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## Supplementary Figures

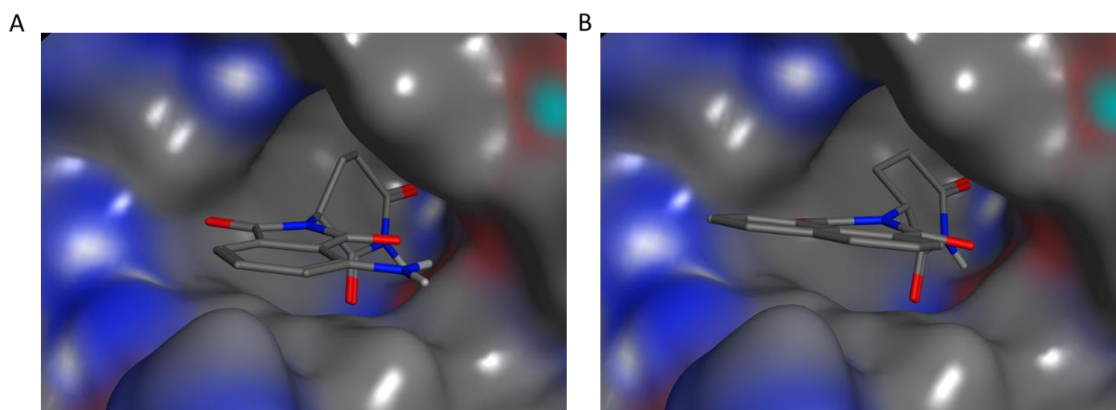


Figure S1 – A Crystal Structure of Pomalidomide Bound to CRBN (PDB ID: 4CI3). B Docked Structure of Compound 12 into the same binding site.

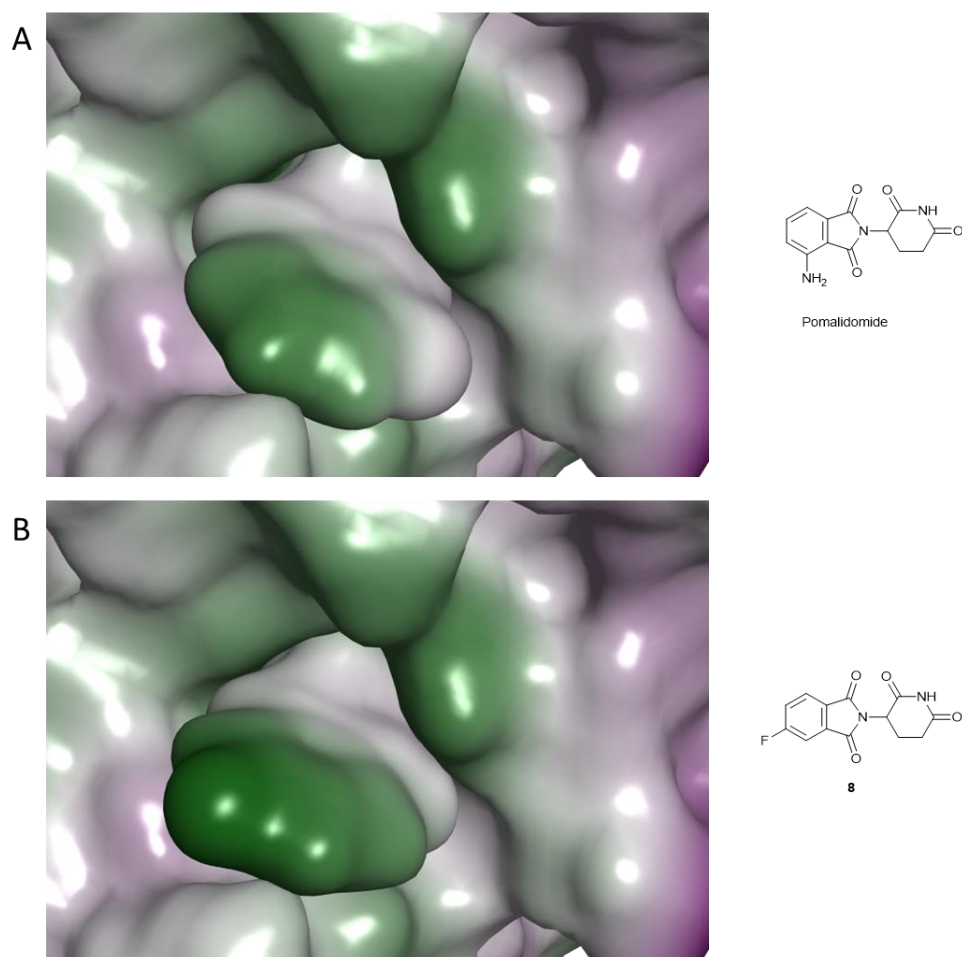


Figure S2 – Changes in protein/ligand complex surfaces with different ligands bound. Surface coloured by lipophilicity calculated using MOE 2016. Green represents lipophilicity and blue represents hydrophilicity.

## **Surface Plasmon Resonance**

The surface plasmon resonance (SPR) experiments were conducted on a S200 Biacore (GE Healthcare). His-tagged cereblon protein was immobilized on a carboxymethylated dextran surface with nitriloacetic acid (NTA), taking advantage of NTA/Ni<sup>2+</sup> chelation. The prepared surface equilibrated overnight in running buffer (10 mM HEPES buffer @ pH 7.4, 150 mM NaCl, 0.4 mg/mL BSA, 0.005% P20, 2% DMSO).

All compounds were prepared in 100% DMSO stock plates with a top concentration of 5mM in a 3x serial dilution. Compounds were transferred from the stock plate to the assay plate and diluted into running buffer containing no DMSO. All compounds were run as a six point-concentration series with a final assay top concentration of 33  $\mu$ M.

Data analysis was performed in S200 Bia-evaluation software (GE Healthcare). Blanks were subtracted and data was corrected for DMSO using a standard DMSO curve. All reported KD values represent an average of at least N=2 and were obtained by fitting to a minimum of five concentrations using a 1:1 fitting algorithm. Errors given are the standard error of the mean from multiple experiments (minimum of 2 repeats).

## **Cellular Evaluation of Compounds**

MM.1S cells were treated for 24 hours with 10  $\mu$ M of each compound then harvested in lysis buffer (25 mM Tris·HCl pH 7.5 with 1% NP-40 and 0.25% deoxycholate, supplemented with protease and phosphatase inhibitors). Following centrifugation at 16,000 x g for 10 min at 4°C to pellet insoluble materials, the protein concentrations of the supernatants were quantitated by BCA assay (Thermo Fisher Scientific). Protein samples were resolved by SDS-PAGE, electrophoretically transferred to nitrocellulose and probed with antibodies for Aiolos, CK1 $\alpha$  and Tubulin. Immunoblots were developed using enhanced chemiluminescence and visualized using a Bio-Rad Chemi-Doc MP Imaging System and quantitated with Image Lab v.5.2.1 software (Bio-Rad Laboratories).

Compounds showing reduced levels of Aiolos were further subjected to dose response experiments in a similar fashion. Protein levels were quantified and normalized to tubulin. The DMSO control was defined as 1.0 and compound treated lanes normalized accordingly. The

data was plotted in Prism v7.01 (GraphPad Software Inc.) and a non-linear curve fit employed to generate DC<sub>50</sub> values.

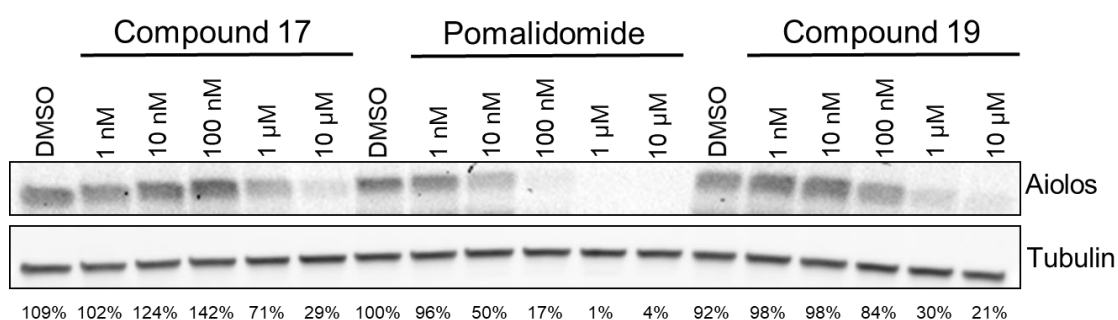


Figure S3 – Dose Response for Aiolos Degradation. MM.1S cells were treated with the indicated concentrations of compounds for 24 hours before immunoblotting for Aiolos and Tubulin as a loading control.

### Cell Proliferation Assays

Following 72 hour treatment of cells as indicated, culture medium was supplemented with 20 μl/well MTS Aqueous One (Promega Corp., Madison, WI) and incubated at 37°C for 2 hours. Mitochondrial reduction of MTS to the formazan derivative was monitored by measuring the medium's absorbance at 490 nm using a Wallac Victor<sup>2</sup> plate reader (Perkin-Elmer Life Sciences, Waltham, MA). Data analysis and statistics performed using Prism v7.0 software (GraphPad Software).

## Synthesis

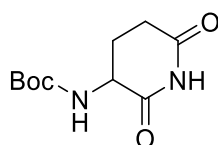
### Safety Issues

The reactions detailed below are performed in sealed reaction tubes at temperatures above that of the boiling point of the solvents employed. Furthermore, the reaction produces gaseous by-products which further increase the pressure developed during the reaction. Care should be taken to perform these reactions in a safe manner. Systems which monitor internal pressure should be employed for microwave reactions and thick-walled tubes used for conventional heating. We recommend the use of a blast shield for this reaction. Following the reaction, the vessel should be allowed to cool to r.t. before careful release of built up pressure.

### General comments

Unless otherwise indicated, common reagents or materials were obtained from commercial source and used without further purification. Tetrahydrofuran (THF) and Dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>) was dried by a PureSolv™ solvent drying system. Flash column chromatography was performed using silica gel 60 (230-400 mesh). Analytical thin layer chromatography (TLC) was carried out on Merck silica gel plates with QF-254 indicator and visualized by UV or KMnO<sub>4</sub>. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on an Agilent DD<sub>2</sub> 500 (500 MHz <sup>1</sup>H; 125 MHz <sup>13</sup>C) or Agilent DD<sub>2</sub> 600 (600 MHz <sup>1</sup>H; 150 MHz <sup>13</sup>C) or Agilent DD<sub>2</sub> 400 (400 MHz <sup>1</sup>H; 100 MHz <sup>13</sup>C) spectrometer at room temperature. Chemical shifts were reported in ppm relative to the residual CDCl<sub>3</sub> (δ 7.26 ppm <sup>1</sup>H; δ 77.00 ppm <sup>13</sup>C), CD<sub>3</sub>OD (δ 3.31 ppm <sup>1</sup>H; δ 49.00 ppm <sup>13</sup>C), or *d*<sup>6</sup>-DMSO (δ 2.50 ppm <sup>1</sup>H; δ 39.52 ppm <sup>13</sup>C). NMR chemical shifts were expressed in ppm relative to internal solvent peaks, and coupling constants were measured in Hz. (bs = broad signal). High-resolution mass spectra (HRMS) were obtained using electrospray ionization (ESI) on a time of flight (TOF) mass spectrometer. All microwave reactions were conducted in sealed reaction vessels (2-5 mL) using a Biotage Initiator+ microwave reactor operating at the normal absorption level. The reaction temperatures were measured using IR. Reaction times refer to the hold time at the desired set temperature.

### tert-butyl (2,6-dioxopiperidin-3-yl)carbamate



5-amino-2-(tert-butoxycarbonylamino)-5-oxo-pentanoic acid (Boc-Gln-OH; 7 g, 28.42 mmol), 1,1'-Carbonyldiimidazole (4.61 g, 28.42 mmol), and DMAP (0.02 g, 0.14 mmol) were

dissolved in anhydrous THF (20 mL) and heated to reflux for 16 h. The reaction slurry was cooled to r.t. and kept at -20° C for 2h. The product was filtered off, washed with THF and dried to constant weight to yield 5.69 g (88%) of tert-butyl N-(2,6-dioxo-3-piperidyl)carbamate as a white solid.

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ = 10.74 (s, 1H), 7.12 (d, *J* = 8.7 Hz, 1H), 4.29 – 4.15 (m, 1H), 2.79 – 2.60 (m, 1H), 2.45 (t, *J* = 3.7 Hz, 1H), 2.01 – 1.82 (m, 2H), 1.39 (s, 9H).

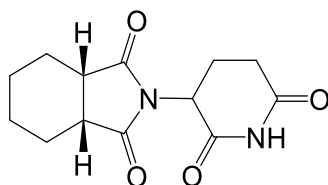
**<sup>13</sup>C NMR** (101 MHz, DMSO-*d*<sub>6</sub>) δ = 172.96, 172.51, 155.39, 78.14, 50.38, 30.97, 28.17, 24.42.

**HRMS**: calc. [M-Boc+H]<sup>+</sup> for C<sub>5</sub>H<sub>9</sub>N<sub>2</sub>O<sub>2</sub> = 129.0659; found = 129.0676 [M-Boc+H]<sup>+</sup>.

### General Procedure 1: Deprotection/Condensation Reaction

A suspension of tert-butyl N-(2,6-dioxo-3-piperidyl)carbamate (1 eq.) and the corresponding anhydride (1 eq.) in Trifluoroethanol was heated for 2 h at 150 °C under microwave conditions. After cooling to r.t. the reaction mixture was cooled to -20° C for 4 h. If the desired product did not precipitate after cooling to -20° C, ethyl acetate (3 drops) was added and the mixture kept at -20° C for additional 4 h. The precipitated product was filtered off, washed with ethyl acetate (3 x 2 ml) and dried to constant weight.

### 2-(2,6-dioxopiperidin-3-yl)hexahydro-1H-isoindole-1,3(2H)-dione, 1



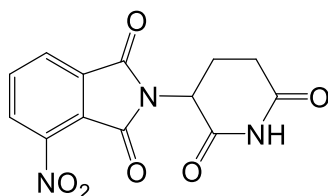
Compound 1 was prepared according to **GP1** using 400 mg of tert-butyl N-(2,6-dioxo-3-piperidyl)carbamate to yield 399 mg (86%) of 2-(2,6-dioxopiperidin-3-yl)hexahydro-1H-isoindole-1,3(2H)-dione.

**<sup>1</sup>H NMR** (500 MHz, DMSO-*d*<sub>6</sub>) δ 11.00 (s, 1H), 4.88 (dd, *J* = 12.8, 5.5 Hz, 1H), 3.05 – 2.93 (m, 2H), 2.81 (ddd, *J* = 17.1, 14.0, 5.5 Hz, 1H), 2.52 (ddd, *J* = 17.0, 4.4, 2.5 Hz, 1H), 2.40 (qd, *J* = 13.1, 4.4 Hz, 1H), 1.86 (dtd, *J* = 13.1, 5.4, 2.4 Hz, 1H), 1.78 – 1.57 (m, 4H), 1.47 – 1.19 (m, 4H).

**<sup>13</sup>C NMR** (126 MHz, DMSO-*d*<sub>6</sub>) δ 179.30, 179.21, 173.14, 169.85, 49.22, 39.28, 31.17, 23.58, 23.39, 21.58, 21.53, 21.48.

**HRMS**: calc. [M-H]<sup>-</sup> for C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub> = 263.1110; found = 263.1165 [M-H]<sup>-</sup>.

## 2-(2,6-dioxopiperidin-3-yl)-4-nitroisindoline-1,3-dione, 2



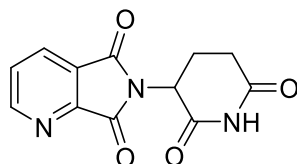
Compound 2 was prepared according to **GP1** using 200 mg of tert-butyl N-(2,6-dioxo-3-piperidyl)carbamate to yield 252 mg (95%) of 2-(2,6-dioxo-3-piperidyl)-4-nitro-isindoline-1,3-dione.

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 11.17 (s, 1H), 8.36 (dd, *J* = 8.1, 0.9 Hz, 1H), 8.24 (dd, *J* = 7.5, 0.9 Hz, 1H), 8.12 (t, *J* = 7.8 Hz, 1H), 5.20 (dd, *J* = 12.9, 5.4 Hz, 1H), 2.95 – 2.82 (m, 1H), 2.66 – 2.52 (m, 2H), 2.12 – 2.03 (m, 1H).

**<sup>13</sup>C NMR** (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 172.67, 169.46, 165.15, 162.50, 144.41, 136.78, 132.98, 128.84, 127.27, 122.53, 49.41, 30.85, 21.71.

**HRMS**: calc.  $[M+H]^+$  for C<sub>13</sub>H<sub>10</sub>N<sub>3</sub>O<sub>6</sub> = 304.0564; found = 304.0572  $[M+H]^+$ .

## 6-(2,6-dioxopiperidin-3-yl)-5H-pyrrolo[3,4-b]pyridine-5,7(6H)-dione, 3



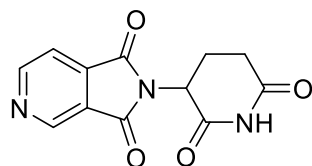
Compound 3 was prepared according to **GP1** using 200 mg of tert-butyl N-(2,6-dioxo-3-piperidyl)carbamate to yield 137 mg (60%) of 6-(2,6-dioxo-3-piperidyl)pyrrolo[3,4-b]pyridine-5,7-dione.

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 9.03 (s, 1H), 8.68 (d, *J* = 3.1 Hz, 1H), 8.21 (d, *J* = 7.9 Hz, 1H), 7.46 (dd, *J* = 7.8, 4.8 Hz, 1H), 3.72 (dd, *J* = 12.1, 5.1 Hz, 1H), 2.71 – 2.51 (m, 2H), 2.12 – 2.01 (m, 1H), 1.90 – 1.76 (m, 1H).

**<sup>13</sup>C NMR** (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 174.18, 174.17, 173.03, 166.85, 151.97, 150.28, 136.65, 129.41, 123.40, 50.33, 30.64, 24.87.

**HRMS**: calc.  $[M+H]^+$  for C<sub>12</sub>H<sub>10</sub>N<sub>3</sub>O<sub>4</sub> = 260.0666; found = 260.0664  $[M+H]^+$ .

## 2-(2,6-dioxopiperidin-3-yl)-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione, 4



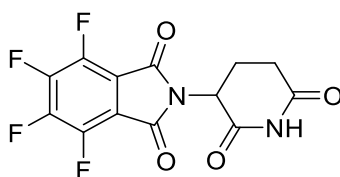
Compound 4 was prepared according to **GP1** using 200 mg of tert-butyl N-(2,6-dioxo-3-piperidyl)carbamate to yield 79 mg (35%) of 2-(2,6-dioxopiperidin-3-yl)-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione.

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ = 11.17 (s, 1H), 9.20 (d, *J* = 1.1 Hz, 1H), 9.16 (d, *J* = 4.8 Hz, 1H), 7.96 (dd, *J* = 4.9, 1.1 Hz, 1H), 5.22 (dd, *J* = 12.9, 5.4 Hz, 1H), 2.96 – 2.83 (m, 1H), 2.67 – 2.56 (m, 1H), 2.55 – 2.44 (m, 1H), 2.12 – 2.02 (m, 1H).

**<sup>13</sup>C NMR** (101 MHz, DMSO-*d*<sub>6</sub>) δ = 172.67, 169.51, 166.39, 166.05, 156.30, 144.34, 138.77, 125.30, 117.12, 49.21, 30.86, 21.78.

**HRMS**: calc. [M+H]<sup>+</sup> for C<sub>12</sub>H<sub>10</sub>N<sub>3</sub>O<sub>4</sub> = 260.0666; found = 260.0687 [M+H]<sup>+</sup>.

#### 2-(2,6-dioxopiperidin-3-yl)-4,5,6,7-tetrafluoroisindoline-1,3-dione, 5



Compound 5 was prepared according to **GP1** using 200 mg of tert-butyl N-(2,6-dioxo-3-piperidyl)carbamate to yield 159,4 mg (55%) of 2-(2,6-dioxo-3-piperidyl)-4,5,6,7-tetrafluoroisindoline-1,3-dione.

