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An Organometallic Structure-Activity Relationship Study Reveals the Essential Role of a $\text{Re}(\text{CO})_3$ Moiety in the Activity Against Gram-Positive Pathogens Including MRSA

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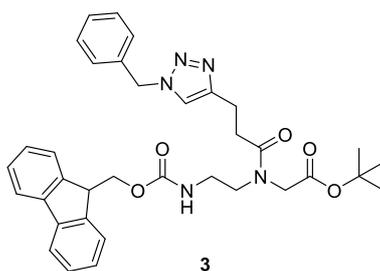
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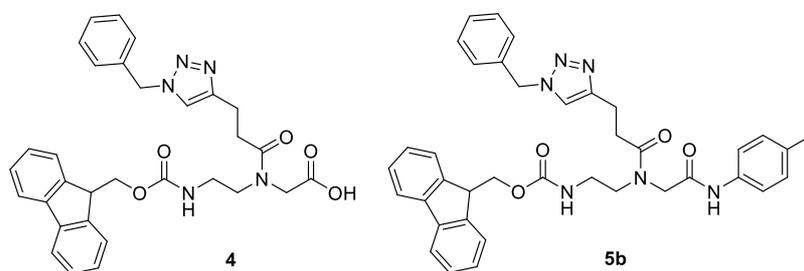
Synthesis and characterization of compounds.



Compound 3. To a stirred solution of **2** (390 mg, 0.82 mmol) and benzyl azide (164 mg, 1.23 mmol) in degassed acetone (15 mL), aqueous solution of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (41 mg, 0.16 mmol in 3.5 mL degassed water) and sodium ascorbate (66 mg, 0.32 mmol in 3.5 mL degassed water). The resulting mixture was allowed to stir at room temperature for 30 h under nitrogen atmosphere and the progress of the reaction was monitored by TLC (silica gel, EtOAc). After completion of the reaction, acetone was removed under vacuum, brine (100 mL) was added and extracted with EtOAc (3×75 mL). The combined organic phase was washed with 50 mL of 0.1M aqueous Na_2EDTA solution (to remove the Cu), brine, dried over anhydrous Na_2SO_4 , filtered and concentrated. Flash column chromatography (silica gel, EtOAc:MeOH 20:0 → 20:1) yielded pure **3** as colorless oil (yield: 410 mg, 82%).

Data for 3. $R_f = 0.57$ (silica gel, EtOAc). ^1H NMR (400 MHz, CDCl_3): δ (ppm) 1.43 (maj) and 1.47 (min) (rotamers, s, 9H, $\text{OC}(\text{CH}_3)_3$), 2.54 (maj) and 2.60 (min) (rotamers, m, 1H, $\text{CH}_2\text{-CH}_2\text{-triazole ring}$), 2.75 (m, 1H, $\text{CH}_2\text{-CH}_2\text{-triazole ring}$), 2.98-3.04 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-triazole ring}$), 3.31 (m, 2H, $\text{NH-CH}_2\text{-CH}_2\text{-N}$), 3.45 (maj) and 3.51 (min) (rotamers, m, 2H, $\text{NH-CH}_2\text{-CH}_2\text{-N}$), 3.90 (maj) and 3.94 (min) (rotamers, s, 2H, $\text{N-CH}_2\text{-COO}^t\text{Bu}$), 4.13 (maj) and 4.20 (min) (rotamers, m, 1H, CH Fmoc), 4.31 (maj) and 4.50 (min) (rotamers, m, 2H, $\text{Fmoc-CH}_2\text{O}$), 5.30 (maj) and 5.39 (min) (rotamers, s, 2H, $\text{triazole-CH}_2\text{-Ph}$), 5.79 (min) and 6.18 (maj) (rotamers, s, br, 1H, NH), 7.12-7.30 (m, 8H, triazole ring , CH Fmoc arom and $\text{benzene ring protons}$), 7.36 (m, 2H, CH Fmoc arom), 7.58 (m, 2H, CH Fmoc arom), 7.73 (d, 2H, $\text{benzene ring protons}$). ^{13}C NMR (62.9 MHz, CDCl_3): δ (ppm) 21.0 (min) and 21.1 (maj) (rotamers, $\text{CH}_2\text{-CH}_2\text{-triazole ring}$), 27.9 (min) and 28.1 (maj) (rotamers, $\text{OC}(\text{CH}_3)_3$), 32.0 (maj) and 32.3 (min) (rotamers, $\text{CH}_2\text{-CH}_2\text{-triazole ring}$), 39.4 ($\text{NH-CH}_2\text{-CH}_2\text{-N}$), 47.1 (maj) and 47.2 (min) (rotamers, CH Fmoc), 48.1 (min) and 49.1 (maj) (rotamers, $\text{NH-CH}_2\text{-CH}_2\text{-N}$), 49.7 (maj) and 51.5 (min) (rotamers, $\text{N-CH}_2\text{-COO}^t\text{Bu}$), 53.8 (maj) 53.9 (min) (rotamers, $\text{Ph-CH}_2\text{-triazole ring}$), 66.6 (min) and 66.8 (maj) (rotamers, $\text{Fmoc-CH}_2\text{O}$), 82.0 (min) and 82.9

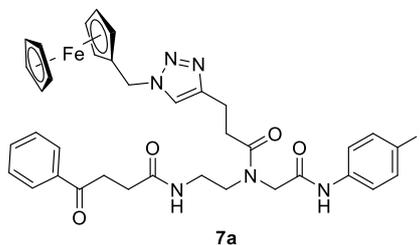
(maj) (rotamers, OC(CH₃)₃), 119.9 (CH Fmoc arom), 121.8 (CH triazole ring), 125.2 (CH Fmoc arom), 127.0 (maj) and 127.1 (min) (rotamers, CH Fmoc arom), 127.6 (maj) and 127.7 (min) (benzene ring C), 127.8 (maj) and 127.9 (min) (benzene ring C), 128.4 (maj) and 128.5 (min) (rotamers, CH Fmoc arom), 128.9 (maj) and 129 (min) (benzene ring C), 134.8 (benzene ring C), 141.1 (br, CH Fmoc arom), 143.9 (CH Fmoc arom), 147.1 (rotamers, C triazole ring), 156.6 (NHCOO), 168.7(min) and 169.5 (maj) (rotamers, COO^tBu), 172.4 (maj) and 173.2 (min) (rotamers, CH₂CON). IR bands(v): 3136w, 1715s, 1644s, 1517w, 1449m, 1367w, 1231s, 1151s, 1077w, 943w, 846w, 728s (br) cm⁻¹. ESI-MS (pos. detection mode): *m/z* (%): 610.29 (100) [M+H]⁺.



Compound 4 and 5b. To a stirred solution of **3** (1 g, 1.64 mmol) in 20 mL of DCM, TFA (6 mL) and triethylsilane (2.5 mL) was added at 0 °C. After 30 minutes, the mixture was allowed to warm to room temperature and stirred for another 4 h. The solvent was then removed under reduced pressure to give colorless oil. Addition of cold hexane gave **4** as white precipitate. The hexane was decanted off and the precipitate was washed several times with hexane to give **4** as white powder which was used for the next step without further purification (yield: 830 mg, 91%).

To a stirred solution of the carboxylic acid **4** (553 mg, 1.0 mmol) in 20 mL of DMF, HATU (760 mg, 2.0 mmol) and *N,N*-diisopropylethylamine (DIPEA) (155 mg, 1.2 mmol) were added. The mixture was allowed to stir for 30 min under nitrogen atmosphere. *P*-iodoaniline (328.5 mg, 1.5 mmol) in 10 mL of DCM was then added and the mixture was stirred for 40 h at room temperature. The reaction mixture was then evaporated under reduced pressure and the residue was diluted with 100 mL of DCM. The organic layer was washed with 0.5M aqueous HCl, brine, dried over anhydrous Na₂SO₄, filtered and concentrated. Flash column chromatography (silica gel, EtOAc:MeOH 15:0 → 15:1) was performed to obtain pure **5b** as light yellowish solid (yield: 392 mg, 52%).

Data for 5b. $R_f = 0.45$ (silica gel, EtOAc:MeOH 15:1). ^1H NMR (400 MHz, CDCl_3): δ (ppm) 2.78 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-triazole}$ ring), 3.01 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-triazole}$ ring), 3.38 (m, 2H, $\text{NH-CH}_2\text{-CH}_2\text{-N}$), 3.49 (m, 2H, $\text{NH-CH}_2\text{-CH}_2\text{-N}$), 4.02 (s, 2H, $\text{N-CH}_2\text{-CO}$), 4.16 (m, 1H, CH Fmoc), 4.32 (m, 2H, $\text{Fmoc-CH}_2\text{O}$), 5.29 (maj) and 5.38 (min) (rotamers, s, 2H, $\text{triazole-CH}_2\text{-Ph}$), 6.11 (min) and 6.50 (maj) (rotamers, s, br, 1H, NH), 7.10-7.15 (m, 2H, triazole ring and CH Fmoc arom), 7.22-7.60 (m, 14H, CH Fmoc arom and $\text{benzene ring protons}$), 7.73 (d, 2H, $\text{benzene ring protons}$), 9.47 (maj) and 9.60 (min) (rotamers, NHCO). ^{13}C NMR (100.6 MHz, CDCl_3): δ (ppm) 20.9 (min) and 21.2 (maj) (rotamers, $\text{CH}_2\text{-CH}_2\text{-triazole}$ ring), 31.6 (min) and 31.9 (maj) (rotamers, $\text{CH}_2\text{-CH}_2\text{-triazole}$ ring), 38.6 (min) and 39.5 (maj) ($\text{NH-CH}_2\text{-CH}_2\text{-N}$), 47.1 (CH Fmoc), 48.1 (min) and 49.5 (maj) (rotamers, $\text{NH-CH}_2\text{-CH}_2\text{-N}$), 51.9 (maj) and 52.7 (min) (rotamers, $\text{N-CH}_2\text{-CO}$), 53.8 (maj) and 53.9 (min) (rotamers, $\text{Ph-CH}_2\text{-triazole}$ ring), 66.6 ($\text{Fmoc-CH}_2\text{O}$), 87.3 (maj) and 87.6 (min) (rotamers, C-I benzene ring), 119.9 (CH Fmoc arom), 121.3 (maj) and 121.6 (min) (rotamers, CH triazole ring), 122.1 (min) and 122.2 (maj) (rotamers, CONH-C benzene ring), 125.2 (CH Fmoc arom), 126.9 (CH Fmoc arom), 127.5 (maj) and 127.6 (min) (rotamers, benzene ring C), 127.8 (maj) and 127.9 (min) (rotamers, benzene ring C), 128.5 (maj) and 128.6 (min) (rotamers, CH Fmoc arom), 128.8 (maj) and 128.9 (min) (rotamers, benzene ring C), 134.5 (benzene ring C), 137.3 (maj) and 137.5 (min) (rotamers, $\text{CONH-benzene ring CH}$), 137.6 (min) and 137.7 (maj) (rotamers, $\text{CONH-benzene ring CH}$), 141.1 (br, CH Fmoc arom), 143.9 (CH Fmoc arom), 147.1 (rotamers, C triazole ring), 156.6 (maj) and 156.7 (min) (rotamers, CONH), 167.2 (min) and 168.5 (maj) (rotamers, CONH), 173.4 (CH_2CON). IR bands(ν): 3309w, 2923m, 2853w, 1677s, 1632s, 1586w, 1545m, 1526s, 1494m, 1302w, 1256s, 1107w, 1012w, 819m, 757w, 730s cm^{-1} . ESI-MS (pos. detection mode): m/z (%): 755.05 (100) $[\text{M}+\text{H}]^+$, 776.93 (25) $[\text{M}+\text{Na}]^+$.

