Electronic Supplementary Material (ESI) for ChemComm.

On-resin synthesis of cyclic peptides *via* tandem N-to S- acyl migration and intramolecular thiol additive-free native chemical ligation

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Supporting information

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General experimental information

All reactions were carried out under nitrogen atmosphere with dry, freshly distilled solvents, under anhydrous conditions, unless otherwise stated. All solvents were purified following procedures described in literature. [1]

All yields refer to chromatographically and spectroscopically (^{1}H-NMR and ^{13}C-NMR) pure products.

NMR spectra were recorded with a Bruker Advance NEO-400, Bruker Avance III 500 MHz or Bruker Avance III 400 MHz equipment. All chemical shifts were related to TMS as internal reference.

All solid phase reactions were monitored by colorimetric test (Kaiser or Chloranil). Amino poliethylenglycol resin (Amino-PEGA, 50-100 mesh, 0.3-0.4 mmol/g) was acquired from NOVABIOCHEM.

HPLC analyses were carried out in a HITACHI LaChrom Elite HPLC with L-2130 pumps and UV L-248 detector. Cosmosil C18 (4.6x150mm, 5µm) column and H_2O: CH_3CN with 0.1 % TFA were used. Final products were purified by preparative HPLC Waters 2487 equipped with Waters 600 pump controller and double λ UV detector, using gradient of H_2O: CH_3CN with 0.1 % TFA as mobile phase and COSMOSIL 5C18-AR-II Packed Column, 4.6 mm I.D. x 150 mm column. Peptides were detected at 220 nm. All mass spectra were acquired with Thermo LC-Q DECA XP Plus LC-MS with electrospray ionization and triple quadrupole linear ion trap mass detector.

2. General synthetic procedure

2.1. Resin loading

620 mg of Amino-PEGA resin (0.4 mmol/g) were added to a syringe peptide synthesis vessel. The resin was treated with NMP three times for one minute each time and CH_2Cl_2 (2 x 0.5 min).

A solution of Fmoc-AA-NEt-Cys(Trt) (2 eq.), OxymaPure® (2.2 eq.) and DIC (2.2 eq.) in dichloroethylene was added and the resin was shaken overnight. Reaction completion was

[1] Perrin, D. D. ; Armarego, W. L. F. "Purification of Laboratory Chemicals", 3th Ed. Pergamon Press, Oxford, 1988.

monitored by Kaiser test. When a negative Kaiser test is obtained the resin is filtered and washed with NMP (0.5 min x 3).

Finally, unreacted sites are capped by treatment with a solution of Ac_2O (300 µL), DIPEA (150 µL) in NMP (2.5 mL) for 15 minutes. After filtering, resin was washed with NMP (5x 0.5min).

2.2. Removal of NHFmoc group

The resin was treated with NMP (3x0.5) and then piperidine solution 20% in NMP and shaken (first for two minutes and then twice for one minute). After filtering the resin was washed with NMP (7 x 0.5min).

2.3 Coupling of subsequent N-Fmoc protected amino acids

A solution of the amino acid Fmoc-AA-OH (4 eq.), HBTU (3.8 eq.) and DIPEA (8eq.) or Fmoc-NMeAA-OH (4eq.), HATU (3.8 eq.) and DIPEA (8eq.) in DMF was added to the peptide synthesis vessel and shaken for 12 minutes. Resin was filtered, washed with NMP (5x 0.5min) and Kaiser or Chloranil test was performed. If the test is negative iterative cycles of Fmoc deprotection and coupling were carried on.

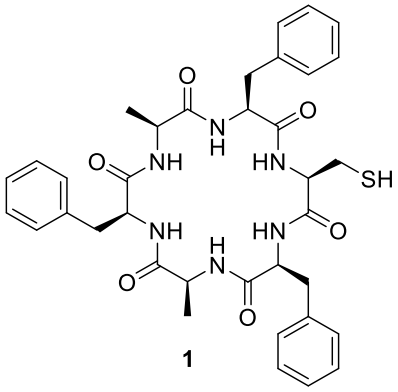
For coupling the last amino acid of every sequence (Fmoc-Cys(Trt)-OH), 4 eq of it were dissolved in DMF: CH_2Cl_2 (50:50) along with OxymaPure® (4eq.) and DIC (4eq.). The solution was added to the resin and shaken for one hour. The resin was washed with NMP and Kaiser or chloranil test was performed. In case of negative result, the resin was further washed with NMP 5 times and the last NHFmoc deprotected. Finally, the resin was washed with NMP (6x 0.5 min), CH_2Cl_2 (5x0.5min).

2.4. Cleavage and cyclization by Native Chemical Ligation (NCL)

Removal of trityl group was achieved by resin treatment with a solution of TIS (0.12 mL), TFA (2.0 mL) and CH_2Cl_2 (2.0 mL) and shaken for 10 minutes. After quick filtering, the resin was washed 4 times with MeOH.

A solution of 0.9 g of urea, 0.5 mL of CH_3CN and 125 µL of acetic acid in 2 mL distilled water was added to the resin and gently shaken at 37ºC for 14 hours. The filtrate was collected and analyzed by analytical HPLC. The main peak was further analyzed by LC-MS for identification of the desired product. The same gradient was used for purifying the crude by preparative HPLC. The product was collected into polypropylene tubes and lyophilized.

3. Characterization Data of Products

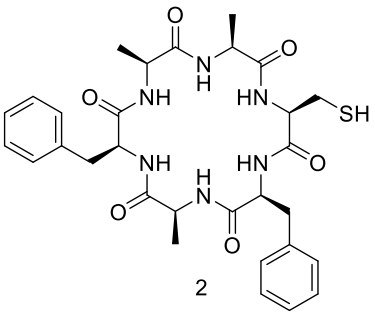


1

Compound **1** was obtained following general synthetic procedure, as a white solid, with 50% yield (8.5 mg, 0.012 mmol) based on the resin employed.

After cyclization reaction, crude mixture was analyzed by HPLC. A binary solvent gradient was applied by linearly increasing a ratio of eluent B (0.1 % TFA in acetonitrile) from 30 to 50 % in 20 min against eluent A (0.1 % TFA in H2O) at a flow rate of 1.0 mL/min after sample injection. Compound 1, identified by ESI-MS eluted within 19.5 minutes. Pure product was access by preparative HPLC and lyophilized.

***Cyclo*-[Cys-Phe-Ala-Phe-Ala-Phe] (1):** White solid (Y=50%). **^{1}H NMR (400 MHz, $CDCl_3$)** 1.09-1.19 (m, 1H), 1.21-1.34 (m, 6H), 2.66-2.79 (m, 1H), 2.96- 3.19 (m, 5H), 3.24 (d, *J*= 7.1 Hz, 2H), 3.78-3.96 (m, 1H), 3.98-4.11 (m, 1H), 4.13-4.28 (m, 1H), 4.31-4.50 (m, 3H), 6.98-7.06 (m, 1H), 7.06-7.13 (m, 1H), 7.14-7.25 (m, 9H), 7.27-7.38 (m, 7H), 7.40-7.49 (m, 1H), 7.50-7.56 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 16.0, 16.4, 25.6, 35.7, 36.2, 36.8, 50.1, 51.4, 55.5, 55.7, 56.2, 56.8, 127.2, 127.3(2C), 128.8 (4C), 128.9 (2C), 129.1 (2C), 129.2(2C), 129.3 (2C), 136.3, 136.4 136.6, 170.6, 171.3 171.7, 171.9, 172.8, 173.2. **ESI-MS** *m/z* calc. for $C_{36}H_{43}N_6O_6S_2$ ($[M+H]^+$) 687.3, found 687.3.

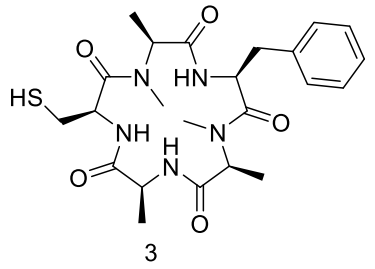


2

Compound **2** was obtained following general synthetic procedure, as a white solid, with 40% yield (6.0 mg, 0.010 mmol) based on the resin employed.

After cyclization reaction, crude mixture was analyzed by HPLC using the same gradient as for compound **1**. Compound **2,** identified by ESI-MS, eluted within 12.0 minutes. Pure product was access by preparative HPLC and lyophilized.

***Cyclo*-[Cys-Phe-Ala-Phe-Ala-Ala] (2):** White solid (Y= 40%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.90-0.98 (m, 1H), 1.36 (d, *J*=7.1 Hz, 3H), 1.42 (d, *J*=6.9 Hz, 3H), 1.57 (d, *J*=7.1 Hz, 3H), 2.65-2.72 (m, 1H), 3.08-3.26 (m, 5H), 3.81-3.89 (m, 1H), 3.96-4.04 (m, 1H), 4.30-4.38 (m, 1H), 4.42-4.50 (m, 2H), 4.50-4.59 (m, 1H), 7.04-7.11 (m, 1H), 7.19-7.27 (m, 8H), 7.29-7.37 (m, 4H), 7.40 (d, *J*=6.8 Hz, 1H), 7.51-7.58 (m, 1H), 7.66 (d, *J*=7.6 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 15.7, 15.8, 16.6, 25.8, 36.1, 36.7, 49.5, 51.3, 51.9, 55.2, 55.3, 55.6, 127.0, 127.4, 128.8 (2C), 128.9 (2C), 129.2(2C), 129.3 (2C), 136.1, 136.8, 170.3, 171.6, 172.1, 172.5, 172.8, 173.2. **ESI-MS** *m/z* calc. for $C_{30}H_{39}N_6O_6S$ ($[M+H]^+$) 611.3, found 611.3.

