

## Synthesis and cellular uptake of neutral rhenium (I) morpholine complexes

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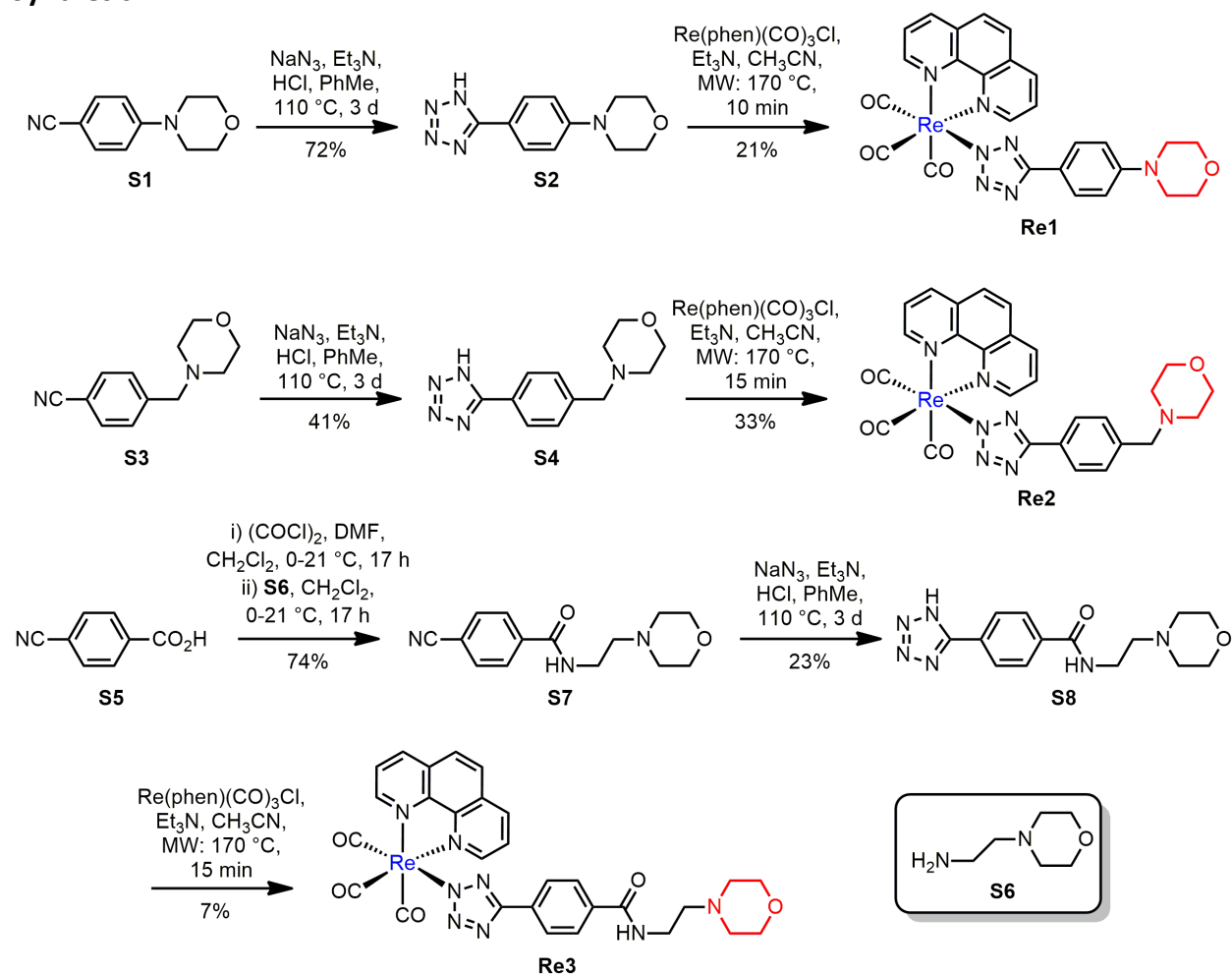
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### Supporting Information

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## Synthesis



**Scheme S1:** Synthesis of **Re1**, **Re2** and **Re3** complexes.

**Synthesis of S2.** Concentrated  $\text{HCl}$  (1.04 mL, 10.2 M) was added to a solution of  $\text{PhMe}$  (30 mL) containing  $\text{Et}_3\text{N}$  (1.48 mL, 10.63 mmol) and the solution stirred for 30 min, after which time  $\text{NaN}_3$  (720 mg, 10.63 mmol) and 4-(4-morpholinyl)benzonitrile **S1** (400 mg, 2.13 mmol) were added. The mixture was then heated at reflux and stirring was maintained for 3 d. The reaction was quenched with  $\text{H}_2\text{O}$  (40 mL) and the reaction mixture was transferred to a separatory funnel. The organic phase was extracted with  $\text{H}_2\text{O}$  ( $3 \times 15$  mL), and the aqueous fractions were combined and treated with concentrated  $\text{HCl}$  (5 drops, 10.2 M). The resulting solid was collected using vacuum filtration, and after washing with  $\text{H}_2\text{O}$  ( $5 \times 5$  mL) and  $\text{Et}_2\text{O}$  ( $2 \times 5$  mL), the product was isolated as a white powder. Yield: 360 mg, 72%. Anal. calc. for  $\text{C}_{11}\text{H}_{13}\text{N}_5\text{O}$ : C 57.13, H 5.67, N 30.28; found: C 56.54, H 5.79, N 30.58. FT-IR (ATR)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 1611 s, 1510 s, 1241 s, 1118 m, 928 m.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  7.89 (2H, d,  $^3J_{\text{H,H}} = 8.9$  Hz,  $\text{H}_{\text{meta}}$ ), 7.13 (2H, d,  $^3J_{\text{H,H}} = 8.9$  Hz,  $\text{H}_{\text{ortho}}$ ),

3.76–3.74 (4H, m, -OCH<sub>2</sub>-), 3.26–3.24 (4H, m, -NCH<sub>2</sub>-). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ 152.7 (Ar C), 128.0 (Ar CH), 114.5 (Ar CH), 113.4 (Ar C), 65.9 (-OCH<sub>2</sub>-), 47.2 (-NCH<sub>2</sub>-).

**Synthesis of Re1.** A solution of tetrazole **S2** (68 mg, 0.29 mmol), Re(phen)(CO)<sub>3</sub>Cl (119 mg, 0.24 mmol), Et<sub>3</sub>N (170 μL, 1.22 mmol), and CH<sub>3</sub>CN (10 mL) was heated at 170 °C for 10 min using MW irradiation. The reaction mixture was concentrated *in vacuo* and the resulting residue underwent column chromatography on silica (20–50–100% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>). The purified fractions were combined and dried *in vacuo*. The resulting residue was dissolved in a minimal amount of CH<sub>2</sub>Cl<sub>2</sub> and filtered through a 0.2 μm PTFE membrane directly into a 50/50 mixture of pet. spirits/Et<sub>2</sub>O (10 mL). The insoluble material was collected using vacuum filtration, and after washing with 50/50 pet. spirits/Et<sub>2</sub>O (3 × 5 mL), the product was isolated as a yellow powder. Yield: 34 mg, 21%. Anal. calc. for C<sub>26</sub>H<sub>20</sub>N<sub>7</sub>O<sub>4</sub>Re: C 45.88, H 2.96, N 14.40; found: C 46.18, H 3.29, N 13.69. FT-IR (ATR)  $\nu_{\max}/\text{cm}^{-1}$ : 2023 s, 1897 s, 1616 w, 1448 m, 1427 m. <sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>) δ 9.64 (2H, dd, <sup>3</sup>J<sub>H,H</sub> = 5.2, <sup>4</sup>J<sub>H,H</sub> = 1.4, H<sub>2</sub>), 8.96 (2H, dd, <sup>3</sup>J<sub>H,H</sub> = 8.3, <sup>4</sup>J<sub>H,H</sub> = 1.4, H<sub>4</sub>), 8.30 (2H, s, H<sub>5</sub>), 8.16 (2H, dd, <sup>3</sup>J<sub>H,H</sub> = 8.3, <sup>3</sup>J<sub>H,H</sub> = 5.2, H<sub>3</sub>), 7.50 (2H, d, <sup>3</sup>J<sub>H,H</sub> = 9.0, H<sub>meta</sub>), 6.80 (2H, d, <sup>3</sup>J<sub>H,H</sub> = 9.0, H<sub>ortho</sub>), 3.75–3.70 (4H, m, -OCH<sub>2</sub>-), 3.10–3.06 (4H, m, -NCH-). <sup>13</sup>C NMR (125 MHz, acetone-*d*<sub>6</sub>) δ 155.1 (C<sub>2</sub>), 152.2 (Ar C), 148.3 (C<sub>7</sub>), 140.3 (C<sub>4</sub>), 131.7 (C<sub>6</sub>), 128.6 (C<sub>5</sub>), 127.6 (C<sub>meta</sub>), 127.3 (C<sub>3</sub>), 122.6 (Ar C), 115.7 (C<sub>ortho</sub>), 67.3 (-OCH<sub>2</sub>-), 49.6 (-NCH<sub>2</sub>-). Crystals of **Re1** for x-ray diffraction studies were grown by the diffusion of pet. spirits into an acetone solution of the complex.

**Synthesis of S4.** Concentrated HCl (610 μL, 10.2 M) was added to a solution of PhMe (15 mL) containing Et<sub>3</sub>N (860 μL, 6.18 mmol) and the solution stirred for 30 min, after which time NaN<sub>3</sub> (400 mg, 6.18 mmol) and 4-(4-morpholinyl)methylbenzotrile **S3** (250 mg, 1.24 mmol) were added. The mixture was then heated at reflux and stirring was maintained for 3 d. The reaction was quenched with H<sub>2</sub>O (40 mL) and the reaction mixture was transferred to a separatory funnel. The organic phase was extracted with H<sub>2</sub>O (3 × 15 mL), and the aqueous fractions were combined and treated with concentrated HCl (5 drops, 10.2 M). The solution was concentrated *in vacuo*, and the resulting solid was suspended in H<sub>2</sub>O (3 mL), and the insoluble material was collected using vacuum filtration. After washing with H<sub>2</sub>O (5 × 5 mL) and Et<sub>2</sub>O (2 × 5 mL), the product was isolated as a beige powder. The filtrate was concentrated, the resulting residue was again suspended in H<sub>2</sub>O (1 mL), and a second crop of product was collected using vacuum filtration after washing with H<sub>2</sub>O (1 mL) and Et<sub>2</sub>O (2 × 5 mL), again as a beige powder. Yield: 137 mg, 41%. Anal. calc. for C<sub>12</sub>H<sub>15</sub>N<sub>5</sub>O·(2H<sub>2</sub>O·0.07NaN<sub>3</sub>): C 50.42, H 6.70, N 25.53; found: C 50.65, H 5.69, N 25.33; due to the solubility of **S4** in H<sub>2</sub>O the final product contained some residual NaN<sub>3</sub>. FT-IR (ATR)  $\nu_{\max}/\text{cm}^{-1}$ : 2690 m, 1499 w, 1455 m, 1443 m, 1377 m, 1124 s, 872 s. <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) δ 8.10 (2H, d, <sup>3</sup>J<sub>H,H</sub> = 8.3 Hz, H<sub>phen</sub>), 7.73

(2H, d,  $^3J_{\text{H,H}} = 8.3$  Hz,  $H_{\text{phen}}$ ), 4.49 (2H, s,  $\text{CH}_2$ ), 4.20–4.08 (2H, m,  $-\text{OCH}_2-$ ), 3.76–3.29 (2H, m,  $-\text{OCH}_2-$ ), 3.57–3.45 (2H, m,  $-\text{NCH}_2-$ ), 3.40–3.27 (2H, m,  $-\text{NCH}_2-$ ).  $^{13}\text{C}$  NMR (125 MHz,  $\text{D}_2\text{O}$ )  $\delta$  tetrazole C not observed, 132.2 (Ar CH), 131.0 (Ar C), 127.9 (Ar CH), 125.7 (Ar C), 63.7 ( $-\text{OCH}_2-$ ), 60.2 ( $\text{CH}_2$ ) 51.4 ( $-\text{NCH}_2$ ).

**Synthesis of Re2.** A solution of tetrazole **S4** (61 mg, 0.25 mmol),  $\text{Re}(\text{phen})(\text{CO})_3\text{Cl}$  (84 mg, 0.20 mmol),  $\text{Et}_3\text{N}$  (136  $\mu\text{L}$ , 0.95 mmol), and  $\text{CH}_3\text{CN}$  (10 mL) was heated at 170 °C for 15 min using MW irradiation. The reaction mixture was concentrated *in vacuo* and the resulting residue underwent column chromatography on BII neutral alumina (10–30–50%  $\text{EtOAc}$  in  $\text{CH}_2\text{Cl}_2$ ). The purified fractions were combined and dried *in vacuo*. The resulting residue was dissolved in a minimal amount of  $\text{CH}_2\text{Cl}_2$  and filtered through a 0.2  $\mu\text{m}$  PTFE membrane directly into a 50/50 mixture of pet. spirits/ $\text{Et}_2\text{O}$  (10 mL). The insoluble material was collected using vacuum filtration, and after washing with 50/50 pet. spirits/ $\text{Et}_2\text{O}$  ( $3 \times 5$  mL), the product was isolated as a yellow powder. Yield: 47 mg, 33%. Anal. calc. for  $\text{C}_{27}\text{H}_{22}\text{N}_7\text{O}_4\text{Re}$ : C 46.68, H 3.19, N 14.11; found: C 46.52, H 3.10, N 14.22. FT-IR (ATR)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 2025 s, 1922 s, 1906 s, 1427 m, 2213 m, 847 m.  $^1\text{H}$  NMR (400 MHz, acetone- $d_6$ )  $\delta$  9.65 (2H, dd,  $^3J_{\text{H,H}} = 5.1$ ,  $^4J_{\text{H,H}} = 1.4$ , H2), 8.97 (2H, dd,  $^3J_{\text{H,H}} = 8.2$ ,  $^4J_{\text{H,H}} = 1.4$ , H4), 8.31 (2H, s, H5), 8.17 (2H, dd,  $^3J_{\text{H,H}} = 8.2$ ,  $^3J_{\text{H,H}} = 5.1$ , H3), 7.57 (2H, d,  $^3J_{\text{H,H}} = 8.3$ ,  $H_{\text{meta}}$ ), 7.19 (2H, d,  $^3J_{\text{H,H}} = 8.3$ ,  $H_{\text{ortho}}$ ), 3.58–3.54 (4H, m,  $-\text{OCH}_2-$ ), 3.39 (2H, s,  $\text{CH}_2$ ), 2.34–3.29 (4H, m,  $-\text{NCH}_2-$ ).  $^{13}\text{C}$  NMR (125 MHz, acetone- $d_6$ )  $\delta$  163.5 (tetrazole C), 155.1 (C2), 148.3 (C7), 140.3 (C4), 139.2 (Ar C), 131.7 (C6), 130.1 (Ar C), 129.7 ( $C_{\text{meta}}$ ), 128.7 ( $C_{\text{ortho}}$ ), 127.4 (C5), 126.5 (C3), 67.4 ( $-\text{OCH}_2-$ ), 63.6 ( $\text{CH}_2$ ), 54.4 ( $-\text{NCH}_2-$ ). Crystals of **Re2** for x-ray diffraction studies were grown by the diffusion of pet. spirits into a  $\text{CH}_2\text{Cl}_2$  solution of the complex.

