

# Supporting Information

## Synthesis of the natural product Marthiapeptide A

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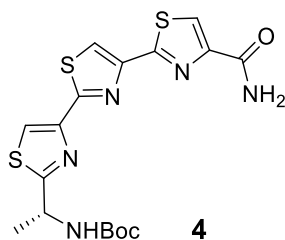
## **General Remarks**

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise stated. Reagents were commercially obtained (Peptides International, ChemImpex, Aldrich, GLbiochem and Acros) at the highest quality and used without further purification. Reactions were monitored via thin-layer chromatography (TLC) carried out on 250µm Whatman silica gel plates (4861-820) using UV light as the visualizing agent and potassium permanganate in water as heat and developing agents. SiliCycle SiliaFlash silica gel (60, particle size 40-63µm) was used for flash chromatography. Automated column chromatography was performed on Teledyne CombiFlash Rf-200 using 12g silica flash columns and 25g solid sample cartridges. Yields refer to spectroscopically and/or chromatographically homogeneous materials.

NMR spectra were obtained at 30°C on either a 600-MHz Varian NMR-S, 500-MHz INOVA, or 300-MHz Varian NMR-S using residual undeuterated solvent as an internal reference. The variable temperature (VT) NMR spectra were taken from 318 K to 248 K. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, b = broad, bd = broad doublet, dd = doublet of doublet, and dq = doublet of quartet.

LC/MS was recorded on an Agilent 1200 Series HPLC system (Zorbax Agilent SB-C<sub>18</sub> column, 3.5µm, 2.1 x 30mm) connected to an Agilent 62440A LC/MS Trap running in the positive electrospray ionization (ESI+) mode. The mobile phase was composed of DDI water with 0.1% (v/v) formic acid (solvent A) and HPLC grade acetonitrile with 0.1% (v/v) formic acid (solvent B). The gradient elution was as follows: flow rate 1.0 mL/min; initial 80% solvent A, 20% solvent B; at 4.5 min 10% solvent A, 90% solvent B hold 0.1 min; at 7 min 85% solvent A, 15% solvent B. HRMS data were obtained at the Bioanalytical Mass Spectrometry Facility within the Mark Wainwright Analytical Centre of the University of New South Wales. HRMS data were recorded on a Thermo LTQ FT LC/MS/MS system. Subsidised access to this facility is gratefully acknowledged.

## Experimental Procedures



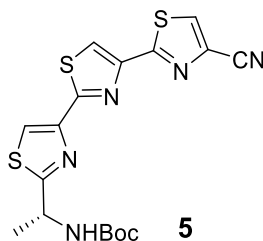
**BocHN-D-Ala-Thiazole-Thiazole-Thiazole-C(O)-NH<sub>2</sub> (4).** BocHN-D-Ala-Thiazole-Thiazole-Thiazole-C(O)-NH<sub>2</sub> was synthesized utilizing 170 mg (0.365 mmol, 1.0 equiv.) of BocHN-D-Ala-Thiazole-Thiazole-Thiazole-OEt in 6 mL of ammonium hydroxide solution (28% in water) and 6 mL of MeOH. The reaction mixture was sonicated for 24 hrs. Upon completion, The reaction was co-vaporized with MeOH 4 times followed by CH<sub>2</sub>Cl<sub>2</sub> 2 times then further dried *in vacuo*; the resulting amine was taken on to the next reaction without further purification (171 mg, quantitative) as a white powder.

R<sub>f</sub>: 0.208 (hexane/ EtOAc 1:1).

<sup>1</sup>H NMR (300 MHz, DMSO): 1.423 (br, 9H, C(CH<sub>3</sub>)<sub>3</sub>); 1.50 (d, *J* = 7.05Hz, 3H, CH<sub>3</sub>CH); 4.92 (dq, *J* = 7.00, 7.19 Hz, 1αH); 7.69 (br, 1H, NH<sub>2</sub>); 7.83 (br, 1H, NH<sub>2</sub>); 7.88 (d, *J* = 7.54Hz, NH); 8.27 (s, 1H, SCHC), 8.31 (s, 1H, SCHC); 8.33 (s, 1H, SCHC).

<sup>13</sup>C NMR (75MHz, DMSO) δ 20.51, 28.19(3C), 48.59, 78.60, 117.94, 118.46, 124.63, 147.07, 148.75, 151.16, 155.11, 161.42, 162.16, 163.12, 177.75.

ES<sup>+</sup>MS *m/z* calcd for C<sub>17</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>S<sub>3</sub> ([M+Na]<sup>+</sup>) 460.07, found 460.65



**BocHN-D-Ala-Thiazole-Thiazole-Thiazole-CN (5).** BocHN-D-Ala-Thiazole-Thiazole-Thiazole-CN was synthesized utilizing 100 mg (0.34 mmol, 1.0 equiv.) of BocHN-D-Ala-Thiazole-Thiazole-Thiazole-C(O)-NH<sub>2</sub> in 24 mL of anhydrous CH<sub>2</sub>Cl<sub>2</sub> under nitrogen atmosphere at -20°C. While stirring, 0.15 ml (0.95 mmol, 2.8 equiv.) DIPEA was added into the reaction mixture in dropwise. After 5 min, 0.07 ml (0.38 mmol, 1.1 equiv.) TFAA was added into the reaction mixture

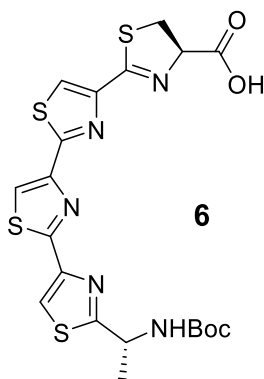
cautiously. The reaction was flushed with nitrogen to remove produced vapour. The reaction was allowed to stir overnight with gradually warm up to room temperature. Upon completion, the reaction was concentrated and re-dissolved in  $\text{CH}_2\text{Cl}_2$  and directly purified over flash column chromatography on silica at gradient elute with hexane and EtOAc to give product as white solid (110mg, 65%).

$R_f$ : 0.833 (hexane/ EtOAc 1:1).

$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ): 1.479 (br, 9H,  $\text{C}(\text{CH}_3)_3$ ); 1.664 (d,  $J = 6.60$  Hz, 3H,  $\text{CH}_3\text{CH}$ ); 5.14 (br, 1H); 7.99 (s, 1H, SCHC); 8.00 (s, 1H, SCHC), 8.31 (s, 1H, SCHC).

$^{13}\text{C}$  NMR (150MHz,  $\text{CDCl}_3$ )  $\delta$  21.84, 28.49(3C), 48.95, 80.54, 114.19, 117.10, 118.81, 127.66, 130.70, 148.32, 148.45, 155.12, 163.81, 164.41, 175.18.

$\text{ES}^+\text{MS}$   $m/z$  calcd for  $\text{C}_{17}\text{H}_{17}\text{N}_5\text{O}_2\text{S}_3$  ( $[\text{M}+\text{Na}]^+$ ) 442.05, found 442.00



**BocHN-D-Ala-Thiazole-Thiazole-Thiazole-(R)-Thiazoline-OH (6).** BocHN-D-Ala-Thiazole-Thiazole-Thiazole-(R)-Thiazoline-OH was synthesized utilizing 110 mg (0.262 mmol, 1.0 equiv.) of BocHN-D-Ala-Thiazole-Thiazole-Thiazole-CN and 33.0 mg (0.275 mmol, 1.05 equiv.) L-Cysteine and 110 mg (1.31 mmol, 5.0 equiv.) of  $\text{NaHCO}_3$  in 5.0 ml of MeOH. While stirring, 1.0 ml of pH = 5.95 phosphate buffer solution was added into the reaction mixture. The reaction mixture was then stirred at  $70^\circ\text{C}$  for 4 hr followed by routine TLC monitoring for reaction progress. Upon completion, the reaction mixture was concentrated to remove all of the solvent then re-dissolved in EtOAc and then poured into the Sat.  $\text{NaHCO}_3$  solution. The organic layer was set aside, the aqueous layer was further extract with EtOAc for 2 times. The aqueous was then acidified using pH = 1 hydrochloric acid solution in dropwise with monitoring until reach pH = 3. The aqueous layer was then extracted with EtOAc 3 times. All organic layer was then collected, combined and dried over anhydrous  $\text{Na}_2\text{SO}_4$

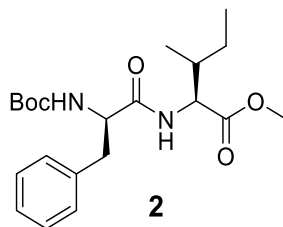
followed by filtration, concentration *in vacuo* and further dried *in silico* to give white powder (134 mg, 98%). The material was subjected for next reaction without further purification.

R<sub>f</sub>: 0.4 (EtOAc/ MeOH 9:1).

<sup>1</sup>H NMR (600 MHz, DMSO): 1.43 (br, 9H, C(CH<sub>3</sub>)<sub>3</sub>); 1.515 (d, *J* = 7.07 Hz, 3H, CH<sub>3</sub>CH); 3.60 (dd, *J* = 8.21, 11.2 Hz, 1H, CH<sub>2</sub>); 3.70 (dd, *J* = 8.21, 11.2 Hz, 1H, CH<sub>2</sub>); 5.14 (br, 1αH); 5.32 (t, *J* = 8.78 Hz, 1H, CHCH<sub>2</sub>); 7.88 (d, *J* = 7.19 Hz, 1H, NH); 8.283 (s, 1H, SCHC); 8.346 (s, 1H, SCHC), 8.40 (s, 1H, SCHC)

<sup>13</sup>C NMR (150MHz, DMSO) δ 20.5, 28.49(3C), 34.48, 48.95, 50.17, 54.90, 61.31, 78.32, 80.04, 117.74, 118.03, 118.7, 122.75, 128.64, 147.03, 148.32, 148.87, 151.81, 155.20, 161.98, 163.11, 171.76 177.73.

ES<sup>+</sup>MS *m/z* calcd for C<sub>20</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub>S<sub>4</sub> ([M+Na]<sup>+</sup>) 546.05, found 546.24



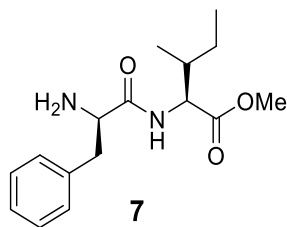
**BocHN-D-Phe-Ile-OMe (2).** BocHN-D-Phe-Ile-OMe was synthesized utilizing 2.12 g (8.0 mmol, 1.0 equiv.) of BocHN-D-Phe-OH and 2.83 g (8.8 mmol, 1.1 equiv.) TBTU dissolved in 60 mL of anhydrous CH<sub>2</sub>Cl<sub>2</sub>, 1.31 g (8.8 mmol, 1.1 equiv.) H<sub>2</sub>N-Ile-OMe dissolved in 20 mL anhydrous CH<sub>2</sub>Cl<sub>2</sub>, 4.18 mL (24.0 mmol, 3.0 equiv.) of DIPEA was added into the free acid containing reaction mixture drop wise then to the amine containing reaction mixture. After 5 min, amine reaction mixture was then taken up and injected into the free acid containing reaction mixture drop wise. Upon completion the reaction the mixture washed with acid and base and purified by flash column on silica gel elute with gradient of hexane and EtOAc to give desired product as white solid (2.88 g, 92%)

R<sub>f</sub>: 0.48 (hexane/ EtOAc 1:1).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 0.75 (d, *J* = 7.6 Hz, 3H, CHCH<sub>3</sub>(Ile)); 0.85 (t, *J* = 8.0 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>); 0.98 (m, 1H, CH<sub>2</sub>CH<sub>3</sub>); 1.27 (m, 1H, CH<sub>2</sub>CH<sub>3</sub>); 1.41 (br, 9H, C(CH<sub>3</sub>)<sub>3</sub>); 1.74 (m, 1H, CH<sub>3</sub>CH); 3.06 (d, *J* = 8.0 Hz, 2H, CH<sub>2</sub>(Phe)); 3.70 (s, 3H, OCH<sub>3</sub>); 4.37 (m, 1H, CH(Phe)); 4.50 (m, 1H, CH(Ile)); 5.00 (br, 1H, NH); 6.35(d, *J* = 9 Hz, 1H, NH); 7.2-7.33 (m, 5H, CH(Phe))

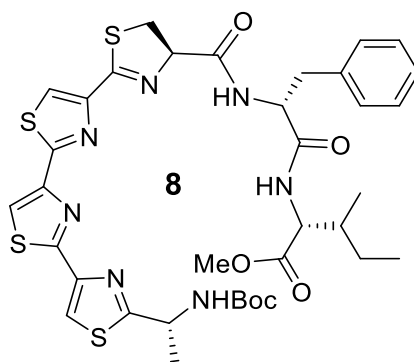
<sup>13</sup>C NMR (75MHz, CDCl<sub>3</sub>) δ 11.61, 15.41, 25.10, 28.38(3C), 37.91, 38.50, 52.20, 56.06, 56.56, 80.44, 127.11, 128.88, 129.38, 136.73, 155.44, 171.11, 172.11.

ES<sup>+</sup>MS *m/z* calcd for C<sub>21</sub>H<sub>32</sub>N<sub>2</sub>O<sub>5</sub> ([M+Na]<sup>+</sup>) 415.23, found 415.18



**H<sub>2</sub>N-D-Phe-Ile-OMe (7).** H<sub>2</sub>N-D-Phe-Ile-OMe was synthesized utilizing 393 mg (1.00 mmol, 1.0 equiv.) of BocHN-D-Phe-Ile-OMe in 8.0 ml of CH<sub>2</sub>Cl<sub>2</sub>. 0.19 ml (2.0 mmol, 2.0 equiv.) of anisole was added into the reaction mixture in dropwise while stirring. 2.0 ml of TFA was added into the reaction mixture in dropwise while stirring. The reaction was allowed to stir for 4 hrs with TLC monitoring. Upon completion, the solvent was evaporated followed by co-evaporation with CH<sub>2</sub>Cl<sub>2</sub> for 6 times. The product was then dried *in silico* and subjected to next reaction without further purification to give clear crystal (301mg, quantitative)

ES<sup>+</sup>MS *m/z* calcd for C<sub>16</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub> ([M+Na]<sup>+</sup>) 315.18, found 315.00



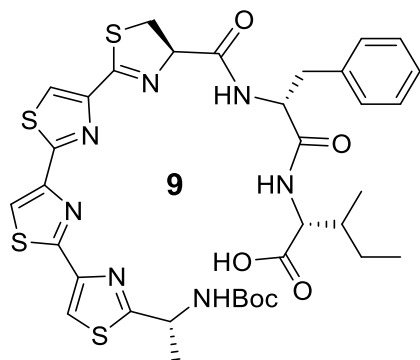
**BocHN-D-Ala-Thiazole-Thiazole-Thiazole-R-Thiazoline-D-Phe-Ile-OMe (8).** BocHN-D-Phe-Ile-OH was synthesized utilizing 0.144 g (0.275 mmol, 1 equiv.) of Boc-D-Ala-Thiazole-Thiazole-Thiazole-R-Thiazoline-OH and 0.09 g (0.30 mmol, 1.1 equiv) HATU were dissolved in 20 mL of CH<sub>2</sub>Cl<sub>2</sub>, 0.38 mL (2.20 mmol, 8.0 equiv.) DIPEA was added to the mixture and finally 87 mg (0.30 mmol, 1.1 equiv.) of NH<sub>2</sub>-D-Phe-Ile-OMe pre-dissolved in 7.5 mL of CH<sub>2</sub>Cl<sub>2</sub> was added to the acid and coupling mixture solution in drop wise. Upon completion, the reaction mixture was purified by flash column on silica gel elute with gradient of hexane and EtOAc to give final product as white solid (0.154 g, 70%).

R<sub>f</sub>: 0.45 (hexane/EtOAc 1:1).

$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.706 (m, 3H,  $\text{CHCH}_3$ ), 0.957 (m, 3H,  $\text{CH}_2\text{CH}_3$ ), 1.069 (m, 1H,  $\text{CH}_2\text{CH}_3$ ); 1.249 (m, 1H,  $\text{CH}_2\text{CH}_3$ ); 1.479 (br, 9H,  $\text{C}(\text{CH}_3)_3$ ); 1.66 (d,  $J = 6.65\text{Hz}$ , 3H,  $\text{CHCH}_3$ ); 1.70 (m, 1H,  $\text{CHCH}_3$ ); 3.141-3.171 (m, 2H,  $\text{CHCH}_2\text{C}$ ); 3.62 (m, 3H,  $\text{OCH}_3$ ); 3.67-3.78 (m, 2H,  $\text{CHCH}_2\text{S}$ ); 4.45 (m, 1H,  $\text{CH}_{(\text{Ile})}$ ); 4.801(m, 1H,  $\text{CH}_{(\text{Phe})}$ ); 5.138 (m, 1H,  $\text{CH}$ ); 5.22 (m, 1H,  $\text{CHCH}_2\text{S}$ ); 6.439 (br, 1H,  $\text{NH}$ ); 7.26 (m, 1H,  $\text{CH}$ ); 7.34 (m, 2H,  $\text{CH}$ ); 7.342 (m, 2H,  $\text{CH}$ ); 7.99 (m, 1H,  $\text{NH}$ ); 7.181(m, 2H,  $\text{CH}$ ), 7.235 (m, 1H,  $\text{CH}$ ); 7.275 (m, 2H,  $\text{CH}$ ); 7.31 (m, 1H,  $\text{NH}$ ); 7.341 (m, 1H,  $\text{NH}$ ); 8.02 (s, 1H,  $\text{SCHC}$ ), 8.04 (m, 1H,  $\text{SCHC}$ ); 8.144 (m, 1H,  $\text{SCHC}$ ).

$^{13}\text{C}$  NMR (150MHz,  $\text{CDCl}_3$ )  $\delta$  11.48, 15.31, 21.81, 25.11, 28.49(3C), 34.89, 37.78, 38.69, 48.93, 52.18, 54.76, 56.67, 77.46, 80.46, 116.86, 117.63, 124.38, 127.13, 128.79, 129.47, 136.7, 148.47, 149.33, 150.10, 155.10, 161.04, 162.78, 163.43, 169.162, 170.38, 171.92, 174.9.

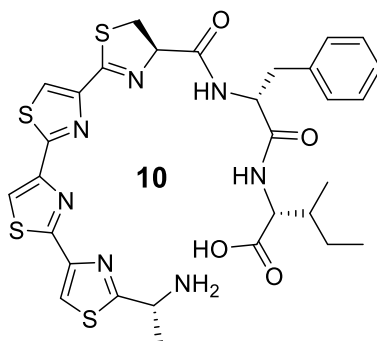
$\text{ES}^+\text{MS } m/z$  calcd for  $\text{C}_{36}\text{H}_{43}\text{N}_7\text{O}_4\text{S}_4$  ( $[\text{M}+\text{Na}]^+$ ) 820.22, found 820.25



**BocHN-D-Ala-Thiazole-Thiazole-Thiazole-R-Thiazoline-D-Phe-Ile-OH (9).** BocHN-D-Ala-Thiazole-Thiazole-Thiazole-(R)-Thiazoline-D-Phe-Ile-OH was synthesized utilizing 100 mg (0.125 mmol, 1.0 equiv.) of BocHN-D-Ala-Thiazole-Thiazole-Thiazole-R-Thiazoline-D-Phe-Ile-OMe in 5.0 ml of MeOH, 49.1 mg (2.04 mmol, 8.0 equiv.)  $\text{LiOH}\cdot\text{H}_2\text{O}$  was added into the reaction mixture in one portion while stirring. Catalytic amount of  $\text{H}_2\text{O}$  was also added into the reaction mixture. The reaction was allowed to proceed at room temperature for overnight followed by ultrasound sonication for 5.0 hrs. Upon completion, the reaction mixture was washed with pH = 1 hydrochloric acid solution and extracted twice with  $\text{CH}_2\text{Cl}_2$  and twice with EtOAc. The organic layer was collected, combined and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The product was subjected to further reaction without purification to give desired product as white solid (96 mg, 98%)

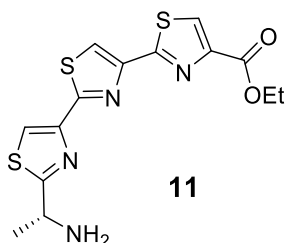
LC-MS  $\text{ES}^+\text{MS } m/z$  calcd for  $\text{C}_{35}\text{H}_{41}\text{N}_7\text{O}_6\text{S}_4$  ( $[\text{M}+\text{Na}]^+$ ) 806.20, found 805.95





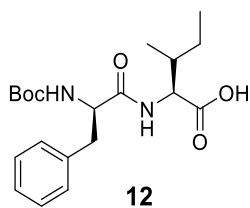
**H<sub>2</sub>N-D-Ala-Thiazole-Thiazole-Thiazole-R-Thiazoline-D-Phe-Ile-OH (10).** H<sub>2</sub>N-D-Ala-Thiazole-Thiazole-Thiazole-R-Thiazoline-D-Phe-Ile-OMe was synthesized utilizing 90 mg (0.115 mmol, 1.0 equiv.) of BocHN-D-Ala-Thiazole-Thiazole-Thiazole-R-Thiazoline-D-Phe-Ile-OH in 3.0 ml of CH<sub>2</sub>Cl<sub>2</sub>. 25μl (0.23 mmol, 2.0 equiv.) of anisole was added into the reaction mixture in dropwise while stirring. 1.0 ml of TFA was added into the reaction mixture in dropwise while stirring. The reaction was allowed to stir for 4 hrs with TLC monitoring. Upon completion, the solvent was evaporated followed by co-evaporation with CH<sub>2</sub>Cl<sub>2</sub> for 6 times. The product was then dried *in vacuo* and subjected to next reaction without further purification to give a brown oil (85mg, quantitative).

ES<sup>+</sup>MS *m/z* calcd for C<sub>30</sub>H<sub>33</sub>N<sub>7</sub>O<sub>4</sub>S<sub>4</sub> ([M+Na]<sup>+</sup>) 706.15, found 705.88



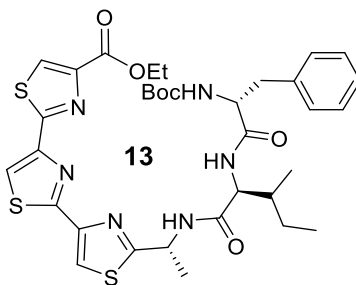
**H<sub>2</sub>N-D-Ala-Thiazole-Thiazole-Thiazole-OEt (11).** BocHN-D-Ala-Thiazole-Thiazole-Thiazole-OEt (400 mg, 0.857 mmol, 1.0 equiv.) was dissolved in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (9.0 mL, 0.1 M) at r.t. Anisole (0.18 mL, 1.72 mmol, 2.0 eq.) was then added into the solution. While stirring, TFA (3.0 mL) was added into the reaction in dropwise. The reaction was allowed to proceed for 3 hrs. Upon completion of reaction, confirmed via TLC, the mixture was then co-evaporate with CH<sub>2</sub>Cl<sub>2</sub> for 6 times. The product free amine was then further dried *in vacuo* to afford brown solid (300mg, quantitative)

ES<sup>+</sup>MS *m/z* calcd for C<sub>14</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub>S<sub>3</sub> ([M+H]<sup>+</sup>) 367.46, found 367.18



**BocHN-D-Phe-Ile-OH (12).** BocHN-D-Phe-Ile-OMe (370.1 mg, 0.943 mmol, 1.0 equiv.) was dissolved in MeOH (15.0 mL, 0.1 M) at r.t. While stirring, LiOH·H<sub>2</sub>O (316.4 mg, 7.54 mmol, 8.0 equiv.) was added into the reaction in one portion. MilliQ H<sub>2</sub>O (1.0 ml) was then added into the reaction mixture. The reaction was allowed to proceed for overnight. Upon reaction completion, confirmed via TLC, the reaction mixture was concentrated followed by re-dissolving in CH<sub>2</sub>Cl<sub>2</sub>, the solution was then poured into pH = 1 hydrochloric acid solution and extracted twice with CH<sub>2</sub>Cl<sub>2</sub> and EtOAc, the organic layers were combined and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtration, and concentrated *in vacuo* to give the desired carboxylic acid product as white solid (360mg, quantitative).

ES<sup>+</sup>MS *m/z* calcd for C<sub>20</sub>H<sub>30</sub>N<sub>2</sub>O<sub>5</sub> ([M+Na]<sup>+</sup>) 401.47, found 401.01



**BocHN-D-Phe-Ile-D-Ala-Thiazole-Thiazole-Thiazole-OEt (13).** BocHN-D-Phe-Ile-D-Ala-Thiazole-Thiazole-Thiazole-OEt was synthesized utilizing 360 mg (0.943 mmol, 1.1 equiv.) of BocHN-D-Phe-Ile-OH and 359 mg (0.943 mmol, 1.1 equiv.) of HATU in 20 mL of CH<sub>2</sub>Cl<sub>2</sub>, 300 mg (0.857 mmol, 1.0 equiv.) of H<sub>2</sub>N-D-Ala-Thiazole-Thiazole-Thiazole-OEt in CH<sub>2</sub>Cl<sub>2</sub>, DIPEA (1.493 ml, 8.573mmol, 10.0 equiv.) was added into the free acid containing reaction mixture in dropwise then to the amine containing reaction mixture. After 5 min, amine reaction mixture was then taken up and injected into the free acid containing reaction mixture in dropwise. The reaction was allowed to stir for 4 hours followed by TLC monitoring. Upon completion, the reaction mixture was washed with pH = 1 hydrochloric acid solution and extracted twice with CH<sub>2</sub>Cl<sub>2</sub> and twice with EtOAc. The organic layer was collected and combined followed by washing with Sat. NaHCO<sub>3</sub> solution and extract twice with CH<sub>2</sub>Cl<sub>2</sub> and twice with EtOAc, the organic layer was collected, combined and dried over anhydrous

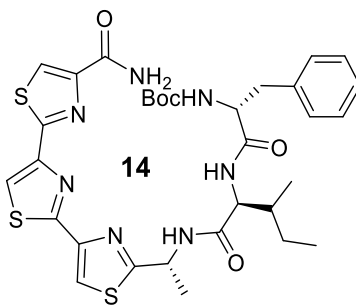
Na<sub>2</sub>SO<sub>4</sub>. The crude material was purified over flash column on silica gel elute with gradient of hexane and EtOAc to give desired product as white solid (450 mg, 72.2%)

R<sub>f</sub>: 0.556 (hexane/EtOAc 1:1).