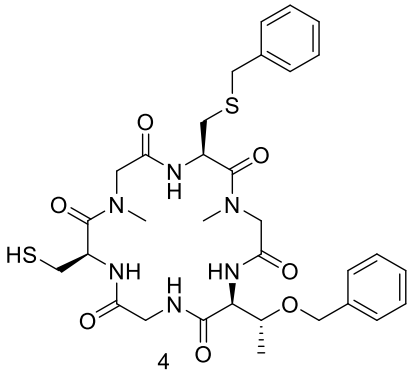


3

Compound **3** was obtained following general synthetic procedure, as a white solid, with 46% yield (5.5 mg, 0.011 mmol) based on the resin employed.

After cyclization reaction, crude mixture was analyzed by HPLC using the same gradient as for compound **1**. Compound **3,** identified by ESI-MS, eluted within 9.9 minutes. Pure product was access by preparative HPLC and lyophilized.

Cyclo-[Cys-NMeAla-Phe-NMeAla-Ala] (3): White solid (Y= 46%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (d, *J*=7.0 Hz, 3H), 1.51 (d, *J*=7.4 Hz, 3H), 1.64-1.71 (m, 1H), 1.84 (d, *J*=7.5Hz, 3H), 2.57-2.66 (m, 1H), 2.74 (s, 3H), 2.88-2.97 (m, 1H), 2.99 (s, 3H), 3.01-3.17 (q, *J*=7.5 Hz, 1H), 4.25-4.36 (m, 1H), 4.85-4.92 (m, 1H), 4.95-5.02 (m, 1H), 5.87 (d, *J*=6.7 Hz, 1H), 7.19-7.26 (m, 2H), 7.30-7.35 (m, 3H), 7.79 (d, *J*=8.6 Hz, 1H), 8.35 (d, *J*=9.6 Hz, 1H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8, 16.2, 18.0, 25.7, 38.1, 38.7, 39.2,50.4, 50.7, 53.6, 61.6, 67.3, 127.3, 128.6 (2C), 129.5 (2C), 135.9, 170.1, 171.0, 171.6, 172.4, 172.9. ESI-MS *m/z* calc. for $C_{23}H_{34}N_5O_5S$ ($[M+H]^+$) 492.2, found 492.3.

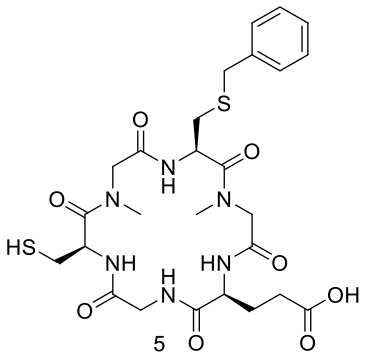


4

Compound **4** was obtained following general synthetic procedure, as a white solid, with 23% yield (4.7 mg, 0.007 mmol) based on the resin employed.

After cyclization reaction, crude mixture was analyzed by HPLC. A binary solvent gradient was applied by linearly increasing a ratio of eluent B (0.1 % TFA in acetonitrile) from 35 to 55 % in 20 min against eluent A (0.1 % TFA in H2O) at a flow rate of 1.0 mL/min after sample injection. Compound **4,** identified by ESI-MS, eluted within 17.5 minutes. Pure product was access by preparative HPLC and lyophilized.

Cyclo-[Cys-NMe-Gly-Cys(Bn)-NMe-Gly-Thr(Bn)-Gly] (4): White solid (Y=23 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, *J*=6.4 Hz, 3H), 1.66 (t, *J*=8.9 Hz, 1H), 2.63 (dd, *J*= 13.6, 5.1 Hz, 1H), 2.68-2.81 (m, 1H), 2.91-3.03 (m, 2H), 3.05 (s, 3H), 3.16 (s, 3H), 3.20 (d, *J*=16.2 Hz, 1H), 3.42 (d, *J* = 14.4 Hz, 1H), 3.63 (dd, *J* = 14.8, 4.4 Hz, 1H), 3.70 (s, 2H), 4.19-4.28 (m, 3H), 4.30 – 4.39 (m, 2H), 4.44 (d, *J* = 11.5 Hz, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 5.00-5.11 (m, 2H), 6.74 (d, *J* = 8.3 Hz, 1H), 7.17 – 7.06 (m, 2H), 7.23-7.25 (m, 2H), 7.27–7.38 (m, 8H), 8.03 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 17.0, 26.0, 32.5, 36.5, 37.0, 38.7, 44.0, 48.3, 52.2, 53.9, 54.3, 58.3, 71.8, 73.3, 127.3, 127.9 (2C), 128.1, 128.5(2C), 128.7(2C), 129.0 (2C), 137.6, 138.2, 167.7, 169.5, 169.6, 171.4, 172.1, 184.0. ESI-MS *m/z* calc. for $C_{32}H_{43}N_6O_7S_2$ ($[M+H]^+$) 687.3, found 687.4.

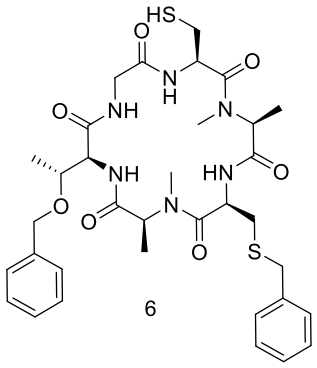


5

Compound **5** was obtained following general synthetic procedure, as a white solid, with 19% yield (3.9 mg, 0.006 mmol) based on the resin employed.

After cyclization reaction, crude mixture was analyzed by HPLC. A binary solvent gradient was applied by linearly increasing a ratio of eluent B (0.1 % TFA in acetonitrile) from 30 to 50 % in 20 min against eluent A (0.1 % TFA in H2O) at a flow rate of 1.0 mL/min after sample injection. Compound 5, identified by ESI-MS eluted within 13.6 minutes. Pure product was access by preparative HPLC and lyophilized.

***Cyclo*-[Cys-NMe-Gly-Cys(Bn)-NMe-Gly-Glu-Gly] (5):** White solid (19 %). **^{1}H NMR (400 MHz, MeOD)** δ 1.87-2.00 (m, 1H) , 2.19-2.34 (m, 1H), 2.37-2.50 (m, 2H), 2.67-2.81 (m, 2H), 2.82-2.94 (m, 2H), 2.97 (d, *J*=5.4 Hz, 1H), 3.15 (s, 3H), 3.25 (s, 3H), 3.46 (d, *J*=16.4 Hz, 1H), 3.55-3.77 (m, 2H), 3.80 (s, 2H), 4.20 (d, *J*=16.4 Hz, 1H), 4.25-4.41 (m, 2H), 4.47-4.68 (m, 1H), 4.73-4.81 (m, 1H), 4.93-5.14 (m, 1H), 7.19-7.45 (m, 5H). **^{13}C NMR (101 MHz, MeOD)** δ 24.4, 25.7, 30.0, 32.2, 36.4, 37.2, 41.5, 44.5, 49.5, 52.4, 53.0, 53.1, 53.2, 126.7, 128.1, 128.2, 128.8, 129.7, 138.7, 169.0, 170.3, 171.1(2C), 171.8, 174.9 175.1. **ESI-MS** *m/z* calc. for $C_{26}H_{37}N_6O_8S_2$ ($[M+H]^+$) 625.2, found 625.3.



6

Compound **6** was obtained following general synthetic procedure, as a white solid, with 18% yield (4.4 mg, 0.006 mmol) based on the resin employed.

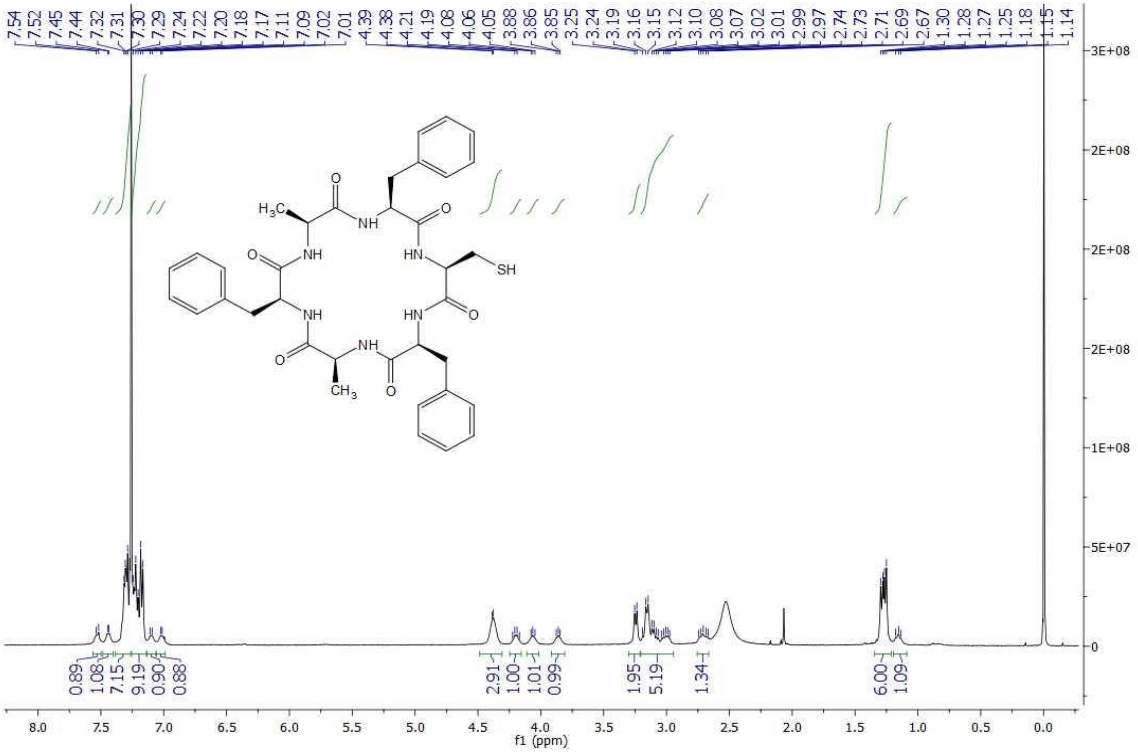
After cyclization reaction, crude mixture was analyzed by HPLC. A binary solvent gradient was applied by linearly increasing a ratio of eluent B (0.1 % TFA in acetonitrile) from 40 to 60% in 20 min against eluent A (0.1 % TFA in H2O) at a flow rate of 1.0 mL/min after sample injection. Compound 6, identified by ESI-MS eluted within 17.5 minutes. Pure product was access by preparative HPLC and lyophilized.

