Supplementary file

Synthesis and Evaluation of Antimycobacterial and Antiplasmodial Activities of Hirsutellide A and its Analogs

Henok Asfaw Sahile [1,2†], Maria Santos Martinez-Martinez [3], Melissa Dillenberger [4], Katja Becker [4] and Peter Imming[1*]

[1] Institut für Pharmazie, Martin-Luther-Universität Halle-Wittenberg, 06120 Halle, Germany. [2] Division of Infectious Diseases, Departments of Medicine, Life Sciences Institute, University of British Columbia, 2350 Health Sciences Mall, V6T 1Z3, Vancouver, British Columbia, Canada. [†] Current affiliation [3] Diseases of the Developing World, Medicines Development Campus, GlaxoSmithKline, Calle de Severo Ochoa, 2, 28760 Tres Cantos, Madrid, Spain. [4] Biochemistry and Molecular Biology, Interdisciplinary Research Center, Justus Liebig University Giessen, Heinrich-Buff-Ring 26-32, 35392 Giessen, Germany.

Contents

S1. General solid phase synthetic methods for the preparation of peptide analogues of hirsutellide A

Loading on 2-CT resin

The resin (1g) was weighed, transferred to a syringe fitted with a filtering frit and was allowed to swell in dry DCM for 20 min while shaking on a mechanical shaker. Fmoc-XX-OH (1.2 eq.) was separately dissolved in a vial with anhydrous DCM and well mixed with DIPEA (2.5 eq.). The solution was then transferred to the syringe and the loading took place for 2 h. Following that, 1 mL distilled methanol was added to the contents of the syringe and continued to be shaken for additional 15 minutes to ensure the capping of remaining trityl chloride groups. The solvent and excess reactants were then filtered off from the syringe and the resin was thoroughly washed with DCM (5X1 min), DCM/MeOH (1:1) (4X1 min) and MeOH (2X1 min). Finally, the resin was dried under vacuum pressure. Mass of the dried loaded resin was weighed and the loading efficiency was calculated from the increase in the mass of the loaded.

Deblocking of Fmoc-protecting group

Removal of the Fmoc protecting group from the resin bound Fmoc peptide prior to coupling of the next amino acid was always achieved by treating the resin with a solution of 20% piperidine in DMF (v/v) for 10 minutes and this was repeated for the second time. The resin was washed with DMF (1X) between each deprotection step and after the final deprotection, the washing was done five times with DMF to make sure the complete removal of traces of piperidine.

HATU mediated coupling for subsequent peptide elongation

In a 10 mL screw fitted vial, the Fmoc-Xaa-OH (3 eq.) and the coupling reagent HATU (3 eq.) were mixed and dissolved in NMP. DIPEA (6 eq.) was then added to the solution, well

mixed by vortexing and the contents were transferred to a prewashed resin in a syringe. The peptide coupling was then allowed to take place for 1h. Finally, the excess unreacted amino acid and other reagents were filtered-off from the syringe and resin was washed with DMF (4X) before proceeding with the next Fmoc cleavage.

Coupling to N-methylated peptide

A solution of Fmoc-Xaa-OH (3 eq.), HATU (3 eq.) and DIPEA (6 eq.) in NMP was added to the resin-bound N-methylamine peptide in the syringe and shaken for 2 h at room temperature. The excess unreacted amino acid and other reagents were filtered-off from the syringe and resin was washed with DMF (4X). The coupling was repeated for the second time.

Peptide cleavage

After swelling in DCM for 30 min, the peptidyl-resin was incubated for 2h with 5% TFA in DCM. The filtrates were then collected and the cleaving solution was removed under strong vacuum to afford the crude TFA salt of the final peptides.

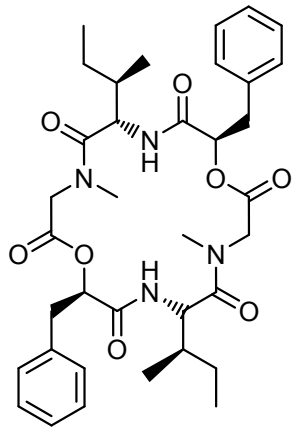
Macrocyclization of the linear peptides

The linear hexapeptide prepared by SPPS approach was dissolved in DMF (1mM) and cooled to 0°C in an ice bath. To the solution was added HATU (3 equiv), and HOAt (3 equiv) under vigorous stirring. DIPEA (10 equiv) was then added to the dilute solution and the reaction mixture was allowed to warm slowly to the room temperature and kept stirring for 3 days. Subsequently, the solvent was removed under reduced pressure and the residue was dissolved in 40 mL saturated $NaHCO_3$ while stirring for about 10 minutes. 20 mL of ethyl acetate was added to the mixture and stirred for further 5 minutes. The content was then transferred to a separatory funnel and the organic layer was collected. The aqueous phase was washed twice with 20 mL ethyl acetate. The combined ethyl acetate fraction was washed with brine, dried

by anhydrous $MgSO_4$, filtered and concentrated under a reduced pressure. The obtained crude solid mass was purified by a column chromatography to give pure cyclic hexapeptides.

S2. Spectral and analytical data for the final target compounds

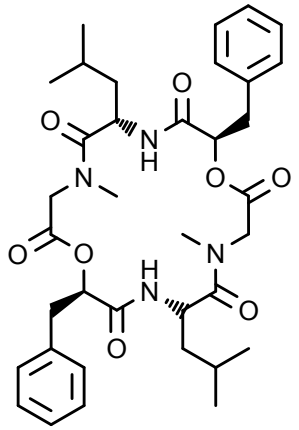
(6S,9R,15S,18R)-9,18-dibenzyl-6,15-di((R)-sec-butyl)-4,13-dimethyl-1,10-dioxa-4,7,13,16-tetraazacyclooctadecane-2,5,8,11,14,17-hexaone (9)



Scheme S1: Chemical structure of compound **9**

^{1}H NMR (400 MHz, $CDCl_3$-d) δ 7.53 (d, *J* = 9.7 Hz, 2H), 7.31 – 7.08 (m, 10H), 5.60 (dd, *J* = 11.7, 3.0 Hz, 2H), 4.87 (t, *J* = 10.1 Hz, 2H), 4.40 (d, *J* = 17.0 Hz, 2H), 3.65 (dd, *J* = 14.2, 3.0 Hz, 2H), 3.26 (s, 6H), 3.17 (d, *J* = 17.1 Hz, 2H), 2.73 (dd, *J* = 14.2, 11.8 Hz, 2H), 2.28 – 2.15 (m, 2H), 1.42 – 1.32 (m, 2H), 1.10 – 1.01 (m, 2H), 0.94 – 0.86 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$-d) δ 174.18, 168.82, 166.76, 136.13, 129.07, 128.56, 127.10, 74.10, 52.95, 51.88, 38.72, 37.89, 36.39, 25.96, 14.32, 11.05. Yield (50%). UPLC-MS (UV) purity: 98%, RT 1.29 min, HRMS m/z: $[M+H]^+$ Calcd for $C_{36}H_{49}N_4O_8$: 665.3550; found: 665.3535.

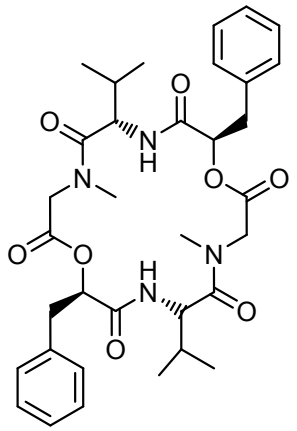
(6S,9R,15S,18R)-9,18-dibenzyl-6,15-diisobutyl-4,13-dimethyl-1,10-dioxa-4,7,13,16-tetraazacyclooctadecane-2,5,8,11,14,17-hexaone (10)



Scheme S2: Chemical structure of compound **10**

^{1}H NMR (400 MHz, $CDCl_3$-d) δ 7.48 (d, *J* = 9.5 Hz, 2H), 7.31 – 7.11 (m, 10H), 5.61 (dd, *J* = 11.4, 3.2 Hz, 2H), 5.22 (dt, *J* = 9.6, 7.4 Hz, 2H), 4.43 (d, *J* = 17.2 Hz, 2H), 3.63 (dd, *J* = 14.2, 3.2 Hz, 2H), 3.26 (s, 6H), 3.18 (d, *J* = 17.2 Hz, 2H), 2.74 (dd, *J* = 14.2, 11.4 Hz, 2H), 1.77 (h, *J* = 6.6 Hz, 4H), 1.53 (dt, *J* = 13.5, 6.6 Hz, 2H), 0.99 – 0.86 (m, 12H).Yield (25%), UPLC-MS (UV) purity: 93%, RT 1.28 min, HRMS m/z: $[M+H]^+$ Calcd for $C_{36}H_{49}N_4O_8$: 665.3550; found: 665.3535.

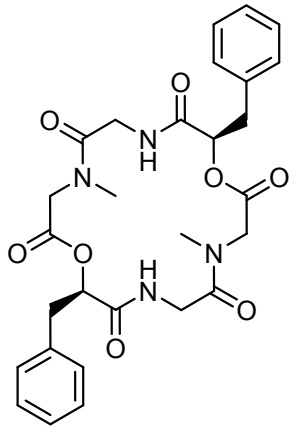
(6S,9R,15S,18R)-9,18-dibenzyl-6,15-diisopropyl-4,13-dimethyl-1,10-dioxa-4,7,13,16-tetraazacyclooctadecane-2,5,8,11,14,17-hexaone (11)



Scheme S3: Chemical structure of compound **11**

^{1}H NMR (500 MHz, CD_3OD-d_4) δ 7.70 (d, *J* = 9.7 Hz, 2H), 7.33 – 7.16 (m, 10H), 5.50 (dd, *J* = 11.2, 3.2 Hz, 2H), 4.88 – 4.78 (m, 2H), 4.31 (d, *J* = 17.3 Hz, 2H), 3.59 – 3.47 (m, 4H), 3.28 (s, 6H), 2.77 (dd, *J* = 14.1, 11.2 Hz, 2H), 2.36 – 2.28 (m, 2H), 0.98 – 0.85 (m, 12H). ^{13}C NMR (126 MHz, cd_3od) δ 173.81, 169.63, 167.26, 136.08, 128.90, 128.31, 126.84, 74.06, 54.23, 51.22, 38.27, 36.93, 30.40, 17.96, 17.29. Yield (39%), UPLC-MS (UV) purity: 98%, RT 1.17 min, HRMS m/z: $[M+H]^+$ Calcd for $C_{34}H_{45}N_4O_8$: 637.3237; found: 637.3222.

