

Supplementary Materials

for

Anti-Inflammatory Activity of Pyrazolo[1,5-*a*]quinazolines

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1. Synthetic procedures for all new compounds

General procedure for compounds 2b-d. To a solution of the appropriate R₄/R₅-hydrazino benzoic acid **1a-d** (0.80 mmol) (**1a** [29], **1b** [30], **1c** [31], **1d** [32]) in 2.5 mL of dry DMF, 0.80 mmol of (ethoxymethylene)malononitrile and 0.96 mmol of anhydrous sodium acetate were added. The mixture was stirred at reflux temperature for 2 hours. After cooling, ice-cold water was added (20 mL) and the precipitate formed was recovered by vacuum filtration to obtain the desired compounds which were purified by crystallisation from isopropyl alcohol (for **2b**) or ethanol (for **2c,d**).

8-Chloro-5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carbonitrile (2b). Yield 91%, mp >300 °C (*i*-PrOH); TLC eluent: toluene/ethyl acetate/methanol 8/2/1.5 v/v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.62 (d, 1H, H₇, *J* = 8.4 Hz); 8.07 (s, 1H, H₉); 8.14 (d, 1H, H₆, *J* = 8.4 Hz); 8.37 (s, 1H, H₂); 13.38 (exch br s, 1H, CONH). ESI-MS calcd. for C₁₁H₅ClN₄O, 244.64; found: *m/z* 246.01 [M + H]⁺. Anal. calcd for C₁₁H₅ClN₄O (C, H, N): C, 54.01; H, 2.06; N, 22.90; found: C, 54.22; H, 2.07; N, 22.99.

8-Nitro-5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carbonitrile (2c). Yield 70%, mp 280-283 °C (EtOH); TLC eluent: toluene/ethyl acetate/methanol 8/2/2 v/v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 8.29 (dd, 1H, H₉, *J*₁ = 2.0 Hz, *J*₂ = 8.8 Hz); 8.37 (d, 1H, H₆, *J* = 8.8 Hz); 8.43 (s, 1H, H₂); 8.64 (d, 1H, H₉, *J* = 2.0 Hz); 13.61 (exch br s, 1H, CONH). ESI-MS calcd. for C₁₁H₅N₅O₃, 255.19; found: *m/z* 256.04 [M + H]⁺. Anal. calcd for C₁₁H₅N₅O₃ (C, H, N): C, 51.77; H, 1.97; N, 27.44; found: C, 51.56; H, 1.96; N, 27.33.

7-Nitro-5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carbonitrile (2d). Yield 71%, mp >295 °C (EtOH); TLC eluent: toluene/ethyl acetate/methanol 8/2/2 v/v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 8.27 (d, 1H, H₉, *J* = 9.2 Hz); 8.45 (s, 1H, H₂); 8.68 (dd, 1H, H₈, *J*₁ = 2.4 Hz, *J*₂ = 9.2 Hz); 8.78 (d, 1H, H₆, *J* = 2.0 Hz); 13.66 (exch br s, 1H, NH). IR (KBr) ν (cm⁻¹): 3120 (NH); 2240 (CN); 1700 (CO); 1520-1350 (NO₂). ESI-MS calcd. for C₁₁H₅N₅O₃, 255.19; found: *m/z* 256.04 [M + H]⁺. Anal. calcd for C₁₁H₅N₅O₃ (C, H, N): C, 51.77; H, 1.97; N, 27.44; found: C, 51.56; H, 1.96; N, 27.33.

General procedure for compounds 3b-d. A solution of intermediates **2b-d** (0.82 mmol) in 2 mL of H₂SO₄ conc. was stirred at 80 °C for 2 hours. After cooling, the mixture was slowly poured into water and ice. The precipitate formed was isolated by vacuum filtration to obtain the desired product.

8-Chloro-5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carboxamide (3b). Yield 88%, mp > 300 °C (2-methoxyethanol); TLC eluent: toluene/ethyl acetate/methanol 8/2/1.5 v/v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.35 (exch br s, 1H, CONH₂); 7.59 (dd, 1H, H₇, *J*₁ = 2.0 Hz, *J*₂ = 8.4 Hz); 7.87 (exch br s, 1H, CONH₂); 8.05 (d, 1H, H₉, *J* = 2.0 Hz); 8.15 (d, 1H, H₆, *J* = 8.4 Hz); 8.30 (s, 1H, H₂); 10.72 (exch br s, 1H, CONH). ESI-MS calcd. for C₁₁H₇ClN₄O₂, 262.65; found: *m/z* 264.02 [M + H]⁺. Anal. calcd for C₁₁H₇ClN₄O₂ (C, H, N): C, 50.30; H, 2.69; N, 21.33; found: C, 50.50; H, 2.70; N, 21.41.

8-Nitro-5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carboxamide (3c). Yield 74%, mp > 295 °C (EtOH); TLC eluent: dichloromethane/methanol 9/1 v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.39 (exch br s, 1H, CONH₂); 7.88 (exch br s, 1H, CONH₂); 8.26 (dd, 1H, H₇, *J*₁ = 2,0 Hz, *J*₂ = 8,8 Hz); 8.38 (d, 1H, H₆, *J* = 8,4 Hz); 8.34 (s, 1H, H₂); 8.65 (d, 1H, H₉, *J* = 2,4 Hz); 11.00 (exch br s, 1H, NH). ESI-MS calcd. for C₁₁H₇N₅O₄, 273.21; found: *m/z* 274.05 [M + H]⁺. Anal. calcd for C₁₁H₇N₅O₄ (C, H, N): C, 48.36; H, 2.58; N, 25.63; found: C, 48.55; H, 2.59; N, 25.73.

7-Nitro-5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carboxamide (3d). Yield 75%, mp > 295 °C (EtOH); TLC eluent: toluene/ethyl acetate/acetic acid 8/2/1 v/v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) 7.40 (exch br s, 1H, CONH₂); 7.88 (exch br s, 1H, CONH₂); 8.24 (d, 1H, H₉, *J* = 9,2 Hz); 8.36 (s, 1H, H₂); 8.67 (dd, 1H, H₈, *J*₁ = 2,8 Hz, *J*₂ = 9,2 Hz); 8.79 (d, 1H, H₆, *J* = 2,4 Hz); 11.06 (exch br s, 1H, NH). ESI-MS calcd. for C₁₁H₇N₅O₄, 273.21; found: *m/z* 274.05 [M + H]⁺. Anal. calcd for C₁₁H₇N₅O₄ (C, H, N): C, 48.36; H, 2.58; N, 25.63; found: C, 48.55; H, 2.59; N, 25.73.

General procedure for compounds 4c,d. To a solution of 2-hydrazineyl-4-nitrobenzoic acid **1c** [31] or 2-hydrazineyl-5-nitrobenzoic acid **1d** [32] (0.42 mmol) in 3 mL of dry DMF, 0.43 mmol of ethyl 2-cyano-3-ethoxyacrylate and 0.42 mmol of anhydrous sodium acetate were added. The mixture was stirred at reflux temperature for 2 hours. After cooling, ice-cold water was added (20 mL) and the

precipitate formed was recovered by vacuum filtration to obtain the desired compounds which were purified by crystallisation.

Ethyl 8-nitro-5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carboxylate (4c). Yield 59%, mp 195-197 °C (EtOH); TLC eluent: toluene/ethyl acetate/methanol 8/2/2 v/v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 1.27 (t, 3H, CH₃, *J* = 7,0 Hz); 4.29 (q, 2H, CH₂, *J* = 7,0 Hz); 8.26 (m, 2H, H₇, H₂); 8.38 (d, 1H, H₆, *J* = 8,8 Hz); 8.66 (s, 1H, H₉); 12.00 (exch br s, 1H, NH). ESI-MS calcd. for C₁₃H₁₀N₄O₅, 302.25; found: *m/z* 303.07 [M + H]⁺. Anal. calcd for C₁₃H₁₀N₄O₅ (C, H, N): C, 51.66; H, 3.34; N, 18.54; found: C, 51.45; H, 3.32; N, 18.46.

Ethyl 7-nitro-5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carboxylate (4d). Yield 78%, mp 217-220 °C (EtOH); TLC eluent: toluene/ethyl acetate/methanol 8/2/2 v/v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 1.29 (t, 3H, CH₃, *J* = 7,0 Hz); 4.30 (q, 2H, CH₂, *J* = 7,0 Hz); 8.27 (m, 2H, H₉, H₂); 8.68 (dd, 1H, H₈, *J*₁ = 2,8 Hz, *J*₂ = 9,2 Hz); 8.81 (d, 1H, H₆, *J* = 2,4 Hz); 12.07 (exch br s, 1H, NH). ESI-MS calcd. for C₁₃H₁₀N₄O₅, 302.25; found: *m/z* 303.07 [M + H]⁺. Anal. calcd for C₁₃H₁₀N₄O₅ (C, H, N): C, 51.66; H, 3.34; N, 18.54; found: C, 51.45; H, 3.33; N, 18.46.

8-Nitropyrazolo[1,5-*a*]quinazolin-5(4*H*)-one (5c). A solution of compound **4c** (0.24 mmol) in 5 mL of HCl 37% was stirred at reflux for 4 hours. After cooling, the mixture was extracted with ethyl acetate (3 x 15 mL). The organic layer was evaporated in vacuum, and the residue was purified by crystallisation. Yield 70%, mp >300 °C (EtOH); TLC eluent: toluene/ethyl acetate/ methanol 8/2/2 v/v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 5.95 (s, 1H, H₃); 7.85 (s, 1H, H₂); 8.20 (m, 1H, H₆); 8.33 (d, 1H, H₇, *J* = 7.6 Hz); 8.63 (s, 1H, H₉); 12.48 (exch br s, 1H, NH). ESI-MS calcd. for C₁₀H₆N₄O₃, 230.18; found: *m/z* 231.05 [M + H]⁺. Anal. calcd for C₁₀H₆N₄O₃ (C, H, N): C, 52.18; H, 2.63; N, 24.34; found: C, 52.39; H, 2.64; N, 24.43.

General procedure for compounds 7b-f. A solution of **4a** [34], **5a** [34] or **2a** [52] (0.23 mmol) in 2.5 mL of dry CH₃CN (or dry DMF for **7e,f**) and anhydrous K₂CO₃ (0.92 mmol) was maintained at room temperature for 15 min., and then the appropriate substituted benzyl bromide (0.35 mmol) was added. The reaction was refluxed, and when the starting material disappeared in TLC (2-24 hours),

the addition of water yielded a precipitate that was filtered, washed with water and diethyl ether and finally purified by crystallisation. (Compound **7a** [30])

Ethyl 4-(4-(methylthio)benzyl)-5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carboxylate (7b). Starting from **4a** and 4-(methylthio)benzyl bromide. Yield 70%, mp 156-159 °C (EtOH); TLC: toluene/ethyl acetate/acetic acid 8/2/1 v/v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 1.20 (t, 3H, CH₂CH₃, *J* = 6.8 Hz); 2.39 (s, 3H, SCH₃); 4.17 (q, 2H, CH₂CH₃, *J* = 6.8 Hz); 5.87 (s, 2H, NCH₂); 7.09 (d, 2H, H_{3'}, H_{5'}, *J* = 7.6 Hz); 7.14 (d, 2H, H_{2'}, H_{6'}, *J* = 8.0 Hz); 7.60 (t, 1H, H₇, *J* = 7.6 Hz); 7.96 (t, 1H, H₈, *J* = 7.6 Hz); 8.20 (m, 2H, H₆ and H₉); 8.25 (s, 1H, H₂). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ 14.5; 15.2; 47.7; 61.0; 99.3; 115.7; 115.9; 126.4; 127.1; 127.7; 128.8; 133.9; 136.1; 137.1; 140.4; 145.3; 159.2; 161.9. ESI-MS calcd. for C₂₁H₁₉N₃O₃S, 393.46; found: *m/z* 394.11 [M + H]⁺. Anal. calcd for C₂₁H₁₉N₃O₃S (C, H, N): C, 64.11; H, 4.87; N, 10.68; found: C, 64.37; H, 4.89; N, 10.72.

Ethyl 5-oxo-4-(4-sulfamoylbenzyl)-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carboxylate (7c). Starting from **4a** and 4-(bromomethyl)benzene sulphonamide. Yield 71%, mp 224-226 °C (EtOH); TLC eluent: dichloromethane/methanol 10/0.5 v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 1.16 (t, 3H, CH₂CH₃, *J* = 7.2 Hz); 4.11 (q, 2H, CH₂CH₃, *J* = 7.2 Hz); 5.92 (s, 2H, NCH₂); 7.29 (exch br s, 2H, SONH₂); 7.38 (d, 2H, H_{2'}, H_{6'}, *J* = 8.0 Hz); 7.60 (t, 1H, H₇, *J* = 8.0 Hz); 7.69 (d, 2H, H_{3'}, H_{5'}, *J* = 8.0 Hz); 7.98 (t, 1H, H₈, *J* = 8.0 Hz); 8.20 (m, 2H, H₆, H₉); 8.27 (s, 1H, H₂). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ 14.5; 48.8; 60.9; 99.2; 115.7; 116.0; 126.1; 127.1; 128.8; 136.1; 137.4; 140.7; 141.7; 143.0; 145.3; 159.2; 161.9. ESI-MS calcd. for C₂₀H₁₈N₄O₅S, 426.45; found: *m/z* 427.10 [M + H]⁺. Anal. calcd for C₂₀H₁₈N₄O₅S (C, H, N): C, 56.33; H, 4.25; N, 13.14; found: C, 56.55; H, 4.27; N, 13.19.

Ethyl 4-[4-(methylsulfonyl)benzyl]-5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carboxylate (7d). Starting from **4a** and 4-(methylsulphonyl)benzyl bromide. Yield 80%, mp 229-232 °C (EtOH 80%); TLC eluent: toluene/ethyl acetate/acetic acid 8/2/1 v/v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 1.14 (t, 3H, CH₂CH₃, *J* = 7.2 Hz); 3.16 (s, 3H, SO₂CH₃); 4.10 (q, 2H, CH₂CH₃, *J* = 7.2 Hz); 5.95 (s, 2H, NCH₂); 7.49 (d, 2H, H_{3'}, H_{5'}, *J* = 8.0 Hz); 7.60 (t, 1H, H₇, *J* = 7.6 Hz); 7.81 (d, 2H, H_{2'}, H_{6'}, *J* = 8.4 Hz); 7.98 (t, 1H, H₈, *J* = 7.6 Hz); 8.18 (d, 1H, H₉, *J* = 8.0 Hz); 8.22 (d, 1H, H₆, *J* = 8.4

Hz); 8.28 (s, 1H, H₂). ¹³C-NMR (100 MHz, DMSO-d₆) δ 14.4; 43.9; 49.0; 60.9; 99.2; 115.7; 116.0; 127.1; 127.5; 128.7; 129.6; 136.1; 137.4; 139.7; 140.7; 143.8; 145.3; 159.2; 161.9. ESI-MS calcd. for C₂₁H₁₉N₃O₅S, 425.46; found: m/z 426.11 [M + H]⁺. Anal. calcd for C₂₁H₁₉N₃O₅S (C, H, N): C, 59.28; H, 4.50; N, 9.88; found: C, 59.52; H, 4.52; N, 9.92.

4-[4-(Methylthio)benzyl]-5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carbonitrile (7e).

Starting from **2a** and 4-(methylthio)benzyl bromide. Yield 70%, mp 189-192 °C (EtOH/H₂O 9:1); TLC eluent: toluene/ethyl acetate/acetic acid 8/2/1 v/v/v. ¹H-NMR (400 MHz, DMSO-d₆) δ (s, 3H, SCH₃); 5.44 (s, 2H, NCH₂); 7.20 (d, 2H, H₃[•], H₅[•], *J* = 8.4 Hz); 7.27 (d, 2H, H₂[•], H₆[•], *J* = 8.4 Hz); 7.64 (t, 1H, H₇, *J* = 7.6 Hz); 7.99 (t, 1H, H₈, *J* = 7.6 Hz); 8.18 (d, 1H, H₉, *J* = 8.4 Hz); 8.24 (d, 1H, H₆, *J* = 8.0 Hz); 8.44 (s, 1H, H₂). ¹³C-NMR (100 MHz, DMSO-d₆) δ 15.1; 47.2; 113.9; 115.6; 116.4; 126.5; 127.5; 127.6; 129.0; 132.2; 136.3; 136.9; 137.8; 142.9; 145.4; 158.5. ESI-MS calcd. for C₁₉H₁₄N₄OS, 346.41; found: m/z 347.09 [M + H]⁺. Anal. calcd for C₁₉H₁₄N₄OS (C, H, N): C, 65.88; H, 4.07; N, 16.17; found: C, 65.62; H, 4.05; N, 16.10.

4-[4-(Methylthio)benzyl]pyrazolo[1,5-*a*]quinazolin-5(4H)-one (7f). Starting from **5a** and 4-(methylthio)benzyl bromide. Yield 90%, mp 137-139 °C (EtOH/H₂O 9:1); TLC eluent: toluene/ethyl acetate/acetic acid 8/2/1 v/v/v. ¹H-NMR (400 MHz, DMSO-d₆) δ 2.42 (s, 3H, SCH₃); 5.23 (s, 2H, NCH₂); 6.26 (s, 1H, H₃); 7.19 (d, 2H, H₃[•], H₅[•], *J* = 8.0 Hz); 7.34 (d, 2H, H₂[•], H₆[•], *J* = 8.0 Hz); 7.52 (t, 1H, H₇, *J* = 7.6 Hz); 7.83 (s, 1H, H₂); 7.90 (t, 1H, H₈, *J* = 7.6 Hz); 8.10 (d, 1H, H₉, *J* = 8.4 Hz); 8.22 (d, 1H, H₆, *J* = 8.0 Hz). ¹³C-NMR (100 MHz, DMSO-d₆) δ 15.1; 47.3; 91.0; 114.8; 115.9; 126.1; 126.5; 128.7; 129.1; 132.9; 135.7; 137.4; 137.9; 140.4; 142.7. ESI-MS calcd. for C₁₈H₁₅N₃OS, 321.40; found: m/z 322.10 [M + H]⁺. Anal. calcd for C₁₈H₁₅N₃OS (C, H, N): C, 67.27; H, 4.70; N, 13.07; found: C, 67.54; H, 4.72; N, 13.12.

4-[4-(Methylsulfonyl)benzyl]pyrazolo[1,5-*a*]quinazolin-5(4H)-one (8). Compound **7f** (0.16 mmol) was dissolved in 4 mL of MeOH. To this solution, at 0 °C, a previously prepared solution composed of 0.64 mmol of OXONE[®] in 4 mL of H₂O was added. The mixture was stirred at 100 °C for 2 hours. After cooling, 10 mL of H₂O was added and the precipitate formed was recovered by

vacuum filtration to obtain the desired compound. Yield 88%, mp 186-188 °C (EtOH); TLC eluent: toluene/ethyl acetate/acetic acid 8/2/1 v/v/v. ¹H-NMR (400 MHz, DMSO-d₆) δ 3.16 (s, 3H, SO₂CH₃); 5.39 (s, 2H, NCH₂); 6.25 (s, 1H, H₃); 7.53 (t, 1H, H₇, *J* = 7.2 Hz); 7.63 (d, 2H, H₂', H₆', *J* = 7.6 Hz); 7.85 (m, 3H, H₃', H₅', H₂); 7.92 (t, 1H, H₈, *J* = 7.2 Hz); 8.12 (d, 1H, H₉, *J* = 8.0 Hz); 8.22 (d, 1H, H₆, *J* = 7.6 Hz). ¹³C-NMR (100 MHz, DMSO-d₆) δ 43.9; 47.5; 90.9; 114.8; 115.8; 126.1; 127.7; 128.5; 129.1; 135.8; 137.5; 140.4; 140.5; 142.3; 142.7; 158.5. ESI-MS calcd. for C₁₈H₁₅N₃O₃S, 353.40; found: *m/z* 354.09 [M + H]⁺. Anal. calcd for C₁₈H₁₅N₃O₃S (C, H, N): C, 61.18; H, 4.28; N, 11.89; found: C, 61.42; H, 4.30; N, 11.94.

General procedure for compounds 9 and 10. To a solution of 176 mg (1 mmol) of HIO₃ in 11 mL of acetone/H₂O (10:1), a small amount of tetra-*n*-butylammonium bromide (TBAB) was added while stirring for 5 minutes. Then, 0.25 mmol of compound **7b** or **7f** were added, and the mixture was stirred at 80 °C for 2 hours. The reaction mixture was cooled, 10 mL of H₂O was added, and the precipitate was collected by vacuum filtration.

3-Iodo-4-[4-(methylsulfinyl)benzyl]pyrazolo[1,5-*a*]quinazolin-5(4*H*)-one (9). Yield 52%, mp 198-201 °C (EtOH); TLC eluent: toluene/ethyl acetate/acetic acid 8/2/1 v/v/v. ¹H-NMR (400 MHz, DMSO-d₆) δ 2.71 (s, 3H, SOCH₃); 5.71 (s, 2H, NCH₂); 7.45 (d, 2H, H₂', H₆', *J* = 8.4 Hz); 7.53 (t, 1H, H₇, *J* = 7.6 Hz); 7.63 (d, 2H, H₃', H₅', *J* = 8.0 Hz); 7.90 (s, 1H, H₂); 7.92 (t, 1H, H₈, *J* = 7.2 Hz); 8.14 (d, 1H, H₉, *J* = 4.0 Hz); 8.16 (d, 1H, H₆, *J* = 4.0 Hz). ¹³C-NMR (100 MHz, DMSO-d₆) δ 43.6; 46.8; 114.7; 115.7; 124.3; 126.4; 127.4; 128.9; 135.8; 137.3; 138.4; 140.2; 145.5; 149.2; 158.7. ESI-MS calcd. for C₁₈H₁₄IN₃O₂S, 463.29; found: *m/z* 463.99 [M + H]⁺. Anal. calcd for C₁₈H₁₄IN₃O₂S (C, H, N): C, 46.67; H, 3.05; N, 9.07; found: C, 46.48; H, 3.04; N, 9.03.

Ethyl 4-[4-(methylsulfinyl)benzyl]-5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carboxylate (10). Yield 75%, mp 179-181 °C (EtOH); TLC eluent: toluene/ethyl acetate/acetic acid 8/2/1 v/v/v. ¹H-NMR (400 MHz, DMSO-d₆) δ 1.14 (t, 3H, CH₂CH₃, *J* = 7.2 Hz); 2.68 (s, 3H, SOCH₃); 4.12 (q, 2H, CH₂CH₃, *J* = 7.2 Hz); 5.94 (s, 2H, NCH₂); 7.39 (d, 2H, H₂', H₆', *J* = 7.6 Hz); 7.57 (d, 2H, H₃', H₅', *J* = 7.6 Hz); 7.60 (t, 1H, H₇, *J* = 7.2 Hz); 7.97 (t, 1H, H₈, *J* = 7.2 Hz); 8.20 (m, 2H, H₆, H₉); 8.27

(s, 1H, H₂). ¹³C-NMR (100 MHz, DMSO-d₆) δ 14.4; 43.6; 48.6; 60.9; 99.3; 115.7; 116.0; 124.1; 127.1; 127.6; 128.8; 136.1; 137.3; 140.5; 140.6; 145.2; 145.3; 159.2; 161.9. ESI-MS calcd. for C₂₁H₁₉N₃O₄S, 409.46; found: m/z 410.11 [M + H]⁺. Anal. calcd for C₂₁H₁₉N₃O₄S (C, H, N): C, 61.60; H, 4.68; N, 10.26; found: C, 61.85; H, 4.70; N, 10.30.

Ethyl 5-methoxypyrazolo[1,5-*a*]quinazoline-3-carboxylate (12). To a solution of **11** (0.11 mmol) [42] in 4 mL of methanol, 0.22 mmol of K₂CO₃ was added and the mixture was stirred at reflux for 1.5 hour. After cooling and evaporation of the solvent, 10 mL of water was added and the precipitate was recovered by vacuum filtration to obtain compound **12**. Yield 71%, mp 182-183 °C (EtOH 80%); TLC eluent: toluene/ethyl acetate/methanol 8/2/1.5 v/v/v. ¹H-NMR (400 MHz, DMSO-d₆) δ 1.33 (t, 3H, CH₂CH₃, *J* = 7.2 Hz); 4.20 (s, 3H, OCH₃); 4.27 (q, 2H, CH₂CH₃, *J* = 7.2 Hz); 7.67 (t, 1H, H₇, *J* = 7.2 Hz); 8.04 (t, 1H, H₈, *J* = 7.2 Hz); 8.19 (d, 1H, H₉, *J* = 7.6 Hz); 8.33 (d, 1H, H₆, *J* = 8.4 Hz); 8.40 (s, 1H, H₂). ¹³C-NMR (100 MHz, DMSO-d₆) δ 14.1; 54.5; 60.9; 99.3; 115.7; 116.0; 124.1; 127.1; 127.6; 128.8; 136.1; 145.3; 159.2; 161.8. ESI-MS calcd. for C₁₄H₁₃N₃O₃, 271.28; found: m/z 272.10 [M + H]⁺. Anal. calcd for C₁₄H₁₃N₃O₃ (C, H, N): C, 61.99; H, 4.83; N, 15.49; found: C, 61.74; H, 4.81; N, 15.43.

General procedure for isomers 13a/14a. A suspension of 4,5-dihydro-5-oxo-pyrazolo[1,5-*a*]quinazoline-3-carboxamide **3a** [52] (80 mg, 0.35 mmol) in anhydrous DMF (2.5 mL) and anhydrous Cs₂CO₃ (0.35 mmol) was maintained at room temperature for 15 min. and then methyl iodide (0.70 mmol) was added. The reaction was heated at 80 °C for 1 h. After cooling, ice-cold water was added (20 mL) and the precipitate formed was recovered by vacuum filtration to obtain the O-alkylated compound **13a**. This compound was also obtained starting from **15** (see below). The aqueous phase was extracted with ethyl acetate (3 x 15 mL), then the organic fraction was dried over sodium sulphate, filtered, and the solvent was removed under reduced pressure to obtain the N-alkylated compound **14a**.

5-Methoxypyrazolo[1,5-*a*]quinazoline-3-carboxamide (13a). Yield 80%, mp 246-247 °C (*i*-PrOH); TLC eluent: toluene/ethyl acetate/methanol 8/2/1.5 v/v/v. ¹H-NMR (400 MHz, DMSO-d₆) δ

4.21 (s, 3H, OCH₃); 7.31 (exch br s, 1H, CONH₂); 7.48 (exch br s, 1H, CONH₂); 7.66 (t, 1H, H₇, *J* = 7.2 Hz); 8.04 (t, 1H, H₈, *J* = 7.2 Hz); 8.19 (d, 1H, H₉, *J* = 8.0 Hz); 8.31 (m, 2H, H₂, H₆). ¹³C-NMR (100 MHz, DMSO-d₆) δ 55.5; 106.5; 111.7; 115.0; 126.0; 126.6; 135.9; 137.0; 142.1; 143.9; 160.6; 163.4. ESI-MS calcd. for C₁₂H₁₀N₄O₂, 242.24; found: *m/z* 243.08 [M + H]⁺. Anal. calcd for C₁₂H₁₀N₄O₂ (C, H, N): C, 59.50; H, 4.16; N, 23.13; found: C, 59.74; H, 4.18; N, 23.22.

4-Methyl-5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carboxamide (14a). Yield 5%, mp 287-289 °C (*i*-PrOH); TLC eluent: toluene/ethyl acetate/methanol 8/2/1.5 v/v/v. ¹H-NMR (400 MHz, DMSO-d₆) δ 3.74 (s, 3H, NCH₃); 7.34 (exch br s, 1H, CONH₂); 7.54 (t, 1H, H₇, *J* = 7.6 Hz); 7.90 (t, 1H, H₈, *J* = 7.6 Hz); 7.95 (exch br s, 1H, CONH₂); 8.09 (s, 1H, H₂); 8.11 (d, 1H, H₉, *J* = 8.4 Hz); 8.17 (d, 1H, H₆, *J* = 7.6 Hz). ¹³C-NMR (100 MHz, DMSO-d₆) δ 33.2; 115.2; 126.5; 128.7; 135.6; 143.3. ESI-MS calcd. for C₁₂H₁₀N₄O₂, 242.24; found: *m/z* 243.08 [M + H]⁺. Anal. calcd for C₁₂H₁₀N₄O₂ (C, H, N): C, 59.50; H, 4.16; N, 23.13; found: C, 59.74; H, 4.18; N, 23.22.

General procedure for compounds 13b-i and 14c. A suspension of 4,5-dihydro-5-oxo-pyrazolo[1,5-*a*]quinazoline-3-carboxamide 3a [52] (150 mg, 0.66 mmol) in anhydrous DMF (3.0 mL) and anhydrous K₂CO₃ (2.64 mmol) was maintained at room temperature for 15 min. and then appropriate substituted benzyl halide (0.99 mmol) was added. The reaction was heated at 50 °C for 2 h. After cooling, ice-cold water was added (20 mL) and the precipitate formed was recovered by vacuum filtration and washed in sequence first with water, then ethanol and diethyl ether to obtain the desired compounds which were purified by crystallization from the suitable solvent.

5-(Benzyloxy)pyrazolo[1,5-*a*]quinazoline-3-carboxamide (13b). From 3a and benzyl bromide. Yield 65%, mp 208-209 °C (EtOH); IR (nujol) cm⁻¹: 3450, 3420, 1676, 1308; TLC eluent: toluene/ethyl acetate/acetic acid 8/2/1.5 v/v/v. ¹H-NMR (400 MHz, DMSO-d₆) δ 5.72 (s, 2H, OCH₂); 7.31 (exch br s, 1H, NH); 7.45 (m, 4H, Ar + NH); 7.60 (d, 2H, Ar, *J* = 8.0 Hz); 7.68 (t, 1H, H₈, *J* = 8.0 Hz); 8.07 (t, 1H, H₇, *J* = 8.0 Hz); 8.25 (d, 1H, H₆, *J* = 8.4 Hz); 8.34 (s, 1H, H₂); 8.38 (d, 1H, H₉, *J* = 8.4 Hz). ESI-MS calcd. for C₁₈H₁₄N₄O₂, 318.34; found: *m/z* 319.12 [M + H]⁺. Anal. calcd for C₁₈H₁₄N₄O₂ (C, H, N): C, 67.92; H, 4.43; N, 17.60; found: C, 67.65; H, 4.41; N, 17.53.

5-[(4-(Methylthio)benzyl)oxy]pyrazolo[1,5-*a*]quinazoline-3-carboxamide (13c). From **3a** and 4-(methylthio)benzyl bromide. Yield 94%, mp 225-226 °C (EtOH); TLC: toluene/ethyl acetate/methanol 8/2/1.5 v/v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 2.43 (s, 3H, SCH₃); 5.68 (s, 2H, OCH₂); 7.31 (m, 3H, H₃, H₅, CONH₂); 7.44 (exch br s, 1H, CONH₂); 7.53 (d, 2H, H₂, H₆, *J* = 8.0 Hz); 7.65 (t, 1H, H₇, *J* = 8.0 Hz); 8.05 (t, 1H, H₈, *J* = 7.6 Hz); 8.20 (d, 1H, H₉, *J* = 8.0 Hz); 8.32 (m, 2H, H₂, H₆). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ 15.0; 69.3; 106.6; 111.8; 115.1; 126.1; 126.3; 126.7; 129.4; 132.7; 136.0; 137.1; 138.9; 142.0; 144.1; 159.9; 163.3. ESI-MS calcd. for C₁₉H₁₆N₄O₂S, 364.42; found: *m/z* 365.10 [M + H]⁺. Anal. calcd for C₁₉H₁₆N₄O₂S (C, H, N): C, 62.62; H, 4.43; N, 15.37; found: C, 62.37; H, 4.41; N, 15.31.

5-[(2-Chlorobenzyl)oxy]pyrazolo[1,5-*a*]quinazoline-3-carboxamide (13d). From **3a** and 2-chlorobenzyl chloride. Yield 13%, mp 227-229 °C (*i*-PrOH); TLC eluent: toluene/ethyl acetate/acetic acid 9/1/0.5 v/v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 5.81 (s, 2H, OCH₂); 7.29 (exch br s, 1H, CONH₂); 7.43 (m, 2H, Ar); 7.51 (exch br s, 1H, CONH₂); 7.56 (d, 1H, Ar, *J* = 6.0 Hz); 7.66 (t, 1H, H₇, *J* = 7.2 Hz); 7.75 (m, 1H, Ar); 8.06 (t, 1H, H₈, *J* = 7.6 Hz); 8.22 (d, 1H, H₉, *J* = 7.6 Hz); 8.34 (m, 2H, H₂, H₆). ESI-MS calcd. for C₁₈H₁₃ClN₄O₂, 352.78; found: *m/z* 354.07 [M + H]⁺. Anal. calcd for C₁₈H₁₃ClN₄O₂ (C, H, N): C, 61.28; H, 3.71; N, 15.88; found: C, 61.52; H, 3.72; N, 15.94.

5-[(3-Chlorobenzyl)oxy]pyrazolo[1,5-*a*]quinazoline-3-carboxamide (13e). From **3a** and 2-chlorobenzyl bromide. Yield 81%, mp 242-245 °C (EtOH); TLC eluent: toluene/ethyl acetate/acetic acid 9/1/0.5 v/v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 5.73 (s, 2H, OCH₂); 7.28 (exch br s, 1H, CONH₂); 7.45 (m, 3H, Ar + CONH₂); 7.57 (d, 1H, Ar, *J* = 6.8 Hz); 7.66 (m, 2H, Ar + H₇); 8.05 (t, 1H, H₈, *J* = 7.6 Hz); 8.24 (d, 1H, H₉, *J* = 7.6 Hz); 8.33 (m, 2H, H₂, H₆). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ 68.6; 115.1; 126.1; 126.7; 127.1; 128.3; 128.6; 130.9; 136.0; 138.8. ESI-MS calcd. for C₁₈H₁₃ClN₄O₂, 352.78; found: *m/z* 354.07 [M + H]⁺. Anal. calcd for C₁₈H₁₃ClN₄O₂ (C, H, N): C, 61.28; H, 3.71; N, 15.88; found: C, 61.52; H, 3.72; N, 15.94.

5-[(4-Bromobenzyl)oxy]pyrazolo[1,5-*a*]quinazoline-3-carboxamide (13f). From **3a** and 4-bromobenzyl bromide. Yield 86%, mp 243-244 °C (EtOH); TLC eluent: toluene/ethyl acetate/acetic

acid 9/1/0.5 v/v/v. ¹H-NMR (400 MHz, DMSO-d₆) δ 5.70 (s, 2H, OCH₂); 7.27 (exch br s, 1H, CONH₂); 7.44 (exch br s, 1H, CONH₂); 7.55 (d, 2H, H₂, H₆, *J* = 8.4 Hz); 7.62 (d, 2H, H₃, H₅, *J* = 8.4 Hz); 7.66 (t, 1H, H₇, *J* = 7.6 Hz); 8.05 (t, 1H, H₈, *J* = 7.6 Hz); 8.23 (d, 1H, H₉, *J* = 8.0 Hz); 8.32 (m, 2H, H₂, H₆). ¹³C-NMR (100 MHz, DMSO-d₆) δ 68.8; 106.6; 111.6; 115.0; 121.9; 126.0; 126.7; 129.5; 130.7; 131.7; 131.9; 135.8; 136.0; 137.1; 141.9; 144.0; 159.8; 163.3. ESI-MS calcd. for C₁₈H₁₃BrN₄O₂, 397.23; found: *m/z* 398.02 [M + H]⁺. Anal. calcd for C₁₈H₁₃BrN₄O₂ (C, H, N): C, 54.43; H, 3.30; N, 14.10; found: C, 54.21; H, 3.28; N, 14.04.