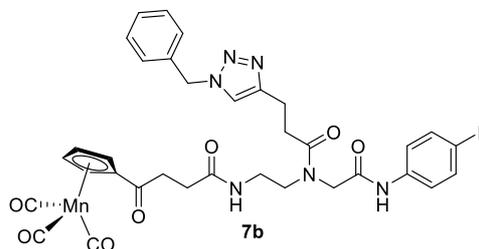


Compound 7a. To a stirred solution of **5a**¹ (600 mg, 0.70 mmol) in 4 mL DMF, 10 mL of 20% piperidine in DMF was added at 0 °C and stirred for 10 min. Then the ice bath was removed and the mixture was stirred 2 h at room temperature. The DMF and piperidine was

removed using high vacuum pump. The resulting residue was washed several times with pentane. The yellow color solid thus obtained was dissolved in 8 mL DMF. The solution was added to a solution of 4-oxo-4-phenylbutanoic acid (**6a**) (278 mg, 1.5 mmol), HATU (570 mg, 1.5 mmol) and DIPEA (193 mg, 1.5 mmol) in DMF (3 mL) which has been initially stirred for 30 minutes at room temperature. The reaction mixture was stirred for 48 h before being diluted with 150 mL of EtOAc. The organic phase was washed with 1M HCl (50 mL), sat. NaHCO₃ solution (50 mL), water (2×75 mL), brine (2×75 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. Flash column chromatography on silica gel (EtOAc:MeOH 20:1 → 15:1 → 10:1) yielded compound **7a** as yellow solid (yield: 228 mg, 42%).

Data for 7a. R_f = 0.07 (silica gel, EtOAc:MeOH 20:1). ¹H NMR (400 MHz, CD₂Cl₂): δ (ppm) 2.29 (m, 2H, Ph-CO-CH₂-CH₂), 2.63 (min) and 2.71 (maj) (rotamers, m, 2H, CH₂-CH₂-triazole ring), 2.92 (m, 2H, CH₂-CH₂-triazole ring), 3.15 (m, 2H, Ph-CO-CH₂-CH₂), 3.30 (m, 2H, NH-CH₂-CH₂-N), 3.38 (m, 2H, NH-CH₂-CH₂-N), 3.95 (maj) and 3.99 (min) (rotamers, s, 2H, N-CH₂-CO), 4.07-4.17 (m, 9H, CH Fc), 5.03 (maj), 5.08, 5.14 (min) (rotamers, s, 2H, triazole-CH₂-Fc), 6.82 (min) and 7.17 (maj) (rotamers, 1 NH-CO), 7.19-7.49 (m, 8H, 1×triazole ring proton, 7×benzene ring protons), 7.84 (m, 2H, benzene ring protons), 9.20 (maj) and 9.31 (min) (rotamers, 1H, NHCO). ¹³C NMR (100.6 MHz, CD₂Cl₂): δ (ppm) 21.2 (min) and 21.6 (maj) (rotamers, CH₂-CH₂-triazole ring), 30.1 (maj) and 30.2 (min) (rotamers, Ph-CO-CH₂-CH₂), 31.8 (maj) and 32.1 (min) (rotamers, CH₂-CH₂-triazole ring), 33.9 (maj) and 34.1 (min) (rotamers, Ph-CO-CH₂-CH₂), 38.4 (maj) and 38.6 (min) (rotamers, NH-CH₂-CH₂-N), 47.8 (maj) and 48.2 (min) (rotamers, NH-CH₂-CH₂-N), 49.7 (min) and 50.2 (maj) (rotamers, N-CH₂-CO), 52.3 (Fc-CH₂-triazole ring), 69.2 (CH Fc), 69.3 (CH Fc), 69.4 (CH Fc), 81.5 (maj) and 81.7 (min) (rotamers, C Fc), 87.2 (maj) and 87.6 (min) (rotamers, C-I), 121.3 (maj) and 121.4 (min) (rotamers, CH triazole ring), 122.4 (maj) and 122.6 (min) (rotamers, benzene ring carbon), 128.2 (benzene ring carbon), 128.9 (benzene ring carbon), 133.4 (maj) and 133.5 (min) (rotamers, benzene ring carbon), 136.9 (min) and 137.1 (maj) (rotamers, benzene ring carbon), 137.9 (maj) and 138.1 (min) (rotamers, benzene ring carbon), 138.3 (min) and 138.5 (maj) (rotamers, benzene ring carbon), 146.8 (C triazole ring), 167.8 (min) and 168.7 (maj) (rotamers, CONH), 172.9, (CONH), 173.9 (maj) and 174.1 (min) (rotamers, CH₂CON), 199.1 (maj) and 199.6 (min) (rotamers, Ph-CO). IR bands(ν): 3266w, 3090w, 2930w, 2360m, 2342w, 1731w, 1682s, 1637s, 1530s, 1484s, 1447w, 1392w,

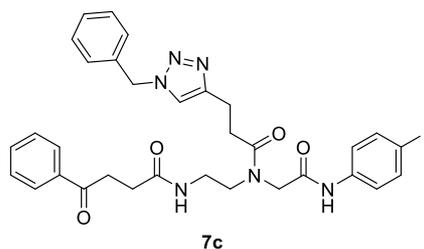
1370w, 1239s, 1180m, 1001m, 818s, 668m, 606s cm^{-1} . ESI-MS (pos. detection mode): m/z (%): 799.95 (100) $[\text{M}]^+$, 822.90 (70) $[\text{M}+\text{Na}]^+$, 838.85 (25) $[\text{M}+\text{K}]^+$.



Compound 7b: To a stirred solution of **5b** (1 g, 1.33 mmol) in 5 mL DMF, 18 mL of 20% piperidine in DMF was added at 0 °C and stirred for 10 min. Then the ice bath was removed and the mixture was stirred 2 h at room temperature. The DMF and piperidine was removed using high vacuum pump. The resulting residue was washed several times with pentane. The light yellow color solid thus obtained was dissolved in 10 mL DMF. The solution was added to a solution of 4-oxo-4-cymantrenylbutanoic acid (**6b**)² (340 mg, 1.12 mmol), HATU (855 mg, 2.25 mmol) and DIPEA (290 mg, 2.25 mmol) in DMF (5 mL), which has been initially stirred for 30 minutes at room temperature. The reaction mixture was stirred for 48 h before being diluted with 150 mL of ethyl acetate. The organic phase was washed with 1M HCl (50 mL), *sat.* NaHCO_3 solution (50 mL), water (2×75 mL) and brine (2×75 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated. After flash column chromatography on silica gel (EtOAc:MeOH 15:1 → 10:1 → 5:1), the solution was concentrated and pentane was added to get a light yellow precipitate. Pentane was decanted off to yield the desired compound **7b** as light yellow powder (yield: 620 mg, 57%).

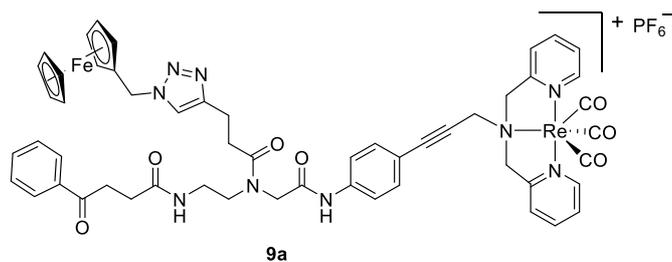
Data for 7b. $R_f = 0.14$ (silica gel, EtOAc:MeOH 10:1). ^1H NMR (250 MHz, CD_2Cl_2): δ (ppm) 2.47 (m, 2H, cymantrene-CO- CH_2 - CH_2), 2.76 (min) and 2.83 (maj) (rotamers, m, 2H, CH_2 - CH_2 -triazole ring), 2.92 (m, 2H, CH_2 - CH_2 -triazole ring), 3.07 (m, 2H, cymantrene-CO- CH_2 - CH_2), 3.45 (m, 2H, NH-CH_2 - CH_2 -N), 3.51 (m, 2H, NH-CH_2 - CH_2 -N), 4.09 (maj) and 4.22 (min) (rotamers, s, 2H, N- CH_2 -CO), 4.88 (m, 2H, CH cymantrene), 5.45 (s, 2H, triazole- CH_2 -Ph), 5.48 (m, 2H, CH cymantrene), 6.87 (min) and 7.01 (maj) (rotamers, 1H, NH-CO), 7.25-7.44 (m, 8H, 1×triazole ring proton, 7×benzene ring protons), 7.51-7.69 (m, 2H, benzene ring protons), 9.49 (maj) and 9.61 (min) (rotamers, 1H, NHCO). ^{13}C NMR (62.9 MHz, CD_2Cl_2): δ (ppm) 21.1 (min) and 21.2 (maj) (rotamers, CH_2 - CH_2 -triazole ring), 29.2

(maj) and 29.4 (min) (rotamers, cymantrene-CO-CH₂-CH₂), 31.5 (maj) and 31.8 (min) (rotamers, CH₂-CH₂-triazole ring), 33.8 (maj) and 33.9 (min) (rotamers, cymantrene-CO-CH₂-CH₂), 37.9 (maj) and 38.1 (min) (rotamers, NH-CH₂-CH₂-N), 47.4 (NH-CH₂-CH₂-N), 49.1 (N-CH₂-CO), 51.8 (Ph-CH₂-triazole ring), 83.9 (maj) and 84.9 (min) (rotamers, CH cymantrene), 86.8 (CH cymantrene), 87.1 (maj) and 87.4 (min) (rotamers, C-I), 91.1 (min) and 91.2 (maj) (rotamers, C cymantrene), 121.6 (CH triazole ring), 121.9 (maj) and 122.1 (min) (rotamers, *benzene ring carbon*), 127.9 (*benzene ring carbon*), 128.5 (*benzene ring carbon*), 129.1 (*benzene ring carbon*), 135.1 (*benzene ring carbon*), 137.5 (maj) and 137.7 (min) (rotamers, *benzene ring carbon*), 137.9 (min) and 138.1 (maj) (rotamers, *benzene ring carbon*), 147.1 (C triazole ring), 167.8 (min) and 168.5 (maj) (rotamers, CONH), 171.9, (CONH), 173.4 (maj) and 173.8 (min) (rotamers, CH₂CON), 196.5 (maj) and 196.3, 197.5 (min) (rotamers, cymantrene-CO), 223.2 (maj) and 224.3 (min) (rotamers, Mn-CO). IR bands(ν): 2023s, 1931s, 1646m (br), 1532m, 1462w, 1392w, 1305w, 1245w, 1181w, 1059w, 1003w, 822w, 730w, 630s cm⁻¹. ESI-MS (pos. detection mode): *m/z* (%): 818.87 (100) [M+H]⁺, 840.84 (35) [M+Na]⁺, 856.79 (15) [M+K]⁺.