**Synthesis of S7.** Oxalyl chloride (720  $\mu\text{L}$ , 8.42 mmol) was added dropwise to a stirring solution of 4-cyanobenzoic acid **S5** (950 mg, 6.48 mmol), DMF (5 drops), and  $\text{CH}_2\text{Cl}_2$  (35 mL) at 0 °C. Stirring was maintained at 0 °C for 1 h before being warmed to ambient temperature and stirred for a further 16 h. The reaction was concentrated *in vacuo* and the resulting residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (10 mL) and added dropwise to a stirring solution of 4-(2-aminoethyl)morpholine **S6** (850  $\mu\text{L}$ , 16.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) at 0 °C. Stirring was maintained at 0 °C for 1 h before being warmed to ambient temperature and stirred for a further 16 h. The reaction mixture was transferred to a separatory funnel and the organic phase was washed with sat.  $\text{Na}_2\text{CO}_3$  ( $3 \times 10$  mL),  $\text{H}_2\text{O}$  (10 mL), dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*, to afford an orange oil that solidified upon cooling. The oil was repeatedly triturated with pet. spirits to afford the product as an off-white powder. Yield: 1.25 g, 74%. Anal. calc. for  $\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}_2 \cdot (0.05\text{CH}_2\text{Cl}_2)$ : C 64.03, H 6.54, N 15.94; found: C 63.78, H 6.82, N 16.03. FT-IR (ATR)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 2234 w (CN), 1636 m, 1547 m, 1305 m, 1116 s, 864 s.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.66 (1H, t,  $^3J_{\text{H,H}} =$

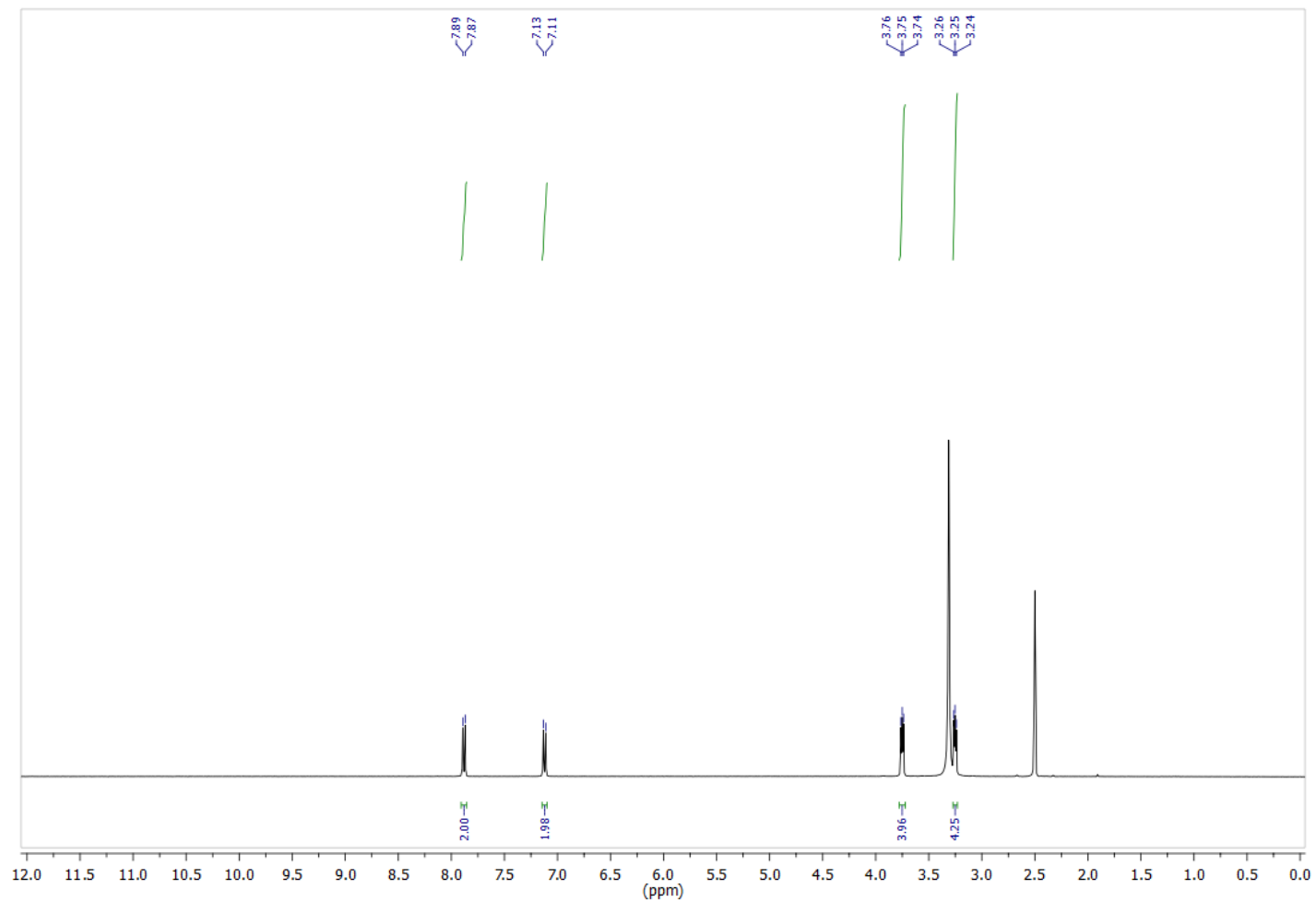
5.5 Hz, NH), 7.97–7.96 (4H, m,  $2 \times H_{\text{meta}}$  and  $2 \times H_{\text{ortho}}$ ), 3.57–3.55 (4H, m,  $-\text{OCH}_2-$ ), 3.42–3.39 (2H, m,  $\text{CONHCH}_2$ ), 2.47–2.45 (2H, m,  $\text{CONHCH}_2\text{CH}_2$ ), 2.42–2.40 (4H, m,  $-\text{NCH}_2-$ ).  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO}-d_6$ )  $\delta$  164.8 (CONH), 138.5 (Ar C), 132.4 (Ar CH), 128.0 (Ar CH), 118.3 (CN), 113.5 (Ar C), 66.1 ( $-\text{OCH}_2-$ ), 57.2 ( $\text{CONHCH}_2$ ) 53.3 ( $-\text{NCH}_2-$ ), 36.7 ( $\text{CONHCH}_2\text{CH}_2$ ).

**Synthesis of S8.** Concentrated HCl (570  $\mu\text{L}$ , 10.2 M) was added to a solution of PhMe (20 mL) containing  $\text{Et}_3\text{N}$  (810  $\mu\text{L}$ , 5.78 mmol) and the solution stirred for 30 min, after which time  $\text{NaN}_3$  (380 mg, 5.78 mmol) and nitrile **S7** (300 mg, 1.16 mmol) were added. The mixture was then heated at reflux and stirring was maintained for 3 d. The reaction was quenched with  $\text{H}_2\text{O}$  (40 mL) and the reaction mixture was transferred to a separatory funnel. The organic phase was extracted with  $\text{H}_2\text{O}$  ( $3 \times 15$  mL), and the aqueous fractions were combined and treated with concentrated HCl (5 drops, 10.2 M). The solution was concentrated *in vacuo*, and the resulting solid was suspended in  $\text{H}_2\text{O}$  (3 mL), and the insoluble material was collected using vacuum filtration. After washing with  $\text{H}_2\text{O}$  ( $3 \times 5$  mL) and  $\text{Et}_2\text{O}$  ( $3 \times 5$  mL), the product was isolated as beige crystals. The filtrate was stored at 4 °C overnight, during which time crystals formed which were then collected using vacuum filtration and washed as before, to give a second crop of beige crystals. Yield: 82 mg, 23%. Anal. calc. for  $\text{C}_{14}\text{H}_{18}\text{N}_6\text{O}_2 \cdot (3.5\text{H}_2\text{O} \cdot 0.1\text{NaN}_3)$ : C 45.22, H 6.78, N 23.73; found: C 45.64, H 6.06, N 23.31; due to the solubility of **S8** in  $\text{H}_2\text{O}$  the final product contained some residual  $\text{NaN}_3$ . FT-IR (ATR)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 1655 s, 1306 m, 1105 s, 856 s.  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$ )  $\delta$  8.12 (2H, d,  $^3J_{\text{H,H}} = 8.4$  Hz,  $H_{\text{phen}}$ ), 7.90 (2H, d,  $^3J_{\text{H,H}} = 8.4$  Hz,  $H_{\text{phen}}$ ), 3.85–3.78 (4H, m,  $-\text{OCH}_2-$ ), 3.64–3.58 (2H, m,  $\text{CONHCH}_2$ ), 2.76–2.71 (2H, m,  $\text{CONHCH}_2\text{CH}_2$ ), 2.70–2.65 (4H, m,  $-\text{NCH}_2-$ ).  $^{13}\text{C}$  NMR (125 MHz,  $\text{D}_2\text{O}$ )  $\delta$  170.2 (CONH), 161.7 (tetrazole C), 160.3 (Ar C), 134.1 (Ar C), 132.0 (Ar C), 127.8 (Ar CH), 126.7 (Ar CH), 66.0 ( $-\text{OCH}_2-$ ), 56.3 ( $\text{CONHCH}_2$ ), 52.5 ( $-\text{NCH}_2-$ ), 36.6 ( $\text{CONHCH}_2\text{CH}_2$ ).

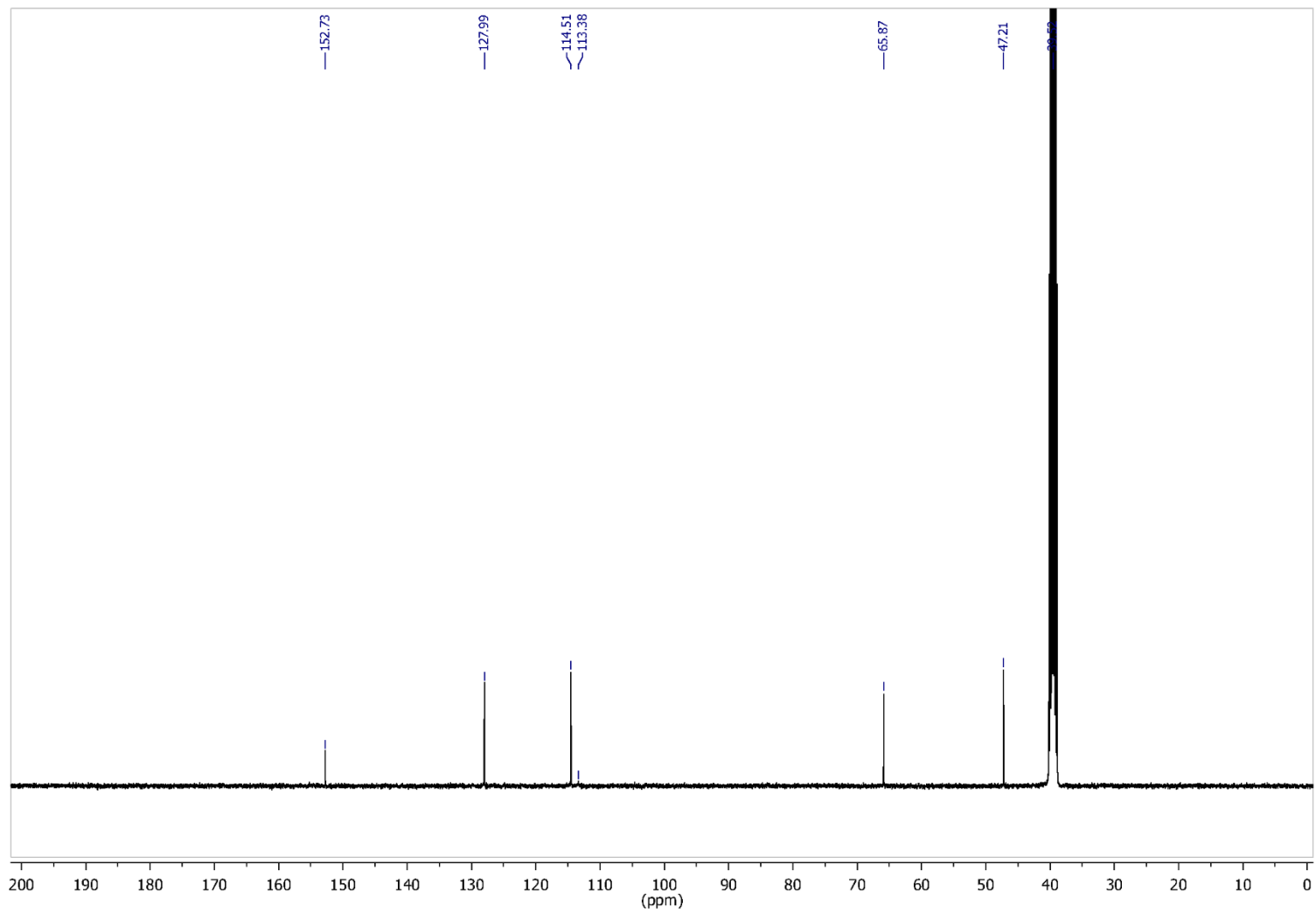
**Synthesis of Re3.** A solution of tetrazole **S8** (50 mg, 0.17 mmol),  $\text{Re}(\text{phen})(\text{CO})_3\text{Cl}$  (62 mg, 0.13 mmol),  $\text{Et}_3\text{N}$  (89  $\mu\text{L}$ , 0.64 mmol), and  $\text{CH}_3\text{CN}$  (10 mL) was heated at 170 °C for 15 min using MW irradiation. The reaction mixture was concentrated *in vacuo* and the resulting residue underwent column chromatography on silica (50% EtOAc in  $\text{CH}_2\text{Cl}_2$  to 10–20% MeOH in EtOAc). The purified fractions were combined and dried *in vacuo*. The resulting residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (5 mL), transferred to a separatory funnel and washed with sat.  $\text{NaHCO}_3$  ( $2 \times 5$  mL),  $\text{H}_2\text{O}$  (5 mL), dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The resulting residue was dissolved in a minimal amount of  $\text{CH}_2\text{Cl}_2$  and filtered through a 0.2  $\mu\text{m}$  PTFE membrane directly into a 50/50 mixture of pet. spirits/ $\text{Et}_2\text{O}$  (10 mL). The insoluble material was collected using vacuum filtration, and after washing with 50/50 pet. spirits/ $\text{Et}_2\text{O}$  ( $3 \times 5$  mL), the product was isolated as a yellow powder. Yield: 6.4 mg, 7%. Anal. calc. for  $\text{C}_{29}\text{H}_{25}\text{N}_8\text{O}_5\text{Re} \cdot (0.7\text{CH}_2\text{Cl}_2)$ : C 43.97, H 3.28, N 13.81; found:

C 43.73, H 3.09, N 13.82. FT-IR (ATR)  $\nu_{\max}/\text{cm}^{-1}$ : 2025 s, 1905 s, 1648 w, 1520 w, 1429 m, 856 m.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  9.66 (2H, dd,  $^3J_{\text{H,H}} = 5.1$ ,  $^4J_{\text{H,H}} = 1.4$ , H2), 8.97 (2H, dd,  $^3J_{\text{H,H}} = 8.3$ ,  $^4J_{\text{H,H}} = 1.4$ , H4), 8.31 (2H, s, H5), 8.18 (2H, dd,  $^3J_{\text{H,H}} = 8.3$ ,  $^3J_{\text{H,H}} = 5.1$ , H3), 7.73 (2H, d,  $^3J_{\text{H,H}} = 8.6$ ,  $\text{H}_{\text{meta}}$ ), 7.68 (2H, d,  $^3J_{\text{H,H}} = 8.6$ ,  $\text{H}_{\text{ortho}}$ ), 3.61–3.56 (4H, m,  $-\text{OCH}_2-$ ), 3.50–3.44 (2H, m,  $\text{CONHCH}_2$ ), 2.54–2.49 (2H, m,  $\text{CONHCH}_2\text{CH}_2$ ), 2.46–2.40 (4H, m,  $-\text{NCH}_2-$ ).  $^{13}\text{C}$  NMR (125 MHz,  $\text{D}_2\text{O}$ )  $\delta$  196.8 (CO), 194.1 (CO), 166.0 (CONH), 161.7 (tetrazole C), 154.3 (C2), 146.5 (C7), 139.8 (C4), 133.6 (Ar C), 131.8 (Ar C), 130.3 (C6), 127.8 (C5), 127.7 (C3), 127.7 ( $\text{C}_{\text{meta}}$ ), 125.2 ( $\text{C}_{\text{ortho}}$ ), 63.4 ( $-\text{OCH}_2-$ ), 55.7 ( $\text{CONHCH}_2$ ), 51.4 ( $-\text{NCH}_2-$ ), 33.9 ( $\text{CONHCH}_2\text{CH}_2$ ). Crystals of **Re3** for x-ray diffraction studies were grown by the diffusion of petroleum spirits into a  $\text{CH}_2\text{Cl}_2$  solution of the complex.