5-[(2-Methylbenzyl)oxy]pyrazolo[1,5-*a*]quinazoline-3-carboxamide (13g). From **3a** and 2-methylbenzyl chloride. Yield 34%, mp 226-227 °C (EtOH); TLC eluent: toluene/ethyl acetate/acetic acid 8/2/1 v/v/v. ¹H-NMR (400 MHz, DMSO-d₆) δ 2.41 (s, 3H, CH₃); 5.74 (s, 2H, OCH₂); 7.26 (m, 3H, Ar); 7.33 (exch br s, 1H, CONH₂); 7.48 (exch br s, 1H, CONH₂); 7.54 (d, 1H, Ar, *J* = 7.2 Hz); 7.65 (t, 1H, H₇, *J* = 7.6 Hz); 8.05 (t, 1H, H₈, *J* = 7.6 Hz); 8.18 (d, 1H, H₉, *J* = 8.0 Hz); 8.33 (m, 2H, H₂, H₆). ¹³C-NMR (100 MHz, DMSO-d₆) δ 19.1; 68.4; 115.1; 126.0; 126.4; 126.8; 129.1; 129.9; 130.8; 136.0. ESI-MS calcd. for C₁₉H₁₆N₄O₂, 332.36; found: *m/z* 333.13 [M + H]⁺. Anal. calcd for C₁₉H₁₆N₄O₂ (C, H, N): C, 68.66; H, 4.85; N, 16.86; found: C, 68.38; H, 4.83; N, 16.79.

5-[(3-Methoxybenzyl)oxy]pyrazolo[1,5-*a*]quinazoline-3-carboxamide (13h). From **3a** and 3-methoxybenzyl bromide. Yield 90%, mp 210-212 °C (EtOH); TLC eluent: toluene/ethyl acetate/acetic acid 8/2/1 v/v/v. ¹H-NMR (400 MHz, DMSO-d₆) δ 3.76 (s, 3H, OCH₃); 5.70 (s, 2H, OCH₂); 6.94 (d, 1H, Ar, *J* = 8.0 Hz); 7.16 (m, 2H, Ar); 7.30 (exch br s, 1H, CONH₂); 7.34 (t, 1H, Ar, *J* = 8.0 Hz); 7.46 (exch br s, 1H, CONH₂); 7.67 (t, 1H, H₇, *J* = 7.6 Hz); 8.05 (t, 1H, H₈, *J* = 8.0 Hz); 8.24 (d, 1H, H₉, *J* = 8.0 Hz); 8.33 (m, 2H, H₂, H₆). ¹³C-NMR (100 MHz, DMSO-d₆) δ 55.5; 69.4; 106.6; 111.8; 114.0; 114.2; 115.2; 120.6; 126.1; 126.7; 130.1; 136.0; 137.1; 137.8; 142.0; 144.1; 159.9; 163.3. ESI-MS calcd. for C₁₉H₁₆N₄O₃, 348.36; found: *m/z* 349.13 [M + H]⁺. Anal. calcd for C₁₉H₁₆N₄O₃ (C, H, N): C, 65.51; H, 4.63; N, 16.08; found: C, 65.77; H, 4.65; N, 16.14.

5-[(4-Sulfamoylbenzyl)oxy]pyrazolo[1,5-*a*]quinazoline-3-carboxamide (13i). From **3a** and 4-(bromomethyl)benzenesulphonamide. Yield 90%, mp 167-168 °C (EtOH); TLC eluent: toluene/ethyl

acetate/acetic acid 8/2/1 v/v/v. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ 5.81 (s, 2H, OCH_2); 7.27 (exch br s, 1H, CONH_2); 7.39 (exch br s, 2H, SO_2NH_2); 7.46 (exch br s, 1H, CONH_2); 7.67 (t, 1H, H_7 , $J = 7.6$ Hz); 7.77 (d, 2H, H_2' , H_6' , $J = 8.0$ Hz); 7.86 (d, 2H, H_3' , H_5' , $J = 8.4$ Hz); 8.06 (t, 1H, H_8 , $J = 7.6$ Hz); 8.27 (d, 1H, H_9 , $J = 8.0$ Hz); 8.33 (d, 1H, H_6 , $J = 8.0$ Hz); 8.33 (s, 1H, H_2). $^{13}\text{C-NMR}$ (100 MHz, DMSO-d_6) δ 68.7; 106.0; 111.7; 115.1; 126.2; 126.4; 127.0; 128.6; 136.3; 137.0; 140.5; 142.1; 143.7; 143.9; 160.0; 163.8. ESI-MS calcd. for $\text{C}_{18}\text{H}_{15}\text{N}_5\text{O}_4\text{S}$, 397.41; found: m/z 398.09 $[\text{M} + \text{H}]^+$. Anal. calcd for $\text{C}_{18}\text{H}_{15}\text{N}_5\text{O}_4\text{S}$ (C, H, N): C, 54.40; H, 3.80; N, 17.62; found: C, 54.61; H, 3.81; N, 17.69.

4-[4-(Methylthio)benzyl]-5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carboxamide (14c).

From **3a** and 4-(methylthio)benzyl bromide. Yield 6%, mp 276-279 °C (EtOH); TLC: toluene/ethyl acetate/methanol 8/2/1.5 v/v/v. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ 2.39 (s, 3H, SCH_3); 5.93 (s, 2H, NCH_2); 7.10 (m, 4H, Ar); 7.34 (exch br s, 1H, CONH_2); 7.57 (t, 1H, H_7 , $J = 8.0$ Hz); 7.85 (exch br s, 1H, CONH_2); 7.94 (t, 1H, H_8 , $J = 7.2$ Hz); 8.12 (s, 1H, H_2); 8.16 (d, 1H, H_9 , $J = 8.4$ Hz); 8.21 (d, 1H, H_6 , $J = 7.6$ Hz). $^{13}\text{C-NMR}$ (100 MHz, DMSO-d_6) δ 15.1; 46.5; 115.4; 115.7; 126.4; 126.8; 128.2; 129.0; 134.0; 136.0; 161.1; 164.2. ESI-MS calcd. for $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_2\text{S}$, 364.42; found: m/z 365.10 $[\text{M} + \text{H}]^+$. Anal. calcd for $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_2\text{S}$ (C, H, N): C, 62.62; H, 4.43; N, 15.37; found: C, 62.37; H, 4.41; N, 15.31.

3-Carbamoylpyrazolo[1,5-*a*]quinazolin-5-yl-4-methylbenzenesulfonate (15). Starting material **3a** [52] (0.31 mmol) was suspended in methylene chloride (10 mL) and 0.70 mmol of 4-toluenesulfonyl chloride and 0.6 mL (in excess) of triethylamine were added. The reaction was maintained at reflux temperature for 2-3 hours, then the solvent was evaporated to dryness. The residue was treated with diethyl ether, filtered and used without further purification to obtain compound **13a** (see above). Yield 85%, mp 246-247 °C (*i*-PrOH); TLC eluent: toluene/ethyl acetate/acetic acid 8/2/1 v/v/v. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ 2.43 (s, 3H, CH_3); 6.72 (exch br s, 1H, CONH_2); 7.53 (d, 2H, H_3' , H_5' , $J = 8.0$ Hz); 7.58 (exch br s, 1H, CONH_2); 7.76 (t, 1H, H_7 , $J = 7.6$ Hz); 8.09 (d, 2H, H_2' , H_6' , $J = 8.0$ Hz); 8.15 (m, 2H, H_8 , H_9); 8.41 (d, 1H, H_6 , $J = 8.4$ Hz); 8.47 (s, 1H, H_2). Anal. calcd for $\text{C}_{18}\text{H}_{14}\text{N}_4\text{O}_4\text{S}$ (C, H, N): C, 56.54; H, 3.69; N, 14.65; found: C, 56.76; H, 3.70; N, 14.71.

5-[(4-(Methylsulfinyl)benzyloxy)pyrazolo[1,5-*a*]quinazoline-3-carboxamide (16). To a solution of 176 mg (1 mmol) of HIO_3 in 11 mL of acetone/ H_2O (10:1), a small amount of tetra-*n*-butylammonium bromide (TBAB) was added while stirring for 5 minutes. Then, 0.25 mmol of compound **13c** was added and the mixture was stirred at 80 °C for 2 hours. The reaction mixture was cooled, 10 mL of H_2O was added and the precipitate formed is collected by vacuum filtration. Yield 88%, mp 225-226 °C (EtOH 80%); TLC eluent: toluene/ethyl acetate/acetic acid 8/2/1 v/v/v. ^1H -NMR (400 MHz, DMSO-d_6) δ 2.73 (s, 3H, SOCH_3); 5.77 (s, 2H, OCH_2); 7.26 (exch brs, 1H, CONH_2); 7.46 (exch brs, 1H, CONH_2); 7.66 (t, 1H, H_7 , $J = 7.2$ Hz); 7.71 (d, 2H, H_2 , H_6 , $J = 7.6$ Hz); 7.77 (d, 2H, H_3 , H_5 , $J = 7.6$ Hz); 8.04 (t, 1H, H_8 , $J = 7.2$ Hz); 8.25 (d, 1H, H_9 , $J = 7.6$ Hz); 8.30 (m, 2H, H_6 , H_2). ^{13}C -NMR (100 MHz, DMSO-d_6) δ 68.9; 106.6; 111.6; 115.0; 124.3; 126.1; 126.7; 129.1; 136.0; 137.1; 139.1; 141.9; 144.0; 146.7; 159.8; 163.3. ESI-MS calcd. for $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_3\text{S}$, 380.42; found: m/z 381.10 $[\text{M} + \text{H}]^+$. Anal. calcd for $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_3\text{S}$ (C, H, N): C, 59.99; H, 4.24; N, 14.73; found: C, 59.75; H, 4.22; N, 14.67.

5-[(4-(Methylsulfonyl)benzyloxy)pyrazolo[1,5-*a*]quinazoline-3-carboxamide (17). Compound **13c** (0.16 mmol) was dissolved in 4 mL of MeOH. To this solution, at 0 °C, a previously prepared solution composed of 0.64 mmol of OXONE[®] in 4 mL of H_2O was added. The mixture was stirred at 100 °C for 2 hours. After cooling, 10 mL of H_2O was added and the precipitate formed was recovered by vacuum filtration to obtain the desired compound. Yield 72%, mp 280-281 °C (EtOH); TLC eluent: toluene/ethyl acetate/acetic acid 8/2/1 v/v/v. ^1H -NMR (400 MHz, DMSO-d_6) δ 3.23 (s, 3H, SO_2CH_3); 5.85 (s, 2H, OCH_2); 7.23 (exch br s, 1H, CONH_2); 7.46 (exch br s, 1H, CONH_2); 7.68 (t, 1H, H_7 , $J = 7.2$ Hz); 7.86 (d, 2H, H_2 , H_6 , $J = 7.6$ Hz); 7.97 (d, 2H, H_3 , H_5 , $J = 7.6$ Hz); 8.06 (t, 1H, H_8 , $J = 7.2$ Hz); 8.29 (d, 1H, H_9 , $J = 8.0$ Hz); 8.33 (m, 2H, H_6 , H_2). ^{13}C -NMR (100 MHz, DMSO-d_6) δ 47.8; 68.5; 115.1; 126.2; 127.0; 127.7; 128.8; 136.3; 142.4. ESI-MS calcd. for $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_4\text{S}$, 396.42; found: m/z 397.09 $[\text{M} + \text{H}]^+$. Anal. calcd for $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_4\text{S}$ (C, H, N): C, 57.57; H, 4.07; N, 14.13; found: C, 57.80; H, 4.09; N, 14.19.

(E)-5-(Benzyloxy)-N-[(dimethylamino)methylene]pyrazolo[1,5-*a*]quinazoline-3-carboxamide

(18). A suspension of **13b** (150 mg, 0.47 mmol) in toluene (8 mL) was added of DMF-DMA (1.6 mmol, 0.5 mL) and refluxed for 2 hours. The final solution was evaporated to dryness and the yellow residue was recovered with ethyl ether and filtered. The product was pure enough to use in the next reaction. Yield 70%, mp 148-150 °C; IR (nujol) cm^{-1} : 1649, 1305; TLC eluent: toluene/ethyl acetate/acetic acid 8/2/1.5 v/v/v. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ 3.17 (s, 3H, N- CH_3); 3.19 (s, 3H, N- CH_3); 5.73 (s, 2H, OCH_2); 7.45 (m, 3H, Ar); 7.63 (d, 2H, Ar, $J = 8.0$ Hz); 7.68 (t, 1H, H_8 , $J = 8.0$ Hz); 8.04 (t, 1H, H_7 , $J = 8.0$ Hz); 8.20 (d, 1H, H_6 , $J = 8.4$ Hz); 8.35 (d, 1H, H_9 , $J = 8.4$ Hz); 8.46 (s, 1H, H_2); 8.59 (s 1H, CH). ESI-MS calcd. for $\text{C}_{21}\text{H}_{19}\text{N}_5\text{O}_2$, 373.42; found: m/z 374.16 $[\text{M} + \text{H}]^+$. Anal. calcd for $\text{C}_{21}\text{H}_{19}\text{N}_5\text{O}_2$ (C, H, N): C, 67.55; H, 5.13; N, 18.76; found: C, 67.82; H, 5.15; N, 18.83.

5-(Benzyloxy)-3-(1H-1,2,4-triazol-5-yl)pyrazolo[1,5-*a*]quinazoline (19). A suspension of **18** (50 mg, 0.13 mmol) in glacial acetic acid (3.0 mL) was added of 60% hydrazine hydrate solution (0.26 mmol, 0.1 mL) and refluxed until a solution was obtained which indicate the end of the reaction. After cooling at room temperature, the precipitate was filtered and washed with water. The residue was purified by recrystallisation. Yield 77%, mp >300 °C (EtOH); IR (nujol) cm^{-1} : 3237, 1310; TLC eluent: toluene/ethyl acetate/acetic acid 8/2/1.5 v/v/v. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ 5.83 (s, 2H, OCH_2); 7.45 (m, 3H, Ar); 7.63 (d, 2H, Ar, $J = 8.0$ Hz); 7.68 (t, 1H, H_8 , $J = 8.0$ Hz); 8.05 (t, 1H, H_7 , $J = 8.0$ Hz); 8.22 (m, 2H, $\text{H}_6 + \text{CH triazole}$); 8.36 (d, 1H, H_9 , $J = 8.4$ Hz); 8.49 (s, 1H, H_2); 13.76 (exch br s, 1H, NH). ESI-MS calcd. for $\text{C}_{19}\text{H}_{14}\text{N}_6\text{O}$, 342.36; found: m/z 343.13 $[\text{M} + \text{H}]^+$. Anal. calcd for $\text{C}_{19}\text{H}_{14}\text{N}_6\text{O}$ (C, H, N): C, 66.66; H, 4.12; N, 24.55; found: C, 66.39; H, 4.10; N, 24.45.

5-{[4-(Methanesulfonyl)phenyl]methoxy}-3-(thiophen-3-yl)pyrazolo[1,5-*a*]quinazoline (20).

Compound 3-(thiophen-3-yl)pyrazolo[1,5-*a*]quinazolin-5(4*H*)-one **6** [37] (0.31 mmol) was suspended in methylene chloride (10 mL) and 0.70 mmol of 4-toluenesulfonyl chloride and 0.6 mL (in excess) of triethylamine were added. The reaction was maintained at reflux temperature for 2-3 hours, then the solvent was evaporated to dryness. The residue was recovered by isopropyl alcohol and crystallised with the same solvent; yield 97%, mp 203 °C; TLC eluent: toluene/ethyl

acetate/acetic acid 8/2/1.5 v/v/v. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ 2.45 (s, 3H, CH_3); 7.43 (d, 1H, H_2 thiophene, $J = 2.8$ Hz); 7.45 (d, 1H, H_4 thiophene, $J = 5.2$ Hz); 7.53 (d, 2H, $\text{H}_3 + \text{H}_5$, $J = 8.0$ Hz); 7.60 (dd, 1H, H_5 thiophene, $J = 2.8$ Hz; $J = 5.2$ Hz); 7.71 (m, 2H, $\text{H}_7 + \text{H}_9$); 8.04 (d, 2H, H_2 and H_6 , $J = 8.0$ Hz); 8.08 (m, 1H, thiophene); 8.13 (t, 1H, H_7 , $J = 8.0$ Hz); 8.37 (d, 1H, H_6 , $J = 8.4$ Hz); 8.60 (s, 1H, H_2). ESI-MS calcd. for $\text{C}_{21}\text{H}_{15}\text{N}_3\text{O}_3\text{S}_2$, 421.49; found: m/z 422.06 $[\text{M} + \text{H}]^+$. Anal. calcd for $\text{C}_{21}\text{H}_{15}\text{N}_3\text{O}_3\text{S}_2$ (C, H, N): C, 59.84; H, 3.59; N, 9.97; found: C, 59.60; H, 3.57; N, 9.93.

General procedure for obtaining compounds 21a,b and 22. To a solution of anhydrous DMF (3 mL), *t*-BuOK (0.28 mmol), the suitable alcohol (0.30 mmol) (benzyl alcohol, for **21a** and 2-aminobenzyl alcohol, for **21b**) was added, and after 15 min. also compound **20** (0.28 mmol), maintaining at reflux temperature for 3 hours. For obtaining compound **22**, to the solution of starting product **20** in DMF was added 0.02 mL of benzylamine and refluxed for 1.30 hours. When starting material disappeared, evaluated by TLC (toluene/ethyl acetate/methanol 8/2/1.5 v/v/v), water and ice were added, and the precipitate was filtered and purified by crystallisation.

5-Benzoyloxy-3-(thiophen-3-yl)pyrazolo[1,5-*a*]quinazoline (21a). Starting from compound **20** and benzyl alcohol; yield 36%, mp 179-181 °C (EtOH). $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ 5.71 (s, 2H, OCH_2); 7.35 (m, 1H, thiophene); 7.41 (m, 2H, thiophene + Ar); 7.61 (m, 4H, Ar); 7.79 (m, 1H, thiophene); 7.92 (m, 1H, H_8); 7.97 (m, 1H, H_7); 8.18 (d, 1H, H_9 , $J = 8.4$ Hz); 8.29 (d, 1H, H_6 , $J = 8.4$ Hz); 8.47 (s, 1H, H_2). ESI-MS calcd. for $\text{C}_{21}\text{H}_{15}\text{N}_3\text{OS}$, 357.43; found: m/z 358.10 $[\text{M} + \text{H}]^+$. Anal. calcd for $\text{C}_{21}\text{H}_{15}\text{N}_3\text{OS}$ (C, H, N): C, 70.57; H, 4.23; N, 11.76; found: C, 70.29; H, 4.21; N, 11.71.

2-({3-(Thiophen-3-yl)pyrazolo[1,5-*a*]quinazolin-5-yl}oxy)methyl)aniline (21b). Starting from compound **20** and 2-aminobenzyl alcohol; yield 30%, mp 125-126 °C (EtOH). $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ 4.74 (exch br s, 2H, NH_2); 4.88 (s, 2H, OCH_2); 6.38 (t, 1H, H_5 , Ar, $J = 7.2$ Hz); 6.43 (d, 1H, H_3 , Ar, $J = 7.2$ Hz); 6.54 (d, 1H, H_6 , Ar, $J = 7.2$ Hz); 6.71 (m, 1H, thiophene); 6.89 (t, 1H, H_4 , Ar, $J = 7.2$ Hz); 7.04 (m, 1H, thiophene); 7.38 (m, 1H, thiophene); 7.52 (t, 1H, H_7 , $J = 8.0$ Hz); 7.79 (s, 1H, H_2); 7.93 (m, 1H, H_8); 8.18 (m, 2 H, $\text{H}_9 + \text{H}_6$). ESI-MS calcd. for $\text{C}_{21}\text{H}_{16}\text{N}_4\text{OS}$, 372.45;

found: m/z 373.11 $[M + H]^+$. Anal. calcd for $C_{21}H_{16}N_4OS$ (C, H, N): C, 67.72; H, 4.33; N, 15.04; found: C, 67.99; H, 4.35; N, 15.10.

N-Benzyl-3-(thiophen-3-yl)pyrazolo[1,5-*a*]quinazolin-5-amine (22). Starting from compound **20** and benzyl amine; yield 33%, mp 176-177 °C (EtOH). 1H -NMR (400 MHz, DMSO- d_6) δ 4.80 (d, 2H, CH_2NH); 7.19 (t, 1H, H_4 , Ar, $J = 7.2$ Hz); 7.30 (t, 2H, H_3 , + H_5 , Ar, $J = 7.6$ Hz); 7.45 (d, 2H, H_2 , + H_6 , Ar, $J = 7.6$ Hz); 7.50 (m, 1H, H_5 , thiophene); 7.53 (t, 1H, H_8 , $J = 8.4$ Hz); 7.64 (d, 1H, H_4 , thiophene, $J = 3.6$ Hz); 7.79 (dd, 1H, H_2 , thiophene, $J = 6.8$ Hz, $J = 2.8$ Hz); 7.89 (t, 1H, H_7 , $J = 8.0$ Hz); 8.21 (d, 1H, H_9 , $J = 8.4$ Hz); 8.23 (s, 1H, H_2); 8.38 (d, 1H, H_6 , $J = 8.0$ Hz); 8.80 (exch br s, 1H, NH). ESI-MS calcd. for $C_{21}H_{16}N_4S$, 356.45; found: m/z 357.11 $[M + H]^+$. Anal. calcd for $C_{21}H_{16}N_4S$ (C, H, N): C, 70.76; H, 4.52; N, 15.72; found: C, 70.47; H, 4.50; N, 15.66.

General procedure for compounds 23a-c. A suspension of 8-chloro-5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carboxamide **3b** (150 mg, 0.66 mmol) in anhydrous DMF (3.0 mL) and anhydrous K_2CO_3 (2.64 mmol) was maintained at room temperature for 15 min. and then appropriate substituted halide (0.99 mmol) was added. The reaction was heated at 50 °C for 2 h. After cooling, ice-cold water was added (20 mL) and the precipitate formed was recovered by vacuum filtration and was purified by flash column chromatography using dichloromethane/methanol 10:0.5 as eluent (for **23a**) or by crystallisation from ethanol (for **23b**) or water/acetic acid 1:1 (for **23c**).

8-Chloro-5-methoxypyrazolo[1,5-*a*]quinazoline-3-carboxamide (23a). From **3b** and methyl iodide. Yield 80%, mp 288-290 °C (EtOH); TLC eluent: dichloromethane/methanol 10/0.5 v/v. 1H -NMR (400 MHz, DMSO- d_6) δ 4.21 (s, 3H, OCH_3); 7.28 (exch br s, 1H, $CONH_2$); 7.51 (exch br s, 1H, $CONH_2$); 7.70 (dd, 1H, H_7 , $J_1 = 2.0$ Hz, $J_2 = 8.8$ Hz); 8.20 (d, 1H, H_6 , $J = 8.8$ Hz); 8.29 (d, 1H, H_9 , $J = 2.0$ Hz); 8.35 (s, 1H, H_2). ESI-MS calcd. for $C_{12}H_9ClN_4O_2$, 276.68; found: m/z 278.04 $[M + H]^+$. Anal. calcd for $C_{12}H_9ClN_4O_2$ (C, H, N): C, 52.09; H, 3.28; N, 20.25; found: C, 52.30; H, 3.29; N, 20.33.

8-Chloro-5-[(4-(methylthio)benzyloxy]pyrazolo[1,5-*a*]quinazoline-3-carboxamide (23b). From **3b** and 4-(methylthio)benzyl bromide. Yield 90%, mp 207-209 °C (EtOH); TLC eluent: toluene/ethyl

acetate/acetic acid 8/2/1 v/v/v. $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ 2.42 (s, 3H, SCH₃); 5.61 (s, 2H, OCH₂); 7.30 (m, 3H, H_{2'}, H_{6'} + 1H CONH₂); 7.47 (exch br s, 1H, CONH₂); 7.53 (d, 2H, H_{3'}, H_{5'}, J = 7.6 Hz); 7.68 (d, 1H, H₇, J = 8.4 Hz); 8.19 (d, 1H, H₆, J = 8.4 Hz); 8.29 (s, 1H, H₉); 8.36 (s, 1H, H₂). $^{13}\text{C-NMR}$ (100 MHz, DMSO- d_6) δ 15.05; 69.52; 106.91; 110.58; 114.62; 126.36; 126.96; 128.29; 129.50; 132.53; 137.75; 139.03; 140.55; 142.38; 144.54; 159.55; 163.10. ESI-MS calcd. for C₁₉H₁₅ClN₄O₂S, 398.87; found: m/z 400.06 [M + H]⁺. Anal. calcd for C₁₉H₁₅ClN₄O₂S (C, H, N): C, 57.21; H, 3.79; N, 14.05; found: C, 57.44; H, 3.80; N, 14.10.

8-Chloro-5-(4-sulfamoylbenzyloxy)pyrazolo[1,5-*a*]quinazoline-3-carboxamide (23c). From **3b** and 4-(bromomethyl)benzene sulphonamide. Yield 61%, mp 177-180 °C (H₂O/CH₃COOH); TLC eluent: toluene/ethyl acetate/methanol 8/2/1.5 v/v/v. $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ 5.78 (s, 2H, OCH₂); 7.26 (exch br s, 1H, CONH₂); 7.39 (exch br s, 2H, SO₂NH₂); 7.48 (exch br s, 1H, CONH₂); 7.69 (dd, 1H, H₇, J_1 = 1.6 Hz, J_2 = 8.4 Hz); 7.75 (d, 2H, H_{2'}, H_{6'}, J = 8.0 Hz); 7.85 (d, 2H, H_{3'}, H_{5'}, J = 8.0 Hz); 8.27 (d, 1H, H₆, J = 8.8 Hz); 8.29 (d, 1H, H₉, J = 2.0 Hz); 8.35 (s, 1H, H₂). $^{13}\text{C-NMR}$ (100 MHz, DMSO- d_6) δ 68.93; 106.00; 110.68; 114.76; 126.38; 127.07; 128.51; 128.77; 137.50; 140.16; 140.69; 142.10; 143.20; 146.70; 159.20; 163.09. ESI-MS calcd. for C₁₈H₁₄ClN₅O₄S, 431.85; found: m/z 433.04 [M + H]⁺. Anal. calcd for C₁₈H₁₄ClN₅O₄S (C, H, N): C, 50.06; H, 3.27; N, 16.22; found: C, 50.26; H, 3.28; N, 16.28.

8-Chloro-5-[(4-(methylsulfinyl)benzyloxy]pyrazolo[1,5-*a*]quinazoline-3-carboxamide (24). Starting from **23b** (1 mmol), HIO₃ in 11 mL of acetone/H₂O (10:1) and a small amount of tetra-*n*-butylammonium bromide (TBAB) following the same procedure used for the synthesis of product **16**. The reaction mixture was cooled and 10 mL of ice-cold water was added. The suspension was extracted with ethyl acetate (3 x 15 mL), then the organic fraction was recovered, dried over sodium sulphate, filtered and the solvent was removed under reduced pressure to obtain the desired compound. Yield 63%, mp 240-242 °C (EtOH); TLC eluent: toluene/ethyl acetate/methanol 8/2/1.5 v/v/v. $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ 2.75 (s, 3H, SOCH₃); 5.80 (s, 2H, OCH₂); 7.24 (exch br s, 1H, CONH₂); 7.47 (exch br s, 1H, CONH₂); 7.70 (d, 1H, H₇, J = 8.8 Hz); 7.74 (d, 2H, H_{2'}, H_{6'}, J =

8.0 Hz); 7.80 (d, 2H, H_{3'}, H_{5'}, $J = 8.0$ Hz); 8.26 (d, 1H, H₆, $J = 8.8$ Hz); 8.31 (s, 1H, H₉); 8.36 (s, 1H, H₂). ESI-MS calcd. for C₁₉H₁₅ClN₄O₃S, 414.86; found: m/z 416.05 [M + H]⁺. Anal. calcd for C₁₉H₁₅ClN₄O₃S (C, H, N): C, 55.01; H, 3.64; N, 13.51; found: C, 55.23; H, 3.65; N, 13.56.

8-Chloro-5-[(4-(methylsulfonyl)benzyloxy)pyrazolo[1,5-*a*]quinazoline-3-carboxamide (25).

Starting from **23b** in MeOH and a solution of OXONE[®]/H₂O, following the same procedure used to synthesise **17**. The row compound was purified by flash column chromatography (dichloromethane/methanol 9.5/0.5 v/v, as eluent). Yield 66%, mp 270-271 °C (EtOH); ¹H-NMR (400 MHz, DMSO-*d*₆) δ 3.23 (s, 3H, SO₂CH₃); 5.85 (s, 2H, OCH₂); 7.22 (exch br s, 1H, CONH₂); 7.48 (exch br s, 1H, CONH₂); 7.71 (d, 1H, H₇, $J = 8.4$ Hz); 7.86 (d, 2H, H_{2'}, H_{6'}, $J = 8.0$ Hz); 7.98 (d, 2H, H_{3'}, H_{5'}, $J = 7.6$ Hz); 8.28 (d, 1H, H₆, $J = 8.4$ Hz); 8.31 (s, 1H, H₉); 8.36 (s, 1H, H₂). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ 43.96; 68.76; 105.77; 115.20; 117.00; 123.00; 124.50; 127.10; 127.73; 128.98; 131.20; 132.30; 140.55; 142.40; 145.00; 153.00; 163.00. ESI-MS calcd. for C₁₉H₁₅ClN₄O₄S, 430.86; found: m/z 432.05 [M + H]⁺. Anal. calcd for C₁₉H₁₅ClN₄O₄S (C, H, N): C, 52.97; H, 3.51; N, 13.00; found: C, 52.75; H, 3.49; N, 12.95.

General procedure for compounds 26 and 27. To a solution of 0.21 mmol of starting material **3b** in 3 mL of anhydrous toluene and 0.3 mL of dry DMF, 0.76 mmol (0.10 mL) of DMF-DMA was added. The reaction was refluxed for 2 h. After cooling, a precipitate was formed and recovered by vacuum filtration to give compound **26**. The evaporation of solvent furnished compound **27**. The same reaction carried out using an excess of DMF-DMA (0.30 mL) led to obtaining only product **27**.

(E)-8-Chloro-N-[(dimethylamino)methylene]-5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carboxamide (26). Using 0.76 mmol of DMF-DMA, yield 83%, mp 288-290 °C (EtOH); TLC eluent: toluene/ethyl acetate/methanol 8/2/2 v/v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 3.15 (s, 3H, NCH₃); 3.23 (s, 3H, NCH₃); 7.60 (d, 1H, H₇, $J = 8.4$ Hz); 8.07 (s, 1H, H₉); 8.17 (d, 1H, H₆, $J = 8.8$ Hz); 8.19 (s, 1H, H₂); 8.67 (s, 1H, N=CH); 10.83 (exch br s, 1H, CONH). ESI-MS calcd. for C₁₄H₁₂ClN₅O₂, 317.73; found: m/z 319.07 [M + H]⁺. Anal. calcd for C₁₄H₁₂ClN₅O₂ (C, H, N): C, 52.92; H, 3.81; N, 22.04; found: C, 52.71; H, 3.79; N, 21.95.

(E)-8-Chloro-N-[(dimethylamino)methylene]-4-methyl-5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carboxamide (27). Using an excess of DMF-DMA, yield 87%, mp 205-207 °C (EtOH/H₂O); TLC eluent: toluene/ethyl acetate/methanol 8/2/2 v/v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 3.10 (s, 3H, NCH₃); 3.17 (s, 3H, NCH₃); 3.89 (s, 3H, NCH₃); 7.56 (d, 1H, H₇, *J* = 7.2 Hz); 8.07 (s, 1H, H₉); 8.15 (d, 1H, H₆, *J* = 8.4 Hz); 8.35 (s, 1H, H₂); 8.53 (s, 1H, N=CH). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ 34.50; 35.54; 41.37; 114.50; 114.93; 125.00; 126.68; 127.51; 131.00; 136.00; 140.22; 143.00; 143.50; 147.00; 160.52. ESI-MS calcd. for C₁₅H₁₄ClN₅O₂, 331.76; found: *m/z* 333.08 [M + H]⁺. Anal. calcd for C₁₅H₁₄ClN₅O₂ (C, H, N): C, 54.31; H, 4.25; N, 21.11; found: C, 54.53; H, 4.26; N, 21.19.

8-Chloro-4-methyl-5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carbohydrazide (29). 0.26 mmol of starting material **28a** [35] was dissolved in 10 mL of hydrazine hydrate and 2 mL of EtOH 96%. The mixture was refluxed for 7 h. After cooling, a precipitate was formed and recovered by vacuum filtration to obtain the desired compound. Yield 63%, mp >300 °C (2-methoxyethanol); TLC eluent: toluene/ethyl acetate/acetic acid 8/2/1 v/v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 3.66 (s, 3H, NCH₃); 4.46 (exch br s, 2H, NH₂); 7.57 (d, 1H, H₇, *J* = 8.4 Hz); 8.05 (s, 1H, H₂); 8.08 (s, 1H, H₉); 8.16 (d, 1H, H₆, *J* = 8.4 Hz); 9.63 (exch br s, 1H, NH). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ 32.83; 89.05; 114.23; 114.77; 125.80; 126.77; 131.03; 137.89; 140.00; 143.27; 153.30; 158.53. ESI-MS calcd. for C₁₂H₁₀ClN₅O₂, 291.70; found: *m/z* 293.05 [M + H]⁺. Anal. calcd for C₁₂H₁₀ClN₅O₂ (C, H, N): C, 49.41; H, 3.46; N, 24.01; found: C, 49.60; H, 3.47; N, 24.10.

(E)-8-Chloro-3-(hydrazineylidenemethyl)-4-methylpyrazolo[1,5-*a*]quinazolin-5(4*H*)-one (30b). 0.19 mmol of starting material **28b** [35] was dissolved in 1 mL of hydrazine hydrate and 2 mL of EtOH 96%. The mixture was stirred at reflux for 1 h. After cooling, ice/cold water (20 mL) was added and the precipitate formed was recovered by vacuum filtration to obtain the desired compound. Yield 55%, mp >300 °C (EtOH); TLC eluent: toluene/ethyl acetate/methanol 8/2/1.5 v/v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 3.64 (s, 3H, NCH₃); 6.52 (exch br s, 2H, NH₂); 7.49 (d, 1H, H₇, *J* = 7.6 Hz); 7.97 (s, 1H, H₉); 8.02 (s, 1H, H₂); 8.10 (d, 1H, H₆, *J* = 8.0 Hz). ¹³C-NMR (100 MHz, DMSO-*d*₆) δ 31.88;

114.25; 114.70; 126.05; 131.00; 131.09; 137.90; 138.07; 140.17; 141.78; 146.30; 158.50. ESI-MS calcd. for $C_{12}H_{10}ClN_5O$, 275.70; found: m/z 277.05 $[M + H]^+$. Anal. calcd for $C_{12}H_{10}ClN_5O$ (C, H, N): C, 52.28; H, 3.66; N, 25.40; found: C, 52.49; H, 3.67; N, 25.50.

(E)-8-Chloro-4-methyl-5-oxo-4,5-dihydropyrazolo[1,5-a]quinazoline-3-carbaldehyde oxime (30c). A suspension of **28b** (0.19 mmol) [35] and 0.57 mmol of hydroxylammonium chloride in 2 mL of H_2O was stirred at 60 °C for 30 minutes, then 0.57 mmol of $NaHCO_3$ was added and the mixture was refluxed for 2.5 hours. After cooling, ice/cold water (20 mL) was added and the precipitate formed was recovered by vacuum filtration. The desired compound was purified using by flash chromatography with cyclohexane/ethyl acetate 1/1 v/v as eluent. Yield 50%, mp 264-267 °C; 1H -NMR (400 MHz, $DMSO-d_6$) δ 3.07 (s, 3H, NCH_3); 7.55 (d, 1H, H_7 , $J = 8.0$ Hz); 8.05 (s, 1H, H_9); 8.12 (s, 1H, H_2); 8.15 (d, 1H, H_6 , $J = 7.6$ Hz); 8.38 (s, 1H, $CHNOH$); 11.05 (exch br s, 1H, NOH). ESI-MS calcd. for $C_{12}H_9ClN_4O_2$, 276.68; found: m/z 278.04 $[M + H]^+$. Anal. calcd for $C_{12}H_9ClN_4O_2$ (C, H, N): C, 52.09; H, 3.28; N, 20.25; found: C, 52.30; H, 3.29; N, 20.33.

