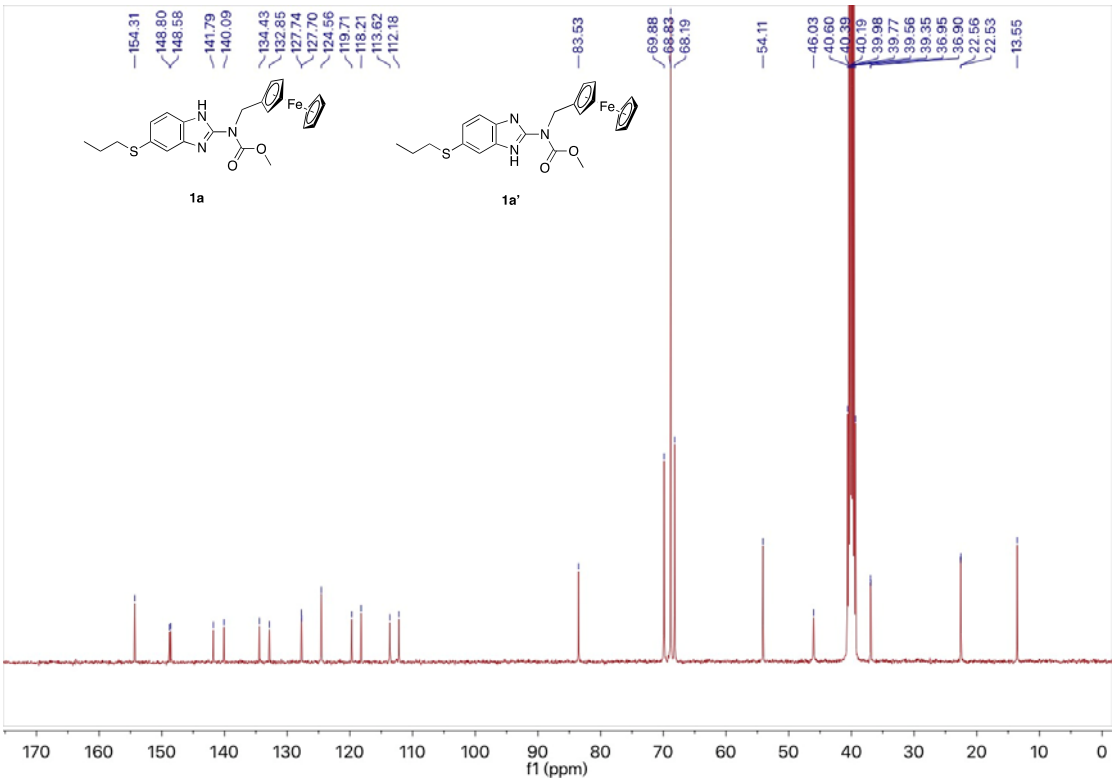


[(2-Ferrocenylvinyl)methyl]trimethylammonium iodide

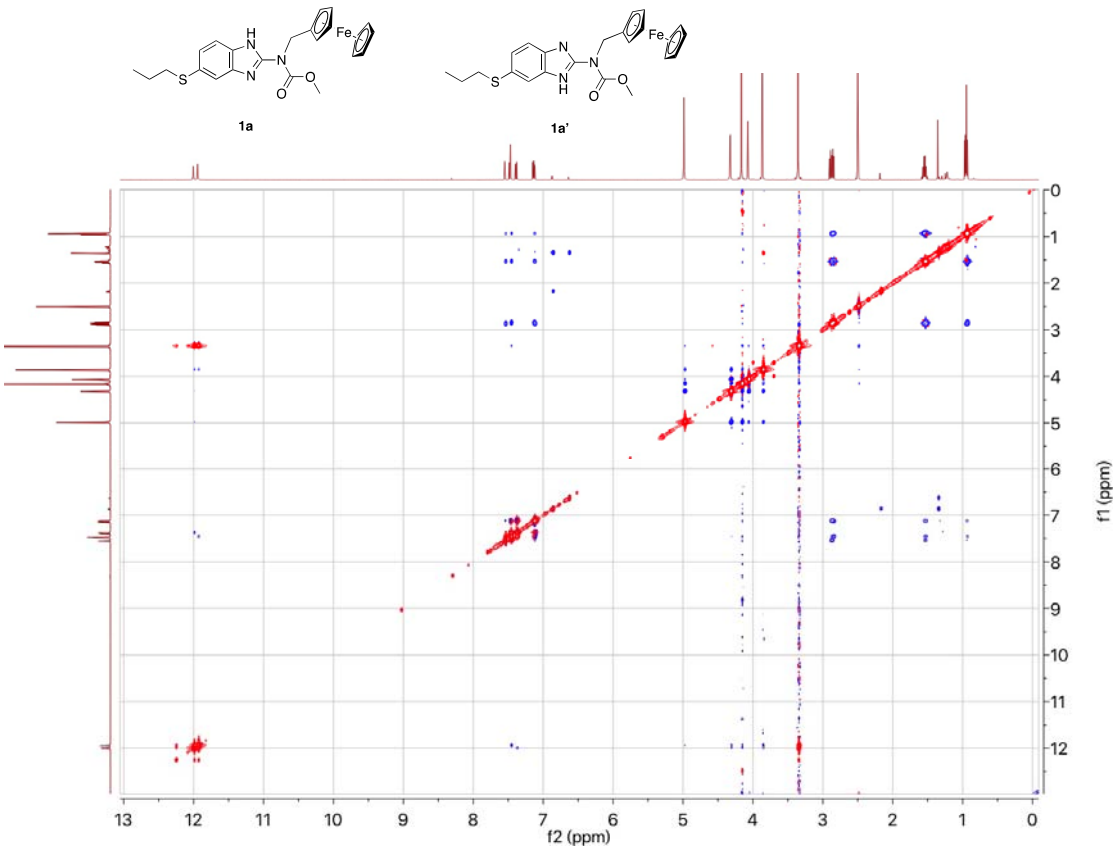


Methyl ferrocenylmethyl(5-(propylthio)-1H-benzo[d]imidazol-2-yl)carbamate 1a

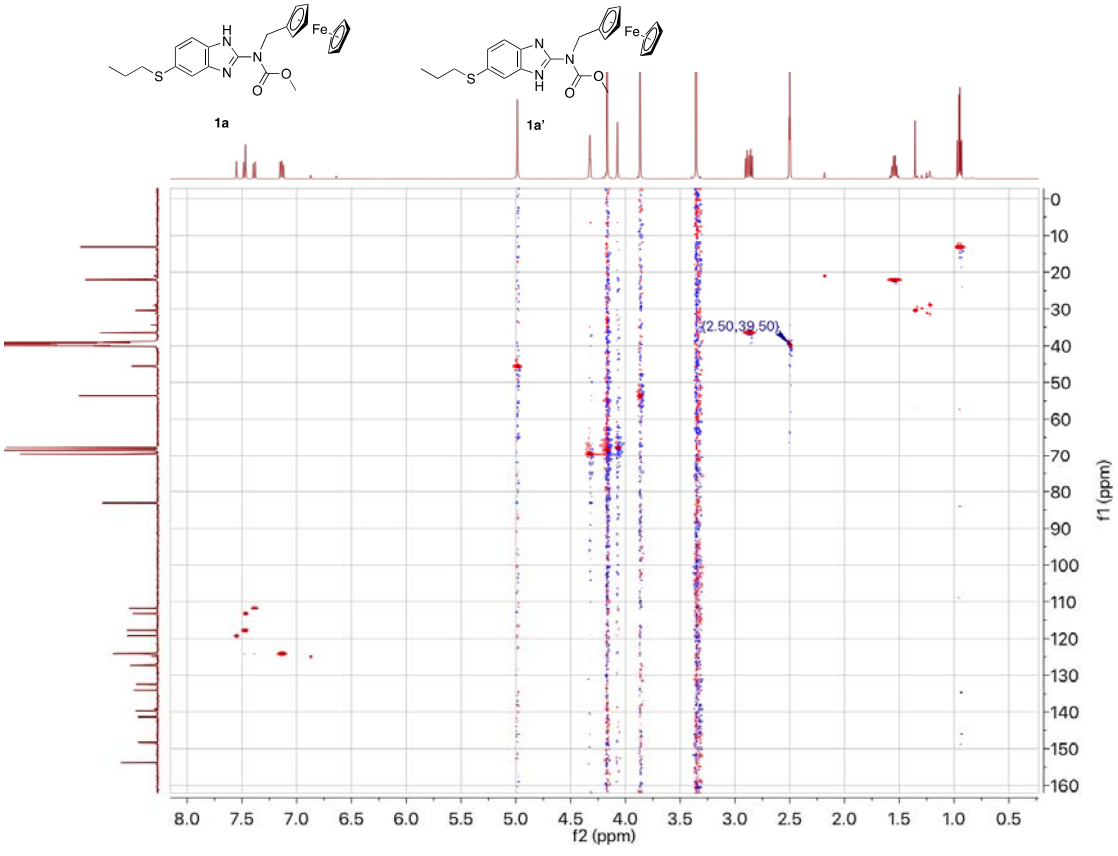




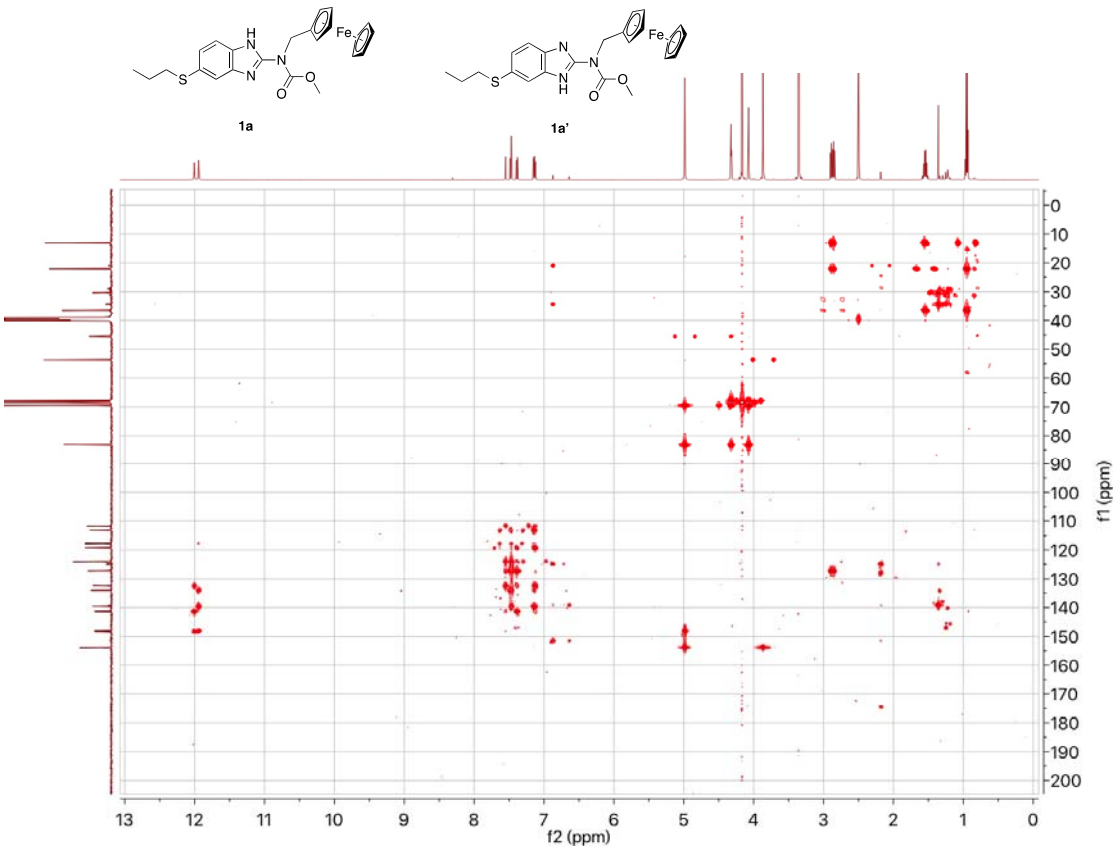
NOESY Spectrum of **1a** in DMSO-D6



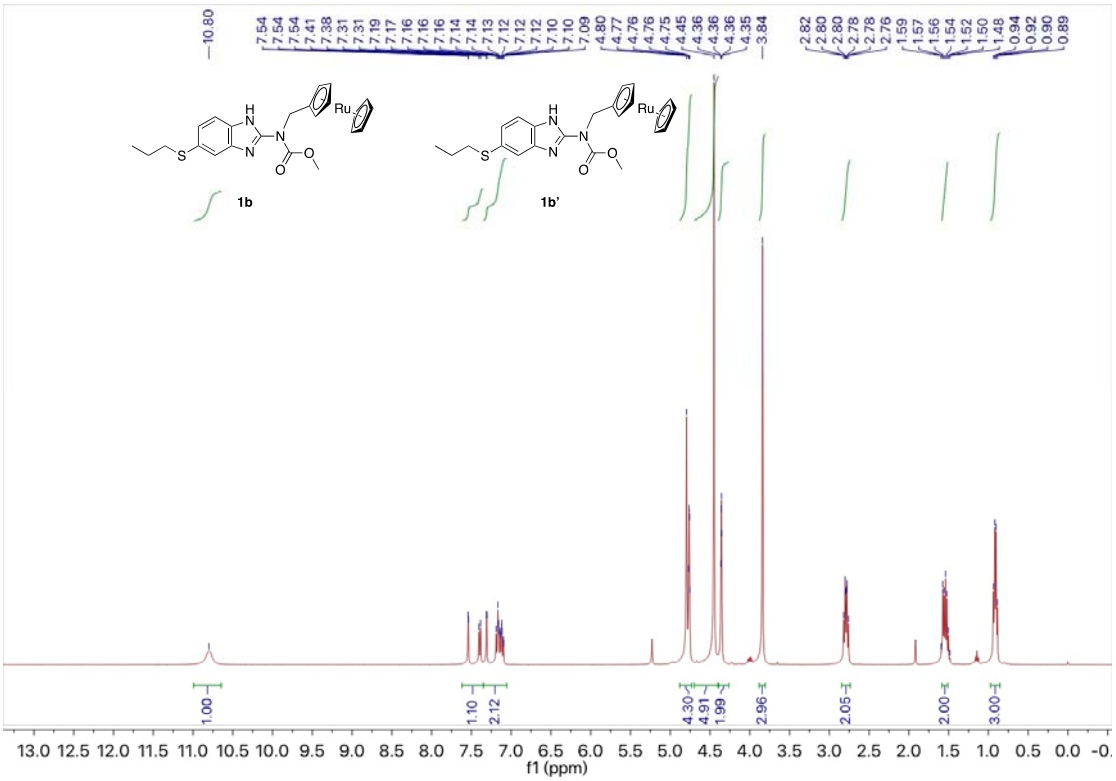
HSQC Spectrum of **1a** in DMSO-D6

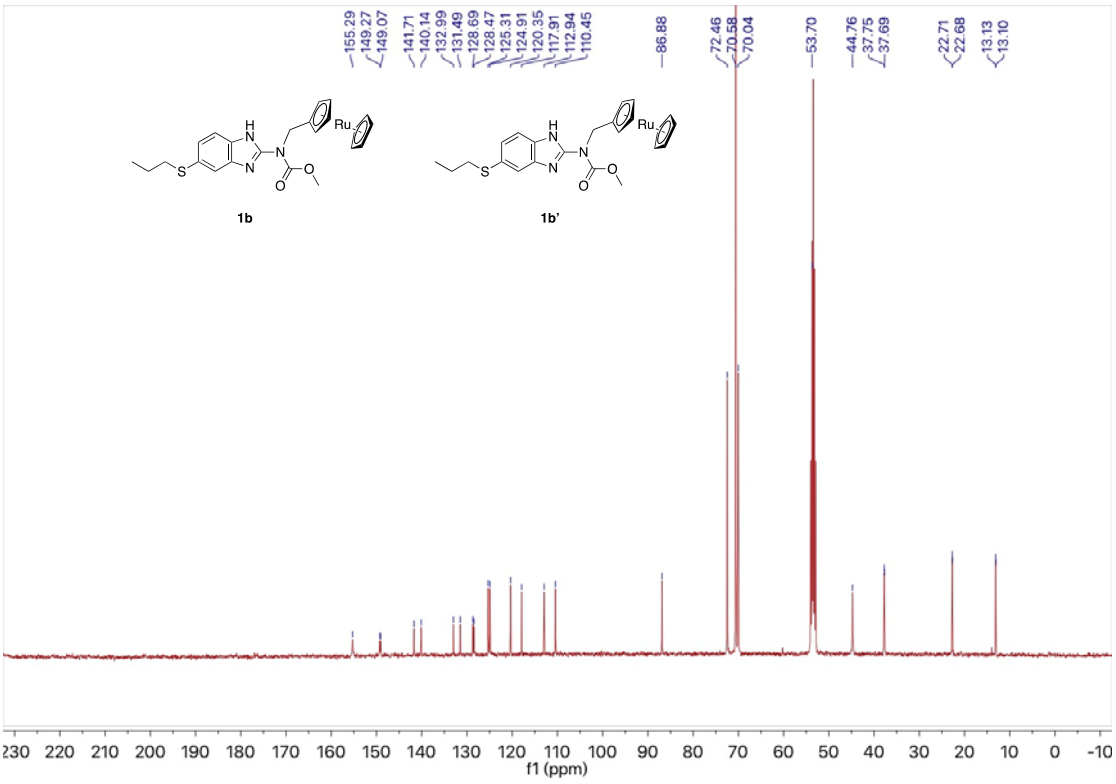


HMBC Spectrum of **1a** in DMSO-D6

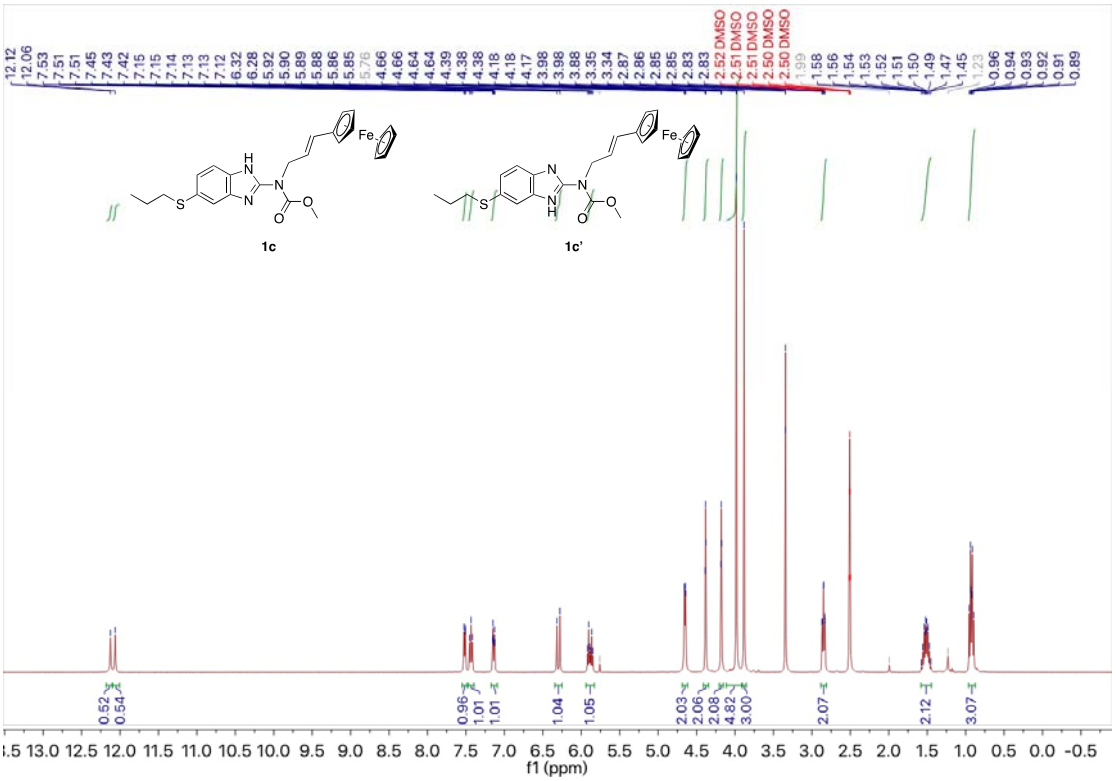


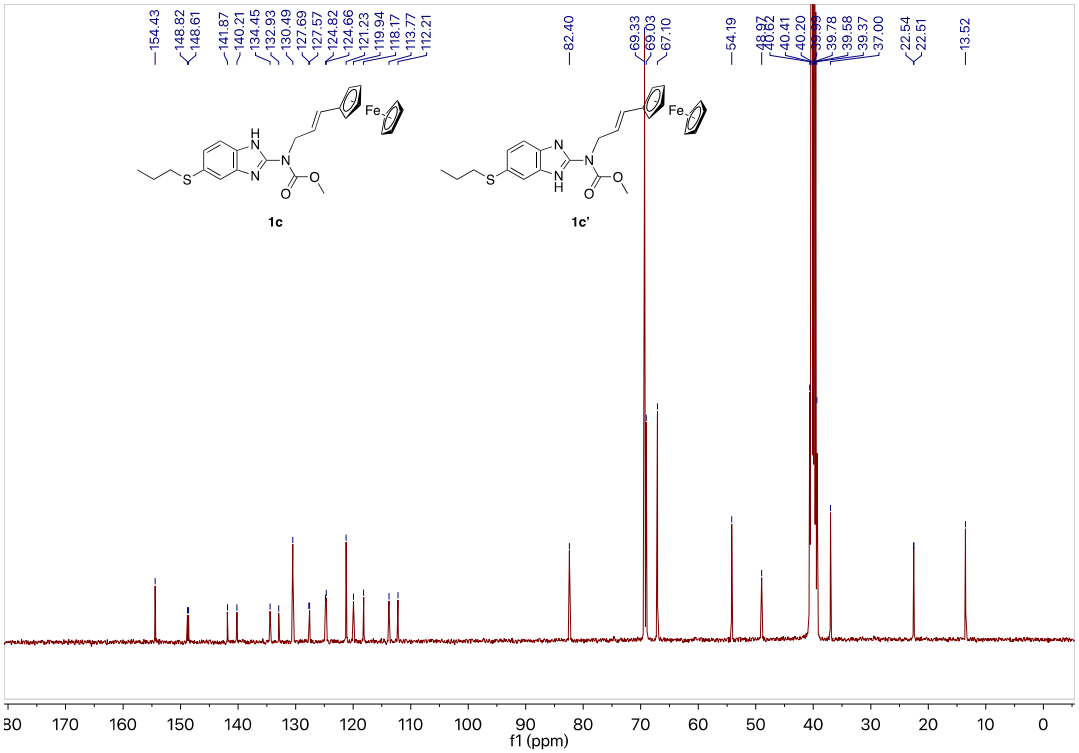
Methyl ruthenocenylmethyl(5-(propylthio)-1H-benzo[d]imidazol-2-yl)carbamate 1b