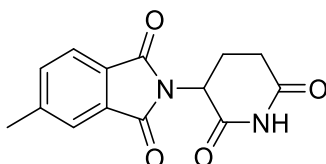
**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ = 11.18 (s, 1H), 5.19 (dd, *J* = 13.0, 5.4 Hz, 1H), 2.97 – 2.77 (m, 1H), 2.67 – 2.55 (m, 1H), 2.49 – 2.38 (m, 1H), 2.18 – 1.95 (m, 1H).

**<sup>13</sup>C NMR** (101 MHz, DMSO-*d*<sub>6</sub>) δ = 172.99, 169.62, 162.27, 145.34 (m), 142.68 (m), 113.79 (d, *J* = 9.2 Hz), 49.97, 31.24, 22.07.

**<sup>19</sup>F NMR** (376 MHz, DMSO-*d*<sub>6</sub>) δ = -138.33 (d, *J* = 12.7 Hz), -143.85 (d, *J* = 12.8 Hz)

**HRMS**: calc. [M+H]<sup>+</sup> for C<sub>13</sub>H<sub>7</sub>F<sub>4</sub>N<sub>2</sub>O<sub>4</sub> = 331,0337; found = 331.0356 [M+H]<sup>+</sup>.

#### 2-(2,6-dioxopiperidin-3-yl)-5-methylisindoline-1,3-dione, 6





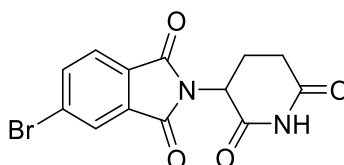
Compound 6 was prepared according to **GP1** using 2000 mg of tert-butyl N-(2,6-dioxo-3-piperidyl)carbamate to yield 1750 mg (74%) of 2-(2,6-dioxopiperidin-3-yl)-5-methylisoindoline-1,3-dione.

$^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  11.09 (s, 1H), 7.77 (d,  $J = 7.6$  Hz, 1H), 7.72 (s, 1H), 7.66 (d,  $J = 7.7$  Hz, 1H), 5.10 (dd,  $J = 13.0, 5.3$  Hz, 1H), 2.95 – 2.77 (m, 1H), 2.61 – 2.40 (m, 5H), 2.08 – 1.94 (m, 1H).

$^{13}\text{C NMR}$  (101 MHz,  $\text{DMSO-}d_6$ )  $\delta$  172.50, 169.63, 167.03, 166.91, 145.68, 134.95, 131.38, 128.41, 123.58, 123.08, 48.72, 30.72, 21.81, 21.16.

**HRMS:** calc.  $[\text{M-H}]^-$  for  $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_4 = 271.0724$ ; found = 271.1587  $[\text{M-H}]^-$ .

### 5-bromo-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione, 7



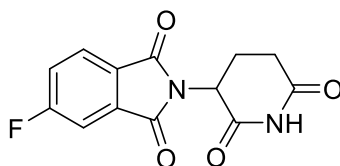
Compound 7 was prepared according to **GP1** using 500 mg of tert-butyl N-(2,6-dioxo-3-piperidyl)carbamate to yield 555 mg (75%) of 5-bromo-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione.

$^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  11.11 (s, 1H), 8.12 (d,  $J = 1.6$  Hz, 1H), 8.06 (dd,  $J = 7.9, 1.7$  Hz, 1H), 7.83 (d,  $J = 7.9$  Hz, 1H), 5.13 (dd,  $J = 12.8, 5.4$  Hz, 1H), 2.86 (ddd,  $J = 17.0, 13.8, 5.4$  Hz, 1H), 2.65 – 2.48 (m, 2H), 2.03 (dtd,  $J = 12.9, 5.2, 2.1$  Hz, 1H).

$^{13}\text{C NMR}$  (101 MHz,  $\text{DMSO-}d_6$ )  $\delta$  173.13, 170.09, 166.86, 166.30, 138.05, 133.58, 130.58, 128.95, 126.82, 125.70, 49.60, 31.33, 22.33.

**HRMS:** calc.  $[\text{M+H}]^+$  for  $\text{C}_{13}\text{H}_9^{81}\text{BrN}_2\text{O}_4 = 338.9798$ ; found = 338.9832  $[\text{M+H}]^+$ .

### 5-fluoro-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione, 8



Compound 8 was prepared according to **GP1** using 500 mg of tert-butyl N-(2,6-dioxo-3-piperidyl)carbamate to yield 342 mg (56%) of 5-fluoro-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione.

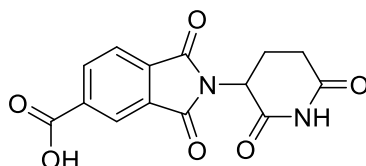
**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.11 (s, 1H), 7.98 (dd, *J* = 8.3, 4.5 Hz, 1H), 7.82 (dd, *J* = 7.4, 2.3 Hz, 1H), 7.69 (ddd, *J* = 10.5, 8.3, 2.4 Hz, 1H), 5.13 (dd, *J* = 12.8, 5.4 Hz, 1H), 2.86 (ddd, *J* = 16.9, 13.7, 5.4 Hz, 1H), 2.66 – 2.52 (m, 2H), 2.03 (dtd, *J* = 13.0, 5.2, 2.1 Hz, 1H).

**<sup>13</sup>C NMR** (101 MHz, DMSO-*d*<sub>6</sub>) δ 173.16, 170.17, 166.60, 166.32 (m), 165.14, 134.64 (d, *J* = 10.0 Hz), 127.86 (d, *J* = 2.7 Hz), 126.71 (d, *J* = 9.7 Hz), 122.19 (d, *J* = 23.8 Hz), 111.88 (d, *J* = 25.3 Hz), 49.60, 31.34, 22.36.

**<sup>19</sup>F NMR** (376 MHz, DMSO-*d*<sub>6</sub>) δ -102.39 (td, *J* = 8.5, 4.7 Hz)

**HRMS**: calc. [M-H]<sup>-</sup> for C<sub>13</sub>H<sub>9</sub>FN<sub>2</sub>O<sub>4</sub> = 275.0474; found = 275.0462 [M-H]<sup>-</sup>.

### 2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindoline-5-carboxylic acid, 9



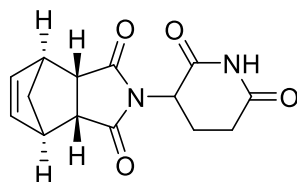
Compound 9 was prepared according to **GP1** using 2000 mg of tert-butyl N-(2,6-dioxo-3-piperidyl)carbamate to yield 1760 mg (66%) of 2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindoline-5-carboxylic acid.

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.12 (s, 1H), 8.37 (dd, *J* = 7.7, 1.4 Hz, 1H), 8.24 (d, *J* = 1.3 Hz, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 5.17 (dd, *J* = 12.8, 5.4 Hz, 1H), 2.87 (ddd, *J* = 16.6, 13.6, 5.2 Hz, 1H), 2.62 – 2.48 (m, 2H), 2.10 – 1.86 (m, 1H).

**<sup>13</sup>C NMR** (101 MHz, DMSO-*d*<sub>6</sub>) δ 173.15, 170.12, 166.84, 166.80, 166.16, 137.33, 136.11, 134.82, 132.07, 124.27, 123.83, 49.63, 31.34, 22.34.

**HRMS:** calc.  $[M-H]^-$  for  $C_{14}H_{10}N_2O_4$  = 301.0466; found = 301.0252  $[M-H]^-$ .

**2-(2,6-dioxopiperidin-3-yl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisindole-1,3(2H)-dione, 10**



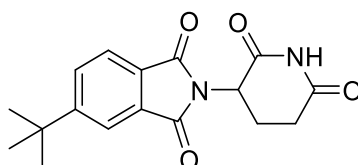
Compound 10 was prepared according to **GP1** using 1500 mg of tert-butyl N-(2,6-dioxo-3-piperidyl)carbamate to yield 1690 mg (94%) of 2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindoline-5-carboxylic acid.

**$^1H$  NMR** (400 MHz,  $DMSO-d_6$ )  $\delta$  10.93 (s, 1H), 6.03 (dd,  $J$  = 6.9, 2.8 Hz, 2H), 4.72 (dd,  $J$  = 12.6, 5.5 Hz, 1H), 3.44 – 3.34 (m, 2H), 3.30 – 3.20 (m, 3H), 2.72 (ddd,  $J$  = 18.4, 14.0, 5.4 Hz, 1H), 2.47 – 2.37 (m, 1H), 2.17 (qd,  $J$  = 13.0, 4.4 Hz, 1H), 1.69 – 1.57 (m, 1H), 1.56 – 1.44 (m, 2H).

**$^{13}C$  NMR** (101 MHz,  $DMSO-d_6$ )  $\delta$  176.98, 176.92, 173.02, 169.27, 134.72, 134.62, 51.95, 49.09, 45.58, 45.49, 45.06, 44.86, 30.93, 21.80.

**HRMS:** calc.  $[M-H]^-$  for  $C_{14}H_{14}N_2O_4$  = 273.0881; found = 273.0917  $[M-H]^-$ .

**5-(tert-butyl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione, 11**



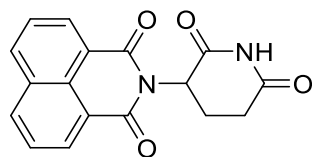
Compound 11 was prepared according to **GP1** using 300 mg of tert-butyl N-(2,6-dioxo-3-piperidyl)carbamate to yield 342 mg (83%) of 5-(tert-butyl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione.

**$^1H$  NMR** (400 MHz,  $DMSO-d_6$ )  $\delta$  11.08 (s, 1H), 7.93 – 7.85 (m, 2H), 7.82 (dd,  $J$  = 7.6, 1.0 Hz, 1H), 5.11 (dd,  $J$  = 13.0, 5.4 Hz, 1H), 3.84 (qd,  $J$  = 9.6, 6.6 Hz, 2H), 2.86 (ddd,  $J$  = 17.4, 14.0, 5.4 Hz, 1H), 2.62 – 2.46 (m, 4H), 2.02 (dtd,  $J$  = 12.9, 5.9, 2.8 Hz, 1H), 1.33 (s, 9H).

**$^{13}C$  NMR** (101 MHz,  $DMSO-d_6$ )  $\delta$  173.19, 170.32, 167.77, 167.46, 159.10, 132.10, 131.99, 129.16, 123.76, 120.73, 49.39, 35.97, 31.38, 31.17, 22.45.

**HRMS:** calc.  $[M-H]^-$  for  $C_{17}H_{18}N_2O_4$  = 313.1267; found = 313.1291  $[M-H]^-$ .

## 2-(2,6-dioxopiperidin-3-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione, 12



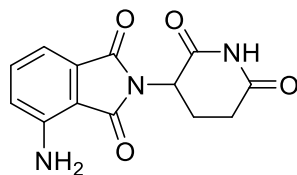
Compound 12 was prepared according to **GP1** except the heating was extended to 6 hours, using 68 mg of tert-butyl N-(2,6-dioxo-3-piperidyl)carbamate to yield 82 mg (80%) of 2-(2,6-dioxopiperidin-3-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione.

**<sup>1</sup>H NMR** (500 MHz, DMSO-*d*<sub>6</sub>) δ 11.01 (bs, 1H), 8.70 – 8.33 (m, 4H), 7.90 (dd, *J* = 8.0 Hz, 2H), 5.85 (dd, *J* = 11.5, 5.7 Hz, 1H), 2.95 (ddd, *J* = 18.2, 15.3, 5.4 Hz, 1H), 2.70 – 2.54 (m, 2H), 2.11 – 2.00 (m, 1H).

**<sup>13</sup>C NMR** (151 MHz, DMSO-*d*<sub>6</sub>) δ 172.86, 170.24, 163.44, 162.62, 134.90, 134.85, 131.55, 131.31, 130.96, 127.43, 127.38, 127.37, 121.83, 121.48, 50.51, 30.86, 21.42.

**HRMS:** (ESI); *m/z* [M+H]<sup>+</sup>: Calcd. for C<sub>17</sub>H<sub>13</sub>N<sub>2</sub>O<sub>4</sub>, 309.0875; found 309.0858.

## 4-amino-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione, 13 - Pomalidomide



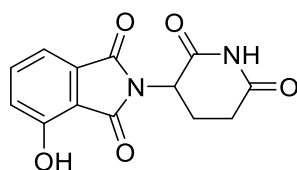
Compound 13 was prepared according to GP1 using 97 mg of tert-butyl N-(2,6-dioxo-3-piperidyl)carbamate to yield 93 mg (80%) of 4-amino-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione.

**<sup>1</sup>H NMR** (500 MHz, DMSO-*d*<sub>6</sub>) δ 11.07 (s, 1H), 7.58 – 7.38 (m, 1H), 7.20 – 6.81 (m, 2H), 6.51 (bs, 2H), 5.04 (dd, *J* = 12.7, 5.4 Hz, 1H), 2.88 (ddd, *J* = 16.6, 13.7, 5.3 Hz, 1H), 2.69 – 2.46 (m, 2H), 2.13 – 1.91 (m, 1H).

**<sup>13</sup>C NMR** (151 MHz, DMSO-*d*<sub>6</sub>) δ 172.83, 170.14, 168.57, 167.38, 146.73, 135.48, 132.01, 121.71, 110.98, 108.52, 48.49, 30.99, 22.17.

**HRMS** (ESI); *m/z* [M+H]<sup>+</sup>: Calcd. for C<sub>13</sub>H<sub>12</sub>N<sub>3</sub>O<sub>4</sub>, 274.0827; found 274.0837.

## 2-(2,6-dioxopiperidin-3-yl)-4-hydroxyisoindoline-1,3-dione, 14



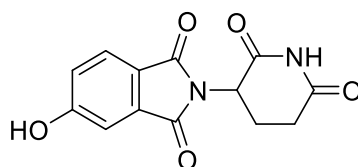
Compound 14 was prepared according to GP1 using 265 mg of tert-butyl N-(2,6-dioxo-3-piperidyl)carbamate to yield 276 mg (86%) of 2-(2,6-dioxopiperidin-3-yl)-4-hydroxyisoindoline-1,3-dione.

**<sup>1</sup>H NMR** (500 MHz, DMSO-*d*<sub>6</sub>) δ 11.17 (s, 1H), 11.08 (s, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 7.1 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 5.07 (dd, *J* = 12.8, 5.4 Hz, 1H), 2.88 (ddd, *J* = 16.8, 13.8, 5.4 Hz, 1H), 2.66 – 2.45 (m, 2H), 2.12 – 1.94 (m, 1H).

**<sup>13</sup>C NMR** (151 MHz, DMSO-*d*<sub>6</sub>) δ 172.83, 170.04, 167.04, 165.83, 155.48, 136.41, 133.16, 123.57, 114.37, 114.31, 48.65, 30.98, 22.05.

**HRMS** (ESI); *m/z*: [M+H]<sup>+</sup> Calcd. for C<sub>13</sub>H<sub>11</sub>N<sub>2</sub>O<sub>5</sub>, 275.1080; found 275.0667.

## 2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindoline-1,3-dione, 15



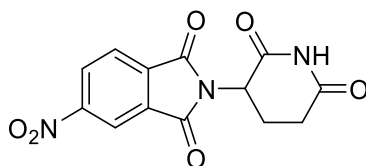
Compound 15 was prepared according to GP1 using 156 mg of tert-butyl N-(2,6-dioxo-3-piperidyl)carbamate to yield 170 mg (91%) of 2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindoline-1,3-dione.

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.08 (s, 1H), 11.03 (s, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.24 – 7.10 (m, 2H), 5.08 (dd, *J* = 12.8, 5.4 Hz, 1H), 2.98 – 2.76 (m, 1H), 2.66 – 2.39 (m, 2H), 2.13 – 1.94 (m, 1H).

**<sup>13</sup>C NMR** (101 MHz, DMSO-*d*<sub>6</sub>) δ 172.74, 169.95, 167.01, 166.90, 163.53, 134.05, 125.59, 121.39, 120.74, 109.95, 48.85, 30.94, 22.09.

**HRMS** (ESI); *m/z*: [M+H]<sup>+</sup> Calcd. for C<sub>13</sub>H<sub>11</sub>N<sub>2</sub>O<sub>5</sub>, 275.1080. Found 275.0580.

### 2-(2,6-dioxopiperidin-3-yl)-5-nitroisindoline-1,3-dione, 16



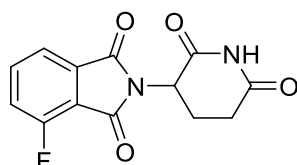
Compound 16 was prepared according to **GP1** using 500 mg of tert-butyl N-(2,6-dioxo-3-piperidyl)carbamate to yield 389 mg (58%) of 2-(2,6-dioxopiperidin-3-yl)-5-nitroisindoline-1,3-dione.

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.15 (s, 1H), 8.64 (dd, *J* = 8.2, 2.0 Hz, 1H), 8.53 (d, *J* = 1.9 Hz, 1H), 8.16 (d, *J* = 8.1 Hz, 1H), 5.21 (dd, *J* = 12.8, 5.4 Hz, 1H), 2.87 (ddd, *J* = 17.0, 13.8, 5.4 Hz, 1H), 2.66 – 2.49 (m, 2H), 2.06 (dtd, *J* = 12.9, 5.2, 2.1 Hz, 1H).

**<sup>13</sup>C NMR** (101 MHz, DMSO-*d*<sub>6</sub>) δ 173.11, 169.92, 165.97, 165.70, 152.14, 136.15, 132.95, 130.50, 125.41, 118.79, 49.91, 31.31, 22.25.

Characterisation matches previous reports.<sup>1</sup>

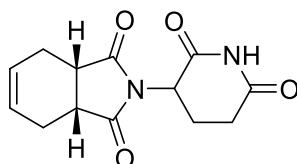
### 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisindoline-1,3-dione, 17



Compound 16 was prepared according to **GP1** using 2000 mg of tert-butyl N-(2,6-dioxo-3-piperidyl)carbamate to yield 1673 mg (69%) of 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisindoline-1,3-dione.

Characterisation matches previous reports.<sup>2</sup>

### 2-(2,6-dioxopiperidin-3-yl)-3a,4,7,7a-tetrahydro-1H-isindole-1,3(2H)-dione, 18



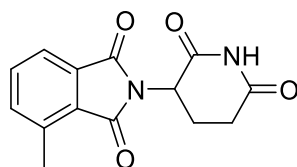
Compound 18 was prepared according to **GP1** using 2000 mg of tert-butyl N-(2,6-dioxo-3-piperidyl)carbamate to yield 1678 mg (73%) of 2-(2,6-dioxopiperidin-3-yl)-3a,4,7,7a-tetrahydro-1H-isindole-1,3(2H)-dione.

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.98 (s, 1H), 5.83 (dt, *J* = 3.4, 1.5 Hz, 2H), 4.86 (dd, *J* = 12.7, 5.5 Hz, 1H), 3.22 – 3.13 (m, 2H), 2.77 (ddd, *J* = 17.1, 13.9, 5.5 Hz, 1H), 2.50 (dd, *J* = 4.5, 2.6 Hz, 1H), 2.32 (dtd, *J* = 15.3, 8.0, 3.7 Hz, 3H), 2.26 – 2.01 (m, 2H), 1.75 (dtd, *J* = 13.2, 5.5, 2.4 Hz, 1H).

**<sup>13</sup>C NMR** (101 MHz, DMSO-*d*<sub>6</sub>) δ 179.61, 173.08, 169.29, 127.76, 127.63, 49.60, 38.85, 38.67, 31.04, 23.45, 23.32, 21.70.

**HRMS:** calc. [M-H]<sup>-</sup> for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub> = 261.0954; found = 261.0947 [M-H]<sup>-</sup>.

### 2-(2,6-dioxopiperidin-3-yl)-4-methylisoindoline-1,3-dione, 19



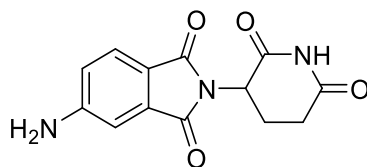
Compound 19 was prepared according to **GP1** using 200 mg of tert-butyl N-(2,6-dioxo-3-piperidinyl)carbamate to yield 174 mg (72%) of 2-(2,6-dioxopiperidin-3-yl)-4-methylisoindoline-1,3-dione.

