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Supporting Information

Blocking the heat shock response and depleting HSF-1 levels through heat shock protein 90 (hsp90) inhibition: a significant advance on current hsp90 chemotherapies.

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Contents

Biology: Results

Chemistry: General solid phase peptide synthesis

General Remarks

All chemicals were purchased from commercial suppliers (Chem-Impex International, Peptide International and GL-Biochem) and used without further purification. All moisture sensitive reactions were performed under nitrogen gas and was monitored by thin-layer chromatography (TLC) and liquid-chromatography mass spectrometry (LC/MS). TLC was performed on aluminium silica gel sheets 250 µm Whatman® (4861-820) using UV light (λ = 254 nm) as visualizing method. The developing agents for TLC include potassium permanganate (general purpose) and ninhydrin (for amine group detection).

SiliCycle SiliaFlash silica gel (60 Å, particle size 40-63 µm) were used for flash chromatography. ^{1}H and ^{13}C NMR spectra were obtained and recorded at 25ºC on Bruker Avance III 500 MHz and 600 MHz. Multiplicity of NMR signals were represented by the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad, dd = doublet of doublet. Assignment of resonances for each amino acid residue was done using ^{1}H, ^{13}C, HMQC, HMBC and COSY. Each residue was assigned using ^{1}H chemical shifts and confirmed by COSY and HMQC crosspeks. The final cyclized structure was characterized by considering long range HMBC correlations from both the α-protons and NH protons to the adjacent carbonyl carbons and the adjacent amino acid residues.

High-resolution mass spectrometry (HRMS) analyses were recorded on a Thermo LTQ Orbitrap XL ESI/APCI with UPLC system at the Bioanalytical Mass Spectrometry Facility in Mark Wainwright Analytical Centre at the University of New South Wales.

LC/MS analyses were performed on Shimadzu Prominence High performance LCMS 2010EV system (Water Symmetry® C18 column, 3.5 µm, 4.65x75 mm) connected to a Shimadzu LCMS 2010EV mass spectrometer. The mobile phase consist 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) at a flow rate of 0.5 mL/min, starting at 70% solvent A, 30% solvent B.

Semi-preparative HPLC for purification was performed on Shimadzu Prominence High performance LCMS 2010EV system (Phenomenex® Jupiter C18 column, 4µm, 250x10 mm). The mobile phase was prepared by 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 were as follow: flow rate 2 mL/min; initial 70% solvent A, 30% solvent B hold for 35 min; at 35 min 100% solvent B hold for 18 min; at 53 min 70% solvent A, 30% solvent B hold for 7 min.

Synthesis: Experimental Procedures

Synthesis of N-methylated peptides:

o-NBS Protection

A solution of o-NBS-Cl (4 equivalents) and collidine (10 equivalents) in CH_2Cl_2 was added to the resin-bound free amine peptide in a round bottom flask and stirred for 4 hours at room temperature. The resin was then washed with DCM (5x). Completion of the reaction was monitored and analyzed by LCMS by treatment of a small amount resin with TFE:CH_2Cl_2 (1:1) to cleave the *o*-NBS-peptides.

N-Methylation under Mitsunobu conditions

A solution of triphenylphosphine (5 equivalents) and MeOH (10 equivalents) in dry THF was added to the resin bound *o*-NBS-protected peptides and stirred for 10 mins. A solution of DIAD (5 equivalents) in dry THF was then added portion by portion to the reaction mixture and stirred for 4 hours at room temperature. The resin was filtered off, and washed with DMF (5x). *N*-Methyl-*N*-*o*-NBS-peptides were then cleaved from resin by treatment of a small amount of resin with TFE:CH_2Cl_2 (1:1) and analyzed by LCMS to monitor the reaction completion.

o-NBS deprotection

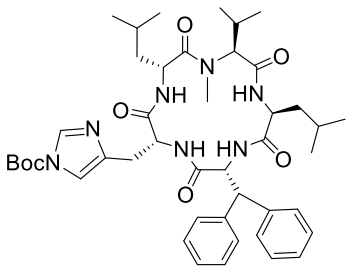
For *o*-NBS deprotection, the resin-bound *N*-Methyl-*N*-*o*-NBS-peptides was treated with a solution of mercaptoethanol (10 equivalents) and DBU (5 equivalents) in DMF for 2 hours. The deprotection procedure was repeated one more time and the resin was washed with DMF (5x).

Benoiton method

The Benoiton method to generate N-methylated amino acid was done by adding iodometane (10 equivalents) as methylating agent in portion wise to a stirred solution of Boc protected amino acid and strong base sodium hydride (60% dispersion in mineral oil, 10 equivalents) in anhydrous THF (0.30 M) to 0 ºC. The mixture was allowed to

stir at room temperature for 24 hours under nitrogen. The completion of the reaction was monitored by TLC. The reaction mixture was then dried *in vacuo* and diluted with ethyl acetate. The organic layer was washed with 10% (v/v) $HCl_{(aq)}$, dried over Na_2SO_4, filtered, concentrated *in vacuo* and subjected to the next reaction without purification.

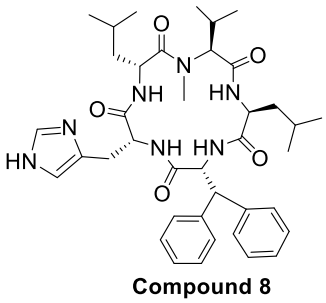
Experimental procedures


Compound 7

Following "**General peptide coupling"** procedure for SPPS and the published procedure for SPPS (Koay, Y. C.; McConnell, J. R.; Wang, Y.; Kim, S. J.; Buckton, L. K.; Mansour, F.; McAlpine, S. R. *ACS Med. Chem. Lett.* **2014**, *5*, 771-776), linear pentapeptide of resin-O-Leu-*N*-Me-Val-D-Leu-D-His(Boc)-3,3-Diphenyl-D-Ala-NH_2 was synthesized by using 1.00 g (0.5 mmol, 1.0 equivalent) of resin-O-Leu-NH_2 and the subsequent peptide coupling in the sequence as mentioned below: 0.53 g (1.5 mmol, 3.0 equivalents) of Fmoc-*N*-Me-Val-OH, 0.53 g (1.5 mmol, 3.0 equivalents) of Fmoc-D-Leu-OH, 0.72 g (1.5 mmol, 3.0 equivalents) of Fmoc-D-His(Boc)-OH and 0.70 g (1.5 mmol, 3.0 equivalents) of Fmoc-3,3-Diphenyl-D-Ala-OH. Each peptide coupling was done in the presence of 0.20 g of HOAt (1.5 mmol, 3.0 equivalents) or 0.20 g of HOBt (1.5 mmol, 3.0 equivalents), 0.47 mL of DIC (3.0 mmol, 6.0 equivalents) and 2.5 mL of DMF to generate a concentration of 0.20 M. Each coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm the reaction completion. The reaction mixture was drained to afford the Fmoc-protected resin-bound pentapeptide and the Fmoc protecting group was removed following the **"General Fmoc removal"** after the completion of each coupling reaction.

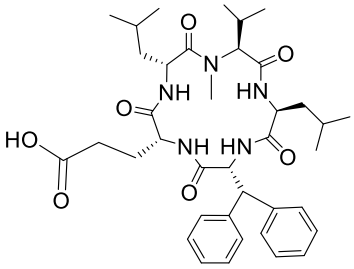
The double deprotected linear pentapeptide (DDLP) HO-Leu-*N*-Me-Val-D-Leu-D-His(Boc)-3,3-Diphe-D-Ala-NH_2 was generated following the **"Resin cleavage of linear peptide"** procedure for SPPS. The linear pentapeptide was cleaved from the resin using a mixed solution of 6 mL of TFE and 6 mL of CH_2Cl_2. The resin containing solution was filtered and dried *in vacuo* to yield the DDLP as a white solid (286 mg, overall 70%).
LC/MS (ESI): *m/z* called for $C_{44}H_{63}N_7O_8$ (M+1) = 818.47, found 818.10.

Cyclo **Leu-*N*-Me-Val-D-Leu-D-His(Boc)-3,3-Diphe-D-Ala (7)** was synthesized using 0.29 g of the DDLP generated (0.35 mmol, 1.0 equivalent), 0.09 g of TBTU (0.28 mmol, 0.80 equivalent), 0.11 g of HATU (0.28 mmol, 0.80 equivalent), 0.08 g of DMTMM (0.28 mmol, 0.80 equivalent), 0.49 mL of DIPEA (2.8 mmol, 8.0 equivalents) in anhydrous CH_2Cl_2 (355 mL, 0.001M) following "**Macrocyclization procedure (syringe pump)"** procedure. The reaction was then stirred overnight and the reaction was monitored via LC/MS. Upon completion, the reaction mixture was subjected to acid-base wash, which was extracted twice with 10% (v/v) $HCl_{(aq)}$. The organic layer was then re-extracted with a saturated of $NaHCO_3$ aqueous solution. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via flash column chromatography on silica gel using an ethyl acetate-hexane gradient system, followed by purification via HPLC to yield compound **7** as white solid (58 mg, 21%).
R_f: 0.58 (EtOAc:MeOH = 0.95:0.05)
LC/MS: *m/z* called for $C_{44}H_{61}N_7O_7Na_1$ ($M+Na^+$) = 822.45, found 822.00.
HRMS (ESI-TOF): $M+Na^+$, found 822.4524 $C_{44}H_{61}N_7O_7Na_1$ requires 822.4530.
^{1}H NMR (600 MHz, DMSO): δ 8.26 (d, *J* = 8.9 Hz, NH), 8.20 (s, D-His), 7.89 (d, *J* = 7.6 Hz, NH), 7.77 (d, *J* = 9.8 Hz, NH), 7.42 (br, NH), 7.34 (m, 3H, D-His, D-Biphe), 7.24-7.10 (m, 8H, D-Biphe), 5.26 (dd, *J* = 10.0, 12.1 Hz, 1H, CHα D-Biphe), 4.57 (d, *J* = 11.5 Hz, 1H, CHα Val), 4.45 (m, 1H, CHα D-His), 4.35 (d, *J* = 12.2 Hz, 1H, CHβ D-Biphe), 4.29 (m, 1H, CHα D-Leu), 3.38 (q, *J* = 11.0 Hz, 1H, CHα Leu), 2.61 (m, 1H, $CH_2\beta_2$ D-His), 2.57 (m, 4H, $CH_2\beta_1$ D-His, NCH_3), 2.13 (m, 1H, CHβ Val), 1.59 (s, 9H, $OC(CH_3)_3$), 1.54 (m, 1H, $CH_2\beta_2$ Leu), 1.48 (m, 1H, $CH_2\beta_2$ D-Leu), 1.41 (m, 1H, $CH_2\beta_1$ Leu), 1.29 (m, 2H, $CH_2\beta_1$ D-Leu, , CHγ Leu), 1.17 (m, 1H, CHγ D-Leu), 0.79-0.67 (m, 18H, $CH_2CH(CH_3)_2$, $CHCH(CH_3)_2$).
^{13}C NMR (150 MHz, DMSO): δ 170.72, 170.00, 169.68, 169.08, 168.56, 147.07, 141.61, 141.30, 139.07, 137.41, 128.66, 128.56, 128.51, 128.48, 127.02, 126.87, 114.88, 85.70, 63.05, 57.01, 53.80, 51.80, 47.90, 41.18, 40.53, 37.97, 30.18, 27.87, 25.33, 24.50, 24.25, 23.53, 22.94, 22.53, 22.51, 19.57, 18.80.


Compound 8

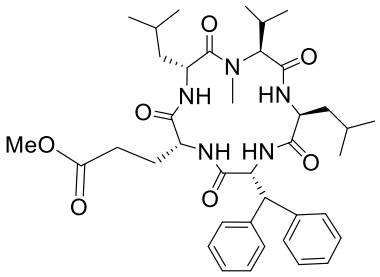
The Boc protecting group of compound **7** was removed following **"Boc removal"** procedure, utilizing a mixture of TFA/CH_2Cl_2 (1:4, 0.1 M) and anisole (2.0 equivalents) to generate compound **8**.
R_f: 0.50 (EtOAc:MeOH = 1:1)
LC/MS: *m/z* called for $C_{39}H_{53}N_7O_5$ (M+1) = 700.41, found 700.00.
HRMS (ESI-TOF): M+1, found 700.4179 $C_{39}H_{53}N_7O_5$ requires 699.4108.
^{1}H NMR (600 MHz, DMSO): δ 8.62 (d, *J* = 8.2 Hz, NH), 8.15 (s, D-His), 8.03 (br, 2NH), 7.84 (d, *J* = 8.0 Hz, 2NH), 7.35-7.13 (m, 11H, D-His, D-Biphe),

5.24 (dd, J = 10.1, 12.1 Hz, 1H, CHα D-Biphe), 4.56 (d, J = 11.3 Hz, 1H, CHα Val), 4.48 (m, 2H, CHβ D-Biphe, CHα D-Leu), 4.26 (m, 1H, CHα D-His), 3.27 (q, J = 7.2 Hz, 1H, CHα Leu), 2.72 (br, 2H, CH_2β D-His), 2.56 (s, 3H, NCH_3), 2.11 (m, 1H, CHβ Val), 1.54 (m, 2H, $CH_2\beta_2$ Leu, $CH_2\beta_2$ D-Leu), 1.40 (m, 1H, $CH_2\beta_1$ D-Leu), 1.27 (m, 3H, $CH_2\beta_1$ Leu, , CHγ Leu, CHγ D-Leu), 0.81-0.65 (m, 18H, $CH_2CH(C\underline{H}_3)_2$, $CHCH(C\underline{H}_3)_2$).
^{13}C NMR (150 MHz, DMSO): δ 170.70, 170.30, 169.56, 169.24, 168.57, 141.69, 141.30, 135.13, 134.94, 128.78, 128.71, 128.52, 128.38, 127.12, 126.78, 116.03, 62.69, 57.16, 54.54, 53.67, 52.06, 47.77, 41.24, 40.53, 37.85, 30.09, 25.35, 24.47, 24.35, 23.49, 22.97, 22.78, 22.53, 19.61, 18.75.



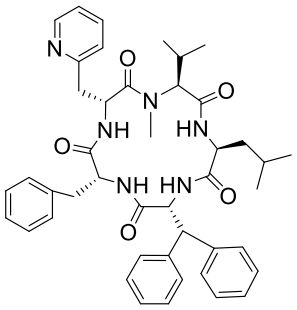
Compound 10

The tBu protecting group of compound **9** was removed following **"*Tert*-butyl group (tBu) Removal"** procedure, utilizing a mixture of TFA/CH_2Cl_2 (2:4, 0.1 M) and anisole (2.0 equivalents) to generate compound **10**. The free acid was taken to the subsequent methyl ester formation without purification.
R_f: 0.20 (EtOAc:MeOH = 0.80:0.20)
LC/MS: *m/z* called for $C_{38}H_{53}N_5O_7$ (M+1) = 692.39, found 692.05.
HRMS (ESI-TOF): M+Na^+, found 714.3834 $C_{38}H_{53}N_5O_7Na_1$ requires 714.3843.
^{1}H NMR (600 MHz, DMSO): δ 8.10 (br, N$\underline{H}$), 7.99 (d, J = 8.9 Hz, N$\underline{H}$), 7.83 (d, J = 7.4 Hz, N$\underline{H}$), 7.49 (d, J = 7.3 Hz, N$\underline{H}$), 7.37-7.12 (m, 10H, D-Biphe), 5.23 (dd, J = 10.0, 11.9 Hz, 1H, CHα D-Biphe), 4.59 (m, 2H, CHα Val, CHα D-Glu), 4.32 (d, J = 12.1 Hz, 1H, CHβ D-Biphe), 3.77 (m, 1H, CHα D-Leu), 3.47 (q, J = 7.3 Hz, 1H, CHα Leu), 2.64 (s, 3H, NCH_3), 2.15 (m, 1H, CHβ Val), 1.65 (m, 4H, CH_2β D-Glu, CH_2β D-Leu), 1.49 (m, 3H, CHγ Leu, CH_2β Leu), 1.39 (m, 2H, CH_2γ D-Glu), 1.25 (m, 1H, CHγ D-Leu), 0.88-0.64 (m, 18H, , $CH_2CH(C\underline{H}_3)_2$, $CHCH(C\underline{H}_3)_2$).
^{13}C NMR (150 MHz, DMSO): δ 174.20, 171.07, 170.81, 170.07, 169.65, 168.85, 141.61, 141.13, 128.95, 128.77, 128.62, 128.43, 127.29, 126.80, 63.22, 56.98, 55.52, 53.63, 51.75, 47.59, 41.46, 37.80, 30.11, 29.73, 26.76, 25.29, 24.77, 24.55, 23.33, 22.91, 22.88, 22.51, 19.62, 18.90.



Compound 11

The free acid of compound **10** was converted to the methyl ester compound **11** using the methylating agent Trimethylsilyl diazomethane (TMSD). Compound of **10** was dissolved in a mixture of anhydrous benzene and methanol (3:1) in a round bottom flask to make a 0.1 M solution. The methylating agent TMSD (2.0 M in diethyl ether) was added drop-wise into the reaction mixture became slightly yellow. The reaction was stirred under nitrogen and monitored by thin layer chromatography (TLC). Upon completion, the solvent was evaporated *in vacuo* and resulting compound **11**.
R_f: 0.48 (Hex:EtOAc = 0.25:0.75)
LC/MS: *m/z* called for $C_{39}H_{48}N_6O_7$ (M+1) = 706.41, found 706.05.
HRMS (ESI-TOF): M+Na^+, found 728.3996 $C_{39}H_{55}N_5O_7Na_1$ requires 728.3999.
^{1}H NMR (600 MHz, DMSO): δ 8.10 (d, J = 7.7 Hz, N$\underline{H}$), 8.00 (d, J = 9.0 Hz, N$\underline{H}$), 7.83 (d, J = 7.6 Hz, N$\underline{H}$), 7.49 (d, J = 8.5 Hz, N$\underline{H}$), 7.36-7.12 (m, 10H, D-Biphe), 5.24 (dd, J = 9.9, 11.9 Hz, 1H, CHα D-Biphe), 4.59 (m, 2H, CHα Val, CHα D-Glu), 4.32 (d, J = 12.1 Hz, 1H, CHβ D-Biphe), 3.76 (m, 1H, CHα D-Leu), 3.56 (s, 3H, $OC\underline{H}_3$), 3.50 (q, J = 7.4 Hz, 1H, CHα Leu), 2.64 (s, 3H, NCH_3), 2.16 (m, 1H, CHβ Val), 1.69 (m, 4H, CH_2β D-Glu, CH_2β D-Leu), 1.48 (m, 3H, CHγ Leu, CH_2β D-Leu), 1.39 (m, 2H, CH_2γ D-Glu), 1.25 (m, 1H, CHγ D-Leu), 0.88-0.63 (m, 18H, $CH_2CH(C\underline{H}_3)_2$, $CHCH(C\underline{H}_3)_2$).
^{13}C NMR (150 MHz, DMSO): δ 172.90, 170.95, 170.82, 170.22, 169.68, 168.89, 141.59, 141.14, 128.91, 128.76, 128.58, 128.44, 128.30, 127.29, 127.14, 126.82, 63.29, 56.88, 55.43, 53.59, 51.72, 51.69, 47.62, 41.42, 37.79, 30.14, 29.60, 26.51, 25.30, 24.78, 24.56, 23.31, 22.90, 22.86, 22.50, 19.60, 18.91.

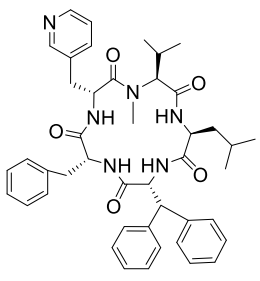


Compound 12

Following "**General peptide coupling"** procedure for SPPS and the published procedure for SPPS (Koay, Y. C.; McConnell, J. R.; Wang, Y.; Kim, S. J.; Buckton, L. K.; Mansour, F.; McAlpine, S. R. *ACS Med. Chem. Lett.* **2014**, *5*, 771-776), linear pentapeptide of resin-O-Leu-*N*-Me-Val-3-(2'-Pyr)-D-Ala-D-Phe-3,3-Diphe-D-Ala-NH_2 was synthesized by using 1.00 g (0.5 mmol, 1.0 equivalent) of resin-O-Leu-NH_2 and the subsequent peptide coupling in the sequence as mentioned below: 0.53 g (1.5 mmol, 3.0 equivalents) of Fmoc-*N*-Me-Val-OH, 0.58 g (1.5 mmol, 3.0 equivalents) of Fmoc-D-3-(2'-Pyr)Ala-OH, 0.58 g (1.5 mmol, 3.0 equivalents) of Fmoc-D-Phe-OH and 0.70 g (1.5 mmol, 3.0 equivalents) of Fmoc-3,3-Diphenyl-D-Ala-OH. Each peptide coupling was done in the presence of 0.20 g of HOAt (1.5 mmol, 3.0 equivalents) or 0.20 g of HOBt (1.5 mmol, 3.0 equivalents), 0.47 mL of DIC (3.0 mmol, 6.0 equivalents) and 2.5 mL of DMF to generate a concentration of 0.20 M. Each coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm the reaction completion. The reaction mixture was drained to afford the Fmoc-protected resin-bound pentapeptide and the Fmoc protecting group was removed following the **"General Fmoc removal"** after the completion of each coupling reaction.

The double deprotected linear pentapeptide (DDLP) HO-Leu-*N*-Me-Val-3-(2'-Pyr)-D-Ala-D-Phe-3,3-Diphe-D-Ala-NH_2 was generated following the **"Resin cleavage of linear peptide"** procedure for SPPS. The linear pentapeptide was cleaved from the resin using a mixed solution of 6 mL of TFE and 6 mL of CH_2Cl_2. The resin containing solution was filtered and dried *in vacuo* to yield the DDLP as a white solid (192 mg, overall 50%).
LC/MS (ESI): *m/z* called for $C_{44}H_{54}N_6O_6$ (M+1) = 763.41, found 763.35.

***Cyclo* Leu-*N*-Me-Val-3-(2'-Pyr)-D-Ala-D-Phe-3,3-Diphe-D-Ala (12)** was synthesized using 0.05 g of the DDLP generated (0.07 mmol, 1.0 equivalent), 0.02 g of TBTU (0.05 mmol, 0.80 equivalent), 0.02 g of HATU (0.05 mmol, 0.80 equivalent), 0.01 g of DMTMM (0.05 mmol, 0.80 equivalent), 0.09 mL of DIPEA (0.52 mmol, 8.0 equivalents) in anhydrous CH_2Cl_2 (65 mL, 0.001M) following "**Macrocyclization procedure (syringe pump)"** procedure. The reaction was then stirred overnight and the reaction was monitored via LC/MS. Upon completion, the reaction mixture was subjected to acid-base wash, which was extracted twice with 10% (v/v) $HCl_{(aq)}$. The organic layer was then re-extracted with a saturated of $NaHCO_3$ aqueous solution. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via flash column chromatography on silica gel using an ethyl acetate-hexane gradient system, followed by purification via HPLC to yield compound **12** as white solid (5 mg, 10%).
*Note: Due to the limited amount of compound, HSQC and HMBC spectra were used for the complete assignment of all the carbon peaks.
R_f: 0.39 (Hex:EtOAc = 0.25:0.75)
LC/MS: *m/z* called for $C_{44}H_{52}N_6O_5S$ (M+1) = 745.40, found 745.35.
HRMS (ESI-TOF): M+1, found 745.4065 $C_{44}H_{52}N_6O_5$ requires 745.3999.
^{1}H NMR (600 MHz, $CHCl_3$): δ 8.36 (br, D-Pyr), 8.01 (br, NH), 7.54 (br, NH), 7.24-7.08 (m, 17H, D-BiPhe, D-Phe, D-Pyr), 6.60 (br, 2NH), 5.38 (m, 1H, CHα D-BiPhe), 4.84 (dd, *J* = 6.9, 10.6 Hz, 1H, CHα D-Phe), 4.38 (d, *J* = 10.7 Hz, 1H, CHβ D-BiPhe), 4.11 (q, *J* = 8.1 Hz, 1H, CHα D-Pyr), 3.80 (m, 1H, CHα D-Val), 3.27 (dd, *J* = 8.3, 14.5 Hz, 1H, CHα Leu), 3.20 (dd, *J* = 4.6, 14.3 Hz, 1H, $CH_2\beta_2$ D-Phe), 3.06 (s, 3H, NCH_3, m, 1H, $CH_2\beta_1$ D-Phe), 2.88 (m, 1H, $CH_2\beta_2$ D-Pyr), 2.79 (m, 1H, $CH_2\beta_1$ D-Pyr), 2.45 (dd, *J* = 8.1, 14.3 Hz, 1H, CHβ Val), 1.48 (m, 1H, $CH_2\beta_2$ Leu), 1.37 (m, 1H, $CH_2\beta_1$ Leu), 0.85-0.66 (m, 13H, CHγ Leu, $CHCH(CH_3)_2$, $CH_2CH(CH_3)_2$).
^{13}C NMR (150 MHz, $CHCl_3$): δ 175.48, 172.99, 172.31, 170.41, 168.97, 157.09, 139.87, 139.62, 138.69, 130.14, 129.40, 129.08, 128.84, 128.71, 128.32, 128.26, 128.06, 127.38, 127.06, 126.24, 122.39, 79.18, 63.47, 59.56, 56.47, 52.05, 50.47, 40.31, 39.24, 38.17, 31.92, 27.63, 24.67, 22.21, 21.96, 19.75, 18.80.



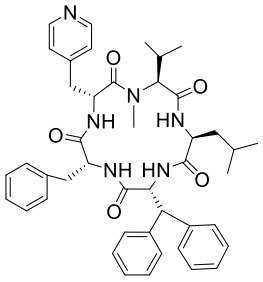
Compound 13

Following "**General peptide coupling"** procedure for SPPS and the published procedure for SPPS (Koay, Y. C.; McConnell, J. R.; Wang, Y.; Kim, S. J.; Buckton, L. K.; Mansour, F.; McAlpine, S. R. *ACS Med. Chem. Lett.* **2014**, *5*, 771-776), linear pentapeptide of resin-O-Leu-*N*-Me-Val-3-(3-pyridyl)-D-Ala-D-Phe-3,3-DiPhe-D-Ala-NH_2 was synthesized by using (0.5 mmol, 1.0 equivalent) of resin-O-Leu-NH_2 and the subsequent peptide coupling in the sequence using 1.5 mmol (3.0 equivalents) of each mentioned below: Fmoc-*N*-Me-Val-OH, Fmoc-3-(3-pyridyl)-D-Ala-OH, Fmoc-D-Phe-OH, and Fmoc-3,3-Diphenyl-D-Ala-OH. Each peptide coupling was done in the presence of HOAt (1.5 mmol, 3.0 equivalents) or HOBt (1.5 mmol, 3.0 equivalents), DIC (3.0 mmol, 6.0 equivalents) and DMF to generate a concentration of 0.20 M based on the amino acid. Each coupling

reaction was run for 3 hours and a negative ninhydrin test was used to confirm the reaction completion. The reaction mixture was drained to afford the Fmoc-protected resin-bound pentapeptide and the Fmoc protecting group was removed following the **"General Fmoc removal"** after the completion of each coupling reaction.

The double deprotected linear pentapeptide (DDLP) HO-Leu-*N*-Me-Val-3-(3-pyridyl)-D-Ala-D-Phe-3,3-DiPhe-D-Ala-NH_2 was generated following the **"Resin cleavage of linear peptide"** procedure for SPPS. The linear pentapeptide was cleaved from the resin using a mixed solution of 6 mL of TFE and 6 mL of CH_2Cl_2. The resin containing solution was filtered and dried *in vacuo* to yield the DDLP as a white solid (Yield 68%).
LC/MS (ESI): *m/z* called for $C_{44}H_{54}N_6O_6$ (M+1) = 763.40, found 763.00.

Cyclo **Leu-*N*-Me-Val-3-(3-pyridyl)-D-Ala-D-Phe-3,3-DiPhe-D-Ala (13)** was synthesized using the DDLP (1.0 equivalent), TBTU (0.80 equivalent), HATU (0.80 equivalent), DMTMM (0.80 equivalent), DIPEA (8.0 equivalents) in anhydrous CH_2Cl_2 (0.001M) following "**Macrocyclization procedure (syringe pump)"** procedure. The reaction was then stirred overnight and the reaction was monitored via LC/MS. Upon completion, the reaction mixture was subjected to acid-base wash, which was extracted twice with 10% (v/v) $HCl_{(aq)}$. The organic layer was then re-extracted with a saturated of $NaHCO_3$ aqueous solution. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via flash column chromatography on silica gel using an ethyl acetate-hexane gradient system, followed by purification via HPLC to yield compound **13** as white solid (Yield 60%).
R_f: 0.25 (Hex:EtOAc = 0.25:0.75)
LC/MS: *m/z* called for $C_{44}H_{52}N_6O_5$ (M+1) = 745.40, found 745.00.
HRMS (ESI-TOF): M+1, found 745.4075 $C_{44}H_{52}N_6O_5$ M+1 requires 745.3999
^{1}H NMR (300 MHz, DMSO): δ 8.53 (s, 2H, NH), 7.80 (d, *J*=7.80, 1H, Pyridyl), 7.55 (s, 1H, NH), 7.40-6.95 (m, 19H, D-BiPhe, D-Phe, Pyridyl, NH), 5.23 (d, *J*=11.32, 1H, CHα D-BiPhe), 4.77 (t, 1H, CHα Pyridyl), 4.66 (d, *J*=11.54, 1H, CHα Val), 4.49 (d, *J*=11.34, 1H, CHβ, D-BiPhe), 4.06 (m, 1H, CHα D-Phe), 3.87 (t, CHα Leu), 3.06 (m, 2H, CH_2β Pyridyl), 2.89 (m, 1H, $CH_2\beta_1$ D-Phe), 2.64 (m, 1H, $CH_2\beta_2$ D-Phe), 2.23 (m, 1H, CHβ Val), 1.54 (m, 2H, CH_2β Leu), 1.24 (m, CHβ Leu), 0.92-0.66 (m, 12H, CHCH(CH_3)$_2$, $CH_2CH(CH_3)_2$).
^{13}C NMR (125 MHz, DMSO): δ 171.44, 170.96, 170.65, 169.99, 141.99, 141.62, 140.08, 140.29, 136.77, 128.69, 128.60, 128.31, 128.25, 128.23, 128.09, 127.40, 127.13, 126.72, 126.55, 126.49, 126.06, 64.22, 57.59, 57.23, 53.12, 52.45, 51.51, 37.66, 36.88, 33.92, 29.68, 29.07, 24.74, 24.37, 24.10, 21.93, 21.28, 21.20, 20.49, 18.68, 18.50, 17.56, 16.63.



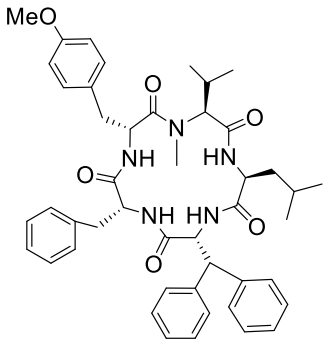
Compound 14

Following "**General peptide coupling"** procedure for SPPS and the published procedure for SPPS (Koay, Y. C.; McConnell, J. R.; Wang, Y.; Kim, S. J.; Buckton, L. K.; Mansour, F.; McAlpine, S. R. *ACS Med. Chem. Lett.* **2014**, *5*, 771-776), linear pentapeptide of resin-O-Leu-*N*-Me-Val-3-(4-pyridyl)-D-Ala-D-Phe-3,3-DiPhe-D-Ala-NH_2 was synthesized by using (0.5 mmol, 1.0 equivalent) of resin-O-Leu-NH_2 and the subsequent peptide coupling in the sequence using 1.5 mmol (3.0 equivalents) of each mentioned below: Fmoc-*N*-Me-Val-OH, Fmoc-3-(4-pyridyl)-D-Ala-OH, Fmoc-D-Phe-OH, and Fmoc-3,3-Diphenyl-D-Ala-OH. Each peptide coupling was done in the presence of HOAt (1.5 mmol, 3.0 equivalents) or HOBt (1.5 mmol, 3.0 equivalents), DIC (3.0 mmol, 6.0 equivalents) and DMF to generate a concentration of 0.20 M based on the amino acid. Each coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm the reaction completion. The reaction mixture was drained to afford the Fmoc-protected resin-bound pentapeptide and the Fmoc protecting group was removed following the **"General Fmoc removal"** after the completion of each coupling reaction.

The double deprotected linear pentapeptide (DDLP) HO-Leu-*N*-Me-Val-3-(4-pyridyl)-D-Ala-D-Phe-3,3-DiPhe-D-Ala-NH_2 was generated following the **"Resin cleavage of linear peptide"** procedure for SPPS. The linear pentapeptide was cleaved from the resin using a mixed solution of 6 mL of TFE and 6 mL of CH_2Cl_2. The resin containing solution was filtered and dried *in vacuo* to yield the DDLP as a white solid (Yield 78%).
LC/MS (ESI): *m/z* called for $C_{44}H_{54}N_6O_6$ (M+1) = 763.40, found 763.00.

Cyclo **Leu-*N*-Me-Val-3-(4-pyridyl)-D-Ala-D-Phe-3,3-DiPhe-D-Ala (14)** was synthesized using the DDLP (1.0 equivalent), TBTU (0.80 equivalent), HATU (0.80 equivalent), DMTMM (0.80 equivalent), DIPEA (8.0 equivalents) in anhydrous CH_2Cl_2 (0.001M) following "**Macrocyclization procedure (syringe pump)"** procedure. The reaction was then stirred overnight and the reaction was monitored via LC/MS. Upon completion, the reaction

mixture was subjected to acid-base wash, which was extracted twice with 10% (v/v) $HCl_{(aq)}$. The organic layer was then re-extracted with a saturated of $NaHCO_3$ aqueous solution. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via flash column chromatography on silica gel using an ethyl acetate-hexane gradient system, followed by purification via HPLC to yield compound **14** as white solid (Yield 38%).
R_f: 0.20 (Hex:EtOAc = 0.25:0.75)
LC/MS: *m/z* called for $C_{44}H_{52}N_6O_5$ (M+1) = 745.40, found 745.00.
HRMS (ESI-TOF): M+1, found 745.4075 $C_{44}H_{52}N_6O_5$ M+1 requires 745.3999
^{1}H NMR (600 MHz, DMSO): δ 8.37 (m, 2H, Pyridyl), 8.21 (d, *J*=8.35, 1H, NH), 8.12 (s, 1H, NH), 7.85 (d, *J*=10.57, 1H, NH), 7.67 (d, *J*=9.27, 1H, NH), 7.30-7.12 (m, 15H, D-BiPhe, D-Phe), 6.82 (m, 2H, Pyridyl), 5.16 (m, 1H, CHα Pyridyl), 4.77 (q, 1H, CHα D-Phe), 4.54 (d, *J*=11.53, 2H, CHα D-BiPhe, CHα Val), 4.35 (d, *J*=11.76, CHβ D-BiPhe), 4.04 (q, 1H, CHα Leu), 3.11 (m, 1H, $CH_2\beta_1$ Pyridyl), 2.81 (m, 1H, $CH_2\beta_2$ Pyridyl), 2.63 (m, 1H, $CH_2\beta_1$ D-Phe), 2.59 (s, 3H, NCH_3), 2.55 (m, 1H, $CH_2\beta_2$ D-Phe), 2.14 (m, 1H, CHβ Val), 1.47 (m, 1H, $CH_2\beta_1$ Leu), 1.36 (m, 1H, $CH_2\beta_2$ Leu), 1.20 (m, 1H, CHβ Leu), 0.83-0.58 (m, 12H, $CHCH(CH_3)_2$, $CH_2CH(CH_3)_2$).



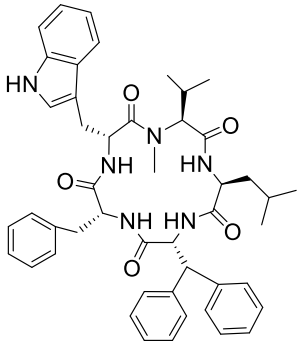
Compound 16

Following "**General peptide coupling"** procedure for SPPS and and the published procedure for SPPS (Koay, Y. C.; McConnell, J. R.; Wang, Y.; Kim, S. J.; Buckton, L. K.; Mansour, F.; McAlpine, S. R. *ACS Med. Chem. Lett.* **2014**, *5*, 771-776), linear pentapeptide of resin-O-Leu-*N*-Me-Val-D-Tyr(OMe)-D-Phe-3,3-Diphe-D-Ala-NH_2 was synthesized by using 1.00 g (0.5 mmol, 1.0 equivalent) of resin-O-Leu-NH_2 and the subsequent peptide coupling in the sequence as mentioned below: 0.53 g (1.5 mmol, 3.0 equivalents) of Fmoc-*N*-Me-Val-OH, 0.63 g (1.5 mmol, 3.0 equivalents) of Fmoc-D-Tyrosine-OMe, 0.58 g (1.5 mmol, 3.0 equivalents) of Fmoc-D-Phe-OH and 0.70 g (1.5 mmol, 3.0 equivalents) of Fmoc-3,3-Diphenyl-D-Ala-OH. Each peptide coupling was done in the presence of 0.20 g of HOAt (1.5 mmol, 3.0 equivalents) or 0.20 g of HOBt (1.5 mmol, 3.0 equivalents), 0.47 mL of DIC (3.0 mmol, 6.0 equivalents) and 2.5 mL of DMF to generate a concentration of 0.20 M. Each coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm the reaction completion. The reaction mixture was drained to afford the Fmoc-protected resin-bound pentapeptide and the Fmoc protecting group was removed following the **"General Fmoc removal"** after the completion of each coupling reaction.

The double deprotected linear pentapeptide (DDLP) HO-Leu-*N*-Me-Val-D-Tyr(OMe)-D-Phe-3,3-Diphe-D-Ala-NH_2 was generated following the **"Resin cleavage of linear peptide"** procedure for SPPS. The linear pentapeptide was cleaved from the resin using a mixed solution of 6 mL of TFE and 6 mL of CH_2Cl_2. The resin containing solution was filtered and dried *in vacuo* to yield the DDLP as a white solid (352 mg, overall 89%).
LC/MS (ESI): *m/z* called for $C_{46}H_{57}N_5O_7$ (M+1) = 792.43, found 792.50.

Cyclo **Leu-*N*-Me-Val-D-Tyr(OMe)-D-Phe-3,3-Diphe-D-Ala (16)** was synthesized using 0.35 g of the DDLP generated (0.44 mmol, 1.0 equivalent), 0.11 g of TBTU (0.35 mmol, 0.80 equivalent), 0.13 g of HATU (0.35 mmol, 0.80 equivalent), 0.10 g of DMTMM (0.35 mmol, 0.80 equivalent), 0.62 mL of DIPEA (3.5 mmol, 8.0 equivalents) in anhydrous CH_2Cl_2 (442 mL, 0.001M) following "**Macrocyclization procedure (syringe pump)"** procedure. The reaction was then stirred overnight and the reaction was monitored via LC/MS. Upon completion, the reaction mixture was subjected to acid-base wash, which was extracted twice with 10% (v/v) $HCl_{(aq)}$. The organic layer was then re-extracted with a saturated of $NaHCO_3$ aqueous solution. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via flash column chromatography on silica gel using an ethyl acetate-hexane gradient system, followed by purification via HPLC to yield compound **16** as white solid (120 mg, 27%).
R_f: 0.51 (EtOAc:Hex = 0.65:0.35)
LC/MS: *m/z* called for $C_{46}H_{55}N_5O_6$ (M+1) = 774.42, found 773.95.
HRMS (ESI-TOF): M+Na^+, found 796.4048 $C_{46}H_{55}N_5O_6Na_1$ requires 796.4050.
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, *J* = 9.1 Hz, NH), 7.33-6.97 (m, 17H, D-BiPhe, D-Phe, *O*-Me-D-Tyr), 6.86 (br, NH), 6.73 (d, *J* = 8.7 Hz, 1H, *O*-Me-D-Tyr), 6.65 (br, NH, 1H, *O*-Me-D-Tyr), 6.61 (d, *J* = 7.1 Hz, NH), 5.13 (t, *J* = 10.7 Hz, 1H, CHα D-BiPhe), 5.06 (m, 1H, CHα D-Phe), 4.62-4.57 (m, 3H, CHα *O*-Me-D-Tyr, CHα Val, CHβ D-BiPhe), 4.30 (br, 1H, CHα Leu), 3.69 (s, 3H, OCH_3), 3.47 (t, *J* = 12.2 Hz, 1H, $CH_2\beta_2$ *O*-Me-D-Tyr), 3.07 (m, 1H, $CH_2\beta_1$ *O*-Me-D-Tyr), 2.98 (m, 1H, $CH_2\beta_2$ D-Phe), 2.87 (m,1H, $CH_2\beta_1$ D-Phe), 2.75 (s, 3H, NCH_3), 1.99 (m, 1H, CHβ Val), 0.94-0.56 (m, 15H, $CH_2\beta$ Leu, CHγ Leu, $CHCH(CH_3)_2$, $CH_2CH(CH_3)_2$).

^{13}C NMR (125 MHz, DMSO): δ 172.70, 172.53, 172.25, 171.28, 169.84, 158.65, 140.37, 140.05, 136.62, 130.42, 129.06, 128.83, 128.71, 128.63, 128.57, 128.30, 127.86, 127.24, 127.00, 126.52, 114.05, 62.40, 57.36, 56.22, 55.30, 55.23, 54.54, 50.58, 37.82, 35.31, 30.62, 30.35, 26.19, 24.71, 22.70, 22.24, 19.78, 19.30.

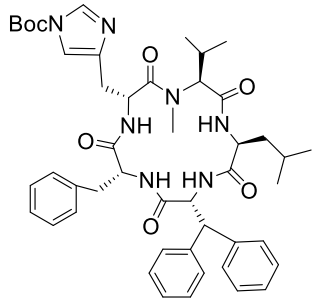


Compound 17

Following "**General peptide coupling"** procedure for SPPS and the published procedure for SPPS (Koay, Y. C.; McConnell, J. R.; Wang, Y.; Kim, S. J.; Buckton, L. K.; Mansour, F.; McAlpine, S. R. *ACS Med. Chem. Lett.* **2014**, *5*, 771-776), linear pentapeptide of resin-O-Leu-*N*-Me-Val-*N*-Boc-D-Trp-D-Phe-3,3-Diphe-D-Ala-NH_2 was synthesized by using 1.00 g (0.5 mmol, 1.0 equivalent) of resin-O-Leu-NH_2 and the subsequent peptide coupling in the sequence as mentioned below: 0.53 g (1.5 mmol, 3.0 equivalents) of Fmoc-*N*-Me-Val-OH, 0.79 g (1.5 mmol, 3.0 equivalents) of Fmoc-*N*-Boc-D-Tryptophan-OH, 0.58 g (1.5 mmol, 3.0 equivalents) of Fmoc-D-Phe-OH and 0.70 g (1.5 mmol, 3.0 equivalents) of Fmoc-3,3-Diphenyl-D-Ala-OH. Each peptide coupling was done in the presence of 0.20 g of HOAt (1.5 mmol, 3.0 equivalents) or 0.20 g of HOBt (1.5 mmol, 3.0 equivalents), 0.47 mL of DIC (3.0 mmol, 6.0 equivalents) and 2.5 mL of DMF to generate a concentration of 0.20 M. Each coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm the reaction completion. The reaction mixture was drained to afford the Fmoc-protected resin-bound pentapeptide and the Fmoc protecting group was removed following the **"General Fmoc removal"** after the completion of each coupling reaction.

The double deprotected linear pentapeptide (DDLP) HO-Leu-*N*-Me-Val-*N*-Boc-D-Trp-D-Phe-3,3-Diphe-D-Ala-NH_2 was generated following the **"Resin cleavage of linear peptide"** procedure for SPPS. The linear pentapeptide was cleaved from the resin using a mixed solution of 6 mL of TFE and 6 mL of CH_2Cl_2. The resin containing solution was filtered and dried *in vacuo* to yield the DDLP as a white solid (315 mg, overall 70%).
LC/MS (ESI): *m/z* called for $C_{52}H_{64}N_6O_8$ (M+1) = 901.48, found 901.60.

Cyclo **Leu-*N*-Me-Val-*N*-Boc-D-Trp-D-Phe-3,3-Diphe-D-Ala** was synthesized using 0.32 g of the DDLP generated (0.35 mmol, 1.0 equivalent), 0.09 g of TBTU (0.28 mmol, 0.80 equivalent), 0.11 g of HATU (0.28 mmol, 0.80 equivalent), 0.08 g of DMTMM (0.28 mmol, 0.80 equivalent), 0.49 mL of DIPEA (2.8 mmol, 8.0 equivalents) in anhydrous CH_2Cl_2 (350 mL, 0.001M) following "**Macrocyclization procedure (syringe pump)"** procedure. The reaction was then stirred overnight and the reaction was monitored via LC/MS. Upon completion, the reaction mixture was subjected to acid-base wash, which was extracted twice with 10% (v/v) $HCl_{(aq)}$. The organic layer was then re-extracted with a saturated of $NaHCO_3$ aqueous solution. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via flash column chromatography on silica gel using an ethyl acetate-hexane gradient system, followed by purification via HPLC. The Boc protecting group was removed following **"Boc removal"** procedure, utilizing a mixture of TFA/CH_2Cl_2 (1:4, 0.1 M) and anisole (2.0 equivalents) to yield compound **17** as white solid (45 mg, 15%).
R_f: 0.38 (EtOAc:Hex = 0.65:0.35)
LC/MS: *m/z* called for $C_{47}H_{54}N_6O_5$ (M+1) = 783.42, found 782.95.
HRMS (ESI-TOF): M+Na^+, found 805.4037 $C_{47}H_{54}N_6O_5Na_1$ requires 805.4156.
^{1}H NMR (600 MHz, DMSO): δ 10.77 (s, NH, D-Trp), 8.10 (t, *J* = 7.5 Hz, NH), 7.79 (d, *J* = 7.4 Hz, NH), 7.57 (d, *J* = 7.9 Hz, NH), 7.51 (d, *J* = 9.6 Hz, NH), 7.30-6.97 (m, 19H, D-BiPhe, D-Phe, D-Trp), 6.86 (m, 1H, D-Trp), 5.18 (dd, *J* = 9.7, 11.8 Hz, 1H, CHα D-BiPhe), 4.84 (m, 1H, CHα D-Phe), 4.52 (d, *J* = 11.3 Hz, 1H, CHα Val), 4.30 (d, *J* = 11.9 Hz, 1H, CHβ D-BiPhe), 4.05 (m, 1H, CHα D-Trp), 3.47 (q, *J* = 7.4 Hz, 1H, CHα Leu), 3.24 (m, 1H, $CH_2\beta_2$ D-Phe), 2.87 (m, 1H, $CH_2\beta_1$ D-Phe), 2.70 (m, 1H, $CH_2\beta_2$ D-Trp), 2.62 (m, 1H, $CH_2\beta_1$ D-Trp), 2.55 (s, 3H, NCH_3), 2.05 (m, 1H, CHβ Val), 1.46 (m, 1H, $CH_2\beta_2$ Leu), 1.39 (m, 1H, $CH_2\beta_1$ Leu), 1.22 (m, 1H, CHγ Leu), 0.79-0.52 (m, 12H, $CHCH(C\underline{H}_3)_2$, $CH_2CH(C\underline{H}_3)_2$).
^{13}C NMR (150 MHz, DMSO): δ 170.84, 170.63, 170.00, 169.89, 169.08, 141.70, 141.07, 137.52, 136.40, 129.32, 128.87, 128.81, 128.75, 128.56, 128.44, 128.15, 127.15, 126.95, 126.82, 123.74, 121.30, 118.88, 118.67, 111.70, 110.76, 63.36, 57.23, 53.73, 52.00, 50.44, 49.06, 40.51, 38.12, 37.50, 30.20, 24.51, 22.87, 22.54, 22.07, 19.67, 18.91.

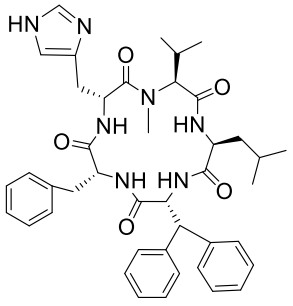


Compound 18

Following "**General peptide coupling"** procedure for SPPS and the published procedure for SPPS (Koay, Y. C.; McConnell, J. R.; Wang, Y.; Kim, S. J.; Buckton, L. K.; Mansour, F.; McAlpine, S. R. *ACS Med. Chem. Lett.* **2014**, *5*, 771-776), linear pentapeptide of resin-O-Leu-*N*-Me-Val-D-Leu-D-His(Boc)-3,3-Diphenyl-D-Ala-NH_2 was synthesized by using 1.00 g (0.5 mmol, 1.0 equivalent) of resin-O-Leu-NH_2 and the subsequent peptide coupling in the sequence as mentioned below: 0.53 g (1.5 mmol, 3.0 equivalents) of Fmoc-*N*-Me-Val-OH, 0.72 g (1.5 mmol, 3.0 equivalents) of Fmoc-D-His(Boc)-OH, 0.58 g (1.5 mmol, 3.0 equivalents) of Fmoc-D-Phe-OH and 0.70 g (1.5 mmol, 3.0 equivalents) of Fmoc-3,3-Diphenyl-D-Ala-OH. Each peptide coupling was done in the presence of 0.20 g of HOAt (1.5 mmol, 3.0 equivalents) or 0.20 g of HOBt (1.5 mmol, 3.0 equivalents), 0.47 mL of DIC (3.0 mmol, 6.0 equivalents) and 2.5 mL of DMF to generate a concentration of 0.20 M. Each coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm the reaction completion. The reaction mixture was drained to afford the Fmoc-protected resin-bound pentapeptide and the Fmoc protecting group was removed following the **"General Fmoc removal"** after the completion of each coupling reaction.

The double deprotected linear pentapeptide (DDLP) HO-Leu-*N*-Me-Val-D-His(Boc)-D-Phe-3,3-Diphe-D-Ala-NH_2 was generated following the **"Resin cleavage of linear peptide"** procedure for SPPS. The linear pentapeptide was cleaved from the resin using a mixed solution of 6 mL of TFE and 6 mL of CH_2Cl_2. The resin containing solution was filtered and dried *in vacuo* to yield the DDLP as a white solid (264 mg, overall 62%).
LC/MS (ESI): *m/z* called for $C_{47}H_{61}N_7O_8$ (M+1) = 852.46, found 852.55.

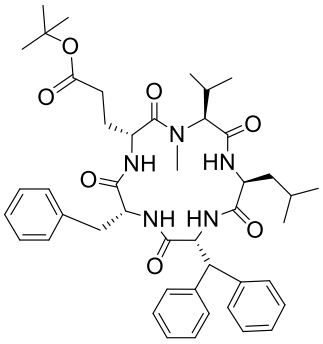
***Cyclo* Leu-*N*-Me-Val-D-His(Boc)-D-Phe-3,3-Diphe-D-Ala (18)** was synthesized using 0.26 g of the DDLP generated (0.31 mmol, 1.0 equivalent), 0.08 g of TBTU (0.25 mmol, 0.80 equivalent), 0.09 g of HATU (0.25 mmol, 0.80 equivalent), 0.07 g of DMTMM (0.25 mmol, 0.80 equivalent), 0.43 mL of DIPEA (2.5 mmol, 8.0 equivalents) in anhydrous CH_2Cl_2 (310 mL, 0.001M) following "**Macrocyclization procedure (syringe pump)"** procedure. The reaction was then stirred overnight and the reaction was monitored via LC/MS. Upon completion, the reaction mixture was subjected to acid-base wash, which was extracted twice with 10% (v/v) $HCl_{(aq)}$. The organic layer was then re-extracted with a saturated of $NaHCO_3$ aqueous solution. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via flash column chromatography on silica gel using an ethyl acetate-hexane gradient system, followed by purification via HPLC to yield compound **18** as white solid (51 mg, 20%).
R_f: 0.40 (EtOAc:MeOH = 0.95:0.05)
LC/MS: *m/z* called for $C_{47}H_{59}N_7O_7$ ($M+Na^+$) = 856.45, found 856.44.
HRMS (ESI-TOF): M+1, found 834.4559 $C_{47}H_{59}N_7O_7$ requires 833.4476.
^{1}H NMR (600 MHz, DMSO): δ 8.12 (s, D-His), 8.07 (d, *J* = 1.2 Hz, 2NH), 7.82 (d, *J* = 7.5 Hz, NH), 7.54 (d, *J* = 9.4 Hz, NH), 7.27-7.16 (m, 14H, D-BiPhe, D-Phe, D-His), 6.84 (m, 2H, D-Phe), 5.17 (dd, *J* = 9.6, 11.8 Hz, 1H, CHα D-Biphe), 4.82 (q, *J* = 7.6 Hz, 1H, CHα D-Phe), 4.55 (d, *J* = 11.5 Hz, 1H, CHα Val), 4.31 (d, *J* = 11.8 Hz, 1H, CHβ D-Phe) 4.03 (m, *J* = 7.5 Hz, 1H CHα D-His), 3.53 (q, *J* = 7.4 Hz, 1H, CHα Leu), 3.02 (m, 1H, $CH_2\beta_2$ D-Phe), 2.77 (m, 1H, $CH_2\beta_1$ D-Phe), 2.69 (m, 1H, $CH_2\beta_2$ D-His), 2.64 (s, 3H, NCH_3), 2.55 (m, 1H, $CH_2\beta_1$ D-His), 2.15 (m, 1H, CHβ Val), 1.53 (s, 9H, t-Bu D-His), 1.47 (m, 1H, $CH_2\beta_2$ Leu), 1.39 (m, 1H, $CH_2\beta_1$ Leu), 1.23 (m, 1H, CHγ Leu), 0.82-0.63 (m, 12H, $CH_2CH(CH_3)_2$, $CHCH(CH_3)_2$).
^{13}C NMR (150 MHz, DMSO): δ 170.38, 170.28, 170.00, 169.95, 168.89, 147.17, 141.71, 141.01, 140.28, 137.51, 136.74, 129.18, 129.02, 128.84, 128.72, 128.59, 128.44, 127.14, 126.84, 126.81, 114.31, 85.46, 63.41, 57.20, 56.84, 53.69, 51.88, 49.26, 40.52, 38.11, 37.67, 30.29, 27.82, 25.25, 24.53, 22.81, 22.57, 19.69, 18.79.



Compound 19

The Boc protecting group of compound **18** was removed following **"Boc removal"** procedure, utilizing a mixture of TFA/CH_2Cl_2 (1:4, 0.1 M) and anisole (2.0 equivalents) to generate compound **19**. The free amine was taken to the subsequent biotinylation reaction without purification.
R_f: 0.63 (EtOAc:MeOH = 1:1)
LC/MS: *m/z* called for $C_{42}H_{51}N_7O_5$ (M+1) = 734.40, found 734.40.
HRMS (ESI-TOF): M+1, found 734.4023 $C_{42}H_{51}N_7O_5$ requires 733.3952.
^{1}H NMR (600 MHz, DMSO): δ 8.83 (s, D-His), 8.25 (d, *J* = 8.5 Hz, NH), 8.08 (d, *J* = 8.3 Hz, NH), 7.90 (d, *J* = 7.7 Hz, NH), 7.63 (d, *J* = 9.5 Hz, NH), 7.26-7.16 (m, 14H, D-BiPhe, D-Phe, D-His), 6.85 (m, 2H, D-Phe), 5.17 (t, *J* = 10.7 Hz, 1H, CHα D-Biphe), 4.81 (q, *J* = 7.5 Hz, 1H, CHα D-Phe), 4.58 (d, *J* = 11.6 Hz, 1H, CHα Val), 4.33 (d, *J* =

11.8 Hz, 1H, CHβ D-Phe) 4.08 (q, *J* = 7.5 Hz, 1H, CHα D-His), 3.62 (q, *J* = 7.5 Hz, 1H, CHα Leu), 3.08 (dd, *J* = 6.2, 15.1 Hz, 1H, $CH_2\beta_2$ D-Phe), 2.87 (dd, *J* = 7.7, 15.1 Hz, 1H, $CH_2\beta_1$ D-Phe), 2.69 (m, 1H, $CH_2\beta_2$ D-His), 2.62 (s, 3H, NCH_3), 2.53 (m, 1H, $CH_2\beta_1$ D-His), 2.20 (m, 1H, CHβ Val), 1.48 (m, 1H, $CH_2\beta_2$ Leu), 1.36 (m, 1H, $CH_2\beta_1$ Leu), 1.20 (m, 1H, CHγ Leu), 0.83-0.61 (m, 12H, $CH_2CH(CH_3)_2$, $CHCH(CH_3)_2$).
^{13}C NMR (150 MHz, DMSO): δ 170.51, 170.01, 169.89, 169.58, 168.59, 141.71, 141.06, 137.42, 133.95, 130.76, 129.10, 128.81, 128.79, 128.69, 128.56, 128.46, 127.12, 126.91, 126.84, 117.02, 63.78, 57.26, 56.32, 53.64, 51.66, 49.37, 40.51, 38.19, 37.84, 30.31, 25.00, 24.47, 22.72, 22.63, 19.70, 18.72.

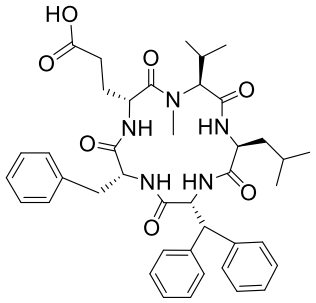


Compound 20

Following "**General peptide coupling"** procedure for SPPS and the published procedure for SPPS (Koay, Y. C.; McConnell, J. R.; Wang, Y.; Kim, S. J.; Buckton, L. K.; Mansour, F.; McAlpine, S. R. *ACS Med. Chem. Lett.* **2014**, *5*, 771-776), linear pentapeptide of resin-O-Leu-*N*-Me-Val-D-Glu(OtBu)-D-Phe-3,3-Diphe-D-Ala-NH_2 was synthesized by using 1.00 g (0.5 mmol, 1.0 equivalent) of resin-O-Leu-NH_2 and the subsequent peptide coupling in the sequence as mentioned below: 0.53 g (1.5 mmol, 3.0 equivalents) of Fmoc-*N*-Me-Val-OH, 0.64 g (1.5 mmol, 3.0 equivalents) of Fmoc-D-Glu-γ-OtBu, 0.58 g (1.5 mmol, 3.0 equivalents) of Fmoc-D-Phe-OH and 0.70 g (1.5 mmol, 3.0 equivalents) of Fmoc-3,3-Diphenyl-D-Ala-OH. Each peptide coupling was done in the presence of 0.20 g of HOAt (1.5 mmol, 3.0 equivalents) or 0.20 g of HOBt (1.5 mmol, 3.0 equivalents), 0.47 mL of DIC (3.0 mmol, 6.0 equivalents) and 2.5 mL of DMF to generate a concentration of 0.20 M. Each coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm the reaction completion. The reaction mixture was drained to afford the Fmoc-protected resin-bound pentapeptide and the Fmoc protecting group was removed following the **"General Fmoc removal"** after the completion of each coupling reaction.

The double deprotected linear pentapeptide (DDLP) HO-Leu-*N*-Me-Val-D-Glu(OtBu)-D-Phe-3,3-Diphe-D-Ala-NH_2 was generated following the **"Resin cleavage of linear peptide"** procedure for SPPS. The linear pentapeptide was cleaved from the resin using a mixed solution of 6 mL of TFE and 6 mL of CH_2Cl_2. The resin containing solution was filtered and dried *in vacuo* to yield the DDLP as a white solid (260 mg, overall 65%).
LC/MS (ESI): *m/z* called for $C_{45}H_{61}N_5O_8$ (M+1) = 800.45, found 800.35.

Cyclo **Leu-*N*-Me-Val-D-Glu(OtBu)-D-Phe-3,3-Diphe-D-Ala (20)** was synthesized using 0.26 g of the DDLP generated (0.33 mmol, 1.0 equivalent), 0.08 g of TBTU (0.26 mmol, 0.80 equivalent), 0.10 g of HATU (0.26 mmol, 0.80 equivalent), 0.07 g of DMTMM (0.26 mmol, 0.80 equivalent), 0.45 mL of DIPEA (2.6 mmol, 8.0 equivalents) in anhydrous CH_2Cl_2 (325 mL, 0.001M) following "**Macrocyclization procedure (syringe pump)"** procedure. The reaction was then stirred overnight and the reaction was monitored via LC/MS. Upon completion, the reaction mixture was subjected to acid-base wash, which was extracted twice with 10% (v/v) $HCl_{(aq)}$. The organic layer was then re-extracted with a saturated of $NaHCO_3$ aqueous solution. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via flash column chromatography on silica gel using an ethyl acetate-hexane gradient system, followed by purification via HPLC to yield compound **20** as white solid (60 mg, 24%).
R_f: 0.63 (Hex:EtOAc = 0.25:0.75)
LC/MS: *m/z* called for $C_{45}H_{59}N_5O_7$ (M+1) = 782.44, found 782.15.
HRMS (ESI-TOF): $M+Na^+$, found 804.4309 $C_{45}H_{59}N_5O_7Na_1$ requires 804.4414.
^{1}H NMR (600 MHz, DMSO): δ 8.01 (br, 2NH), 7.88 (d, *J* = 7.4 Hz, NH), 7.55 (d, *J* = 9.3 Hz, NH), 7.31-7.15 (m, 13H, D-Biphe, D-Phe), 6.92 (m, 2H, D-Phe), 5.19 (t, *J* = 10.7 Hz, 1H, CHα D-Biphe), 4.59 (d, *J* = 11.5 Hz, 1H, CHα Val), 4.44 (q, *J* = 7.3 Hz, 1H, CHα D-Glu), 4.31 (d, *J* = 11.9 Hz, 1H, CHβ D-Biphe), 4.16 (m, 1H, CHα D-Phe), 3.55 (q, *J* = 7.4 Hz, 1H, CHα Leu), 2.75 (m, 2H, $CH_2\beta$ D-Phe), 2.59 (s, 3H, NCH_3), 2.20 (m, 1H, CHβ Val), 2.03 (t, *J* = 7.6 Hz, 2H, $CH_2\gamma$ D-Glu), 1.90 (m, 1H, $CH_2\beta_2$ D-Glu), 1.70 (m, 1H, $CH_2\beta_1$ D-Glu), 1.41 (m, 11H, $CH_2\beta$ Leu, $OC(CH_3)_3$), 1.22 (m, 1H, CHγ Leu), 0.83-0.62 (m, 12H, $CH_2CH(CH_3)_2$, $CHCH(CH_3)_2$).
^{13}C NMR (150 MHz, DMSO): δ 172.34, 172.21, 170.25, 170.13, 169.77, 168.77, 141.72, 141.09, 137.20, 129.35, 128.80, 128.70, 128.60, 128.45, 128.10, 127.17, 127.03, 126.83, 79.95, 63.39, 57.27, 56.29, 53.75, 51.68, 49.20, 38.11, 37.85, 31.82, 30.16, 28.24, 27.28, 25.18, 24.49, 22.82, 22.55, 19.66, 18.07.



Compound 21

The tBu protecting group of compound **20** was removed following **"*Tert*-butyl group (tBu) Removal"** procedure, utilizing a mixture of TFA/CH_2Cl_2 (2:4, 0.1 M) and anisole (2.0 equivalents) to generate compound **21**. The free acid was taken to the subsequent methyl ester formation without purification.

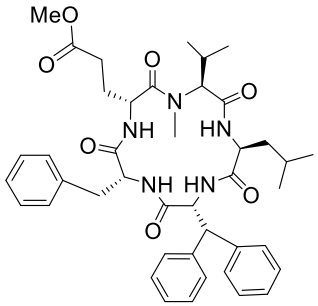
R_f: 0.30 (100% EtOAc)

LC/MS: *m/z* called for $C_{41}H_{51}N_5O_7$ (M+1) = 726.38, found 726.10.

HRMS (ESI-TOF): M+Na^+, found 748.3679 $C_{41}H_{51}N_5O_7Na_1$ requires 748.3788.

^{1}H NMR (600 MHz, DMSO): δ 8.08 (br, 2NH), 7.93 (br, NH), 7.62 (br, NH), 7.30-7.13 (m, 13H, D-Biphe, D-Phe), 6.91 (m, 2H, D-Phe), 5.17 (t, *J* = 10.8 Hz, 1H, CHα D-Biphe), 4.59 (d, *J* = 11.4 Hz, 1H, CHα Val), 4.49 (m, 1H, CHα D-Glu), 4.31 (d, *J* = 11.9 Hz, 1H, CHβ D-Biphe), 4.16 (q, *J* = 7.5 Hz, 1H, CHα D-Phe), 3.48 (m, 1H, CHα Leu), 2.76 (m, 1H, $CH_2\beta_1$ D-Phe), 2.65 (m, 1H, $CH_2\beta_2$ D-Phe), 2.59 (s, 3H, NCH_3), 2.15 (m, 1H, CHβ Val), 2.09 (m, 2H, $CH_2\gamma$ D-Glu), 1.95 (m, 1H, $CH_2\beta_1$ D-Glu), 1.76 (m, 1H, $CH_2\beta_2$ D-Glu), 1.47 (m, 1H, $CH_2\beta_1$ Leu), 1.39 (m, 1H, $CH_2\beta_2$ Leu), 1.23 (m, 1H, CHγ Leu), 0.83-0.63 (m, 12H, $CH_2CH(CH_3)_2$, $CHCH(CH_3)_2$).

^{13}C NMR (150 MHz, DMSO): δ 174.96, 171.78, 170.54, 169.93, 169.77, 168.79, 141.76, 141.07, 137.37, 129.28, 128.84, 128.80, 128.57, 128.39, 128.09, 127.13, 126.97, 126.78, 63.20, 57.35, 56.39, 53.77, 51.81, 49.34, 38.00, 37.94, 30.16, 29.77, 27.42, 25.22, 24.50, 22.87, 22.53, 19.70, 18.82.



Compound 22

The free acid of compound **21** was converted to the methyl ester compound **22** using the methylating agent Trimethylsilyl diazomethane (TMSD) in a mixture of anhydrous benzene and methanol (3:1) in a round bottom flask to make a 0.1 M solution. The methylating agent TMSD (2.0 M in diethyl ether) was added drop-wise into the reaction mixture became slightly yellow. The reaction was stirred under nitrogen and monitored by thin layer chromatography (TLC). Upon completion, the solvent was evaporated *in vacuo* and resulting compound **22**.

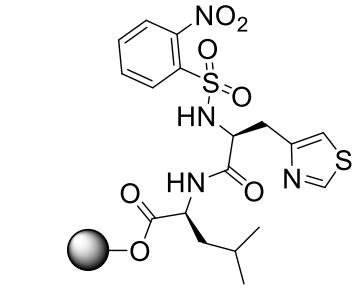
R_f: 0.33 (Hex:EtOAc = 0.25:0.75)

LC/MS: *m/z* called for $C_{42}H_{53}N_5O_7$ (M+1) = 740.39, found 740.00.

HRMS (ESI-TOF): M+Na^+, found 762.3831 $C_{42}H_{53}N_5O_7Na$ requires 762.3945.

^{1}H NMR (600 MHz, DMSO): δ 8.33 (br, NH), 8.22 (br, NH), 7.93 (br, 2NH), 7.29-7.14 (m, 13H, D-Biphe, D-Phe), 6.93 (m, 2H, D-Phe), 5.15 (t, *J* = 10.7 Hz, 1H, CHα D-Biphe), 4.57 (d, *J* = 11.4 Hz, 1H, CHα Val), 4.45 (q, *J* = 7.3 Hz, 1H, CHα D-Glu), 4.33 (d, *J* = 11.9 Hz, 1H, CHβ D-Biphe), 4.18 (q, *J* = 7.4 Hz, 1H, CHα D-Phe), 3.59 (s, 3H, OCH_3), 3.44 (m, 1H, CHα Leu), 2.77 (m, 1H, $CH_2\beta_2$ D-Phe), 2.66 (m, 1H, $CH_2\beta_1$ D-Phe), 2.55 (s, 3H, NCH_3), 2.14 (m, 3H, CHβ Val, $CH_2\gamma$ D-Glu), 1.92 (m, 1H, $CH_2\beta_2$ D-Glu), 1.73 (m, 1H, $CH_2\beta_1$ D-Glu), 1.45 (m, 1H, $CH_2\beta_2$ Leu), 1.40 (m, 1H, $CH_2\beta_1$ Leu), 1.22 (m, 1H, CHγ Leu), 0.82-0.61 (m, 12H, $CH_2CH(CH_3)_2$, $CHCH(CH_3)_2$).

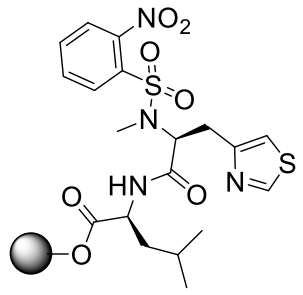
^{13}C NMR (150 MHz, DMSO): δ 173.54, 170.62, 170.22, 169.89, 169.73, 168.63, 141.80, 141.09, 137.39, 129.29, 128.81, 128.77, 128.57, 128.44, 128.33, 127.07, 126.93, 126.73, 63.14, 57.54, 56.26, 53.79, 51.84, 51.72, 49.20, 38.01, 37.91, 30.23, 30.12, 27.11, 25.18, 24.49, 22.86, 22.54, 19.72, 18.71.



Resin-O-Leu-3-(4-Thia)Ala-NH-o-NBS

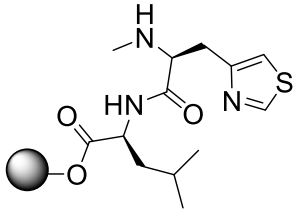
Dipeptide resin-O-Leu-3-(4-Thia)Ala-Fmoc was synthesized following "**General peptide coupling"** procedure, by using 1.00 g (0.5 mmol, 1.0 equivalent) of resin-O-Leu-NH_2, 0.59 g (1.5 mmol, 3.0 equivalents) of Fmoc-3-(4-Thiazoyl)Ala-OH, 0.20 g of HOBt (1.5 mmol, 3.0 equivalents), 0.47 mL of DIC (3.0 mmol, 6.0 equivalents) and 2.5 mL of DMF to generate a concentration of 0.20 M and the Fmoc group was removed following the **"General Fmoc removal"** procedure for SPPS. *o*-NBS protected resin-bound dipeptide was synthesized following the **"*o*-NBS Protection"** procedure, by using 0.44 g of *o*-NBS-Cl (2.0 mmol, 4 equivalents) and 0.65 mL of collidine (5.0 mmol, 10 equivalents) and 17 mL of CH_2Cl_2 to generate a concentration of 0.03 M.

LC/MS (ESI): *m/z* called for $C_{18}H_{22}N_4O_7S_2$ (M+1) = 471.09, found 471.55.



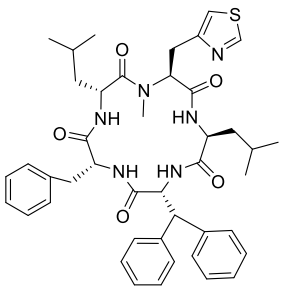
Resin-O-Leu-3-(4-Thia)Ala-NCH$_3$-o-NBS

A solution of 0.66 g of triphenylphosphine (2.5 mmol, 5 equivalents) and 0.20 mL of MeOH (10 equivalents) in dry THF was added to the resin bound *o*-NBS-protected peptides and stirred for 10 mins. A solution of 0.49 mL DIAD (5 equivalents) in dry THF was then added portion by portion to the reaction mixture and stirred for 4 hours at room temperature. The resin was filtered off, and washed with DMF (5x). *N*-Methyl-*N*-*o*-NBS-peptides were then cleaved from resin by treatment of a small amount of resin with TFE:CH_2Cl_2 (1:1) and analyzed by LCMS to monitor the reaction completion to generate resin-O-Leu-3-(4-Thia)Ala-NCH$_3$-*o*-NBS.
LC/MS (ESI): *m/z* called for $C_{19}H_{24}N_4O_7S_2$ (M+1) = 485.11, found 485.60.



Resin-O-Leu-3-(4-Thia)Ala-NH-CH$_3$

For *o*-NBS deprotection, the resin-bound *N*-Methyl-*N*-*o*-NBS-peptides was treated with a solution of 0.35 mL mercaptoethanol (10 equivalents) and 0.37 mL DBU (5 equivalents) in DMF for 2 hours. The deprotection procedure was repeated one more time and the resin was washed with DMF (5x) to generate resin-O-Leu-3-(4-Thia)Ala-NH-CH$_3$.
LC/MS (ESI): *m/z* called for $C_{13}H_{21}N_3O_3S$ (M+1) = 300.13, found 300.20.



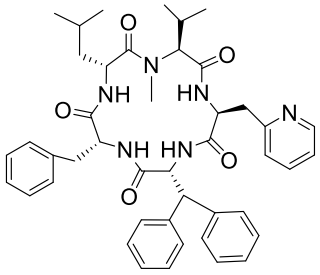
Compound 23

Following "**General peptide coupling"** and published procedure for SPPS (Koay, Y. C.; McConnell, J. R.; Wang, Y.; Kim, S. J.; Buckton, L. K.; Mansour, F.; McAlpine, S. R. *ACS Med. Chem. Lett.* **2014**, *5*, 771-776), linear pentapeptide of resin-O-Leu-*N*-Me-3-(4-Thia)Ala-D-Leu-D-Phe-3,3-Diphe-D-Ala-NH$_2$ was synthesized by using resin-O-Leu-3-(4-Thia)Ala-NH-CH$_3$ and the subsequent peptide coupling in the sequence as mentioned below: 0.53 g (1.5 mmol, 3.0 equivalents) of Fmoc-D-Leu-OH, 0.58 g (1.5 mmol, 3.0 equivalents) of Fmoc-D-Phe-OH and 0.70 g (1.5 mmol, 3.0 equivalents) of Fmoc-3,3-Diphe-D-Ala-OH. Each peptide coupling was done in the presence of 0.20 g of HOAt (1.5 mmol, 3.0 equivalents) or 0.20 g of HOBt (1.5 mmol, 3.0 equivalents), 0.47 mL of DIC (3.0 mmol, 6.0 equivalents) and 2.5 mL of DMF to generate a concentration of 0.20 M. Each coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm the reaction completion. The reaction mixture was drained to afford the Fmoc-protected resin-bound pentapeptide and the Fmoc protecting group was removed following the **"General Fmoc removal"** after the completion of each coupling reaction.

The double deprotected linear pentapeptide (DDLP) HO-Leu-*N*-Me-3-(4-Thia)Ala-D-Leu-D-Phe-3,3-Diphe-D-Ala-NH$_2$ was generated following the **"Resin cleavage of linear peptide"** procedure for SPPS. The linear pentapeptide was cleaved from the resin using a mixed solution of 6 mL of TFE and 6 mL of CH_2Cl_2. The resin containing solution was filtered and dried *in vacuo* to yield the DDLP as a white solid (301 mg, overall 77%).
LC/MS (ESI): *m/z* called for $C_{43}H_{54}N_6O_6S$ (M+1) = 783.39, found 783.45.

***Cyclo* Leu-*N*-Me-3-(4-Thia)Ala-D-Leu-D-Phe-3,3-Diphe-D-Ala (23)** was synthesized using 0.30 g of the DDLP generated (0.38 mmol, 1.0 equivalent), 0.10 g of TBTU (0.31 mmol, 0.8 equivalent), 0.12 g of HATU (0.31 mmol, 0.8 equivalent), 0.09 g of DMTMM (0.31 mmol, 0.80 equivalent), 0.55 mL of DIPEA (3.13 mmol, 8.0 equivalents) in anhydrous CH_2Cl_2 (391 mL, 0.001M) following "**Macrocyclization procedure (syringe pump)"** procedure. The reaction was then stirred overnight and the reaction was monitored via LC/MS. Upon completion, the reaction mixture was subjected to acid-base wash, which was extracted twice with 10% (v/v) $HCl_{(aq)}$. The organic layer was then re-extracted with a saturated of $NaHCO_3$ aqueous solution. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via flash column chromatography on silica gel using an ethyl acetate-hexane gradient system, followed by purification via HPLC to yield compound **23** as white solid (95 mg, 32%).
R_f: 0.28 (100% EtOAc)
LC/MS: *m/z* called for $C_{43}H_{52}N_6O_5S_1$ (M+1) = 765.37, found 765.00.
HRMS (ESI-TOF): M+Na$^+$, found 787.3616 $C_{43}H_{52}N_6O_5S_1Na_1$ requires 787.3618.

^{1}H NMR (600 MHz, DMSO): δ 8.99 (d, *J* = 1.8 Hz, 1H, D-Thia), 8.04 (d, *J* = 6.6 Hz, NH), 7.88 (d, *J* = 8.1 Hz, NH), 7.80 (d, *J* = 9.1 Hz, NH), 7.64 (d, *J* = 6.3 Hz, NH), 7.26-7.13 (m, 15H, D-Phe, D-BiPhe), 6.94 (m, 1H, D-Thia), 5.43 (dd, *J* = 6.1, 10.2 Hz, 1H, CHα D-Phe), 5.07 (dd, *J* = 9.3, 11.7 Hz, 1H, CHα D-Biphe), 4.32 (m, 2H, CHβ D-Biphe, CHα Leu), 3.99 (m, 1H, CHα Thia), 3.70 (q, *J* = 7.0 Hz, 1H, CHα D-Leu), 3.09 (dd, *J* = 10.2, 15.0 Hz, 1H, $CH_2\beta_2$ D-Phe), 3.00 (m, 1H, $CH_2\beta_2$ Thia), 2.81 (s, 3H, NCH_3), 2.70 (m, 2H, $CH_2\beta_1$ Thia, $CH_2\beta_1$ D-Phe), 1.53 (m, 1H, $CH_2\beta_2$ D-Leu,), 1.45 (m, 2H, $CH_2\beta_2$ Leu, $CH_2\beta_1$ D-Leu), 1.32 (m, 1H, $CH_2\beta_1$ Leu), 1.12 (m, 1H, CHγ D-Leu), 1.01 (m, 1H, CHγ Leu), 0.73-0.60 (m, 12H, $CH_2CH(CH_3)_2$).
^{13}C NMR (150 MHz, DMSO): δ 171.95, 170.74, 170.71, 170.10, 169.57, 154.06, 153.72, 141.77, 141.23, 138.06, 129.34, 128.72, 128.70, 128.64, 128.63, 128.52, 128.05, 127.00, 126.73, 115.80, 60.23, 57.56, 57.45, 52.87, 52.80, 48.69, 40.63, 38.64, 36.83, 30.92, 29.59, 24.71, 24.26, 23.15, 22.99, 22.94, 22.54.

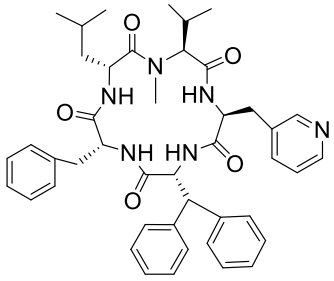


Compound 24

Following "**General peptide coupling"** procedure for SPPS and the published procedure for SPPS (Koay, Y. C.; McConnell, J. R.; Wang, Y.; Kim, S. J.; Buckton, L. K.; Mansour, F.; McAlpine, S. R. *ACS Med. Chem. Lett.* **2014**, *5*, 771-776), linear pentapeptide of Resin-O-D-Phe-3,3-DiPhe-D-Ala-3-(2-pyridyl)-Ala-*N*-Me-Val-D-Leu-NH_2 was synthesized by using (1.0 equivalent) of resin-O-D-Phe-NH_2 and the subsequent peptide coupling in the sequence as mentioned below: Fmoc-3,3-Diphenyl-D-Ala-OH (1.5 mmol, 3.0 equivalents), Fmoc-3-(2-pyridyl)-Ala OH, Fmoc-*N*-Me-Val-OH (1.5 mmol, 3.0 equivalents), and Fmoc-D-Leu-OH (1.5 mmol, 3.0 equivalents). Each peptide coupling was done in the presence of HOAt (1.5 mmol, 3.0 equivalents) or HOBt (1.5 mmol, 3.0 equivalents), DIC (3.0 mmol, 6.0 equivalents) and DMF to generate a concentration of 0.20 M based on the amino acid. Each coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm the reaction completion. The reaction mixture was drained to afford the Fmoc-protected resin-bound pentapeptide and the Fmoc protecting group was removed following the **"General Fmoc removal"** after the completion of each coupling reaction.

The double deprotected linear pentapeptide (DDLP) HO-D-Phe-3,3-DiPhe-D-Ala-3-(2-pyridyl)-Ala-*N*-Me-Val-D-Leu-NH_2 was generated following the **"Resin cleavage of linear peptide"** procedure for SPPS. The linear pentapeptide was cleaved from the resin using a mixed solution of 6 mL of TFE and 6 mL of CH_2Cl_2. The resin containing solution was filtered and dried *in vacuo* to yield the DDLP as a white solid (Yield 93%).
LC/MS (ESI): *m/z* called for $C_{44}H_{54}N_6O_6$ (M+1) = 763.40, found 763.00 and (½ M+1) 382.00

***Cyclo* D-Phe-3,3-DiPhe-D-Ala-3-(2-pyridyl)-Ala-*N*-Me-Val-D-Leu (24)** was synthesized using the DDLP (1.0 equivalent), TBTU (0.80 equivalent), HATU (0.80 equivalent), DMTMM (0.80 equivalent), DIPEA (8.0 equivalents) in anhydrous CH_2Cl_2 (0.001M) following "**Macrocyclization procedure (syringe pump)"** procedure. The reaction was then stirred overnight and the reaction was monitored via LC/MS. Upon completion, the reaction mixture was subjected to acid-base wash, which was extracted twice with 10% (v/v) $HCl_{(aq)}$. The organic layer was then re-extracted with a saturated of $NaHCO_3$ aqueous solution. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via flash column chromatography on silica gel using an ethyl acetate-hexane gradient system, followed by purification via HPLC to yield compound **24** as white solid (Yield 63%).
R_f: 0.43 (Hex:EtOAc = 0.25:0.75)
LC/MS: *m/z* called for $C_{44}H_{52}N_6O_5$ (M+1) = 745.40, found 745.00.
HRMS (ESI-TOF): $M+Na^+$, found 767.3887 $C_{44}H_{52}N_6O_5Na_1$ requires 767.3897.
^{1}H NMR (300 MHz, DMSO): δ 8.75 (d, *J* = 7.52, 1H, Pyridyl), 8.31 (d, *J* = 4.45, 1H, Pyridyl), 7.70 (t, 1H, Pyridyl), 7.60 (d, *J* = 4.40, 1H, NH) 7.40-7.03 (m, 15H, D-BiPhe, D-Phe), 6.95 (t, 1H, Pyridyl) 6.65 (d, *J* = 7.61, 1H, NH), 6.58 (d, *J* = 6.87, 2H, NH) 4.95-4.75 (m, 4H, CHα D-BiPhe, CHα Leu, CHα D-Phe, CHβ D-BiPhe), 4.49 (d, *J* = 10.76, 1H, CHα Val), 4.42 (m, 1H, CHα Pyridyl), 3.34 (m, 2H, $CH_2\beta$ Pyridyl), 2.77 (s, 3H, NCH), 2.67 (m, 2H, CHβ Leu, CHβ Val), 2.14 (m, 1H, $CH_2\beta_1$ D-Phe), 1.81 (m, 1H, $CH_2\beta_2$ D-Phe), 1.53 (m, 2H, $CH_2\beta$ Leu), 1.48 (m, 0.5H, CHβ Val), 0.98-0.68 (m, 12H, $CHCH(CH_3)_2$, $CH_2CH(CH_3)_2$).
^{13}C NMR (125 MHz, DMSO): δ 172.93, 171.82, 171.17, 170.42, 170.02, 169.72, 156.09, 146.57, 141.62, 140.46, 138.70, 136.13, 129.21, 129.04, 128.58, 128.42, 128.11, 127.81, 127.33, 126.83, 126.74, 124.08, 122.41, 62.63, 60.40, 58.45, 57.21, 53.42, 51.85, 49.89, 48.46, 40.93, 38.45, 6.50, 29.87, 25.14, 24.55, 22.93, 22.12, 21.05, 19.22, 18.34, 14.19.

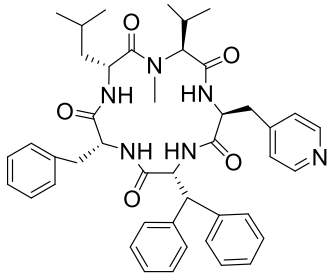


Compound 25

Following "**General peptide coupling"** procedure for SPPS and the published procedure for SPPS (Koay, Y. C.; McConnell, J. R.; Wang, Y.; Kim, S. J.; Buckton, L. K.; Mansour, F.; McAlpine, S. R. *ACS Med. Chem. Lett.* **2014**, *5*, 771-776), linear pentapeptide of Resin-O-D-Phe-3,3-Diphe-D-Ala-3-(3-pyridyl)-Ala-*N*-Me-Val-D-Leu-NH_2 was synthesized by using (1.0 equivalent) of resin-O-D-Phe-NH_2 and the subsequent peptide coupling in the sequence as mentioned below: Fmoc-3,3-Diphenyl-D-Ala-OH (1.5 mmol, 3.0 equivalents), Fmoc-3-(3-pyridyl)-Ala OH, Fmoc-*N*-Me-Val-OH (1.5 mmol, 3.0 equivalents), and Fmoc-D-Leu-OH (1.5 mmol, 3.0 equivalents). Each peptide coupling was done in the presence of HOAt (1.5 mmol, 3.0 equivalents) or HOBt (1.5 mmol, 3.0 equivalents), DIC (3.0 mmol, 6.0 equivalents) and DMF to generate a concentration of 0.20 M based on the amino acid. Each coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm the reaction completion. The reaction mixture was drained to afford the Fmoc-protected resin-bound pentapeptide and the Fmoc protecting group was removed following the **"General Fmoc removal"** after the completion of each coupling reaction.

The double deprotected linear pentapeptide (DDLP) HO-D-Phe-3,3-Diphe-D-Ala-3-(3-pyridyl)-Ala-*N*-Me-Val-D-Leu-NH_2 was generated following the **"Resin cleavage of linear peptide"** procedure for SPPS. The linear pentapeptide was cleaved from the resin using a mixed solution of 6 mL of TFE and 6 mL of CH_2Cl_2. The resin containing solution was filtered and dried *in vacuo* to yield the DDLP as a white solid (Yield 79%).
LC/MS (ESI): *m/z* called for $C_{44}H_{54}N_6O_6$ (M+1) = 763.40, found 763.00 and (½ M+1) 382.00

***Cyclo* D-Phe-3,3-DiPhe-D-Ala-3-(3-pyridyl)-Ala-*N*-Me-Val-D-Leu (25)** was synthesized using the DDLP (1.0 equivalent), TBTU (0.80 equivalent), HATU (0.80 equivalent), DMTMM (0.80 equivalent), DIPEA (8.0 equivalents) in anhydrous CH_2Cl_2 (0.001M) following "**Macrocyclization procedure (syringe pump)"** procedure. The reaction was then stirred overnight and the reaction was monitored via LC/MS. Upon completion, the reaction mixture was subjected to acid-base wash, which was extracted twice with 10% (v/v) $HCl_{(aq)}$. The organic layer was then re-extracted with a saturated of $NaHCO_3$ aqueous solution. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via flash column chromatography on silica gel using an ethyl acetate-hexane gradient system, followed by purification via HPLC to yield compound **25** as white solid (Yield 32%).
R_f: 0.25 (Hex:EtOAc = 0.25:0.75)
LC/MS: *m/z* called for $C_{44}H_{52}N_6O_5$ (M+1) = 745.40, found 745.00.
HRMS (ESI-TOF): $M+Na^+$, found 767.3893 $C_{44}H_{52}N_6O_5Na_1$ requires 767.3897.
^{1}H NMR (600 MHz, DMSO): δ 8.37 (m, 2H, Pyridyl), 8.01 (m, 1H, NH), 7.93 (d, 1H, *J* = 7.45, Pyridyl), 7.57 (m, 1H, Pyridyl) 7.38-7.10 (m, 15H, D-BiPhe, D-Phe, NH), 6.89 (m, 3H, NH) 5.21 (m, 1H, CHα D-BiPhe), 4.49 (m, 1H, CHα Pyridyl) 4.30 (d, *J* = 11.68, 1H, CHβ D-BiPhe) 4.17 (d, *J* = 10.76, 1H, CHα Val), 4.11 (m, 1H, CHα D-Phe), 3.71 (m, 1H, CHα Leu), 2.98 (m, 1H, $CH_2\beta_1$ Pyridyl), 2.88 (m, 1H, $CH_2\beta_1$ Pyridyl), 2.74 (m, 1H, $CH_2\beta_1$ Phe), 2.65 (s, 3H, NCH_3), 2.59 (m, 1H, CHα D-Phe), 2.08 (m, 1H, CHβ Leu), 1.92 (m, 0.5H, CHβ Val), 1.60 (m, 1H, $CH_2\beta_1$ Leu), 1.48 (m, 0.5H, CHβ Val), 1.35 (m, 1H, $CH_2\beta_2$ Leu), 0.91-0.44 (m, 12H, $CHCH(CH_3)_2$, $CH_2CH(CH_3)_2$).
^{13}C NMR (125 MHz, DMSO): δ 171.39, 171.18, 170.19, 140.80,140.13, 136.80, 129.03, 128.88, 128.71, 128.53, 128.32, 128.24, 128.09, 127.95, 127.04, 126.65, 126.53, 60.40, 57.65, 55.06, 50.80, 48.02, 40.68, 32.72, 30.62, 29.69, 26.10, 25.85, 24.85, 24.65, 22.81, 22.62, 22.46, 21.05, 19.39, 18.08, 18.28, 17.83.



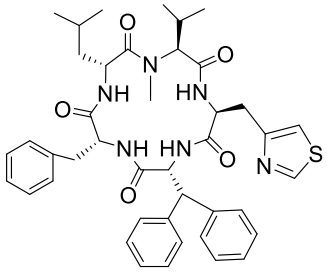
Compound 26

Following "**General peptide coupling"** procedure for SPPS and the published procedure for SPPS (Koay, Y. C.; McConnell, J. R.; Wang, Y.; Kim, S. J.; Buckton, L. K.; Mansour, F.; McAlpine, S. R. *ACS Med. Chem. Lett.* **2014**, *5*, 771-776), linear pentapeptide of Resin-O-D-Phe-3,3-DiPhe-D-Ala-3-(4-pyridyl)-Ala-*N*-Me-Val-D-Leu-NH_2 was synthesized by using (1.0 equivalent) of resin-O-D-Phe-NH_2 and the subsequent peptide coupling in the sequence as mentioned below: Fmoc-3,3-Diphenyl-D-Ala-OH (1.5 mmol, 3.0 equivalents), Fmoc-3-(3-pyridyl)-Ala OH, Fmoc-*N*-Me-Val-OH (1.5 mmol, 3.0 equivalents), and Fmoc-D-Leu-OH (1.5 mmol, 3.0 equivalents). Each peptide coupling was done in the presence of HOAt (1.5 mmol, 3.0 equivalents) or HOBt (1.5 mmol, 3.0 equivalents), DIC (3.0 mmol, 6.0 equivalents) and DMF to generate a concentration of 0.20 M based on the amino acid. Each coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm the reaction completion. The reaction mixture

was drained to afford the Fmoc-protected resin-bound pentapeptide and the Fmoc protecting group was removed following the **"General Fmoc removal"** after the completion of each coupling reaction.

The double deprotected linear pentapeptide (DDLP) HO-D-Phe-3,3-DiPhe-D-Ala-3-(4-pyridyl)-Ala-*N*-Me-Val-D-Leu-NH_2 was generated following the **"Resin cleavage of linear peptide"** procedure for SPPS. The linear pentapeptide was cleaved from the resin using a mixed solution of 6 mL of TFE and 6 mL of CH_2Cl_2. The resin containing solution was filtered and dried *in vacuo* to yield the DDLP as a white solid (Yield 89%).
LC/MS (ESI): *m/z* called for $C_{44}H_{54}N_6O_6$ (M+1) = 763.40, found 763.00.

***Cyclo* D-Phe-3,3-DiPhe-D-Ala-3-(4-pyridyl)-Ala-*N*-Me-Val-D-Leu (26)** was synthesized using the DDLP (1.0 equivalent), TBTU (0.80 equivalent), HATU (0.80 equivalent), DMTMM (0.80 equivalent), DIPEA (8.0 equivalents) in anhydrous CH_2Cl_2 (0.001M) following "**Macrocyclization procedure (syringe pump)"** procedure. The reaction was then stirred overnight and the reaction was monitored via LC/MS. Upon completion, the reaction mixture was subjected to acid-base wash, which was extracted twice with 10% (v/v) $HCl_{(aq)}$. The organic layer was then re-extracted with a saturated of $NaHCO_3$ aqueous solution. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via flash column chromatography on silica gel using an ethyl acetate-hexane gradient system, followed by purification via HPLC to yield compound **26** as white solid (Yield 60%).
R_f: 0.20 (Hex:EtOAc = 0.25:0.75)
LC/MS: *m/z* called for $C_{44}H_{52}N_6O_5$ (M+1) = 745.40, found 745.00.
HRMS (ESI-TOF): $M+Na^+$, found 745.4070 $C_{42}H_{50}N_6O_5S_1Na_1$ requires 773.3461.
^{1}H NMR (300 MHz, DMSO): δ 8.45 (d, *J* = 2.0 Hz 1H, NH), 8.41 (dd, *J* = 1.27 Hz, 2H, D-Pyridyl [meta]), 8.04 (m, 2H, Pyridyl [ortho]), 7.67 (m, 2H, NH), 7.49-6.79 (m, 16H, D-BiPhe, D-Phe, NH), 5.22 (m, 1H, CHα D-BiPhe), 4.31 (d, *J* = 11.79, 1H, CHα Val) 3.71 (m, 1H, CHα Pyridyl), 3.08 (m, 1H, $CH_2\beta_1$ Pyridyl), 3.02-2.73 (m, 2H, $CH_2\beta_2$ Pyridyl, $CH_2\beta_1$ D-BiPhe), 2.65 (s, 3H, NCH_3), 2.58 (m, 1H, CHα D-BiPhe), 2.20-1.83 (m, 1H, CHβ Val), 1.62 (m, 1H, CHγ Leu), 1.38 (m, 2H, $CH_2\beta$ Leu), 0.97-0.36 (m, 12H, $CHCH(CH_3)_2$, $CH_2CH(CH_3)_2$).

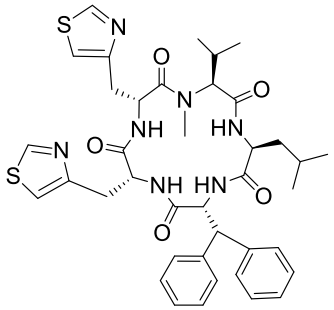

Compound 27

Following "**General peptide coupling"** procedure for SPPS and the published procedure for SPPS (Koay, Y. C.; McConnell, J. R.; Wang, Y.; Kim, S. J.; Buckton, L. K.; Mansour, F.; McAlpine, S. R. *ACS Med. Chem. Lett.* **2014**, *5*, 771-776), linear pentapeptide of resin-O-D-Leu-D-Phe-3,3-Diphe-D-Ala-3-(4-Thia)Ala-*N*-Me-Val-NH_2 was synthesized by using 1.00 g (0.53 mmol, 1.0 equivalent) of resin-O-D-Leu-NH_2 and the subsequent peptide coupling in the sequence as mentioned below: 0.62 g (1.6 mmol, 3.0 equivalents) of Fmoc-D-Phe-OH, 0.74 g (1.6 mmol, 3.0 equivalents) of Fmoc-3,3-Diphenyl-D-Ala-OH, 0.63 g (1.6 mmol, 3.0 equivalents) of Fmoc-3-(4-Thiazoyl)Ala-OH and 0.56 g (1.6 mmol, 3.0 equivalents) of Fmoc-*N*-Me-Val-OH. Each peptide coupling was done in the presence of 0.22 g of HOAt (1.6 mmol, 3.0 equivalents) or 0.21 g of HOBt (1.6 mmol, 3.0 equivalents), 0.50 mL of DIC (3.2 mmol, 6.0 equivalents) and 2.65 mL of DMF to generate a concentration of 0.20 M. Each coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm the reaction completion. The reaction mixture was drained to afford the Fmoc-protected resin-bound pentapeptide and the Fmoc protecting group was removed following the **"General Fmoc removal"** after the completion of each coupling reaction.

The double deprotected linear pentapeptide (DDLP) HO-D-Leu-D-Phe-3,3-Diphe-D-Ala-3-(4-Thia)Ala-*N*-Me-Val-NH_2 was generated following the **"Resin cleavage of linear peptide"** procedure for SPPS. The linear pentapeptide was cleaved from the resin using a mixed solution of 6 mL of TFE and 6 mL of CH_2Cl_2. The resin containing solution was filtered and dried *in vacuo* to yield the DDLP as a white solid (204 mg, overall 50%).
LC/MS (ESI): *m/z* called for $C_{42}H_{52}N_6O_6$ (M+1) = 769.37, found 769.10.

***Cyclo* D-Leu-D-Phe-3,3-Diphe-D-Ala-3-(4-Thia)Ala-*N*-Me-Val (27)** was synthesized using 0.20 g of the DDLP generated (0.27 mmol, 1.0 equivalent), 0.07 g of TBTU (0.21 mmol, 0.80 equivalent), 0.08 g of HATU (0.21 mmol, 0.80 equivalent), 0.06 g of DMTMM (0.21 mmol, 0.80 equivalent), 0.37 mL of DIPEA (2.1 mmol, 8.0 equivalents) in anhydrous CH_2Cl_2 (265 mL, 0.001M) following "**Macrocyclization procedure (syringe pump)"** procedure. The reaction was then stirred overnight and the reaction was monitored via LC/MS. Upon completion, the reaction mixture was subjected to acid-base wash, which was extracted twice with 10% (v/v) $HCl_{(aq)}$. The organic layer was then re-extracted with a saturated of $NaHCO_3$ aqueous solution. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via

flash column chromatography on silica gel using an ethyl acetate-hexane gradient system, followed by purification via HPLC to yield compound **27** as white solid (5 mg, 2.5%).
*Note: Cyclization at the bulky residue of *N*-methyl has resulted a poor reaction and thus HPLC yield. Due to the limited amount of compound, HSQC and HMBC spectra were used for the complete assignment of all the carbon peaks.
R_f: 0.51 (Hex:EtOAc = 0.25:0.75)
LC/MS: *m/z* called for $C_{42}H_{50}N_6O_5S$ (M+1) = 751.36, found 750.95.
HRMS (ESI-TOF): M+Na^+, found 773.3450 $C_{42}H_{50}N_6O_5S_1Na_1$ requires 773.3461.
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.67 (m, 1H, Thia), 7.53 (br, NH), 7.42 (m, NH), 7.27-7.08 (m, 15H, D-BiPhe, D-Phe), 6.91 (m, 1H, Thia), 6.79 (m, NH), 6.71 (m, NH), 5.08 (m, 1H, CHα D-BiPhe), 4.94 (m, 1H, CHα D-Phe), 4.88 (m, 2H, CHα Val, CHβ D-BiPhe), 4.57 (m, 1H, CHα D-Leu), 4.45 (m, 1H, CHα Thia), 3.32 (m, 1H, $CH_2\beta_2$ D-Phe), 3.15 (m, 1H, $CH_2\beta_1$ D-Phe), 2.93 (m, 5H, $CH_2\beta_1$ Thia, NCH_3), 2.08 (m, 2H, $CH_2\beta$ D-Leu), 1.60 (m, 1H, CHγ D-Leu), 0.84-0.76 (m, 12H, $CHCH(CH_3)_2$, $CH_2CH(CH_3)_2$).
^{13}C NMR (125 MHz, DMSO): δ 174.32, 173.31, 172.15, 171.14, 170.23, 161.49, 153.34, 140.75, 140.35, 136.97, 130.81, 129.02, 128.89, 128.68, 128.07, 127.58, 127.18, 127.08, 126.86, 116.23, 64.04, 60.34, 57.09, 55.55, 53.07, 52.38, 41.42, 37.18, 33.49, 31.96, 29.68, 26.43, 24.81, 22.83, 19.49, 18.09.

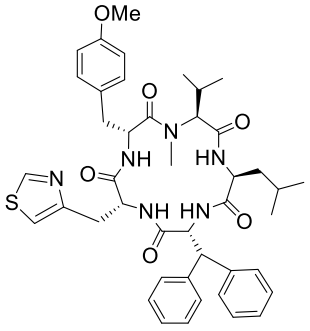

Compound 28

Following "**General peptide coupling"** procedure for SPPS and the published procedure for SPPS (Koay, Y. C.; McConnell, J. R.; Wang, Y.; Kim, S. J.; Buckton, L. K.; Mansour, F.; McAlpine, S. R. *ACS Med. Chem. Lett.* **2014**, *5*, 771-776), linear pentapeptide of resin-O-Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala-NH_2 was synthesized by using 1.00 g (0.5 mmol, 1.0 equivalent) of resin-O-Leu-NH_2 and the subsequent peptide coupling in the sequence as mentioned below: 0.53 g (1.5 mmol, 3.0 equivalents) of Fmoc-*N*-Me-Val-OH, 0.59 g (1.5 mmol, 3.0 equivalents) of Fmoc-D-3-(4-Thiazoyl)Ala-OH, 0.59 g (1.5 mmol, 3.0 equivalents) of Fmoc-D-3-(4-Thiazoyl)Ala-OH and 0.70 g (1.5 mmol, 3.0 equivalents) of Fmoc-3,3-Diphenyl-D-Ala-OH. Each peptide coupling was done in the presence of 0.20 g of HOAt (1.5 mmol, 3.0 equivalents) or 0.20 g of HOBt (1.5 mmol, 3.0 equivalents), 0.47 mL of DIC (3.0 mmol, 6.0 equivalents) and 2.5 mL of DMF to generate a concentration of 0.20 M. Each coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm the reaction completion. The reaction mixture was drained to afford the Fmoc-protected resin-bound pentapeptide and the Fmoc protecting group was removed following the **"General Fmoc removal"** after the completion of each coupling reaction.

The double deprotected linear pentapeptide (DDLP) HO-Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala-NH_2 was generated following the **"Resin cleavage of linear peptide"** procedure for SPPS. The linear pentapeptide was cleaved from the resin using a mixed solution of 6 mL of TFE and 6 mL of CH_2Cl_2. The resin containing solution was filtered and dried *in vacuo* to yield the DDLP as a white solid (310 mg, overall 80%).
LC/MS (ESI): *m/z* called for $C_{39}H_{49}N_7O_6S_2$ (M+1) = 776.32, found 775.95.

***Cyclo* Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala (28)** was synthesized using 0.31 g of the DDLP generated (0.52 mmol, 1.0 equivalent), 0.13 g of TBTU (0.42 mmol, 0.80 equivalent), 0.16 g of HATU (0.42 mmol, 0.80 equivalent), 0.12 g of DMTMM (0.42 mmol, 0.80 equivalent), 0.72 mL of DIPEA (4.2 mmol, 8.0 equivalents) in anhydrous CH_2Cl_2 (520 mL, 0.001M) following "**Macrocyclization procedure (syringe pump)"** procedure. The reaction was then stirred overnight and the reaction was monitored via LC/MS. Upon completion, the reaction mixture was subjected to acid-base wash, which was extracted twice with 10% (v/v) $HCl_{(aq)}$. The organic layer was then re-extracted with a saturated of $NaHCO_3$ aqueous solution. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via flash column chromatography on silica gel using an ethyl acetate-hexane gradient system, followed by purification via HPLC to yield compound **28** as white solid (140 mg, 36%).
R_f: 0.53 (EtOAc:MeOH = 0.975:0.025)
LC/MS: *m/z* called for $C_{39}H_{47}N_7O_5S_2$ (M+1) = 758.31, found 757.90.
HRMS (ESI-TOF): M+Na^+, found 780.2971 $C_{39}H_{47}N_7O_5S_2Na$ requires 780.3080.
^{1}H NMR (600 MHz, DMSO): δ 9.02 (s, 1H, D-Thia2), 8.94 (s, 1H, D-Thia1), 8.41 (br, NH), 8.21 (br, NH), 7.87 (d, *J* = 7.1 Hz, NH), 7.82 (br, NH), 7.36-7.12 (m, 11H, D-BiPhe, D-Thia2), 6.88 (s, 1H, D-Thia1), 5.22 (t, *J* = 10.9 Hz, 1H, CHα D-BiPhe), 4.99 (q, *J* = 7.7 Hz, 1H, CHα D-Thia2), 4.52 (d, *J* = 11.3 Hz, 1H, CHα Val), 4.36 (d, *J* = 12.1 Hz, 1H, CHβ D-BiPhe), 4.19 (m, 1H, CHα D-Thia1), 3.20 (m, 1H, CHα Leu), 2.90-2.79 (m, 4H, $CH_2\beta$ D-

Thia2, $CH_2\beta$ D-Thia1), 2.61 (s, 3H, NCH_3), 2.10 (m, 1H, CHβ Val), 1.50 (m, 1H, $CH_2\beta_2$ Leu), 1.39 (m, 1H, $CH_2\beta_1$ Leu), 1.24 (m, 1H, CHγ Leu), 0.80-0.60 (m, 12H, $CHCH(C\underline{H}_3)_2$, $CH_2CH(C\underline{H}_3)_2$).
^{13}C NMR (150 MHz, DMSO): δ 170.30, 170.06, 169.78, 169.71, 168.69, 154.26, 154.20, 153.38, 153.11, 141.71, 141.23, 128.89, 128.75, 128.53, 128.37, 127.17, 126.76, 115.88, 115.19, 63.03, 57.06, 55.12, 53.73, 51.94, 49.27, 37.91, 33.51, 33.07, 30.13, 25.31, 24.52, 22.89, 22.58, 19.65, 18.69.

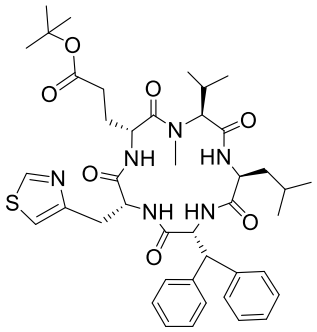


Compound 29

Following "**General peptide coupling"** procedure for SPPS and the published procedure for SPPS (Koay, Y. C.; McConnell, J. R.; Wang, Y.; Kim, S. J.; Buckton, L. K.; Mansour, F.; McAlpine, S. R. *ACS Med. Chem. Lett.* **2014**, *5*, 771-776), linear pentapeptide of resin-O-Leu-*N*-Me-Val-D-Tyr(OMe)-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala-NH_2 was synthesized by using 1.00 g (0.5 mmol, 1.0 equivalent) of resin-O-Leu-NH_2 and the subsequent peptide coupling in the sequence as mentioned below: 0.53 g (1.5 mmol, 3.0 equivalents) of Fmoc-*N*-Me-Val-OH, 0.63 g (1.5 mmol, 3.0 equivalents) of Fmoc-D-Tyrosine-OMe, 0.59 g (1.5 mmol, 3.0 equivalents) of Fmoc-D-3-(4-Thiazoyl)Ala-OH and 0.70 g (1.5 mmol, 3.0 equivalents) of Fmoc-3,3-Diphenyl-D-Ala-OH. Each peptide coupling was done in the presence of 0.20 g of HOAt (1.5 mmol, 3.0 equivalents) or 0.20 g of HOBt (1.5 mmol, 3.0 equivalents), 0.47 mL of DIC (3.0 mmol, 6.0 equivalents) and 2.5 mL of DMF to generate a concentration of 0.20 M. Each coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm the reaction completion. The reaction mixture was drained to afford the Fmoc-protected resin-bound pentapeptide and the Fmoc protecting group was removed following the **"General Fmoc removal"** after the completion of each coupling reaction.

The double deprotected linear pentapeptide (DDLP) HO-Leu-*N*-Me-Val-D-Tyr(OMe)-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala-NH_2 was generated following the **"Resin cleavage of linear peptide"** procedure for SPPS. The linear pentapeptide was cleaved from the resin using a mixed solution of 6 mL of TFE and 6 mL of CH_2Cl_2. The resin containing solution was filtered and dried *in vacuo* to yield the DDLP as a white solid (320 mg, overall 80%).
LC/MS (ESI): *m/z* called for $C_{43}H_{54}N_6O_7S$ (M+1) = 799.38, found 798.95.

***Cyclo* Leu-*N*-Me-Val-D-Tyr(OMe)-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala (29)** was synthesized using 0.32 g of the DDLP generated (0.40 mmol, 1.0 equivalent), 0.10 g of TBTU (0.32 mmol, 0.80 equivalent), 0.12 g of HATU (0.32 mmol, 0.80 equivalent), 0.09 g of DMTMM (0.32 mmol, 0.80 equivalent), 0.56 mL of DIPEA (3.2 mmol, 8.0 equivalents) in anhydrous CH_2Cl_2 (400 mL, 0.001M) following "**Macrocyclization procedure (syringe pump)"** procedure. The reaction was then stirred overnight and the reaction was monitored via LC/MS. Upon completion, the reaction mixture was subjected to acid-base wash, which was extracted twice with 10% (v/v) $HCl_{(aq)}$. The organic layer was then re-extracted with a saturated of $NaHCO_3$ aqueous solution. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via flash column chromatography on silica gel using an ethyl acetate-hexane gradient system, followed by purification via HPLC to yield compound **29** as white solid (110 mg, 35%).
R_f: 0.56 (100% EtOAc)
LC/MS: *m/z* called for $C_{43}H_{52}N_6O_6S$ (M+1) = 781.37, found 781.05.
HRMS (ESI-TOF): $M+Na^+$, found 803.3560 $C_{43}H_{52}N_6O_6S_1Na_1$ requires 803.3669.
^{1}H NMR (600 MHz, DMSO): δ 9.02 (s, 1H, D-Thia), 8.42 (br, N$\underline{H}$), 8.15 (d, *J* = 8.2 Hz, N$\underline{H}$), 7.84 (d, *J* = 7.1 Hz, N$\underline{H}$), 7.79 (d, *J* = 8.6 Hz, N$\underline{H}$), 7.31-7.05 (m, 12H, D-BiPhe, *O*-Me-D-Tyr), 6.81 (d, *J* = 8.6 Hz, 1H, D-Thia), 6.76 (d, *J* = 8.3 Hz, 2H, *O*-Me-D-Tyr), 5.21 (t, *J* = 10.9 Hz, 1H, CHα D-BiPhe), 4.71 (q, *J* = 7.5 Hz, 1H, CHα D-Thia), 4.52 (d, *J* = 11.3 Hz, 1H, CHα Val), 4.36 (d, *J* = 12.1 Hz, 1H, CHβ D-BiPhe), 4.15 (m, 1H, CHα *O*-Me-D-Tyr), 3.68 (s, 3H, NCH_3), 3.01 (m, 1H, CHα Leu), 2.83 (m, 2H, $CH_2\beta$ *O*-Me-D-Tyr), 2.59 (m, 2H, $CH_2\beta$ D-Thia), 2.56 (s, 3H, NCH_3), 2.08 (m, 1H, CHβ Val), 1.49 (m, 1H, $CH_2\beta_2$ Leu), 1.40 (m, 1H, $CH_2\beta_1$ Leu), 1.26 (m, 1H, CHγ Leu), 0.81-0.58 (m, 12H, $CHCH(C\underline{H}_3)_2$, $CH_2CH(C\underline{H}_3)_2$).
^{13}C NMR (150 MHz, DMSO): δ 170.46, 170.32, 169.85, 169.68, 168.77, 158.06, 154.92, 153.50, 141.76, 141.26, 131.19, 129.46, 129.41, 128.92, 128.87, 127.87, 127.70, 126.62, 114.37, 114.34, 62.90, 56.20, 55.00, 54.10, 53.50, 52.10, 50.60, 37.70, 37.00, 33.30, 29.40, 25.40, 24.90, 24.12, 23.27, 19.20, 18.44.

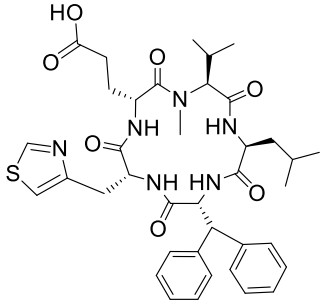


Compound 30

Following "**General peptide coupling"** procedure for SPPS and the published procedure for SPPS (Koay, Y. C.; McConnell, J. R.; Wang, Y.; Kim, S. J.; Buckton, L. K.; Mansour, F.; McAlpine, S. R. *ACS Med. Chem. Lett.* **2014**, *5*, 771-776), linear pentapeptide of resin-O-Leu-*N*-Me-Val-D-Glu(OtBu)-3-(4-Thia)-D-Ala-3,3-Diphenyl-D-Ala-NH_2 was synthesized by using 1.00 g (0.5 mmol, 1.0 equivalent) of resin-O-Leu-NH_2 and the subsequent peptide coupling in the sequence as mentioned below: 0.53 g (1.5 mmol, 3.0 equivalents) of Fmoc-*N*-Me-Val-OH, 0.64 g (1.5 mmol, 3.0 equivalents) of Fmoc-D-Glu-γ-OtBu, 0.59 g (1.5 mmol, 3.0 equivalents) of Fmoc-D-3-(4-Thiazoyl)Ala-OH and 0.70 g (1.5 mmol, 3.0 equivalents) of Fmoc-3,3-Diphenyl-D-Ala-OH. Each peptide coupling was done in the presence of 0.20 g of HOAt (1.5 mmol, 3.0 equivalents) or 0.20 g of HOBt (1.5 mmol, 3.0 equivalents), 0.47 mL of DIC (3.0 mmol, 6.0 equivalents) and 2.5 mL of DMF to generate a concentration of 0.20 M. Each coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm the reaction completion. The reaction mixture was drained to afford the Fmoc-protected resin-bound pentapeptide and the Fmoc protecting group was removed following the **"General Fmoc removal"** after the completion of each coupling reaction.

The double deprotected linear pentapeptide (DDLP) HO-Leu-*N*-Me-Val-D-Glu(OtBu)-3-(4-Thia)-D-Ala-3,3-Diphenyl-D-Ala-NH_2 was generated following the **"Resin cleavage of linear peptide"** procedure for SPPS. The linear pentapeptide was cleaved from the resin using a mixed solution of 6 mL of TFE and 6 mL of CH_2Cl_2. The resin containing solution was filtered and dried *in vacuo* to yield the DDLP as a white solid (278 mg, overall 69%).
LC/MS (ESI): *m/z* called for $C_{42}H_{58}N_6O_8S$ (M+1) = 807.40, found 807.05.

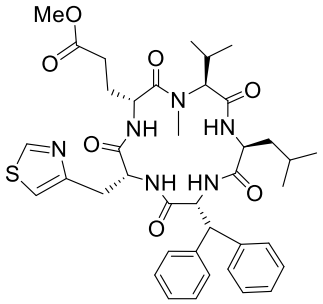
***Cyclo* Leu-*N*-Me-Val-D-Glu(OtBu)-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala-NH_2 (30)** was synthesized using 0.28 g of the DDLP generated (0.34 mmol, 1.0 equivalent), 0.09 g of TBTU (0.28 mmol, 0.80 equivalent), 0.10 g of HATU (0.28 mmol, 0.80 equivalent), 0.08 g of DMTMM (0.28 mmol, 0.80 equivalent), 0.48 mL of DIPEA (2.8 mmol, 8.0 equivalents) in anhydrous CH_2Cl_2 (383 mL, 0.001M) following "**Macrocyclization procedure (syringe pump)"** procedure. The reaction was then stirred overnight and the reaction was monitored via LC/MS. Upon completion, the reaction mixture was subjected to acid-base wash, which was extracted twice with 10% (v/v) $HCl_{(aq)}$. The organic layer was then re-extracted with a saturated of $NaHCO_3$ aqueous solution. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via flash column chromatography on silica gel using an ethyl acetate-hexane gradient system, followed by purification via HPLC to yield compound **30** as white solid (80 mg, 29%).
R_f: 0.67 (EtOAc:MeOH = 0.95:0.05)
LC/MS: *m/z* called for $C_{42}H_{56}N_6O_7S$ (M+1) = 789.39, found 789.10.
HRMS (ESI-TOF): $M+Na^+$, found 811.3832 $C_{42}H_{56}N_6O_7S_1Na_1$ requires 811.3931.
^{1}H NMR (600 MHz, DMSO): δ 9.14 (d, *J* = 1.9 Hz, 1H, D-Thia), 8.29 (d, *J* = 8.6 Hz, NH), 7.91 (m, 2NH), 7.71 (d, *J* = 9.8 Hz, NH), 7.37-7.12 (m, 11H, D-Biphe, D-Thia), 5.30 (t, *J* = 11.0 Hz, 1H, CHα D-Biphe), 4.58 (d, *J* = 11.5 Hz, 1H, CHα Val), 4.48 (q, *J* = 7.6 Hz, 1H, CHα D-Glu), 4.33 (m, 2H, CHβ D-Biphe, CHα D-Thia), 3.42 (q, *J* = 7.3 Hz, 1H, CHα Leu), 2.87 (d, *J* = 6.2 Hz, 2H, CH_2β D-Thia), 2.56 (s, 3H, NCH_3), 2.17 (m, 2H, CHβ Val, $CH_2γ_2$ D-Glu), 1.98 (m, 2H, $CH_2γ_1$ D-Glu, $CH_2β_2$ D-Glu), 1.83 (m, 1H, $CH_2β_1$ D-Glu), 1.53 (m, 2H, CH_2β Leu), 1.40 (s, 9H, $OC(CH_3)_3$), 1.31 (m, 1H, CHγ Leu), 0.82-0.65 (m, 12H, $CH_2CH(CH_3)_2$, $CHCH(CH_3)_2$).
^{13}C NMR (150 MHz, DMSO): δ 172.34, 170.28, 170.24, 169.68, 169.37, 168.57, 154.63, 152.73, 141.59, 141.30, 128.90, 128.58, 128.55, 128.49, 127.24, 126.87, 116.35, 79.88, 63.05, 56.90, 54.56, 53.88, 51.72, 48.26, 37.99, 32.90, 31.66, 30.06, 28.27, 27.52, 25.31, 24.49, 22.94, 22.51, 19.55, 18.77.



Compound 31

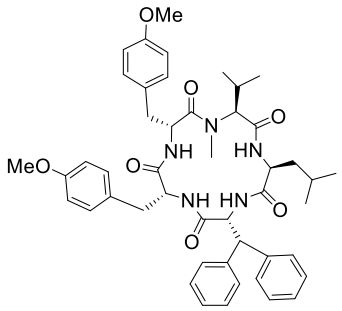
The tBu protecting group of compound **30** was removed following **"*Tert*-butyl group (tBu) Removal"** procedure, utilizing a mixture of TFA/CH_2Cl_2 (2:4, 0.1 M) and anisole (2.0 equivalents) to generate compound **31**. The free acid was taken to the subsequent methyl ester formation without purification.
R_f: 0.30 (100% EtOAc)
LC/MS: *m/z* called for $C_{38}H_{48}N_6O_7S$ (M+1) = 733.33, found 733.00.
HRMS (ESI-TOF): $M+Na^+$, found 755.3194 $C_{38}H_{48}N_6O_7S_1Na_1$ requires 755.3305.
^{1}H NMR (600 MHz, DMSO): δ 9.11 (d, *J* = 1.9 Hz, 1H, D-Thia), 8.24 (d, *J* = 8.6 Hz, NH), 7.90 (m, 2NH), 7.66 (d, *J* = 9.8 Hz, NH), 7.35-7.11 (m, 10H, D-Biphe), 7.08 (s, 1H, D-Thia), 5.28 (dd, *J* = 9.9, 12.1 Hz, 1H, CHα D-Biphe), 4.58 (d, *J* = 11.5 Hz, 1H, CHα Val), 4.49 (m, 1H, CHα D-Glu), 4.33 (m, 2H, CHβ D-Biphe, CHα D-Thia), 3.22

(dd, J = 10.0, 14.1 Hz, 1H, CHα Leu), 2.87 (m, 2H, CH_2β D-Thia), 2.56 (s, 3H, NCH_3), 2.18 (m, 1H, CHβ Val), 2.01 (m, 2H, CH_2γ D-Glu), 1.84 (m, 1H, $CH_2\beta_2$ D-Glu), 1.56 (m, 1H, $CH_2\beta_1$ D-Glu), 1.39 (m, 2H, CH_2β Leu), 1.29 (m, 1H, CHγ Leu), 0.82-0.65 (m, 12H, $CH_2CH(CH_3)_2$, $CHCH(CH_3)_2$).
^{13}C NMR (150 MHz, DMSO): δ 174.63, 170.40, 170.32, 169.68, 169.38, 168.62, 154.64, 152.72, 141.60, 141.29, 128.91, 128.60, 128.53, 128.49, 127.24, 126.87, 116.35, 63.06, 56.91, 54.64, 53.85, 51.70, 49.03, 38.00, 32.95, 30.40, 30.10, 27.47, 25.32, 24.48, 22.92, 22.51, 19.56, 18.81.



Compound 32

The free acid of compound **31** was converted to the methyl ester compound **32** using the methylating agent Trimethylsilyl diazomethane (TMSD), which was dissolved in a mixture of anhydrous benzene and methanol (3:1) in a round bottom flask to make a 0.1 M solution and methylating agent TMSD (2.0 M in diethyl ether) was added drop-wise into the reaction mixture. The reaction was stirred under nitrogen and monitored by thin layer chromatography (TLC). Upon completion, the solvent was evaporated *in vacuo* and resulting compound **32**.
R_f: 0.51 (EtOAc:MeOH = 0.95:0.05)
LC/MS: *m/z* called for $C_{39}H_{50}N_6O_7S$ (M+1) = 747.35, found 747.05.
HRMS (ESI-TOF): $M+Na^+$, found 769.3346 $C_{39}H_{50}N_6O_7SNa$ requires 769.3462.
^{1}H NMR (600 MHz, DMSO): δ 9.09 (s, 1H, D-Thia), 8.40 (br, NH), 8.05 (br, NH), 7.99 (d, J = 7.2 Hz, NH), 7.89 (br, NH), 7.34-7.15 (m, 10H, D-Biphe), 7.06 (s, 1H, D-Thia), 5.26 (t, J = 11.2 Hz, 1H, CHα D-Biphe), 4.56 (d, J = 11.4 Hz, 1H, CHα Val), 4.49 (q, J = 7.5 Hz, 1H, CHα D-Glu), 4.35 (m, 2H, CHβ D-Biphe, CHα D-Thia), 3.60 (s, 3H, OCH_3), 3.22 (m, 1H, CHα Leu), 2.87 (m, 1H, $CH_2\beta_2$ D-Thia), 2.60 (m, 1H, $CH_2\beta_1$ D-Thia), 2.53 (s, 3H, NCH_3), 2.09 (m, 3H, CHβ Val, CH_2γ D-Glu), 1.88 (m, 1H, $CH_2\beta_2$ D-Glu), 1.60 (m, 1H, $CH_2\beta_1$ D-Glu), 1.50 (m, 1H, $CH_2\beta_2$ Leu), 1.41 (m, 1H, $CH_2\beta_1$ Leu), 1.29 (m, 1H, CHγ Leu), 0.81-0.65 (m, 12H, $CH_2CH(CH_3)_2$, $CHCH(CH_3)_2$).
^{13}C NMR (150 MHz, DMSO): δ 173.56, 170.47, 170.26, 169.69, 169.36, 168.50, 154.56, 152.78, 141.65, 141.28, 128.89, 128.68, 128.53, 128.41, 126.85, 126.80, 116.28, 62.89, 57.06, 54.45, 53.83, 51.79, 51.70, 48.92, 37.85, 33.09, 30.04, 29.95, 27.34, 25.31, 24.49, 22.97, 22.49, 19.59, 18.72.



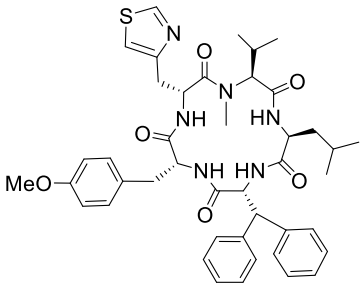
Compound 33

Following "**General peptide coupling"** procedure for SPPS and the published procedure for SPPS (Koay, Y. C.; McConnell, J. R.; Wang, Y.; Kim, S. J.; Buckton, L. K.; Mansour, F.; McAlpine, S. R. *ACS Med. Chem. Lett.* **2014**, *5*, 771-776), linear pentapeptide of resin-O-Leu-*N*-Me-Val-(4-Methoxy)-D-Phe-(4-Methoxy)-D-Phe-3,3-Diphe-D-Ala-NH_2 was synthesized by using (0.5 mmol, 1.0 equivalent) of resin-O-Leu-NH_2 and the subsequent peptide coupling in the sequence using 1.5 mmol (3.0 equivalents) of each mentioned below: Fmoc-*N*-Me-Val-OH, Fmoc-(4-Methoxy)-D-Phe-OH, Fmoc-(4-Methoxy)-D-Phe-OH, Fmoc-D-Phe-OH, and Fmoc-3,3-Diphenyl-D-Ala-OH. Each peptide coupling was done in the presence of HOAt (1.5 mmol, 3.0 equivalents) or HOBt (1.5 mmol, 3.0 equivalents), DIC (3.0 mmol, 6.0 equivalents) and DMF to generate a concentration of 0.20 M based on the amino acid. Each coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm the reaction completion. The reaction mixture was drained to afford the Fmoc-protected resin-bound pentapeptide and the Fmoc protecting group was removed following the **"General Fmoc removal"** after the completion of each coupling reaction.

The double deprotected linear pentapeptide (DDLP) HO-Leu-*N*-Me-Val-3-(3-pyridyl)-D-Ala-D-Phe-3,3-Diphe-D-Ala-NH_2 was generated following the **"Resin cleavage of linear peptide"** procedure for SPPS. The linear pentapeptide was cleaved from the resin using a mixed solution of 6 mL of TFE and 6 mL of CH_2Cl_2. The resin containing solution was filtered and dried *in vacuo* to yield the DDLP as a white solid (Quantitative yield)
LC/MS (ESI): *m/z* called for $C_{47}H_{59}N_5O_8$ (M+1) = 822.42, found 822.00.

***Cyclo* Leu-*N*-Me-Val-(4-Methoxy)-D-Phe-(4-Methoxy)-D-Phe-3,3-Diphe-D-Ala (33)** was synthesized using the DDLP (1.0 equivalent), TBTU (0.80 equivalent), HATU (0.80 equivalent), DMTMM (0.80 equivalent), DIPEA (8.0 equivalents) in anhydrous CH_2Cl_2 (0.001M) following "**Macrocyclization procedure (syringe pump)"** procedure. The reaction was then stirred overnight and the reaction was monitored via LC/MS. Upon completion, the reaction mixture was subjected to acid-base wash, which was extracted twice with 10% (v/v) $HCl_{(aq)}$. The organic layer was then re-extracted with a saturated of $NaHCO_3$ aqueous solution. The combined organic layers

were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via flash column chromatography on silica gel using an ethyl acetate-hexane gradient system, followed by purification via HPLC to yield compound **33** as white solid (Yield 16%).
R_f: 0.75 (Hex:EtOAc = 0.25:0.75)
LC/MS: *m/z* called for $C_{47}H_{57}N_5O_7$ (M+1) = 804.42, found 804.00.
HRMS (ESI-TOF): M+Na^+, found 826.4149 $C_{47}H_{57}N_5O_7Na_1$ requires 826.4156.
^{1}H NMR (600 MHz, DMSO): δ 8.09 (m, 2H, NH), 7.82 (d, *J* = 7.26 Hz, 1H, NH), 7.56 (s, 1H, NH), 7.30-7.03 (m, 10H, D-BiPhe), 6.91-6.71 (m, 8H, Methoxy-D-Phe), 5.16 (q, 1H, CHα D-BiPhe), 4.68 (q, 1H, CHα Methoxy-D-Phe), 4.52 (d, *J* = 11.38 Hz, 1H, CHα Val), 4.31 (d, *J* = 11.85 Hz, 1H, CHβ D-BiPhe), 3.97 (m, 1H, CHα Methoxy-D-Phe), 3.35 (m, 1H, CHα Leu), 3.03 (m, 1H, $CH_2\beta_1$ Methoxy-D-Phe), 2.85 (m, 2H, $CH_2\beta_2$ Methoxy-D-Phe), 2.70 (m, 1H, $CH_2\beta_1$ Methoxy-D-Phe), 2.56 (s, 3H, NCH_3), 2.09 (m, 1H, $CH_2\beta$ Val), 1.45 (m, 1H, $CH_2\beta_2$ Leu), 1.38 (m, 1H, $CH_2\beta_1$ Leu), 1.20 (m, 1H, CHγ Leu), 0.83-0.55 (m, 18H, CH_3 Val, CH_3 Leu, CH_3 Methoxy-D-Phe).

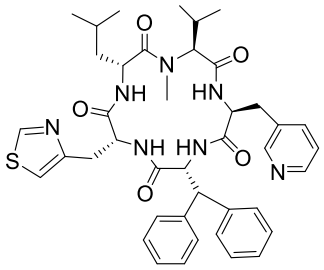


Compound 34

Following "**General peptide coupling"** procedure for SPPS and the published procedure for SPPS (Koay, Y. C.; McConnell, J. R.; Wang, Y.; Kim, S. J.; Buckton, L. K.; Mansour, F.; McAlpine, S. R. *ACS Med. Chem. Lett.* **2014**, *5*, 771-776), linear pentapeptide of resin-O-Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-(4-Methoxy)-D-Phe-3,3-Diphe-D-Ala-NH_2 was synthesized by using (0.5 mmol, 1.0 equivalent) of resin-O-Leu-NH_2 and the subsequent peptide coupling in the sequence using 1.5 mmol (3.0 equivalents) of each mentioned below: Fmoc-*N*-Me-Val-OH, Fmoc-3-(4-Thia)-D-Ala-OH, Fmoc-(4-Methoxy)-D-Phe-OH, Fmoc-D-Phe-OH, and Fmoc-3,3-Diphenyl-D-Ala-OH. Each peptide coupling was done in the presence of HOAt (1.5 mmol, 3.0 equivalents) or HOBt (1.5 mmol, 3.0 equivalents), DIC (3.0 mmol, 6.0 equivalents) and DMF to generate a concentration of 0.20 M based on the amino acid. Each coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm the reaction completion. The reaction mixture was drained to afford the Fmoc-protected resin-bound pentapeptide and the Fmoc protecting group was removed following the **"General Fmoc removal"** after the completion of each coupling reaction.

The double deprotected linear pentapeptide (DDLP) HO-Leu-*N*-Me-Val-3-(3-pyridyl)-D-Ala-D-Phe-3,3-Diphe-D-Ala-NH_2 was generated following the **"Resin cleavage of linear peptide"** procedure for SPPS. The linear pentapeptide was cleaved from the resin using a mixed solution of 6 mL of TFE and 6 mL of CH_2Cl_2. The resin containing solution was filtered and dried *in vacuo* to yield the DDLP as a white solid (Quantitative yield)
LC/MS (ESI): *m/z* called for $C_{43}H_{54}N_6O_7S$ (M+1) = 798.37, found 799.00.

***Cyclo* Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-(4-Methoxy)-D-Phe-3,3-Diphe-D-Ala (34)** was synthesized using the DDLP (1.0 equivalent), TBTU (0.80 equivalent), HATU (0.80 equivalent), DMTMM (0.80 equivalent), DIPEA (8.0 equivalents) in anhydrous CH_2Cl_2 (0.001M) following "**Macrocyclization procedure (syringe pump)"** procedure. The reaction was then stirred overnight and the reaction was monitored via LC/MS. Upon completion, the reaction mixture was subjected to acid-base wash, which was extracted twice with 10% (v/v) $HCl_{(aq)}$. The organic layer was then re-extracted with a saturated of $NaHCO_3$ aqueous solution. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via flash column chromatography on silica gel using an ethyl acetate-hexane gradient system, followed by purification via HPLC to yield compound **34** as white solid (Yield 26%).
R_f: 0.25 (Hex:EtOAc = 0.25:0.75)
LC/MS: *m/z* called for $C_{43}H_{52}N_6O_6S$ (M+1) = 780.37, found 745.00.
HRMS (ESI-TOF): M+Na^+, and M+H found 803.3564 and 781.3748 $C_{43}H_{52}N_6O_6S_1Na_1$ requires 803.3567 and $C_{43}H_{52}N_6O_6S$ + H requires 781.3669.
^{1}H NMR (600 MHz, DMSO): δ 8.96 (d, *J* = 1.94 Hz, 1H, D-Thia), 8.13 (m, 2H, NH), 7.85 (d, *J* = 7.46 Hz, 1H, NH), 7.66 (d, *J* = 8.66 Hz, 1H, NH), 7.27-7.11 (m, 10H, D-BiPhe), 6.77 (m, 4H, Methoxy-D-Phe), 5.17 (m, 2H, CHα D-BiPhe, CHα D-Thia), 4.95 (q, 1H, CHα Methoxy-D-Phe), 4.52 (d, *J* = 11.46 Hz, 1H, CHα Val), 4.31 (d, *J* = 11.87 Hz, 1H, CHβ D-BiPhe), 4.01 (m, 1H, CHα Leu), 3.47-3.22 (m, 2H, $CH_2\beta_1$ D-Thia, $CH_2\beta_1$ Methoxy-D-Phe), 3.03-3.22 (m, 2H, $CH_2\beta_2$ D-Thia, $CH_2\beta_2$ Methoxy-D-Phe), 2.62 (s, 3H, NCH_3), 2.10 (m, 1H, CHβ Val), 1.46 (m, 1H, $CH_2\beta_1$ Leu), 1.38 (m, 1H, $CH_2\beta_2$ Leu), 1.19 (m, 1H, CHγ Leu), 0.79 (d, *J* = 6.43 Hz, 3H, Methoxy-D-Phe) 0.75-0.57 (m, 12H, $CHCH(CH_3)_2$, $CH_2CH(CH_3)_2$).

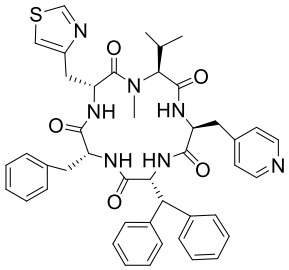


Compound 35

Following "**General peptide coupling"** procedure for SPPS and the published procedure for SPPS (Koay, Y. C.; McConnell, J. R.; Wang, Y.; Kim, S. J.; Buckton, L. K.; Mansour, F.; McAlpine, S. R. *ACS Med. Chem. Lett.* **2014**, *5*, 771-776), linear pentapeptide of resin-O-D-Leu-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala-3-(4'-Pyr)Ala-*N*-Me-Val-NH_2 was synthesized by using 1.00 g (0.53 mmol, 1.0 equivalent) of resin-O-D-Leu-NH_2 and the subsequent peptide coupling in the sequence as mentioned below: 0.63 g (1.6 mmol, 3.0 equivalents) of Fmoc-3-(4-Thiazoyl)Ala-OH, 0.74 g (1.6 mmol, 3.0 equivalents) of Fmoc-3,3-Diphenyl-D-Ala-OH, 0.62 g (1.6 mmol, 3.0 equivalents) of Fmoc-3-(4'Pyridyl)Ala-OH and 0.56 g (1.6 mmol, 3.0 equivalents) of Fmoc-*N*-Me-Val-OH. Each peptide coupling was done in the presence of 0.22 g of HOAt (1.6 mmol, 3.0 equivalents) or 0.21 g of HOBt (1.6 mmol, 3.0 equivalents), 0.50 mL of DIC (3.2 mmol, 6.0 equivalents) and 2.65 mL of DMF to generate a concentration of 0.20 M. Each coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm the reaction completion. The reaction mixture was drained to afford the Fmoc-protected resin-bound pentapeptide and the Fmoc protecting group was removed following the **"General Fmoc removal"** after the completion of each coupling reaction.

The double deprotected linear pentapeptide (DDLP) HO-D-Leu-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala-3-(4'-Pyr)Ala-*N*-Me-Val-NH_2 was generated following the **"Resin cleavage of linear peptide"** procedure for SPPS. The linear pentapeptide was cleaved from the resin using a mixed solution of 6 mL of TFE and 6 mL of CH_2Cl_2. The resin containing solution was filtered and dried *in vacuo* to yield the DDLP as a white solid (196 mg, overall 48%).
LC/MS (ESI): *m/z* called for $C_{41}H_{51}N_7O_6S$ (M+1) = 770.36, found 770.10.

***Cyclo* D-Leu-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala-3-(4'-Pyr)Ala-*N*-Me-Val (35)** was synthesized using 0.20 g of the DDLP generated (0.26 mmol, 1.0 equivalent), 0.07 g of TBTU (0.21 mmol, 0.80 equivalent), 0.08 g of HATU (0.21 mmol, 0.80 equivalent), 0.06 g of DMTMM (0.21 mmol, 0.80 equivalent), 0.36 mL of DIPEA (2.1 mmol, 8.0 equivalents) in anhydrous CH_2Cl_2 (260 mL, 0.001M) following "**Macrocyclization procedure (syringe pump)"** procedure. The reaction was then stirred overnight and the reaction was monitored via LC/MS. Upon completion, the reaction mixture was subjected to acid-base wash, which was extracted twice with 10% (v/v) $HCl_{(aq)}$. The organic layer was then re-extracted with a saturated of $NaHCO_3$ aqueous solution. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via flash column chromatography on silica gel using an ethyl acetate-hexane gradient system, followed by purification via HPLC to yield compound **35** as white solid (6 mg, 3%).
*Note: Cyclization at the bulky residue of *N*-methyl has resulted a poor reaction and thus HPLC yield. Due to the limited amount of compound, HSQC and HMBC spectra were used for the complete assignment of all the carbon peaks.
R_f: 0.63 (100% EtOAc)
LC/MS: *m/z* called for $C_{41}H_{49}N_7O_5S$ (M+1) = 752.35, found 752.50.
HRMS (ESI-TOF): $M+Na^+$, found 774.3414 $C_{41}H_{49}N_7O_5S_1Na_1$ requires 774.3399.
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.32 (br, D-Thia), 9.09 (br, NH), 8.68 (m, 2H, Pyr), 7.67 (m, NH, D-Thia), 7.47-7.00 (m, 12H, D-BiPhe, Pyr, 2NH), 5.09 (m, 2H, CHα D-BiPhe, CHβ D-BiPhe), 4.89 (m, 1H, CHα Pyr), 4.79 (m, 2H, CHα Leu, CHα D-Thia), 4.59 (d, *J* = 11.3 Hz, 1H, CHα Val), 3.44 (m, 1H, $CH_2\beta_2$ Pyr), 2.82 (m, 2H, $CH_2\beta_2$ D-Thia, $CH_2\beta_1$ Pyr), 2.68 (m, 4H, $CH_2\beta_1$ D-Thia, NCH_3), 2.12 (m, 1H, CHβ Val), 1.28 (m, 3H, $CH_2\beta$ Leu, CHγ Leu), 0.84-0.76 (m, 12H, $CHCH(CH_3)_2$, $CH_2CH(CH_3)_2$).
^{13}C NMR (150 MHz, DMSO): δ 175.55, 173.17, 172.11, 171.26, 169.25, 153.73, 152.77, 149.55, 145.96, 140.33, 139.32, 138.33, 136.25, 129.91, 128.84, 128.37, 128.06, 127.91, 127.35, 124.32, 115.05, 62.40, 57.48, 52.54, 52.31, 51.75, 48.30, 40.45, 37.37, 31.71, 29.07, 27.16, 25.47, 24.52, 22.54, 19.16, 18.13.



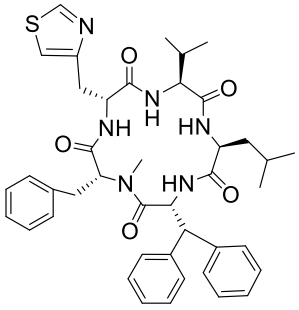
Compound 36

Following "**General peptide coupling"** procedure for SPPS and the published procedure for SPPS (Koay, Y. C.; McConnell, J. R.; Wang, Y.; Kim, S. J.; Buckton, L. K.; Mansour, F.; McAlpine, S. R. *ACS Med. Chem. Lett.* **2014**, *5*, 771-776), linear pentapeptide of Resin-O-D-Phe-3,3-Diphe-D-Ala-3-(2-pyridyl)-Ala-*N*-Me-Val-3-(4-Thia)-D-Ala-NH_2 was synthesized by using (1.0 equivalent) of resin-O-D-Phe-NH_2 and the subsequent peptide coupling in the sequence as mentioned below: Fmoc-3,3-Diphenyl-D-Ala-OH (1.5 mmol, 3.0 equivalents), Fmoc-3-(2-pyridyl)-D-Ala OH, Fmoc-*N*-Me-Val-OH (1.5 mmol, 3.0 equivalents), and Fmoc-3-(4-Thia)-D-Ala-OH (1.5 mmol, 3.0 equivalents). Each peptide coupling was done in the presence of HOAt (1.5 mmol,

3.0 equivalents) or HOBt (1.5 mmol, 3.0 equivalents), DIC (3.0 mmol, 6.0 equivalents) and DMF to generate a concentration of 0.20 M based on the amino acid. Each coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm the reaction completion. The reaction mixture was drained to afford the Fmoc-protected resin-bound pentapeptide and the Fmoc protecting group was removed following the **"General Fmoc removal"** after the completion of each coupling reaction.

