Optimizing side chains for crystal growth from water: case study of aromatic amide foldamers

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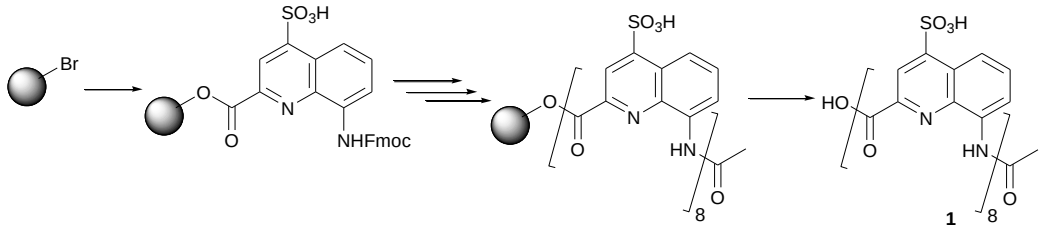
S1 General Procedures

All reagents, unless otherwise specified, were purchased from commercial sources, and used without further purification. Anhydrous THF, DCM and toluene were dispensed from a solvent purification system. *N*,*N*-Diisopropylethylamine (DIPEA) was distilled over CaH_2 prior to synthesis. Milli-Q water and HPLC grade acetonitrile were used for RP-HPLC analyses and purification. Methyl 4-bromo-8-nitroquinoline-2-carboxylate, and Fmoc-Q^{OMe}-OH were prepared as previously reported in the literatures.[1] Procedures (unless otherwise specified) for preparing bromide resin, resin loading, Fmoc group removal, acid chloride activation and coupling, and resin cleavage were used as previously published [2] as well. Solid phase synthesis (SPS) was carried out using a CEM Discover microwave oven at atmospheric pressure manually and a vacuum station. The mixture of the microwave-assisted reaction was placed in the proprietary reactor vessel and the temperature of the reaction was controlled by an optical fibre probe which was internal to the reaction mixture and linked to an IR detector. ^{1}H NMR and ^{13}C{^{1}H}NMR spectra were recorded at 300 MHz. Chemical shifts are reported in ppm and are calibrated against residual solvent signals of $CDCl_3$ (δ 7.26 ppm for ^{1}H, 77.2 ppm for ^{13}C), DMSO-d_6 (δ 2.50 ppm for ^{1}H, 39.5 ppm for ^{13}C), or to the reference signal of TMS (δ 0.00 ppm for ^{1}H) from 10 μM 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt in H_2O/D_2O (9:1, *v*/*v*%). All coupling constants were reported in Hz and signal multiplicities were abbreviated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet or overlapped signals; and br, broad. Silica gel chromatography was performed by using Merck Kieselgel Si 60. RP-HPLC analyses were carried out at 1.0 mL·min^{-1} (unless otherwise specified) by using a Macherey-Nagel Nucleodur C18 gravity column (4.6 × 100 mm, 3 μm). The mobile phase was composed of 0.1% (*v*/*v*%) TFA in MilliQ-H_2O (solvent A), 0.1% (*v*/*v*%) TFA in acetonitrile (solvent B, always using solvent A as the aqueous component), 12.5 mM NH_4Ac-NH_4OH in MilliQ-H_2O (pH 8.5, solvent C) and acetonitrile (solvent D, always using solvent C as the aqueous component). Column effluent was monitored by UV detection at 214, 254 and 300 nm with a diode array detector. Purification of crude oligoamides from SPS was carried out by semi-preparative RP-HPLC at a 3.0 mL/min flow using a Macherey-Nagel Nucleodur C18 HTEC column (21 mm × 125 mm, 5 μm). The running solvents of semi-preparative RP-HPLC were the same as analytical RP-HPLC. Monitoring was performed by UV detection at 254 and 300 nm with a diode array detector. High-resolution electrospray ionization time of flight (ESI-TOF) mass spectra were obtained in either positive or negative ion mode.

S2 Synthetic Method

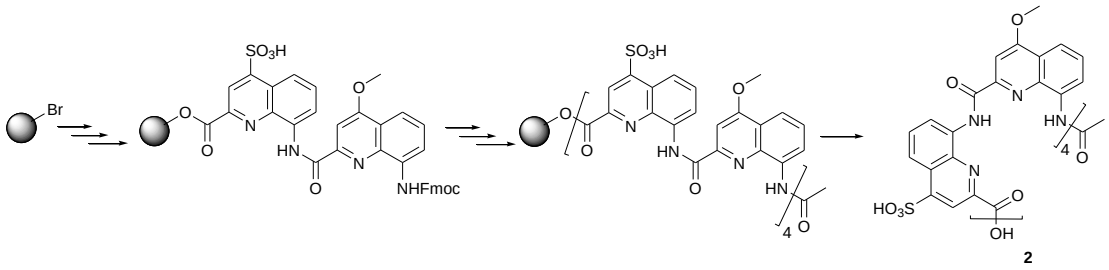
Solid Phase Synthesis

Scheme S1. Solid Phase Synthesis of Compound **1**.



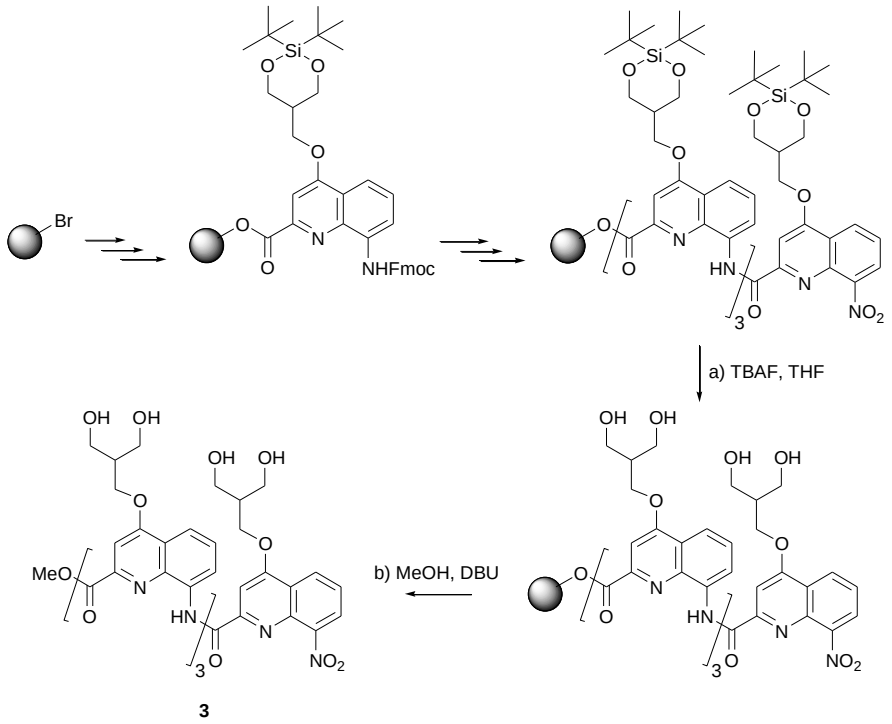
Compound 1: Compound **1** was synthesized using the SPS procedures (note: anhydrous THF was used instead of anhydrous DCM during acid chloride activation because of solubility issues) previously reported [2] on a 41 μmol scale (100 mg of Wang resin, manufacturer's loading 0.41 mmolg^{-1}). The crude product was purified by semi-preparative RP-HPLC (0-10% D, over 15 min) to afford the title compound as a yellow solid (14 mg, 17%, purity by RP-HPLC: > 99%). RP-HPLC (0-10% D, over 10 min) R_t =3.8 min. ^{1}H NMR (300 MHz, 10%D_2O/H_2O *v/v* %): δ 11.47 (s, 1H), 11.32 (s, 1H), 11.26 (s, 1H), 11.22 (s, 1H), 10.86 (s, 1H), 10.76 (s, 1H), 10.65 (s, 1H), 9.13 (s, 1H), 8.56 (m, 2H), 8.38-7.38 (m, 28H), 7.22 (d, *J* = 7.5 Hz, 1H), 7.10 (s, 1H), 1.30 (s, 3H). HRMS: calcd. for $C_{82}H_{50}N_{16}O_{34}S_8$ $[M - 2H]^{2-}$ 1029.0226; found 1029.0239.

Scheme S2. Solid Phase Synthesis of Compound **2**.



Compound 2: Compound **2** was synthesized using the SPS procedures (note: anhydrous THF was used instead of anhydrous DCM during acid chloride activation because of solubility issues) previously reported [2] on a 10.25 μmol scale (25 mg of Wang resin, manufacturer's loading 0.41 mmolg^{-1}). The crude product was purified by semi-preparative RP-HPLC (15-25% D, over 15 min) to afford the title compound as a yellow solid (5 mg, 26%, purity by RP-HPLC: 98%). RP-HPLC (15-25% D, over 10 min) R_t =10.0 min. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 11.09 (m, 3H), 10.93 (s, 1H), 10.74 (m, 3H), 8.57 (d, *J* = 8.1 Hz, 1H), 8.34 (m, 4H), 8.03-7.29 (m, 21H), 7.08 (m, 3H), 6.76 (s, 1H), 6.55 (s, 1H), 6.19 (s, 1H), 5.87 (s, 1H), 4.08 (s, 3H), 4.07 (s, 3H), 3.92 (s, 3H), 3.85 (s, 3H), 1.12 (s, 3H). HRMS: calcd. for $C_{86}H_{61}N_{16}O_{26}S_4$ $[M + H]^+$ 1861.2820; found 1861.2889.

Scheme S3. Solution Phase Synthesis of Compound **3**.



3

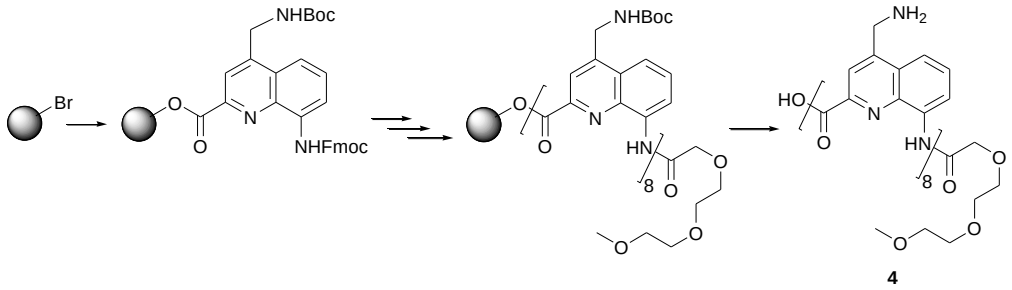
Compound 3: Compound **3** was synthesized using the SPS procedures (except **steps a** and **b** which are described below) previously reported [2] on a 10.25 μmol scale (25 mg of Wang resin, manufacturer's loading 0.41 mmolg^{-1}). The crude product was purified by semi-preparative RP-HPLC (0-70% B, over 10 min) to afford the title compound as a yellow solid (3.6 mg, 30%, purity by RP-HPLC: > 99%). RP-HPLC (0-70% B, over 10 min, 3 mL/min flow rate) R_t =4.6 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.04 (s, 1H), 11.72 (s, 1H), 11.42 (s, 1H), 9.08 (m, 1H), 8.59 (m, 1H), 8.39 (m, 1H), 8.07-7.52 (m, 10H), 7.37 (s, 1H), 6.90 (s, 1H), 6.69 (s, 1H), 4.74-4.18 (m, 7H), 3.75-2.95 (m, overlapped with water peak), 2.70-2.26 (m, overlapped with DMSO peak). HRMS: calcd. for $C_{57}H_{59}N_8O_{19}$ $[M + H]^+$ 1159.3891; found 1159.3899.

On-resin (di-*tert*-butyl) silyl deprotection (step a): The resin bound quinoline tetramer (started from 25 mg of Wang resin, manufacturer's loading 0.41 mmolg^{-1}, 10.25 μmol, 1 equiv) was suspended in 0.9 mL anhydrous THF and a 1 M solution of TBAF in THF (164 μL, 0.164 mmol, 16 equiv) was added. It was then treated with microwaves (50 W, ramp to 50 °C over 5 min, then hold at 60 °C for 15 min). The resin was washed briefly with anhydrous THF, and the process repeated once. The resin was then washed thoroughly with DMF and stirred for 2 min at room temperature in DMF. Then washed with DMF, DCM, DCM/MeOH (50/50%, *v/v*%), and MeOH/H_2O (50/50%, *v/v*%) in that order for three cycles.

On-resin methylation (step b): The above resin-bound foldamer was washed with anhydrous THF and transferred to a pressure-resistant glass tube. To the resin were then added 2 mL of anhydrous

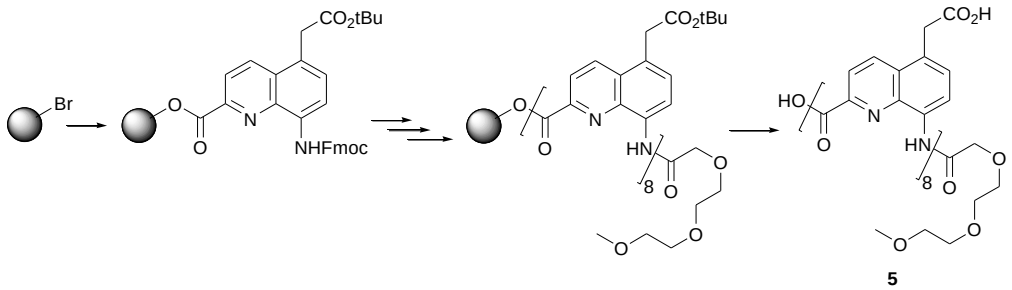
THF, 2 mL of MeOH and 0.1 mL of 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU). The mixture was stirred in the sealed pressure-resistant glass tube for 2 h at 80 °C. The resin was then removed by filtration and the filtrate was concentrated under the reduced pressure. The resulting oily solid was precipitated with Et_2O, triturated, filtered and washed with Et_2O, at last, dried under high vacuum to yield 9 mg of crude product as a yellow solid. This crude product was further purified by semi-preparative RP-HPLC.

Scheme S4. Solid Phase Synthesis of Compound **4**.



Compound 4: Compound **4** was synthesized using the SPS procedures previously reported [2] on a 10.25 μmol scale (25 mg of Wang resin, manufacturer's loading 0.41 $mmolg^{-1}$). The crude product was purified by semi-preparative RP-HPLC (5-15% B, over 15 min) to afford the title compound as a yellow solid (7.9 mg, 44%, purity by RP-HPLC: 99%). RP-HPLC (5-15% B, over 10 min) R_t =11.1 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.26 (s, 1H), 11.24 (s, 1H), 11.18 (s, 1H), 11.07 (s, 1H), 11.00 (s, 1H), 10.93 (s, 1H), 10.83 (s, 1H), 9.51 (s, 1H), 8.91-7.88 (m, 22H, containing signals of protonated -NH_2 residues), 7.90-7.06 (m, 33H, containing signals of protonated –NH_2), 4.87-4.08 (m, 19H), 3.50-3.00 (m, overlapped with water peak), 2.64 (s, 3H), 2.60-2.30 (m, overlapped with DMSO peak). HRMS: calcd. for $C_{95}H_{87}N_{24}O_{13}$ $[M + H]^+$ 1771.6879; found 1771.6925.

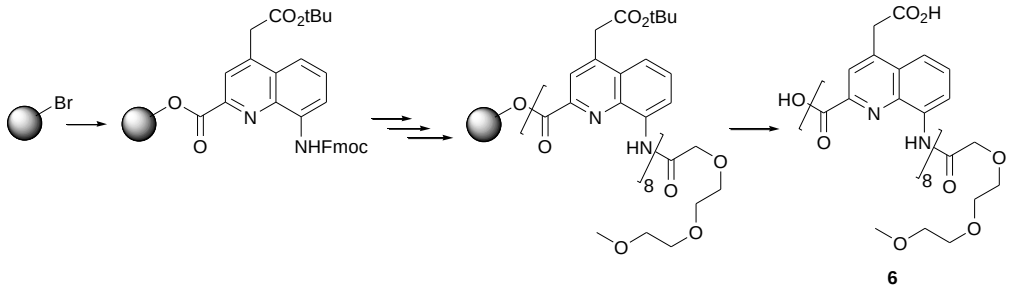
Scheme S5. Solid Phase Synthesis of Compound **5**.



Compound 5: Compound **5** was synthesized using the SPS procedures previously reported [2] on a 10.25 μmol scale (25 mg of Wang resin, manufacturer's loading 0.41 $mmolg^{-1}$). The crude product

was purified by semi-preparative RP-HPLC (0-10% D, over 15 min) to afford the title compound as a yellow solid (6.5 mg, 32%, purity by RP-HPLC: > 99%). RP-HPLC (0-10% D, over 10 min) R_t = 5.0 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.06 (m, 3H), 10.84 (m, 3H), 10.62 (br, 1H), 9.33 (s, 1H), 8.55-6.85 (m, 32H), 4.20-3.10 (m, overlapped with water peak), 2.70 (s, 3H), 2.55 (m, overlapped with DMSO peak), 2.30-1.93 (m, 6H). HRMS: calcd. for $C_{103}H_{80}N_{16}O_{29}$ $[M + 2H]^{2+}$ 1002.7655; found 1002.7680.

Scheme S6. Solid Phase Synthesis of Compound **6**.



Compound 6: Compound **6** was synthesized using the SPS procedures previously reported [2] on a 10.25 μmol scale (25 mg of Wang resin, manufacturer's loading 0.41 mmolg^{-1}). The crude product was purified by semi-preparative RP-HPLC (0-5% D, over 15 min) to afford the title compound as a yellow solid (9.5 mg, 46%, purity by RP-HPLC: 97%). RP-HPLC (0-5% D, over 10 min) R_t =6.9 min. ^{1}H NMR (300 MHz, 10%D_2O/H_2O *v/v* %): δ 11.41 (s, 1H), 11.40 (s, 1H), 11.25 (s, 1H), 11.19 (s, 1H), 10.77 (s, 1H), 10.65 (s, 1H), 10.59 (s, 1H), 9.70 (s, 1H), 8.08-7.06 (m, 27H), 6.98 (s, 1H), 6.89 (s, 1H), 6.86 (s, 1H), 6.66 (s, 1H), 6.55 (s, 1H),4.30-3.69 (m, overlapped with water), 3.46-3.22 (m, 3H), 2.81 (m, 1H), 2.53 (s, 3H), 2.52-2.11 (m, 5H). HRMS: calcd. for $C_{103}H_{79}N_{16}O_{29}Na$ $[M + H + Na]^{2+}$ 1013.7565; found 1013.7594.

Solution Phase Synthesis

Compound 7: Methyl 8-aminoquinoline-2-carboxylate (200 mg, 1 mmol, 1 equiv) was dissolved in 10 mL dioxane. Then trimethylsilyl chlorosulfonate (0.23 mL, 1.5 mmol, 1.5 equiv) was added slowly to the solution at room temperature under N_2. The reaction was stirred at 100 ^{o}C overnight. The resulting mixture was allowed to cool down and DCM added to have a full precipitation. Filtered, washed with DCM and dried to afford the title compound as a grey powder (265 mg, 94%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.22 (d, J = 9.0 Hz, 1H), 8.11 (d, J = 9.0 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 6.93 (d, J = 8.1 Hz, 1H), 5.75 (s, DCM), 4.86 (s, H_2O), 3.96 (s, 3H), 3.57 (s, 1,4-dioxane). ^{13}C{^{1}H}NMR (300 MHz, DMSO-d_6): δ 165.07, 145.56, 138.58, 138.53, 137.55, 137.42, 127.57, 126.16, 121.44, 115.01, 66.40 (1,4-dioxane), 52.80. HRMS: calcd. for $C_{11}H_9N_2O_5S$ $[M - H]^-$ 281.0238; found 281.0236.

Compound 9: Compound **7** (282 mg, 1 mmol, 1 equiv) was dissolved in 20 mL of THF/H_2O (1:1) mixture and stirred at room temperature. NaOH (60 mg, 1.5 mmol, 1.5 equiv) was then added and the mixture stirred for 1 h at room temperature. 1 M HCl was then added to acidify the mixture to approximately pH 4. The resulting mixture was then concentrated to dryness under reduced pressure to afford compound **8** as a brown powder (quantitative) which was used directly in the next step without further purification. Then the above compound **8** was dissolved in 18 mL 10% *w/v* $NaHCO_3$ solution (21 mmol, 21 equiv). To the resulting solution was added a solution of Fmoc-Cl (336 mg, 1.3 mmol, 1.3 equiv) in 10 mL dioxane dropwise over 30 min at 0 °C. The mixture was then stirred for a further hour at 0 °C, then at room temperature overnight. 1 M HCl was added to acidify the mixture to approximately pH 4. The mixture was then washed several times with Et_2O until precipitation occurred. Filtered and washed once with small amount of water and once with DCM. The resulting solid was dried to yield the title compound as a grey powder (315 mg, 64%, purity by RP-HPLC: 98%). RP-HPLC (50-60% B, over 10 min) R_t =5.5 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.61 (br, 1H), 10.48 (s, 1H), 9.38 (d, *J* = 9.0 Hz, 1H), 8.25 (m, 2H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 7.90 (d, *J* = 7.2 Hz, 2H), 7.42 (m, 4H), 4.63 (d, *J* = 6.6 Hz, 2H), 4.46 (t, *J* = 6.6 Hz, 1H), 3.33 (s, H_2O). ^{13}C{^{1}H}NMR (300 MHz, DMSO-d_6): δ 165.40, 153.50, 145.04, 143.73, 140.84, 138.23, 137.62, 136.72, 136.39, 127.81, 127.43, 127.26, 125.85, 125.18, 120.50, 120.26, 114.15, 66.54, 46.61. HRMS: calcd. for $C_{25}H_{17}N_2O_7S$ $[M - H]^-$ 489.0762; found 489.0769.

Compound 10: Methyl 4-bromo-8-nitroquinoline-2-carboxylate [1] (5 g, 16 mmol, 1 equiv) and thiourea (2.4 g, 32 mmol, 2 equiv) were dissolved in 80 mL acetone. The reaction mixture was allowed to reflux under N_2 overnight. After the reaction cooled down, it was filtered and washed with acetone and dried to afford the title compound as a grey powder (4.6 g, 92%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.13 (m, 4H), 8.63 (s, 1H), 8.52 (m, 2H), 8.09 (m, 1H), 4.00 (s, 3H), 3.38 (s, H_2O). ^{13}C{^{1}H}NMR (300 MHz, DMSO-d_6): δ 167.07, 163.78, 149.14, 148.86, 138.59, 135.12, 131.34, 130.10, 128.19, 124.94, 53.37. HRMS: calcd. for $C_{12}H_{11}N_4O_4S$ $[M + H]^+$ 307.0496; found 307.0502.

Compound 11: Compound **10** (4.5 g, 14.7 mmol, 1 equiv) was dissolved in 60 mL of MeOH/H_2O (1:3) mixed solvent. NaOH (2.94 g, 73.5 mmol, 5 equiv) was then added and the mixture stirred for 3 h at room temperature. 1 M HCl was then added to acidify the mixture to approximately pH 4 to allow full precipitation. Filtered, washed with THF and dried to afford the title compound as a dark red solid (2.1 g, 60%) which was used directly in the next step without further purification.

Compound 12: The solution of 30% H_2O_2 (1.8 mL, 15 mmol, 5 equiv) in 18 mL formic acid was stirred at room temperature under N_2 for 1 h. It was then cooled down to 0 °C and to which was added carefully a suspension of compound **11** (750 mg, 3 mmol, 1 equiv) in 4 mL formic acid. The reaction mixture was stirred at 0 °C for 2 h under N_2 to form a suspension. It was filtered while it was still cold. The solid was washed with cold water and dried to afford the title compound as a

white powder (0.65 g, 72%). (**Note: the filtrate should be quenched carefully.** Dropwise adding the filtrate to 200 mL $Na_2S_2O_3$ (7.1 g, 45 mmol, 15 equiv) aqueous solution was recommended) ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.96 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.27 (s, 1H), 8.14 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.68 (s, 1H), 5.75 (s, DCM). ^{13}C{^{1}H}NMR (300 MHz, DMSO-d_6): δ 165.34, 153.42, 150.56, 148.63, 138.58, 130.96, 127.61, 125.16, 123.65, 119.24. HRMS: calcd. for $C_{10}H_5N_2O_7S$ [M - H]$^-$ 296.9823; found 296.9812.

Compound 13: Compound **12** (0.6 g, 2 mmol) was dissolved in 40 mL MeOH and the flask flushed with N_2. 60 mg (10% by mass) 10% Pd/C was then added and N_2 exchanged with H_2. The mixture was allowed to stir under an H_2 atmosphere at room temperature for one day. The resulting mixture was filtered over celite and solvents were evaporated under reduced pressure to yield the title compound as a bright yellow powder (0.54 g, quant) which was used directly in the next step without further purification.

Compound 14: Compound **13** (540 g, 2 mmol, 1 equiv) was dissolved in 36 mL 10% *w/v* $NaHCO_3$ solution (42 mmol, 21 equiv). To the resulting slurry was added a solution of Fmoc-Cl (672 mg, 2.6 mmol, 1.3 equiv) in 20 mL dioxane dropwise at 0 °C over 1 h. The mixture was stirred at 0 °C for a further hour, then at room temperature overnight. 1 M HCl was added to acidify the mixture to approximately pH 4. The resulting mixture was washed several times with Et_2O until precipitation occurred. Filtered, solid was washed once with small amount of water and once with DCM. The resulting solid was dried to yield the title compound as a yellow powder (680 mg, 69%, purity by RP-HPLC: > 99%). RP-HPLC (30-60% B, over 10 min) R_t =4.3 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.59 (br, 1H), 10.40 (s, H), 8.48 (m, 2H), 8.32 (br, 1H), 7.93 (d, *J* = 7.2 Hz, 2H), 7.79 (d, *J* = 7.5 Hz, 2H), 7.66 (t, *J* = 8.1 Hz, 1H), 7.37 (m, 4H), 4.61 (d, *J* = 6.6 Hz, 2H), 4.45 (t, *J* = 6.6 Hz, 1H). ^{13}C{^{1}H}NMR (300 MHz, DMSO-d_6): δ 165.28, 153.87, 153.52, 145.16, 143.74, 140.84, 137.68, 135.68, 129.16, 127.81, 127.26, 125.29, 125.20, 120.68, 120.27, 117.78, 115.96, 66.47, 46.63. HRMS: calcd. for $C_{25}H_{19}N_2O_7S$ [M + H]$^+$ 491.0908; found 491.0912.

Compound 15: Compound **15** was synthesized by using modified literature protocol.[3] 2-Hydroxymethylpropanediol (1g, 9.43 mmol, 1 equiv) was dissolved in 183 mL anhydrous THF and then anhydrous pyridine (3.3 mL, 40.5 mmol, 4.3 equiv) was added. The mixture was cooled to -78 °C and stirred under N_2 in a round bottom flask with dropping funnel attached. Di-*tert*-butylsilyl ditriflate (3.1 mL, 9.43 mmol, 1.0 equiv) was diluted with 37 mL anhydrous THF under N_2, and transferred via a cannula to the dropping funnel, then added dropwise to the 2-hydroxymethylpropanediol solution at -78 °C under N_2 over 1 h. The reaction was allowed to slowly reach -30 °C over 2 hours, then it was removed from the cooling bath and allowed to reach room temperature over 1 h. A saturated solution of $NaHCO_3$ (90 mL) was added and the mixture stirred at room temperature for a further 30 min. Organic solvents were evaporated under reduced pressure, and the remaining aqueous suspension extracted three times with EtOAc. The combined organic layers were washed once with ice-cold HCl (0.1 M), once with saturated $NaHCO_3$, and once with

brine. The organic layer was dried over $MgSO_4$ and then solvents were evaporated under reduced pressure. The resulting oil was purified by column chromatography (100% cyclohexane to cyclohexane/EtOAc = 9/1) to afford the title compound as a pale yellow oil (1.5 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.18 (m, 2H), 3.92 (m, 2H), 3.51 (d, *J* = 6.0 Hz, 2H), 2.30 (m, 1H), 1.54 (s, H_2O), 1.04 (s, 9H), 1.02 (s, 9H). ^{13}C{^{1}H}NMR (300 MHz, $CDCl_3$): δ 67.06, 61.43, 42.86, 27.52, 27.37, 22.67, 20.48. HRMS: calcd. for $C_{12}H_{27}O_3Si$ $[M + H]^+$ 247.1724; found 247.1721.

Compound 16: Methyl 8-nitro-(1H)-4-quinolinone-2-carboxylate (735 mg, 2.96 mmol, 1 equiv), compound **15** (1.46 g, 5.93 mmol, 2.0 equiv) and triphenylphosphine (1.0 g, 3.9 mmol, 1.3 equiv) were suspended in 11 mL anhydrous THF and stirred under N_2 at 0 °C. DIAD (738 µL, 3.9 mmol, 1.3 equiv) was then added to the mixture dropwise at 0 °C over 20 min. The resulting slurry was then stirred at room temperature for a further 2 h, and then heated to 50 °C under N_2 for 2 h. The mixture was allowed to come to room temperature and solvents evaporated under reduced pressure. The oily residue was triturated in MeOH and the resulting precipitate was left at -18 °C for 15 h. Solid was isolated by filtration, washed with ice-cold MeOH and dried to afford the title compound as an off-white powder (1.1 g, 74%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (dd, *J* = 8.4, 1.5 Hz, 1H), 8.11 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.68 (m, 1H), 7.63 (s, 1H), 4.37 (m, 2H), 4.18 (m, 4H), 4.04 (s, 3H), 2.78 (m, 1H), 1.09 (s, 9H), 1.08 (s, 9H). ^{13}C{^{1}H}NMR (300 MHz, $CDCl_3$): δ 165.55, 162.24, 151.32, 148.55, 140.08, 126.42, 126.10, 125.25, 123.05, 102.16, 67.76, 66.49, 53.51, 40.01, 27.47, 27.36, 22.65, 20.62. HRMS: calcd. for $C_{46}H_{64}N_4O_{14}Si_2Na$ $[2M + Na]^+$ 975.3856; found 975.3834

Compound 17: Compound **16** (1.1 g, 2.20 mmol, 1 equiv) was dissolved in 80 mL THF/H_2O (4:1) mixed solvent and $LiOH{\cdot}H_2O$ (139 mg, 3.31 mmol, 1.5 equiv) was added. The reaction mixture was allowed to stir at room temperature for 1 h. 1M HCl was then added to acidify the mixture to approximately pH 4. The resulting mixture was extracted three times with DCM. The combined organic layers were washed twice with H_2O, once with brine, and the aqueous phases back-extracted once with DCM. The combined organic phases were dried over $MgSO_4$. Then solvents were evaporated under reduced pressure to afford the title compound as a pale brown powder (1.0 g, quant). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.25 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.76 (m, 1H), 7.72 (s, 1H), 4.39 (m, 2H), 4.24 (d, *J* = 6.3 Hz, 2H), 4.15 (m, 2H), 2.79 (m, 1H), 1.09 (s, 9H), 1.08 (s, 9H). ^{13}C{^{1}H}NMR (300 MHz, $CDCl_3$): δ 163.74, 163.50, 149.39, 147.22, 138.41, 127.04, 126.94, 126.48, 123.45, 100.30, 68.35, 66.36, 39.93, 27.46, 27.37, 22.62, 20.67. HRMS: calcd. for $C_{22}H_{30}N_2O_7SiNa$ $[M + Na]^+$ 485.1720; found 485.1705

Compound 18: Compound **17** (1.03 g, 2.23 mmol) was dissolved in 43 mL THF and the flask was flushed with N_2. 103 mg (10% by mass) 10% Pd/C was added and N_2 exchanged with H_2. The reaction mixture was allowed to stir at room temperature under an H_2 atmosphere overnight. The resulting mixture was filtered over celite and solvents were evaporated under reduced pressure to yield the title compound as a bright yellow powder (1.01 g, quant) which was used directly in the next step without further purification.

