

# Supporting information for

## Gossypol with Hydrophobic Linear Esters Exhibits

### Enhanced Anti-tumor Activity as an Inhibitor of

### Antiapoptotic Proteins

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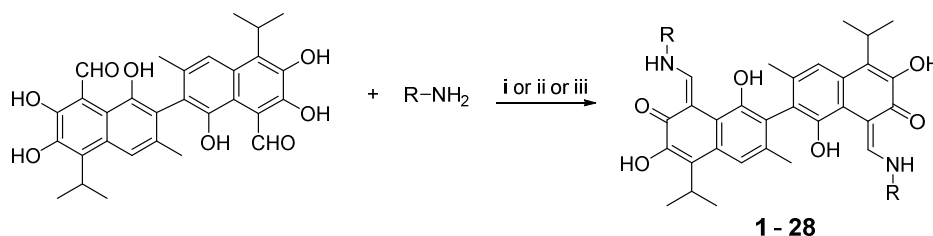
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## Part I. Chemistry: experimental procedures and chemical data for compounds 1-28

**General methods.** Unless otherwise noted, reagents and materials were obtained from commercial suppliers and were used without further purification. All solvents were purified according to reported procedures. Reactions were monitored by thin-layer chromatography (TLC), and column chromatography purifications were performed using a 230–400 mesh silica gel. NMR spectra were measured on a Bruker Biospin AV400 instrument at 400 MHz for  $^1\text{H}$  NMR spectra, 100 MHz for  $^{13}\text{C}$  NMR spectra and calibrated from the residual solvent signal. High-resolution mass spectra were obtained from the Shanghai Mass Spectrometry Center. Melting points were determined by an X-4 Beijing Tech melting point apparatus and were uncorrected. All compounds assayed were  $> 95\%$  pure, as determined by an HPLC analysis conducted on an Agilent Technologies 1220 Infinity system with UV detection at 254 nm using a normal-phase column and a reversed-phase column. The normal-phase HPLC was recorded on a Thermo Scientific Hypersil Silica column using hexane/ethyl acetate (90:10) as the eluent, and the reversed-phase HPLC was recorded on an Agilent ZORBAX SB-C18 column using MeOH/ $\text{H}_2\text{O}$ / $\text{CF}_3\text{COOH}$  (95:5:0.01%) as the eluent.

**Synthesis.** All types of gossypol Schiff bases were obtained by the reaction of the corresponding commercially available primary amine or modified amine with gossypol acetate, respectively (Scheme 1). Single enantiomers (+)-gossypol and (-)-gossypol were obtained by using L-tryptophan methyl ester as the resolution reagent as previously described.<sup>1</sup>

**Scheme 1.** Synthetic route for gossypol Schiff bases.



Reagents and conditions: (i) EtOH, r.t.; (ii)  $\text{Et}_3\text{N}$ , EtOH, r.t.; (iii) KOH, MeOH/ $\text{H}_2\text{O}$ ,

70 °C.

**General procedure for the preparation of target compounds (1-11, 20-25).**

Primary amine or amino acid (3.0 eq) was added to a suspension of gossypol acetate (1.0 eq) in EtOH, the resulting suspension was stirred at room temperature and monitored by TLC. After the reaction was completed, the precipitate was filtered off and washed three times with EtOH, and dried under vacuum overnight.

**General procedure for the preparation of target compounds (12-19).** SOCl<sub>2</sub> was added dropwise to dry MeOH at 0 °C, the resulting solution was stirred at room temperature for 1 h, amino acids were then added to the solution, and reflux at 90 °C for another 15 h. The reaction mixture was cooled to room temperature and evaporated, the crude amino acid methyl ester salts were recrystallized from MeOH/Et<sub>2</sub>O. Et<sub>3</sub>N (6.0 eq) was added to a solution of amino acid methyl ester salts (3.0 eq) in EtOH, the resulting mixture was stirred at room temperature for 15 min, gossypol acetate (1.0 eq) was then added, the resulting suspension was stirred at room temperature and monitored by TLC. After the reaction was completed, the precipitate was filtered off and washed three times with EtOH, and dried under vacuum overnight. (+)-**16** And (-)-**16** were prepared from (+)-gossypol and (-)-gossypol follow this procedure, respectively.

**General procedure for the preparation of target compounds 26.** To a solution of methyl 6-aminocaproate hydrochloride in MeOH was added benzylamine, the resulting solution was heated to 80 °C and stirred for 24 h. The solution was concentrated under reduced pressure, and the crude product was purified by silica gel chromatography (MeOH/DCM = 1:15) to afford 6-amino-*N*-benzylhexanamide. 6-Amino-*N*-benzylhexanamide (3.0 eq) was added to a suspension of gossypol acetate (1.0 eq) in EtOH, the resulting suspension was stirred at room temperature and monitored by TLC. After the reaction was completed, the precipitate was filtered off and washed three times with EtOH, and dried under vacuum overnight.

**General procedure for the preparation of target compounds 27 and 28.** Taurine or tramiprosate dissolved in water was added to a solution of KOH in MeOH/H<sub>2</sub>O (v/v = 4:1), the resulting mixture was heated to 70 °C. Then gossypol acetate was

added, the resulting mixture was heated and refluxed for 2 h. The precipitate was filtered off and washed three times with hot water, and dried under vacuum overnight.

(±)-Gossypol bis-(*tert*-Butylamine) Schiff base (**1**). Reacting of *tert*-butylamine and (±)-gossypol yielded compound **1**. Yellow solid, 88% yield, mp 274-276 °C. (lit.<sup>2</sup>) HPLC purity > 99%,  $t_R$  = 4.162 min. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  13.65 (d,  $J$  = 12.8 Hz, 1H), 9.82 (d,  $J$  = 13.2 Hz, 1H), 8.04 (brs, 1H), 7.62 (s, 1H), 5.59 (s, 1H), 3.82-3.66 (m, 1H), 2.12 (s, 3H), 1.53 (dd,  $J$  = 6.8, 5.2 Hz, 6H), 1.44 (s, 9H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  171.94, 158.92, 148.86, 147.28, 131.59, 128.88, 127.04, 118.17, 115.61, 114.91, 102.84, 54.41, 29.79, 27.44, 20.41, 20.36, 20.13. HRMS (ESI):  $m/z$  (M + H)<sup>+</sup> calcd for C<sub>38</sub>H<sub>49</sub>N<sub>2</sub>O<sub>6</sub> 629.3591, found 629.3594.

(±)-Gossypol bis-(*tert*-octylamine) Schiff base (**2**). Reacting of *tert*-octylamine and (±)-gossypol yielded compound **2**. Yellow solid, 73% yield, mp 295-297 °C. HPLC purity > 99%,  $t_R$  = 4.160 min. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  13.74 (d,  $J$  = 13.2 Hz, 1H), 9.78 (d,  $J$  = 13.2 Hz, 1H), 8.06 (brs, 1H), 7.62 (s, 1H), 5.60 (s, 1H), 3.80-3.68 (m, 1H), 2.13 (s, 3H), 1.72 (s, 2H), 1.56-1.51 (m, 6H), 1.47 (s, 6H), 1.00 (s, 9H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  171.84, 158.84, 148.93, 147.35, 131.52, 128.80, 126.89, 118.18, 118.13, 115.61, 114.98, 102.85, 57.85, 55.36, 31.82, 31.48, 29.77, 29.64, 27.43, 20.42, 20.37, 20.18. HRMS (ESI):  $m/z$  (M + H)<sup>+</sup> calcd for C<sub>46</sub>H<sub>65</sub>N<sub>2</sub>O<sub>6</sub> 741.4843, found 741.4837.

(±)-Gossypol bis-(cyclohexylamine) Schiff base (**3**). Reacting of cyclohexylamine and (±)-gossypol yielded compound **3**. Yellow solid, 91% yield, mp 291-292 °C. (lit.<sup>2</sup>) HPLC purity 97.04%,  $t_R$  = 4.106 min. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  13.40 (s, 1H), 9.72 (d,  $J$  = 7.6 Hz, 1H), 8.04 (s, 1H), 7.59 (s, 1H), 5.64 (s, 1H), 3.86-3.64 (m, 1H), 3.48-3.28 (m, 1H), 2.12 (s, 3H), 1.94-2.07 (m, 2H), 1.85-1.75 (m, 2H), 1.66-1.57 (m, 2H), 1.54-1.48 (m, 7H), 1.39-1.39 (m, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  172.12, 160.88, 148.90, 147.22, 131.62, 128.86, 127.08, 118.18, 118.13, 115.66, 114.82, 103.01, 59.06, 33.60, 27.42, 25.09, 24.38, 20.40, 20.36, 20.08. HRMS (ESI):  $m/z$  (M + H)<sup>+</sup> calcd for C<sub>42</sub>H<sub>53</sub>N<sub>2</sub>O<sub>6</sub> 681.3904, found 681.3898.

(±)-Gossypol bis-(4-*tert*-Butylcyclohexylamine) Schiff base (**4**). Reacting of 4-*tert*-butylcyclohexylamine and (±)-gossypol yielded compound **4**. Brown solid,

76% yield, mp 276-277 °C. HPLC purity > 99%,  $t_R$  = 4.166 min.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  13.85 (s, 1H), 9.70 (d,  $J$  = 12.4 Hz, 1H), 8.08 (brs, 1H), 7.59 (s, 1H), 5.74 (s, 1H), 3.90-3.61 (m, 2H), 2.11 (s, 3H), 2.01-1.84 (m, 2H), 1.74-1.67 (m, 2H), 1.57-1.48 (m, 6H), 1.43-1.33 (m, 2H), 1.25 (s, 1H), 1.14-1.03 (m, 2H), 0.87 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  172.06, 161.35, 149.02, 148.96, 147.30, 131.58, 128.73, 126.84, 118.02, 115.72, 114.81, 103.36, 59.64, 55.43, 47.57, 46.85, 34.14, 32.62, 32.34, 31.96, 31.79, 29.73, 27.52, 27.47, 25.94, 21.54, 21.52, 20.40, 20.37, 20.14. HRMS (ESI):  $m/z$  ( $M + H$ ) $^+$  calcd for  $\text{C}_{46}\text{H}_{65}\text{N}_2\text{O}_6$  793.5156, found 793.5150.

( $\pm$ )-*Gossypol bis-(amantadine) Schiff base (5)*. Reacting of amantadine and ( $\pm$ )-gossypol yielded compound **5**. Yellow solid, 79% yield, mp > 300 °C. HPLC purity > 99%,  $t_R$  = 4.112 min.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  13.57 (d,  $J$  = 13.6 Hz, 1H), 9.80 (d,  $J$  = 12.4 Hz, 1H), 7.61 (s, 1H), 5.60 (brs, 1H), 3.79-3.66 (m, 1H), 2.15-2.21 (m, 3H), 2.12 (s, 3H), 1.90-1.96 (m, 5H), 1.82-1.62 (m, 7H), 1.51-1.54 (m, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.77, 158.07, 148.84, 147.30, 131.49, 128.87, 126.94, 118.16, 118.11, 115.58, 114.98, 102.90, 54.56, 42.93, 35.81, 29.23, 27.43, 20.41, 20.37, 20.11. HRMS (ESI):  $m/z$  ( $M + H$ ) $^+$  calcd for  $\text{C}_{50}\text{H}_{61}\text{N}_2\text{O}_6$  785.4530, found 785.4524.

( $\pm$ )-*Gossypol bis-((-)-isopinocampheylamine) Schiff base (6)*. Reacting of (-)-isopinocampheylamine and ( $\pm$ )-gossypol yielded compound **6**. Yellow solid, 69% yield, mp 286-288 °C. HPLC purity > 99%,  $t_R$  = 4.080 min.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  13.46 (s, 1H), 9.70 (d,  $J$  = 10.4 Hz, 1H), 8.02 (brs, 1H), 7.60 (s, 1H), 5.64 (d,  $J$  = 8.4 Hz, 1H), 3.81-3.64 (m, 2H), 2.6-2.53 (m, 1H), 2.51-2.46 (m, 1H), 2.19-2.16 (m, 1H), 2.13 (s, 3H), 2.04-1.93 (m, 2H), 1.88 (t,  $J$  = 5.5 Hz, 1H), 1.56-1.48 (m, 6H), 1.44 (dd,  $J$  = 6.8, 3.2 Hz, 1H), 1.24 (s, 3H), 1.12 (dd,  $J$  = 7.2, 4.0 Hz, 3H), 1.07-1.05 (m, 1H), 0.99 (m, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 172.19, 161.59, 148.95, 147.23, 131.70, 131.63, 128.87, 127.15, 118.16, 115.65, 114.81, 102.75, 60.91, 47.31, 45.83, 41.32, 38.54, 37.02, 35.22, 27.93, 27.42, 23.41, 20.41, 20.36, 20.22, 20.14. HRMS (ESI):  $m/z$  ( $M + H$ ) $^+$  calcd for  $\text{C}_{50}\text{H}_{65}\text{N}_2\text{O}_6$  789.4843, found 789.4837.

( $\pm$ )-*Gossypol bis-(anthranilic acid methyl ester) Schiff base (7)*. Reacting of anthranilic acid methyl ester and ( $\pm$ )-gossypol yielded compound **7**. Yellow solid,

93% yield, mp 249-250 °C. HPLC purity > 99%,  $t_R$  = 4.249 min.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  14.99 (d,  $J$  = 12.4 Hz, 1H), 10.20 (d,  $J$  = 12.4 Hz, 1H), 8.08 (d,  $J$  = 8.0 Hz, 1H), 7.96 (s, 1H), 7.60 (s, 1H), 7.53-7.45 (m, 2H), 7.19-7.12 (m, 1H), 5.88 (s, 1H), 4.04 (s, 3H), 3.74-3.63 (m, 1H), 2.16 (s, 3H), 1.56-1.50 (m, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  175.77, 166.63, 151.37, 149.52, 147.19, 141.66, 134.38, 133.31, 132.07, 130.47, 128.84, 124.22, 118.89, 118.26, 116.72, 116.53, 114.53, 106.62, 52.73, 27.57, 20.26, 20.21, 20.14. HRMS (ESI):  $m/z$  ( $M + H$ ) $^+$  calcd for  $\text{C}_{46}\text{H}_{45}\text{N}_2\text{O}_{10}$  785.3074, found 785.3068.

( $\pm$ )-Gossypol bis-(benzylamine) Schiff base (**8**). Reacting of benzylamine and ( $\pm$ )-gossypol yielded compound **8**. Yellow solid, 93% yield, mp 259-261 °C. (lit.<sup>3</sup>) HPLC purity > 99%,  $t_R$  = 4.164 min.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  13.60 (d,  $J$  = 12.0 Hz, 1H), 9.73 (d,  $J$  = 12.0 Hz, 1H), 7.95 (brs, 1H), 7.59 (s, 1H), 7.38-7.27 (m, 5H), 5.59 (s, 1H), 4.67 (d,  $J$  = 4.3 Hz, 2H), 3.81-3.65 (m, 1H), 2.11 (s, 3H), 1.52 (dd,  $J$  = 6.4, 4.4 Hz, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  172.98, 163.00, 149.04, 147.12, 136.24, 132.01, 129.07, 128.24, 127.60, 127.37, 118.23, 115.89, 114.67, 103.48, 77.40, 77.28, 77.08, 76.76, 54.49, 27.47, 20.39, 20.35, 20.13. HRMS (ESI):  $m/z$  ( $M + H$ ) $^+$  calcd for  $\text{C}_{44}\text{H}_{45}\text{N}_2\text{O}_6$  697.3278, found 697.3272.

( $\pm$ )-Gossypol bis-(4-tert-Butylaniline) Schiff base (**9**). Reacting of 4-tert-butylaniline and ( $\pm$ )-gossypol yielded compound **9**. Yellow solid, 88% yield, mp 293-295 °C. HPLC purity > 99%,  $t_R$  = 4.092 min.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  14.88 (d,  $J$  = 11.2 Hz, 1H), 10.17 (d,  $J$  = 11.2 Hz, 1H), 7.90 (s, 1H), 7.62 (s, 1H), 7.37 (d,  $J$  = 8.4 Hz, 2H), 7.23 (d,  $J$  = 8.8 Hz, 2H), 5.95 (s, 1H), 3.79-3.63 (m, 1H), 2.16 (s, 3H), 1.51-1.56 (m, 6H), 1.29 (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.84, 154.33, 149.43, 149.29, 147.03, 136.91, 132.63, 129.60, 128.58, 126.74, 118.57, 117.99, 116.37, 114.54, 104.97, 34.56, 31.28, 27.57, 20.35, 20.17. HRMS (ESI):  $m/z$  ( $M + H$ ) $^+$  calcd for  $\text{C}_{50}\text{H}_{57}\text{N}_2\text{O}_6$  781.4217, found 681.4211.

( $\pm$ )-Gossypol bis-(piperonylamine) Schiff base (**10**). Reacting of piperonylamine and ( $\pm$ )-gossypol yielded compound **10**. Yellow solid, 90% yield, mp 263-365 °C. HPLC purity > 99%,  $t_R$  = 4.148 min.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  13.51 (s, 1H), 9.70 (d,  $J$  = 12.0 Hz, 1H), 7.94 (s, 1H), 7.59 (s, 1H), 6.84-6.63 (m, 3H), 5.94 (s, 2H),

5.59 (s, 1H), 4.55 (d,  $J = 4.0$ , 2H), 3.79-3.63 (m, 1H), 2.11 (s, 3H), 1.56-1.47 (m, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  172.97, 162.67, 148.99, 148.24, 147.61, 147.10, 131.99, 129.93, 129.04, 127.59, 121.03, 118.24, 115.81, 114.62, 108.61, 107.94, 103.41, 101.30, 54.30, 27.44, 20.36, 20.31, 20.10. HRMS (ESI):  $m/z$  ( $\text{M} + \text{H}$ ) $^+$  calcd for  $\text{C}_{46}\text{H}_{45}\text{N}_2\text{O}_{10}$  785.3074, found 785.3069.

( $\pm$ )-*Gossypol bis-(furfurylamine) Schiff base (11)*. Reacting of furfurylamine and ( $\pm$ )-gossypol yielded compound **11**. Yellow solid, 85% yield, mp 267-268 °C. HPLC purity 99.05%,  $t_{\text{R}} = 4.165$  min.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  13.46 (s, 1H), 9.71 (d,  $J = 11.2$  Hz, 1H), 7.92 (brs, 1H), 7.59 (s, 1H), 7.39-7.34 (m, 1H), 6.35-6.27 (m, 2H), 5.63 (s, 1H), 4.62 (s, 2H), 3.76-3.66 (m, 1H), 2.11 (s, 3H), 1.52 (dd,  $J = 6.8, 3.2$  Hz, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.16, 162.81, 149.13, 149.04, 147.05, 143.29, 132.07, 129.08, 127.73, 115.87, 114.60, 110.65, 108.79, 103.58, 46.92, 27.45, 20.36, 20.32, 20.10. HRMS (ESI):  $m/z$  ( $\text{M} + \text{H}$ ) $^+$  calcd for  $\text{C}_{40}\text{H}_{41}\text{N}_2\text{O}_8$  677.2863, found 677.2857.

( $\pm$ )-*Gossypol bis-(L-valine methyl ester) Schiff base (12)*. Start from *L*-valine, by reacting of *L*-valine methyl ester hydrochloride and ( $\pm$ )-gossypol yielded compound **12**. Yellow solid, 85% yield, mp 284-285 °C. HPLC purity 97.78%,  $t_{\text{R}} = 4.158$  min.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  13.64 (s, 1H), 9.56 (s, 1H), 7.95 (s, 1H), 7.59 (brs, 1H), 5.61 (s, 1H), 3.94-3.86 (m, 1H), 3.79 (s, 3H), 3.75-3.66 (m, 1H), 2.40-2.31 (m, 1H), 2.11 (s, 3H), 1.54-1.49 (m, 6H), 1.05-0.99 (m, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.48, 170.35, 162.08, 149.05, 149.03, 147.11, 132.12, 129.19, 127.82, 118.29, 115.90, 114.54, 103.64, 69.22, 52.72, 32.13, 27.44, 20.28, 20.11, 20.08, 19.17, 17.54. HRMS (ESI):  $m/z$  ( $\text{M} + \text{H}$ ) $^+$  calcd for  $\text{C}_{42}\text{H}_{53}\text{N}_2\text{O}_{10}$  745.3700, found 745.3695.

( $\pm$ )-*Gossypol bis-(L-methionine methyl ester) Schiff base (13)*. Start from *L*-methionine, by reacting of *L*-methionine methyl ester hydrochloride and ( $\pm$ )-gossypol yielded compound **13**. Yellow solid, 78% yield, mp 271-272 °C. HPLC purity > 99%,  $t_{\text{R}} = 4.133$  min.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  13.54 (s, 1H), 9.62 (d,  $J = 11.6$  Hz, 1H), 7.91 (s, 1H), 7.59 (s, 1H), 5.62 (s, 1H), 4.44-4.36 (m, 1H), 3.79 (s, 3H), 3.75-3.67 (m, 1H), 2.72-2.62 (m, 1H), 2.59-2.49 (m, 1H), 2.35-2.25 (m, 1H), 2.22-2.15 (m, 1H), 2.11 (s, 3H), 2.07 (s, 3H), 1.55-1.49 (m, 6H).  $^{13}\text{C}$  NMR (100 MHz,

CDCl<sub>3</sub>)  $\delta$  173.72, 170.68, 162.02, 149.09, 147.01, 132.31, 129.26, 128.12, 118.35, 115.98, 114.42, 103.88, 61.01, 53.05, 31.97, 29.67, 27.45, 20.28, 20.10, 15.17. HRMS (ESI):  $m/z$  (M + H)<sup>+</sup> calcd for C<sub>42</sub>H<sub>53</sub>N<sub>2</sub>O<sub>10</sub>S<sub>2</sub> 809.3142, found 809.3136.

( $\pm$ )-Gossypol bis-(glycine methyl ester) Schiff base (**14**). Start from glycine, by reacting of glycine methyl ester hydrochloride and ( $\pm$ )-gossypol yielded compound **14**. Yellow solid, 91% yield, mp 233-235 °C. (lit.<sup>4</sup>) HPLC purity > 99%,  $t_R$  = 4.096 min. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  13.36 (s, 1H), 9.56 (s, 1H), 7.89 (brs, 1H), 7.57 (s, 1H), 5.68 (s, 1H), 4.23 (s, 2H), 3.77 (s, 3H), 3.74-3.65 (m, 1H), 2.10 (s, 2H), 1.51 (dd,  $J$  = 6.4 Hz, 4.8, 6H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  173.79, 168.58, 163.16, 149.08, 146.99, 132.32, 129.25, 128.09, 118.29, 116.07, 114.45, 104.01, 52.85, 50.88, 27.45, 20.31, 20.28, 20.07. HRMS (ESI):  $m/z$  (M + H)<sup>+</sup> calcd for C<sub>36</sub>H<sub>41</sub>N<sub>2</sub>O<sub>10</sub> 661.2761, found 661.2756.

( $\pm$ )-Gossypol bis-( $\beta$ -alanine methyl ester) Schiff base (**15**). Start from  $\beta$ -alanine, by reacting of  $\beta$ -alanine methyl ester hydrochloride and ( $\pm$ )-gossypol yielded compound **15**. Yellow solid, 87% yield, mp 236-237 °C. HPLC purity > 99%,  $t_R$  = 4.252 min. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  13.37 (s, 1H), 9.66 (s, 1H), 7.99 (brs, 1H), 7.58 (s, 1H), 5.61 (s, 1H), 3.82-3.73 (m, 3H), 3.71 (s, 3H), 2.72 (t,  $J$  = 7.6 Hz, 2H), 2.10 (s, 3H), 1.57-1.47 (m, 6H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  173.03, 171.20, 163.13, 148.99, 147.11, 131.93, 129.03, 127.54, 118.20, 115.80, 114.62, 103.32, 52.21, 46.18, 34.90, 27.42, 20.36, 20.31, 20.07. HRMS (ESI):  $m/z$  (M + H)<sup>+</sup> calcd for C<sub>38</sub>H<sub>45</sub>N<sub>2</sub>O<sub>10</sub> 689.3074, found 689.3069.

( $\pm$ )-Gossypol bis-( $\gamma$ -aminobutyric acid methyl ester) Schiff base (**16**). Start from  $\gamma$ -aminobutyric acid, by reacting of  $\gamma$ -aminobutyric acid methyl ester hydrochloride and ( $\pm$ )-gossypol yielded compound **16**. Yellow solid, 89% yield, mp 211-213 °C. HPLC purity > 99%,  $t_R$  = 4.097 min. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  13.34 (s, 1H), 9.63 (s, 1H), 7.97 (brs, 1H), 7.59 (s, 1H), 5.62 (s, 1H), 3.7-3.78 (m, 1H), 3.65 (s, 3H), 3.55 (t,  $J$  = 6.8 Hz, 2H), 2.43 (t,  $J$  = 7.2 Hz, 2H), 2.11 (s, 3H), 2.07-1.99 (m, 2H), 1.53 (dd,  $J$  = 6.8, 4.4 Hz, 6H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  172.83, 172.78, 163.04, 148.95, 147.10, 131.88, 128.98, 127.48, 118.26, 118.20, 115.77, 114.62, 103.26, 51.82, 49.74, 30.65, 27.43, 25.84, 20.37, 20.33, 20.06. HRMS (ESI):  $m/z$  (M + H)<sup>+</sup> calcd for

C<sub>38</sub>H<sub>49</sub>N<sub>2</sub>O<sub>6</sub> 717.3387, found 717.3381.

(+)-Gossypol bis-( $\gamma$ -aminobutyric acid methyl ester) Schiff base ((+)-**16**). Start from  $\gamma$ -aminobutyric acid, by reacting of  $\gamma$ -aminobutyric acid methyl ester hydrochloride and (+)-gossypol yielded compound (+)-**16**. Yellow solid, % yield.  $[\alpha]_D^{20} = (+)-484.3^\circ$  ( $c = 0.24$ , CHCl<sub>3</sub>), <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  13.35 (s, 1H), 9.63 (d,  $J = 10.0$ , 1H), 7.97 (s, 1H), 7.59 (s, 1H), 5.59 (s, 1H), 3.77-3.70 (m, 1H), 3.65 (s, 3H), 3.60-3.50 (m, 2H), 2.43 (t,  $J = 7.2$ , 2H), 2.11 (s, 3H), 2.07-2.00 (m, 2H), 1.53 (dd,  $J = 6.8, 4.4$ , 6H).

(-)-Gossypol bis-( $\gamma$ -aminobutyric acid methyl ester) Schiff base ((-)-**16**). Start from  $\gamma$ -aminobutyric acid, by reacting of  $\gamma$ -aminobutyric acid methyl ester hydrochloride and (-)-gossypol yielded compound (-)-**16**. Yellow solid, % yield.  $[\alpha]_D^{20} = (-)-478.1^\circ$  ( $c = 0.24$ , CHCl<sub>3</sub>), <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  13.34 (s, 1H), 9.63 (s, 1H), 7.98 (s, 1H), 7.59 (s, 1H), 5.61 (s, 1H), 3.75-3.68 (m, 1H), 3.65 (s, 3H), 3.58-3.52 (m, 2H), 2.42 (t,  $J = 7.2$ , 2H), 2.11 (s, 3H), 2.06-1.98 (m, 2H), 1.52 (dd,  $J = 6.9, 4.4$ , 6H).

( $\pm$ )-Gossypol bis-(5-aminovaleric acid methyl ester) Schiff base (**17**). Start from 5-aminovaleric acid, by reacting of 5-aminovaleric acid methyl ester hydrochloride and ( $\pm$ )-gossypol yielded compound **17**. Yellow solid, 89% yield, mp 210-212 °C. HPLC purity > 99%,  $t_R = 4.266$  min. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  13.32 (s, 1H), 9.63 (s, 1H), 7.59 (s, 1H), 5.66 (s, 1H), 3.77-3.68 (m, 1H), 3.64 (s, 3H), 3.53-3.43 (s, 2H), 2.38-2.30 (m, 2H), 2.11 (s, 3H), 1.79-1.66 (m, 4H), 1.52 (dd,  $J = 6.0, 3.2$  Hz, 6H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  173.45, 172.53, 162.97, 148.96, 147.13, 131.83, 128.90, 127.39, 118.15, 115.80, 114.68, 103.18, 51.68, 50.45, 33.35, 30.04, 27.43, 21.87, 20.39, 20.34, 20.10. HRMS (ESI):  $m/z$  (M + H)<sup>+</sup> calcd for C<sub>42</sub>H<sub>53</sub>N<sub>2</sub>O<sub>10</sub> 745.3700, found 745.3695.

( $\pm$ )-Gossypol bis-(6-aminocaproic acid methyl ester) Schiff base (**18**). Start from 6-aminocaproic acid, by reacting of 6-aminocaproic acid methyl ester hydrochloride and ( $\pm$ )-gossypol yielded compound **18**. Yellow solid, 88% yield, mp 174-175 °C. HPLC purity > 99%,  $t_R = 4.299$  min. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  13.32 (s, 1H), 9.63 (s, 1H), 7.59 (s, 1H), 5.62 (s, 1H), 3.76-3.67 (m, 1H), 3.64 (s, 3H), 3.48 (t,  $J = 6.4$  Hz, 2H), 2.30 (t,  $J = 7.2$  Hz, 2H), 2.11 (s, 3H), 1.74-1.60 (m, 4H), 1.55-1.49 (m,

6H), 1.47-1.38 (m, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.85, 172.47, 162.98, 148.94, 147.14, 131.78, 128.88, 127.32, 118.15, 115.73, 114.68, 103.11, 51.58, 50.53, 33.73, 30.28, 27.42, 26.03, 24.37, 20.39, 20.34, 20.09. HRMS (ESI):  $m/z$  ( $\text{M} + \text{H}$ ) $^+$  calcd for  $\text{C}_{44}\text{H}_{57}\text{N}_2\text{O}_{10}$  773.4013, found 773.4008.

( $\pm$ )-*Gossypol bis-(7-aminoheptanoic acid methyl ester) Schiff base (19)*. Start from 7-aminoheptanoic acid, by reacting of 7-aminoheptanoic acid methyl ester hydrochloride and ( $\pm$ )-gossypol yielded compound **19**. Yellow solid, 81% yield, mp 202-203 °C. HPLC purity > 99%,  $t_{\text{R}}$  = 4.259 min.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  13.31 (s, 1H), 9.64 (s, 1H), 7.59 (s, 1H), 5.67 (s, 1H), 3.79-3.69 (m, 1H), 3.61 (s, 3H), 3.51-3.40 (m, 2H), 2.28 (t,  $J$  = 6.8 Hz, 2H), 2.11 (s, 3H), 1.77-1.67 (m, 2H), 1.66-1.57 (m, 2H), 1.56-1.48 (m, 6H), 1.46-1.29 (m, 4H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  174.05, 172.39, 163.01, 148.98, 147.15, 131.77, 128.86, 127.29, 118.10, 115.79, 114.72, 103.12, 51.50, 50.65, 33.84, 30.36, 28.56, 27.42, 26.19, 24.64, 20.39, 20.34, 20.09. HRMS (ESI):  $m/z$  ( $\text{M} + \text{H}$ ) $^+$  calcd for  $\text{C}_{46}\text{H}_{61}\text{N}_2\text{O}_{10}$  801.4326, found 801.4321.

( $\pm$ )-*Gossypol bis-(glycine) Schiff base (20)*. Reacting of glycine and ( $\pm$ )-gossypol yielded compound **20**. Yellow solid, 73% yield, mp 275-277 °C. (lit.<sup>5</sup>) HPLC purity > 99%,  $t_{\text{R}}$  = 5.091 min.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  13.13 (brs, 1H), 9.66 (d,  $J$  = 9.6 Hz, 1H), 8.44 (brs, 1H), 7.86 (brs, 1H), 7.44 (s, 1H), 4.38 (s, 2H), 3.73-3.66 (m, 1H), 1.93 (s, 3H), 1.44 (dd,  $J$  = 6.8, 5.6 Hz, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$  173.36, 171.34, 163.68, 150.60, 147.21, 132.29, 127.95, 127.61, 121.11, 117.50, 116.69, 104.48, 51.62, 27.44, 21.99, 21.25, 21.22, 21.12. HRMS (ESI):  $m/z$  ( $\text{M} + \text{H}$ ) $^+$  calcd for  $\text{C}_{34}\text{H}_{37}\text{N}_2\text{O}_{10}$  633.2448, found 633.2443.

( $\pm$ )-*Gossypol bis-( $\beta$ -alanine) Schiff base (21)*. Reacting of  $\beta$ -alanine and ( $\pm$ )-gossypol yielded compound **21**. Yellow solid, 68% yield, mp 243-244 °C. (lit.<sup>6</sup>) HPLC purity > 99%,  $t_{\text{R}}$  = 4.952 min.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  13.16 (brs, 1H), 9.76 (d,  $J$  = 7.6 Hz, 1H), 8.41 (brs, 1H), 7.44 (s, 1H), 3.72-3.64 (m, 3H), 2.65 (t,  $J$  = 6.0 Hz, 2H), 1.93 (s, 3H), 1.47-1.38 (m, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$  172.49, 171.88, 149.61, 146.25, 138.31, 131.14, 126.84, 126.38, 120.15, 115.85, 109.50, 103.05, 46.28, 34.78, 26.46, 20.30, 20.27, 20.19. HRMS (ESI):  $m/z$  ( $\text{M} + \text{H}$ ) $^+$  calcd for  $\text{C}_{36}\text{H}_{41}\text{N}_2\text{O}_{10}$  661.2761, found 661.2756.

(±)-Gossypol bis-(γ-aminobutyric acid) Schiff base (**22**). Reacting of γ-aminobutyric acid and (±)-gossypol yielded compound **22**. Yellow solid, 70% yield, mp 172-174 °C. HPLC purity 96.52%,  $t_R$  = 5.782 min.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  13.27 (brs, 1H), 9.78 (s, 1H), 8.43 (brs, 1H), 7.44 (s, 1H), 3.74-3.67 (m, 1H), 3.60-3.48 (m, 2H), 2.29 (t,  $J$  = 7.2 Hz, 2H), 1.94 (s, 3H), 1.90-1.81 (m, 2H), 1.44 (dd,  $J$  = 6.8, 6.0 Hz, 6H).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  173.86, 171.69, 162.45, 149.81, 146.19, 131.16, 126.75, 126.44, 120.41, 115.93, 103.18, 49.16, 30.66, 25.69, 20.31, 20.28, 20.22. HRMS (ESI):  $m/z$  ( $M + H$ ) $^+$  calcd for  $\text{C}_{38}\text{H}_{45}\text{N}_2\text{O}_{10}$  689.3074, found 689.3069.

(±)-Gossypol bis-(5-aminovaleric acid) Schiff base (**23**). Reacting of 5-aminovaleric acid and (±)-gossypol yielded compound **23**. Yellow solid, 76% yield, mp 279-280 °C. HPLC purity 98.1%,  $t_R$  = 6.146 min.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  13.32 (s, 1H), 12.07 (brs, 1H), 9.76 (d,  $J$  = 10.8 Hz, 1H), 8.42 (brs, 1H), 7.85 (s, 1H), 7.45 (s, 1H), 3.74-3.67 (m, 1H), 3.55-3.48 (m, 2H), 2.27 (t,  $J$  = 7.2 Hz, 2H), 1.93 (s, 3H), 1.69-1.52 (m, 4H), 1.48-1.38 (m, 6H).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  174.21, 171.62, 162.44, 149.58, 146.25, 131.12, 126.80, 126.36, 120.09, 115.84, 103.09, 49.58, 33.05, 29.50, 26.46, 21.51, 20.32, 20.29, 20.20. HRMS (ESI):  $m/z$  ( $M + H$ ) $^+$  calcd for  $\text{C}_{40}\text{H}_{49}\text{N}_2\text{O}_{10}$  717.3387, found 717.3382.

(±)-Gossypol bis-(6-aminocaproic acid) Schiff base (**24**). Reacting of 6-aminocaproic acid and (±)-gossypol yielded compound **24**. Yellow solid, 85% yield, mp 235-236 °C. HPLC purity 96.24%,  $t_R$  = 5.746 min.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  13.27 (brs, 1H), 9.83 (s, 1H), 8.40 (brs, 1H), 7.42 (s, 1H), 3.76-3.64 (m, 1H), 3.59-3.41 (m, 2H), 2.24-2.12 (m, 2H), 1.93 (s, 3H), 1.68-1.59 (m, 2H), 1.56-1.49 (m, 2H), 1.47-1.37 (m, 6H), 1.37-1.27 (m, 2H).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  174.56, 171.53, 162.50, 150.04, 146.13, 131.03, 126.60, 126.33, 120.98, 116.18, 113.81, 103.16, 49.62, 33.74, 29.77, 25.47, 24.09, 20.32, 20.30, 20.24. HRMS (ESI):  $m/z$  ( $M + H$ ) $^+$  calcd for  $\text{C}_{42}\text{H}_{53}\text{N}_2\text{O}_{10}$  745.3700, found 745.3695.

(±)-Gossypol bis-(7-aminoheptanoic acid) Schiff base (**25**). Reacting of 7-aminoheptanoic acid and (±)-gossypol yielded compound **25**. Yellow solid, 75% yield, mp 264-265 °C. (lit.<sup>6</sup>) HPLC purity 97.43%,  $t_R$  = 6.161 min.  $^1\text{H}$  NMR (400

MHz, DMSO-*d*<sub>6</sub>)  $\delta$  13.31 (s, 1H), 11.96 (brs, 1H), 9.77 (d,  $J$  = 9.6 Hz, 1H), 8.43 (brs, 1H), 7.85 (brs, 1H), 7.45 (s, 1H), 3.78-3.65 (m, 1H), 3.57-3.47 (m, 2H), 2.18 (t,  $J$  = 7.2 Hz, 2H), 1.93 (s, 3H), 1.68-1.58 (m, 2H), 1.53-1.47 (m, 2H), 1.47-1.41 (m, 6H), 1.38-1.26 (m, 4H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  174.42, 171.58, 149.57, 146.26, 131.11, 126.79, 126.31, 120.06, 115.85, 103.06, 49.76, 33.50, 29.85, 28.04, 26.45, 25.70, 24.31, 20.32, 20.29, 20.19. HRMS (ESI):  $m/z$  (M + H)<sup>+</sup> calcd for C<sub>44</sub>H<sub>57</sub>N<sub>2</sub>O<sub>10</sub> 773.4013, found 773.4008.

(±)-*Gossypol bis-(6-amino-N-benzylhexanamide) Schiff base (26)*. Yellow solid, 76% yield, mp 195-196 °C. HPLC purity > 99%,  $t_R$  = 4.283 min. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  13.28 (s, 1H), 9.63 (d,  $J$  = 8.8 Hz, 1H), 7.97 (s, 1H), 7.59 (s, 1H), 7.33-7.27 (m, 2H), 7.25-7.16 (m, 3H), 5.99-5.85 (m, 1H), 5.76 (s, 1H), 4.33 (d,  $J$  = 5.6 Hz, 2H), 3.79-3.66 (m, 1H), 3.54-3.42 (m, 2H), 2.17 (t,  $J$  = 7.2 Hz, 2H), 2.11 (s, 3H), 1.74-1.67 (m, 4H), 1.55-1.48 (m, 6H), 1.46-1.37 (m, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  172.48, 172.42, 163.07, 149.00, 147.08, 138.24, 131.84, 128.81, 128.69, 127.78, 127.50, 127.39, 115.99, 114.75, 103.14, 50.43, 43.54, 36.27, 30.16, 27.42, 26.09, 25.03, 20.40, 20.35, 20.12. HRMS (ESI):  $m/z$  C<sub>56</sub>H<sub>67</sub>N<sub>4</sub>O<sub>8</sub> (M + H)<sup>+</sup> calcd for 923.4959, found 923.4953.

(±)-*Gossypol bis-(potassium taurine) Schiff base (27)*. Reacting of taurine and (±)-gossypol yielded compound **27**. Brown solid, 66% yield, mp > 300 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  12.92 (d,  $J$  = 10.2 Hz, 1H), 9.71 (d,  $J$  = 13.2 Hz, 1H), 8.42 (s, 1H), 7.84 (s, 1H), 7.43 (s, 1H), 3.77 (dd,  $J$  = 11.7, 5.7 Hz, 2H), 3.73-3.65 (m, 1H), 2.83 (s, 2H), 1.92 (s, 3H), 1.53-1.33 (m, 6H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  195.94, 171.72, 161.79, 149.51, 146.49, 131.02, 126.84, 126.42, 120.24, 116.42, 116.11, 103.12, 50.93, 47.66, 26.48, 20.32, 20.19.

(±)-*Gossypol bis-(potassium homotaurine) Schiff base (28)*. Reacting of homotaurine and (±)-gossypol yielded compound **28**. Yellow solid, 71% yield, mp > 300 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  13.19 (d,  $J$  = 10.4, 1H), 9.76 (d,  $J$  = 10.0 Hz, 1H), 8.43 (s, 1H), 7.88 (s, 1H), 7.44 (s, 1H), 3.72-3.69 (m, 1H), 3.68-3.62 (m, 2H), 2.57 (t,  $J$  = 7.6 Hz, 2H), 2.01-1.94 (m, 2H), 1.92 (s, 3H), 1.43 (dd,  $J$  = 6.4, 4.8 Hz, 6H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  171.59, 162.51, 149.66, 146.32, 131.07,

126.77, 126.43, 120.22, 116.38, 115.97, 103.19, 48.90, 47.78, 26.47, 20.33, 20.21.

## **PART 2. Molecular modeling and biochemical assays**

**Molecular modeling.** The coordinates of Bcl-2 were extracted from its complex crystal structure PDB code: 4LVT. Small molecule 3D structures were generated by Chemaxon Sketch and Space. The 3D conformation of the small molecule could be adjusted manually by Moloc. The protein receptor and small molecules files were prepared by Chimera. Spheres were generated by SPHGEN of dock 6.6 package. All spheres with 10.0 Angstroms RMSD from ligand were selected. Automatically constructing box was chosen with 8.0 Angstroms extra margin. Grid was created with the default grid parameters. Rigid and flex ligand docking were used to evaluate the pose of the molecule. Amber score was applied to analyze the complex binding difference with consideration MD of the receptor and ligand.

**Cell viability assays.** The assay relied upon the spectrophotometric measurement of solubilized purple formazan, produced by the mitochondrial reduction of MTT in viable cells. First, cancer cell lines (5000 per well) were seeded into 96-well plates and incubated for 24 h (37 °C, 95% air/5% CO<sub>2</sub>). Then, medium containing 0.33 µM,

1.0  $\mu$ M, 3.3  $\mu$ M, 10  $\mu$ M, 33  $\mu$ M, and 100  $\mu$ M of the tested compounds (compounds dissolved in DMSO were added to the culture medium, and the control medium received an equivalent dilution of DMSO; the final concentration of DMSO was < 1%, with four wells for each experiment concentration) were introduced into wells. After incubation for 72 h, 20  $\mu$ L of MTT (5  $\mu$ g/mL) was added into each well, and the cancer cell lines were incubated for 4 h. Consequently, the culture medium containing MTT was removed, and 160  $\mu$ L of DMSO was added into each well. The absorbance was tested with a multi-scan spectrophotometer MK3 (Thermo Electron Corporation) at 492 nm. Each compound's IC<sub>50</sub> value was calculated using the Probit analysis program in SPSS10.0. For the purpose of comparison, the activities of (-)-gossypol and (+)-gossypol were also determined using the same method described above.