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 0.764 (m, 3H, CHCH<sub>3</sub>), 0.845 (m, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.382 (br, 9H, C(CH<sub>3</sub>)<sub>3</sub>); 1.46 (t, *J* = 7.56 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>); 1.54-1.70 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>); 1.685 (d, *J* = 6.66 Hz, 3H, CHCH<sub>3</sub>); 1.99 (m, 1H, CHCH); 3.076-3.138 (m, 2H, CHCH<sub>2</sub>C); 4.216 (m, 1H, NHCHCH); 4.315 (m, 1H, NHCHCH<sub>2</sub>); 4.45 (q, *J* = 7.06 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>); 5.023 (br, 1H, NH); 5.425 (m, 1H, NH); 6.38 (m, 1H, NH); 7.176 (m, 2H, CH), 7.21 (m, 1H, CH); 7.271 (m, 2H, CH); 7.30 (m, 1H, NH); 7.948 (s, 1H, SCHC), 8.132 (s, 1H, SCHC); 8.183 (s, 1H, SCHC).

<sup>13</sup>C NMR (from 2D NMR) δ 11.56, 14.39, 15.60, 20.61, 24.69, 28.29(3C), 36.23, 37.85, 47.45, 56.45, 57.95, 61.54, 80.69, 116.802, 117.93, 127.21, 127.79, 128.85, 129.12, 136.07, 147.87, 147.95, 148.18, 149.12, 155.02, 161.46, 163.07, 163.37, 171.23, 171.38, 173.62.

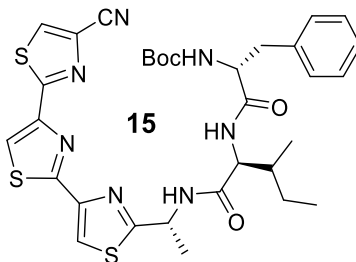
ES<sup>+</sup>MS *m/z* calcd for C<sub>34</sub>H<sub>42</sub>N<sub>6</sub>O<sub>6</sub>S<sub>3</sub> ([M+Na]<sup>+</sup>) 749.22, found 748.97

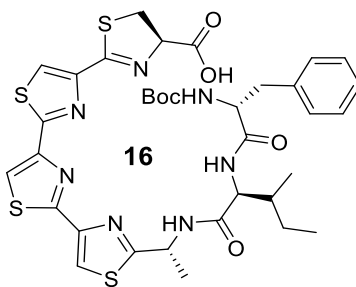


**BocHN-D-Phe-Ile-D-Ala-Thiazole-Thiazole-Thiazole-C(O)-NH<sub>2</sub> (14).** BocHN-D-Phe-Ile-D-Ala-Thiazole-Thiazole-Thiazole-C(O)-NH<sub>2</sub> was synthesized utilizing 450 mg (0.619 mmol, 1.0 equiv.) of BocHN-D-Phe-Ile-D-Ala-Thiazole-Thiazole-Thiazole-OEt in 30 mL of ammonium hydroxide solution (28% w/v) and 75 mL of MeOH. The reaction mixture was sonicated for 48 hrs. Upon completion of reaction, confirmed via TLC, the reaction mixture was then concentrated *in vacuo* followed by co-evaporation with MeOH for 5 times; the resulting amide was taken on to the next reaction without further purification (350 mg, 81%) as a white powder.

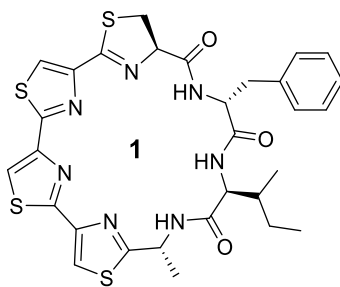
R<sub>f</sub>: 0.222 (hexane/EtOAc 1:1).

<sup>1</sup>H NMR (600 MHz, CD<sub>3</sub>OD): δ 0.764 (m, 3H, CHCH<sub>3</sub>), 0.845 (m, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.382 (br, 9H, C(CH<sub>3</sub>)<sub>3</sub>); 1.46 (t, *J* = 7.56 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>); 1.54-1.70 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>); 1.685 (d, *J* = 6.66 Hz, 3H, CHCH<sub>3</sub>); 1.99 (m, 1H, CHCH); 3.076-3.138 (m, 2H, CHCH<sub>2</sub>C); 4.216 (m, 1H, NHCHCH); 4.315 (m, 1H, NHCHCH<sub>2</sub>); 4.45 (q, *J* = 7.06 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>); 5.023 (br, 1H,

ES<sup>+</sup>MS *m/z* calcd for C<sub>32</sub>H<sub>39</sub>N<sub>7</sub>O<sub>5</sub>S<sub>3</sub> ([M+Na]<sup>+</sup>) 698.23, found 697.99ES<sup>+</sup>MS *m/z* calcd for C<sub>32</sub>H<sub>37</sub>N<sub>7</sub>O<sub>4</sub>S<sub>3</sub> ([M+Na]<sup>+</sup>) 680.22, found 680.00



**BocHN-D-Phe-Ile-D-Ala-Thiazole-Thiazole-Thiazole-(R)-Thiazoline-OH (16).** 200 mg (0.295 mmol, 1.0 equiv.) of BocHN-D-Phe-Ile-D-Ala-Thiazole-Thiazole-Thiazole-CN and 43.0 mg (0.353 mmol, 1.2 equiv.) L-Cysteine and 124 mg (1.47 mmol, 5.0 equiv.) of NaHCO<sub>3</sub> in 10.0 ml of MeOH. While stirring, 5.0 ml of pH = 5.95 phosphate buffer solution was added into the reaction mixture. The reaction mixture was then stirred at 70°C for 4 hr. followed by routine TLC monitoring for reaction progress. Upon starting material was fully consumed, the reaction mixture was concentrated to remove all of the solvent then re-dissolved in EtOAc and then poured into the Sat. NaHCO<sub>3</sub> solution. The organic layer was set aside, the aqueous layer was further extract with EtOAc for 2 times. The aqueous layer was then acidified using pH = 1 hydrochloric acid solution in dropwise with pH monitoring until reach pH = 3. The aqueous layer was then extracted with EtOAc 3 times. All organic layer was then collected, combined and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> followed by filtration, concentration *in vacuo* and further dried *in silico* to give white solid. The material was subjected for next reaction without further purification. ES<sup>+</sup>MS *m/z* calcd for C<sub>35</sub>H<sub>41</sub>N<sub>7</sub>O<sub>6</sub>S<sub>4</sub> ([M+H]<sup>+</sup>) 784.21, found 784.01



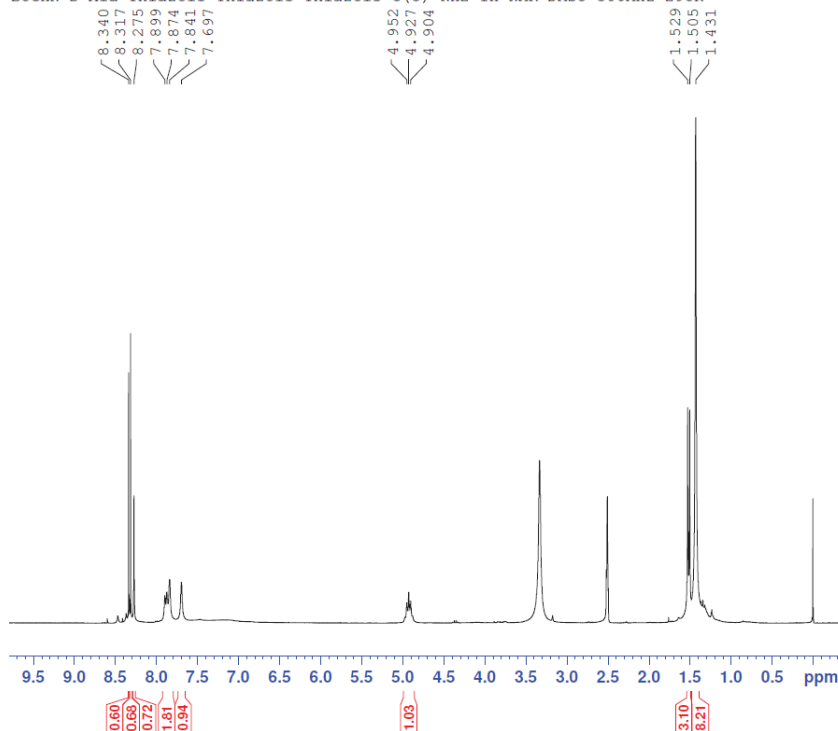
**Cyclo-D-Phe-Ile-D-Ala-Thiazole-Thiazole-Thiazole-R-Thiazoline (1).** BocHN-D-Phe-Ile-D-Ala-Thiazole-Thiazole-Thiazole-R-Thiazoline-OH (130 mg, 0.166 mmol, 1.0 equiv.) dissolved in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (4.0 ml) at r.t. Anisole (54μL, 0.498 mmol, 3.0 eq.) was then added into the solution. While stirring, TFA (1.0 mL) was added into the reaction in dropwise. The reaction was allowed to proceed for 3 hrs. Upon completion of reaction, confirmed via TLC, the mixture was then co-

evaporate with  $\text{CH}_2\text{Cl}_2$  6 times. The product free amine was then further dried *in vacuo* to afford linear precursor. The coupling reagent cocktail contains 63 mg (0.166 mmol, 1.0 equiv.) HATU and 46 mg (0.166 mmol, 1.0 equiv.) DMTMM was weighted into the heat gun blow dried round bottom flask followed by immediate vacuum. 120 ml of anhydrous  $\text{CH}_2\text{Cl}_2$  was then added into the coupling reagent cocktail containing flask followed by nitrogen purging. Pre-dried linear precursor (120 mg, 0.166 mmol, 1.0 equiv.) was weighted in a round bottom flask and vacuumed to remove all of the air moisture. 40 ml of anhydrous  $\text{CH}_2\text{Cl}_2$  was charged into the flask followed by nitrogen purging. The 250  $\mu\text{l}$  (0.166 mmol, 1.0 equiv.) of HOAt in DMF was added into the coupling reagent containing cocktails in dropwise while stirring. After 1hr, 290  $\mu\text{l}$  (1.66 mmol, 10.0 equiv.) of DIPEA was added into the coupling cocktail containing flask followed by linear precursor containing flask in dropwise. After 5 min, the linear precursor solution was withdraw from the flask using a 30 ml syringe and then injected into the coupling reagent containing flask at a rate of 0.25ml/min with utilization of a syringe pump. Upon completion of injecting all of the linear precursor solution, the reaction progress was monitored via LC-MS routinely every 1 hr. Upon completion of reaction, the reaction mixture was concentrate the redissolved in  $\text{CH}_2\text{Cl}_2$  then poured into the pH = 1 hydrochloric acid solution, the aqueous layer was further extract twice with  $\text{CH}_2\text{Cl}_2$  and EtOAc. Combined organic layer was poured into the Sat.  $\text{NaHCO}_3$  solution, the aqueous layer was extracted twice with  $\text{CH}_2\text{Cl}_2$  and EtOAc. All organic layer was collected, combined, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in *vacuo*. The crude material was then underwent flash column chromatographical purification on silica gel at gradient running (10%EtOAc /90% Hexane – 100%EtOAc – 30%MeOH/ 70%EtOAc). After LC-MS characterization, the product containing column fractions was combined and concentrated in *vacuo* then redissolved in HPLC grade MeOH and re-purified via reverse phase HPLC twice to give final product as white solid (3mg, 2.7%).

# Spectral Data

## Compound 4 (DMSO)

BocHN-D-Ala-Thiazole-Thiazole-Thiazole-C(O)-NH<sub>2</sub> 1H NMR DMSO 300MHz 298K

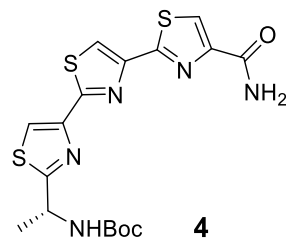


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PROCNO 3

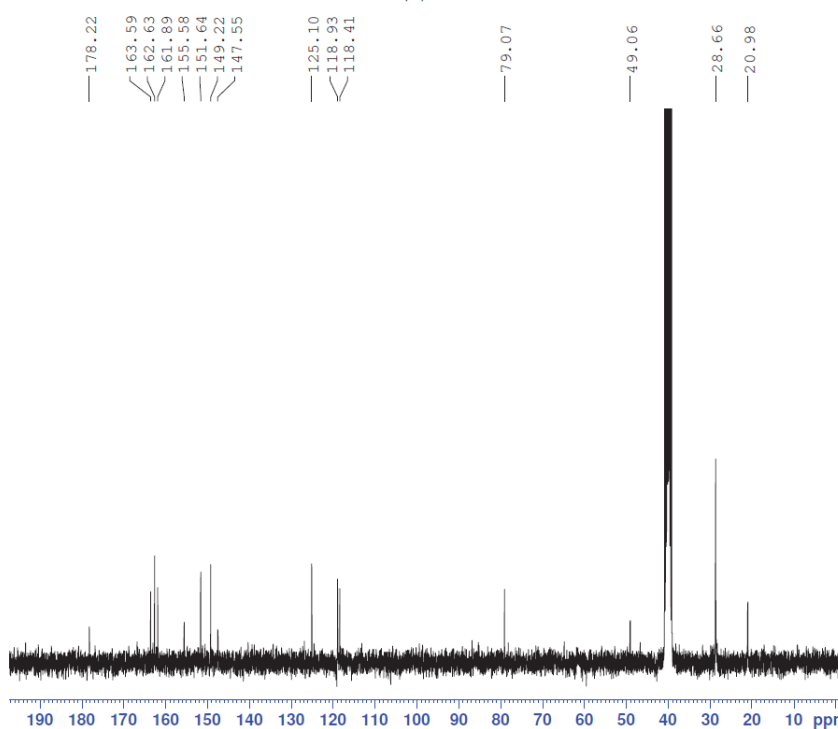
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SOLVENT DMSO  
NS 128  
DS 0  
SWH 4801.537 Hz  
FIDRES 0.146531 Hz  
AQ 3.4122410 sec  
RG 114  
DW 104.133 usec  
DE 9.44 usec  
TE 298.0 K  
D1 5.00000000 sec  
TD0 4

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NUC1 1H  
P1 16.56 usec  
PLW1 8.19999981 W

F2 - Processing parameters  
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WDW EM  
SSB 0  
LB 0.10 Hz  
GB 0  
PC 1.00



BocHN-D-Ala-Thiazole-Thiazole-Thiazole-C(O)-NH<sub>2</sub> 13C NMR DMSO 75MHz 298K



Current Data Parameters  
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EXPNO 2  
PROCNO 1

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SOLVENT DMSO  
NS 3072  
DS 2  
SWH 18028.846 Hz  
FIDRES 0.275098 Hz  
AQ 1.8175317 sec  
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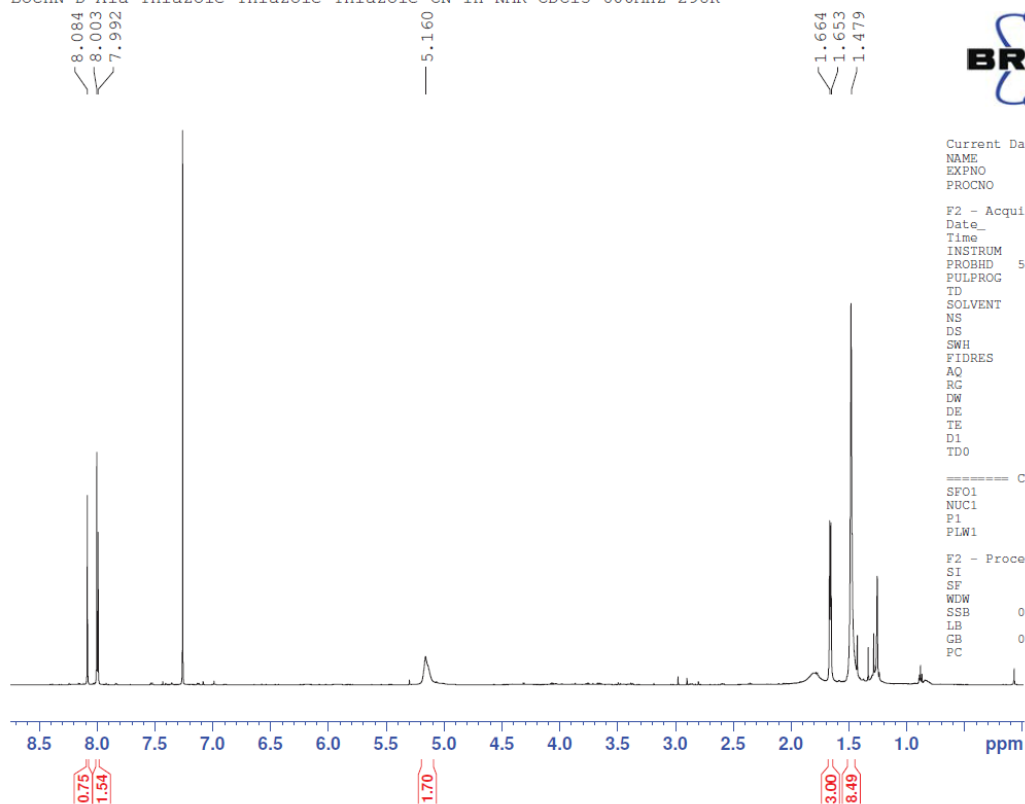
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NUC2 1H  
CPDPRG[2] bi\_waltz65\_256  
PCPD2 90.00 usec  
PLM2 8.20349979 W  
PLW12 0.27774000 W  
PLW13 0.22497000 W

F2 - Processing parameters  
SI 32768  
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WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

# Compound 5 (CDCl<sub>3</sub>)

BocHN-D-Ala-Thiazole-Thiazole-Thiazole-CN 1H NMR CDCl<sub>3</sub> 600MHz 298K

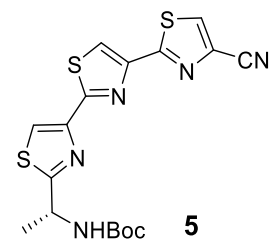


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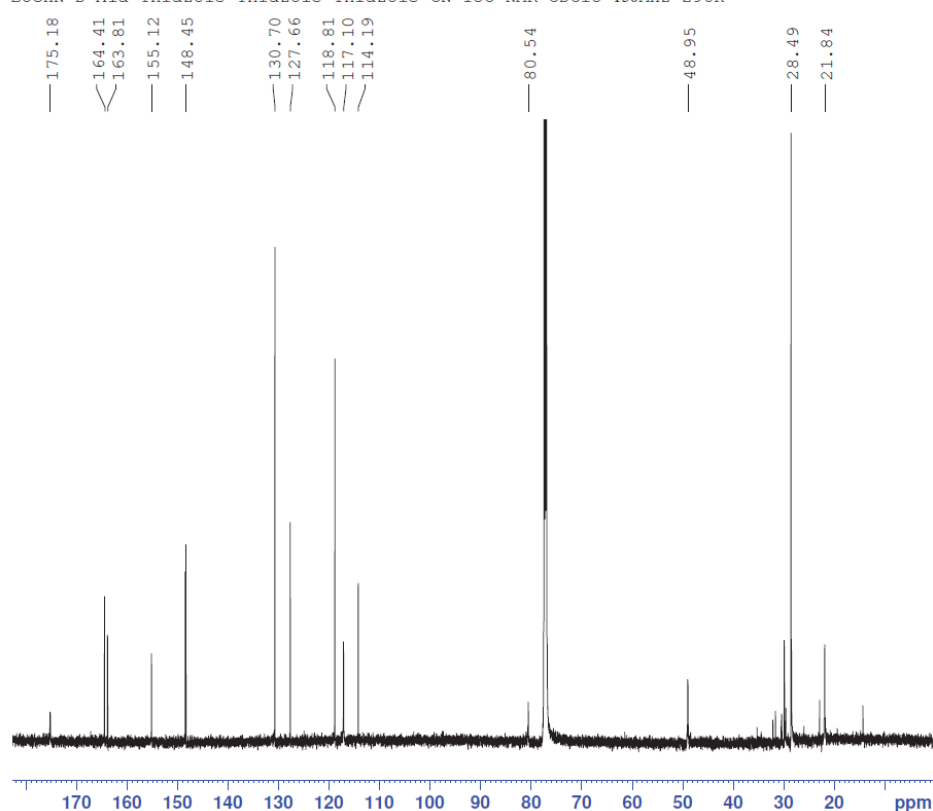
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 SOLVENT CDCl<sub>3</sub>  
 NS 16  
 DS 0  
 SWH 9009.009 Hz  
 FIDRES 0.137467 Hz  
 AQ 3.6372480 sec  
 RG 55.96  
 DW 55.500 usec  
 DE 33.22 usec  
 TE 298.0 K  
 D1 5.00000000 sec  
 TD0 1

===== CHANNEL f1 =====  
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 NUC1 1H  
 P1 8.00 usec  
 PLW1 3.81069994 W

F2 - Processing parameters  
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 SF 600.1600152 MHz  
 WDW EM  
 SSB 0  
 LB 0.30 Hz  
 GB 0  
 PC 1.00



BocHN-D-Ala-Thiazole-Thiazole-Thiazole-CN 13C NMR CDCl<sub>3</sub> 150MHz 298K



Current Data Parameters  
 NAME 140912-hwa  
 EXPNO 2  
 PROCNO 2

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 SOLVENT CDCl<sub>3</sub>  
 NS 5120  
 DS 4  
 SWH 32894.738 Hz  
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 AQ 0.9961472 sec  
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 TD0 1

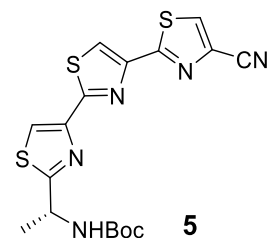
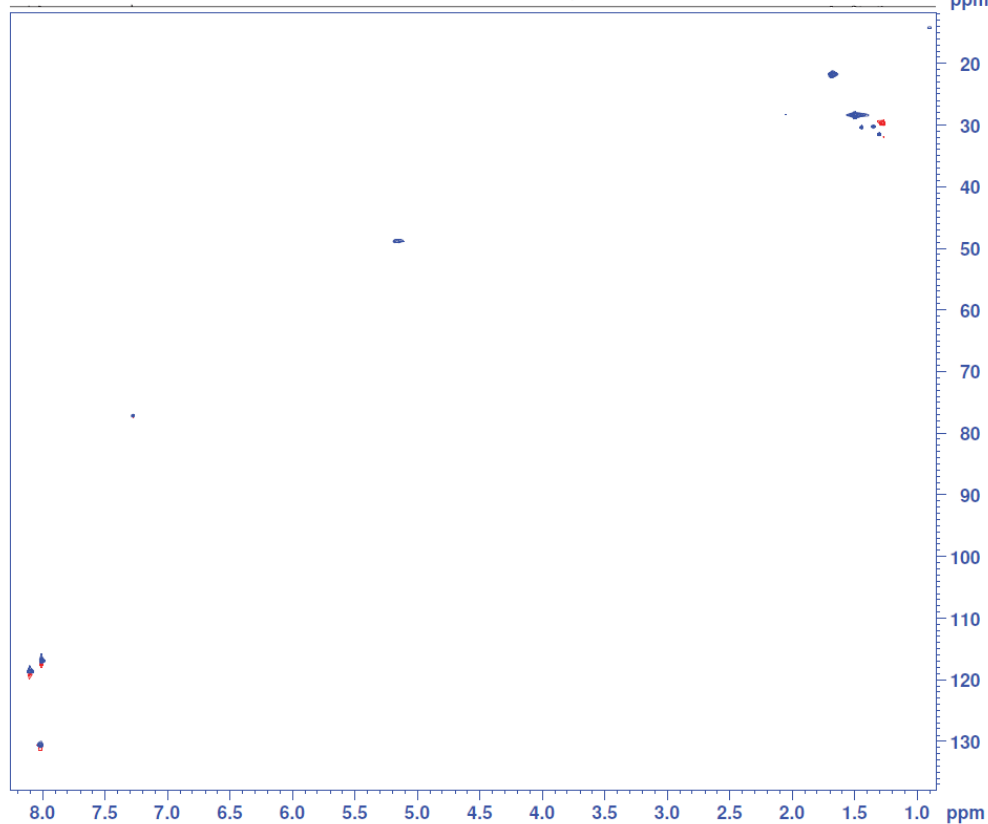
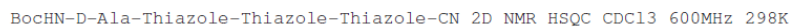
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 PLW1 100.00000000 W

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 PLW2 3.81069994 W  
 PLW12 0.04977200 W  
 PLW13 0.02438800 W

F2 - Processing parameters  
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Compound **5** (CDCl<sub>3</sub>)



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PROCNO       2
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PCPDPRG2      hsqacqddpdprg2-4
SOLVENT       CDCl3
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RG            202.23
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CONFTY1      -0.50000 D
CPDPRG2       0.000000
SU            1.0000000
SU1           0.00344828
SU2           0.00344828
SU3           0.00344828
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[illegible]

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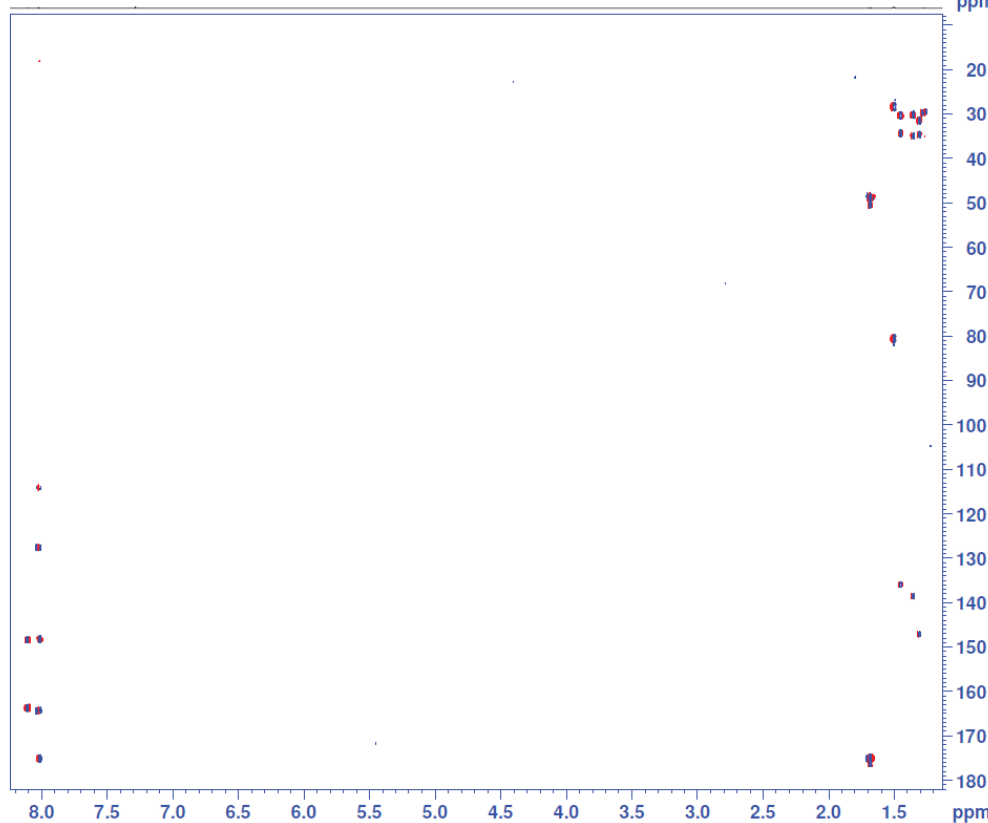
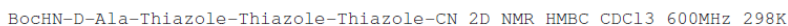
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F2 - Processing parameters
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F3 - Processing parameters
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EXPNO     2
PROCNO    1