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.08 (s, 1H), 7.71 (d, *J* = 6.3 Hz, 2H), 7.64 (dd, *J* = 5.9, 2.9 Hz, 1H), 5.10 (dd, *J* = 13.0, 5.4 Hz, 1H), 2.87 (ddd, *J* = 17.2, 13.9, 5.3 Hz, 1H), 2.60 (s, 3H), 2.58 – 2.44 (m, 2H), 2.02 (ddt, *J* = 10.6, 5.6, 3.3 Hz, 1H).

**<sup>13</sup>C NMR** (101 MHz, DMSO-*d*<sub>6</sub>) δ 173.20, 170.32, 168.25, 167.47, 138.03, 137.33, 134.79, 132.06, 128.33, 121.47, 49.22, 31.39, 22.44, 17.48.

**HRMS:** calc. [M-H]<sup>-</sup> for C<sub>14</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub> = 271.0797; found = 271.1587 [M-H]<sup>-</sup>.

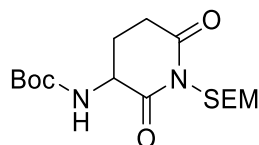
### 5-amino-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione, 20



Following a literature procedure, a catalytic amount of Pd/C (50 mg, 10%) was added to a solution of 16 (500 mg/1.65 mmol) in 30 mL of acetone. The mixture was stirred at ambient temperature for 20 hours under an atmosphere of H<sub>2</sub> (g). The mixture was then filtered through a pad of celite and the celite was washed with copious amounts of acetone. The solvent was evaporated *in vacuo* to yield 451 mg (66%) of 5-amino-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione.

Characterisation matches previous reports.<sup>1</sup>

**tert-butyl (2,6-dioxo-1-((2-(trimethylsilyl)ethoxy)methyl)piperidin-3-yl)carbamate**



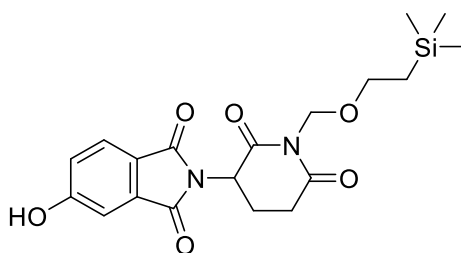
To a solution of tert-butyl N-(2,6-dioxo-3-piperidyl)carbamate (69 mg, 0.3 mmol) in DMF (1 mL) was added NaH (60%, 12.09 mg, 0.3 mmol) at 0 °C, then the reaction was stirred for 15 min at the same temperature. Then 2-(Trimethylsilyl)ethoxymethyl chloride (60.48 mg, 0.36 mmol) was added and the reaction mixture was stirred at room temperature for an additional 1 h. Reaction mixture was poured into an aqueous solution of HCl (1N, 30 mL) and product was extracted with AcOEt (30 mL), organic layer was washed with aqueous HCl (1N, 3x20 mL), water (20 mL), dried Na<sub>2</sub>SO<sub>4</sub> and evaporated under vacuum. Crude product was purified by flash chromatography (SiO<sub>2</sub>-12g, Hex-AcOEt, 100% to 4:6 in 15 min), to give 70 mg of product as a white solid (65% yield).

**<sup>1</sup>H NMR** (400 MHz, Chloroform-d) δ 5.42 (s, 1H), 5.23 (d, J = 9.5 Hz, 1H), 5.14 (d, J = 9.5 Hz, 1H), 4.37 – 4.18 (m, 1H), 3.66 – 3.48 (m, 2H), 2.88 (dd, J = 20.5, 2.4 Hz, 1H), 2.73 (ddd, J = 18.4, 13.6, 5.5 Hz, 1H), 2.56 – 2.38 (m, 1H), 1.82 (qd, J = 13.3, 4.8 Hz, 1H), 1.45 (s, 9H), 0.98 – 0.82 (m, 2H), -0.02 (s, 9H).

**<sup>13</sup>C NMR** (101 MHz, cdcl<sub>3</sub>) δ 172.04, 171.31, 155.62, 80.52, 69.29, 67.54, 52.59, 31.89, 28.40, 24.72, 18.20, -1.32.

**HRMS:** Calcd. for C<sub>16</sub>H<sub>30</sub>N<sub>2</sub>O<sub>5</sub>SiNa, 381.1821. Found 381.1870.

**2-(2,6-dioxo-1-((2-(trimethylsilyl)ethoxy)methyl)piperidin-3-yl)-5-hydroxyisoindoline-1,3-dione, 21**



Compound 21 was prepared according to **GPI** followed by concentration *in vacuo* and purification by preparative-TLC (1:1 Hexane/Ethyl Acetate) using 37 mg of tert-butyl (2,6-dioxo-1-((2-(trimethylsilyl)ethoxy)methyl)piperidin-3-yl)carbamate to yield 23 mg (55%) of 2-



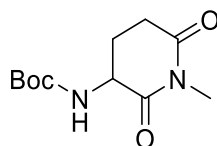
(2,6-dioxo-1-((2-(trimethylsilyl)ethoxy)methyl)piperidin-3-yl)-5-hydroxyisoindoline-1,3-dione.

**<sup>1</sup>H NMR** (500 MHz, Chloroform-d)  $\delta$  7.83 (bs, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.13 (d, J = 2.2 Hz, 1H), 7.05 (dd, J = 8.2, 2.3 Hz, 1H), 5.36 – 5.21 (m, 2H), 5.05 – 4.93 (m, 1H), 3.75 – 3.54 (m, 2H), 3.08 – 2.95 (m, 1H), 2.91 – 2.66 (m, 2H), 2.17 – 2.09 (m, 1H), 0.96 (dd, J = 9.1, 7.7 Hz, 2H), 0.00 (s, 9H).

**<sup>13</sup>C NMR** (126 MHz, dmsO)  $\delta$  172.10, 170.40, 167.42, 167.30, 164.04, 134.50, 126.08, 121.81, 121.26, 110.41, 68.73, 66.39, 49.88, 31.64, 21.54, 17.89, -0.90.

**HRMS** (ESI); m/z [M+Na]<sup>+</sup>: Calcd. for C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O<sub>6</sub>SiNa, 427.1301. Found 427.1344.

#### **tert-butyl (1-methyl-2,6-dioxopiperidin-3-yl)carbamate**



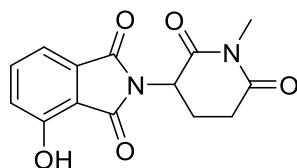
To a solution of tert-butyl N-(2,6-dioxo-3-piperidyl)carbamate (371 mg, 1.63 mmol) in DMF (5 mL) was added NaH (60%, 65.01 mg, 1.63 mmol) at 0 °C, then the reaction was stirred for 15 min at the same temperature. Then the reaction mixture was stirred at room temperature for an additional 20 min. Then CH<sub>3</sub>I (0.12 ml, 1.95 mmol) was added into the reaction mixture at room temperature, and stirred for 2 h at the same temperature. Reaction mixture was poured into an aqueous solution of HCl (1N, 30 mL) and product was extracted with AcOEt (30 mL), organic layer was washed with aqueous HCl (1N, 3x20 mL), water (20 mL), dried Na<sub>2</sub>SO<sub>4</sub> and evaporated under vacuum. Crude product was purified by flash chromatography (SiO<sub>2</sub>-25g, Hex-AcOEt, 100% to 4:6 in 15 min), to give 260 mg of product (66%) as a white solid.

**<sup>1</sup>H NMR** (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  7.19 (d, J = 8.7 Hz, 1H), 4.39 – 4.21 (m, 1H), 2.97 (s, 3H), 2.85 – 2.73 (m, 1H), 2.71 – 2.53 (m, 1H), 2.09 – 1.75 (m, 2H), 1.40 (s, 9H).

**<sup>13</sup>C NMR** (151 MHz, dmsO)  $\delta$  172.28, 172.01, 155.43, 78.18, 50.93, 31.14, 28.18, 26.46, 23.48.

**HRMS** (ESI); m/z [M+H]<sup>+</sup>: Calcd. for C<sub>11</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>Na, 265.1164. Found 265.1165.

#### 4-hydroxy-2-(1-methyl-2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione, 22



Compound 22 was prepared according to **GP1** using 143 mg of tert-butyl (1-methyl-2,6-dioxopiperidin-3-yl)carbamate to yield 147 mg (88%) of 4-hydroxy-2-(1-methyl-2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione.

**<sup>1</sup>H NMR** (400 MHz, DMSO-d<sub>6</sub>) δ 11.17 (s, 1H), 7.66 (dd, J = 8.4, 7.2 Hz, 1H), 7.32 (d, J = 7.2 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 5.14 (dd, J = 13.0, 5.4 Hz, 1H), 3.01 (s, 3H), 3.00 – 2.87 (m, 1H), 2.82 – 2.69 (m, 1H), 2.61 – 2.49 (m, 1H), 2.09 – 1.96 (m, 1H).

**<sup>13</sup>C NMR** (151 MHz, DMSO-d<sub>6</sub>) δ 171.79, 169.76, 167.00, 165.79, 155.49, 136.42, 133.13, 123.58, 114.34, 114.30, 49.20, 31.11, 26.60, 21.23.

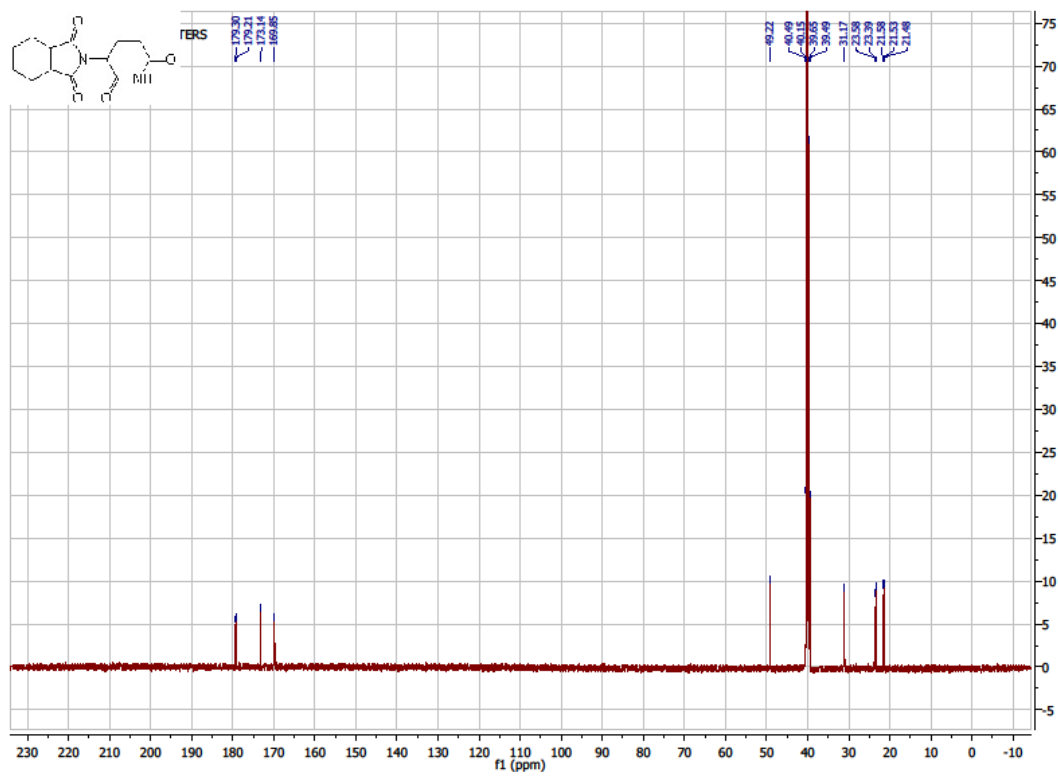
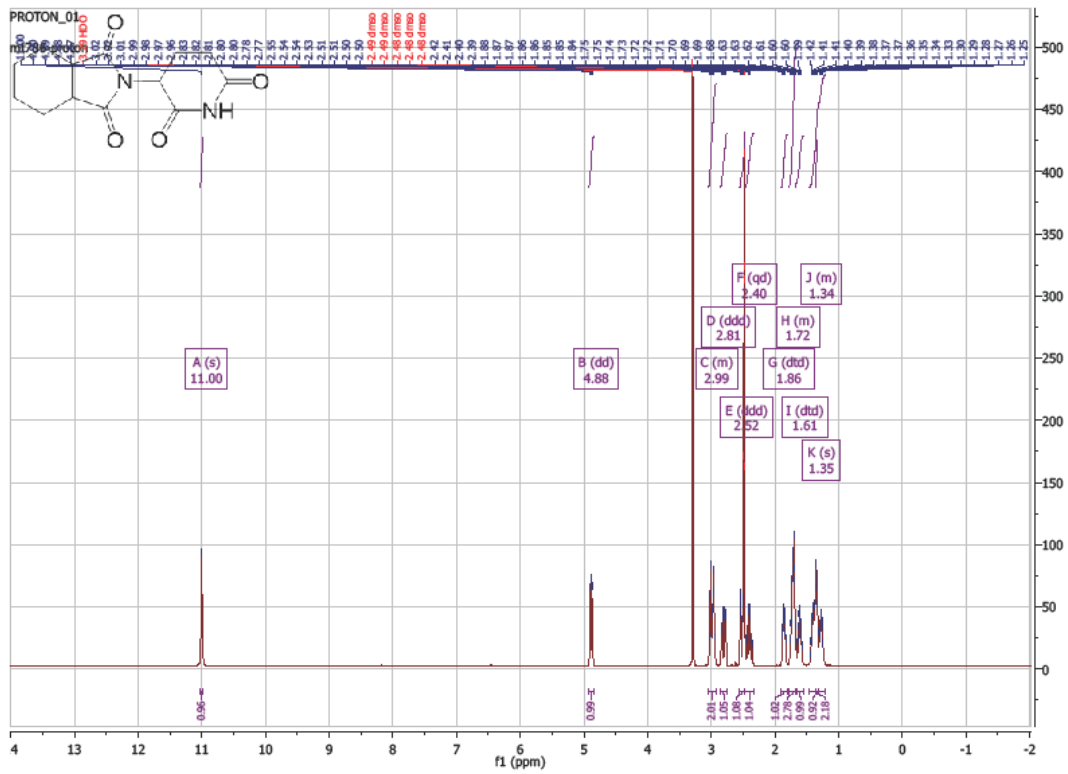
**HRMS** (ESI); m/z [M+H]<sup>+</sup>: Calcd. for C<sub>14</sub>H<sub>13</sub>N<sub>2</sub>O<sub>5</sub>, 289.0824. Found 289.0789.

#### References

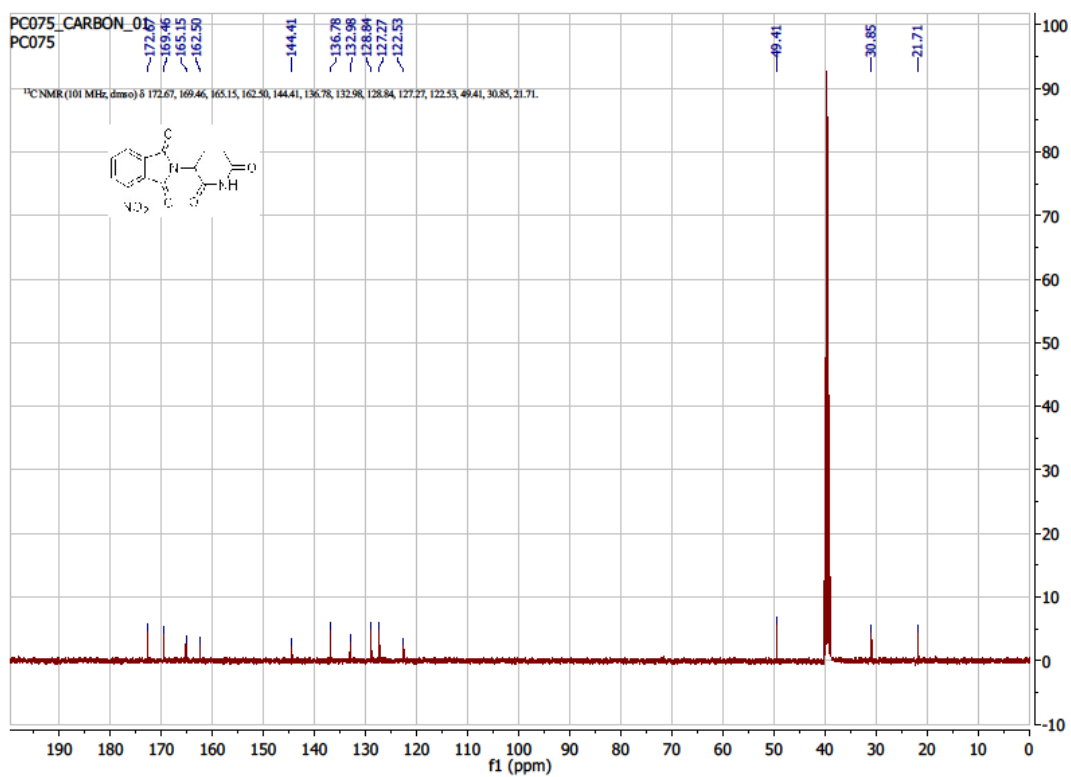
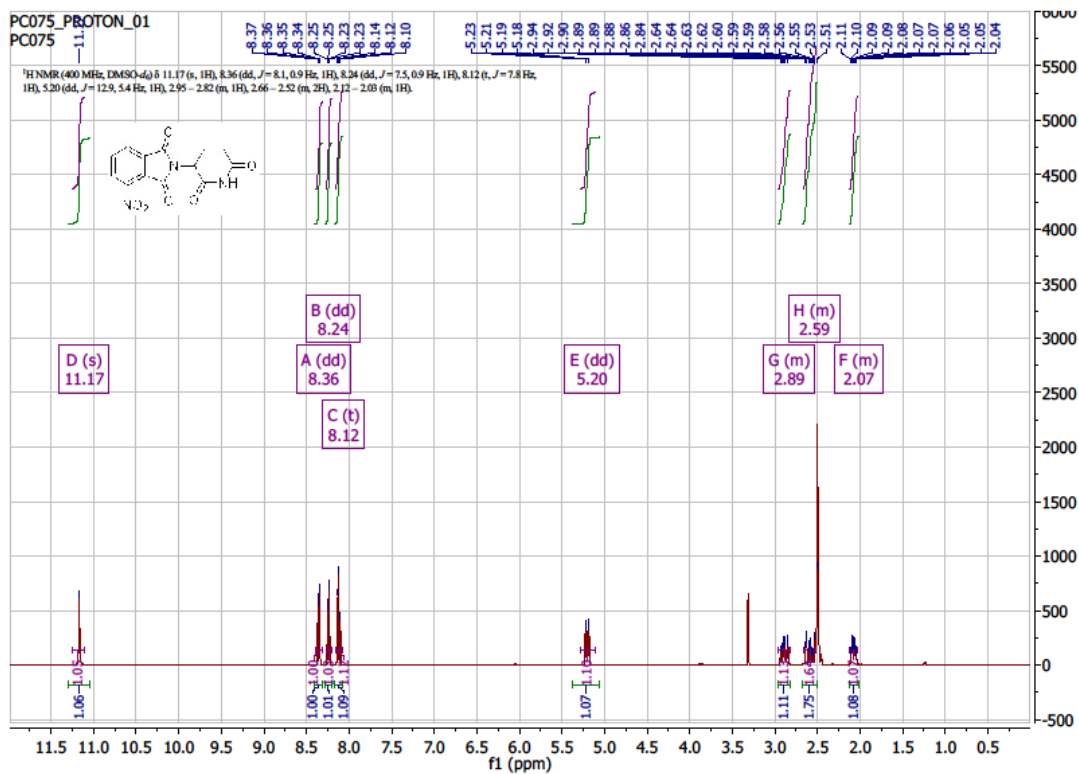
1. S. M. Capitosti, T. P. Hansen and M. L. Brown, *Org. Lett.*, 2003, **5**, 2865-2867.
2. J. Lu, Y. Qian, M. Altieri, H. Dong, J. Wang, K. Raina, J. Hines, J. D. Winkler, A. P. Crew, K. Coleman and C. M. Crews, *Chem Biol*, 2015, **22**, 755-763.

