Hydrazine hydrate facilitates efficient synthesis of cyclodipeptides for antibacterial screening

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Supporting Information

Contents

1. Syntheses and characterizations……...……S2

2. Chiral HPLC traces……...……S18

3. Absorption and CD spectra……S19

4. Crystal data……...……S21

5. ^{1}H NMR and ^{13}C NMR spectra……..S24

6. HRMS spectra……....…….……S56

1. Syntheses and characterizations

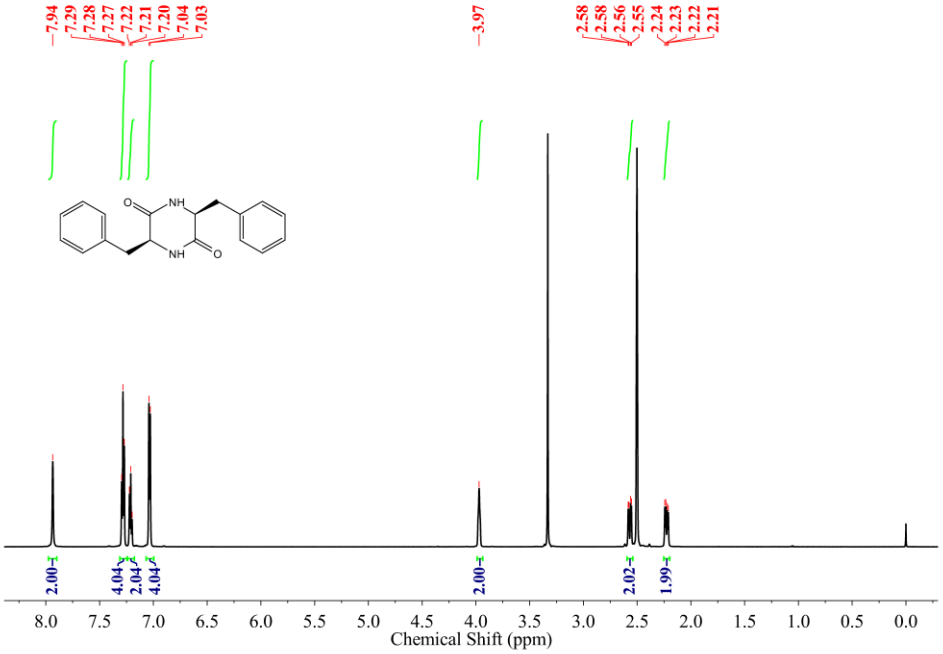


Figure S1. ^{1}H NMR spectrum (600 MHz, DMSO-d_6) of the product obtained via the synthetic route depicted in **Scheme 2**. The presence of only one set of proton signals for the phenylalanine residues indicates a high degree of structural symmetry, consistent with the cyclic diphenylalanine structure **1**.

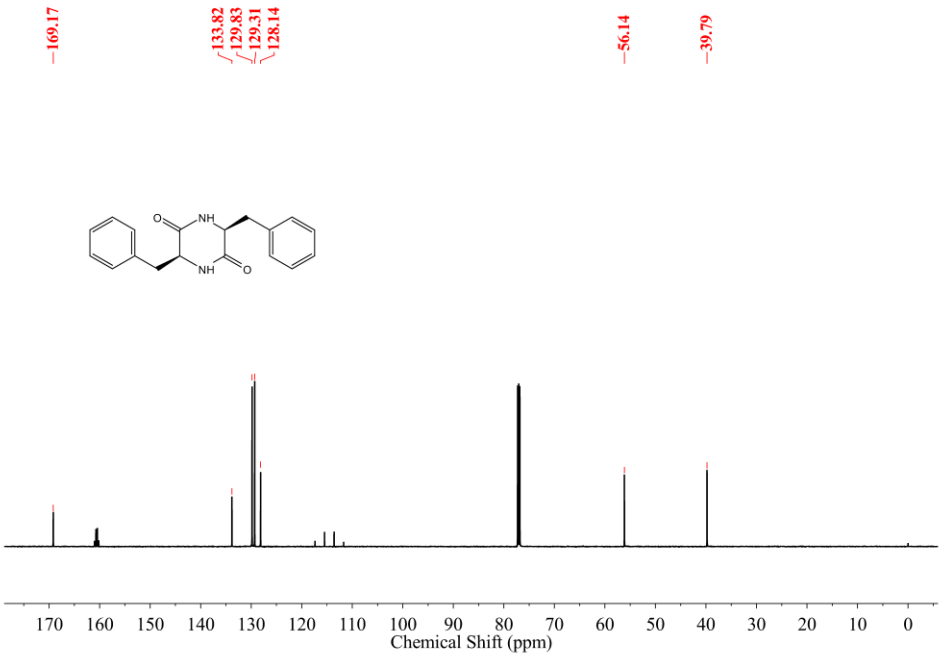


Figure S2. ^{13}C NMR spectrum (151 MHz, $CDCl_3$-CF_3COOH) of the product obtained via the synthetic depicted in **Scheme 2**, which is consistent with the structure of cyclic diphenylalanine **1**.

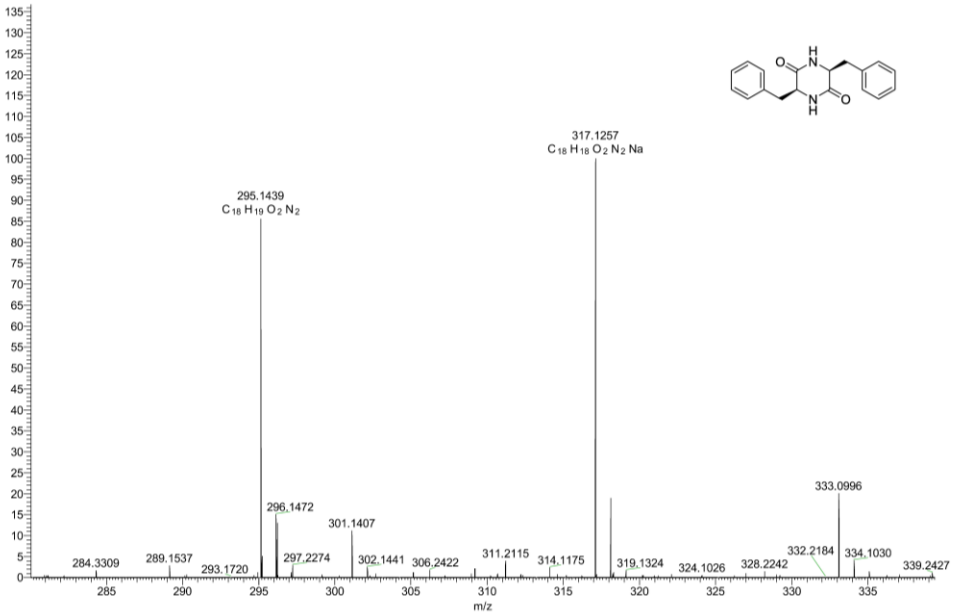


Figure S3. HRMS spectrum of the product obtained via the synthetic route depicted in **Scheme 2**, which is consistent with the structure of cyclic diphenylalanine **1**.

Table S1. Crystal data and structure refinement for the product obtained via the synthetic route depicted in **Scheme 2** [a]

Identification code	exp_6055_auto
Empirical formula	$C_{18}H_{18}N_2O_2$
Formula weight	294.34
Temperature/K	100.00(10)
Crystal system	orthorhombic
Space group	$P2_12_12$
a/Å	23.3026(3)
b/Å	10.36460(10)
c/Å	6.15900(10)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1487.53(3)
Z	4
ρ_{calc}g/cm^3	1.314
μ/mm^{-1}	0.695
F(000)	624.0
Crystal size/mm^3	0.26 × 0.22 × 0.18
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.588 to 153.79
Index ranges	$-29 \le h \le 29$, $-12 \le k \le 13$, $-5 \le l \le 7$
Reflections collected	14316
Independent reflections	3036 [R_{int} = 0.0479, R_{sigma} = 0.0340]
Data/restraints/parameters	3036/0/199
Goodness-of-fit on F^2	1.080
Final R indexes [I>=2σ (I)]	R_1 = 0.0450, wR_2 = 0.1229
Final R indexes [all data]	R_1 = 0.0471, wR_2 = 0.1242
Largest diff. peak/hole / e Å^{-3}	0.31/-0.24
Flack parameter	0.09(14)

[a] Grown in DMSO solution via slow evaporation.

Table S2. Yields of **1** obtained in the cyclization reactions using 36.2 mg of **1-a** in EtOH (1.0 mL) stirred at 25 ºC for 12 h in the presence of different amounts of $N_2H_4 \cdot H_2O$

Entry	$N_2H_4 \cdot H_2O$ / equiv	Yield / % [a]
1	0	0
2	0.5	34
3	1.0	74
4	2.0	97

[a] Reaction yields determined by ^{1}H NMR spectra.

Table S3. Yields of **1** obtained in the cyclization reactions using 36.2 mg of **1-a** in EtOH (1.0 mL) stirred at different temperatures for 12 h in the presence of 2.0 equiv $N_2H_4 \cdot H_2O$

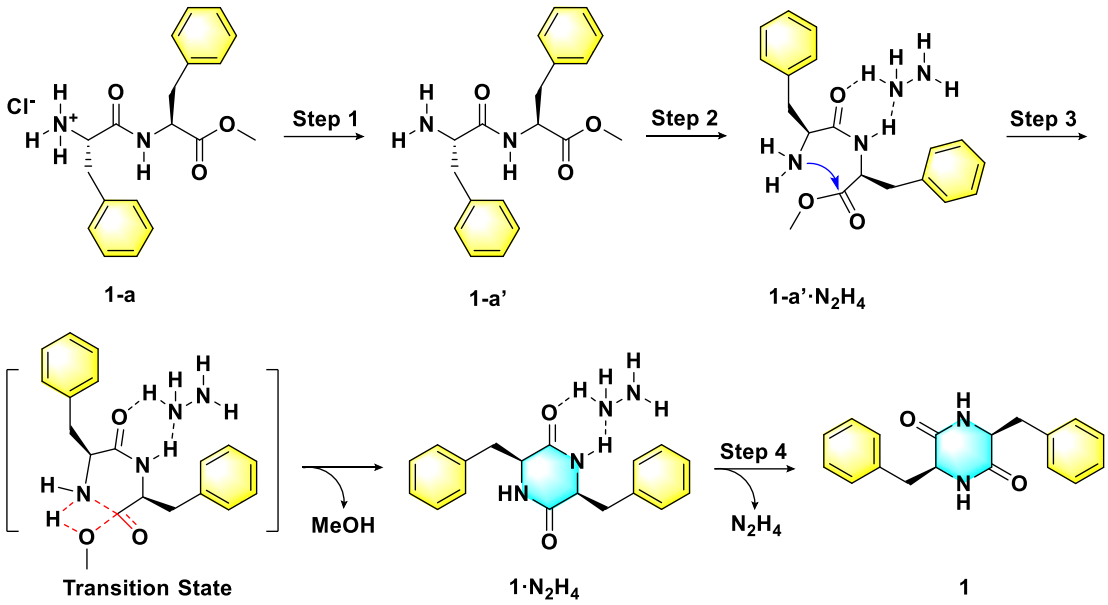
Entry	T / ºC	Yield / % [a]
1	25	97
2	40	97
3	60	99
4	80	99

[a] Reaction yields determined by ^{1}H NMR spectra.

Table S4. Yields of **1** obtained in the cyclization reactions using 36.2 mg of **1-a** in EtOH (1.0 mL) stirred at 25 ºC for different durations in the presence of 2.0 equiv $N_2H_4 \cdot H_2O$

Entry	Time / h	Yield / % [a]
1	3	65
2	6	82
3	12	97
4	24	98

[a] Reaction yields determined by ^{1}H NMR spectra.



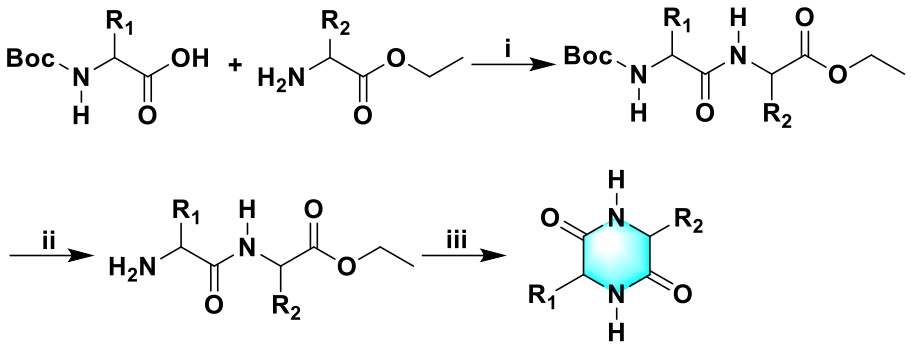
Scheme S1. Plausible mechanism for the intramolecular aminolysis cyclization. The efficient cyclization of the linear dipeptide to the diketopiperazine **1** is facilitated by the multifunctional role of hydrazine hydrate ($N_2H_4·H_2O$). The process involves initial deprotonation, conformational preorganization via hydrogen bonding, and a concerted cyclization step, accounting for the mild reaction conditions and high yield.

Step 1: Deprotonation. One equivalent of $N_2H_4·H_2O$ acts as a mild base to deprotonate the hydrochloride salt (**1-a**), affording the free linear dipeptide (**1-a'**).

Step 2: Preorganization. A second equivalent of hydrazine forms hydrogen bonds with the dipeptide backbone, shifting the conformational equilibrium towards the otherwise disfavored *cis*-amide conformer. This brings the nucleophilic amine into close proximity to the methyl ester.

Step 3: Concerted Cyclization. In the basic microenvironment, intramolecular aminolysis proceeds via a low-energy cyclic transition state involving hydrazine-mediated proton shuttling. This yields the cyclic dipeptide-hydrazine complex (**1·N_2H_4**).

Step 4: Isolation. The free diketopiperazine **1** precipitates directly from the reaction mixture and is obtained after simple washing to remove residual hydrazine.

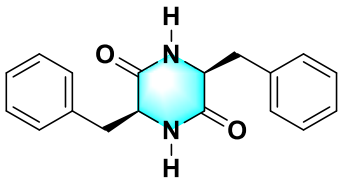


Scheme S2. Developed three-step synthetic procedure for cyclodipeptides using *N*-Boc-protected amino acids and amino acid ethyl ester as initial substrates.

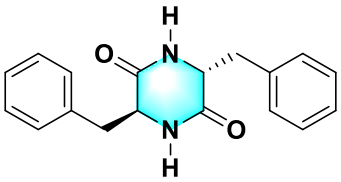
(i) To a chilled solution of Boc-protected amino acid containing R_1 side chain (10.0 mmol) and Et_3N (10.0 mmol) in $CHCl_3$ (30 mL) was added 1-hydroxybenzotriazole (HOBT, 11.0 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 11.0 mmol) at 0 ºC. After stir for 30 min, amino acid ethyl ester hydrochloride containing R_2 side chain (10.0 mmol) was added. The mixture was left to stand at room temperature for 24 hours, evaporated *in vacuo*, and the solid residue was dissolved in EtOAc. The solution was washed successively with 1% $NH_3{\cdot}H_2O$, 1% HCl and saturated NaCl, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, to obtain Boc-protected dipeptide ethyl ester.

(ii) 10 mL CH_2Cl_2 and 10 mL CF_3COOH was added in Boc-protected dipeptide ethyl ester, and then the solution was stirred at room temperature for 5 hours, evaporated *in vacuo* at room temperature to obtain dipeptide ethyl ester in the trifluoroacetate salt form.

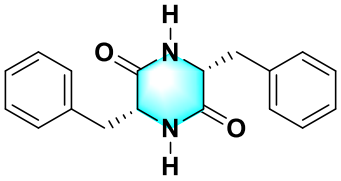
(iii) To the solution of dipeptide ethyl ester in EtOH (30 mL), $N_2H_4{\cdot}H_2O$ (85%, 6 mL, 11 equiv) was added, and then the solution was stirred at 25 ºC for 24 hours, evaporated *in vacuo* at room temperature. Purification via washing by ethyl ether or recrystallization, to obtain pure cyclodipeptide product.



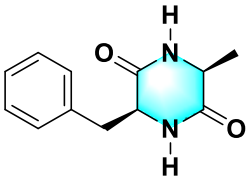
1: Purification via washing by ethyl ether to obtain 2.66 g white solid. Overall yield: 90%. Mp > 320.0 ºC. $[\alpha]_D$ = -114.0º (*c* 0.1, DMSO). IR (KBr): 3211 cm^{-1}, 3054 cm^{-1}, 2947 cm^{-1}, 1665 cm^{-1}, 1457 cm^{-1}, 1336 cm^{-1}, 760 cm^{-1}, 700 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.94 (s, 2H), 7.28 (t, J = 7.5 Hz, 4H), 7.21 (t, J = 7.3 Hz, 2H), 7.03 (d, J = 7.3 Hz, 4H), 3.97 (s, 2H), 2.57 (dd, J = 13.6, 4.7 Hz, 2H), 2.23 (dd, J = 13.6, 6.1 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$-CF_3COOH): δ (ppm) 169.17, 133.82, 129.83, 129.31, 128.14, 56.14, 39.79. HRMS (ESI): calcd for $[C_{18}H_{19}N_2O_2]^+$: 295.1441, found: 295.1439.



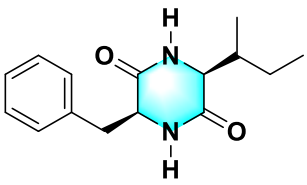
2: Purification via washing by ethyl ether to obtain 2.66 g white solid. Overall yield: 90%. Mp = 293.6~295.2 ºC. $[\alpha]_D$ = 0.0º (*c* 0.1, DMSO). IR (KBr): 3202 cm^{-1}, 3077 cm^{-1}, 2970 cm^{-1}, 1675 cm^{-1}, 1455 cm^{-1}, 1330 cm^{-1}, 845 cm^{-1}, 700 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 8.04 (s, 2H), 7.29 – 7.18 (m, 6H), 7.13 (d, *J* = 6.7 Hz, 4H), 3.39 (s, 2H), 3.00 (dd, *J* = 13.5, 3.1 Hz, 2H), 2.72 (dd, *J* = 13.6, 4.6 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$-CF_3COOH): δ (ppm) 170.42, 133.24, 129.71, 129.25, 128.22, 55.45, 39.00. HRMS (ESI): calcd for $[C_{18}H_{19}N_2O_2]^+$: 295.1441, found: 295.1436.



3: Purification via washing by ethyl ether to obtain 2.68 g white solid. Overall yield: 91%. Mp > 320.0 ºC. $[\alpha]_D$ = +114.0º (*c* 0.1, DMSO). IR (KBr): 3206 cm^{-1}, 3060 cm^{-1}, 2958 cm^{-1}, 1669 cm^{-1}, 1457 cm^{-1}, 1342 cm^{-1}, 756 cm^{-1}, 700 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.93 (s, 2H), 7.28 (t, *J* = 7.5 Hz, 4H), 7.21 (t, *J* = 7.2 Hz, 2H), 7.03 (d, *J* = 7.5 Hz, 4H), 3.97 (s, 2H), 2.57 (dd, *J* = 13.6, 4.8 Hz, 2H), 2.23 (dd, *J* = 13.6, 6.2 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$-CF_3COOH): δ (ppm) 169.02, 133.86, 129.82, 129.28, 128.09, 56.13, 39.79. HRMS (ESI): calcd for $[C_{18}H_{19}N_2O_2]^+$: 295.1441, found: 295.1466.

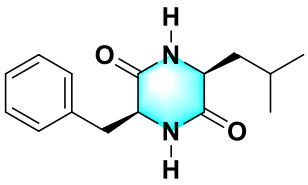


4: Purification via washing by ethyl ether to obtain 1.73 g white solid. Overall yield: 79%. Mp = 295.6~297.2 ºC. $[\alpha]_D$ = -6.7º (*c* 0.1, DMSO). IR (KBr): 3190 cm^{-1}, 3046 cm^{-1}, 2984 cm^{-1}, 2902 cm^{-1}, 1667 cm^{-1}, 1463 cm^{-1}, 1336 cm^{-1}, 869 cm^{-1}, 698 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 8.12 (s, 1H), 8.02 (s, 1H), 7.28 (t, *J* = 7.4 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.15 (d, *J* = 7.0 Hz, 2H), 4.17 (s, 1H), 3.62 (q, *J* = 6.9 Hz, 1H), 3.12 (dd, *J* = 13.4, 3.7 Hz, 1H), 2.85 (dd, *J* = 13.4, 4.9 Hz, 1H), 0.46 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 168.13, 166.28, 136.52, 130.84, 128.49, 127.12, 55.82, 50.17, 38.78, 20.16. HRMS (ESI): calcd for $[C_{12}H_{15}N_2O_2]^+$: 219.1123, found: 219.1135.

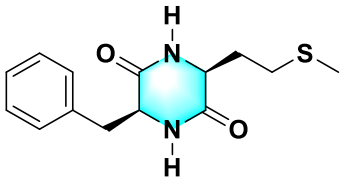


5: Purification via washing by ethyl ether to obtain 2.14 g white solid. Overall yield: 82%. Mp = 271.2~272.9 ºC. $[\alpha]_D$ = -58.3º (*c* 0.1, DMSO). IR (KBr): 3192 cm^{-1}, 3056 cm^{-1}, 2966 cm^{-1}, 2880 cm^{-1}, 1667 cm^{-1}, 1455 cm^{-1}, 1334 cm^{-1}, 859 cm^{-1}, 700 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 8.10 (s, 1H), 7.88 (s, 1H), 7.50 – 6.78 (m, 5H), 4.21 (s, 1H), 3.58 (s, 1H), 3.16 (dd, *J* = 13.2, 3.0 Hz, 1H), 2.85 (dd, *J* = 13.2, 4.2 Hz, 1H), 1.40 (s, 1H), 0.66 (q, *J* = 15.3, 10.2 Hz, 1H), 0.62 – 0.47 (m, 7H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 166.87, 166.82,

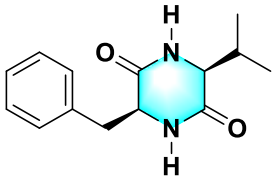
136.76, 130.89, 128.37, 126.94, 59.18, 55.48, 38.24, 38.04, 23.58, 14.91, 12.26. HRMS (ESI): calcd for $[C_{15}H_{21}N_2O_2]^+$: 261.1592, found: 261.1590.



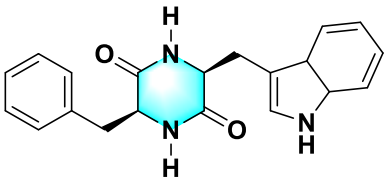
6: Purification via washing by ethyl ether to obtain 2.17 g white solid. Overall yield: 83%. Mp = 279.8~280.7 ºC. $[\alpha]_D$ = -26.0º (*c* 0.1, DMSO). IR (KBr): 3194 cm^{-1}, 3048 cm^{-1}, 2964 cm^{-1}, 2892 cm^{-1}, 1677 cm^{-1}, 1461 cm^{-1}, 1336 cm^{-1}, 1095 cm^{-1}, 846 cm^{-1}, 758 cm^{-1}, 705 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 8.10 (s, 1H), 8.06 (s, 1H), 7.27 (t, *J* = 7.3 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.14 (d, *J* = 7.0 Hz, 2H), 4.16 (s, 1H), 3.51 – 3.43 (m, 1H), 3.13 (dd, *J* = 13.4, 3.8 Hz, 1H), 2.83 (dd, *J* = 13.4, 4.9 Hz, 1H), 1.48 – 1.37 (m, 1H), 0.82 – 0.72 (m, 1H), 0.63 (d, *J* = 6.5 Hz, 3H), 0.60 (d, *J* = 6.6 Hz, 3H), 0.16 – 0.07 (m, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 167.93, 166.59, 136.57, 130.85, 128.55, 127.19, 55.91, 52.72, 44.09, 38.92, 23.38, 23.27, 21.85. HRMS (ESI): calcd for $[C_{15}H_{21}N_2O_2]^+$: 261.1592, found: 261.1605.



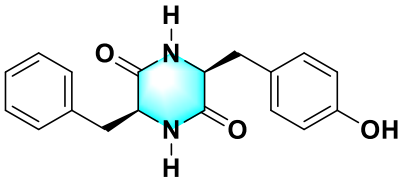
7: Purification via washing by ethyl ether to obtain 1.89 g white solid. Overall yield: 68%. Mp = 210.8~212.2 ºC. $[\alpha]_D$ = -42.3º (*c* 0.1, DMSO). IR (KBr): 3455 cm^{-1}, 3315 cm^{-1}, 3190 cm^{-1}, 3048 cm^{-1}, 2978 cm^{-1}, 2894 cm^{-1}, 1669 cm^{-1}, 1455 cm^{-1}, 1344 cm^{-1}, 1097 cm^{-1}, 844 cm^{-1}, 758 cm^{-1}, 700 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 8.24 (s, 1H), 8.10 (s, 1H), 7.27 (t, *J* = 7.3 Hz, 2H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.15 (d, *J* = 7.2 Hz, 2H), 4.21 (s, 1H), 3.72 (s, 1H), 3.16 (dd, *J* = 13.4, 3.3 Hz, 1H), 2.83 (dd, *J* = 13.4, 4.8 Hz, 1H), 1.87 (s, 3H), 1.86 – 1.80 (m, 2H), 1.37 – 1.19 (m, 1H), 1.04 – 0.87 (m, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 166.97, 166.56, 136.43, 130.87, 128.43, 127.28, 55.70, 53.35, 38.48, 33.27, 28.38, 14.89. HRMS (ESI): calcd for $[C_{14}H_{19}N_2O_2S]^+$: 279.1162, found: 279.1165.



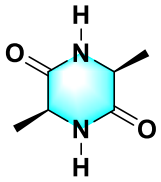
8: Purification via washing by ethyl ether to obtain 2.17 g white solid. Overall yield: 88%. Mp = 269.8~271.4 ºC. $[\alpha]_D$ = -54.0º (*c* 0.1, DMSO). IR (KBr): 3202 cm^{-1}, 3077 cm^{-1}, 2970 cm^{-1}, 1675 cm^{-1}, 1455 cm^{-1}, 1330 cm^{-1}, 845 cm^{-1}, 700 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 8.09 (s, 1H), 7.90 (s, 1H), 7.24 (t, 2H), 7.21 – 7.08 (m, 3H), 4.21 (s, 1H), 3.53 (s, 1H), 3.15 (dd, *J* = 13.5, 4.0 Hz, 1H), 2.87 (dd, *J* = 13.5, 4.9 Hz, 1H), 1.76 – 1.63 (m, 1H), 0.65 (d, *J* = 7.0 Hz, 3H), 0.26 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 167.02, 166.89, 136.80, 130.79, 128.41, 126.96, 59.64, 55.50, 38.26, 31.47, 18.70, 16.63. HRMS (ESI): calcd for $[C_{14}H_{19}N_2O_2]^+$: 247.1436, found: 247.1435.



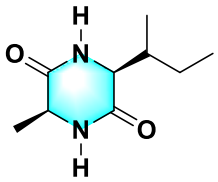
9: Purification via washing by ethyl ether to obtain 2.84 g white solid. Overall yield: 85%. Mp = 295.8~297.2 ºC. $[\alpha]_D$ = -112.2º (*c* 0.1, DMSO). IR (KBr): 3420 cm^{-1}, 3186 cm^{-1}, 3058 cm^{-1}, 2964 cm^{-1}, 2878 cm^{-1}, 1677 cm^{-1}, 1457 cm^{-1}, 1325 cm^{-1}, 1089 cm^{-1}, 742 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 10.89 (s, 1H), 7.91 (s, 1H), 7.71 (s, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.22 – 7.13 (m, 3H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 1.1 Hz, 1H), 6.71 (d, *J* = 6.6 Hz, 2H), 3.97 (s, 1H), 3.86 (s, 1H), 2.80 (dd, *J* = 14.4, 4.2 Hz, 1H), 2.54 (dd, *J* = 5.7 Hz, 1H), 2.46 (dd, *J* = 13.4, 4.5 Hz, 1H), 1.86 (dd, *J* = 13.4, 7.0 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 167.27, 166.65, 137.00, 136.51, 130.18, 128.51, 127.99, 126.84, 124.88, 121.36, 119.23, 118.89, 111.80, 109.28, 56.08, 55.73, 30.16. HRMS (ESI): calcd for $[C_{20}H_{22}N_3O_2]^+$: 336.1707, found: 336.1614.



10: Purification via washing by ethyl ether to obtain 2.46 g white solid. Overall yield: 79%. Mp = 313.4~314.6 ºC. $[\alpha]_D$ = -137.3º (*c* 0.1, DMSO). IR (KBr): 3535 cm^{-1}, 3229 cm^{-1}, 3091 cm^{-1}, 3038 cm^{-1}, 2962 cm^{-1}, 2931 cm^{-1}, 2855 cm^{-1}, 1661 cm^{-1}, 1613 cm^{-1}, 1174 cm^{-1}, 1513 cm^{-1}, 1461 cm^{-1}, 1334 cm^{-1}, 1270 cm^{-1}, 1198 cm^{-1}, 1093 cm^{-1}, 812 cm^{-1}, 758 cm^{-1}, 698 cm^{-1}, 651 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 9.21 (s, 1H), 7.84 (s, 2H), 7.28 (t, *J* = 7.5 Hz, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 7.2 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 6.67 (d, *J* = 8.4 Hz, 2H), 3.94 (s, 1H), 3.89 (s, 1H), 2.58 (dd, *J* = 13.7, 4.9 Hz, 1H), 2.52 (dd, *J* = 4.7 Hz, 1H), 2.22 – 2.15 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$-CF_3COOH): δ (ppm) 169.50, 169.37, 154.50, 133.57, 131.12, 129.86, 129.35, 128.26, 126.46, 116.15, 56.23, 56.11, 39.75, 38.95. HRMS (ESI): calcd for $[C_{18}H_{19}N_2O_3]^+$: 311.1379, found: 311.1388.

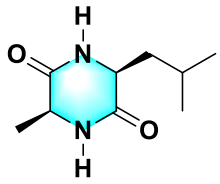


11: Purification via recrystallization to obtain 0.76 g white solid. Overall yield: 53%. Mp = 291.7~292.8 ºC. $[\alpha]_D$ = -44.0º (*c* 0.1, DMSO). IR (KBr): 3196 cm^{-1}, 3087 cm^{-1}, 2986 cm^{-1}, 2890 cm^{-1}, 1685 cm^{-1}, 1601 cm^{-1}, 1434 cm^{-1}, 1313 cm^{-1}, 1153 cm^{-1}, 1120 cm^{-1}, 828 cm^{-1}, 764 cm^{-1}, 672 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 8.08 (s, 2H), 3.90 (q, *J* = 6.8 Hz, 2H), 1.25 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 169.53, 50.25, 18.98. HRMS (ESI): calcd for $[C_6H_{11}N_2O_2]^+$: 143.0810, found: 143.0814.

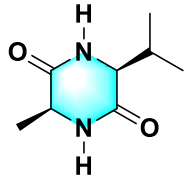


12: Purification via washing by ethyl ether to obtain 1.31 g white solid. Overall yield: 71%. Mp = 246.5~247.9 ºC. $[\alpha]_D$ = -52.9º (*c* 0.1, DMSO). IR

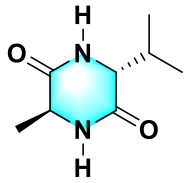
(KBr): 3192 cm^{-1}, 3077 cm^{-1}, 2966 cm^{-1}, 2873 cm^{-1}, 1683 cm^{-1}, 1432 cm^{-1}, 1319 cm^{-1}, 779 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 8.12 (s, 1H), 7.98 (s, 1H), 3.88 (q, J = 6.9 Hz, 1H), 3.75 (s, 1H), 1.88 – 1.81 (m, 1H), 1.43 – 1.36 (m, 1H), 1.27 (d, 3H), 1.22 – 1.14 (m, 1H), 0.91 (d, J = 7.1 Hz, 3H), 0.85 (t, J = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 169.04, 167.07, 59.24, 50.07, 38.43, 24.61, 20.33, 15.47, 12.38. HRMS (ESI): calcd for $[C_9H_{17}N_2O_2]^+$: 185.1285, found: 185.1279.



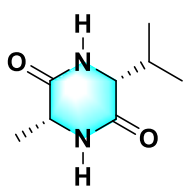
13: Purification via washing by ethyl ether to obtain 1.37 g white solid. Overall yield: 74%. Mp = 254.1~256.2 ºC. $[\alpha]_D$ = -63.7º (c 0.1, DMSO). IR (KBr): 3190 cm^{-1}, 3087 cm^{-1}, 2954 cm^{-1}, 2878 cm^{-1}, 1687 cm^{-1}, 1447 cm^{-1}, 1323 cm^{-1}, 826 cm^{-1}, 726 cm^{-1}, 668 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 8.12 (s, 1H), 8.10 (s, 1H), 3.86 (d, J = 6.5 Hz, 1H), 3.77 (s, 1H), 1.90 – 1.72 (m, 1H), 1.67 – 1.54 (m, 1H), 1.52 – 1.40 (m, 1H), 1.27 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.5 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 169.35, 168.85, 53.07, 50.37, 43.04, 24.08, 23.44, 22.34, 20.03. HRMS (ESI): calcd for $[C_9H_{17}N_2O_2]^+$: 185.1284, found: 185.1284.



14: Purification via washing by ethyl ether to obtain 1.16 g white solid. Overall yield: 68%. Mp = 270.1~271.1 ºC. $[\alpha]_D$ = -64.0º (c 0.1, DMSO). IR (KBr): 3192 cm^{-1}, 3052 cm^{-1}, 2964 cm^{-1}, 2896 cm^{-1}, 1673 cm^{-1}, 1459 cm^{-1}, 1338 cm^{-1}, 863 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 8.14 (s, 1H), 8.00 (s, 1H), 3.88 (q, 1H), 3.68 (s, 1H), 2.20 – 2.11 (m, 1H), 1.27 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 7.1 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 169.16, 167.08, 59.84, 50.12, 31.51, 20.53, 18.96, 17.32. HRMS (ESI): calcd for $[C_8H_{15}N_2O_2]^+$: 171.1123, found: 171.1123.

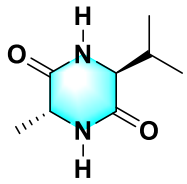


15: Purification via washing by ethyl ether to obtain 1.09 g white solid. Overall yield: 64%. Mp = 277.8~278.9 ºC. $[\alpha]_D$ = -15.7º (c 0.1, DMSO). IR (KBr): 3184 cm^{-1}, 3048 cm^{-1}, 2962 cm^{-1}, 2884 cm^{-1}, 1671 cm^{-1}, 1447 cm^{-1}, 1344 cm^{-1}, 861 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 8.13 (s, 1H), 8.10 (s, 1H), 3.92 (q, J = 6.9 Hz, 1H), 3.54 (t, J = 3.5 Hz, 1H), 2.15 – 2.06 (m, 1H), 1.24 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 7.0 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 169.39, 167.95, 60.73, 49.47, 32.66, 19.10, 19.03, 17.69. HRMS (ESI): calcd for $[C_8H_{15}N_2O_2]^+$: 171.1123, found: 171.1127.

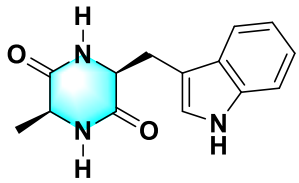


16: Purification via washing by ethyl ether to obtain 1.13 g white solid. Overall yield: 66%. Mp = 263.1~264.4 ºC. $[\alpha]_D$ = +65.0º (c 0.1, DMSO). IR (KBr):

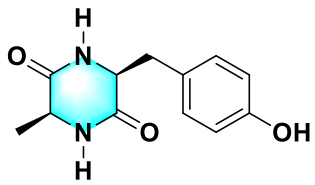
3184 cm^{-1}, 3050 cm^{-1}, 2966 cm^{-1}, 2896 cm^{-1}, 1671 cm^{-1}, 1463 cm^{-1}, 1342 cm^{-1}, 861 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 8.12 (s, 1H), 7.99 (s, 1H), 3.88 (q, J = 7.0 Hz, 1H), 3.68 (s, 1H), 2.19 – 2.11 (m, 1H), 1.27 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 7.1 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 169.17, 167.08, 59.84, 50.13, 31.52, 20.54, 18.95, 17.32. HRMS (ESI): calcd for $[C_8H_{15}N_2O_2]^+$: 171.1123, found: 171.1127.



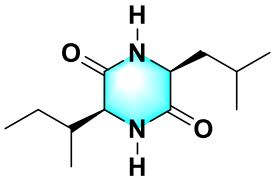
17: Purification via washing by ethyl ether to obtain 1.06 g white solid. Overall yield: 62%. Mp = 278.5~279.3 ºC. $[\alpha]_D$ = +15.0º (*c* 0.1, DMSO). IR (KBr): 3184 cm^{-1}, 3048 cm^{-1}, 2964 cm^{-1}, 2886 cm^{-1}, 1671 cm^{-1}, 1451 cm^{-1}, 1342 cm^{-1}, 861 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 8.13 (s, 1H), 8.10 (s, 1H), 3.91 (q, J = 6.9 Hz, 1H), 3.54 (t, J = 3.5 Hz, 1H), 2.15 – 2.07 (m, 1H), 1.24 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 7.0 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 169.39, 167.95, 60.73, 49.48, 32.66, 19.10, 19.02, 17.69. HRMS (ESI): calcd for $[C_8H_{15}N_2O_2]^+$: 171.1123, found: 171.1128.



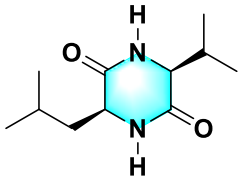
18: Purification via washing by ethyl ether to obtain 1.57 g white solid. Overall yield: 61%. Mp = 298.8~300.1 ºC. $[\alpha]_D$ = -12.0º (*c* 0.1, DMSO). IR (KBr): 3414 cm^{-1}, 3188 cm^{-1}, 3054 cm^{-1}, 1661 cm^{-1}, 1455 cm^{-1}, 1327 cm^{-1}, 838 cm^{-1}, 742 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 10.89 (s, 1H), 8.01 (s, 1H), 7.90 (s, 1H), 7.56 (d, J = 7.9 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.04 (d, J = 2.3 Hz, 1H), 7.02 (d, J = 7.9 Hz, 1H), 6.94 (t, J = 7.4 Hz, 1H), 4.11 (s, 1H), 3.59 (q, J = 7.1 Hz, 1H), 3.24 (dd, J = 14.4, 4.1 Hz, 1H), 3.01 (dd, J = 14.4, 4.5 Hz, 1H), 0.42 (d, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 168.21, 167.24, 136.27, 128.27, 125.03, 121.27, 119.44, 118.84, 111.56, 108.98, 55.87, 50.26, 29.32, 20.01. HRMS (ESI): calcd for $[C_{14}H_{16}N_3O_2]^+$: 258.1237, found: 258.1234.