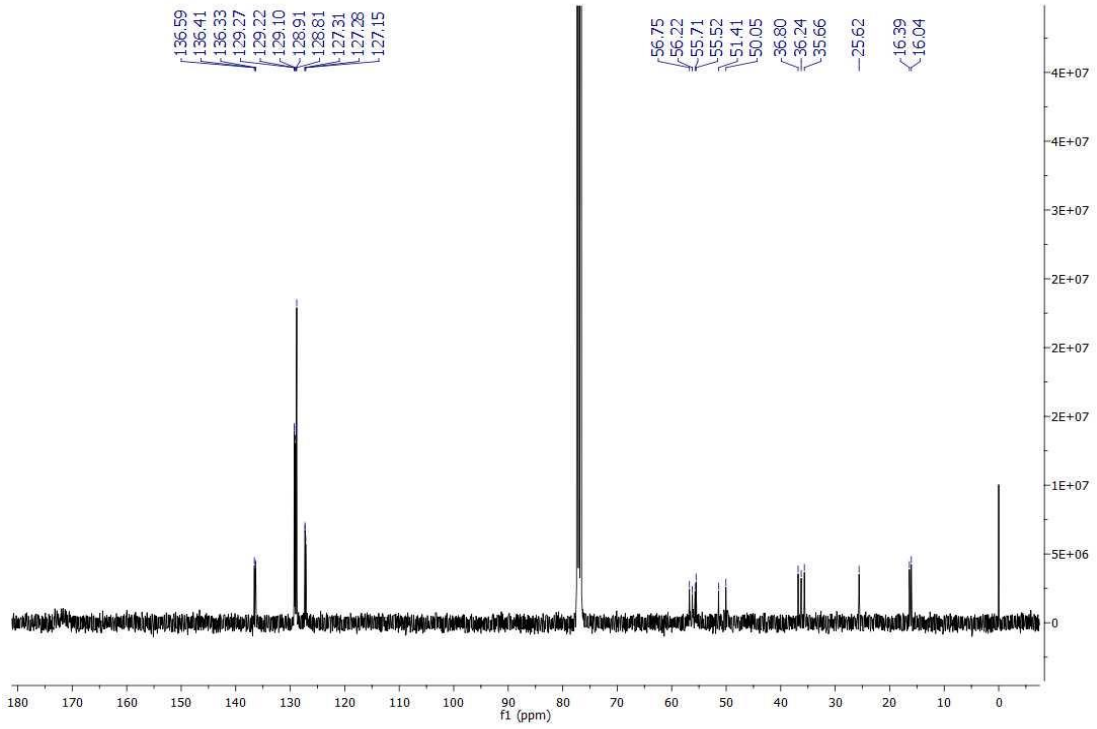
Cyclo-[Cys-NMe-Ala-Cys(Bn)-NMe-Ala-Thr(Bn)-Gly] (6): White solid (18 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, *J* = 6.4 Hz, 3H), 1.42 (d, *J* = 6.9 Hz, 3H), 1.53 (m, 4H), 2.71 (m, 3H), 2.78 (s, 3H), 3.00 (m, 1H), 3.15 (s, 3H), 3.53 (d, *J* = 17.4 Hz, 1H), 3.58-3.66 (m, 1H), 3.77 (s, 2H), 4.35 (d, *J* = 7.6 Hz, 1H), 4.47 (d, *J* = 11.7 Hz, 1H), 4.52-4.60 (m, 2H), 4.74 (dd, *J* = 17.4, 8.7 Hz, 1H), 4.88-5.01 (m, 2H), 5.26-5.33 (m, 1H), 6.19 (d, *J* = 7.8 Hz, 1H), 6.66 (d, *J* = 8.9 Hz, 1H), 7.24 (m, 2H), 7.27-7.38 (m, 8H), 7.55 (d, *J* = 5.9 Hz, 1H), 7.82 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 12.9, 14.7, 17.7, 25.7, 29.0, 34.5, 37.2, 39.2, 41.6, 49.2, 50.7, 56.0, 58.8, 61.9, 71.7, 73.6, 127.3 (2 C), 127.6 (2C), 127.8, 128.4 (2C), 128.7, 129.0 (2 C), 138.1, 138.2, 169.0, 170.0, 170.4, 170.5, 170.8, 171.3. ESI-MS *m/z* calc. for $C_{34}H_{47}N_6O_7S_2$ ([M+H]) 715.3, found 715.3.

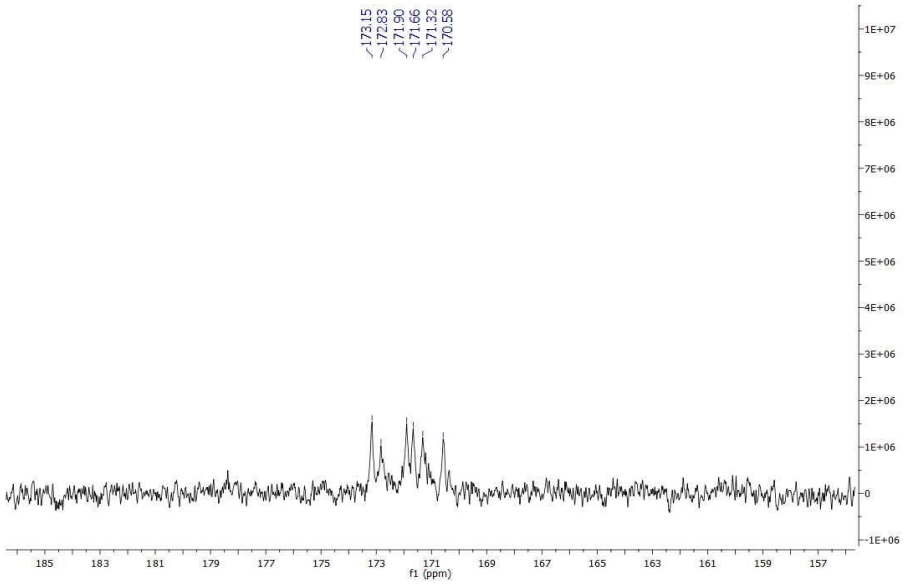
^{1}H and ^{13}C NMR Spectra and ESI-MS data of Compounds

(1): *Cyclo*-[Cys-Phe-Ala-Phe-Ala-Phe]

NMR in $CDCl_3$



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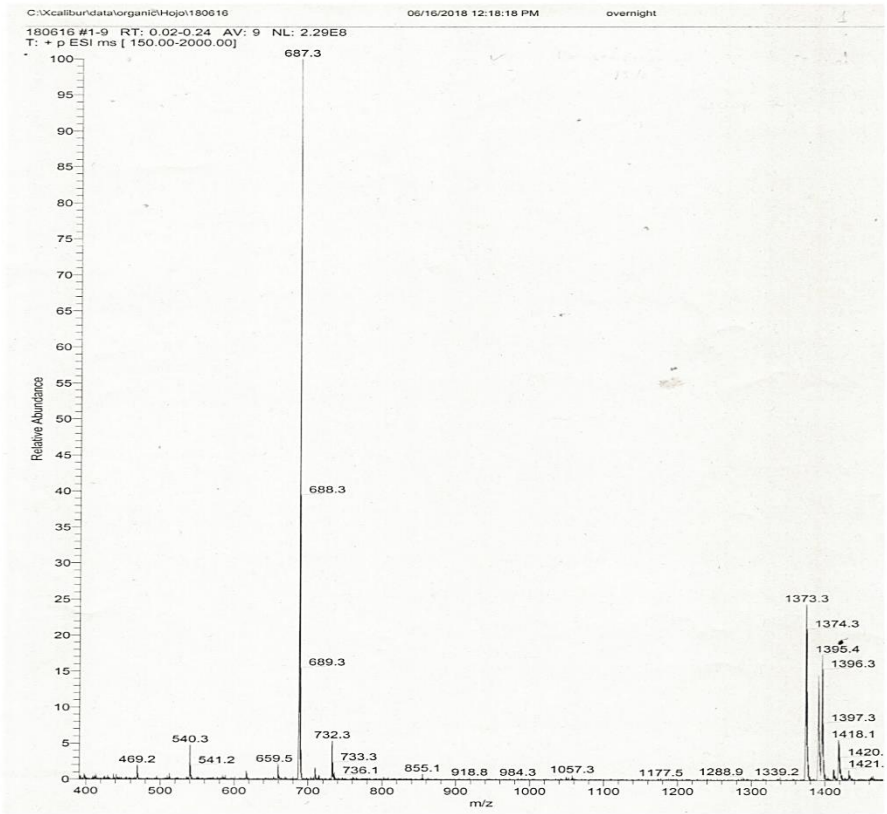
f1 (ppm)