Compound 7c. To a stirred solution of **5b** (600 mg, 0.79 mmol) in 4 mL DMF, 10 mL of 20% piperidine in DMF was added at 0 °C and stirred for 10 min. Then the ice bath was removed and the mixture was stirred 2 h at room temperature. The DMF and piperidine was removed using high vacuum pump. The resulting residue was washed several times with pentane. The white color solid thus obtained was dissolved in 9 mL DMF. The solution was added to a solution of 4-oxo-4-phenylbutanoic acid (**6a**) (255 mg, 1.43 mmol), HATU (544 mg, 1.43 mmol) and DIPEA (185 mg, 1.43 mmol) in DMF (4 mL), which has been initially stirred for 30 minutes at room temperature. The reaction mixture was stirred for 40 h before the solvent was removed. Flash column chromatography on silica gel (THF:MeOH 10:0 → 10:1) yielded the desired compound **7c** as white solid (yield: 310 mg, 56%). For analytical purpose the compound was washed with little amount of DCM.

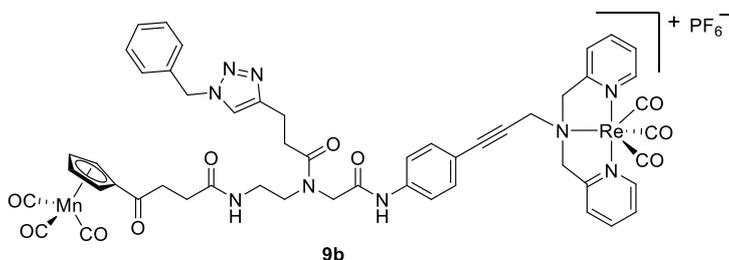
Data for 7c. $R_f = 0.45$ (silica gel, EtOAc:MeOH 12:1). ^1H NMR (400 MHz, DMSO- d_6): δ (ppm) 2.47 (maj) and 2.59 (min) (rotamers, m, 2H, PhCO-CH₂-CH₂), 2.76 (m, 2H, CH₂-CH₂-triazole ring), 2.87 (m, 2H, CH₂-CH₂-triazole ring), 3.22 (m, 4H, NH-CH₂-CH₂-N and PhCO-CH₂-CH₂), 3.41 (m, 2H, NH-CH₂-CH₂-N), 4.11(maj) and 4.16, 4.29 (min) (rotamers, s, 2H, N-CH₂-CO), 5.52 (maj) and 5.51, 5.55 (min) (rotamers, s, 2H, triazole-CH₂-Ph), 7.25-7.54 (m, 7H, triazole ring and benzene ring protons), 7.59-7.65 (m, 4H, benzene ring protons), 7.84-8.12 (m, 4H, benzene ring protons), 10.1 (min) and 10.2 (maj) (rotamers, 1H, NHCO), 10.5 (min), 10.6 (maj) (rotamers, 1H NHCO). ^{13}C NMR (100.6 MHz, DMSO- d_6): δ (ppm) 21.2 (min) and 21.3, 21.4 (maj) (rotamers, CH₂-CH₂-triazole ring), 29.4, 29.5 (min) and 29.6, 29.8 (maj) (rotamers, PhCO-CH₂-CH₂), 31.5, 32.1 (min) and 31.8, 32.5 (maj) (rotamers, CH₂-CH₂-triazole ring), 33.8 (maj) and 33.9 (min) (rotamers, PhCO-CH₂-CH₂) 37.1, 37.8 (maj) and 37.5, 38.6 (min) (NH-CH₂-CH₂-N), 46.4, 47.4 (min) and 46.9, 48.3 (maj) (rotamers, NH-CH₂-CH₂-N), 50.1, 51.9 (maj) and 50.3, 51.7 (min) (rotamers, N-CH₂-CO), 53.1 (min) and 53.2 (maj) (rotamers, Ph-CH₂-triazole ring), 86.9, 92.1 (maj) and 87.3, 92.2 (min) (rotamers, C-I benzene ring), 115.7 (maj) and 119.1 (min) (rotamers, benzene ring C), 121.8 (maj) and 121.9 (min) (rotamers, CH triazole ring), 122.6 (min) and 122.7 (maj) (rotamers, CONH-C benzene ring), 126.0 (min) and 126.1 (maj) (rotamers, benzene ring C), 128.2 (maj) and 128.3 (min) (rotamers, benzene ring C), 128.4 (maj) and 128.6 (min) (rotamers, benzene ring C), 129.1, 129.7 (min) and 129.2 (maj) (rotamers, benzene ring C), 133.5 (benzene ring C), 136.6 (min) and 136.9 (maj) (rotamers, benzene ring C), 139.1, 139.3 (maj) and 139.2 (min) (rotamers, benzene ring C), 143.9 (min) and 144.1 (maj) (rotamers, benzene ring C), 146.8 (min) and 147.1 (rotamers, C triazole ring), 167.8, 168.1 (min) and 168.4 (maj) (rotamers, CONH), 171.8, 171.9 (min) and 172.0, 172.2 (maj) (rotamers, CONH), 174.6 (min) and 174.7 (maj) (rotamers, CH₂CON), 199.1 (Ph-CO). IR bands(ν): 3236m, 1680m, 1654m, 1625m, 1589m, 1438s, 1400s, 1351w, 1207s, 1135s, 1114s, 935w, 769s, 640m cm^{-1} . ESI-MS (pos. detection mode): m/z (%): 715.02 (100) $[\text{M}+\text{Na}]^+$.



Compound 9a. A solution of **7a** (240 mg, 0.35 mmol) and **8** (163 mg, 0.25 mmol) in 9 mL DMF/ NEt_3 mixture (2/1, v/v) was degassed by two ‘freeze-pump-thaw’ cycles. Then CuBr (4.4 mg, 0.029 mmol) and cis-dichlorobis (triphenylphosphine) palladium(II) (5.3 mg, 0.0075 mmol) were added under nitrogen atmosphere and the mixture was degassed again by one ‘freeze-pump-thaw’ cycles. The wine color solution thus obtained was allowed to stir 22 h at room temperature. The reaction mixture was then diluted with 100 mL of CH_2Cl_2 and washed with distilled water (4×60 mL) and brine (2×60 mL). The CH_2Cl_2 layer was dried over Na_2SO_4 , filtered and concentrated. Addition of 40 mL of diethyl ether gave a brown color solid which was collected and further washed with 15 mL of cold ethyl acetate. The solid was then loaded on a silica column and eluted immediately with CH_2Cl_2 :MeOH 5:1. The combined fractions was evaporated and redissolved in minimum volume CH_2Cl_2 and filtered. Filtrate was dried to give the desired compound **9a** as light brown solid (yield: 144 mg, 41%). (Note: If the compound stacks in the column, CH_2Cl_2 :MeOH 5:1 saturated with KPF_6 should be used as eluent).

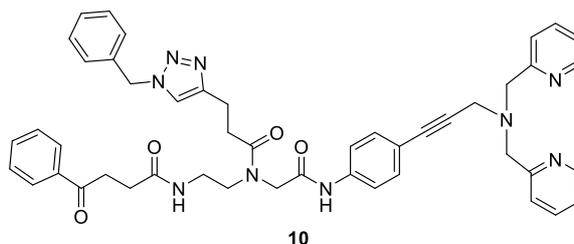
Data for 9a. $R_f = 0.66$ (silica gel, DCM:MeOH 5:1). t_R (RP-HPLC) = 17.3 min. ^1H NMR (400 MHz, CD_2Cl_2): δ (ppm) 2.33-2.79 (m, 4H, $\text{PhCO-CH}_2\text{-CH}_2$ and $\text{CH}_2\text{-CH}_2\text{-triazole}$ ring), 2.84-3.01 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-triazole}$ ring), 3.23 (m, 2H, $\text{PhCO-CH}_2\text{-CH}_2$), 3.30-3.45 (m, 4H, $\text{NH-CH}_2\text{-CH}_2\text{-N}$ and $\text{NH-CH}_2\text{-CH}_2\text{-N}$), 4.11 (s, br, 2H, $\text{N-CH}_2\text{-CO}$), 4.15-4.30 (m, 9H, CH Fc), 4.66 (s, br, 2H, $\text{N-CH}_2\text{-C}\equiv\text{C}$), 4.83 (s, 4H, $2\times\text{N-CH}_2\text{-Py}$), 5.15 (maj) and 5.20 (min) (rotamers, s, 2H, $\text{triazole-CH}_2\text{-Fc}$), 6.89 (min) and 6.98 (maj) (rotamers, s, br, 1H, NHCO), 7.29-7.96 (m, 16H, $1\times\text{triazole ring proton}$ and $15\times\text{aromatic protons}$), 8.76 (m, 2H, aromatic protons), 9.04, 9.28, 9.55 (min) and 9.19 (maj) (rotamers, s, br, 1H, NHCO). ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ (ppm) 20.9 (min) and 21.2 (maj) (rotamers, $\text{CH}_2\text{-CH}_2\text{-triazole}$ ring), 29.6 (min) and 30.2 (maj) (rotamers, $\text{PhCO-CH}_2\text{-CH}_2$), 31.7 (maj) and 32.3 (min) (rotamers, $\text{CH}_2\text{-CH}_2\text{-triazole}$ ring), 33.9 ($\text{PhCO-CH}_2\text{-CH}_2$), 37.7 (min) and 38.3 (maj) (rotamers, $\text{NH-CH}_2\text{-CH}_2\text{-N}$), 48.4 ($\text{NH-CH}_2\text{-CH}_2\text{-N}$), 50.2 ($\text{N-CH}_2\text{-CO}$), 52.1 ($\text{Fc-CH}_2\text{-triazole}$ ring), 59.6 ($\text{N-CH}_2\text{-C}\equiv\text{C}$), 68.4 ($2\times\text{N-CH}_2\text{-Py}$), 69.2 (CH Fc), 69.3 (CH Fc), 69.4 (CH Fc), 81.1 ($\text{C}\equiv\text{C-CH}_2\text{-}$

N), 81.5 (*C* Fe), 90.6 (N-CH₂-C≡C), 116.7 (maj) and 117.1 (min) (rotamers, *aromatic carbon*), 120.1 (maj) and 120.3 (min) (rotamers, *aromatic carbon*), 121.6 (min) and 121.9 (maj) (rotamers, CH triazole ring), 124.2 (*aromatic carbon*), 125.7 (min) and 126.3 (maj) (rotamers, *aromatic carbon*), 128.4 (*aromatic carbon*), 129.1 (*aromatic carbon*), 133.2 (*aromatic carbon*), 133.6 (*aromatic carbon*), 136.7 (min) and 136.8 (maj) (rotamers, *aromatic carbon*), 139.3 (min) and 139.6 (maj) (rotamers, *aromatic carbon*), 140.9 (*aromatic carbon*), 146.7 (maj) and 147.1 (min) (rotamers, *C* triazole ring), 152.1 (*aromatic carbon*), 160.1 (*aromatic carbon*), 168.1, 168.3 (min) and 169.0, 169.1 (maj) (rotamers, CONH), 173.3 (maj) and 173.5 (min) (CONH), 174.5 (min) and 174.7 (maj) (rotamers, CH₂CON), 195.7 (Re-CO), 199.1 (maj) and 200.4 (min) (rotamers, Ph-CO). IR bands(ν): 2030s, 1910s, 1648m (br), 1610w, 1514m, 1365w, 1293w, 1105w, 1000w, 834s, 733m, 622w cm⁻¹. ESI-MS (pos. detection mode): *m/z* (%): 1179.93 (100) [M-PF₆]⁺.