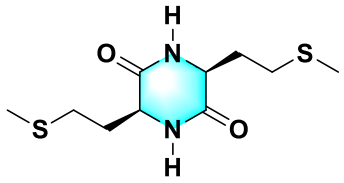
19: Purification via washing by ethyl ether to obtain 1.48 g white solid. Overall yield: 63%. Mp = 294.8~296.4 ºC. $[\alpha]_D$ = -13.0º (*c* 0.1, DMSO). IR (KBr): 3309 cm^{-1}, 3202 cm^{-1}, 3048 cm^{-1}, 2873 cm^{-1}, 1673 cm^{-1}, 1519 cm^{-1}, 1478 cm^{-1}, 1330 cm^{-1}, 1241 cm^{-1}, 1110 cm^{-1}, 838 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 9.20 (s, 1H), 8.03 (s, 1H), 7.98 (s, 1H), 6.93 (d, J = 8.0 Hz, 2H), 6.65 (d, J = 8.1 Hz, 2H), 4.07 (s, 1H), 3.62 (d, J = 6.7 Hz, 1H), 3.01 (dd, J = 13.5, 2.9 Hz, 1H), 2.73 (dd, J = 13.6, 4.4 Hz, 1H), 0.53 (d, J = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 168.15, 166.43, 156.62, 131.77, 126.44, 115.30, 56.04, 50.23, 38.06, 20.28. HRMS (ESI): calcd for $[C_{12}H_{15}N_2O_3]^+$: 235.1077, found: 235.1076.



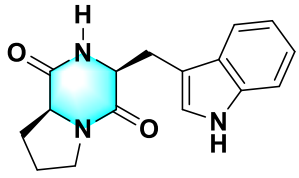
20: Purification via washing by ethyl ether to obtain 1.43 g white solid. Overall yield: 63%. Mp = 294.9~296.7 ºC. $[\alpha]_D$ = -58.0º (*c* 0.1, DMSO). IR (KBr): 3451 cm^{-1}, 3186 cm^{-1}, 3097 cm^{-1}, 3054 cm^{-1}, 2964 cm^{-1}, 2875 cm^{-1}, 1665 cm^{-1}, 1453 cm^{-1}, 1325 cm^{-1}, 1142 cm^{-1}, 851 cm^{-1}, 766 cm^{-1}, 684 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 8.17 (s, 1H), 8.04 (s, 1H), 3.82 – 3.72 (m, 1H), 3.69 (s, 1H), 2.01 – 1.73 (m, 2H), 1.66 – 1.56 (m, 1H), 1.51 – 1.32 (m, 2H), 1.25 – 1.08 (m, 1H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.87 – 0.78 (m, 6H).^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 168.84, 167.32, 59.27, 52.79, 44.13, 38.74, 24.79, 24.02, 23.57, 22.22, 15.63, 12.26. HRMS (ESI): calcd for $[C_{12}H_{23}N_2O_2]^+$: 227.1755, found: 227.1757.



21: Purification via washing by ethyl ether to obtain 1.73 g white solid. Overall yield: 81%. Mp = 284.3~286.5 ºC. $[\alpha]_D$ = -63.7º (*c* 0.1, DMSO). IR (KBr): 3192 cm^{-1}, 3056 cm^{-1}, 2962 cm^{-1}, 2882 cm^{-1}, 1669 cm^{-1}, 1451 cm^{-1}, 849 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): *δ* (ppm) 8.18 (s, 1H), 8.05 (s, 1H), 3.76 (s, 1H), 3.62 (s, 1H), 2.17 – 2.04 (m, 1H), 1.89 – 1.78 (m, 1H), 1.67 – 1.55 (m, 1H), 1.50 – 1.36 (m, 1H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.87 – 0.77 (m, 6H). ^{13}C NMR (151 MHz, DMSO-d_6): *δ* (ppm) 168.92, 167.32, 59.99, 52.84, 44.40, 31.91, 24.02, 23.56, 22.22, 19.23, 17.81. HRMS (ESI): calcd for $[C_{11}H_{21}N_2O_2]^+$: 213.1592, found: 213.1597.

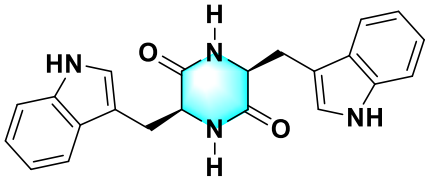


22: Purification via washing by ethyl ether to obtain 1.80 g white solid. Overall yield: 69%. Mp = 230.4~231.6 ºC. $[\alpha]_D$ = -84.0º (*c* 0.1, DMSO). IR (KBr): 3315 cm^{-1}, 3194 cm^{-1}, 3093 cm^{-1}, 3048 cm^{-1}, 2966 cm^{-1}, 2915 cm^{-1}, 2865 cm^{-1}, 1677 cm^{-1}, 1443 cm^{-1}, 1336 cm^{-1}, 1290 cm^{-1}, 1108 cm^{-1}, 960 cm^{-1}, 818 cm^{-1}, 676 cm^{-1}, 635 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 8.25 (s, 2H), 3.96 (s, 2H), 2.61 – 2.51 (m, 4H), 2.04 (s, 6H), 2.00 – 1.93 (m, 2H), 1.93 – 1.83 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 168.27, 53.44, 32.81, 29.19, 14.90. HRMS (ESI): calcd for $[C_{10}H_{19}N_2O_2S_2]^+$: 263.0883, found: 263.0888.

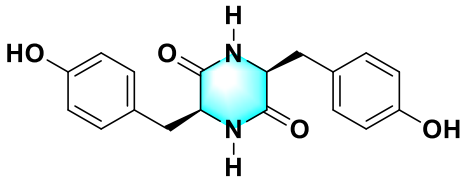


23: Purification via washing by ethyl ether to obtain 1.82 g pale yellow solid. Overall yield: 64%. Mp = 168.7~170.1 ºC. $[\alpha]_D$ = -124.0º (*c* 0.1, DMSO). IR (KBr): 3287 cm^{-1}, 3052 cm^{-1}, 2984 cm^{-1}, 2943 cm^{-1}, 2871 cm^{-1}, 1675 cm^{-1}, 1650 cm^{-1}, 1428 cm^{-1}, 1241 cm^{-1}, 1108 cm^{-1}, 742 cm^{-1}, 692 cm^{-1}, 637 cm^{-1}, 563 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): *δ* (ppm) 10.85 (s, 1H), 7.73 (s, 1H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.18 (s, 1H), 7.05 (t, *J* = 7.3 Hz, 1H), 6.96 (t, *J* = 7.3 Hz, 1H), 4.30 (s, 1H), 4.06 (t, *J* = 8.0 Hz, 1H), 3.38 (dd, *J* = 18.9,

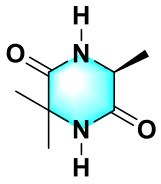
8.2 Hz, 1H), 3.24 (d, *J* = 11.0 Hz, 2H), 3.07 (dd, *J* = 14.8, 5.5 Hz, 1H), 2.03 – 1.87 (m, 1H), 1.67 (dd, *J* = 18.1, 8.7 Hz, 1H), 1.65 – 1.54 (m, 1H), 1.44 – 1.33 (m, 1H). ^{13}C NMR (151 MHz, DMSO-*d*$_6$): *δ* (ppm) 169.48, 165.98, 136.45, 127.83, 124.86, 121.35, 119.12, 118.70, 111.70, 109.77, 58.90, 55.71, 45.07, 28.15, 26.29, 22.35. HRMS (ESI): calcd for $[C_{16}H_{18}N_3O_2]^+$: 284.1394, found: 284.1392.



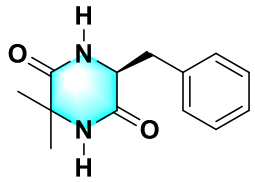
24: Purification via recrystallization to obtain 2.57 g white solid. Overall yield: 69%. Mp = 274.7~276.1 ºC. $[\alpha]_D$ = -101.7º (*c* 0.1, DMSO). IR (KBr): 3420 cm^{-1}, 3361 cm^{-1}, 3178 cm^{-1}, 3052 cm^{-1}, 2966 cm^{-1}, 2908 cm^{-1}, 2878 cm^{-1}, 1675 cm^{-1}, 1459 cm^{-1}, 1336 cm^{-1}, 1233 cm^{-1}, 1091 cm^{-1}, 1013 cm^{-1}, 923 cm^{-1}, 849 cm^{-1}, 748 cm^{-1}, 592 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-*d*$_6$): *δ* (ppm) 10.83 (s, 2H), 7.69 (s, 2H), 7.35 (d, J = 7.8 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.04 (t, J = 7.4 Hz, 2H), 6.95 (t, J = 7.4 Hz, 2H), 6.60 (s, 2H), 3.86 (s, 2H), 2.70 (dd, J = 14.2, 3.7 Hz, 2H), 2.18 (dd, J = 14.2, 6.5 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-*d*$_6$): *δ* (ppm) 167.20, 136.53, 127.83, 124.87, 121.26, 119.01, 118.82, 111.72, 109.24, 55.75, 30.45. HRMS (ESI): calcd for $[C_{22}H_{21}N_4O_2]^+$: 373.1659, found: 373.1692.



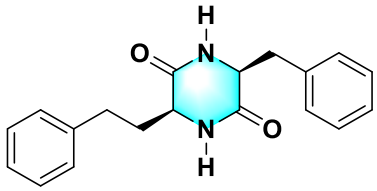
25: Purification via washing by ethyl ether to obtain 2.45 g white solid. Overall yield: 75%. Mp = 292.6~293.4 ºC. $[\alpha]_D$ = -121.0º (*c* 0.1, DMSO). IR (KBr): 3439 cm^{-1}, 3237 cm^{-1}, 3056 cm^{-1}, 1673 cm^{-1}, 1611 cm^{-1}, 1515 cm^{-1}, 1463 cm^{-1}, 1342 cm^{-1}, 1243 cm^{-1}, 830 cm^{-1}, 772 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-*d*$_6$/CD_3CN-*d*$_3$, v/v = 1/9): *δ* (ppm) 8.85 (s, 2H), 7.07 (s, 2H), 6.90 (d, *J* = 8.2 Hz, 4H), 6.74 (d, *J* = 8.3 Hz, 4H), 3.89 (s, 2H), 2.66 (dd, *J* = 13.7, 4.1 Hz, 2H), 2.12 (dd, *J* = 13.6, 7.1 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-*d*$_6$): *δ* (ppm) 166.73, 156.54, 131.22, 127.01, 115.50, 56.21, 39.27. HRMS (ESI): calcd for $[C_{18}H_{19}N_2O_4]^+$: 327.1323, found: 327.1338.



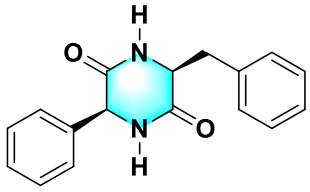
26: Purification via washing by ethyl ether to obtain 1.21 white solid. Overall yield: 77%. Mp = 307.8~310.4 ºC. $[\alpha]_D$ = -45.6º (*c* 0.1, DMSO). IR (KBr): 3190 cm^{-1}, 3042 cm^{-1}, 2982 cm^{-1}, 2894 cm^{-1}, 1681 cm^{-1}, 1441 cm^{-1}, 1309 cm^{-1}, 1198 cm^{-1}, 1167 cm^{-1}, 844 cm^{-1}, 684 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-*d*$_6$): *δ* (ppm) 8.16 (s, 1H), 8.03 (s, 1H), 3.94 (q, J = 6.9 Hz, 1H), 1.29 (d, J = 3.7 Hz, 6H), 1.26 (d, J = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-*d*$_6$): *δ* (ppm) 171.27, 168.71, 55.50, 50.38, 27.90, 19.61. HRMS (ESI): calcd for $[C_7H_{13}N_2O_2]^+$: 157.0972, found: 157.0972.



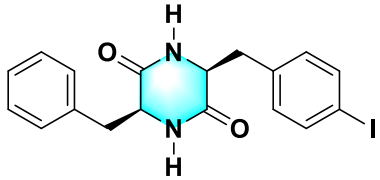
27: Purification via washing by ethyl ether to obtain 1.93 g white solid. Overall yield: 83%. Mp = 276.5~278.1 ºC. $[\alpha]_D$ = +19.0º (*c* 0.1, DMSO). IR (KBr): 3188 cm^{-1}, 3044 cm^{-1}, 2980 cm^{-1}, 2902 cm^{-1}, 1673 cm^{-1}, 1490 cm^{-1}, 1451 cm^{-1}, 1309 cm^{-1}, 1198 cm^{-1}, 863 cm^{-1}, 768 cm^{-1}, 707 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 8.08 (s, 1H), 8.04 (s, 1H), 7.26 (t, *J* = 7.3 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.16 (d, 2H), 4.23 – 4.19 (m, 1H), 3.15 (dd, *J* = 13.4, 3.5 Hz, 1H), 2.85 (dd, *J* = 13.5, 4.9 Hz, 1H), 1.16 (s, 3H), 0.47 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 170.59, 165.77, 136.52, 130.87, 128.45, 127.11, 56.11, 55.17, 38.76, 28.75, 28.12. HRMS (ESI): calcd for $[C_{13}H_{17}N_2O_2]^+$: 233.1279, found: 233.1284.



28: Purification via washing by ethyl ether to obtain 2.53 g white solid. Overall yield: 82%. Mp = 293.1~294 ºC. $[\alpha]_D$ = -51.0º (*c* 0.1, DMSO). IR (KBr): 3194 cm^{-1}, 3048 cm^{-1}, 2964 cm^{-1}, 2892 cm^{-1}, 1677 cm^{-1}, 1461 cm^{-1}, 1336 cm^{-1}, 1095 cm^{-1}, 846 cm^{-1}, 758 cm^{-1}, 705 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 8.22 (s, 1H), 8.17 (s, 1H), 7.24 (dd, J = 13.6, 7.2 Hz, 4H), 7.18 (d, J = 7.3 Hz, 2H), 7.13 (t, J = 7.3 Hz, 1H), 7.09 (t, J = 7.2 Hz, 1H), 6.97 (d, J = 7.3 Hz, 2H), 4.23 (s, 1H), 3.65 (s, 1H), 3.18 (dd, J = 13.4, 3.3 Hz, 1H), 2.86 (dd, J = 13.4, 4.8 Hz, 1H), 2.17 – 1.85 (m, 2H), 1.45 – 1.22 (m, 1H), 1.13 – 0.91 (m, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 167.21, 166.68, 141.88, 136.50, 130.91, 128.63, 128.60, 128.44, 127.17, 126.10, 55.76, 54.00, 38.49, 35.45, 30.01. HRMS (ESI): calcd for $[C_{19}H_{21}N_2O_2]^+$: 309.1592, found: 309.1598.

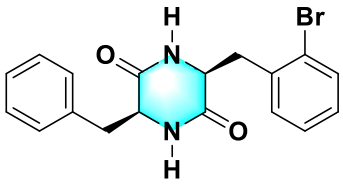


29: Purification via washing by ethyl ether to obtain 2.14 g white solid. Overall yield: 76%. Mp = 247.3~248.1 ºC. $[\alpha]_D$ = -23.0º (*c* 0.1, DMSO). IR (KBr): 3223 cm^{-1}, 3122 cm^{-1}, 2958 cm^{-1}, 2855 cm^{-1}, 1671 cm^{-1}, 1430 cm^{-1}, 1336 cm^{-1}, 1274 cm^{-1}, 1091 cm^{-1}, 797 cm^{-1}, 705 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 8.43 (s, 1H), 8.25 (s, 1H), 7.41 – 7.23 (m, 8H), 7.21 (d, *J* = 7.1 Hz, 2H), 4.36 (s, 1H), 4.24 (s, 1H), 3.22 (dd, *J* = 13.6, 3.8 Hz, 1H), 2.95 (dd, *J* = 13.6, 4.9 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 167.28, 166.63, 139.46, 136.58, 130.69, 128.81, 128.54, 128.30, 127.75, 127.16, 58.84, 55.50, 38.39. HRMS (ESI): calcd for $[C_{17}H_{17}N_2O_2]^+$: 281.1279, found: 281.1281.

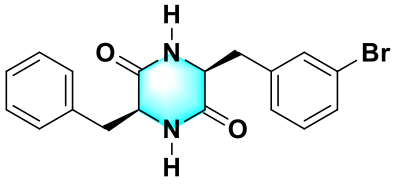


30: Purification via washing by ethyl ether to obtain 3.04 g white solid. Overall yield: 72%. Mp = 296.8~298.9 ºC. $[\alpha]_D$ = -101.0º (*c* 0.1, DMSO). IR (KBr): 3459 cm^{-1}, 3319 cm^{-1}, 3204

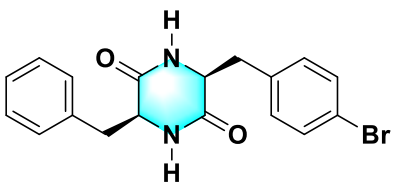
cm^{-1}, 3085 cm^{-1}, 3058 cm^{-1}, 2968 cm^{-1}, 2929 cm^{-1}, 2888 cm^{-1}, 1671 cm^{-1}, 1459 cm^{-1}, 1336 cm^{-1}, 1101 cm^{-1}, 1013 cm^{-1}, 807 cm^{-1}, 756 cm^{-1}, 696 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-*d*$_6$): δ (ppm) 8.04 (s, 1H), 7.98 (s, 1H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.28 (t, *J* = 6.8 Hz, 2H), 7.23 (d, *J* = 6.8 Hz, 1H), 7.06 (d, *J* = 6.9 Hz, 2H), 6.80 (d, *J* = 7.5 Hz, 2H), 4.06 (s, 1H), 3.93 (s, 1H), 2.66 (dd, *J* = 13.3, 3.9 Hz, 1H), 2.53 (dd, *J* = 4.7 Hz, 1H), 2.45 (dd, *J* = 13.5, 4.0 Hz, 1H), 2.08 (dd, *J* = 13.3, 6.1 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-*d*$_6$): δ (ppm) 166.68, 166.56, 137.34, 136.85, 132.60, 130.38, 128.66, 126.98, 93.00, 55.71, 55.59, 39.37, 39.22. HRMS (ESI): calcd for [$C_{18}H_{18}N_2O_2I$]$^+$: 421.0408, found: 421.0412.



31: Purification via washing by ethyl ether to obtain 2.92 g white solid. Overall yield: 78%. Mp = 278.8~280.2 ºC. [α]$_D$ = -192.0º (*c* 0.1, DMSO). IR (KBr): 3445 cm^{-1}, 3330 cm^{-1}, 3184 cm^{-1}, 3056 cm^{-1}, 2974 cm^{-1}, 2886 cm^{-1}, 1677 cm^{-1}, 1461 cm^{-1}, 1334 cm^{-1}, 1101 cm^{-1}, 1023 cm^{-1}, 846 cm^{-1}, 818 cm^{-1}, 750 cm^{-1}, 705 cm^{-1}, 583 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-*d*$_6$): δ (ppm) 8.25 (s, 1H), 7.84 (s, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.37 (t, *J* = 7.3 Hz, 2H), 7.25 (t, *J* = 7.3 Hz, 2H), 7.22 (d, *J* = 7.3 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 7.2 Hz, 1H), 4.17 (s, 1H), 3.85 (s, 1H), 2.99 (dd, *J* = 13.3, 3.8 Hz, 1H), 2.84 (dd, *J* = 13.3, 4.4 Hz, 1H), 2.61 (dd, *J* = 13.5, 4.5 Hz, 1H), 1.66 (dd, *J* = 13.4, 8.8 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-*d*$_6$): δ (ppm) 166.58, 166.54, 136.78, 136.35, 132.98, 132.79, 130.87, 129.16, 128.83, 127.95, 127.30, 124.56, 56.08, 53.92, 41.18, 39.22. HRMS (ESI): calcd for [$C_{18}H_{18}N_2O_2Br$]$^+$: 373.0547, found: 373.0549.



32: Purification via washing by ethyl ether to obtain 2.74 g white solid. Overall yield: 74%. Mp = 279.4~280.5 ºC. [α]$_D$ = -80.0º (*c* 0.1, DMSO). IR (KBr): 3451 cm^{-1}, 3326 cm^{-1}, 3192 cm^{-1}, 3089 cm^{-1}, 3050 cm^{-1}, 2970 cm^{-1}, 2921 cm^{-1}, 2884 cm^{-1}, 1663 cm^{-1}, 1461 cm^{-1}, 1340 cm^{-1}, 1206 cm^{-1}, 1095 cm^{-1}, 830 cm^{-1}, 768 cm^{-1}, 700 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-*d*$_6$): δ (ppm) 8.05 (s, 2H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.28 (t, *J* = 7.4 Hz, 2H), 7.25 – 7.15 (m, 3H), 7.06 (d, *J* = 7.3 Hz, 2H), 7.02 (d, *J* = 7.6 Hz, 1H), 4.03 (s, 1H), 3.99 (s, 1H), 2.64 (dd, *J* = 13.6, 4.8 Hz, 1H), 2.52 (dd, 1H), 2.42 (dd, *J* = 13.6, 5.6 Hz, 1H), 2.19 (dd, *J* = 13.6, 6.1 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-*d*$_6$): δ (ppm) 166.71, 166.49, 139.88, 136.89, 132.92, 130.76, 130.39, 129.90, 129.38, 128.64, 127.05, 121.94, 55.81, 55.61, 40.51, 39.30. HRMS (ESI): calcd for [$C_{18}H_{18}N_2O_2Br$]$^+$: 373.0547, found: 373.0550.



33: Purification via washing by ethyl ether to obtain 2.64 g

white solid. Overall yield: 71%. Mp = 283.9~284.5 ºC. $[\alpha]_D$ = -101.7º (*c* 0.1, DMSO). IR (KBr): 3192 cm^{-1}, 3085 cm^{-1}, 3052 cm^{-1}, 2966 cm^{-1}, 2927 cm^{-1}, 2873 cm^{-1}, 1667 cm^{-1}, 1459 cm^{-1}, 1338 cm^{-1}, 1204 cm^{-1}, 1099 cm^{-1}, 1015 cm^{-1}, 816 cm^{-1}, 760 cm^{-1}, 700 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ (ppm) 8.04 (d, *J* = 1.6 Hz, 1H), 7.98 (d, *J* = 1.8 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 7.1 Hz, 2H), 6.94 (d, *J* = 8.3 Hz, 2H), 4.07 (s, 1H), 3.94 (s, 1H), 2.67 (dd, *J* = 13.6, 4.9 Hz, 1H), 2.55 (dd, *J* = 13.7, 5.3 Hz, 1H), 2.47 (dd, *J* = 13.7, 5.0 Hz, 1H), 2.09 (dd, *J* = 13.6, 6.4 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 166.69, 166.57, 136.84, 136.48, 132.39, 131.46, 130.39, 128.66, 126.98, 120.24, 55.73, 55.60, 39.34, 39.07. HRMS (ESI): calcd for $[C_{18}H_{18}N_2O_2Br]^+$: 373.0547, found: 373.0549.

2. Chiral HPLC traces

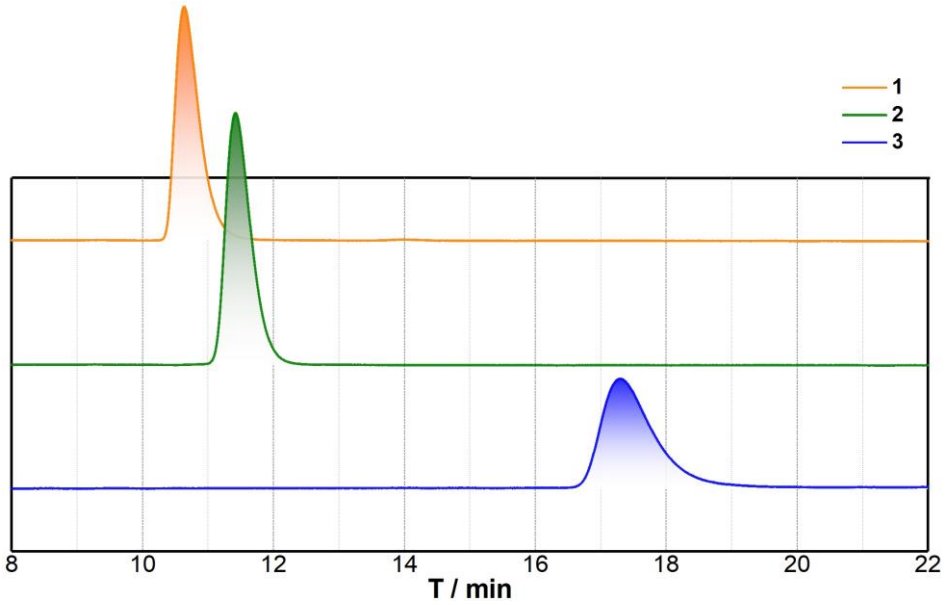


Figure S4. HPLC traces of synthesized **1**, **2**, and **3**. For HPLC, column: Chiralpak@ID (250 × 4.6 mm); mobile phase: 80:20 (v/v) *n*-hexane/2-propanol; flow rate: 1.0 mL/min; UV detection wavelength: 250 nm.

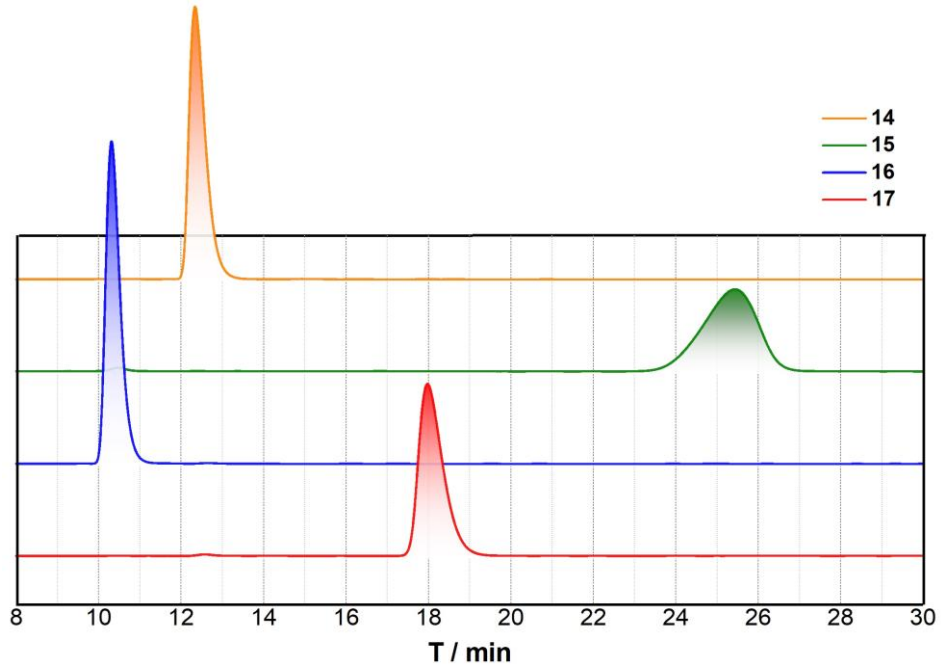


Figure S5. HPLC traces of synthesized **14**, **15**, **16**, and **17**. For HPLC, column: Chiralpak@ID (250 × 4.6 mm); mobile phase: 80:20 (v/v) *n*-hexane/2-propanol; flow rate: 1.0 mL/min; UV detection wavelength: 205 nm.

3. Absorption and CD spectra

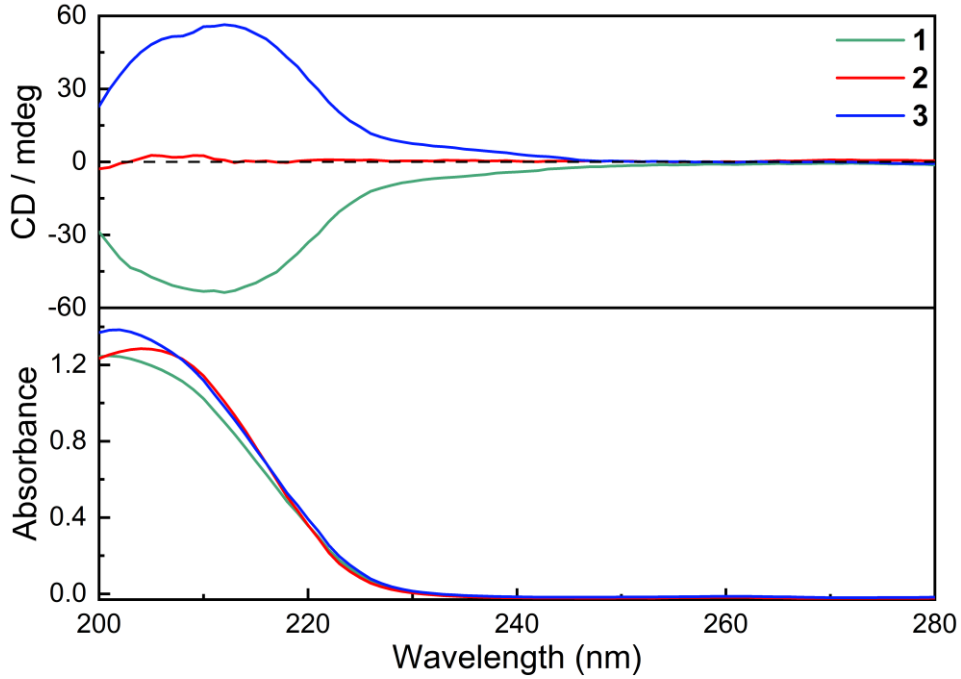


Figure S6. Absorption and CD spectra of **1**, **2**, and **3** in MeCN. The concentration is 50 μM.

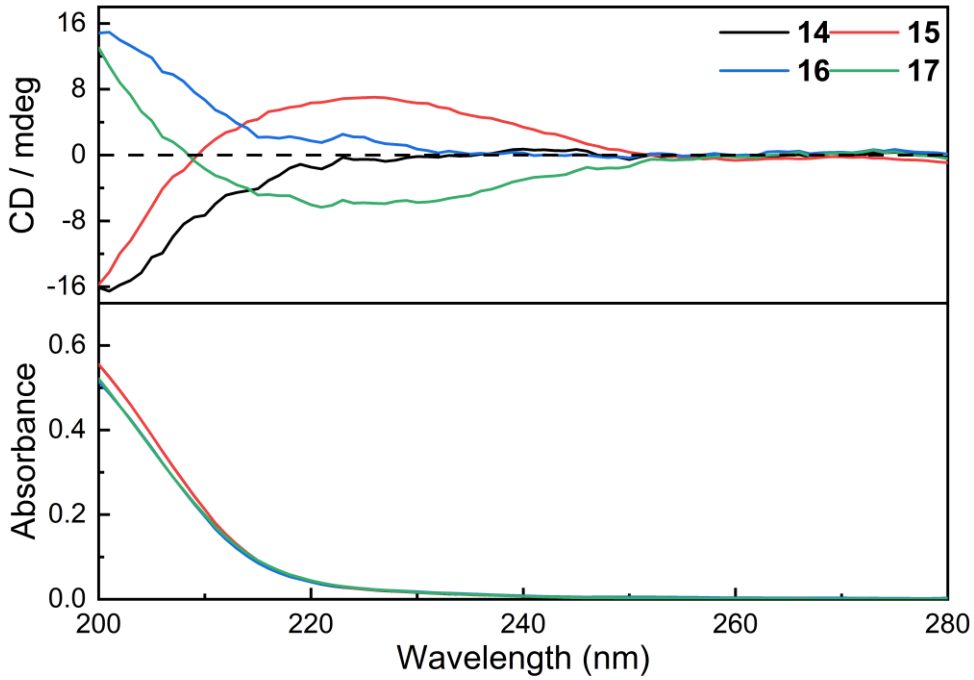


Figure S7. Absorption and CD spectra of **14**, **15**, **16**, and **17** in MeCN. The concentration is 50 μM.

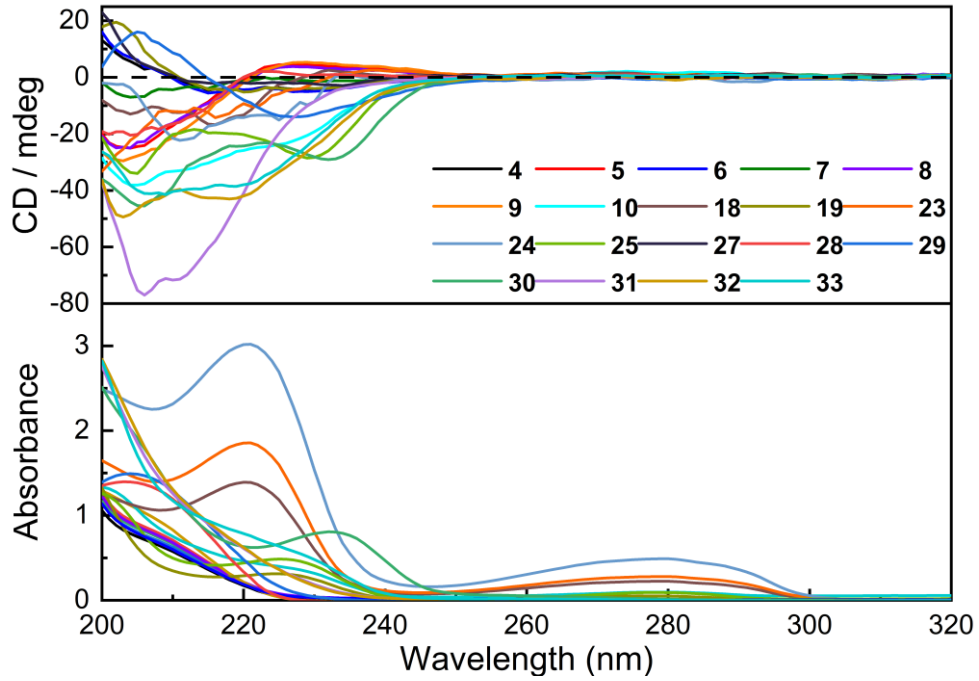


Figure S8. Absorption and CD spectra of **4**, **5**, **6**, **7**, **8**, **9**, **10**, **18**, **19**, **23**, **24**, **25**, **27**, **28**, **29**, **30**, **31**, **32**, and **33** in MeCN. The concentration is 50 μM.

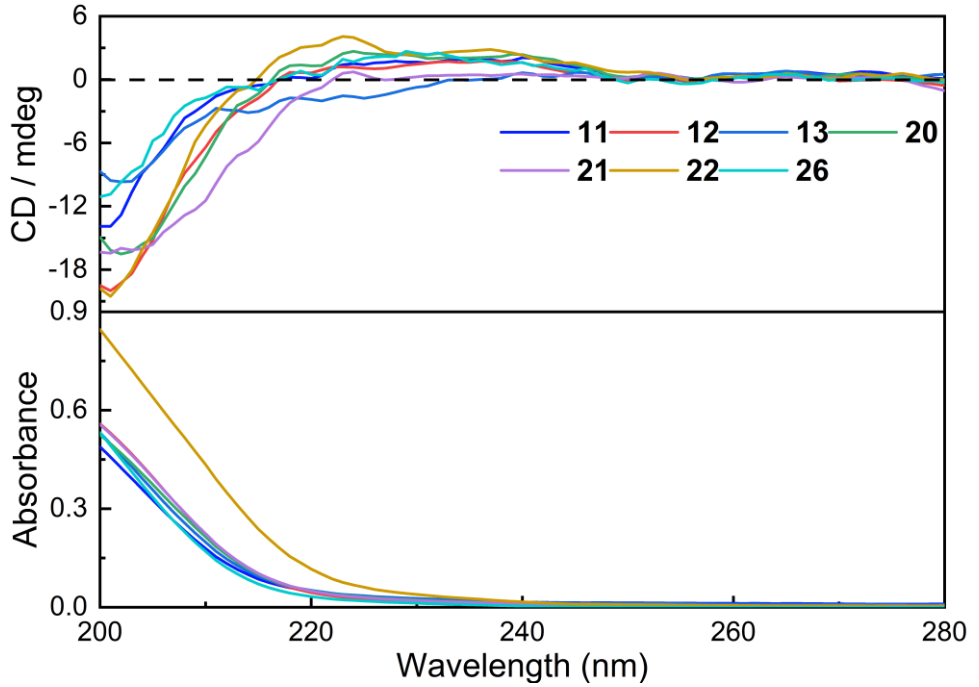


Figure S9. Absorption and CD spectra of **11**, **12**, **13**, **20**, **21**, **22**, and **26** in MeCN. The concentration is 50 μM.

4. Crystal data

Table S5. Crystal data and structure refinement for **26** [a]

Identification code	**26**
Empirical formula	$C_7H_{12}N_2O_2$
Formula weight	156.19
Temperature/K	100.15
Crystal system	triclinic
Space group	P1
a/Å	6.1202(4)
b/Å	7.0189(5)
c/Å	9.3471(5)
α/°	100.217(6)
β/°	94.013(5)
γ/°	90.202(5)
Volume/Å^3	394.14(4)
Z	2
ρ_{calc}g/cm^3	1.316
μ/mm^{-1}	0.807
F(000)	168.0
Crystal size/mm^3	0.21 × 0.21 × 0.21
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.64 to 153.034
Index ranges	$-7 \le h \le 5$, $-8 \le k \le 8$, $-11 \le l \le 11$
Reflections collected	3254
Independent reflections	1875 [R_{int} = 0.0429, R_{sigma} = 0.0500]
Data/restraints/parameters	1875/3/213
Goodness-of-fit on F^2	1.107
Final R indexes [I>=2σ (I)]	R_1 = 0.0551, wR_2 = 0.1539
Final R indexes [all data]	R_1 = 0.0589, wR_2 = 0.1576
Largest diff. peak/hole / e Å^{-3}	0.45/-0.34
Flack parameter	-0.3(4)
CCDC	2491940

[a] Grown in MeOH solution via slow evaporation.

Table S6. Crystal data and structure refinement for **27** [a]

Identification code	**27**
Empirical formula	$C_{13}H_{16}N_2O_2$
Formula weight	232.28
Temperature/K	100.01(13)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	9.4693(4)
b/Å	6.1019(2)
c/Å	10.6945(4)
α/°	90
β/°	101.868(4)
γ/°	90
Volume/Å^3	604.73(4)
Z	2
ρ_{calc}g/cm^3	1.276
μ/mm^{-1}	0.706
F(000)	248.0
Crystal size/mm^3	0.23 × 0.20 × 0.19
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.448 to 152.22
Index ranges	$-11 \le h \le 11$, $-7 \le k \le 7$, $-13 \le l \le 13$
Reflections collected	10559
Independent reflections	2376 [R_{int} = 0.0411, R_{sigma} = 0.0304]
Data/restraints/parameters	2376/1/156
Goodness-of-fit on F^2	1.081
Final R indexes [I>=2σ (I)]	R_1 = 0.0325, wR_2 = 0.0835
Final R indexes [all data]	R_1 = 0.0352, wR_2 = 0.0852
Largest diff. peak/hole / e Å^{-3}	0.16/-0.24
Flack parameter	0.03(13)
CCDC	2416472

[a] Grown in DMSO solution via slow evaporation.