ESI-MS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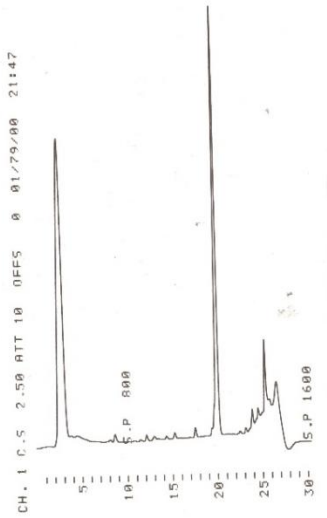
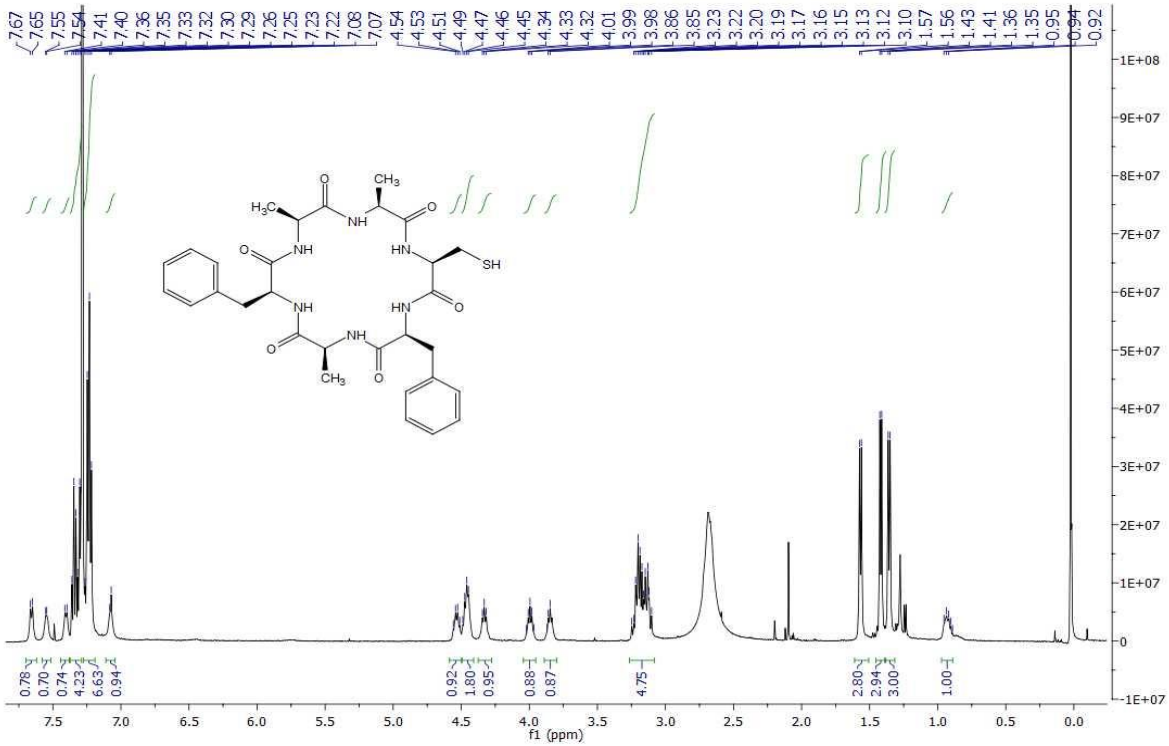
RP-HPLC chromatogram (1)

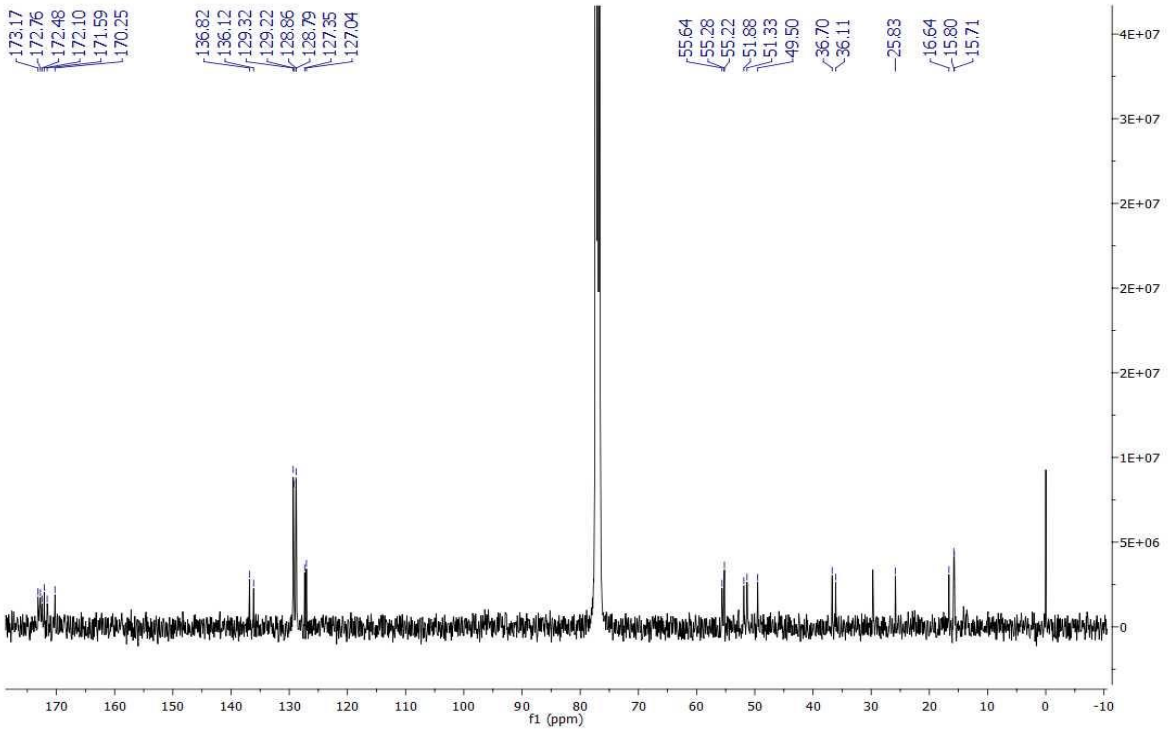


RP-HPLC chromatogram of crude cyclopeptide **1** (Gradient: increasing a ratio of eluent B (0.1 % TFA in acetonitrile) from 30% to 50 % in 20 min against eluent A (0.1 % TFA in H_2O)).

(2): *Cyclo*-[Cys-Phe-Ala-Phe-Ala-Ala]

NMR in $CDCl_3$

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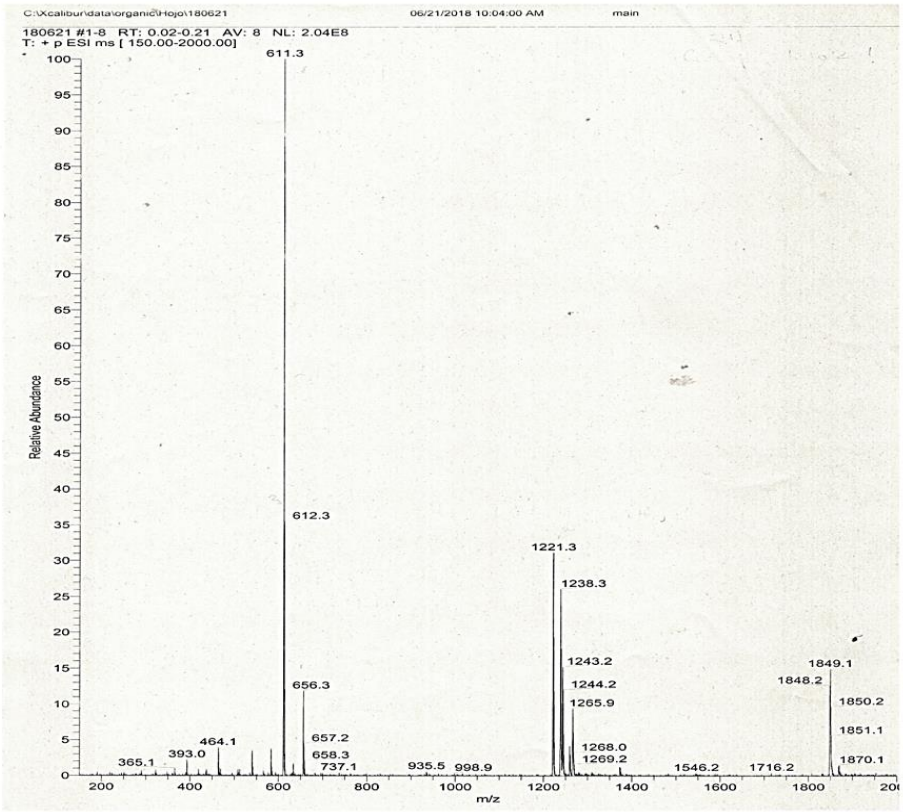
f1 (ppm)