8-Chloro-4-methyl-3-[(4-(methylthio)benzyloxy)methyl]pyrazolo[1,5-a]quinazolin-5(4H)-one (31). A solution of intermediate **30a** (0.23 mmol) [35] and 0.70 mmol of sodium hydride (60% dispersion in mineral oil) in 2 mL of dry CH_3CN was stirred at room temperature for 20 minutes, then 0.35 mmol of 4-methylthiobenzyl bromide was added and the mixture was stirred at reflux for 24 hours. After cooling, the solvent was evaporated and the solid obtained was washed with water. The crude compound was purified by flash chromatography using toluene/ethyl acetate/acetic acid 9/1/0.5 v/v/v as eluent. Yield 11%, mp 132-133 °C; 1H -NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3H, SCH_3); 3.82 (s, 3H, NCH_3); 4.53 (s, 2H, CH_2); 4.58 (s, 2H, CH_2); 7.25 (m, 4H, Ar); 7.38 (dd, 1H, H_7 , $J_1 = 1.6$ Hz, $J_2 = 8.8$ Hz); 7.70 (s, 1H, H_2); 8.18 (d, 1H, H_9 , $J = 1.6$ Hz); 8.23 (d, 1H, H_6 , $J = 8.4$ Hz). ^{13}C -NMR (100 MHz, $CDCl_3$) δ 15.77; 30.42; 36.62; 62.04; 71.41; 101.51; 114.03; 114.94; 126.17; 126.52; 128.66; 129.48; 130.50; 134.12; 137.89; 138.35; 138.87; 141.33; 144.90; 158.57. ESI-MS calcd. for $C_{20}H_{18}ClN_3O_2S$, 399.89; found: m/z 401.08 $[M + H]^+$. Anal. calcd for $C_{20}H_{18}ClN_3O_2S$ (C, H, N): C, 60.07; H, 4.54; N, 10.51; found: C, 60.31; H, 4.56; N, 10.55.

N-(4-Aminophenyl)-8-chloro-4-methyl-5-oxo-4,5-dihydropyrazolo[1,5-a]quinazoline-3-

carboxamide (32). A solution of starting material **28c** (0.36 mmol) [35] in 3 mL of SOCl₂ was stirred at reflux for 2 hours. After cooling, the solvent was evaporated and the solid obtained was dissolved in 2 mL of dry CH₂Cl₂. To this solution, 1.08 mmol of benzene-1,4-diamine and 1.08 mmol of triethylamine were added and the mixture was stirred at reflux temperature for 4 hours. After cooling, the solvent was evaporated and the final compound was purified by flash column chromatography using dichloromethane/methanol 9.5/0.5 v/v as eluent. Yield 20%, mp 155-157 °C; ¹H-NMR (400 MHz, DMSO-d₆) δ 3.58 (s, 3H, NCH₃); 5.01 (exch br s, 1H, NH₂); 6.57 (d, 2H, H_{3'}, H_{5'}, *J* = 8.0 Hz); 7.28 (d, 2H, H_{2'}, H_{6'}, *J* = 8.0 Hz); 7.56 (d, 1H, H₇, *J* = 8.0 Hz); 8.08 (s, 1H, H₉); 8.12 (s, 1H, H₂); 10.03 (exch br s, 1H, NH). ESI-MS calcd. for C₁₈H₁₄ClN₅O₂, 367.79; found: *m/z* 369.08 [M + H]⁺. Anal. calcd for C₁₈H₁₄ClN₅O₂ (C, H, N): C, 58.78; H, 3.84; N, 19.04; found: C, 58.54; H, 3.82; N, 18.96.

General procedure for compounds 33a, b. The starting material **3c** or **3d** (0.35 mmol) were treated in anhydrous DMF (2.5 mL), K₂CO₃ (0.35 mmol) and stirred at room temperature for 15 min. then methyl iodide (0.70 mmol) was added. The reaction was heated at 80 °C for 1 h and, after cooling, ice-cold water was added (20 mL), and the precipitate formed was recovered by vacuum filtration. The crude compounds were purified by flash column chromatography using dichloromethane/methanol/acetic acid 97/3/03 v/v/v (for **33a**) or toluene/ethyl acetate/acetic acid 8/2/1 v/v/v (for **33b**) as eluents.

5-Methoxy-8-nitropyrazolo[1,5-a]quinazoline-3-carboxamide (33a). From **3c**, yield 58%, mp > 300 °C; TLC eluent: dichloromethane/methanol/acetic acid 97/3/03 v/v/v. ¹H-NMR (400 MHz, DMSO-d₆) δ 4.25 (s, 3H, CH₃); 7.27 (exch br s, 1H, NH₂); 7.56 (exch br s, 1H, NH₂); 8.36 (dd, 1H, H₂, *J*₁ = 2.0 Hz, *J*₂ = 8.8 Hz); 8.42 (m, 2H, H₇, H₆); 8.88 (d, 1H, H₉, *J* = 1.6 Hz). ¹³C-NMR (400 MHz, DMSO-d₆) δ 56.1; 110.5; 120.5; 128.8; 131.2; 144.9. ESI-MS calcd. for C₁₂H₉N₅O₄, 287.24; found: *m/z* 288.07 [M + H]⁺. Anal. calcd for C₁₂H₉N₅O₄ (C, H, N): C, 50.18; H, 3.16; N, 24.38; found: C, 50.38; H, 3.17; N, 24.47.

5-Methoxy-7-nitropyrrazolo[1,5-*a*]quinazoline-3-carboxamide (33b). From **3d**, yield 40%, mp 269-271 °C; TLC eluent: toluene/ethyl acetate/acetic acid 8/2/1 v/v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 4.26 (s, 3H, CH₃); 7.28 (exch br s, 1H, NH₂); 7.58 (exch br s, 1H, NH₂); 8.44 (s, 1H, H₂); 8.47 (d, 1H, H₉, *J* = 9.2 Hz); 8.77 (dd, 1H, H₈, *J*₁ = 2.4 Hz, *J*₂ = 9.2 Hz); 8.86 (d, 1H, H₆, *J* = 2.4 Hz). ¹³C-NMR (400 MHz, DMSO-*d*₆) δ 56.1; 107.4; 112.1; 117.1; 122.3; 130.1; 140.2; 144.8; 145.7; 160.4; 163.0. ESI-MS calcd. for C₁₂H₉N₅O₄, 287.24; found: *m/z* 288.07 [M + H]⁺. Anal. calcd for C₁₂H₉N₅O₄ (C, H, N): C, 50.18; H, 3.16; N, 24.38; found: C, 50.38; H, 3.17; N, 24.47.

5-Methoxy-8-nitropyrrazolo[1,5-*a*]quinazoline-3-carbonitrile (34). A solution of **33a** (0.27 mmol) in 3 mL of POCl₃ was stirred at 80 °C for 2 hours. After cooling and evaporation of the solvent, ice/cold water (20 mL) was added and the solid obtained was recovered by vacuum filtration and purified by recrystallisation. Yield 92%, mp >300 °C (EtOH); TLC eluent: toluene/ethyl acetate/methanol 8/2/2 v/v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 4.24 (s, 3H, CH₃); 8.41 (dd, 1H, H₇, *J*₁ = 2.2 Hz, *J*₂ = 9.0 Hz); 8.46 (d, 1H, H₆, *J* = 8.8 Hz); 8.68 (s, 1H, H₂); 8.89 (d, 1H, H₉, *J* = 2.0 Hz). ¹³C-NMR (400 MHz, DMSO-*d*₆) δ 56.15; 83.08; 110.68; 114.91; 116.42; 121.28; 128.90; 136.87; 146.35; 148.05; 151.31; 161.18. ESI-MS calcd. for C₁₂H₇N₅O₃, 269.22; found: *m/z* 270.06 [M + H]⁺. Anal. calcd for C₁₂H₇N₅O₃ (C, H, N): C, 53.54; H, 2.62; N, 26.01; found: C, 53.75; H, 2.63; N, 26.11.

8-Nitro-5-oxo-4,5-dihydropyrrazolo[1,5-*a*]quinazoline-3-carbaldehyde (35). To a solution of 0.43 mmol of starting material **5c** in 5 mL of glacial acetic acid, 4.30 mmol of hexamethylenetetramine (HTMA) was added and the reaction was stirred at reflux temperature for 3 hours. After cooling, water was added, the suspension was extracted with ethyl acetate (3 x 15 mL), dried over anhydrous sodium sulphate, filtered, and finally evaporated to obtain the desired compound. Yield 73%, mp 150-153 °C (EtOH); TLC eluent: toluene/ethyl acetate/methanol 8/2/2 v/v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 8.30-8.42 (m, 3H, H₂, H₇, H₆); 8.67 (s, 1H, H₉); 9.99 (s, 1H, CHO). ESI-MS calcd. for C₁₁H₆N₄O₄, 258.19; found: *m/z* 259.04 [M + H]⁺. Anal. calcd for C₁₁H₆N₄O₄ (C, H, N): C, 51.17; H, 2.34; N, 21.70; found: C, 51.37; H, 2.35; N, 21.78.

(E)-8-Nitro-5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carbaldehyde oxime (36). Starting material **35** was reacted with hydroxylammonium chloride following the same procedure for obtaining **30c**. At the end of the reaction, the suspension was extracted with ethyl acetate (3 x 15 mL), dried over sodium sulphate, filtered and finally evaporated. The final compound was purified by flash column chromatography, using cyclohexane/ethyl acetate 1/5 v/v as eluent. Yield 65%, mp 243-246 °C; ¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.65 (s, 1H, H₂); 8.24 (d, 1H, H₆, *J* = 8.4 Hz); 8.36 (d, 1H, H₇, *J* = 8.4 Hz); 8.49 (s, 1H, CH); 8.65 (s, 1H, H₉); 11.49 (exch br s, 1H, OH). ESI-MS calcd. for C₁₁H₇N₅O₄, 273.21; found: *m/z* 274.05 [M + H]⁺. Anal. calcd for C₁₁H₇N₅O₄ (C, H, N): C, 48.36; H, 2.58; N, 25.63; found: C, 48.16; H, 2.57; N, 25.52.

4-Methyl-8-nitro-5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carbonitrile (37). Starting material **2c** was reacted in anhydrous DMF, K₂CO₃, and methyl iodide following the procedure used for obtaining **33a,b**. Yield 94%, mp 260-263 °C dec. (EtOH); TLC eluent: toluene/ethyl acetate/methanol 8/2/2 v/v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 3.74 (s, 3H, CH₃); 8.32 (dd, 1H, H₇, *J*₁ = 8.6 Hz, *J*₂ = 2.2 Hz); 8.44 (d, 1H, H₉, *J* = 8.8); 8.54 (s, 1H, H₂); 8.69 (d, 1H, H₆, *J* = 2.0 Hz). ¹³C-NMR (400 MHz, DMSO-*d*₆) δ 37.30; 77.47; 110.84; 113.99; 120.81; 121.42; 131.47; 136.89; 144.26; 146.24; 151.66; 157.48. ESI-MS calcd. for C₁₂H₇N₅O₃, 269.22; found: *m/z* 270.06 [M + H]⁺. Anal. calcd for C₁₂H₇N₅O₃ (C, H, N): C, 53.54; H, 2.62; N, 26.01; found: C, 53.75; H, 2.63; N, 26.11.

4-Methyl-8-nitro-5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carboxamide (38). Starting compound **37** (0.82 mmol) was solubilised in 2 mL of H₂SO₄ conc., and stirred at 80 °C for 2 hours. After cooling, the mixture was slowly poured into water and ice. The precipitate formed was isolated by vacuum filtration to obtain the desired product. Yield 89%, mp 286-289 °C (EtOH); TLC eluent: toluene/ethyl acetate/methanol 8/2/2 v/v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 3.74 (s, 3H, CH₃); 7.39 (exch br s, 1H, NH); 7.93 (exch br s, 1H, NH); 8.19 (s, 1H, H₂); 8.25 (dd, 1H, H₇, *J*₁ = 2.2 Hz, *J*₂ = 8.6 Hz); 8.39 (d, 1H, H₆, *J* = 8.4 Hz); 8.70 (d, 1H, H₉, *J* = 2.0 Hz). ¹³C-NMR (400 MHz, DMSO-*d*₆) δ 37.04; 104.2; 110.34; 111.00; 120.20; 121.25; 131.28; 137.40; 139.81; 151.49; 158.29; 163.77. ESI-

MS calcd. for $C_{12}H_9N_5O_4$, 287.24; found: m/z 288.07 $[M + H]^+$. Anal. calcd for $C_{12}H_9N_5O_4$ (C, H, N): C, 50.18; H, 3.16; N, 24.38; found: C, 50.38; H, 3.17; N, 24.47.

General procedure for compounds 39a-c. To a solution of 0.39 mmol of suitable starting material (**2c**, **2d**, or **4d**) in 2.7 mL of $POCl_3$, 3.60 mmol of PCl_5 was added. The mixture was stirred at 200 °C for 2.5-4.5 hours. After cooling to room temperature, ice/cold water (20 mL) was added and the precipitate formed was recovered by vacuum filtration to obtain the desired compounds.

5-Chloro-8-nitropyrazolo[1,5-*a*]quinazoline-3-carbonitrile (39a). From **2c**, yield 75%, mp > 295 °C (EtOH); TLC eluent: toluene/ethyl acetate/acetic acid 8/2/1 v/v/v. 1H -NMR (400 MHz, DMSO- d_6) δ 8.52 (dd, 1H, H_7 , $J_1 = 2.0$ Hz, $J_2 = 8.8$ Hz); 8.63 (d, 1H, H_6 , $J = 9.2$ Hz); 8.92 (s, 1H, H_2); 9.02 (d, 1H, H_9 , $J = 2.4$ Hz). ESI-MS calcd. for $C_{11}H_4ClN_5O_2$, 273.64; found: m/z 275.00 $[M + H]^+$. Anal. calcd for $C_{11}H_4ClN_5O_2$ (C, H, N): C, 48.28; H, 1.47; N, 25.59; found: C, 48.47; H, 1.47; N, 25.69.

5-Chloro-7-nitropyrazolo[1,5-*a*]quinazoline-3-carbonitrile (39b). From **2d**, yield 84%, mp 222-224 °C (EtOH); TLC eluent: toluene/ethyl acetate/acetic acid 8/2/1 v/v/v. 1H -NMR (400 MHz, DMSO- d_6) δ 8.66 (d, 1H, H_9 , $J = 9.2$ Hz); 8.90 (dd, 1H, H_8 , $J_1 = 2.4$ Hz, $J_2 = 9.2$ Hz); 8.93 (s, 1H, H_2); 9.01 (d, 1H, H_6 , $J = 2.0$ Hz). ESI-MS calcd. for $C_{11}H_4ClN_5O_2$, 273.64; found: m/z 275.00 $[M + H]^+$. Anal. calcd for $C_{11}H_4ClN_5O_2$ (C, H, N): C, 48.28; H, 1.47; N, 25.59; found: C, 48.47; H, 1.47; N, 25.69.

Ethyl 5-chloro-7-nitropyrazolo[1,5-*a*]quinazoline-3-carboxylate (39c). From **4d**, yield 88%, mp 169-172 °C (EtOH); TLC eluent: toluene/ethyl acetate/methanol 8/2/2 v/v/v. 1H -NMR (400 MHz, DMSO- d_6) δ 1.32 (t, 3H, CH_3 , $J = 7.0$ Hz); 4.33 (q, 2H, CH_2 , $J = 7.1$ Hz); 8.65 (d, 1H, H_9 , $J = 9.2$ Hz); 8.72 (s, 1H, H_2); 8.87 (dd, 1H, H_8 , $J_1 = 2.4$ Hz, $J_2 = 9.2$ Hz); 8.98 (d, 1H, H_6 , $J = 2.4$ Hz). ESI-MS calcd. for $C_{13}H_9ClN_4O_4$, 320.69; found: m/z 322.03 $[M + H]^+$. Anal. calcd for $C_{13}H_9ClN_4O_4$ (C, H, N): C, 48.69; H, 2.83; N, 17.47; found: C, 48.49; H, 2.82; N, 17.40.

General procedure for compounds 40 and 42b-d. To a suspension of 0.29 mmol of suitable starting material **39a-c** in 5.0 mL of isopropyl alcohol, 0.58 mmol of substituted aniline and a catalytic amount of triethylamine (3 g) were added. The mixture was stirred at reflux for 2-20 hours (the reaction was

monitored by TLC until the starting materials disappeared). After cooling, a precipitate was obtained, recovered by vacuum filtration and purified by crystallisation from suitable solvent.

Ethyl 5-[(4-aminophenyl)amino]-7-nitropyrrazolo[1,5-*a*]quinazoline-3-carboxylate (40). Starting from **39c** and 1,4-phenylenediamine. Yield 94%, mp 269-271 °C (2-methoxyethanol); TLC eluent: dichloromethane/methanol 10/1 v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 1.32 (t, 3H, CH₃, *J* = 7.0 Hz); 4.23 (q, 2H, CH₂, *J* = 7.0 Hz); 5.05 (exch br s, 2H, NH₂); 6.61 (d, 2H, H_{3'}, H_{5'}, *J* = 8.8 Hz); 7.88 (d, 2H, H_{2'}, H_{6'}, *J* = 8.8 Hz); 8.32 (s, 1H, H₂); 8.40 (d, 1H, H₉, *J* = 8.8 Hz); 8.67 (dd, 1H, H₈, *J*₁ = 2.4 Hz, *J*₂ = 9.2 Hz); 9.68 (d, 1H, H₆, *J* = 2.0 Hz); 10.08 (exch br s, 1H, NH). ¹³C-NMR (400 MHz, DMSO-*d*₆) δ 15.1; 59.8; 101.1; 112.4; 113.9; 117.0; 162.8; 122.2; 123.2; 128.6; 128.7; 139.7; 144.8; 146.0; 146.5; 146.8; 151.3. ESI-MS calcd. for C₁₉H₁₆N₆O₄, 392.38; found: *m/z* 393.13 [M + H]⁺. Anal. calcd for C₁₉H₁₆N₆O₄ (C, H, N): C, 58.16; H, 4.11; N, 21.42; found: C, 58.39; H, 4.13; N, 21.50.

5-[(4-(methylthiophenyl)amino]-8-nitropyrrazolo[1,5-*a*]quinazoline-3-carbonitrile (42b). Starting from **39a** and 4-(methylthio)aniline. Yield 73%, mp > 295 °C (*i*-PrOH); IR (nujol) cm⁻¹: 3120, 2240, 1440-1360; TLC eluent: toluene/ethyl acetate/methanol 8/2/2 v/v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 2.52 (s, 3H, CH₃); 7.34 (d, 2H, H_{3'}, H_{5'}, *J* = 8.4 Hz); 7.71 (exch br s, 1H, NH); 7.80 (s, 2H, H_{2'}, H_{6'}, *J* = 8.8 Hz); 8.17 (m, 2H, H₂, H₆); 8.38 (dd, 1H, H₇, *J*₁ = 1.6 Hz, *J*₂ = 8.8 Hz); 9.26 (d, 1H, H₉, *J* = 2.0 Hz). ESI-MS calcd. for C₁₈H₁₂N₆O₂S, 376.39; found: *m/z* 377.08 [M + H]⁺. Anal. calcd for C₁₈H₁₂N₆O₂S (C, H, N): C, 57.44; H, 3.21; N, 22.33; found: C, 57.66; H, 3.22; N, 22.42.

5-[(4-Aminophenyl)amino]-8-nitropyrrazolo[1,5-*a*]quinazoline-3-carbonitrile (42c). Starting from **39a** and 1,4-phenylenediamine. Yield 79%, mp >295 °C (2-methoxyethanol); TLC eluent: dichloromethane/methanol 9/1 v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 5.10-5.40 (exch br s, 2H, NH₂); 6.61 (m, 2H, H_{3'}, H_{5'}); 7.43 (m, 2H, H_{2'}, H_{6'}); 8.37 (m, 2H, H₂, H₆); 8.78 (m, 2H, H₉, H₇); 10.11 (exch br s, 1H, NH). ESI-MS calcd. for C₁₇H₁₁N₇O₂, 345.32; found: *m/z* 346.10 [M + H]⁺. Anal. calcd for C₁₇H₁₁N₇O₂ (C, H, N): C, 59.13; H, 3.21; N, 28.39; found: C, 59.36; H, 3.22; N, 28.50.

5-[(4-Aminophenyl)amino]-7-nitropyrrazolo[1,5-*a*]quinazoline-3-carbonitrile (42d). Starting from **39b** and 1,4-phenylenediamine. Yield 61%, mp >295 °C (2-methoxyethanol); IR (nujol) cm⁻¹:

3350; 3300; 2220; 1450-1350; TLC eluent: dichloromethane/methanol 9/1 v/v. ¹H-NMR (400 MHz, DMSO-d₆) δ 7.28 (d, 2H, H_{3'}, H_{5'}, *J* = 8.4 Hz); 7.85 (d, 2H, H_{2'}, H_{6'}, *J* = 8.4 Hz); 8.46 (d, 1H, H₉, *J* = 9.2 Hz); 8.53 (s, 1H, H₂); 8.76 (dd, 1H, H₈, *J*₁ = 2.0 Hz, *J*₂ = 9.2 Hz); 9.00-9.50 (exch br s, 2H, NH₂); 9.72 (d, 1H, H₆, *J* = 1.6 Hz); 10.61 (exch br s, 1H, NH). ¹³C-NMR (400 MHz, DMSO-d₆) δ 79.7; 112.8; 114.1; 114.5; 117.1; 122.4; 124.9; 127.2; 129.0; 139.5; 145.0; 146.5; 146.6; 150.2; 152.7. ESI-MS calcd. for C₁₇H₁₁N₇O₂, 345.32; found: *m/z* 346.10 [M + H]⁺. Anal. calcd for C₁₇H₁₁N₇O₂ (C, H, N): C, 59.13; H, 3.21; N, 28.39; found: C, 59.36; H, 3.22; N, 28.50.

Ethyl 5-[[4-(cyclopropanecarboxamido)phenyl]amino]-7-nitropyrrazolo[1,5-*a*]quinazoline-3-carboxylate (41). A cold solution (0 °C) of 0.13 mmol of compound **40** in 2.0 mL of dry CH₂Cl₂ added of cyclopropane carbonyl chloride (0.32 mmol) and a catalytic amount of triethylamine (0.03 mL), was stirred for 2 hours, and then at room temperature for another 2 hours. The precipitate formed was recovered by vacuum filtration to obtain the desired compound. Yield 85%, mp >295 °C (2-methoxyethanol); TLC eluent: toluene/ethyl acetate/acetic acid 8/2/1 v/v/v. ¹H-NMR (400 MHz, DMSO-d₆) δ 0.78 (m, 4H, 2 x CH₂ cC₃H₅); 1.35 (t, 3H, CH₃, *J* = 7.0 Hz); 1.77 (m, 1H, CH cC₃H₅); 4.27 (q, 2H, CH₂, *J* = 7.0 Hz); 7.63 (d, 2H, H_{2'}, H_{6'}, *J* = 8.8 Hz); 8.19 (d, 2H, H_{3'}, H_{5'}, *J* = 8.8 Hz); 8.36 (s, 1H, H₂); 8.43 (d, 1H, H₉, *J* = 9.2 Hz); 8.70 (dd, 1H, H₈, *J*₁ = 2.0 Hz, *J*₂ = 9.2 Hz); 9.75 (d, 1H, H₆, *J* = 1.6 Hz); 10.20 (exch br s, 1H, NH); 10.24 (exch br s, 1H, NH). ¹³C-NMR (400 MHz, DMSO-d₆) δ 6.9; 14.1; 14.4; 59.3; 108.0; 115.1; 116.7; 118.7; 119.3; 122.1; 127.1; 128.5; 130.5; 136.5; 145.5; 146.6; 161.8; 165.0; 172.0; 180.7. ESI-MS calcd. for C₂₃H₂₀N₆O₂, 460.45; found: *m/z* 461.15 [M + H]⁺. Anal. calcd for C₂₃H₂₀N₆O₂ (C, H, N): C, 60.00; H, 4.38; N, 18.25; found: C, 60.24; H, 4.40; N, 18.32.

5-(Methylamino)-8-nitropyrrazolo[1,5-*a*]quinazoline-3-carbonitrile (42a). To a solution of 0.25 mmol of starting material **39a** in 4.0 mL of 1,4-dioxane, 0.76 mmol of methylamine and 0.38 mmol of N,N-diisopropylethylamine (DIPEA) were added. The mixture was stirred at room temperature for 1.5 hours. Then, ice/cold water (20 mL) was added and the precipitate obtained was recovered by vacuum filtration to obtain the desired compound. Yield 67%, mp >300 °C (EtOH); TLC eluent:

toluene/ethyl acetate/methanol 8/2/2 v/v/v. ¹H-NMR (400 MHz, DMSO-d₆) δ 3.06 (d, 3H, CH₃ *J* = 4.4 Hz); 8.37 (d, 1H, H₇, *J* = 2.0 Hz); 8.39 (s, 1H, H₂); 8.54 (d, 1H, H₆, *J* = 8.8 Hz); 8.75 (d, 1H, H₉, *J* = 2.0 Hz); 8.98 (exch br d, 1H, NH). ¹³C-NMR (400 MHz, DMSO-d₆) δ 28.7; 66.4; 114.5; 116.1; 119.9; 121.8; 125.5; 135.7; 146.1; 150.2; 154.4; 163.2. ESI-MS calcd. for C₁₂H₈N₆O₂, 268.24; found: *m/z* 269.07 [M + H]⁺. Anal. calcd for C₁₂H₈N₆O₂ (C, H, N): C, 53.73; H, 3.01; N, 31.33; found: C, 53.51; H, 2.99; N, 31.20.

5-(Methylamino)-8-nitropyrzolo[1,5-*a*]quinazoline-3-carboxamide (43). Starting compound **42a** (0.82 mmol) was transformed into the corresponding carboxamide following the same procedure for obtaining compound **38**. Yield 70%, mp > 300 °C (EtOH); TLC eluent: toluene/ethyl acetate/methanol 8/2/2 v/v/v. ¹H-NMR (400 MHz, DMSO-d₆) δ 3.04 (s, 3H, CH₃); 7.24 (exch br s, 1H, NH); 7.48 (exch br s, 1H, NH); 8.14 (s, 1H, H₂); 8.30 (d, 1H, H₇, *J* = 8.4 Hz); 8.52 (d, 1H, H₆, *J* = 8.8 Hz); 8.74 (s, 2H, H₉ + NH). ESI-MS calcd. for C₁₂H₁₀N₆O₃, 286.25; found: *m/z* 287.08 [M + H]⁺. Anal. calcd for C₁₂H₁₀N₆O₃ (C, H, N): C, 50.35; H, 3.52; N, 29.36; found: C, 50.55; H, 3.53; N, 29.47.

5-[(4-(Methylsulfinylphenyl)amino)-8-nitropyrzolo[1,5-*a*]quinazoline-3-carbonitrile (44). Starting compound **42b** was oxidated with HIO₃ in acetone/H₂O (10:1) following the procedure used for synthesising **24**. Yield 72%, mp 241-243 °C (EtOH); TLC eluent: toluene/ethyl acetate/methanol 8/2/2 v/v/v. ¹H-NMR (400 MHz, DMSO-d₆) δ 2.77 (s, 3H, SOCH₃); 7.76 (d, 2H, H₂, H₆, *J* = 7.6 Hz); 8.05 (d, 2H, H₃, H₅, *J* = 6.0 Hz); 8.44 (m, 2H, H₂, H₆); 8.81 (m, 2H, H₉, H₇); 10.48 (exch br s, 1H, NH). ESI-MS calcd. for C₁₈H₁₂N₆O₃S, 392.39; found: *m/z* 393.07 [M + H]⁺. Anal. calcd for C₁₈H₁₂N₆O₃S (C, H, N): C, 55.10; H, 3.08; N, 21.42; found: C, 55.32; H, 3.09; N, 21.50.

5-[(4-(methylsulfonylphenyl)amino)-8-nitropyrzolo[1,5-*a*]quinazoline-3-carbonitrile (45). Starting compound **42b** was oxidated with OXONE[®] following the same procedure used to synthesise **17**. Yield 69%, mp 187-189 °C (EtOH); TLC eluent: toluene/ethyl acetate/methanol 8/2/2 v/v/v. ¹H-NMR (400 MHz, DMSO-d₆) δ 3.24 (s, 3H, SO₂CH₃); 7.98 (d, 2H, H₂, H₆, *J* = 8.4 Hz); 8.20 (d, 2H, H₃, H₅, *J* = 8.4 Hz); 8.52 (m, 1H, H₆); 8.58 (s, 1H, H₂); 8.90 (s, 1H, H₉); 8.98 (d, 1H, H₇, *J* = 8.4

Hz); 10.59 (exch br s, 1H, NH). ESI-MS calcd. for $C_{18}H_{12}N_6O_4S$, 408.39; found: m/z 409.07 $[M + H]^+$. Anal. calcd for $C_{18}H_{12}N_6O_4S$ (C, H, N): C, 52.94; H, 2.96; N, 20.58; found: C, 53.15; H, 2.97; N, 20.66.

General procedure for compounds 46a-c. To a cold solution (0 °C) of 0.11 mmol of suitable starting material (**33a**, **42a** or **43**) in 2 mL of HCl 37%, 1.10 mmol of tin powder was added. The reaction was stirred at 0 °C for 30 minutes. The suspension was then filtered off on a celite pad, and the pH of the filtrate was adjusted to 9-10 with NaOH 6N. The precipitate formed was collected by vacuum filtration to obtain the desired compound. The final compounds **46a-c** were purified by crystallisation.

8-Amino-5-methoxypyrazolo[1,5-*a*]quinazoline-3-carboxamide (46a). Starting from **33a**. Yield 98%, mp >300 °C (EtOH); TLC eluent: dichloromethane/methanol 8/2 v/v. 1H -NMR (400 MHz, DMSO- d_6) δ 4.09 (s, 3H, OCH₃); 6.79 (m, 3H, H₇ + NH₂ exch); 7.23 (s, 1H, H₉); 7.33 (exch br s, 2H, NH₂); 7.80 (d, 1H, H₆, J = 8.8 Hz); 8.18 (s, 1H, H₂). ^{13}C -NMR (400 MHz, DMSO- d_6) δ 54.0; 94.0; 99.1; 104.2; 114.7; 127.5; 139.3; 143.1; 143.2; 155.8; 160.7; 163.8. ESI-MS calcd. for $C_{12}H_{11}N_5O_2$, 257.25; found: m/z 258.09 $[M + H]^+$. Anal. calcd for $C_{12}H_{10}N_6O_3$ (C, H, N): C, 56.03; H, 4.31; N, 27.22; found: C, 56.25; H, 4.33; N, 27.33.

8-Amino-5-(methylamino)pyrazolo[1,5-*a*]quinazoline-3-carbonitrile (46b). Starting from **42a**. Yield 76%, mp >300 °C (EtOH); TLC eluent: toluene/ethyl acetate/methanol 8/2/2 v/v/v. 1H -NMR (400 MHz, DMSO- d_6) δ 2.96 (s, 3H, CH₃); 6.48 (exch br s, 2H, NH₂); 6.73 (d, 1H, H₇, J = 8.8 Hz); 7.17 (s, 1H, H₉); 8.00 (d, 1H, H₆, J = 8.8 Hz); 8.17 (s, 1H, H₂); 8.27 (exch br s, 1H, NH). ESI-MS calcd. for $C_{12}H_{10}N_6$, 238.25; found: m/z 239.10 $[M + H]^+$. Anal. calcd for $C_{12}H_{10}N_6$ (C, H, N): C, 60.50; H, 4.23; N, 35.27; found: C, 60.26; H, 4.21; N, 35.12.

8-Amino-5-(methylamino)pyrazolo[1,5-*a*]quinazoline-3-carboxamide (46c). Starting from **43**. Yield 66%, mp >300 °C (EtOH); TLC eluent: toluene/ethyl acetate/methanol 8/2/2 v/v/v. 1H -NMR (400 MHz, DMSO- d_6) δ 2.96 (s, 3H, CH₃); 6.41 (exch br s, 2H, NH₂); 6.73 (m, 1H, H₇); 7.06 (s, 1H, H₉); 7.21 (exch br s, 1H, NH); 7.67 (exch br s, 1H, NH); 7.95 (m, 1H, H₆); 7.99 (exch br s, 1H, NH);

8.14 (s, 1H, H₂). ESI-MS calcd. for C₁₂H₁₂N₆O, 256.27; found: m/z 257.11 [M + H]⁺. Anal. calcd for C₁₂H₁₂N₆O (C, H, N): C, 56.24; H, 4.72; N, 32.79; found: C, 56.46; H, 4.74; N, 32.92.

8-Amino-5-methoxypyrazolo[1,5-*a*]quinazoline-3-carbonitrile (47). Starting material **46a** was dehydrated with POCl₃ following the same procedure used to synthesise **34**. Yield 72%, mp >300 °C (EtOH); TLC eluent: toluene/ethyl acetate/methanol 8/2/2 v/v/v. ¹H-NMR (400 MHz, DMSO-d₆) δ 4.08 (s, 3H, OCH₃); 6.83 (s, 3H, H₇, NH₂, exch); 7.23 (s, 1H, H₉); 7.80 (d, 1H, H₆, *J* = 8.0 Hz); 8.42 (s, 1H, H₂). ¹³C-NMR (400 MHz, DMSO-d₆) δ 54.5; 80.6; 100.8; 114.6; 115.7; 127.4; 134.3; 139.1; 145.0; 148.2; 156.0; 161.7. ESI-MS calcd. for C₁₂H₉N₅O, 239.24; found: m/z 240.08 [M + H]⁺. Anal. calcd for C₁₂H₉N₅O (C, H, N): C, 60.25; H, 3.79; N, 29.27; found: C, 60.49; H, 3.80; N, 29.39.

General procedure for compounds 48 and 49. Starting compounds **37** and **38** were reduced with tin powder, as reported for synthesizing **46a-c**.

8-Amino-4-methyl-5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carbonitrile (48). Starting from **37**. Yield 94%, mp 286-288 °C (EtOH); TLC eluent: toluene/ethyl acetate/methanol 8/2/2 v/v/v. ¹H-NMR (400 MHz, DMSO-d₆) δ 3.65 (s, 3H, CH₃); 6.66 (exch br s, 2H, NH₂); 6.71 (d, 1H, H₇, *J* = 8.8 Hz); 7.11 (s, 1H, H₉); 7.80 (d, 1H, H₆, *J* = 8.8 Hz); 8.33 (s, 1H, H₂). ¹³C-NMR (400 MHz, DMSO-d₆) δ 37.3; 77.5; 96.0; 103.9; 114.8; 118.0; 125.0; 130.5; 142.9; 145.0; 150.0; 155.8. ESI-MS calcd. for C₁₂H₉N₅O, 239.24; found: m/z 240.08 [M + H]⁺. Anal. calcd for C₁₂H₉N₅O (C, H, N): C, 60.25; H, 3.79; N, 29.27; found: C, 60.49; H, 3.80; N, 29.38.

8-Amino-4-methyl-5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carboxamide (49). Starting from **38**. Yield 74%, mp > 300 °C (EtOH); TLC eluent: dichloromethane/methanol 8/2 v/v. ¹H-NMR (400 MHz, DMSO-d₆) δ 3.64 (s, 3H, CH₃); 6.48 (exch br s, 2H, NH₂); 6.65 (d, 1H, H₇, *J* = 8.0 Hz); 7.12 (s, 1H, H₉); 7.20 (exch br s, 1H, NH₂); 7.79 (d, 2H, H₆ + 1H NH₂, *J* = 8.8 Hz); 8.02 (s, 1H, H₂). ¹³C-NMR (400 MHz, DMSO-d₆) δ 32.7; 96.0; 103.1; 103.8; 113.6; 130.3; 138.8; 139.6; 142.9; 155.4; 158.9; 164.3. ESI-MS calcd. for C₁₂H₁₁N₅O₂, 257.25; found: m/z 258.09 [M + H]⁺. Anal. calcd for C₁₂H₁₁N₅O₂ (C, H, N): C, 56.03; H, 4.31; N, 27.22; found: C, 56.25; H, 4.33; N, 27.32.