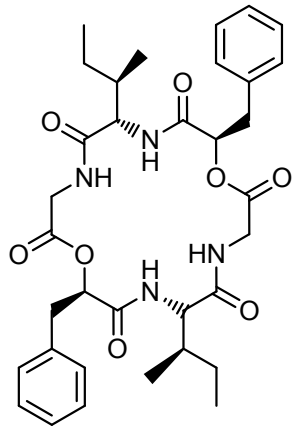
(9R,18R)-9,18-dibenzyl-4,13-dimethyl-1,10-dioxa-4,7,13,16-tetraazacyclooctadecane-2,5,8,11,14,17-hexaone (12)



Scheme S4: Chemical structure of compound **12**

^{1}H NMR (500 MHz, CD_3OD-d_4) δ 7.33 – 7.18 (m, 10H), 5.43 (dd, *J* = 7.7, 4.2 Hz, 2H), 4.20 (d, *J* = 17.5 Hz, 2H), 4.09 – 3.96 (m, 4H), 3.91 (d, *J* = 16.3 Hz, 2H), 3.25 (dd, *J* = 14.3, 4.2 Hz, 2H), 3.15 (q, *J* = 6.6 Hz, 2H), 3.11 (s, 6H). ^{13}C NMR (126 MHz, cd_3od) δ 169.93, 169.86, 168.51, 135.99, 129.21, 128.05, 126.63, 74.26, 51.44, 47.99, 40.05, 37.48, 35.60. Yield (43%), UPLC-MS (UV) purity: 99.9%, RT 0.92 min, ESI-MS m/z: $[M+H]^+$ Calcd for $C_{28}H_{33}N_4O_8$: 553.22; found: 553.22

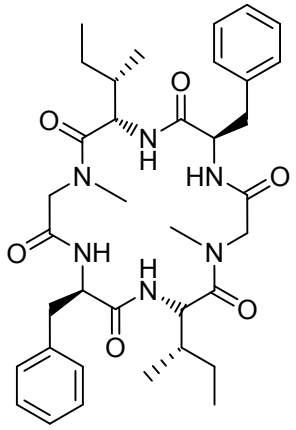
(6S,9R,15S,18R)-9,18-dibenzyl-6,15-di((R)-sec-butyl)-1,10-dioxa-4,7,13,16-tetraazacyclooctadecane-2,5,8,11,14,17-hexaone (13)



Scheme S5: Chemical structure of compound **13**

^{1}H NMR (400 MHz, $CDCl_3$-d) δ 7.46 (d, *J* = 8.8 Hz, 2H), 7.32 – 7.11 (m, 10H), 7.01 (t, *J* = 5.8 Hz, 2H), 5.73 (dd, *J* = 10.9, 3.7 Hz, 2H), 4.18 (dd, *J* = 10.9, 8.8 Hz, 2H), 4.04 (dd, *J* = 17.4, 5.2 Hz, 2H), 3.66 (dd, *J* = 14.3, 3.7 Hz, 2H), 3.39 (dd, *J* = 17.4, 6.2 Hz, 2H), 2.82 (dd, *J* = 14.3, 10.9 Hz, 2H), 2.31 (ttd, *J* = 13.1, 6.7, 3.0 Hz, 2H), 1.54 (dqd, *J* = 14.9, 7.3, 3.1 Hz, 2H), 1.20 – 1.10 (m, 2H), 0.96 – 0.79 (m, 12H). ^{13}C NMR (101 MHz, $cdcl_3$) δ 173.30, 169.64, 166.81, 135.96, 129.08, 128.62, 127.08, 73.41, 57.04, 42.34, 38.06, 32.76, 24.33, 15.68, 9.97. Yield (45%), UPLC-MS (UV) purity: 99.9%, RT 1.13 min HRMS m/z: $[M+H]^+$ Calcd for $C_{34}H_{45}N_4O_8$: 637.3237; found: 637.3224.

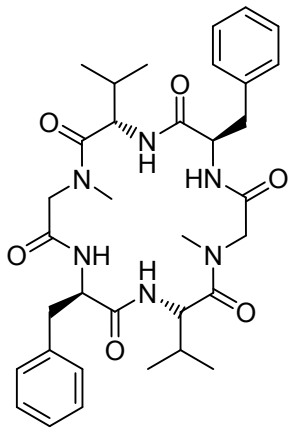
Cyclo (D-Phe- Ile-Sar-D-Phe- Ile-Sar) (14)



Scheme S6: Chemical structure of compound **14**

^{1}H NMR (400 MHz, $CDCl_3$-d) δ 7.43 – 7.34 (m, 3H), 7.33 – 7.17 (m, 9H), 7.02 (s, 2H), 5.04 (d, *J* = 17.2 Hz, 2H), 4.74 (td, *J* = 9.0, 5.9 Hz, 2H), 4.26 (t, *J* = 8.6 Hz, 2H), 3.40 (t, *J* = 12.3 Hz, 2H), 3.26 (dd, *J* = 14.1, 5.9 Hz, 2H), 3.13 – 3.07 (m, 2H), 3.04 (s, 6H), 1.83 (dt, *J* = 9.4, 3.3 Hz, 2H), 1.66 (ddt, *J* = 14.9, 7.5, 3.7 Hz, 2H), 1.21 (td, *J* = 15.3, 14.5, 7.8 Hz, 2H), 0.90 (q, *J* = 7.2 Hz, 12H). UPLC-MS (ELSD) purity: 99.9%, RT 1.13 min HRMS m/z: $[M+H]^+$ Calcd for $C_{36}H_{51}N_6O_6$: 663.3870; found: 663.3852.

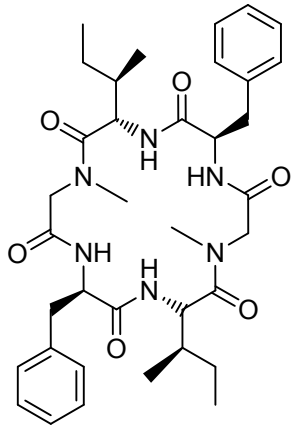
Cyclo (D-Phe- Val-Sar-D-Phe- Val-Sar) (15)



Scheme S7: Chemical structure of compound **15**

^{1}H NMR (400 MHz, $CDCl_3$-d) δ 7.43 – 7.35 (m, 3H), 7.33 – 7.17 (m, 9H), 7.03 (d, *J* = 7.1 Hz, 2H), 5.00 (s, 2H), 4.75 (ddd, *J* = 10.0, 8.8, 6.1 Hz, 2H), 4.17 (dd, *J* = 9.5, 7.1 Hz, 2H), 3.39 (dd, *J* = 14.2, 9.9 Hz, 2H), 3.31 – 3.21 (m, 2H), 3.12 (d, *J* = 6.8 Hz, 2H), 3.04 (s, 6H), 2.00 (dq, *J* = 9.5, 6.6 Hz, 2H), 1.04 (d, *J* = 6.6 Hz, 6H), 0.92 (d, *J* = 6.7 Hz, 6H). UPLC-MS (UV) purity: 99.9%, RT 1.04 min HRMS m/z: $[M+H]^+$ Calcd for $C_{34}H_{46}N_6O_6$: 635.3552; found: 635.3538.

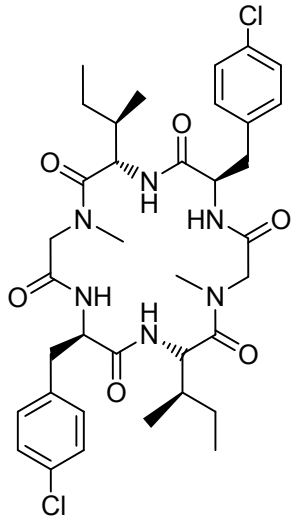
Cyclo (D-Phe-*allo*-Ile-Sar-D-Phe-*allo*-Ile-Sar) (16)



Scheme S8: Chemical structure of compound **16**

^{1}H NMR (500 MHz, $CDCl_3$-d) δ 7.42 – 7.18 (m, 12H), 7.07 (d, *J* = 7.4 Hz, 2H), 5.00 (s, 2H), 4.77 (td, *J* = 9.2, 6.2 Hz, 2H), 4.27 (t, *J* = 8.1 Hz, 2H), 3.39 (dd, *J* = 14.2, 9.9 Hz, 2H), 3.27 (dd, *J* = 14.3, 6.0 Hz, 2H), 3.17 – 3.06 (m, 2H), 3.03 (s, 6H), 1.79 (dtt, *J* = 9.9, 6.6, 3.5 Hz, 2H), 1.40 (dtd, *J* = 11.3, 7.5, 4.0 Hz, 2H), 1.15 – 1.04 (m, 2H), 1.01 (d, *J* = 6.6 Hz, 6H), 0.89 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (126 MHz, $cdcl_3$) δ 173.34, 172.08, 169.65, 137.41, 129.46, 128.41, 126.62, 55.17, 52.91, 51.92, 36.53, 35.99, 34.77, 25.83, 15.46, 11.50. Yield (30%), UPLC-MS (UV) purity: 99.9%, RT 1.11 min, HRMS m/z: $[M+H]^+$ Calcd for $C_{36}H_{51}N_6O_6$: 663.3870; found: 663.3853.

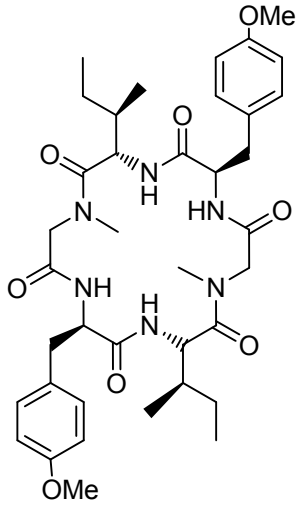
Cyclo (D-Phe(4-Cl)-*allo*-Ile-Sar-D-Phe (4-Cl)-*allo*-Ile-Sar) (17)



Scheme S9: Chemical structure of compound **17**

^{1}H NMR (400 MHz, $CDCl_3$-d) δ 7.36 – 7.22 (m, 8H), 7.22 – 7.10 (m, 2H), 7.10 (s, 2H), 4.97 (d, *J* = 14.9 Hz, 2H), 4.70 (tt, *J* = 10.1, 6.4 Hz, 2H), 4.24 (dd, *J* = 9.0, 4.6 Hz, 2H), 3.34 (dd, *J* = 14.2, 10.0 Hz, 2H), 3.23 – 3.06 (m, 4H), 3.03 (s, 6H), 1.77 (qt, *J* = 10.4, 6.7 Hz, 2H), 1.39 (dqd, *J* = 14.1, 7.3, 3.8 Hz, 2H), 1.15 – 1.04 (m, 2H), 1.00 (d, *J* = 6.7 Hz, 6H), 0.88 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (101 MHz, $cdcl_3$) δ 173.23, 171.93, 169.89, 135.84, 132.51, 130.79, 128.54, 55.13, 52.64, 51.92, 36.58, 35.95, 33.91, 25.80, 15.46, 11.49. Yield (50%), UPLC-MS (UV) purity: 98%, RT 1.24 min HRMS m/z: $[M+H]^+$ Calcd for $C_{36}H_{49}Cl_2N_6O_6$: 731.3091; found: 731.3073

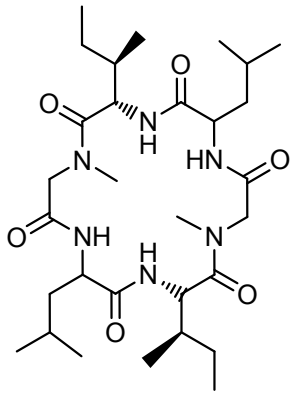
Cyclo (D-Phe(4-OMe)-*allo*-Ile-Sar-D-Phe(4-OMe)-*allo*-Ile-Sar) (18)