#### **Fluorescence polarization assays (FPAs).**

A 21-residue Bid BH3 peptide (QEDIIRNIARHLAQVGDSMDR, residues 79–99)<sup>7</sup> bearing a 6-carboxy-fluorescein succinimidyl ester fluorescence tag (FAM-Bid) was synthesized at HD Biosciences (Shanghai, China). A 21-residue Bid BH3 peptide (QEDIIRNIARHLAQVGDSMDR, residues 79–99)<sup>7</sup> Gene sequence of human Mcl-1 (Uniprot: Q07820) and human Bcl-2 (Uniprot: P10415) were purchased from General Biosystems Inc. (Xuzhou, China) and subcloned into an expression vector pGEX-4T-1. Soluble Mcl-1 and Bcl-2 proteins were expressed in *E. coli* BL21 and purified according to published procedures.<sup>8</sup>

For the competitive binding assay for Bcl-2 protein, FAM-Bid peptide (10 nM) and Bcl-2 protein (140 nM) were preincubated in the assay buffer (100 mM potassium phosphate, pH 7.5; 100 mg/mL bovine gamma globulin; 0.02% sodium azide, 1% Triton X-100). Each inhibitor was first dissolved in pure DMSO to obtain a 4 mM stock solution. Then the stock solution was diluted successively to get the solution with different concentration gradients (400 mM, 200 mM, 100 mM, 50 mM, 25 mM, 12.5 mM, 6.25 mM, 3.125 mM, 1.5625 mM and 0.78125 mM). Next, serial dilutions of compounds were added. After 30 min incubation, the polarization values were measured using the Spectra Max M5 Detection System in a black 96-well plate. Saturation experiments determined that FAM-Bid binds to the Bcl-2 protein with a  $K_d$

value of 125 nM. For Mcl-1, assays were performed in the same manner as that for Bcl-2 with the following exceptions: 55 nM Mcl-1 and 10 nM FAM-Bid peptide were used in the assay buffer (25 mM Tris, pH 8.0; 150 mM NaCl). FAM-Bid peptide binds to the Mcl-1 protein with a  $K_d$  value of 13 nM. ( $\pm$ )-Gossypol was used as comparison in our assay. The  $K_i$  value for each inhibitor was calculated using the equation developed for FP-based assays.<sup>9</sup> The computer program for calculating values for FP-based assays is available free of charge at [http://sw16.im.med.umich.edu/software/calc\\_ki/](http://sw16.im.med.umich.edu/software/calc_ki/).

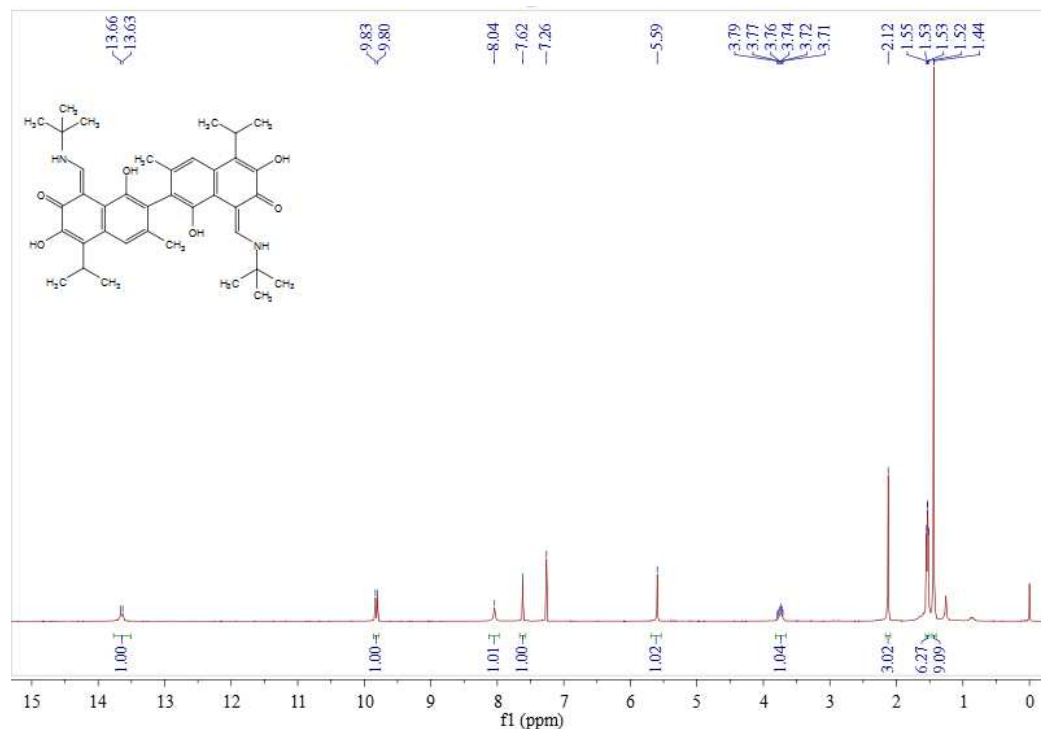
**Liver Microsomal Stability.** Pooled human (Mongolian, DXOV, Research Institute for Liver Diseases, Shanghai) or rat liver microsomes (BDVH, Research Institute for Liver Diseases, Shanghai) were preincubated with test compounds at 37 °C for 5 min in the absence of NADPH. The reaction was initiated by addition of NADPH and then incubated under the same conditions. The final incubation concentrations were 4.75  $\mu$ M test compound, 4 mM NADPH, and 0.5 mg/mL (total protein) liver microsomes in phosphate-buffered saline (PBS) at pH 7.4. One aliquot (100  $\mu$ L) of the incubation mixture was withdrawn at 1 h and combined immediately with 200  $\mu$ L of ACN. After mixing, the sample was centrifuged at approximately 13,000 rpm for 20 min. The supernatant (100 $\mu$ L) was extracted with mobile phase EA (200  $\mu$ L), and the amount of test compound (20  $\mu$ L) was quantified using the HPLC (Agilent Technologies 1220 Infinity system). The change of the AUC (area under the curve) of the control group 1 (blank) as function of time was used as a measure of microsomal stability.

#### **Chemical stability of compound 16**

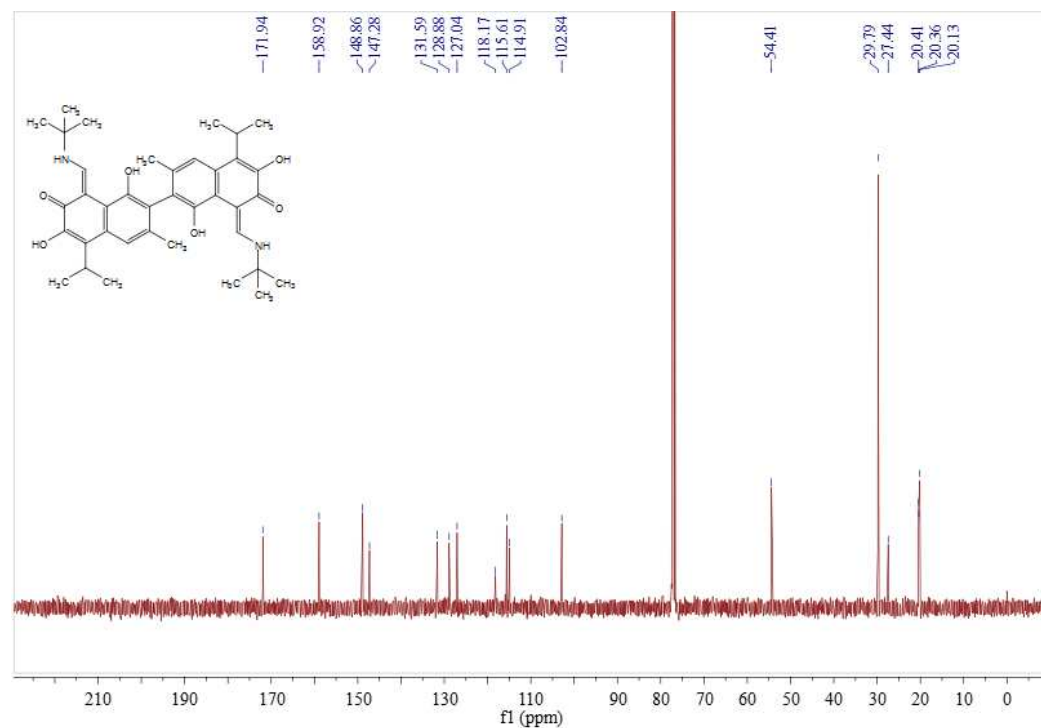
Compound **16** in THF (100  $\mu$ L, 0.1 mmol/mL) was added to the stirred hydrochloric acid solution with different pH (2 mL). After 3 h, the reaction mixture (100  $\mu$ L) was extract with mobile phase EA (200  $\mu$ L), and determined by normal phase HPLC. The change of the AUC (area under the curve) of the control group (pH = 7) as function of time was used as a measure of chemical stability.