Table S7. Crystal data and structure refinement for **29** [a]

Identification code	**29**
Empirical formula	$C_{34}H_{32}N_4O_4$
Formula weight	560.63
Temperature/K	100.15
Crystal system	monoclinic
Space group	$P2_1$
a/Å	7.63700(10)
b/Å	15.9982(2)
c/Å	11.00670(10)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1344.78(3)
Z	2
ρ_{calc}g/cm^3	1.385
μ/mm^{-1}	0.741
F(000)	592.0
Crystal size/mm^3	0.22 × 0.21 × 0.20
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.032 to 154.768
Index ranges	$-9 \le h \le 9$, $-20 \le k \le 20$, $-13 \le l \le 13$
Reflections collected	25538
Independent reflections	5061 [R_{int} = 0.0396, R_{sigma} = 0.0272]
Data/restraints/parameters	5061/1/393
Goodness-of-fit on F^2	1.132
Final R indexes [I>=2σ (I)]	R_1 = 0.1056, wR_2 = 0.2702
Final R indexes [all data]	R_1 = 0.1069, wR_2 = 0.2716
Largest diff. peak/hole / e Å^{-3}	0.21/-0.06
Flack parameter	0.16(10)
CCDC	2491941

[a] Grown in MeOH/DMSO solution via slow evaporation.

5. ^{1}H NMR and ^{13}C NMR spectra

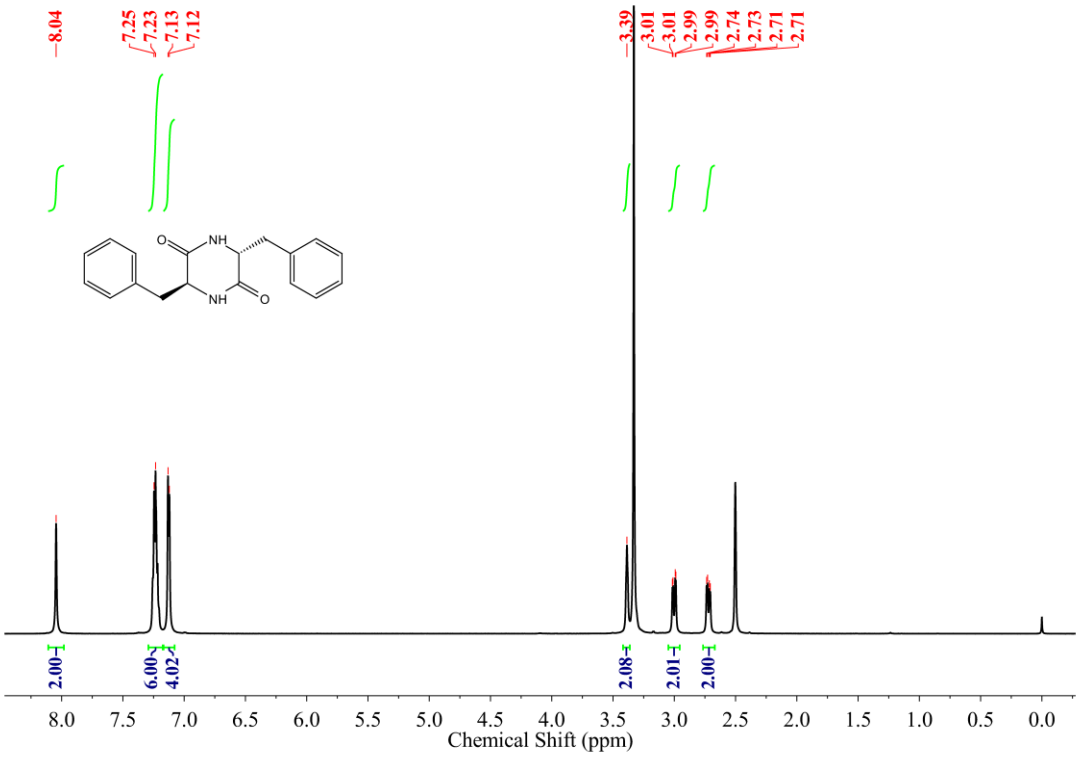


Figure S10. ^{1}H NMR spectrum of **2** (600 MHz, DMSO-d_6).

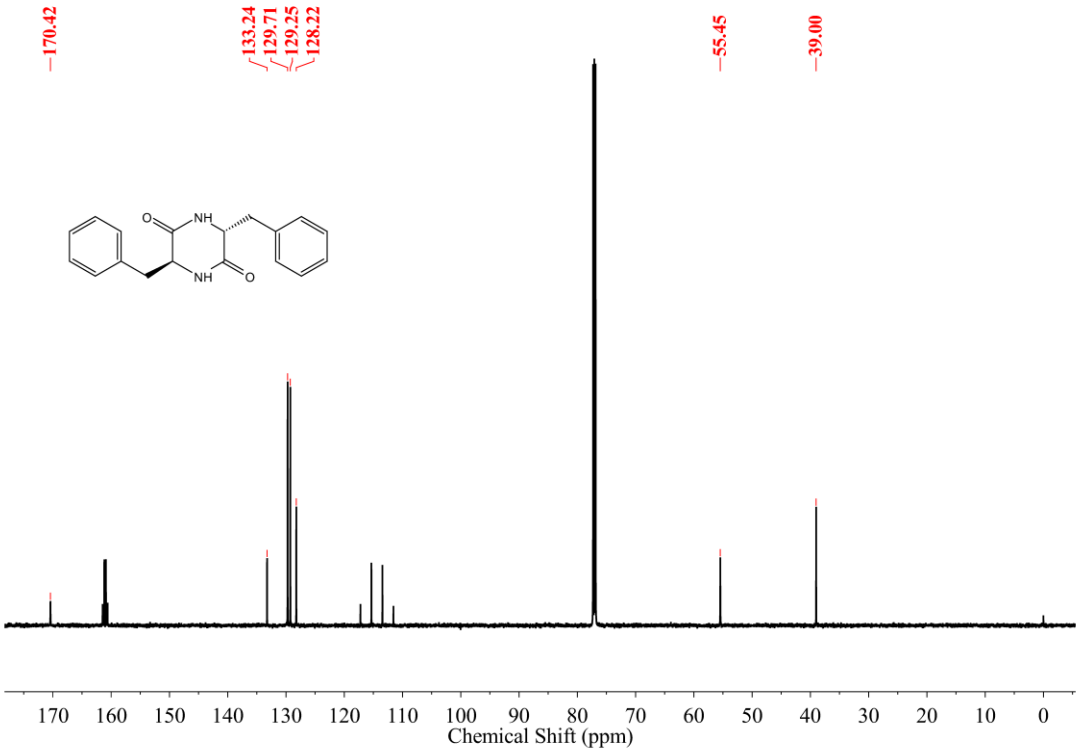


Figure S11. ^{13}C NMR spectrum of **2** (151 MHz, $CDCl_3$-CF_3COOH).

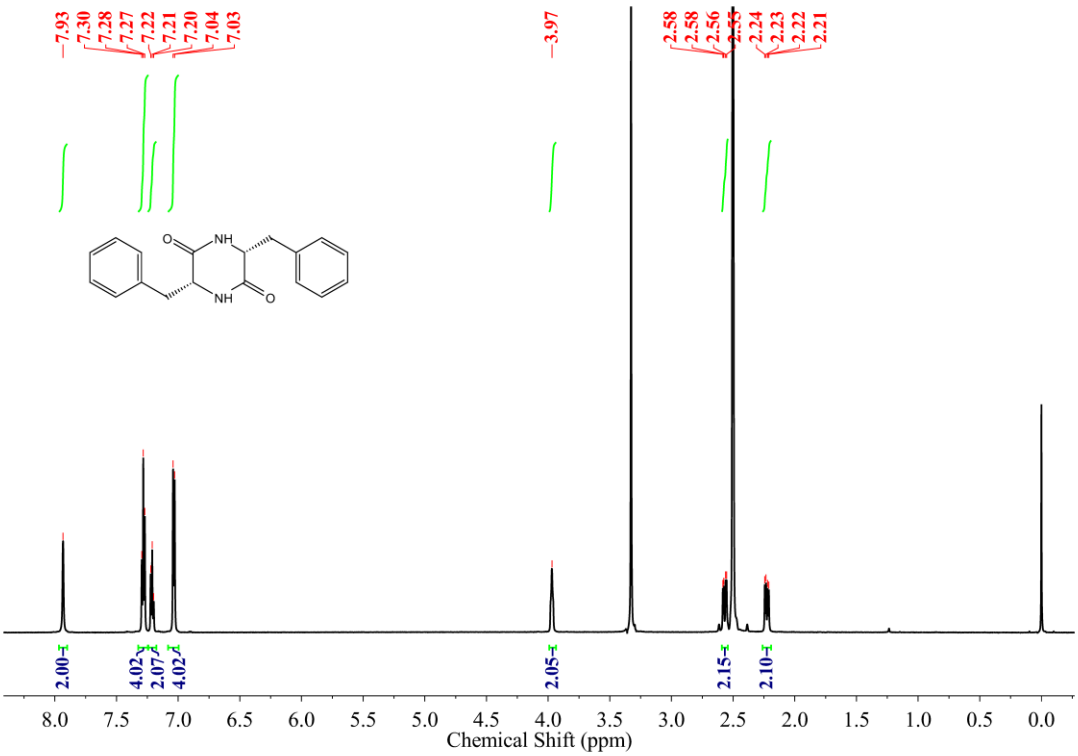


Figure S12. ^{1}H NMR spectrum of **3** (600 MHz, DMSO-d_6).

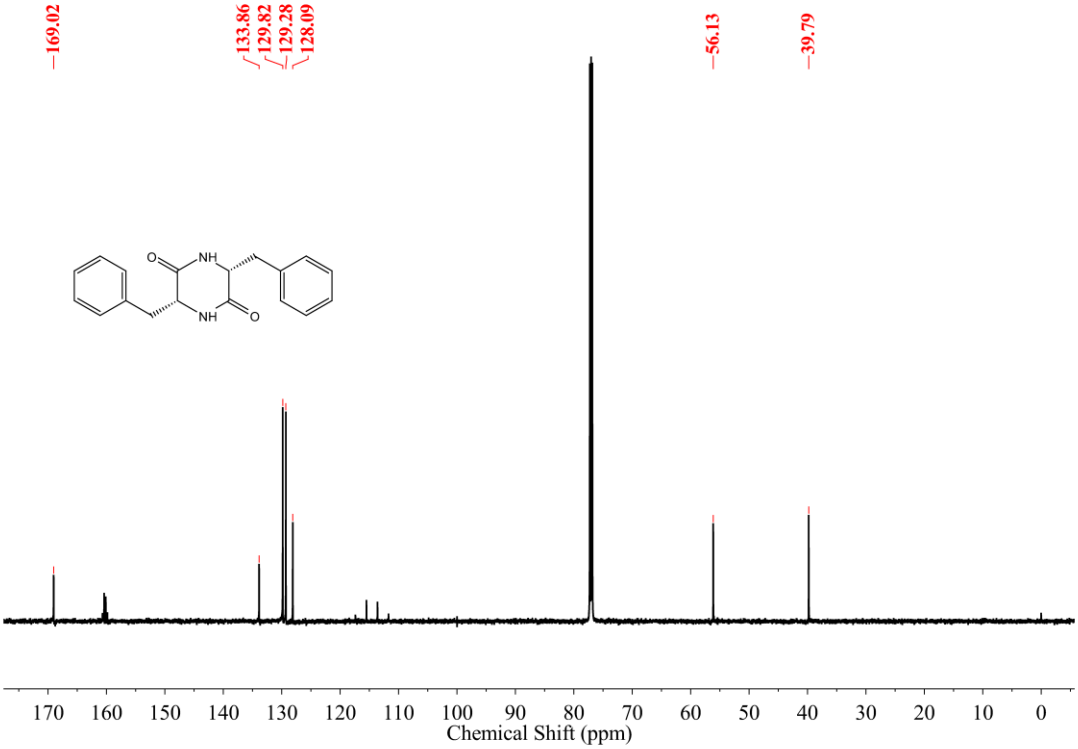


Figure S13. ^{13}C NMR spectrum of **3** (151 MHz, $CDCl_3$-CF_3COOH).

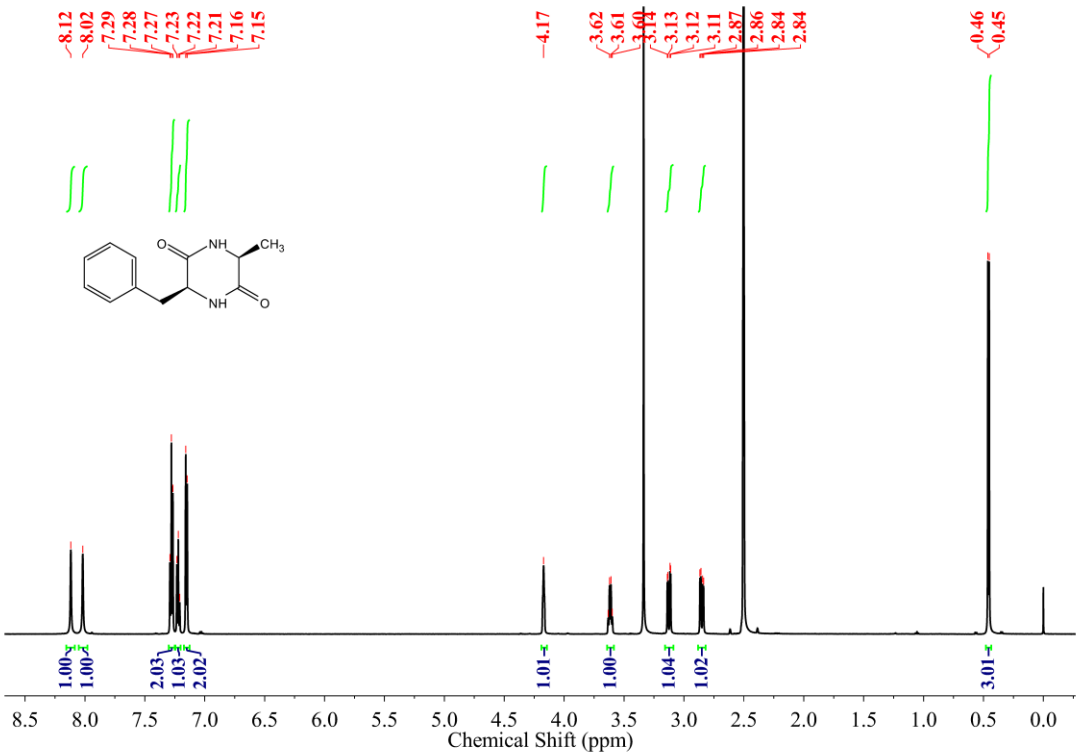


Figure S14. ^{1}H NMR spectrum of **4** (600 MHz, DMSO-d_6).

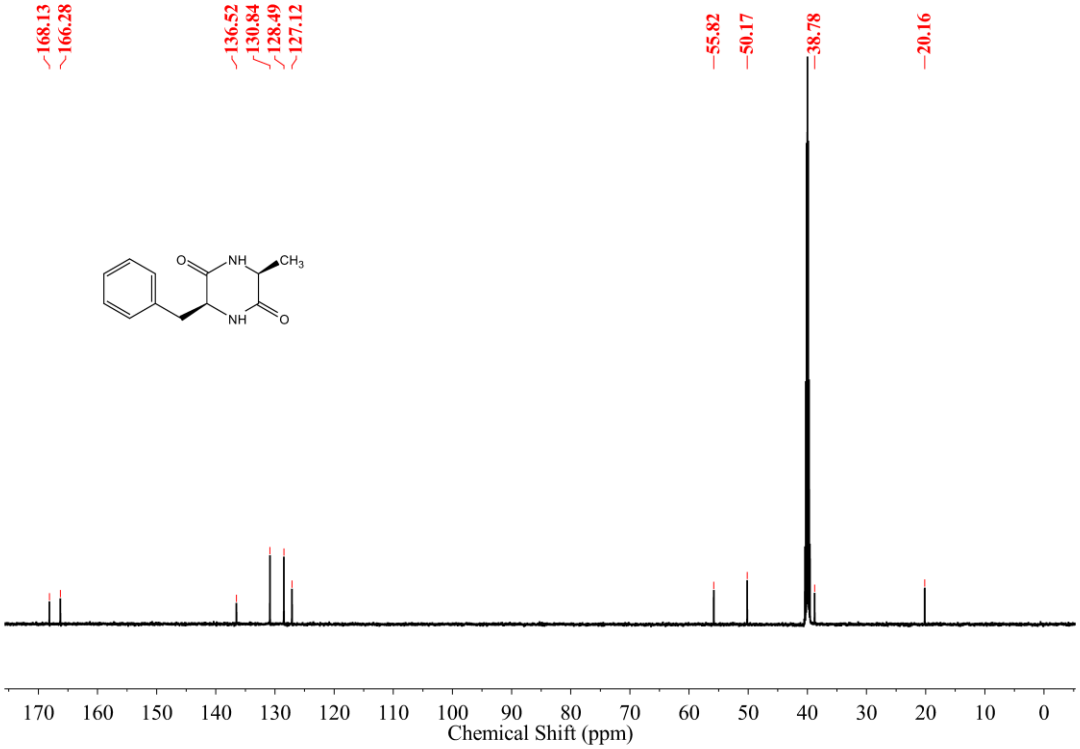


Figure S15. ^{13}C NMR spectrum of **4** (151 MHz, DMSO-d_6).

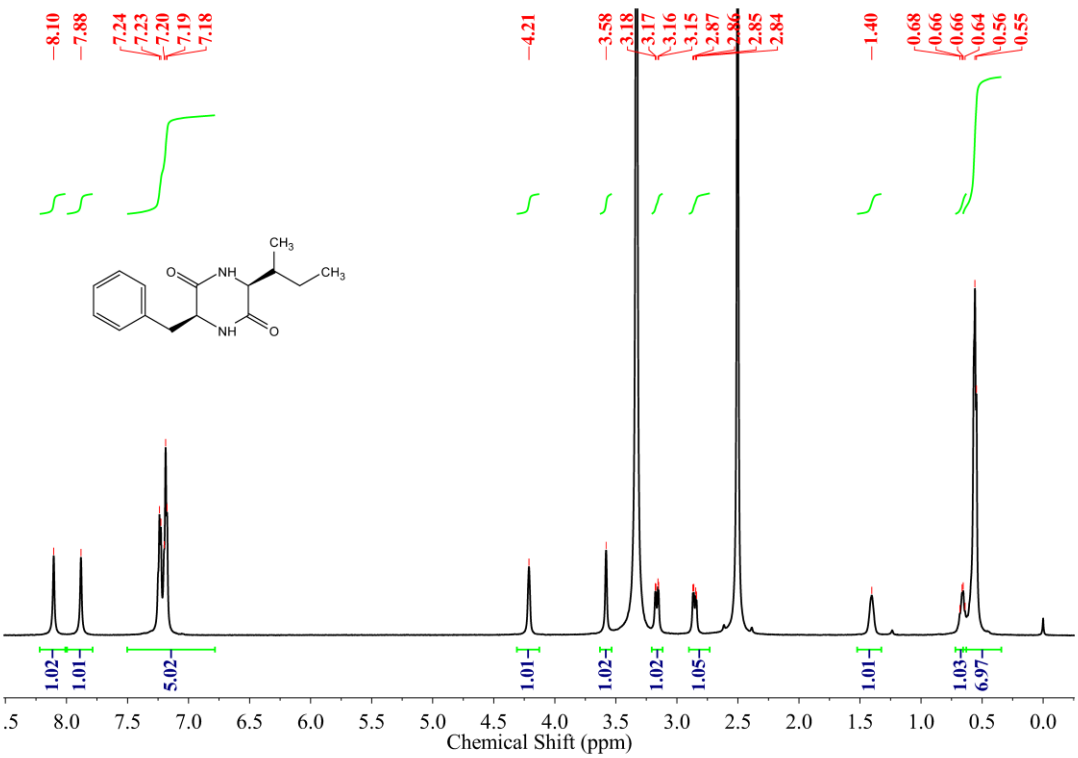


Figure S16. ^{1}H NMR spectrum of **5** (600 MHz, DMSO-d_6).

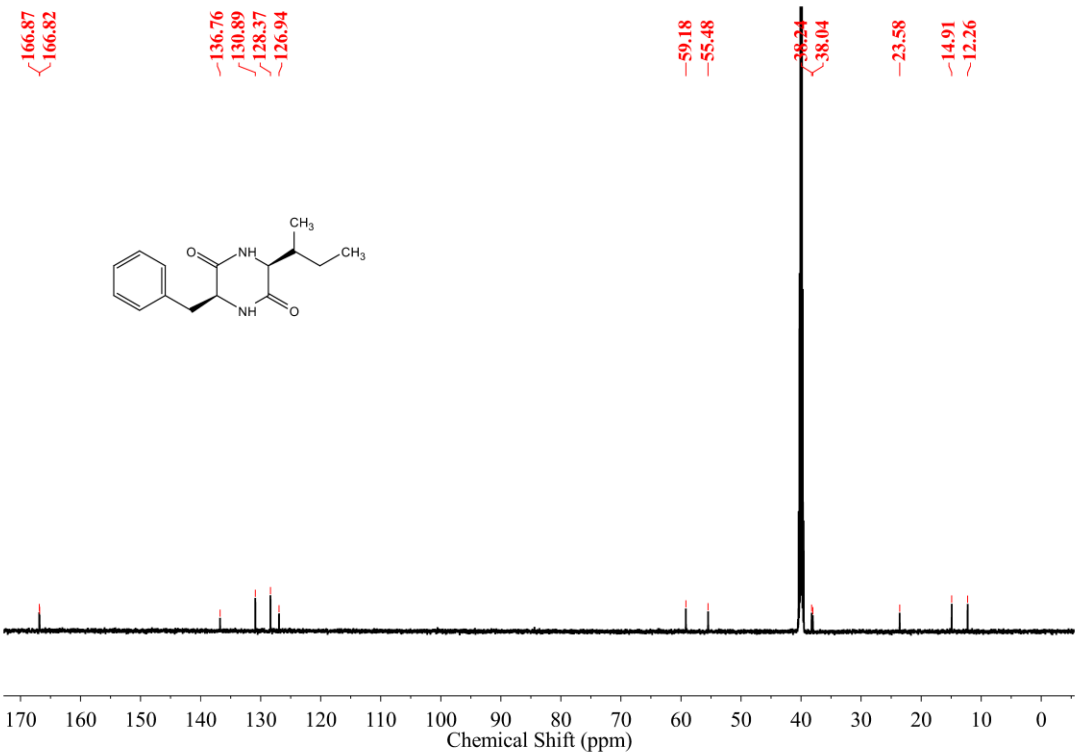


Figure S17. ^{13}C NMR spectrum of **5** (151 MHz, DMSO-d_6).

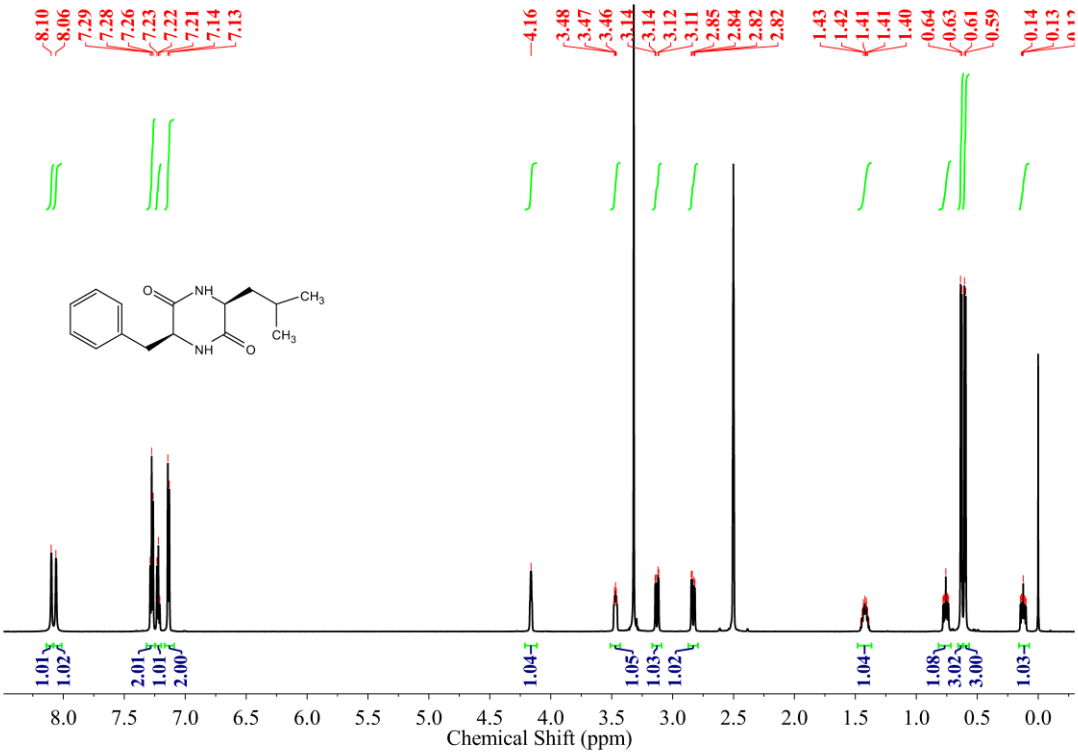


Figure S18. ^{1}H NMR spectrum of **6** (600 MHz, DMSO-d_6).

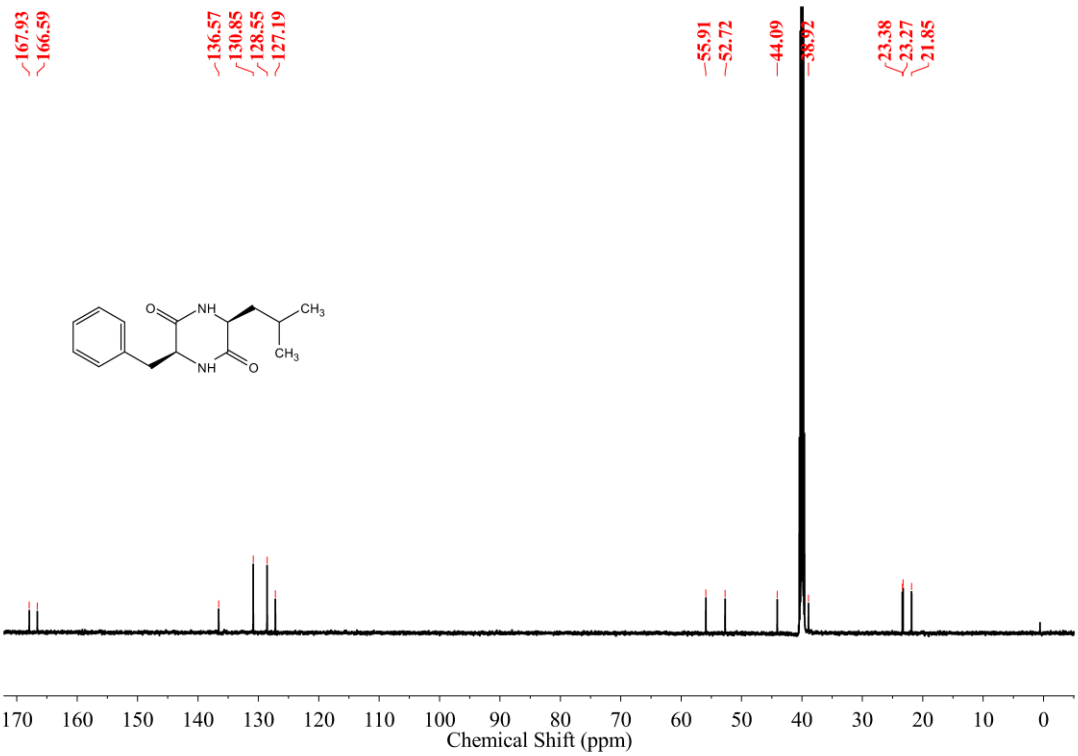


Figure S19. ^{13}C NMR spectrum of **6** (151 MHz, DMSO-d_6).

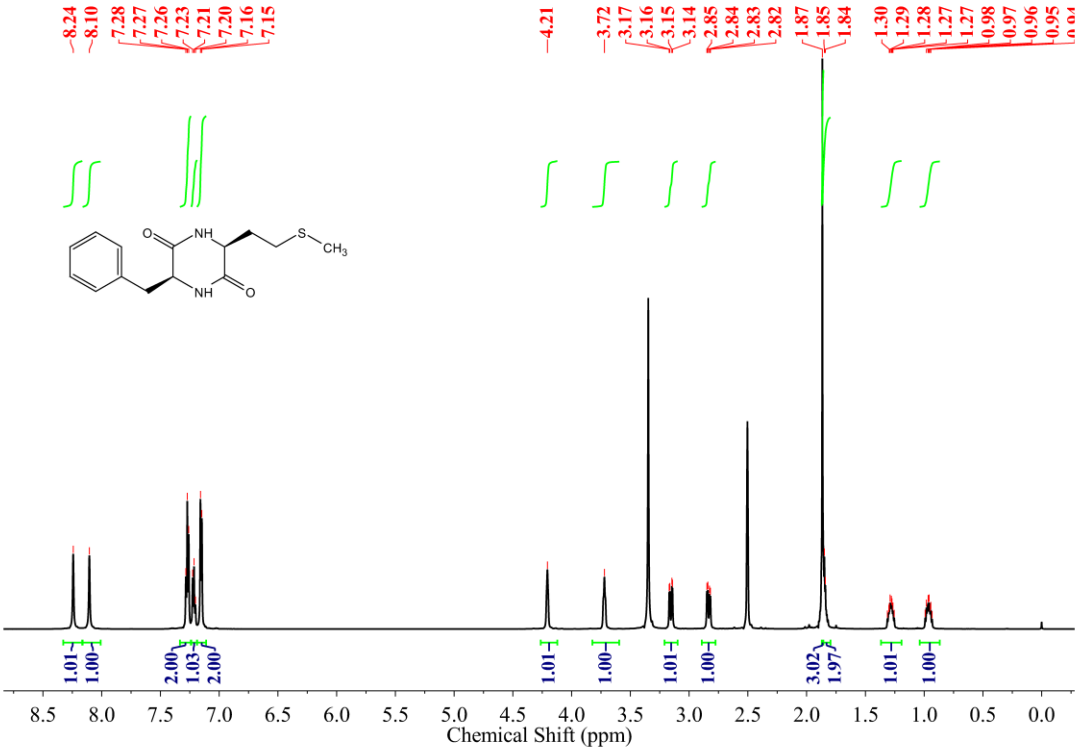


Figure S20. ^{1}H NMR spectrum of **7** (600 MHz, DMSO-d_6).

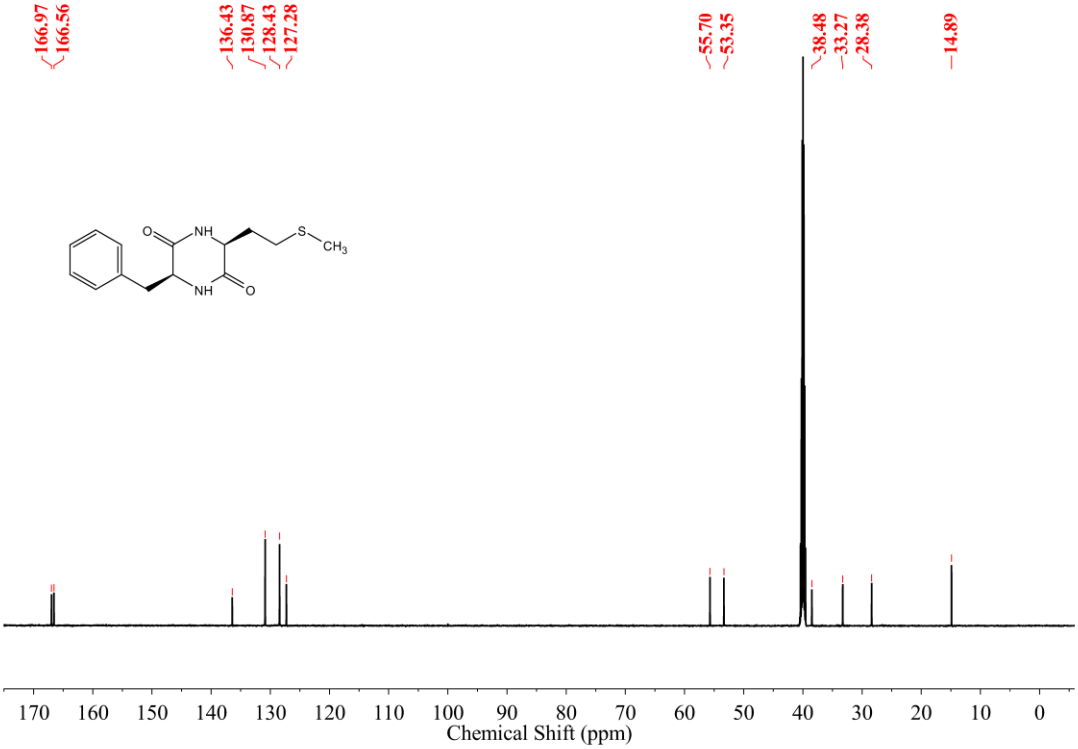


Figure S21. ^{13}C NMR spectrum of **7** (151 MHz, DMSO-d_6).

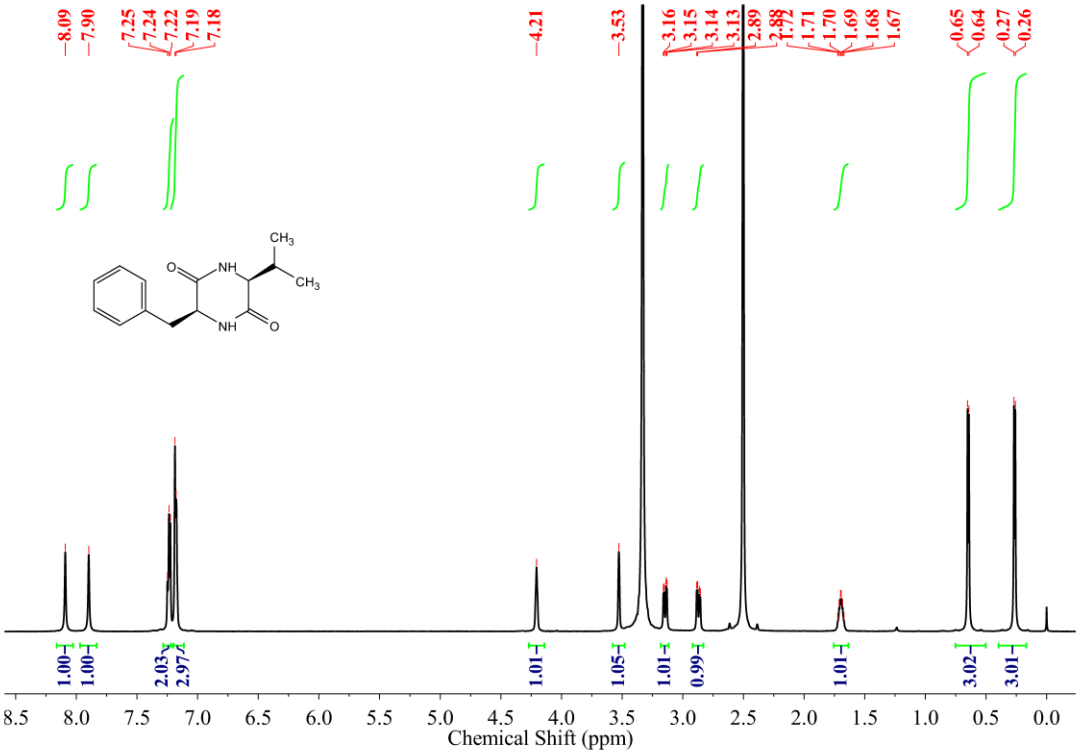


Figure S22. ^{1}H NMR spectrum of **8** (600 MHz, DMSO-d_6).

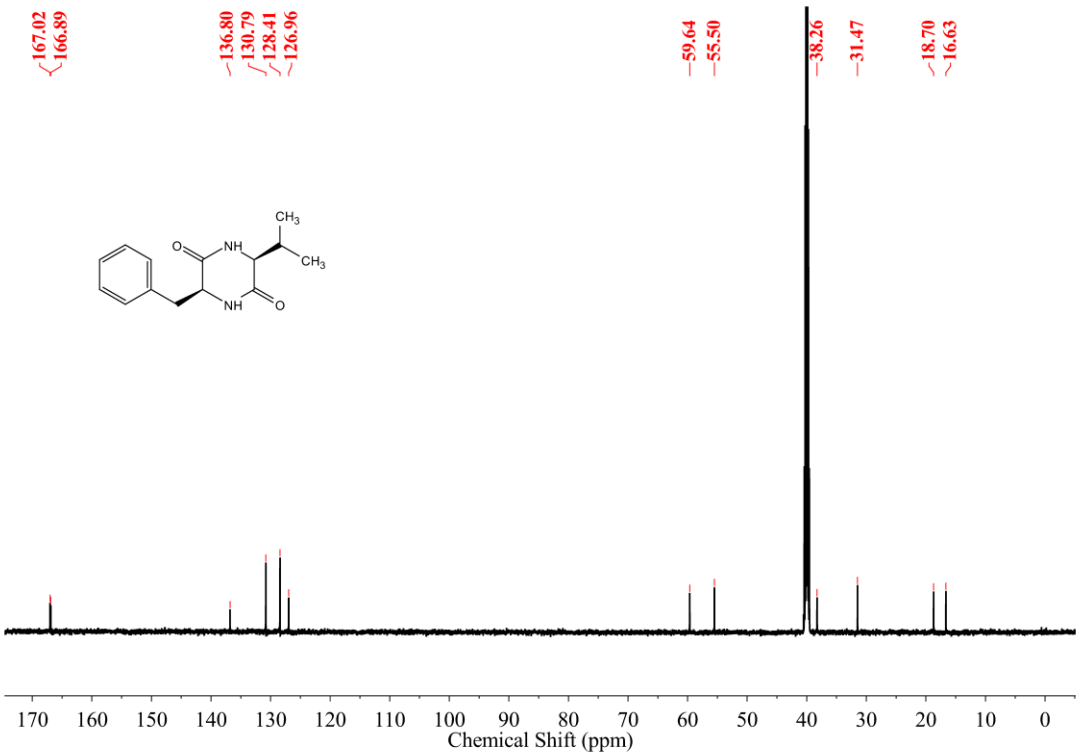


Figure S23. ^{13}C NMR spectrum of **8** (151 MHz, DMSO-d_6).