Compound 19: Compound **18** (1.0 g, 2.34 mmol, 1 equiv) was dissolved in 13 mL dioxane and 42 mL of a 10% *w/v* $NaHCO_3$ solution (50 mmol, 21 equiv) was added. To the resulting slurry was added a solution of Fmoc-Cl (786 mg, 3.04 mmol, 1.3 equiv) in 42 mL dioxane dropwise at 0 °C over 1 h. The reaction mixture was allowed to stir at 0 °C for one hour and then at room temperature overnight. The resulting mixture was diluted with 60 mL H_2O and pH was brought to 2-3 by dropwise addition of 1 M HCl. The mixture was then extracted three times with CH_2Cl_2 and the combined organic phases were washed three times with brine, dried over $MgSO_4$. Solvents were evaporated under reduced pressure. The resulting oily residue was purified by column chromatography (100% CH_2Cl_2 to CH_2Cl_2/MeOH = 9/1) to yield the title compound as a light green powder (930 mg, 61%, purity by RP-HPLC: 98%). RP-HPLC (30-100% B, over 13 min) R_t =16.3 min. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 10.35 (br, 1H), 8.33 (br, 1H), 7.93 (m, 2H), 7.77 (m, 3H), 7.59 (m, 2H), 7.39 (m, 4H), 4.60 (d, *J* = 6.6 Hz, 2H), 4.43 (t, *J* = 6.6 Hz, 1H), 4.27 (m, 4H), 4.09 (m, 2H), 2.65 (m, 1H), 1.03 (s, 9H), 1.01 (s, 9H). ^{13}C{^{1}H}NMR (300 MHz, DMSO-*d*$_6$): δ 166.34, 161.99, 153.33, 143.69, 140.78, 137.48, 135.42, 128.91, 128.03, 127.74, 127.20, 125.11, 121.34, 120.21, 120.01, 116.07, 114.39, 100.72, 66.90, 66.39, 65.93, 46.56, 27.27, 27.06, 22.14, 19.93. HRMS: calcd. for $C_{37}H_{43}N_2O_7Si$ $[M + H]^+$ 655.2834; found 655.2826.

Compound 20: Methyl 8-nitro-(1H)-4-quinolinone-2-carboxylate (3.75 g, 15 mmol, 1 equiv) and fleshly distilled pyridine (4 mL, 50 mmol, 3.3 equiv) were dissolved in 100 mL anhydrous DCM. To the solution was slowly added triflic anhydride (3.75 mL, 22.5 mmol, 1.5 equiv) at 0 °C, under N_2 atmosphere. The reaction mixture was stirred at room temperature overnight and then the resulting mixture was neutralized with a saturated solution of NH_4Cl at 0 °C. The mixture was extracted three times with CH_2Cl_2. The combined organic phases washed with brine, dried over $MgSO_4$ and solvents were evaporated under reduced pressure. The resulting solid was triturated in water, then filtered and washed with water three times and dried to afford the title compound as a grey powder (5.6 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (dd, *J* = 8.7, 1.2 Hz, 1H), 8.30 (s, 1H), 8.24 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.92 (m, 1H), 4.08 (s, 3H), 1.57 (s, H_2O). ^{13}C{^{1}H}NMR (300 MHz, $CDCl_3$): δ 163.96, 153.55, 151.23, 140.88, 129.46, 126.06, 124.87, 123.25, 120.85, 116.60, 113.89, 53.91. HRMS: calcd. for $C_{12}H_8N_2O_7SF_3$ $[M + H]^+$ 381.0004; found 380.9990.

Compound 21: A mixture of compound **20** (2 g, 5.2 mmol, 1 equiv), KCN (0.68 g, 10.4 mmol, 2 equiv) and $Pd(PPh_3)_4$ (480 mg, 0.41 mmol, 0.08 equiv) in an anhydrous toluene/DMF (60 mL/6 mL) mixed solvent was heated at 100 °C for 2 h under N_2. Toluene was evaporated and the resulting mixture was diluted with ethyl acetate and washed three times with a saturated solution of $NaHCO_3$, once with water and once with brine. The organic layer was dried over $MgSO_4$ and then solvents were evaporated under reduced pressure. The resulting solid was triturated in methanol which was filtered and washed with methanol three times and dried to afford the title compound as a grey powder (1.25 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.64 (s, 1H), 8.49 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.27 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.98 (m, 1H), 4.09 (s, 3H), 1.55 (s, H_2O). ^{13}C{^{1}H}NMR (300 MHz,

DMSO-d_6): δ 163.28, 149.32, 148.42, 137.58, 130.98, 128.50, 127.31, 126.67, 125.76, 120.08, 114.57, 53.34. HRMS: calcd. for $C_{12}H_8N_3O_4$ $[M + H]^+$ 258.0515; found 258.0526.

Compound 23: Compound **21** (1.54 g, 6 mmol, 1 equiv) was suspended in a AcOH/THF (50 mL/10 mL) mixed solvent. The flask was flushed with N_2 and 154 mg (10% by mass) 10% Pd/C was then added. N_2 was exchanged with H_2 and the mixture stirred under the H_2 atmosphere at room temperature overnight. The resulting mixture was filtered over celite and solvents of the filtrate were evaporated under reduced pressure. The resulting solid was triturated in diethyl ether, filtered and dried, to yield compound **22** as, an acetic salt, a dark brown powder (quantitative) which was used directly in the next step without further purification. A mixture of the above compound **22** and DIPEA (2.1 mL, 12 mmol, 2 equiv) in DCM/CH_3CN (50 mL/30 mL) mixed solvent was cooled to 0 °C and followed by slowly adding a solution of Boc_2O (1.4 g, 6.6 mmol, 1.1 equiv) in DCM over 30 min. The reaction was allowed to stir at room temperature under N_2 overnight. The reaction mixture was washed three times with a saturated solution of NH_4Cl, once with water and once with brine. The organic layer was dried over $MgSO_4$ and then solvents were evaporated under reduced pressure. The resulting solid was triturated in acetonitrile. Then solid was isolated by filtration, washed with small amount of acetonitrile and dried to afford the title compound as a brown powder (1.8 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.45 (m, 1H), 7.28 (m, overlapped with C*H*Cl_3), 6.95 (dd, *J* = 7.5, 1.2 Hz, 1H), 4.99 (br, 1H), 4.80 (d, *J* = 5.7 Hz, 2H), 4.03 (s, 3H), 2.47 (br, H_2O), 1.49 (s, 9H). ^{13}C{^{1}H}NMR (300 MHz, $CDCl_3$): δ 166.13, 155.96, 145.96, 145.28, 144.39, 137.47, 130.32, 128.20, 118.84, 110.48, 110.34, 80.24, 52.86, 41.77, 28.51. HRMS: calcd. for $C_{17}H_{22}N_3O_4$ $[M + H]^+$ 332.1605; found 332.1605.

Compound 25: Compound **23** (1.3 g, 4 mmol, 1 equiv) was dissolved in 125 mL of THF/H_2O (4:1) mixed solvent. $LiOH·H_2O$ (252 mg, 6 mmol, 1.5 equiv) was added and the reaction mixture was allowed to stir at room temperature for another hour. Citric acid hydrate (420 mg, 2 mmol, 0.5 equiv) was then added to neutralize the reaction and the solvents were evaporated under reduced pressure to afford a suspension. It was then filtered and the solid was dried to afford compound **24** as a light yellow powder (quantitative) which was used directly in the next step without further purification. The above compound **24** was dissolved in 21 mL dioxane, and 71 mL of a 10% *w/v* $NaHCO_3$ aqueous solution (84 mmol, 21 equiv) was added. To the resulting slurry was added a solution of Fmoc-Cl (1.34 g, 5.2 mmol, 1.3 equiv) in 75 mL dioxane dropwise at 0 °C over 1 h. The mixture was stirred at 0 °C for a further hour, then at room temperature overnight. The reaction pH was brought to 4 by adding 5% *w/v* citric acid solution in water. The mixture was then extracted three times with CH_2Cl_2. The combined organic layers washed three times with brine, dried over $MgSO_4$ and solvents were evaporated under reduced pressure. To the resulting oily residue was added acetonitrile to allow full precipitation. The solid was isolated by filtration, washed with small amount of acetonitrile and dried to afford the title compound as a white powder (1.98 g, 92%, purity by RP-HPLC: 99%). RP-HPLC (60-70% B, over 10 min) R_t =9.9 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.60 (br, 1H), 10.47 (s, 1H), 8.36 (br, 1H), 8.10 (br, 1H),7.93 (d, *J* = 7.2 Hz, 2H), 7.77 (m,

5H), 7.36 (m, 4H), 4.64 (m, 4H), 4.46 (t, J = 6.6 Hz, 1H), 3.32 (s, H_2O), 1.43 (s, 9H). $^{13}C\{^1H\}$NMR (300 MHz, DMSO-d_6): δ 165.49, 155.87, 153.48, 148.30, 145.00, 143.69, 140.80, 136.54, 136.24, 129.48, 127.76, 127.23, 127.20, 125.13, 120.22, 117.65, 116.49, 116.03, 78.39, 66.42, 46.58, 40.79, 28.18. HRMS: calcd. for $C_{31}H_{30}N_3O_6$ $[M + H + Na]^{2+}$ 540.2129; found 540.2129.

Compound 26: 5-bromo-2-nitroaniline (40.6 g, 187 mmol, 1 equiv) was dissolved in 600 mL acetic acid at 70 °C. Ethylvinylether (55 mL, 560 mmol, 3 equiv), then concentrated H_2SO_4 (20 mL, 380 mmol, 2 equiv) were added to the solution. The mixture was stirred at 70 °C for 15 min, then another 15 min at 120 °C. After cooling down to room temperature, the reaction mixture was poured over ice and 1 L 30% *w/v* NaOH was added while stirring. The resulting suspension was stirred with ethyl acetate and then filtered through celite to eliminate a few tars. The organic phase was separated and dried over $MgSO_4$. Solvents were evaporated and the resulting solid was solubilised in 170 mL boiling isopropanol. After cooling down to room temperature, the mixture was sonicated to allow full precipitation. The solid was isolated by filtration, washed with cyclohexane, and dried to afford the title compound as a grey powder (22 g, 45%). ^1H NMR (300 MHz, DMSO-d_6): δ 8.53 (d, J = 8.7 Hz, 1H), 8.18 (d, J = 8.1 Hz, 1H), 8.07 (d, J = 8.1 Hz, 1H), 7.76 (d, J = 8.7 Hz, 1H), 3.32 (s, H_2O), 2.72 (s, 3H). $^{13}C\{^1H\}$NMR (300 MHz, DMSO-d_6): δ 162.73, 147.23, 138.47, 135.31, 128.72, 126.00, 125.59, 124.49, 123.41, 24.91. HRMS: calcd. for $C_{10}H_8BrN_2O_2$ $[M + H]^+$ 266.9764; found 266.9768.

Compound 27: compound **26** (22 g, 82 mmol, 1 equiv) and SeO_2 (18.3 g, 165 mmol, 2 equiv) were stirred in 300 mL pyridine at 80 °C for 48 hours. Pyridine was evaporated under reduce pressure. The resulting solid was stirred in boiling ethanol for 30 min. The hot mixture was filtered through celite and the filtrate was evaporated under reduce pressure. 1 L $KHSO_4/K_2SO_4$ buffer was added to the resulting oil and the flask was sonicated for 30 min. The resulting solid was isolated by filtration and dried to afford the title compound as a grey powder (23 g, 95%). ^1H NMR (300 MHz, DMSO-d_6): δ 13.90 (br, 1H), 8.83 (d, J = 8.7 Hz, 1H), 8.38 (d, J = 8.7 Hz, 1H), 8.30 (m, 2H), 3.32 (s, H_2O). $^{13}C\{^1H\}$NMR (300 MHz, DMSO-d_6): δ 165.15, 151.37, 147.92, 138.37, 137.47, 131.43, 128.31, 124.76, 124.62, 124.14. HRMS: calcd. for $C_{10}H_6BrN_2O_4$ $[M + H]^+$ 296.9506; found 296.9515.

Compound 28: compound **27** (22 g, 74 mmol, 1 equiv), K_2CO_3 (12 g, 89 mmol, 1.2 equiv) and benzyl bromide (11 mL, 89 mmol, 1.2 equiv) were stirred in 300 mL DMF at room temperature for 12 hours. DMF was evaporated under reduce pressure and water was added to the resulting solid. The mixture was extracted with ethyl acetate two times and the organic layer was dried over $MgSO_4$. After filtration, ethyl acetate was evaporated and the solid was triturated in ethanol. The resulting solid was isolated by filtration, washed with cyclohexane and dried to afford the title compound as a grey powder (18 g, 64%). ^1H NMR (300 MHz, DMSO-d_6): δ 8.87 (d, J = 9.0 Hz, 1H), 8.42 (d, J = 9.0 Hz, 1H), 8.32 (m, 2H), 7.43 (m, 5H), 5.49 (s, 2H), 3.32 (s, H_2O). $^{13}C\{^1H\}$NMR (300 MHz, DMSO-d_6): δ 163.30, 150.06, 147.82, 138.36, 137.76, 135.60, 131.70, 128.51, 128.42, 128.24,

128.01, 124.89, 124.86, 124.13, 67.19. HRMS: calcd. for $C_{17}H_{12}BrN_2O_4$ $[M + H]^+$ 386.9975; found 386.9982.

Compound 29: bis(dibenzylidene acetone)-palladium [0] (505 mg, 0.88 mmol, 0.02 equiv) and 1,2,3,4,5-pentaphenyl-1'-(di-*tert*-butylphosphino)ferrocene (624 mg, 0.88 mmol, 0.02 equiv) were added to a screw cap flask containing compound **28** (17 g, 44 mmol, 1 equiv) in 350 ml THF under nitrogen atmosphere. Then 2-*tert*-butoxy-2-oxoethyl zinc (II) bromide [4] (22.9 g, 88 mmol, 2 equiv) was added and the mixture was stirred at 70 °C for 12 h. The reaction vessel was allowed to cool to room temperature. The mixture was filtered and the filtrate was poured into 1.2 L water. Then $KHSO_4$ was added to bring the pH to approximately 3. The mixture was extracted with DCM three times. The combined organic layers was washed once with brine and dried over $MgSO_4$. The resulting solution was concentrated to around 50 mL and stirred with silica for 5 min, then filtered and washed with DCM. Solvent was evaporated and isopropanol was added to the resulting oil to allow precipitation occurred. The resulting solid was isolated by filtration and dried to afford the title compound as a white powder (8.4 g, 45%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.58 (d, *J* = 9.0 Hz, 1H), 8.32 (d, *J* = 9.0 Hz, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.52 (m, 2H), 7.41 (m, 3H), 5.50 (s, 2H), 4.04 (s, 2H), 1.59 (s, H_2O), 1.38 (s, 9H). ^{13}C{^{1}H}NMR (300 MHz, $CDCl_3$): δ 168.92, 164.49, 149.82, 148.24, 139.51, 136.74, 135.57, 134.36, 128.98, 128.79, 128.50, 128.28, 124.43, 122.63, 82.54, 67.86, 40.31, 28.04. HRMS: calcd. for $C_{23}H_{23}N_2O_6$ $[M + H]^+$ 423.1551; found 423.1559.

Compound 30: Compound **29** (8.86 g, 21 mmol, 1 equiv) was dissolved in 800 mL THF and the flask flushed with N_2. 886 mg (10% by mass) 10% Pd/C was then added. N_2 was exchanged with H_2 and the reaction was allowed to stir at room temperature under the H_2 atmosphere for one day. The mixture was filtered over celite and solvents were evaporated under reduced pressure to yield the title compound as an orange powder (6.16 g, 97%) which was used directly in the next step without further purification.

Compound 31: Compound **30** (4.72 g, 15.6 mmol, 1 equiv) was dissolved in 200 mL dioxane, and 265 mL of a 10% *w/v* $NaHCO_3$ aqueous solution (312 mmol, 20 equiv) was added. To the resulting slurry was added a solution of Fmoc-Cl (5.25 g, 20.3 mmol, 1.3 equiv) in 100 mL dioxane dropwise at 0 °C over 1 h. The reaction mixture was allowed to stir at 0 °C for one hour, then at room temperature overnight. The reaction pH was brought to 4 by adding 5% *w/v* citric acid solution in water. The mixture was then extracted three times with CH_2Cl_2. The combined organic layers were washed three times with brine and dried over $MgSO_4$. Solvents were evaporated under reduced pressure. The resulting oily residue was purified by column chromatography (100% CH_2Cl_2 to CH_2Cl_2/MeOH = 99/1) to afford the title compound as a white powder (5.3 g, 65%, purity by RP-HPLC: 98%). RP-HPLC (40-100% B, over 5 min) R_t =18.7 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.77 (s, 1H), 8.37 (m, 3H), 7.79 (m, 4H), 7.42 (m, 5H), 5.30 (s, DCM), 4.53 (d, *J* = 7.2 Hz, 2H), 4.28 (t, *J* =7.2 Hz, 1H), 3.73 (s, 2H), 1.55 (s, H_2O), 1.31 (s, 9H). ^{13}C{^{1}H}NMR (300 MHz, $CDCl_3$):

δ 170.06, 162.49, 153.40, 143.91, 143.85, 141.52, 137.48, 135.90, 135.03, 132.24, 128.67, 127.98, 127.36, 125.43, 124.67, 121.46, 120.19, 115.92, 81.76, 67.72, 47.18, 39.34, 28.03. HRMS: calcd. for $C_{31}H_{29}N_2O_6$ $[M + H]^+$ 525.2020; found 525.2018.

Compound 32: Methyl 4-bromo-8-nitroquinoline-2-carboxylate [1] (11.8 g, 38 mmol, 1 equiv) was dissolved in 600 mL of THF/H_2O (3:1) mixed solvent. $LiOH{\cdot}H_2O$ (2.41 g, 57 mmol, 1.5 equiv) was added and the reaction mixture was allowed to stir at room temperature for one hour. 1 M HCl was then added to acidify the reaction to approximately pH 3. The resulting mixture was filtered and the solid was washed with water and dried to afford the title compound as a light yellow powder (10.5 g, 94%). ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 8.40 (m, 3H), 7.94 (m, 1H), 3.49 (s, H_2O). $^{13}C\{^1H\}$NMR (300 MHz, DMSO-*d*$_6$): δ 165.32, 155.30, 148.40, 138.40, 134.06, 129.91, 128.42, 127.87, 126.69, 124.64. HRMS: calcd. for $C_{10}H_6BrN_2O_4$ $[M + H]^+$ 296.9506; found 296.9513.

Compound 33: Compound **32** (9.8 g, 33 mmol, 1 equiv), K_2CO_3 (5.34 g, 40 mmol, 1.2 equiv) and benzyl bromide (4.9 mL, 40 mmol, 1.2 equiv) were stirred in 200 mL DMF at room temperature for 12 hours. DMF was evaporated under reduce pressure and water was added to the resulting solid and filtered. The solid was washed once with water, once with ethanol, once with cyclohexane and dried to afford the title compound as a grey powder (12.3 g, 97%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57 (s, 1H), 8.48 (dd, *J* = 8.4, 1.2 Hz, 1H),8.15 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.82 (m, 1H),7.51 (m, 2H), 7.41 (m, 3H), 5.50 (s, 2H), 1.56 (s, H_2O). $^{13}C\{^1H\}$NMR (300 MHz, $CDCl_3$): δ 163.48, 149.66, 149.04, 139.59, 135.53, 135.30, 130.76, 129.51, 128.81, 128.62, 128.58, 128.38, 126.78, 125.30, 68.17. HRMS: calcd. for $C_{17}H_{12}BrN_2O_4$ $[M + H]^+$ 386.9975; found 386.9981.

Compound 34: To a flask containing a solution of compound **33** (9 g, 23.3 mmol, 1 equiv), bis(dibenzylidene acetone)-palladium [0] (275 mg, 0.47 mmol, 0.02 equiv) and 1,2,3,4,5-pentaphenyl-1'-(di-*tert*-butylphosphino)ferrocene (330 mg, 0.47 mmol, 0.02 equiv) in 100 mL anhydrous THF under N_2 atmosphere was added slowly a suspension of 2-*tert*-butoxy-2-oxoethyl zinc (II) bromide (12.2 g, 47 mmol, 2 equiv) in 64 mL anhydrous THF. The reaction mixture was stirred at room temperature for 4 h. The resulting mixture was filtered and the filtrate was poured into 1 L water. Then $KHSO_4$ was added to bring the pH to approximately 3. The mixture was extracted with DCM three times. The combined organic layers was washed once with brine and dried over $MgSO_4$. The resulting solution was concentrated to around 50 mL and stirred with silica for 5 min. It was then filtered and washed with DCM. Solvents were evaporated and isopropanol was added to the resulting oil to allow precipitation occurred. The solid was isolated by filtration and dried to afford the title compound as a white powder (5.8 g, 59%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (dd, *J* = 8.7, 1.2 Hz, 1H), 8.20 (s, 1H), 8.09 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.75 (m, 1H), 7.51 (m, 2H), 7.41 (m, 3H), 5.49 (s, 2H), 4.07 (s, 2H), 1.55 (s, H_2O), 1.39 (s, 9H). $^{13}C\{^1H\}$NMR (300 MHz, $CDCl_3$): δ 168.33, 164.49, 149.81, 149.54, 143.08, 139.46, 135.54, 129.45, 128.78, 128.51, 128.33, 127.95, 127.39, 124.27, 124.02, 82.71, 67.88, 40.34, 28.01. HRMS: calcd. for $C_{23}H_{23}N_2O_6$ $[M + H]^+$ 423.1551; found 423.1554.

Compound 35: Compound **34** (6 g, 14.2 mmol, 1 equiv) was dissolved in 300 mL THF and the flask flushed with N_2. 600 mg (10% by mass) 10% Pd/C was added and N_2 was exchanged with H_2. The reaction mixture was allowed to stir at room temperature under the H_2 atmosphere for one day. The resulting mixture was filtered over celite and solvents were evaporated under reduced pressure to afford the title compound as an yellow powder (4 g, 93%) which was used directly in the next step without further purification. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.00 (s, 1H), 7.44 (m, 1H), 7.06 (dd, J = 8.4, 1.2 Hz, 1H), 6.89 (dd, J = 7.5, 1.2 Hz, 1H), 6.60 (br, 2H), 4.09 (s, 2H), 3.33 (br, H_2O), 1.38 (s, 9H). ^{13}C{^{1}H}NMR (300 MHz, DMSO-d_6): δ 169.36, 165.68, 147.19, 142.67, 142.61, 135.67, 130.53, 129.38, 121.18, 108.95, 108.69, 80.79, 39.01, 27.61. HRMS: calcd. for $C_{16}H_{19}N_2O_4$ $[M + H]^+$ 303.1339; found 303.1352.

Compound 36: compound **35** (3.6 g, 12 mmol, 1 equiv) was dissolved in 60 mL dioxane, and 211 mL of a 10% *w/v* $NaHCO_3$ aqueous solution (252 mmol, 21 equiv) was added. To the resulting slurry was added a solution of Fmoc-Cl (4.03 g, 15.6 mmol, 1.3 equiv) in dioxane (200 mL) dropwise at 0 °C over 1 h. The reaction mixture was allowed to stir at 0 °C for one hour, then at room temperature overnight. The reaction pH was brought to 4 by adding 5% *w/v* citric acid solution in water. The mixture was then extracted three times with CH_2Cl_2. The combined organic layers were washed three times with brine and dried over $MgSO_4$. Then solvents were evaporated under reduced pressure. The resulting oily residue was added diethyl ether to allow full precipitation. Solid was isolated by filtration, washed with diethyl ether and dried to afford the title compound as a white powder (3.9 g, 62%, purity by RP-HPLC: 97%). RP-HPLC (60-80% B, over 10 min) R_t =10.1 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.98 (br, 1H), 8.40 (br, 1H), 8.23 (s, 1H), 7.80 (d, J = 7.5 Hz, 2H), 7.68 (m, 4H),7.42 (m, 4H), 4.69 (d, J = 6.0 Hz, 2H), 4.40 (t, J = 6.3 Hz, 1H), 4.06 (s, 2H), 1.55 (br, H_2O), 1.41 (s, 9H). ^{13}C{^{1}H}NMR (300 MHz, $CDCl_3$): δ 168.97, 165.80, 154.35, 144.43, 143.85, 143.80, 141.49, 137.31, 135.61, 130.05, 129.28, 127.94, 127.34, 125.10, 122.34, 120.15, 117.28, 117.02, 82.47, 67.83, 47.15, 40.31, 28.05. HRMS: calcd. for $C_{31}H_{29}N_2O_6$ $[M + H]^+$ 525.2020; found 525.2022.

S3 Methods for X-ray crystallography

Crystallization and X-ray diffraction measurements

For crystallization, lyophilized powders of foldamers **2-6** were dissolved using ultrapure water (for **3**, in water/acetonitrile 3:1) such that the foldamer solutions had a final concentration of 2 mM. Crystallization experiments were performed at 293K using standard aqueous hanging-drop vapor diffusion in 24-well Linbro-style plates. Screening of crystallization conditions was carried out using commercial sparse matrix screen JBScreen Basic 1 to 4, from Jena Biosciences.[5,6] The aqueous drops composed of 0.75 to 1.0 µL of the foldamer solution and an equal volume of the crystallization reagent. The crystallization conditions are summarized in **Table S1**. For low

temperature diffraction measurements, the crystals (see **Figure S1**) were mounted on cryo-loops after quick soaking on Paratone-N oil and flash-frozen. Diffraction measurements were carried out at Proxima-1 beamline (Synchrotron SOLEIL, Paris) using a DECTRIS PILATUS 6M pixel-array detector; at ID29 and BM30A beamlines (ESRF, Grenoble) using ADSC Q315r CCD detector and at IECB x-ray facility (UMS3033) using a micro-focus rotating anode (2.9 kW) Rigaku FRX diffractometer, with Cu Kα radiation and a PILATUS 200K hybrid pixel detector. Diffraction data were processed and scaled using the packages *CrystalClear-SM 1.36*, *XDS* and *CrysAlisPro*.[7,8,9]

Table S1: Crystallization conditions of the water soluble Foldamers

Foldamer	Crystallization reagent	Crystallogenesis	
		Duration	Crystal size
2	100 mM HEPES (pH 7.5), 200 mM $CaCl_2$, 28% v/v PEG 400	21 days	(0.10 x 0.04 x 0.04) mm
3	100 mM HEPES (pH 7.5), 500 mM $(NH_4)_2SO_4$, 30% v/v (+/-) MPD	14 days	(0.50 x 0.01 x 0.01) mm
4	100 mM HEPES (pH 7.0), 200 mM $(NH_4)_2SO_4$, 20 mM $Mg(OAc)_2$, 5% w/v PEG 4000	2 days	(0.15 x 0.15 x 0.03) mm
4	50 mM Imidazole (pH 7.2), 20 mM $ZnSO_4$, 10% w/v PEG 4000	2 days	(0.07 x 0.07 x 0.03) mm
5	100 mM MES (pH 6.5), 200 mM $Ca(OAc)_2$, 28% w/v PEG 8000	5 days	(0.15 x 0.05 x 0.03) mm
6	100 mM MES (pH 6.5), 200 mM $(NH_4)_2SO_4$, 30% w/v PEG 8000	30 days	(0.20 x 0.03 x 0.03) mm

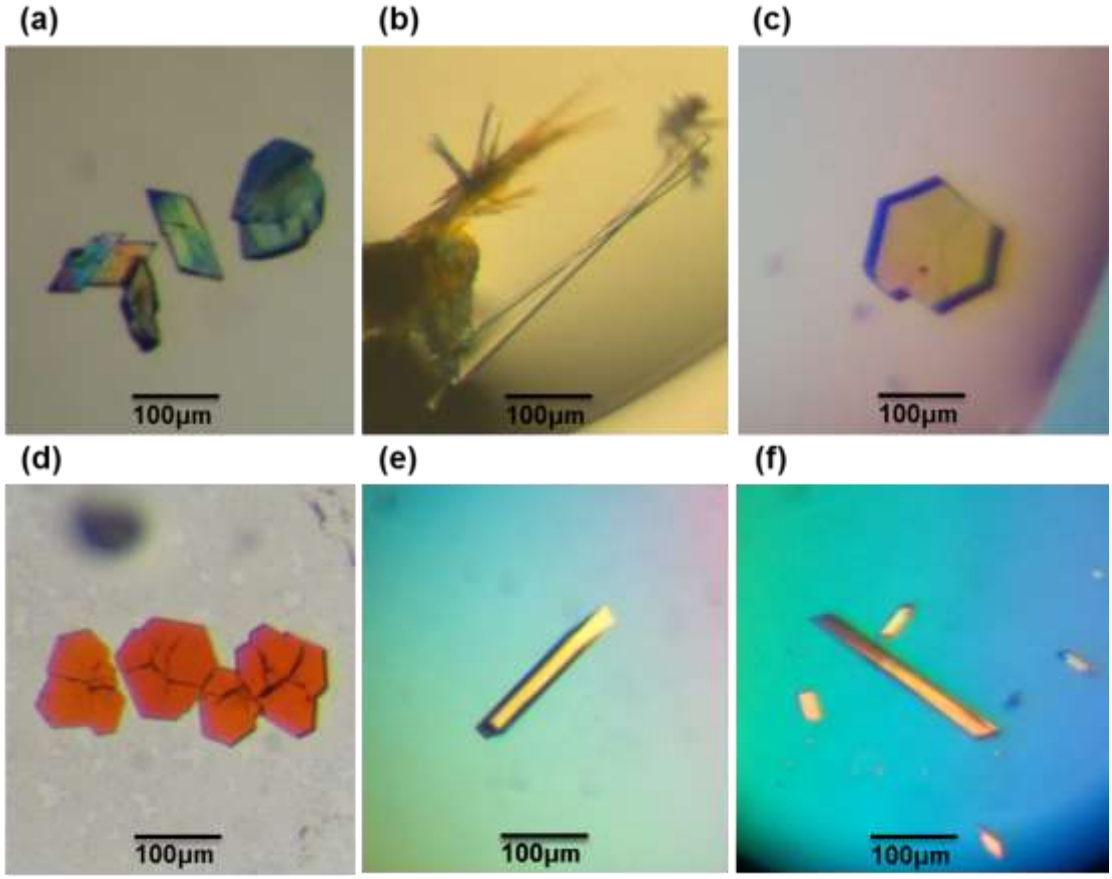


Figure S1: Crystals of water soluble Foldamers: (a) **2**, (b) **3**, (c, d) **4**, (e) **5** and (e) **6**

Structure determination and refinement

All structures were solved by direct method using the charge-flipping program *Superflip*.[10] The phase set calculated allowed identifying most of Foldamers (including the N-terminal tails for **5** and **6**). The structures were refined by full-matrix least-squares method on F^2 with *SHELXL-2014* [11] within the *Olex2* suite.[12] Non-hydrogen atoms for main chains were refined with anisotropic displacement parameters. In case of side chains and solvent molecules, the non-hydrogen atoms were refined with anisotropic or isotropic displacement parameters. Hydrogen atoms were included for the Foldamers in idealized positions using HFIX and refined with a riding model. For solvent molecules, positions of hydrogen atom were not determined. After several attempts to model the disordered water molecules, the PLATON/SQUEEZE[13] procedure was implemented for all structures. DFIX, DELU, SIMU, ISOR, RIGU, AFIX 116, EADP instructions were used to model displacement parameters and the geometry of molecules. The FVAR function was used during refinement of occupancy factors of disordered parts.

The final cif files were checked using IUCR's *checkcif* algorithm. Due to the characteristics of the crystals mentioned above (large volume fractions of disordered solvent molecules and side chains, weak diffraction intensity, incompleteness of data and moderate resolution) a number of A-

level and B-level alerts remain in the check cif files. These alerts are explicitly listed below and have been divided into two groups. They are inherent to the data and refinement procedure. They illustrate the limited practicality of the *checkcif* tool for medium sized molecule crystallography. The first group illustrates the weak quality of the data and refinement statistics if compared to that expected for small molecule structures from highly diffracting crystals. The second group is connected with decisions made during refinement and explained below.