ESI-MS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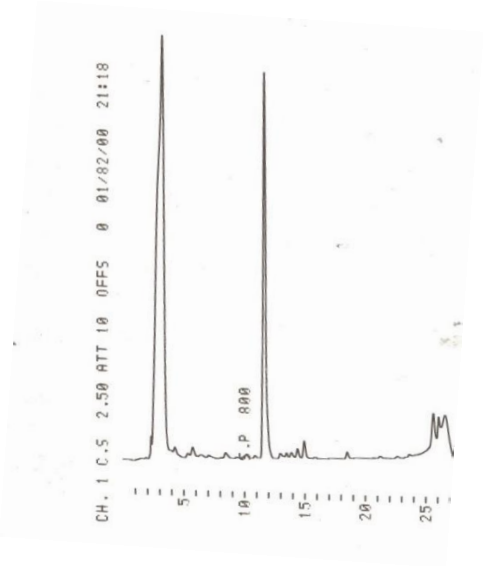
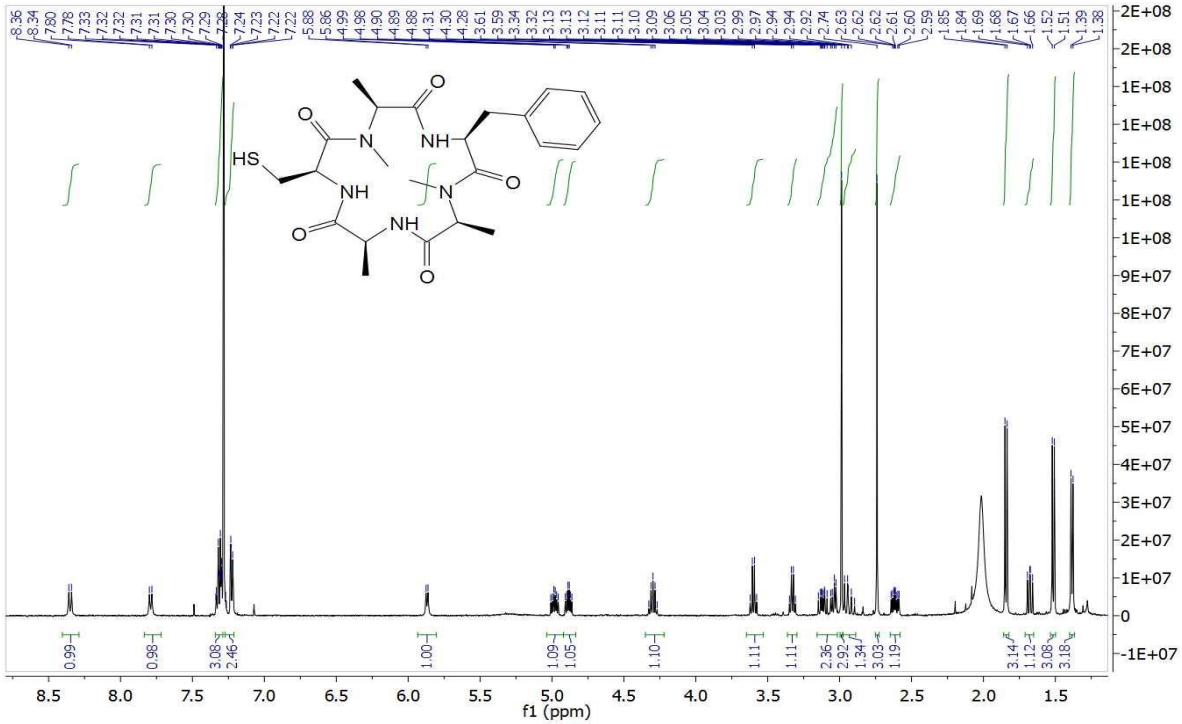
RP-HPLC chromatogram (2)

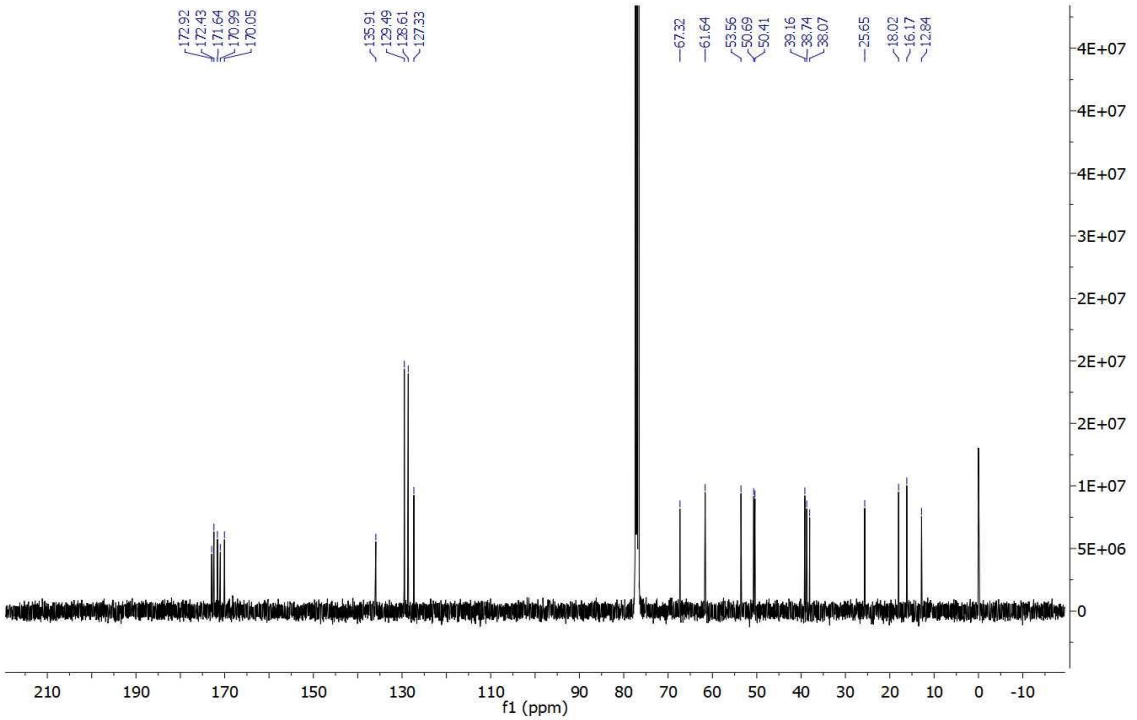


RP-HPLC chromatogram of crude cyclopeptide **2** (Gradient: increasing a ratio of eluent B (0.1 % TFA in acetonitrile) from 30% to 50 % in 20 min against eluent A (0.1 % TFA in H_2O)).

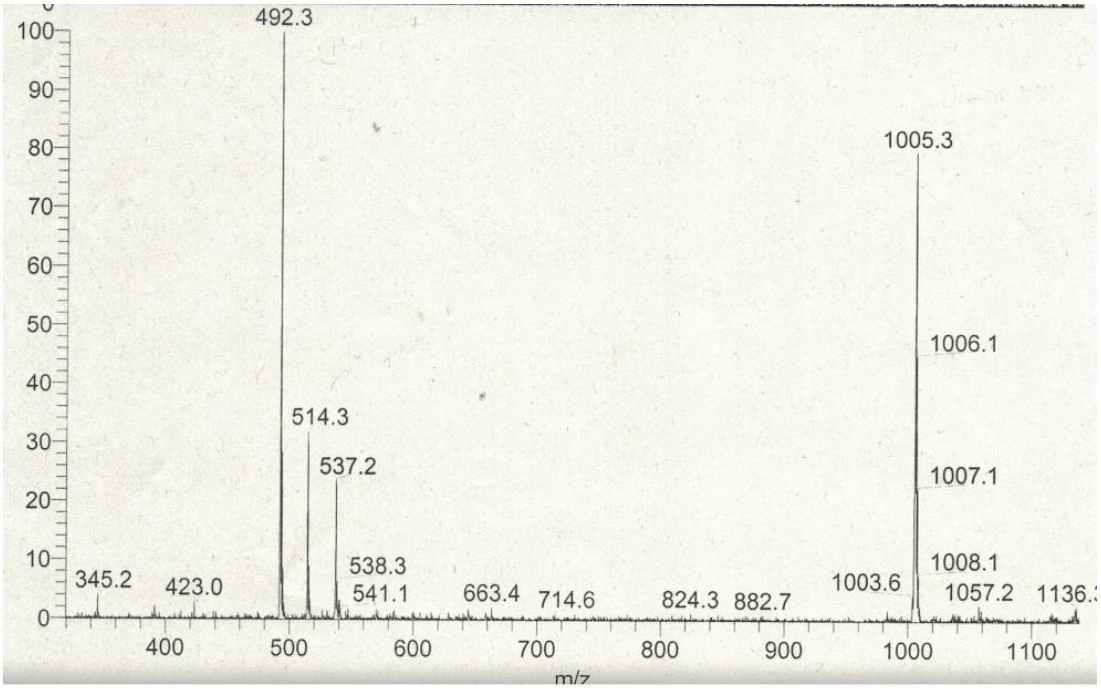
(3): *Cyclo*-[Cys-NMeAla-Phe-NMeAla-Ala]

NMR in $CDCl_3$

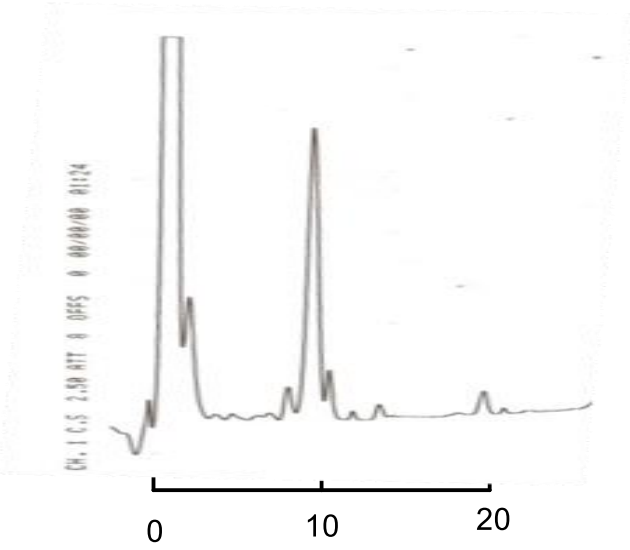



172.92
172.43
171.64
170.99
170.05
135.91
129.49
128.61
127.33
67.32
61.64
53.56
50.69
50.41
39.16
38.74
38.07
25.65
18.02
16.17
12.84
4E+07
4E+07
4E+07
3E+07
2E+07
2E+07
2E+07
1E+07
5E+06
0
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

ESI-MS


492.3
1005.3
1006.1
514.3
537.2
1007.1
538.3
1008.1
345.2
423.0
541.1
663.4
714.6
824.3
882.7
1003.6
1057.2
1136.
100
90
80
70
60
50
40
30
20
10
0
400
500
600
700
800
900
1000
1100
m/z