The double deprotected linear pentapeptide (DDLP) HO-D-Phe-3,3-Diphe-D-Ala-3-(2-pyridyl)-Ala-*N*-Me-Val-3-(4-Thia)-D-Ala-NH_2 was generated following the **"Resin cleavage of linear peptide"** procedure for SPPS. The linear pentapeptide was cleaved from the resin using a mixed solution of 6 mL of TFE and 6 mL of CH_2Cl_2. The resin containing solution was filtered and dried *in vacuo* to yield the DDLP as a white solid (Yield 48%).
LC/MS (ESI): *m/z* called for $C_{44}H_{49}N_7O_5S$ (M+1) = 804.34, found 804.00.

***Cyclo* D-Phe-3,3-Diphe-D-Ala-3-(2-pyridyl)-Ala-*N*-Me-Val-3-(4-Thia)-D-Ala (36)** was synthesized using the DDLP (1.0 equivalent), TBTU (0.80 equivalent), HATU (0.80 equivalent), DMTMM (0.80 equivalent), DIPEA (8.0 equivalents) in anhydrous CH_2Cl_2 (0.001M) following "**Macrocyclization procedure (syringe pump)"** procedure. The reaction was then stirred overnight and the reaction was monitored via LC/MS. Upon completion, the reaction mixture was subjected to acid-base wash, which was extracted twice with 10% (v/v) $HCl_{(aq)}$. The organic layer was then re-extracted with a saturated of $NaHCO_3$ aqueous solution. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via flash column chromatography on silica gel using an ethyl acetate-hexane gradient system, followed by purification via HPLC to yield compound **36** as white solid (Yield 48%).
R_f: 0.13 (Hex:EtOAc = 0.25:0.75)
LC/MS: *m/z* called for $C_{44}H_{47}N_7O_5S$ (M+1) = 786.34, found 786.00.
HRMS (ESI-TOF): $M+Na^+$, found 786.3434 $C_{44}H_{47}N_7O_5S$ requires 786.3359.
^{1}H NMR (600 MHz, DMSO): δ 8.98 (d, *J* = 1.9 Hz, 1H, D-Thia), 8.65 (s, 1H, NH), 8.39 (m, 1H, Pyridyl), 8.30 (s, 1H, NH), 7.94 (s, 1H, NH), 7.60 (m, 1H, NH) 7.40-7.07 (m, 15H, D-BiPhe, D-Phe), 7.00 (d, , *J* = 7.79 1H, Pyridyl), 6.71 (d, *J* = 7.05 2H, Pyridyl), 5.21 (m, 2H, CHα D-BiPhe, CHα D-Thia), 4.61 (2, *J* = 12.02 Hz, 1H, CHβ D-BiPhe), 4.45 (m, 1H, CHα D-Phe), 4.23 (d, *J* = 11.17 Hz, 1H, CHα Val), 3.82 (m, 1H, CHα Pyridyl), 3.33 (m, 1H, $CH_2\beta_1$ D-Thia), 2.98 (dd, *J* = 14.05 Hz 1H, $CH_2\beta_2$ D-Thia), 2.90-2.73 (m, 2H, $CH_2\beta$ Pyridyl), 2.64 (s, 3H, NCH_3), 2.34 (m, 1H, $CH_2\beta_1$ D-Phe), 2.17 (dd, 1H, *J* = 13.82 Hz, $CH_2\beta_2$ D-Phe), 1.83 (m, 1H, CH Val), 0.43 (d, *J* = 6.56 , 3H, CH_3 Val), 0.32 (d, *J* = 6.42 1H, CH_3 Val)


Compound 37

Following "**General peptide coupling"** procedure for SPPS and the published procedure for SPPS (Koay, Y. C.; McConnell, J. R.; Wang, Y.; Kim, S. J.; Buckton, L. K.; Mansour, F.; McAlpine, S. R. *ACS Med. Chem. Lett.* **2014**, *5*, 771-776), linear pentapeptide of resin-O-Leu-Val-3-(4-Thia)-D-Ala-*N*-Me-D-Phe-3,3-Diphenyl-D-Ala-NH_2 was synthesized by using 1.00 g (0.5 mmol, 1.0 equivalent) of resin-O-Leu-NH_2 and the subsequent peptide coupling in the sequence as mentioned below: 0.51 g (1.5 mmol, 3.0 equivalents) of Fmoc-Val-OH, 0.59 g (1.5 mmol, 3.0 equivalents) of Fmoc-D-3-(4-Thiazoyl)Ala-OH, 0.60 g (1.5 mmol, 3.0 equivalents) of Fmoc-*N*-Me-D-Phe-OH and 0.70 g (1.5 mmol, 3.0 equivalents) of Fmoc-3,3-Diphenyl-D-Ala-OH. Each peptide coupling was done in the presence of 0.20 g of HOAt (1.5 mmol, 3.0 equivalents) or 0.20 g of HOBt (1.5 mmol, 3.0 equivalents), 0.47 mL of DIC (3.0 mmol, 6.0 equivalents) and 2.5 mL of DMF to generate a concentration of 0.20 M. Each coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm the reaction completion. The reaction mixture was drained to afford the Fmoc-protected resin-bound pentapeptide and the Fmoc protecting group was removed following the **"General Fmoc removal"** after the completion of each coupling reaction.

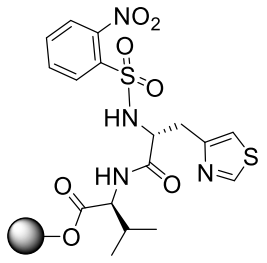
The double deprotected linear pentapeptide (DDLP) HO-Leu-Val-3-(4-Thia)-D-Ala-*N*-Me-D-Phe-3,3-Diphenyl-D-Ala-NH_2 was generated following the **"Resin cleavage of linear peptide"** procedure for SPPS. The linear pentapeptide was cleaved from the resin using a mixed solution of 6 mL of TFE and 6 mL of CH_2Cl_2. The resin containing solution was filtered and dried *in vacuo* to yield the DDLP as a white solid (311 mg, overall 81%).
LC/MS (ESI): *m/z* called for $C_{42}H_{52}N_6O_6S$ (M+1) = 769.37, found 769.50.

***Cyclo* Leu-Val-3-(4-Thia)-D-Ala-*N*-Me-D-Phe-3,3-Diphe-D-Ala (37)** was synthesized using 0.31 g of the DDLP generated (0.40 mmol, 1.0 equivalent), 0.10 g of TBTU (0.32 mmol, 0.80 equivalent), 0.12 g of HATU (0.32 mmol, 0.80 equivalent), 0.09 g of DMTMM (0.32 mmol, 0.80 equivalent), 0.56 mL of DIPEA (3.2 mmol, 8.0

equivalents) in anhydrous CH_2Cl_2 (404 mL, 0.001M) following "**Macrocyclization procedure (syringe pump)"** procedure. The reaction was then stirred overnight and the reaction was monitored via LC/MS. Upon completion, the reaction mixture was subjected to acid-base wash, which was extracted twice with 10% (v/v) $HCl_{(aq)}$. The organic layer was then re-extracted with a saturated of $NaHCO_3$ aqueous solution. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via flash column chromatography on silica gel using an ethyl acetate-hexane gradient system, followed by purification via HPLC to yield compound **37** as white solid (155 mg, 51%).
R_f: 0.30 (100% EtOAc)
LC/MS: *m/z* called for $C_{42}H_{50}N_6O_5S$ (M+1) = 751.36, found 751.45.
HRMS (ESI-TOF): $M+Na^+$, found 773.3450 $C_{42}H_{50}N_6O_5S_1Na_1$ requires 773.3461.

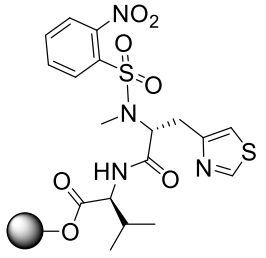
a) **Major conformer**
^{1}H NMR (600 MHz, DMSO): δ 9.05 (d, *J* = 1.9 Hz, 1H), 9.01 (dd, *J* = 3.8, 5.7 Hz, 2NH), 8.08 (dd, *J* = 8.1, 12.8 Hz, NH), 8.01 (d, *J* = 8.6 Hz, NH), 7.43-7.06 (m, 13H, D-BiPhe, D-Phe), 6.96 (m, 2H, D-Phe), 6.35 (m, 1H), 5.42 (dd, *J* = 9.8, 4.0 Hz, 1H, CHα D-Phe), 5.26 (t, *J* = 10.4 Hz, 1H, CHα D-BiPhe), 4.49 (q, *J* = 7.3 Hz, 1H, CHα D-Thia), 4.38 (d, *J* = 11.2 Hz, 1H, CHβ D-BiPhe), 4.10 (m, 1H, CHα Leu), 3.71 (t, *J* = 9.0 Hz, 1H, CHα Val), 3.44 (dd, *J* = 3.8, 14.3 Hz, 1H, $CH_2\beta_2$ D-Phe), 3.19 (dd, *J* = 6.7, 14.4 Hz, 1H, $CH_2\beta_2$ D-Thia), 3.10 (m, 1H, $CH_2\beta_1$ D-Thia), 2.80 (dd, *J* = 9.9, 14.3 Hz, 1H, $CH_2\beta_1$ D-Phe), 2.50 (s, 3H, NCH_3), 1.89 (m, 1H, CHβ Val), 1.27 (m, 1H, $CH_2\beta_2$ Leu), 0.89 (m, 2H, CHγ Leu, $CH_2\beta_1$ Leu), 0.82-0.56 (m, 12H, $CH_2CH(CH_3)_2$, $CHCH(CH_3)_2$).
^{13}C NMR (150 MHz, DMSO): δ 172.34, 172.21, 170.25, 170.13, 169.77, 168.77, 141.72, 141.09, 137.20, 129.35, 128.80, 128.70, 128.60, 128.45, 128.10, 127.17, 127.03, 126.83, 79.95, 63.39, 57.27, 56.29, 53.75, 51.68, 49.20, 38.11, 37.85, 31.82, 30.16, 28.24, 27.28, 25.18, 24.49, 22.82, 22.55, 19.66, 18.07.

b) **Minor conformer**
.^{1}H NMR (600 MHz, DMSO): δ 9.01 (m, NH, 1H), 8.27 (d, *J* = 6.5 Hz, NH), 8.01 (d, *J* = 8.6, NH), 7.43-7.24 (m, 13H, D-BiPhe, D-Phe), 6.96 (m, 2H, D-Phe), 6.76 (m, 1H), 5.51 (dd, *J* = 8.4, 11.5 Hz, 1H, CHα D-Phe), 5.26 (t, *J* = 10.4 Hz, 1H, CHα D-BiPhe), 4.63 (m, 1H, CHα D-Thia), 4.44 (d, *J* = 11.6 Hz, 1H, CHβ D-BiPhe), 4.10 (m, 1H, CHα Leu), 3.75 (m, 1H, CHα Val), 3.28 (m, 1H, $CH_2\beta_2$ D-Phe), 3.10 (m, 1H, $CH_2\beta_2$ D-Thia), 3.01 (dd, *J* = 5.9, 13.9 Hz, 1H, $CH_2\beta_1$ D-Thia), 2.92 (dd, *J* = 9.9, 14.3 Hz, 1H, $CH_2\beta_1$ D-Phe), 2.92 (s, 3H, NCH_3), 2.67 (m, 1H, $CH_2\beta_1$ D-Phe), 1.94 (m, 1H, CHβ Val), 1.48 (m, 1H, $CH_2\beta_2$ Leu), 1.30 (m, 1H, CHγ Leu), 1.26 (m, 1H, $CH_2\beta_1$ Leu), 0.71-0.66 (m, 12H, $CH_2CH(CH_3)_2$, $CHCH(CH_3)_2$).



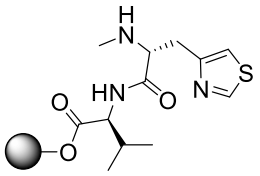
Resin-O-Val-3-(4-Thia)-D-Ala-NH-o-NBS

Dipeptide resin-O-Val-3-(4-Thia)-D-Ala-Fmoc was synthesized following "**General peptide coupling"** procedure, by using 1.00 g (0.74 mmol, 1.0 equivalent) of resin-O-Val-NH_2, 0.88 g (2.22 mmol, 3.0 equivalents) of Fmoc-D-3-(4-Thiazoyl)Ala-OH, 0.30 g of HOBt (2.22 mmol, 3.0 equivalents), 0.70 mL of DIC (4.44 mmol, 6.0 equivalents) and 3.7 mL of DMF to generate a concentration of 0.20 M and the Fmoc group was removed following the **"General Fmoc removal"** procedure for SPPS. *o*-NBS protected resin-bound dipeptide was synthesized following the **"*o*-NBS Protection"** procedure, by using 0.66 g of *o*-NBS-Cl (2.96 mmol, 4 equivalents) and 0.98 mL of collidine (7.4 mmol, 10 equivalents) and 25 mL of CH_2Cl_2 to generate a concentration of 0.03 M.
LC/MS (ESI): *m/z* called for $C_{17}H_{20}N_4O_7S_2$ (M+1) = 456.08, found 456.80.



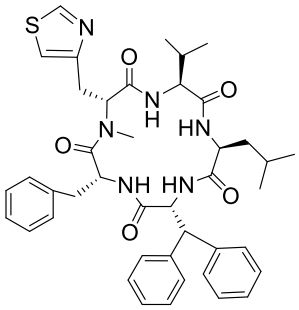
Resin-O-Val-3-(4-Thia)-D-Ala-NCH_3-o-NBS

A solution of 0.97 g of triphenylphosphine (3.7 mmol, 5 equivalents) and 0.30 mL of MeOH (10 equivalents) in dry THF was added to the resin bound *o*-NBS-protected peptides and stirred for 10 mins. A solution of 0.73 mL DIAD (5 equivalents) in dry THF was then added portion by portion to the reaction mixture and stirred for 4 hours at room temperature. The resin was filtered off, and washed with DMF (5x). *N*-Methyl-*N*-*o*-NBS-peptides were then cleaved from resin by treatment of a small amount of resin with TFE:CH_2Cl_2 (1:1) and analysed by LCMS to monitor the reaction completion.
LC/MS (ESI): *m/z* called for $C_{18}H_{22}N_4O_7S_2$ (M+1) = 471.09, found 470.85.



Resin-O-Val-3-(4-Thia)-D-Ala-NH(CH_3)

For *o*-NBS deprotection, the resin-bound *N*-Methyl-*N*-*o*-NBS-peptides was treated with a solution of 0.52 mL mercaptoethanol (10 equivalents) and 0.55 mL DBU (5 equivalents) in DMF for 2 hours. The deprotection procedure was repeated one more time and the resin was washed with DMF (5x).
LC/MS (ESI): *m/z* called for $C_{12}H_{19}N_3O_3S$ (M+1) = 286.11, found 285.80.

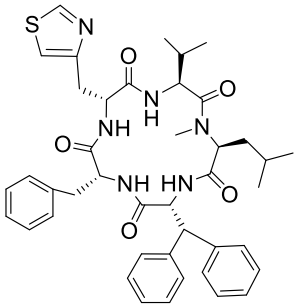


Compound 38

Following "**General peptide coupling"** and published procedure for SPPS (Koay, Y. C.; McConnell, J. R.; Wang, Y.; Kim, S. J.; Buckton, L. K.; Mansour, F.; McAlpine, S. R. *ACS Med. Chem. Lett.* **2014**, *5*, 771-776), linear pentapeptide of resin-O-Val-*N*-Me-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala-Leu-NH_2 was synthesized by using resin-O-Val-3-(4-Thia)-D-Ala-NH-CH_3 and the subsequent peptide coupling in the sequence as mentioned below: 0.86 g (2.2 mmol, 3.0 equivalents) of Fmoc-D-Phe-OH, 1.03 g (2.2 mmol, 3.0 equivalents) of Fmoc-3,3-Diphe-D-Ala-OH and 0.78 g (2.2 mmol, 3.0 equivalents) of Fmoc-Leu-OH. Each peptide coupling was done in the presence of 0.30 g of HOAt (2.2 mmol, 3.0 equivalents) or 0.30 g of HOBt (2.2 mmol, 3.0 equivalents), 0.70 mL of DIC (4.4 mmol, 6.0 equivalents) and 3.7 mL of DMF to generate a concentration of 0.20 M. Each coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm the reaction completion. The reaction mixture was drained to afford the Fmoc-protected resin-bound pentapeptide and the Fmoc protecting group was removed following the **"General Fmoc removal"** after the completion of each coupling reaction.

The double deprotected linear pentapeptide (DDLP) HO-Val-*N*-Me-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala-Leu-NH_2 was generated following the **"Resin cleavage of linear peptide"** procedure for SPPS. The linear pentapeptide was cleaved from the resin using a mixed solution of 6 mL of TFE and 6 mL of CH_2Cl_2. The resin containing solution was filtered and dried *in vacuo* to yield the DDLP as a white solid (284 mg, overall 50%).
LC/MS (ESI): *m/z* called for $C_{42}H_{52}N_6O_6$ (M+1) = 769.37, found 769.40.

***Cyclo* Val-*N*-Me-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala-Leu (38)** was synthesized using 0.15 g of the DDLP generated (0.20 mmol, 1.0 equivalent), 0.05 g of TBTU (0.16 mmol, 0.80 equivalent), 0.07 g of HATU (0.20 mmol, 1.0 equivalent), 0.03 g of DMTMM (0.12 mmol, 0.60 equivalent), 0.27 mL of DIPEA (1.6 mmol, 8.0 equivalents) in anhydrous CH_2Cl_2 (195 mL, 0.001M) following "**Macrocyclization procedure (syringe pump)"** procedure. The reaction was then stirred overnight and the reaction was monitored via LC/MS. Upon completion, the reaction mixture was subjected to acid-base wash, which was extracted twice with 10% (v/v) $HCl_{(aq)}$. The organic layer was then re-extracted with a saturated of $NaHCO_3$ aqueous solution. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via flash column chromatography on silica gel using an ethyl acetate-hexane gradient system, followed by purification via HPLC to yield compound **38** as white solid (40 mg, 27%).
R_f: 0.28 (100% EtOAc)
LC/MS: *m/z* called for $C_{42}H_{50}N_6O_5S$ (M+1) = 751.36, found 750.95.
HRMS (ESI-TOF): M+1, found 751.3636 $C_{42}H_{50}N_6O_5S$ requires 751.3636.
^{1}H NMR (600 MHz, DMSO): δ 9.02 (d, *J* = 1.9 Hz, 1H, D-Thia), 8.46 (d, *J* = 9.1 Hz, NH), 7.84 (d, *J* = 6.7 Hz, NH), 7.67 (d, *J* = 7.3 Hz, NH), 7.48 (d, *J* = 10.0 Hz, NH), 7.37-7.15 (m, 13H, D-BiPhe, D-Phe), 6.95 (m, 3H, D-Phe, D-Thia), 5.03 (dd, *J* = 9.1, 11.7 Hz, 1H, CHα D-BiPhe), 4.67 (m, 1H, CHα D-Thia), 4.41 (d, *J* = 11.7 Hz, 1H, CHβ D-BiPhe), 3.99 (m, 2H, CHα Val, CHα D-Phe), 3.87 (m, 1H, CHα Leu), 3.43 (dd, *J* = 3.8, 14.9 Hz, 1H, $CH_2\beta_2$ D-Phe), 3.12 (dd, *J* = 9.5, 14.9 Hz, 1H, $CH_2\beta_1$ D-Phe), 2.69 (m, 1H, $CH_2\beta_2$ D-Thia), 2.59 (s, 3H, NCH_3), 2.56 (d, *J* = 4.6 Hz, 1H, $CH_2\beta_1$ D-Thia), 1.76 (m, 1H, CHβ Val), 1.50 (m, 1H, $CH_2\beta_2$ Leu), 1.22 (m, 1H, $CH_2\beta_1$ Leu), 1.14 (m, 1H, CHγ Leu), 0.79 (t, *J* = 6.6 Hz, 6H, $CHCH(CH_3)_2$), 0.67 (d, *J* = 6.5 Hz, 3H, $CH_2CH(CH_3)_2$), 0.56 (d, *J* = 6.5 Hz, 3H, $CH_2CH(CH_3)_2$).
^{13}C NMR (150 MHz, DMSO): δ 170.61, 170.22, 170.16, 169.92, 168.17, 155.06, 154.02, 142.28, 141.14, 137.14, 129.85, 129.26, 128.97, 128.63, 128.55, 128.35, 127.06, 126.86, 126.79, 115.57, 65.09, 61.01, 58.52, 52.73, 52.22, 50.77, 40.53, 39.13, 38.68, 31.74, 29.63, 25.14, 23.39, 21.81, 19.66, 19.53.

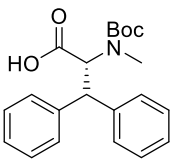


Compound 39

Following "**General peptide coupling"** procedure for SPPS and the published procedure for SPPS (Koay, Y. C.; McConnell, J. R.; Wang, Y.; Kim, S. J.; Buckton, L. K.; Mansour, F.; McAlpine, S. R. *ACS Med. Chem. Lett.* **2014**, *5*, 771-776), linear pentapeptide of resin-O-D-Phe-3,3-Diphe-D-Ala-*N*-Me-D-Leu-Val-3-(4-Thia)-D-Ala-NH_2 was synthesized by using 1.00 g (0.72 mmol, 1.0 equivalent) of resin-O-D-Phe-NH_2 and the subsequent peptide coupling in the sequence as mentioned below: 1.00 g (2.2 mmol, 3.0 equivalents) of Fmoc-3,3-Diphe-D-Ala-OH, 0.79 g (2.2 mmol, 3.0 equivalents) of Fmoc-*N*-Me-D-Leu-OH, 0.73 g (2.2 mmol, 3.0 equivalents) of Fmoc-Val-OH and 0.85 g (2.2 mmol, 3.0 equivalents) of Fmoc-D-3-(4-Thiazoyl)Ala-OH. Each peptide coupling was done in the presence of 0.29 g of HOAt (2.2 mmol, 3.0 equivalents) or 0.29 g of HOBt (2.2 mmol, 3.0 equivalents), 0.68 mL of DIC (4.3 mmol, 6.0 equivalents) and 3.6 mL of DMF to generate a concentration of 0.20 M. Each coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm the reaction completion. The reaction mixture was drained to afford the Fmoc-protected resin-bound pentapeptide and the Fmoc protecting group was removed following the **"General Fmoc removal"** after the completion of each coupling reaction.

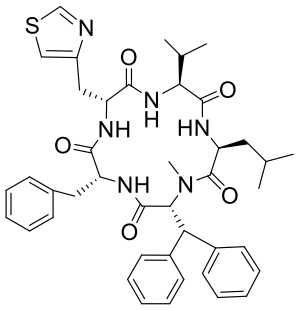
The double deprotected linear pentapeptide (DDLP) HO-D-Phe-3,3-Diphe-D-Ala-*N*-Me-D-Leu-Val-3-(4-Thia)-D-Ala-NH_2 was generated following the **"Resin cleavage of linear peptide"** procedure for SPPS. The linear pentapeptide was cleaved from the resin using a mixed solution of 6 mL of TFE and 6 mL of CH_2Cl_2. The resin containing solution was filtered and dried *in vacuo* to yield the DDLP as a white solid (393 mg, overall 71%).
LC/MS (ESI): *m/z* called for $C_{42}H_{52}N_6O_6S$ (M+1) = 769.37, found 769.00.

***Cyclo* D-Phe-3,3-Diphe-D-Ala-*N*-Me-D-Leu-Val-3-(4-Thia)-D-Ala (39)** was synthesized using 0.39 g of the DDLP generated (0.51 mmol, 1.0 equivalent), 0.13 g of TBTU (0.41 mmol, 0.80 equivalent), 0.16 g of HATU (0.41 mmol, 0.80 equivalent), 0.11 g of DMTMM (0.41 mmol, 0.80 equivalent), 0.71 mL of DIPEA (4.1 mmol, 8.0 equivalents) in anhydrous CH_2Cl_2 (511 mL, 0.001M) following "**Macrocyclization procedure (syringe pump)"** procedure. The reaction was then stirred overnight and the reaction was monitored via LC/MS. Upon completion, the reaction mixture was subjected to acid-base wash, which was extracted twice with 10% (v/v) $HCl_{(aq)}$. The organic layer was then re-extracted with a saturated of $NaHCO_3$ aqueous solution. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via flash column chromatography on silica gel using an ethyl acetate-hexane gradient system, followed by purification via HPLC to yield compound **39** as white solid (63 mg, 16%).
R_f: 0.30 (100% EtOAc)
LC/MS: *m/z* called for $C_{42}H_{50}N_6O_5S$ (M+1) = 751.36, found 751.00.
HRMS (ESI-TOF): M+Na^+, found 773.3455 $C_{42}H_{50}N_6O_5S_1Na_1$ requires 773.3461.
^{1}H NMR (600 MHz, DMSO): δ 9.10 (d, *J* = 9.1 Hz, 1H), 9.02 (m, 2NH), 8.34 (*br*, NH), 7.68 (*br*, NH), 7.41-7.15 (m, 15H, D-BiPhe, D-Phe), 6.88 (d, *J* = 9.1 Hz, 1H), 5.19 (t, *J* = 10.9 Hz, 1H, CHα D-BiPhe), 4.78 (q, *J* = 7.4 Hz, 1H, CHα D-Phe), 4.56 (*br*, 1H, CHα Leu), 4.50 (d, *J* = 12.3 Hz, 1H, CHβ D-BiPhe), 4.28 (t, *J* = 9.1 Hz, 1H, CHα Val), 3.82 (q, *J* = 7.5 Hz, 1H, CHα D-Thia), 3.15 (dd, *J* = 7.3, 14.2 Hz, 1H, $CH_2\beta_2$ D-Phe), 3.08 (dd, *J* = 6.9, 14.0 Hz, 1H, $CH_2\beta_1$ D-Phe), 2.90 (m, 2H, CH_2β D-Thia), 2.74 (s, 3H, NCH_3), 2.02 (m, 1H, CHβ Val), 0.99 (m, 1H, $CH_2\beta_2$ Leu), 0.85-0.56 (m, 14H, CHγ Leu, $CH_2\beta_1$ Leu, $CH_2CH(CH_3)_2$, $CHCH(CH_3)_2$).
^{13}C NMR (150 MHz, DMSO): δ 171.51, 171.14, 170.61, 170.57, 169.62, 153.83, 152.75, 141.80, 141.10, 138.00, 129.09, 129.03, 128.82, 128.77, 128.61, 128.13, 127.19, 126.97, 126.73, 116.19, 59.11, 57.11, 57.00, 54.43, 52.32, 52.26, 39.43, 36.51, 34.87, 30.00, 29.96, 24.20, 23.15, 22.63, 20.02, 18.50.



Boc-N-Me-3,3-Diphe-D-Ala-OH

Following "**Benoiton method**" procedure for *N*-methylation, Boc-*N*-Me-3,3-Diphe-D-Ala-OH was synthesized using 1.00 g (2.93 mmol, 1 equivalent) of Boc-3,3-Diphe-D-Ala-NH_2, 1.17 g of NaH (29.3 mmol, 10 equivalents) and 4.16 g of CH_3I (29.3 mmol, 10 equivalents) in anhydrous CH_2Cl_2 (325 mL, 0.001M). The completion of the reaction was monitored by TLC. The reaction mixture was then dried *in vacuo* and diluted with ethyl acetate. The organic layer was washed with 10% (v/v) $HCl_{(aq)}$, dried over Na_2SO_4, filtered, concentrated *in vacuo* and subjected to the next reaction without purification.
LC/MS (ESI): *m/z* called for $C_{21}H_{25}NO_4Na$ (M+ Na^+) = 378.1681, found 378.00.



Compound 40

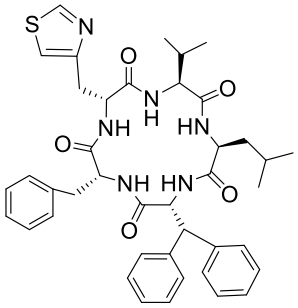
Following "**General peptide coupling**" procedure for SPPS and the published procedure for SPPS (Koay, Y. C.; McConnell, J. R.; Wang, Y.; Kim, S. J.; Buckton, L. K.; Mansour, F.; McAlpine, S. R. *ACS Med. Chem. Lett.* **2014**, *5*, 771-776), linear pentapeptide of resin-O-Leu-Val-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphenyl-D-Ala-$NH(CH_3)$ was synthesized by using 1.00 g (0.5 mmol, 1.0 equivalent) of resin-O-Leu-NH_2 and the subsequent peptide coupling in the sequence as mentioned below: 0.51 g (1.5 mmol, 3.0 equivalents) of Fmoc-Val-OH, 0.59 g (1.5 mmol, 3.0 equivalents) of Fmoc-D-3-(4-Thiazoyl)Ala-OH, 0.58 g (1.5 mmol, 3.0 equivalents) of Fmoc-D-Phe-OH and 0.53 g (1.5 mmol, 3.0 equivalents) of Boc-*N*-Me-3,3-Diphenyl-D-Ala-OH. Each peptide coupling was done in the presence of 0.20 g of HOAt (1.5 mmol, 3.0 equivalents) or 0.20 g of HOBt (1.5 mmol, 3.0 equivalents), 0.47 mL of DIC (3.0 mmol, 6.0 equivalents) and 2.5 mL of DMF to generate a concentration of 0.20 M. Each coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm the reaction completion. The reaction mixture was drained to afford the Fmoc-protected resin-bound pentapeptide and the Fmoc protecting group was removed following the **"General Fmoc removal"** after the completion of each coupling reaction.

The double deprotected linear pentapeptide (DDLP) HO-Leu-Val-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphenyl-D-Ala-$NH(CH_3)$ was generated following the **"Resin cleavage of linear peptide"** procedure for SPPS. The linear pentapeptide was cleaved from the resin using a mixed solution of 6 mL of TFA and 6 mL of CH_2Cl_2. The resin containing solution was filtered and dried *in vacuo* to yield the DDLP as a white solid (261 mg, overall 68%).
LC/MS (ESI): *m/z* called for $C_{42}H_{52}N_6O_6$ (M+1) = 769.37, found 769.40.

***Cyclo* Leu-Val-3-(4-Thia)-D-Ala-D-Phe-*N*-Me-3,3-Diphe-D-Ala (40)** was synthesized using 0.25 g of the DDLP generated (0.33 mmol, 1.0 equivalent), 0.06 g of TBTU (0.20 mmol, 0.60 equivalent), 0.15 g of HATU (0.39 mmol, 1.20 equivalent), 0.05 g of DMTMM (0.20 mmol, 0.60 equivalent), 0.45 mL of DIPEA (2.6 mmol, 8.0 equivalents) in anhydrous CH_2Cl_2 (325 mL, 0.001M) following "**Macrocyclization procedure (syringe pump)"** procedure. The reaction was then stirred overnight and the reaction was monitored via LC/MS. Upon completion, the reaction mixture was subjected to acid-base wash, which was extracted twice with 10% (v/v) $HCl_{(aq)}$. The organic layer was then re-extracted with a saturated of $NaHCO_3$ aqueous solution. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via flash column chromatography on silica gel using an ethyl acetate-hexane gradient system, followed by purification via HPLC to yield compound **40** as white solid (27 mg, 11%).
R_f: 0.39 (Hex:EtOAc = 0.25:0.75)
LC/MS: *m/z* called for $C_{42}H_{50}N_6O_5S$ (M+1) = 751.36, found 751.30.
HRMS (ESI-TOF): M+1, found 751.3636 $C_{42}H_{50}N_6O_5S$ requires 751.3635.

a) Major conformer
^{1}H NMR (600 MHz, DMSO): δ 9.06 (d, *J* = 1.9 Hz, 1H, D-Thia), 8.55 (d, *J* = 7.6 Hz, NH), 8.49 (d, *J* = 6.1 Hz, NH), 7.73 (m, NH), 7.47-7.01 (m, 15H, D-BiPhe, D-Phe, NH), 6.67 (m, 1H, D-Thia), 5.87 (d, *J* = 11.6 Hz, 1H, CHα D-BiPhe), 4.71 (m, 1H, CHα D-Phe), 4.55 (d, *J* = 11.5 Hz, 1H, CHβ D-BiPhe), 4.41 (ddd, *J* = 3.8, 11.4, 11.4 Hz, 1H, CHα D-Thia), 3.92 (m, 1H, CHα Leu), 3.81 (dd, *J* = 5.2, 7.6 Hz, 1H, CHα Val), 3.24 (dd, *J* = 8.7, 14.3 Hz, 1H, $CH_2\beta_2$ D-Phe), 3.12 (m, 1H, $CH_2\beta_1$ D-Phe), 2.99 (m, 1H, $CH_2\beta_2$ D-Thia), 2.64 (dd, *J* = 11.2, 13.6 Hz, 1H, $CH_2\beta_1$ D-Thia), 2.54 (s, 3H, NCH_3), 2.06 (m, 1H, CHβ Val), 1.44 (m, 1H, $CH_2\beta_2$ Leu), 0.81-0.60 (m, 14H, $CH_2\beta_1$ Leu, CHγ Leu, $CHCH(CH_3)_2$), $CH_2CH(CH_3)_2$).
^{13}C NMR (150 MHz, DMSO): δ 173.42, 172.70, 170.10, 169.34, 168.35, 154.12, 152.60, 142.54, 141.06, 137.63, 129.52, 129.24, 129.07, 128.81, 128.69, 128.08, 127.18, 126.73, 126.09, 116.16, 61.47, 59.96, 58.58, 54.24, 53.67, 49.03, 47.24, 42.21, 39.62, 29.68, 28.94, 23.50, 22.42, 19.58, 17.74.

b) Minor conformer
^{1}H NMR (600 MHz, DMSO): δ 9.01 (d, *J* = 1.9 Hz, 1H, D-Thia), 8.22 (d, *J* = 6.8 Hz, NH), 8.02 (d, *J* = 7.7 Hz, NH), 7.71 (br, NH), 7.64 (d, *J* = 7.9 Hz, NH), 7.47-7.01 (m, 15H, D-BiPhe, D-Phe), 6.74 (m, 1H, D-Thia), 5.82 (d, *J* = 11.6 Hz, 1H, CHα D-BiPhe), 4.71 (m, 1H, CHβ D-BiPhe), 4.64 (m, 1H, CHα D-Phe), 4.34 (m, 1H, CHα Leu), 3.64 (m, 1H, CHα Val), 3.45 (m, 1H, CHα D-Thia), 3.12 (m, 1H, $CH_2\beta_2$ D-Phe), 2.99 (m, 3H, $CH_2\beta_1$ D-Phe, $CH_2\beta_2$ D-Thia, $CH_2\beta_1$ D-Thia), 2.70 (s, 3H, NCH_3), 1.85 (m, 1H, CHβ Val), 1.67 (m, 1H, $CH_2\beta_2$ Leu), 1.36 (m, 1H, CHγ Leu), 1.10 (m, 1H, $CH_2\beta_1$ Leu), 0.81-0.60 (m, 12H, $CHCH(CH_3)_2$), $CH_2CH(CH_3)_2$).



Compound 41

Following "**General peptide coupling"** procedure for SPPS and the published procedure for SPPS (Koay, Y. C.; McConnell, J. R.; Wang, Y.; Kim, S. J.; Buckton, L. K.; Mansour, F.; McAlpine, S. R. *ACS Med. Chem. Lett.* **2014**, *5*, 771-776), linear pentapeptide of resin-O-Leu-Val-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphenyl-D-Ala-NH_2 was synthesized by using 1.00 g (0.5 mmol, 1.0 equivalent) of resin-O-Leu-NH_2 and the subsequent peptide coupling in the sequence as mentioned below: 0.51 g (1.5 mmol, 3.0 equivalents) of Fmoc-Val-OH, 0.59 g (1.5 mmol, 3.0 equivalents) of Fmoc-D-3-(4-Thiazoyl)Ala-OH, 0.58 g (1.5 mmol, 3.0 equivalents) of Fmoc-D-Phe-OH and 0.70 g (1.5 mmol, 3.0 equivalents) of Fmoc-3,3-Diphenyl-D-Ala-OH. Each peptide coupling was done in the presence of 0.20 g of HOAt (1.5 mmol, 3.0 equivalents) or 0.20 g of HOBt (1.5 mmol, 3.0 equivalents), 0.47 mL of DIC (3.0 mmol, 6.0 equivalents) and 2.5 mL of DMF to generate a concentration of 0.20 M. Each coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm the reaction completion. The reaction mixture was drained to afford the Fmoc-protected resin-bound pentapeptide and the Fmoc protecting group was removed following the **"General Fmoc removal"** after the completion of each coupling reaction.

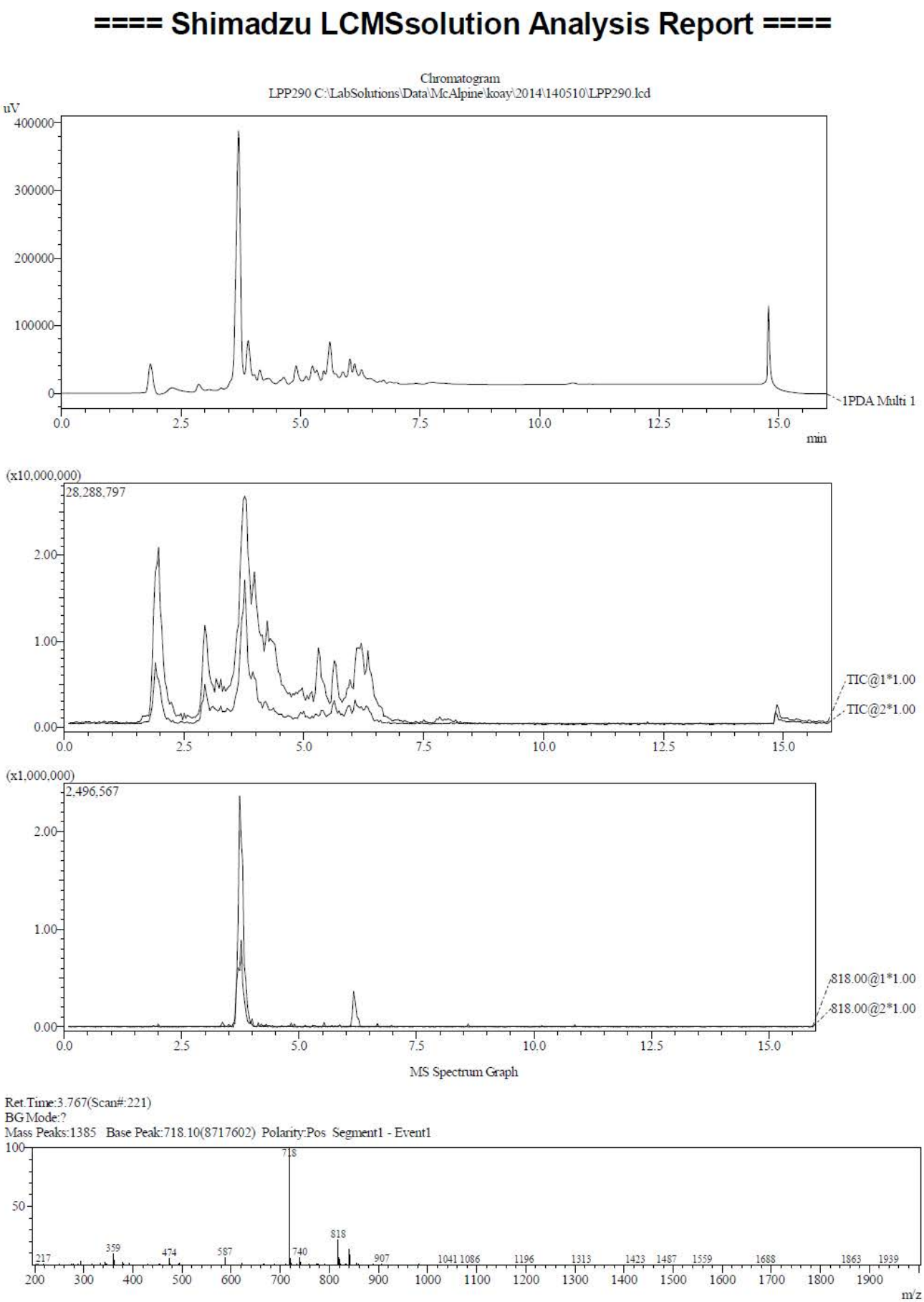
The double deprotected linear pentapeptide (DDLP) HO-Leu-Val-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala-NH_2 was generated following the **"Resin cleavage of linear peptide"** procedure for SPPS. The linear pentapeptide was cleaved from the resin using a mixed solution of 6 mL of TFE and 6 mL of CH_2Cl_2. The resin containing solution was filtered and dried *in vacuo* to yield the DDLP as a white solid (271 mg, overall 72%).
LC/MS (ESI): *m/z* called for $C_{41}H_{50}N_6O_6$ (M+1) = 755.35, found 755.05.

Cyclo **Leu-Val-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala (41)** was synthesized using 0.27 g of the DDLP generated (0.36 mmol, 1.0 equivalent), 0.09 g of TBTU (0.29 mmol, 0.80 equivalent), 0.11 g of HATU (0.29 mmol, 0.80 equivalent), 0.08 g of DMTMM (0.29 mmol, 0.80 equivalent), 0.50 mL of DIPEA (2.9 mmol, 8.0 equivalents) in anhydrous CH_2Cl_2 (359 mL, 0.001M) following "**Macrocyclization procedure (syringe pump)"** procedure. The reaction was then stirred overnight and the reaction was monitored via LC/MS. Upon completion, the reaction mixture was subjected to acid-base wash, which was extracted twice with 10% (v/v) $HCl_{(aq)}$. The organic layer was then re-extracted with a saturated of $NaHCO_3$ aqueous solution. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product was purified via flash column chromatography on silica gel using an ethyl acetate-hexane gradient system, followed by purification via HPLC to yield compound **41** as white solid (35 mg, 13%).
R_f: 0.33 (EtOAc:MeOH = 0.95:0.05)
LC/MS: *m/z* called for $C_{41}H_{48}N_6O_5S$ (M+1) = 737.34, found 737.00.
HRMS (ESI-TOF): $M+Na^+$, found 759.3293 $C_{41}H_{48}N_6O_5S_1Na_1$ requires 759.3305.

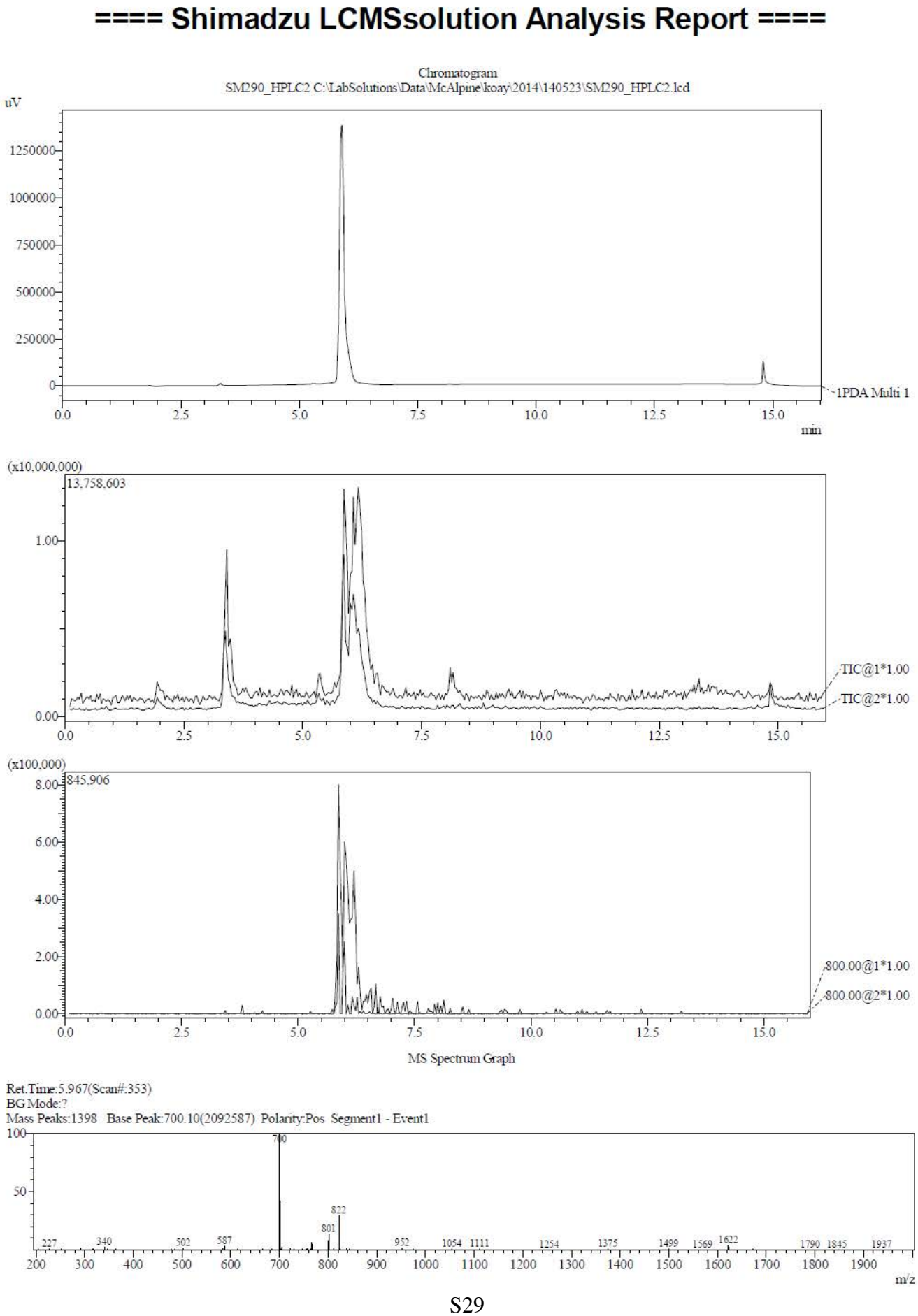
a) Major conformer
^{1}H NMR (500 MHz, DMSO): δ 8.98 (d, *J* = 1.9 Hz, 1H, D-Thia), 8.60 (br, NH), 8.33 (br, NH), 8.13 (m, 2NH), 7.60 (br, NH), 7.38-7.12 (m, 15H, D-BiPhe, D-Phe), 6.76 (m, 1H, D-Thia), 5.14 (t, *J* = 10.8 Hz, 1H, CHα D-BiPhe), 4.55 (m, 2H, CHα D-Phe, CHα Val), 3.88 (m, 3H, CHβ D-BiPhe, CHα Leu, CHα D-Thia), 3.22 (dd, *J* = 7.6, 14.5 Hz, 1H, $CH_2\beta_2$ D-Phe), 3.03 (dd, *J* = 7.2, 14.5 Hz, 1H, $CH_2\beta_1$ D-Phe), 2.81 (dd, *J* = 7.6, 13.7 Hz, 1H, $CH_2\beta_2$ D-Thia), 2.62 (dd, *J* = 6.9, 13.7 Hz, 1H, $CH_2\beta_1$ D-Thia), 1.81 (m, 1H, CHβ Val), 1.19 (m, 2H, CH_2β Leu), 0.84 (m, 1H, CHγ Leu), 0.73-0.59 (m, 12H, $CHCH(CH_3)_2$, $CH_2CH(CH_3)_2$).
^{13}C NMR (125 MHz, DMSO): δ 171.73, 171.39, 170.85, 170.62, 170.27, 153.88, 153.73, 141.80, 141.48, 137.79, 129.17, 128.90, 128.86, 128.73, 128.51, 128.46, 127.17, 126.73, 126.68, 115.33, 61.25, 59.16, 55.39, 53.34, 52.91, 51.59, 37.26, 32.84, 29.55, 24.24, 23.04, 22.20, 21.60, 19.34, 19.13.

b) Minor conformer
^{1}H NMR (500 MHz, DMSO): δ 8.98 (d, *J* = 1.9 Hz, 1H, D-Thia), 8.60 (br, NH), 8.33 (br, NH), 8.27 (m, *J* = 6.7 Hz, NH), 7.95 (d, *J* = 8.6 Hz, NH), 7.43 (d, *J* = 7.4 Hz, NH), 7.38-7.12 (m, 15H, D-BiPhe, D-Phe), 6.94 (d, *J* = 6.8 Hz, 1H, D-Thia), 5.06 (m, 1H, CHα D-BiPhe), 4.38 (m, 1H, CHα D-Phe), 4.33 (m, *J* = 11.8 Hz, 1H, CHα Val), 3.98 (m, 1H, CHα D-Thia), 3.88 (m, 1H, CHβ D-BiPhe), 3.73 (m, *J* = 8.5 Hz, 1H, CHα Leu), 3.16 (m, 1H, $CH_2\beta_2$ D-Phe), 2.98 (m, 2H, $CH_2\beta_1$ D-Phe, $CH_2\beta_2$ D-Thia), 2.44 (dd, *J* = 6.3, 13.7 Hz, 1H, $CH_2\beta_1$ D-Thia), 1.44 (m, 1H, CHβ Val), 1.16 (m, 2H, CH_2β Leu), 0.78 (m, 1H, CHγ Leu), 0.73-0.59 (m, 12H, $CHCH(CH_3)_2$, $CH_2CH(CH_3)_2$).

Compound **7**: LCMS of DDLP HO-Leu-*N*-Me-Val-D-Leu-D-His(Boc)-3,3-Diphe-D-Ala-NH_2



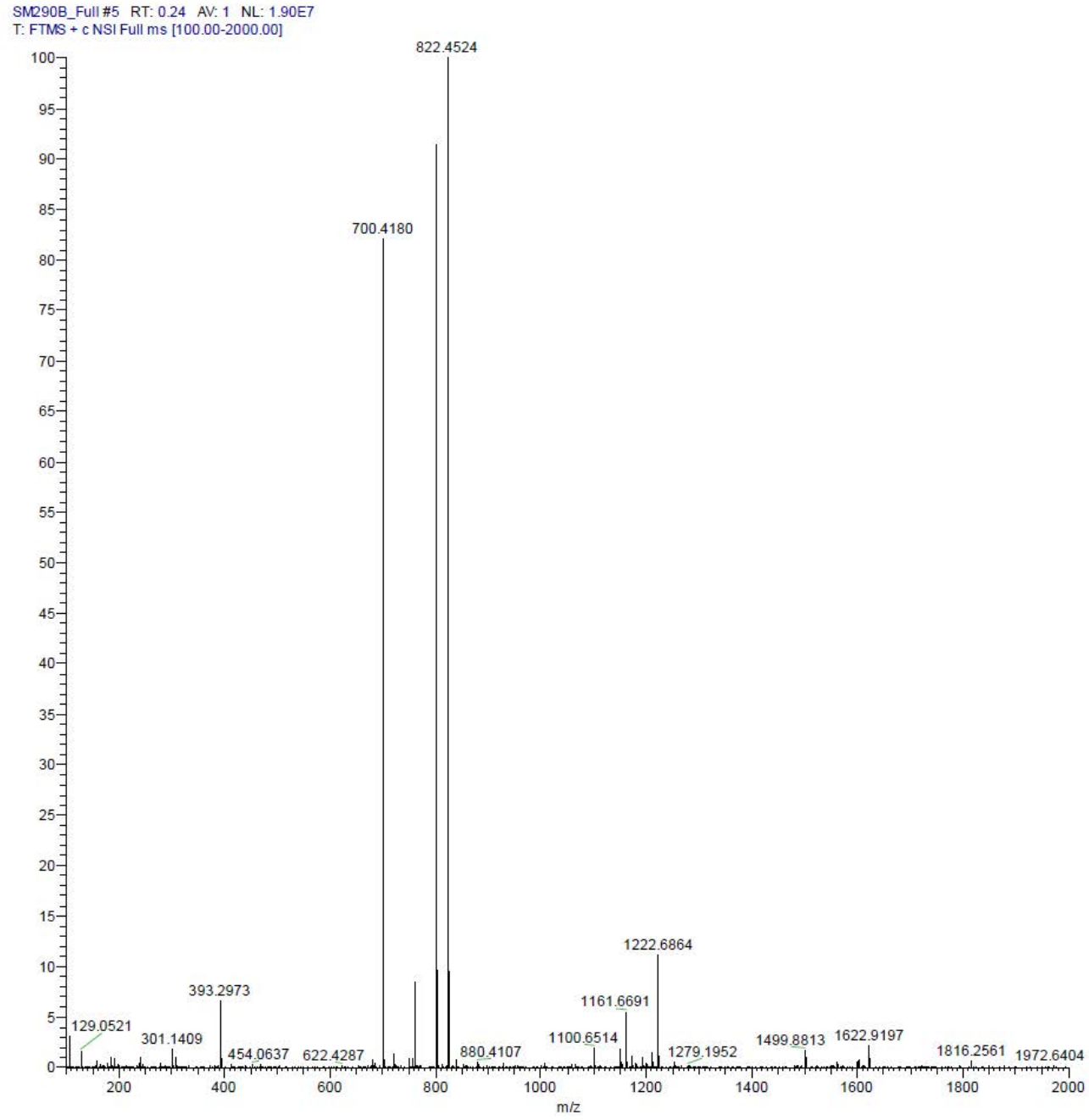
Compound **7**: LCMS of cyclo Leu-*N*-Me-Val-D-Leu-D-His(Boc)-3,3-Diphe-D-Ala



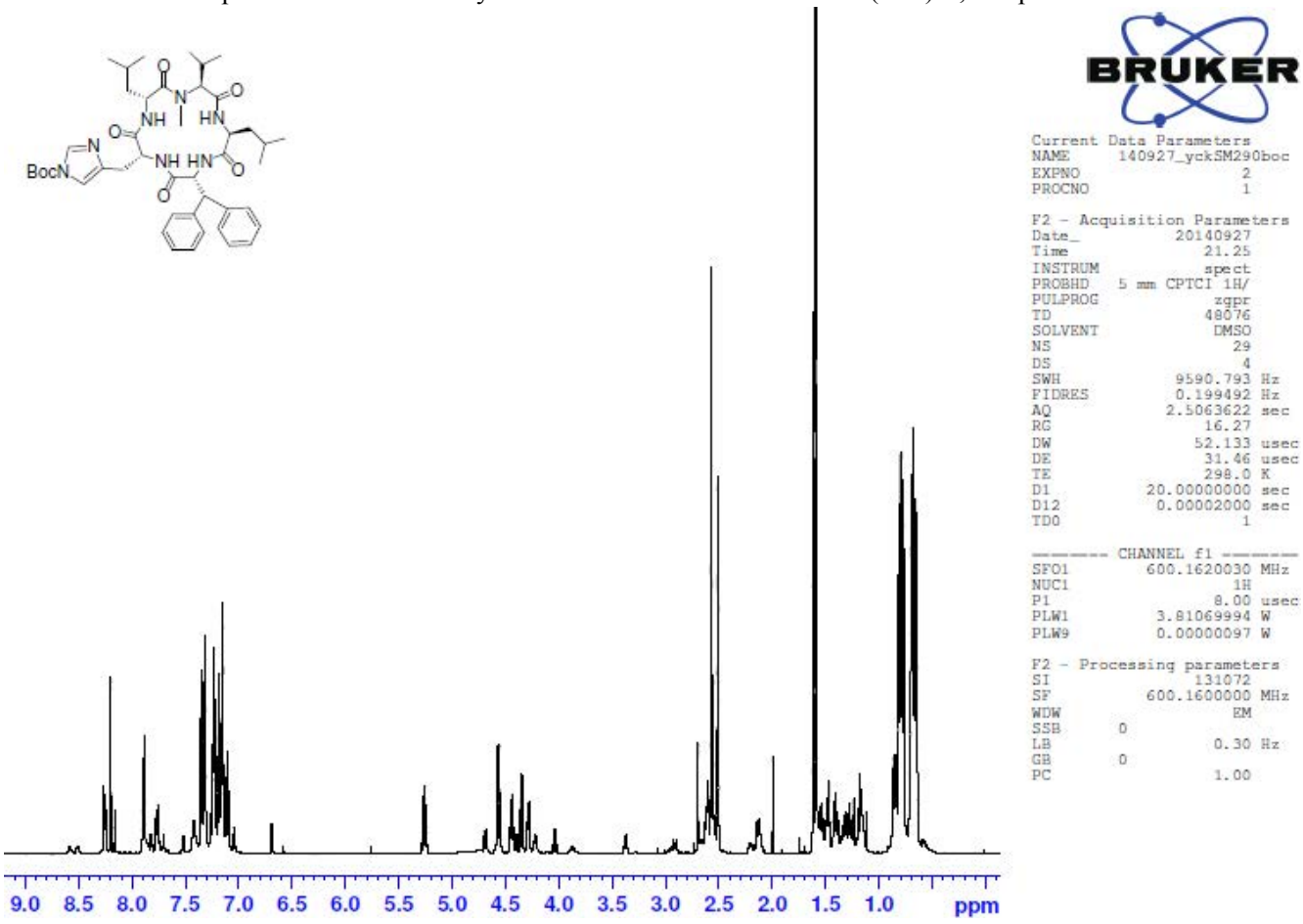
Compound **7**: HRMS of cyclo Leu-*N*-Me-Val-D-Leu-D-His(Boc)-3,3-Diphe-D-Ala

MS Data from Orbitrap

Full spectrum



Compound **7**: ^{1}HNMR of cyclo Leu-*N*-Me-Val-D-Leu-D-His(Boc)-3,3-Diphe-D-Ala

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PROCNO                     1

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Time               21.25
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PULPROG            zgpr
TD                 48076
SOLVENT             DMSO
NS                    29
DS                     4
SWH             9590.793 Hz
FIDRES          0.199492 Hz
AQ              2.5063622 sec
RG                 16.27
DW                52.133 usec
DE                31.46 usec
TE                298.0 K
D1           20.00000000 sec
D12           0.00002000 sec
TD0                    1

======== CHANNEL f1 ========
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NUC1                   1H
P1                   8.00 usec
PLW1          3.81069994 W
PLW9          0.00000097 W

F2 - Processing parameters
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SF           600.1600000 MHz
WDW                    EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.00
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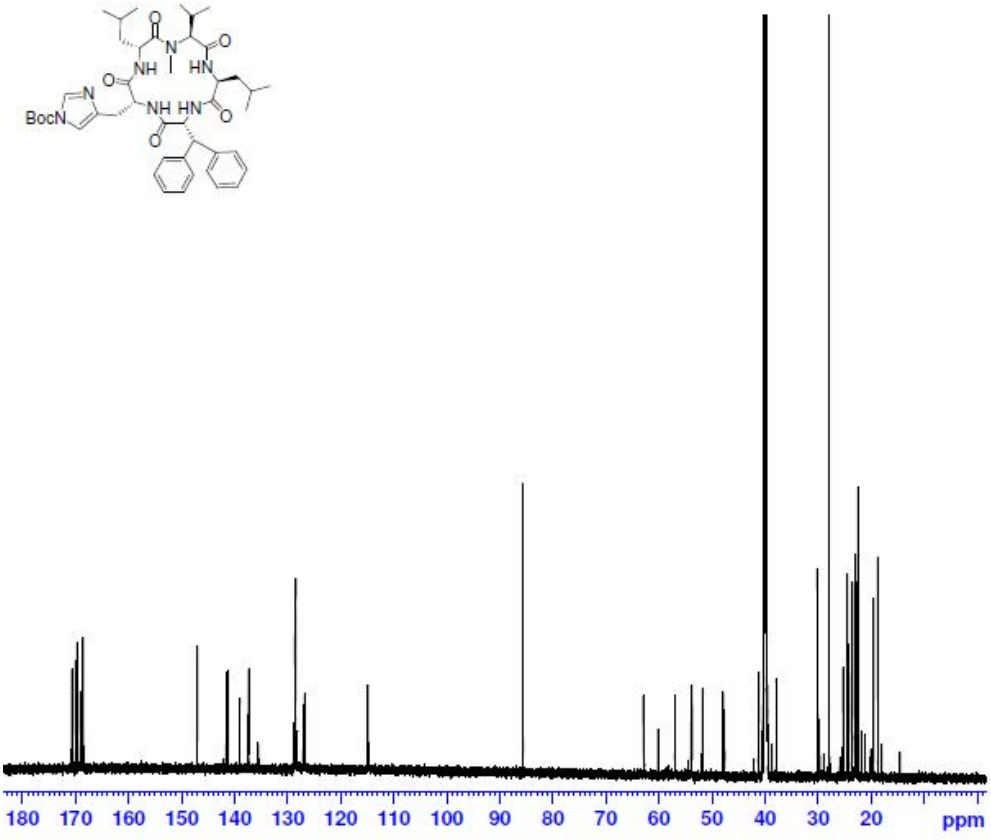
Compound **7**: ^{13}CNMR of cyclo Leu-*N*-Me-Val-D-Leu-D-His(Boc)-3,3-Diphe-D-Ala

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Current Data Parameters
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EXPNO                      3
PROCNO                     1

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Time               23.57
INSTRUM            spect
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TD                 65536
SOLVENT             DMSO
NS                  2662
DS                     4
SWH            31512.605 Hz
FIDRES          0.480844 Hz
AQ              1.0398378 sec
RG                202.23
DW                15.867 usec
DE                16.72 usec
TE                298.0 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
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NUC1                   13C
P1                  11.50 usec
PLW1        100.00000000 W

======== CHANNEL f2 ========
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NUC2                   1H
CPDPRG[2 bi_waltz65_256
PCPD2                70.00 usec
PLW2          3.81069994 W
PLW12         0.04977200 W
PLW13         0.02438800 W

F2 - Processing parameters
SI                  32768
SF           150.9103520 MHz
WDW                    no
SSB       0
LB        0 Hz
GB        0
PC                  1.00
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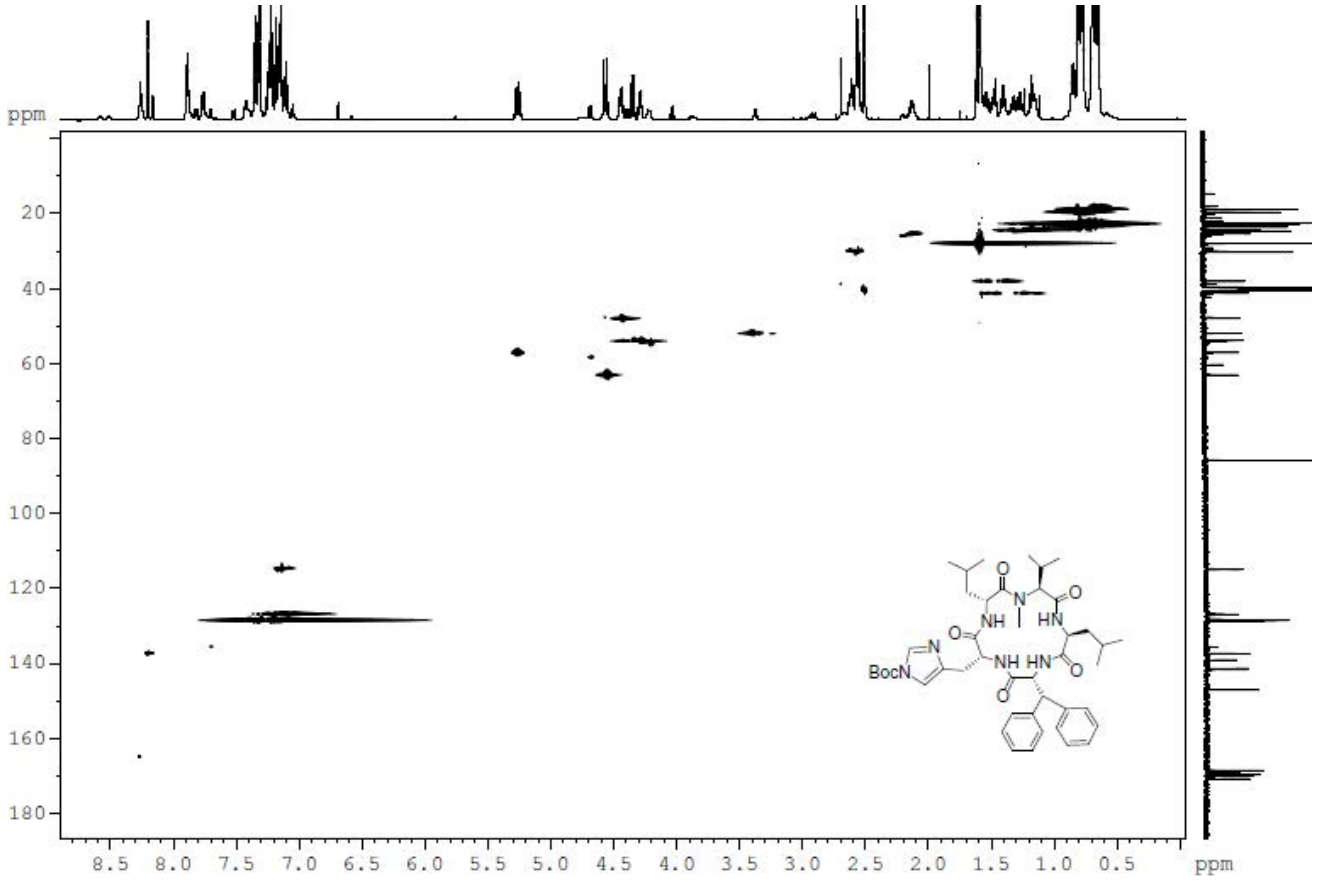
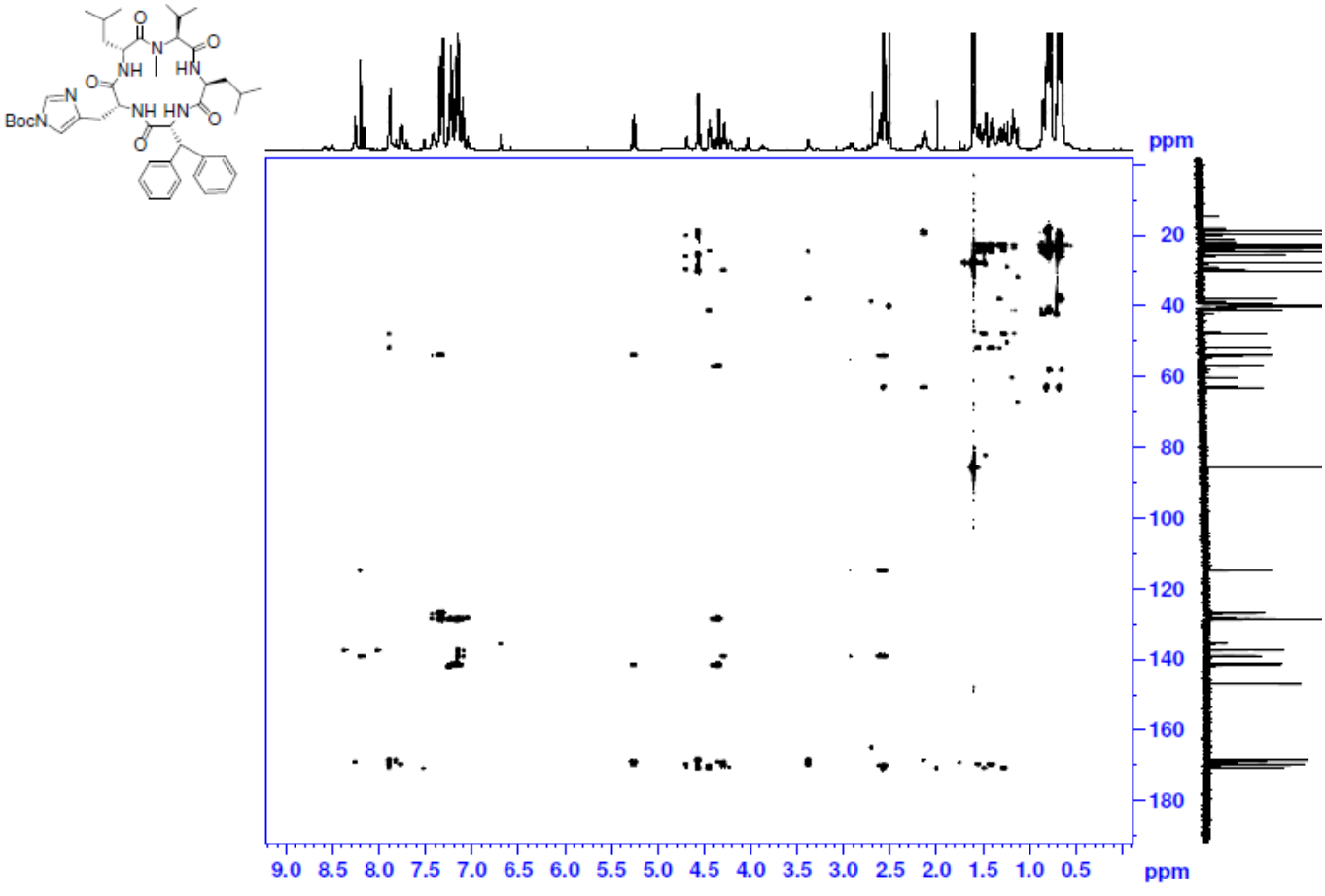
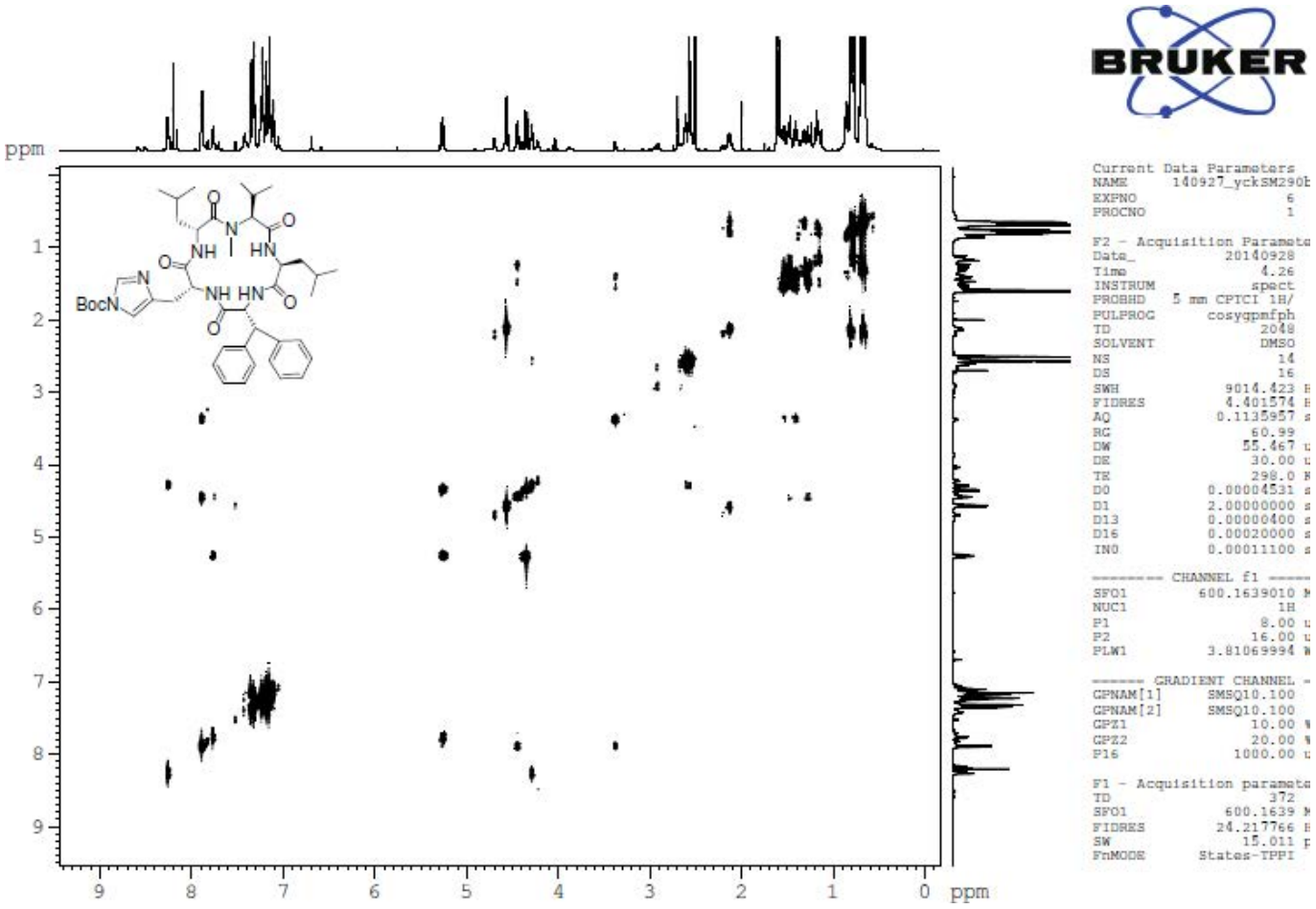
Compound **7**: ^{1}H-^{13}C HSQC of cyclo Leu-*N*-Me-Val-D-Leu-D-His(Boc)-3,3-Diphe-D-Ala



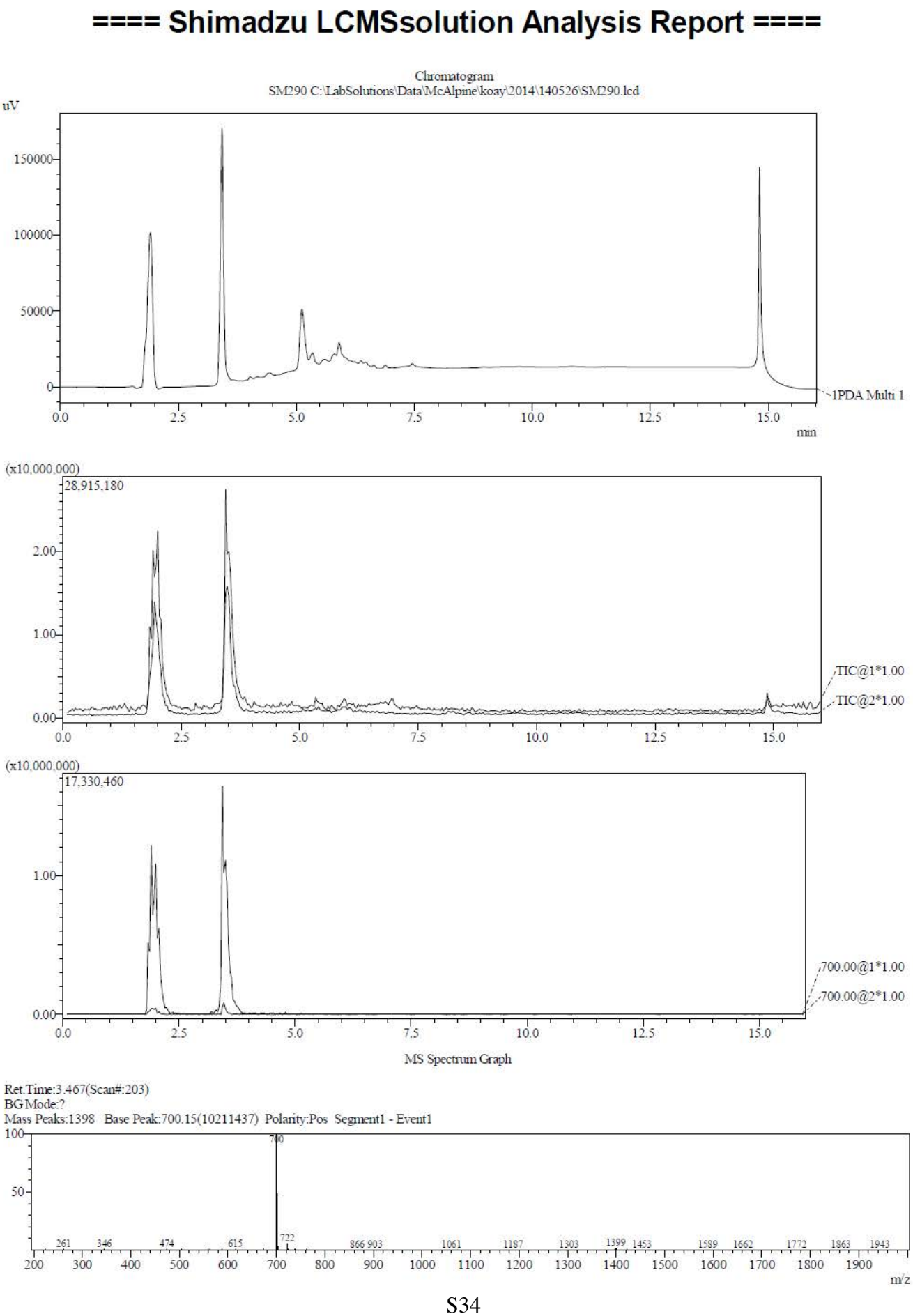
Compound **7**: ^{1}H-^{13}C HMBC of cyclo Leu-*N*-Me-Val-D-Leu-D-His(Boc)-3,3-Diphe-D-Ala



Compound **7**: ^{1}H-^{1}H COSY of cyclo Leu-*N*-Me-Val-D-Leu-D-His(Boc)-3,3-Diphe-D-Ala



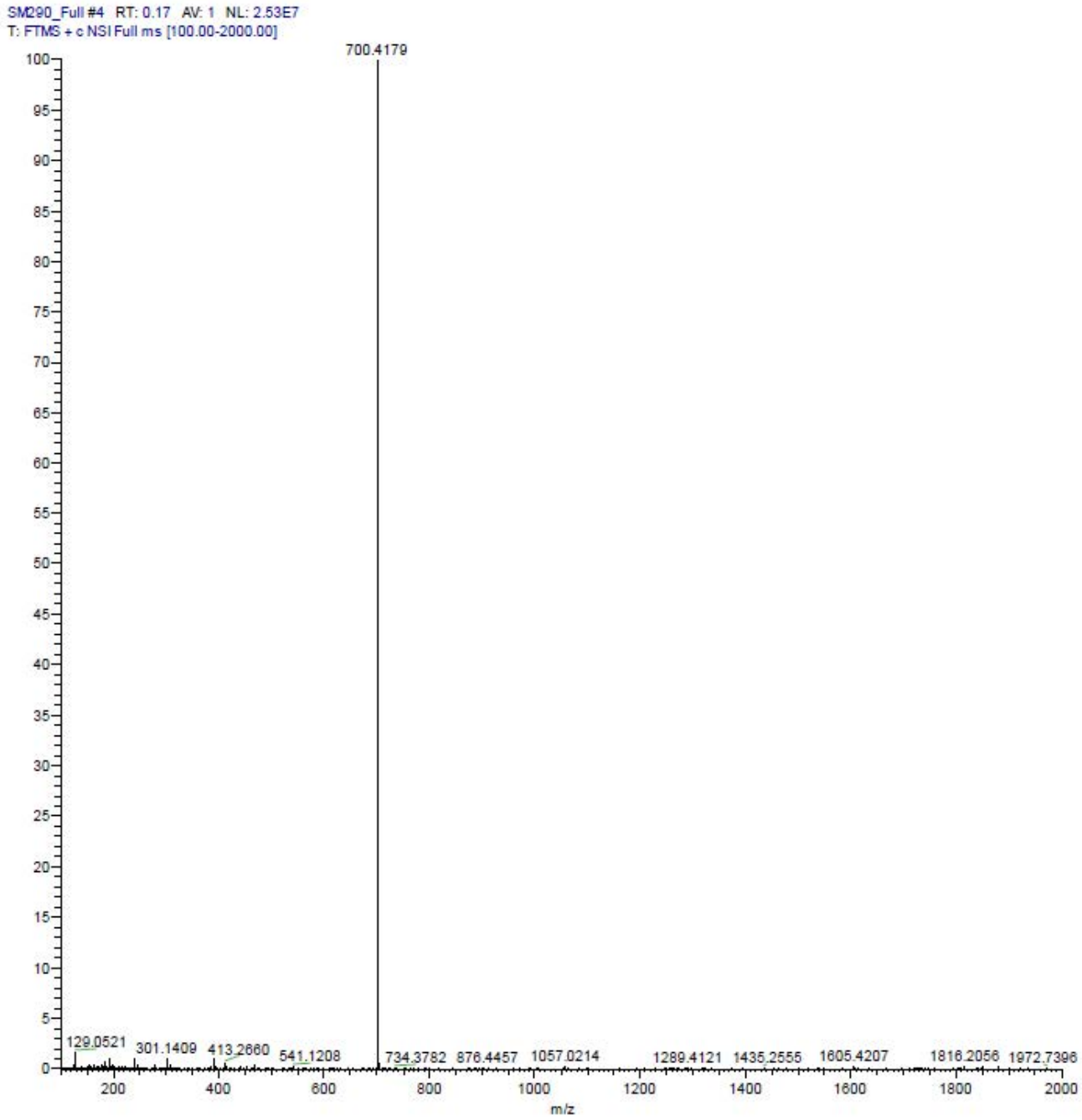
Compound **8**: LCMS of cyclo Leu-*N*-Me-Val-D-Leu-D-His-3,3-Diphe-D-Ala



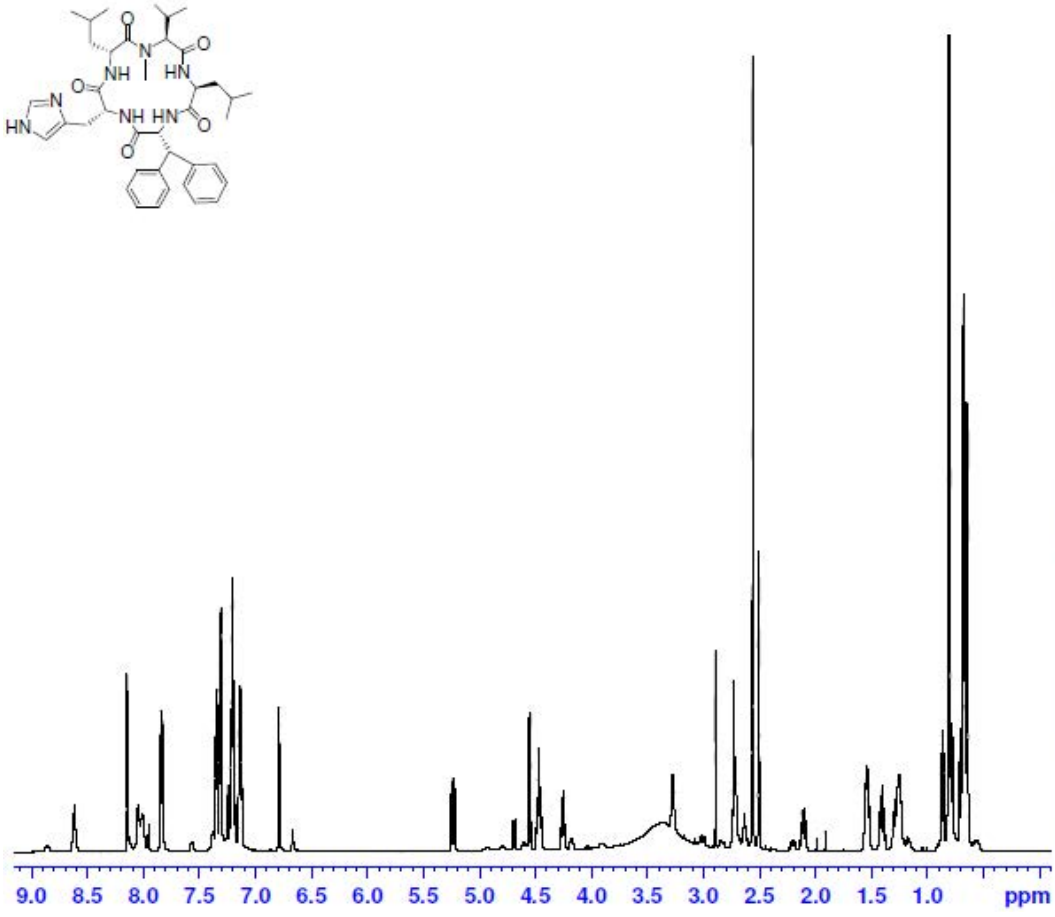
Compound **8**: HRMS of cyclo Leu-*N*-Me-Val-D-Leu-D-His-3,3-Diphe-D-Ala

MS Data from Orbitrap

Full spectrum



Compound **8**: ^{1}HNMR of cyclo Leu-*N*-Me-Val-D-Leu-D-His-3,3-Diphe-D-Ala

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PROCNO                     1

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PULPROG                  zg
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        0
SWH                9009.009 Hz
FIDRES             0.137467 Hz
AQ                 3.6372480 sec
RG                     11.02
DW                    55.500 usec
DE                    33.22 usec
TE                    298.0 K
D1              5.00000000 sec
TD0                        1

======== CHANNEL f1 ========
SFO1           600.1639010 MHz
NUC1                   1H
P1                    8.00 usec
PLW1           3.81069994 W

F1 - Acquisition parameters
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SFO1               600.1639 MHz
FIDRES            24.217766 Hz
SW                    15.011 ppm
FnMODE         States-TPPI

F2 - Processing parameters
SI                     131072
SF              600.1600000 MHz
WDW                      EM
SSB         0
LB                    0.30 Hz
GB          0
PC                    1.00

F1 - Processing parameters
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MC2          echo-antiecho
SF              600.1600000 MHz
WDW                    QSINE
SSB                        2
LB                    0.30 Hz
GB                     0.1
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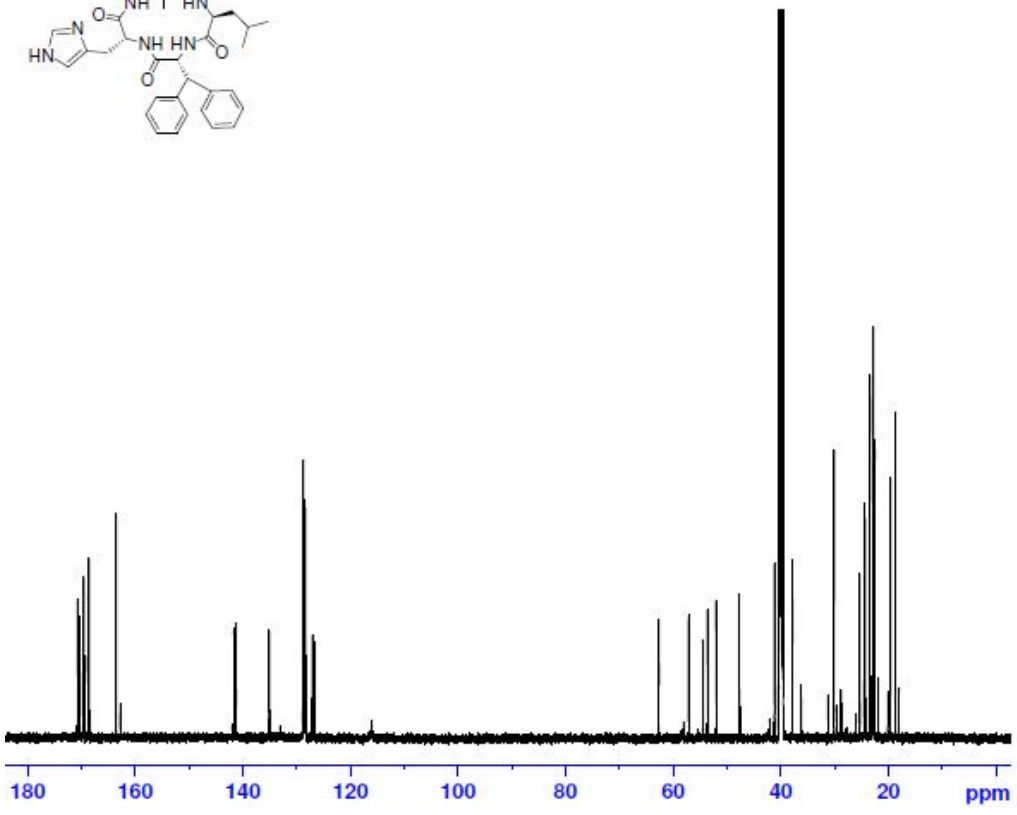
Compound **8**: ^{13}CNMR of cyclo Leu-*N*-Me-Val-D-Leu-D-His-3,3-Diphe-D-Ala

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Current Data Parameters
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EXPNO                      8
PROCNO                     1

F2 - Acquisition Parameters
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Time                   9.53
INSTRUM               spect
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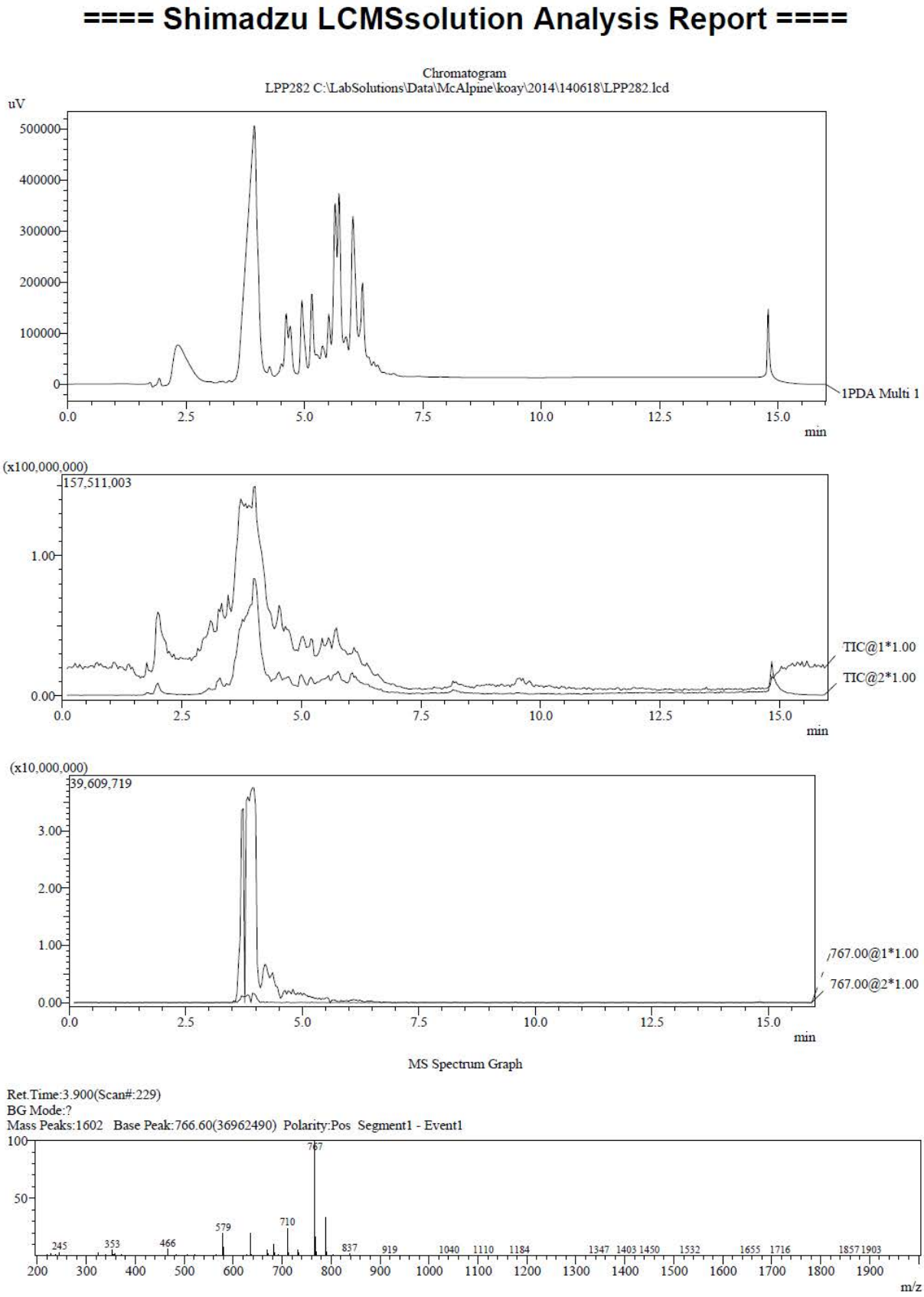
PULPROG            zgpg30
TD                    65536
SOLVENT                DMSO
NS                      5120
DS                         4
SWH               31512.605 Hz
FIDRES             0.480844 Hz
AQ                 1.0398378 sec
RG                    202.23
DW                    15.867 usec
DE                     16.72 usec
TE                    298.0 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                        1

======== CHANNEL f1 ========
SFO1           150.9246885 MHz
NUC1                   13C
P1                   11.50 usec
PLW1          100.00000000 W

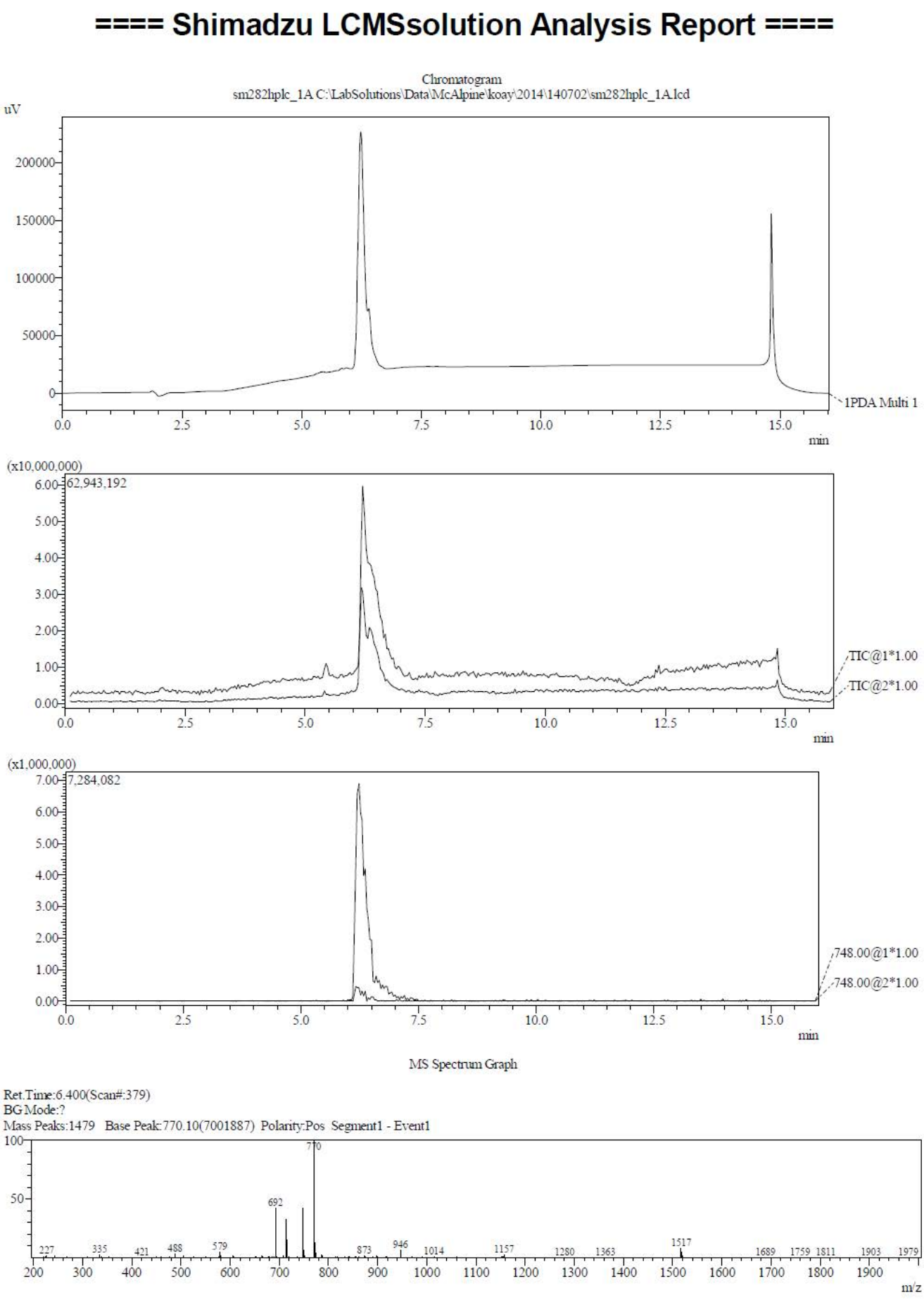
======== CHANNEL f2 ========
SFO2           600.1624006 MHz
NUC2                   1H
CPDPRG[2 bi_waltz65_256
PCPD2                 70.00 usec
PLW2           3.81069994 W
PLW12          0.04977200 W
PLW13          0.02438800 W

F2 - Processing parameters
SI                     32768
SF              150.9103520 MHz
WDW                       no
SSB         0
LB          0 Hz
GB          0
PC                    1.40
```

Compound **9**: LCMS of DDLP HO-Leu-*N*-Me-Val-D-Leu-D-Glu(OtBu)-3,3-Diphe-D-Ala-NH_2



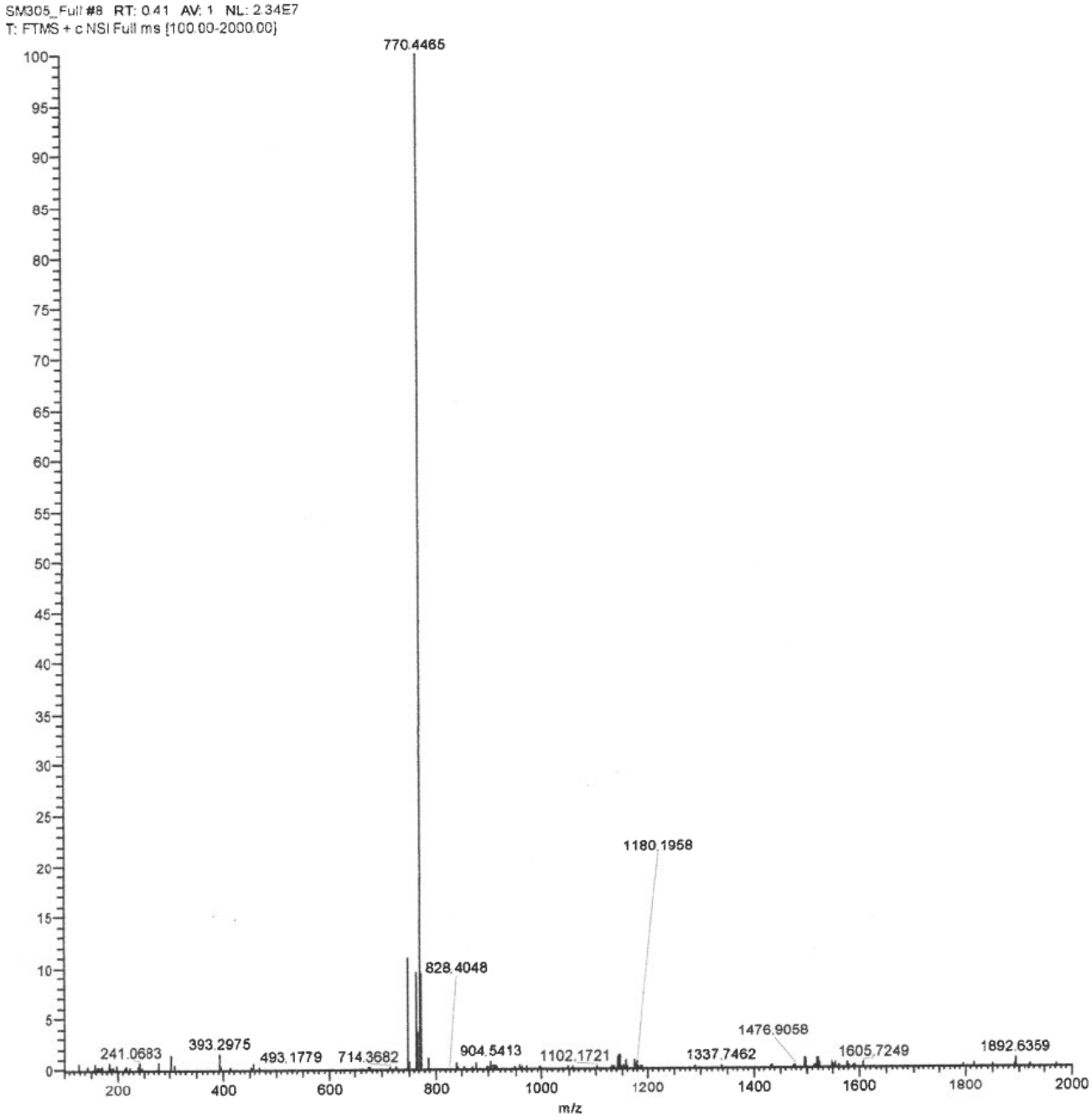
Compound **9**: LCMS of cyclo Leu-*N*-Me-Val-D-Leu-D-Glu(OtBu)-3,3-Diphe-D-Ala



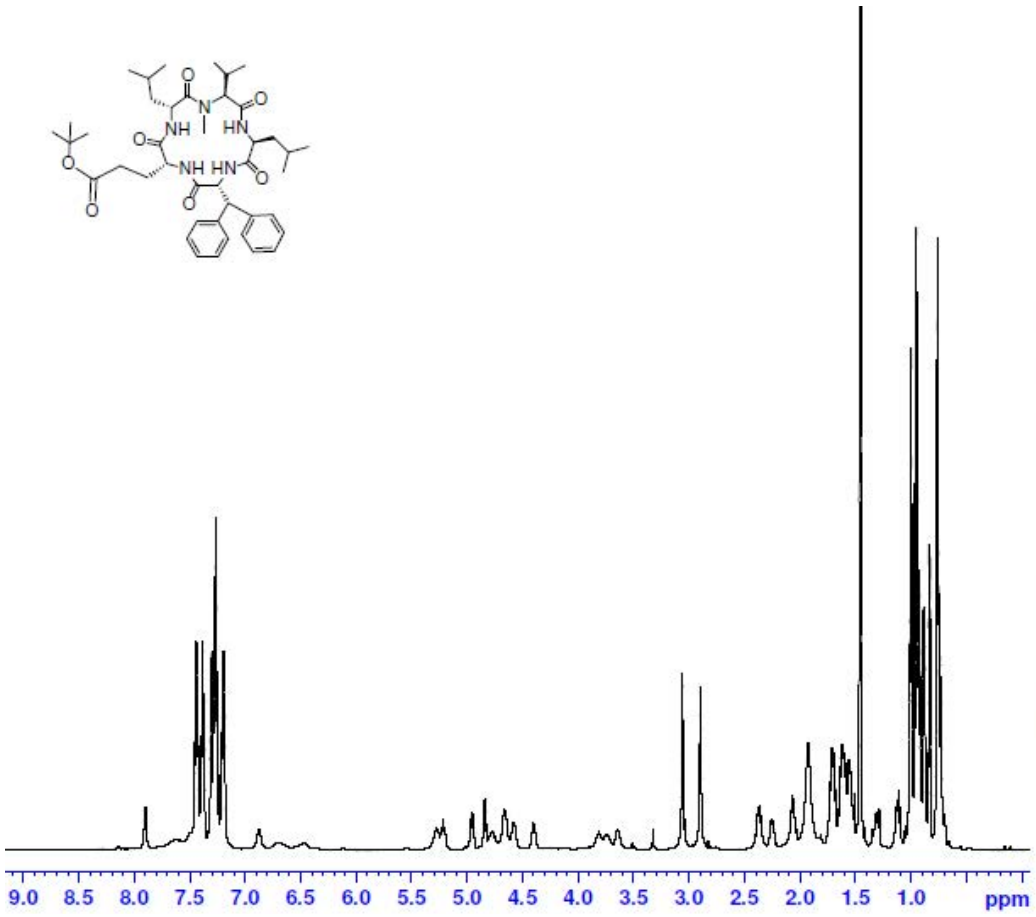
Compound **9**: HRMS of cyclo Leu-*N*-Me-Val-D-Leu-D-Glu(OtBu)-3,3-Diphe-D-Ala

MS Data from Orbitrap

Full spectrum:



Compound **9**: ^{1}HNMR of cyclo Leu-*N*-Me-Val-D-Leu-D-Glu(OtBu)-3,3-Diphe-D-Ala

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Current Data Parameters
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EXPNO                   6
PROCNO                  1

F2 - Acquisition Parameters
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INSTRUM            spect
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PULPROG              zg
TD                65536
SOLVENT           CDCl3
NS                    8
DS                    0
SWH            9009.009 Hz
FIDRES        0.137467 Hz
AQ            3.6372480 sec
RG                17.18
DW               55.500 usec
DE               33.22 usec
TE               308.0 K
D1            5.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1        600.1639010 MHz
NUC1                   1H
P1                   8.00 usec
PLW1          3.81069994 W

F2 - Processing parameters
SI                131072
SF          600.1600000 MHz
WDW                   EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
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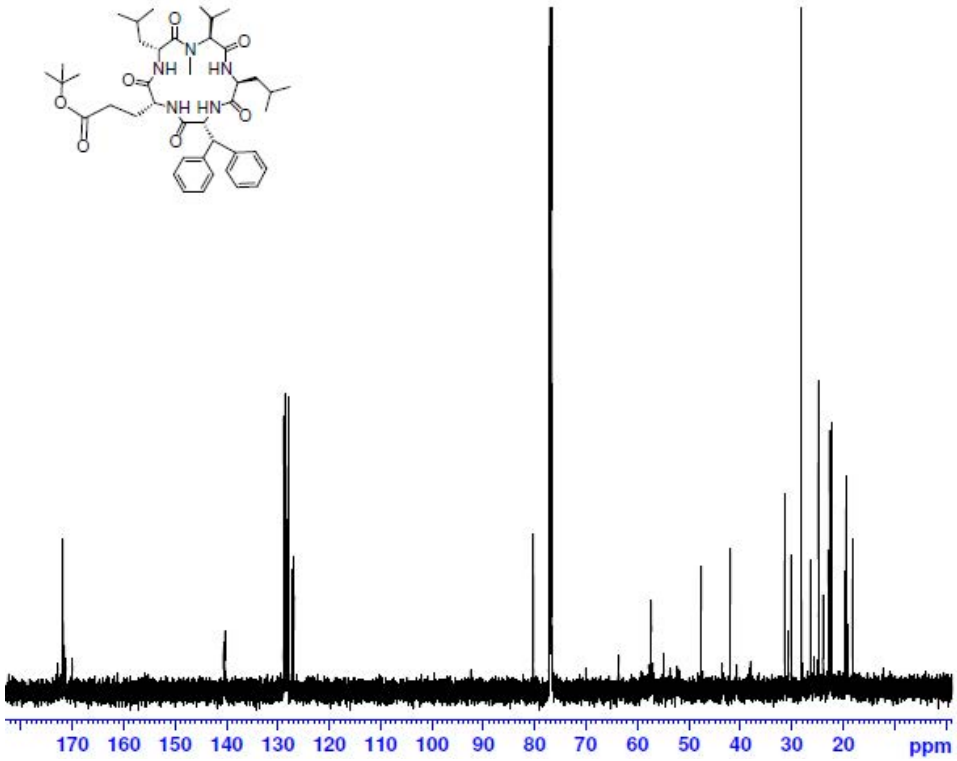
Compound **9**: ^{13}CNMR of cyclo Leu-*N*-Me-Val-D-Leu-D-Glu(OtBu)-3,3-Diphe-D-Ala

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Current Data Parameters
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EXPNO                   7
PROCNO                  1

F2 - Acquisition Parameters
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Time               14.22
INSTRUM            spect
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PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                 1024
DS                    4
SWH           31512.605 Hz
FIDRES        0.480844 Hz
AQ            1.0398378 sec
RG               202.23
DW               15.867 usec
DE                16.72 usec
TE               308.0 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1        150.9246885 MHz
NUC1                  13C
P1                11.50 usec
PLW1       100.00000000 W

======== CHANNEL f2 ========
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NUC2                   1H
CPDPRG[2 bi_waltz65_256
PCPD2              70.00 usec
PLW2          3.81069994 W
PLW12         0.04977200 W
PLW13         0.02438800 W

F2 - Processing parameters
SI                 32768
SF          150.9103520 MHz
WDW                   no
SSB       0
LB        0 Hz
GB        0
PC                1.40
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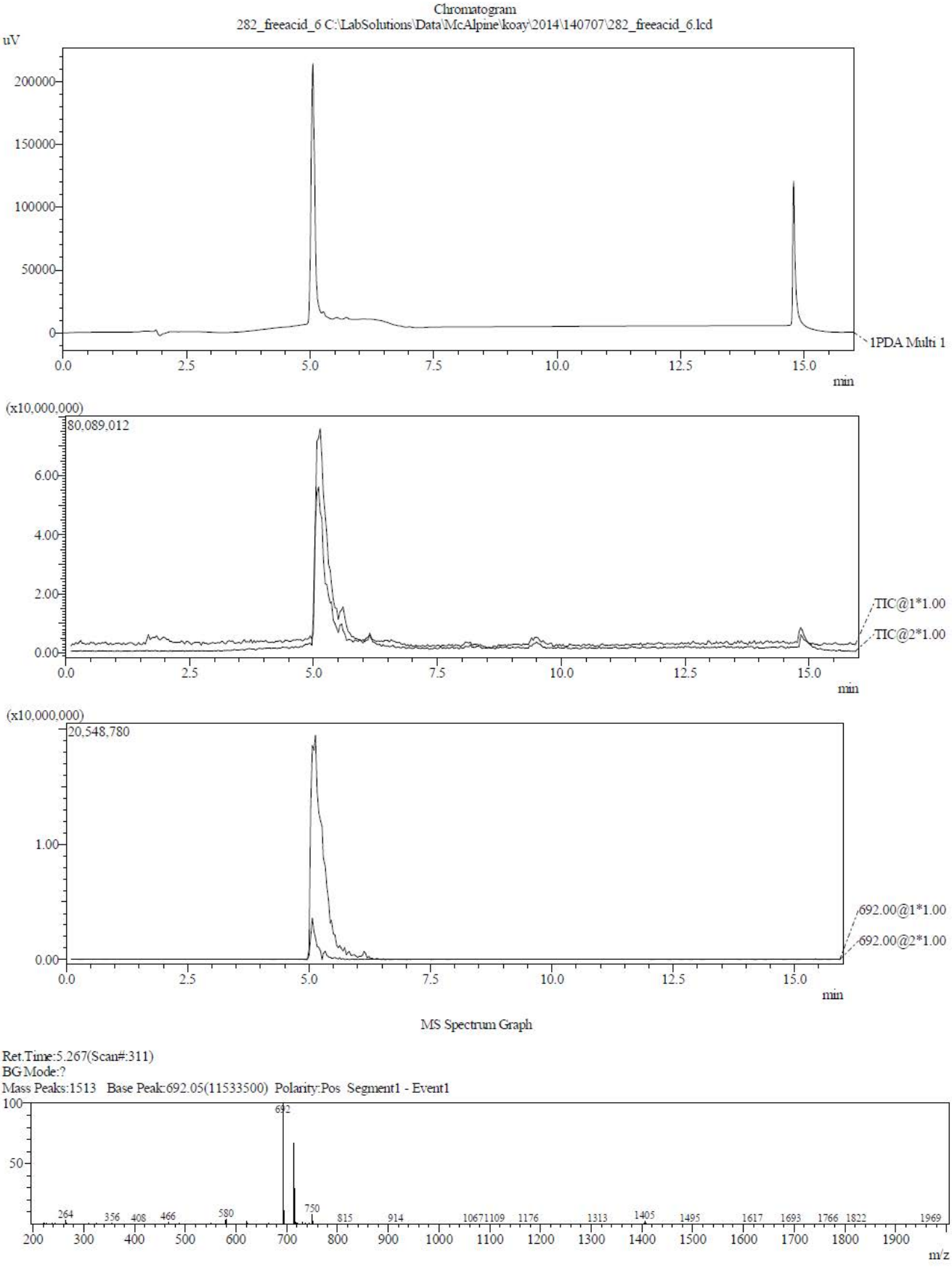
Compound **10**: LCMS of cyclo Leu-*N*-Me-Val-D-Leu-D-Glu-3,3-Diphe-D-Ala

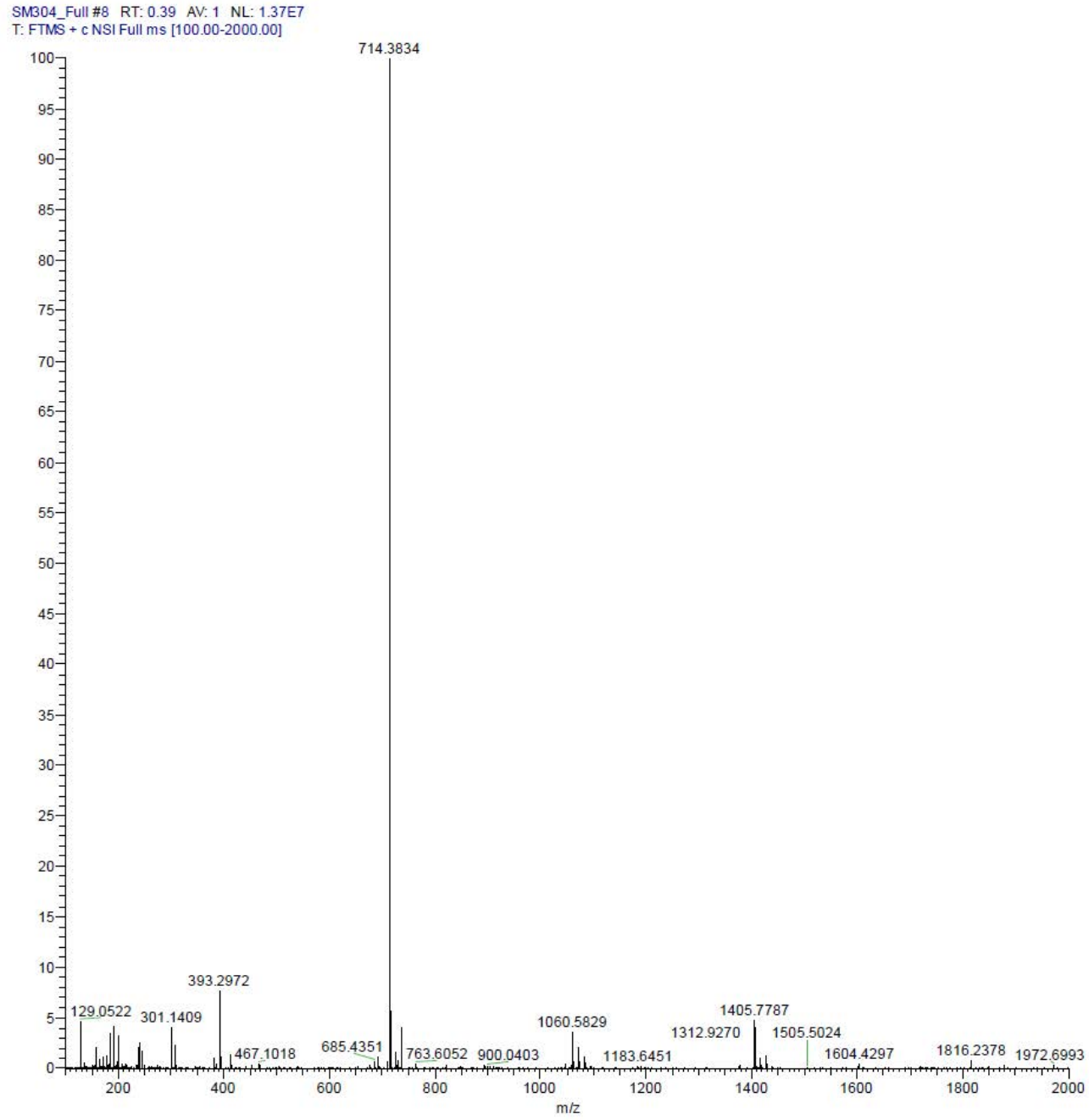
==== Shimadzu LCMSsolution Analysis Report ====



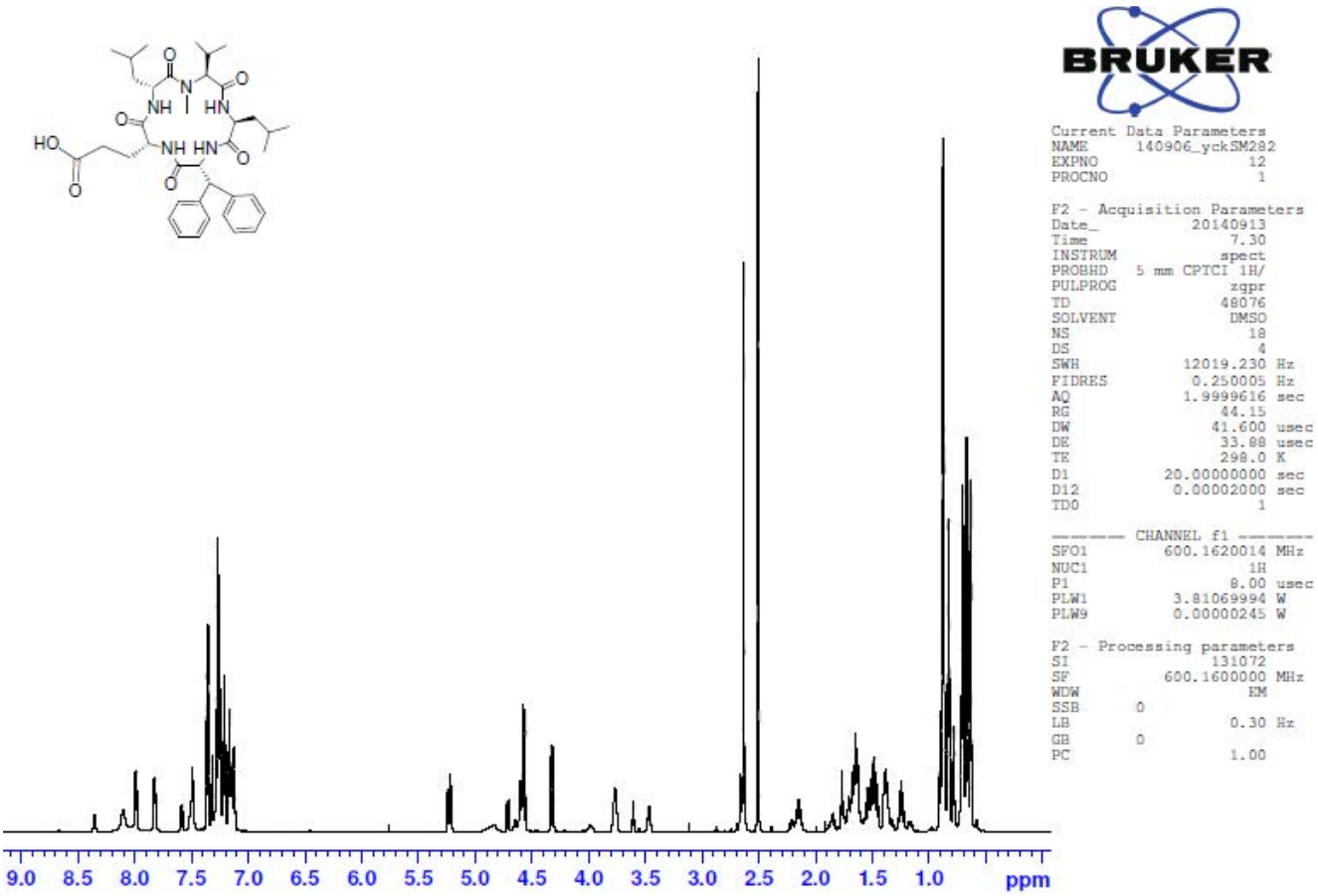
Compound **10**: HRMS of cyclo Leu-*N*-Me-Val-D-Leu-D-Glu-3,3-Diphe-D-Ala

MS Data from Orbitrap

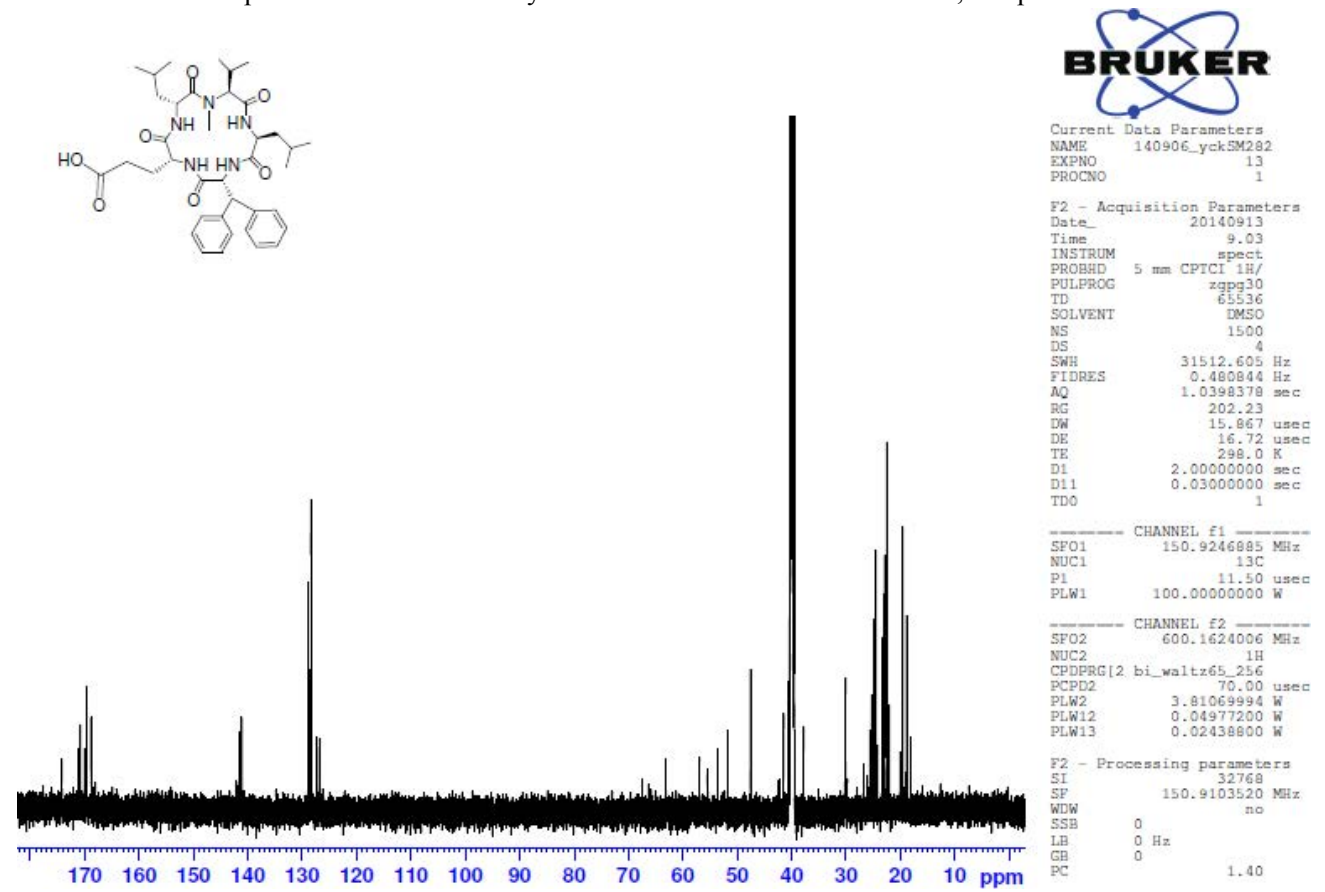
Full spectrum



Compound **10**: [1]HNMR of cyclo Leu-*N*-Me-Val-D-Leu-D-Glu-3,3-Diphe-D-Ala

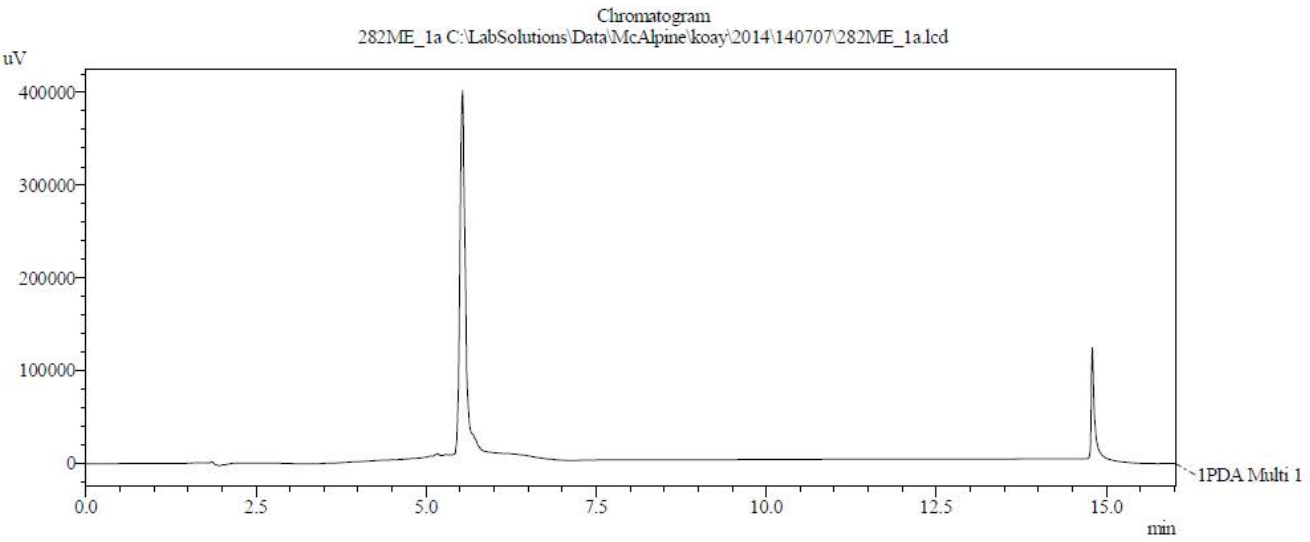


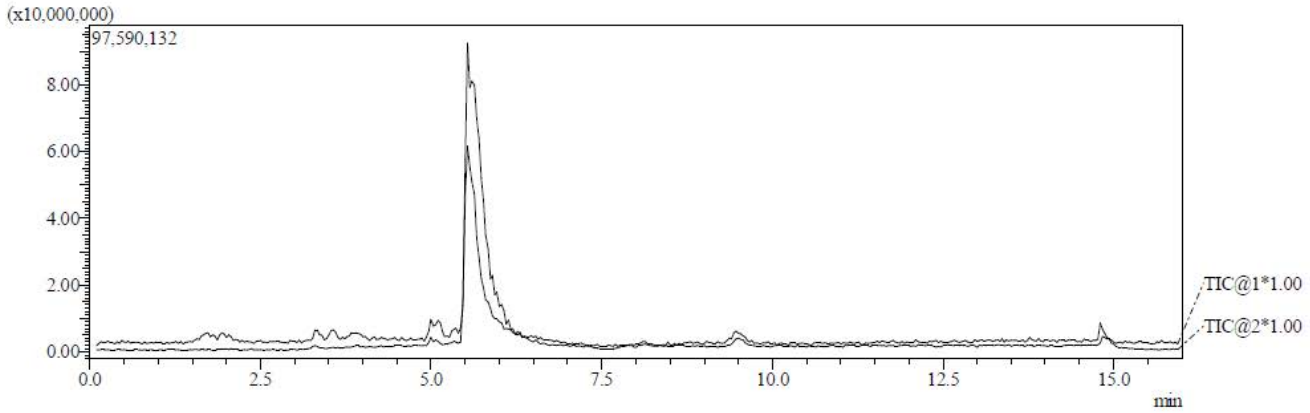
Compound **10**: [13]CNMR of cyclo Leu-*N*-Me-Val-D-Leu-D-Glu-3,3-Diphe-D-Ala

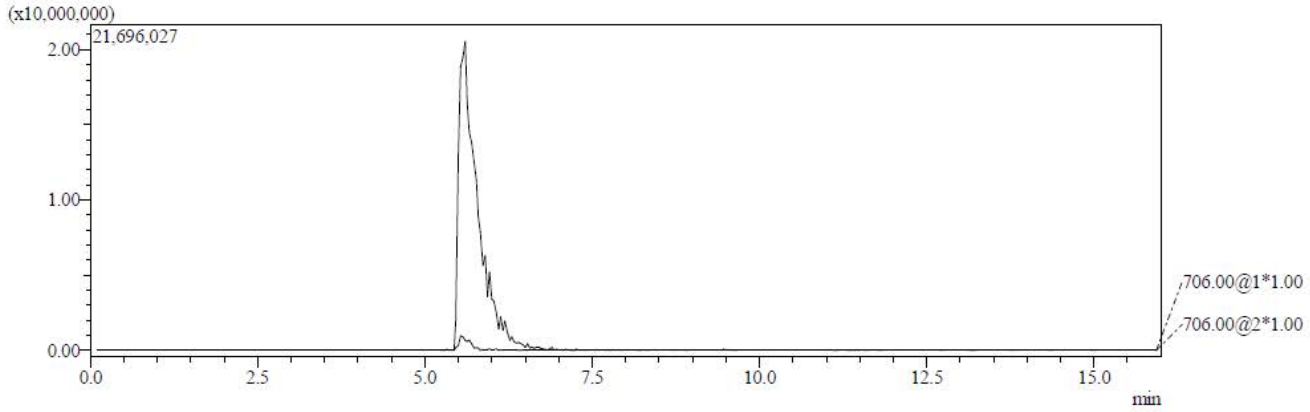


Compound **11**: LCMS of cyclo Leu-*N*-Me-Val-D-Leu-D-Glu(OMe)-3,3-Diphe-D-Ala

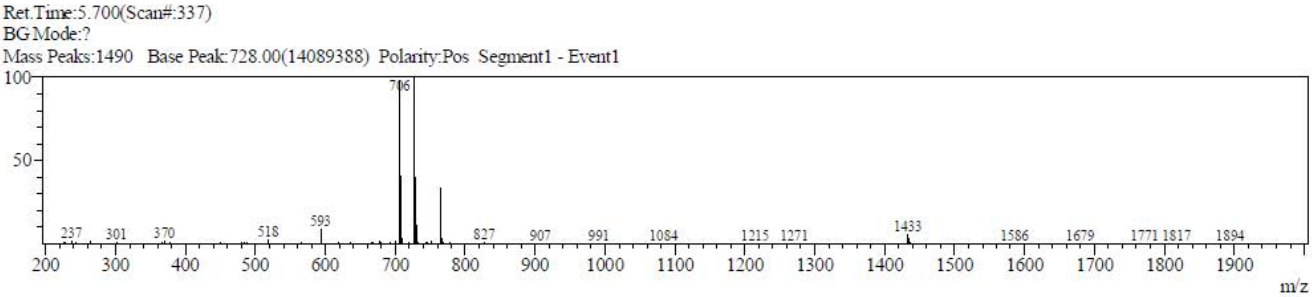
==== Shimadzu LCMSsolution Analysis Report ====







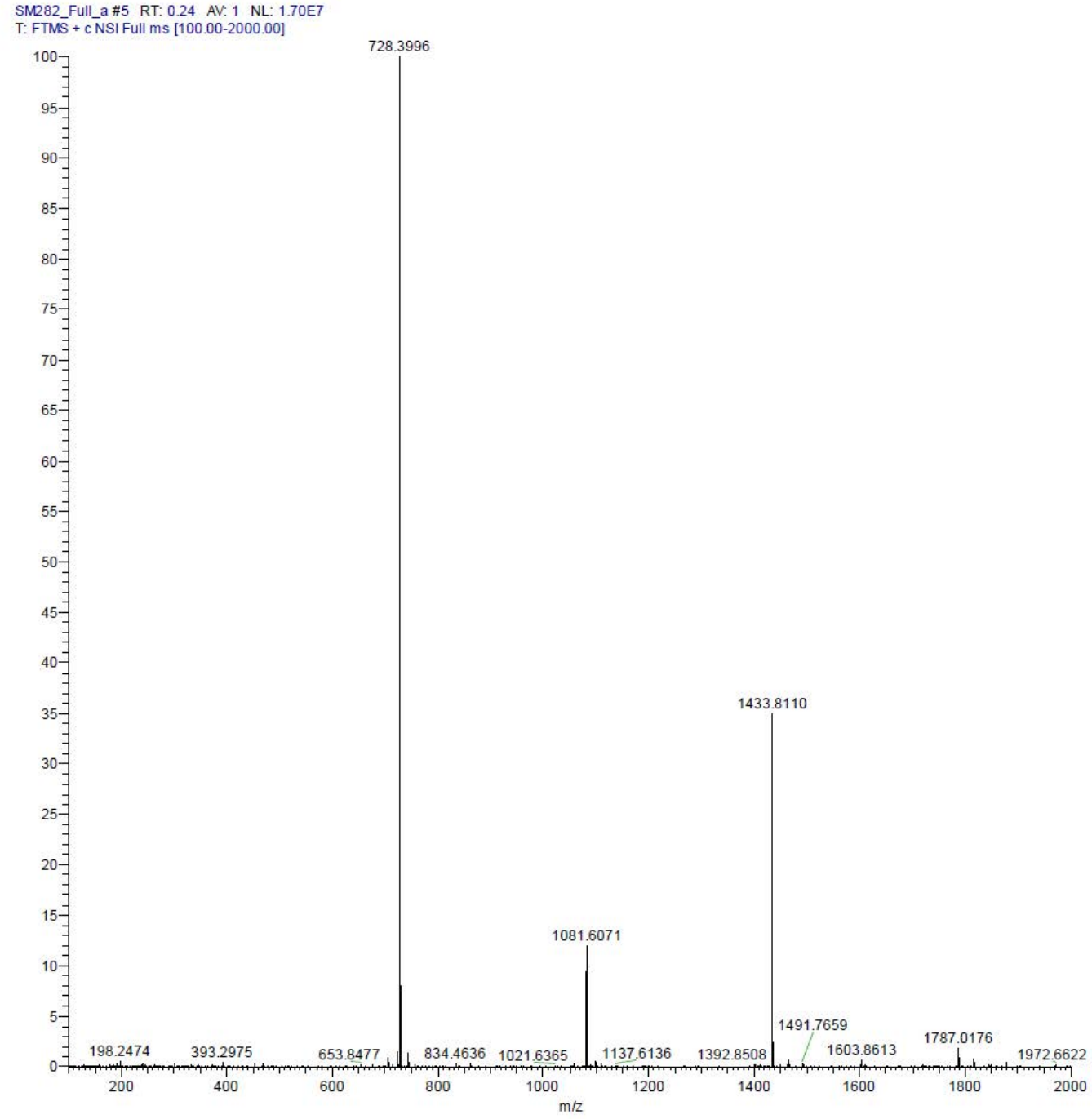
MS Spectrum Graph



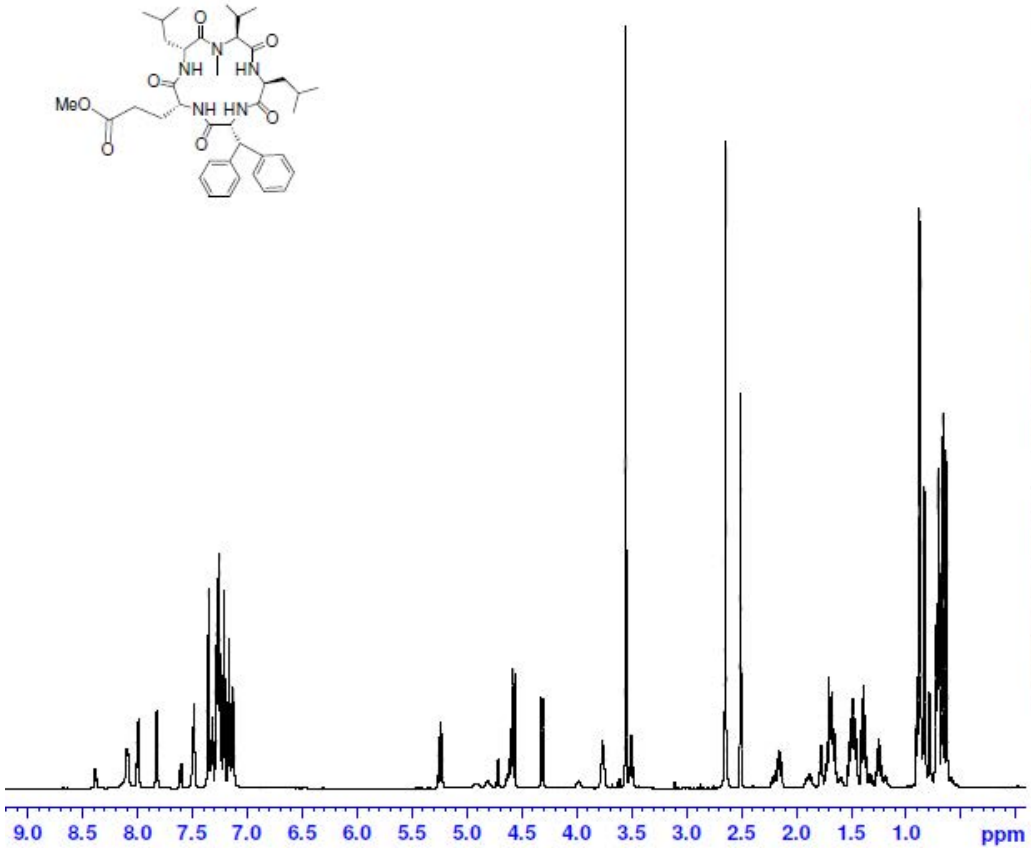
Compound **11**: HRMS of cyclo Leu-*N*-Me-Val-D-Leu-D-Glu(OMe)-3,3-Diphe-D-Ala

MS Data from Orbitrap

Full spectrum



Compound **11**: [1]HNMR of cyclo Leu-*N*-Me-Val-D-Leu-D-Glu(OMe)-3,3-Diphe-D-Ala



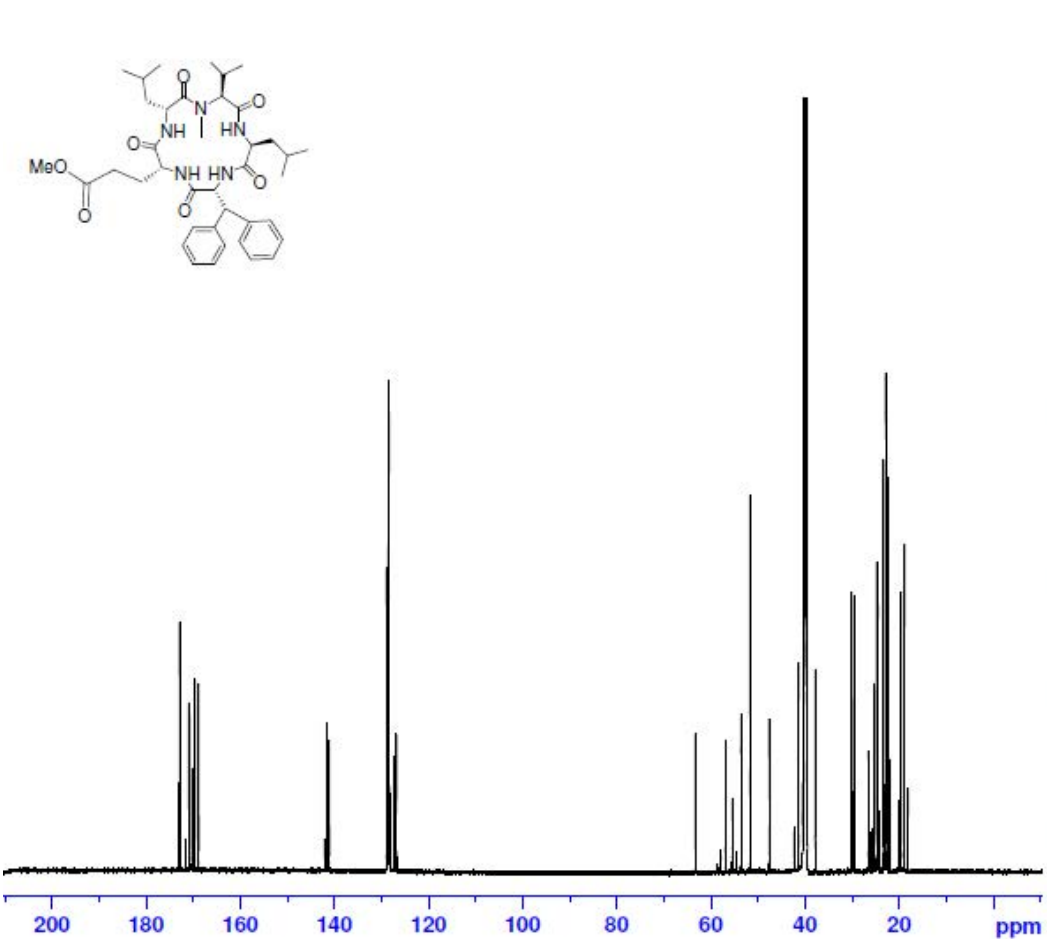

```
Current Data Parameters
NAME      140720_yck_SM282ME
EXPNO                      2
PROCNO                     1