Ethyl 7-[(4-methylphenyl)sulfonamido]-6-oxo-6,7-dihydropyrazolo[1,5-*a*]pyrido[3,4-*e*]pyrimidine-3-carboxylate (51a). A mixture of diethyl 7-[(*E*)-2-(dimethylamino)ethenyl]pyrazolo[1,5-*a*]pyrimidine-3,6-dicarboxylate **50** [38] (0.01 mmol) and 4-tolylsulphonylhydrazide (0.015 mmol) was heated to reflux under magnetic stirring in glacial acetic acid (20 mL) for 3 hours. On cooling, the precipitate was filtered, washed and recrystallised by ethanol; yield 97 %, mp 203 °C (EtOH); TLC eluent: toluene/ethyl acetate/acetic acid 8/2/1.5 v/v/v. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 1.34 (t, 3H, CH₂CH₃, *J* = 7.2 Hz); 2.42 (s, 3H, CH₃); 4.35 (q, 2H, CH₂CH₃, *J* = 7.2 Hz); 7.25 (d, 1H, H₉, *J* = 8.0 Hz); 7.37 (d, 2H, H_{3'}, H_{5'}, *J* = 8.4 Hz); 7.65 (d, 2H, H_{2'}, H_{6'}, *J* = 8.4 Hz); 8.21 (d, 1H, H₈, *J* = 8.0 Hz); 8.78 (s, 1H, H₂); 9.04 (s, 1H, H₅); 11.96 (exch br s, 1H, NH). ESI-MS calcd. for C₁₉H₁₇N₅O₅S, 427.44; found: *m/z* 428.10 [M + H]⁺. Anal. calcd for C₁₉H₁₇N₅O₅S (C, H, N): C, 53.39; H, 4.01; N, 16.38; found: C, 53.60; H, 4.03; N, 16.44.

General procedure for compounds 53a,b. The commercial starting materials ethyl 7-amino-6-cyanopyrazolo[1,5-*a*]pyrimidine-3-carboxylate **52a** or 7-amino-6-cyanopyrazolo[1,5-*a*]pyrimidine **52b** (2 mmol) were suspended in formamide (15 mL) and refluxed for 8 hours. The reaction was monitored by TLC (dichloromethane/methanol 9:1, v/v as eluent) until the starting materials disappeared. The cooling to room temperature yielded a precipitate separated by filtration and crystallised from a suitable solvent.

Ethyl 4-oxo-1,4-dihydropyrazolo[1,5-*a*]pyrimido[5,4-*e*]pyrimidine-7-carboxylate (53a).

Yield 55 %, mp >300 °C (CH₃COOH). ¹H-NMR (400 MHz, DMSO-*d*₆) δ 1.20 (t, 3H, CH₃, *J* = 7.2 Hz); 4.14 (q, 2H, CH₂, *J* = 7.2 Hz); 8.54 (s, 1H, H₂); 8.58 (s, 1H, H₈); 9.37 (s, 1H, H₅). ESI-MS calcd. for C₁₁H₉N₅O₃, 259.23; found: *m/z* 260.07 [M + H]⁺. Anal. calcd for C₁₁H₉N₅O₃ (C, H, N): C, 50.97; H, 3.50; N, 27.02; found: C, 50.76; H, 3.48; N, 26.91.

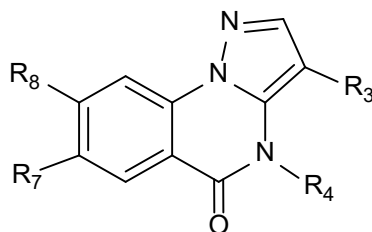
Pyrazolo[1,5-*a*]pyrimido[5,4-*e*]pyrimidin-4(1*H*)-one (53b). Yield 38 %, mp >300 °C (2-methoxyethanol). ¹H-NMR (400 MHz, DMSO-*d*₆) δ 6.84 (d, 1H, H₃, *J* = 2.0 Hz); 8.24 (d, 1H, H₂, *J* = 2.0 Hz); 8.36 (exch br s, 1H, NH); 8.58 (s, 1H, H₈); 9.20 (s, 1H, H₅). ESI-MS calcd. for C₈H₅N₅O,

187.16; found: m/z 188.05 $[M + H]^+$. Anal. calcd for $C_8H_5N_5O$ (C, H, N): C, 51.34; H, 2.69; N, 37.42; found: C, 51.54; H, 2.70; N, 38.42.

Ethyl (*Z*)-3-[(4-phenyl-1*H*-pyrazol-5-yl)amino]-2-(1*H*-pyrazol-1-yl)acrylate (56**).** A mixture of 3-amino-4-phenylpyrazole **54** (1 mmol) and ethyl 2-(pyrazol-1'-yl)-2-formylacetate **55** (1 mmol) [39] was heated to reflux under magnetic stirring in diglyme (20 mL) for 3 hours. Evaporation of the solvent gave a residue which was purified by recrystallisation; yield 80 %, mp 152-155 °C (EtOH/H₂O); TLC eluent: dichloromethane/methanol 10/1 v/v; from TLC is evidenced the formation of the two isomers, *cis* and *trans*. The reported ¹H-NMR data are related to the isomer in high quantity. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 1.40 (t, 3H, CH₃, J = 7.2 Hz); 4.35 (q, 2H, CH₂, J = 7.2 Hz); 6.58 (t, 1H, H_{4'} pyrazole, J = 2.4 Hz); 7.26 (m, 1H, Ar); 7.58-7.63 (m, 4H, Ar); 7.83 (d, 1H, H_{5'} pyrazole, J = 1.6 Hz); 8.15 (s, 1H, H₃ pyrazole); 8.22 (d, 1H, H_{3'} pyrazole, J = 2.4 Hz); 8.35 (d, 1H, -C=CH, J = 12.4 Hz); 9.81 (exch br d, 1H, =C-NH, J = 12.4 Hz); 12.80 (exch br s, 1H, NH pyrazole). ESI-MS calcd. for $C_{17}H_{17}N_5O_2$, 323.36; found: m/z 324.14 $[M + H]^+$. Anal. calcd for $C_{17}H_{17}N_5O_2$ (C, H, N): C, 63.15; H, 5.30; N, 21.66; found: C, 63.40; H, 5.32; N, 21.75.

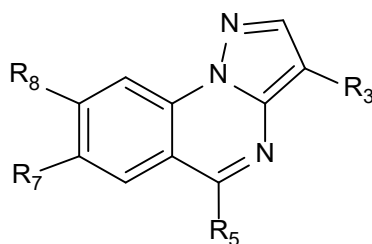
2. Chemical structures of all tested compounds (Tables S1-S3)

Table S1



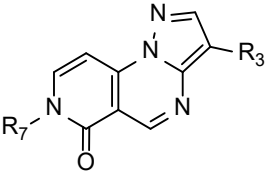
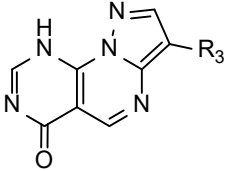
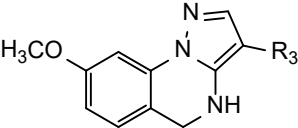
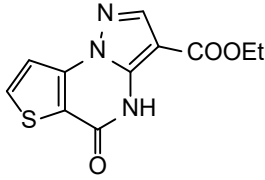
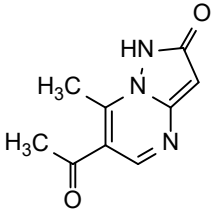
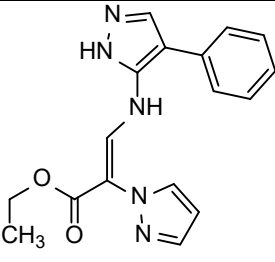
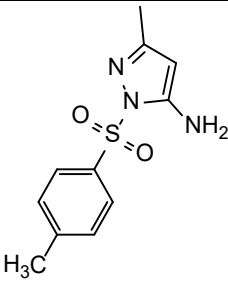
Comp.	R ₃	R ₄	R ₇	R ₈
2c	CN	H	H	NO ₂
2d	CN	H	NO ₂	H
3a [34]	CONH ₂	H	H	H
4c	COOEt	H	H	NO ₂
4d	COOEt	H	NO ₂	H
4e [36]	COOEt	H	H	OCH ₃
7a [30]	COOEt	CH ₃	H	H
7b	COOEt	CH ₂ (4-SCH ₃)Ph	H	H
7c	COOEt	CH ₂ (4-SO ₂ NH ₂)Ph	H	H
7d	COOEt	CH ₂ (4-SO ₂ CH ₃)Ph	H	H
7e	CN	CH ₂ (4-SCH ₃)Ph	H	H
7f	H	CH ₂ (4-SCH ₃)Ph	H	H
8	H	CH ₂ (4-SO ₂ CH ₃)Ph	H	H
9	I	CH ₂ (4-SOCH ₃)Ph	H	H
10	COOEt	CH ₂ (4-SOCH ₃)Ph	H	H
14c	CONH ₂	CH ₂ (4-SCH ₃)Ph	H	H
26	CON=CHN(CH ₃) ₂	H	H	Cl
27	CON=CHN(CH ₃) ₂	CH ₃	H	Cl
29	CONHNH ₂	CH ₃	H	Cl
30a [35]	CH ₂ OH	CH ₃	H	Cl
30b	CH=NNH ₂	CH ₃	H	Cl
30c	CH=NOH	CH ₃	H	Cl
31	CH ₂ OCH ₂ (4-SCH ₃)Ph	CH ₃	H	Cl
32	CONH(4-NH ₂)Ph	CH ₃	H	Cl
36	CH=NOH	H	H	NO ₂
37	CN	CH ₃	H	NO ₂
38	CONH ₂	CH ₃	H	NO ₂
48	CN	CH ₃	H	NH ₂
49	CONH ₂	CH ₃	H	NH ₂

Table S2



Comp.	R ₃	R ₅	R ₇	R ₈
12	COOEt	OCH ₃	H	H
13a	CONH ₂	OCH ₃	H	H
13b	CONH ₂	OCH ₂ Ph	H	H
13c	CONH ₂	OCH ₂ (4-SCH ₃)Ph	H	H
13d	CONH ₂	OCH ₂ (2-Cl)-Ph	H	H
13e	CONH ₂	OCH ₂ (3-Cl)-Ph	H	H
13f	CONH ₂	OCH ₂ (4-Br)-Ph	H	H
13g	CONH ₂	OCH ₂ (2-CH ₃)-Ph	H	H
13h	CONH ₂	OCH ₂ (3-OCH ₃)-Ph	H	H
13i	CONH ₂	OCH ₂ (4-SO ₂ NH ₂)-Ph	H	H
16	CONH ₂	OCH ₂ (4-SOCH ₃)Ph	H	H
17	CONH ₂	OCH ₂ (4-SO ₂ CH ₃)Ph	H	H
19	1,2,4-triazol-3-yl	OCH ₂ Ph	H	H
20	3-thienyl	OSO ₂ (4-Me)Ph	H	H
21a	3-thienyl	OCH ₂ Ph	H	H
21b	3-thienyl	OCH ₂ (2-NH ₂)Ph	H	H
22	3-thienyl	NHCH ₂ Ph	H	H
23a	CONH ₂	OCH ₃	H	Cl
23b	CONH ₂	OCH ₂ (4-SCH ₃)Ph	H	Cl
23c	CONH ₂	OCH ₂ (4-SO ₂ NH ₂)-Ph	H	Cl
24	CONH ₂	OCH ₂ (4-SOCH ₃)Ph	H	Cl
25	CONH ₂	OCH ₂ (4-SO ₂ CH ₃)Ph	H	Cl
33a	CONH ₂	OCH ₃	H	NO ₂
33b	CONH ₂	OCH ₃	NO ₂	H
34	CN	OCH ₃	H	NO ₂
40	COOEt	NH(4-NH ₂)Ph	NO ₂	H
41	COOEt	NH(4-NHCO- <i>c</i> -Pr)Ph	NO ₂	H
42a	CN	NHCH ₃	H	NO ₂
42b	CN	NH(4-SCH ₃)Ph	H	NO ₂
42c	CN	NH(4-NH ₂)Ph	H	NO ₂
42d	CN	NH(4-NH ₂)Ph	NO ₂	H
43	CONH ₂	NHCH ₃	H	NO ₂
44	CN	NH(4-SOCH ₃)Ph	H	NO ₂
45	CN	NH(4-SO ₂ CH ₃)Ph	H	NO ₂
46a	CONH ₂	OCH ₃	H	NH ₂
46b	CN	NHCH ₃	H	NH ₂
46c	CONH ₂	NHCH ₃	H	NH ₂
47	CN	OCH ₃	H	NH ₂
57 [42]	CONHCH ₂ (2-OCH ₃)Ph	H	H	OCH ₃

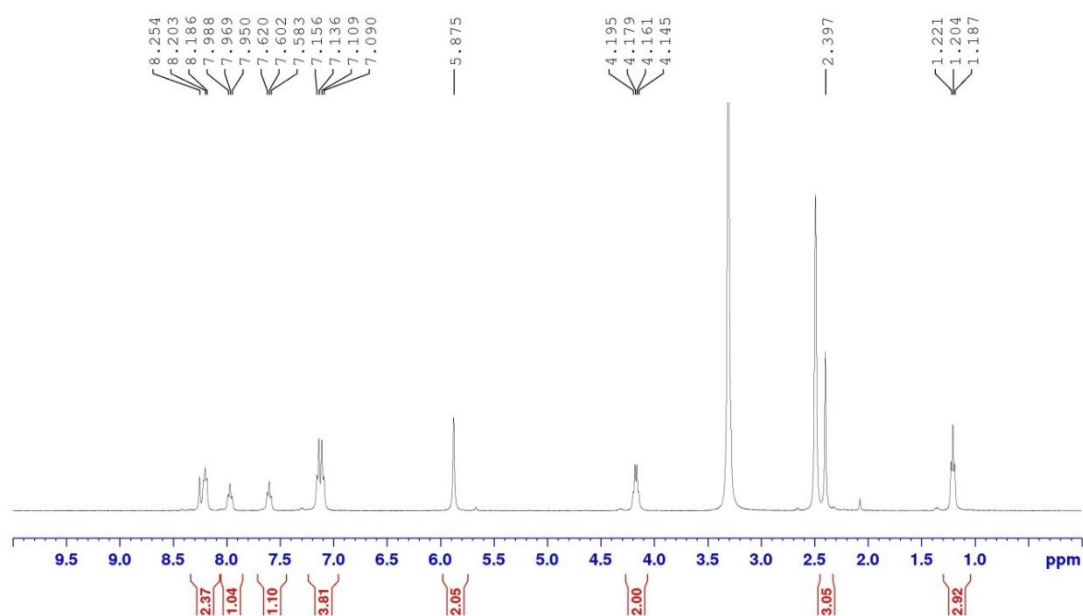
Table S3

	Compound	R ₃	R ₇
	51a	COOEt	-SO ₂ -Ph-4-CH ₃
	51b [38]	CN	-NHCONH ₂
	51c [38]	CN	-NHCO-Ph-4-NO ₂
	51d [38]	COOEt	-NHCONH ₂
	51e [29]	CN	-OH
	53a	COOEt	-
	53b	H	-
	58a [42]	CONH ₂	-
	58b [42]	CONHCH ₂ -2-Thienyl	-
	58c [42]	CONHCH ₂ -Ph	-
 59 [30]	 60 [31]		
 56	 61 [32]		

3. ^1H -NMR and ^{13}C -NMR of representative compounds

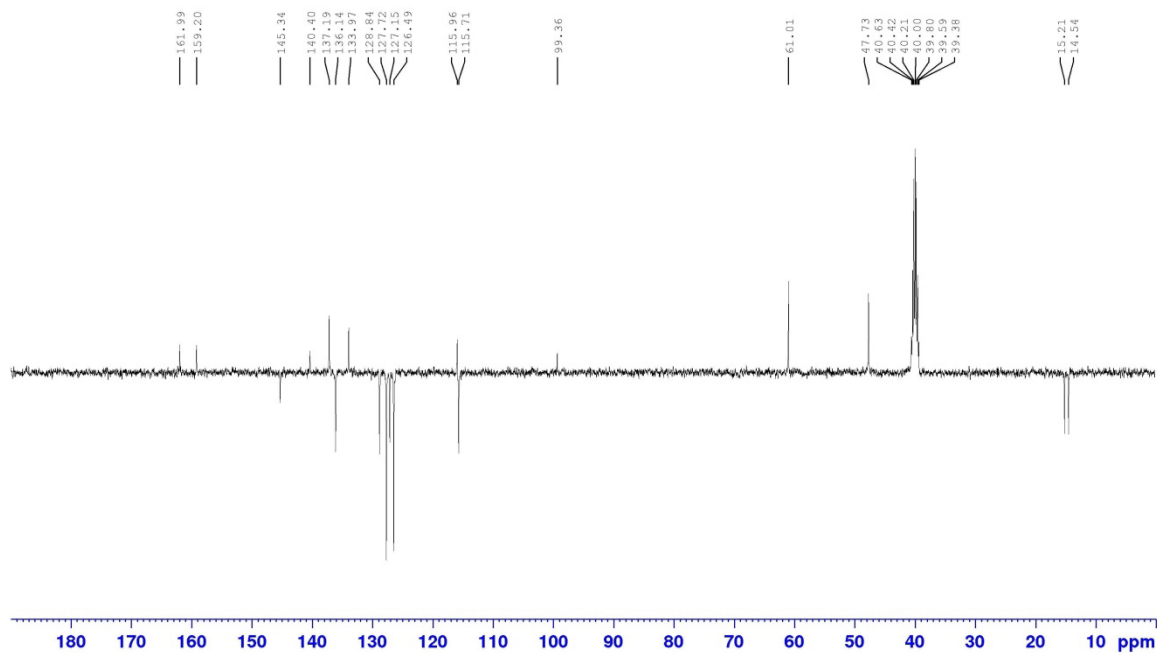
^1H NMR Compound 7b
DMSO

Figure S1. ^1H NMR of Compound 7b.



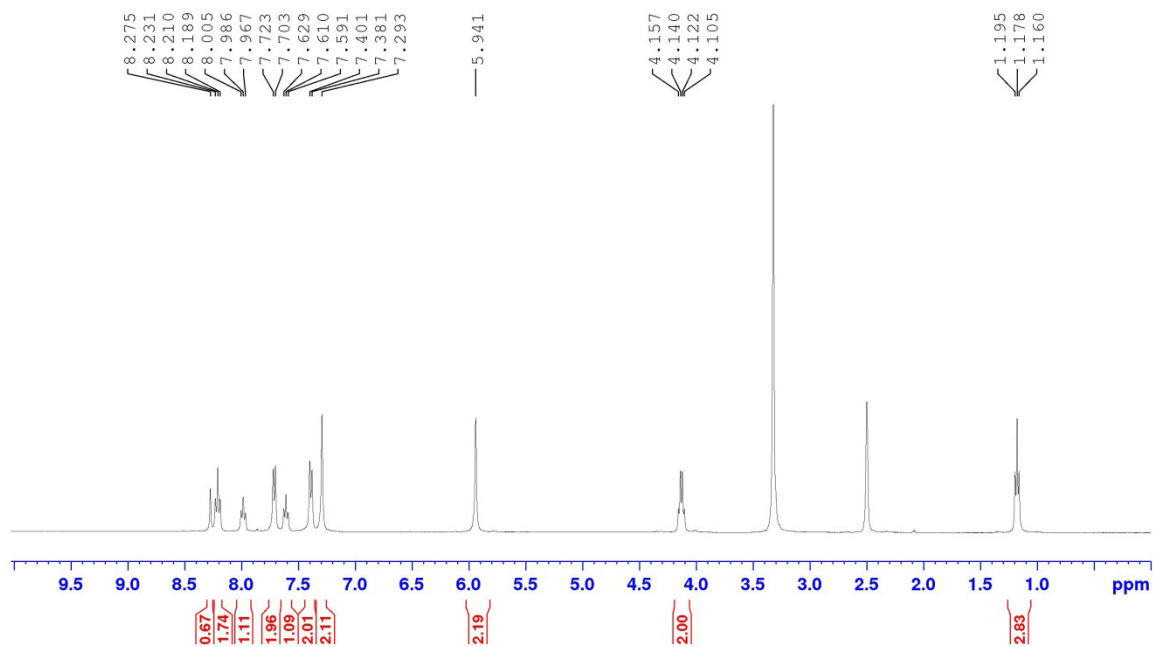
^{13}C NMR Compound 7b
DMSO

Figure S2. ^{13}C NMR of Compound 7b.



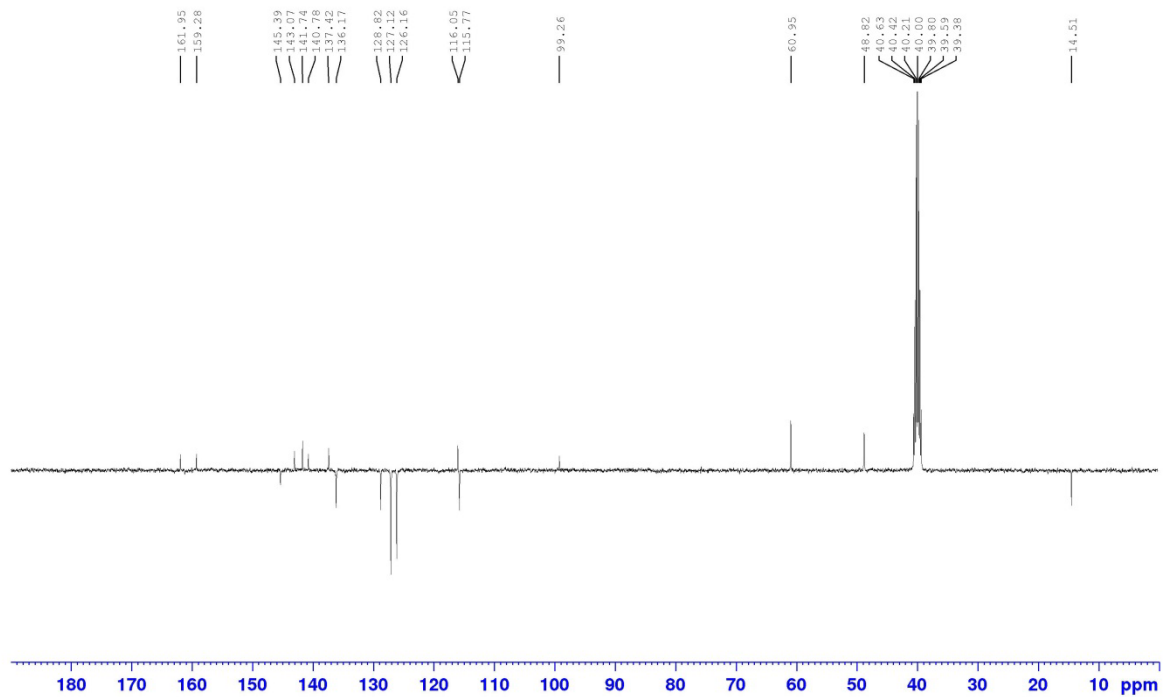
¹H NMR Compound 7c
DMSO

Figure S3. ¹H NMR of Compound 7c.



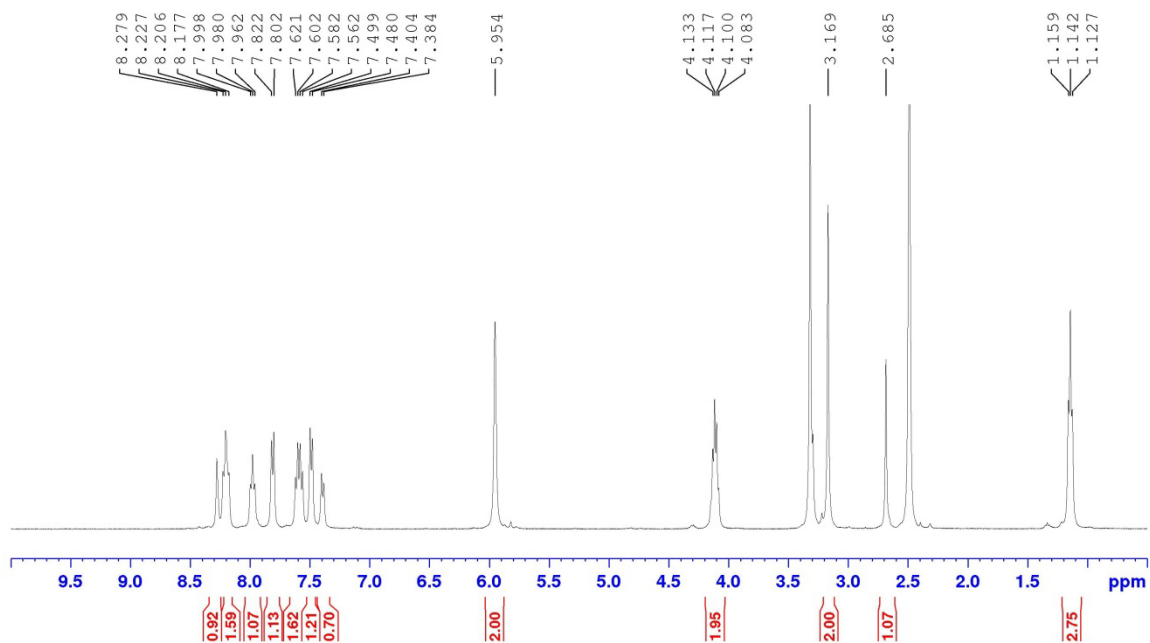
¹³C NMR Compound 7c
DMSO

Figure S4. ¹³C NMR of Compound 7c.



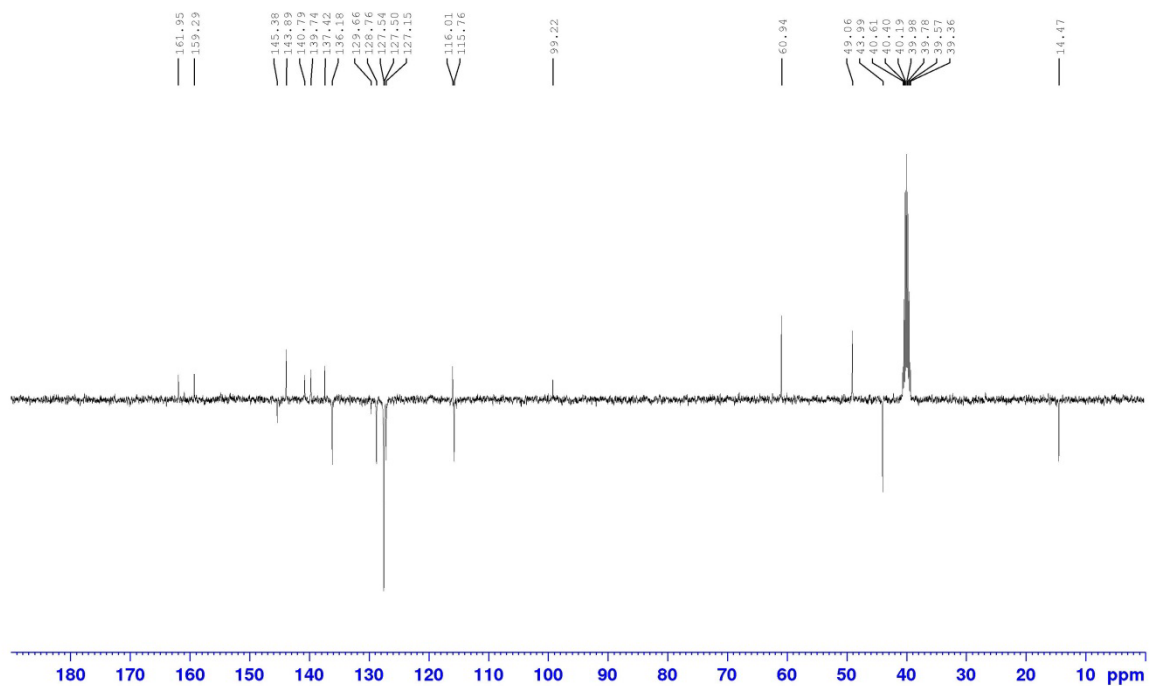
¹H NMR Compound 7d
DMSO

Figure S5. ¹H NMR of Compound 7d.



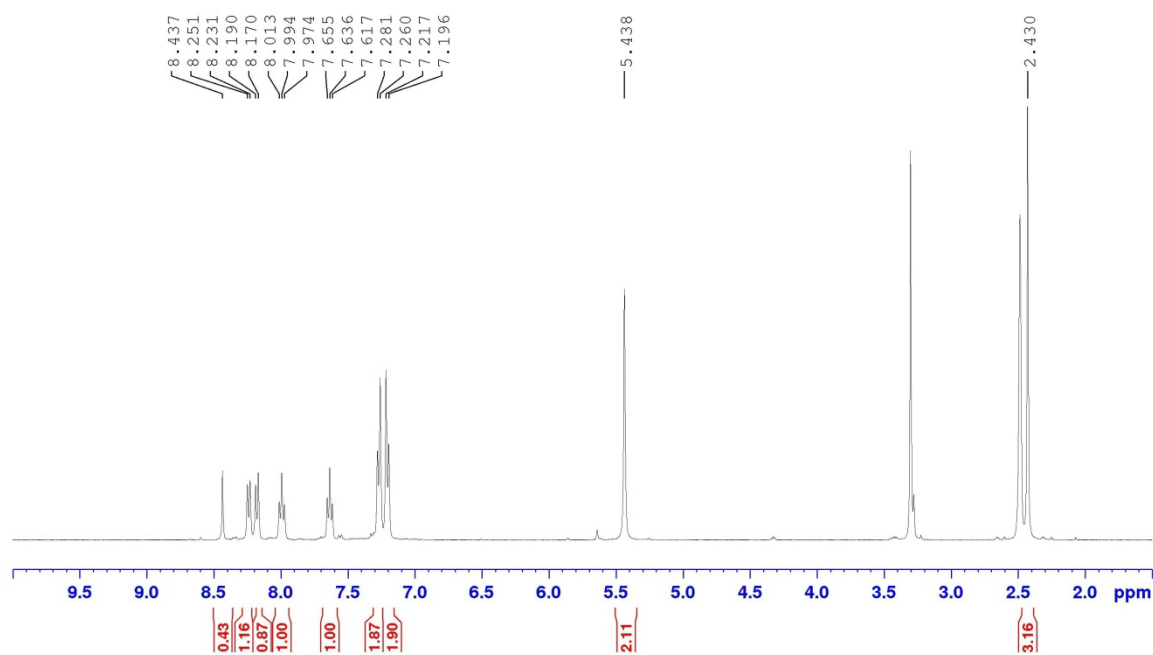
¹³C NMR Compound 7d
DMSO

Figure S6. ¹³C NMR of Compound 7d.



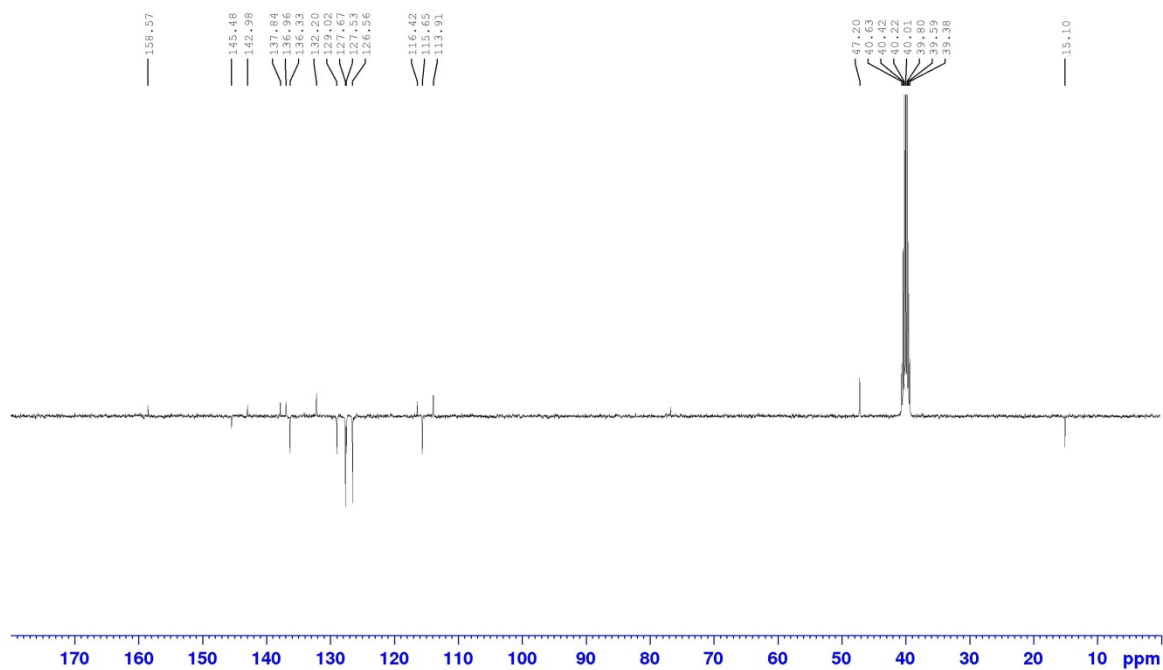
¹H NMR Compound 7e
DMSO

Figure S7. ¹H NMR of Compound 7e.



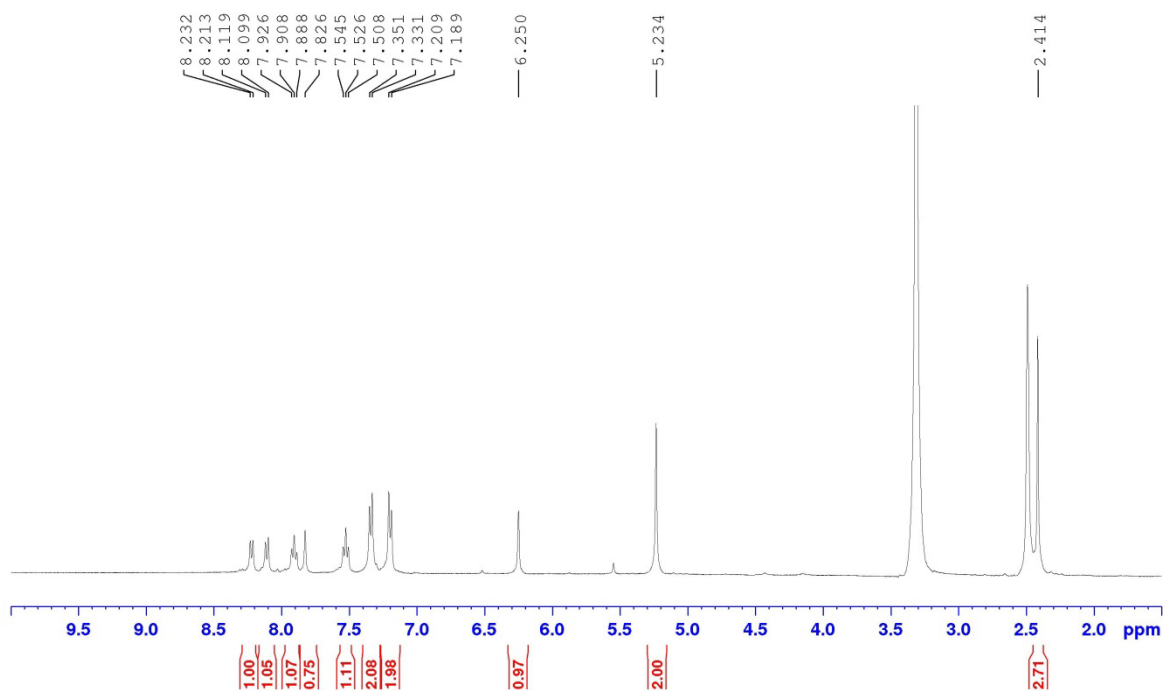
¹³C NMR Compound 7e
DMSO

Figure S8. ¹³C NMR of Compound 7e.