Scheme S10: Chemical structure of compound **18**

^{1}H NMR (400 MHz, $CDCl_3$-d) δ 7.34 – 7.22 (m, 4H), 7.18 (d, *J* = 8.7 Hz, 2H), 7.04 (d, *J* = 7.1 Hz, 2H), 6.88 – 6.75 (m, 4H), 4.99 (d, *J* = 17.6 Hz, 2H), 4.69 (td, *J* = 9.1, 6.3 Hz, 2H), 4.30 – 4.19 (m, 2H), 3.78 (s, 6H), 3.35 – 3.25 (m, 2H), 3.22 – 3.07 (m, 4H), 3.04 (s, 6H), 1.77 (tdd, *J* = 9.7, 6.4, 3.6 Hz, 2H), 1.38 (ttd, *J* = 11.4, 7.7, 3.7 Hz, 2H), 1.12 – 1.03 (m, 2H), 0.99 (d, *J* = 6.7 Hz, 6H), 0.87 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (101 MHz, $cdcl_3$) δ 173.35, 172.01, 169.56, 158.34, 130.41, 129.36, 113.81, 55.23, 53.09, 51.93, 36.58, 35.94, 33.99, 25.82, 15.42, 11.48. Yield (50%), UPLC-MS (UV) purity: 99.9%, RT 1.06 min, HRMS m/z: $[M+H]^+$ Calcd for $C_{38}H_{55}N_6O_8$: 723.4081; found: 723.4068

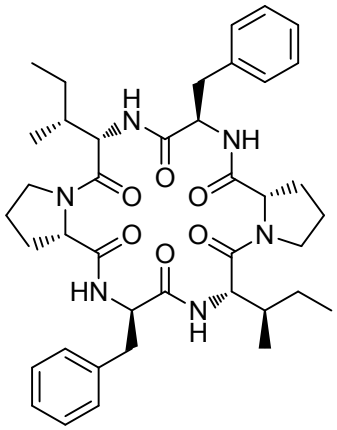
Cyclo (D-Leu-*allo*-Ile-Sar-D-Leu-*allo*-Ile-Sar) (19)



Scheme S11: Chemical structure of compound 1**9**

^{1}H NMR (400 MHz, $CDCl_3$-d) δ 7.04 (dd, *J* = 18.1, 7.9 Hz, 4H), 5.06 (s, 2H), 4.51 (q, *J* = 8.0 Hz, 2H), 4.24 (t, *J* = 8.2 Hz, 2H), 3.39 – 3.11 (m, 8H), 1.88 – 1.65 (m, 6H), 1.62 – 1.50 (m, 2H), 1.43 (ddt, *J* = 14.9, 11.5, 5.3 Hz, 2H), 1.12 (dtd, *J* = 16.2, 7.9, 4.6 Hz, 2H), 1.05 – 0.81 (m, 24H). Yield (45%), UPLC-MS (UV) purity: 93%, RT 1.13 min, HRMS m/z: $[M+H]^+$ Calcd for $C_{38}H_{55}N_6O_8$: 594.4183; found: 595.4167

Cyclo (D-Phe-*allo*-Ile-Pro-D-Phe-*allo*-Ile-Pro) (20)



Scheme S12: Chemical structure of compound **20**

^{1}H NMR (400 MHz, $CDCl_3$-d) δ 7.45 (d, *J* = 8.1 Hz, 2H), 7.25 – 7.12 (m, 10H), 6.22 (d, *J* = 9.6 Hz, 2H), 4.90 (ddd, *J* = 9.6, 7.0, 5.9 Hz, 2H), 4.79 (dd, *J* = 8.1, 2.8 Hz, 2H), 3.99 (dd, *J* =

9.5, 6.8 Hz, 2H), 3.61 (t, *J* = 8.6 Hz, 2H), 3.50 (td, *J* = 10.1, 5.9 Hz, 2H), 3.17 (qd, *J* = 14.0, 6.5 Hz, 4H), 2.09 (dq, *J* = 14.5, 8.3, 7.1 Hz, 2H), 1.99 (ddd, *J* = 12.2, 9.6, 6.3 Hz, 2H), 1.93 – 1.77 (m, 6H), 1.42 (dp, *J* = 14.2, 7.2 Hz, 2H), 1.19 – 1.08 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 6H), 0.65 (d, *J* = 6.8 Hz, 6H). Yield (43%), UPLC-MS (ELSD) purity: 99.9%, RT 1.07 min, HRMS m/z: $[M+H]^+$ Calcd for $C_{40}H_{55}N_6O_6$: 715.4178; found: 715.4166

S3. Selected ^{1}H NMR and ^{13}C NMR spectra of the synthesized target compounds