**$^1\text{H}$  and  $^{13}\text{C}$  spectra**

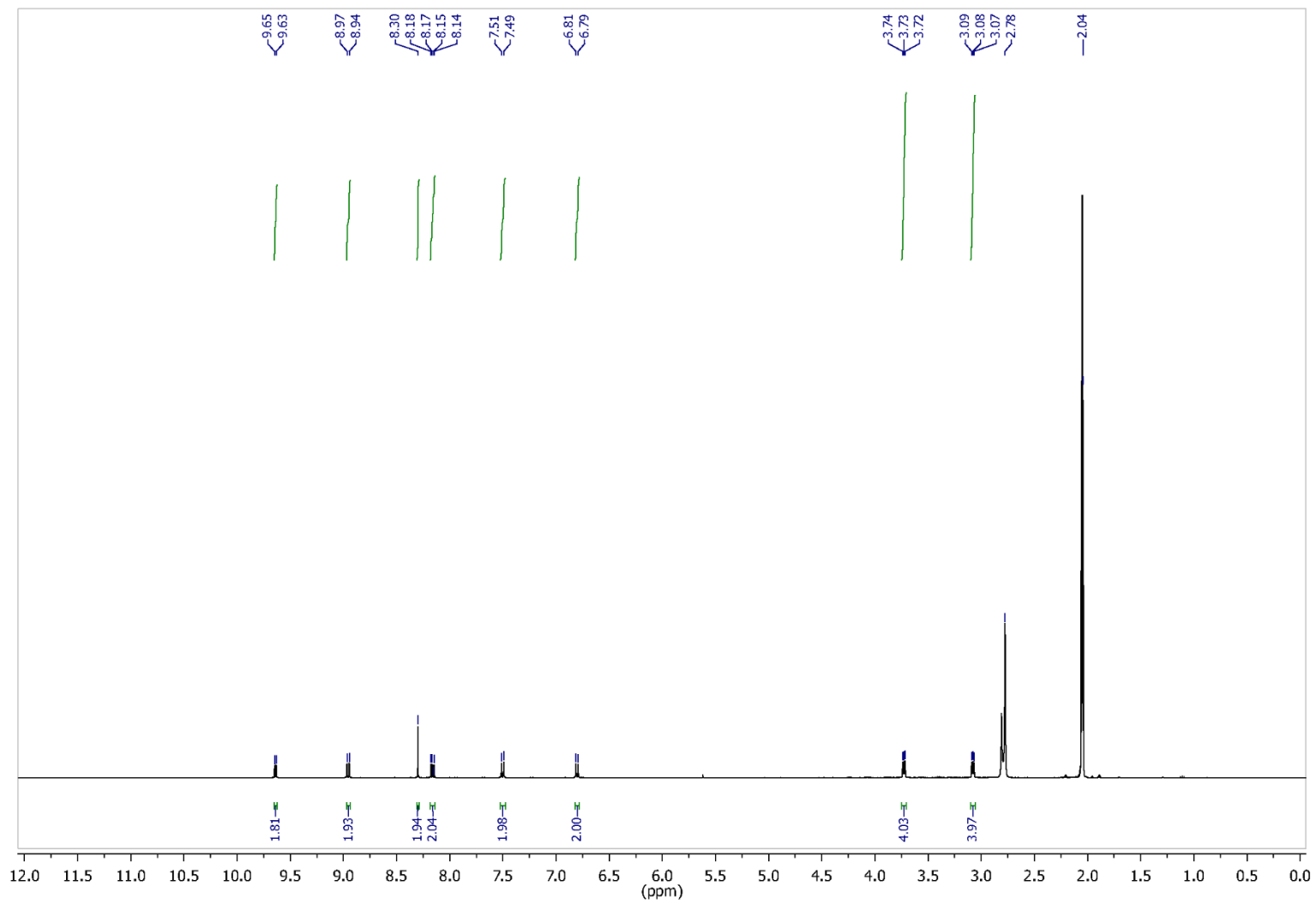


**Figures S1:**  $^1\text{H}$  NMR (400 MHz) of S2 in DMSO- $d_6$ .

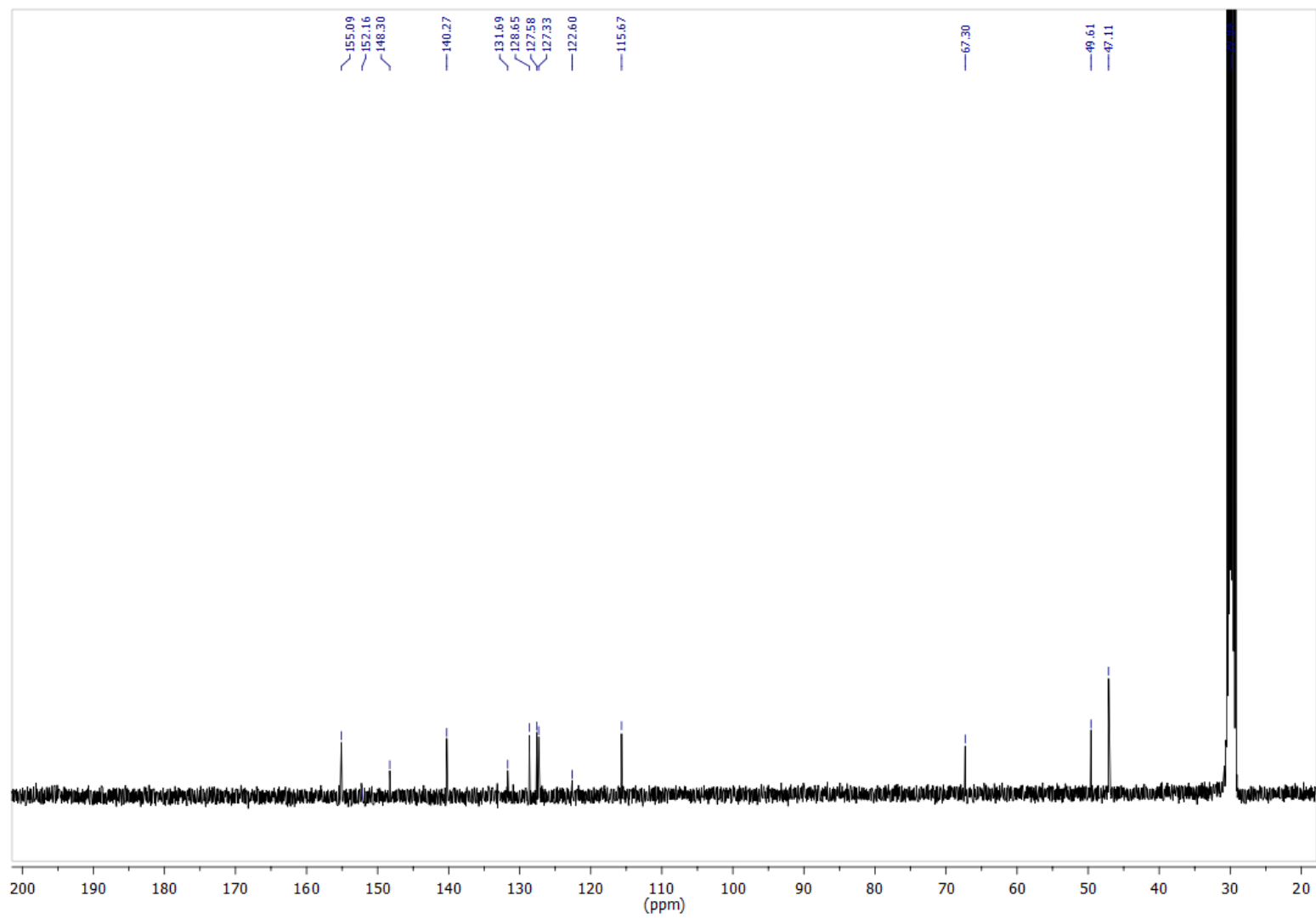


Figures S2:  $^{13}\text{C}$  NMR (125 MHz) of S2 in  $\text{DMSO-}d_6$ .