F2 - Acquisition Parameters
Date_            20140720
Time                12.53
INSTRUM             spect
PROBHD   5 mm CPTCI 1H/
PULPROG             zgpr
TD                 48076
SOLVENT             DMSO
NS                    32
DS                     4
SWH             10204.082 Hz
FIDRES          0.212249 Hz
AQ              2.3557241 sec
RG                 11.02
DW                49.000 usec
DE                34.88 usec
TE                298.0 K
D1           20.00000000 sec
D12           0.00002000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1          600.1620041 MHz
NUC1                    1H
P1                   8.00 usec
PLW1           3.81069994 W
PLW9           0.00000245 W

F2 - Processing parameters
SI                  131072
SF            600.1600000 MHz
WDW                    EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.00
```

Compound **11**: [13]CNMR of cyclo Leu-*N*-Me-Val-D-Leu-D-Glu(OMe)-3,3-Diphe-D-Ala

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Current Data Parameters
NAME      140720_yck_SM282ME
EXPNO                      3
PROCNO                     1

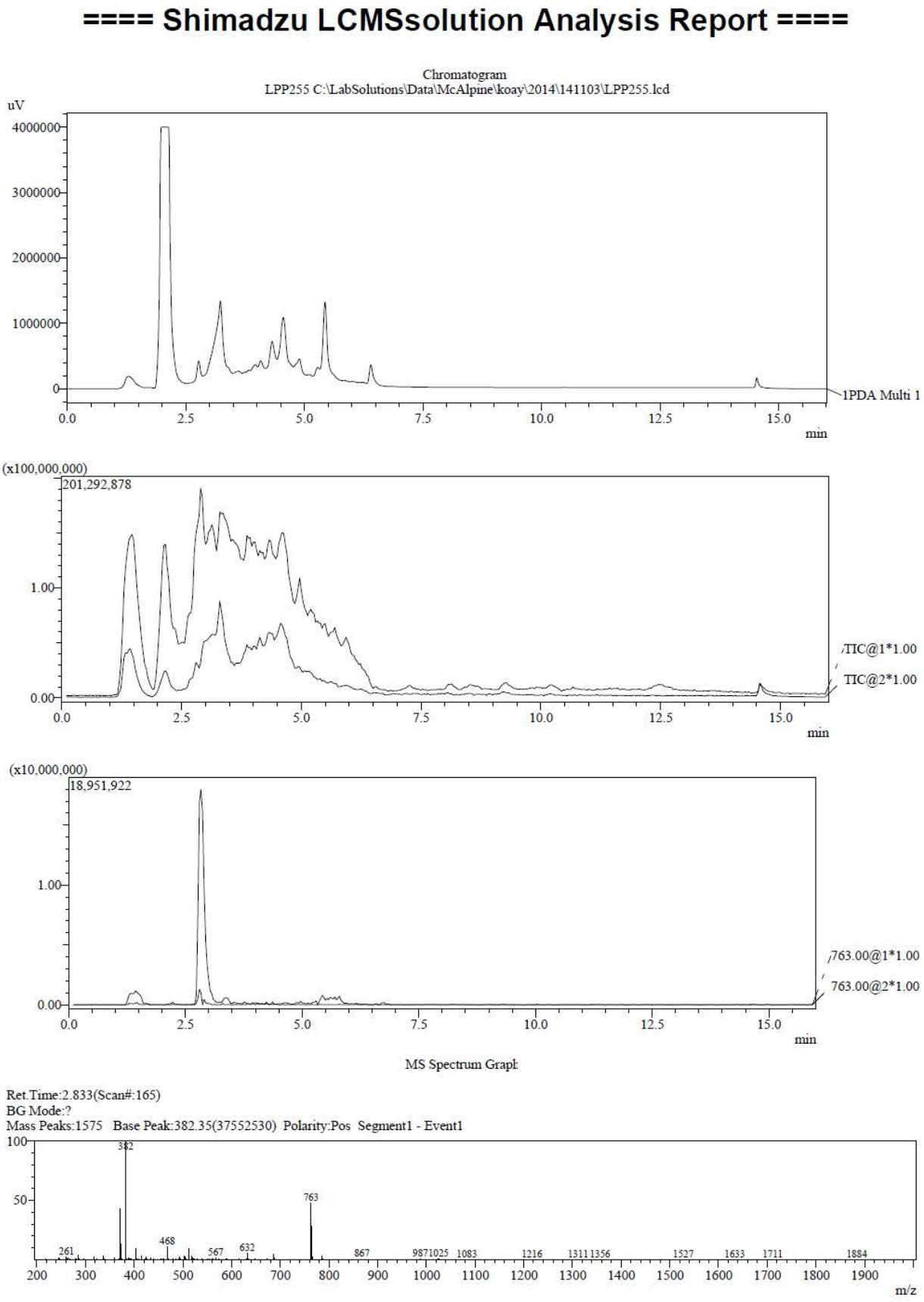
F2 - Acquisition Parameters
Date_            20140720
Time                15.59
INSTRUM             spect
PROBHD   5 mm CPTCI 1H/
PULPROG           zgpg30
TD                 65536
SOLVENT             DMSO
NS                  3200
DS                     4
SWH             33333.332 Hz
FIDRES          0.508626 Hz
AQ              0.9830400 sec
RG                202.23
DW                15.000 usec
DE                15.55 usec
TE                298.0 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1          150.9254430 MHz
NUC1                    13C
P1                  11.50 usec
PLW1         100.00000000 W

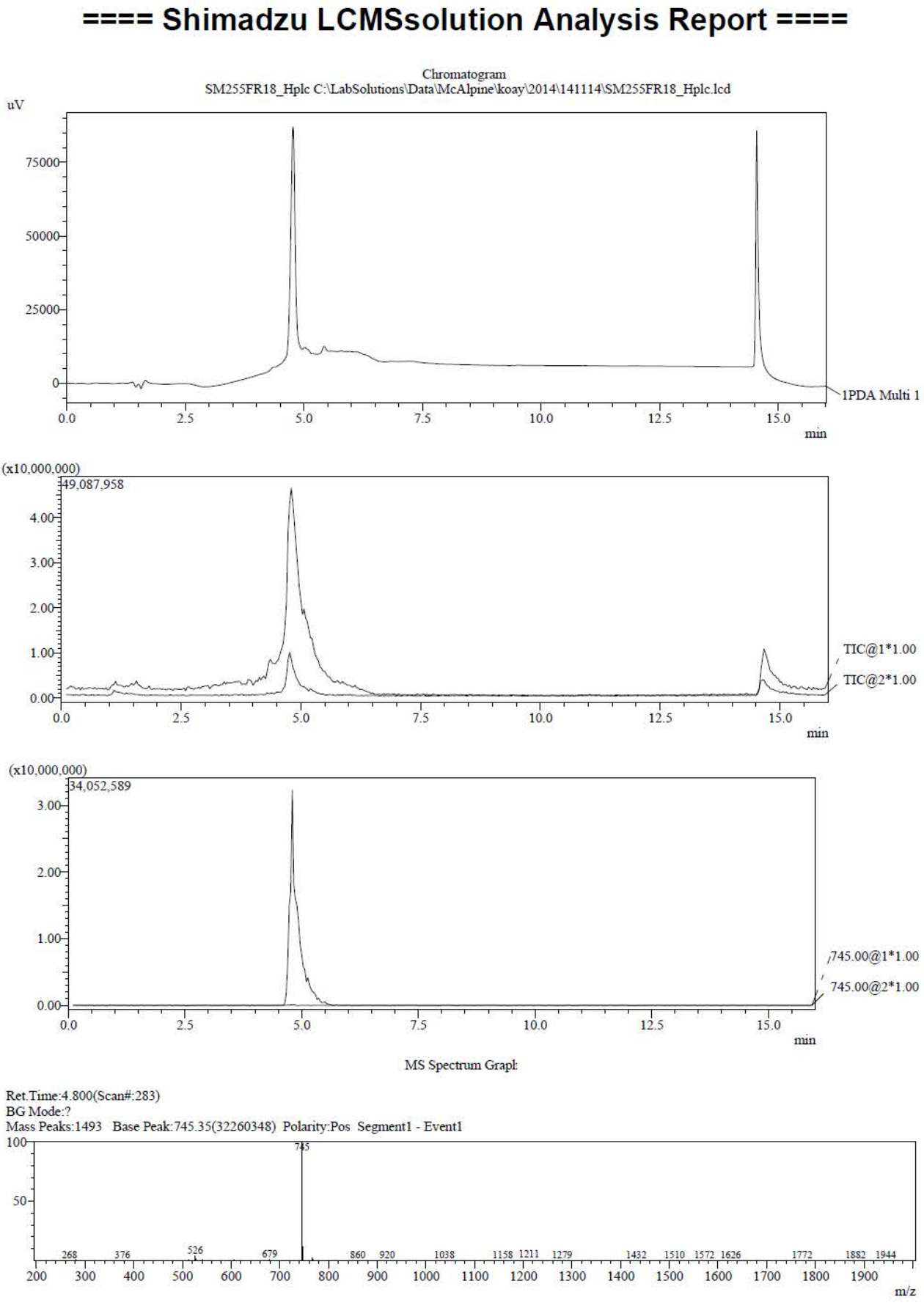
======== CHANNEL f2 ========
SFO2          600.1624006 MHz
NUC2                    1H
CPDPRG[2 bi_waltz65_256
PCPD2                70.00 usec
PLW2           3.81069994 W
PLW12          0.04977200 W
PLW13          0.02438800 W

F2 - Processing parameters
SI                  32768
SF            150.9103520 MHz
WDW                    EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  1.40
```

Compound **12**: LCMS of DDLP HO-Leu-*N*-Me-Val-3-(2'-Pyr)-D-Ala-D-Phe-3,3-Diphe-D-Ala-NH_2



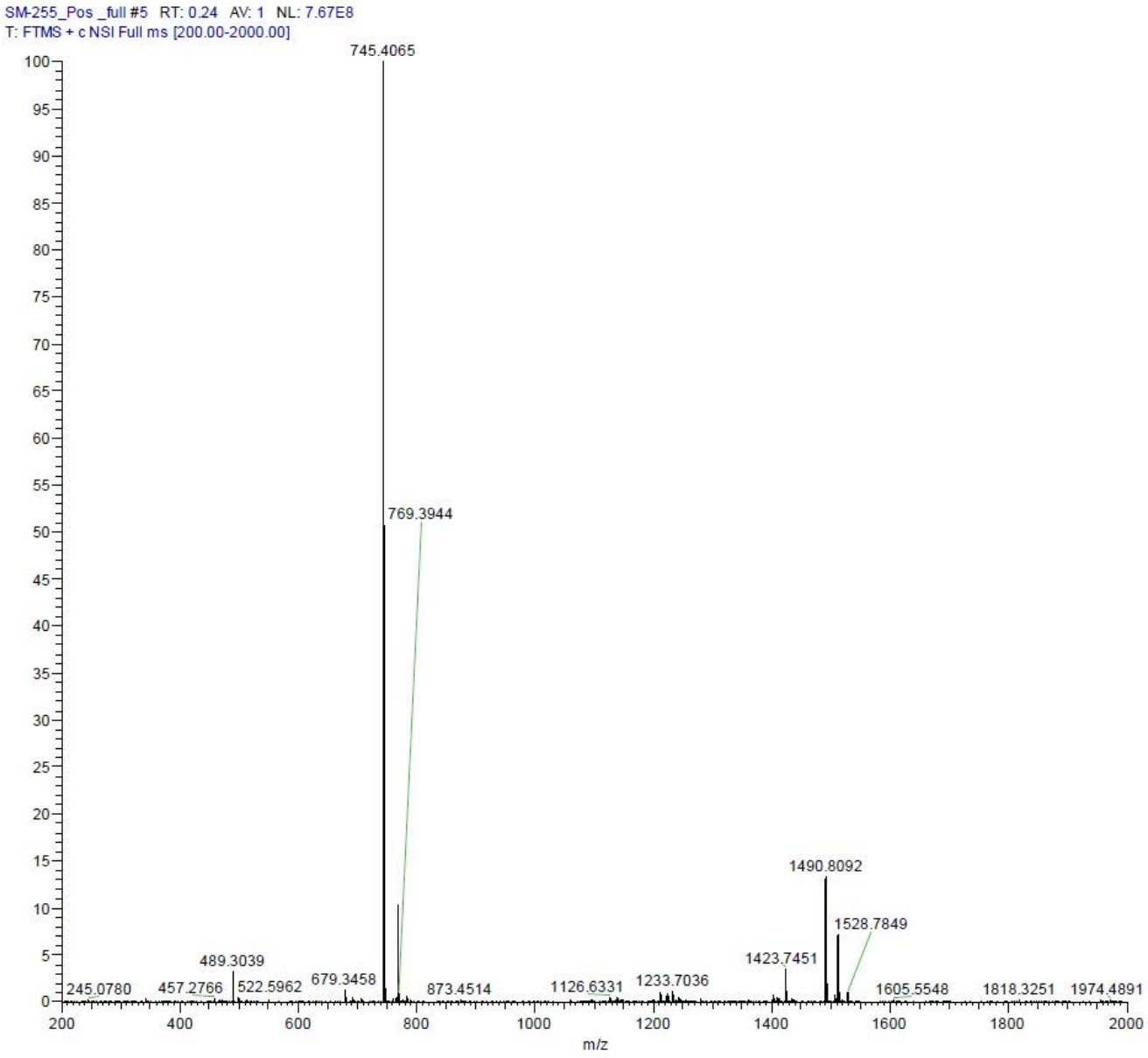
Compound **12**: LCMS of cyclo Leu-*N*-Me-Val-3-(2'-Pyr)-D-Ala-D-Phe-3,3-Diphe-D-Ala



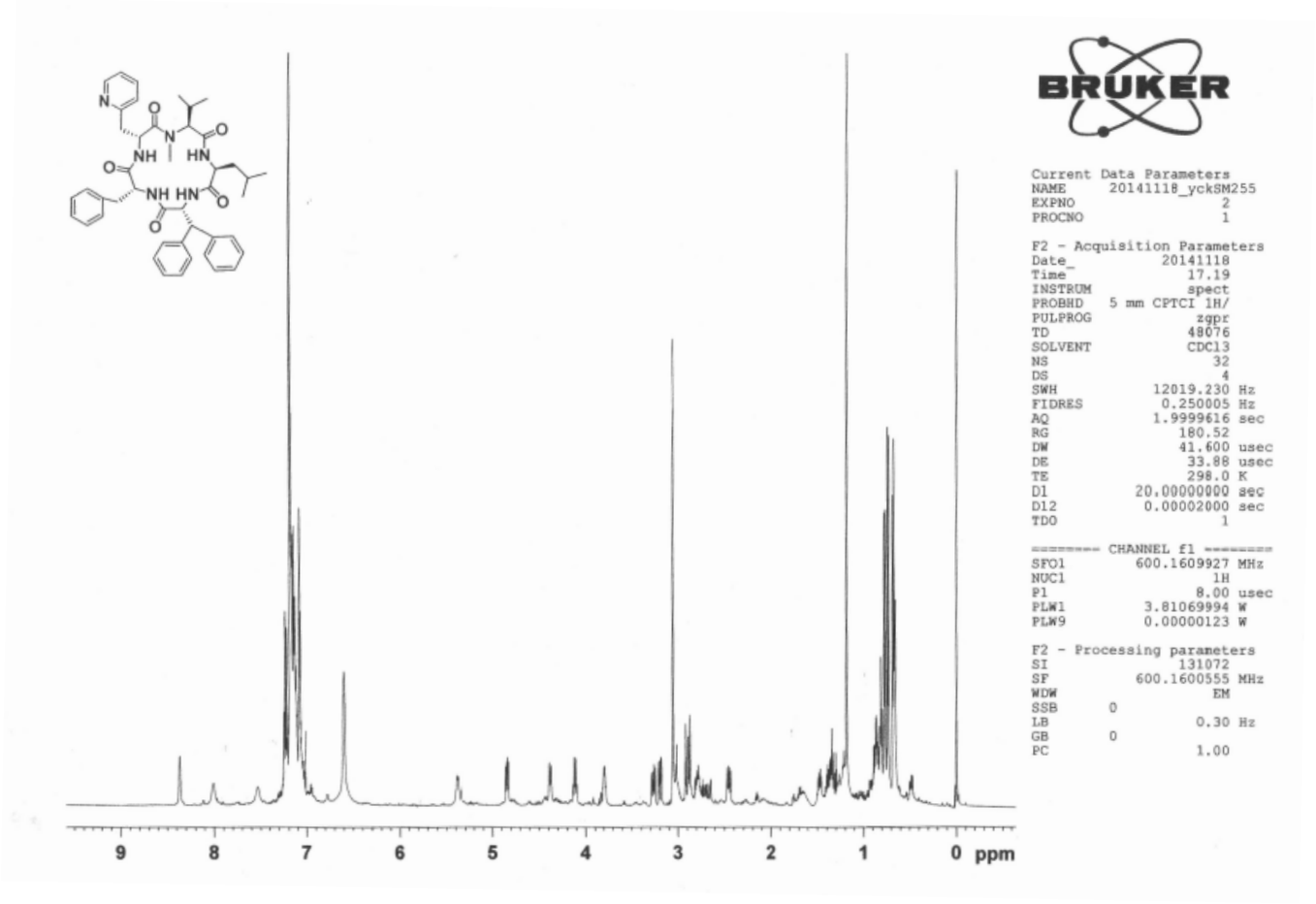
Compound **12**: HRMS of cyclo Leu-*N*-Me-Val-3-(2'-Pyr)-D-Ala-D-Phe-3,3-Diphe-D-Ala

MS Data from Orbitrap

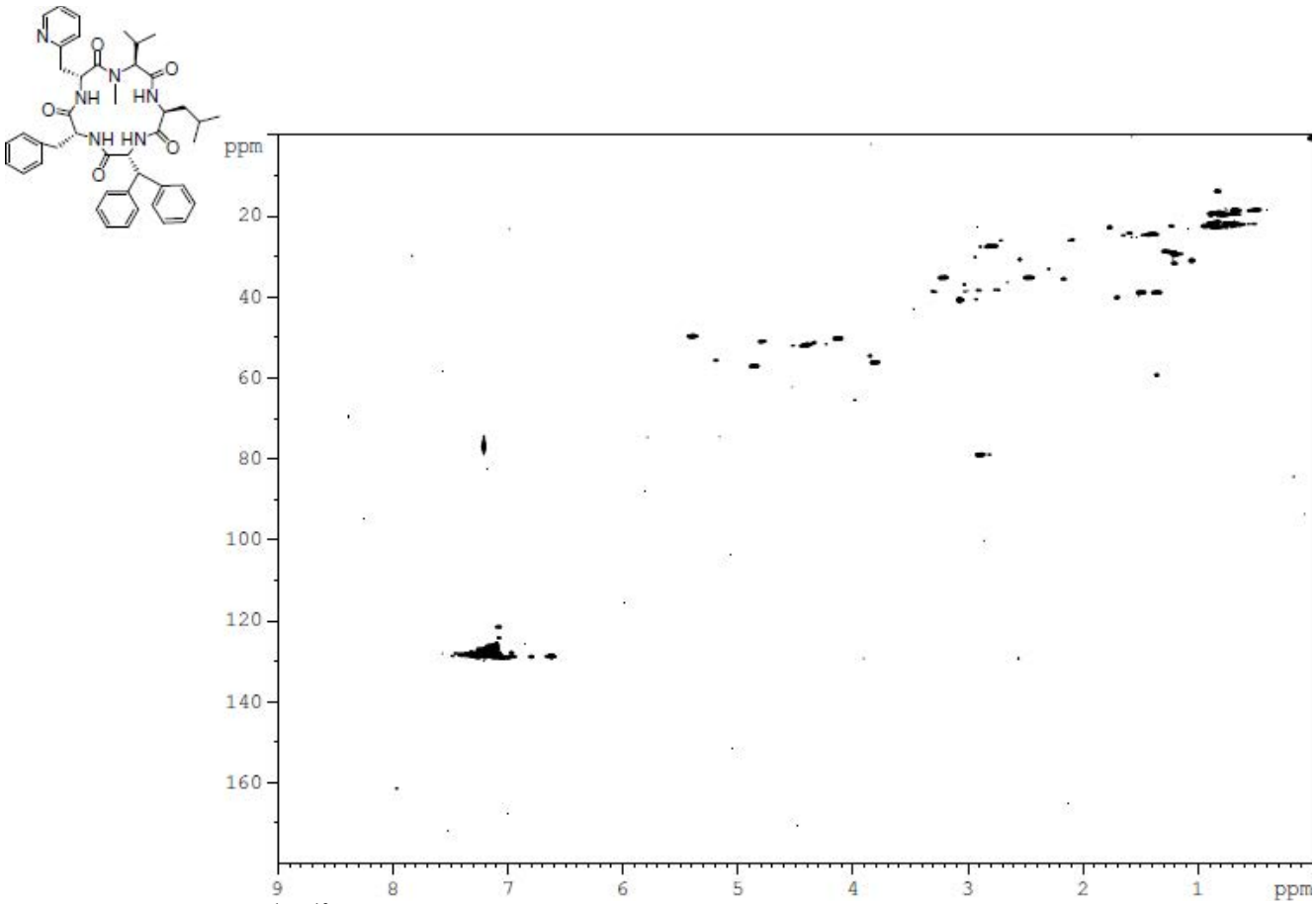
Full spectrum



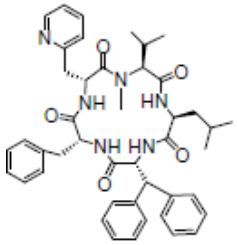
Compound **12**: ^{1}HNMR of cyclo Leu-*N*-Me-Val-3-(2'-Pyr)-D-Ala-D-Phe-3,3-Diphe-D-Ala

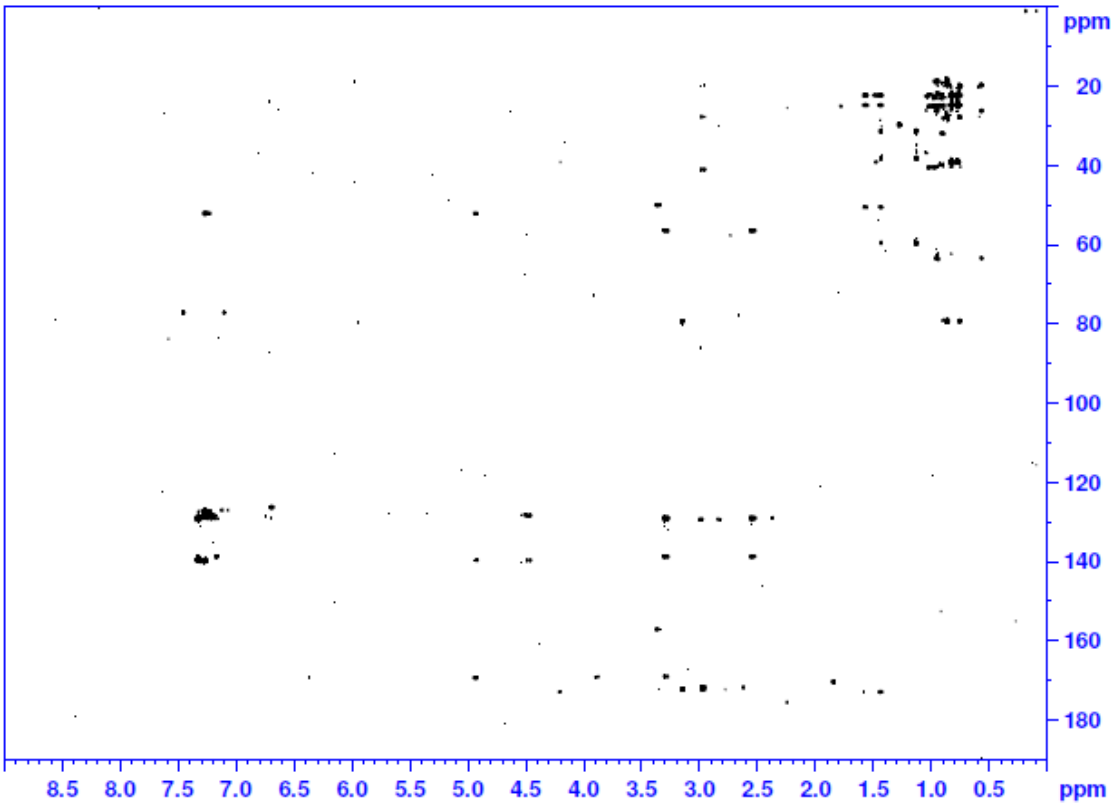


Compound **12**: ^{1}H-^{13}C HSQC of cyclo Leu-*N*-Me-Val-3-(2'-Pyr)-D-Ala-D-Phe-3,3-Diphe-D-Ala

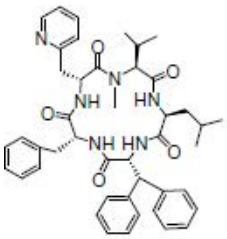


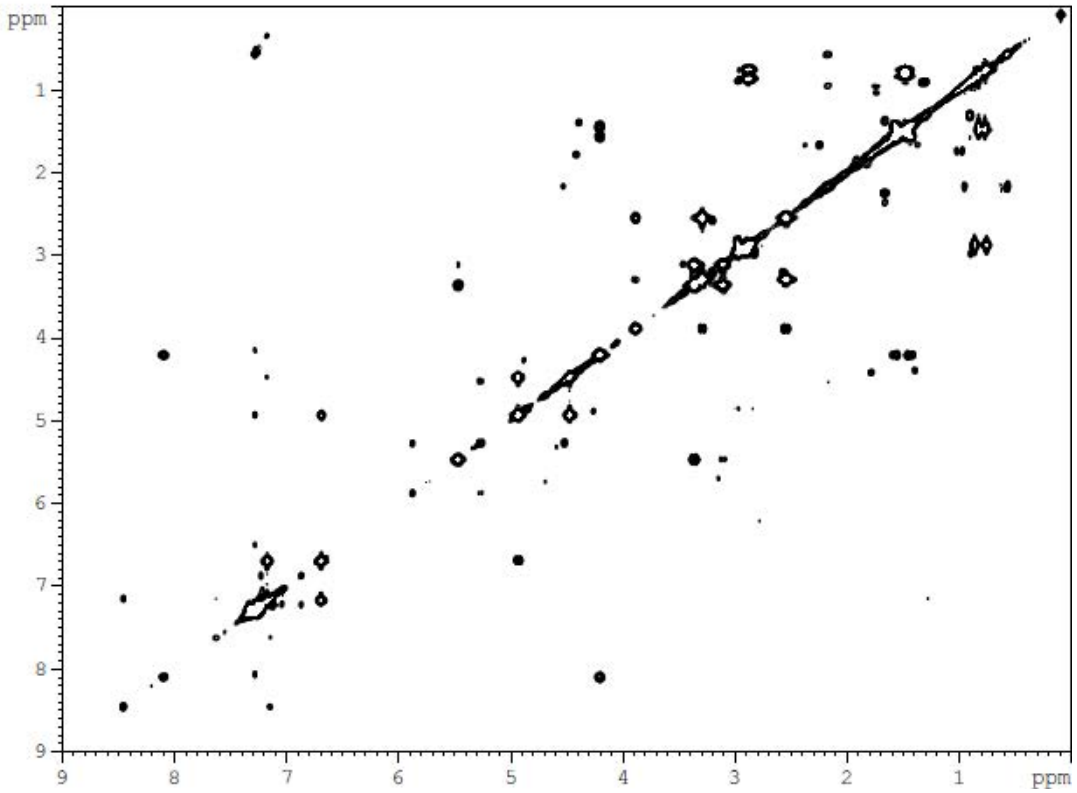
Compound **12**: ^{1}H-^{13}C HMBC of cyclo Leu-*N*-Me-Val-3-(2'-Pyr)-D-Ala-D-Phe-3,3-Diphe-D-Ala





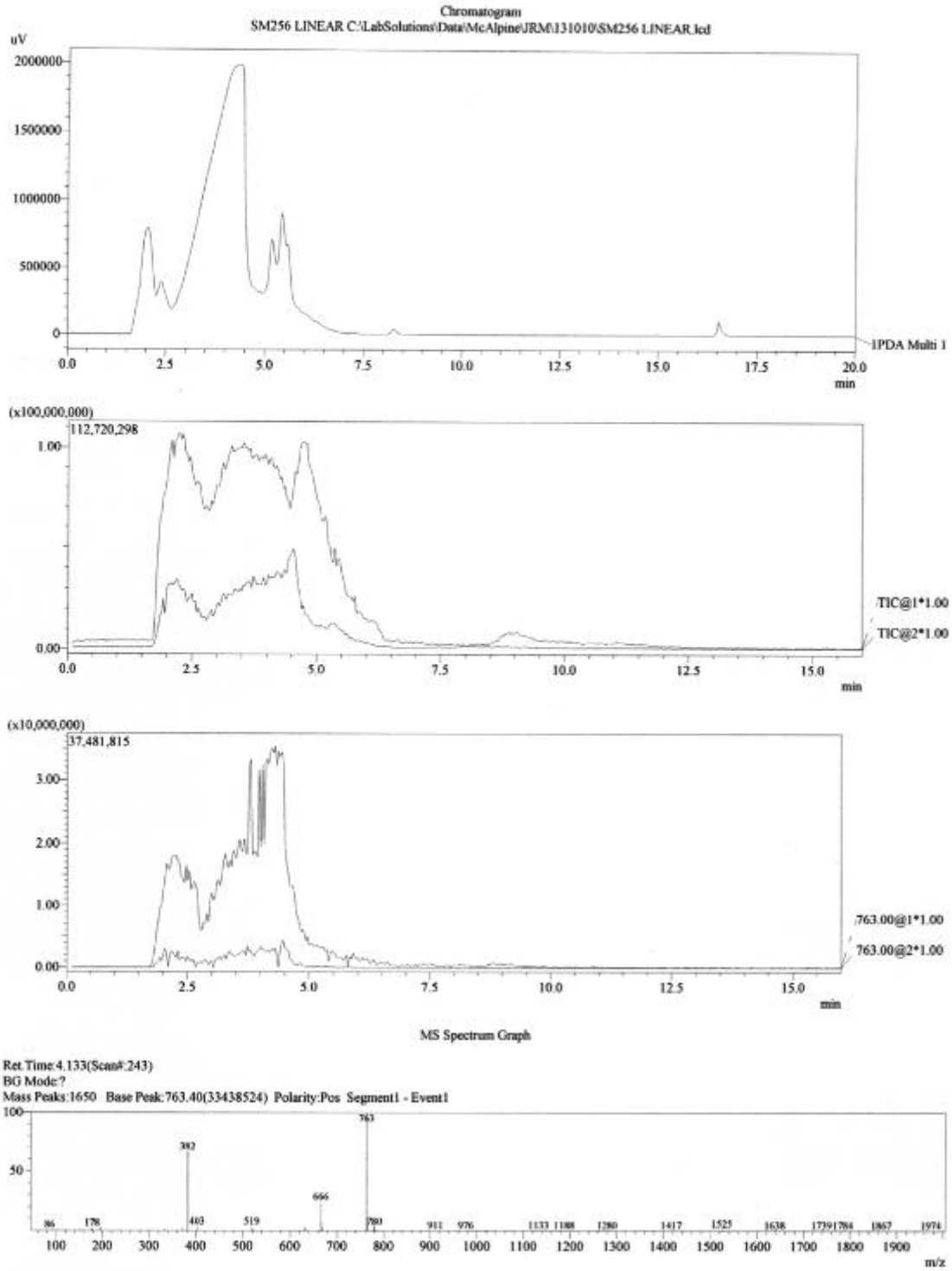
Compound **12**: ^{1}H-^{1}H COSY of cyclo Leu-*N*-Me-Val-3-(2'-Pyr)-D-Ala-D-Phe-3,3-Diphe-D-Ala





Compound **13**: LCMS of DDLP HO-Leu-*N*-Me-Val-3-(3-pyridyl)-D-Ala-D-Phe-3,3-DiPhe-D-Ala-NH_2

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

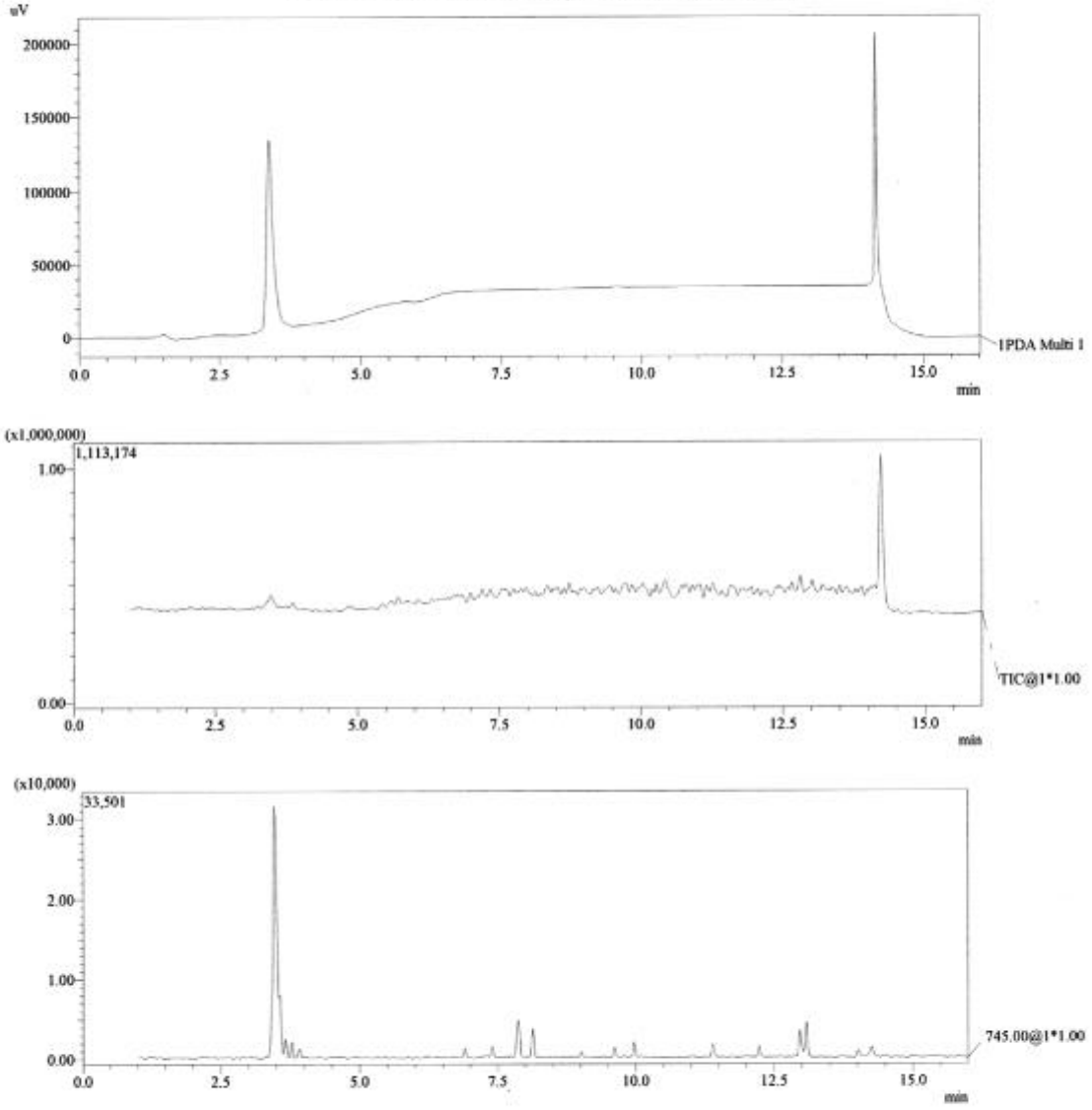


Compound **13**: LCMS of Leu-*N*-Me-Val-3-(3-pyridyl)-D-Ala-D-Phe-3,3-DiPhe-D-Ala

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

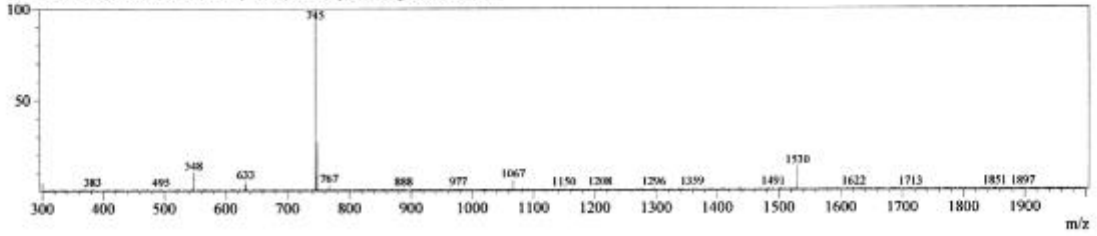
Chromatogram

SM256 FINAL C:\LabSolutions\Data\McAlpine\JRM\140114\SM256 FINAL.lcd

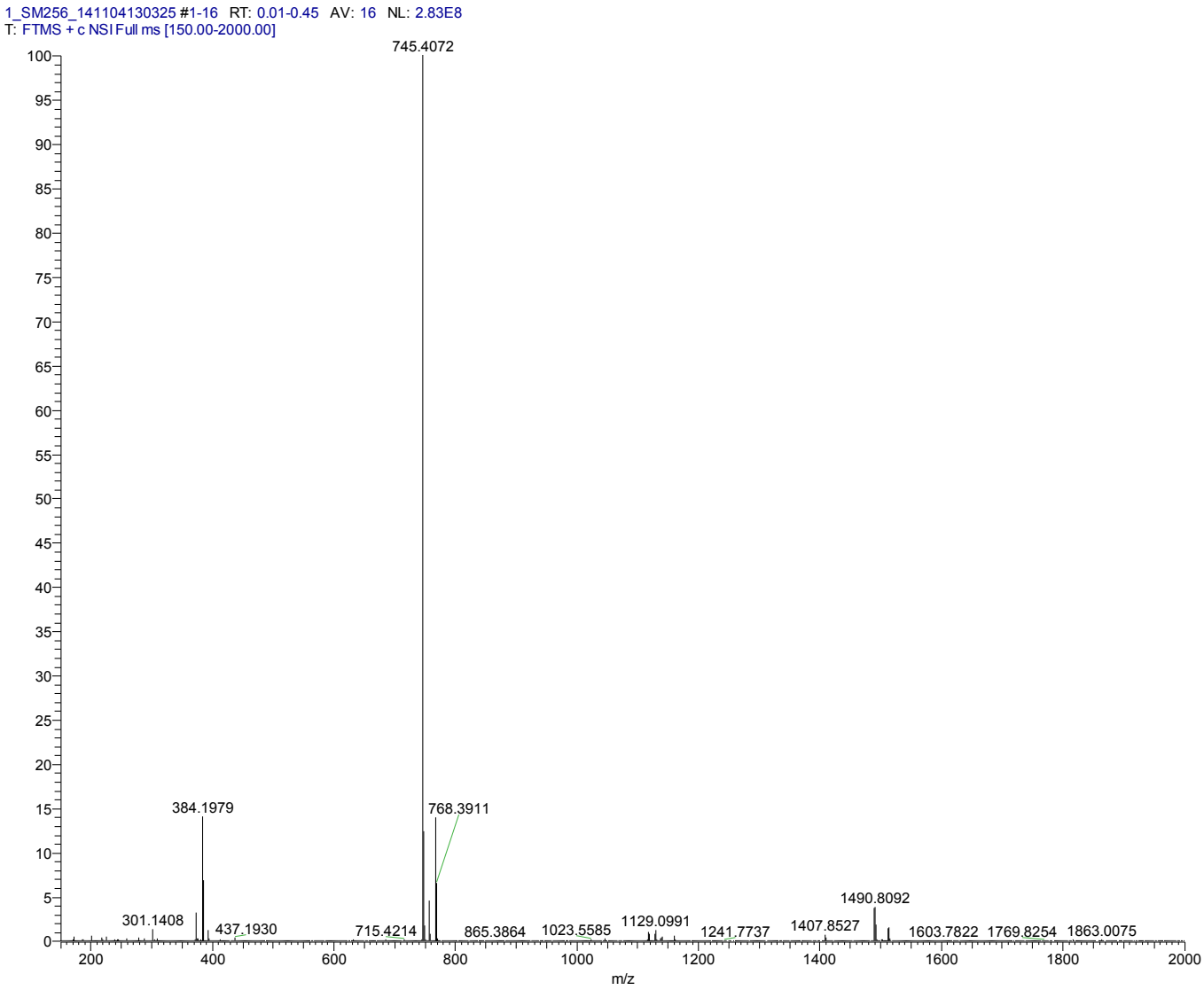


MS Spectrum Graph

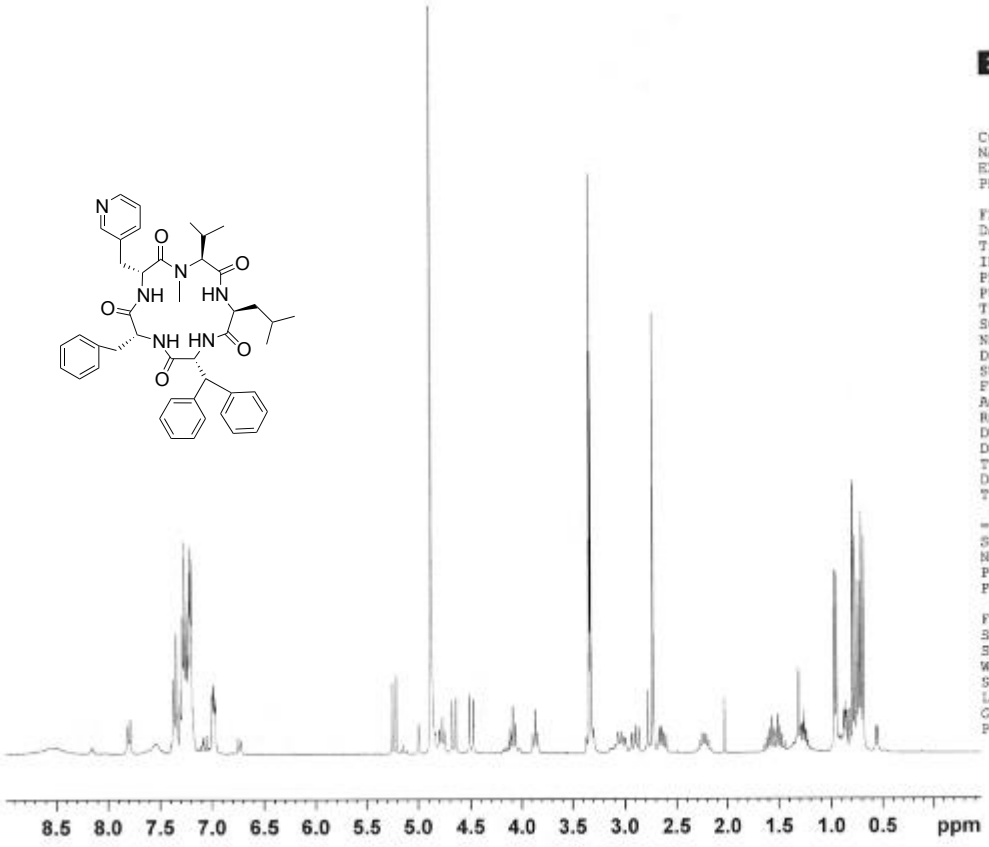
Ret.Time:3.467(Scan#:149)
BG Mode:?
Mass Peaks:1585 Base Peak:745.05(41606) Polarity:Pos Segment1 - Event1



Compound **13**: HRMS of cyclo Leu-*N*-Me-Val-3-(3-pyridyl)-D-Ala-D-Phe-3,3-DiPhe-D-Ala



Compound **13**: [1]HNMR of cyclo Leu-*N*-Me-Val-3-(3-pyridyl)-D-Ala-D-Phe-3,3-DiPhe-D-Ala




```
Current Data Parameters
NAME                  140117-jrm
EXPNO                          1
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20140118
Time                       16.41
INSTRUM                    spect
PROBHD     5 mm PABBO BB-
PULPROG                       zg
TD                         32768
SOLVENT                     MeOD
NS                            64
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                    5.00000000 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                  300.1700000 MHz
WDW                            EM
SSB                 0
LB                           0.10 Hz
GB                  0
PC                           1.00
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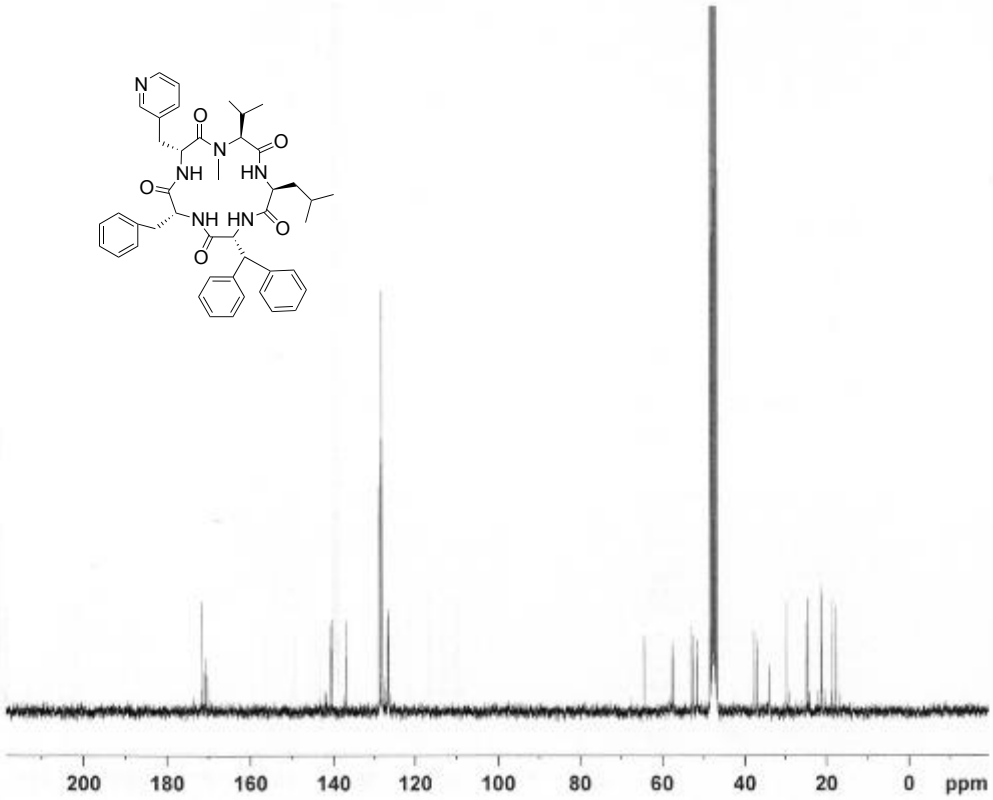
Compound **13**: [13]C NMR of cyclo Leu-*N*-Me-Val-3-(3-pyridyl)-D-Ala-D-Phe-3,3-DiPhe-D-Ala

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Current Data Parameters
NAME                  140117-jrm
EXPNO                          2
PROCNO                         1

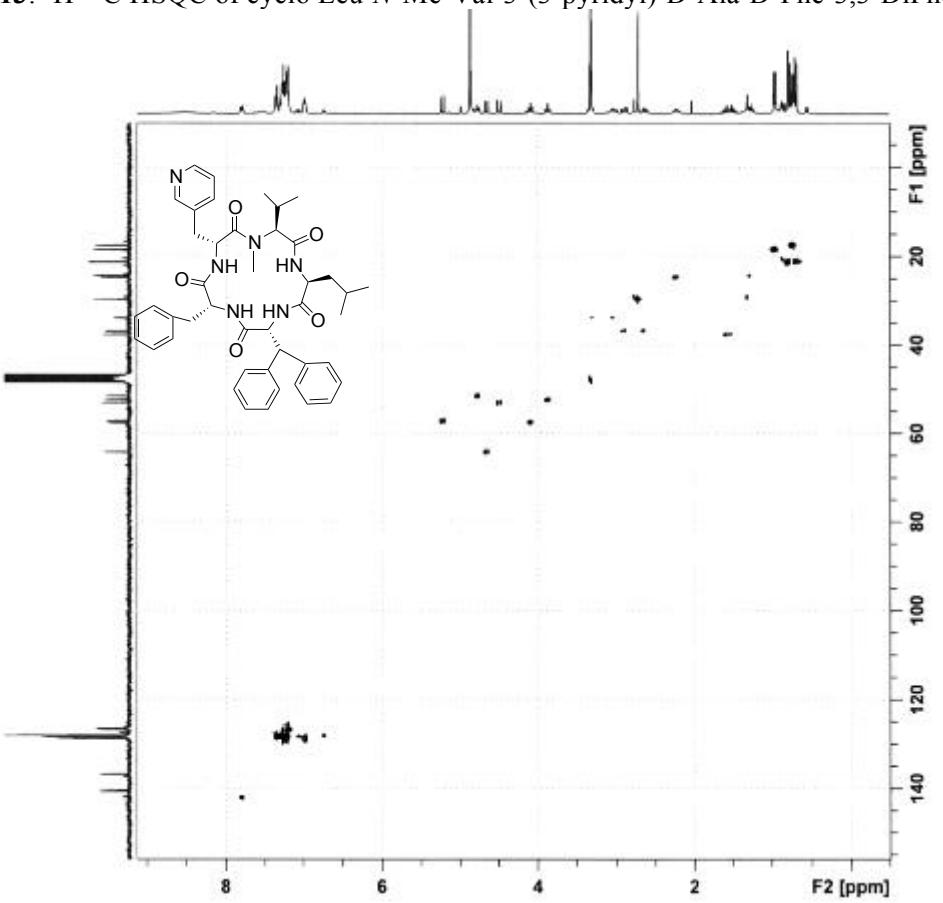
F2 - Acquisition Parameters
Date_                   20140118
Time                       16.54
INSTRUM                    spect
PROBHD     5 mm PABBO BB-
PULPROG                 zgpg30
TD                         65536
SOLVENT                     MeOD
NS                          4608
DS                             2
SWH                    18028.846 Hz
FIDRES                  0.275098 Hz
AQ                      1.8175317 sec
RG                           203
DW                        27.733 usec
DE                          6.80 usec
TE                         298.0 K
D1                    0.50000000 sec
D11                   0.03000000 sec
TD0                            18

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

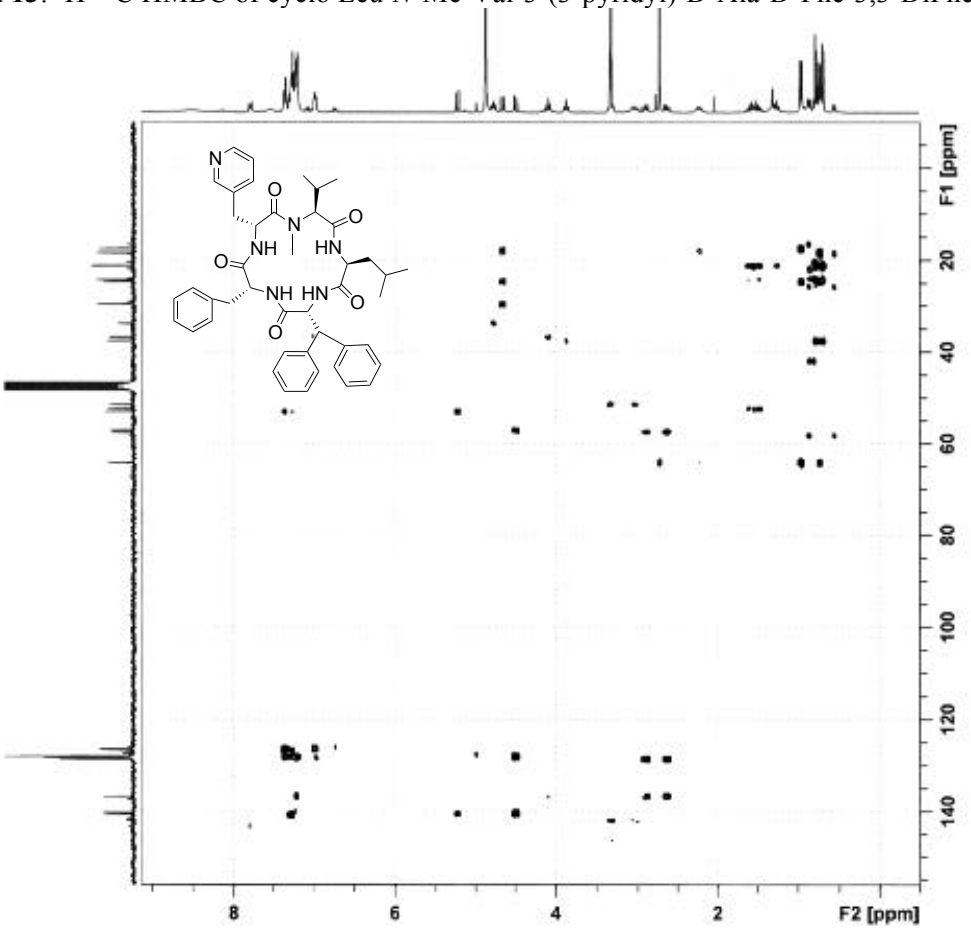
======== CHANNEL f2 ========
SFO2                300.1712007 MHz
NUC2                        1H
CPDPRG[2 bi_waltz65_256
PCPD2                      90.00 usec
PLW2                 8.20349979 W
PLW12                0.27774000 W
PLW13                0.22497000 W

F2 - Processing parameters
SI                         32768
SF                  75.4778070 MHz
WDW                            EM
SSB                 0
LB                           1.00 Hz
GB                  0
PC                           1.40
```

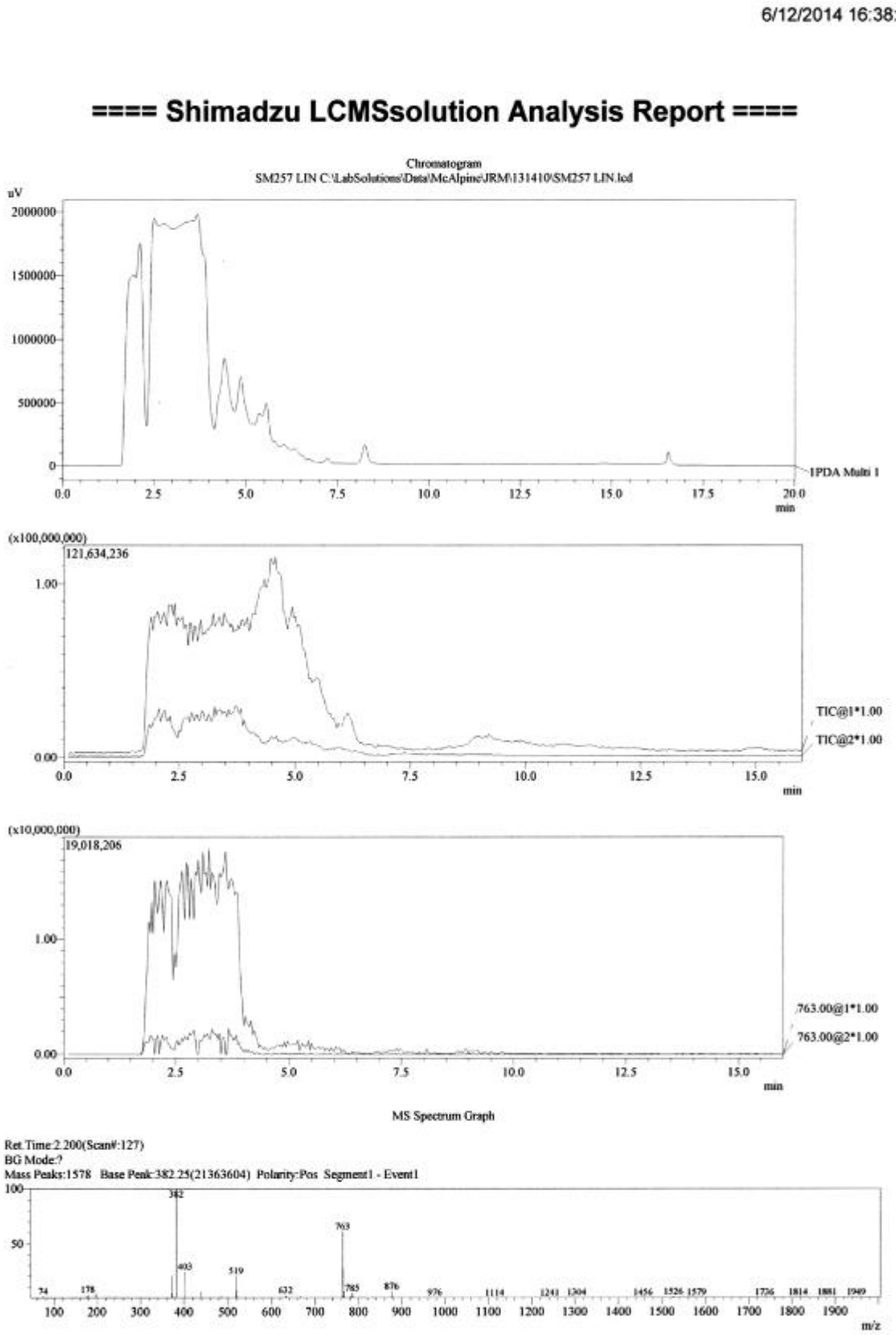
Compound **13**: ^{1}H-^{13}C HSQC of cyclo Leu-*N*-Me-Val-3-(3-pyridyl)-D-Ala-D-Phe-3,3-DiPhe-D-Ala



Compound **13**: ^{1}H-^{13}C HMBC of cyclo Leu-*N*-Me-Val-3-(3-pyridyl)-D-Ala-D-Phe-3,3-DiPhe-D-Ala



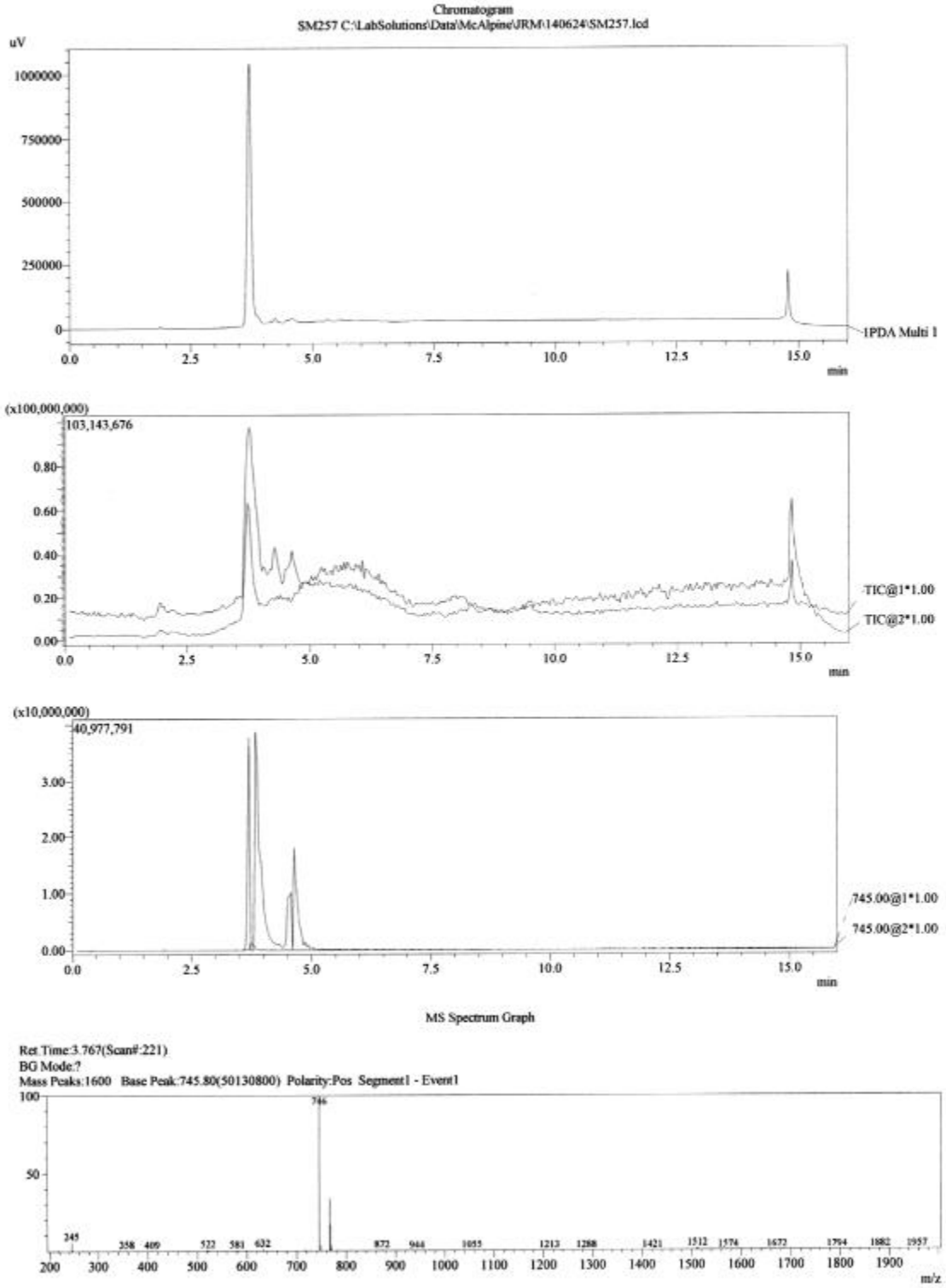
Compound **14**: LCMS of DDLP HO-Leu-*N*-Me-Val-3-(4-pyridyl)-D-Ala-D-Phe-3,3-DiPhe-D-Ala-NH_2



Compound **14**: LCMS of Leu-*N*-Me-Val-3-(4-pyridyl)-D-Ala-D-Phe-3,3-DiPhe-D-Ala

1/12/2014 10:27:38 1 / 1

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



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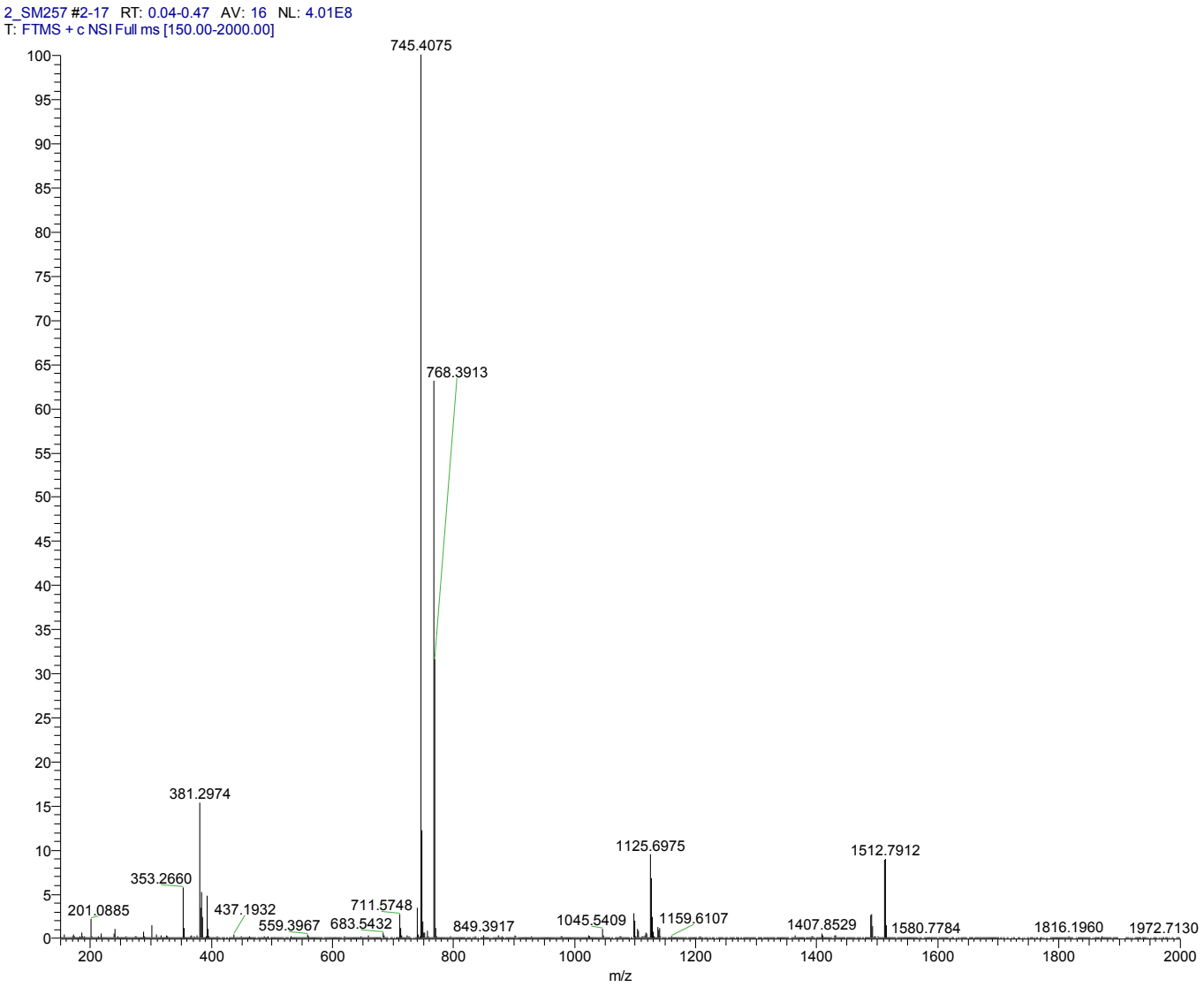
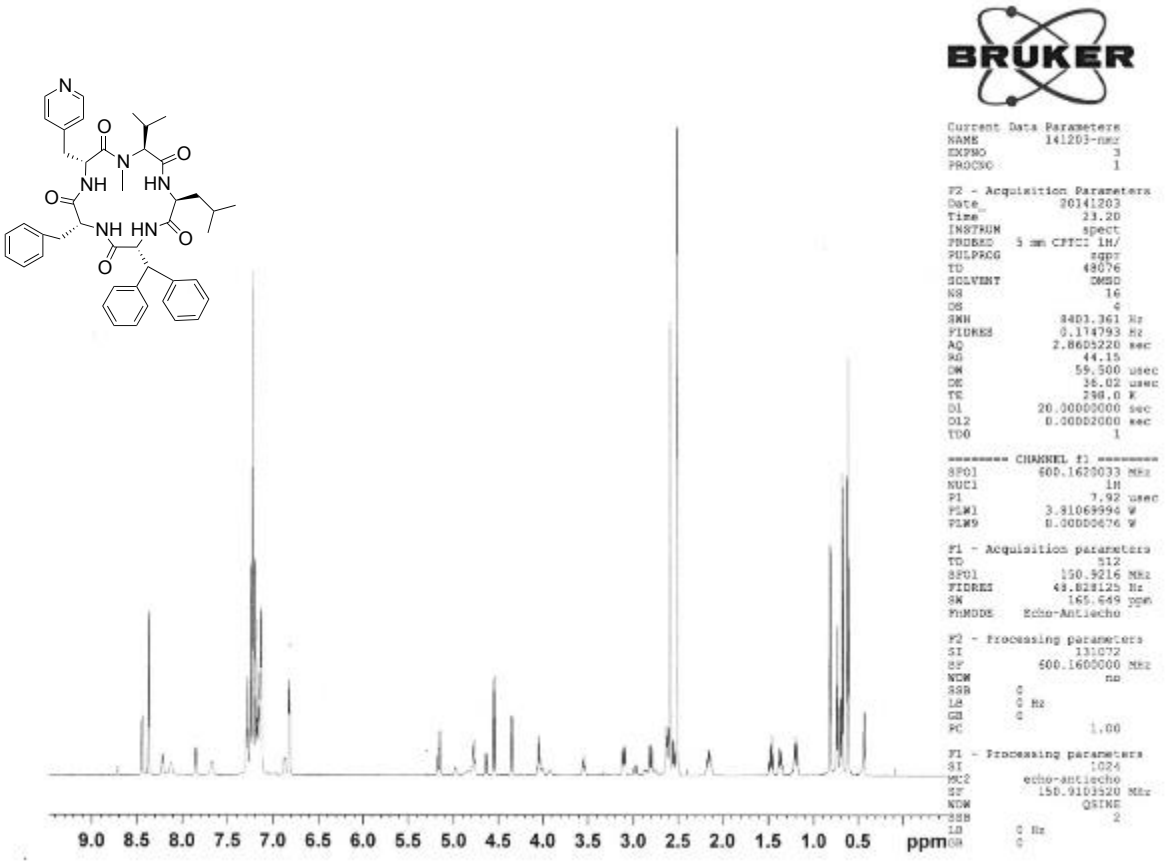
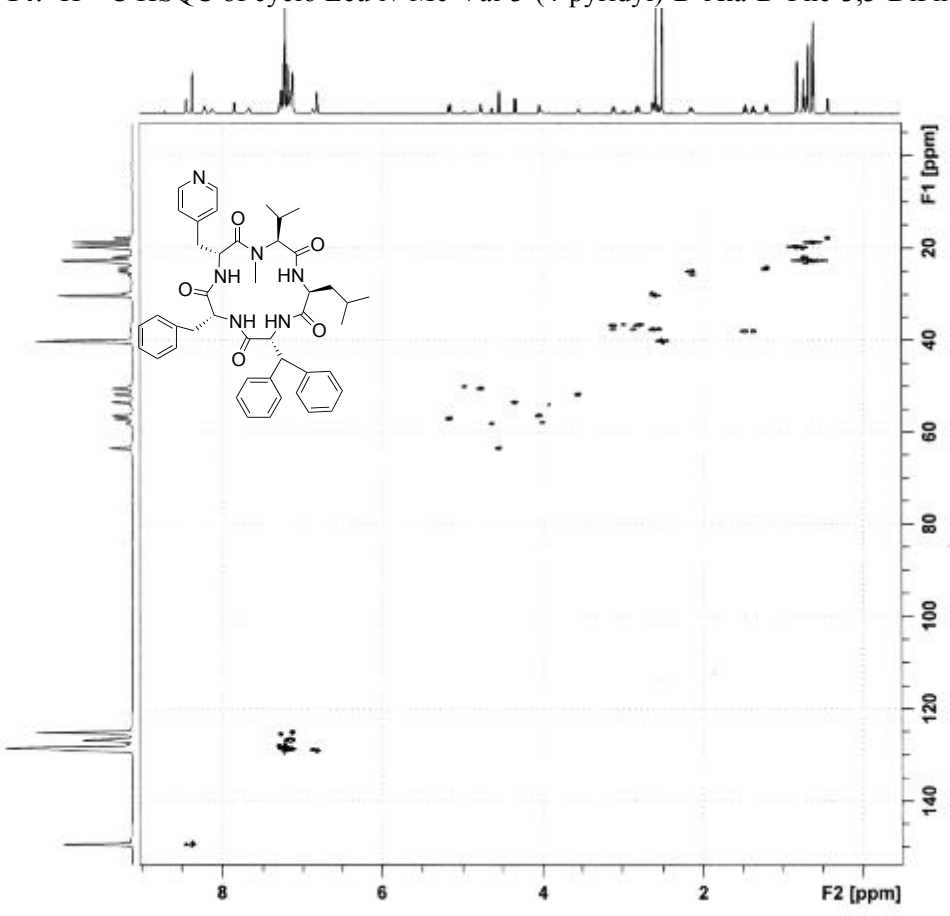
Compound **14**: HRMS of cyclo Leu-*N*-Me-Val-3-(4-pyridyl)-D-Ala-D-Phe-3,3-DiPhe-D-Ala



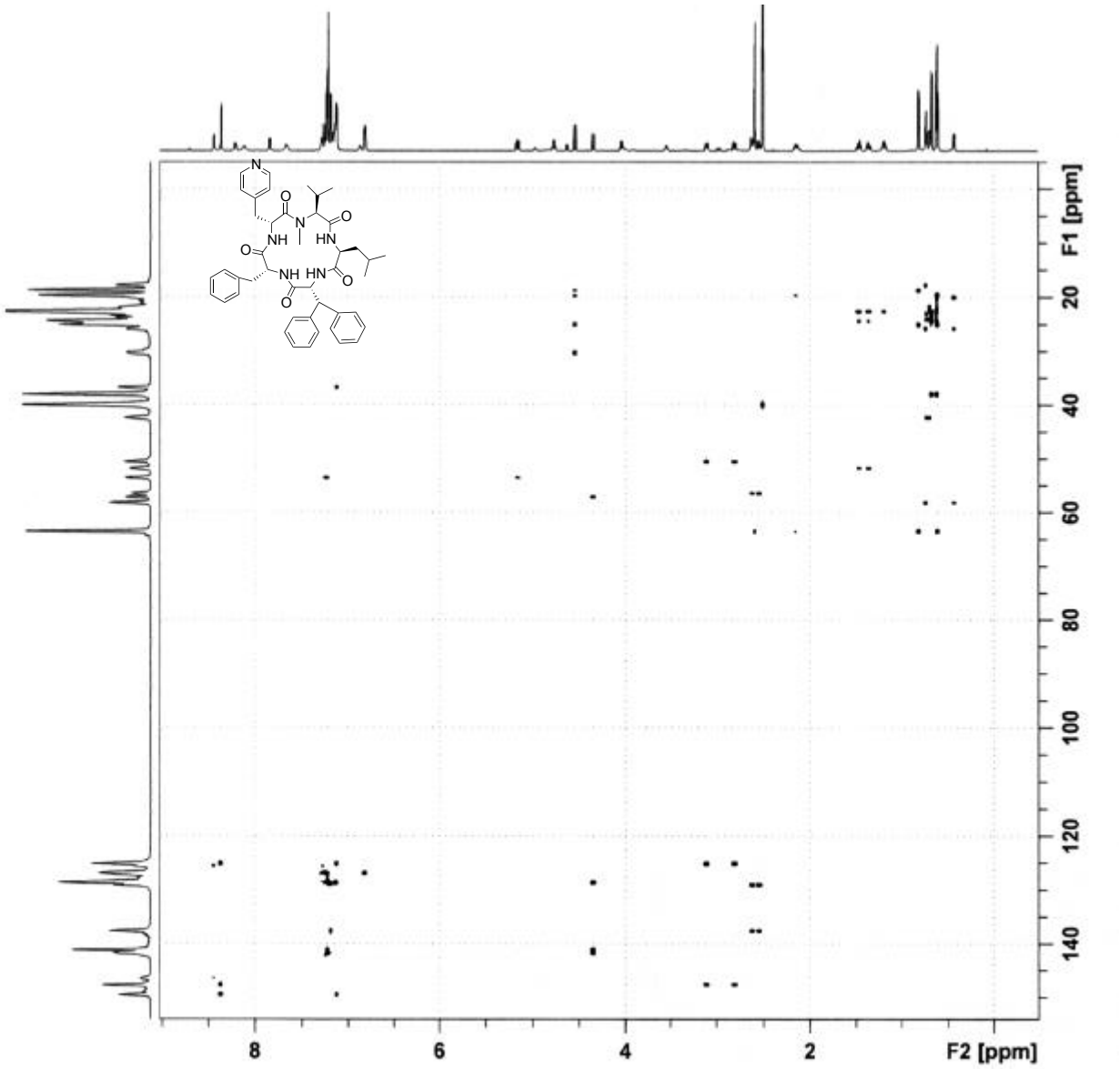
Compound **14**: ^{1}HNMR of cyclo Leu-*N*-Me-Val-3-(4-pyridyl)-D-Ala-D-Phe-3,3-DiPhe-D-Ala



Compound **14**: ^{1}H-^{13}C HSQC of cyclo Leu-*N*-Me-Val-3-(4-pyridyl)-D-Ala-D-Phe-3,3-DiPhe-D-Ala



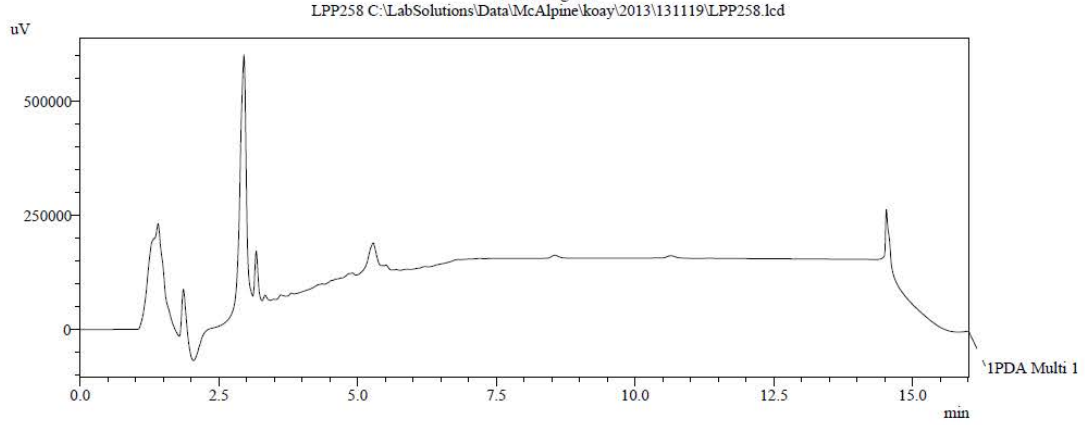
Compound **1**4: ^{1}H-^{13}C HMBC of cyclo Leu-*N*-Me-Val-3-(4-pyridyl)-D-Ala-D-Phe-3,3-DiPhe-D-Ala

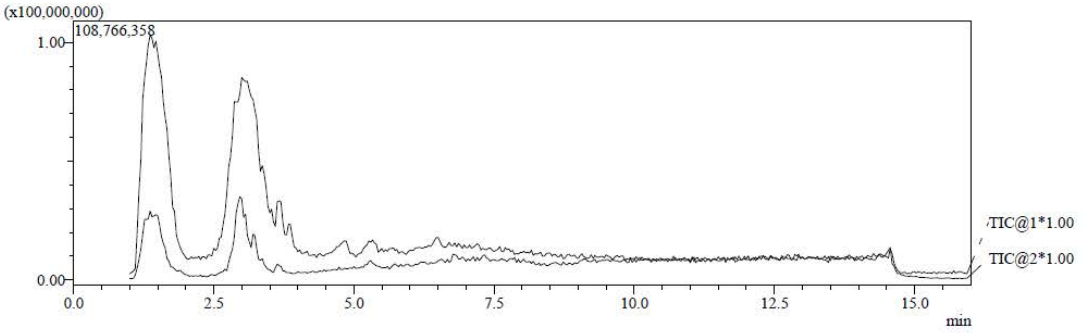


Compound **15**: LCMS of DDLP HO-Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala-NH_2

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

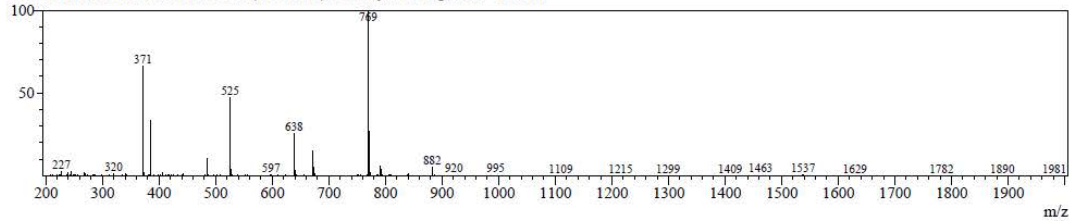
Chromatogram
LPP258 C:\LabSolutions\Data\McAlpine\koay\2013\131119\LPP258.lcd





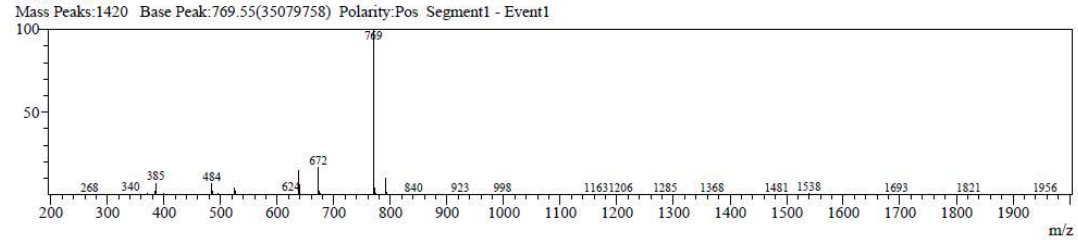
MS Spectrum Graph

Ret.Time:1.433(Scan#:27)
BG Mode:?
Mass Peaks:1466 Base Peak:769.10(18063412) Polarity:Pos Segment1 - Event1



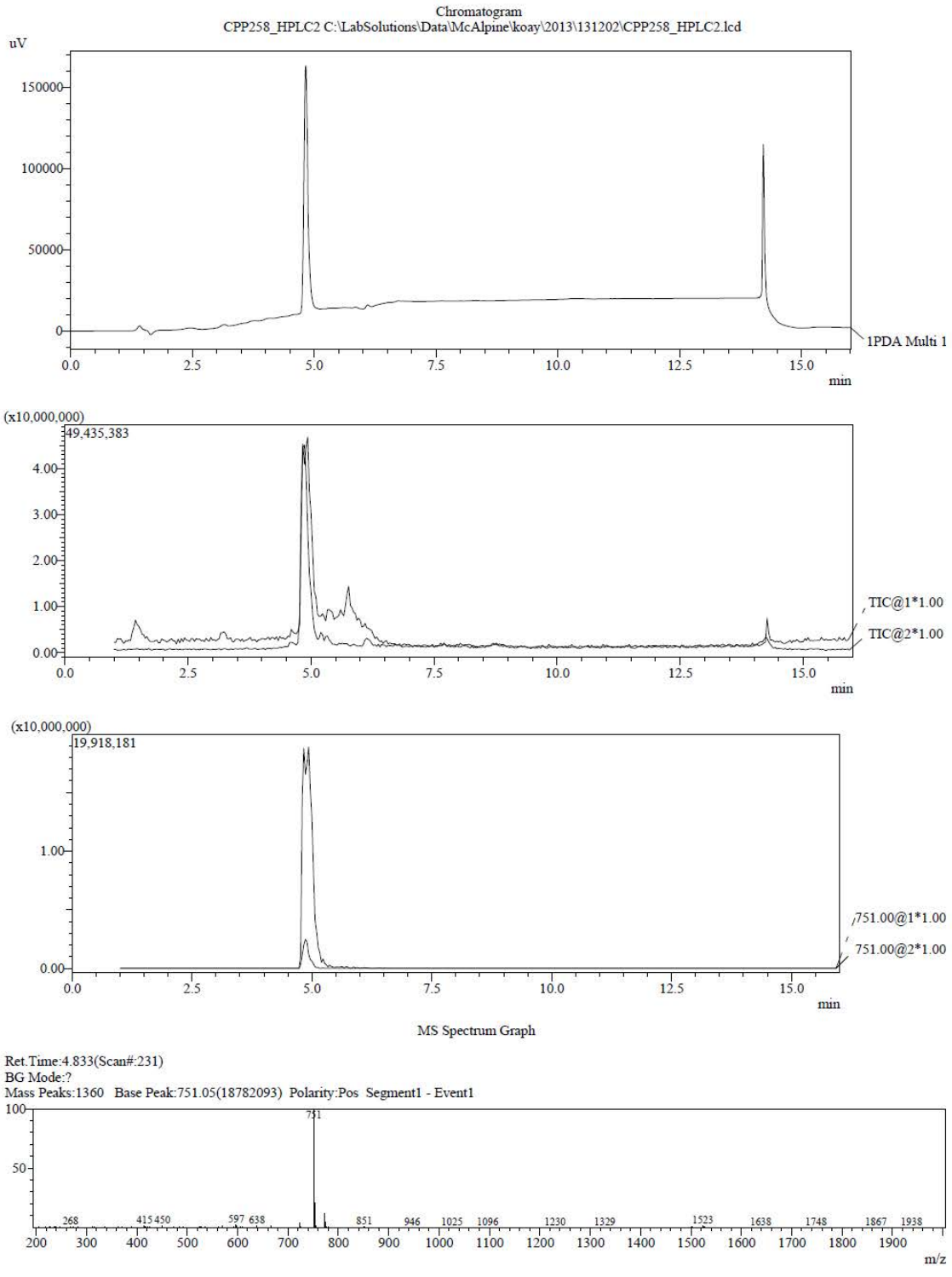
MS Spectrum Graph

Ret.Time:3.033(Scan#:123)
BG Mode:None
Mass Peaks:1420 Base Peak:769.55(35079758) Polarity:Pos Segment1 - Event1



Compound **15**: LCMS of cyclo Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala

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

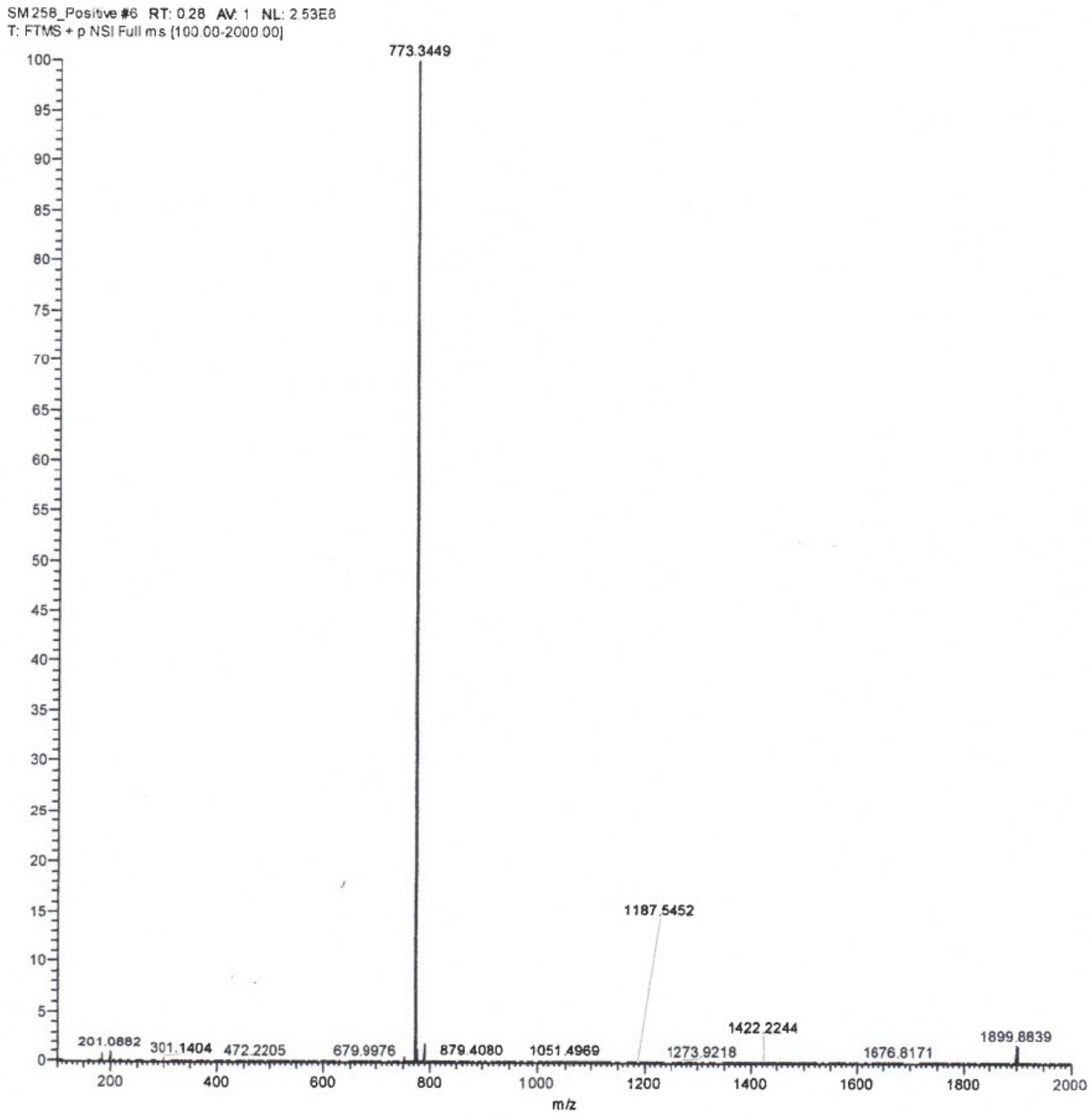


C:\LabSolutions\Data\McAlpine\koay\2013\131202\CPP258_HPLC2.lcd

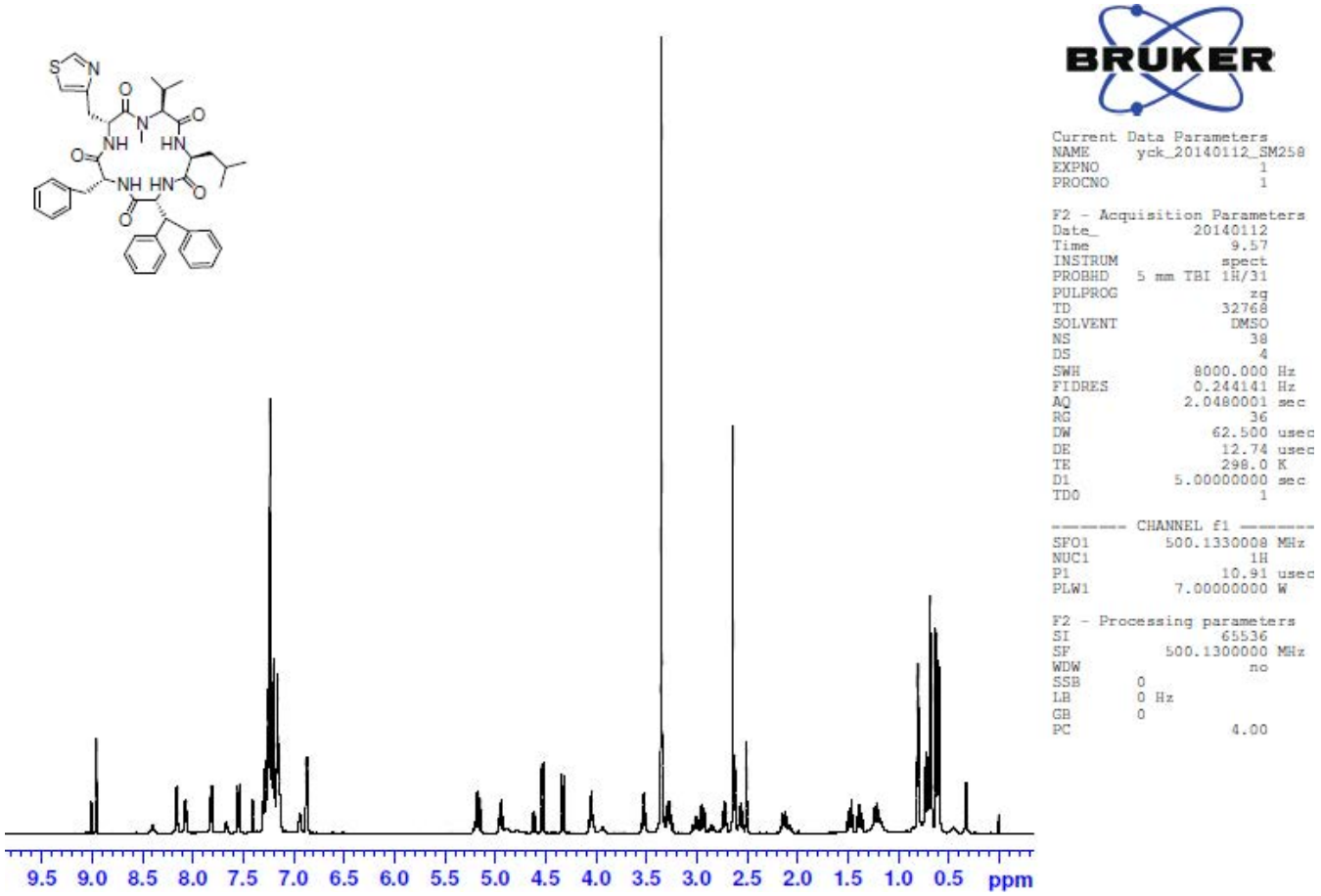
Compound **15**: HRMS of cyclo Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala

MS Data from Orbitrap

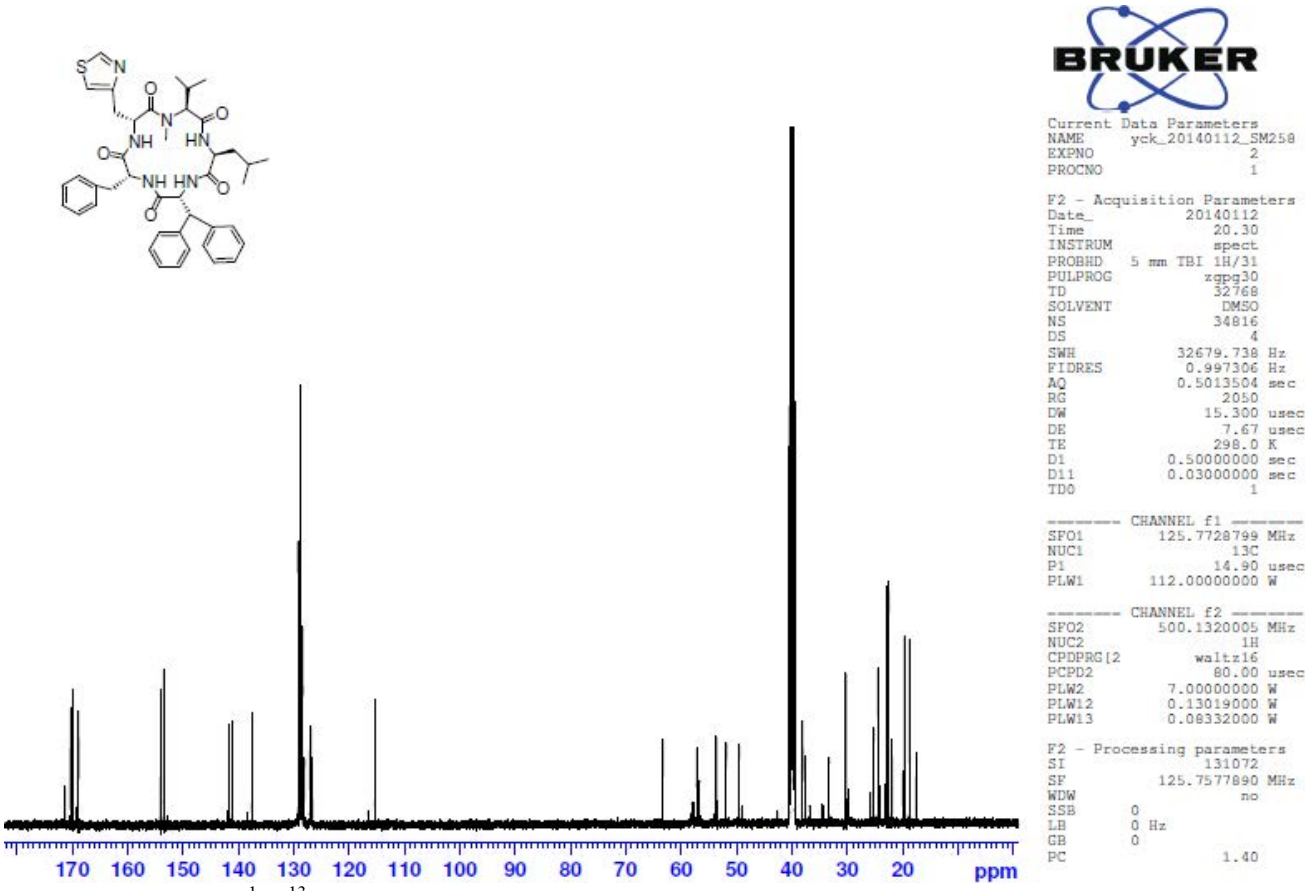
Full spectrum



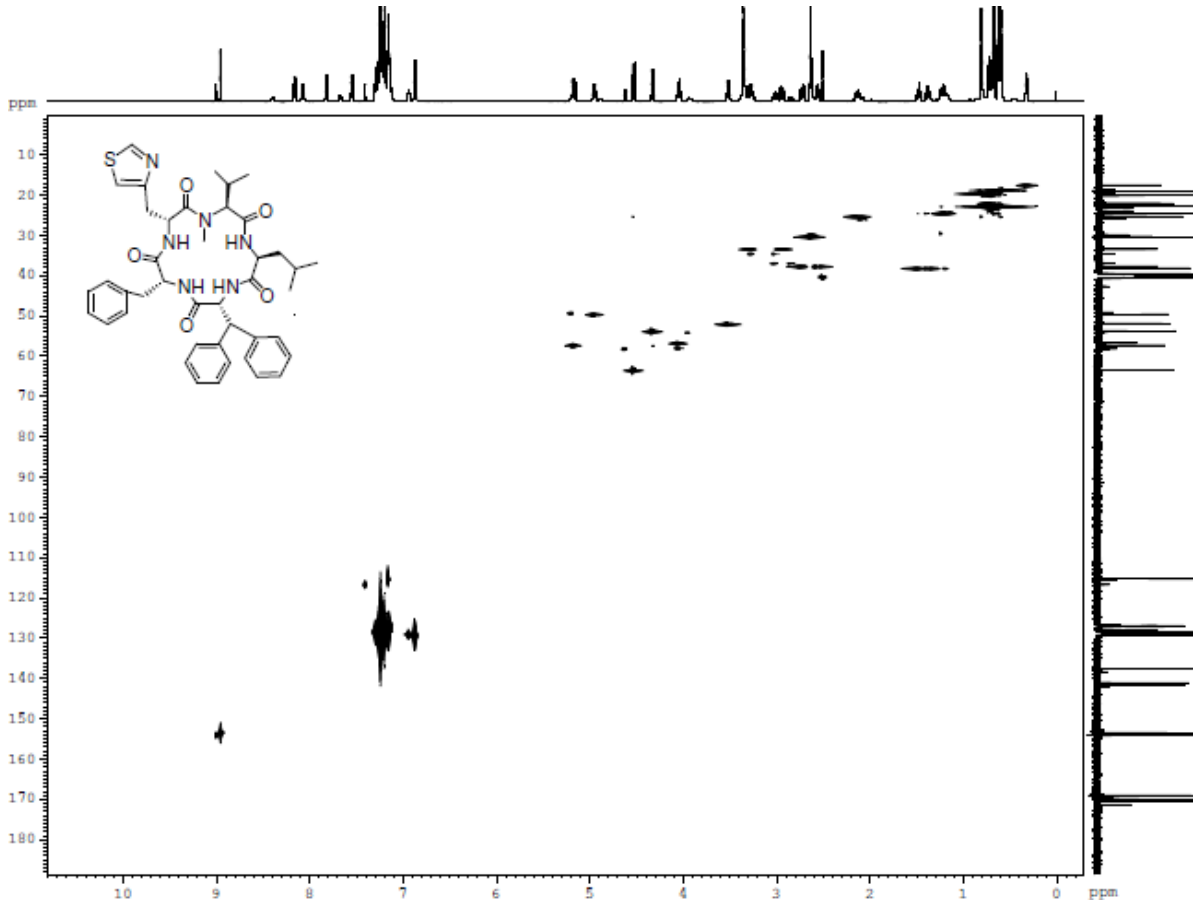
Compound **15**: [1]HNMR of cyclo Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala



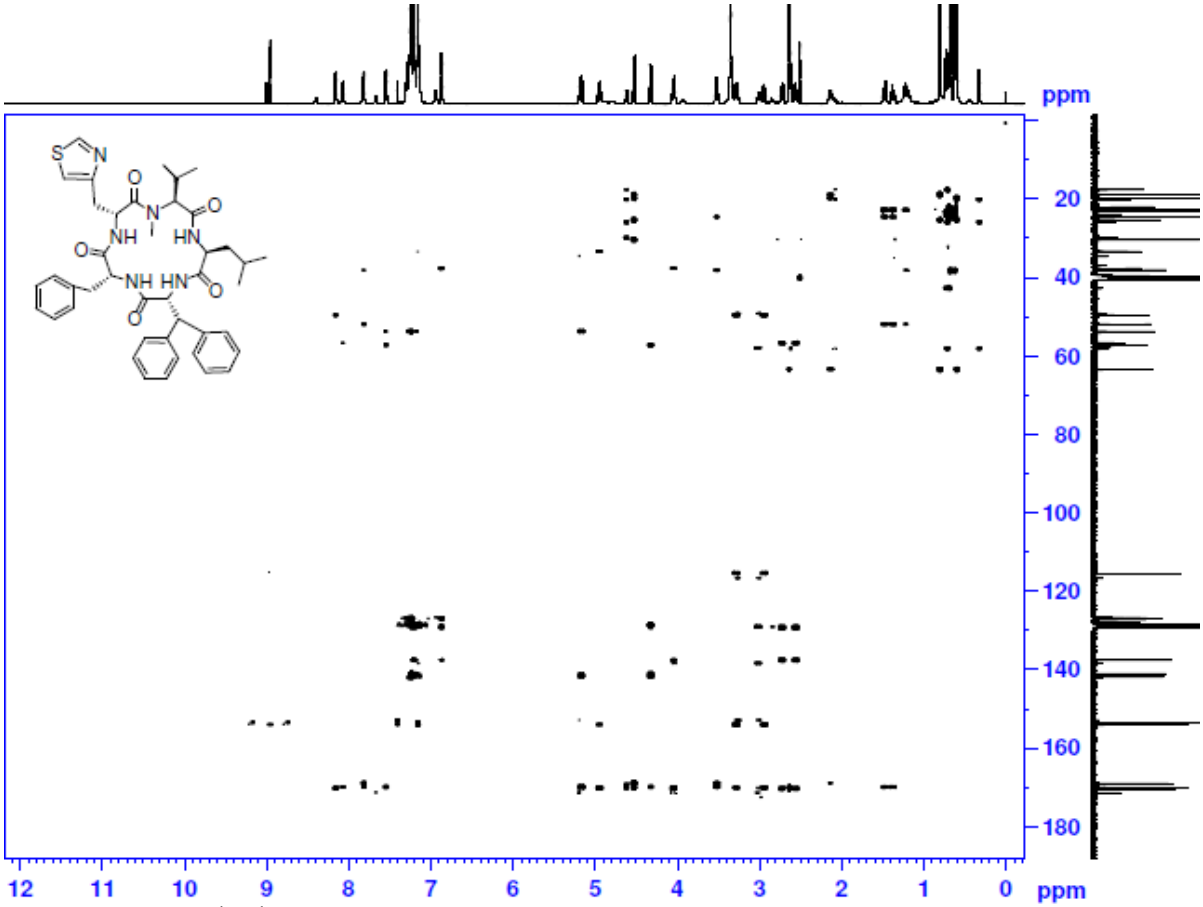
Compound **15**: [13]CNMR of cyclo Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala



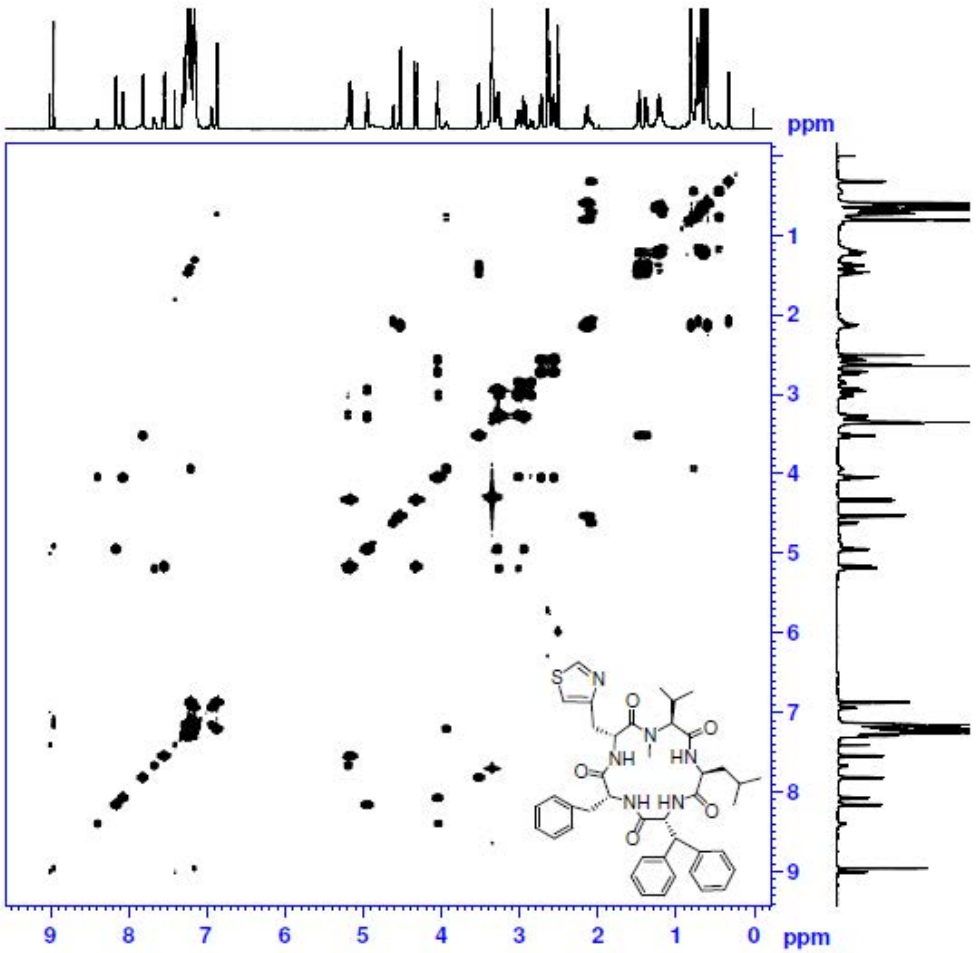
Compound **15**: ^{1}H-^{13}C HSQC of cyclo Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala

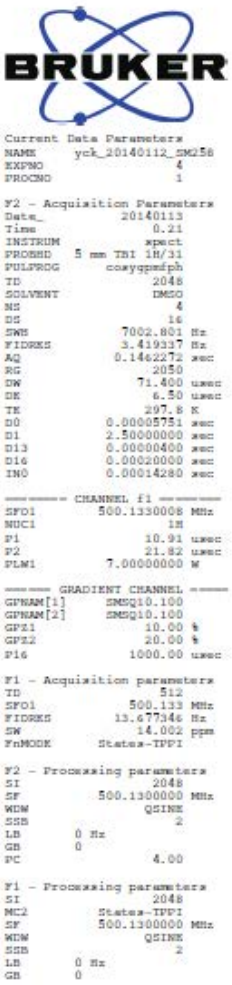


Compound **15**: ^{1}H-^{13}C HMBC of cyclo Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala

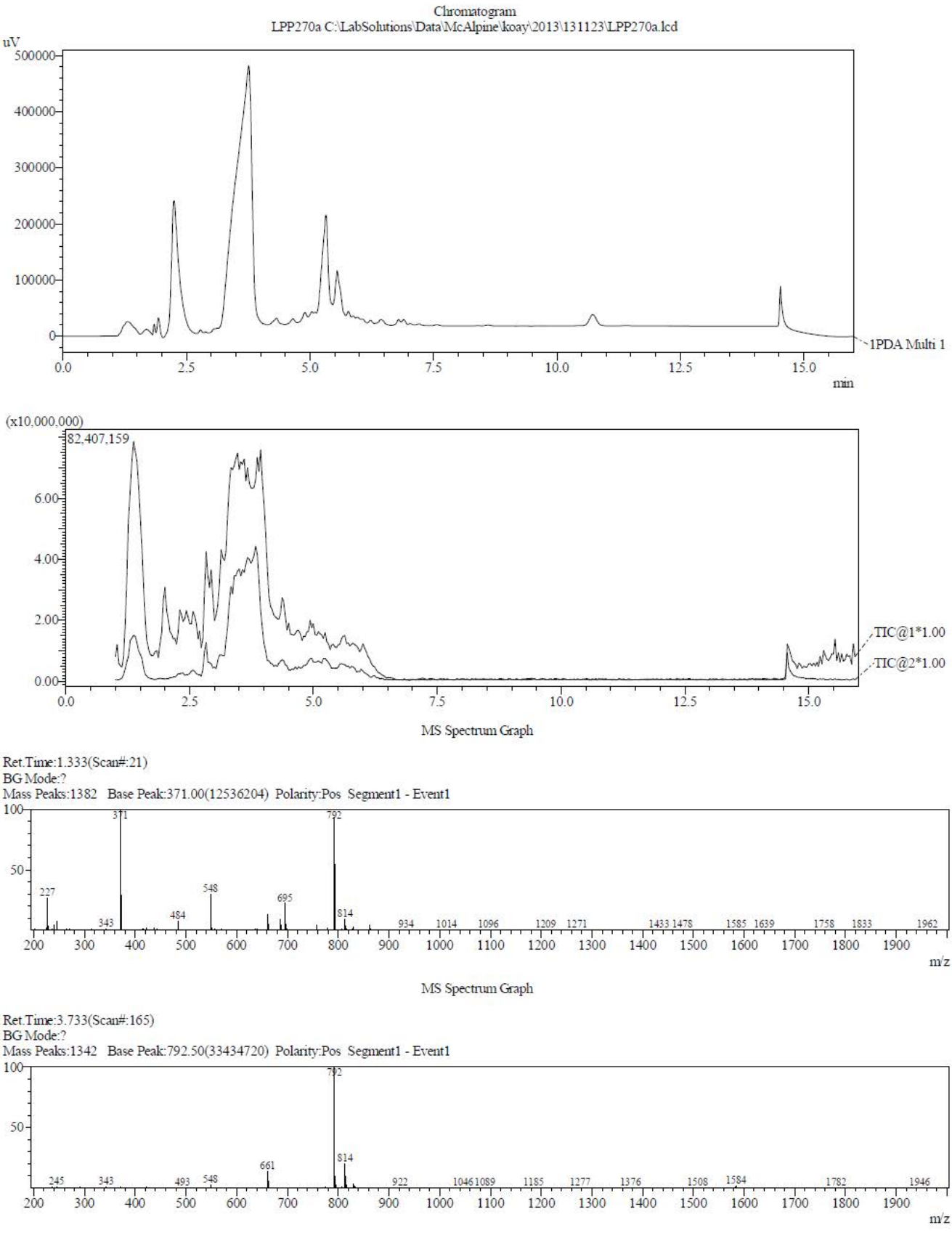


Compound **15**: ^{1}H-^{1}H COSY of cyclo Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala



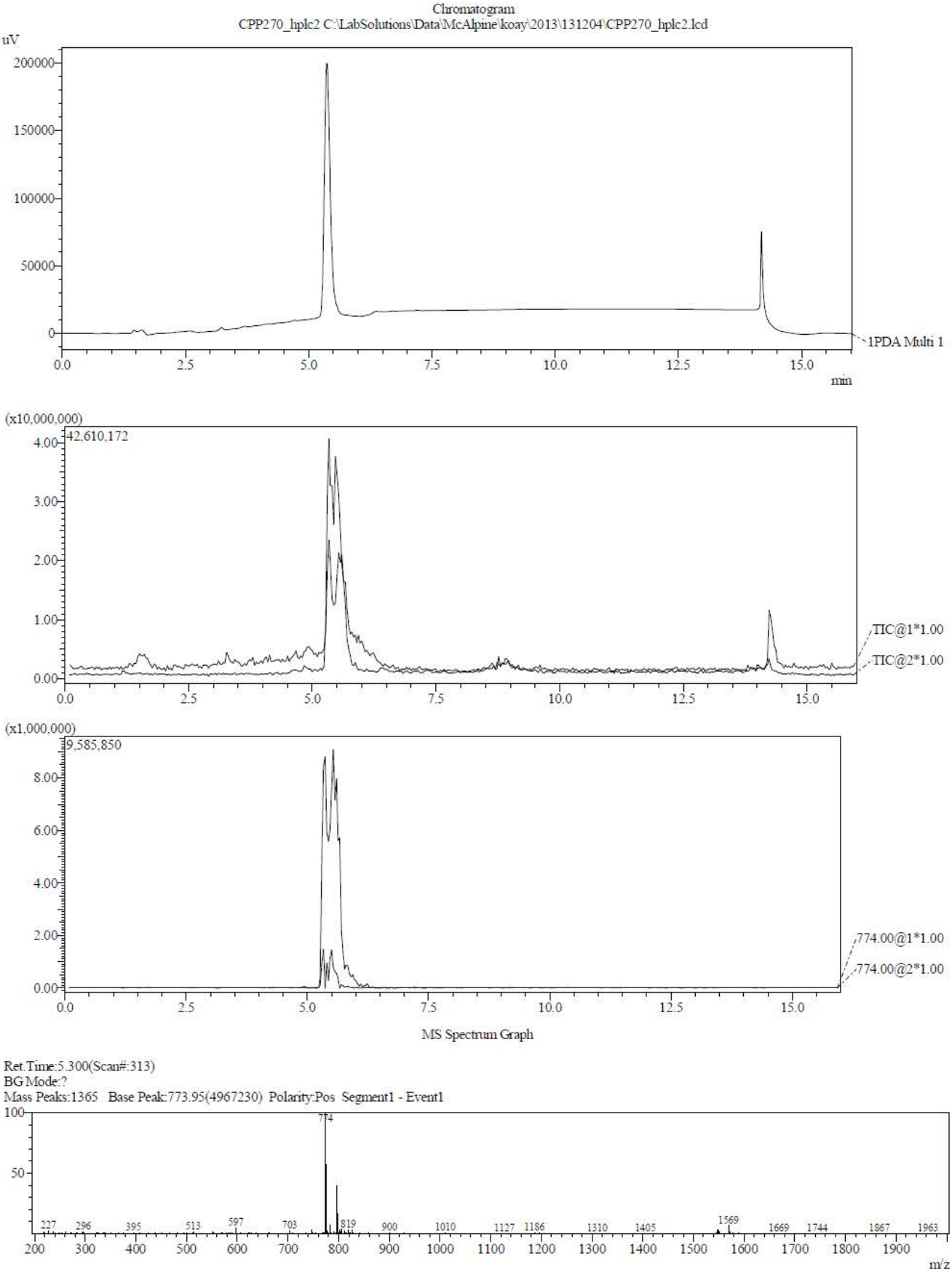


Compound **16**: LCMS of DDLP HO-Leu-*N*-Me-Val-D-Tyr(OMe)-D-Phe-3,3-Diphe-D-Ala-NH_2



Compound **16**: LCMS of cyclo Leu-*N*-Me-Val-D-Tyr(OMe)-D-Phe-3,3-Diphe-D-Ala

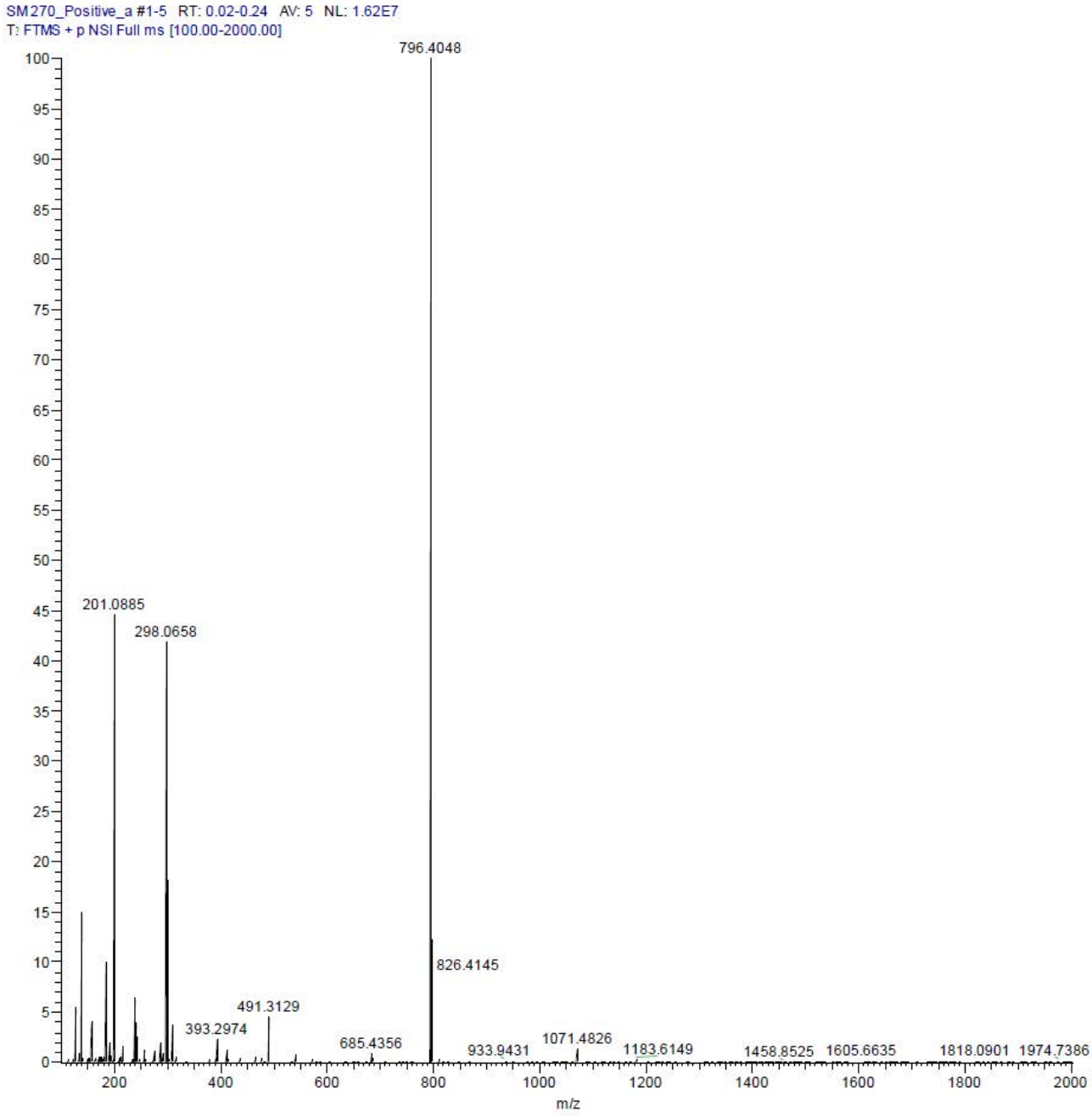
==== Shimadzu LCMSsolution Analysis Report ====



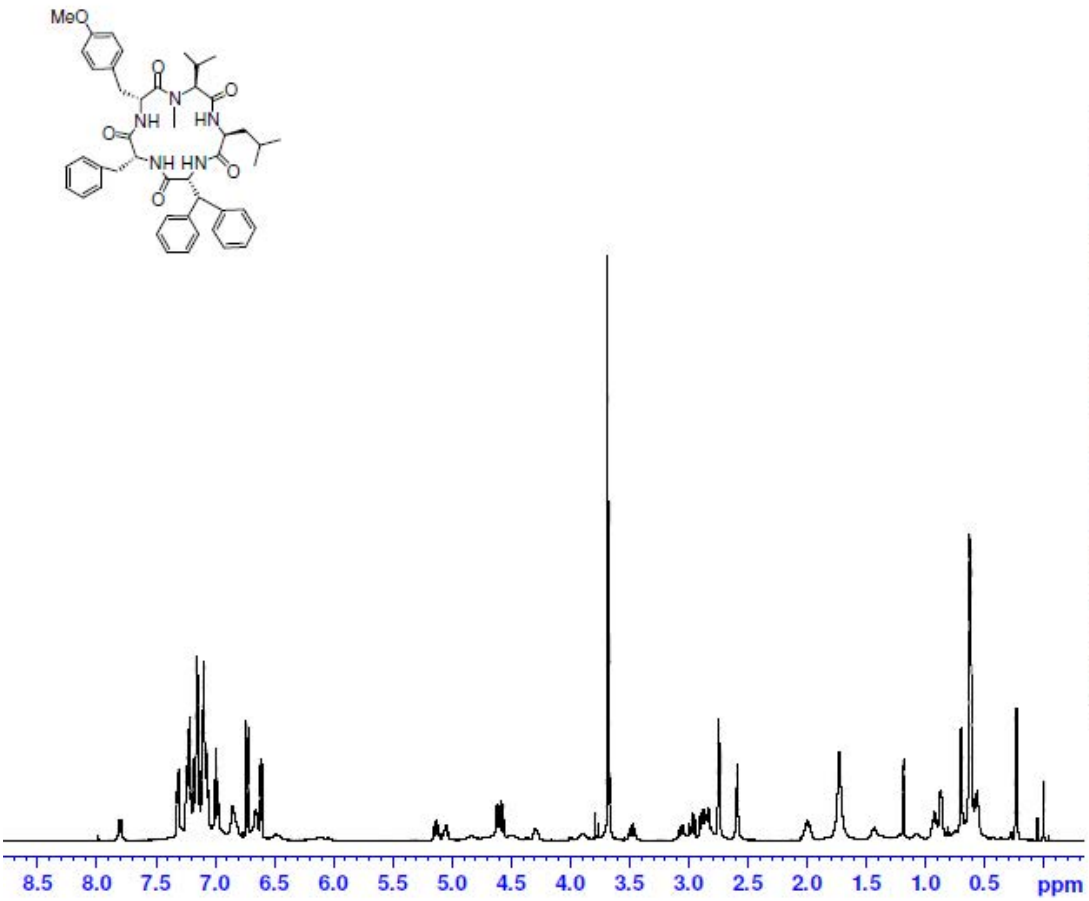
Compound **16**: HRMS of cyclo Leu-*N*-Me-Val-D-Tyr(OMe)-D-Phe-3,3-Diphe-D-Ala

MS Data from Orbitrap

Full spectrum



Compound **16**: [1]HNMR of cyclo Leu-*N*-Me-Val-D-Tyr(OMe)-D-Phe-3,3-Diphe-D-Ala



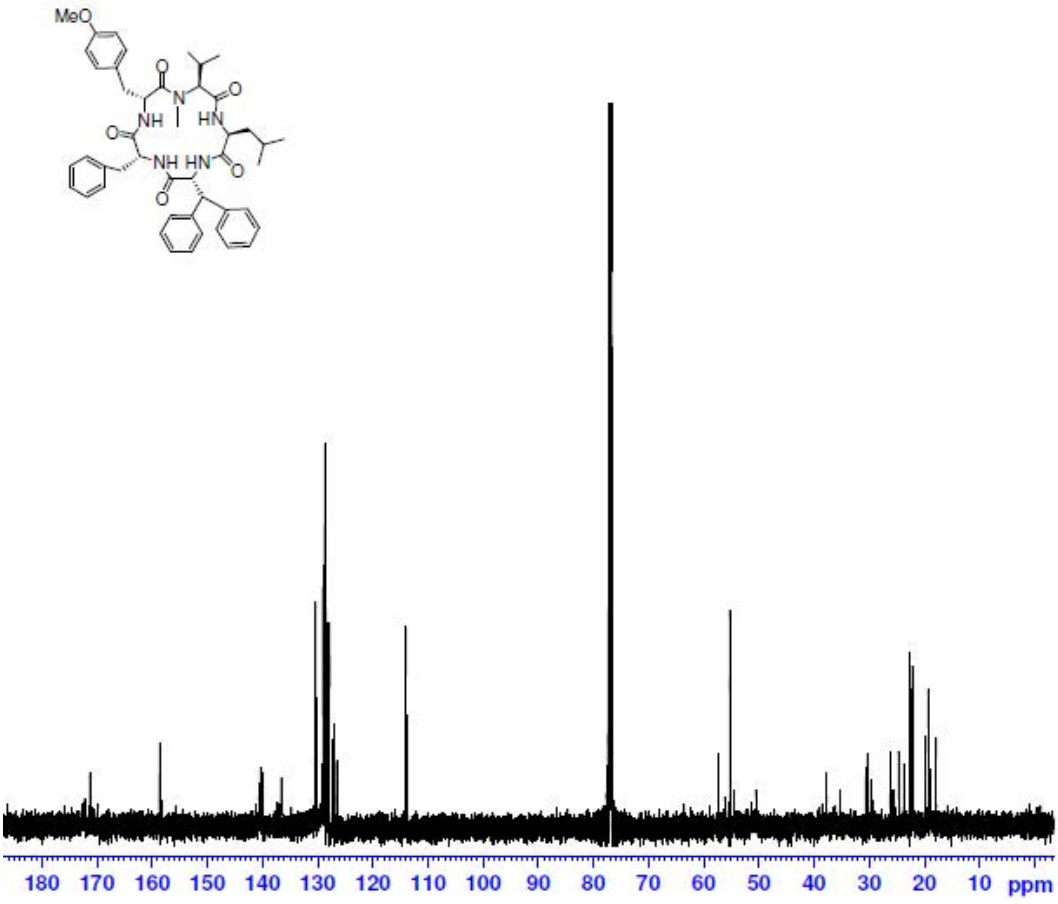

```
Current Data Parameters
NAME          yck_04012014
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_          20140104
Time              12.41
INSTRUM           spect
PROBHD   5 mm TBI 1H/31
PULPROG             zg
TD                32768
SOLVENT           CDCl3
NS                   32
DS                    4
SWH            8000.000 Hz
FIDRES            0.244141 Hz
AQ             2.0480001 sec
RG                 80.6
DW                62.500 usec
DE                12.74 usec
TE                298.0 K
D1             5.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1          500.1330008 MHz
NUC1                  1H
P1                 10.91 usec
PLW1           7.00000000 W

F2 - Processing parameters
SI                 65536
SF            500.1300462 MHz
WDW                   no
SSB          0
LB           0 Hz
GB           0
PC                 4.00
```

Compound **16**: [13]CNMR of cyclo Leu-*N*-Me-Val-D-Tyr(OMe)-D-Phe-3,3-Diphe-D-Ala




```
Current Data Parameters
NAME          yck_04012014
EXPNO                    2
PROCNO                   1

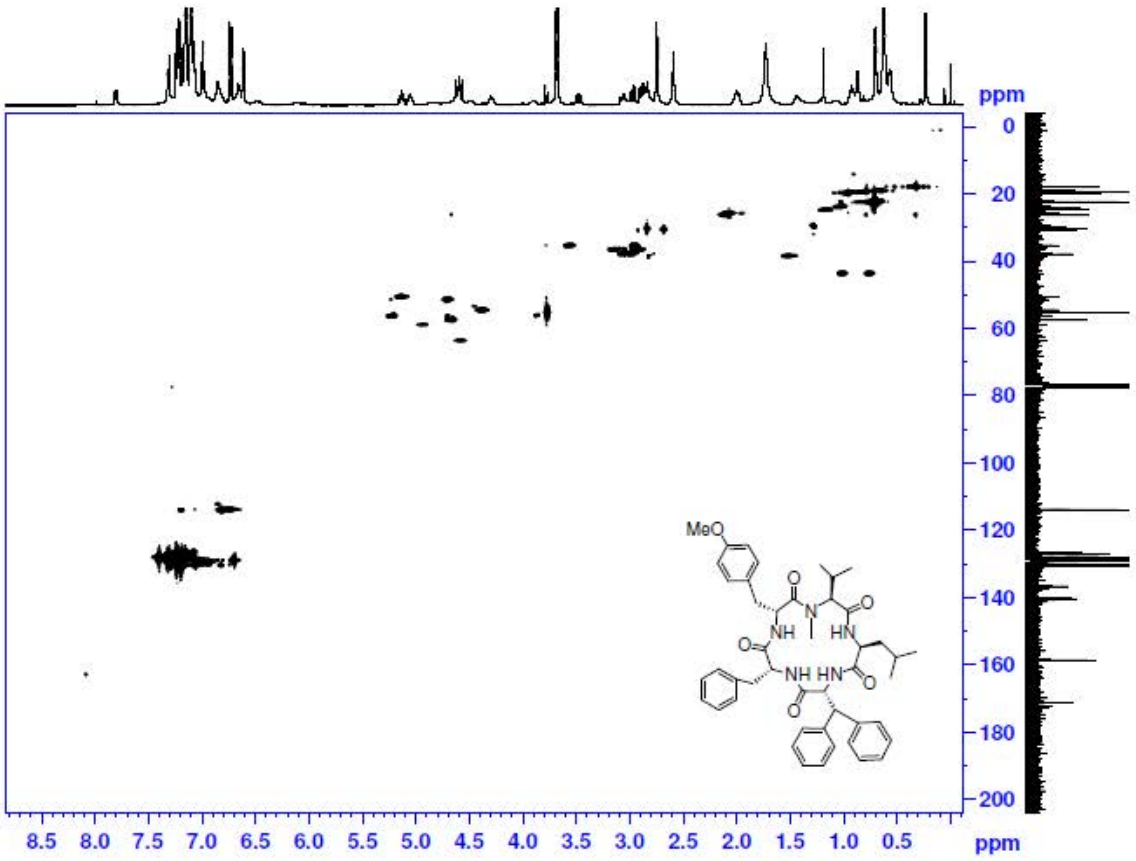
F2 - Acquisition Parameters
Date_          20140105
Time               5.51
INSTRUM           spect
PROBHD   5 mm TBI 1H/31
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                23552
DS                    4
SWH           32679.738 Hz
FIDRES            0.997306 Hz
AQ             0.5013504 sec
RG                 2050
DW                15.300 usec
DE                 7.67 usec
TE                298.0 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1          125.7728799 MHz
NUC1                 13C
P1                 14.90 usec
PLW1         112.00000000 W

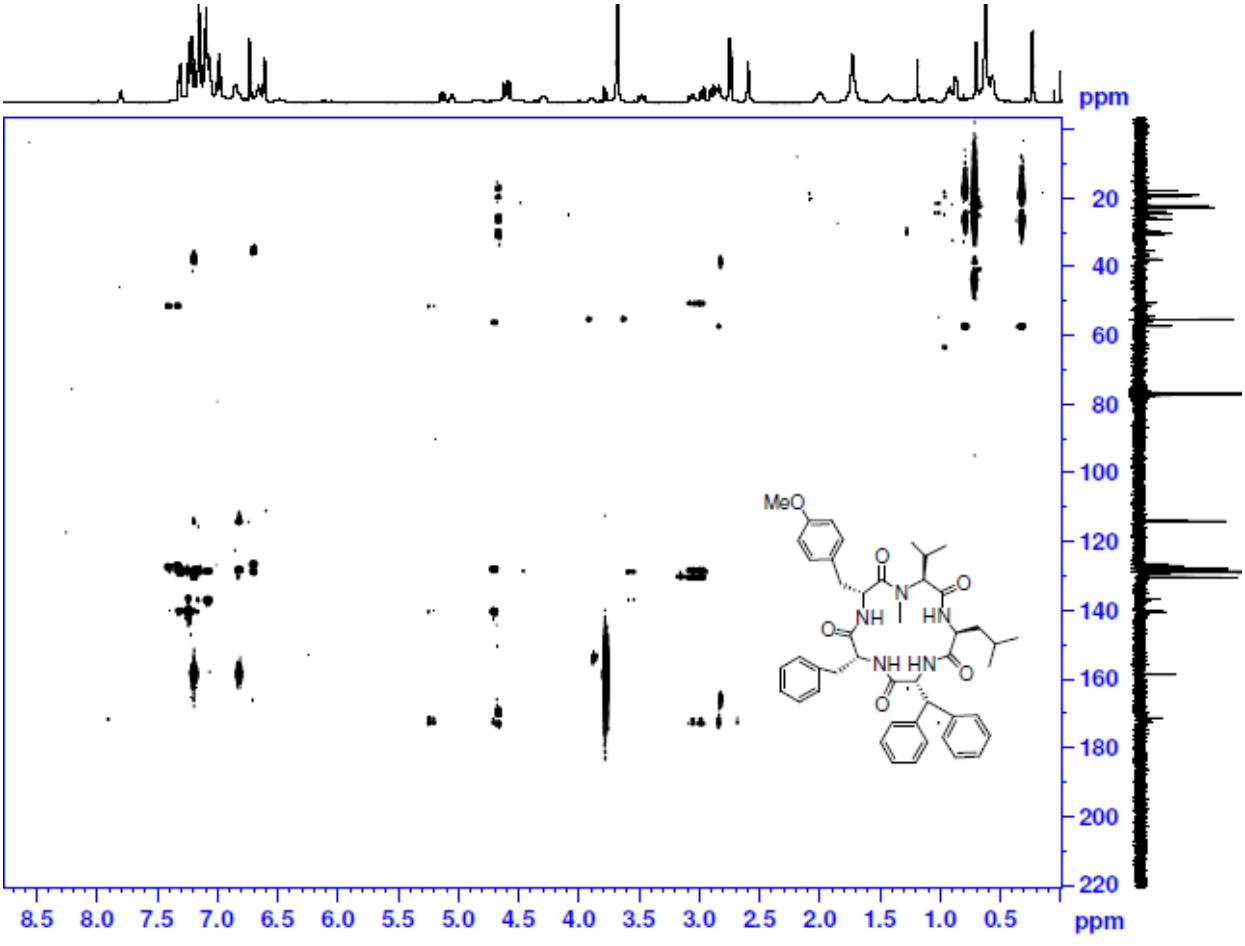
======== CHANNEL f2 ========
SFO2          500.1320005 MHz
NUC2                  1H
CPDPRG[2          waltz16
PCPD2              80.00 usec
PLW2           7.00000000 W
PLW12          0.13019000 W
PLW13          0.08332000 W

F2 - Processing parameters
SI                131072
SF            125.7577890 MHz
WDW                   no
SSB          0
LB           0 Hz
GB           0
PC                 1.40
```

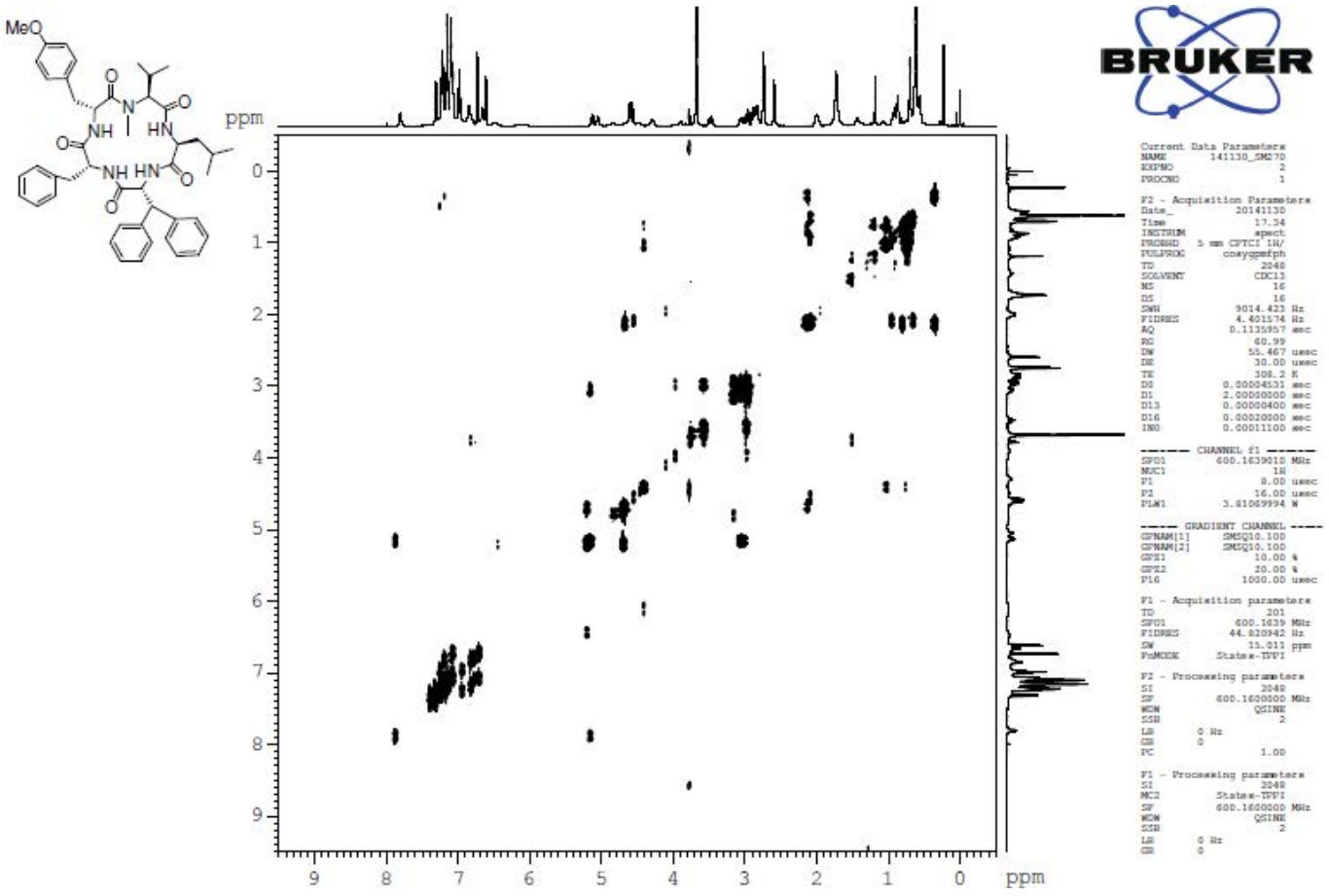
Compound **16**: ^{1}H-^{13}C HSQC of cyclo Leu-*N*-Me-Val-D-Tyr(OMe)-D-Phe-3,3-Diphe-D-Ala



Compound **16**: ^{1}H-^{13}C HMBC of cyclo Leu-*N*-Me-Val-D-Tyr(OMe)-D-Phe-3,3-Diphe-D-Ala

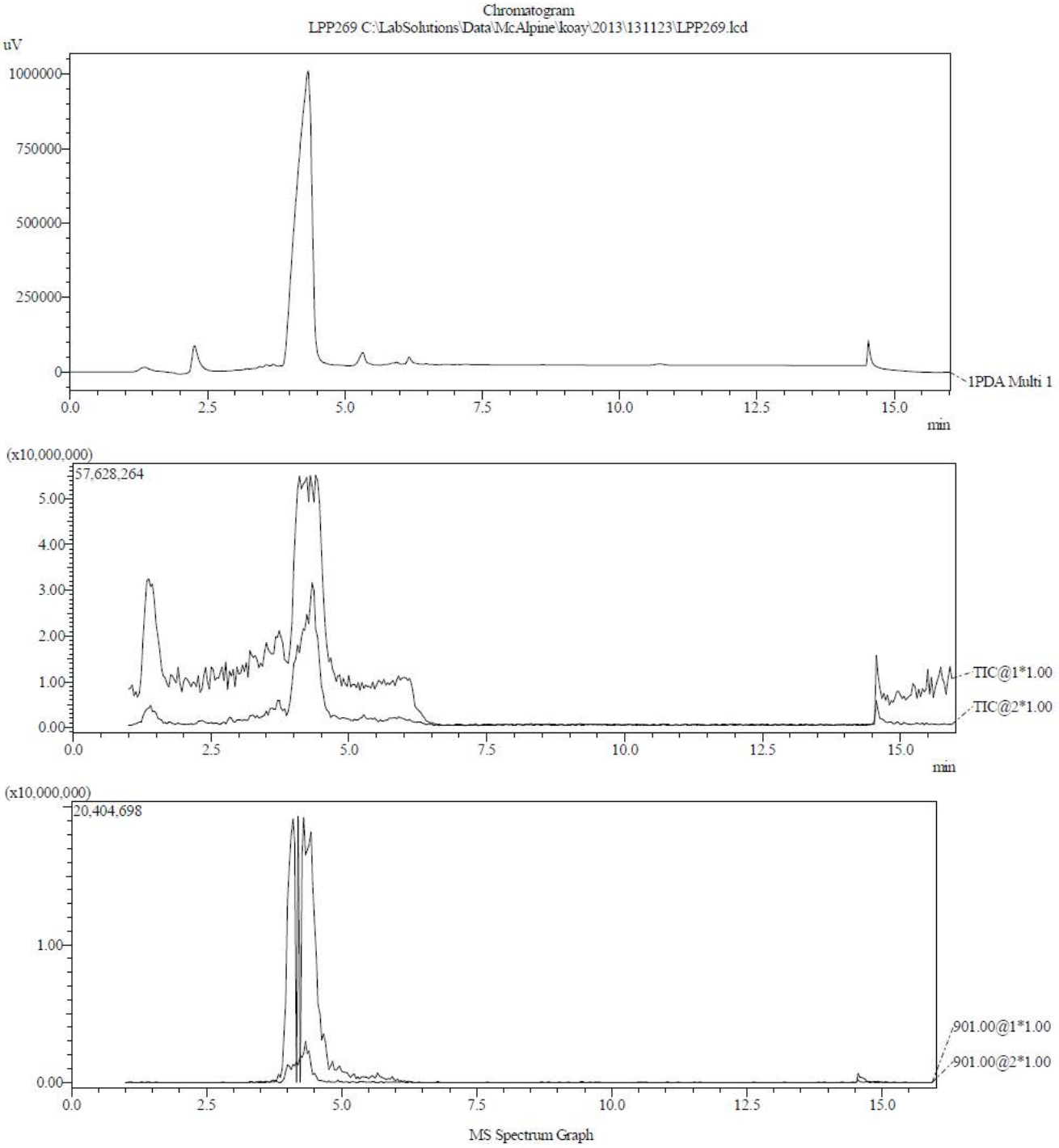


Compound **16**: ^{1}H-^{1}H COSY of cyclo Leu-*N*-Me-Val-D-Tyr(OMe)-D-Phe-3,3-Diphe-D-Ala