Group 1 alerts in crystal structures of **2**, **3**, **5** and **6**:

RFACR01_ALERT_3_A The value of the weighted R factor is > 0.45

THETM01_ALERT_3_A The value of sine(theta_max)/wavelength is less than 0.550

PLAT029_ALERT_3_A _diffrn_measured_fraction_theta_full value Low

PLAT084_ALERT_3_B High wR2 Value (i.e. > 0.25)

PLAT234_ALERT_4_A Large Hirshfeld Difference

PLAT934_ALERT_3_B Number of (Iobs - Icalc)/SigmaW > 10

REFNR01_ALERT_3_B Ratio of reflections to parameters is < 8 for a centrosymmetric structure

PLAT088_ALERT_3_B Poor Data / Parameter Ratio

PLAT341_ALERT_3_B Low Bond Precision on C - C Bonds

PLAT911_ALERT_3_B Missing # FCF Refl Between THmin & STh/L= 0.526

Group 2 alerts for crystal structure **2**:

PLAT306_ALERT_2_B Isolated Oxygen Atom (H - atoms Missing ?)

This alert concerns position of hydrogen atoms not calculated for solvent molecules

PLAT430_ALERT_2_B Short Inter D...A Contact

This alert concerns disordered solvent molecules.

Group 2 alerts for crystal structure **3**:

PLAT245_ALERT_2_A U(iso) H35 Smaller than U(eq) C35 by ... 0.150 AngSq

PLAT312_ALERT_2_A Strange C-O-H Geometry (C-O < 1.25 Ang) .... O2BA Check

PLAT241_ALERT_2_B High 'MainMol' Ueq as Compared to Neighbors of C01U Check

These alerts concern disorder in diol side chains.

PLAT097_ALERT_2_B Large Reported Max. (Positive) Residual Density 1.49 eA-3

This concerns a residual peak in **3** corresponding to symmetry related, partially occupied side chain.

Group 2 alerts for crystal structure **5**:

PLAT201_ALERT_2_B Isotropic non-H Atoms in Main Residue(s) ..... 2 Report

This alert concerns high thermal motion in few side chains or N-terminal tail.

PLAT213_ALERT_2_B Atom N67C has ADP max/min Ratio ..... 4.2 oblate

PLAT213_ALERT_2_B Atom C18C has ADP max/min Ratio ..... 4.6 prolat

PLAT213_ALERT_2_B Atom C26G has ADP max/min Ratio ..... 4.3 prolat

PLAT213_ALERT_2_B Atom C36C has ADP max/min Ratio ..... 4.2 oblate

This alert concerns main chain atoms that were not ideally shaped, however with correct atom type assignment.

PLAT220_ALERT_2_B Non-Solvent Resd 1 C Ueq(max)/Ueq(min) Range 9.4 Ratio

PLAT220_ALERT_2_B Non-Solvent Resd 1 O Ueq(max)/Ueq(min) Range 8.9 Ratio

PLAT241_ALERT_2_B High 'MainMol' Ueq as Compared to Neighbors of O8D Check

PLAT241_ALERT_2_B High 'MainMol' Ueq as Compared to Neighbors of O24H Check

PLAT242_ALERT_2_B Low 'MainMol' Ueq as Compared to Neighbors of Ca02 Check

PLAT242_ALERT_2_B Low 'MainMol' Ueq as Compared to Neighbors of O2E Check

PLAT242_ALERT_2_B Low 'MainMol' Ueq as Compared to Neighbors of C14H Check

PLAT242_ALERT_2_B Low 'MainMol' Ueq as Compared to Neighbors of C22H Check

PLAT242_ALERT_2_B Low 'MainMol' Ueq as Compared to Neighbors of C26D Check

PLAT242_ALERT_2_B Low 'MainMol' Ueq as Compared to Neighbors of C26H Check

These alerts concern thermal motions in side chain or bound Ca^{2+} ions.

PLAT306_ALERT_2_B Isolated Oxygen Atom (H-atoms Missing ?)

This alert concerns position of hydrogen atoms not calculated for solvent molecules

PLAT430_ALERT_2_B Short Inter D...A Contact

This alert concerns disordered solvent molecules.

Group 2 alerts for crystal structure **6**:

PLAT430_ALERT_2_A Short Inter D...A Contact O1 .. O55 .. 2.48 Ang.

PLAT430_ALERT_2_A Short Inter D...A Contact O2 .. O9A .. 2.47 Ang.

PLAT430_ALERT_2_A Short Inter D...A Contact O0AA .. O8BA .. 2.32 Ang.

PLAT430_ALERT_2_A Short Inter D...A Contact O11 .. O9AA .. 2.43 Ang.

PLAT430_ALERT_2_A Short Inter D...A Contact O1DA .. O24 .. 2.41 Ang

This alert concerns disordered solvent molecules.

PLAT201_ALERT_2_B Isotropic non - H Atoms in Main Residue(s)

This alert concerns high thermal motion of side chains or N-terminal tail

PLAT097_ALERT_2_B Large Reported Max. (Positive) Residual Density 1.27 eA-3

This alert concerns a peak that was observed to have short contact with the side chain.

PLAT241_ALERT_2_B High 'MainMol' Ueq as Compared to Neighbors of C7F Check

PLAT242_ALERT_2_B Low 'MainMol' Ueq as Compared to Neighbors of C10H Check

PLAT242_ALERT_2_B Low 'MainMol' Ueq as Compared to Neighbors of C4E Check

PLAT242_ALERT_2_B Low 'MainMol' Ueq as Compared to Neighbors of C11 Check

PLAT242_ALERT_2_B Low 'MainMol' Ueq as Compared to Neighbors of C279 Check

PLAT242_ALERT_2_B Low 'MainMol' Ueq as Compared to Neighbors of C16F Check

PLAT242_ALERT_2_B Low 'MainMol' Ueq as Compared to Neighbors of C82 Check

PLAT242_ALERT_2_B Low 'MainMol' Ueq as Compared to Neighbors of C4K Check

This alert concerns high thermal motion of side chains or N-terminal tail

PLAT306_ALERT_2_B Isolated Oxygen Atom (H-atoms Missing ?)

This alert concerns position of hydrogen atoms not calculated for solvent molecules

Refinement statistics are given in **Table S2**. Atomic coordinates and structure factors for the crystal structures of **2**, **3**, **5** and **6** have been deposited in the Cambridge Crystallographic Data Centre (CCDC) with accession codes 1521878, 1525865, 1525770 and 1523119 respectively. These data are available free of charge upon request (www.ccdc.cam.ac.uk/).

Table S2: Crystallographic data for the water soluble Foldamers

Foldamers	**2**	**3**	**5**	**6**
Formula	$C_{172}H_{112}Ca_2N_{32}O_{111}S_8$	$C_{56}H_{53..25}N_8O_{17.25}$	$C_{205.5}H_{135.5}Ca_{6.25}N_{32}O_{82.50}$	$C_{397}H_{230}N_{64}O_{135}$
M	4539.58	1098.32	4623.43	8056.44
Crystal system	Monoclinic	Triclinic	Orthorhombic	Monoclinic
Z	8	2	8	4
Space group	*C*2/*c*	*P*-1	*Pbca*	$P2_1/n$
a/Å	34.1155 (11)	7.4720 (15)	34.859 (7)	28.255 (4)
b/Å	45.9981 (11)	20.571 (4)	29.286 (6)	51.842 (7)
c/Å	33.3135 (14)	24.604 (5)	51.432 (10)	30.331 (4)
α/°	90	69.40 (3)	90	90
β/°	109.407 (4)	84.50 (3)	90	110.957 (2)
γ/°	90	85.66 (3)	90	90
V/Å^3	49307 (3)	3520.0 (14)	52506 (18)	41490 (10)
T/K	130	100	100	100
ρ/g cm^{-3}	1.277	1.059	1.304	1.290
Color and shape	Yellow rhombohedra	Yellow needles	Yellow orthorhombic	Yellow needles
Size (mm)	0.10 x 0.04 x 0.04	0.50 x 0.01 x 0.01	0.15 x 0.05 x 0.03	0.20 x 0.03 x 0.03
λ/Å	1.54178	0.77492	0.8856	1.54178
μ/mm^{-1}	1.901	0.096	0.383	0.848
Collected reflections	19582	7913	27211	51893
unique data [$Fo>2\ \sigma Fo$)]	10778	5206	25357	23207
R_{int} %	0.0813	0.0601	0.0389	0.0726
Parameters/restraints	2558/551	728/166	2720/219	4313/3954
R_1, wR_2 ($I > 2\sigma(I)$)	0.1324/0.4119	0.1300/0.4082	0.1568/0.5118	0.1773/0.5229
Goodness of fit	1.480	1.643	2.893	1.688
Total potential solvent accessible void volume from SQUEEZE Å^3	7194.4	1027.5	12657.7	5626
Electron count/cell	2147	311	4648	1526
CCDC number	1521878	1525865	1525770	1523119

Space group and unit cell for **4**: $P2_1/n$; a = 19.3860 Å, b = 51.1220 Å, c = 30.5320 Å, α = 90°, β = 92.318° and γ = 90°

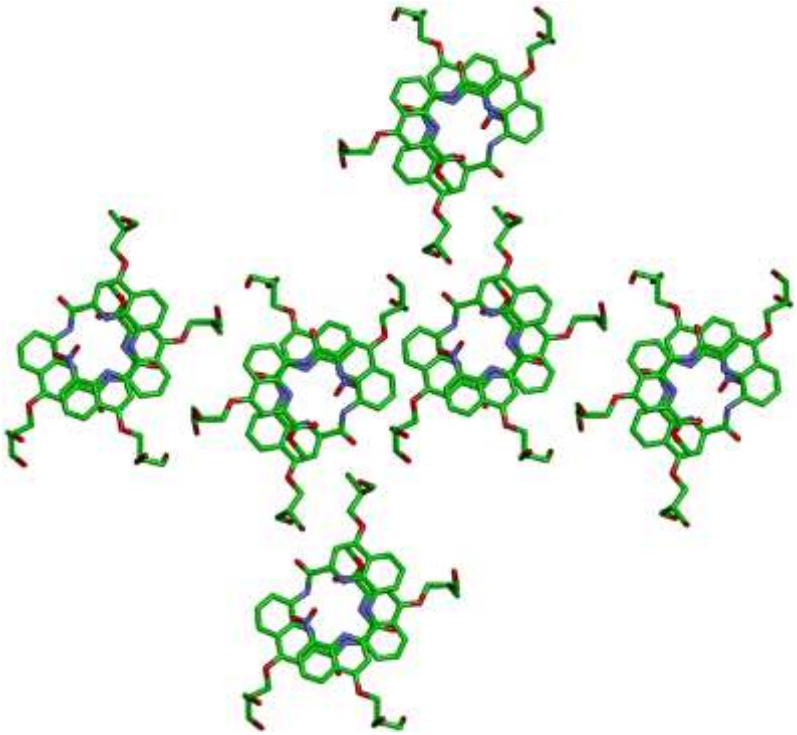


Figure S2. Crystal packing of **3**.

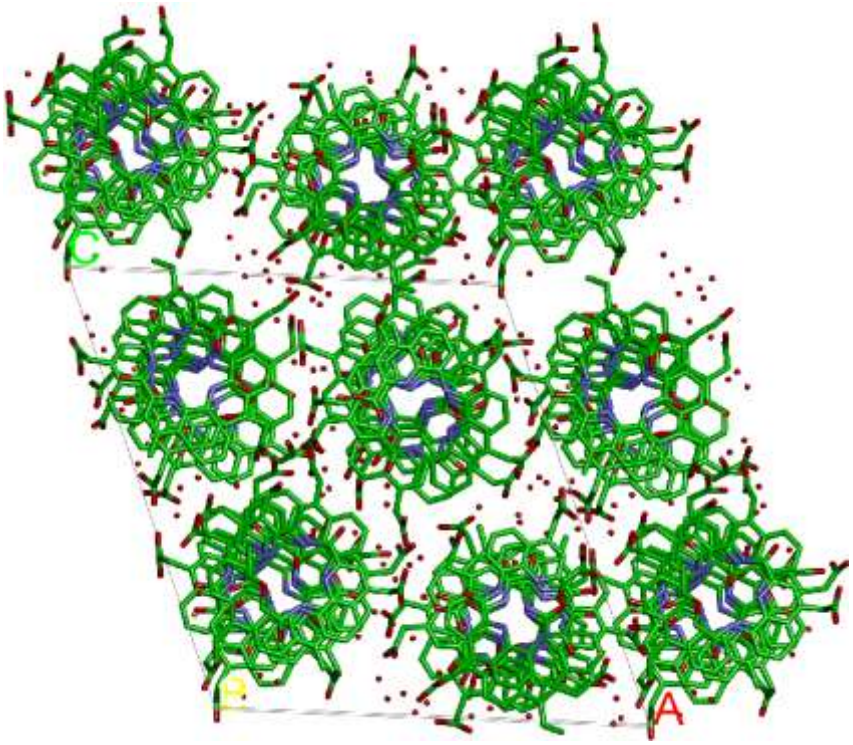


Figure S3. Crystal packing of **6**.

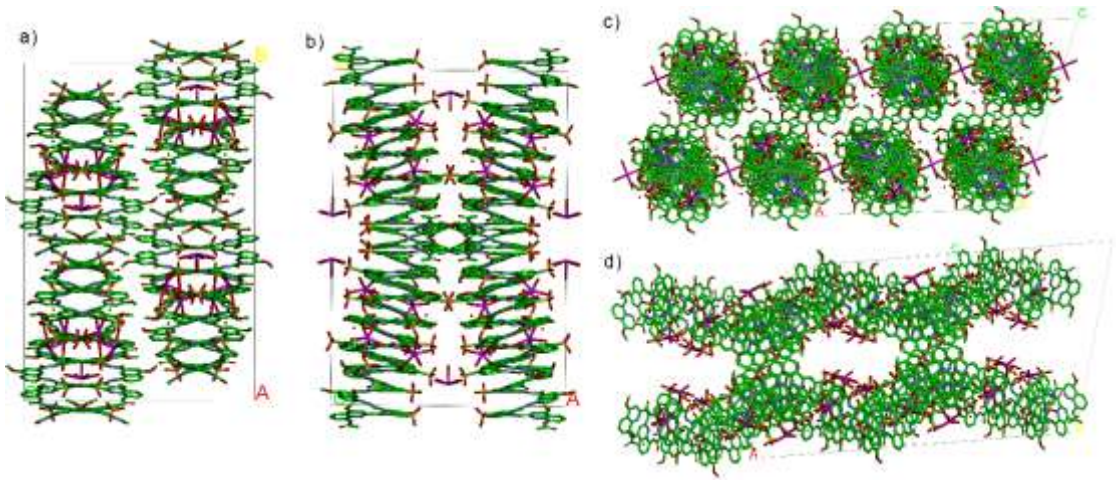


Figure S4. Crystal packing of **2**. (a) from cell axis A; (b) from cell axis C; (c) from cell axis B; (d) from a diagonal of the AB plane.

S4 Solubility Study [14]

Determination of concentration via NMR: Compound **1** (2.57 mg) was dissolved in DMSO-d_6 (500 uL) containing 2.0 mM pyridine (figure S5a), to which was added pyridine again to reach 4.0 mM (figure S5b). The concentration of **1** could then be ascertained (2.4 mM) by comparing integral difference of pyridine signals and nearby foldamer signal.

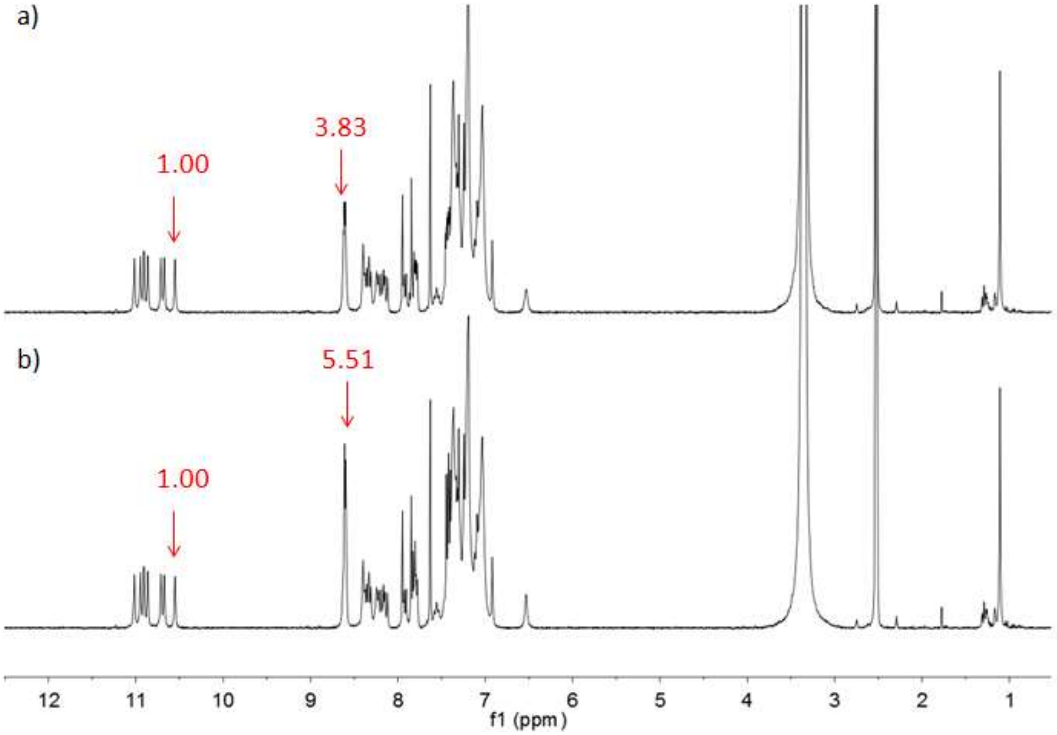


Figure S5: Expansion of ^{1}H NMR spectra of compound **1** in DMSO-d_6 containing (a) 2.0 mM or (b) 4.0 mM pyridine. Integrals used are marked (pyridine 2 x CHAr δ: 8.6 ppm). The integral of one foldamer signal was always set to 1.00 as the reference.

Generation of UV calibration curve: The NMR sample of **1** was then serially diluted with MilliQ-water (containing 0.1 M HCl) and UV absorbance at 370 nm was recorded using a 1 cm path length cuvette. With these data, a calibration curve (Figure S6) was generated. Then, according to the formula Abs = ε·c·l, the extinction coefficient (ε) of **1** at 370 nm was obtained as 20959 $L \cdot mol^{-1} \cdot cm^{-1}$.

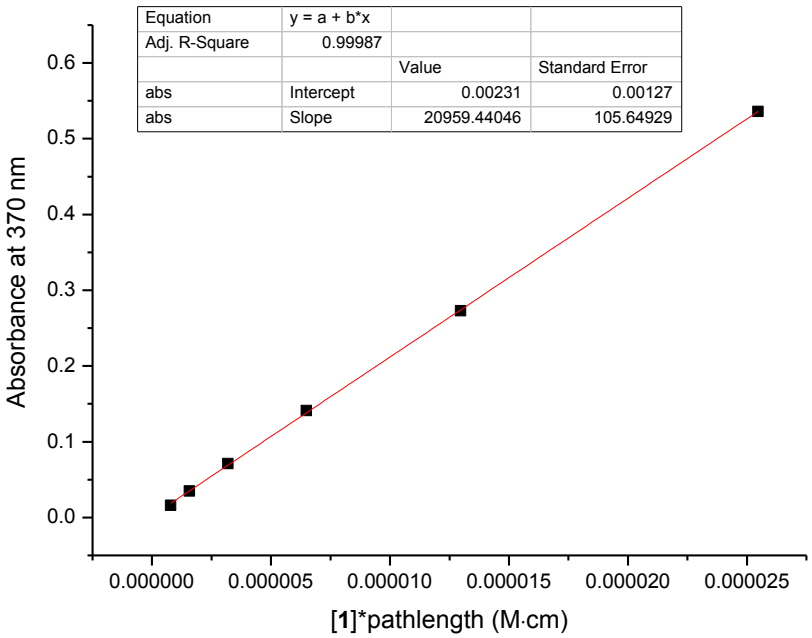


Figure S6: UV absorbance calibration curve affording the extinction coefficient (ε) of **1** at 370 nm as 20959 $L \cdot mol^{-1} \cdot cm^{-1}$

Calculation of solubility: A saturated solution of **1** was produced by adding excess solid material (10.4 mg) to MilliQ-water (30 µL, containing 0.1 M HCl) at 20 °C. The homogeneous suspension was then centrifuged at 6000 rpm for 5 minutes to afford a clear supernatant at the top. An accurately measured volume (2.0 µL) of the supernatant was then removed and diluted to a concentration appropriate for UV absorbance measurement. According to the formula Abs = ε·c·l, the concentration ([**1**] measured, see table S3) of measured solution could be extrapolated. Thereby, with the known dilution factor, original concentration of saturated solution could also be deduced (experiment was repeated twice, table S3).

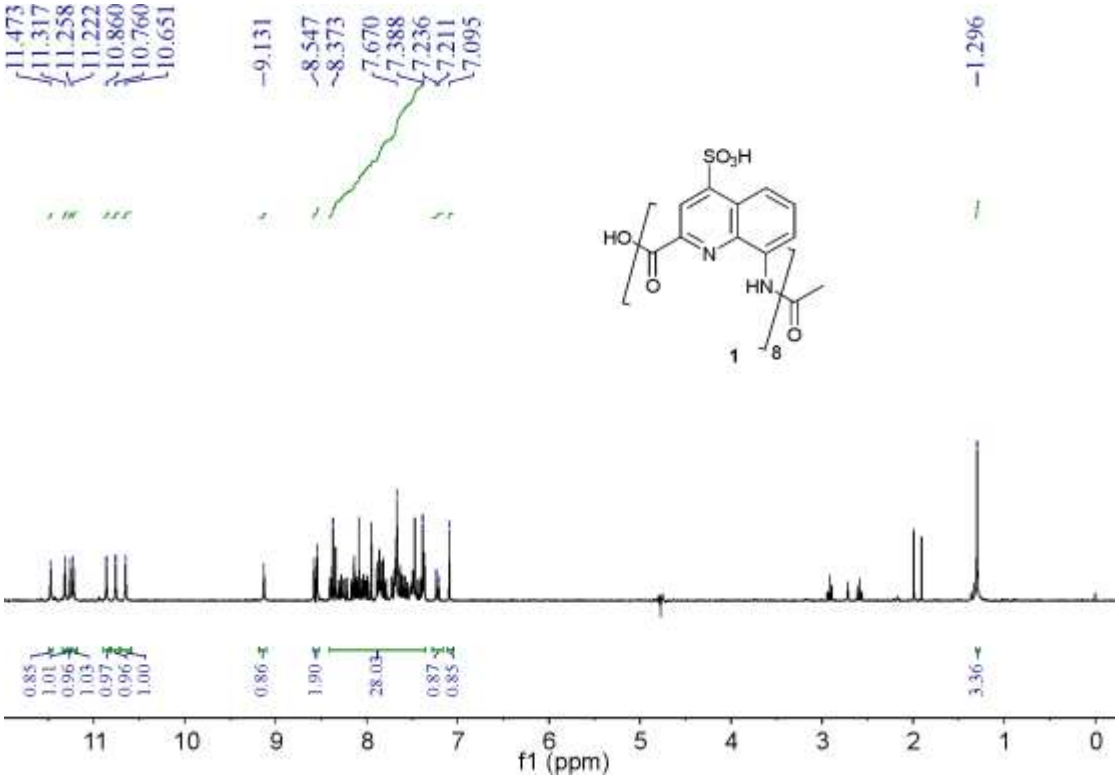
Table S3: Determination of solubility

Experiment	Abs	Volume (µL) [a]	[**1**] measured (mM)	Solubility (mM) [b]
1	0.530	0.24	0.0253	105
2	0.553	0.24	0.0264	110
3	0.543	0.24	0.0259	108
Average	-	-	-	108

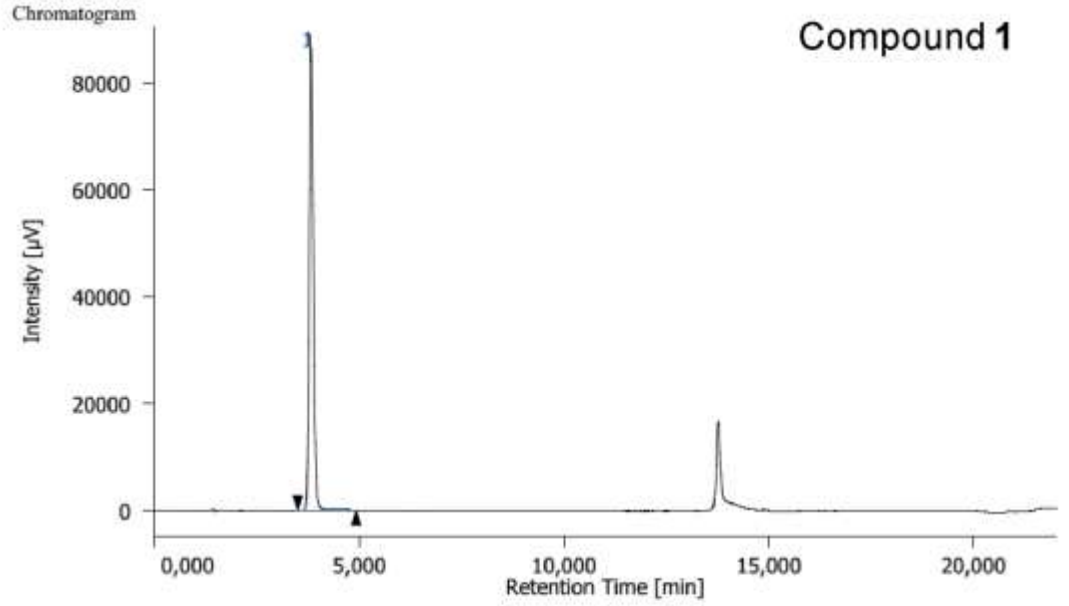
[a] Refer to the net (after calculation) volume of original saturated solution. [b] Equal to the concentration of the original saturated solution of **1**.

S5 1D NMR spectra and RP-HPLC Chromatograms

Compound 1: ^{1}H NMR (300 MHz, 10%D_2O/H_2O *v/v* %)



Compound 1: RP-HPLC. The peak near 14 mn belongs to the solvent and is present in the blank.

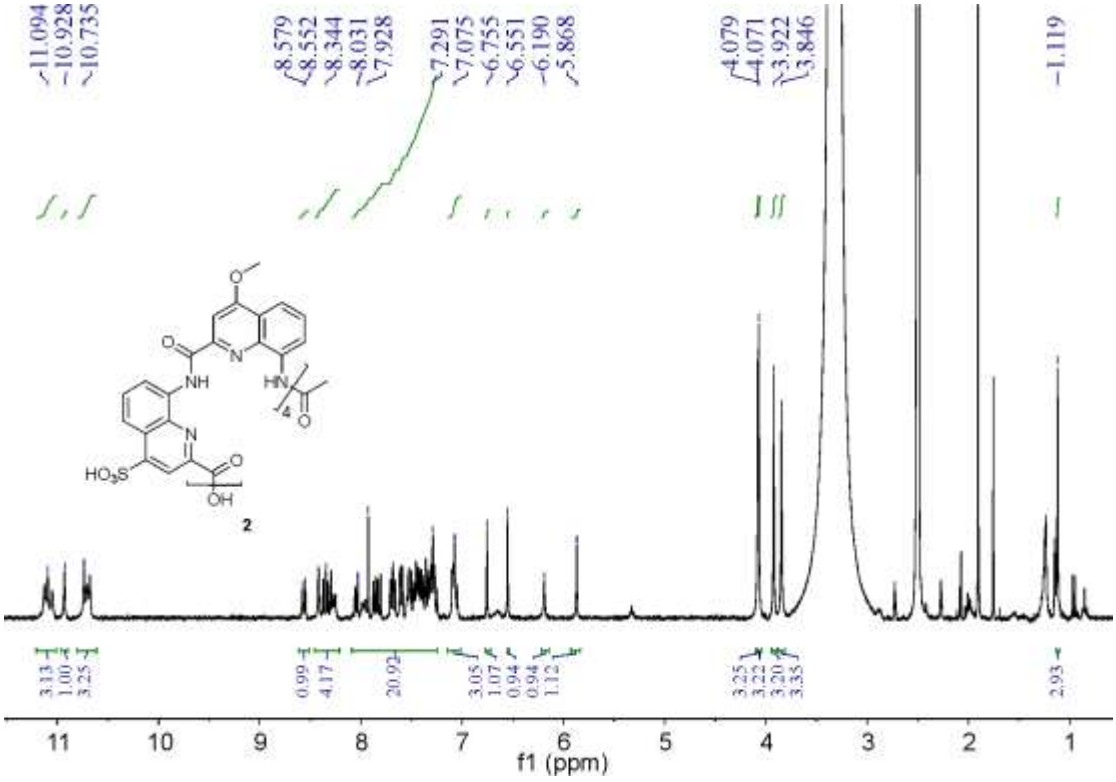


Peak Information

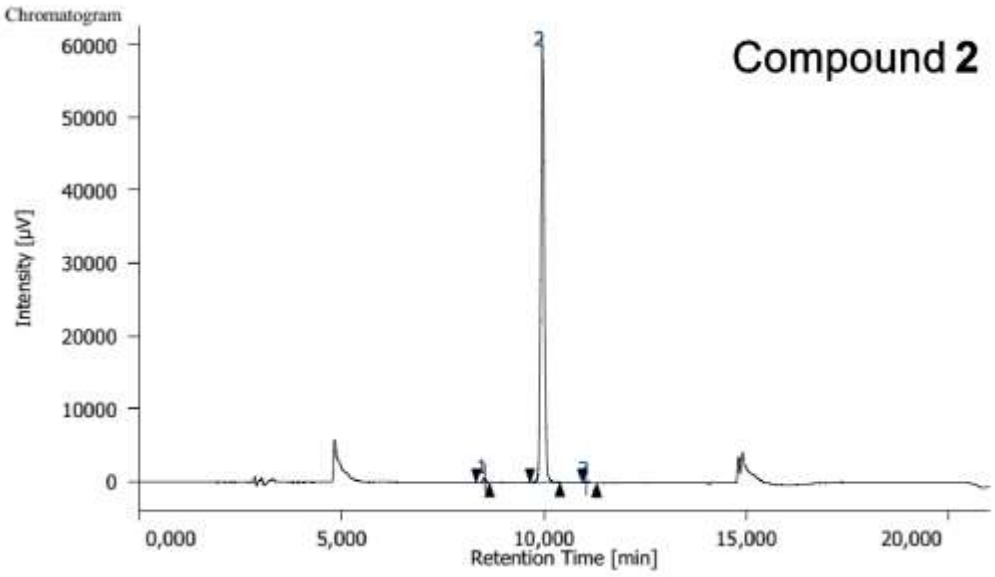
#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor
1	Unknown	3	3,817	633026	86355	100,000	100,000	N/A	6561	N/A	1,239

#	Warning
1	

Compound 2: ^{1}H NMR (300 MHz, DMSO-d_6)



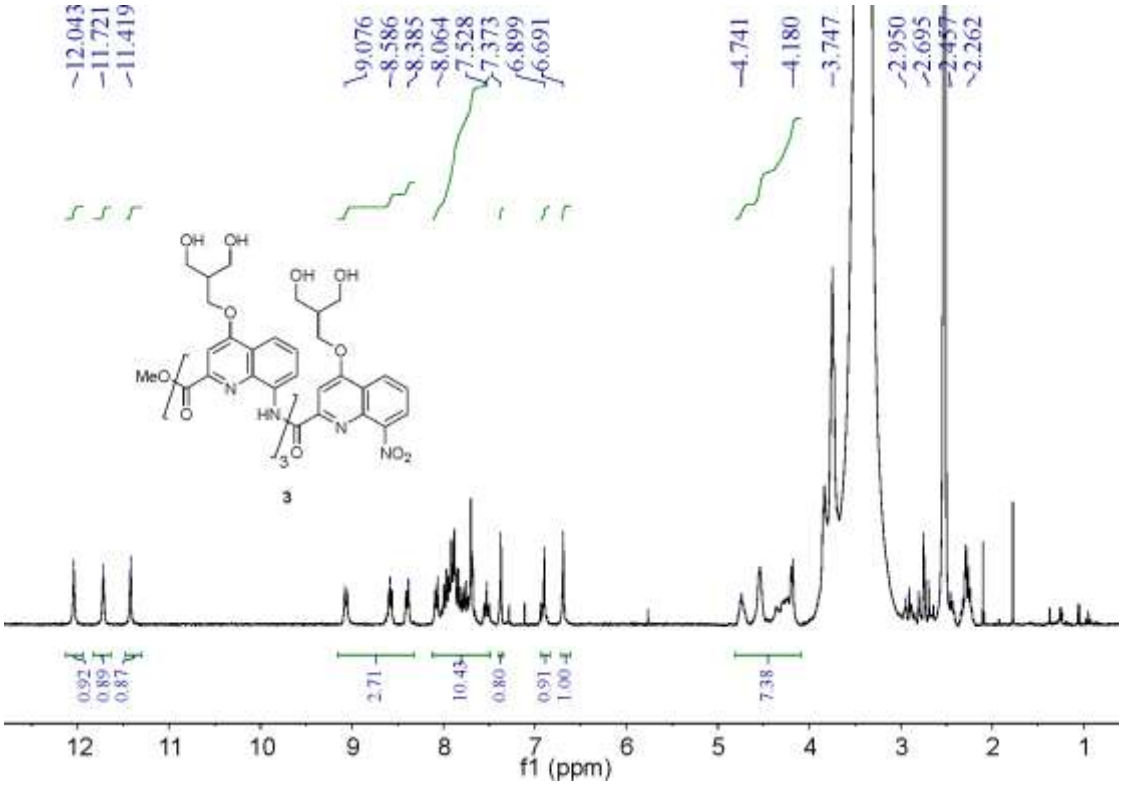
Compound 2: RP-HPLC. The peaks near 5 and 15 mn belong to the solvent and are present in the blank.