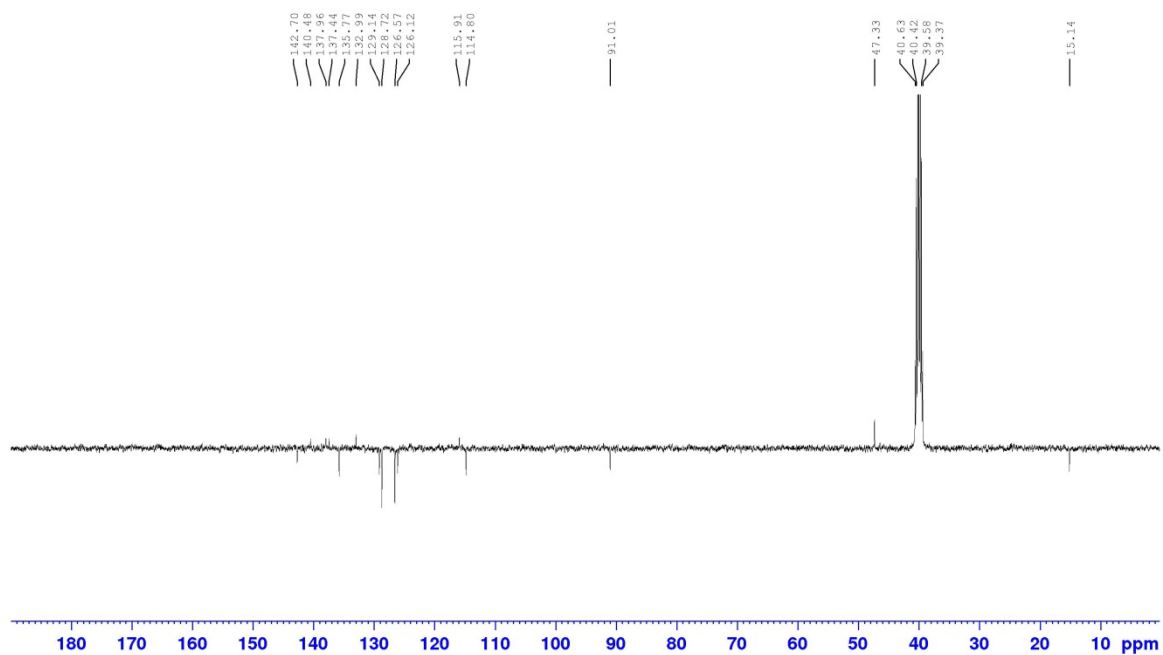
¹H NMR Compound 7f
DMSO

Figure S9. ¹H NMR of Compound 7f.



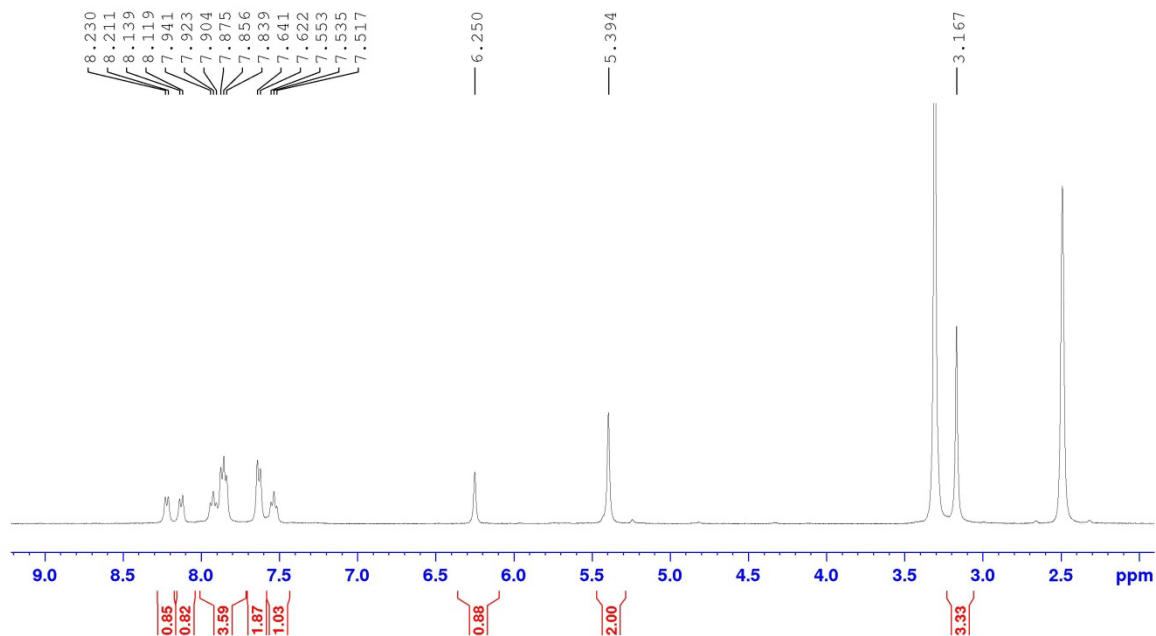
¹³C NMR Compound 7f
DMSO

Figure S10. ¹³C NMR of Compound 7f.



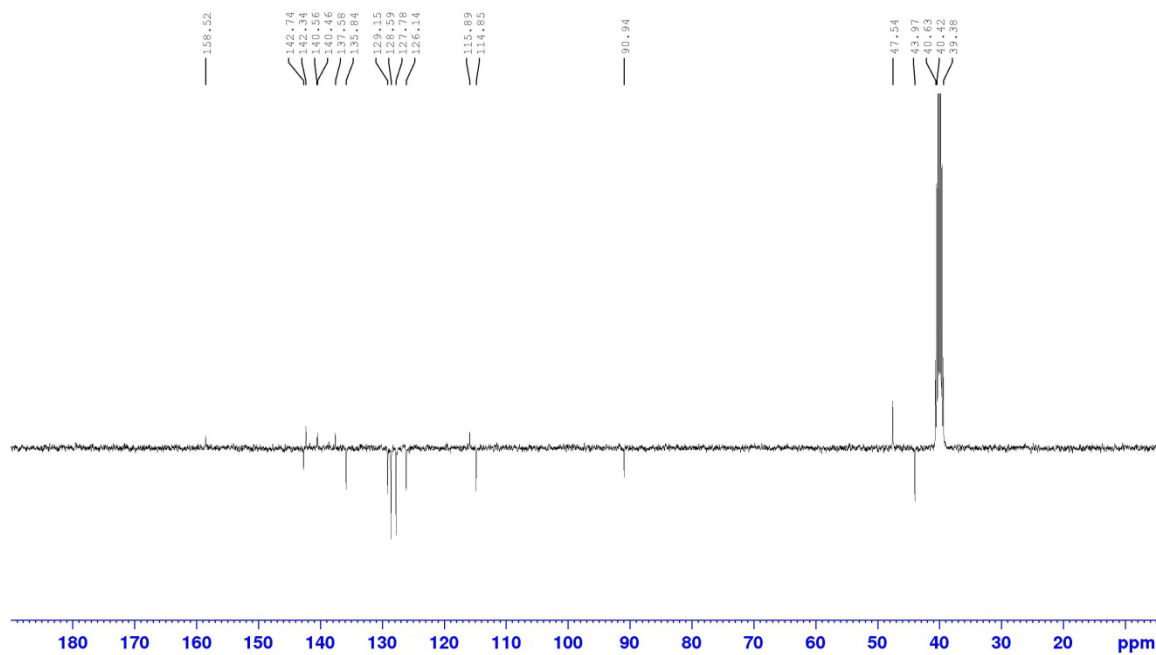
¹H NMR Compound 8
DMSO

Figure S11. ¹H NMR of Compound 8.



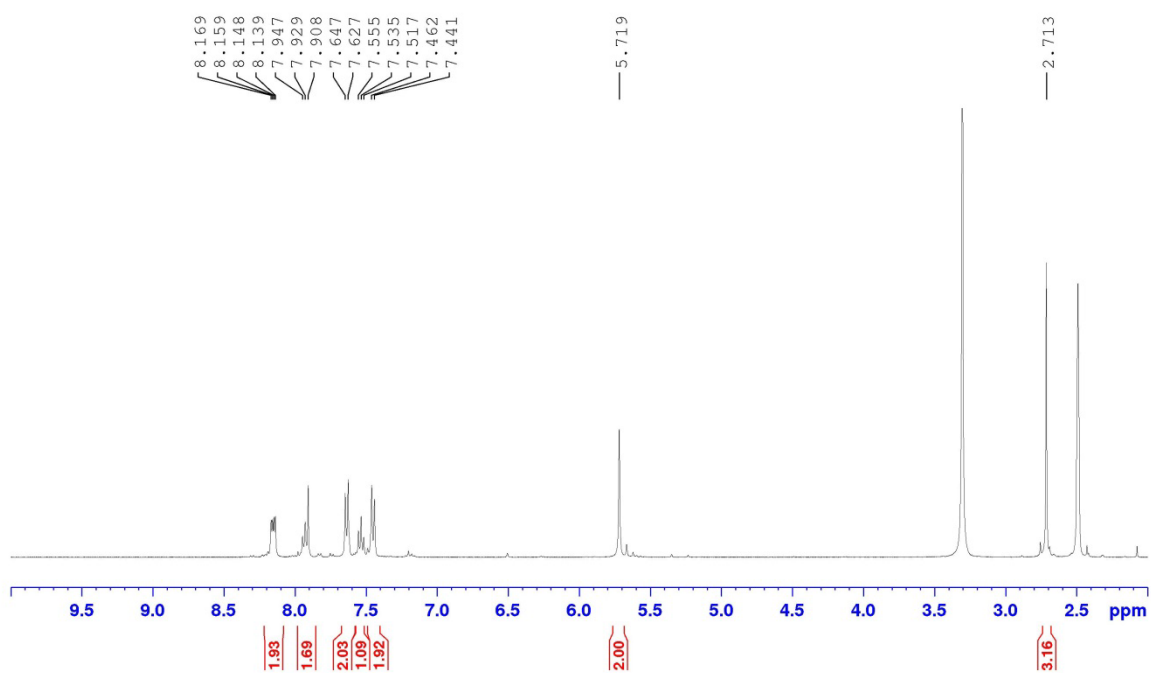
¹³C NMR Compound 8
DMSO

Figure S12. ¹³C NMR of Compound 8.



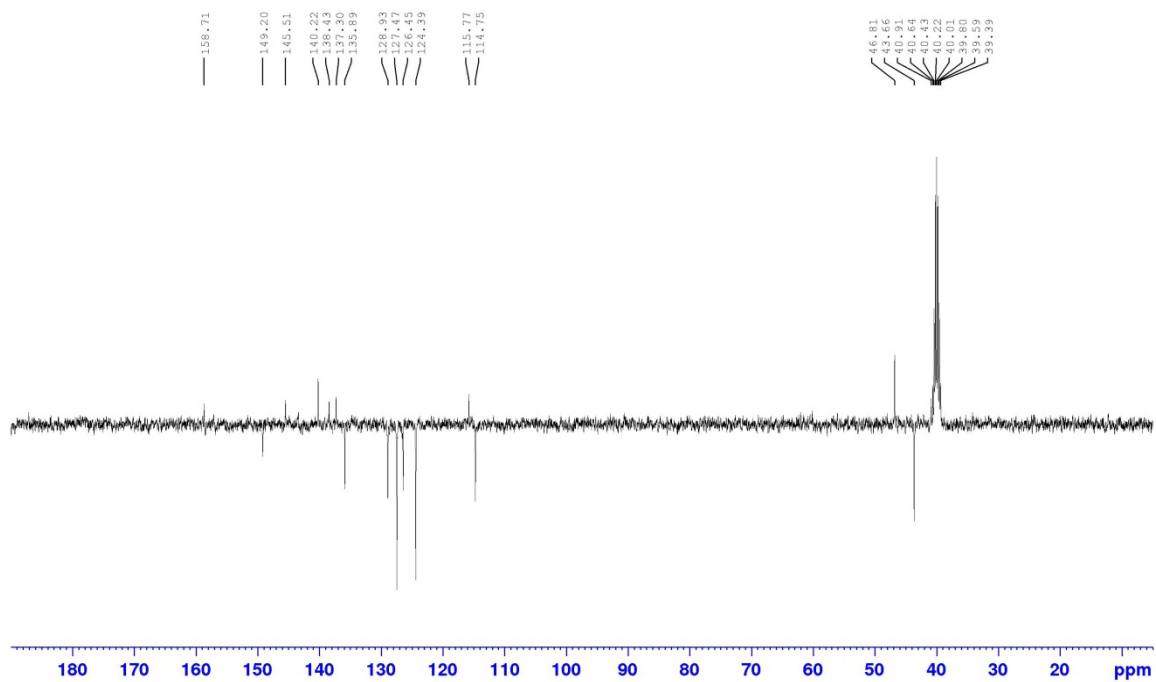
¹H NMR Compound 9
DMSO

Figure S13. ¹H NMR of Compound 9.



¹³C NMR Compound 9
DMSO

Figure S14. ¹³C NMR of Compound 9.



¹H NMR Compound 10
DMSO

Figure S15. ¹H NMR of Compound 10.

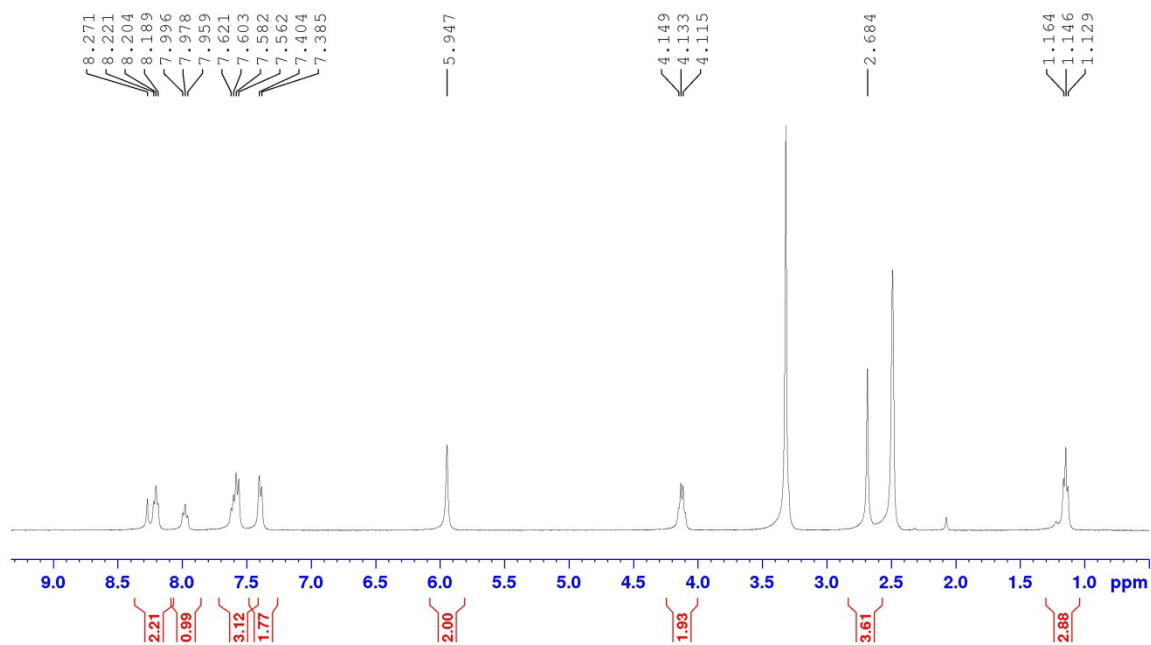
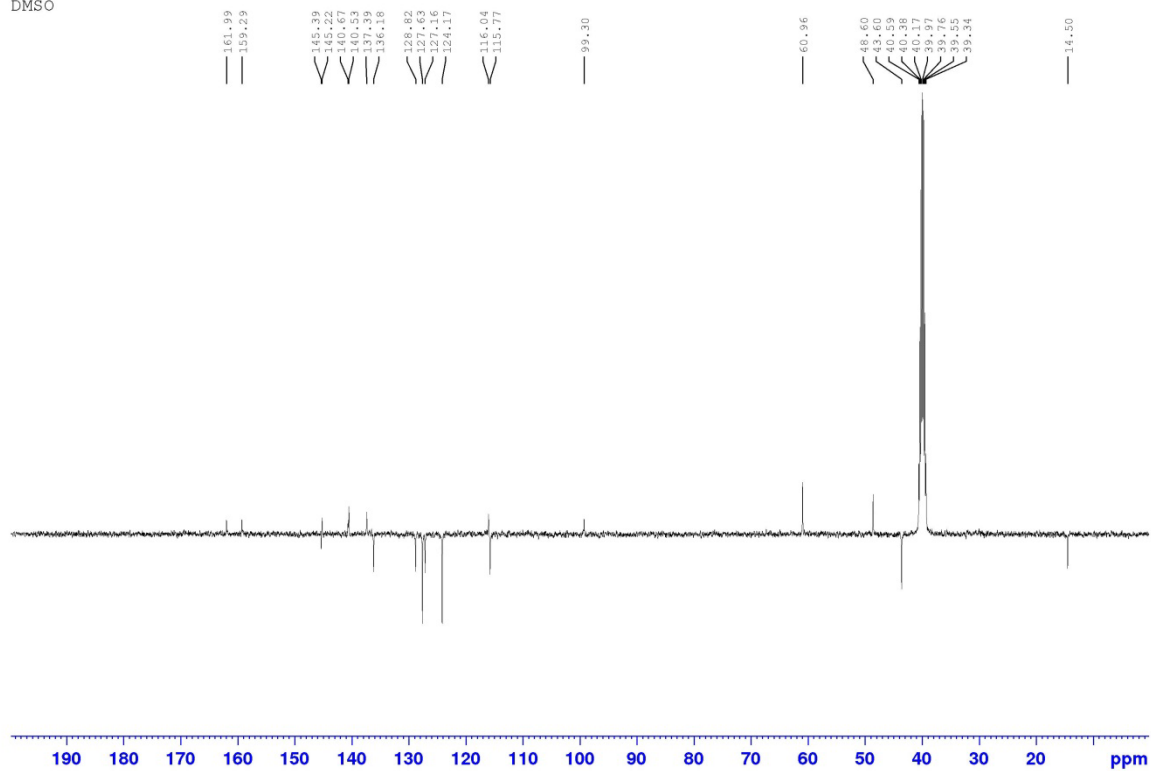


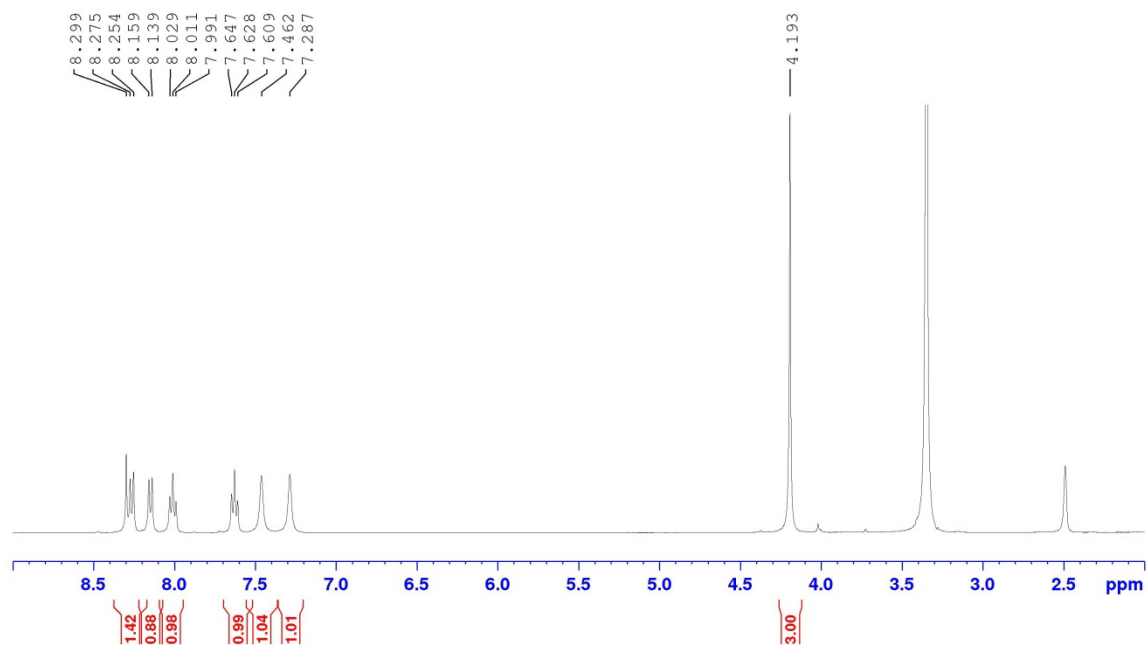
Figure S16. ¹³C NMR of Compound 10.

¹³C NMR Compound 10
DMSO



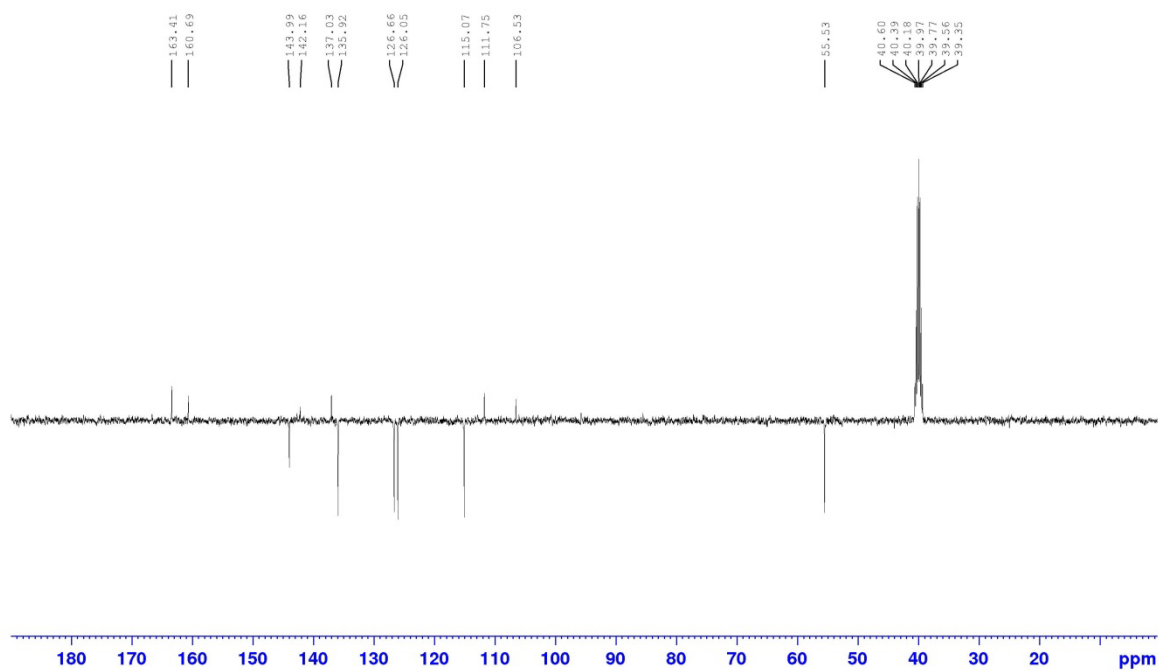
¹H NMR Compound 13a
DMSO

Figure S17. ¹H NMR of Compound 13a.



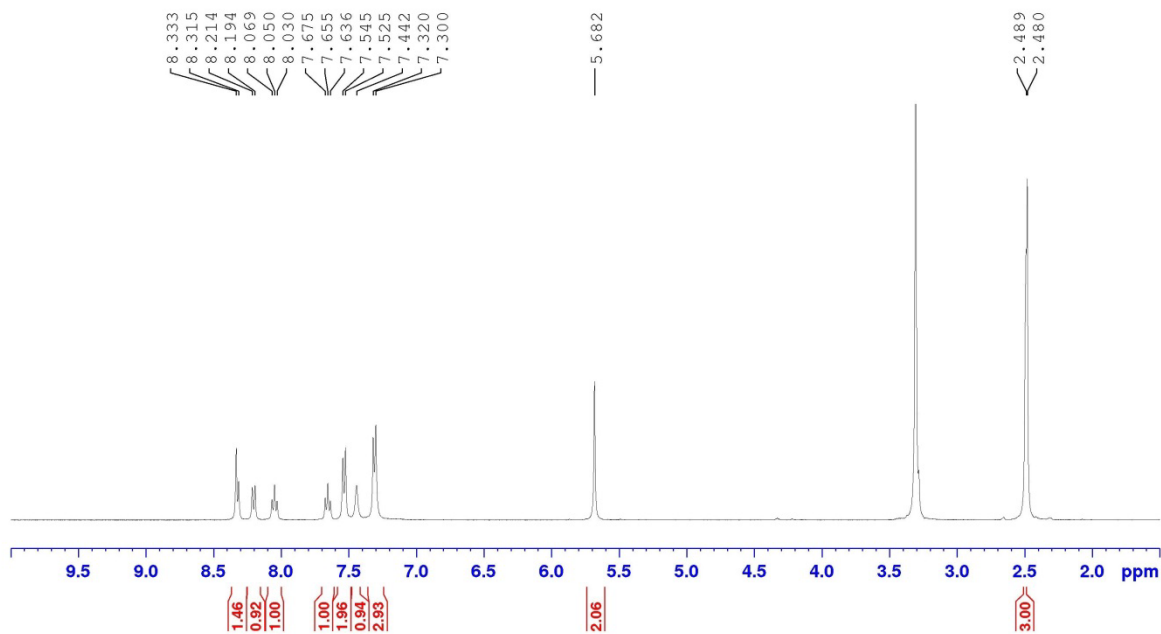
¹³C NMR Compound 13a
DMSO

Figure S18. ¹³C NMR of Compound 13a.



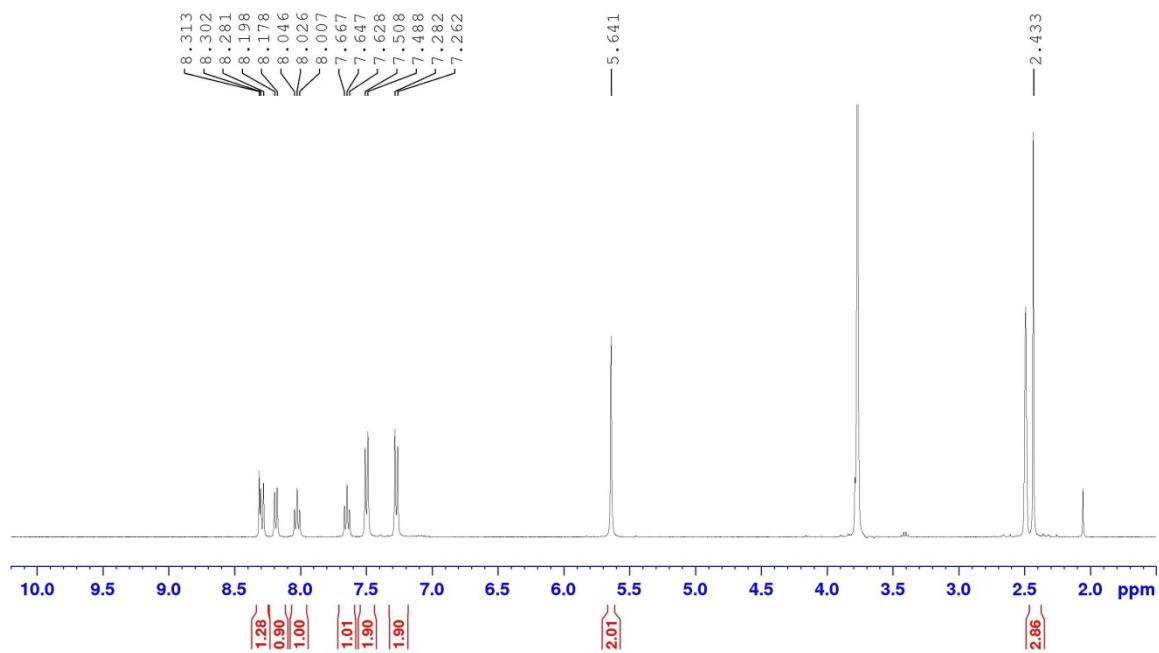
¹H NMR Compound 13c
DMSO

Figure S19. ¹H NMR of Compound 13c.



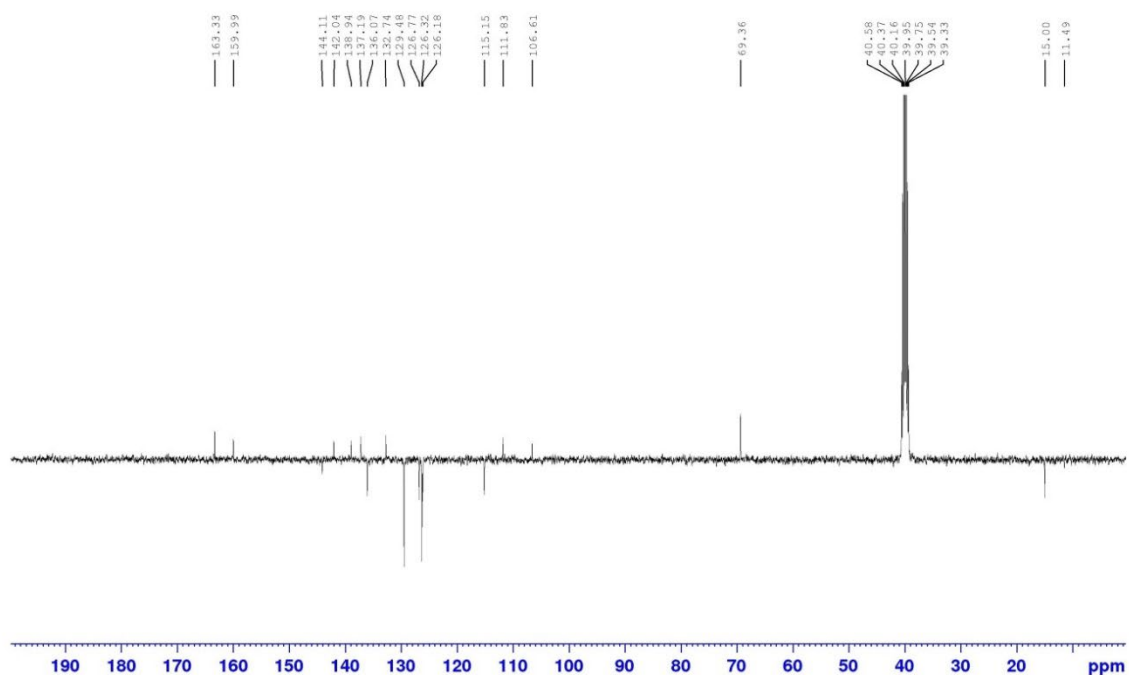
¹H NMR Compound 13c
DMSO + D₂O

Figure S20. ¹H NMR of Compound 13c + D₂O



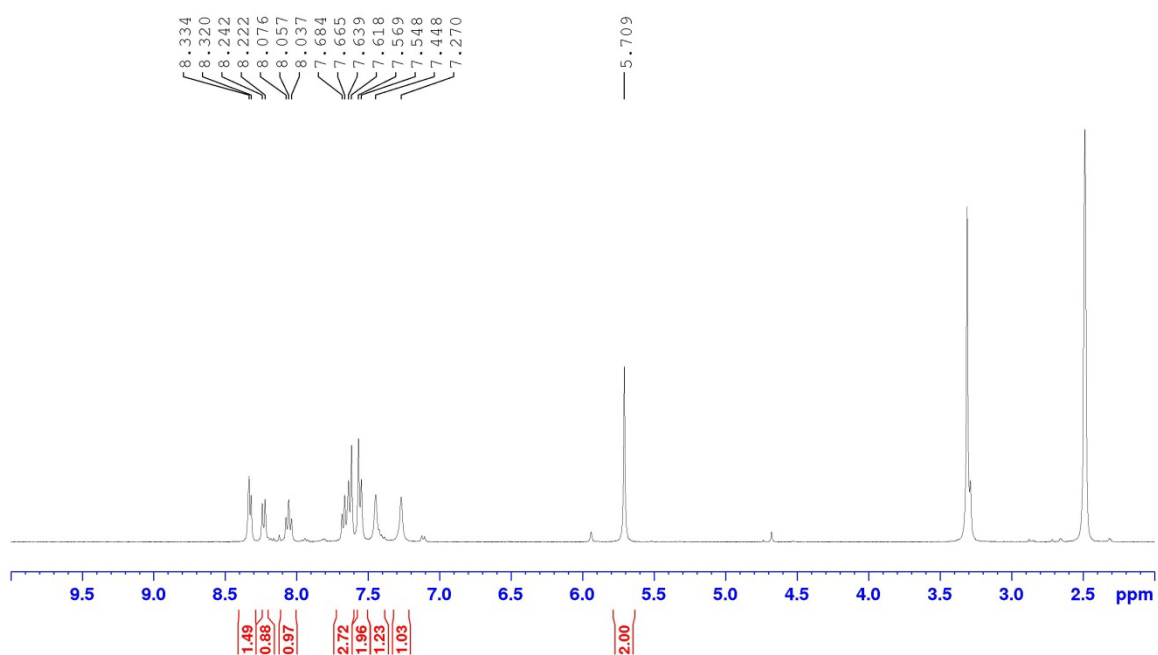
¹³C NMR Compound 13c
DMSO

Figure S21. ¹³C NMR of Compound 13c.



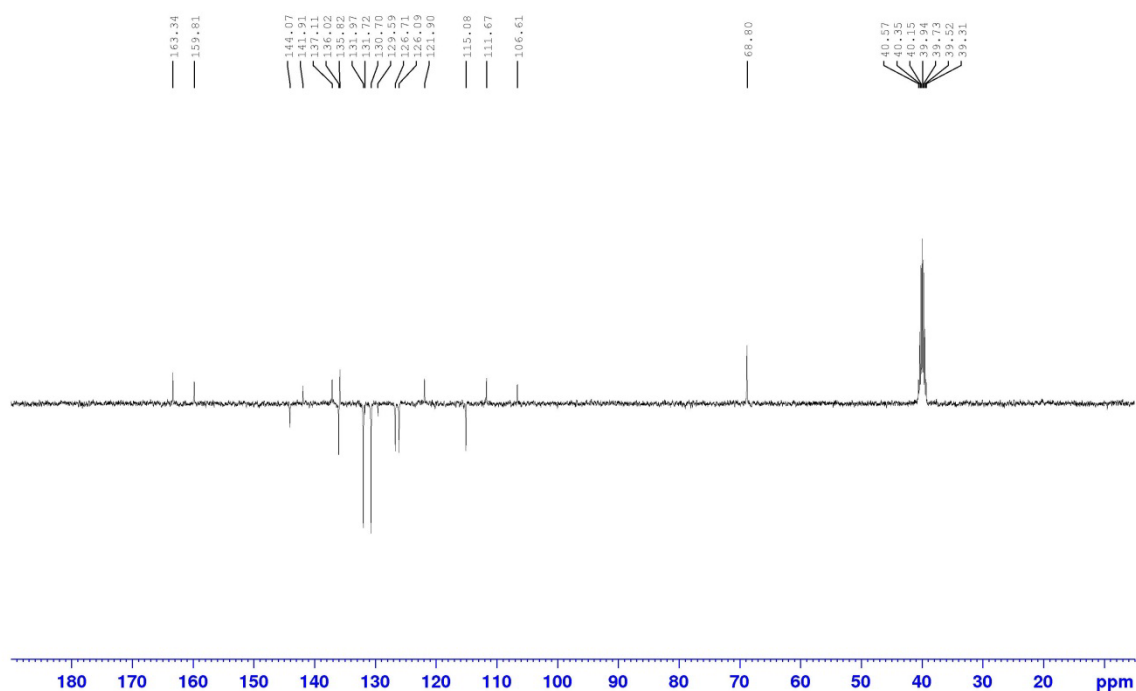
¹H NMR Compound 13f
DMSO

Figure S22. ¹H NMR of Compound 13f.