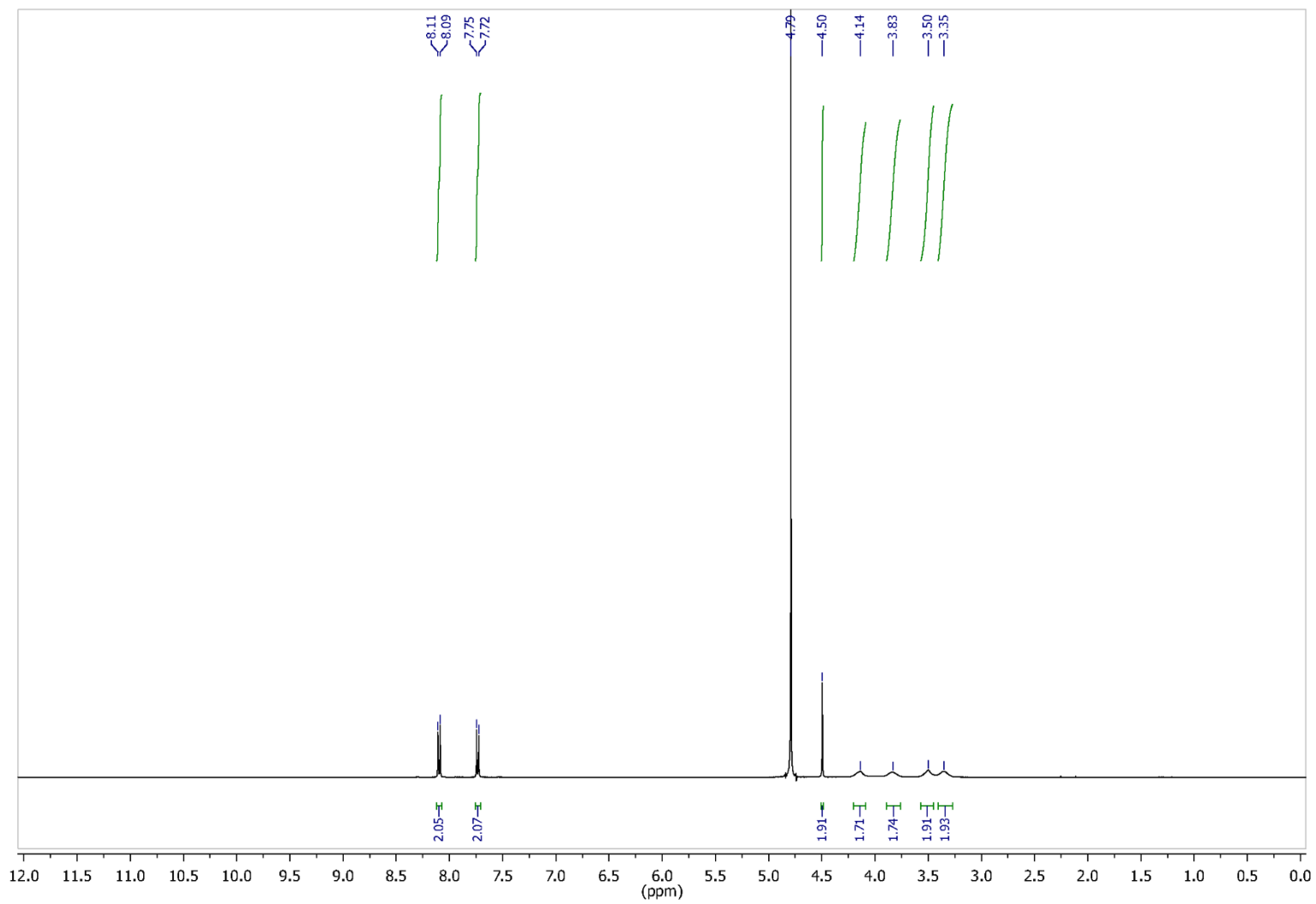




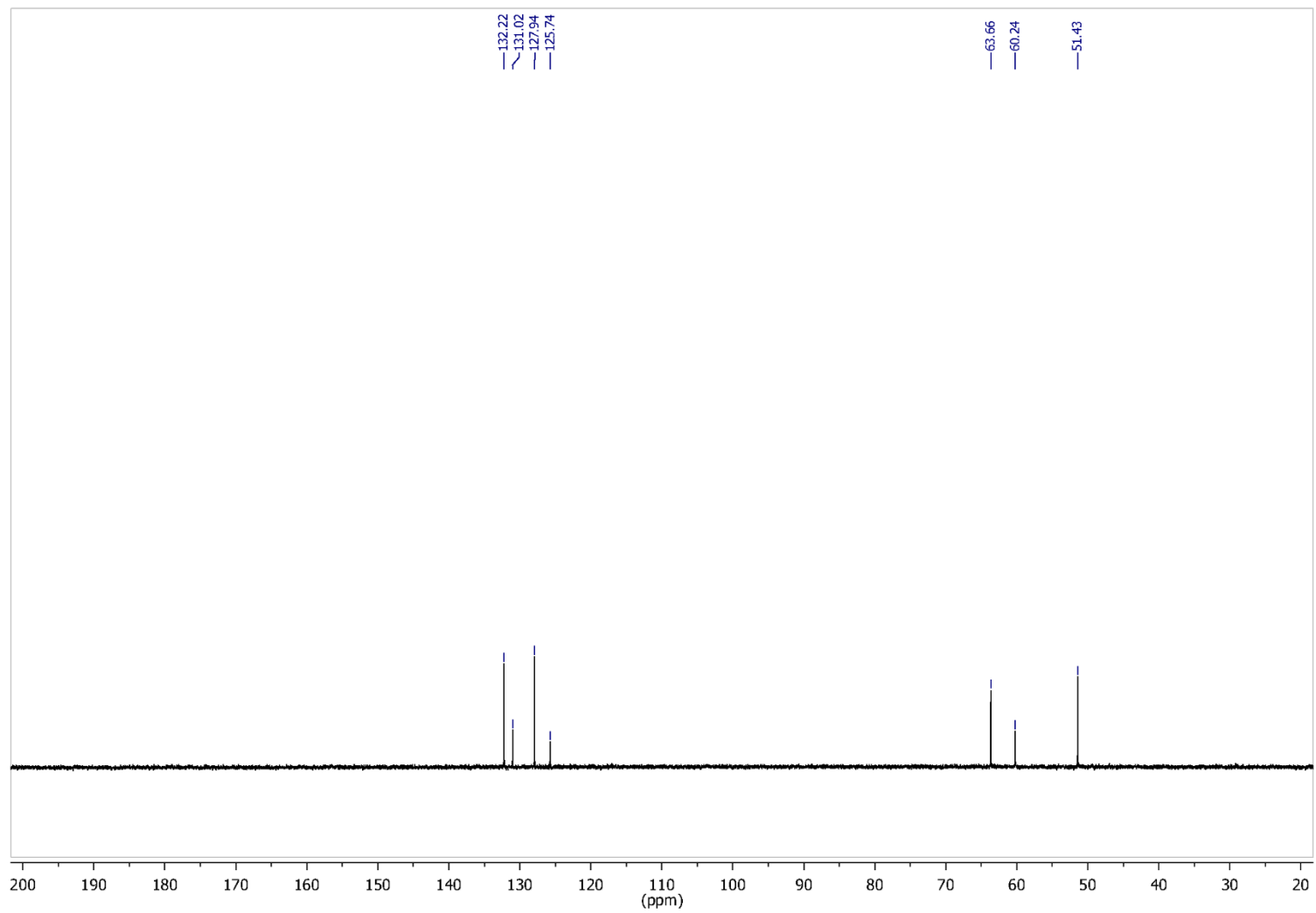
Figures S3:  $^1\text{H}$  NMR (400 MHz) of Re1 in acetone- $d_6$ .



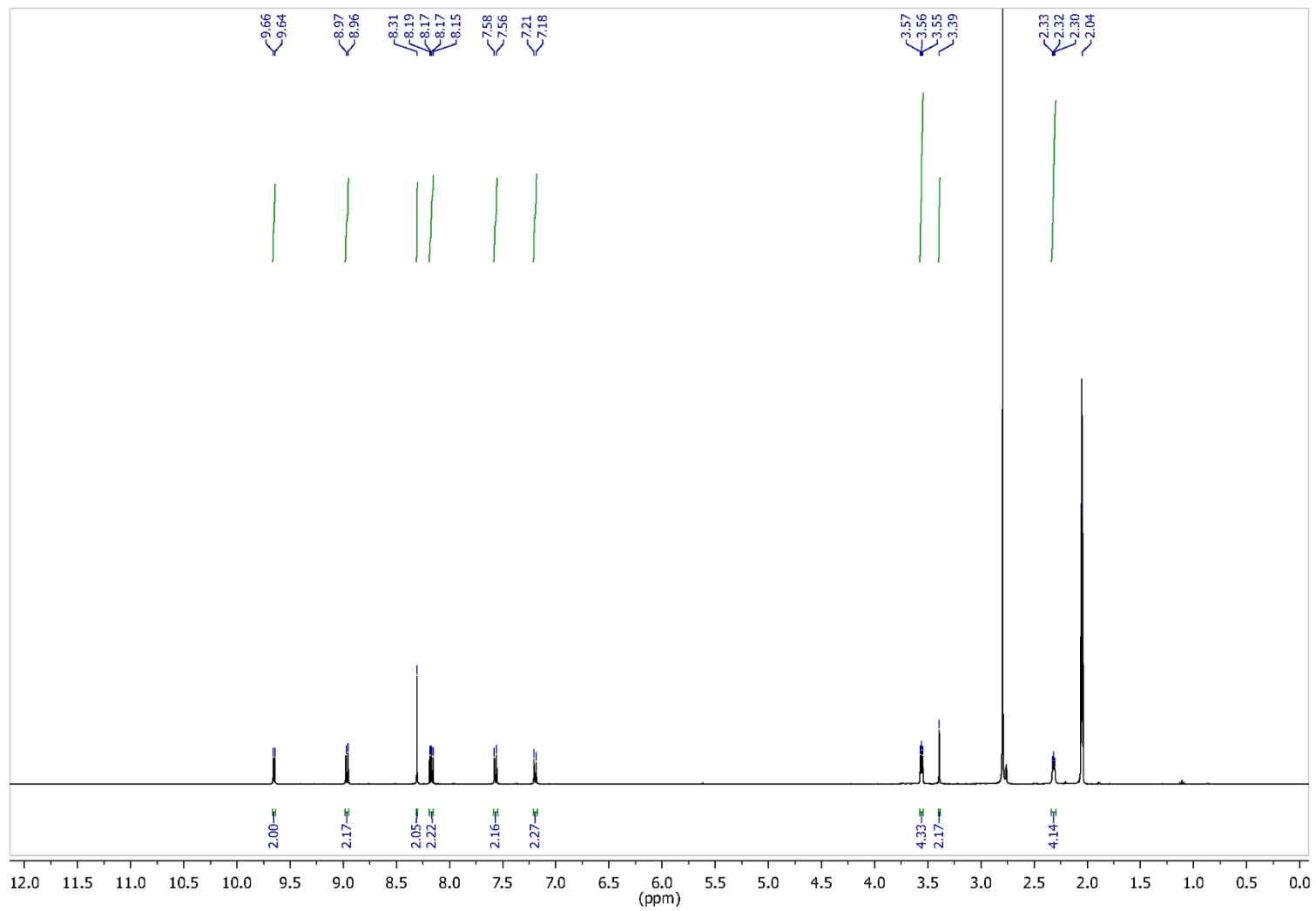
Figures S4:  $^{13}\text{C}$  NMR (125 MHz) of Re1 in acetone- $d_6$ .



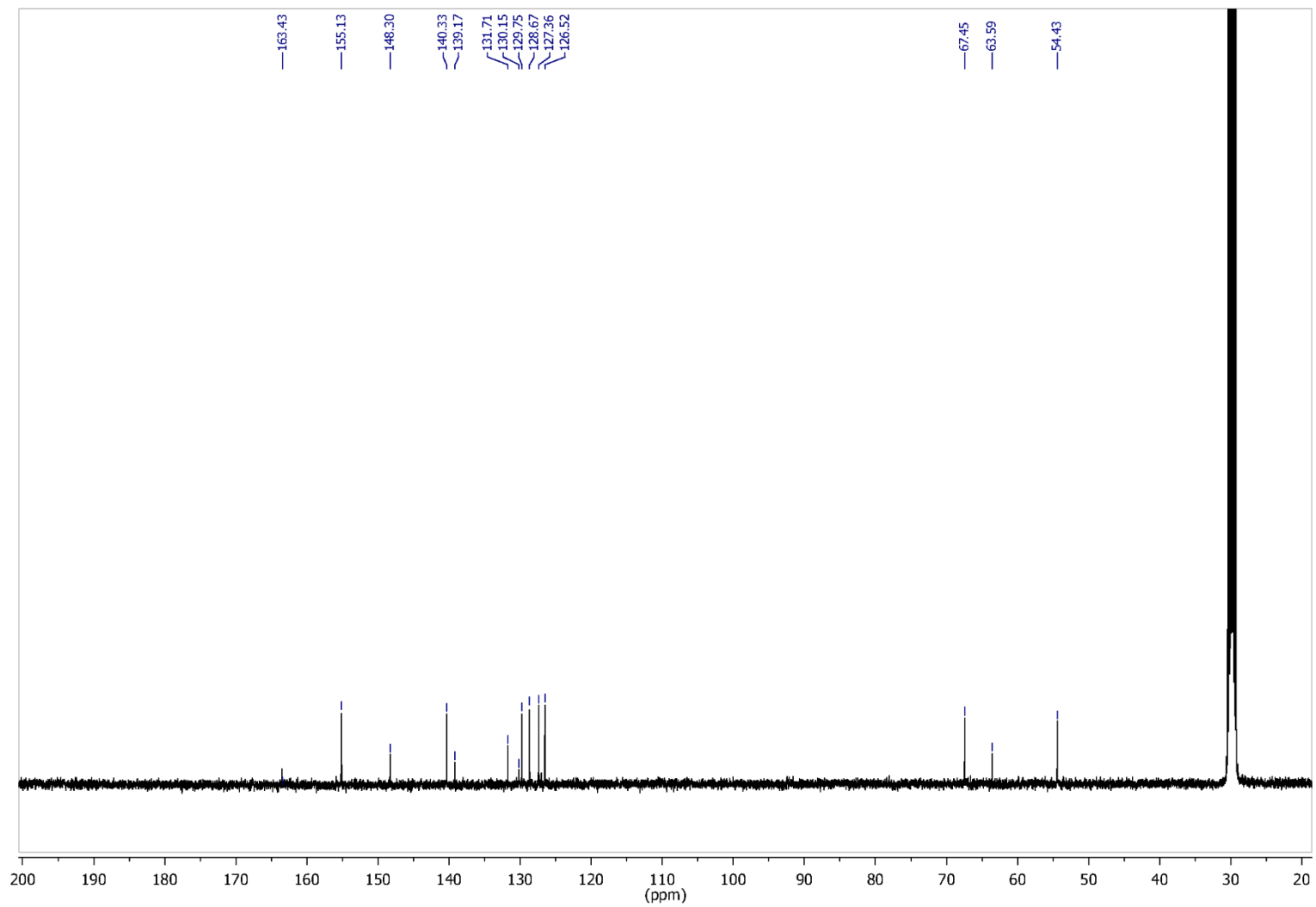
Figures S5:  $^1\text{H}$  NMR (400 MHz) of **S4** in  $\text{D}_2\text{O}$ .



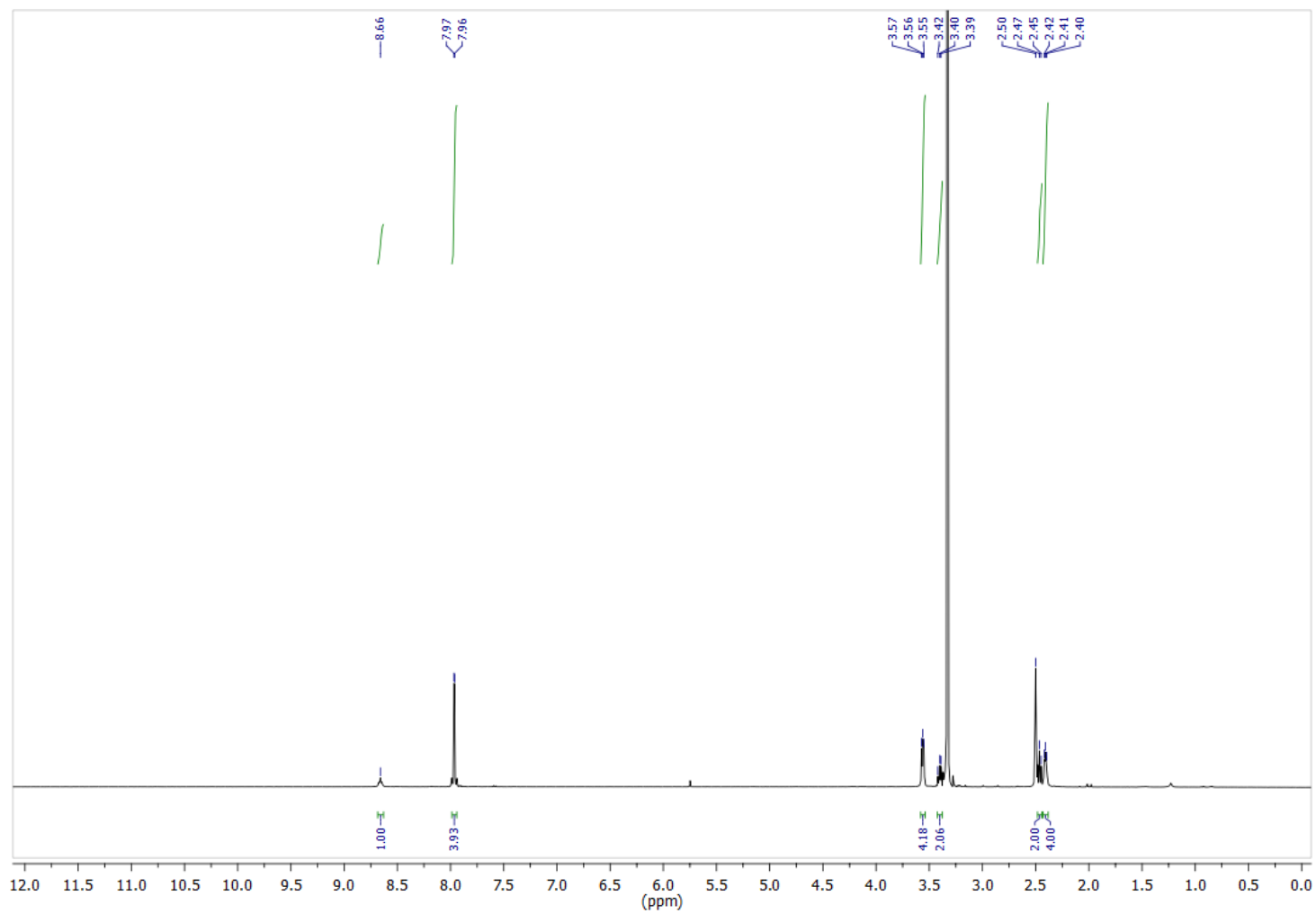
Figures S6:  $^{13}\text{C}$  NMR (125 MHz) of S4 in  $\text{D}_2\text{O}$ .