F2 - Acquisition Parameters
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TD0         25
SOLVENT     CDCl3
NS          36
DS          16
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FIDRES      4.650012 Hz
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RG           250
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P2         2000.00 usec
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CP03      8.00 %
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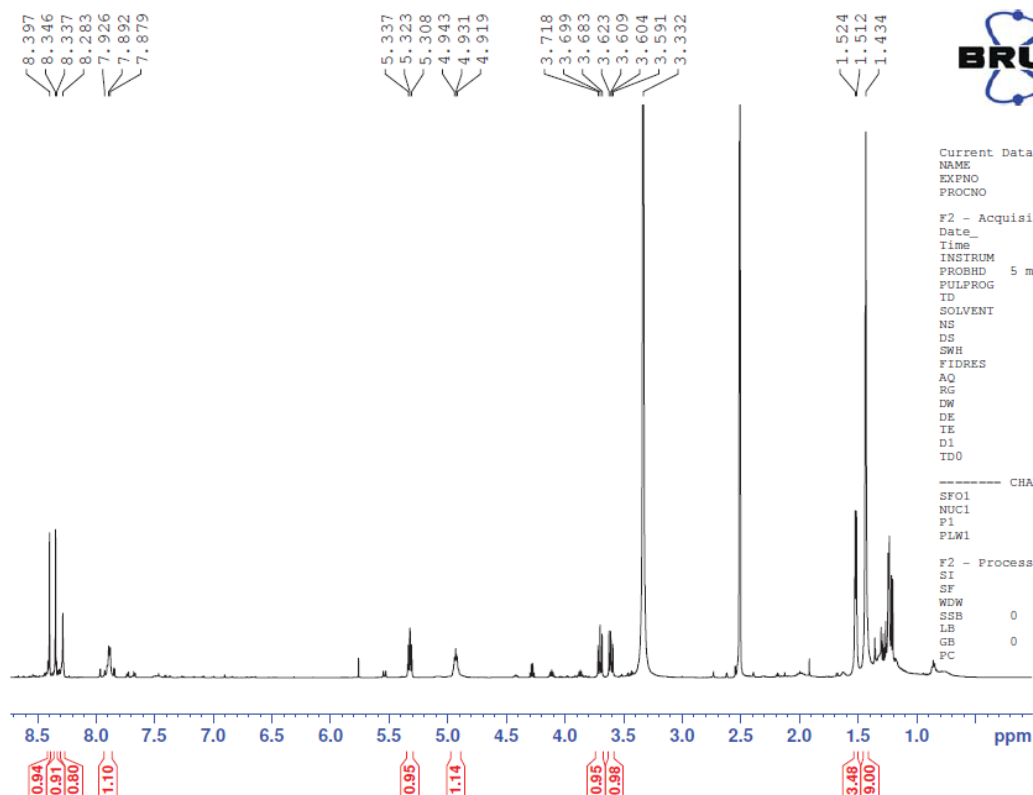
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SSB         2
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# Compound 6 (DMSO)

BocHN-D-Ala-Thiazole-Thiazole-Thiazole-R-Thiazoline-OH 1H NMR DMSO 600MHz 298K

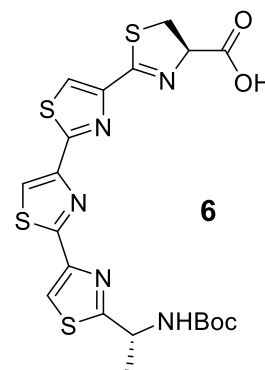


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PROCNO 2

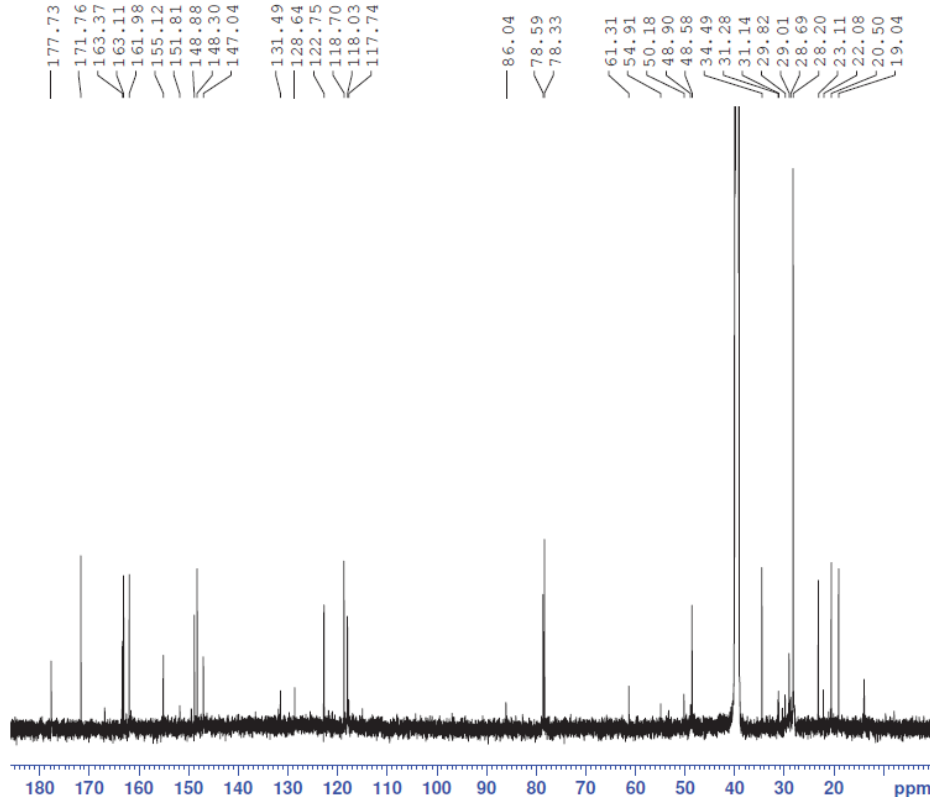
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NS 32  
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FIDRES 0.137467 Hz  
AQ 3.6372480 sec  
RG 35.72  
DW 55.500 usec  
DE 33.22 usec  
TE 298.0 K  
D1 5.00000000 sec  
TD0 1

CHANNEL f1  
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NUC1 1H  
P1 8.00 usec  
PLW1 3.81069994 W

F2 - Processing parameters  
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WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00



BocHN-D-Ala-Thiazole-Thiazole-Thiazole-R-Thiazoline-OH 13C NMR DMSO 150MHz 298K



Current Data Parameters  
NAME 141025-nmr  
EXPNO 7  
PROCNO 2

F2 - Acquisition Parameters  
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Time 20.05  
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PULPROG zgpg30  
TD 65536  
SOLVENT DMSO  
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DS 4  
SWH 32894.738 Hz  
FIDRES 0.501934 Hz  
AQ 0.9961472 sec  
RG 202.23  
DW 15.200 usec  
DE 17.51 usec  
TE 298.0 K  
D1 2.00000000 sec  
D11 0.03000000 sec  
TD0 10

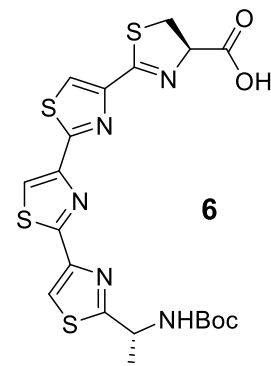
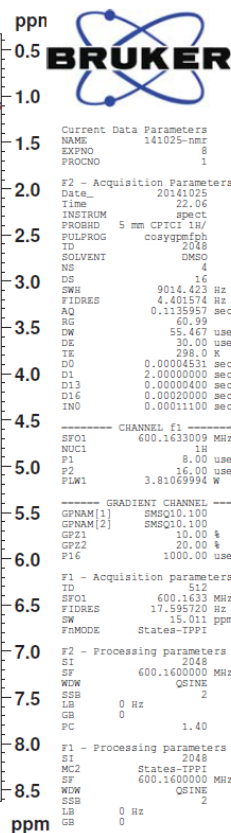
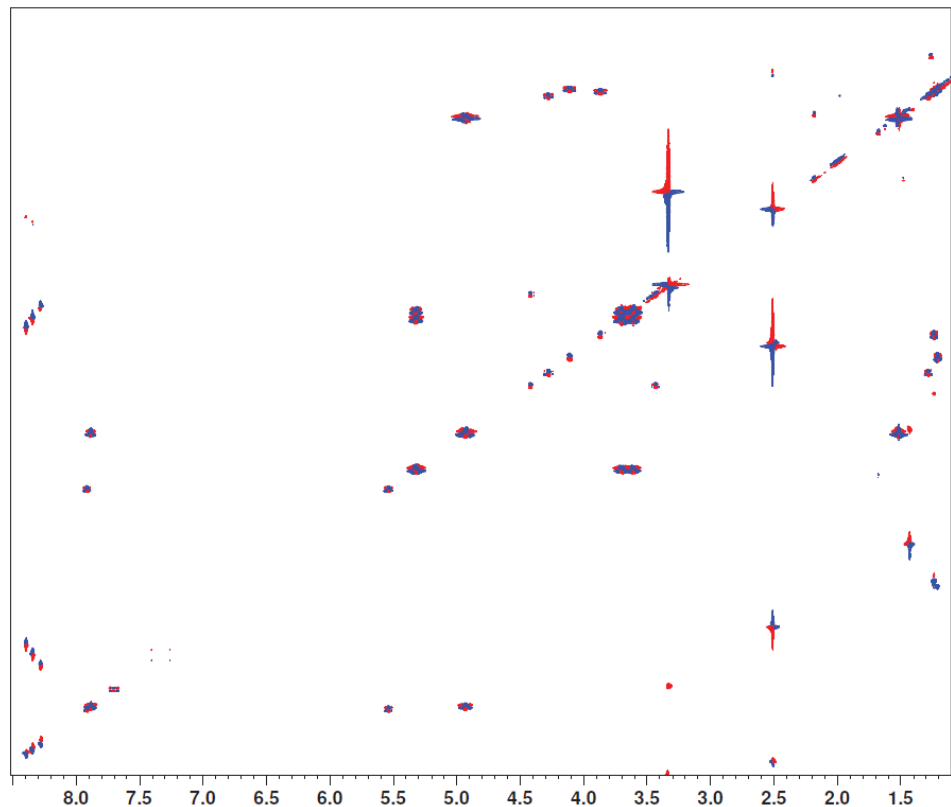
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CHANNEL f2  
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NUC2 1H  
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PLW13 0.02438800 W

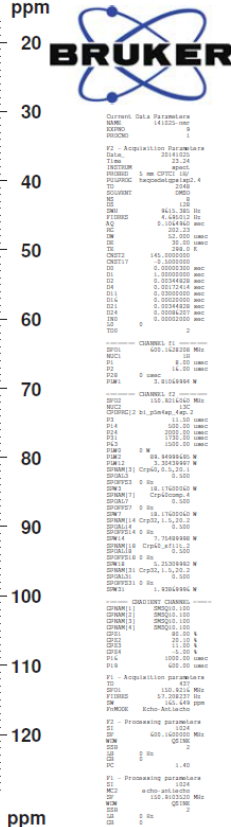
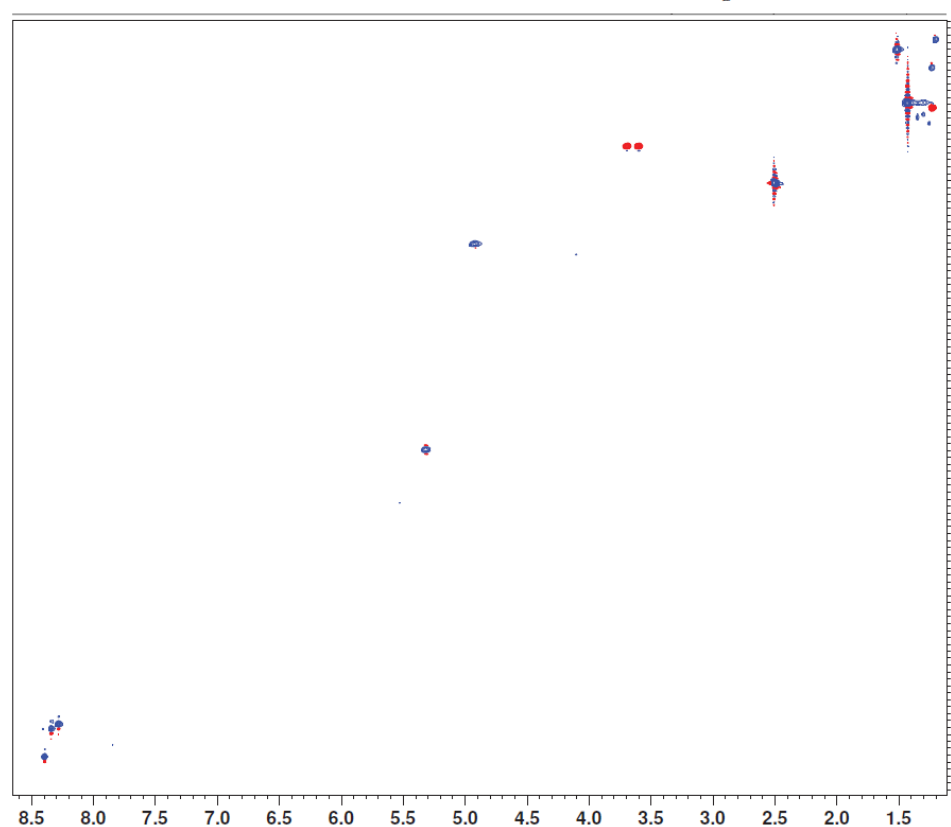
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GB 0  
PC 1.40

# Compound 6 (DMSO)

BocHN-D-Ala-Thiazole-Thiazole-Thiazole-R-Thiazoline-OH 2D NMR COSY DMSO 600MHz ;

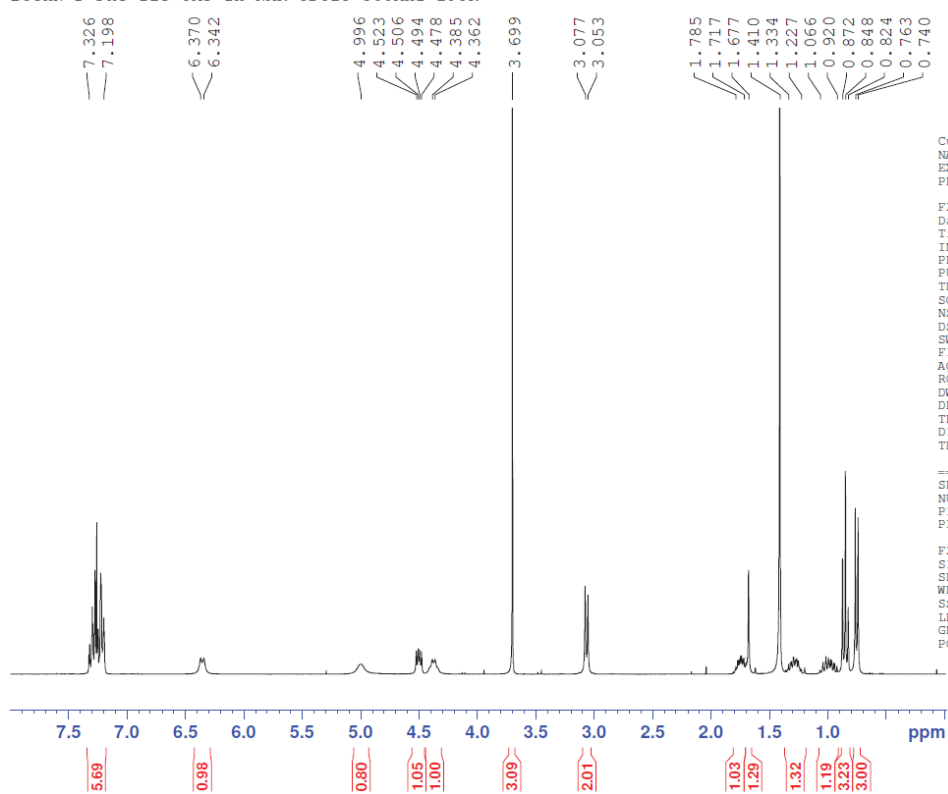


BocHN-D-Ala-Thiazole-Thiazole-Thiazole-R-Thiazoline-OH 2D NMR HSQC DMSO 600MHz 298K



# Compound 2 (CDCl<sub>3</sub>)

BocHN-D-Phe-Ile-OMe 1H NMR CDCl<sub>3</sub> 300MHz 298K

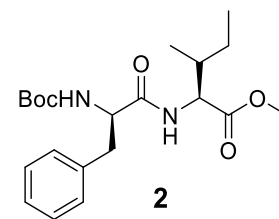


Current Data Parameters  
NAME 150220-  
EXPNO 5  
PROCNO 2

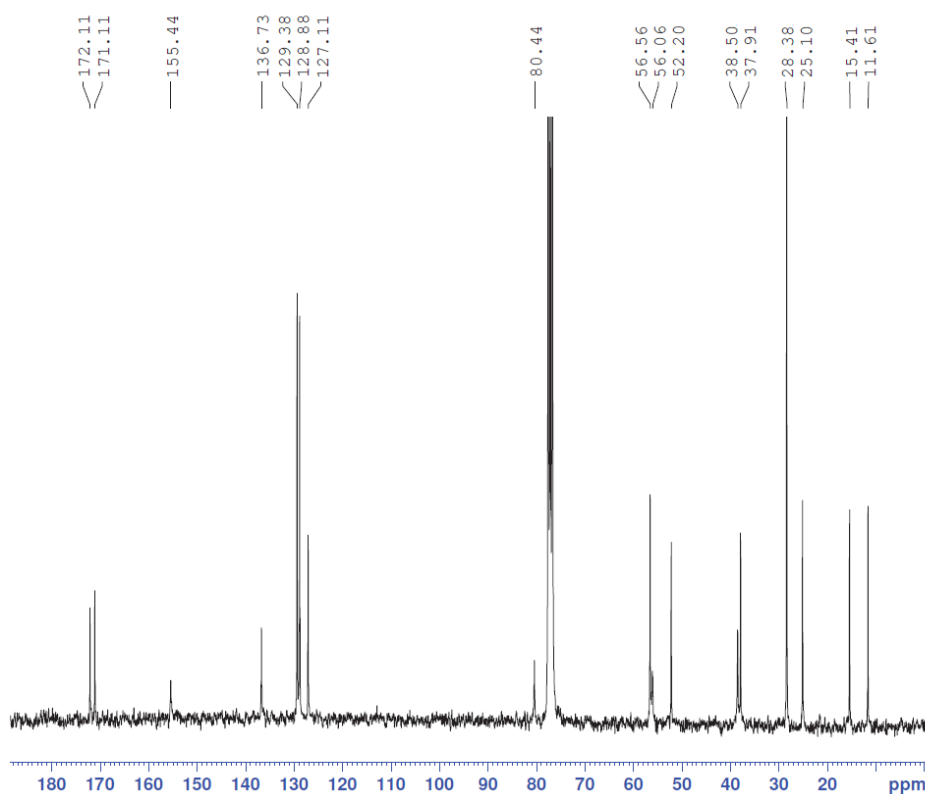
F2 - Acquisition Parameters  
Date\_ 20150221  
Time\_ 0.41  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zg  
TD 32768  
SOLVENT CDCl<sub>3</sub>  
NS 16  
DS 0  
SWH 4801.537 Hz  
FIDRES 0.146531 Hz  
AQ 3.4122410 sec  
RG 80.6  
DW 104.133 usec  
DE 9.44 usec  
TE 298.0 K  
D1 5.0000000 sec  
TD0 1

===== CHANNEL f1 =====  
SFO1 300.1719511 MHz  
NUC1 1H  
P1 16.56 usec  
PLW1 8.19999981 W

F2 - Processing parameters  
SI 131072  
SF 300.1700073 MHz  
WDW EM  
SSB 0  
LB 0.10 Hz  
GB 0  
PC 1.00



BocHN-D-Phe-Ile-OMe 13C NMR CDCl<sub>3</sub> 75MHz 298K



Current Data Parameters  
NAME 150220-  
EXPNO 10  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20150222  
Time\_ 8.05  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl<sub>3</sub>  
NS 4096  
DS 2  
SWH 18028.846 Hz  
FIDRES 0.275098 Hz  
AQ 1.8175317 sec  
RG 203  
DW 27.733 usec  
DE 6.80 usec  
TE 298.1 K  
D1 1.00000000 sec  
D11 0.03000000 sec  
TD0 16

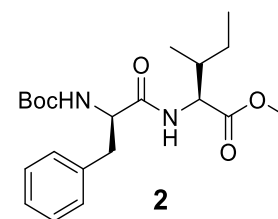
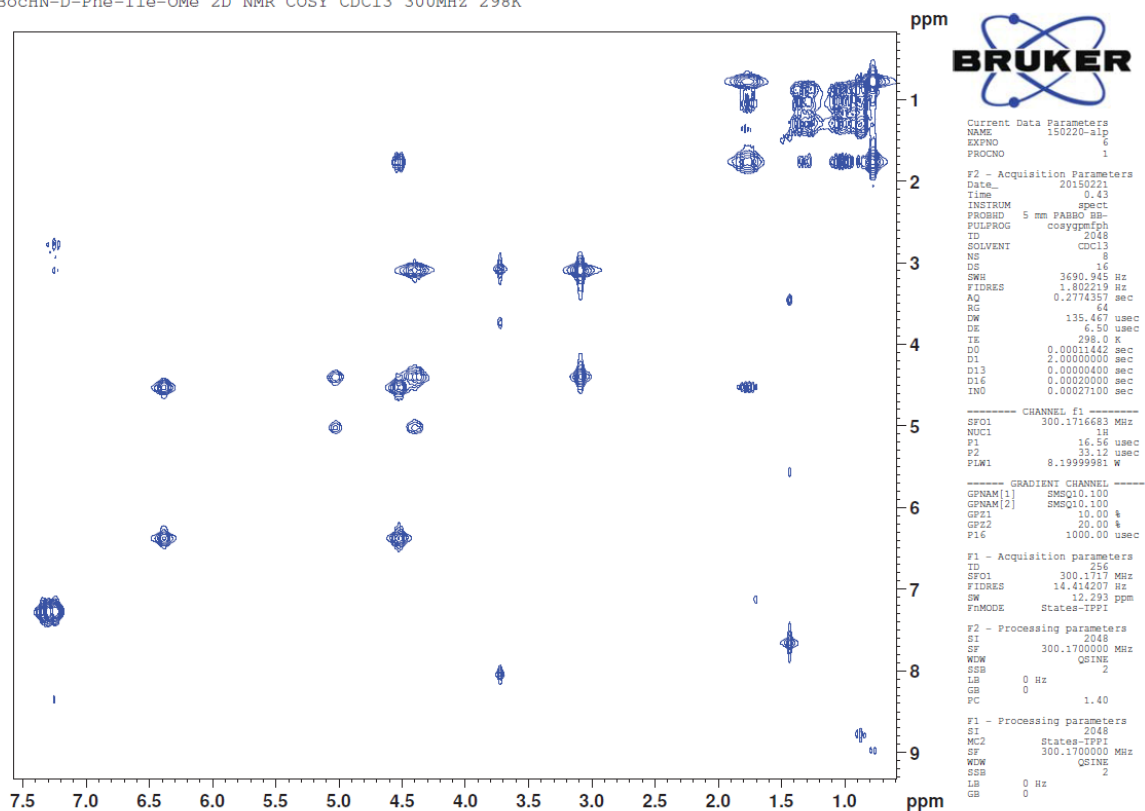
===== CHANNEL f1 =====  
SFO1 75.4853543 MHz  
NUC1 13C  
P1 9.90 usec  
PLW1 33.00000000 W

===== CHANNEL f2 =====  
SFO2 300.1712007 MHz  
NUC2 1H  
CPDPRG[2] bi\_waltz65\_256  
PCPD2 90.00 usec  
PLW2 8.20349979 W  
PLW12 0.27774000 W  
PLW13 0.22497000 W

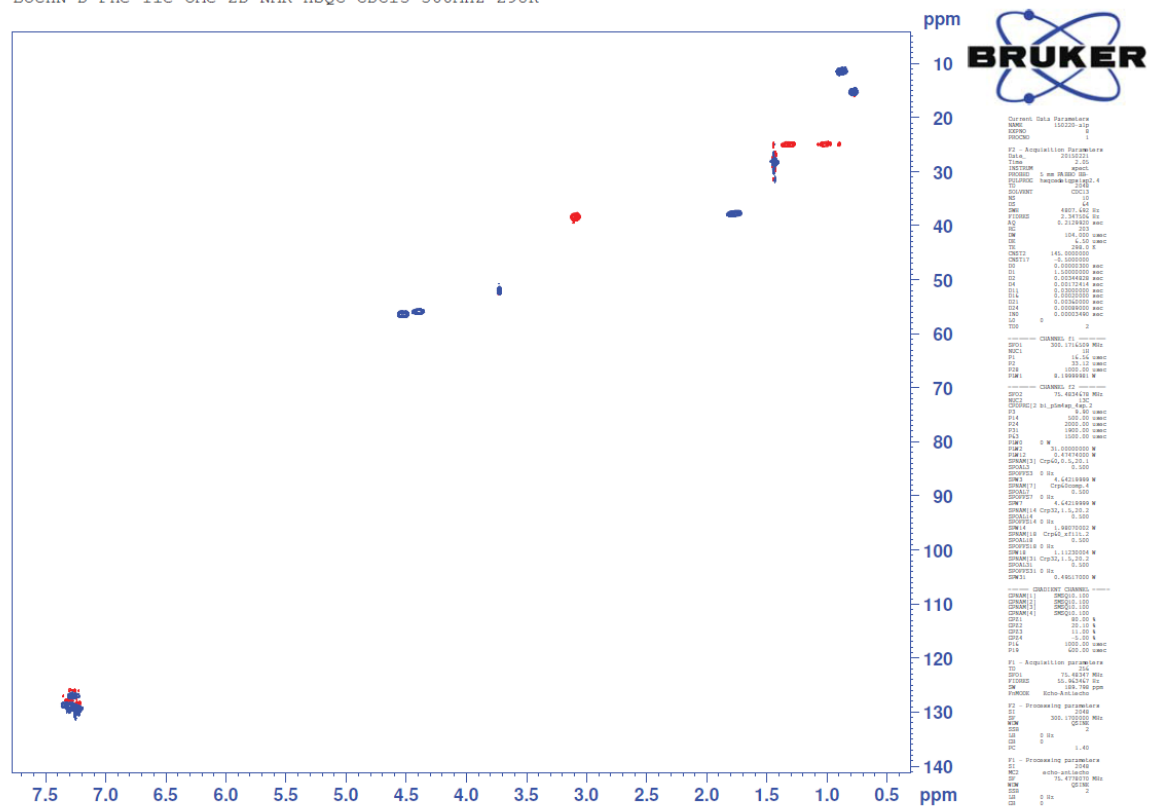
F2 - Processing parameters  
SI 32768  
SF 75.4777967 MHz  
WDW EM  
SSB 0  
LB 5.00 Hz  
GB 0  
PC 1.40