# Spectra

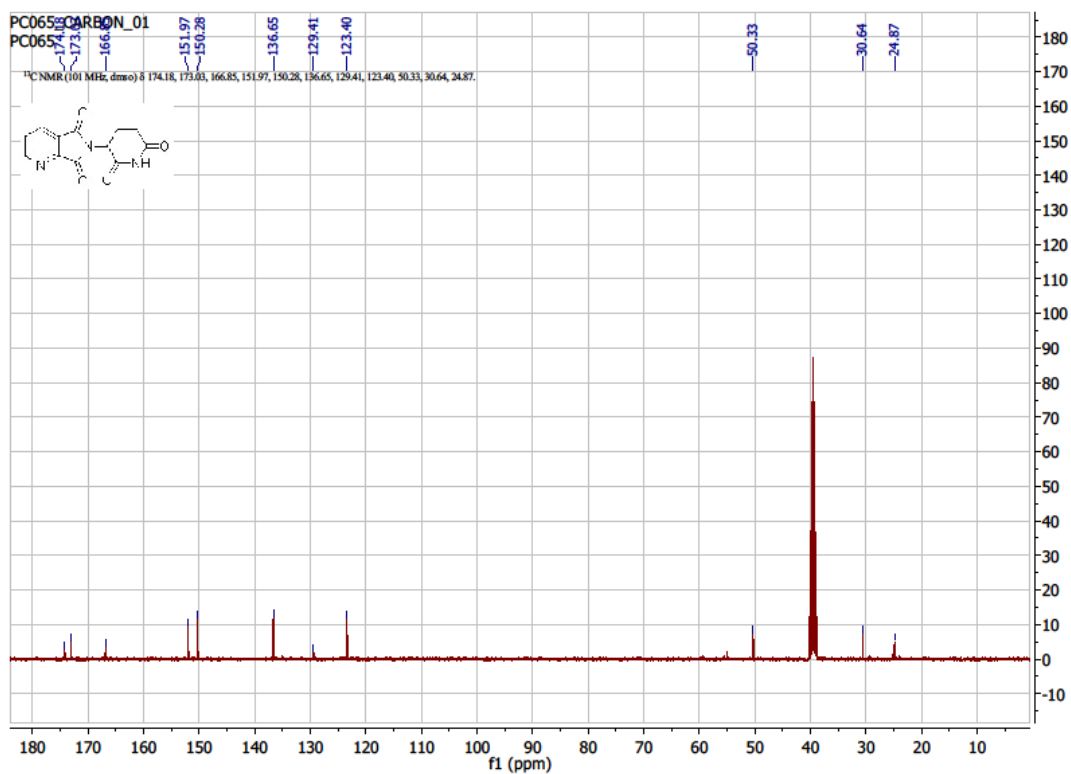
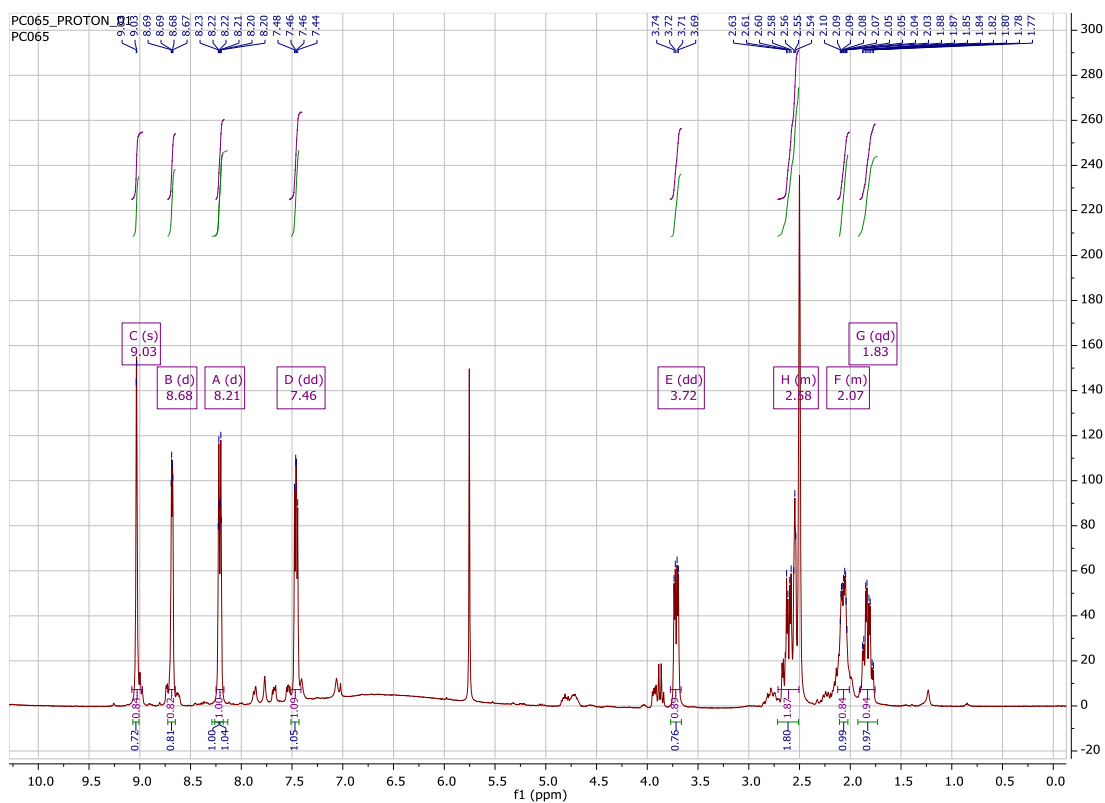
## Compound 1



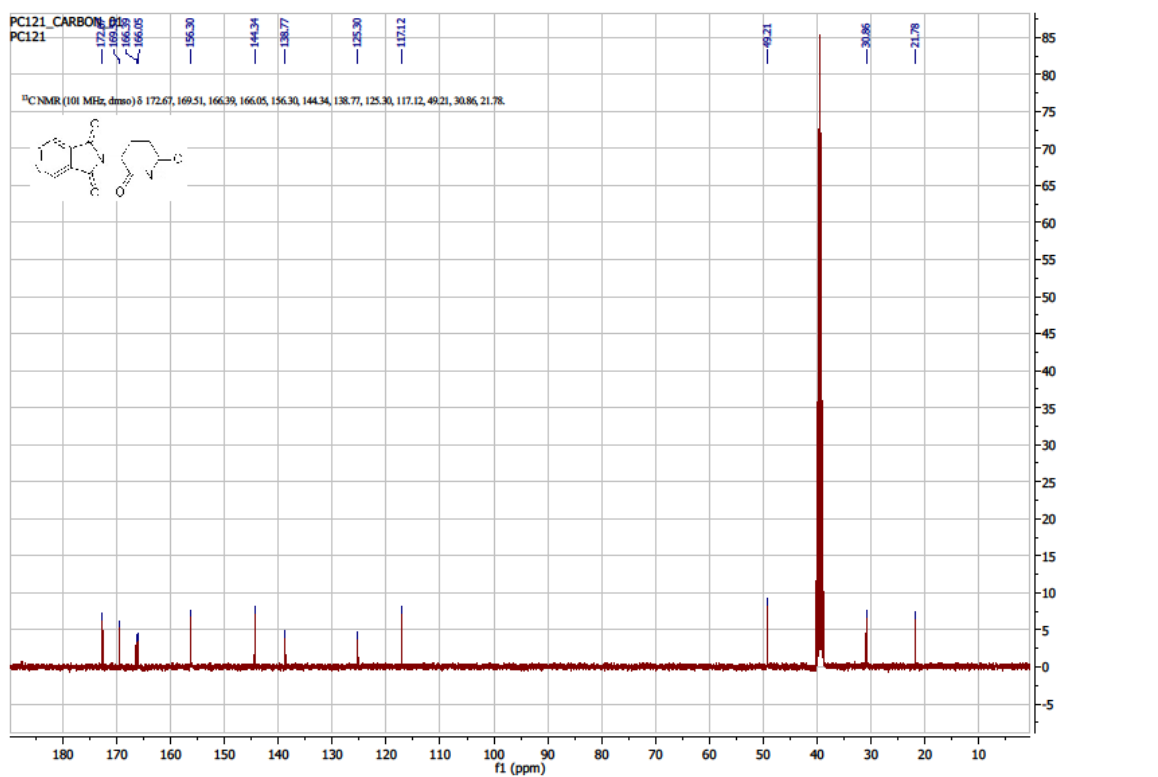
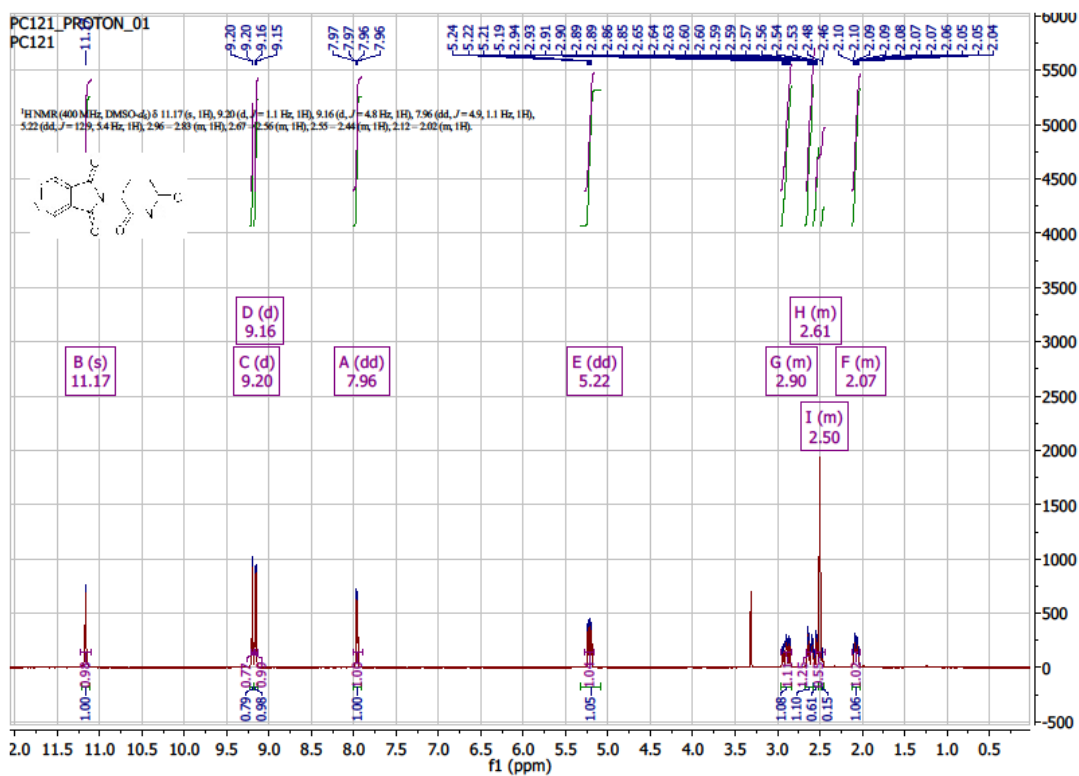
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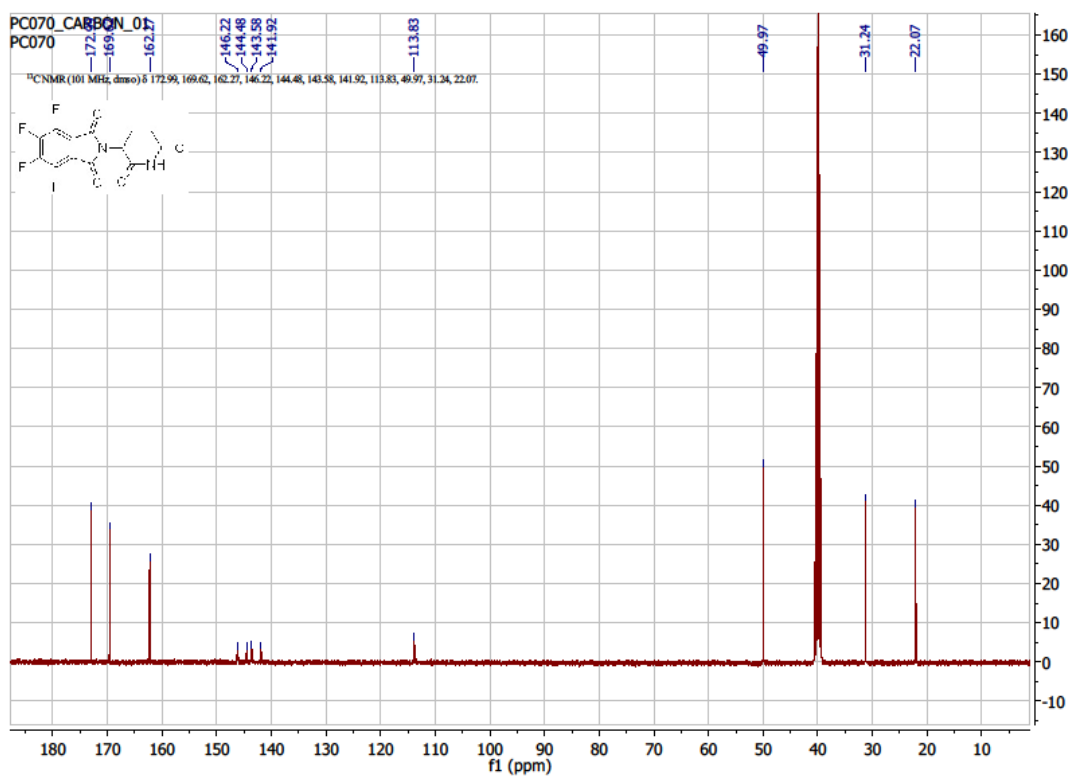
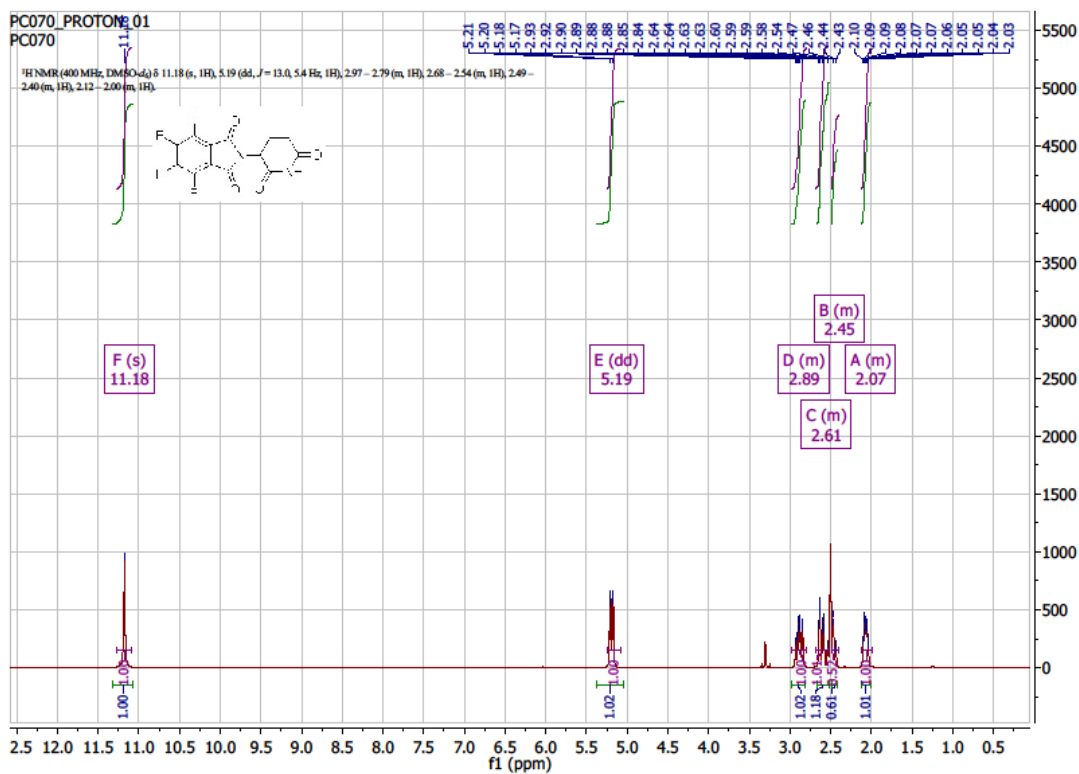
# Compound 3



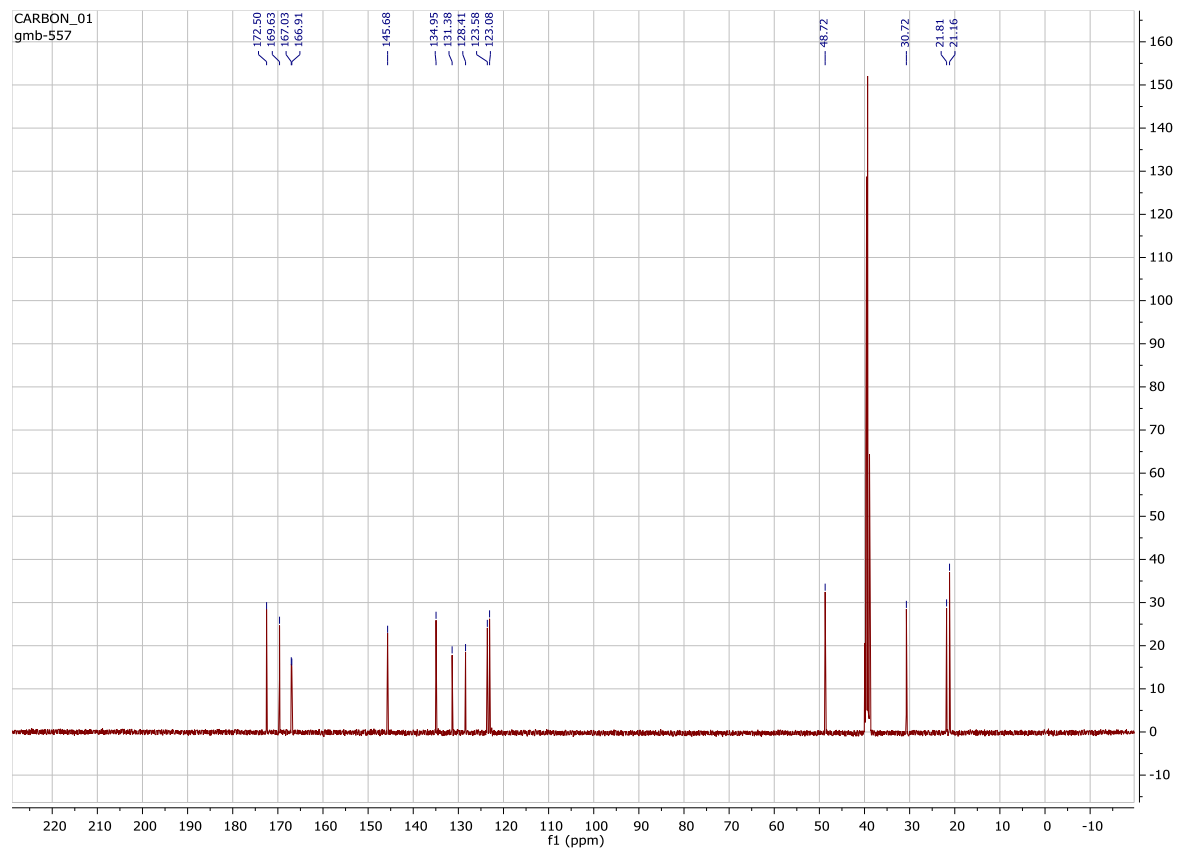
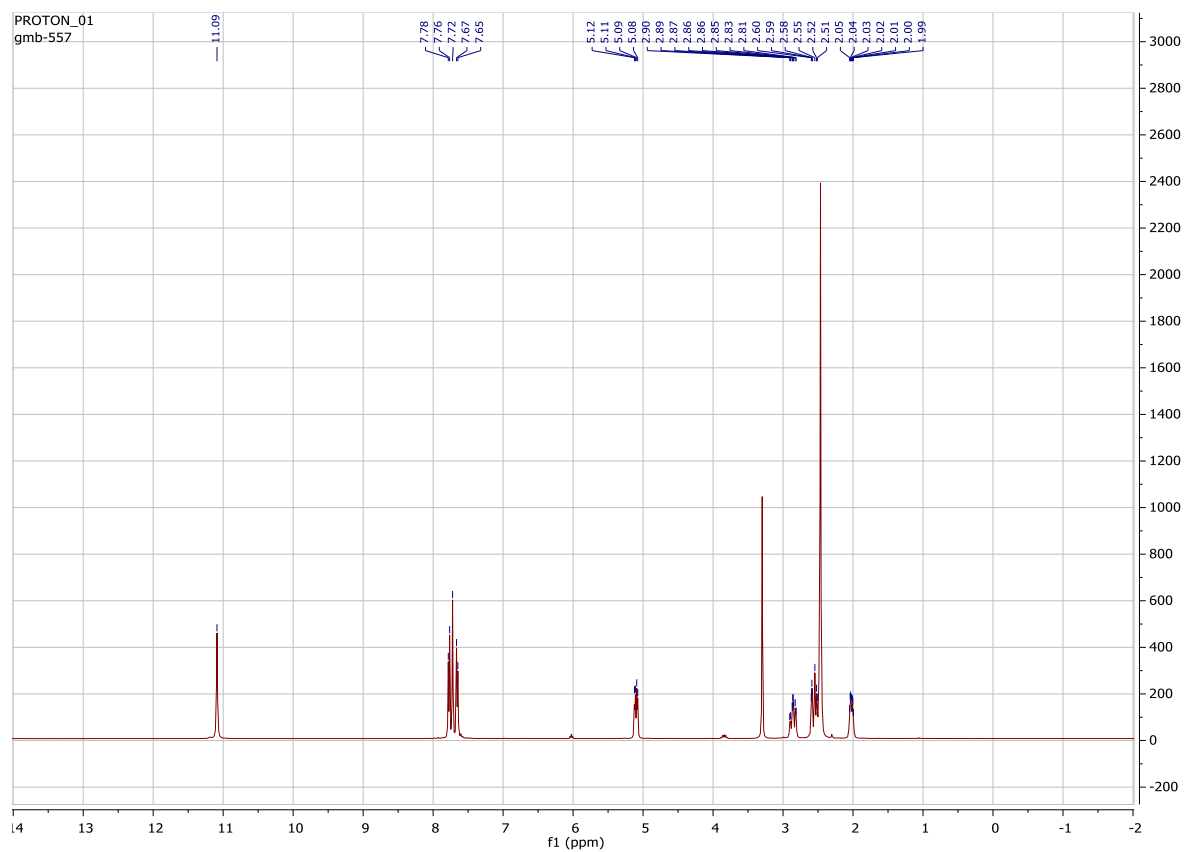
# Compound 4