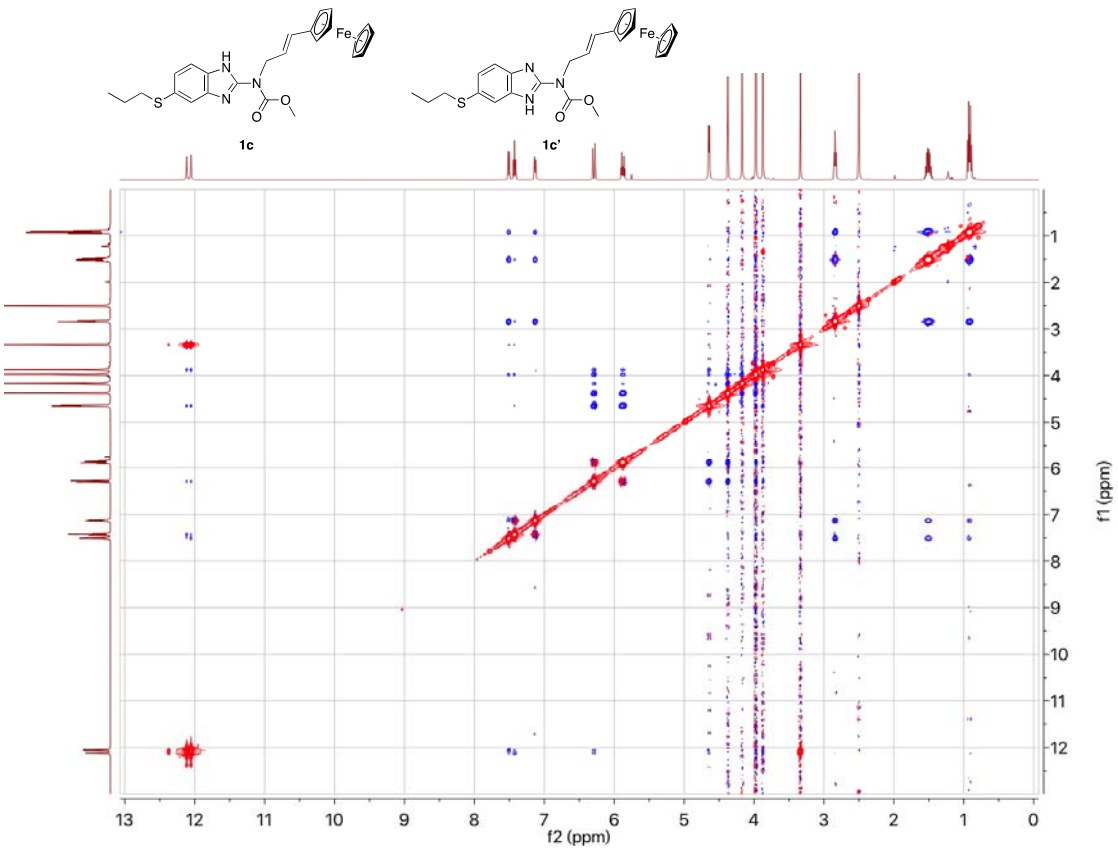


Methyl (2-Ferrocenylvinyl)-methyl-(5-(propylthio)-1H-benzo[d]imidazol-2-yl)carbamate 1c

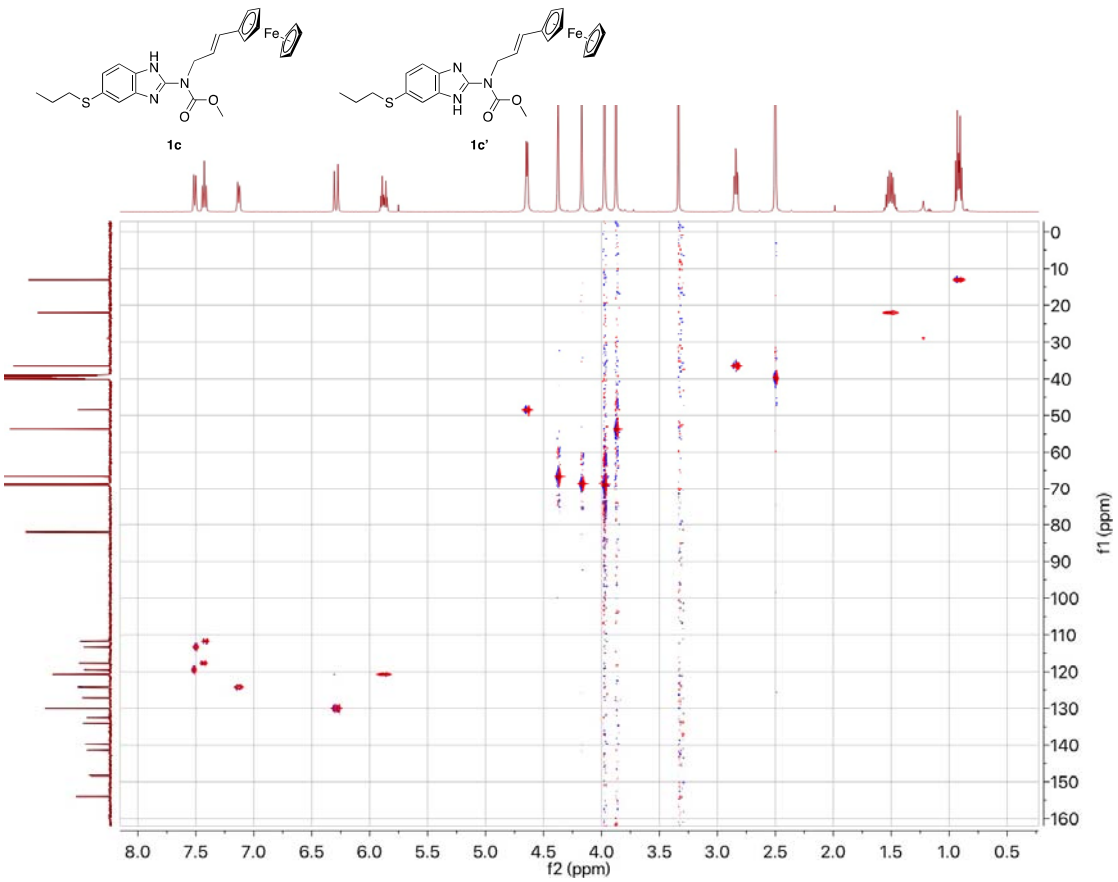




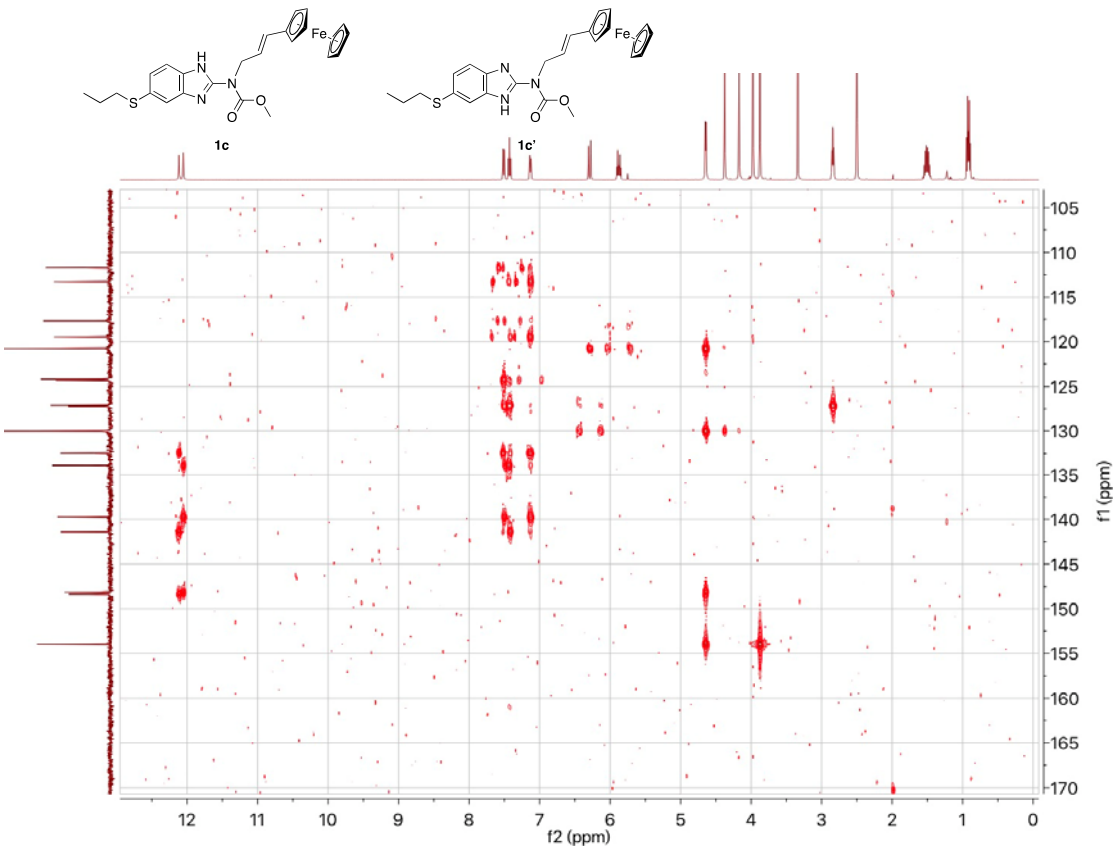
NOESY Spectrum of **1c** in DMSO-D6



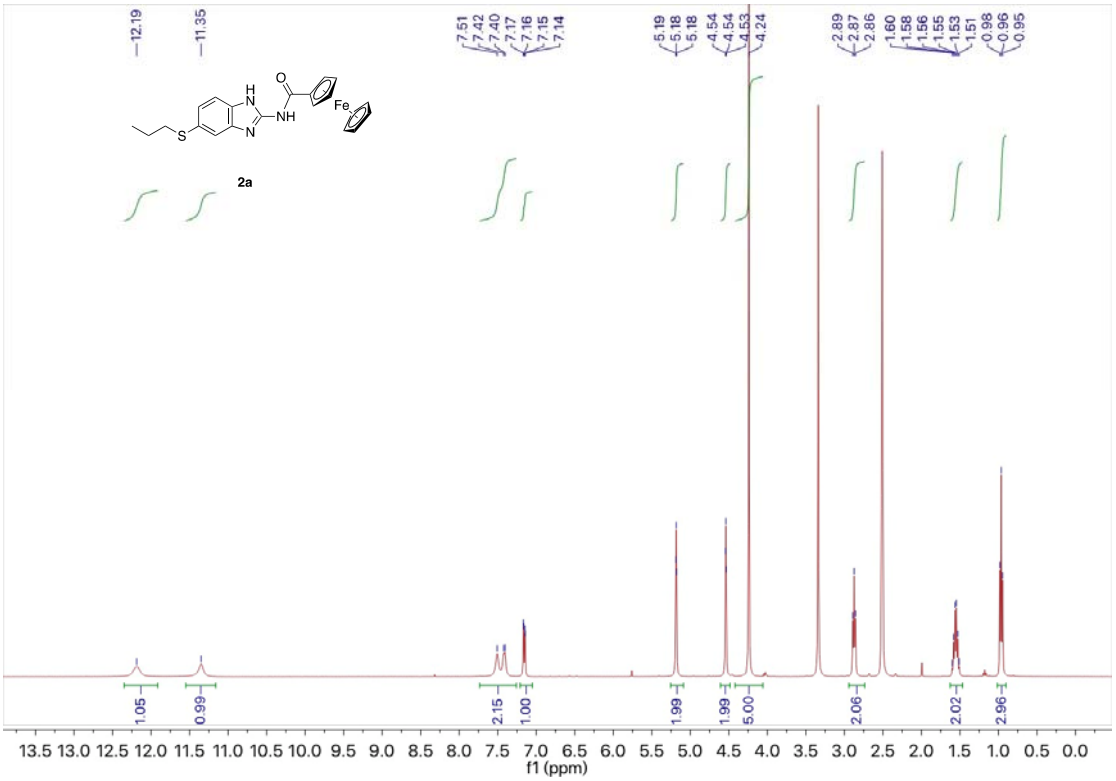
HSQC Spectrum of **1c** in DMSO-D6

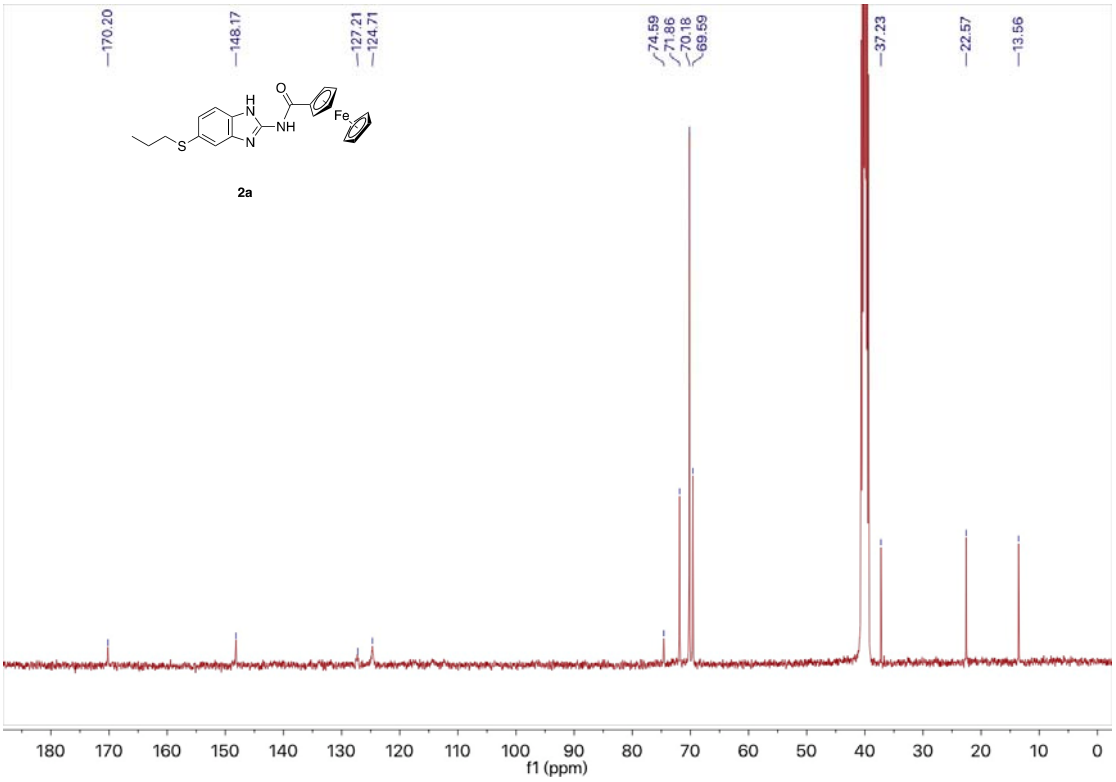


HMBC Spectrum of **1c** in DMSO-D6

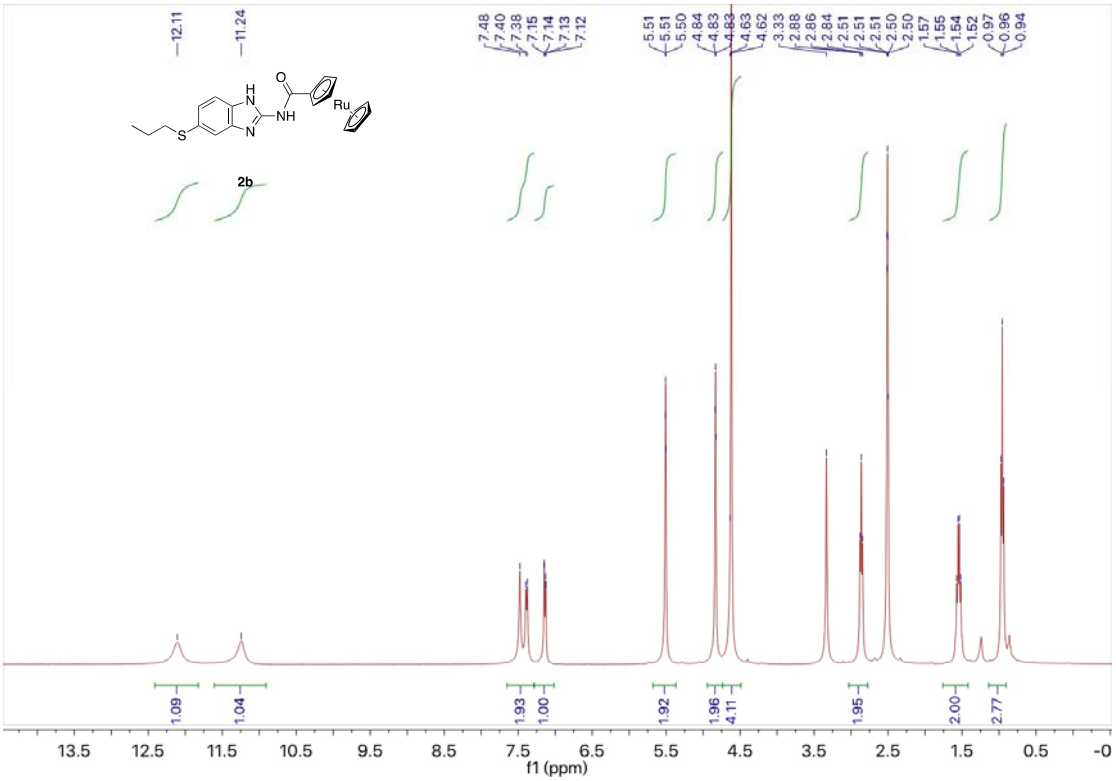


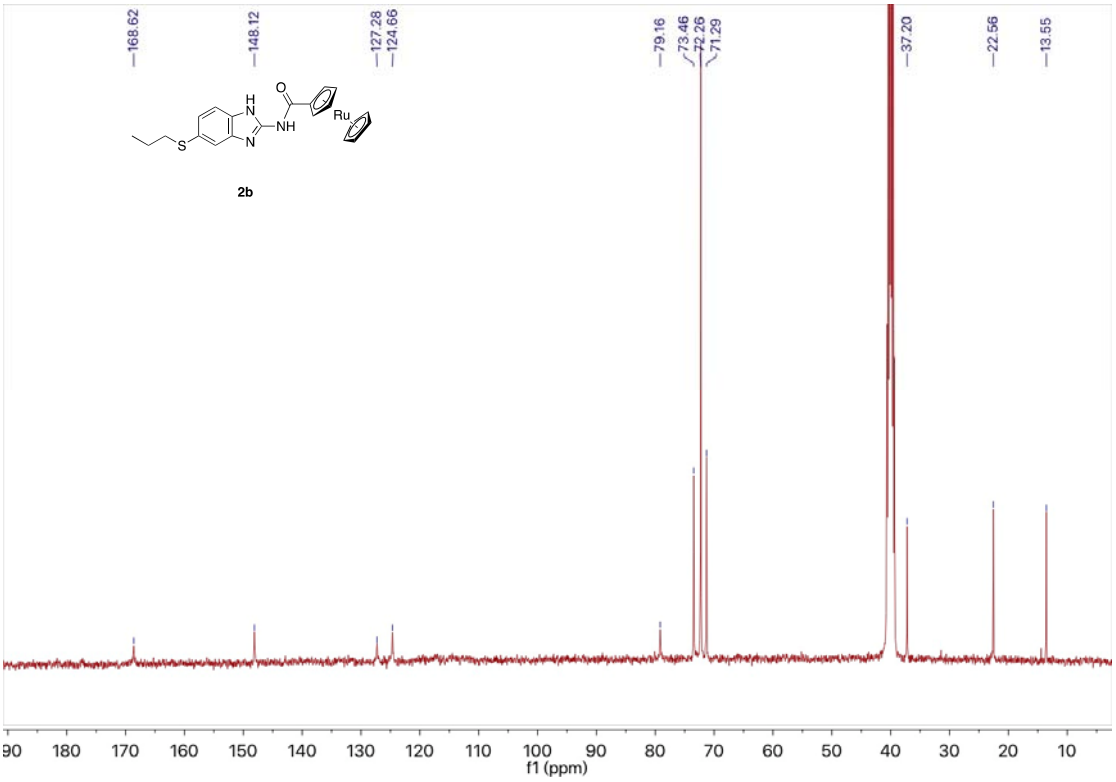
N-(5-(propylthio)-1H-benzo[d]imidazol-2-yl)ferrocenamide 2a