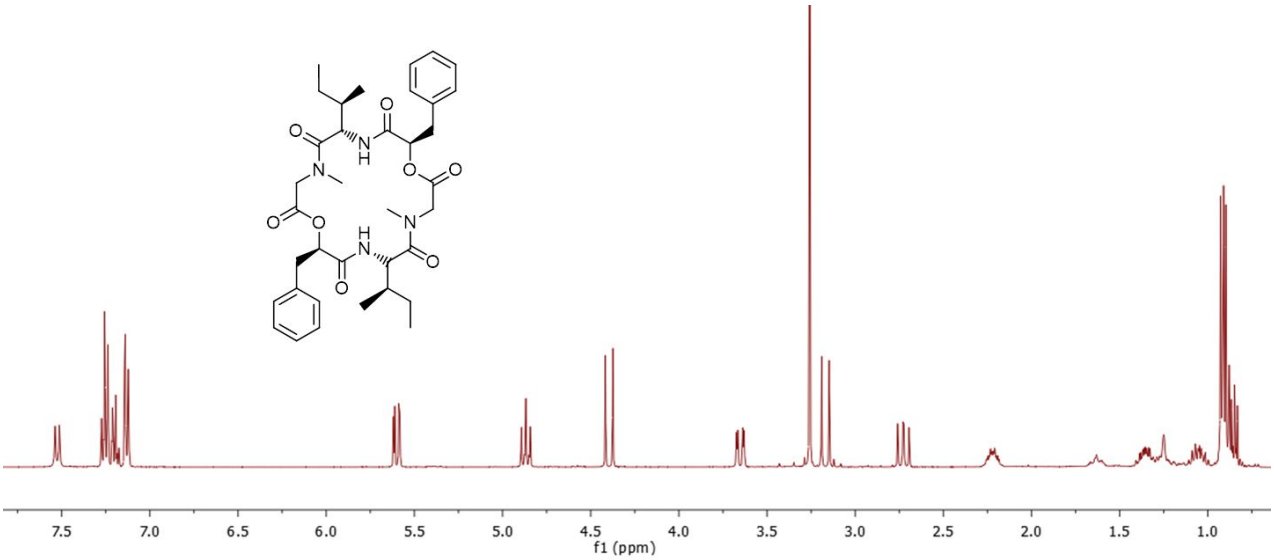


Figure S1: ^{1}HNMR (400 MHz, $CDCl_3$-d) spectrum of compound **9**

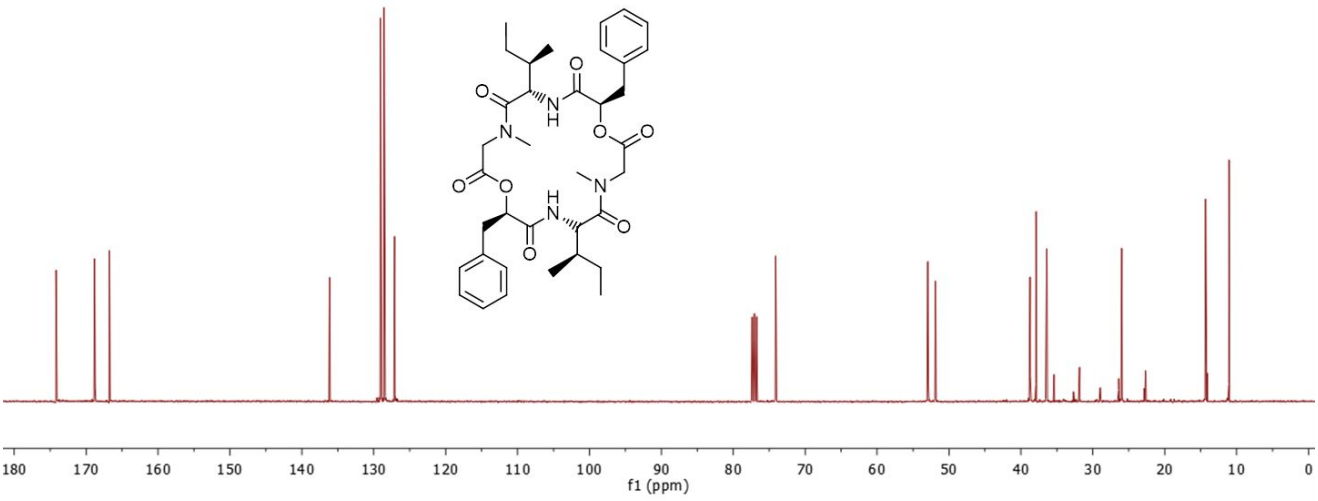


Figure S2: ^{13}C NMR (101 MHz, $CDCl_3$-d) spectrum of compound **9**

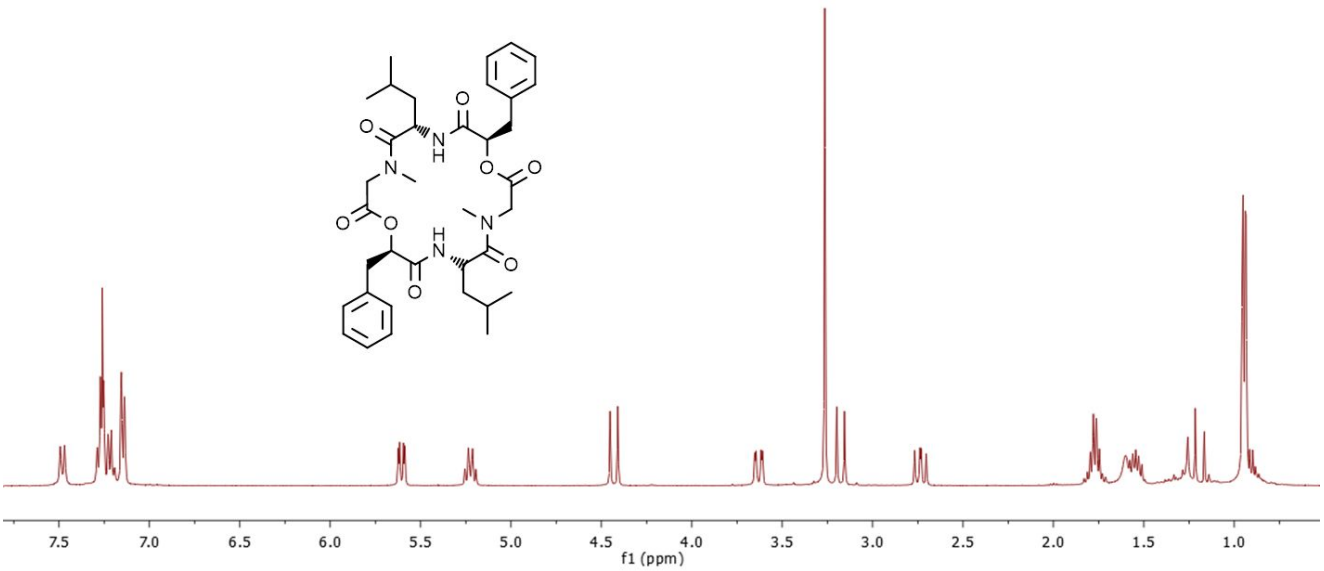


Figure S3: ^{1}H NMR (400 MHz, $CDCl_3$-d) spectrum of compound **10**

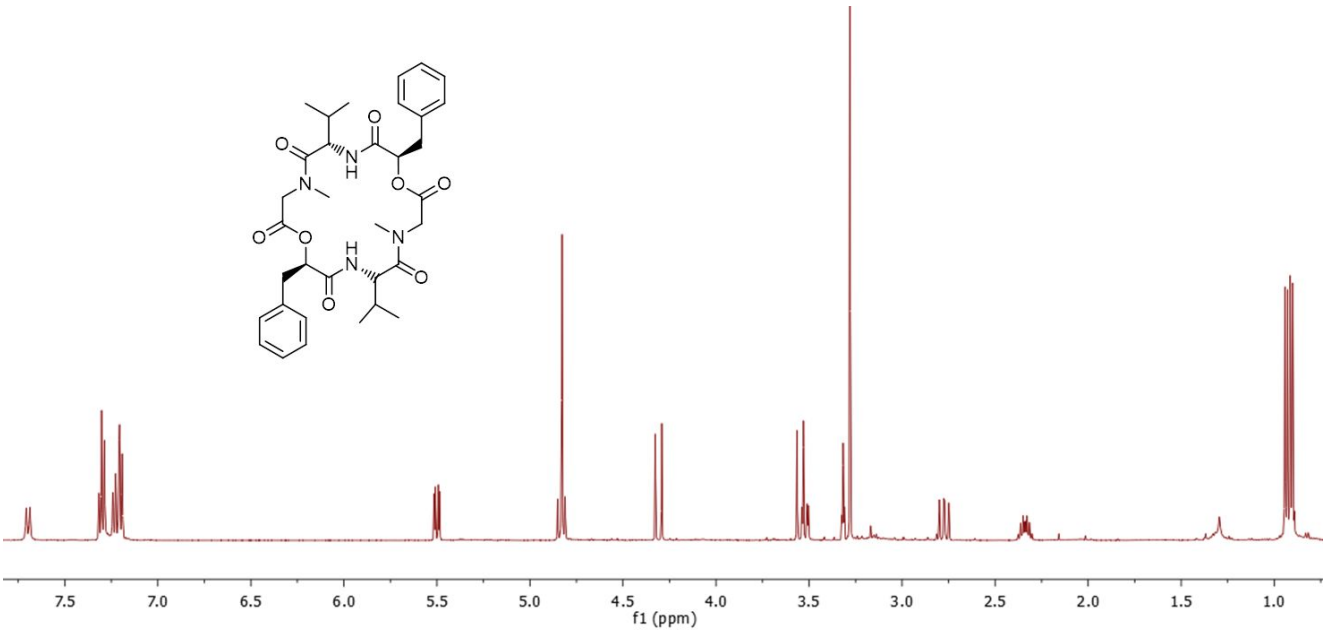


Figure S4: ^{1}HNMR (400 MHz, $CDCl_3$-d) spectrum of compound **11**

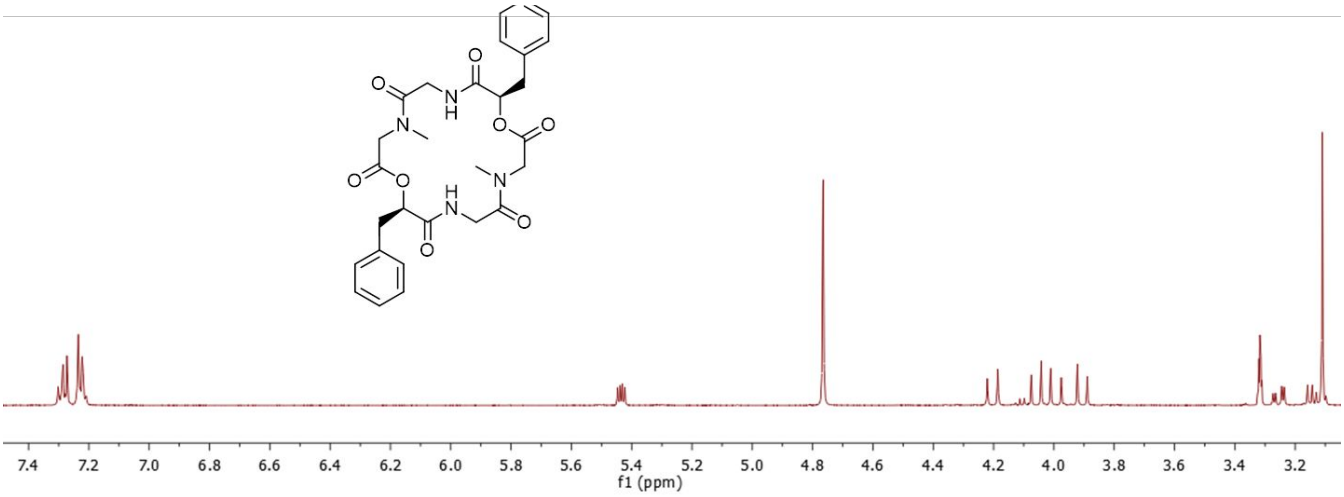


Figure S5: ^{1}HNMR (400 MHz, $CDCl_3$-d) spectrum of compound **12**

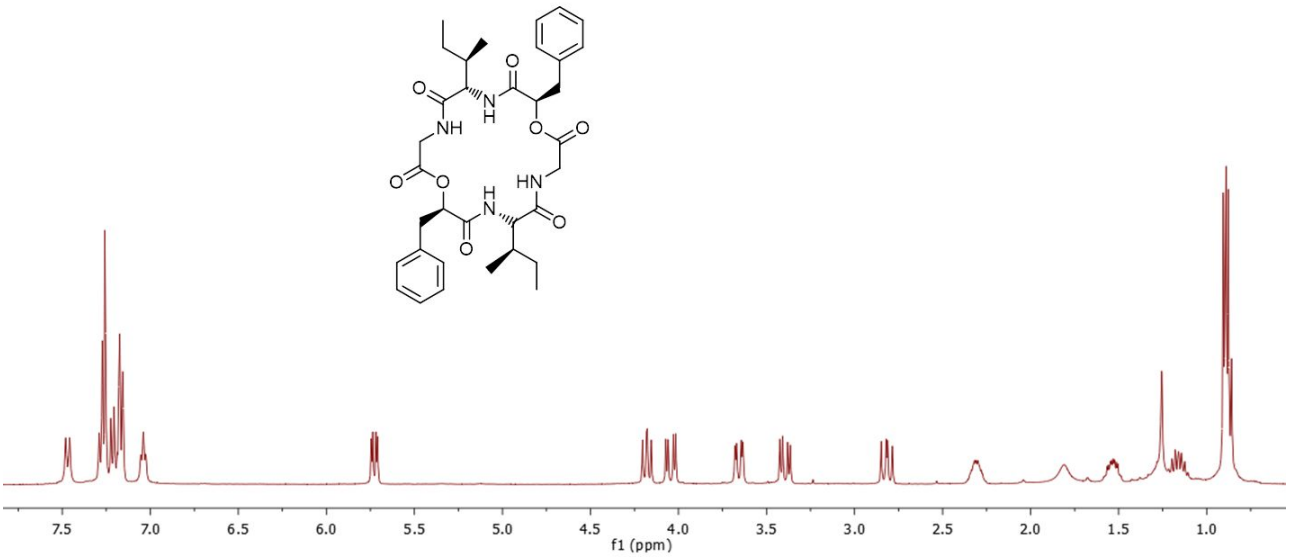