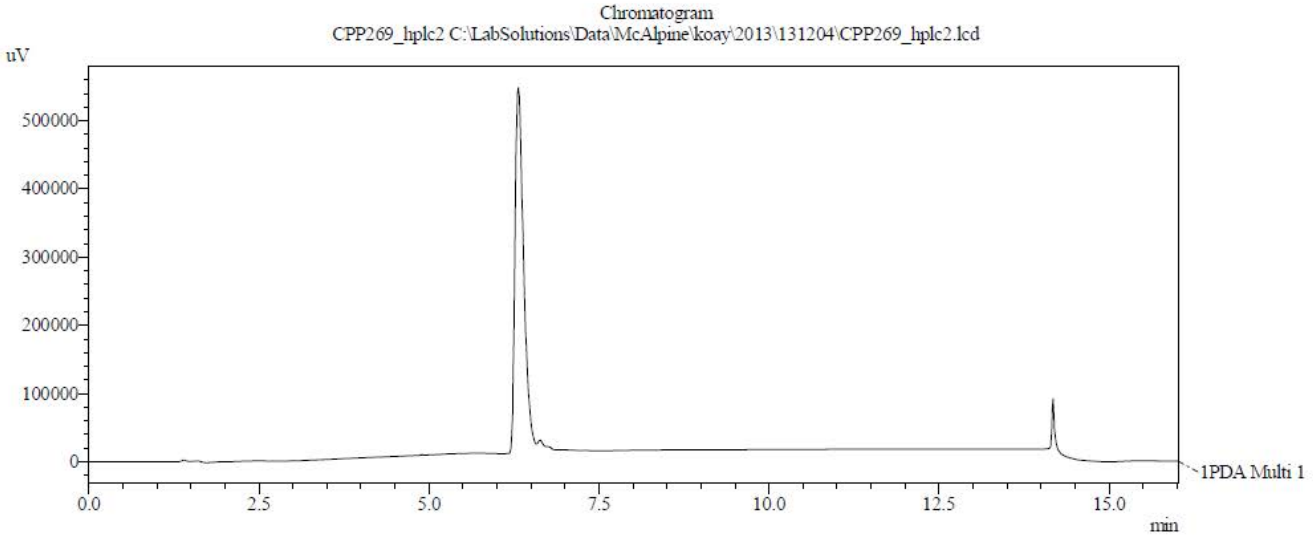
Compound **17**: LCMS of DDLP HO-Leu-*N*-Me-Val-D-Trp(Boc)-D-Phe-3,3-Diphe-D-Ala-NH_2

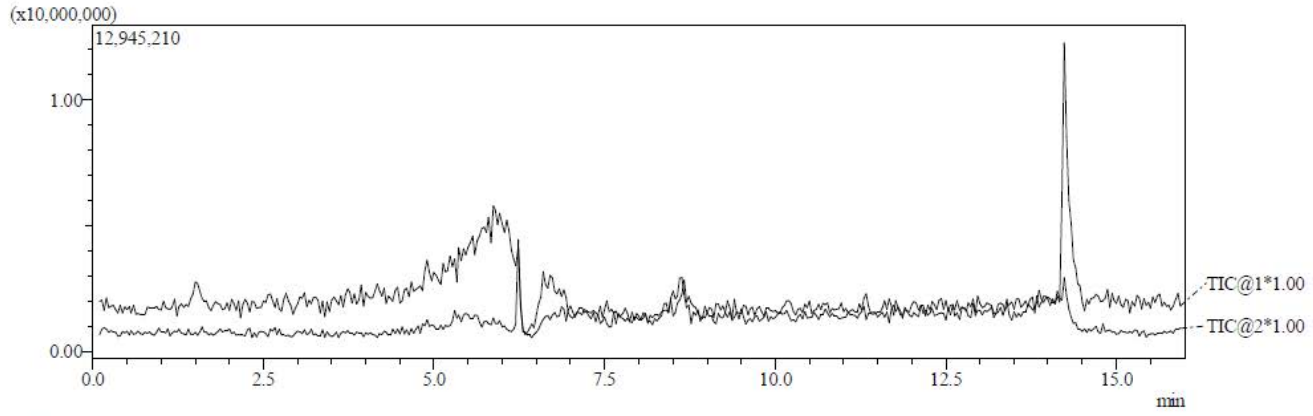
==== Shimadzu LCMSsolution Analysis Report ====

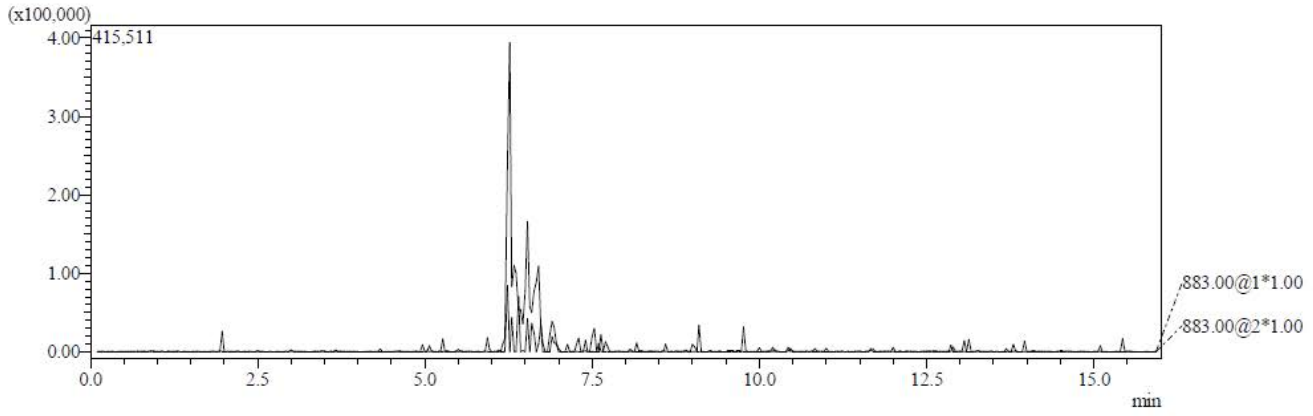


Compound **17**: LCMS of cyclo Leu-*N*-Me-Val-D-Trp(Boc)-D-Phe-3,3-Diphe-D-Ala

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

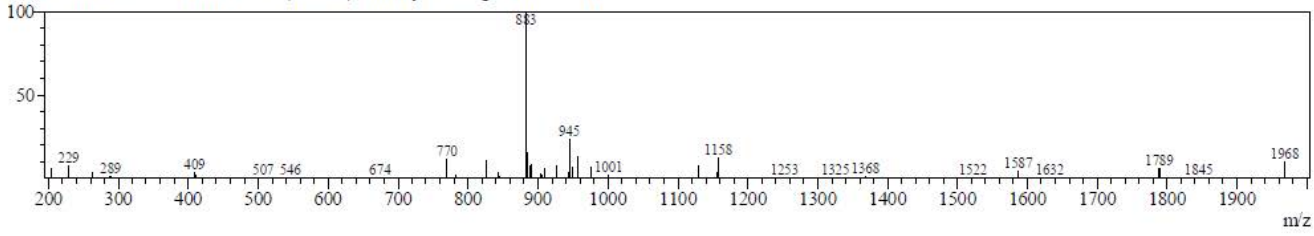




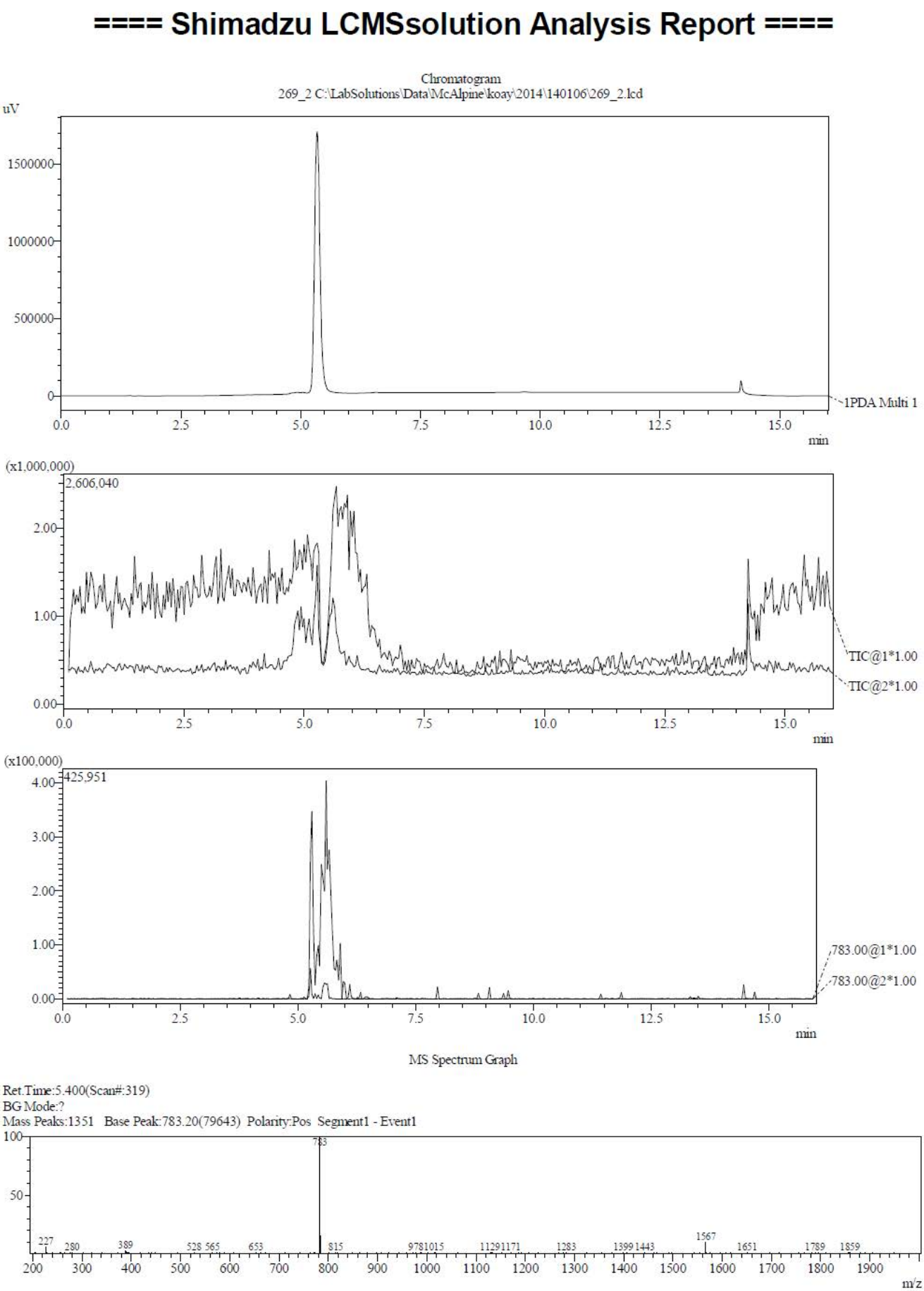


MS Spectrum Graph

Ret.Time:6.533(Scan#:387)
BG Mode:?
Mass Peaks:1397 Base Peak:883.20(165981) Polarity:Pos Segment1 - Event1



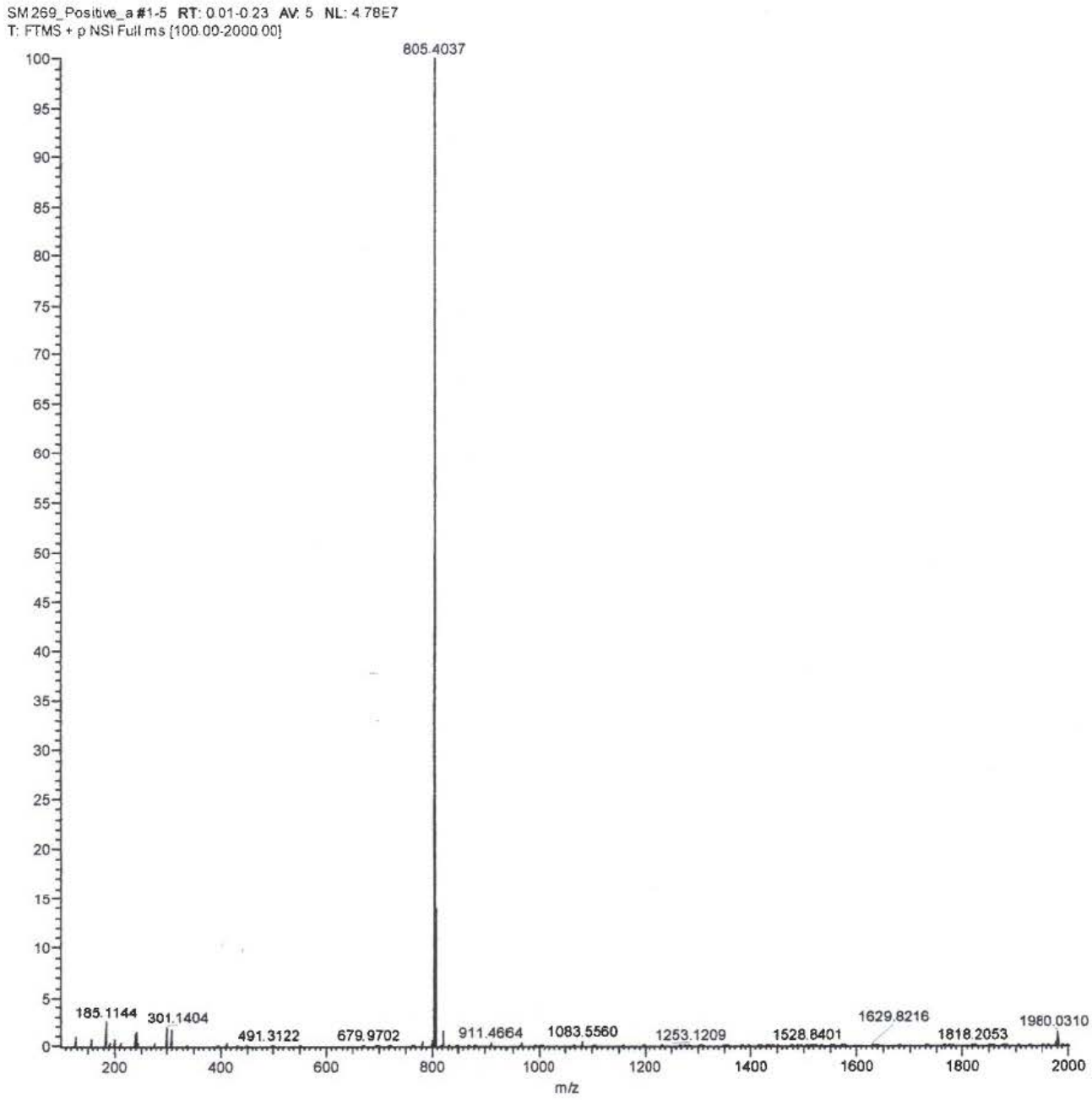
Compound **17**: LCMS of cyclo Leu-*N*-Me-Val-D-Trp-D-Phe-3,3-Diphe-D-Ala



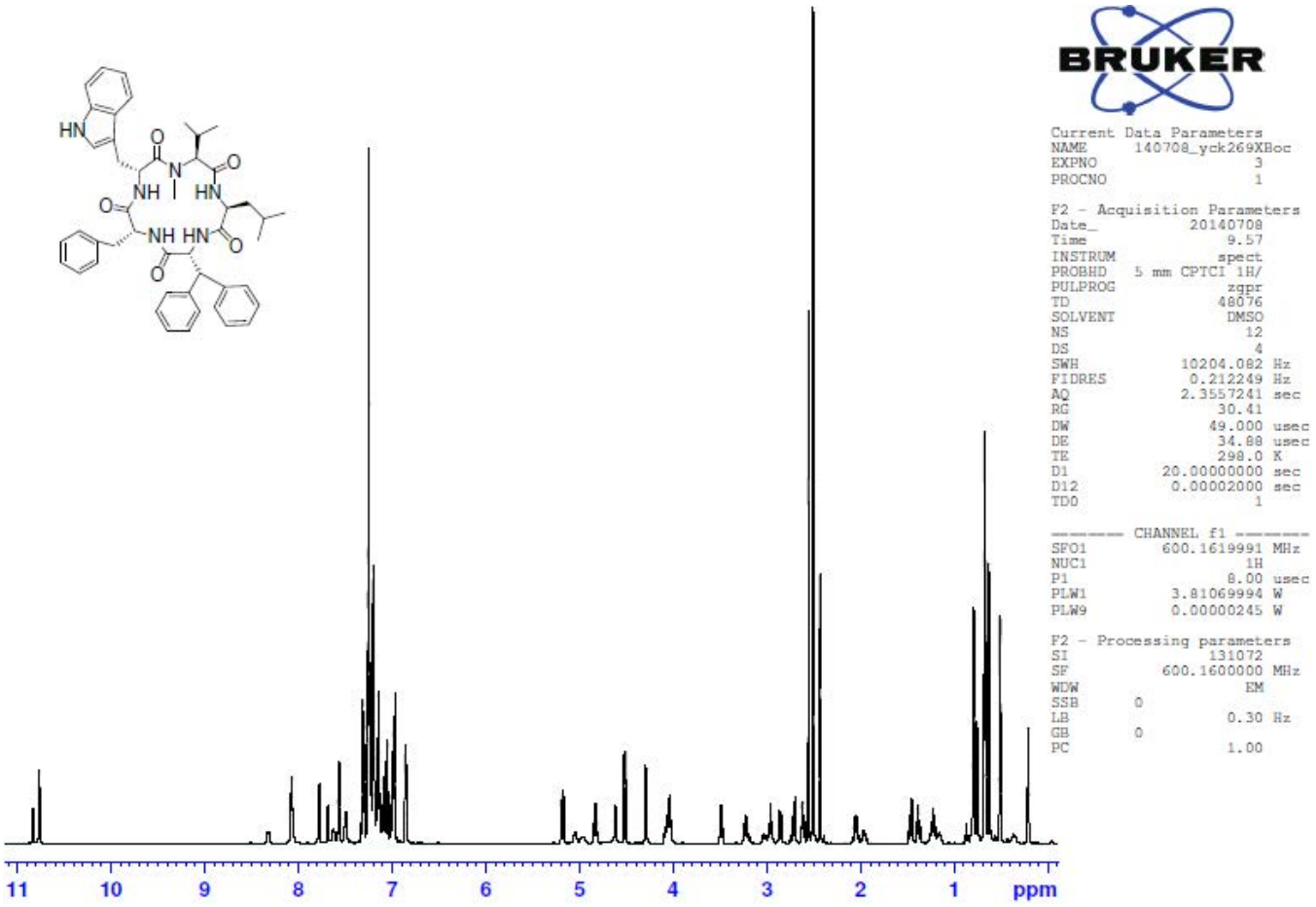
Compound **17**: HRMS of cyclo Leu-*N*-Me-Val-D-Trp-D-Phe-3,3-Diphe-D-Ala

MS Data from Orbitrap

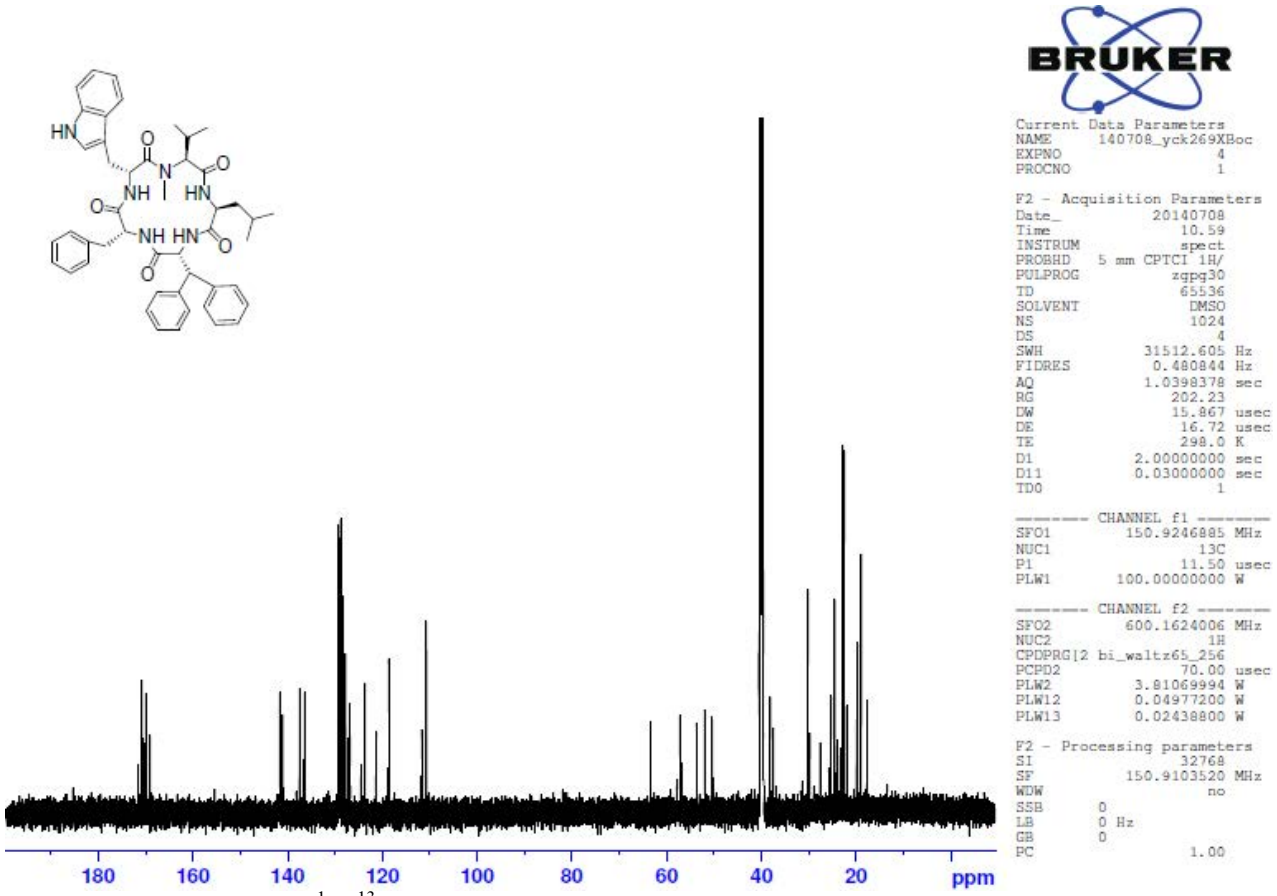
Full spectrum



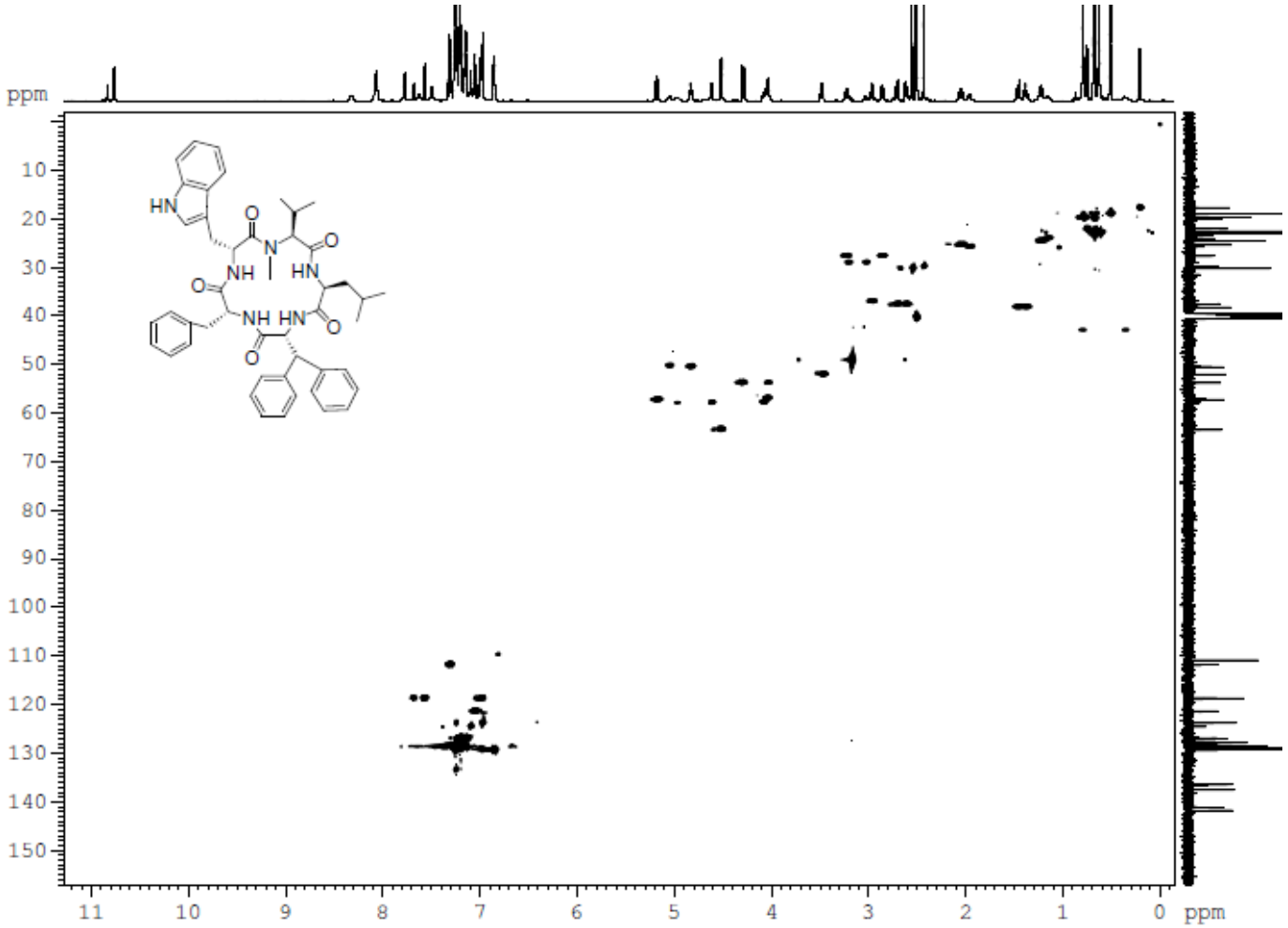
Compound **17**: ^{1}HNMR of cyclo Leu-*N*-Me-Val-D-Trp-D-Phe-3,3-Diphe-D-Ala



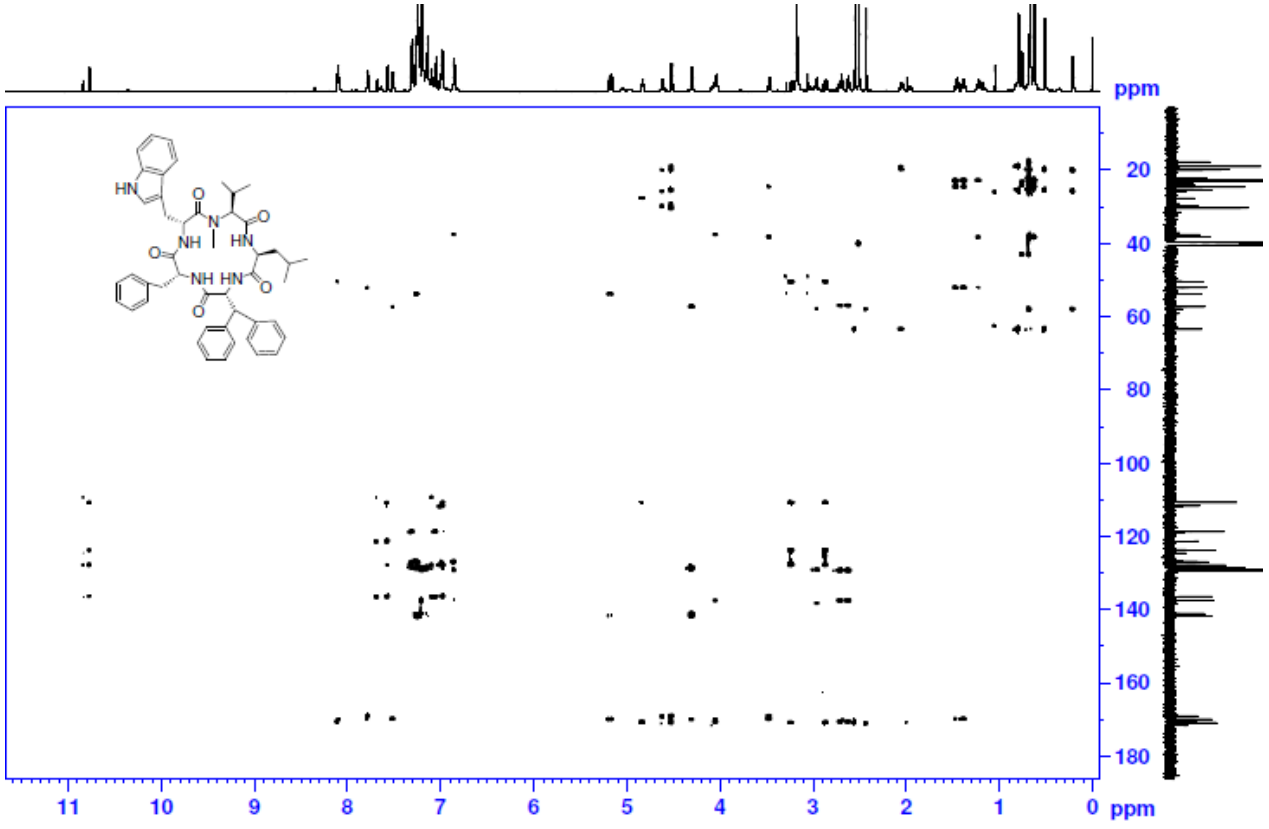
Compound **17**: ^{13}CNMR of cyclo Leu-*N*-Me-Val-D-Trp-D-Phe-3,3-Diphe-D-Ala



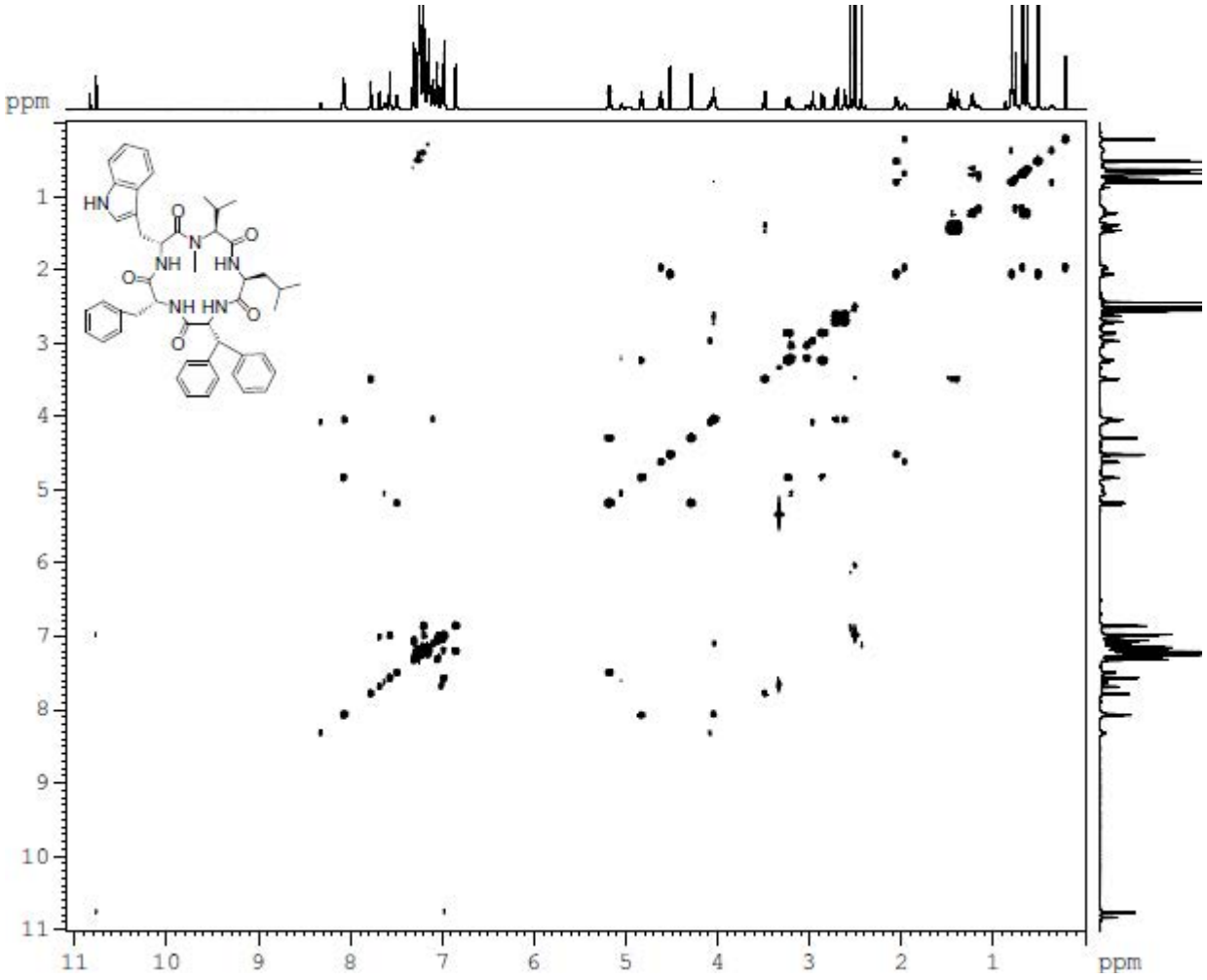
Compound **17**: ^{1}H-^{13}C HSQC of cyclo Leu-*N*-Me-Val-D-Trp-D-Phe-3,3-Diphe-D-Ala



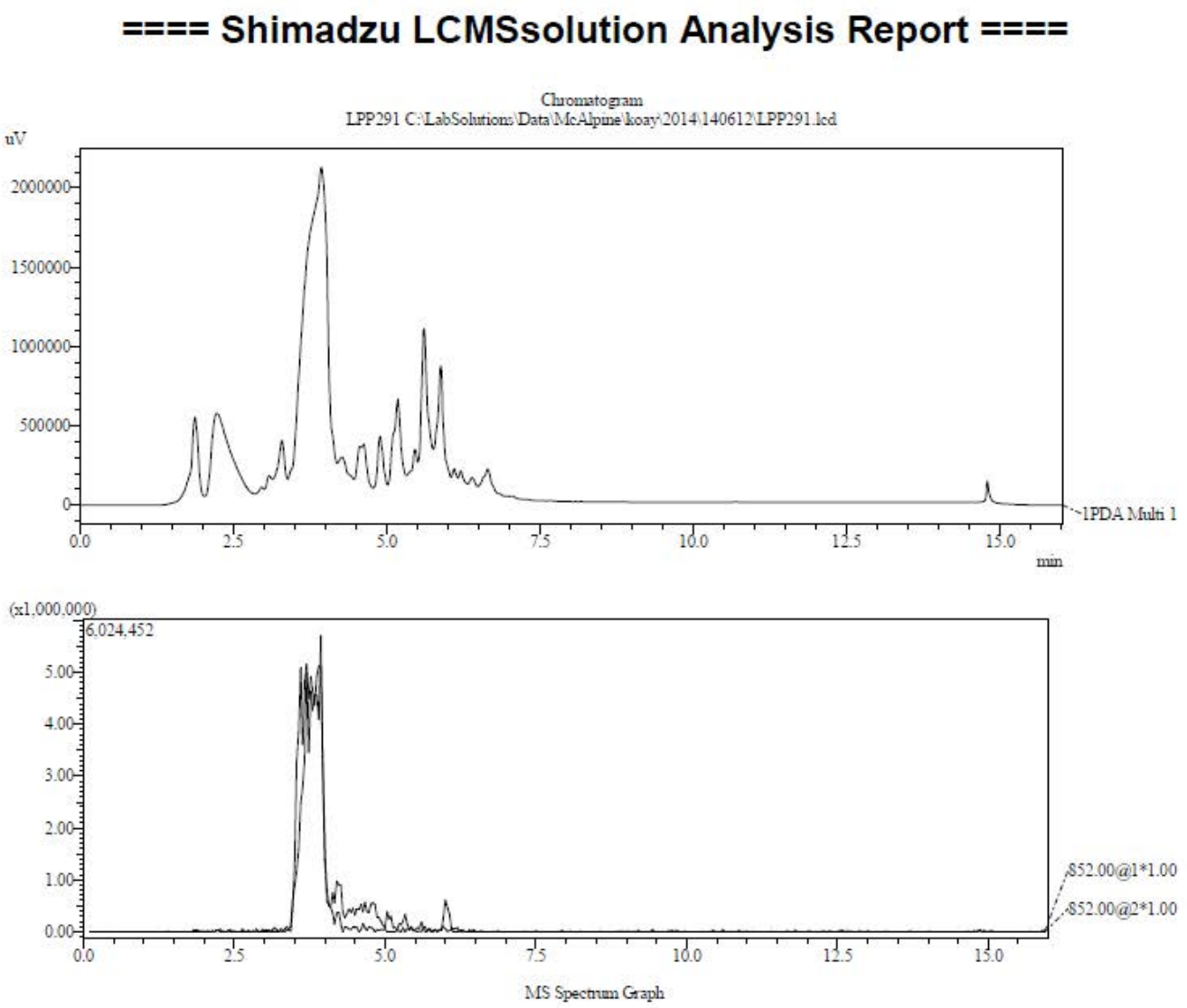
Compound **17**: ^{1}H-^{13}C HMBC of cyclo Leu-*N*-Me-Val-D-Trp-D-Phe-3,3-Diphe-D-Ala



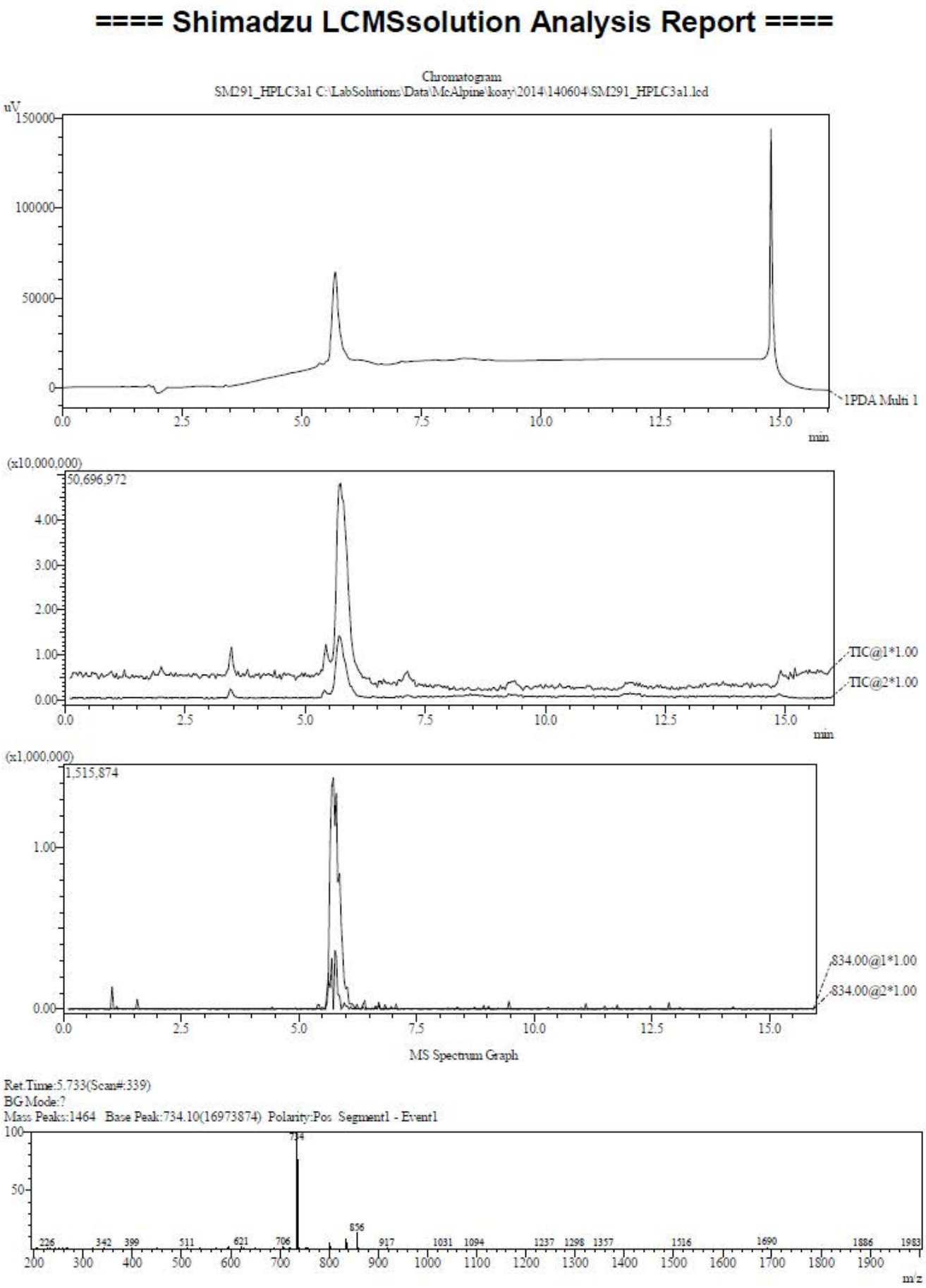
Compound **17**: ^{1}H-^{1}H COSY of cyclo Leu-*N*-Me-Val-D-Trp-D-Phe-3,3-Diphe-D-Ala



Compound **18**: LCMS of DDLP HO-Leu-*N*-Me-Val-D-His(Boc)-D-Phe-3,3-Diphe-D-Ala-NH_2



Compound **18**: LCMS of cyclo Leu-*N*-Me-Val-D-His(Boc)-D-Phe-3,3-Diphe-D-Ala

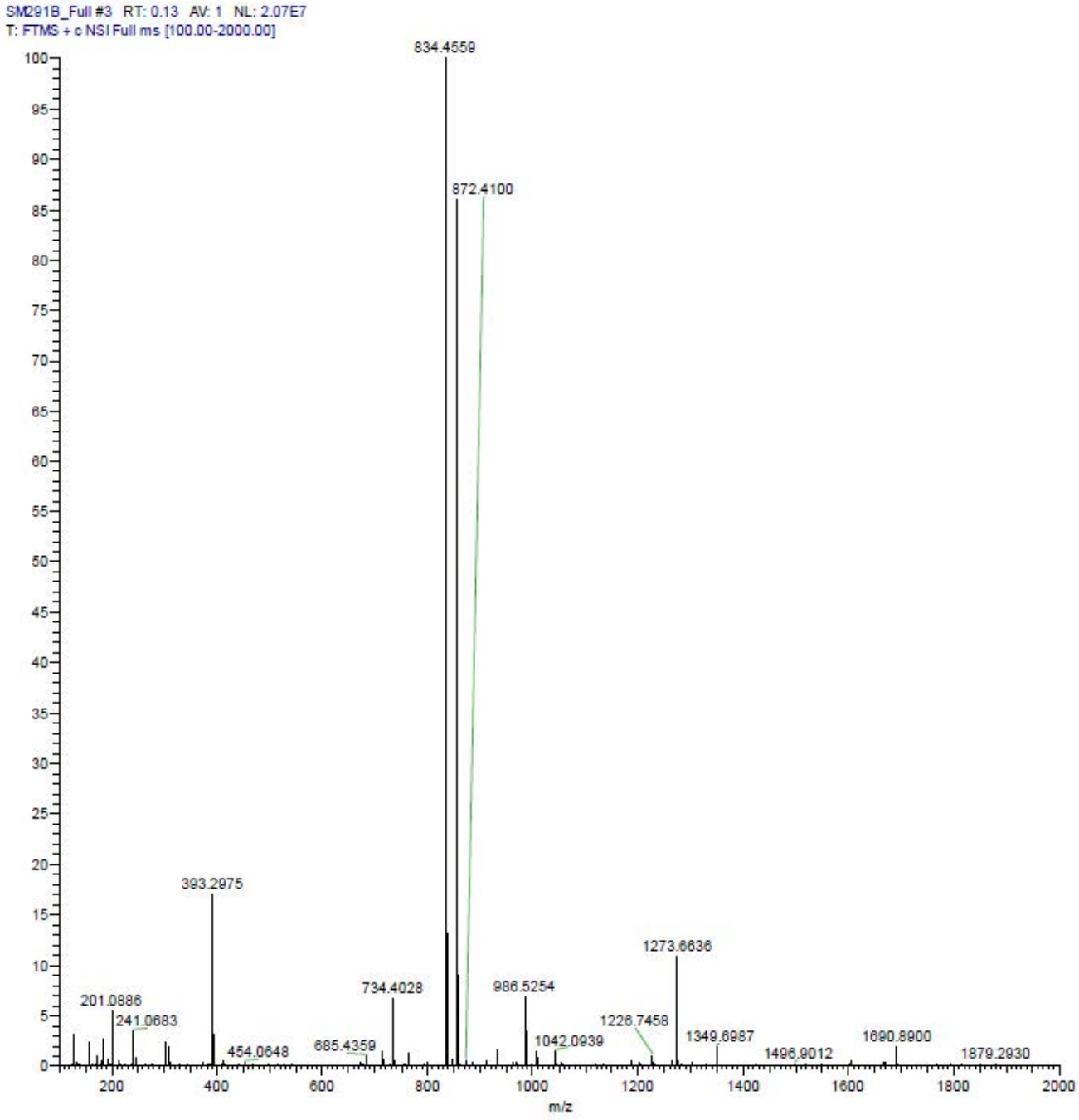


Compound **18**: HRMS of cyclo Leu-*N*-Me-Val-D-His(Boc)-D-Phe-3,3-Diphe-D-Ala

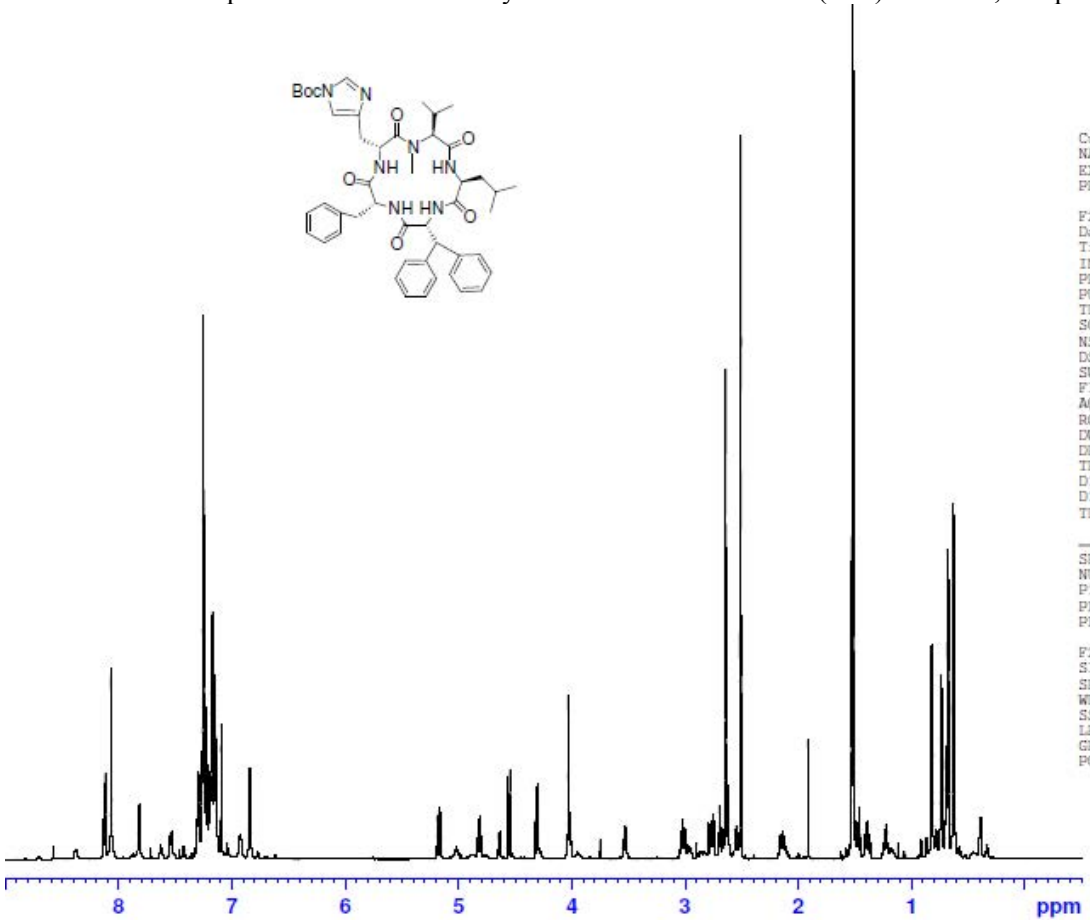
MS Data from Orbitrap

Sample: SM291

Full spectrum:



Compound **18**: ^{1}HNMR of cyclo Leu-*N*-Me-Val-D-His(Boc)-D-Phe-3,3-Diphe-D-Ala



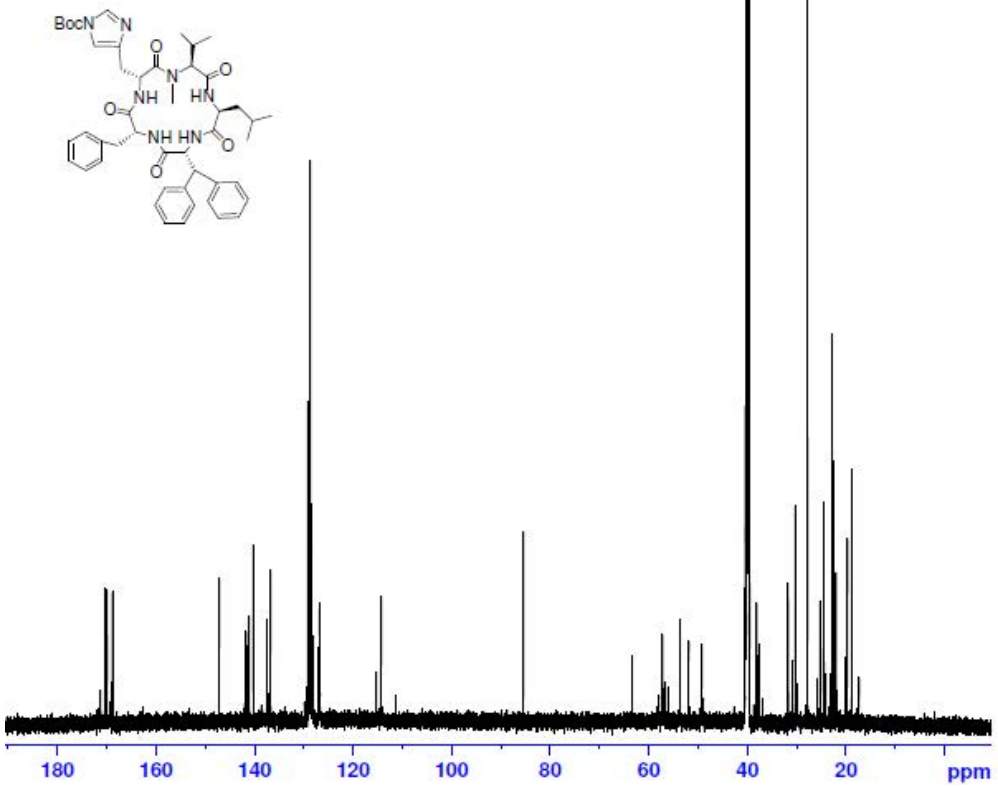

```
Current Data Parameters
NAME      140708_yckSM291wBoc
EXPNO                       2
PROCNO                      1

F2 - Acquisition Parameters
Date_              20140708
Time                  17.45
INSTRUM               spect
PROBHD    5 mm CPTCI 1H/
PULPROG               zgpr
TD                   48076
SOLVENT               DMSO
NS                      32
DS                       4
SWH               9590.793 Hz
FIDRES            0.199492 Hz
AQ                2.5063622 sec
RG                    16.27
DW                  52.133 usec
DE                  31.46 usec
TE                  298.0 K
D1               20.00000000 sec
D12               0.00002000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1            600.1620038 MHz
NUC1                    1H
P1                    8.00 usec
PLW1             3.81069994 W
PLW9             0.00000245 W

F2 - Processing parameters
SI                    131072
SF              600.1600000 MHz
WDW                     no
SSB          0
LB           0 Hz
GB           0
PC                    1.00
```

Compound **18**: ^{13}CNMR of cyclo Leu-*N*-Me-Val-D-His(Boc)-D-Phe-3,3-Diphe-D-Ala




```
Current Data Parameters
NAME      140708_yckSM291wBoc
EXPNO                       4
PROCNO                      1

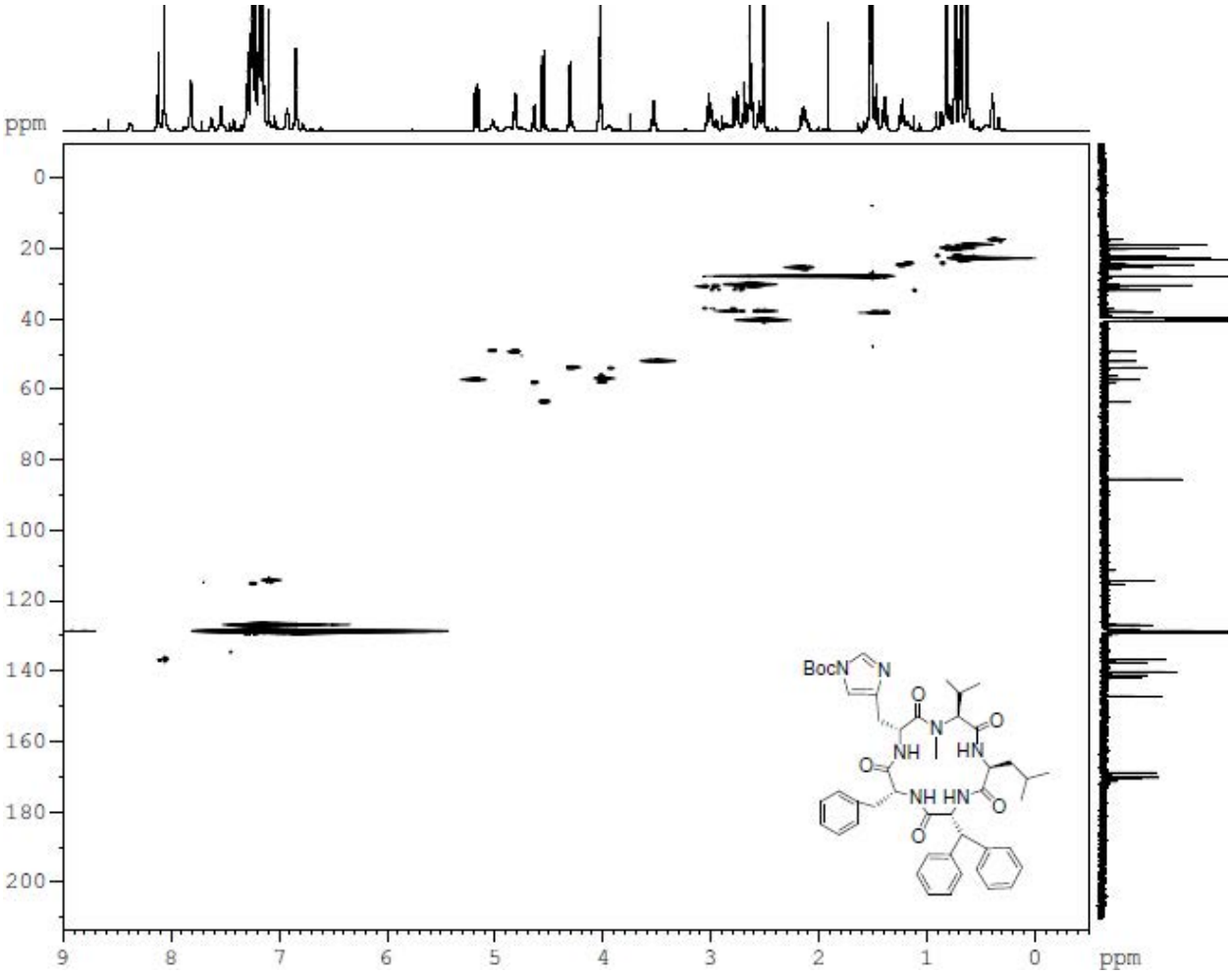
F2 - Acquisition Parameters
Date_              20141027
Time                  16.46
INSTRUM               spect
PROBHD    5 mm CPTCI 1H/
PULPROG             zgpg30
TD                   65536
SOLVENT               DMSO
NS                    2048
DS                       4
SWH              33333.332 Hz
FIDRES            0.508626 Hz
AQ                0.9830400 sec
RG                   202.23
DW                  15.000 usec
DE                  15.55 usec
TE                  298.0 K
D1               2.00000000 sec
D11              0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1            150.9254430 MHz
NUC1                    13C
P1                   11.50 usec
PLW1           100.00000000 W

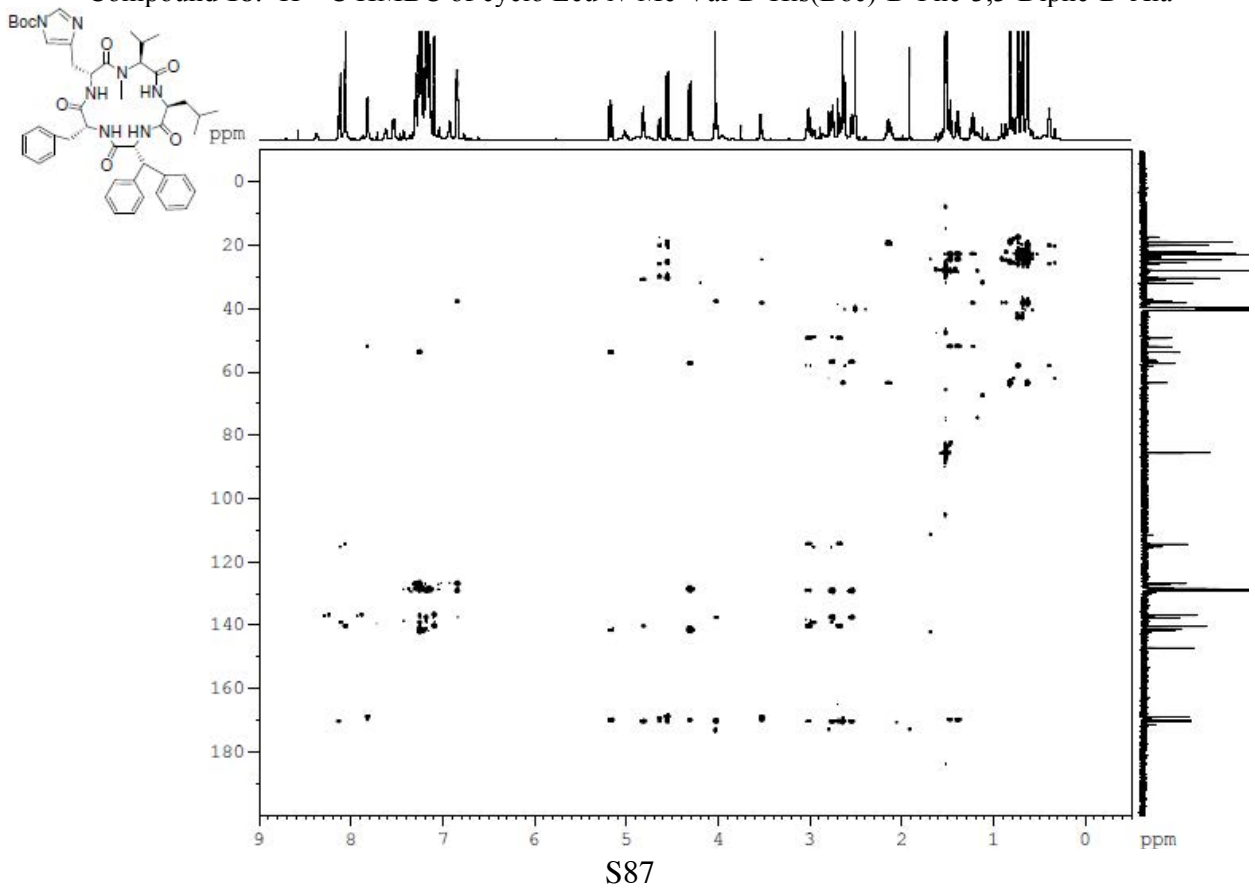
======== CHANNEL f2 ========
SFO2            600.1624006 MHz
NUC2                    1H
CPDPRG[2 bi_waltz65_256
PCPD2                70.00 usec
PLW2             3.81069994 W
PLW12            0.04977200 W
PLW13            0.02438800 W

F2 - Processing parameters
SI                    32768
SF              150.9103520 MHz
WDW                     no
SSB          0
LB           0 Hz
GB           0
PC                    1.40
```

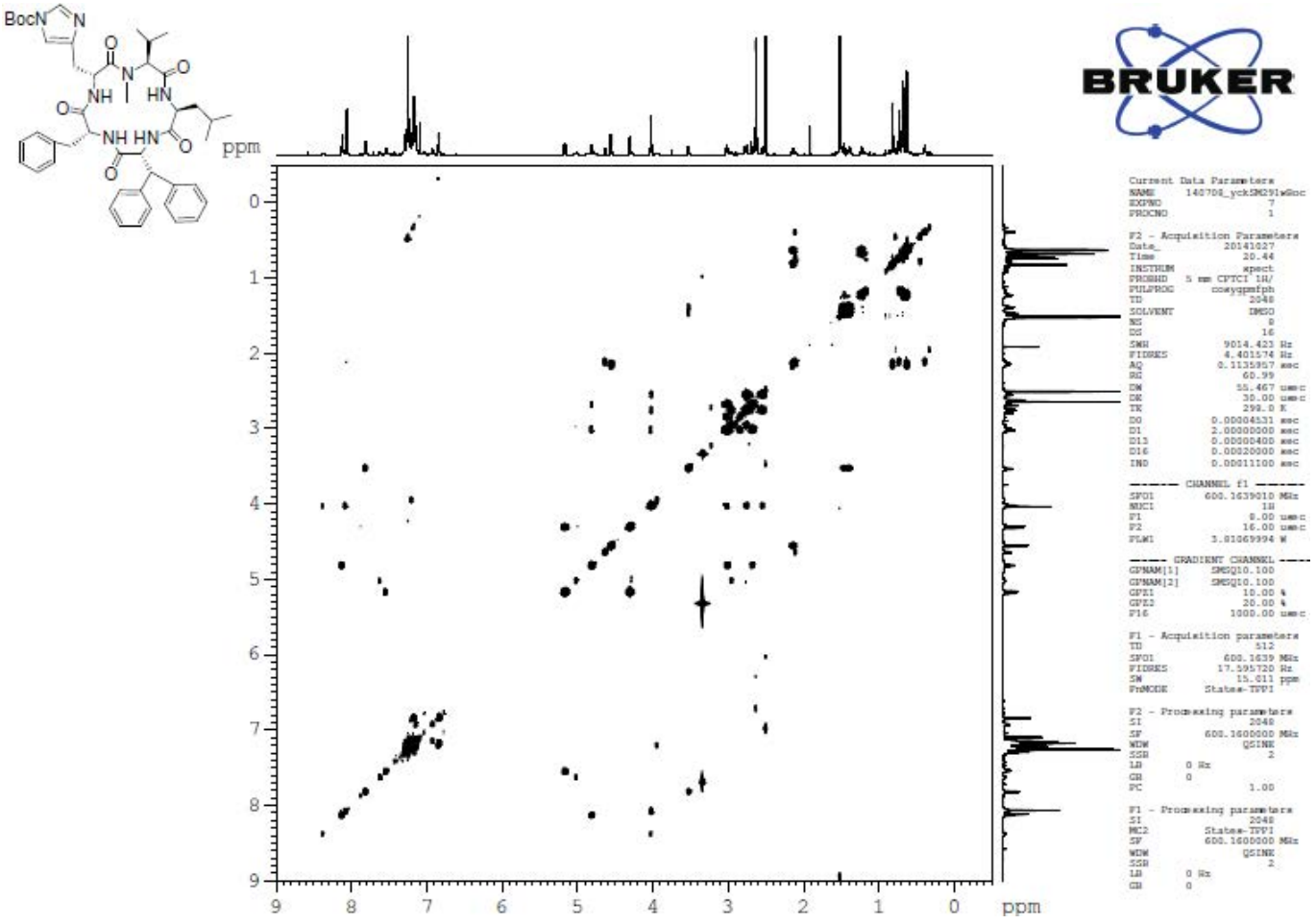
Compound **18**: ^{1}H-^{13}C HSQC of cyclo Leu-*N*-Me-Val-D-His(Boc)-D-Phe-3,3-Diphe-D-Ala



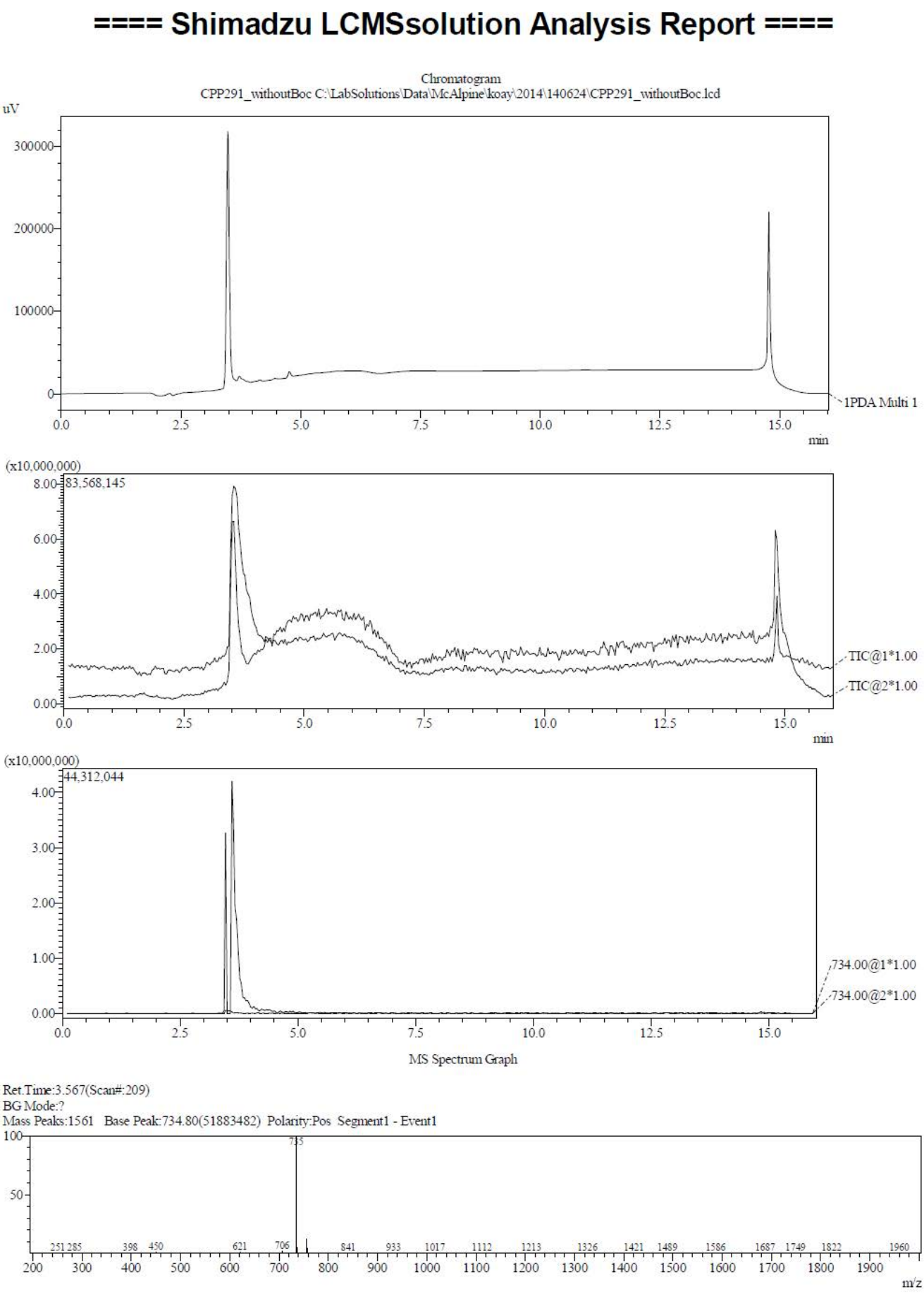
Compound **18**: ^{1}H-^{13}C HMBC of cyclo Leu-*N*-Me-Val-D-His(Boc)-D-Phe-3,3-Diphe-D-Ala



Compound **18**: ^{1}H-^{1}H COSY of cyclo Leu-*N*-Me-Val-D-His(Boc)-D-Phe-3,3-Diphe-D-Ala



Compound **19**: LCMS of cyclo Leu-*N*-Me-Val-D-His-D-Phe-3,3-Diphe-D-Ala

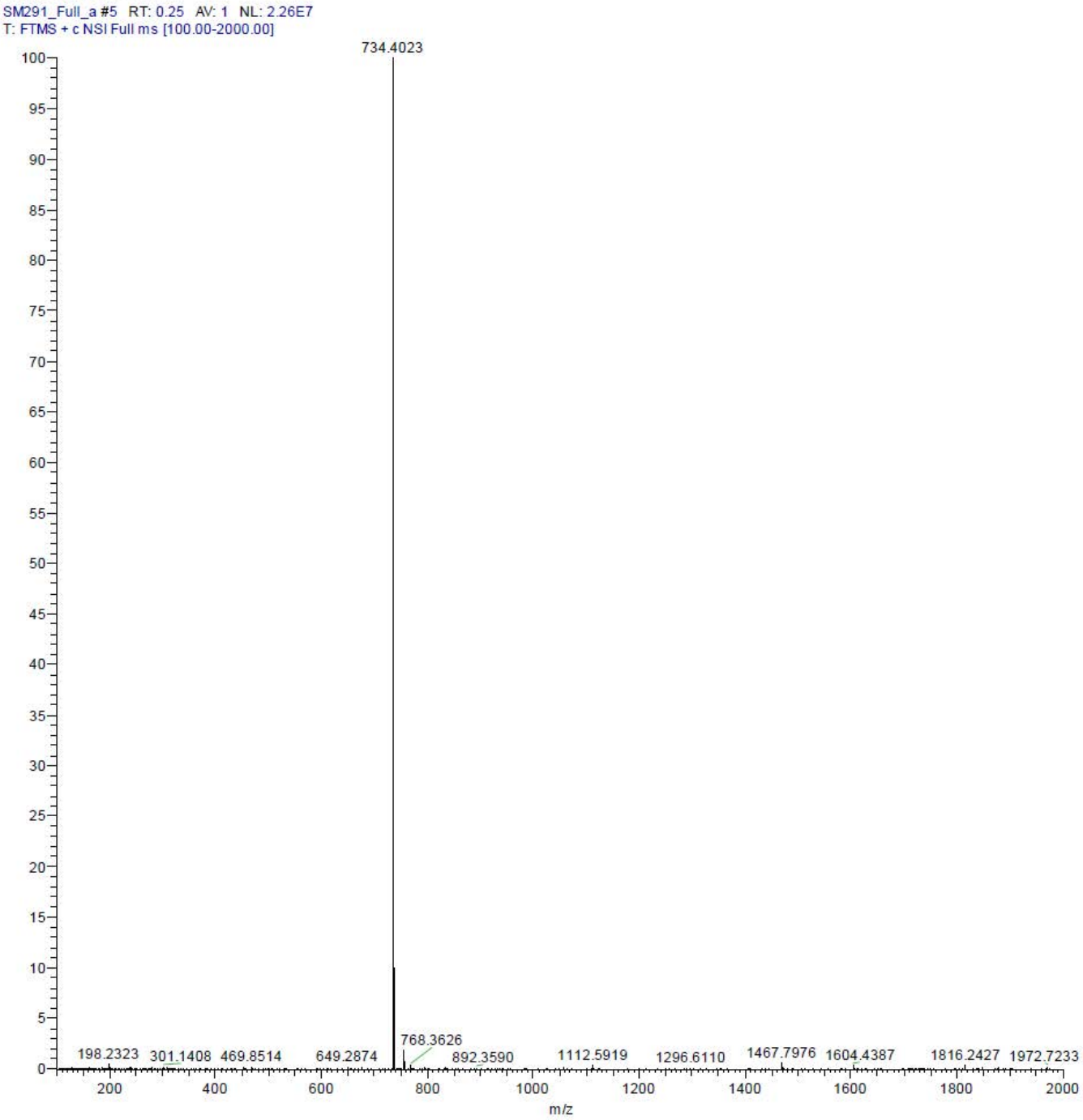


Compound **19**: HRMS of cyclo Leu-*N*-Me-Val-D-His-D-Phe-3,3-Diphe-D-Ala

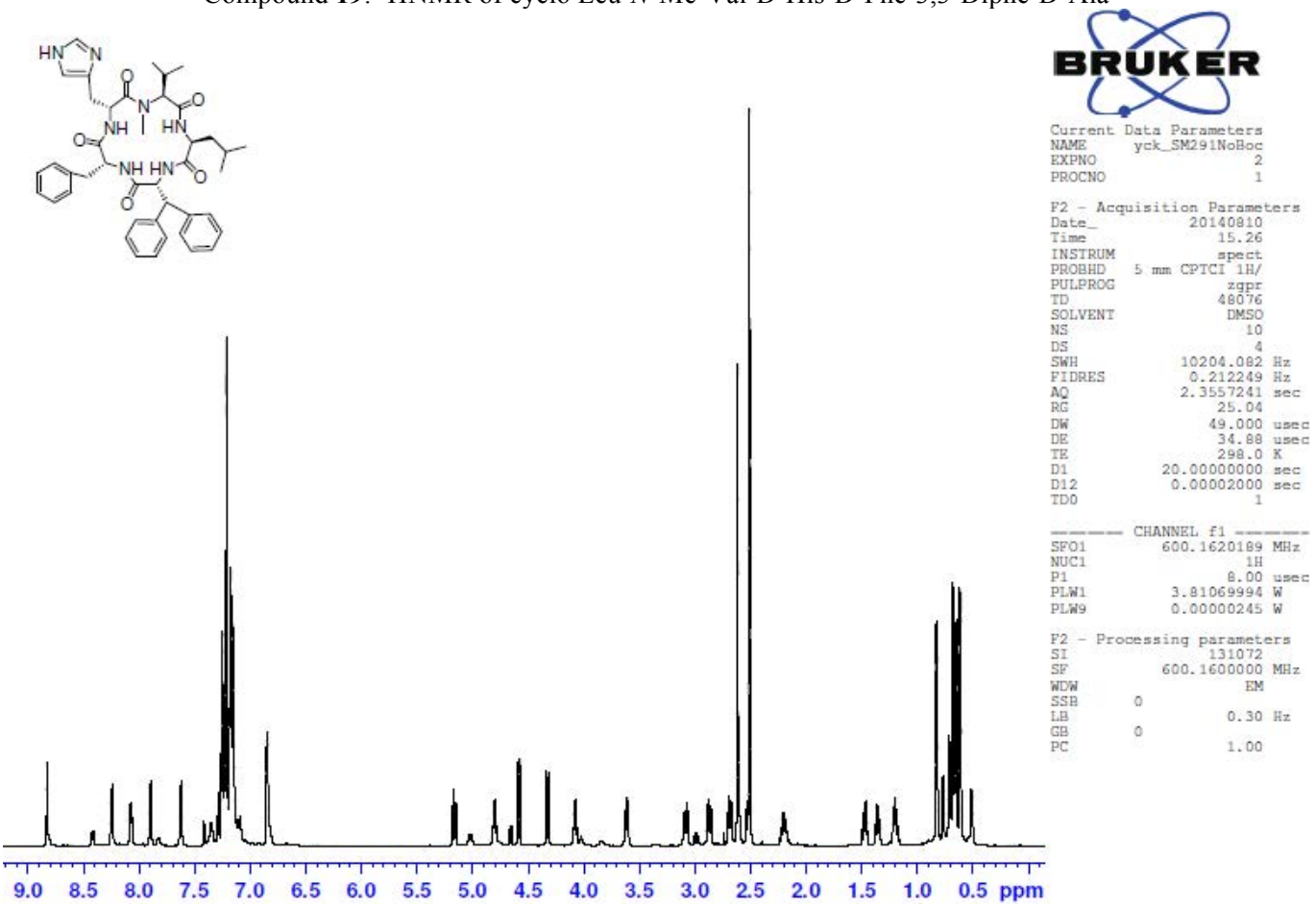
MS Data from Orbitrap

Sample: SM291

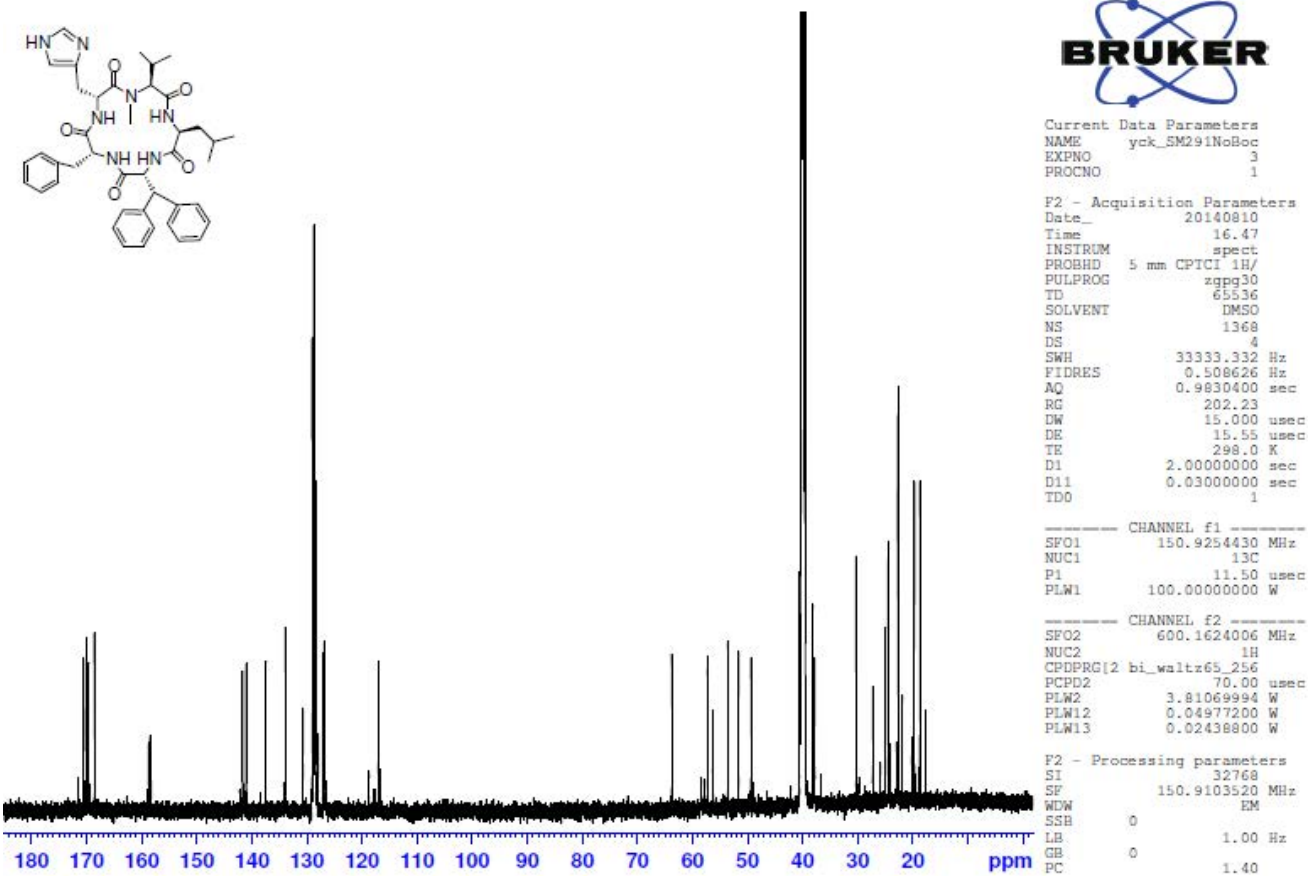
Full spectrum:



Compound **19**: ^{1}HNMR of cyclo Leu-*N*-Me-Val-D-His-D-Phe-3,3-Diphe-D-Ala



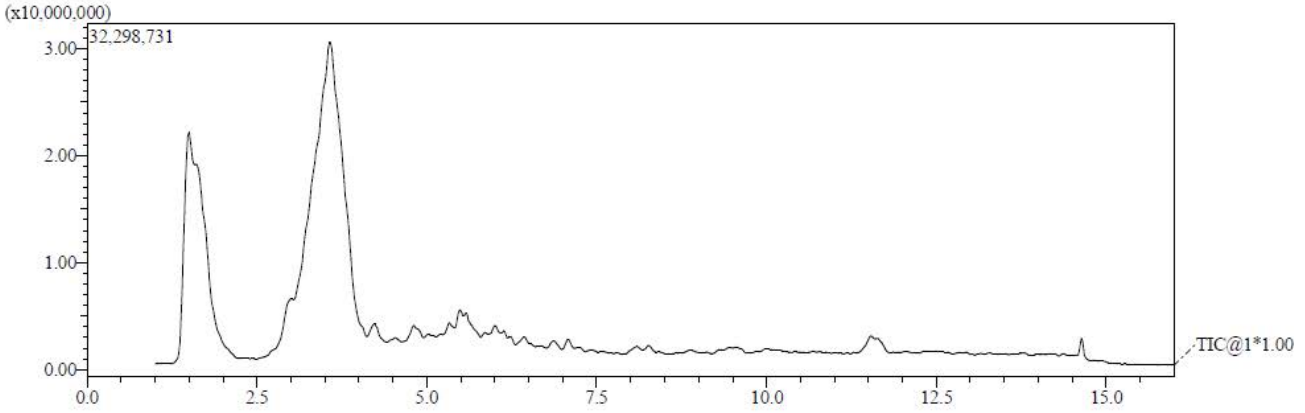
Compound **19**: ^{13}CNMR of cyclo Leu-*N*-Me-Val-D-His-D-Phe-3,3-Diphe-D-Ala

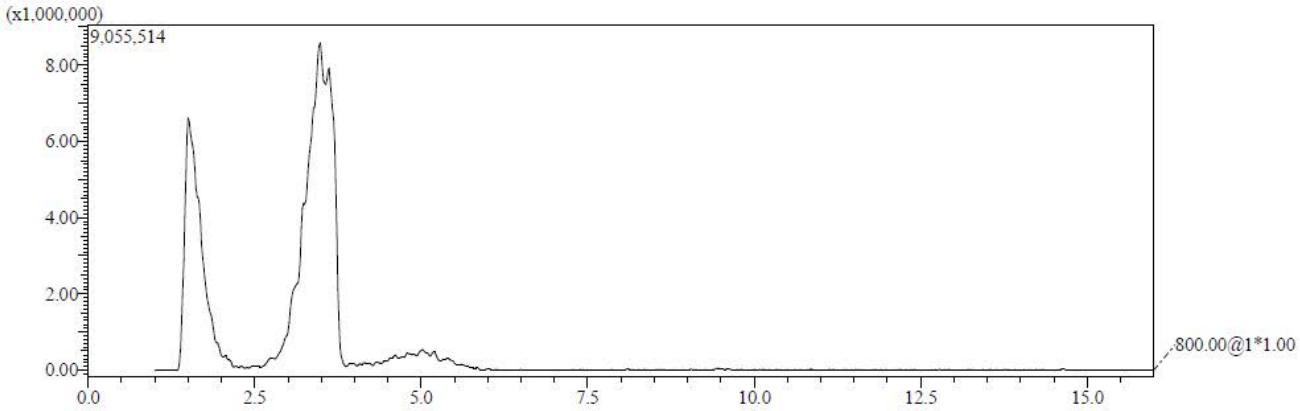


Compound **20**: LCMS of DDLP HO-Leu-*N*-Me-Val-D-Glu(OtBu)-D-Phe-3,3-Diphe-D-Ala-NH_2

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

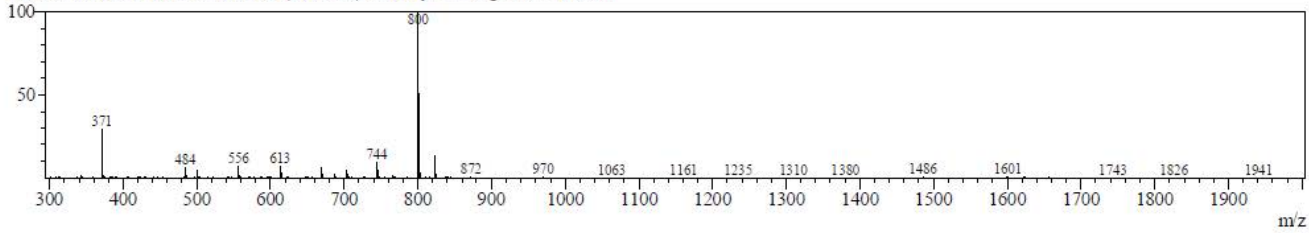
Chromatogram
LPP280 C:\LabSolutions\Data\McAlpine\koay\2014\140327\LPP280a.lcd





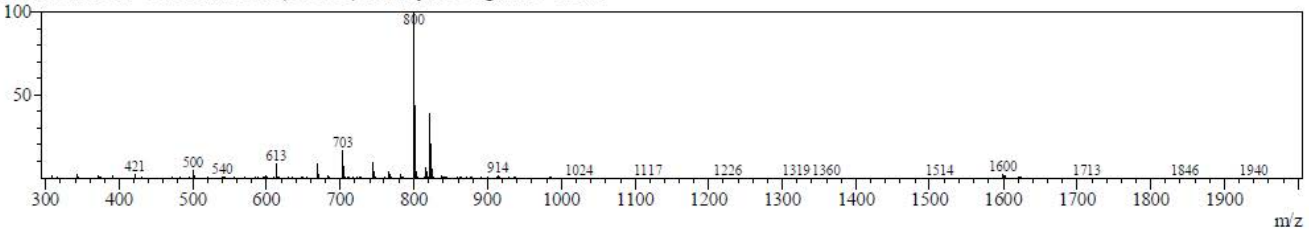
MS Spectrum Graph

Ret.Time:1.533(Scan#:33)
BG Mode:None
Mass Peaks:1576 Base Peak:800.30(6198406) Polarity:Pos Segment1 - Event1

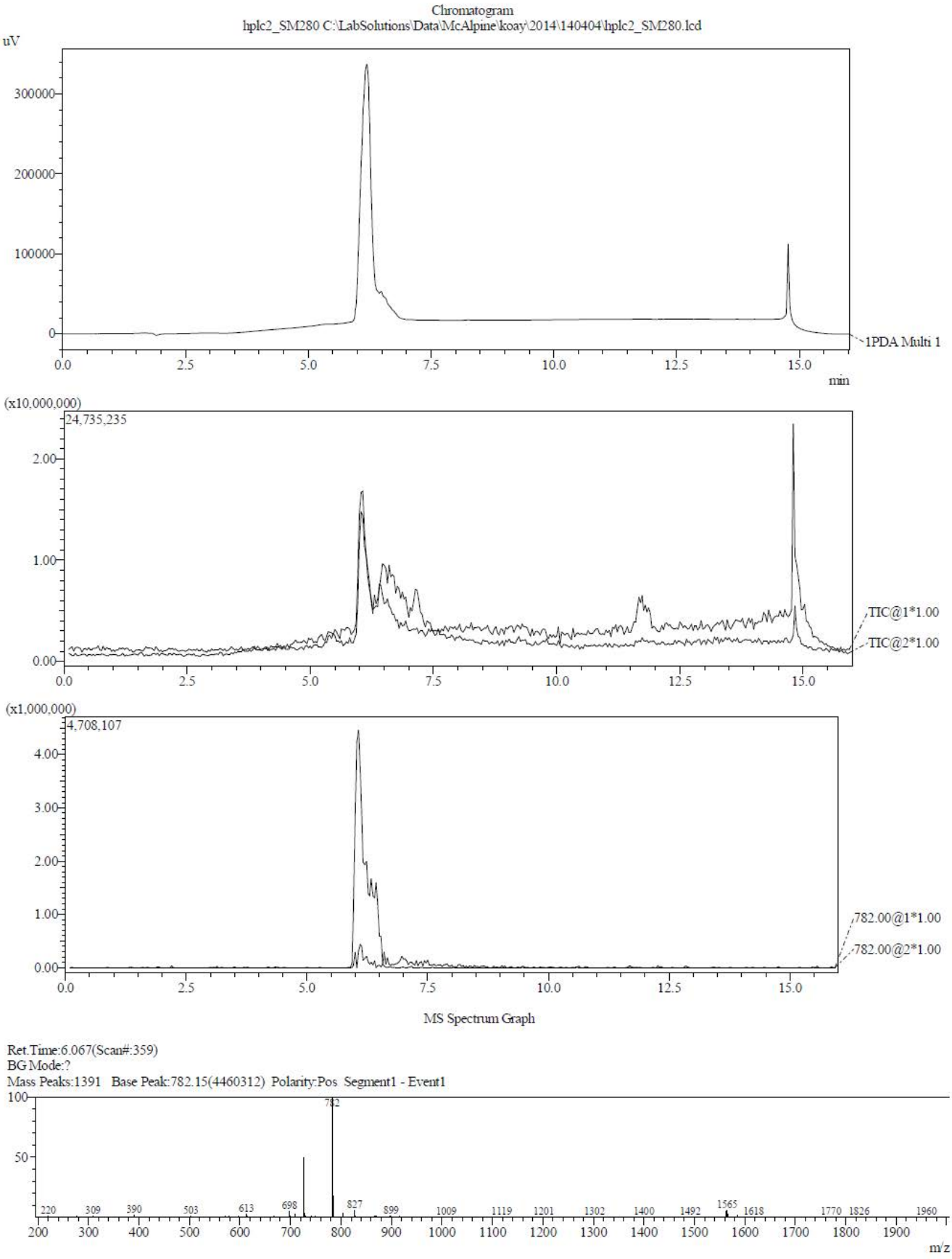


MS Spectrum Graph

Ret.Time:3.650(Scan#:160)
BG Mode:?
Mass Peaks:1591 Base Peak:800.35(7064787) Polarity:Pos Segment1 - Event1



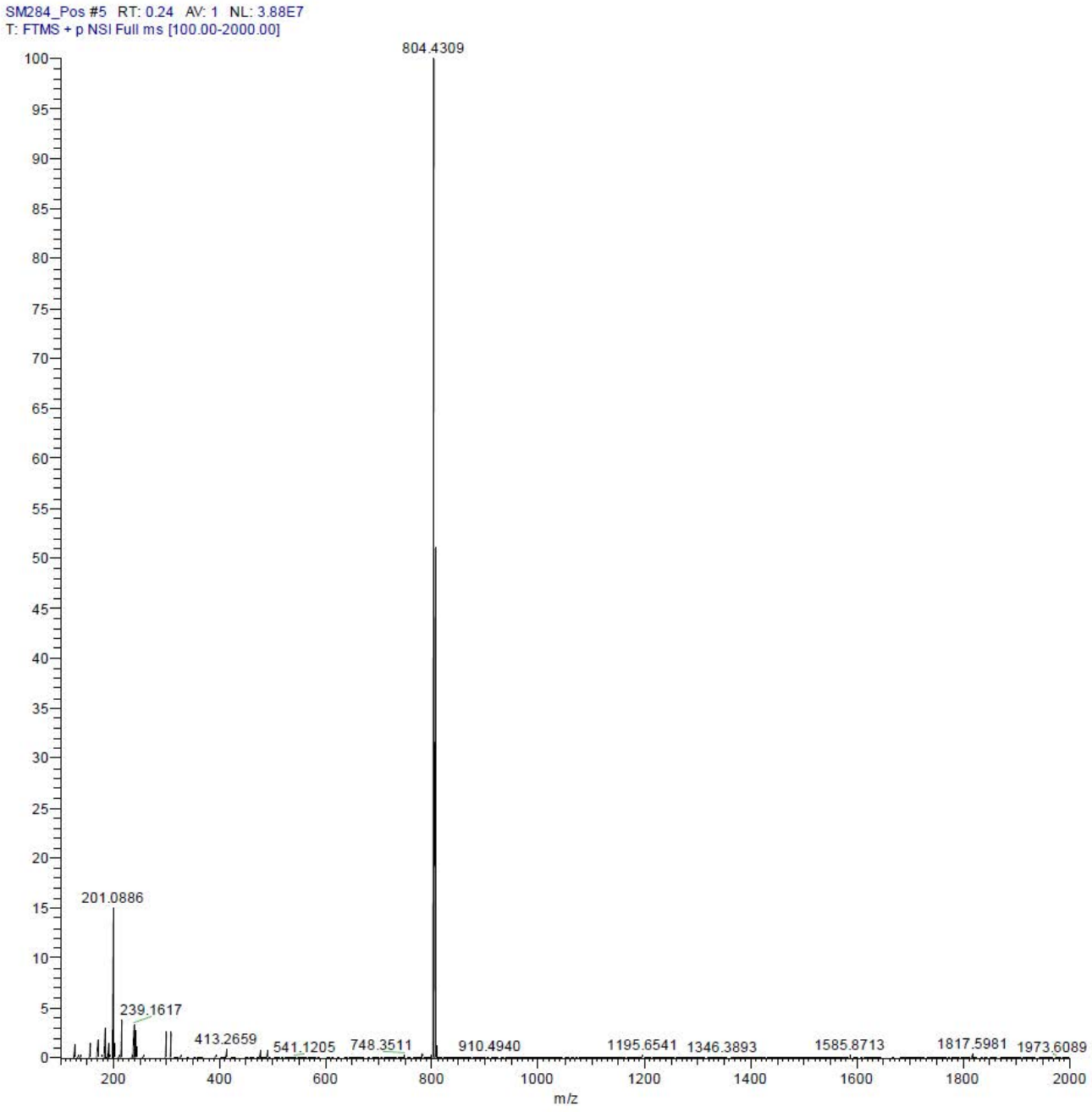
Compound **20**: LCMS of cyclo Leu-*N*-Me-Val-D-Glu(OtBu)-D-Phe-3,3-Diphe-D-Ala



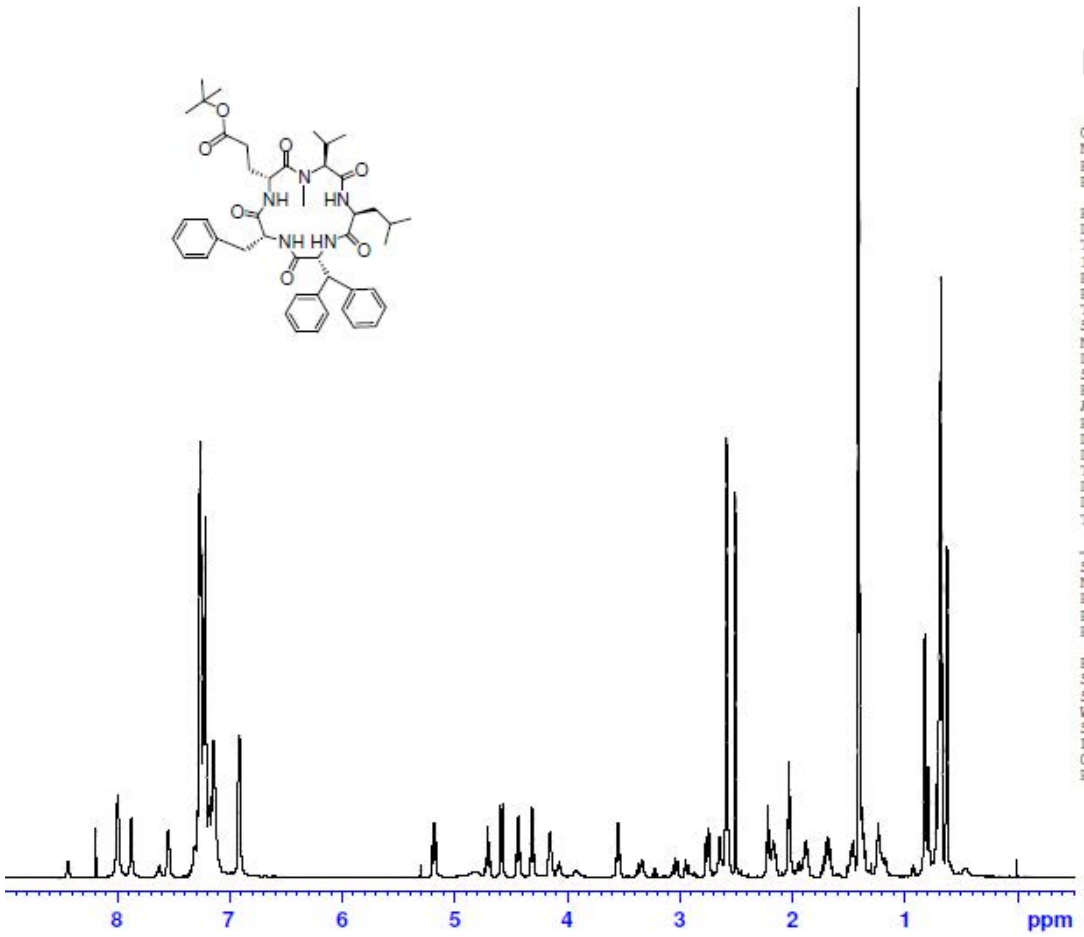
Compound **20**: HRMS of cyclo Leu-*N*-Me-Val-D-Glu(OtBu)-D-Phe-3,3-Diphe-D-Ala

MS Data from Orbitrap

Full spectrum



Compound **20**: ^{1}HNMR of cyclo Leu-*N*-Me-Val-D-Glu(OtBu)-D-Phe-3,3-Diphe-D-Ala



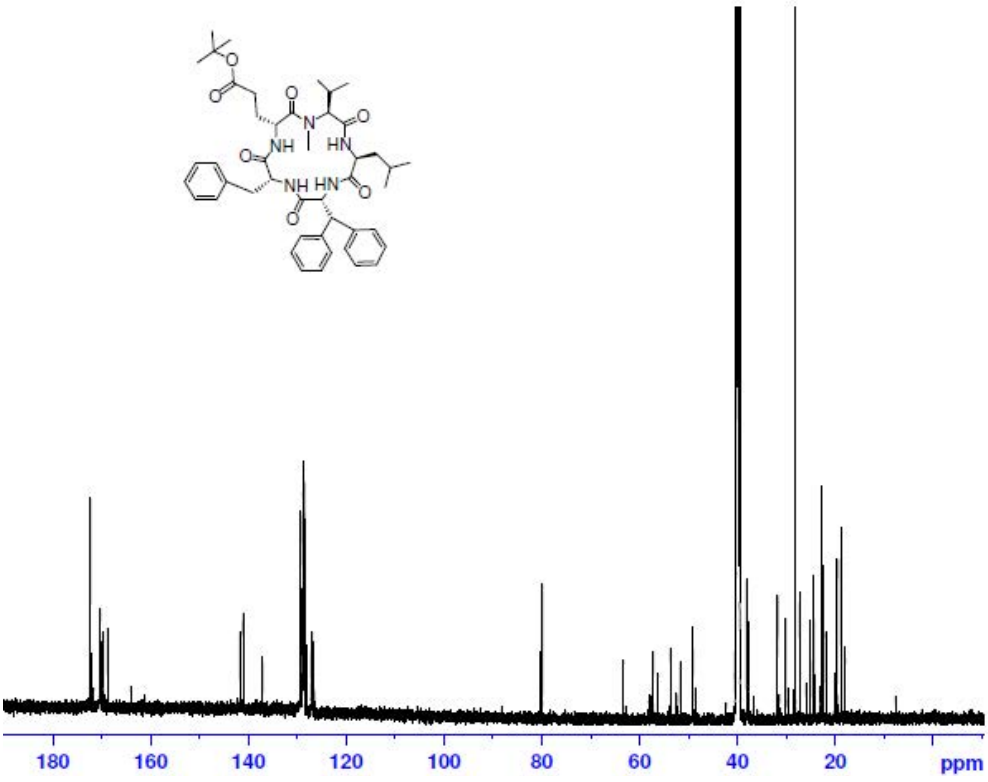

```
Current Data Parameters
NAME                  140602-yck
EXPNO                         15
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20140602
Time                       18.32
INSTRUM                    spect
PROBHD     5 mm CPTCI 1H/
PULPROG                    zgpr
TD                        48076
SOLVENT                    DMSO
NS                             8
DS                             4
SWH                     9009.009 Hz
FIDRES                  0.187391 Hz
AQ                      2.6682179 sec
RG                         16.27
DW                        55.500 usec
DE                        33.22 usec
TE                        298.0 K
D1                     20.00000000 sec
D12                     0.00002000 sec
TD0                            1

======== CHANNEL f1 ========
SFO1                  600.1620027 MHz
NUC1                          1H
P1                         8.00 usec
PLW1                    3.81069994 W
PLW9                    0.00000010 W

F2 - Processing parameters
SI                        131072
SF                    600.1600000 MHz
WDW                           EM
SSB                    0
LB                          0.30 Hz
GB                     0
PC                         1.00
```

Compound **20**: ^{13}CNMR of cyclo Leu-*N*-Me-Val-D-Glu(OtBu)-D-Phe-3,3-Diphe-D-Ala_




```
Current Data Parameters
NAME                  140602-yck
EXPNO                         16
PROCNO                         1

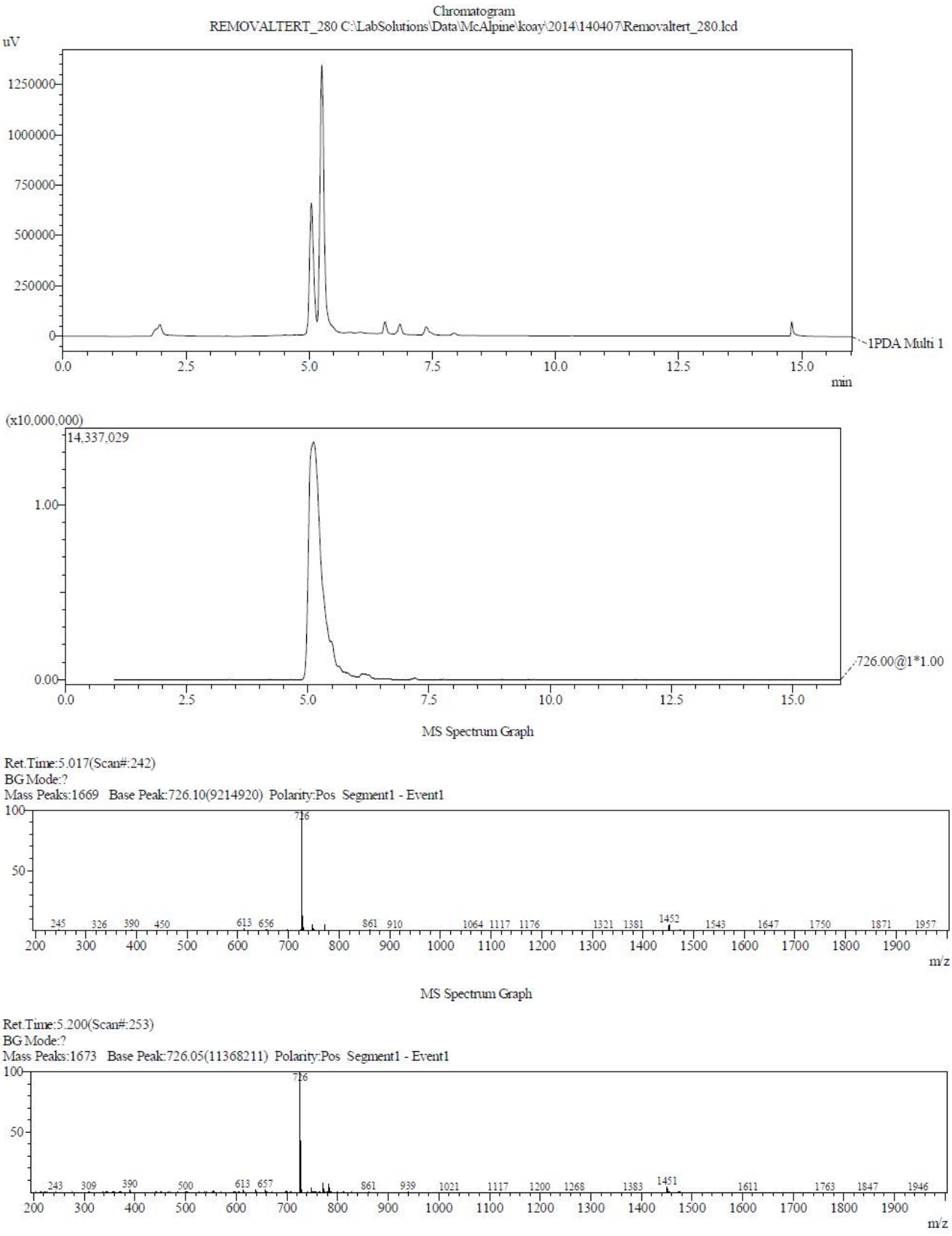
F2 - Acquisition Parameters
Date_                   20140602
Time                       18.37
INSTRUM                    spect
PROBHD     5 mm CPTCI 1H/
PULPROG                 zgpg30
TD                        65536
SOLVENT                    DMSO
NS                           800
DS                             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                            1

======== CHANNEL f1 ========
SFO1                  150.9239339 MHz
NUC1                          13C
P1                        11.50 usec
PLW1                  100.00000000 W

======== CHANNEL f2 ========
SFO2                  600.1624006 MHz
NUC2                          1H
CPDPRG[2 bi_waltz65_256
PCPD2                     70.00 usec
PLW2                    3.81069994 W
PLW12                   0.04977200 W
PLW13                   0.02438800 W

F2 - Processing parameters
SI                         32768
SF                    150.9103520 MHz
WDW                           EM
SSB                    0
LB                          1.00 Hz
GB                     0
PC                         1.40
```

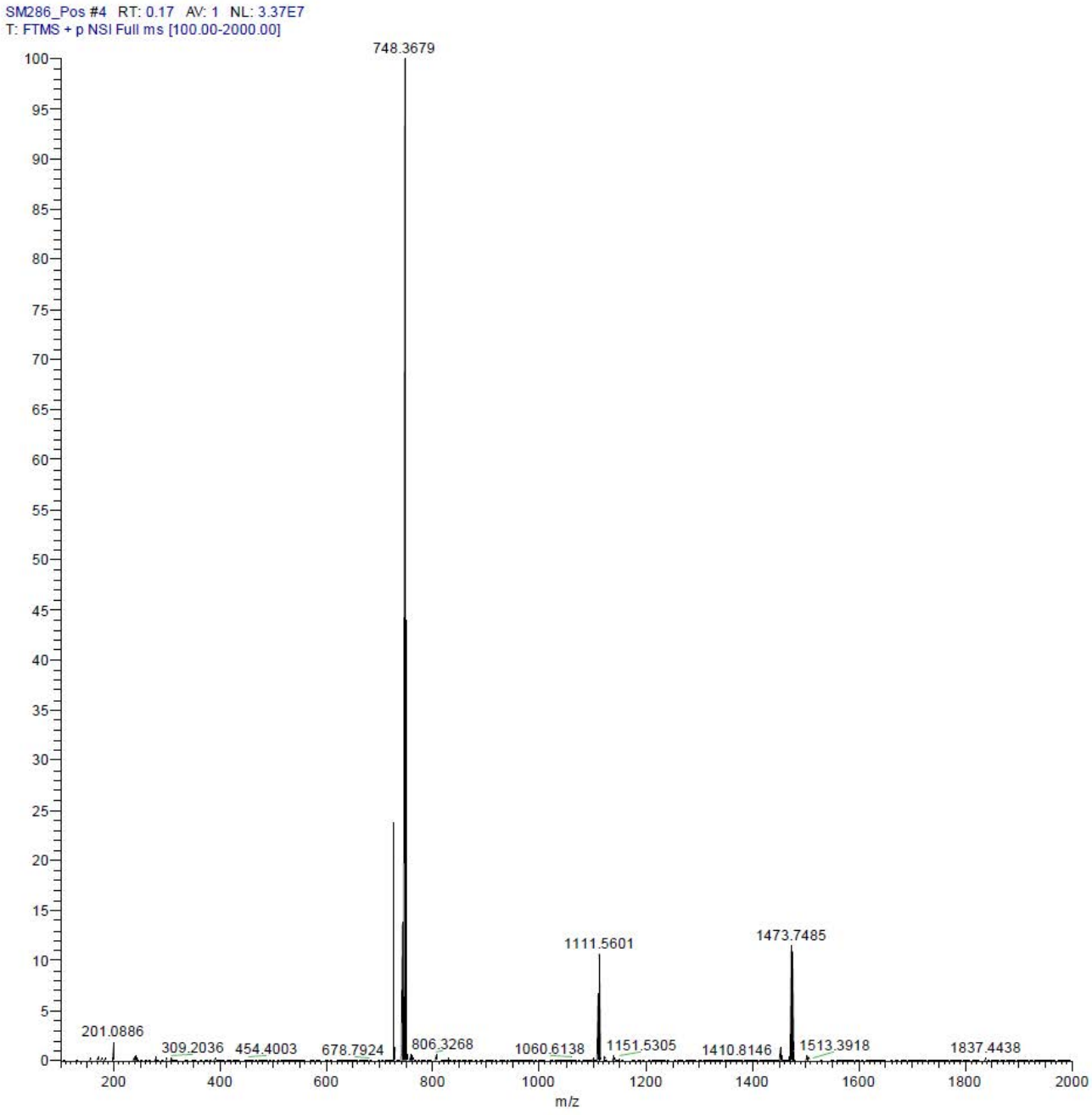
Compound **21**: LCMS of cyclo Leu-*N*-Me-Val-D-Glu-D-Phe-3,3-Diphe-D-Ala



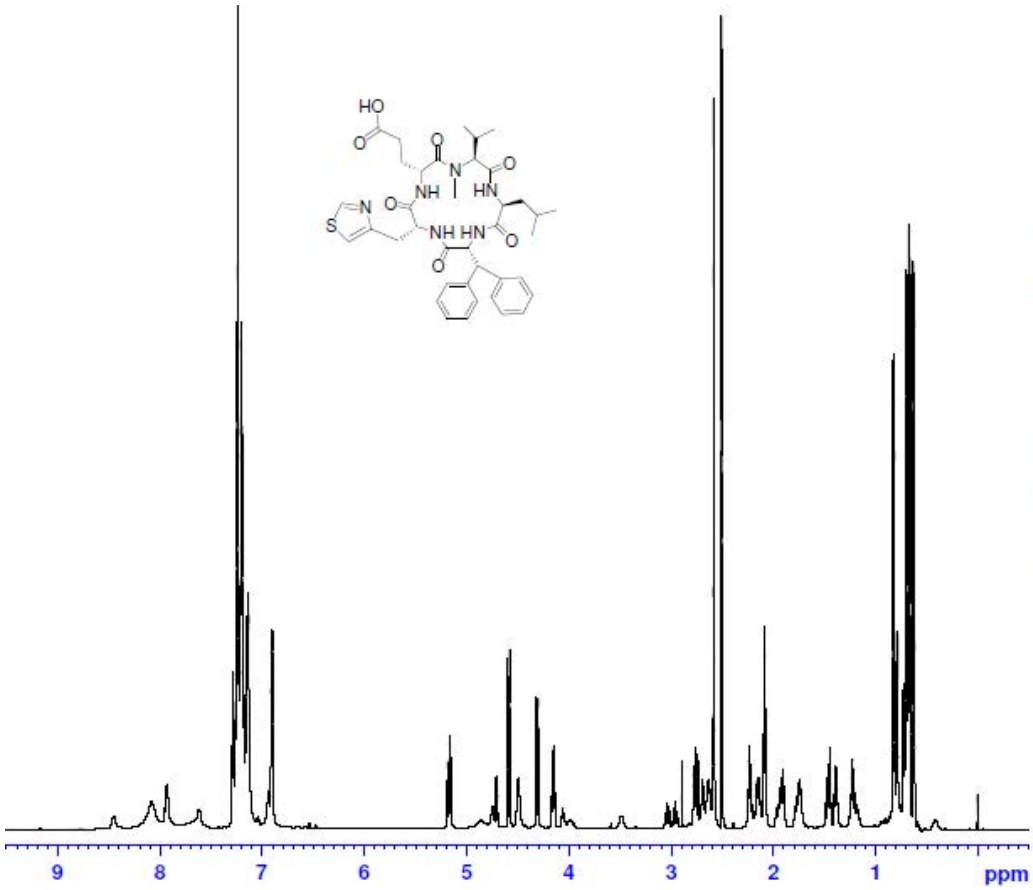
Compound **21**: HRMS of cyclo Leu-*N*-Me-Val-D-Glu-D-Phe-3,3-Diphe-D-Ala

MS Data from Orbitrap

Full spectrum



Compound **21**: ^{1}HNMR of cyclo Leu-*N*-Me-Val-D-Glu-D-Phe-3,3-Diphe-D-Ala



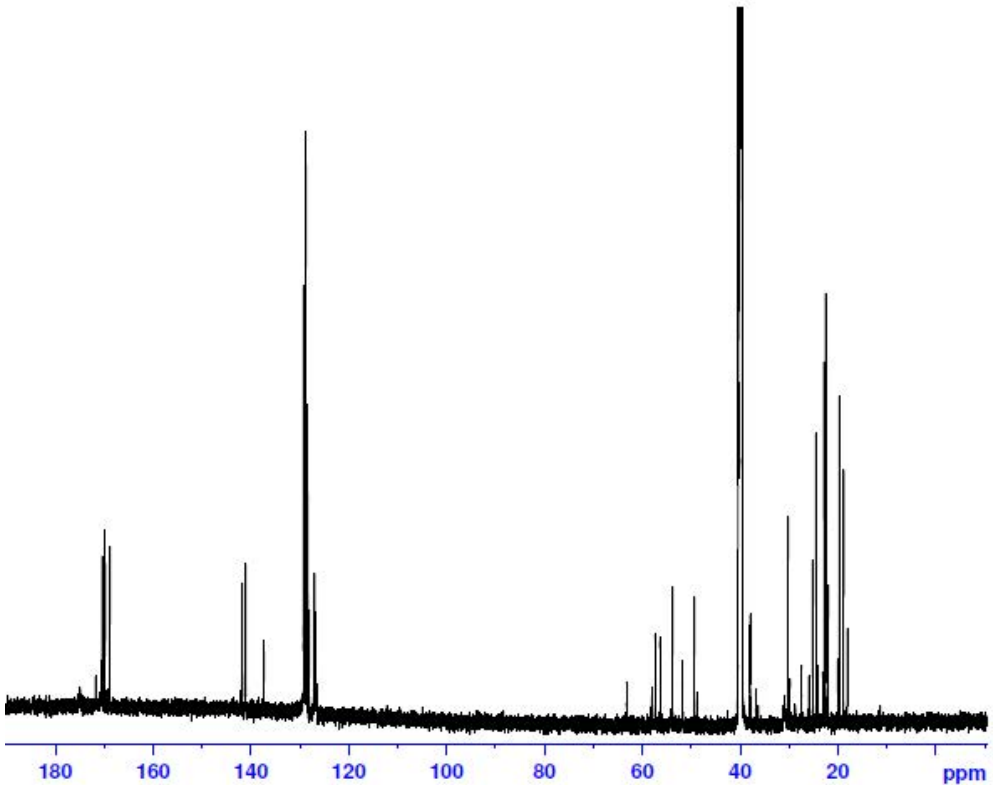

```
Current Data Parameters
NAME                  140602-yck
EXPNO                          3
PROCNO                         1

F2 - Acquisition Parameters
Date_                  20140602
Time                      10.09
INSTRUM                   spect
PROBHD     5 mm CPTCI 1H/
PULPROG                   zgpr
TD                       48076
SOLVENT                   DMSO
NS                           21
DS                            4
SWH                   9009.009 Hz
FIDRES                0.187391 Hz
AQ                    2.6682179 sec
RG                        28.36
DW                       55.500 usec
DE                       33.22 usec
TE                       298.0 K
D1                  20.00000000 sec
D12                  0.00002000 sec
TD0                           1

======== CHANNEL f1 ========
SFO1                600.1620061 MHz
NUC1                        1H
P1                        8.00 usec
PLW1                3.81069994 W
PLW9                0.00000245 W

F2 - Processing parameters
SI                       131072
SF                  600.1600000 MHz
WDW                         EM
SSB                  0
LB                        0.30 Hz
GB                   0
PC                        1.00
```

Compound **21**: ^{13}CNMR of cyclo Leu-*N*-Me-Val-D-Glu-D-Phe-3,3-Diphe-D-Ala




```
Current Data Parameters
NAME                  140602-yck
EXPNO                          4
PROCNO                         1

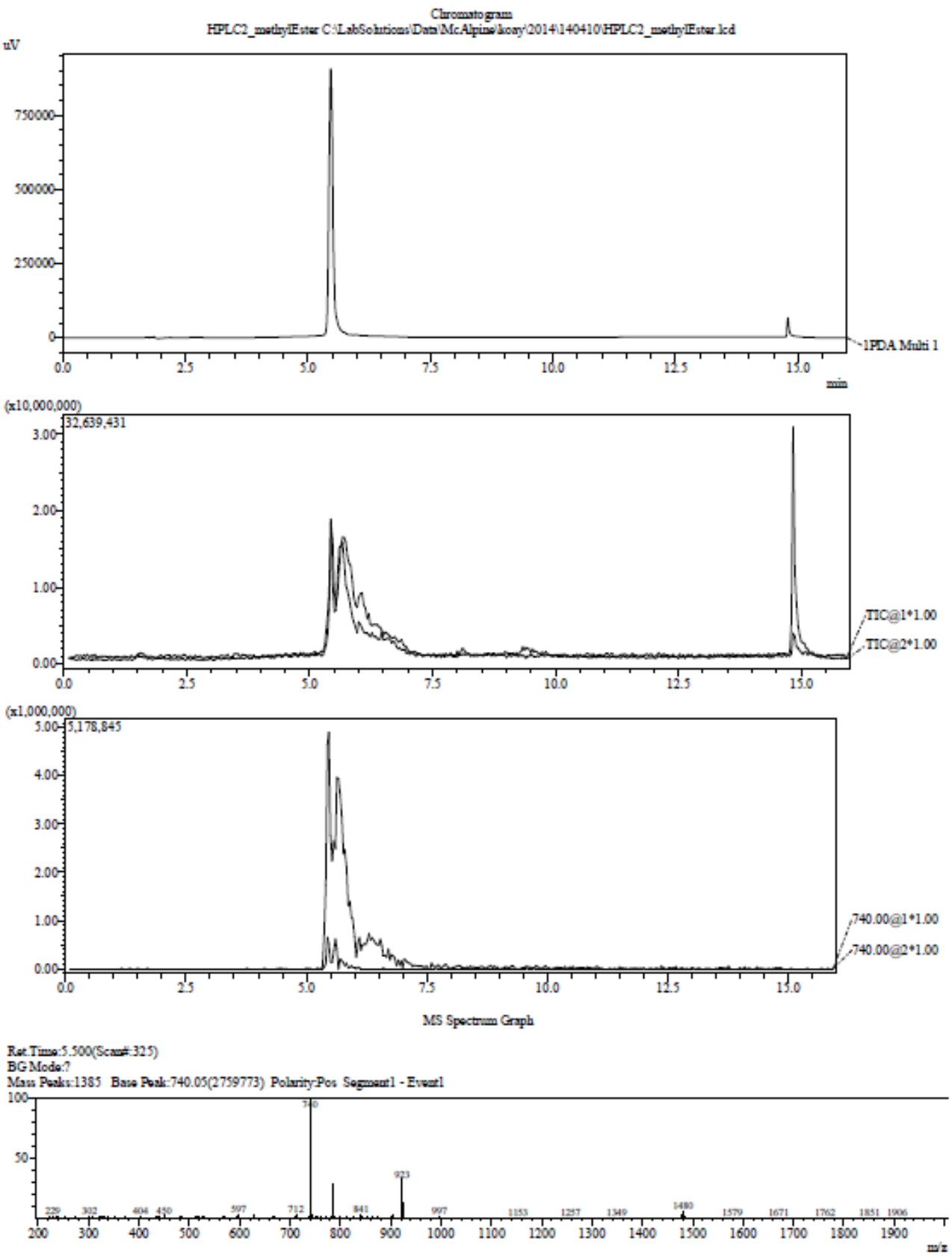
F2 - Acquisition Parameters
Date_                  20140602
Time                      11.34
INSTRUM                   spect
PROBHD     5 mm CPTCI 1H/
PULPROG                 zgpg30
TD                       65536
SOLVENT                   DMSO
NS                         1699
DS                            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                           1

======== CHANNEL f1 ========
SFO1                150.9239339 MHz
NUC1                        13C
P1                       11.50 usec
PLW1               100.00000000 W

======== CHANNEL f2 ========
SFO2                600.1624006 MHz
NUC2                        1H
CPDPRG[2 bi_waltz65_256
PCPD2                    70.00 usec
PLW2                3.81069994 W
PLW12               0.04977200 W
PLW13               0.02438800 W

F2 - Processing parameters
SI                        32768
SF                  150.9103520 MHz
WDW                         EM
SSB                  0
LB                        1.00 Hz
GB                   0
PC                        1.40
```

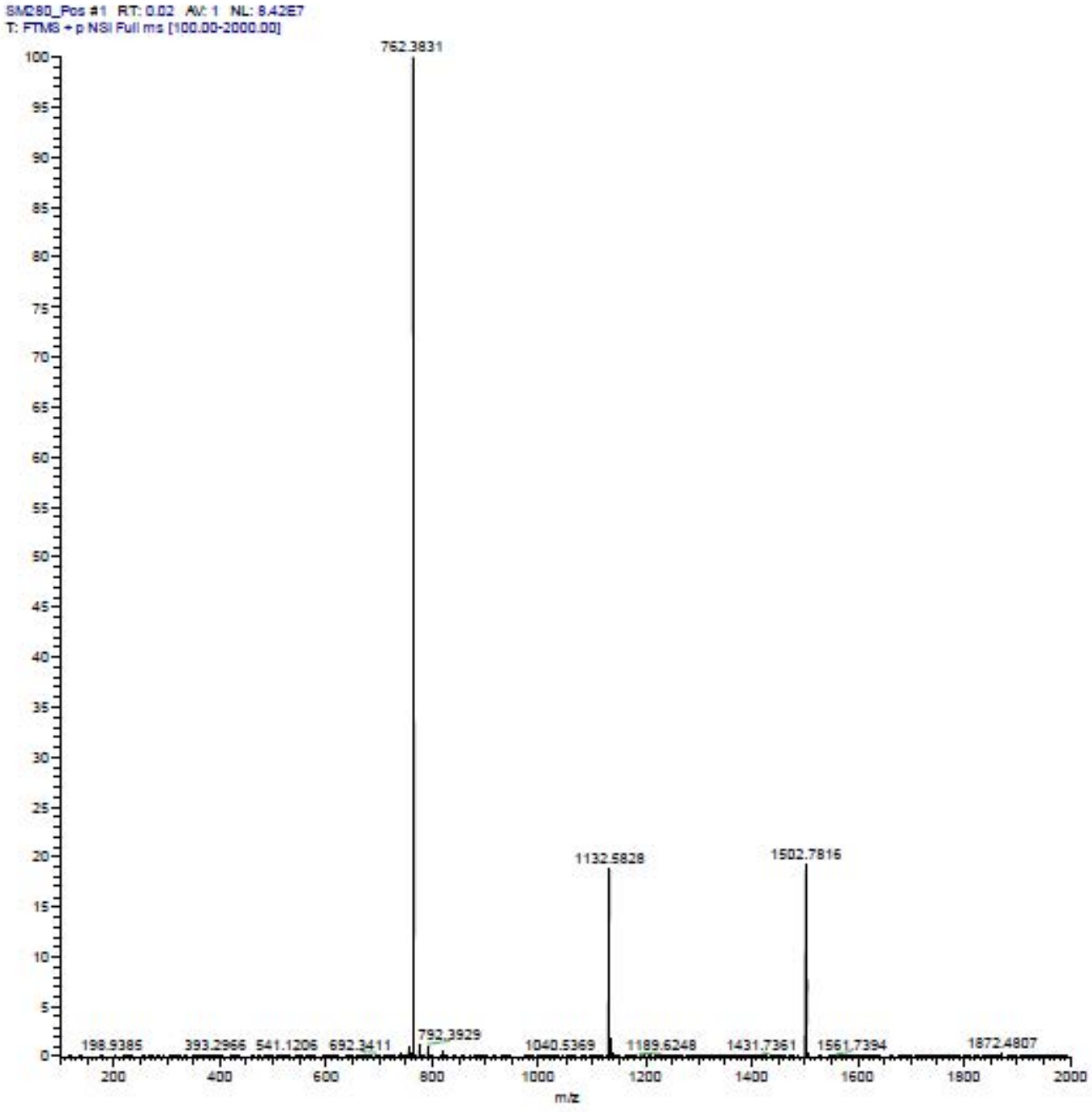
Compound **22**: LCMS of cyclo Leu-*N*-Me-Val-D-Glu(OMe)-D-Phe-3,3-Diphe-D-Ala



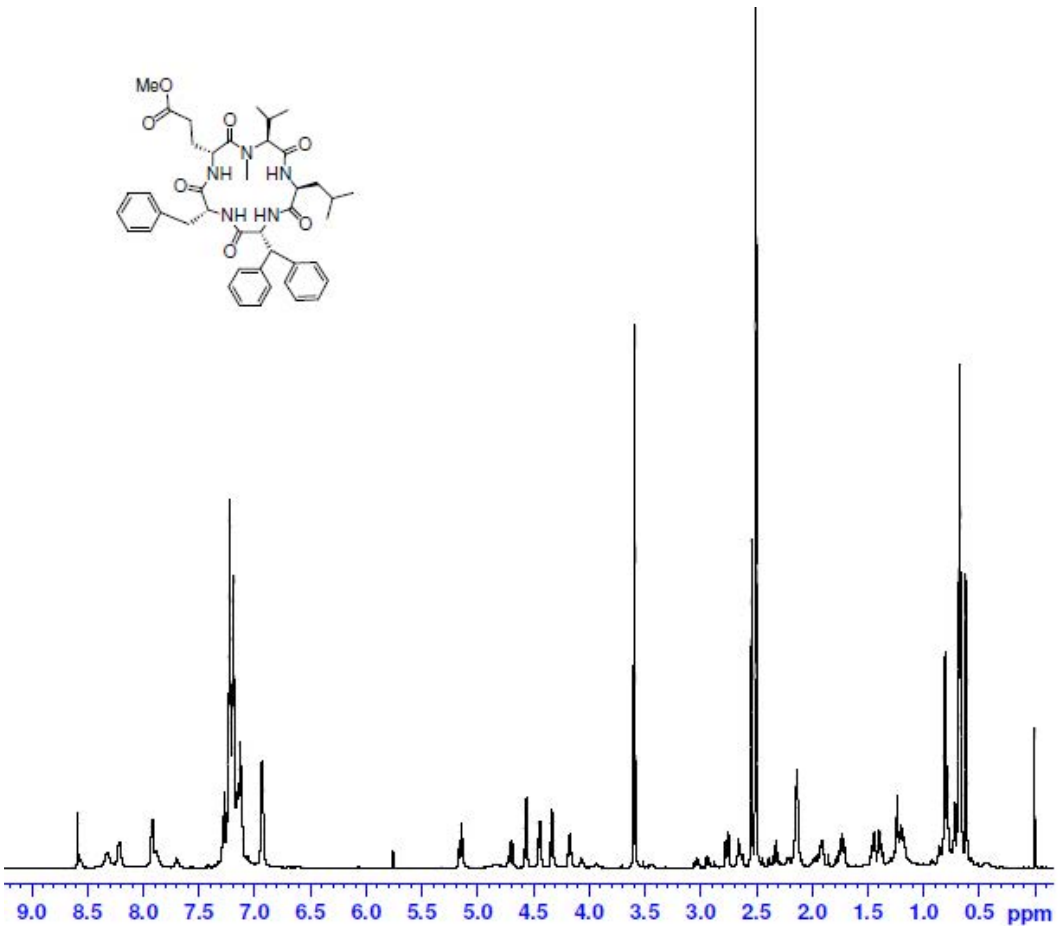
Compound **22**: HRMS of cyclo Leu-*N*-Me-Val-D-Glu(OMe)-D-Phe-3,3-Diphe-D-Ala

MS Data from Orbitrap

Full spectrum



Compound **22**: ^{1}HNMR of cyclo Leu-*N*-Me-Val-D-Glu(OMe)-D-Phe-3,3-Diphe-D-Ala



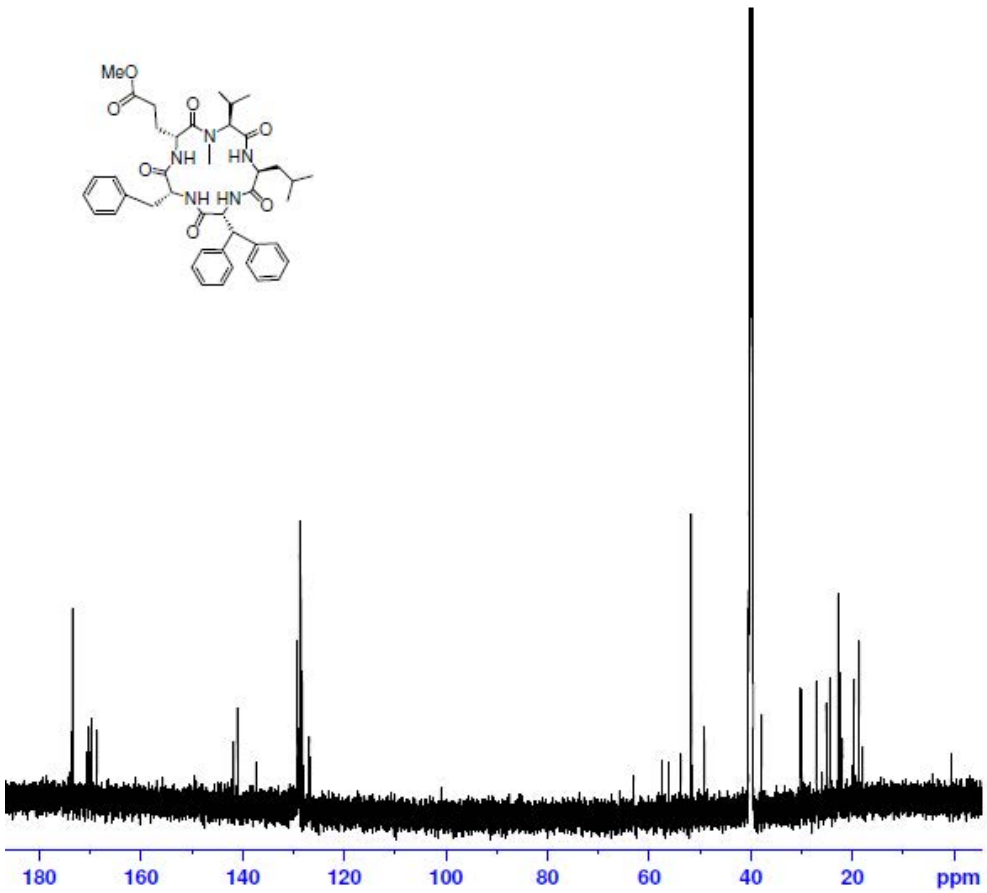

```
Current Data Parameters
NAME      140510_yck280ME
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_           20140510
Time              16.34
INSTRUM           spect
PROBHD   5 mm CPTCI 1H/
PULPROG           zgpr
TD               48076
SOLVENT           DMSO
NS                  12
DS                   4
SWH           9009.009 Hz
FIDRES        0.187391 Hz
AQ            2.6682179 sec
RG                80.39
DW               55.500 usec
DE               33.19 usec
TE               298.0 K
D1          20.00000000 sec
D12          0.00002000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1        600.1619996 MHz
NUC1                1H
P1                8.05 usec
PLW1         3.81069994 W
PLW9         0.00000987 W

F2 - Processing parameters
SI              131072
SF          600.1600000 MHz
WDW                EM
SSB       0
LB              0.30 Hz
GB        0
PC              1.00
```

Compound **22**: ^{13}CNMR of cyclo Leu-*N*-Me-Val-D-Glu(OMe)-D-Phe-3,3-Diphe-D-Ala




```
Current Data Parameters
NAME      140510_yck280ME
EXPNO                   3
PROCNO                  1

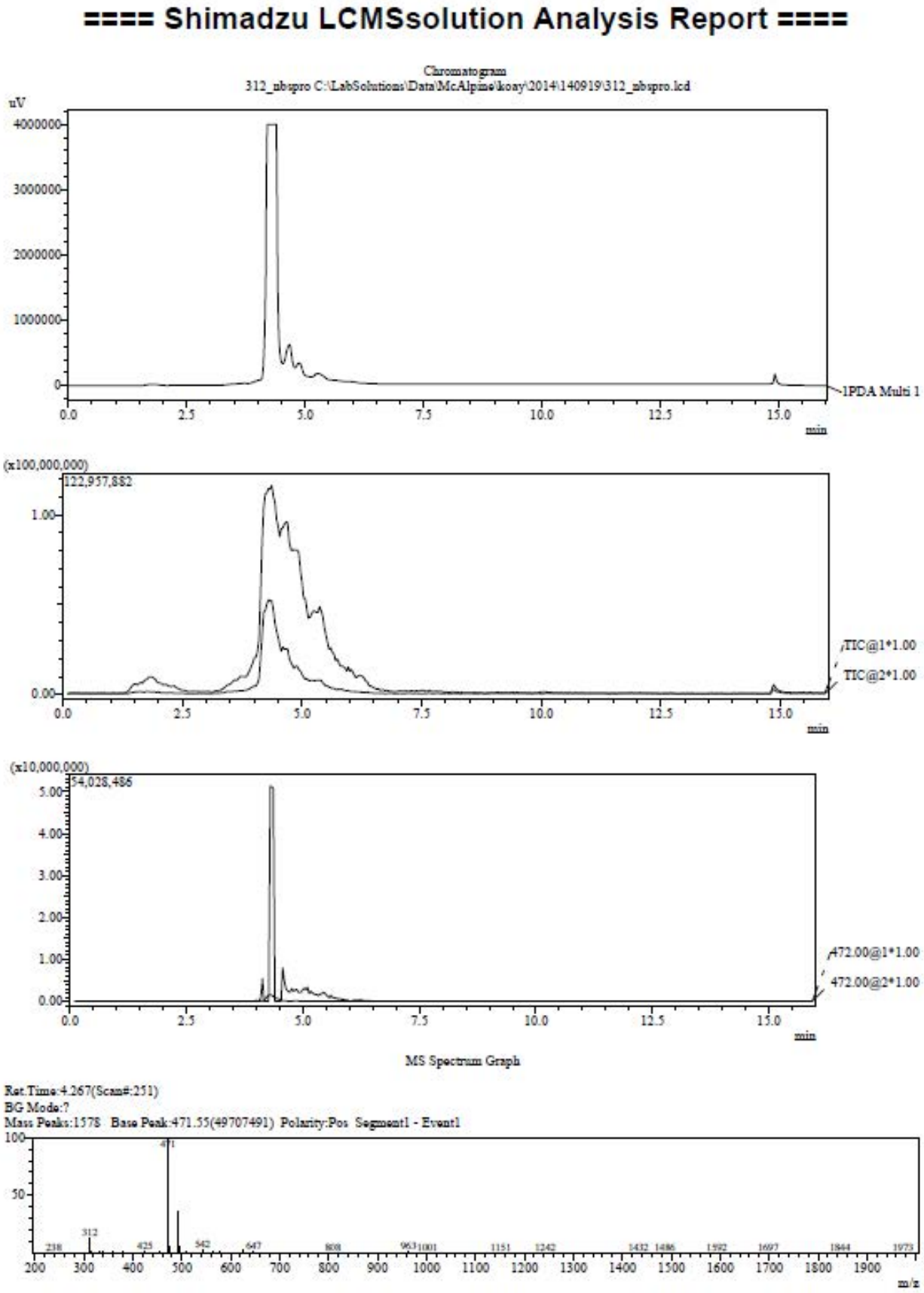
F2 - Acquisition Parameters
Date_           20140510
Time              16.44
INSTRUM           spect
PROBHD   5 mm CPTCI 1H/
PULPROG         zgpg30
TD               65536
SOLVENT           DMSO
NS                6144
DS                   4
SWH          32894.738 Hz
FIDRES        0.501934 Hz
AQ            0.9961472 sec
RG               202.23
DW               15.200 usec
DE               17.51 usec
TE               298.0 K
D1          1.00000000 sec
D11         0.03000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1        150.9246869 MHz
NUC1                13C
P1               11.50 usec
PLW1       100.00000000 W

======== CHANNEL f2 ========
SFO2        600.1624006 MHz
NUC2                1H
CPDPRG[2 bi_waltz65_256
PCPD2            70.00 usec
PLW2         3.81069994 W
PLW12        0.04977200 W
PLW13        0.02438800 W

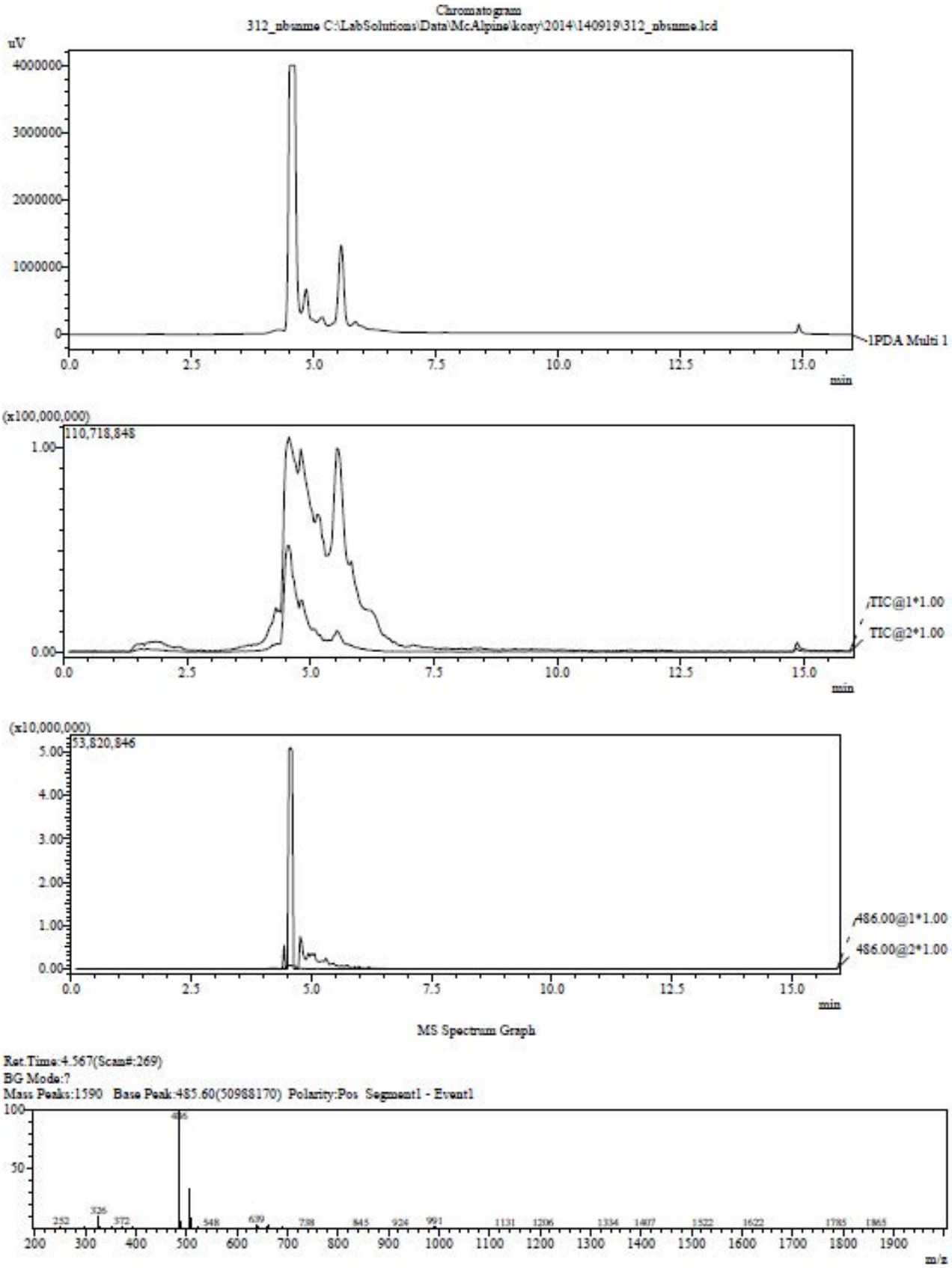
F2 - Processing parameters
SI                32768
SF          150.9103520 MHz
WDW                 no
SSB       0
LB        0 Hz
GB        0
PC              1.40
```