## PART 3. $^1\text{H}$ NMR and $^{13}\text{C}$ NMR spectra of final compounds

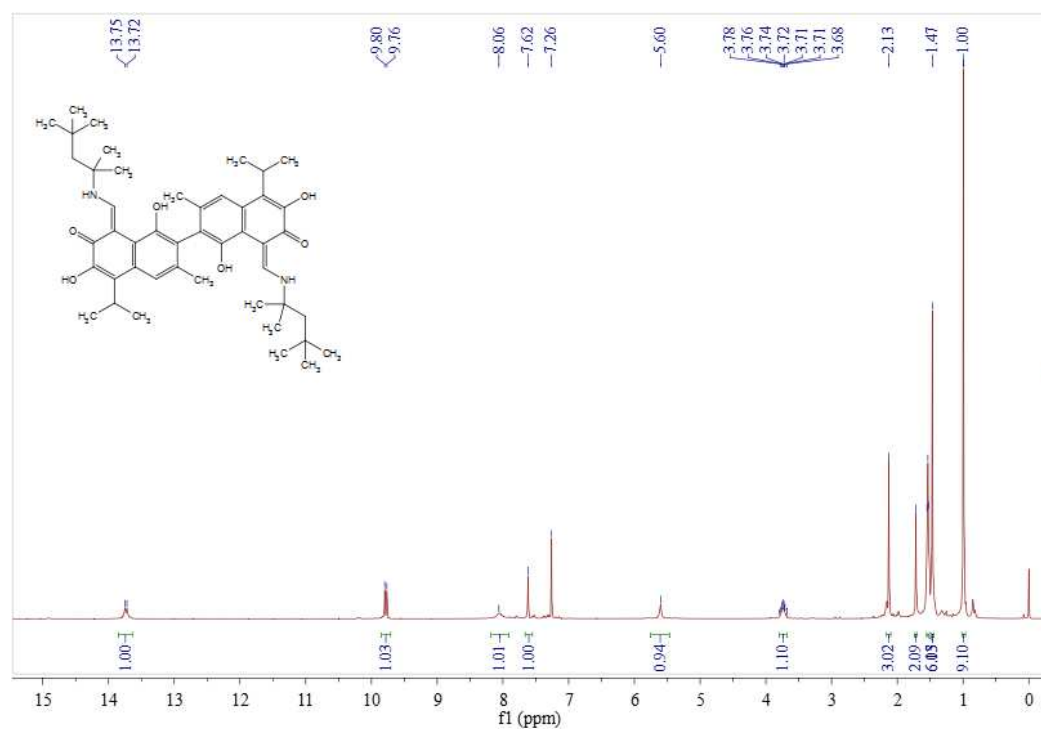
### $^1\text{H}$ NMR of compound 1



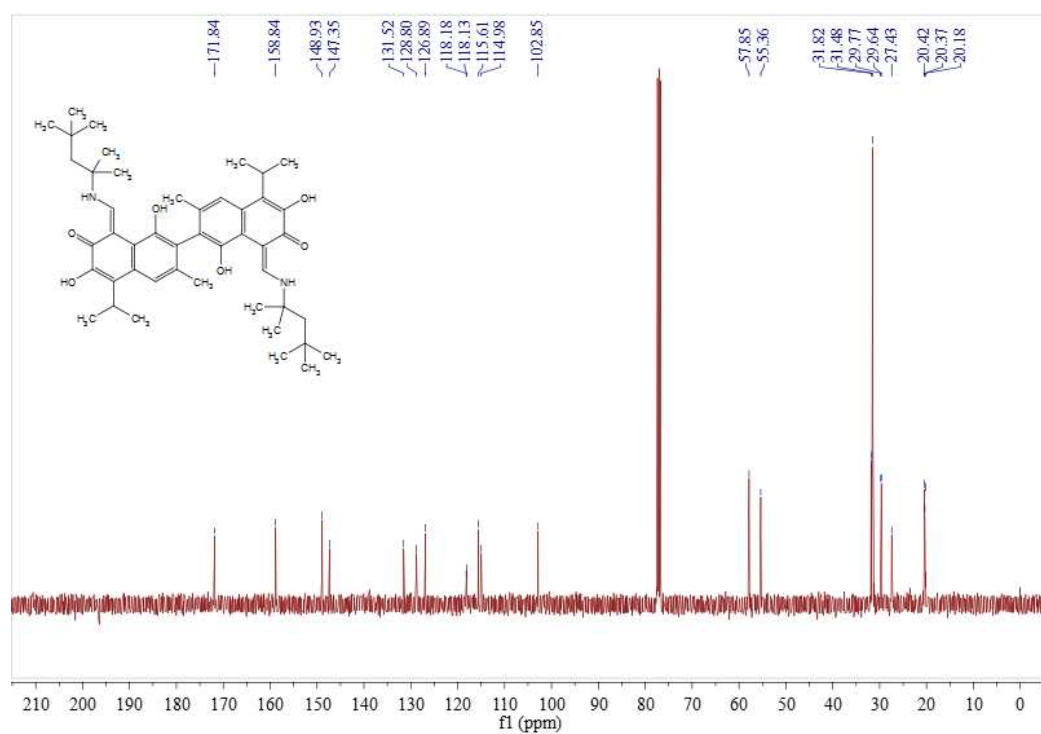
### $^{13}\text{C}$ NMR of compound 1



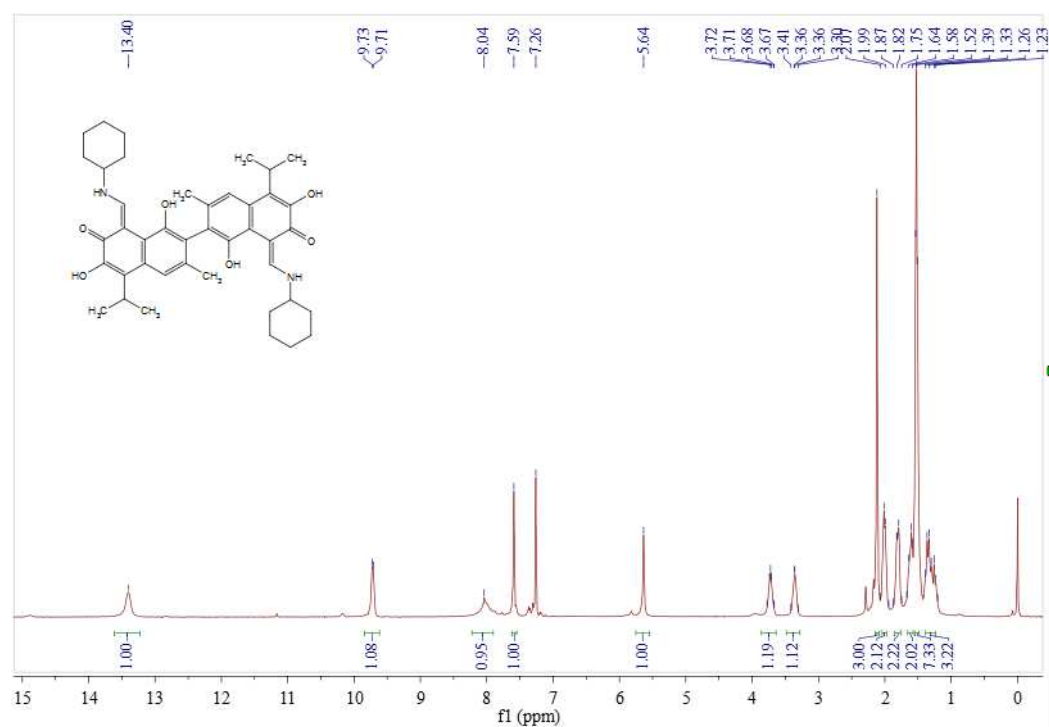
# <sup>1</sup>H NMR of compound 2



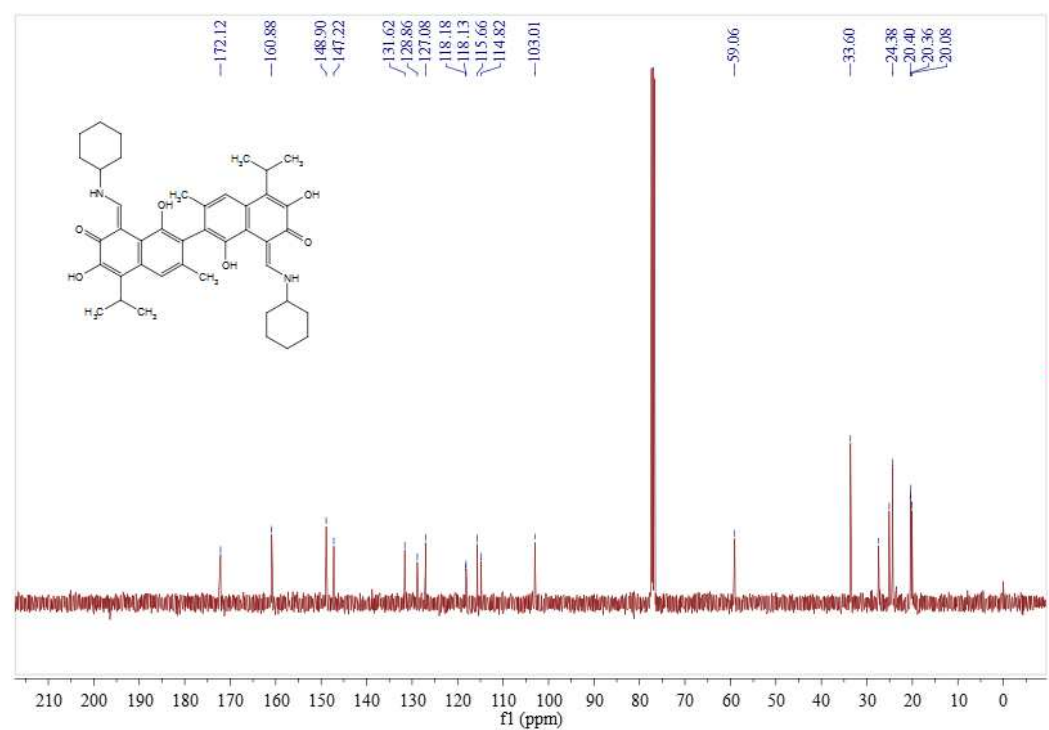
# <sup>13</sup>C NMR of compound 2



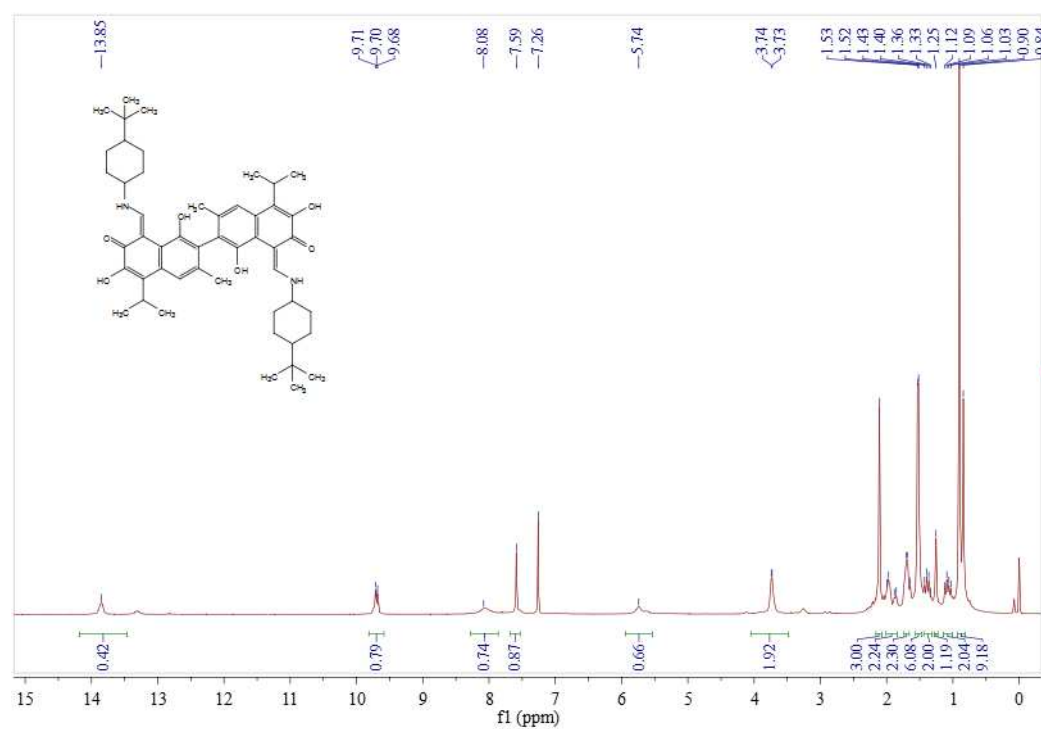
### <sup>1</sup>H NMR of compound 3



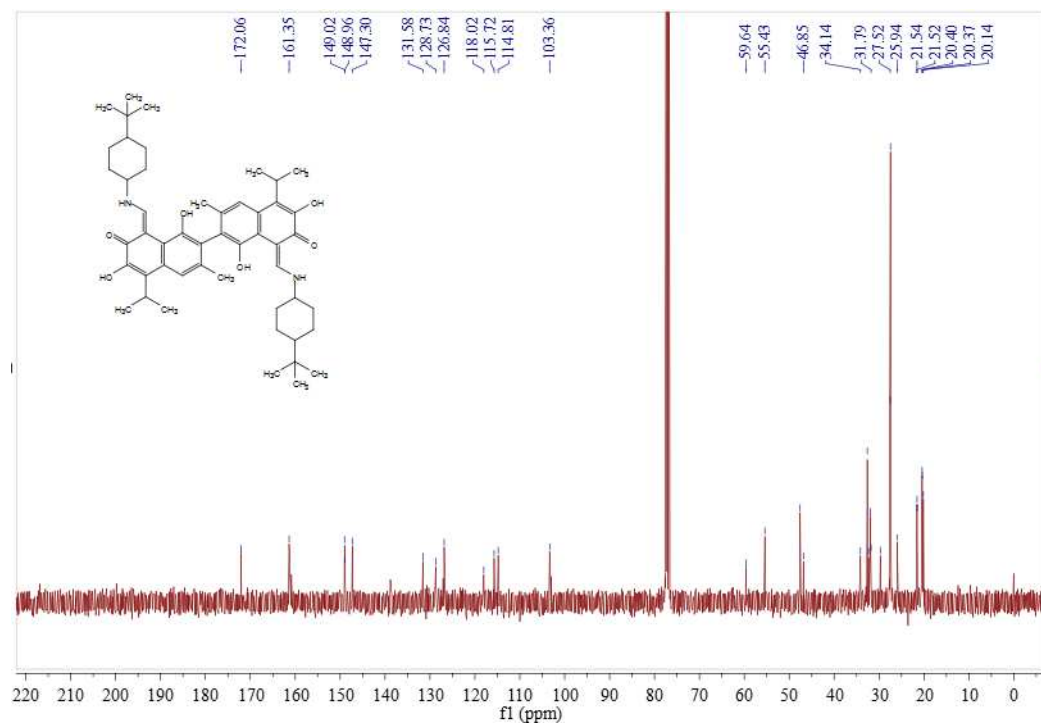
### <sup>13</sup>C NMR of compound 3



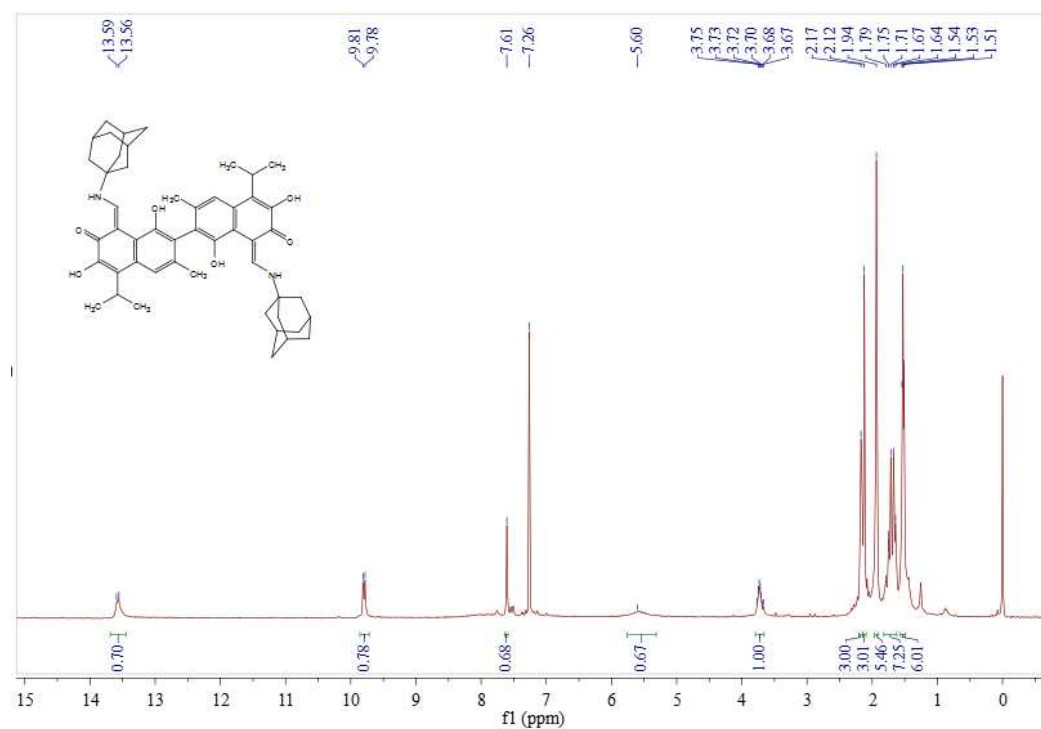
# <sup>1</sup>H NMR of compound 4



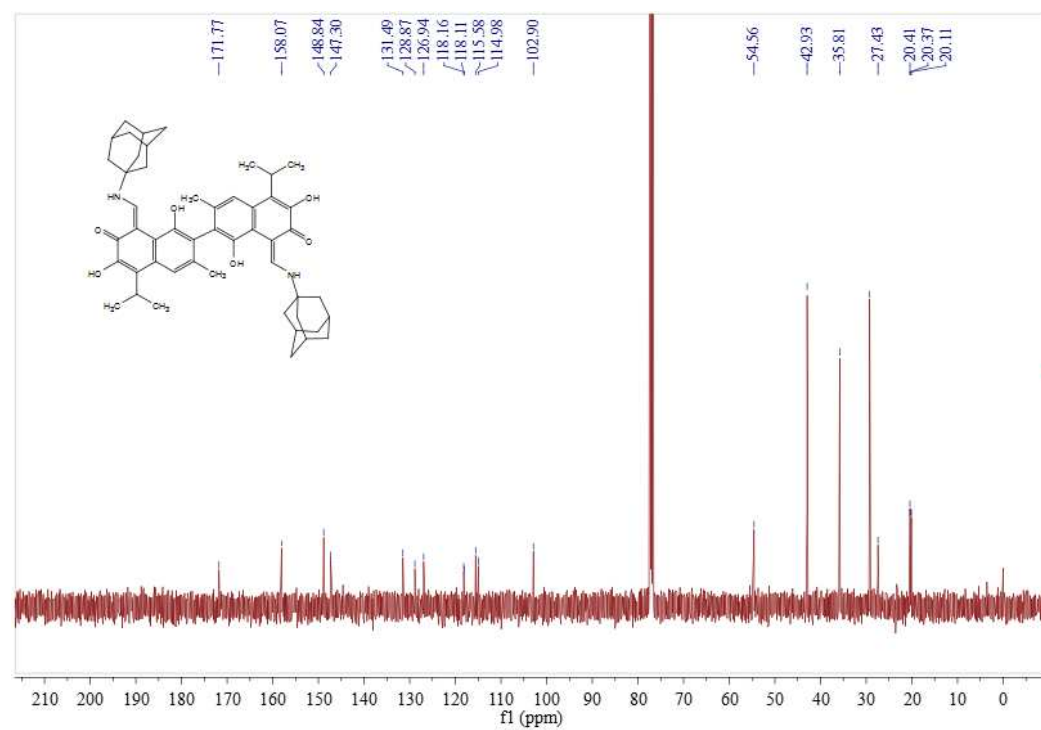
# <sup>13</sup>C NMR of compound 4



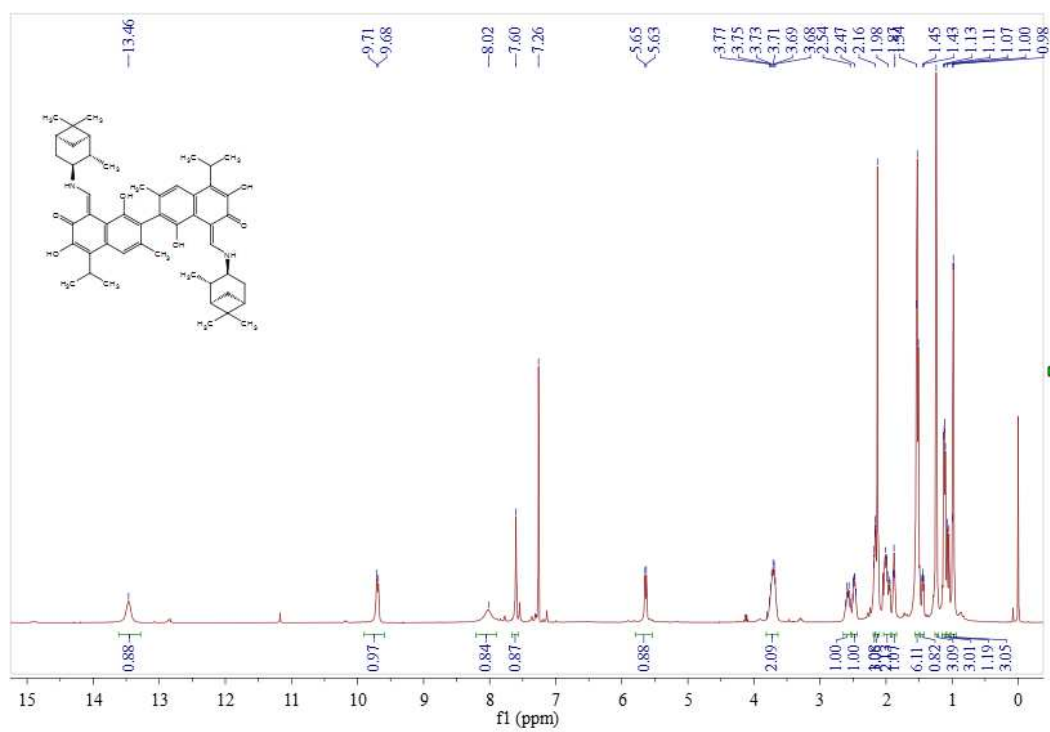
# <sup>1</sup>H NMR of compound 5



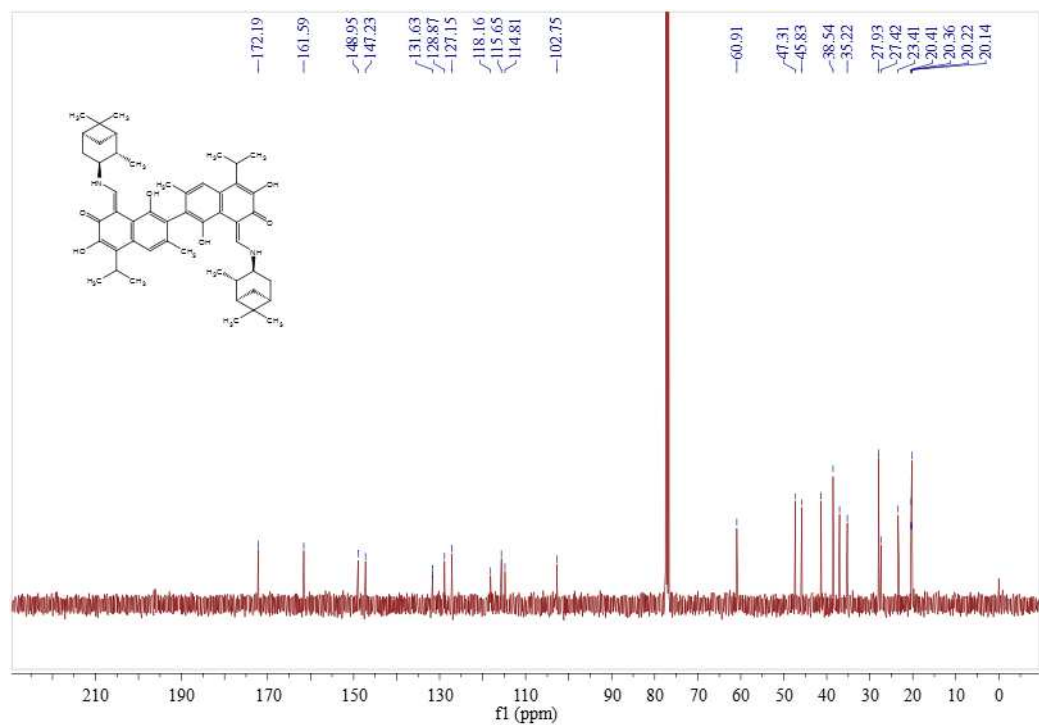
# <sup>13</sup>C NMR of compound 5



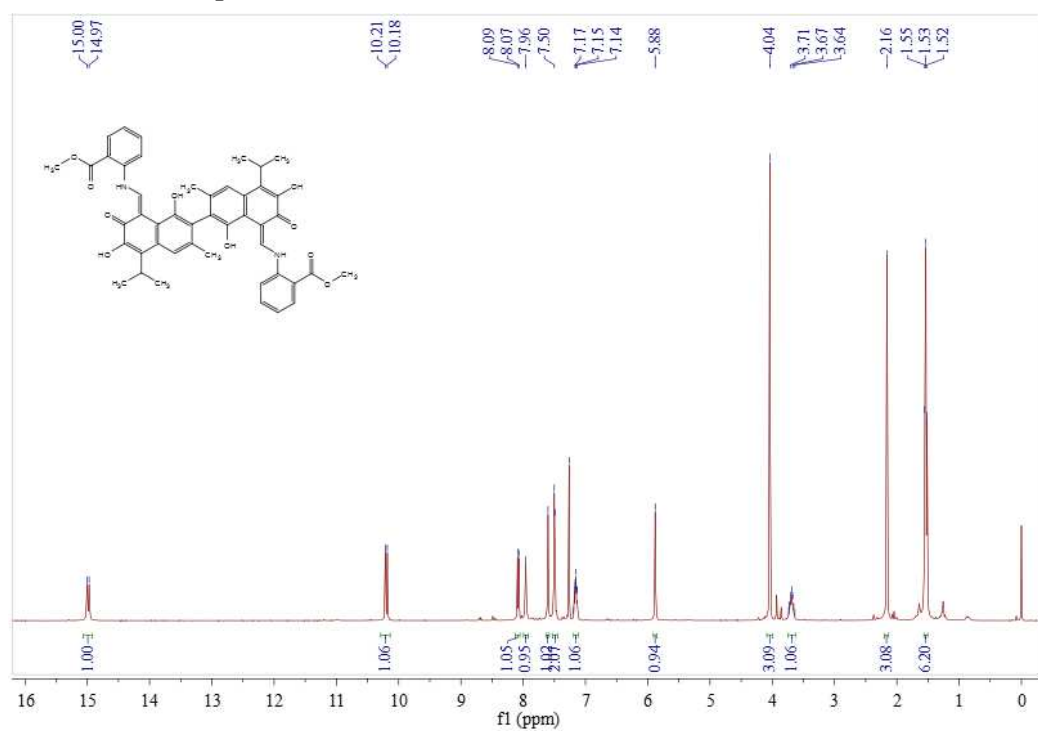
### <sup>1</sup>H NMR of compound 6



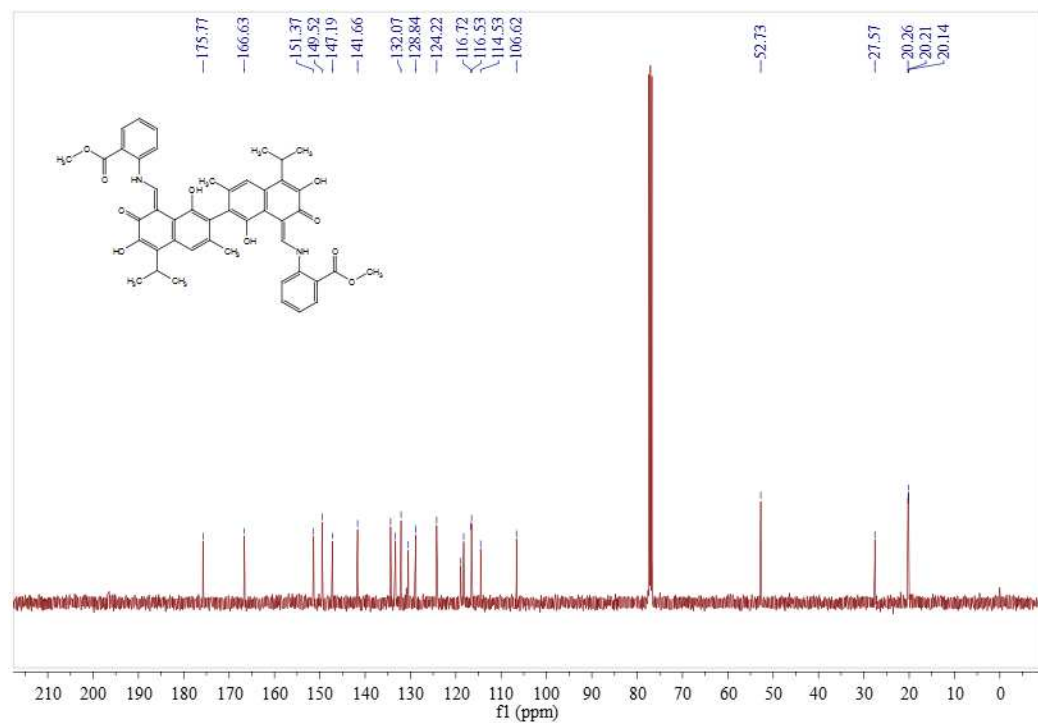
### <sup>13</sup>C NMR of compound 6



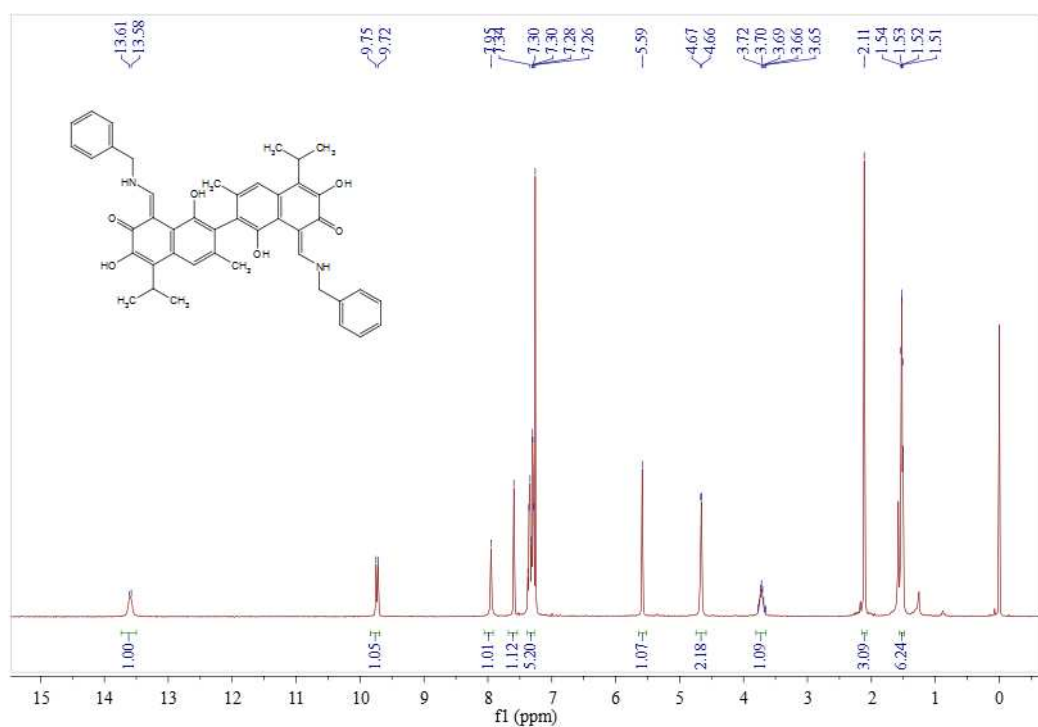
# <sup>1</sup>H NMR of compound 7



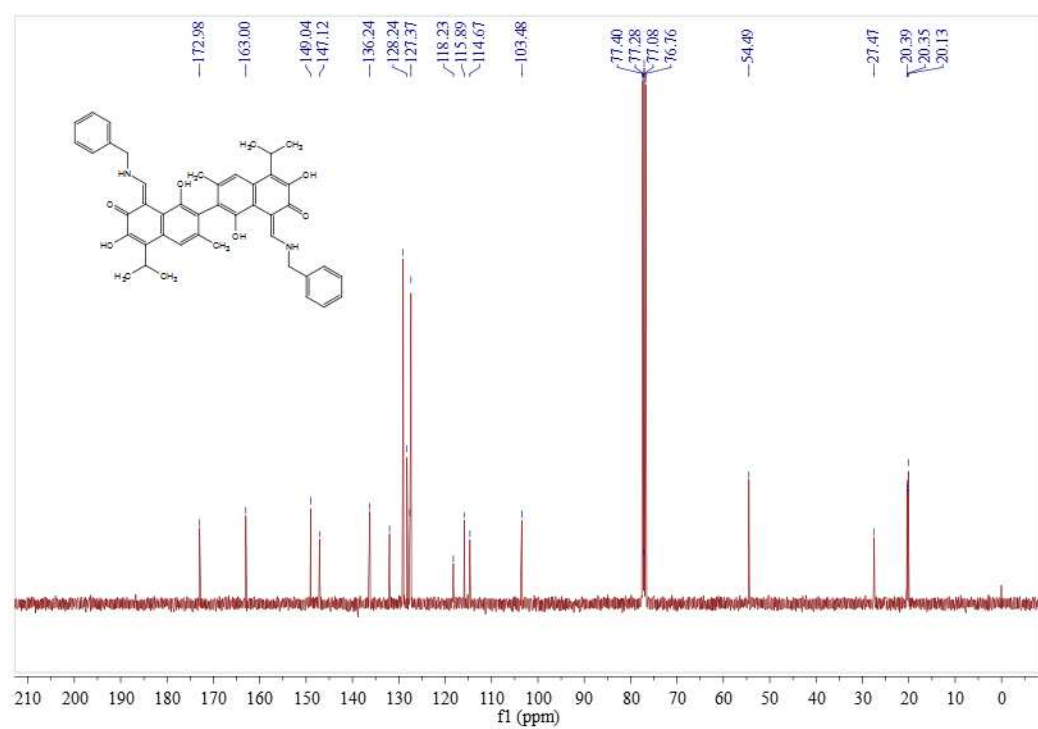
# <sup>13</sup>C NMR of compound 7



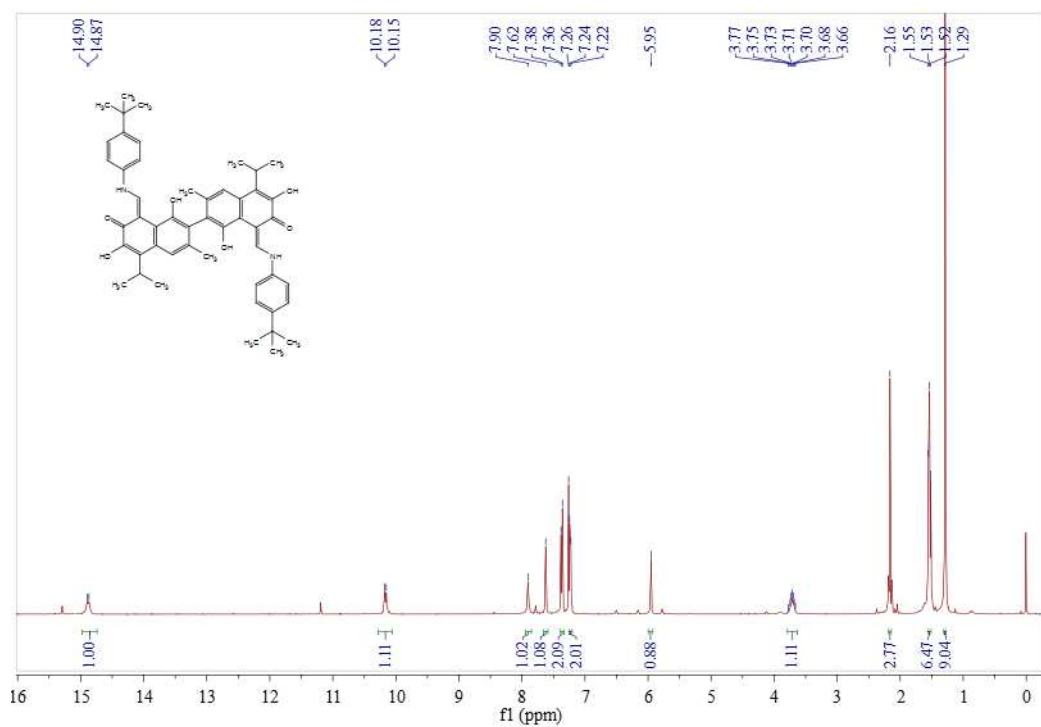
# <sup>1</sup>H NMR of compound 8



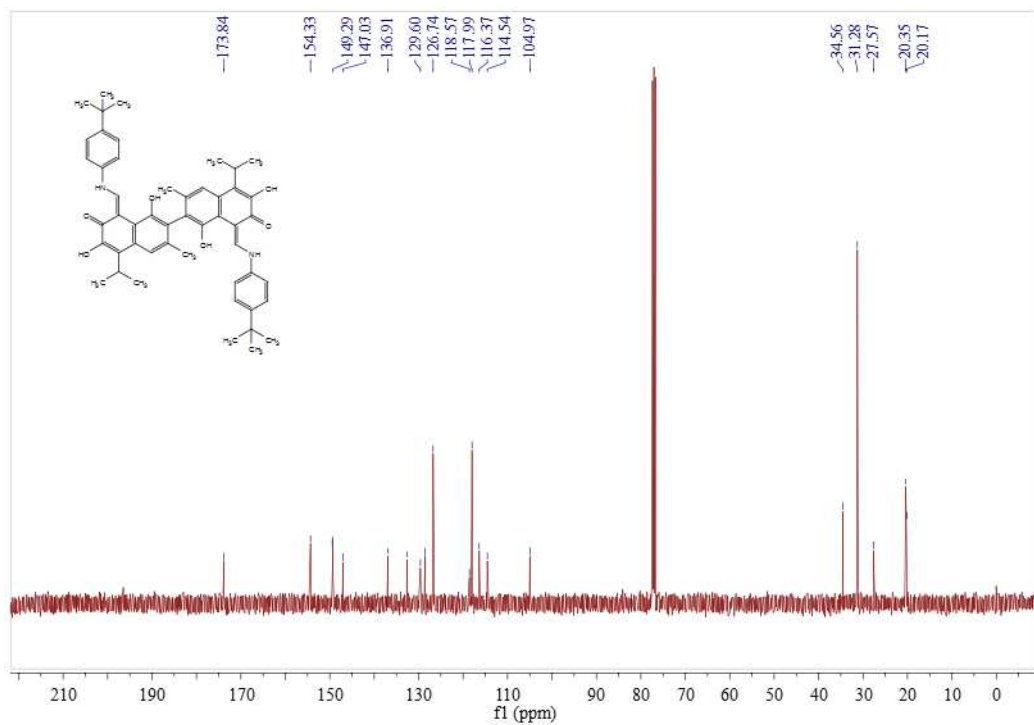
# <sup>13</sup>C NMR of compound 8



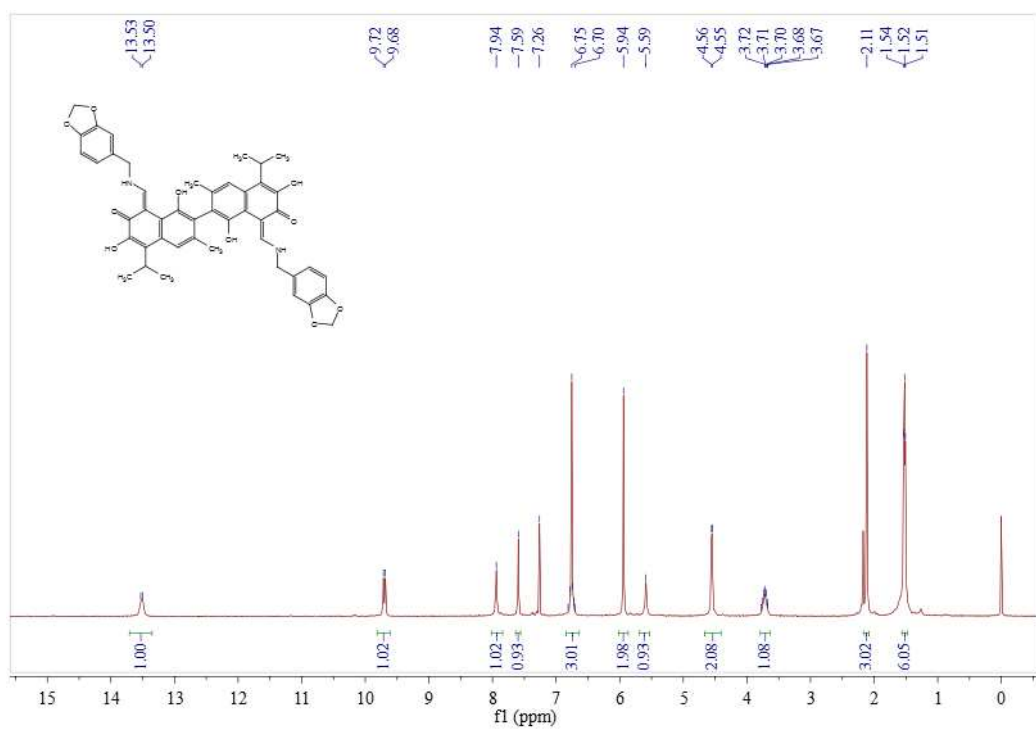
# <sup>1</sup>H NMR of compound 9



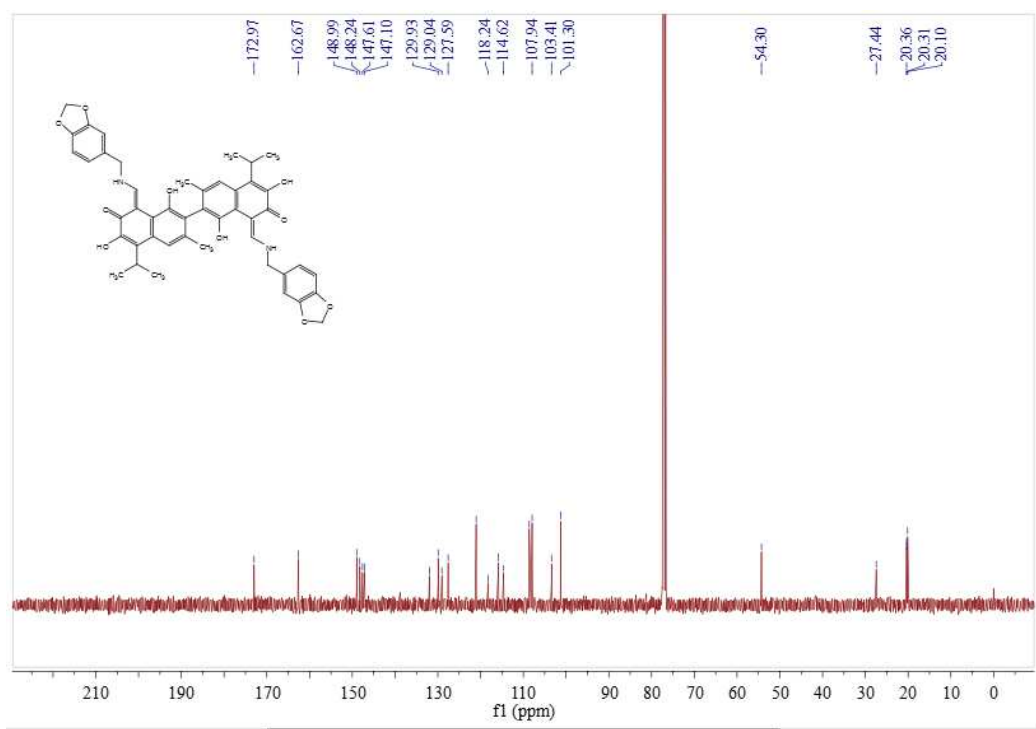
# <sup>13</sup>C NMR of compound 9



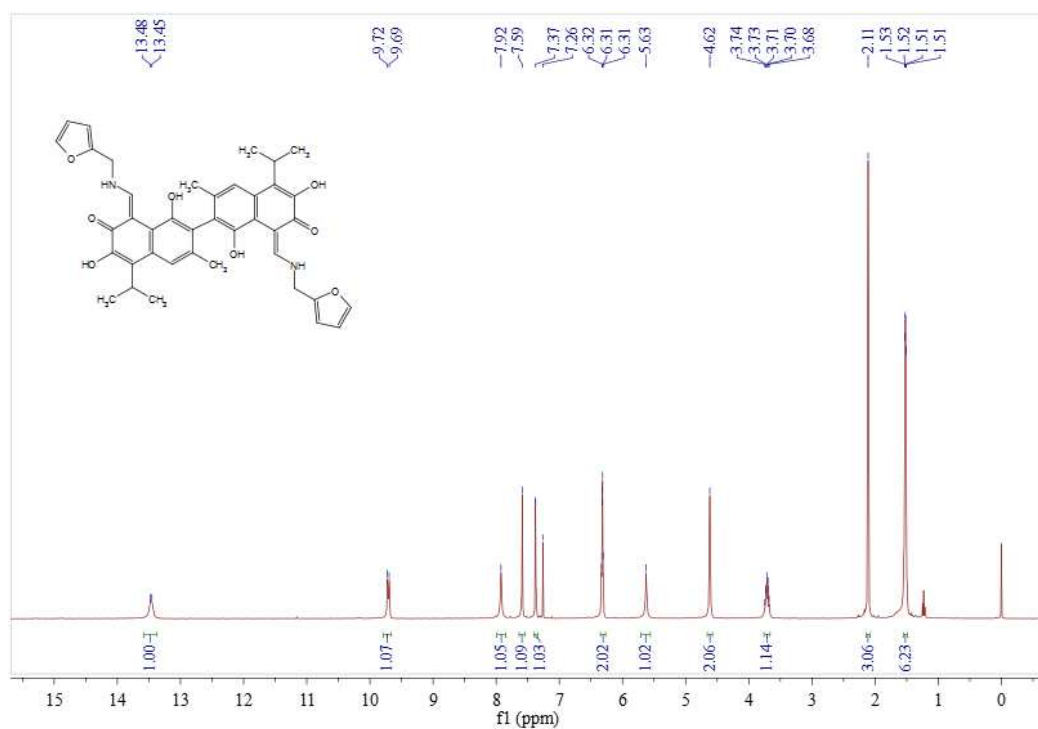
# <sup>1</sup>H NMR of compound 10



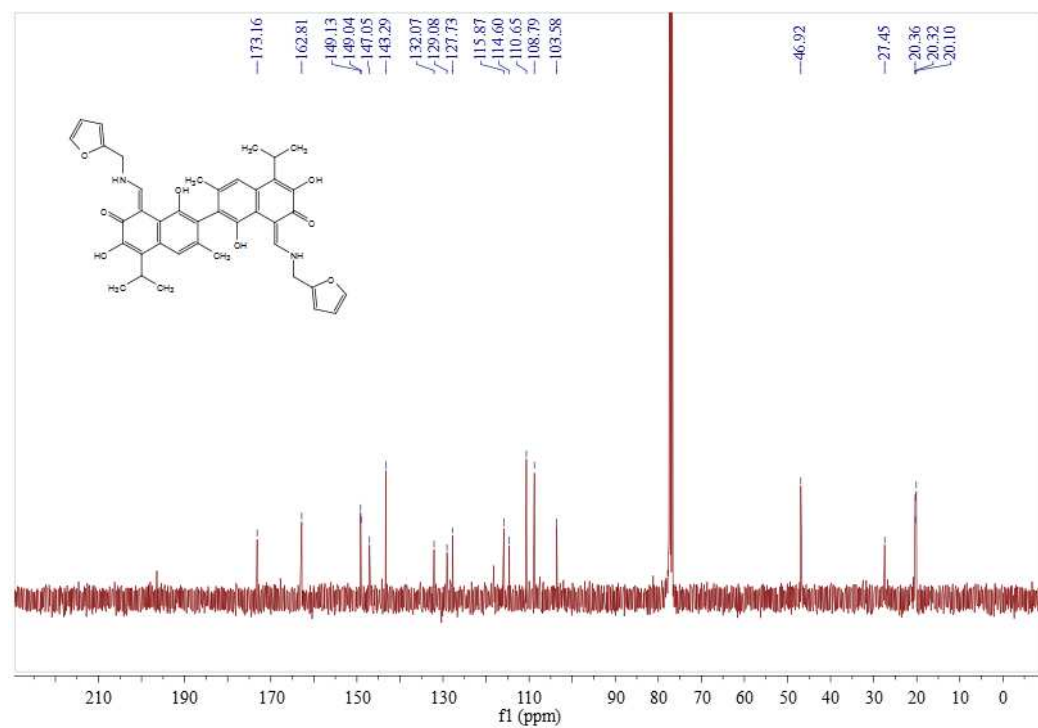
# <sup>13</sup>C NMR of compound 10



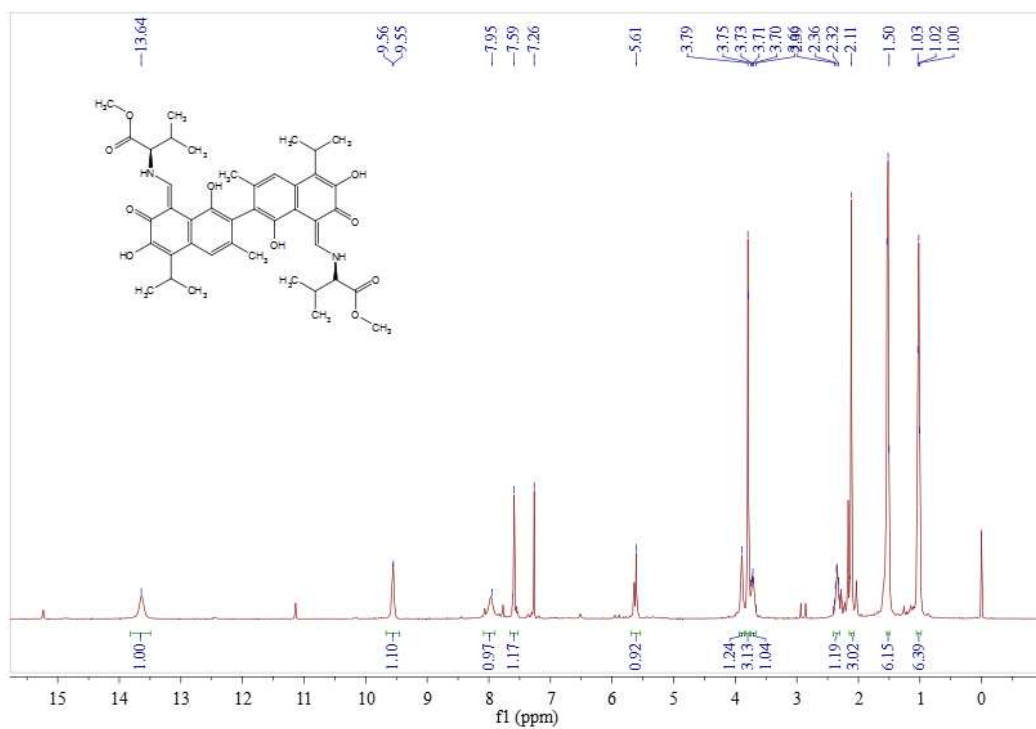
# <sup>1</sup>H NMR of compound 11



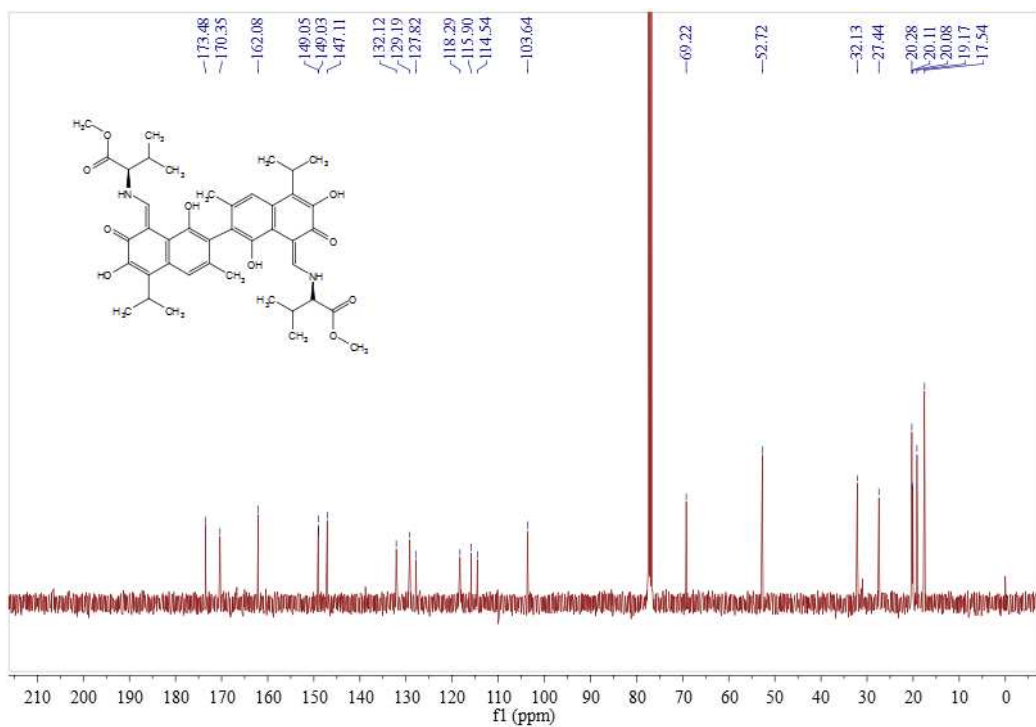
# <sup>13</sup>C NMR of compound 11



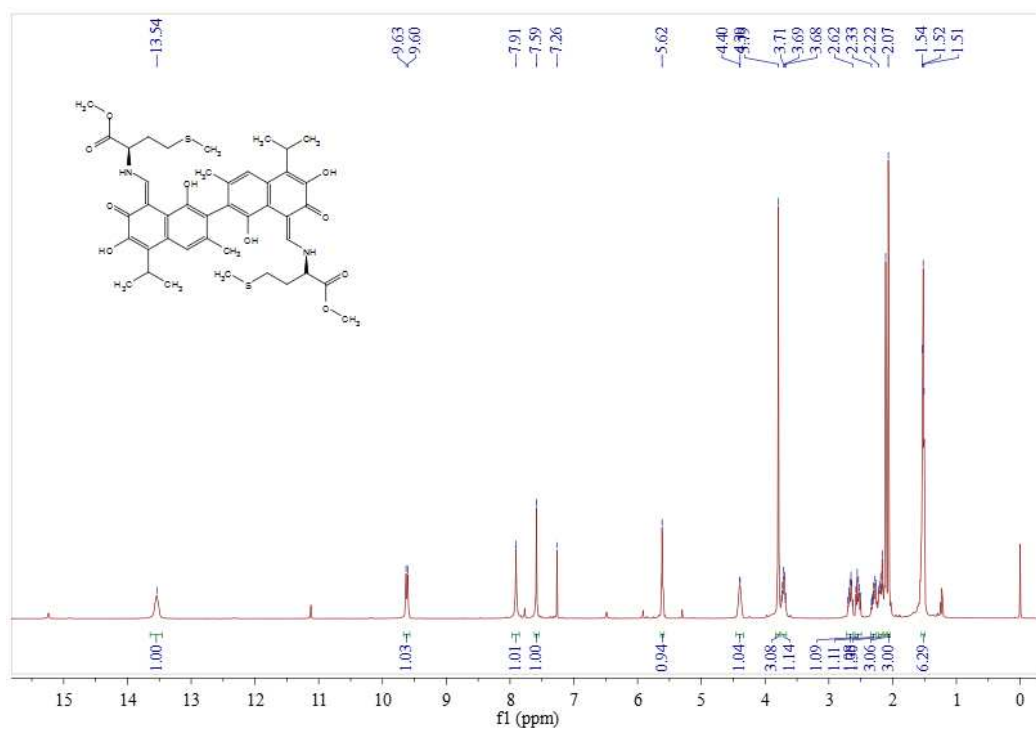
# <sup>1</sup>H NMR of compound 12



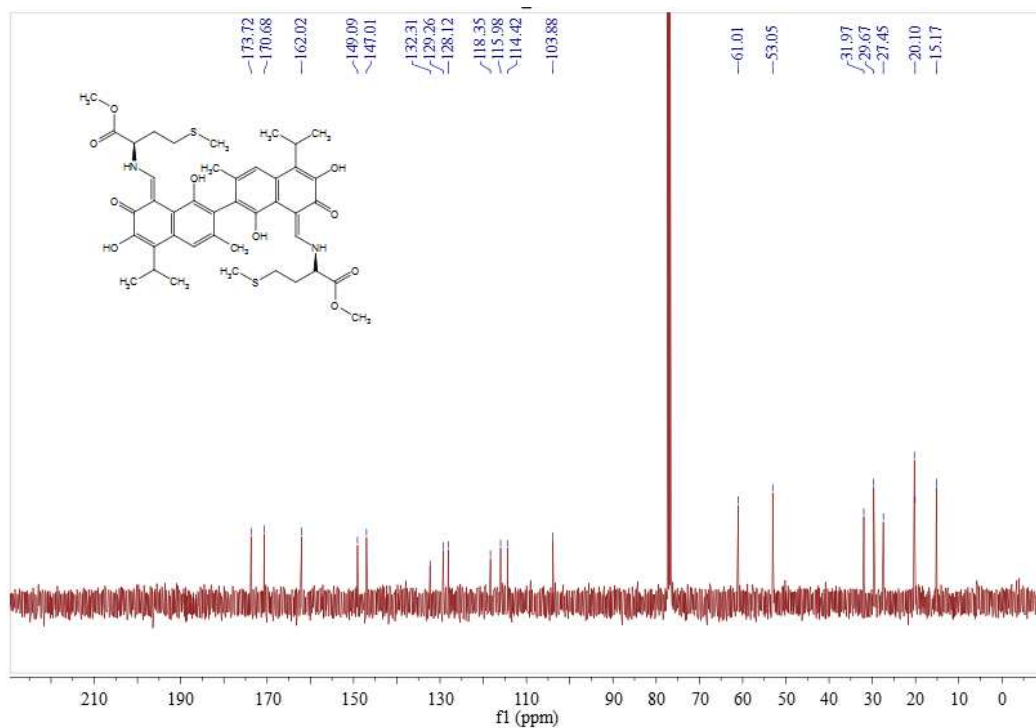