Figure S6: ^{1}HNMR (400 MHz, $CDCl_3$-d) spectrum of compound **13**

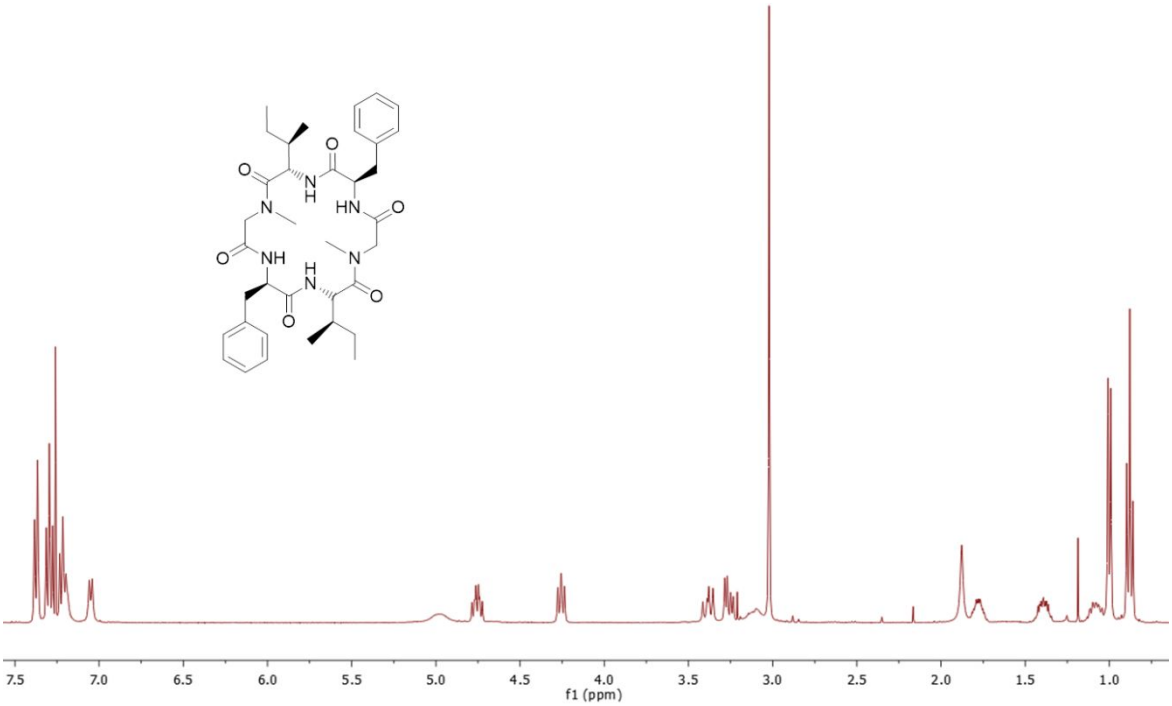


Figure S7: ^{1}HNMR (400 MHz, $CDCl_3$-d) spectrum of compound **16**

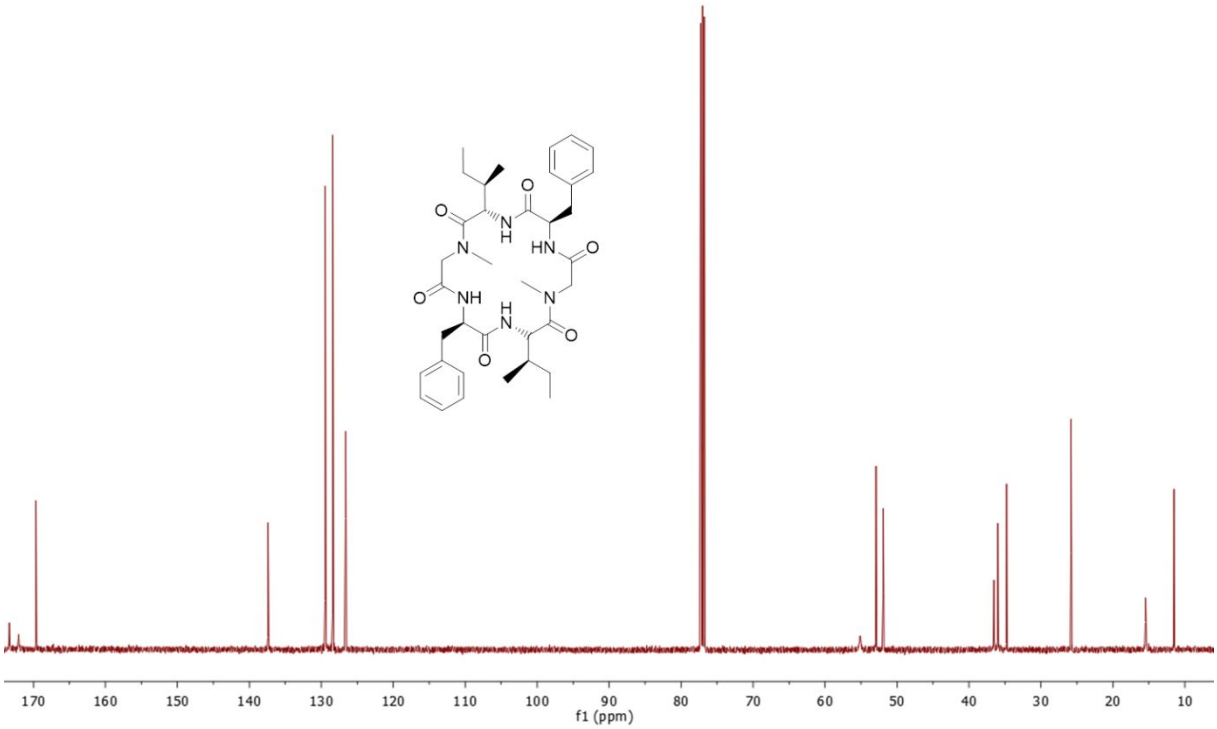


Figure S8: ^{13}C NMR (101 MHz, $CDCl_3$-d) spectrum of compound **16**

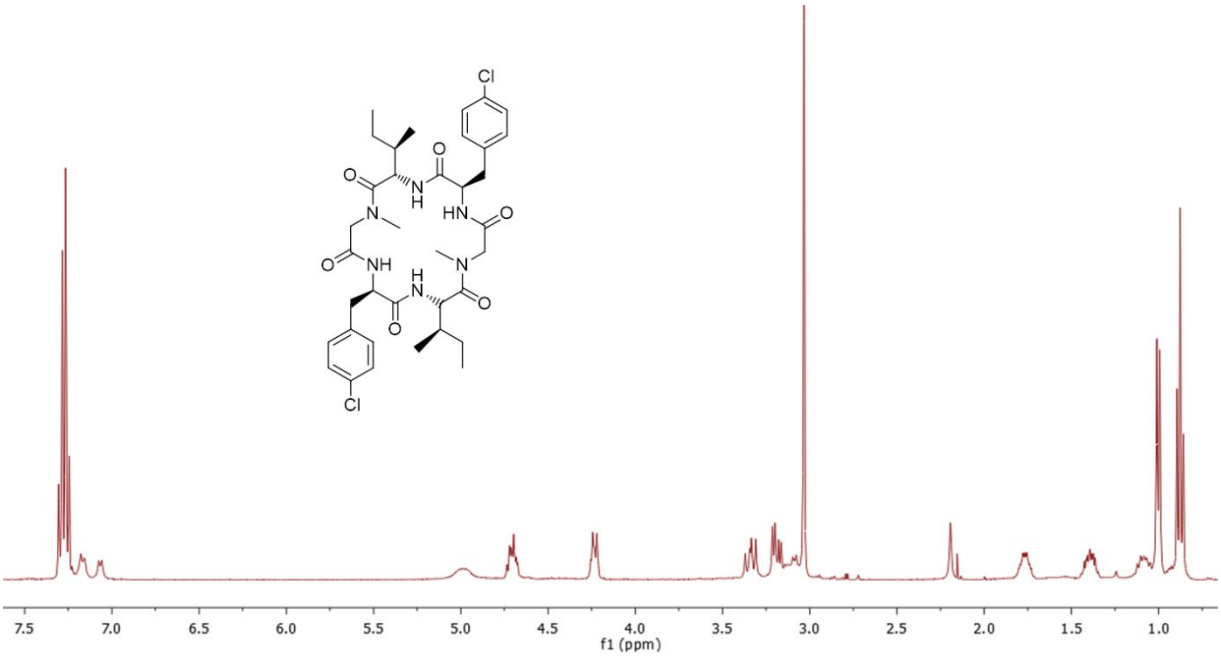


Figure S9: ^{1}HNMR (400 MHz, $CDCl_3$-d) spectrum of compound **17**

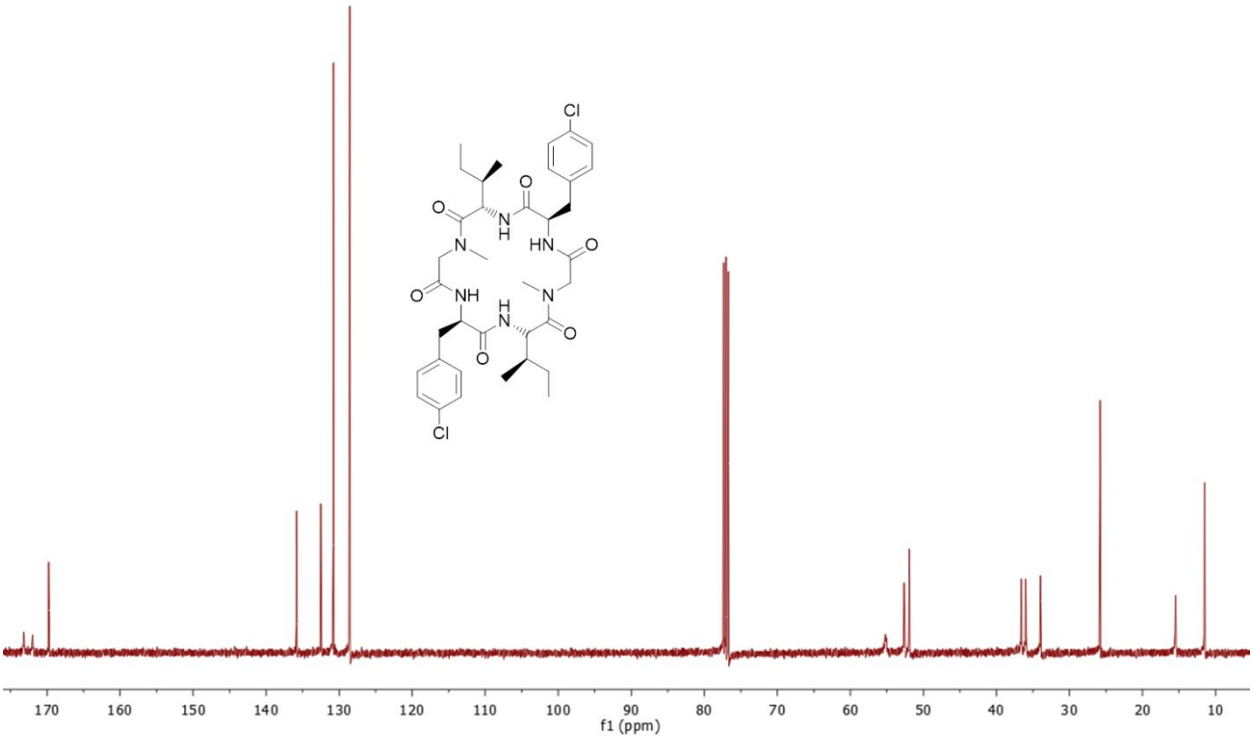


Figure S10: ^{13}C NMR (101 MHz, $CDCl_3$-d) spectrum of compound **17**

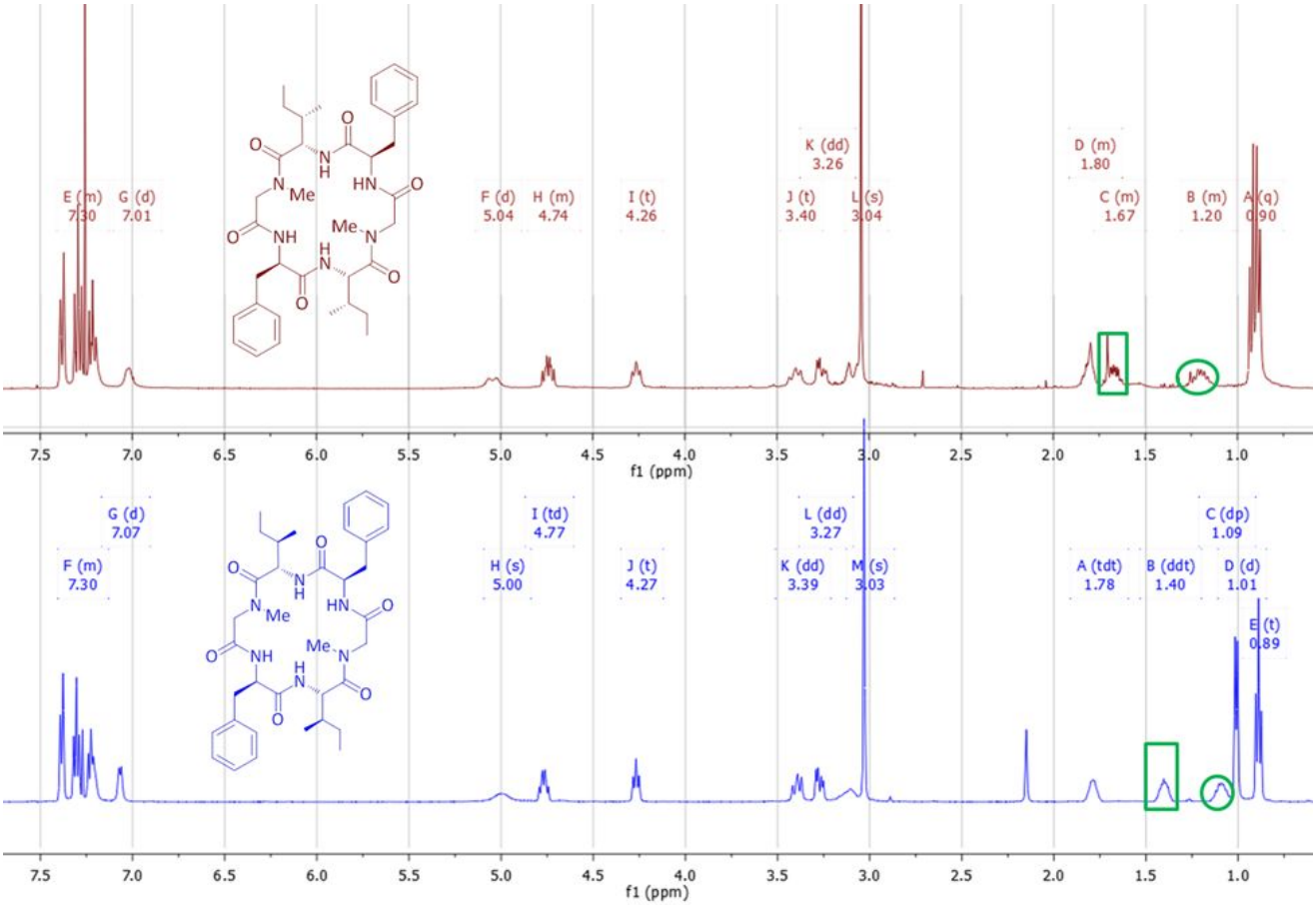


Figure S11: comparison of ^{1}H NMR spectra of peptide analogues (**14** and **16**) of hirsutellide A