Compound **23**: LCMS of HO-Leu-3-(4-Thia)Ala-NH-*o*-NBS



Compound **23**: LCMS of HO-Leu-3-(4-Thia)Ala-NCH_3-*o*-NBS

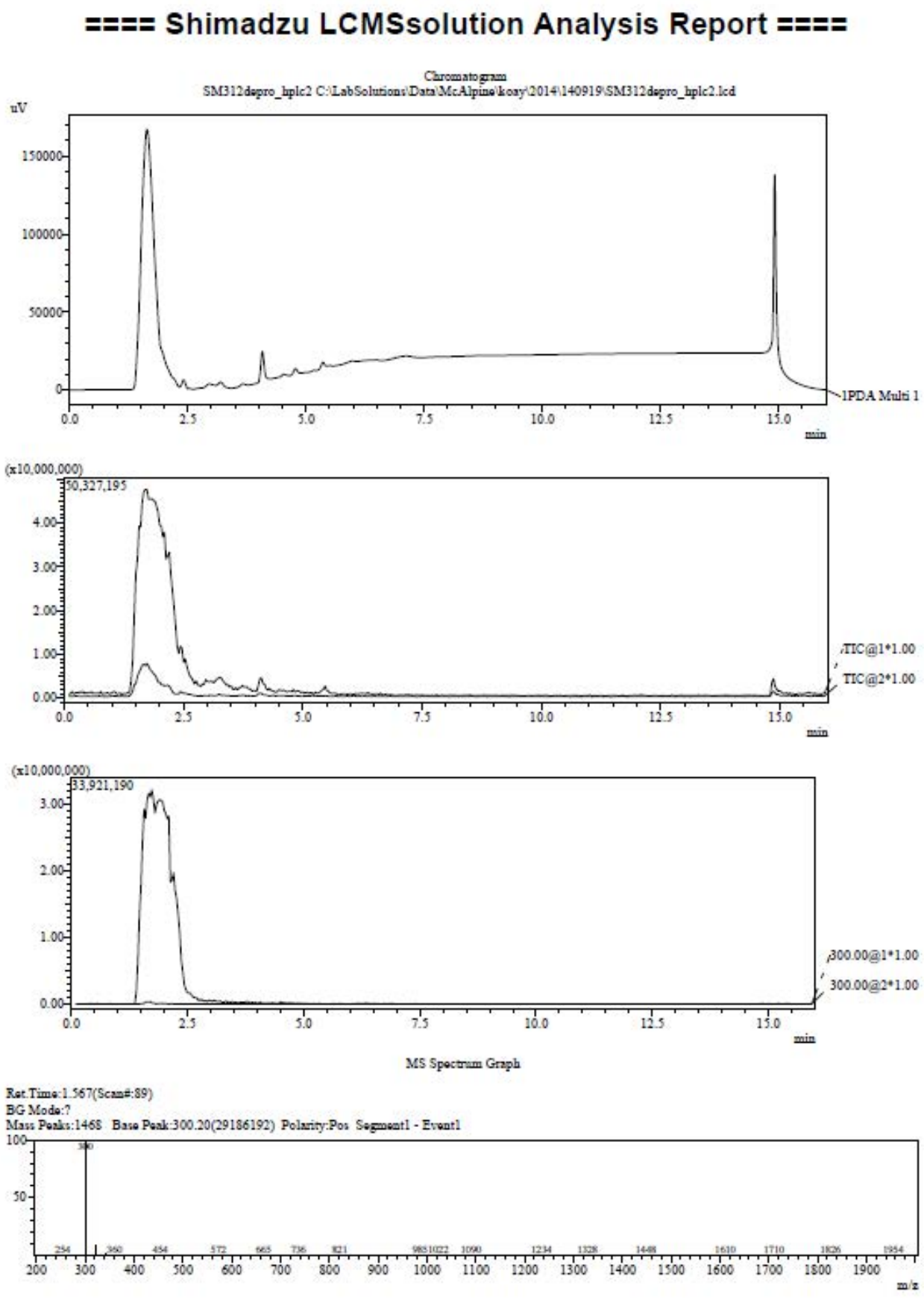
==== Shimadzu LCMSsolution Analysis Report ====



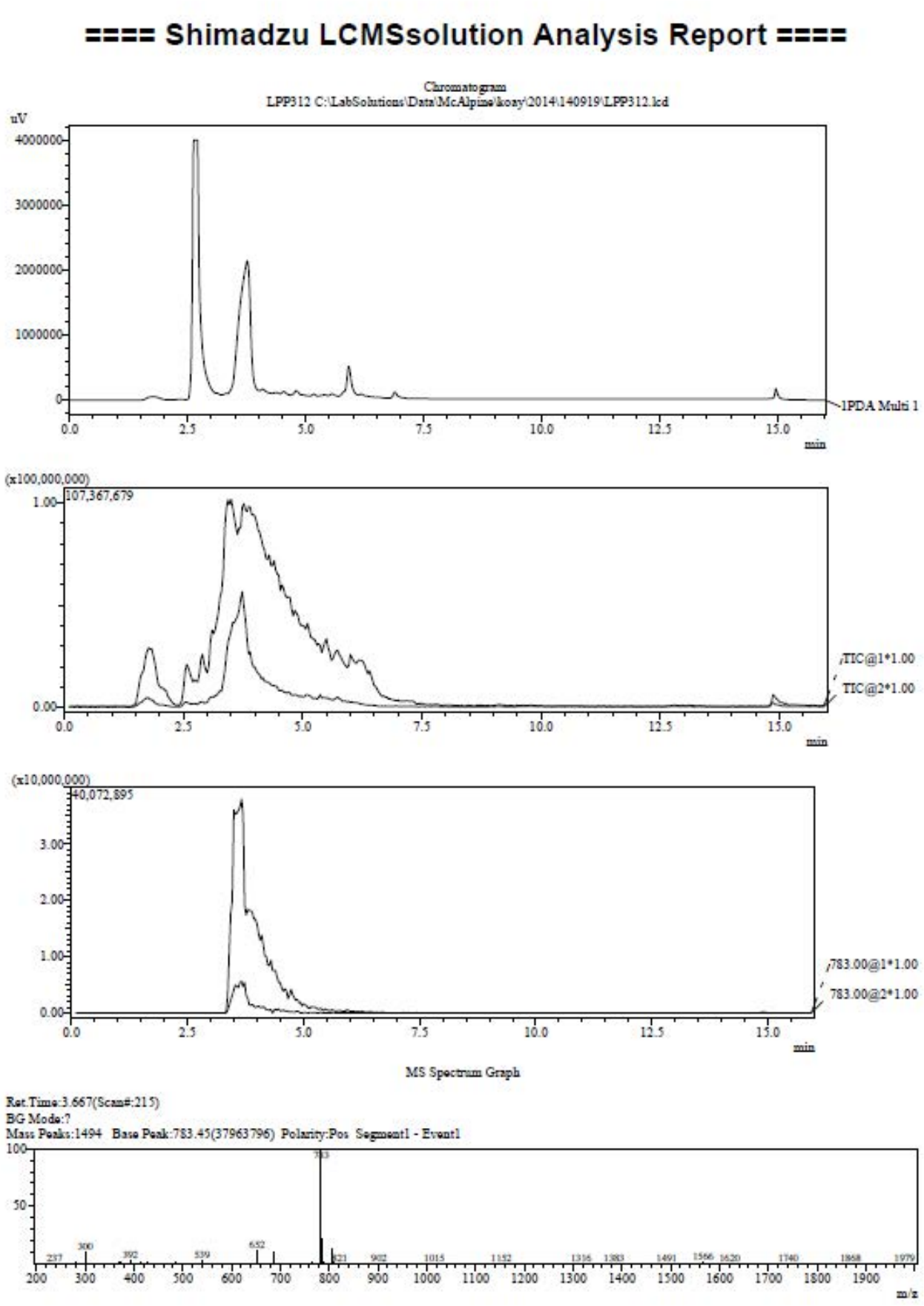
MS Spectrum Graph

Ret.Time:4.567(Scan#:269)
BG Mode:?
Mass Peaks:1590 Base Peak:485.60(50988170) Polarity:Pos Segment1 - Event1

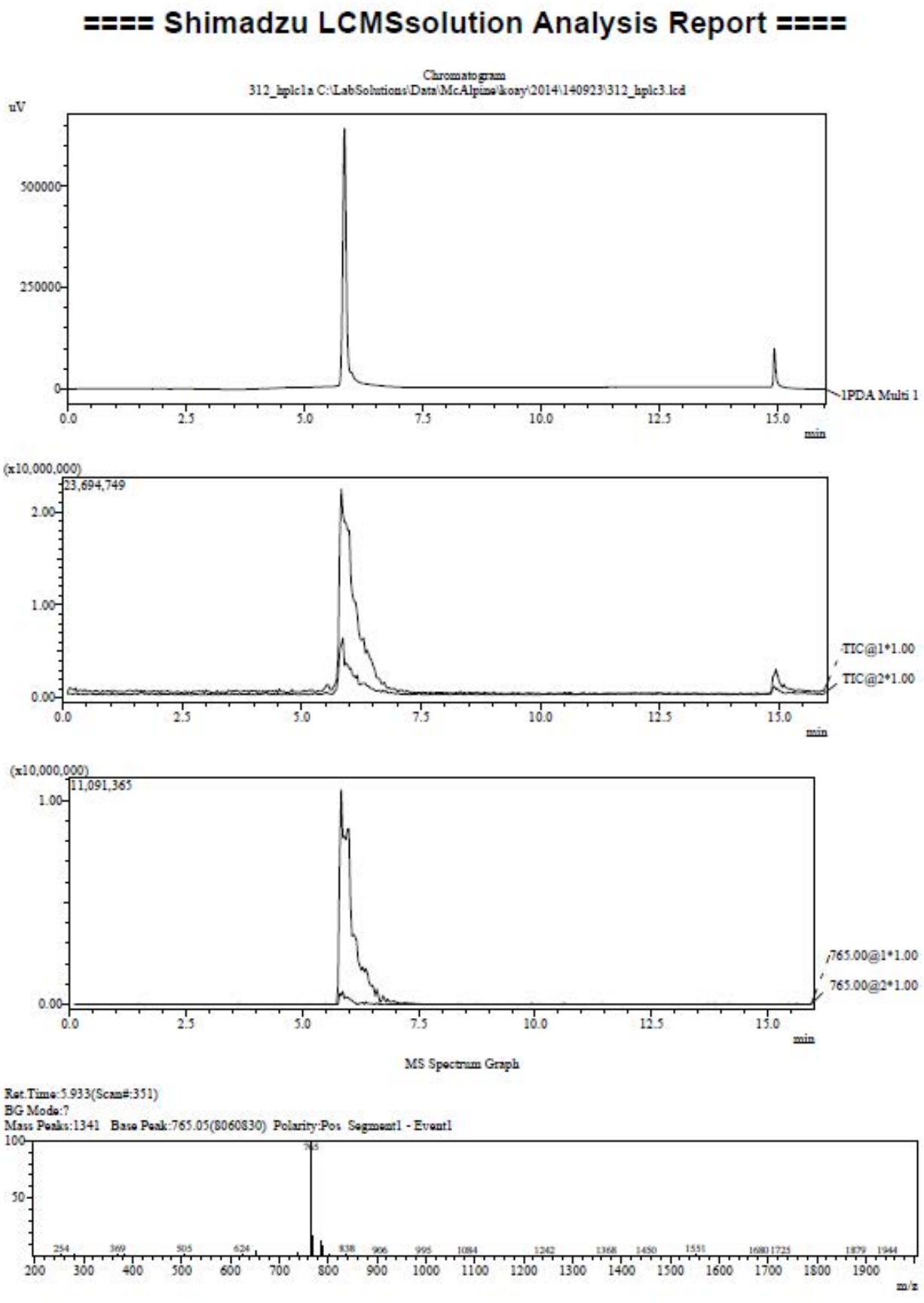
Compound **23**: LCMS of HO-Leu-3-(4-Thia)Ala-NH(CH_3)



Compound **23**: LCMS of DDLP HO-Leu-*N*-Me-3-(4-Thia)Ala-D-Leu-D-Phe-3,3-Diphe-D-Ala-NH_2



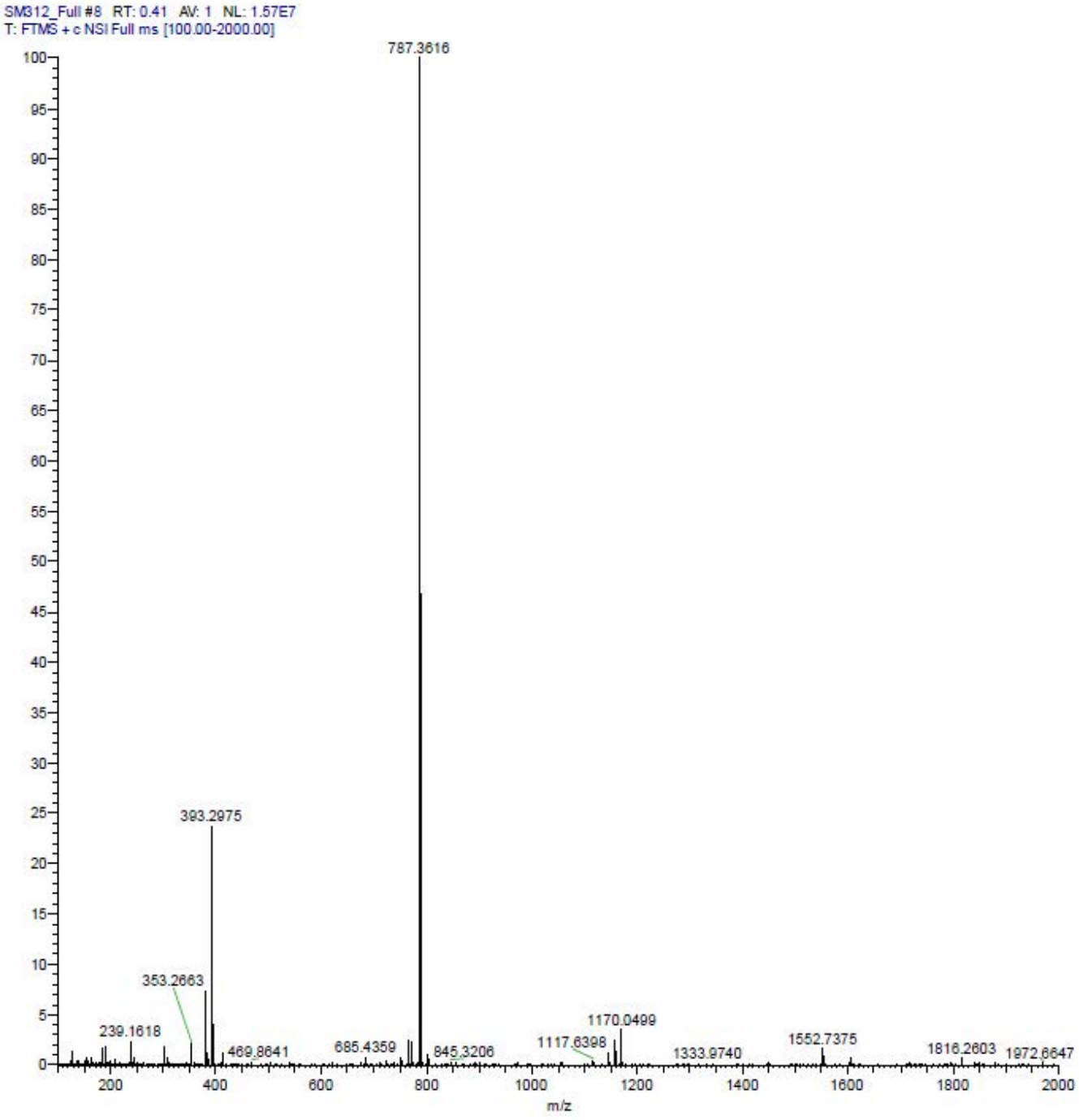
Compound **23**: LCMS of cyclo Leu-*N*-Me-3-(4-Thia)Ala-D-Leu-D-Phe-3,3-Diphe-D-Ala



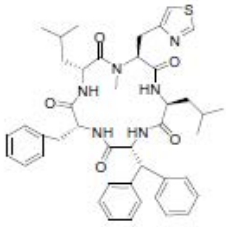
Compound **23**: HRMS of cyclo Leu-*N*-Me-3-(4-Thia)Ala-D-Leu-D-Phe-3,3-Diphe-D-Ala

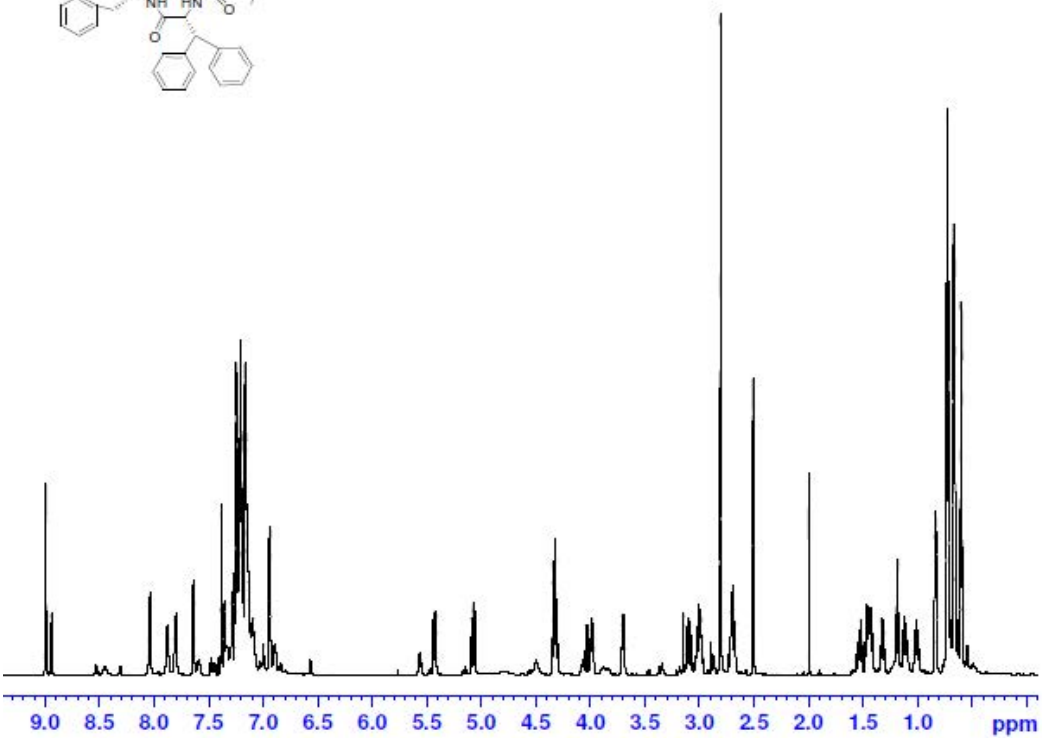
MS Data from Orbitrap

Full spectrum



Compound **23**: ^{1}HNMR of cyclo Leu-*N*-Me-3-(4-Thia)Ala-D-Leu-D-Phe-3,3-Diphe-D-Ala





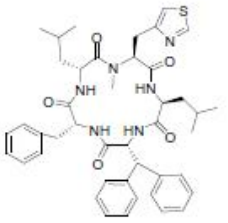

```
Current Data Parameters
NAME      140927_yckSM312
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_           20140927
Time                7.41
INSTRUM            spect
PROBHD   5 mm CPTCI 1H/
PULPROG             zgpr
TD                 48076
SOLVENT             DMSO
NS                    12
DS                     4
SWH             9009.009 Hz
FIDRES          0.187391 Hz
AQ              2.6682179 sec
RG                 16.27
DW                55.500 usec
DE                33.22 usec
TE                298.0 K
D1           20.00000000 sec
D12           0.00002000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         600.1620038 MHz
NUC1                   1H
P1                   8.00 usec
PLW1          3.81069994 W
PLW9          0.00000097 W

F2 - Processing parameters
SI                131072
SF          600.1600000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

Compound **23**: ^{13}CNMR of cyclo Leu-*N*-Me-3-(4-Thia)Ala-D-Leu-D-Phe-3,3-Diphe-D-Ala




```
Current Data Parameters
NAME      140927_yckSM312
EXPNO                   3
PROCNO                  1

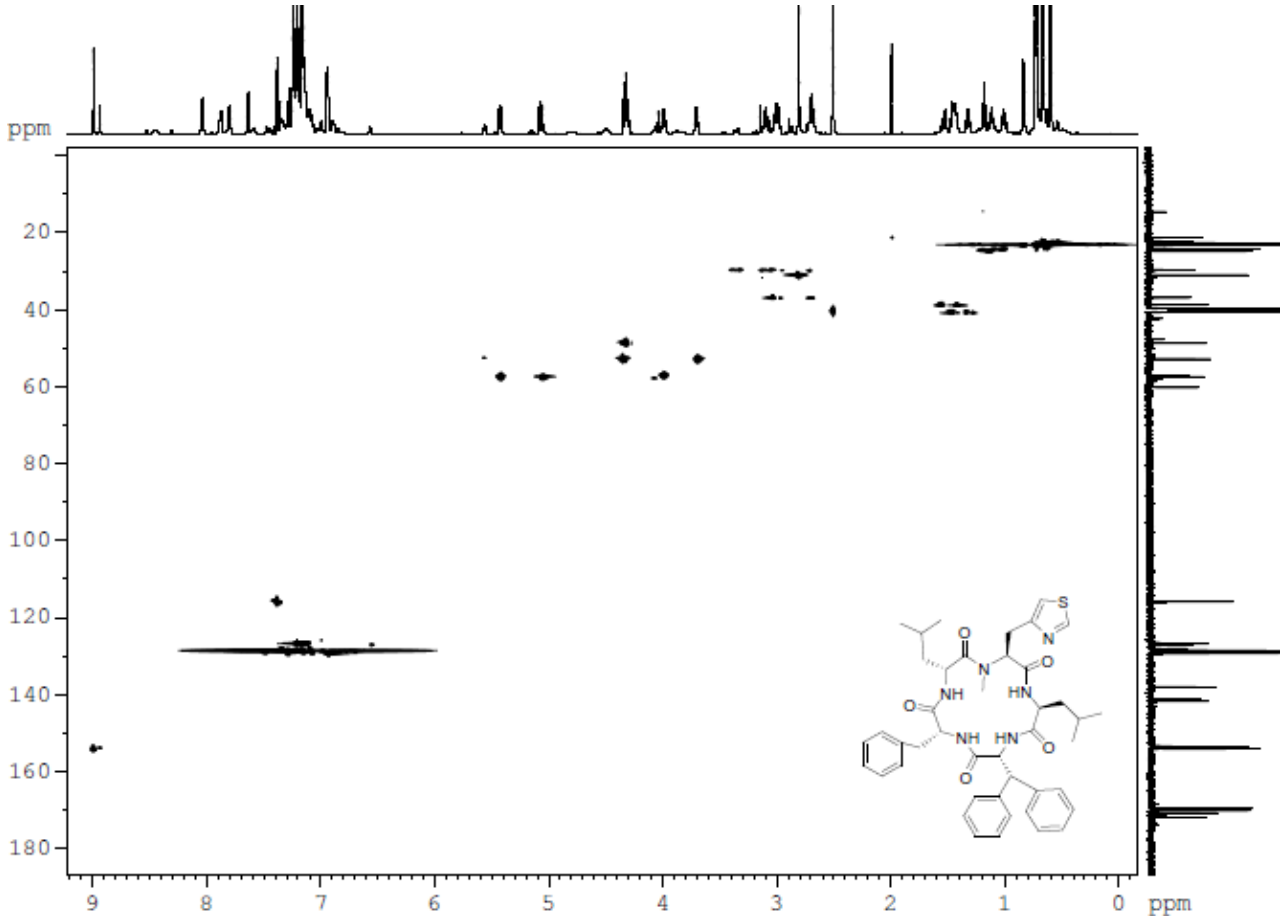
F2 - Acquisition Parameters
Date_           20140927
Time                8.46
INSTRUM            spect
PROBHD   5 mm CPTCI 1H/
PULPROG          zgpg30
TD                 65536
SOLVENT             DMSO
NS                  1024
DS                     4
SWH            33333.332 Hz
FIDRES          0.508626 Hz
AQ              0.9830400 sec
RG                202.23
DW                15.000 usec
DE                 15.55 usec
TE                298.0 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         150.9254430 MHz
NUC1                   13C
P1                  11.50 usec
PLW1        100.00000000 W

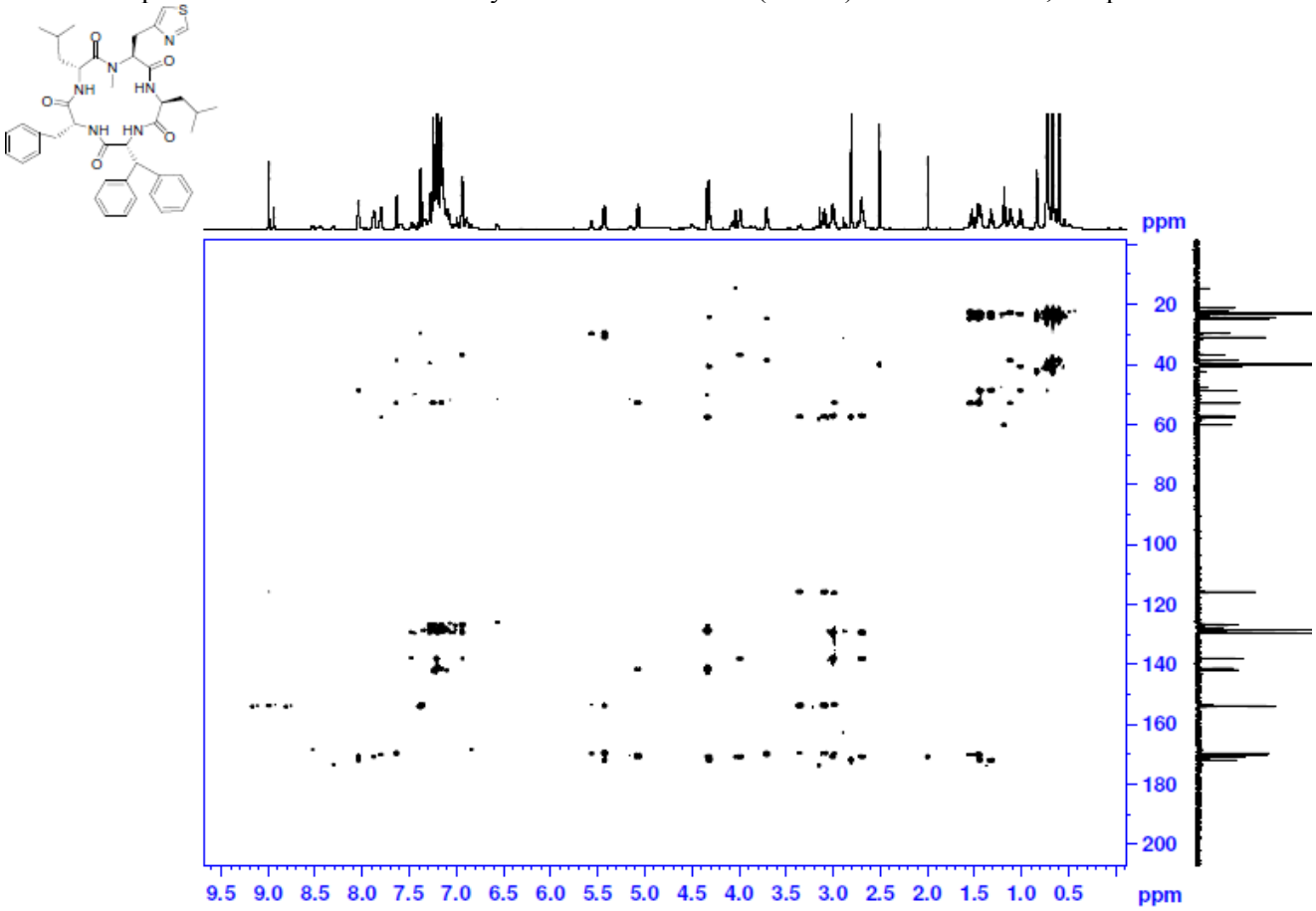
======== CHANNEL f2 ========
SFO2         600.1624006 MHz
NUC2                   1H
CPDPRG[2 bi_waltz65_256
PCPD2                70.00 usec
PLW2          3.81069994 W
PLW12         0.04977200 W
PLW13         0.02438800 W

F2 - Processing parameters
SI                 32768
SF          150.9103520 MHz
WDW                   no
SSB       0
LB        0 Hz
GB        0
PC                 1.40
```

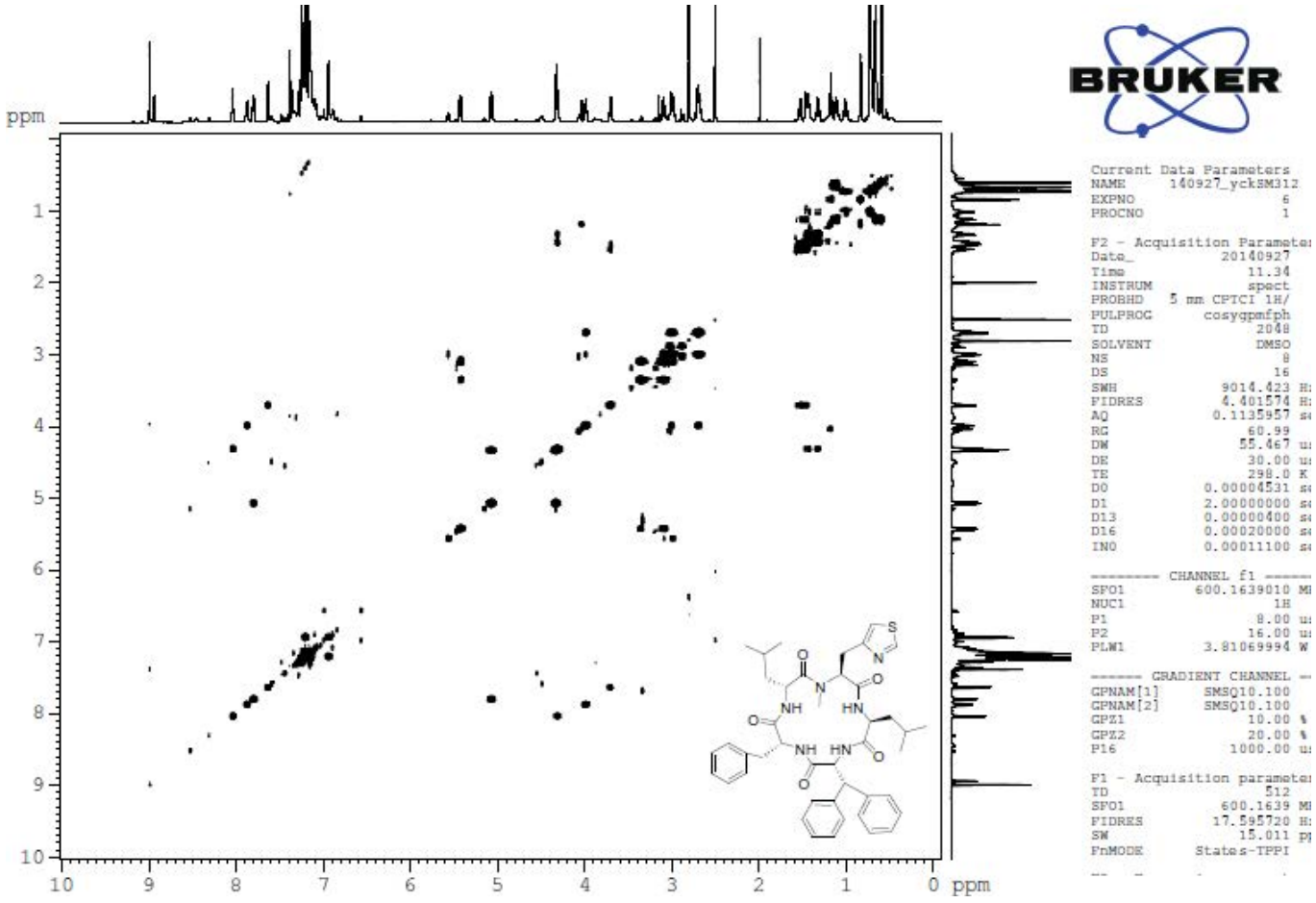
Compound **23**: ^{1}H-^{13}C HSQC of cyclo Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala



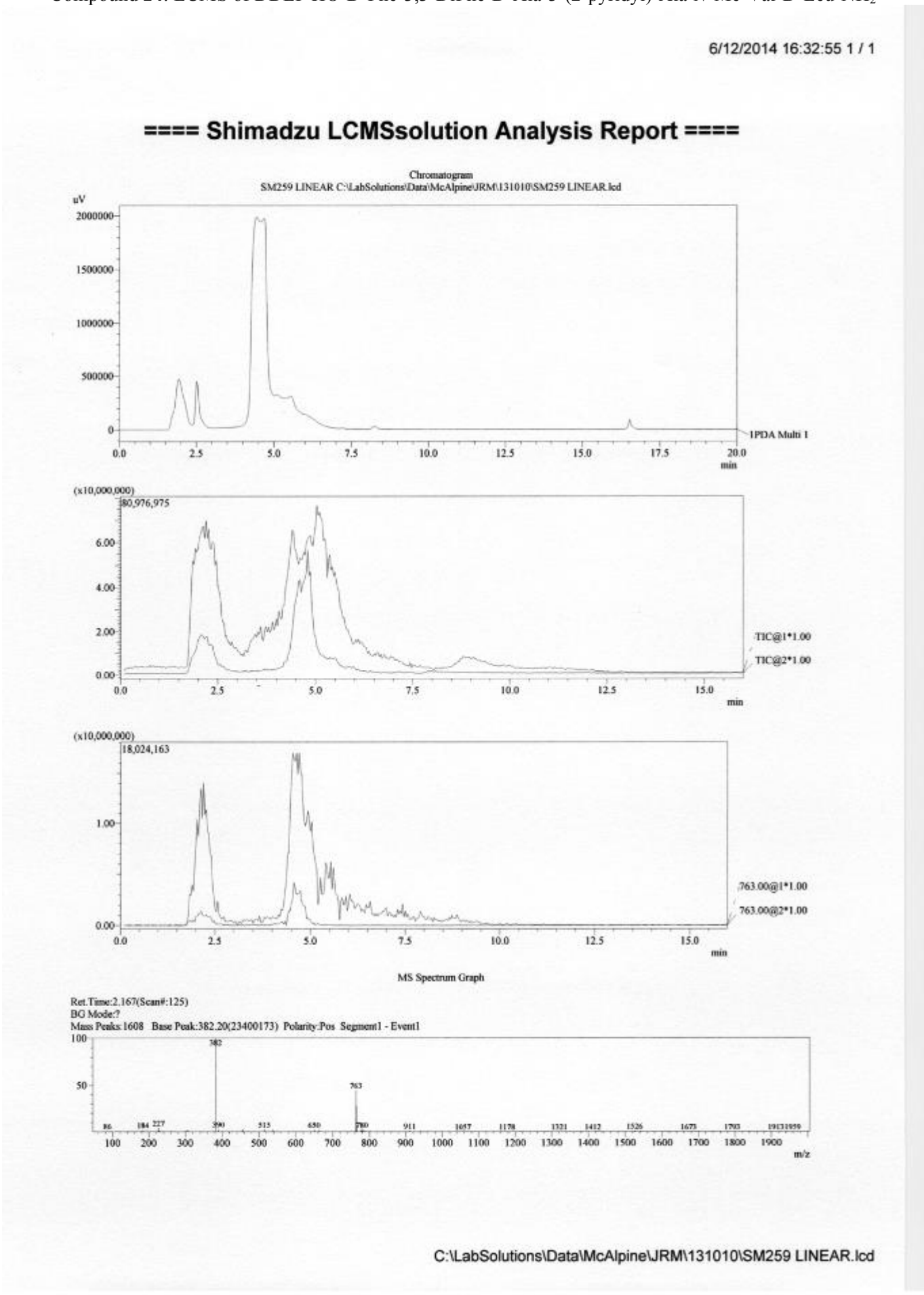
Compound **23**: ^{1}H-^{13}C HMBC of cyclo Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala



Compound **23**: ^{1}H-^{1}H COSY of cyclo Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala

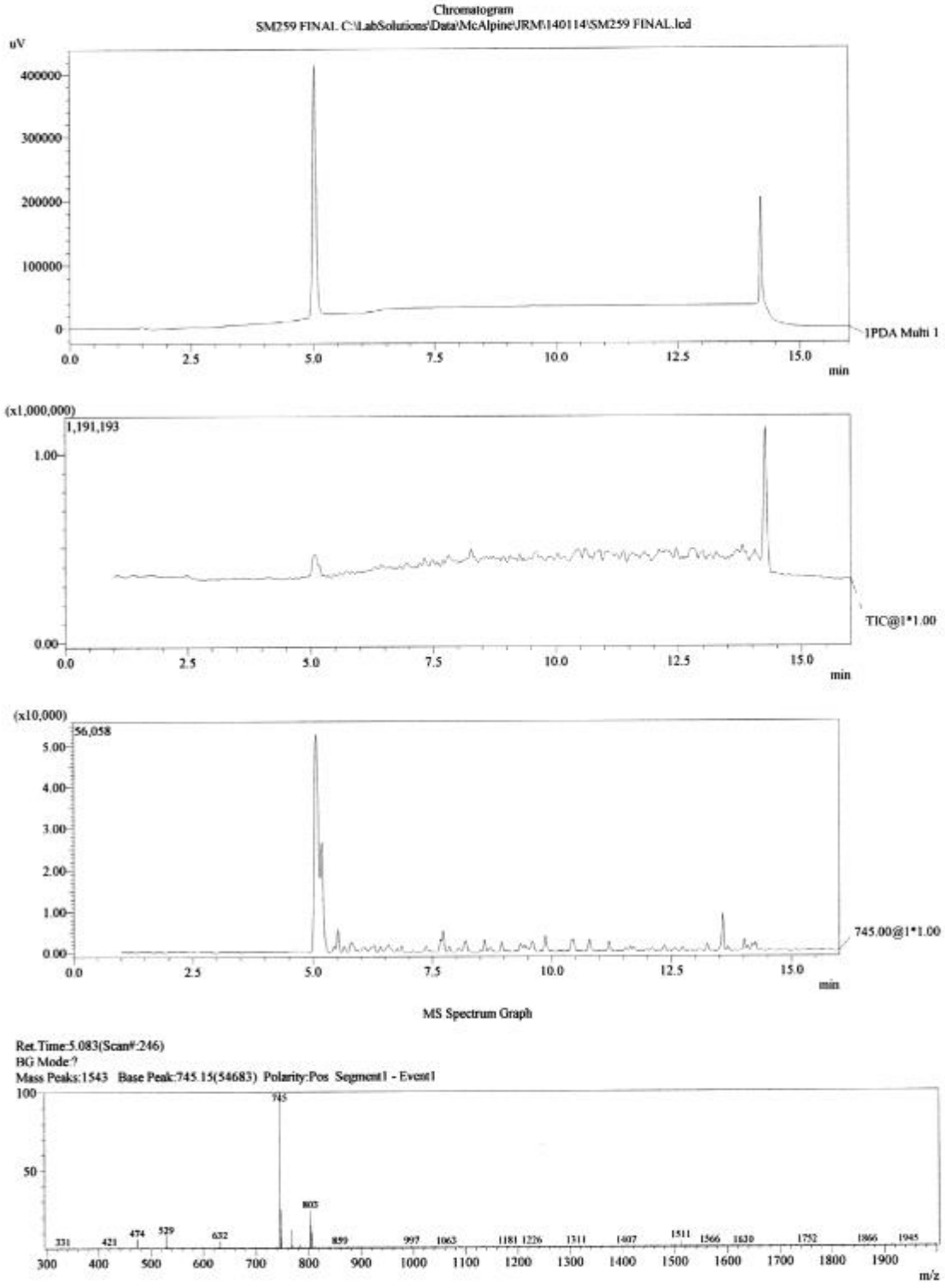


Compound **24**: LCMS of DDLP HO-D-Phe-3,3-DiPhe-D-Ala-3-(2-pyridyl)-Ala-*N*-Me-Val-D-Leu-NH_2



Compound **24**: LCMS *cyclo* D-Phe-3,3-DiPhe-D-Ala-3-(2-pyridyl)-Ala-*N*-Me-Val-D-Leu

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



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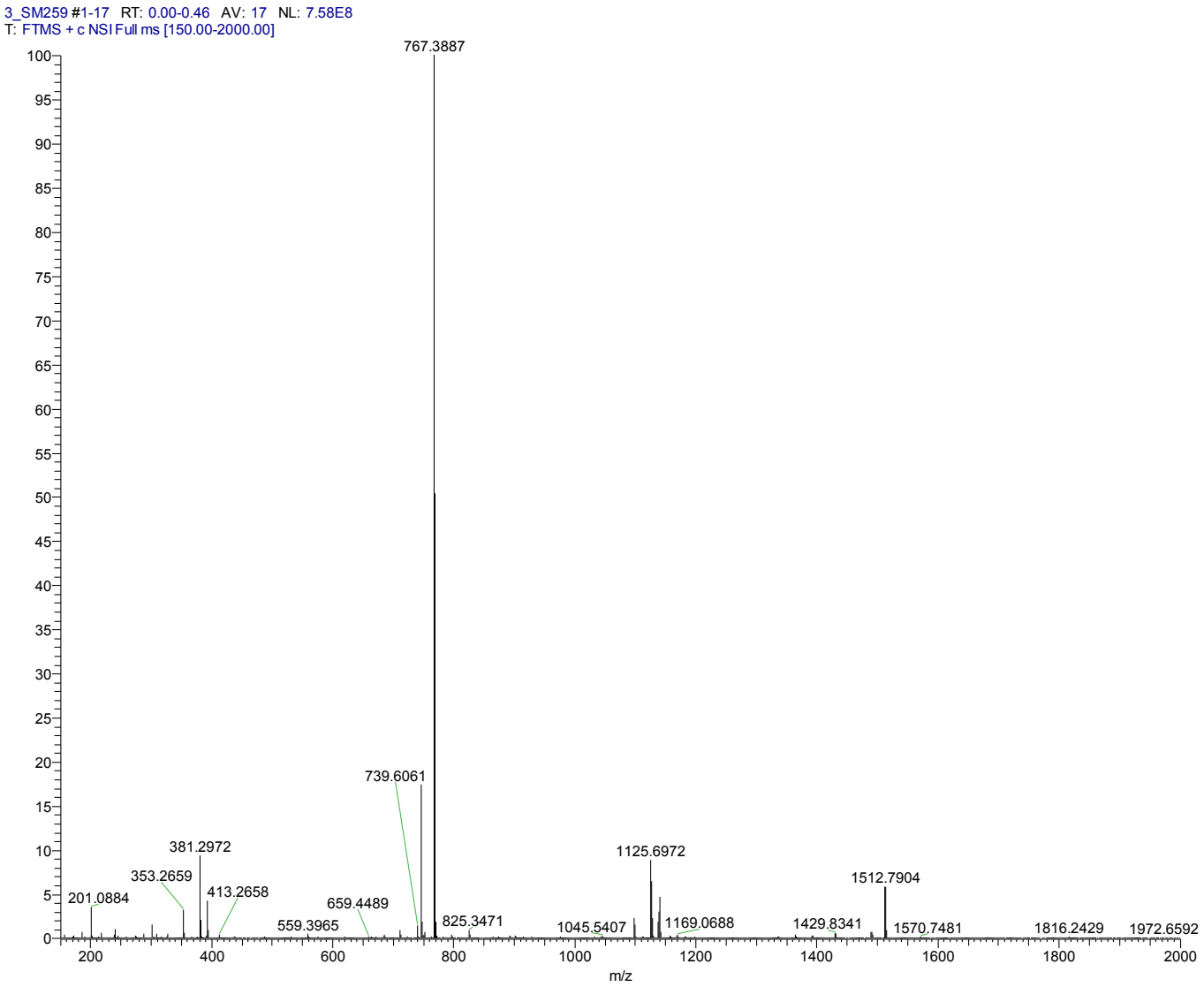
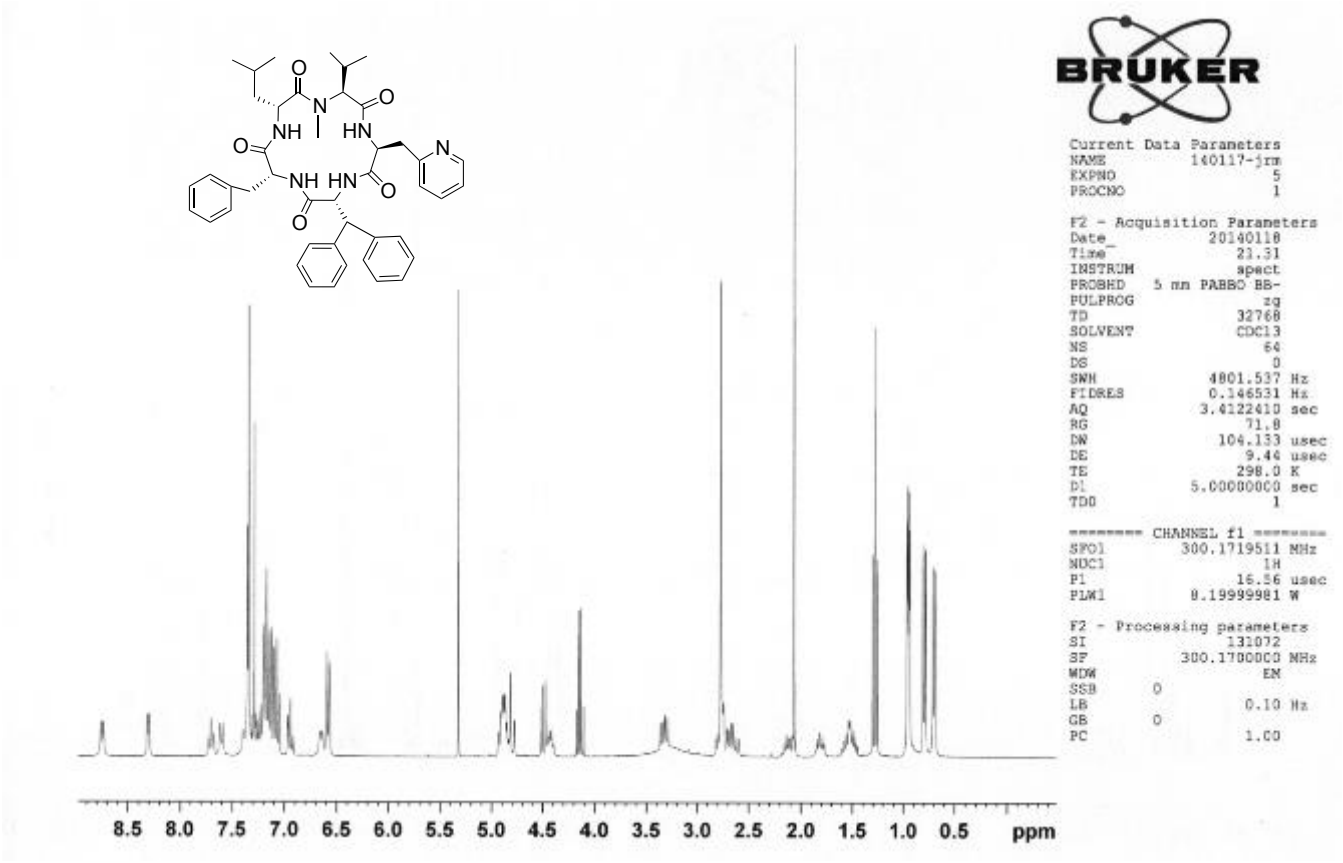
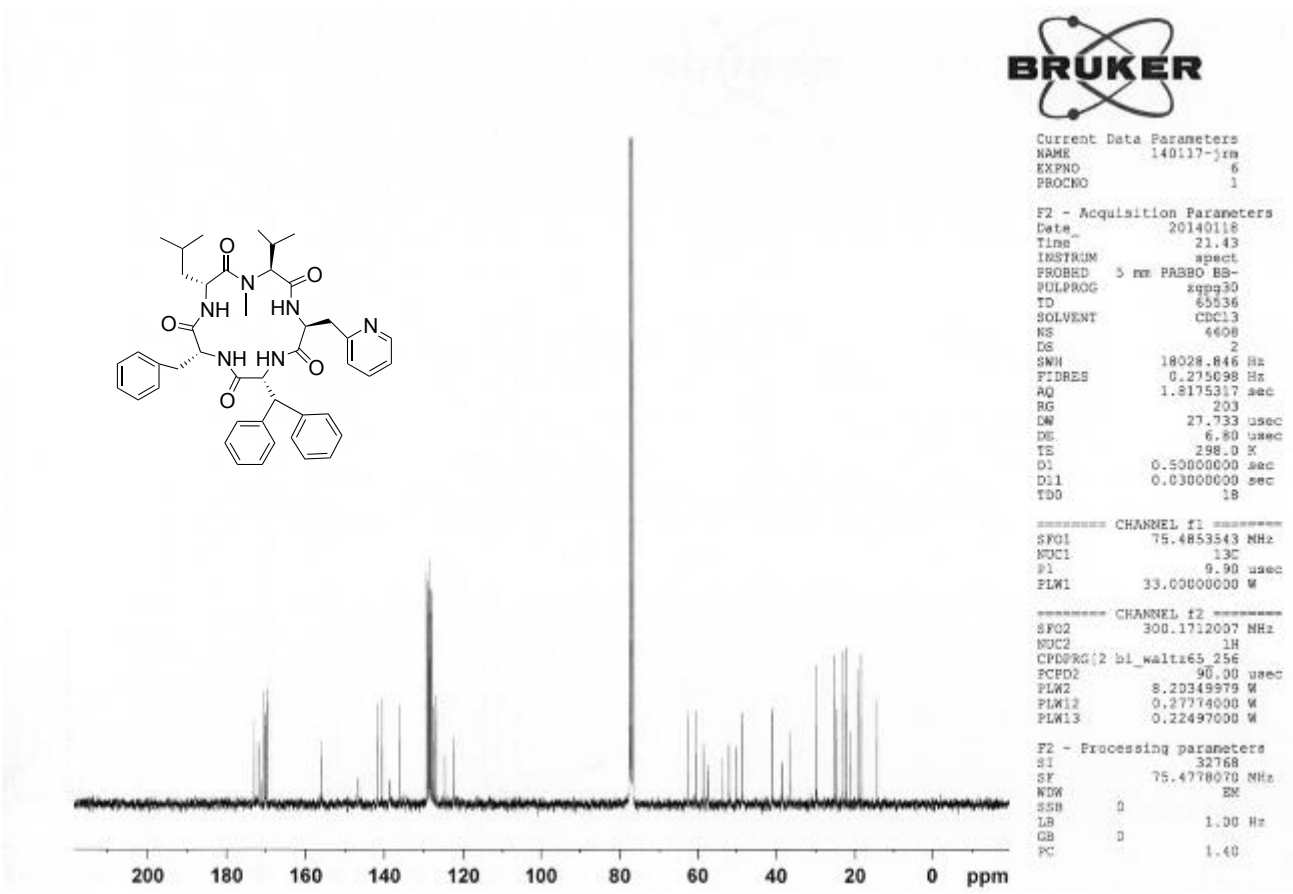
Compound **24**: HRMS of *cyclo* D-Phe-3,3-DiPhe-D-Ala-3-(2-pyridyl)-Ala-*N*-Me-Val-D-Leu



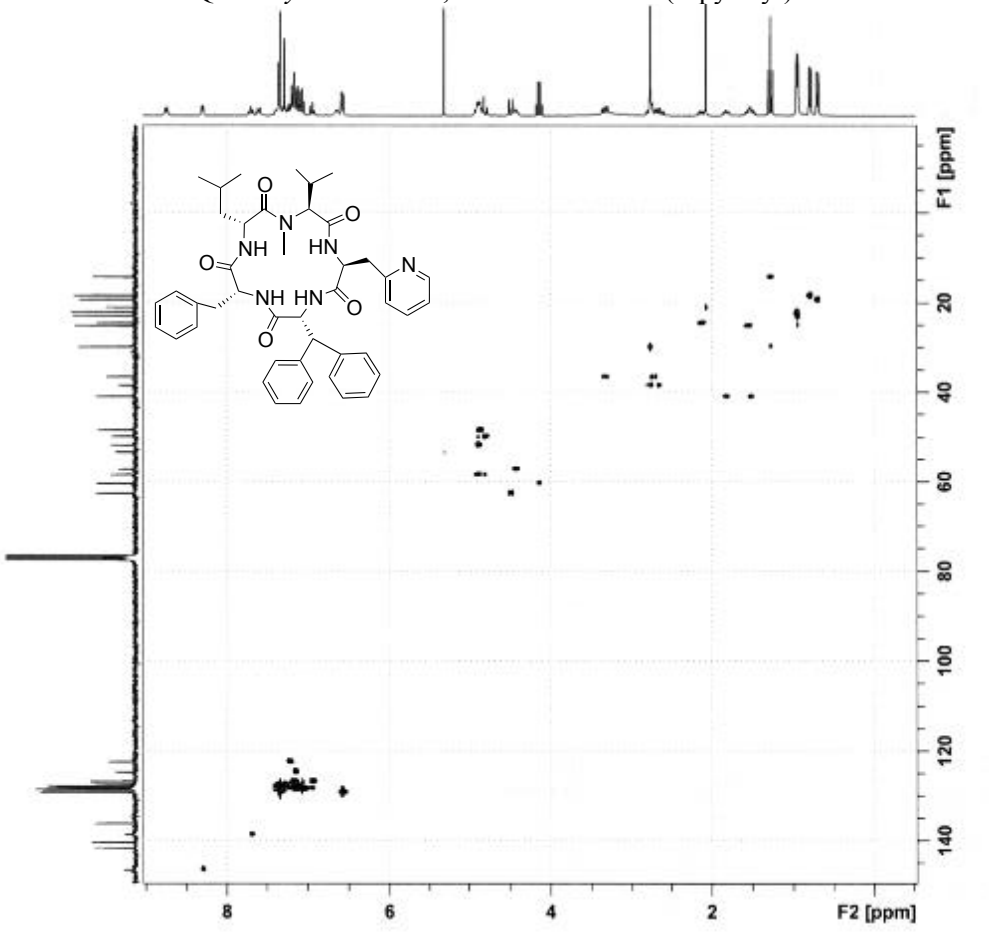
Compound **24**: ^{1}HNMR of *cyclo* D-Phe-3,3-DiPhe-D-Ala-3-(2-pyridyl)-Ala-*N*-Me-Val-D-Leu



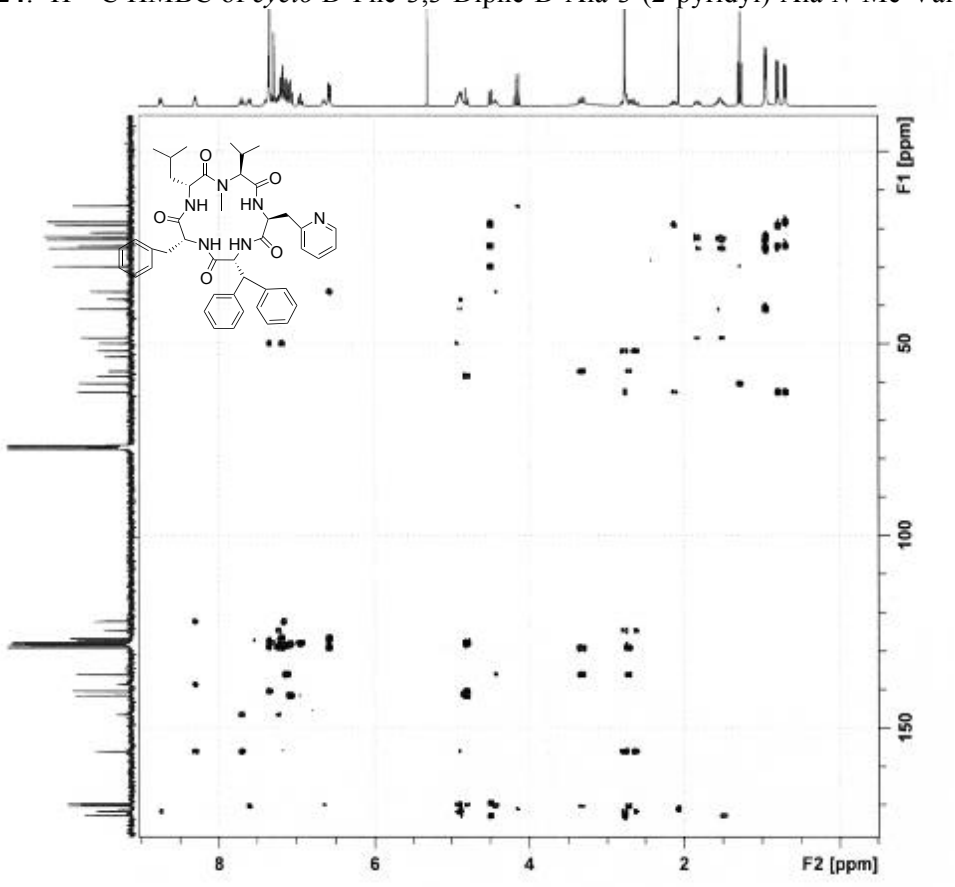
Compound **24**: ^{1}H-^{13}C HSQC of *cyclo* D-Phe-3,3-DiPhe-D-Ala-3-(2-pyridyl)-Ala-*N*-Me-Val-D-Leu



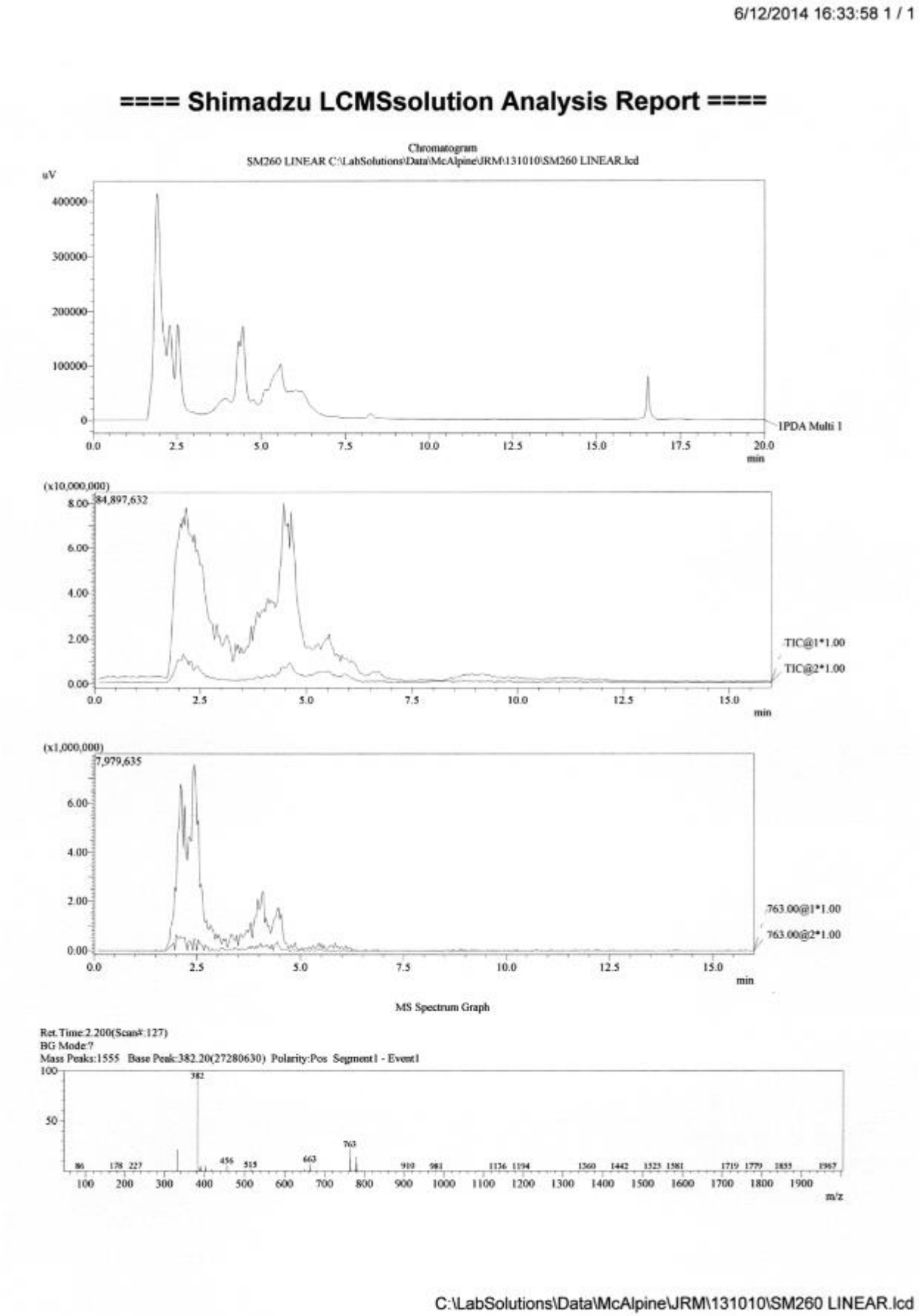
Compound **24**: ^{1}H-^{13}C HSQC of *cyclo* D-Phe-3,3-DiPhe-D-Ala-3-(2-pyridyl)-Ala-*N*-Me-Val-D-Leu



Compound **24**: ^{1}H-^{13}C HMBC of *cyclo* D-Phe-3,3-Diphe-D-Ala-3-(2-pyridyl)-Ala-*N*-Me-Val-D-Leu

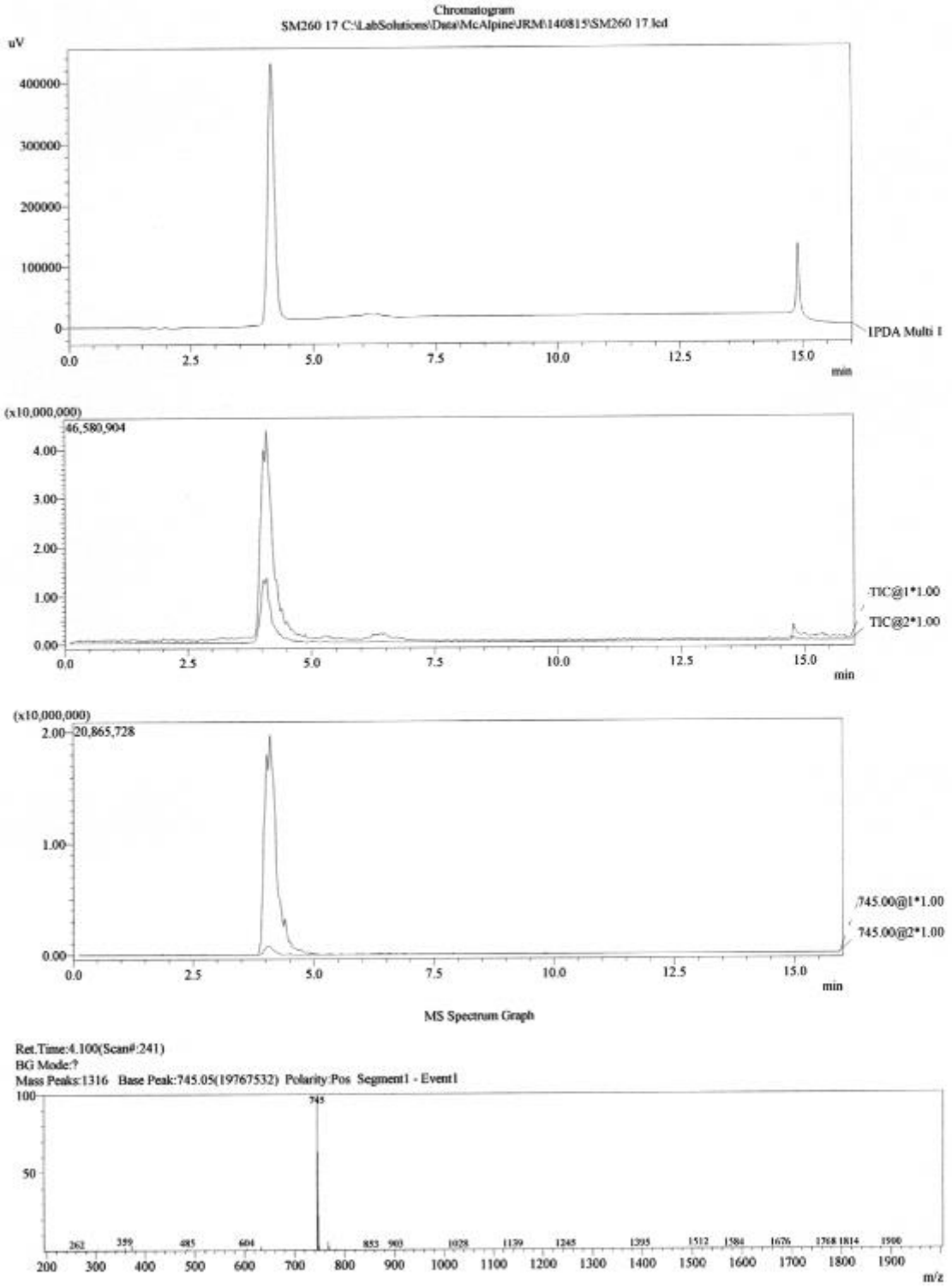


Compound **25**: LCMS of DDLP HO-D-Phe-3,3-DiPhe-D-Ala-3-(3-pyridyl)-Ala-*N*-Me-Val-D-Leu-NH_2



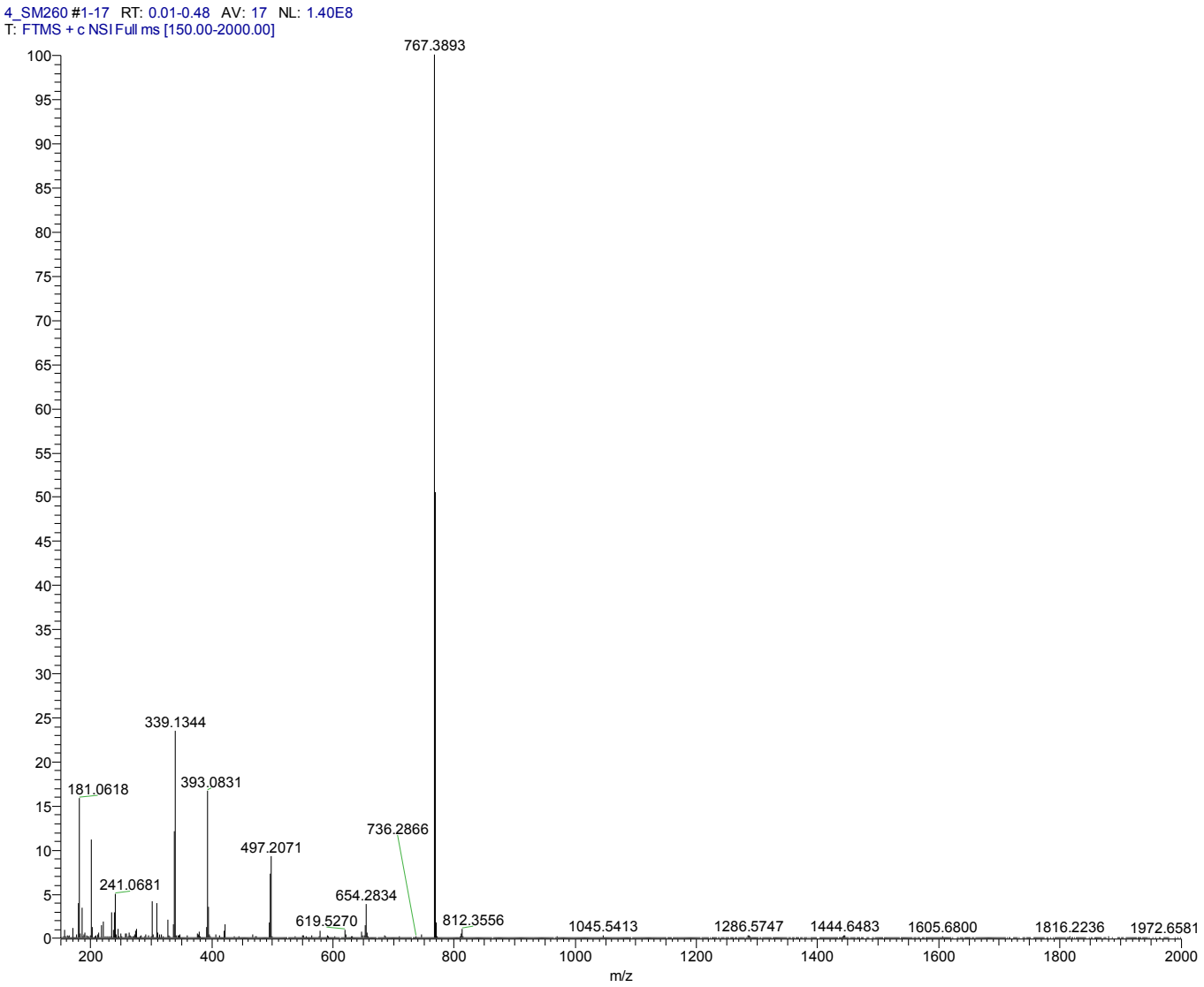
Compound **25**: LCMS *cyclo* D-Phe-3,3-DiPhe-D-Ala-3-(3-pyridyl)-Ala-*N*-Me-Val-D-Leu

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

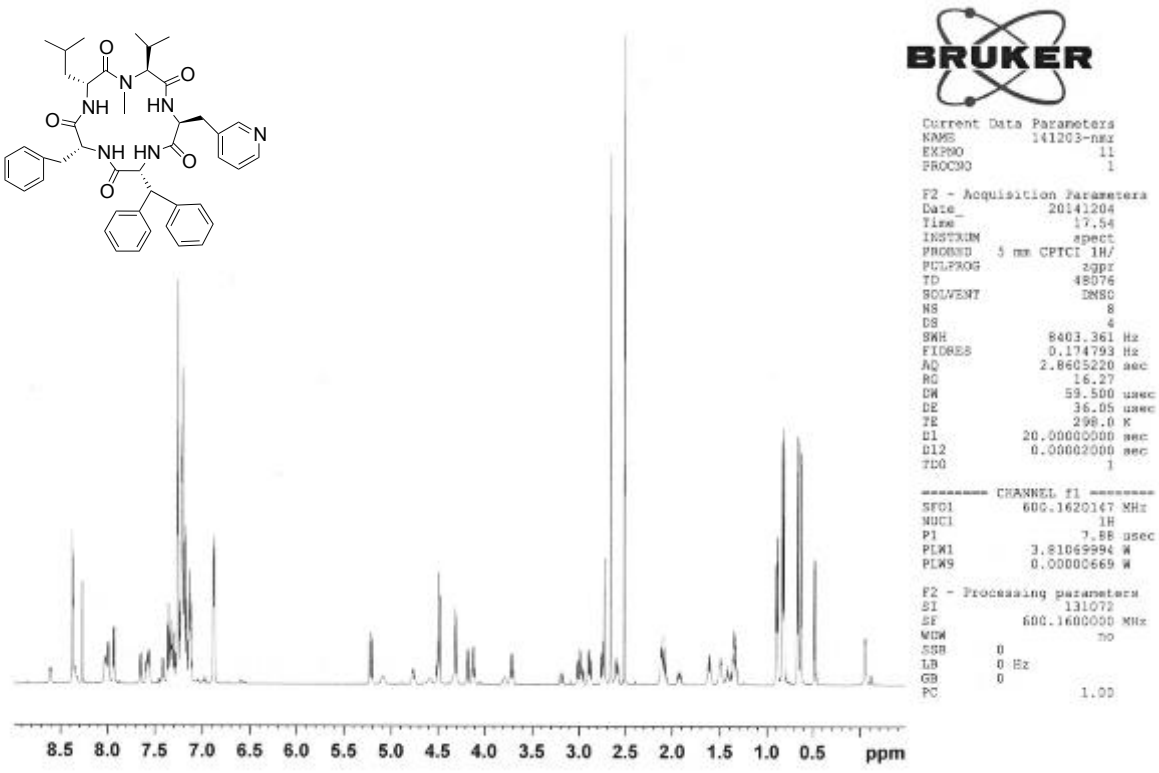


C:\LabSolutions\Data\McAlpine\JRM\140815\SM260 17.lcd

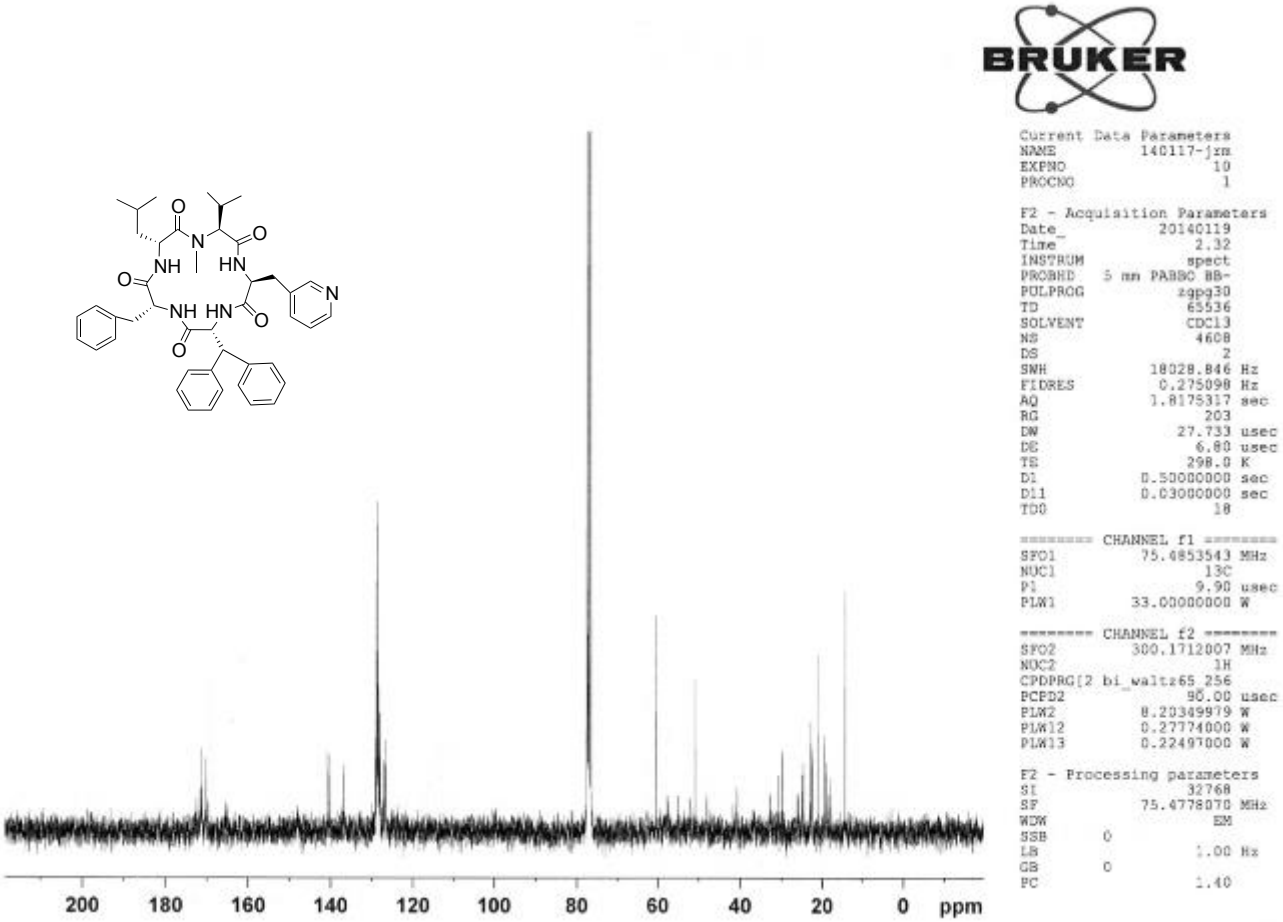
Compound **25**: HRMS of *cyclo* D-Phe-3,3-DiPhe-D-Ala-3-(3-pyridyl)-Ala-*N*-Me-Val-D-Leu



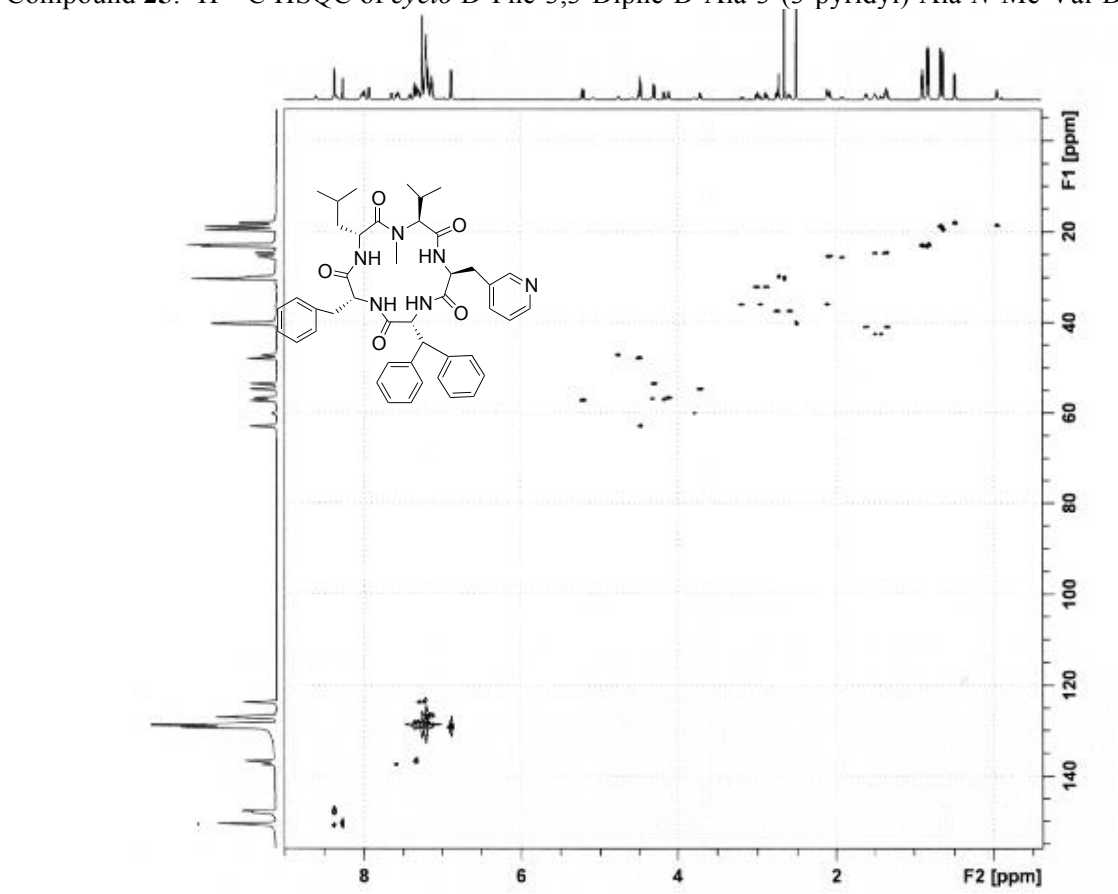
Compound **25**: ^{1}HNMR of *cyclo* D-Phe-3,3-DiPhe-D-Ala-3-(3-pyridyl)-Ala-*N*-Me-Val-D-Leu



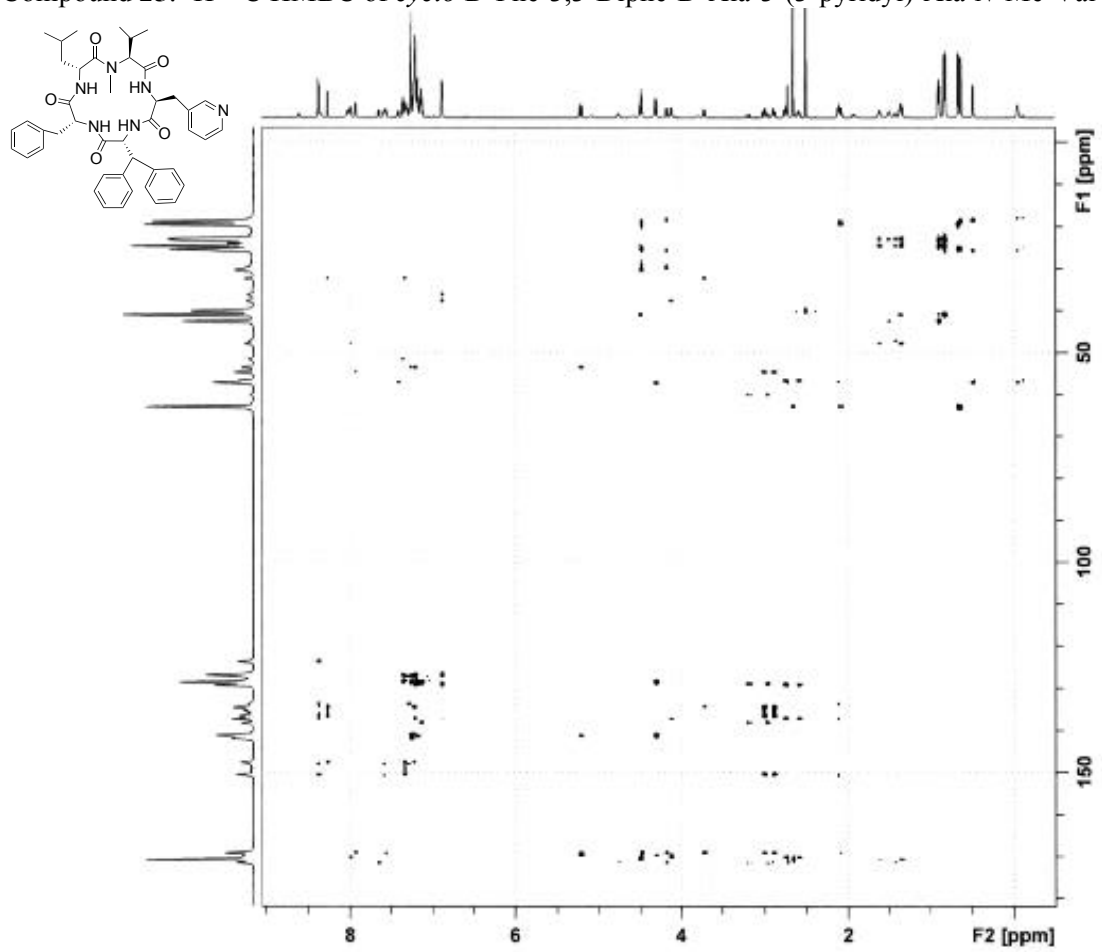
Compound **25**: ^{13}C NMR of *cyclo* D-Phe-3,3-DiPhe-D-Ala-3-(3-pyridyl)-Ala-*N*-Me-Val-D-Leu



Compound **25**: ^{1}H-^{13}C HSQC of *cyclo* D-Phe-3,3-Diphe-D-Ala-3-(3-pyridyl)-Ala-*N*-Me-Val-D-Leu

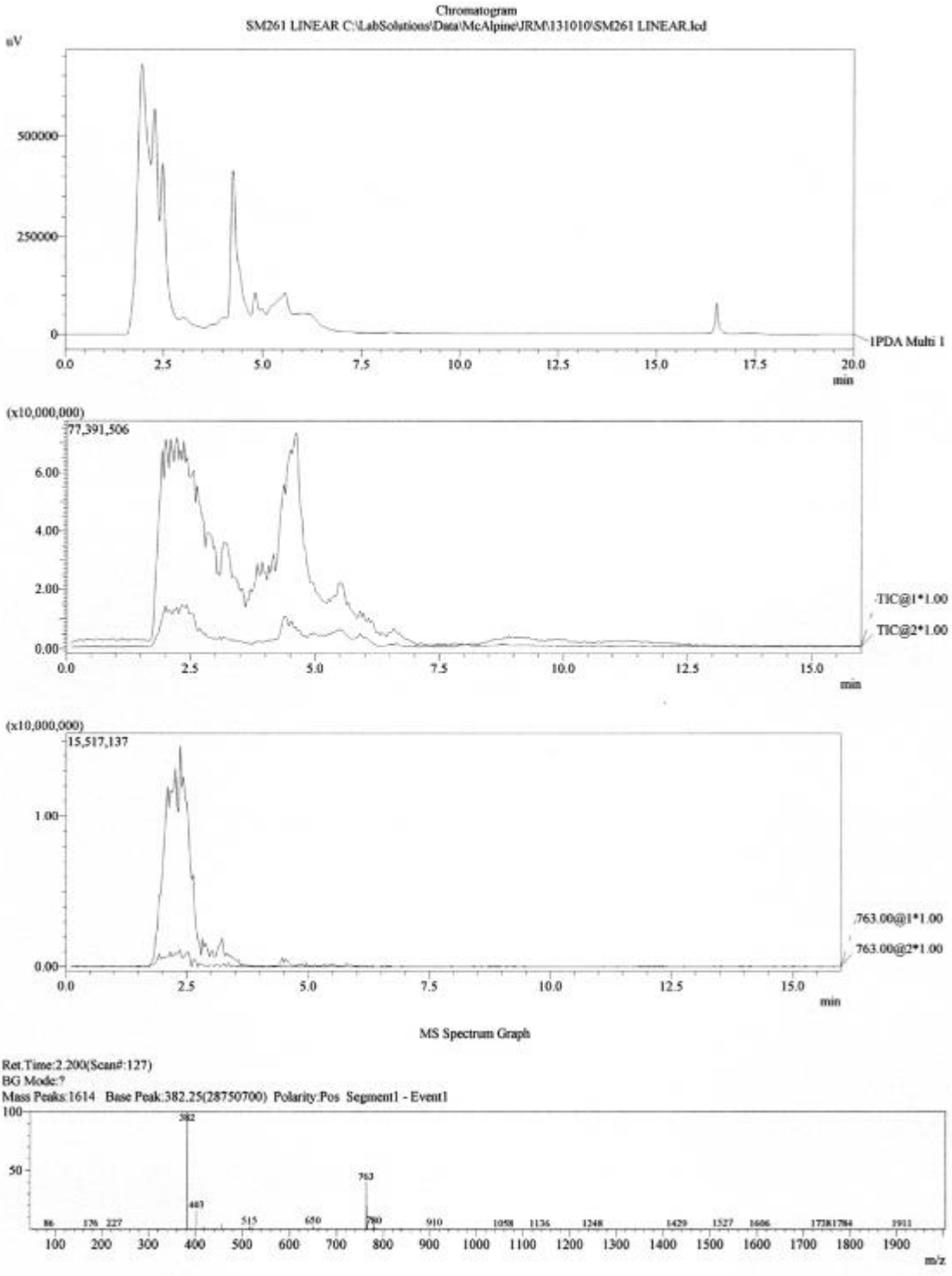


Compound **25**: ^{1}H-^{13}C HMBC of *cyclo* D-Phe-3,3-Diphe-D-Ala-3-(3-pyridyl)-Ala-*N*-Me-Val-D-Leu



Compound **26**: LCMS of DDLP HO-D-Phe-3,3-DiPhe-D-Ala-3-(4-pyridyl)-Ala-*N*-Me-Val-D-Leu-NH_2

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



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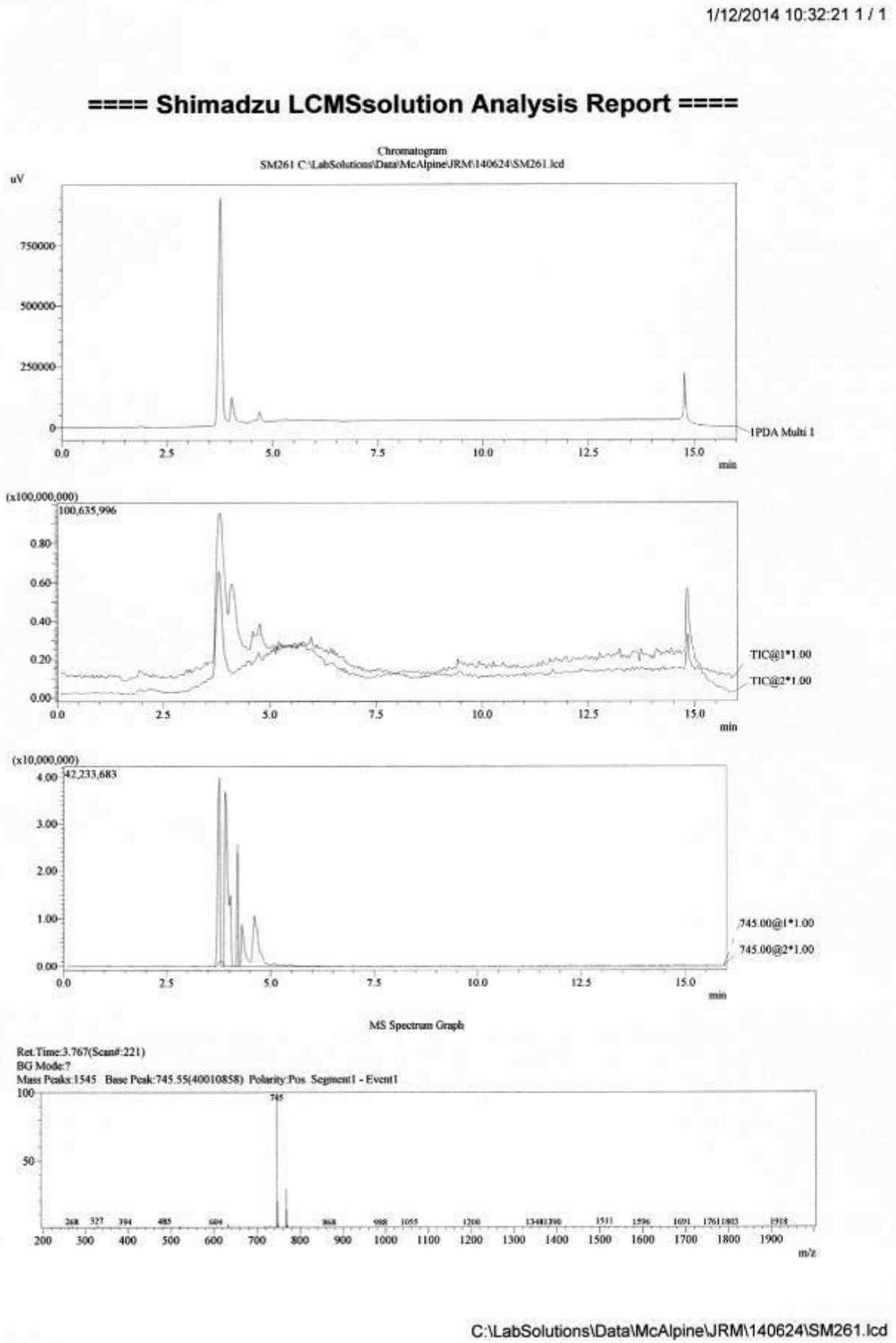
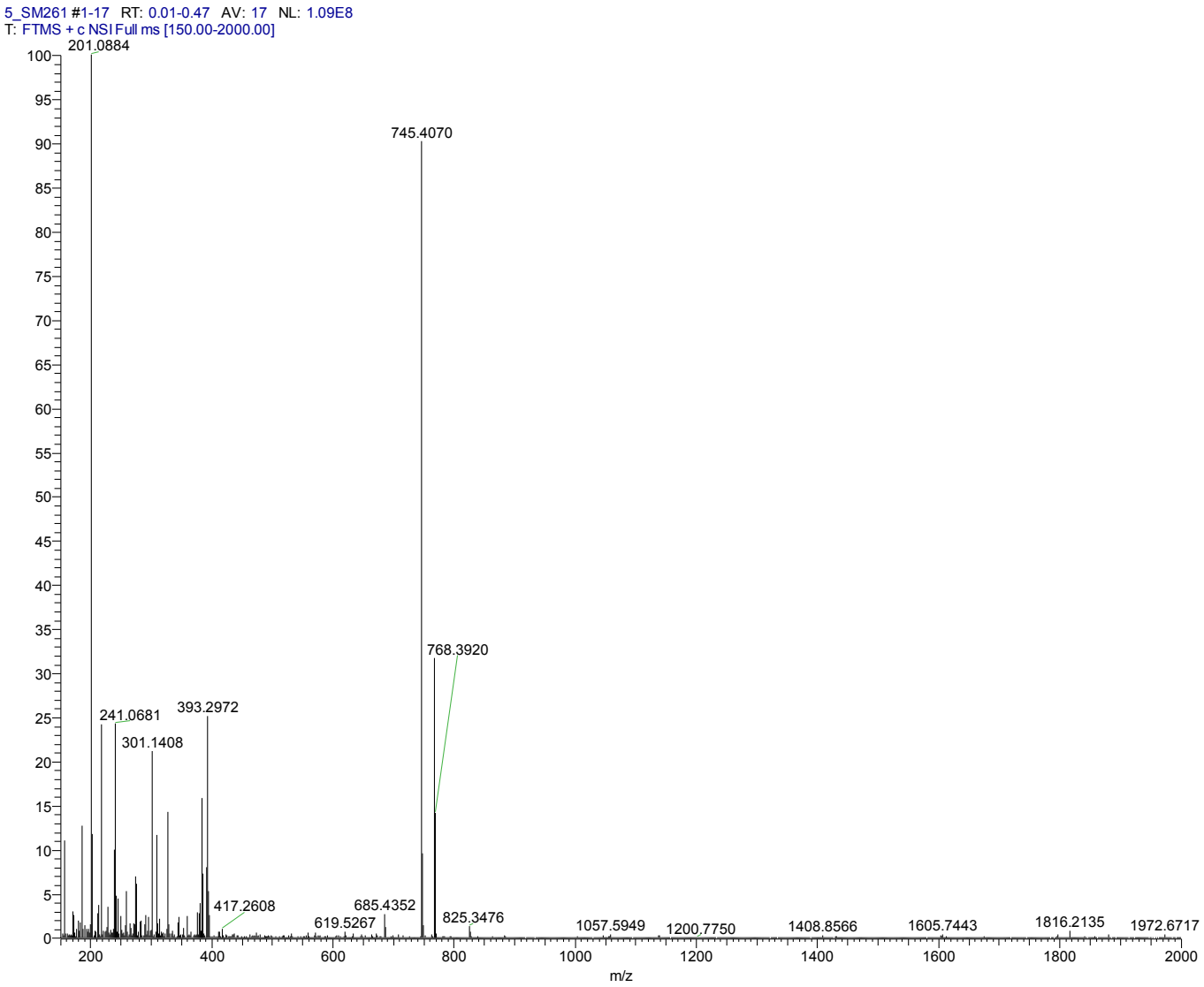
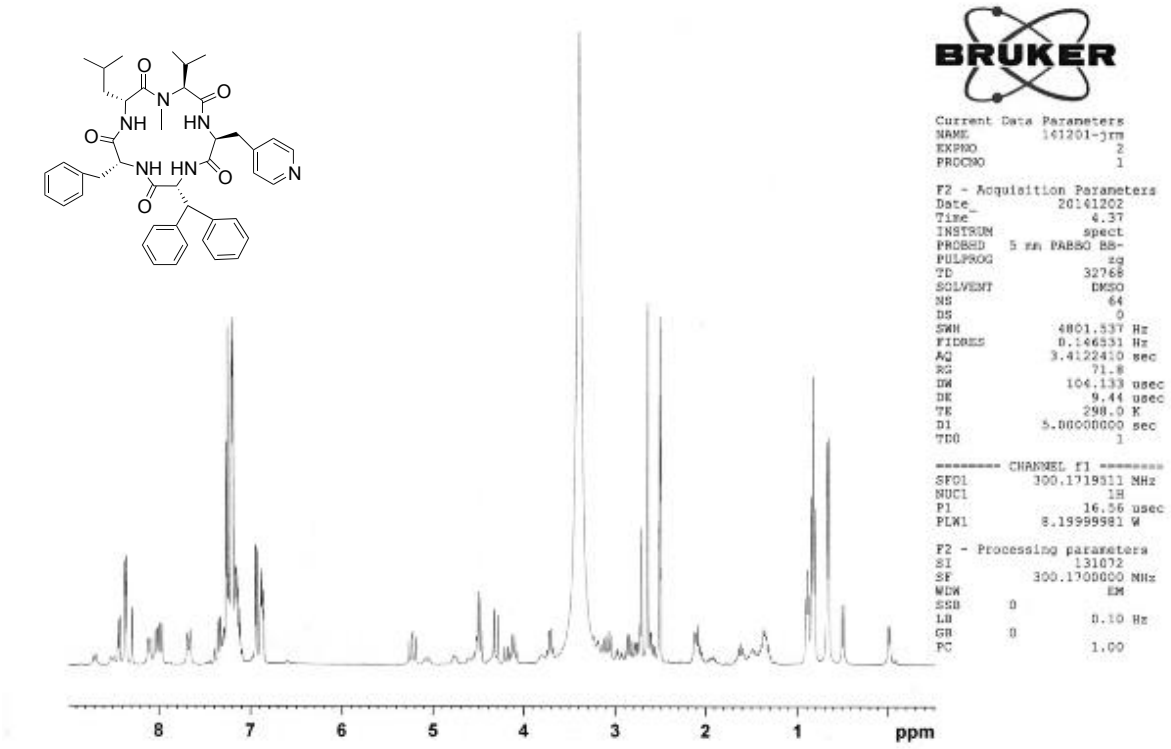
Compound **26**: LCMS *cyclo* D-Phe-3,3-DiPhe-D-Ala-3-(4-pyridyl)-Ala-*N*-Me-Val-D-Leu



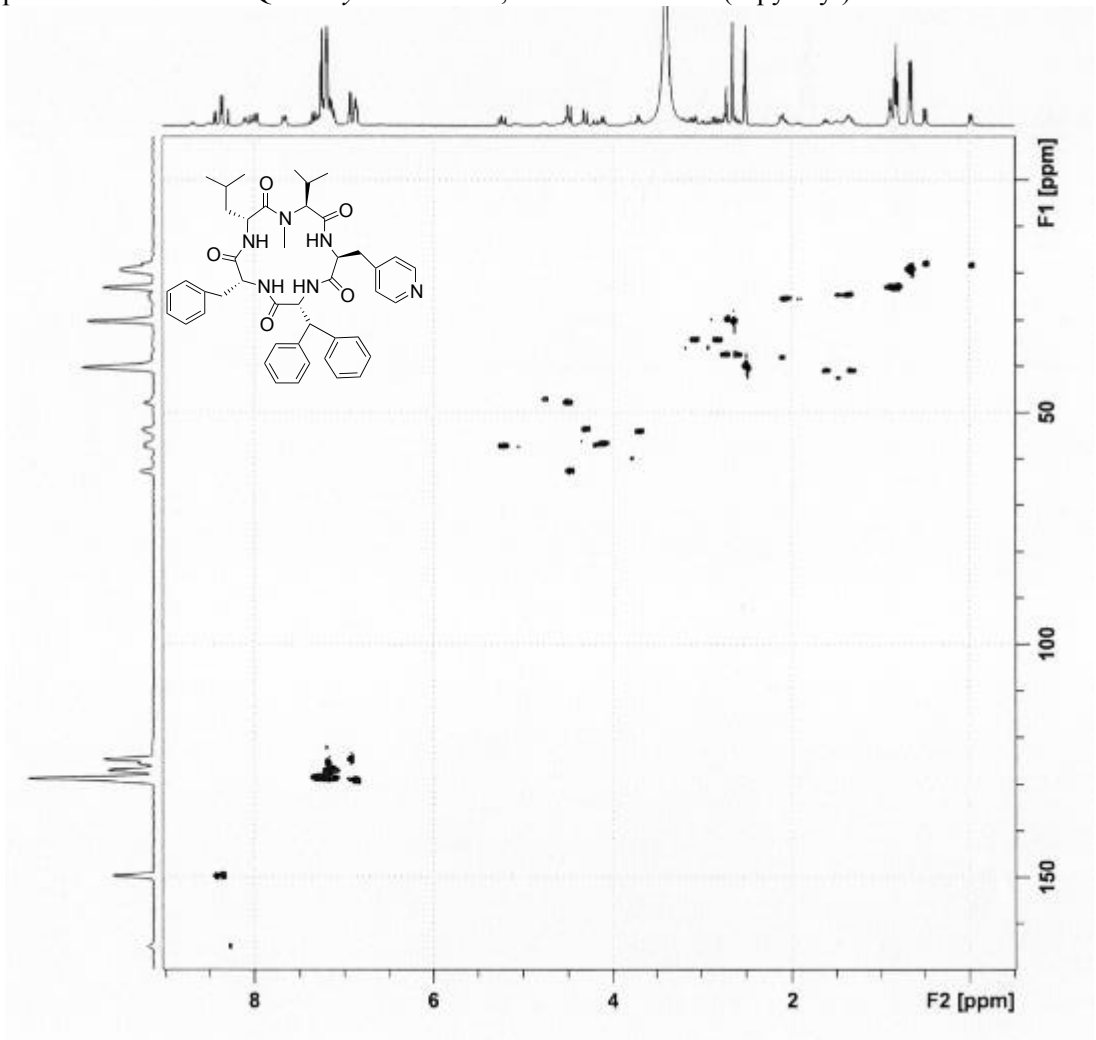
Compound **26**: HRMS of *cyclo* D-Phe-3,3-DiPhe-D-Ala-3-(4-pyridyl)-Ala-*N*-Me-Val-D-Leu



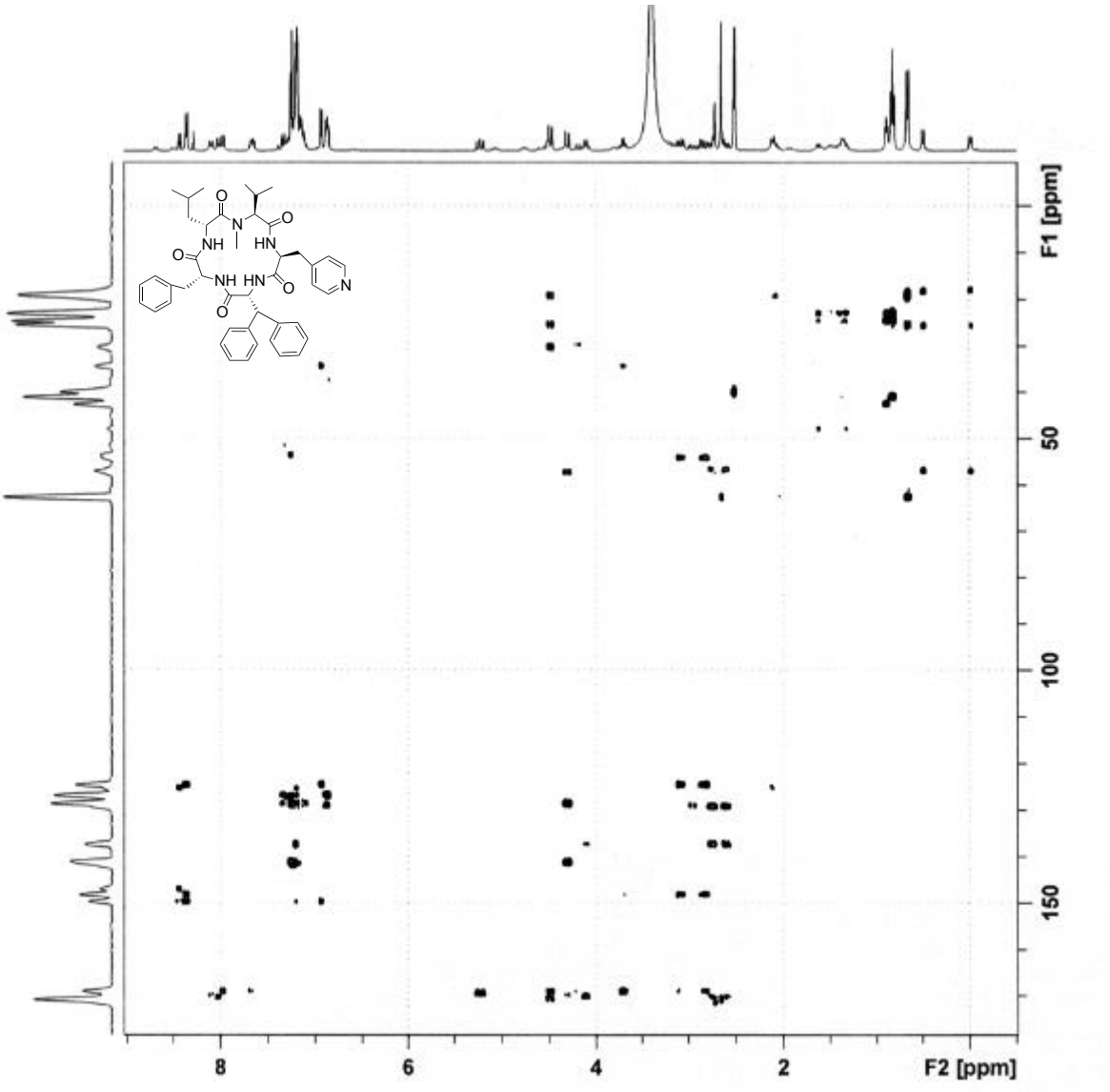
Compound **26**: ^{1}HNMR of *cyclo* D-Phe-3,3-DiPhe-D-Ala-3-(4-pyridyl)-Ala-*N*-Me-Val-D-Leu



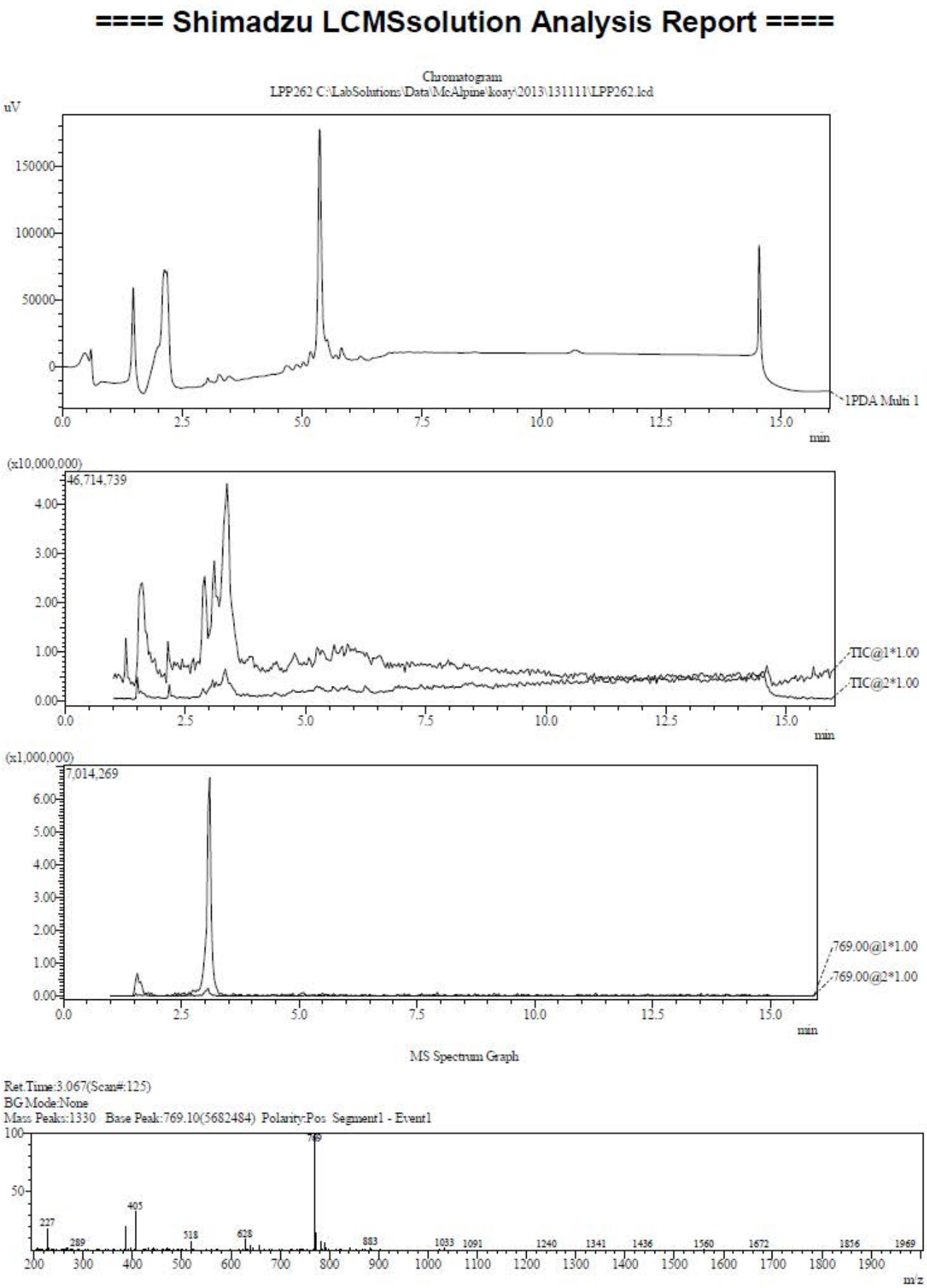
Compound **26**: ^{1}H-^{13}C HSQC of *cyclo* D-Phe-3,3-DiPhe-D-Ala-3-(4-pyridyl)-Ala-*N*-Me-Val-D-Leu



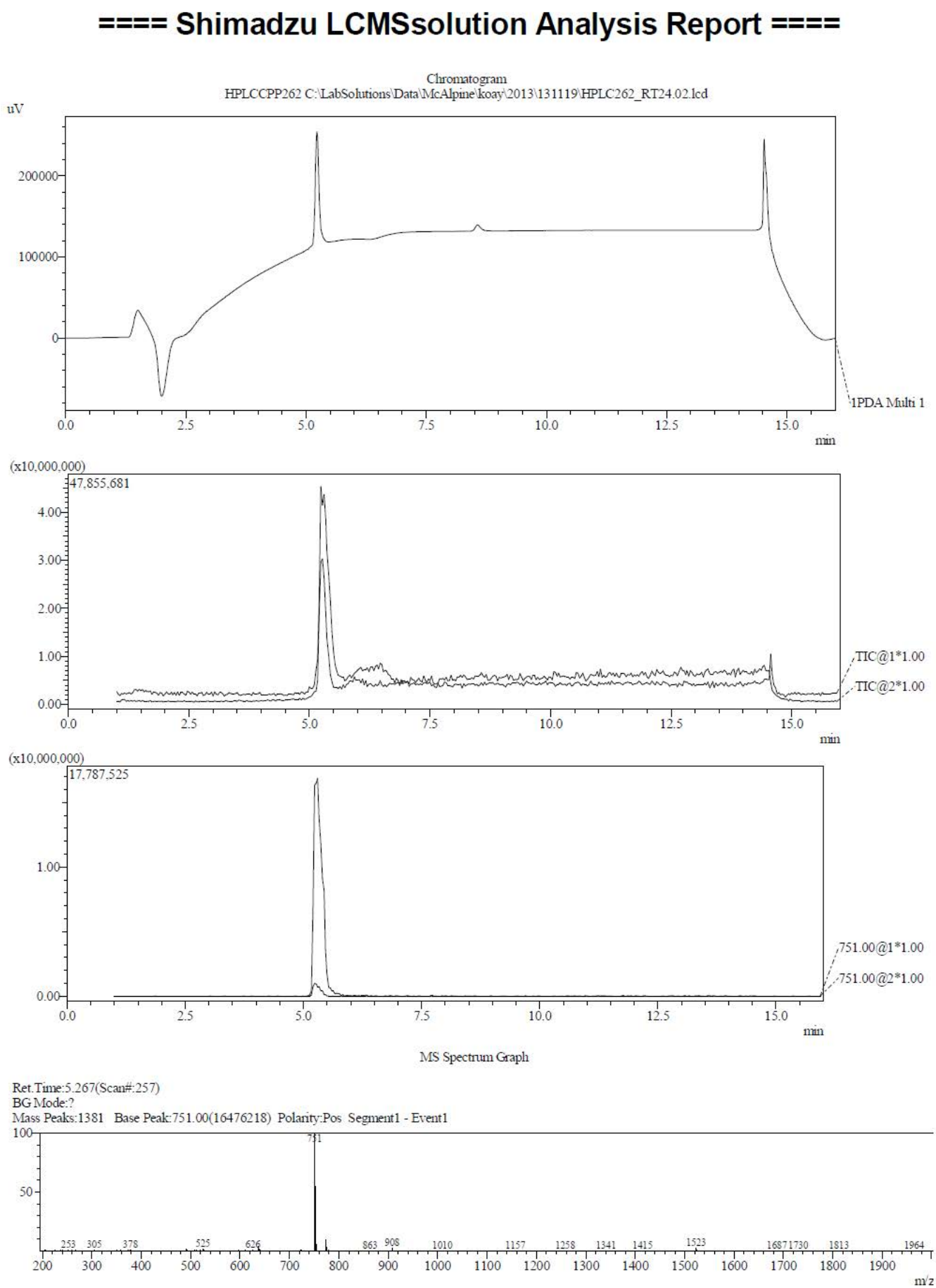
Compound **26**: ^{1}H-^{13}C HMBC of *cyclo* D-Phe-3,3-DiPhe-D-Ala-3-(4-pyridyl)-Ala-*N*-Me-Val-D-Leu



Compound **27**: LCMS of DDLP HO-D-Leu-D-Phe-3,3-Diphe-D-Ala-3-(4-Thia)Ala-Val-NH(CH_3)



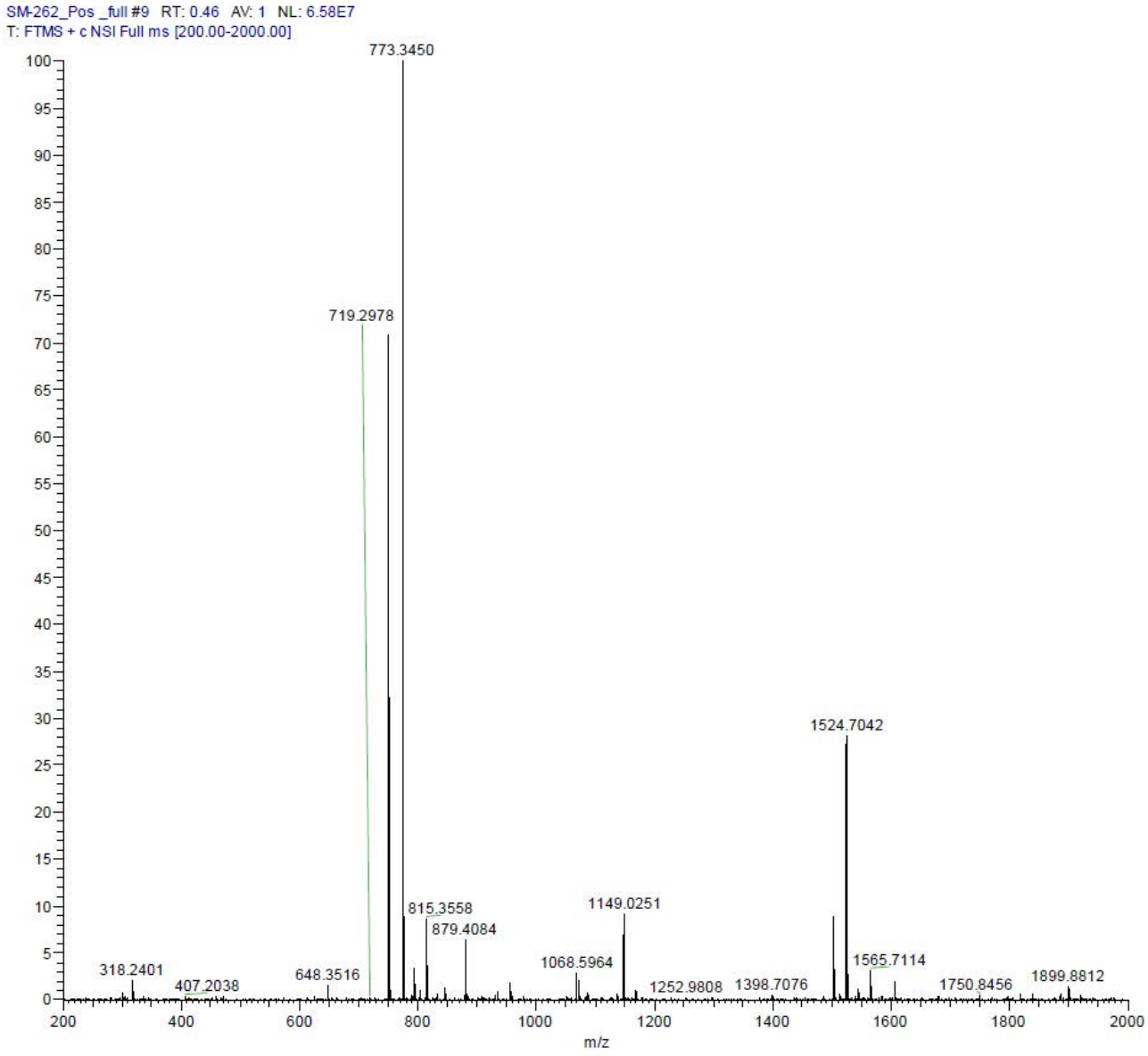
Compound **27**: LCMS of cyclo D-Leu-D-Phe-3,3-Diphe-D-Ala-3-(4-Thia)Ala-*N*-Me-Val



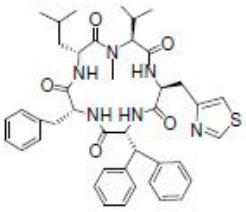
Compound **27**: HRMS of cyclo D-Leu-D-Phe-3,3-Diphe-D-Ala-3-(4-Thia)Ala-*N*-Me-Val

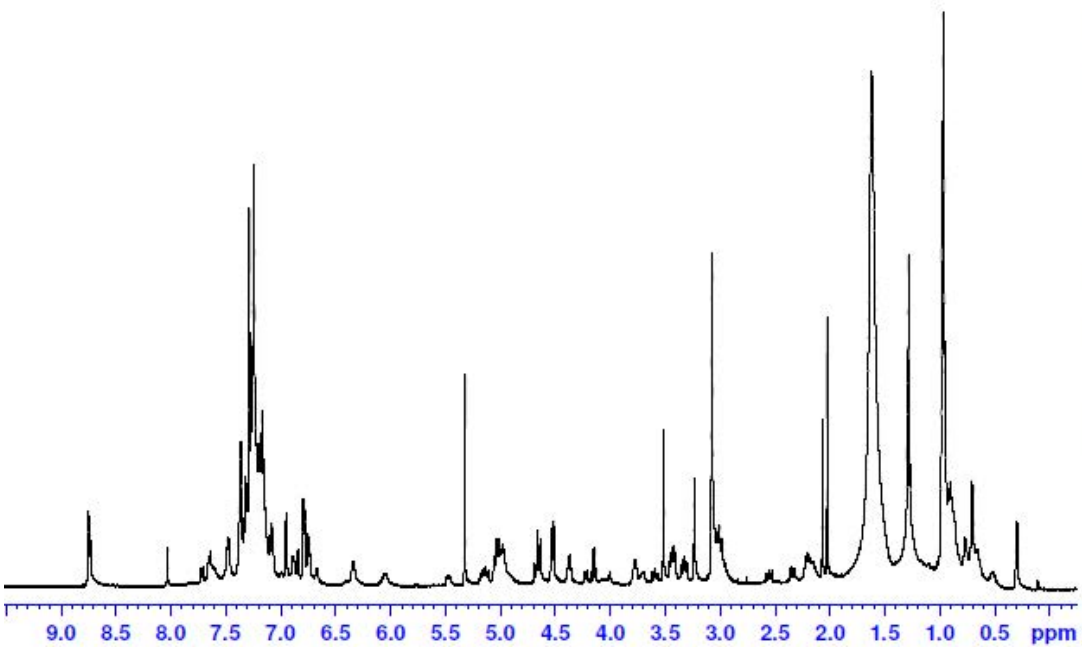
MS Data from Orbitrap

Full spectrum



Compound **27**: ^{1}HNMR of cyclo D-Leu-D-Phe-3,3-Diphe-D-Ala-3-(4-Thia)Ala-*N*-Me-Val



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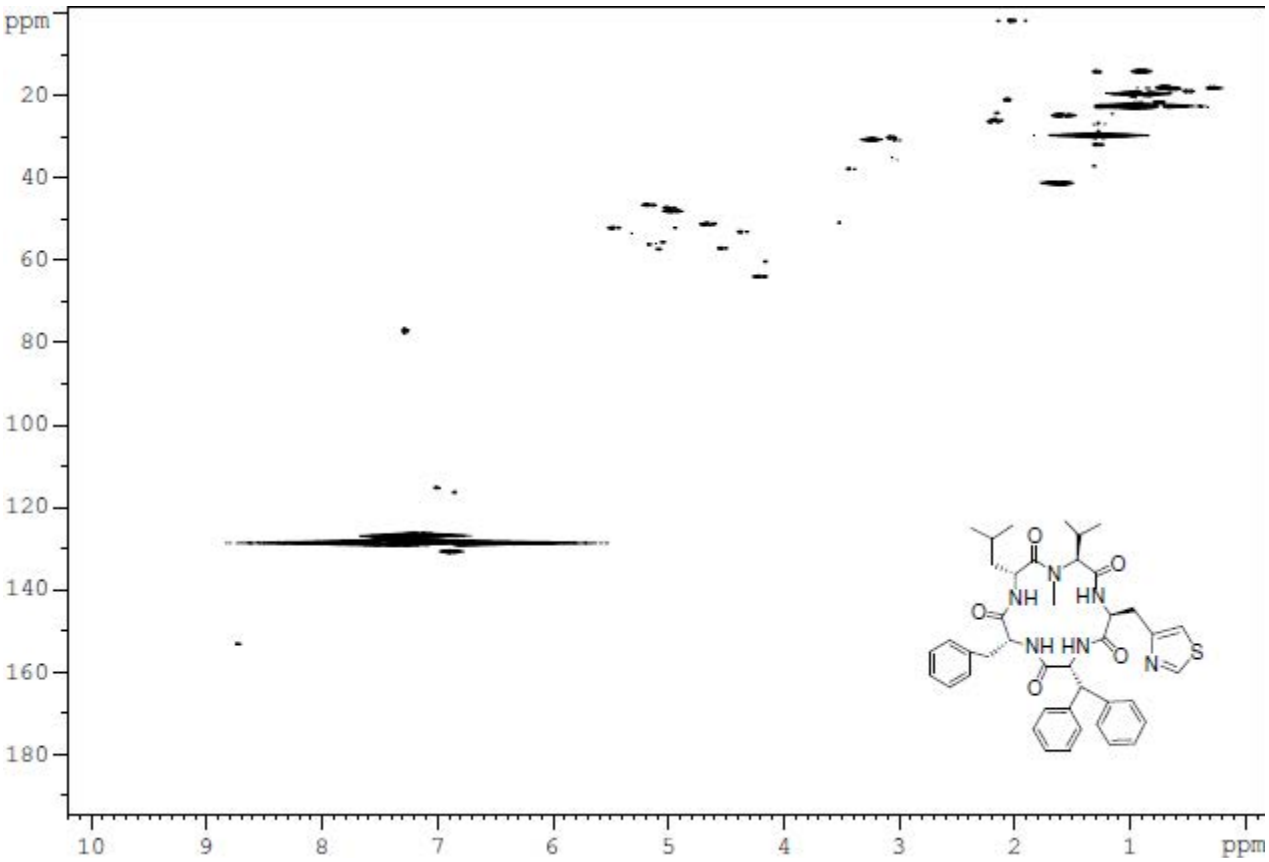
Current Data Parameters
NAME      yck-2014-1-18-SM262
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_              20140118
Time                 12.12
INSTRUM              spect
PROBHD   5 mm TBI 1H/31
PULPROG                 zg
TD                   32768
SOLVENT              CDCl3
NS                      64
DS                       4
SWH               8000.000 Hz
FIDRES               0.244141 Hz
AQ                2.0480001 sec
RG                     287
DW                  62.500 usec
DE                  12.74 usec
TE                  305.0 K
D1              5.00000000 sec
TD0                      1

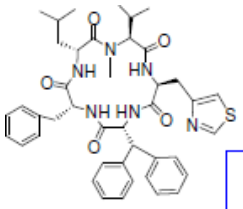
======== CHANNEL f1 ========
SFO1           500.1330008 MHz
NUC1                    1H
P1                   10.91 usec
PLW1            7.00000000 W

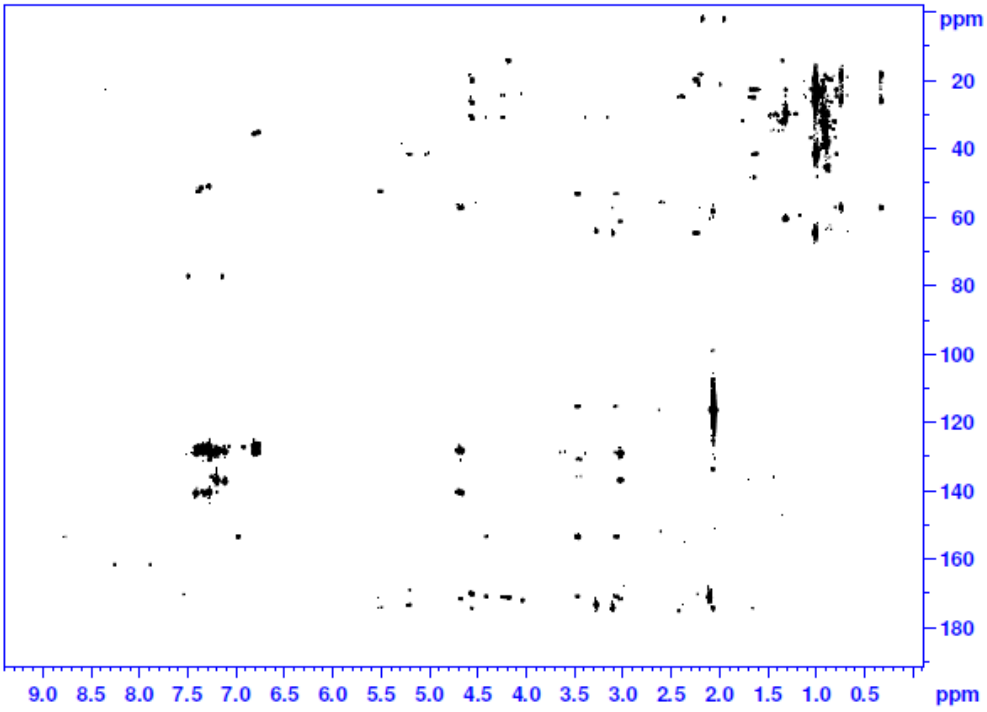
F2 - Processing parameters
SI                   65536
SF             500.1300000 MHz
WDW                     no
SSB          0
LB           0 Hz
GB           0
PC                    4.00
```

Compound **27**: ^{1}H-^{13}C HSQC of cyclo D-Leu-D-Phe-3,3-Diphe-D-Ala-3-(4-Thia)Ala-*N*-Me-Val

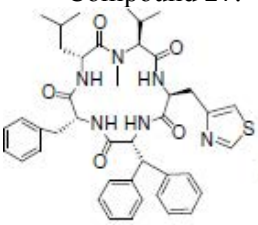


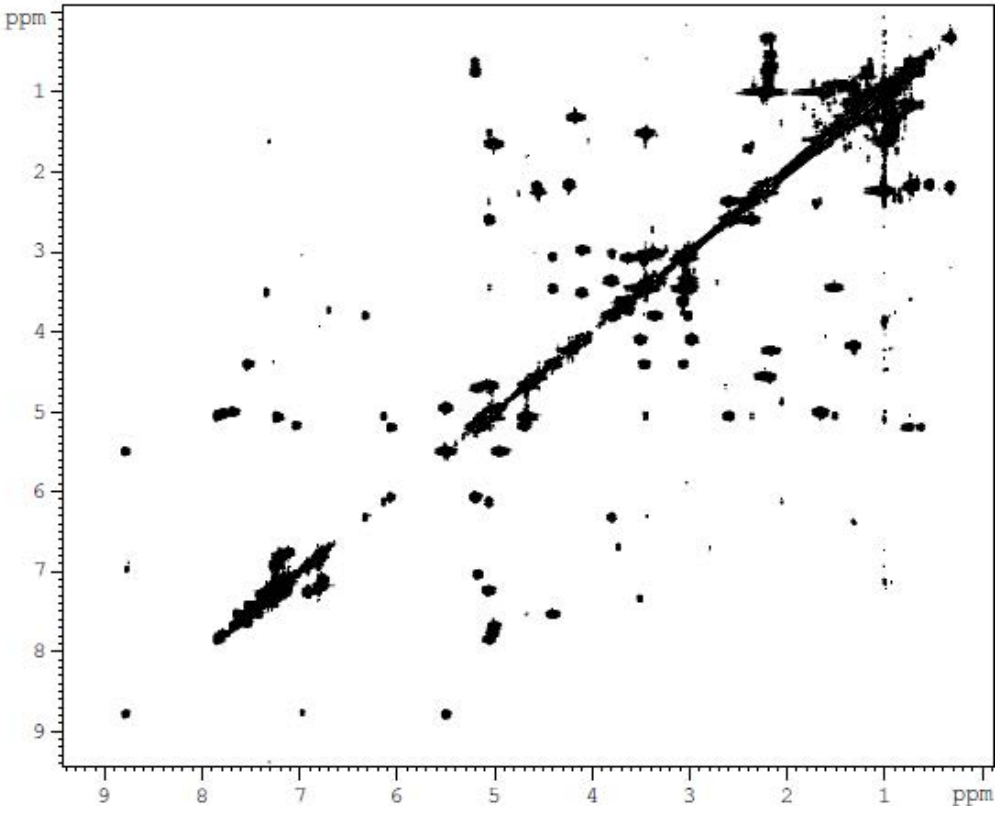
Compound **27**: ^{1}H-^{13}C HMBC of cyclo D-Leu-D-Phe-3,3-Diphe-D-Ala-3-(4-Thia)Ala-*N*-Me-Val



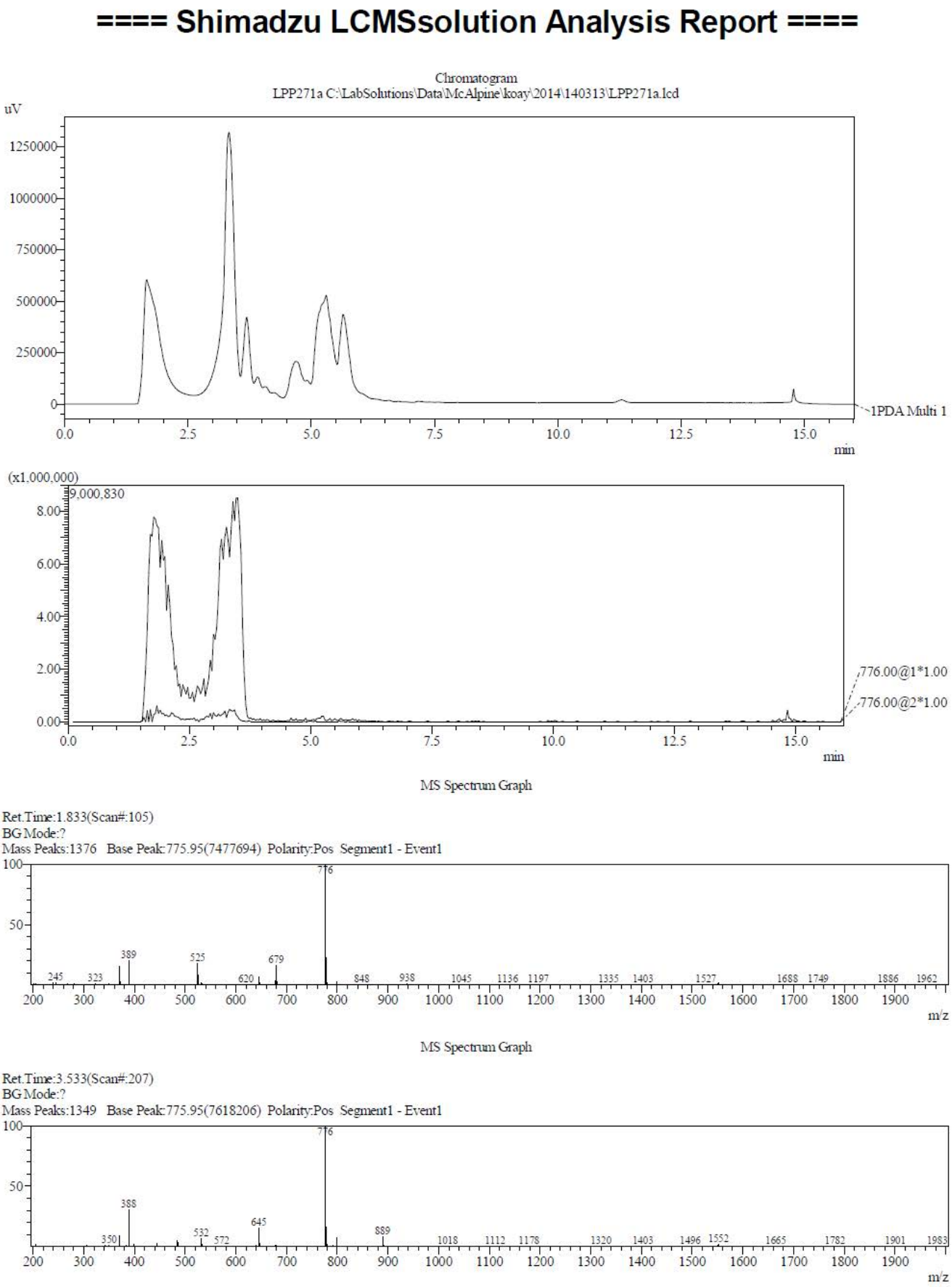


Compound **27**: ^{1}H-^{1}H COSY of cyclo D-Leu-D-Phe-3,3-Diphe-D-Ala-3-(4-Thia)Ala-*N*-Me-Val

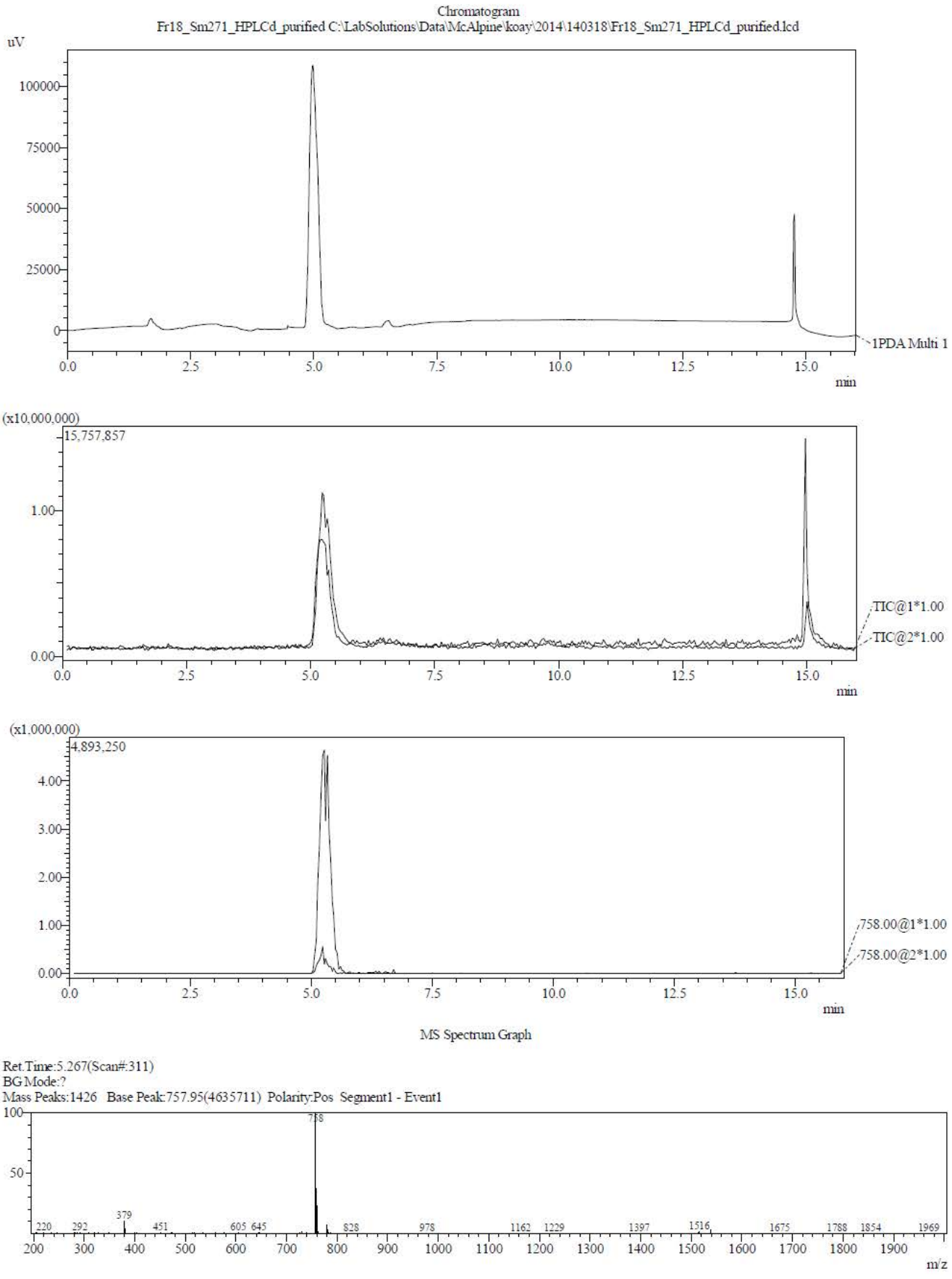




Compound **28**: LCMS of DDLP HO-Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala-NH_2



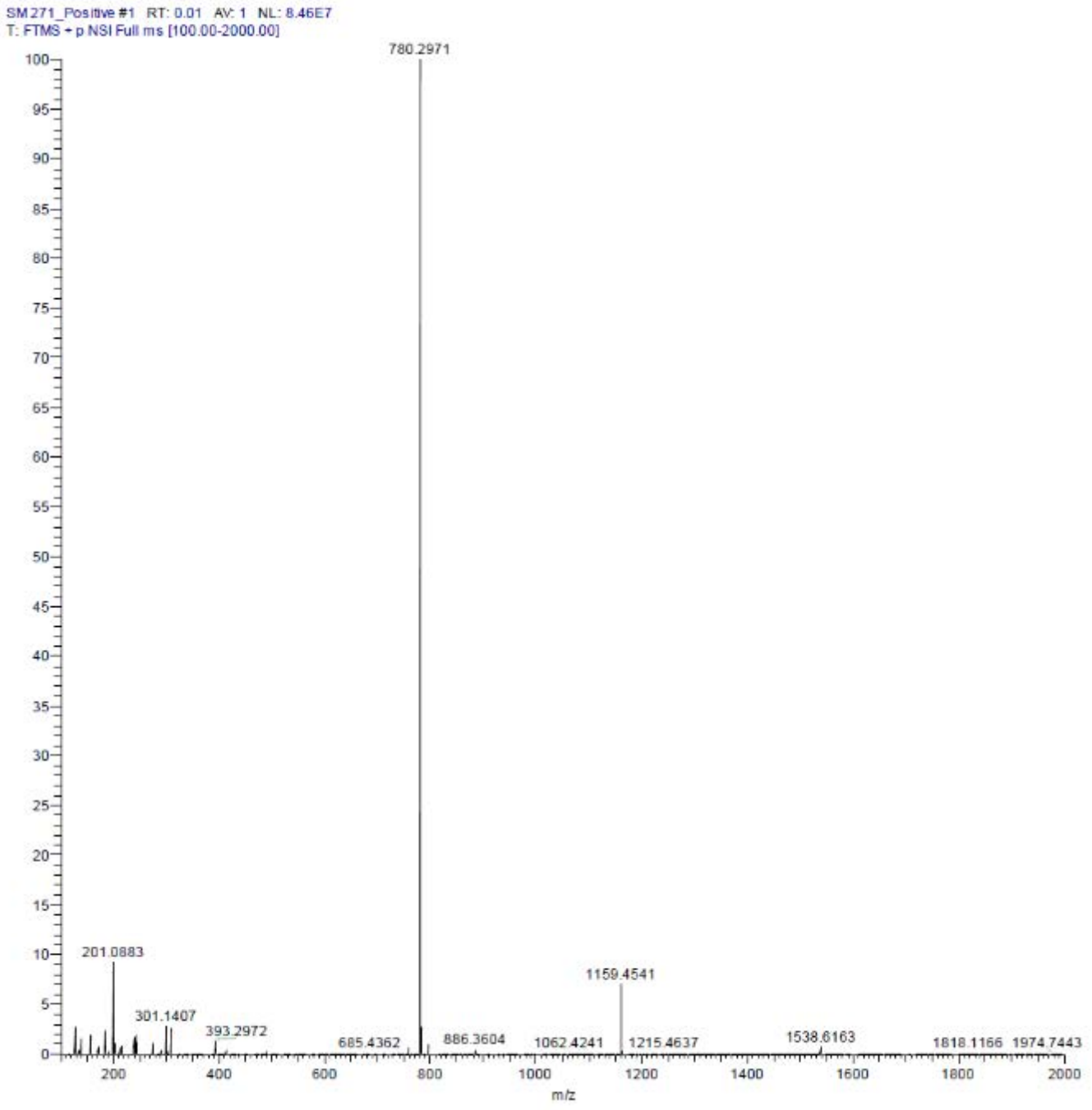
Compound **28**: LCMS of cyclo Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala



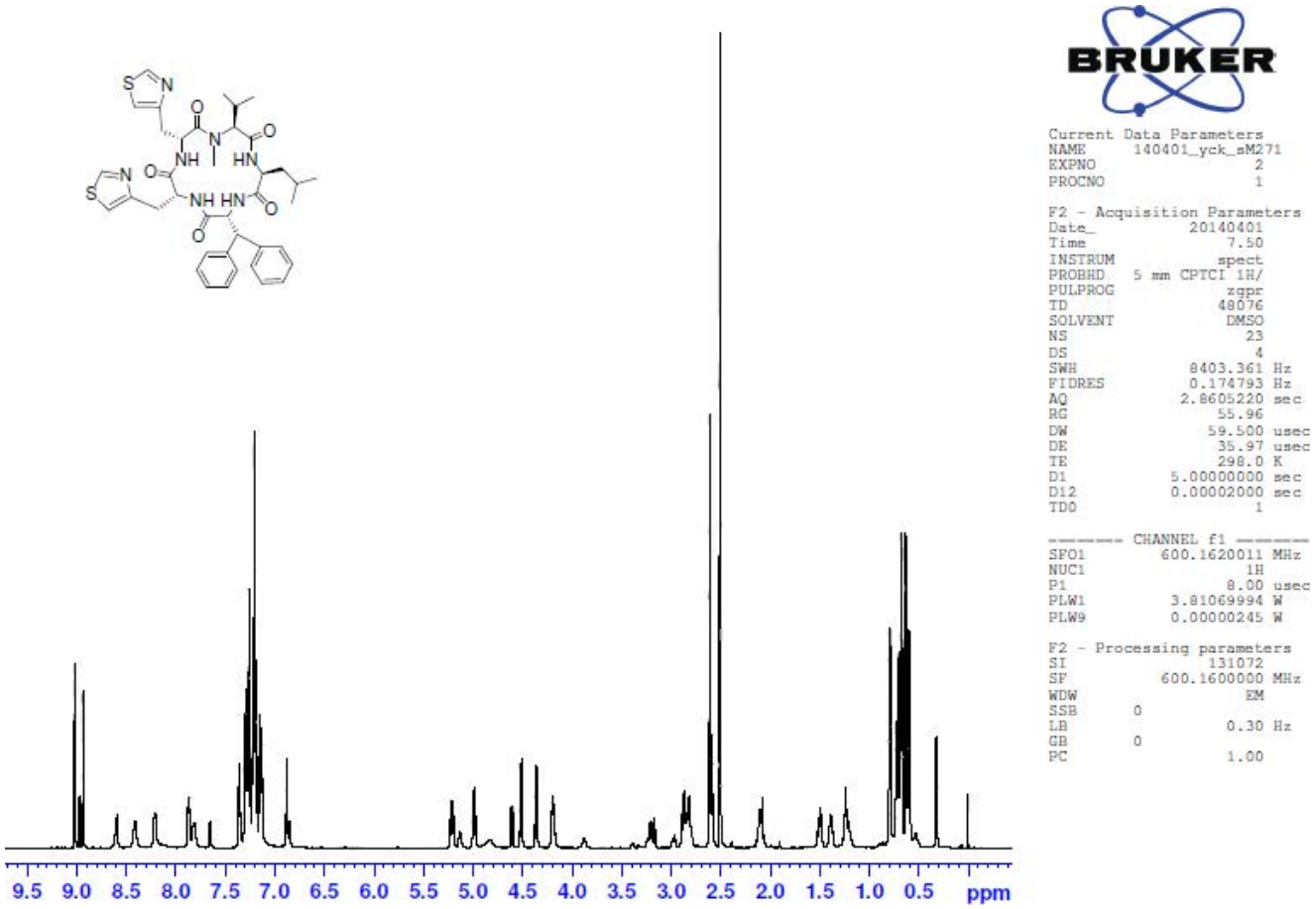
Compound **28**: HRMS of cyclo Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala

MS Data from Orbitrap

Full spectrum



Compound **28**: ^{1}HNMR of cyclo Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala

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Current Data Parameters
NAME      140401_yck_sM271
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_              20140401
Time                   7.50
INSTRUM               spect
PROBHD    5 mm CPTCI 1H/
PULPROG                zgpr
TD                    48076
SOLVENT                DMSO
NS                       23
DS                        4
SWH                8403.361 Hz
FIDRES             0.174793 Hz
AQ                 2.8605220 sec
RG                     55.96
DW                    59.500 usec
DE                    35.97 usec
TE                    298.0 K
D1                 5.00000000 sec
D12                0.00002000 sec
TD0                       1

======== CHANNEL f1 ========
SFO1             600.1620011 MHz
NUC1                     1H
P1                     8.00 usec
PLW1               3.81069994 W
PLW9               0.00000245 W

F2 - Processing parameters
SI                     131072
SF               600.1600000 MHz
WDW                      EM
SSB          0
LB                     0.30 Hz
GB           0
PC                     1.00
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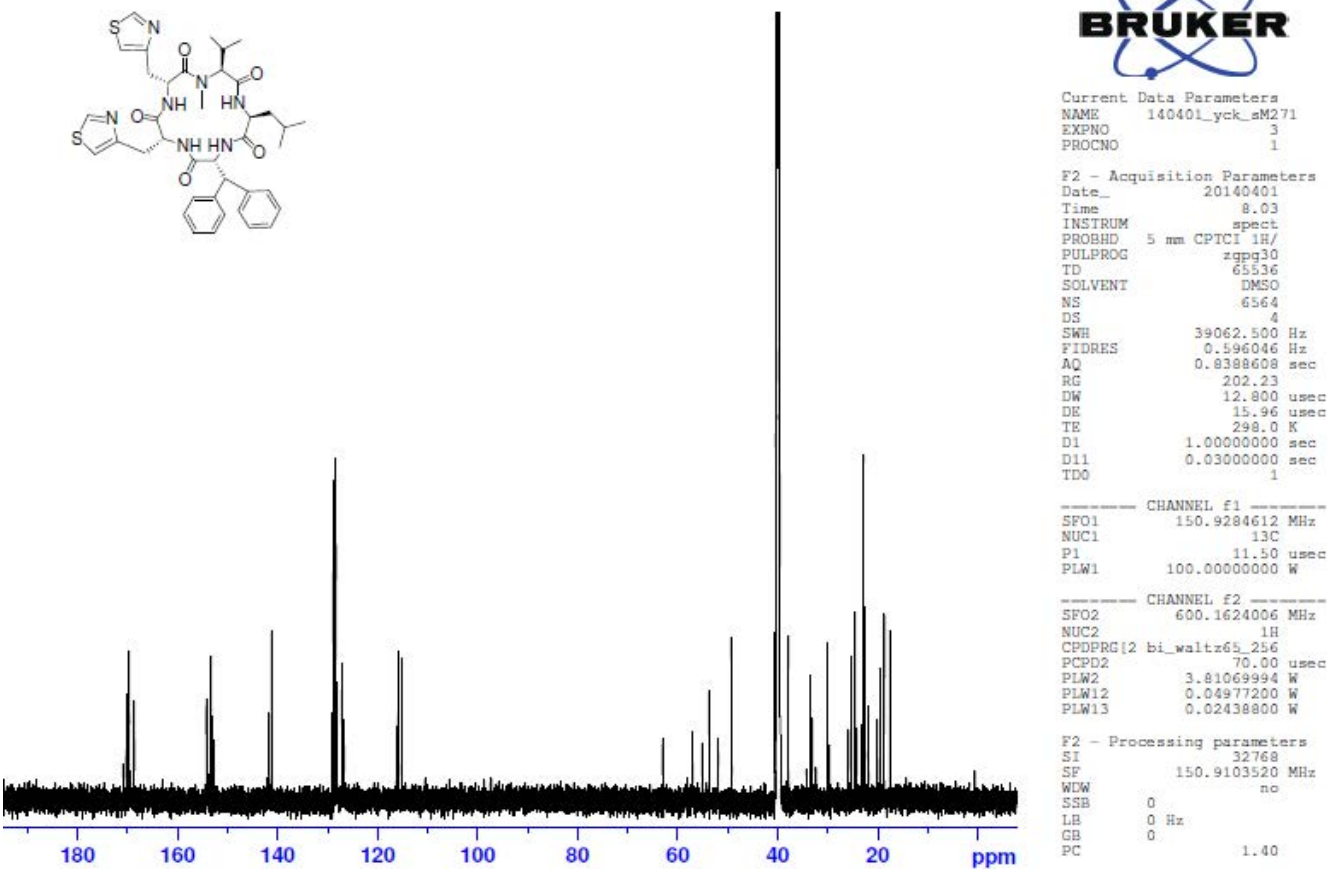
Compound **28**: ^{13}CNMR of cyclo Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala




```
Current Data Parameters
NAME      140401_yck_sM271
EXPNO                    3
PROCNO                   1

F2 - Acquisition Parameters
Date_              20140401
Time                   8.03
INSTRUM               spect
PROBHD    5 mm CPTCI 1H/
PULPROG             zgpg30
TD                    65536
SOLVENT                DMSO
NS                     6564
DS                        4
SWH               39062.500 Hz
FIDRES             0.596046 Hz
AQ                 0.8388608 sec
RG                    202.23
DW                    12.800 usec
DE                    15.96 usec
TE                    298.0 K
D1                 1.00000000 sec
D11                0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
SFO1             150.9284612 MHz
NUC1                     13C
P1                    11.50 usec
PLW1             100.00000000 W

======== CHANNEL f2 ========
SFO2             600.1624006 MHz
NUC2                     1H
CPDPRG[2 bi_waltz65_256
PCPD2                 70.00 usec
PLW2               3.81069994 W
PLW12              0.04977200 W
PLW13              0.02438800 W

F2 - Processing parameters
SI                      32768
SF               150.9103520 MHz
WDW                      no
SSB          0
LB           0 Hz
GB           0
PC                     1.40
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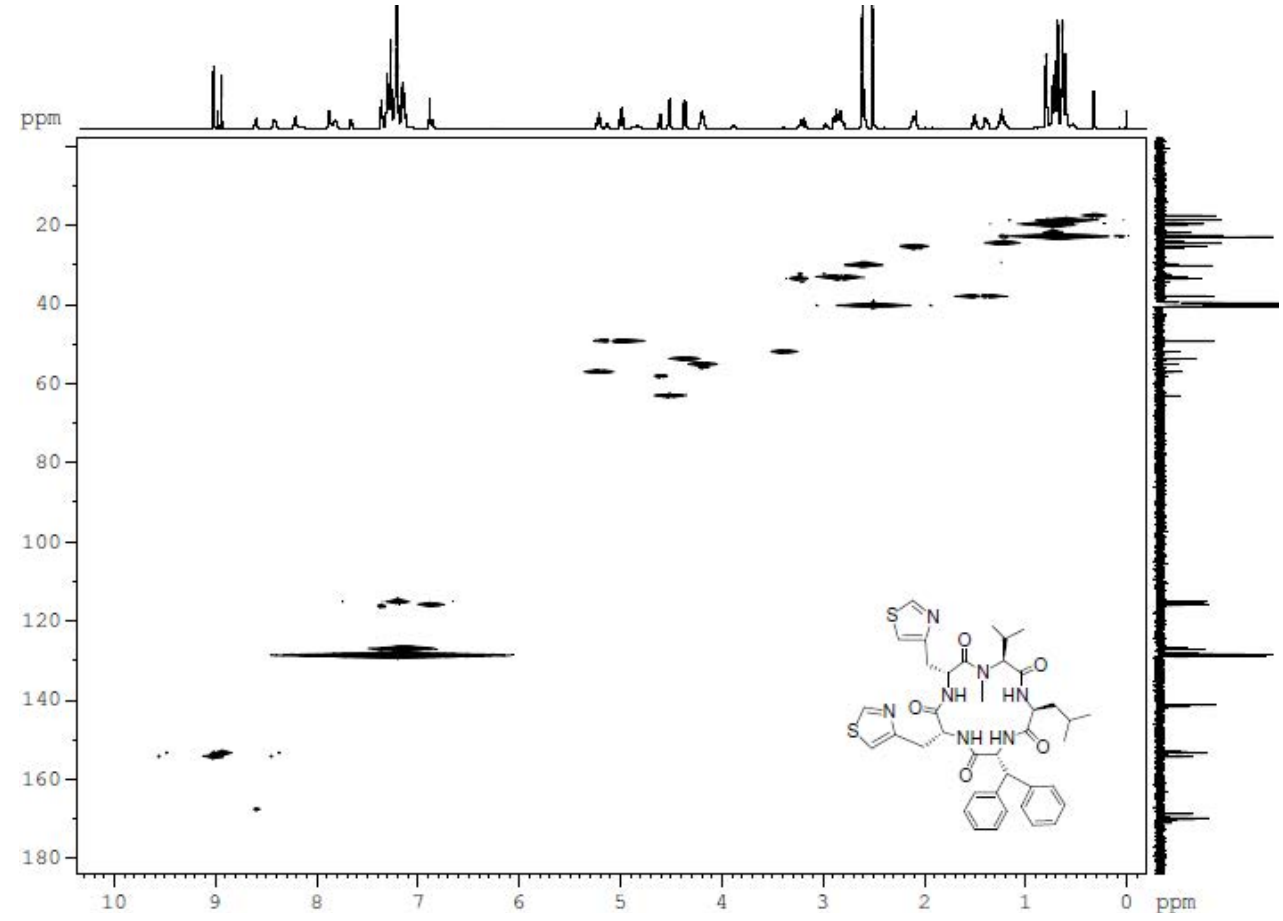
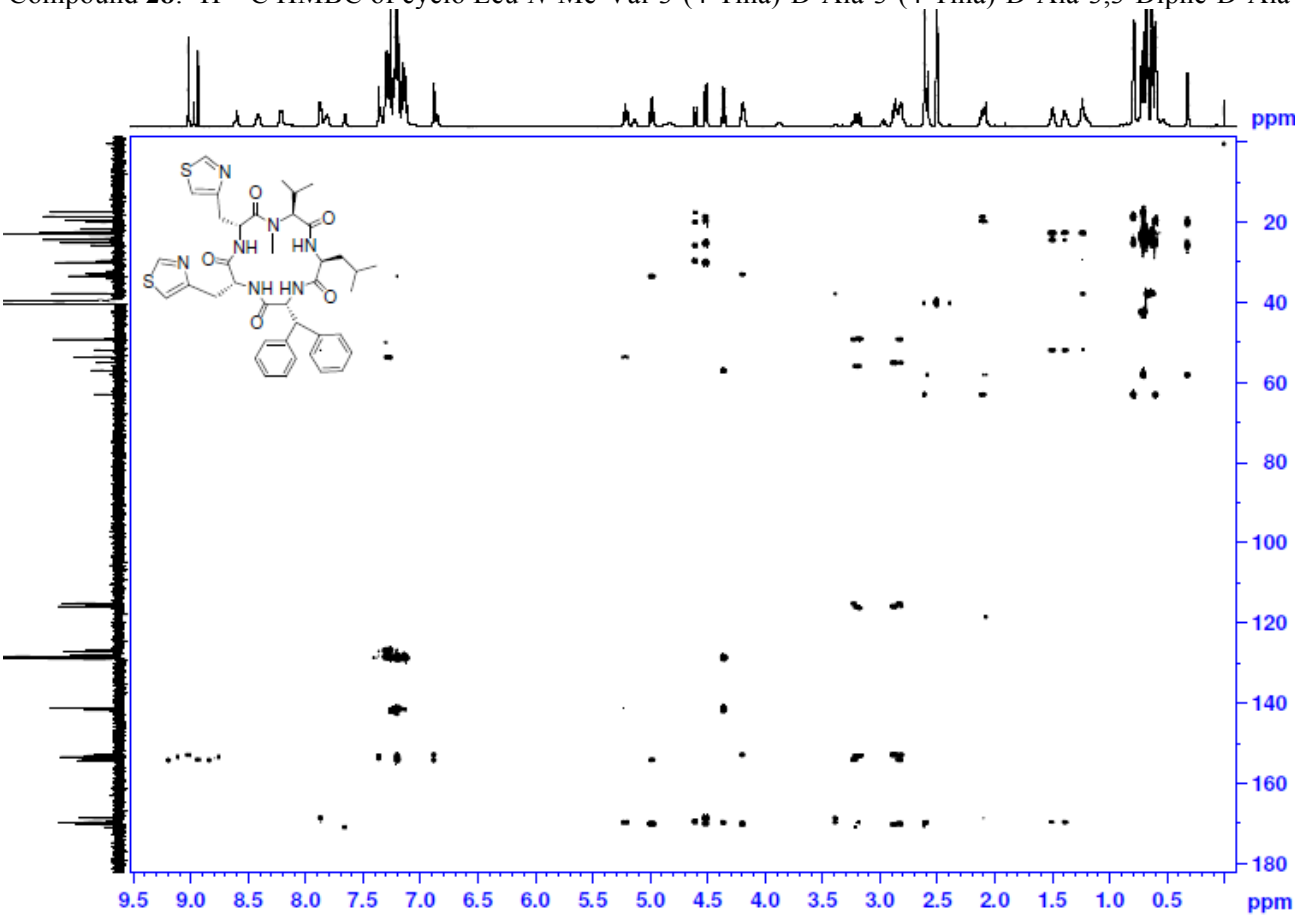
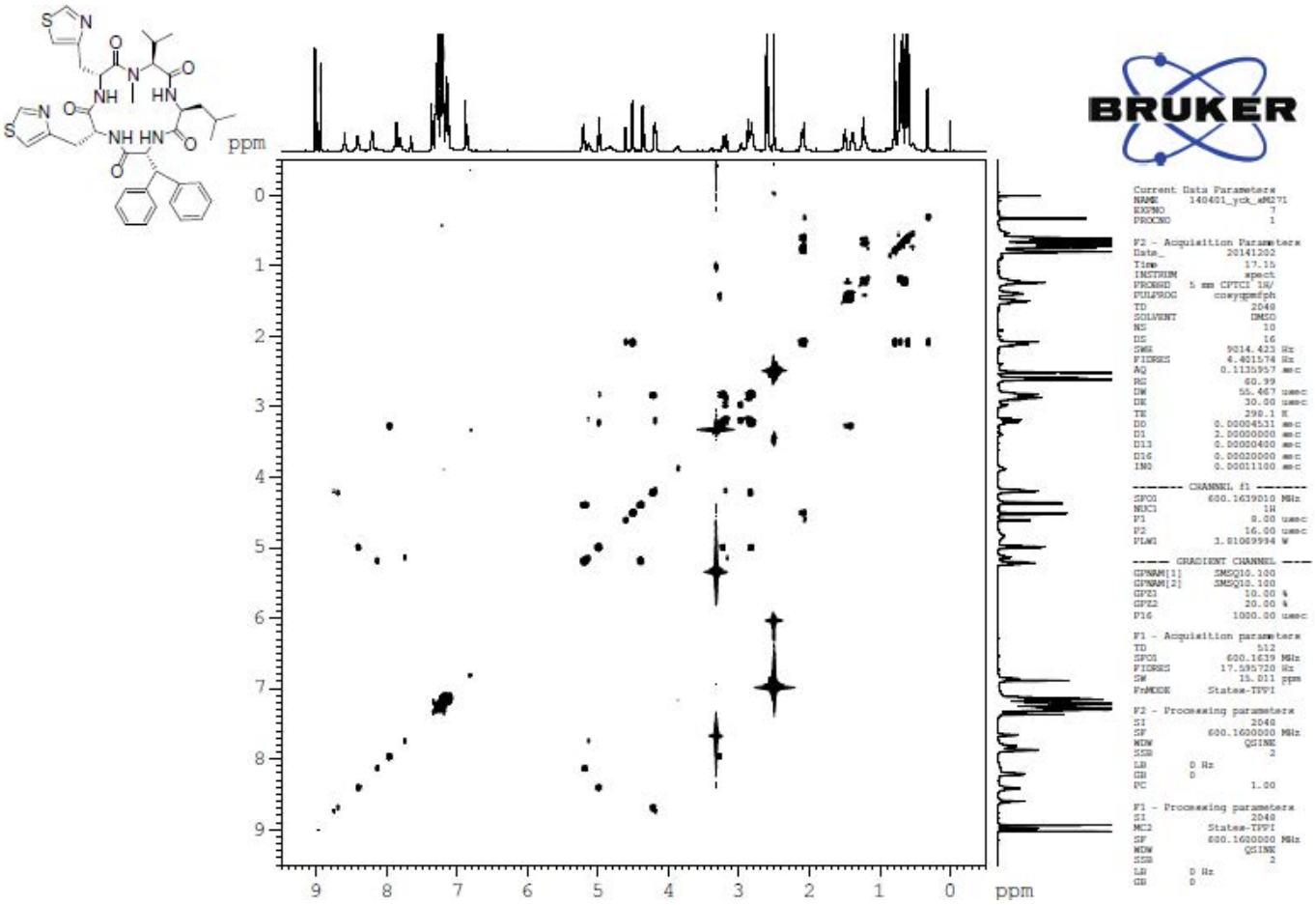
Compound **28**: ^{1}H-^{13}C HSQC of cyclo Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala



Compound **28**: ^{1}H-^{13}C HMBC of cyclo Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala

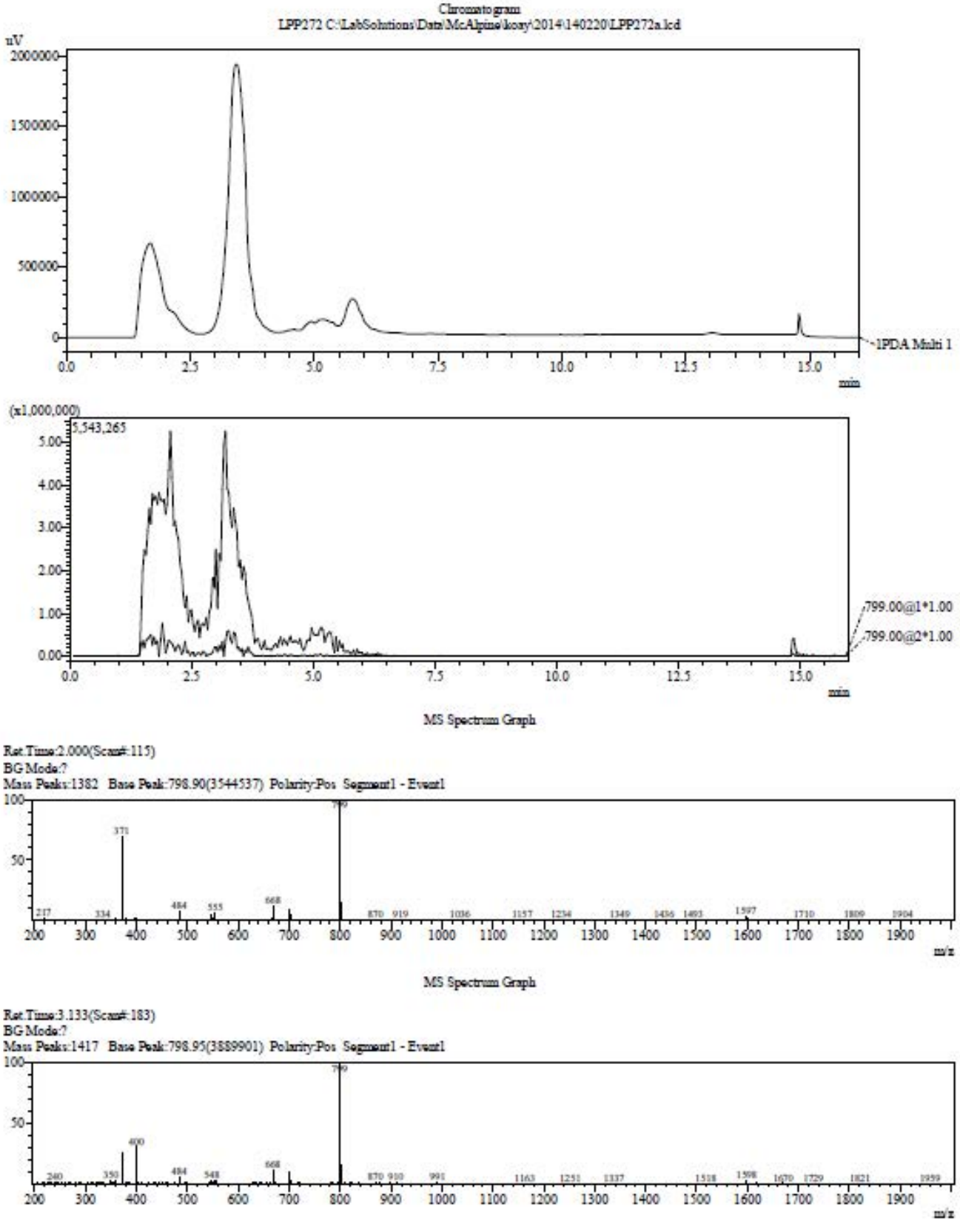


Compound **28**: ^{1}H-^{1}H COSY of cyclo Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala



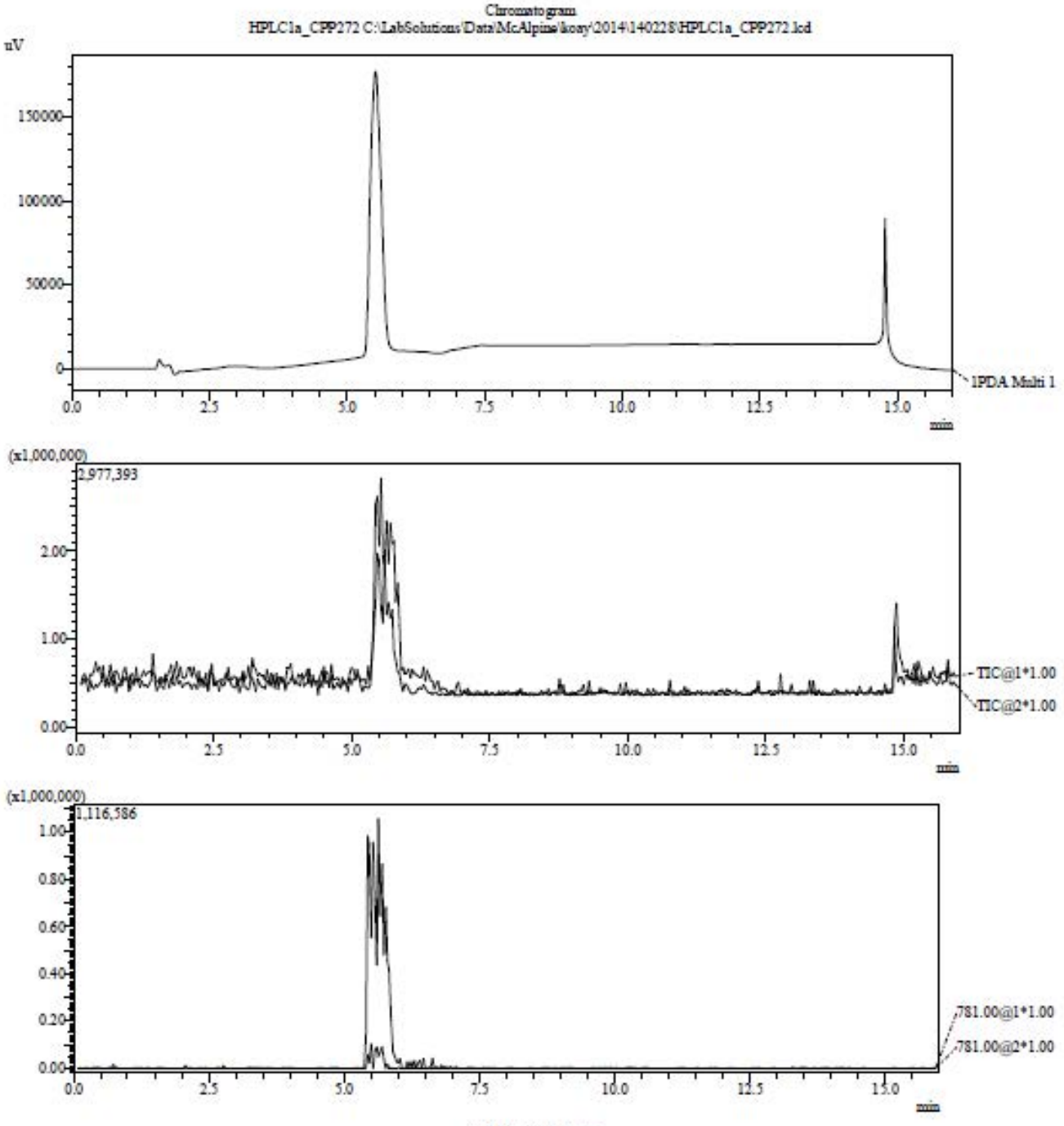
Compound **29**: LCMS of DDLP HO-Leu-*N*-Me-Val-D-Tyr(OMe)-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala-NH_2

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



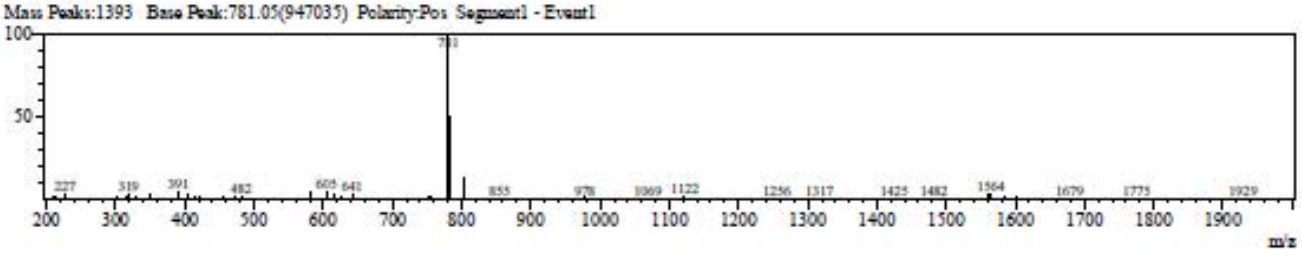
Compound **29**: LCMS of cyclo Leu-*N*-Me-Val-D-Tyr(OMe)-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala

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



MS Spectrum Graph

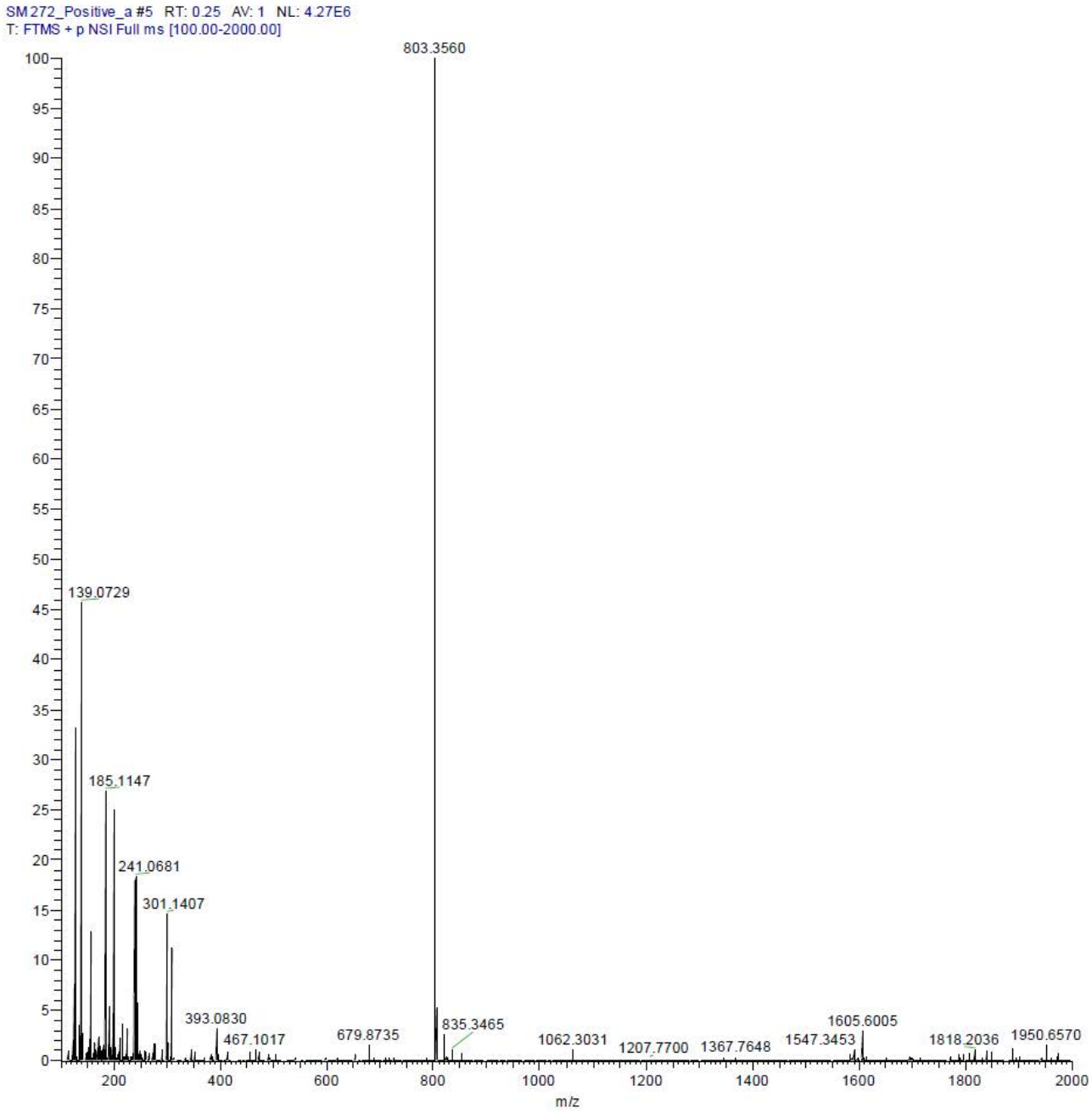
Ret.Time:5.467(Scan#:323)
BG Mode:?
Mass Peaks:1393 Base Peak:781.05(947035) Polarity:Pos Segment1 - Event1



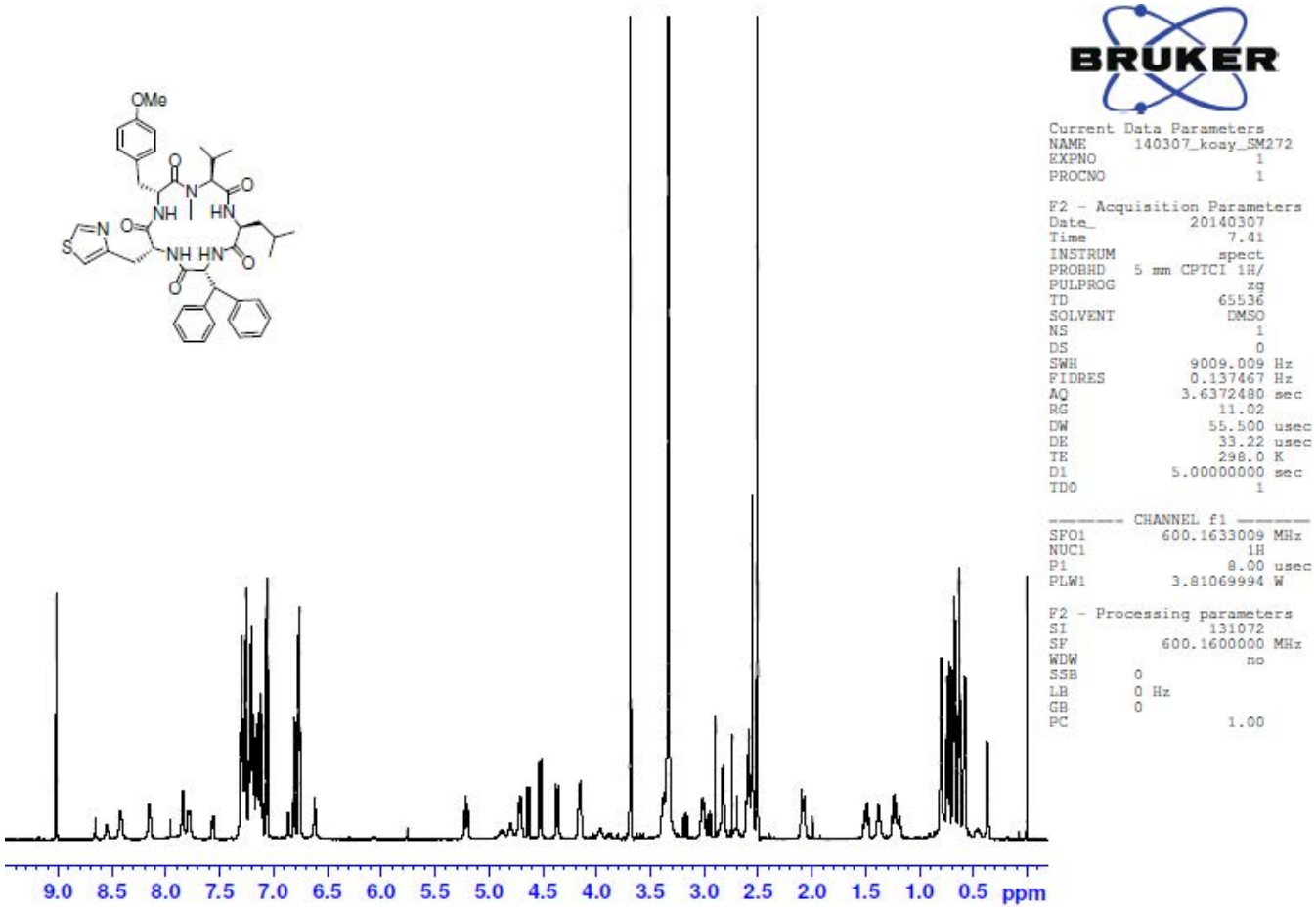
Compound **29**: HRMS of cyclo Leu-*N*-Me-Val-D-Tyr(OMe)-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala

MS Data from Orbitrap

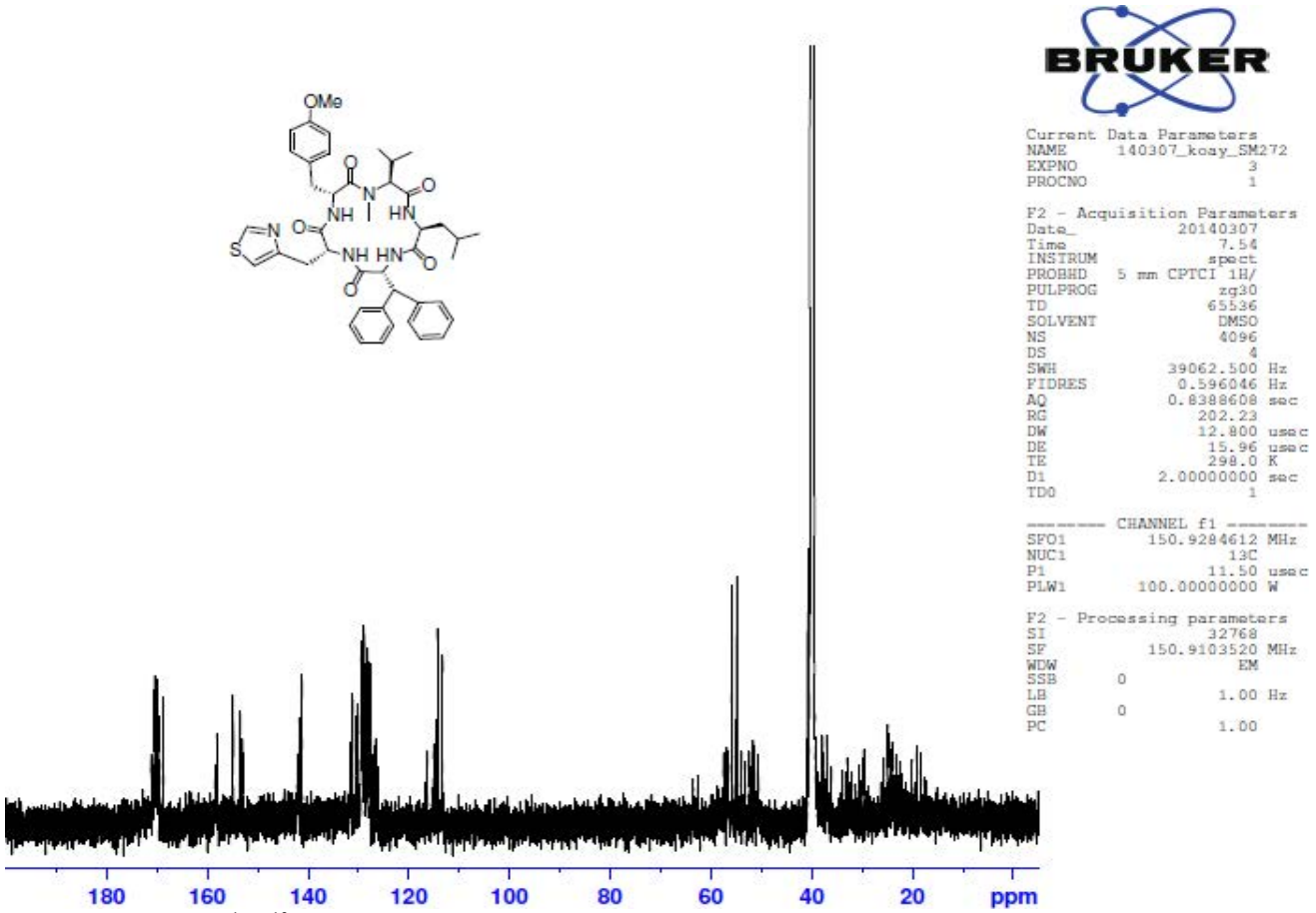
Full spectrum



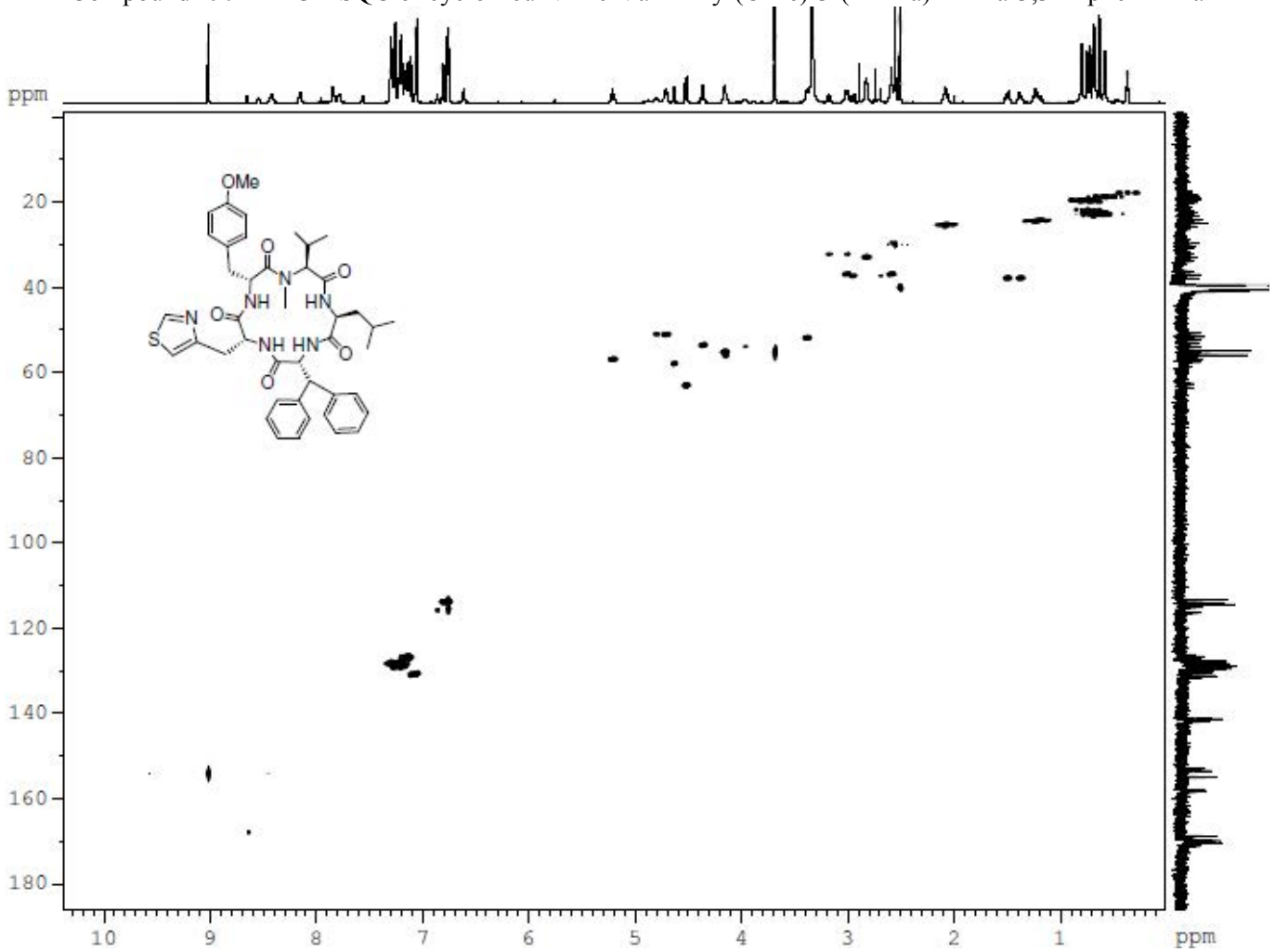
Compound **29**: ^{1}HNMR of cyclo Leu-*N*-Me-Val-D-Tyr(OMe)-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala



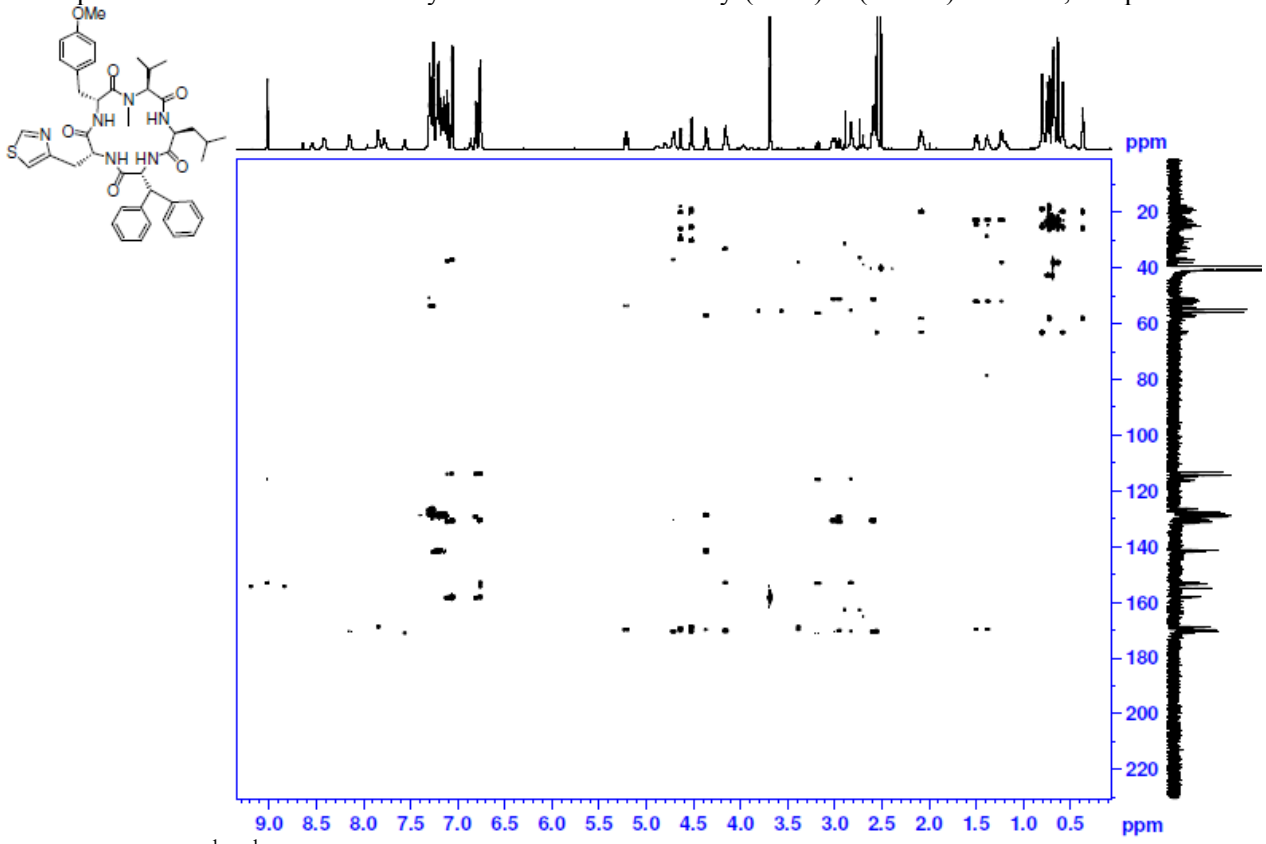
Compound **29**: ^{13}CNMR of cyclo Leu-*N*-Me-Val-D-Tyr(OMe)-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala



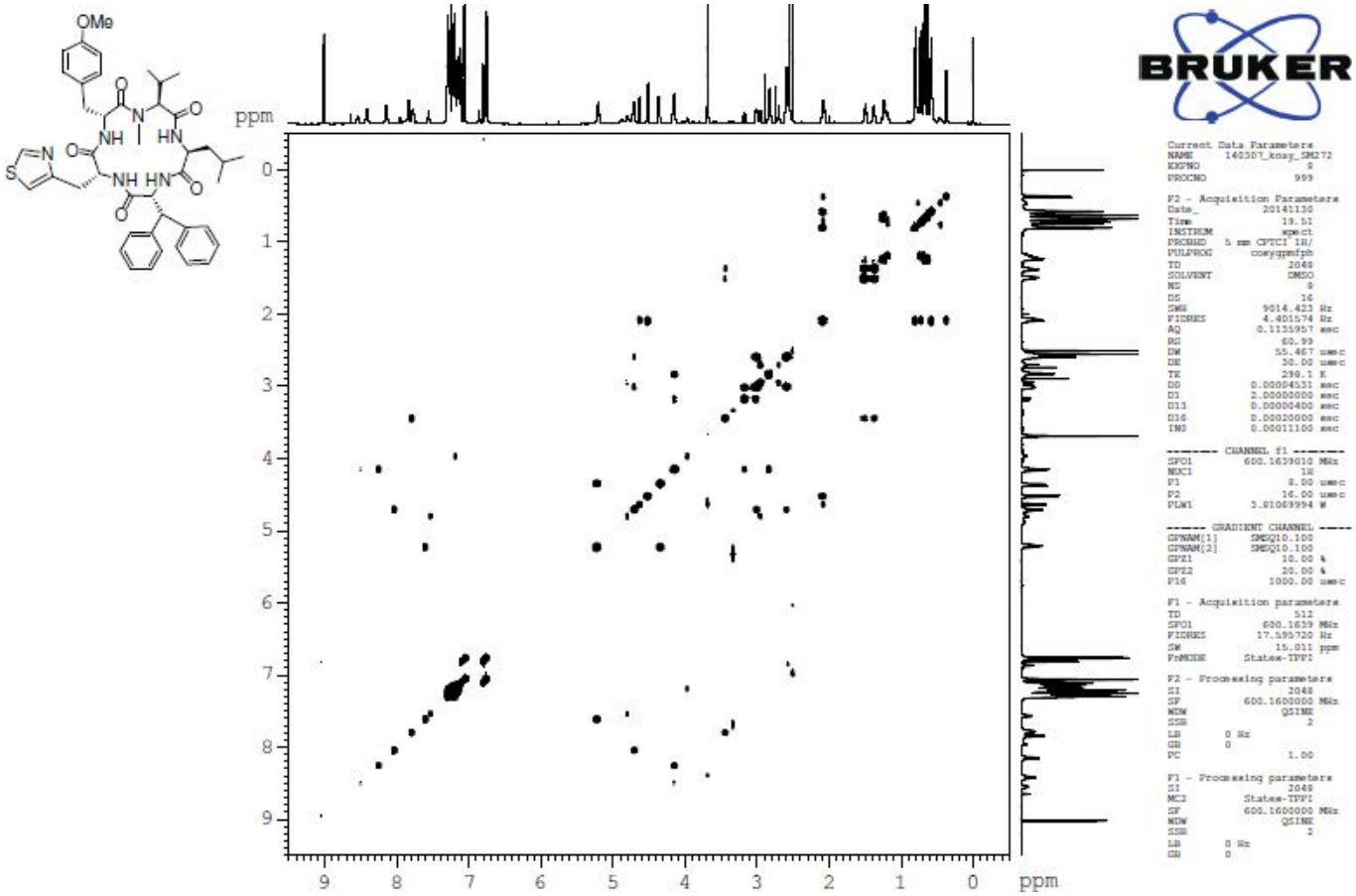
Compound **29**: ^{1}H-^{13}C HSQC of cyclo Leu-*N*-Me-Val-D-Tyr(OMe)-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala



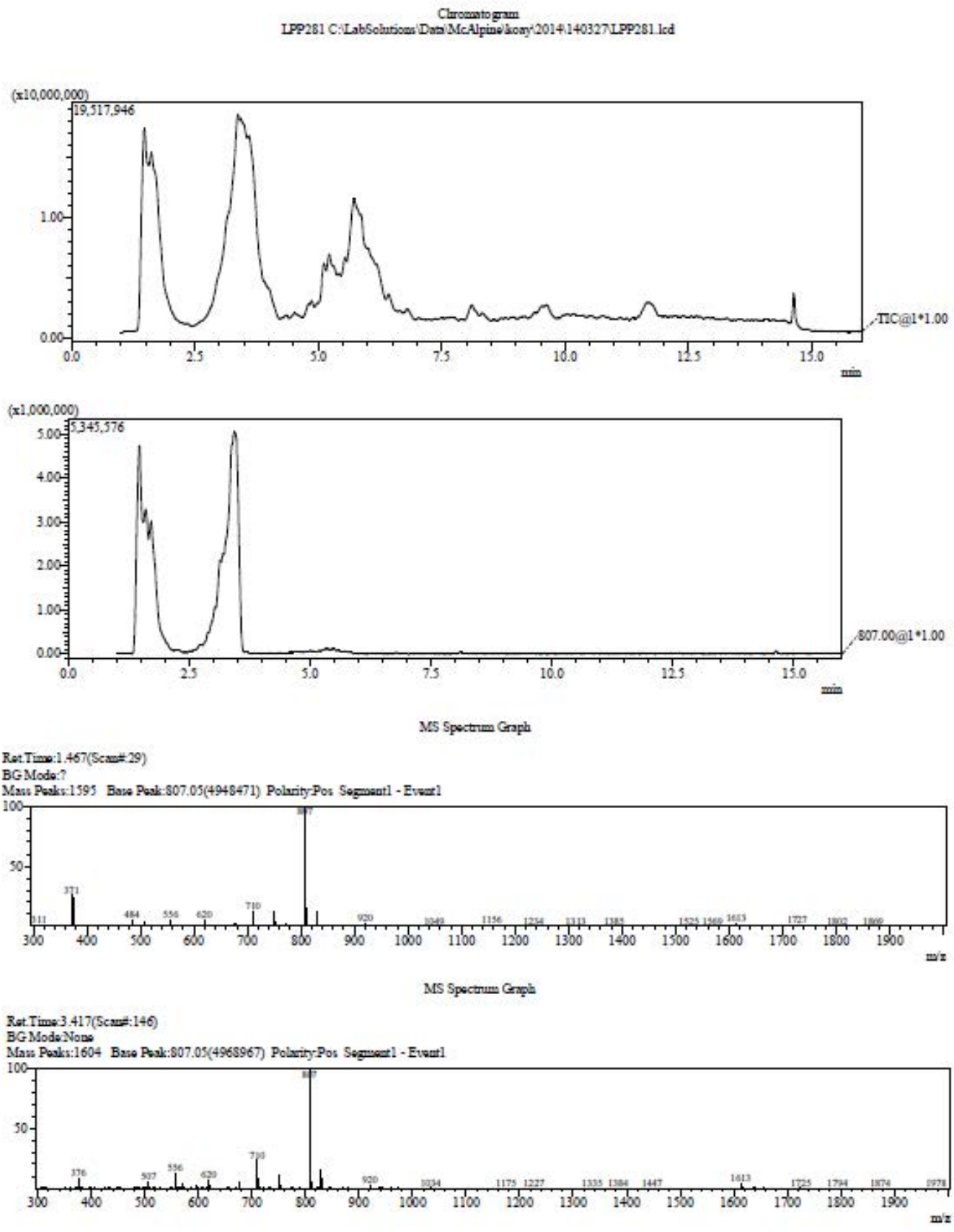
Compound **29**: ^{1}H-^{13}C HMBC of cyclo Leu-*N*-Me-Val-D-Tyr(OMe)-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala



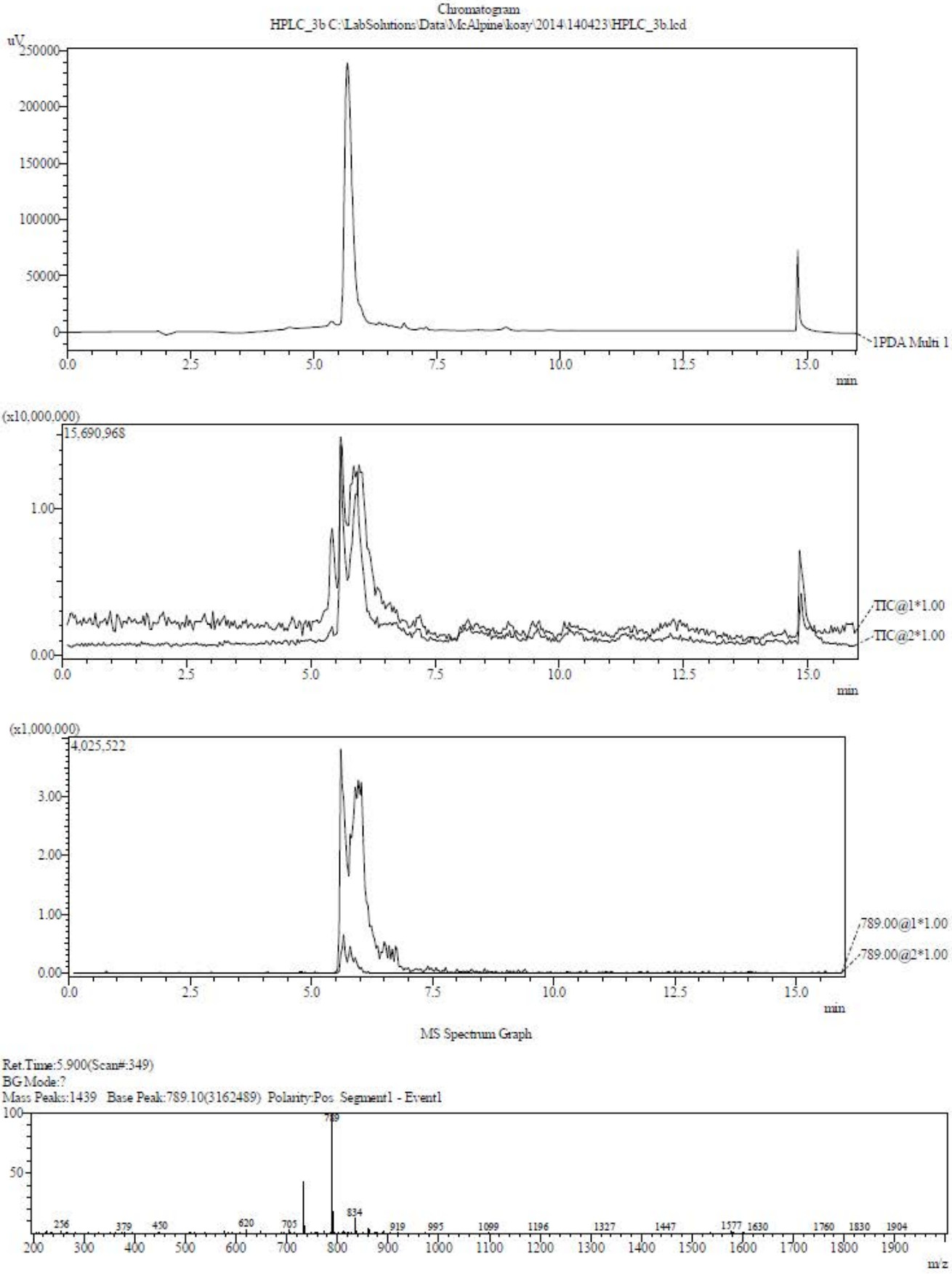
Compound **29**: ^{1}H-^{1}H COSY of cyclo Leu-*N*-Me-Val-D-Tyr(OMe)-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala



Compound **30**: LCMS of DDLP HO-Leu-*N*-Me-Val-D-Glu(OtBu)-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala-NH_2



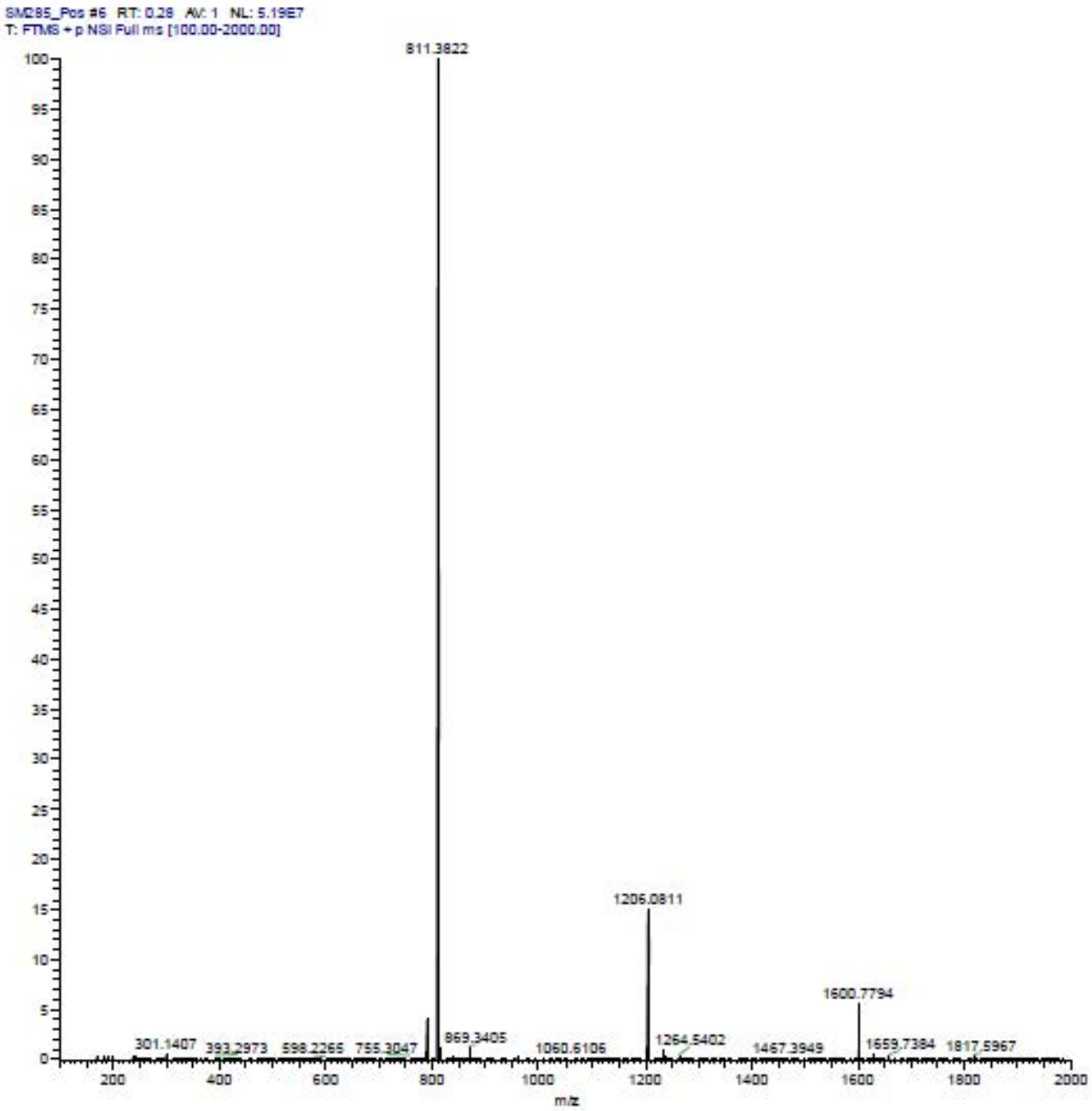
Compound **30**: LCMS of cyclo Leu-*N*-Me-Val-D-Glu(OtBu)-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala



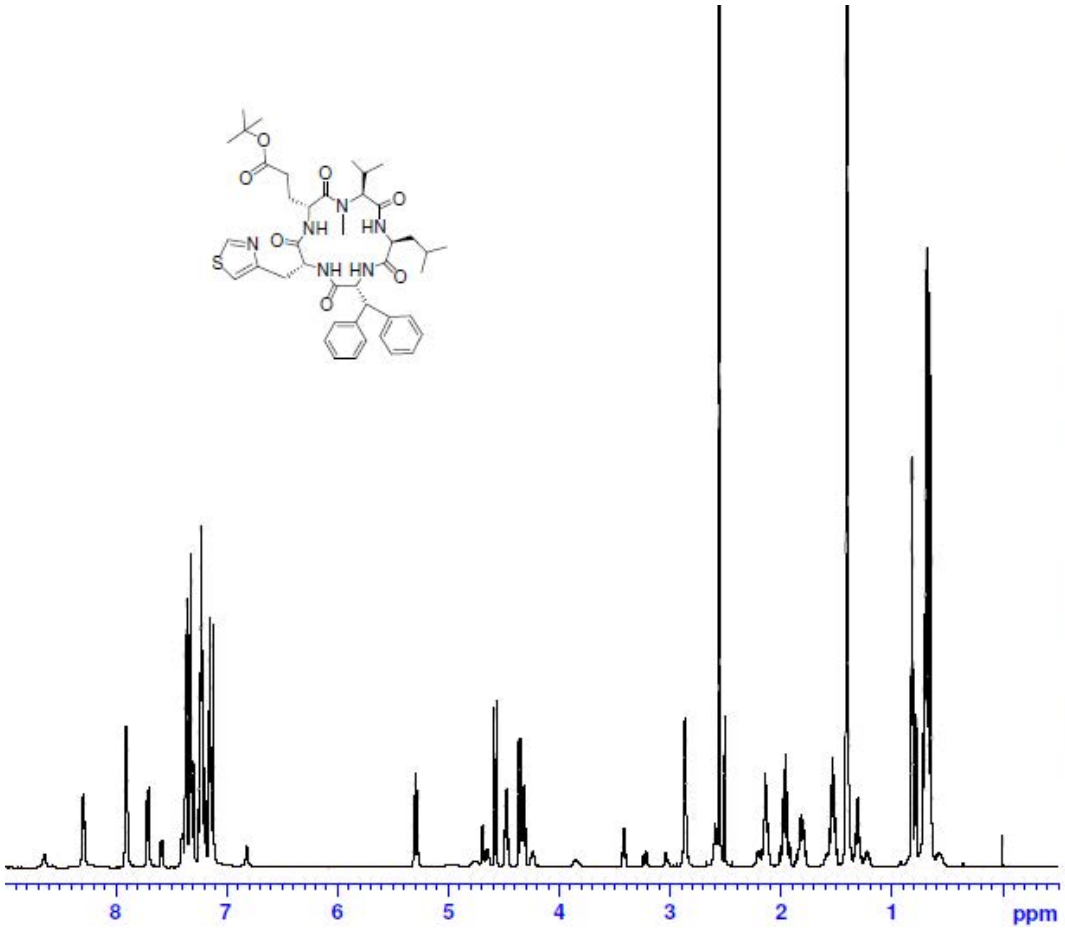
Compound **30**: HRMS of cyclo Leu-*N*-Me-Val-D-Glu(OtBu)-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala

MS Data from Orbitrap

Full spectrum



Compound **30**: ^{1}HNMR of cyclo Leu-*N*-Me-Val-D-Glu(OtBu)-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala

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Current Data Parameters
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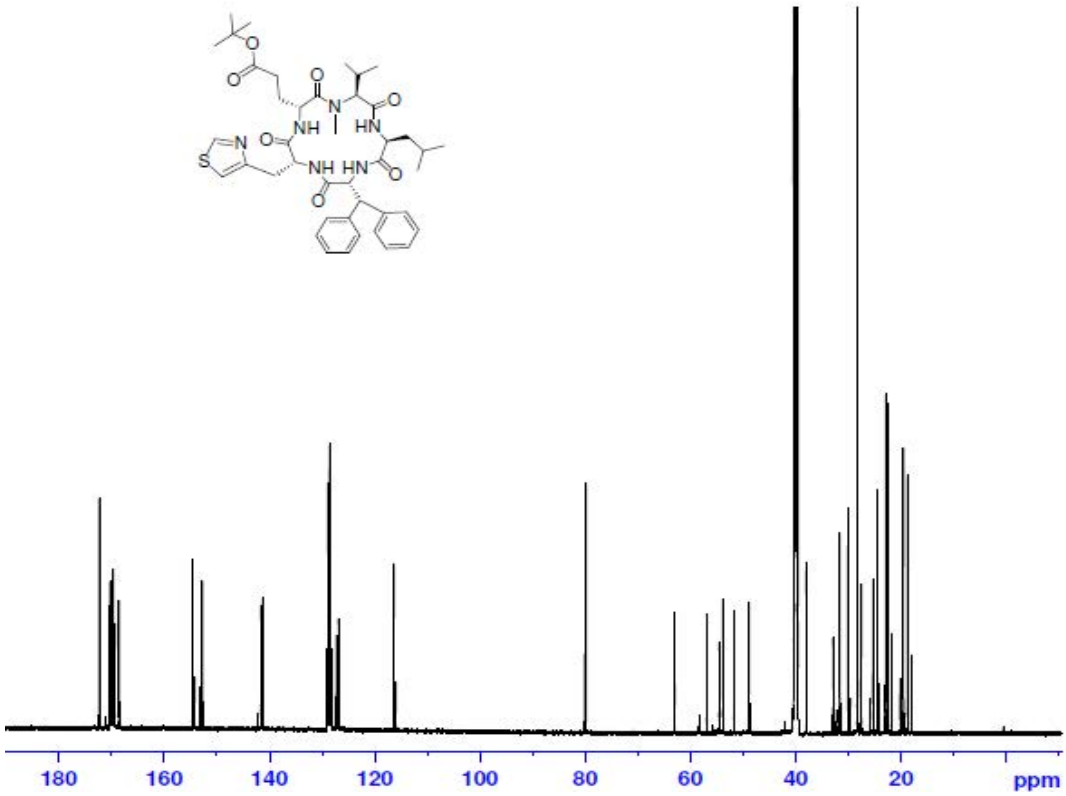
EXPNO                 12
PROCNO                 1

F2 - Acquisition Parameters
Date_           20140602
Time              17.18
INSTRUM           spect
PROBHD   5 mm CPTCI 1H/
PULPROG           zgpr
TD               48076
SOLVENT           DMSO
NS                   13
DS                    4
SWH            9009.009 Hz
FIDRES         0.187391 Hz
AQ             2.6682179 sec
RG                 6.54
DW                55.500 usec
DE                33.22 usec
TE                298.0 K
D1            20.00000000 sec
D12            0.00002000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         600.1620062 MHz
NUC1                   1H
P1                   8.00 usec
PLW1          3.81069994 W
PLW9          0.00000245 W

F2 - Processing parameters
SI                131072
SF          600.1600000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

Compound **30**: ^{13}CNMR of cyclo Leu-*N*-Me-Val-D-Glu(OtBu)-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala




```
Current Data Parameters
NAME          140602-yck
EXPNO                 13
PROCNO                 1

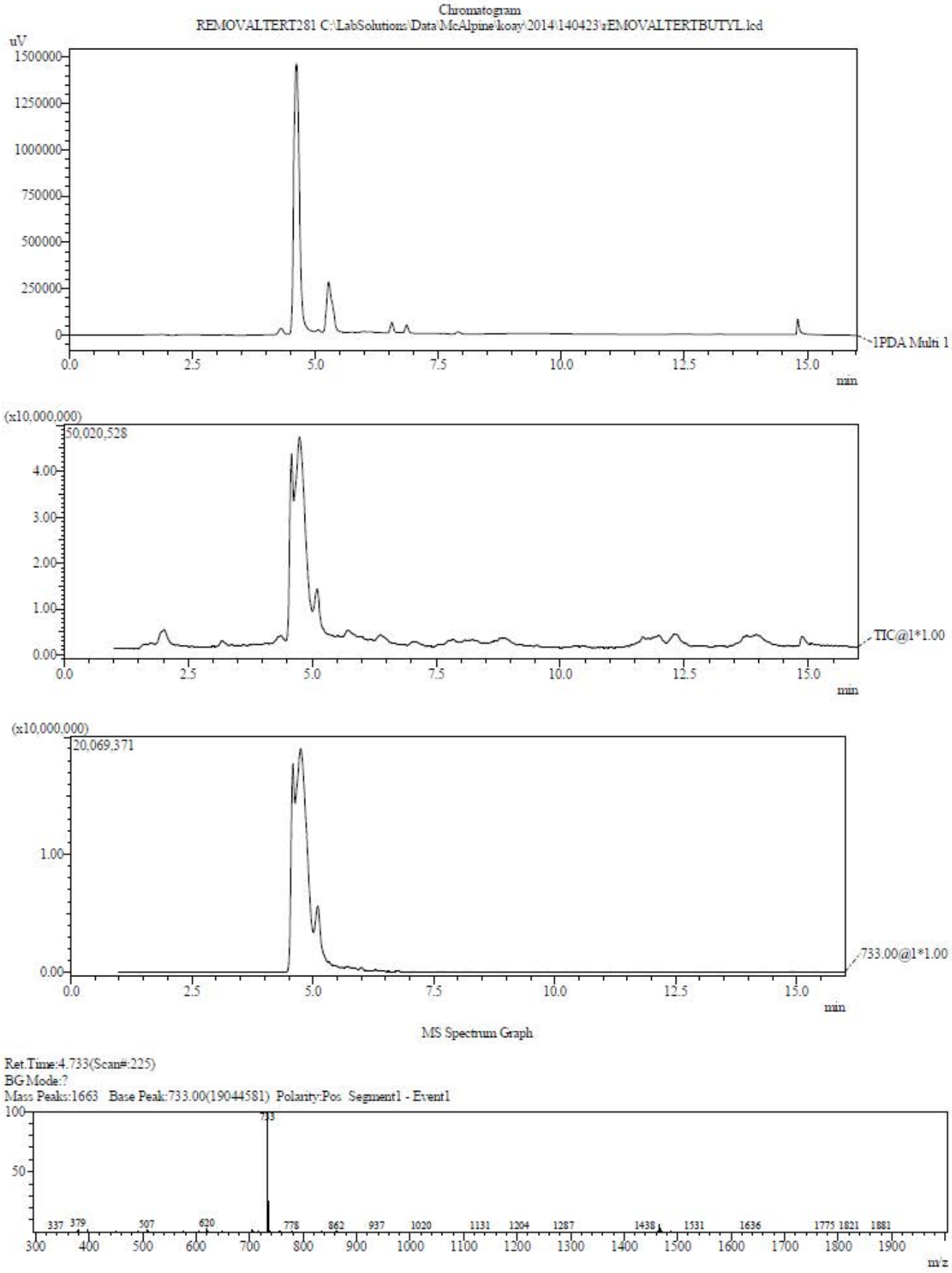
F2 - Acquisition Parameters
Date_           20140602
Time              17.26
INSTRUM           spect
PROBHD   5 mm CPTCI 1H/
PULPROG          zgpg30
TD               65536
SOLVENT           DMSO
NS                 1024
DS                    4
SWH           32894.738 Hz
FIDRES         0.501934 Hz
AQ             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                    1

======== CHANNEL f1 ========
SFO1         150.9239339 MHz
NUC1                  13C
P1                  11.50 usec
PLW1        100.00000000 W

======== CHANNEL f2 ========
SFO2         600.1624006 MHz
NUC2                   1H
CPDPRG[2 bi_waltz65_256
PCPD2               70.00 usec
PLW2          3.81069994 W
PLW12         0.04977200 W
PLW13         0.02438800 W

F2 - Processing parameters
SI                 32768
SF          150.9103520 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

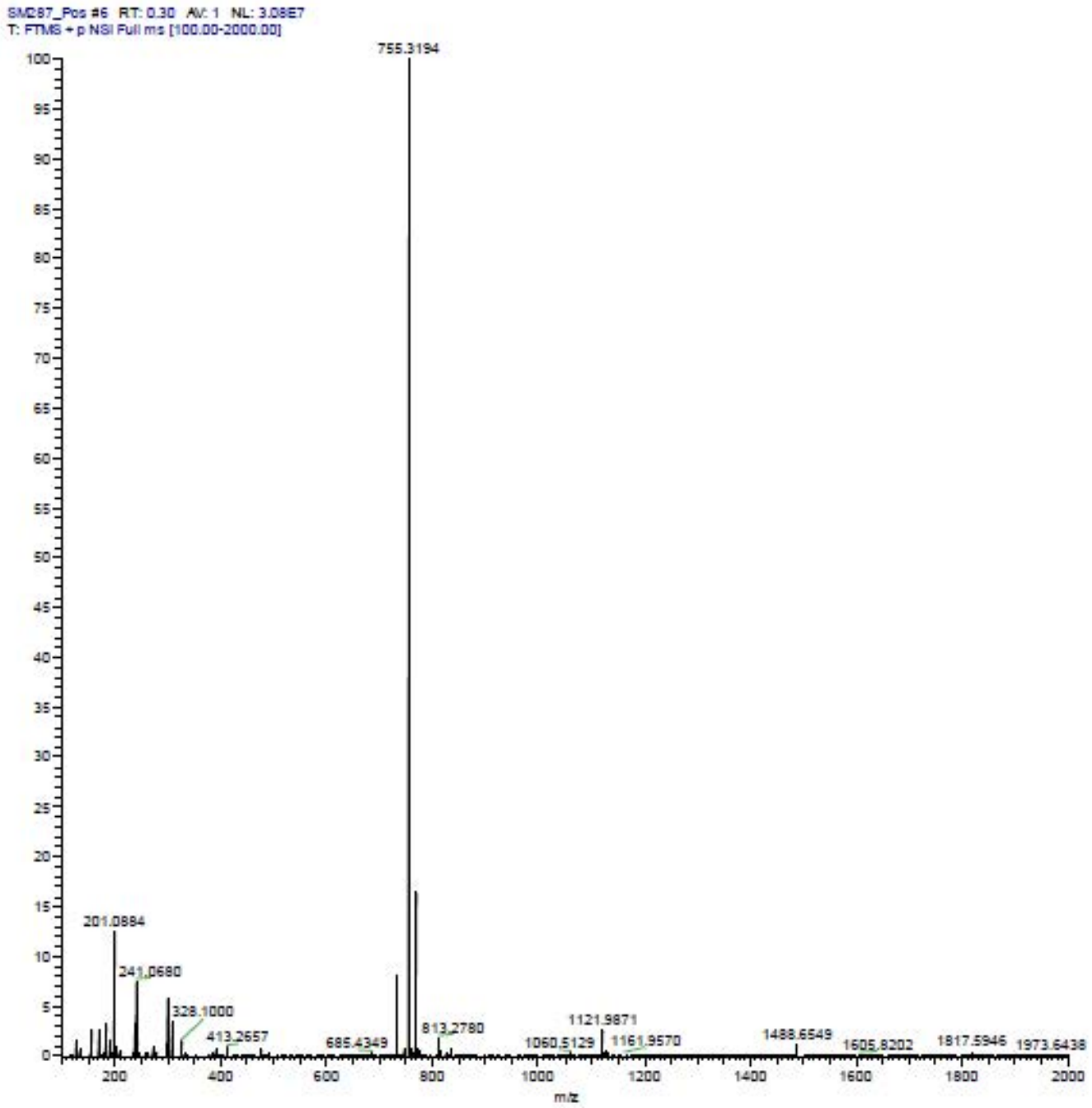
Compound **31**: LCMS of cyclo Leu-*N*-Me-Val-D-Glu-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala



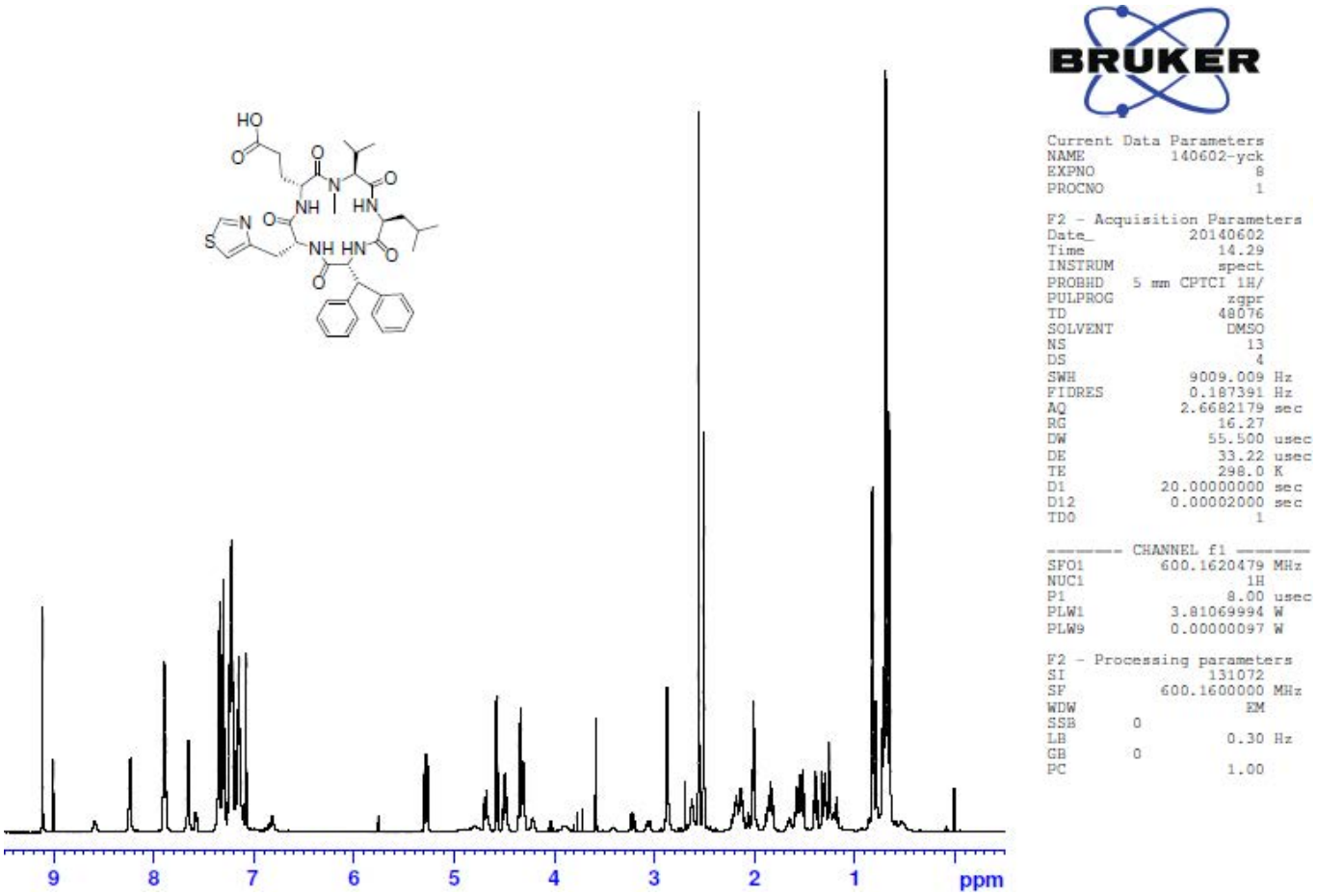
Compound **31**: HRMS of cyclo Leu-*N*-Me-Val-D-Glu-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala

MS Data from Orbitrap

Full spectrum



Compound **31**: [1]HNMR of cyclo Leu-*N*-Me-Val-D-Glu-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala



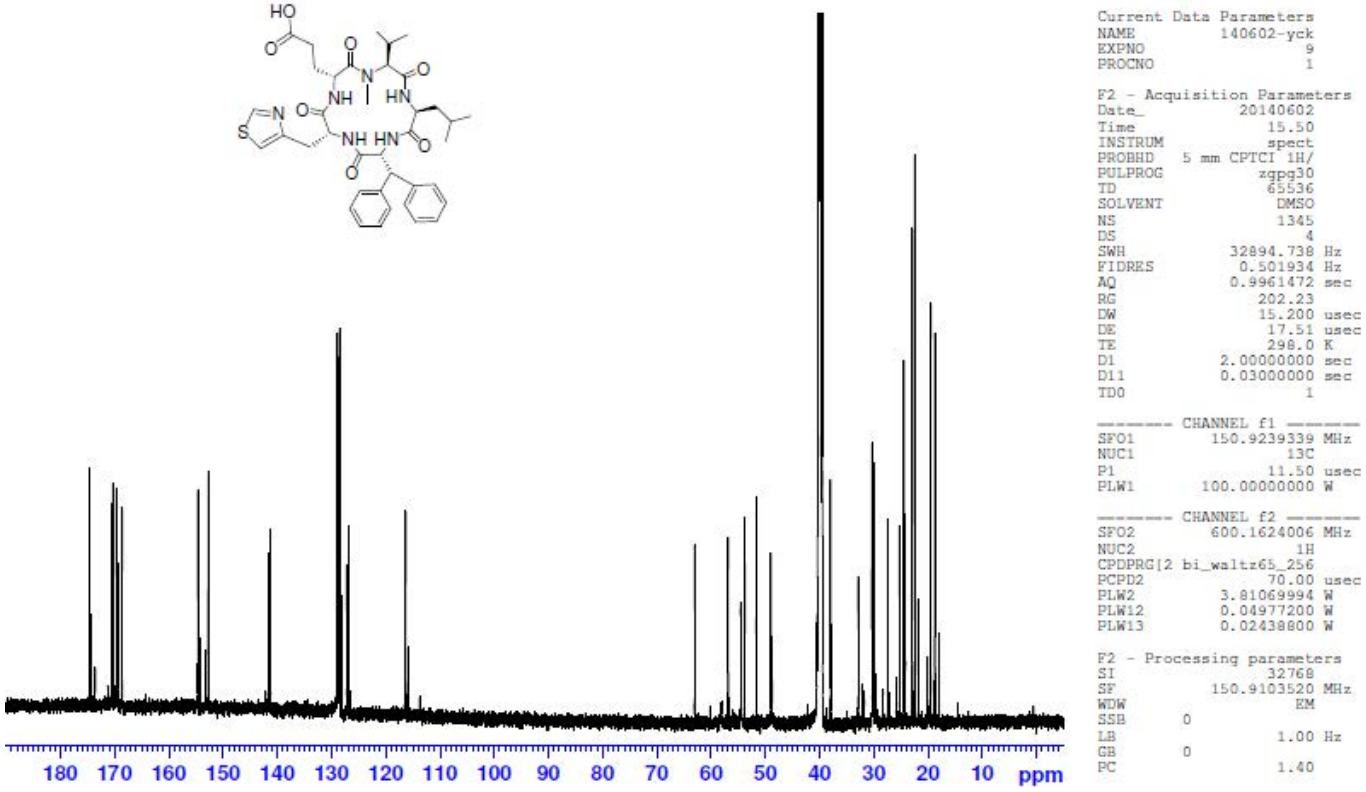

```
Current Data Parameters
NAME          140602-yck
EXPNO                  8
PROCNO                 1

F2 - Acquisition Parameters
Date_           20140602
Time               14.29
INSTRUM            spect
PROBHD   5 mm CPTCI 1H/
PULPROG            xgpr
TD                48076
SOLVENT            DMSO
NS                    13
DS                     4
SWH             9009.009 Hz
FIDRES          0.187391 Hz
AQ              2.6682179 sec
RG                 16.27
DW                55.500 usec
DE                33.22 usec
TE                298.0 K
D1           20.00000000 sec
D12           0.00002000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         600.1620479 MHz
NUC1                   1H
P1                   8.00 usec
PLW1          3.81069994 W
PLW9          0.00000097 W

F2 - Processing parameters
SI                131072
SF          600.1600000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

Compound **31**: ^{13}CNMR of cyclo Leu-*N*-Me-Val-D-Glu-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala




```
Current Data Parameters
NAME          140602-yck
EXPNO                  9
PROCNO                 1

F2 - Acquisition Parameters
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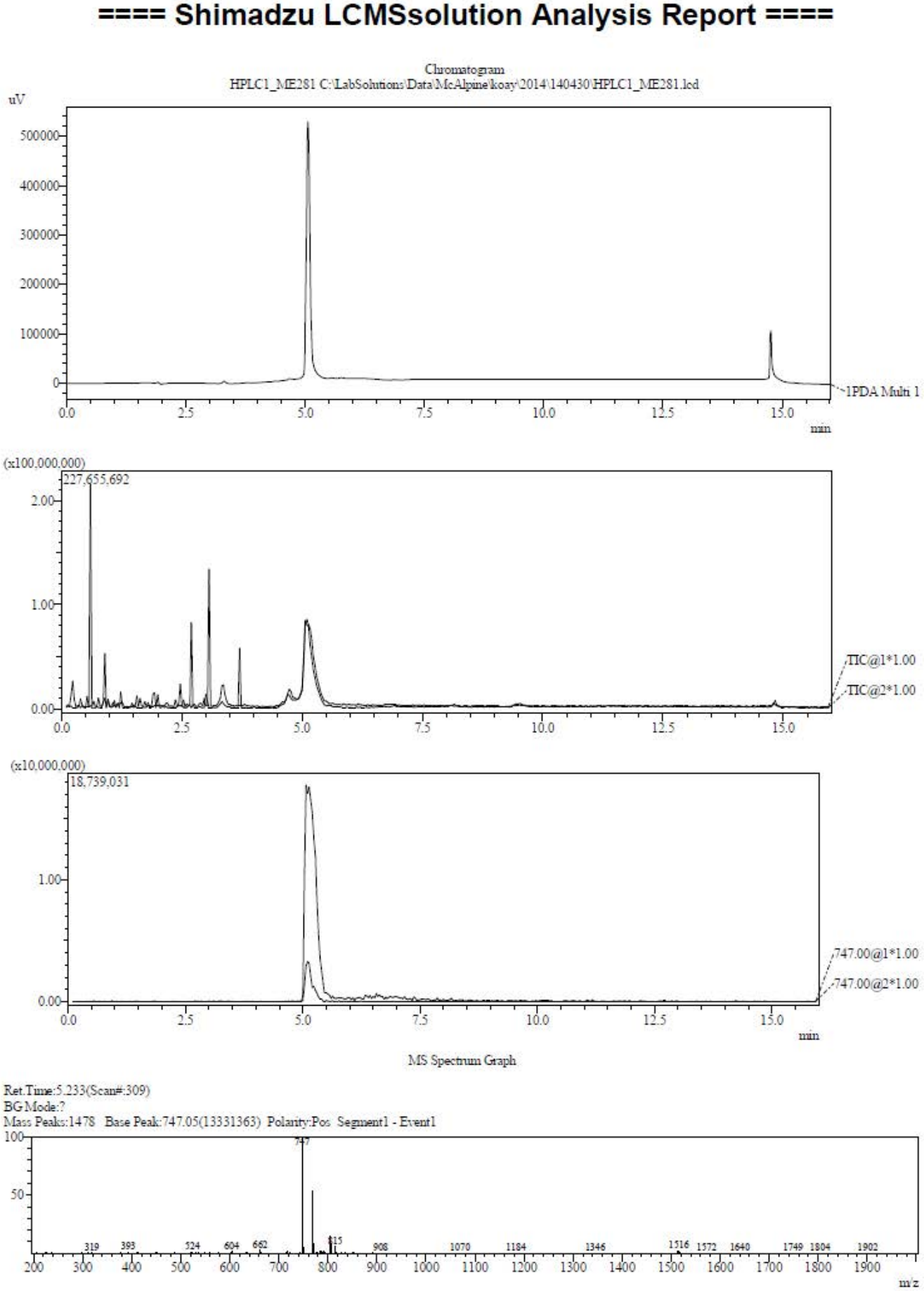
Time               15.50
INSTRUM            spect
PROBHD   5 mm CPTCI 1H/
PULPROG         zgpg30
TD                65536
SOLVENT            DMSO
NS                  1345
DS                     4
SWH            32894.738 Hz
FIDRES          0.501934 Hz
AQ              0.9961472 sec
RG                202.23
DW                15.200 usec
DE                17.51 usec
TE                298.0 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         150.9239339 MHz
NUC1                   13C
P1                  11.50 usec
PLW1        100.00000000 W

======== CHANNEL f2 ========
SFO2         600.1624006 MHz
NUC2                   1H
CPDPRG[2 bi_waltz65_256
PCPD2                70.00 usec
PLW2          3.81069994 W
PLW12         0.04977200 W
PLW13         0.02438800 W

F2 - Processing parameters
SI                 32768
SF          150.9103520 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

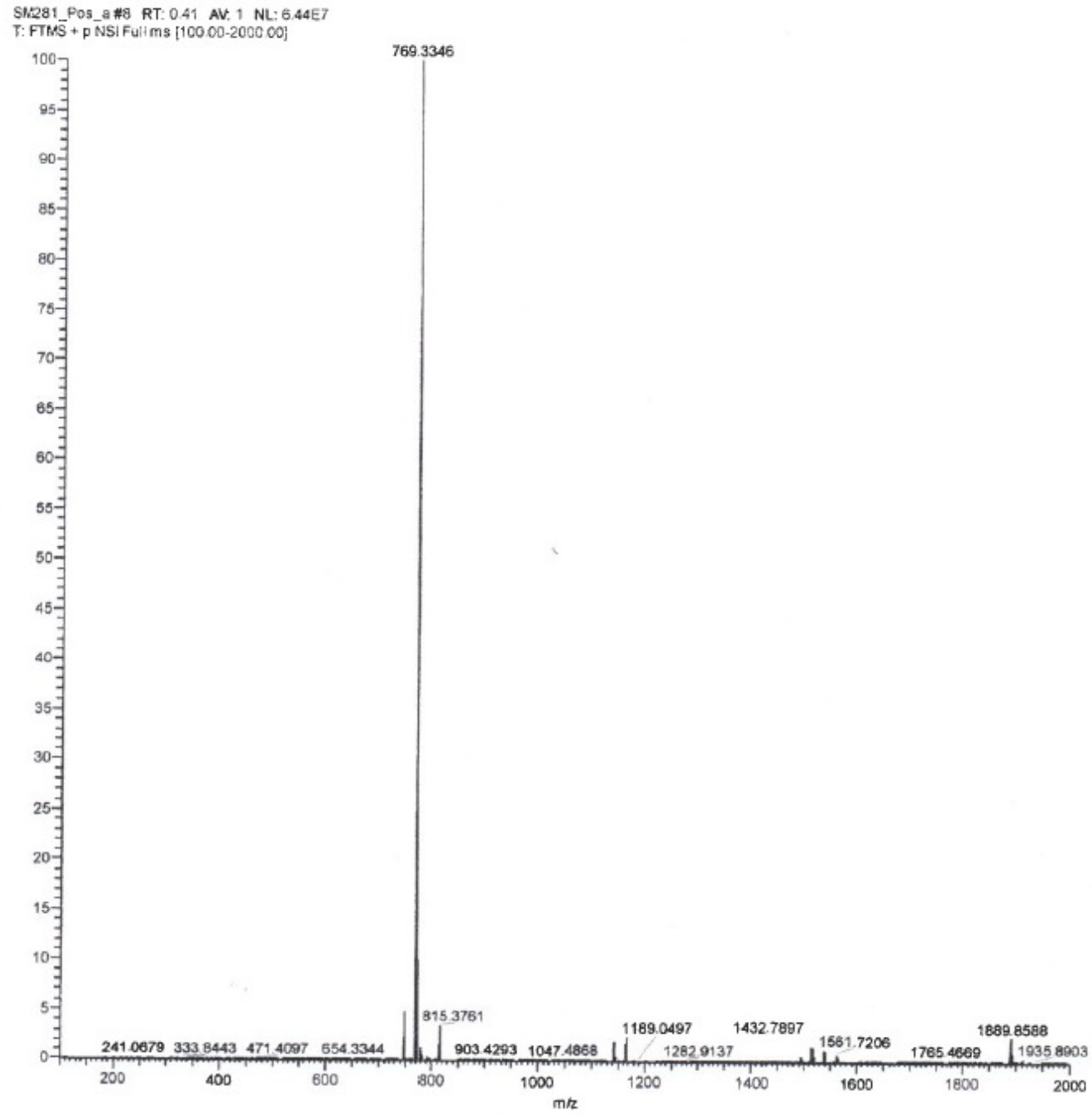
Compound **32**: LCMS of cyclo Leu-*N*-Me-Val-D-Glu(OMe)-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala



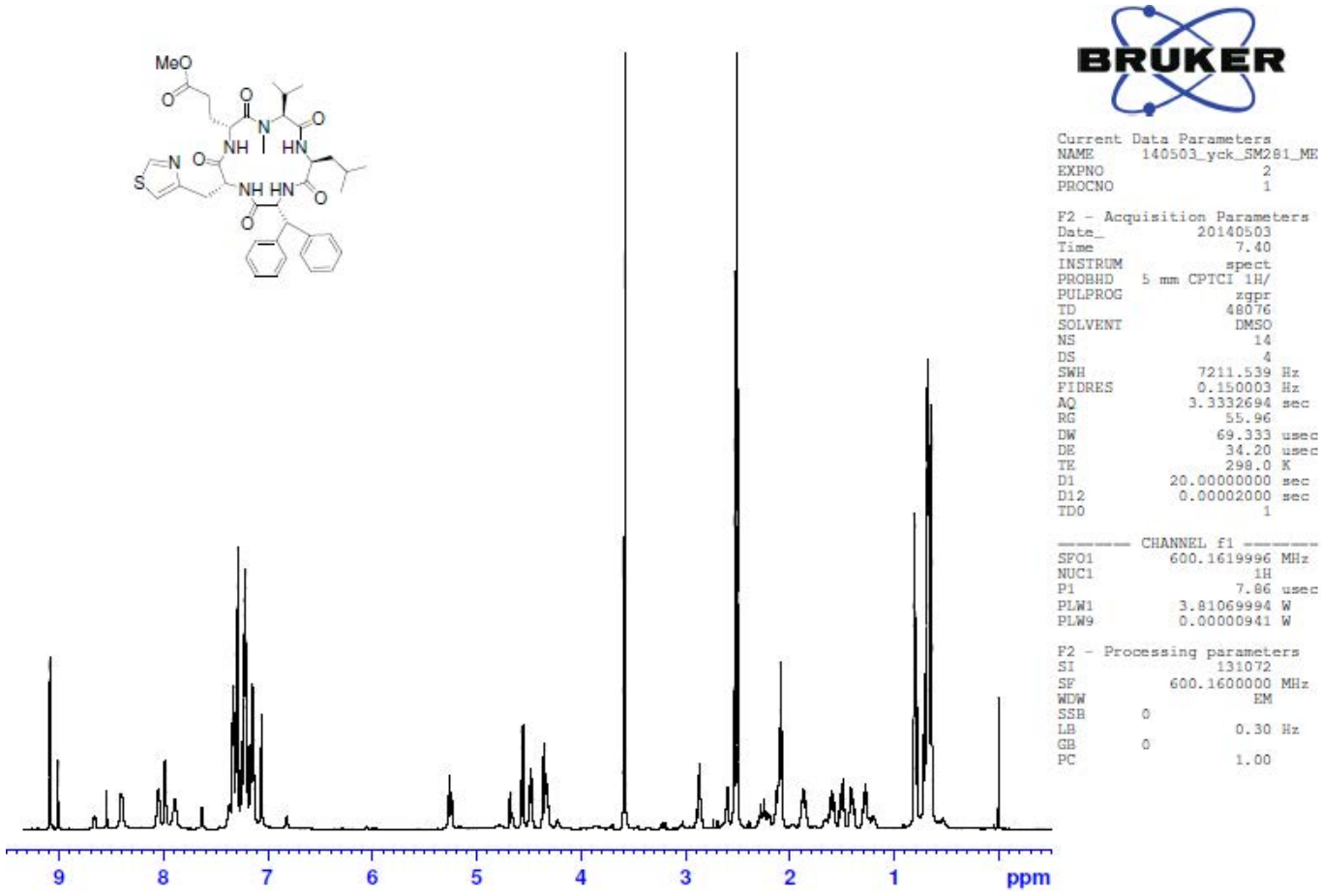
Compound **32**: HRMS of cyclo Leu-*N*-Me-Val-D-Glu(OMe)-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala

MS Data from Orbitrap

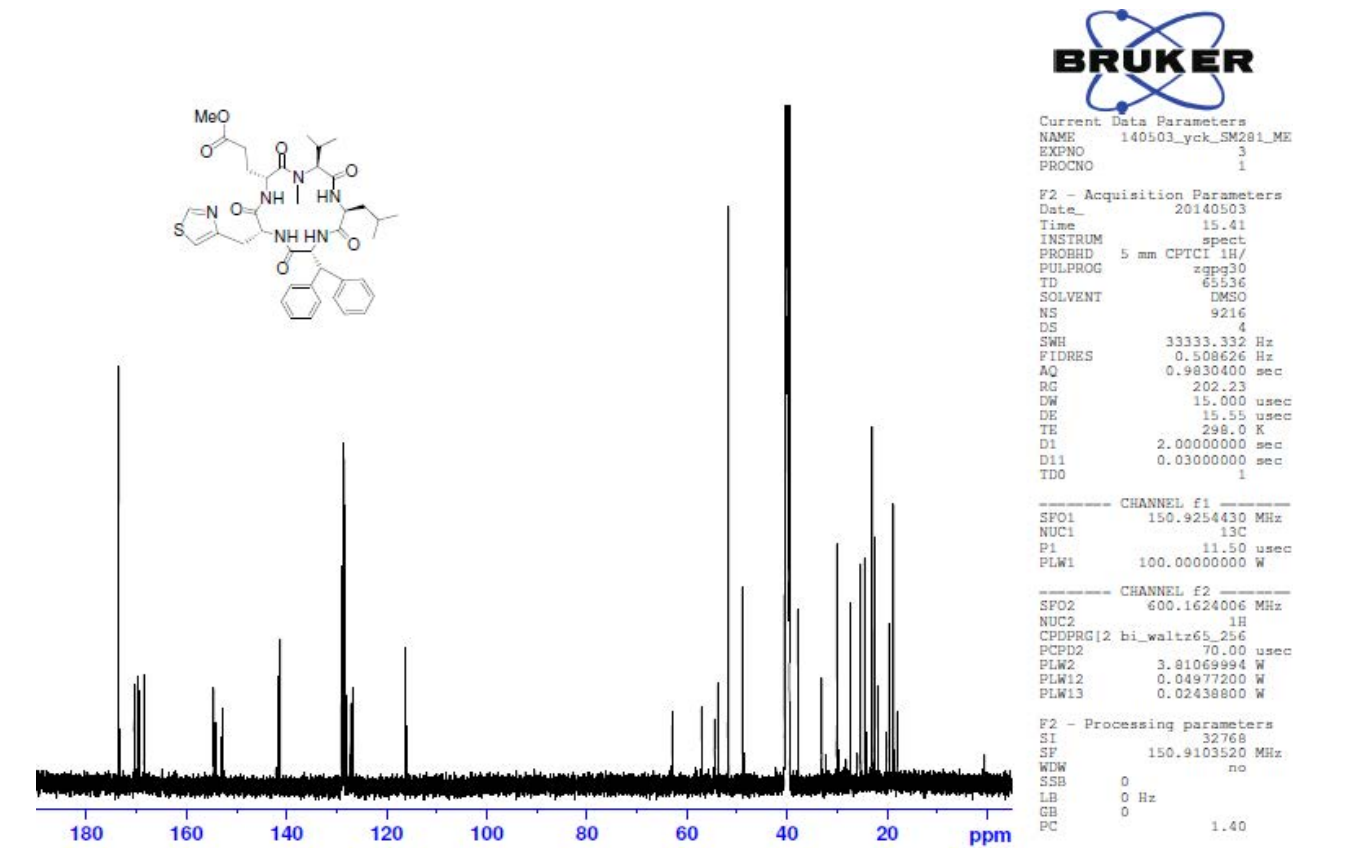
Full spectrum



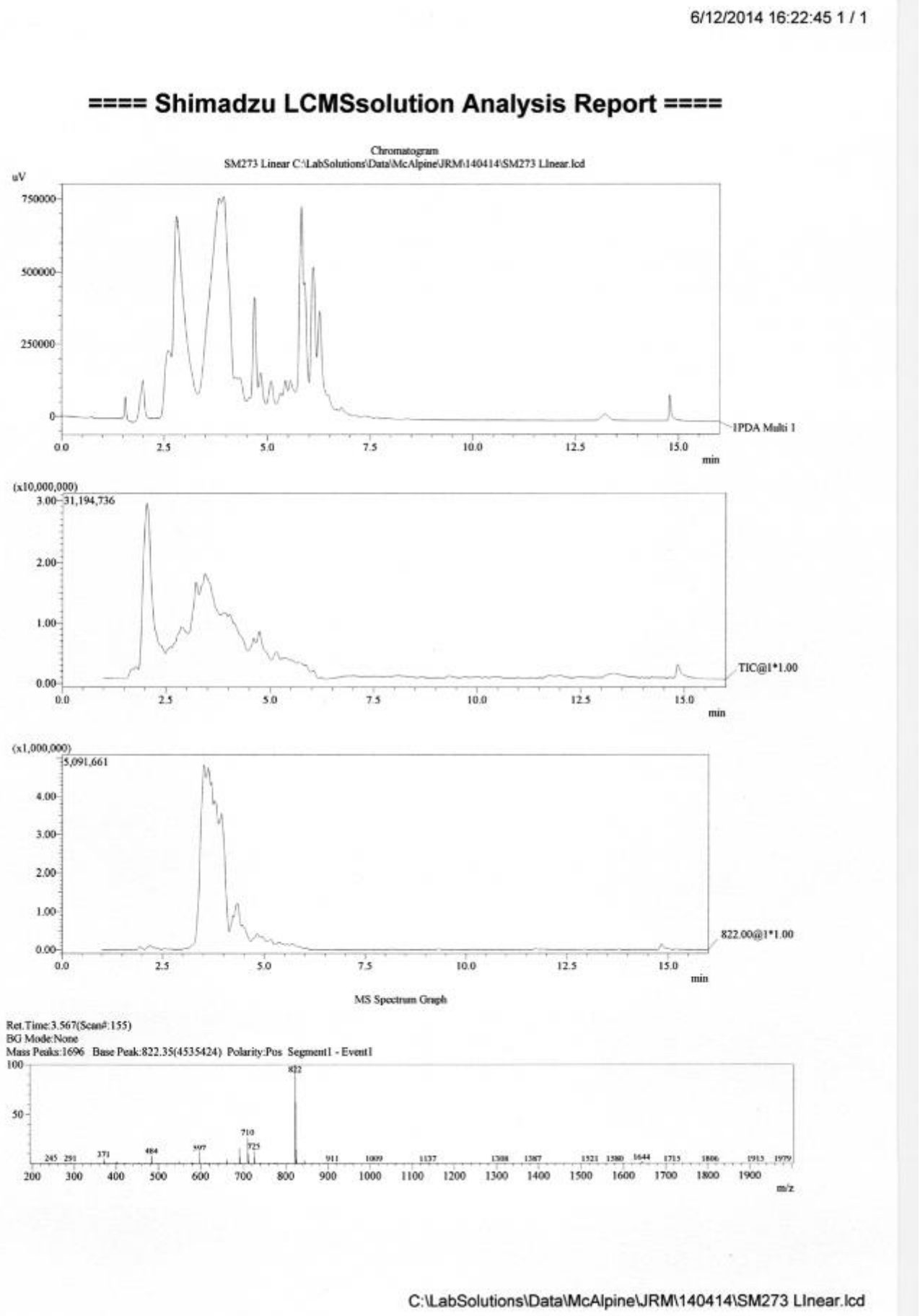
Compound **32**: [1]HNMR of cyclo Leu-*N*-Me-Val-D-Glu(OMe)-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala



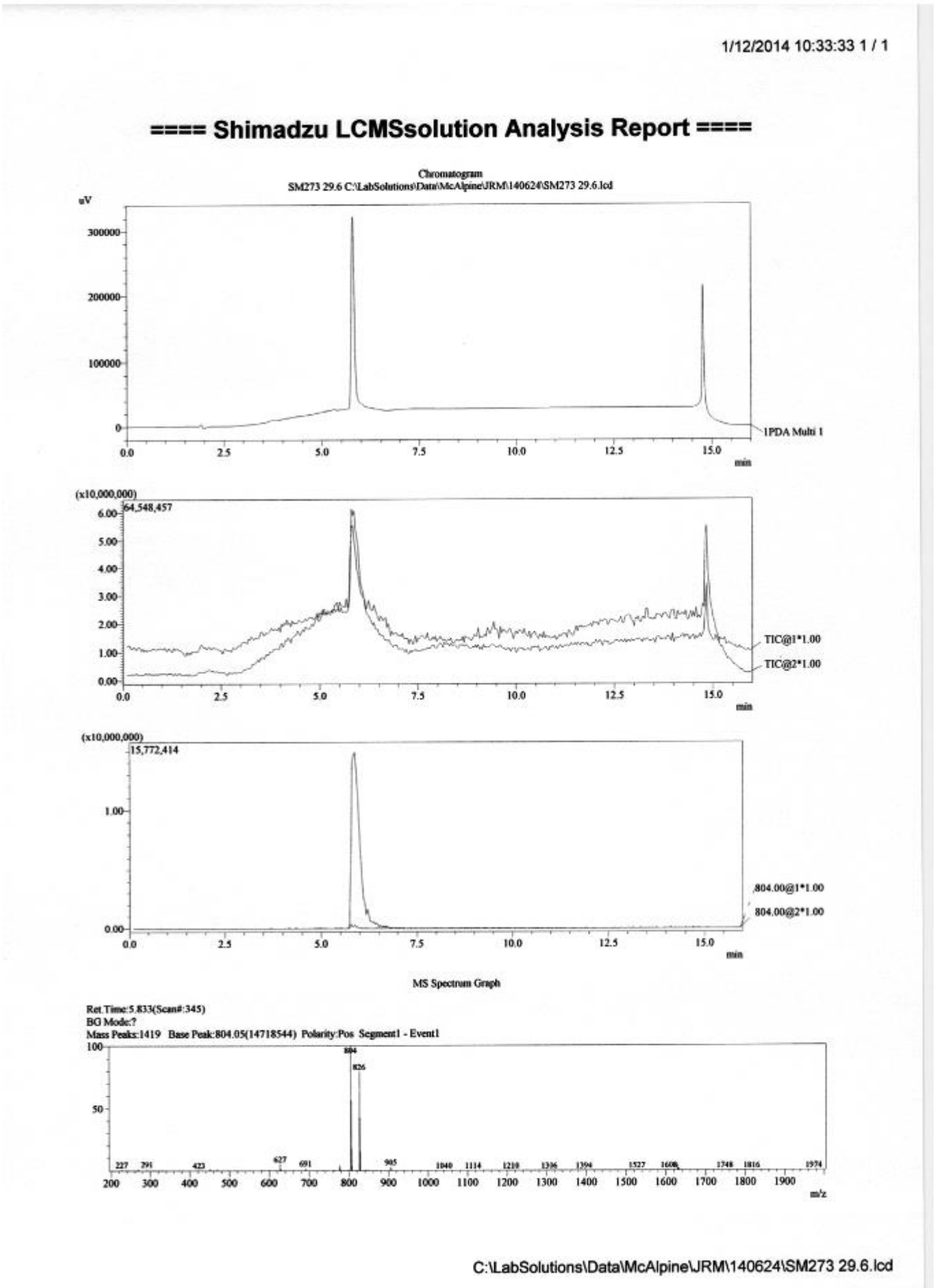
Compound **32**: ^{13}CNMR of cyclo Leu-*N*-Me-Val-D-Glu(OMe)-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala



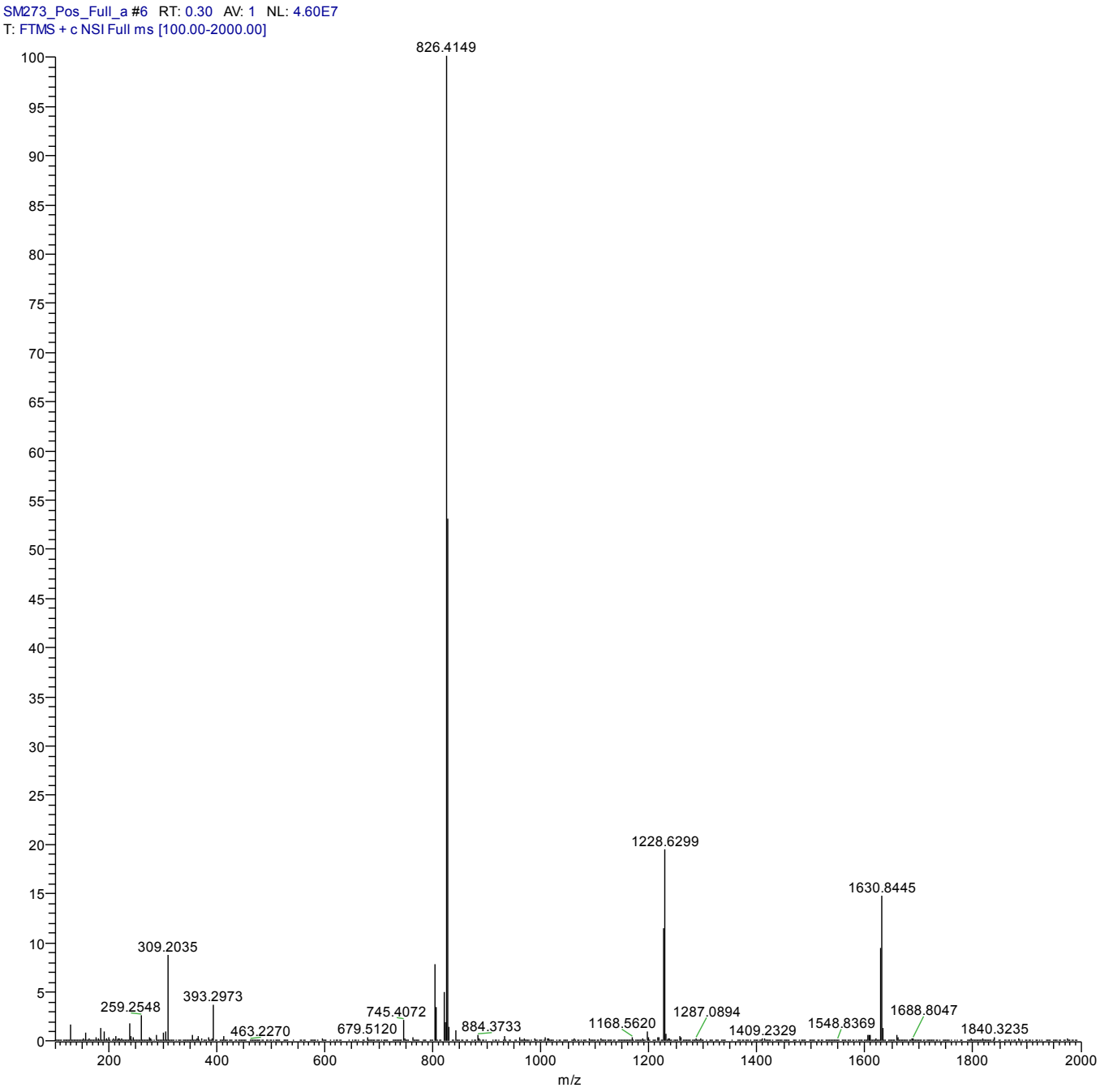
Compound **33**: LCMS of DDLP HO-Leu-*N*-Me-Val-(4-Methoxy)-D-Phe-(4-Methoxy)-D-Phe-3,3-Diphe-D-Ala-NH_2



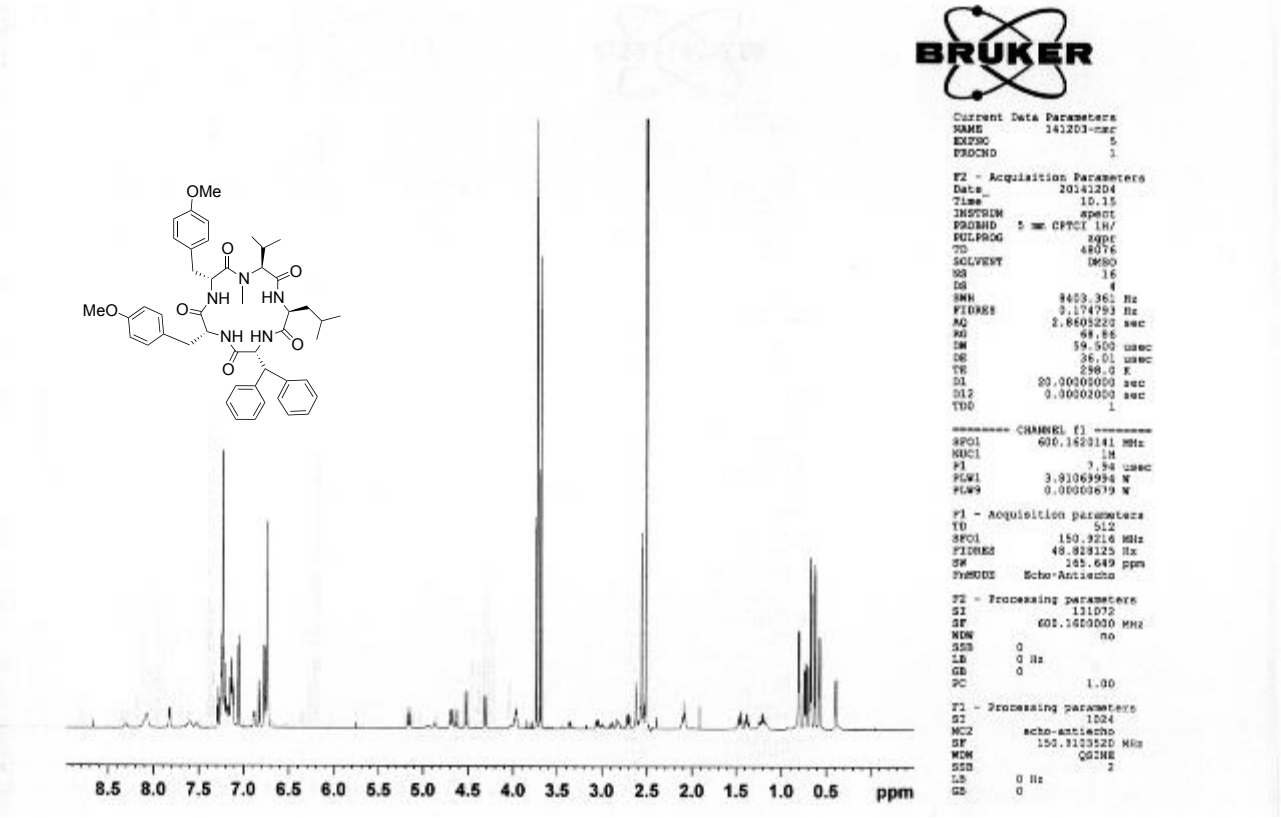
Compound **33**: LCMS of *Cyclo* Leu-*N*-Me-Val-(4-Methoxy)-D-Phe-(4-Methoxy)-D-Phe-3,3-Diphe-D-Ala



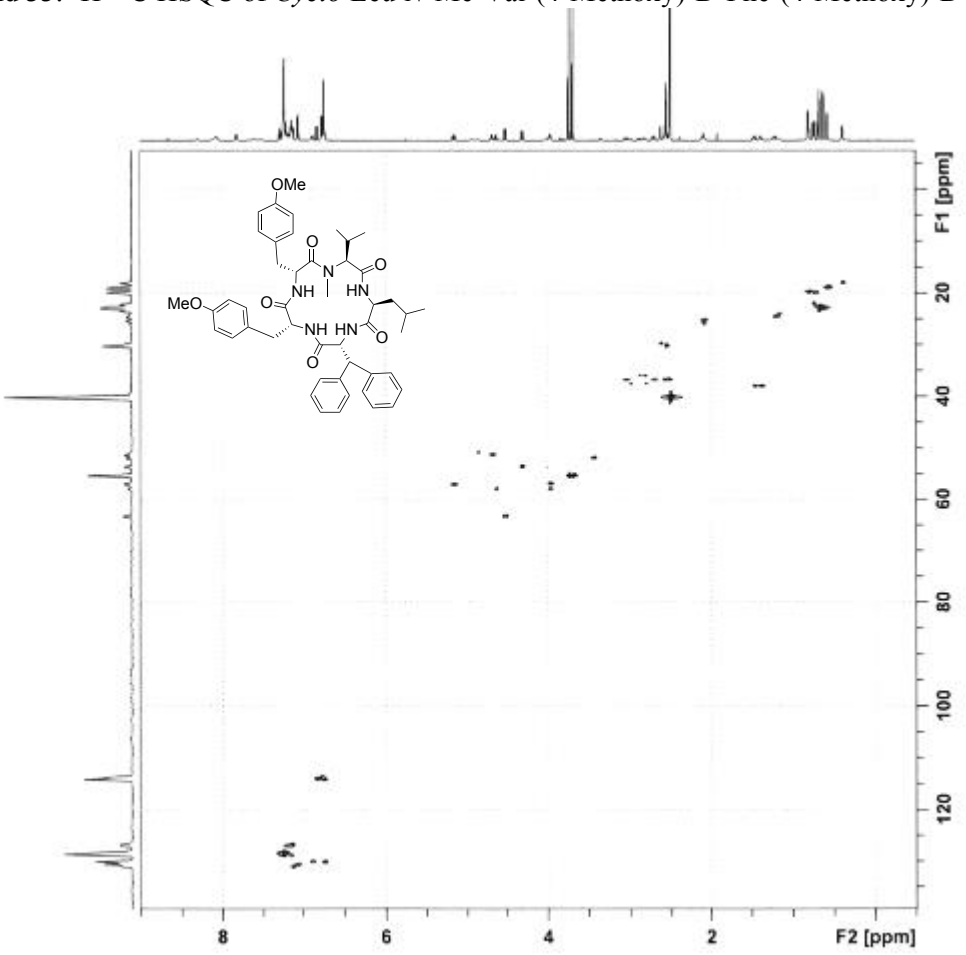
Compound **33**: HRMS of *Cyclo* Leu-*N*-Me-Val-(4-Methoxy)-D-Phe-(4-Methoxy)-D-Phe-3,3-Diphe-D-Ala



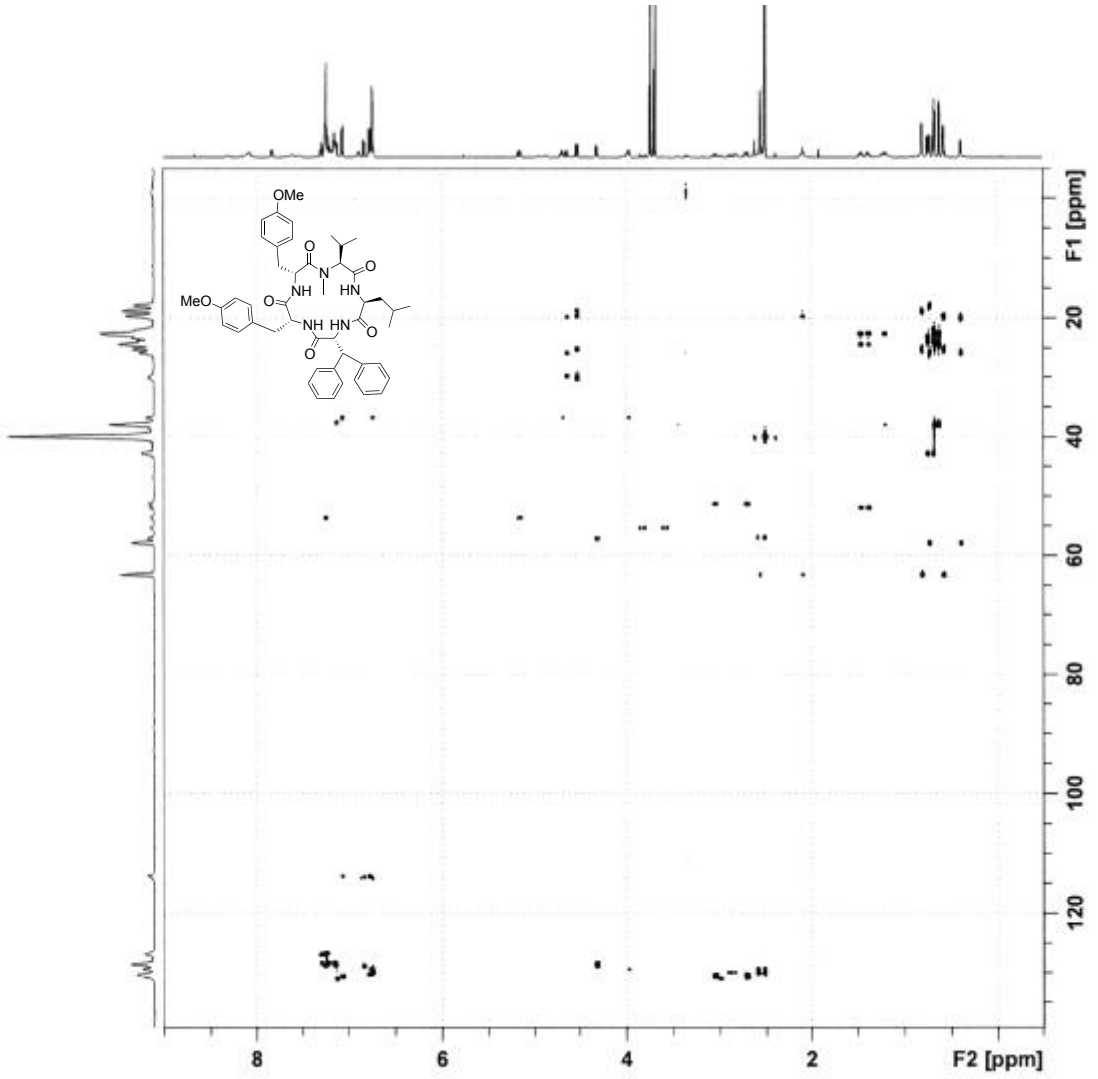
Compound **33**: ^{1}HNMR of *Cyclo* Leu-*N*-Me-Val-(4-Methoxy)-D-Phe-(4-Methoxy)-D-Phe-3,3-Diphe-D-Ala



Compound **33**: ^{1}H-^{13}C HSQC of *Cyclo* Leu-*N*-Me-Val-(4-Methoxy)-D-Phe-(4-Methoxy)-D-Phe-3,3-Diphe-D-Ala



Compound **33**: ^{1}H-^{13}C HMBC of *Cyclo* Leu-*N*-Me-Val-(4-Methoxy)-D-Phe-(4-Methoxy)-D-Phe-3,3-Diphe-D-Ala

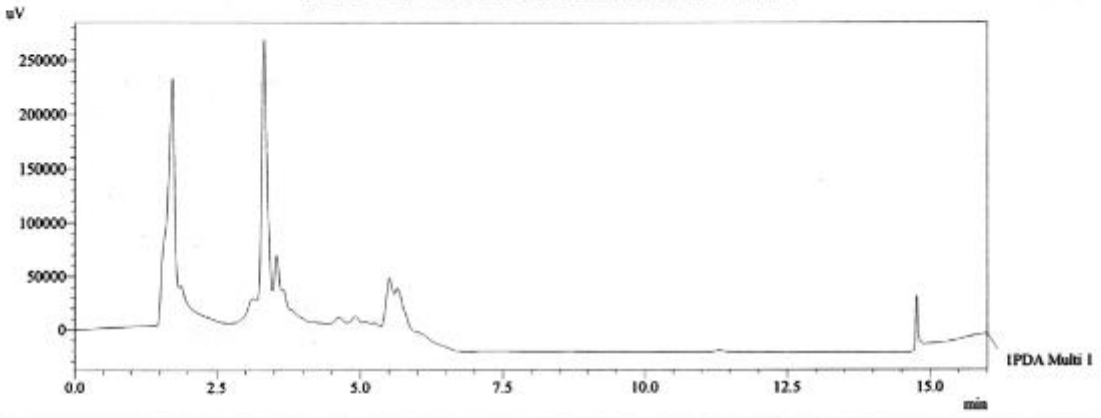


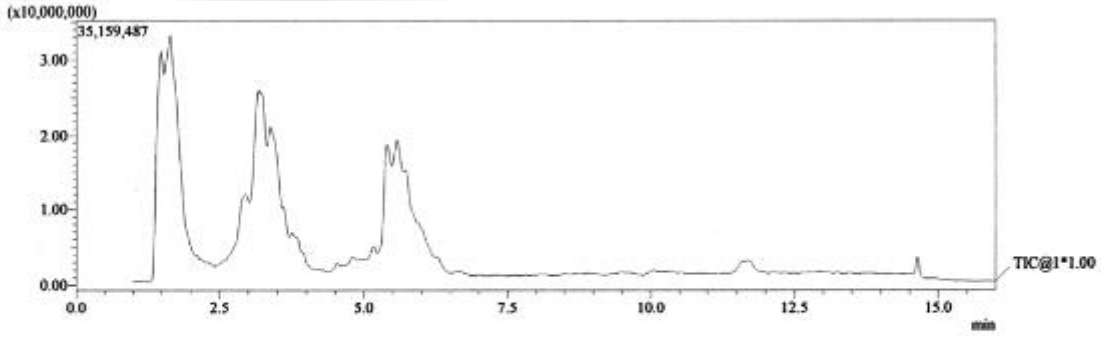
Compound **34**: LCMS of DDLP HO-Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-(4-Methoxy)-D-Phe-3,3-Diphe-D-Ala-NH_2

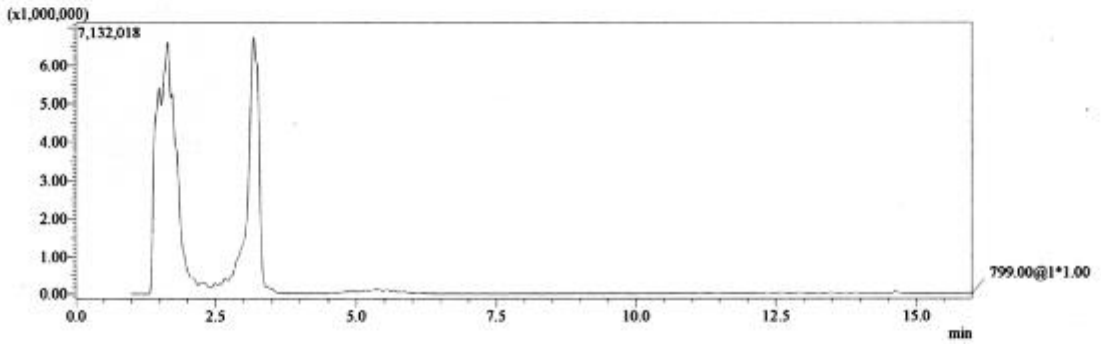
6/12/2014 16:29:55 1 / 1

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

Chromatogram
SM274 linear C:\LabSolutions\Data\McAlpine\JRM\140328\SM274 linear.lcd

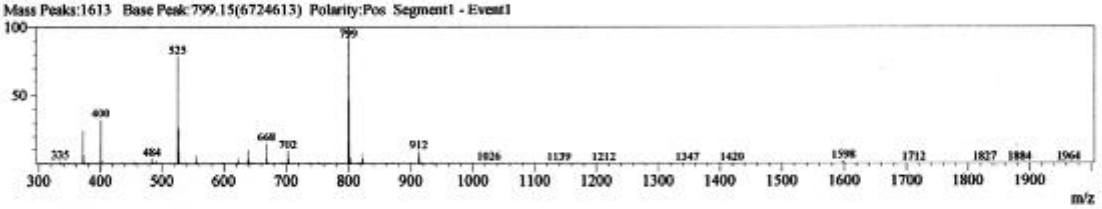






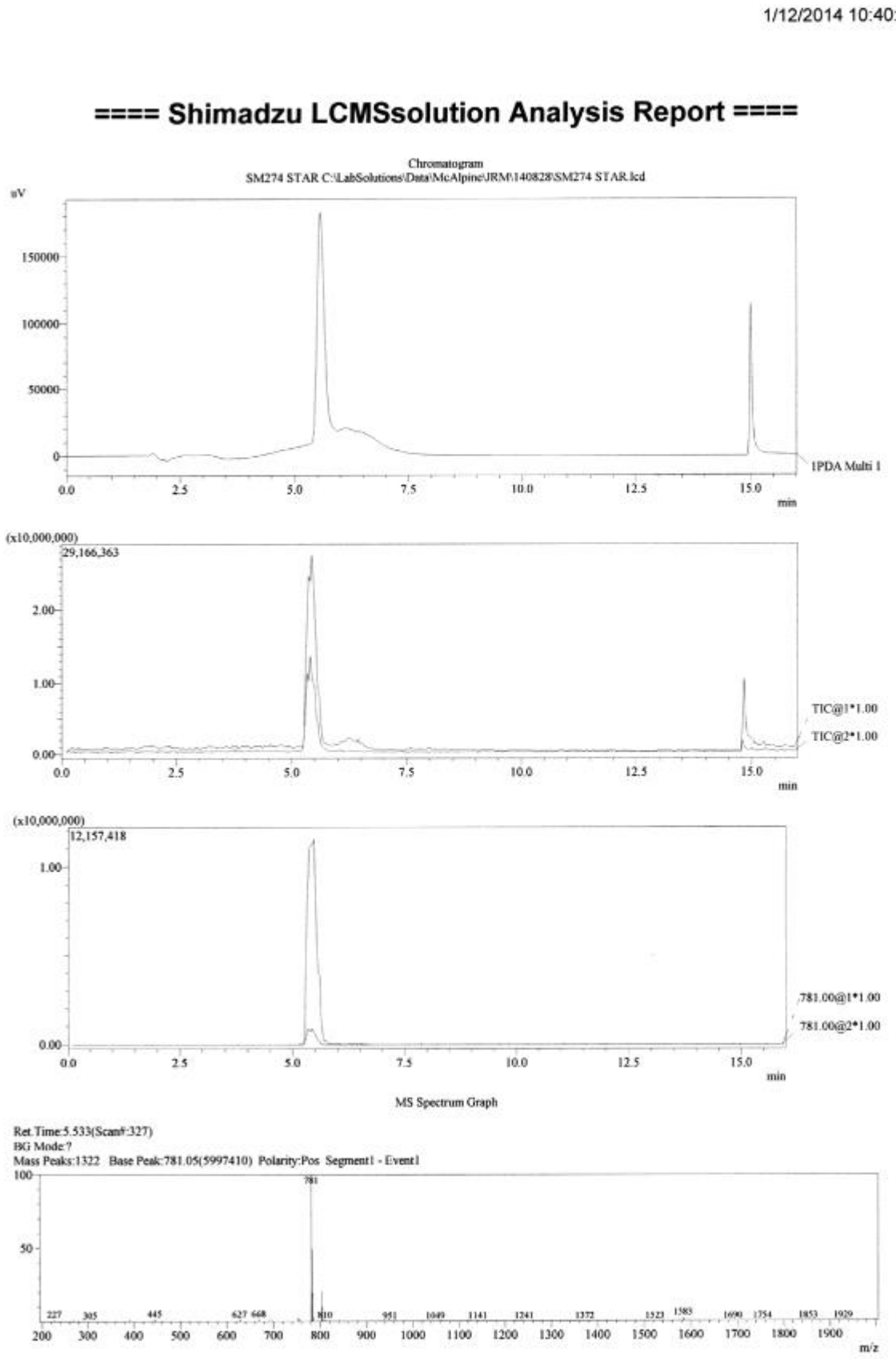
MS Spectrum Graph

Ret.Time:1.633(Scan#:39)
BG Mode:?
Mass Peaks:1613 Base Peak:799.15(6724613) Polarity:Pos Segment1 - Event1

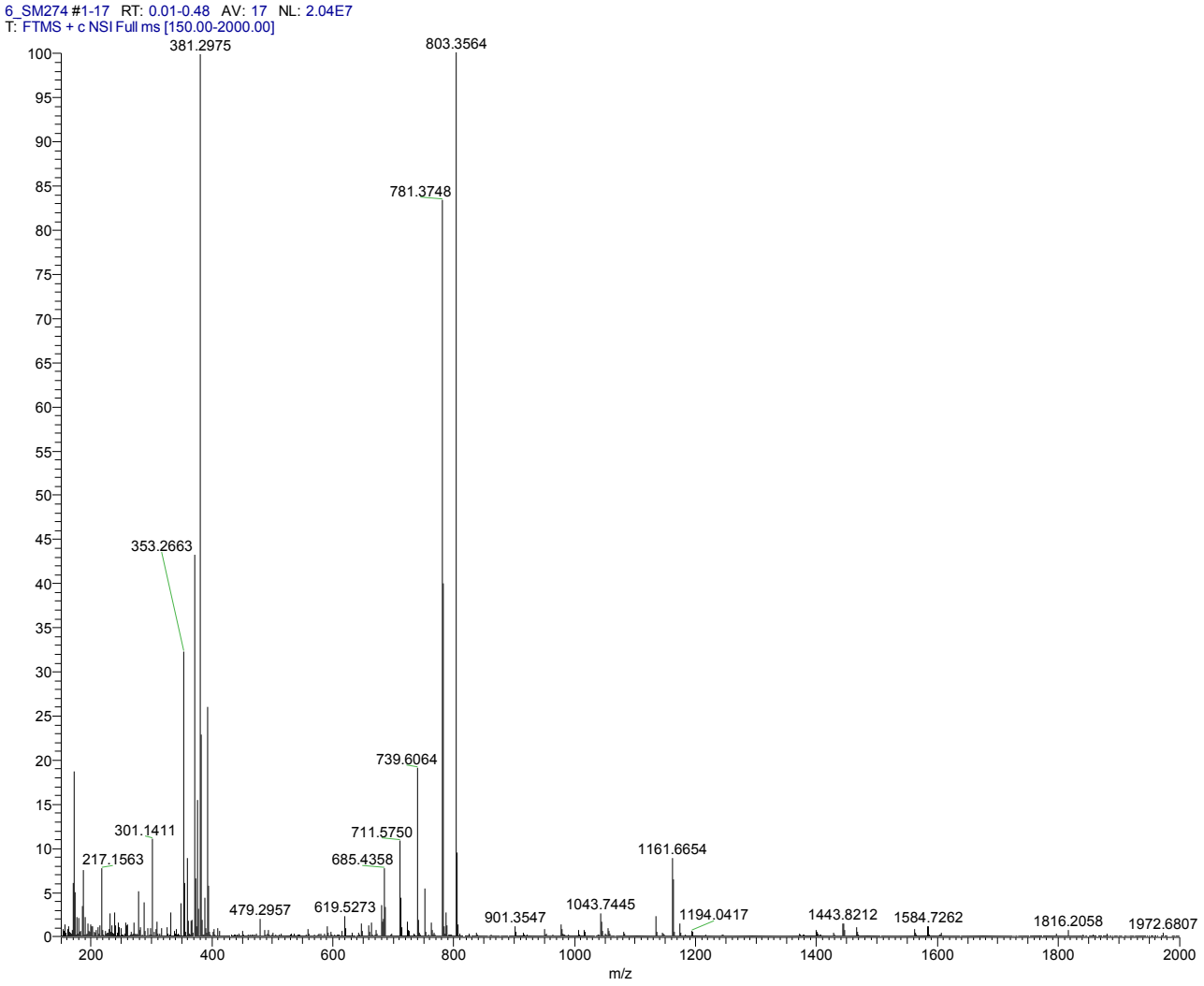


C:\LabSolutions\Data\McAlpine\JRM\140328\SM274 linear.lcd

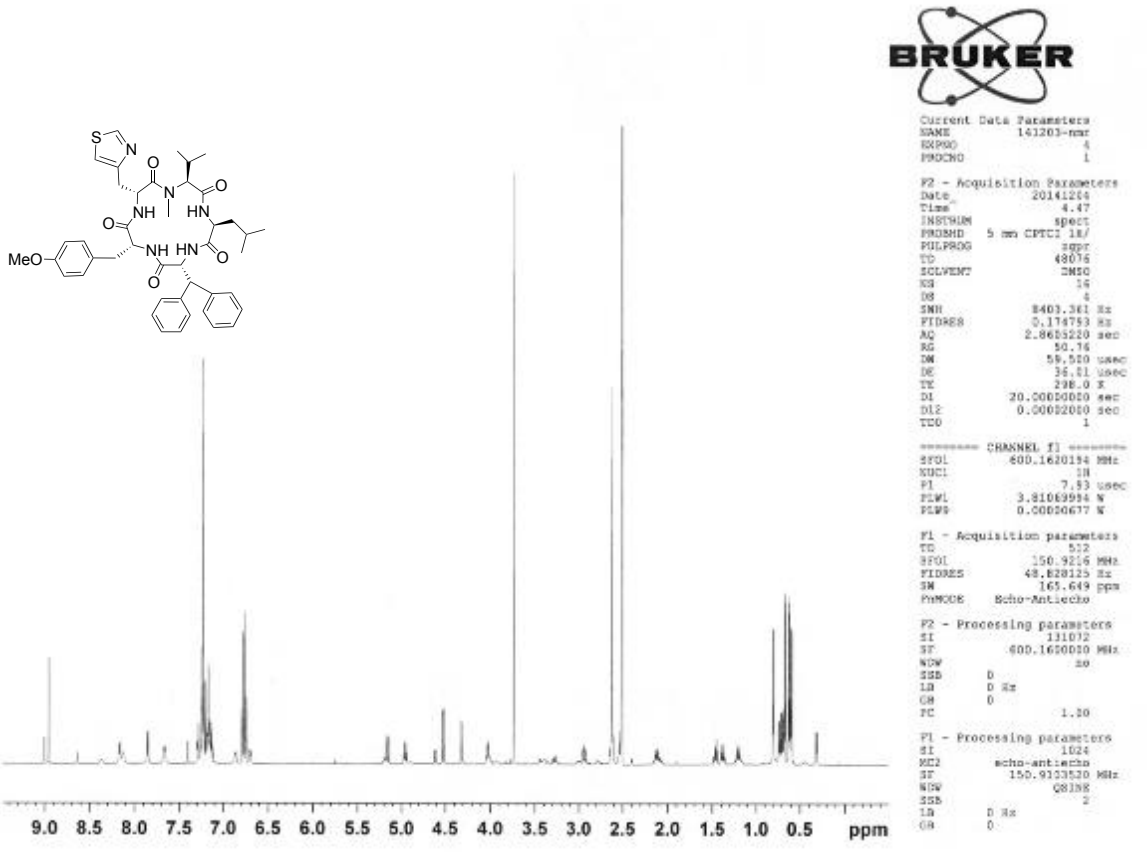
Compound **34**: LCMS of Cyclo Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-(4-Methoxy)-D-Phe-3,3-Diphe-D-Ala