# Compound 2 (CDCl<sub>3</sub>)

BocHN-D-Phe-Ile-OMe 2D NMR COSY CDCl<sub>3</sub> 300MHz 298K

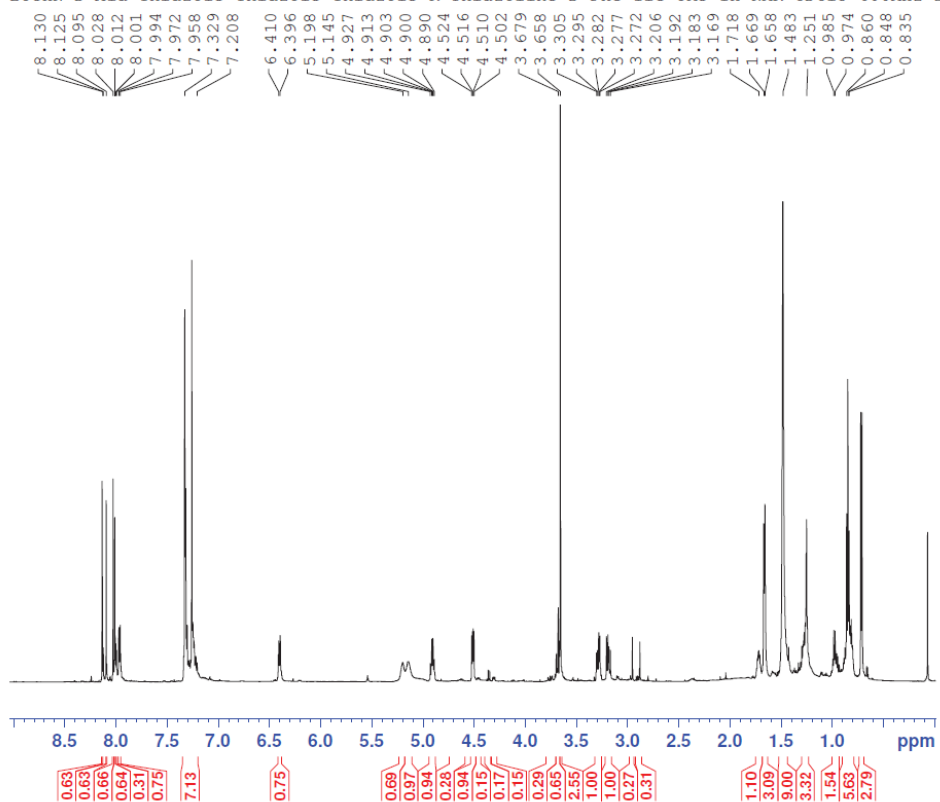


BocHN-D-Phe-Ile-OMe 2D NMR HSQC CDCl<sub>3</sub> 300MHz 298K



# Compound 8 (CDCl<sub>3</sub>)

BocHN-D-Ala-Thiazole-Thiazole-Thiazole-R-Thiazoline-D-Phe-Ile-OMe 1H NMR CDCl<sub>3</sub> 600MHz 298K

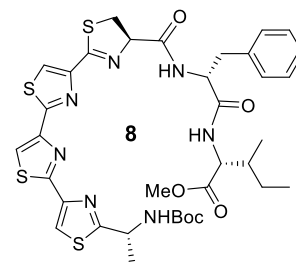


Current Data Parameters  
NAME 141014-alp  
EXPNO 1  
PROCNO 1

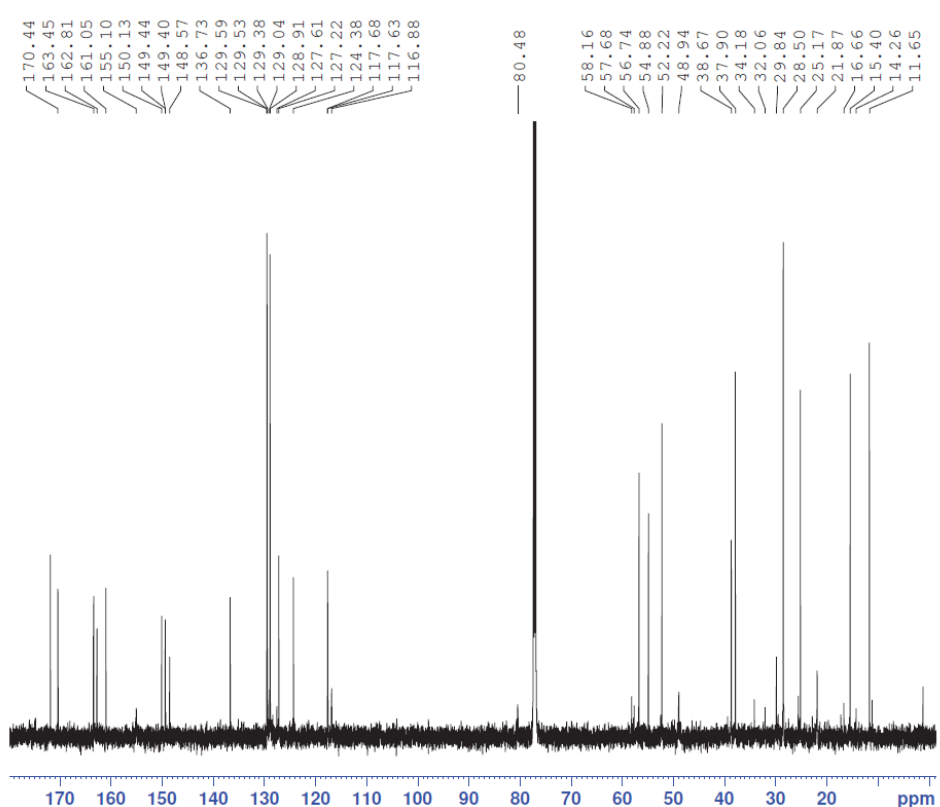
F2 - Acquisition Parameters  
Date\_ 20141014  
Time 11.28  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zg  
TD 65536  
SOLVENT CDCl<sub>3</sub>  
NS 16  
DS 2  
SWH 9009.009 Hz  
FIDRES 0.137467 Hz  
AQ 3.6372480 sec  
RG 45.2  
DW 55.500 usec  
DE 9.61 usec  
TE 298.0 K  
D1 5.00000000 sec  
TD0 1

===== CHANNEL f1 =====  
SFO1 600.1333007 MHz  
NUC1 1H  
P1 12.40 usec  
PLW1 16.59600067 W

F2 - Processing parameters  
SI 131072  
SF 600.1300149 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00



BocHN-D-Ala-Thiazole-Thiazole-Thiazole-R-Thiazoline-D-Phe-Ile-OMe 13C NMR CDCl<sub>3</sub> 150MHz 298K



Current Data Parameters  
NAME 141014-alp  
EXPNO 2  
PROCNO 1

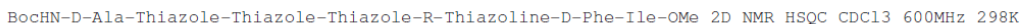
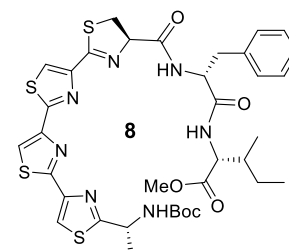
F2 - Acquisition Parameters  
Date\_ 20141014  
Time 11.52  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl<sub>3</sub>  
NS 3072  
DS 4  
SWH 32894.738 Hz  
FIDRES 0.501934 Hz  
AQ 0.9961472 sec  
RG 2050  
DW 15.200 usec  
DE 7.93 usec  
TE 298.0 K  
D1 2.00000000 sec  
D11 0.03000000 sec  
TD0 12

===== CHANNEL f1 =====  
SFO1 150.9171431 MHz  
NUC1 13C  
P1 11.90 usec  
PLW1 115.09999847 W

===== CHANNEL f2 =====  
SFO2 600.1324005 MHz  
NUC2 1H  
CPDPRG2 bi\_waltz65\_256  
PCPD2 70.00 usec  
PLW2 16.59600067 W  
PLW12 0.52078003 W  
PLW13 0.25518000 W

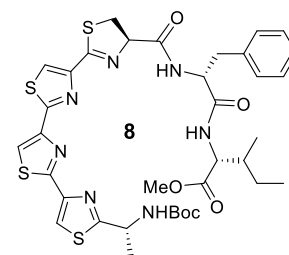
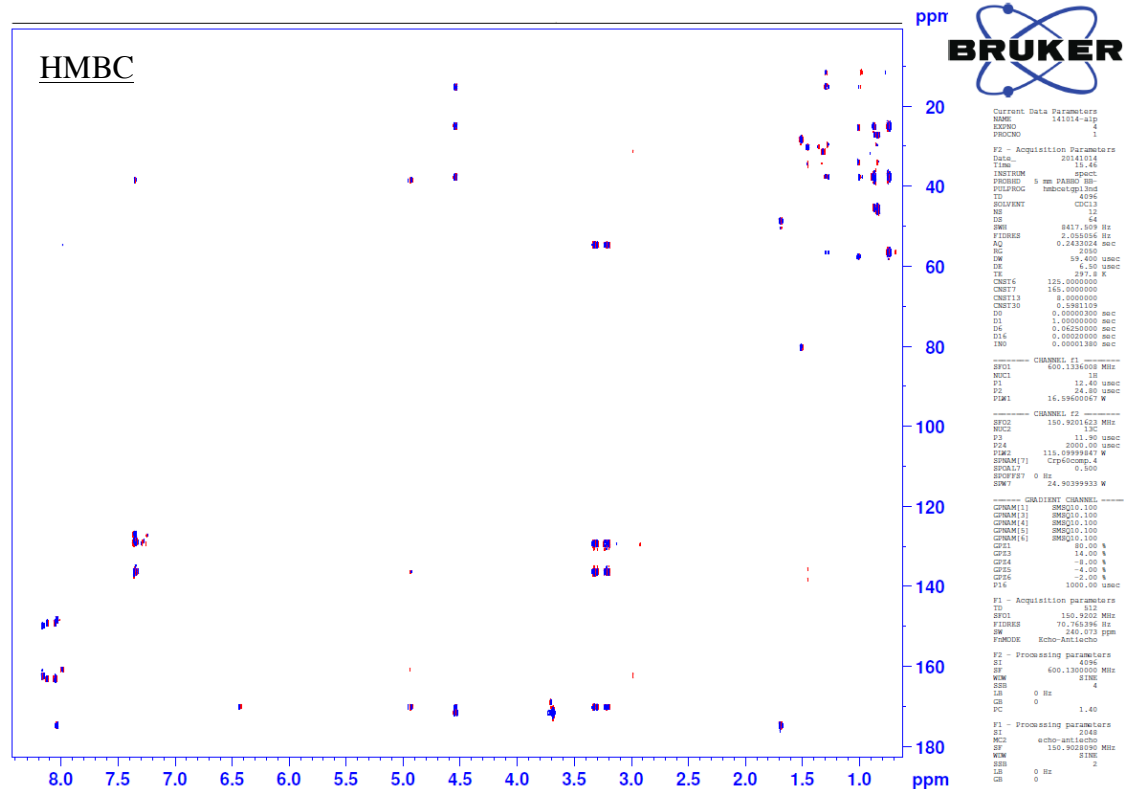
F2 - Processing parameters  
SI 32768  
SF 150.9027890 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

BocHN-D-Ala-Thiazole-Thiazole-Thiazole-R-Thiazoline-D-Phe-Ile-OMe 2D NMR COSY CDCl<sub>3</sub> 600MHz 298K



Compound **8** (CDCl<sub>3</sub>)

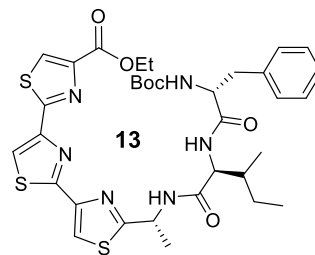
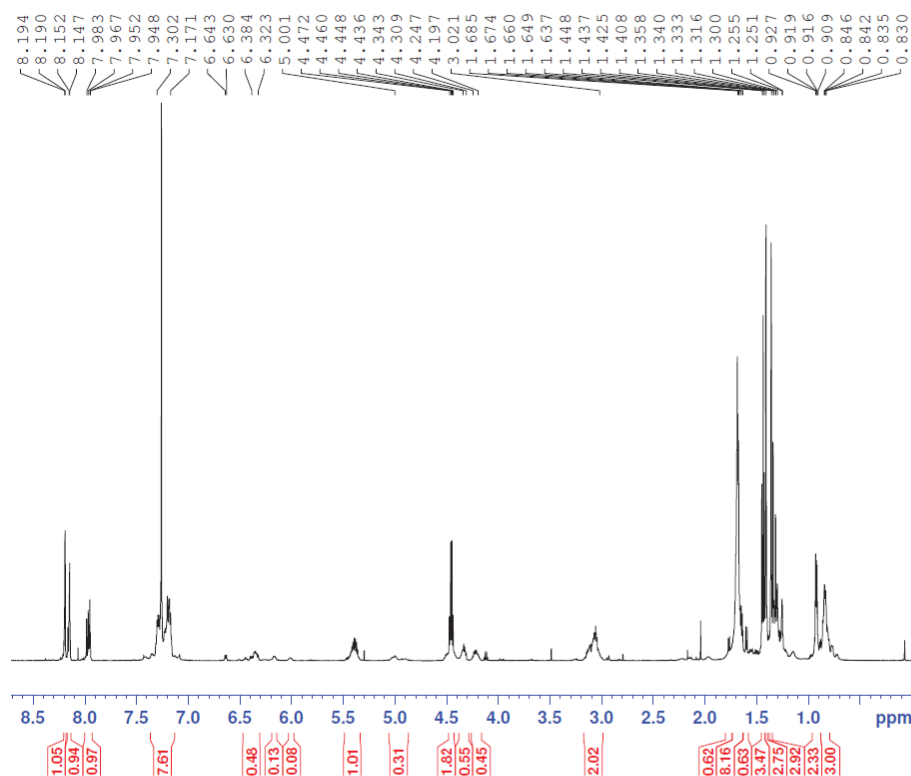
BocHN-D-Ala-Thiazole-Thiazole-Thiazole-R-Thiazoline-D-Phe-Ile-OMe 2D NMR HMBC CDCl<sub>3</sub> 600MHz 298K



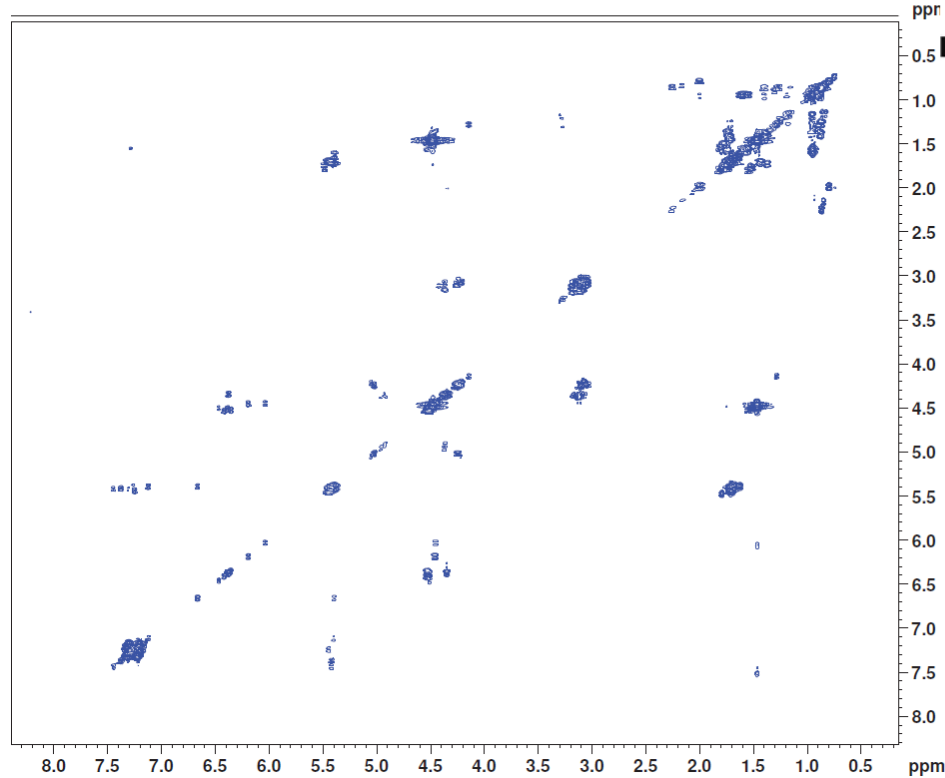


# Compound 13 (CDCl<sub>3</sub>)

BocHN-D-Phe-Ile-D-Ala-Thiazole-Thiazole-Thiazole-OEt 1H NMR CDCl<sub>3</sub> 600MHz 298K

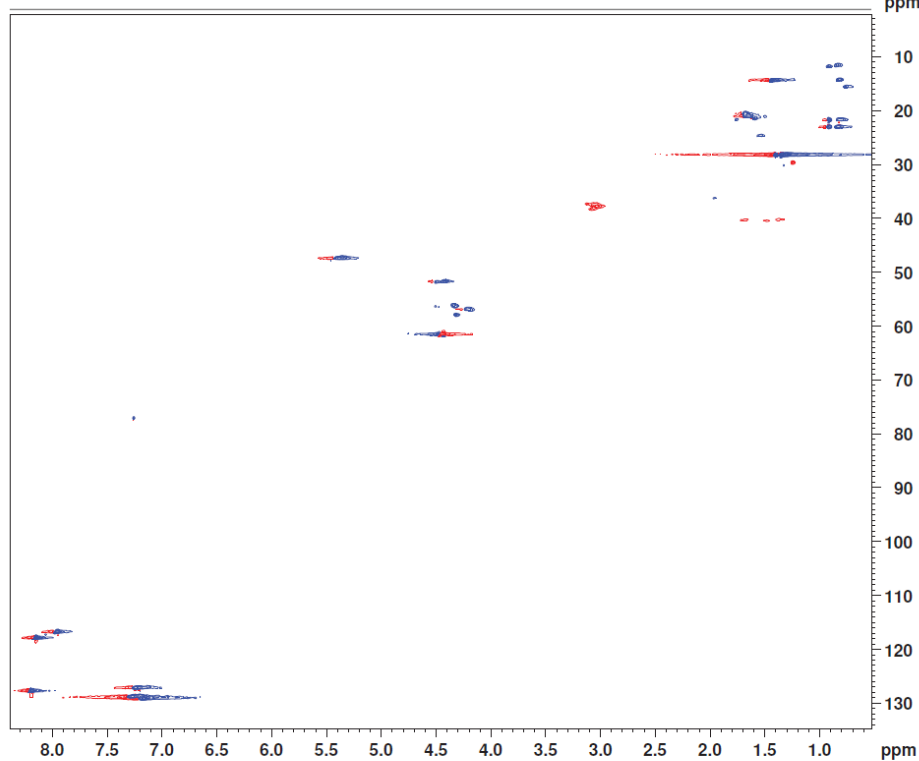


BocHN-D-Phe-Ile-D-Ala-Thiazole-Thiazole-Thiazole-OEt 2D NMR COSY CDCl<sub>3</sub> 600MHz 298K



Compound **13** (CDCl<sub>3</sub>)

BocHN-D-Phe-Ile-D-Ala-Thiazole-Thiazole-Thiazole-OEt 2D NMR HSQC CDCl3 600MHz 298K



```
Current Data Parameters
NAME          182727     nmr
KEPNO        6
PROCNO       2

F2 - Acquisition Parameters
=====
Date_   20100901
Time    15.50
INSTRUM   spect
PROBHD    5 mm BBO-CPDPR
PULPROG   zgpg30tempzr2.4
TD        65536
SOLVENT   CDCl3
NS         0
DS         0
SWH        9615.38 Hz
FIDRES     4.48602E-01
AQ         0.181362 sec
RG          320
SR          250.13 MHz
OR         6.50 umm
CMT2       140.000000 Hz
CMTW1      -0.500000 mm
D0         0.0000000 sec
d1         0.0000000 sec
DELTA      0.0004428 sec
DELC1      0.0000000 sec
D12        0.0000000 sec
D13        0.0000000 sec
D14        0.0000000 sec
D15        0.0004428 sec
D16        0.0000000 sec
D17        0.0004428 sec
D18        0.0000000 sec
L0         0.0000000 sec
```

```

SFO1      600.1328204 MHz
NXC1      10
P1         12.00 usec
P2         24.00 usec
P2R        1000.00 usec
PWR1       16.5860067 W

```

```

CPU0: 100.00% 0.000000000 Mhz
MUC2: 100.00% 1300
CPU0M2: 100.00% 1300
P0: 11.00% 0.000000000 Mhz
P14: 500.00% 0.000000000 Mhz
P14: 500.00% 0.000000000 Mhz
P31: 1730.00% 0.000000000 Mhz
P43: 100.00% 0.000000000 Mhz
CPU0: 0 Mhz
PWR2: 115.000000000 Mhz
PWR12: 4.527590000 Mhz
CPU0M2: Cpu0,0.0 0.000
CPU0L3: 0.000
CPU0P2: 0 Mhz
CPU0M2: 24.922080000 Mhz
CPU0P1: 24.922080000 Mhz
CPU0P2: 0 Mhz
CPU0M2: 24.922080000 Mhz
CPU0P1: 14.Cpu2,1.2,20.2 0.000
CPU0P14: 0.000
CPU0M2: 13.946000000 Mhz
CPU0P1: 14.Cpu4,0.711,2 0.000
CPU0P12: 0 Mhz
CPU0M2: 7.197000022 Mhz
CPU0P1: 14.Cpu2,1.2,20.2 0.000
CPU0P14: 0.000
CPU0P12: 0 Mhz

```

GRADIENT CHANNEL	
CPHAR[1]	SHGQUS.100
CPHAR[2]	SHGQUS.100
CPHAR[3]	SHGQUS.100
CPHAR[4]	SHGQUS.100
CP21	80.00 %
CP23	20.00 %
CP24	11.00 %
CP24	-5.00 %
P14	1000.00 US\$
P19	600.00 US\$

```
F1 - Acquisition parameters
TD          322
SFO1       150.9141 MHz
FIDRES     48.828125 Hz
SW         165.457 ppm
PULPROG    Echo-Atlascho

F2 - Processing parameters
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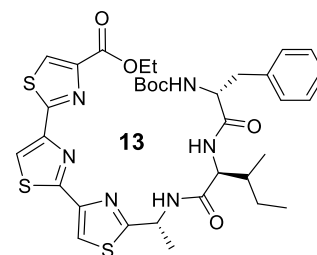
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SF          600.1300130 MHz
NMW
SDR
LW          0 Hz
CW          0
PC          1.40

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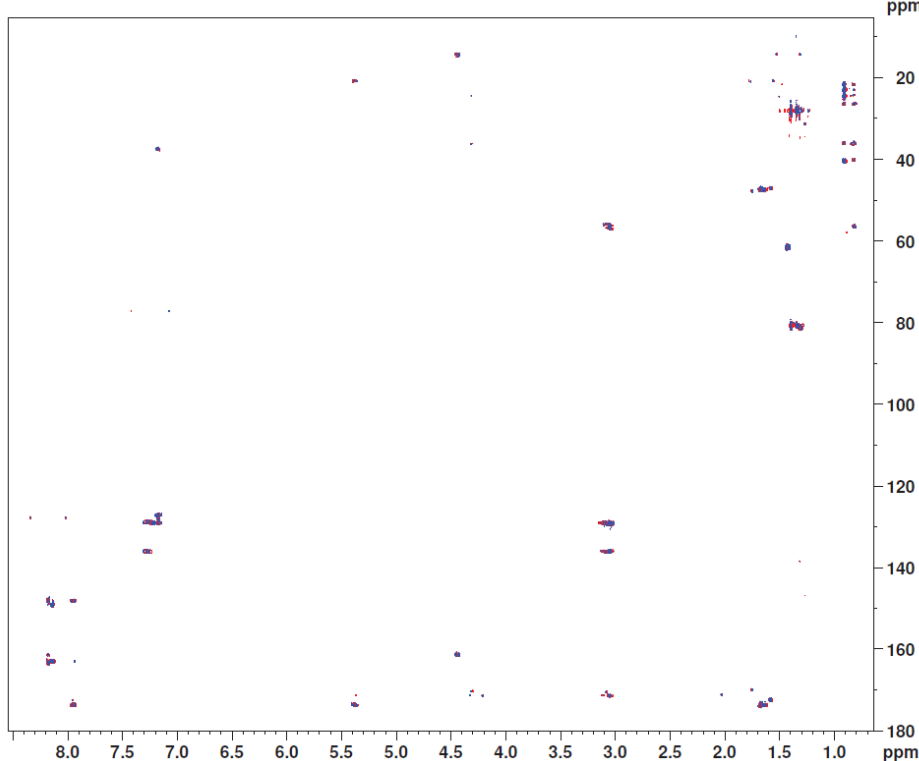
Fl - Processing parameters

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MC2      echo-poll-echo
DF        150.00280001 MHz
WDM       QC190
SDS       2
LD        0 Hz
CD        0
```