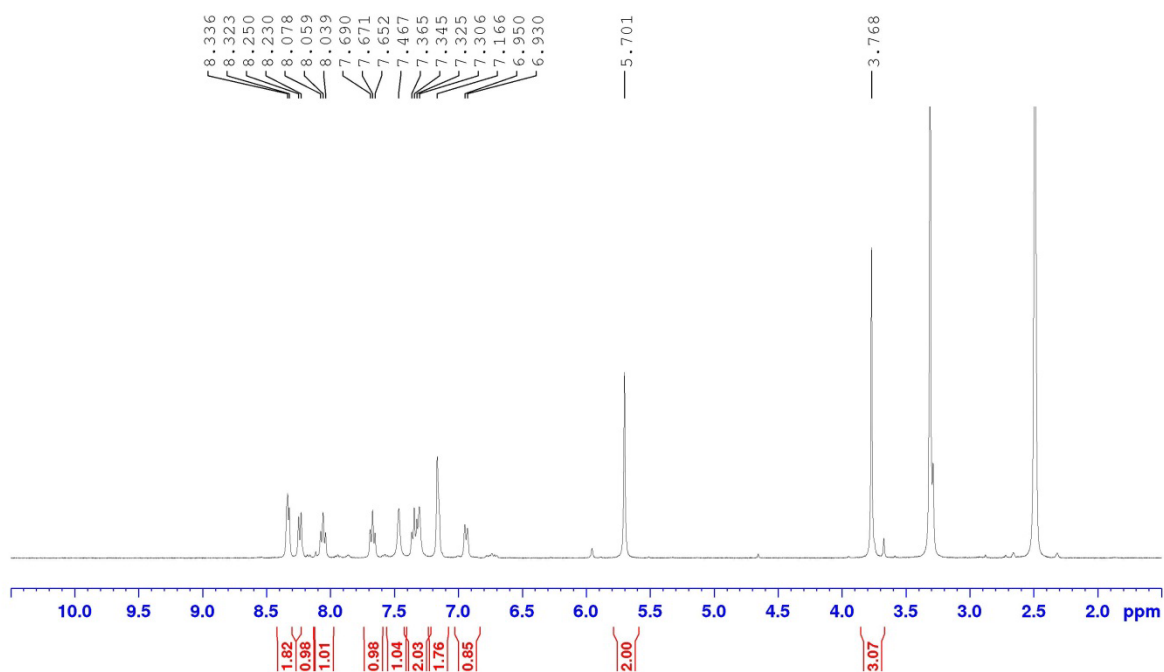
¹³C NMR Compound 13f
DMSO

Figure S23. ¹³C NMR of Compound 13f.



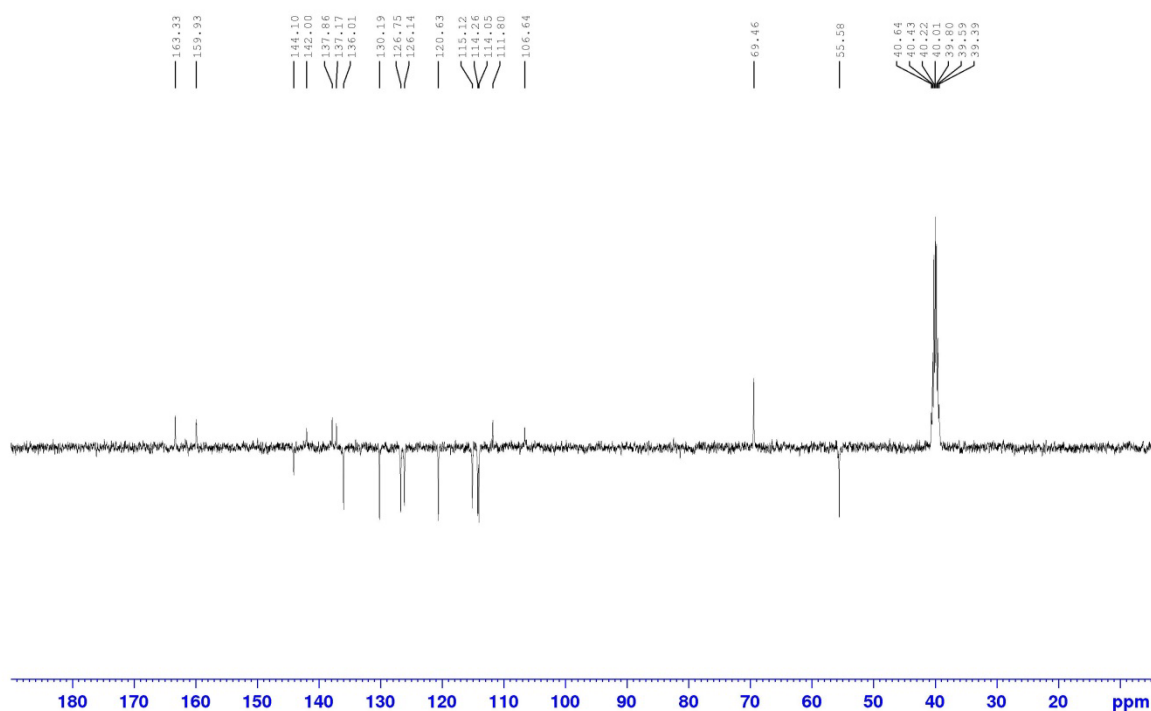
¹H NMR Compound 13h
DMSO

Figure S24. ¹H NMR of Compound 13h.



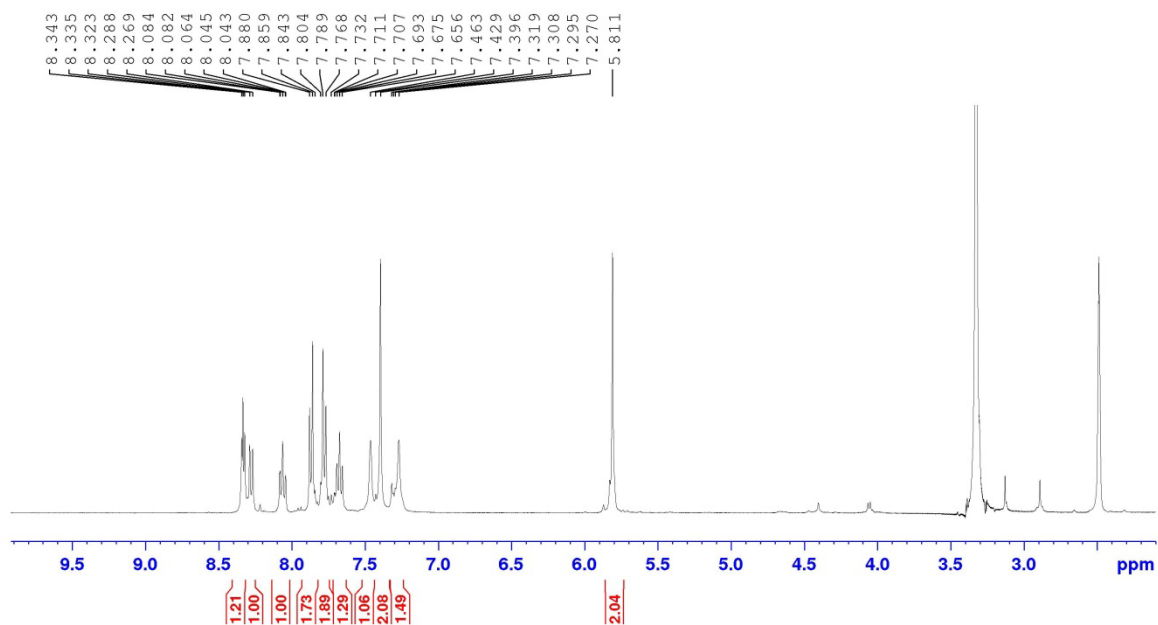
¹³C NMR Compound 13h
DMSO

Figure S25. ¹³C NMR of Compound 13h.



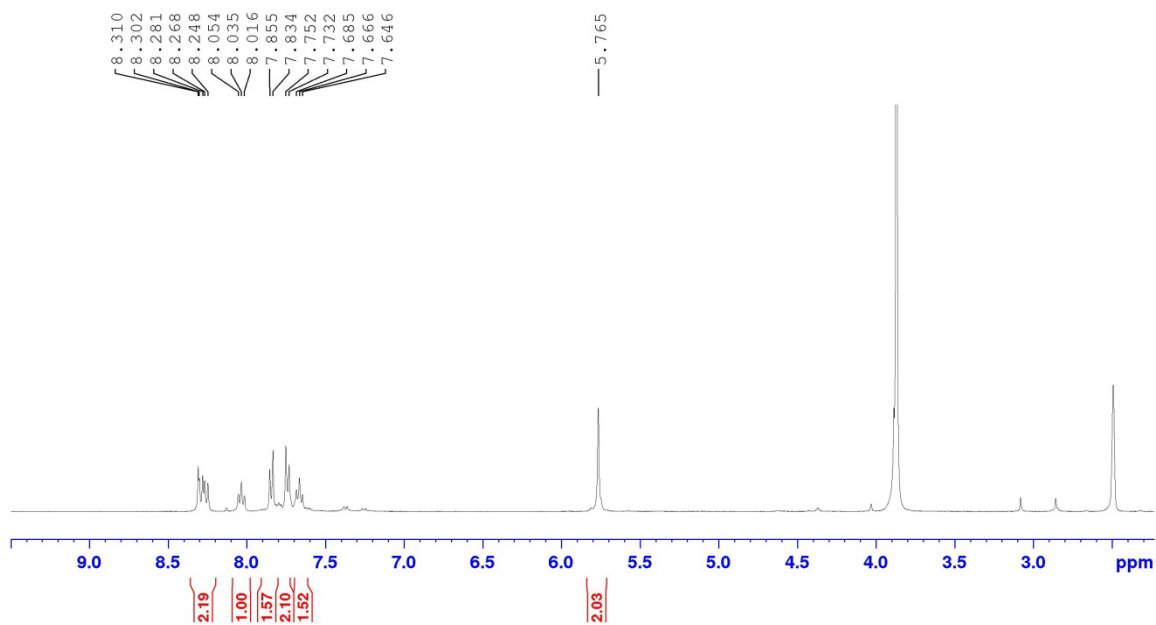
¹H NMR Compound 13i
DMSO

Figure S26. ¹H NMR of Compound 13i.



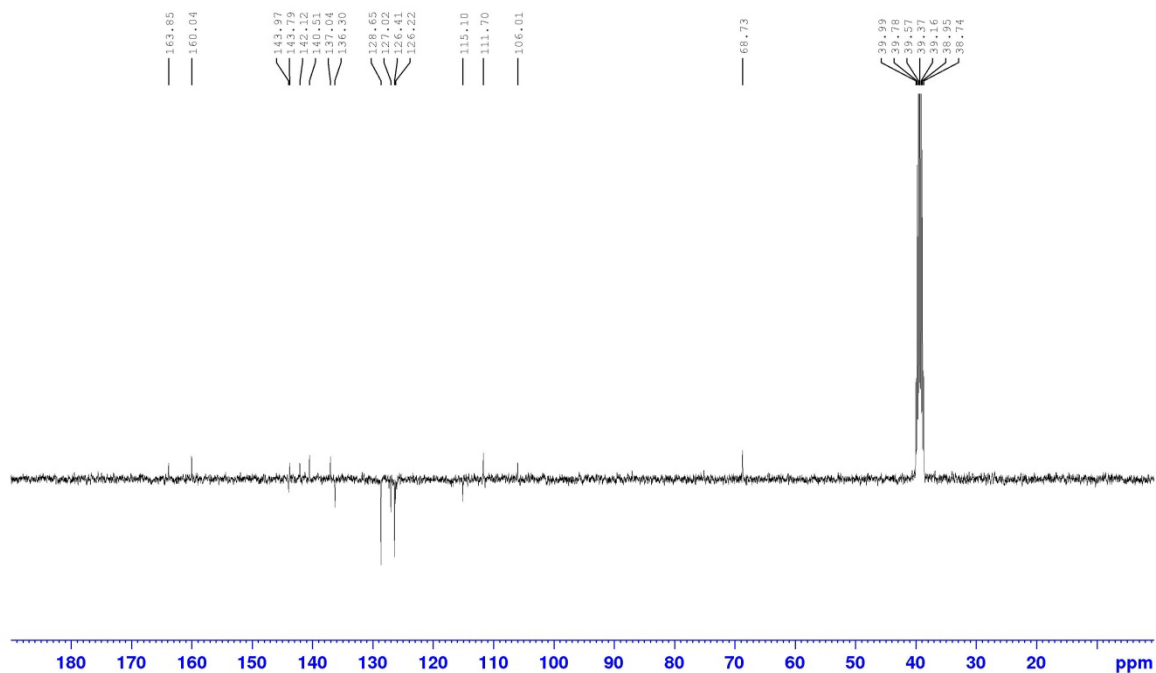
¹H NMR Compound 3i
DMSO + D₂O

Figure S27. ¹H NMR of Compound 13i + D₂O.



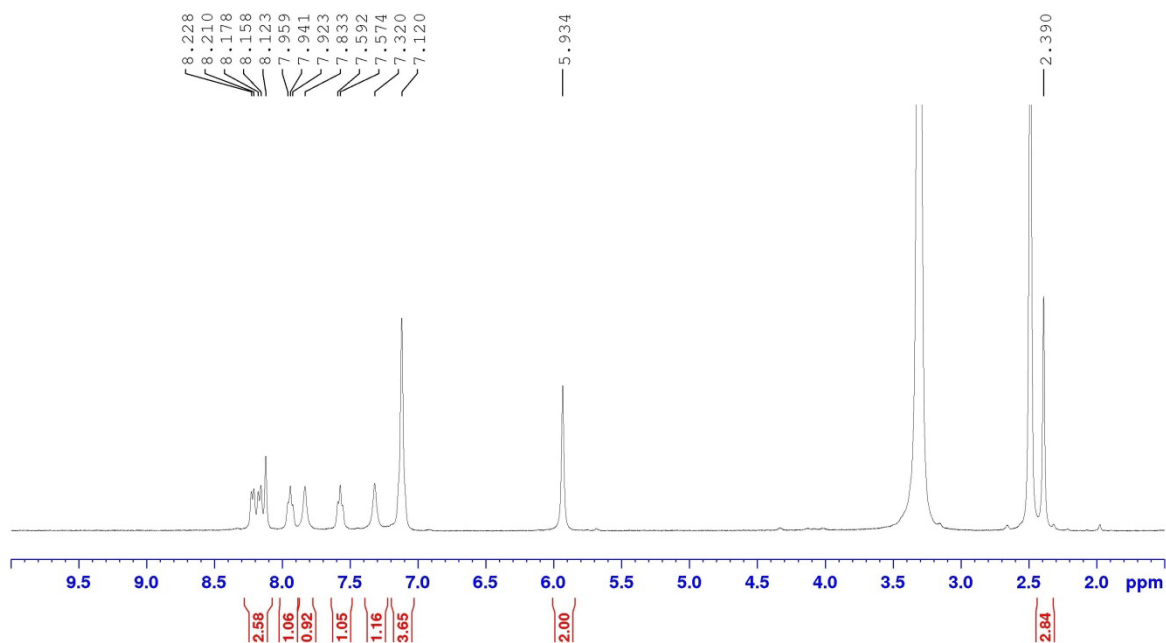
¹³C NMR Compound 13i
DMSO

Figure S28. ¹³C NMR of Compound 13i.



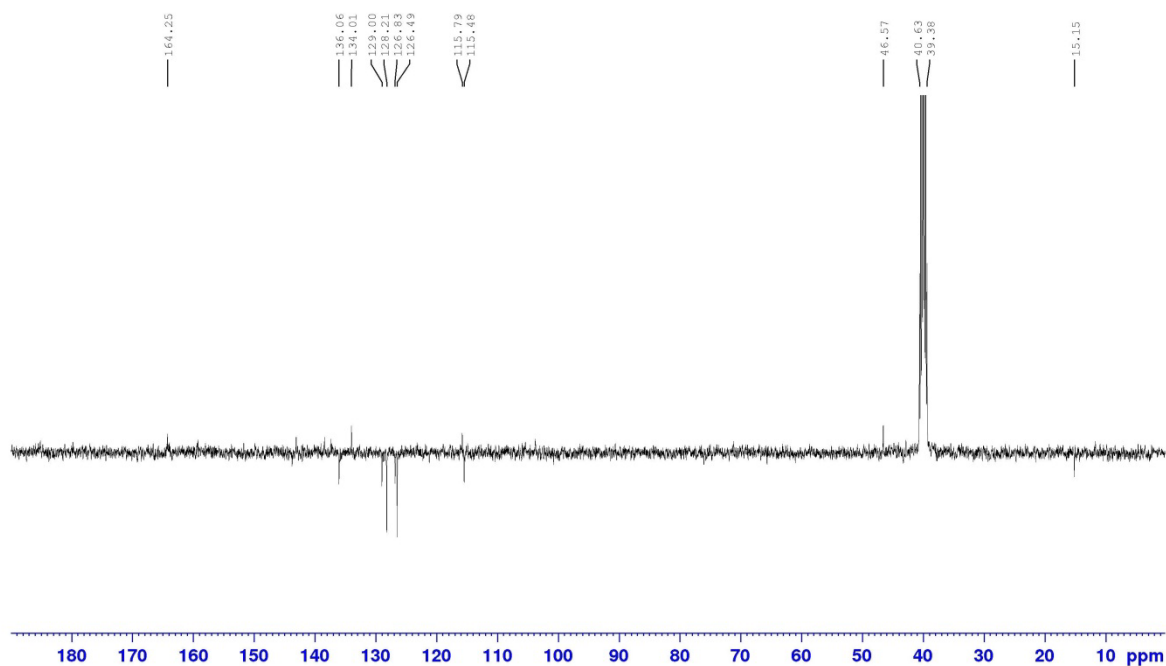
¹H NMR Compound 14c
DMSO

Figure S29. ¹H NMR of Compound 14c.



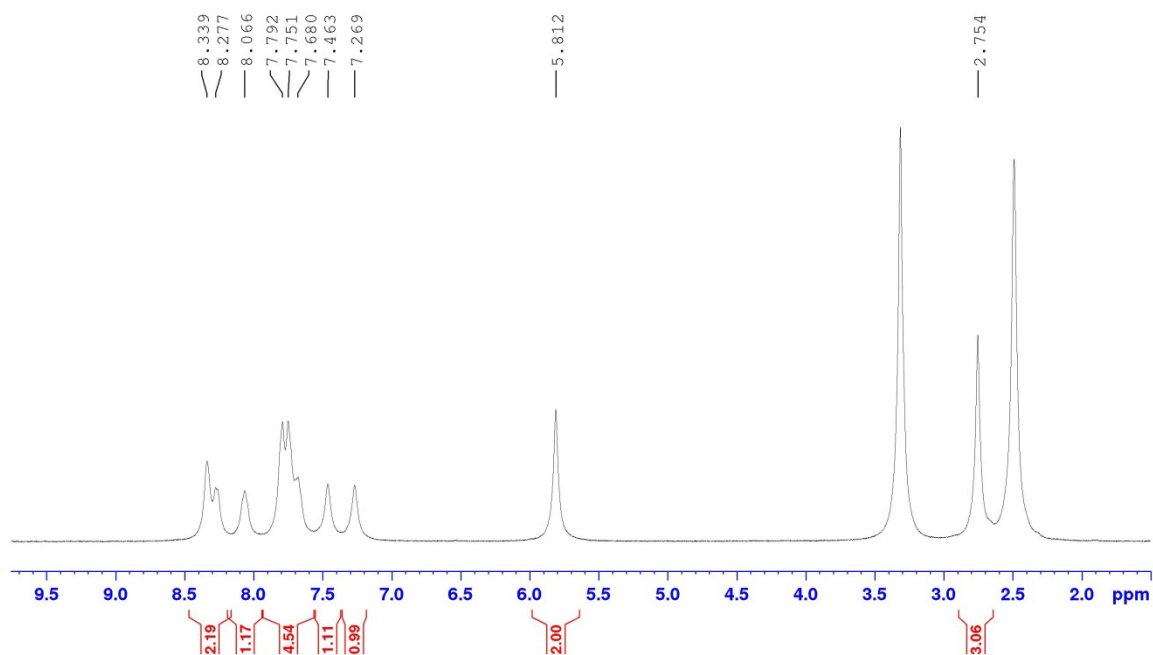
¹³C NMR Compound 14c
DMSO

Figure S30. ¹³C NMR of Compound 14c.



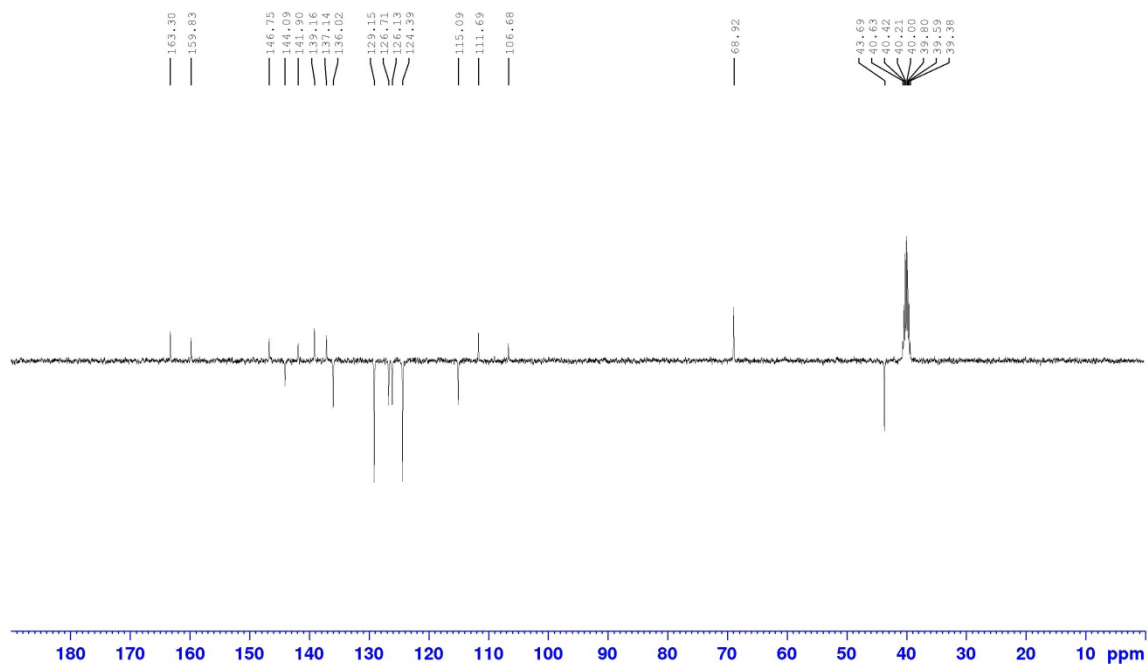
¹H NMR Compound 16
DMSO

Figure S31. ¹H NMR of Compound 16.



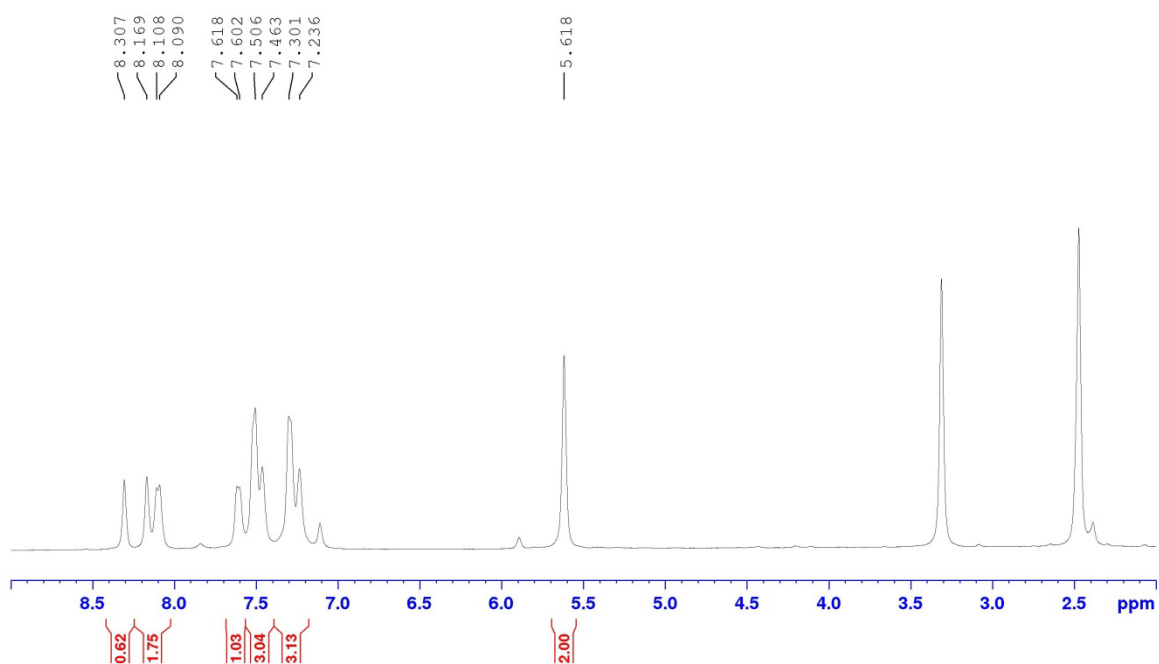
¹³C NMR Compound 16
DMSO

Figure S32. ¹³C NMR of Compound 16.



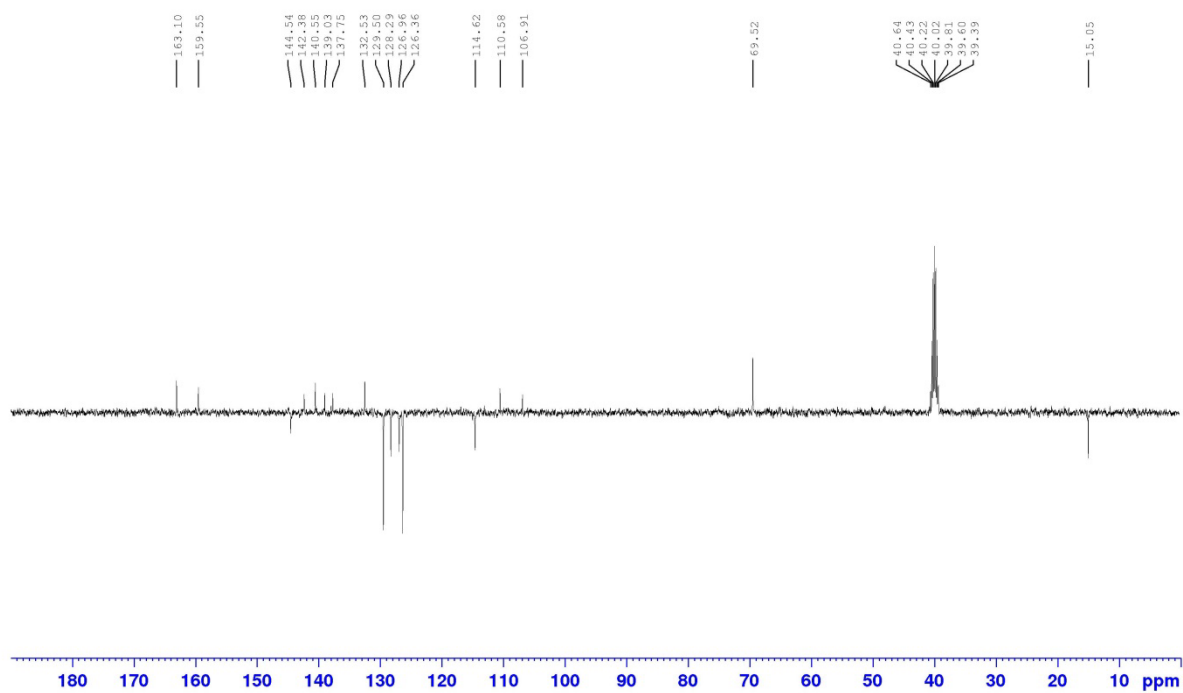
¹H NMR Compound 23b
DMSO

Figure S33. ¹H NMR of Compound 23b.



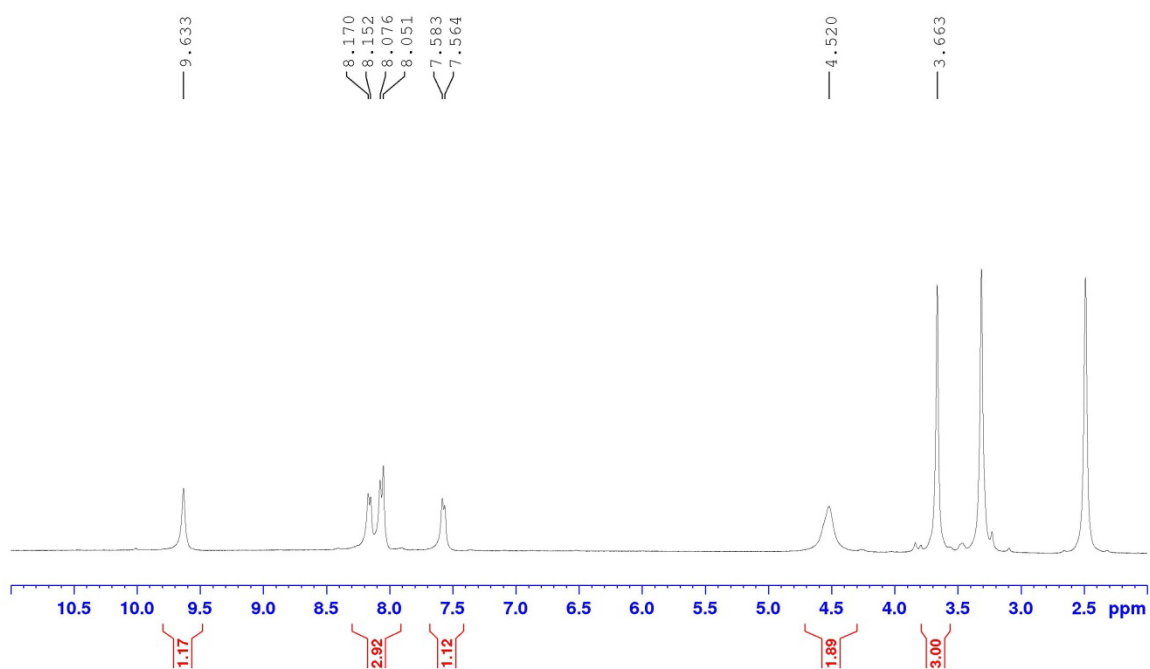
¹³C NMR Compound 23b
DMSO

Figure S34. ¹³C NMR of Compound 23b.



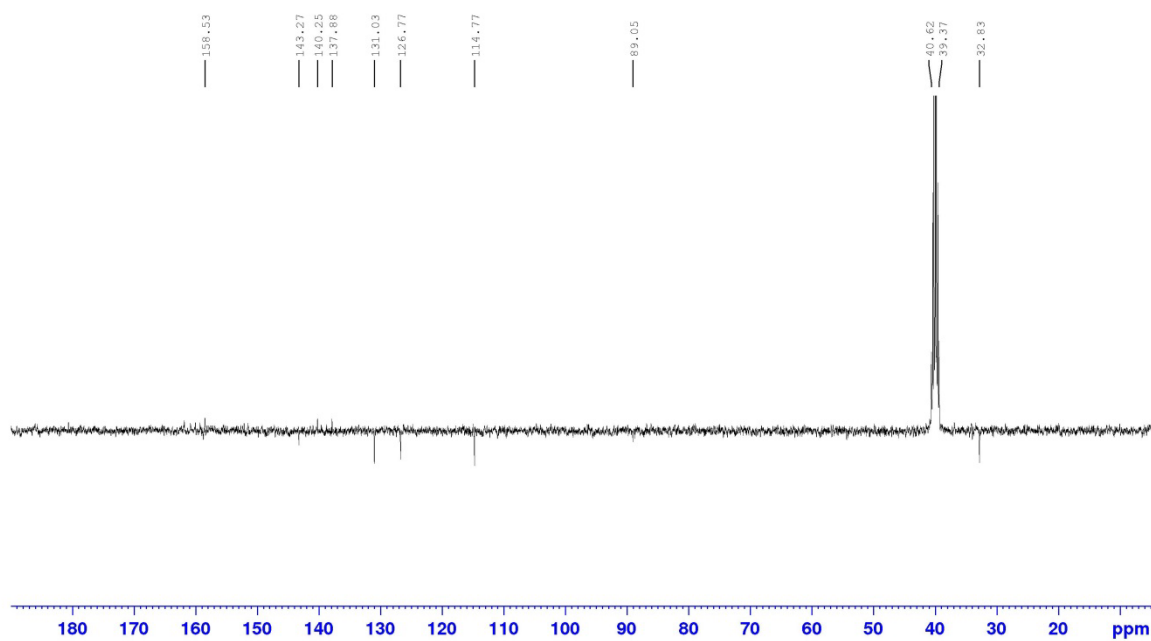
¹H NMR Compound 29
DMSO

Figure S35. ¹H NMR of Compound 29.



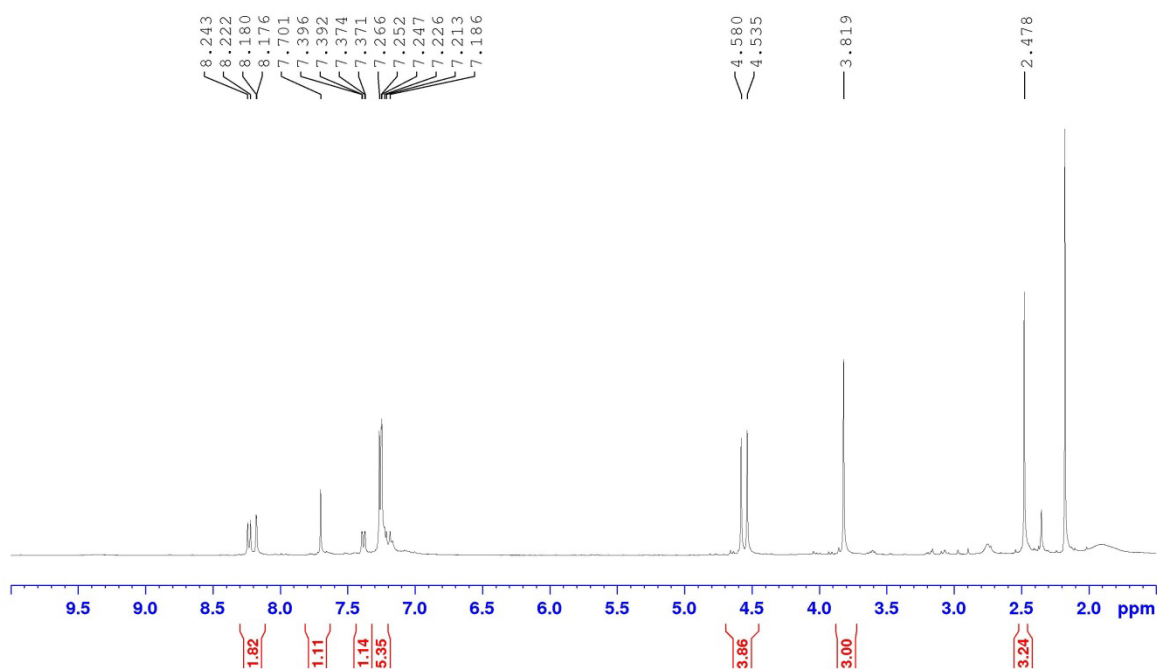
¹³C NMR Compound 29
DMSO

Figure S36. ¹³C NMR of Compound 29.