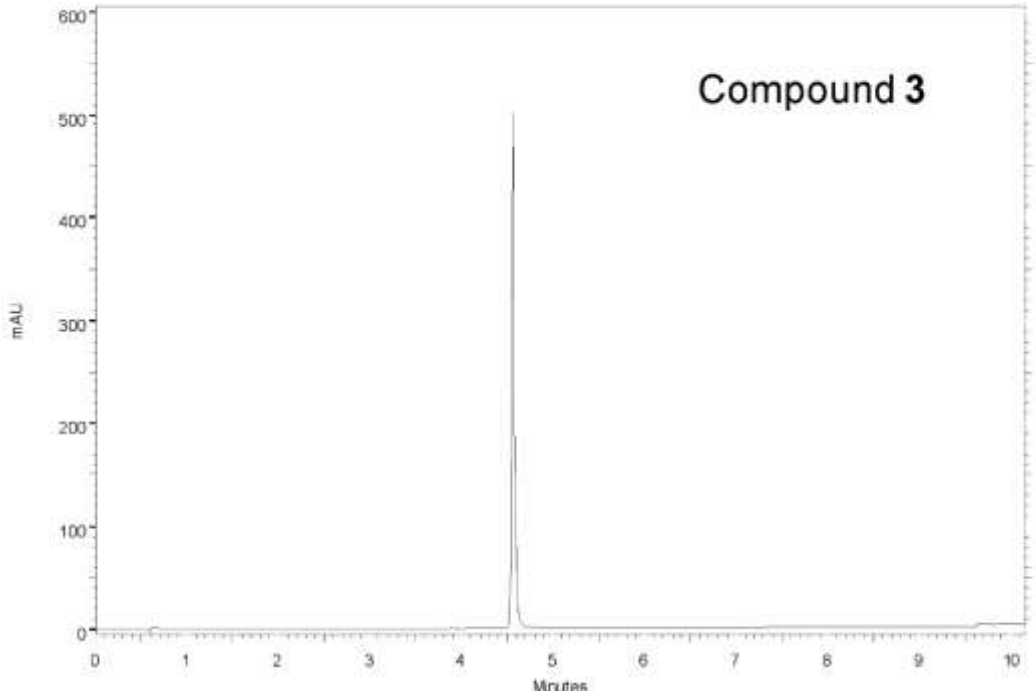
Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	8,525	4093	671	1,043	1,107	N/A	45349	8,736	1,001	
2	Unknown	3	9,958	386689	59667	98,516	98,497	N/A	55636	6,332	1,086	
3	Unknown	3	11,050	1732	239	0,441	0,395	N/A	62470	N/A	1,407	

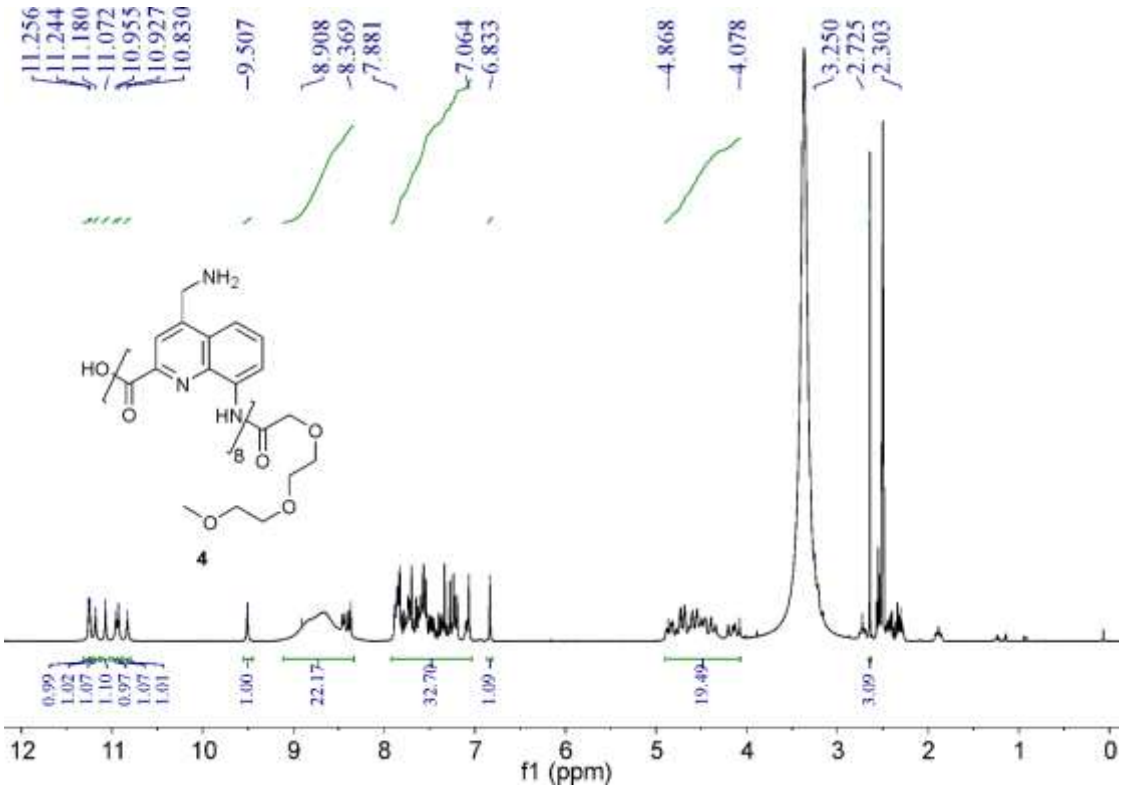
Compound 3: ^{1}H NMR (300 MHz, DMSO-d_6)



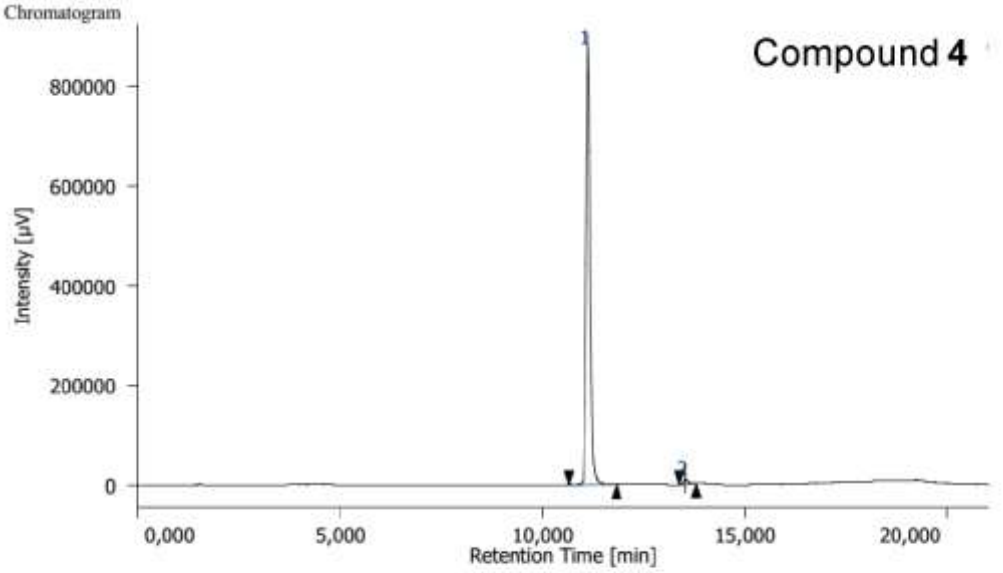
Compound 3: RP-HPLC



Compound 4: ^{1}H NMR (300 MHz, DMSO-d_6)



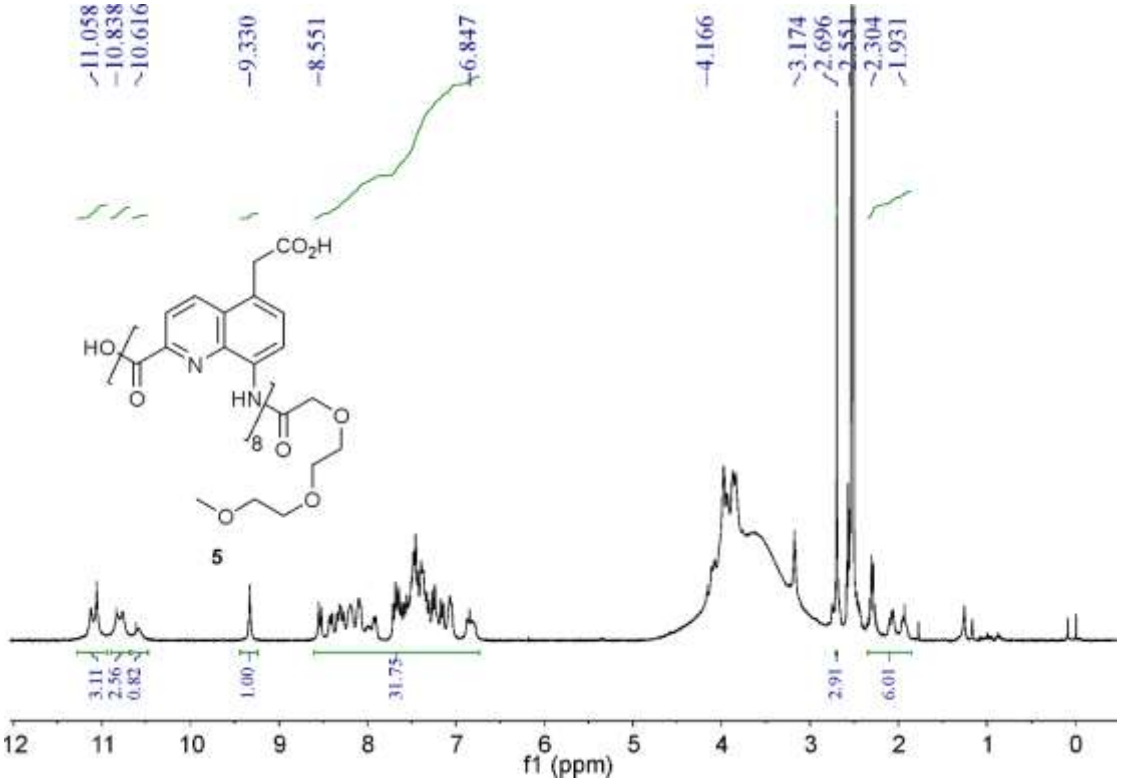
Compound 4: RP-HPLC



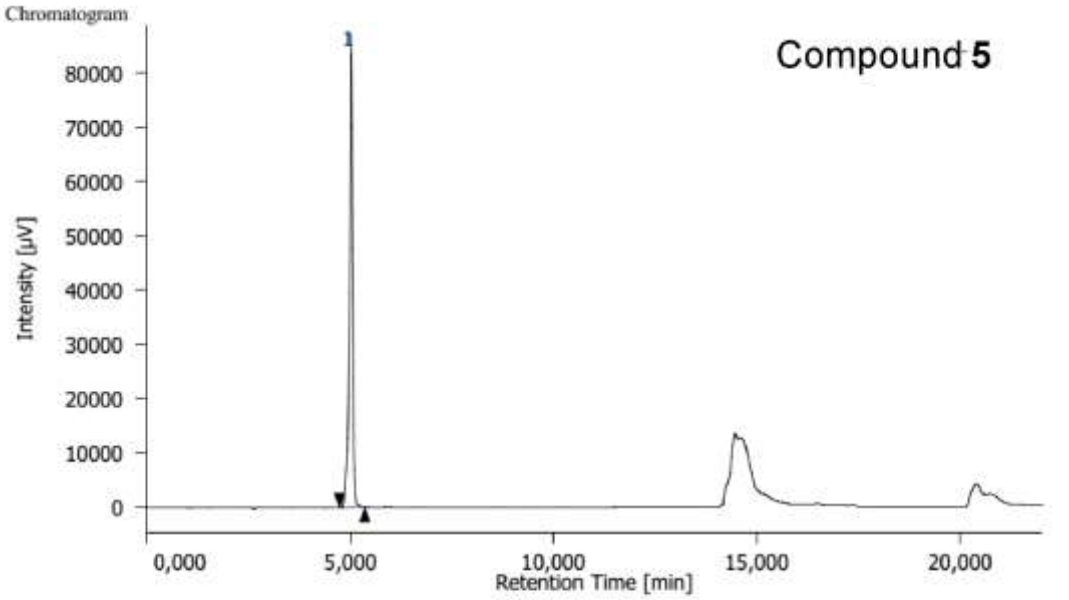
Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	2	11,108	6233273	879532	98,829	98,946	N/A	59619	12,303	1,229	
2	Unknown	2	13,508	73830	9370	1,171	1,054	N/A	66702	N/A	2,231	

Compound 5: ^{1}H NMR (300 MHz, DMSO-d_6)



Compound 5: RP-HPLC. The peaks near 15 and 22 mn belong to the solvent and are present in the blank

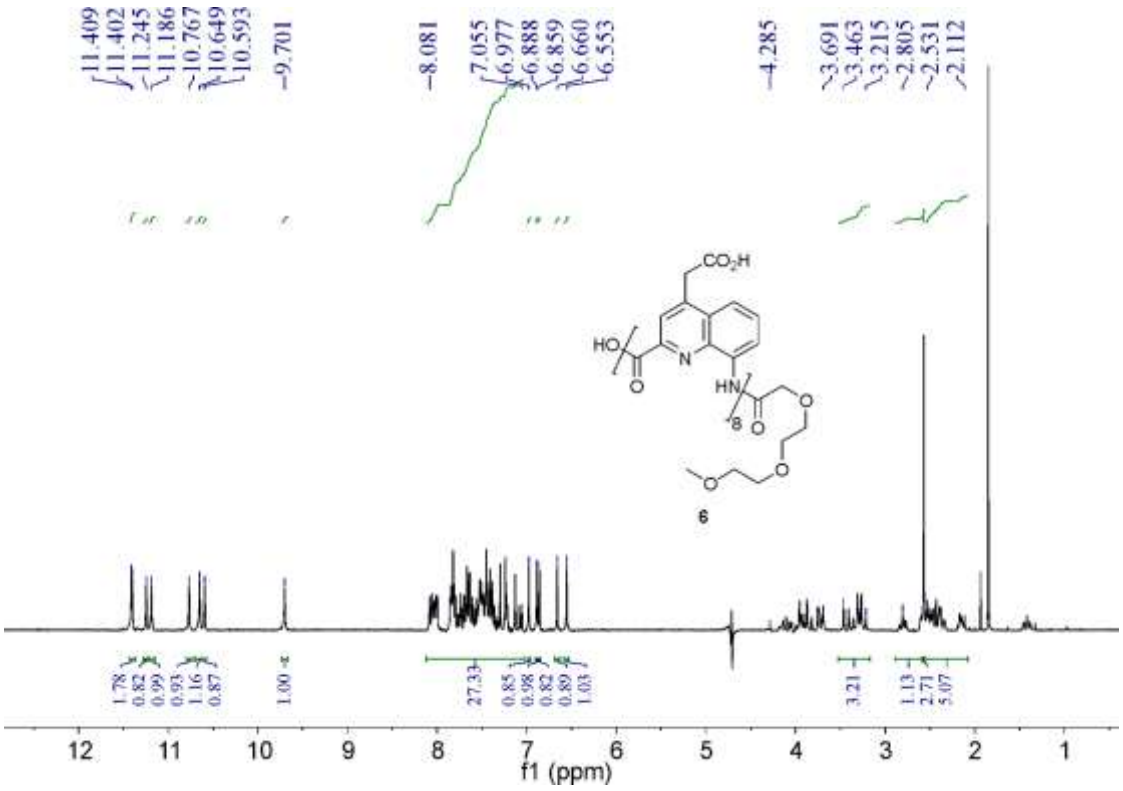


Peak Information

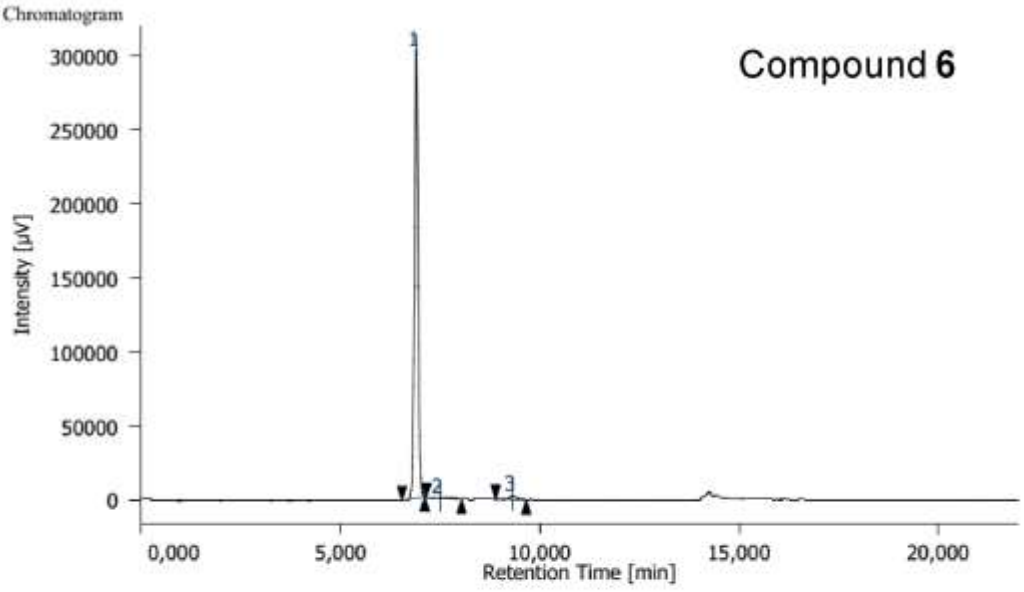
#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor
1	Unknown	3	5,025	464062	84492	100,000	100,000	N/A	25622	N/A	0,798

#	Warning
1	

Compound 6: ^{1}H NMR (300 MHz, 10%D_2O/H_2O *v/v* %)



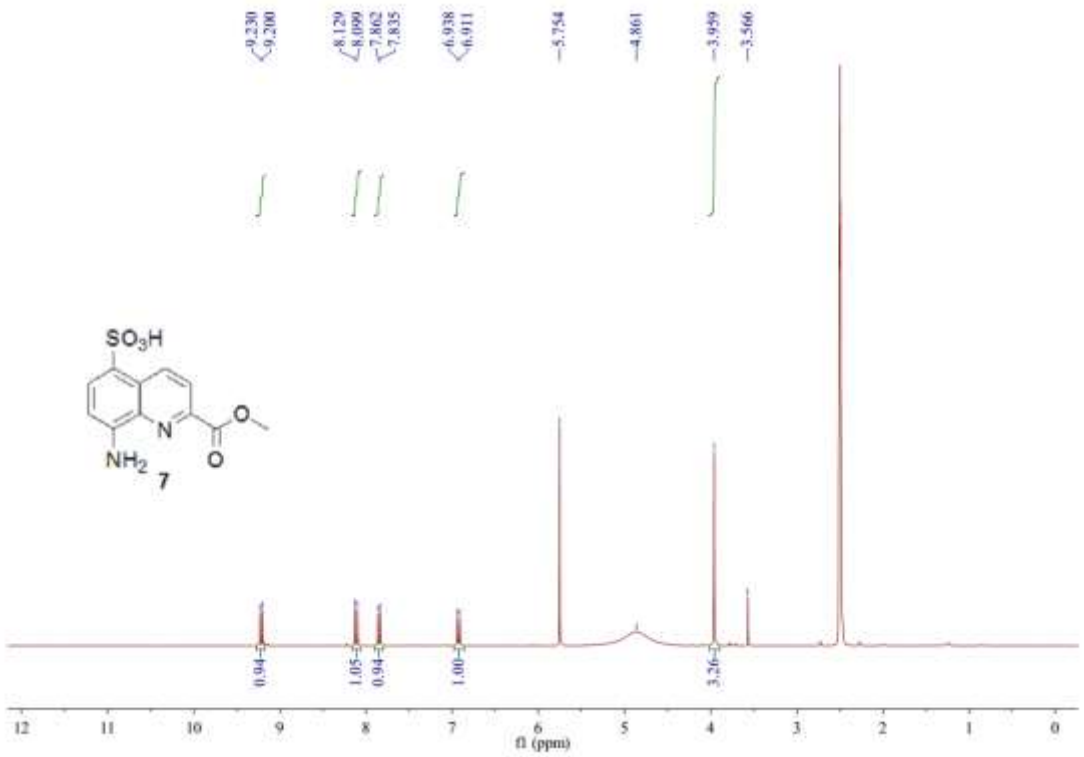
Compound 6: RP-HPLC. The peak near 14 mn belongs to the solvent and is present in the blank.



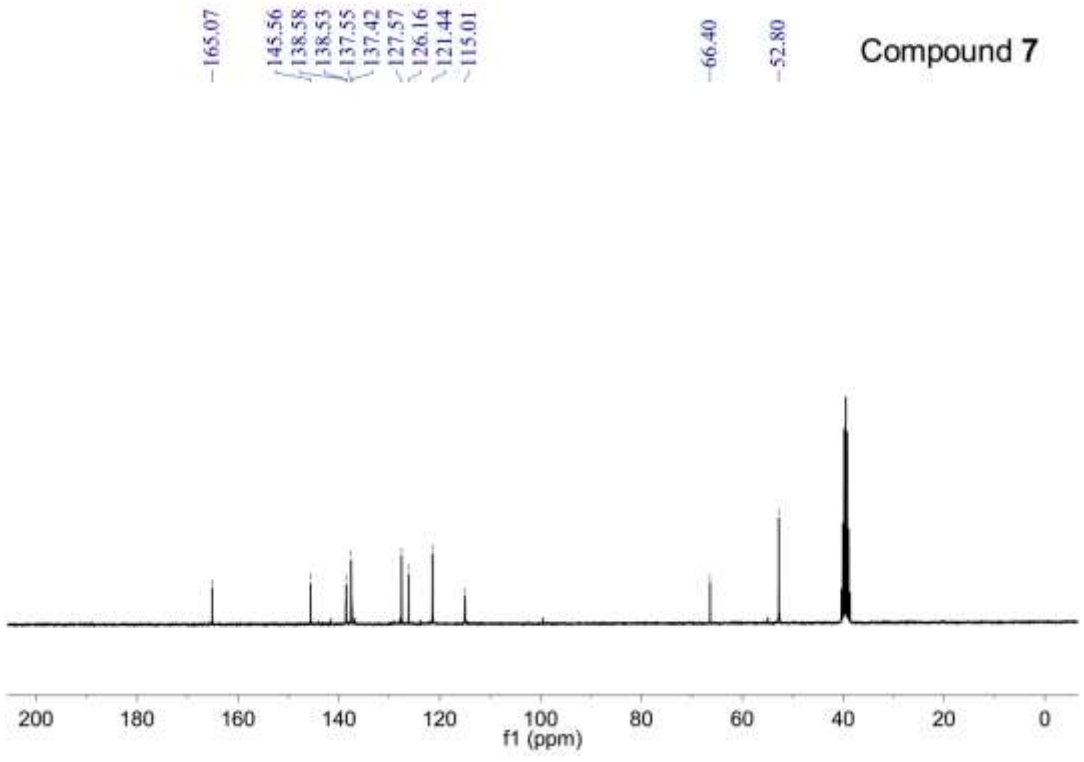
Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	6,908	1942062	303777	97,419	99,024	N/A	29171	1,061	0,963	
2	Unknown	3	7,500	17355	533	0,871	0,174	N/A	984	2,777	2,376	
3	Unknown	3	9,317	34095	2461	1,710	0,802	N/A	10989	N/A	0,886	

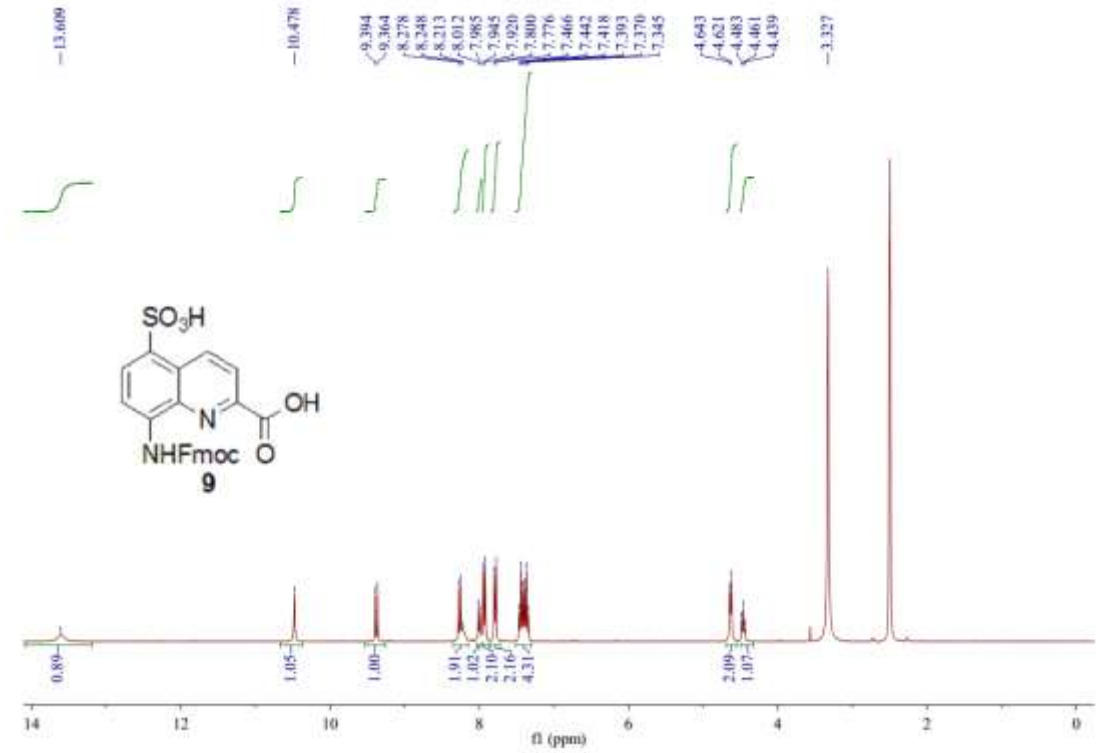
Compound 7: ^{1}H NMR (300 MHz, DMSO-d_6)



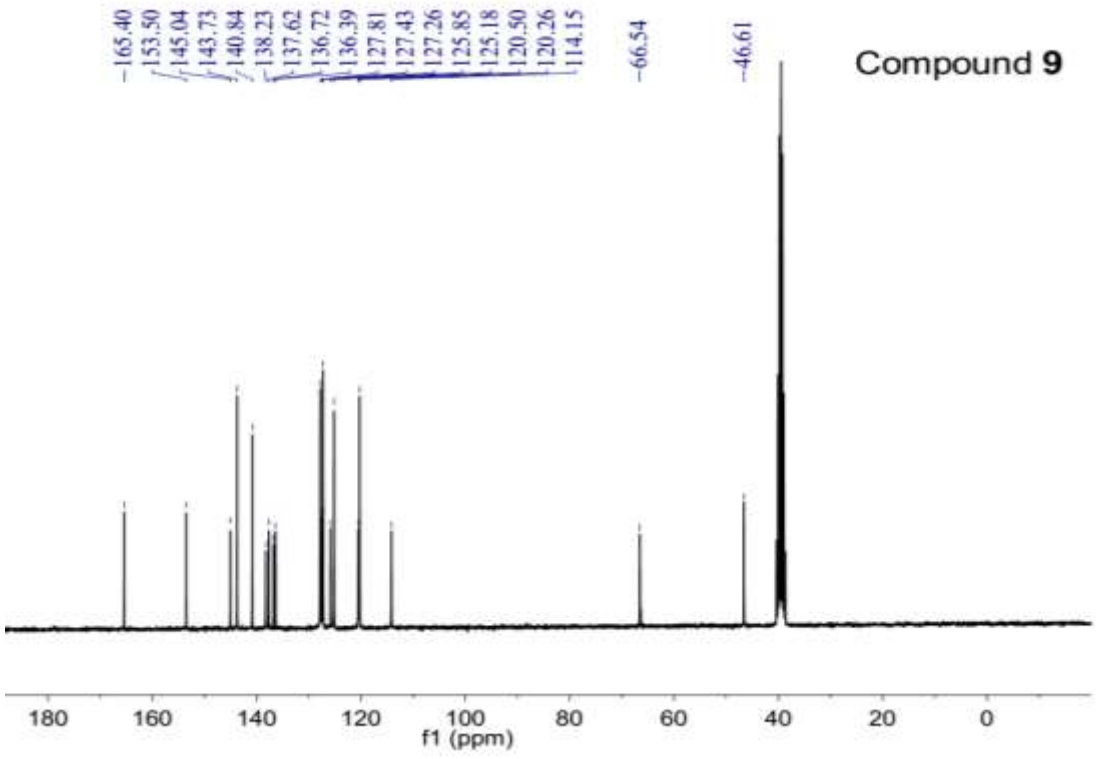
Compound 7: ^{13}C{^{1}H}NMR (300 MHz, DMSO-d_6)