13

BocHN-D-Phe-Ile-D-Ala-Thiazole-Thiazole-Thiazole-OEt 2D NMR HMBC CDCl3 600MHz 298K



```
Current Data Parameters
NAME      150227-als
EXPNO     1
PROCNO    2
```

```

F2 - Acquisition Parameters
Date_      20150227
Time       17:11:00
INSTRUM    spect
CIRCUIT     5 mm P1
PULPROG     hmbzgpg130
TD          4096
SOLVENT     CDCl3
NS          14
DS          4
SWH         28417.50150
FIDRES      0.05050505
AQ          0.2433021
RG          205.00
SR          59.400
DE          6.50
TE          297.9
CNH376     125.00000000
CNH377     163.00000000
CNH378     8.00000000
CNH379     0.9881101
DO          0.000000300
D1         1.000000000
D2         0.042500000
D16        0.000000000
INO         0.00001380

```

SFO1	600.1336006
NUC1	18.40
P1	12.40
P2	24.80
PLW1	16.5960006

```

----- CHANNEL F2 -----
SF02      150.9201621
NUC2      130
P3         11.96
P24        2000.00
PLW2      115.0999984
SPNAM[7]   Crp60comp.4
SPCAL7     0.300
SPCRFS7    0 Hz

```

```

----- GRADIENT CHANNEL -----
CPNAM[1]      SMSQ10.100
CPNAM[3]      SMSQ10.100
CPNAM[4]      SMSQ10.100
CPNAM[5]      SMSQ10.100
CPNAM[6]      SMSQ10.100
CPE1          80.00
CPE3          14.00
CPE4          -8.00
CPE5          -4.00
CPE6          -2.00
P16           1000.00

```

F1 - Acquisition param	
TD	512
SFO1	150.9202
FIDRES	70.765394
SM	240.072
FMODE	Echo-Attenuch

```
F2 - Processing parameters
SI          4096
SF          600.130023
KW          SINE
SSB         4
LB          0 Hz
```

CH	0	
PC		1.40
F1 - Processing parameters		
SI		2048
MC2		echo-antiecho
SE		150.902809

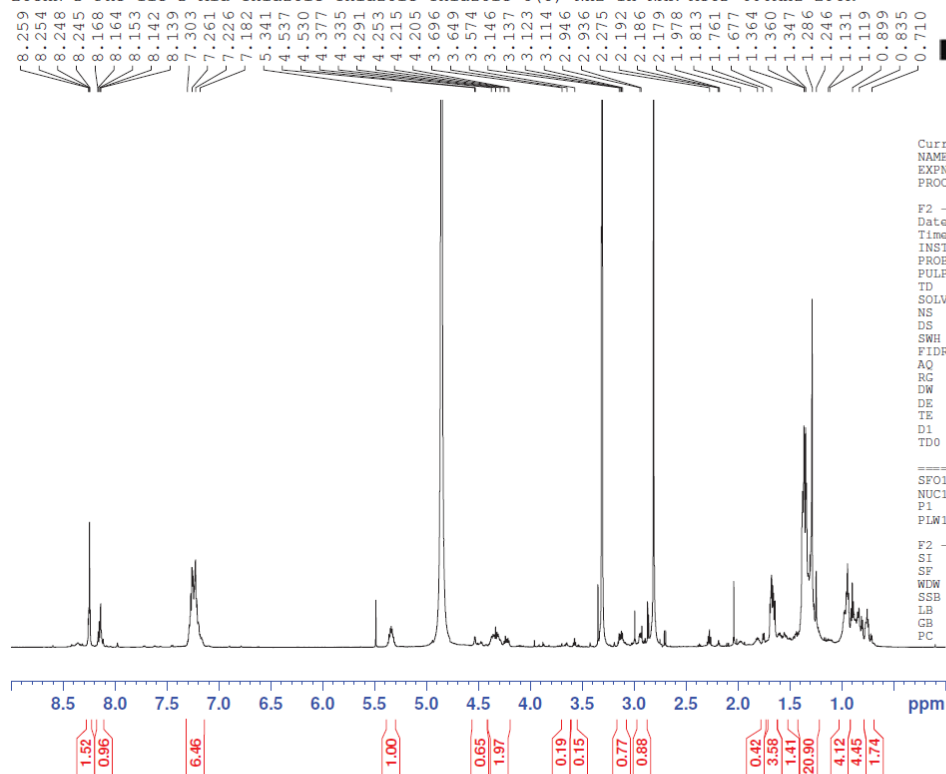
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SSB
LB      0 Hz
GB      0

```

# Compound 14 (CD<sub>3</sub>OD)

BocHN-D-Phe-Ile-D-Ala-Thiazole-Thiazole-Thiazole-C(O)-NH<sub>2</sub> 1H NMR MeOD 600MHz 298K

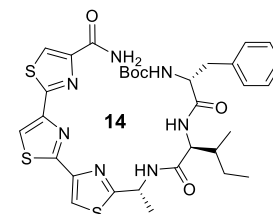


Current Data Parameters  
 NAME 150307-1p  
 EXPNO 5  
 PROCNO 2

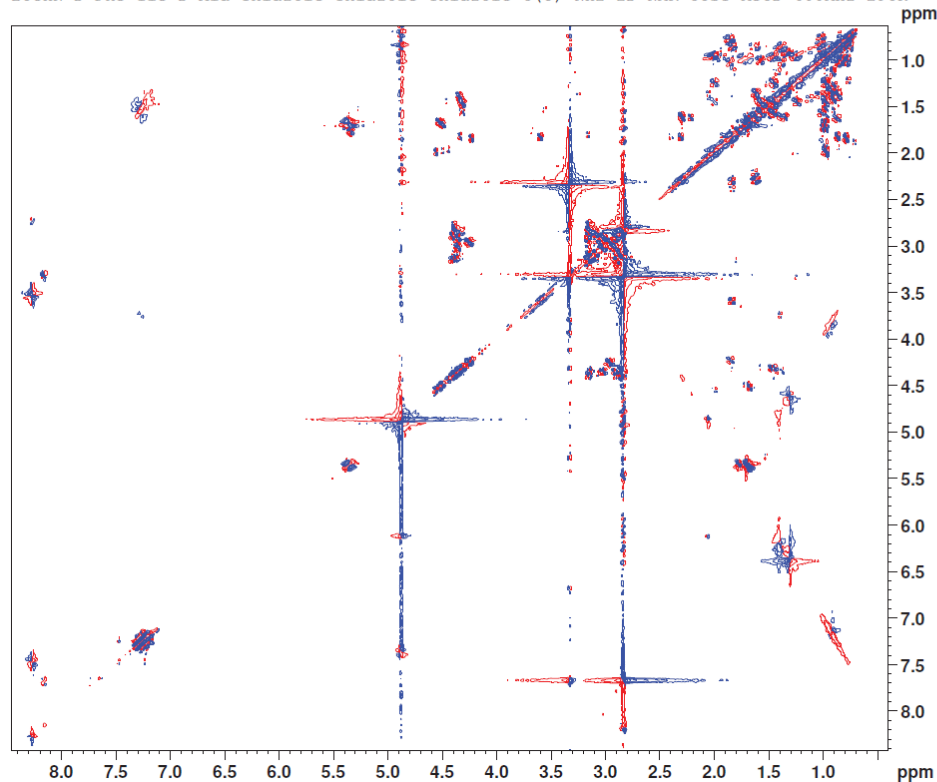
F2 - Acquisition Parameters  
 Date\_ 20150307  
 Time 20.39  
 INSTRUM spect  
 PROBHD 5 mm PABBO BB-  
 PULPROG zg  
 TD 65536  
 SOLVENT MeOD  
 NS 16  
 DS 0  
 SWH 9009.009 Hz  
 FIDRES 0.137467 Hz  
 AQ 3.6372480 sec  
 RG 71.8  
 DW 55.500 usec  
 DE 9.61 usec  
 TE 298.0 K  
 D1 5.00000000 sec  
 TD0 1

===== CHANNEL f1 =====  
 SFO1 600.1333007 MHz  
 NUC1 1H  
 P1 12.40 usec  
 PLW1 16.59600067 W

F2 - Processing parameters  
 SI 131072  
 SF 600.1300114 MHz  
 WDW EM  
 SSB 0  
 LB 0.30 Hz  
 GB 0  
 PC 1.00



BocHN-D-Phe-Ile-D-Ala-Thiazole-Thiazole-Thiazole-C(O)-NH<sub>2</sub> 2D NMR COSY MeOD 600MHz 298K



Current Data Parameters  
 NAME 150308-1p  
 EXPNO 1  
 PROCNO 1

F2 - Acquisition Parameters  
 Date\_ 20150308  
 Time 2.36  
 INSTRUM spect  
 PROBHD 5 mm PABBO BB-  
 PULPROG cosygmph  
 TD 2048  
 SOLVENT MeOD  
 NS 4  
 DS 16  
 SWH 9014.423 Hz  
 FIDRES 4.401574 Hz  
 AQ 0.1135957 sec  
 RG 1620  
 DW 55.467 usec  
 DE 6.50 usec  
 TE 298.0 K  
 D0 0.00003971 sec  
 D1 2.00000000 sec  
 D13 0.00000000 sec  
 D16 0.00020000 sec  
 IN0 0.00011100 sec

===== CHANNEL f1 =====  
 SFO1 600.1333007 MHz  
 NUC1 1H  
 P1 12.40 usec  
 P2 24.80 usec  
 PLW1 16.59600067 W

===== GRADIENT CHANNEL =====  
 GPMAM[1] SMSQ10.100  
 GPMAM[2] SMSQ10.100  
 GPF1 15.00 %  
 GPF2 20.00 %  
 P16 1000.00 usec

F1 - Acquisition parameters  
 TD 512  
 SFO1 600.1333 MHz  
 FIDRES 17.595720 Hz  
 SW 15.012 ppm  
 FNAME States-TPPI

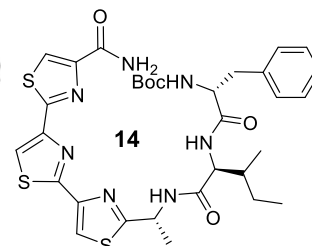
F2 - Processing parameters  
 SI 2048  
 SF 600.1300000 MHz  
 WDW QSI  
 SSB 2  
 LB 0 Hz  
 GB 0  
 PC 1.40

F1 - Processing parameters  
 SI 2048  
 MC2 States-TPPI  
 SF 600.1300000 MHz  
 WDW QSI  
 SSB 2  
 LB 0 Hz  
 GB 0

BoCHN-D-Phe-Ile-D-Ala-Thiazole-Thiazole-Thiazole-C(O)-NH2 2D NMR HSQC MeOD 600MHz 298K



```
Current Data Parameters
NAME      103077-aiq
KEYNO     6
PZ         4
FZ         Acquisition Parameters
UNIT       2010307
TIME       20.52
INSTRUM    spect
PROCNO     5
PDIR       5.00 mm/sec
POLPROG    hsqzdetestp2-4
TS         2940
TS2        2940
NS         10
DS         512
CWI        0.615, 385.0 Hz
F2FORMS    4, 6.00012 Hz
AQ         0.10000000
RG         2000
RG2         52.000000
DE         1.0
DE2         1.0
CWI2       145.000000 Hz
CWI2F      0.50000000
D0          0.00000300 mm
D1          0.00000300 mm
D2          0.00046828 mm
D4          0.00172414 mm
D8          0.00311111 mm
D16         0.00520100 mm
D32         0.00836468 mm
D64         0.00836468 mm
D128        0.00836468 mm
D256        0.00200200 mm
D512        0.00200200 mm
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BocHN-D-Phe-Ile-D-Ala-Thiazole-Thiazole-Thiazole-C(O)-NH<sub>2</sub> 2D NMR HMBC MeOD 600MHz 298K



```

Current Data Parameters
NAME          150307-siz
EXPNO        1
PROCNO       1

F2 - Acquisition Parameters
Date_         20150507
Time          22.32
INSTRUM       spect
PROBHD        5 mm PABBO 5H
PULPROG       hzgpgzg1d
TD            4096
SOLVENT       MeOD
NUC1           1H
NUC2           13C
AQ            64
SWH           8417.500 Hz
FIDRES        0.20550 sec
AQ            0.242512 sec
RG            256
DS            59.400 unac
TE            300.2
DE            1.50
TE           297.9 K
CHRG1         125.0000000
CHRG2         155.0000000
CHRG3         8.0000000
CHRG4         0.5981109
DO            0.0000000 sec
DQ            1.0000000 sec
DE            0.26250000 sec
DQ            0.0020000 sec
DQ            0.00118 sec

```

```

CHANNEL F1
SF01 600.1336008 MHz
NOC1 1H
P1 12.40 usac
P2 24.80 usac
P1M1 16.59600867 W

CHANNEL F2
SF02 150.9201623 MHz
NOC2 13C
P3 11.90 usac
P2 2000.00
P1M2 115.0909847 W
SPNAM[7] Crp60comp.4
SPCAL7 0 0.50
SPOFFS7 0 Hz
SPW7 24.90399933 W

```

```

----- GRADIENT CHANNEL -----
CPNAM[1]      SMSQ10.100
CPNAM[3]      SMSQ10.100
CPNAM[4]      SMSQ10.100
CPNAM[5]      SMSQ10.100
CPNAM[6]      SMSQ10.100
CPZ1          80.00 %
CPZ3          14.00 %
CPZ4          -8.00 %
CPZ5          -4.00 %
CPZ6          -2.00 %
P16           1000.00 unrec

```

```

F1 - Acquisition parameters
TD          512
SF01        150.9202 MHz
FIDRES      70.765396 Hz
SW          240.073 ppm
FMOD0      Echo-Antiecho

F2 - Processing parameters
SI          4096
SF          600.1300114 MHz
WDW         SINC
SSB         4
LB          0 Hz
GB          0
PC          1.40

```

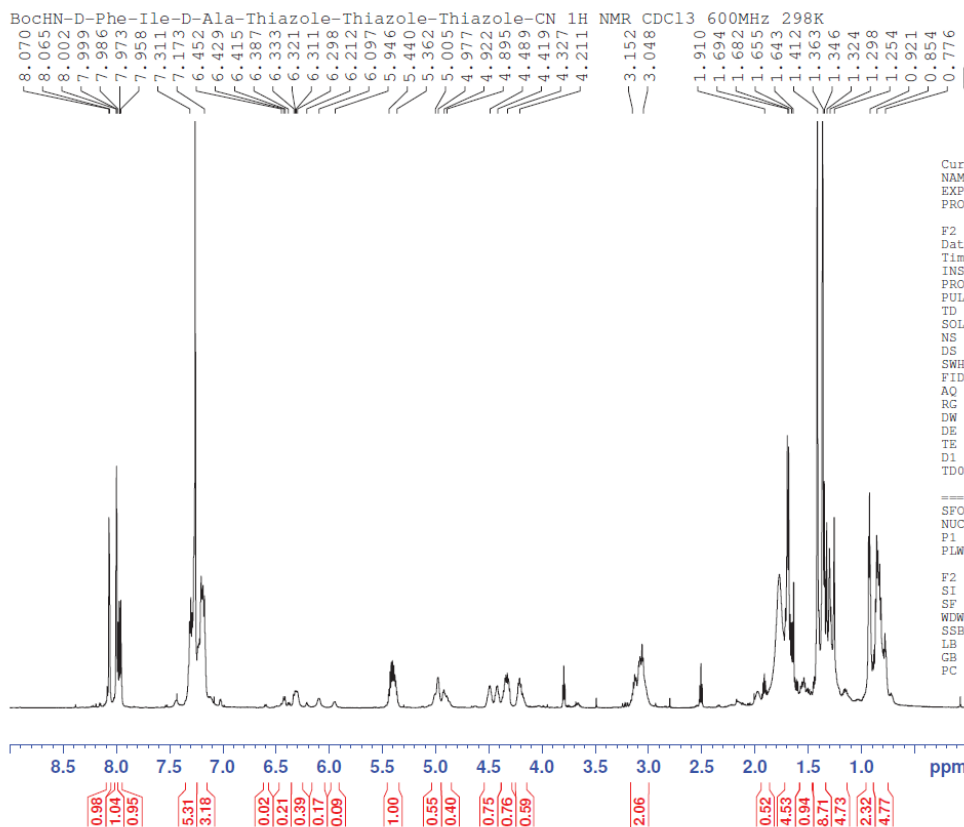
```

F1 - Processing parameters
SI          2048
MC2        echo-antecho
SF          150.9028090 MHz
WIN         SINK
SSB         2
LB          0 Hz
CB          0

```

# Compound 15 (CDCl<sub>3</sub>)

BocHN-D-Phe-Ile-D-Ala-Thiazole-Thiazole-Thiazole-CN 1H NMR CDCl<sub>3</sub> 600MHz 298K

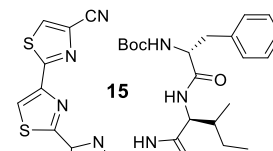


Current Data Parameters  
NAME 150307-alp  
EXPNO 1  
PROCNO 2

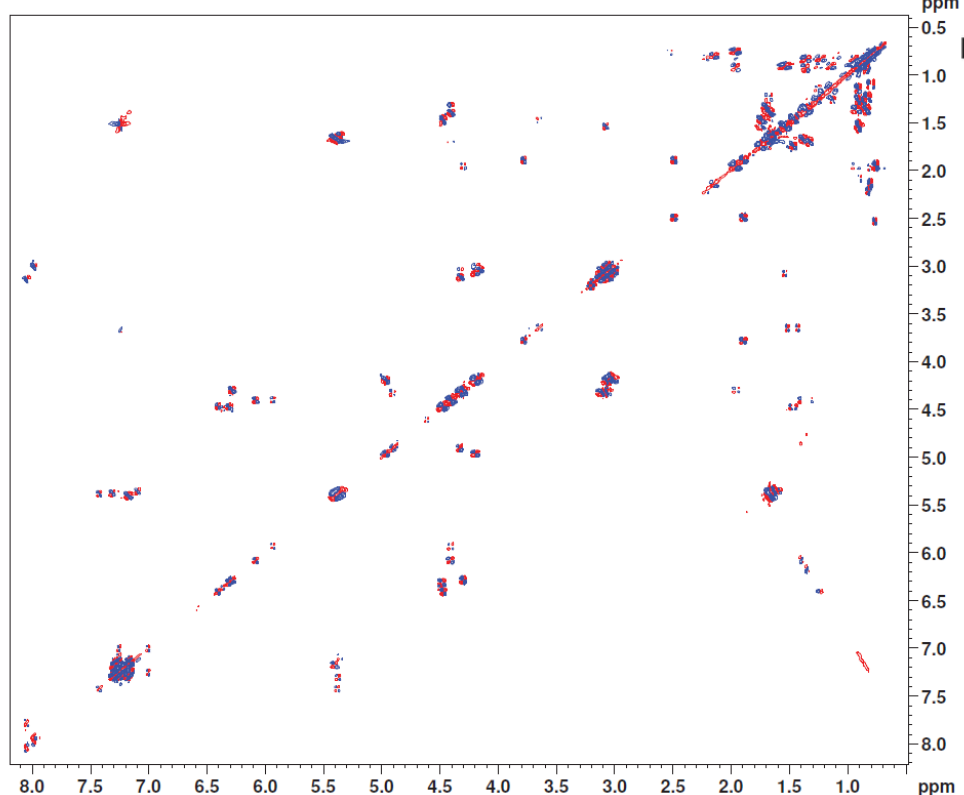
F2 - Acquisition Parameters  
Date\_ 20150307  
Time 13.09  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zg  
TD 65536  
SOLVENT CDCl<sub>3</sub>  
NS 64  
DS 0  
SWH 9009.009 Hz  
FIDRES 0.137467 Hz  
AQ 3.6372480 sec  
RG 114  
DW 55.500 usec  
DE 9.61 usec  
TE 298.0 K  
D1 5.00000000 sec  
TD0 1

===== CHANNEL f1 =====  
SFO1 600.1333007 MHz  
NUC1 1H  
P1 12.40 usec  
PLW1 16.59600067 W

F2 - Processing parameters  
SI 131072  
SF 600.1300148 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00



BocHN-D-Phe-Ile-D-Ala-Thiazole-Thiazole-Thiazole-CN 2D NMR COSY CDCl<sub>3</sub> 600MHz 298K



Current Data Parameters  
NAME 150307-alp  
EXPNO 4  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20150307  
Time 18.28  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG coasygmph  
TD 2048  
SOLVENT CDCl<sub>3</sub>  
NS 6  
DS 16  
SWH 9014.423 Hz  
FIDRES 4.401574 Hz  
AQ 0.1135957 sec  
RG 2050  
DW 55.467 usec  
DE 6.50 usec  
TE 297.9 K  
D0 0.00003971 sec  
D1 2.00000000 sec  
D13 0.00000400 sec  
D16 0.00020000 sec  
IN0 0.0001100 sec

===== CHANNEL f1 =====  
SFO1 600.1333007 MHz  
NUC1 1H  
P1 12.40 usec  
P2 24.80 usec  
PLW1 16.59600067 W

===== GRADIENT CHANNEL =====  
GPMAM[1] SMSQ10.100  
GPMAM[2] SMSQ10.100  
GP21 10.00 %  
GP22 10.00 %  
P16 1000.00 usec

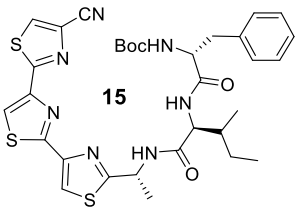
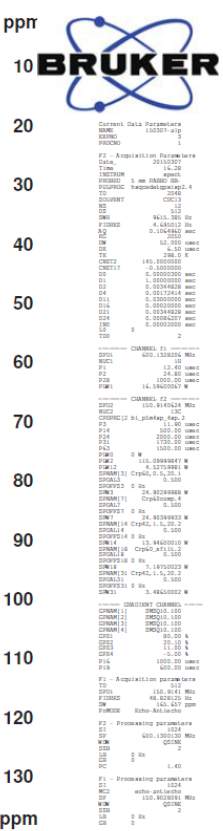
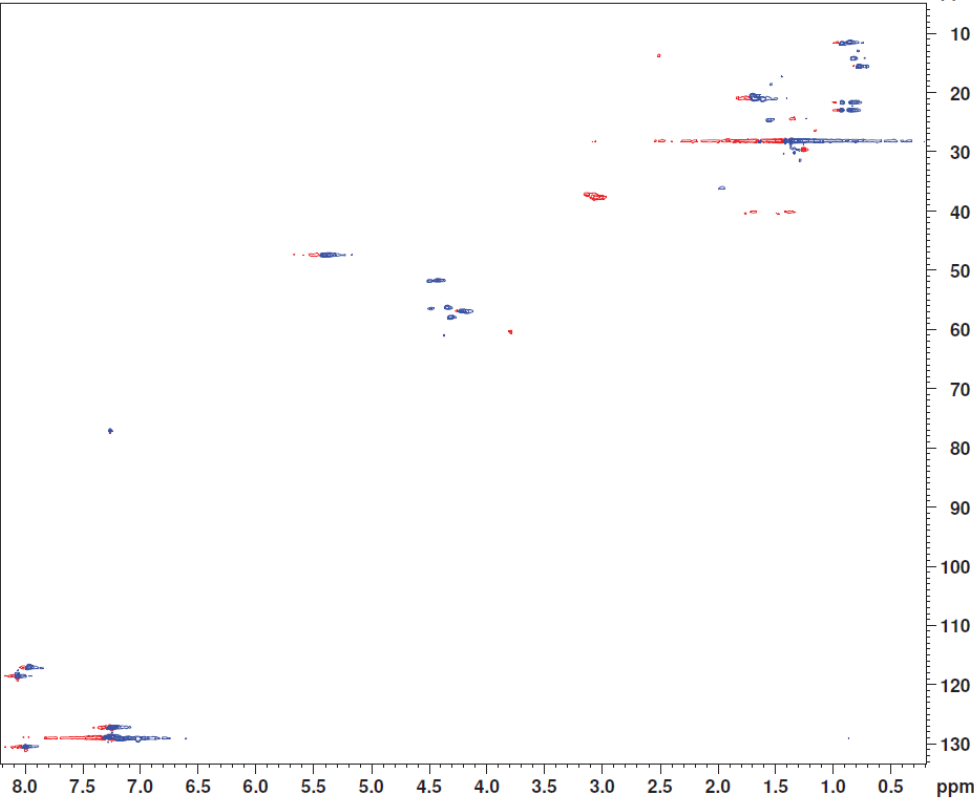
F1 - Acquisition parameters  
ID 512  
SFO1 600.1333 MHz  
FIDRES 17.595720 Hz  
SW 15.012 ppm  
F2MODE States-TPPI

F2 - Processing parameters  
SI 2048  
SF 600.1300253 MHz  
WDW QSINE  
SSB 2  
LB 0 Hz  
GB 0  
PC 1.40

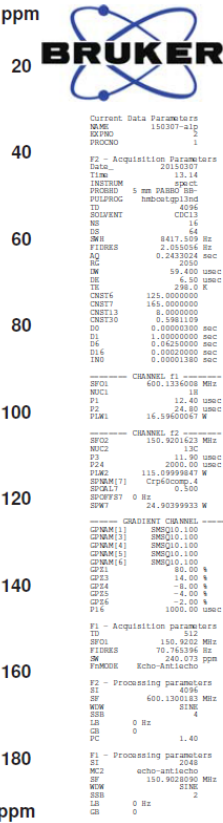
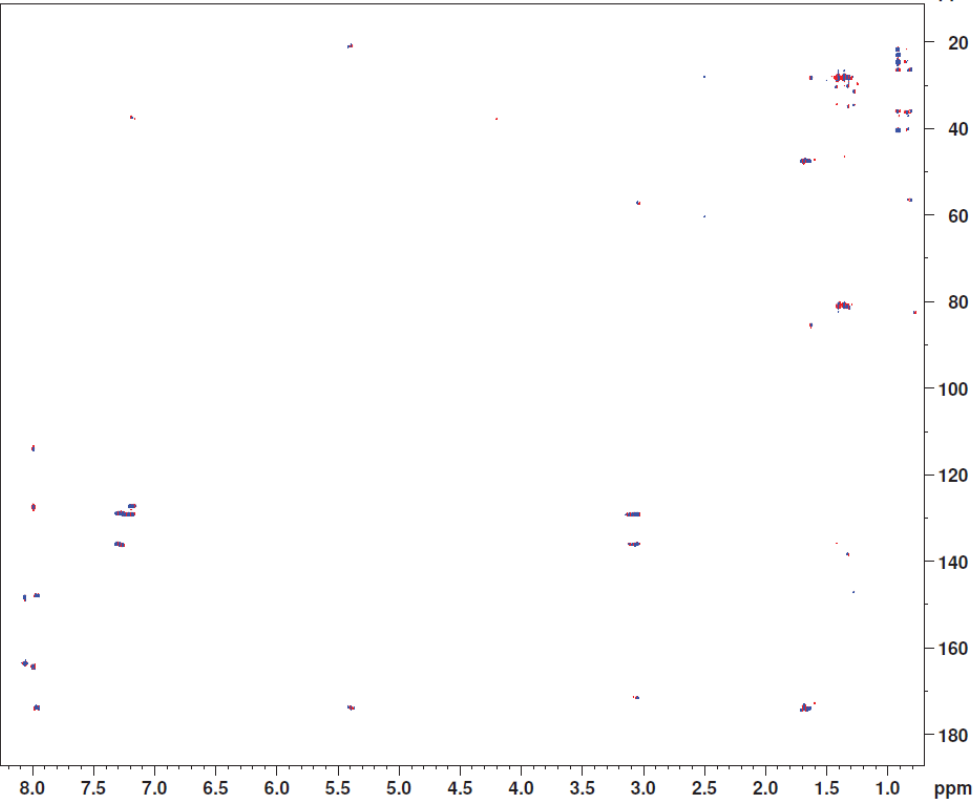
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MC2 States-TPPI  
SF 600.1300253 MHz  
WDW QSINE  
SSB 2  
LB 0 Hz  
GB 0