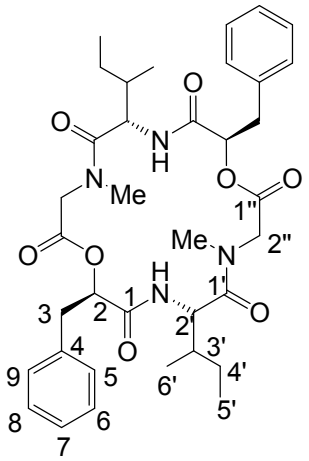


Table S1: Comparison of the ^{13}C chemical shifts of hirsutellide A, the stereoisomer (**II**) in the literature and the newly synthesized compound (**9**)

Unit		**δ_C, multiplicity (*J* in Hz)**		
		Hirsutellide A	**Streoisomer (II)**	**Compound 9**
2-hydroxy-3-phenyl-propanoic acid	1	168.8	168.8	168.8
	2	74.1	74.1	74.1
	3	38.7	38.7	38.7
	4	136.1	136.2	136.1
	5,9	129.1	129.1	129.1
	6,8	128.6	128.6	128.6
	7	127.1	127.1	127.1
L-*allo*-isoleucine	1‘	174.1	174.1	174.2
	2‘	52.3	52.3	52.9
	3‘	35.8	35.7	36.4
	4‘	24.2	24.3	26.0
	5‘	10.2	10.2	11.1
	6‘	15.4	15.4	14.3
Sarcosine	1‘‘	166.8	166.8	166.8
	2‘‘	51.7	51.8	51.9
	NMe	37.9	37.9	37.9