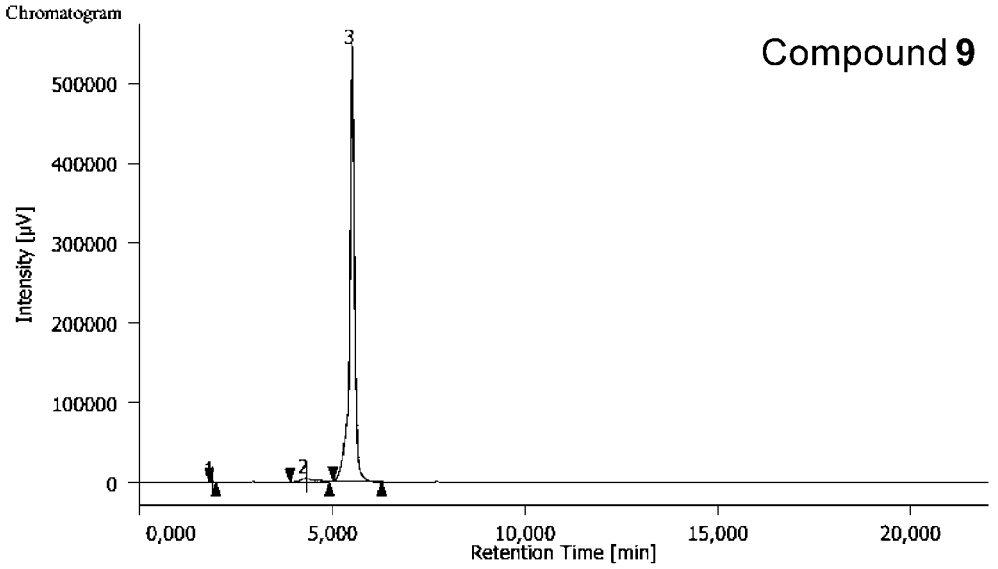
Compound 9: ^{1}H NMR (300 MHz, DMSO-d_6)



Compound 9: ^{13}C{^{1}H}NMR (300 MHz, DMSO-d_6)



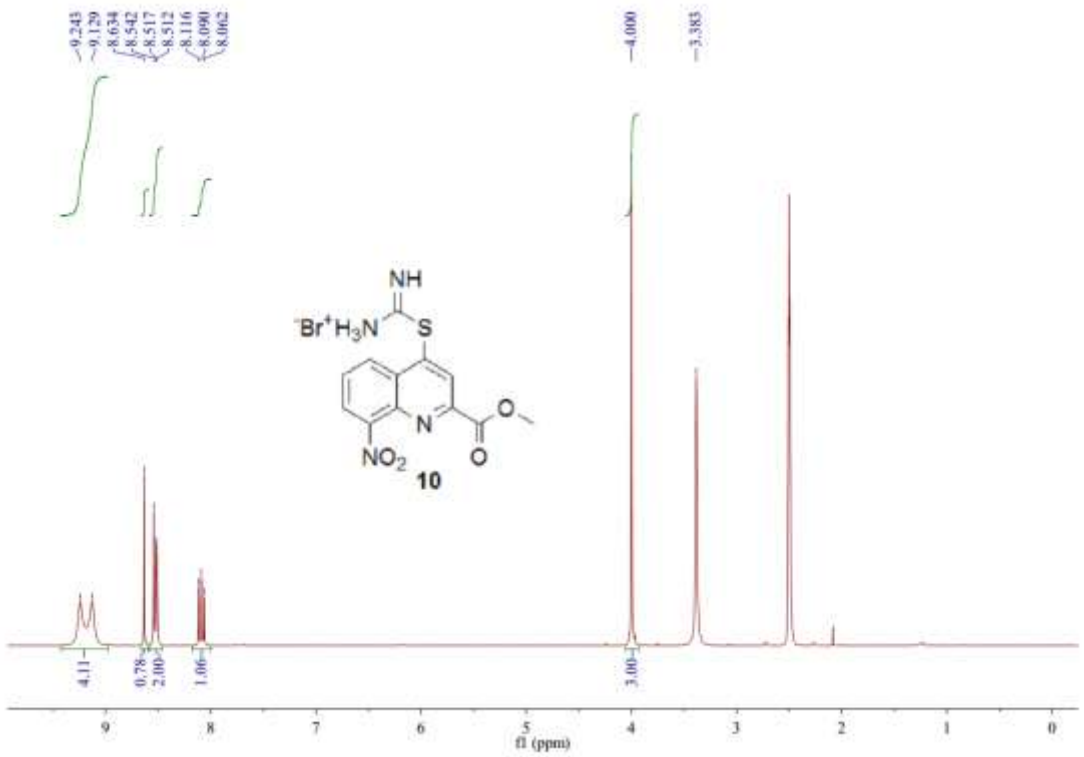
Compound 9: RP-HPLC



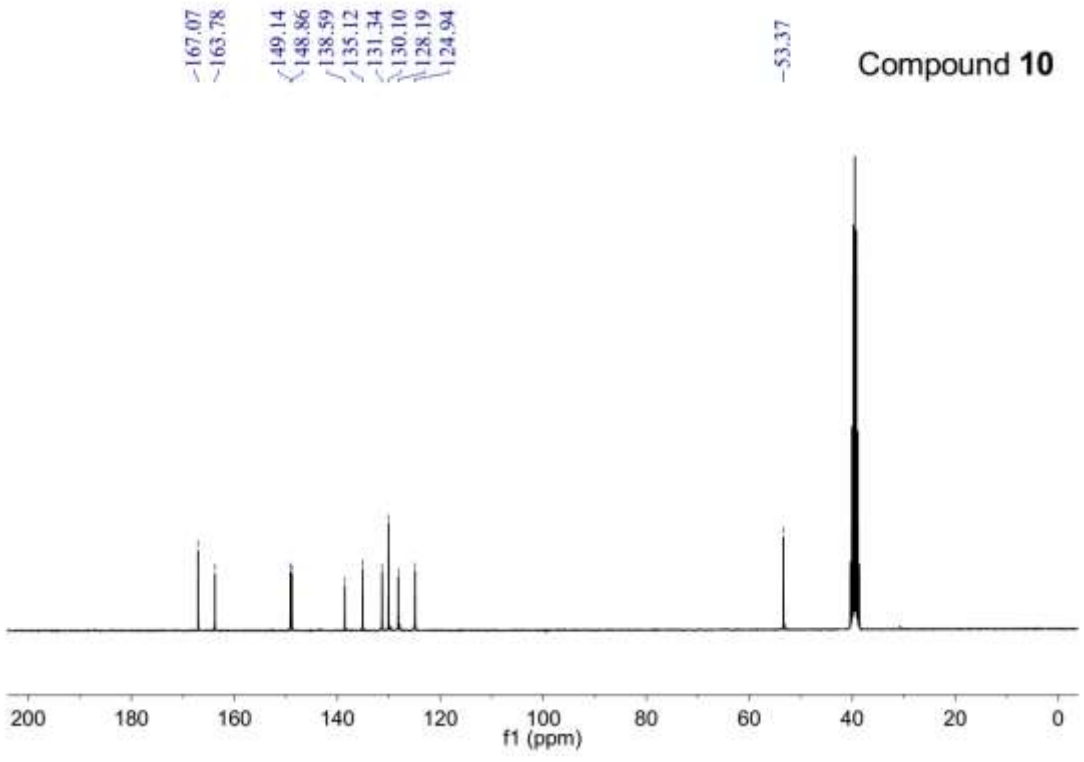
Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	1,875	9562	2415	0,186	0,437	N/A	4965	7,558	1,060	
2	Unknown	3	4,317	119019	5133	2,313	0,929	N/A	1017	3,210	1,249	
3	Unknown	3	5,508	5017200	545137	97,501	98,634	N/A	11781	N/A	0,813	

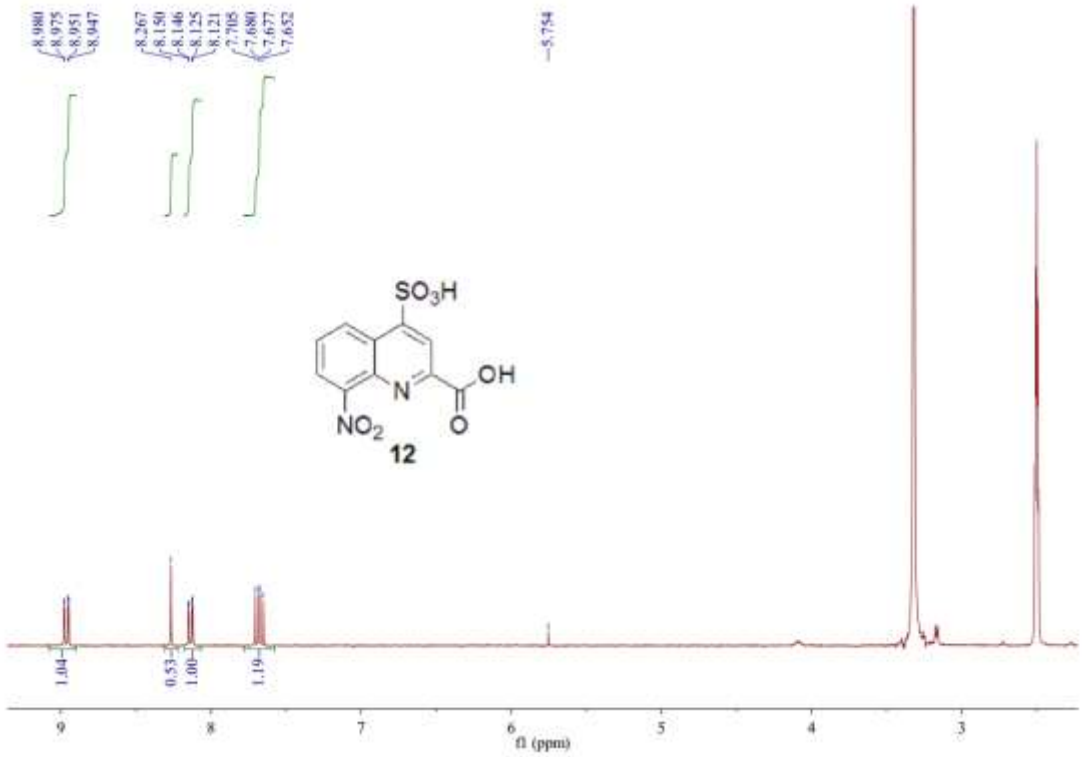
Compound 10: ^{1}H NMR (300 MHz, DMSO-d_6)



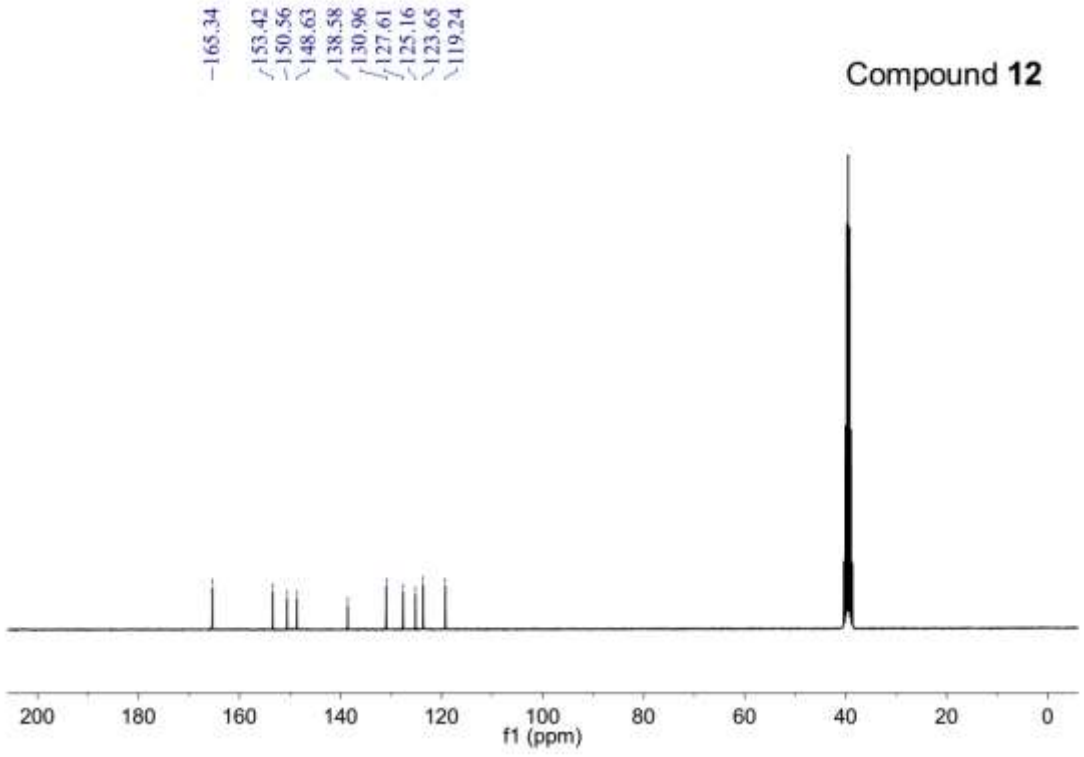
Compound 10: ^{13}C{^{1}H}NMR (300 MHz, DMSO-d_6)



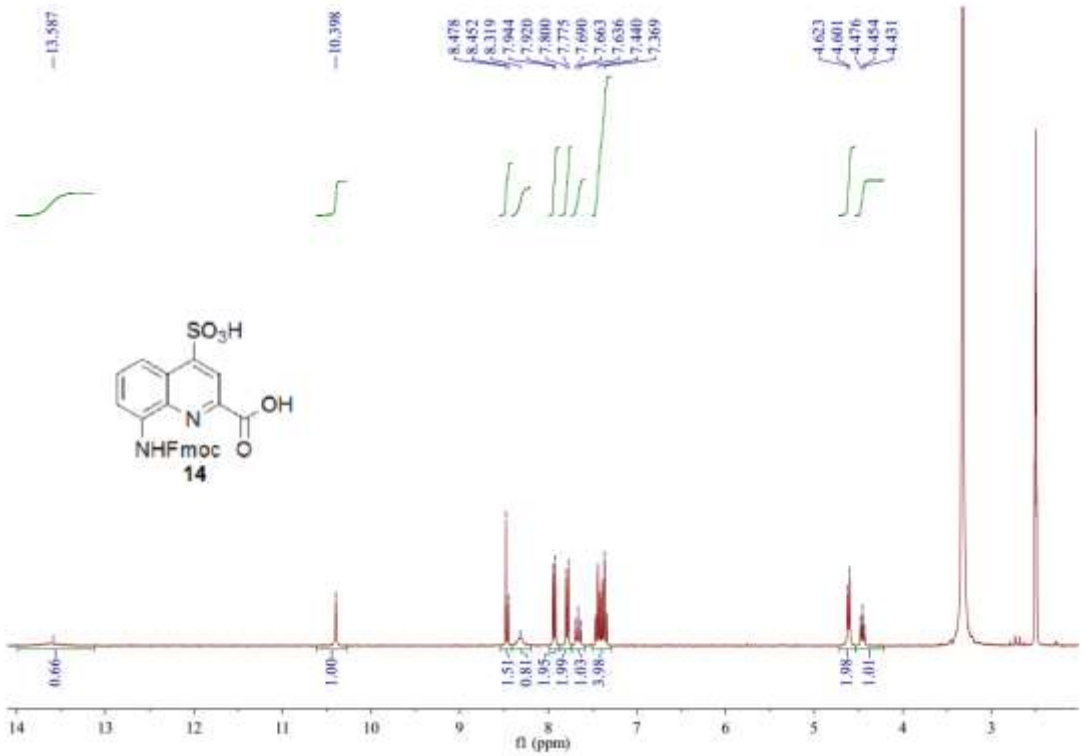
Compound 12: ^{1}H NMR (300 MHz, DMSO-d_6)



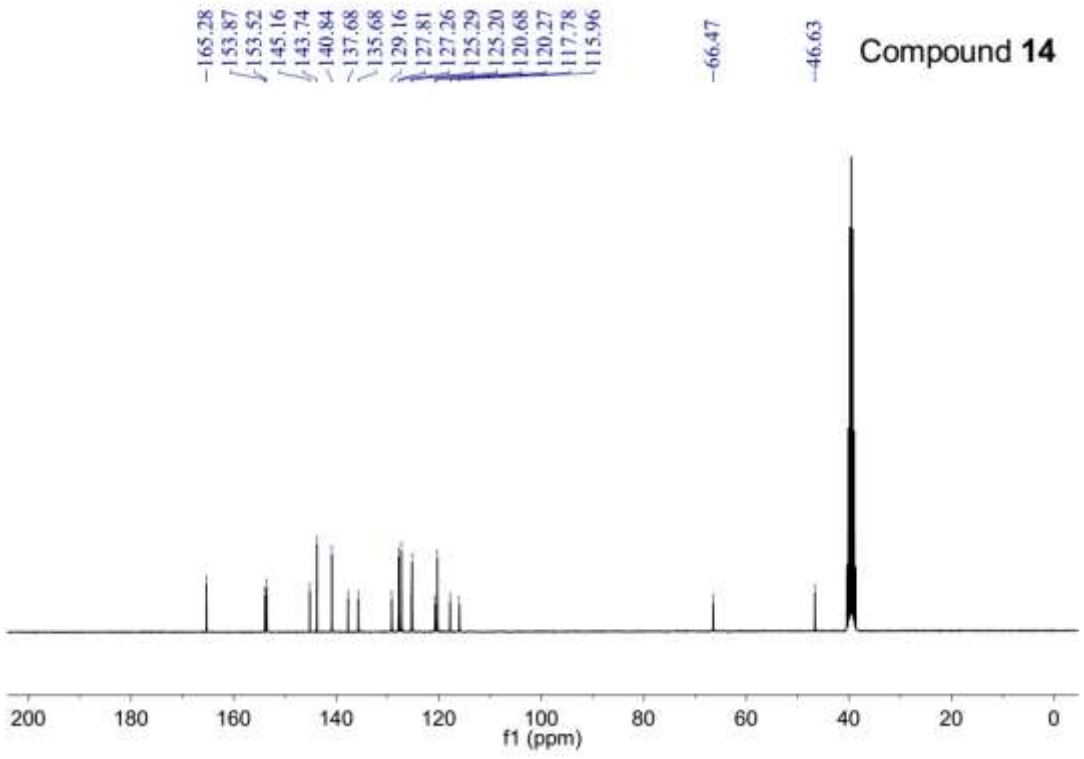
Compound 12: ^{13}C{^{1}H}NMR (300 MHz, DMSO-d_6)



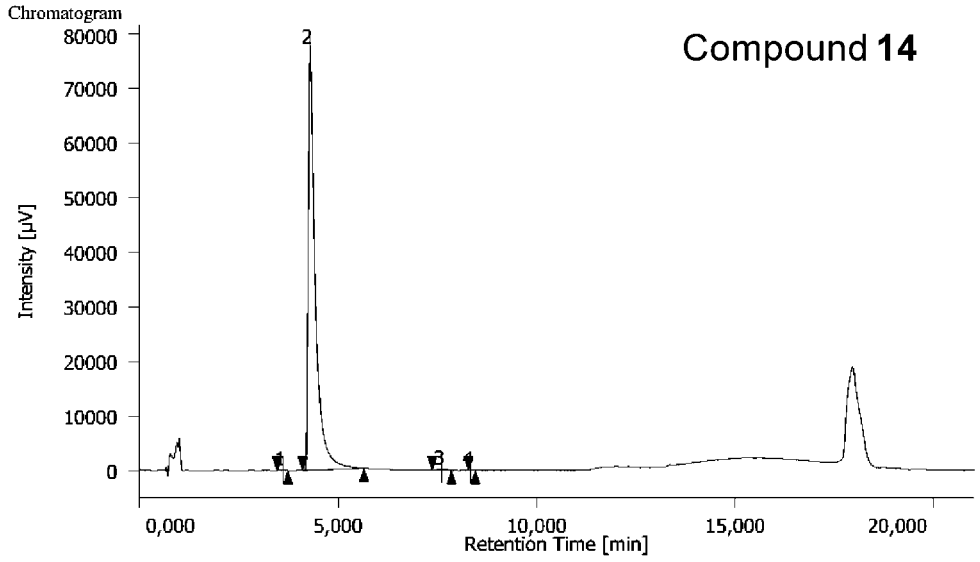
Compound 14: ^{1}H NMR (300 MHz, DMSO-d_6)



Compound 14: ^{13}C{^{1}H}NMR (300 MHz, DMSO-d_6)



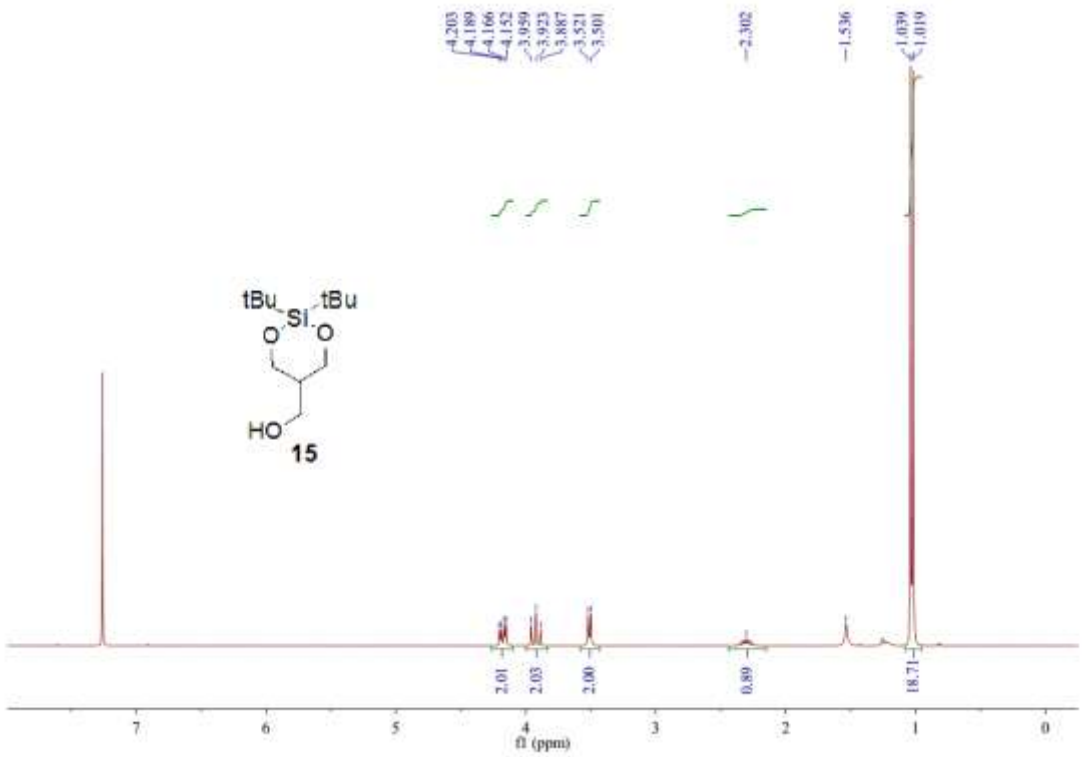
Compound 14: RP-HPLC



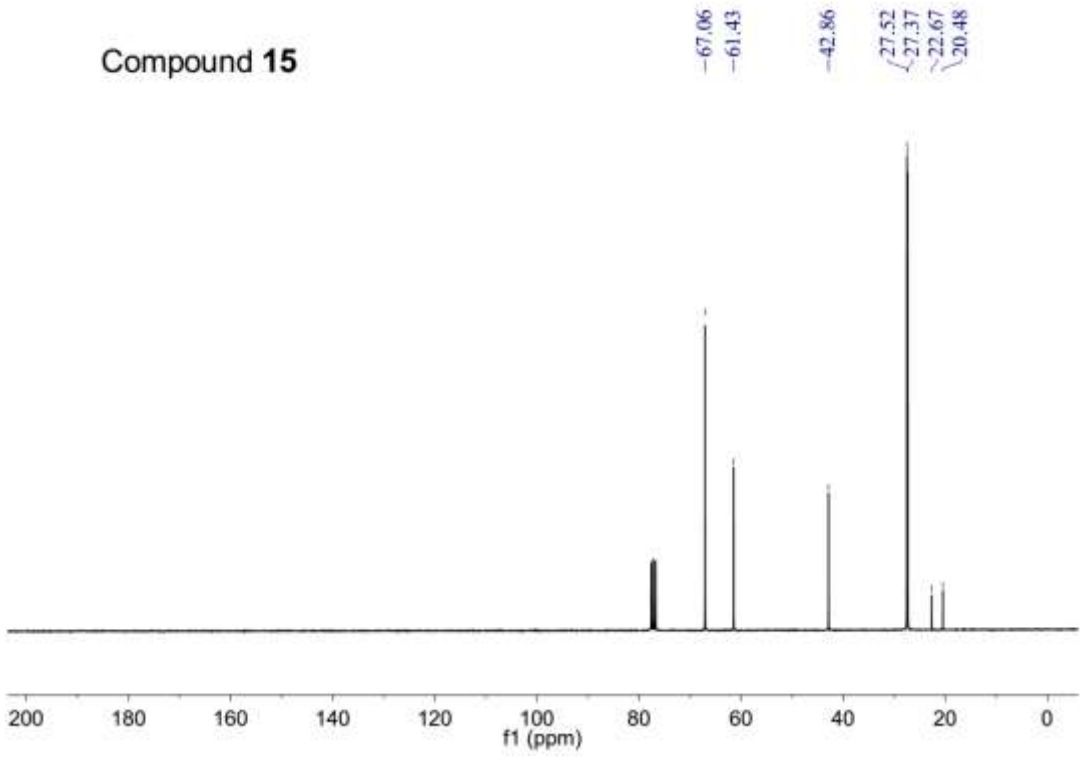
Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	3,608	1043	167	0,106	0,214	N/A	8909	3,117	0,917	
2	Unknown	3	4,292	981763	77569	99,532	99,453	N/A	3586	9,678	2,818	
3	Unknown	3	7,617	3495	245	0,354	0,314	N/A	5736	2,581	1,010	
4	Unknown	3	8,342	79	15	0,008	0,019	N/A	42989	N/A	1,463	

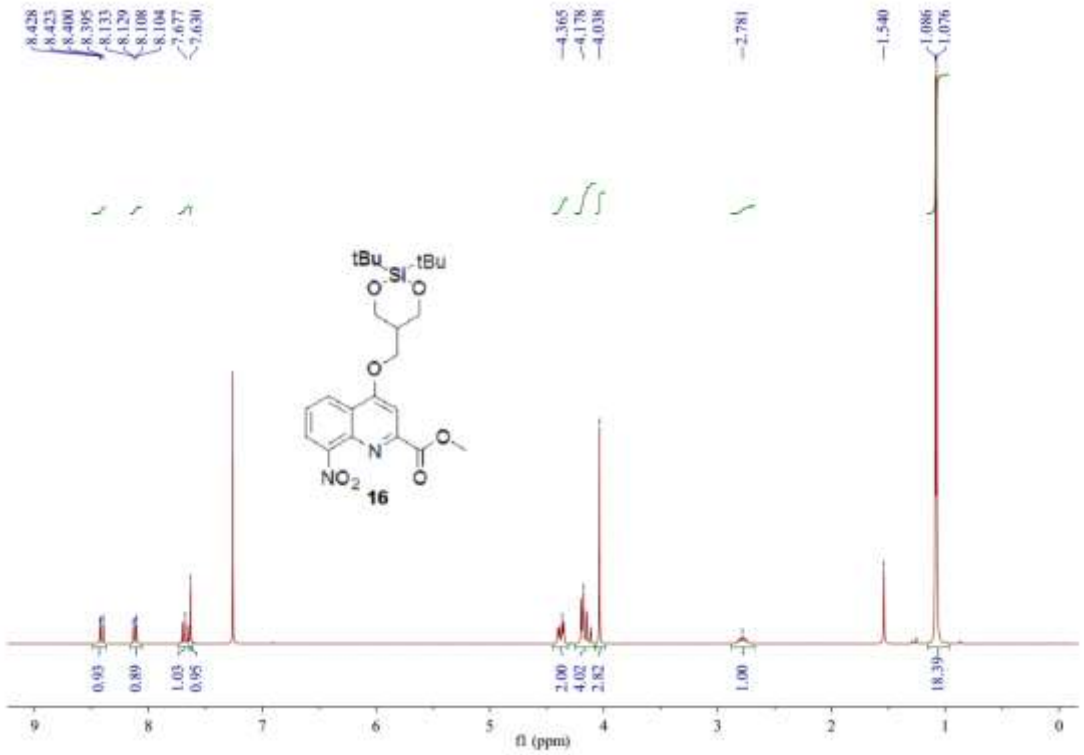
Compound 15: ^{1}H NMR (300 MHz, $CDCl_3$)



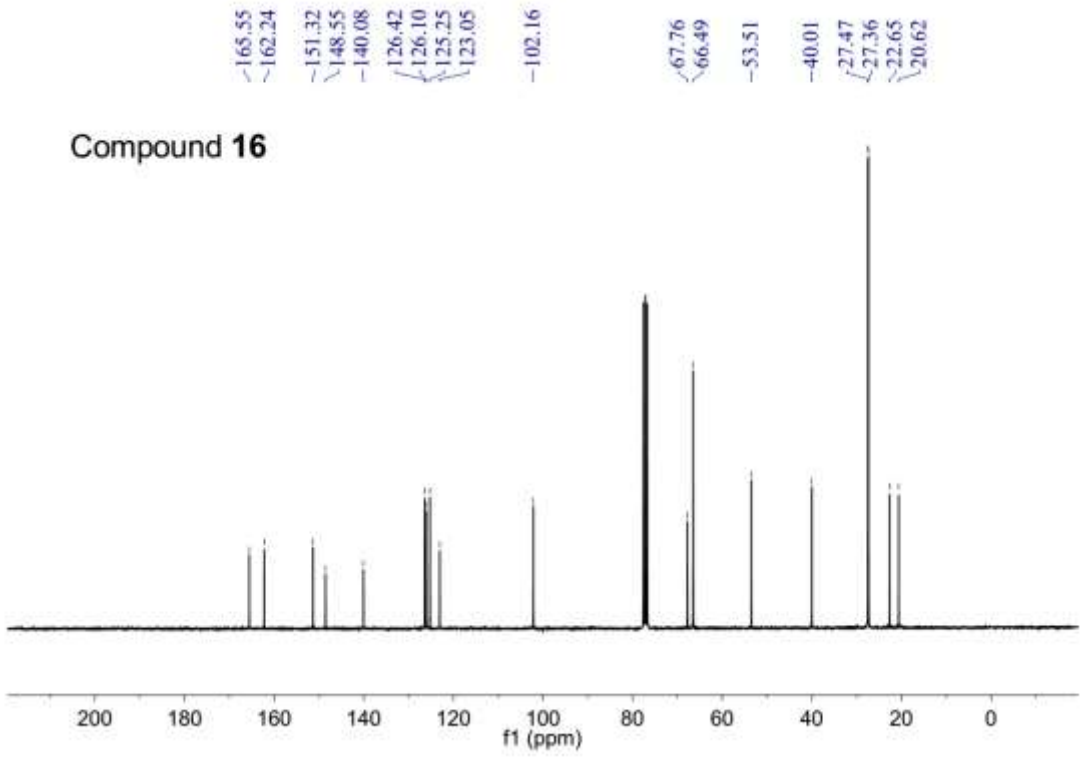
Compound 15: $^{13}C\{^{1}H\}$NMR (300 MHz, $CDCl_3$)