# <sup>13</sup>C NMR of compound 12



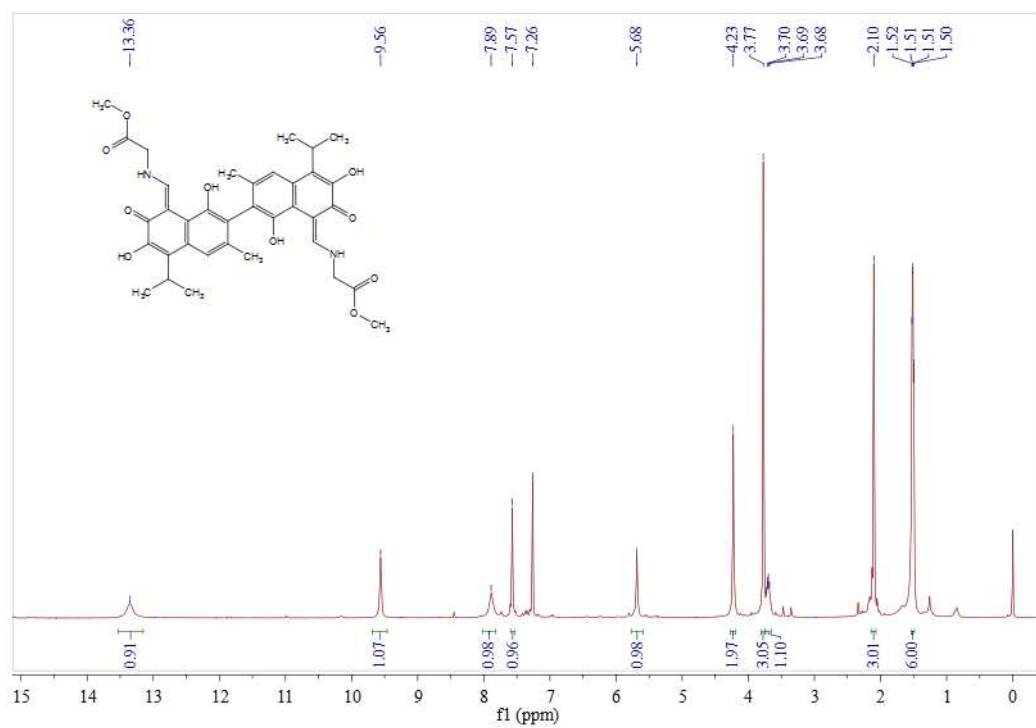
# <sup>1</sup>H NMR of compound 13



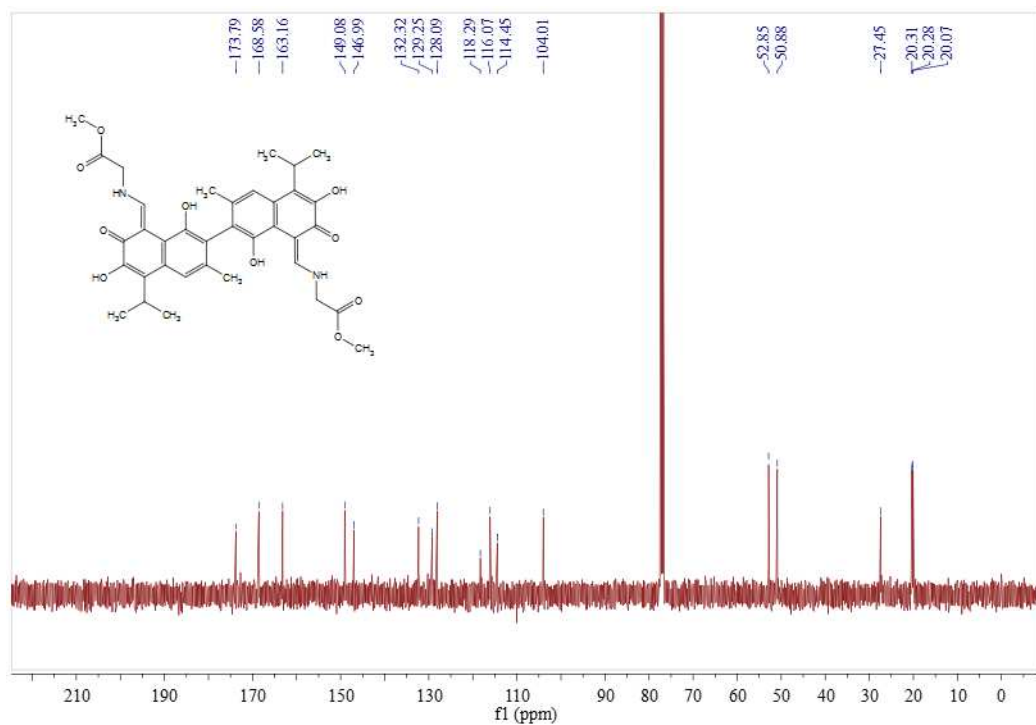
# <sup>13</sup>C NMR of compound 13



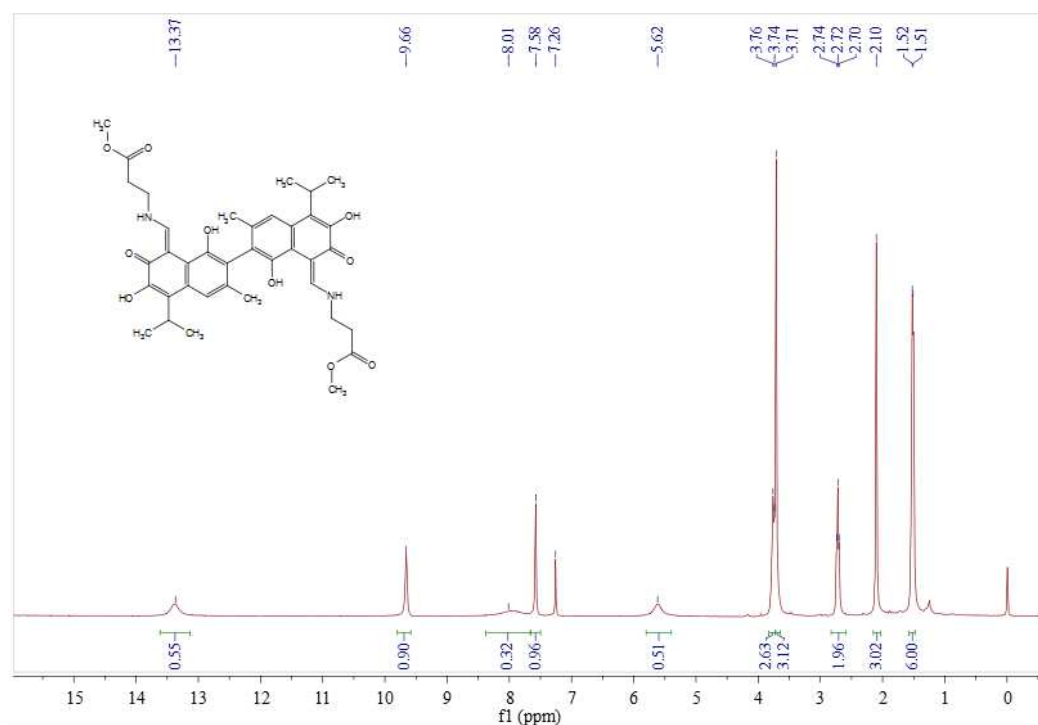
# <sup>1</sup>H NMR of compound 14



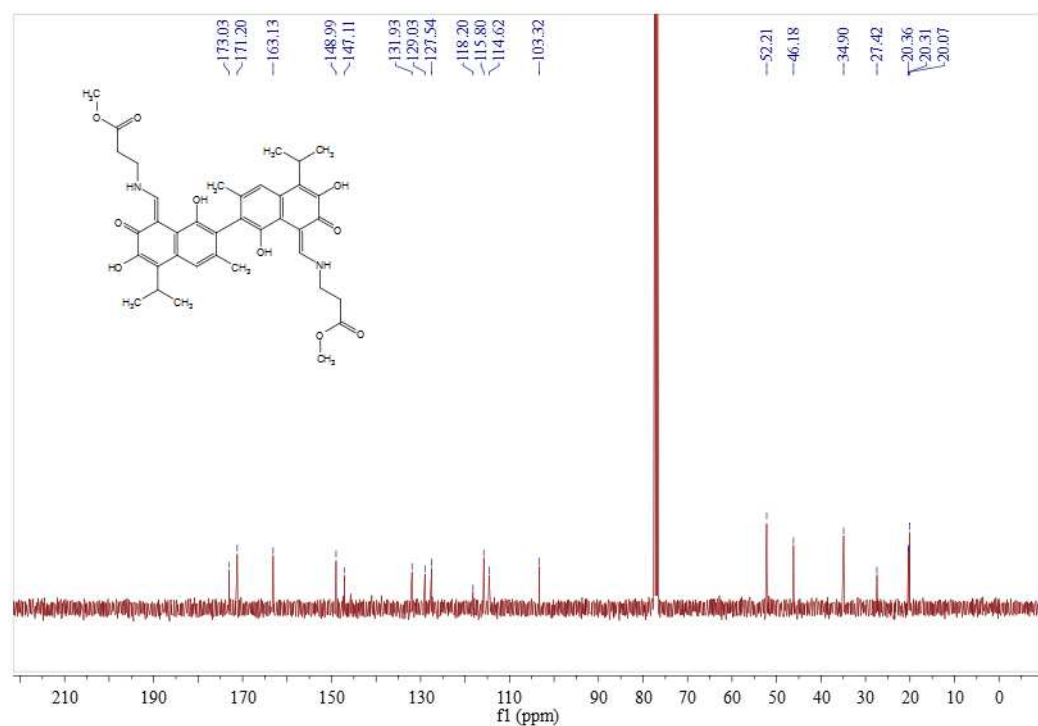
# <sup>13</sup>C NMR of compound 14



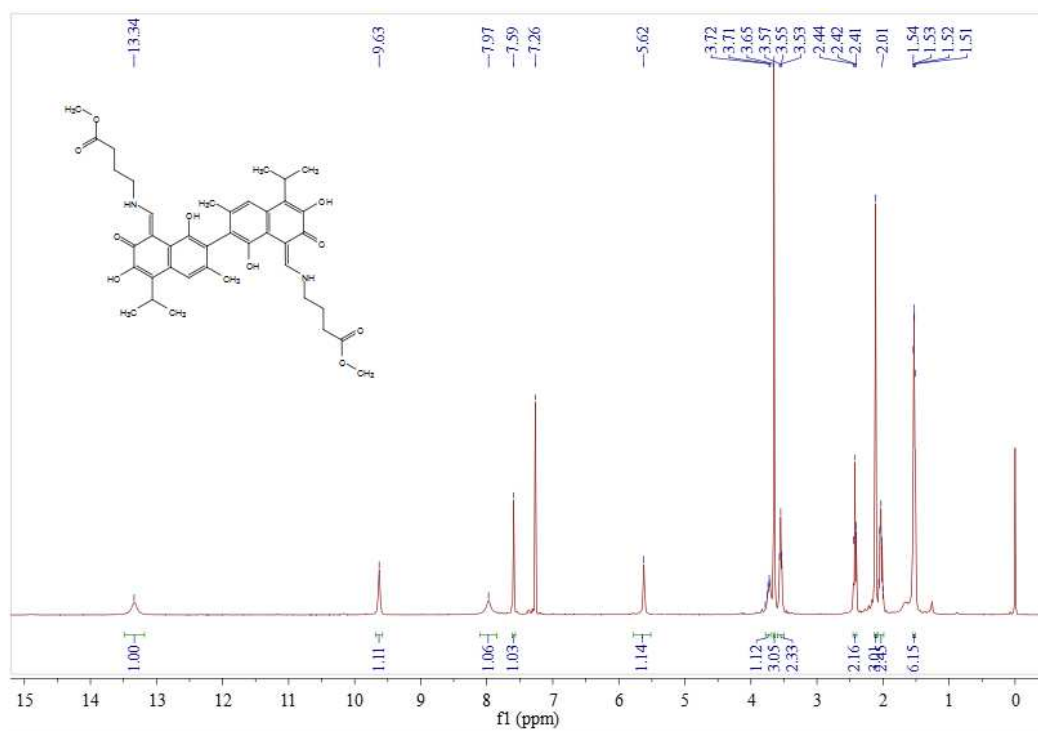
# <sup>1</sup>H NMR of compound 15



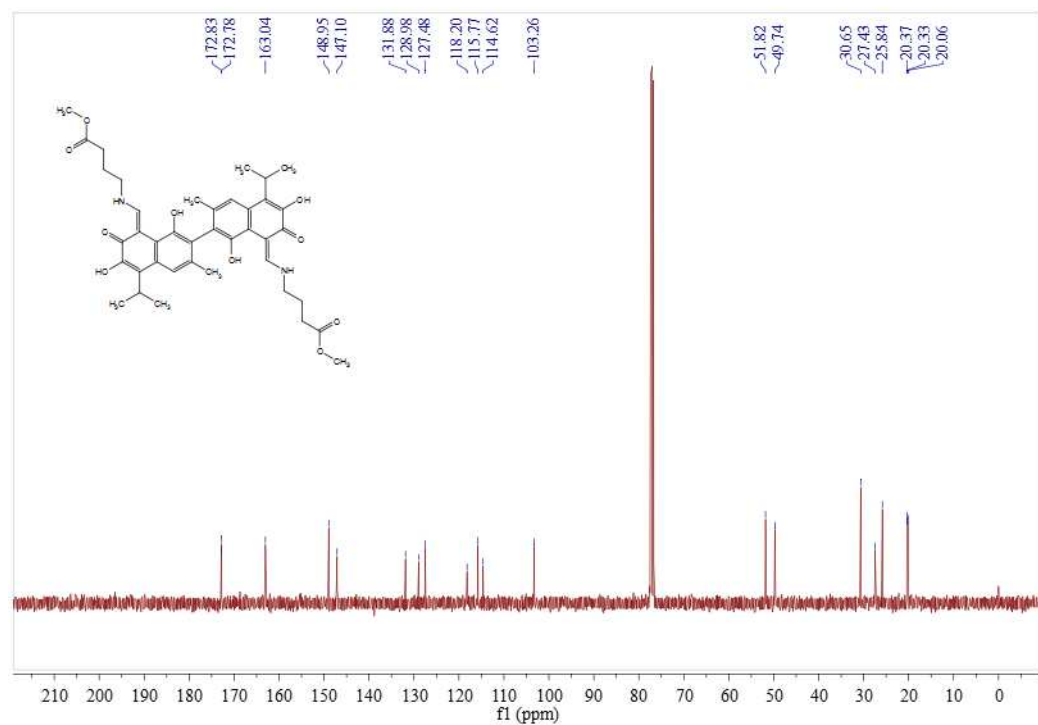
# <sup>13</sup>C NMR of compound 15



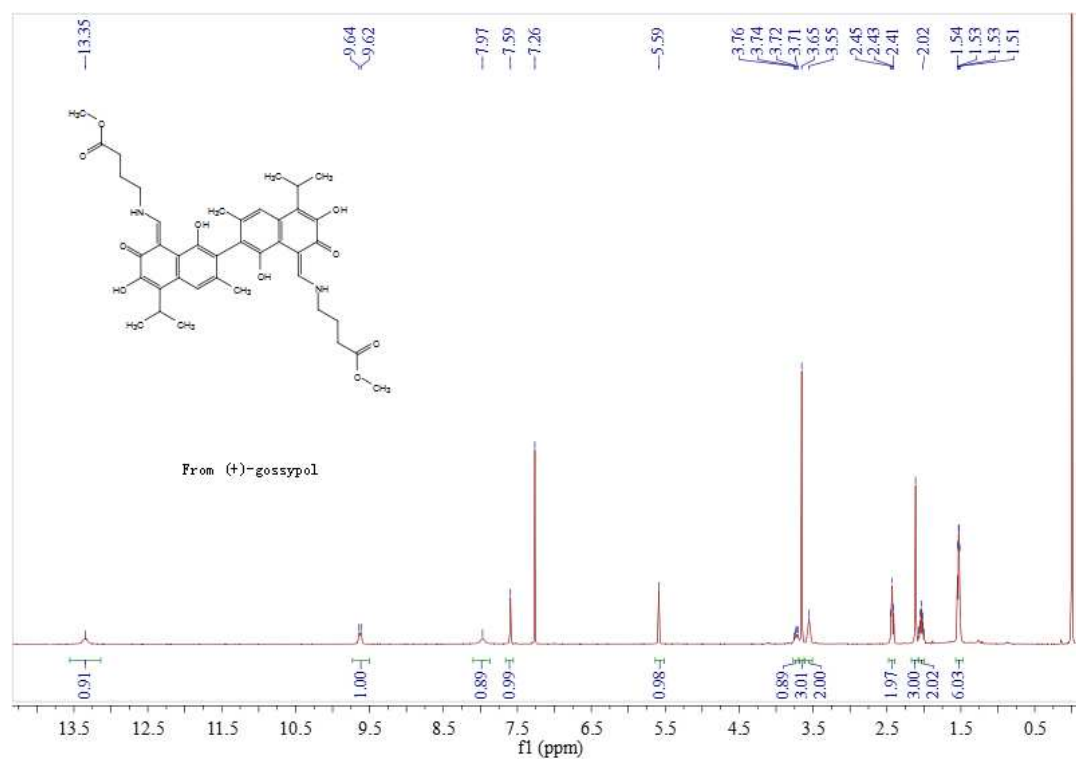
# <sup>1</sup>H NMR of compound 16



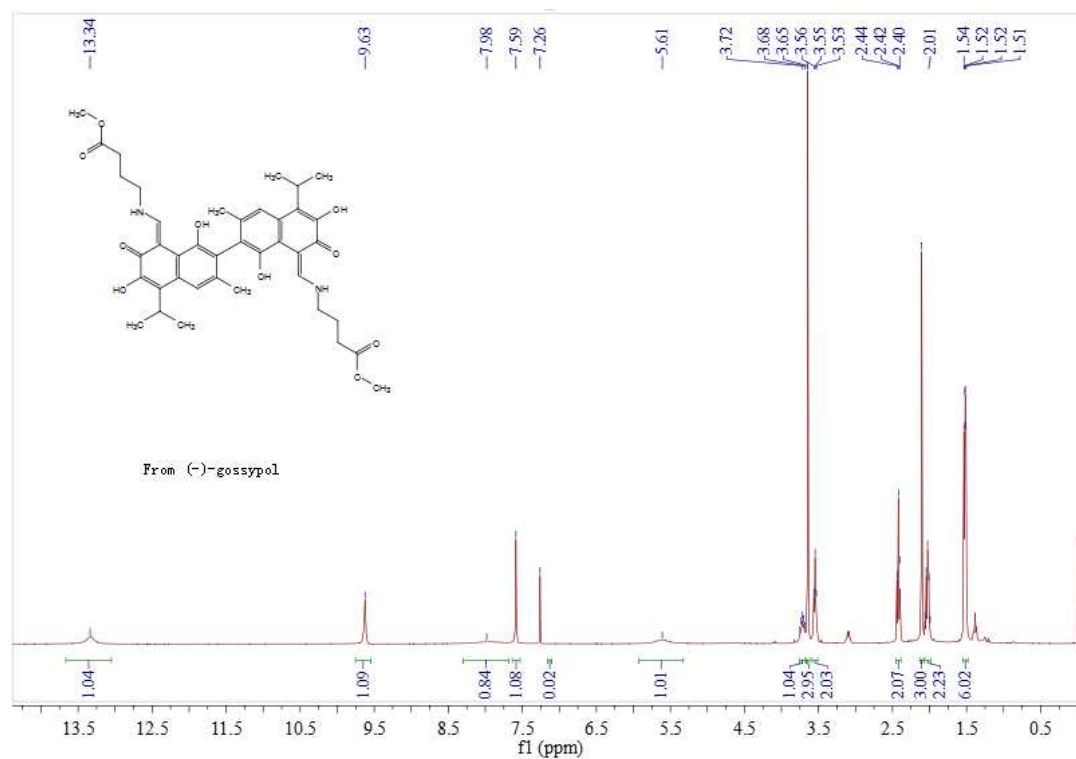
# <sup>13</sup>C NMR of compound 16



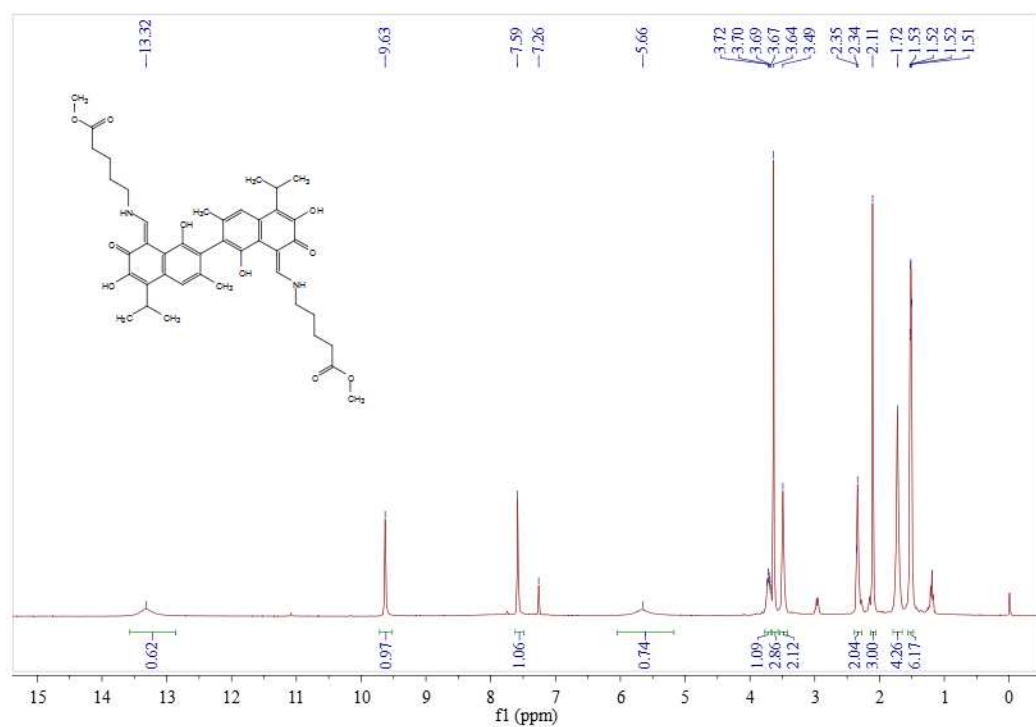
# <sup>1</sup>H NMR of compound (+)-16



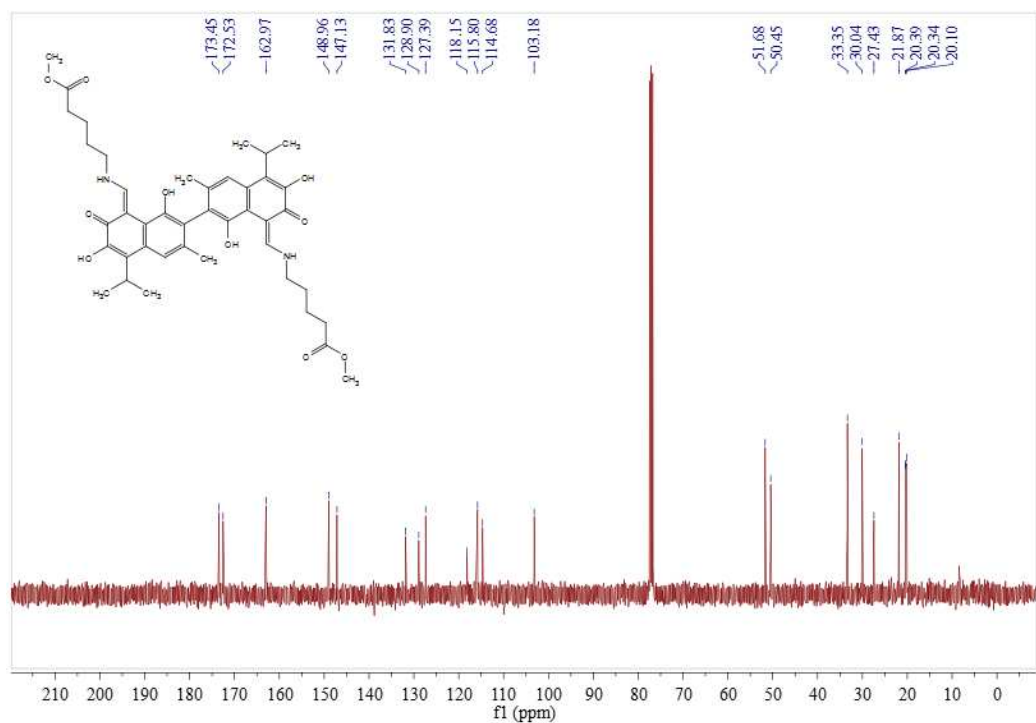
# <sup>1</sup>H NMR of compound (-)-16



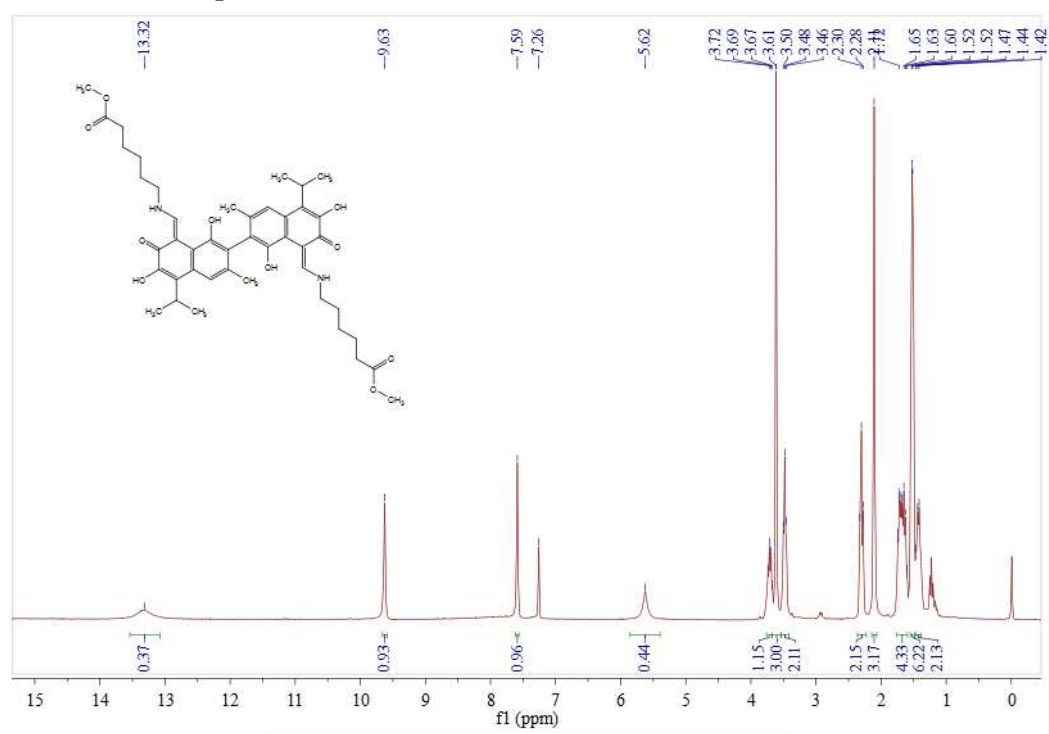
# <sup>1</sup>H NMR of compound 17



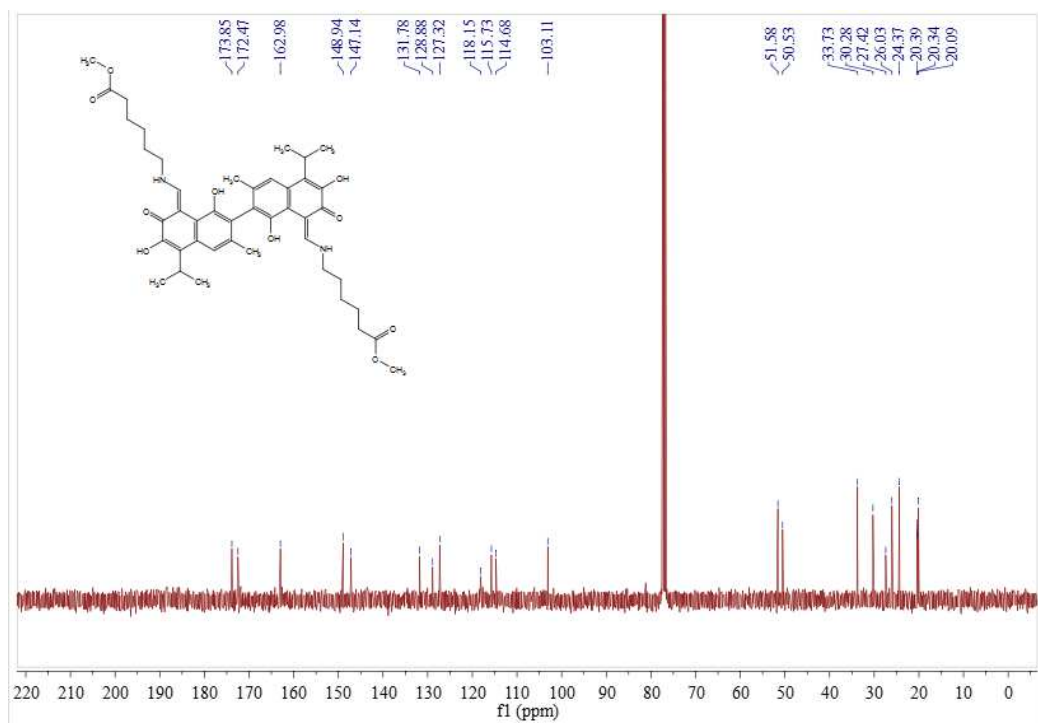
# <sup>13</sup>C NMR of compound 17



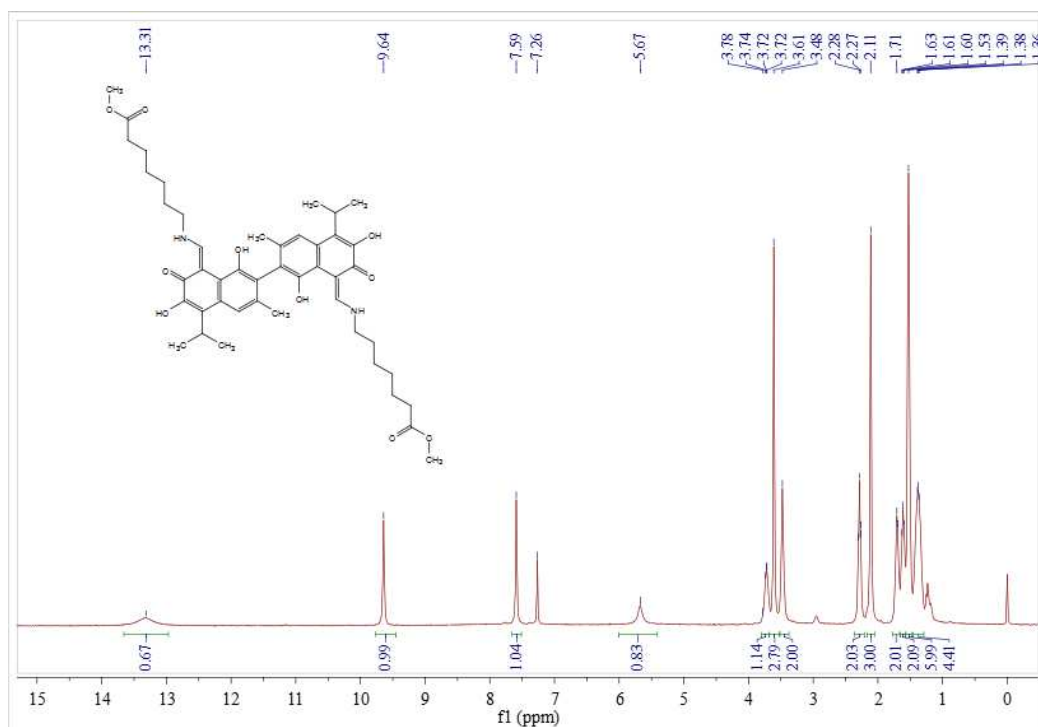
# <sup>1</sup>H NMR of compound 18



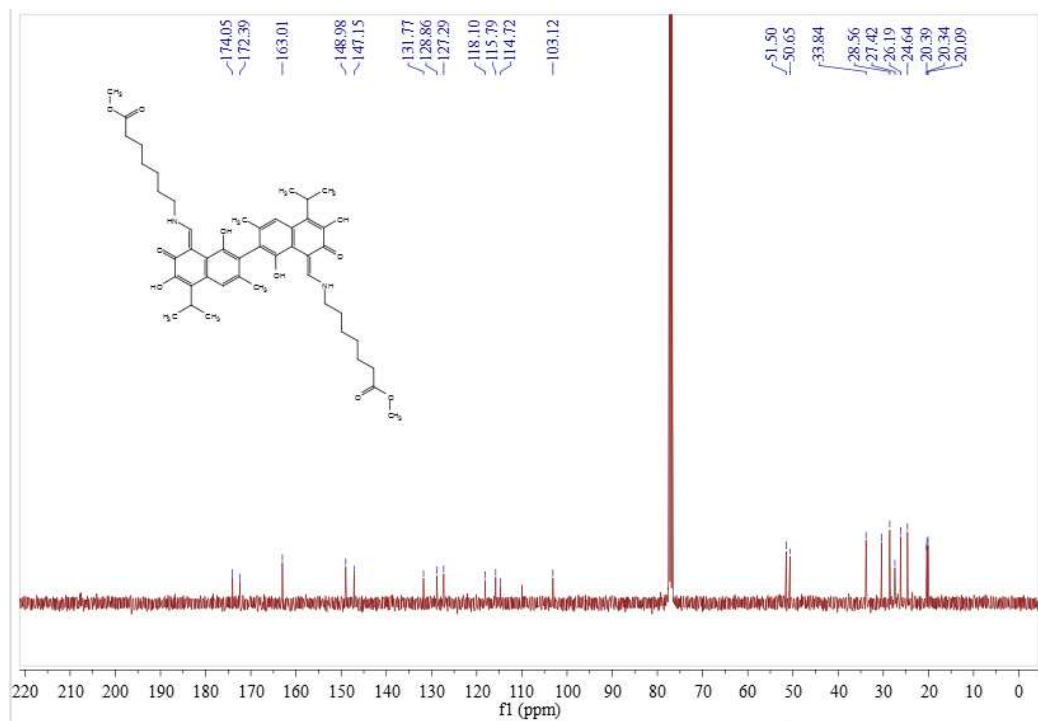
# <sup>13</sup>C NMR of compound 18



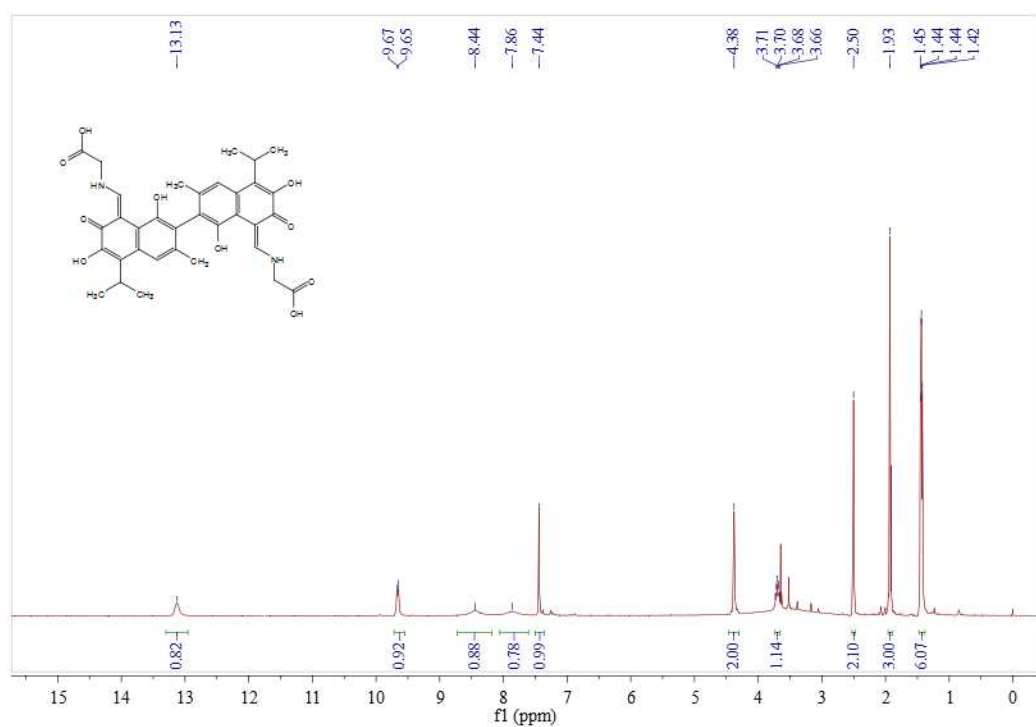
# <sup>1</sup>H NMR of compound 19



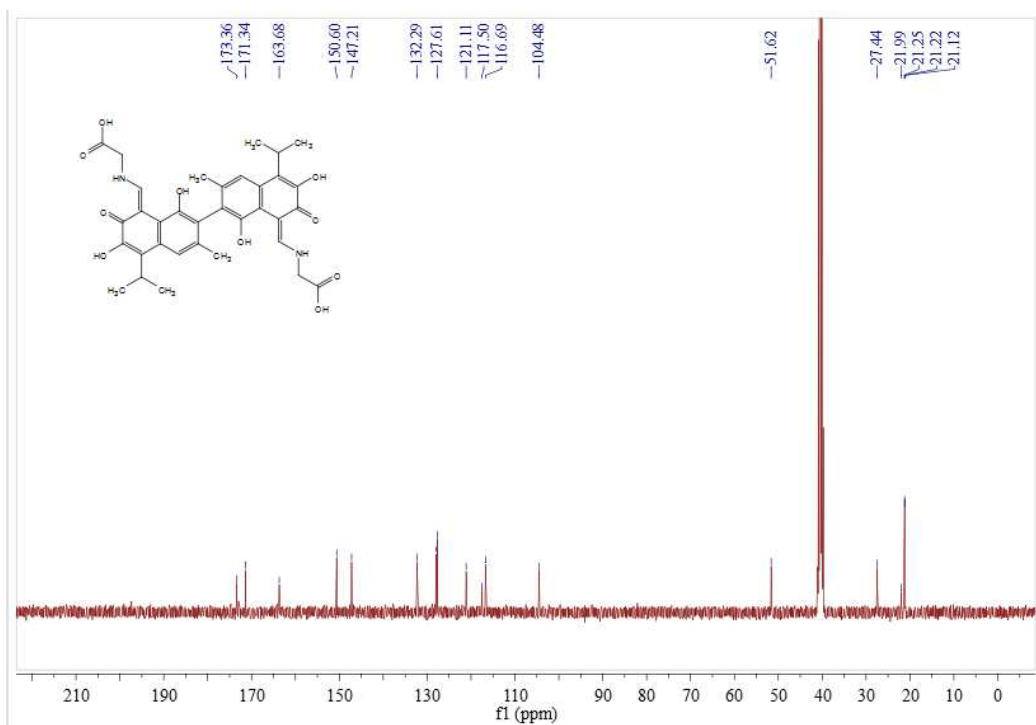
# <sup>13</sup>C NMR of compound 19



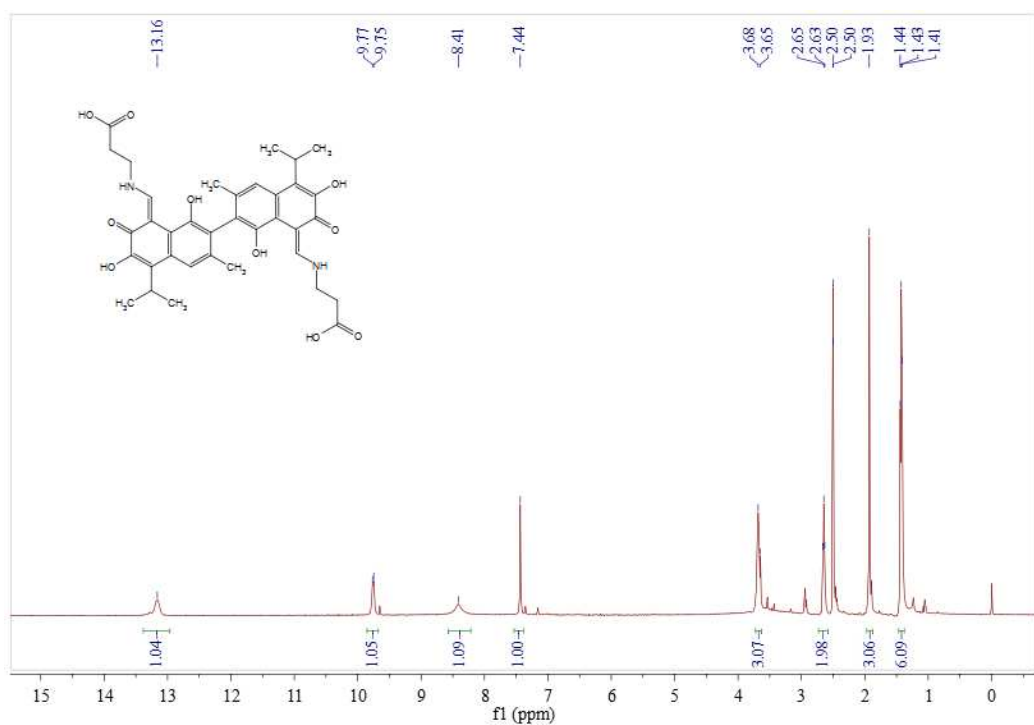
# <sup>1</sup>H NMR of compound 20



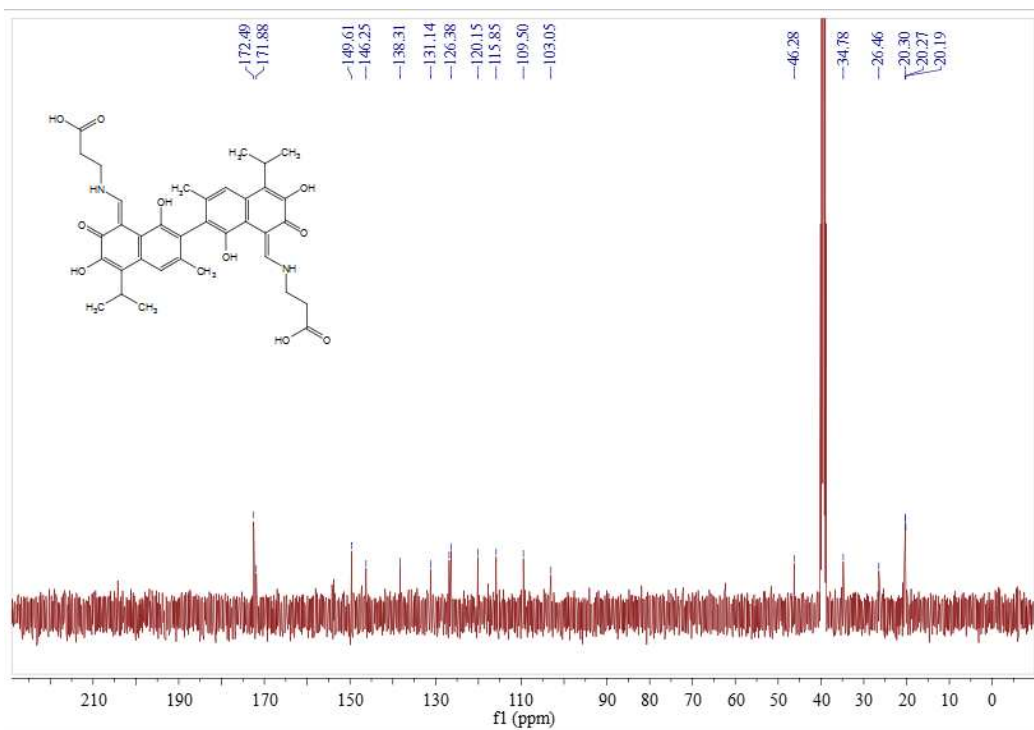
# <sup>13</sup>C NMR of compound 20



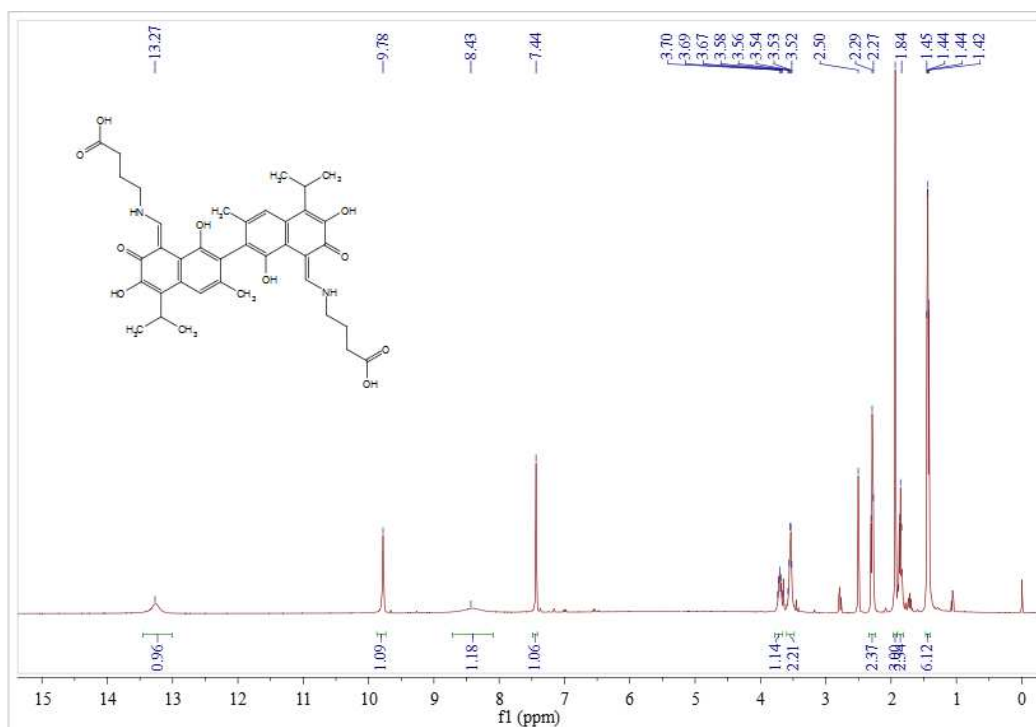
# <sup>1</sup>H NMR of compound 21



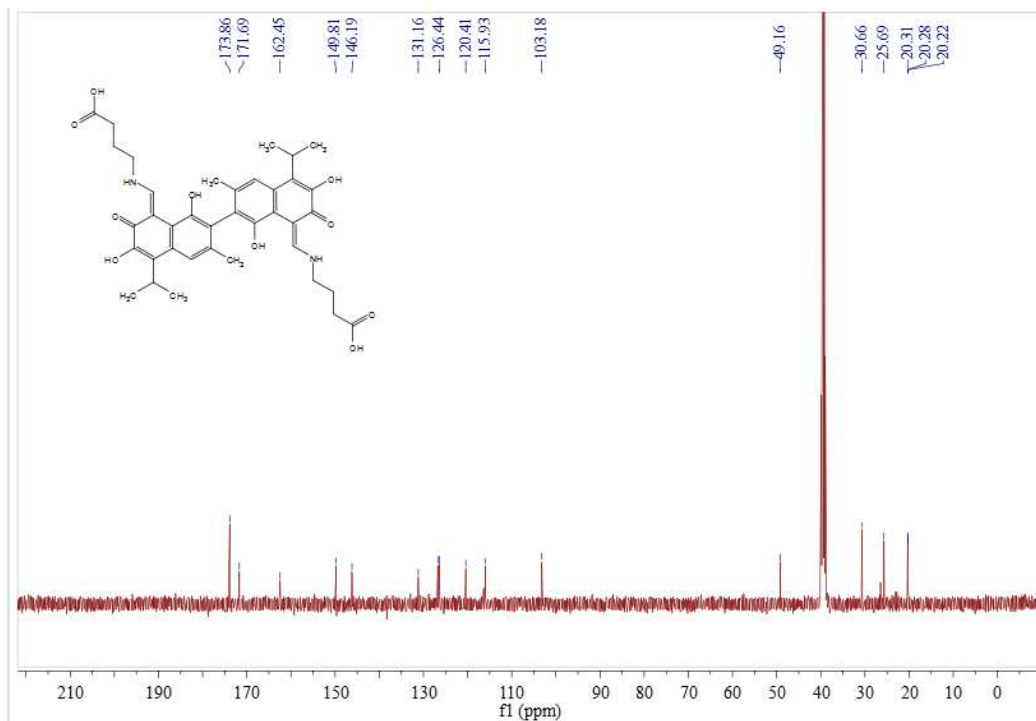
# <sup>13</sup>C NMR of compound 21



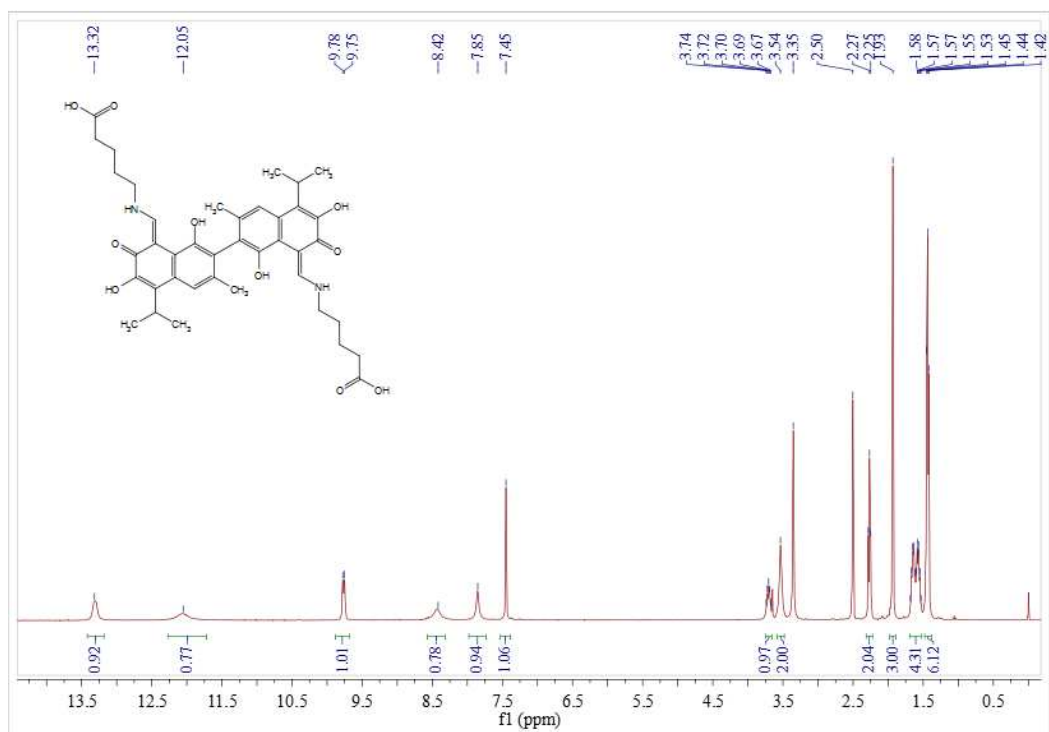
# <sup>1</sup>H NMR of compound 22



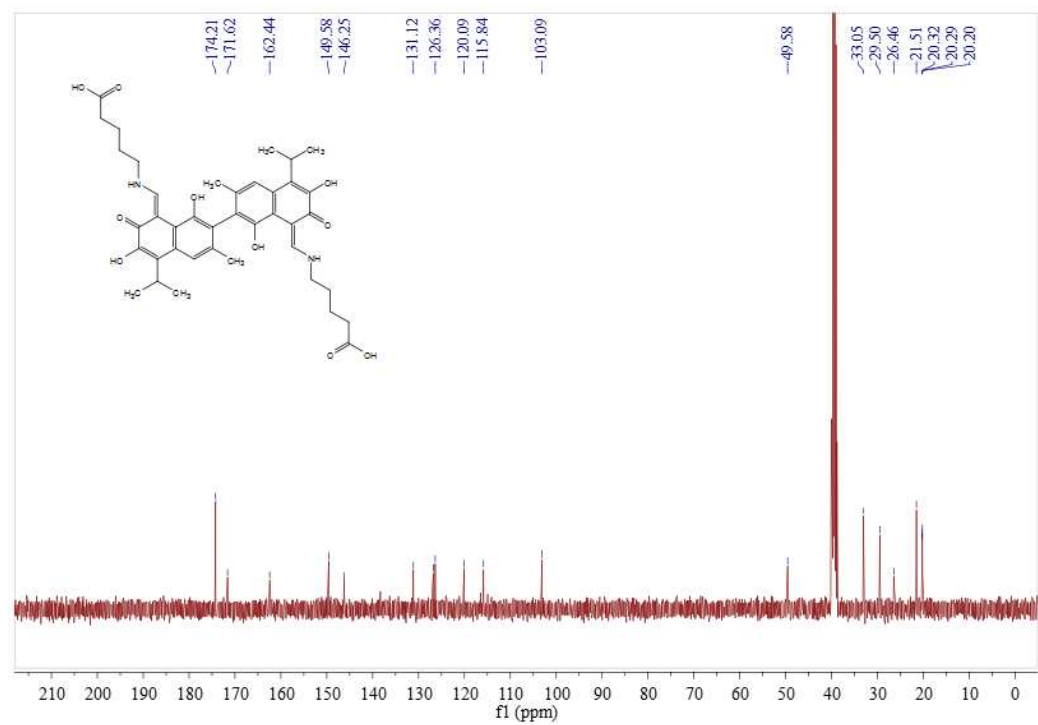
# <sup>13</sup>C NMR of compound 22



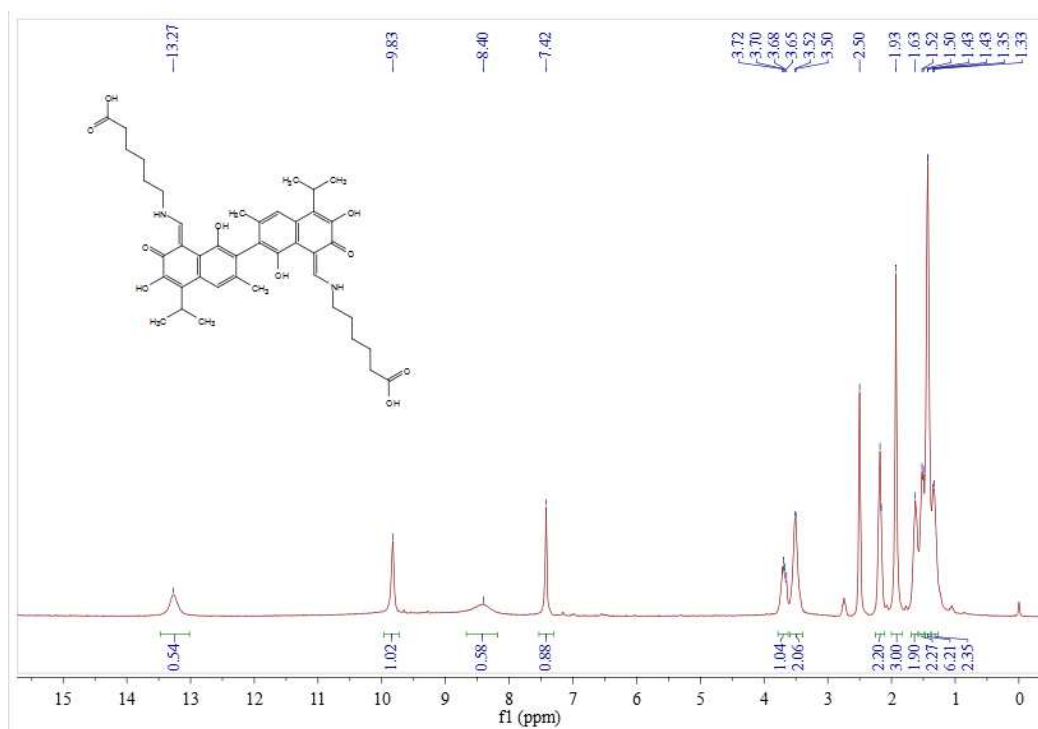
# <sup>1</sup>H NMR of compound 23



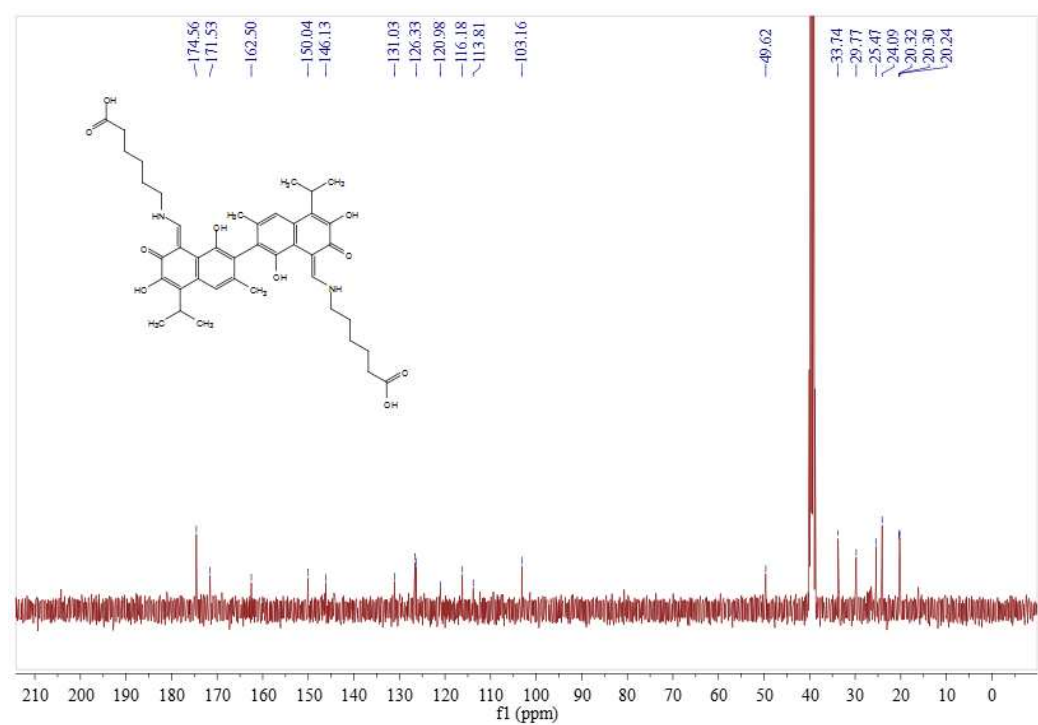
# <sup>13</sup>C NMR spectrum of compound 23