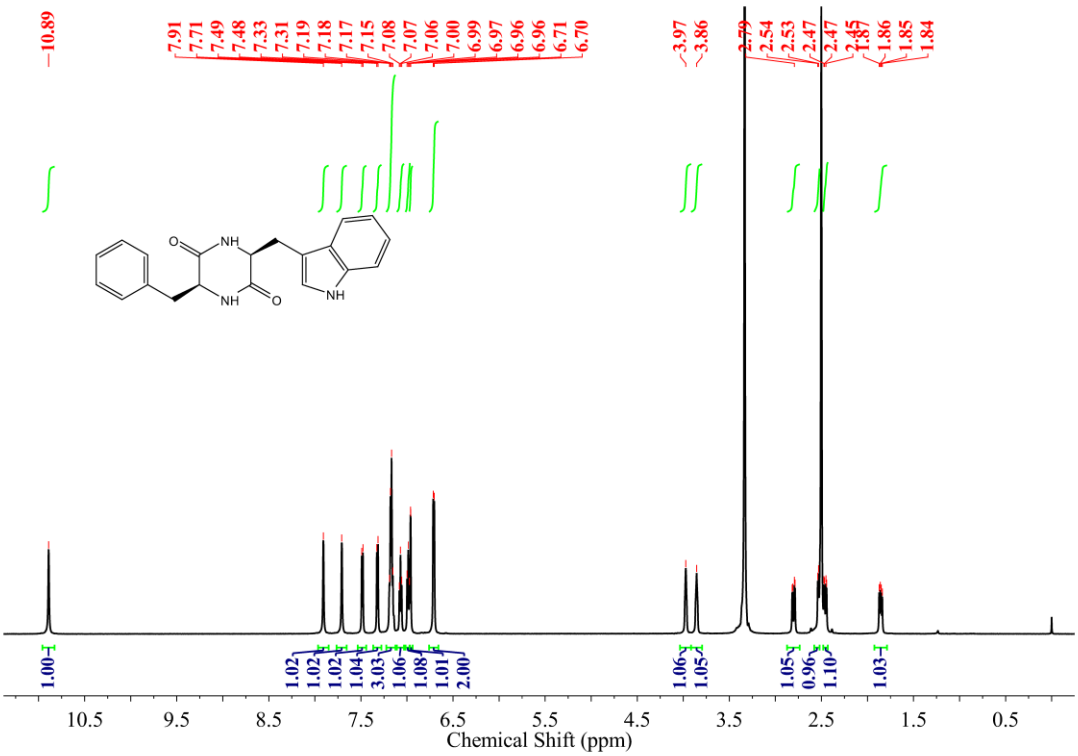


Figure S24. ^{1}H NMR spectrum of **9** (600 MHz, DMSO-d_6).

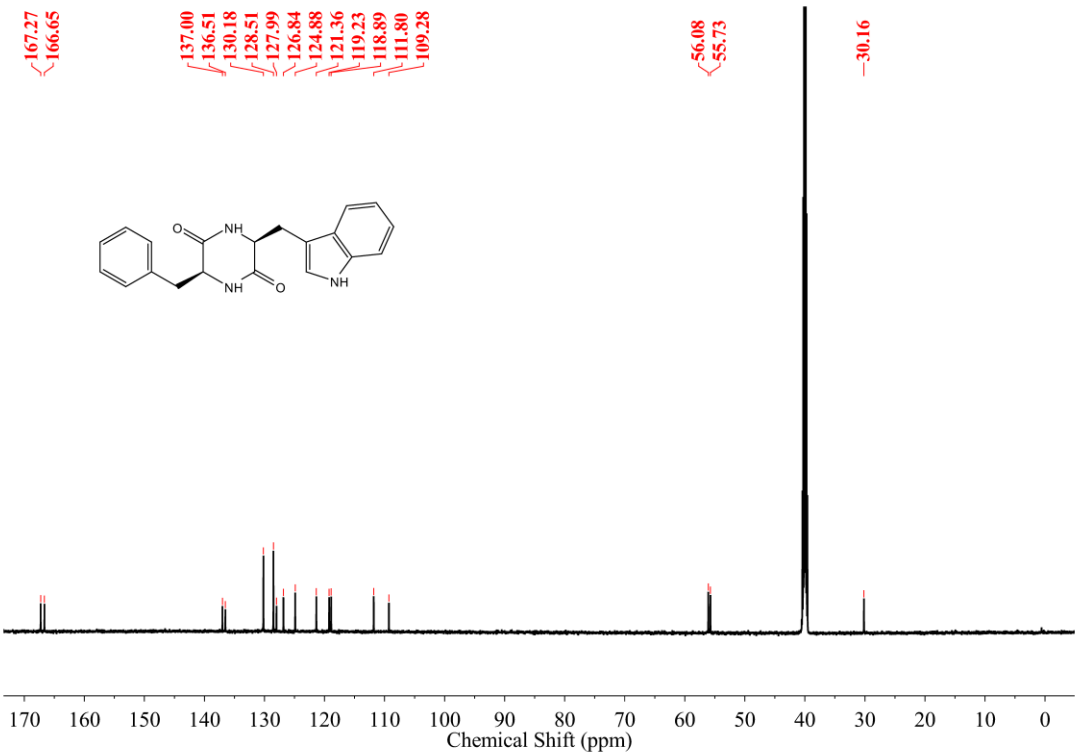


Figure S25. ^{13}C NMR spectrum of **9** (151 MHz, DMSO-d_6).

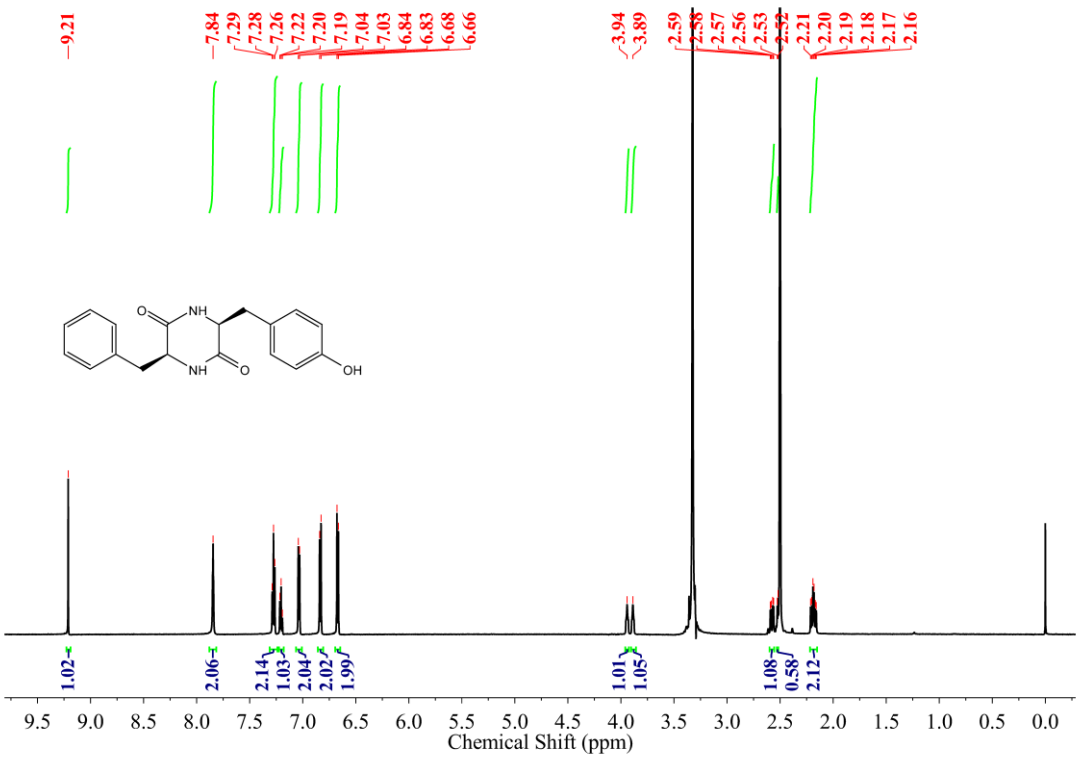


Figure S26. ^{1}H NMR spectrum of **10** (600 MHz, DMSO-d_6).

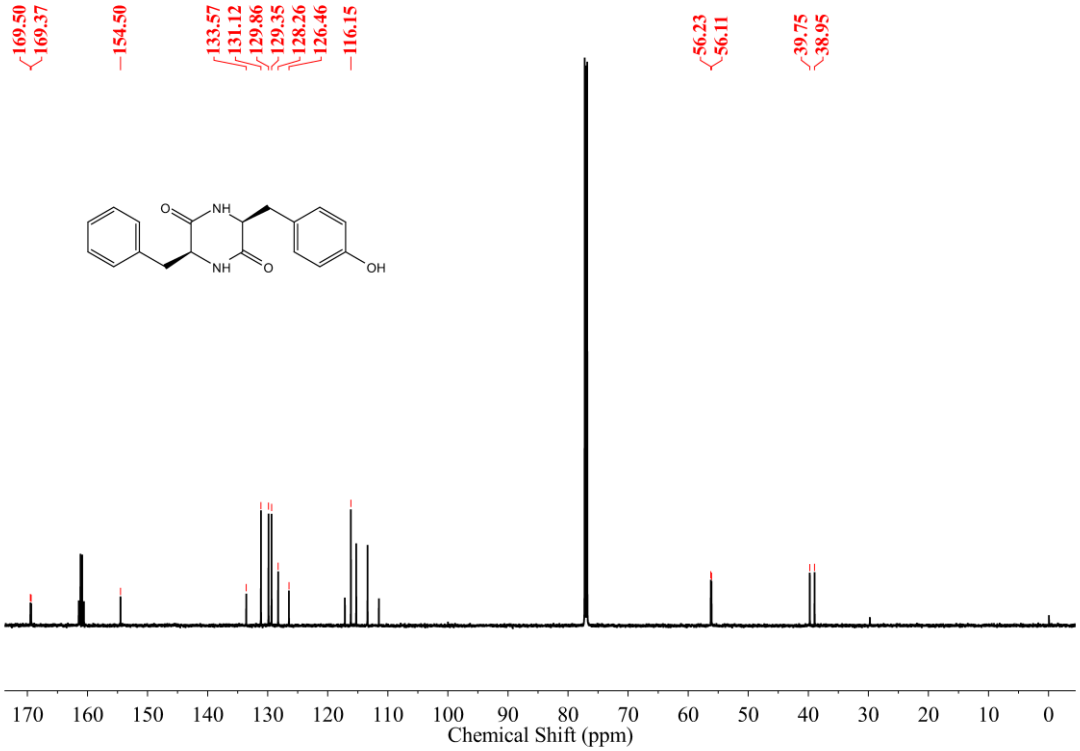


Figure S27. ^{13}C NMR spectrum of **10** (151 MHz, $CDCl_3$-CF_3COOH).

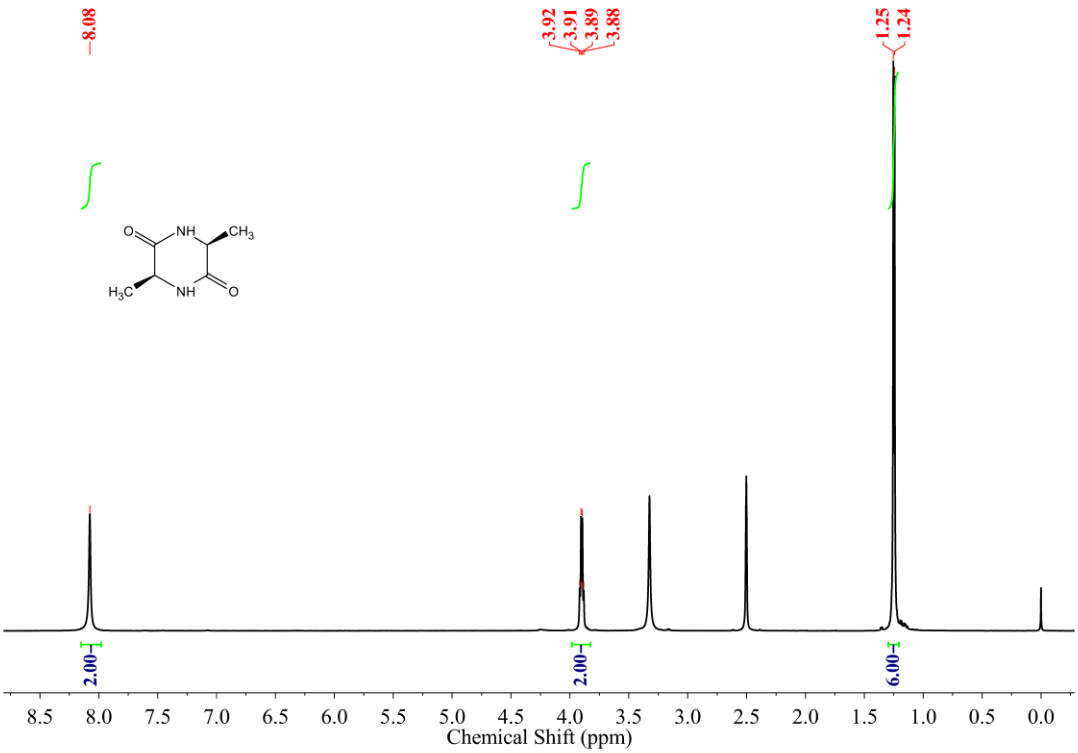


Figure S28. ^{1}H NMR spectrum of **11** (600 MHz, DMSO-d_6).

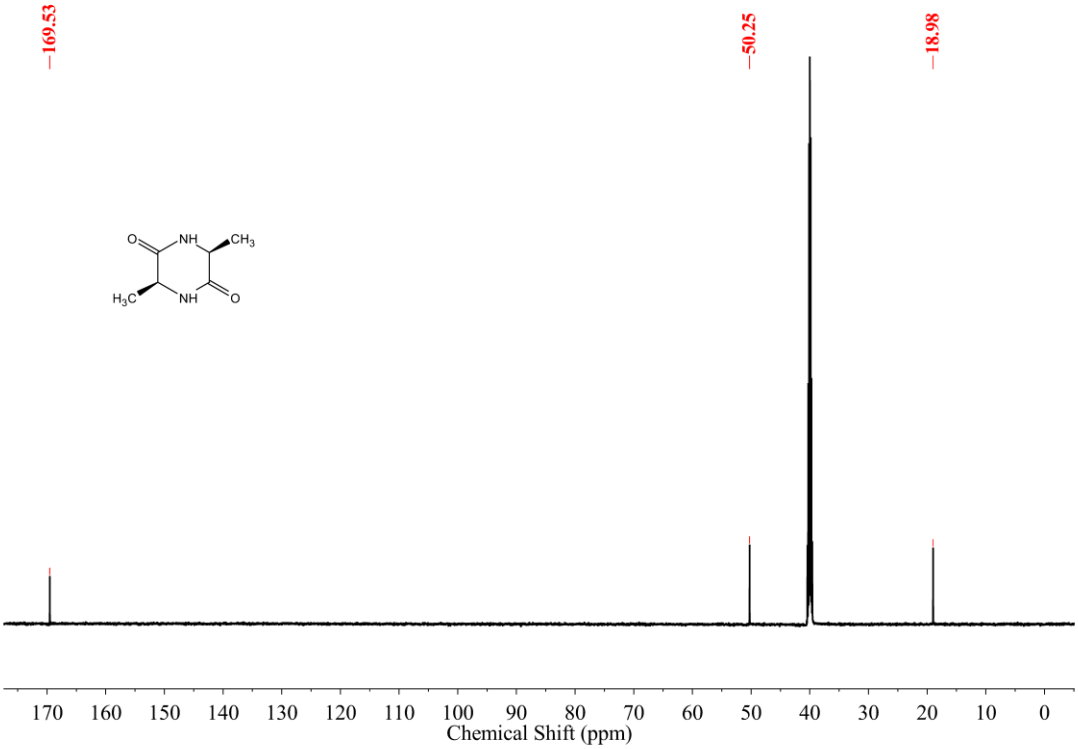


Figure S29. ^{13}C NMR spectrum of **11** (151 MHz, DMSO-d_6).

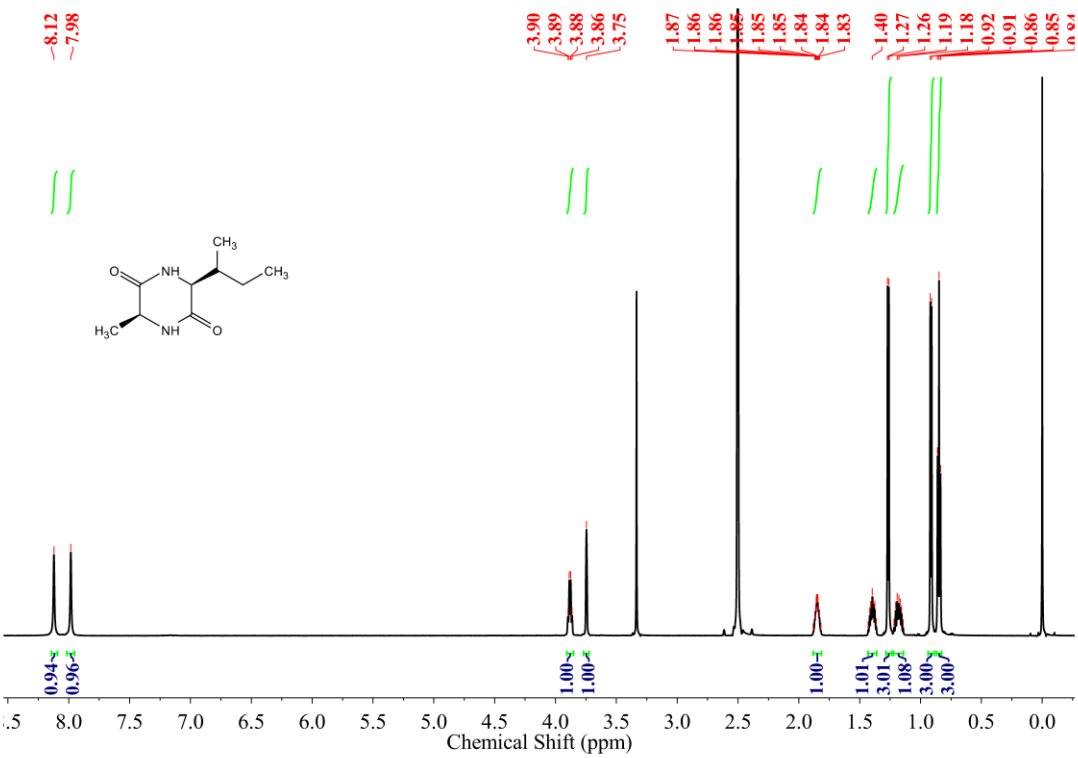


Figure S30. ^{1}H NMR spectrum of **12** (600 MHz, DMSO-d_6).

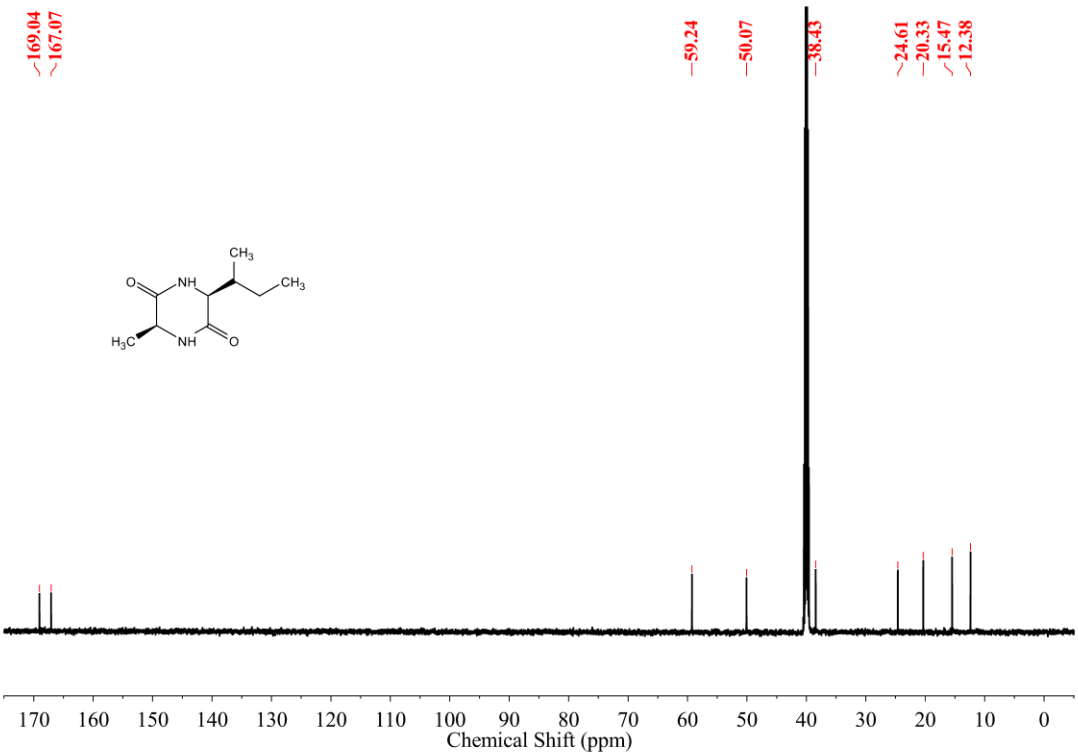


Figure S31. ^{13}C NMR spectrum of **12** (151 MHz, DMSO-d_6).

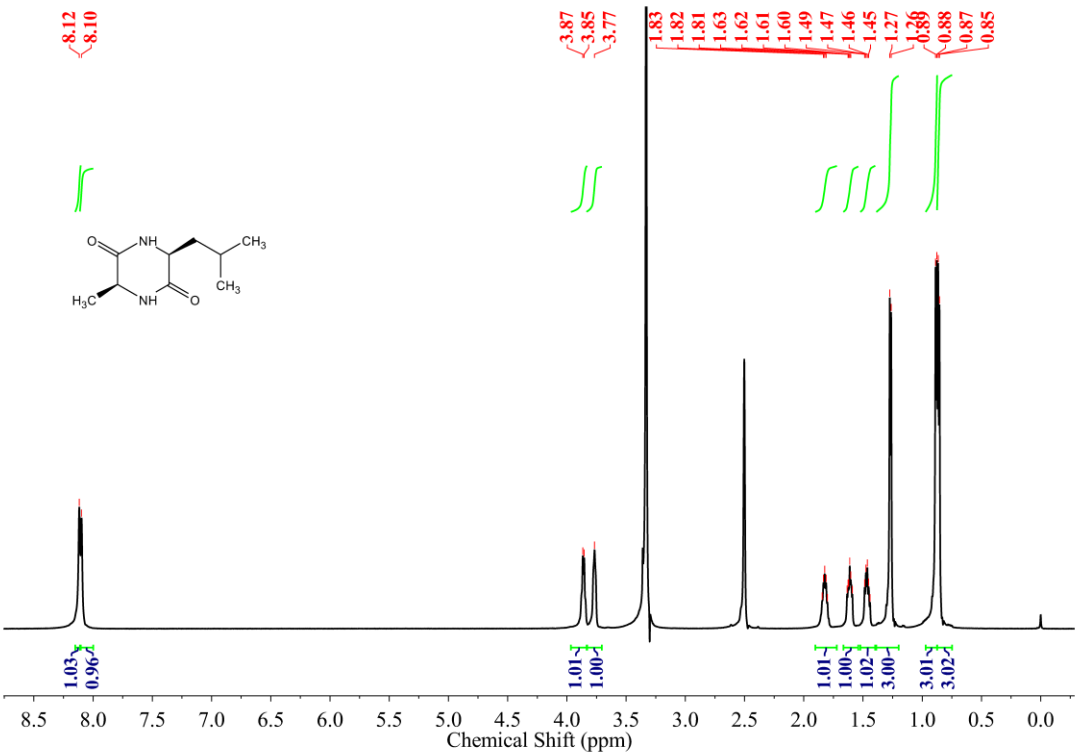


Figure S32. ^{1}H NMR spectrum of **13** (600 MHz, DMSO-d_6).

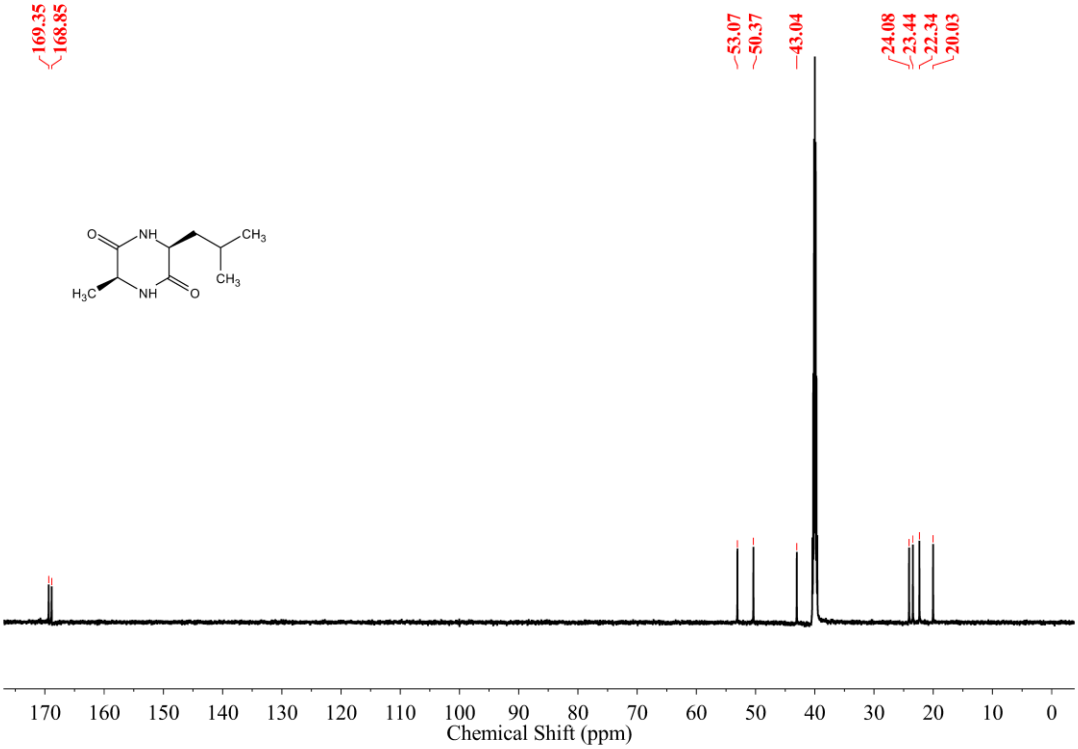


Figure S33. ^{13}C NMR spectrum of **13** (151 MHz, DMSO-d_6).

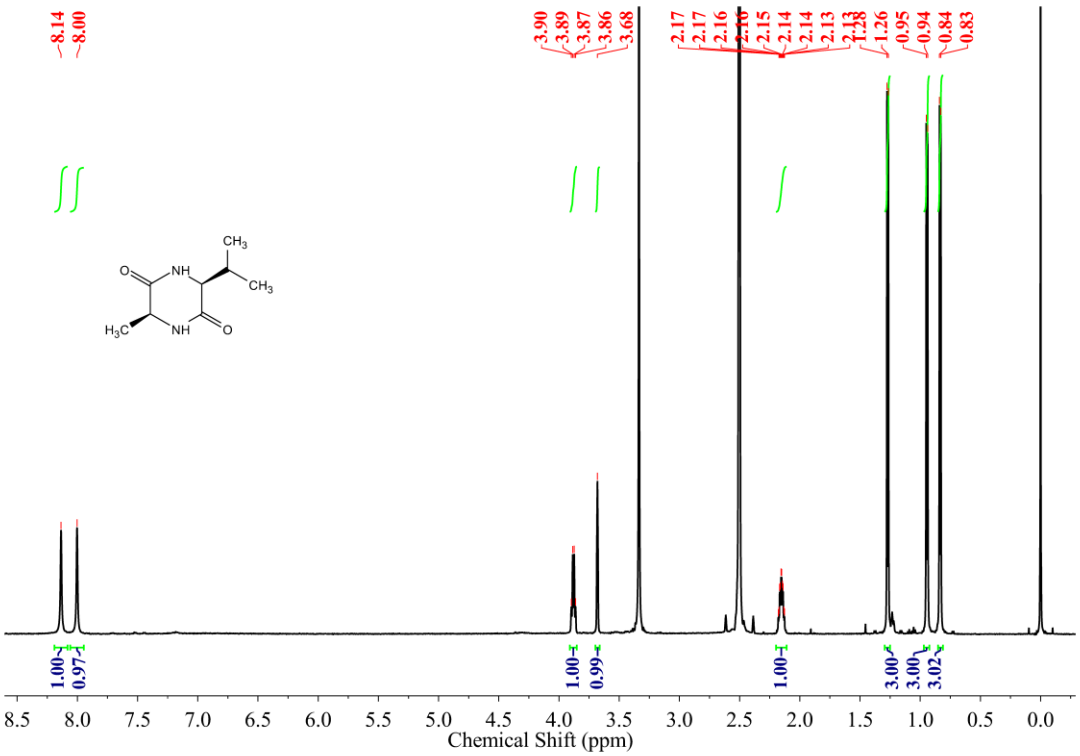


Figure S34. ^{1}H NMR spectrum of **14** (600 MHz, DMSO-d_6).

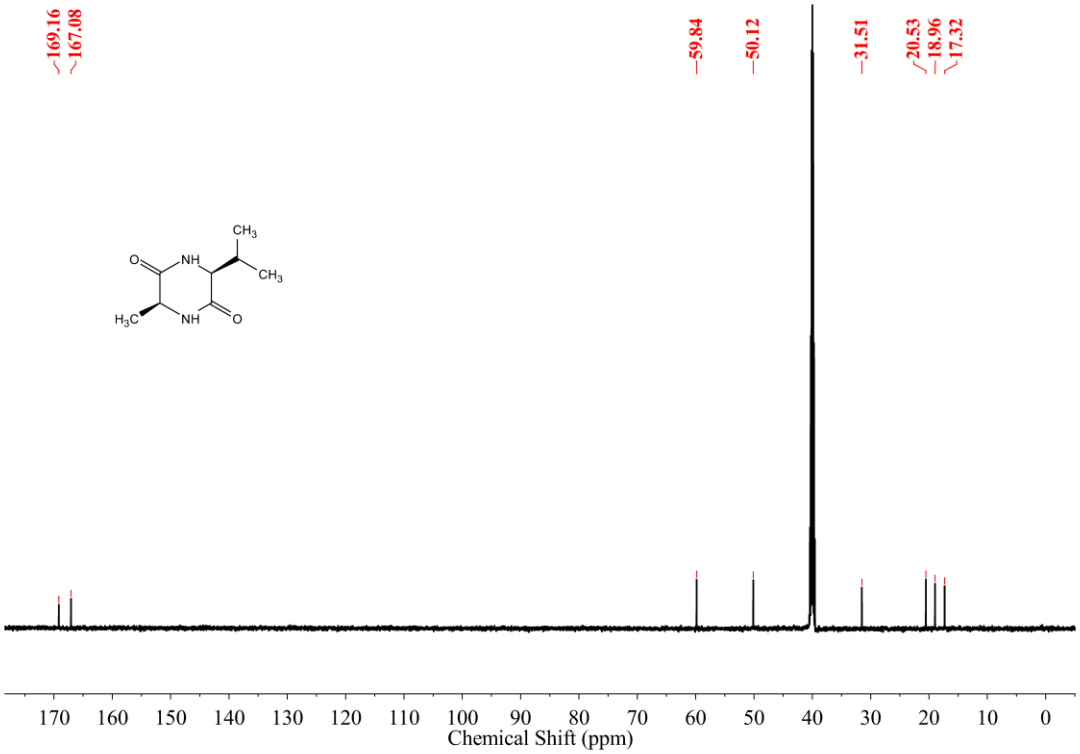


Figure S35. ^{13}C NMR spectrum of **14** (151 MHz, DMSO-d_6).

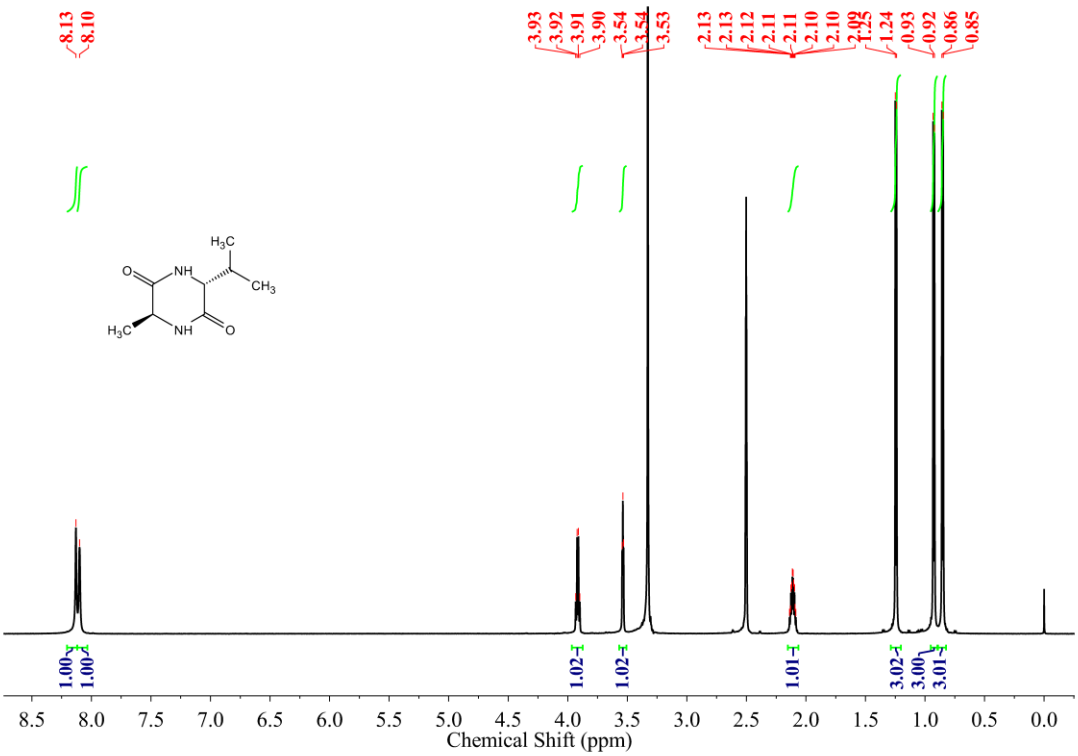


Figure S36. ^{1}H NMR spectrum of **15** (600 MHz, DMSO-d_6).

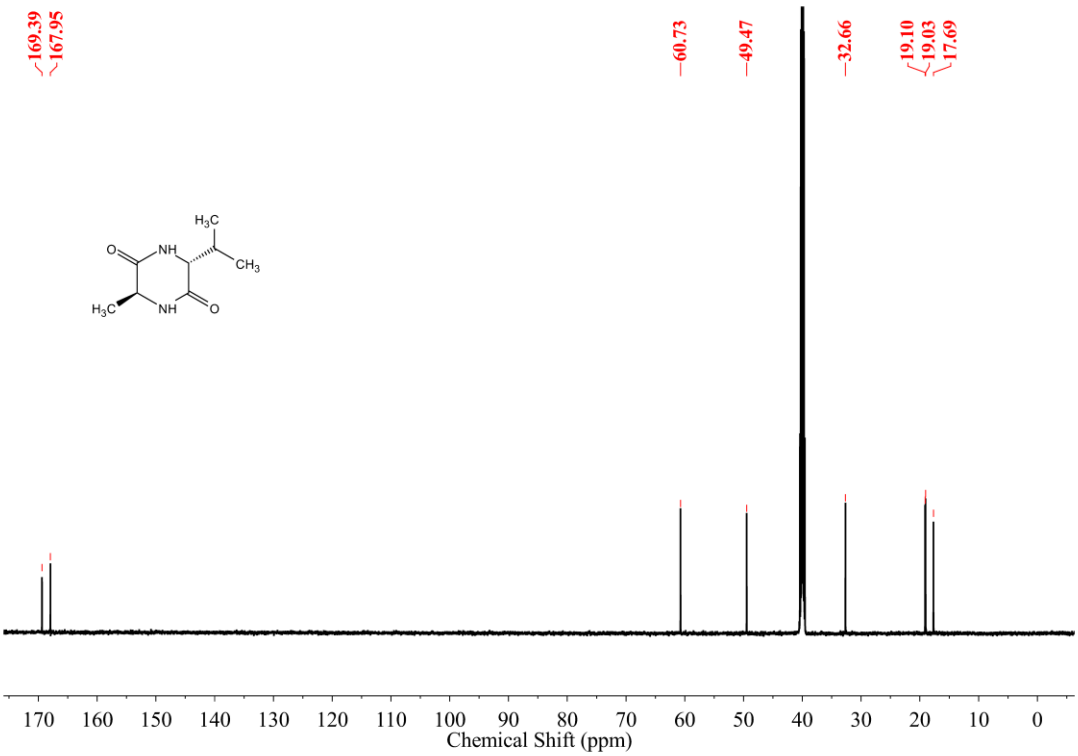


Figure S37. ^{13}C NMR spectrum of **15** (151 MHz, DMSO-d_6).

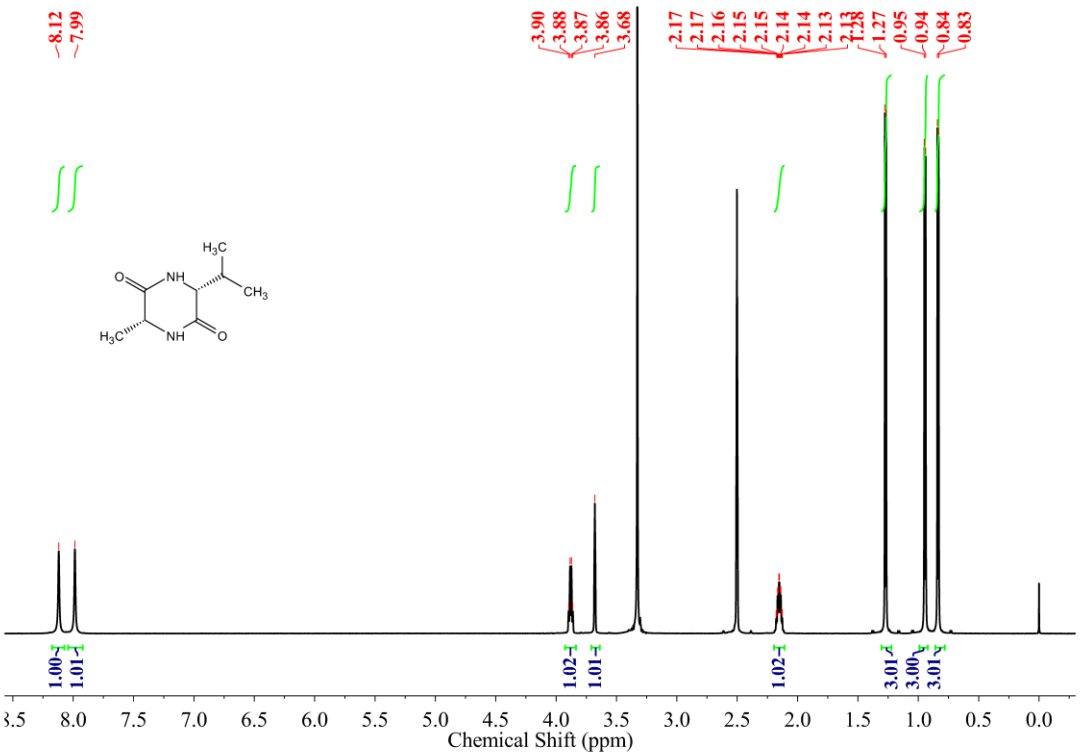


Figure S38. ^{1}H NMR spectrum of **16** (600 MHz, DMSO-d_6).