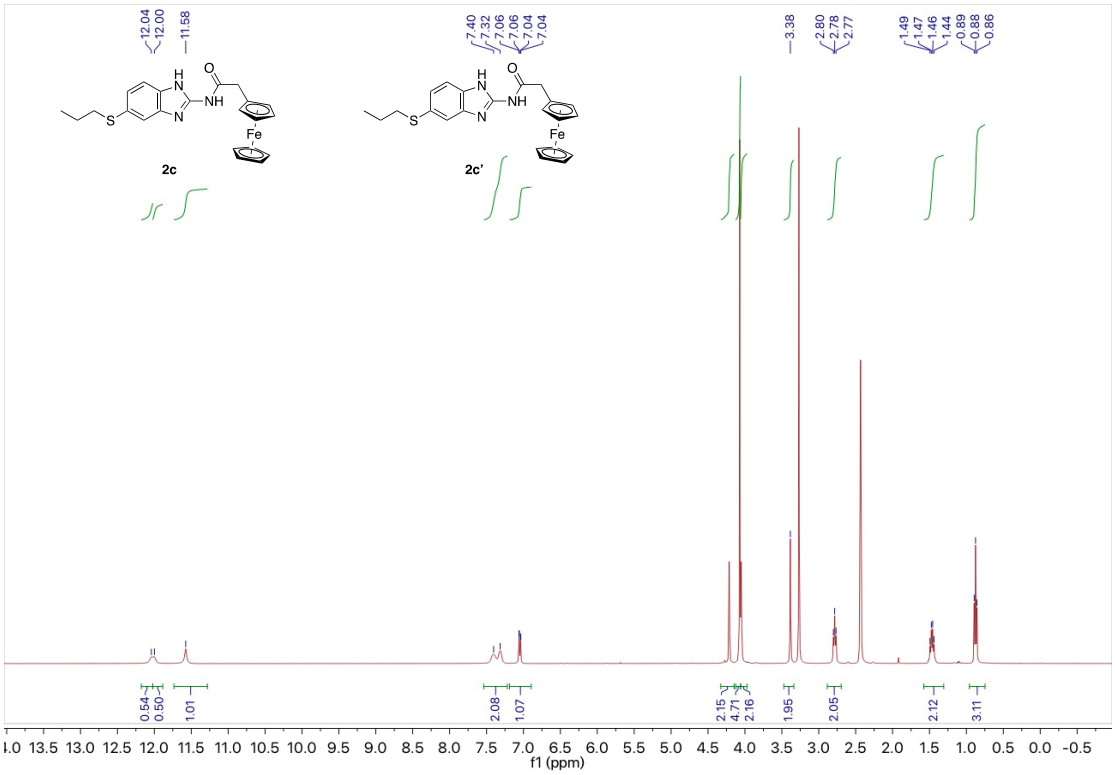


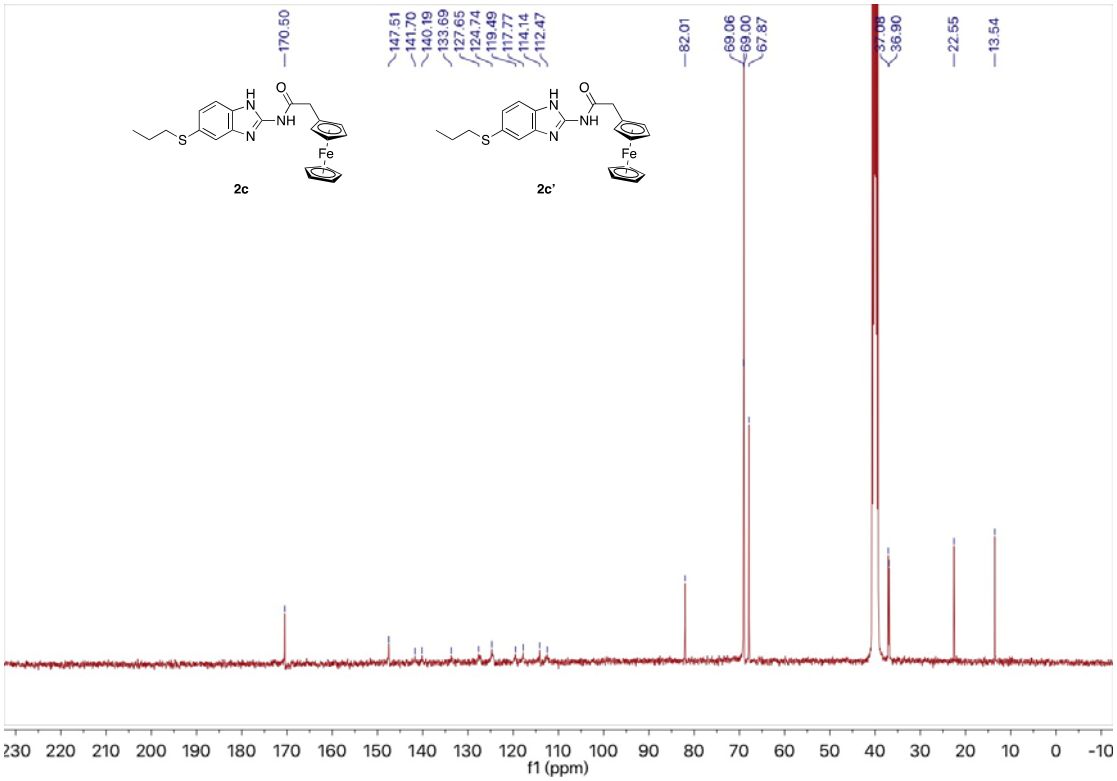
N-(5-(propylthio)-1H-benzo[d]imidazol-2-yl)ruthenocenamide 2b