# Compound 5

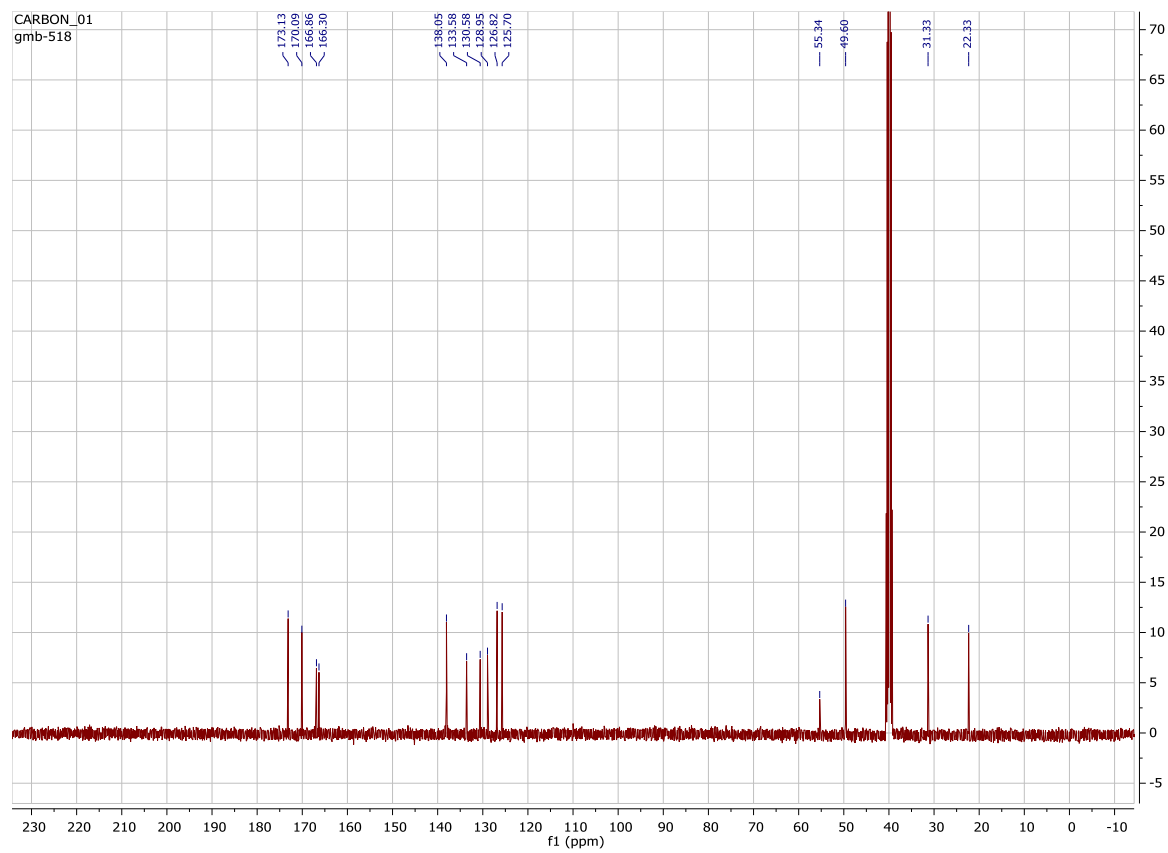
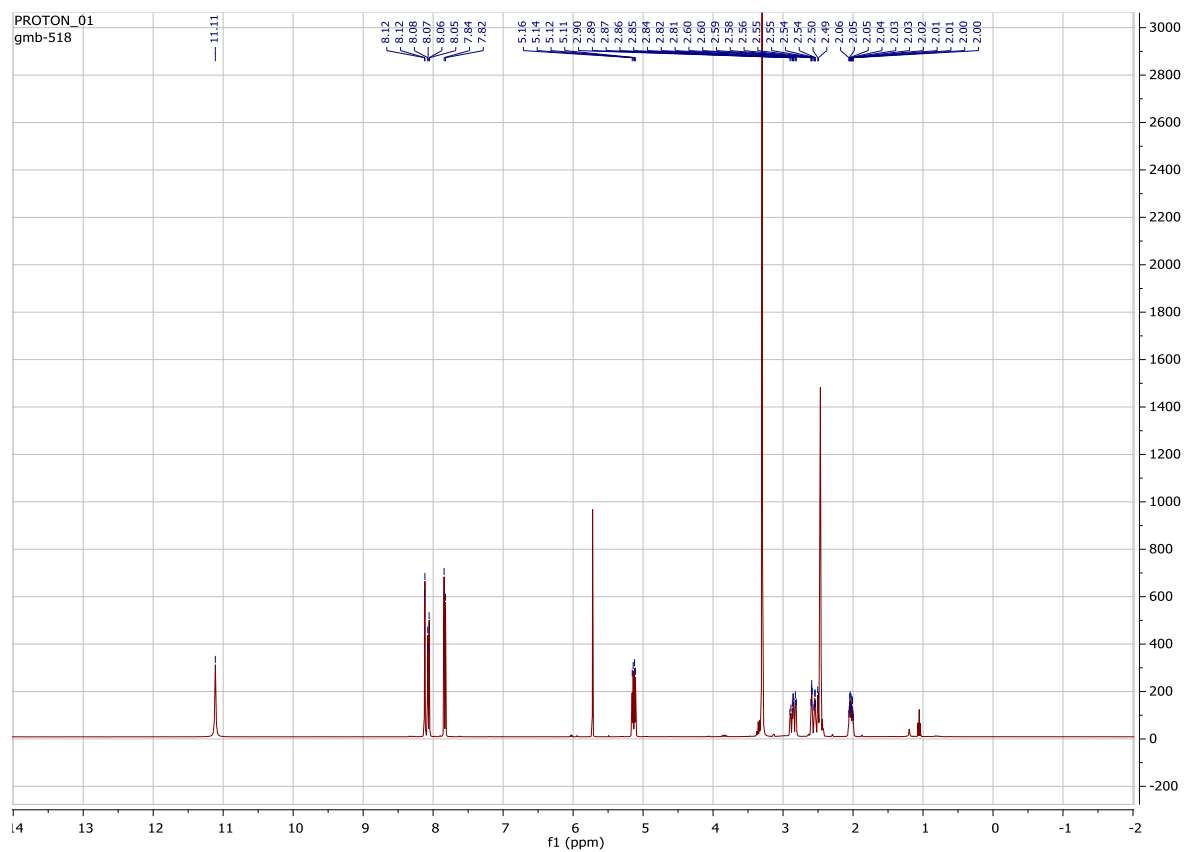


# Compound 6

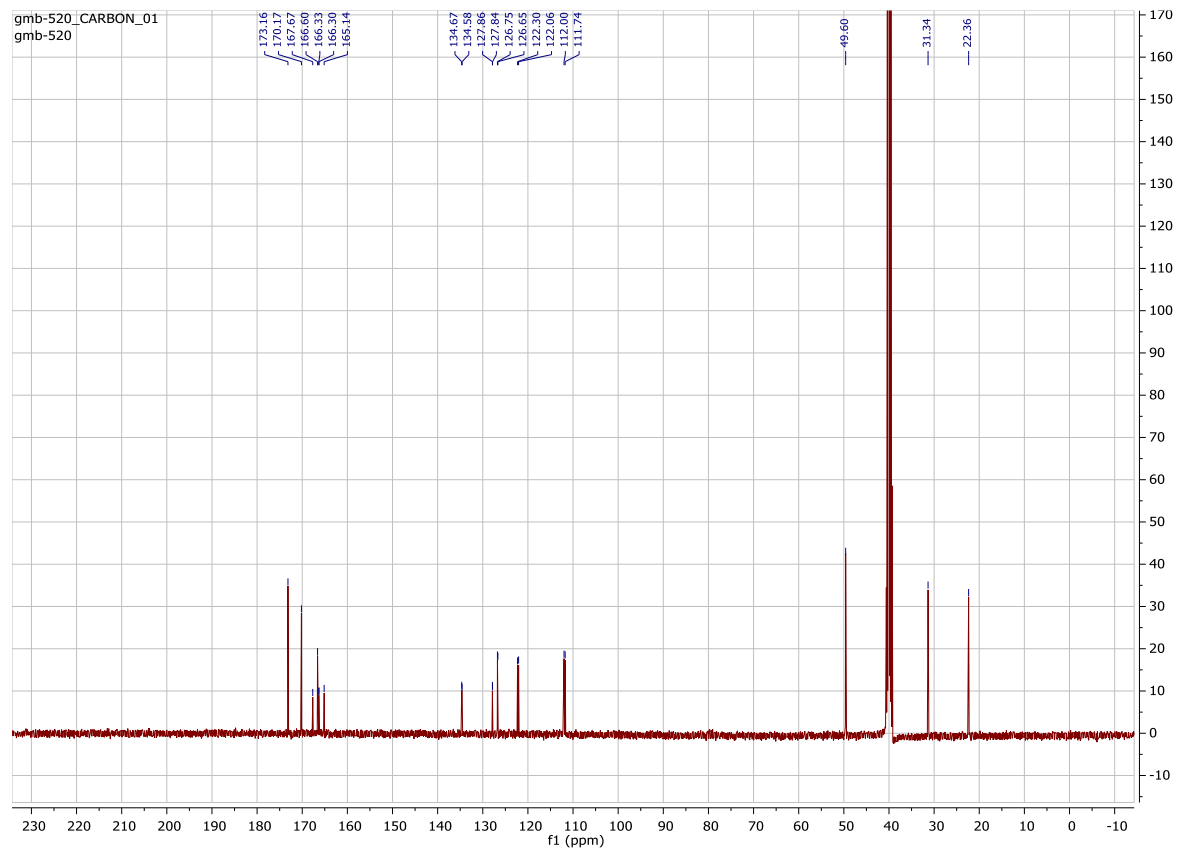
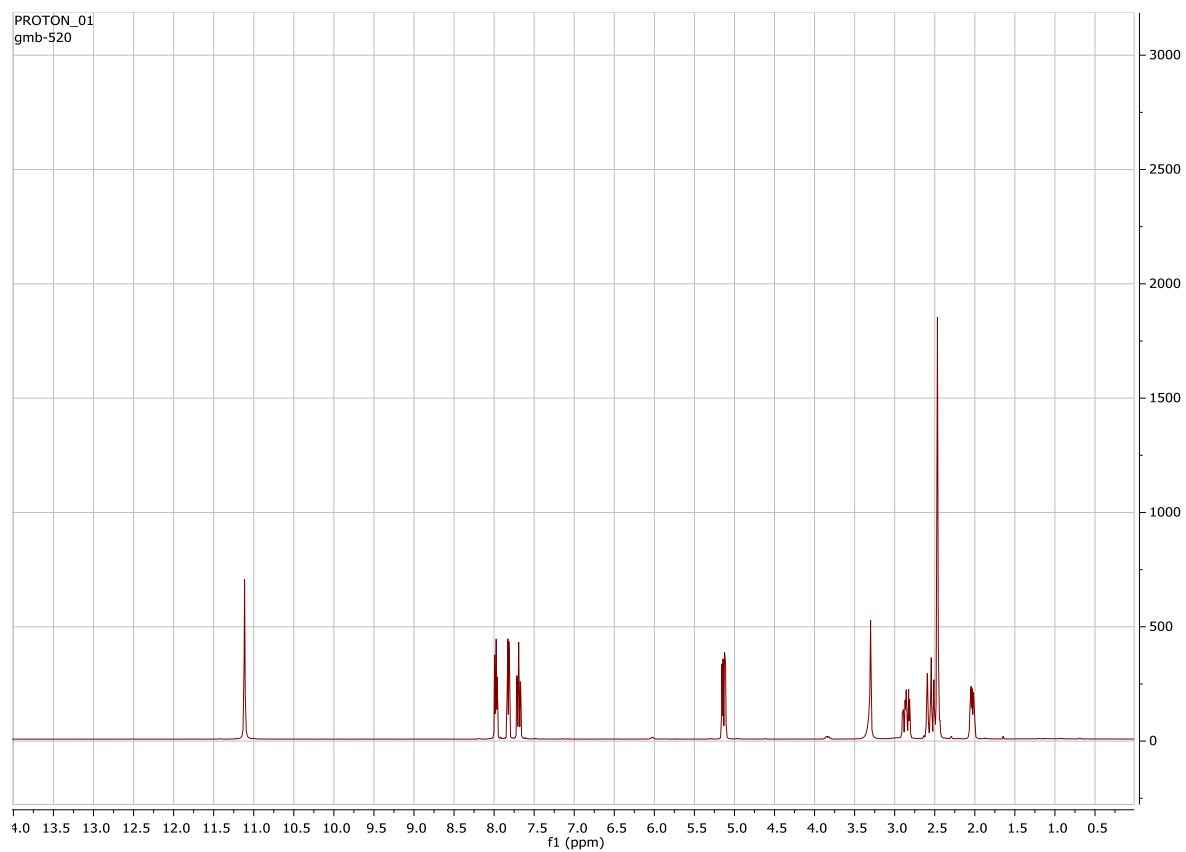




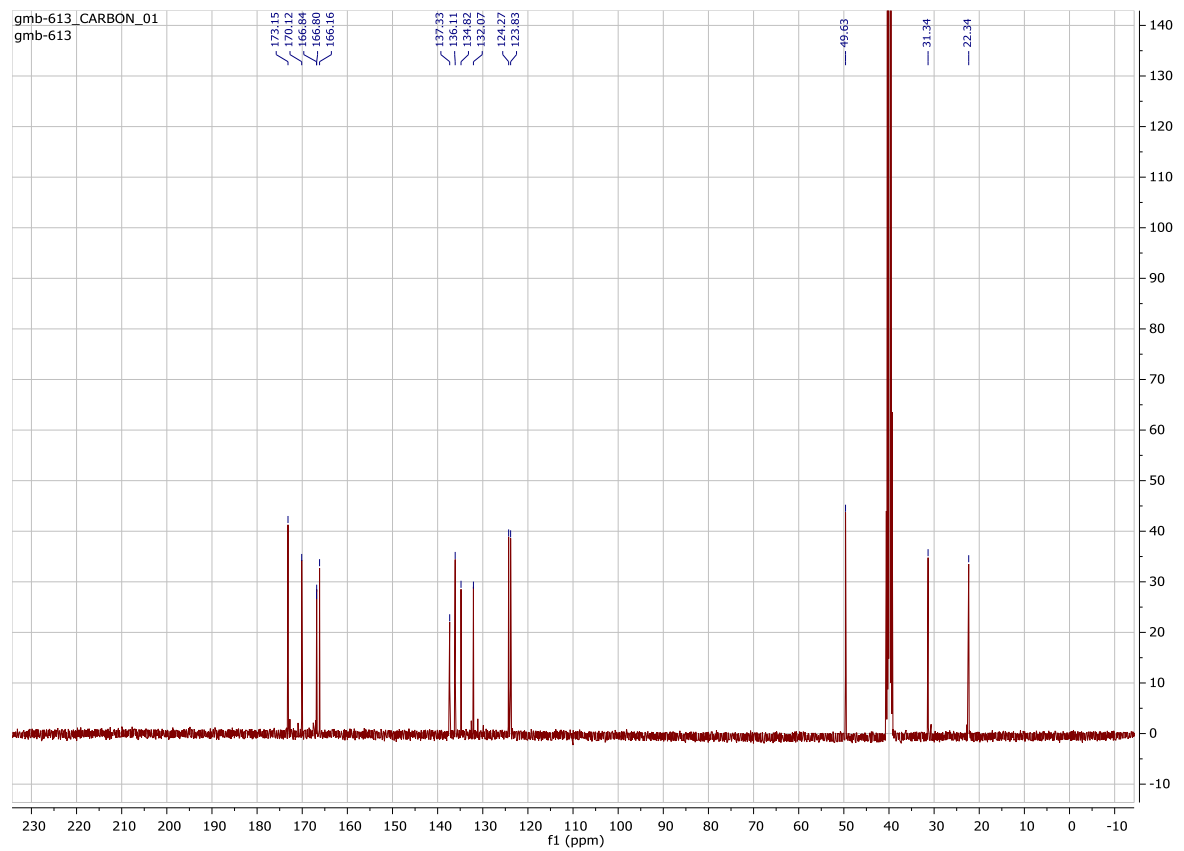
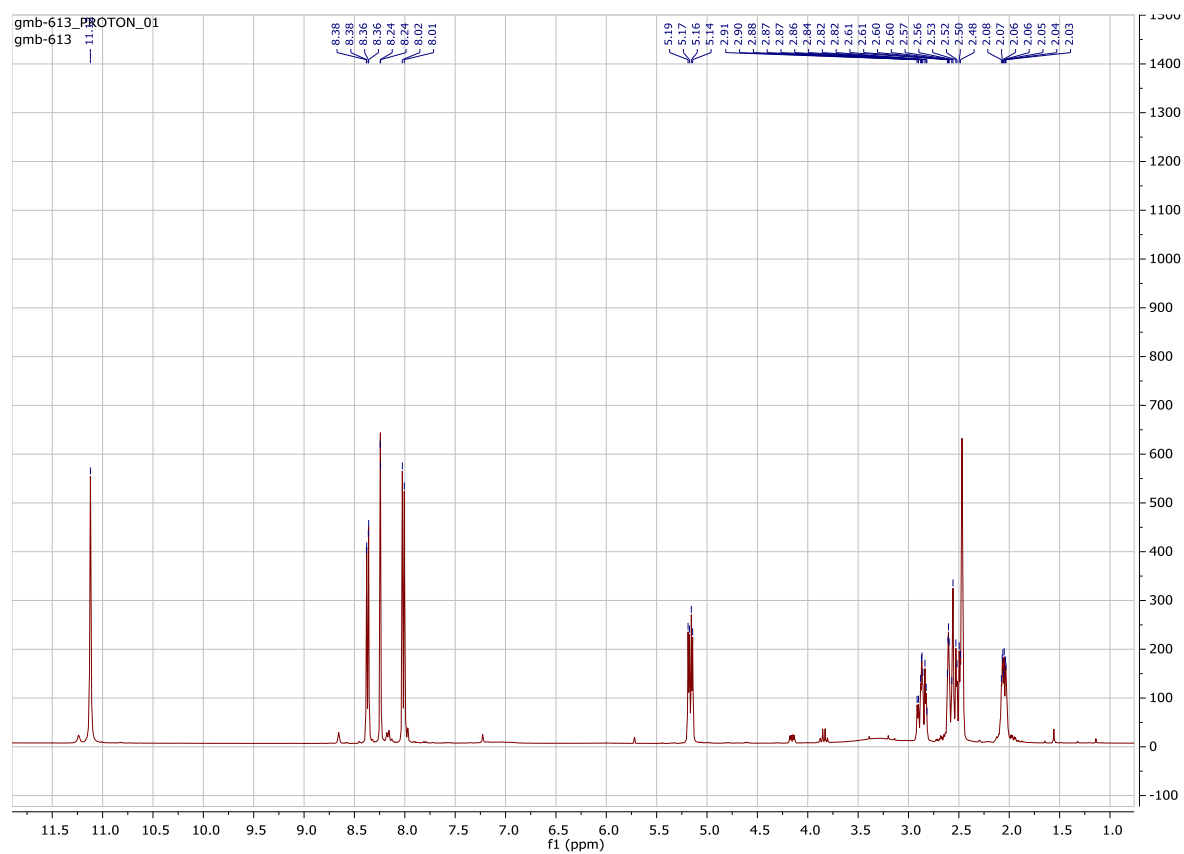
# Compound 7