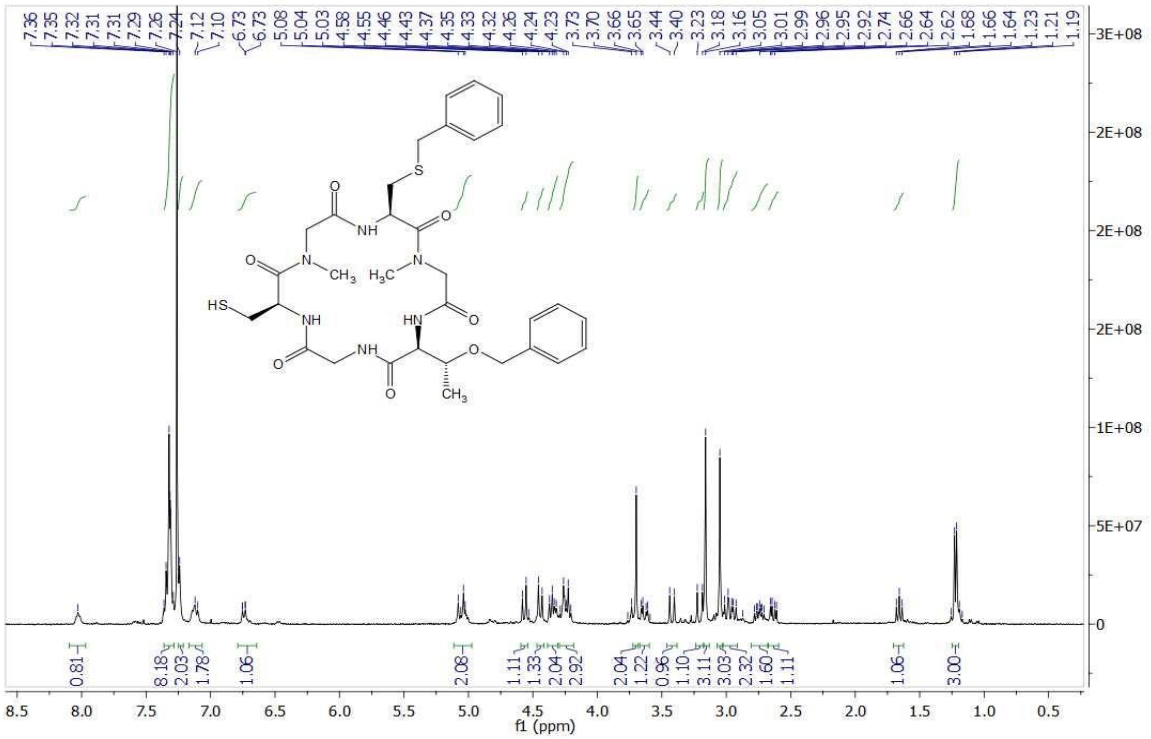
RP-HPLC chromatogram (3)

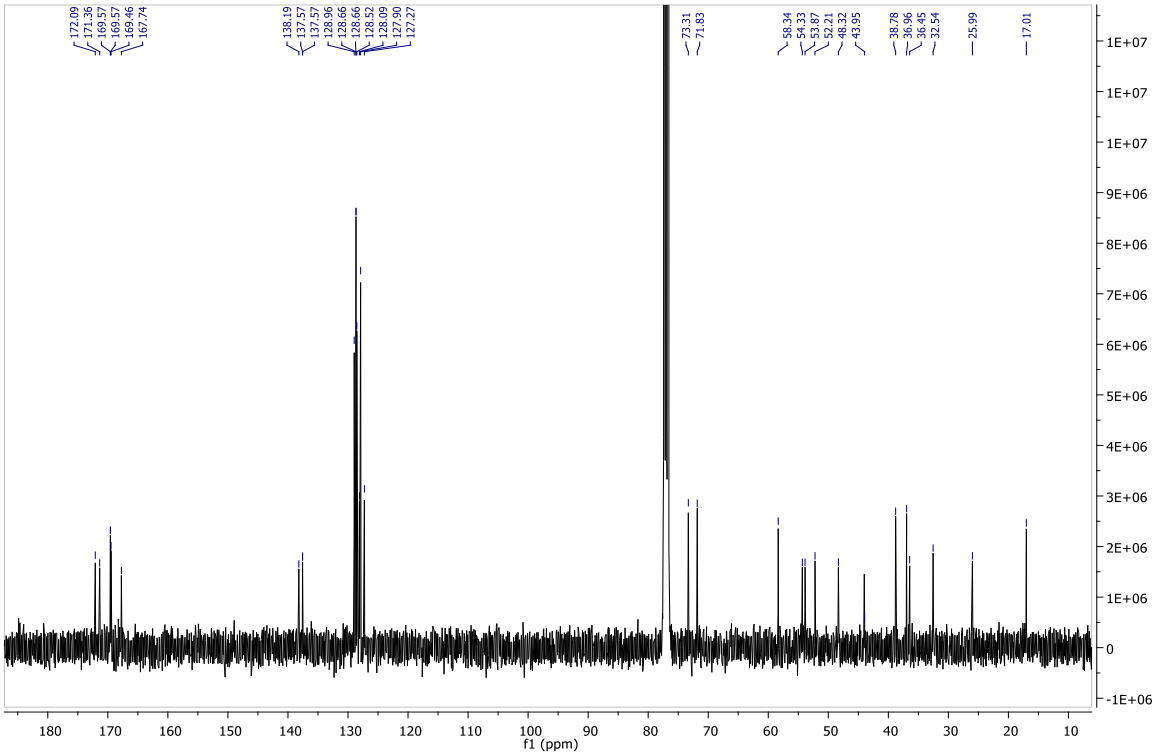


RP-HPLC chromatogram of crude cyclopeptide **3** (Gradient: increasing a ratio of eluent B (0.1 % TFA in acetonitrile) from 30% to 50 % in 20 min against eluent A (0.1 % TFA in H_2O)).

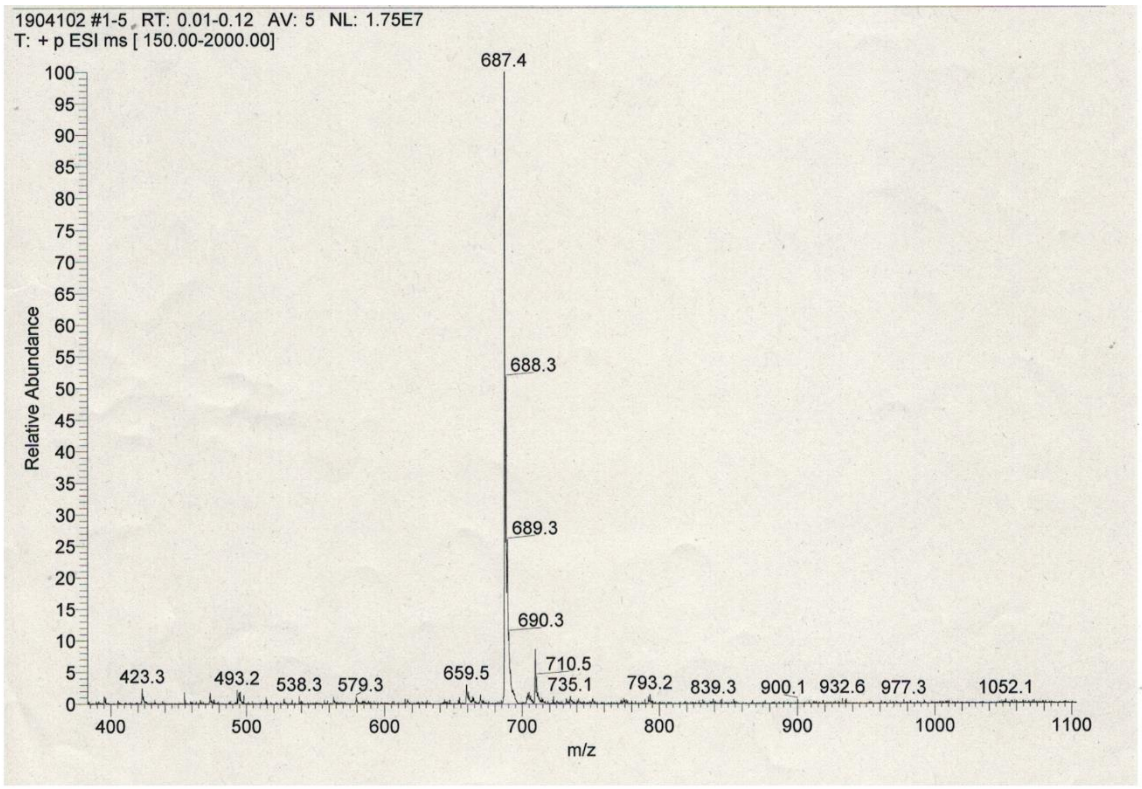
(4): *Cyclo*-[Cys-NMe-Gly-Cys(Bn)-NMe-Gly-Thr(Bn)-Gly]

NMR in $CDCl_3$

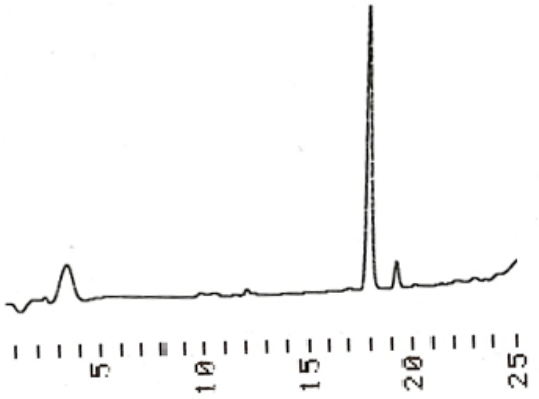



172.09
171.36
169.57
169.57
169.46
167.74
138.19
137.57
137.57
128.96
128.66
128.66
128.32
128.09
127.90
127.27
73.31
71.83
58.34
54.33
53.87
52.21
48.32
43.95
38.78
36.96
36.45
32.54
25.99
17.01
1E+07
1E+07
1E+07
9E+06
8E+06
7E+06
6E+06
5E+06
4E+06
3E+06
2E+06
1E+06
0
-1E+06
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