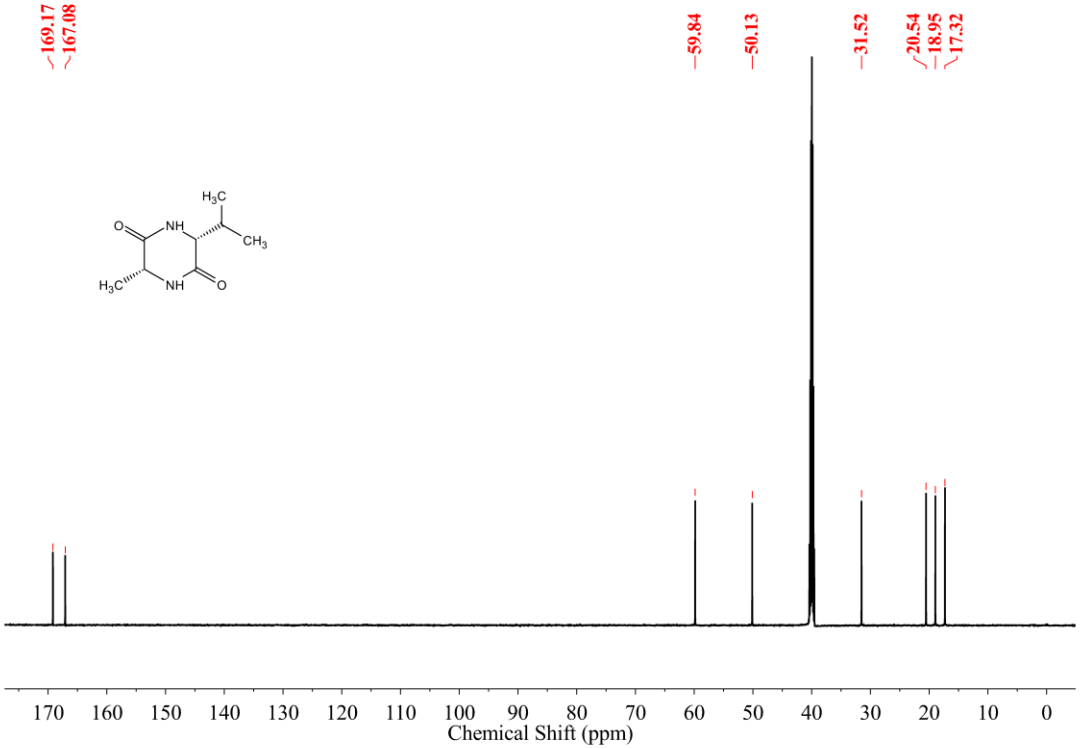


Figure S39. ^{13}C NMR spectrum of **16** (151 MHz, DMSO-d_6).

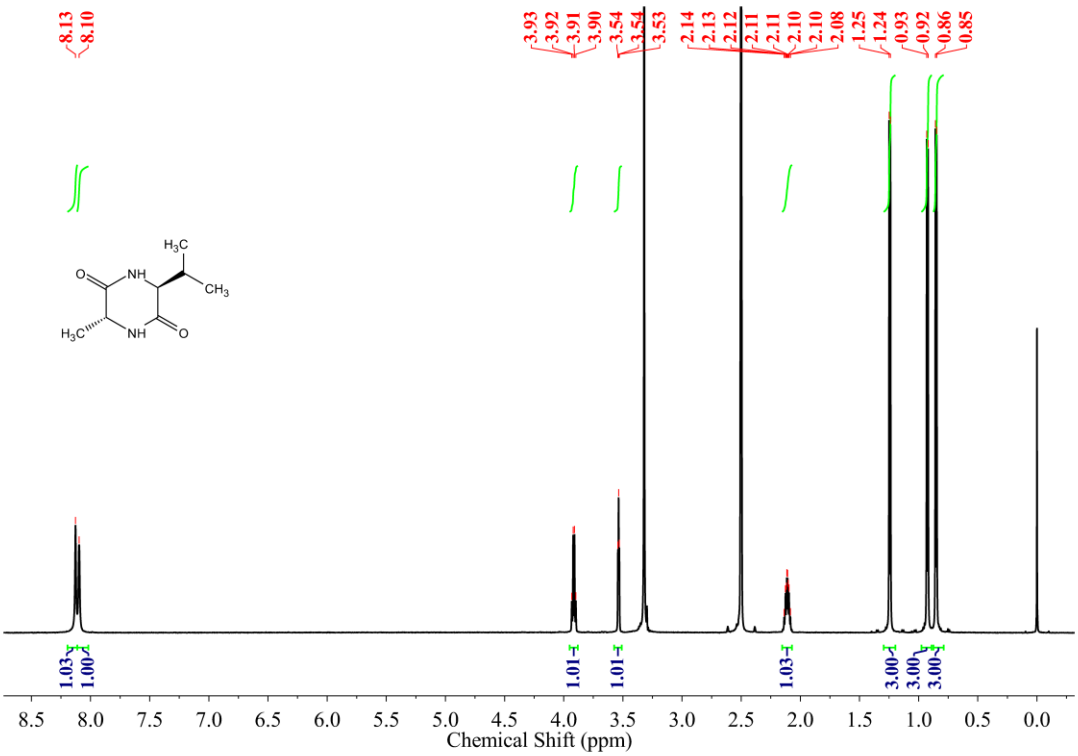


Figure S40. ^{1}H NMR spectrum of **17** (600 MHz, DMSO-d_6).

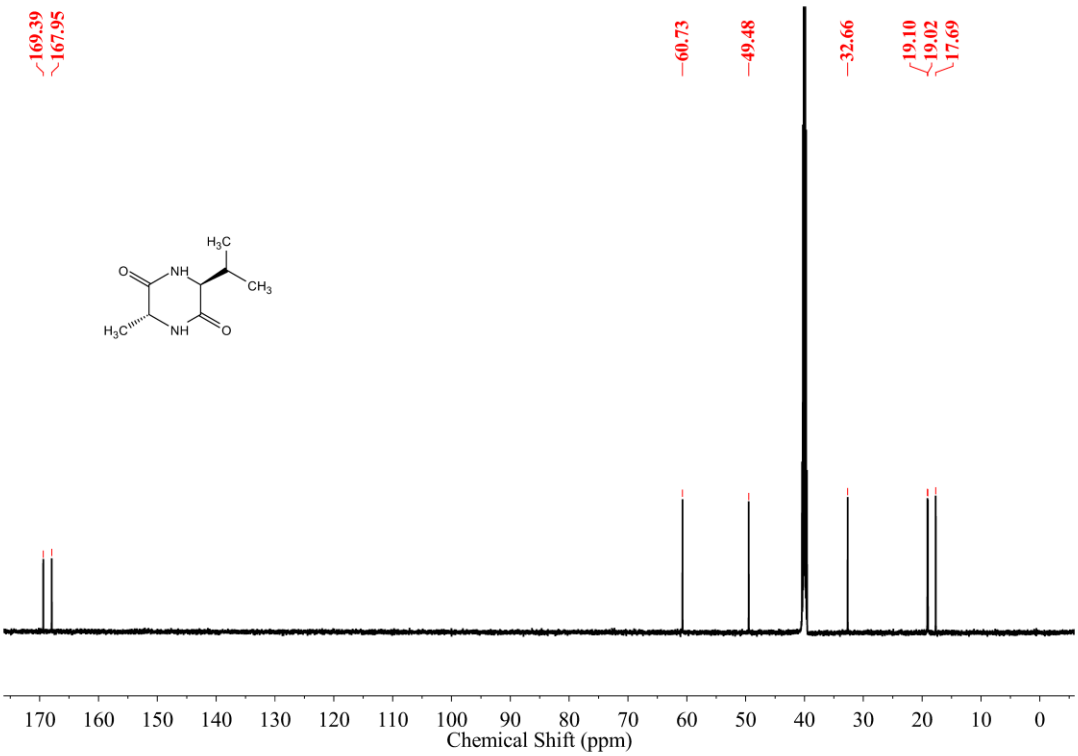


Figure S41. ^{13}C NMR spectrum of **17** (151 MHz, DMSO-d_6).

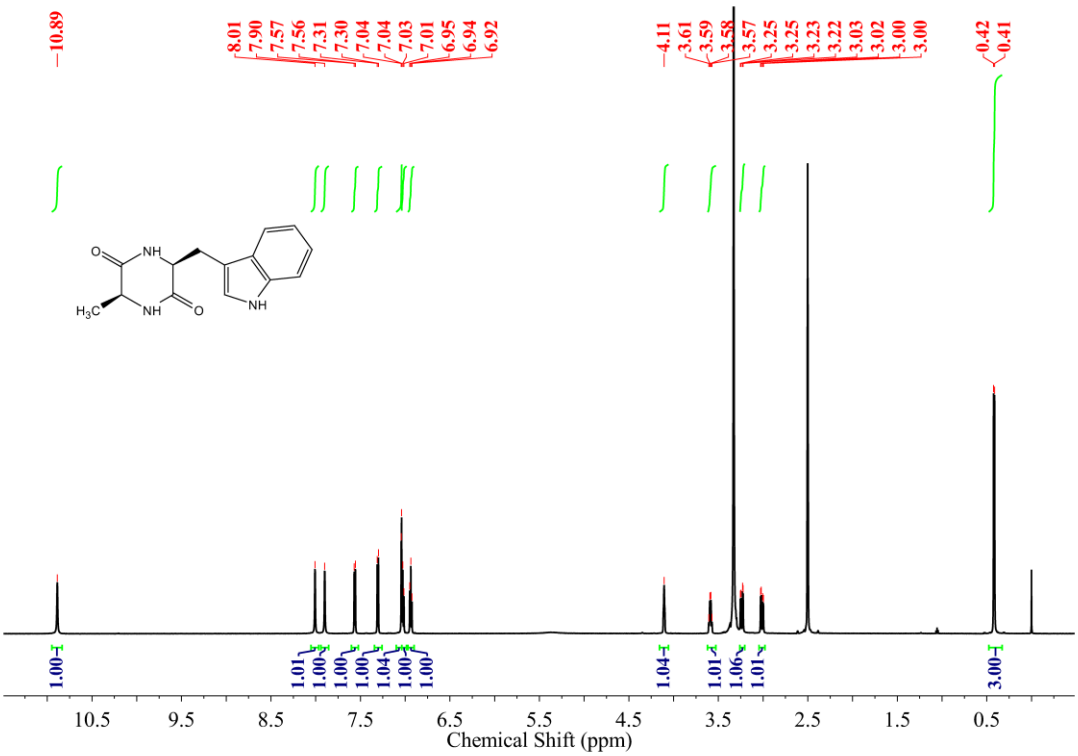


Figure S42. ^{1}H NMR spectrum of **18** (600 MHz, DMSO-d_6).

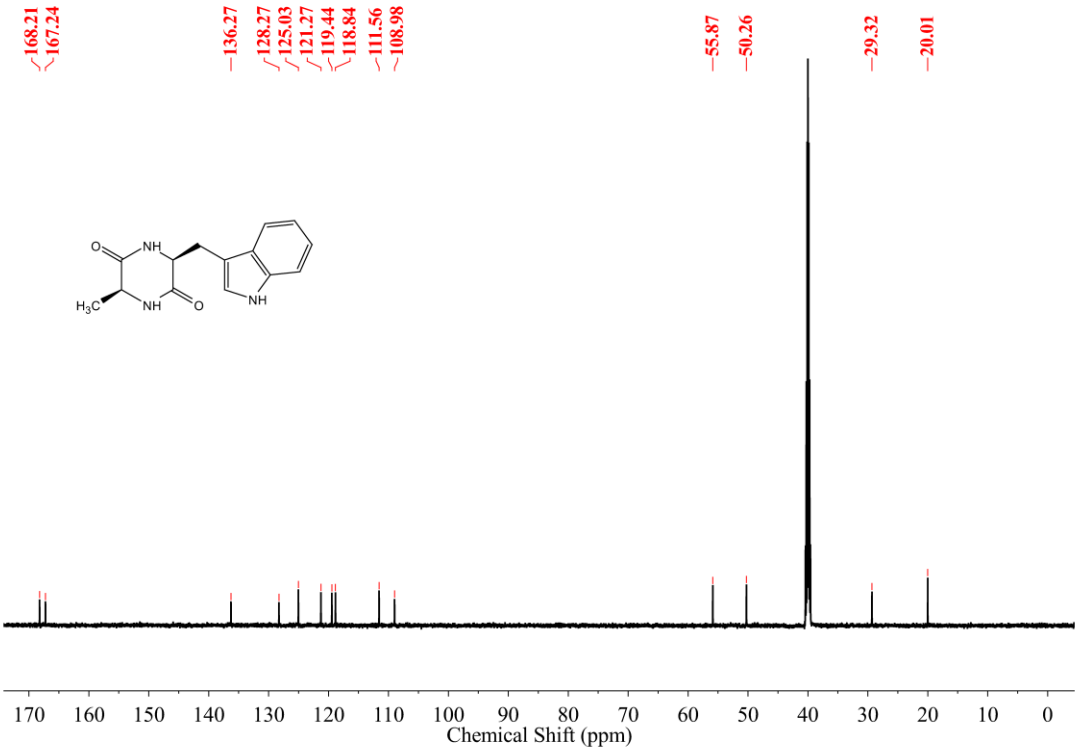


Figure S43. ^{13}C NMR spectrum of **18** (151 MHz, DMSO-d_6).

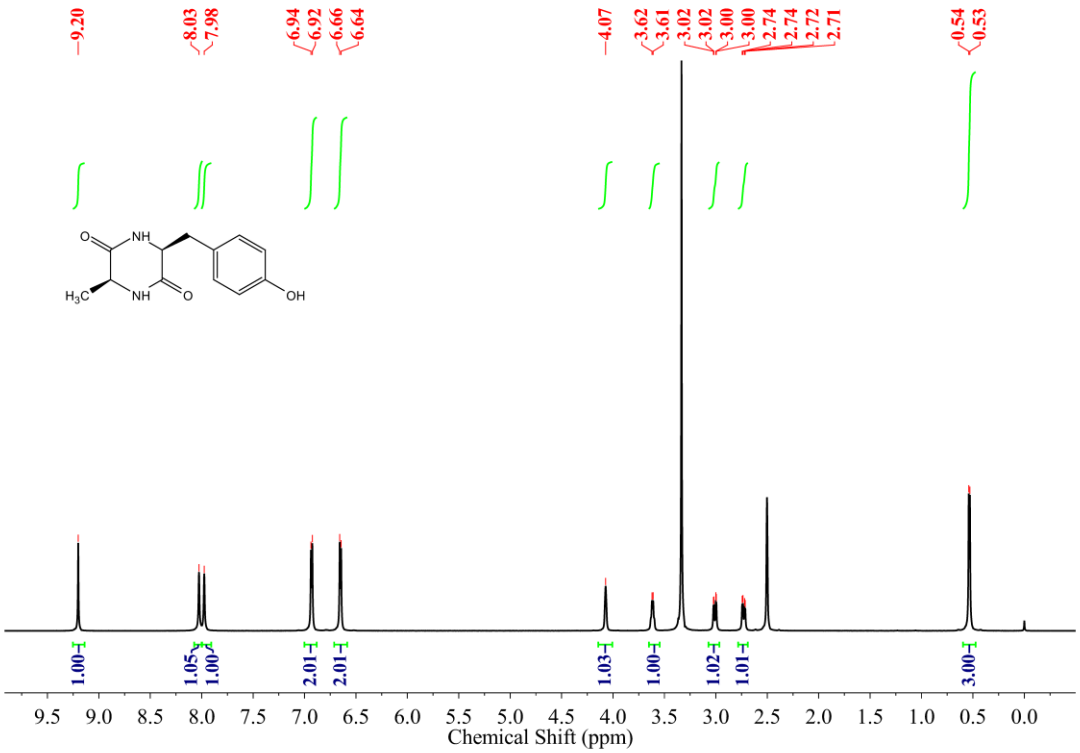


Figure S44. ^{1}H NMR spectrum of **19** (600 MHz, DMSO-d_6).

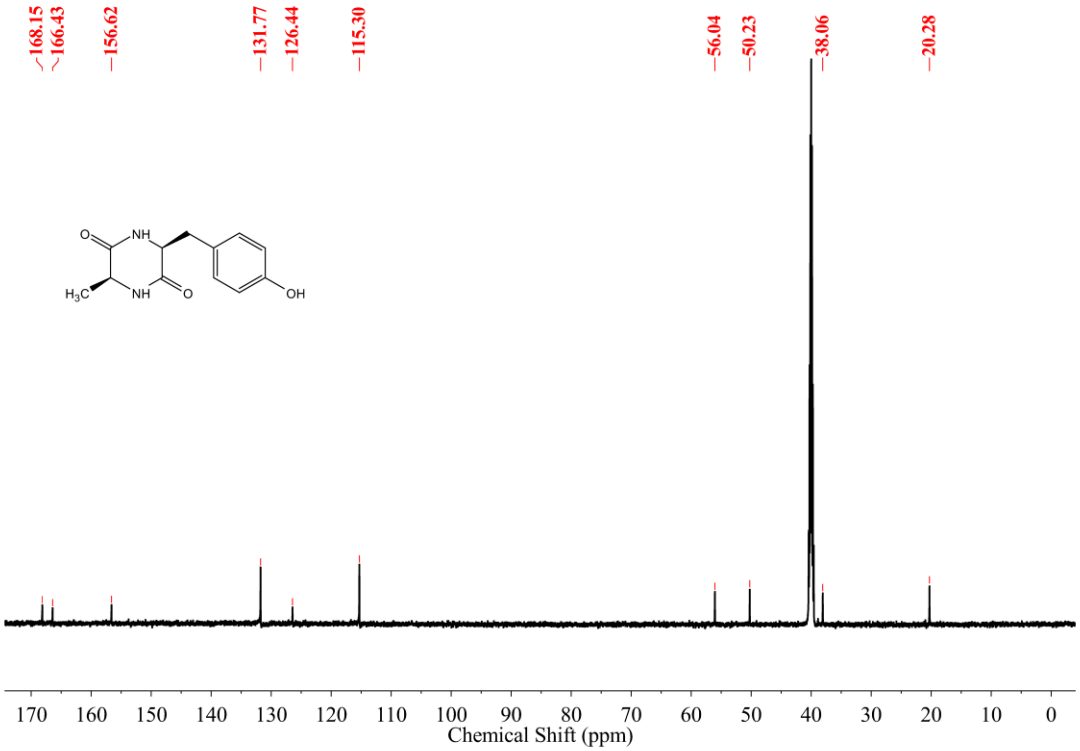


Figure S45. ^{13}C NMR spectrum of **19** (151 MHz, DMSO-d_6).

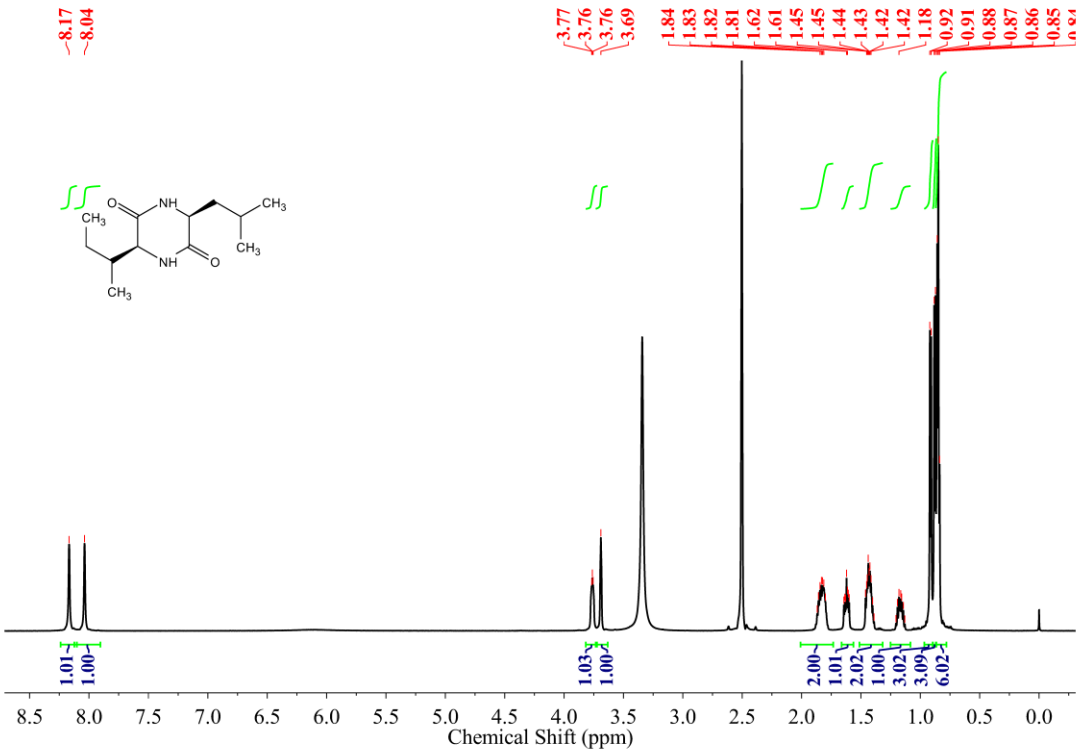


Figure S46. ^{1}H NMR spectrum of **20** (600 MHz, DMSO-d_6).

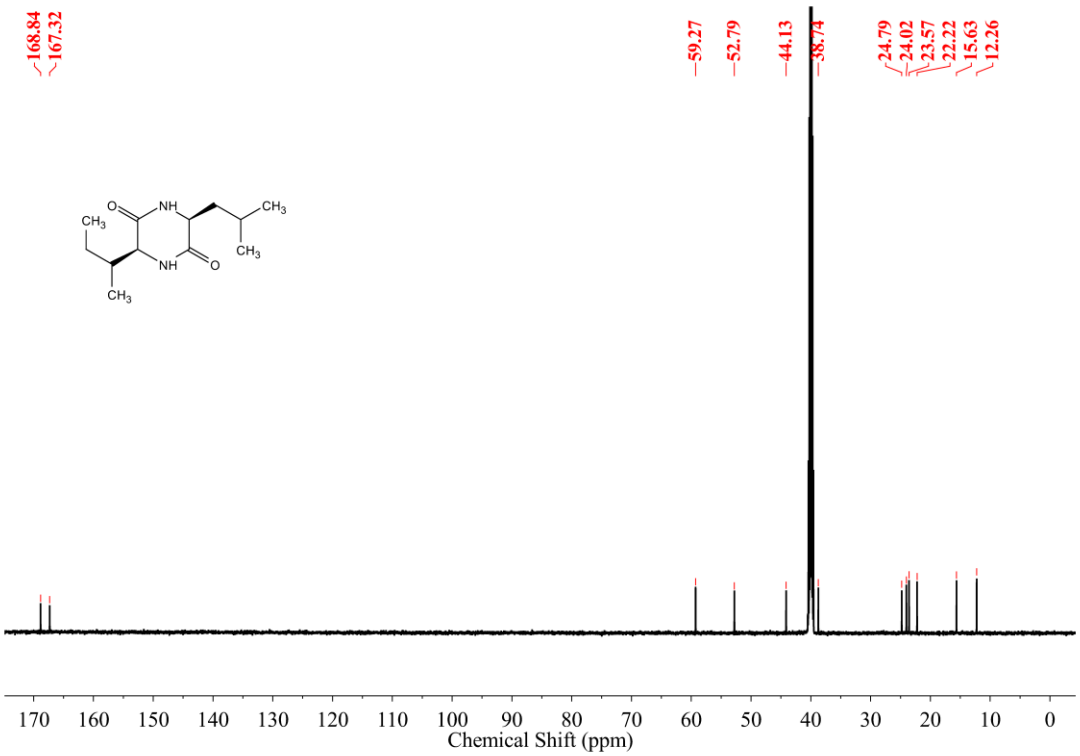


Figure S47. ^{13}C NMR spectrum of **20** (151 MHz, DMSO-d_6).

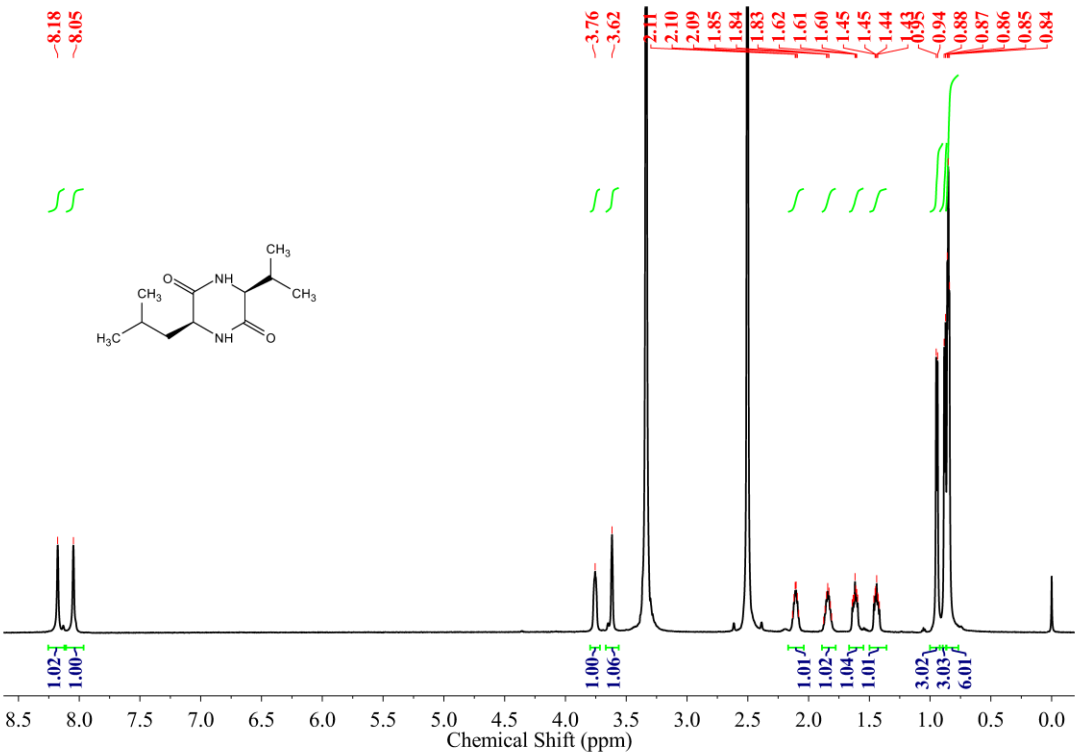


Figure S48. ^{1}H NMR spectrum of **21** (600 MHz, DMSO-d_6).

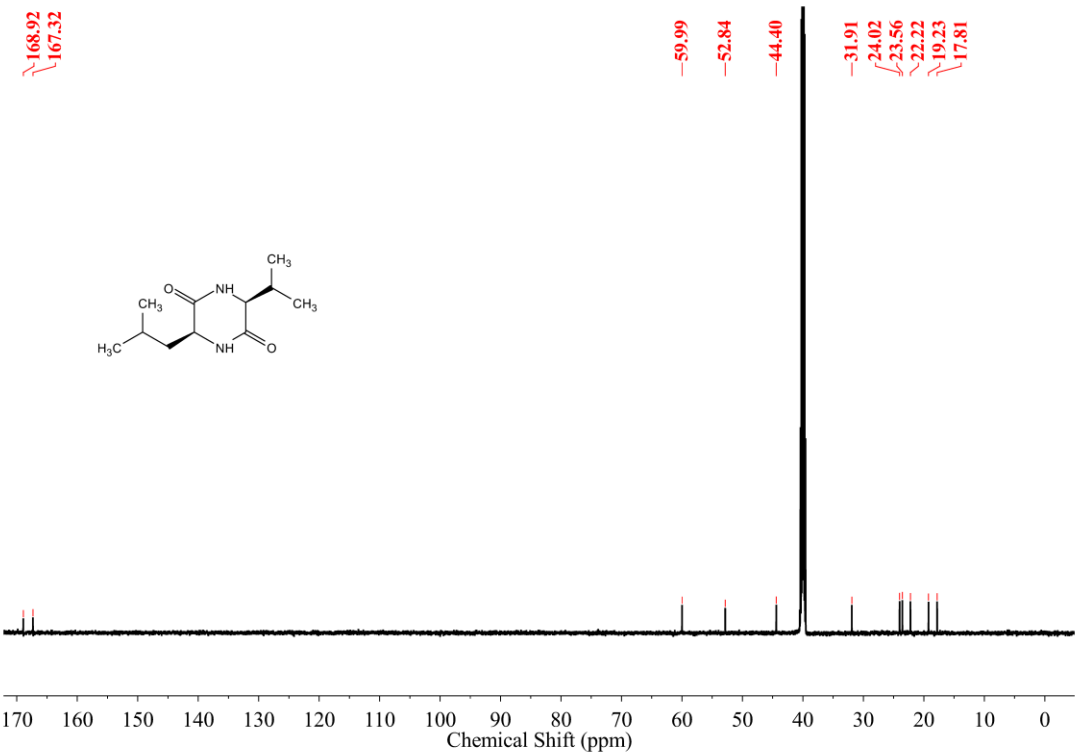


Figure S49. ^{13}C NMR spectrum of **21** (151 MHz, DMSO-d_6).

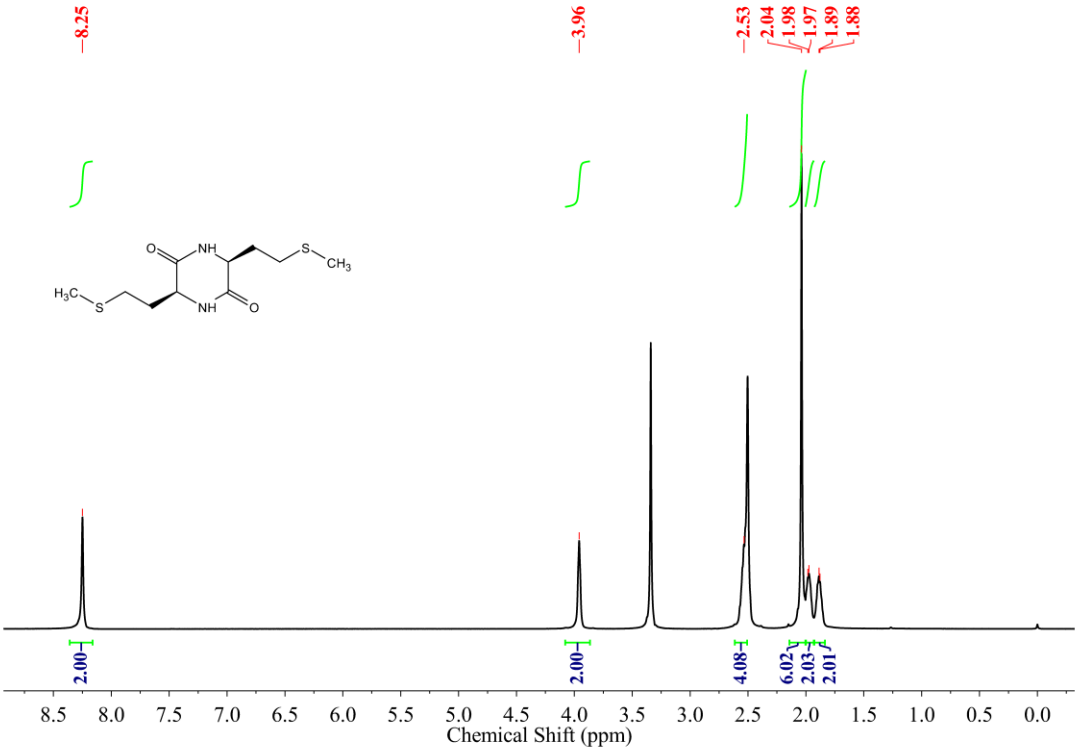


Figure S50. ^{1}H NMR spectrum of **22** (600 MHz, DMSO-d_6).

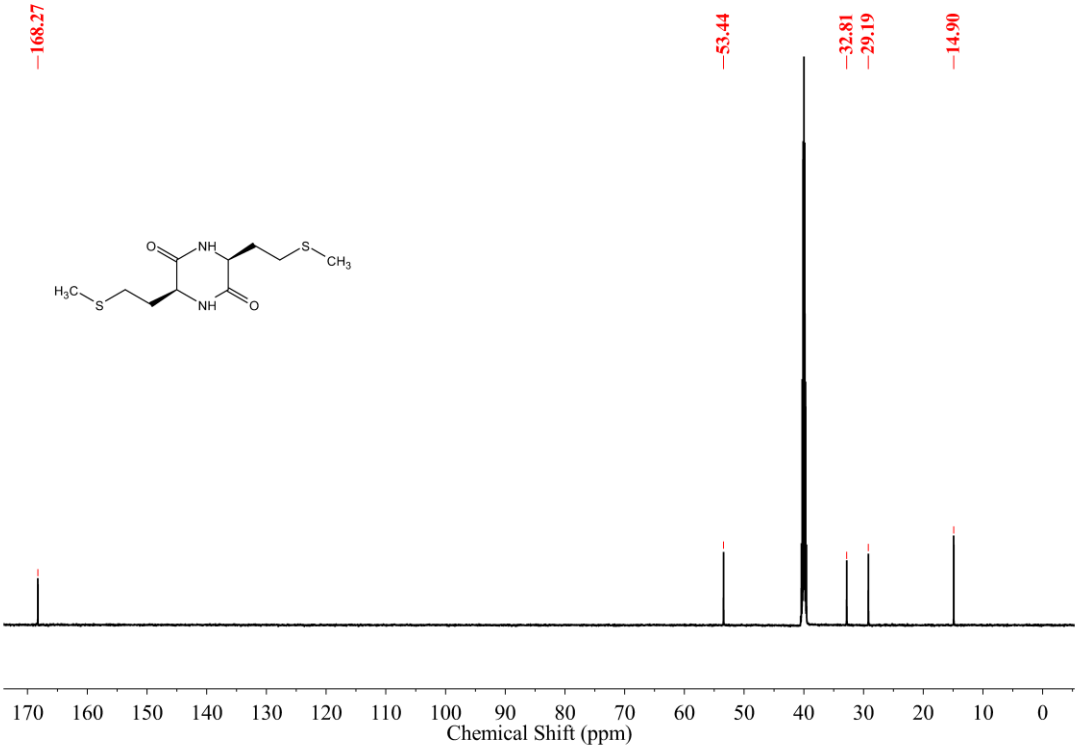


Figure S51. ^{13}C NMR spectrum of **22** (151 MHz, DMSO-d_6).

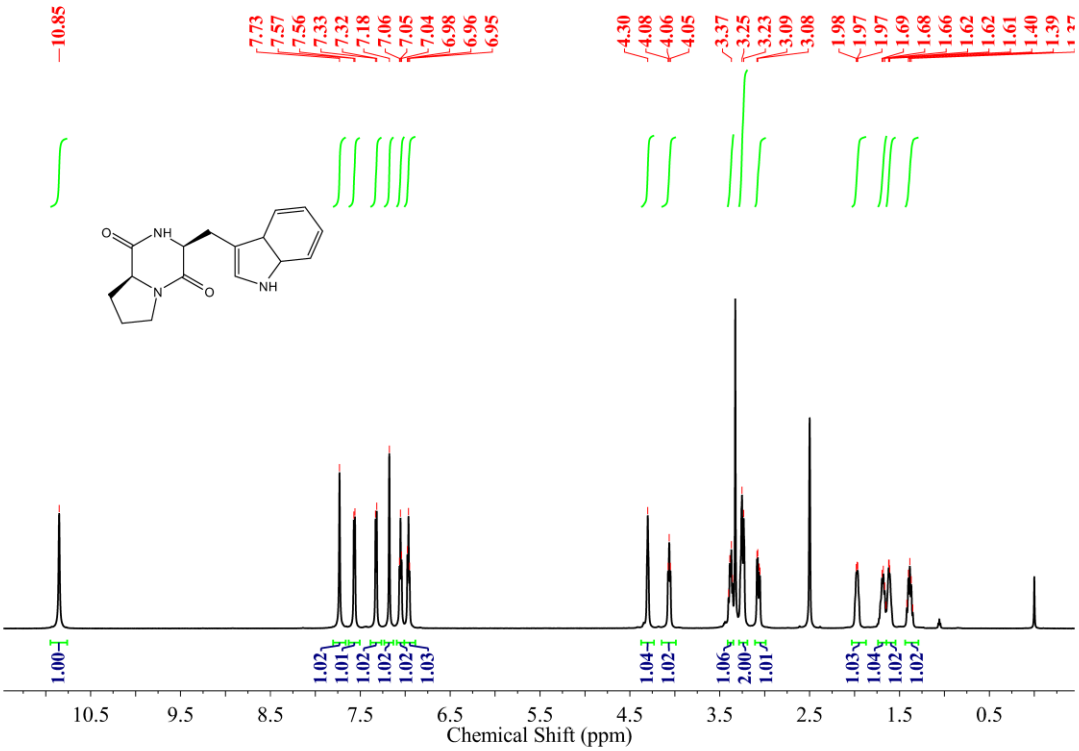


Figure S52. ^{1}H NMR spectrum of **23** (600 MHz, DMSO-d_6).

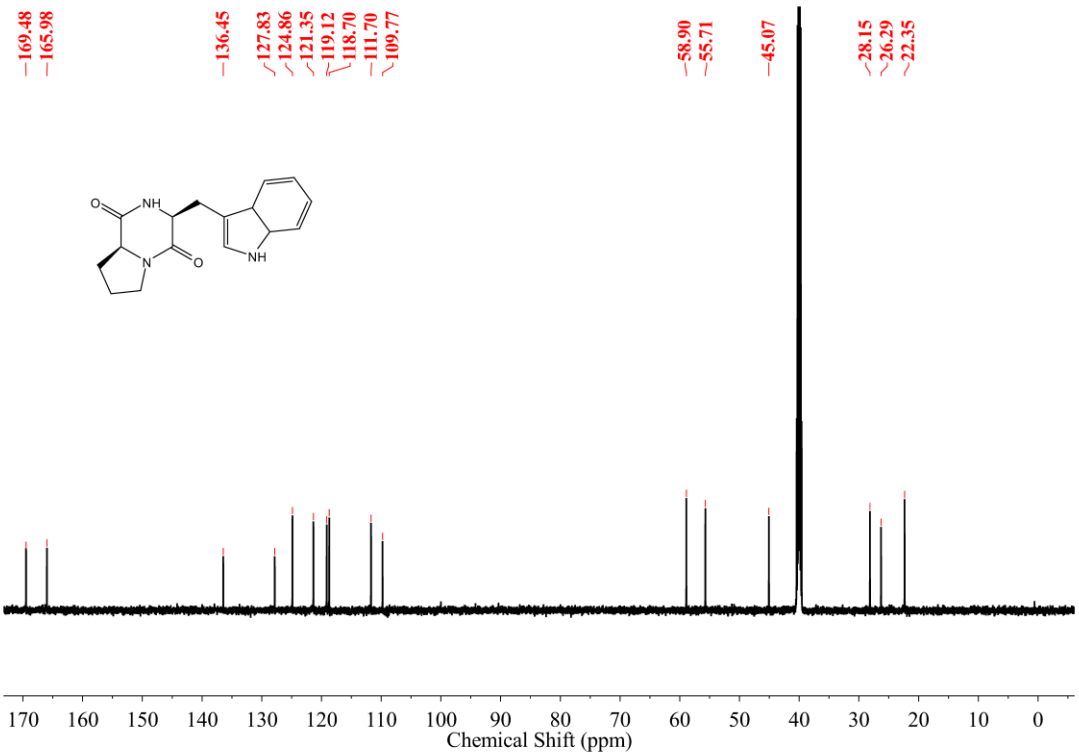


Figure S53. ^{13}C NMR spectrum of **23** (151 MHz, DMSO-d_6).