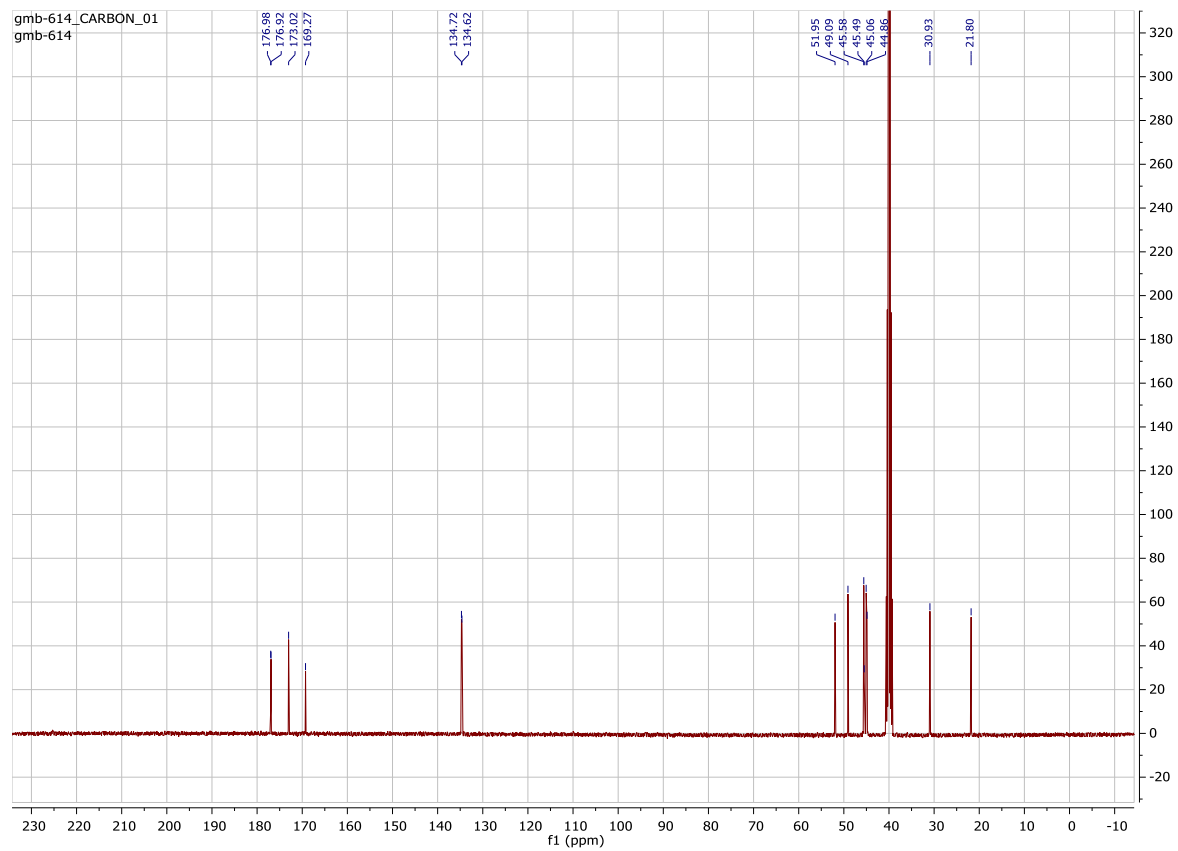
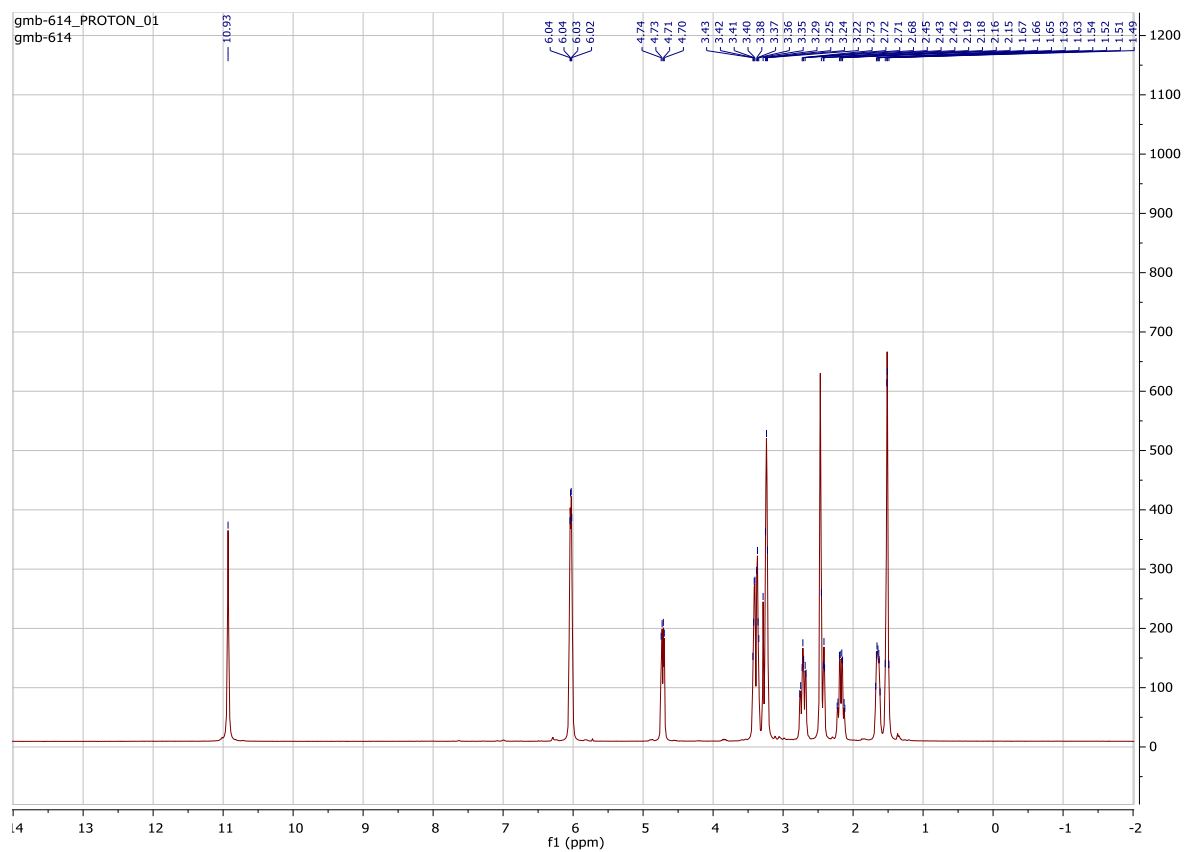
# Compound 8



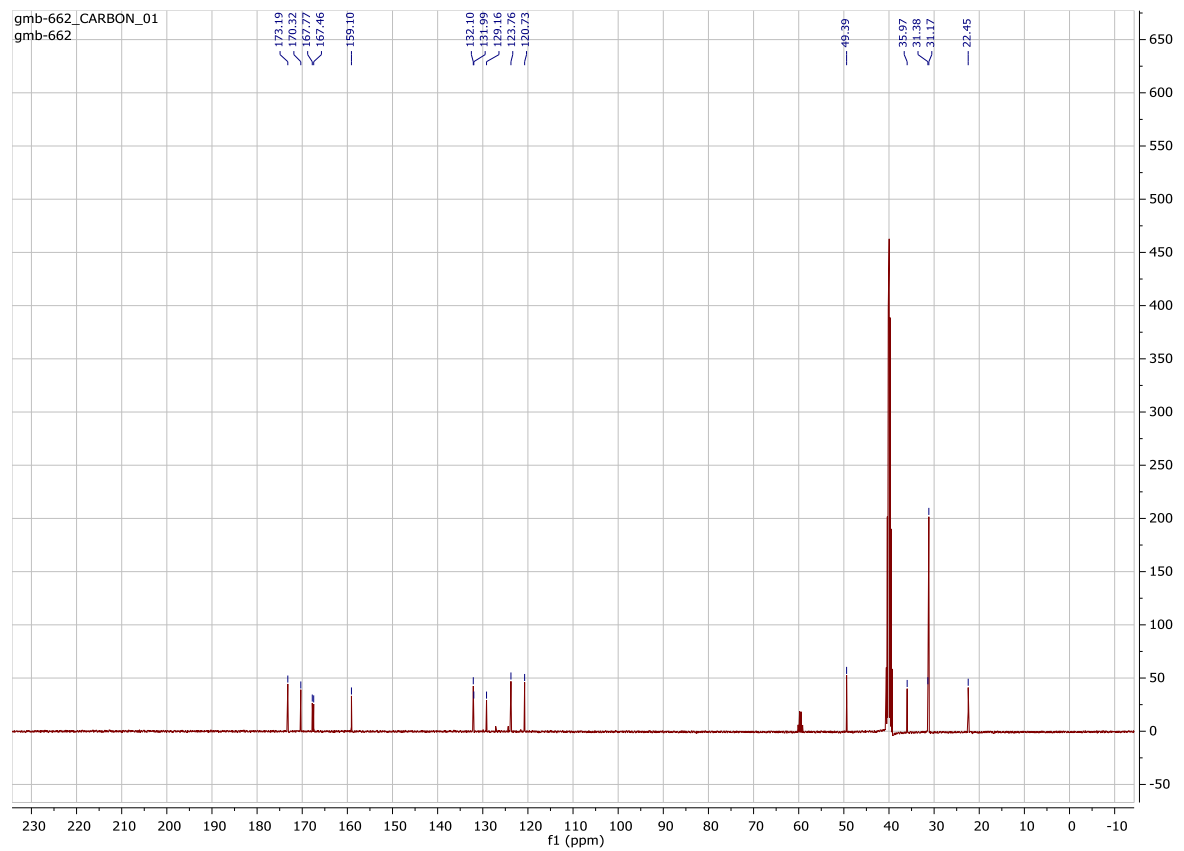
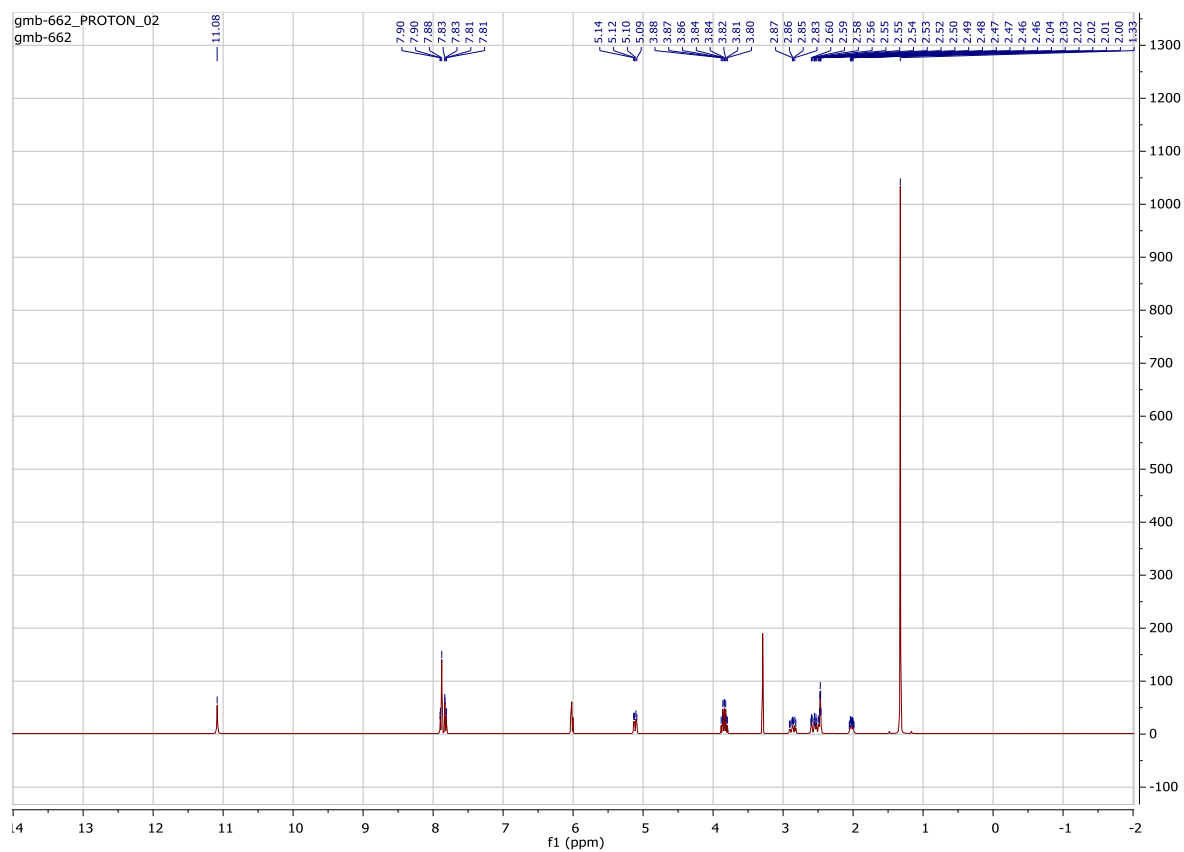
# Compound 9



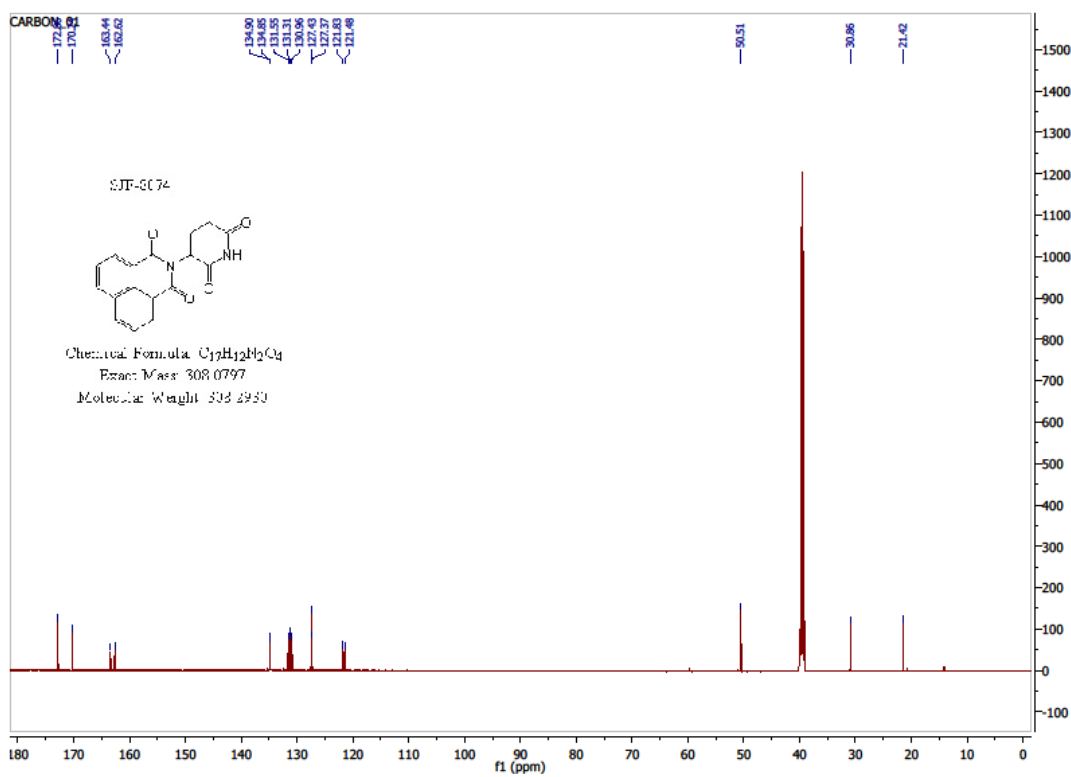
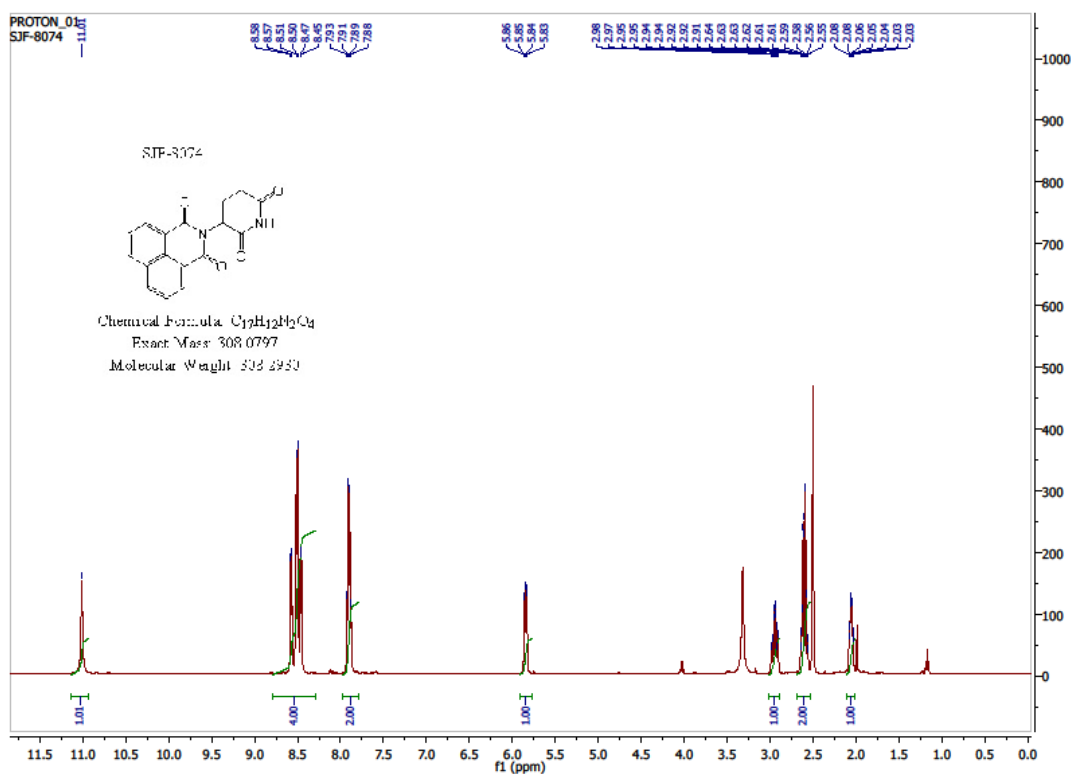
# Compound 10