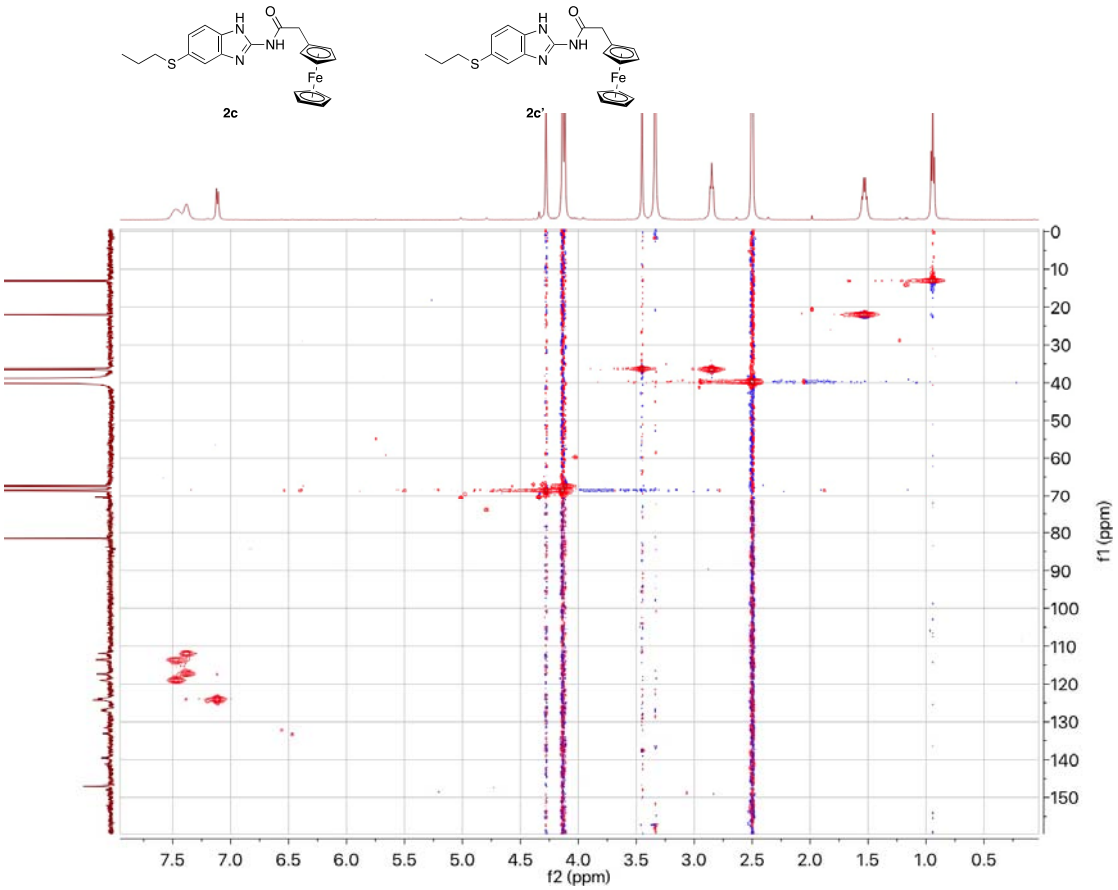


2-Ferrocenyl-N-(5-(propylthio)-1H-benzo[d]imidazol-2-yl)acetamide 2c

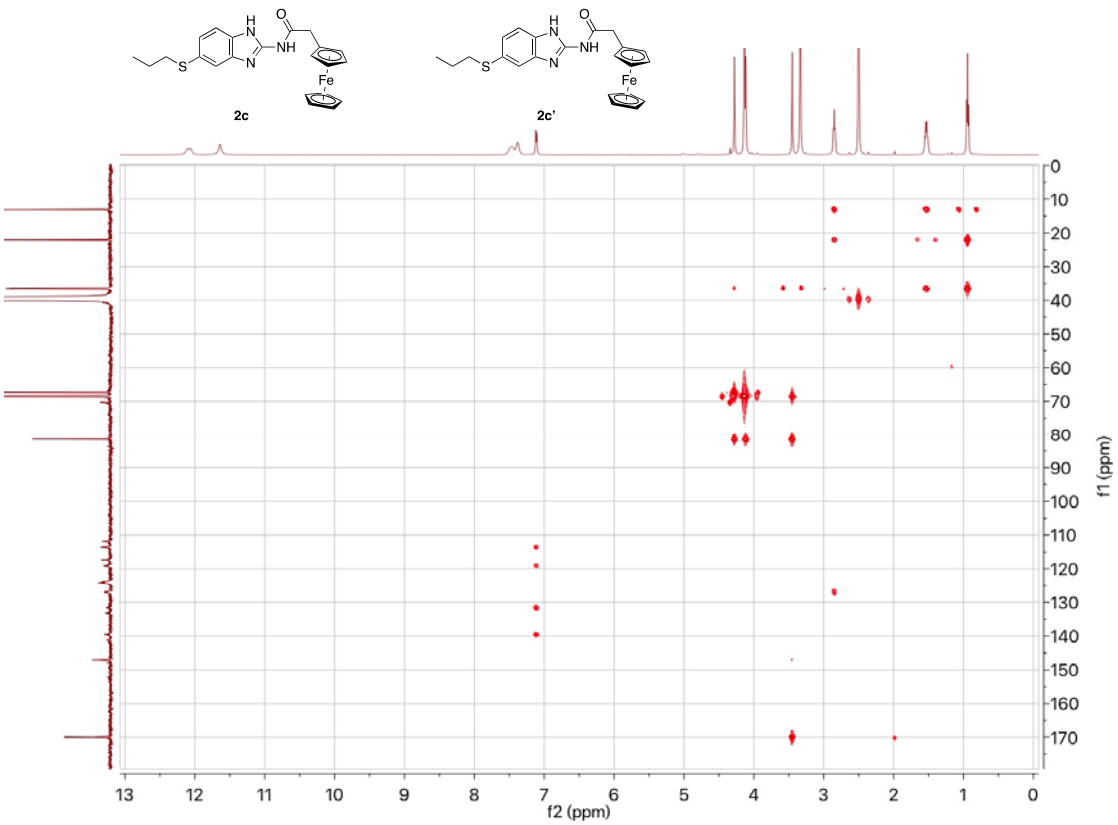




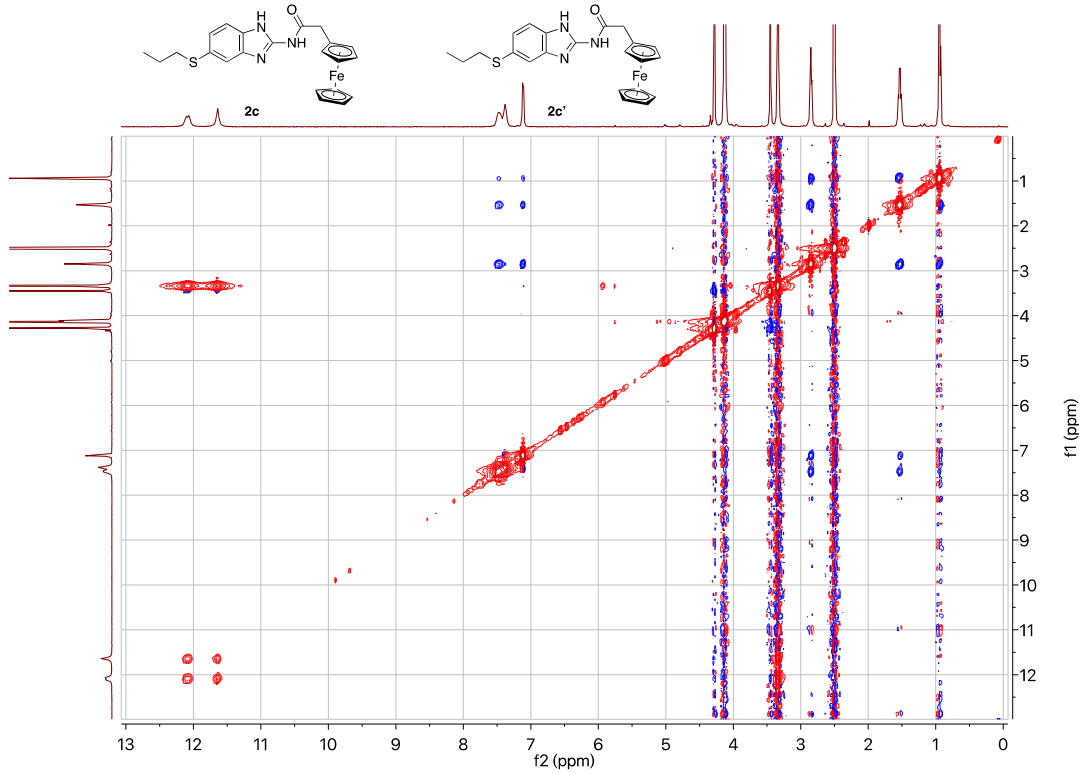
HSQC Spectrum of **2c** in DMSO-D6



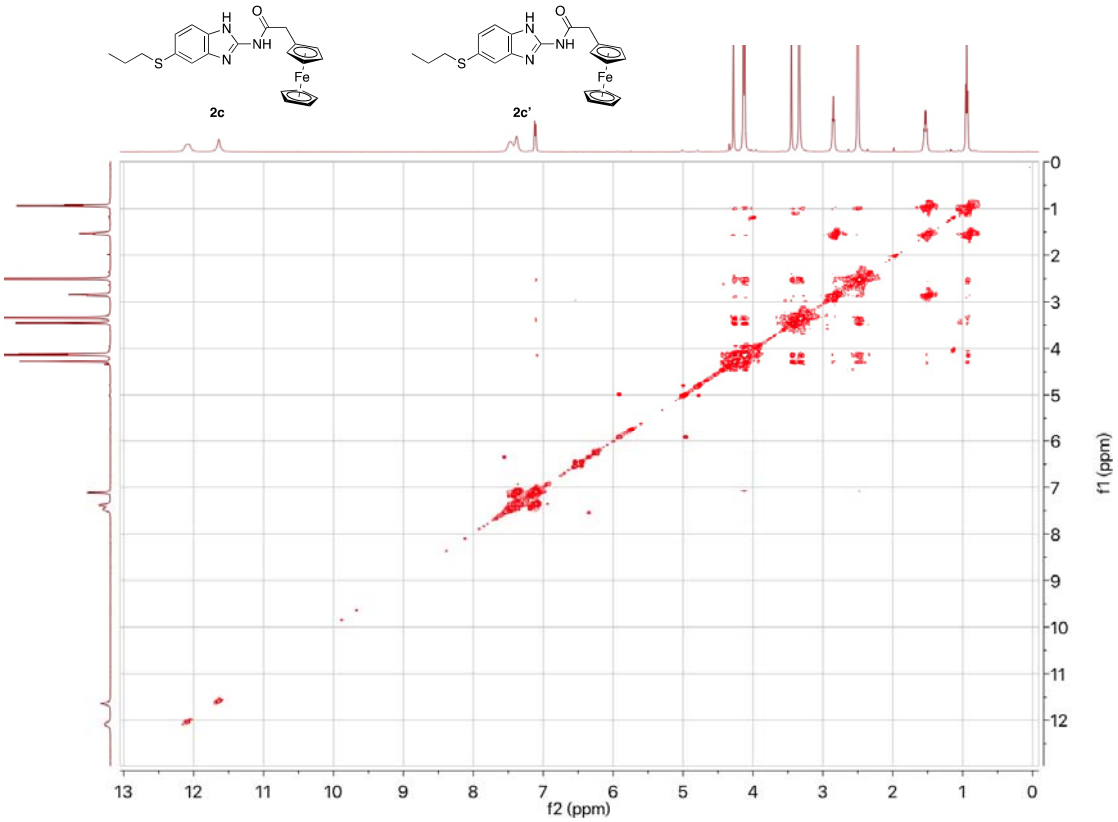
HMBC Spectrum of **2c** in DMSO-D6



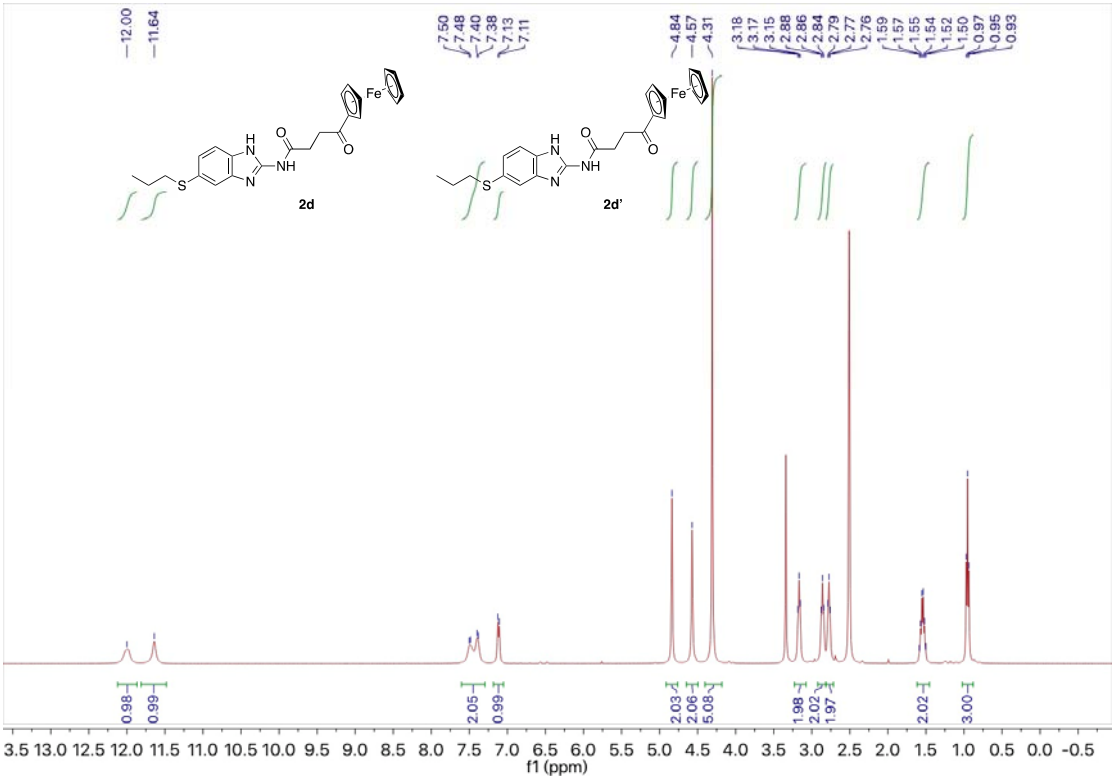
NOESY Spectrum of **2c** in DMSO-D6

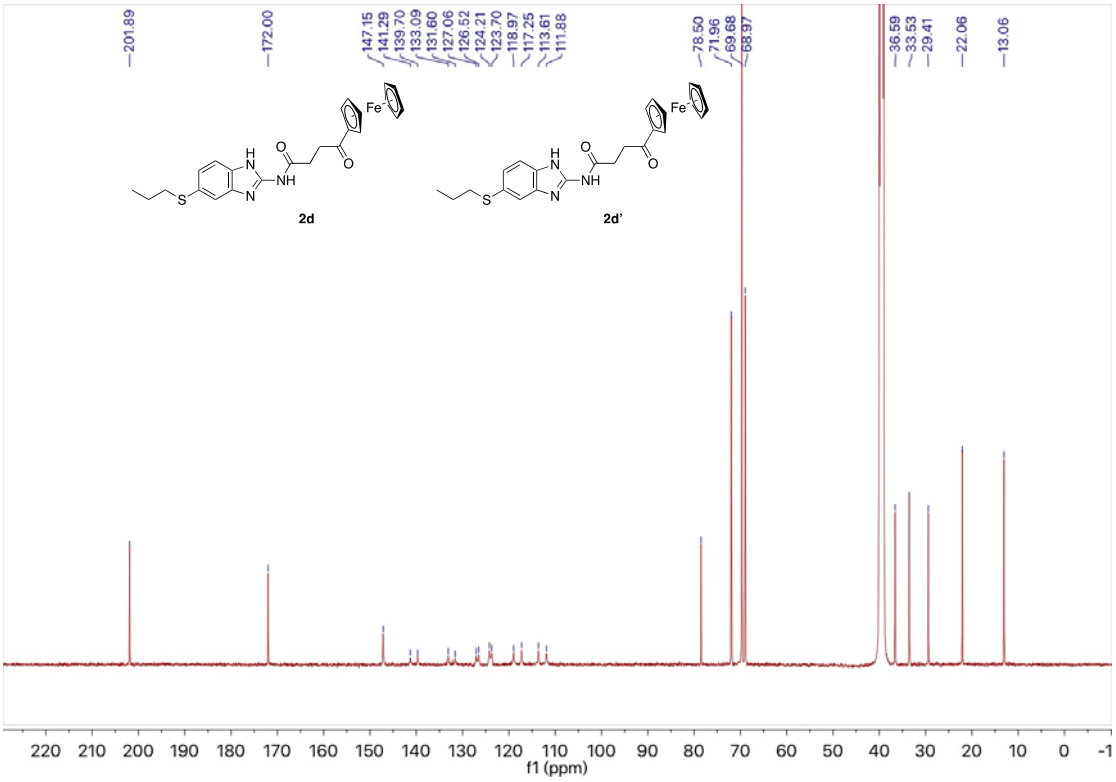


COSY Spectrum of **2c** in DMSO-D6

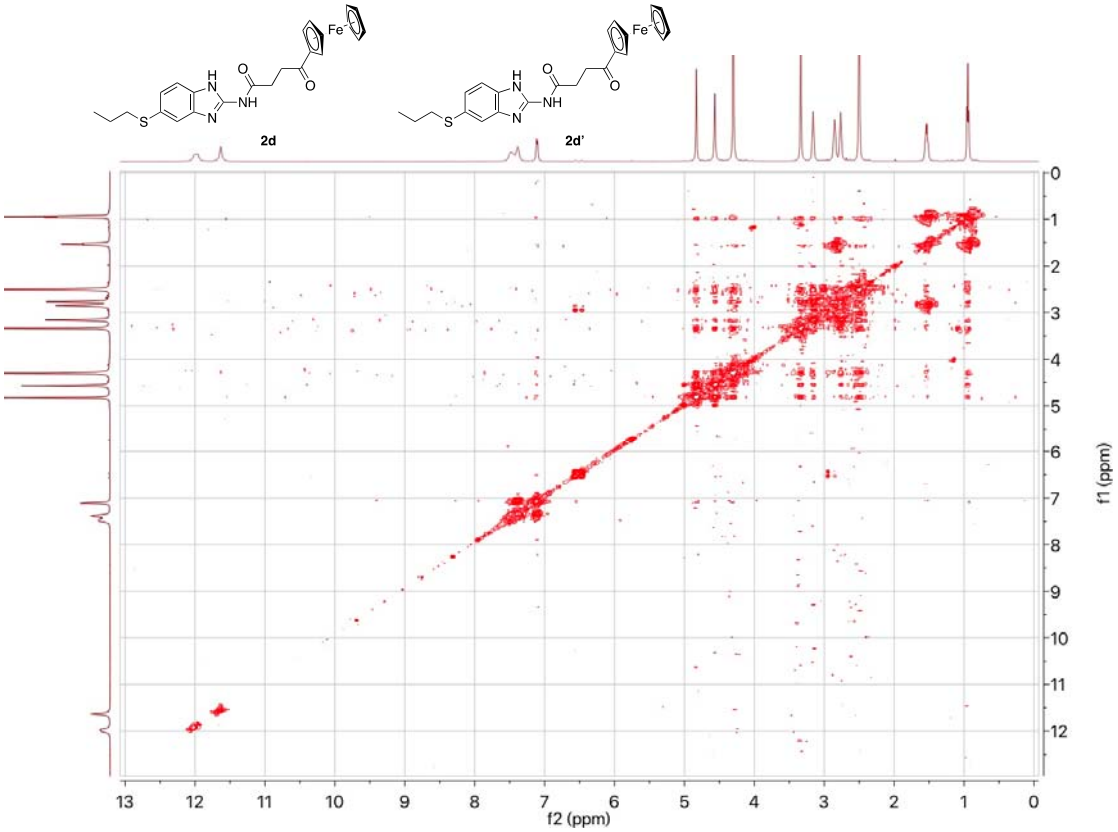


4-Oxo-4-ferrocenyl-N-(5-(propylthio)-1H-benzo[d]imidazol-2-yl)butanamide 2d

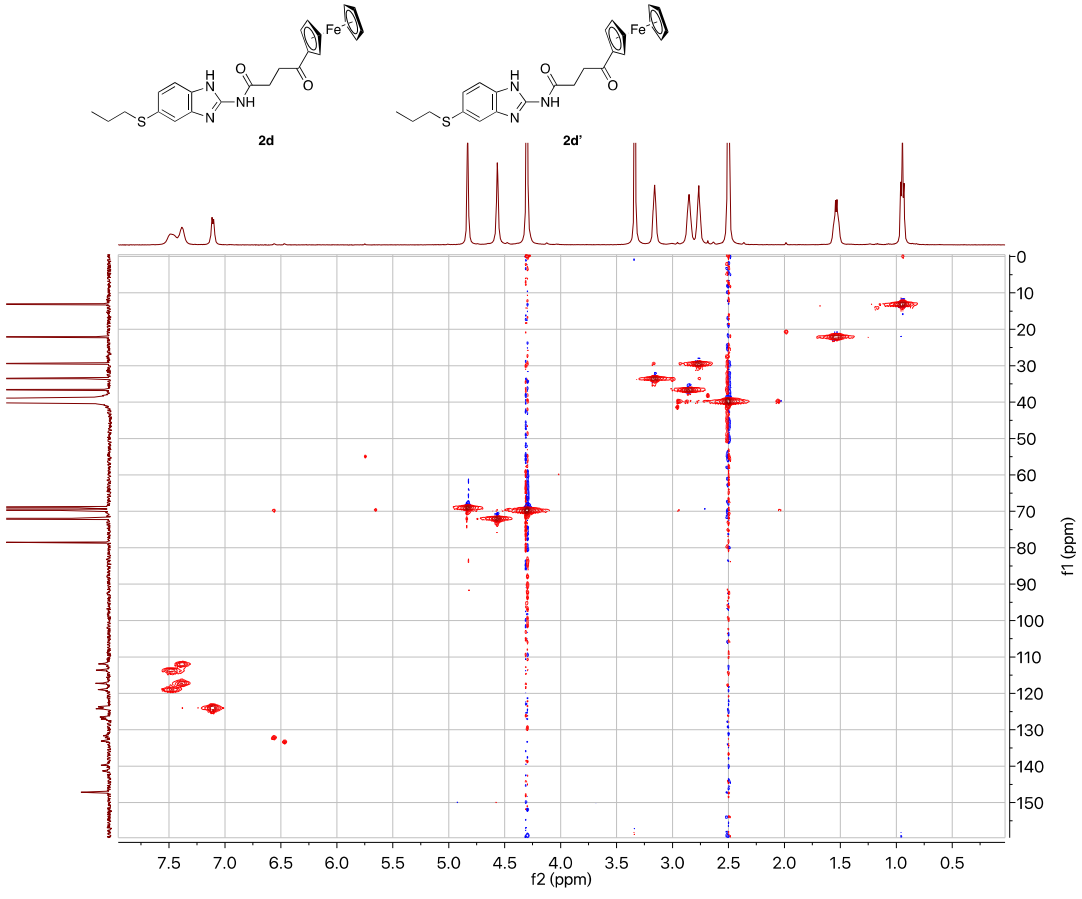




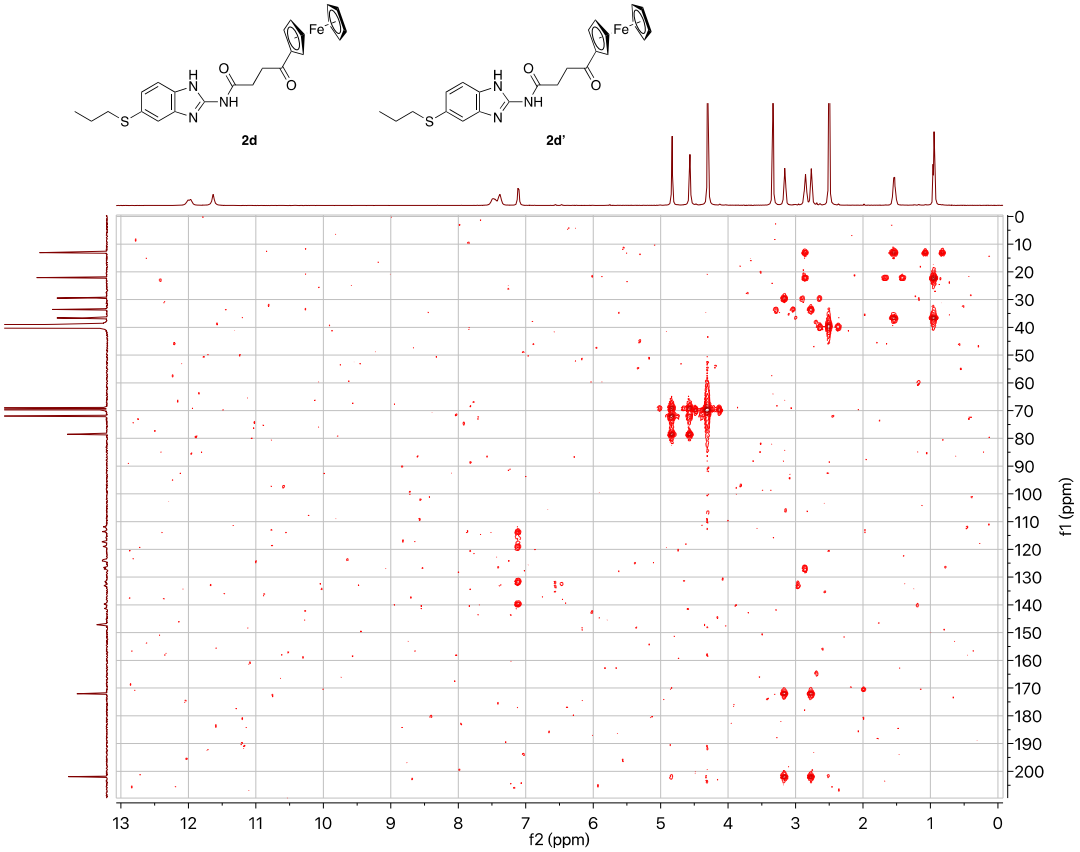
COSY Spectrum of **2d** in DMSO-D6



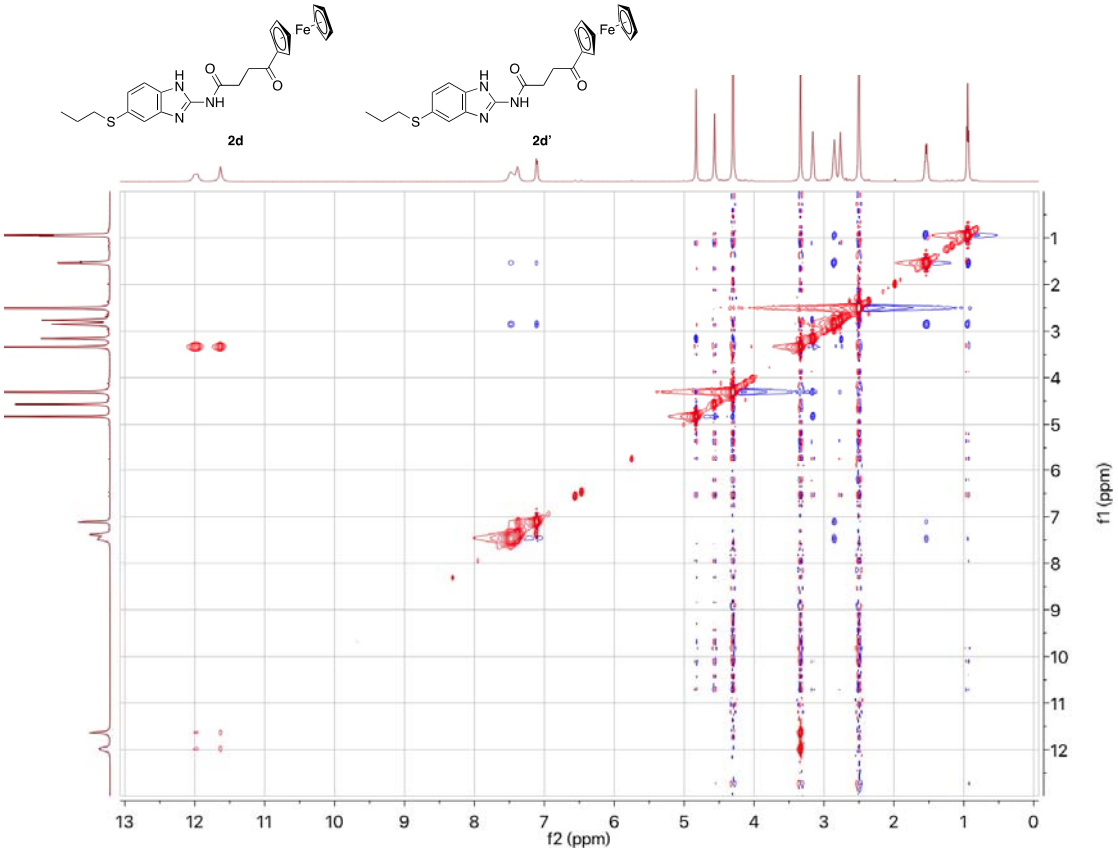
HSQC Spectrum of **2d** in DMSO-D6



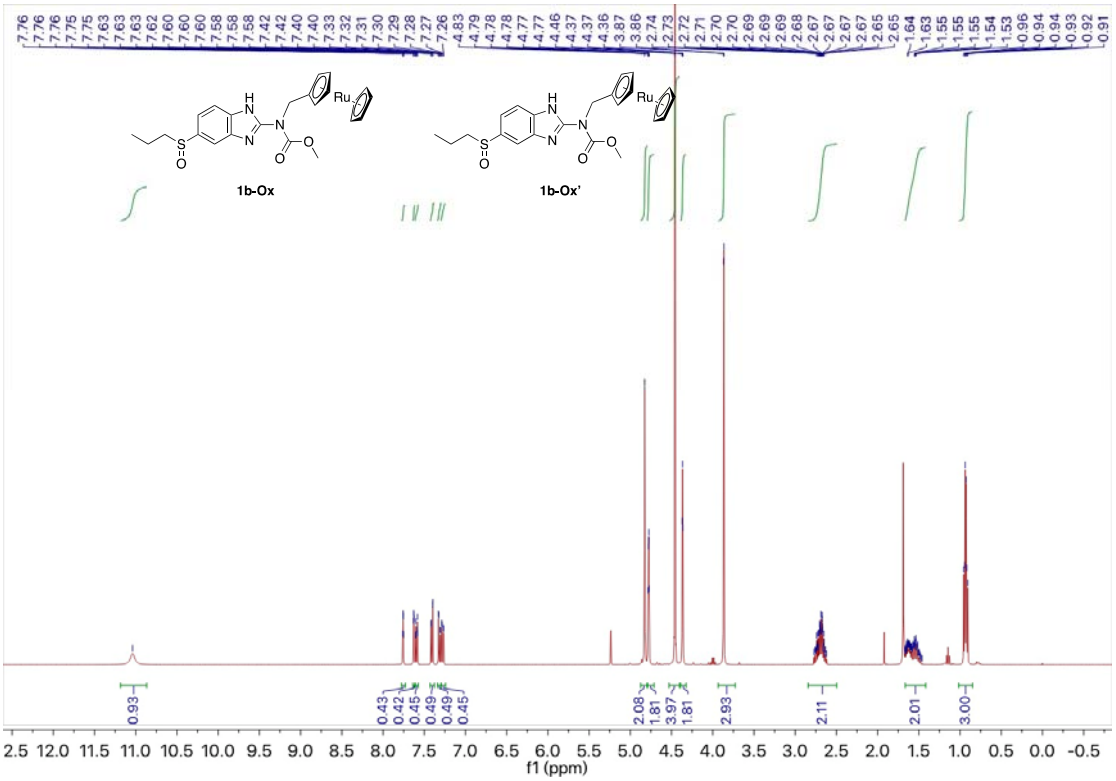
HMBC Spectrum of **2d** in DMSO-D6

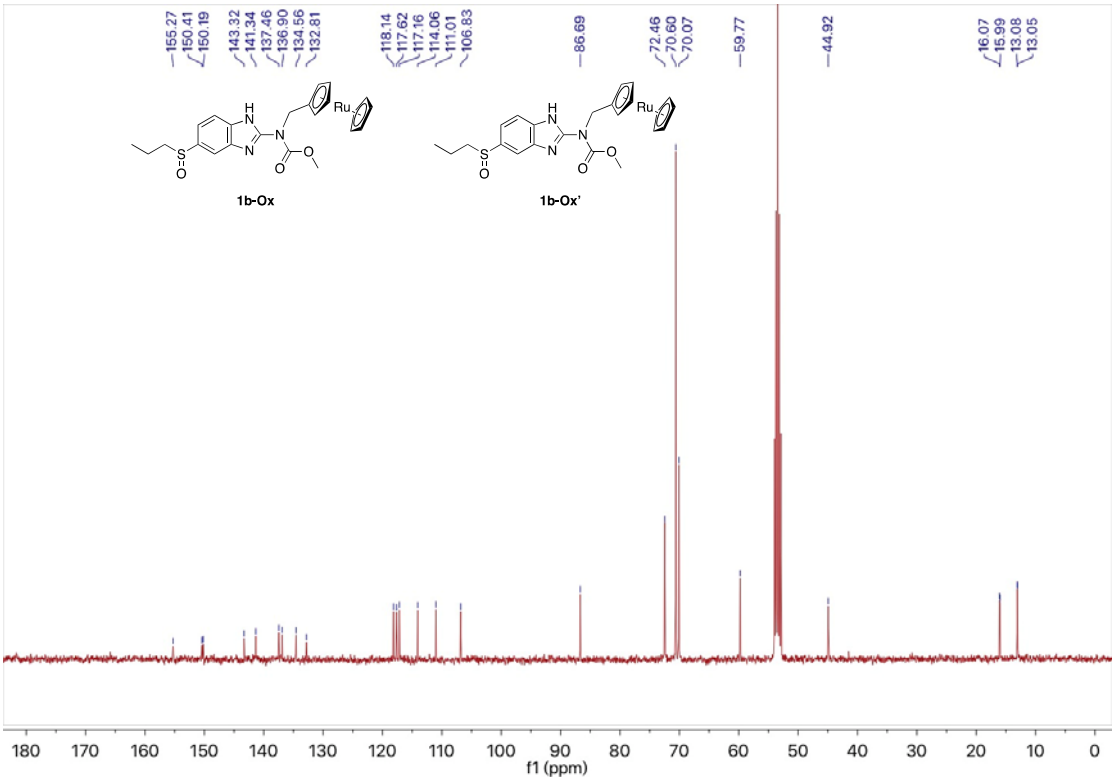


NOESY Spectrum of **2d** in DMSO-D6

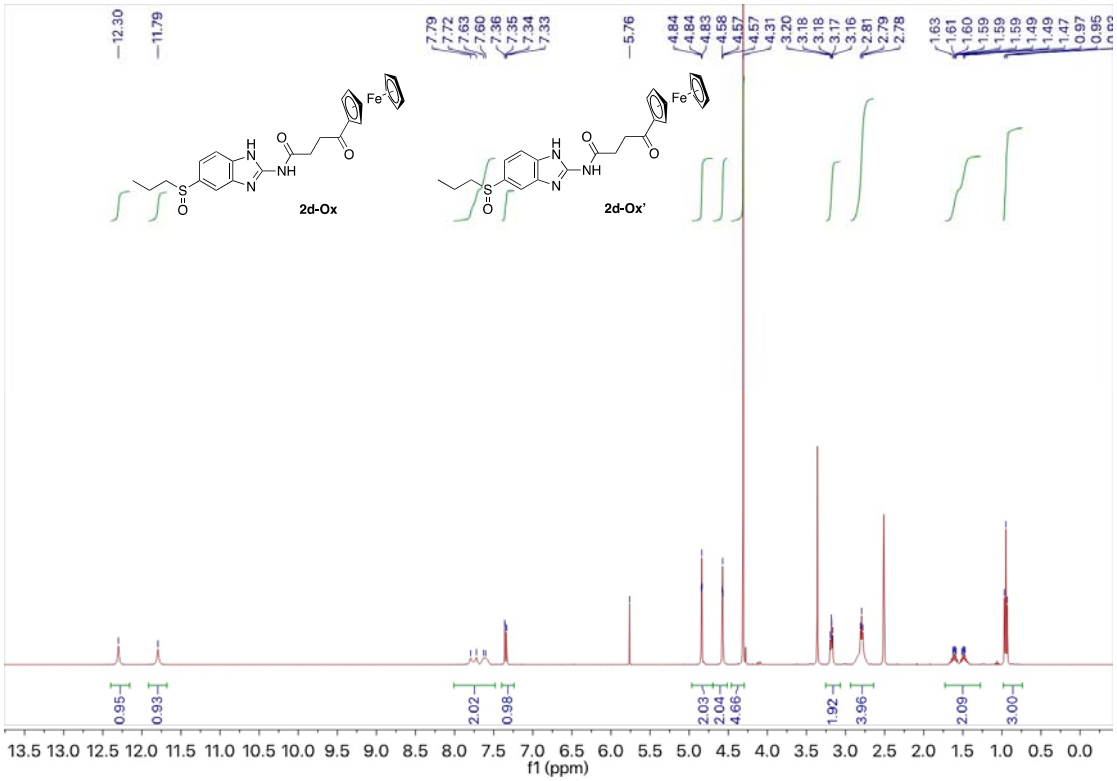


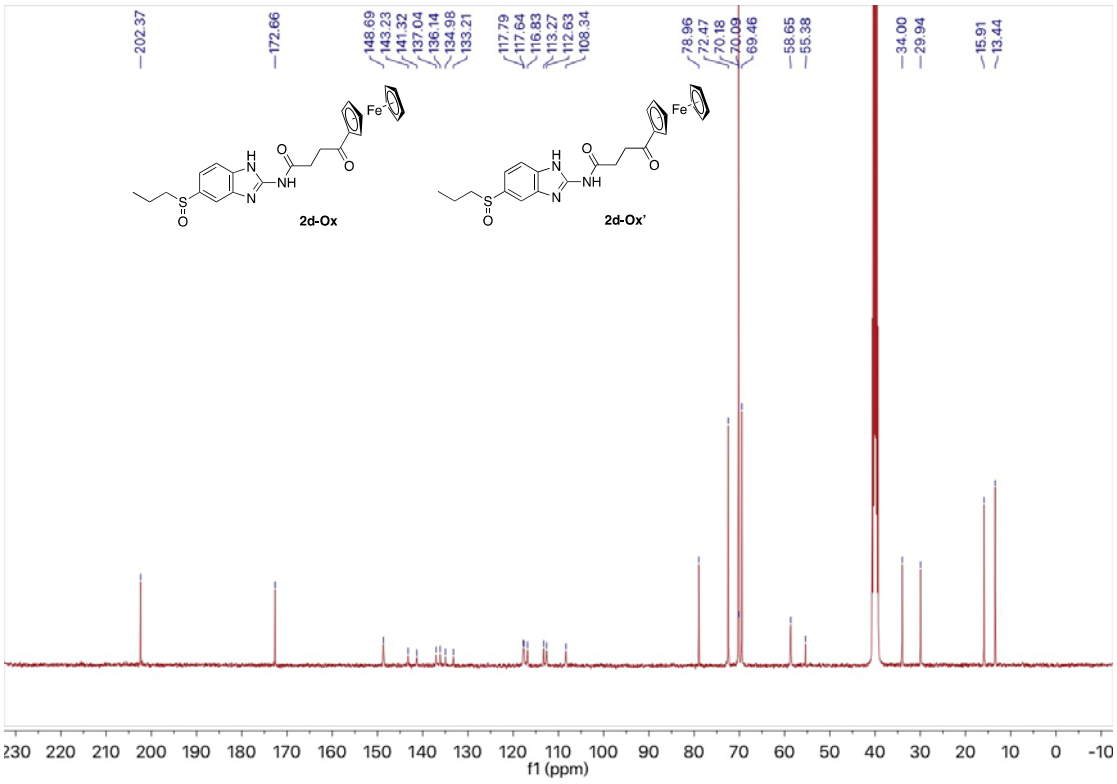
Methyl ruthenocenylmethyl(5-(propylsulfinyl)-1H-benzo[d]imidazol-2-yl)carbamate 1b-Ox