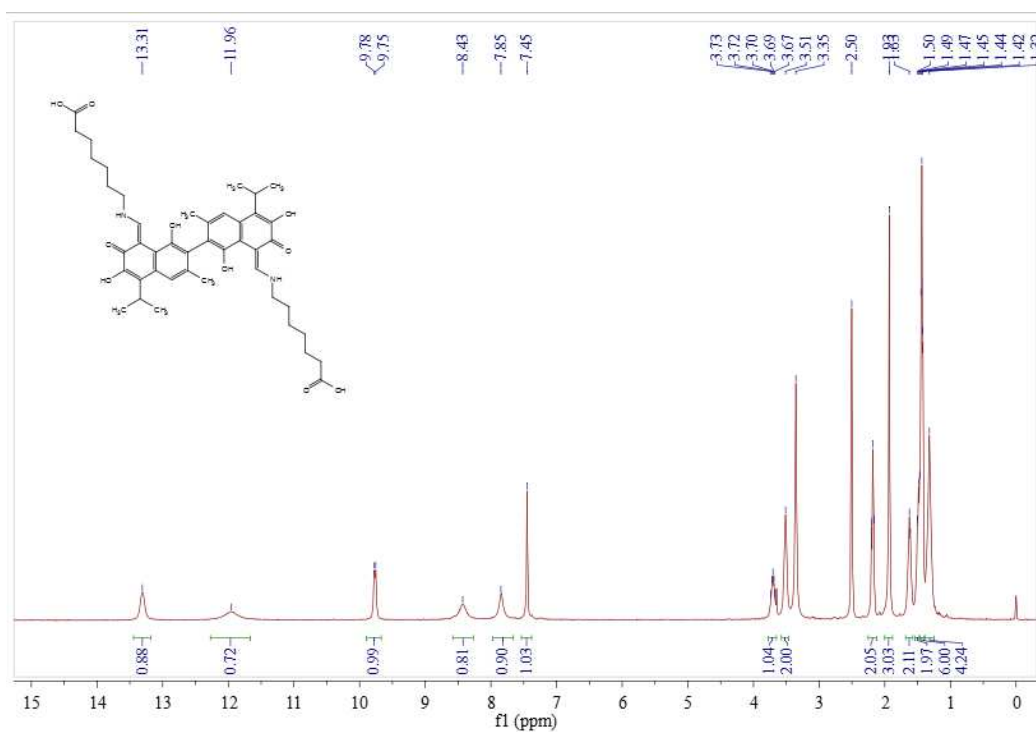
# <sup>1</sup>H NMR of compound 24



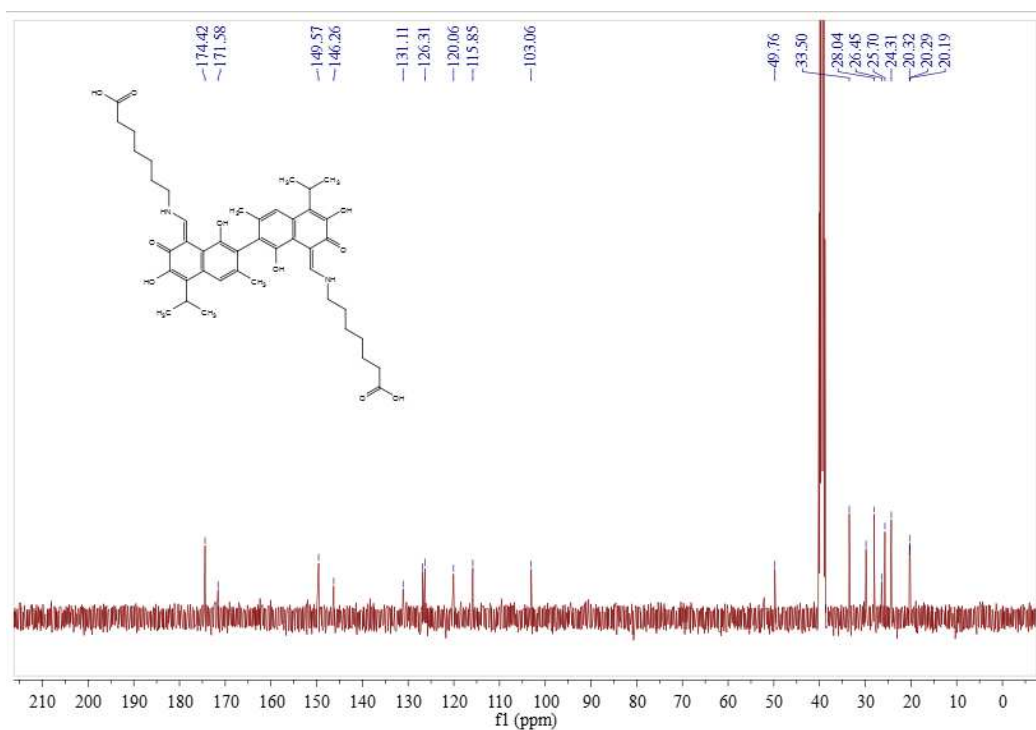
# <sup>13</sup>C NMR of compound 24



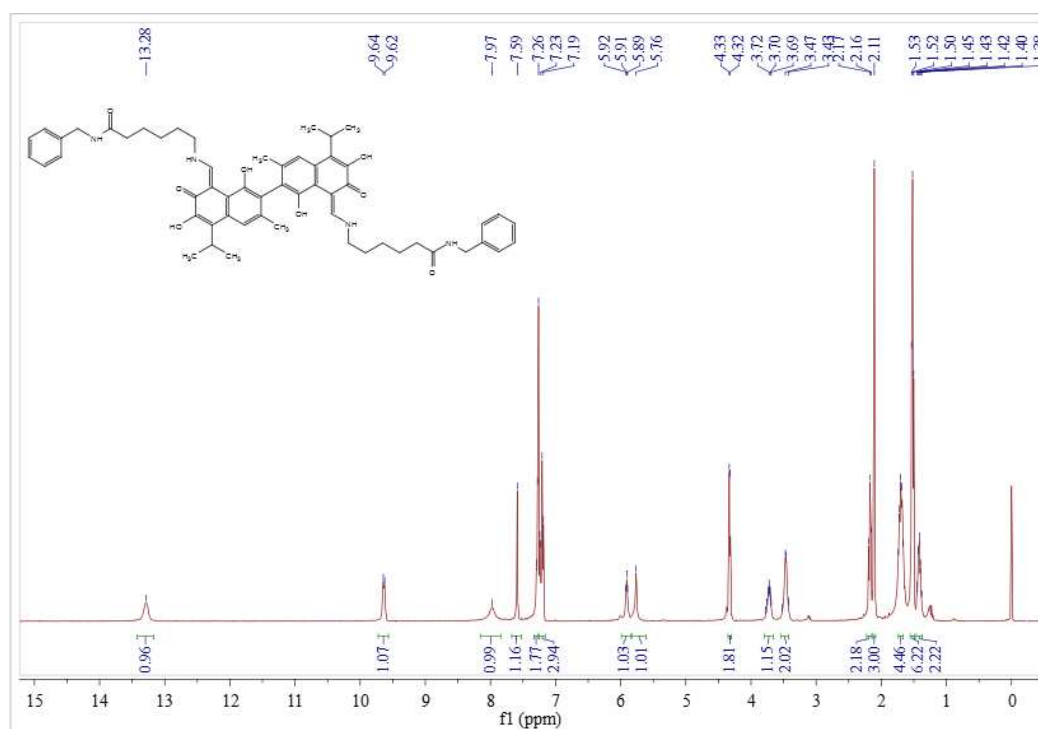
# <sup>1</sup>H NMR of compound 25



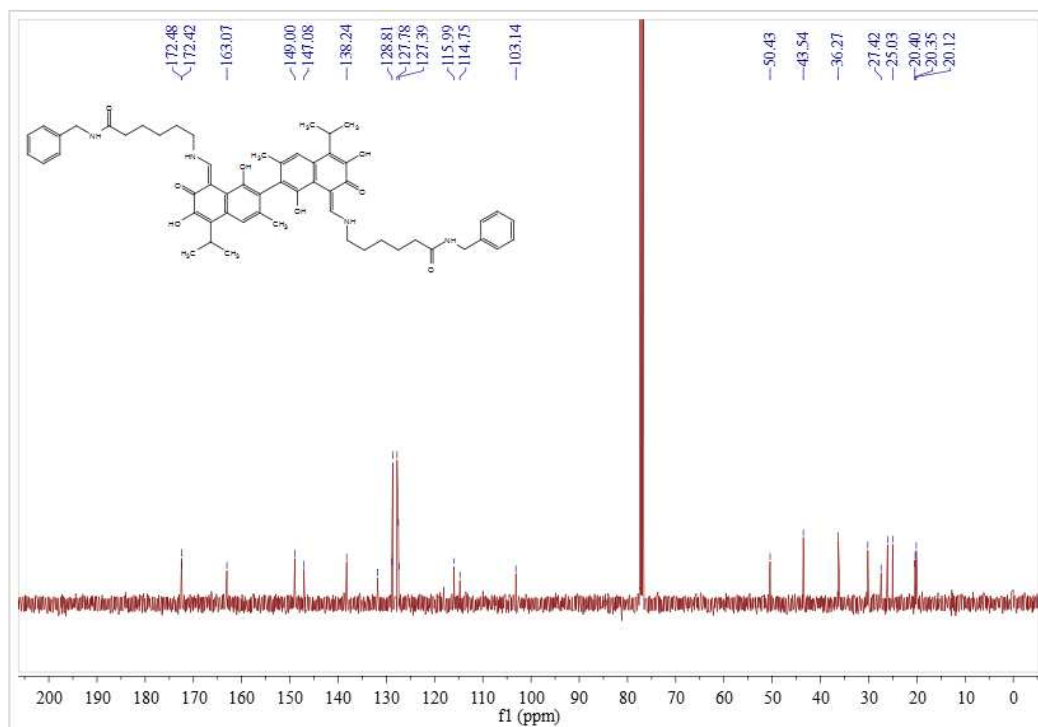
# <sup>13</sup>C NMR of compound 25



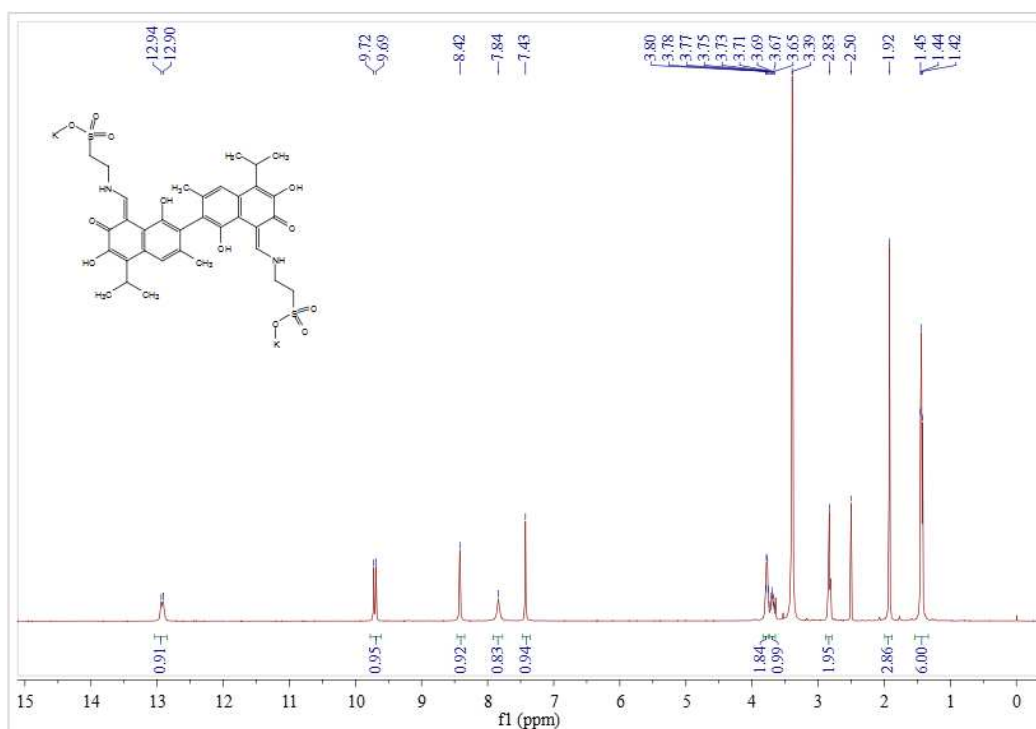
# <sup>1</sup>H NMR of compound 26



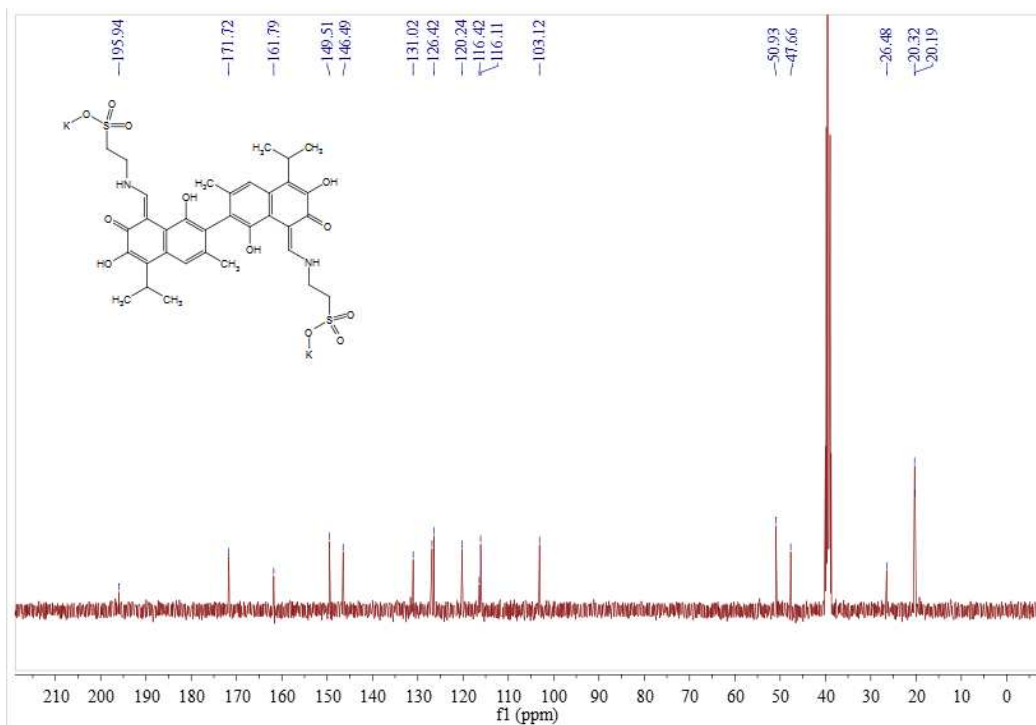
# <sup>13</sup>C NMR of compound 26



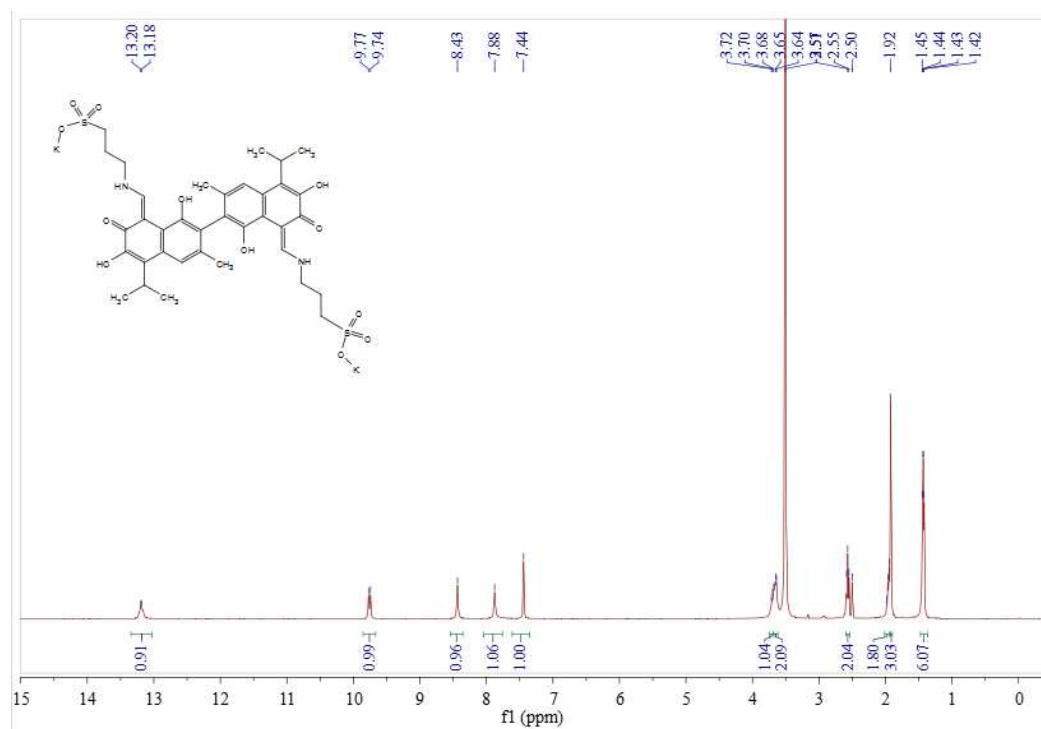
# <sup>1</sup>H NMR of compound 27



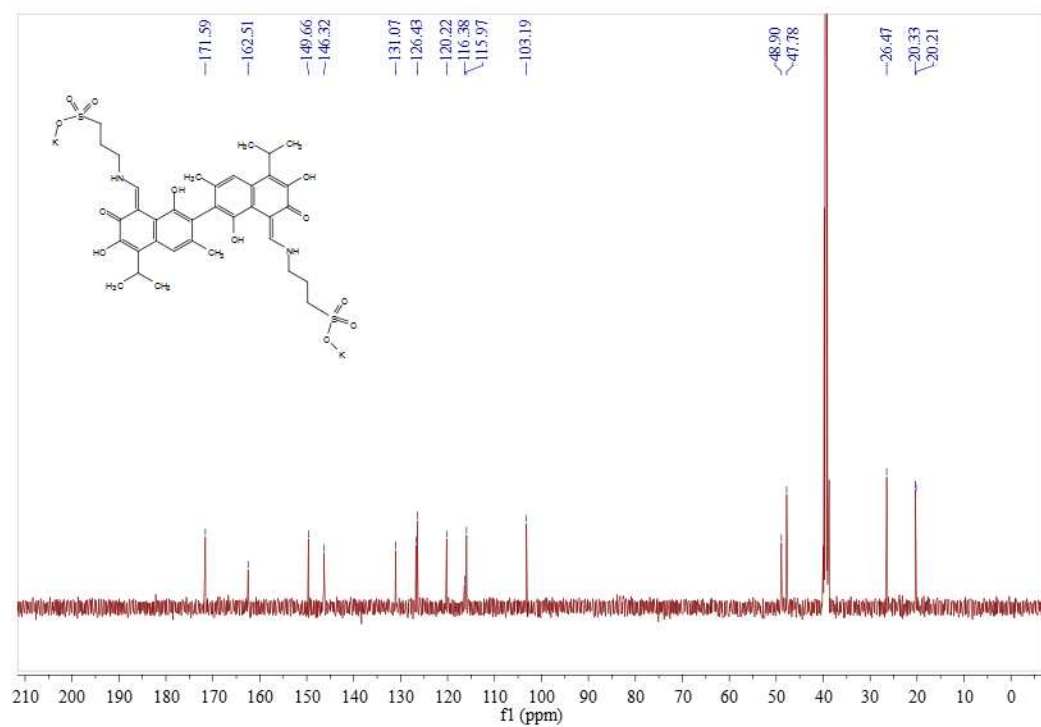
# <sup>13</sup>C NMR of compound 27



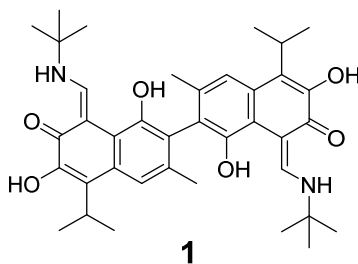
# <sup>1</sup>H NMR of compound 28



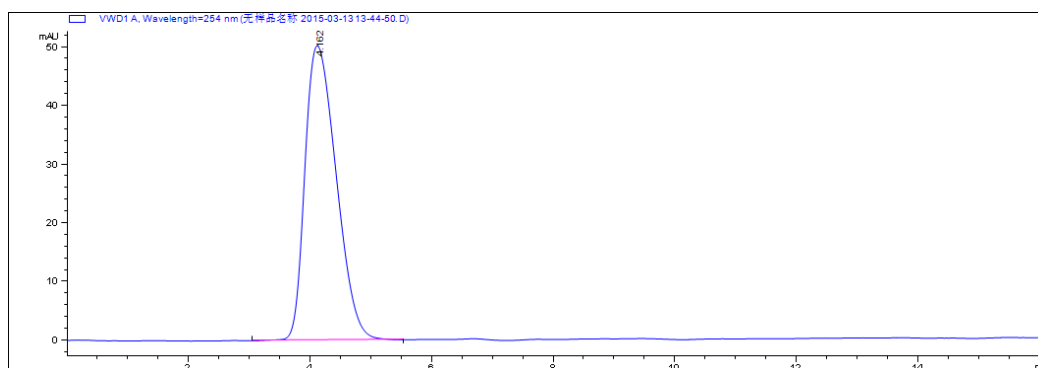
# <sup>13</sup>C NMR spectrum of compound 28



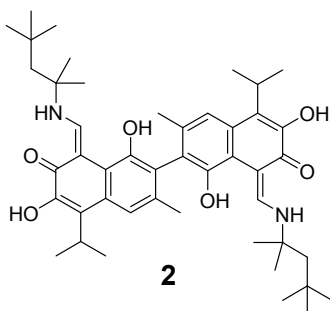
## PART 4. HPLC spectra of final compounds



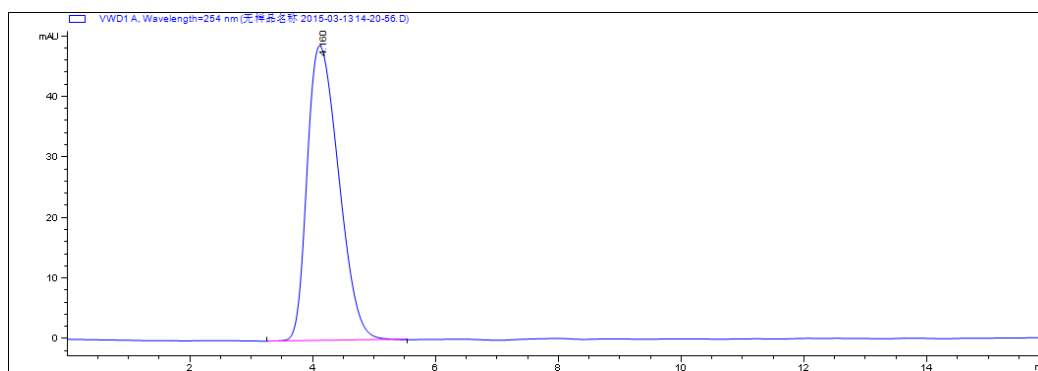
Normal phase (Lyz001-157 Method EA:Hexane = 10:90, flow rate 1.0 mL/min)



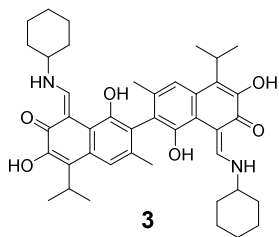
| Peak | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|------|---------------------|-------------|-------------|---------|
| 1    | 4.162               | 1795.5      | 48          | 100.00  |



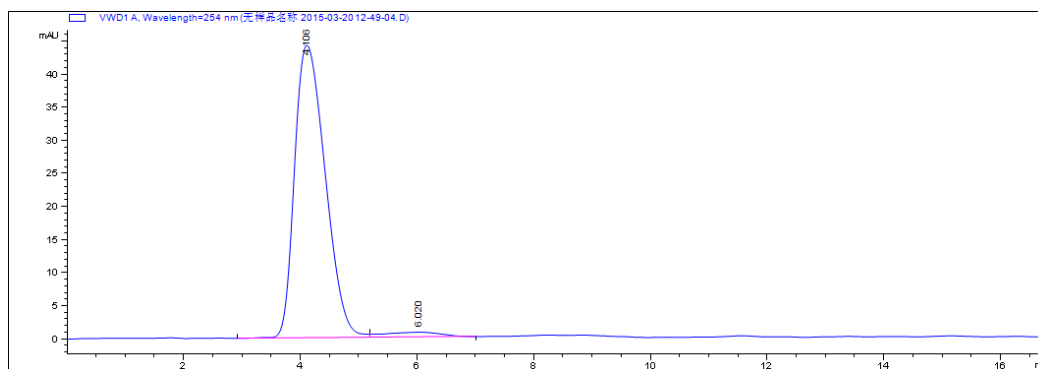
Normal phase (Lyz001-158 Method EA:Hexane = 10:90, flow rate 1.0 mL/min)



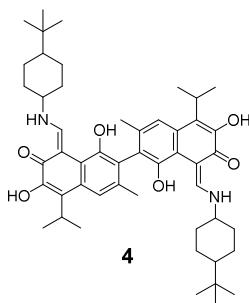
| Peak  | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|-------|---------------------|-------------|-------------|---------|
| 1     | 4.16                | 1734        | 46.6        | 100.00  |
| Total |                     |             |             | 100.00  |



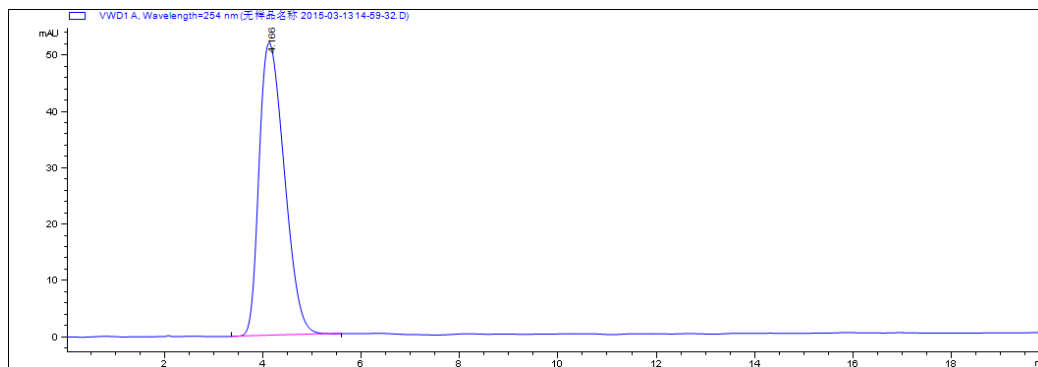
Normal phase (Lyz001-134 Method EA:Hexane = 10:90, flow rate 1.0 mL/min)



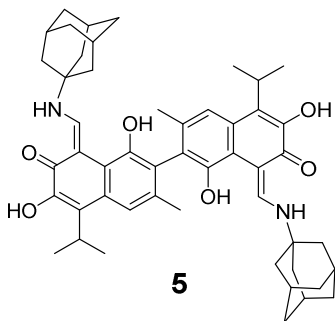
| Peak  | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|-------|---------------------|-------------|-------------|---------|
| 1     | 4.106               | 1613.9      | 44.3        | 97.044  |
| 2     | 6.02                | 49.2        | 7.3         | 2.956   |
| Total |                     |             |             | 100.00  |



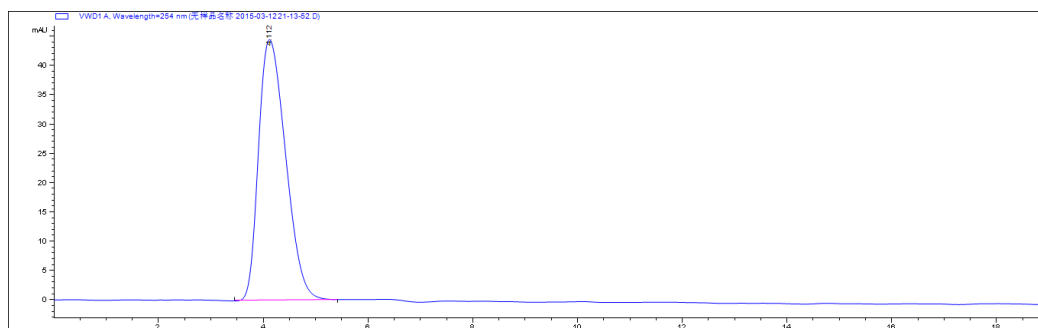
Normal phase (Lyz001-159 Method EA:Hexane = 10:90, flow rate 1.0 mL/min)



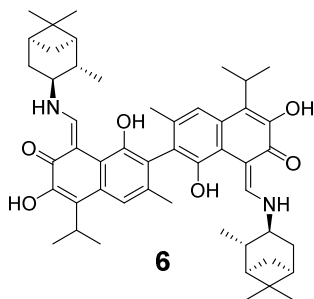
| Peak  | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|-------|---------------------|-------------|-------------|---------|
| 1     | 4.166               | 1852.8      | 49.8        | 100.00  |
| Total |                     |             |             | 100.00  |



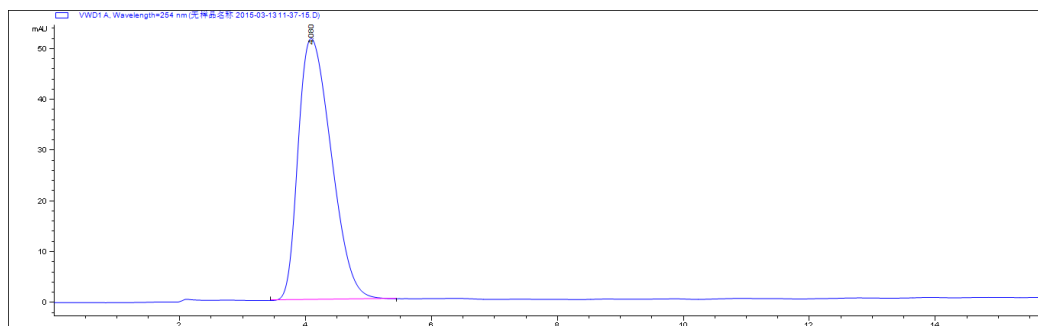
Normal phase (Lyz001-135 Method EA:Hexane = 10:90, flow rate 1.0 mL/min)



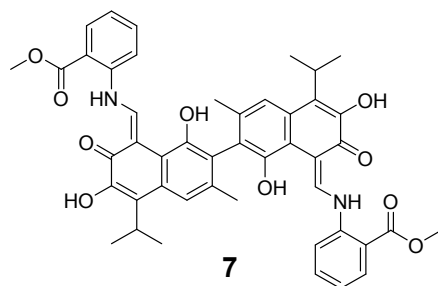
| Peak  | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|-------|---------------------|-------------|-------------|---------|
| 1     | 4.112               | 1601.1      | 44.6        | 100.00  |
| Total |                     |             |             | 100.00  |



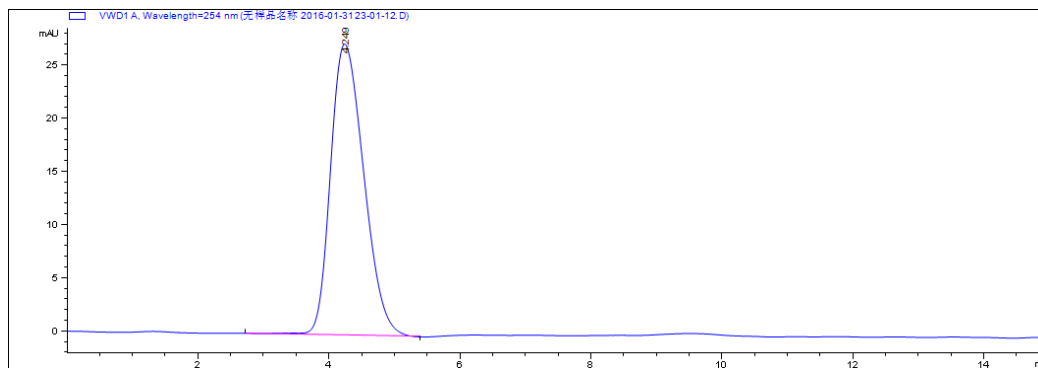
Normal phase (Lyz001-142 Method EA:Hexane = 10:90, flow rate 1.0 mL/min)



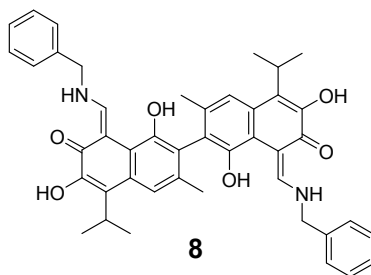
| Peak  | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|-------|---------------------|-------------|-------------|---------|
| 1     | 4.08                | 1879.4      | 51.6        | 100.00  |
| Total |                     |             |             | 100.00  |



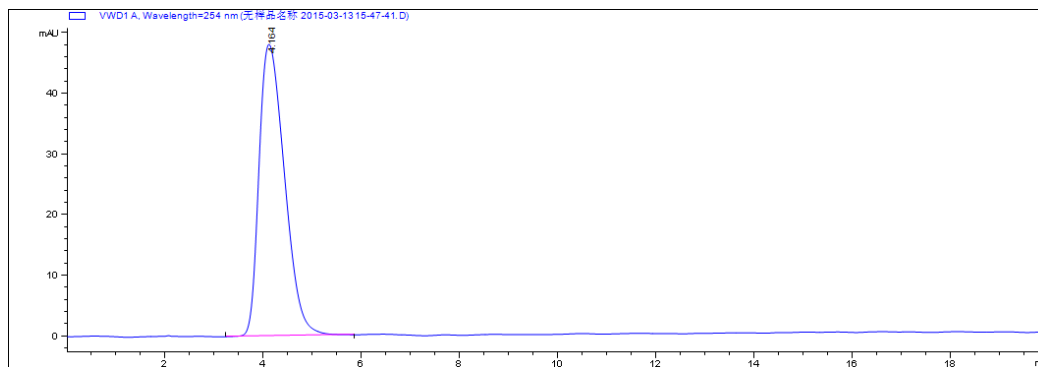
Normal phase (Lyz001-140 Method EA:Hexane = 10:90, flow rate 1.0 mL/min)



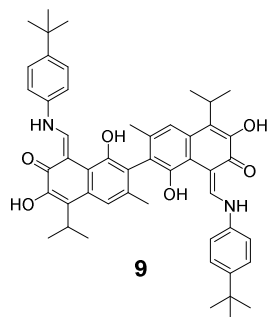
| Peak  | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|-------|---------------------|-------------|-------------|---------|
| 1     | 4.249               | 972.4       | 27.4        | 100.00  |
| Total |                     |             |             | 100.00  |



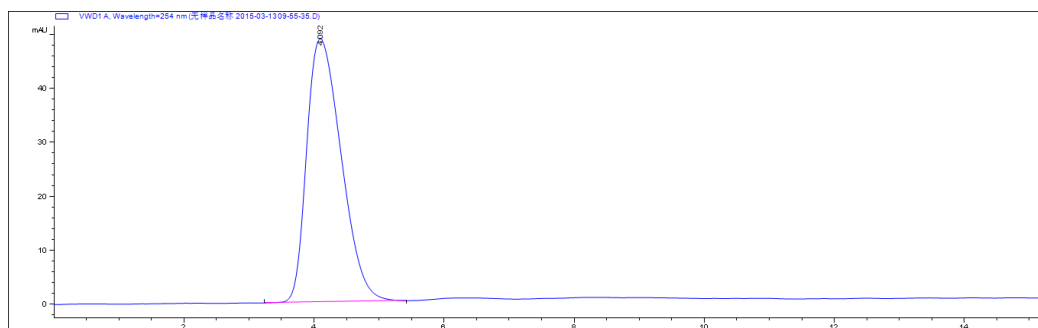
Normal phase (Lyz001-119 Method EA:Hexane = 10:90, flow rate 1.0 mL/min)



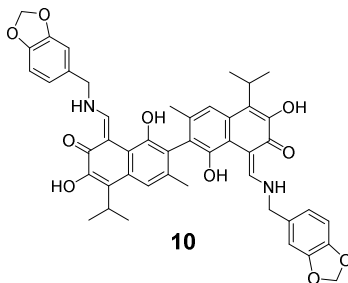
| Peak  | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|-------|---------------------|-------------|-------------|---------|
| 1     | 4.164               | 1742.1      | 46.2        | 100.00  |
| Total |                     |             |             | 100.00  |



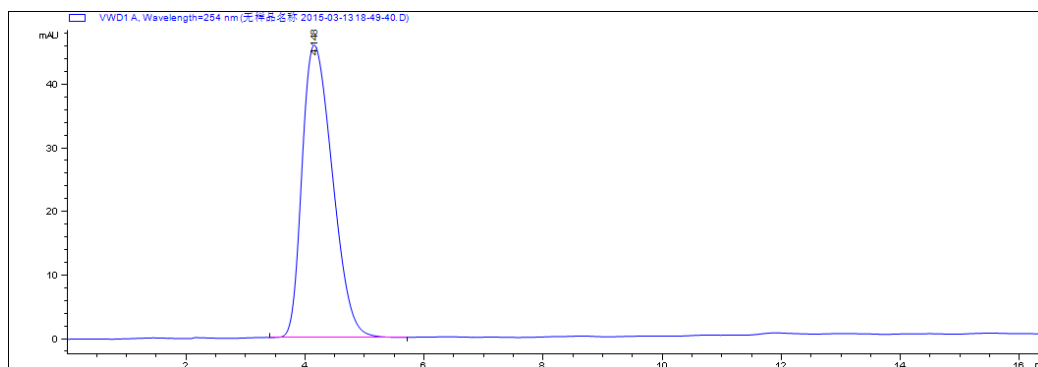
Normal phase (Lyz001-141 Method EA:Hexane = 10:90, flow rate 1.0 mL/min)



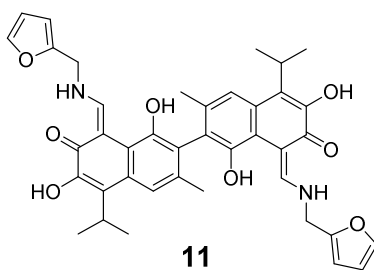
| Peak  | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|-------|---------------------|-------------|-------------|---------|
| 1     | 4.092               | 1794.5      | 48.7        | 100.00  |
| Total |                     |             |             | 100.00  |



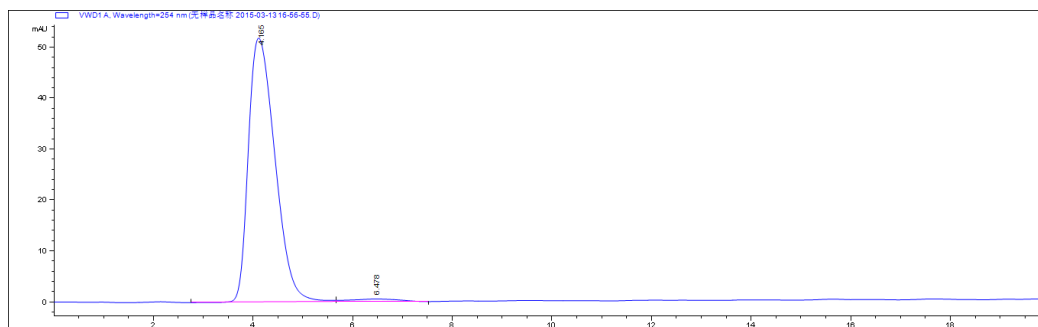
Normal phase (Lyz002-09 Method EA:Hexane = 10:90, flow rate 1.0 mL/min)



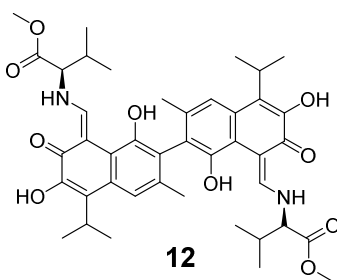
| Peak  | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|-------|---------------------|-------------|-------------|---------|
| 1     | 4.148               | 1625.7      | 45.9        | 100.00  |
| Total |                     |             |             | 100.00  |



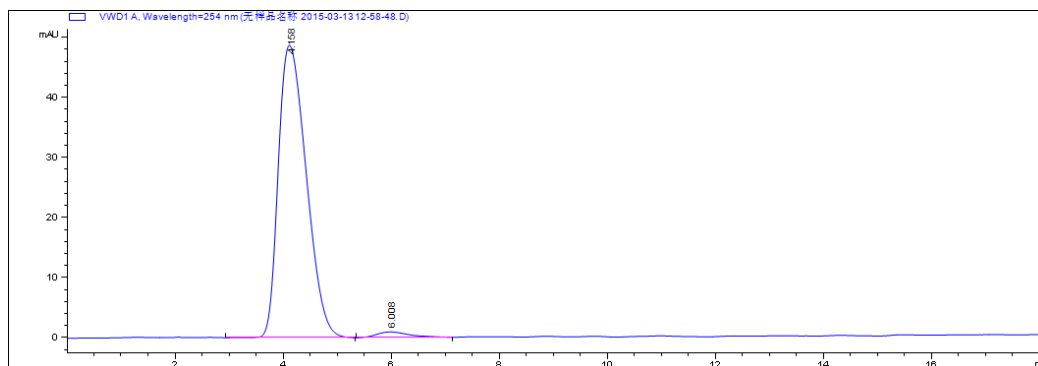
Normal phase (Lyz002-02 Method EA:Hexane = 10:90, flow rate 1.0 mL/min)



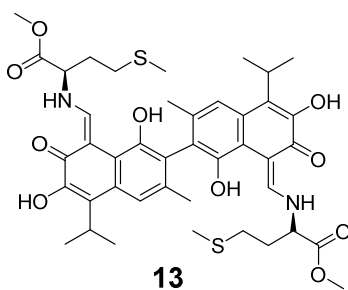
| Peak  | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|-------|---------------------|-------------|-------------|---------|
| 1     | 4.165               | 1926.8      | 49.8        | 98.051  |
| 2     | 6.478               | 38.3        | 5.5         | 1.949   |
| Total |                     |             |             | 100.00  |



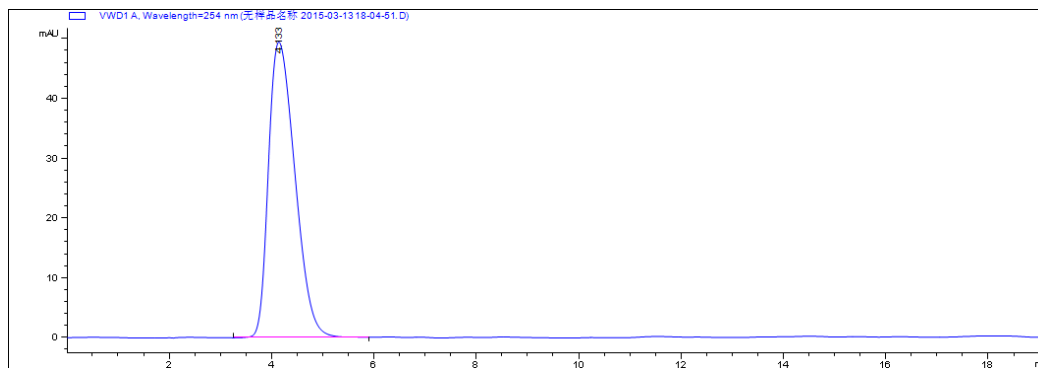
Normal phase (Lyz001-151 Method EA:Hexane = 10:90, flow rate 1.0 mL/min)



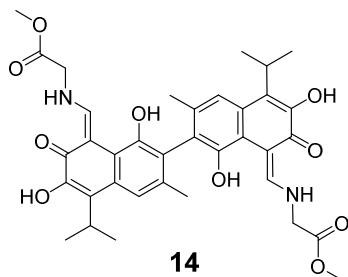
| Peak  | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|-------|---------------------|-------------|-------------|---------|
| 1     | 4.158               | 1753.1      | 46.7        | 97.776  |
| 2     | 6.008               | 39.9        | 8.7         | 2.224   |
| Total |                     |             |             | 100.00  |



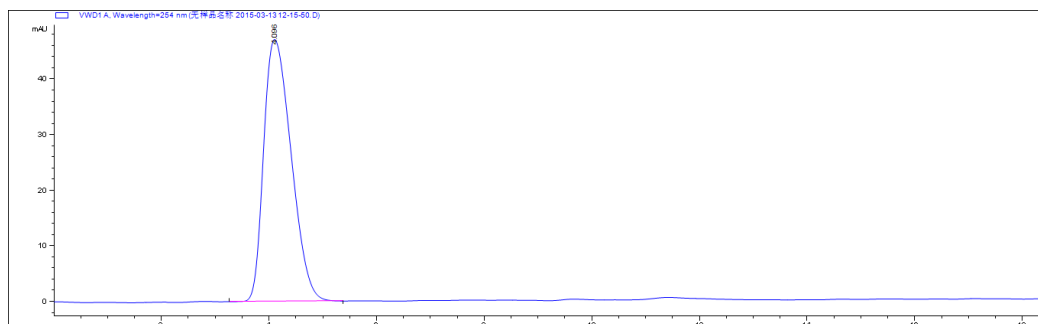
Normal phase (Lyz002-03 Method EA:Hexane = 10:90, flow rate 1.0 mL/min)



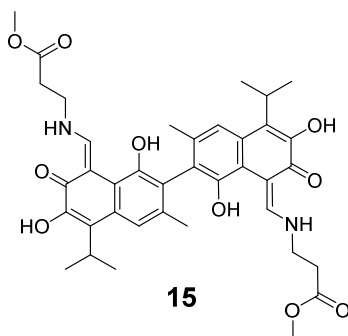
| Peak  | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|-------|---------------------|-------------|-------------|---------|
| 1     | 4.133               | 1767.4      | 49.3        | 100.00  |
| Total |                     |             |             | 100.00  |