S4. HR-MS results of selected compounds

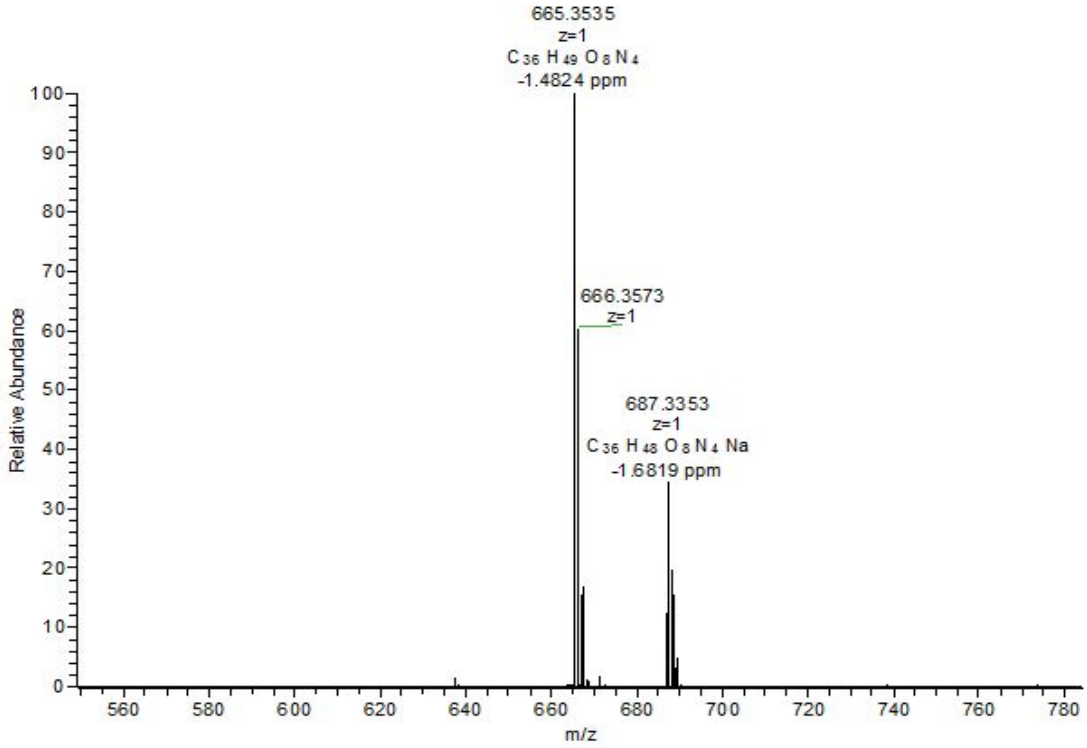


Figure S12: Result of HRMS m/z: $[M+H]^+$ for compound **9**

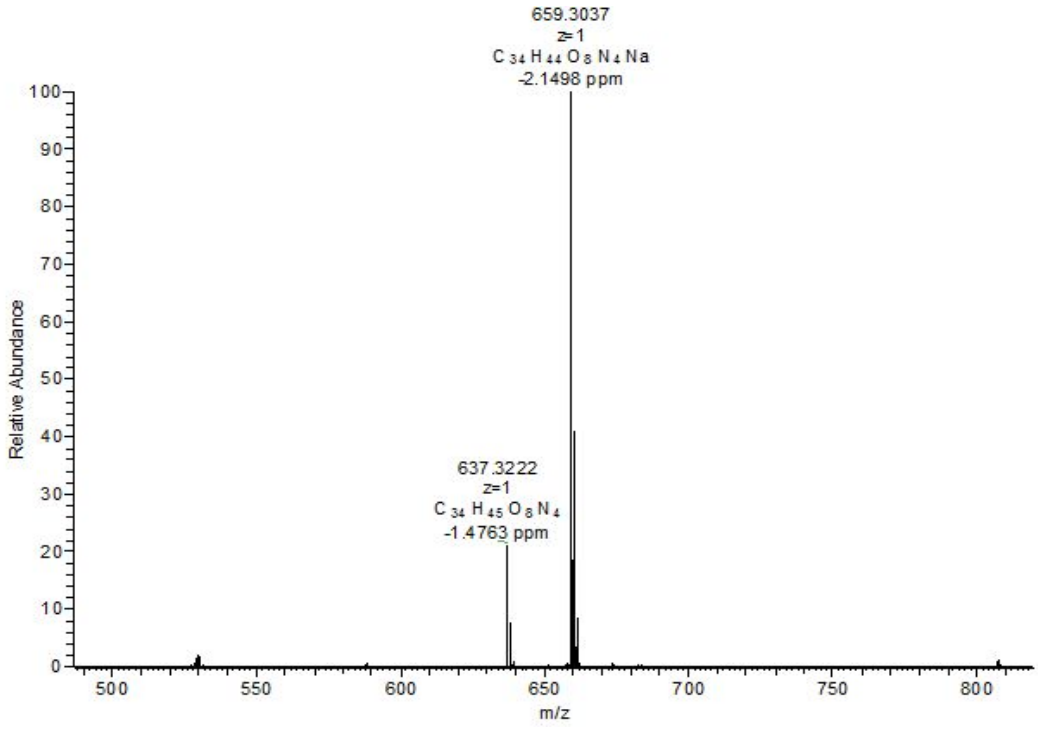


Figure S13: Result of HRMS m/z: $[M+H]^+$ for compound **11**

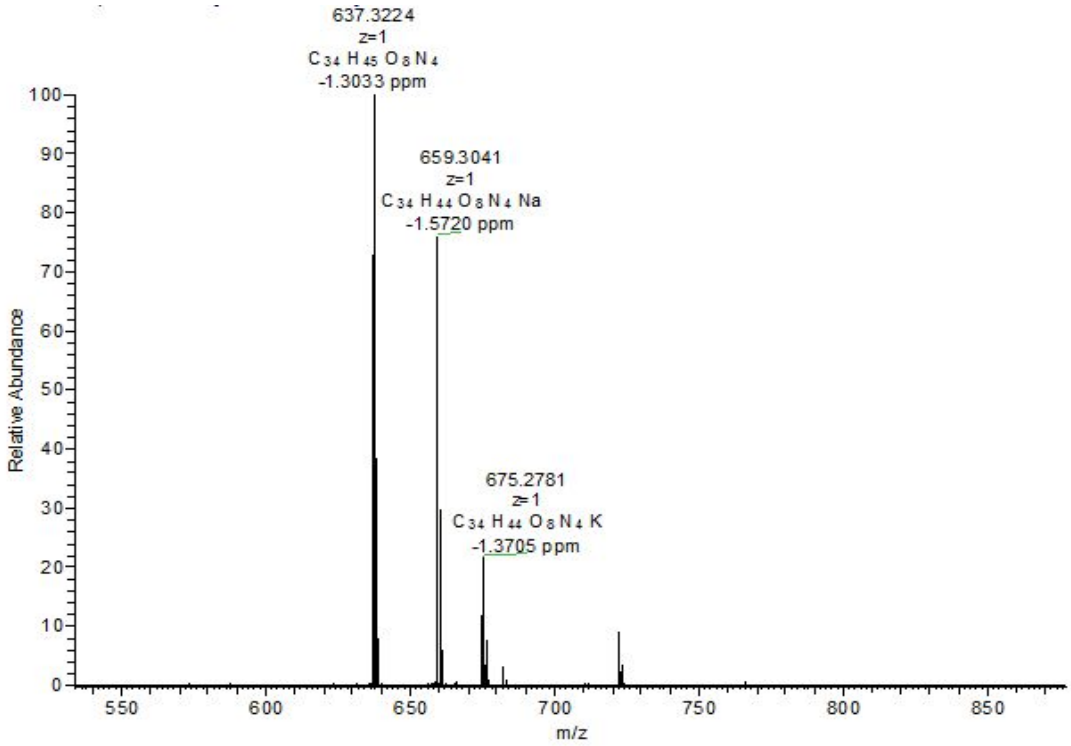


Figure S14: Result of HRMS m/z: $[M+H]^+$ for compound **13**

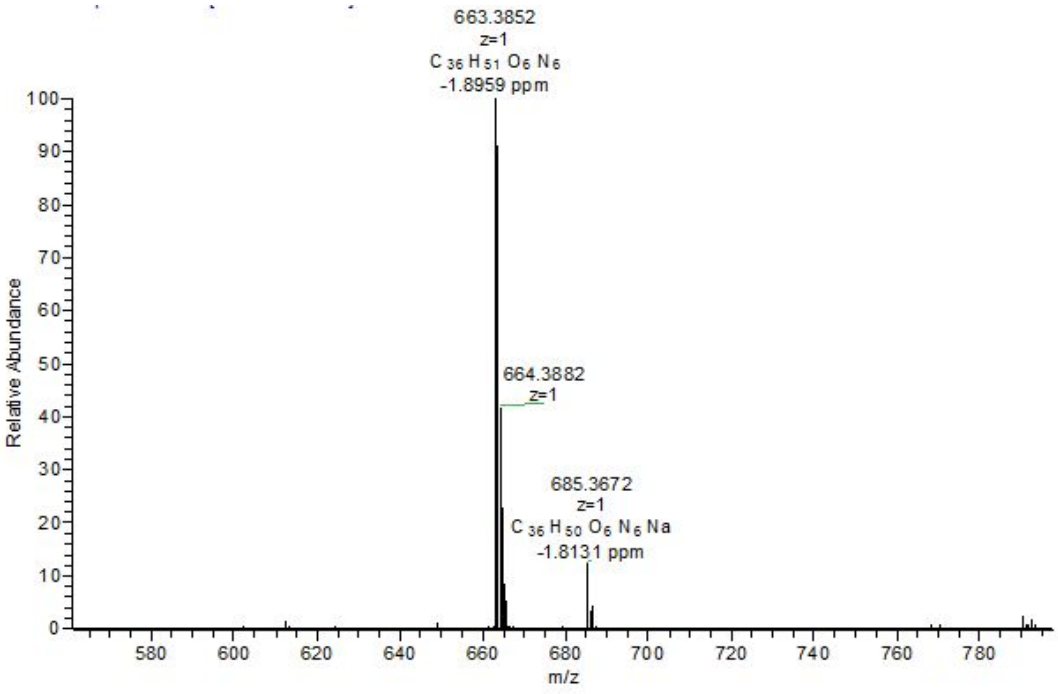


Figure S15: Result of HRMS m/z: $[M+H]^+$ for compound **14**

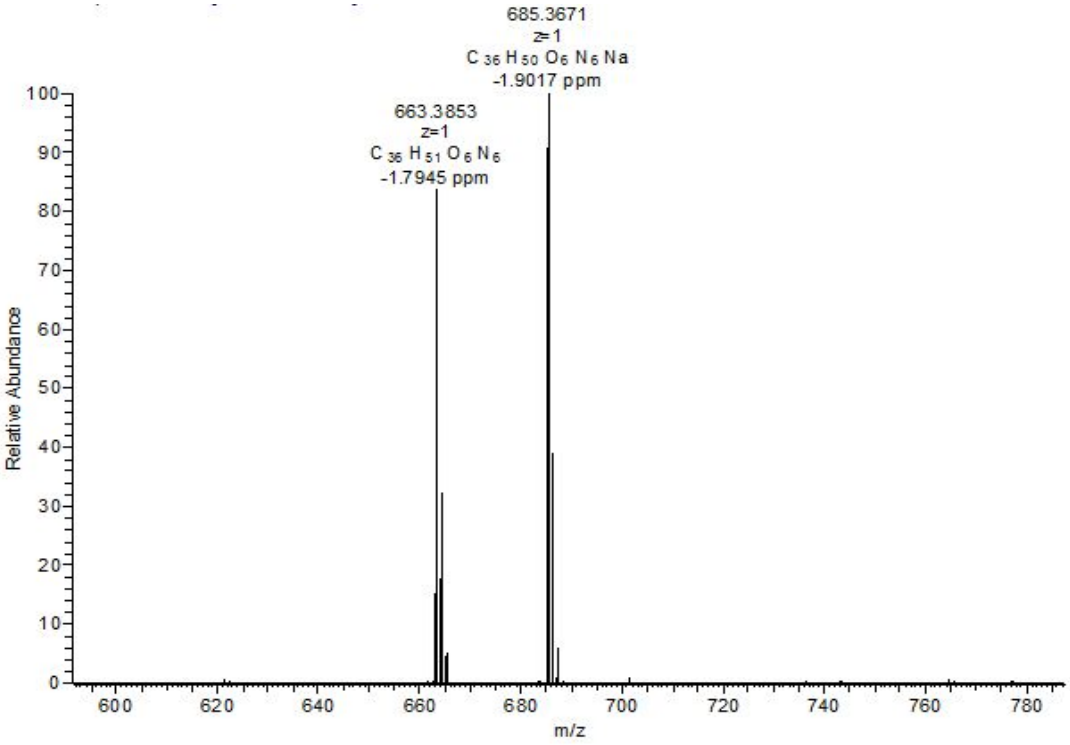


Figure S16: Result of HRMS m/z: $[M+H]^+$ for compound **16**