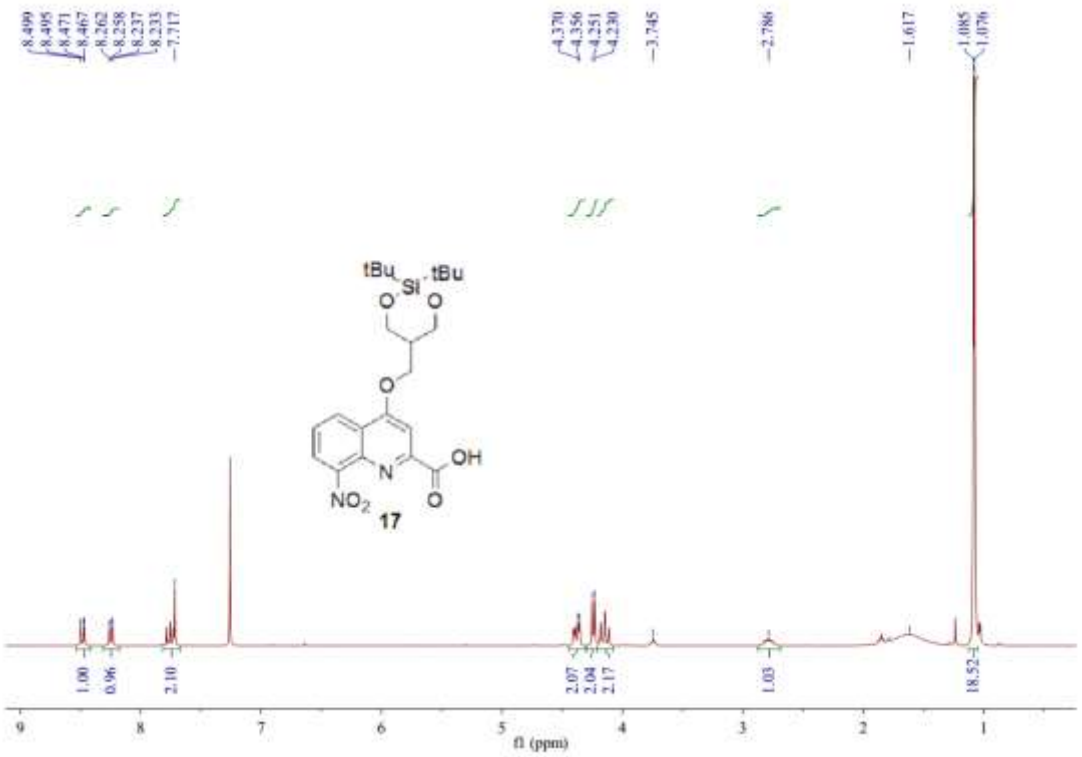
Compound 16: ^{1}H NMR (300 MHz, $CDCl_3$)



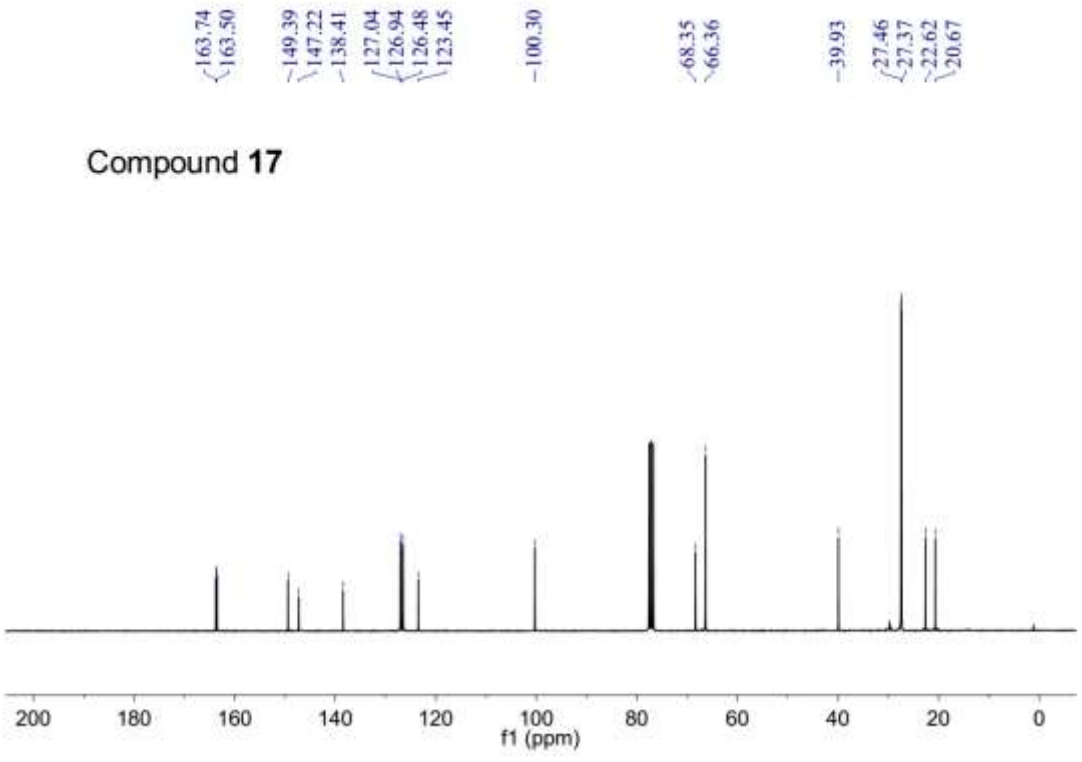
Compound 16: $^{13}C\{^{1}H\}$NMR (300 MHz, $CDCl_3$)



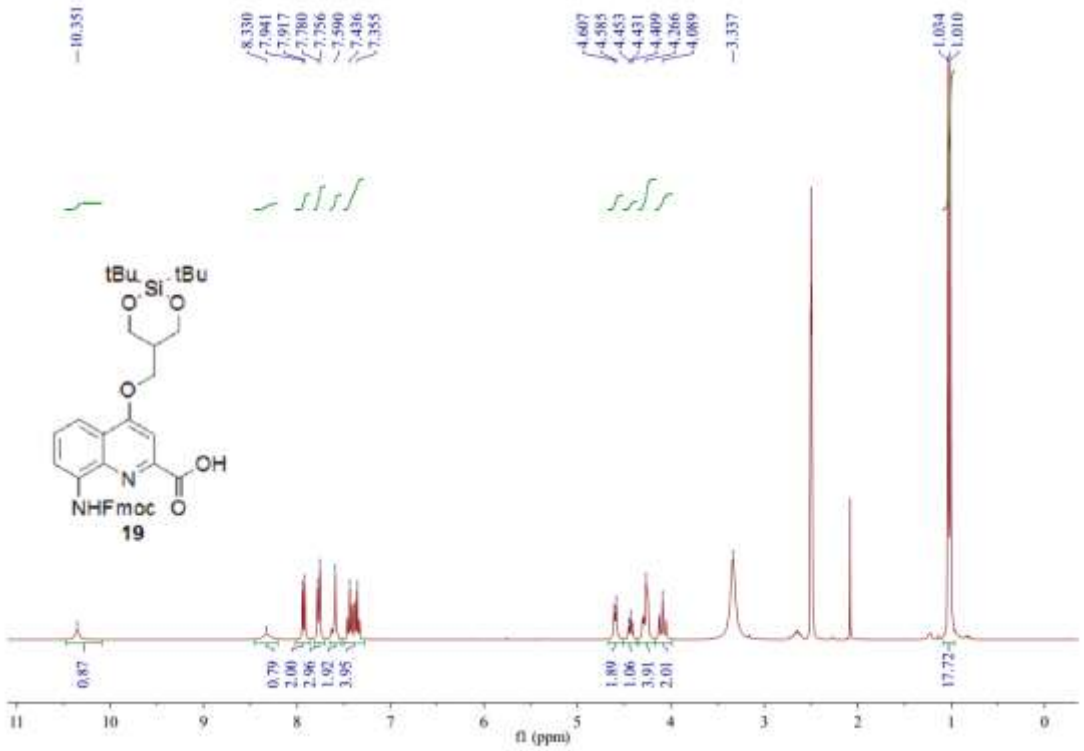
Compound 17: ^{1}H NMR (300 MHz, $CDCl_3$)



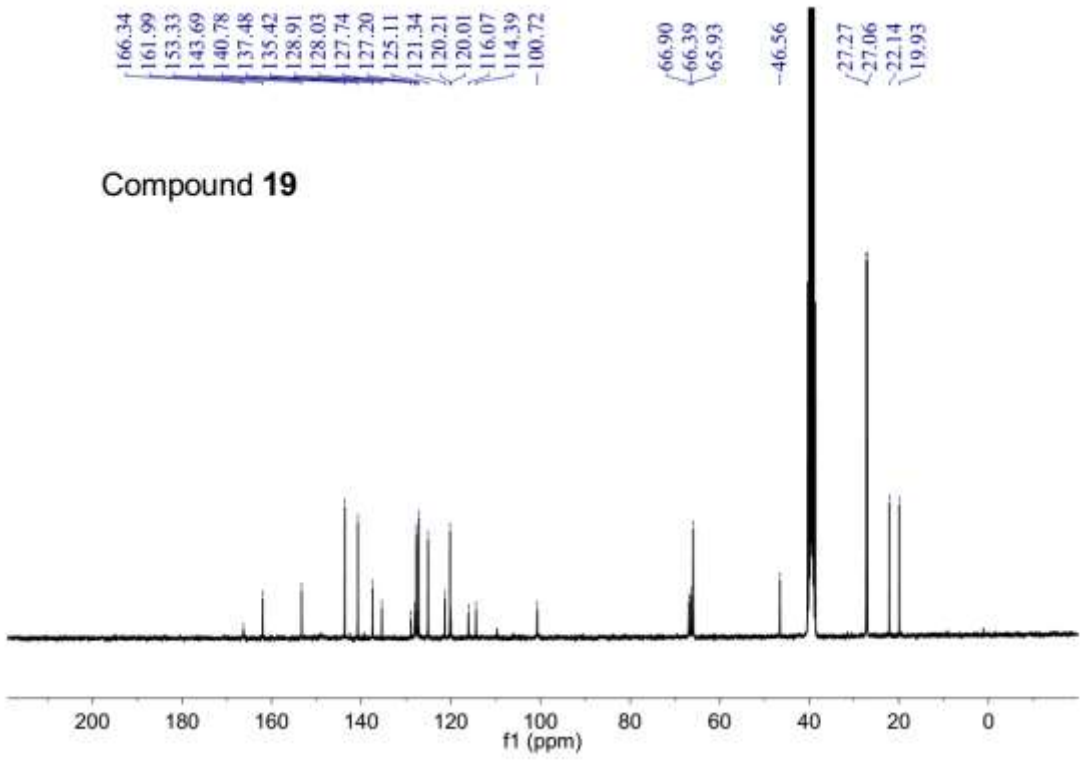
Compound 17: $^{13}C\{^{1}H\}$NMR (300 MHz, $CDCl_3$)



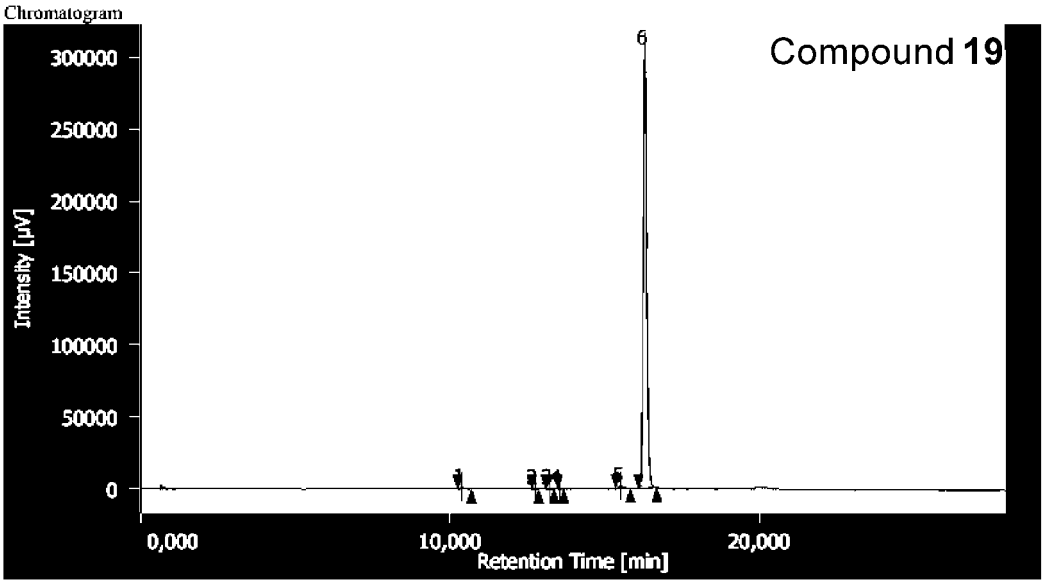
Compound 19: ^{1}H NMR (300 MHz, DMSO-d_6)



Compound 19: ^{13}C{^{1}H}NMR (300 MHz, DMSO-d_6)



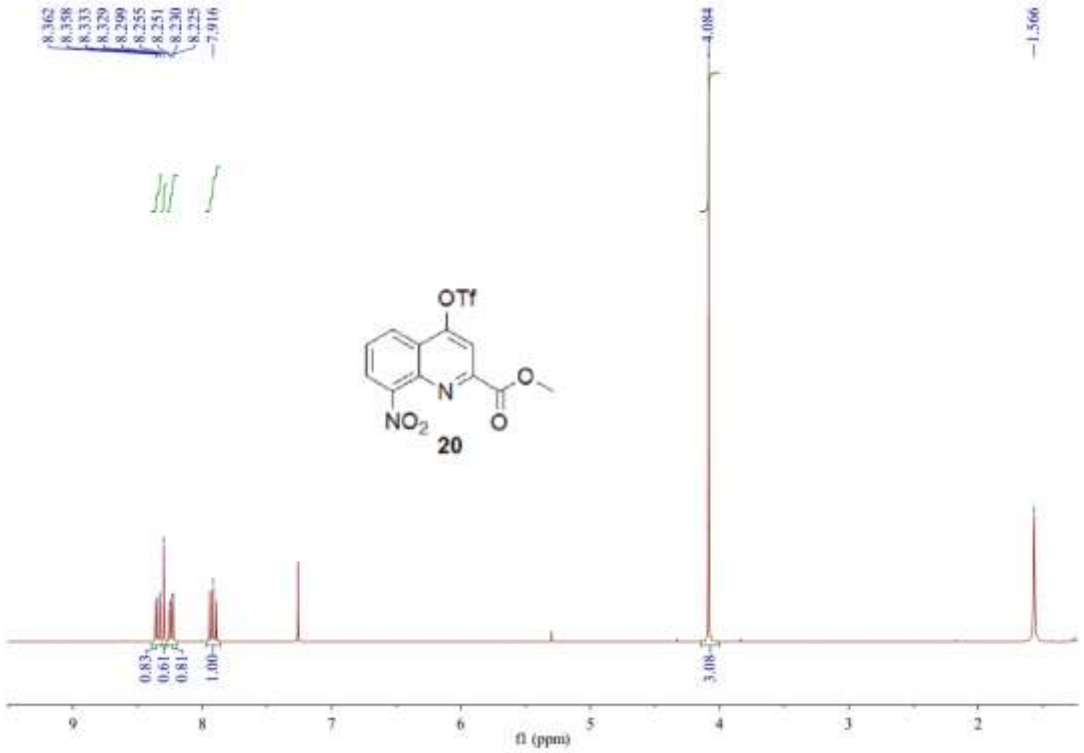
Compound 19: RP-HPLC



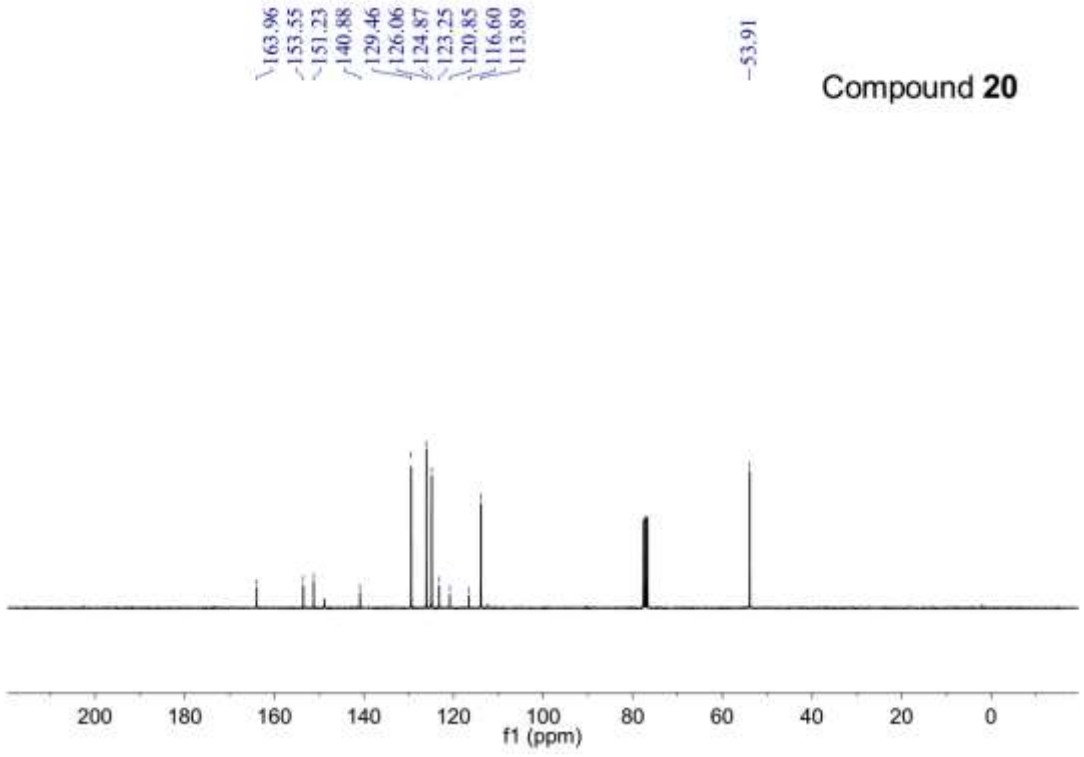
Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor
1	Unknown	3	10,375	14198	1556	0,592	0,499	N/A	51610	13,888	2,310
2	Unknown	3	12,733	3579	613	0,149	0,197	N/A	104103	2,970	1,301
3	Unknown	3	13,217	2430	398	0,101	0,127	N/A	98421	2,027	1,248
4	Unknown	3	13,525	1200	232	0,050	0,074	N/A	156947	9,696	1,796
5	Unknown	3	15,500	21050	1944	0,877	0,623	N/A	51984	3,377	1,729
6	Unknown	3	16,292	2357242	307169	98,231	98,479	N/A	108059	N/A	1,165

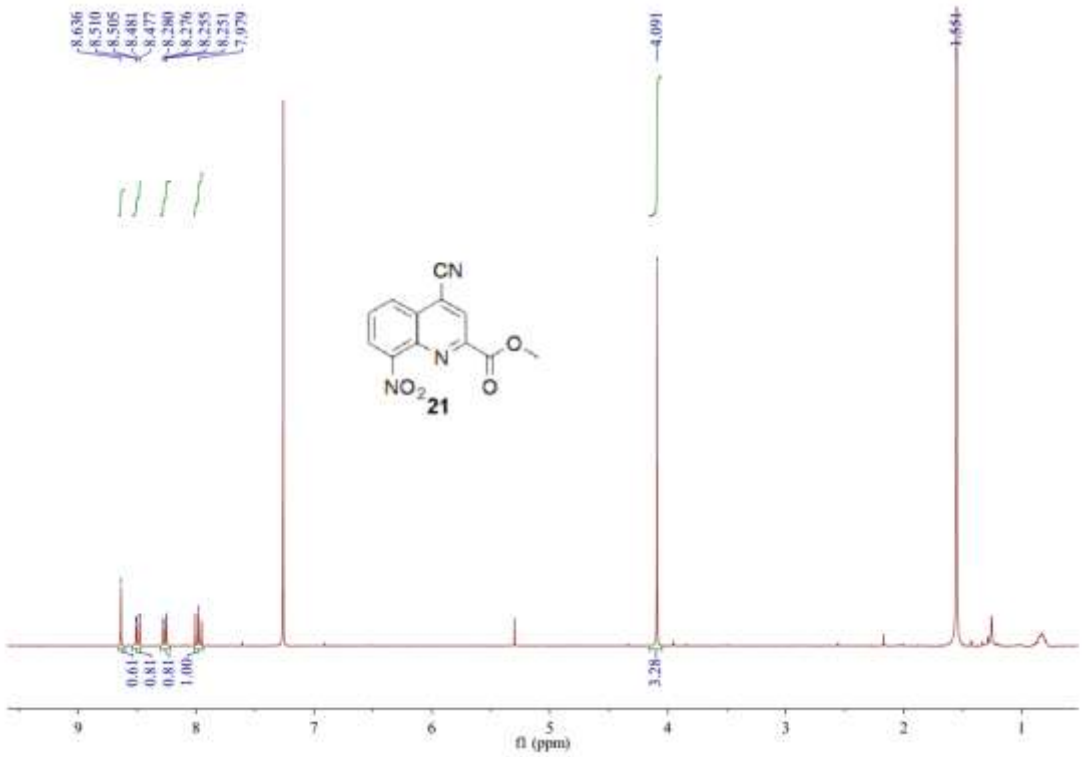
Compound 20: ^{1}H NMR (300 MHz, $CDCl_3$)



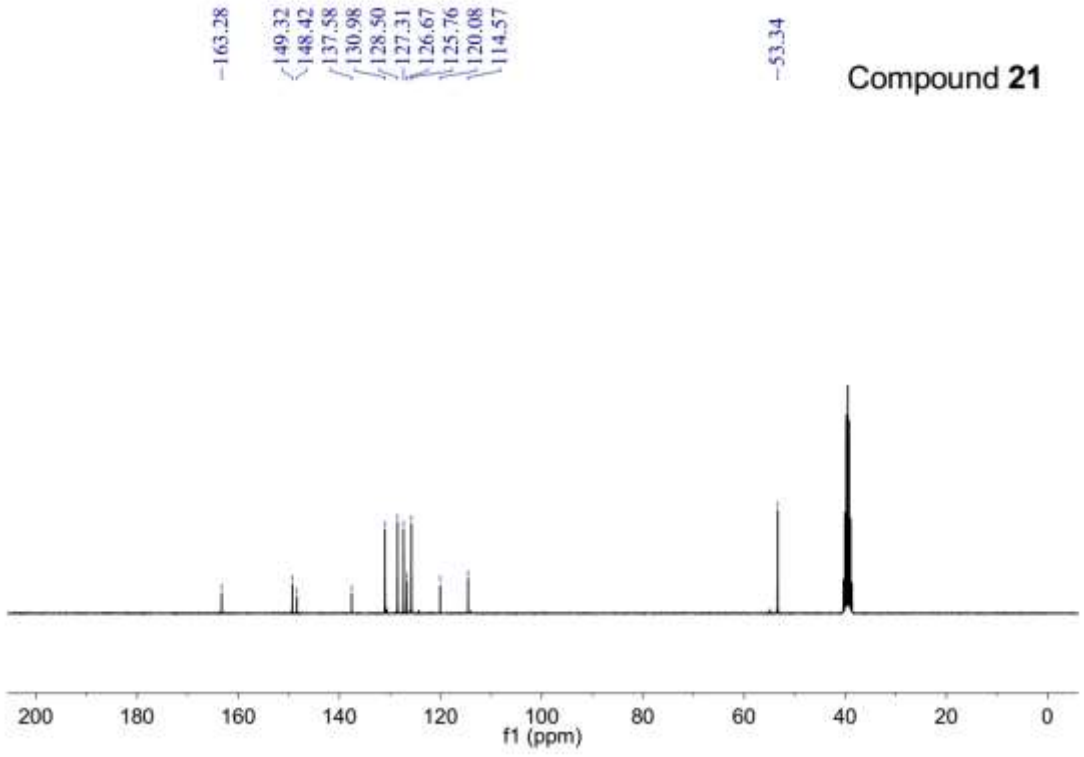
Compound 20: $^{13}C\{^{1}H\}$NMR (300 MHz, $CDCl_3$)



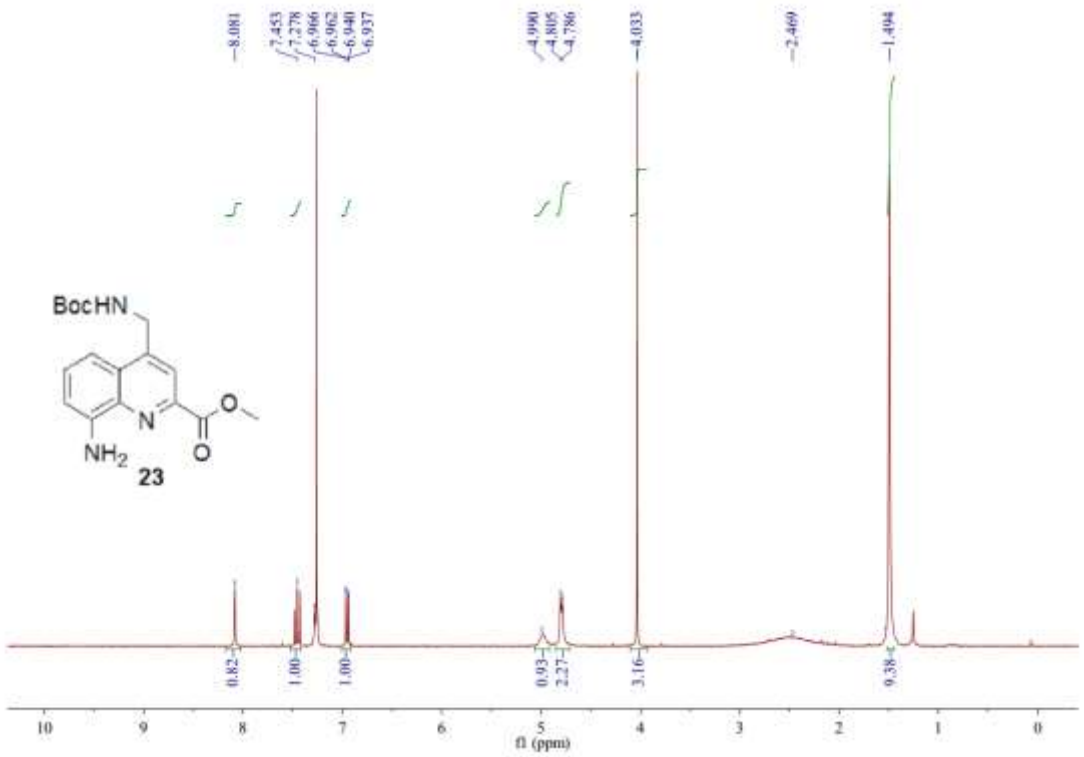
Compound 21: ^{1}H NMR (300 MHz, $CDCl_3$)



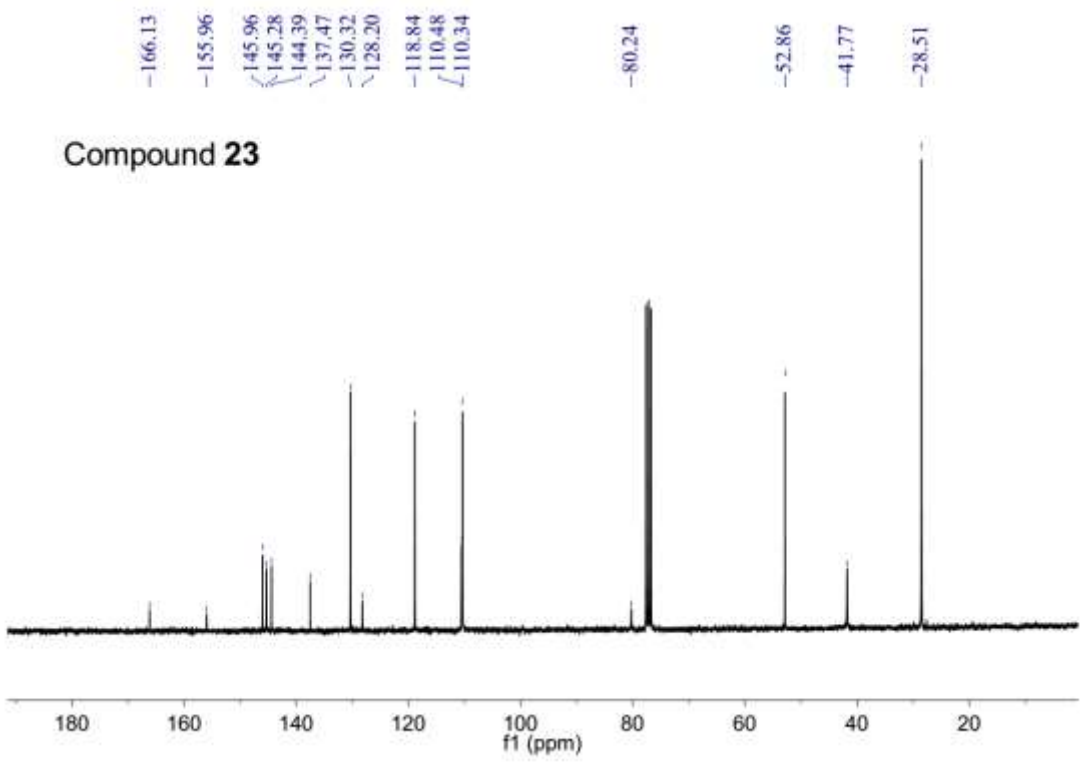
Compound 21: $^{13}C\{^{1}H\}$NMR (300 MHz, DMSO-d_6)



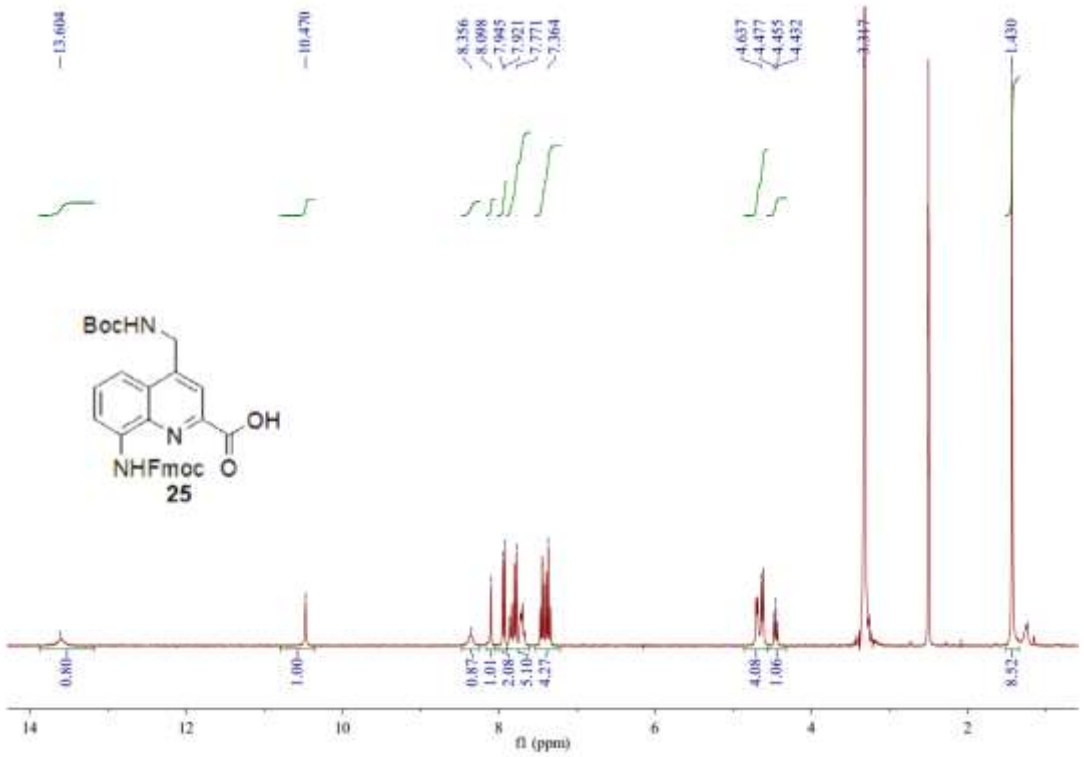
Compound 23: ^{1}H NMR (300 MHz, $CDCl_3$)