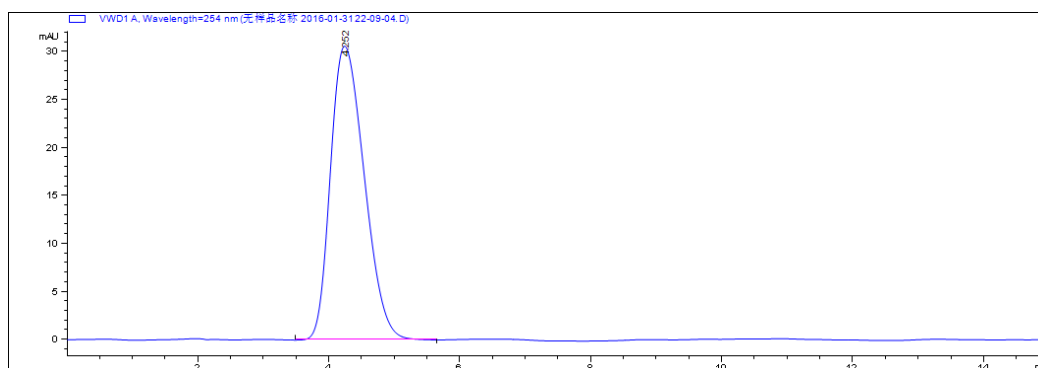
Normal phase (Lyz001-143 Method EA:Hexane = 10:90, flow rate 1.0 mL/min)



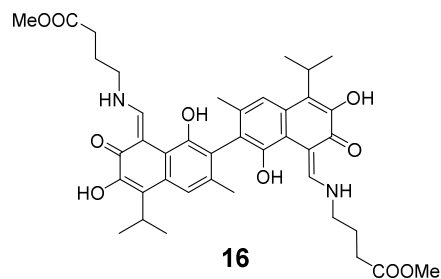
| Peak  | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|-------|---------------------|-------------|-------------|---------|
| 1     | 4.096               | 1679.4      | 47.3        | 100.00  |
| Total |                     |             |             | 100.00  |



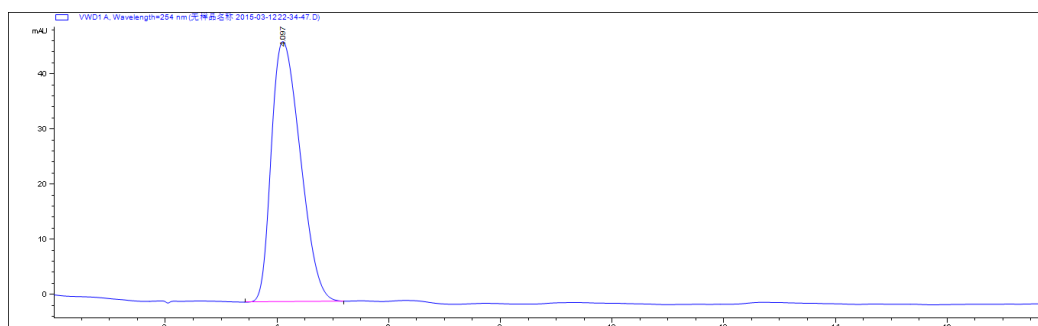
Normal phase (Lyz002-83 Method EA:Hexane = 10:90, flow rate 1.0 mL/min)



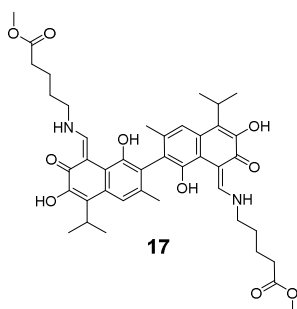
| Peak  | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|-------|---------------------|-------------|-------------|---------|
| 1     | 4.252               | 1099.9      | 30.6        | 100.00  |
| Total |                     |             |             | 100.00  |



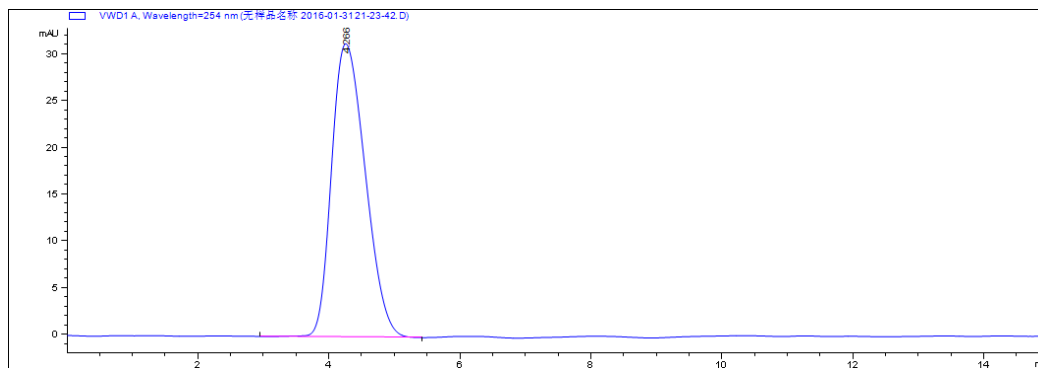
Normal phase (Lyz001-136 Method EA:Hexane = 10:90, flow rate 1.0 mL/min)



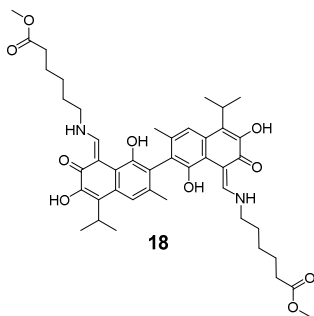
| Peak  | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|-------|---------------------|-------------|-------------|---------|
| 1     | 4.097               | 1709.6      | 47.4        | 100.00  |
| Total |                     |             |             | 100.00  |



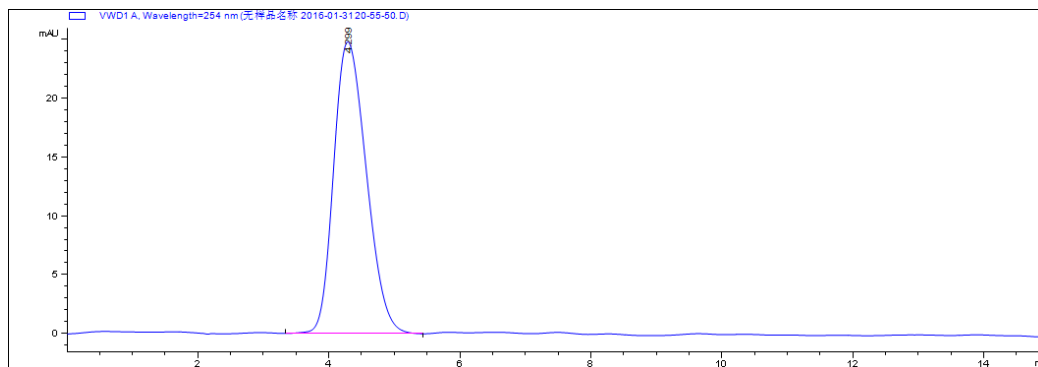
Normal phase (Lyz002-84 Method EA:Hexane = 10:90, flow rate 1.0 mL/min)



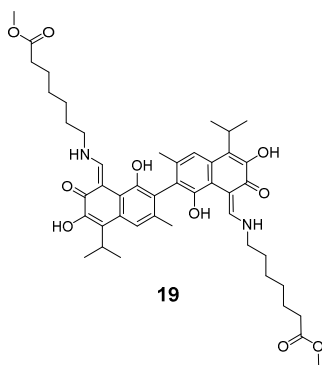
| Peak  | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|-------|---------------------|-------------|-------------|---------|
| 1     | 4.266               | 1123.1      | 31.4        | 100.00  |
| Total |                     |             |             | 100.00  |



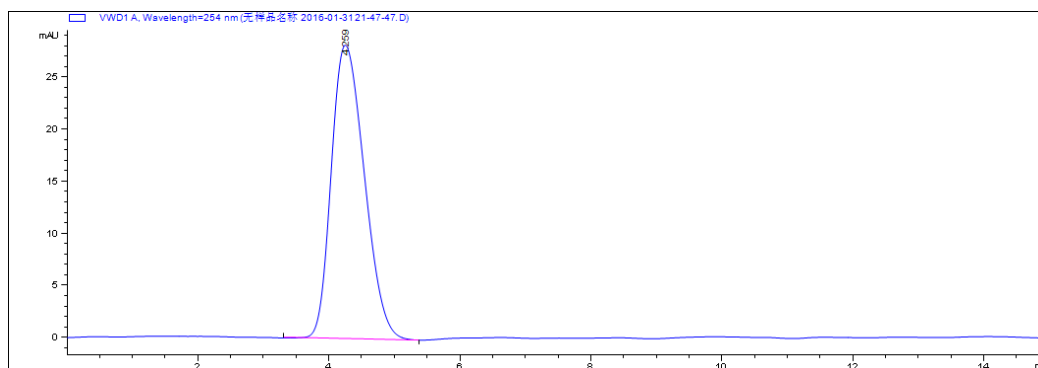
Normal phase (Lyz002-79 Method EA:Hexane = 10:90, flow rate 1.0 mL/min)



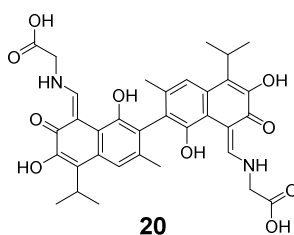
| Peak  | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|-------|---------------------|-------------|-------------|---------|
| 1     | 4.299               | 855.7       | 24.3        | 100.00  |
| Total |                     |             |             | 100.00  |



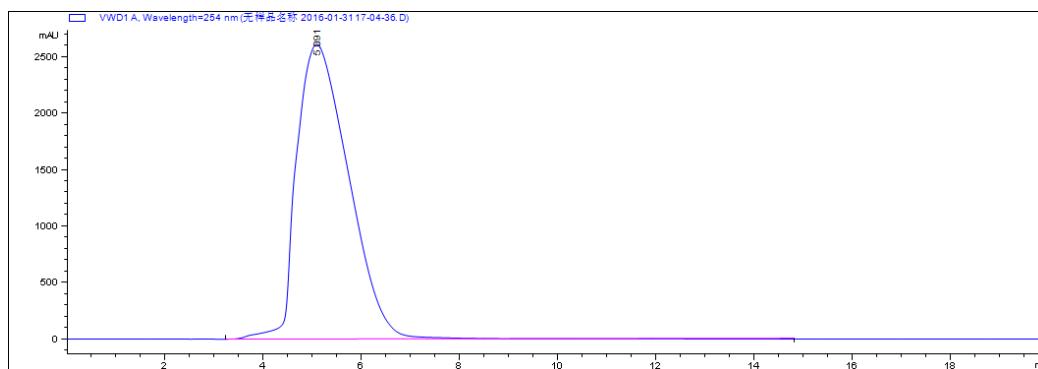
Normal phase (Lyz002-94 Method EA:Hexane = 10:90, flow rate 1.0 mL/min)



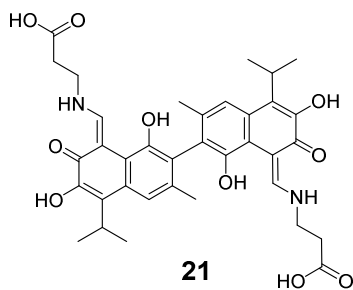
| Peak  | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|-------|---------------------|-------------|-------------|---------|
| 1     | 4.259               | 990.4       | 28.2        | 100.00  |
| Total |                     |             |             | 100.00  |



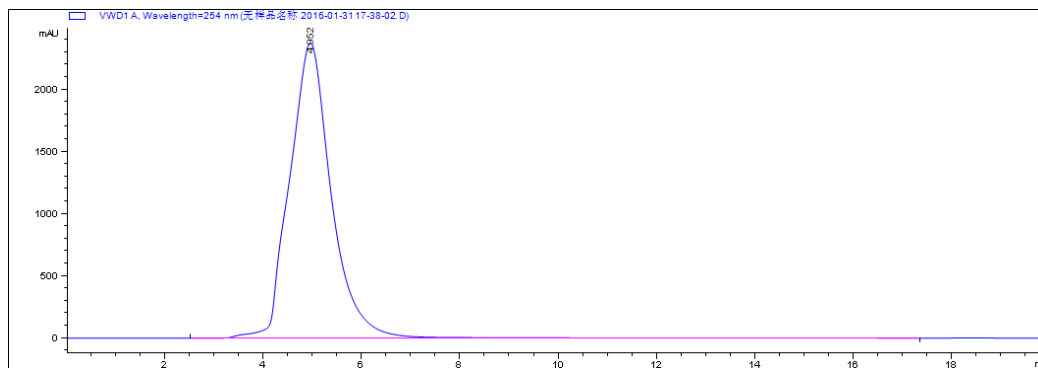
Reverse phase (MeOH:H<sub>2</sub>O:CF<sub>3</sub>COOH = 95:5:0.01%, flow rate = 1.0 mL/min)



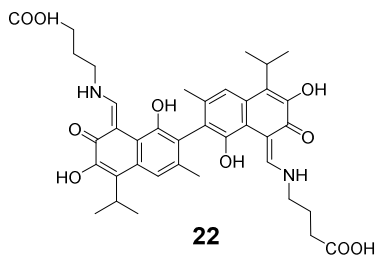
| Peak  | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|-------|---------------------|-------------|-------------|---------|
| 1     | 5.091               | 191808.1    | 2603.4      | 100.00  |
| Total |                     |             |             | 100.00  |



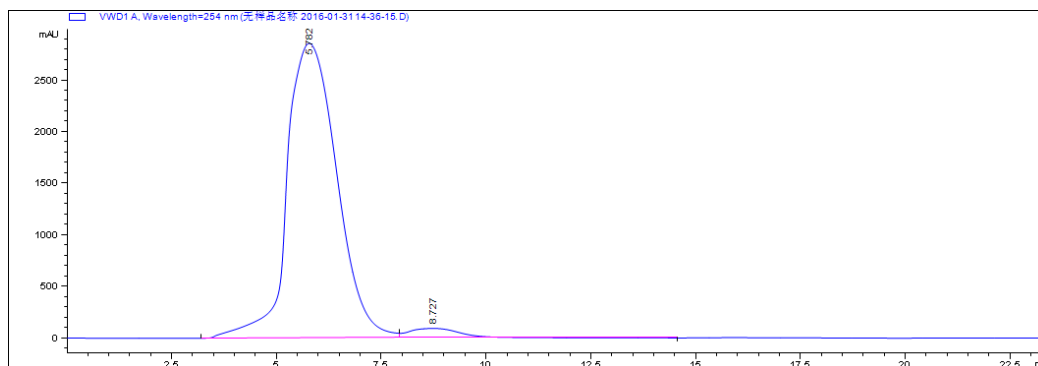
Reverse phase (MeOH:H<sub>2</sub>O:CF<sub>3</sub>COOH = 95:5:0.01%, flow rate = 1.0 mL/min)



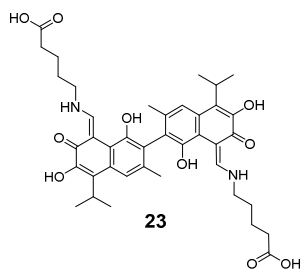
| Peak  | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|-------|---------------------|-------------|-------------|---------|
| 1     | 4.952               | 139847      | 2362.8      | 100.00  |
| Total |                     |             |             | 100.00  |



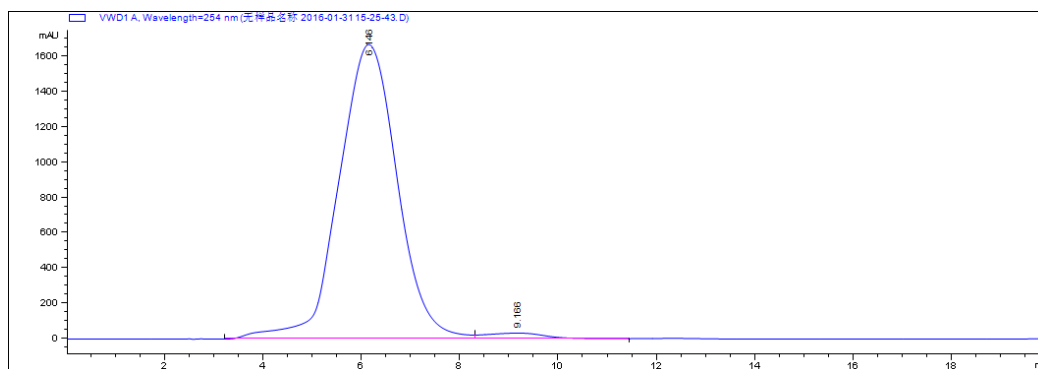
Reverse phase (MeOH:H<sub>2</sub>O:CF<sub>3</sub>COOH = 95:5:0.01%, flow rate = 1.0 mL/min)



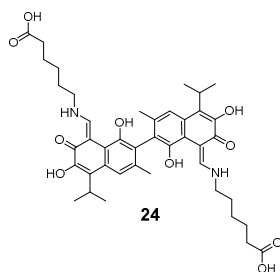
| Peak  | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|-------|---------------------|-------------|-------------|---------|
| 1     | 5.782               | 235974.6    | 2848.8      | 96.524  |
| 2     | 8.727               | 8498.2      | 93.2        | 3.476   |
| Total |                     |             |             | 100.00  |



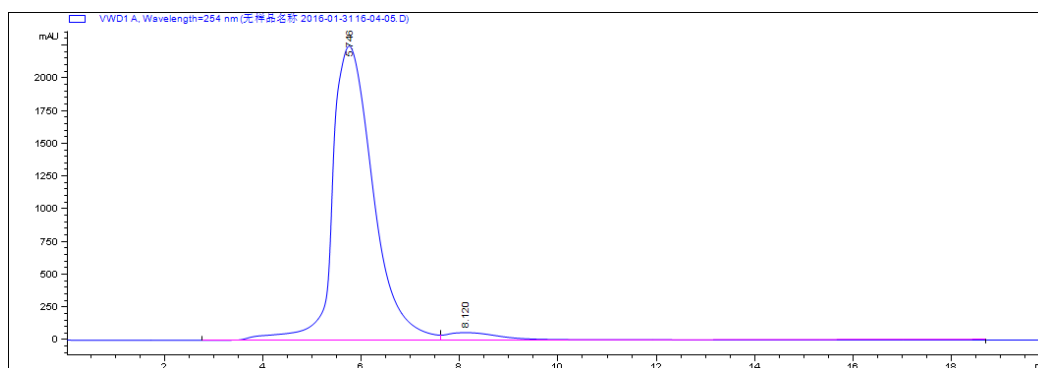
Reverse phase (MeOH:H<sub>2</sub>O:CF<sub>3</sub>COOH = 95:5:0.01%, flow rate = 1.0 mL/min)



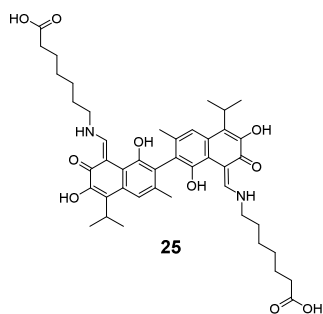
| Peak  | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|-------|---------------------|-------------|-------------|---------|
| 1     | 6.146               | 137342.5    | 1660        | 98.098  |
| 2     | 9.166               | 2663.3      | 31.9        | 1.902   |
| Total |                     |             |             | 100.00  |



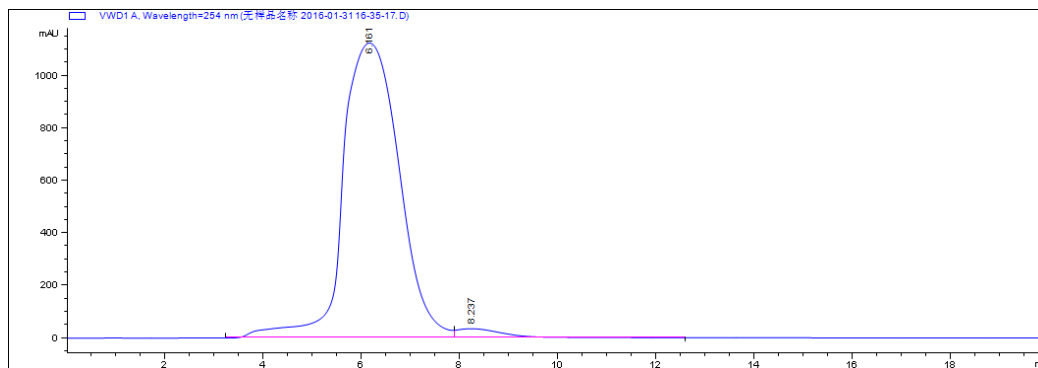
Reverse phase (MeOH:H<sub>2</sub>O:CF<sub>3</sub>COOH = 95:5:0.01%, flow rate = 1.0 mL/min)



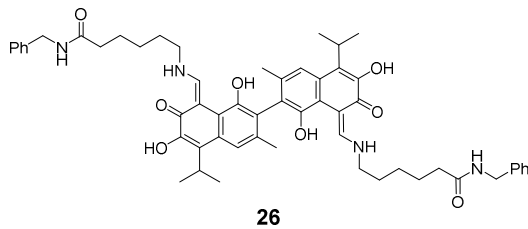
| Peak  | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|-------|---------------------|-------------|-------------|---------|
| 1     | 5.746               | 129077.4    | 2239.2      | 96.236  |
| 2     | 8.12                | 5049.2      | 57.4        | 3.764   |
| Total |                     |             |             | 100.00  |



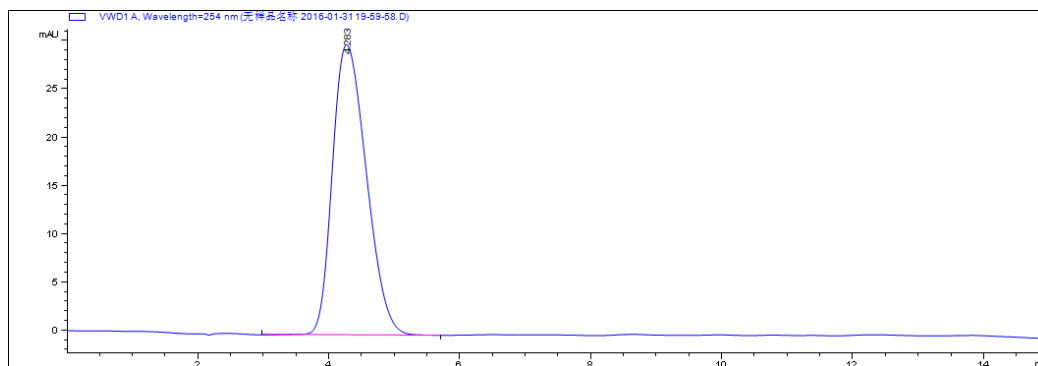
Reverse phase (MeOH:H<sub>2</sub>O:CF<sub>3</sub>COOH = 95:5:0.01%, flow rate = 1.0 mL/min)



| Peak  | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|-------|---------------------|-------------|-------------|---------|
| 1     | 6.161               | 89520       | 1122.8      | 97.432  |
| 2     | 8.237               | 2359.9      | 34.7        | 2.568   |
| Total |                     |             |             | 100.00  |



Normal phase (Ly002-106 Method EA:Hexane = 10:90, flow rate 1.0 mL/min)



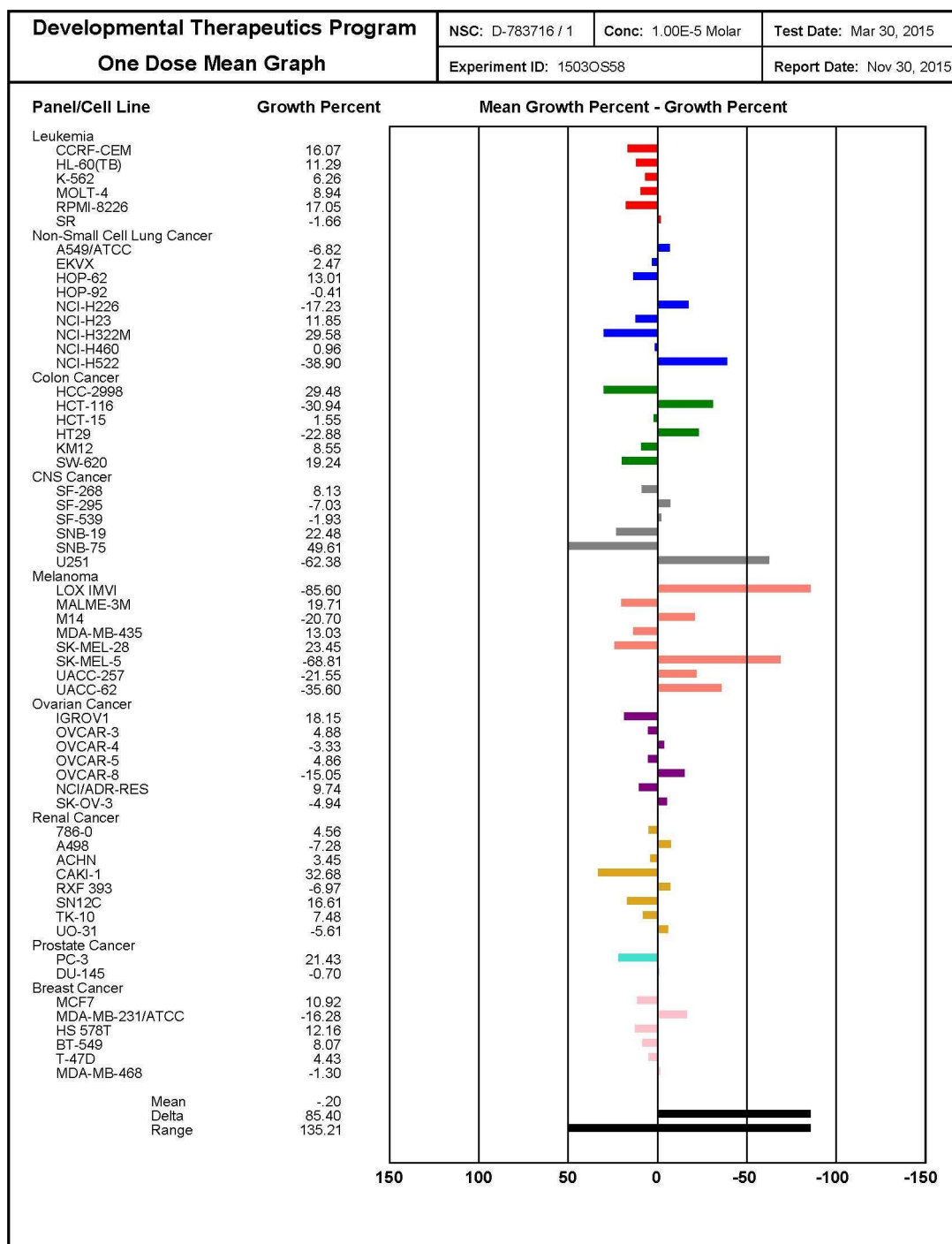
| Peak  | Retention Time(min) | Area(Mau*s) | Height(mAU) | Area(%) |
|-------|---------------------|-------------|-------------|---------|
| 1     | 4.283               | 1087        | 29.6        | 100.00  |
| Total |                     |             |             | 100.00  |

**Table S1.** NCI60 one dose (10  $\mu$ M) screening data for compounds **1-3, 8, 9, 11, 14, 16-20, 23-26, 28**

| Compounds             | Growth percent |       | Range  |
|-----------------------|----------------|-------|--------|
|                       | Mean           | Delta |        |
| <b>1</b>              | 91.76          | 37.63 | 60.66  |
| <b>2</b>              | 94.48          | 18.28 | 37.83  |
| <b>3</b>              | 96.92          | 21.44 | 38.26  |
| <b>8</b>              | 83.90          | 35.01 | 70.96  |
| <b>9</b>              | 100.70         | 21.10 | 34.20  |
| <b>11</b>             | 53.43          | 24.07 | 67.09  |
| <b>14<sup>a</sup></b> | 22.21          | 35.77 | 71.04  |
| <b>16<sup>a</sup></b> | -0.20          | 85.40 | 135.21 |
| <b>17<sup>a</sup></b> | 19.35          | 29.46 | 62.89  |
| <b>18<sup>a</sup></b> | 20.54          | 42.39 | 83.63  |
| <b>19</b>             | 26.09          | 32.58 | 83.74  |
| <b>20</b>             | 98.01          | 59.71 | 79.24  |
| <b>23</b>             | 46.01          | 23.54 | 62.65  |
| <b>24</b>             | 72.73          | 40.61 | 86.39  |
| <b>25</b>             | 30.21          | 25.74 | 70.24  |
| <b>26</b>             | 50.20          | 31.50 | 73.59  |
| <b>28</b>             | 65.19          | 28.97 | 64.96  |

<sup>a</sup> Compounds have detailed NCI-60 information.

**Figure S1.** Details of the one dose (10  $\mu$ M) information (example: compound 16)



**Table S2.** Cell growth inhibition data for compounds **14** and **16-18** (GI<sub>50</sub>,  $\mu$ M) against a panel of 60 human cancer cells.

| Cell type                  | Cell line      | Cell growth inhibition (GI <sub>50</sub> , $\mu$ M) <sup>a</sup> |                           |                 |           |           |           |
|----------------------------|----------------|------------------------------------------------------------------|---------------------------|-----------------|-----------|-----------|-----------|
|                            |                | ABT-199 <sup>b</sup>                                             | (±)-Gossypol <sup>b</sup> | <b>14</b>       | <b>16</b> | <b>17</b> | <b>18</b> |
| Leukemia                   | CCRF-CEM       | 2.51                                                             | 2.00                      | 2.14            | 0.33      | 0.75      | 0.95      |
|                            | HL-60(TB)      | 0.25                                                             | 2.00                      | ND <sup>c</sup> | 0.93      | 1.13      | 1.09      |
|                            | K-562          | 3.16                                                             | 3.16                      | 1.88            | 0.25      | 0.64      | 1.07      |
|                            | MOLT-4         | 2.00                                                             | 2.00                      | 1.36            | ND        | 0.78      | 1.05      |
|                            | RPMI-8226      | 1.58                                                             | 2.51                      | 2.72            | 0.59      | 0.62      | 0.95      |
|                            | SR             | 3.16                                                             | 3.16                      | 1.32            | 0.71      | 0.92      | 1.09      |
| Non-Small Cell Lung Cancer | A549/ATCC      | 2.51                                                             | 3.16                      | 2.13            | 0.26      | 0.98      | 1.35      |
|                            | EKVX           | ND                                                               | 2.00                      | 1.20            | 0.32      | 0.93      | 1.18      |
|                            | HOP-62         | 3.98                                                             | 2.51                      | 2.41            | 0.94      | 1.22      | 1.35      |
|                            | HOP-92         | 1.26                                                             | 3.98                      | 1.38            | 0.37      | 0.78      | 0.80      |
|                            | NCI-H226       | 2.51                                                             | 3.61                      | ND              | 0.58      | 1.30      | 3.15      |
|                            | NCI-H23        | 3.16                                                             | 2.51                      | 1.53            | 0.36      | 1.07      | 1.32      |
|                            | NCI-H322M      | 3.16                                                             | 3.16                      | 1.74            | 0.70      | 1.30      | 2.02      |
|                            | NCI-H460       | 2.51                                                             | 1.58                      | 1.52            | 0.37      | 1.04      | 1.28      |
|                            | NCI-H522       | 2.51                                                             | 3.16                      | 1.32            | 0.38      | 0.84      | 0.97      |
| Colon Cancer               | COLO 205       | 2.00                                                             | 2.51                      | 1.28            | 0.38      | 0.85      | 1.18      |
|                            | HCC-2998       | 2.00                                                             | 3.98                      | 1.92            | 0.68      | 1.19      | 2.15      |
|                            | <b>HCT-116</b> | 3.16                                                             | 2.51                      | 1.79            | 0.16      | 0.90      | 1.23      |
|                            | HCT-15         | 3.16                                                             | 3.16                      | 1.49            | 0.59      | 1.06      | 1.55      |
|                            | HT29           | 2.51                                                             | 3.16                      | 1.58            | 0.54      | 0.98      | 1.29      |
|                            | KM12           | 3.16                                                             | 2.00                      | 1.39            | 0.16      | 0.80      | 1.28      |
|                            | SW-620         | 3.98                                                             | 5.01                      | 1.96            | 0.74      | 1.27      | 1.37      |
| CNS Cancer                 | SF-268         | 3.98                                                             | 3.16                      | 1.88            | 0.44      | 1.34      | 1.51      |
|                            | SF-295         | 2.51                                                             | 2.51                      | 1.46            | 0.25      | 0.83      | 0.91      |
|                            | SF-539         | 2.51                                                             | 2.51                      | 1.77            | 0.99      | 1.53      | 1.60      |
|                            | SNB-19         | 3.98                                                             | 3.98                      | 1.53            | 0.17      | 0.71      | 1.21      |
|                            | SNB-75         | 3.98                                                             | 3.16                      | 1.61            | 1.43      | 2.60      | 2.55      |
|                            | U251           | 3.16                                                             | 2.51                      | 1.53            | 0.30      | 0.58      | 1.00      |
| Melanoma                   | LOX IMVI       | 2.00                                                             | 1.58                      | 1.56            | 0.54      | 0.82      | 1.28      |
|                            | MALME-3M       | 2.00                                                             | 5.01                      | 2.23            | 0.90      | 1.47      | 2.45      |
|                            | M14            | 2.51                                                             | 2.51                      | 2.09            | 0.75      | 1.23      | 2.30      |
|                            | MDA-MB-435     | 2.00                                                             | ND                        | 2.46            | 1.06      | 1.46      | 1.82      |
|                            | SK-MEL-2       | 1.58                                                             | 2.00                      | 0.83            | 0.86      | 1.38      | 2.20      |
|                            | SK-MEL-28      | 1.26                                                             | 5.01                      | 2.00            | 1.10      | 1.77      | 1.95      |
|                            | SK-MEL-5       | 1.58                                                             | 3.16                      | 4.29            | 1.24      | 1.83      | 4.46      |
|                            | UACC-257       | 2.00                                                             | 3.98                      | 7.89            | 1.77      | ND        | ND        |
|                            | UACC-62        | 0.79                                                             | 2.51                      | 2.23            | 0.66      | ND        | ND        |

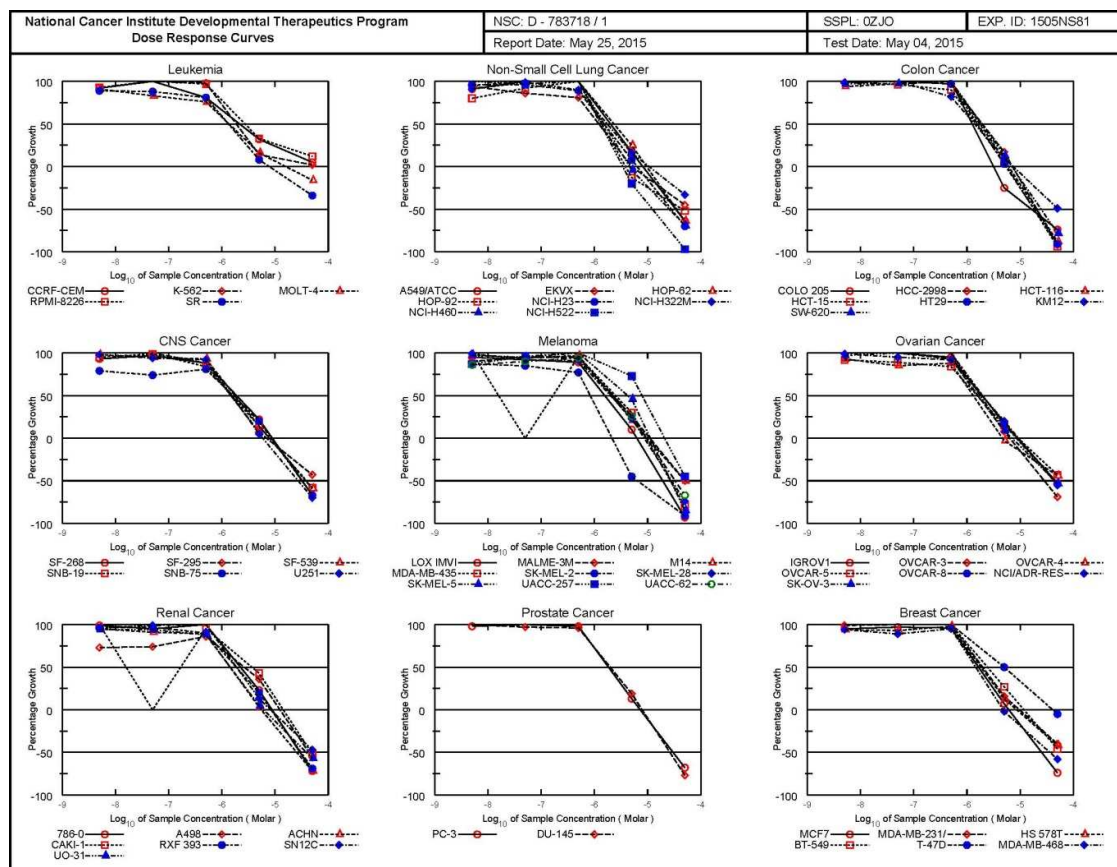
|                 |               |      |       |      |      |      |      |
|-----------------|---------------|------|-------|------|------|------|------|
| Ovarian Cancer  | IGROV1        | 3.16 | 5.01  | 1.92 | 0.50 | 1.41 | 1.76 |
|                 | OVCAR-3       | 2.51 | 3.16  | 1.61 | 0.32 | 1.02 | 1.27 |
|                 | OVCAR-4       | 3.16 | 3.16  | 1.29 | 0.23 | 0.89 | 1.05 |
|                 | OVCAR-5       | 3.16 | 3.98  | 1.56 | 0.78 | ND   | ND   |
|                 | OVCAR-8       | 3.16 | 3.16  | 2.05 | 0.60 | 0.96 | 1.27 |
|                 | NCI/ADR-RES   | 5.01 | ND    | 1.93 | 0.83 | 2.33 | 9.04 |
|                 | SK-OV-3       | 3.16 | 2.51  | 1.79 | 0.86 | 0.98 | 1.51 |
| Renal Cancer    | 786-0         | 3.16 | 3.16  | 2.35 | 1.07 | 1.34 | 1.77 |
|                 | A498          | 1.58 | 3.98  | 2.60 | 1.36 | 1.79 | 2.74 |
|                 | ACHN          | 3.16 | 3.16  | 1.42 | 0.21 | 1.15 | 1.42 |
|                 | CAKI-1        | 3.16 | 3.98  | 3.74 | 1.51 | 1.17 | 6.17 |
|                 | RXF 393       | 1.58 | 2.00  | 1.85 | 0.65 | 0.60 | 0.85 |
|                 | SN12C         | 3.16 | 5.01  | 1.97 | 0.84 | 1.14 | 1.30 |
|                 | TK-10         | 2.51 | 0.794 | ND   | 0.34 | 1.05 | 1.15 |
|                 | UO-31         | 2.51 | 3.16  | 1.43 | 0.56 | 0.92 | 1.24 |
| Prostate Cancer | PC-3          | 2.00 | ND    | 1.84 | 0.26 | 0.79 | 1.03 |
|                 | <b>DU-145</b> | 5.01 | ND    | 1.99 | 0.56 | 1.39 | 1.78 |
| Breast Cancer   | <b>MCF7</b>   | 3.16 | ND    | 1.64 | 0.64 | 0.92 | 1.04 |
|                 | MDA-MB-231/A  | 2.00 | ND    | 1.99 | 0.74 | 1.08 | 1.36 |
|                 | TCC           |      |       |      |      |      |      |
|                 | HS 578T       | 3.16 | ND    | 1.83 | 0.98 | 1.49 | 1.68 |
|                 | BT-549        | 3.16 | ND    | 2.65 | 1.19 | 1.50 | 3.00 |
|                 | T-47D         | 3.16 | ND    | 5.09 | 0.56 | 0.69 | 1.25 |
|                 | MDA-MB-468    | 2.00 | ND    | 1.46 | 0.35 | 0.78 | 1.97 |

<sup>a</sup> GI<sub>50</sub>: concentration required for 50% cell growth inhibition.

<sup>b</sup> Data obtained from NCI's *in vitro* 60 cell 5-dose screen.

<sup>c</sup> ND: not determined.