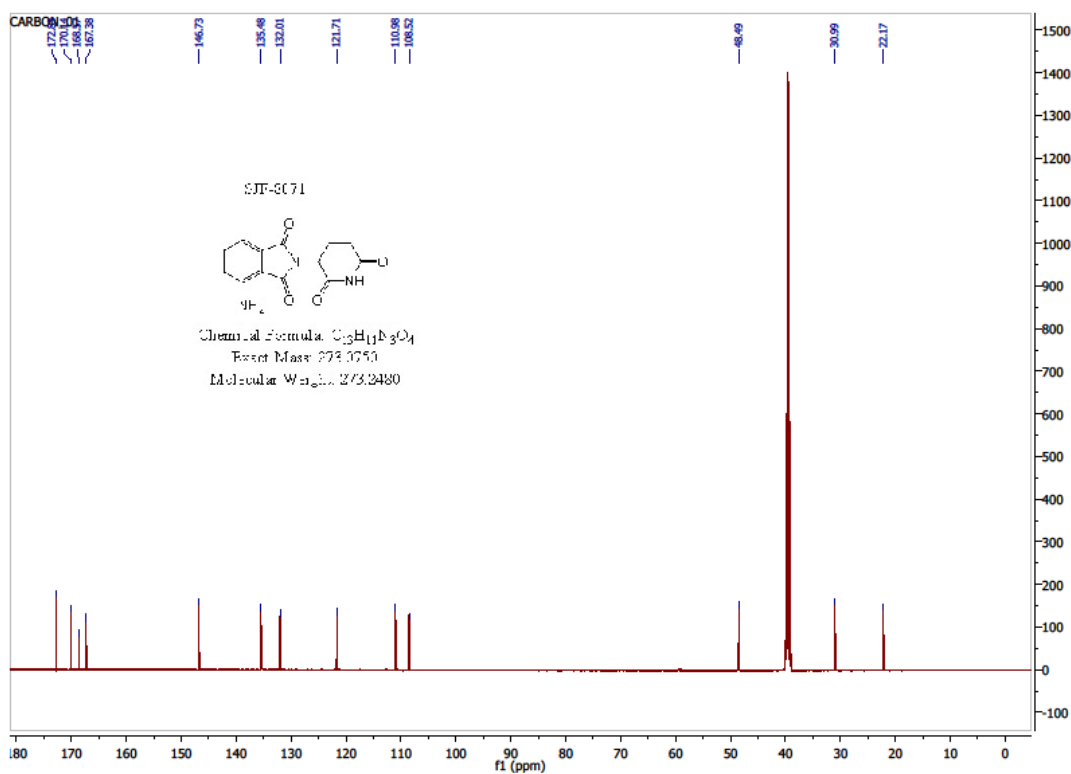
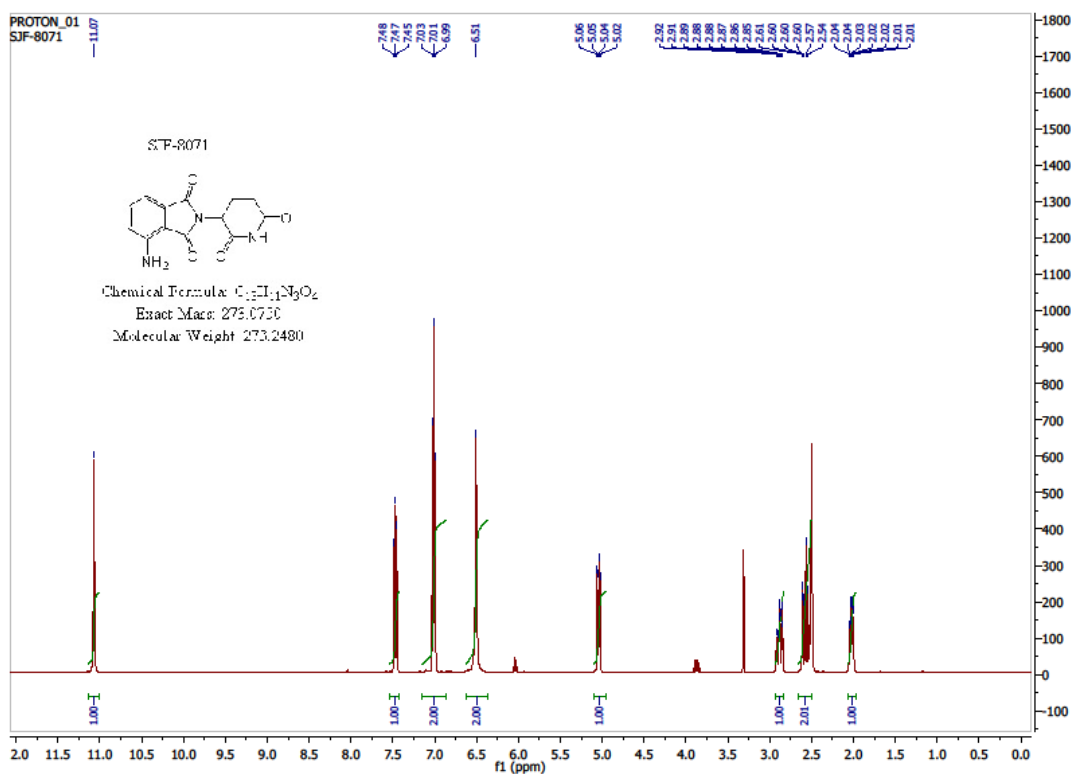
# Compound 11



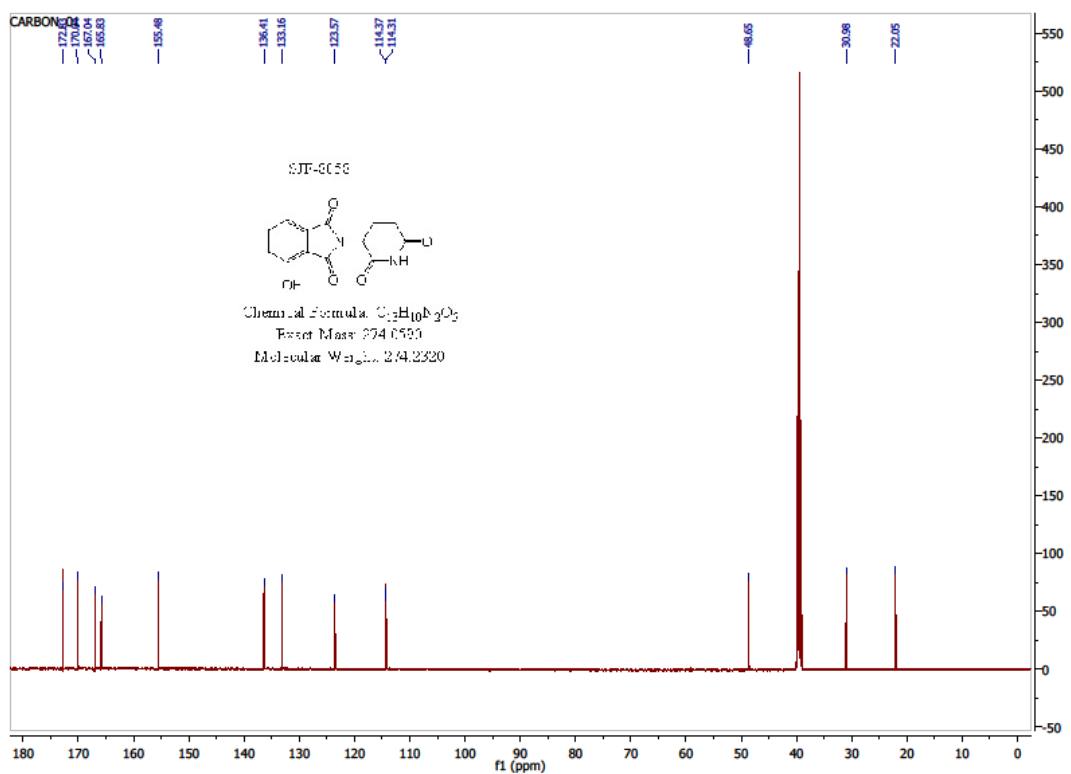
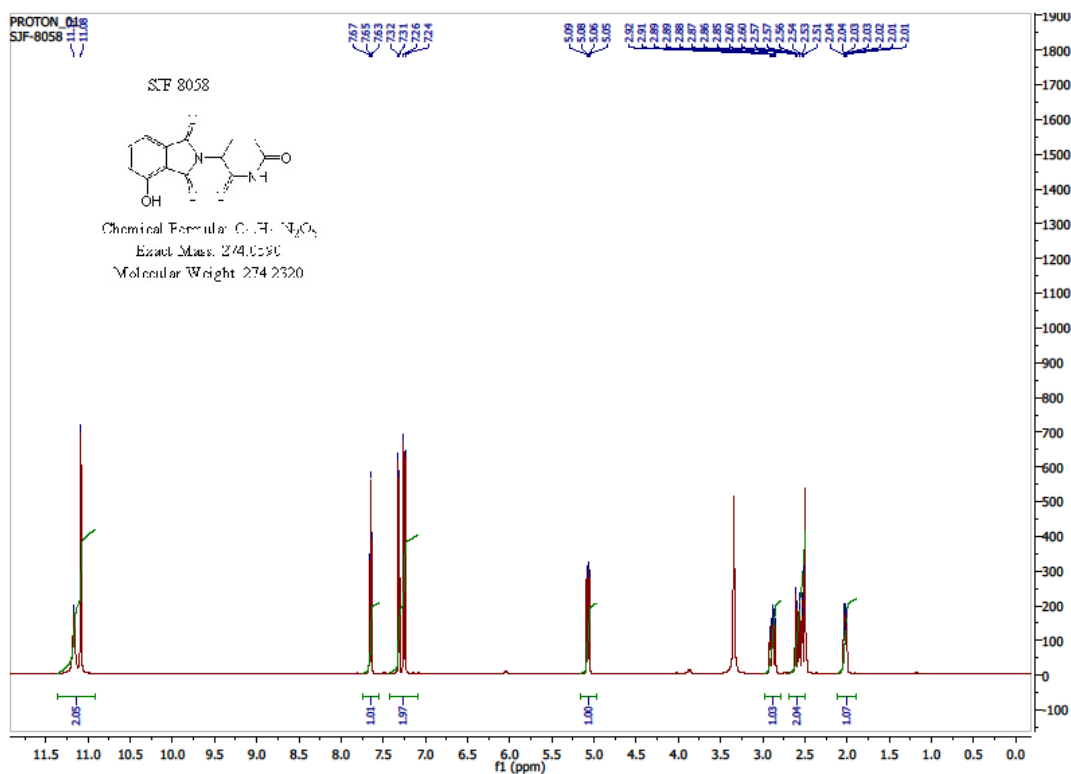
# Compound 12



# Compound 13

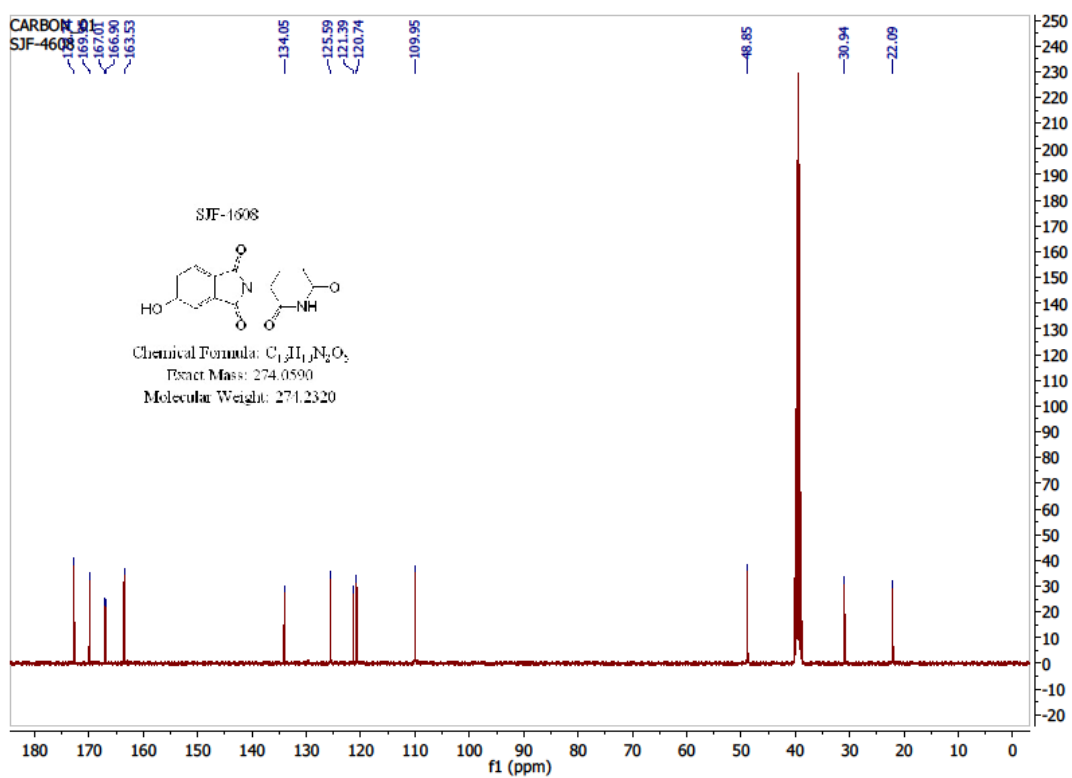
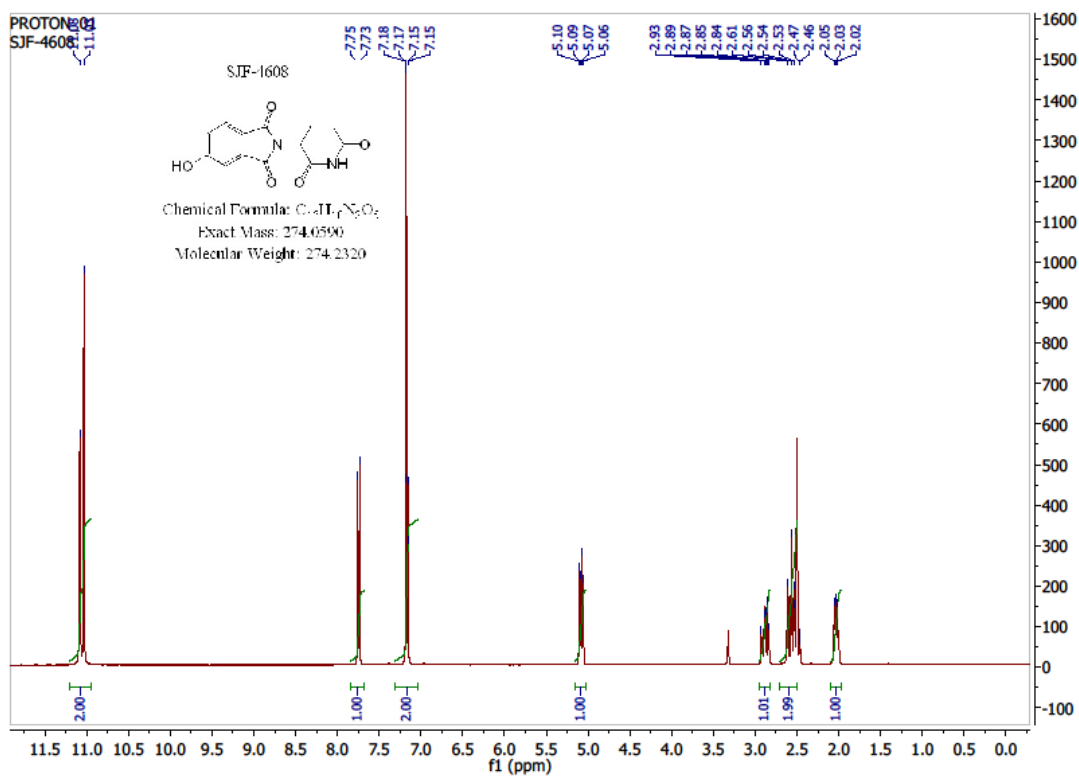


# Compound 14

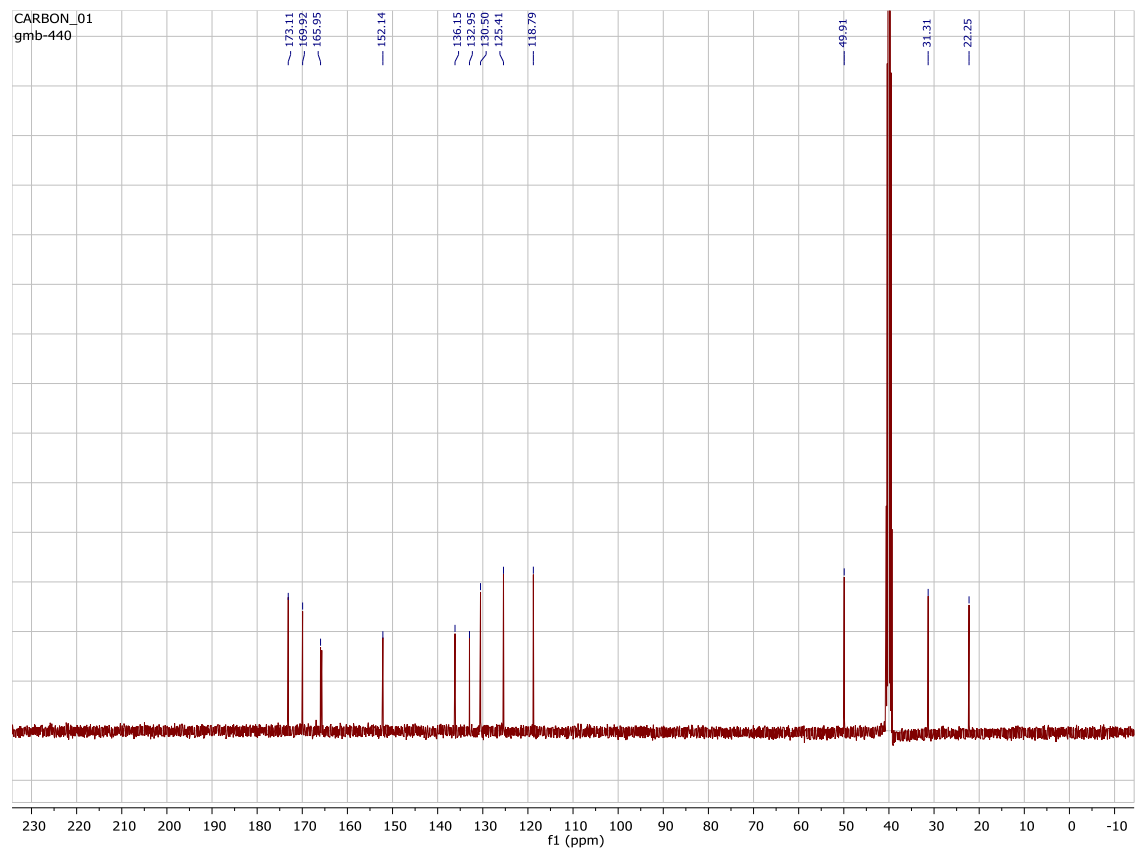
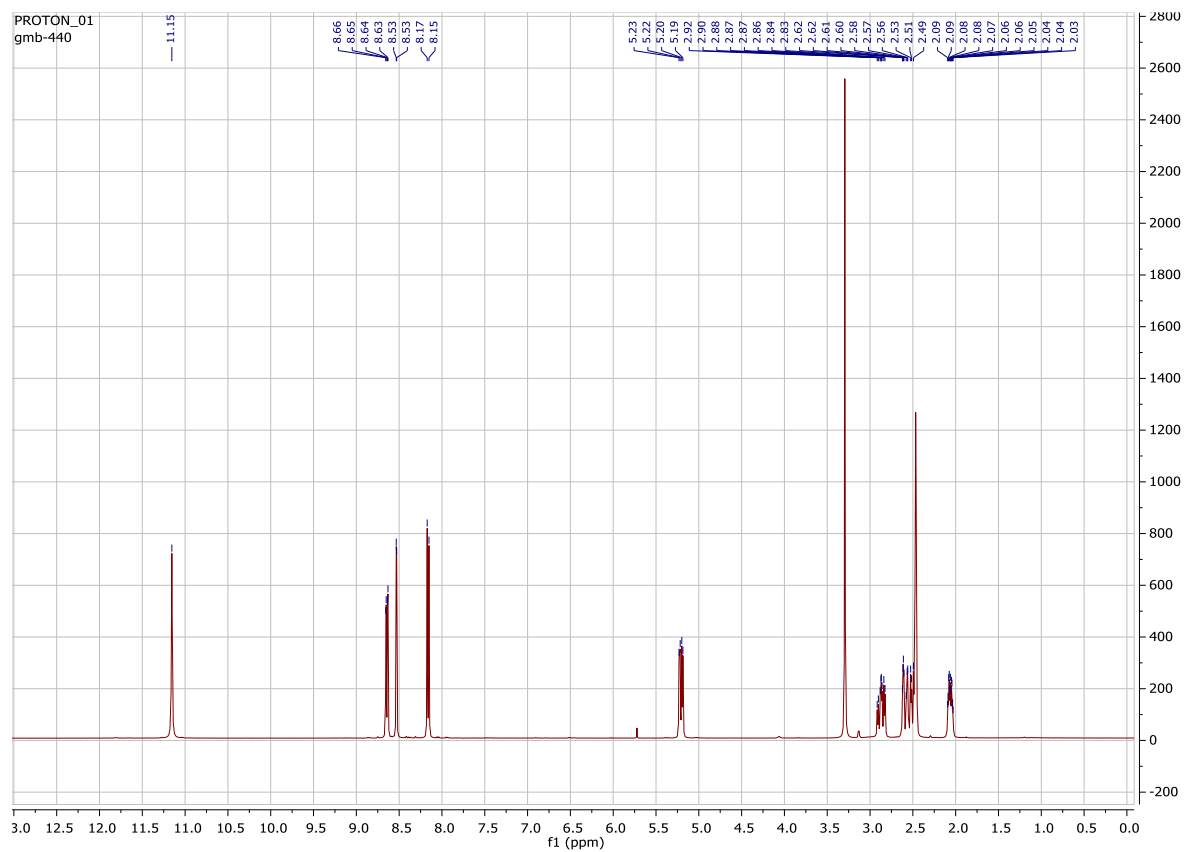