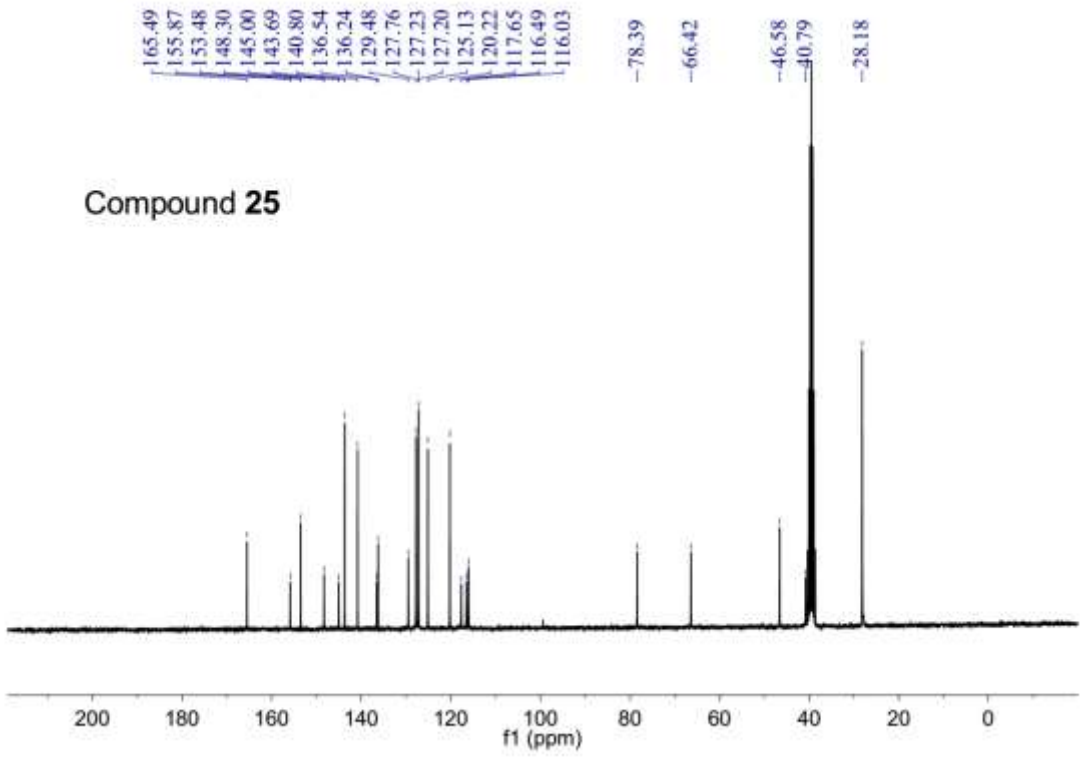
Compound 23: $^{13}C\{^{1}H\}$NMR (300 MHz, $CDCl_3$)



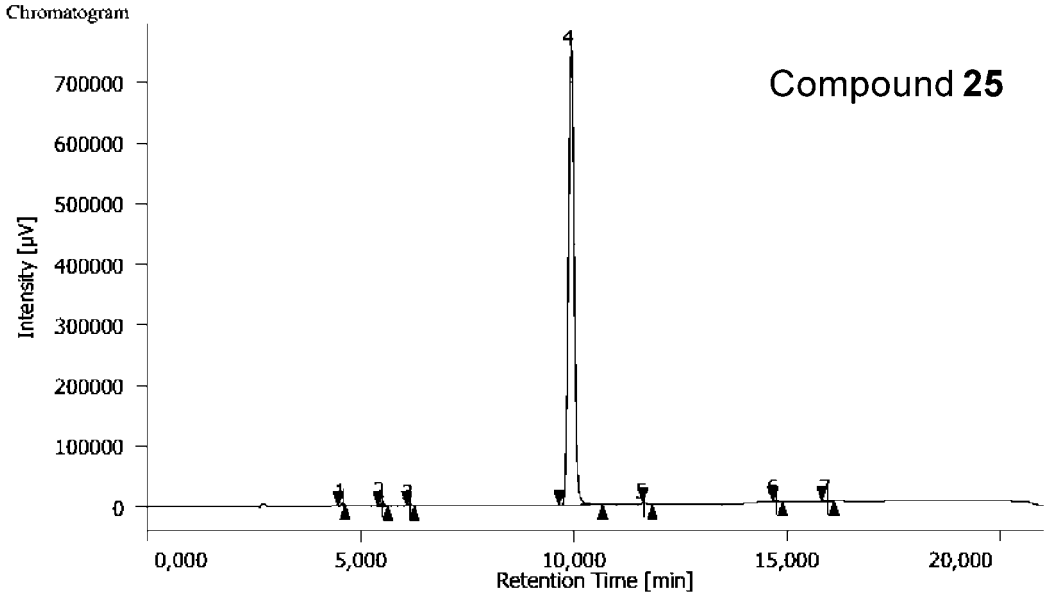
Compound 25: ^{1}H NMR (300 MHz, DMSO-d_6)



Compound 25: ^{13}C{^{1}H}NMR (300 MHz, DMSO-d_6)



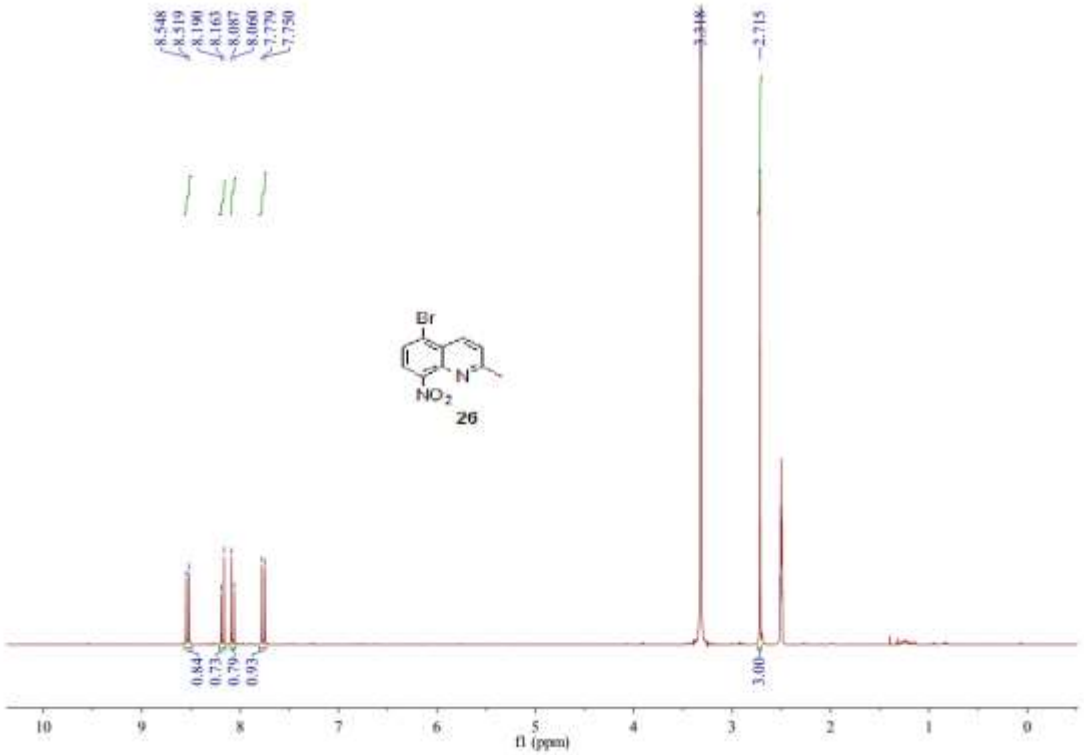
Compound 25: RP-HPLC



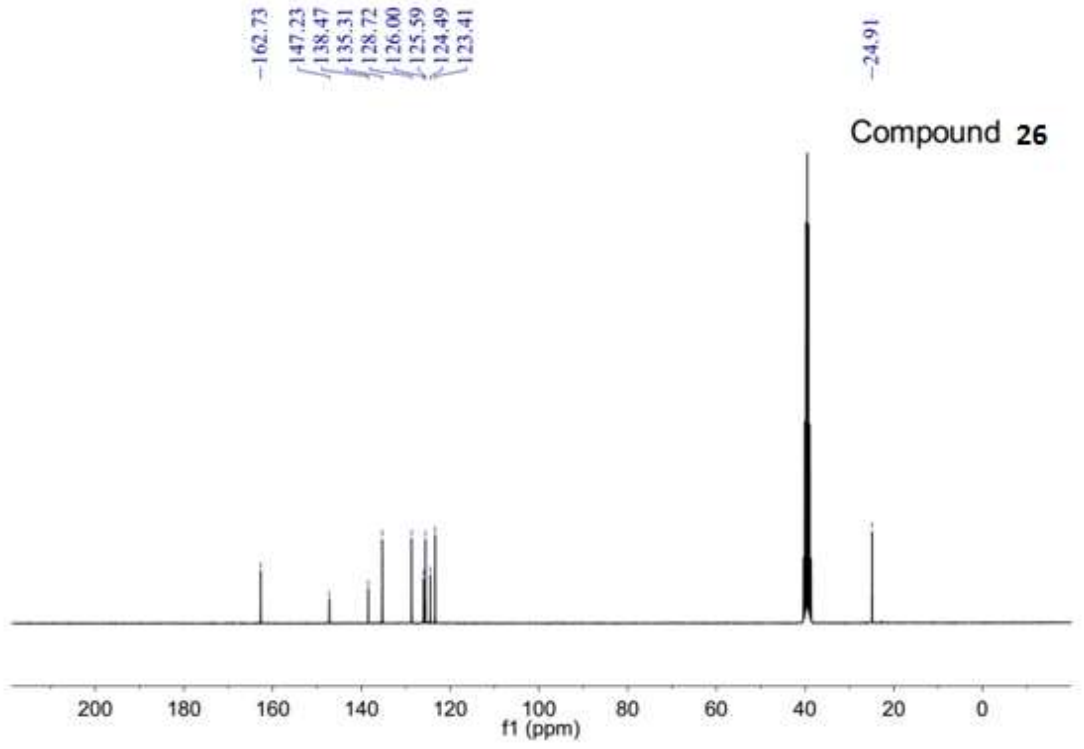
Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor
1	Unknown	2	4,575	16214	3887	0,225	0,503	N/A	26343	7,455	0,784
2	Unknown	2	5,508	31526	6104	0,438	0,790	N/A	25374	4,543	1,059
3	Unknown	2	6,167	12483	2250	0,173	0,291	N/A	26231	19,089	1,011
4	Unknown	2	9,933	7106375	755240	98,746	97,755	N/A	26651	8,706	1,079
5	Unknown	2	11,642	3532	618	0,049	0,080	N/A	96245	21,786	2,452
6	Unknown	2	14,733	13317	2564	0,185	0,332	N/A	192054	7,799	1,302
7	Unknown	2	15,942	13141	1921	0,183	0,249	N/A	130973	N/A	1,175

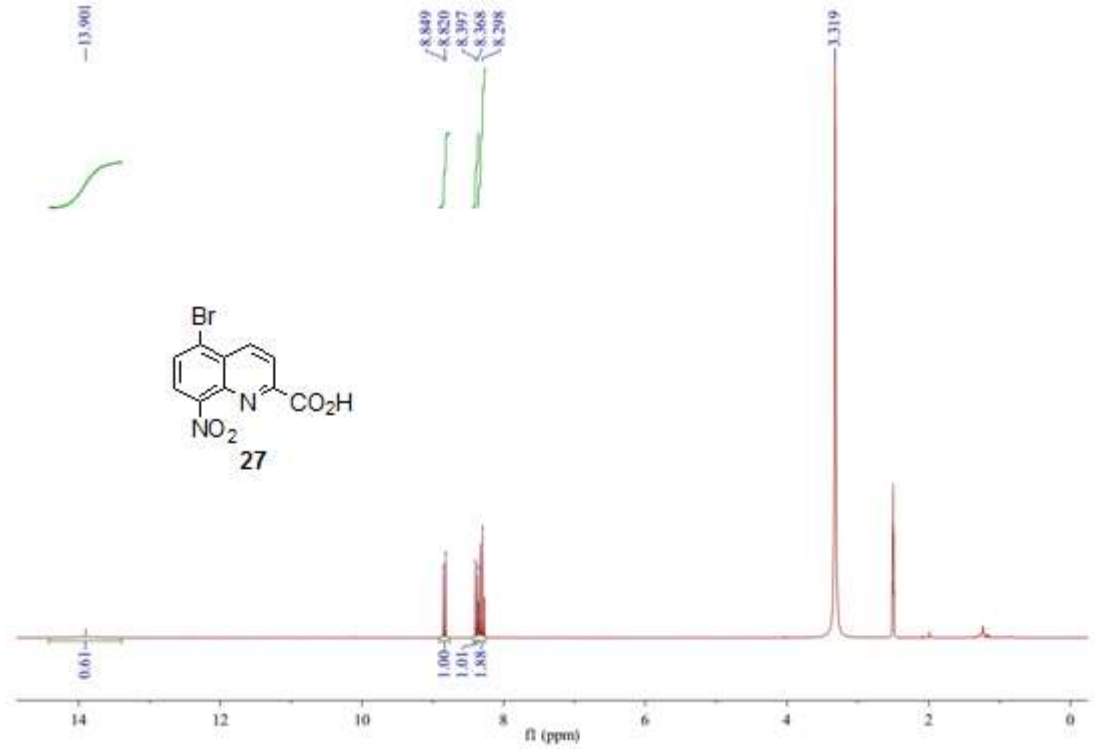
Compound 26: ^{1}H NMR (300 MHz, DMSO-d_6)



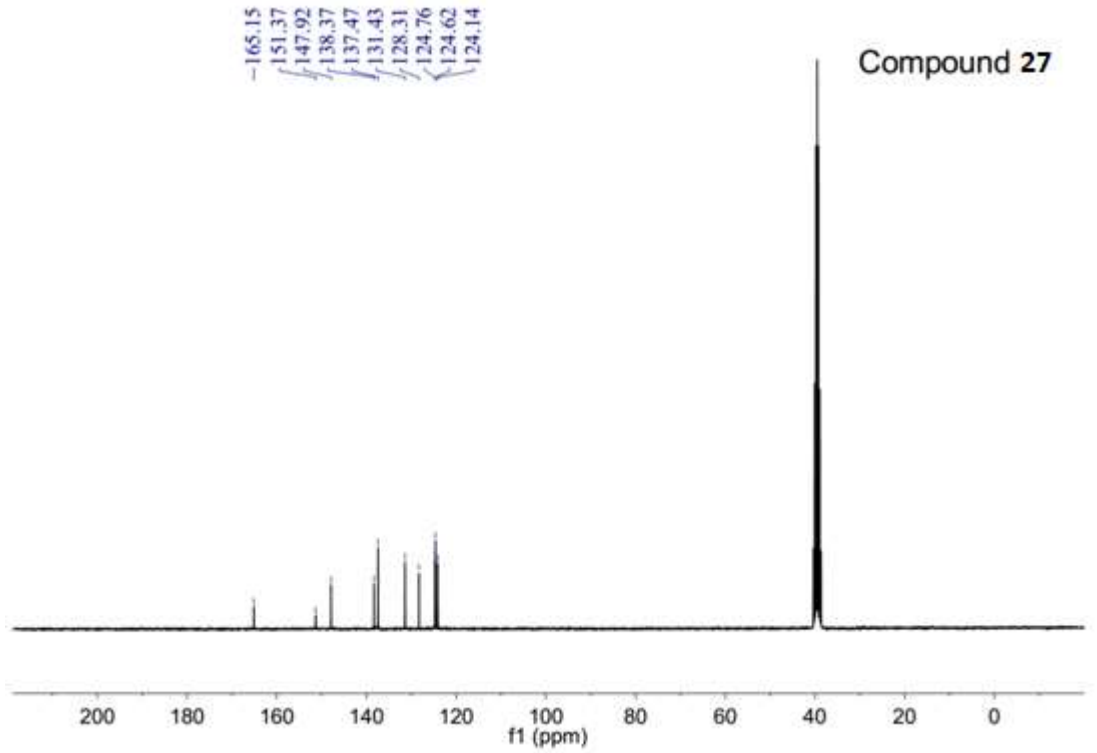
Compound 26: ^{13}C{^{1}H}NMR (300 MHz, DMSO-d_6)



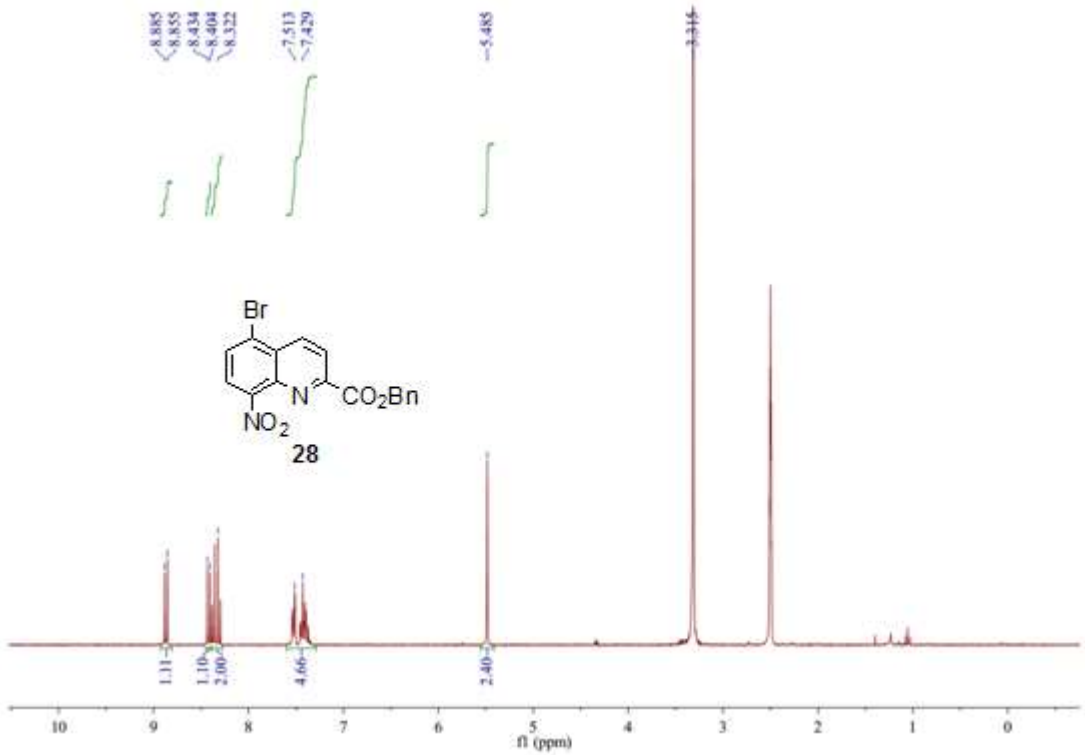
Compound 27: ^{1}H NMR (300 MHz, DMSO-d_6)



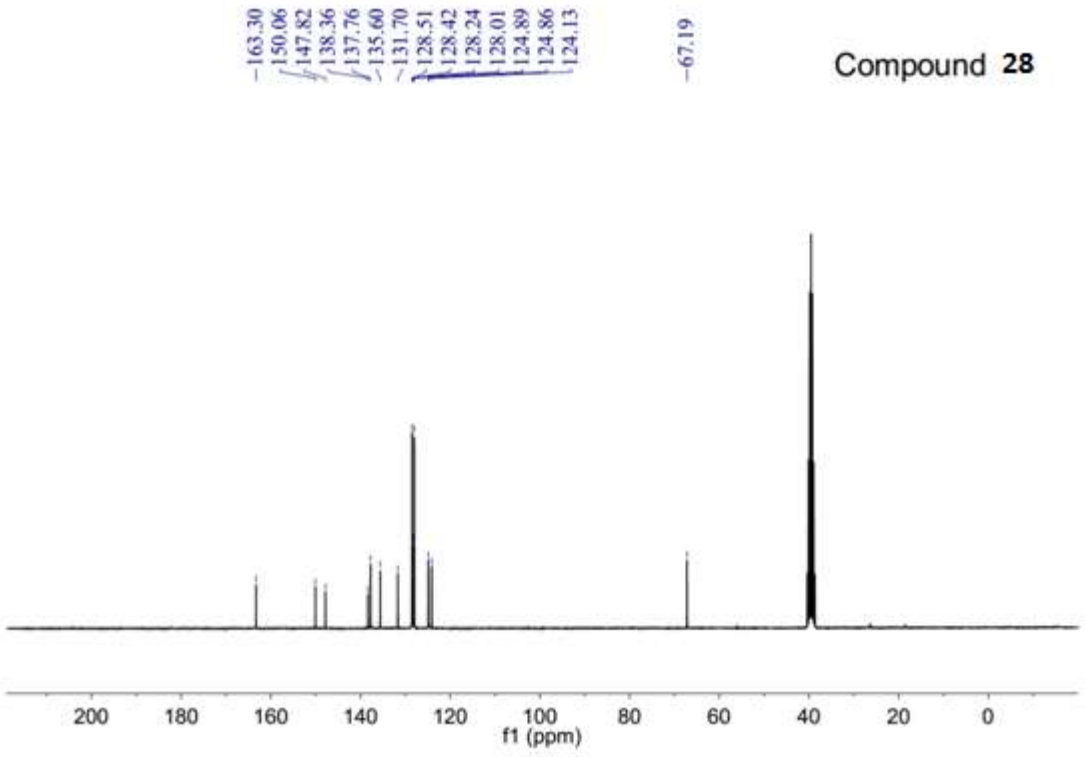
Compound 27: ^{13}C{^{1}H}NMR (300 MHz, DMSO-d_6)



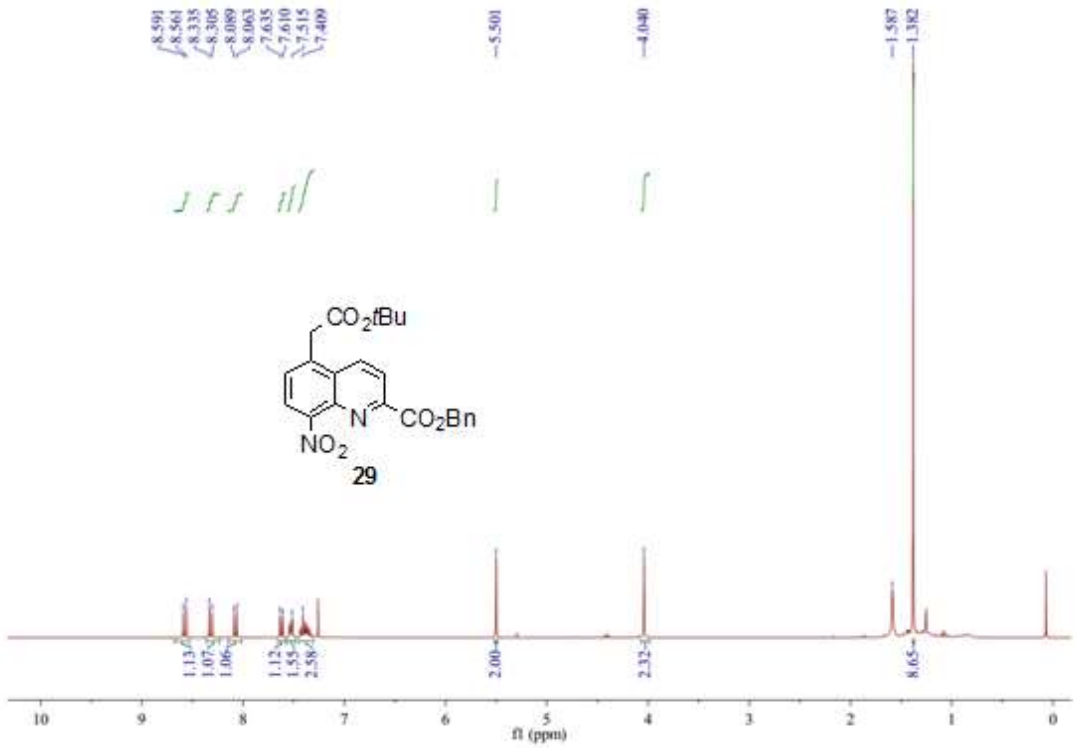
Compound 28: ^{1}H NMR (300 MHz, DMSO-d_6)



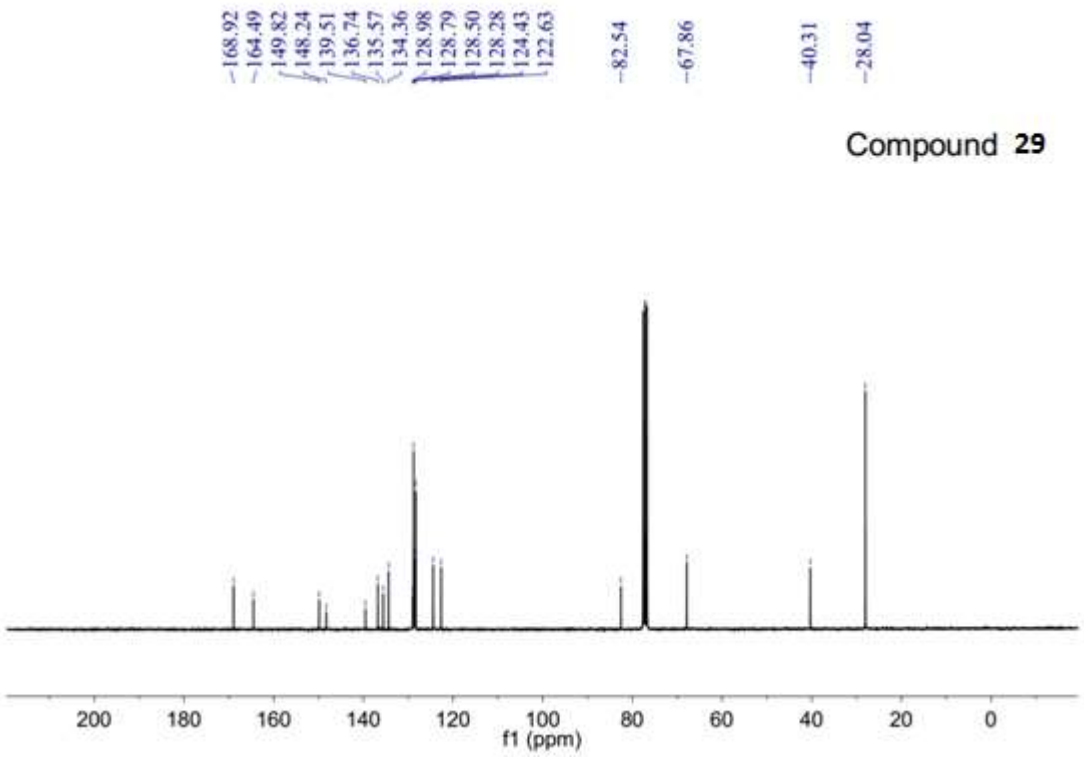
Compound 28: ^{13}C{^{1}H}NMR (300 MHz, DMSO-d_6)



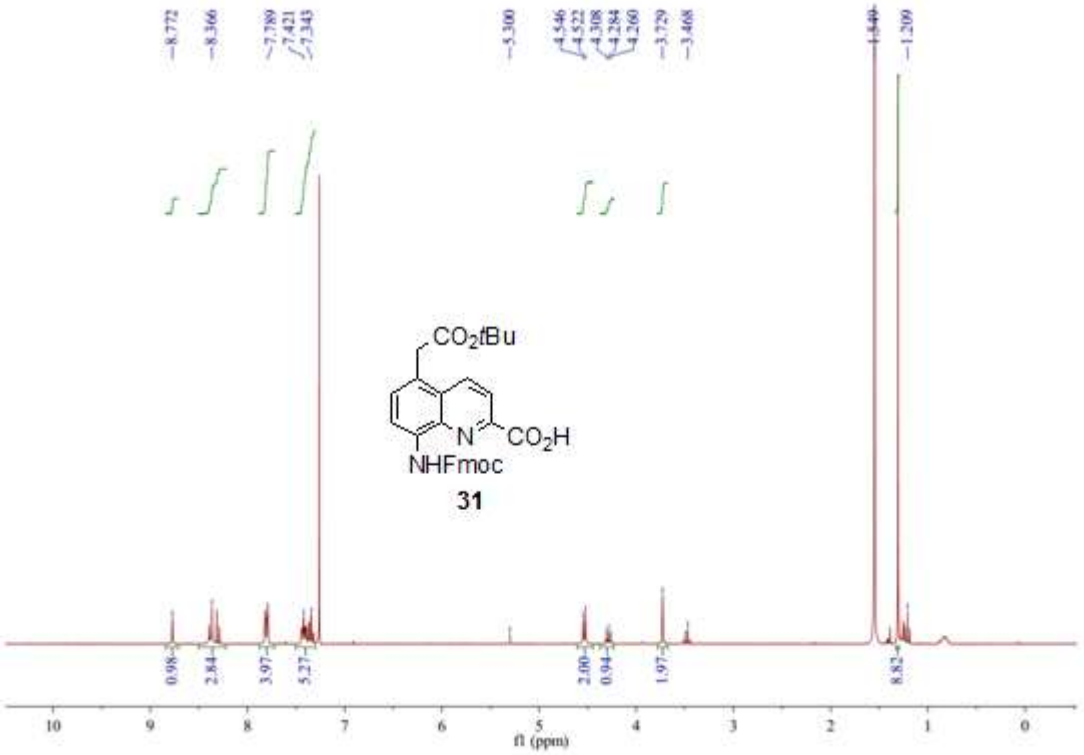
Compound 29: ^{1}H NMR (300 MHz, $CDCl_3$)



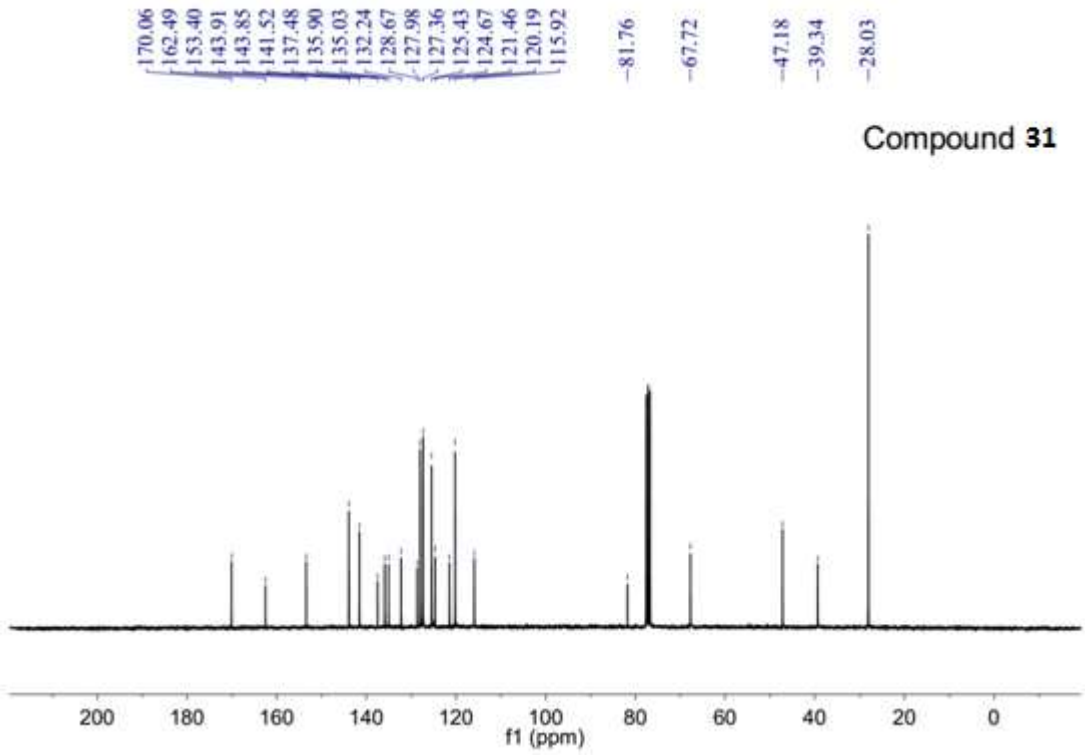
Compound 29: $^{13}C\{^{1}H\}$NMR (300 MHz, $CDCl_3$)