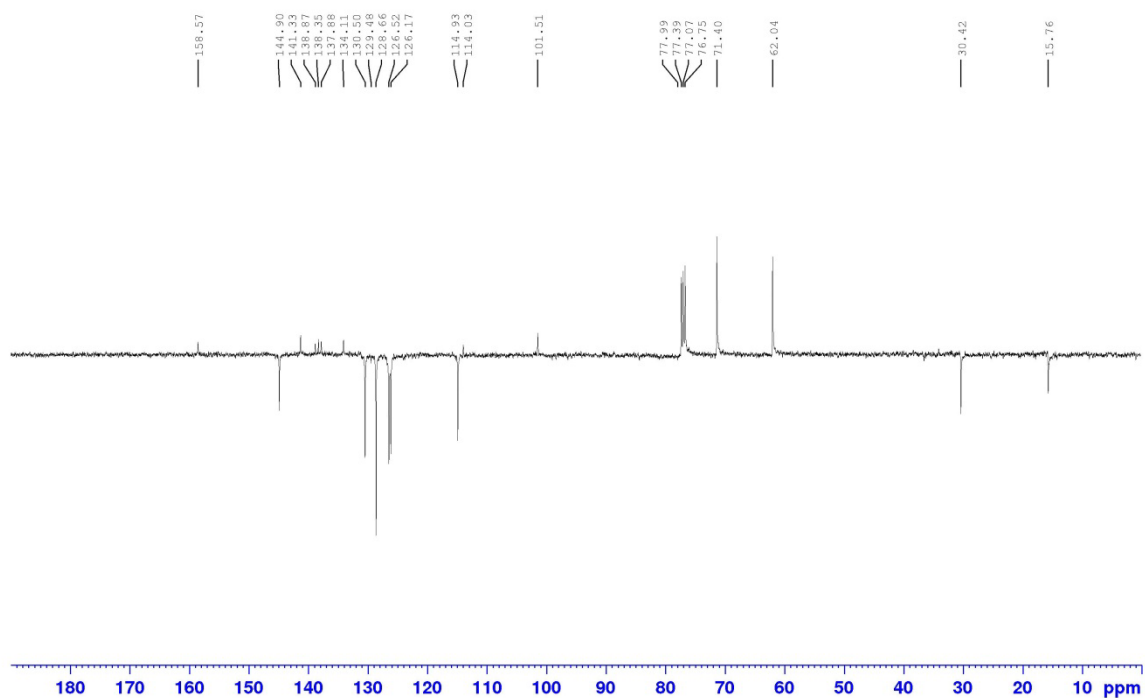
¹H NMR Compound 31
CDCl₃

Figure S37. ¹H NMR of Compound 31.



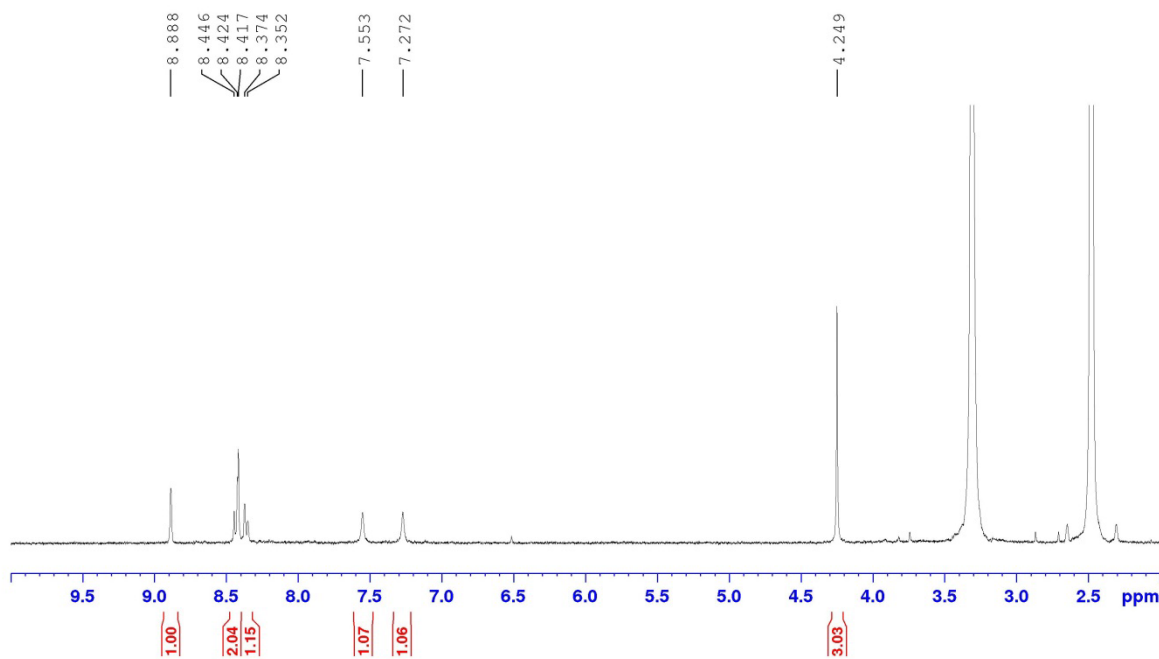
¹³C NMR Compound 31
CDCl₃

Figure S38. ¹³C NMR of Compound 31.



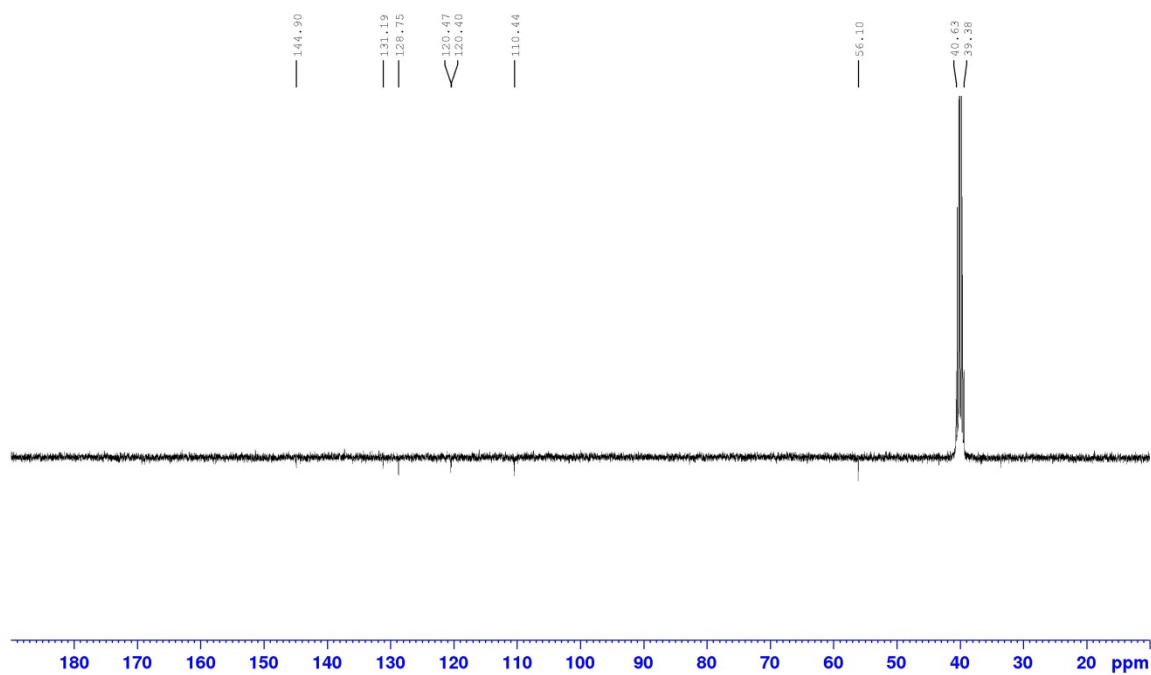
¹H NMR Compound 33a
DMSO

Figure S39. ¹H NMR of Compound 33a.



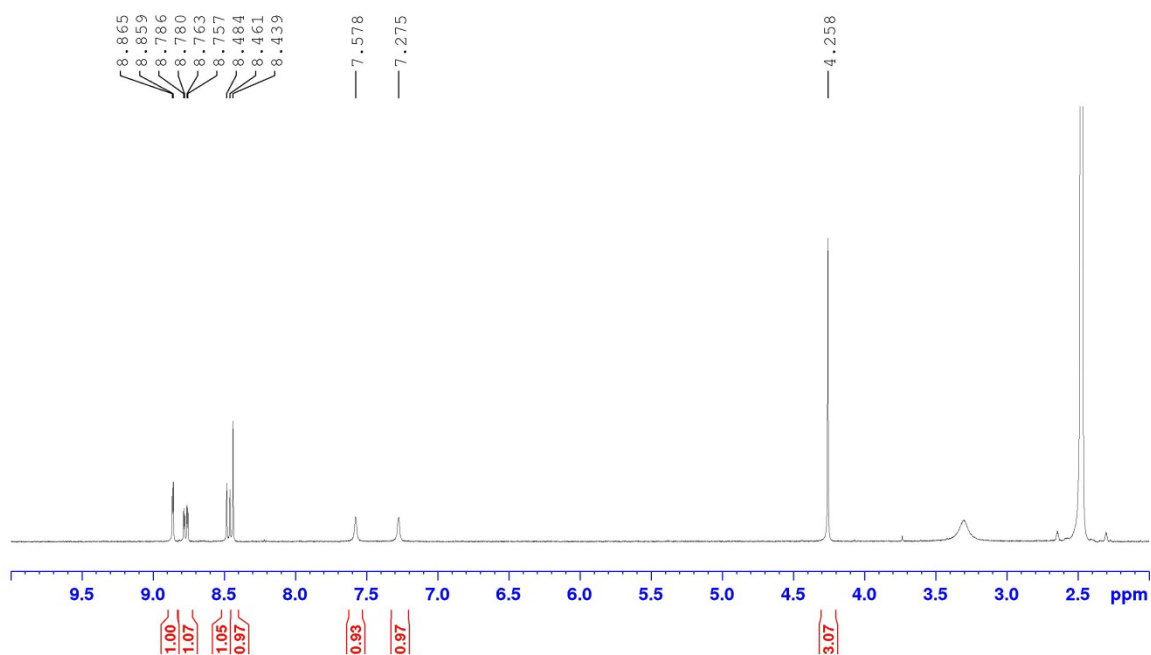
¹³C NMR Compound 33a
DMSO

Figure S40. ¹³C NMR of Compound 33a.



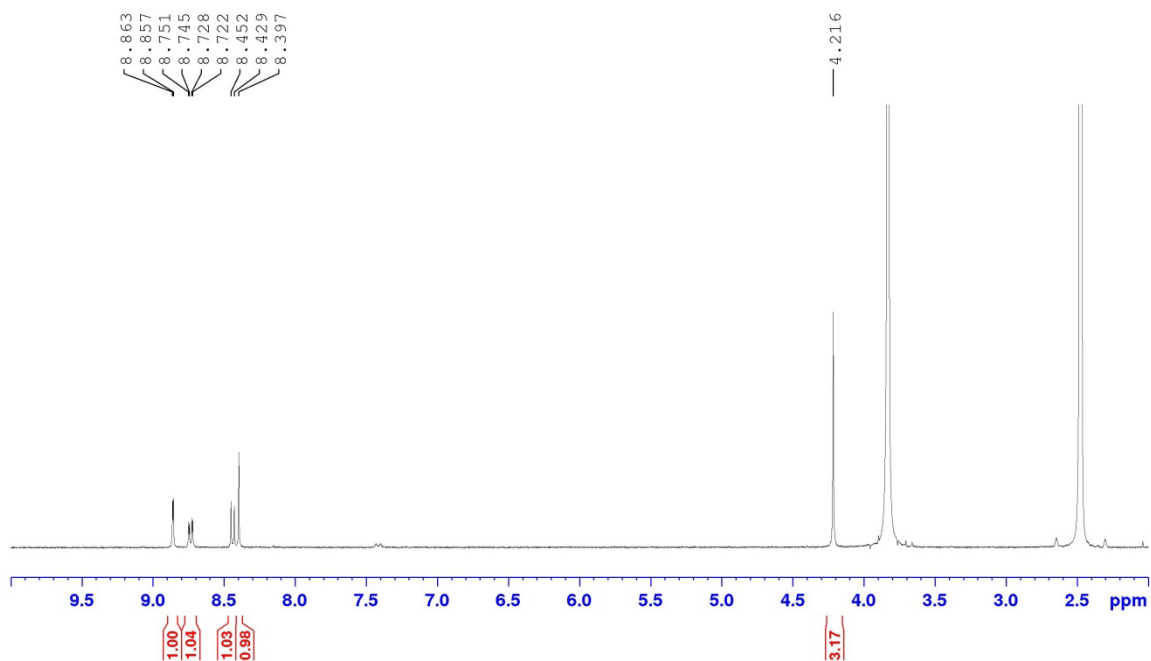
¹H NMR Compound 33b
DMSO

Figure S41. ¹H NMR of Compound 33b.



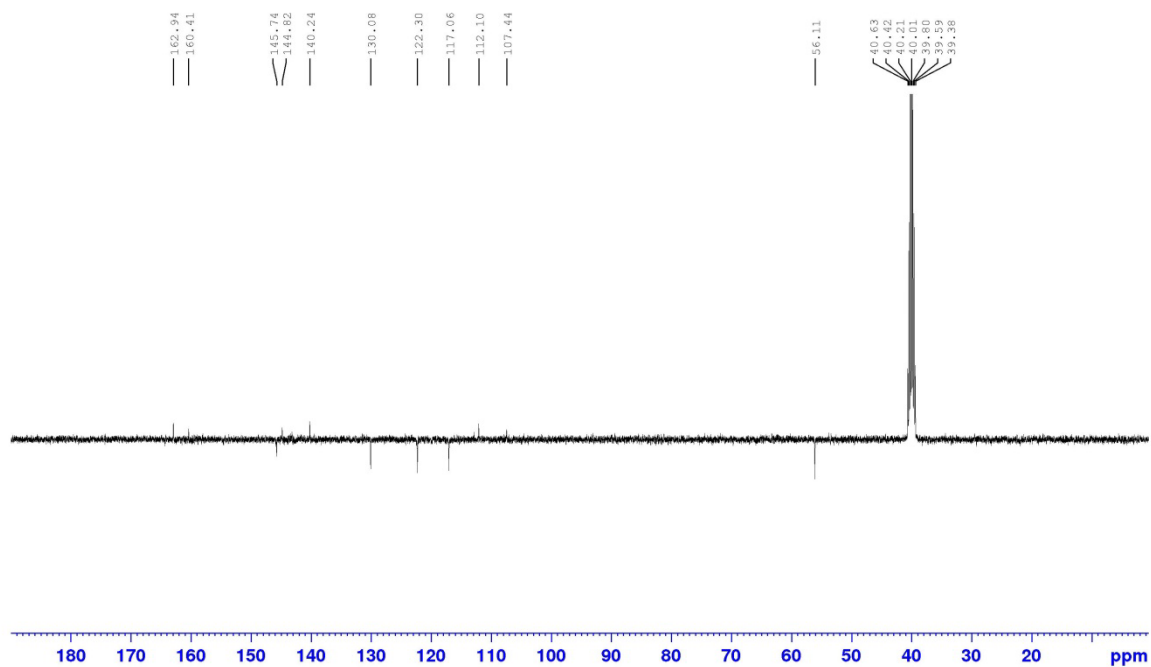
¹H NMR Compound 33b
DMSO + D₂O

Figure S42. ¹H NMR of Compound 33b + D₂O.



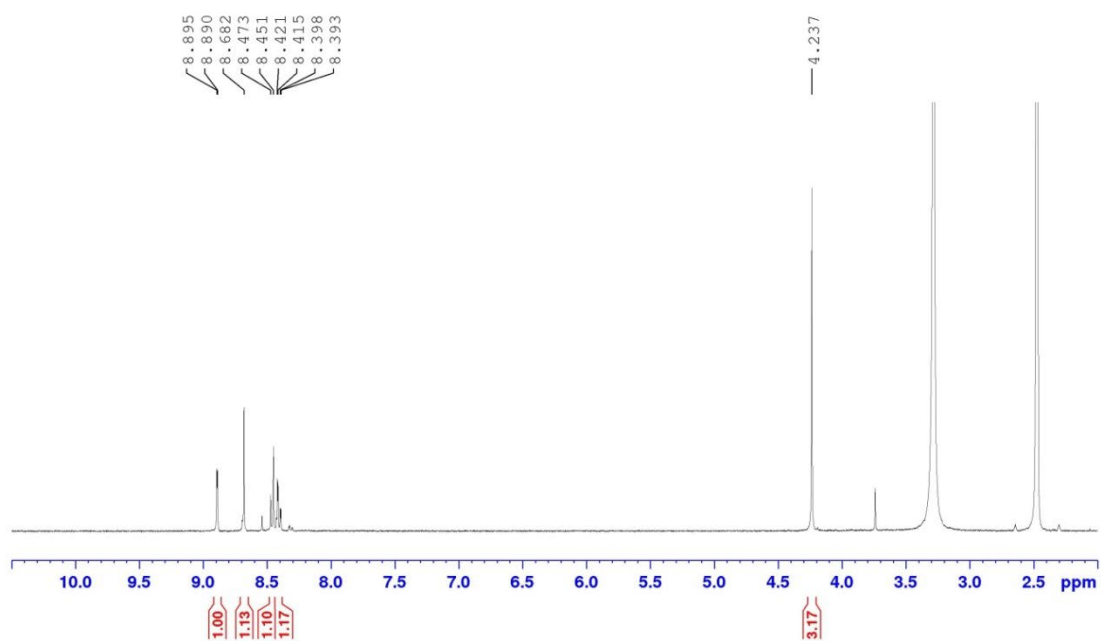
¹³C NMR Compound 33b
DMSO

Figure S43. ¹³C NMR of Compound 33b.



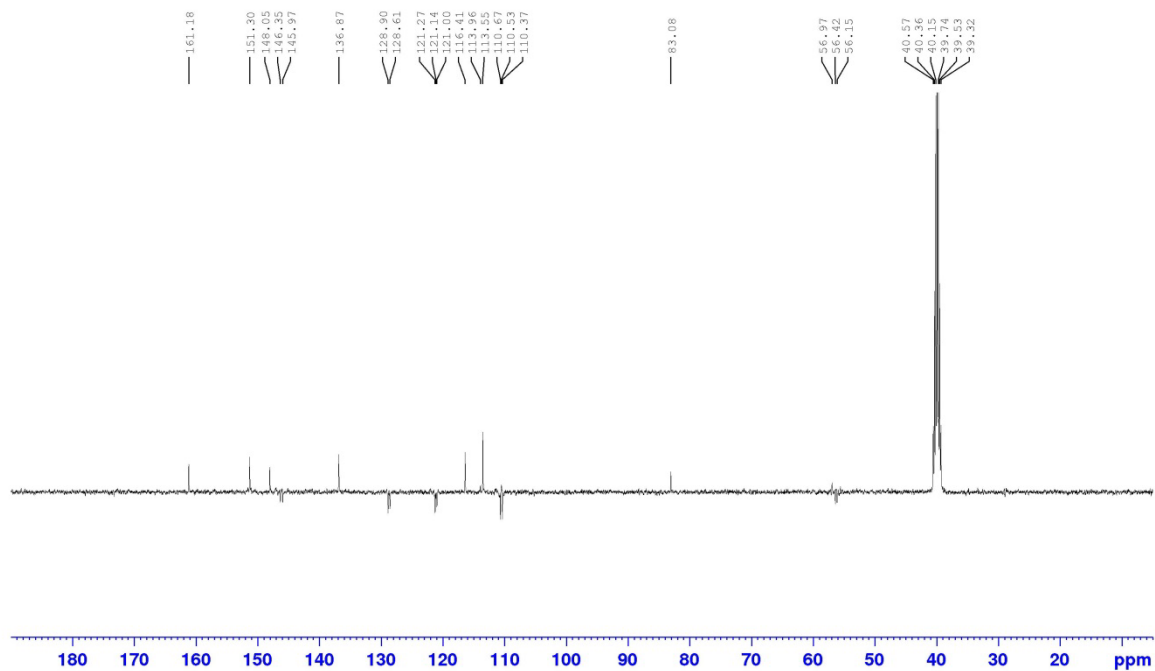
¹H NMR Compound 34
DMSO

Figure S44. ¹H NMR of Compound 34.



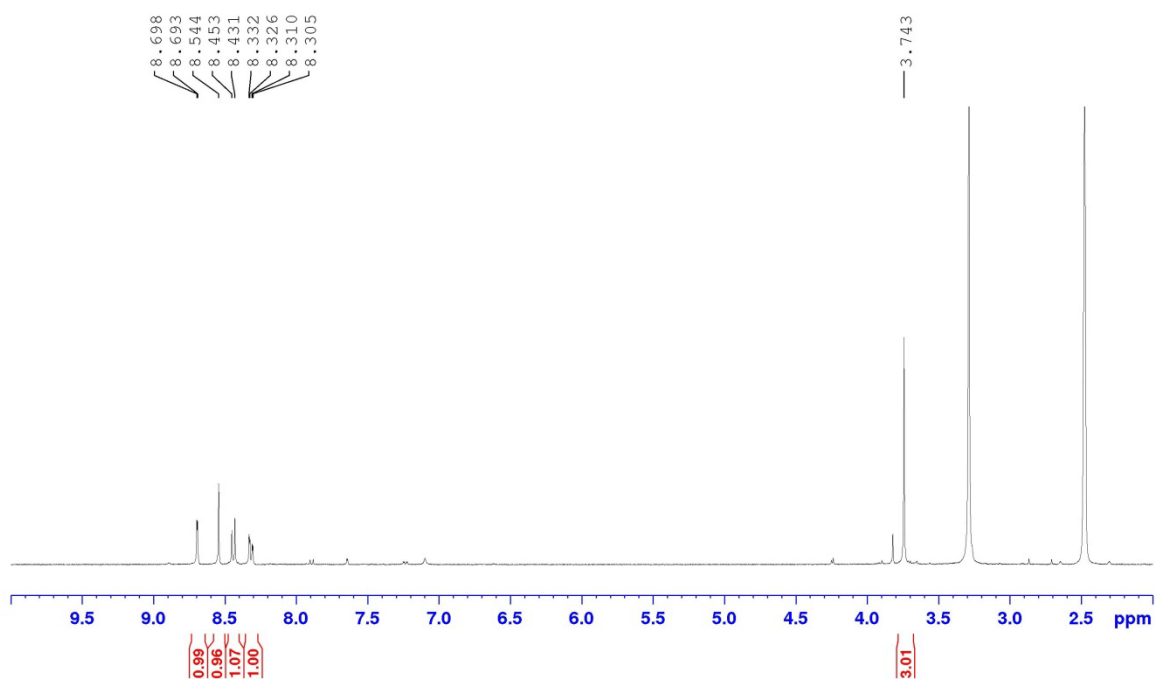
¹³C NMR Compound 34
DMSO

Figure S45. ¹³C NMR of Compound 34.



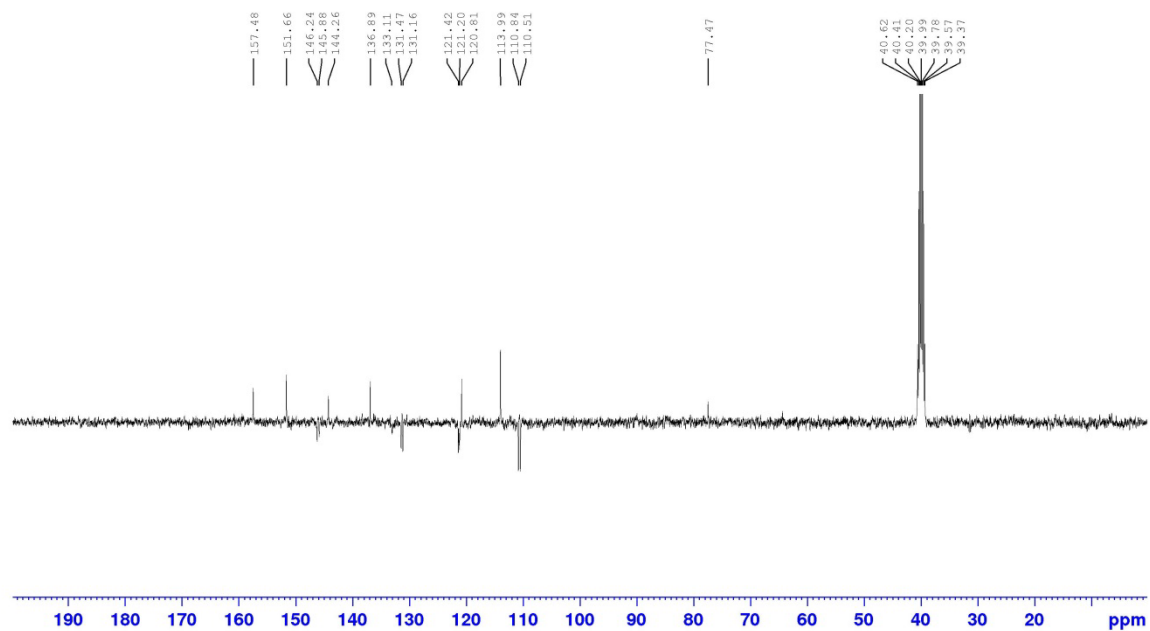
¹H NMR Compound 37
DMSO

Figure S46. ¹H NMR of Compound 37.



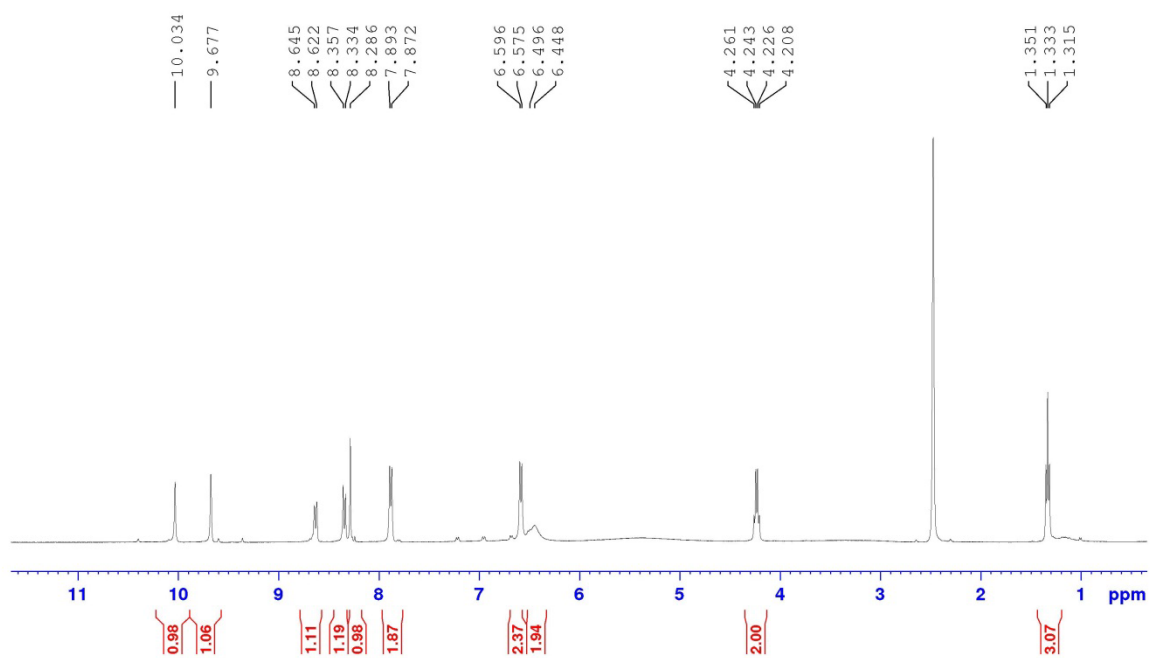
¹³C NMR Compound 37
DMSO

Figure S47. ¹³C NMR of Compound 37.



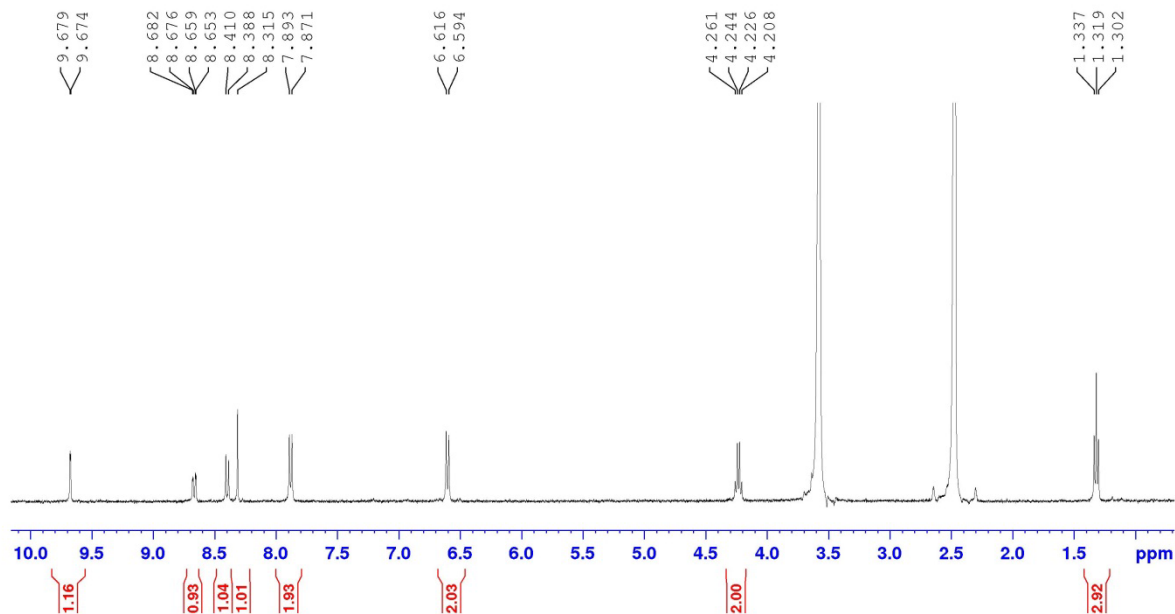
¹H NMR Compound 40
DMSO

Figure S48. ¹H NMR of Compound 40.



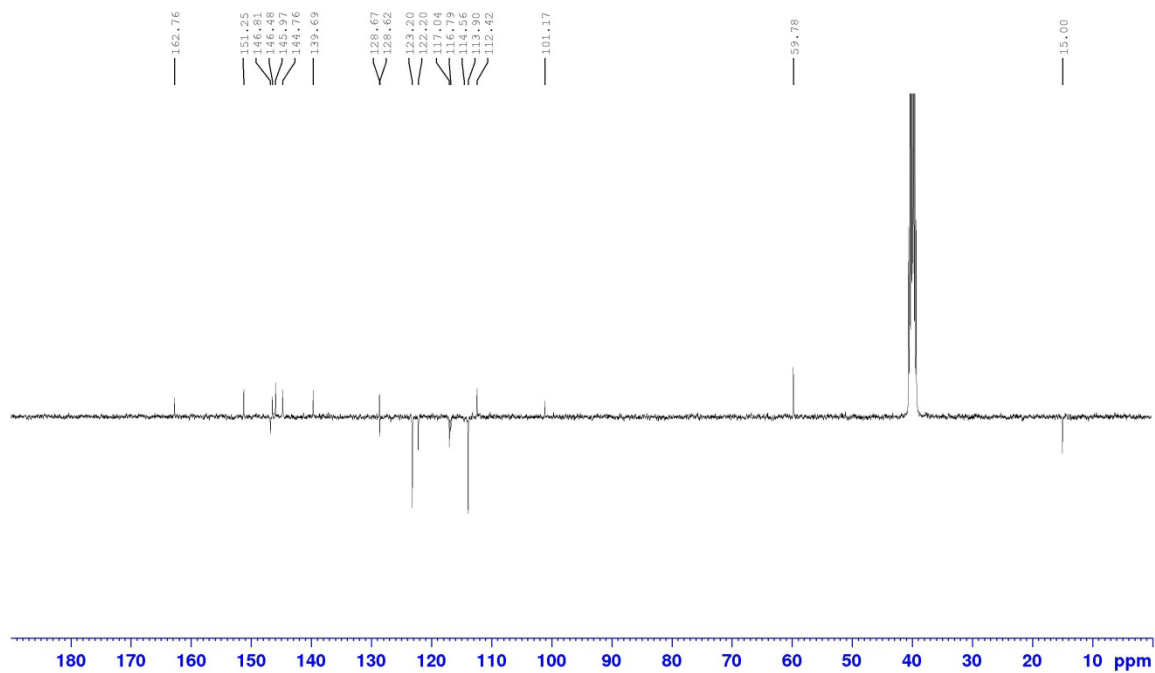
¹H NMR Compound 40
DMSO + D₂O

Figure S49. ¹H NMR of Compound 40 + D₂O.



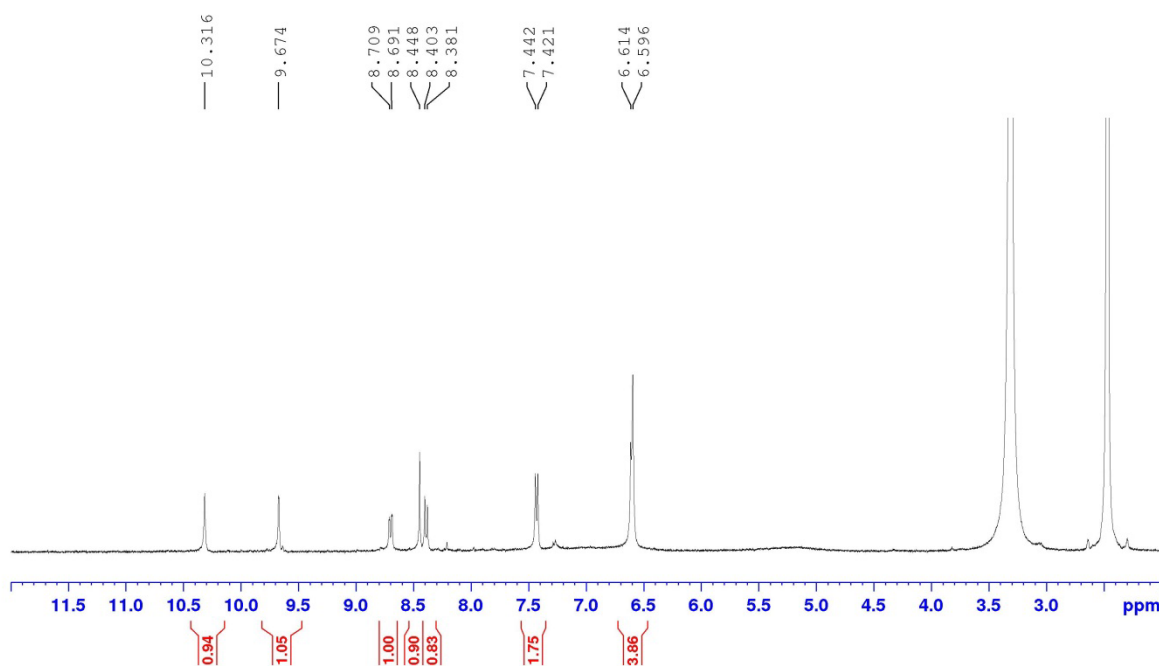
¹³C NMR Compound 40
DMSO

Figure S50. ¹³C NMR of Compound 40.



¹H NMR Compound 42d
DMSO

Figure S51. ¹H NMR of Compound 42d.



¹H NMR Compound 42d
DMSO + D₂O

Figure S52. ¹H NMR of Compound 42d + D₂O.