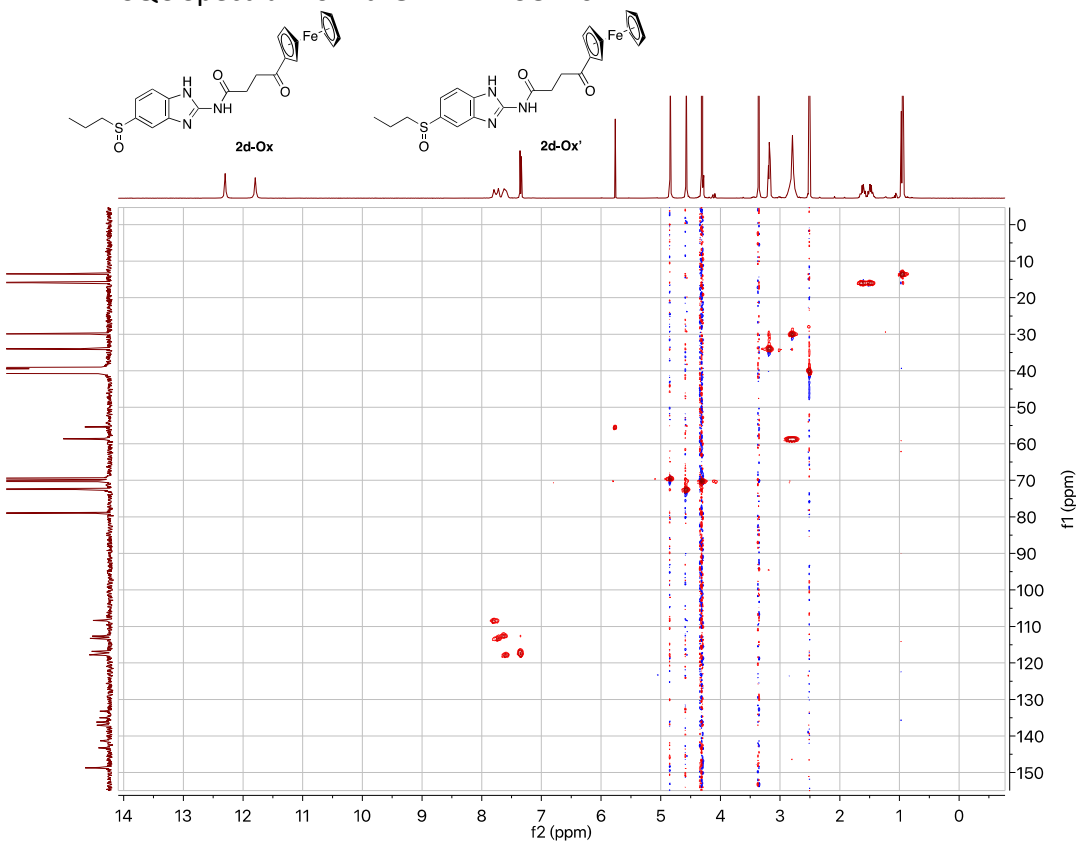


4-Oxo-4-ferrocenyl-N-(5-(propylsulfinyl)-1H-benzo[d]imidazol-2-yl)butanamide 2d-Ox





HSQC Spectrum of **2d-Ox** in DMSO-D6



Material and Methods for stability measurements in human plasma

The stability of the complexes was evaluated with caffeine as an internal standard. The pooled human plasma was obtained from Bio-west and caffeine from TCI Chemicals. To 975 µL of plasma, 12.5 µL of the respective compound (5.0 mM in DMSO) and 12.5 µL caffeine (5.0 mM in Water) were added to a total volume of 1000 µL. The resulting aqueous solutions were incubated for specific hours (0 h, 1 h, 3 h, 6 h and 24 h) at 37°C with continuous and gentle shaking at 700 rpm (*Thermo-Shaker TS-100*) while protected from light. Then the plasma solution was quenched with 1 mL MeOH and 3 mL CH_2Cl_2, the resulted mixture was shaken for 30 min at room temperature followed by centrifugation (5000 rpm – about 2660 G) for 10 min. The organic layer was separated from the aqueous layer and removed CH_2Cl_2 under rotary evaporator. The obtained residue was dissolved in 200 µL CH_3CN (HPLC grade). The solution was filtered through a 0.2 µm membrane filter and analysed using a 1260 Infinity HPLC System (Agilent Technology). A Pursuit XRs 5 C18 (250 x 4.6 mm) reverse phase column has been measured with a flow rate of 1mL/min and a linear gradient of purified H_2O and HPLC-grade CH_3CN (method 1: t = 0-3 min 85% CH_3CN, 15% H_2O; t = 7-9 min 100% CH_3CN; t =11 min 85% CH_3CN; method 2: t = 0-2 min 80% CH_3CN, 20% H_2O; t = 2.1-10 min 100% CH_3CN; method 3: t = 0-3 min 5% CH_3CN, 95% H_2O; t = 13-18 min 100% CH_3CN), Phenomenex LC C12 Column 250 x 4.6 mm has been measured with a flow rate of 1mL/min and a linear gradient of 0.02% HCOOH containing purified H_2O and HPLC-grade CH_3CN (method 4: t = 0 min 50% CH_3CN, 50% H_2O; t = 10 min 80% CH_3CN, 20% H_2O; t = 13-15 min 100% CH_3CN).

HPLC and LC-MS spectrums of human plasma stability

Methyl ferrocenylmethyl(5-(propylthio)-1H-benzo[d]imidazol-2-yl)carbamate 1a

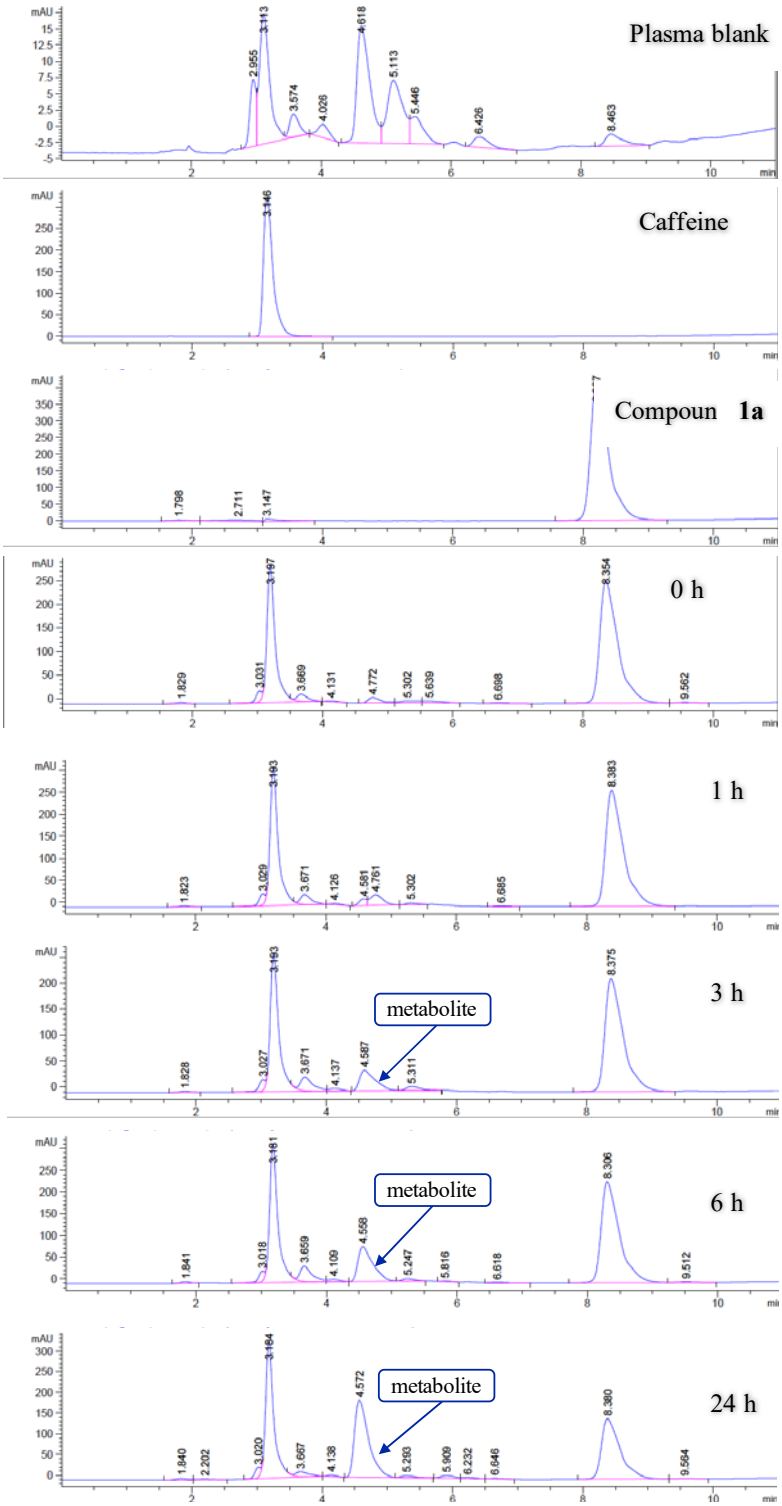


Figure S1. Stacked HPLC Chromatogram (UV traces at 265nm) of **1a** after incubation in human plasma with C18 column by method 1.

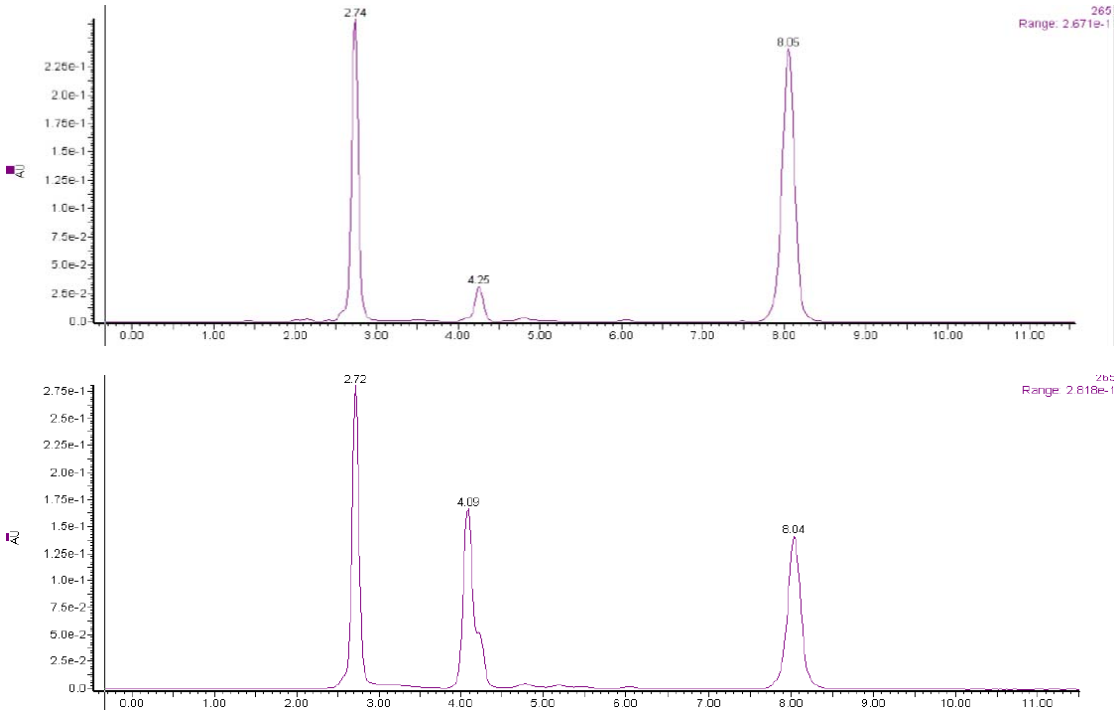


Figure S2. Chromatogram (UV traces at 265nm) of LC analysis of **1a** after incubation in human plasma at *t* = 0 h (above) and *t* = 24 h (below)

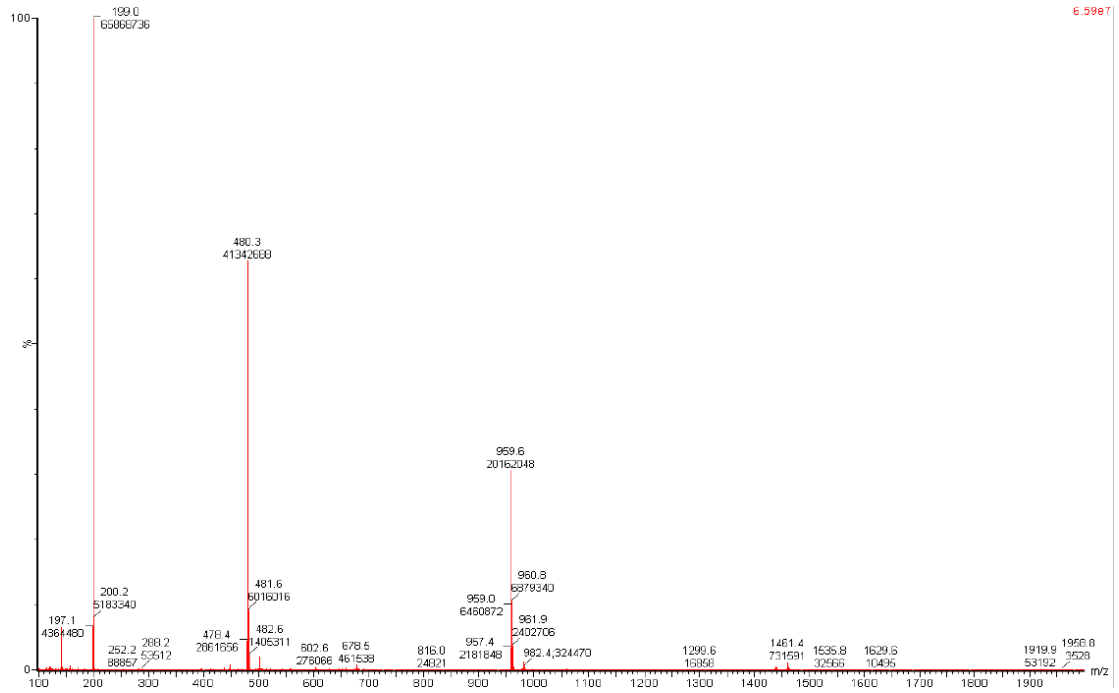


Figure S3. MS spectrum corresponding to the peak at 4.09 min.

Methyl ruthenocenylmethyl(5-(propylthio)-1H-benzo[d]imidazol-2-yl)carbamate 1b

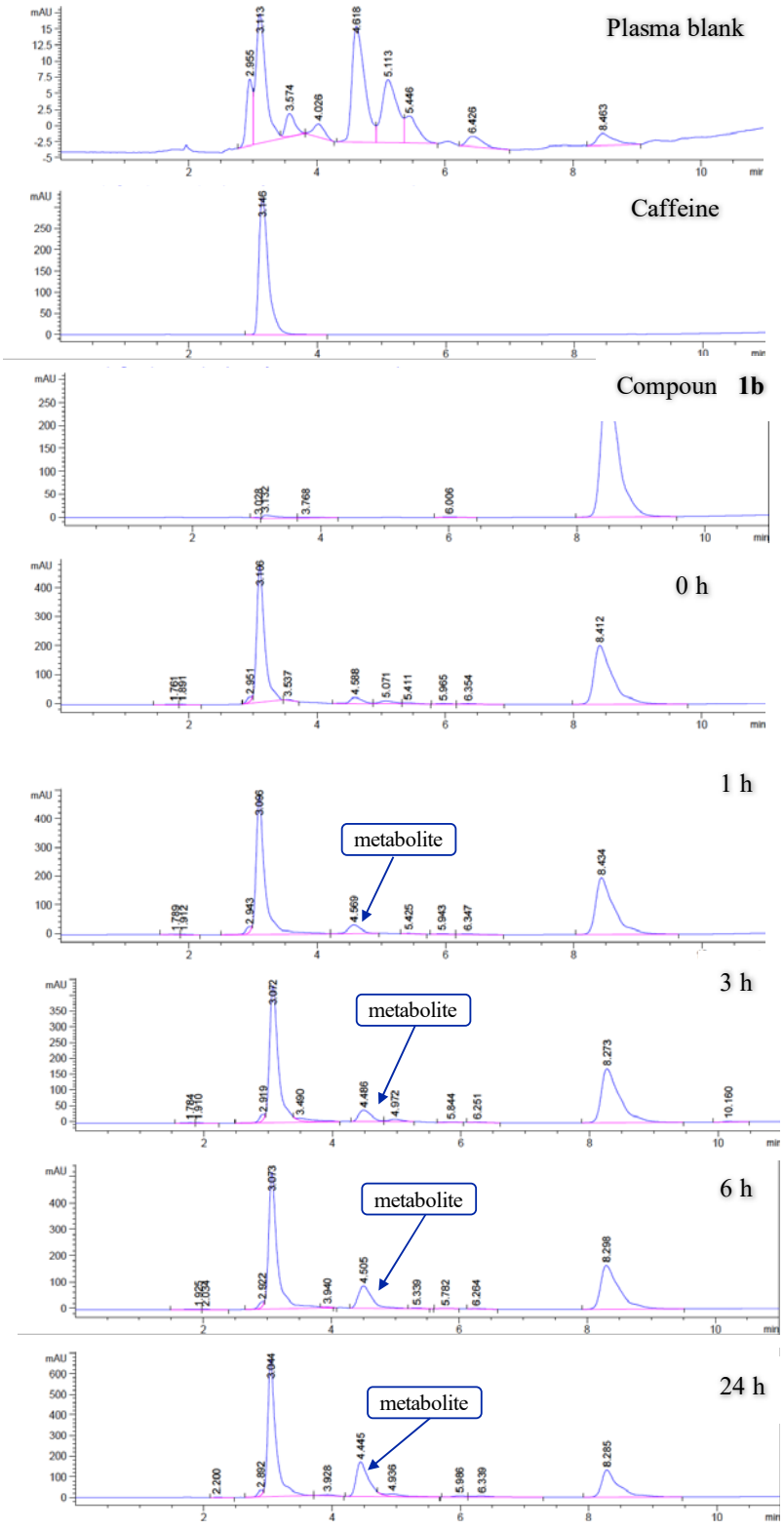


Figure S4. Stacked HPLC Chromatogram (UV traces at 265nm) of **1b** after incubation in human plasma with C18 column by method 1.

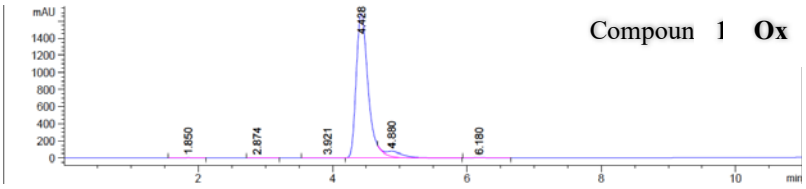


Figure S5. HPLC Chromatogram (UV traces at 265nm) of **1b-Ox** with C18 column by method 1.