Compounds 9b. A stirred solution of **7b** (300 mg, 0.37 mmol) and **8** (199 mg, 0.31 mmol) in 9 mL DMF/NEt₃ mixture (2/1, v/v) was degassed by two ‘freeze-pump-thaw’ cycles. Then CuBr (5.4 mg, 0.03 mmol) and cis-dichlorobis (triphenylphosphine) palladium(II) (6.4 mg, 0.0091 mmol) were added under nitrogen atmosphere and the mixture was degassed again by one ‘freeze-pump-thaw’ cycle. The wine color solution thus obtained was allowed to stir 22 h at room temperature. The reaction mixture was then diluted with 100 mL of CH₂Cl₂ and washed with distilled water (4×60 mL) and brine (2×60 mL). The CH₂Cl₂ layer was dried over anhydrous Na₂SO₄, filtered and concentrated. Addition of 40 mL of pentane gave a brown color solid. Flash column chromatography on silica gel (eluent: EtOAc:MeOH 5:1 and then DCM:MeOH 3:1 saturated with KPF₆ to elute the **9b**) was done. The fractions containing the desired compound was combined and evaporated. The residue was dissolved in 10 mL of CH₂Cl₂ and filtered. The residue obtained after evaporation was loaded again on a small filter silica column and eluted immediately with DCM:MeOH 5:1. The desired fractions are combined and dried, redissolved in minimum volume CH₂Cl₂ and filtered. Filtrate was dried to give the desired compound **9b** as light brown solid (yield: 180 mg, 44%).

Data for 9b. $R_f = 0.27$ (silica gel, $\text{CH}_2\text{Cl}_2:\text{MeOH}$ 5:1). t_R (RP-HPLC) = 17.1 min. ^1H NMR (250 MHz, DMSO-d_6): δ (ppm) 2.37 (m, 2H, cymantrene-CO- $\text{CH}_2\text{-CH}_2$), 2.50 (maj) and 2.57 (min) (rotamers, m, 2H, $\text{CH}_2\text{-CH}_2\text{-triazole ring}$), 2.71-2.95 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-triazole ring}$), 3.15-3.48 (m, 6H, cymantrene-CO- $\text{CH}_2\text{-CH}_2$, NH- $\text{CH}_2\text{-CH}_2\text{-N}$ and NH- $\text{CH}_2\text{-CH}_2\text{-N}$), 4.11 (maj) and 4.25 (min) (rotamers, s, 2H, N- $\text{CH}_2\text{-CO}$), 4.83 (s, 2H, N- $\text{CH}_2\text{-C}\equiv\text{C}$), 4.85 (min) and 4.92 (maj) (rotamers, s, 2H, N- $\text{CH}_2\text{-Py}$), 5.03 (maj) and 5.10 (min) (rotamers, s, 2H, N- $\text{CH}_2\text{-Py}$), 5.18 (maj) and 5.25 (min) (rotamers, m, 2H, CH cymantrene), 5.54 (s, 2H, triazole- $\text{CH}_2\text{-Ph}$), 5.78 (rotamers, m, 2H, CH cymantrene), 6.43 (min) and 6.50 (maj) (rotamers, 1H, NHCO), 7.25-7.54 (m, 8H, 1 \times triazole ring proton and 7 \times aromatic protons), 7.66 (m, 4H, aromatic protons), 7.82-8.04 (m, 4H, aromatic protons), 8.85 (d, 2H, aromatic protons), 10.21 (maj) and 10.35 (min) (rotamers, s, 1H, NHCO). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ (ppm) 21.1, 21.2 (min) and 21.3 (maj) (rotamers, $\text{CH}_2\text{-CH}_2\text{-triazole ring}$), 29.2, 29.5 (min) and 29.4 (maj) (rotamers, cymantrene-CO- $\text{CH}_2\text{-CH}_2$), 31.8 (maj) and 32.3 (min) (rotamers, $\text{CH}_2\text{-CH}_2\text{-triazole ring}$), 34.2 (cymantrene-CO- $\text{CH}_2\text{-CH}_2$), 37.1 (min) and 37.7 (maj) (rotamers, NH- $\text{CH}_2\text{-CH}_2\text{-N}$), 48.3 (min) and 50.2 (maj) (rotamers, NH- $\text{CH}_2\text{-CH}_2\text{-N}$), 51.3 (min) and 53.1 (maj) (rotamers, N- $\text{CH}_2\text{-CO}$), 55.1 (Ph- $\text{CH}_2\text{-triazole ring}$), 58.4 (maj) and 59.8 (min) (rotamers, N- $\text{CH}_2\text{-C}\equiv\text{C}$), 68.2 (maj) and 70.1 (min) (rotamers, 2 \times N- $\text{CH}_2\text{-Py}$), 82.9 (maj) and 83.1 (min) (rotamers, $\text{C}\equiv\text{C-CH}_2\text{-N}$), 85.3 (CH cymantrene), 87.9 (CH cymantrene), 89.1 (N- $\text{CH}_2\text{-C}\equiv\text{C}$), 92.3 (C cymantrene), 115.9 (maj) and 116.2 (min) (rotamers, aromatic carbon), 119.3 (maj) and 119.4 (min) (rotamers, aromatic carbon), 122.7 (CH triazole ring), 124.1 (aromatic carbon), 126.1 (aromatic carbon), 128.2 (aromatic carbon), 128.4 (aromatic carbon), 129.1 (aromatic carbon), 132.9 (aromatic carbon), 136.5 (aromatic carbon), 139.9 (min) and 140.2 (maj) (rotamers, aromatic carbon), 140.9 (aromatic carbon), 146.9 (C triazole ring), 152.4 (aromatic carbon), 160.8 (aromatic carbon), 168.0, 168.1 (min) and 168.4 (maj) (rotamers, CONH), 171.4, 171.9 (min) and 171.6 (maj) (CONH), 172.3 (maj) and 172.4, 171.5 (min) (rotamers, CH_2CON), 195.6 (min) 196.1 (maj) (rotamers, Re- $\text{C}\equiv\text{O}$), 197.1 (maj) and 197.2 (min) (rotamers, cymantrene-CO-), 224.1 (maj) and 225.4, 225.6 (min) (rotamers, Mn-CO). IR bands(ν): 2027s, 1910s (br), 1670m (br), 1518m, 1445w, 1311w, 1245w, 1060w, 832s, 765m, 667w, 629m cm^{-1} . ESI-MS (pos. detection mode): m/z (%): 610.6 (50) $[\text{M}+\text{Na-PF}_6]^{2+}$, 1197.91 (100) $[\text{M-PF}_6]^+$.

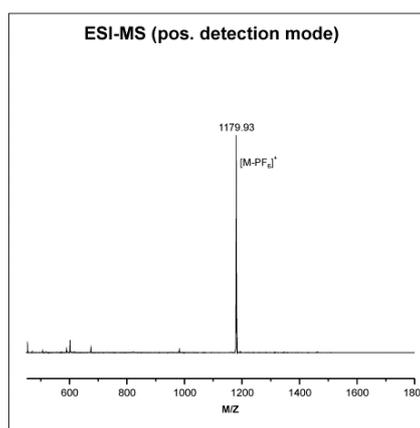
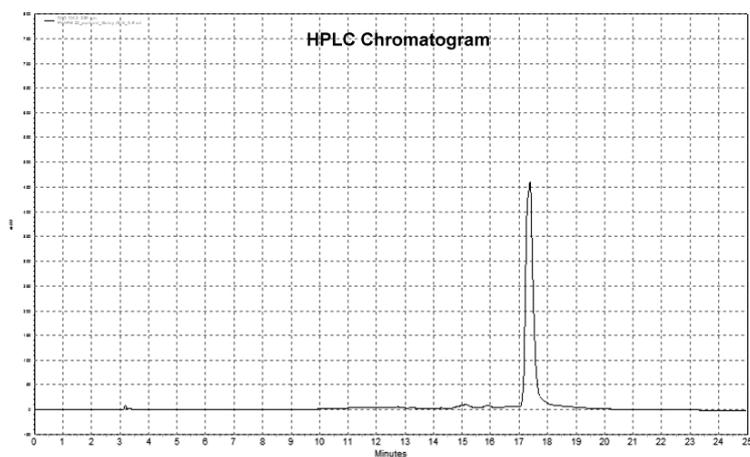
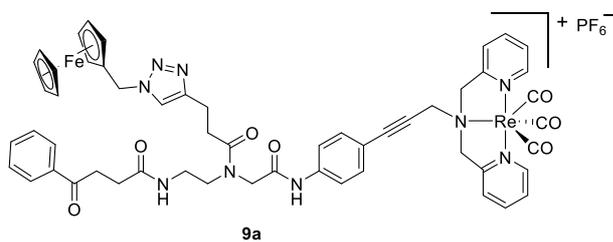


Compound 10. A solution of **7c** (180 mg, 0.26 mmol) and *N,N*-bis(pyridine-2-ylmethyl)prop-2-yn-1-amine³ (62 mg, 0.26 mmol) in 9 mL DMF/NEt₃ mixture (2/1, v/v) was degassed by two ‘freeze-pump-thaw’ cycles. Then CuBr (60 mg, 0.31 mmol) and *cis*-dichlorobis(triphenylphosphine) palladium (II) (21 mg, 0.03 mmol) were added under nitrogen atmosphere and the mixture was degassed again by one ‘freeze-pump-thaw’ cycle. The wine color solution thus obtained was allowed to stir 20 h at room temperature. The DMF and NEt₃ were removed and the residue was diluted with 125 mL of CH₂Cl₂/isopropanol mixture (5/1, v/v). The organic phase was washed with aqueous *sat.* Na₂EDTA, brine, dried over anhydrous Na₂SO₄, filtered and concentrated. Flash column chromatography (two times) (silica gel, CH₂Cl₂:CH₃CN:MeOH:NH₄OH 50:50:25:2) with the residue was performed. The resulting solution was dried and the residue was redissolved in 15 mL DCM and filtered to remove the silica. Evaporation of the CH₂Cl₂ solution afforded the desired compound **10** as brown sticky solid (yield: 69 mg, 35%). For biological applications purpose **10** was further purified by RP-HPLC.