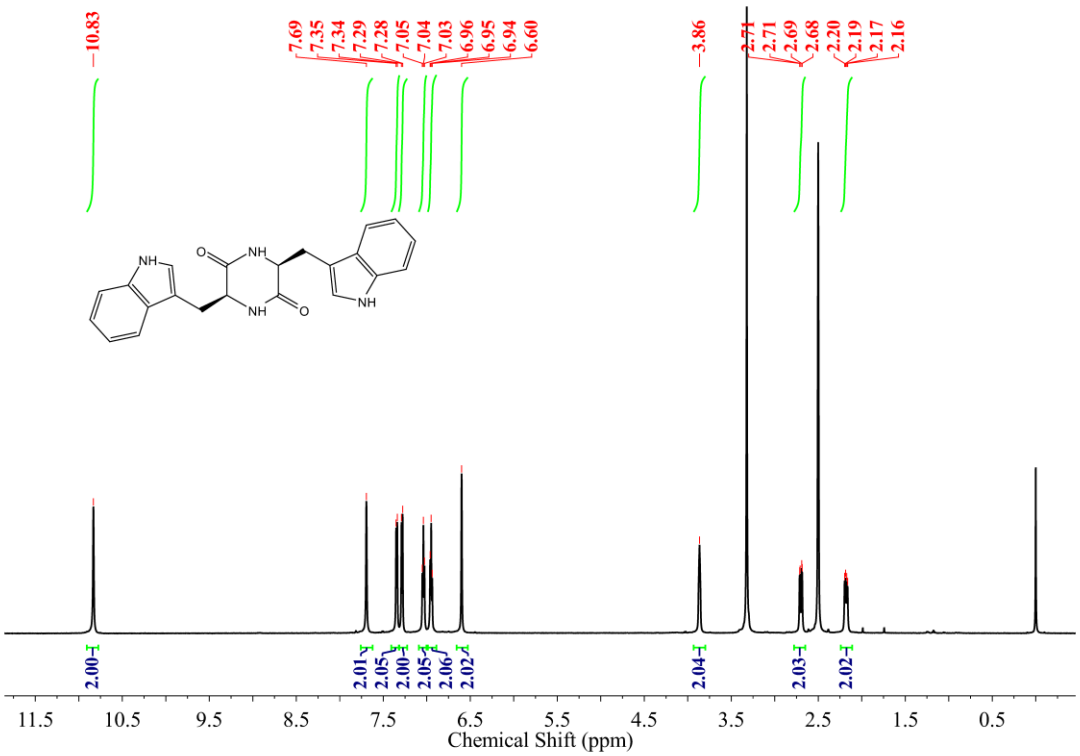


Figure S54. ^{1}H NMR spectrum of **24** (600 MHz, DMSO-d_6).

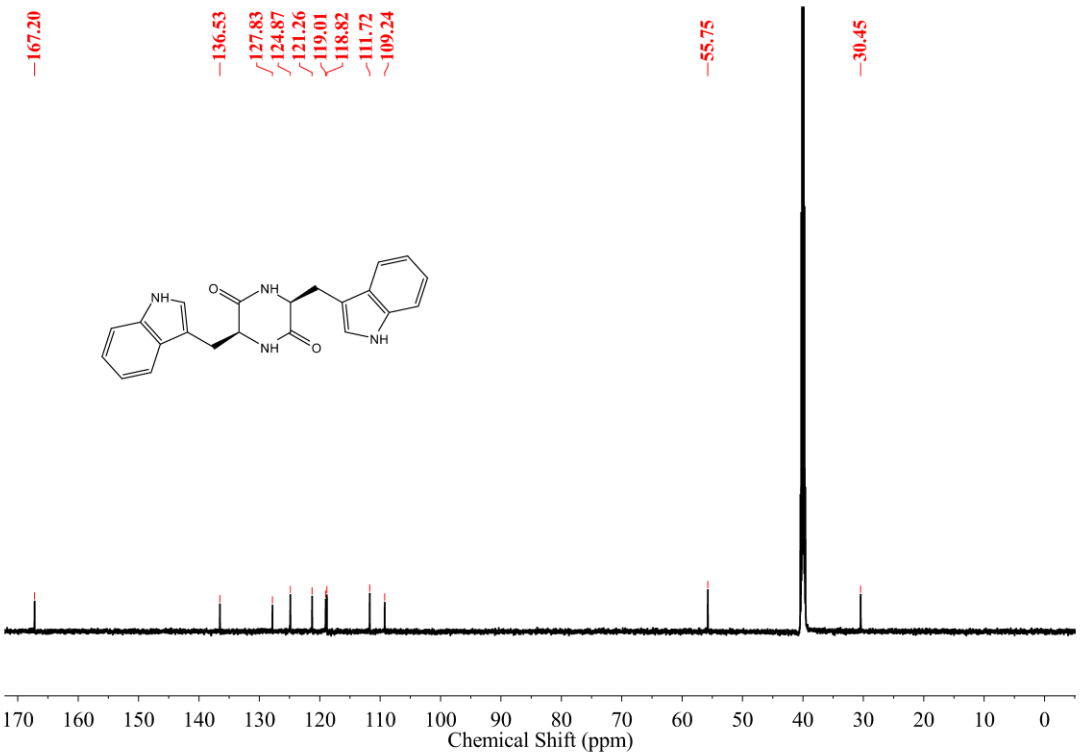


Figure S55. ^{13}C NMR spectrum of **24** (151 MHz, DMSO-d_6).

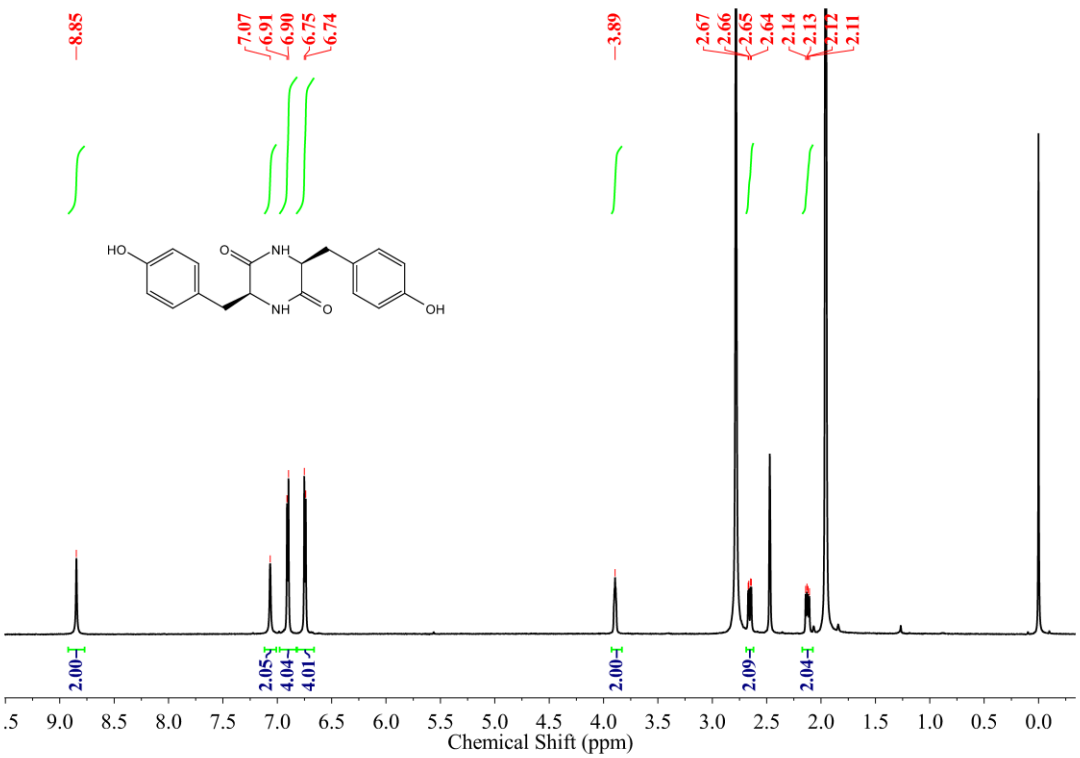


Figure S56. ^{1}H NMR spectrum of **25** (600 MHz, DMSO-d_6/CD_3CN, v/v = 1/9).

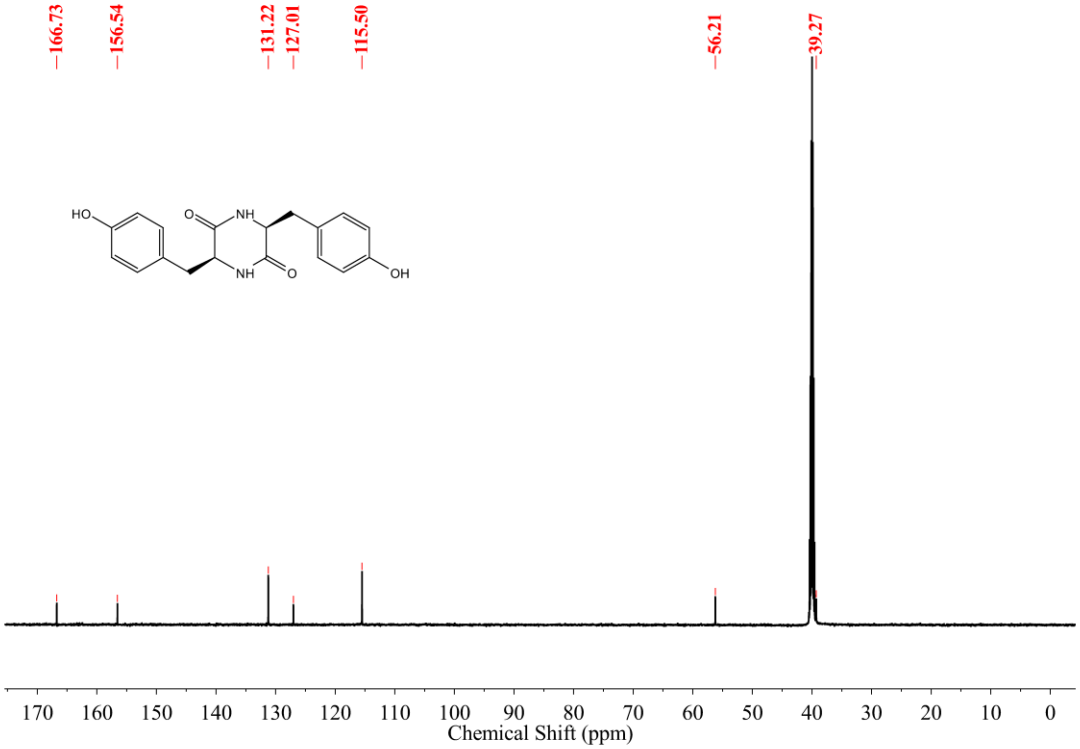


Figure S57. ^{13}C NMR spectrum of **25** (151 MHz, DMSO-d_6).

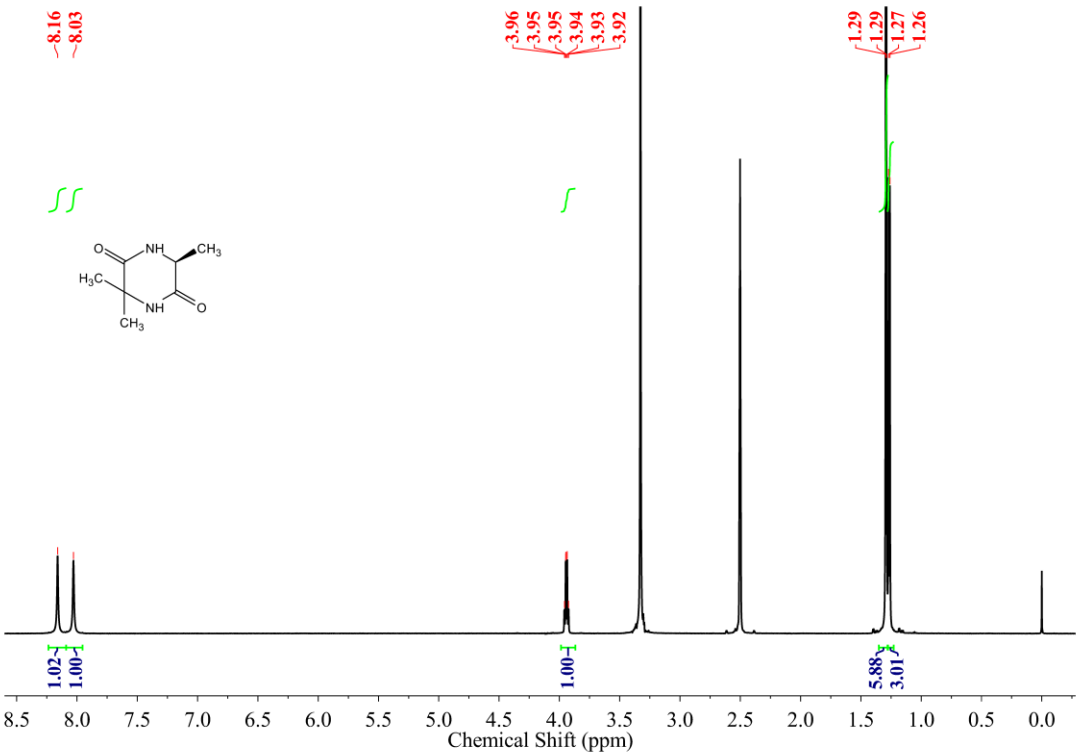


Figure S58. ^{1}H NMR spectrum of **26** (600 MHz, DMSO-d_6).

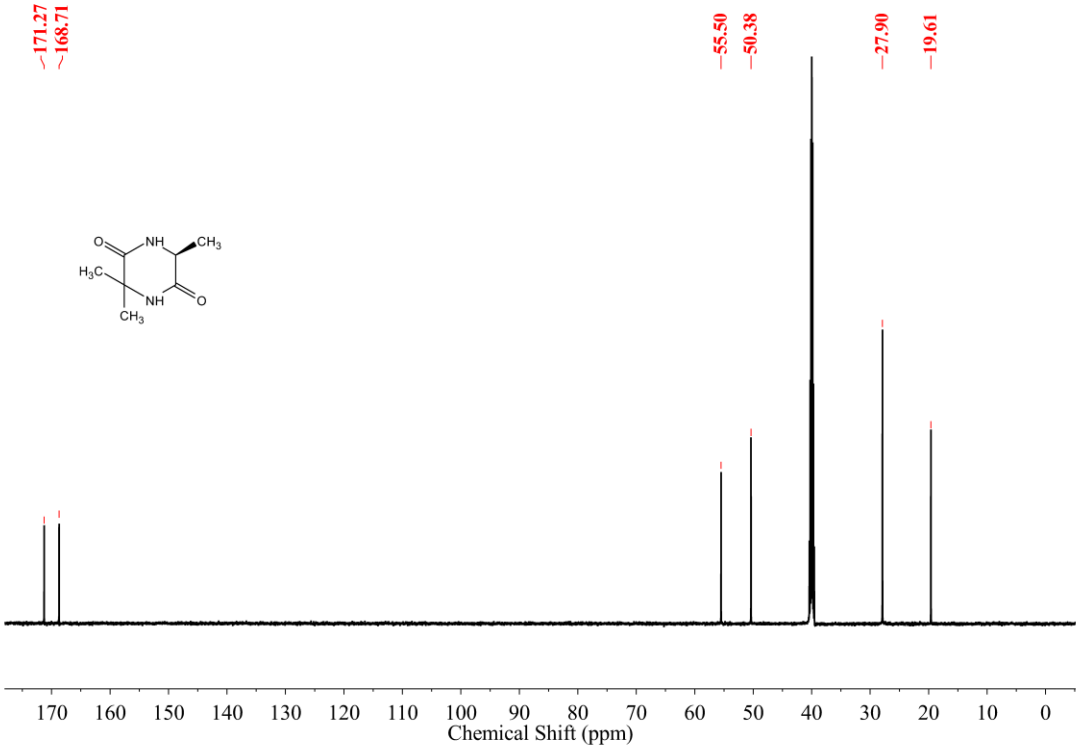


Figure S59. ^{13}C NMR spectrum of **26** (151 MHz, DMSO-d_6).

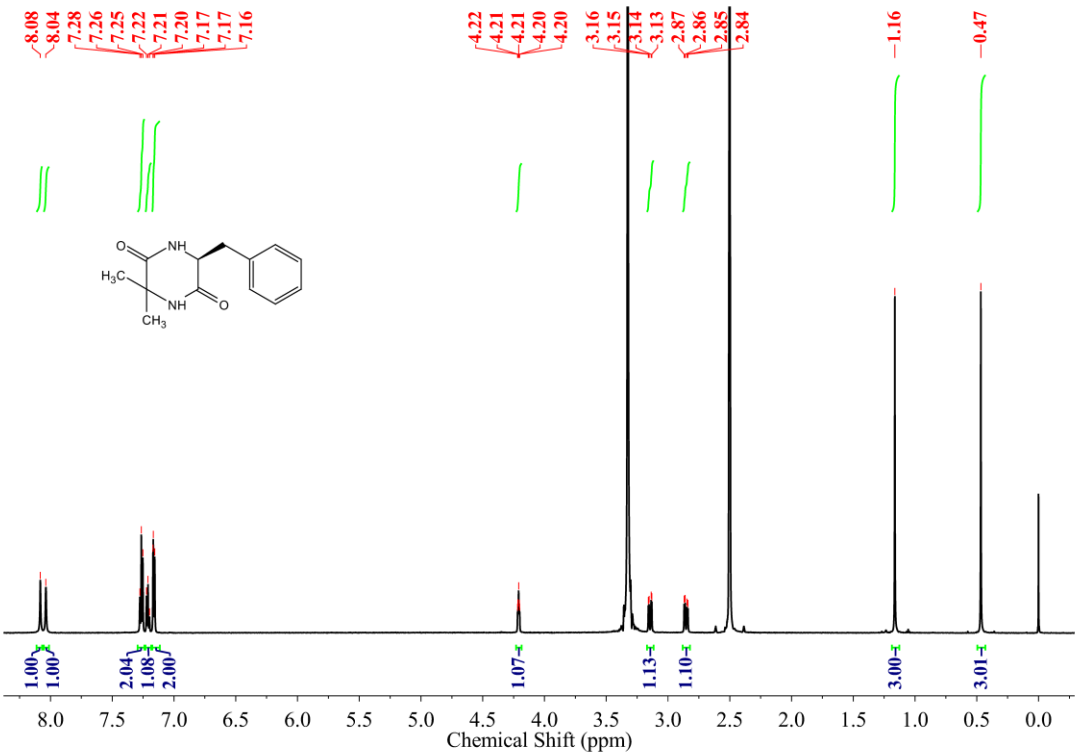


Figure S60. ^{1}H NMR spectrum of **27** (600 MHz, DMSO-d_6).

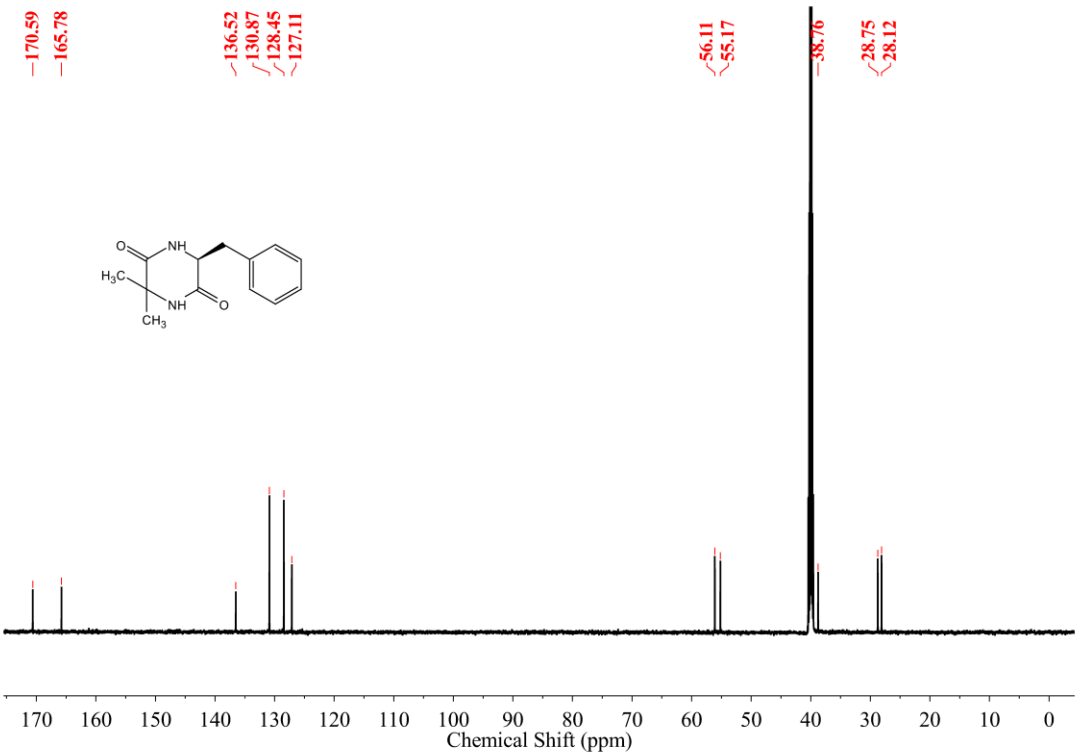


Figure S61. ^{13}C NMR spectrum of **27** (151 MHz, DMSO-d_6).

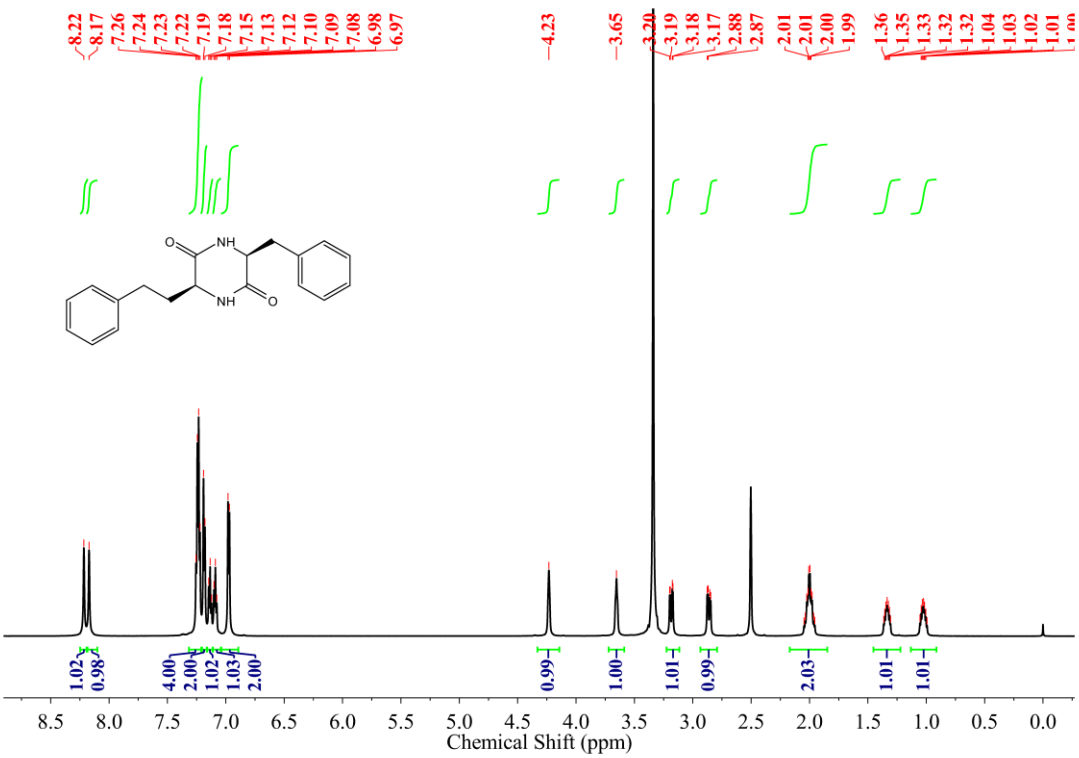


Figure S62. ^{1}H NMR spectrum of **28** (600 MHz, DMSO-d_6).

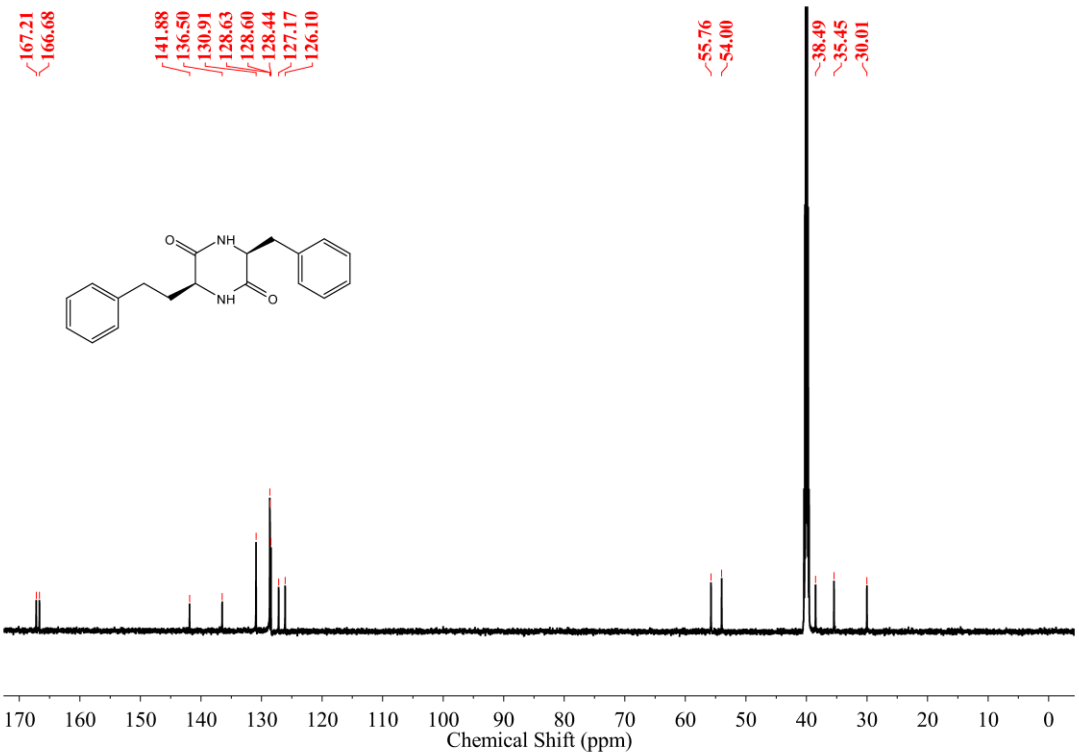


Figure S63. ^{13}C NMR spectrum of **28** (151 MHz, DMSO-d_6).

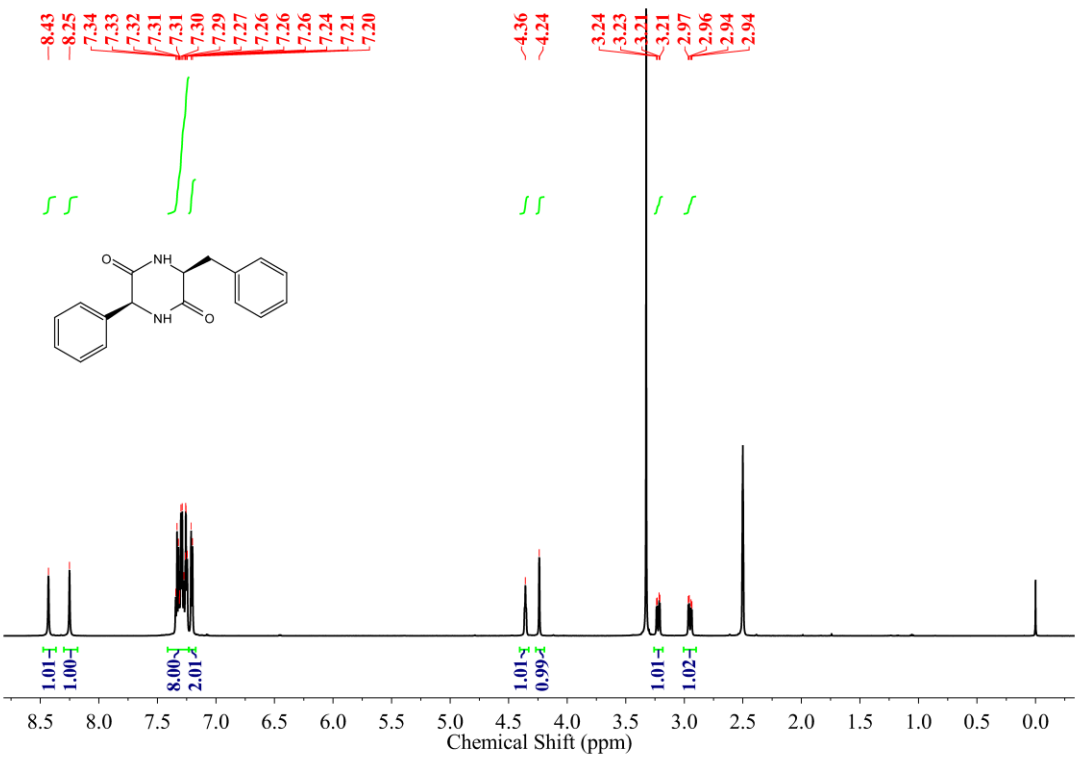


Figure S64. ^{1}H NMR spectrum of **29** (600 MHz, DMSO-d_6).

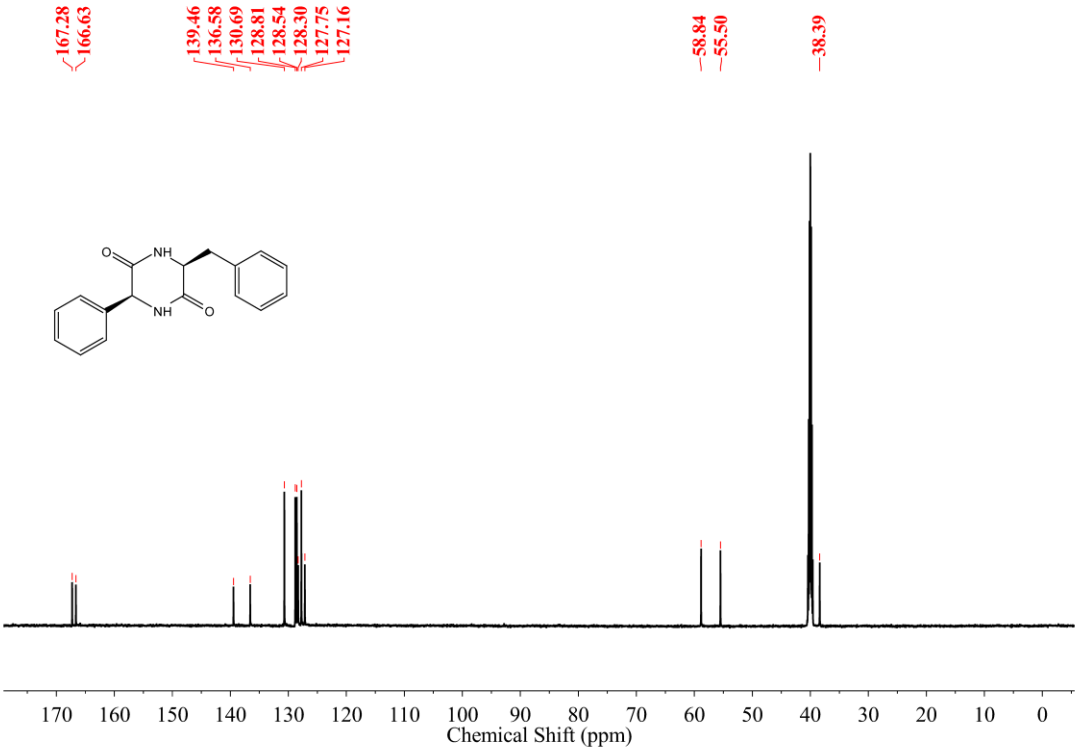


Figure S65. ^{13}C NMR spectrum of **29** (151 MHz, DMSO-d_6).

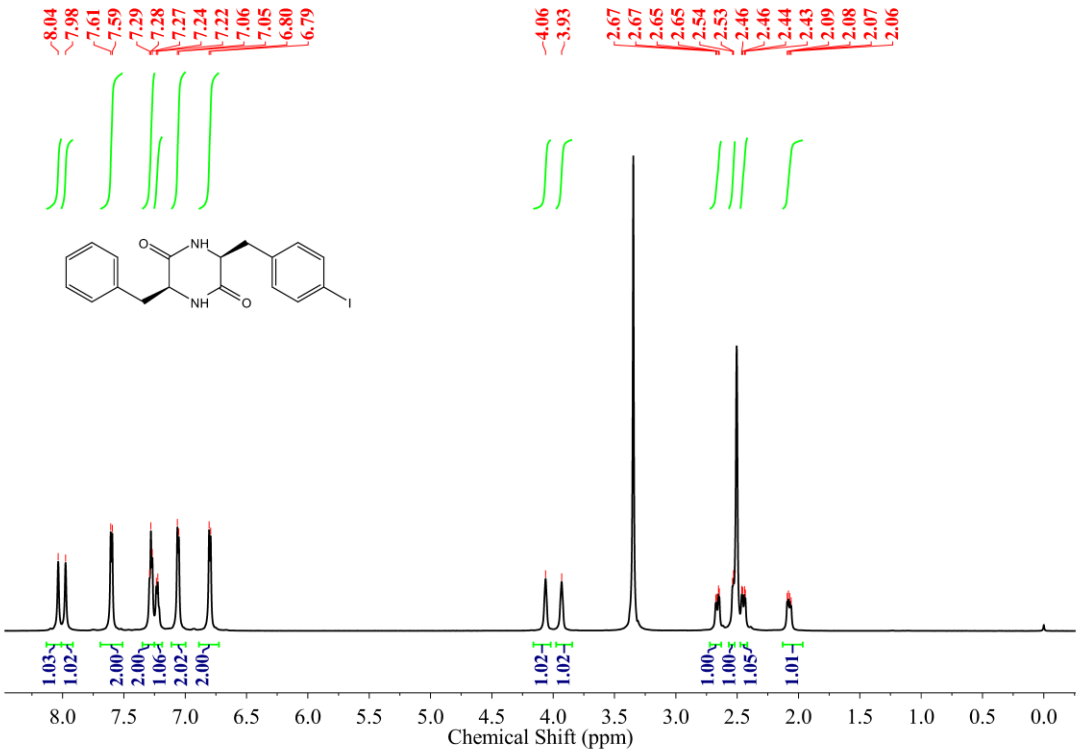


Figure S66. ^{1}H NMR spectrum of **30** (600 MHz, DMSO-d_6).

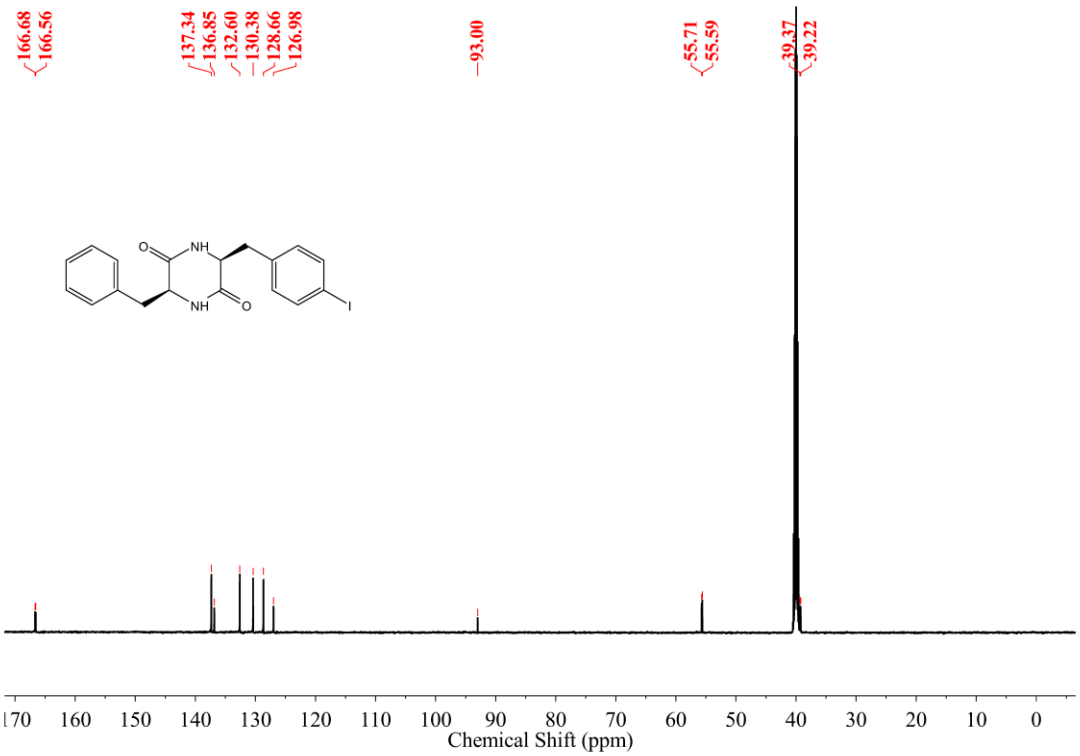


Figure S67. ^{13}C NMR spectrum of **30** (151 MHz, DMSO-d_6).

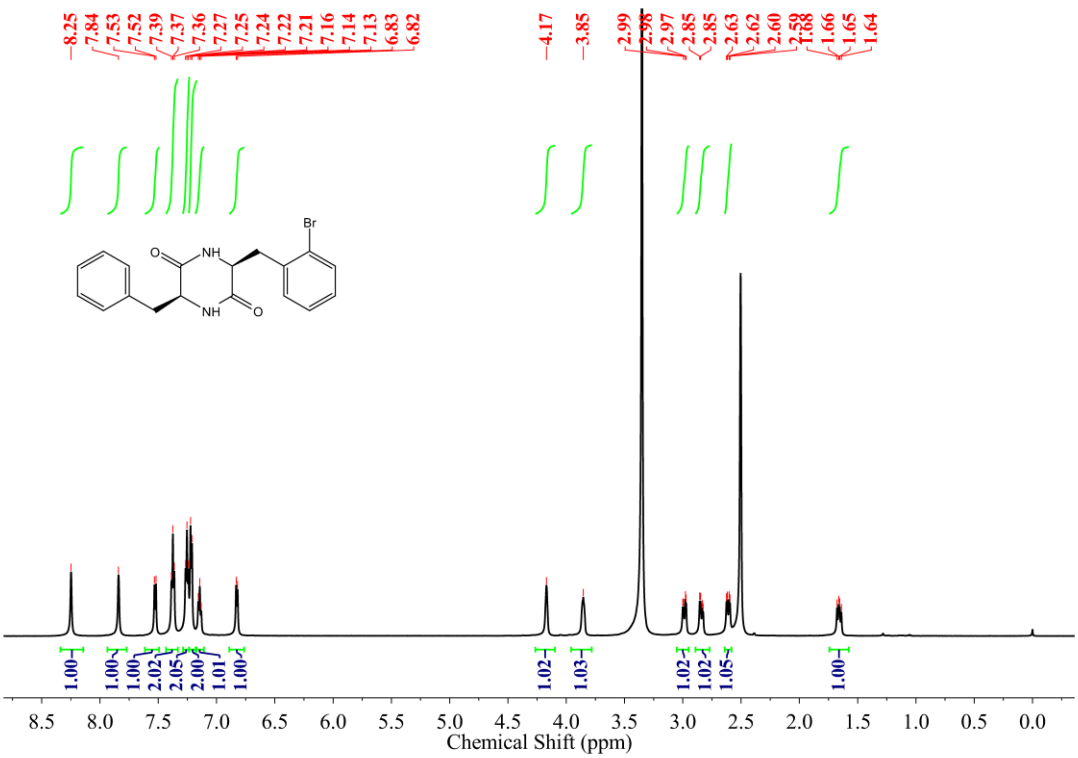


Figure S68. ^{1}H NMR spectrum of **31** (600 MHz, DMSO-d_6).