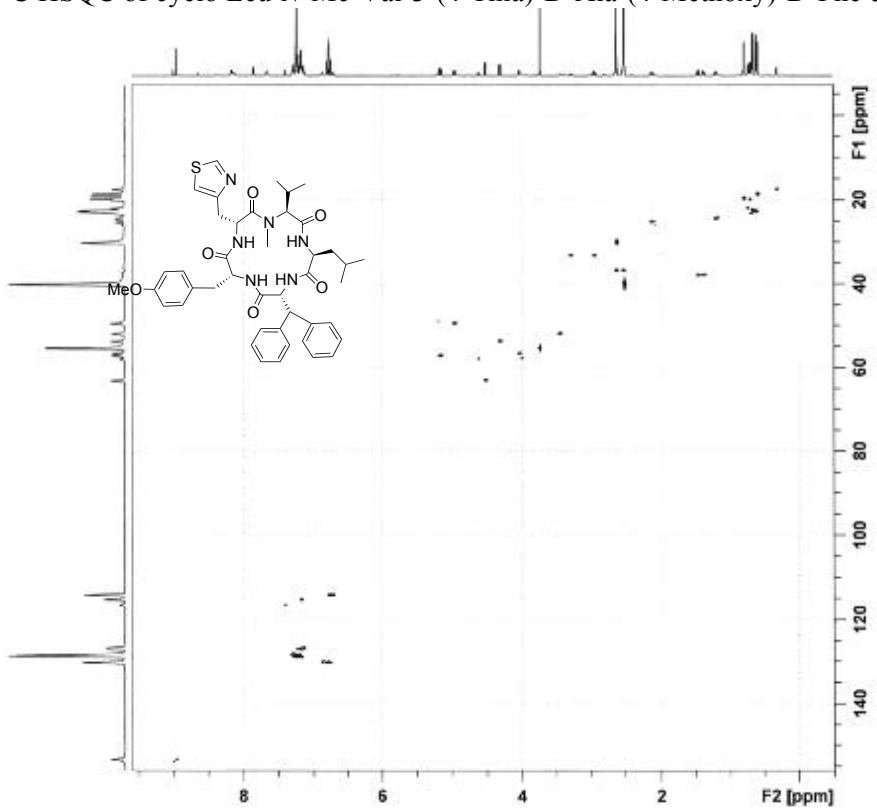
Compound **34**: HRMS of cyclo Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-(4-Methoxy)-D-Phe-3,3-Diphe-D-Ala



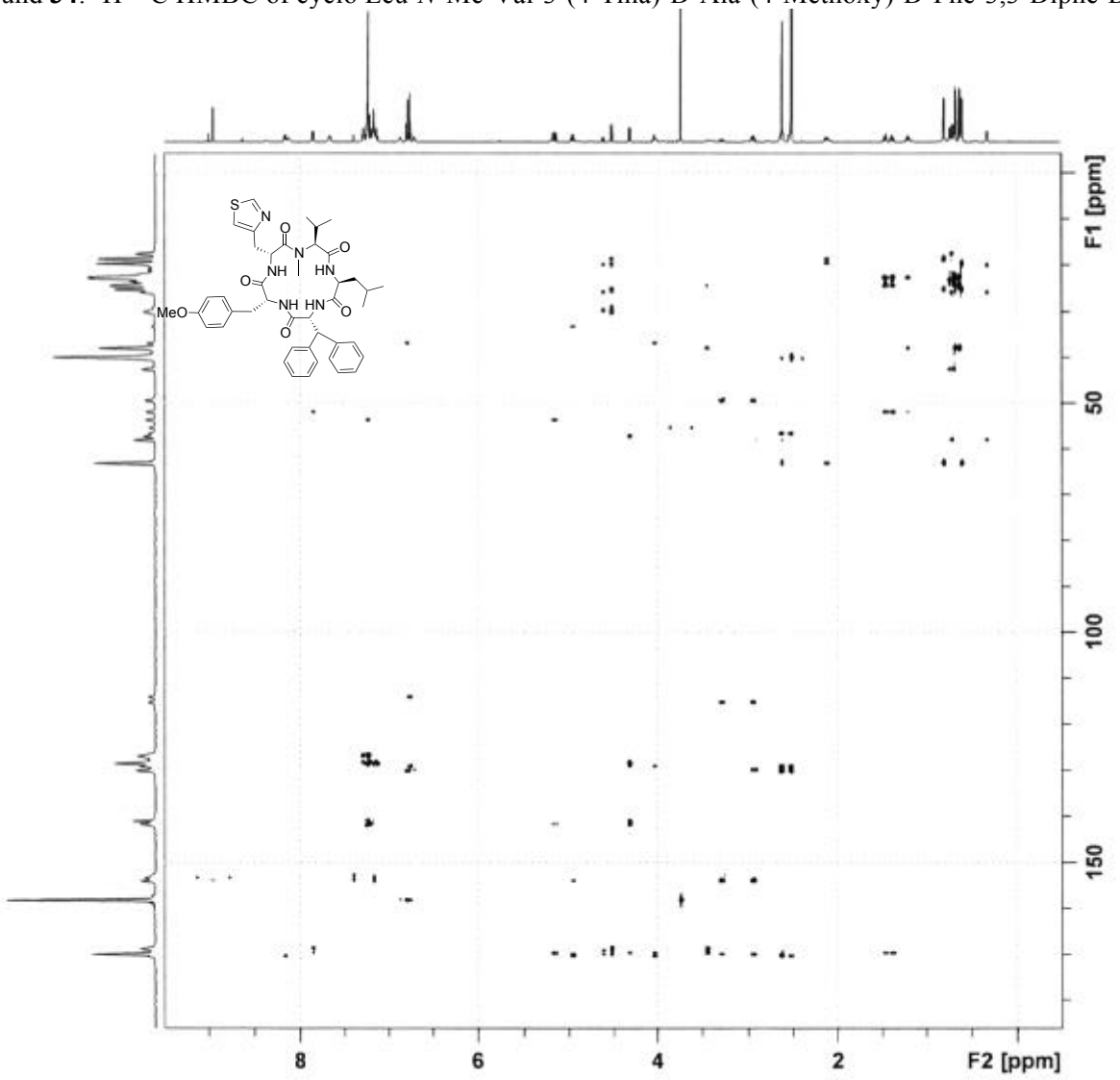
Compound **34**: ^{1}H NMR of cyclo Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-(4-Methoxy)-D-Phe-3,3-Diphe-D-Ala



Compound **34**: ^{1}H-^{13}C HSQC of cyclo Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-(4-Methoxy)-D-Phe-3,3-Diphe-D-Ala

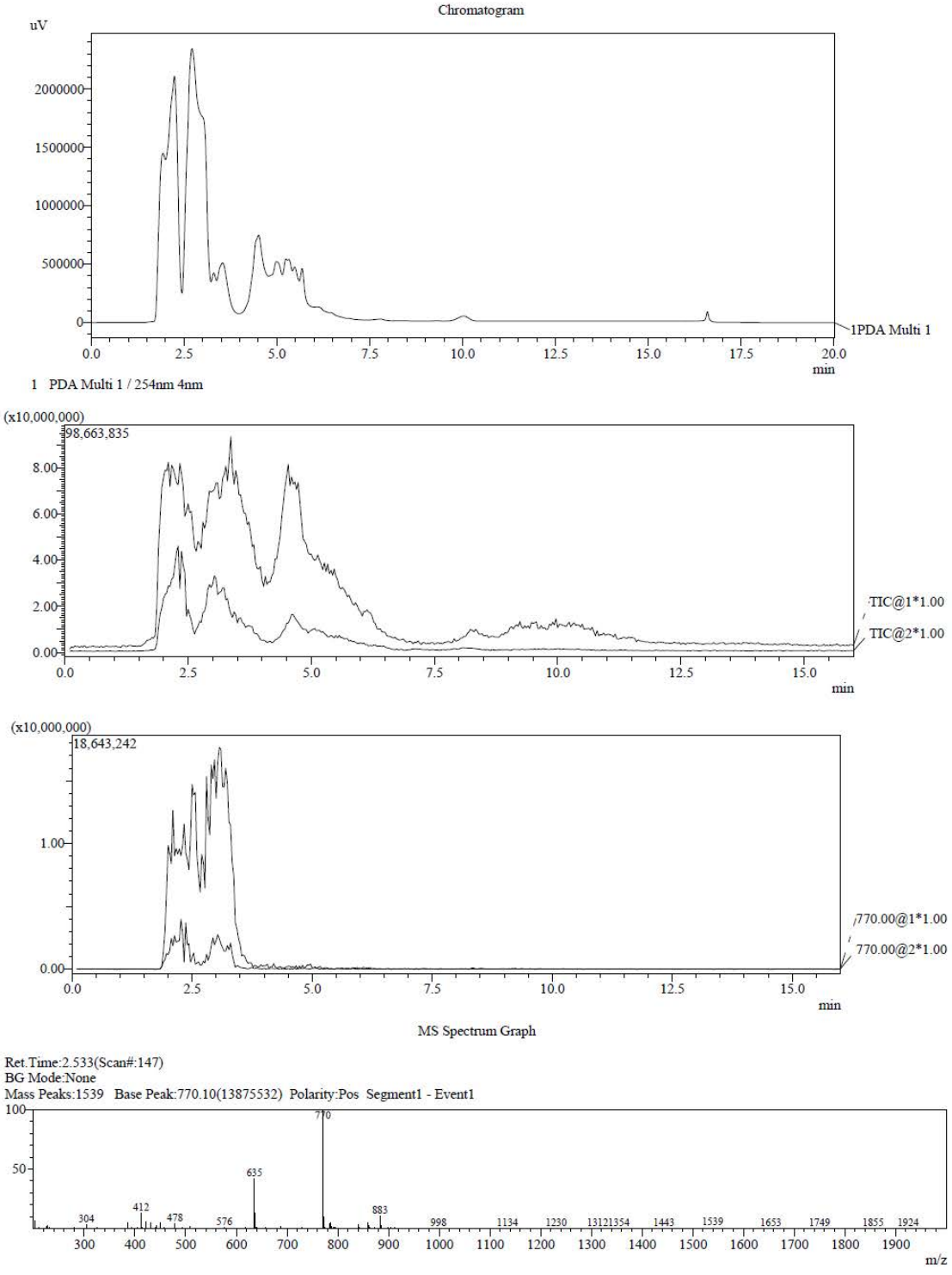


Compound **34**: ^{1}H-^{13}C HMBC of cyclo Leu-*N*-Me-Val-3-(4-Thia)-D-Ala-(4-Methoxy)-D-Phe-3,3-Diphe-D-Ala



Compound **35**: LCMS of DDLP HO-D-Leu-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala-3-(4'-Pyr)Ala-Val-NH(CH_3)

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



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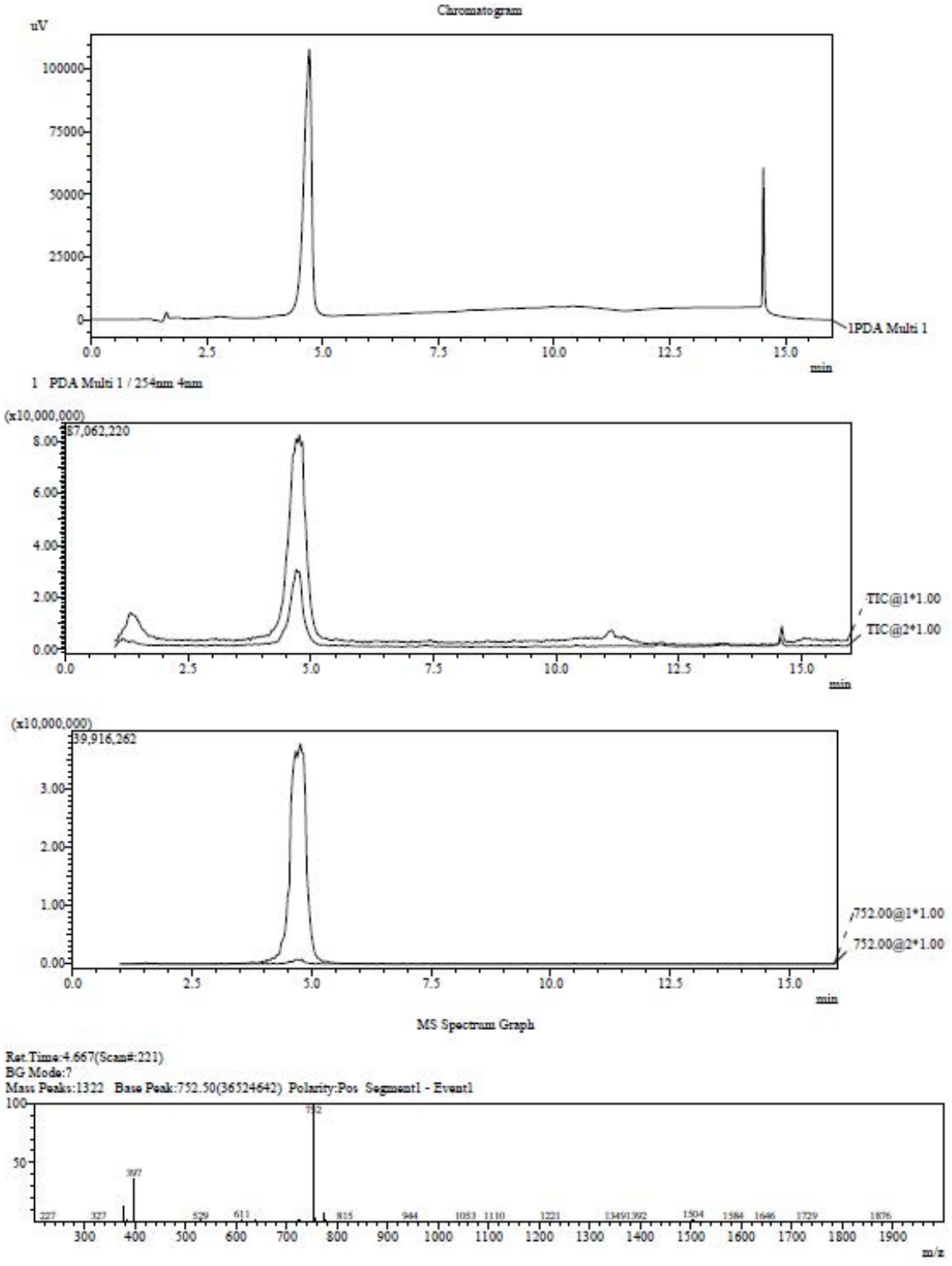
Compound **35**: LCMS of cyclo D-Leu-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala-3-(4'-Pyr)Ala-N-Me-Val

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



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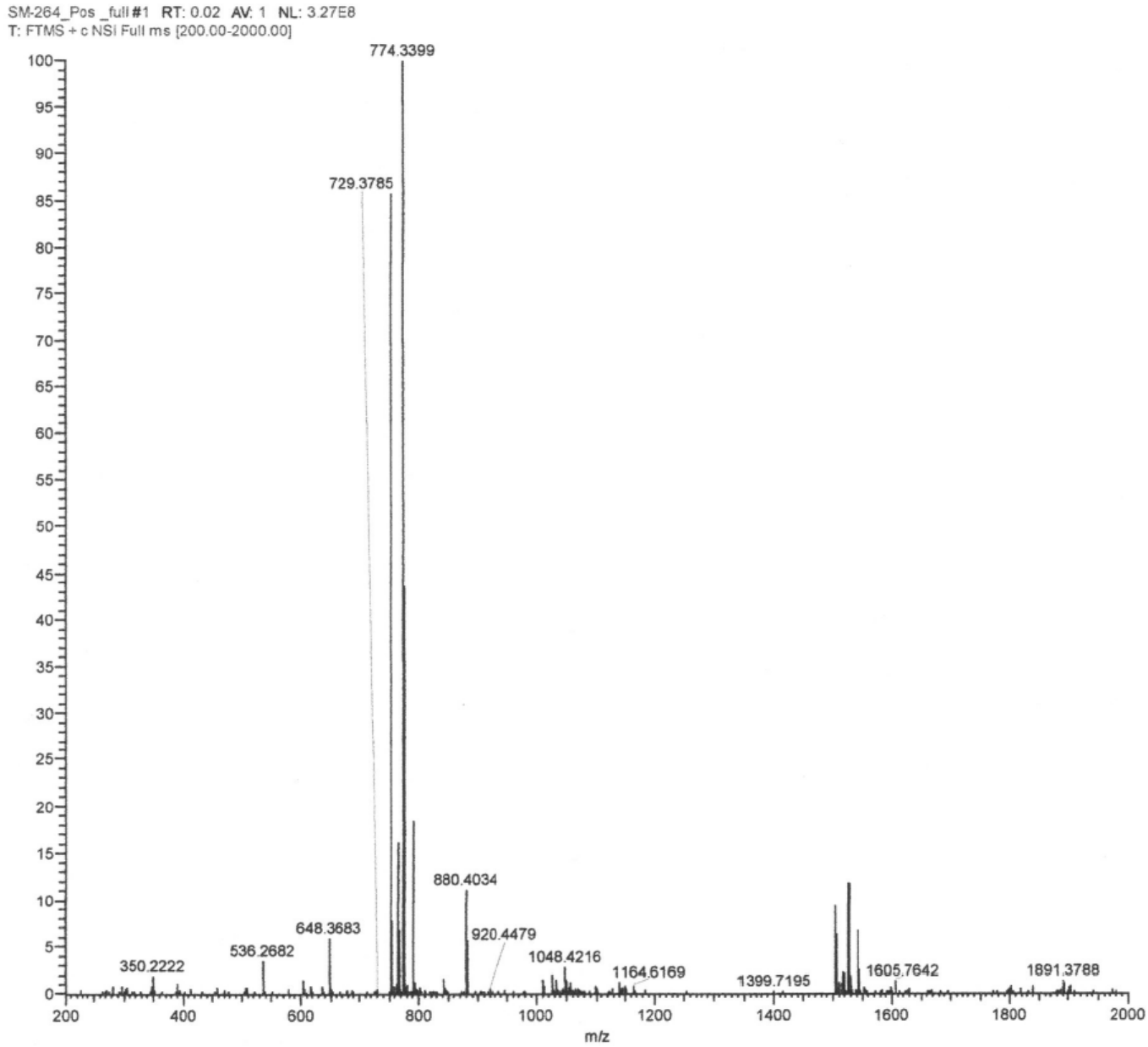
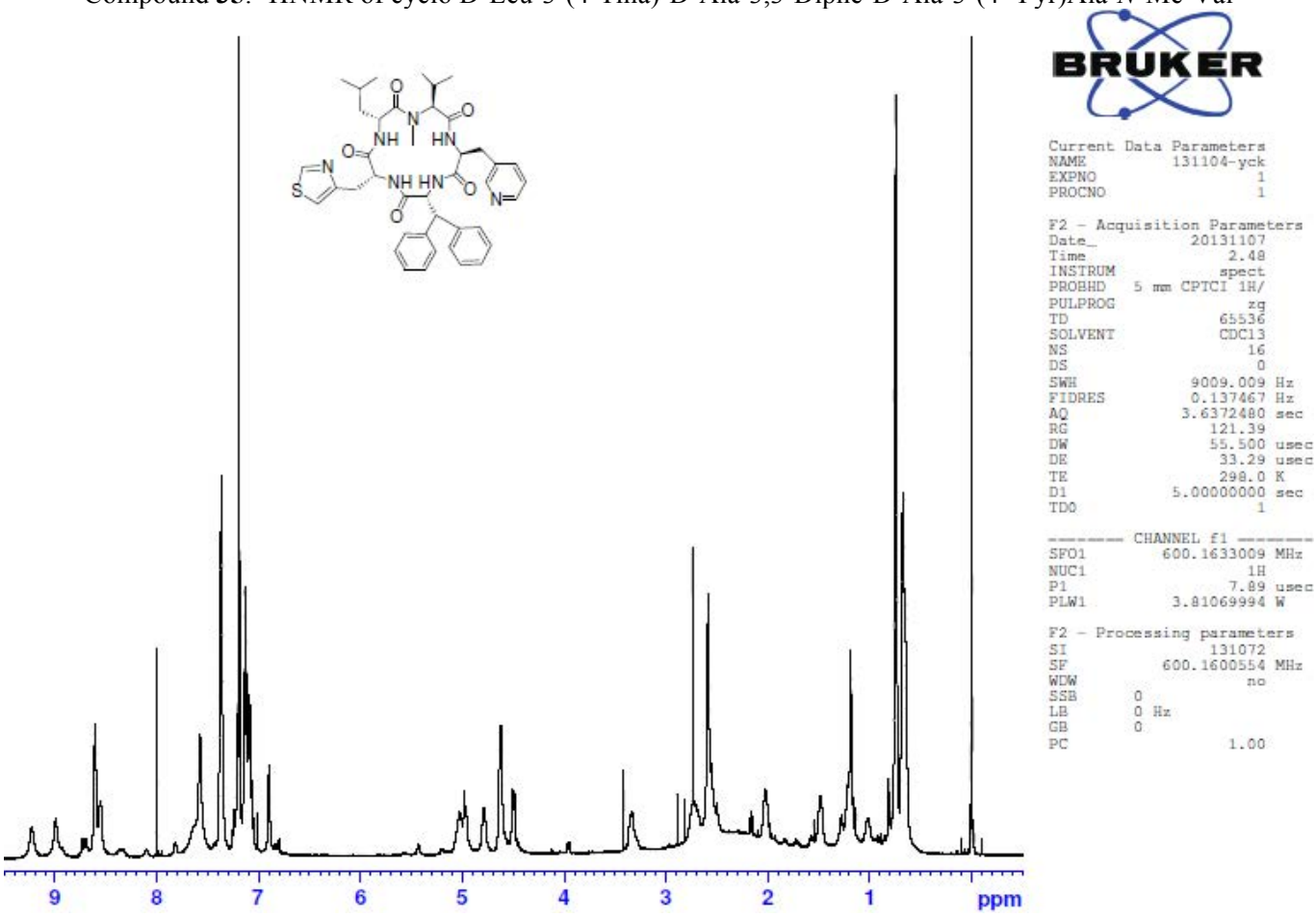
Compound **35**: HRMS of cyclo D-Leu-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala-3-(4'-Pyr)Ala-*N*-Me-Val

MS Data from Orbitrap

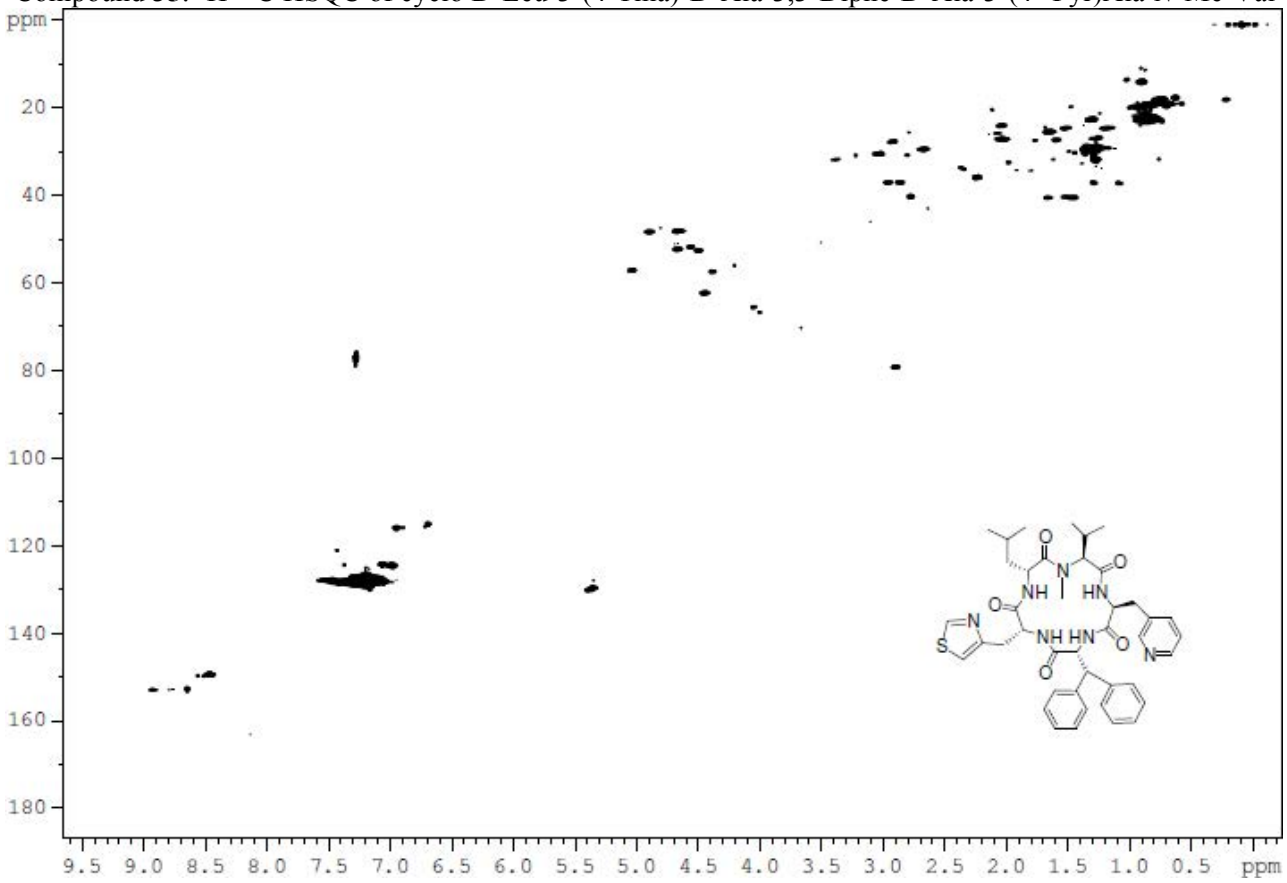
Full spectrum



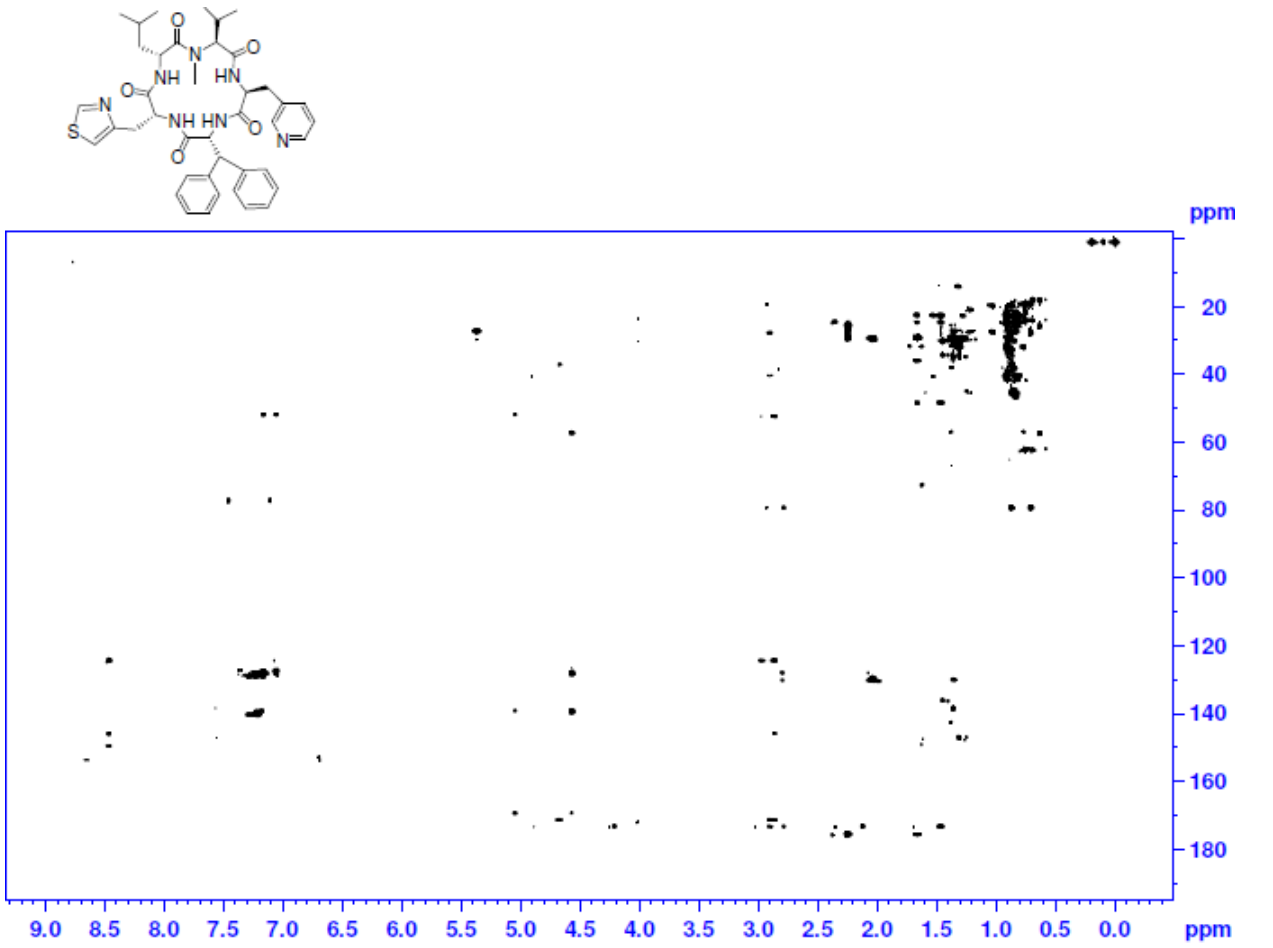
Compound **35**: ^{1}HNMR of cyclo D-Leu-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala-3-(4'-Pyr)Ala-*N*-Me-Val



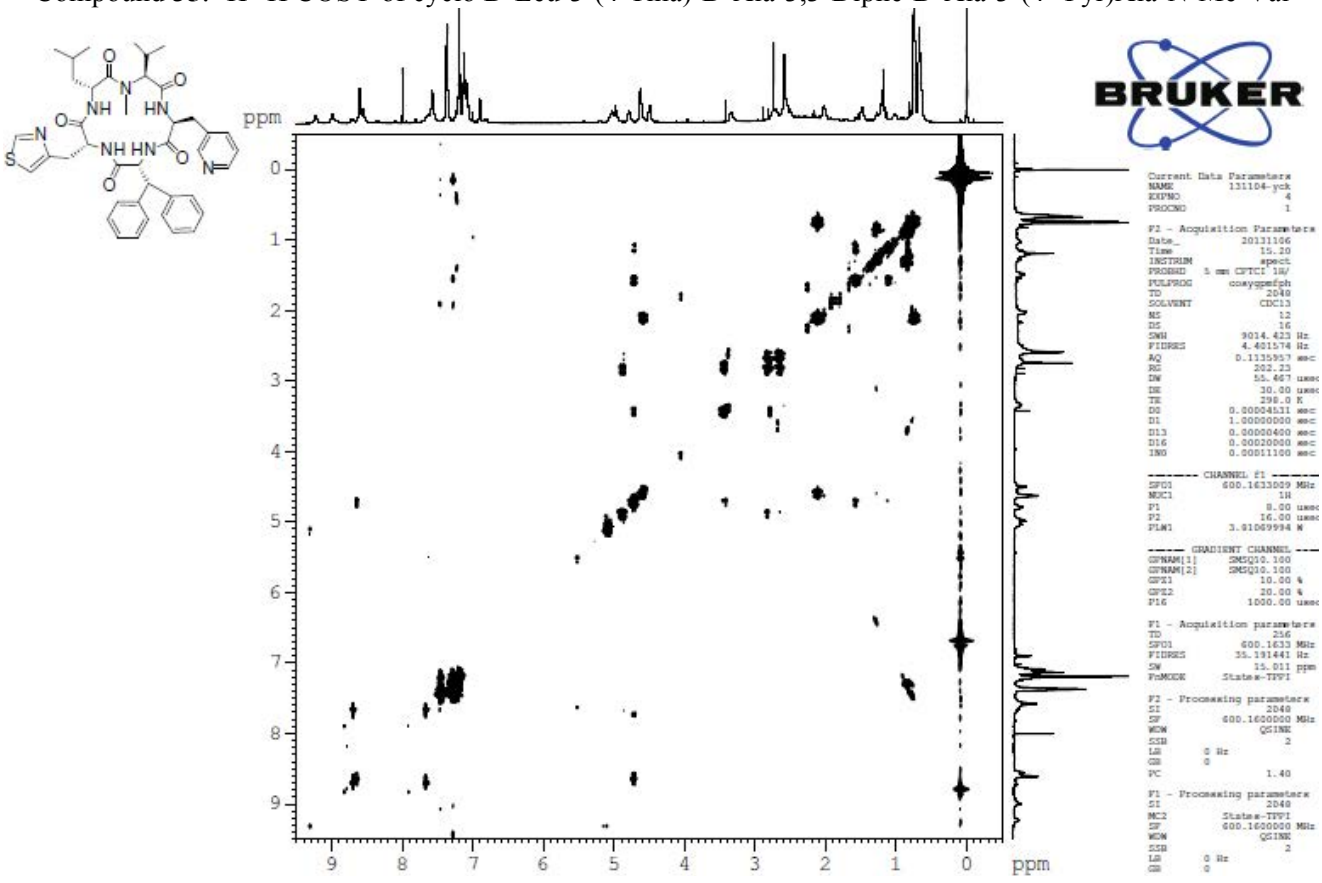
Compound **35**: ^{1}H-^{13}C HSQC of cyclo D-Leu-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala-3-(4'-Pyr)Ala-*N*-Me-Val



Compound **35**: ^{1}H-^{13}C HMBC of cyclo D-Leu-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala-3-(4'-Pyr)Ala-*N*-Me-Val



Compound **35**: ^{1}H-^{1}H COSY of cyclo D-Leu-3-(4-Thia)-D-Ala-3,3-Diphe-D-Ala-3-(4'-Pyr)Ala-N-Me-Val

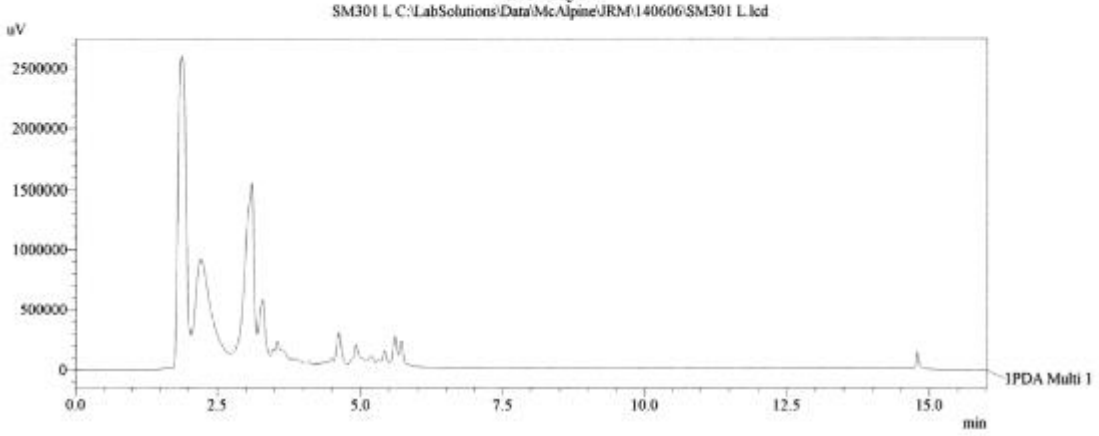


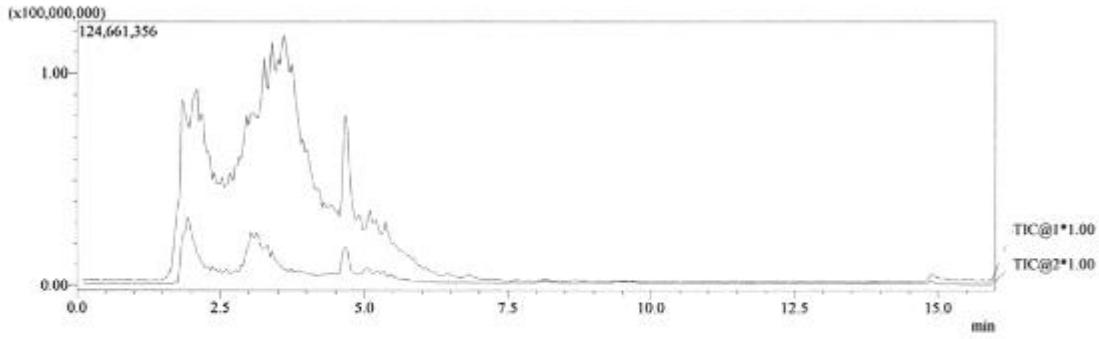
Compound **36**: LCMS of DDLP HO-D-Phe-3,3-Diphe-D-Ala-3-(2-pyridyl)-Ala-*N*-Me-Val-3-(4-Thia)-D-Ala

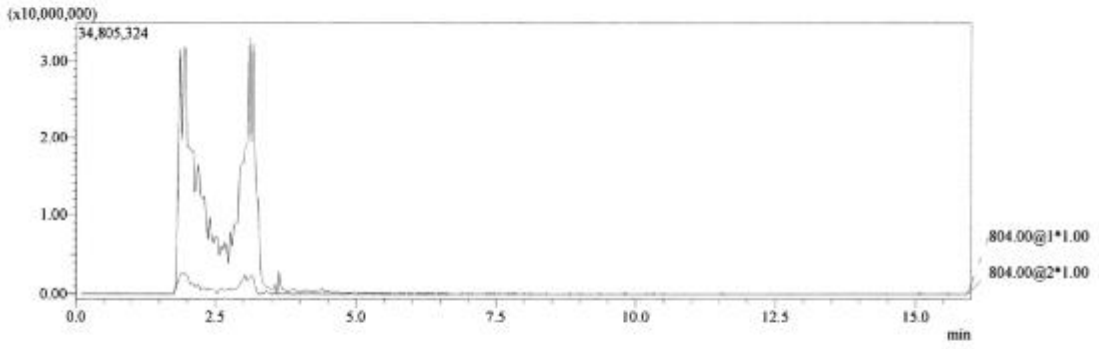
==== Shimadzu LCMSsolution Analysis Report ====

Chromatogram

SM301 L C:\LabSolutions\Data\McAlpine\JRM\140606\SM301 L.lcd

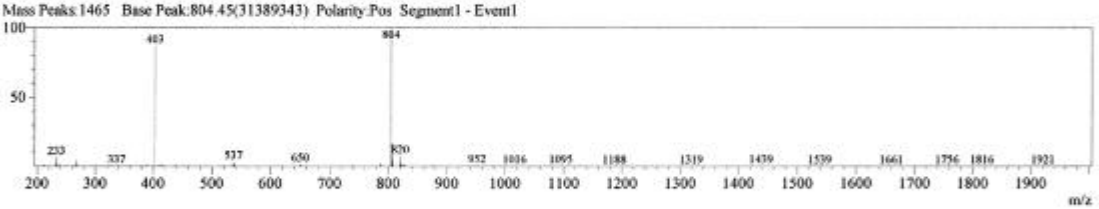






MS Spectrum Graph

Ret.Time:1.867(Scan#:107)
BG Mode:None
Mass Peaks:1465 Base Peak:804.45(31389343) Polarity:Pos Segment1 - Event1



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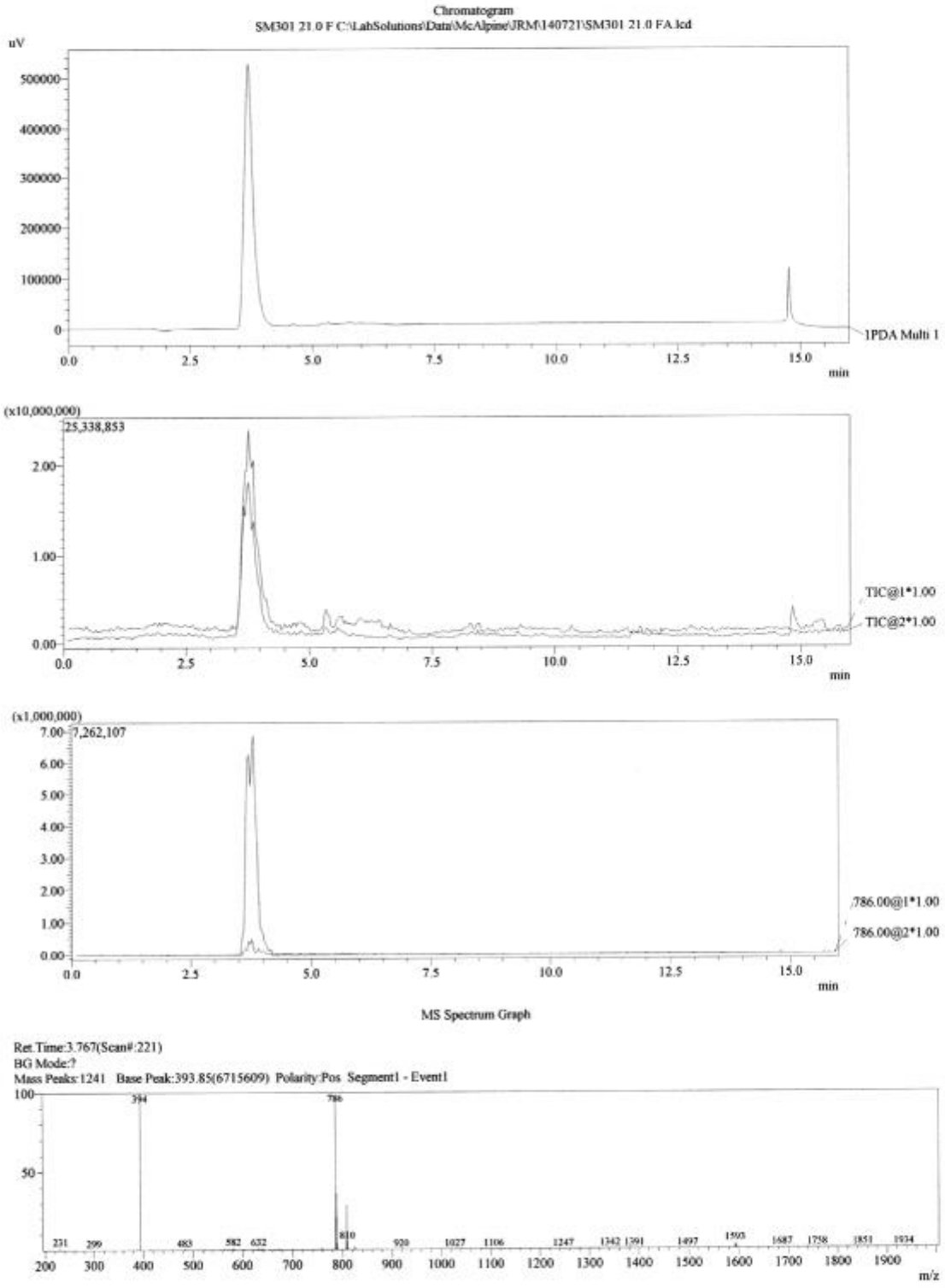
Compound **36**: LCMS of *Cyclo* D-Phe-3,3-Diphe-D-Ala-3-(2-pyridyl)-Ala-*N*-Me-Val-3-(4-Thia)-D-Ala

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



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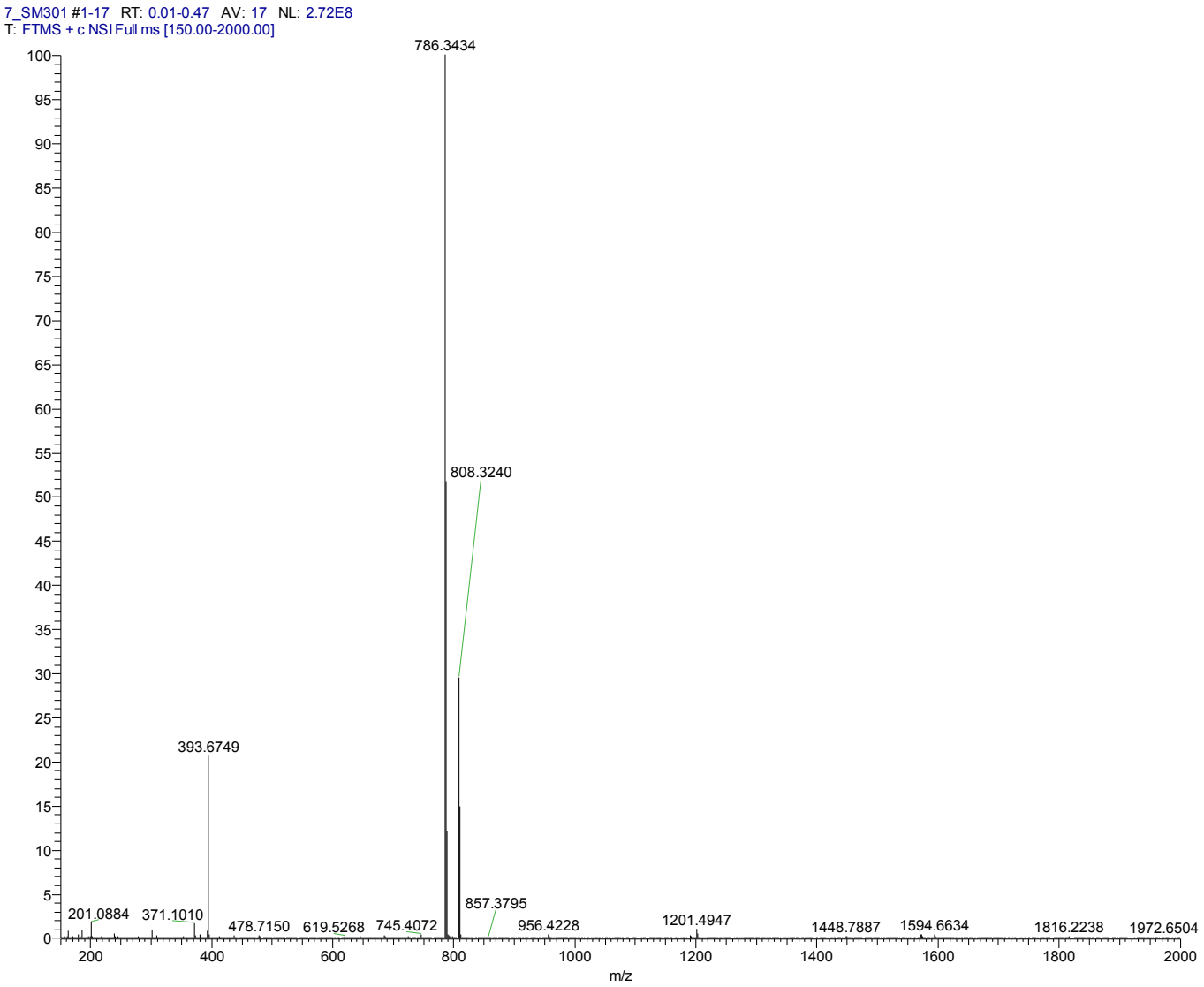
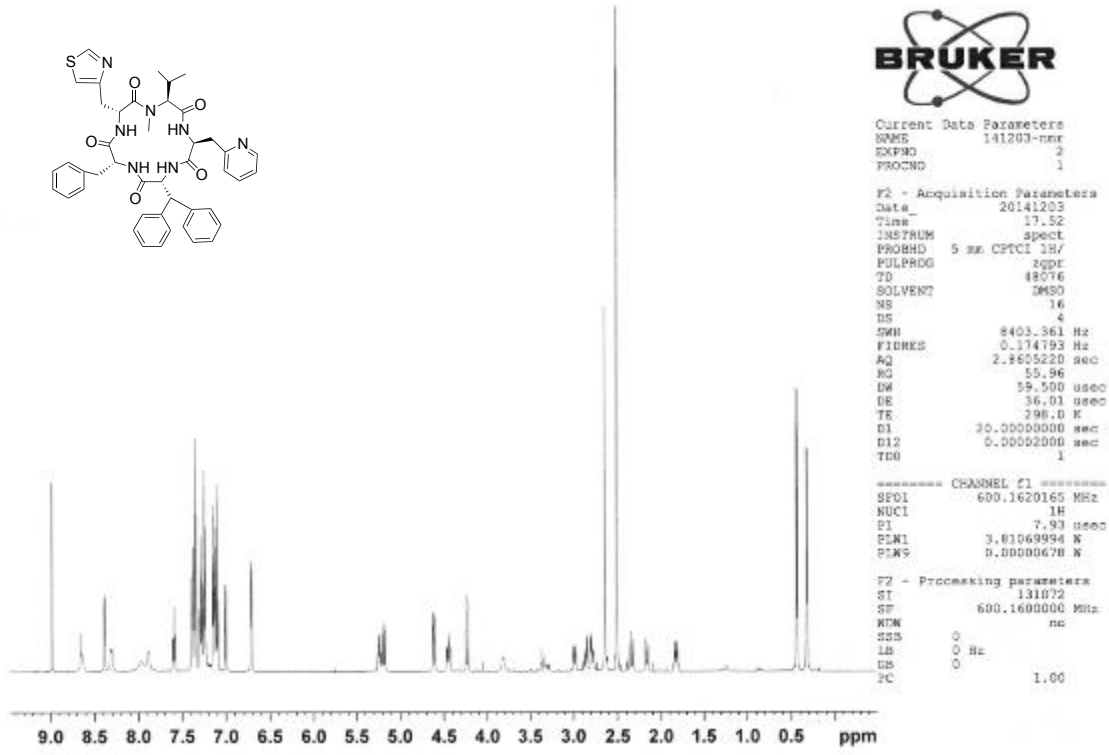
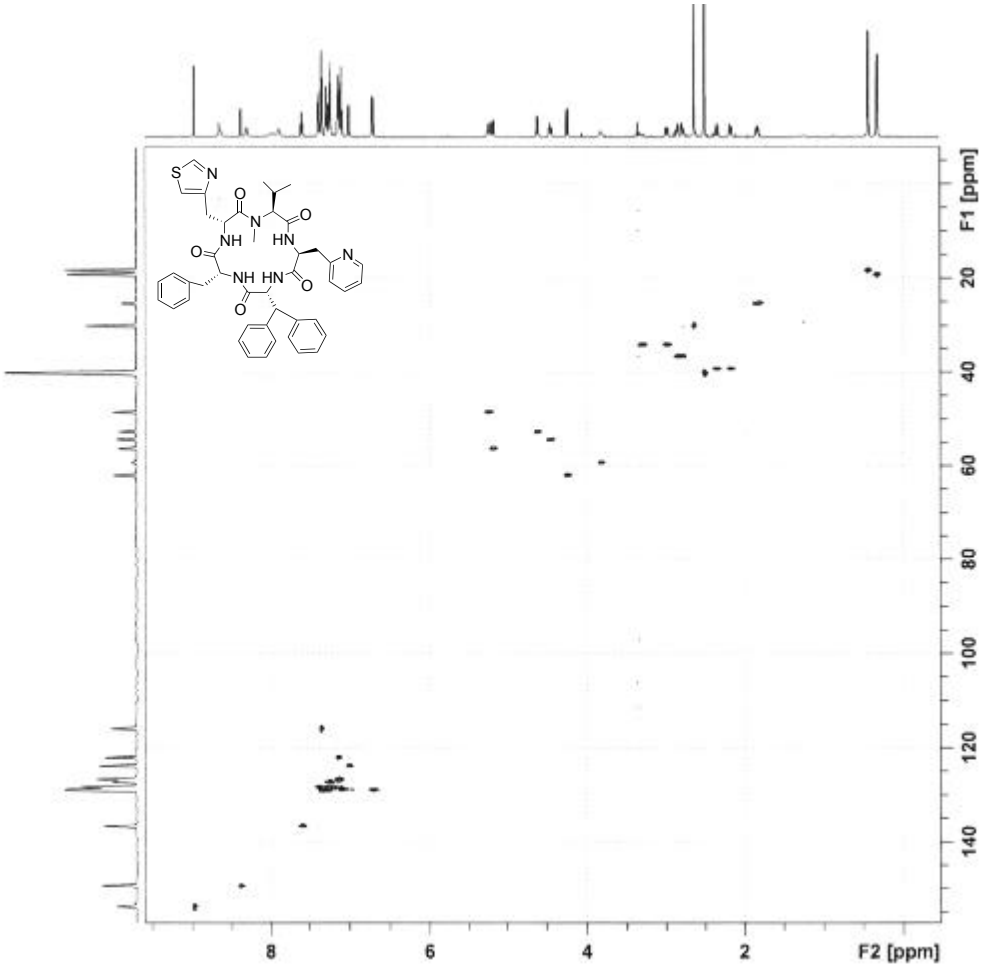
Compound **36**: HRMS of *Cyclo* D-Phe-3,3-Diphe-D-Ala-3-(2-pyridyl)-Ala-N-Me-Val-3-(4-Thia)-D-Ala



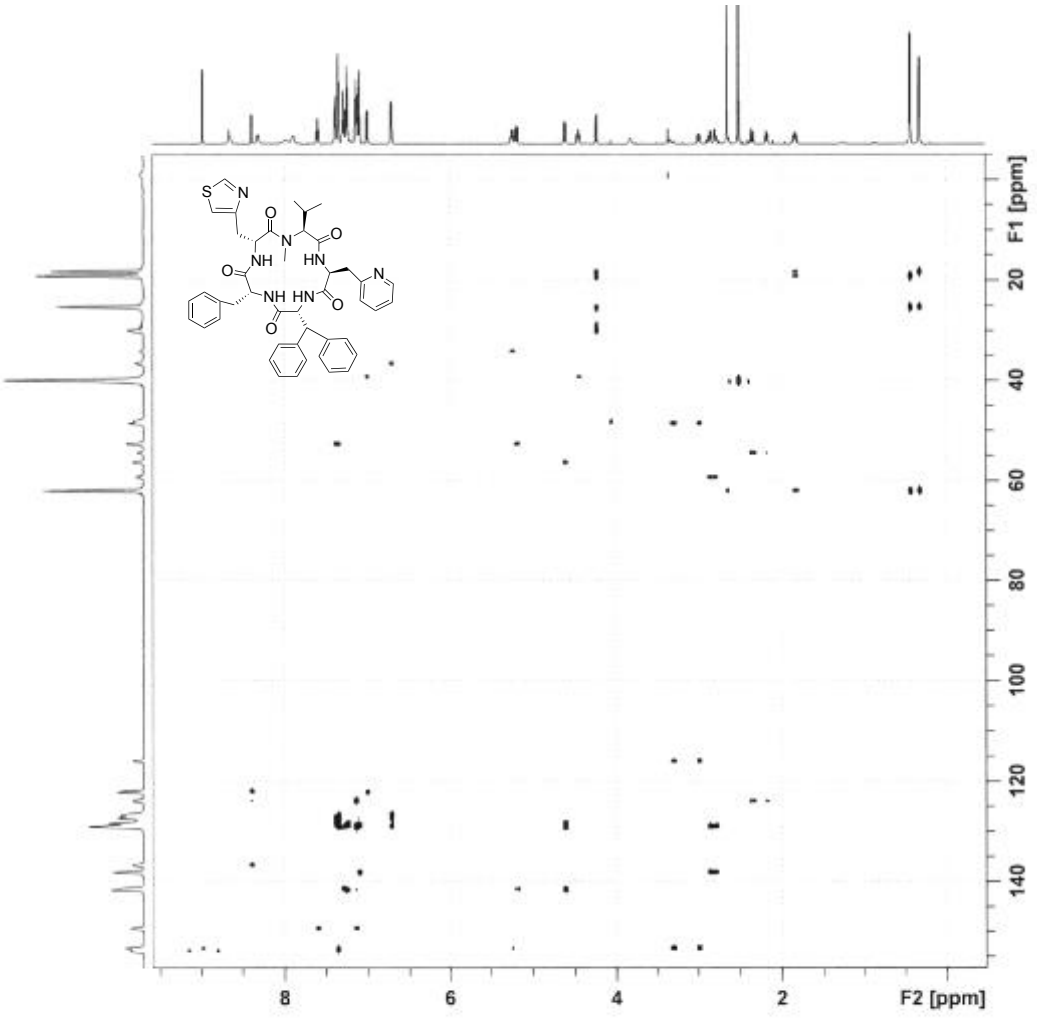
Compound **36**: ^{1}HNMR of *cyclo* D-Phe-3,3-Diphe-D-Ala-3-(2-pyridyl)-Ala-*N*-Me-Val-3-(4-Thia)-D-Ala



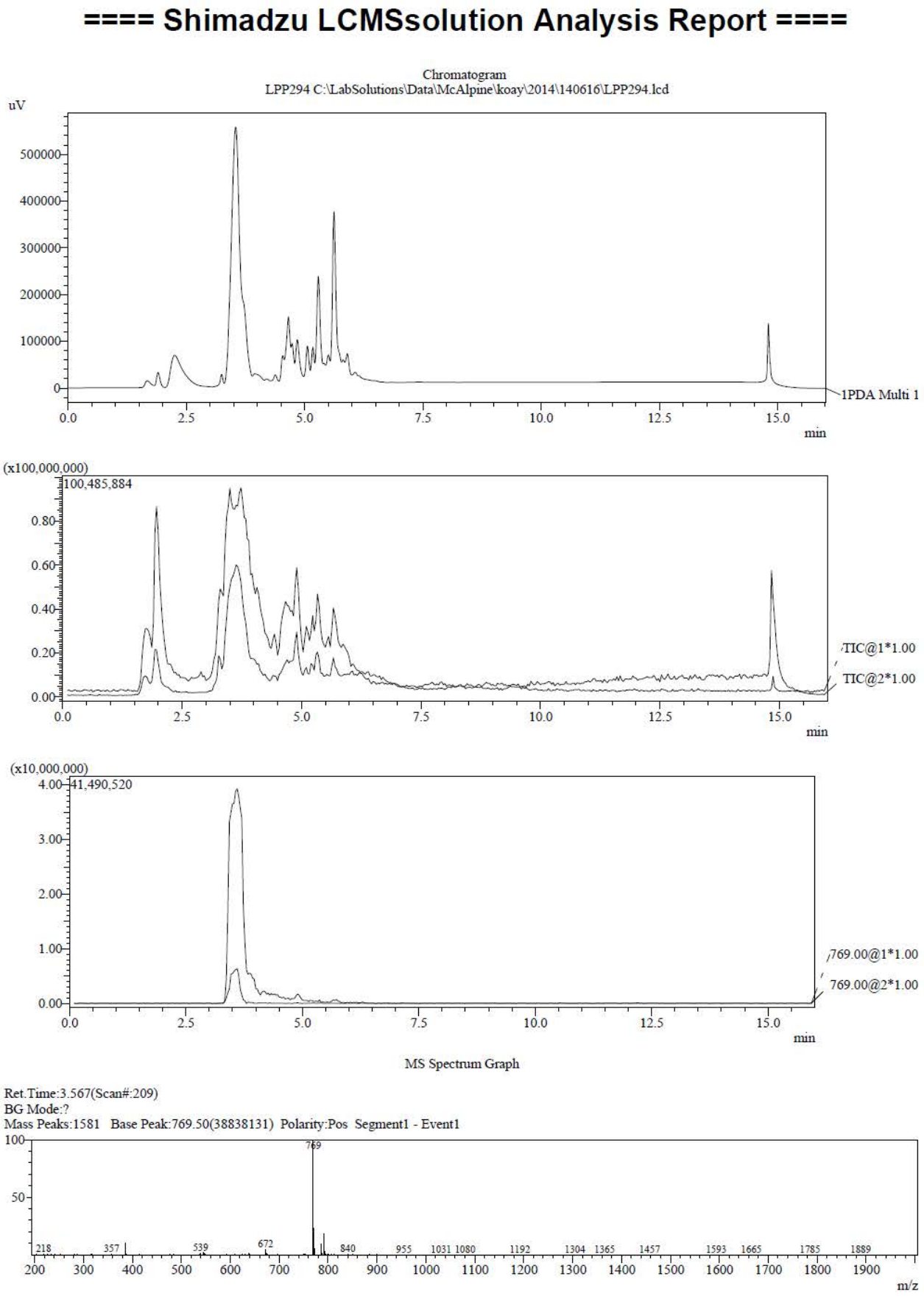
Compound **36**: ^{1}H-^{13}C HSQC of *cyclo* D-Phe-3,3-Diphe-D-Ala-3-(2-pyridyl)-Ala-*N*-Me-Val-3-(4-Thia)-D-Ala



Compound **36**: ^{1}H-^{13}C HMBC of *cyclo* D-Phe-3,3-Diphe-D-Ala-3-(2-pyridyl)-Ala-*N*-Me-Val-3-(4-Thia)-D-Ala

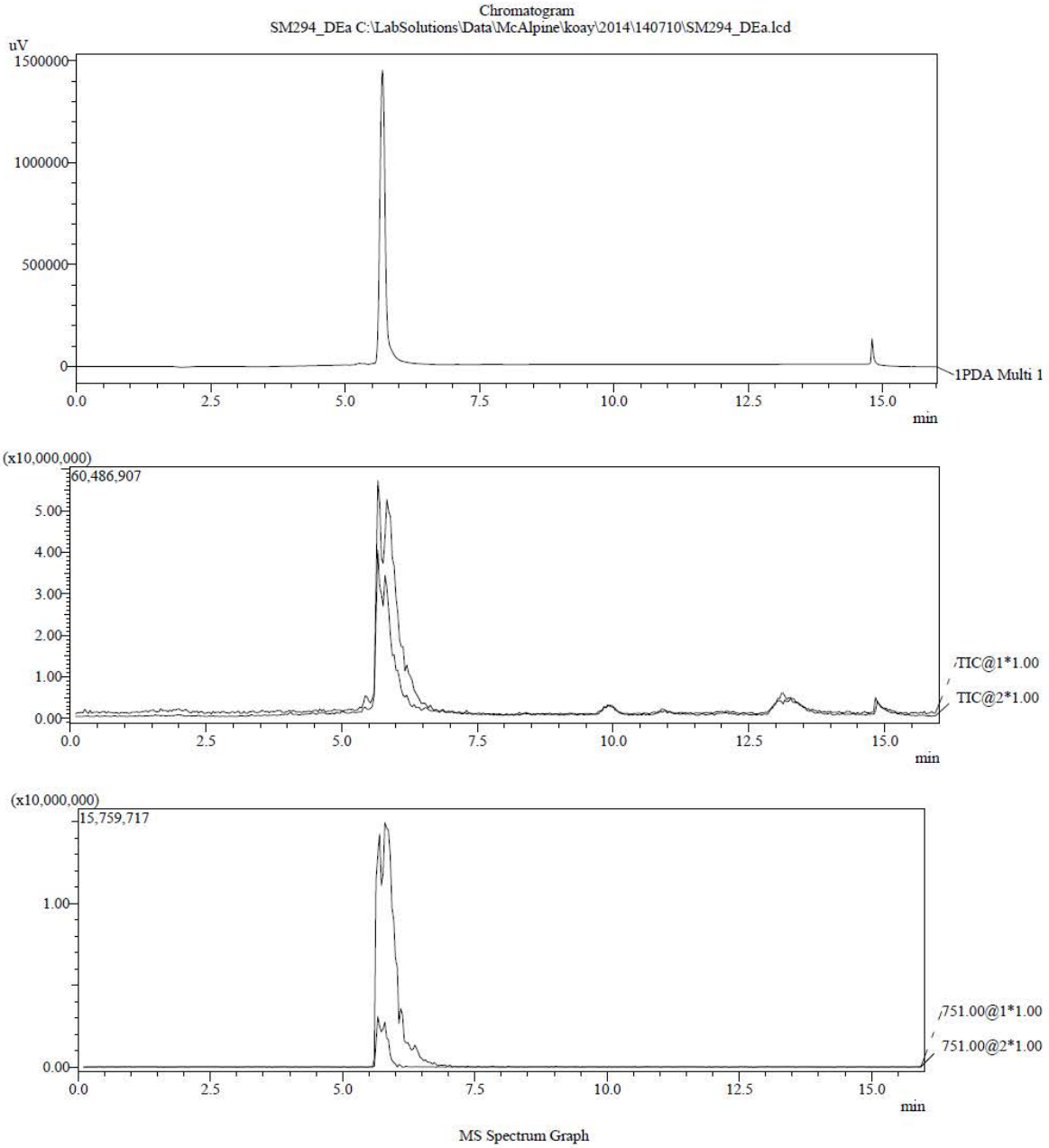


Compound **37**: LCMS of DDLP HO-Leu-Val-3-(4-Thia)-D-Ala-*N*-Me-D-Phe-3,3-Diphe-D-Ala-NH_2



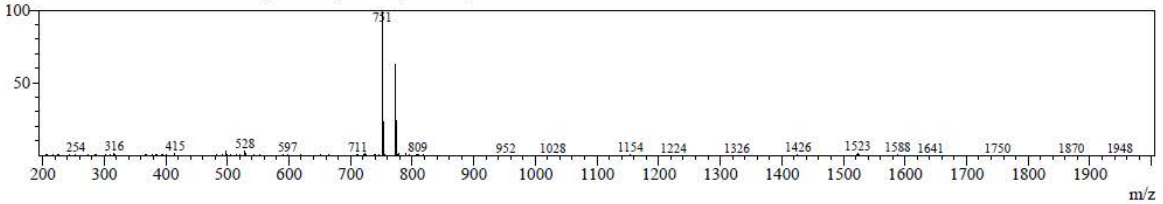
Compound **37**: LCMS of cyclo Leu-Val-3-(4-Thia)-D-Ala-*N*-Me-D-Phe-3,3-Diphe-D-Ala

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



MS Spectrum Graph

Ret.Time:5.767(Scan#:341)
BG Mode:?
Mass Peaks:1464 Base Peak:750.95(11805165) Polarity:Pos Segment1 - Event1



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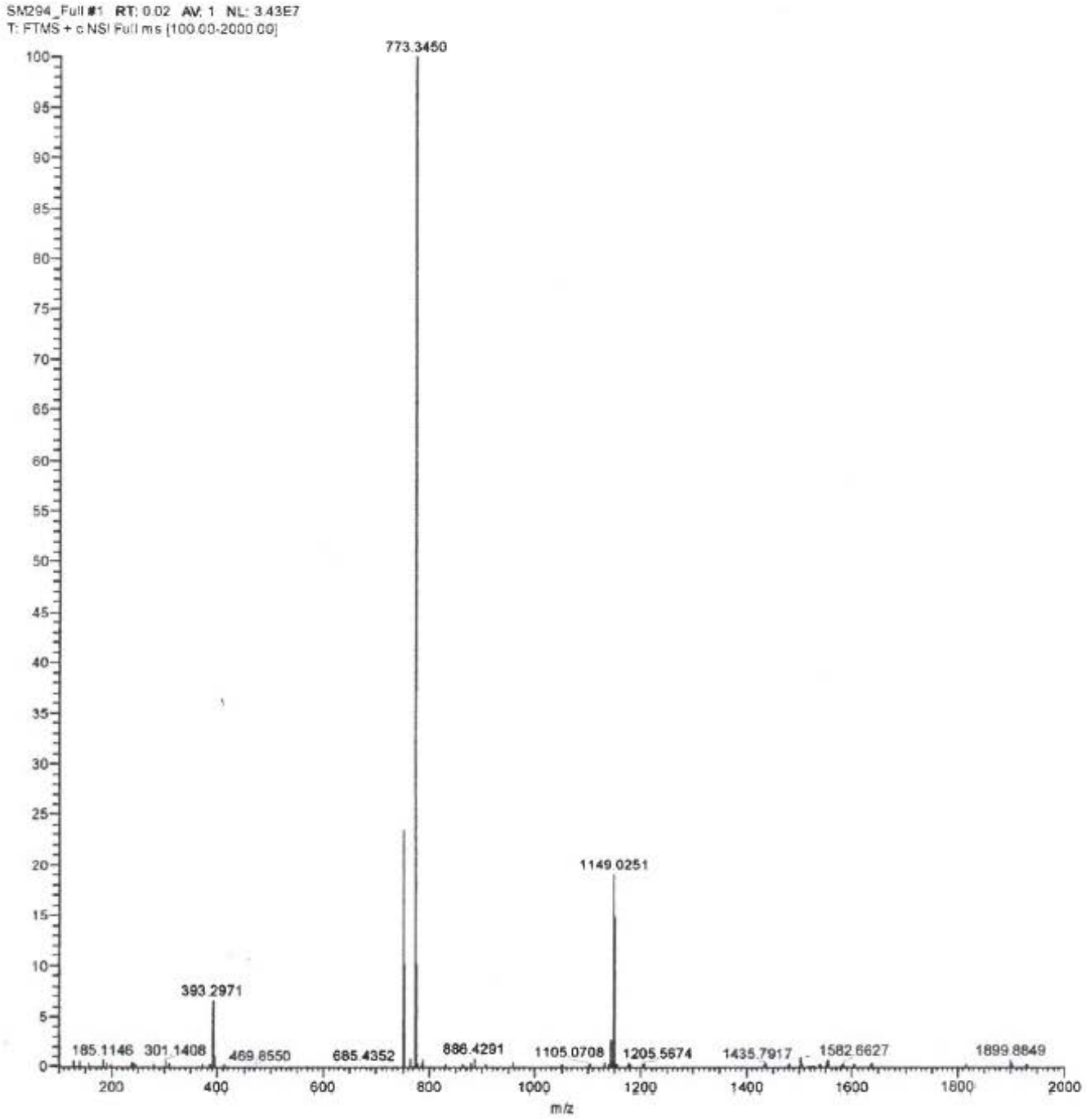
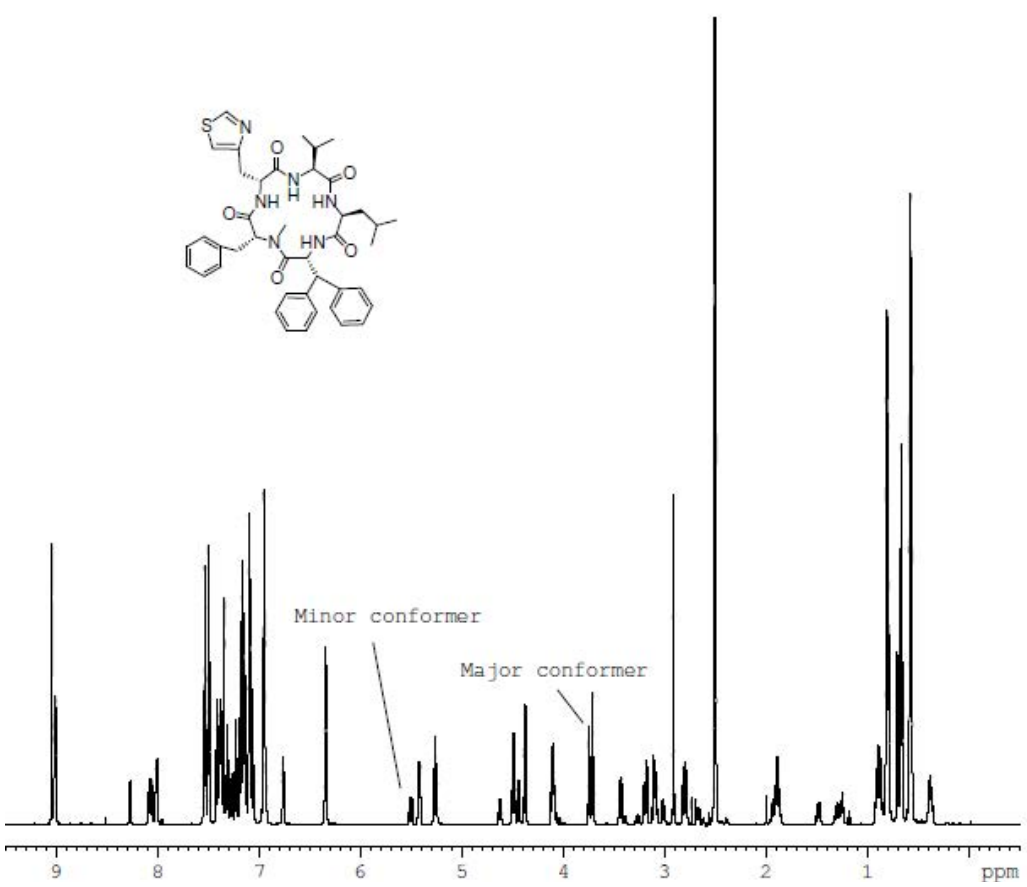
Compound **37**: HRMS of cyclo Leu-Val-3-(4-Thia)-D-Ala-*N*-Me-D-Phe-3,3-Diphe-D-Ala

MS Data from Orbitrap

Full spectrum



Compound **37**: ^{1}HNMR of cyclo Leu-Val-3-(4-Thia)-D-Ala-*N*-Me-D-Phe-3,3-Diphe-D-Ala

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EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20140708
Time               13.57
INSTRUM            spect
PROBHD   5 mm CPTCI 1H/
PULPROG            zgpr
TD                48076
SOLVENT            DMSO
NS                   20
DS                    4
SWH             9009.009 Hz
FIDRES          0.187391 Hz
AQ              2.6682179 sec
RG                 16.27
DW                55.500 usec
DE                33.22 usec
TE                298.0 K
D1             20.00000000 sec
D12             0.00002000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1          600.1620022 MHz
NUC1                  1H
P1                 8.00 usec
PLW1           3.81069994 W
PLW9           0.00000245 W

F2 - Processing parameters
SI                131072
SF          600.1600000 MHz
WDW                   EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
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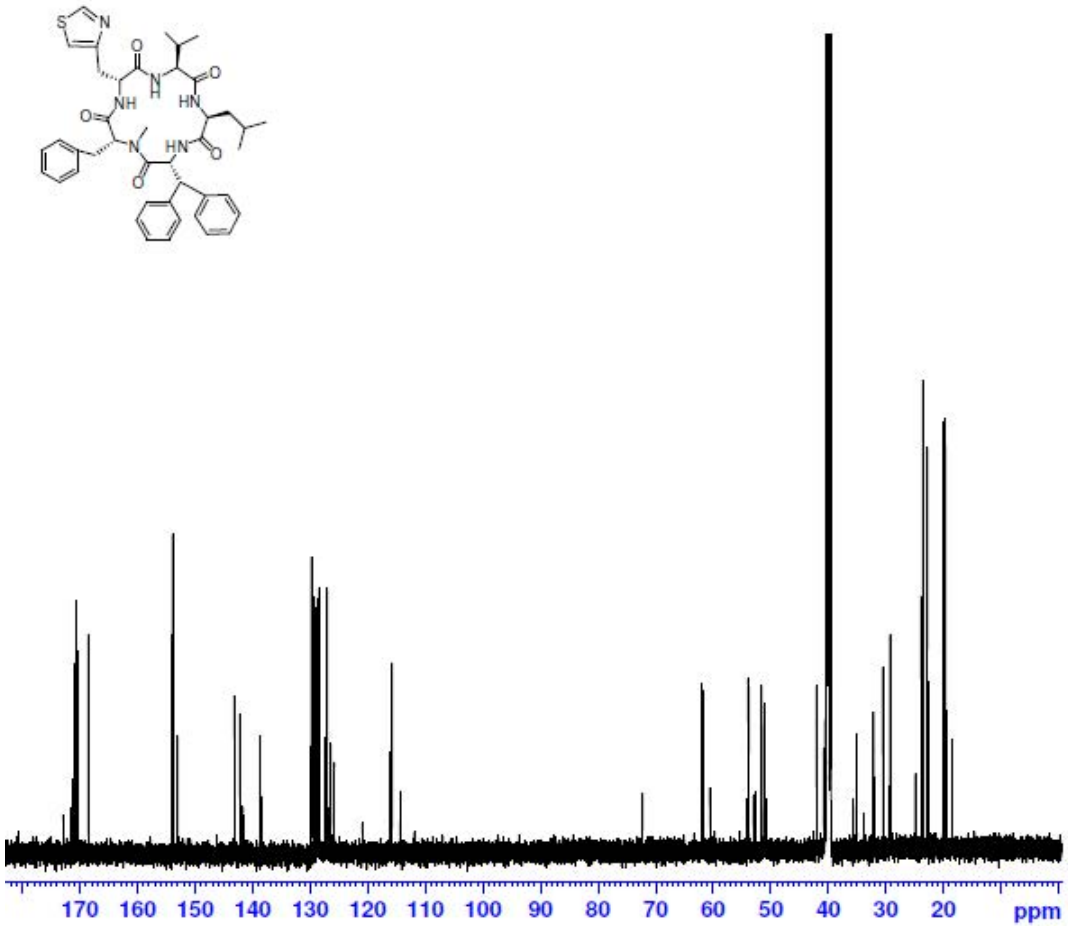
Compound **37**: ^{13}CNMR of cyclo Leu-Val-3-(4-Thia)-D-Ala-*N*-Me-D-Phe-3,3-Diphe-D-Ala

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Current Data Parameters
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PROCNO                 1

F2 - Acquisition Parameters
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Time               15.07
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PULPROG          zgpg30
TD                65536
SOLVENT            DMSO
NS                 1024
DS                    4
SWH            31512.605 Hz
FIDRES          0.480844 Hz
AQ              1.0398378 sec
RG                202.23
DW                15.867 usec
DE                16.72 usec
TE                298.0 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1          150.9246885 MHz
NUC1                  13C
P1                11.50 usec
PLW1          100.00000000 W

======== CHANNEL f2 ========
SFO2          600.1624006 MHz
NUC2                  1H
CPDPRG[2 bi_waltz65_256
PCPD2             70.00 usec
PLW2           3.81069994 W
PLW12          0.04977200 W
PLW13          0.02438800 W

F2 - Processing parameters
SI                 32768
SF          150.9103520 MHz
WDW                   no
SSB       0
LB        0 Hz
GB        0
PC                1.00
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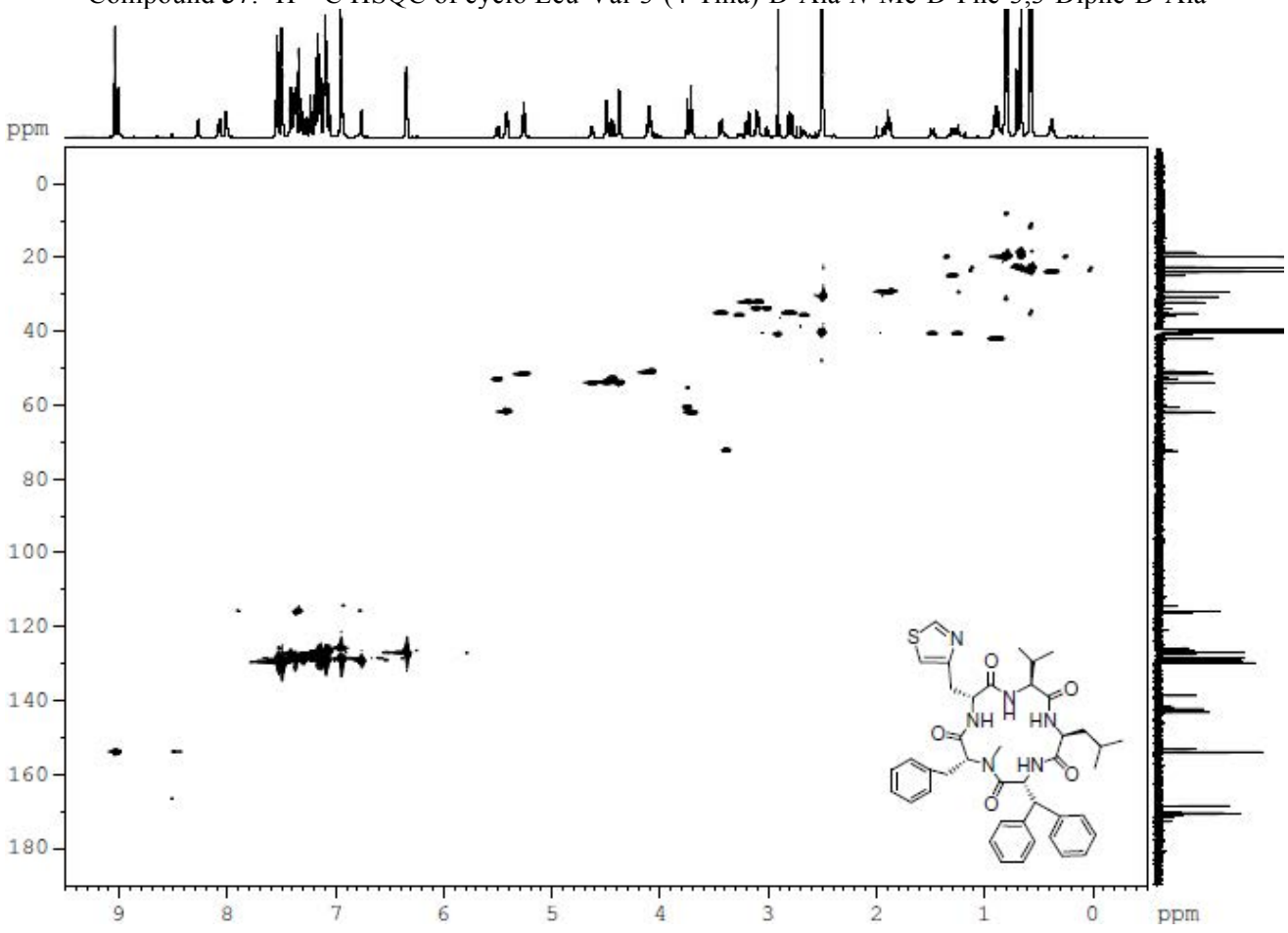
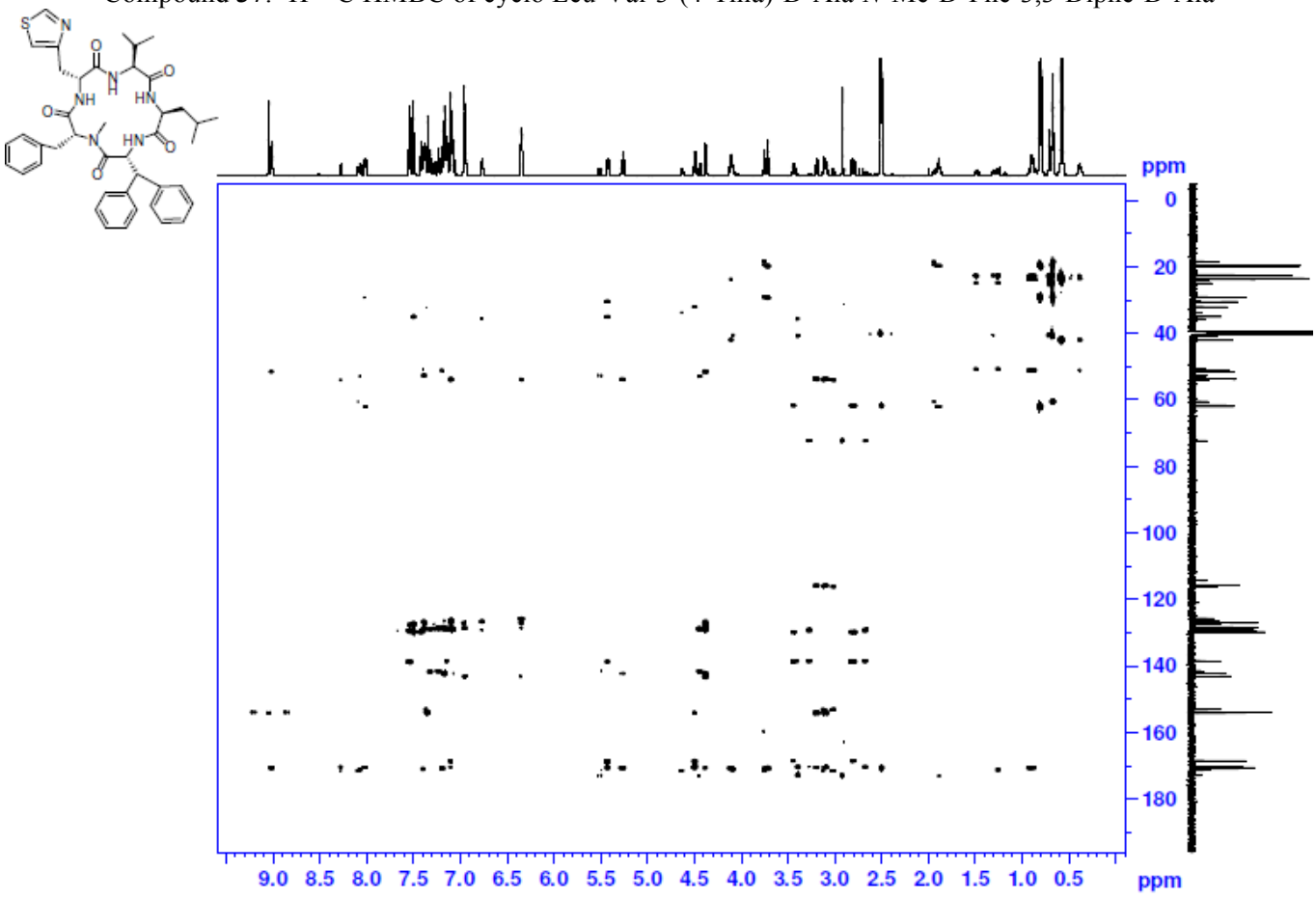
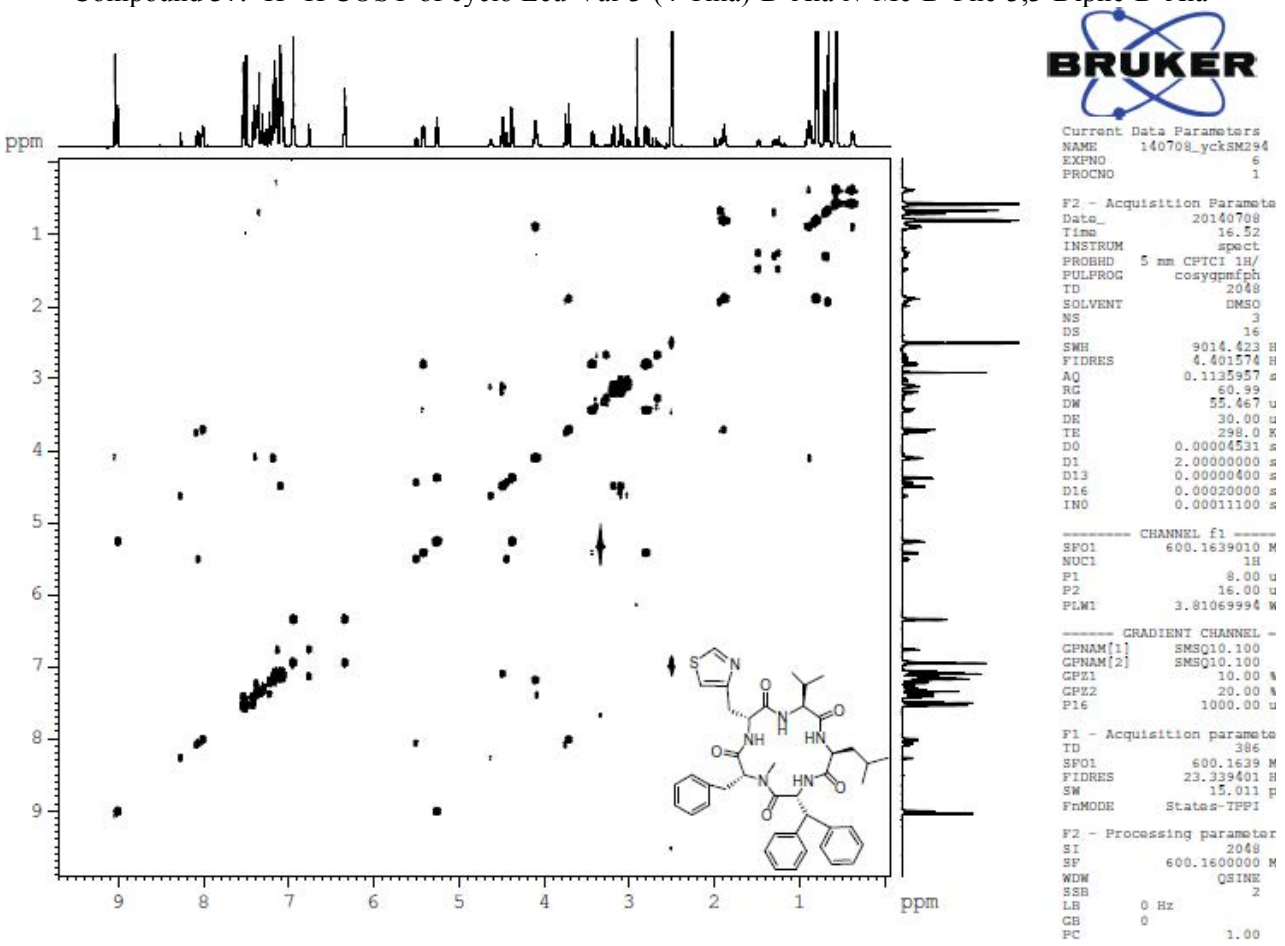
Compound **37**: ^{1}H-^{13}C HSQC of cyclo Leu-Val-3-(4-Thia)-D-Ala-*N*-Me-D-Phe-3,3-Diphe-D-Ala



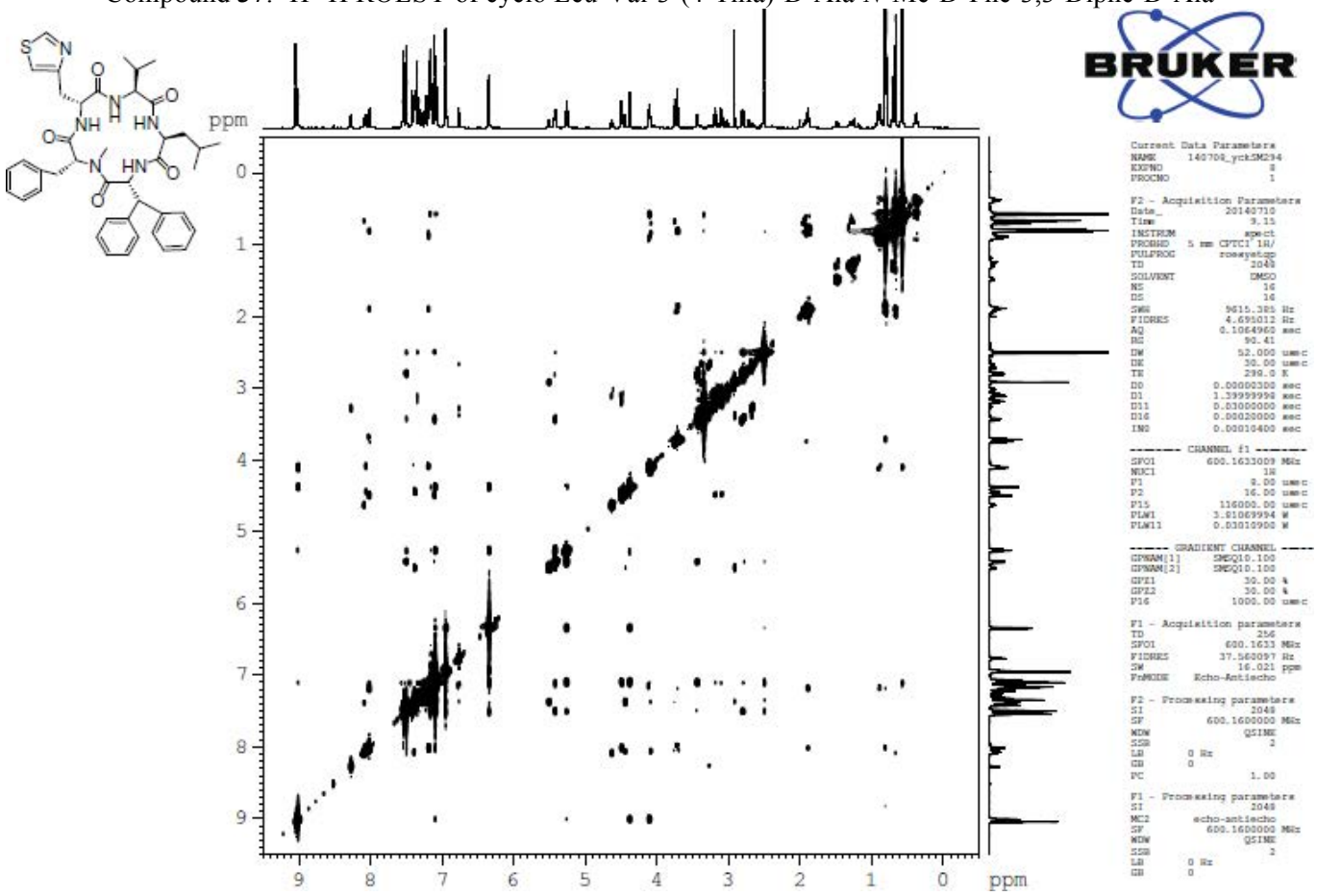
Compound **37**: ^{1}H-^{13}C HMBC of cyclo Leu-Val-3-(4-Thia)-D-Ala-*N*-Me-D-Phe-3,3-Diphe-D-Ala



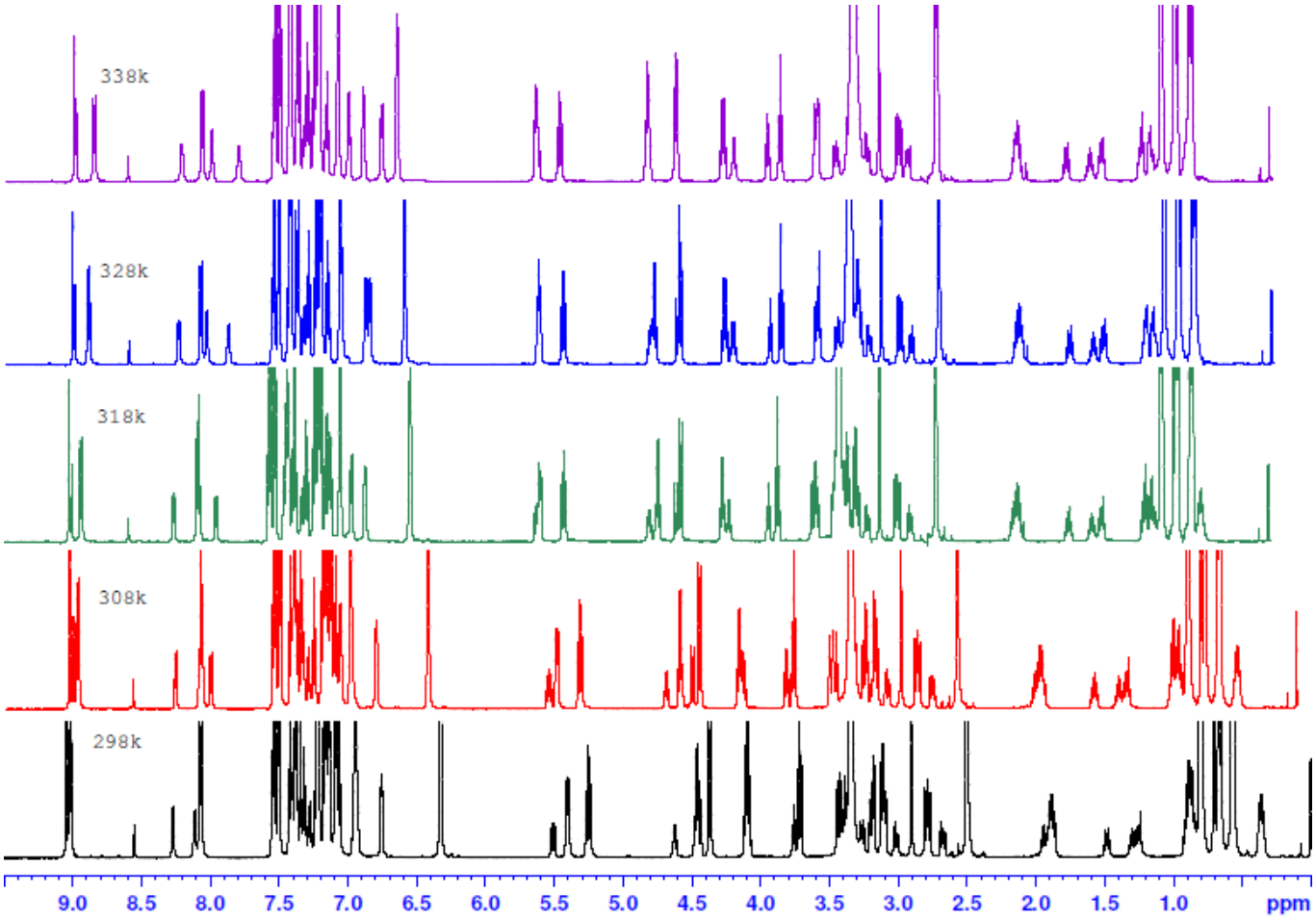
Compound **37**: ^{1}H-^{1}H COSY of cyclo Leu-Val-3-(4-Thia)-D-Ala-*N*-Me-D-Phe-3,3-Diphe-D-Ala



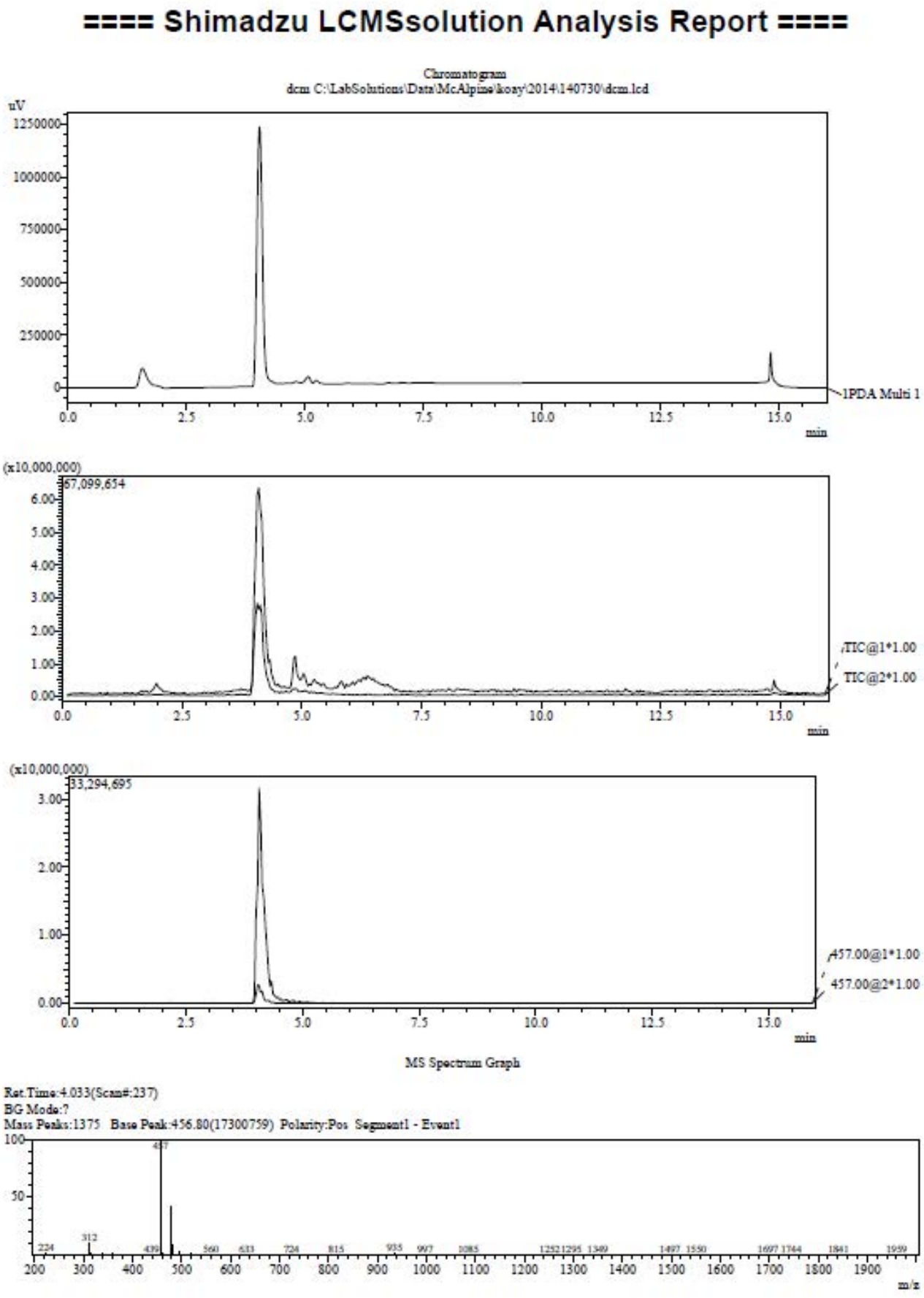
Compound **37**: ^{1}H-^{1}H ROESY of cyclo Leu-Val-3-(4-Thia)-D-Ala-*N*-Me-D-Phe-3,3-Diphe-D-Ala



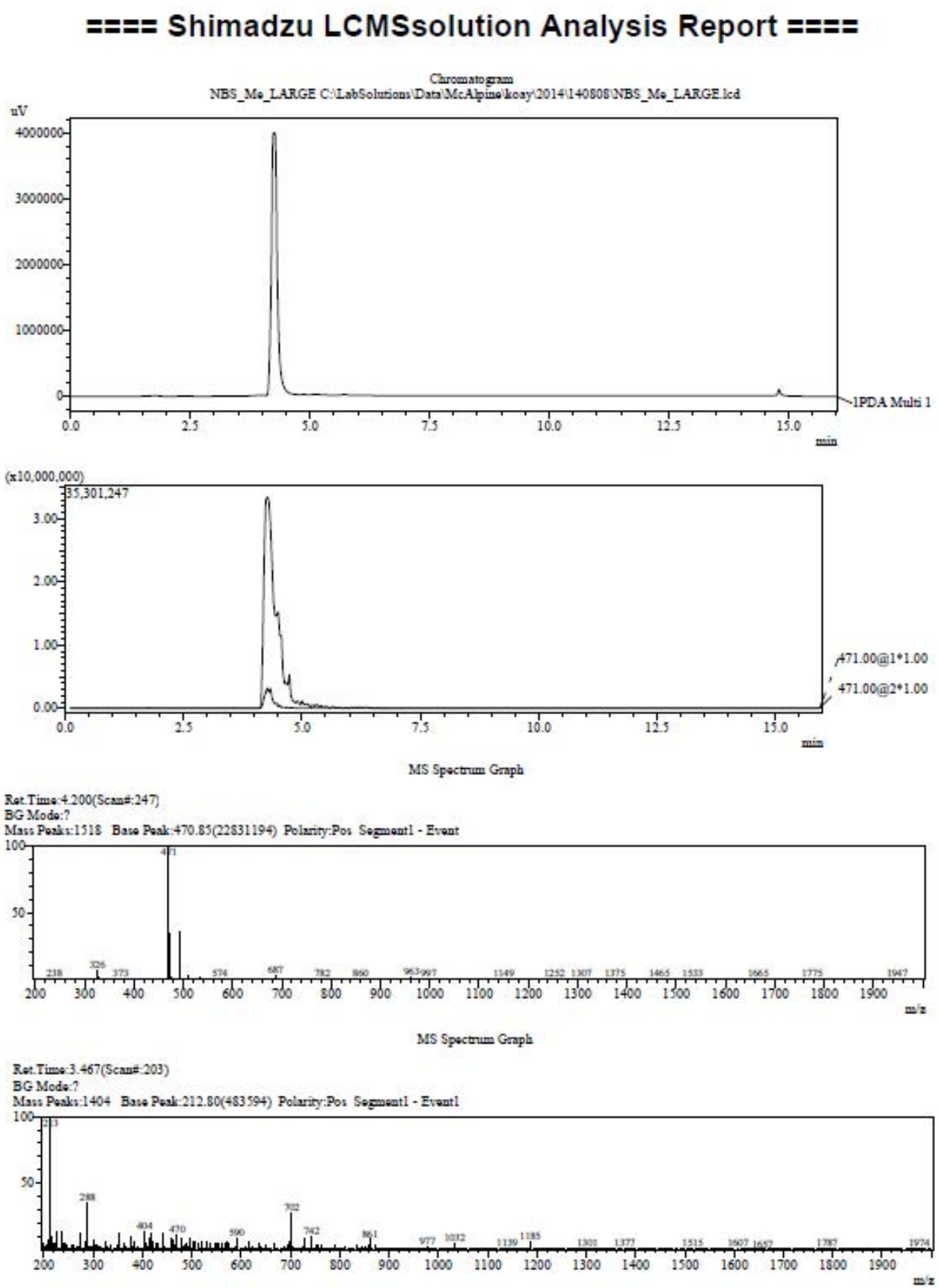
Compound **37**: Variant temperature ^{1}HNMR of cyclo Leu-*N*-Me-Val-D-His-D-Phe-3,3-Diphe-D-Ala



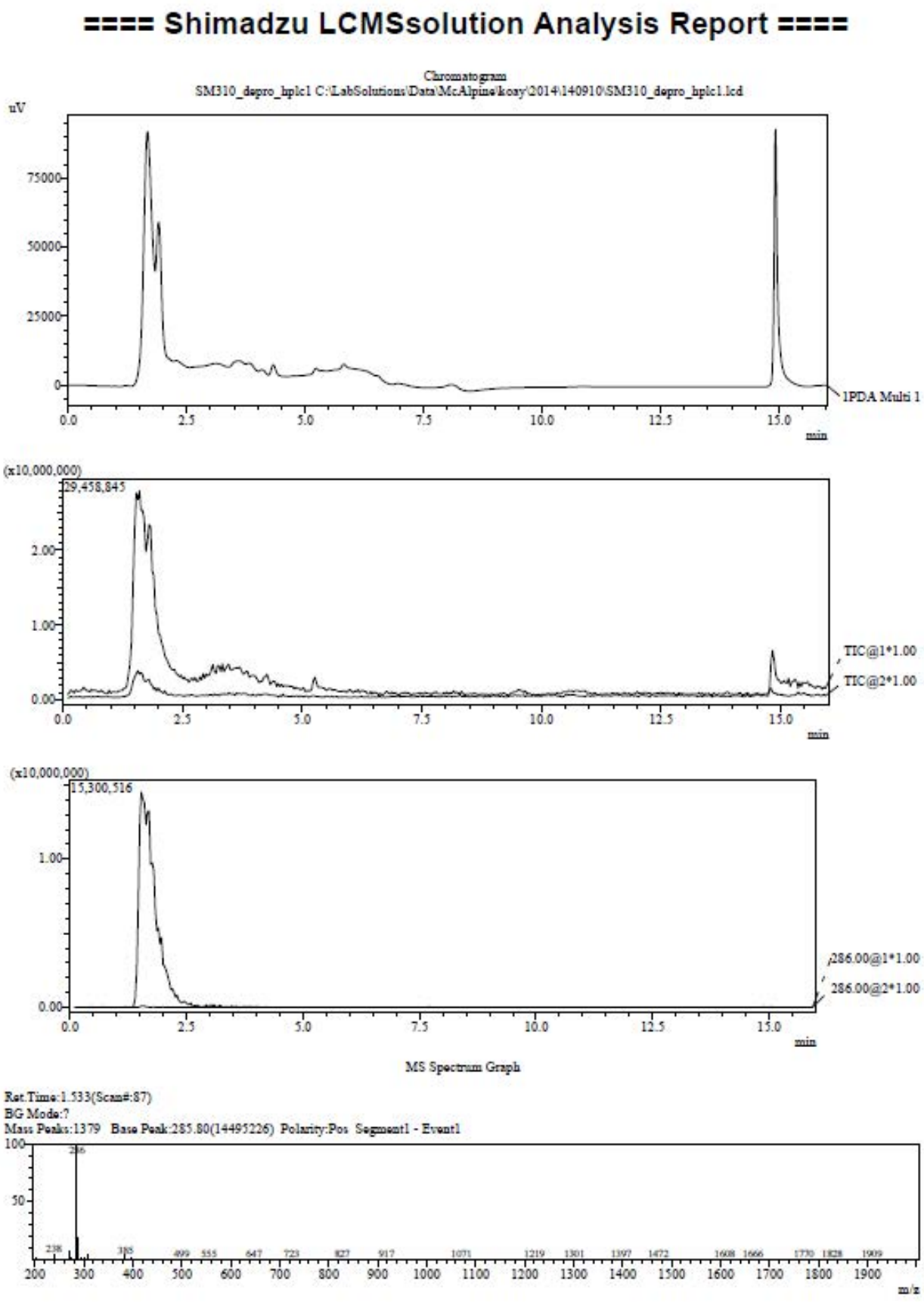
Compound **38**: LCMS of HO-Val-3-(4-Thia)-D-Ala-NH-*o*-NBS



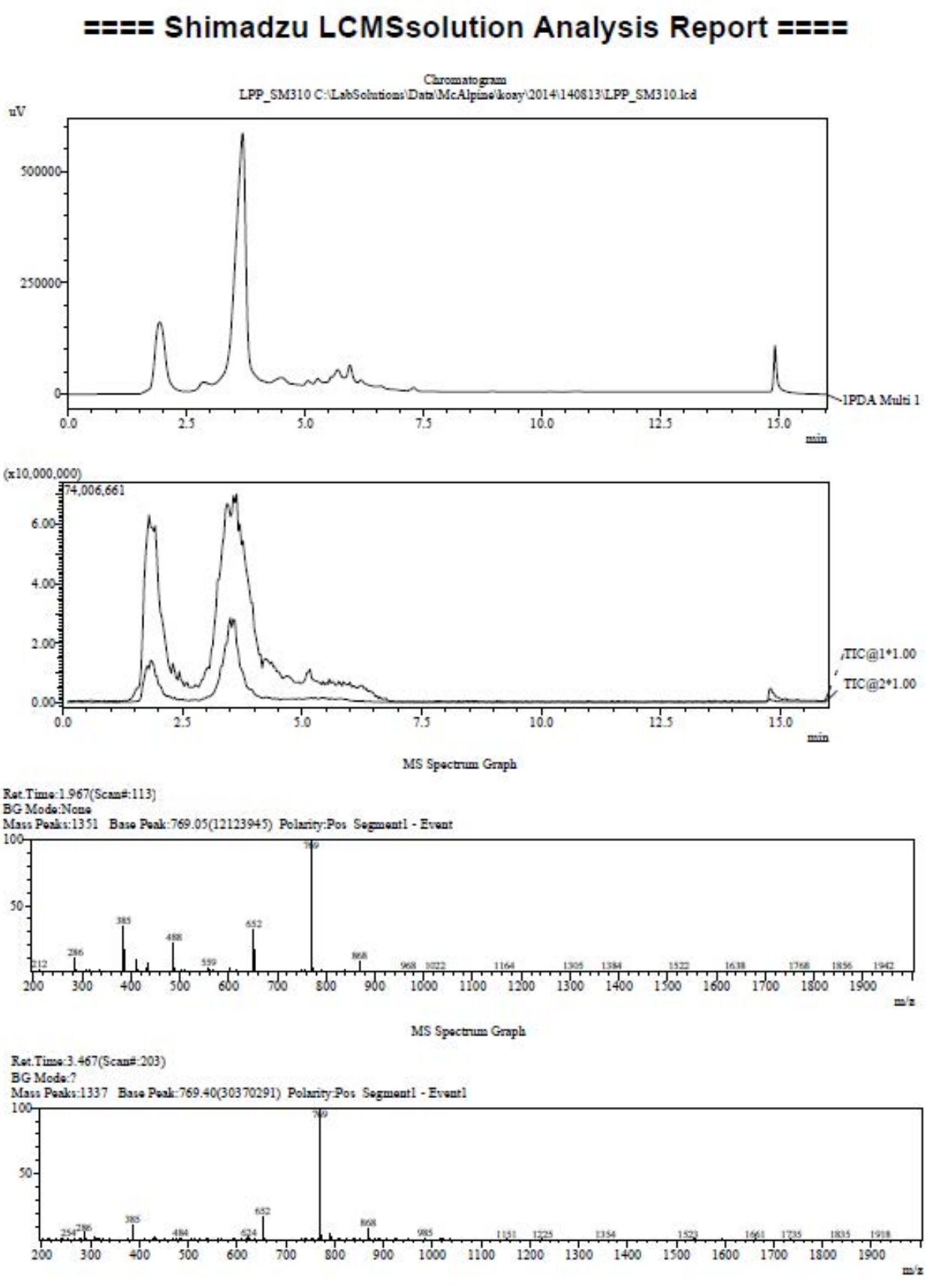
Compound **38**: LCMS of HO-Val-3-(4-Thia)-D-Ala-NCH_3-*o*-NBS



Compound **38**: LCMS of HO-Val-3-(4-Thia)-D-Ala-NH(CH_3)

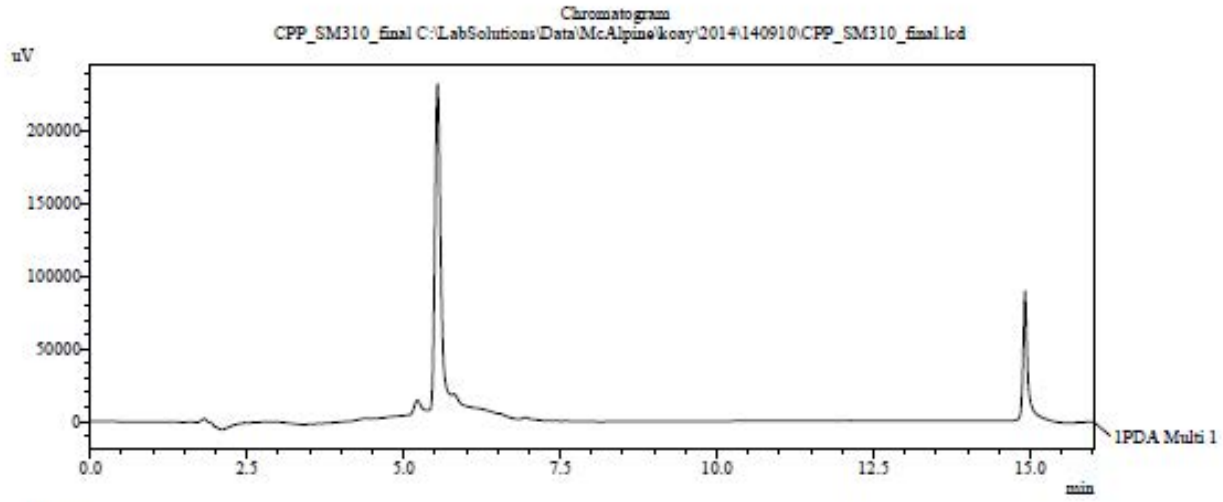


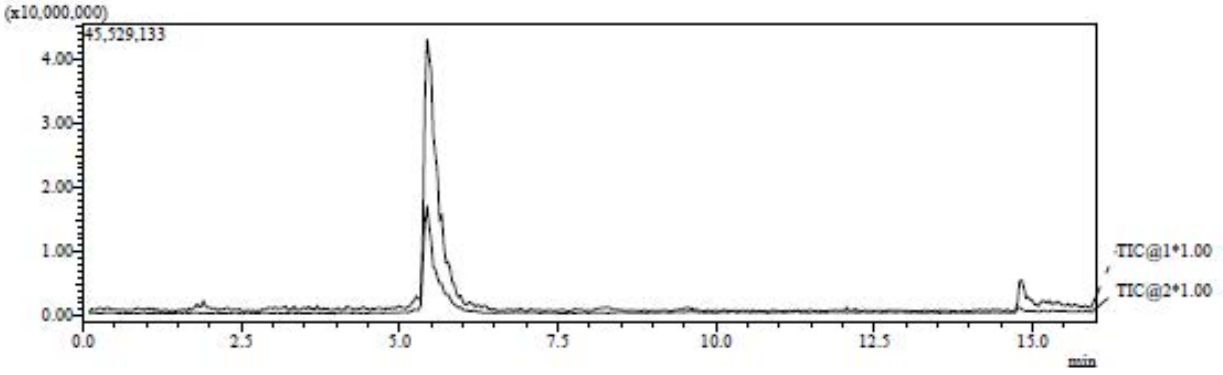
Compound **38**: LCMS of DDLP HO-Val-*N*-Me-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala-Leu-NH_2

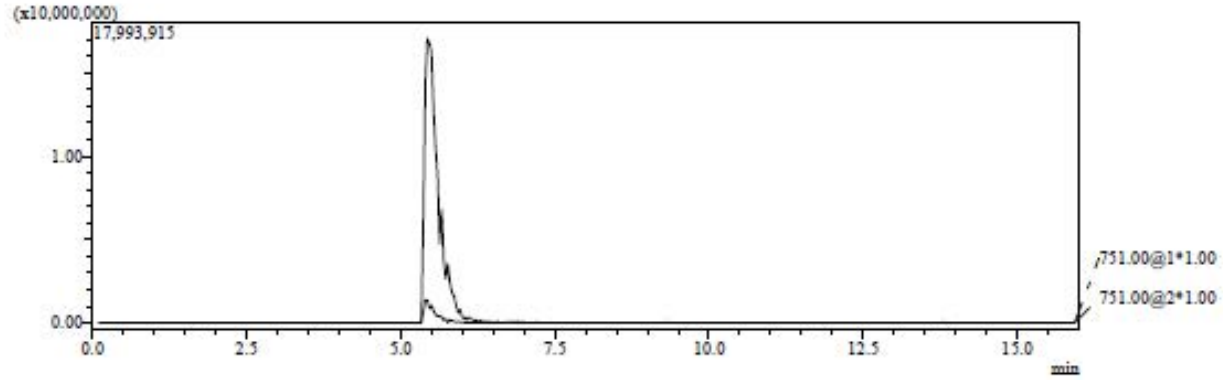


Compound **38**: LCMS of cyclo Val-*N*-Me-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala-Leu

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

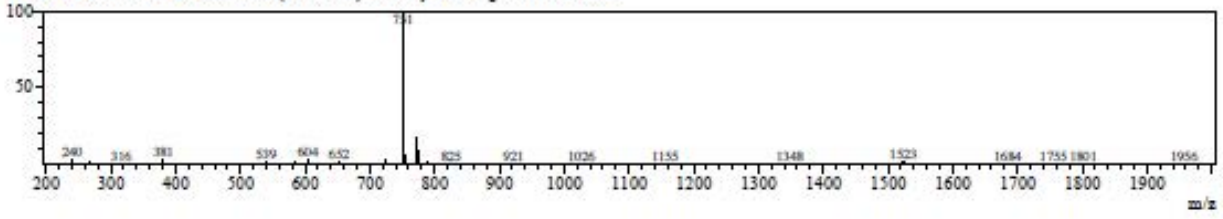






MS Spectrum Graph

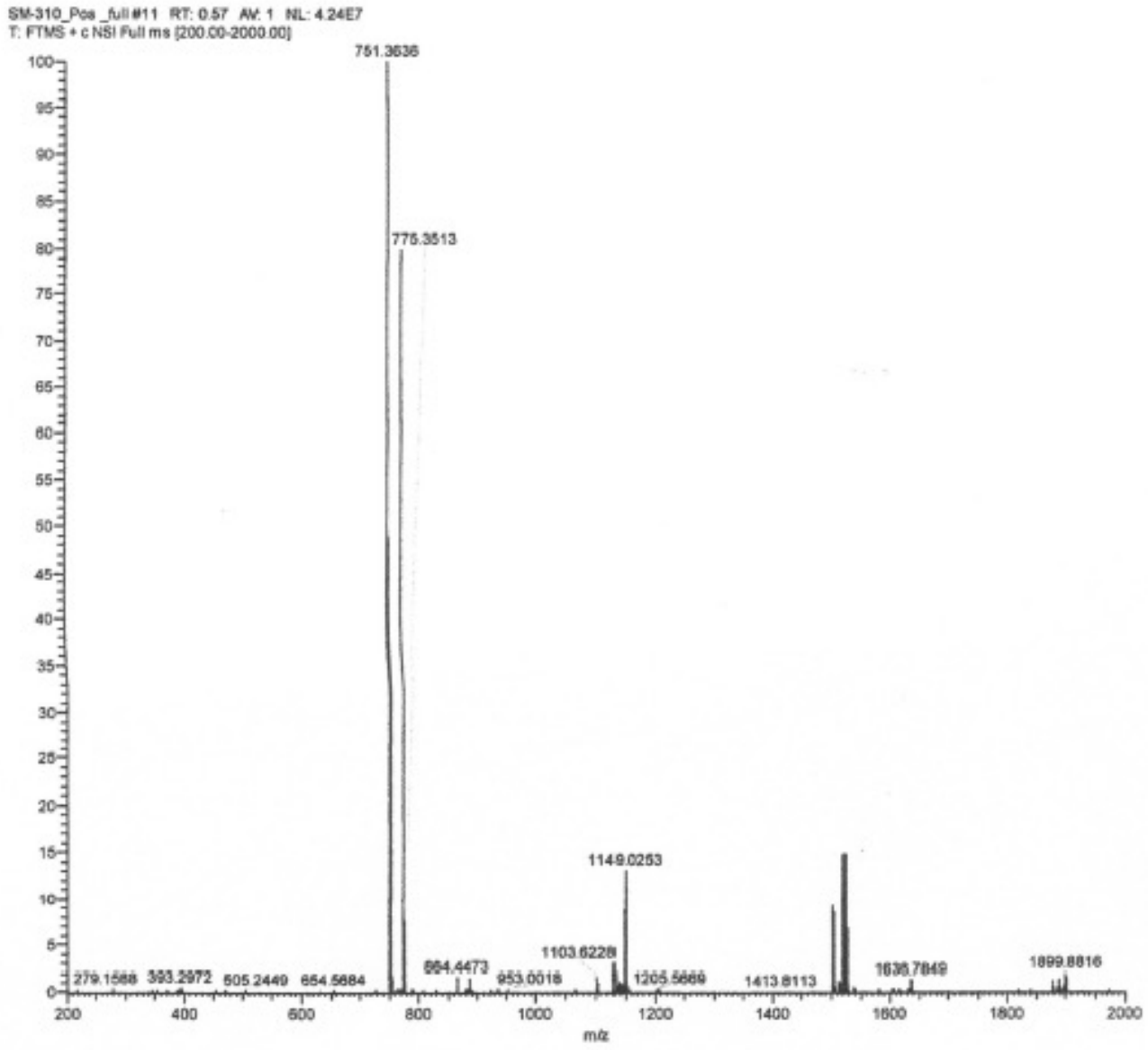
Ret.Time:5.433(Scan#:321)
BG Mode:?
Mass Peaks:1430 Base Peak:750.95(17046867) Polarity:Pos Segment1 - Event1



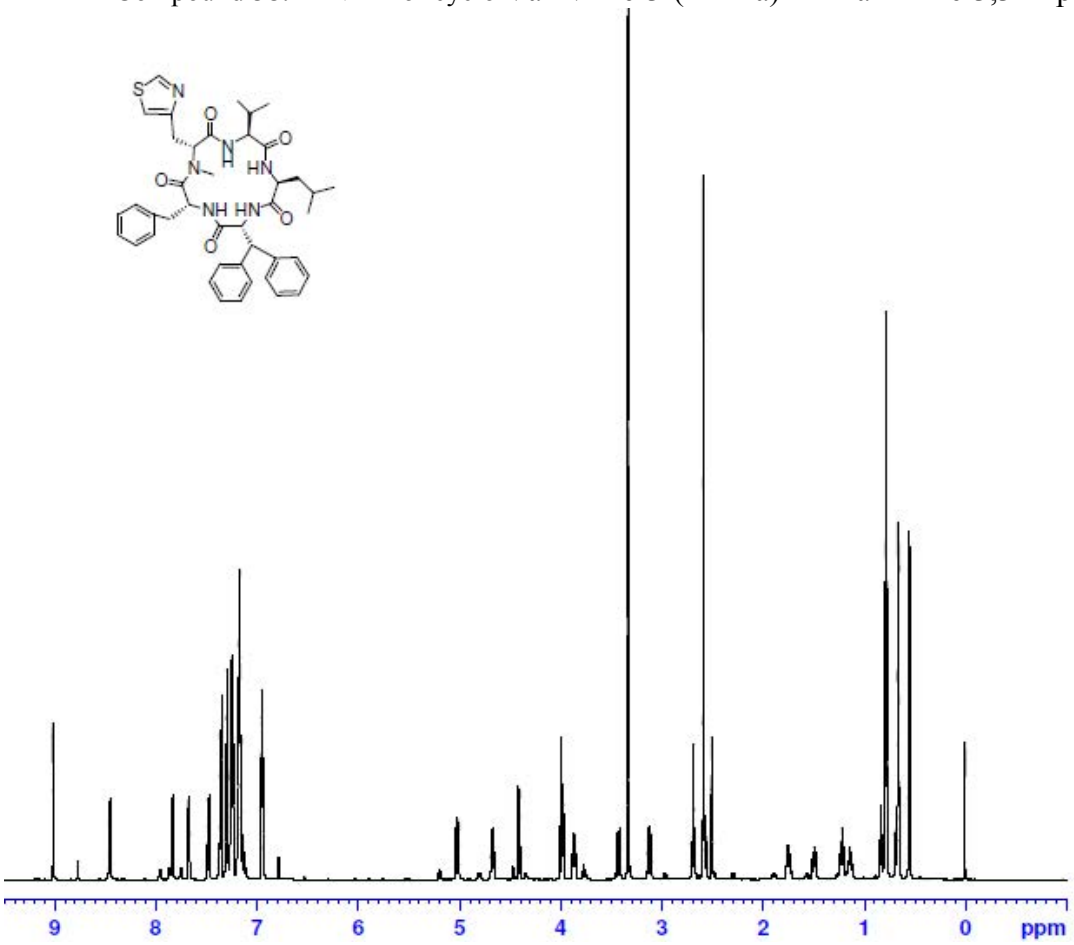
Compound **38**: HRMS of cyclo Val-*N*-Me-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala-Leu

MS Data from Orbitrap

Full spectrum



Compound **38**: ^{1}HNMR of cyclo Val-*N*-Me-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala-Leu



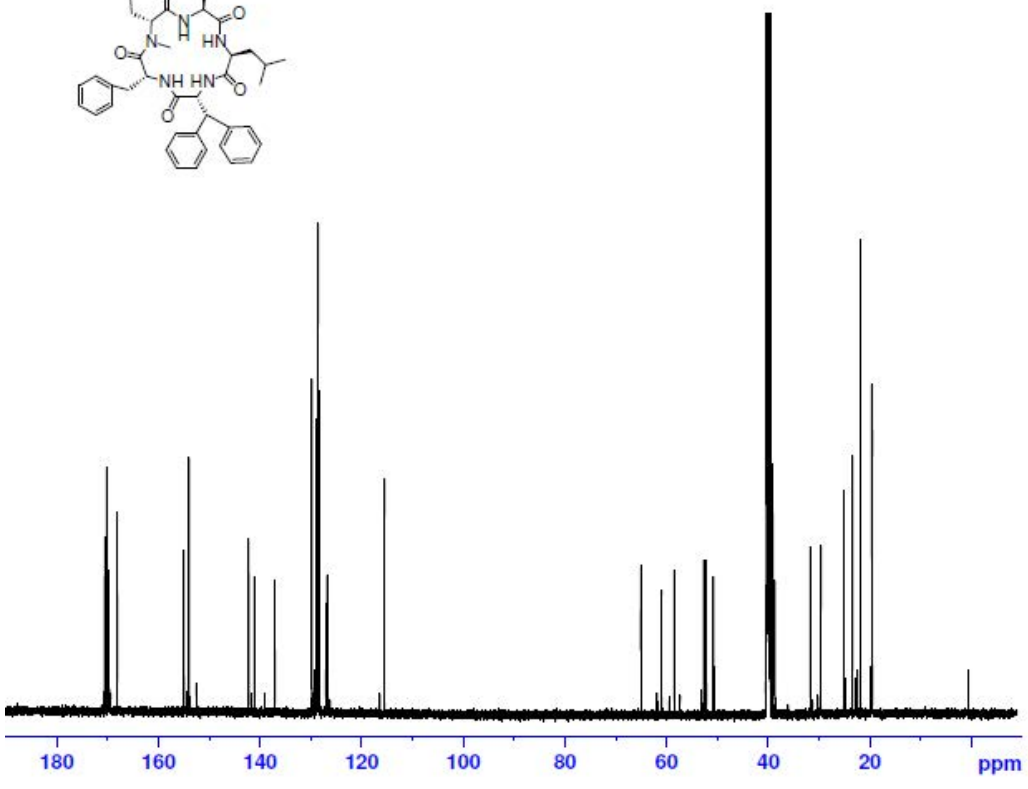

```
Current Data Parameters
NAME                  140906_yck
EXPNO                        151
PROCNO                         1

F2 - Acquisition Parameters
Date_                  20140906
Time                      10.02
INSTRUM                   spect
PROBHD    5 mm CPTCI 1H/
PULPROG                      zg
TD                        65536
SOLVENT                    DMSO
NS                            8
DS                            0
SWH                    9009.009 Hz
FIDRES                 0.137467 Hz
AQ                     3.6372480 sec
RG                        11.02
DW                        55.500 usec
DE                        33.22 usec
TE                        298.0 K
D1                     5.00000000 sec
TD0                            1

======== CHANNEL f1 ========
SFO1                 600.1639010 MHz
NUC1                          1H
P1                         8.00 usec
PLW1                   3.81069994 W

F2 - Processing parameters
SI                           131072
SF                     600.1600000 MHz
WDW                            EM
SSB                   0
LB                         0.30 Hz
GB                    0
PC                             1.00
```

Compound **38**: ^{13}CNMR of cyclo Val-*N*-Me-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala-Leu




```
Current Data Parameters
NAME                  140906_yck
EXPNO                        152
PROCNO                         1

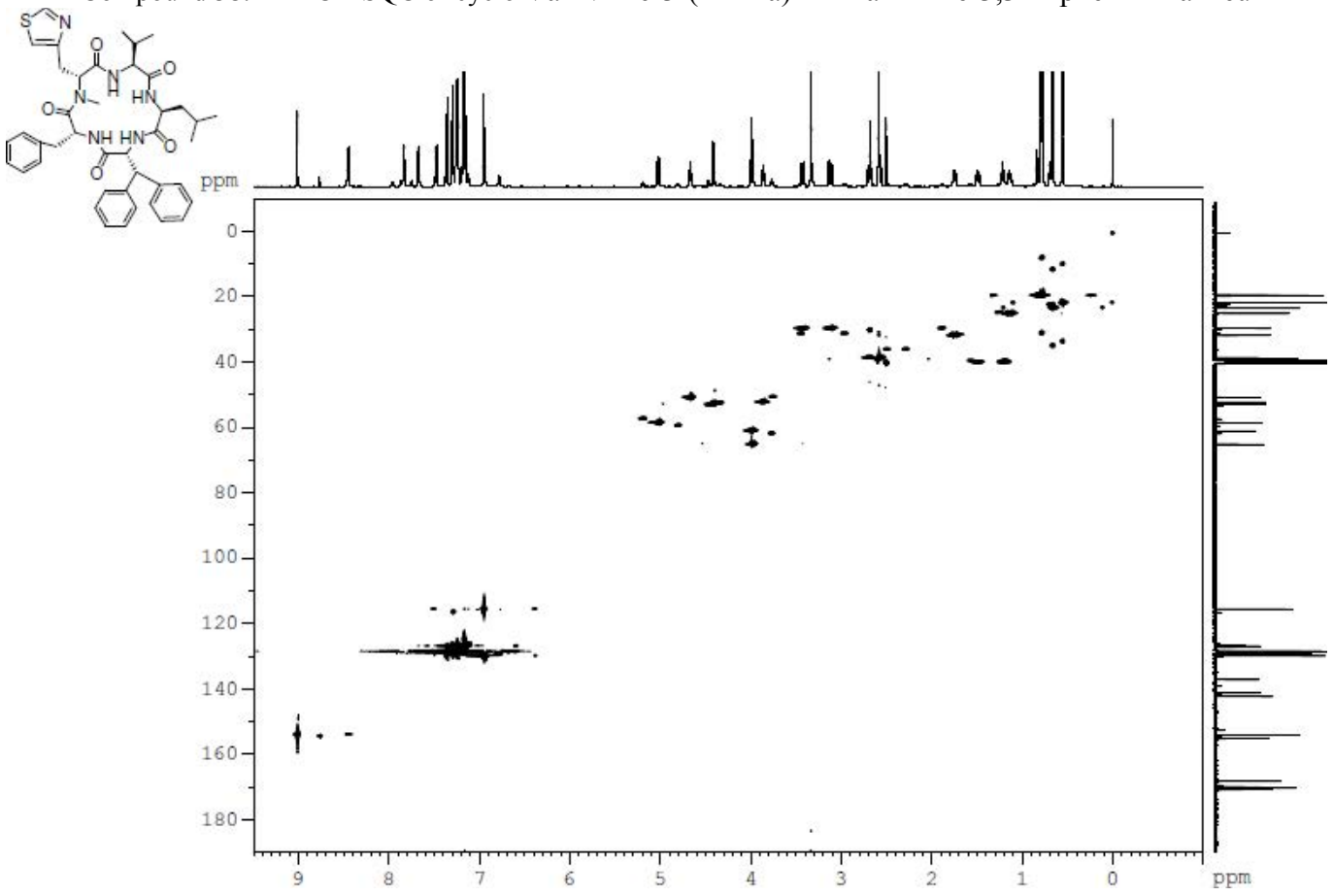
F2 - Acquisition Parameters
Date_                  20140906
Time                      12.16
INSTRUM                   spect
PROBHD    5 mm CPTCI 1H/
PULPROG                 zgpg30
TD                        65536
SOLVENT                    DMSO
NS                         2500
DS                            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                            1

======== CHANNEL f1 ========
SFO1                 150.9254430 MHz
NUC1                          13C
P1                        11.50 usec
PLW1                 100.00000000 W

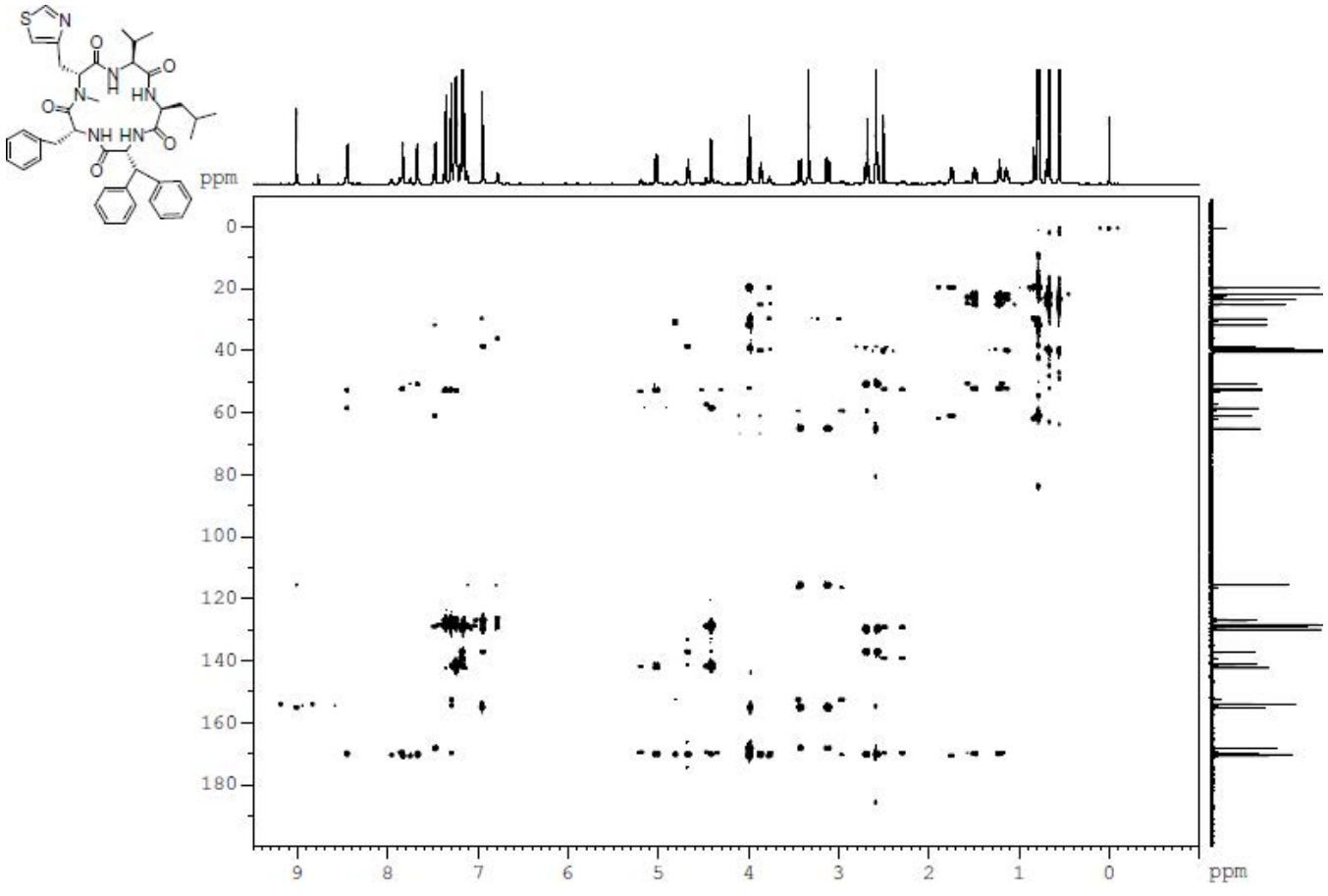
======== CHANNEL f2 ========
SFO2                 600.1624006 MHz
NUC2                          1H
CPDPRG[2 bi_waltz65_256
PCPD2                     70.00 usec
PLW2                   3.81069994 W
PLW12                  0.04977200 W
PLW13                  0.02438800 W

F2 - Processing parameters
SI                            32768
SF                     150.9103520 MHz
WDW                            no
SSB                   0
LB                    0 Hz
GB                    0
PC                             1.40
```