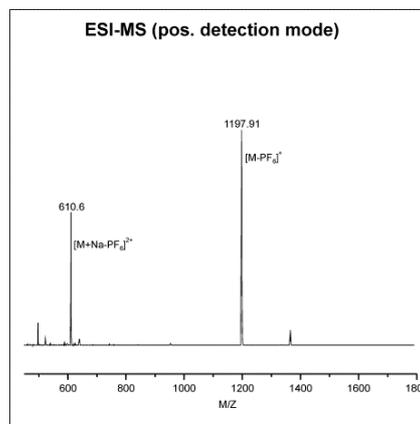
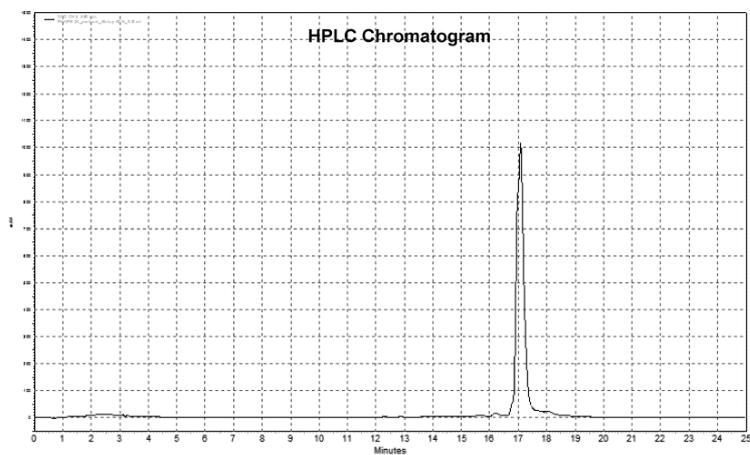
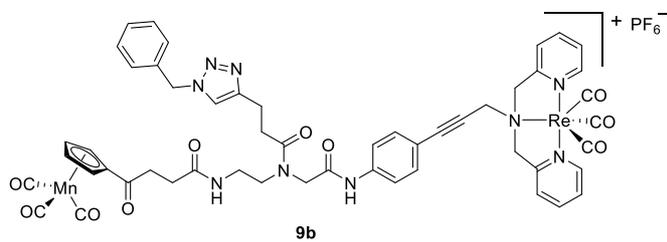
Data for 10. *t_R* (RP-HPLC) = 14.1 min. IR bands(ν): 2926w, 2360w, 1648s (br), 1594s, 1529s, 1435s, 1308m, 1179m, 1118m, 999w, 839m, 722s, 693s cm⁻¹. ESI-MS (pos. detection mode): *m/z* (%): 802.35 (100) [M+H]⁺, 824.19 (25) [M+Na]⁺.

HPLC traces and ESI mass spectra of 9a, 9b and 9c' and 10.

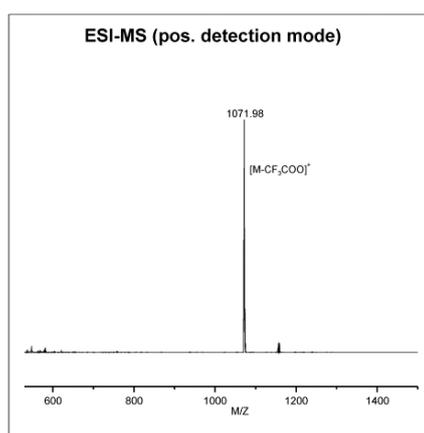
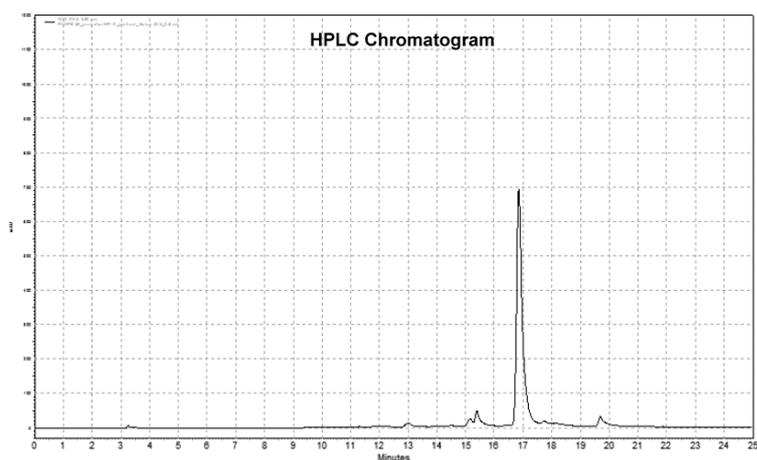
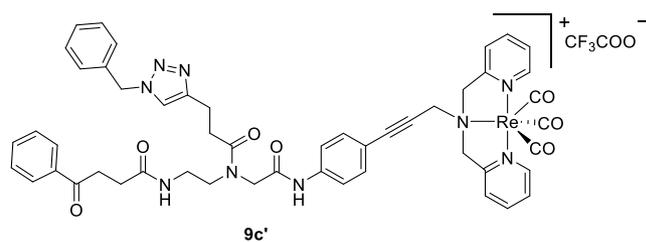
Compound 9a.



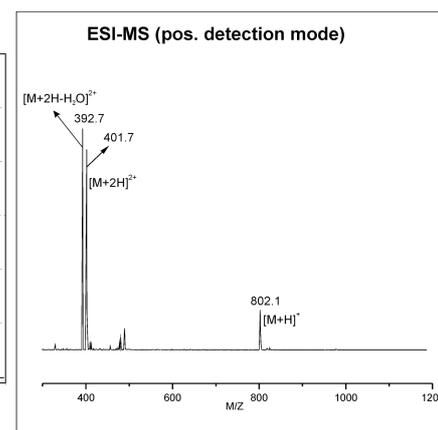
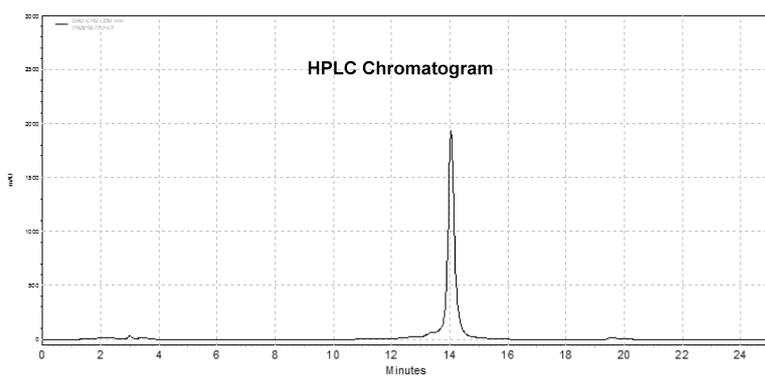
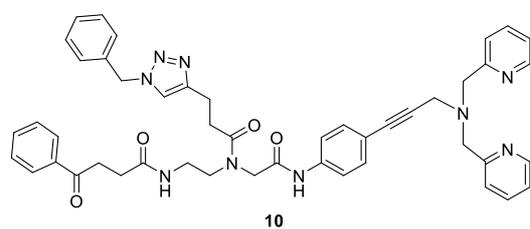
Compound 9b.



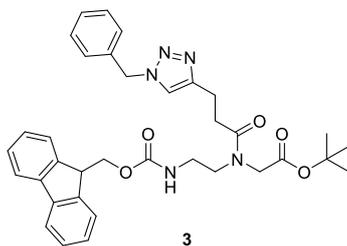
Compound 9c' (after RP-HPLC purification).



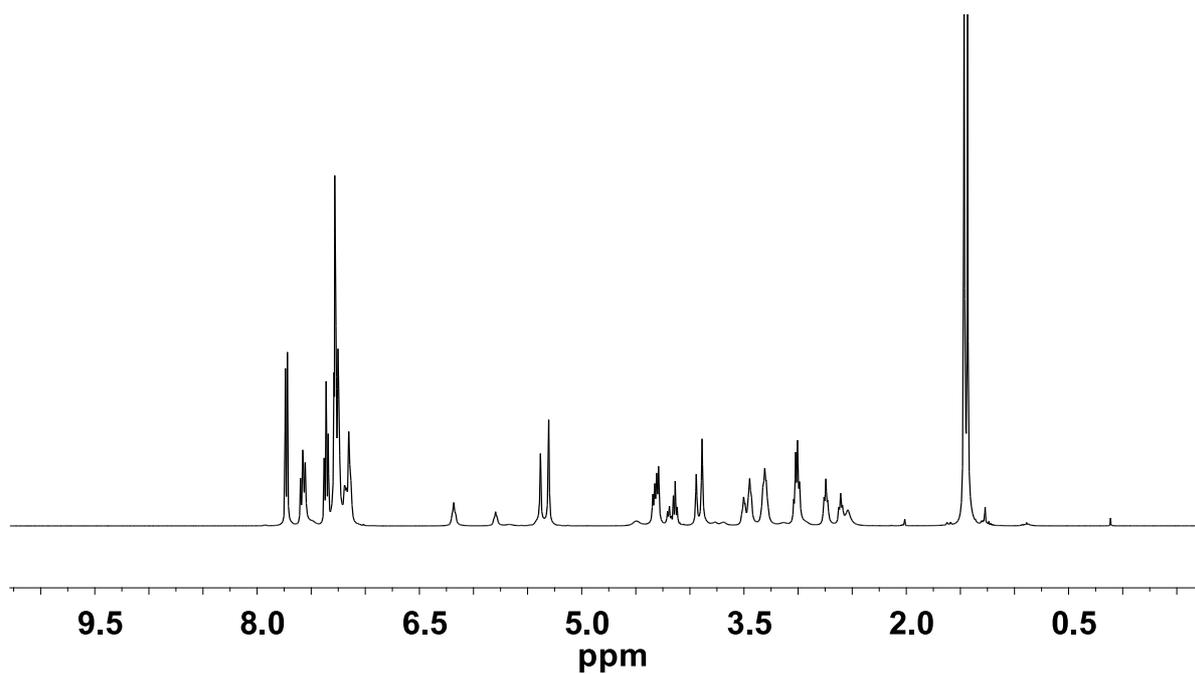
Compound 10 (after RP-HPLC purification).



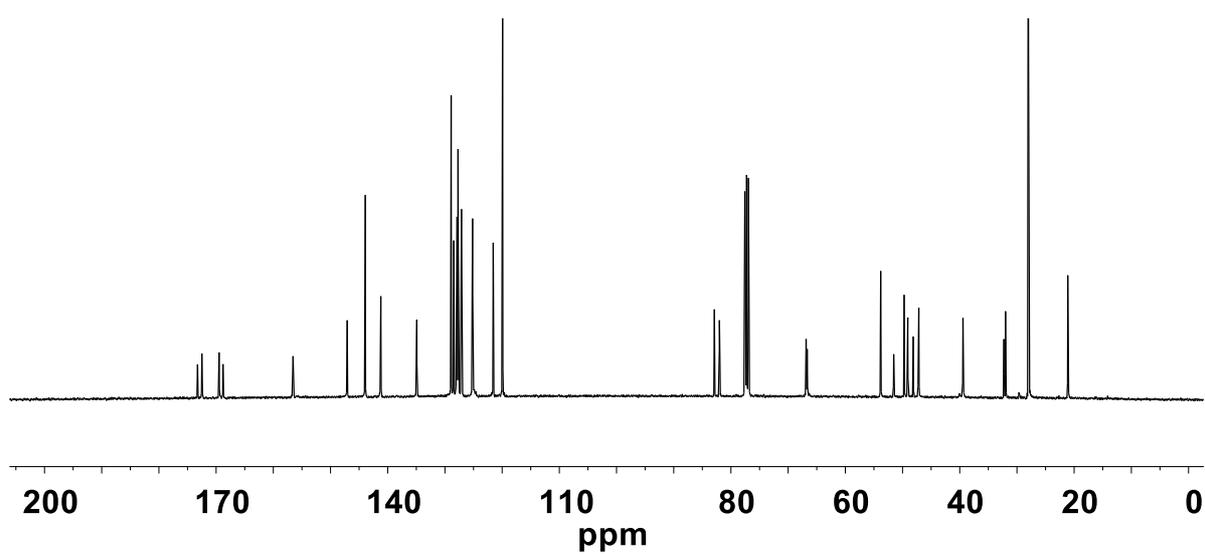
^1H and ^{13}C NMR spectra.