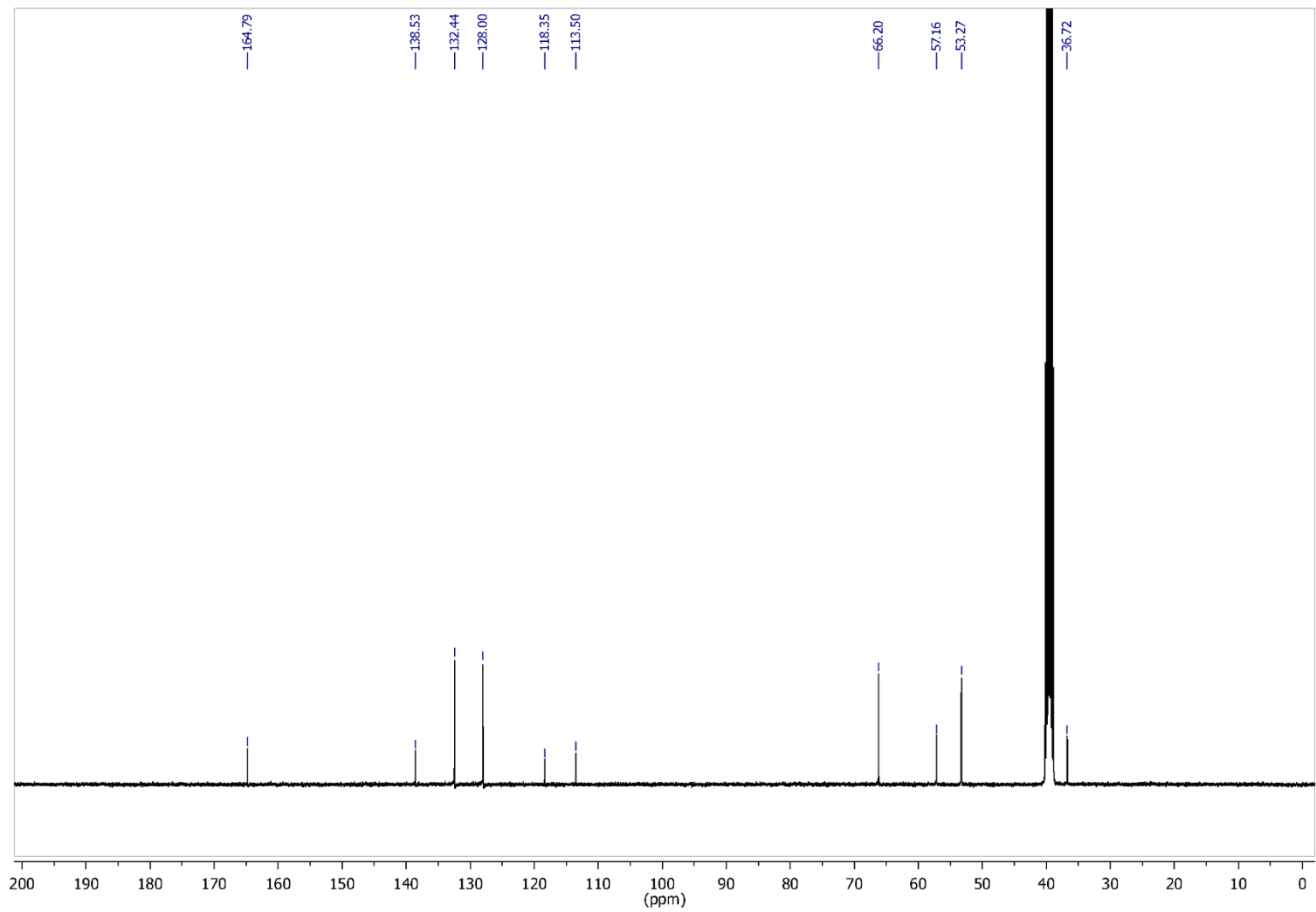
Figures S7:  $^1\text{H}$  NMR (400 MHz) of Re2 in acetone- $d_6$ .



Figures S8:  $^{13}\text{C}$  NMR (125 MHz) of Re2 in acetone- $d_6$ .

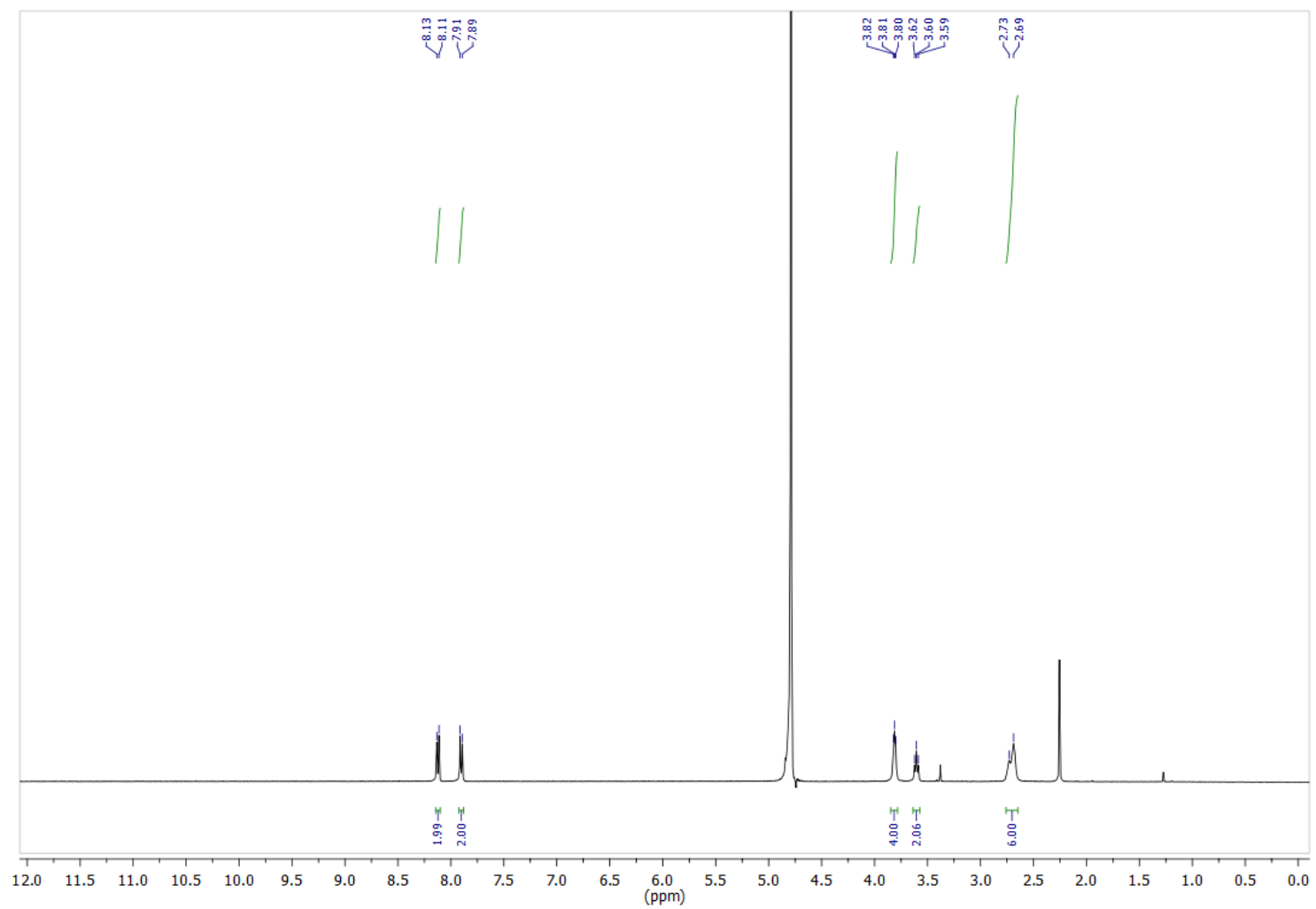


Figures S9:  $^1\text{H}$  NMR (400 MHz) of S7 in  $\text{DMSO}-d_6$ .

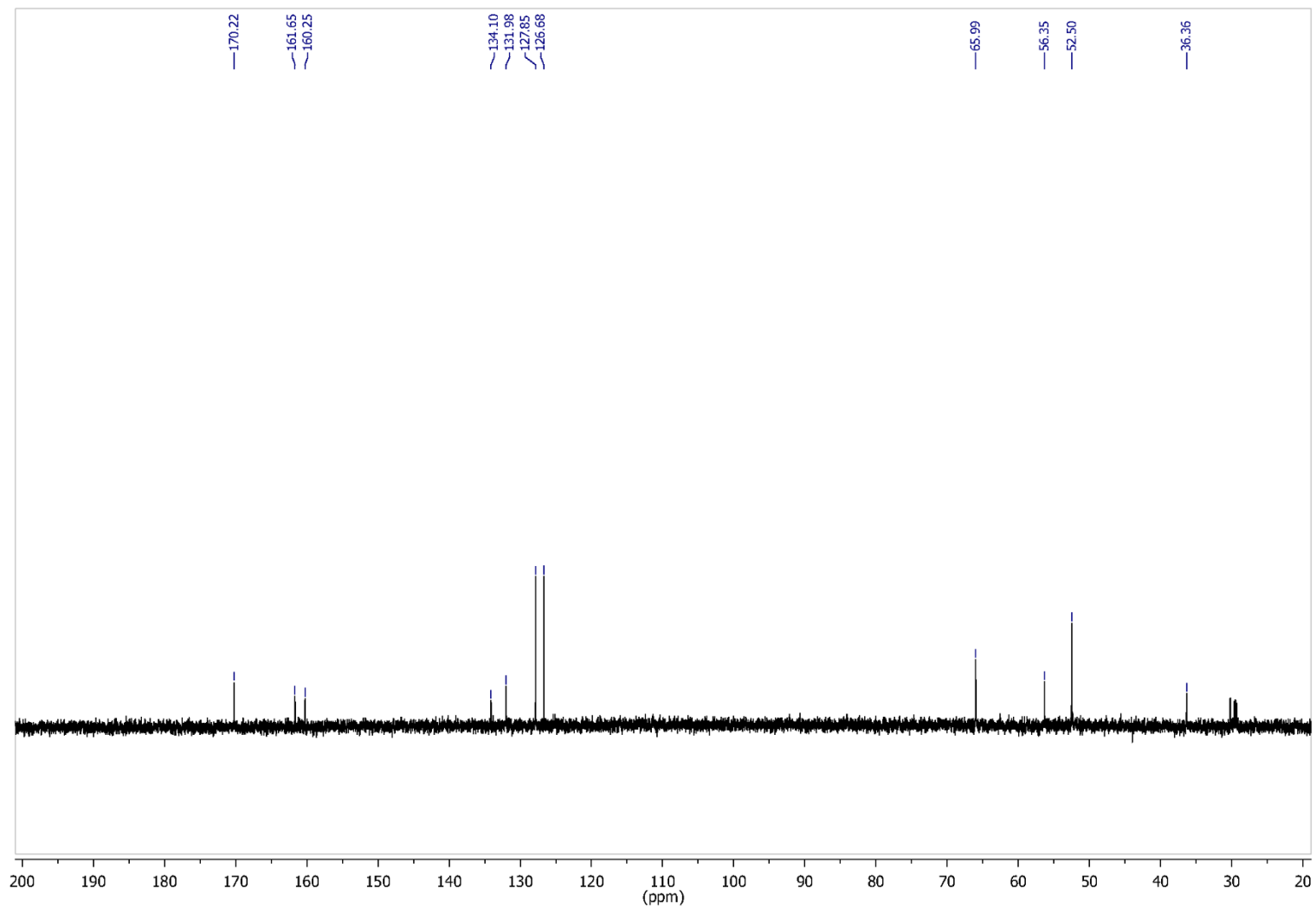


Figures S10:  $^{13}\text{C}$  NMR (125 MHz) of **S7** in  $\text{DMSO-}d_6$ .