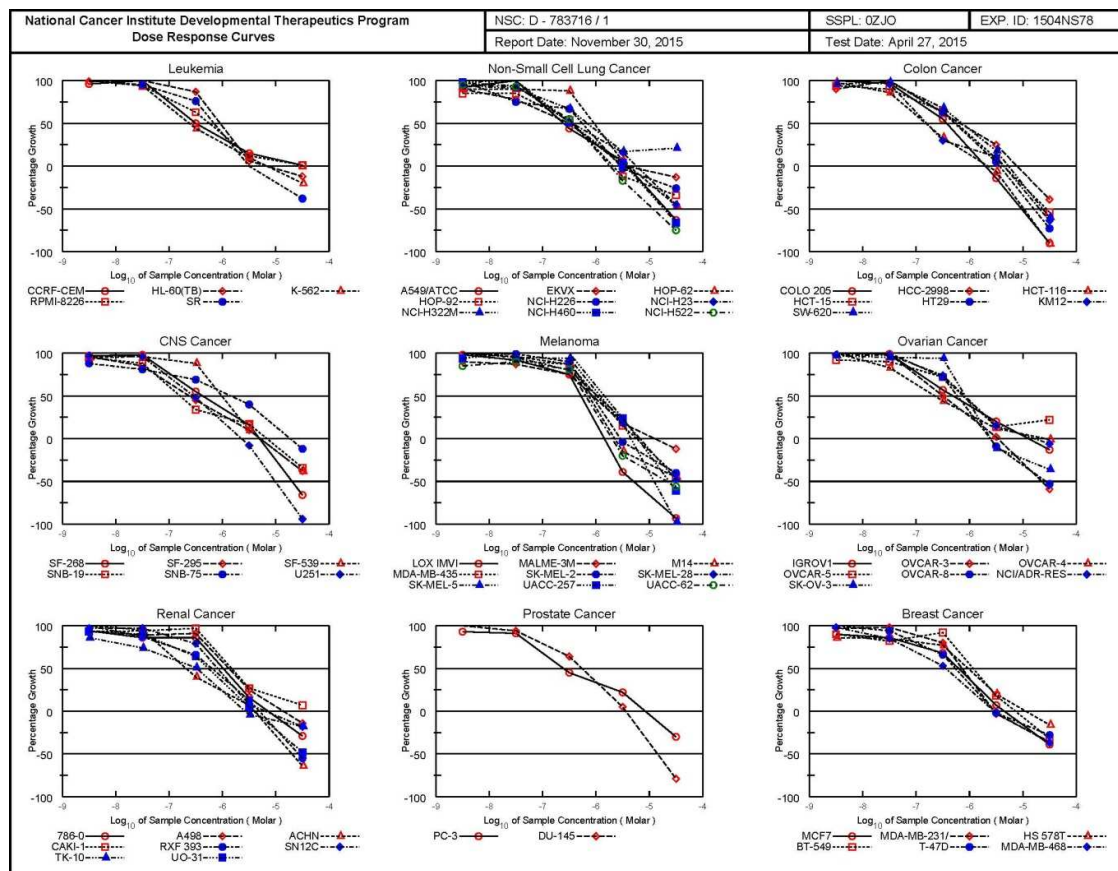
**Figure S2. Dose response curves of compound 14**



**Figure S3. Details of the *in vitro* testing results of compound 14**

| National Cancer Institute Developmental Therapeutics Program<br>In-Vitro Testing Results |           |       |                                       |       |       |       |       |      |                |      |      |      |               |           |           |  |
|------------------------------------------------------------------------------------------|-----------|-------|---------------------------------------|-------|-------|-------|-------|------|----------------|------|------|------|---------------|-----------|-----------|--|
| NSC : D - 783718 / 1                                                                     |           |       | Experiment ID : 1505NS81              |       |       |       |       |      | Test Type : 08 |      |      |      | Units : Molar |           |           |  |
| Report Date : May 25, 2015                                                               |           |       | Test Date : May 04, 2015              |       |       |       |       |      | QNS :          |      |      |      | MC :          |           |           |  |
| COMI : LYZ001-143                                                                        |           |       | Stain Reagent : SRB Dual-Pass Related |       |       |       |       |      | SSPL : 0ZJO    |      |      |      |               |           |           |  |
| Panel/Cell Line                                                                          | Time Zero | Ctrl  | Log10 Concentration                   |       |       |       |       |      | Percent Growth |      |      |      | GI50          | TGI       | LC50      |  |
|                                                                                          |           |       | -8.3                                  | -7.3  | -6.3  | -5.3  | -4.3  | -8.3 | -7.3           | -6.3 | -5.3 | -4.3 |               |           |           |  |
| Leukemia                                                                                 |           |       |                                       |       |       |       |       |      |                |      |      |      |               |           |           |  |
| Leukemia                                                                                 | 0.202     | 1.708 | 1.588                                 | 1.715 | 1.424 | 0.681 | 0.279 | 92   | 100            | 81   | 32   | 5    | 2.14E-6       | > 5.00E-5 | > 5.00E-5 |  |
| K-562-CEM                                                                                | 0.172     | 2.230 | 2.311                                 | 2.284 | 2.197 | 0.463 | 0.208 | 104  | 103            | 98   | 14   | 2    | 1.83E-6       | > 5.00E-5 | > 5.00E-5 |  |
| MOLT-4                                                                                   | 0.429     | 2.332 | 2.163                                 | 2.016 | 1.879 | 0.732 | 0.362 | 91   | 83             | 76   | 16   | -16  | 1.36E-6       | > 5.00E-5 | > 5.00E-5 |  |
| RPMI-8226                                                                                | 0.791     | 2.792 | 2.647                                 | 2.789 | 2.730 | 1.455 | 1.024 | 93   | 100            | 97   | 33   | 12   | 2.72E-6       | > 5.00E-5 | > 5.00E-5 |  |
| SR                                                                                       | 0.258     | 1.451 | 1.326                                 | 1.313 | 1.221 | 0.354 | 0.171 | 89   | 88             | 81   | 8    | -34  | 1.32E-6       | > 5.00E-5 | > 5.00E-5 |  |
| Non-Small Cell Lung Cancer                                                               |           |       |                                       |       |       |       |       |      |                |      |      |      |               |           |           |  |
| A549/ATCC                                                                                | 0.535     | 1.738 | 1.626                                 | 1.746 | 1.818 | 0.735 | 0.190 | 91   | 101            | 107  | 17   | -64  | 2.13E-6       | 8.02E-6   | 3.31E-5   |  |
| EKVX                                                                                     | 0.843     | 1.751 | 1.700                                 | 1.623 | 1.575 | 0.843 | 0.462 | 94   | 86             | 81   |      | -45  | 1.20E-6       | 4.99E-6   | > 5.00E-5 |  |
| HOP-62                                                                                   | 0.753     | 1.785 | 1.738                                 | 1.842 | 1.819 | 1.015 | 0.271 | 95   | 105            | 103  | 25   | -64  | 2.41E-6       | 9.61E-6   | 3.49E-5   |  |
| HOP-92                                                                                   | 1.291     | 1.826 | 1.717                                 | 1.784 | 1.827 | 1.118 | 0.620 | 80   | 92             | 100  | -13  | -52  | 1.38E-6       | 3.81E-6   | 4.43E-5   |  |
| NCH-H23                                                                                  | 0.632     | 2.147 | 2.080                                 | 2.084 | 1.983 | 0.758 | 0.187 | 96   | 96             | 89   | 8    | -70  | 1.53E-6       | 6.37E-6   | 2.75E-5   |  |
| NCH-H322M                                                                                | 0.809     | 2.174 | 2.049                                 | 2.160 | 2.043 | 1.027 | 0.542 | 91   | 99             | 90   | 16   | -33  | 1.74E-6       | 1.06E-5   | > 5.00E-5 |  |
| NCH-H460                                                                                 | 0.317     | 2.936 | 2.933                                 | 3.033 | 2.949 | 0.304 | 0.100 | 100  | 104            | 100  | -4   | -69  | 1.52E-6       | 4.57E-6   | 2.57E-5   |  |
| NCH-H522                                                                                 | 1.078     | 2.046 | 2.104                                 | 2.013 | 2.052 | 0.866 | 0.030 | 106  | 97             | 101  | -20  | -97  | 1.32E-6       | 3.43E-6   | 1.23E-5   |  |
| Colon Cancer                                                                             |           |       |                                       |       |       |       |       |      |                |      |      |      |               |           |           |  |
| COLO 205                                                                                 | 0.480     | 1.694 | 1.731                                 | 1.729 | 1.718 | 0.358 | 0.124 | 103  | 103            | 102  | -25  | -74  | 1.28E-6       | 3.16E-6   | 1.59E-5   |  |
| HCC-2998                                                                                 | 0.497     | 1.562 | 1.554                                 | 1.579 | 1.531 | 0.674 | 0.040 | 99   | 102            | 97   | 17   | -92  | 1.92E-6       | 7.10E-6   | 2.05E-5   |  |
| HCT-116                                                                                  | 0.333     | 2.334 | 2.219                                 | 2.264 | 2.385 | 0.490 | 0.041 | 94   | 97             | 103  | 8    | -88  | 1.79E-6       | 6.04E-6   | 2.02E-5   |  |
| HCT-15                                                                                   | 0.350     | 2.023 | 2.015                                 | 1.951 | 1.860 | 0.436 | 0.021 | 100  | 96             | 90   | 5    | -94  | 1.49E-6       | 5.63E-6   | 1.80E-5   |  |
| HT29                                                                                     | 0.308     | 1.841 | 1.841                                 | 1.860 | 1.793 | 0.352 | 0.028 | 100  | 101            | 97   | 3    | -91  | 1.58E-6       | 5.36E-6   | 1.83E-5   |  |
| KM12                                                                                     | 0.511     | 2.741 | 2.698                                 | 2.771 | 2.342 | 0.724 | 0.262 | 98   | 101            | 82   | 10   | -49  | 1.39E-6       | 7.29E-6   | > 5.00E-5 |  |
| SW-620                                                                                   | 0.286     | 2.001 | 1.945                                 | 1.945 | 2.072 | 0.509 | 0.062 | 97   | 97             | 104  | 13   | -78  | 1.96E-6       | 6.94E-6   | 2.45E-5   |  |
| CNS Cancer                                                                               |           |       |                                       |       |       |       |       |      |                |      |      |      |               |           |           |  |
| SF-268                                                                                   | 0.590     | 2.281 | 2.157                                 | 2.232 | 2.085 | 0.954 | 0.195 | 93   | 97             | 88   | 22   | -67  | 1.88E-6       | 8.75E-6   | 3.21E-5   |  |
| SF-295                                                                                   | 0.781     | 2.705 | 2.737                                 | 2.784 | 2.466 | 0.916 | 0.442 | 102  | 104            | 88   | 7    | -43  | 1.46E-6       | 6.89E-6   | > 5.00E-5 |  |
| SF-539                                                                                   | 1.154     | 2.843 | 2.814                                 | 2.765 | 2.732 | 1.395 | 0.475 | 98   | 95             | 93   | 14   | -59  | 1.77E-6       | 7.84E-6   | 3.78E-5   |  |
| SNB-19                                                                                   | 0.645     | 1.972 | 1.909                                 | 1.955 | 1.755 | 0.837 | 0.271 | 95   | 99             | 84   | 14   | -58  | 1.53E-6       | 7.92E-6   | 3.88E-5   |  |
| SNB-75                                                                                   | 1.007     | 1.765 | 1.607                                 | 1.566 | 1.622 | 1.159 | 0.336 | 79   | 74             | 81   | 20   | -67  | 1.61E-6       | 8.50E-6   | 3.21E-5   |  |
| U251                                                                                     | 0.529     | 2.120 | 2.084                                 | 2.020 | 1.998 | 0.611 | 0.160 | 98   | 94             | 92   | 5    | -70  | 1.53E-6       | 5.85E-6   | 2.72E-5   |  |
| Melanoma                                                                                 |           |       |                                       |       |       |       |       |      |                |      |      |      |               |           |           |  |
| LOX IMVI                                                                                 | 0.362     | 2.444 | 2.346                                 | 2.271 | 2.215 | 0.575 | 0.024 | 95   | 92             | 89   | 10   | -93  | 1.56E-6       | 6.28E-6   | 1.91E-5   |  |
| MALME-3M                                                                                 | 0.792     | 1.481 | 1.416                                 | 1.450 | 1.446 | 0.970 | 0.398 | 90   | 95             | 95   | 26   | -50  | 2.23E-6       | 1.10E-5   | > 5.00E-5 |  |
| M14                                                                                      | 0.520     | 2.077 | 2.046                                 | 1.989 | 2.038 | 0.849 | 0.260 | 98   | 94             | 97   | 21   | -50  | 2.09E-6       | 9.90E-6   | > 5.00E-5 |  |
| MDA-MB-435                                                                               | 0.617     | 3.008 | 3.187                                 |       | 2.908 | 1.324 | 0.122 | 107  |                | 96   | 30   | -80  | 2.46E-6       | 9.30E-6   | 2.65E-5   |  |
| SK-MEL-2                                                                                 | 1.068     | 1.658 | 1.584                                 | 1.570 | 1.523 | 0.585 | 0.093 | 87   | 85             | 77   | -45  | -91  | 8.32E-7       | 2.13E-6   | 6.33E-6   |  |
| SK-MEL-28                                                                                | 0.766     | 2.257 | 2.242                                 | 2.131 | 2.127 | 1.106 | 0.202 | 99   | 92             | 91   | 23   | -74  | 2.00E-6       | 8.61E-6   | 2.84E-5   |  |
| SK-MEL-5                                                                                 | 0.784     | 2.448 | 2.406                                 | 2.358 | 2.456 | 1.557 | 0.115 | 97   | 95             | 100  | 46   | -85  | 4.29E-6       | 1.13E-5   | 2.70E-5   |  |
| UACC-257                                                                                 | 1.007     | 1.910 | 1.793                                 | 1.875 | 1.950 | 1.670 | 0.558 | 87   | 96             | 104  | 73   | -45  | 7.89E-6       | 2.09E-5   | > 5.00E-5 |  |
| UACC-62                                                                                  | 0.922     | 2.742 | 2.491                                 | 2.563 | 2.640 | 1.394 | 0.301 | 86   | 90             | 94   | 26   | -67  | 2.23E-6       | 9.48E-6   | 3.25E-5   |  |
| Ovarian Cancer                                                                           |           |       |                                       |       |       |       |       |      |                |      |      |      |               |           |           |  |
| IGROV1                                                                                   | 0.923     | 2.664 | 2.681                                 | 2.700 | 2.578 | 1.236 | 0.432 | 101  | 102            | 95   | 18   | -53  | 1.92E-6       | 8.94E-6   | 4.51E-5   |  |
| OVCAR-3                                                                                  | 0.551     | 1.894 | 1.966                                 | 1.933 | 1.803 | 0.659 | 0.169 | 105  | 103            | 93   | 8    | -69  | 1.61E-6       | 6.34E-6   | 2.81E-5   |  |
| OVCAR-4                                                                                  | 0.865     | 1.669 | 1.615                                 | 1.547 | 1.569 | 0.835 | 0.482 | 93   | 85             | 88   | -3   | -44  | 1.29E-6       | 4.58E-6   | > 5.00E-5 |  |
| OVCAR-5                                                                                  | 0.781     | 2.028 | 1.926                                 | 1.885 | 1.828 | 0.972 | 0.444 | 92   | 89             | 84   | 15   | -43  | 1.56E-6       | 9.14E-6   | > 5.00E-5 |  |
| OVCAR-8                                                                                  | 0.618     | 2.001 | 2.016                                 | 2.101 | 2.060 | 0.837 | 0.283 | 101  | 107            | 104  | 16   | -54  | 2.05E-6       | 8.40E-6   | 4.34E-5   |  |
| NCI/ADR-RES                                                                              | 0.679     | 2.178 | 2.159                                 | 2.106 | 2.064 | 0.980 | 0.308 | 99   | 95             | 92   | 20   | -55  | 1.93E-6       | 9.28E-6   | 4.33E-5   |  |
| SK-OV-3                                                                                  | 0.964     | 1.886 | 1.856                                 | 1.912 | 1.897 | 1.043 | 0.454 | 97   | 103            | 101  | 9    | -53  | 1.79E-6       | 6.89E-6   | 4.48E-5   |  |
| Renal Cancer                                                                             |           |       |                                       |       |       |       |       |      |                |      |      |      |               |           |           |  |
| 786-O                                                                                    | 0.666     | 2.341 | 2.320                                 | 2.251 | 2.419 | 1.055 | 0.187 | 99   | 95             | 105  | 23   | -72  | 2.35E-6       | 8.77E-6   | 2.94E-5   |  |
| A498                                                                                     | 1.665     | 2.224 | 2.071                                 | 2.080 | 2.148 | 1.864 | 0.735 | 73   | 74             | 86   | 36   | -56  | 2.60E-6       | 1.22E-5   | 4.31E-5   |  |
| ACHN                                                                                     | 0.537     | 2.232 | 2.156                                 | 2.077 | 2.043 | 0.595 | 0.148 | 95   | 91             | 89   | 3    | -72  | 1.42E-6       | 5.54E-6   | 2.53E-5   |  |
| CAKI-1                                                                                   | 0.956     | 3.300 | 3.539                                 |       | 3.190 | 1.975 | 0.462 | 110  |                | 95   | 43   | -52  | 3.74E-6       | 1.43E-5   | 4.80E-5   |  |
| RXF 393                                                                                  | 0.976     | 1.603 | 1.578                                 | 1.584 | 1.537 | 1.102 | 0.300 | 96   | 97             | 90   | 20   | -69  | 1.85E-6       | 8.39E-6   | 3.04E-5   |  |
| SN12C                                                                                    | 0.795     | 2.474 | 2.404                                 | 2.452 | 2.558 | 1.005 | 0.424 | 96   | 99             | 105  | 13   | -47  | 1.97E-6       | 8.13E-6   | > 5.00E-5 |  |
| UO-31                                                                                    | 0.805     | 2.736 | 2.623                                 | 2.625 | 2.496 | 0.904 | 0.344 | 94   | 94             | 88   | 5    | -57  | 1.43E-6       | 6.04E-6   | 3.82E-5   |  |
| Prostate Cancer                                                                          |           |       |                                       |       |       |       |       |      |                |      |      |      |               |           |           |  |
| PC-3                                                                                     | 0.566     | 2.078 | 2.046                                 | 2.090 | 2.050 | 0.764 | 0.183 | 98   | 101            | 98   | 13   | -68  | 1.84E-6       | 7.26E-6   | 3.02E-5   |  |
| DU-145                                                                                   | 0.402     | 1.960 | 2.019                                 | 1.914 | 1.904 | 0.699 | 0.094 | 104  | 97             | 96   | 19   | -77  | 1.99E-6       | 7.91E-6   | 2.64E-5   |  |
| Breast Cancer                                                                            |           |       |                                       |       |       |       |       |      |                |      |      |      |               |           |           |  |
| MCF7                                                                                     | 0.501     | 2.622 | 2.513                                 | 2.548 | 2.528 | 0.651 | 0.129 | 95   | 97             | 96   | 7    | -74  | 1.64E-6       | 6.11E-6   | 2.52E-5   |  |
| MDA-MB-231/ATCC                                                                          | 0.712     | 1.726 | 1.714                                 | 1.726 | 1.737 | 0.875 | 0.426 | 99   | 100            | 101  | 16   | -40  | 1.99E-6       | 9.64E-6   | > 5.00E-5 |  |
| HS 578T                                                                                  | 0.932     | 1.860 | 1.808                                 | 1.798 | 1.842 | 1.051 | 0.544 | 94   | 93             | 98   | 13   | -42  | 1.83E-6       | 8.58E-6   | > 5.00E-5 |  |
| BT-549                                                                                   | 1.139     | 2.163 | 2.172                                 | 2.221 | 2.254 | 1.421 | 0.615 | 101  | 106            | 109  | 27   | -46  | 2.65E-6       | 1.18E-5   | > 5.00E-5 |  |
| T-47D                                                                                    | 1.062     | 2.205 | 2.364                                 | 2.544 | 2.309 | 1.639 | 1.011 | 114  | 130            | 109  | 50   | -5   | 5.09E-6       | 4.09E-5   | > 5.00E-5 |  |
| MDA-MB-468                                                                               | 0.798     | 1.627 | 1.581                                 | 1.539 | 1.587 | 0.784 | 0.336 | 94   | 89             | 95   | -2   | -58  | 1.46E-6       | 4.80E-6   | 3.61E-5   |  |

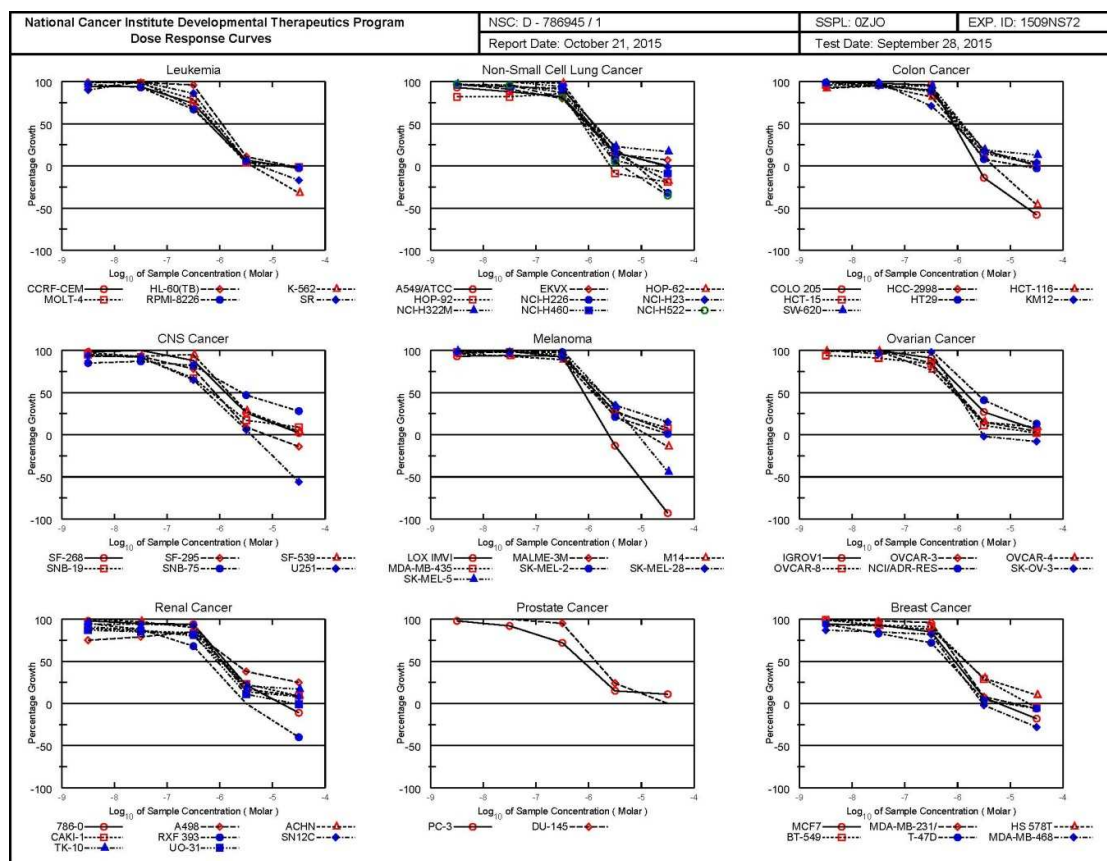
**Figure S4. Dose response curves of compound 16**



**Figure S5.** Details of the *in vitro* testing results of compound 16

| National Cancer Institute Developmental Therapeutics Program<br>In-Vitro Testing Results |              |       |                     |                                       |       |       |       |                |      |      |      |               |         |           |           |  |
|------------------------------------------------------------------------------------------|--------------|-------|---------------------|---------------------------------------|-------|-------|-------|----------------|------|------|------|---------------|---------|-----------|-----------|--|
| NSC : D - 783716 / 1                                                                     |              |       |                     | Experiment ID : 1504NS78              |       |       |       | Test Type : 08 |      |      |      | Units : Molar |         |           |           |  |
| Report Date : November 30, 2015                                                          |              |       |                     | Test Date : April 27, 2015            |       |       |       | QNS :          |      |      |      | MC :          |         |           |           |  |
| COMI : LY2001-136                                                                        |              |       |                     | Stain Reagent : SRB Dual-Pass Related |       |       |       | SSPL : 0ZJO    |      |      |      |               |         |           |           |  |
| Panel/Cell Line                                                                          | Time<br>Zero | Ctrl  | Log10 Concentration |                                       |       |       |       | Percent Growth |      |      |      |               | GI50    | TGI       | LC50      |  |
|                                                                                          |              |       | -8.5                | -7.5                                  | -6.5  | -5.5  | -4.5  | -8.5           | -7.5 | -6.5 | -5.5 | -4.5          |         |           |           |  |
| Leukemia                                                                                 |              |       |                     |                                       |       |       |       |                |      |      |      |               |         |           |           |  |
| CCIX/CEM                                                                                 | 0.571        | 1.613 | 1.574               | 1.619                                 | 1.095 | 0.723 | 0.586 | 96             | 101  | 50   | 15   | 1             | 3.31E-7 | > 3.25E-5 | > 3.25E-5 |  |
| HL-60(TB)                                                                                | 0.898        | 2.535 | 2.518               | 2.636                                 | 2.326 | 0.993 | 0.787 | 99             | 106  | 87   | 6    | -12           | 9.31E-7 | 6.78E-6   | > 3.25E-5 |  |
| K-562                                                                                    | 0.271        | 1.553 | 1.553               | 1.471                                 | 0.836 | 0.397 | 0.216 | 100            | 94   | 44   | 10   | -20           | 2.46E-7 | 6.88E-6   | > 3.25E-5 |  |
| RPMI-8226                                                                                | 0.877        | 2.331 | 2.417               | 2.247                                 | 1.797 | 1.055 | 0.888 | 106            | 94   | 63   | 12   | 1             | 5.92E-7 | > 3.25E-5 | > 3.25E-5 |  |
| SR                                                                                       | 0.502        | 1.235 | 1.276               | 1.195                                 | 1.058 | 0.498 | 0.311 | 106            | 95   | 76   | .    | -38           | 7.06E-7 | 3.17E-6   | > 3.25E-5 |  |
| Non-Small Cell Lung Cancer                                                               |              |       |                     |                                       |       |       |       |                |      |      |      |               |         |           |           |  |
| A549/ATCC                                                                                | 0.484        | 1.510 | 1.430               | 1.518                                 | 0.925 | 0.530 | 0.172 | 92             | 101  | 44   | 6    | -63           | 2.55E-7 | 4.01E-6   | 2.11E-5   |  |
| EKVX                                                                                     | 0.948        | 1.897 | 1.806               | 1.690                                 | 1.420 | 0.957 | 0.824 | 90             | 78   | 50   | 1    | -13           | 3.17E-7 | 3.80E-6   | > 3.25E-5 |  |
| HOP-62                                                                                   | 1.224        | 2.173 | 2.077               | 2.074                                 | 2.060 | 1.279 | 0.665 | 90             | 90   | 88   | 6    | -46           | 9.42E-7 | 4.21E-6   | > 3.25E-5 |  |
| HOP-92                                                                                   | 1.137        | 1.558 | 1.493               | 1.496                                 | 1.363 | 0.999 | 0.745 | 85             | 85   | 54   | -12  | -34           | 3.70E-7 | 2.13E-6   | > 3.25E-5 |  |
| NCI-H226                                                                                 | 0.664        | 1.288 | 1.287               | 1.133                                 | 1.085 | 0.644 | 0.494 | 100            | 75   | 67   | -3   | -26           | 5.75E-7 | 2.94E-6   | > 3.25E-5 |  |
| NCI-H23                                                                                  | 0.815        | 2.641 | 2.589               | 2.536                                 | 1.759 | 1.115 | 0.451 | 97             | 94   | 52   | 16   | -45           | 3.63E-7 | 6.03E-6   | > 3.25E-5 |  |
| NCI-H322M                                                                                | 0.936        | 2.433 | 2.342               | 2.295                                 | 1.937 | 1.184 | 1.249 | 94             | 91   | 67   | 17   | 21            | 7.04E-7 | > 3.25E-5 | > 3.25E-5 |  |
| NCI-H460                                                                                 | 0.293        | 2.842 | 2.800               | 2.858                                 | 1.598 | 0.401 | 0.101 | 98             | 101  | 51   | 4    | -66           | 3.45E-7 | 3.74E-6   | 1.95E-5   |  |
| NCI-H522                                                                                 | 1.015        | 2.270 | 2.204               | 2.189                                 | 1.703 | 0.846 | 0.255 | 95             | 93   | 55   | -17  | -75           | 3.79E-7 | 1.90E-6   | 1.21E-5   |  |
| Colon Cancer                                                                             |              |       |                     |                                       |       |       |       |                |      |      |      |               |         |           |           |  |
| COLO 205                                                                                 | 0.354        | 1.313 | 1.351               | 1.288                                 | 0.880 | 0.304 | 0.035 | 104            | 97   | 55   | -14  | -90           | 3.82E-7 | 2.03E-6   | 9.64E-6   |  |
| HCC-2998                                                                                 | 0.552        | 1.906 | 1.771               | 1.917                                 | 1.387 | 0.894 | 0.334 | 90             | 101  | 62   | 25   | -39           | 6.79E-7 | 7.98E-6   | > 3.25E-5 |  |
| HCT-116                                                                                  | 0.295        | 1.512 | 1.492               | 1.340                                 | 0.699 | 0.278 | 0.028 | 98             | 86   | 33   | -6   | -91           | 1.56E-7 | 2.31E-6   | 1.08E-5   |  |
| HCT-15                                                                                   | 0.246        | 1.535 | 1.462               | 1.405                                 | 1.075 | 0.357 | 0.113 | 94             | 90   | 64   | 9    | -54           | 5.87E-7 | 4.45E-6   | 2.80E-5   |  |
| HT29                                                                                     | 0.393        | 2.235 | 2.228               | 2.227                                 | 1.548 | 0.493 | 0.107 | 100            | 100  | 63   | 5    | -73           | 5.42E-7 | 3.81E-6   | 1.66E-5   |  |
| KM12                                                                                     | 0.671        | 3.130 | 3.121               | 3.037                                 | 1.419 | 0.948 | 0.240 | 100            | 96   | 30   | 11   | -64           | 1.64E-7 | 4.58E-6   | 2.10E-5   |  |
| SW-620                                                                                   | 0.311        | 2.219 | 2.145               | 2.182                                 | 1.606 | 0.653 | 0.125 | 96             | 98   | 68   | 18   | -60           | 7.40E-7 | 5.52E-6   | 2.43E-5   |  |
| CNS Cancer                                                                               |              |       |                     |                                       |       |       |       |                |      |      |      |               |         |           |           |  |
| SF-268                                                                                   | 0.570        | 2.009 | 1.972               | 1.982                                 | 1.360 | 0.805 | 0.195 | 97             | 98   | 55   | 16   | -66           | 4.35E-7 | 5.13E-6   | 2.08E-5   |  |
| SF-295                                                                                   | 0.681        | 2.533 | 2.450               | 2.263                                 | 1.523 | 0.863 | 0.423 | 96             | 85   | 45   | 10   | -38           | 2.50E-7 | 5.22E-6   | > 3.25E-5 |  |
| SF-539                                                                                   | 1.081        | 2.872 | 2.776               | 2.806                                 | 2.664 | 1.252 | 0.673 | 95             | 96   | 88   | 10   | -38           | 9.97E-7 | 5.17E-6   | > 3.25E-5 |  |
| SNB-19                                                                                   | 0.730        | 2.179 | 2.103               | 2.011                                 | 1.229 | 0.982 | 0.484 | 95             | 88   | 34   | 17   | -34           | 1.67E-7 | 7.10E-6   | > 3.25E-5 |  |
| SNB-75                                                                                   | 0.898        | 1.835 | 1.727               | 1.659                                 | 1.543 | 1.269 | 0.791 | 88             | 81   | 69   | 40   | -12           | 1.43E-6 | 1.91E-5   | > 3.25E-5 |  |
| U251                                                                                     | 0.626        | 2.171 | 2.120               | 2.115                                 | 1.370 | 0.574 | 0.038 | 97             | 96   | 48   | -8   | -94           | 2.98E-7 | 2.31E-6   | 9.95E-6   |  |
| Melanoma                                                                                 |              |       |                     |                                       |       |       |       |                |      |      |      |               |         |           |           |  |
| LOX IMVI                                                                                 | 0.511        | 2.967 | 2.916               | 2.766                                 | 2.348 | 0.312 | 0.034 | 98             | 92   | 75   | -39  | -93           | 5.37E-7 | 1.48E-6   | 5.17E-6   |  |
| MALME-3M                                                                                 | 0.762        | 1.466 | 1.397               | 1.372                                 | 1.293 | 0.690 | 0.670 | 90             | 87   | 75   | 18   | -12           | 9.02E-7 | 1.29E-5   | > 3.25E-5 |  |
| M14                                                                                      | 0.421        | 1.298 | 1.306               | 1.259                                 | 1.188 | 0.357 | 0.230 | 101            | 96   | 87   | -15  | -45           | 7.53E-7 | 2.31E-6   | > 3.25E-5 |  |
| MDA-MB-435                                                                               | 0.491        | 2.704 | 2.715               | 2.498                                 | 2.416 | 0.818 | 0.280 | 101            | 91   | 87   | 15   | -43           | 1.06E-6 | 5.85E-6   | > 3.25E-5 |  |
| SK-MEL-2                                                                                 | 1.336        | 2.623 | 2.649               | 2.609                                 | 2.488 | 1.279 | 0.797 | 102            | 99   | 90   | -4   | -40           | 8.58E-7 | 2.93E-6   | > 3.25E-5 |  |
| SK-MEL-28                                                                                | 0.557        | 1.789 | 1.787               | 1.729                                 | 1.542 | 0.844 | 0.292 | 100            | 95   | 80   | 23   | -48           | 1.10E-6 | 6.92E-6   | > 3.25E-5 |  |
| SK-MEL-5                                                                                 | 0.782        | 3.270 | 3.284               | 3.137                                 | 3.114 | 1.240 | 0.027 | 101            | 95   | 94   | 18   | -97           | 1.24E-6 | 4.70E-6   | 1.28E-5   |  |
| UACC-257                                                                                 | 0.960        | 1.554 | 1.517               | 1.613                                 | 1.695 | 1.101 | 0.375 | 94             | 110  | 124  | 24   | -61           | 1.77E-6 | 6.19E-6   | 2.41E-5   |  |
| UACC-62                                                                                  | 0.903        | 2.679 | 2.407               | 2.509                                 | 2.335 | 0.726 | 0.399 | 85             | 90   | 81   | -20  | -56           | 6.57E-7 | 2.07E-6   | 2.25E-5   |  |
| Ovarian Cancer                                                                           |              |       |                     |                                       |       |       |       |                |      |      |      |               |         |           |           |  |
| IGROV1                                                                                   | 0.764        | 2.470 | 2.486               | 2.460                                 | 1.734 | 1.108 | 0.663 | 101            | 99   | 57   | 20   | -13           | 4.99E-7 | 1.30E-5   | > 3.25E-5 |  |
| OVCA-3                                                                                   | 0.412        | 1.549 | 1.569               | 1.534                                 | 0.977 | 0.431 | 0.171 | 102            | 99   | 50   | 2    | -59           | 3.20E-7 | 3.46E-6   | 2.34E-5   |  |
| OVCA-4                                                                                   | 0.731        | 1.926 | 1.931               | 1.723                                 | 1.259 | 0.871 | 0.724 | 100            | 83   | 44   | 12   | -1            | 2.29E-7 | 2.70E-5   | > 3.25E-5 |  |
| OVCA-5                                                                                   | 0.531        | 1.633 | 1.545               | 1.528                                 | 1.327 | 0.685 | 0.771 | 92             | 90   | 72   | 14   | 22            | 7.81E-7 | > 3.25E-5 | > 3.25E-5 |  |
| OVCA-8                                                                                   | 0.537        | 1.822 | 1.831               | 1.834                                 | 1.461 | 0.487 | 0.254 | 101            | 101  | 72   | -9   | -53           | 6.04E-7 | 2.50E-6   | 2.82E-5   |  |
| NCI/ADR-RES                                                                              | 0.580        | 2.161 | 2.129               | 2.132                                 | 1.751 | 0.822 | 0.544 | 98             | 98   | 74   | 15   | -6            | 8.34E-7 | 1.66E-5   | > 3.25E-5 |  |
| SK-OV-3                                                                                  | 0.870        | 1.715 | 1.694               | 1.677                                 | 1.664 | 0.778 | 0.561 | 97             | 95   | 94   | -11  | -36           | 8.55E-7 | 2.57E-6   | > 3.25E-5 |  |
| Renal Cancer                                                                             |              |       |                     |                                       |       |       |       |                |      |      |      |               |         |           |           |  |
| 786-O                                                                                    | 0.684        | 2.065 | 1.986               | 1.872                                 | 1.873 | 0.911 | 0.489 | 94             | 86   | 86   | 16   | -29           | 1.07E-6 | 7.54E-6   | > 3.25E-5 |  |
| A498                                                                                     | 1.272        | 2.155 | 2.103               | 2.059                                 | 2.079 | 1.492 | 1.097 | 94             | 89   | 91   | 25   | -14           | 1.36E-6 | 1.43E-5   | > 3.25E-5 |  |
| ACHN                                                                                     | 0.542        | 2.145 | 2.177               | 2.059                                 | 1.177 | 0.656 | 0.197 | 102            | 95   | 40   | 7    | -64           | 2.10E-7 | 4.09E-6   | 2.08E-5   |  |
| CAKI-1                                                                                   | 0.516        | 3.057 | 2.882               | 2.898                                 | 2.987 | 1.190 | 0.707 | 93             | 94   | 97   | 27   | 7             | 1.51E-6 | > 3.25E-5 | > 3.25E-5 |  |
| RFX 393                                                                                  | 0.712        | 1.608 | 1.607               | 1.491                                 | 1.305 | 0.825 | 0.321 | 100            | 87   | 66   | 13   | -55           | 6.51E-7 | 5.00E-6   | 2.75E-5   |  |
| SN12C                                                                                    | 0.798        | 2.452 | 2.396               | 2.406                                 | 2.112 | 0.938 | 0.658 | 97             | 97   | 79   | 8    | -18           | 8.44E-7 | 6.85E-6   | > 3.25E-5 |  |
| TK-10                                                                                    | 0.989        | 1.633 | 1.541               | 1.463                                 | 1.318 | 0.948 | 0.815 | 86             | 74   | 51   | -4   | -18           | 3.40E-7 | 2.73E-6   | > 3.25E-5 |  |
| UO-31                                                                                    | 0.813        | 2.698 | 2.572               | 2.519                                 | 2.015 | 0.909 | 0.421 | 93             | 90   | 64   | 5    | -48           | 5.58E-7 | 4.05E-6   | > 3.25E-5 |  |
| Prostate Cancer                                                                          |              |       |                     |                                       |       |       |       |                |      |      |      |               |         |           |           |  |
| PC-3                                                                                     | 0.475        | 1.481 | 1.407               | 1.386                                 | 0.933 | 0.696 | 0.334 | 93             | 91   | 45   | 22   | -30           | 2.58E-7 | 8.64E-6   | > 3.25E-5 |  |
| DU-145                                                                                   | 0.473        | 1.994 | 2.006               | 1.904                                 | 1.441 | 0.551 | 0.100 | 101            | 94   | 64   | 5    | -79           | 5.56E-7 | 3.74E-6   | 1.47E-5   |  |
| Breast Cancer                                                                            |              |       |                     |                                       |       |       |       |                |      |      |      |               |         |           |           |  |
| MCF7                                                                                     | 0.530        | 2.792 | 2.571               | 2.481                                 | 2.063 | 0.699 | 0.324 | 90             | 86   | 68   | 7    | -39           | 6.41E-7 | 4.71E-6   | > 3.25E-5 |  |
| MDA-MB-231/ATCC                                                                          | 0.820        | 1.743 | 1.715               | 1.727                                 | 1.556 | 0.795 | 0.523 | 97             | 98   | 80   | -3   | -36           | 7.43E-7 | 2.99E-6   | > 3.25E-5 |  |
| HS 578T                                                                                  | 1.252        | 2.240 | 2.098               | 2.092                                 | 2.017 | 1.449 | 1.051 | 86             | 85   | 77   | 20   | -16           | 9.75E-7 | 1.16E-5   | > 3.25E-5 |  |
| BT-549                                                                                   | 1.061        | 1.875 | 1.792               | 1.729                                 | 1.812 | 1.204 | 0.717 | 90             | 82   | 92   | 18   | -32           | 1.19E-6 | 7.28E-6   | > 3.25E-5 |  |
| T-47D                                                                                    | 0.856        | 1.576 | 1.591               | 1.530                                 | 1.330 | 0.841 | 0.617 | 102            | 94   | 66   | -2   | -28           | 5.58E-7 | 3.06E-6   | > 3.25E-5 |  |
| MDA-MB-468                                                                               | 0.720        | 1.512 | 1.496               | 1.395                                 | 1.138 | 0.705 | 0.456 | 98             | 85   | 53   | -2   | -37           | 3.64E-7 | 2.97E-6   | > 3.25E-5 |  |

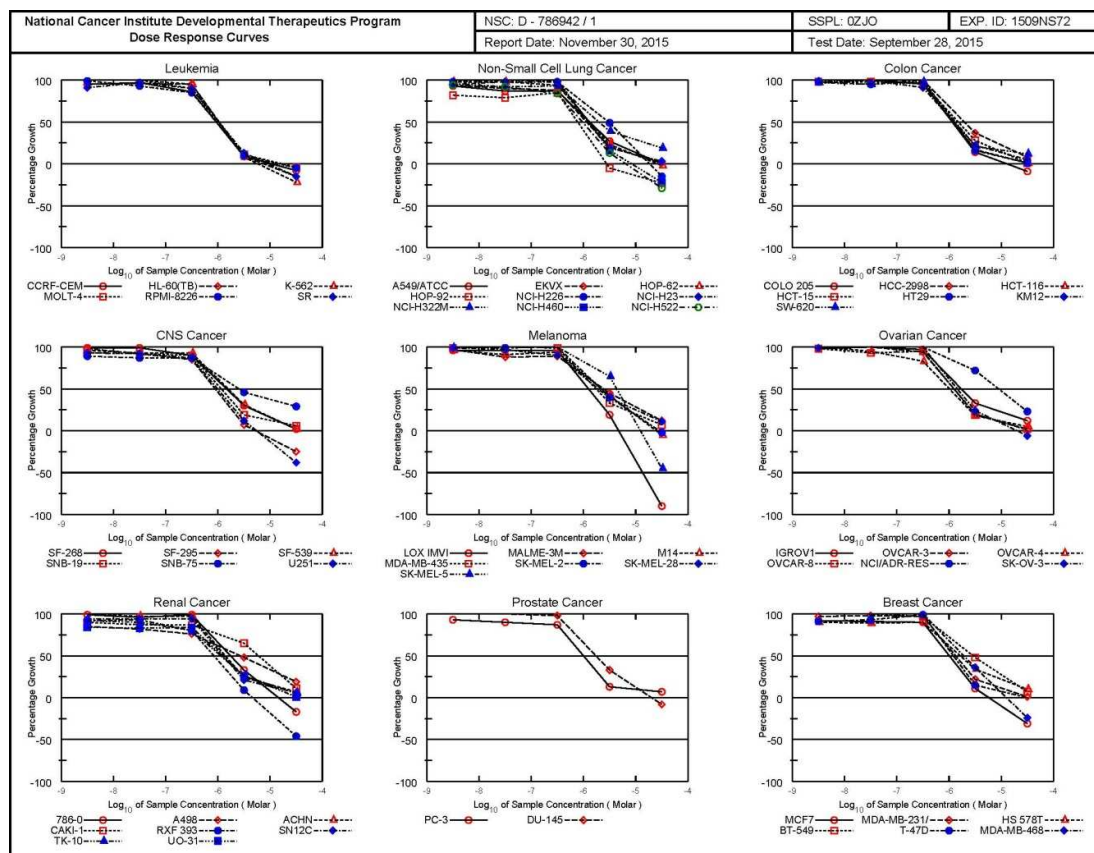
**Figure S6. Dose response curves of compound 17**