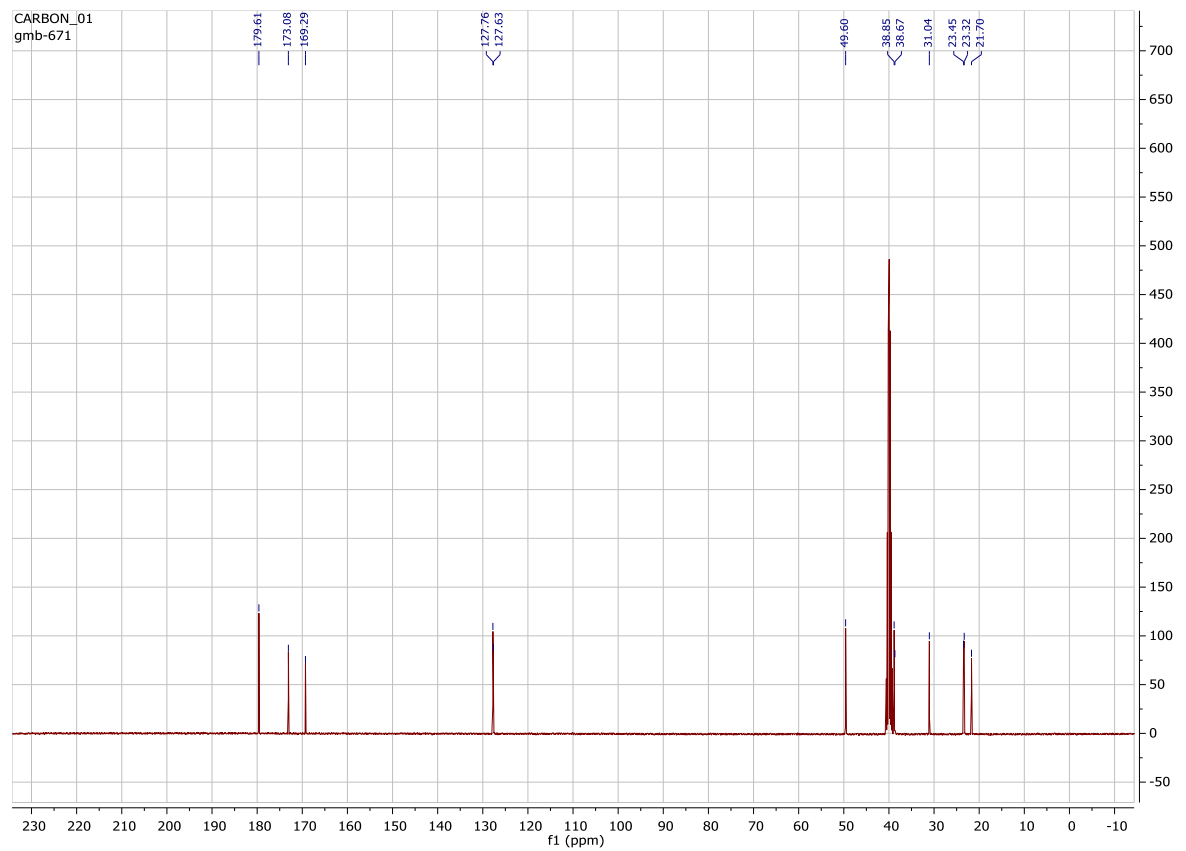
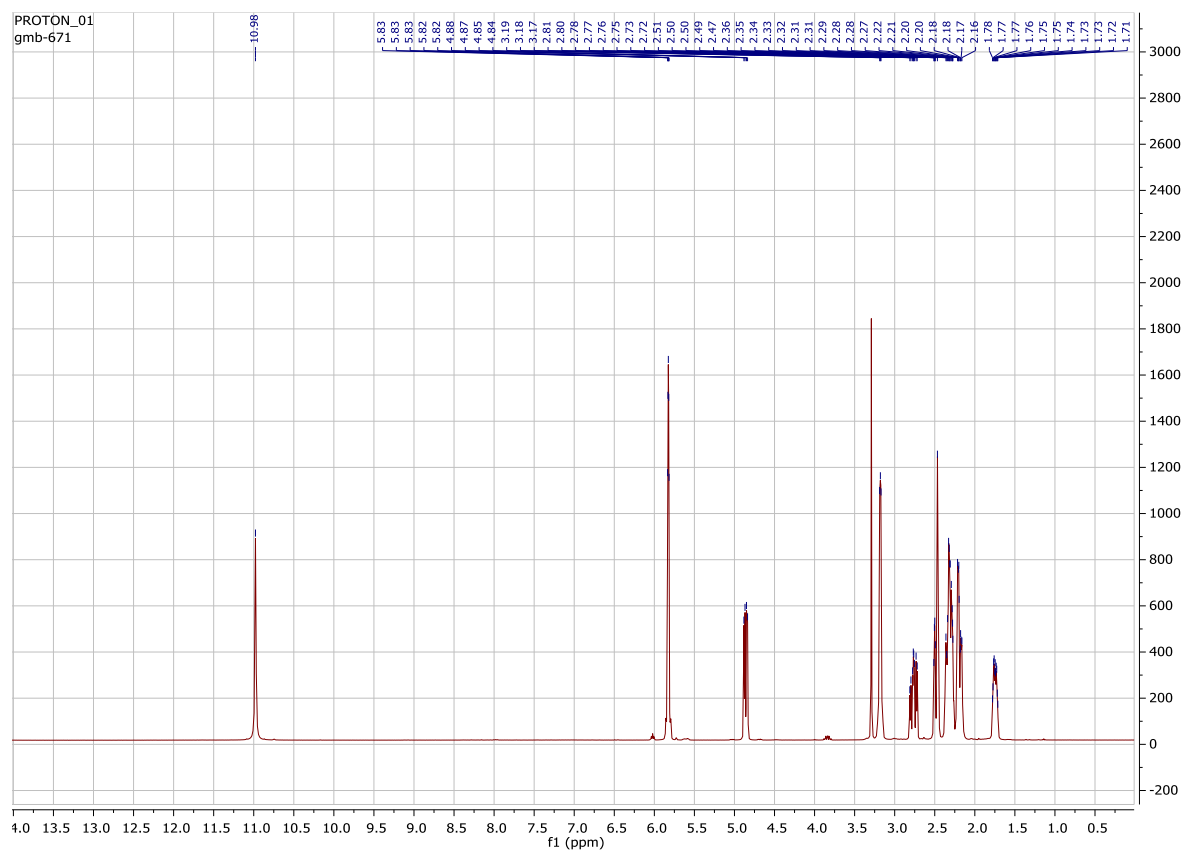
# Compound 15



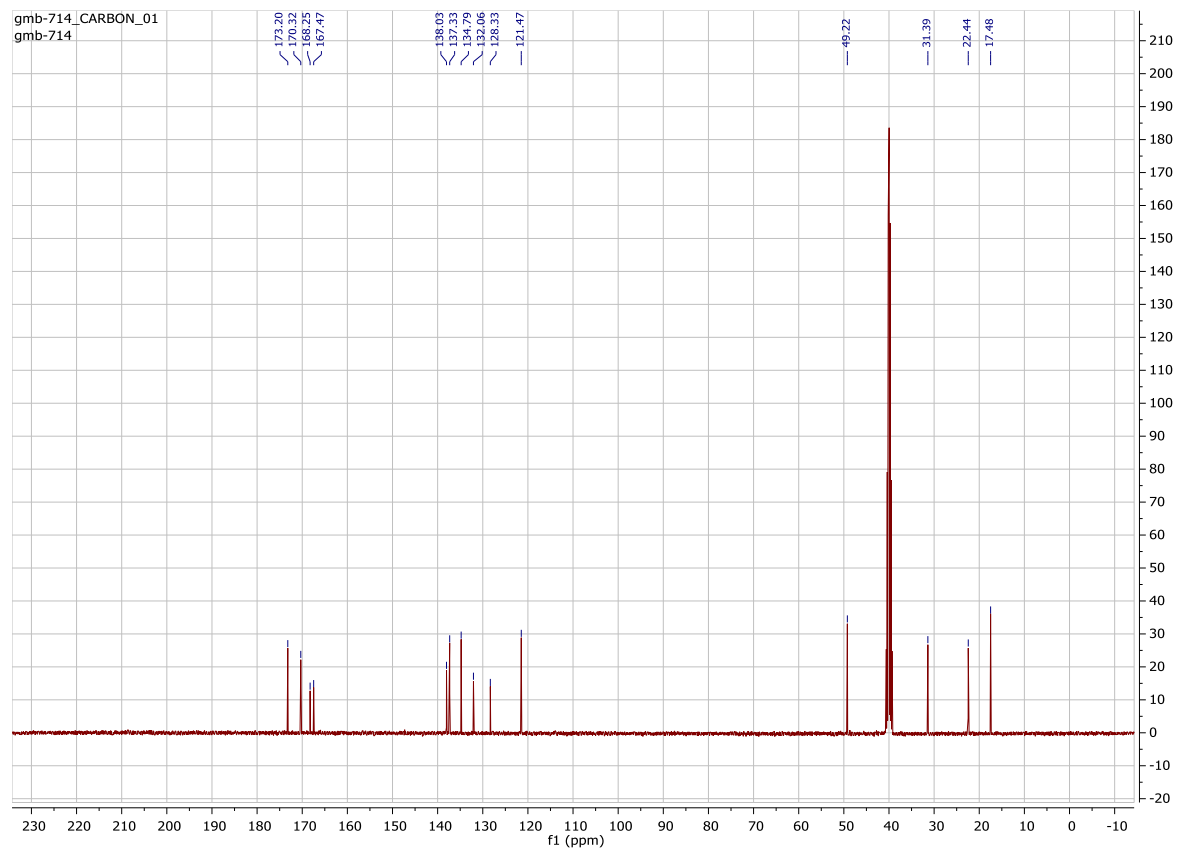
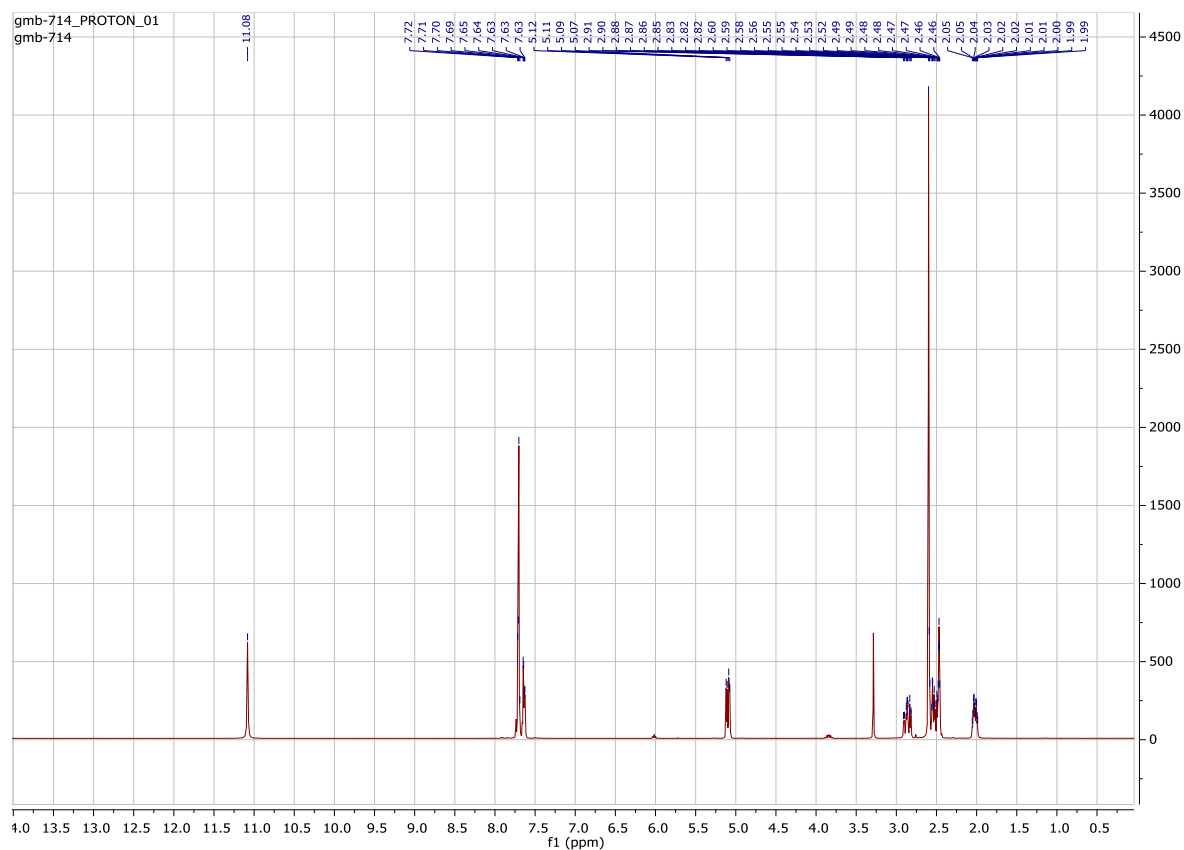
# Compound 16



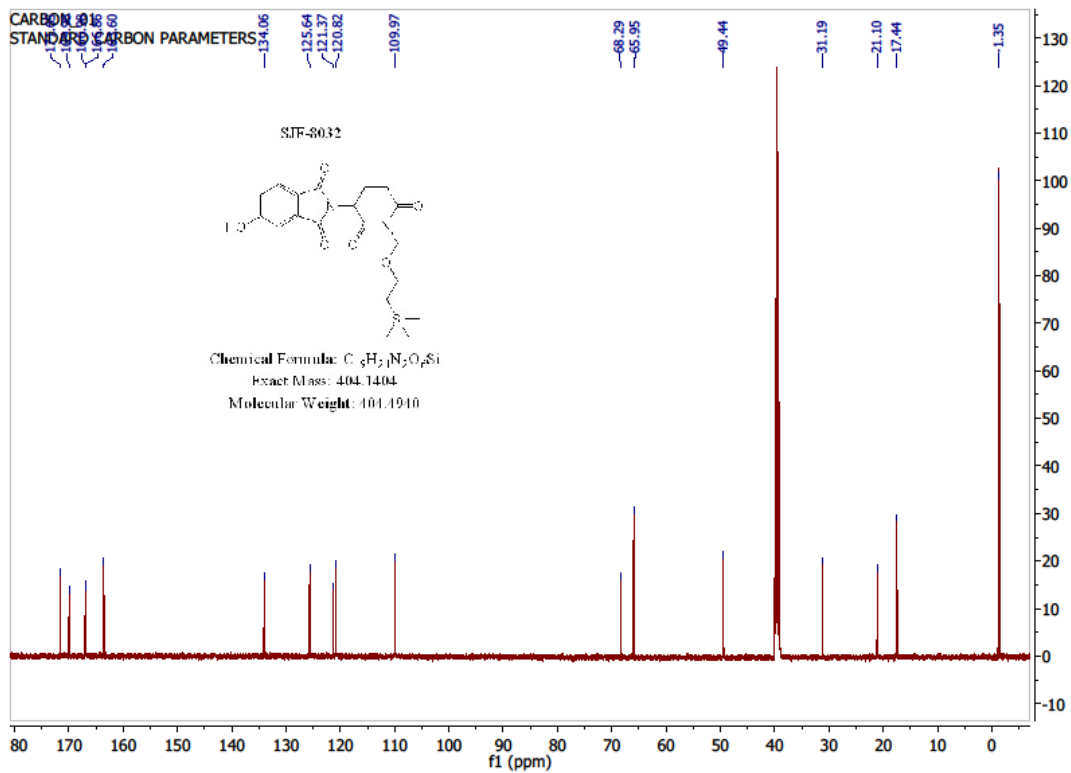
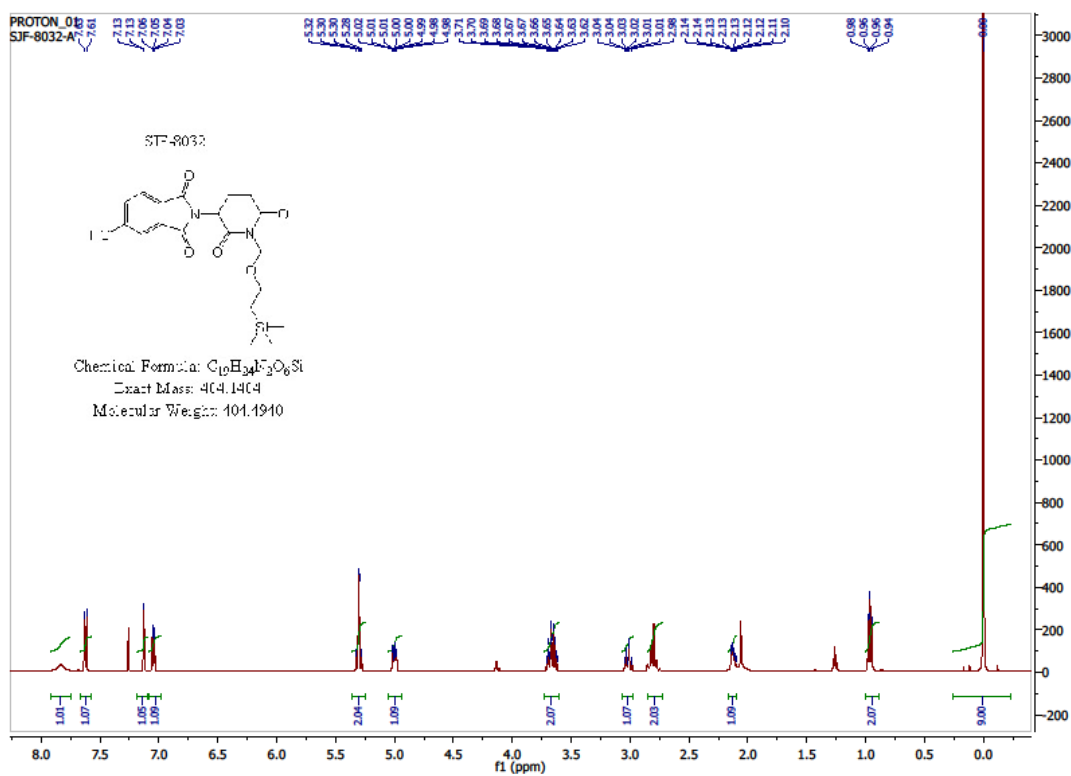
# Compound 18



# Compound 19



# Compound 21



# Compound 22