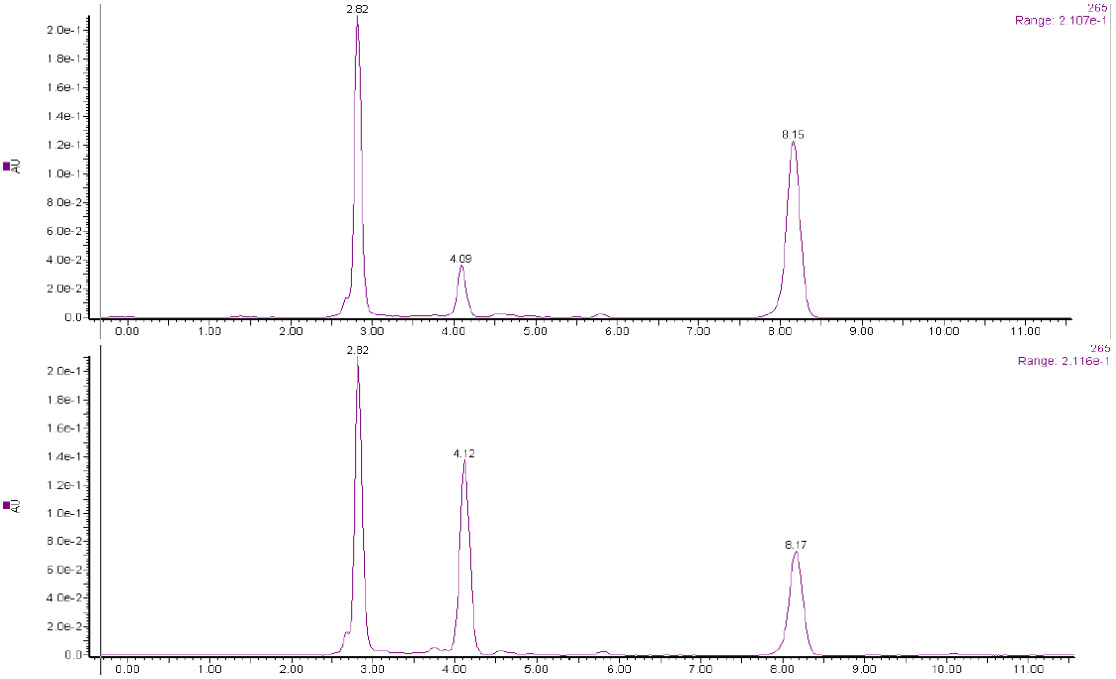


Figure S6. Chromatogram (UV traces at 265nm) of LC analysis of **1b** after incubation in human plasma at *t* = 0 h (above) and *t* = 24 h (below)

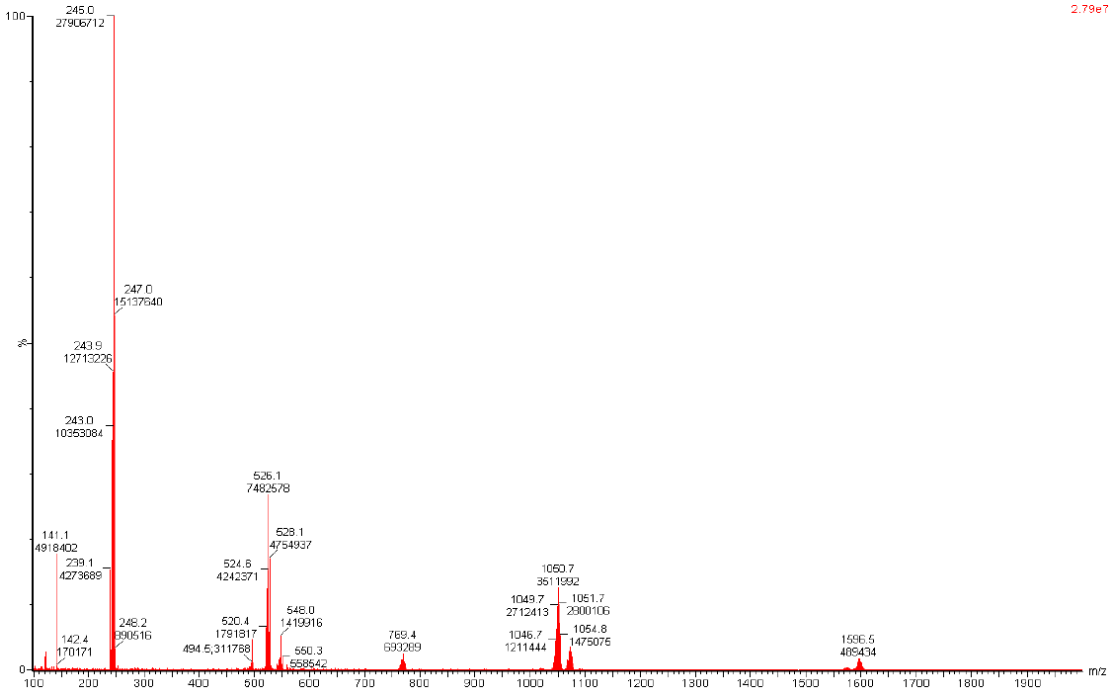


Figure S7. MS spectrum corresponding to the peak at 4.12 min.

Methyl (2-Ferrocenylvinyl)-methyl-(5-(propylthio)-1H-benzo[d]imidazol-2-yl)carbamate 1c

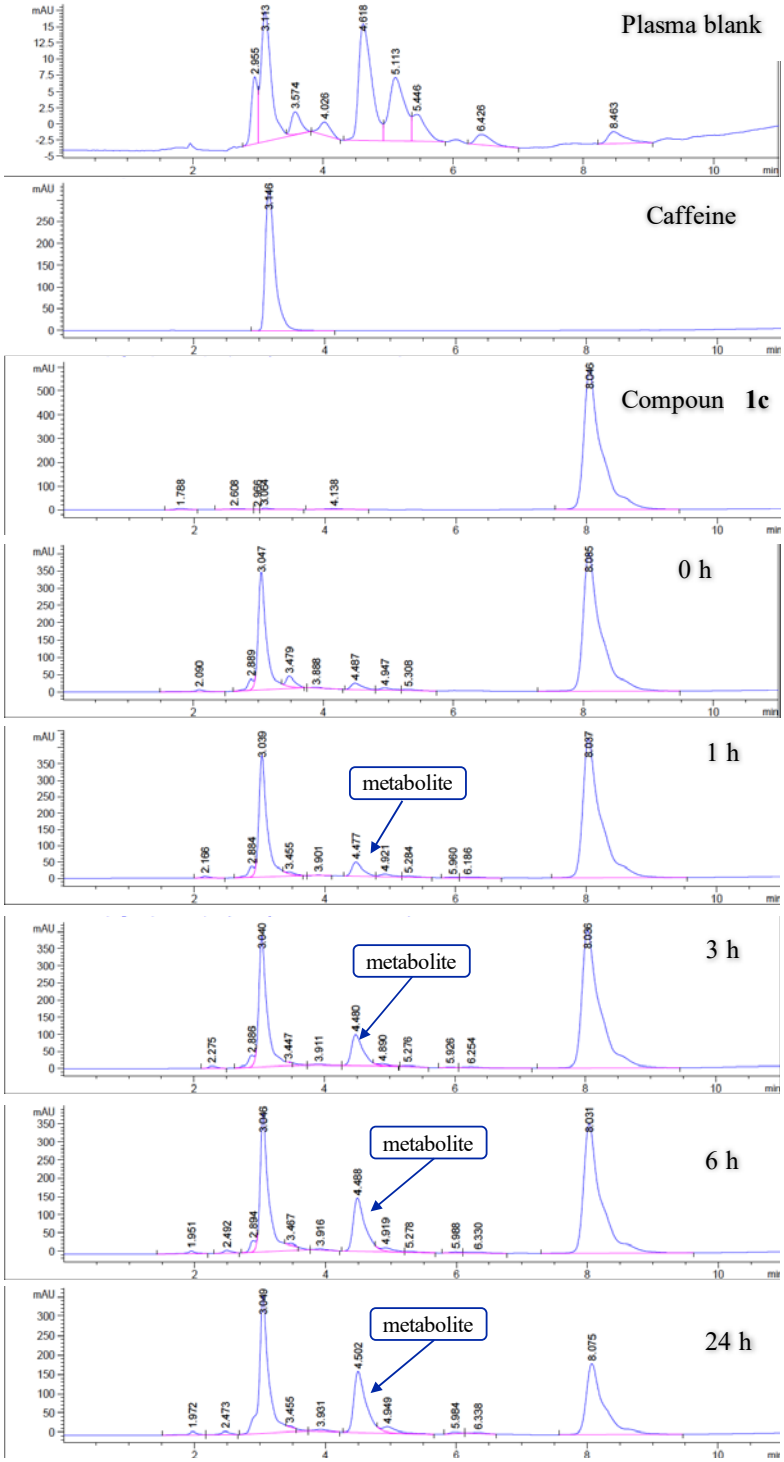


Figure S8. Stacked HPLC Chromatogram (UV traces at 265nm) of **1c** after incubation in human plasma with C18 column by method 1.

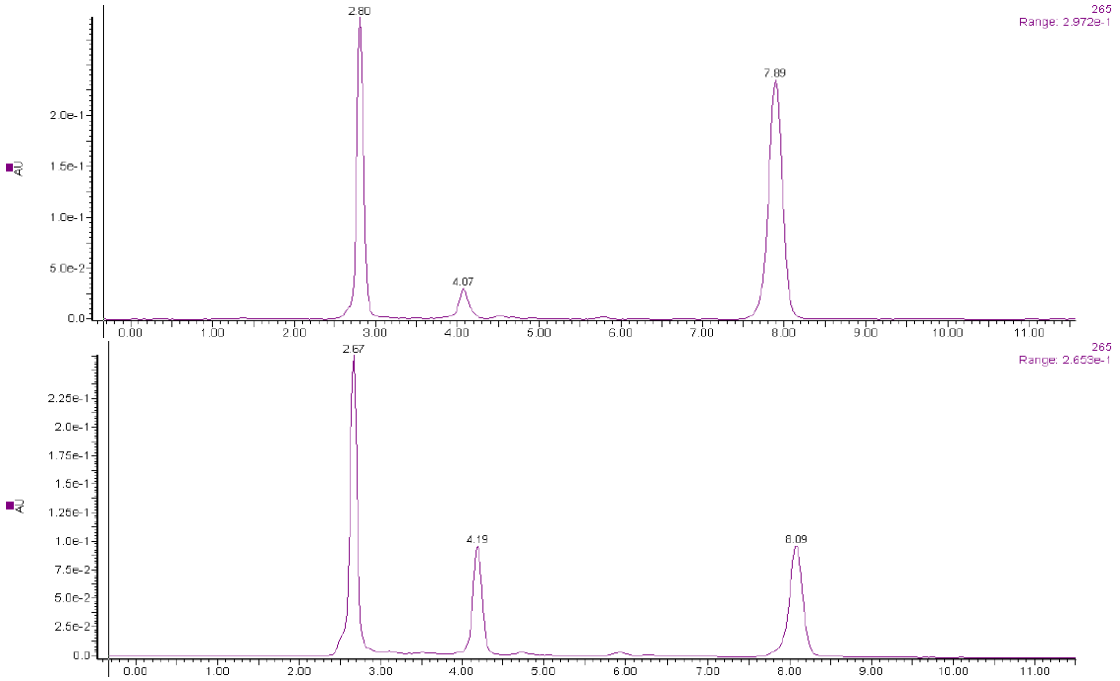


Figure S9. Chromatogram (UV traces at 265nm) of LC analysis of **1c** after incubation in human plasma at *t* = 0 h (above) and *t* = 24 h (below)

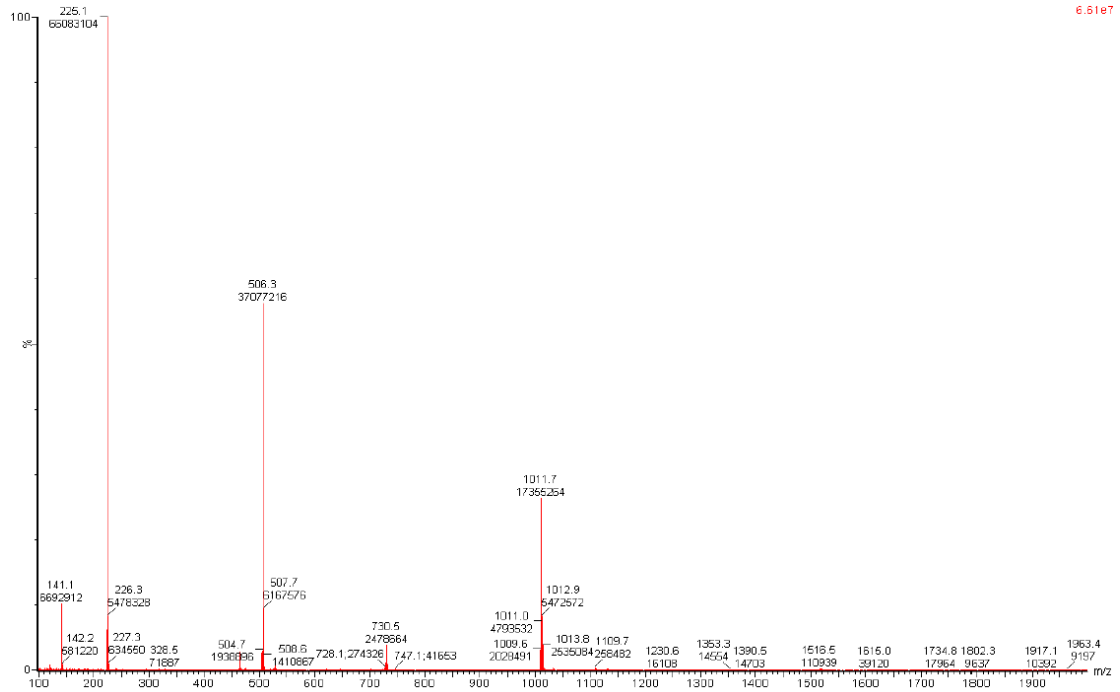


Figure S10. MS spectrum corresponding to the peak at 4.19 min.

N-(5-(propylthio)-1H-benzo[d]imidazol-2-yl)ferrocenamide 2a

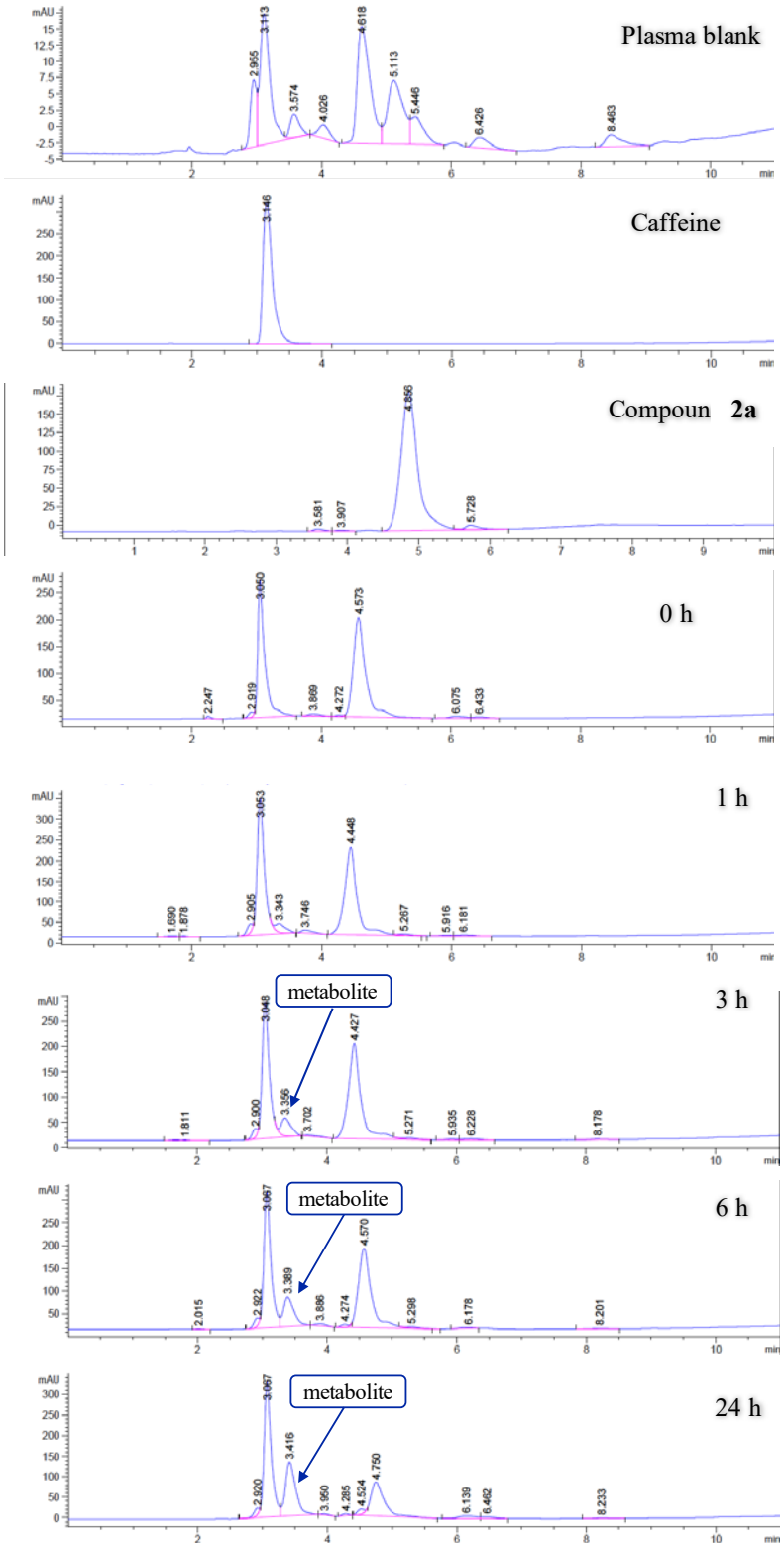


Figure S11. Stacked HPLC Chromatogram (UV traces at 265nm) of **2a** after incubation in human plasma with C18 column by method 1.

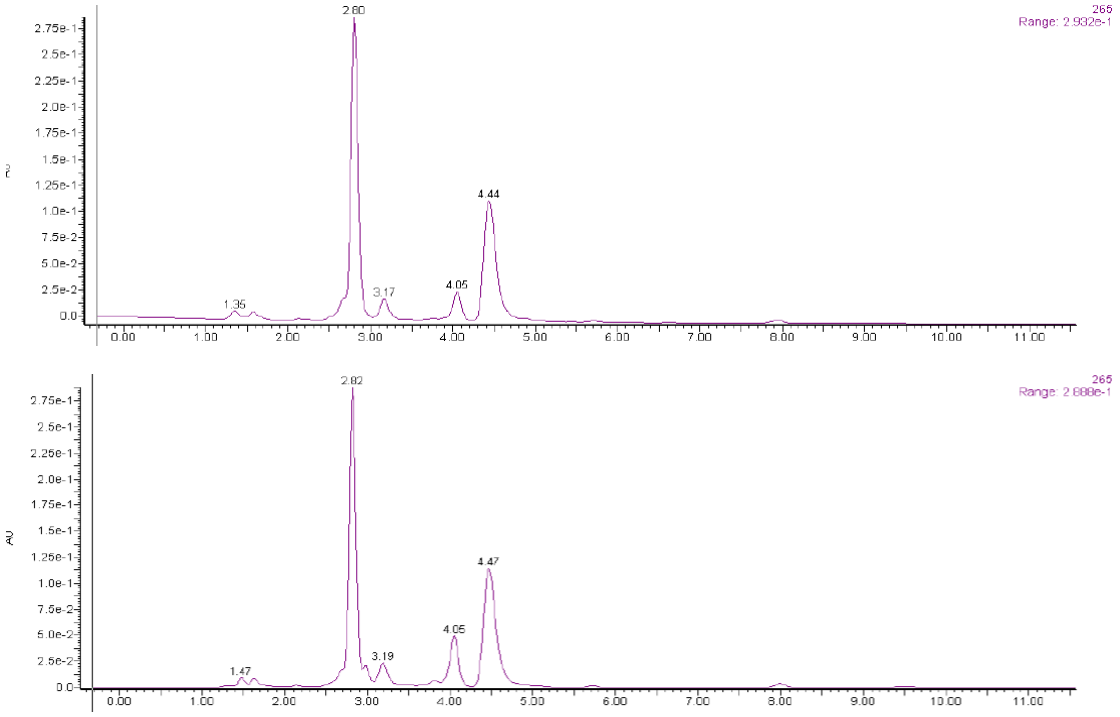


Figure S12. Chromatogram (UV traces at 265nm) of LC analysis of **2a** after incubation in human plasma at *t* = 0 h (above) and *t* = 24 h (below)

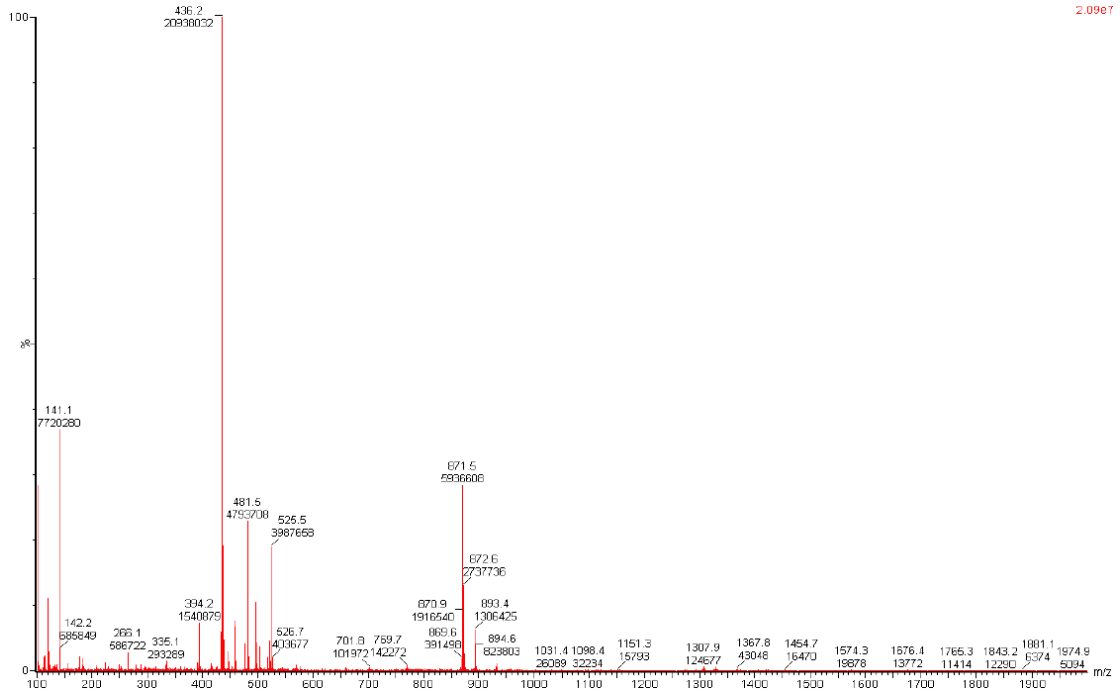


Figure S13. MS spectrum corresponding to the peak at 3.19 min.