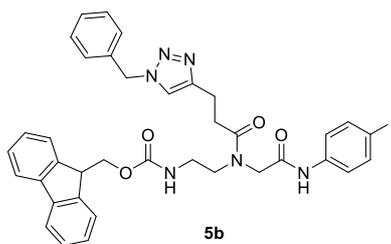


^1H , CDCl_3 , 400 MHz

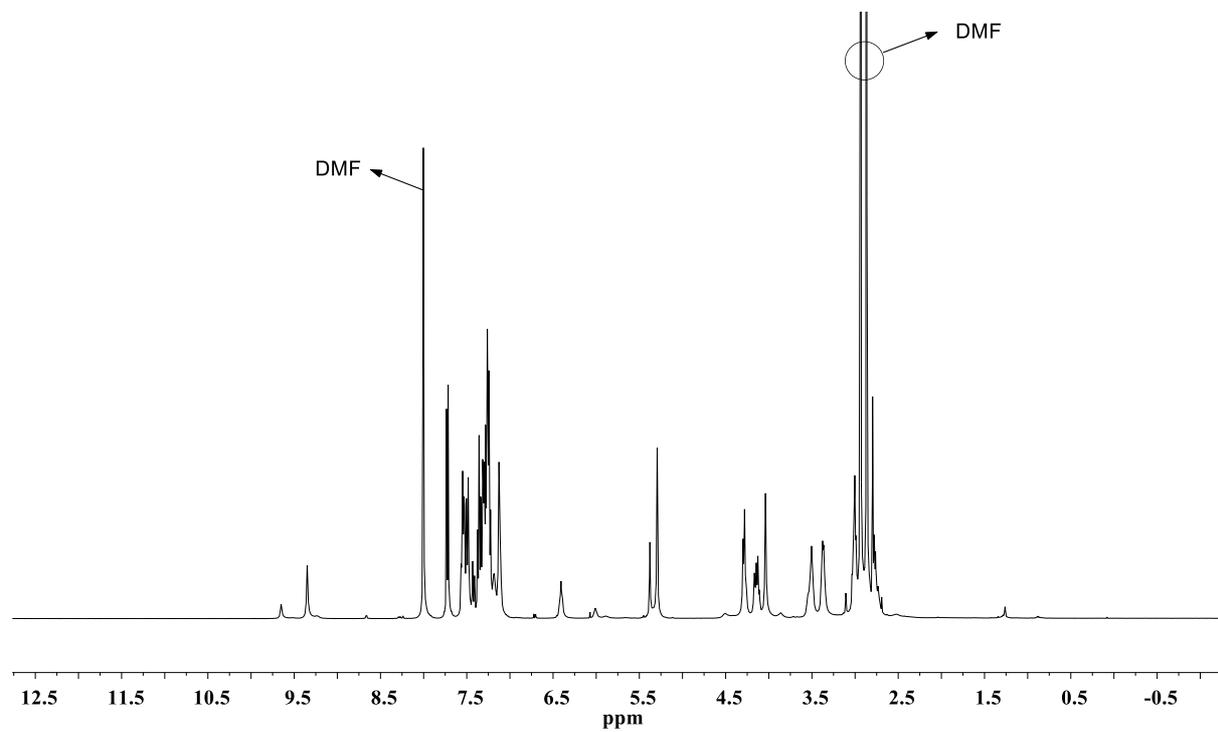


^{13}C , CDCl_3 , 62.9 MHz

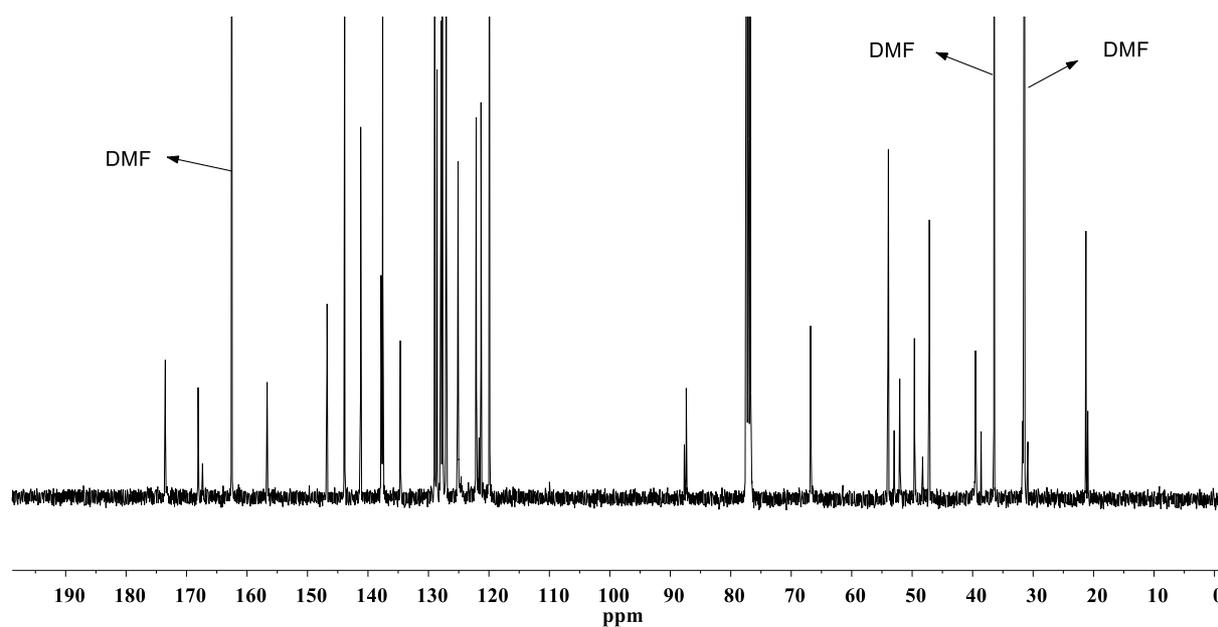


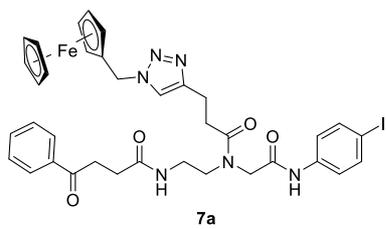


^1H , CDCl_3 , 100.6 MHz

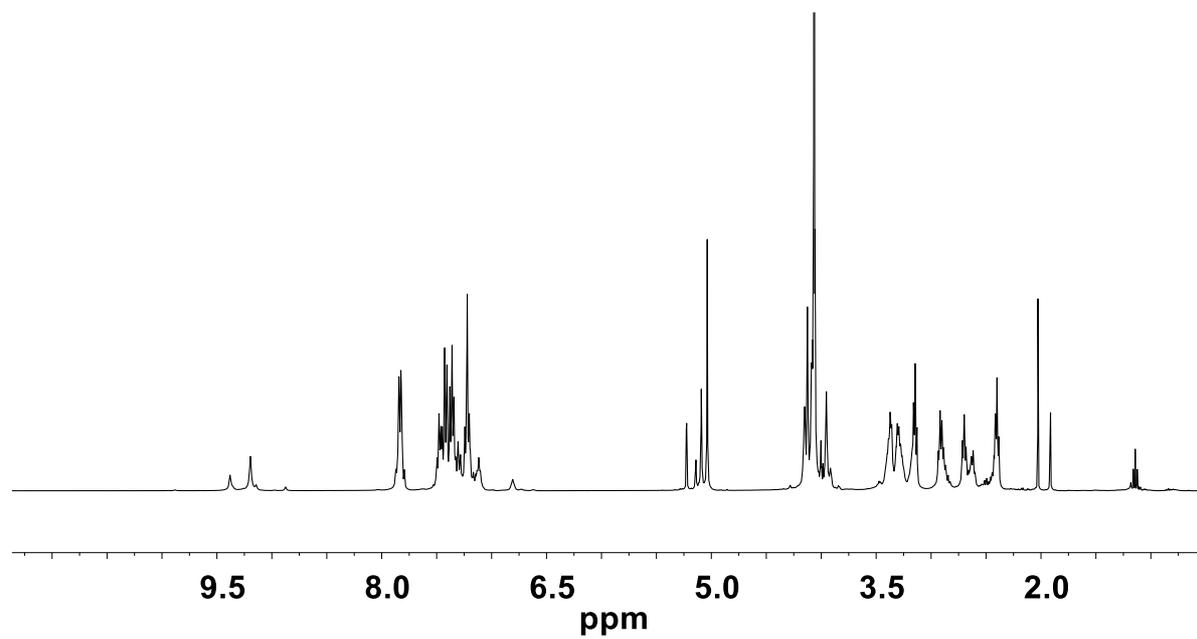


^{13}C , CDCl_3 , 250 MHz

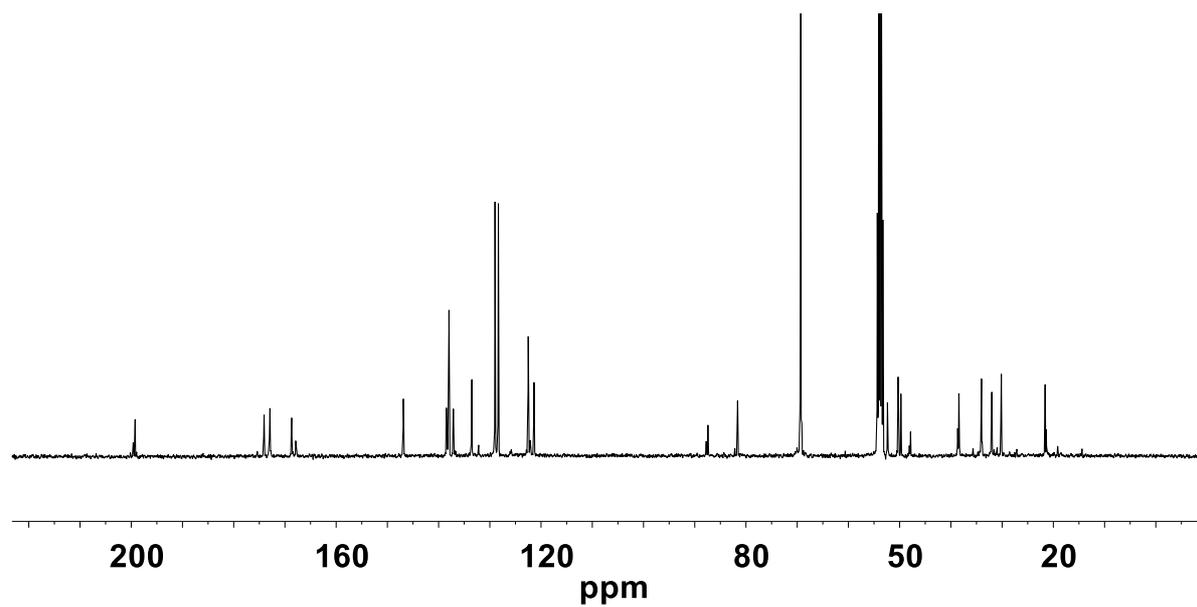


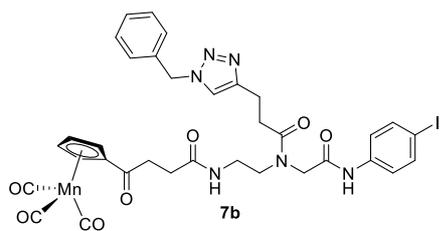