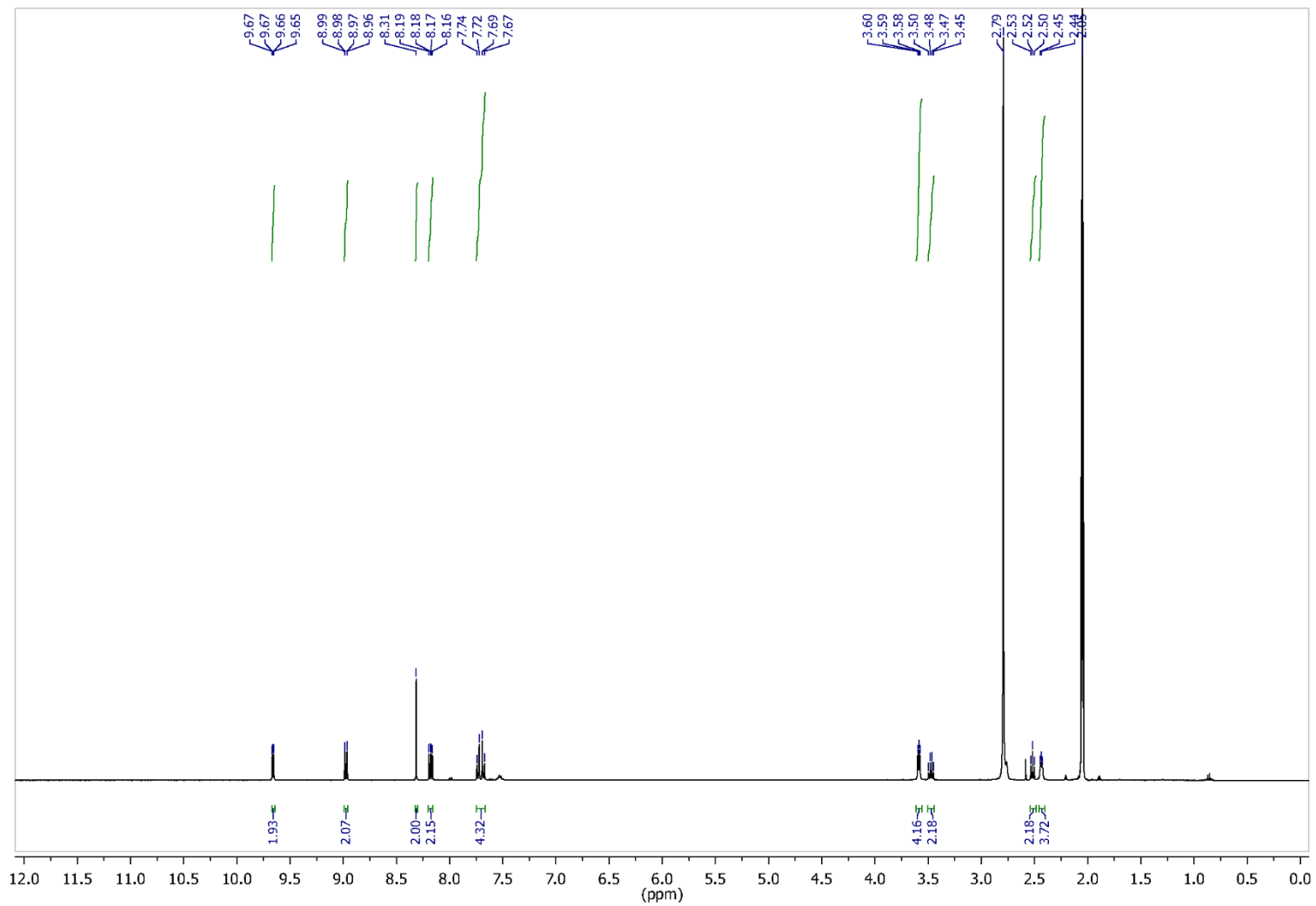




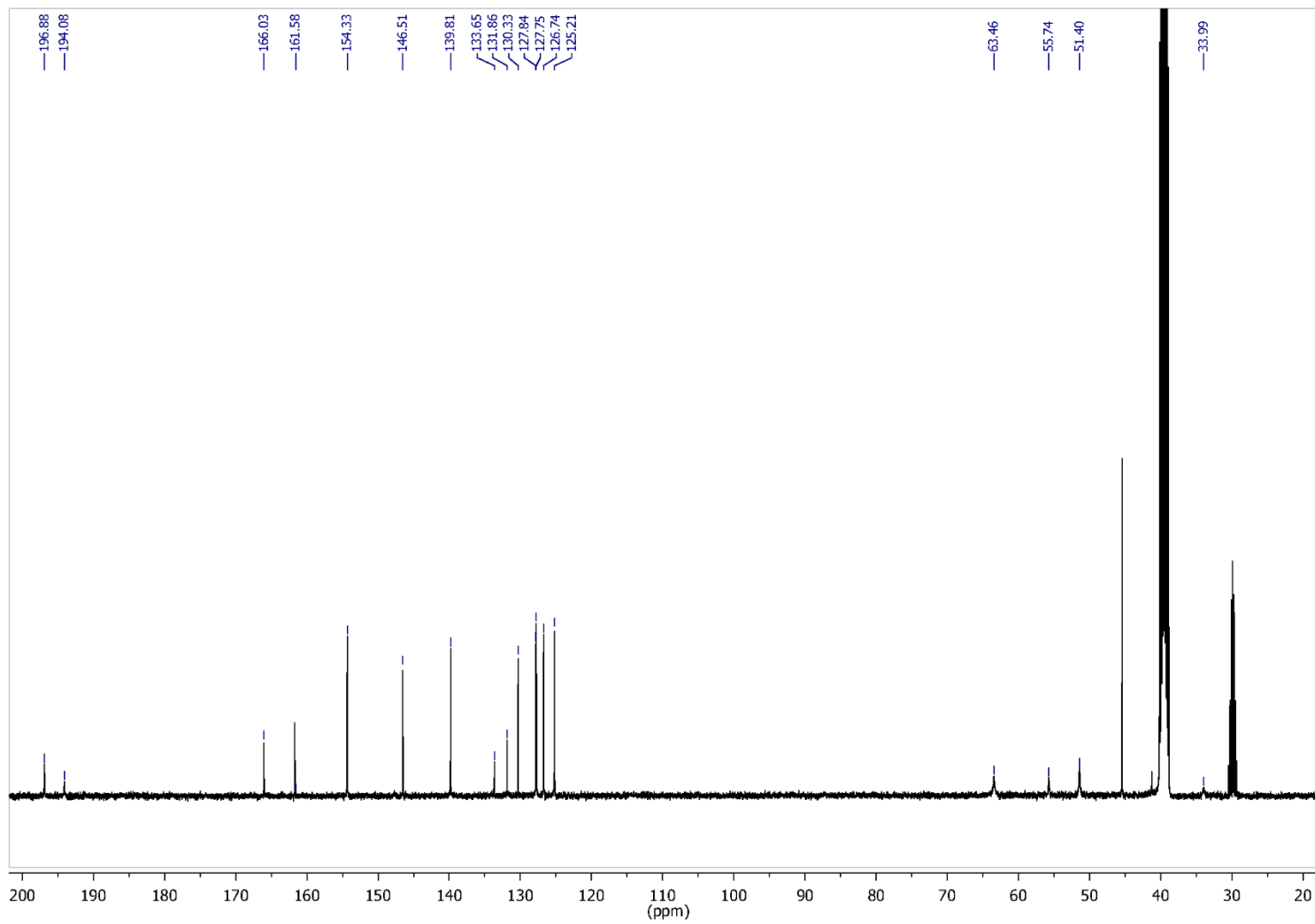
Figures S11:  $^1\text{H}$  NMR (400 MHz) of S8 in  $\text{D}_2\text{O}$ .



Figures S12:  $^{13}\text{C}$  NMR (125 MHz) of S8 in  $\text{D}_2\text{O}$ .

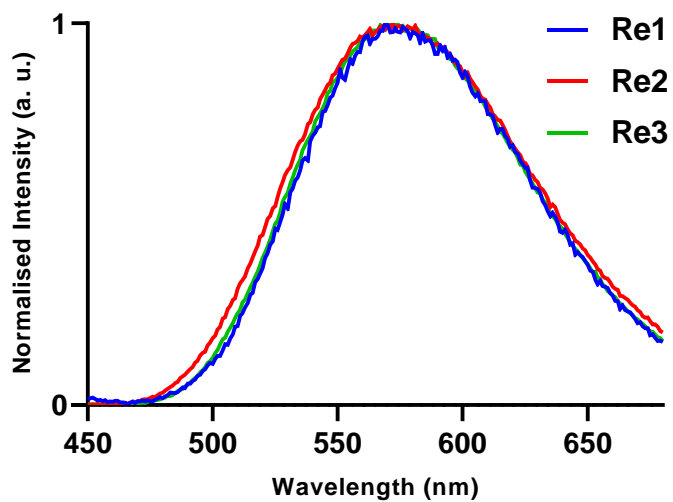
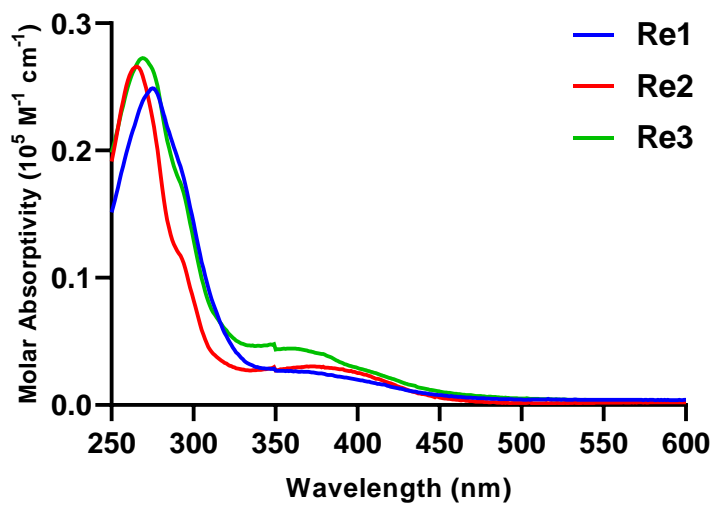


Figures S13:  $^1\text{H}$  NMR (400 MHz) of Re3 in  $\text{DMSO-}d_6$ .

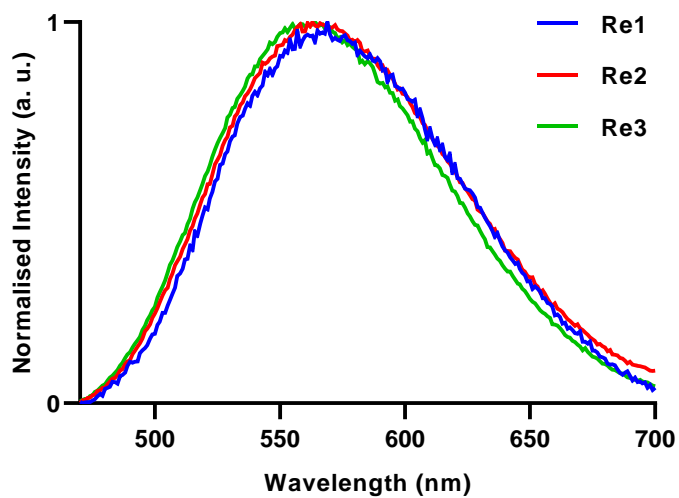
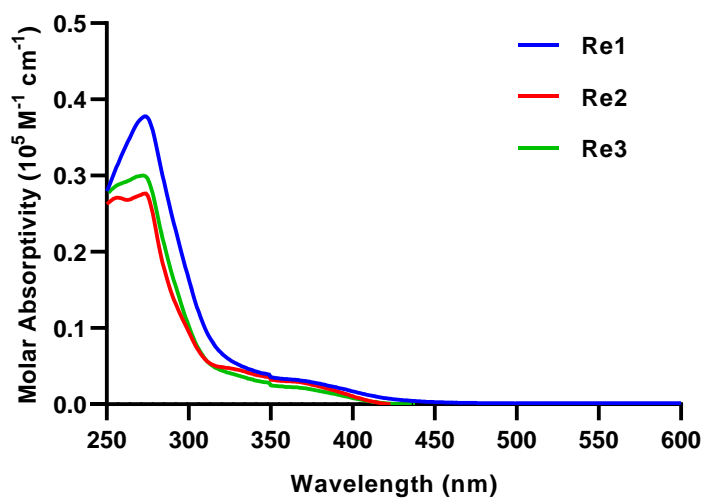


Figures S14:  $^{13}\text{C}$  NMR (125 MHz) of Re3 in  $\text{DMSO-}d_6$ .

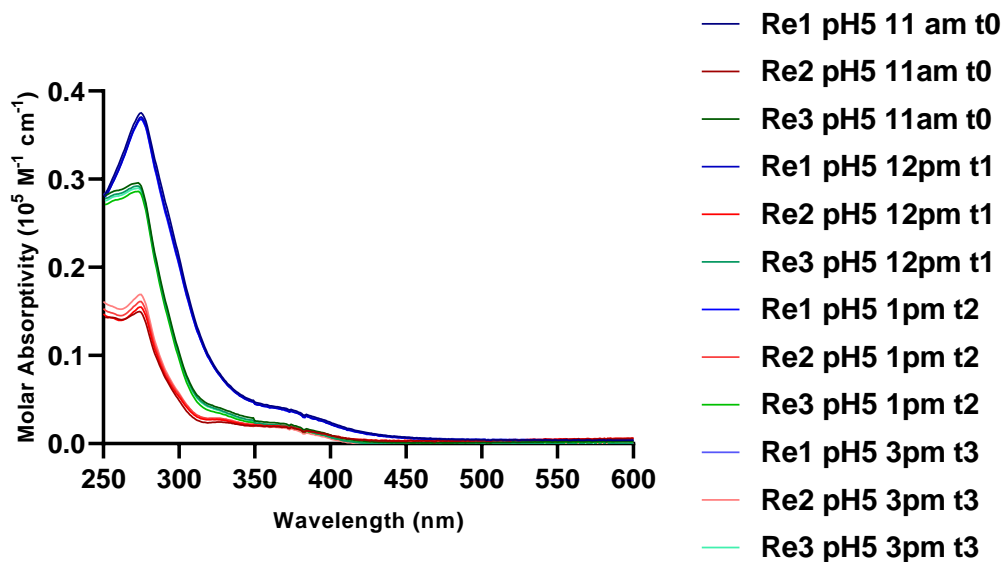
## Photophysical studies



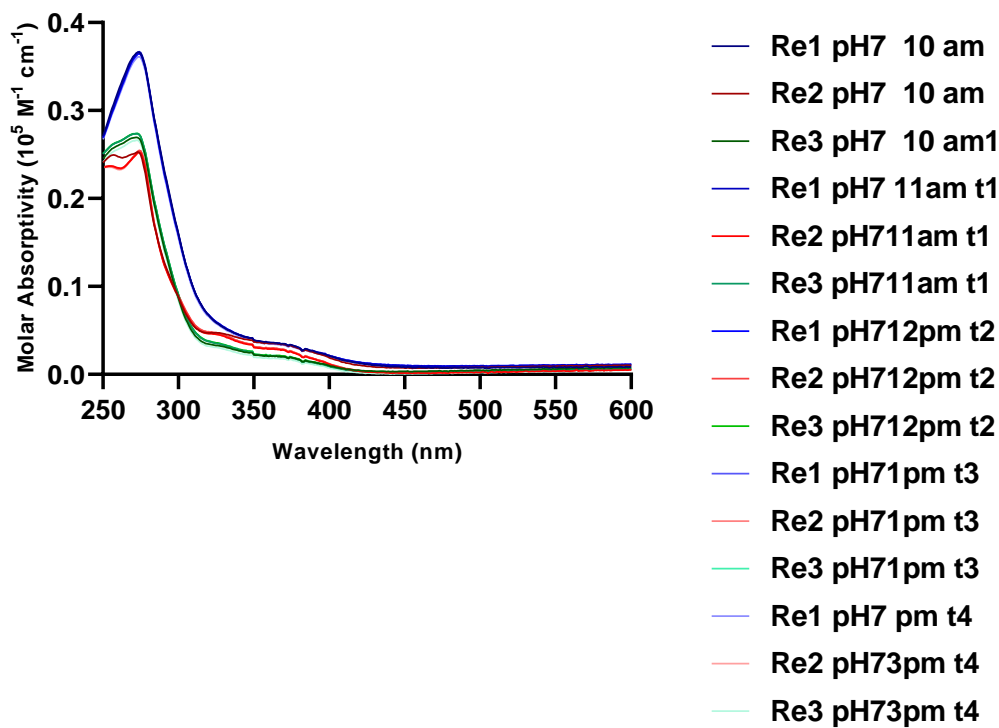
**Figure S15.** Absorption (top panel) and emission spectra (bottom panel) of rhenium morpholine complexes from a *ca*  $10^{-5}$  M solution in dichloromethane at 298 K.



**Figure S16.** Absorption (top panel) and emission spectra (bottom panel) of rhenium morpholine complexes from a *ca*  $10^{-5}$  M solution in  $\text{H}_2\text{O}$  (1% DMSO) at 298 K.



**Figure S17.** Absorption spectra of rhenium morpholine complexes from a *ca*  $10^{-5}$  M solution in H<sub>2</sub>O (1% DMSO) at 298 K, recorded at pH=5 over 5 hours.



**Figure S18.** Absorption spectra of rhenium morpholine complexes from a *ca*  $10^{-5}$  M solution in H<sub>2</sub>O (1% DMSO) at 298 K, recorded at pH=7 over 5 hours.

## Crystallographic refinement data

Single-crystal X-ray diffraction data were measured from single crystals using an Oxford Xcalibur-S (**Re1** and **Re3**) and Gemini-R Ultra CCD diffractometer (**Re2**) at  $T = 100(2)$  K operating with monochromatic MoK $\alpha$  ( $\lambda = 0.71073$  Å) radiation. The data were corrected for Lorentz and polarization effects, and absorption corrections were applied using multiple symmetry equivalent reflections. The structure was solved using direct methods and refined against  $F^2$  with full-matrix least-squares using the SHELX program suite.[1] Anisotropic displacement parameters were applied for the non-hydrogen atoms. All hydrogen atoms were added to calculated positions and refined using a riding model with the isotropic displacement parameters based on those of the parent atom. Crystallographic data for the structure reported here have been deposited at the Cambridge Crystallographic Data Centre (CCDC). Copies with CCDC numbers 1908893, 1908896 and 1908895 can be obtained free of charge via <https://www.ccdc.cam.ac.uk/structures/> or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax+ 441223336033; email deposit@ccdc.cam.ac.uk).