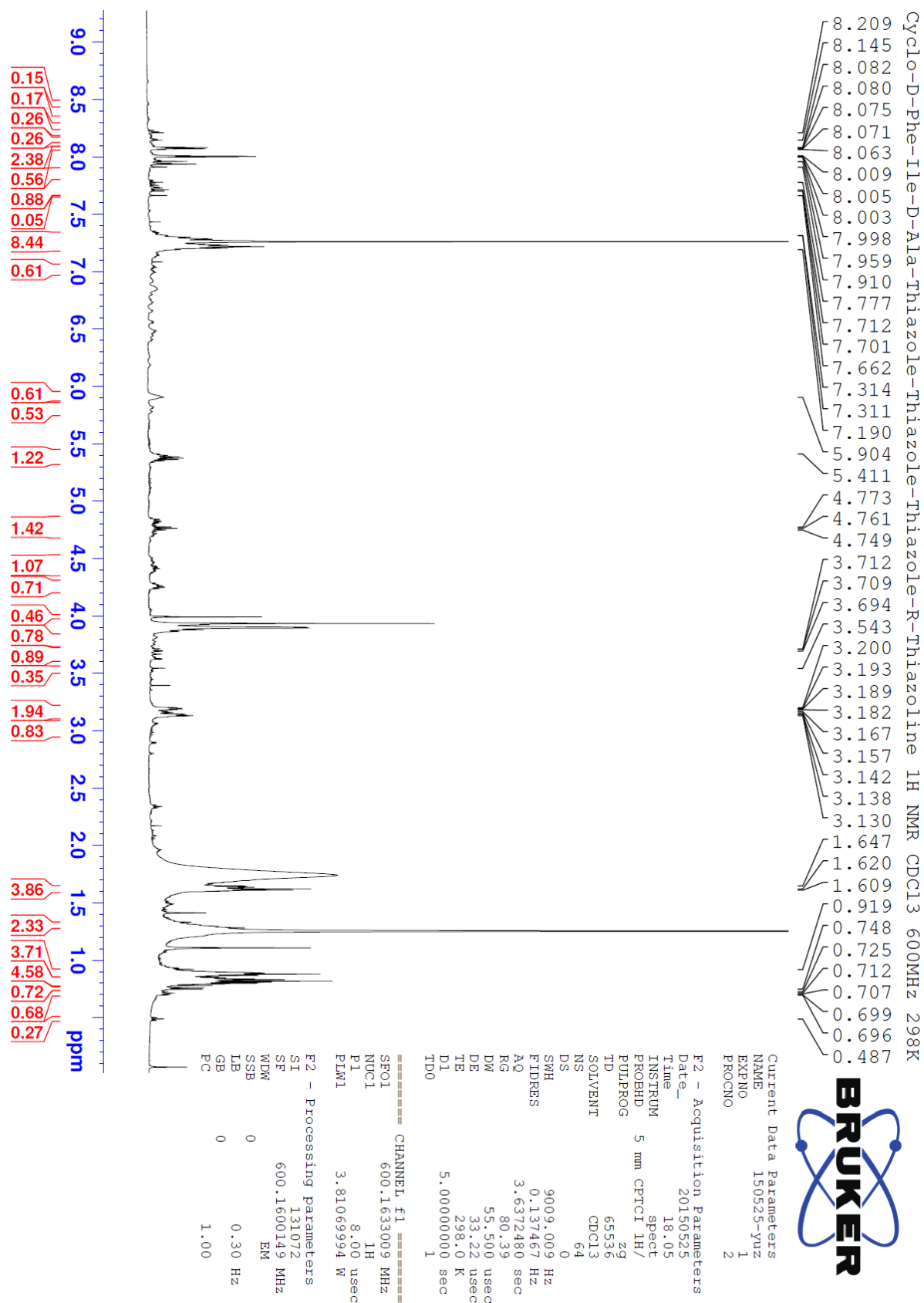
Compound 15 (CDCl3)

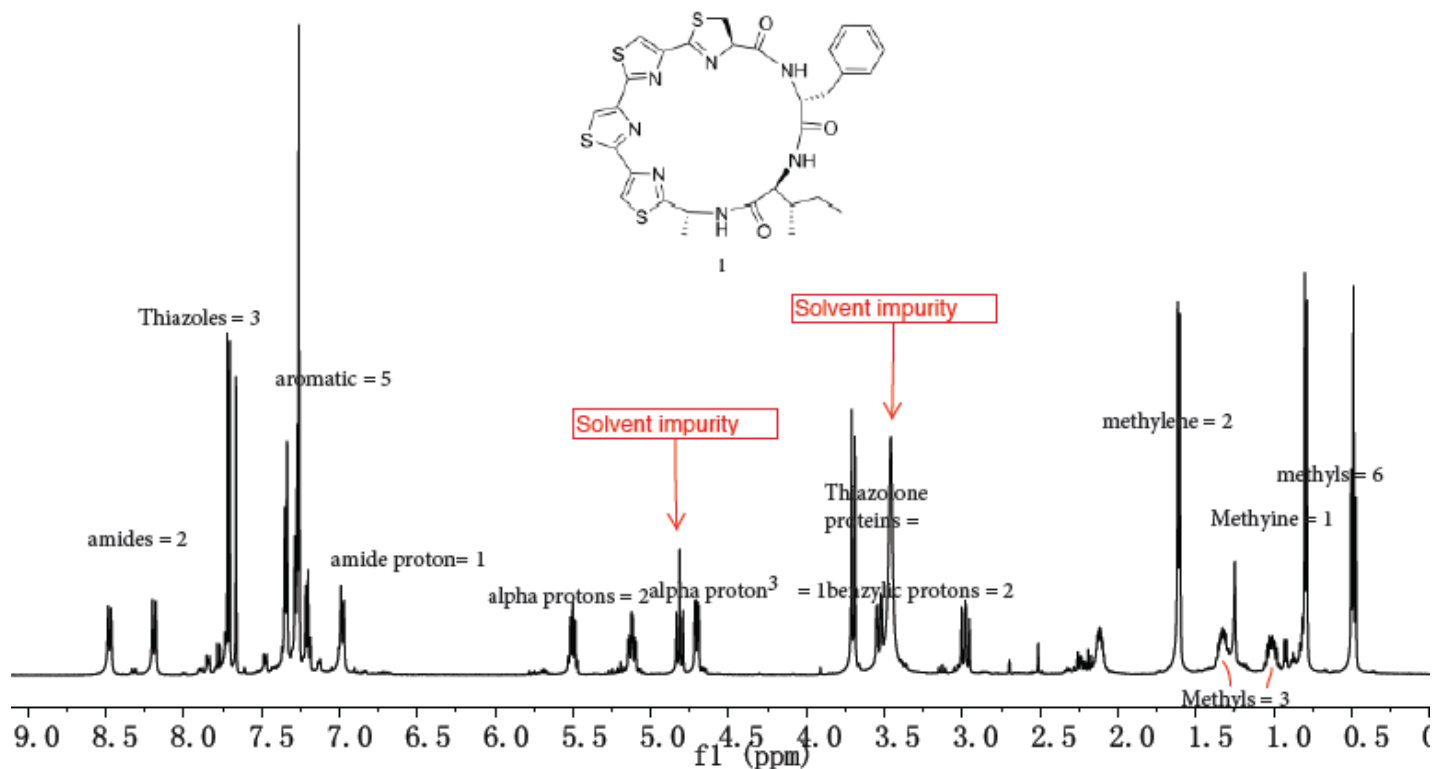
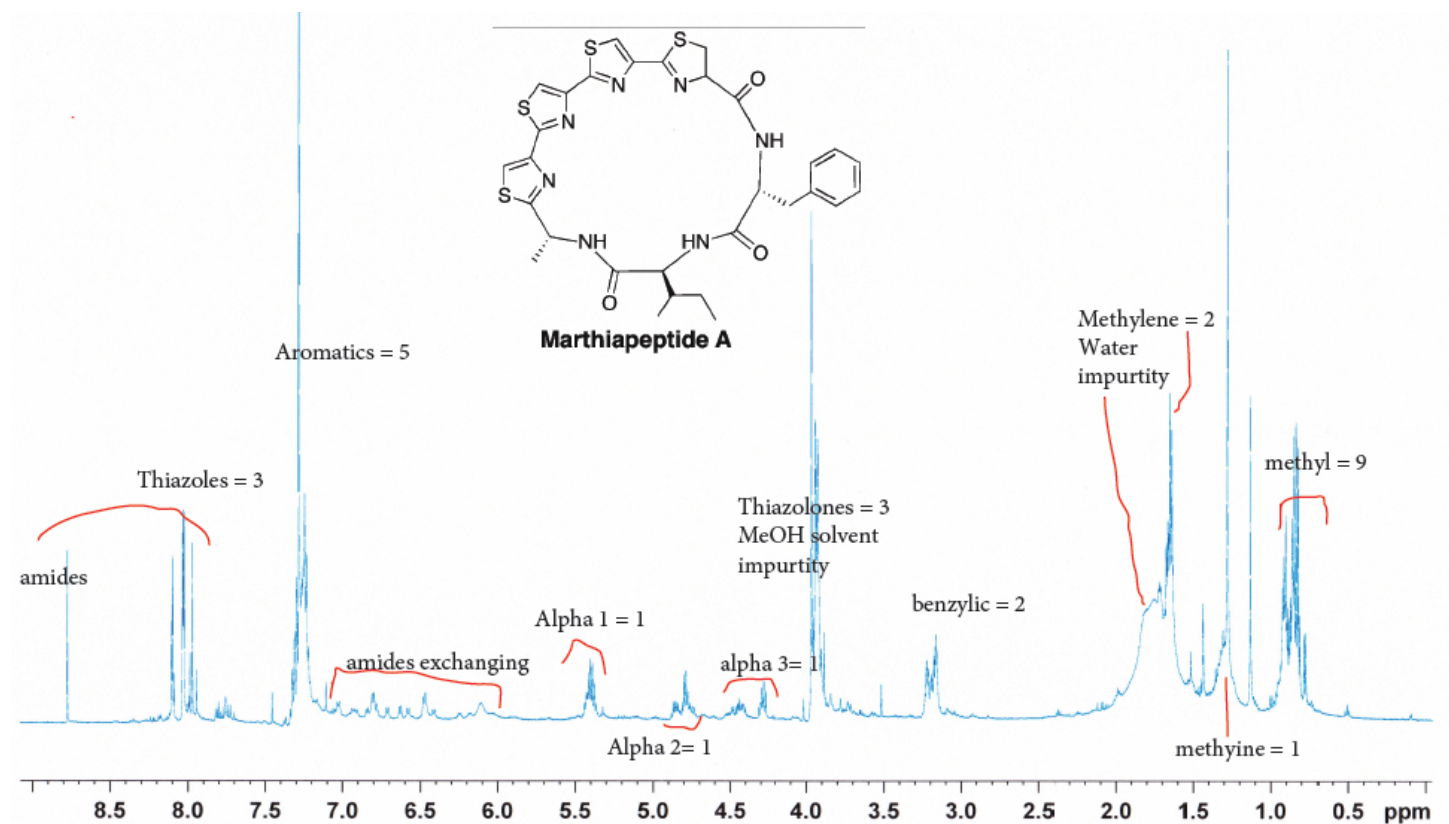
BocHN-D-Phe-Ile-D-Ala-Thiazole-Thiazole-Thiazole-CN 2D NMR HSQC CDCl3 600MHz 298K



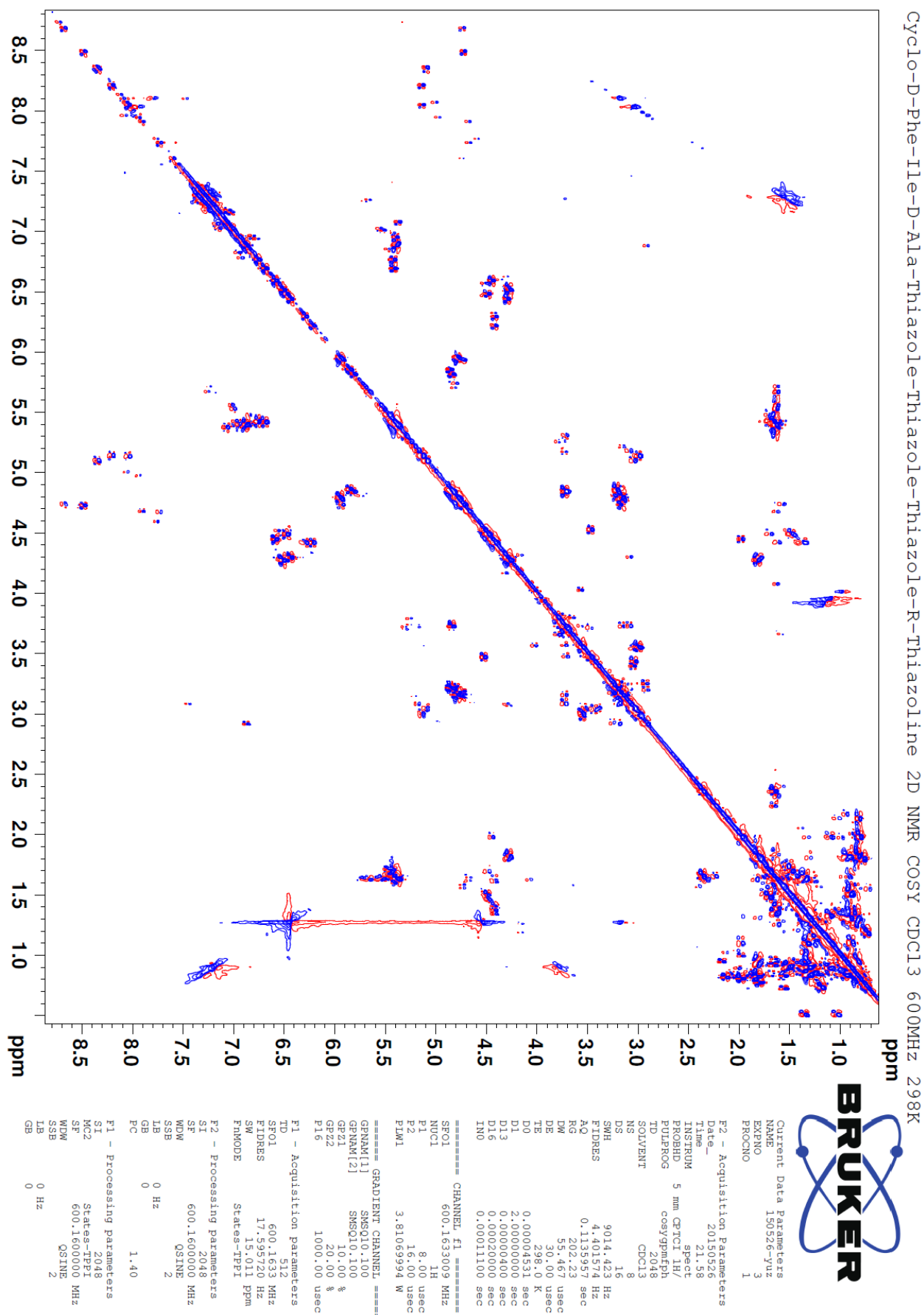
BocHN-D-Phe-Ile-D-Ala-Thiazole-Thiazole-Thiazole-CN 2D NMR HMBC CDCl3 600MHz 298K