^1H , CD_2Cl_2 , 400 MHz

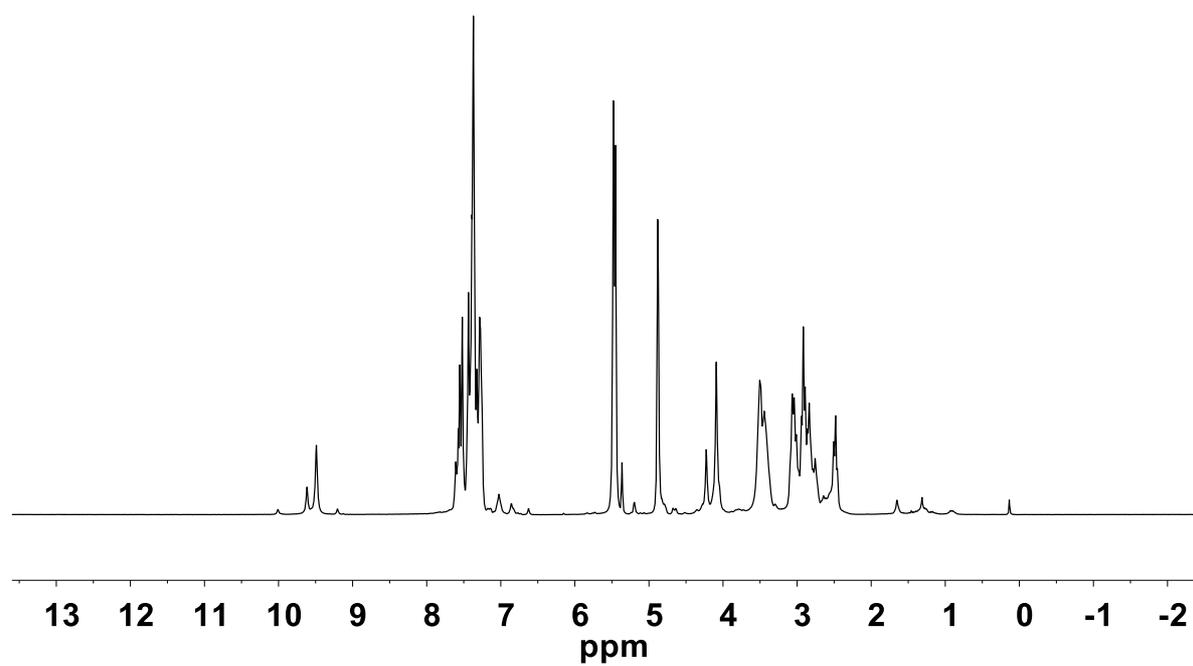


^{13}C , CD_2Cl_2 , 100.6 MHz

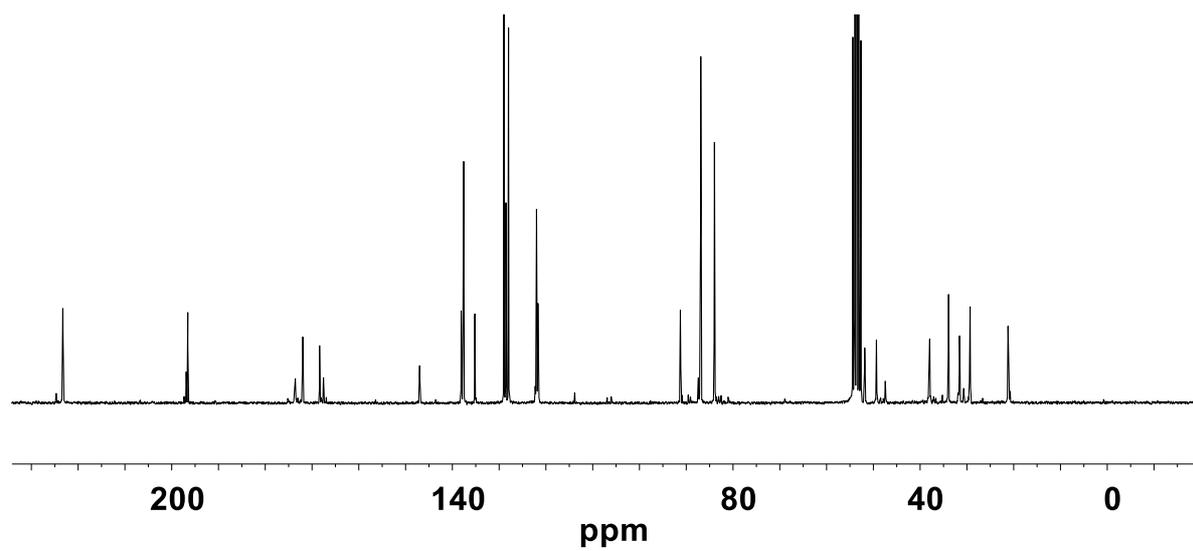


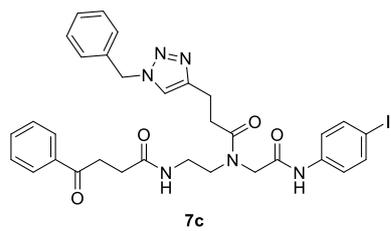


^1H , CD_2Cl_2 , 250 MHz

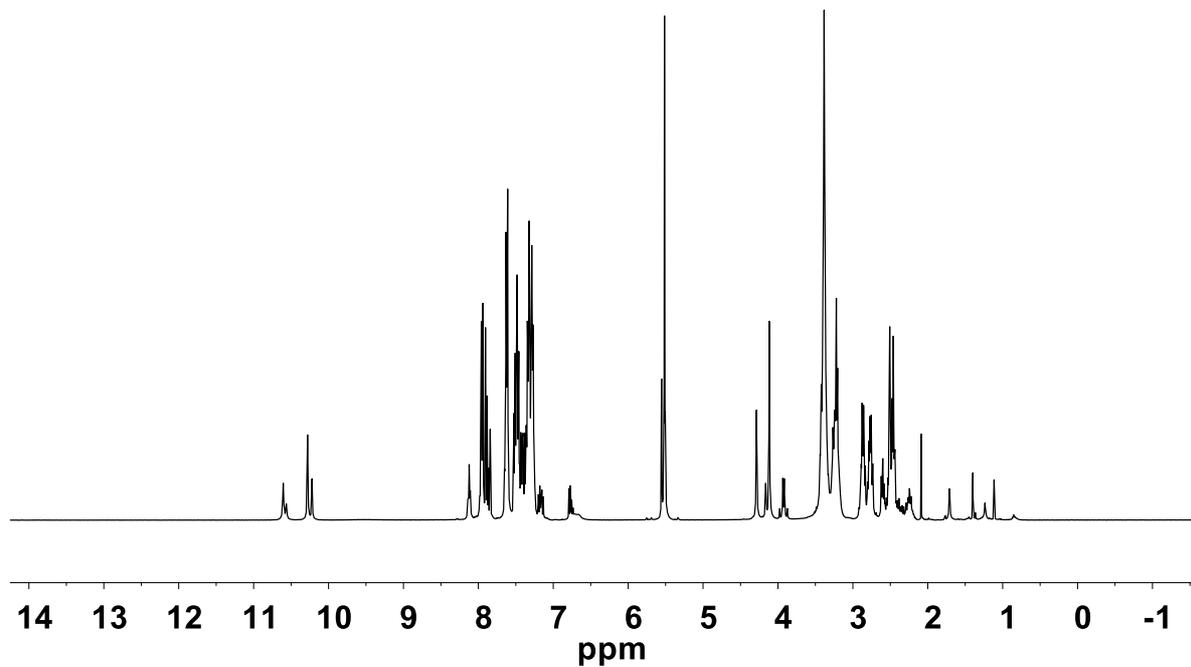


^{13}C , CD_2Cl_2 , 62.9 MHz

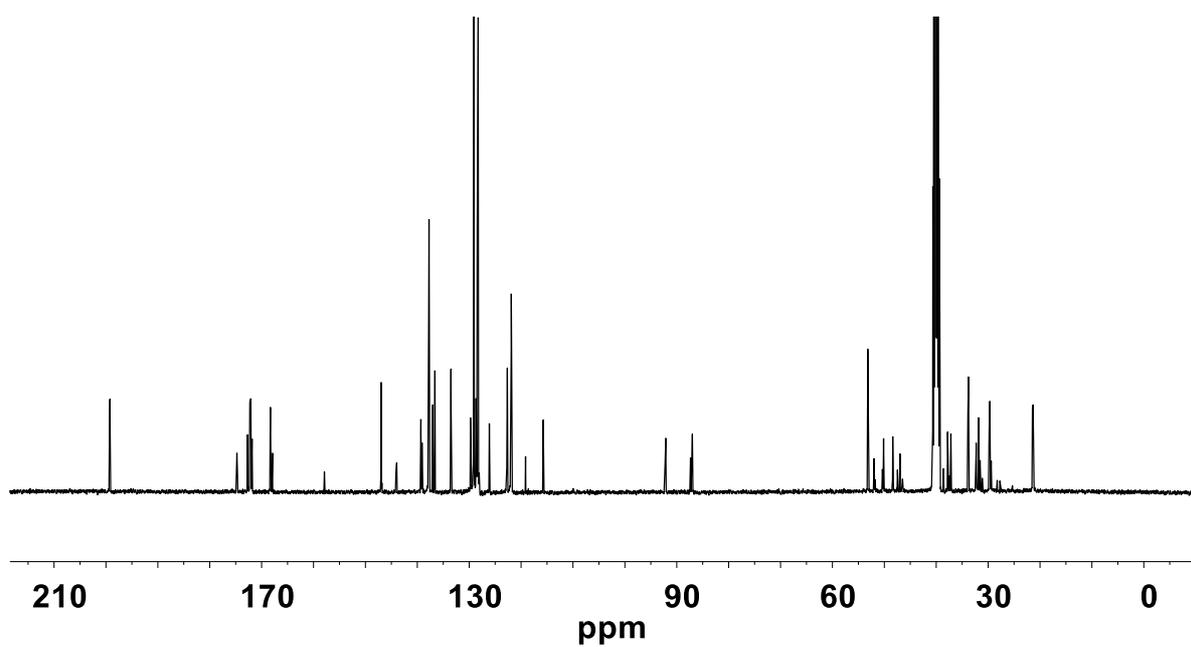


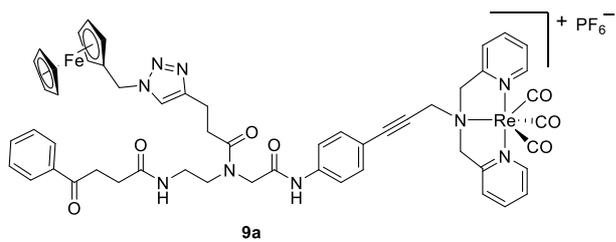


^1H , DMSO- d_6 , 400 MHz