N-(5-(propylthio)-1H-benzo[d]imidazol-2-yl)ruthenocenamide 2b

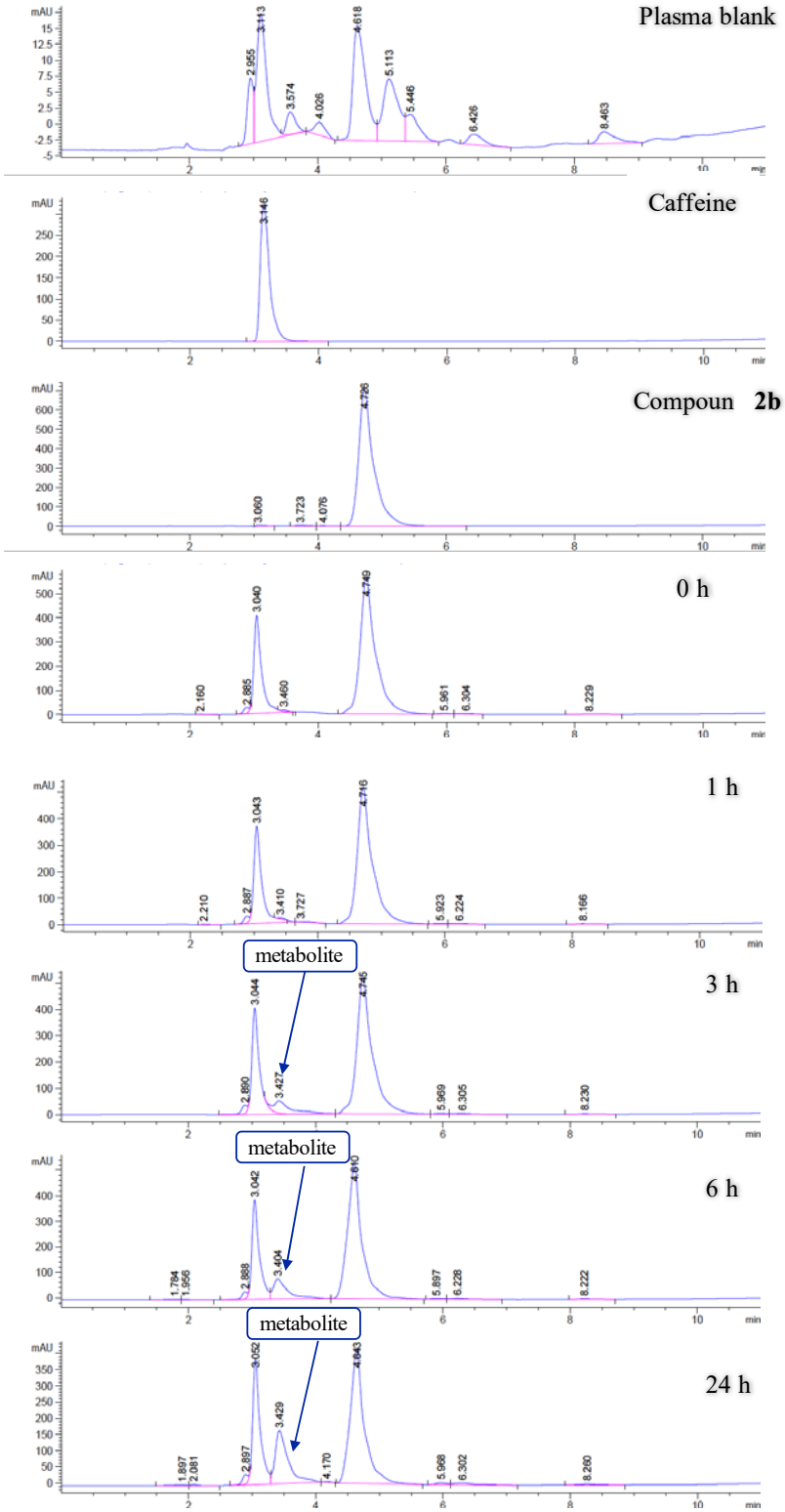


Figure S14. Stacked HPLC Chromatogram (UV traces at 265nm) of **2b** after incubation in human plasma with C18 column by method 1.

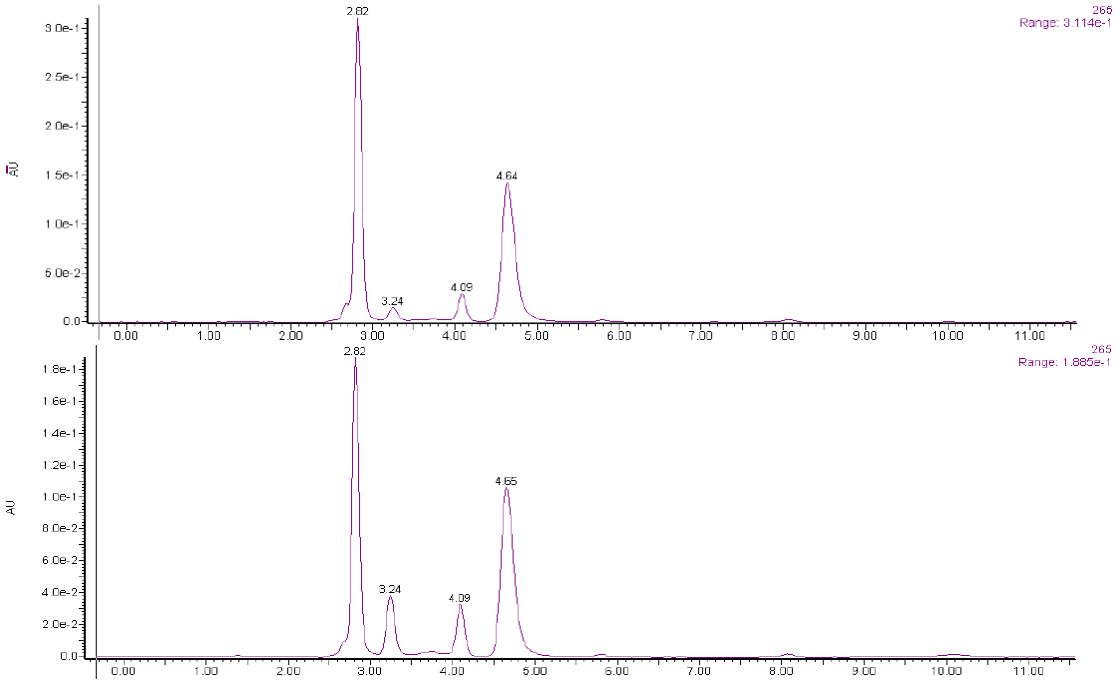


Figure S15. Chromatogram (UV traces at 265nm) of LC analysis of **2b** after incubation in human plasma at *t* = 0 h (above) and *t* = 24 h (below)

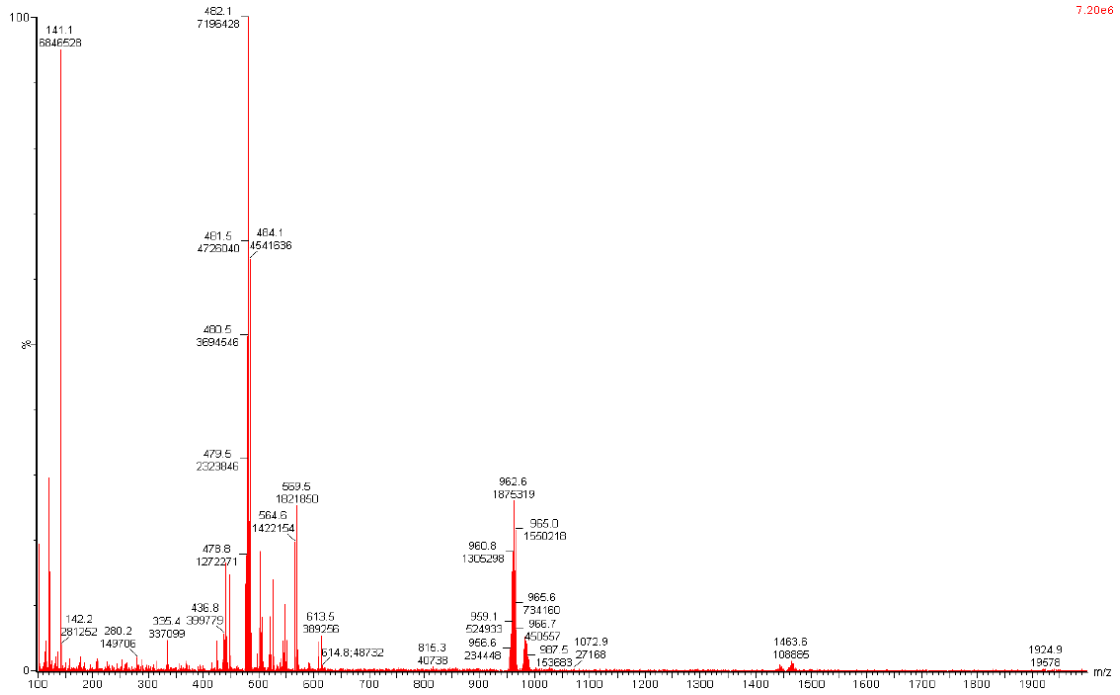


Figure S16. MS spectrum corresponding to the peak at 3.24 min.

2-Ferrocenyl-N-(5-(propylthio)-1H-benzo[d]imidazol-2-yl)acetamide 2c

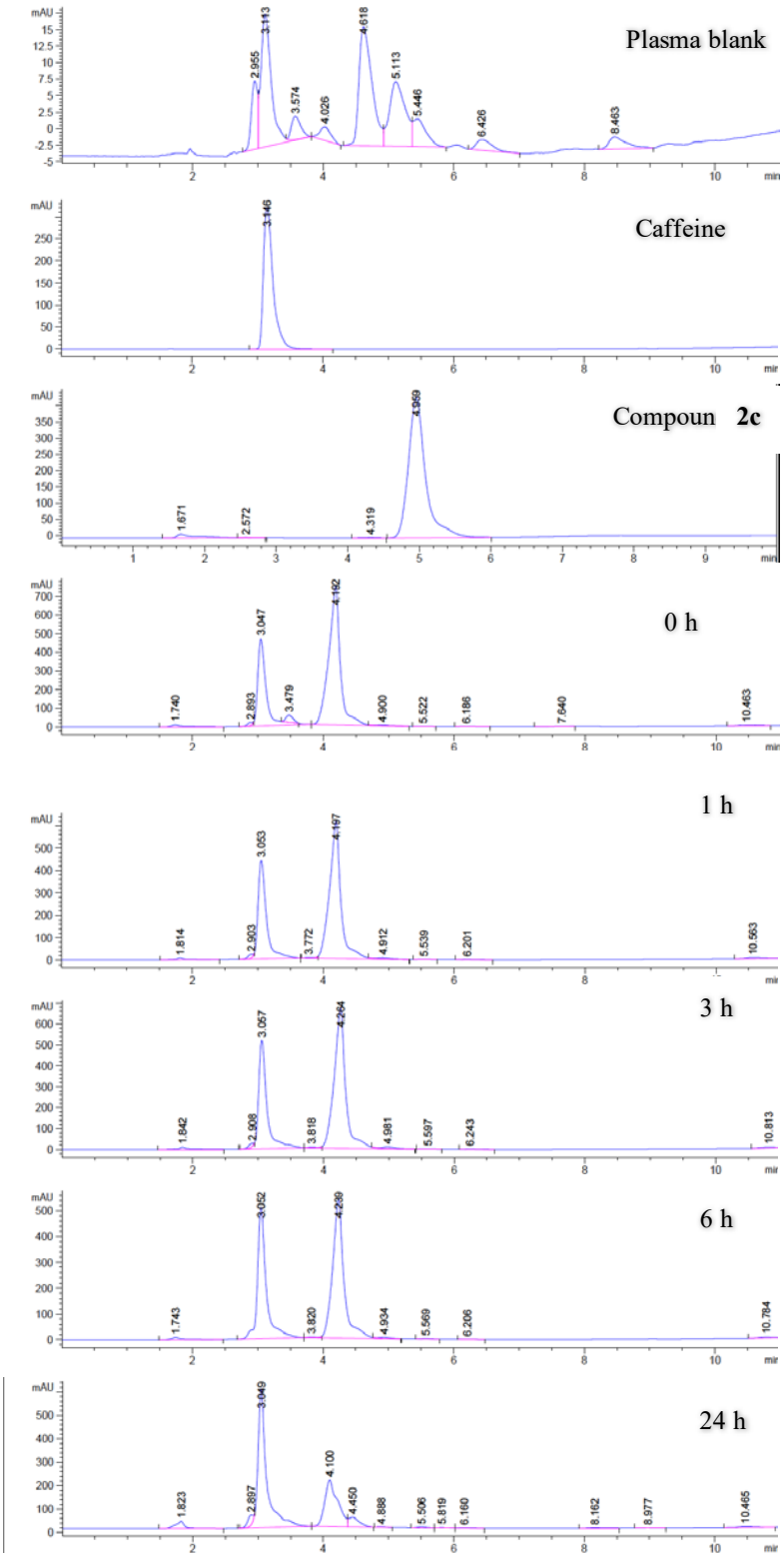


Figure S17. Stacked HPLC Chromatogram (UV traces at 265nm) of **2c** after incubation in human plasma with C18 column by method 1.

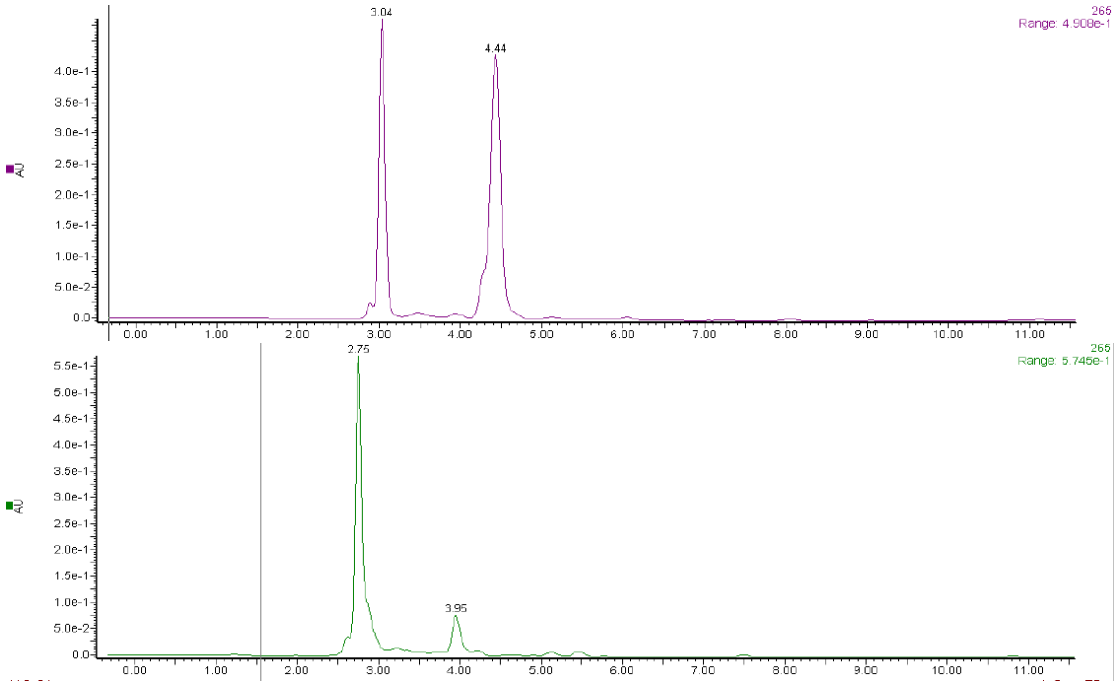


Figure S18. Chromatogram (UV traces at 265nm) of LC analysis of **2c** after incubation in human plasma at *t* = 0 h (above) and *t* = 24 h (below)

4-Oxo-4-ferrocenyl-N-(5-(propylthio)-1H-benzo[d]imidazol-2-yl)butanamide 2d

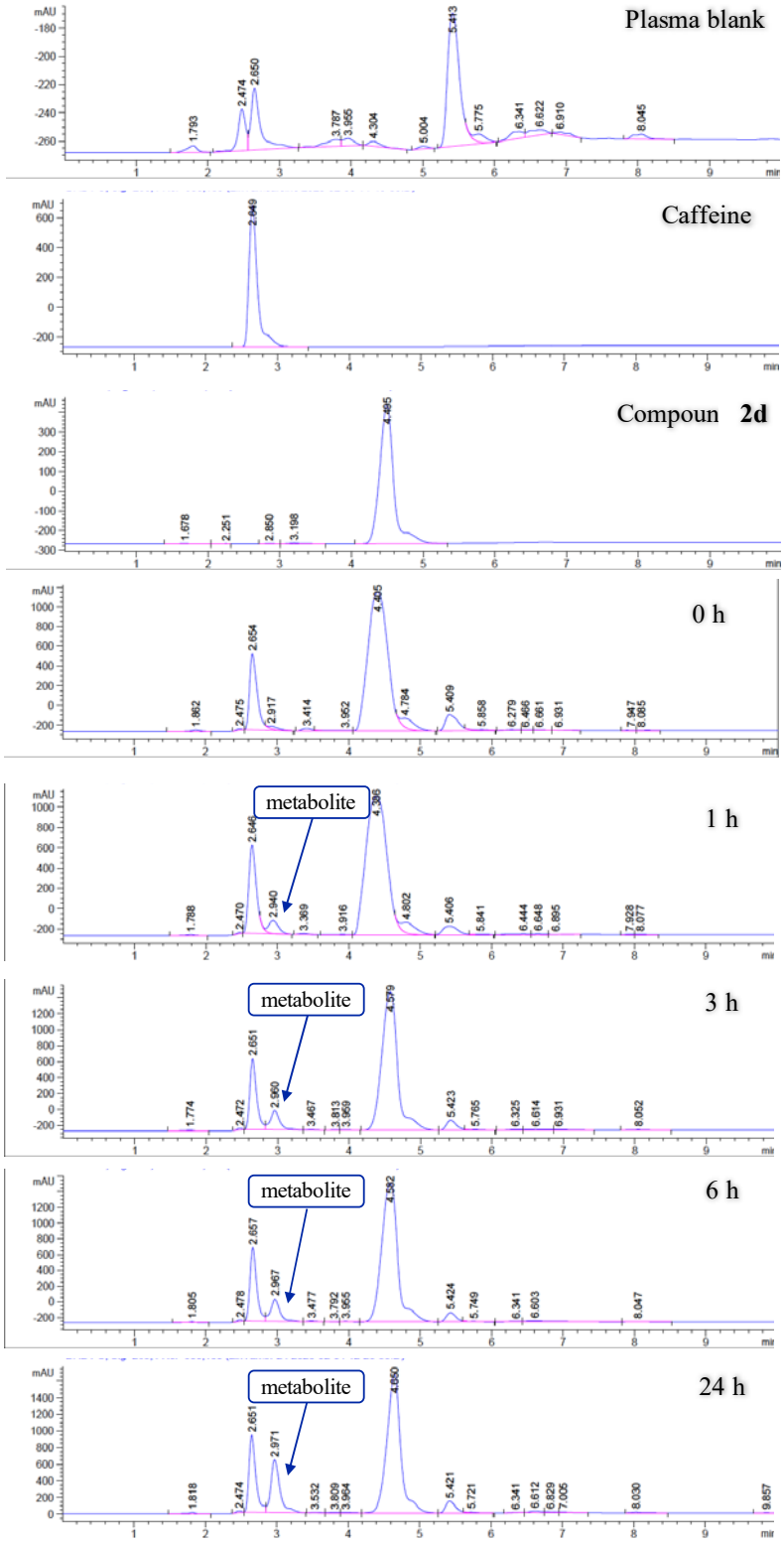


Figure S19. Stacked HPLC Chromatogram (UV traces at 265nm) of **2d** after incubation in human plasma with C18 column by method 2.