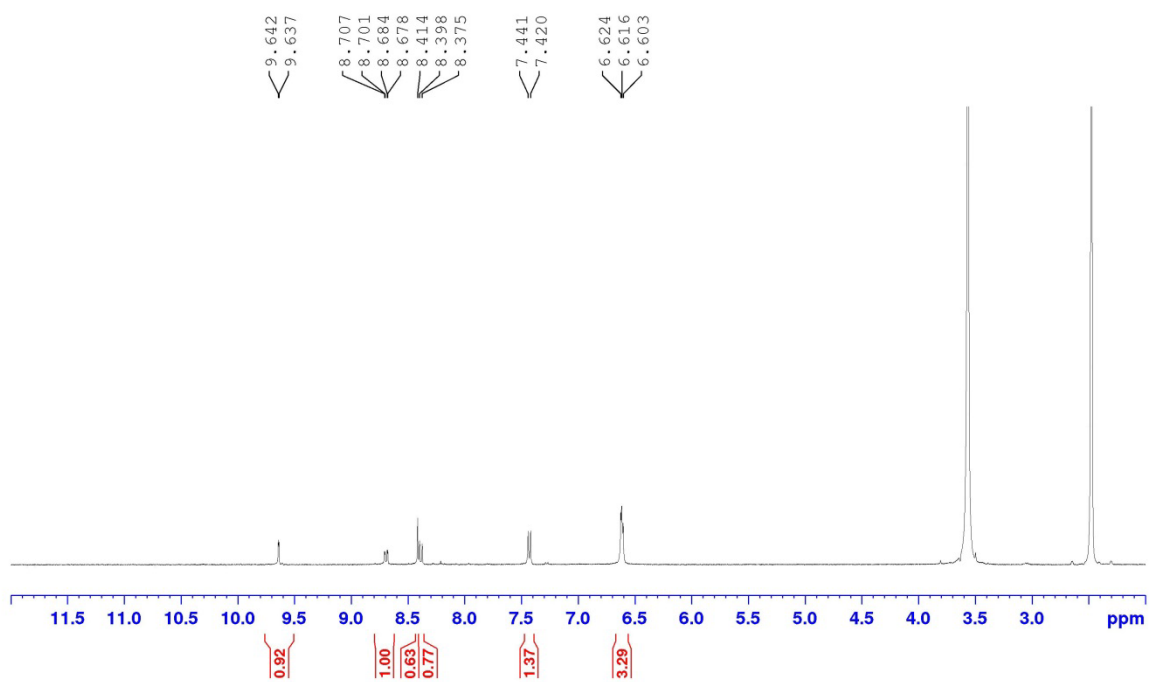


Figure S53. ^{13}C NMR of Compound 42d.

^{13}C NMR Compound 42d
DMSO

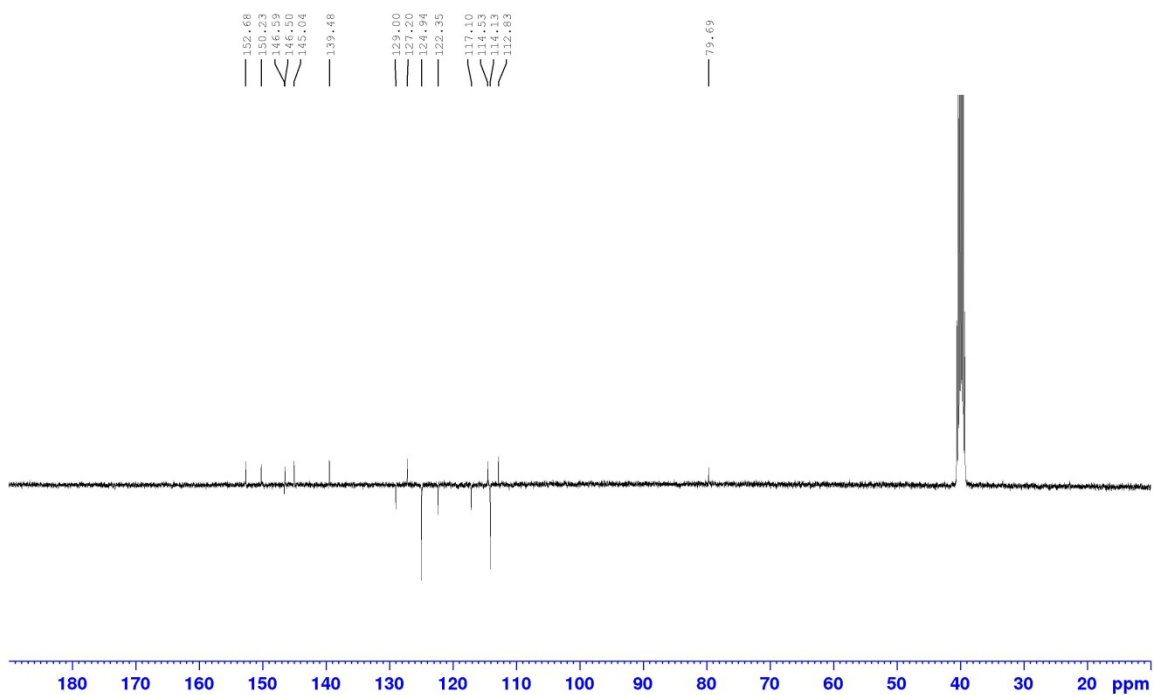
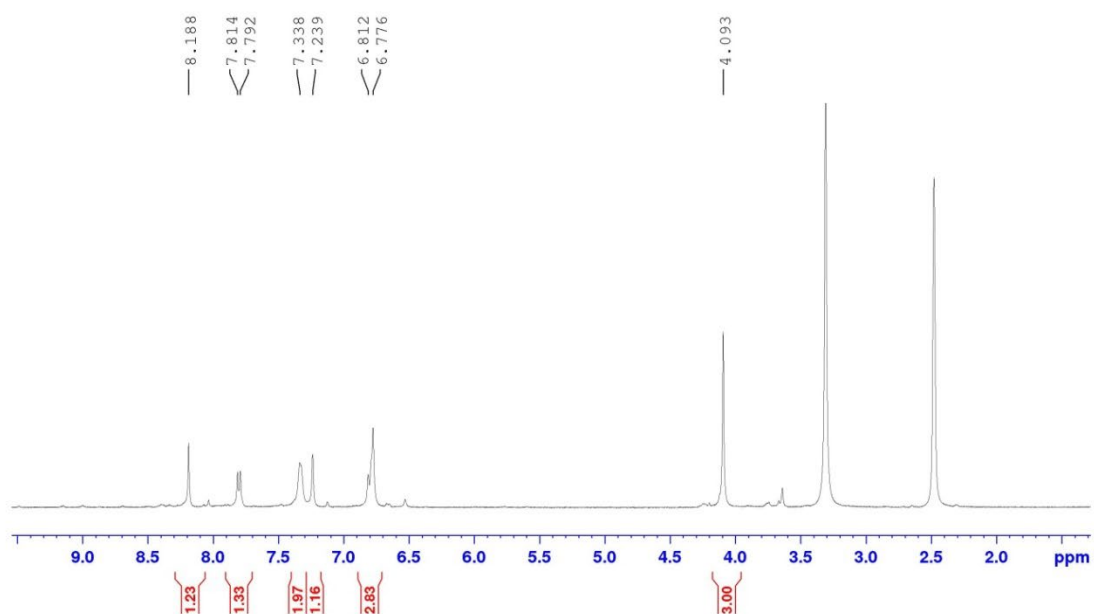


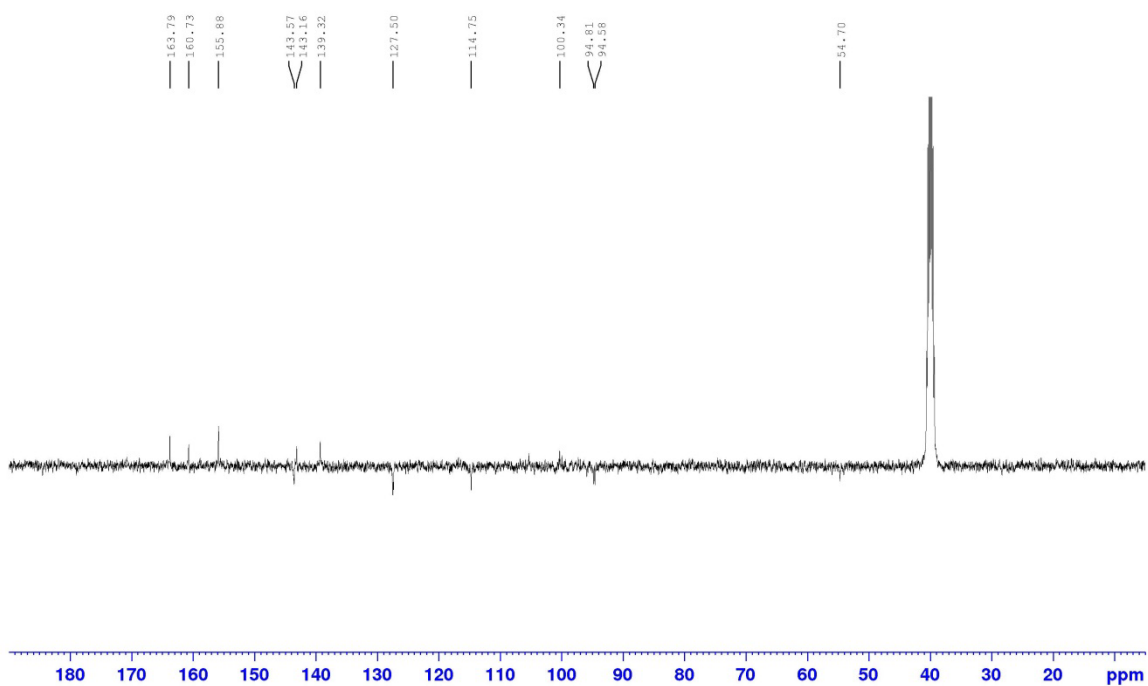
Figure S54. ^1H NMR of Compound 46a.

^1H NMR Compound 46a
DMSO



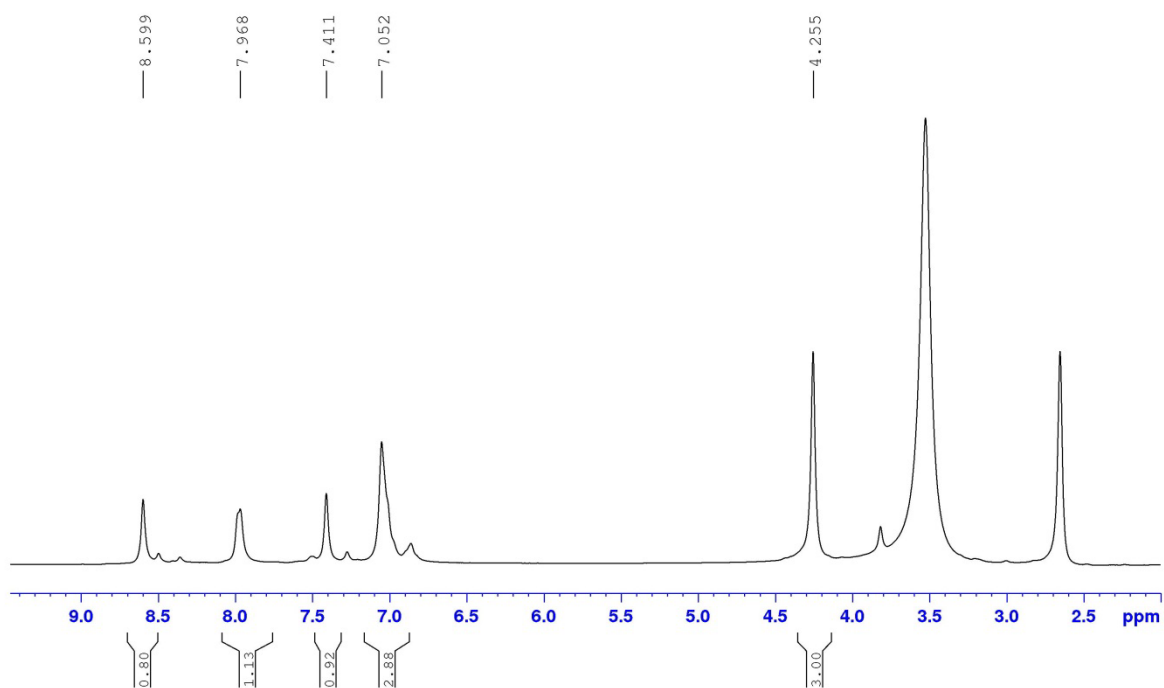
¹³C NMR Compound 46a
DMSO

Figure S55. ¹³C NMR of Compound 46a.



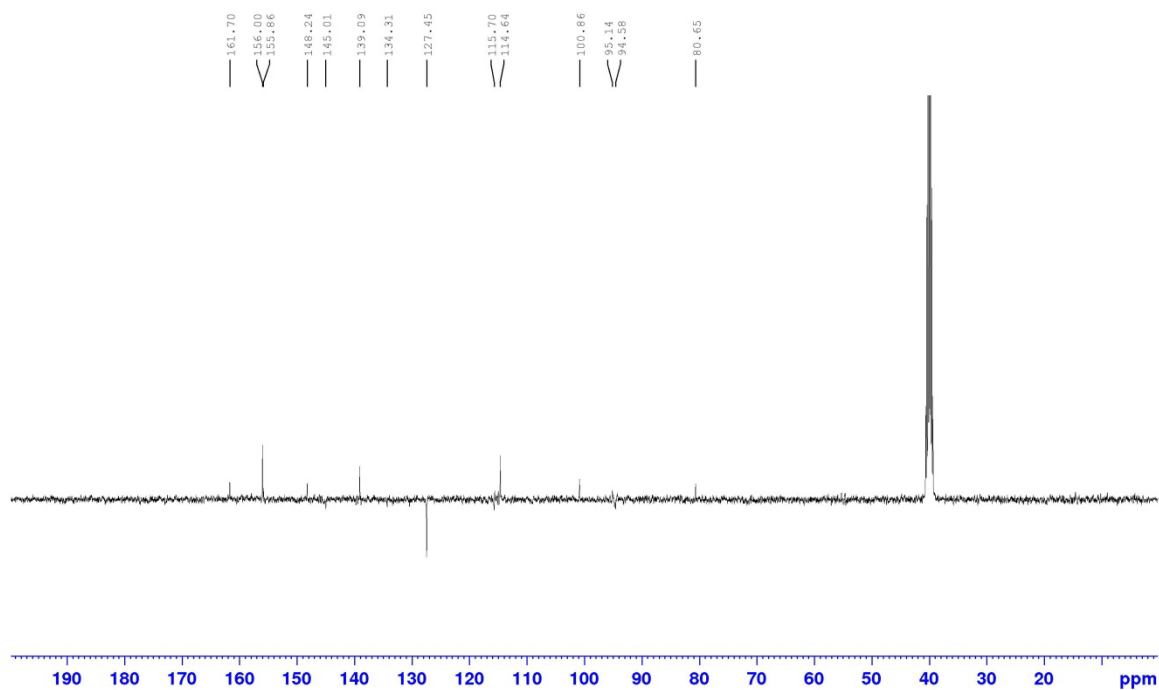
¹H NMR Compound 47
DMSO

Figure S56. ¹H NMR of Compound 47.



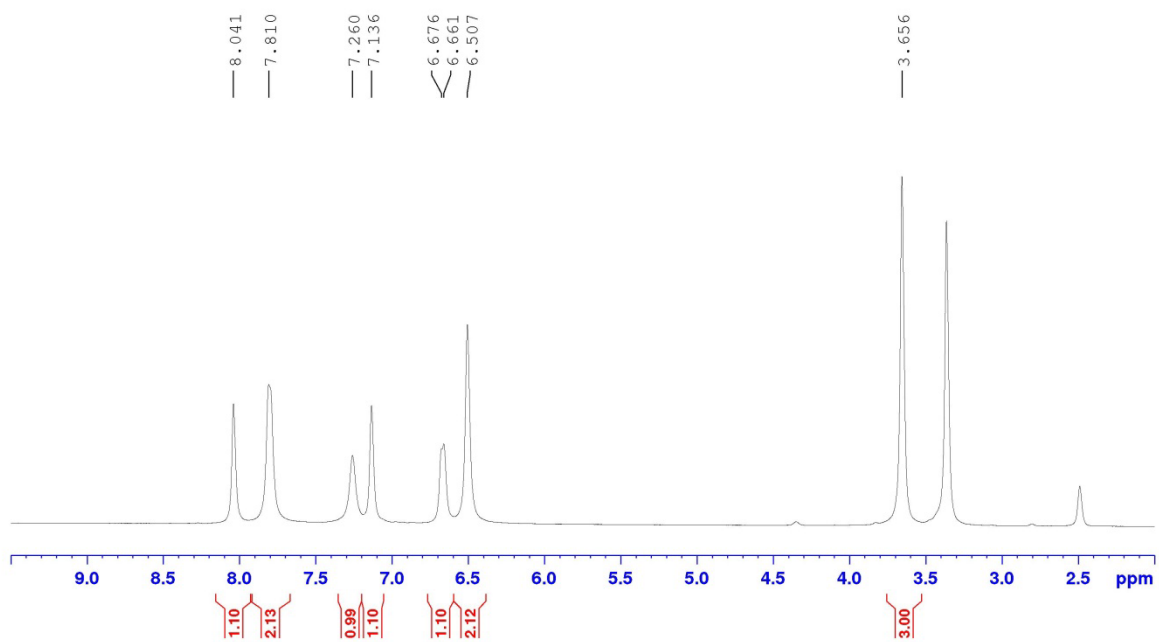
¹³C NMR Compound 47
DMSO

Figure S57. ¹³C NMR of Compound 47.



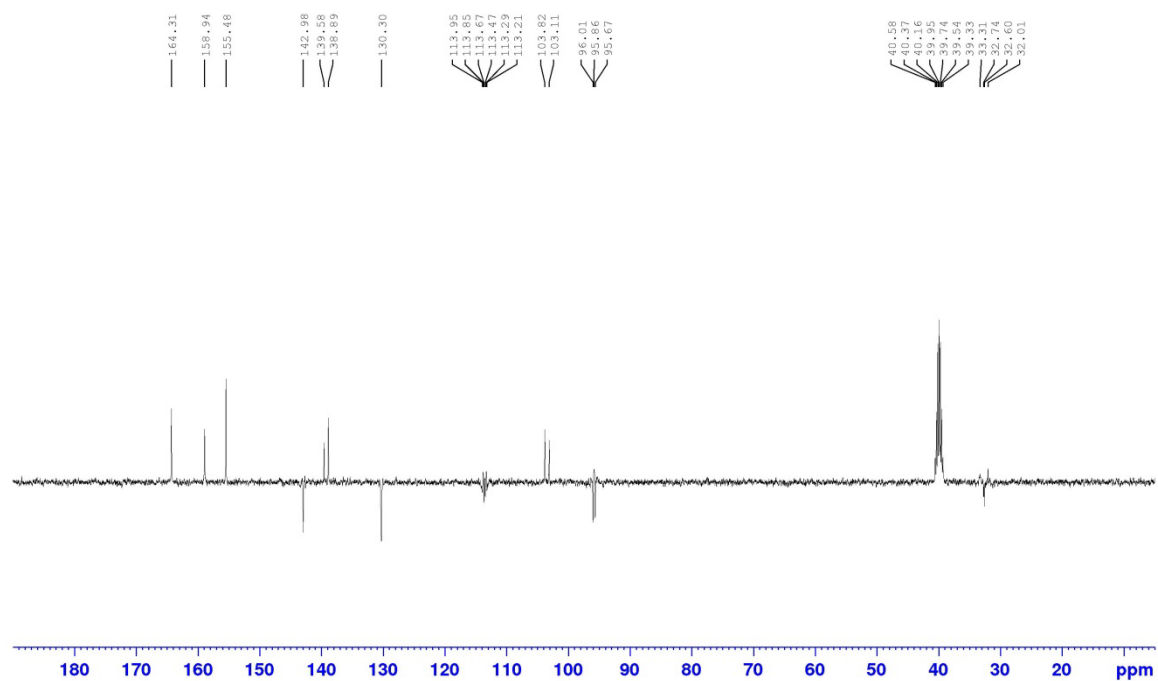
¹H NMR Compound 49
DMSO

Figure S58. ¹H NMR of Compound 49.



¹³C NMR Compound 49
DMSO

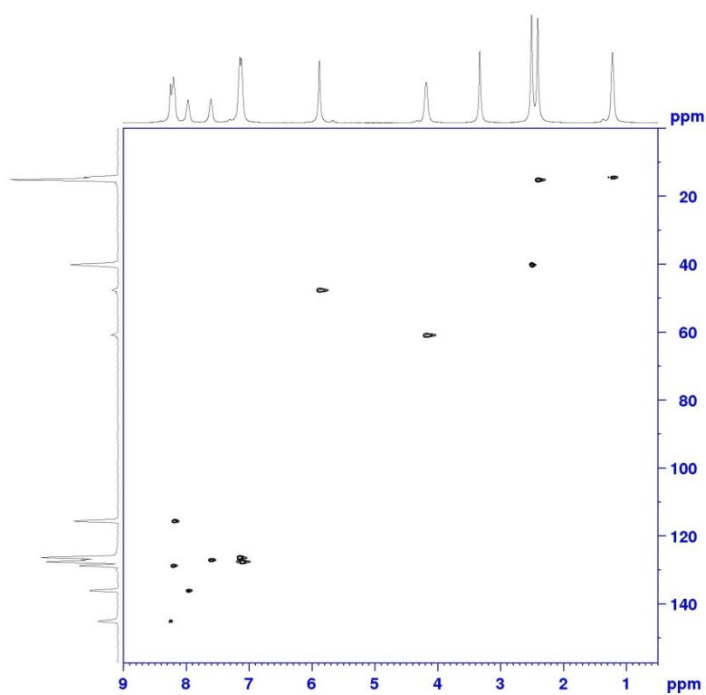
Figure S59. ¹³C NMR of Compound 49.



4. HSQC and HMBC of compounds 7b and 14c.

HSQC Compound 7b

Figure S60. HSQC of Compound 7b.



HMBC Compound 7b

Figure S61. HMBC of Compound 7b.

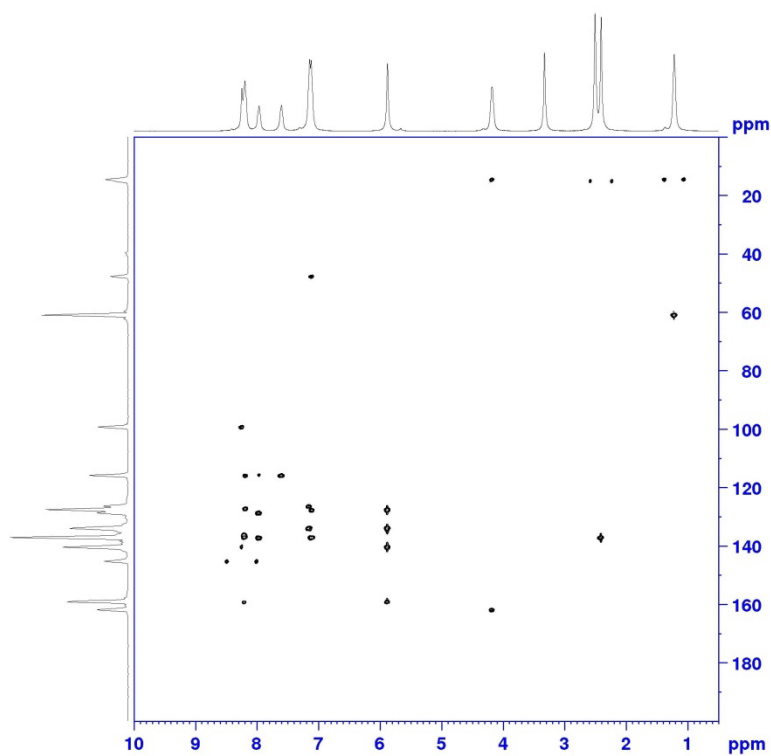


Figure S62. HSQC of Compound 14c.

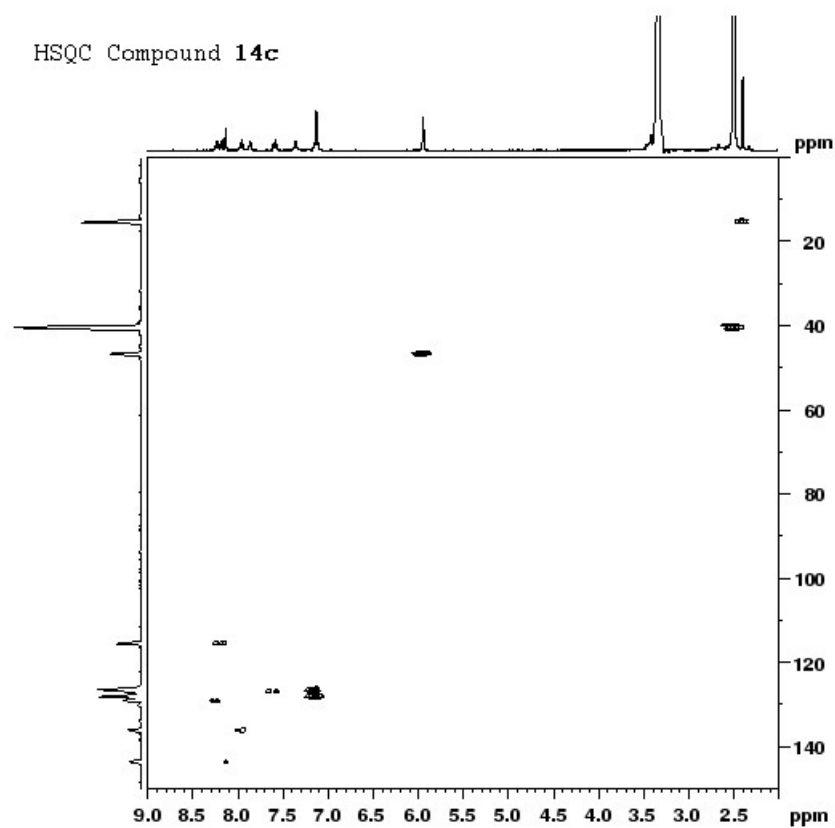
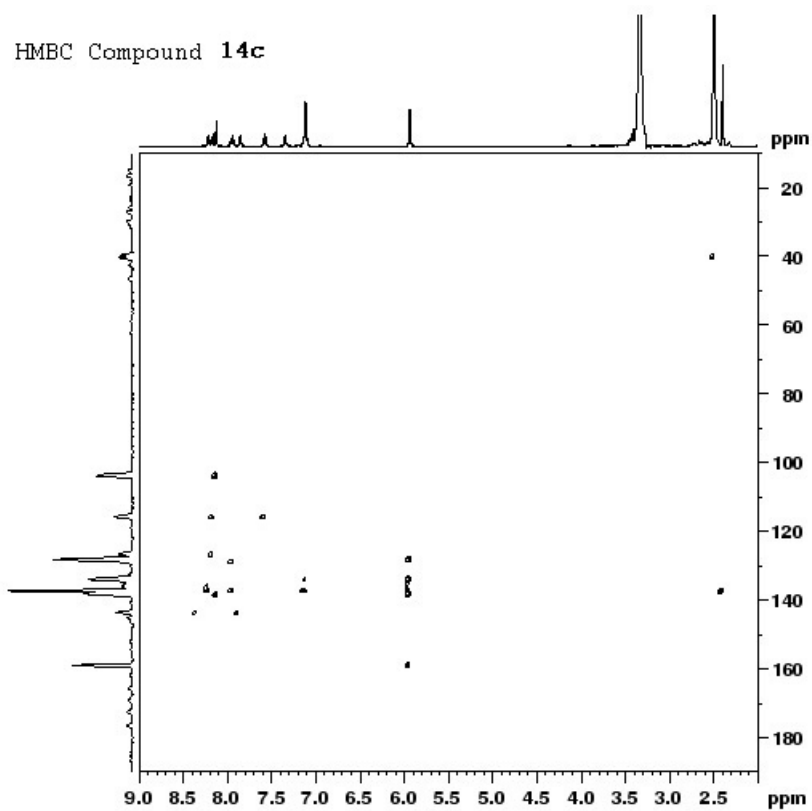


Figure S63. HMBC of Compound 14c.



5. Table S4. Potential human protein targets for compounds **13i** and **16** identified by PharmMapper

	PDB	Targets for Compound 13i	Fit Score	Normalized Fit Score
1	1JD0	Carbonic anhydrase 12	2.999	0.9998
2	1PME	Mitogen-activated protein kinase 1 (ERK2)	2.976	0.9919
3	3EKO	Heat shock protein HSP 90-alpha	2.965	0.9883
4	1YB1	Estradiol 17-beta-dehydrogenase 11	2.949	0.983
5	1MUO	Serine/threonine-protein kinase 6 (PAK6)	2.949	0.983
6	1GFW	Caspase-3	2.925	0.975
7	1PQ9	Oxysterols receptor LXR-beta	2.923	0.9743
8	1DVZ	Transthyretin	2.923	0.9742
9	1REU	Bone morphogenetic protein 2	2.914	0.9714
10	1ZUC	Progesterone receptor	2.91	0.97
11	1EUB	Collagenase 3	2.906	0.9687
12	2HD6	Carbonic anhydrase 2	3.869	0.9673
13	1W7H	Mitogen-activated protein kinase 14 (p38 α)	2.902	0.9672
14	1CZM	Carbonic anhydrase 1	2.891	0.9638
15	2VTA	Cell division protein kinase 2	2.877	0.959
16	3HVC	Mitogen-activated protein kinase 14 (p38 α)	2.876	0.9588
17	2OHP	Beta-secretase 1	2.87	0.9568
18	3EQM	Cytochrome P450 19A1	2.865	0.9549
19	1OZN	Reticulon-4 receptor	2.856	0.9521
20	2PIN	Thyroid hormone receptor beta	2.853	0.951
21	1YA8	Liver carboxylesterase 1	2.846	0.9488
22	1QKM	Estrogen receptor beta	2.837	0.9458
23	2PG2	Kinesin-like protein KIF11	2.835	0.945
24	1PMV	Mitogen-activated protein kinase 10 (JNK3)	2.81	0.9368
25	1UKI	Mitogen-activated protein kinase 8 (JNK1)	2.807	0.9358
26	1RS0	Complement factor B	2.806	0.9354
27	2P3G	MAP kinase-activated protein kinase 2	2.799	0.9329
28	2PIR	Androgen receptor	2.794	0.9312
29	2ITX	Epidermal growth factor receptor	2.788	0.9293
30	1YA3	Mineralocorticoid receptor	3.702	0.9255

	PDB	Targets for Compound 16	Fit Score	Normalized Fit Score
1	1PME	Mitogen-activated protein kinase 1 (ERK2)	2.991	0.9972
2	1CZM	Carbonic anhydrase 1	2.973	0.9908
3	1W7H	Mitogen-activated protein kinase 14 (p38 α)	2.969	0.9896
4	1JD0	Carbonic anhydrase 12	2.964	0.9879
5	3EKO	Heat shock protein HSP 90-alpha	2.951	0.9837
6	2PIN	Thyroid hormone receptor beta	2.946	0.9821
7	1LYW	Cathepsin D	2.937	0.979
8	2PG2	Kinesin-like protein KIF11	2.934	0.9779
9	1OKL	Carbonic anhydrase 2	2.93	0.9768
10	1REU	Bone morphogenetic protein 2	2.914	0.9714
11	1DVZ	Transthyretin	2.911	0.9704
12	1NO9	Prothrombin	2.902	0.9674
13	1TBB	cAMP-specific 3,5-cyclic phosphodiesterase 4D	3.86	0.9651
14	3HVC	Mitogen-activated protein kinase 14 (p38 α)	2.893	0.9645
15	2OHP	Beta-secretase 1	2.886	0.9621
16	2VTA	Cell division protein kinase 2	2.873	0.9577
17	3GAM	Ribosyldihydronicotinamide dehydrogenase	2.866	0.9552
18	2BRG	Serine/threonine-protein kinase Chk1	2.862	0.9539

19	1YA8	Liver carboxylesterase 1	2.828	0.9428
20	1RS0	Complement factor B	2.823	0.941
21	1PMV	Mitogen-activated protein kinase 10 (JNK3)	2.811	0.9372
22	3EQM	Cytochrome P450 19A1	2.81	0.9367
23	1UKI	Mitogen-activated protein kinase 8 (JNK1)	2.809	0.9364
24	2A4Z	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma isoform	2.796	0.9321
25	1QKM	Estrogen receptor beta	2.776	0.9252
26	2OCF	Estrogen receptor	2.77	0.9234
27	3DEJ	Caspase-3	2.743	0.9145
28	2PIR	Androgen receptor	2.738	0.9128
29	2OVM	Progesterone receptor	2.733	0.9108
30	2C3I	Serine/threonine-protein kinase Pim-1	2.725	0.9082

6. Molecular modelling for complexes of compounds 13i and 16 with JNK3 (PDB: 4WHZ) using AUTODOCK 4.1 program with further optimization using the amber99sb force field.

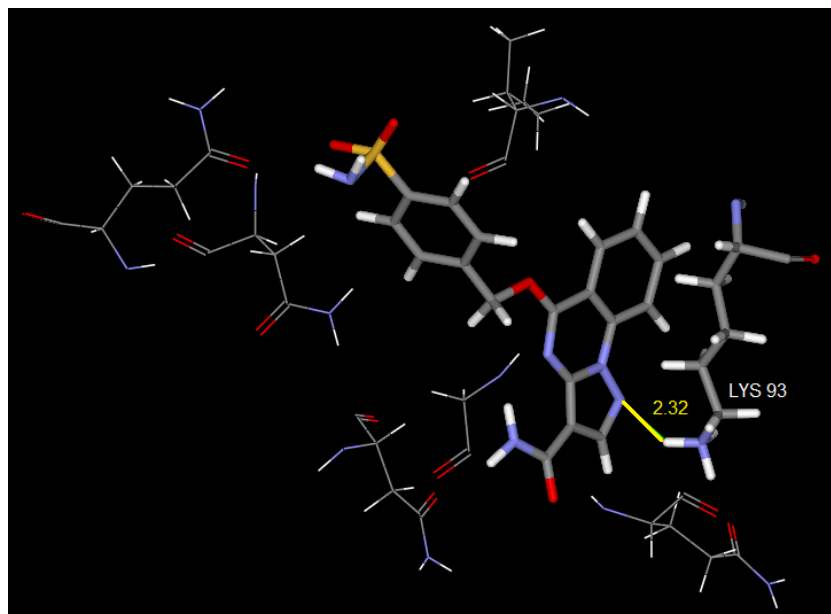


Figure S64. Complex of JNK3-13i.

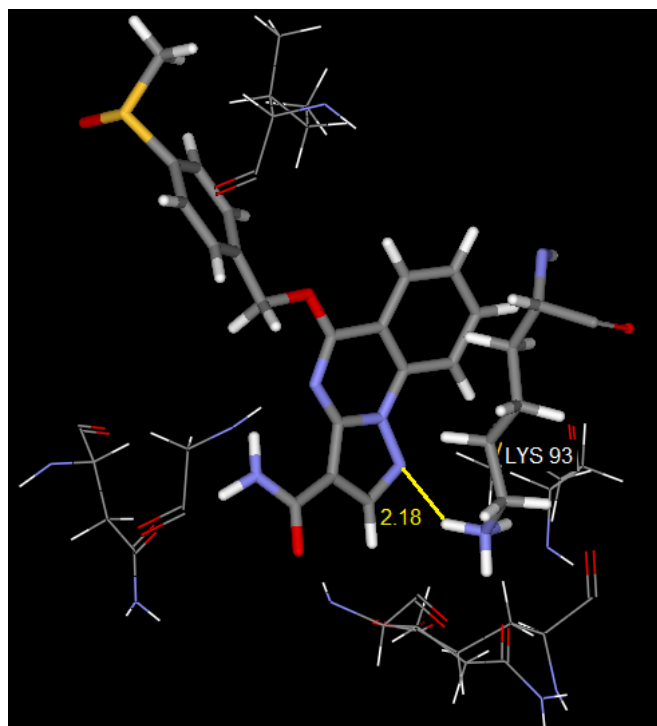


Figure S65. Complex of JNK3-16.

7. **Table S5.** H-bonding interactions obtained from the docking of ligands 13i and 16 into the binding sites of JNK3 (PDB: 4WHZ) obtained using AUTODOCK 4.1 program and geometry optimization with the amber99sb force-field.

Ligand	Atom in the protein residue	Atom in the ligand	Distance (Å)
13i	OE1 (Gln155)	H62	2.11
	OD1 (Asn194)	H86	1.91
	H (Gln75)	O28	2.91
	HZ2 (Lys93)	N18	2.32
	HZ3 (Lys93)	N18	2.98
	H (Asn152)	O4	2.47
16	OD1 (Asn194)	H88	1.93
	H (Gln75)	O54	2.19
	HZ2 (Lys93)	N22	2.18