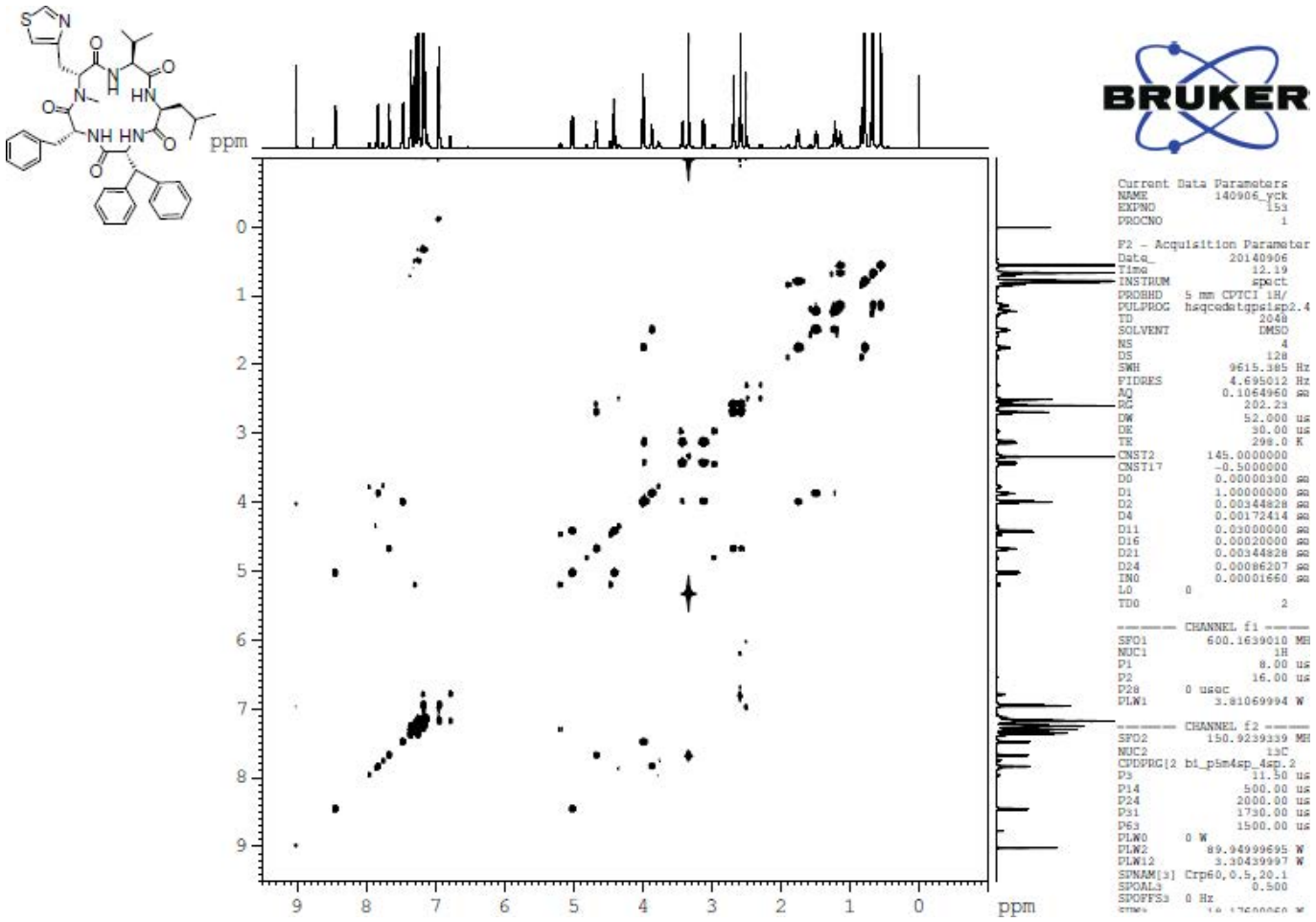
Compound **38**: ^{1}H-^{13}C HSQC of cyclo Val-*N*-Me-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala-Leu



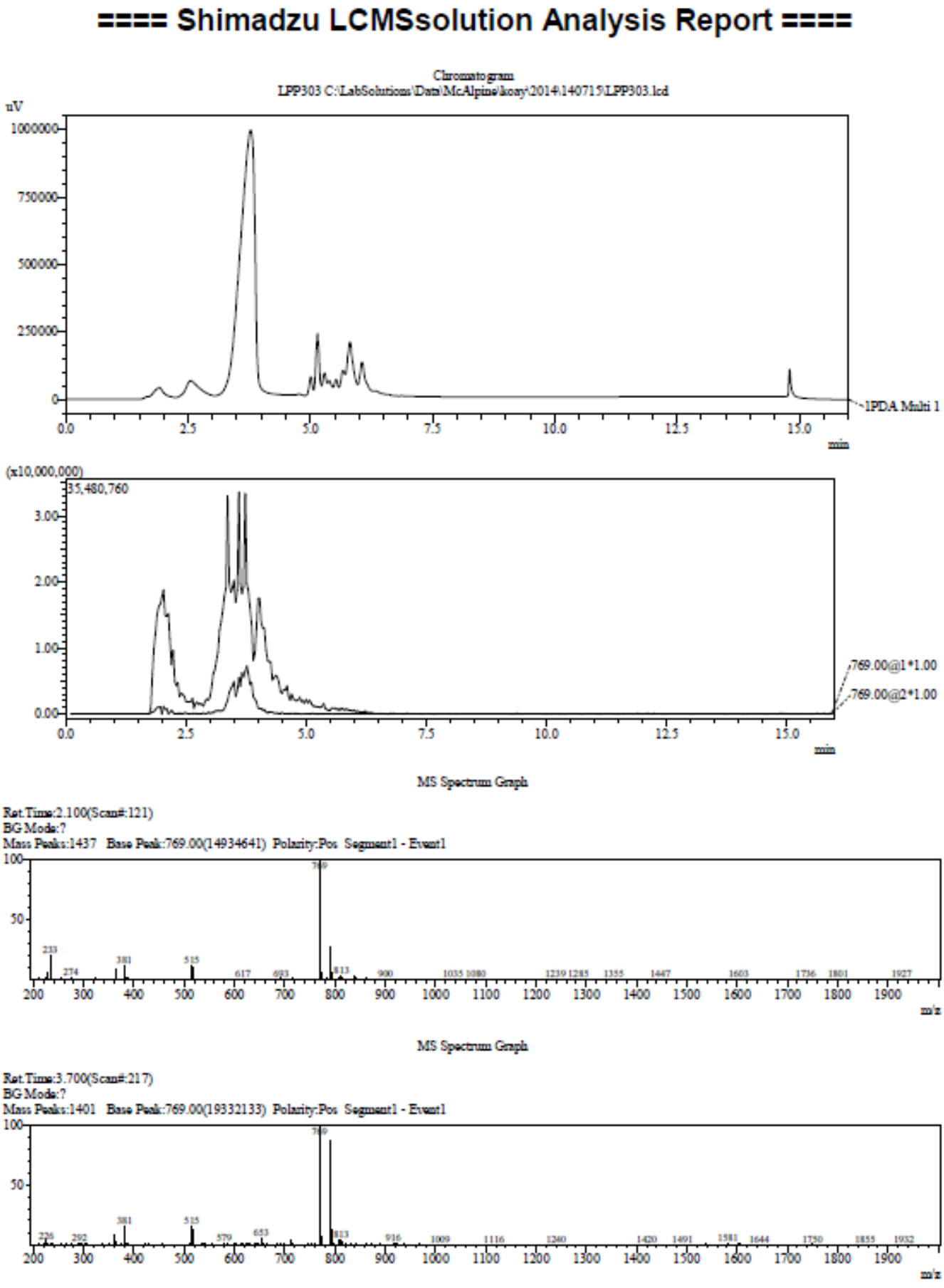
Compound **38**: ^{1}H-^{13}C HMBC of cyclo Val-*N*-Me-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala-Leu



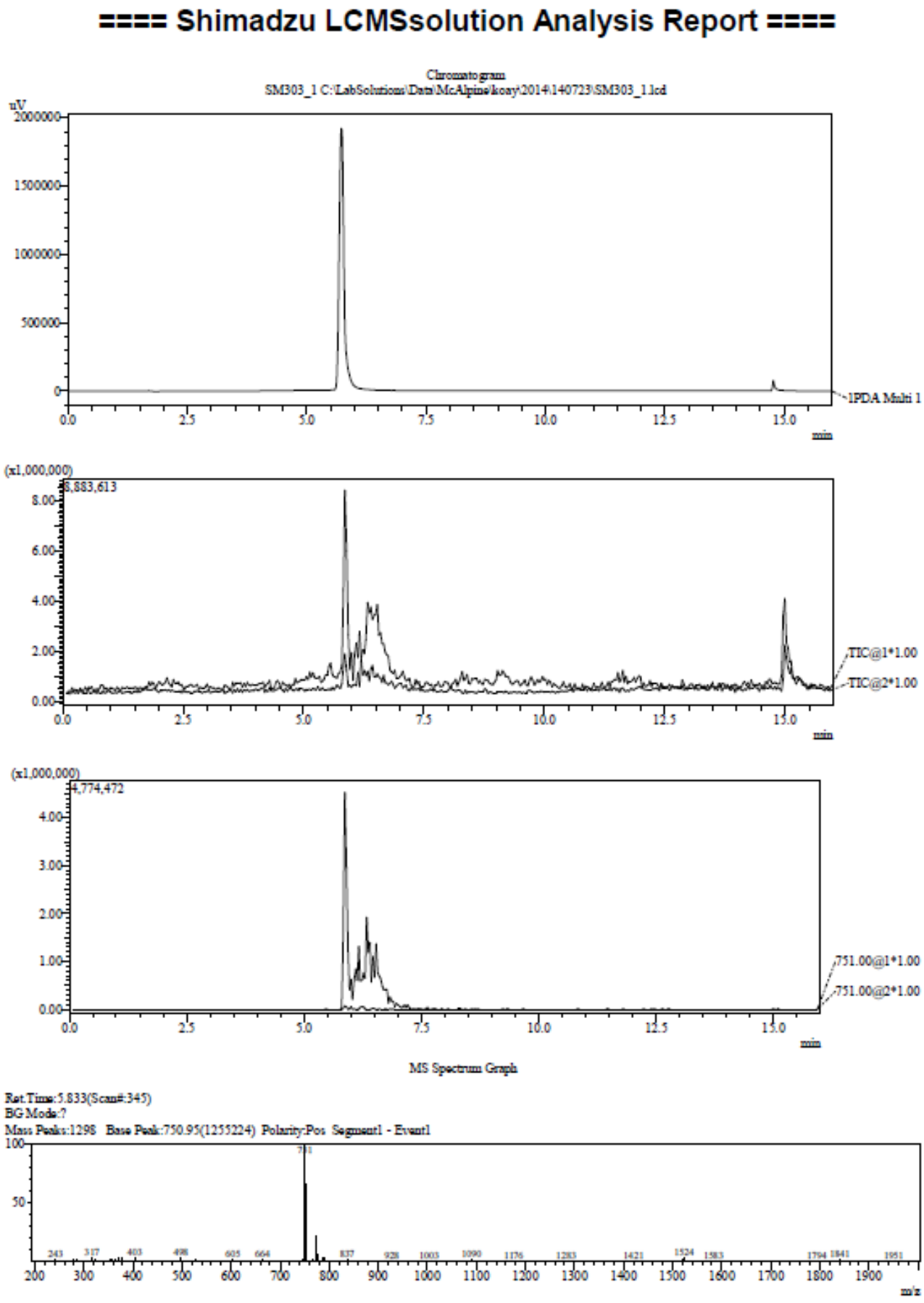
Compound **38**: ^{1}H-^{1}H COSY of cyclo Val-*N*-Me-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala-Leu



Compound **39**: LCMS of DDLP HO-D-Phe-3,3-Diphe-D-Ala-*N*-Me-Leu-Val-3-(4-Thia)-D-Ala-NH_2



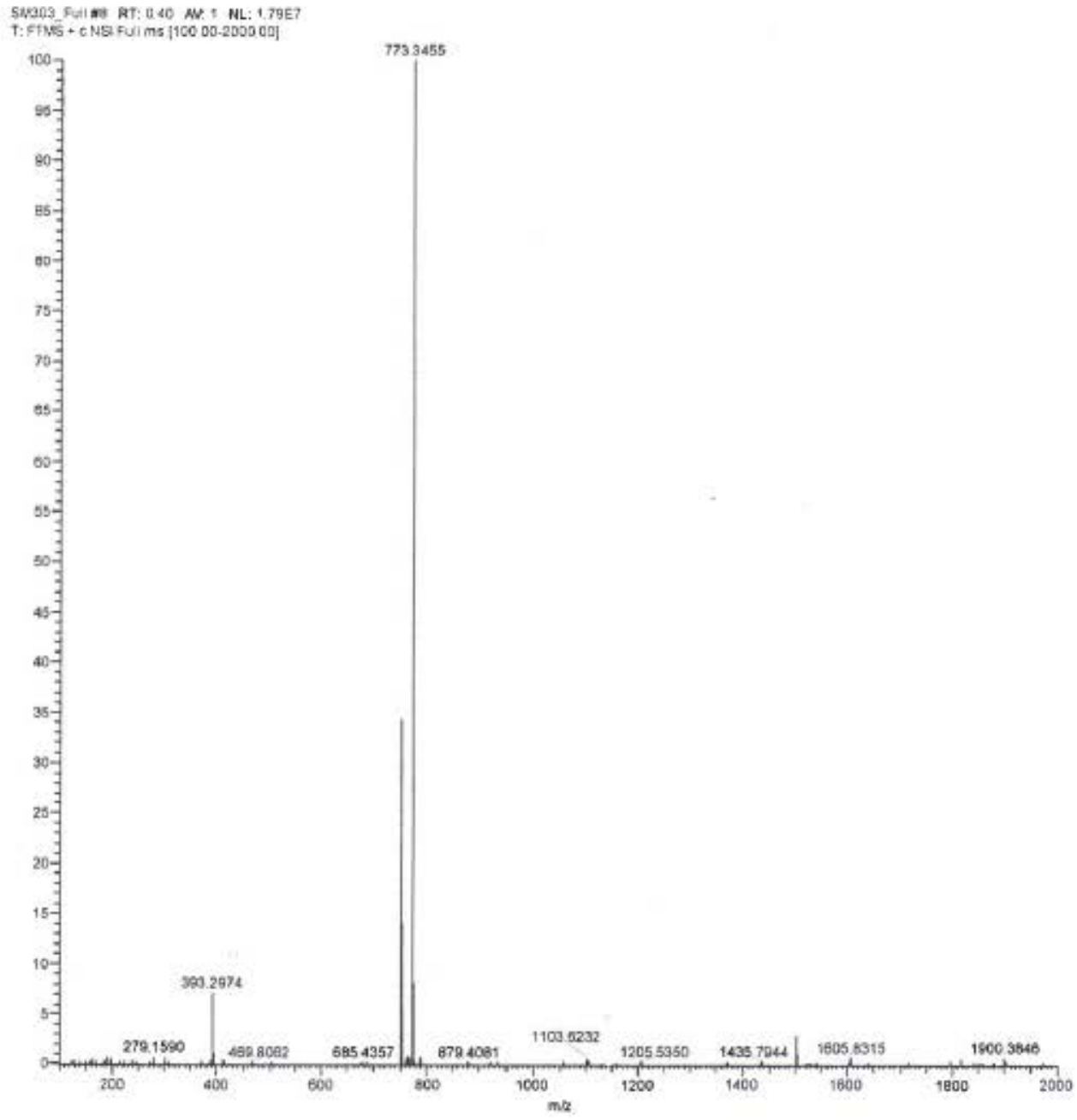
Compound **39**: LCMS of cyclo D-Phe-3,3-Diphe-D-Ala-*N*-Me-Leu-Val-3-(4-Thia)-D-Ala



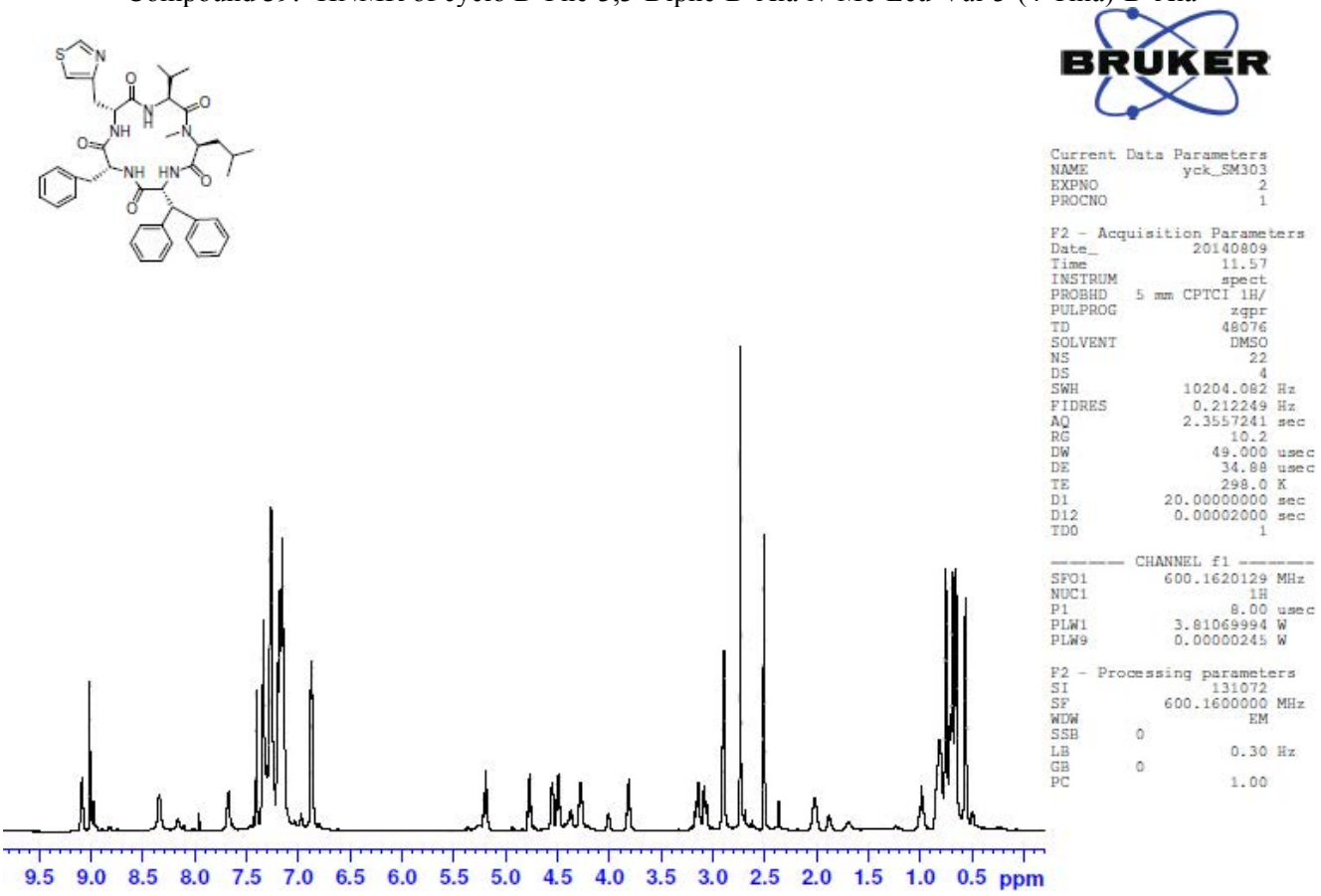
Compound **39**: HRMS of cyclo D-Phe-3,3-Diphe-D-Ala-*N*-Me-Leu-Val-3-(4-Thia)-D-Ala

MS Data from Orbitrap

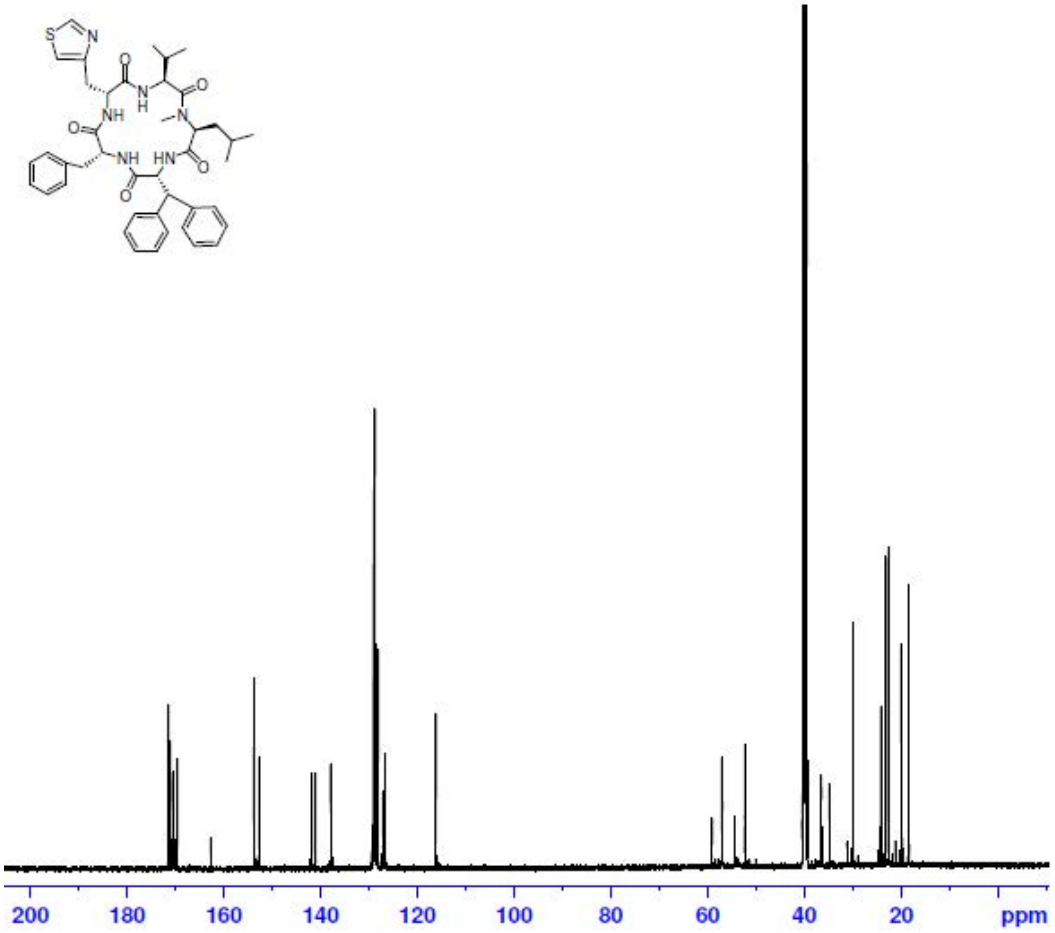
Full spectrum



Compound **39**: [1]HNMR of cyclo D-Phe-3,3-Diphe-D-Ala-*N*-Me-Leu-Val-3-(4-Thia)-D-Ala



Compound **39**: [13]CNMR of cyclo D-Phe-3,3-Diphe-D-Ala-*N*-Me-Leu-Val-3-(4-Thia)-D-Ala




```
Current Data Parameters
NAME                  yck_SM303
EXPNO                         3
PROCNO                        1

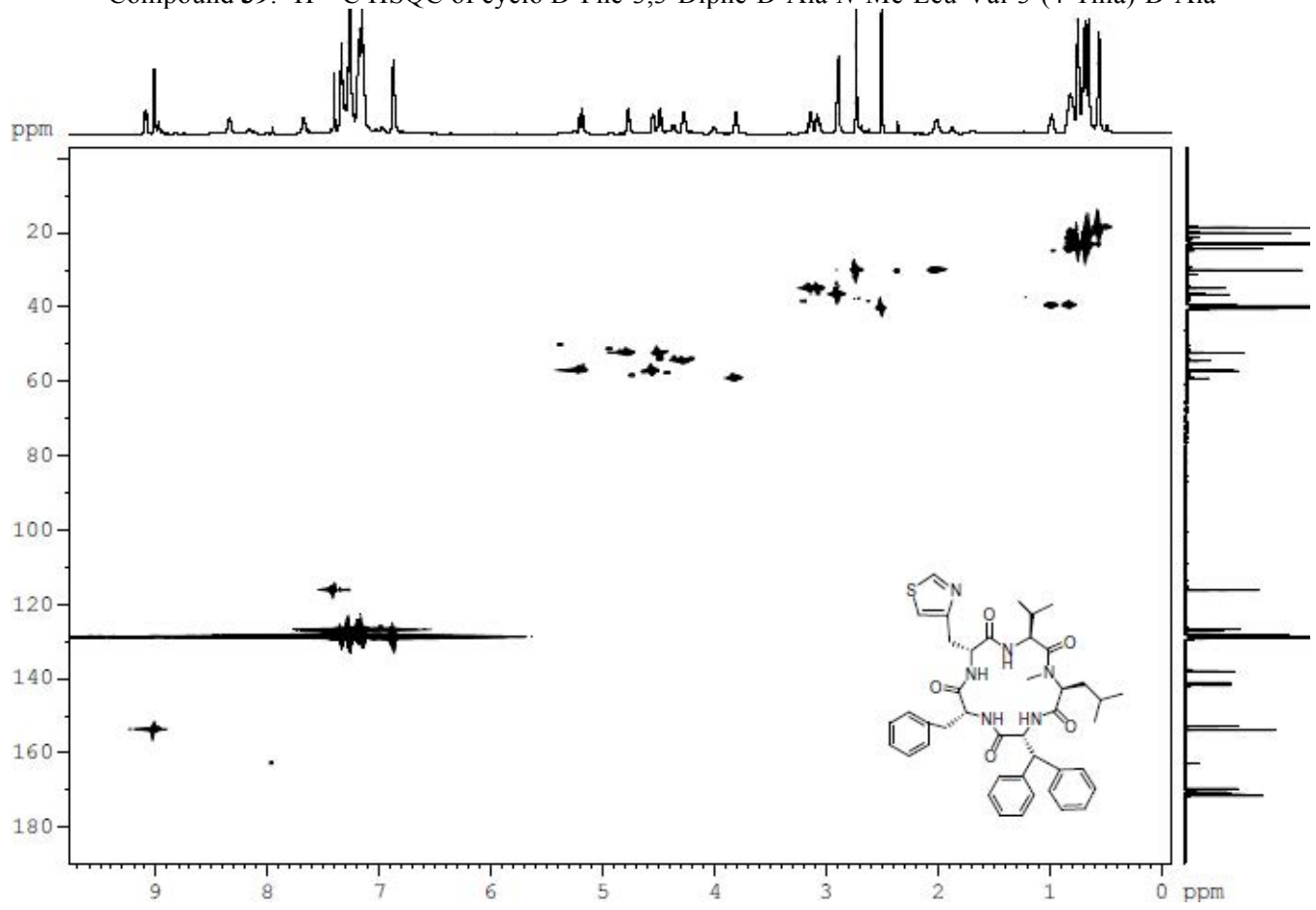
F2 - Acquisition Parameters
Date_                  20140809
Time                      15.20
INSTRUM                   spect
PROBHD    5 mm CPTCI 1H/
PULPROG                 zgpg30
TD                       65536
SOLVENT                   DMSO
NS                        3600
DS                           4
SWH                  33333.332 Hz
FIDRES                0.508626 Hz
AQ                    0.9830400 sec
RG                       202.23
DW                       15.000 usec
DE                        15.55 usec
TE                        298.0 K
D1                   2.00000000 sec
D11                  0.03000000 sec
TD0                           1

======== CHANNEL f1 ========
SFO1                150.9246885 MHz
NUC1                        13C
P1                        11.50 usec
PLW1               100.00000000 W

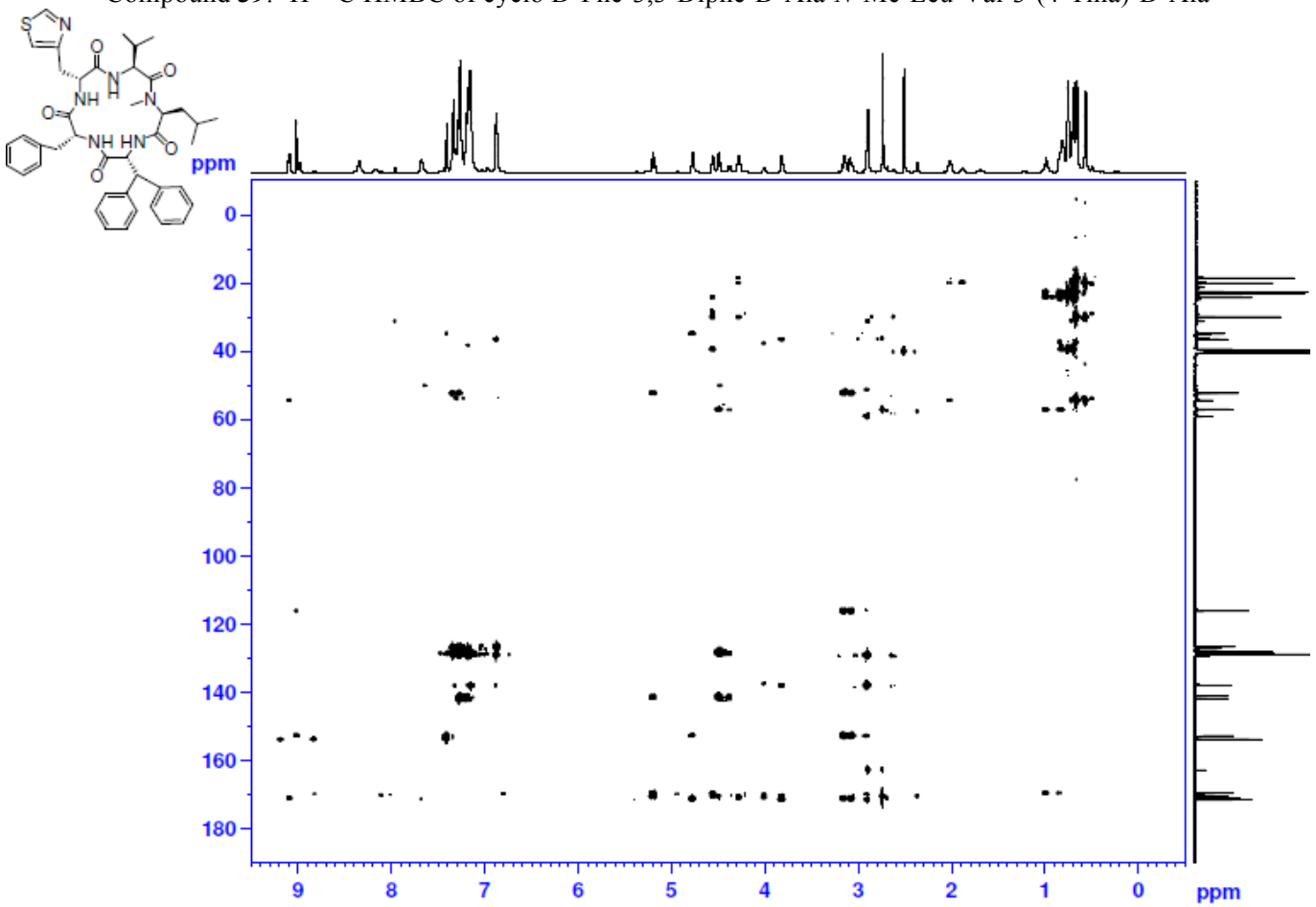
======== CHANNEL f2 ========
SFO2                600.1624006 MHz
NUC2                        1H
CPDPRG[2 bi_waltz65_256
PCPD2                     70.00 usec
PLW2                 3.81069994 W
PLW12                0.04977200 W
PLW13                0.02438800 W

F2 - Processing parameters
SI                        32768
SF                  150.9103520 MHz
WDW                          no
SSB                 0
LB                  0 Hz
GB                  0
PC                        1.40
```

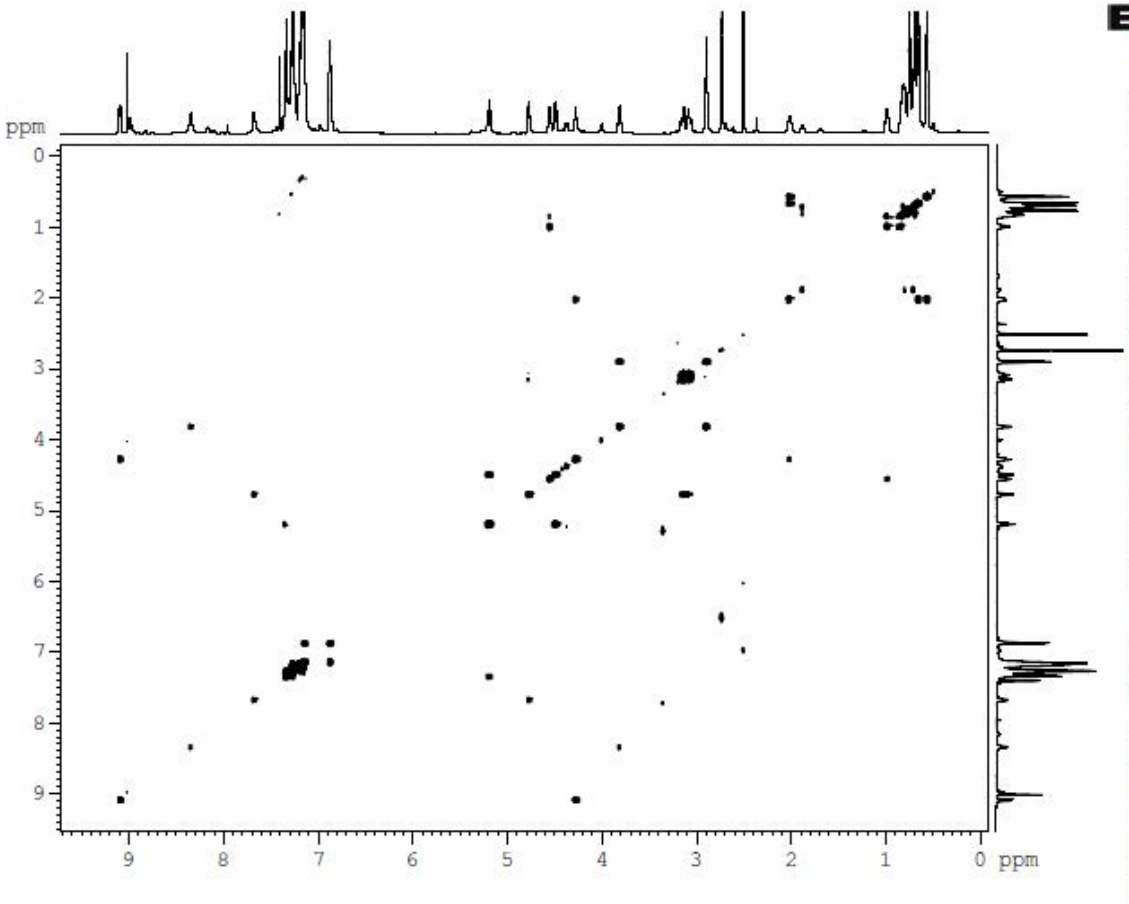
Compound **39**: ^{1}H-^{13}C HSQC of cyclo D-Phe-3,3-Diphe-D-Ala-*N*-Me-Leu-Val-3-(4-Thia)-D-Ala



Compound **39**: ^{1}H-^{13}C HMBC of cyclo D-Phe-3,3-Diphe-D-Ala-*N*-Me-Leu-Val-3-(4-Thia)-D-Ala



Compound **39**: ^{1}H-^{1}H COSY of cyclo D-Phe-3,3-Diphe-D-Ala-*N*-Me-Leu-Val-3-(4-Thia)-D-Ala



Current Data Parameters
NAME yck_SM303
EXPNO 6
PROCNO 1

F2 - Acquisition Parameter
Date_ 20140809
Time 19.49
INSTRUM spect
PROBHD 5 mm CPTCI 1H/
PULPROG cosygpmfph
TD 2048
SOLVENT DMSO
NS 4
DS 16
SWH 9014.423 H
FIDRES 4.401574 H
AQ 0.1135957 s
RG 60.99
DW 55.467 u
DE 30.00 u
TE 298.0 K
D0 0.00004531 s
D1 2.00000000 s
D13 0.00000400 s
D16 0.00020000 s
IN0 0.00011100 s

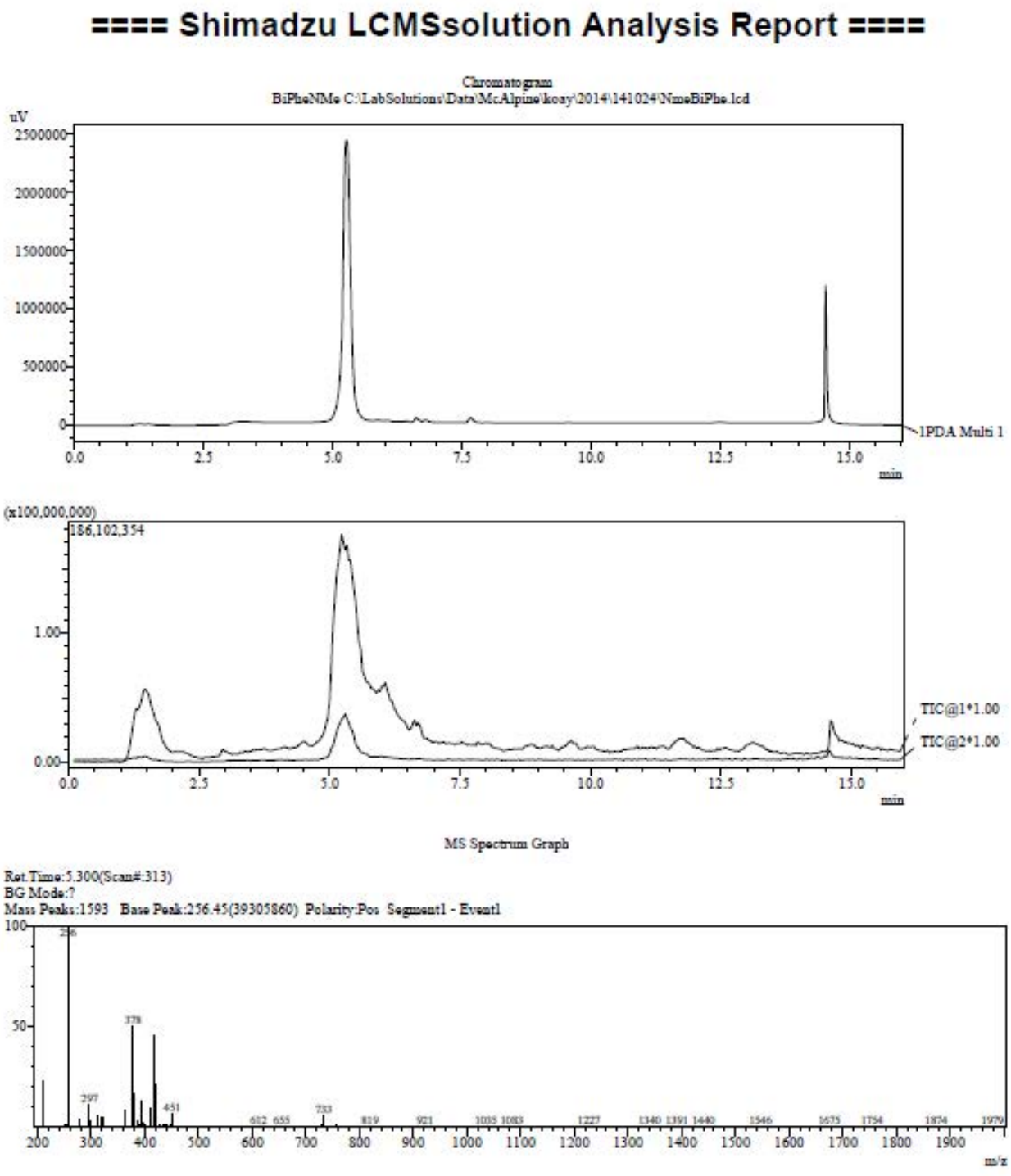
======== CHANNEL f1 ======
SFO1 600.1639010 M
NUC1 1H
P1 8.00 u
P2 16.00 u
PLW1 3.81069994 W

====== GRADIENT CHANNEL ==
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPZ1 10.00 %
GPZ2 20.00 %
P16 1000.00 u

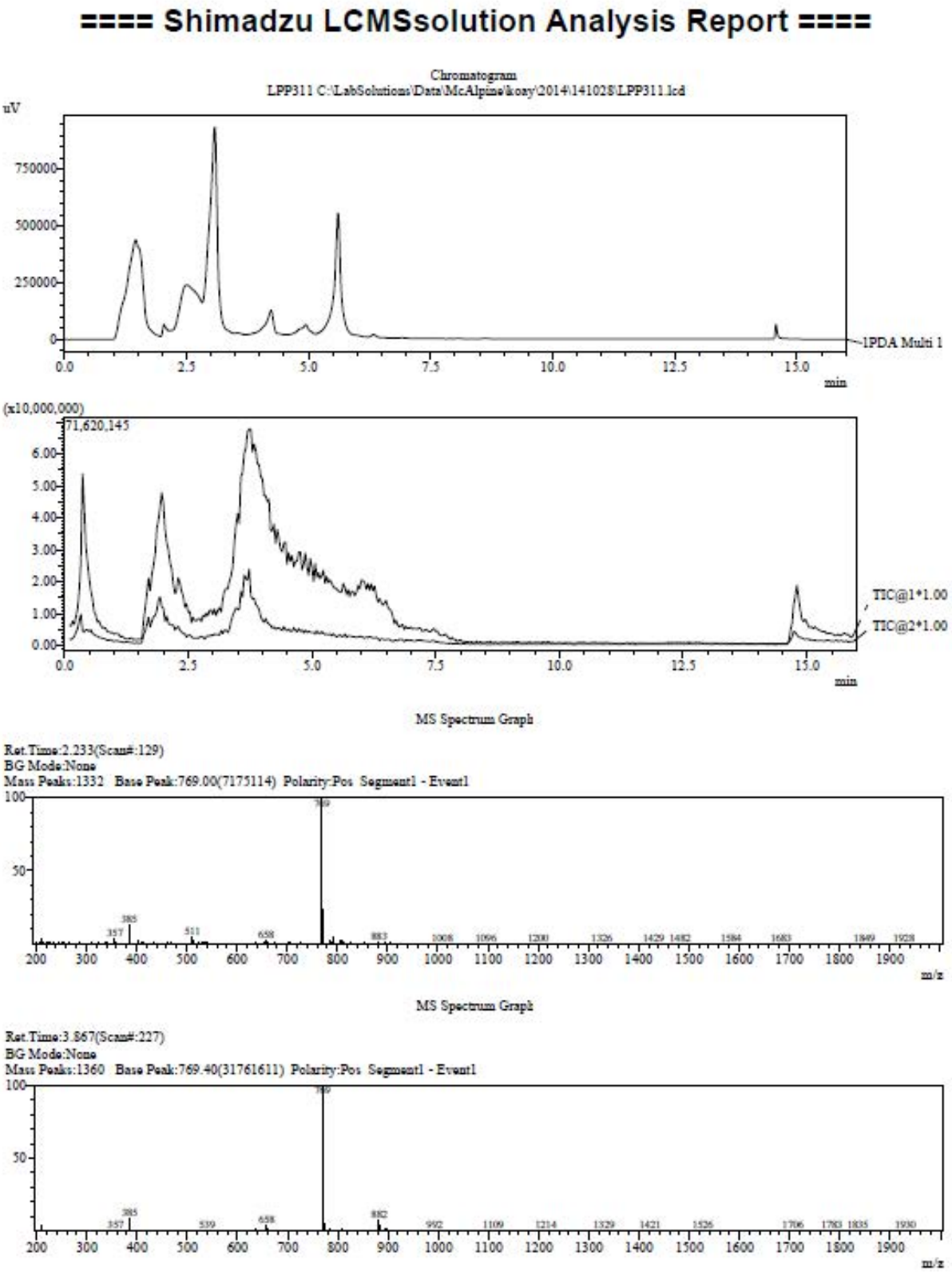
F1 - Acquisition parameter
TD 512
SFO1 600.1639 M
FIDRES 17.595720 H
SW 15.011 p
FnMODE States-TPPI

F2 - Processing parameters
SI 2048
SF 600.1600000 M
WDW QSINE
SSB 2

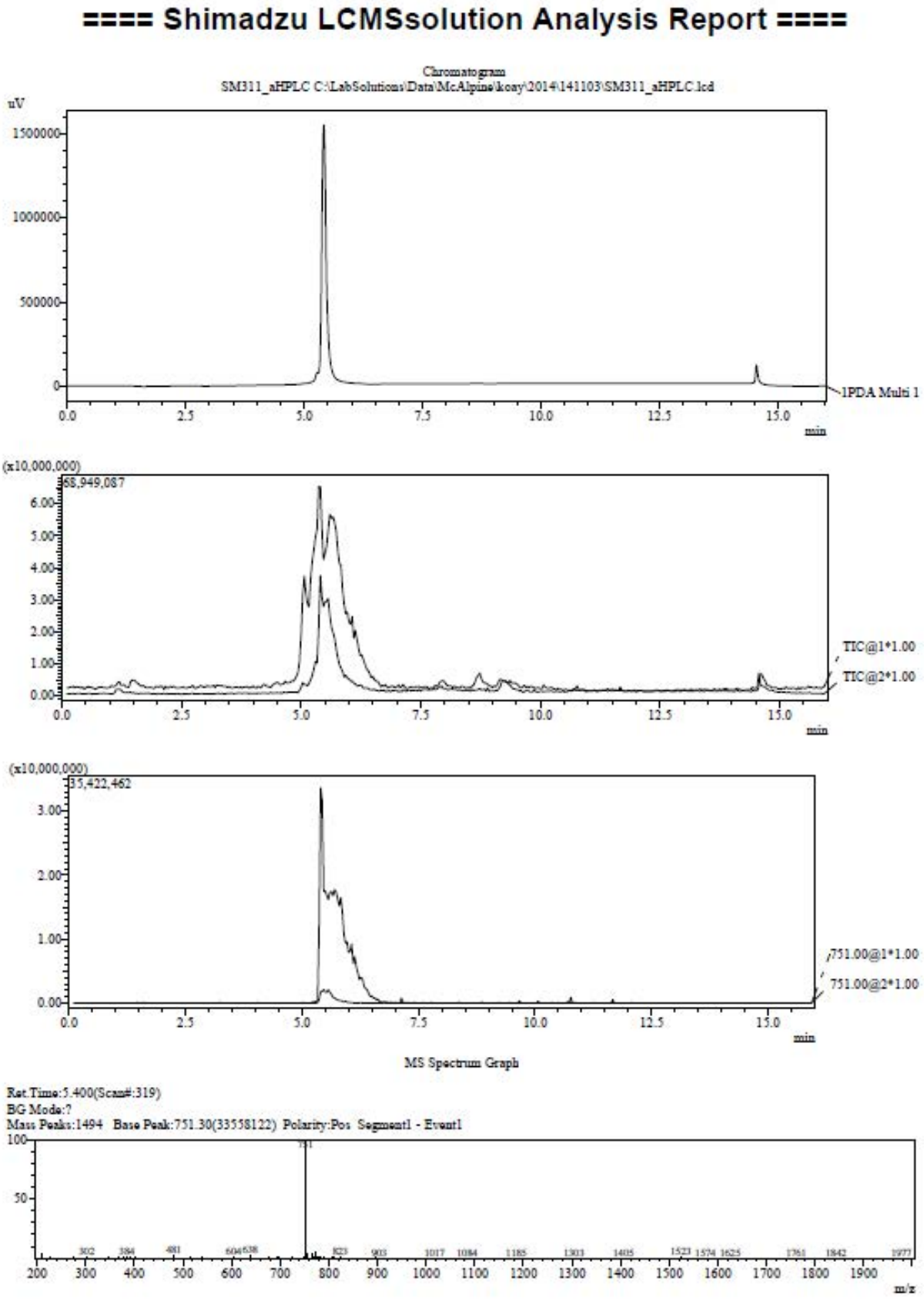
Compound **40**: LCMS of DDLP Boc-*N*-Me-3,3-Diphe-D-Ala-OH



Compound **40**: LCMS of DDLP HO-Leu-Val-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala-NH(CH_3)



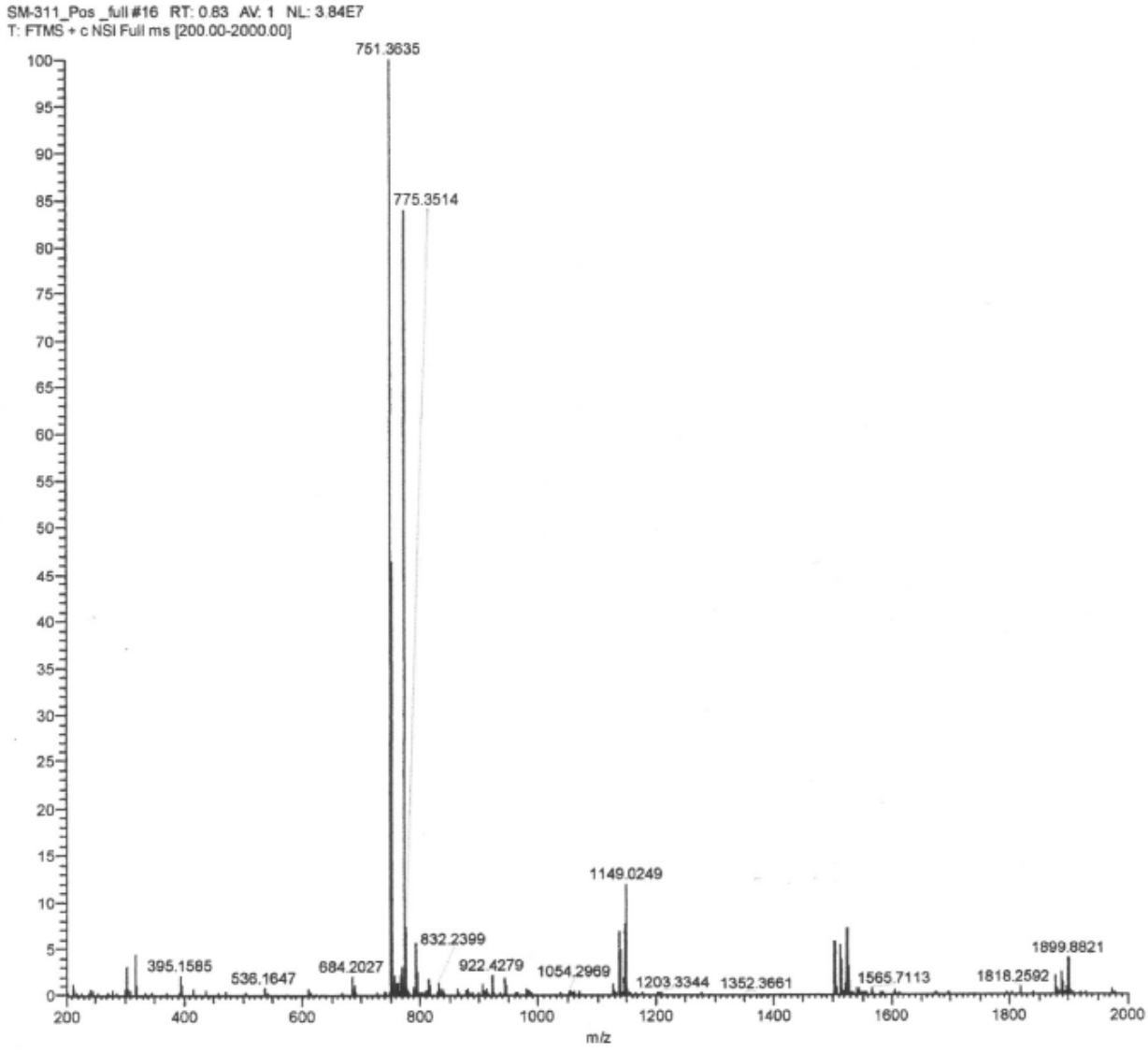
Compound **40**: LCMS of cyclo Leu-Val-3-(4-Thia)-D-Ala-D-Phe-*N*-Me-3,3-Diphe-D-Ala



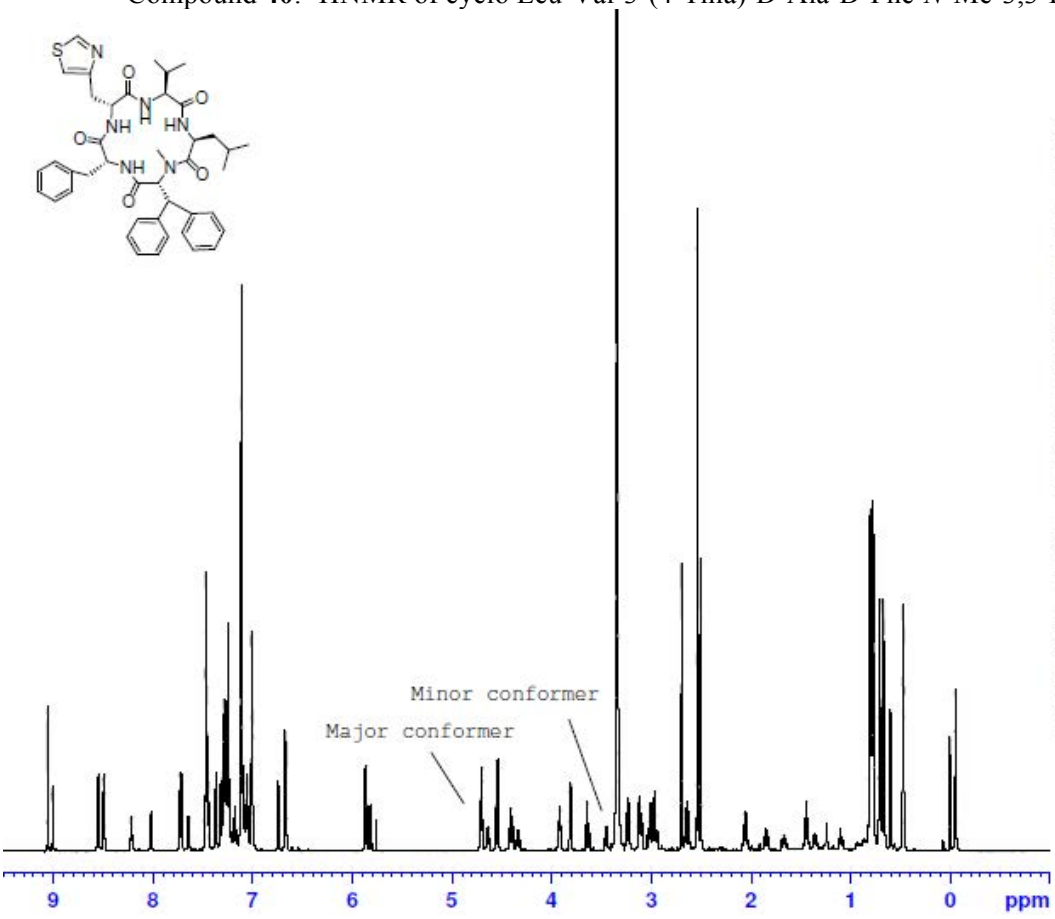
Compound **40**: HRMS of cyclo Leu-Val-3-(4-Thia)-D-Ala-D-Phe-*N*-Me-3,3-Diphe-D-Ala

MS Data from Orbitrap

Full spectrum



Compound **40**: [1]HNMR of cyclo Leu-Val-3-(4-Thia)-D-Ala-D-Phe-*N*-Me-3,3-Diphe-D-Ala



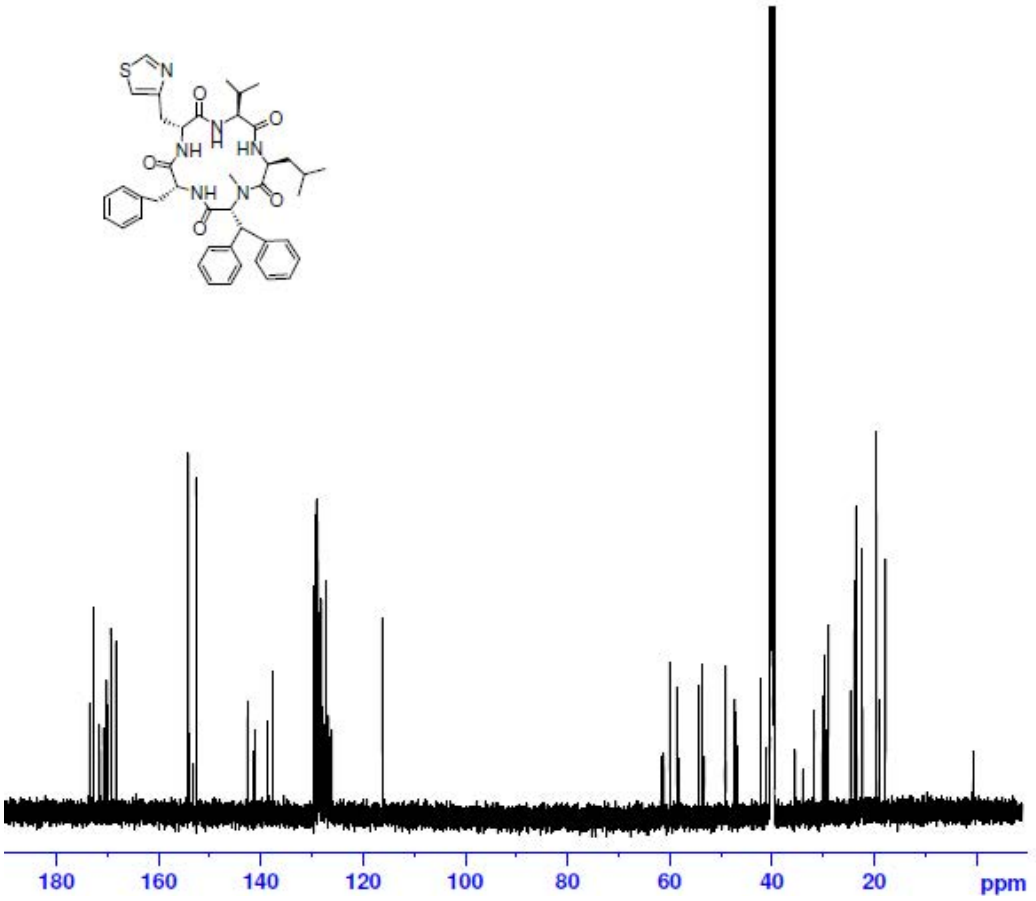

```
Current Data Parameters
NAME       141115_yck311
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20141115
Time                9.19
INSTRUM            spect
PROBHD   5 mm CPTCI 1H/
PULPROG              zg
TD                65536
SOLVENT            DMSO
NS                     8
DS                     0
SWH             9009.009 Hz
FIDRES          0.137467 Hz
AQ              3.6372480 sec
RG                 17.18
DW                55.500 usec
DE                33.22 usec
TE                298.0 K
D1             5.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         600.1639010 MHz
NUC1                   1H
P1                   8.00 usec
PLW1          3.81069994 W

F2 - Processing parameters
SI                131072
SF          600.1600000 MHz
WDW                  EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

Compound **40**: [13]CNMR of cyclo Leu-Val-3-(4-Thia)-D-Ala-D-Phe-*N*-Me-3,3-Diphe-D-Ala




```
Current Data Parameters
NAME       141115_yck311
EXPNO                  3
PROCNO                 1

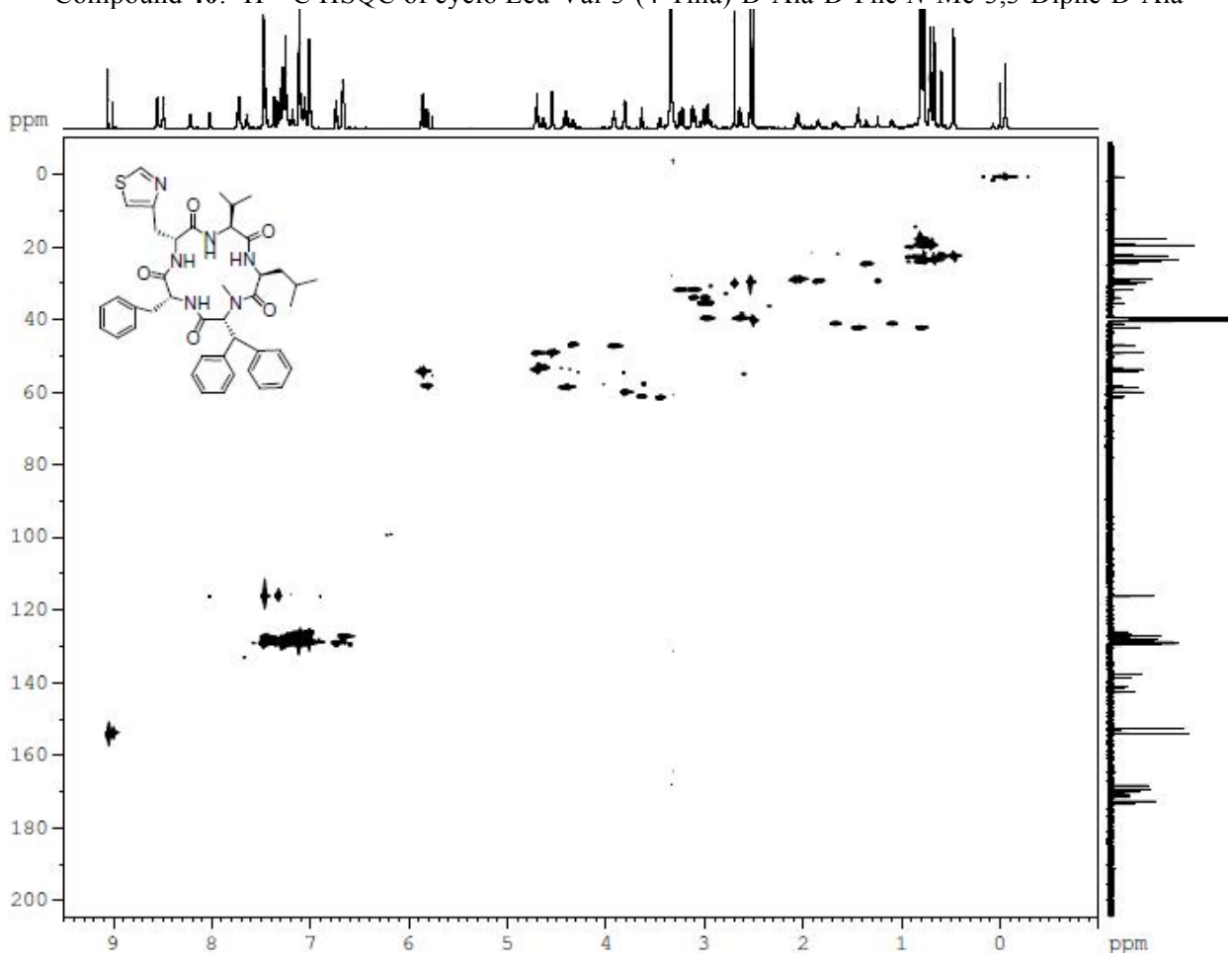
F2 - Acquisition Parameters
Date_           20141115
Time                9.33
INSTRUM            spect
PROBHD   5 mm CPTCI 1H/
PULPROG          zgpg30
TD                65536
SOLVENT            DMSO
NS                 1200
DS                    4
SWH            32894.738 Hz
FIDRES          0.501934 Hz
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                    1

======== CHANNEL f1 ========
SFO1         150.9254430 MHz
NUC1                   13C
P1                  11.50 usec
PLW1        100.00000000 W

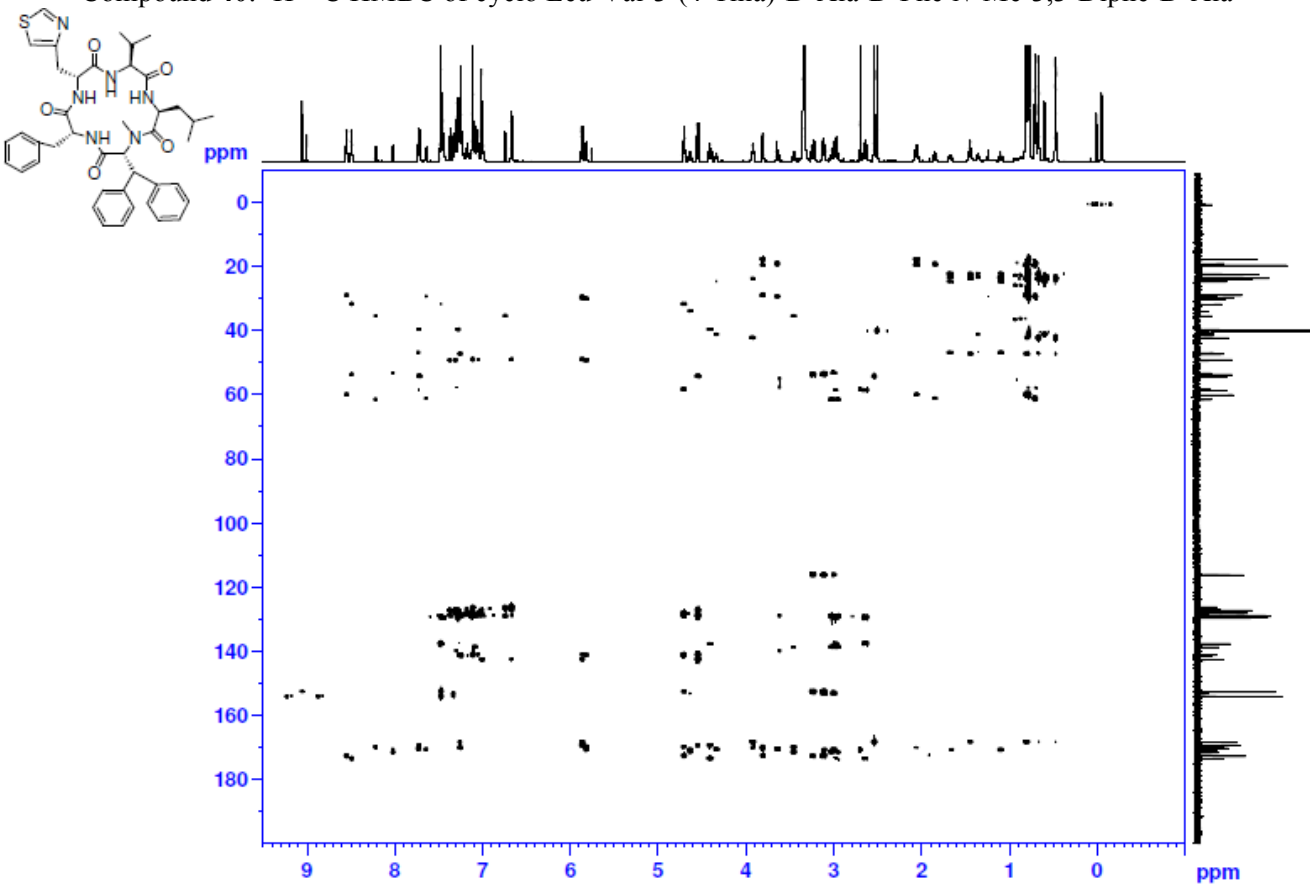
======== CHANNEL f2 ========
SFO2         600.1624006 MHz
NUC2                   1H
CPDPRG[2 bi_waltz65_256
PCPD2                70.00 usec
PLW2          3.81069994 W
PLW12         0.04977200 W
PLW13         0.02438800 W

F2 - Processing parameters
SI                 32768
SF          150.9103520 MHz
WDW                   no
SSB       0
LB        0 Hz
GB        0
PC                1.40
```

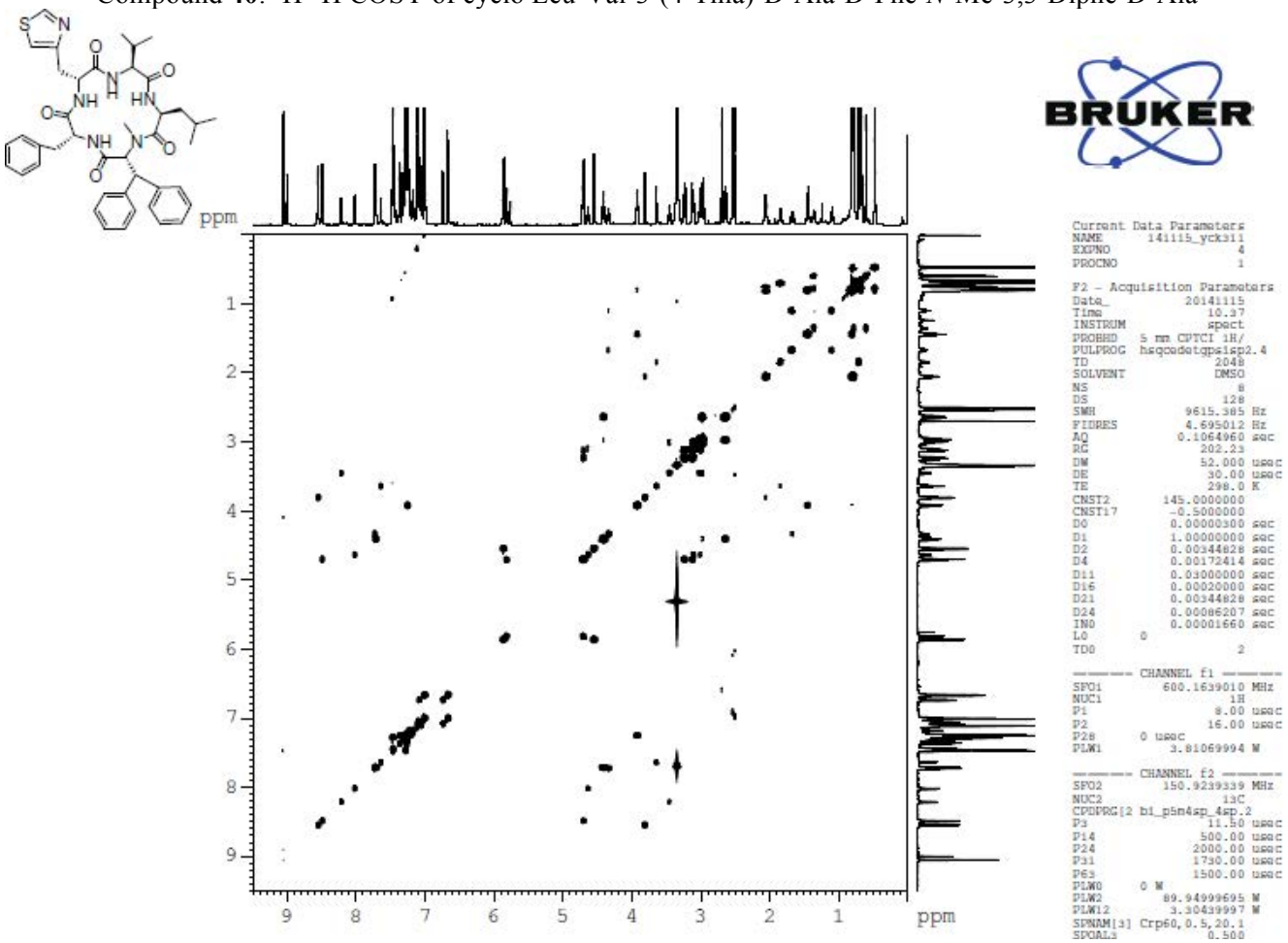
Compound **40**: ^{1}H-^{13}C HSQC of cyclo Leu-Val-3-(4-Thia)-D-Ala-D-Phe-*N*-Me-3,3-Diphe-D-Ala



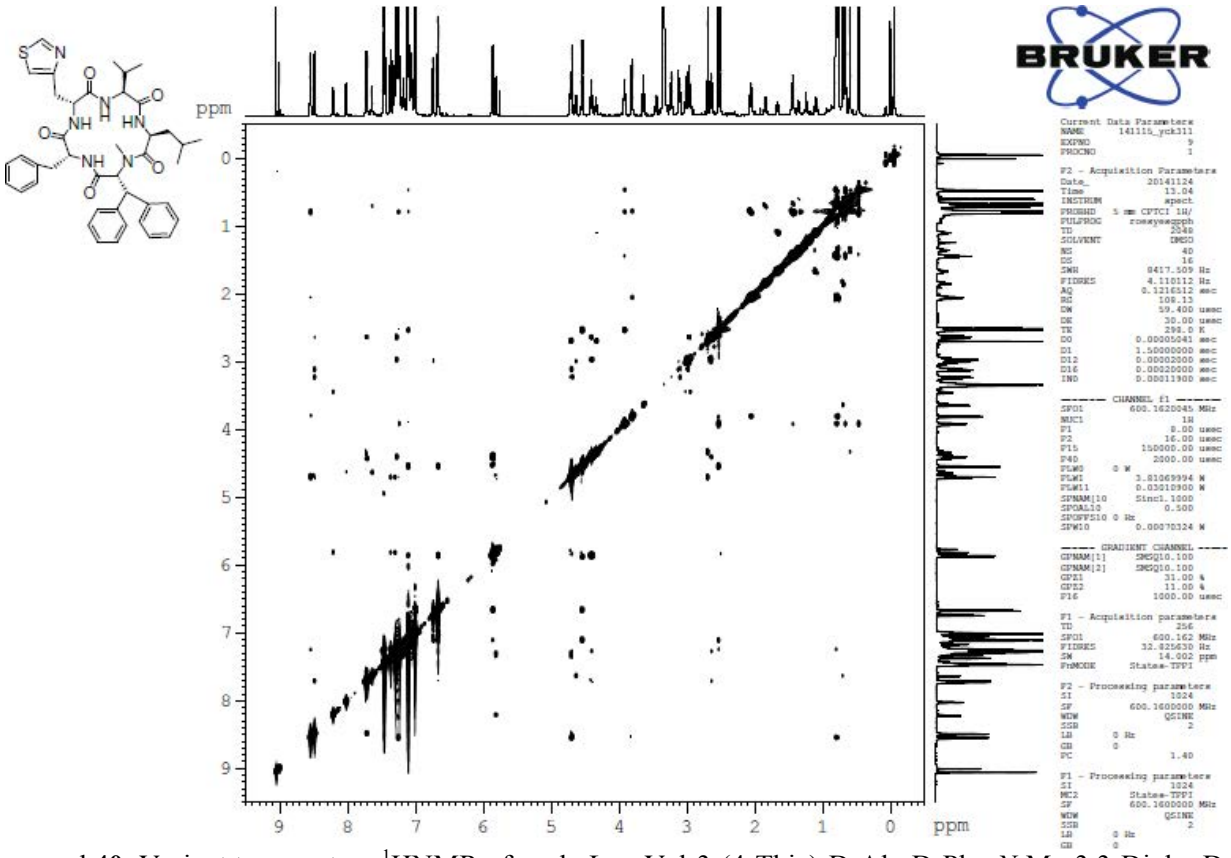
Compound **40**: ^{1}H-^{13}C HMBC of cyclo Leu-Val-3-(4-Thia)-D-Ala-D-Phe-*N*-Me-3,3-Diphe-D-Ala



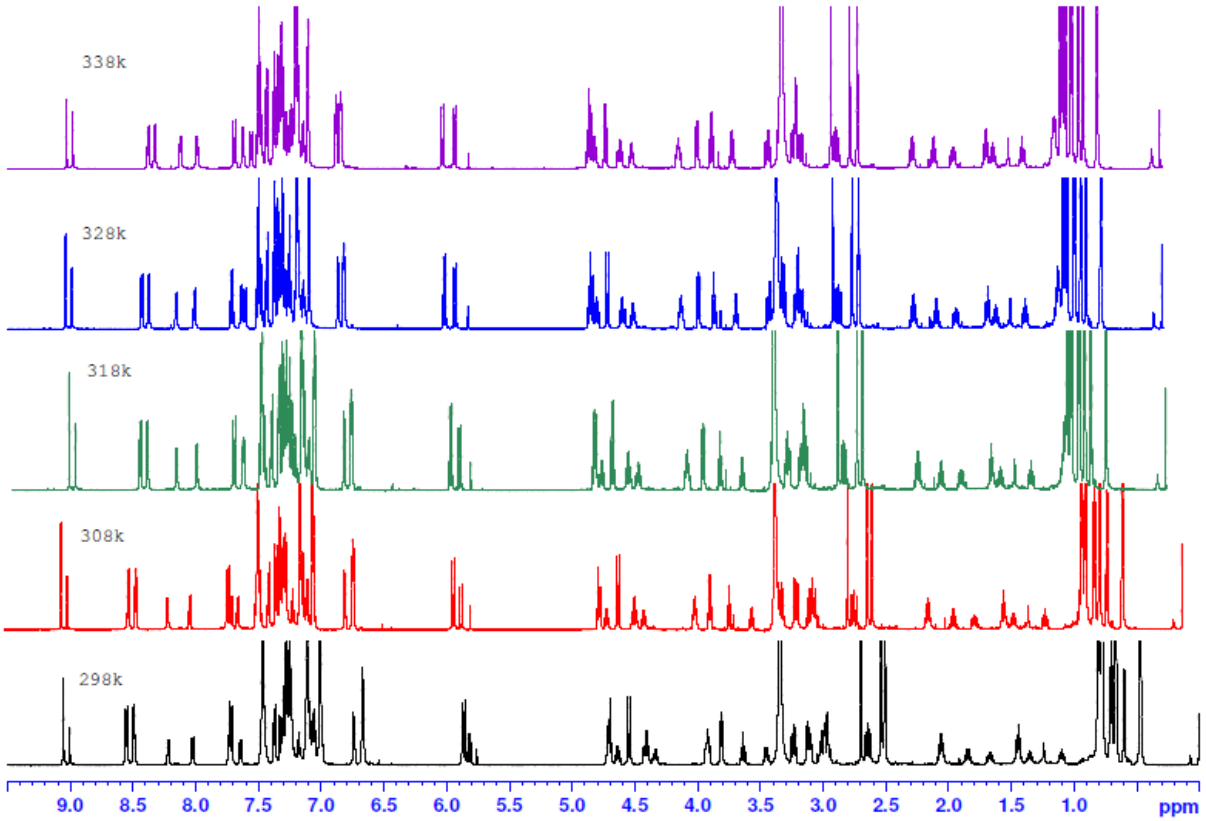
Compound **40**: ^{1}H-^{1}H COSY of cyclo Leu-Val-3-(4-Thia)-D-Ala-D-Phe-*N*-Me-3,3-Diphe-D-Ala



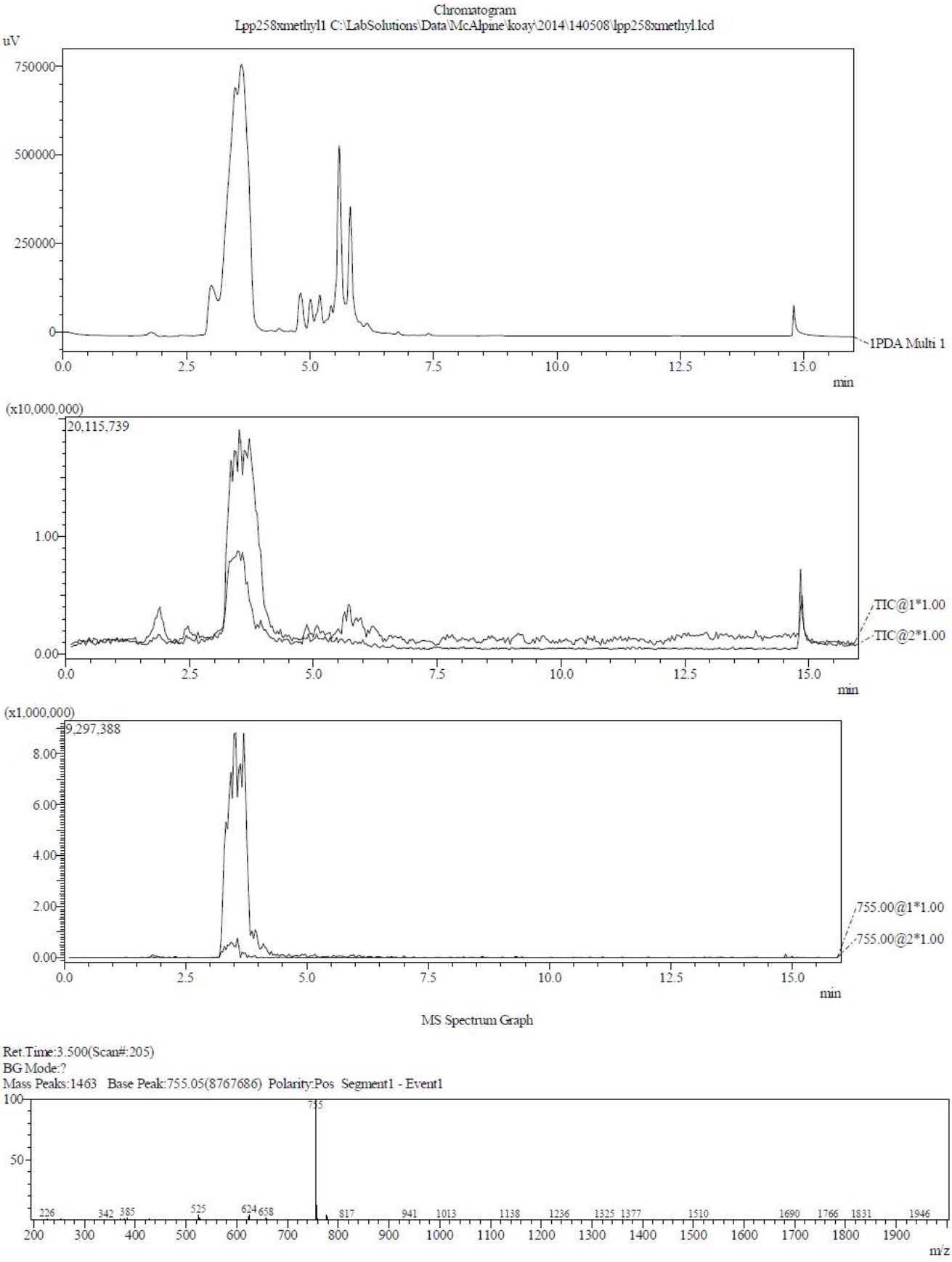
Compound **40**: ^{1}H-^{1}H ROESY of cyclo Leu-Val-3-(4-Thia)-D-Ala-D-Phe-*N*-Me-3,3-Diphe-D-Ala



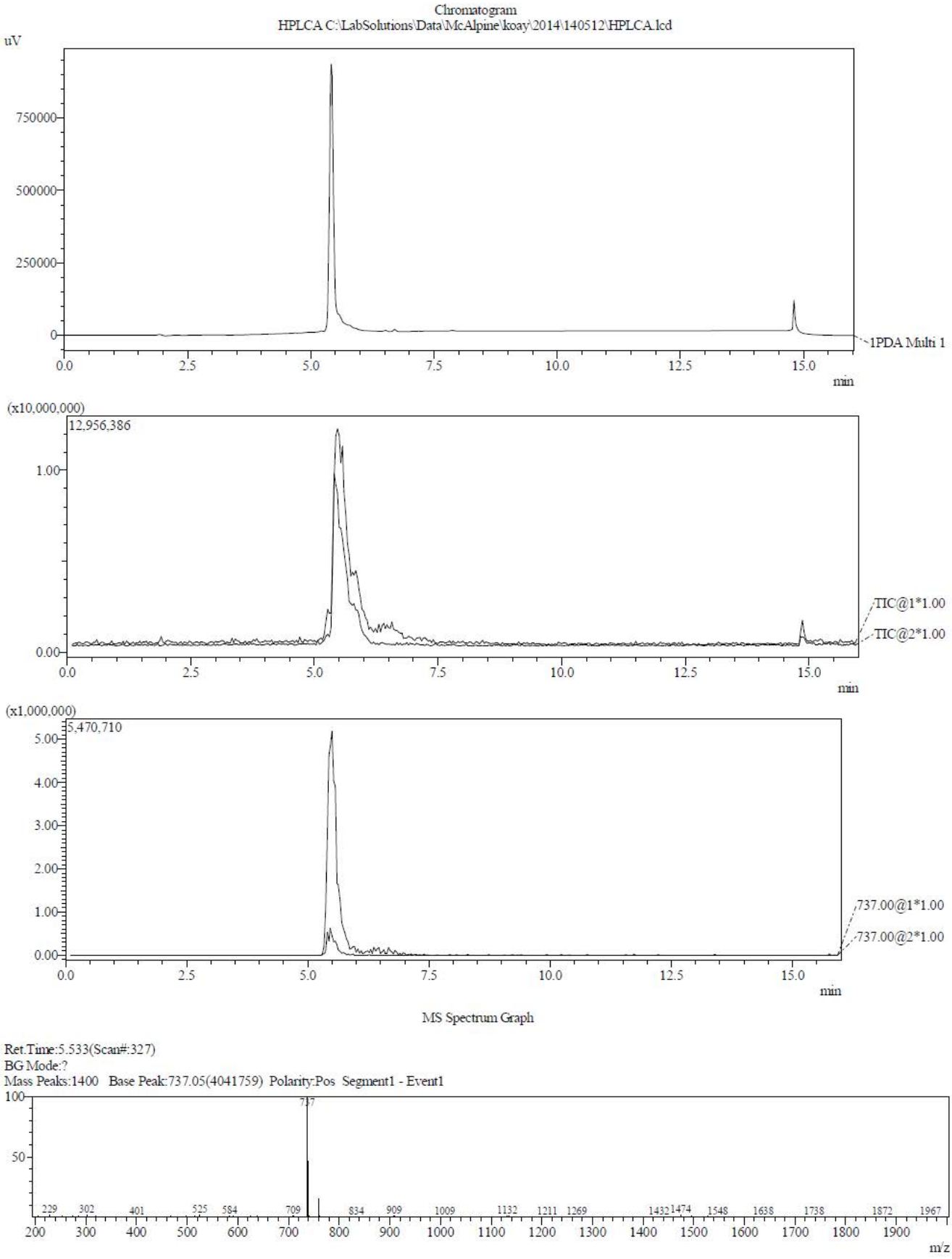
Compound **40**: Variant temperature ^{1}HNMR of cyclo Leu-Val-3-(4-Thia)-D-Ala-D-Phe-*N*-Me-3,3-Diphe-D-Ala



Compound **41**: LCMS of DDLP HO-Leu-Val-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala-NH_2



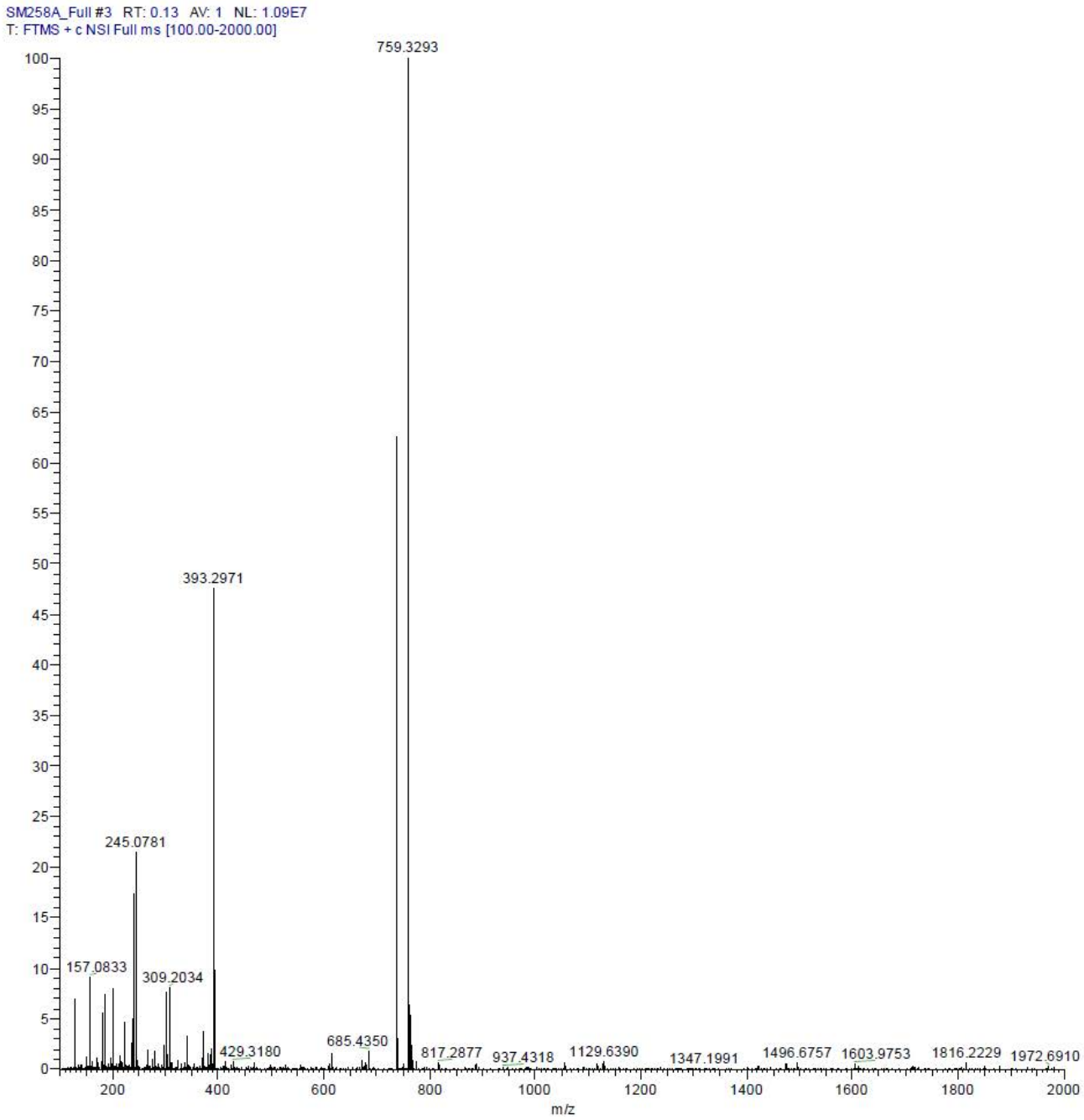
Compound **41**: LCMS of cyclo Leu-Val-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala



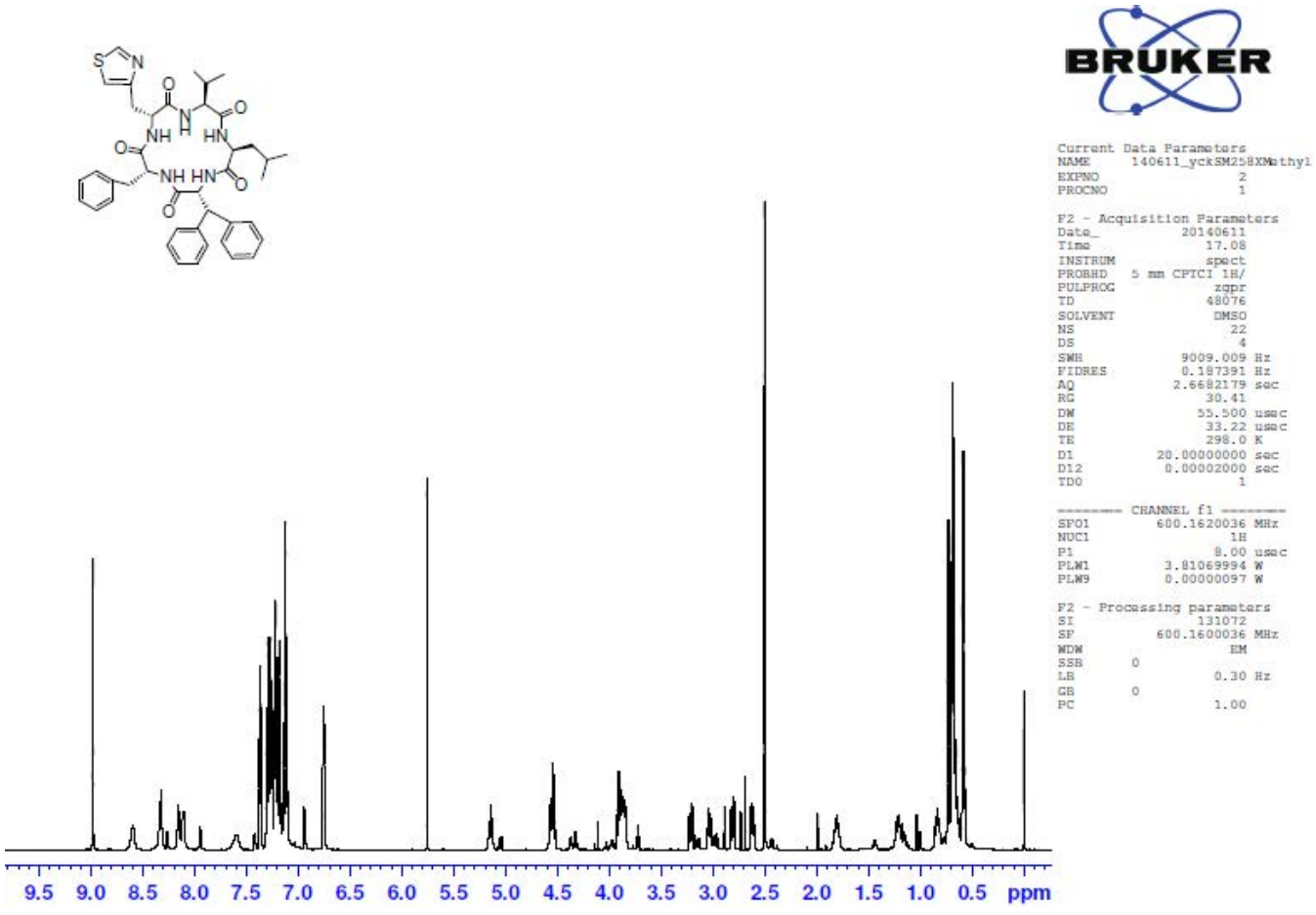
Compound **41**: HRMS of cyclo Leu-Val-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala

MS Data from Orbitrap

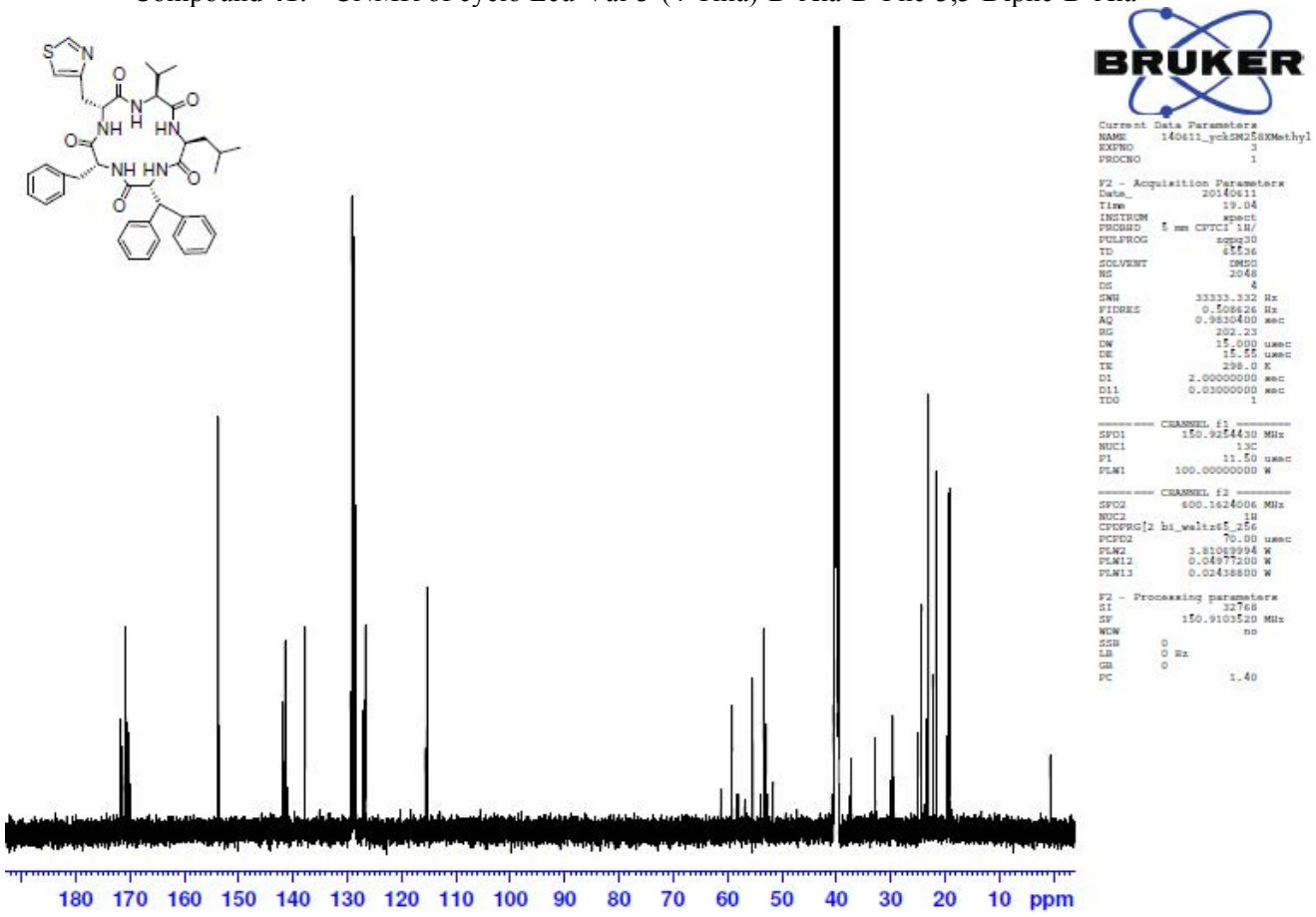
Full spectrum



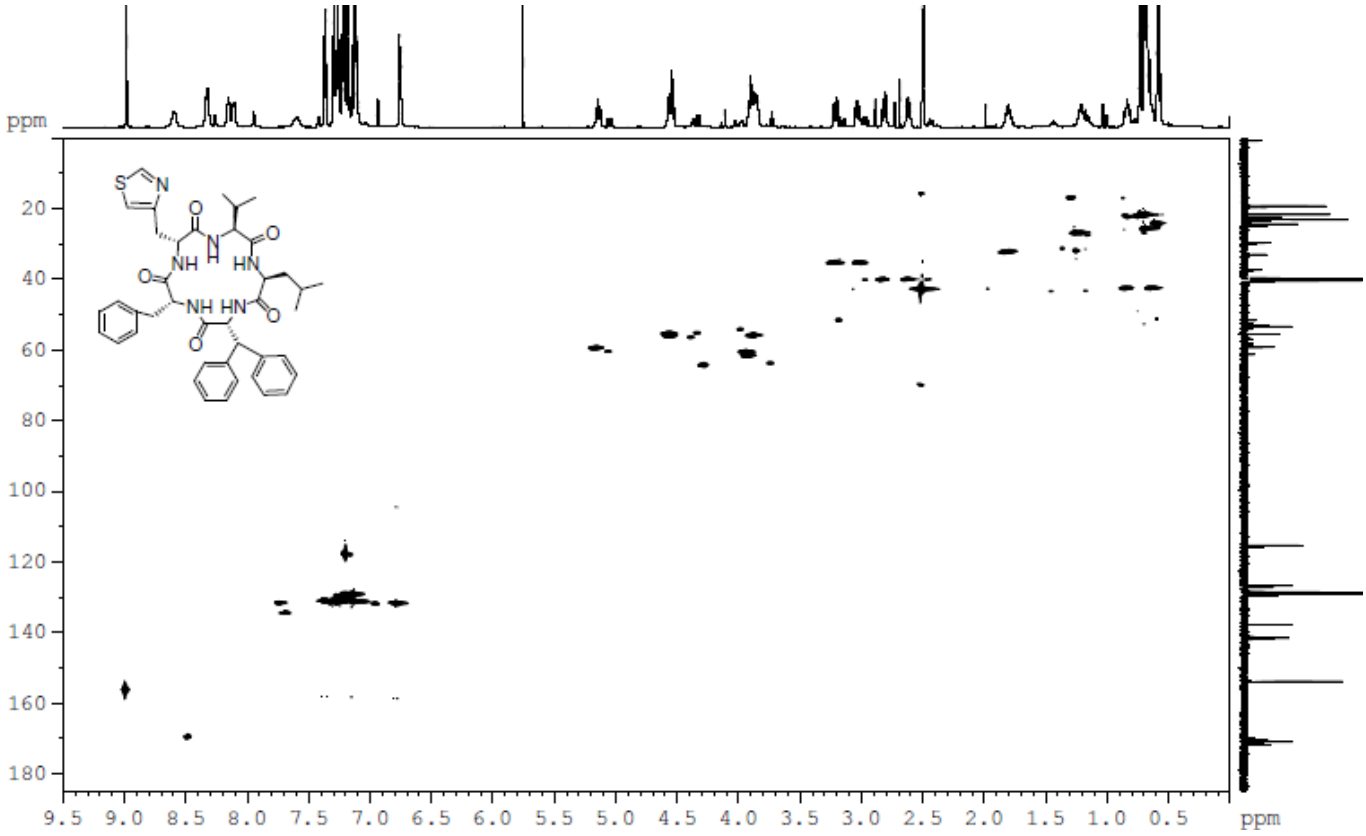
Compound **41**: ^{1}HNMR of cyclo Leu-Val-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala



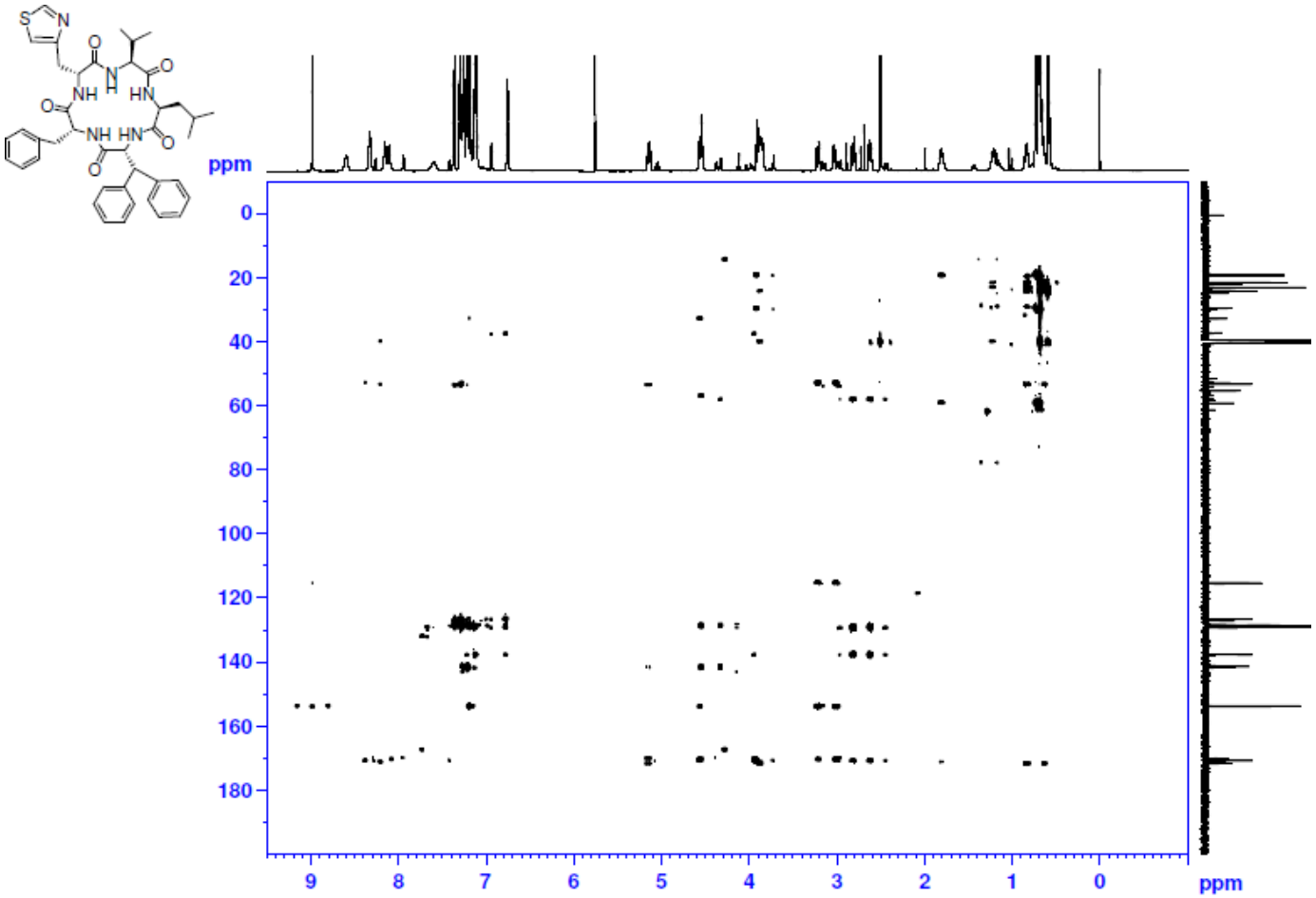
Compound **41**: ^{13}CNMR of cyclo Leu-Val-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala



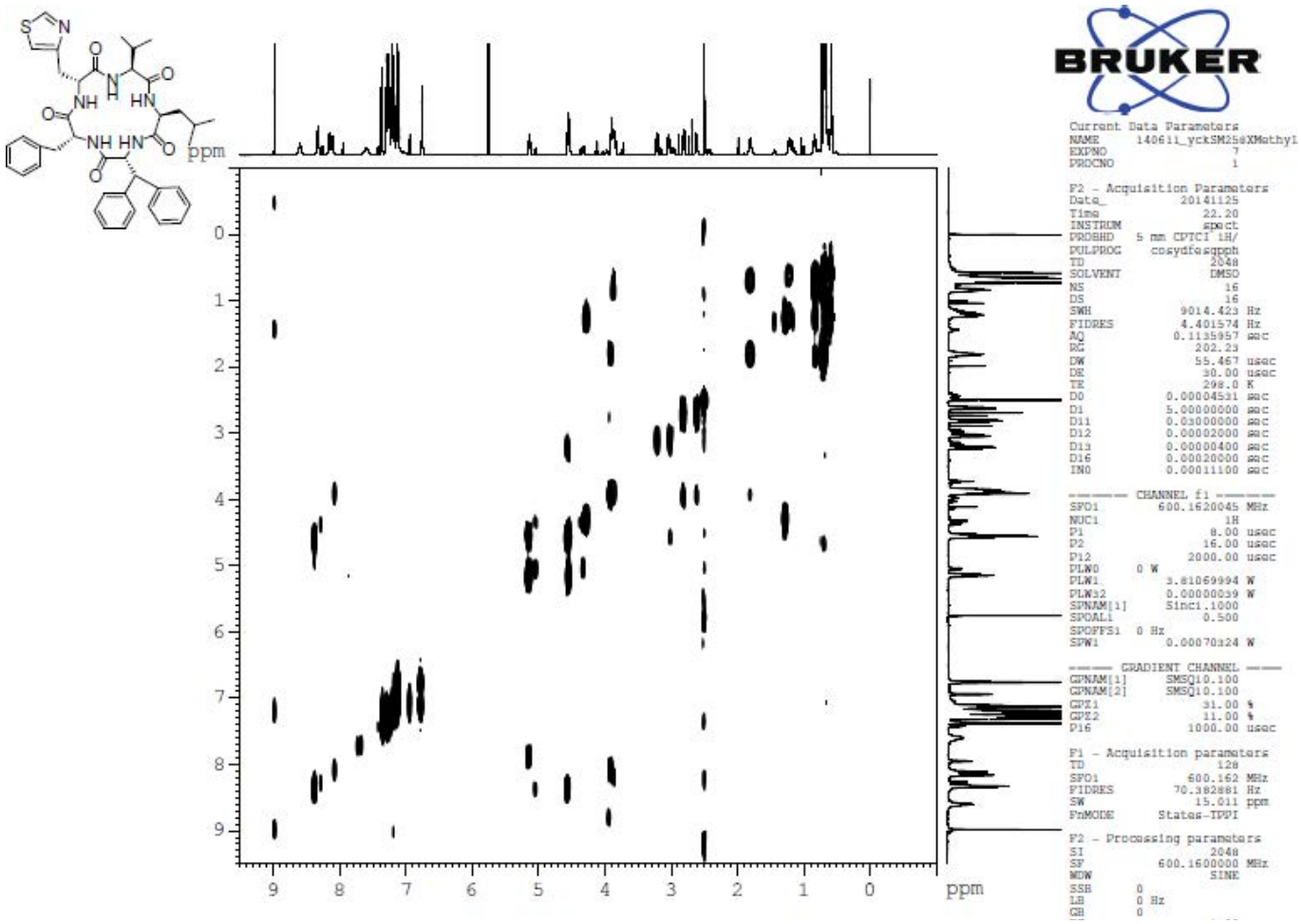
Compound **41**: ^{1}H-^{13}C HSQC of cyclo Leu-Val-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala



Compound **41**: ^{1}H-^{13}C HMBC of cyclo Leu-Val-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala

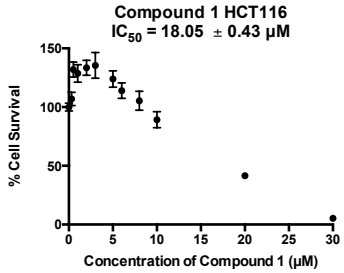


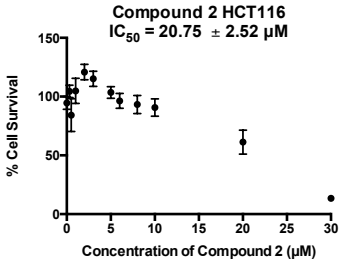
Compound **41**: ^{1}H-^{1}H COSY of cyclo Leu-Val-3-(4-Thia)-D-Ala-D-Phe-3,3-Diphe-D-Ala

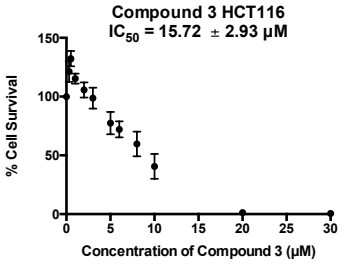


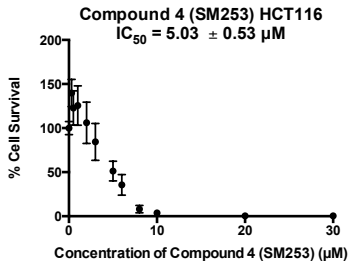
Biology: Results

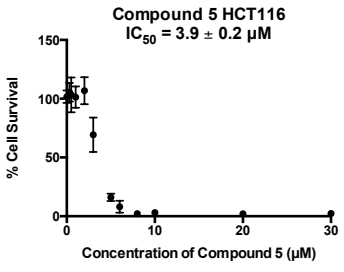
Cytotoxicity

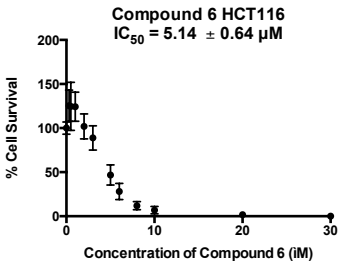

Compound 1 HCT116
IC50 = 18.05 ± 0.43 µM
% Cell Survival
Concentration of Compound 1 (µM)

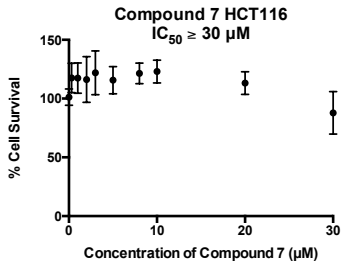

Compound 2 HCT116
IC50 = 20.75 ± 2.52 µM
% Cell Survival
Concentration of Compound 2 (µM)

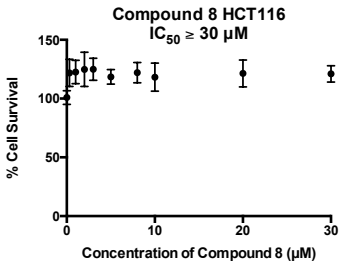

Compound 3 HCT116
IC50 = 15.72 ± 2.93 µM
% Cell Survival
Concentration of Compound 3 (µM)

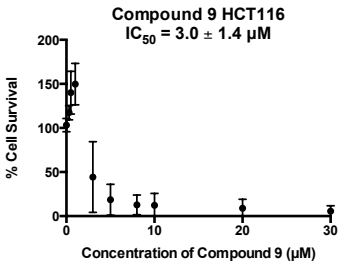

Compound 4 (SM253) HCT116
IC50 = 5.03 ± 0.53 µM
% Cell Survival
Concentration of Compound 4 (SM253) (µM)

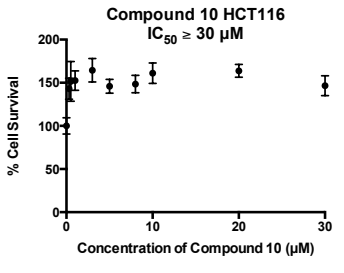

Compound 5 HCT116
IC50 = 3.9 ± 0.2 µM
% Cell Survival
Concentration of Compound 5 (µM)

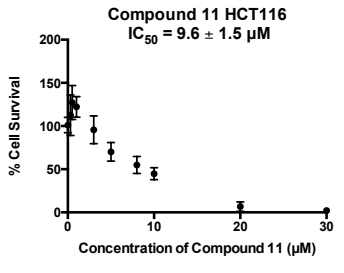

Compound 6 HCT116
IC50 = 5.14 ± 0.64 µM
% Cell Survival
Concentration of Compound 6 (iM)

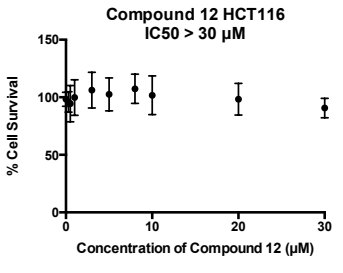

Compound 7 HCT116
IC50 ≥ 30 µM
% Cell Survival
Concentration of Compound 7 (µM)

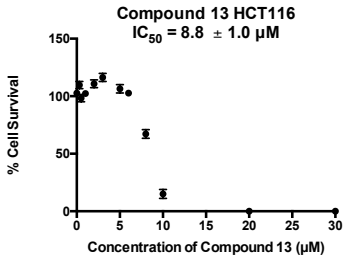

Compound 8 HCT116
IC50 ≥ 30 µM
% Cell Survival
Concentration of Compound 8 (µM)

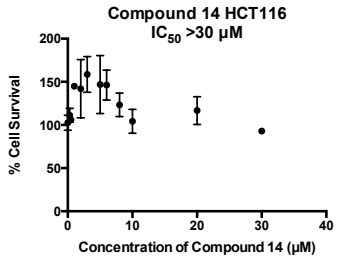

Compound 9 HCT116
IC50 = 3.0 ± 1.4 µM
% Cell Survival
Concentration of Compound 9 (µM)

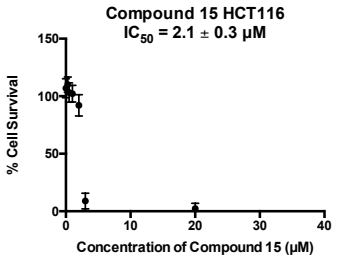

Compound 10 HCT116
IC50 ≥ 30 µM
% Cell Survival
Concentration of Compound 10 (µM)

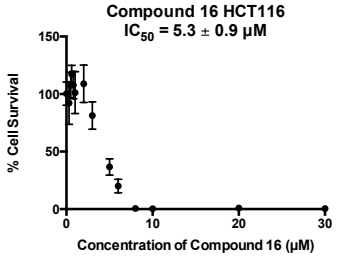

Compound 11 HCT116
IC50 = 9.6 ± 1.5 µM
% Cell Survival
Concentration of Compound 11 (µM)

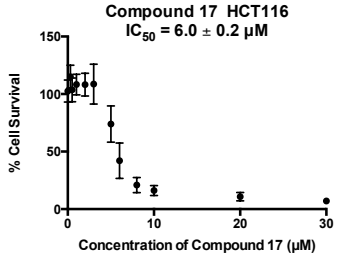

Compound 12 HCT116
IC50 > 30 µM
% Cell Survival
Concentration of Compound 12 (µM)

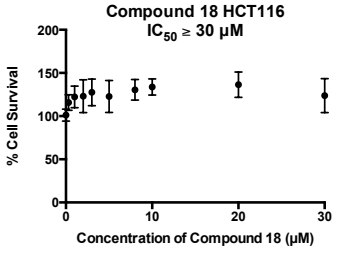

Compound 13 HCT116
IC50 = 8.8 ± 1.0 µM
% Cell Survival
Concentration of Compound 13 (µM)

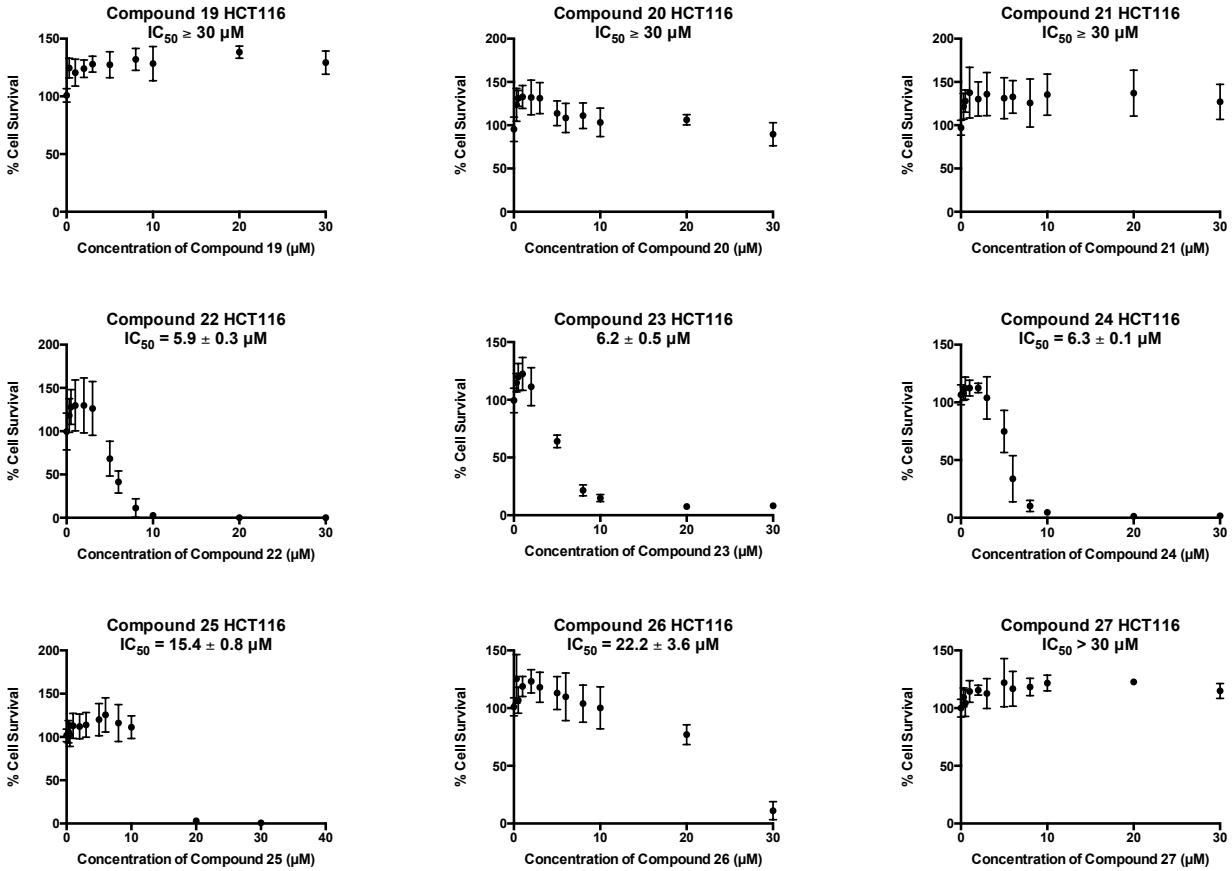

Compound 14 HCT116
IC50 >30 µM
% Cell Survival
Concentration of Compound 14 (µM)


Compound 15 HCT116
IC50 = 2.1 ± 0.3 µM
% Cell Survival
Concentration of Compound 15 (µM)

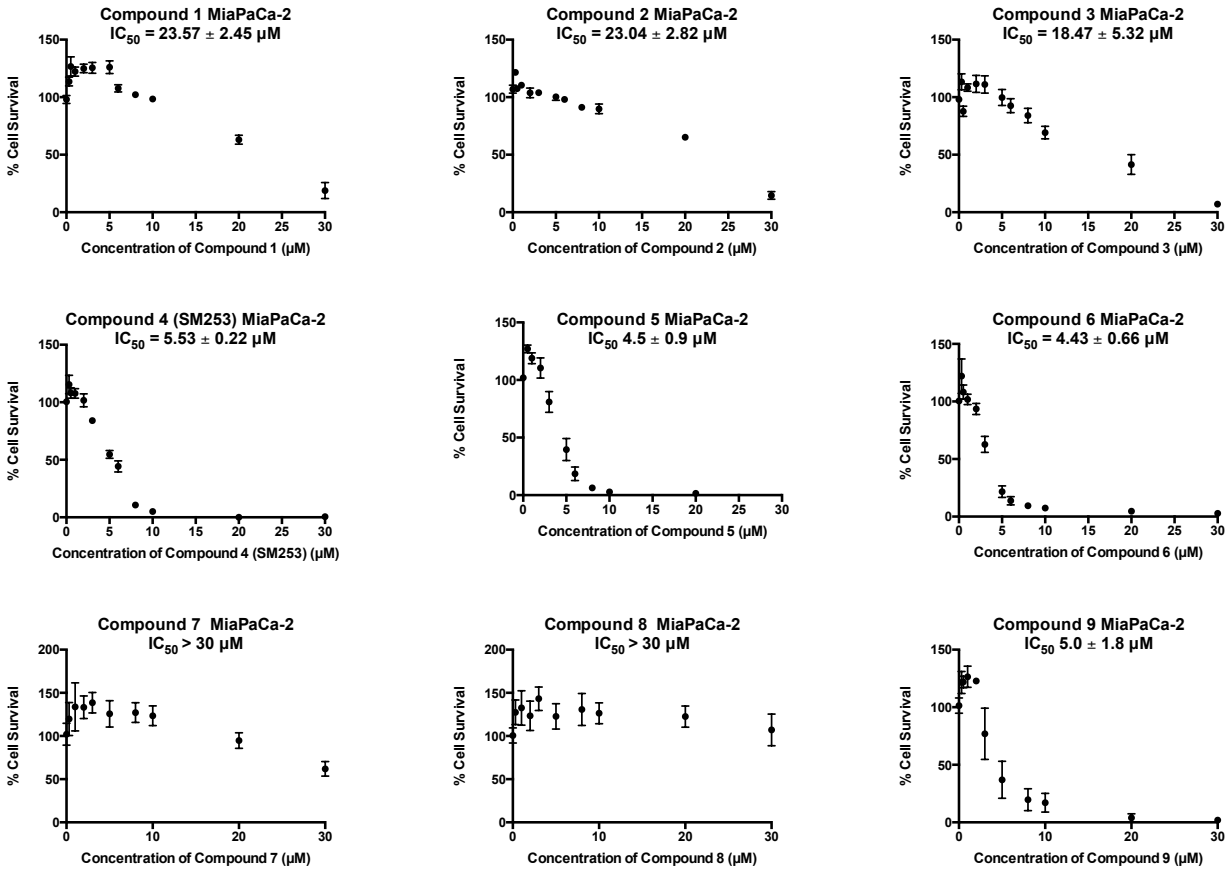

Compound 16 HCT116
IC50 = 5.3 ± 0.9 µM
% Cell Survival
Concentration of Compound 16 (µM)

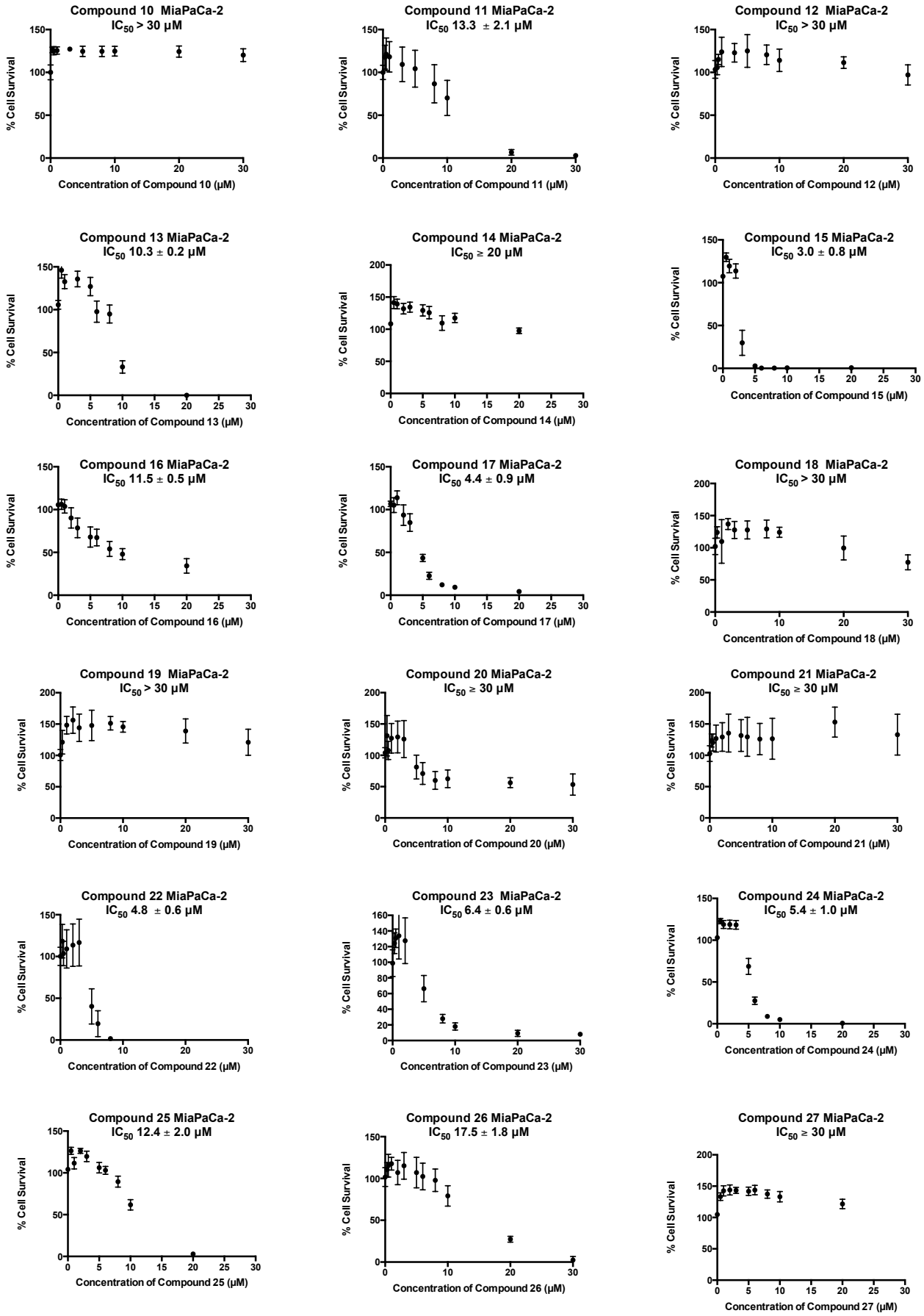

Compound 17 HCT116
IC50 = 6.0 ± 0.2 µM
% Cell Survival
Concentration of Compound 17 (µM)


Compound 18 HCT116
IC50 ≥ 30 µM
% Cell Survival
Concentration of Compound 18 (µM)

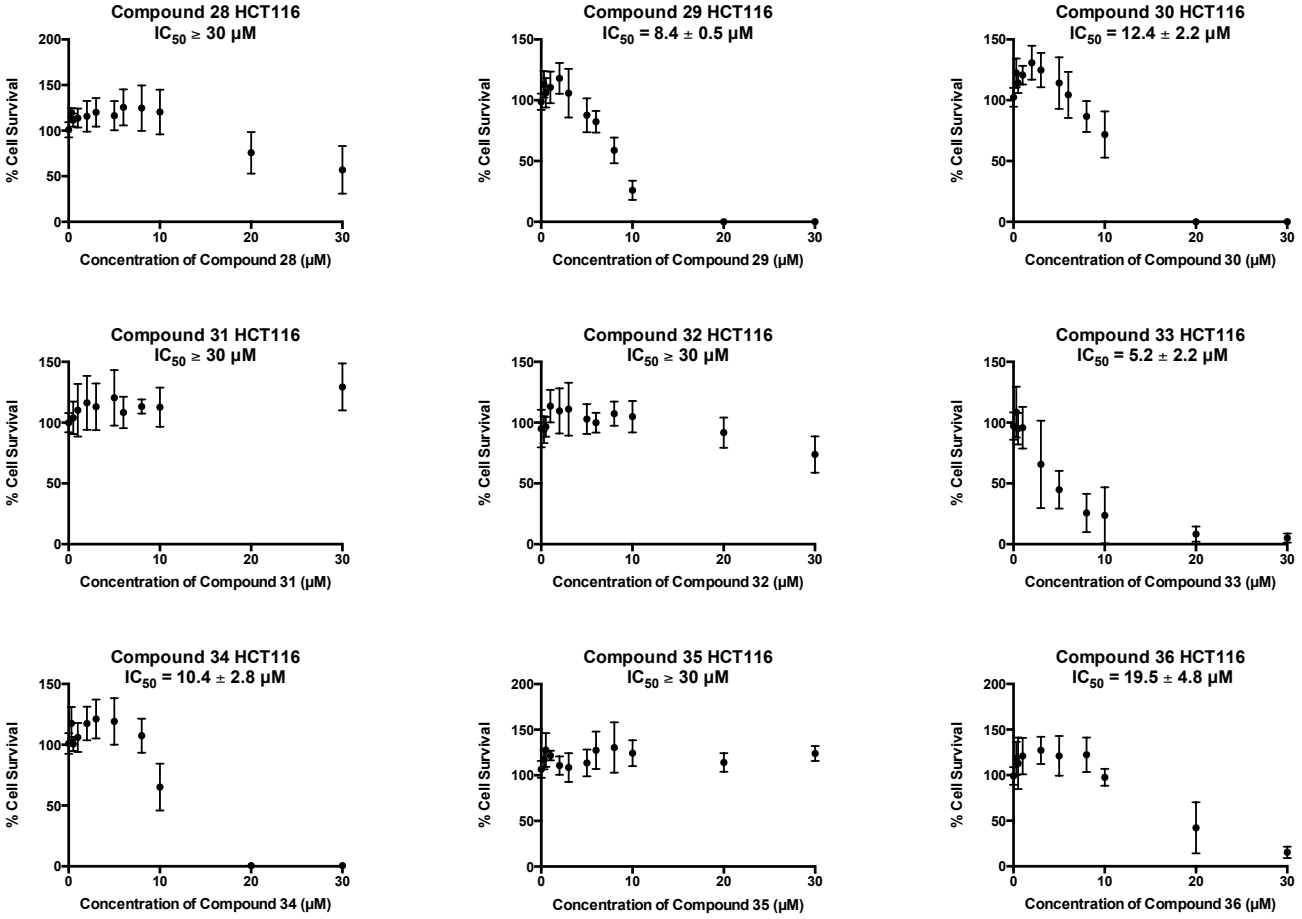


Supplemental Figure S1: Series I-IV (GI_{50}) IC_{50} results HCT-116

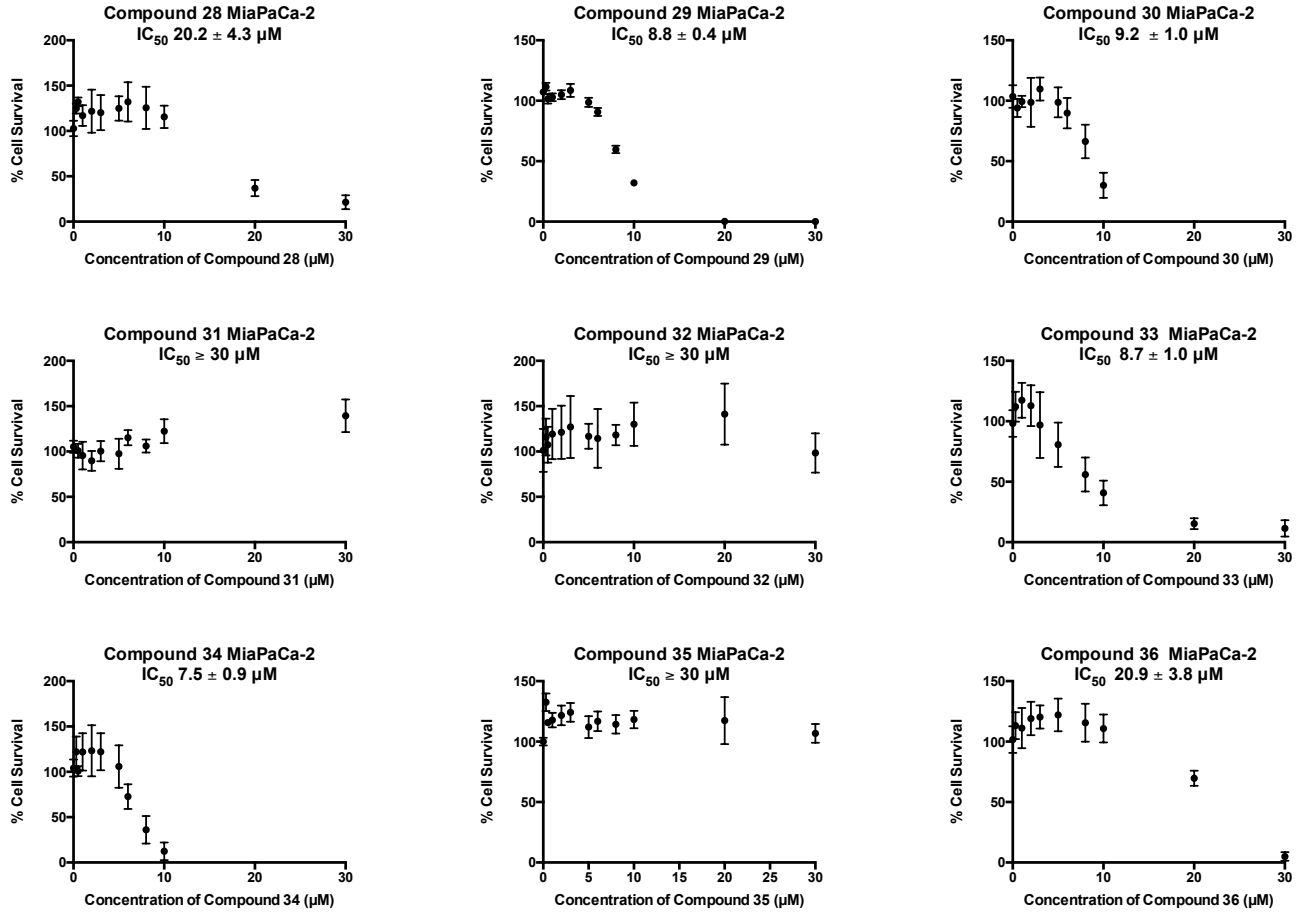




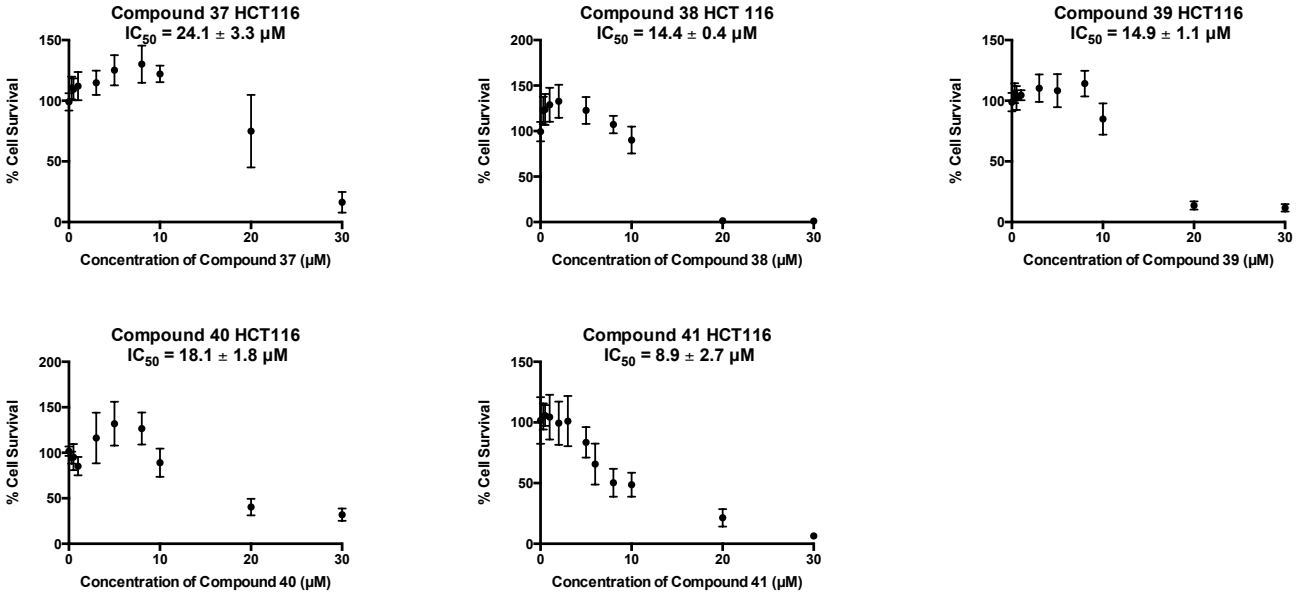
Supplemental Figure S2: Series I-IV (GI_{50}) IC_{50} results MiaPaCa-2



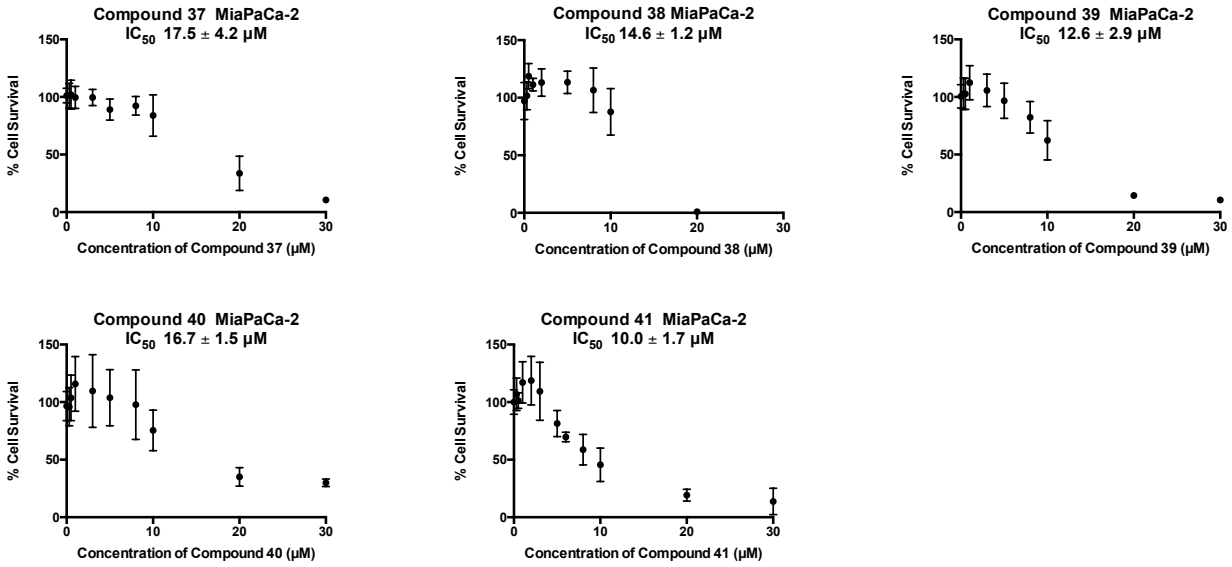
Supplemental Figure S3: Series V-VII (GI_{50}) IC_{50} results HCT-116



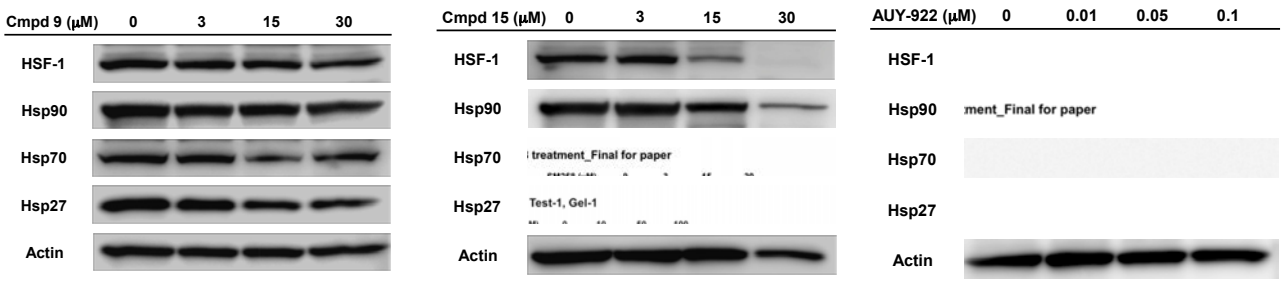
Supplemental Figure S4: Series V-VII (GI_{50}) IC_{50} results MiaPaCa-2



Supplemental Figure S5: N-methyl analogues (GI_{50}) IC_{50} results HCT-116



Supplemental Figure S6: N-methyl analogues (GI_{50}) IC_{50} results MiaPaCa-2



Supplemental Figure S7: Representative western blots of protein levels after treatment with Compound **9, 15**, and **AUY922.**