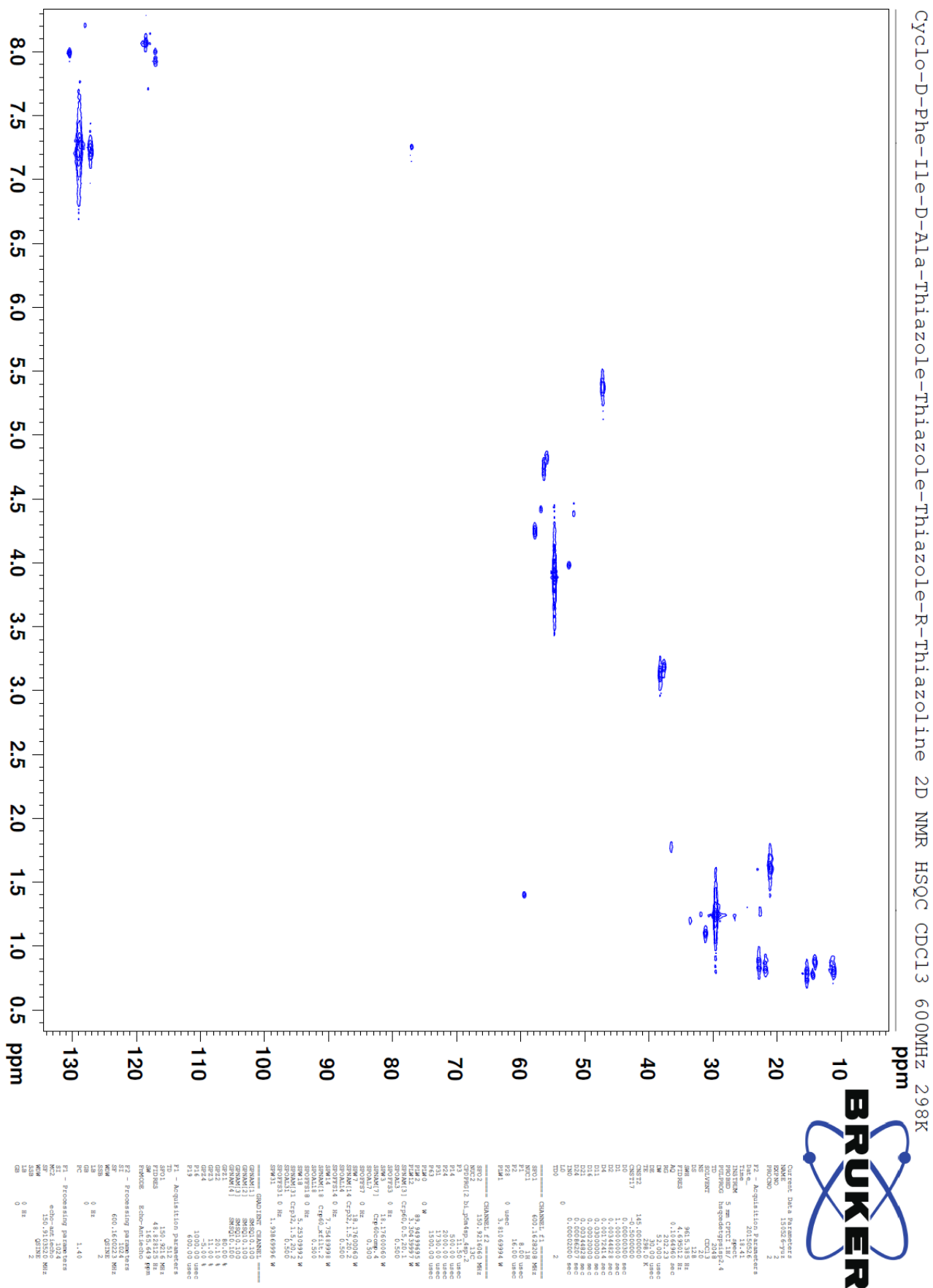


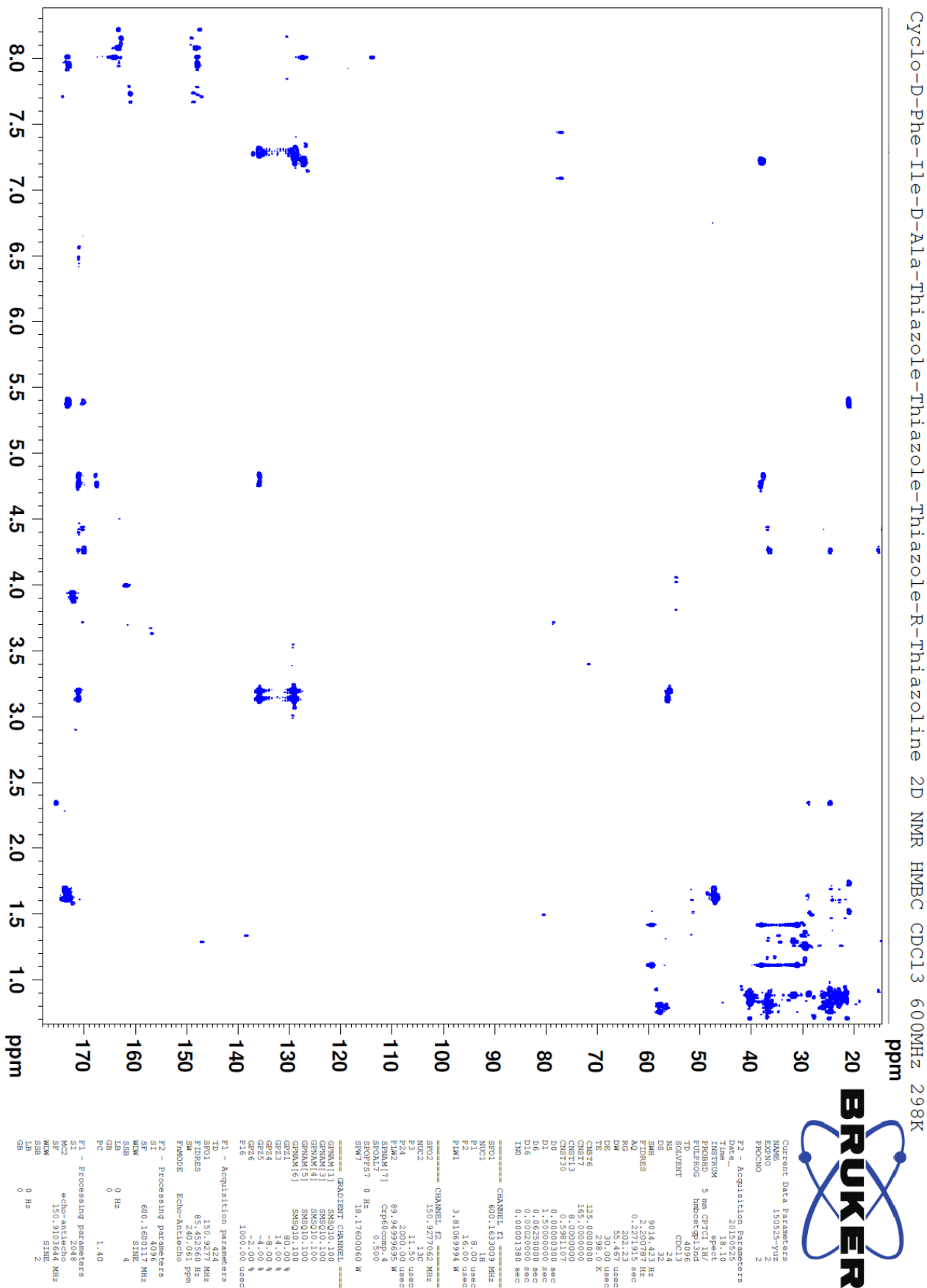


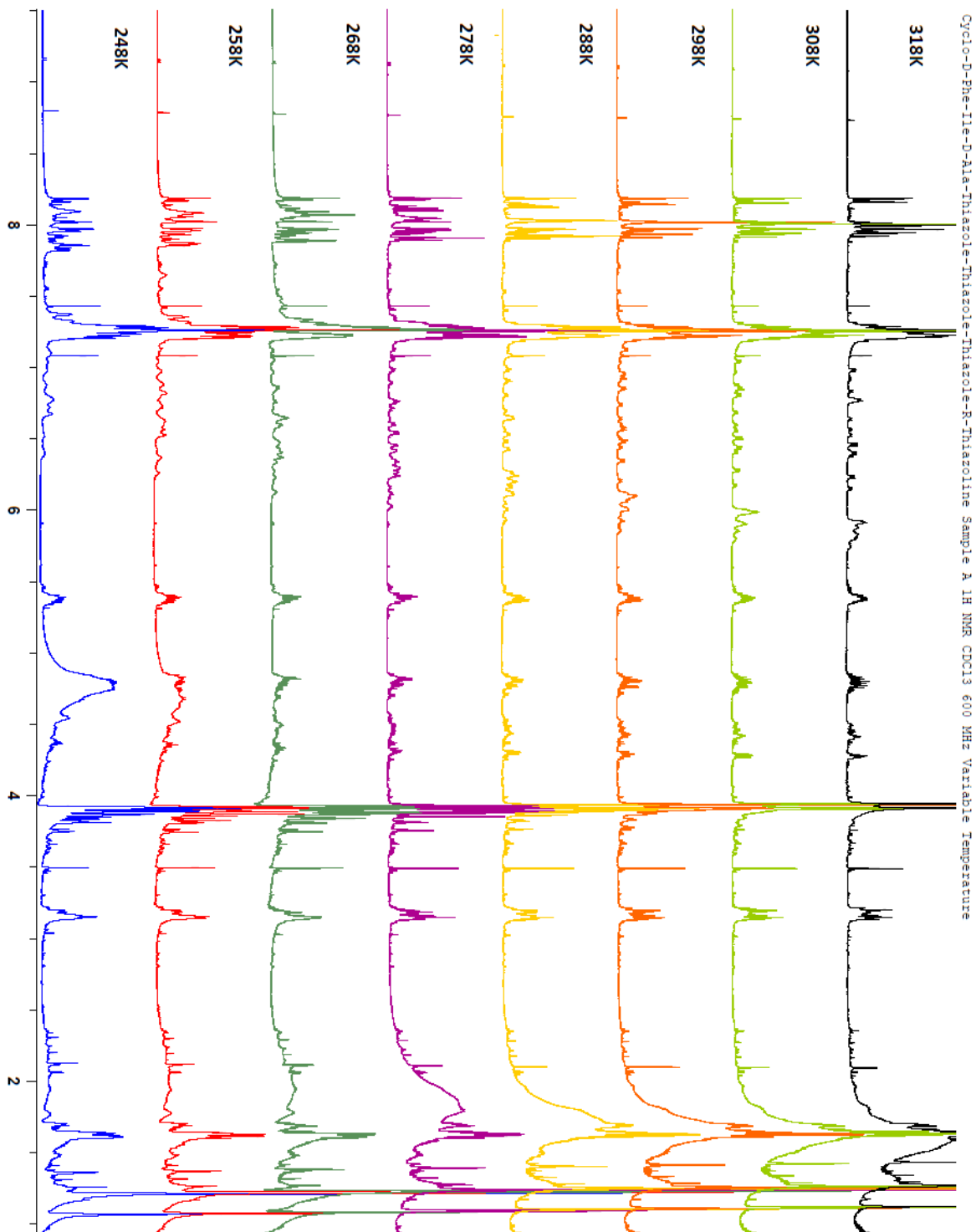




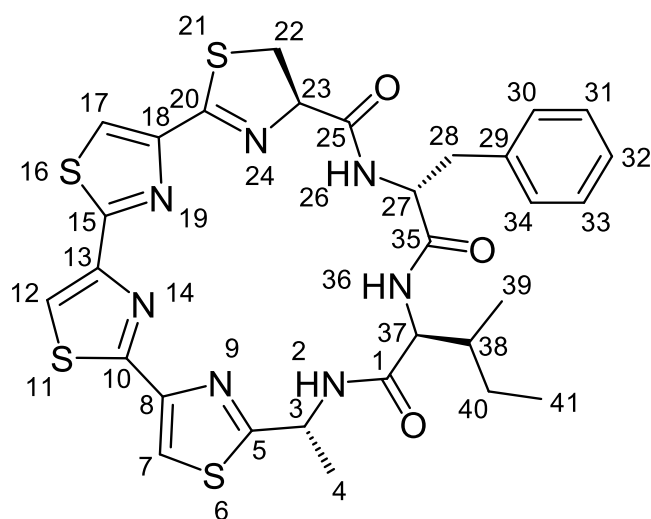








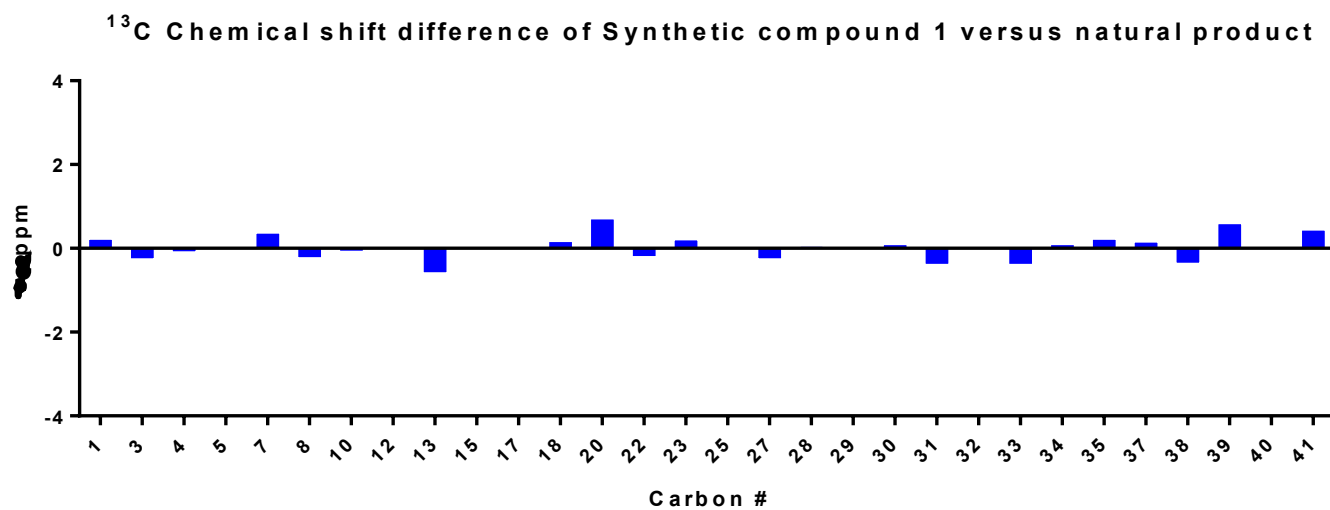
# Marthiapeptide A Natural product vs Synthetic Compound 1



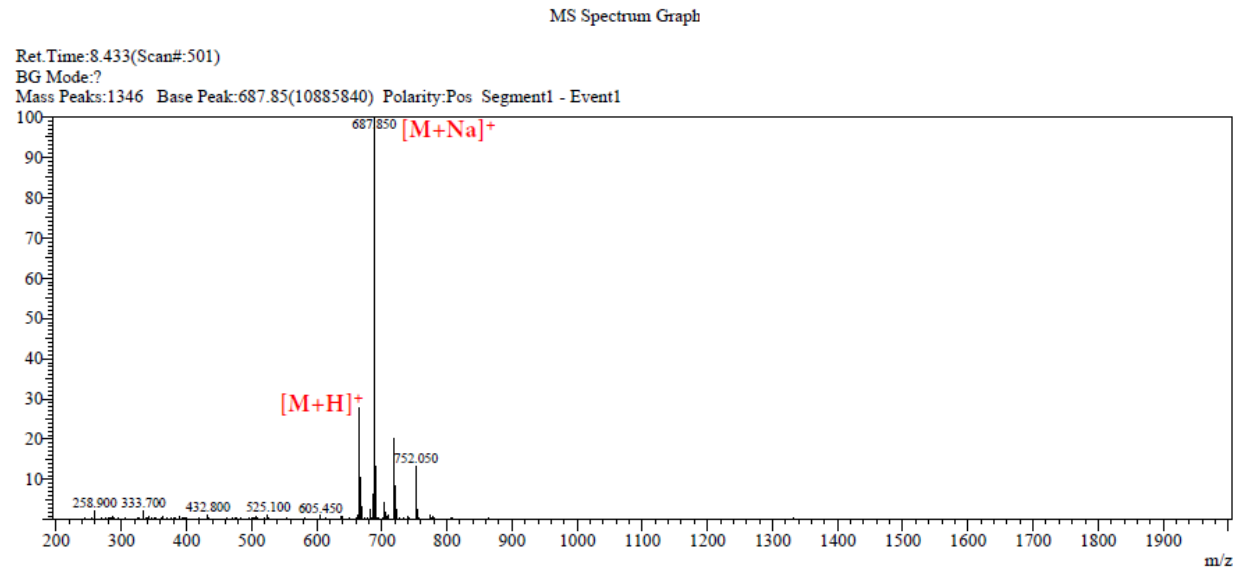
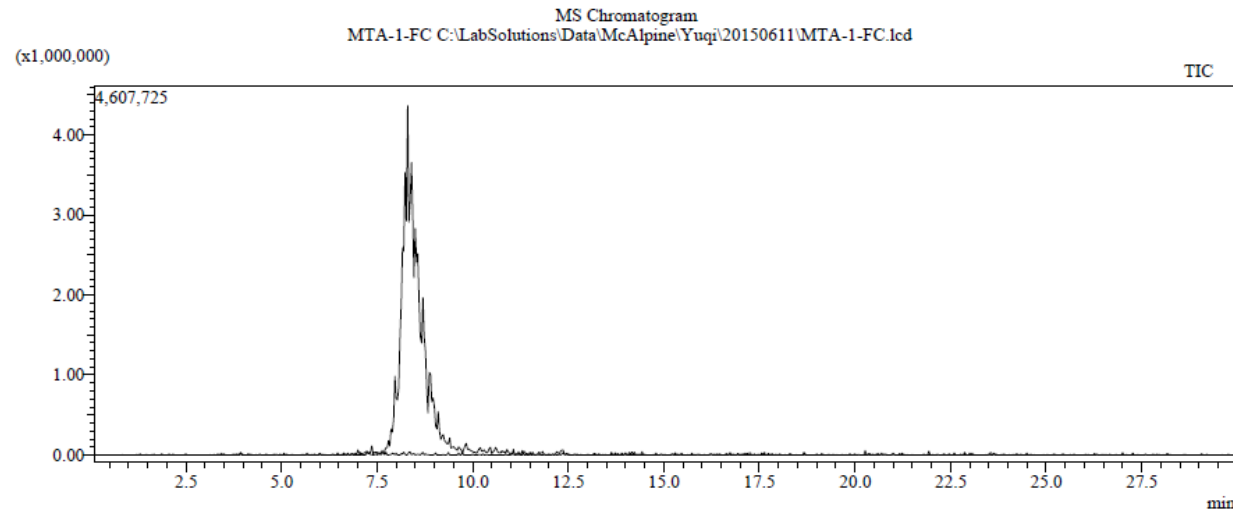
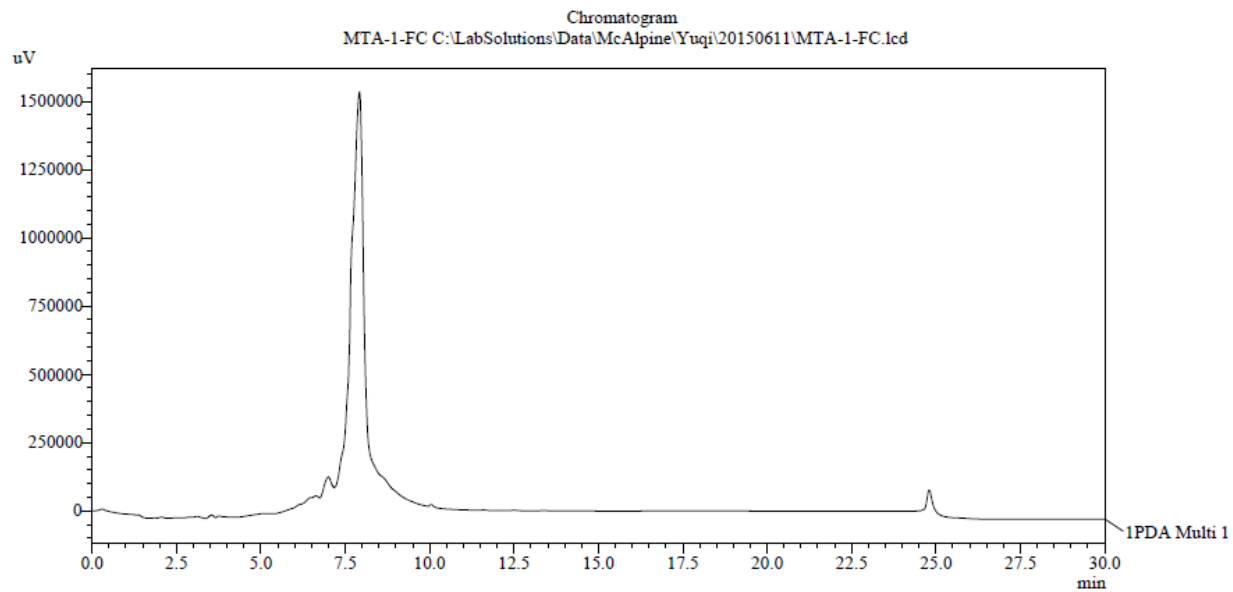
	$\delta_H$ , multi. (J in Hz)		$\delta_C$	
Position #	Natural product*	Synthetic* Compound 1	Natural product	Synthetic Compound 1
1			171.30	171.39
2	6.99, d (8.1)	7.00, m		
3	5.50, m	5.51, m	47.1	47.07
4	1.61, d (7.1)	1.615, m	23.0	22.96
5			174.3	174.21
7	7.74, s	7.74, s	118.2	118.6
8			147.2	147.11
10			161.1	161.07
12	7.72, s	7.721, s	118.3	118.42
13			148.1	148.9
15			161.0	161.13
17	7.66, s	7.68, s	122.3	122.8
18			148.9	148.87
20			161.7	161.05
22	3.70, d (10.5)	3.703, m)	36.3	36.24
23	4.81, t (10.5)	4.819, m	78.8	78.70
25			170.3	170.3
26	8.19, d (10.2)	8.20, d (10.0)		
27	5.12, td (10.2, 3.8)	5.12, m	56.4	56.36
28	2.98, dd (12.6, 10.2); 3.53, dd (13.6, 3.8)	2.98, m 3.536, m	40.3	40.3
29			137.1	137.08
30/34	7.34, d (7.4)	7.34, m	129.4	129.38
31/33	7.27, t (7.4)	7.29, m	128.5	128.82
32	7.20, t (7.4)	7.208, m	126.9	126.6
35			172.0	172.0
36	8.48, d (9.6)	8.49, d (9.34)		
37	4.70, dd (9.6, 3.7)	4.66, m	58.0	58.68
38	2.12, m	2.14, m	36.6	36.8

<b>39</b>	0.79, d (7.1)	0.816, d (7.00)	16.0	16.0
<b>40</b>	1.02, m; 1.34, m	1.034, m; 1.32, m	24.8	24.6
<b>41</b>	0.49, t (7.4)	0.485, (7.36)	11.8	11.8

**\*Note:** Both **natural product** and synthetic compound **1** NMR experiment was performed using CDCl<sub>3</sub> as solvent

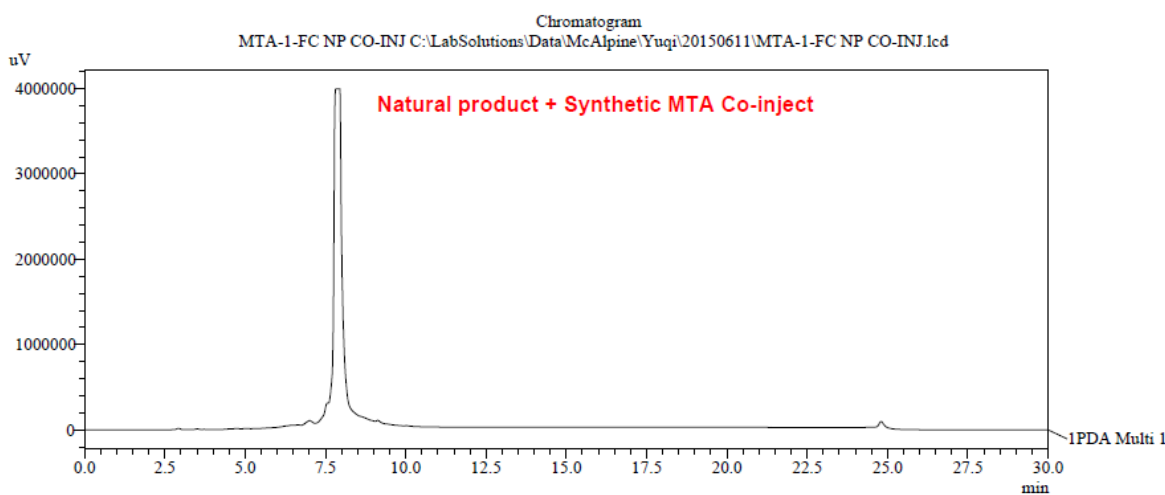
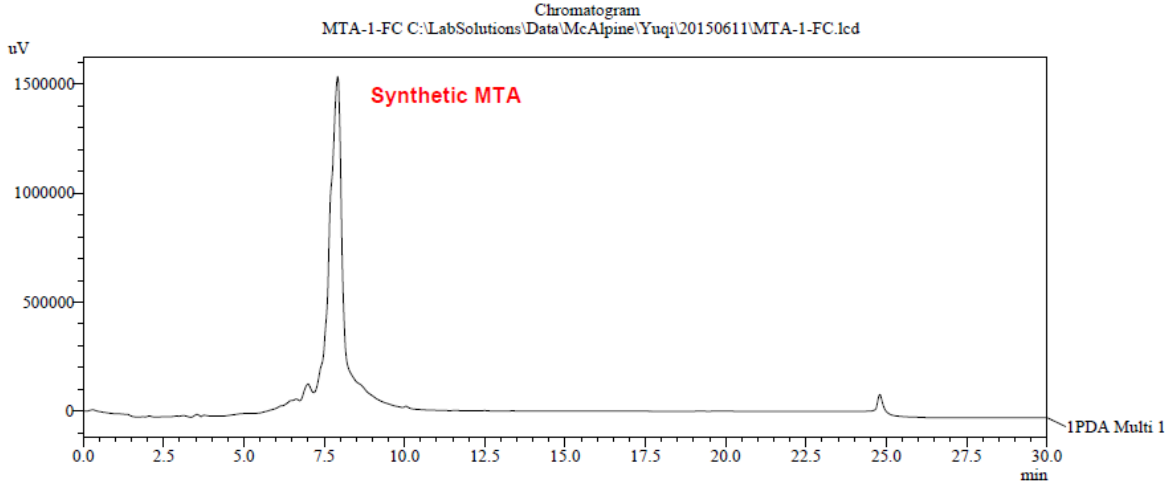
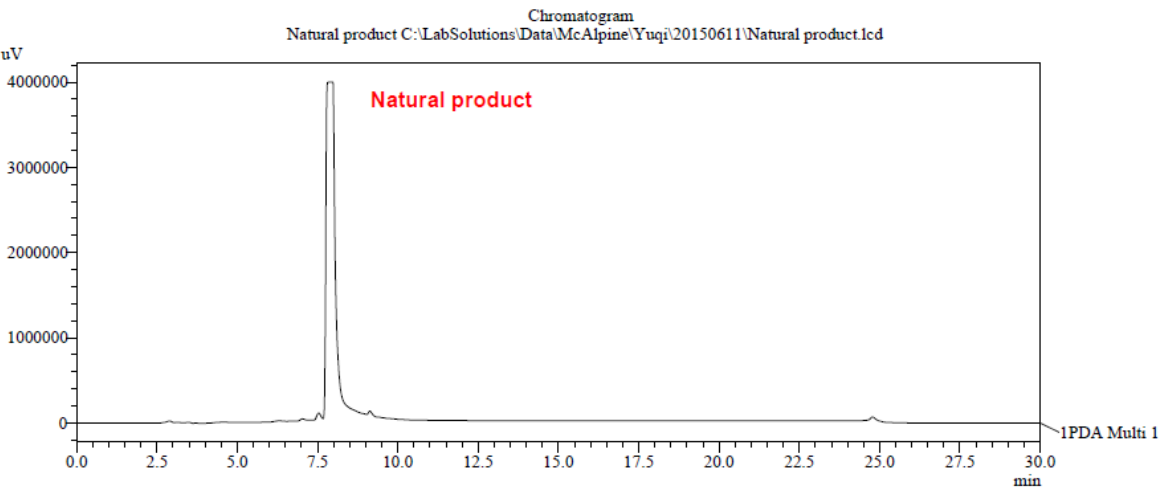


==== Shimadzu LCMSSolution Analysis Report ====



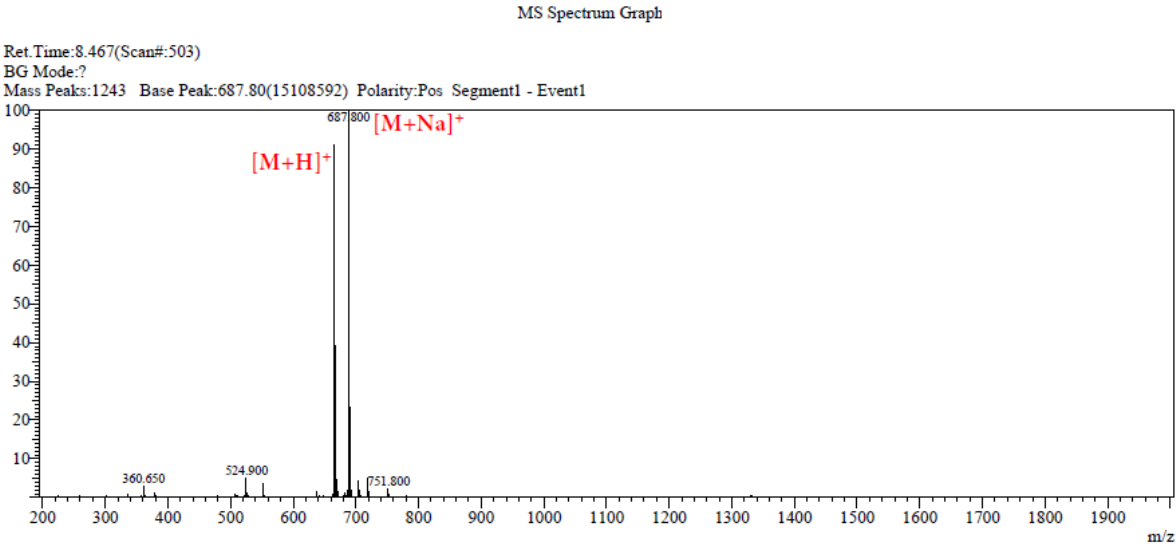
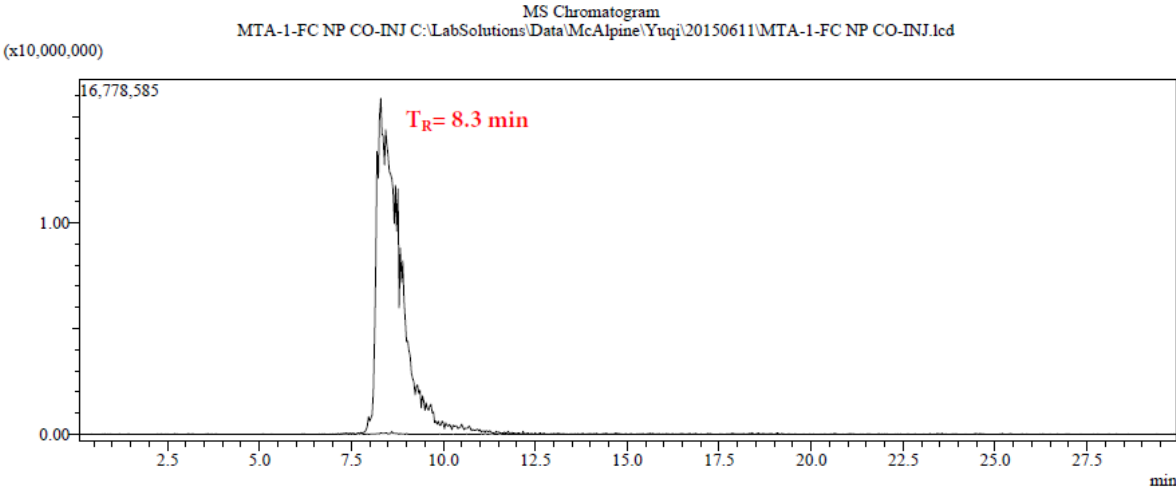
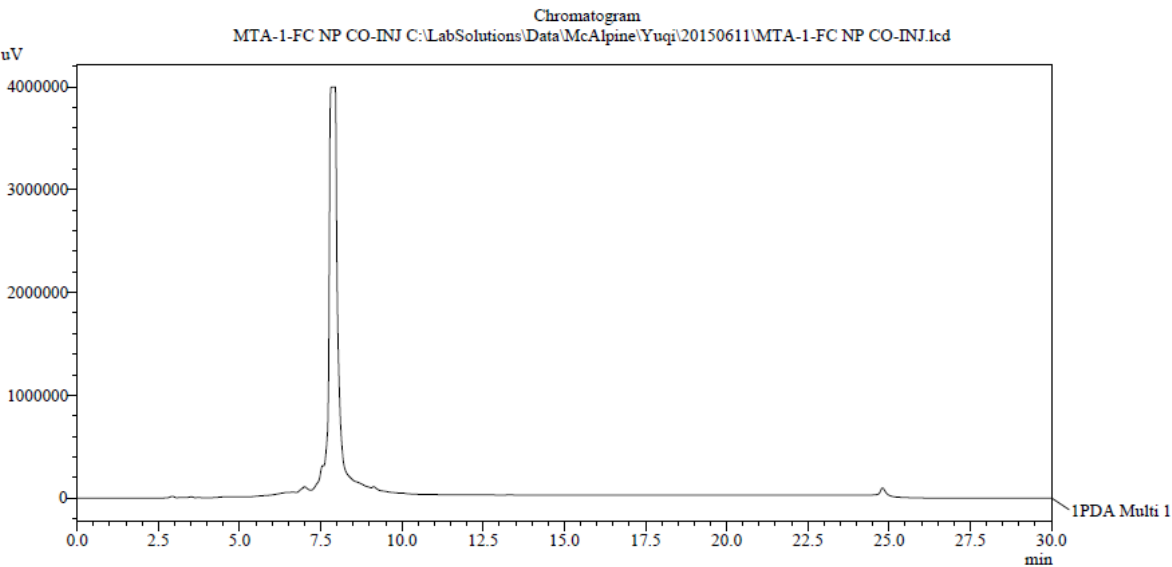
16/06/2015 15:01:48 1 / 1

==== Shimadzu LCMSsolution Analysis Report ====





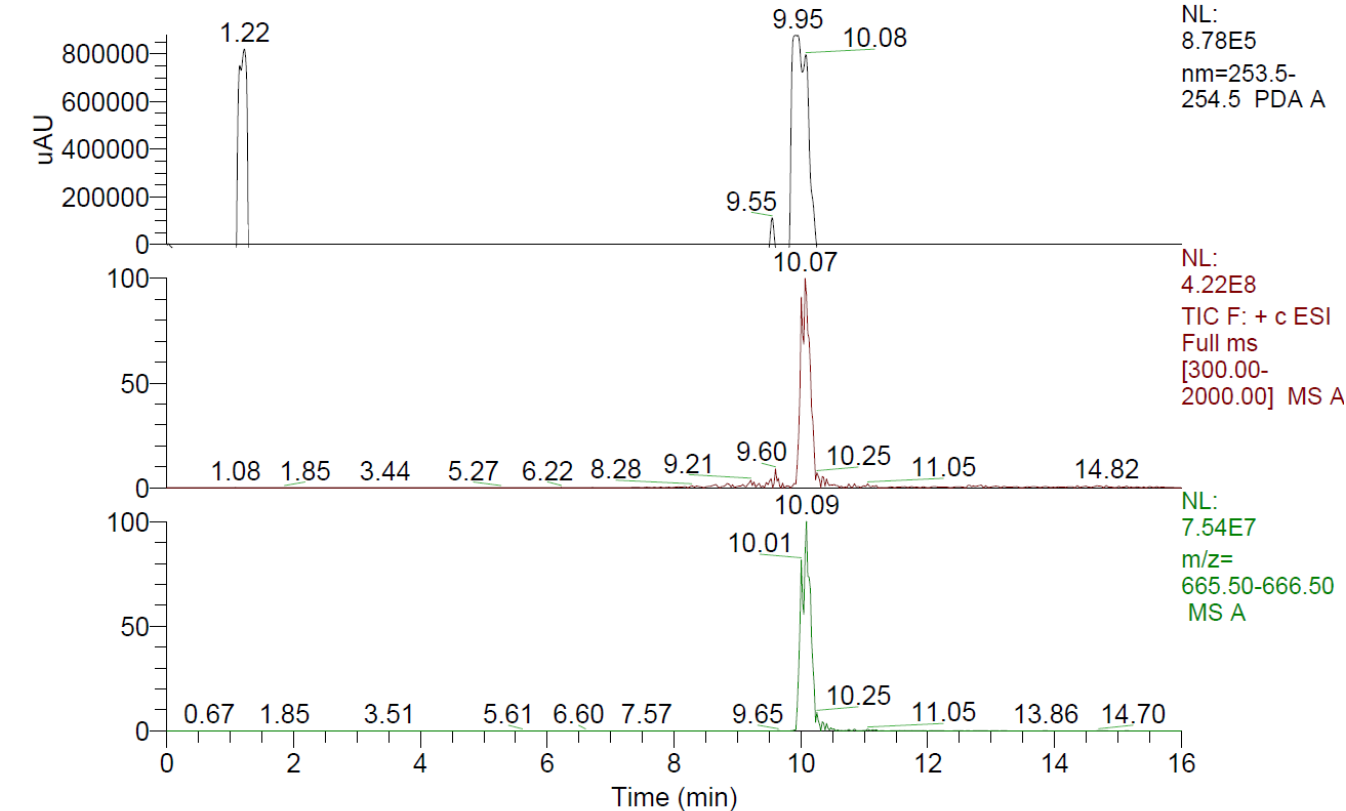
==== Shimadzu LCMSsolution Analysis Report ====