**Figure S7. Details of the *in vitro* testing results of compound 17**

| National Cancer Institute Developmental Therapeutics Program<br>In-Vitro Testing Results |           |       |       |                                       |       |       |       |      |      |                |      |      |         |               |           |  |
|------------------------------------------------------------------------------------------|-----------|-------|-------|---------------------------------------|-------|-------|-------|------|------|----------------|------|------|---------|---------------|-----------|--|
| NSC : D - 786945 / 1                                                                     |           |       |       | Experiment ID : 1509NS72              |       |       |       |      |      | Test Type : 08 |      |      |         | Units : Molar |           |  |
| Report Date : October 21, 2015                                                           |           |       |       | Test Date : September 28, 2015        |       |       |       |      |      | QNS :          |      |      |         | MC :          |           |  |
| COMI : Lyz002-84                                                                         |           |       |       | Stain Reagent : SRB Dual-Pass Related |       |       |       |      |      | SSPL : 0ZJO    |      |      |         |               |           |  |
| Log10 Concentration                                                                      |           |       |       |                                       |       |       |       |      |      |                |      |      |         |               |           |  |
| Panel/Cell Line                                                                          | Time Zero | Ctrl  | -8.5  | -7.5                                  | -6.5  | -5.5  | -4.5  | -8.5 | -7.5 | -6.5           | -5.5 | -4.5 | GI50    | TGI           | LC50      |  |
| Leukemia                                                                                 |           |       |       |                                       |       |       |       |      |      |                |      |      |         |               |           |  |
| CCRF-CEM                                                                                 | 0.764     | 2.790 | 2.675 | 2.667                                 | 2.265 | 0.912 | 0.744 | 94   | 94   | 74             | 7    | -3   | 7.46E-7 | 1.75E-5       | > 3.25E-5 |  |
| HL-60(TB)                                                                                | 0.932     | 2.843 | 2.819 | 2.822                                 | 2.768 | 1.136 | 0.914 | 99   | 99   | 96             | 11   | -2   | 1.13E-6 | 2.28E-5       | > 3.25E-5 |  |
| K-562                                                                                    | 0.320     | 2.351 | 2.475 | 2.413                                 | 1.729 | 0.392 | 0.219 | 106  | 103  | 69             | 4    | -32  | 6.40E-7 | 4.09E-6       | > 3.25E-5 |  |
| MOLT-4                                                                                   | 0.869     | 3.039 | 3.040 | 2.999                                 | 2.574 | 0.950 | 0.860 | 100  | 98   | 79             | 4    | -1   | 7.82E-7 | 1.92E-5       | > 3.25E-5 |  |
| RPMI-8226                                                                                | 0.958     | 2.808 | 2.751 | 2.676                                 | 2.192 | 1.078 | 0.942 | 97   | 93   | 67             | 6    | -2   | 6.16E-7 | 2.03E-5       | > 3.25E-5 |  |
| SR                                                                                       | 0.465     | 1.781 | 1.646 | 1.785                                 | 1.601 | 0.540 | 0.384 | 90   | 100  | 86             | 6    | -17  | 9.17E-7 | 5.72E-6       | > 3.25E-5 |  |
| Non-Small Cell Lung Cancer                                                               |           |       |       |                                       |       |       |       |      |      |                |      |      |         |               |           |  |
| A549/ATCC                                                                                | 0.552     | 2.291 | 2.168 | 2.085                                 | 1.972 | 0.823 | 0.560 | 93   | 88   | 82             | 16   | .    | 9.79E-7 | > 3.25E-5     | > 3.25E-5 |  |
| EKVX                                                                                     | 0.759     | 2.195 | 2.157 | 2.063                                 | 1.913 | 0.953 | 0.856 | 97   | 91   | 80             | 14   | 7    | 9.25E-7 | > 3.25E-5     | > 3.25E-5 |  |
| HOP-62                                                                                   | 0.741     | 2.031 | 2.097 | 2.048                                 | 1.999 | 0.935 | 0.606 | 105  | 101  | 98             | 15   | -18  | 1.22E-6 | 9.21E-6       | > 3.25E-5 |  |
| HOP-92                                                                                   | 1.379     | 1.822 | 1.741 | 1.741                                 | 1.760 | 1.262 | 1.119 | 82   | 82   | 86             | -9   | -19  | 7.82E-7 | 2.64E-6       | > 3.25E-5 |  |
| NCH-H226                                                                                 | 0.573     | 1.655 | 1.612 | 1.589                                 | 1.573 | 0.811 | 0.393 | 96   | 94   | 92             | 22   | -32  | 1.30E-6 | 8.38E-6       | > 3.25E-5 |  |
| NCH-H23                                                                                  | 0.805     | 2.271 | 2.211 | 2.210                                 | 2.081 | 1.033 | 0.794 | 96   | 96   | 87             | 16   | -1   | 1.07E-6 | 2.70E-5       | > 3.25E-5 |  |
| NCH-H322M                                                                                | 0.813     | 2.302 | 2.255 | 2.219                                 | 2.168 | 1.157 | 1.064 | 97   | 94   | 91             | 23   | 17   | 1.30E-6 | > 3.25E-5     | > 3.25E-5 |  |
| NCH-H460                                                                                 | 0.269     | 2.939 | 2.978 | 2.930                                 | 2.767 | 0.468 | 0.246 | 101  | 100  | 94             | 7    | -9   | 1.04E-6 | 9.48E-6       | > 3.25E-5 |  |
| NCH-H522                                                                                 | 0.815     | 2.477 | 2.427 | 2.407                                 | 2.164 | 0.905 | 0.533 | 97   | 96   | 81             | 5    | -35  | 8.38E-7 | 4.43E-6       | > 3.25E-5 |  |
| Colon Cancer                                                                             |           |       |       |                                       |       |       |       |      |      |                |      |      |         |               |           |  |
| COLO 205                                                                                 | 0.598     | 1.939 | 1.981 | 1.908                                 | 1.881 | 0.516 | 0.250 | 103  | 98   | 96             | -14  | -58  | 8.50E-7 | 2.44E-6       | 2.13E-5   |  |
| HCC-2998                                                                                 | 0.728     | 2.352 | 2.237 | 2.278                                 | 2.186 | 1.044 | 0.735 | 93   | 95   | 90             | 19   | .    | 1.19E-6 | > 3.25E-5     | > 3.25E-5 |  |
| HCT-116                                                                                  | 0.174     | 1.486 | 1.382 | 1.427                                 | 1.245 | 0.312 | 0.094 | 92   | 95   | 82             | 10   | -46  | 9.04E-7 | 4.98E-6       | > 3.25E-5 |  |
| HCT-15                                                                                   | 0.386     | 2.121 | 2.060 | 2.048                                 | 1.907 | 0.639 | 0.424 | 96   | 96   | 88             | 15   | 2    | 1.06E-6 | > 3.25E-5     | > 3.25E-5 |  |
| HT29                                                                                     | 0.371     | 2.452 | 2.432 | 2.388                                 | 2.220 | 0.531 | 0.360 | 99   | 97   | 89             | 8    | -3   | 9.78E-7 | 1.71E-5       | > 3.25E-5 |  |
| KM12                                                                                     | 0.450     | 2.706 | 2.677 | 2.693                                 | 2.055 | 0.834 | 0.544 | 99   | 99   | 71             | 17   | 4    | 7.99E-7 | > 3.25E-5     | > 3.25E-5 |  |
| SW-620                                                                                   | 0.278     | 2.474 | 2.433 | 2.354                                 | 2.353 | 0.700 | 0.558 | 98   | 95   | 95             | 19   | 13   | 1.27E-6 | > 3.25E-5     | > 3.25E-5 |  |
| CNS Cancer                                                                               |           |       |       |                                       |       |       |       |      |      |                |      |      |         |               |           |  |
| SF-268                                                                                   | 0.470     | 1.785 | 1.765 | 1.794                                 | 1.623 | 0.817 | 0.495 | 98   | 101  | 88             | 26   | 2    | 1.34E-6 | > 3.25E-5     | > 3.25E-5 |  |
| SF-295                                                                                   | 0.639     | 1.916 | 1.822 | 1.833                                 | 1.642 | 0.748 | 0.553 | 93   | 93   | 78             | 9    | -14  | 8.30E-7 | 7.92E-6       | > 3.25E-5 |  |
| SF-539                                                                                   | 0.838     | 2.795 | 2.732 | 2.660                                 | 2.688 | 1.390 | 0.923 | 97   | 93   | 95             | 28   | 4    | 1.53E-6 | > 3.25E-5     | > 3.25E-5 |  |
| SNB-19                                                                                   | 0.580     | 2.126 | 2.049 | 2.006                                 | 1.616 | 0.846 | 0.718 | 95   | 92   | 67             | 17   | 9    | 7.13E-7 | > 3.25E-5     | > 3.25E-5 |  |
| SNB-75                                                                                   | 0.963     | 1.888 | 1.751 | 1.765                                 | 1.718 | 1.394 | 1.227 | 85   | 87   | 82             | 47   | 28   | 2.60E-6 | > 3.25E-5     | > 3.25E-5 |  |
| U251                                                                                     | 0.360     | 1.660 | 1.582 | 1.550                                 | 1.203 | 0.437 | 0.159 | 94   | 92   | 65             | 6    | -56  | 5.81E-7 | 4.05E-6       | 2.60E-5   |  |
| Melanoma                                                                                 |           |       |       |                                       |       |       |       |      |      |                |      |      |         |               |           |  |
| LOX IMVI                                                                                 | 0.471     | 2.831 | 2.875 | 2.689                                 | 2.663 | 0.408 | 0.032 | 93   | 94   | 93             | -13  | -93  | 8.22E-7 | 2.43E-6       | 9.33E-6   |  |
| MALME-3M                                                                                 | 0.836     | 1.582 | 1.649 | 1.673                                 | 1.611 | 1.074 | 0.872 | 96   | 99   | 92             | 28   | 4    | 1.47E-6 | > 3.25E-5     | > 3.25E-5 |  |
| M14                                                                                      | 0.544     | 2.019 | 1.956 | 1.916                                 | 1.853 | 0.868 | 0.470 | 96   | 93   | 89             | 22   | -14  | 1.23E-6 | > 3.25E-5     | > 3.25E-5 |  |
| MDA-MB-435                                                                               | 0.598     | 2.976 | 2.930 | 2.932                                 | 2.880 | 1.212 | 0.781 | 98   | 98   | 95             | 26   | 8    | 1.46E-6 | > 3.25E-5     | > 3.25E-5 |  |
| SK-MEL-2                                                                                 | 1.127     | 2.597 | 2.603 | 2.566                                 | 2.570 | 1.442 | 1.147 | 100  | 98   | 98             | 21   | 1    | 1.38E-6 | > 3.25E-5     | > 3.25E-5 |  |
| SK-MEL-28                                                                                | 0.577     | 1.933 | 1.901 | 1.949                                 | 1.831 | 1.049 | 0.786 | 98   | 101  | 92             | 35   | 15   | 1.77E-6 | > 3.25E-5     | > 3.25E-5 |  |
| SK-MEL-5                                                                                 | 0.934     | 3.045 | 3.025 | 3.075                                 | 3.076 | 1.630 | 0.527 | 99   | 101  | 101            | 33   | -44  | 1.83E-6 | 8.75E-6       | > 3.25E-5 |  |
| Ovarian Cancer                                                                           |           |       |       |                                       |       |       |       |      |      |                |      |      |         |               |           |  |
| IGROV1                                                                                   | 0.520     | 1.819 | 1.825 | 1.884                                 | 1.705 | 0.865 | 0.594 | 100  | 105  | 91             | 27   | 6    | 1.41E-6 | > 3.25E-5     | > 3.25E-5 |  |
| OVCAR-3                                                                                  | 0.381     | 1.604 | 1.646 | 1.647                                 | 1.423 | 0.559 | 0.430 | 103  | 104  | 85             | 15   | 4    | 1.02E-6 | > 3.25E-5     | > 3.25E-5 |  |
| OVCAR-4                                                                                  | 0.673     | 1.516 | 1.510 | 1.505                                 | 1.319 | 0.804 | 0.753 | 99   | 99   | 77             | 15   | 9    | 8.86E-7 | > 3.25E-5     | > 3.25E-5 |  |
| OVCAR-8                                                                                  | 0.644     | 2.516 | 2.401 | 2.348                                 | 2.222 | 0.857 | 0.689 | 94   | 91   | 84             | 11   | 2    | 9.59E-7 | > 3.25E-5     | > 3.25E-5 |  |
| NCI/ADR-RES                                                                              | 0.525     | 1.675 | 1.688 | 1.696                                 | 1.686 | 1.001 | 0.673 | 101  | 102  | 101            | 41   | 13   | 2.33E-6 | > 3.25E-5     | > 3.25E-5 |  |
| SK-OV-3                                                                                  | 1.047     | 2.050 | 2.101 | 2.008                                 | 2.029 | 1.022 | 0.967 | 105  | 96   | 98             | -2   | -8   | 9.76E-7 | 3.08E-6       | > 3.25E-5 |  |
| Renal Cancer                                                                             |           |       |       |                                       |       |       |       |      |      |                |      |      |         |               |           |  |
| 786-O                                                                                    | 0.747     | 2.565 | 2.526 | 2.474                                 | 2.459 | 1.155 | 0.663 | 98   | 95   | 94             | 22   | -11  | 1.34E-6 | 1.51E-5       | > 3.25E-5 |  |
| A498                                                                                     | 1.299     | 2.329 | 2.070 | 2.112                                 | 2.177 | 1.686 | 1.554 | 75   | 79   | 85             | 38   | 25   | 1.79E-6 | > 3.25E-5     | > 3.25E-5 |  |
| ACHN                                                                                     | 0.437     | 2.206 | 2.203 | 2.161                                 | 2.032 | 0.734 | 0.603 | 100  | 97   | 90             | 17   | 9    | 1.15E-6 | > 3.25E-5     | > 3.25E-5 |  |
| CAKI-1                                                                                   | 0.622     | 2.756 | 2.529 | 2.466                                 | 2.418 | 1.109 | 0.808 | 89   | 86   | 84             | 23   | 9    | 1.17E-6 | > 3.25E-5     | > 3.25E-5 |  |
| RXF-393                                                                                  | 0.805     | 1.363 | 1.335 | 1.297                                 | 1.185 | 0.800 | 0.483 | 95   | 88   | 68             | .    | -40  | 5.96E-7 | 3.18E-6       | > 3.25E-5 |  |
| SN12C                                                                                    | 0.684     | 2.642 | 2.530 | 2.533                                 | 2.508 | 0.959 | 0.845 | 94   | 94   | 93             | 14   | 8    | 1.14E-6 | > 3.25E-5     | > 3.25E-5 |  |
| TK-10                                                                                    | 0.866     | 1.962 | 1.860 | 1.817                                 | 1.747 | 1.096 | 1.056 | 91   | 87   | 80             | 21   | 17   | 1.05E-6 | > 3.25E-5     | > 3.25E-5 |  |
| UO-31                                                                                    | 0.833     | 2.332 | 2.130 | 2.113                                 | 2.066 | 1.000 | 0.824 | 87   | 85   | 82             | 11   | -1   | 9.23E-7 | 2.65E-5       | > 3.25E-5 |  |
| Prostate Cancer                                                                          |           |       |       |                                       |       |       |       |      |      |                |      |      |         |               |           |  |
| PC-3                                                                                     | 0.593     | 2.124 | 2.096 | 1.996                                 | 1.692 | 0.824 | 0.759 | 98   | 92   | 72             | 15   | 11   | 7.87E-7 | > 3.25E-5     | > 3.25E-5 |  |
| DU-145                                                                                   | 0.329     | 1.573 | 1.575 | 1.572                                 | 1.515 | 0.624 | 0.331 | 100  | 100  | 95             | 24   | .    | 1.39E-6 | > 3.25E-5     | > 3.25E-5 |  |
| Breast Cancer                                                                            |           |       |       |                                       |       |       |       |      |      |                |      |      |         |               |           |  |
| MCF7                                                                                     | 0.372     | 2.178 | 2.069 | 2.054                                 | 1.910 | 0.502 | 0.305 | 94   | 93   | 85             | 7    | -18  | 9.17E-7 | 6.26E-6       | > 3.25E-5 |  |
| MDA-MB-231/ATCC                                                                          | 0.465     | 1.172 | 1.156 | 1.157                                 | 1.142 | 0.523 | 0.437 | 98   | 98   | 96             | 8    | -6   | 1.08E-6 | 1.21E-5       | > 3.25E-5 |  |
| HS 578T                                                                                  | 1.103     | 2.289 | 2.217 | 2.194                                 | 2.149 | 1.463 | 1.228 | 94   | 92   | 88             | 30   | 10   | 1.49E-6 | > 3.25E-5     | > 3.25E-5 |  |
| BT-549                                                                                   | 1.325     | 2.573 | 2.555 | 2.490                                 | 2.461 | 1.691 | 1.264 | 99   | 93   | 91             | 29   | -5   | 1.50E-6 | 2.38E-5       | > 3.25E-5 |  |
| T-47D                                                                                    | 0.781     | 1.663 | 1.610 | 1.515                                 | 1.420 | 0.818 | 0.731 | 94   | 83   | 72             | 4    | -6   | 6.93E-7 | 8.04E-6       | > 3.25E-5 |  |
| MDA-MB-468                                                                               | 0.687     | 1.224 | 1.155 | 1.144                                 | 1.128 | 0.672 | 0.492 | 87   | 85   | 82             | -2   | -28  | 7.80E-7 | 3.06E-6       | > 3.25E-5 |  |

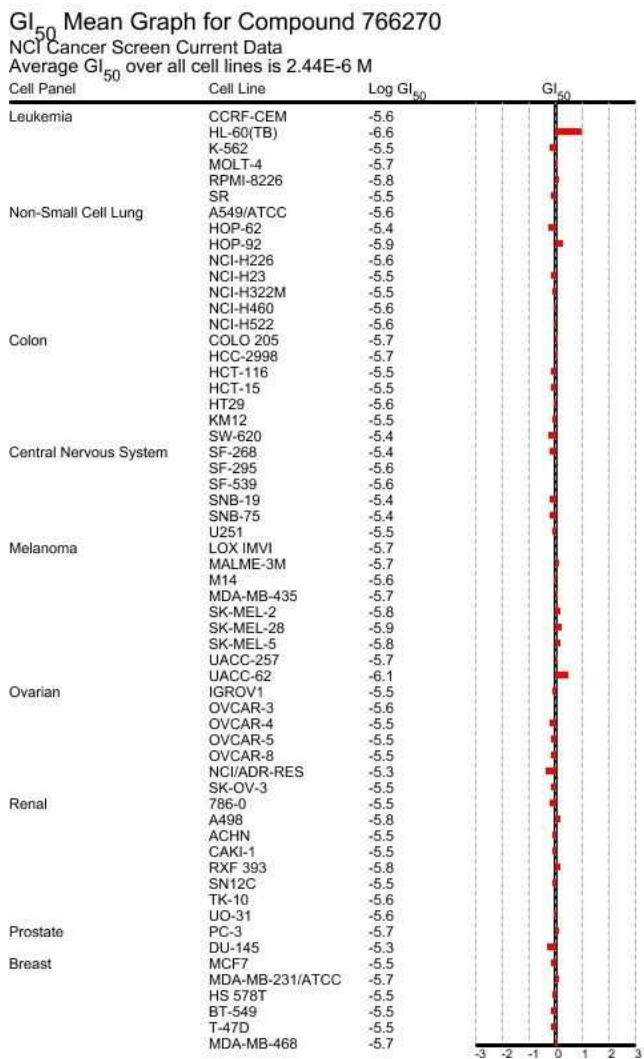
**Figure S8. Dose response curves of compound 18**



**Figure S9.** Details of the *in vitro* testing results of compound **18**

| National Cancer Institute Developmental Therapeutics Program<br>In-Vitro Testing Results |              |       |                                       |       |       |       |       |      |                |      |      |               |         |           |           |  |
|------------------------------------------------------------------------------------------|--------------|-------|---------------------------------------|-------|-------|-------|-------|------|----------------|------|------|---------------|---------|-----------|-----------|--|
| NSC : D - 786942 / 1                                                                     |              |       | Experiment ID : 1509NS72              |       |       |       |       |      | Test Type : 08 |      |      | Units : Molar |         |           |           |  |
| Report Date : November 30, 2015                                                          |              |       | Test Date : September 28, 2015        |       |       |       |       |      | QNS :          |      |      | MC :          |         |           |           |  |
| COMI : Lyz002-79                                                                         |              |       | Stain Reagent : SRB Dual-Pass Related |       |       |       |       |      | SSPL : OZJO    |      |      |               |         |           |           |  |
| Panel/Cell Line                                                                          | Time<br>Zero | Ctrl  | Log10 Concentration                   |       |       |       |       |      | Percent Growth |      |      |               | GI50    | TGI       | LC50      |  |
|                                                                                          |              |       | -8.5                                  | -7.5  | -6.5  | -5.5  | -4.5  | -8.5 | -7.5           | -6.5 | -5.5 | -4.5          |         |           |           |  |
| Leukemia                                                                                 |              |       |                                       |       |       |       |       |      |                |      |      |               |         |           |           |  |
| CCRF-CEM                                                                                 | 0.764        | 3.089 | 2.963                                 | 3.021 | 2.756 | 0.968 | 0.705 | 95   | 97             | 86   | 9    | -8            | 9.46E-7 | 1.11E-5   | > 3.25E-5 |  |
| HL-60(TB)                                                                                | 0.932        | 3.164 | 3.058                                 | 3.084 | 3.046 | 1.142 | 0.794 | 95   | 96             | 95   | 9    | -15           | 1.09E-6 | 7.92E-6   | > 3.25E-5 |  |
| K-562                                                                                    | 0.320        | 2.310 | 2.440                                 | 2.322 | 2.211 | 0.482 | 0.249 | 107  | 101            | 95   | 8    | -22           | 1.07E-6 | 6.03E-6   | > 3.25E-5 |  |
| MOLT-4                                                                                   | 0.869        | 3.086 | 3.076                                 | 3.101 | 2.872 | 1.109 | 0.830 | 100  | 101            | 90   | 11   | -4            | 1.05E-6 | 1.65E-5   | > 3.25E-5 |  |
| RPMI-8226                                                                                | 0.958        | 2.794 | 2.773                                 | 2.672 | 2.516 | 1.138 | 0.912 | 99   | 93             | 85   | 10   | -5            | 9.46E-7 | 1.51E-5   | > 3.25E-5 |  |
| SR                                                                                       | 0.465        | 1.863 | 1.731                                 | 1.818 | 1.729 | 0.652 | 0.395 | 91   | 97             | 90   | 13   | -15           | 1.09E-6 | 9.60E-6   | > 3.25E-5 |  |
| Non-Small Cell Lung Cancer                                                               |              |       |                                       |       |       |       |       |      |                |      |      |               |         |           |           |  |
| A549(ATCC                                                                                | 0.552        | 2.326 | 2.195                                 | 2.101 | 2.104 | 1.032 | 0.556 | 93   | 87             | 87   | 27   | .             | 1.35E-6 | > 3.25E-5 | > 3.25E-5 |  |
| EKVX                                                                                     | 0.759        | 2.274 | 2.178                                 | 2.121 | 2.089 | 1.064 | 0.776 | 94   | 90             | 88   | 20   | 1             | 1.18E-6 | > 3.25E-5 | > 3.25E-5 |  |
| HOP-62                                                                                   | 0.741        | 2.142 | 2.114                                 | 2.107 | 2.057 | 1.063 | 0.730 | 98   | 98             | 94   | 23   | -2            | 1.35E-6 | 2.81E-5   | > 3.25E-5 |  |
| HOP-92                                                                                   | 1.379        | 1.912 | 1.819                                 | 1.799 | 1.832 | 1.315 | 1.062 | 82   | 79             | 85   | -5   | -23           | 7.97E-7 | 2.88E-6   | > 3.25E-5 |  |
| NCH-H226                                                                                 | 0.573        | 1.625 | 1.604                                 | 1.621 | 1.600 | 1.093 | 0.487 | 98   | 100            | 98   | 49   | -15           | 3.15E-6 | 1.90E-5   | > 3.25E-5 |  |
| NCH-H23                                                                                  | 0.805        | 2.301 | 2.233                                 | 2.269 | 2.269 | 1.091 | 0.843 | 95   | 98             | 98   | 19   | 3             | 1.32E-6 | > 3.25E-5 | > 3.25E-5 |  |
| NCH-H322M                                                                                | 0.813        | 2.238 | 2.178                                 | 2.127 | 2.137 | 1.365 | 1.078 | 96   | 92             | 93   | 39   | 19            | 2.02E-6 | > 3.25E-5 | > 3.25E-5 |  |
| NCH-H460                                                                                 | 0.269        | 2.884 | 2.907                                 | 2.928 | 2.901 | 0.677 | 0.210 | 101  | 102            | 101  | 16   | -22           | 1.28E-6 | 8.42E-6   | > 3.25E-5 |  |
| NCH-H522                                                                                 | 0.815        | 2.344 | 2.251                                 | 2.228 | 2.094 | 1.008 | 0.578 | 94   | 92             | 84   | 13   | -29           | 9.68E-7 | 6.52E-6   | > 3.25E-5 |  |
| Colon Cancer                                                                             |              |       |                                       |       |       |       |       |      |                |      |      |               |         |           |           |  |
| COLO 205                                                                                 | 0.598        | 2.089 | 2.091                                 | 2.135 | 2.028 | 0.808 | 0.544 | 100  | 103            | 96   | 14   | -9            | 1.18E-6 | 1.32E-5   | > 3.25E-5 |  |
| HCC-2998                                                                                 | 0.728        | 2.272 | 2.275                                 | 2.308 | 2.400 | 1.304 | 0.847 | 100  | 102            | 108  | 37   | 8             | 2.15E-6 | > 3.25E-5 | > 3.25E-5 |  |
| HCT-116                                                                                  | 0.174        | 1.427 | 1.388                                 | 1.427 | 1.367 | 0.388 | 0.187 | 97   | 100            | 95   | 17   | 1             | 1.23E-6 | > 3.25E-5 | > 3.25E-5 |  |
| HCT-15                                                                                   | 0.386        | 2.065 | 2.037                                 | 2.032 | 1.997 | 0.859 | 0.410 | 98   | 98             | 96   | 28   | 1             | 1.55E-6 | > 3.25E-5 | > 3.25E-5 |  |
| HT29                                                                                     | 0.371        | 2.366 | 2.327                                 | 2.269 | 2.365 | 0.700 | 0.393 | 98   | 95             | 100  | 16   | 1             | 1.29E-6 | > 3.25E-5 | > 3.25E-5 |  |
| KM12                                                                                     | 0.450        | 2.576 | 2.560                                 | 2.577 | 2.384 | 0.917 | 0.561 | 99   | 100            | 91   | 22   | 5             | 1.28E-6 | > 3.25E-5 | > 3.25E-5 |  |
| SW-620                                                                                   | 0.278        | 2.409 | 2.352                                 | 2.308 | 2.357 | 0.735 | 0.543 | 97   | 95             | 98   | 21   | 12            | 1.37E-6 | > 3.25E-5 | > 3.25E-5 |  |
| CNS Cancer                                                                               |              |       |                                       |       |       |       |       |      |                |      |      |               |         |           |           |  |
| SF-268                                                                                   | 0.470        | 1.776 | 1.764                                 | 1.765 | 1.646 | 0.862 | 0.493 | 99   | 99             | 90   | 30   | 2             | 1.51E-6 | > 3.25E-5 | > 3.25E-5 |  |
| SF-295                                                                                   | 0.639        | 2.025 | 1.998                                 | 1.917 | 1.816 | 0.736 | 0.478 | 98   | 92             | 85   | 7    | -25           | 9.11E-7 | 5.34E-6   | > 3.25E-5 |  |
| SF-539                                                                                   | 0.838        | 2.757 | 2.682                                 | 2.627 | 2.618 | 1.433 | 0.879 | 96   | 93             | 93   | 31   | 2             | 1.60E-6 | > 3.25E-5 | > 3.25E-5 |  |
| SNB-19                                                                                   | 0.580        | 2.061 | 1.961                                 | 1.948 | 1.920 | 0.867 | 0.686 | 93   | 92             | 90   | 19   | 6             | 1.21E-6 | > 3.25E-5 | > 3.25E-5 |  |
| SNB-75                                                                                   | 0.963        | 1.811 | 1.720                                 | 1.699 | 1.699 | 1.350 | 1.205 | 89   | 87             | 87   | 46   | 29            | 2.55E-6 | > 3.25E-5 | > 3.25E-5 |  |
| U251                                                                                     | 0.360        | 1.589 | 1.508                                 | 1.488 | 1.427 | 0.503 | 0.225 | 93   | 92             | 87   | 12   | -38           | 1.00E-6 | 5.60E-6   | > 3.25E-5 |  |
| Melanoma                                                                                 |              |       |                                       |       |       |       |       |      |                |      |      |               |         |           |           |  |
| LOX IMVI                                                                                 | 0.471        | 2.867 | 2.769                                 | 2.774 | 2.770 | 0.918 | 0.045 | 96   | 96             | 96   | 19   | -90           | 1.28E-6 | 4.82E-6   | 1.38E-5   |  |
| MALME-3M                                                                                 | 0.836        | 1.657 | 1.634                                 | 1.562 | 1.569 | 1.202 | 0.938 | 97   | 88             | 89   | 45   | 12            | 2.45E-6 | > 3.25E-5 | > 3.25E-5 |  |
| M14                                                                                      | 0.544        | 2.021 | 1.959                                 | 1.893 | 1.933 | 1.167 | 0.519 | 96   | 91             | 94   | 42   | -5            | 2.30E-6 | 2.59E-5   | > 3.25E-5 |  |
| MDA-MB-435                                                                               | 0.598        | 2.910 | 2.897                                 | 2.900 | 2.897 | 1.367 | 0.763 | 99   | 100            | 99   | 33   | 7             | 1.82E-6 | > 3.25E-5 | > 3.25E-5 |  |
| SK-MEL-2                                                                                 | 1.127        | 2.520 | 2.558                                 | 2.501 | 2.534 | 1.678 | 1.102 | 103  | 99             | 101  | 40   | -2            | 2.20E-6 | 2.87E-5   | > 3.25E-5 |  |
| SK-MEL-28                                                                                | 0.577        | 1.904 | 1.895                                 | 1.871 | 1.772 | 1.090 | 0.719 | 99   | 97             | 90   | 39   | 11            | 1.95E-6 | > 3.25E-5 | > 3.25E-5 |  |
| SK-MEL-5                                                                                 | 0.934        | 3.215 | 3.186                                 | 3.214 | 3.228 | 2.423 | 0.511 | 99   | 100            | 101  | 65   | -45           | 4.46E-6 | 1.26E-5   | > 3.25E-5 |  |
| Ovarian Cancer                                                                           |              |       |                                       |       |       |       |       |      |                |      |      |               |         |           |           |  |
| IGROV1                                                                                   | 0.520        | 1.740 | 1.713                                 | 1.752 | 1.707 | 0.920 | 0.667 | 98   | 101            | 97   | 33   | 12            | 1.76E-6 | > 3.25E-5 | > 3.25E-5 |  |
| OVCAR-3                                                                                  | 0.381        | 1.573 | 1.588                                 | 1.603 | 1.497 | 0.617 | 0.391 | 101  | 102            | 94   | 20   | 1             | 1.27E-6 | > 3.25E-5 | > 3.25E-5 |  |
| OVCAR-4                                                                                  | 0.673        | 1.495 | 1.502                                 | 1.452 | 1.355 | 0.824 | 0.717 | 101  | 95             | 83   | 18   | 5             | 1.05E-6 | > 3.25E-5 | > 3.25E-5 |  |
| OVCAR-8                                                                                  | 0.644        | 2.470 | 2.439                                 | 2.350 | 2.374 | 0.998 | 0.683 | 98   | 93             | 95   | 19   | 2             | 1.27E-6 | > 3.25E-5 | > 3.25E-5 |  |
| NCI/ADR-RES                                                                              | 0.525        | 1.681 | 1.730                                 | 1.724 | 1.719 | 1.356 | 0.787 | 104  | 104            | 103  | 72   | 23            | 9.04E-6 | > 3.25E-5 | > 3.25E-5 |  |
| SK-OV-3                                                                                  | 1.047        | 2.111 | 2.102                                 | 2.106 | 2.134 | 1.303 | 0.980 | 99   | 100            | 102  | 24   | -6            | 1.51E-6 | 2.00E-5   | > 3.25E-5 |  |
| Renal Cancer                                                                             |              |       |                                       |       |       |       |       |      |                |      |      |               |         |           |           |  |
| 786-O                                                                                    | 0.747        | 2.555 | 2.536                                 | 2.491 | 2.528 | 1.335 | 0.619 | 99   | 96             | 99   | 33   | -17           | 1.77E-6 | 1.47E-5   | > 3.25E-5 |  |
| A498                                                                                     | 1.299        | 2.366 | 2.210                                 | 2.177 | 2.115 | 1.810 | 1.506 | 85   | 82             | 76   | 48   | 19            | 2.74E-6 | > 3.25E-5 | > 3.25E-5 |  |
| ACHN                                                                                     | 0.437        | 2.121 | 2.166                                 | 2.063 | 2.068 | 0.839 | 0.552 | 103  | 97             | 97   | 24   | 7             | 1.42E-6 | > 3.25E-5 | > 3.25E-5 |  |
| CAKI-1                                                                                   | 0.622        | 2.733 | 2.512                                 | 2.466 | 2.456 | 1.994 | 0.855 | 90   | 87             | 87   | 65   | 11            | 6.17E-6 | > 3.25E-5 | > 3.25E-5 |  |
| RXF 393                                                                                  | 0.805        | 1.379 | 1.336                                 | 1.337 | 1.263 | 0.854 | 0.432 | 92   | 93             | 80   | 9    | -46           | 8.50E-7 | 4.65E-6   | > 3.25E-5 |  |
| SN12C                                                                                    | 0.684        | 2.623 | 2.505                                 | 2.498 | 2.500 | 1.096 | 0.805 | 94   | 94             | 94   | 21   | 6             | 1.30E-6 | > 3.25E-5 | > 3.25E-5 |  |
| TK-10                                                                                    | 0.866        | 1.997 | 1.906                                 | 1.879 | 1.766 | 1.157 | 0.928 | 92   | 90             | 80   | 26   | 5             | 1.15E-6 | > 3.25E-5 | > 3.25E-5 |  |
| UO-31                                                                                    | 0.833        | 2.265 | 2.031                                 | 2.024 | 2.035 | 1.199 | 0.850 | 84   | 83             | 84   | 26   | 1             | 1.24E-6 | > 3.25E-5 | > 3.25E-5 |  |
| Prostate Cancer                                                                          |              |       |                                       |       |       |       |       |      |                |      |      |               |         |           |           |  |
| PC-3                                                                                     | 0.593        | 2.327 | 2.210                                 | 2.151 | 2.096 | 0.825 | 0.714 | 93   | 90             | 87   | 13   | 7             | 1.03E-6 | > 3.25E-5 | > 3.25E-5 |  |
| DU-145                                                                                   | 0.329        | 1.497 | 1.510                                 | 1.547 | 1.478 | 0.714 | 0.304 | 101  | 104            | 98   | 33   | -8            | 1.78E-6 | 2.11E-5   | > 3.25E-5 |  |
| Breast Cancer                                                                            |              |       |                                       |       |       |       |       |      |                |      |      |               |         |           |           |  |
| MCF7                                                                                     | 0.372        | 2.254 | 2.112                                 | 2.075 | 2.071 | 0.572 | 0.256 | 92   | 91             | 90   | 11   | -31           | 1.04E-6 | 5.83E-6   | > 3.25E-5 |  |
| MDA-MB-231/ATCC                                                                          | 0.465        | 1.187 | 1.169                                 | 1.170 | 1.162 | 0.621 | 0.470 | 97   | 98             | 97   | 22   | 1             | 1.36E-6 | > 3.25E-5 | > 3.25E-5 |  |
| HS 578T                                                                                  | 1.103        | 2.334 | 2.214                                 | 2.196 | 2.215 | 1.520 | 1.231 | 90   | 89             | 90   | 34   | 10            | 1.68E-6 | > 3.25E-5 | > 3.25E-5 |  |
| BT-549                                                                                   | 1.325        | 2.545 | 2.590                                 | 2.549 | 2.506 | 1.915 | 1.408 | 104  | 100            | 97   | 48   | 7             | 3.00E-6 | > 3.25E-5 | > 3.25E-5 |  |
| T-47D                                                                                    | 0.781        | 1.661 | 1.580                                 | 1.604 | 1.653 | 0.916 | 0.776 | 91   | 93             | 99   | 15   | .             | 1.25E-6 | 2.94E-5   | > 3.25E-5 |  |
| MDA-MB-468                                                                               | 0.687        | 1.194 | 1.195                                 | 1.197 | 1.199 | 0.869 | 0.522 | 100  | 101            | 101  | 36   | -24           | 1.97E-6 | 1.29E-5   | > 3.25E-5 |  |

**Figure S10.** Details of the *in vitro* testing results of compound **ABT-199** (venetoclax)



**Table S3.** Microsomal stability of compound **16**.

|                                                      | Time = 1 h                                           |
|------------------------------------------------------|------------------------------------------------------|
| Groups                                               | Microsomal stability <sup>a</sup> (spectral purity%) |
| Control 1 ( <b>16</b> + PBS)                         | >99%                                                 |
| Control 2 ( <b>16</b> + PBS + Microsomal)            | >99%                                                 |
| Control 3 ( <b>16</b> + PBS + NADPH)                 | >99%                                                 |
| 190 nM ( <b>16</b> + PBS + NADPH + Rat Microsomal)   | >99%                                                 |
| 190 nM ( <b>16</b> + PBS + NADPH + human Microsomal) | >99%                                                 |

<sup>a</sup> Data was the means of two independent experiments.

**Table S4.** Chemical stability of compound **16**.

|            |                        | HPLC purity (%) / Time <sup>a</sup> |      |      |      |
|------------|------------------------|-------------------------------------|------|------|------|
| No.        | pH                     | 3 h                                 | 12 h | 24 h | 72 h |
| 1(control) | 7                      | >99                                 | >99  | >99  | >99  |
| 2          | 10                     | >99                                 | >99  | 99   | 99   |
| 3          | 5                      | >99                                 | >99  | >99  | >99  |
| 4          | 3                      | >99                                 | >99  | 98   | 98   |
| 5          | 1                      | >99                                 | >99  | 96   | 96   |
| 6          | Con. HCl in AcOH (37%) | 0%                                  |      |      |      |

<sup>a</sup> Also confirmed by TLC analysis.

**Table S5.** Toxicities of compounds in HEK 293T and Vero cells.

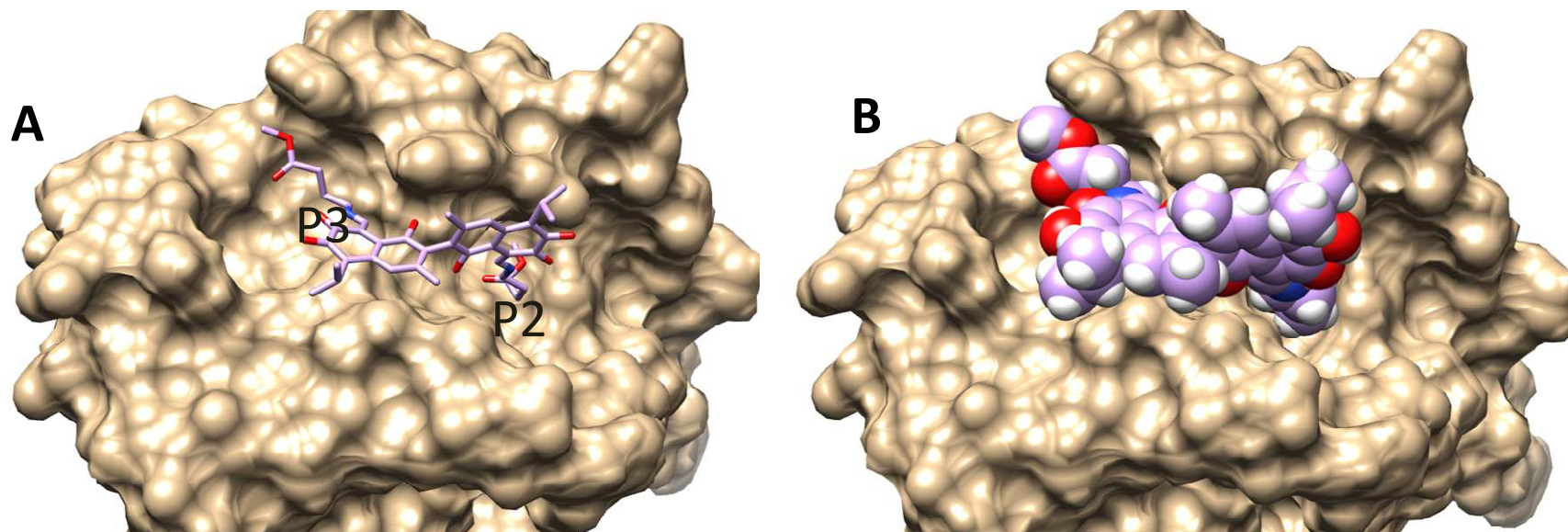
|           | Cytotoxicity in HEK 293T cells     | Cytotoxicity in Vero cells         |
|-----------|------------------------------------|------------------------------------|
| Compounds | TC <sub>50</sub> <sup>a</sup> (μM) | IC <sub>50</sub> <sup>a</sup> (μM) |
| <b>14</b> | 50                                 | >100                               |
| <b>15</b> | 68                                 | ND <sup>b</sup>                    |
| <b>16</b> | >200                               | >100                               |
| <b>17</b> | >200                               | >100                               |
| <b>18</b> | >200                               | >100                               |
| <b>20</b> | ~100                               | ND                                 |
| <b>21</b> | >200                               | ND                                 |
| <b>22</b> | 60                                 | ND                                 |
| <b>23</b> | 69                                 | ND                                 |
| <b>24</b> | ~100                               | ND                                 |
| <b>25</b> | 70                                 | ND                                 |
| <b>26</b> | 75                                 | ND                                 |
| Gossypol  | 75                                 | 7.3 <sup>c</sup>                   |

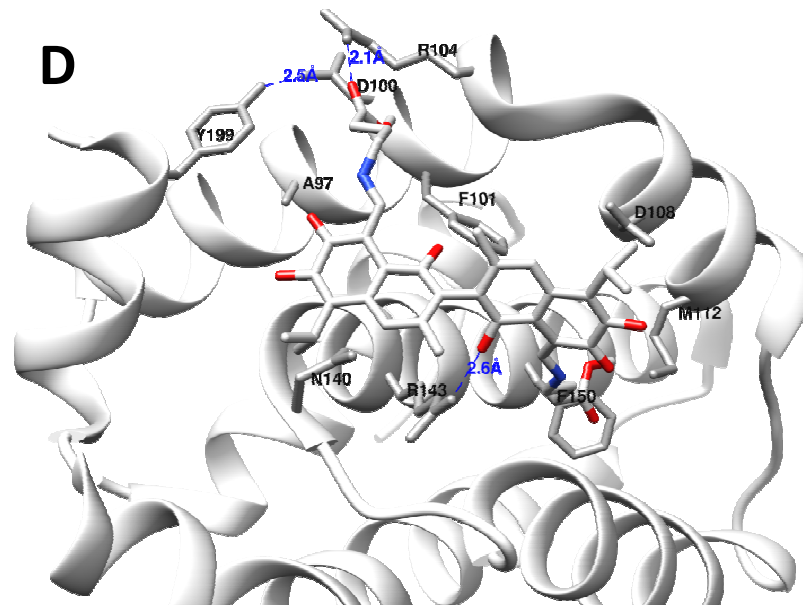
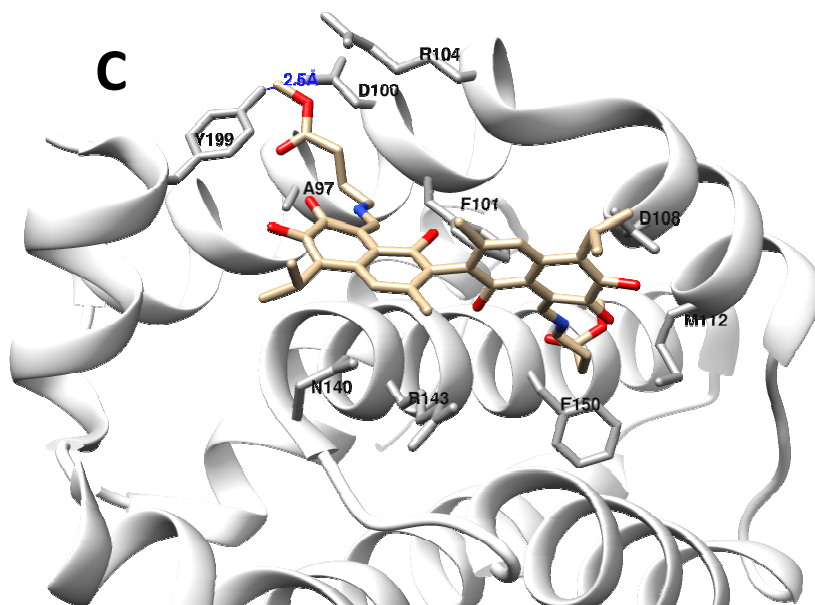
<sup>a</sup> TC<sub>50</sub>, IC<sub>50</sub> values were the means of three independent experiments.

<sup>b</sup> ND: not determined.

<sup>c</sup> Similar observed results to Ref. 10 and 11.<sup>10,11</sup>

**Figure S11.** Enlarged pictures of Figure 4 in manuscript.





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