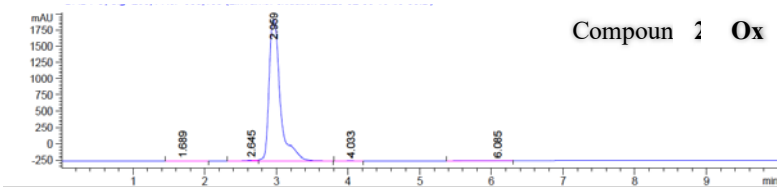
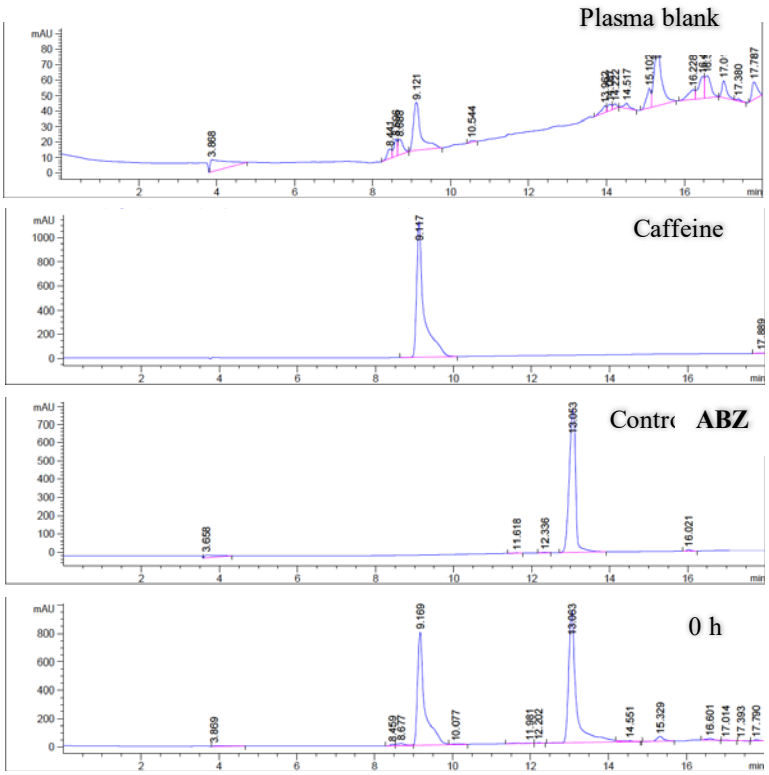


Figure S20. HPLC Chromatogram (UV traces at 265nm) of **2d-Ox** with C18 column by method 2.



Albendazole

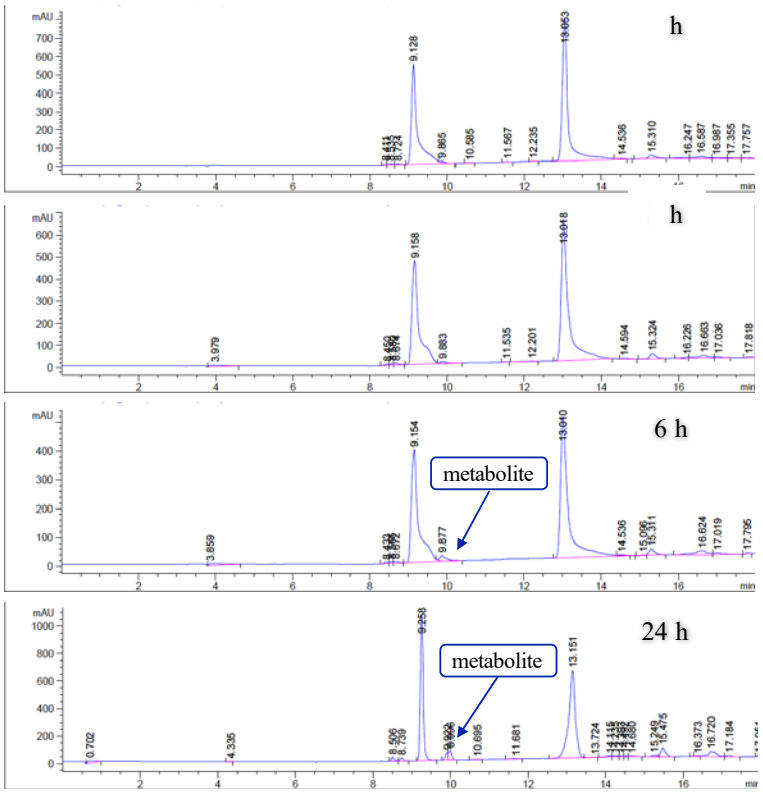


Figure S21. Stacked HPLC Chromatogram (UV traces at 265nm) of **ABZ** after incubation in human plasma with C18 column by method 3.

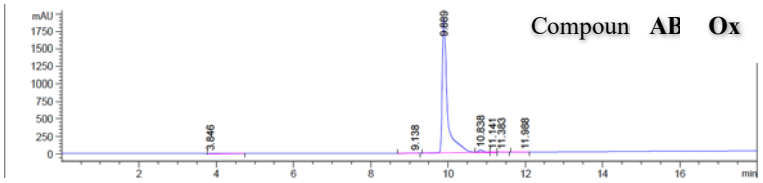


Figure S22. HPLC Chromatogram (UV traces at 265nm) of **ABZ-Ox** with C18 column by method 3.

***Albendazole-amine* ABZ-NH_2**

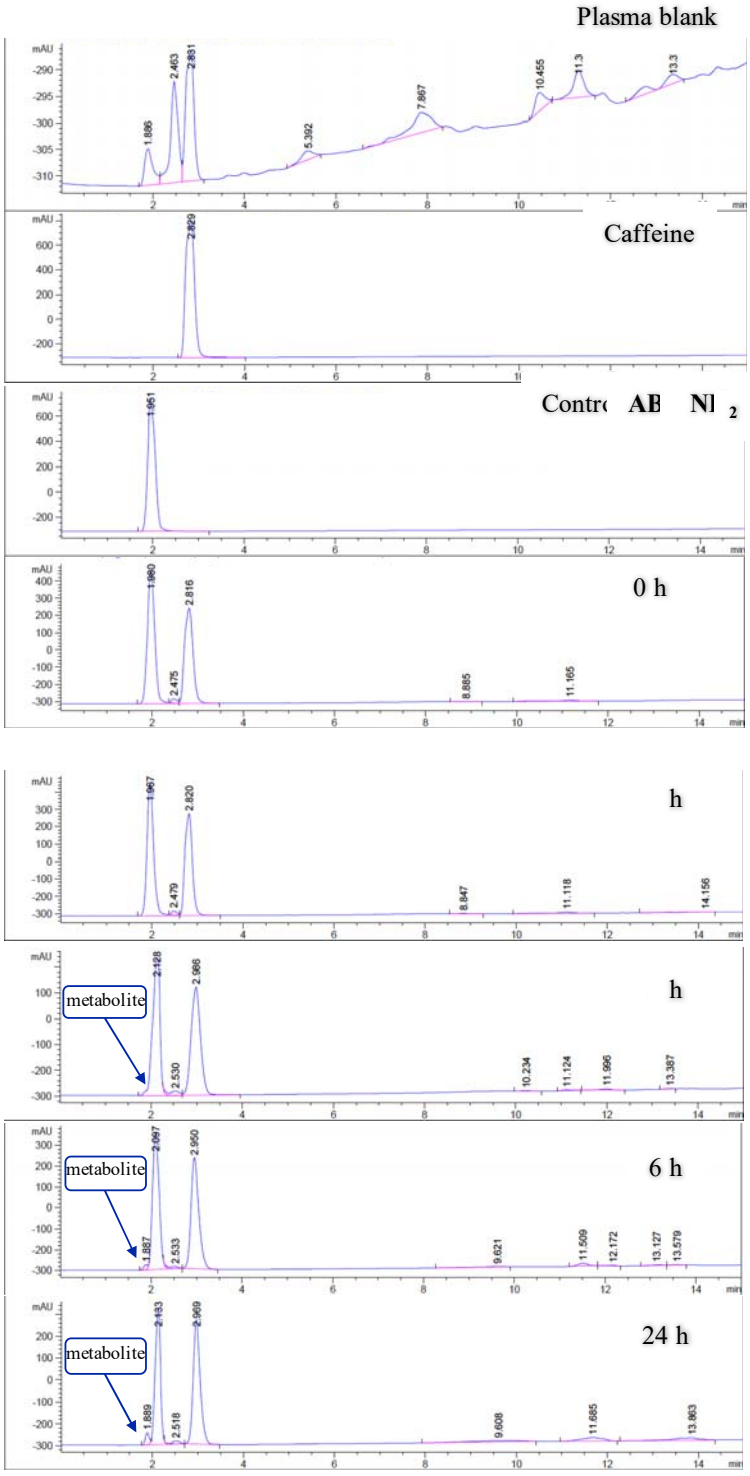


Figure S23. Stacked HPLC Chromatogram (UV traces at 265nm) of **ABZ-NH_2** after incubation in human plasma with C12 column by method 4.

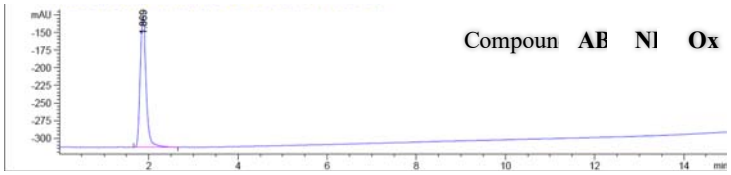


Figure S24. HPLC Chromatogram (UV traces at 265nm) of **ABZ-NH_2-Ox** with C12 column by method 4.

X-ray crystallography

Complexes **1a, 1b** and **1c** were fully characterized using single-crystal X-ray diffraction studies (Figures S25, S26, S27). The X-ray diffraction data were collected at 160(1) K on a Rigaku Oxford Diffraction Synergy (Pilatus 200K detector) diffractometer[7] equipped with an Oxford liquid-nitrogen Cryostream cooler and using a single wavelength X-ray source from a micro-focus sealed X-ray tube with the Cu K_{α} radiation (□□= 1.54184 Å). The selected single crystals were mounted using polybutene oil on a flexible loop fixed on a goniometer head and transferred to the diffractometer. Pre-experiments, data collections, data reductions and analytical absorption corrections[8] were performed with the program suite *CrysAlisPro*.[7] Using *Olex2*,[9] the structures were solved with the SHELXT[10] small molecule structure solution program and refined with the *SHELXL2018/3* program package[11] by full-matrix least-squares minimization on F^2. CCDC 1987083 (for **1a**), 1987085 (for **1b**) and 1987084 (for **1c**) contain the supplementary crystallographic data for these compounds, and can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Crystal data for **1a**: $C_{23}H_{25}FeN_3O_2S$ (M = 463.37 g/mol), orthorhombic, space group $P2_12_12_1$ (no. 19), a = 5.83485(14) Å, b = 17.7768(6) Å, c = 20.0446(5) Å, V = 2079.12(10) Å^3, Z = 4, T = 160(1) K, μ(CuKα) = 6.961 mm^{-1}, D_{calc} = 1.480 g/cm^3, 17347 reflections measured (6.65° ≤ 2Θ ≤ 148.98°), 4249 unique (R_{int} = 0.0633, R_{sigma} = 0.0535) which were used in all calculations. The final R_1 was 0.0485 (I > 2σ(I)) and wR_2 was 0.1265 (all data). Crystal data for **1b**: $C_{23}H_{25}N_3O_2RuS$ (M = 508.59 g/mol), monoclinic, space group $P2_1/c$ (no. 14), a = 14.3677(5) Å, b = 5.7086(2) Å, c = 24.4132(7) Å, □ = 97.675(3)°, V = 1984.42(12) Å^3, Z = 4, T = 160(1) K, μ(CuKα) = 7.595 mm^{-1}, D_{calc} = 1.702 g/cm^3, 22576 reflections measured (6.21° ≤ 2Θ ≤ 136.78°), 22576 unique (R_{sigma} = 0.0383) which were used in all calculations. The final R_1 was 0.0309 (I > 2σ(I)) and wR_2 was 0.0765 (all data). The crystal structure of **1b** was refined as a 2-component twin with a ratio of 0.5358(8) / 0.4642(8). The second component (with the smaller scale) is rotated by 180° around [-0.08 -0.00 1.00] (reciprocal space) or [0 0 1] (direct space). Crystal data for **1c**: $C_{25}H_{27}FeN_3O_2S$ (M = 489.40 g/mol), monoclinic, space group $P2_1/c$ (no. 14), a = 16.3901(5) Å, b = 5.60261(16) Å, c = 23.9440(6) Å, □ = 92.292(3)°, V = 2196.96(11) Å^3, Z = 4, T = 160(1) K, μ(CuKα) = 6.620 mm^{-1}, D_{calc} = 1.480 g/cm^3, 16361 reflections measured (7.39° ≤ 2Θ ≤ 148.91°), 4423 unique (R_{int} = 0.0829, R_{sigma} = 0.0828) which were used in all calculations. The final R_1 was 0.0595 (I > 2σ(I)) and wR_2 was 0.1563 (all data).

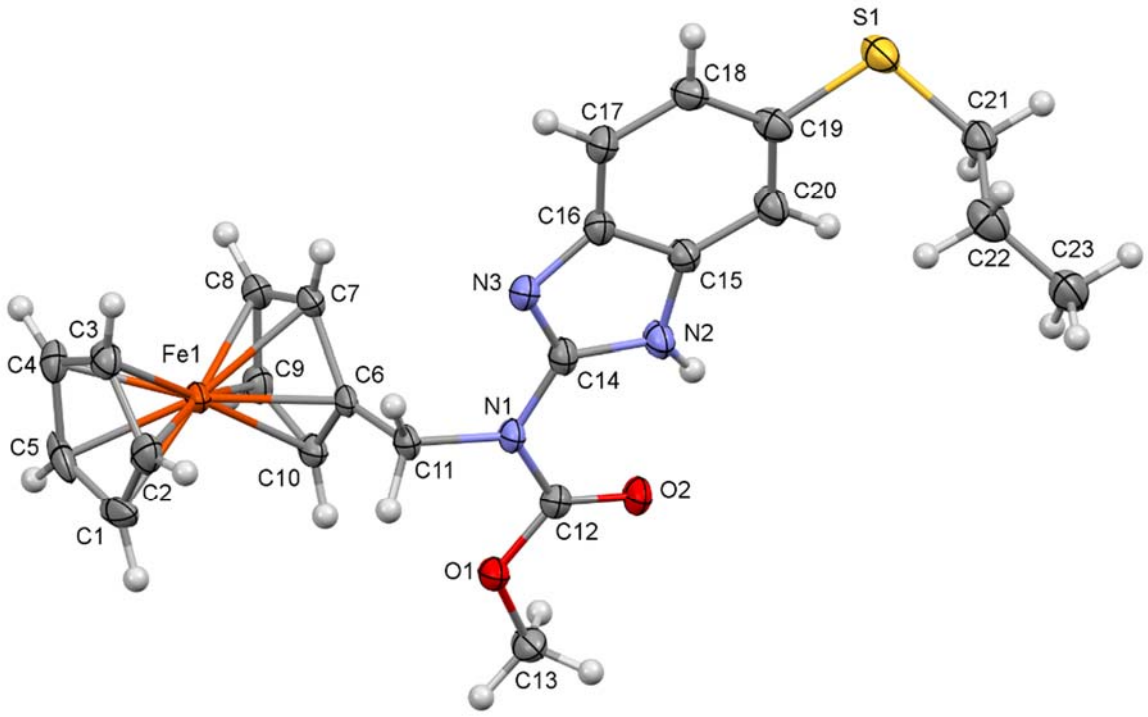


Figure S25. Molecular structure of 1a. The thermal ellipsoids are drawn at the 30% probability level.

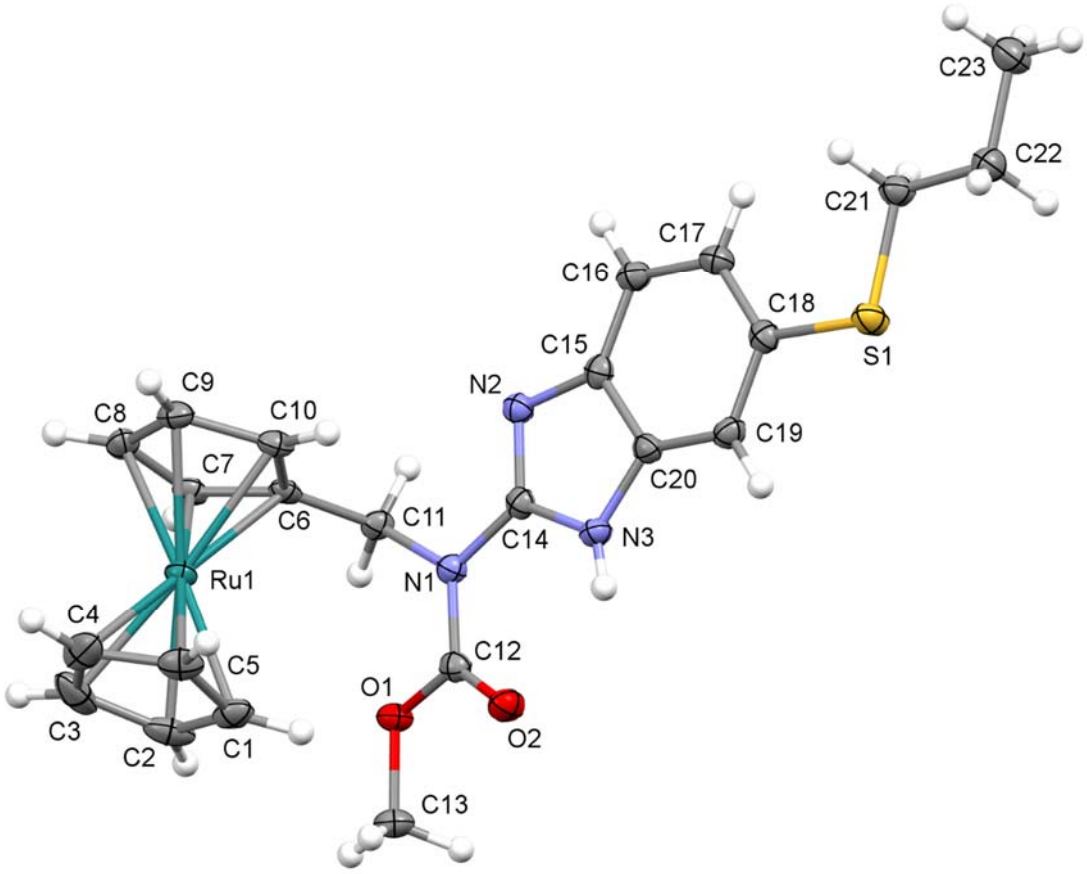


Figure S26. Molecular structure of 1b. The thermal ellipsoids are drawn at the 50% probability level.

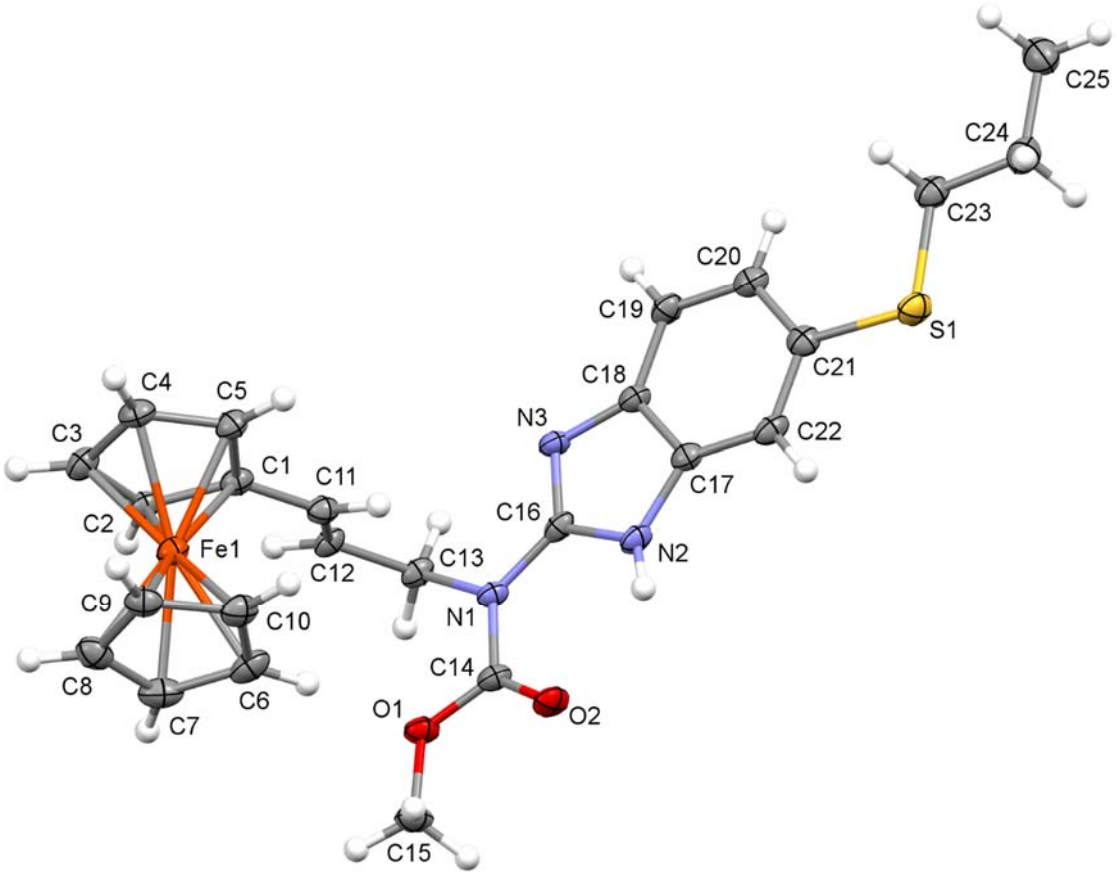


Figure S27. Molecular structure of 1c. The thermal ellipsoids are drawn at the 30% probability level.

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