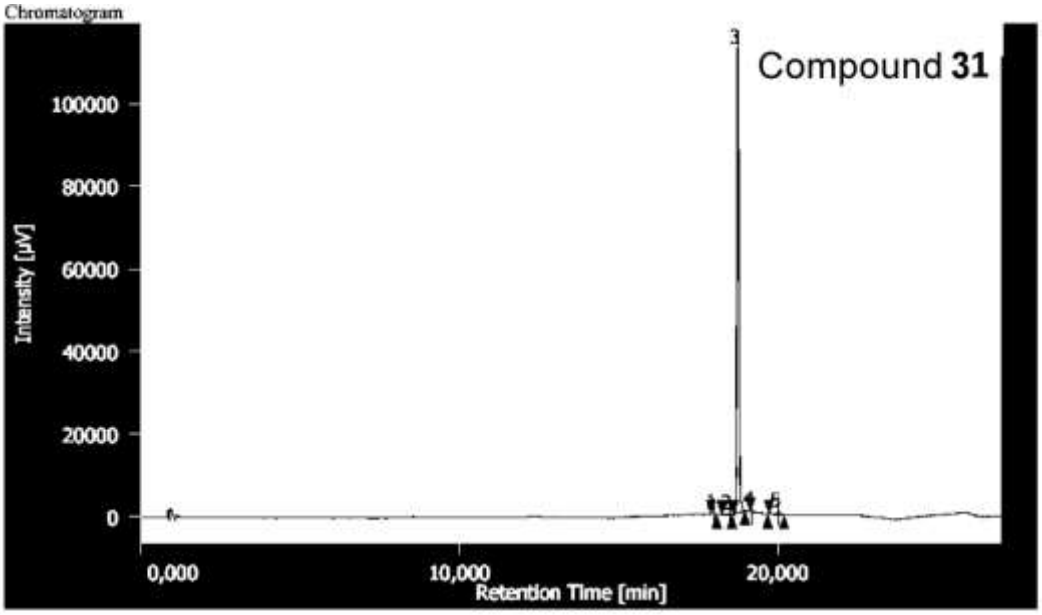
Compound 31: ^{1}H NMR (300 MHz, $CDCl_3$)



Compound 31: $^{13}C\{^{1}H\}$NMR (300 MHz, $CDCl_3$)



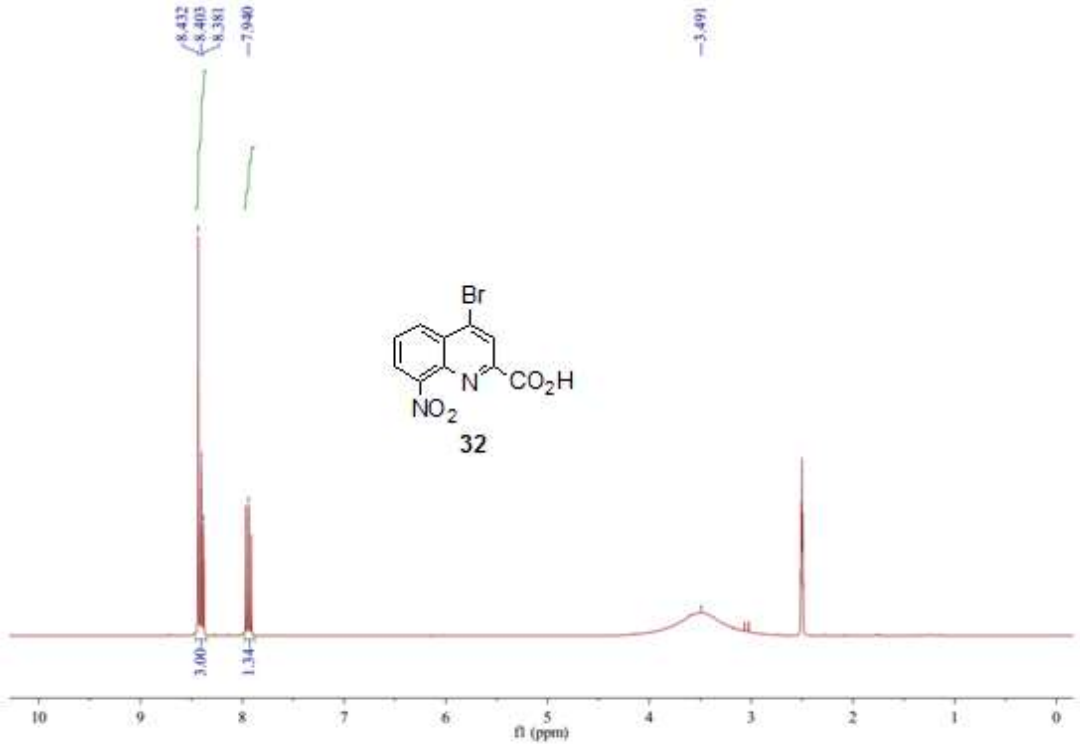
Compound 31: RP-HPLC



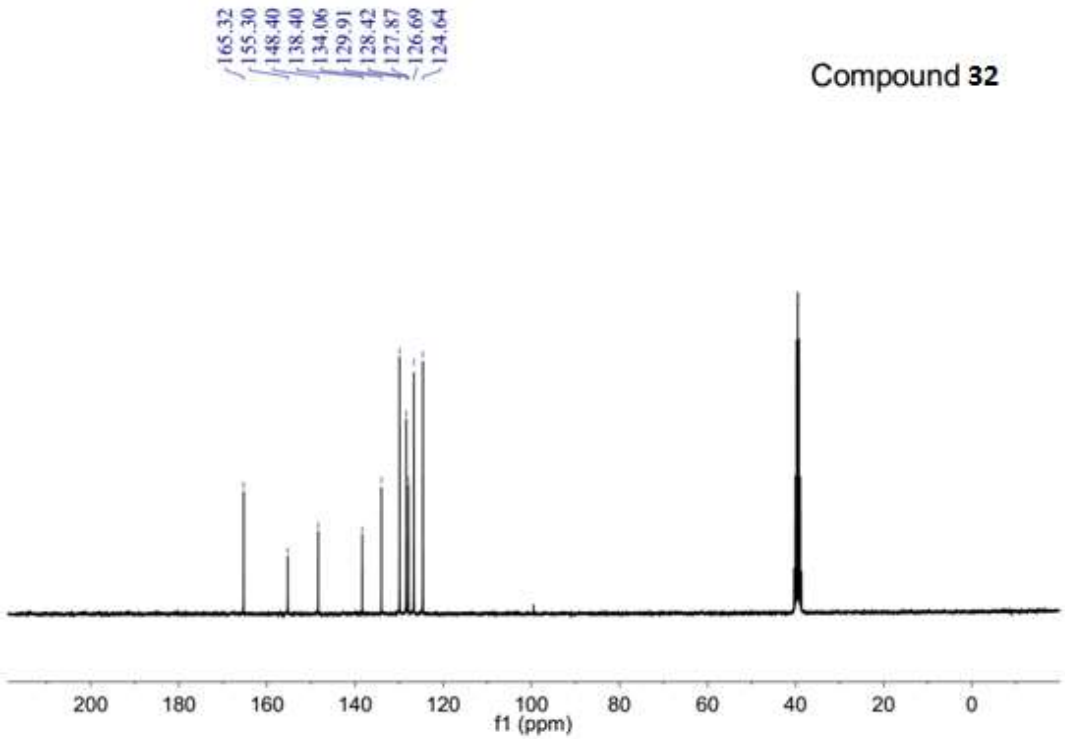
Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor
1	Unknown	3	17,983	1110	275	0,226	0,241	N/A	470331	2,175	1,095
2	Unknown	3	18,458	1797	163	0,367	0,143	N/A	49157	1,205	0,705
3	Unknown	3	18,725	478277	112670	97,599	98,668	N/A	458133	3,809	1,202
4	Unknown	3	19,175	2609	298	0,532	0,261	N/A	368994	6,153	4,922
5	Unknown	3	20,000	6252	786	1,276	0,688	N/A	314712	N/A	0,751

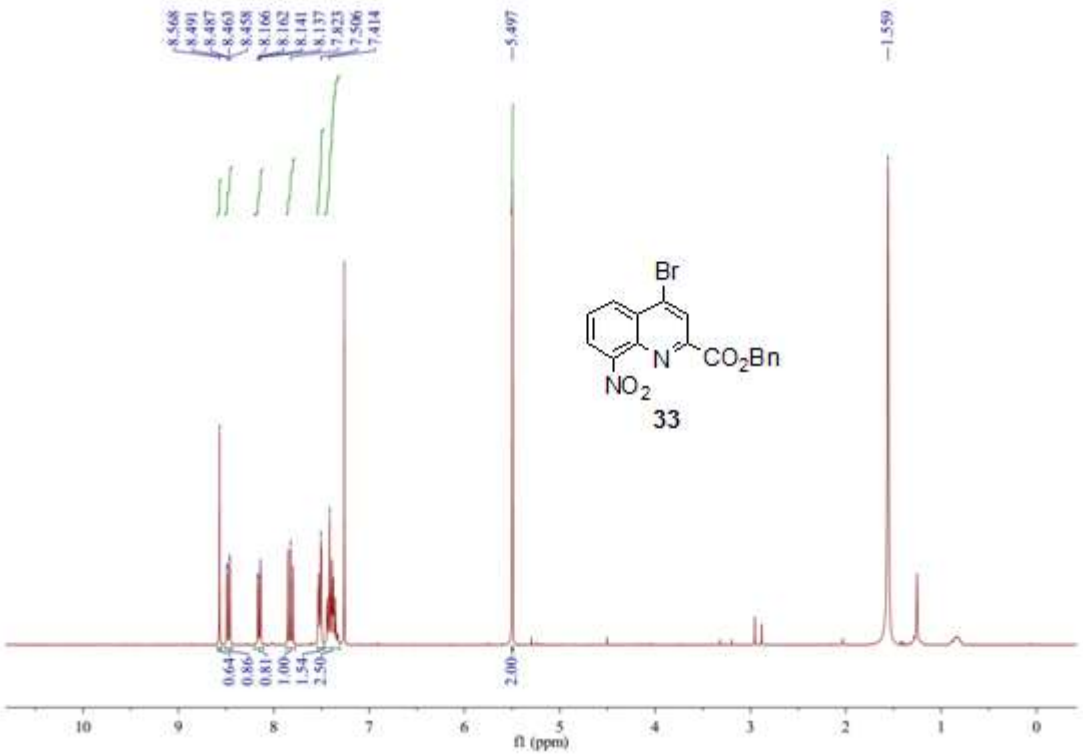
Compound 32: ^{1}H NMR (300 MHz, DMSO-d_6)



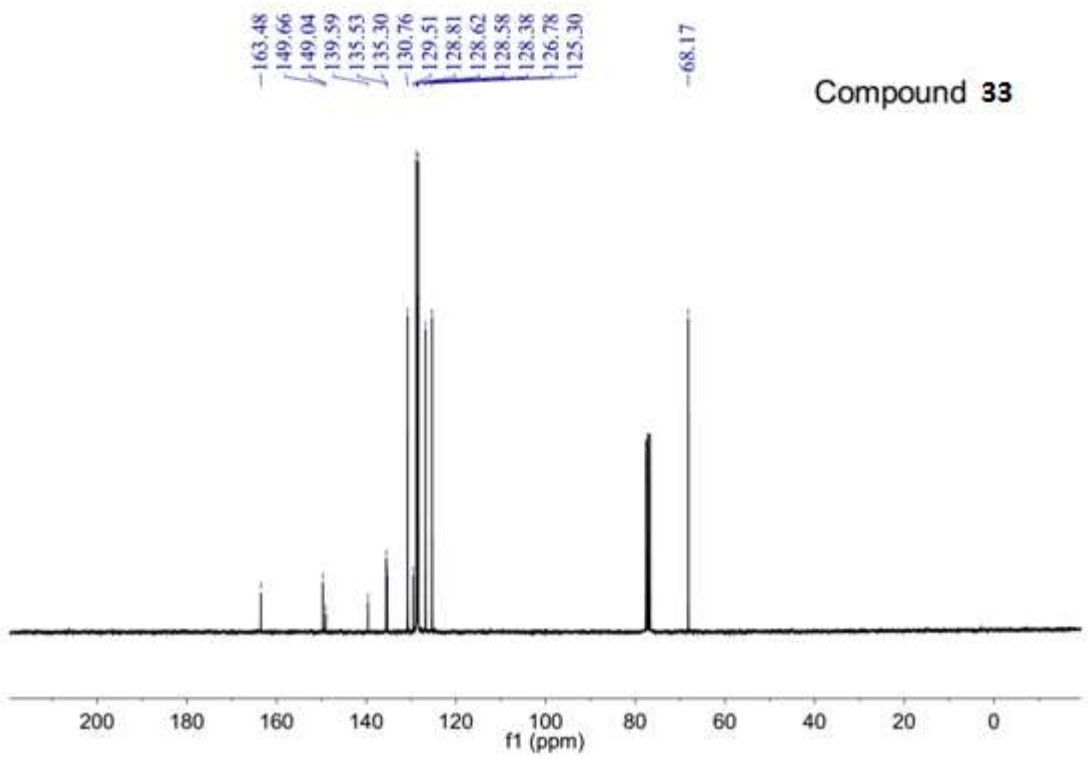
Compound 32: ^{13}C{^{1}H}NMR (300 MHz, DMSO-d_6)



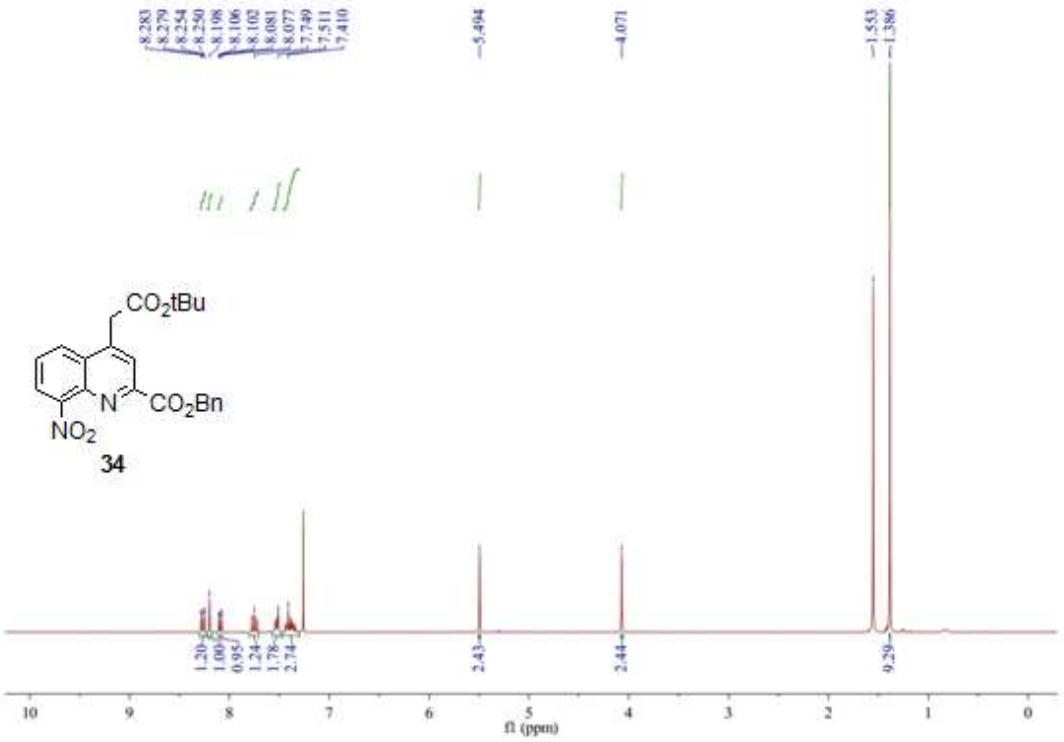
Compound 33: ^{1}H NMR (300 MHz, $CDCl_3$)



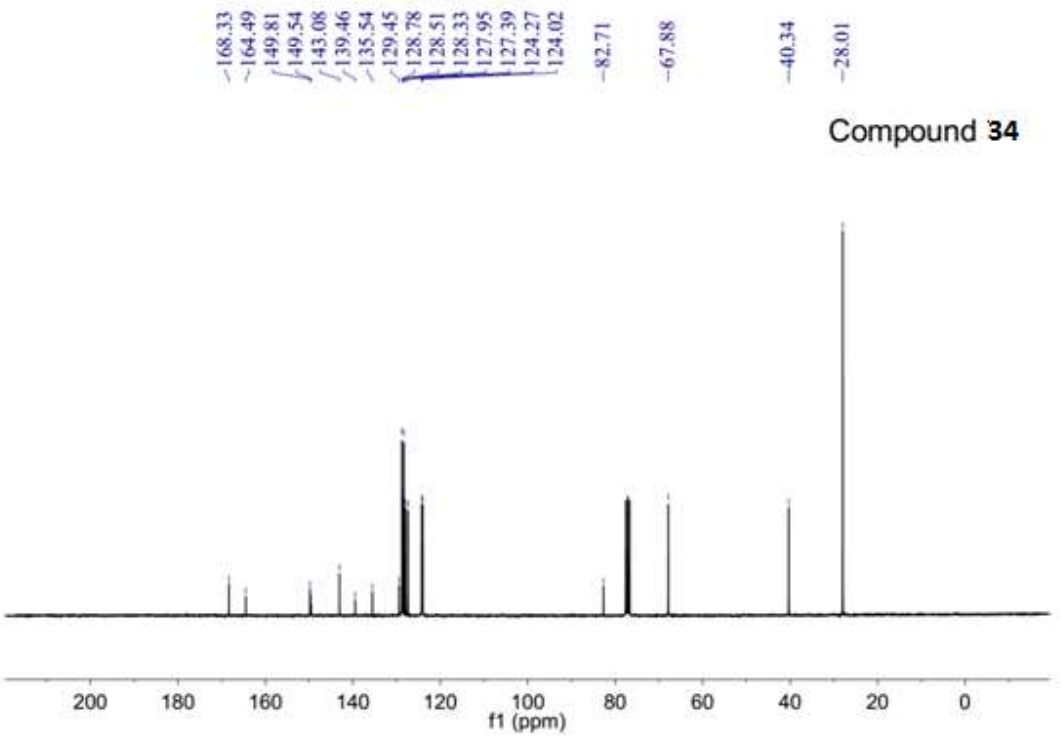
Compound 33: $^{13}C\{^{1}H\}$NMR (300 MHz, $CDCl_3$)



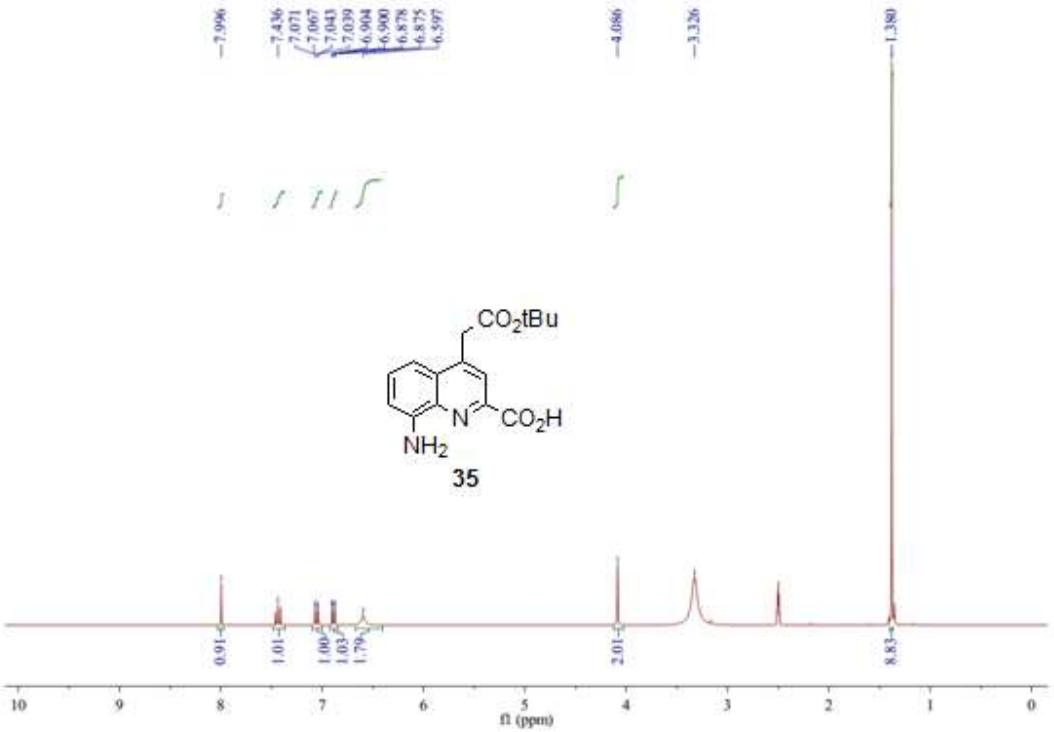
Compound 34: ^{1}H NMR (300 MHz, $CDCl_3$)



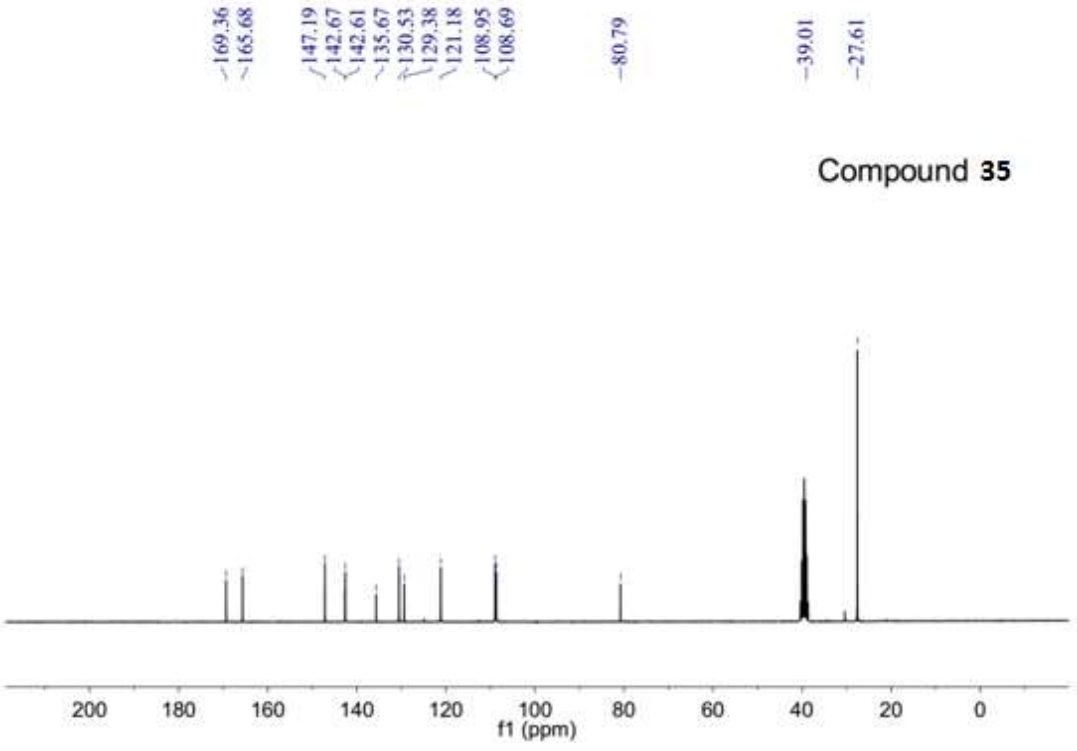
Compound 34: $^{13}C\{^{1}H\}$NMR (300 MHz, $CDCl_3$)



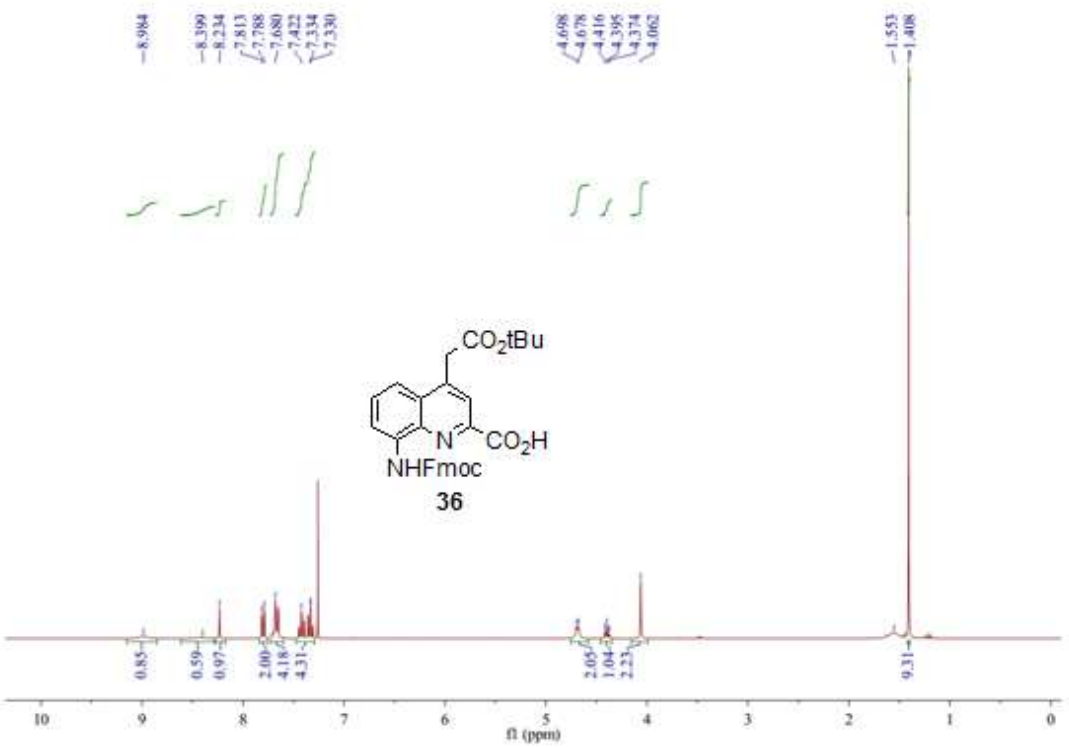
Compound 35: ^{1}H NMR (300 MHz, DMSO-d_6)



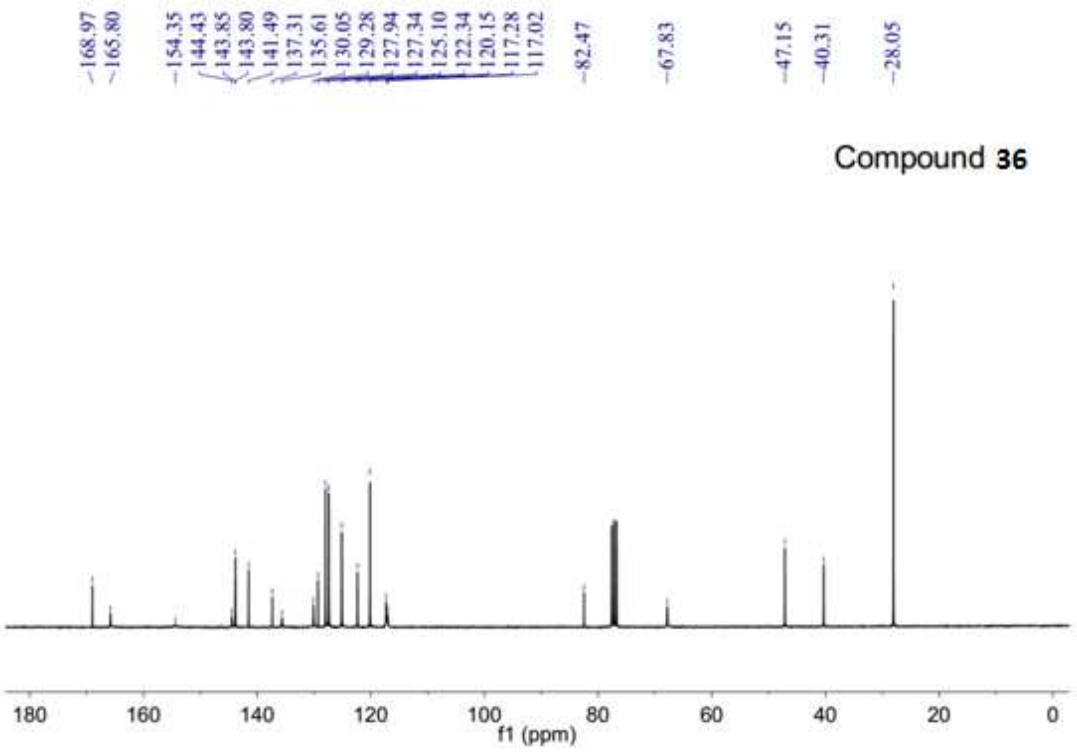
Compound 35: ^{13}C{^{1}H}NMR (300 MHz, DMSO-d_6)



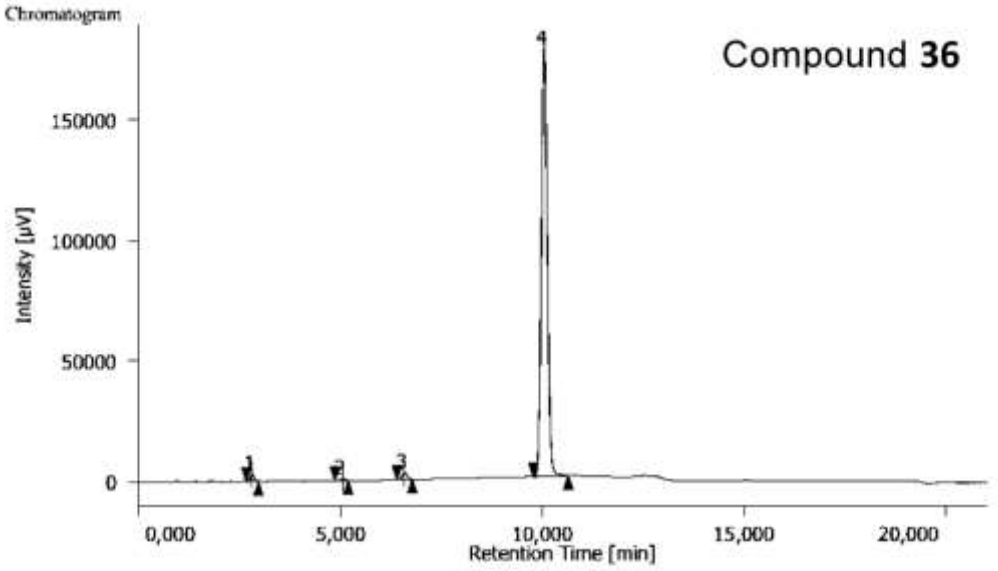
Compound 36: ^{1}H NMR (300 MHz, $CDCl_3$)



Compound 36: $^{13}C\{^{1}H\}$NMR (300 MHz, $CDCl_3$)



Compound 36: RP-HPLC



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	2.808	20342	3225	1.086	1.745	N/A	4453	11.756	1.173	
2	Unknown	3	5.058	7877	993	0.421	0.537	N/A	8819	6.804	0.941	
3	Unknown	3	6.583	24701	2825	1.319	1.528	N/A	12660	13.850	1.068	
4	Unknown	3	10.050	1820203	177776	97.175	96.189	N/A	22517	N/A	1.064	

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