ESI-MS


1904102 #1-5 RT: 0.01-0.12 AV: 5 NL: 1.75E7
T: + p ESI ms [150.00-2000.00]
687.4
688.3
689.3
690.3
710.5
735.1
423.3
493.2
538.3
579.3
659.5
793.2
839.3
900.1
932.6
977.3
1052.1
Relative Abundance
m/z

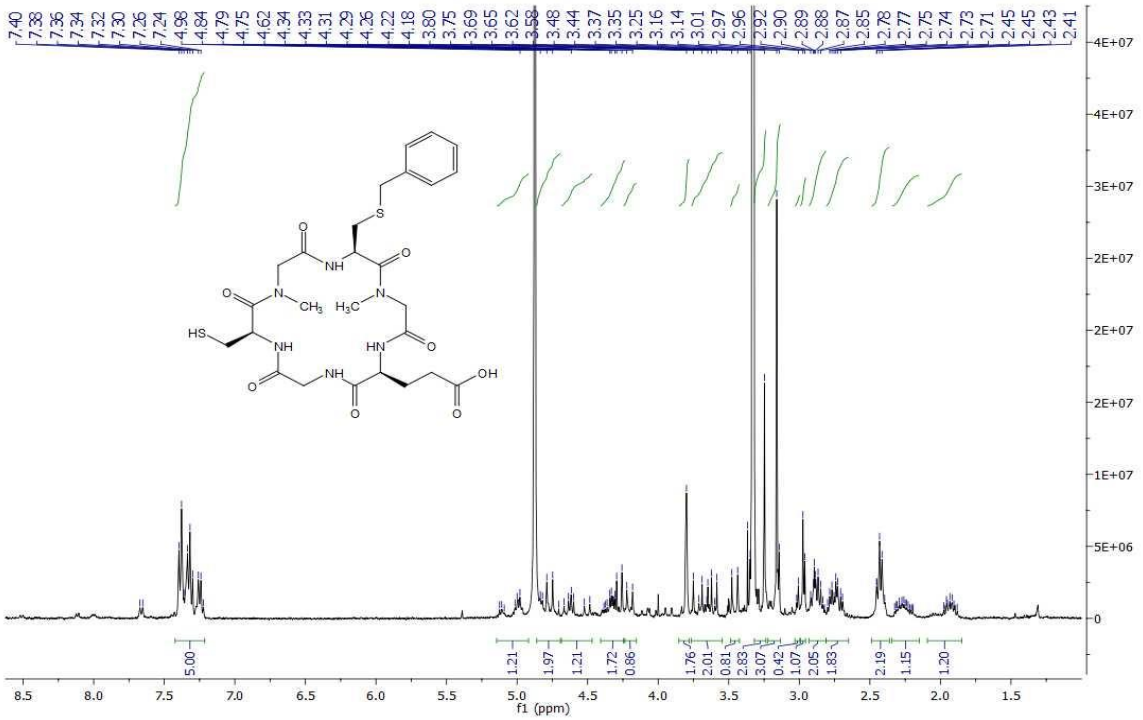
RP-HPLC chromatogram (4)

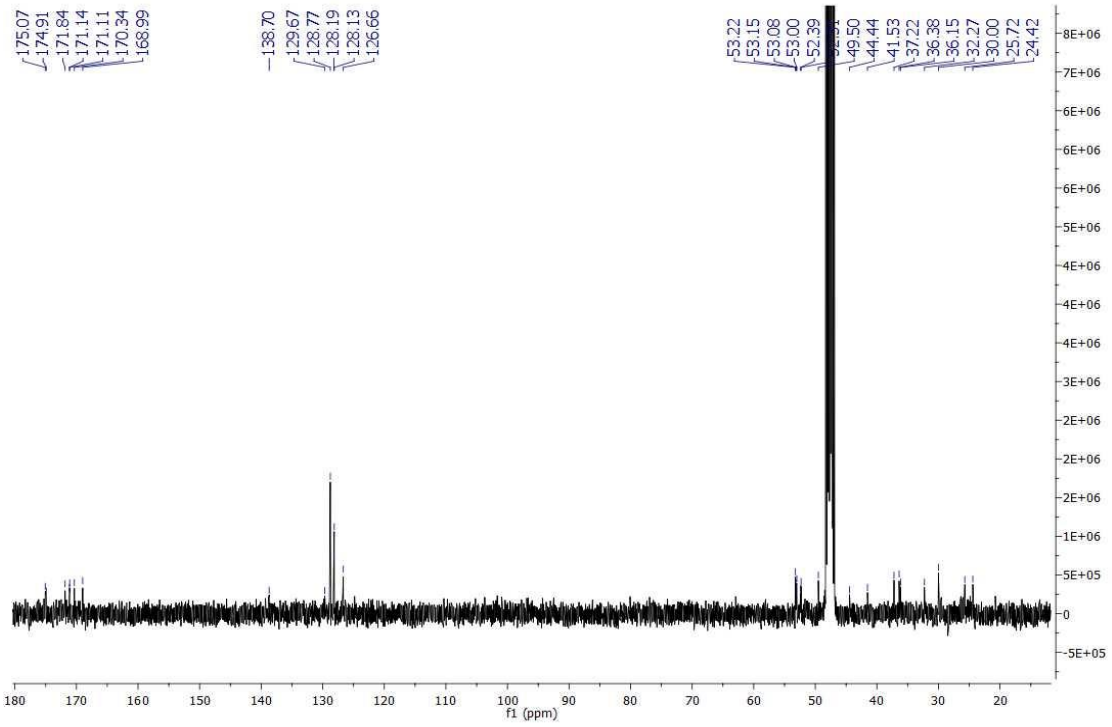


RP-HPLC chromatogram of crude cyclopeptide **4** (Gradient: increasing a ratio of eluent B (0.1 % TFA in acetonitrile) from 35% to 55 % in 20 min against eluent A (0.1 % TFA in H_2O)).

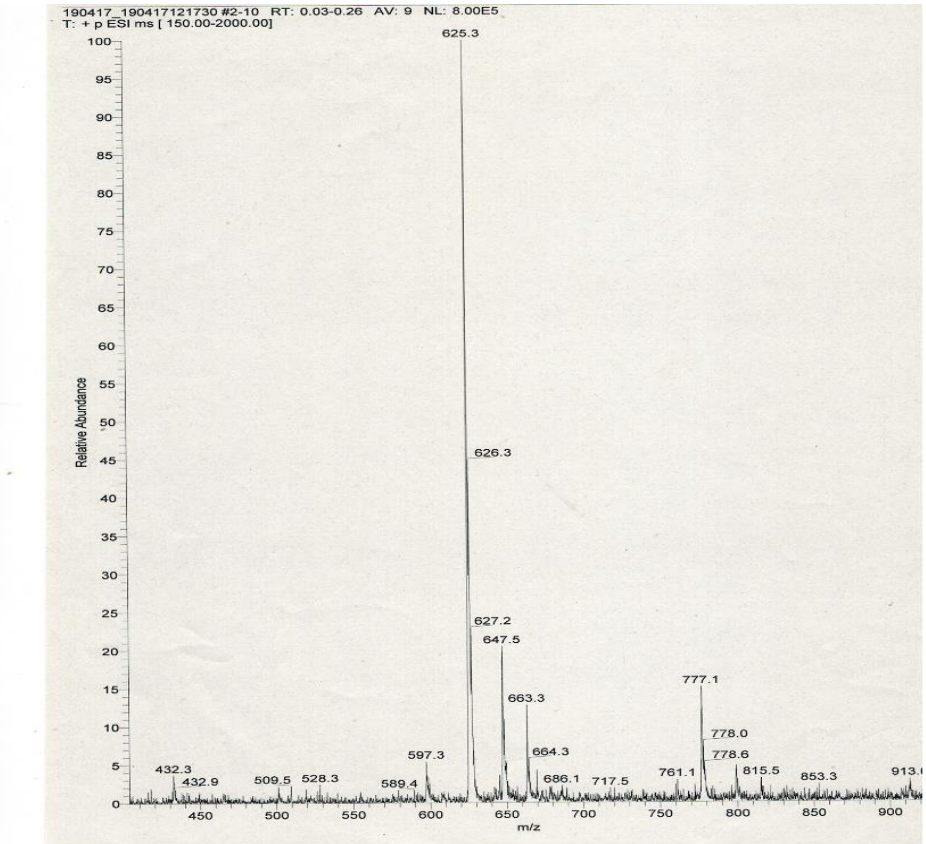
(5): *Cyclo*-[Cys-NMe-Gly-Cys(Bn)-NMe-Gly-Glu-Gly]

NMR in CD_3OD

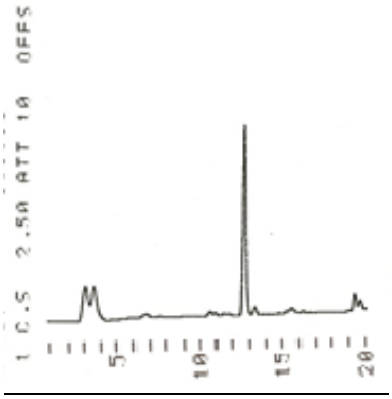



175.07
174.91
171.84
171.14
171.11
170.34
168.99
138.70
129.67
128.77
128.19
128.13
126.66
53.22
53.15
53.08
53.00
52.39
49.50
44.44
41.53
37.22
36.38
36.15
32.27
30.00
25.72
24.42
f1 (ppm)

ESI-MS


190417_190417121730 #2-10 RT: 0.03-0.26 AV: 9 NL: 8.00E5
T: + p ESI ms [150.00-2000.00]
Relative Abundance
m/z
625.3
626.3
627.2
647.5
663.3
664.3
597.3
432.3
432.9
509.5
528.3
589.4
686.1
717.5
761.1
777.1
778.0
778.6
815.5
853.3