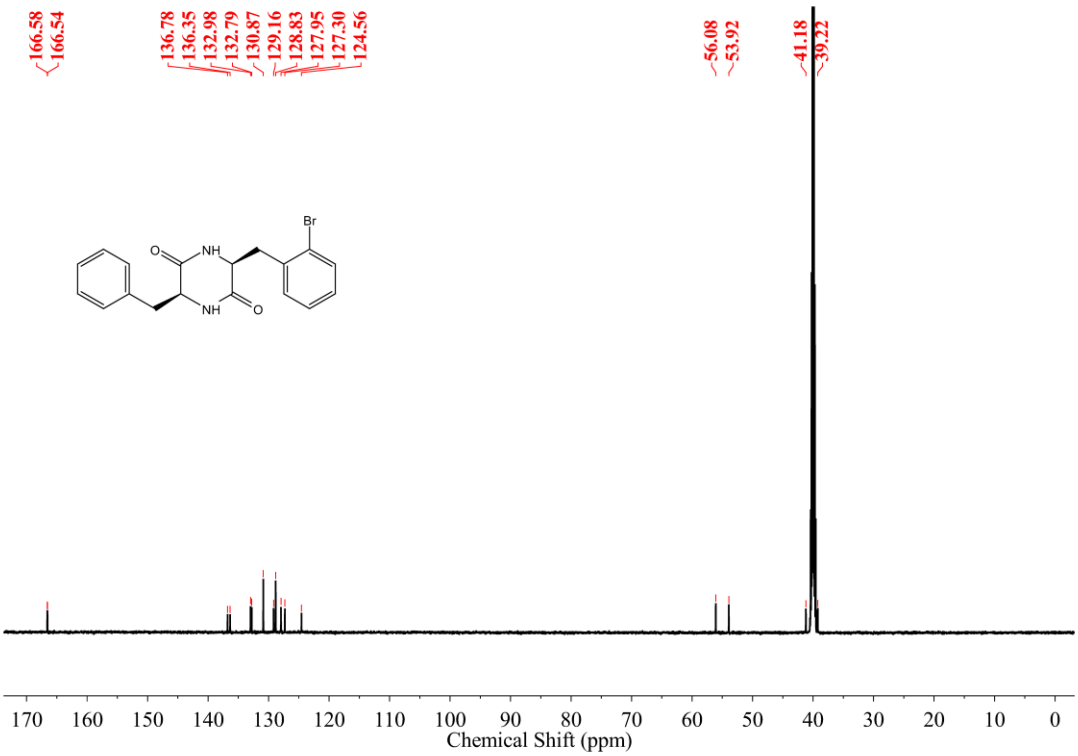


Figure S69. ^{13}C NMR spectrum of **31** (151 MHz, DMSO-d_6).

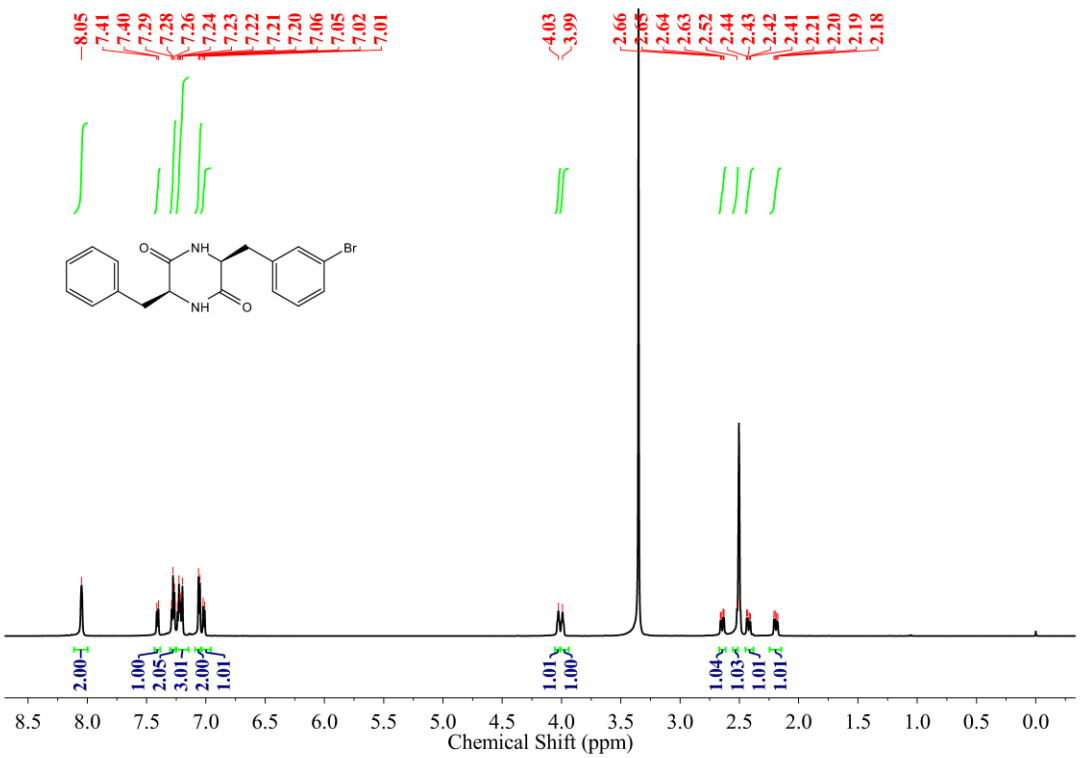


Figure S70. ^{1}H NMR spectrum of **32** (600 MHz, DMSO-d_6).

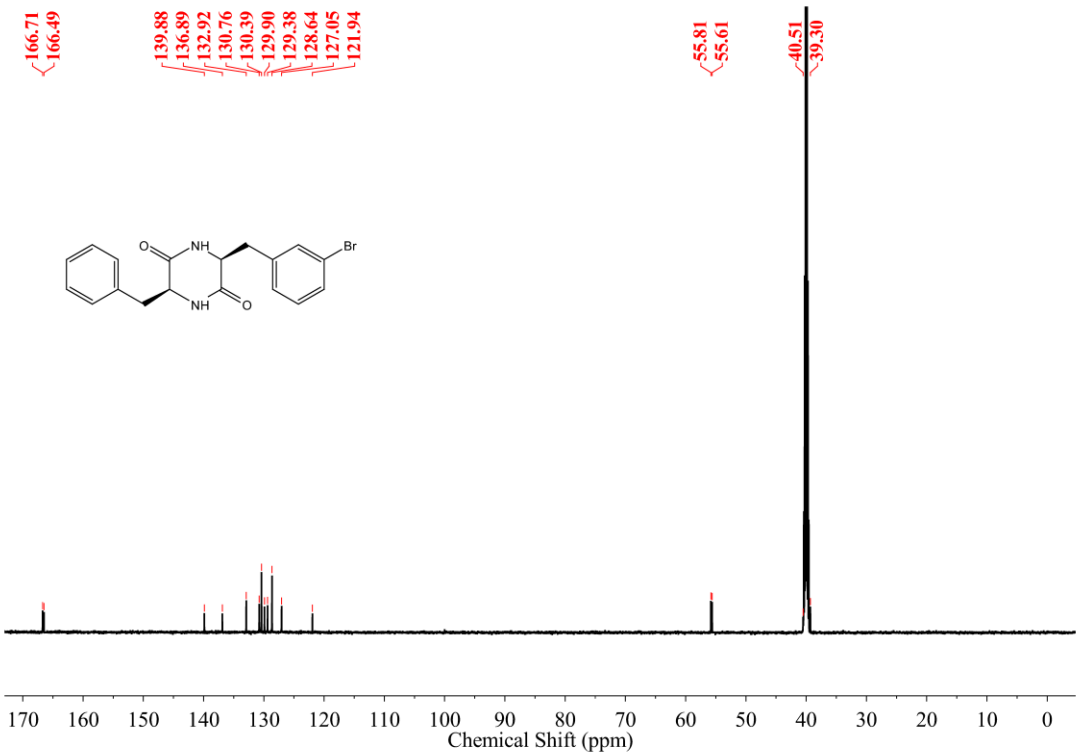


Figure S71. ^{13}C NMR spectrum of **32** (151 MHz, DMSO-d_6).

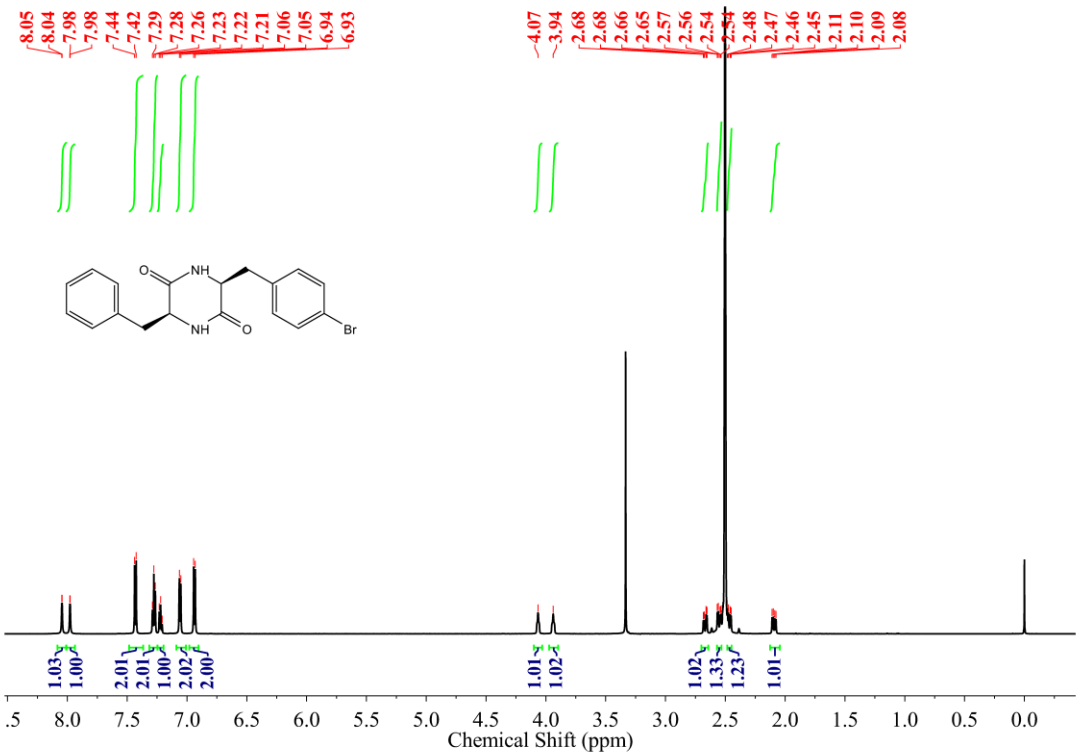


Figure S72. ^{1}H NMR spectrum of **33** (600 MHz, DMSO-d_6).

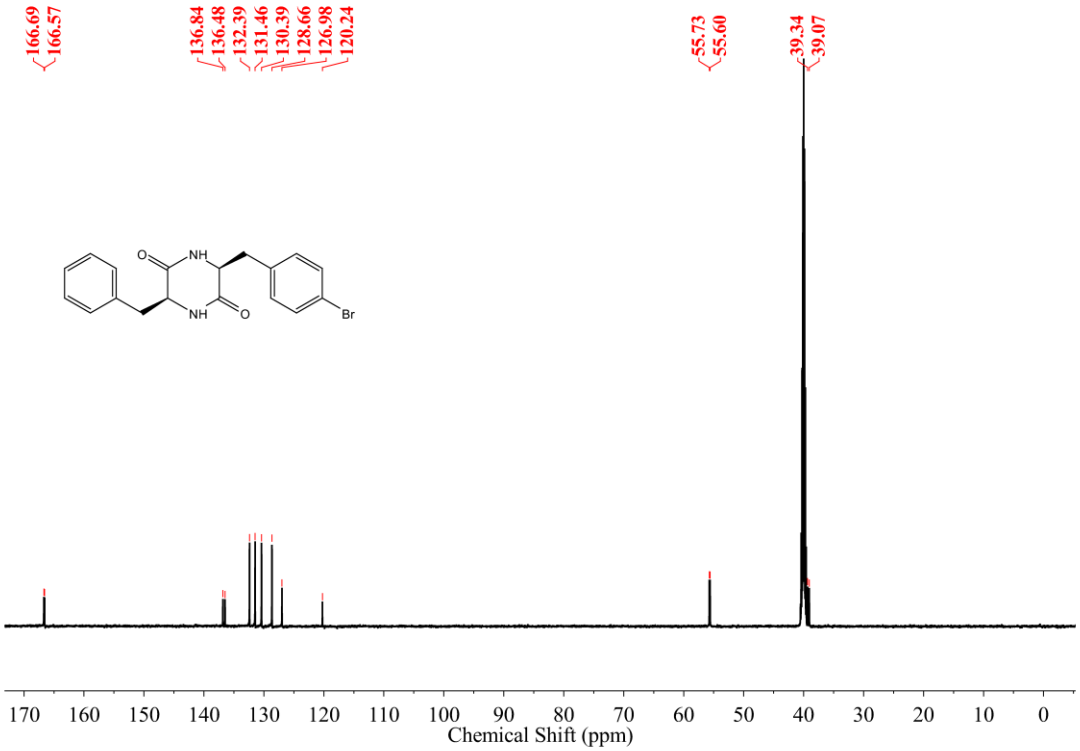


Figure S73. ^{13}C NMR spectrum of **33** (151 MHz, DMSO-d_6).

6. HRMS spectra

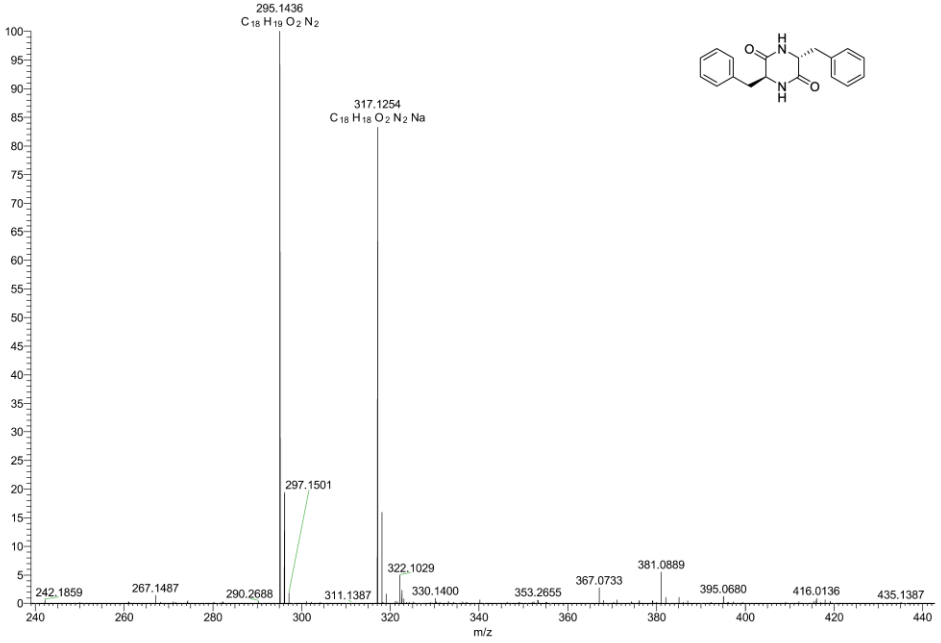


Figure S74. HRMS spectrum of **2**.

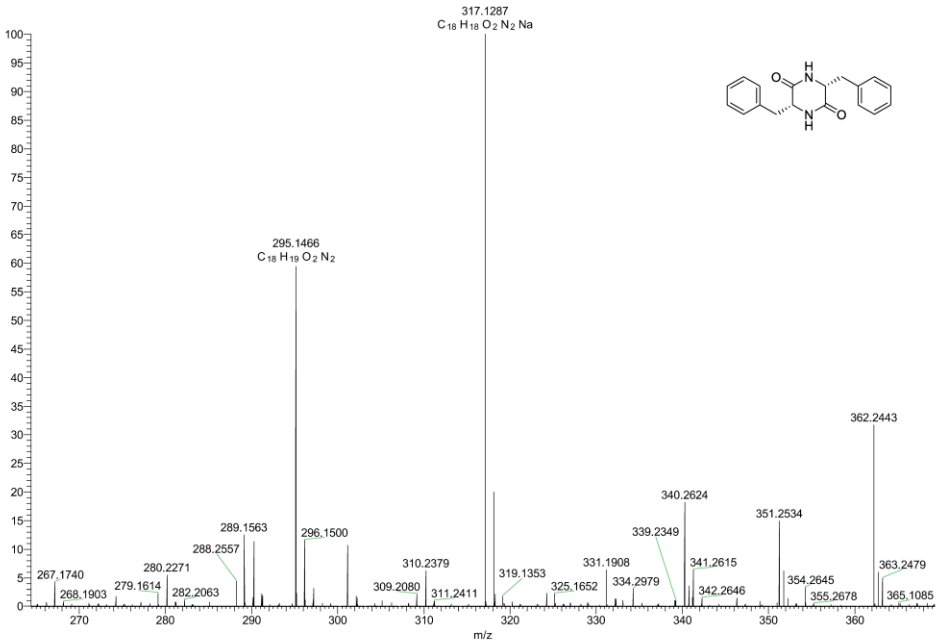


Figure S75. HRMS spectrum of **3**.

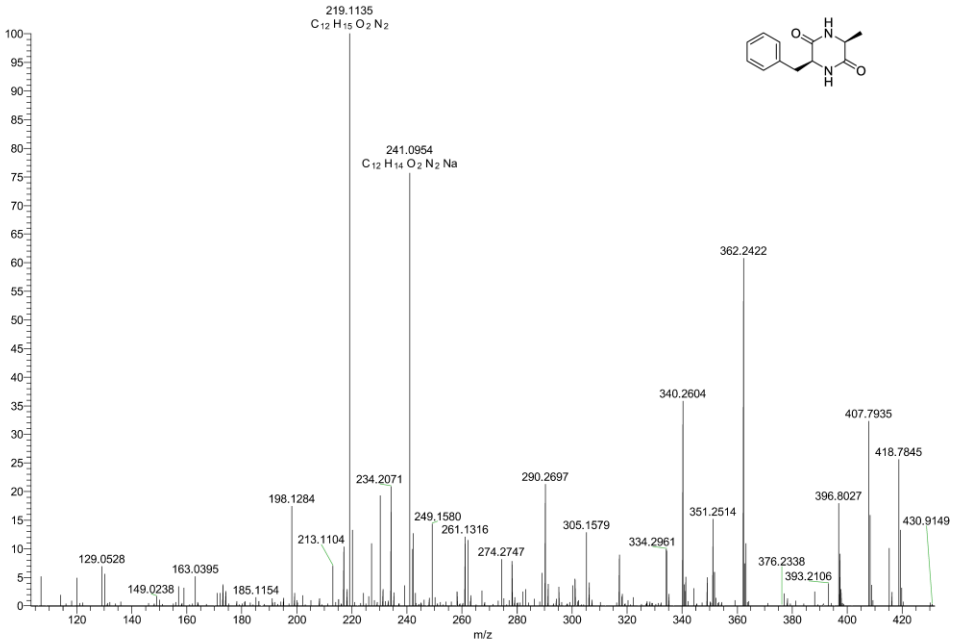


Figure S76. HRMS spectrum of **4**.

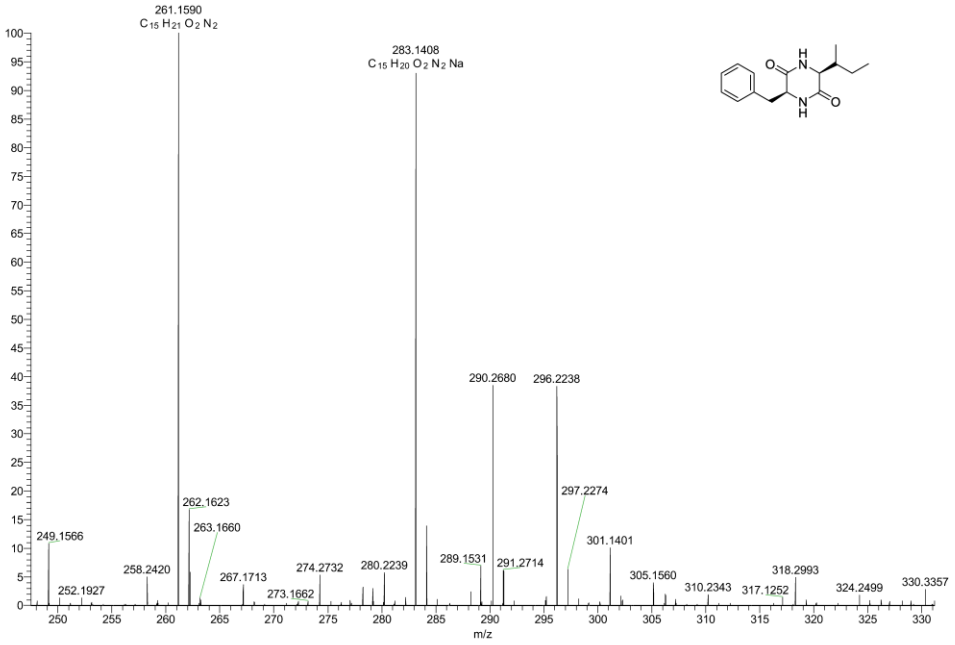


Figure S77. HRMS spectrum of **5**.

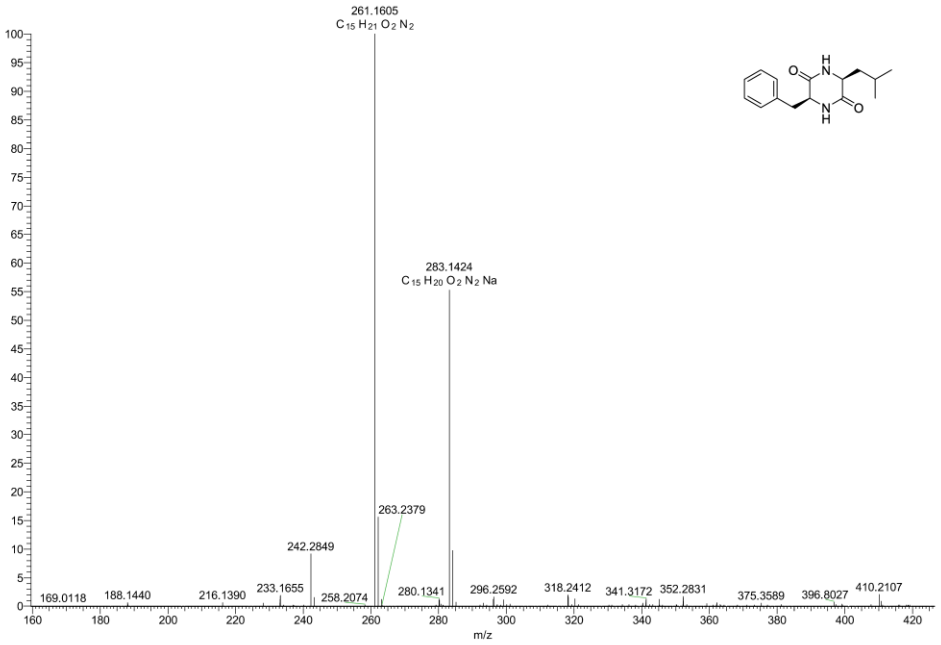


Figure S78. HRMS spectrum of **6**.

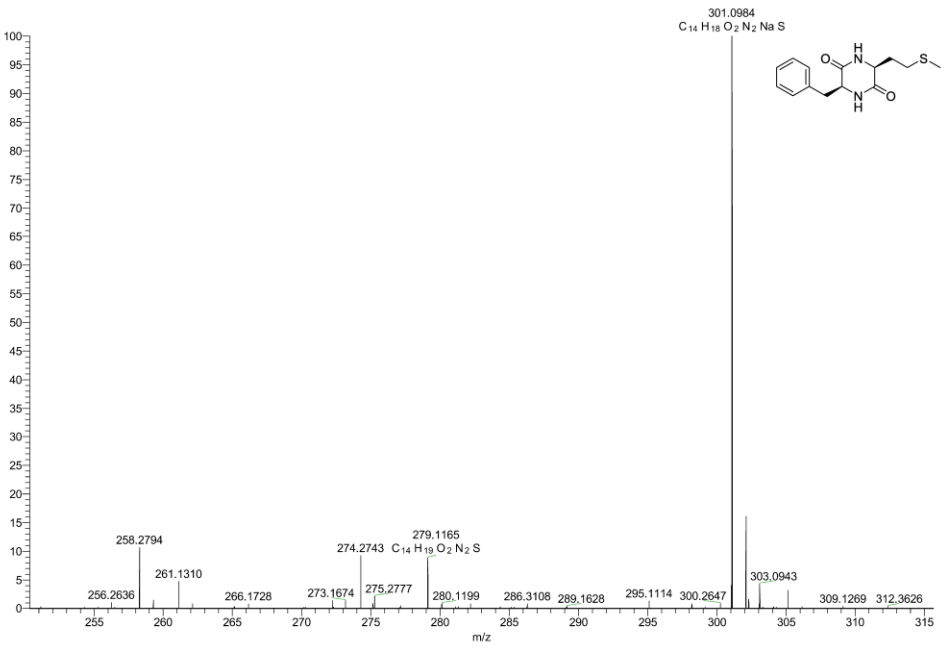


Figure S79. HRMS spectrum of **7**.

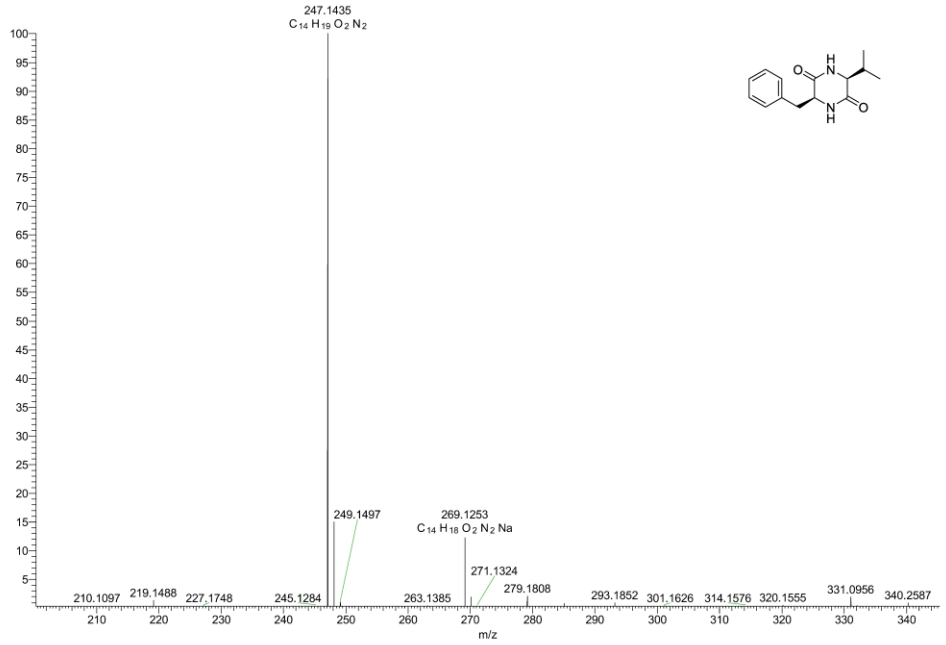


Figure S80. HRMS spectrum of **8**.

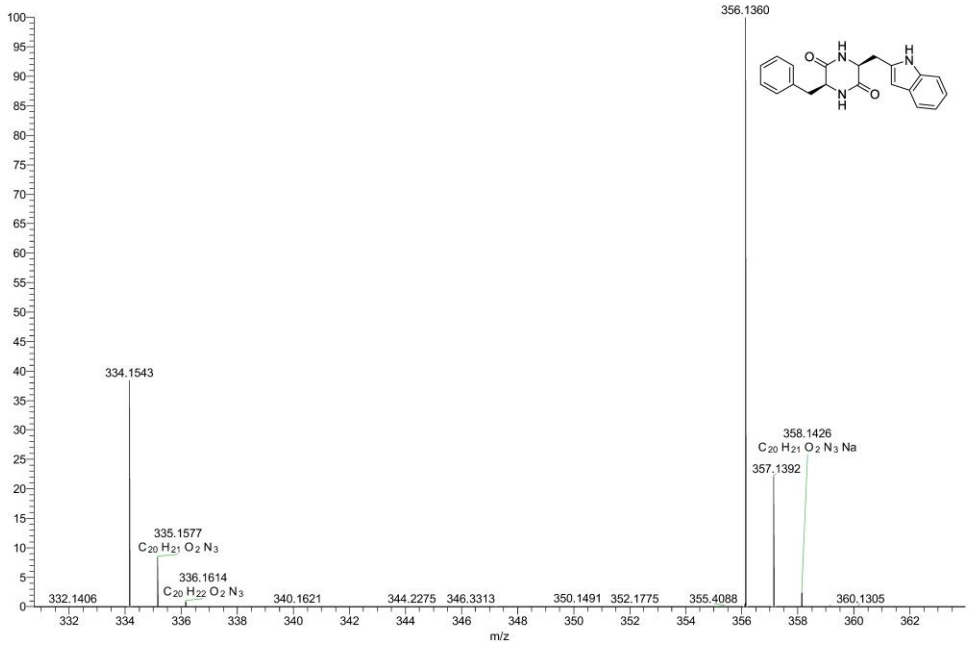


Figure S81. HRMS spectrum of **9**.

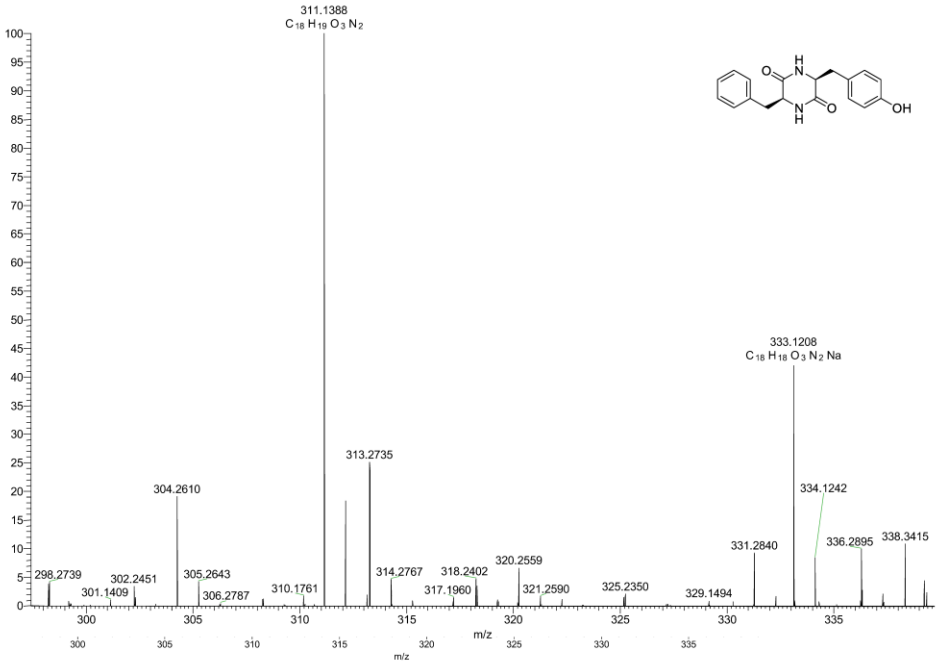


Figure S82. HRMS spectrum of **10**.

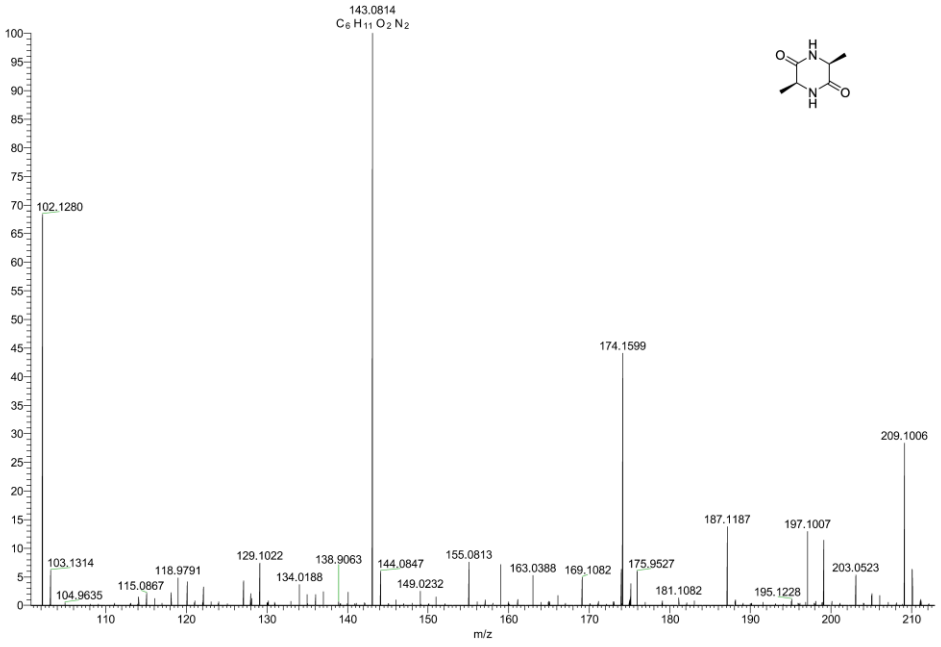


Figure S83. HRMS spectrum of **11**.

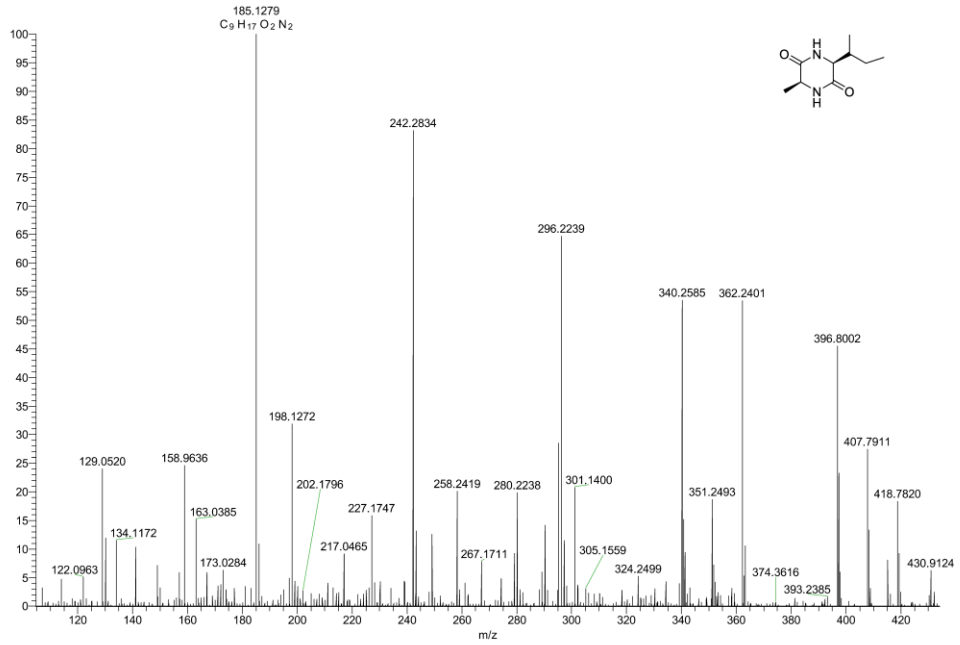


Figure S84. HRMS spectrum of **12**.

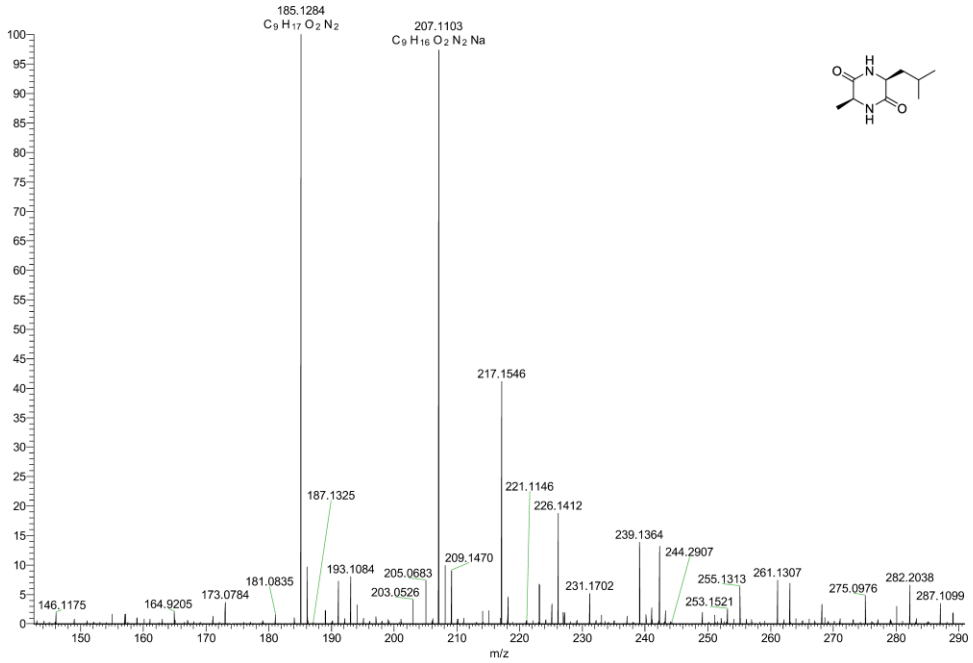


Figure S85. HRMS spectrum of **13**.

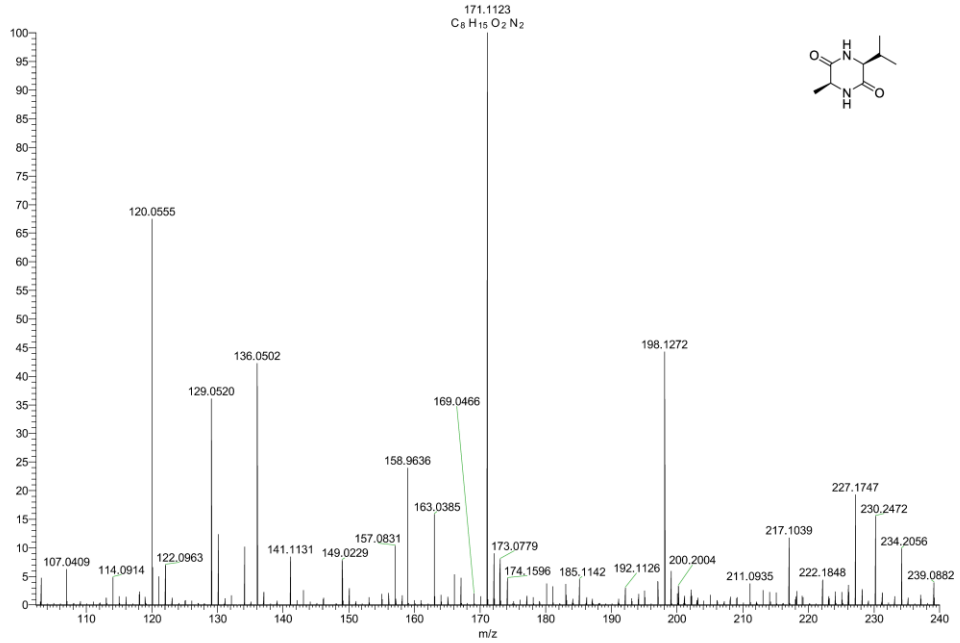


Figure S86. HRMS spectrum of **14**.