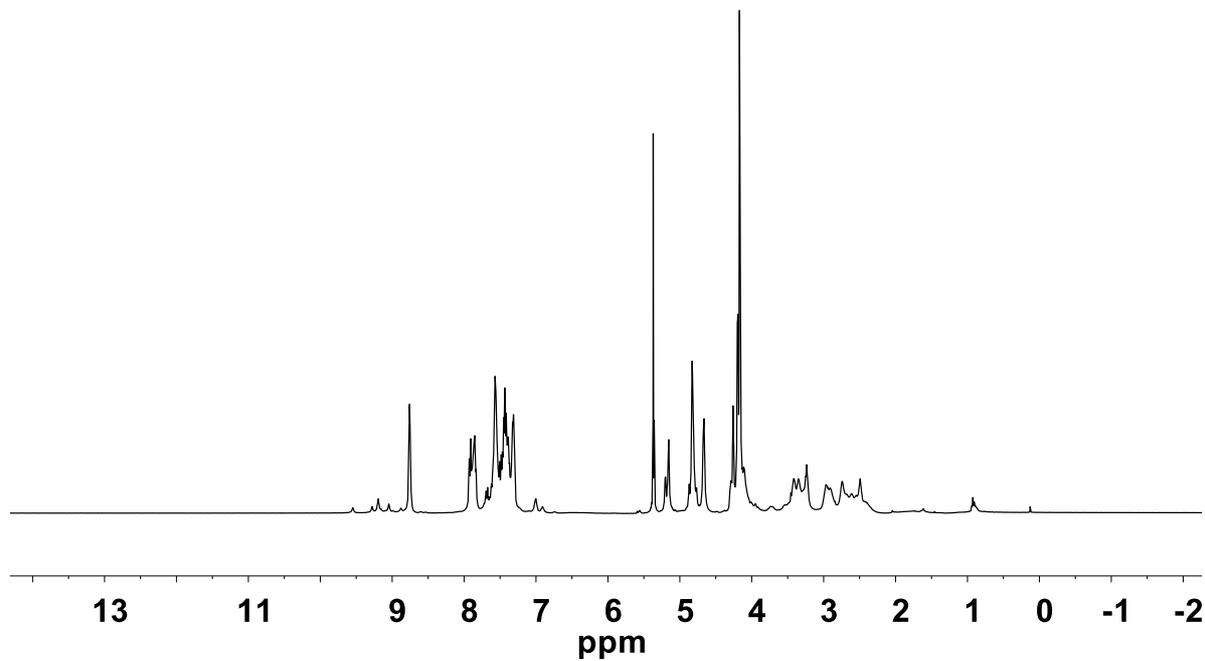


^{13}C , DMSO- d_6 , 100.6 MHz

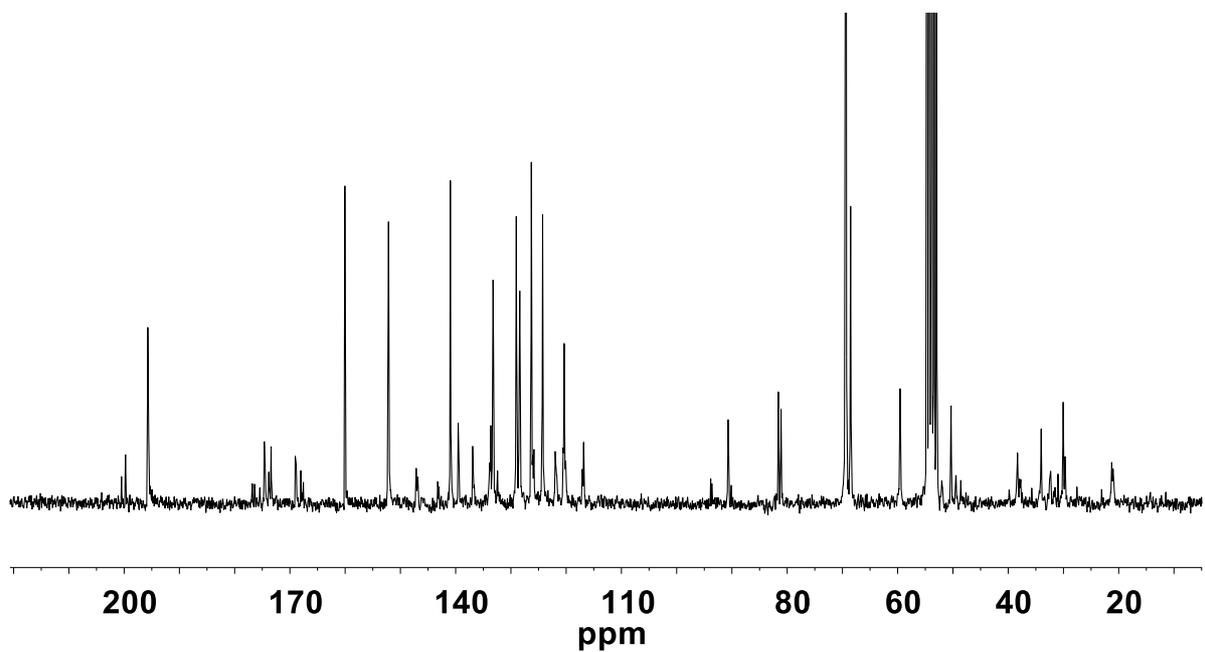


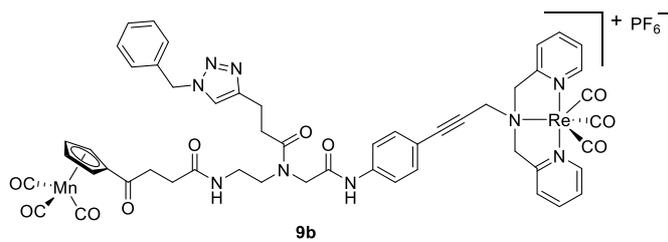


^1H , CD_2Cl_2 , 400 MHz

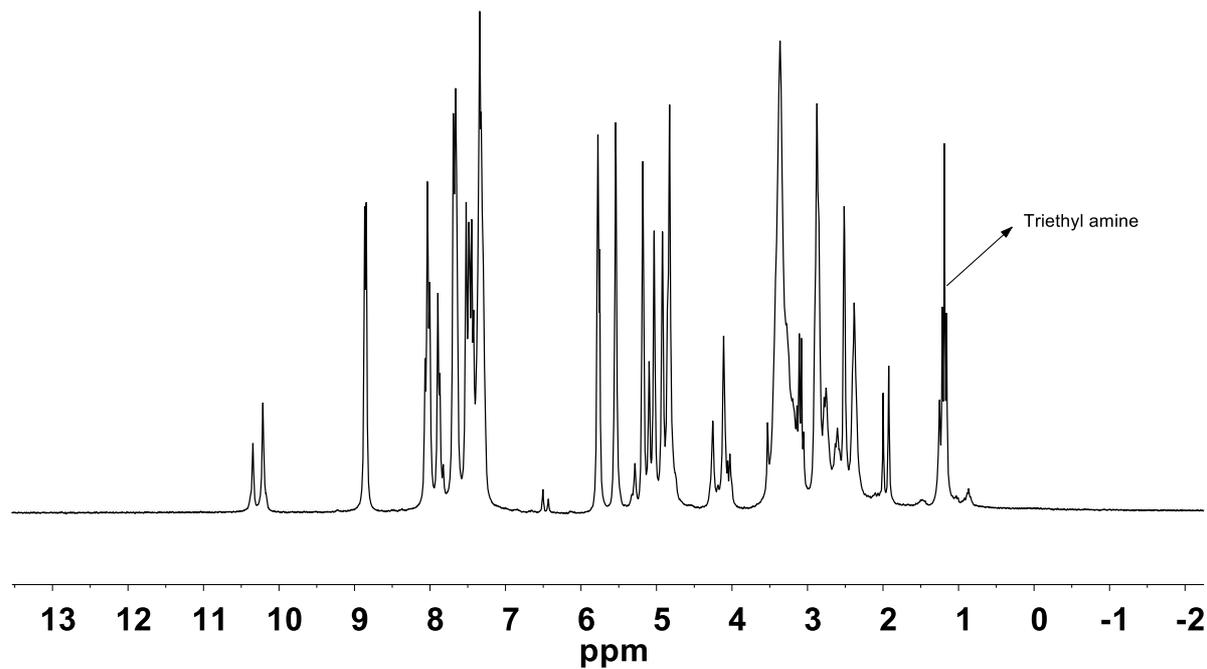


^{13}C , CD_2Cl_2 , 100.6 MHz

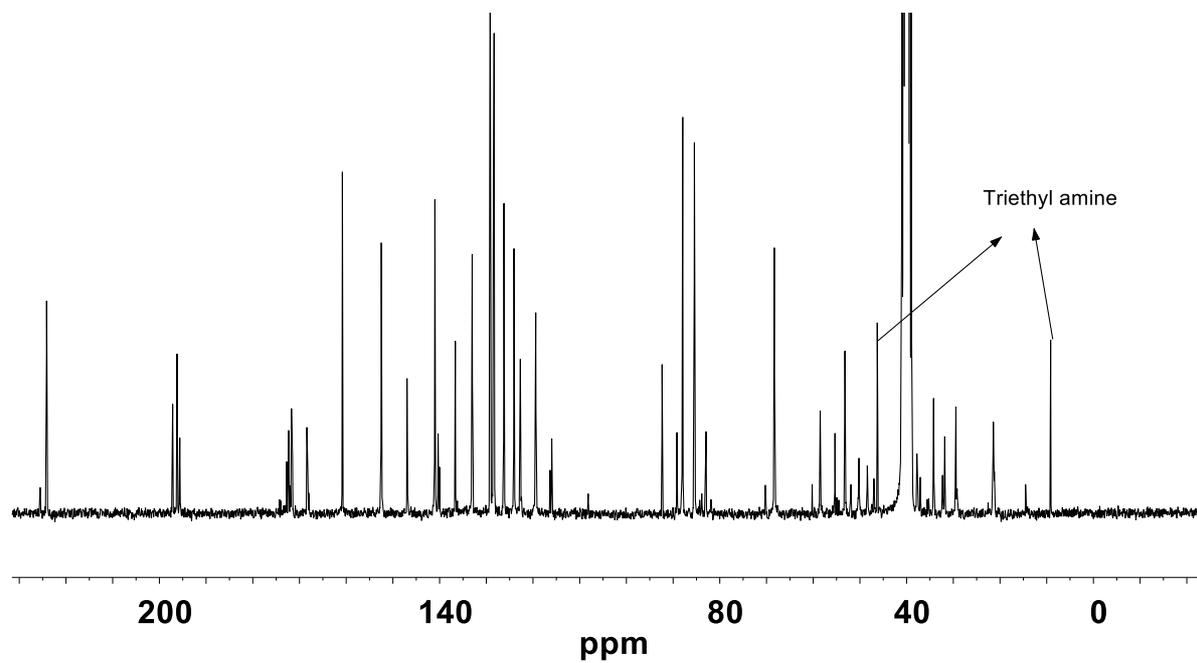




^1H , DMSO- d_6 , 250 MHz



^{13}C , DMSO- d_6 , 62.9 MHz



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