S5. UPLC-MS purity assay data for some selected compounds

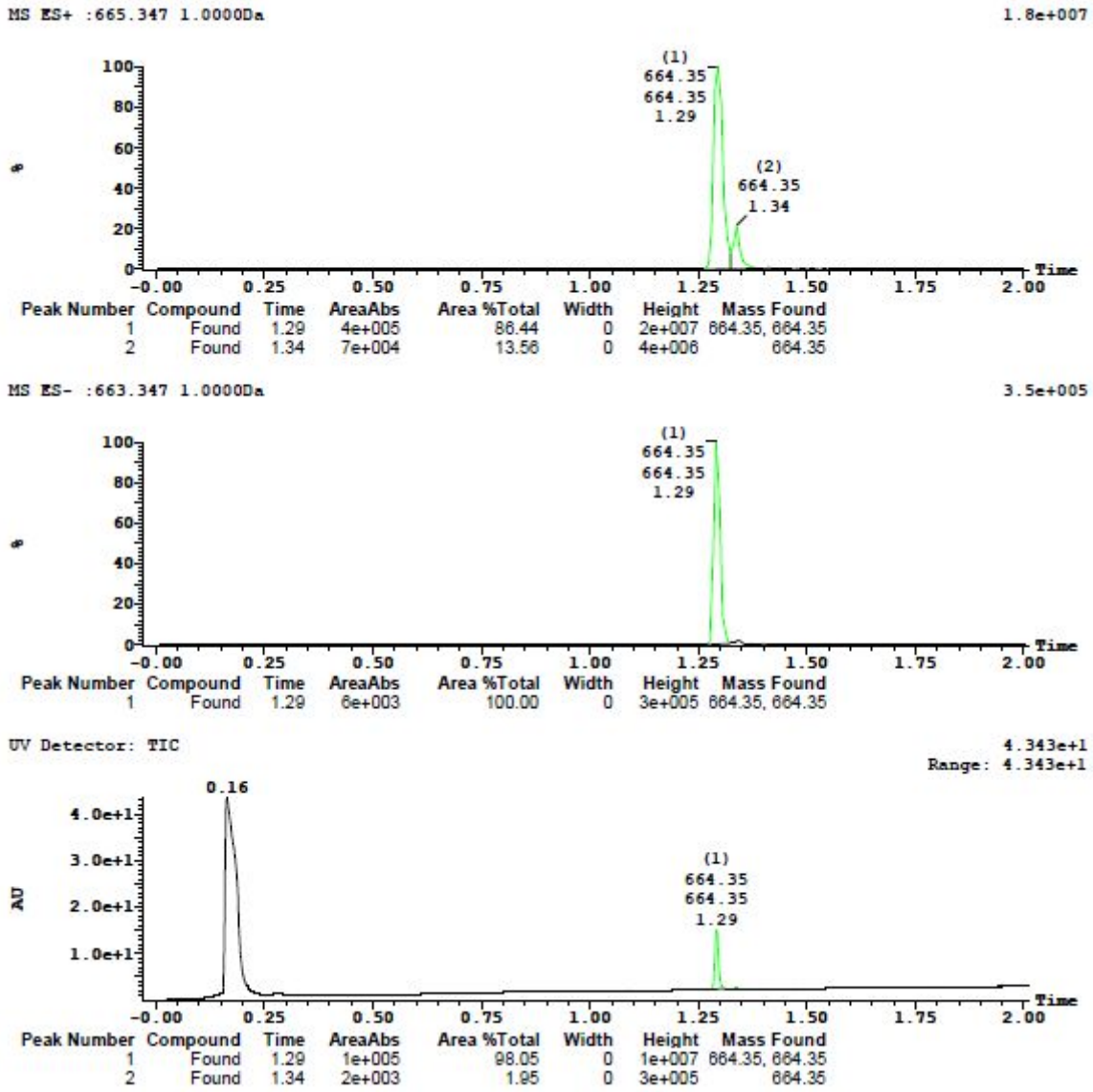


Figure S17: Result of UPLC-MS (UV) purity assay for compound **9**

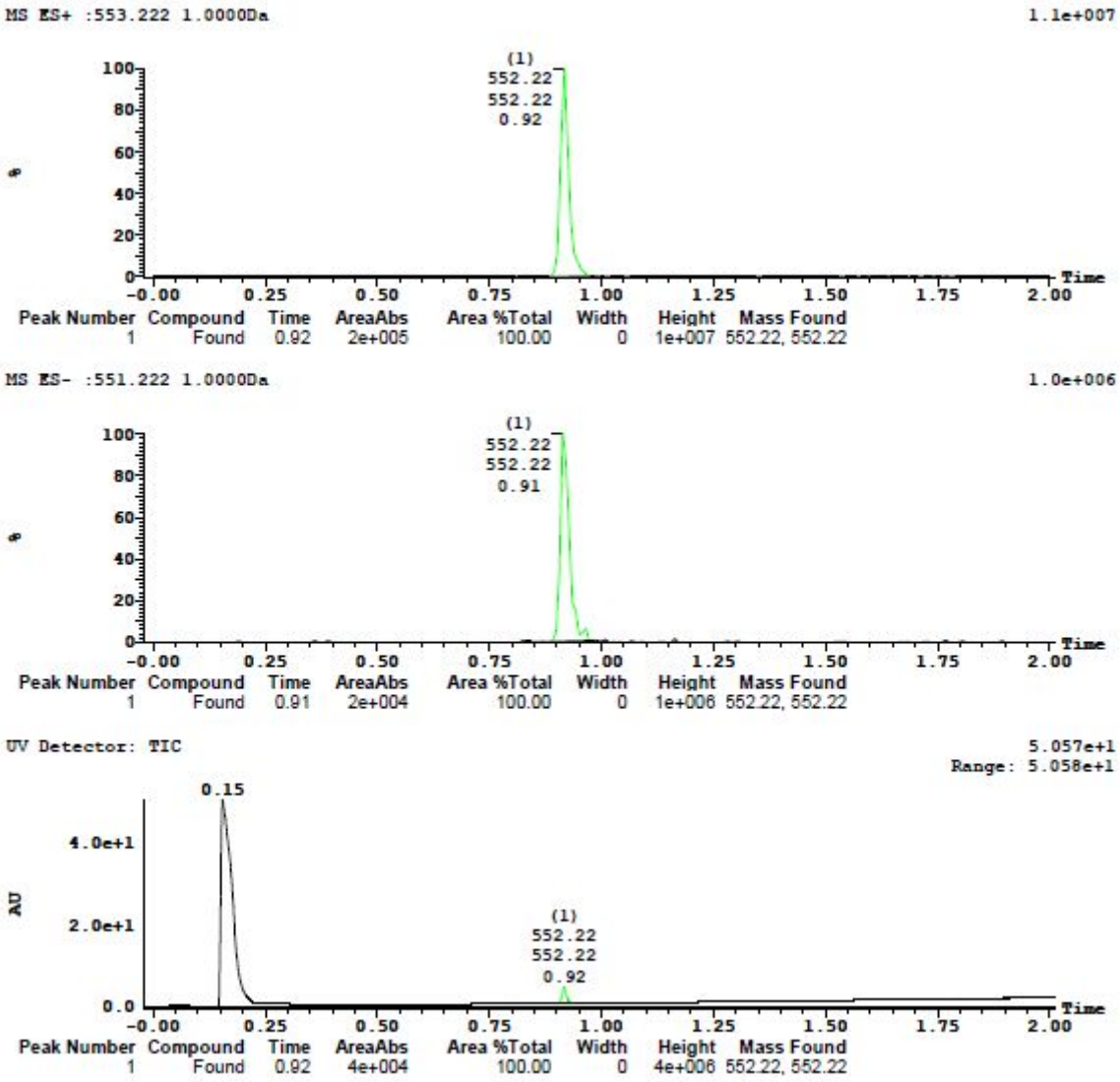


Figure S18: Result of UPLC-MS purity assay for compound **12**

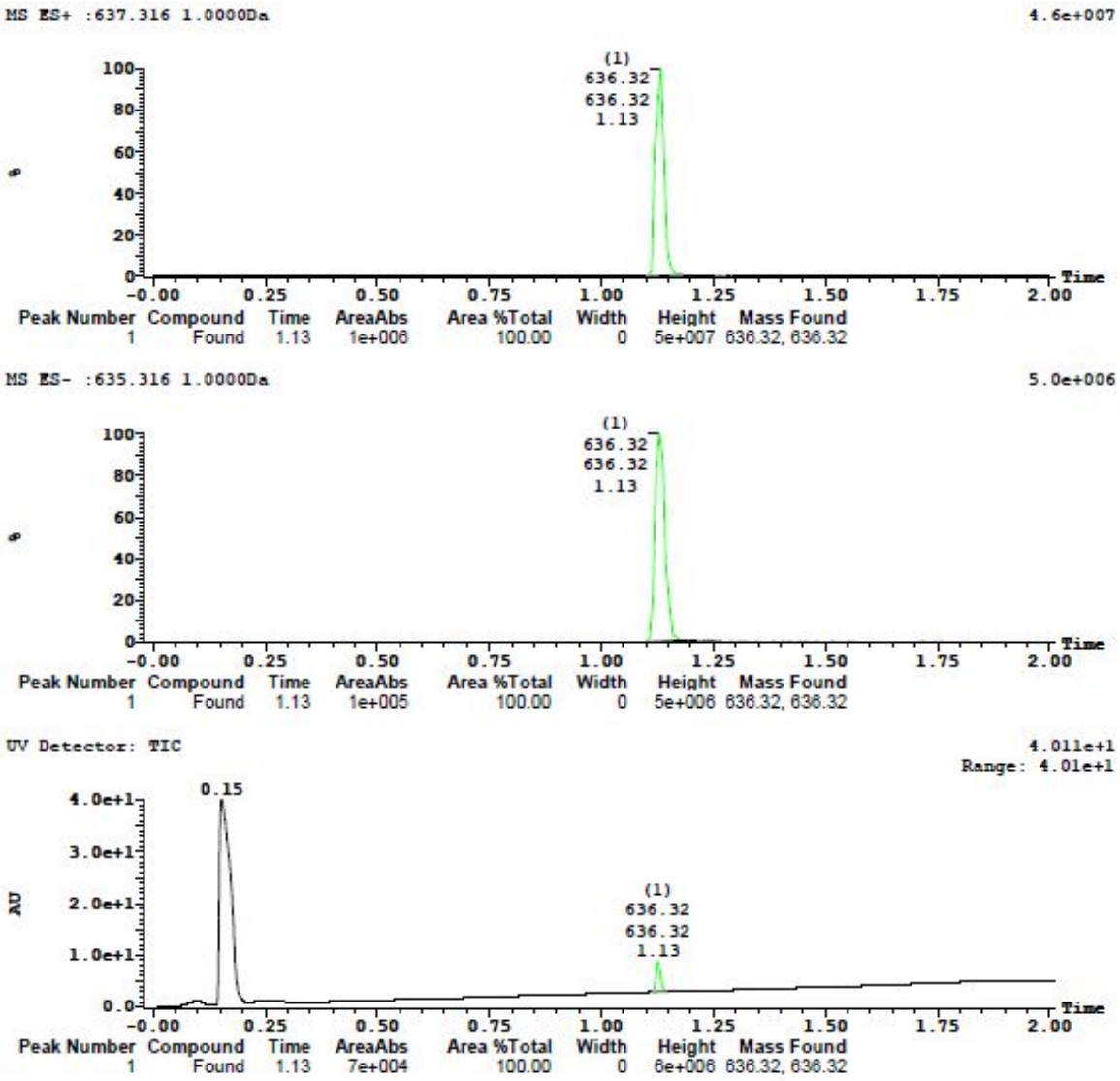


Figure S19: Result of UPLC-MS purity assay for compound **13**

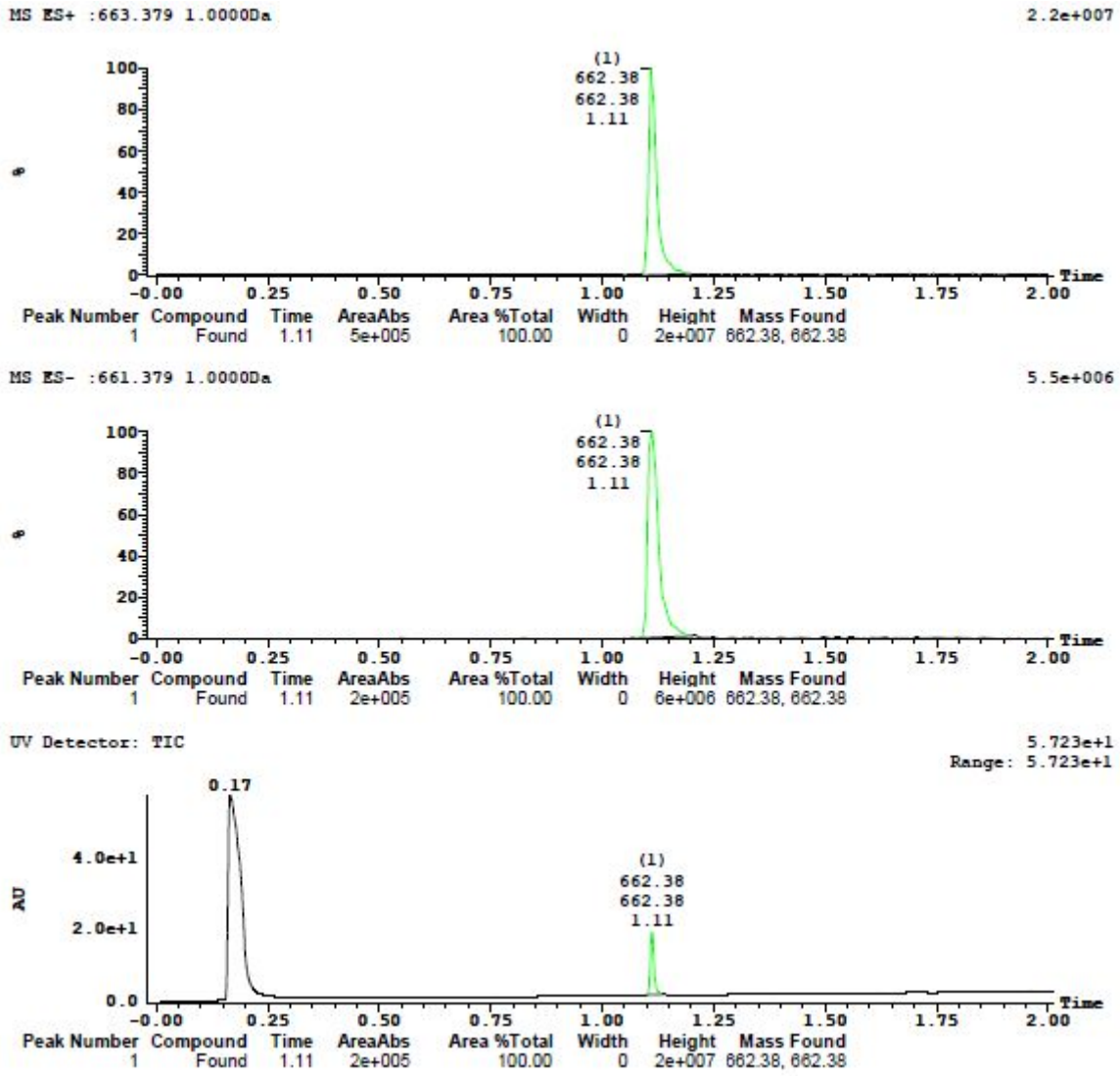


Figure S20: Result of UPLC-MS purity assay for compound **16**

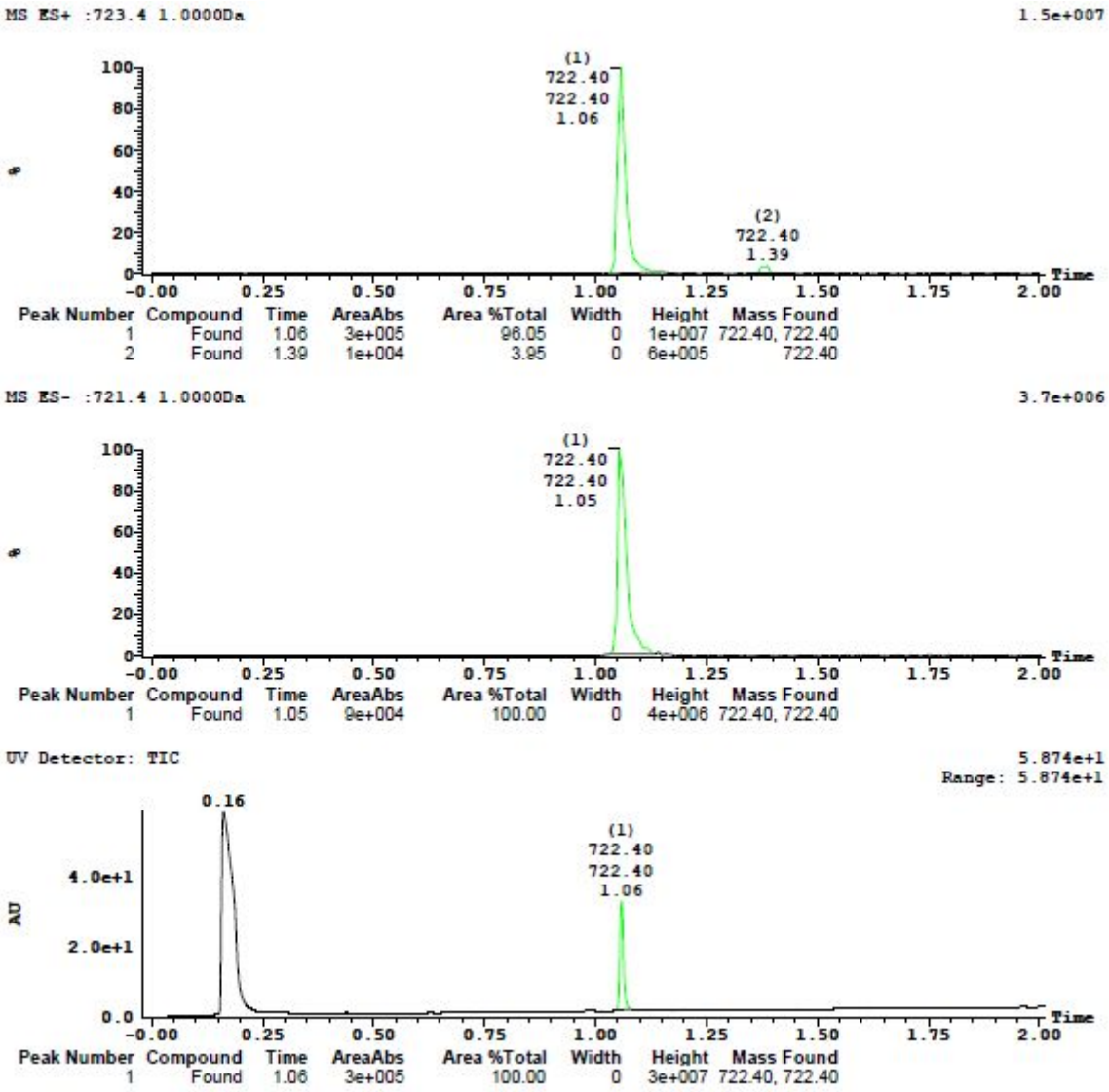


Figure S21: Result of UPLC-MS purity assay for compound **18**