**Re1 (CCDC 1908893).**  $2(\text{C}_{26}\text{H}_{20}\text{N}_7\text{O}_4\text{Re})$ ,  $\text{C}_3\text{H}_6\text{O}$ ;  $\text{C}_{55}\text{H}_{46}\text{N}_{14}\text{O}_9\text{Re}_2$ ,  $M = 1419.46$ , yellow prism,  $0.223 \times 0.202 \times 0.166$  mm<sup>3</sup>, monoclinic, space group  $P2_1/n$  (No. 14),  $a = 9.0338(1)$ ,  $b = 11.1396(1)$ ,  $c = 28.5974(5)$  Å,  $\beta = 92.845(1)^\circ$ ,  $V = 2874.29(6)$  Å<sup>3</sup>,  $Z = 2$ ,  $D_c = 1.640$  g cm<sup>-3</sup>,  $\mu = 4.274$  mm<sup>-1</sup>.  $F_{000} = 1392$ , MoK $\alpha$  radiation,  $\lambda = 0.71073$  Å,  $T = 100(2)$  K,  $2\theta_{\text{max}} = 63.8^\circ$ , 58556 reflections collected, 9501 unique ( $R_{\text{int}} = 0.0384$ ). Final  $\text{Goof} = 1.004$ ,  $R1 = 0.0433$ ,  $wR2 = 0.1050$ ,  $R$  indices based on 8290 reflections with  $I > 2\sigma(I)$  (refinement on  $F^2$ ),  $|\Delta\rho|_{\text{max}} = 4.8(2)$  e Å<sup>-3</sup>, 379 parameters, 12 restraints. Lp and absorption corrections applied.

**Re2 (CCDC 1908896).**  $\text{C}_{27}\text{H}_{22}\text{N}_7\text{O}_4\text{Re}$ ,  $M = 694.71$ , yellow plate,  $0.404 \times 0.240 \times 0.024$  mm<sup>3</sup>, monoclinic, space group  $P2_1/n$  (No. 14),  $a = 12.7738(4)$ ,  $b = 9.4891(3)$ ,  $c = 22.3890(6)$  Å,  $\beta = 92.512(3)^\circ$ ,  $V = 2711.20(14)$  Å<sup>3</sup>,  $Z = 4$ ,  $D_c = 1.702$  g cm<sup>-3</sup>,  $\mu = 4.528$  mm<sup>-1</sup>.  $F_{000} = 1360$ , MoK $\alpha$  radiation,  $\lambda = 0.71073$  Å,  $T = 100(2)$  K,  $2\theta_{\text{max}} = 57.3^\circ$ , 21273 reflections collected, 6354 unique ( $R_{\text{int}} = 0.0587$ ). Final  $\text{Goof} = 1.000$ ,  $R1 = 0.0440$ ,  $wR2 = 0.0949$ ,  $R$  indices based on 4568 reflections with  $I > 2\sigma(I)$  (refinement on  $F^2$ ),  $|\Delta\rho|_{\text{max}} = 1.5(2)$  e Å<sup>-3</sup>, 352 parameters, 0 restraints. Lp and absorption corrections applied.

**Re3 (CCDC 1908895).**  $\text{C}_{29}\text{H}_{25}\text{N}_8\text{O}_5\text{Re}$ ,  $\text{CH}_2\text{Cl}_2$  [+ solvent];  $\text{C}_{30}\text{H}_{27}\text{Cl}_2\text{N}_8\text{O}_5\text{Re}$ ,  $M = 836.69$ , yellow block,  $0.300 \times 0.211 \times 0.147$  mm<sup>3</sup>, triclinic, space group  $P-1$  (No. 2),  $a = 11.0763(3)$ ,  $b = 11.6224(3)$ ,  $c = 13.4832(4)$  Å,  $\alpha = 100.225(2)$ ,  $\beta = 106.812(2)$ ,  $\gamma = 95.543(2)^\circ$ ,  $V = 1614.87(8)$  Å<sup>3</sup>,  $Z = 2$ ,  $D_c = 1.721$  g cm<sup>-3</sup>,  $\mu = 3.980$  mm<sup>-1</sup>.  $F_{000} = 824$ , MoK $\alpha$  radiation,  $\lambda = 0.71073$  Å,  $T = 100(2)$  K,  $2\theta_{\text{max}} = 65.4^\circ$ , 35882 reflections collected, 11025 unique ( $R_{\text{int}} = 0.0441$ ). Final  $\text{Goof} = 1.001$ ,  $R1 = 0.0488$ ,  $wR2 = 0.1076$ ,  $R$  indices based on 8441 reflections



with  $I > 2\sigma(I)$  (refinement on  $F^2$ ),  $|\Delta\rho|_{\max} = 4.1(2) \text{ e \AA}^{-3}$ , 415 parameters, 0 restraints. Lp and absorption corrections applied.

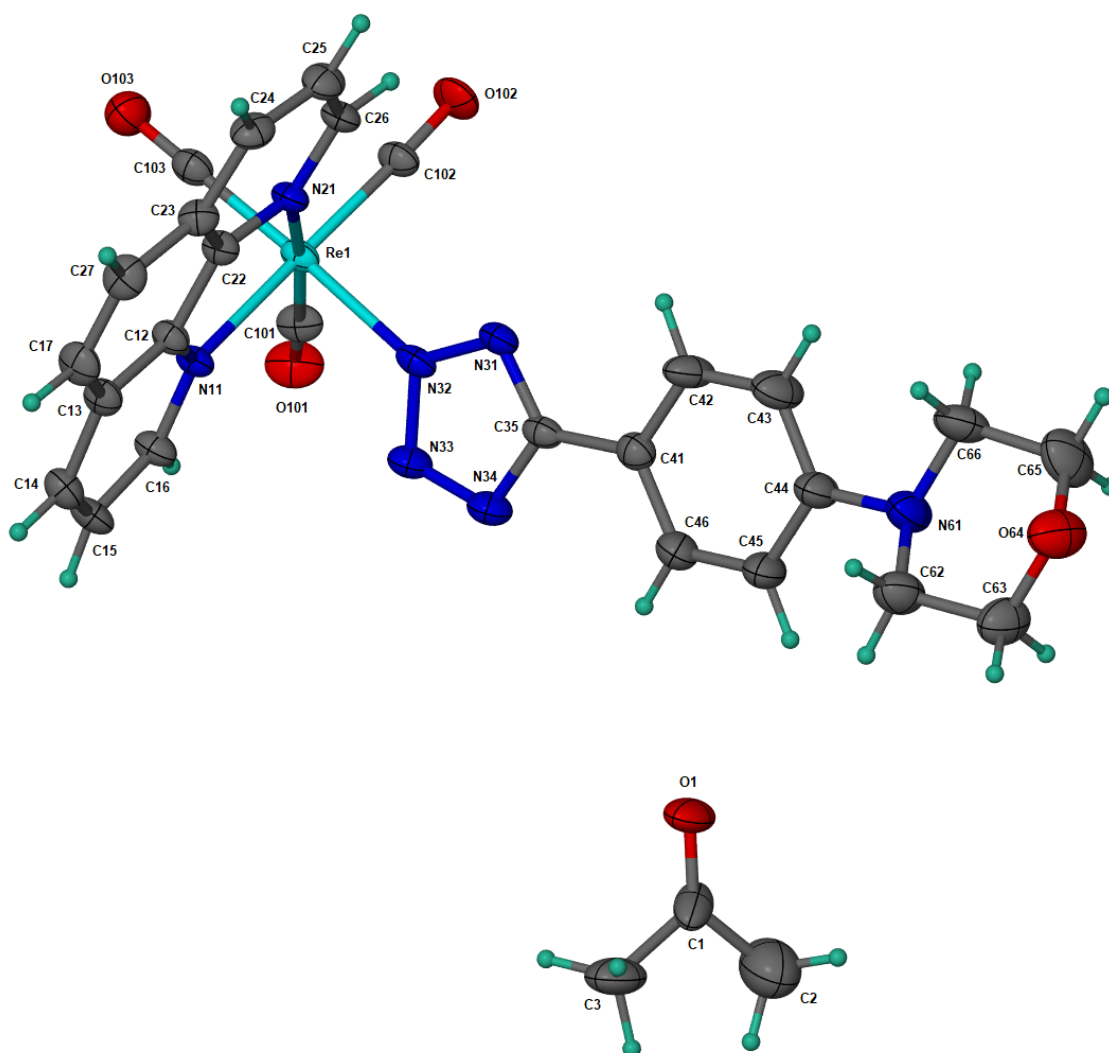


Figure S19 ADP of Re1 generated using X-Seed software: Barbour, L. J. (2020). *J. Appl. Cryst.*, 53, 1141-1146; <http://academic.sun.ac.za/barbour/Software.html>

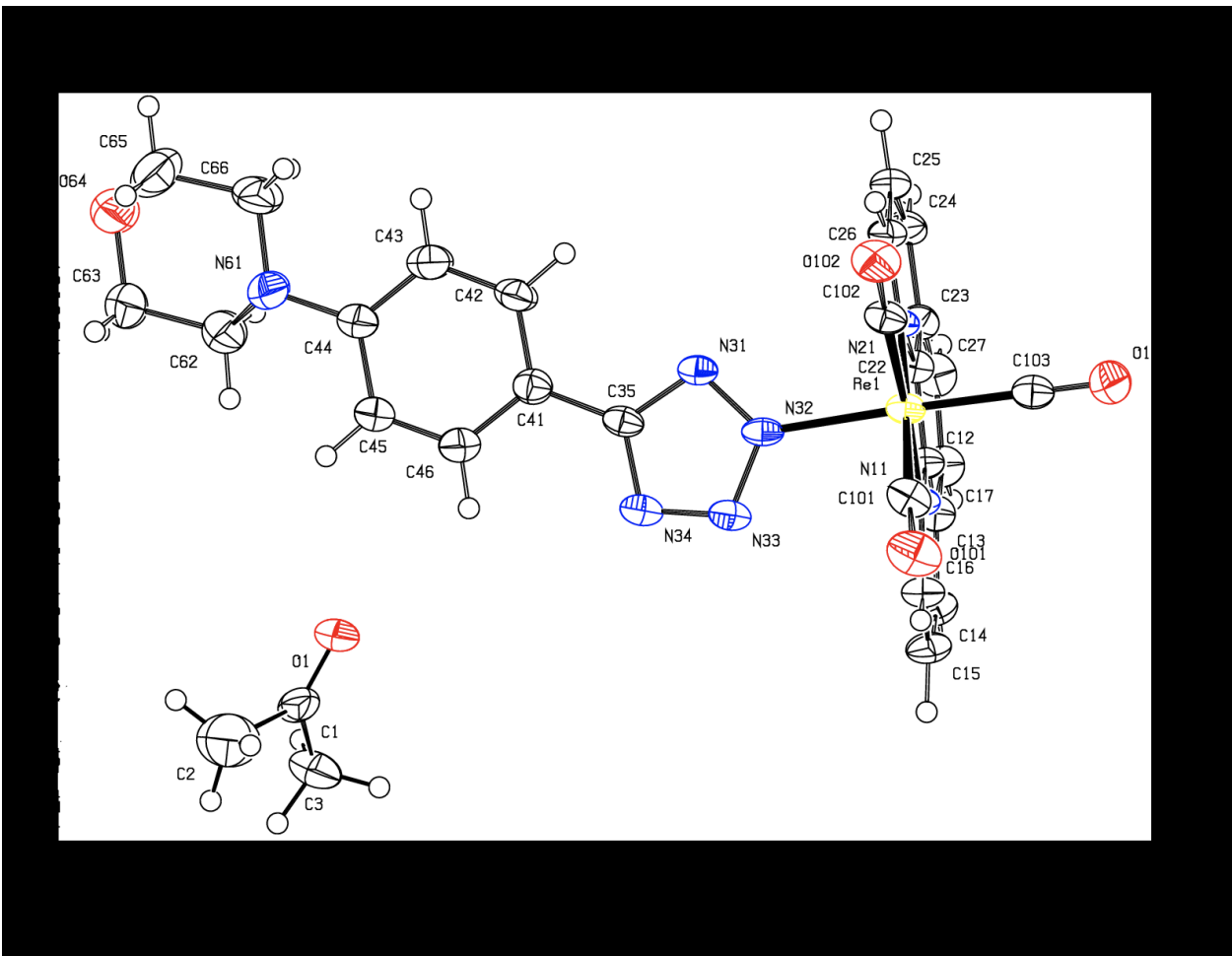


Figure S20 ADP of Re1 generated automatically using IUCr checkCIF software <http://checkcif.iucr.org/>

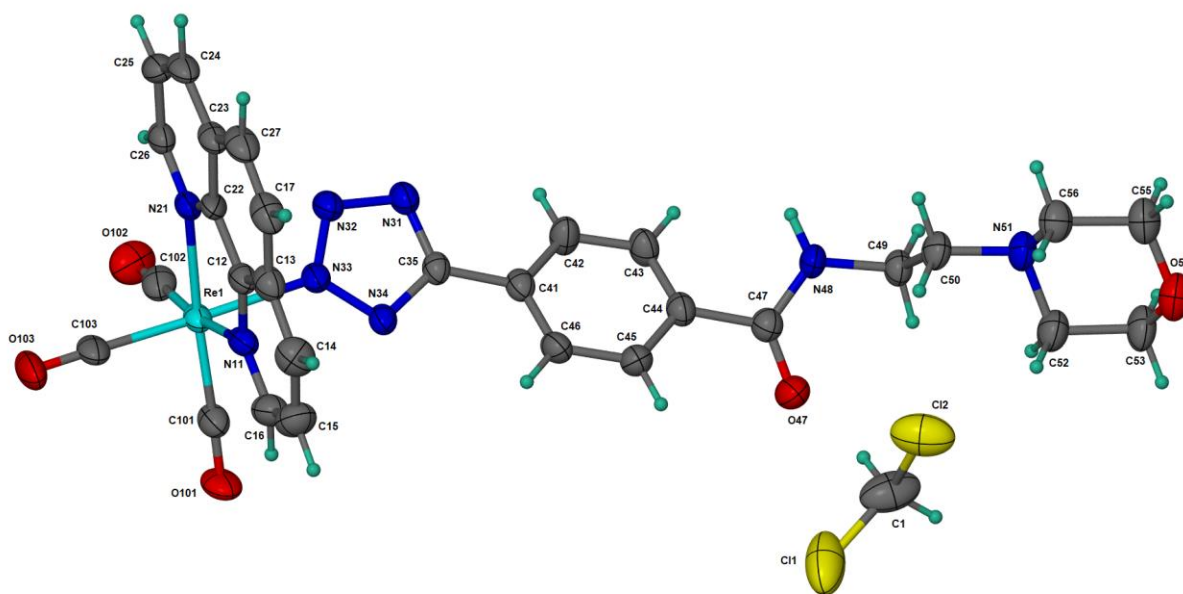


Figure S21 ADP of Re2 generated using X-Seed software: Barbour, L. J. (2020). *J. Appl. Cryst.*, 53, 1141-1146; <http://academic.sun.ac.za/barbour/Software.html>