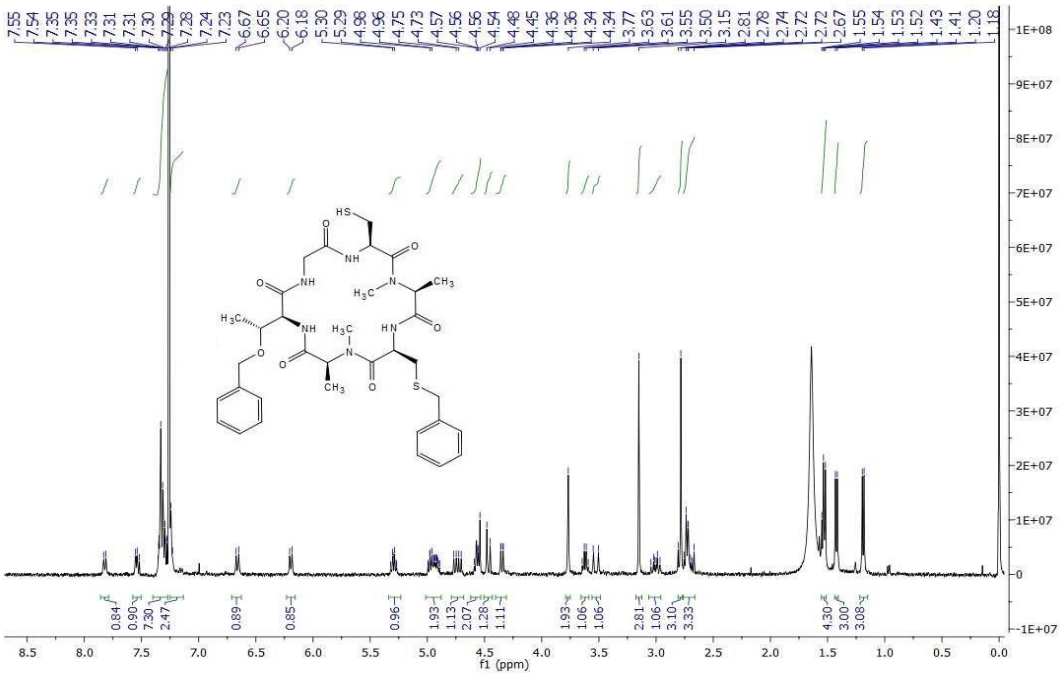
RP-HPLC chromatogram (5)

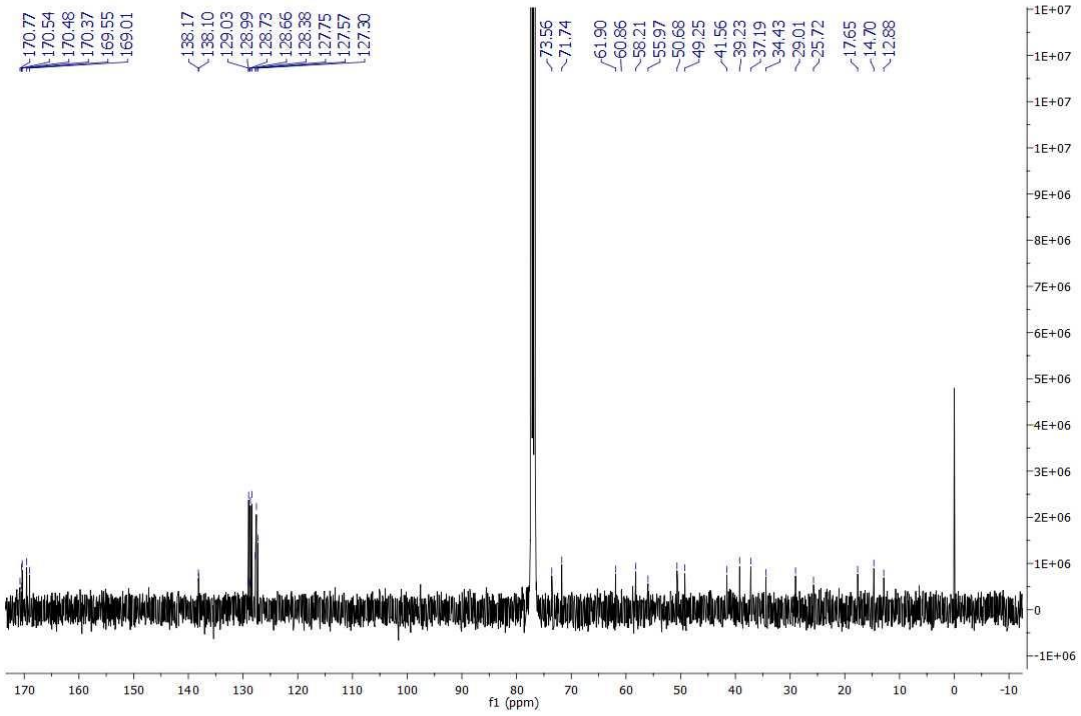


RP-HPLC chromatogram of crude cyclopeptide **5** (Gradient: increasing a ratio of eluent B (0.1 % TFA in acetonitrile) from 30% to 50 % in 20 min against eluent A (0.1 % TFA in H_2O)).

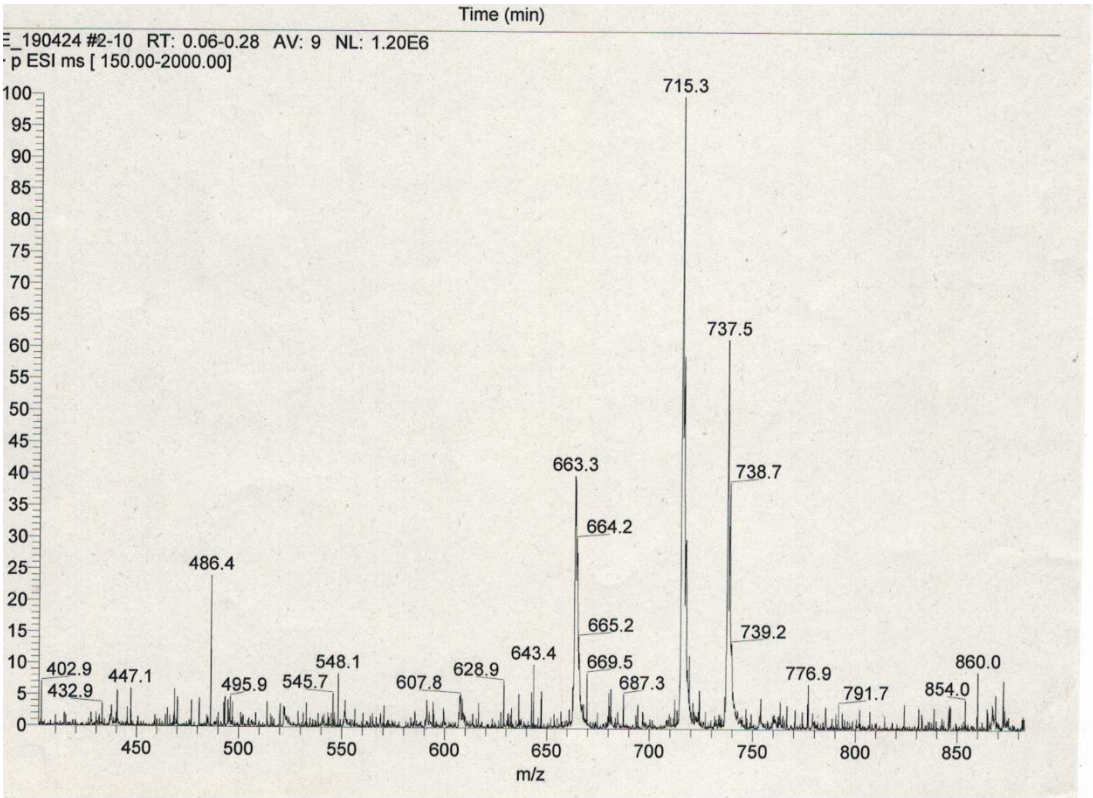
(6): *Cyclo*-[Cys-NMe-Ala-Cys(Bn)-NMe-Ala-Thr(Bn)-Gly]

NMR in $CDCl_3$

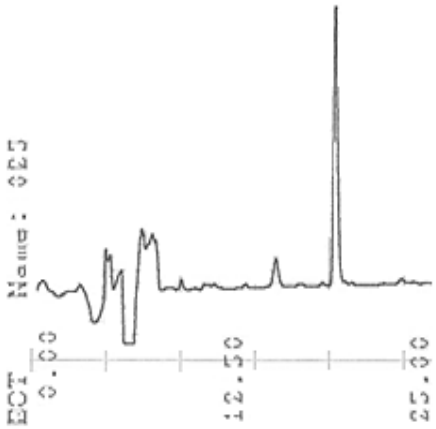



170.77
170.54
170.48
170.37
169.55
169.01
138.17
138.10
129.03
128.99
128.73
128.66
128.38
127.75
127.57
127.30
73.56
71.74
61.90
60.86
58.21
55.97
50.68
49.25
41.56
39.23
37.19
34.43
29.01
25.72
17.65
14.70
12.88
f1 (ppm)

ESI_MS


Time (min)
_190424 #2-10 RT: 0.06-0.28 AV: 9 NL: 1.20E6
p ESI ms [150.00-2000.00]
715.3
737.5
663.3
738.7
664.2
486.4
665.2
739.2
669.5
548.1
643.4
402.9
447.1
432.9
495.9
545.7
607.8
628.9
687.3
776.9
791.7
860.0
854.0
m/z

RP-HPLC chromatogram (6)



RP-HPLC chromatogram of crude cyclopeptide **1** (Gradient: increasing a ratio of eluent B (0.1 % TFA in acetonitrile) from 40% to 60 % in 20 min against eluent A (0.1 % TFA in H_2O)).