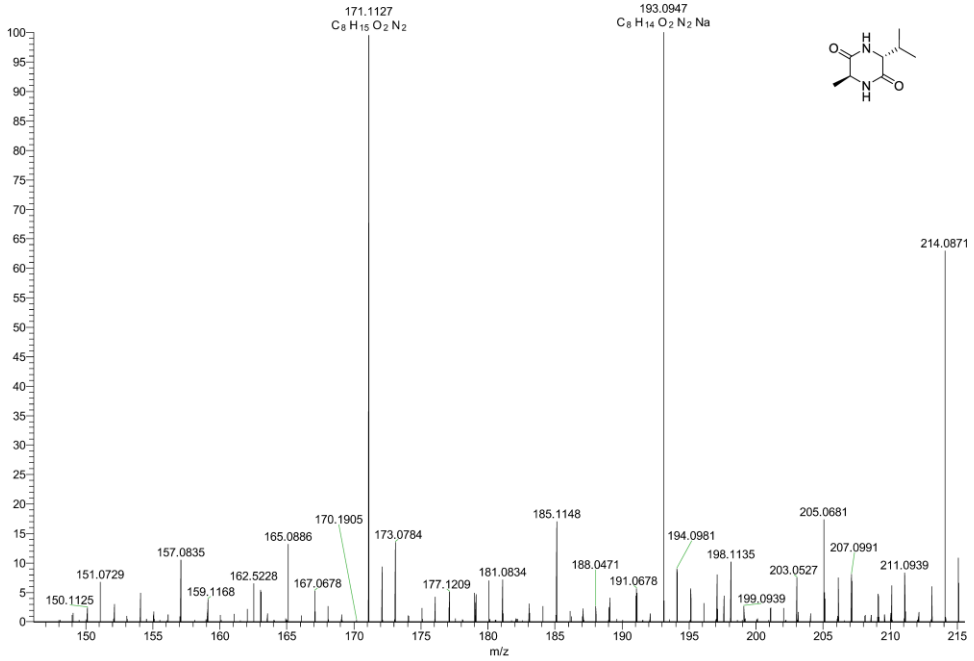


Figure S87. HRMS spectrum of **15**.

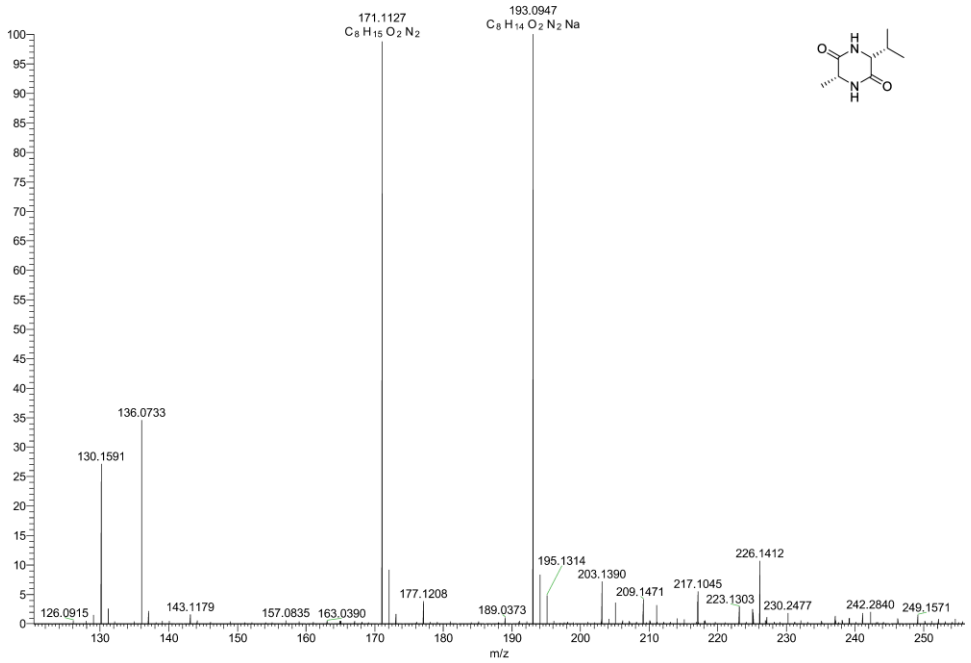


Figure S88. HRMS spectrum of **16**.

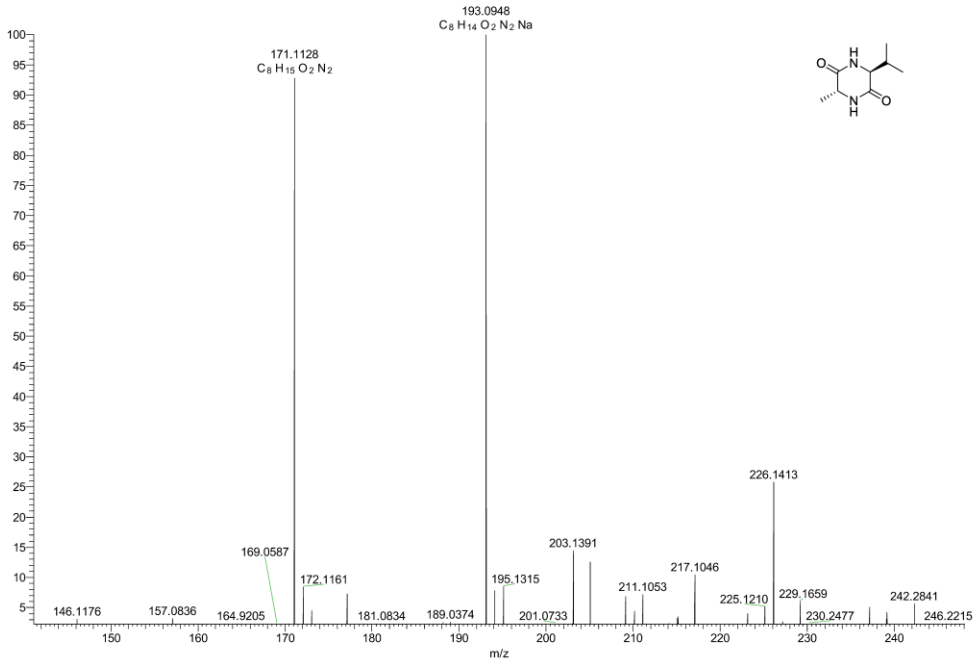


Figure S89. HRMS spectrum of **17**.

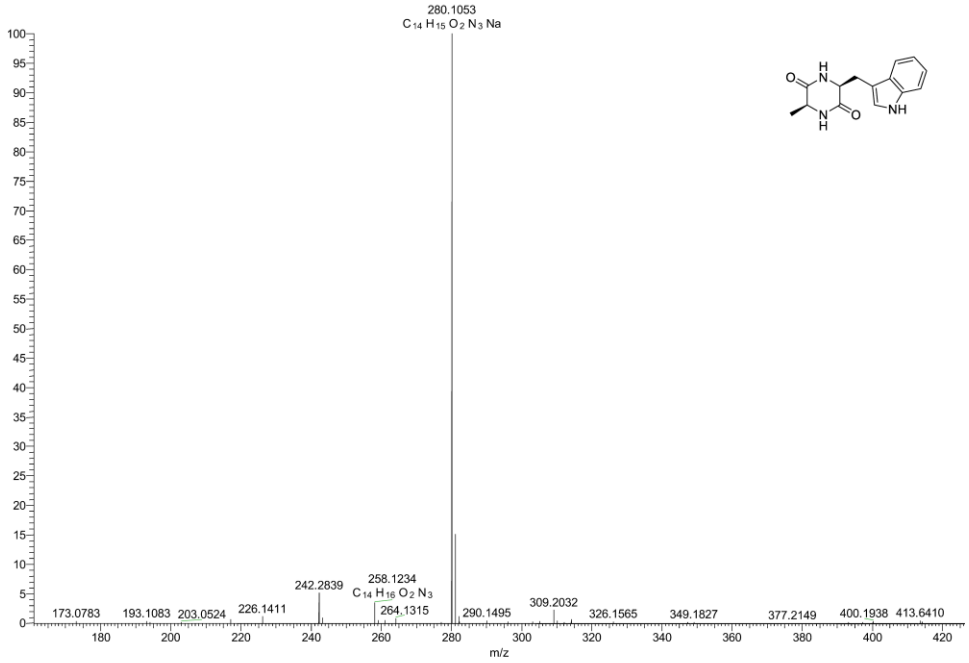


Figure S90. HRMS spectrum of **18**.

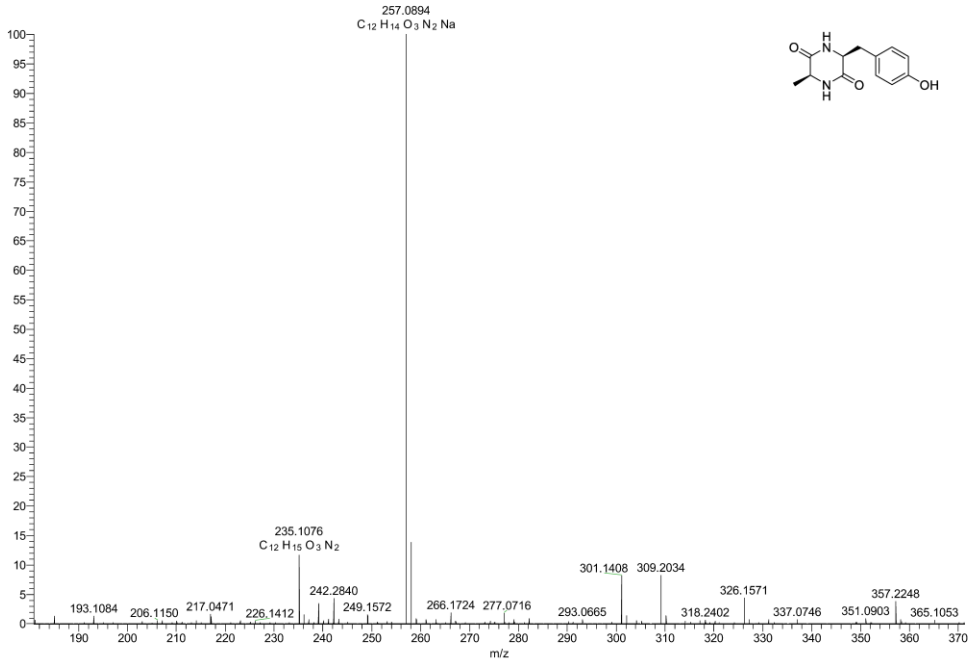


Figure S91. HRMS spectrum of **19**.

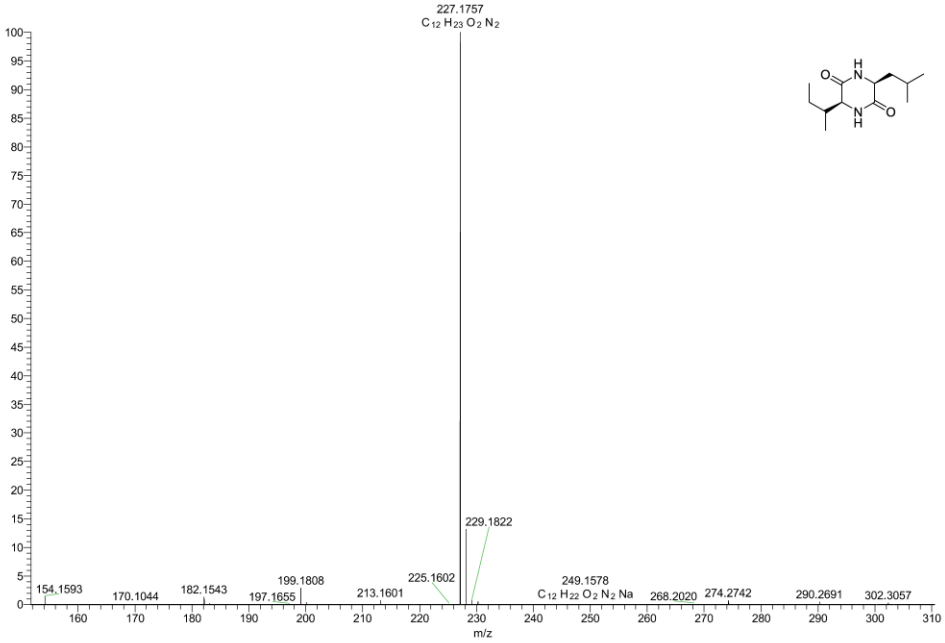


Figure S92. HRMS spectrum of **20**.

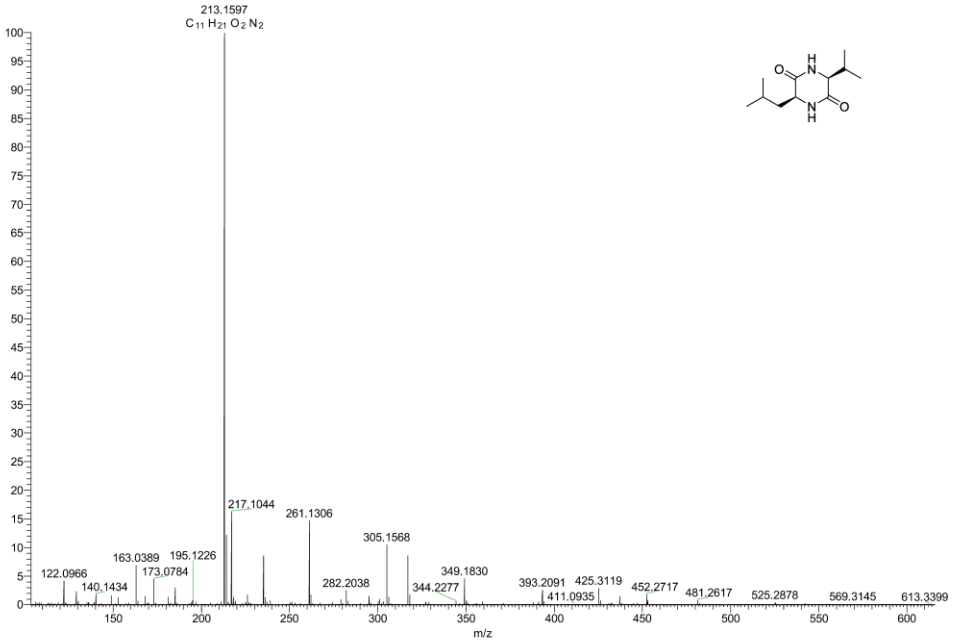


Figure S93. HRMS spectrum of **21**.

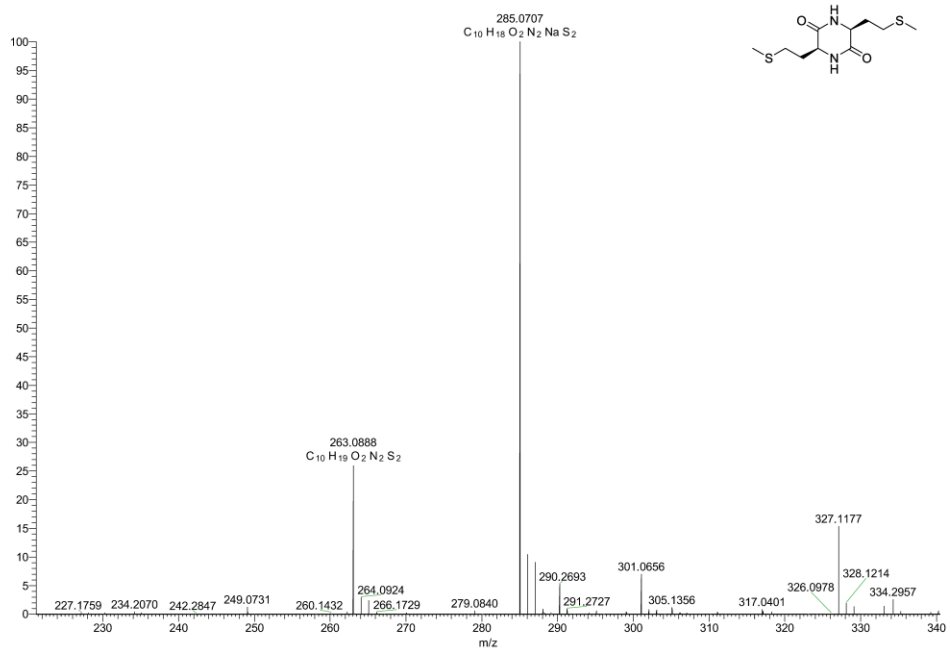


Figure S94. HRMS spectrum of **22**.

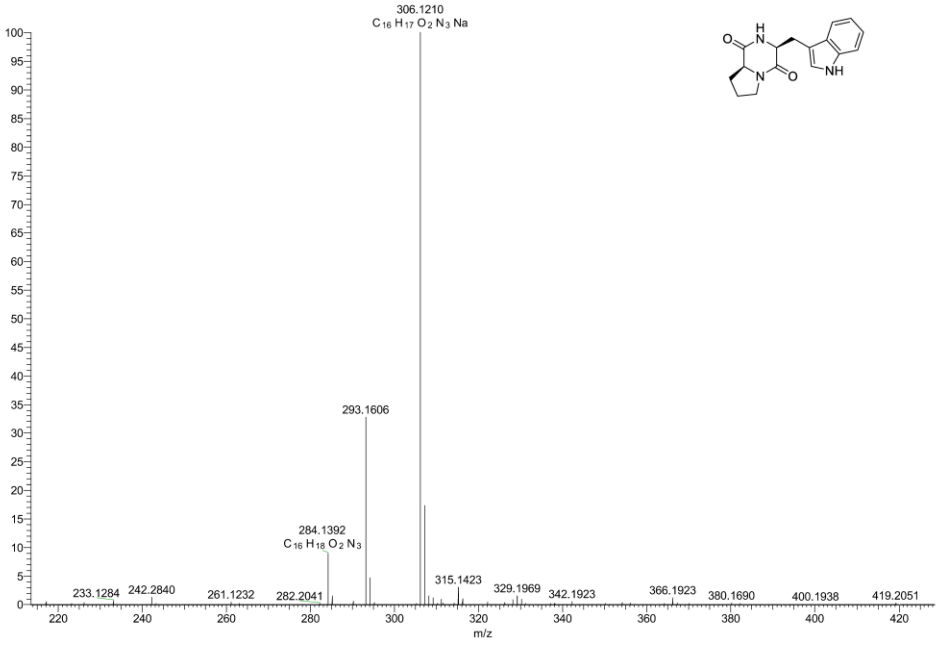


Figure S95. HRMS spectrum of **23**.

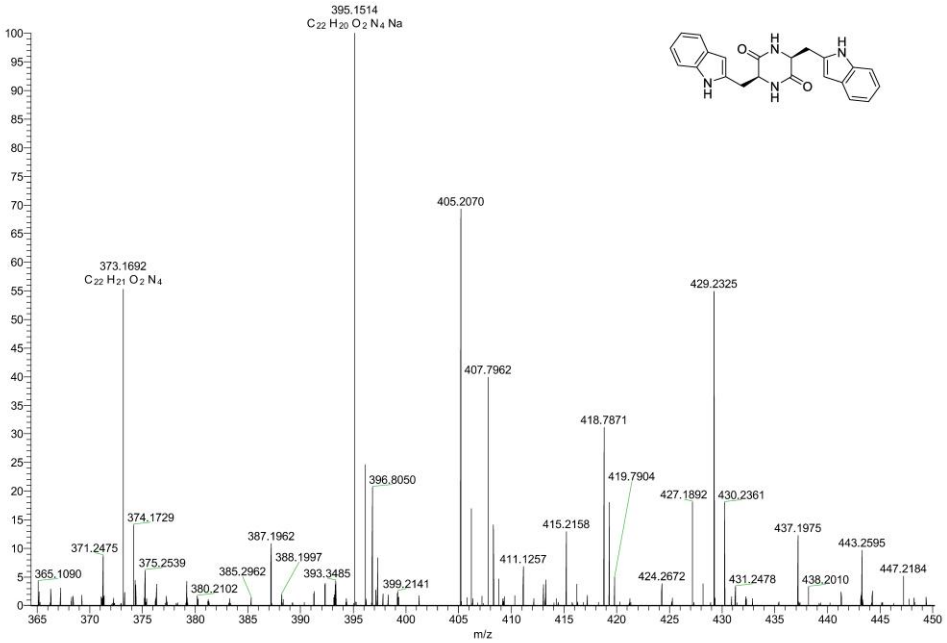


Figure S96. HRMS spectrum of **24**.

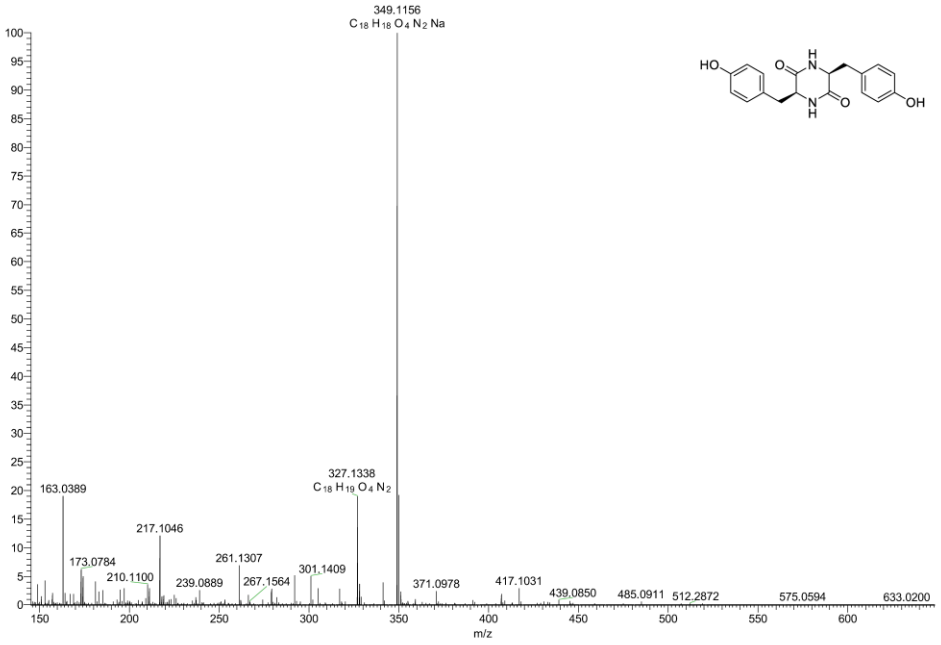


Figure S97. HRMS spectrum of **25**.

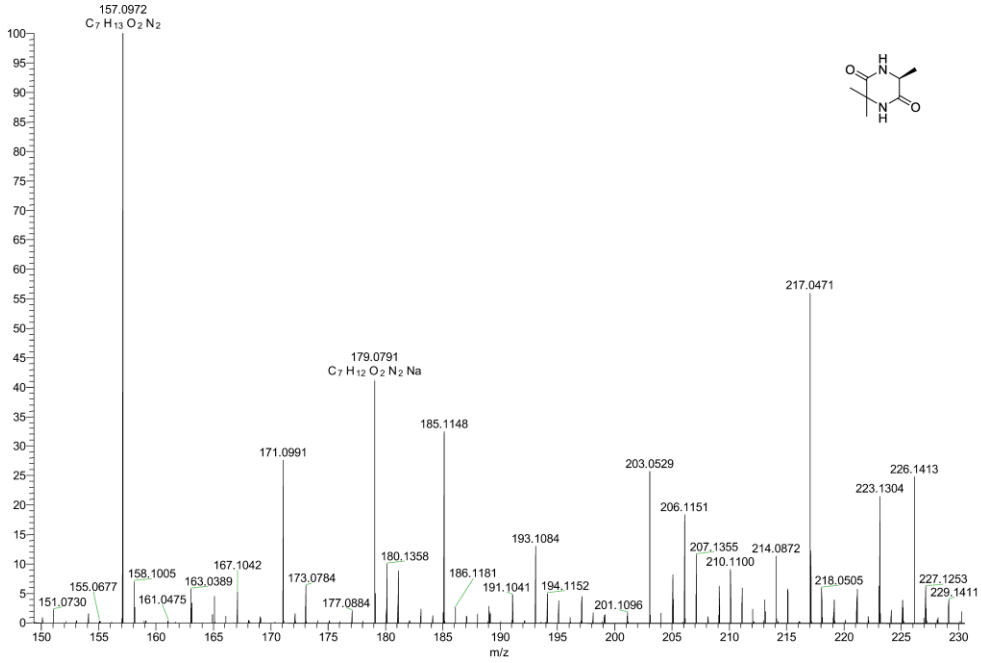


Figure S98. HRMS spectrum of **26**.

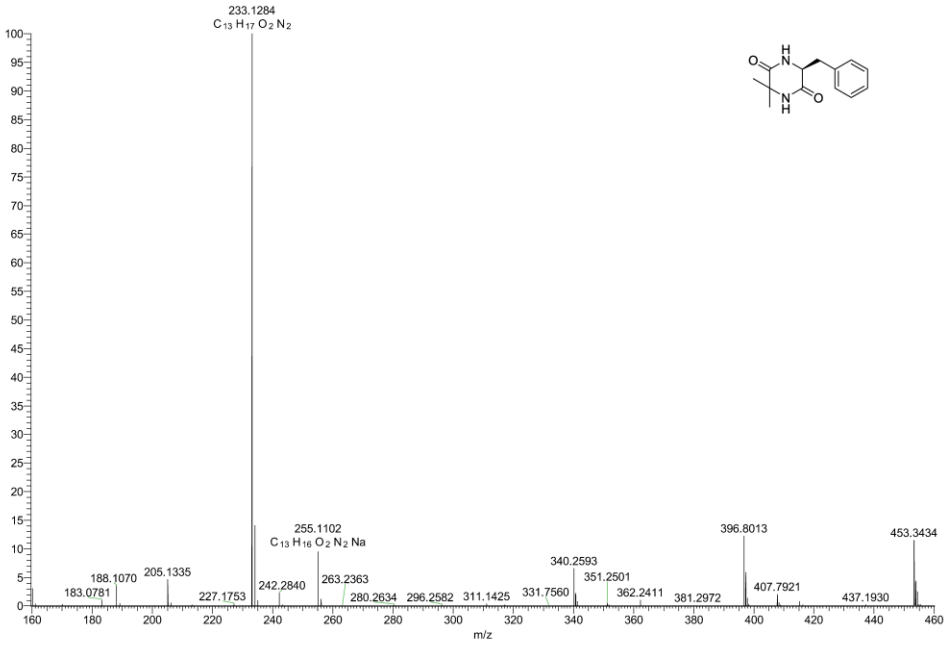


Figure S99. HRMS spectrum of **27**.

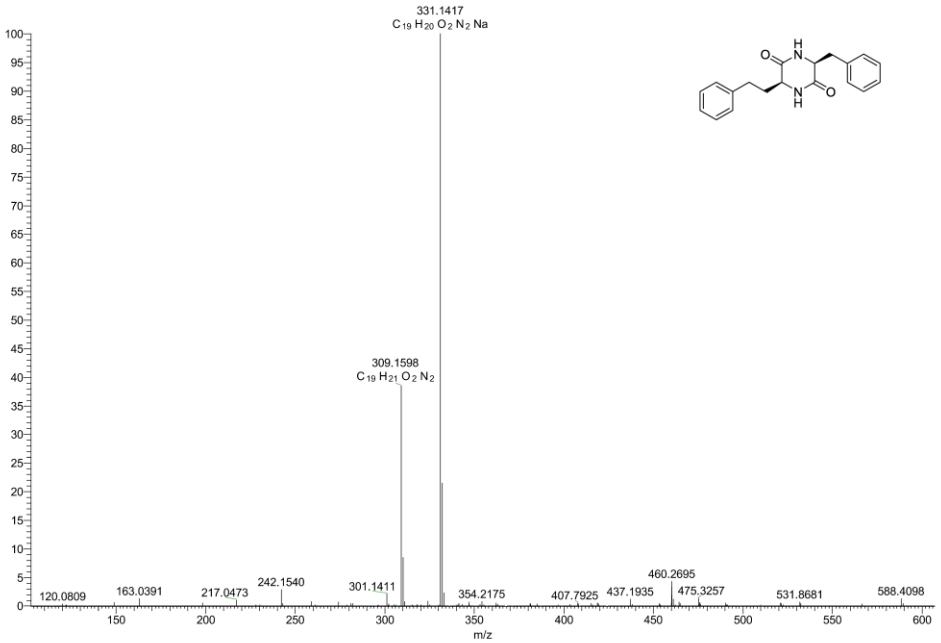


Figure S100. HRMS spectrum of **28**.

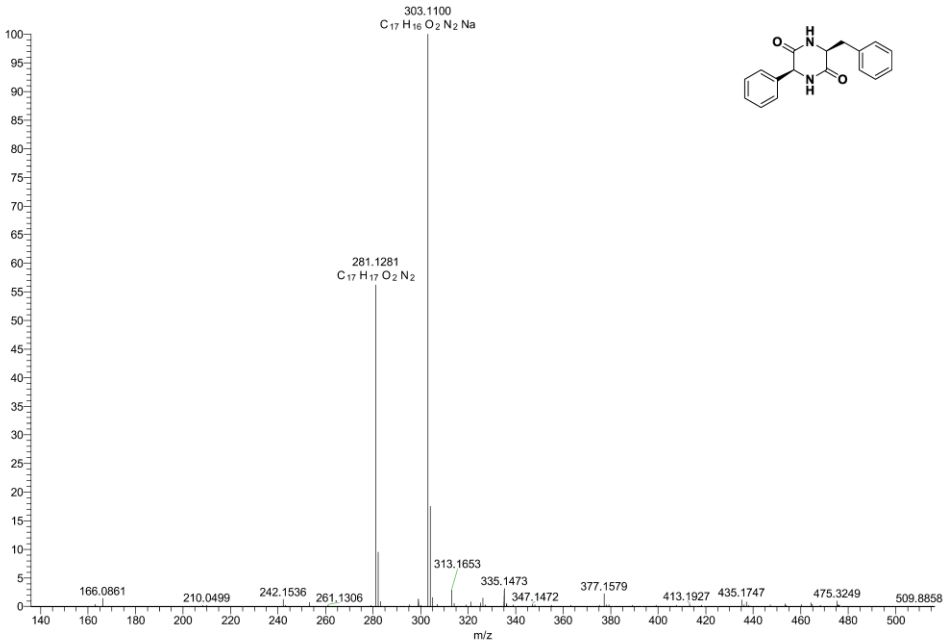


Figure S101. HRMS spectrum of **29**.

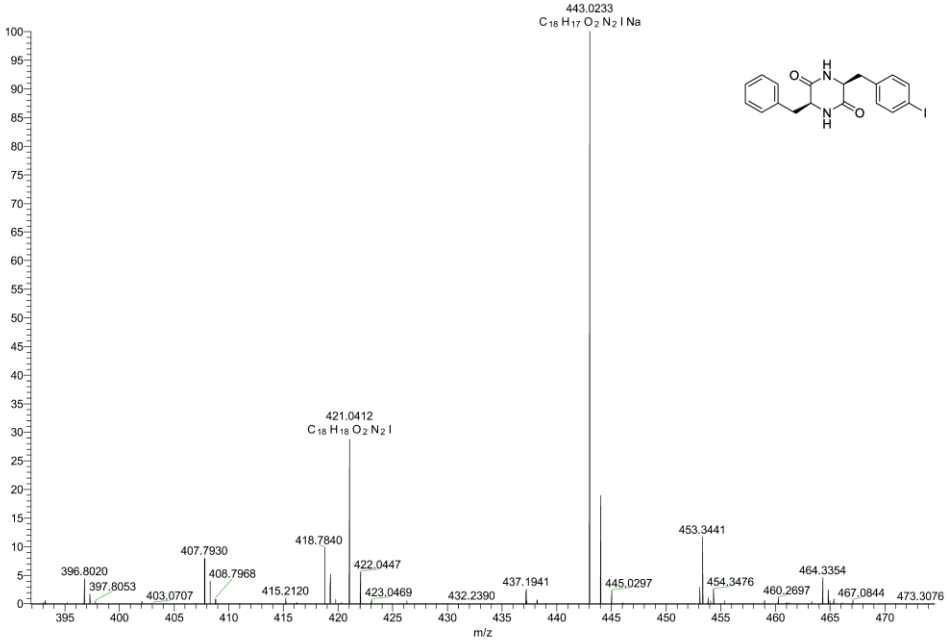


Figure S102. HRMS spectrum of **30**.

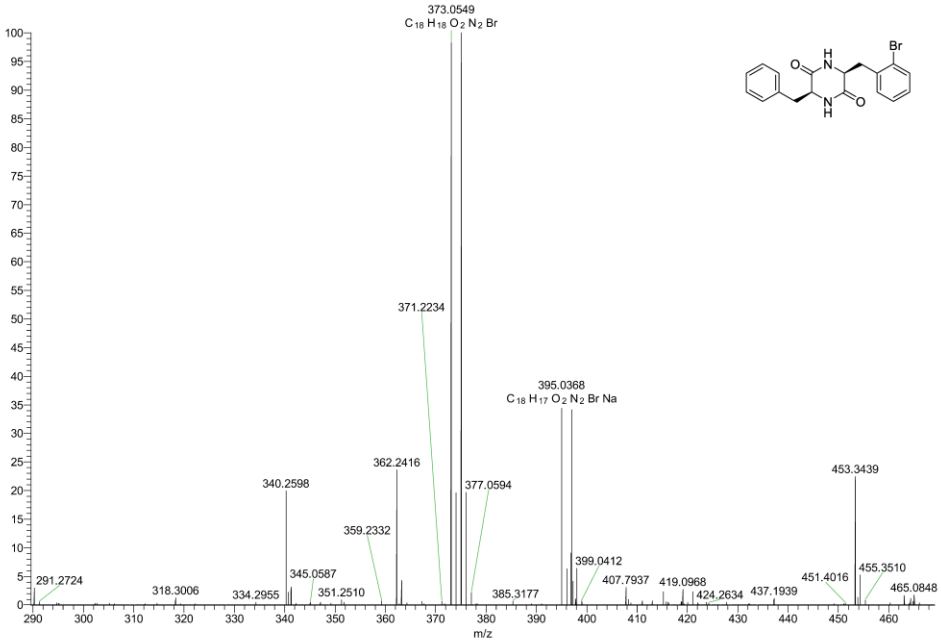


Figure S103. HRMS spectrum of **31**.

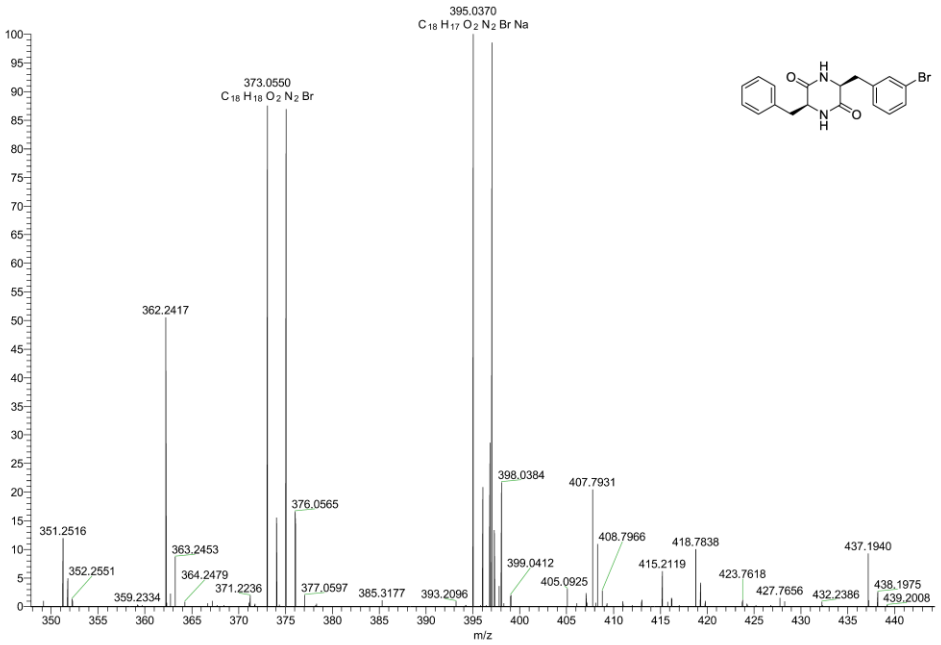


Figure S104. HRMS spectrum of **32**.

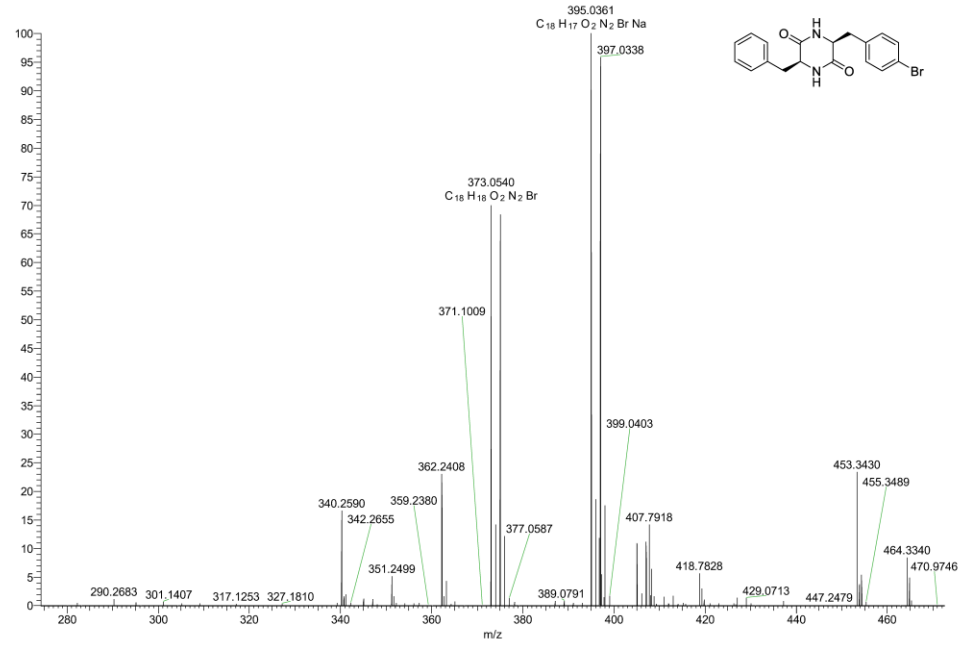


Figure S105. HRMS spectrum of **33**.