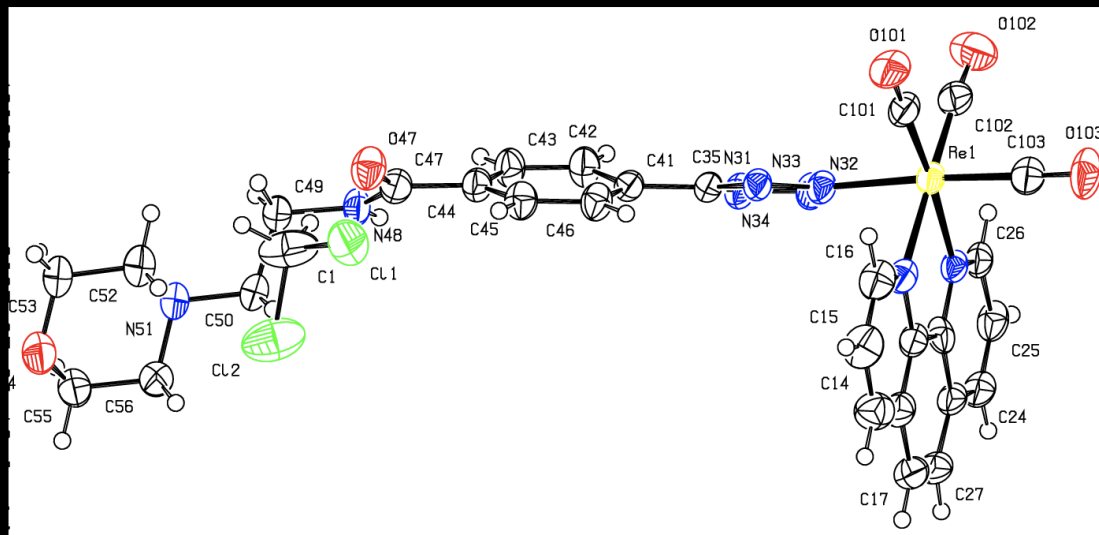


Figure S22 ADP of Re2 generated automatically using IUCr checkCIF software <http://checkcif.iucr.org/>

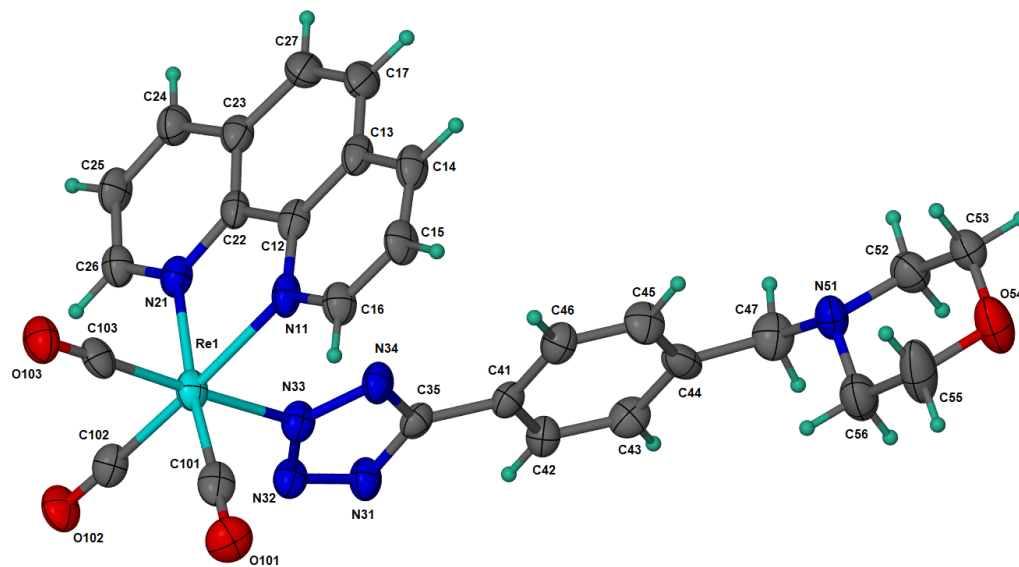


Figure S23 ADP of Re3 generated using X-Seed software: Barbour, L. J. (2020). *J. Appl. Cryst.*, 53, 1141-1146;  
<http://academic.sun.ac.za/barbour/Software.html>

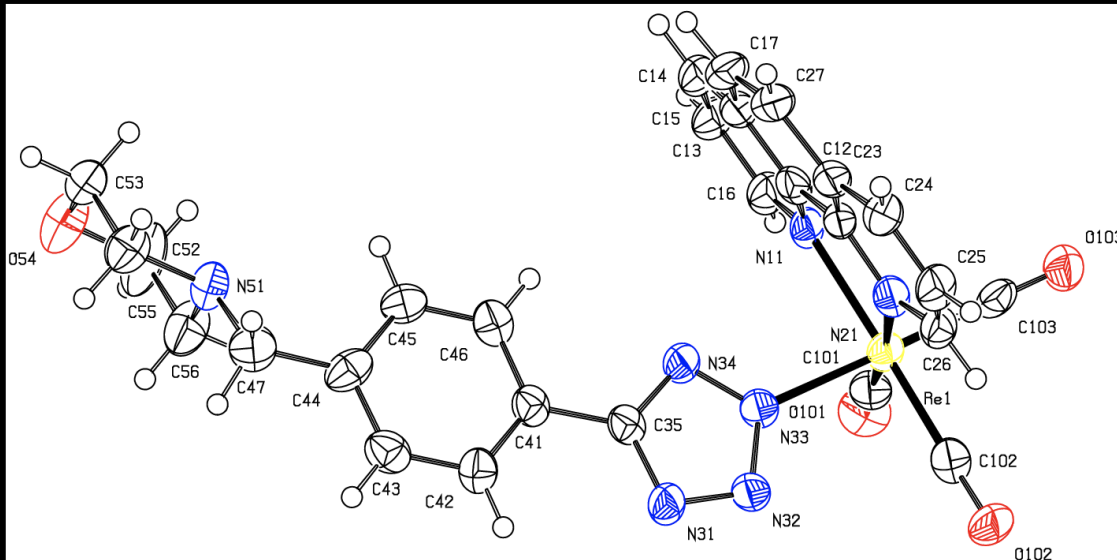
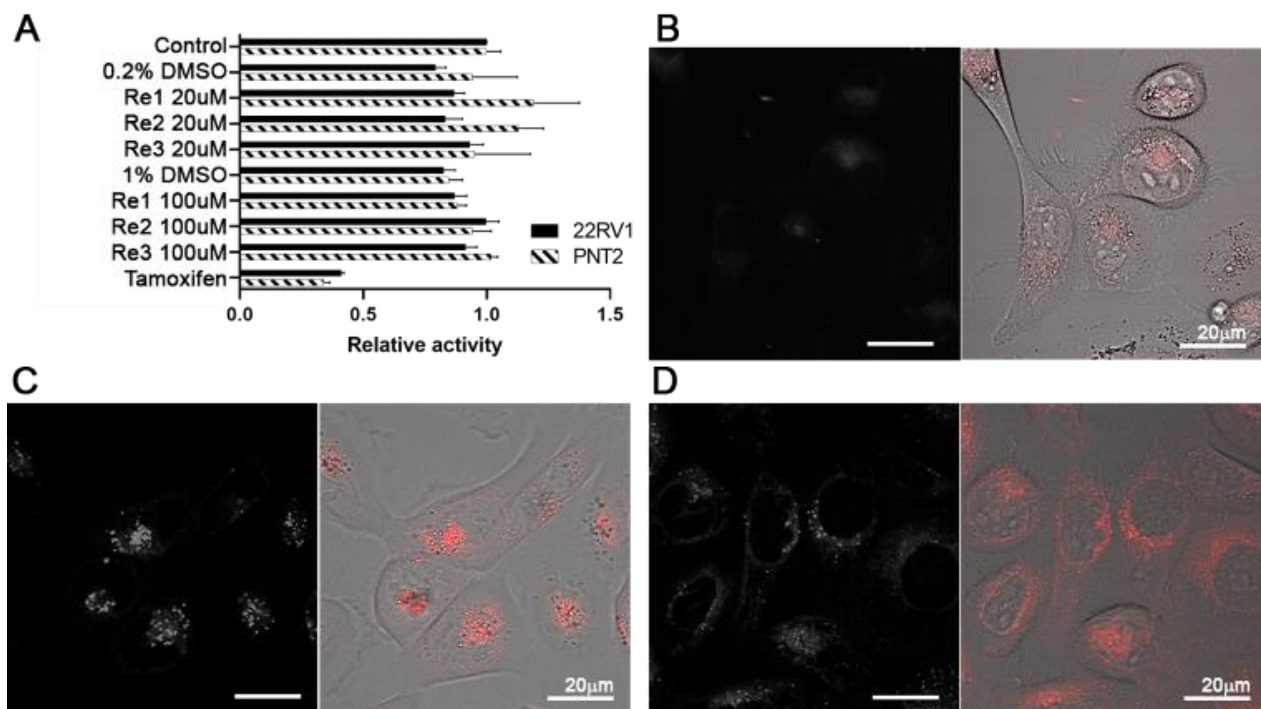
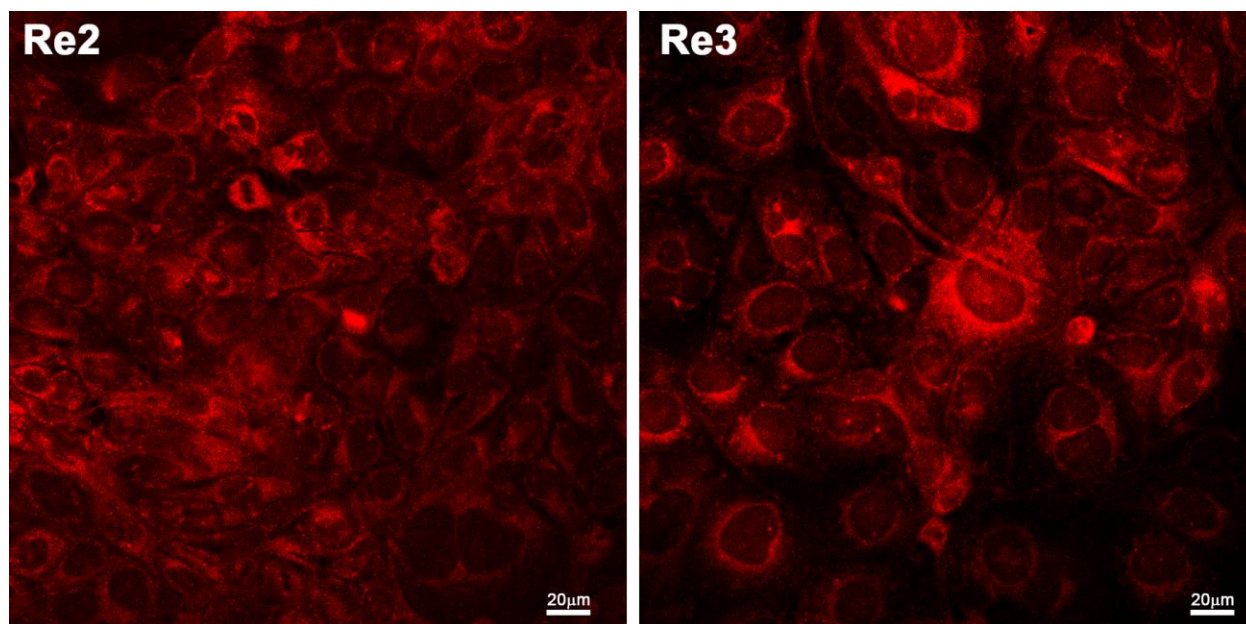


Figure S24 ADP of Re3 generated automatically using IUCr checkCIF software <http://checkcif.iucr.org/>

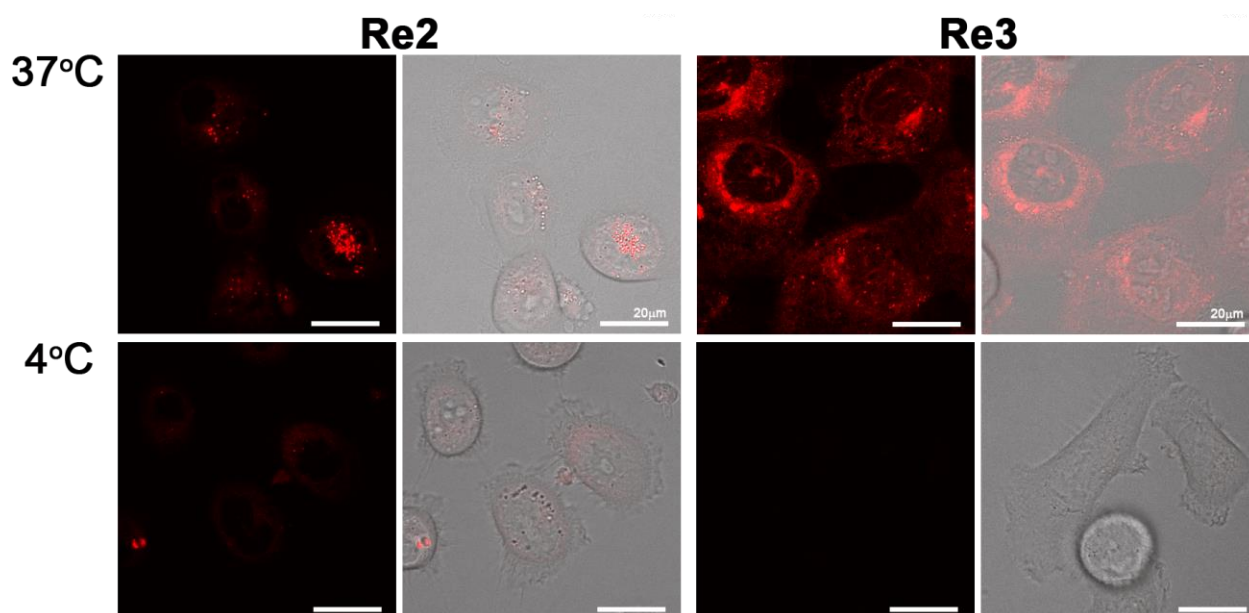
## Cell images and videos



**Figure S25 A.** Cytotoxicity of complexes was measured in PNT2 cells (black and white bars) or 22RV1 cells (grey bars). Cells were incubated for 3 h with the complexes as indicated. DMSO was used as a vehicle at either 0.2% for 20  $\mu$ M of complex or 1% for 100  $\mu$ M of complex. Cytotoxicity was measured using resazurin as an indicator of cell viability and is reported as mean  $\pm$  SEM relative intensity of three biological repeats normalised against a control group. **B–D.** Results of confocal imaging of rhenium morpholine complexes detected in cell: PNT2 cells incubated with 100  $\mu$ M of **Re1** (**B**), **Re2** (**C**) or **Re3** (**D**) for 1 h.



**Figure S26.** Lysosome localisation is lost in fixed cells. PNT2 cells stained with Re-morpholine complexes following fixation.



**Figure S27.** Rhenium morpholine complex internalisation is inhibited at 4°C. Cells were incubated with 100 μM of each complex at 37°C or 4°C, for 1 hour.



**Video S1: PNT2 Re3 60min wash** – good quality images observed in the first 5 minutes in live cells with **Re3**.

**Video S2: 22RV1 Re 2** – Cellular blebbing consistent with signs of apoptosis occurred in live cells upon extended imaging with **Re2**.

## References

1. Sheldrick, G.M. Crystal structure refinement with SHELXL. *Acta Crystallographica Section C: Structural Chemistry* **2015**, *71*, 3-8.