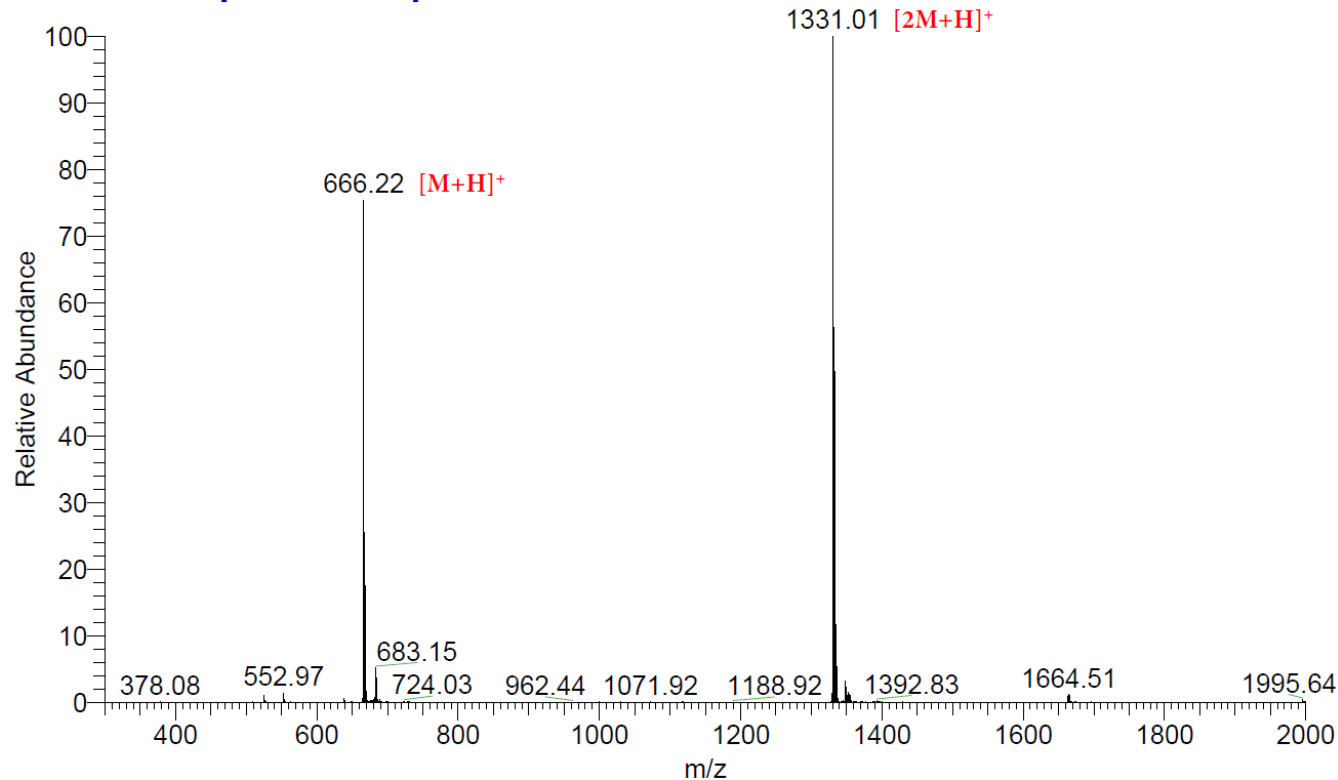
BMSF LC-MS analysis of Natural product injection

M:\bmsf\_all\...\Yuqi\2015-09-03\A

RT: 0.00 - 16.00



A #195-207 RT: 9.96-10.21 AV: 13 NL: 5.92E7  
T: + c ESI Full ms [300.00-2000.00]

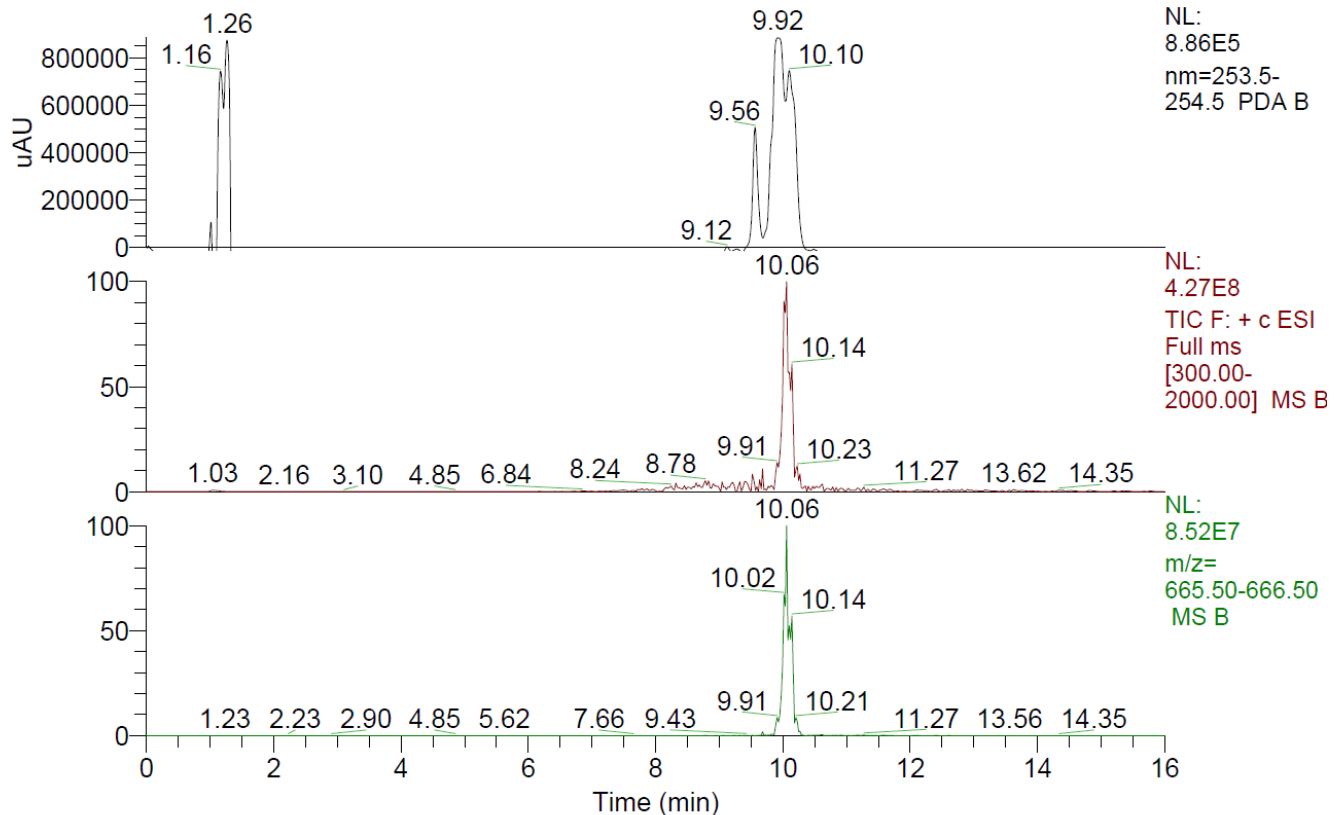


# BMSF LC-MS analysis of Natural product + compound 1

M:\bmsf\_all\...\Yuqi\2015-09-03\B

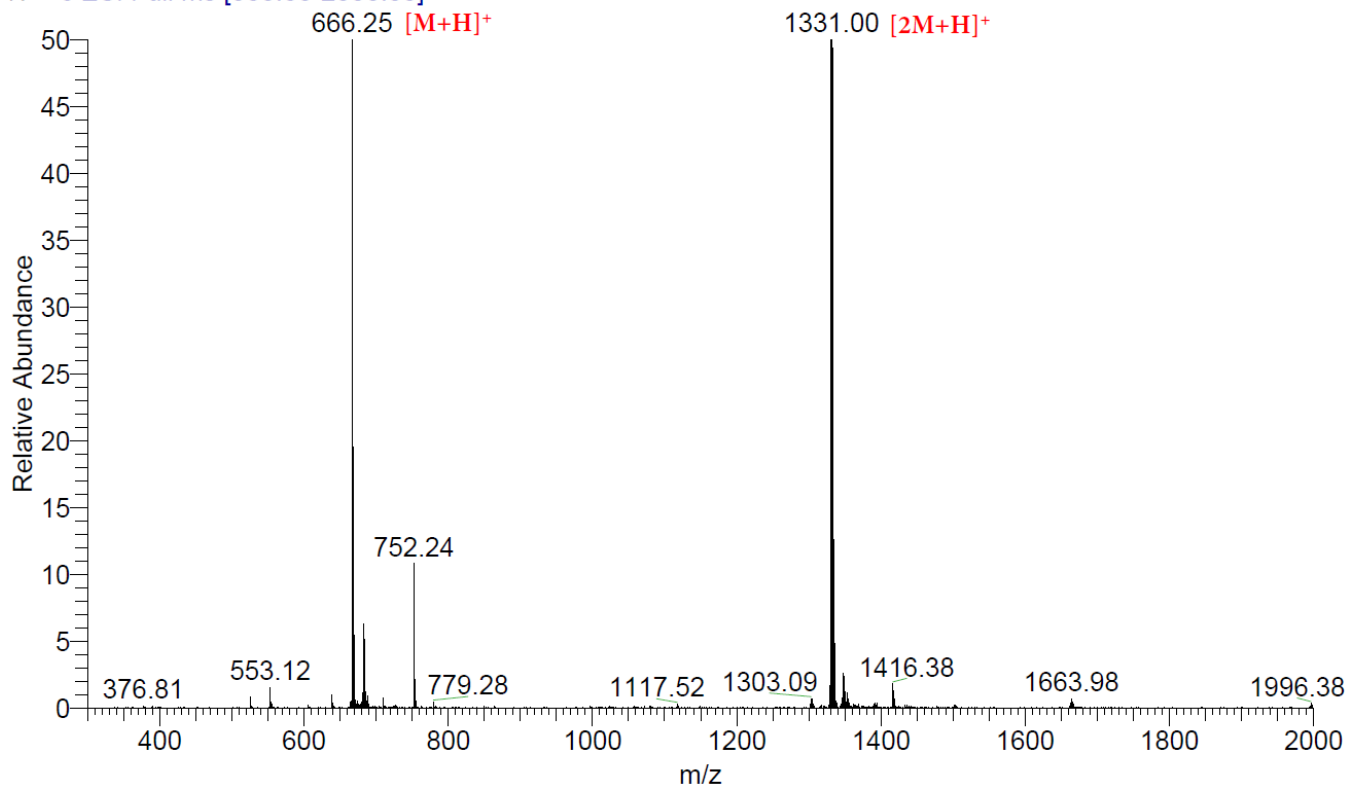
3/09/2015 2:16:19 PM

RT: 0.00 - 16.00



B #216-226 RT: 9.95-10.16 AV: 11 NL: 4.78E7

T: + c ESI Full ms [300.00-2000.00]

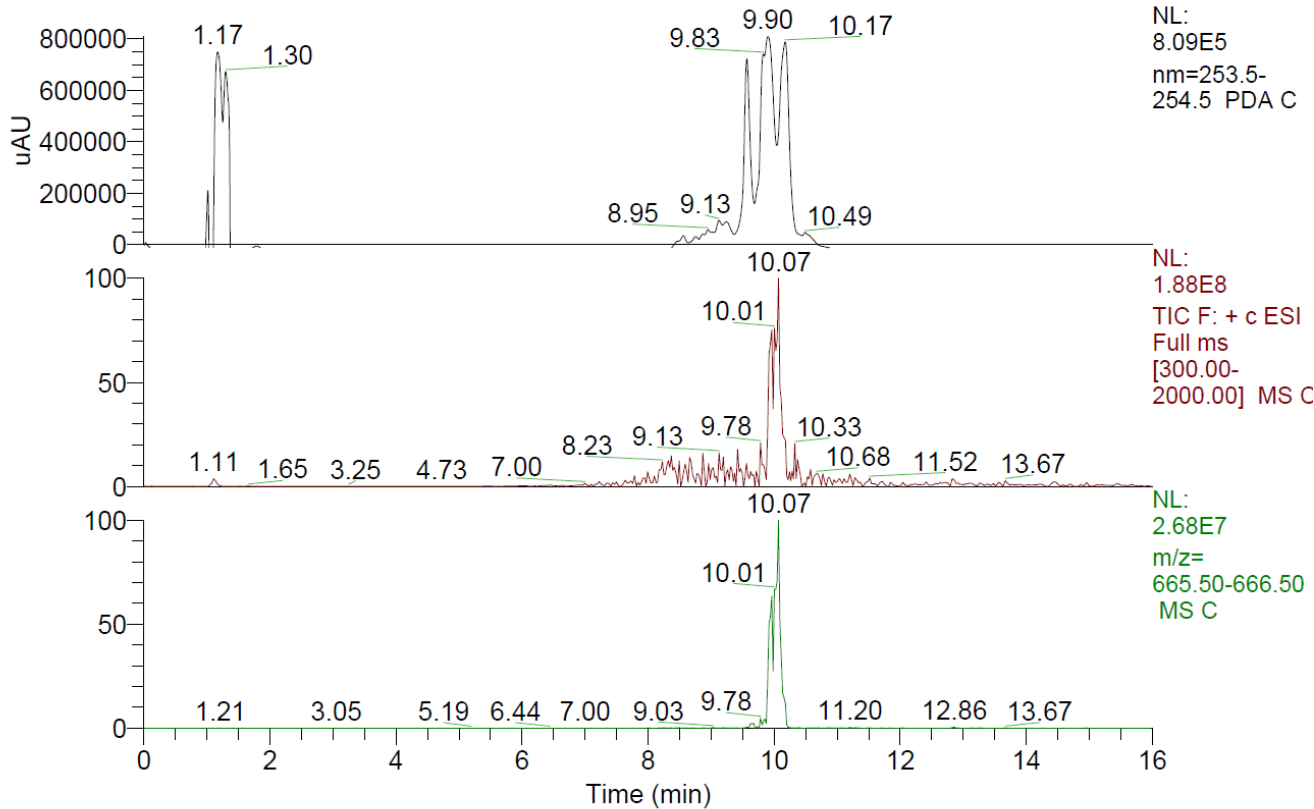


BMSF LC-MS Compound 1

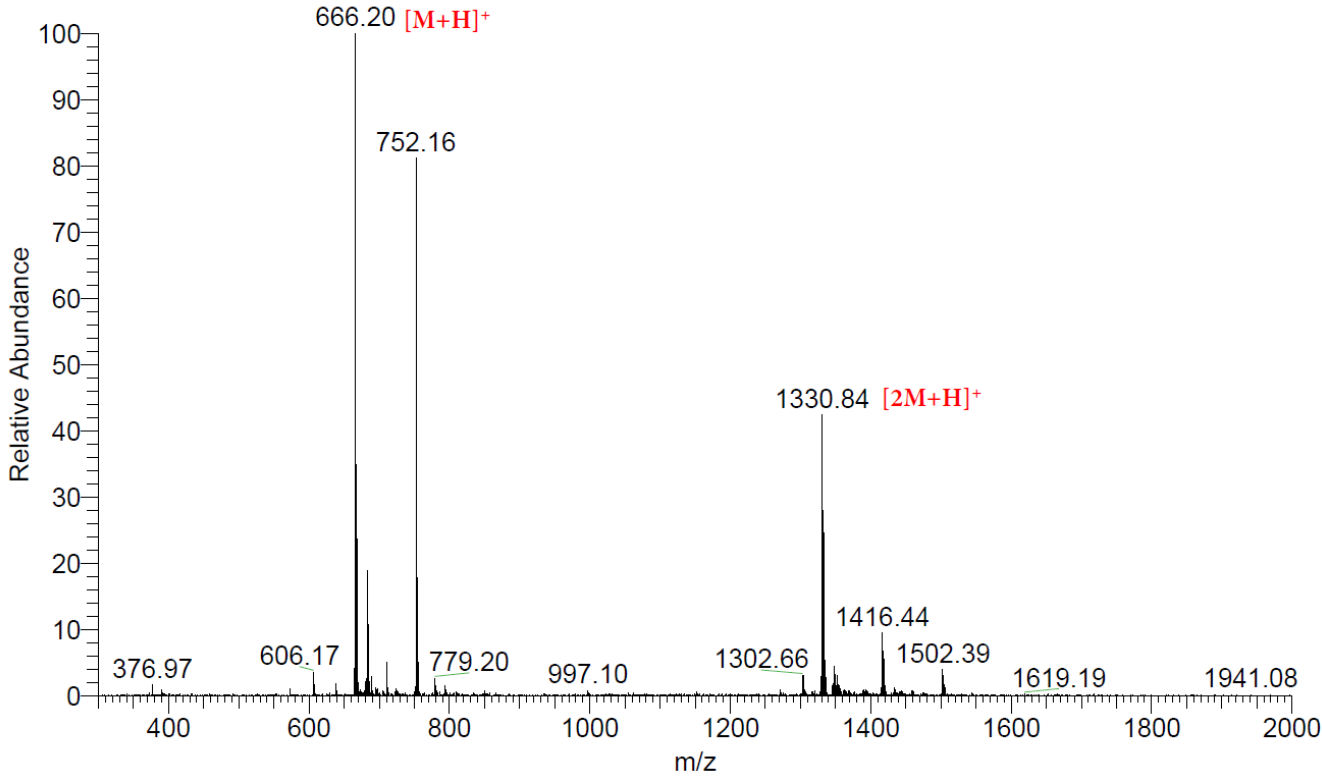
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3/09/2015 2:33:15 PM

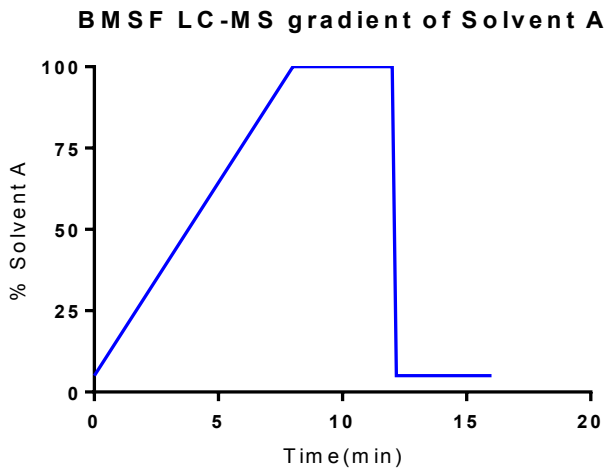
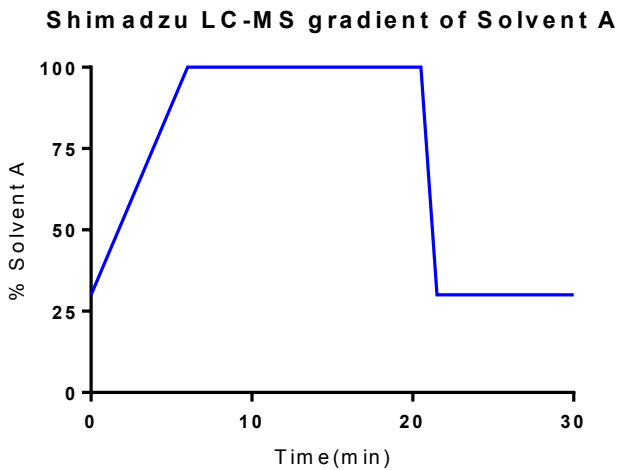
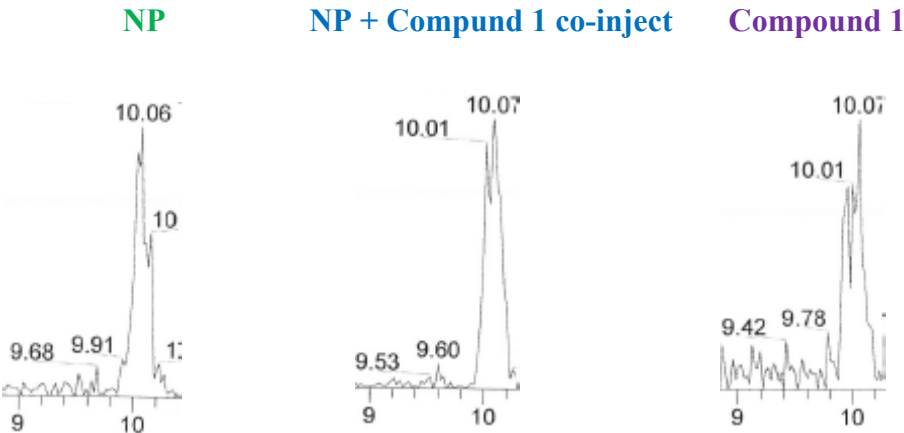
RT: 0.00 - 16.00



C #225-236 RT: 9.90-10.14 AV: 12 NL: 1.39E7  
T: + c ESI Full ms [300.00-2000.00]

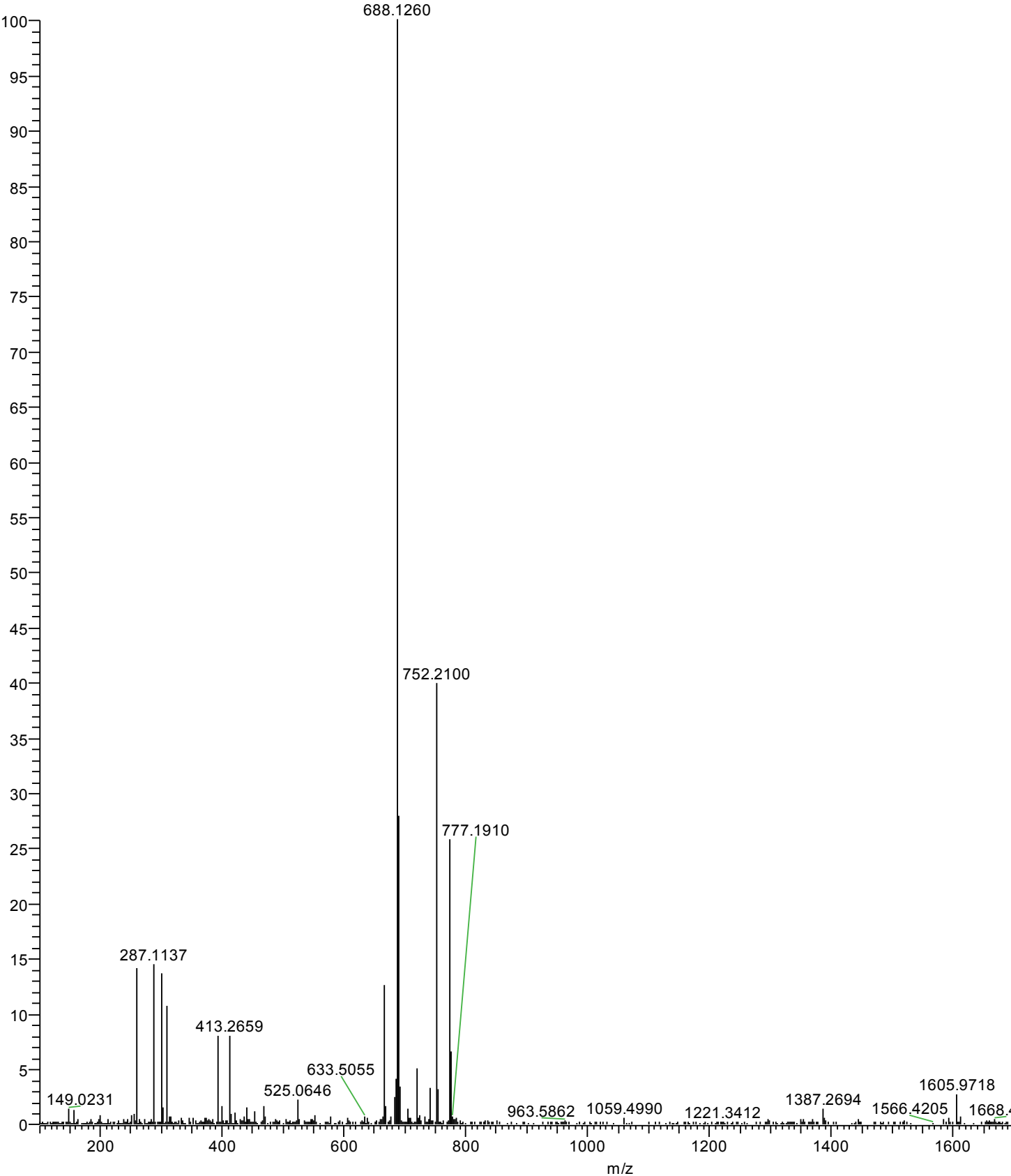


Synthetic compound 1 and Natural product (NP) BMSF LC-MS TIC analysis



Synthetic Compound **1** HRMS analysis (Calculated  $[M+Na]^+$ :688.1269, found 688.1260) (HRMS from Orbitrap)

MTA1-FC\_Full\_Pos\_a #19 RT: 1.00 AV: 1 NL: 6.89E6  
T: FTMS + c NSI Full ms [100.00-2000.00]



Zoomed spectrum:

