Supplementary information

Ammonium carboxylates in ammonia-Ugi reaction: one-pot synthesis of α,α-disubstituted amino acid derivatives including unnatural dipeptides

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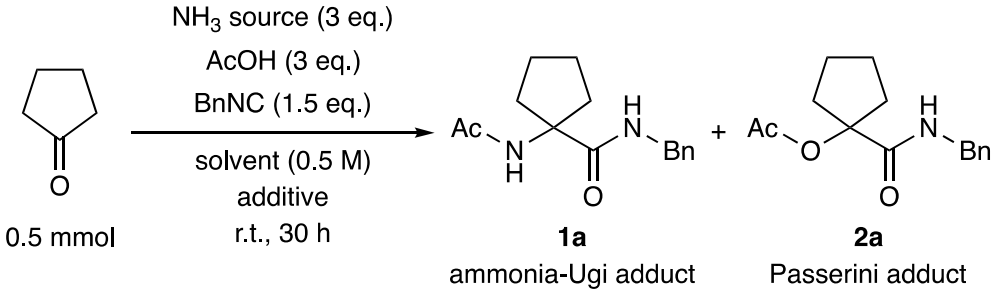
1. General Experimental Information

Analytical thin layer chromatography (TLC) was performed using TLC Silica gel 60 F_{254} (Merck) and visualized by UV light at 254 nm and stained with an acidic solution of *p*-anisaldehyde (concentrated H_2SO_4 in EtOH) or with ninhydrin spray. Medium pressure liquid chromatography (MPLC) was performed using a Yamazen EPCLC AL-580S. Preparative TLC was performed using PTC Silica gel 60 F_{254}, 0.5 mm (Merck). The NMR spectra were recorded at room temperature on JEOL ECA 600 or ECS 400 instruments with tetramethylsilane (TMS) as an internal standard. The ^{1}H NMR data are presented as follows. Chemical shift (δ in ppm), multiplicity, integration, and coupling constant *J* (in Hz and rounded to 0.1 Hz). Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), multiplet (m), and broad (br), or a combination of them. The ^{13}C NMR data are reported in terms of chemical shift (δ in ppm and rounded to 0.1 Hz). The IR spectra were recorded using a JASCO FT/IR 4700 with substance as a neat film on KBr plate or a pellet in a mixture with KBr, and described as wave numbers (cm^{-1}). The TOFMS spectra were obtained from a Bruker Daltonics micrOTOF-KSIfocus spectrometer. The optical rotation was measured with an Anton Paar polarimeter MCP300 in a 100 mm-long 2 mL cell at 589 nm at 20 °C. All solvents used were of guaranteed reagent grade and used as received. $CHCl_3$ and MeOH for spectrophotometry were purchased from TCI, Kanto, or Fujifilm Wako and used as received. Milli-Q water was used throughout. *p*-Fluorobenzyl isocyanide was synthesized according to the reported procedure.[1] Other chemicals were purchased from TCI, Nacalai, Fujifilm Wako, Sigma-Aldrich, Watanabe Chemical, Peptide Institute, and Kanto, and used as received.

2. Supplementary Table S1

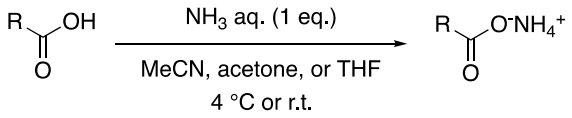
Table S1. Screening of the ammonia-Ugi reaction conditions



Entry	Solvent	Additive	Yield of **1a** (%)[a]	Yield of **2a** (%)[a]
1	EtOH	-	44[d]	1
2	2-propanol	-	50[d]	6
3	*t*-BuOH	-	16[d]	3
4	TFE/H_2O (9:1)[b]	-	79	10
5	2-propanol/H_2O (9:1)[b]	-	29[d]	6
6	*t*-BuOH/H_2O (9:1)[b]	-	11[d]	6
7	TFE	MS3A[c]	91	3
8	TFE	MS4A[c]	86	3
9	TFE	$MgSO_4$[c]	51[d]	6

[a]Isolated yield. [b]v/v. [c]100 mg. [d]Starting materials remained.

3. General Synthetic Procedure of Ammonium Carboxylates



To a solution of carboxylic acid (1 eq.) in MeCN, acetone, or THF, aqueous NH_3 (15.5 M, 1 eq.) was added dropwise at 4 °C or room temperature and the resulting mixture was stirred at 4 °C or room temperature. Then, the precipitated ammonium carboxylate was collected by paper filtration and washed thoroughly with cold MeCN, acetone, or THF. The obtained ammonium carboxylate was dried overnight in a vacuum desiccator and used without further purification in the following ammonia-Ugi reaction.

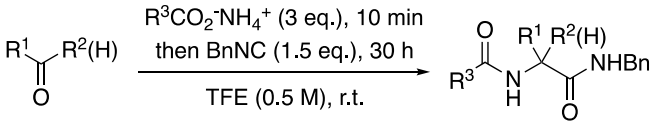
4. Supplementary Table S2

Table S2. Preparation of ammonium carboxylates

Entry	Ammonium carboxylate	Solvent	Reaction scale (mmol)	Concentration (M)	Temp.	Yield (%)
1	4-$NO_2PhCO_2^-NH_4^+$	THF	5	0.56	4 °C	76
2	$ClCH_2CO_2^-NH_4^+$	MeCN	5	2.5	4 °C	83
3	2-$NO_2PhCO_2^-NH_4^+$	MeCN	5	0.63	4 °C	90
4	Boc-Gly-$O^-NH_4^+$	acetone	10	0.2	4 °C	80
5	Bz-Gly-$O^-NH_4^+$	acetone	4	0.07	4 °C	73
6	Cbz-Gly-$O^-NH_4^+$	acetone	10	0.2	4 °C	80
7	Ac-Phe-$O^-NH_4^+$	MeCN	5	0.04	r.t.	96
8	Boc-Val-$O^-NH_4^+$	MeCN	4	0.2	4 °C	65
9	Boc-Phe-$O^-NH_4^+$	MeCN	2	0.4	4 °C	85
10	Boc-Pro-$O^-NH_4^+$	MeCN	4	0.2	4 °C	65
11	Boc-Met-$O^-NH_4^+$	MeCN	1	1	4 °C	86
12	Boc-Thr(Bn)-$O^-NH_4^+$	MeCN	4	0.4	4 °C	62
13	Boc-Glu(O*t*-Bu)-$O^-NH_4^+$	MeCN	1	0.33	4 °C	78
14	Boc-Trp(CHO)-$O^-NH_4^+$	MeCN	10	0.2	4 °C	82
15	Boc-Aib-$O^-NH_4^+$	MeCN	2	0.2	4 °C	72
16	Boc-D-Leu-$O^-NH_4^+$	MeCN	10	0.2	4 °C	88

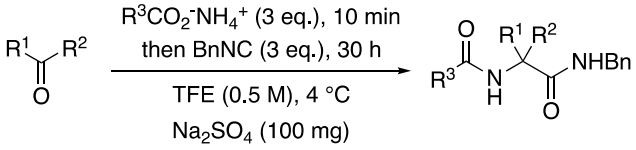
5. General Synthetic Procedures A–G

General synthetic procedure A for the ammonia-Ugi reaction



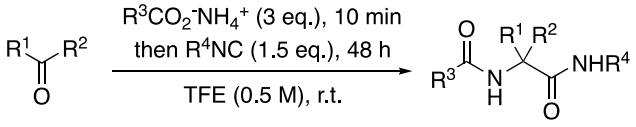
To a solution of ketone or aldehyde (0.5 mmol, 1 eq.) in TFE (0.5 M, 1 mL) in a screw-capped vial, ammonium carboxylate (1.5 mmol, 3 eq.) was added at room temperature and the resulting mixture was stirred at room temperature for 10 min. Then, benzyl isocyanide (0.75 mmol, 1.5 eq.) was added dropwise at room temperature and the reaction mixture was stirred at room temperature for 30 hours. The resulting solution was concentrated *in vacuo*, and then the crude mixture was purified by MPLC.

General synthetic procedure B for the ammonia-Ugi reaction



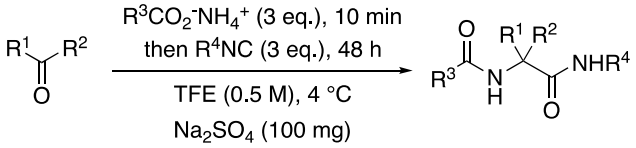
To a solution of ketone (0.5 mmol, 1 eq.) and Na_2SO_4 (100 mg) in TFE (0.5 M, 1 mL) in a screw-capped vial, ammonium carboxylate (1.5 mmol, 3 eq.) was added at 4 °C and the resulting mixture was stirred at 4 °C for 10 min. Then, benzyl isocyanide (1.5 mmol, 3 eq.) was added dropwise at 4 °C and the reaction mixture was stirred at room temperature for 30 hours. The resulting solution was concentrated *in vacuo*, and then the crude mixture was purified by MPLC.

General synthetic procedure C for the ammonia-Ugi reaction



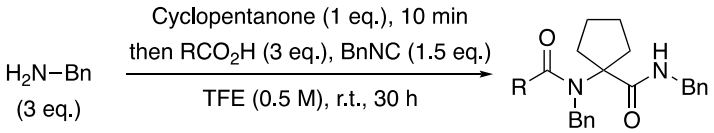
To a solution of ketone (0.5 mmol, 1 eq.) in TFE (0.5 M, 1 mL) in a screw-capped vial, ammonium carboxylate (1.5 mmol, 3 eq.) was added at room temperature and the resulting mixture was stirred at room temperature for 10 min. Then, isocyanide (0.75 mmol, 1.5 eq.) was added dropwise at room temperature and the reaction mixture was stirred at room temperature for 48 hours. The reaction solution was concentrated *in vacuo*, and then the crude mixture was dissolved in $CHCl_3$ and washed with sat. $NaHCO_3$ aq. (three times) and with water, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting mixture was purified by MPLC.

General synthetic procedure D for the ammonia-Ugi reaction



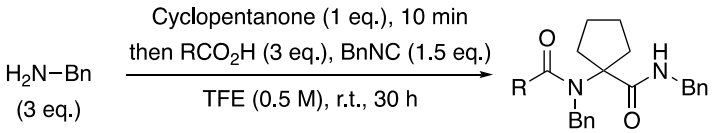
To a solution of ketone (0.5 mmol, 1 eq.) and Na_2SO_4 (100 mg) in TFE (0.5 M, 1 mL) in a screw-capped vial, ammonium carboxylate (1.5 mmol, 3 eq.) was added at 4 °C and the resulting mixture was stirred at room temperature for 10 min. Then, isocyanide (1.5 mmol, 3 eq.) was added at 4 °C and the reaction mixture was stirred at 4 °C for 48 hours. The reaction solution was concentrated *in vacuo*, and then the crude mixture was dissolved in $CHCl_3$ and washed with sat. $NaHCO_3$ aq. (three times) and with water, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting mixture was purified by MPLC.

General synthetic procedure E for the Ugi reaction



To a solution of cyclopentanone (0.5 mmol, 1 eq.) in TFE (0.5 M, 1 mL) in a screw-capped vial, benzylamine (1.5 mmol, 3 eq.) was added at room temperature and the resulting mixture was stirred at room temperature for 10 min. Then, carboxylic acid (1.5 mmol, 3 eq.) and benzyl isocyanide (0.75 mmol, 1.5 eq.) were successively added at room temperature and the reaction mixture was stirred at room temperature for 30 hours. The resulting solution was concentrated *in vacuo*, and then the crude mixture was purified by MPLC.

General synthetic procedure F for the Ugi reaction



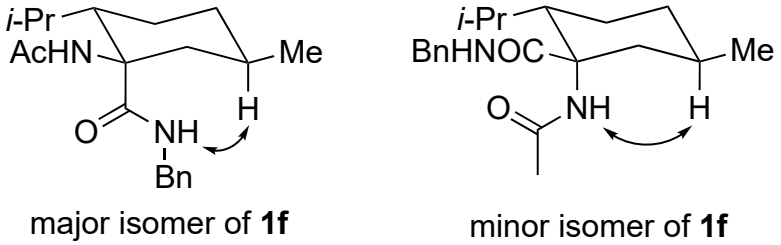
To a solution of cyclopentanone (0.5 mmol, 1 eq.) in TFE (0.5 M, 1 mL) in a screw-capped vial, benzylamine (1.5 mmol, 3 eq.) was added at room temperature and the resulting mixture was stirred at room temperature for 10 min. Then, carboxylic acid (1.5 mmol, 3 eq.) and benzyl isocyanide (0.75 mmol, 1.5 eq.) were successively added at room temperature and the reaction mixture was stirred at room temperature for 30 hours. The reaction solution was concentrated *in vacuo*, and then the crude mixture was dissolved in $CHCl_3$ and washed with sat.

$NaHCO_3$ aq. (three times) and with water, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting mixture was purified by MPLC.

General synthetic procedure G for deprotection of Boc

A solution of Boc-D-Leu-Aic-NH-R in 4 M HCl/dioxane (1 mL) was stirred at 4 °C to room temperature for 1–1.5 h. The reaction solution was concentrated *in vacuo*, and then the product was purified by recrystallization from Et_2O/MeOH (unless otherwise noted).

6. Supplementary Figure S1

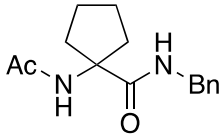


major isomer of **1f** minor isomer of **1f**

Figure S1. Key NOESY correlations of 1f

7. Synthetic Details for Table 1

Synthesis of 1a and 2a



1a

According to the general procedure A, cyclopentanone, ammonium acetate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **1a** in 90% yield (117.54 mg) as a colorless solid and the Passerini adduct **2a** in 6% yield (7.36 mg) as a colorless amorphous, respectively, after purification by MPLC (hexane/ethyl acetate = 77:23 to 0:100).

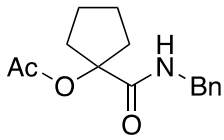
1a: 1-Acetamido-*N*-benzylcyclopentane-1-carboxamide (Ac-Ac$_5$c-NH-Bn)

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38 (1H, br s), 7.31–7.34 (2H, m), 7.24–7.27 (3H, m), 5.72 (1H, s), 4.45 (2H, d, *J* = 5.4 Hz), 2.31–2.36 (2H, m), 1.99–2.03 (2H, s), 2.00 (3H, s), 1.71–1.81 (4H, m).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.5 (C), 171.2 (C), 138.7 (C), 128.5 (CH), 127.2 (CH), 127.1 (CH), 67.4 (C), 43.4 (CH_2), 36.6 (CH_2), 24.0 (CH_2), 23.5 (CH_3).

IR (KBr): cm^{-1} 3318, 3290, 2958, 1657, 1533, 721.

HRMS (ESI-TOF): *m/z* calcd for $C_{15}H_{20}N_2NaO_2$ ([M + Na]$^+$): 283.1417; found: 283.1417.



2a

2a: 1-(Benzylcarbamoyl)cyclopentyl acetate

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 (2H, t, *J* = 7.2 Hz), 7.25–7.29 (3H, m), 5.97 (1H, br s), 4.47 (2H, d, *J* = 6.6 Hz), 2.30–2.36 (2H, m), 2.05 (3H, s), 2.00–2.05 (2H, m), 1.74–1.80 (4H, m).

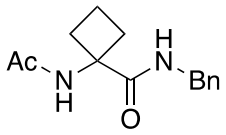
^{13}C NMR (101 MHz, $CDCl_3$): δ 172.4 (C), 170.1 (C), 138.4 (C), 128.8 (CH), 127.7 (CH), 127.6 (CH), 90.2 (C), 43.6 (CH_2), 37.0 (CH_2), 24.9 (CH_2), 21.7 (CH_3).

IR (KBr): cm^{-1} 3431, 3321, 2963, 1738, 1654, 1537, 1254, 1238, 698.

HRMS (ESI-TOF): *m/z* calcd for $C_{15}H_{19}NNaO_3$ ([M + Na]$^+$): 284.1257; found: 284.1257.

8. Synthetic Details for Scheme 1

Synthesis of 1b and 2b



1b

According to the general procedure A, cyclobutanone, ammonium acetate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **1b** in 54% yield (65.9 mg) as a colorless solid and the Passerini adduct **2b** and in 32% yield (39.2 mg) as a colorless solid, respectively, after purification by MPLC (hexane/ethyl acetate = 76:24 to 0:100).

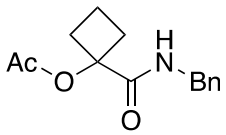
1b: 1-Acetamido-*N*-benzylcyclobutane-1-carboxamide (Ac-Ac$_4$c-NH-Bn)

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.45 (1H, br s), 7.31–7.33 (2H, m), 7.24–7.26 (3H, m), 5.94 (1H, br s), 4.45 (2H, d, *J* = 5.4 Hz), 2.72–2.76 (2H, m), 2.20–2.25 (2H, m), 2.01 (3H, s), 1.90–2.03 (2H, m).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.9 (C), 171.0 (C), 138.5 (C), 128.7 (CH), 127.4 (CH), 127.3 (CH), 59.9 (C), 43.5 (CH_2), 31.1 (CH_2), 23.5 (CH_3), 15.6 (CH_2).

IR (KBr): cm^{-1} 3287, 1653, 1538. 702.

HRMS (ESI-TOF): *m/z* calcd for $C_{14}H_{18}N_2NaO_2$ ([M + Na]$^+$): 269.1261; found: 269.1259.



2b

2b: 1-(Benzylcarbamoyl)cyclobutyl acetate

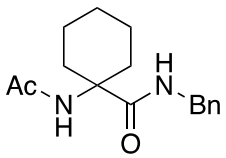
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 (2H, t, *J* = 7.5 Hz), 7.24–7.29 (3H, m), 6.06 (1H, br s), 4.48 (2H, d, *J* = 6.0 Hz), 2.72–2.76 (2H, m), 2.31–2.36 (2H, m), 2.07 (3H, s), 1.91–2.02 (2H, m).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.5 (C), 169.7 (C), 138.3 (C), 128.8 (CH), 127.6 (CH), 80.8 (C), 43.4 (CH_2), 32.2 (CH2), 21.3 (CH_3), 14.5 (CH_2).

IR (KBr): cm^{-1} 3272, 1737, 1656, 1543, 1366, 1248, 1227, 1135, 745, 702.

HRMS (ESI-TOF): *m/z* calcd for $C_{14}H_{17}NNaO_3$ ([M + Na]$^+$): 270.1101; found: 270.1101.

Synthesis of 1c



1c

According to the general procedure A, cyclohexanone, ammonium acetate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **1c** in 96% yield (135 mg) as a colorless solid, after purification by MPLC (hexane/ethyl acetate = 78:22 to 0:100).

1c: 1-Acetamido-*N*-benzylcyclohexane-1-carboxamide (Ac-Ac$_6$c-NH-Bn)

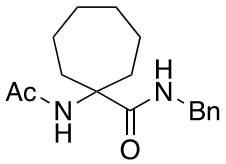
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40 (1H, br s), 7.24–7.33 (5H, m), 5.39 (1H, s), 4.45 (2H, d, J = 6.0 Hz), 2.13–2.15 (2H, m), 2.04 (3H, s), 1.89–1.94 (2H, m), 1.60–1.68 (3H, m), 1.32–1.43 (3H, m).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.6 (C), 171.1 (C), 138.7 (C), 128.6 (CH), 127.4 (CH), 127.2 (CH), 60.3 (C), 43.4 (CH_2), 32.3 (CH_2), 25.3 (CH_2), 23.9 (CH_3), 21.6 (CH_2).

IR (KBr): cm^{-1} 3330, 2935, 1656, 1544, 1525, 739, 699, 588.

HRMS (ESI-TOF): *m/z* calcd for $C_{16}H_{22}N_2NaO_2$ ([M + Na]$^+$): 297.1574; found: 297.1572.

Synthesis of 1d



1d

According to the general procedure A, cycloheptanone, ammonium acetate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **1d** in 96% yield (138 mg) as a colorless solid, after purification by MPLC (hexane/ethyl acetate = 77:23 to 0:100).

1d: 1-Acetamido-*N*-benzylcycloheptane-1-carboxamide (Ac-Ac$_7$c-NH-Bn)

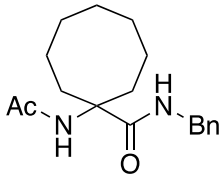
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31–7.34 (2H, m), 7.24–7.28 (3H, m), 7.14 (1H, br s), 5.48 (1H, br s), 4.44 (2H, d, J = 5.4 Hz), 2.22–2.26 (2H, m), 2.03–2.07 (2H, m), 2.02 (3H, s), 1.64–1.69 (2H, m), 1.58–1.61 (4H, m), 1.47–1.52 (2H, m).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.8 (C), 170.7 (C), 138.7 (C), 128.7 (CH), 127.6 (CH), 127.3 (CH), 64.1 (C), 43.7 (CH_2), 36.4 (CH_2), 29.3 (CH_2), 24.1 (CH_3), 22.7 (CH_2).

IR (KBr): cm^{-1} 3331, 3284, 2928, 2858, 1655, 1537, 1454, 1368, 1303, 1264, 732, 696, 591.

HRMS (ESI-TOF): *m/z* calcd for $C_{17}H_{24}N_2NaO_2$ ([M + Na]$^+$): 311.1730; found: 311.1730.

Synthesis of 1e



1e

According to the general procedure A, cyclooctanone, ammonium acetate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **1e** in 53% yield (80.5 mg) as a colorless solid, after purification by MPLC (hexane/ethyl acetate = 87:13 to 0:100).

1e: 1-Acetamido-*N*-benzylcyclooctane-1-carboxamide (Ac-Ac$_8$c-NH-Bn)

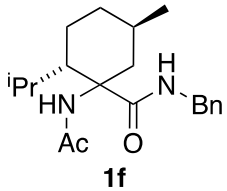
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23–7.34 (5H, m), 7.14 (1H, br s), 5.38 (1H, br s), 4.45 (2H, d, *J* = 5.6 Hz), 2.19–2.25 (2H, m), 2.03–2.09 (2H, m), 2.00 (3H, s), 1.49–1.64 (10H, m).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.0 (C), 170.5 (C), 138.8 (C), 128.7 (CH), 127.7 (CH), 127.4 (CH), 64.1 (C), 43.8 (CH_2), 30.9 (CH_2), 28.2 (CH_2), 25.0 (CH_2), 24.2 (CH_3), 22.0 (CH_2).

IR (KBr): cm^{-1} 3318, 2917, 1652, 1539, 743, 691, 651.

HRMS (ESI-TOF): *m/z* calcd for $C_{18}H_{26}N_2NaO_2$ ([M + Na]$^+$): 325.1887; found: 325.1887.

Synthesis of 1f



1f

According to the general procedure A, (–)-menthone (the purity: 93.4%), ammonium acetate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **1f** in 76% yield (117 mg) as a colorless solid, after purification by MPLC (hexane/ethyl acetate = 85:15 to 20:80). The diastereomeric ratio of **1f** was determined to be approximately 2:1 by the ^{1}H NMR analysis. NOTE: The yield was calculated based on the purity of starting (–)-menthone.

1f: 1-Acetamido-*N*-benzyl-2-isopropyl-5-methylcyclohexane-1-carboxamide

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25–7.36 (5.35H, m), 6.47 (0.65H, br s), 6.28 (0.65H, s), 5.50 (0.35H, s), 4.38–4.50 (2H, m), 2.85–2.88 (0.35H, m), 2.47–2.50 (0.65H, m), 2.07 (1.05H, s), 0.97–2.04 (8H, m), 2.00 (1.95H, s),

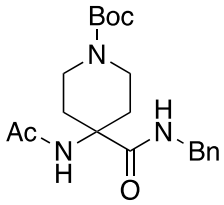
0.95 (3H, d, J = 6.6 Hz), 0.92 (1.05H, d, J = 7.2 Hz), 0.89 (1.95H, d, J = 6.0 Hz), 0.88 (1.05H, d, J = 6.0 Hz), 0.73 (1.95H, d, J = 7.2 Hz).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.8 and 172.5 (C, diastereomers), 171.2 and 169.8 (C, diastereomers), 138.5 and 137.9 (C, diastereomers), 128.7 (CH), 128.6 (CH), 127.7 (CH), 127.5 (CH), 127.2 (CH), 67.2 and 63.2 (C, diastereomers), 48.8 and 47.0 (CH, diastereomers), 44.1 mad 43.7 (CH_2, diastereomers), 42.9 and 39.2 (CH_2, diastereomers), 34.3 and 34.2 (CH_2, diastereomers), 29.9 and 28.3 (CH, diastereomers), 27.6 and 26.3 (CH, diastereomers), 24.7 and 24.5 (CH_3, diastereomers), 24.3 and 23.7 (CH_3, diastereomers), 22.8 and 22.3 (CH_2, diastereomers), 22.7 and 21.8 (CH_3, diastereomers), 19.5 and 18.0 (CH_3, diastereomers).

IR (KBr): cm^{-1} 3444, 3330, 2952, 1649, 1518, 1454, 1368, 1280, 732, 699.

HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{30}N_2NaO_2$ ($[M + Na]^+$): 353.2200; found: 353.2199.

Synthesis of 1g



1g

According to the general procedure A, 1-(*tert*-butoxycarbonyl)-4-piperidone, ammonium acetate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **1g** in 96% yield (181 mg) as a colorless amorphous, respectively, after purification by MPLC (hexane/ethyl acetate = 66:34 to 0:100).

1g: *tert*-Butyl 4-acetamido-4-(benzylcarbamoyl)piperidine-1-carboxylate

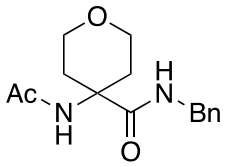
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.47 (1H, br t, J = 5.4 Hz), 7.31–7.33 (2H, m), 7.24–7.27 (3H, m), 5.43 (1H, s), 4.44 (2H, d, J = 5.4 Hz), 3.75 (2H, br s), 3.18 (2H, ddd, J = 3.6, 10.2, 13.8 Hz), 2.17 (2H, ddd, J = 3.6, 10.2, 14.1 Hz), 2.04–2.09 (2H, m), 2.04 (3H, s), 1.45 (9H, s).

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.5 (C), 171.5 (C), 154.7 (C), 138.3 (C), 128.7 (CH), 127.4 (CH), 127.3 (CH), 79.9 (C), 58.4 (C), 43.5 (CH_2), 39.9 (CH_2), 39.0 (CH_2), 31.9 (CH_2), 28.5 (CH_3), 23.7 (CH_3).

IR (KBr): cm^{-1} 3548, 3382, 3325, 3264, 2972, 1690, 1661, 1639, 1550, 1524, 1419, 1366, 1279, 1249, 1159, 697.

HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{29}N_3NaO_4$ ($[M + Na]^+$): 398.2050; found: 398.2052.

Synthesis of 1h



1h

According to the general procedure A, tetrahydro-4*H*-pyran-4-one, ammonium acetate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **1h** in 89% yield (123 mg) as a colorless solid, after purification by MPLC (hexane/ethyl acetate = 32:68 to 0:100).

1h: 4-Acetamido-*N*-benzyltetrahydro-2*H*-pyran-4-carboxamide

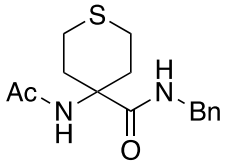
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.52 (1H, br s), 7.25–7.34 (5H, m), 5.45 (1H, br s), 4.45 (2H, d, *J* = 6.0 Hz), 3.78–3.82 (2H, m), 3.64–3.68 (2H, m), 2.28–2.33 (2H, m), 2.04 (3H, s), 2.03–2.07 (2H, m).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.9 (C), 171.5 (C), 138.4 (C), 128.8 (CH), 127.5 (CH), 127.5 (CH), 63.6 (CH_2), 57.9 (C), 43.7 (CH_2), 33.0 (CH_2), 24.1 (CH_3).

IR (KBr): $cm^{-1.}$ 3315, 3297, 1657, 1545, 1301, 1114, 1034, 732, 702.

HRMS (ESI-TOF): *m/z* calcd for $C_{15}H_{20}N_2NaO_3$ ($[M + Na]^+$): 299.1366; found: 299.1365.

Synthesis of 1i



1i

According to the general procedure A, tetrahydro-4*H*-thiopyran-4-one, ammonium acetate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **1i** in 92% yield (136 mg) as a colorless solid, respectively, after purification by MPLC (hexane/ethyl acetate = 76:24 to 0:100).

1i: 4-Acetamido-*N*-benzyltetrahydro-2*H*-thiopyran-4-carboxamide

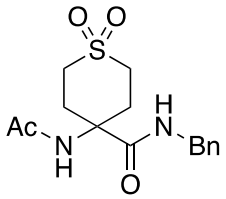
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25–7.34 (6H, m), 5.37 (1H, br s), 4.44 (2H, d, *J* = 6.6 Hz), 2.71–2.76 (2H, m), 2.61–2.65 (2H, m), 2.41–2.44 (2H, m), 2.31–2.36 (2H, m), 2.05 (3H, s).

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.1 (C), 171.2 (C), 138.4 (C), 128.8 (CH), 127.6 (CH), 127.5 (CH), 59.6 (C), 43.8 (CH_2), 33.7 (CH_2), 24.2 (CH_3), 23.7 (CH_2).

IR (KBr): cm^{-1} 3375, 3268, 1659, 1553, 1514, 1369, 1272, 701, 605.

HRMS (ESI-TOF): *m/z* calcd for $C_{15}H_{20}N_2NaO_2S$ ($[M + Na]^+$): 315.1138; found: 315.1142.

Synthesis of 1j



1j

According to the general procedure A, tetrahydrothiopyran-4-one 1,1-dioxide, ammonium acetate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **1j** in 86% yield (140 mg) as a colorless solid, after purification by MPLC (ethyl acetate/MeOH = 95:5) followed by recrystallization from *i*-Pr_2O/$CHCl_3$/MeOH.

1j: 4-Acetamido-*N*-benzyltetrahydro-2*H*-thiopyran-4-carboxamide 1,1-dioxide

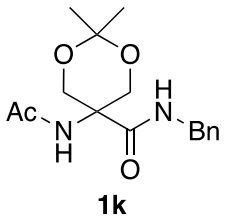
^{1}H NMR (600 MHz, DMSO-d_6): δ 8.34 (1H, br t, *J* = 6.0 Hz), 8.02 (1H, br s), 7.19–7.30 (5H, m), 4.26 (2H, d, *J* = 6.0 Hz), 3.18–3.23 (2H, m), 3.07–3.09 (2H, m), 2.44–2.46 (2H, m), 2.32–2.37 (2H, m), 1.94 (3H, s).

^{13}C NMR (151 MHz, DMSO-d_6): δ 172.4 (C), 170.3 (C), 139.7 (C), 128.2 (CH), 126.7 (CH), 126.5 (CH), 56.6 (C), 46.5 (CH_2), 42.3 (CH_2), 30.4 (CH_2), 23.3 (CH_3).

IR (KBr): cm^{-1} 3377, 3269, 1663, 1551, 1512, 1299, 1285, 1130, 855, 699.

HRMS (ESI-TOF): *m/z* calcd for $C_{15}H_{20}N_2NaO_4S$ ($[M + Na]^+$): 347.1036; found: 347.1037.

Synthesis of 1k and 2k



1k

According to the general procedure A, 2,2-dimethyl-1,3-dioxan-5-one, ammonium acetate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **1k** in 57% yield (88.0 mg) as a colorless solid and the Passerini adduct **2k** in 23% (36.0 mg) as a colorless solid, after purification by MPLC (ethyl acetate/hexane = 72:28 to 10:90).

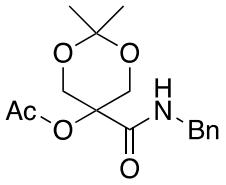
1k: 5-Acetamido-*N*-benzyl-2,2-dimethyl-1,3-dioxane-5-carboxamide

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.74 (1H, br s), 7.27–7.36 (5H, m), 6.69 (1H, s), 4.85 (2H, d, *J* = 11.4 Hz), 4.53 (2H, d, *J* = 5.4 Hz), 3.77 (2H, d, *J* = 12.0 Hz), 2.03 (3H, s), 1.66 (3H, s), 1.38 (3H, s).

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.6 (C), 170.5 (C), 137.7 (C), 128.8 (CH), 127.6 (CH), 127.3 (CH), 99.0 (C), 61.5 (CH_2), 54.3 (C), 43.9 (CH_2), 26.9 (CH_3), 24.3 (CH_3), 20.6 (CH_3).

IR (KBr): cm^{-1} 3317, 2993, 1659, 1537, 1374, 1201, 1091, 829, 729, 699.

HRMS (ESI-TOF): *m/z* calcd for $C_{16}H_{22}N_2NaO_4$ ([M + Na]$^+$): 329.1472; found: 329.1472.



2k

2k: 5-(Benzylcarbamoyl)-2,2-dimethyl-1,3-dioxan-5-yl acetate

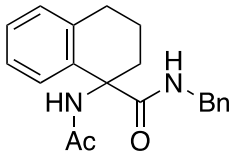
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–7.37 (5H, m), 7.06 (1H, br s), 4.56 (2H, d, *J* = 5.2 Hz), 4.36 (2H, d, *J* = 12.4 Hz), 3.97 (2H, d, *J* = 12.4 Hz), 2.13 (3H, s), 1.48 (3H, s), 1.35 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.1 (C), 169.5 (C), 138.0 (C), 128.8 (CH), 127.6 (CH), 99.7 (C), 74.5 (C), 64.2 (CH_2), 43.5 (CH_2), 26.4 (CH_3), 21.0 (CH_3), 20.1 (CH_3).

IR (KBr): cm^{-1} 3303, 1741, 1664, 1546, 1373, 1253, 1226, 1086, 697.

HRMS (ESI-TOF): *m/z* calcd for $C_{16}H_{21}NNaO_5$ ([M + Na]$^+$): 330.1312; found: 330.1310.

Synthesis of 1l



1l

According to the general procedure A (NOTE: The reaction time was 2 weeks), α-tetralone, ammonium acetate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **1l** of pale-yellow solid in 22% yield (35.3 mg), after purification by MPLC (hexane/ethyl acetate = 77:23 to 0:100).

1l: 1-Acetamido-*N*-benzyl-1,2,3,4-tetrahydronaphthalene-1-carboxamide

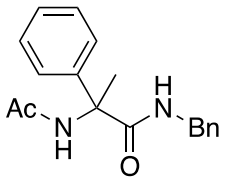
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.10–7.30 (10H, m), 5.67 (1H, br s), 4.37–4.45 (2H, m), 2.99 (1H, ddd, *J* = 5.4, 11.4, 16.2 Hz), 2.77 (1H, td, *J* = 4.2, 16.2 Hz), 2.69 (1H, dt, *J* = 3.6, 13.2 Hz), 2.10–2.14 (1H, m), 1.94–1.99 (1H, m), 1.98 (3H, s), 1.74–1.82 (1H, m).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.3 (C), 168.7 (C), 138.6 (C), 137.8 (C), 135.5 (C), 129.6 (CH), 128.7 (CH), 128.0 (CH), 127.5 (CH), 127.2 (CH), 127.1 (CH), 126.9 (CH), 62.3 (C), 44.0 (CH_2), 32.8 (CH_2), 29.2 (CH_2), 24.1 (CH_3), 20.9 (CH_2).

IR (KBr): cm^{-1} 3346, 3314, 2934, 1671, 1650, 1527, 1496, 1453, 1364, 750, 731, 689, 586.

HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{22}N_2NaO_2$ ([M + Na]$^+$): 345.1574; found: 345.1574.

Synthesis of 1m



1m

According to the general procedure A, acetophenone, ammonium acetate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **1m** in 40% yield (59.6 mg) as a colorless oil, after purification by MPLC (hexane/ethyl acetate = 100:0 to 0:100).

1m: 2-Acetamido-*N*-benzyl-2-phenylpropanamide

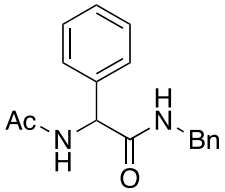
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40–7.41 (2H, m), 7.34–7.37 (2H, m), 7.22–7.30 (5H, m), 7.05 (2H, d, *J* = 7.2 Hz), 5.85 (1H, br s), 4.42 (1H, dd, *J* = 5.4, 15.0 Hz), 4.35 (1H, dd, *J* = 5.4, 15.0 Hz), 2.00 (6H, s).

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.8 (C), 169.0 (C), 141.2 (C), 137.8 (C), 128.9 (CH), 128.7 (CH), 127.9 (CH), 127.5 (CH), 127.2 (CH), 126.0 (CH), 62.3 (C), 43.9 (CH_2), 24.1 (CH_3), 23.5 (CH_3).

IR (KBr): cm^{-1} 3317, 3061, 3030, 1655, 1496, 1448, 1370, 1292, 751, 731, 698.

HRMS (ESI-TOF): *m/z* calcd for $C_{18}H_{20}N_2NaO_2$ ($[M + Na]^+$): 319.1417; found: 319.1416.

Synthesis of 1n



1n

According to the general procedure A (NOTE: The reaction was 3 h), benzaldehyde, ammonium acetate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **1n** in 80% yield (113 mg) as a colorless solid, by washing the crude mixture with cold hexane and cold water.

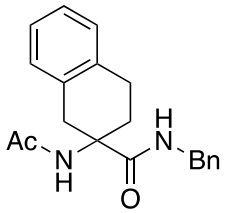
1n: 2-Acetamido-*N*-benzyl-2-phenylacetamide (Ac-DL-Phg-NH-Bn)[2]

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24–7.40 (8H, m), 7.12 (2H, d, *J* = 6.6 Hz), 6.84–6.87 (1H, m), 5.92–5.98 (1H, m), 5.45 (2H, d, *J* = 6.6 Hz), 4.47 (1H, dd, *J* = 6.0, 15.0 Hz), 4.40 (1H, dd, *J* = 6.0, 15.0 Hz), 2.02 (3H, s).

IR (KBr): cm^{-1} 3299, 1633, 1537, 1378, 722, 696.

HRMS (ESI-TOF): *m/z* calcd for $C_{17}H_{18}N_2NaO_2$ ($[M + Na]^+$): 305.1261; found: 305.1260.

Synthesis of 1o



1o

According to the general procedure A, β-tetralone, ammonium acetate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **1o** in 73% yield (118 mg) as a beige solid, after purification by MPLC (hexane/ethyl acetate = 79:21 to 0:100).

1o: 2-Acetamido-*N*-benzyl-1,2,3,4-tetrahydronaphthalene-2-carboxamide

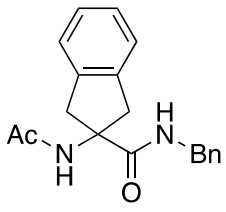
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32 (2H, t, *J* = 7.2 Hz), 7.08–7.26 (8H, m), 5.57 (1H, s), 4.47–4.48 (2H, m), 3.45 (1H, d, *J* = 17.1 Hz), 3.05 (1H, d, *J* = 17.1 Hz), 2.86–2.91 (1H, m), 2.74–2.81 (2H, m), 2.12–2.17 (1H, m), 1.95 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.7 (C), 171.4 (C), 138.4 (C), 135.1 (C), 132.5 (C), 129.7 (CH), 128.9 (CH), 128.7 (CH), 127.4 (CH), 127.3 (CH), 126.6 (CH), 126.3 (CH), 59.3 (C), 43.6 (CH_2), 38.0 (CH_2), 28.2 (CH_2), 25.5 (CH_2), 23.6 (CH_3).

IR (KBr): cm^{-1} 3303, 1652, 1536, 1297, 752.

HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{22}N_2NaO_2$ ($[M + Na]^+$): 345.1574; found: 345.1571.

Synthesis of 1p



1p

According to the general procedure B, 2-indanone, ammonium acetate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **1p** in 76% yield (117 mg) as a pale-yellow solid, after purification by MPLC (hexane/ethyl acetate = 76:24 to 0:100).

1p: 2-Acetamido-*N*-benzyl-2,3-dihydro-1*H*-indene-2-carboxamide (Ac-Aic-NH-Bn)

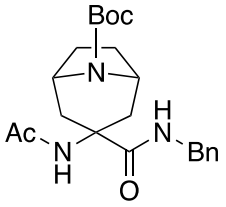
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.17–7.32 (m, 9H), 6.82 (1H, br s), 6.26 (1H, br s), 4.44 (2H, d, *J* = 5.4 Hz), 3.58 (2H, d, *J* = 16.2 Hz), 3.53 (2H, d, *J* = 16.2 Hz), 1.98 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.3 (C), 170.9 (C), 140.2 (C), 138.2 (C), 128.8 (CH), 127.5 (CH), 127.4 (CH), 127.4 (CH), 125.0 (CH), 67.3 (C), 43.8 (CH_2), 42.6 (CH_2), 24.2 (CH_3).

IR (KBr): cm^{-1} 3319, 1658, 1547, 1366, 1301, 1233, 752, 739.

HRMS (ESI-TOF): *m/z* calcd for $C_{19}H_{20}N_2NaO_2$ ($[M + Na]^+$): 331.1417; found: 331.1418.

Synthesis of 1q



1q

According to the general procedure A, *N*-Boc-nortropinone, ammonium acetate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **1q** in 44% yield (88.6 mg) as a colorless amorphous, after purification by MPLC (hexane/ethyl acetate = 54:46 to 0:100).

1q: *tert*-Butyl 3-acetamido-3-(benzylcarbamoyl)-8-azabicyclo[3.2.1]octane-8-carboxylate

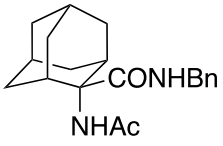
^{1}H NMR (600 MHz, DMSO-d_6): δ 7.95 (1H, t, *J* = 6.0 Hz), 7.92 (1H, s), 7.18–7.29 (5H, m), 4.23 (2H, d, *J* = 6.0 Hz), 4.03 (2H, br s), 1.78–2.22 (8H, m), 1.91 (3H, s), 1.39 (9H, s).

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.1 (C), 171.5 (C), 153.4 (C), 138.4 (C), 128.7 (CH), 127.4 (CH), 127.4 (CH), 79.8 (C), 58.5 (C), 52.5 (CH), 43.7 (CH_2), 35.7 (CH_2), 28.6 (CH_3), 27.5 (CH_2), 24.2 (CH_3).

IR (KBr): cm^{-1} 3318, 2977, 1699, 1660, 1531, 1168, 1106, 732.

HRMS (ESI-TOF): *m/z* calcd for $C_{22}H_{31}N_3NaO_4$ ($[M + Na]^+$): 424.2207; found: 424.2206.

Synthesis of 1r



1r

According to the general procedure A, 2-adamantanone, ammonium acetate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **1r** in 86% yield (139 mg) as a colorless solid, after purification by MPLC ($CHCl_3$/ethyl acetate = 100:0 to 64:36).

1r: 2-Acetamido-*N*-benzyladamantane-2-carboxamide[3]

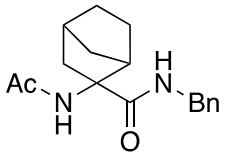
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.68 (1H, br s), 7.23–7.32 (5H, m), 5.30 (1H, s), 4.45 (2H, d, *J* = 6.0 Hz), 2.71

(2H, s), 1.98–2.00 (2H, m), 1.97 (3H, s), 1.90–1.92 (2H, m), 1.82–1.85 (2H, m), 1.68–1.76 (6H, m).

IR (KBr): cm^{-1} 3392, 3327, 3268, 2914, 2857, 1638, 1533, 1453, 1424, 1370, 1307, 725.

HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{26}N_2NaO_2$ ($[M + Na]^+$): 349.1887; found: 349.1886.

Synthesis of 1s



1s

According to the general procedure A, 2-norbornanone, ammonium acetate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **1s** in 86% yield (124 mg) as a colorless solid, after purification by MPLC (hexane/ethyl acetate = 81:19 to 0:100). The diastereomeric ratio of **1s** was determined to be approximately 3:2 by the ^{1}H NMR analysis.

1s: 2-Acetamido-*N*-benzylbicyclo[2.2.1]heptane-2-carboxamide

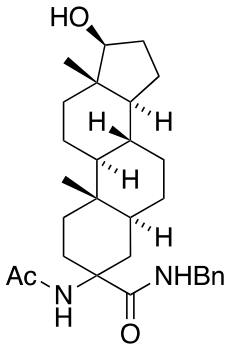
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 (0.6H, br s), 7.83 (0.4H, br s), 7.22–7.33 (5H, m), 5.76 (0.6H, br s), 5.44 (0.4H, br s), 4.36–4.49 (2H, m), 3.13 (0.6H, br d, J = 3.6 Hz), 3.11 (0.4H, br d, J = 3.0 Hz), 2.98 (0.3H, dd, J = 2.4, 4.8 Hz), 2.96 (0.3H, dd, J = 3.0, 4.8 Hz), 2.61 (0.2H, d, J = 2.4 Hz), 2.59 (0.2H, d, J = 2.4 Hz), 2.32–2.33 (0.4H, m), 2.27–2.29 (0.6H, m), 2.00 (1.8H, s), 1.97 (1.2H, s), 1.63–1.65 (0.4H, m), 1.19–1.60 (6H, m), 0.90 (0.3H, d, J = 2.4 Hz), 0.88 (0.3H, d, J = 2.4 Hz).

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.8, 172.2, 171.9, 170.8 (C, diastereomers), 138.9 and 138.9 (C, diastereomers), 128.7, 127.7, 127.4, 127.3, 127.2 (CH, diastereomers), 68.7 and 67.1 (C, diastereomers), 44.4 and 44.0 (CH, diastereomers), 43.8 (CH_2), 42.4 and 41.8 (CH_2, diastereomers), 38.1 and 37.2 (CH_2, diastereomers), 36.5 and 36.0 (CH, diastereomers), 29.3 and 28.0 (CH_2, diastereomers), 24.2 and 23.8 (CH_3, diastereomers), 23.7 and 23.2 (CH_2, diastereomers).

IR (KBr): cm^{-1} 3395, 2962, 1651, 1557, 1533, 733, 700.

HRMS (ESI-TOF): *m/z* calcd for $C_{17}H_{22}N_2NaO_2$ ($[M + Na]^+$): 309.1574; found: 309.1575.

Synthesis of 1t



1t

According to the general procedure A, stanolone, ammonium acetate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **1t** in 97% yield (227 mg) as a colorless solid, after washing the crude mixture with cold hexane and cold water followed by recrystallization from hexane/THF. The diastereomeric ratio of **1t** was determined to be >20:1 by the ^{1}H NMR analysis.

1t: 3-Acetamido-*N*-benzyl-17-hydroxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthrene-3-carboxamide

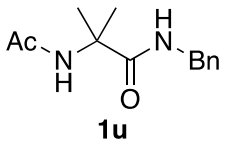
^{1}H NMR (600 MHz, DMSO-d_6): δ 8.08 (1H, t, J = 6.0 Hz), 7.74 (1H, s), 7.26 (2H, t, J = 7.2 Hz), 7.18–7.25 (3H, m), 4.41 (1H, d, J = 4.8 Hz), 4.27 (1H, dd, J = 6.0, 15.6 Hz), 4.19 (1H, dd, J = 6.0, 15.6 Hz), 3.89–3.43 (1H, m), 2.36–239 (1H, m), 1.94–1.97 (1H, m), 1.75–1.84 (1H, m), 1.78 (3H, s), 1.67–1.70 (1H, m), 1.58–1.61 (1H, m), 1.08–1.48 (12H, m), 0.72–0.93 (4H m), 0.77 (3H, s), 0.61 (3H, s), 0.50–0.54 (1H, m).

^{13}C NMR (151 MHz, DMSO-d_6): δ 173.0 (C), 168.9 (C), 140.3 (C), 128.0 (CH), 126.7 (CH), 126.4 (CH), 80.0 (CH), 58.4 (C), 54.1 (CH), 50.6 (CH), 42.6 (C), 42.1 (CH_2), 41.4 (CH), 37.0 (CH_2), 36.6 (CH_2), 35.2 (C), 35.1 (CH), 35.1 (CH_2), 31.3 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 28.1 (CH_2), 23.1 (CH_3), 23.1 (CH_2), 20.2 (CH_2), 11.7 (CH_3), 11.3 (CH_3).

IR (KBr): cm^{-1} 3532, 3433, 3368, 3249, 3076, 2941, 2870, 1666, 1637, 1563, 1517, 1447, 1372, 1052, 724.

HRMS (ESI-TOF): *m/z* calcd for $C_{29}H_{42}N_2NaO_3$ ([M + Na]$^{+}$): 489.3088; found: 489.3090.

Synthesis of 1u



1u

According to the general procedure A, acetone, ammonium acetate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **1u** in 79% yield (92.7 mg) as a colorless solid, after purification by MPLC (hexane/ethyl acetate = 76:24 to 0:100).

1u: 2-Acetamido-*N*-benzyl-2-methylpropanamide (Ac-Aib-NH-Bn)

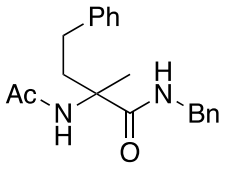
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–7.36 (5H, m), 6.81 (1H, br s), 6.09 (1H, s), 4.46 (2H, d, *J* = 5.2 Hz), 1.99 (3H, s), 1.60 (6H, s).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.7 (C), 170.4 (C), 138.4 (C), 128.7 (CH), 127.4 (CH), 127.4 (CH), 57.3 (C), 43.7 (CH_2), 25.2 (CH_3), 24.0 (CH_3).

IR (KBr): cm^{-1} 3350, 3299, 3059, 2983, 2941, 1660, 1543, 1429, 1363, 1301, 1184, 720, 700, 674, 592.

HRMS (ESI-TOF): *m/z* calcd for $C_{13}H_{18}N_2NaO_2$ ($[M + Na]^+$): 257.1261; found: 257.1257.

Synthesis of 1v



1v

According to the general procedure A, 4-phenyl-2-butanone, ammonium acetate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **1v** in 94% yield (153 mg) as a colorless amorphous, after purification by MPLC (hexane/ethyl acetate = 80:20 to 0:100).

1v: 2-Acetamido-*N*-benzyl-2-methyl-4-phenylbutanamide

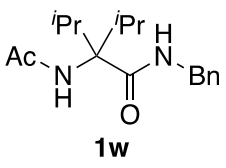
^{1}H NMR (600 MHz, $CDCl_3$): 7.23–7.36 (7H, m), 7.15–7.18 (1H, m), 7.08 (2H, d, *J* = 6.6. Hz), 6.54 (1H, br s), 6.50 (1H, br s), 4.43–4.50 (2H, m), 2.75–2.80 (1H, m), 2.56–2.61 (1H, m), 2.38–2.43 (1H, m), 1.95 (3H, s), 1.89–1.95 (1H, m), 1.64 (3H, s).

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.0 (C), 170.0 (C), 141.2 (C), 138.2 (C), 128.8 (CH), 128.5 (CH), 128.4 (CH), 127.7 (CH), 127.6 (CH), 126.0 (CH), 60.5 (C), 43.9 (CH_2), 38.4 (CH_2), 30.6 (CH_2), 24.1 (CH_3), 23.6 (CH_3).

IR (KBr): cm^{-1} 3318, 3062, 3028, 2933, 1649, 1535, 1510, 1454, 1371, 1288, 1263, 746, 699.

HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{24}N_2NaO_2$ ($[M + Na]^+$): 347.1730; found: 347.1732.

Synthesis of 1w



1w

According to the general procedure A, 2,4-dimethyl-3-pentanone, ammonium acetate, and benzyl isocyanide

were converted into the ammonia-Ugi adduct **1w** in 16% yield (23.4 mg) as a colorless solid, after purification by MPLC (hexane/ethyl acetate = 89:11 to 20:80).

1w: 2-Acetamido-*N*-benzyl-2-isopropyl-3-methylbutanamide

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29–7.37 (5H, m), 6.82 (1H, br s), 6.03 (1H, br s), 4.49 (2H, d, J = 5.4 Hz), 2.85 (2H, sept, J = 7.2 Hz), 2.05 (3H, s), 0.97 (3H, d, J = 7.2 Hz), 0.95 (3H, d, J = 7.2 Hz).

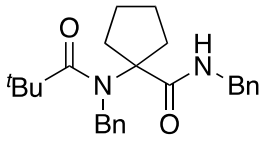
^{13}C NMR (151 MHz, $CDCl_3$): δ 172.6 (C), 169.9 (C), 137.9 (C), 129.0 (CH), 128.1 (CH), 127.9 (CH), 71.8 (C), 44.6 (CH_2), 30.9 (CH), 25.3 (CH_3), 18.2 (CH_3), 18.1 (CH_3).

IR (KBr): cm^{-1} 3351, 3276, 2968, 1663, 1650, 1637, 1556, 1528, 1510, 696.

HRMS (ESI-TOF): *m/z* calcd for $C_{17}H_{26}N_2NaO_2$ ($[M + Na]^+$): 313.1887; found: 313.1888.

9. Synthetic Details for Table 2

Synthesis of 3a



3a

According to the general procedure E, cyclopentanone, benzylamine, pivalic acid, and benzyl isocyanide were converted into the Ugi adduct **3a** in 92% yield (180 mg) as a colorless solid, after purification by MPLC (hexane/ethyl acetate = 86:14 to 65:35).

3a: *N*-Benzyl-*N*-pivaroyl-Ac$_5$c-NH-Bn

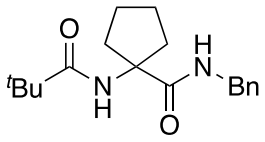
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24–7.33 (10H, m), 6.52 (1H, br s), 4.87 (2H, s), 4.39 (2H, d, J = 5.4 Hz), 2.43–2.48 (2H, m), 1.81–1.86 (2H, m), 1.49–1.65 (4H, m), 1.23 (9H, s).

^{13}C NMR (151 MHz, $CDCl_3$): δ 180.1 (C), 174.6 (C), 139.2 (C), 138.8 (C), 128.5 (CH), 128.5 (CH), 127.7 (CH), 127.1 (CH), 127.1 (CH), 126.3 (CH), 74.5 (C), 50.7 (CH_2), 43.6 (CH_2), 40.1 (C), 36.0 (CH_2), 28.8 (CH_3), 23.7 (CH_2).

IR (KBr): cm^{-1} 3365, 2958, 1650, 1631, 1524, 1355, 1177, 749, 727, 698.

HRMS (ESI-TOF): *m/z* calcd for $C_{25}H_{32}N_2NaO_2$ ([M + Na]$^+$): 415.2356; found: 415.2356.

Synthesis of 4a



4a

Preparation of ammonium pivalate: To a solution of pivalic acid (1.5 mmol) in MeCN (3 mL), NH_3 aq. (3 mmol) was added dropwise at 4 °C and the mixture was stirred at 4 °C for 1 h and then concentrated *in vacuo*. The obtained ammonium pivalate was used without further purification in the following ammonia-Ugi reaction.

Ammonia-Ugi reaction: According to the general procedure A, cyclopentanone, ammonium pivalate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **4a** was obtained in 86% yield (131 mg) as a colorless solid, after purification by MPLC (hexane/ethyl acetate = 97:3 to 20:80).

4a: *N*-Pivaroyl-Ac$_5$c-NH—Bn

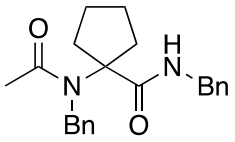
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.56 (1H, br s), 7.22–7.31 (5H, m), 5.81 (1H, br s), 4.44 (2H, d, J = 5.4 Hz), 2.32–2.37 (2H, m), 1.98–2.03 (2H, m), 1.68–1.82 (4H, m), 1.16 (9H, s).

^{13}C NMR (151 MHz, $CDCl_3$): δ 179.4 (C), 173.8 (C), 138.7 (C), 128.6 (CH), 127.4 (CH), 127.2 (CH), 67.7 (C), 43.5 (CH_2), 39.1 (C), 36.6 (CH_2), 27.5 (CH_3), 23.8 (CH_2).

IR (KBr): cm^{-1} 3329. 3300, 2961, 1658, 1631, 1516, 1454, 1207, 700.

HRMS (ESI-TOF): *m/z* calcd for $C_{18}H_{26}N_2NaO_2$ ([M + Na]$^+$): 325.1887; found: 325.1888.

Synthesis of 3b



3b

According to the general procedure E, cyclopentanone, benzylamine, acetic acid, and benzyl isocyanide were converted into the Ugi adduct **3b** in 88% yield (153 mg) as a pale-yellow solid, after purification by MPLC (hexane/ethyl acetate = 71:29 to 50:50).

3b: *N*-Acetyl-*N*-benzyl-Ac$_5$c-NH-Bn

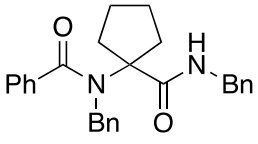
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.23–7.35 (10H, m), 7.13 (1H, br s), 4.66 (2H, br s), 4.45 (2H, br s), 2.67 (2H, br s), 2.07 (3H, s), 1.88 (2H, br s), 1.64 (4H, br s).

^{13}C NMR (151 MHz, DMSO-d_6): δ 174.3 (C), 171.5 (C), 140.2 (C), 139.4 (C), 128.7 (CH), 128.0 (CH), 126.8 (CH), 126.7 (CH), 126.4 (CH), 125.7 (CH), 72.1 (C), 50.7 (CH_2), 42.4 (CH_2), 36.2 (CH_2), 23.9 (CH_2), 23.0 (CH_3).

IR (KBr): cm^{-1} 3320, 2959, 1673, 1629, 1537, 1418, 730.

HRMS (ESI-TOF): *m/z* calcd for $C_{22}H_{26}N_2NaO_2$ ([M + Na]$^+$): 373.1887; found: 373.1885.

Synthesis of 3c



3c

According to the general procedure F, cyclopentanone, benzylamine, benzoic acid, and benzyl isocyanide were converted into the Ugi adduct **3c** in 83% yield (170 mg) as a colorless solid, after purification by MPLC (hexane/ethyl acetate = 74:26 to 53:47).

3c: *N*-Benzoyl-*N*-benzyl-Ac$_5$c-NH-Bn

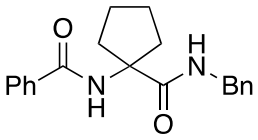
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41 (1H, br t, *J* = 5.4 Hz), 7.28–7.36 (10H, m), 7.18–7.23 (3H, m), 7.10–7.11 (2H, m), 4.66 (2H, s), 4.37 (2H, d, *J* = 5.4 Hz), 2.70–2.74 (2H, m), 2.02–2.07 (2H, m), 1.69–1.75 (4H, m).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.8 (C), 173.6 (C), 138.7 (C), 138.3 (C), 137.0 (C), 130.0 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 127.6 (CH), 127.3 (CH), 127.2 (CH), 126.9 (CH), 126.8 (CH), 73.6 (C), 53.1 (CH_2), 43.6 (CH_2), 36.3 (CH_2), 23.2 (CH_2).

IR (KBr): cm^{-1} 3391, 2962, 1663, 1607, 1511, 1453, 1398, 1250, 1213, 738, 724, 701, 612.

HRMS (ESI-TOF): *m/z* calcd for $C_{27}H_{28}N_2NaO_2$ ($[M + Na]^+$): 435.2043; found: 435.2043.

Synthesis of 4c



4c

According to the general procedure C (NOTE: The reaction time was 30 h), cyclopentanone, ammonium benzoate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **4c** in 73% yield (117 mg) as a colorless solid, after purification by MPLC ($CHCl_3$/ethyl acetate = 100:0 to 90:10).

4c: *N*-Benzoyl-Ac_5c-NH-Bn

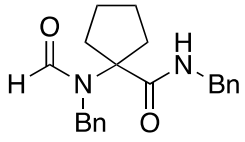
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.73–7.74 (2H, m), 7.44–7.55 (4H, m), 7.23–7.32 (5H, m), 6.37 (1H, s), 4.49 (2H, d, *J* = 6.0 Hz), 2.43–2.47 (2H, m), 2.15–2.19 (2H, m), 1.81–1.87 (4H, m).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.8 (C), 168.2 (C), 138.7 (C), 134.4 (C), 132.1 (CH), 128.9 (CH), 128.7 (CH), 127.5 (CH), 127.3 (CH), 127.1 (CH), 68.4 (C), 43.8 (CH_2), 37.0 (CH_2), 24.2 (CH_2).

IR (KBr): cm^{-1} 3310, 3276, 1651, 1634, 1535, 1316, 694.

HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{22}N_2NaO_2$ ($[M + Na]^+$): 345.1574; found: 345.1573.

Synthesis of 3d



3d

According to the general procedure E, cyclopentanone, benzylamine, formic acid, and benzyl isocyanide were converted into the Ugi adduct **3d** in 83% yield (140 mg) as a colorless oil, after purification by MPLC (hexane/ethyl acetate = 56:44 to 35:65).

3d: *N*-Benzyl-*N*-formyl-Ac_5c-NH-Bn

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (0.65H, s, rotamer), 8.30 (0.35H, s, rotamer), 7.09–7.33 (10H, m), 6.98 (0.35H, br s, rotamer), 5.76 (0.65H, br s, rotamer), 4.59 (1.3H, s, rotamer), 4.54 (0.7H, s, rotamer), 4.34 (0.7H,

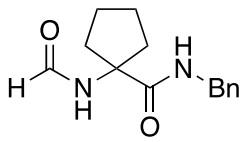
d, J = 5.8 Hz, rotamer), 4.20 (1.3H, d, J = 5.8 Hz, rotamer), 2.60–2.64 (0.7H, m, rotamer), 2.32–2.38 (1.3H, m, rotamer), 1.91–2.04 (2H, m), 1.60–1.81 (4H, m).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.6 and 172.8 (C, rotamers), 163.6 and 165.4 (CH, rotamers), 138.2 and 138.4 (C, rotamers), 137.8 and 137.8 (C, rotamers), 126.7, 127.3, 127.4, 127.5, 127.6, 127.7, 127.7, 128.0, 128.6, 129.0 (CH×6, rotamers), 72.1 and 73.6 (C, rotamers), 46.9 and 51.0 (CH_2, rotamers), 43.7 and 43.9 (CH_2, rotamers), 35.4 and 35.9 (CH_2, rotamers), 22.7 and 22.8 (CH_2, rotamers).

IR (neat): cm^{-1} 3340, 2958, 1649, 1529, 1496, 1454, 1432, 1377, 1358, 1262, 1218, 1197, 1079, 1029, 976, 750, 728, 699.

HRMS (ESI-TOF): *m/z* calcd for $C_{21}H_{24}N_2NaO_2$ ([M + Na]$^+$): 359.1730; found: 359.1730.

Synthesis of 4d



4d

According to the general procedure A, cyclopentanone, ammonium formate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **4d** was obtained in 92% yield (113 mg) as a colorless solid, after purification by MPLC (hexane/ethyl acetate = 77:23 to 0:100).

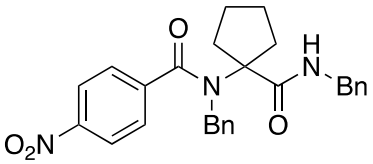
4d: *N*-Formyl-Ac_5c-NH-Bn[4]

^{1}H NMR (600 MHz, $CDCl_3$): 8.24 (0.15H, d, J = 11.4 Hz), 8.14 (0.85H, s), 7.24–7.34 (5H, m), 7.21 (1H, br s), 5.74 (1H, br s), 4.46 (2H, d, J = 5.4 Hz), 2.33–2.42 (2H, m), 1.76–2.09 (m, 6H).

IR (KBr): cm^{-1} 3277, 3033, 2962, 2874, 1651, 1537, 1454, 1388, 755, 700.

HRMS (ESI-TOF): *m/z* calcd for $C_{14}H_{18}N_2NaO_2$ ([M + Na]$^+$): 269.1261; found: 269.1260.

Synthesis of 3e



3e

According to the general procedure F, cyclopentanone, benzylamine, 4-nitrobenzoic acid, and benzyl isocyanide were converted into the Ugi adduct **3e** was obtained in 73% yield (167 mg) as a colorless oil, after purification by MPLC (hexane/ethyl acetate = 69:31 to 48:52).

3e: *N*-Benzyl-*N*-4-nitrobenzoyl-Ac$_5$c-NH-Bn

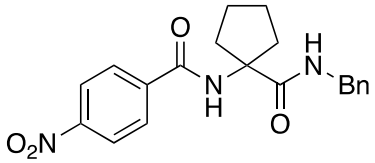
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.10 (2H, d, *J* = 9.0 Hz), 7.40 (2H, d, *J* = 9.0 Hz), 7.22–7.38 (8H, m), 7.12 (2H, d, *J* =6.0 Hz), 6.94 (1H, br t, *J* = 5.4 Hz), 4.61 (2H, s), 4.48 (2H, d, *J* = 5.4 Hz), 2.68–2.72 (2H, m), 2.04–2.09 (2H, m), 1.73–1.75 (4H, m).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.4 (C), 172.2 (C), 148.1 (C), 143.0 (C), 138.5 (C), 138.1 (C), 128.8 (CH), 128.6 (CH), 127.6 (CH), 127.4 (CH), 127.3 (CH), 126.1 (CH), 123.5 (CH), 73.9 (C), 52.7 (CH_2), 43.7 (CH_2), 36.1 (CH_2), 23.4 (CH_2).

IR (KBr): cm^{-1} 3357, 2956, 1639, 1522, 1348, 858, 732, 700.

HRMS (ESI-TOF): *m/z* calcd for $C_{27}H_{27}N_3NaO_4$ ([M + Na]$^+$): 480.1894; found: 480.1895.

Synthesis of 4e



4e

According to the general procedure C (NOTE: The reaction time was 30 h), cyclopentanone, ammonium 4-nitrobenzoate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **4e** in 42% yield (76.9 mg) as a pale-yellow solid, after purification by MPLC (hexane/ethyl acetate = 78:22 to 20:80).

4e: *N*-4-Nitrobenzoyl-Ac$_5$c-NH-Bn

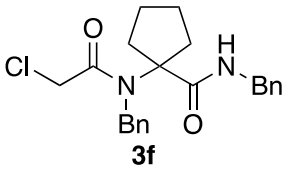
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.30 (2H, d, *J* = 8.7 Hz), 7.91 (2H, d, *J* = 8.7 Hz), 7.32–7.34 (2H, m), 7.26–7.29 (3H, m), 6.98 (1H, br s), 6.69 (1H, br s), 4.50 (2H, d, *J* = 5.4 Hz), 2.38–2.42 (2H, m), 2.21–2.25 (2H, m), 1.84–1.94 (4H, m).

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.6 (C), 165.9 (C), 149.9 (C), 140.0 (C), 138.4 (C), 128.9 (CH), 128.4 (CH), 127.6 (CH), 127.6 (CH), 124.0 (CH), 68.4 (C), 44.0 (CH_2), 37.0 (CH_2), 24.5 (CH_2).

IR (KBr): cm^{-1} 3277, 1655, 1601, 1524, 1348.

HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{21}N_3NaO_4$ ([M + Na]$^+$): 390.1424; found: 390.1423.

Synthesis of 3f



3f

According to the general procedure E, cyclopentanone, benzylamine, chloroacetic acid, and benzyl isocyanide

were converted into the Ugi adduct **3f** was obtained in 63% yield (122 mg) as a slightly pink solid, after purification by MPLC (hexane/ethyl acetate = 73:27 to 52:48).

3f: *N*-Benzyl-*N*-chloroacetyl-Ac$_5$c-NH-Bn

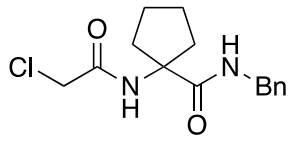
^{1}H NMR (600 MHz, $CDCl_3$): 7.23–7.38 (10H, m), 6.88 (1H, br s), 4.73 (2H, br s), 4.45 (2H, d, *J* = 6.0 Hz), 3.95 (2H, s), 2.65–2.69 (2H, m), 1.89–1.94 (2H, m), 1.66–1.68 (4H, m).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.1 (C), 169.0 (C), 138.4 (C), 137.7 (C), 129.2 (CH), 128.6 (CH), 127.7 (CH), 127.6 (CH), 127.3 (CH), 125.4 (CH), 74.0 (C), 50.5 (CH_2), 43.8 (CH_2), 42.7 (CH_2) 36.0 (CH_2), 23.3 (CH_2).

IR (KBr): cm^{-1} 3363, 2948, 1671, 1648, 1527, 1415, 1247, 1207, 725, 698.

HRMS (ESI-TOF): *m/z* calcd for $C_{22}H_{25}ClN_2NaO_2$ ([M + Na]$^+$): 407.1497; found: 407.1498.

Synthesis of 4f



4f

According to the general procedure A, cyclopentanone, ammonium chloroacetate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **4f** in 81% yield (120 mg) as a colorless solid, after purification by MPLC ($CHCl_3$/ethyl acetate = 100:0 to 80:20).

4f: *N*-Chloroacetyl-Ac$_5$c-NH-Bn

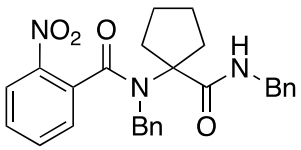
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32–7.34 (2H, m), 7.25–7.28 (3H, m), 7.01 (1H, br s), 6.77 (br s, 1H), 4.46 (2H, d, *J* = 5.4 Hz), 4.01 (2H, s), 2.34–2.38 (2H, m), 2.04–2.09 (2H, m), 1.76–1.83 (4H, m).

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.3 (C), 166.7 (C), 138.4 (C), 128.6 (CH), 127.3 (CH), 67.9 (C), 43.6 (CH_2), 42.7 (CH_2), 36.6 (CH_2), 24.0 (CH_2).

IR (KBr): cm^{-1} 3280, 3064, 2959, 2871, 1659, 1550, 1537, 1449, 1233, 748, 699.

HRMS (ESI-TOF): *m/z* calcd for $C_{15}H_{19}ClN_2NaO_2$ ([M + Na]$^+$): 317.1027; found: 317.1026.

Synthesis of 3g



3g

According to the general procedure F, cyclopentanone, benzylamine, *o*-nitrobenzoic acid, and benzyl isocyanide were converted into the Ugi adduct **3g** was obtained in 55% yield (125 mg) as a colorless amorphous, after

purification by MPLC ($CHCl_3$).

3g: *N*-Benzyl-*N*-*o*-nitrobenzoyl Ac_5c-NH-Bn

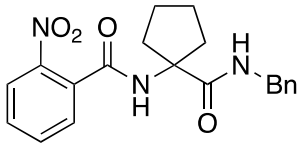
^{1}H NMR (600 MHz, $CDCl_3$): 8.07–8.10 (1H, m), 7.41–7.46 (2H, m), 7.33–7.37 (4H, m), 7.19–7.30 (7H, m), 6.87 (1H, br s), 4.50 (2H, d, J = 6.0 Hz), 4.52 (2H, br s), 2.60–2.65 (2H, m), 2.13–2.19 (2H, m), 1.74–1.78 (4H, m).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.6 (C), 170.1 (C), 144.7 (C), 138.8 (C), 138.1 (C), 134.2 (CH), 133.4 (C), 129.8 (CH), 128.8 (CH), 128.8 (CH), 128.4 (CH), 128.0 (CH), 127.4 (CH), 127.4 (CH), 126.3 (CH), 124.7 (CH), 73.8 (C), 51.8 (CH_2), 44.1 (CH_2), 36.0 (CH_2), 24.0 (CH_2).

IR (KBr): cm^{-1} 3447, 3382, 2956, 1649, 1528, 1402, 1346, 744, 733, 699.

HRMS (ESI-TOF): *m/z* calcd for $C_{27}H_{27}N_3NaO_4$ ([M + Na]$^+$): 480.1894; found: 480.1895.

Synthesis of 4g



4g

According to the general procedure A, cyclopentanone, ammonium *o*-nitrobenzoate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **4g** in 91% yield (166 mg) as a colorless solid, after purification by MPLC (hexane/ethyl acetate = 77:23 to 0:100).

4g: *N*-*o*-Nitrobenzoyl-Ac_5c-NH-Bn

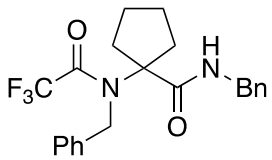
^{1}H NMR (600 MHz, DMSO-d_6): δ 8.87 (1H, s), 8.13 (1H, br t, J = 6.0 Hz), 8.06 (1H, d, J = 7.8 Hz), 7.84–7.85 (1H, m), 7.79-7.82 (1H, m), 7.68–7.71 (1H, m), 7.25–7.29 (4H, m), 7.19–7.21 (1H, m), 4.33 (2H, d, J = 6.0 Hz), 2.03–2.14 (4H, m), 1.64–1.74 (4H, m).

^{13}C NMR (151 MHz, DMSO-d_6): δ 173.1 (C), 165.4 (C), 146.5 (C), 139.9 (C), 133.5 (CH) 132.8 (C), 130.5 (CH), 129.8 (CH), 128.1 (CH), 126.7 (CH), 126.4 (CH), 123.9 (CH), 67.0 (C), 42.4 (CH_2), 35.8 (CH_2), 24.0 (CH_2).

IR (KBr): cm^{-1} 3318, 3267, 1653, 1523, 1346, 701.

HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{21}N_3NaO_4$ ([M + Na]$^+$): 390.1424; found: 390.1423.

Synthesis of 3h



3h

According to the general procedure E, cyclopentanone, benzylamine, trifluoroacetic acid, and benzyl isocyanide were converted into the Ugi adduct **3h** in 6% yield (11.2 mg) as a colorless amorphous, after purification by MPLC (hexane/ethyl acetate = 85:15 to 64:36) followed by PTLC ($CHCl_3$/ethyl acetate = 95:5).

3h: *N*-Benzyl-*N*-trifluoroacetyl-Ac_5c-NH-Bn

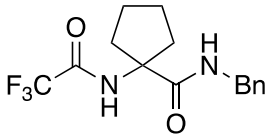
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32–7.36 (4H, m), 7.23–7.30 (6H, m), 6.27 (1H, br s), 4.84 (2H, s), 4.43 (2H, d, J = 5.4 Hz), 2.49–2.52 (2H, m), 1.90–1.95 (2H, m), 1.58–1.63 (4H, m).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.4 (C), 159.5 (C, q, $^2J_{CF}$ = 36.1 Hz), 138.2 (C), 137.4 (C), 129.0 (CH), 128.9 (CH), 127.8 (CH), 127.7 (CH), 126.1 (CH), 116.6 (C, q, $^1J_{CF}$ = 289.2 Hz), 75.2 (C), 50.5 (CH_2), 44.2 (CH_2), 35.6 (CH_2), 23.5 (CH_2).

IR (KBr): cm^{-1} 3389, 1674, 1525, 1447, 1215, 1180, 1145, 730, 695.

HRMS (ESI-TOF): *m/z* calcd for $C_{22}H_{23}F_3N_2NaO_2$ ([M + Na]$^+$): 427.1604; found: 427.1604.

Synthesis of 4h



4h

According to the general procedure A, cyclopentanone, ammonium trifluoroacetate, and benzyl isocyanide were converted into the ammonia-Ugi adduct **4h** in 53% yield (83.3 mg) as a colorless solid, after purification by MPLC (hexane/ethyl acetate = 86:14 to 0:100).

4h: *N*-Trifluoroacetyl-Ac_5c-NH-Bn

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24–7.36 (5H, m), 7.05 (1H, br s), 6.37 (1H, br s), 4.48 (2H, d, J = 6.0 Hz), 2.25–2.30 (2H, m), 2.16–2.20 (2H, m), 1.91–1.98 (2H, m), 1.76–1.83 (2H, m).

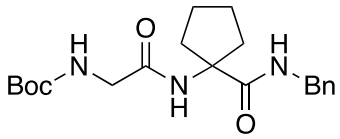
^{13}C NMR (151 MHz, $CDCl_3$): δ 172.7 (C), 157.1 (C, q, $^2J_{CF}$ = 37.6 Hz), 137.9 (C), 128.9 (CH), 127.7 (CH), 127.5 (CH), 115.7 (C, q, $^1J_{CF}$ = 289.2 Hz), 67.9 (C), 44.1 (CH_2), 36.6 (CH_2), 24.7 (CH_2).

IR (KBr): cm^{-1} 3310, 3281, 1724, 1700, 1672, 1652, 1548, 1185, 727, 702.

HRMS (ESI-TOF): *m/z* calcd for $C_{15}H_{17}F_3N_2NaO_2$ ([M + Na]$^+$): 337.1134; found: 337.1136.

10. Synthetic Details for Scheme 2

Synthesis of 5a



5a

According to the general procedure A (NOTE: The reaction time was 48 h), cyclopentanone, Boc-Gly-O$^-NH_4^+$, and benzyl isocyanide were converted into the ammonia-Ugi adduct **5a** in 97% yield (182 mg) as a colorless solid, after washing the crude mixture with cold hexane and cold water.

5a: Boc-Gly-Ac$_5$c-NH-Bn

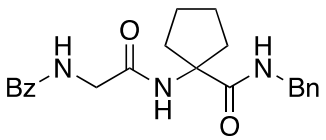
^{1}H NMR (600 MHz, DMSO-d_6): δ 8.03 (1H, br t, J = 6.0 Hz), 8.00 (1H, s), 7.28 (2H, t, J = 7.8 Hz), 7.18–7.22 (3H, m), 6.98 (1H, br t, J = 6.0 Hz), 4.26 (2H, d, J = 6.0 Hz), 3.55 (2H, d, J = 6.0 Hz), 2.02–2.07 (2H, m), 1.91–1.95 (2H, m), 1.62–1.64 (4H, m), 1.34 (9H, s).

^{13}C NMR (151 MHz, DMSO-d_6): δ 173.7 (C), 169.4 (C), 156.1 (C), 139.8 (C), 128.1 (CH), 126.7 (CH), 126.4 (CH), 78.2 (C), 66.3 (C), 43.8 (CH_2), 42.3 (CH_2), 36.5 (CH_2), 28.1 (CH_3), 24.1 (CH_2).

IR (KBr): cm^{-1} 3340, 3251, 3058, 2975, 1695, 1675, 1636, 1547, 1299, 1244, 1173, 1162.

HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{29}N_3NaO_4$ ([M + Na]$^+$): 398.2050; found: 398.2052.

Synthesis of 5b



5b

According to the general procedure C, cyclopentanone, Bz-Gly-O$^-NH_4^+$, and benzyl isocyanide were converted into the ammonia-Ugi adduct **5b** in 72% yield (137 mg) as a colorless solid, after washing the crude mixture with cold hexane and cold water.

5b: Bz-Gly-Ac$_5$c-NH-Bn

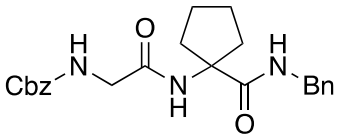
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70 (2H, d, J = 7.2 Hz), 7.52–7.55 (1H, m), 7.43 (2H, t, J = 7.8 Hz), 7.18–7.26 (6H, m), 6.93 (1H, br s), 6.53 (1H, br s), 4.45 (2H, d, J = 5.4 Hz), 4.01 (2H, d, J = 4.8 Hz), 2.32–2.37 (2H, m), 2.00–2.04 (2H, m), 1.71–1.83 (4H, m).

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.6 (C), 169.7 (C), 168.7 (C), 138.7 (C), 133.1 (C), 132.3 (CH), 128.8 (CH), 128.6 (CH), 127.5 (CH), 127.3 (CH), 127.3 (CH), 67.9 (C), 44.9 (CH_2), 43.8 (CH_2), 37.2 (CH_2), 24.3 (CH_2).

IR (KBr): cm^{-1} 3331, 3255, 3060, 1674, 1650, 1632, 1544, 1420, 1324, 727, 692.

HRMS (ESI-TOF): *m/z* calcd for $C_{22}H_{25}N_3NaO_3$ ([M + Na]$^+$): 402.1788; found: 402.1787.

Synthesis of 5c



5c

According to the general procedure A (NOTE: The reaction time was 48 h), cyclopentanone, Cbz-Gly-O$^-NH_4^+$, and benzyl isocyanide were converted into the ammonia-Ugi adduct **5c** in 96% yield (197 mg) as a colorless solid, after washing the crude mixture with cold hexane and cold water.

5c: Cbz-Gly-Ac$_5$c-NH-Bn

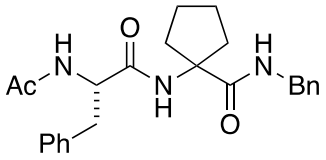
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.22–7.36 (11H, m), 6.21 (1H, s), 5.32 (1H, br s), 5.01 (2H, s), 4.44 (2H, d, *J* = 6.0 Hz), 3.75 (2H, d, *J* = 6.0 Hz), 2.30–2.34 (2H, m), 1.93–1.97 (2H, m), 1.65–1.81 (4H, m).

^{13}C NMR (151 MHz, DMSO-d_6): δ 173.6 (C), 169.2 (C), 156.6 (C), 139.9 (C), 137.0 (C), 128.3 (CH), 128.1 (CH), 127.8 (CH), 127.7 (CH), 126.7 (CH), 126.4 (CH), 66.3 (C), 65.5 (CH_2), 43.9 (CH_2), 42.3 (CH_2), 36.5 (CH_2), 24.1 (CH_2).

IR (KBr): cm^{-1} 3364, 3247, 3059, 2955, 1703, 1676, 1631, 1555, 1277, 701.

HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{27}N_3NaO_4$ ([M + Na]$^+$): 432.1894; found: 432.1894.

Synthesis of 5d



5d

According to the general procedure C (NOTE: The reaction concentration was 0.1 M), cyclopentanone, Ac-Gly-O$^-NH_4^+$, and benzyl isocyanide were converted into the ammonia-Ugi adduct **5d** in 23% yield (46.6 mg) as a colorless solid, after purification by MPLC (hexane/ethyl acetate = 66:34 to 0:100). The enantiomeric ratio of **5d** was > 99.5:0.5. A sample for $[\alpha]_D^{20}$ measurement was obtained by recrystallization from hexane/THF and drying overnight in a vacuum desiccator.

5d: Ac-Phe-Ac$_5$c-NH-Bn

$[\alpha]_D^{20}$ –2.47° (*c* 0.24, $CHCl_3$/MeOH = 9:1)

^{1}H NMR (600 MHz, DMSO-d_6): δ 8.29 (1H, d. *J* = 6.0 Hz), 8.16 (1H, s), 7.93 (1H, br t, *J* = 6.0 Hz), 7.17–7.28 (10H, m), 4.34–4.37 (1H, m), 4.27 (1H, dd, *J* = 6.0, 15.9 Hz), 4.18 (1H, dd, *J* = 6.0, 15.9 Hz), 2.87 (1H, dd, *J* = 7.2, 13.8 Hz), 2.82 (1H, dd, *J* = 7.2, 13.8 Hz), 2.04–2.09(1H, m), 1.85–1.89 (1H, m), 1.75–1.82 (2H, m), 1.66 (3H, s), 1.44–1.55 (2H, m), 1.33–1.40 (1H, m), 1.23–1.29 (1H, m).

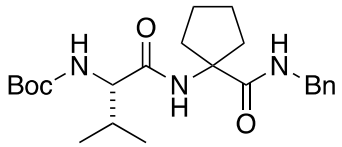
^{13}C NMR (151 MHz, DMSO-d_6): δ 173.6 (C), 171.6 (C), 170.3 (C), 139.7 (C), 137.3 (C), 129.2 (CH), 128.0 (CH), 128.0 (CH), 126.7 (CH), 126.3 (CH), 66.4 (C), 55.0 (CH), 42.3 (CH_2), 37.7 (CH_2), 36.8 (CH_2), 34.6 (CH_2), 24.0 (CH_2), 23.9 (CH_2), 22.1 (CH_3).

IR (KBr): cm^{-1} 3368, 3291, 3060, 2965, 1656, 1645, 1545, 1454, 1370, 1245, 745, 696.

HRMS (ESI-TOF): *m/z* calcd for $C_{24}H_{29}N_3NaO_3$ ([M + Na]$^+$): 430.2101; found: 430.2100.

HPLC: Daicel CHIRALPAK ID, EtOH = 100, flow = 0.8 mL/min, λ = 210 nm, t_R(*R*) = 4.8 min, t_R(*S*) = 23.5 min.

Synthesis of 5e



5e

According to the general procedure C, cyclopentanone, Boc-Val-O$^-$NH$_4^+$, and benzyl isocyanide were converted into the ammonia-Ugi adduct **5e** was obtained in 94% yield (196 mg) as a colorless solid, after purification by MPLC (hexane/ethyl acetate = 66:34 to 45:55). The enantiomeric ratio of **5e** was > 99.5:0.5. A sample for $[\alpha]_D^{20}$ measurement was obtained by recrystallization from hexane/dichloromethane and drying overnight in a vacuum desiccator.

5e: Boc-Val-Ac$_5$c-NH-Bn

$[\alpha]_D^{20}$ –12.36° (*c* 0.37, $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.50 (1H, br s), 7.25–7.30 (4H, m), 7.21 (1H, t, *J* = 7.2 Hz), 6.08 (1H, br s), 4.87 (1H, br s), 4.44 (2H, d, *J* = 5.4 Hz), 3.63 (1H, br t, *J* = 5.4 Hz), 2.32–2.38 (2H, m), 1.94–2.11 (3H, m), 1.79–1.84 (2H, m), 1.65–1.73 (2H, m), 1.36 (9H, s), 0.94 (3H, d, *J* = 6.6 Hz), 0.92 (3H, br d, *J* = 7.2 Hz).

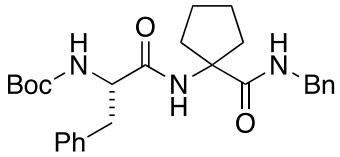
^{13}C NMR (151 MHz, $CDCl_3$): δ 173.7 (C), 172.2 (C), 156.4 (C), 138.8 (C), 128.5 (CH), 127.4 (CH), 127.0 (CH), 80.4 (C), 67.8 (C), 61.3 (CH), 43.6 (CH_2), 37.6 (CH_2), 36.5 (CH_2), 30.3 (CH) 28.3 (CH_3), 24.2 (CH_2), 19.3 (CH_3), 18.5 (CH_3).

IR (KBr): cm^{-1} 3336, 3284, 2966, 1684, 1673, 1640, 1531, 1497, 1454, 1367, 1300, 1251, 1171, 698.

HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{35}N_3NaO_4$ ([M + Na]$^+$): 440.2520; found: 440.2520.

HPLC: Daicel CHIRALPAK ID, MeCN = 100, flow = 0.5 mL/min, λ = 210 nm, t_R(*R*) = 8.5 min, t_R(*S*) = 11.1 min.

Synthesis of 5f



5f

According to the general procedure C, cyclopentanone, Boc-Phe-O$^-NH_4^+$, and benzyl isocyanide were converted into the ammonia-Ugi adduct **5f** in 97% yield (227 mg) as a colorless solid, after purification by MPLC (hexane/ethyl acetate = 56:44 to 35:65). The enantiomeric ratio of **5f** was > 99.5:0.5. A sample for $[\alpha]_D^{20}$ measurement was obtained by recrystallization from *n*-heptane/THF and drying overnight in a vacuum desiccator.

5f: Boc-Phe-Ac$_5$c-NH-Bn

$[\alpha]_D^{20}$ –3.43° (*c* 0.44, $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.20–7.31 (9H, m), 7.16 (2H, d, *J* = 6.6 Hz), 5.85 (1H, s), 4.93 (1H, br s), 4.42 (2H, d, *J* = 6.6 Hz), 4.10 (1H, q, *J* = 7.2 Hz), 3.01 (2H, d, *J* = 7.2 Hz), 2.25–2.30 (2H, m), 1.68–1.85 (4H, m), 1.41–1.50 (2H, m), 1.33 (9H, s).

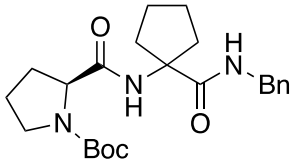
^{13}C NMR (151 MHz, $CDCl_3$): δ 173.7 (C), 171.5 (C), 156.0 (C), 138.9 (C), 136.3 (C), 129.2 (CH), 128.8 (CH), 128.5 (CH), 127.3 (CH), 127.2 (CH), 126.9 (CH), 80.6 (C), 67.6 (C), 56.9 (CH), 43.5 (CH_2), 37.9 (CH_2), 37.6 (CH_2), 36.5 (CH_2), 28.2 (CH_3), 24.3 (CH_2).

IR (KBr): cm^{-1} 3346, 3309, 2655, 1696, 1682, 1665, 1645, 1535, 1453, 1252, 1173, 696.

HRMS (ESI-TOF): *m/z* calcd for $C_{27}H_{35}N_3NaO_4$ ([M + Na]$^+$): 488.2520; found: 488.2522.

HPLC: Daicel CHIRALPAK ID, EtOH = 100, flow = 0.5 mL/min, λ = 210 nm, $t_R(R)$ = 10.3 min, $t_R(S)$ = 33.6 min.

Synthesis of 5g



5g

According to the general procedure A (NOTE: The reaction time was 48 h), cyclopentanone, Boc-Pro-O$^-NH_4^+$, and benzyl isocyanide were converted into the ammonia-Ugi adduct **5g** in 97% yield (201 mg) as a colorless solid, after washing the crude mixture with cold hexane and cold water. The enantiomeric ratio of **5g** was > 99.5:0.5. A sample for $[\alpha]_D^{20}$ measurement was obtained by recrystallization from hexane/dichloromethane and drying overnight in a vacuum desiccator.

5g: Boc-Pro-Ac$_5$c-NH-Bn

$[\alpha]_D^{20}$ –62.72° (*c* 0.38, $CHCl_3$)

^{1}H NMR (600 MHz, DMSO-d_6): δ 8.25 (0.65H, br s), 7.97–7.98 (1H, m), 7.73 (0.35H, br t, *J* = 6.0 Hz), 7.18–7.28 (5H, m), 4.34–4.41 (1H, m), 4.07–4.21 (2H, m). 3.20–3.37 (1H, m), 2.29–2.33 (0.35H, m), 1.57–2.14 (12.65H, m), 1.32 (3.15H, s), 1.29 (5.85H, s).

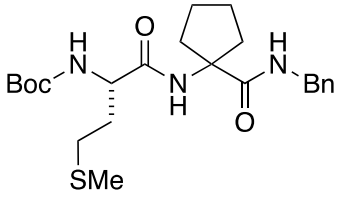
^{13}C NMR (151 MHz, $CDCl_3$): δ 173.9 (C), 172.4 (C), 155.5 (C), 139.0 (C), 128.2 (CH), 127.2 (CH), 126.7 (CH), 80.4 (C), 67.3 (C), 60.6 (CH), 47.1 (CH_2), 43.3 (CH_2), 37.9 (CH_2), 36.8 (CH_2), 29.0 (CH_2), 28.2 (CH_3), 24.6 (CH_2), 24.4 (CH_2), 24.3 (CH_2).

IR (KBr): cm^{-1} 3328, 3272, 2979, 1685, 1634, 1550, 1415, 1161, 1135, 732, 695.

HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{33}N_3NaO_4$ ([M + Na]$^+$): 438.2363; found: 438.2363.

HPLC: Daicel CHIRALPAK ID, MeCN = 100, flow = 0.5 mL/min, λ = 210 nm, $t_R(R)$ = 8.5 min, $t_R(S)$ = 9.4 min.

Synthesis of 5h



5h

According to the general procedure C, cyclopentanone, Boc-Met-O$^-$NH$_4^+$, and benzyl isocyanide were converted into the ammonia-Ugi adduct **5h** in 78% yield (176 mg) as a colorless solid, after purification by MPLC ($CHCl_3$/MeOH = 100:0 to 99:1). The enantiomeric ratio of **5h** was 99:3:0.7. A sample for $[\alpha]_D^{20}$ measurement was obtained by recrystallization from hexane/THF and drying overnight in a vacuum desiccator.

5h: Boc-Met-Ac$_5$c-NH-Bn

$[\alpha]_D^{20}$ –16.48° (*c* 0.45, $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41 (1H, br s), 7.21–7.31 (5H, m), 6.41 (1H, br s), 5.08 (1H, br s), 4.46 (1H, dd, *J* = 6.0, 15.0 Hz), 4.42 (1H, dd, *J* = 5.4, 15.0 Hz), 4.07 (1H, dt, *J* = 6.6, 7.2 Hz), 2.46–2.58 (2H, m), 2.30–2.39 (2H, m), 2.07 (3H, s), 2.02–2.08 (2H, m), 1.79–1.96 (4H, m), 1.66–1.73 (2H, m).1.36 (9H, s).

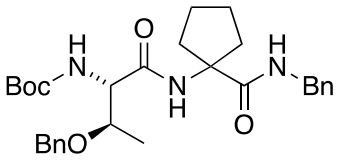
^{13}C NMR (151 MHz, $CDCl_3$): 173.7 (C), 172.0 (C), 156.1 (C), 138.7 (C), 128.4 (CH), 127.2 (CH), 126.9 (CH), 80.3 (C), 67.5 (C), 54.5 (CH), 43.4 (CH_2), 37.7 (CH_2), 36.2 (CH_2), 30.4 (CH_2), 30.2 (CH_2), 28.2 (CH_3), 24.1 (CH_2), 15.2 (CH_3).

IR (KBr): cm^{-1} 3292, 1706, 1658, 1647, 1558, 1504, 1275, 1250 ,1166, 701.

HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{35}N_3NaO_4S$ ([M + Na]$^+$): 472.2241; found: 472.2242.

HPLC: Daicel CHIRALPAK ID, MeCN = 100, flow = 0.5 mL/min, λ = 210 nm, $t_R(R)$ = 4.7 min, $t_R(S)$ = 7.6 min.

Synthesis of 5i



5i

According to the general procedure C, cyclopentanone, Boc-Thr(Bn)-O$^-NH_4^+$, and benzyl isocyanide were converted into the ammonia-Ugi adduct **5i** in 73% yield (186 mg) as a colorless amorphous, after purification by MPLC (hexane/ethyl acetate = 78:22 to 57:43) followed by PTLC ($CHCl_3$:MeOH = 97:3). The diastereomeric ratio of **5i** was > 99.5:0.5.

5i: Boc-Thr(Bn)-Ac$_5$c-NH-Bn

$[\alpha]_D^{20}$ –2.60° (*c* 0.82, $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.21–7.35 (11H, m), 6.51 (1H, s), 5.43 (1H, br d, *J* = 6.0 Hz), 4.55 (1H, d, *J* = 10.8 Hz), 4.40–4.45 (2H, m), 4.33 (1H, dd, *J* = 4.8, 15.0 Hz), 4.08–4.14 (2H, m), 2.24–2.36 (2H, m), 1.82–1.94 (2H, m), 1.72–1.79 (2H, m), 1.59–1.65 (2H, m), 1.42 (9H, s), 1.14 (3H, d, *J* = 7.2 Hz).

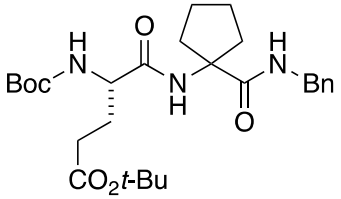
^{13}C NMR (101 MHz, $CDCl_3$): δ 173.4 (C), 170.2 (C), 155.9 (C), 138.7 (C), 137.6 (C), 128.6 (CH), 128.6 (CH), 128.1 (CH), 127.8 (CH), 127.6 (CH), 127.2 (CH), 80.6 (C), 74.6 (CH), 71.6 (CH_2), 67.8 (C), 58.6 (CH), 43.6 (CH_2), 37.3 (CH_2), 36.9 (CH_2), 28.3 (CH_3), 24.2 (CH_2), 24.1 (CH_2), 15.5 (CH_3).

IR (KBr): cm^{-1} 3330, 2976, 1674, 1529, 1496, 1454, 1366, 1248, 1167, 735, 697.

HRMS (ESI-TOF): *m/z* calcd for $C_{29}H_{39}N_3NaO_5$ ([M + Na]$^+$): 532.2782; found: 532.2782.

HPLC: Daicel CHIRALPAK ID, EtOH = 100, flow = 0.5 mL/min, λ = 210 nm, $t_R(R)$ = 9.2 min, $t_R(S)$ = 10.6 min.

Synthesis of 5j



5j

According to the general procedure C, cyclopentanone, Boc-Glu(O*t*-Bu)-O$^-NH_4^+$, and benzyl isocyanide were converted into the ammonia-Ugi adduct **5j** in 79% yield (199 mg) as a colorless solid, after purification by MPLC (hexane/ethyl acetate = 69:31 to 48:52). The enantiomeric ratio of **5j** was > 99.5:0.5. A sample for

$[\alpha]_D^{20}$ measurement was obtained by recrystallization from hexane/1,2-dichloroethane and drying overnight in a vacuum desiccator.

5j: Boc-Glu(O*t*-Bu)-Ac$_5$c-NH-Bn

$[\alpha]_D^{20}$ –12.06° (*c* 0.74, $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46 (1H, br s), 7.20–7.30 (5H, m), 6.47 (1H, s), 5.38 (1H, br s), 4.44 (2H, d, *J* = 6.0 Hz), 3.90–3.94 (1H, m), 2.24–2.42 (4H, m), 1.97–2.00 (3H, m), 1.79–1.91 (3H, m), 1.67–1.73 (2H, m), 1.45 (9H, s), 1.35 (9H, s).

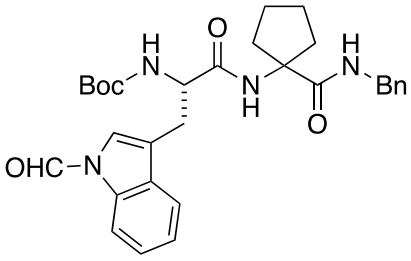
^{13}C NMR (101 MHz, $CDCl_3$): δ 173.7 (C), 172.7 (C), 172.0 (C), 156.2 (C), 138.8 (C), 128.4 (CH), 127.3 (CH), 126.9 (CH), 81.0 (C), 80.2 (C), 67.4 (C), 55.1 (CH), 43.4 (CH_2), 37.3 (CH_2), 36.8 (CH_2), 31.8 (CH_2), 28.2 (CH_3), 28.0 (CH_3), 26.6 (CH_2), 24.1 (CH_2).

IR (KBr): cm^{-1} 3276, 2979, 1729, 1704, 1660, 1548, 1514, 1367, 1253, 1163.

HRMS (ESI-TOF): *m/z* calcd for $C_{27}H_{41}N_3NaO_6$ ([M + Na]$^+$): 526.2888; found: 526.2888.

HPLC: Daicel CHIRALPAK ID, MeCN = 100, flow = 0.5 mL/min, λ = 210 nm, t_R(*R*) = 8.5 min, t_R(*S*) = 10.8 min.

Synthesis of 5k



5k

According to the general procedure C, cyclopentanone, Boc-Trp(CHO)-O$^-NH_4^+$, and benzyl isocyanide were converted into the ammonia-Ugi adduct **5k** in 87% yield (230 mg) as a colorless amorphous, after purification by MPLC ($CHCl_3$/ethyl acetate = 100:0 to 85:15). The enantiomeric ratio of **5k** was > 99.5:0.5.

5k: Boc-Trp(CHO)-Ac$_5$c-NH-Bn

$[\alpha]_D^{20}$ –13.64° (*c* 0.36, $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.36 (0.35H, br s, rotamer), 8.91 (0.65H, br s, rotamer), 8.40 (br d, *J* = 6.0 Hz, rotamer), 7.59–7.67 (1.35H, m), 7.11–7.41 (9H, m), 6.08–6.16 (1H, m), 5.02 (1H, br s), 4.38–4.45 (2H, m), 4.25–4.32 (1H, m), 3.08–3.23 (2H, m), 2.20–2.30 (2H, m), 1.66–1.87 (4H, m), 1.32–1.46 (2H, m), 1.35 (9H, s).

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.8 (C), 171.8 (C), 159.6 and 155.8 (CH, rotamers), 156.1 (C), 138.7 (C), 135.3 and 134.3 (C, rotamers), 131.0 and 130.6 (C, rotamers), 128.4 (CH), 127.1 (CH), 127.0 (CH), 125.5, 125.1, 124.7, 124.2. 124.1 (CH, rotamers), 120.1 and 119.0 (CH, rotamers), 119.8 and 118.4 (C, rotamers),

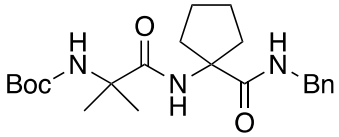
116.2 and 109.8 (CH, rotamers), 80.6 (C), 67.4 (C), 55.1 (CH), 43.4 (CH_2), 37.8 (CH_2), 36.3 (CH_2), 36.2 (CH_2), 28.2 (CH_3), 26.9 (CH_2), 24.1 (CH_2).

IR (KBr): cm^{-1} 3318, 2973, 1696, 1528, 1458, 1366, 1164, 793, 749.

HRMS (ESI-TOF): *m/z* calcd for $C_{30}H_{36}N_4NaO_5$ ($[M + Na]^+$): 555.2578; found: 555.2576.

HPLC: Daicel CHIRALPAK ID, MeCN = 100, flow = 0.5 mL/min, λ = 210 nm, $t_R(S)$ = 9.9 min, $t_R(R)$ = 11.2 min.

Synthesis of 5l



5l

According to the general procedure C, cyclopentanone, Boc-Aib-$O^-NH_4^+$, and benzyl isocyanide were converted into the ammonia-Ugi adduct **5l** in 87% yield (175 mg) as a colorless solid, after purification by MPLC (hexane/ethyl acetate = 77:23 to 15:85) followed by recrystallization from hexane/THF.

5l: Boc-Aib-Ac_5c-NH-Bn

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.83 (1H, br s), 7.25–7.30 (4H, m), 7.19 (1H, t, *J* = 7.2 Hz), 6.33 (1H, br s), 4.80 (1H, br s), 4.45 (2H, d, *J* = 5.4 Hz), 2.34–2.39 (2H, m), 1.80–1.91 (4H, m), 1.63–1.70 (2H, m), 1.41 (6H, s), 1.30 (9H, s).

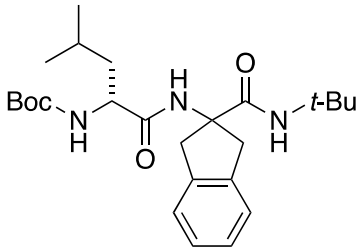
^{13}C NMR (151 MHz, $CDCl_3$): δ 174.0 (C), 173.7 (C), 155.4 (C), 139.2 (C), 128.4 (CH), 127.8 (CH), 126.9 (CH), 81.1 (C), 67.2 (C), 57.2 (C), 43.7 (CH_2), 37.7 (CH_2), 28.2 (CH_3), 25.4 (CH_3), 24.6 (CH_2).

IR (KBr): cm^{-1} 3318, 1690, 1650, 1537, 1517, 1169, 696.

HRMS (ESI-TOF): *m/z* calcd for $C_{22}H_{33}N_3NaO_4$ ($[M + Na]^+$): 426.2363; found: 426.2363.

11. Synthetic Details for Scheme 3

Synthesis of Boc-D-Leu-Aic-NH-*t*-Bu



Boc-D-Leu-Aic-NH-*t*-Bu

According to the general procedure D, 2-indanone, Boc-D-Leu-O$^-NH_4^+$, and *tert*-butyl isocyanide were converted into the ammonia-Ugi adduct **Boc-D-Leu-Aic-NH-*t*-Bu** in 65% yield (145 mg) as a colorless solid, after purification by MPLC (hexane/ethyl acetate = 96:4 to 40:60) followed by recrystallization from hexane/THF. The enantiomeric ratio of **Boc-D-Leu-Aic-NH-*t*-Bu** was > 99.5:0.5. A sample for $[\alpha]_D^{20}$ measurement was obtained by recrystallization from *n*-heptane/dichloromethane and drying overnight in a vacuum desiccator.

Boc-D-Leu-Aic-NH-*t*-Bu

$[\alpha]_D^{20}$ 20.10° (*c* 0.24, $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.16–7.20 (4H, m), 6.67 (1H, br s), 6.46 (1H, br s), 4.80 (1H, d, *J* = 6.6 Hz), 3.90–3.94 (1H, m), 3.62 (1H, d, *J* = 15.6 Hz), 3.53 (1H, d, *J* = 16.2 Hz), 3.36 (1H, d, *J* = 15.6 Hz), 3.33 (1H, d, *J* = 16.2 Hz), 1.52–1.61 (2H, m), 1.42 (9H, s), 1.37–1.42 (1H, m), 1.31 (9H, s), 0.87 (3H, d, *J* = 6.0 Hz), 0.84 (3H, d, *J* = 5.4 Hz).

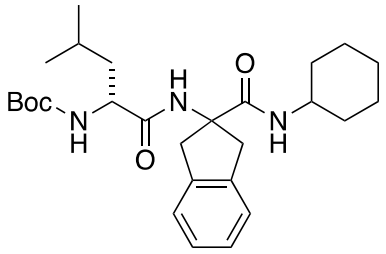
^{13}C NMR (151 MHz, $CDCl_3$): δ 172.6 (C), 171.9 (C), 155.8 (C), 140.5 (C), 140.2 (C), 127.1 (CH), 127.0 (CH), 124.8 (CH), 124.7 (CH), 80.4 (C), 67.7 (C), 54.0 (CH), 51.2 (C), 43.1 (CH_2), 42.8 (CH_2), 40.8 (CH_2), 28.6 (CH_3), 28.4 (CH_3), 24.8 (CH), 22.7 (CH_3), 22.1 (CH_3).

IR (KBr): cm^{-1} 3376, 3314, 2964, 1689, 1673, 1520, 1364, 1281, 1171, 752.

HRMS (ESI-TOF): *m/z* calcd for $C_{25}H_{39}N_3NaO_4$ ([M + Na]$^+$): 468.2833; found: 468.2834.

HPLC: Daicel CHIRALPAK ID, MeCN = 100, flow = 0.5 mL/min, λ = 210 nm, t_R(*S*) = 8.1 min, t_R(*R*) = 10.9 min.

Synthesis of Boc-D-Leu-Aic-NH-cyclo-C_6H_{11}



Boc-D-Leu-Aic-NH-cyclo-C_6H_{11}

According to the general procedure D, 2-indanone, Boc-D-Leu-$O^-NH_4^+$, and cyclohexyl isocyanide were converted into the ammonia-Ugi adduct **Boc-D-Leu-Aic-NH-cyclo-C_6H_{11}** in 57% yield (137 mg) as a colorless solid, after purification by MPLC (hexane/ethyl acetate = 86:14 to 30:70) followed by recrystallization from hexane/THF. The enantiomeric ratio of **Boc-D-Leu-Aic-NH-cyclo-C_6H_{11}** was > 99.5:0.5. A sample for $[\alpha]_D^{20}$ measurement was obtained by recrystallization from *n*-heptane/dichloromethane and drying overnight in a vacuum desiccator.

Boc-D-Leu-Aic-NH-cyclo-C_6H_{11}

$[\alpha]_D^{20}$ 19.82° (*c* 0.25, $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.15–7.18 (4H, m), 6.71–6.74 (2H, m), 4.96 (1H, br d, *J* = 5.4 Hz), 3.88–3.91 (1H, m), 3.72–3.76 (1H, m), 3.66 (1H, d, *J* = 16.2 Hz), 3.58 (1H, d, *J* = 16.2 Hz), 3.32 (2H, d, *J* = 16.2 Hz), 1.82–1.88 (2H, m), 1.61–1.67 (2H, m), 1.42 (9H, s), 1.29–1.57 (6H, m), 1.11–1.20 (3H, m), 0.84 (3H, d, *J* = 6.0 Hz), 0.80 (3H, d, *J* = 6.6 Hz).

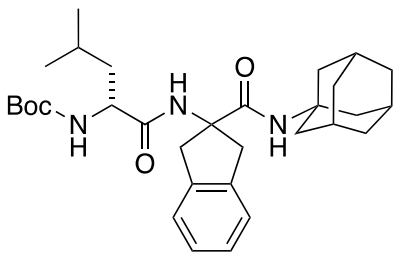
^{13}C NMR (151 MHz, $CDCl_3$): δ 172.6 (C), 171.7 (C), 156.0 (C), 140.5 (C), 140.3 (C), 127.0 (CH), 127.0 (CH), 124.8 (CH), 124.7 (CH), 80.5 (C), 67.5 (C), 54.2 (CH), 48.6 (CH), 43.3 (CH_2), 43.2 (CH_2), 40.6 (CH_2), 32.7 (CH_2), 32.6 (CH_2), 28.4 (CH_3), 25.6 (CH_2), 24.8 (CH_2), 24.8 (CH), 22.6 (CH_3), 22.1 (CH_3).

IR (KBr): cm^{-1} 3262, 2933, 2855, 1697, 1650, 1535, 1260, 1166, 741.

HRMS (ESI-TOF): *m/z* calcd for $C_{27}H_{41}N_3NaO_4$ ($[M + Na]^+$): 494.2989; found: 494.2989.

HPLC: Daicel CHIRALPAK ID, MeCN = 100, flow = 0.5 mL/min, λ = 210 nm, $t_R(S)$ = 12.1 min, $t_R(R)$ = 15.5 min.

Synthesis of Boc-D-Leu-Aic-NH-1-adamantyl



Boc-D-Leu-Aic-NH-1-adamantyl

According to the general procedure D, 2-indanone, Boc-D-Leu-O$^-NH_4^+$, and 1-adamantyl isocyanide were converted into the ammonia-Ugi adduct **Boc-D-Leu-Aic-NH-1-adamantyl** in 62% yield (162 mg) as a colorless solid, after purification by MPLC (hexane/ethyl acetate = 93:7 to 45:55) followed by recrystallization from hexane/THF. The enantiomeric ratio of **Boc-D-Leu-Aic-NH-1-adamantyl** was > 99.5:0.5. A sample for $[\alpha]_D^{20}$ measurement was obtained by recrystallization from *n*-heptane/dichloromethane and drying overnight in a vacuum desiccator.

Boc-D-Leu-Aic-NH-1-adamantyl

$[\alpha]_D^{20}$ 18.39° (*c* 0.26, $CHCl_3$)

^{1}H NMR (600 MHz, DMSO-d_6): δ 8.28 (1H, s), 7.10–7.17 (4H, m), 6.93 (1H, d, *J* = 7.2 Hz), 6.61 (1H, s), 3.79–3.83 (1H, m), 3.50 (1H, d, *J* = 16.2 Hz), 3.18 (1H, d, *J* = 16.2 Hz), 3.14 (1H, d, *J* = 16.2 Hz), 1.98–2.00 (3H, m), 1.88–1.93 (6H, m), 1.57–1.63 (6H, m), 1.89–1.46 (2H, m), 1.36 (9H, s), 0.74 (3H, d, *J* = 6.2 Hz), 0.70 (3H, d, *J* = 6.8 Hz).

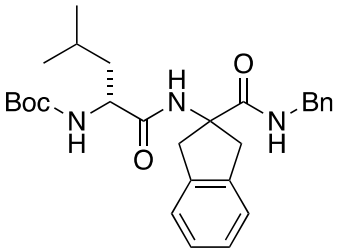
^{13}C NMR (151 MHz, $CDCl_3$): δ 172.6 (C), 171.7 (C), 155.8 (C), 140.5 (C), 140.4 (C), 127.0 (CH), 124.8 (CH), 124.7 (CH), 80.3 (C), 67.6 (C), 53.9 (CH), 51.8 (C), 42.9 (CH_2), 41.3 (CH_2), 40.9 (CH_2), 36.4 (CH_2), 29.5 (CH), 28.4 (CH_3), 24.8 (CH), 22.7 (CH_3), 22.2 (CH_3).

IR (KBr): cm^{-1} 3285, 2909, 2851, 1712, 1686, 1648, 1519, 1490, 1364, 1241, 1170, 754.

HRMS (ESI-TOF): *m/z* calcd for $C_{31}H_{45}N_3NaO_4$ ([M + Na]$^+$): 546.3302; found: 546.3302.

HPLC: Daicel CHIRALPAK ID, hexane/2-propanol = 1:1, flow = 0.5 mL/min, λ = 210 nm, $t_R(S)$ = 10.3 min, $t_R(R)$ = 13.5 min.

Synthesis of Boc-D-Leu-Aic-NH-Bn



Boc-D-Leu-Aic-NH-Bn

According to the general procedure D, 2-indanone, Boc-D-Leu-O$^-NH_4^+$, and benzyl isocyanide were converted into the ammonia-Ugi adduct **Boc-D-Leu-Aic-NH-Bn** in 68% yield (164 mg) as a colorless solid, after purification by MPLC (hexane/ethyl acetate = 76:24 to 55:45) followed by recrystallization from hexane/THF. The enantiomeric ratio of **Boc-D-Leu-Aic-NH-Bn** was > 99.5:0.5. A sample for $[\alpha]_D^{20}$ measurement was obtained by recrystallization from H_2O/acetone and drying overnight in a vacuum desiccator.

Boc-D-Leu-Aic-NH-Bn

$[\alpha]_D^{20}$ 33.85° (*c* 0.41, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16–7.32 (10H, m), 6.54 (1H, br s), 4.76 (1H, br s), 4.47 (2H, d, *J* = 5.2 Hz), 3.81–3.87 (1H, m), 3.72 (1H, d, *J* = 16.4 Hz), 3.71 (1H, d, *J* = 16.4 Hz), 3.38 (1H, d, *J* = 16.4 Hz), 3.30 (1H, d, *J* = 16.4 Hz), 1.45–1.57 (2H, m), 1.33–1.39 (1H, m), 1.31 (9H, s), 0.83 (3H, d, *J* = 6.4 Hz), 0.79 (3H, d, *J* = 6.0 Hz).

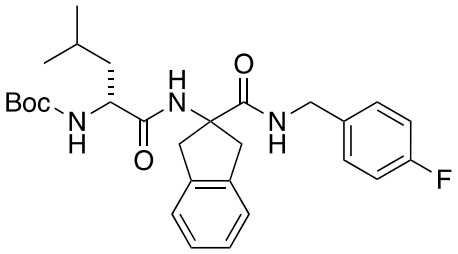
^{13}C NMR (151 MHz, $CDCl_3$): δ 172.9 (C), 172.7 (C), 156.2 (C), 140.4 (C), 140.0 (C), 138.6 (C), 128.6 (CH), 127.4 (CH), 127.2 (CH), 127.1 (CH), 127.1 (CH), 124.8 (CH), 80.7 (C), 67.8 (C), 54.2 (CH), 43.9 (CH_2), 43.7 (CH_2), 43.1 (CH_2), 40.4 (CH_2), 28.2 (CH_3), 24.8 (CH), 22.6 (CH_3), 22.1 (CH_3).

IR (KBr): cm^{-1} 3346, 3286, 2959, 1717, 1701, 1677, 1649, 1536, 1501, 1366, 1249, 1168, 747.

HRMS (ESI-TOF): *m/z* calcd for $C_{28}H_{37}N_3NaO_4$ ([M + Na]$^+$): 502.2676; found: 502.2676.

HPLC: Daicel CHIRALPAK ID, MeCN = 100, flow = 0.5 mL/min, λ = 210 nm, t_R(*S*) = 9.7 min, t_R(*R*) = 11.0 min.

Synthesis of Boc-D-Leu-Aic-NH-CH_2Ph(*p*-F)



Boc-D-Leu-Aic-NH-CH_2Ph(*p*-F)

According to the general procedure D (NOTE: The reaction scale was 0.4 mmol), 2-indanone, Boc-D-Leu-O$^-$ NH_4^+, and *p*-fluorobenzyl isocyanide were converted into the ammonia-Ugi adduct **Boc-D-Leu-Aic-NH-CH_2Ph(*p*-F)** in 60% yield (121 mg) as a pale-yellow solid, after purification by MPLC (hexane/ethyl acetate = 77:23 to 65:44) followed by recrystallization from hexane/THF. The enantiomeric ratio of **Boc-D-Leu-Aic-NH-CH_2Ph(*p*-F)** was > 99.5:0.5. A sample for $[\alpha]_D^{20}$ measurement was obtained by recrystallization from *n*-heptane/dichloromethane and drying overnight in a vacuum desiccator. *p*-Fluorobenzyl isocyanide was prepared using *p*-fulorobenzylamine, sodium chlorodifluoroacetate, and potassium carbonate according to the reported procedure[1].

Boc-D-Leu-Aic-NH-CH_2Ph(*p*-F)

$[\alpha]_D^{20}$ 33.47° (*c* 0.16, $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$): 7.43 (1H, br s), 7.17–7.24 (6H, m), 6.97–7.00 (2H, m), 6.47 (1H, br s), 4.77 (1H, br s), 4.46 (1H, dd, *J* = 5.7, 15.0 Hz), 4.41 (1H, dd, *J* = 5.7, 15.0 Hz), 3.79–3.82 (1H, m), 3.74 (1H, d, *J* = 15.6

Hz), 3.72 (1H, d, J = 15.6 Hz), 3.34 (1H, d, J = 16.8 Hz), 3.26 (1H, d, J = 16.8 Hz), 1.33–1.58 (3H, m), 1.31 (9H, s), 0.83 (3H, d, J = 7.2 Hz), 0.78 (3H, d, J = 6.0 Hz).

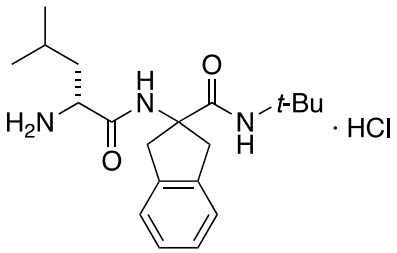
^{13}C NMR (151 MHz, $CDCl_3$): δ 172.9 (C), 172.7 (C), 162.1 (C, d, $^1J_{CF}$ = 245.8 Hz), 156.3 (C), 140.3 (C), 140.0 (C), 134.4 (C), 129.1 (CH, d, $^3J_{CF}$ = 7.2 Hz), 127.2 (CH), 127.1 (CH), 124.8 (CH), 115.4 (CH, d, $^2J_{CF}$ = 21.7 Hz), 80.9 (C), 67.9 (C), 54.4. (CH), 44.1 (CH_2), 43.2 (CH_2), 43.1 (CH_2), 40.3 (CH_2), 28.2 (CH_3), 24.8 (CH), 22.6 (CH_3), 22.1 (CH_3).

IR (KBr): cm^{-1} 3331, 3282, 2956, 2932, 1690, 1648, 1537, 1510, 1367, 1226, 1166, 745.

HRMS (ESI-TOF): *m/z* calcd for $C_{28}H_{36}FN_3NaO_4$ ($[M + Na]^+$): 520.2582; found: 520.2581.

HPLC: Daicel CHIRALPAK ID, MeCN = 100, flow = 0.5 mL/min, λ = 210 nm, t_R(*S*) = 8.9 min, t_R(*R*) = 10.5 min.

Synthesis of 7a



7a

According to the general procedure G, Boc-D-Leu-Aic-NH-*t*-Bu (0.137 mmol, 61.1 mg) was converted into **7a** in 65% yield (34.1 mg) as a colorless solid.

7a: D-Leu-Aic-NH-*t*-Bu·HCl

$[\alpha]_D^{20}$ –42.55° (*c* 0.13, MeOH)

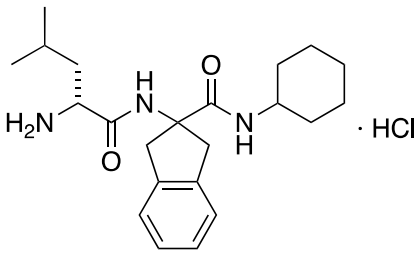
^{1}H NMR (600 MHz, DMSO-d_6): δ 8.91 (1H, s), 8.25 (3H, br s), 7.18–7.21 (2H, m), 7.14-7.16 (2H, m), 6.96 (1H, br s), 3.73 (1H, t, *J* = 7.2 Hz), 3.58 (1H, d, *J* = 16.5 Hz), 3.40 (1H d, *J* = 16.5 Hz), 3.23 (1H, d, *J* = 16.5 Hz), 3.20 (1H, d, *J* = 16.5 Hz), 1.60–1.64 (1H, m), 1.43–1.54 (2H, m), 1.25 (9H, s), 0.82 (3H, d, *J* = 6.0 Hz), 0.78 (3H, d, *J* = 6.6 Hz).

^{13}C NMR (151 MHz, DMSO-d_6): δ 171.1 (C), 169.1 (C), 140.6 (C), 140.2 (C), 126.5 (CH), 126.5 (CH), 124.4 (CH), 124.3 (CH), 67.3 (C), 50.8 (CH), 50.3 (C), 42.5 (CH_2), 42.4 (CH_2), 39.9 (CH_2), 28.4 (CH_3), 23.6 (CH), 22.4 (CH_3), 21.9 (CH_3).

IR (KBr): cm^{-1} 3417, 3272, 2959, 2932, 1681, 1665, 1522, 740.

HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{32}N_3O_2$ ([M + H]$^+$): 346.2489; found: 346.2490.

Synthesis of 7b



7b

According to the general procedure G, Boc-D-Leu-Aic-NH-cyclo-C_6H_{11} (0.141 mmol, 66.6 mg) was converted into **7b** in 57% yield (32.6 mg) as a colorless solid.

7b: D-Leu-Aic-NH-cyclo-C_6H_{11}·HCl

$[\alpha]_D^{20}$ –28.18° (*c* 0.15, MeOH)

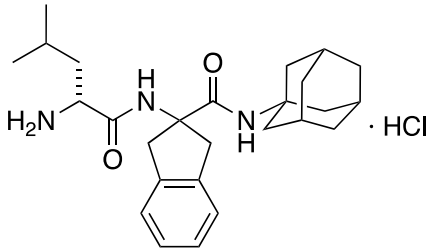
^{1}H NMR (600 MHz, DMSO-d_6): δ 8.92 (1H, s), 8.25 (3H, br s), 7.51 (1H, d, J = 9.0 Hz), 7.14–7.21 (4H, m), 3.69 (1H, t, J = 6.9 Hz), 3.51–3.57 (1H, m), 3.54 (1H, d, J = 16.2 Hz), 3.43 (1H, d, J = 16.2 Hz), 3.21 (1H, d, J = 16.2 Hz), 3.19 (1H, d, J = 16.2 Hz), 1.54–1.69 (6H, m), 1.19–1.45 (6H, m), 1.03–1.11 (1H, m), 0.78 (3H, d, J = 6.0 Hz), 0.71 (3H, d, J = 6.0 Hz).

^{13}C NMR (151 MHz, DMSO-d_6): δ 170.8 and 170.7 (C), 169.0 (C), 140.7 and 140.6 (C), 140.1 (C), 126.5 (CH), 126.4 (CH), 124.4 (CH), 124.3 (CH), 66.8 (C), 51.0 (CH), 48.2 (CH), 43.4 and 43.3 (CH_2), 42.2 (CH_2), 39.5 (CH_2), 32.1 (CH_2), 25.2 (CH_2) 24.9 (CH_2), 24.8 (CH_2), 23.7 (CH), 22.2 (CH_3).

IR (KBr): cm^{-1} 3276, 3024, 2930, 2853, 1687, 1643, 1529, 737.

HRMS (ESI-TOF): *m/z* calcd for $C_{22}H_{34}N_3O_2$ ([M + H]$^+$): 372.2646; found: 372.2646.

Synthesis of 7c



7c

According to the general procedure G, Boc-D-Leu-Aic-NH-1-adamantyl (0.119 mmol, 62.1 mg) was converted into **7c** in 51% yield (27.8 mg) as a colorless solid. The product was purified by recrystallization from hexane/ethyl acetate.

7c: D-Leu-Aic-NH-1-adamantyl·HCl

$[\alpha]_D^{20}$ –39.01° (c 0.54, MeOH)

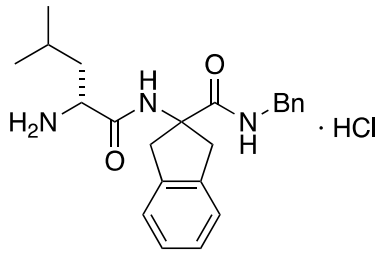
^{1}H NMR (600 MHz, DMSO-d_6): δ 8.90 (1H, s), 8.19 (3H, br s), 7.13–7.20 (4H, m), 6.77 (1H, s), 3.73 (1H, t, J = 7.2 Hz), 3.56 (1H, d, J = 16.8 Hz), 3.43 (1H, d, J = 16.8 Hz), 3.24 (1H, d, J = 16.8 Hz), 3.22 (1H, d, J = 16.8 Hz), 1.99–2.01 (3H, m), 1.90–1.95 (6H, m), 1.44–1.64 (9H, m), 0.83 (3H, d, J = 6.6 Hz), 0.79 (3H, d, J = 6.0 Hz).

^{13}C NMR (151 MHz, DMSO-d_6): δ 170.8 (C), 169.1 (C), 140.6 (C), 140.2 (C), 126.6 (CH), 126.5 (CH), 124.5 (CH), 124.3 (CH), 67.4 (C), 51.0 (C), 50.8 (CH), 42.6 (CH_2), 42.4 (CH_2), 41.8 (CH_2), 39.9 (CH_2), 36.1 (CH_2), 28.8 (CH), 23.6 (CH), 22.4 (CH_3), 22.0 (CH_3).

IR (KBr): cm^{-1} 3420, 3209, 3028, 2910, 2850, 1681, 1523, 744.

HRMS (ESI-TOF): *m/z* calcd for $C_{26}H_{38}N_3O_2$ ([M + H]$^+$): 424.2959; found: 424.2958.

Synthesis of 7d



7d

According to the general procedure G, Boc-D-Leu-Aic-NH-Bn (41.1 mg, 0.086 mmol) was converted into **7d** in 74% yield (26.5 mg) as a colorless solid.

7d: D-Leu-Aic-NH-Bn·HCl

$[\alpha]_D^{20}$ –10.75° (*c* 0.29, MeOH)

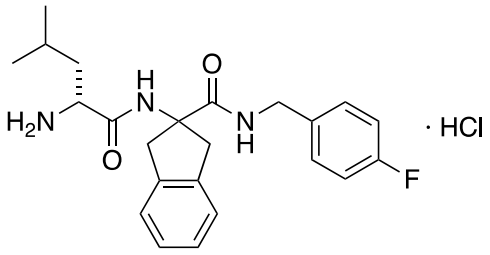
^{1}H NMR (400 MHz, MeOD): δ 7.17–7.30 (9H, m), 4.55 (1H, d, *J* = 14.8 Hz), 4.33 (1H, d, *J* = 14.8 Hz), 3.77–3.81 (1H, m), 3.59–3.67 (2H, m), 3.37 (1H, d, *J* = 16.5 Hz), 3.31 (1H, d, *J* = 16.5 Hz), 1.42–1.63 (3H, m), 0.85 (3H, d, *J* = 6.0 Hz), 0.78–0.81 (3H, m).

^{13}C NMR (101 MHz, MeOD): δ 174.7 (C), 171.0 (C), 141.4 (C), 141.0 (C), 140.1 (C), 129.4 (CH), 128.4 (CH), 128.1 (CH), 128.1 (CH), 128.0 (CH), 125.8 (CH), 125.6 (CH), 69.2 (C), 52.9 (CH), 44.5 (CH_2), 44.4 (CH_2), 43.2 (CH_2), 41.5 (CH_2), 25.3 (CH), 22.8 (CH_3), 22.1 (CH_3).

IR (KBr): cm^{-1} 3393, 3234, 3044, 2959, 1671, 1531, 1474, 1266, 742, 721.

HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{30}N_3O_2$ ($[M + H]^+$): 380.2333; found: 380.2335.

Synthesis of 7e



7e

According to the general procedure G, Boc-D-Leu-Aic-NH-CH_2Ph(*p*-F) (51.0 mg, 0.103 mmol) was converted into **7e** in 48% yield (21.2 mg) as a colorless solid.

7e: D-Leu-Aic-NH-CH_2Ph(*p*-F)·HCl

$[\alpha]_D^{20}$ –13.62° (*c* 0.13, MeOH)

^{1}H NMR (600 MHz, DMSO-d_6): δ 9.07 (1H, s), 8.56 (1H, br t, J = 6.0 Hz), 8.35 (3H, br s), 7.29–7.31 (2H, m), 7.14–7.22 (4H, m), 7.10–7.12 (2H, m), 4.36 (1H, dd, J = 6.0, 15.3 Hz), 4.19 (1H, dd, J = 6.0, 15.3 Hz), 3.70 (1H, br t, J = 7.2 Hz), 3.59 (1H, d, J = 16.8 Hz), 3.42 (1H, d, J = 16.8 Hz), 3.24 (2H, d, J = 16.8 Hz), 1.49–1.54 (1H, m), 1.31–1.40 (2H, m), 0.74 (3H, d, J = 6.6 Hz), 0.65 (3H, d, J = 6.0 Hz).

^{13}C NMR (101 MHz, DMSO-d_6): δ 172.0 (C), 169.2 (C), 161.1 (C, d, $^{1}J_{CF}$ = 241.7 Hz), 140.9 (C), 139.9 (C), 136.0 (C, d, $^{4}J_{CF}$ = 2.9 Hz), 129.0 (CH, d, $^{3}J_{CF}$ = 7.7 Hz), 126.7 (CH), 126.6 (CH), 124.5 (CH), 124.4 (CH), 114.9 (CH, d, $^{2}J_{CF}$ = 21.2 Hz), 67.0 (C), 51.0 (CH), 43.9 (CH_2), 41.9 (CH_2), 41.8 (CH_2), 39.4 (CH_2), 23.7 (CH), 22.3 (CH_3), 22.1 (CH_3).

IR (KBr): cm^{-1} 3342, 3289, 2960, 1676, 1656, 1526, 1510, 1226, 837.

HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{29}FN_3O_2$ ($[M + H]^+$): 398.2238; found: 398.2239.

12. α-Chymotrypsin Inhibitory Assay

Bovine pancreatic α-chymotrypsin was purchased from Sigma-Aldrich (C4129) and used as received. Enzyme solutions were kept on ice during the experiments. The molecular mass of α-chymotrypsin was taken as 25 kDa. Acetyl-tyrosine ethyl ester (ATEE) was purchased from Peptide Institute and prepared as a 10 mM stock solution in Tris-HCl buffer (80 mM, pH 7.8), and it stored at 4 °C. D-Leu-Phe-NH-Bn and D-Leu-Phe-NH-CH_2Ph(*p*-F) were synthesized according to the previous report[5] and used as positive controls. DMSO for biochemical research was purchased from Nacalai and used as received. Other reagents were purchased from Nacalai and used as received. Absorbance was measured with a JASCO V-660 spectrometer at 25 °C. According to the reported procedure,[5] the assay was performed in Tris-HCl buffer (80 mM, pH 7.8) containing ATEE (1 mM, final concentration) and $CaCl_2$ (50 mM, final concentration) and inhibitor. The enzymatic reaction was initiated by adding α-chymotrypsin (0.015 units/mL, final concentration) to give a final volume of 800 μL. Reaction progress was monitored by absorbance at 237 nm at 25 °C for 5 min. The final concentration of DMSO was 0.25% (v/v). K_i values were calculated by GraphPad Prism 8 software using non-liner fitting to the Michaelis-Menten equation.

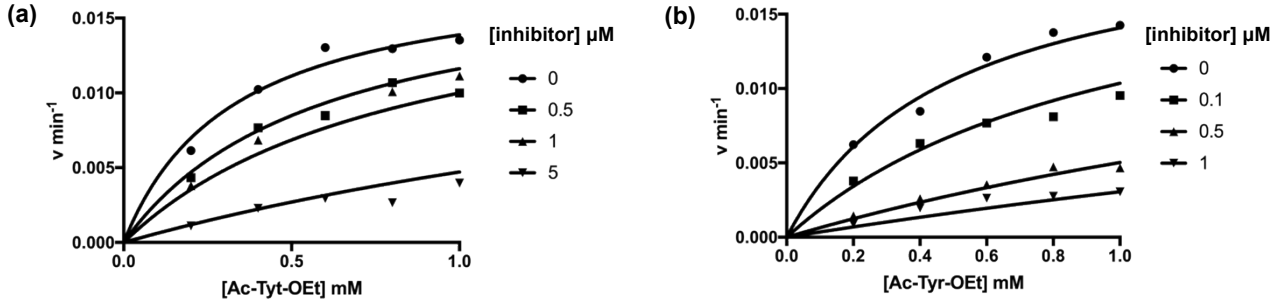


Figure S2. Michaelis-Menten fitting of D-Leu-Phe-NH-Bn (a) and **7e** (b).

13. References

[1] Y.-X. Si, P.-F. Zhu, S.-L. Zhang, *Org. Lett.* **2020**, *22*, 9086–9090.

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[3] C. Battilocchio, I. R. Baxendale, M. Biava, M. O. Kitching, S. V. Ley. *Org. Process Res. Dev.* **2012**, *16*, 798–810.

[4] A. Gesù, C. Pozzoli, E. Torre, S. Aprile, T. Pirali. *Org. Lett.* **2016**, *18*, 1992–1995.

[5] Y. Shimohigashi, I. Maeda, T. Nose, K. Ikesue, H. Sakamoto, T. Ogawa, Y. Ide, M. Kawahara, T. Nezu, Y. Terada, K. Kawano, M. Ohno. *J. Chem. Soc., Perkin Trans. 1*, **1996**, 2479–2485.

14. Supplementary Figures S3-127 (NMR spectra)

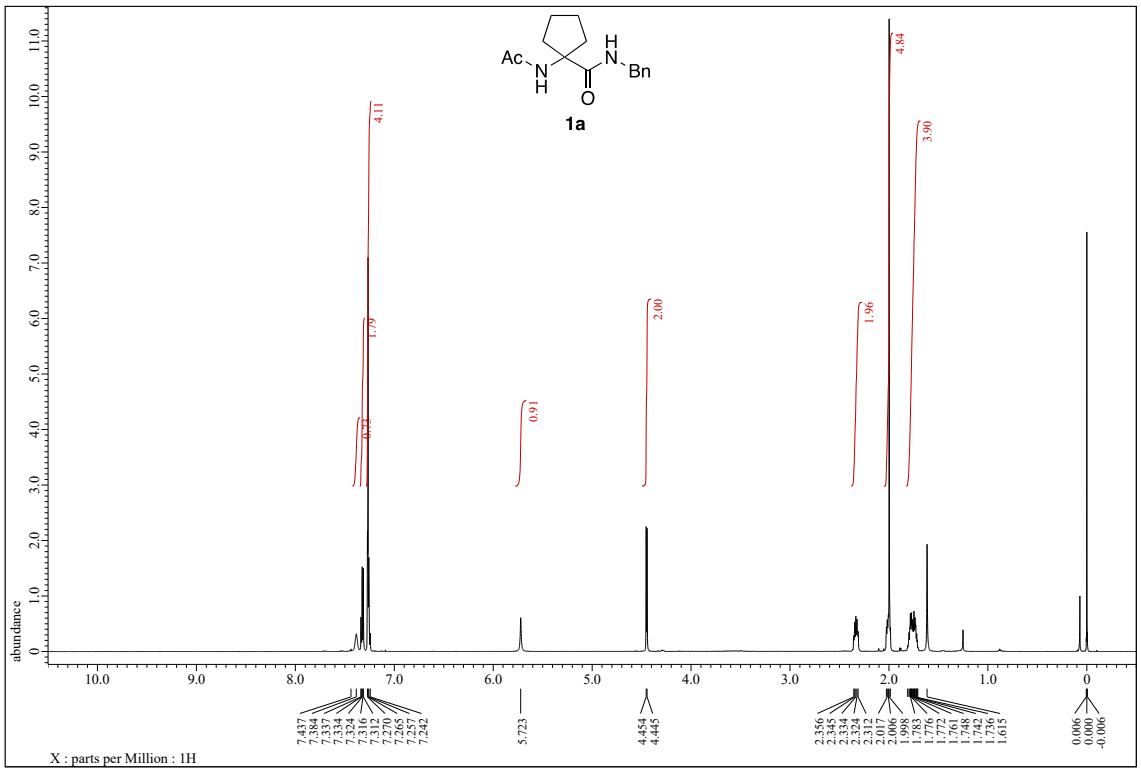

Figure S3. ^{1}H NMR spectrum (600 MHz) of **1a** in $CDCl_3$.

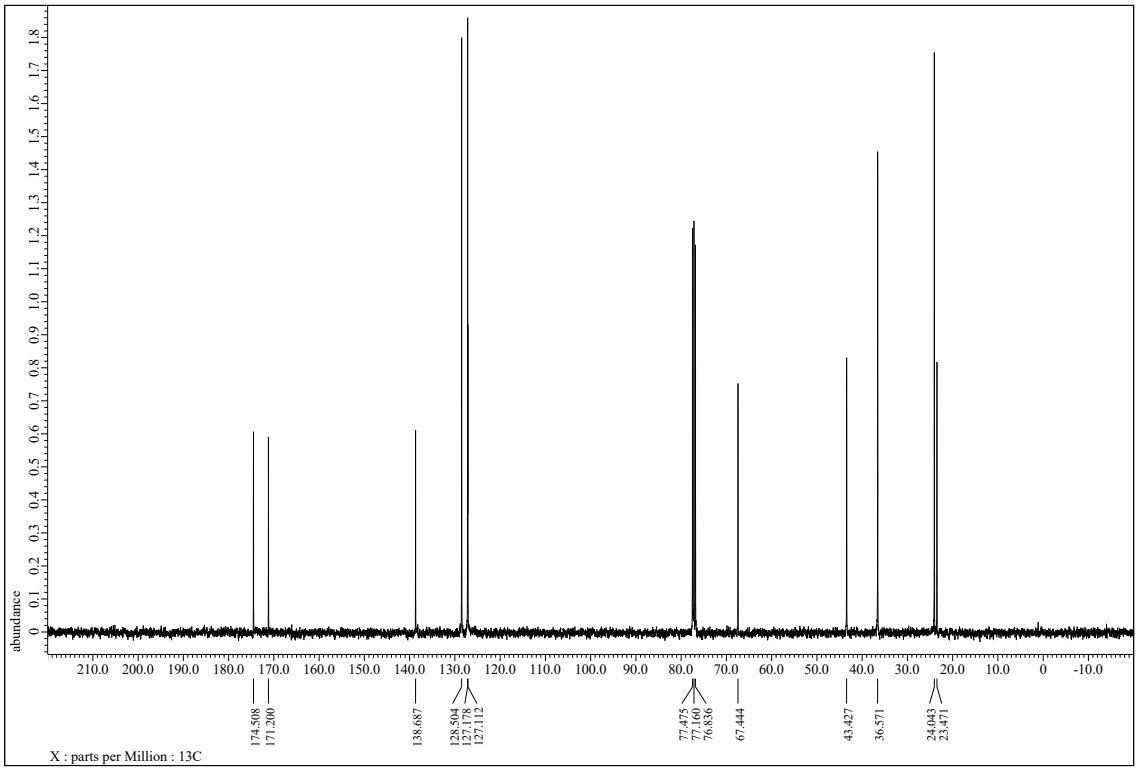

Figure S4. ^{13}C NMR spectrum (101 MHz) of **1a** in $CDCl_3$.

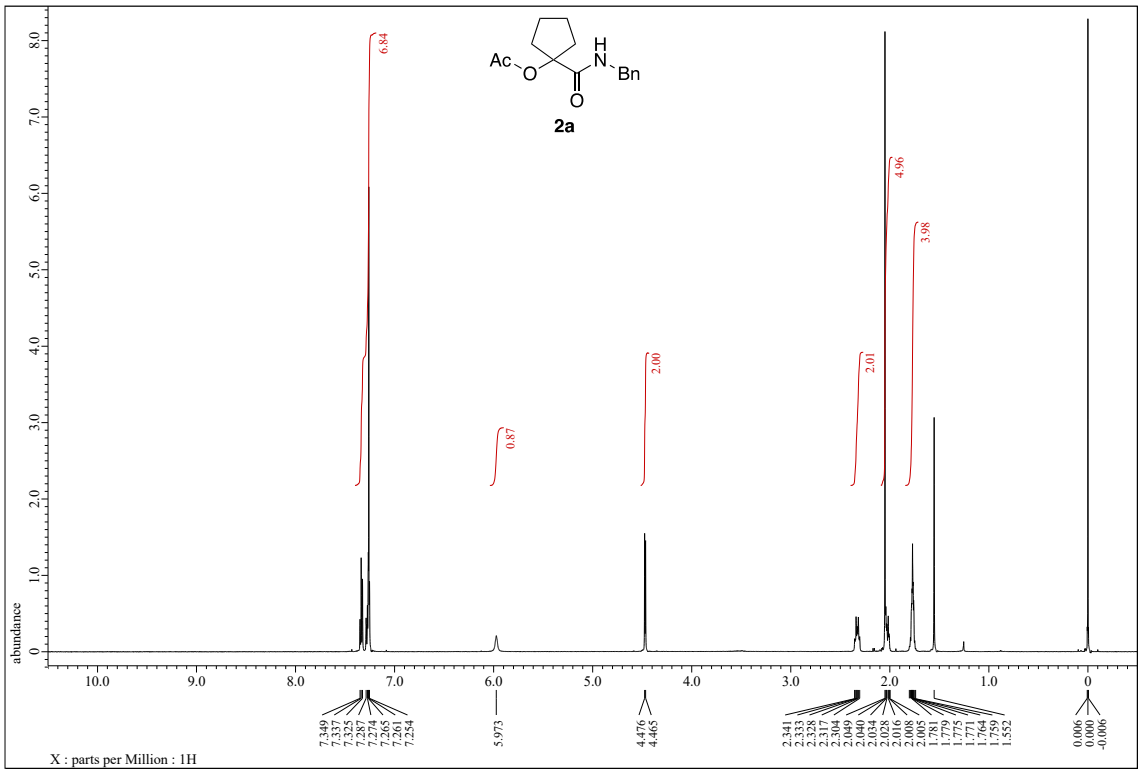

Figure S5. ^{1}H NMR spectrum (600 MHz) of **2a** in $CDCl_3$.

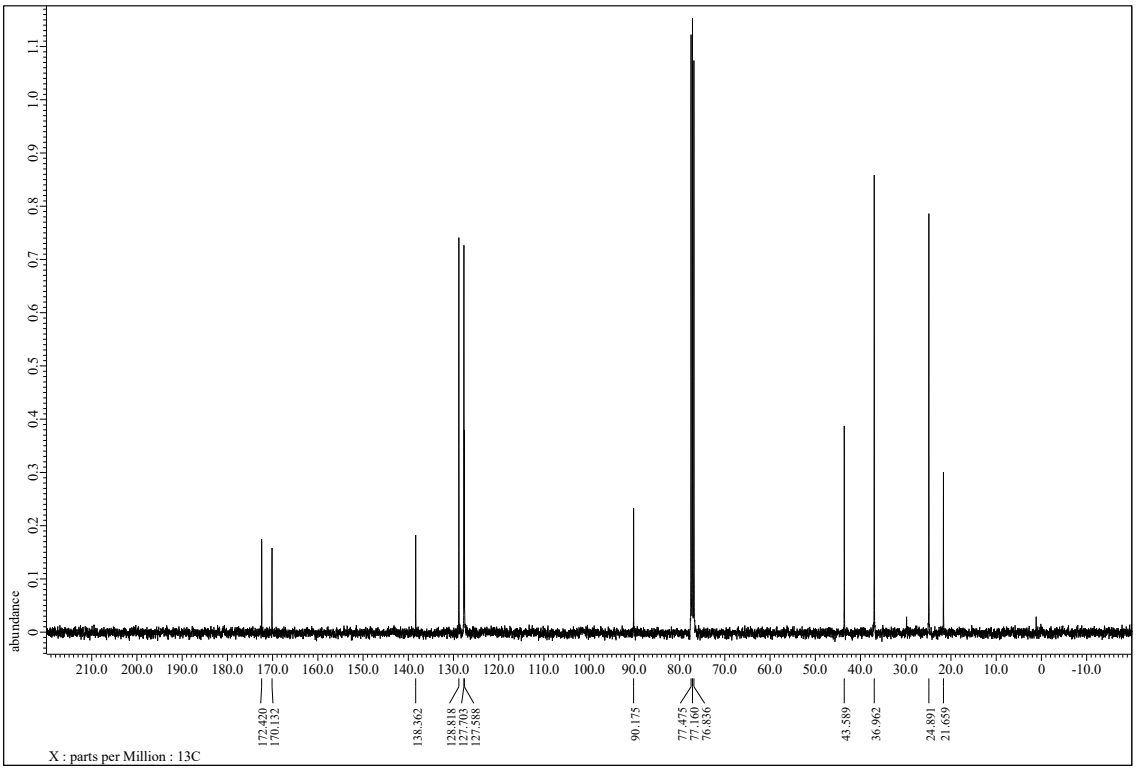

Figure S6. ^{13}C NMR spectrum (101 MHz) of **2a** in $CDCl_3$.

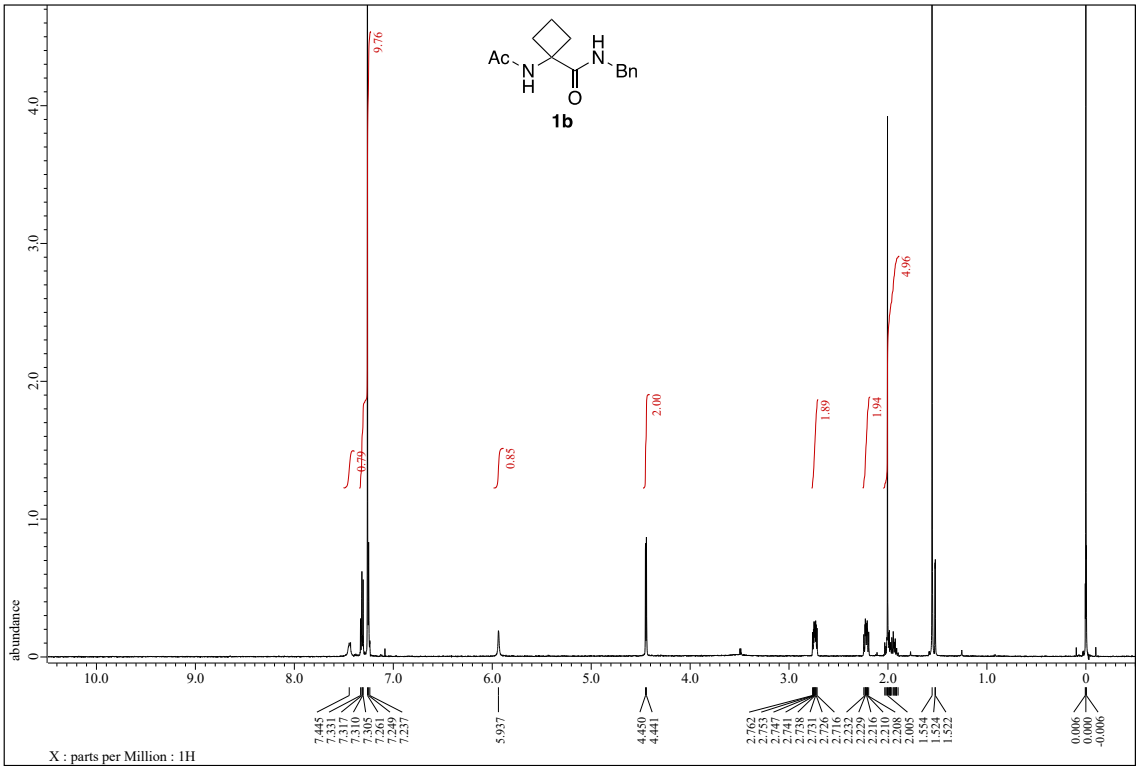

Figure S7. ^{1}H NMR spectrum (600 MHz) of **1b** in $CDCl_3$.

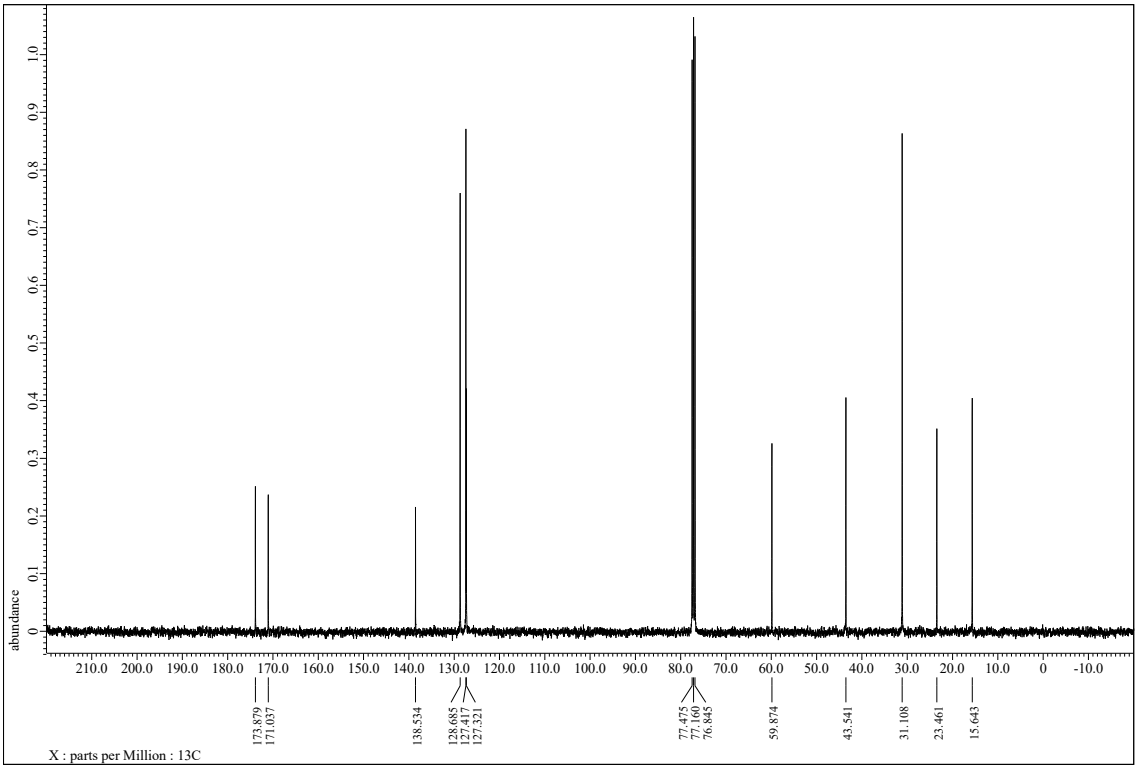

Figure S8. ^{13}C NMR spectrum (101 MHz) of **1b** in $CDCl_3$.

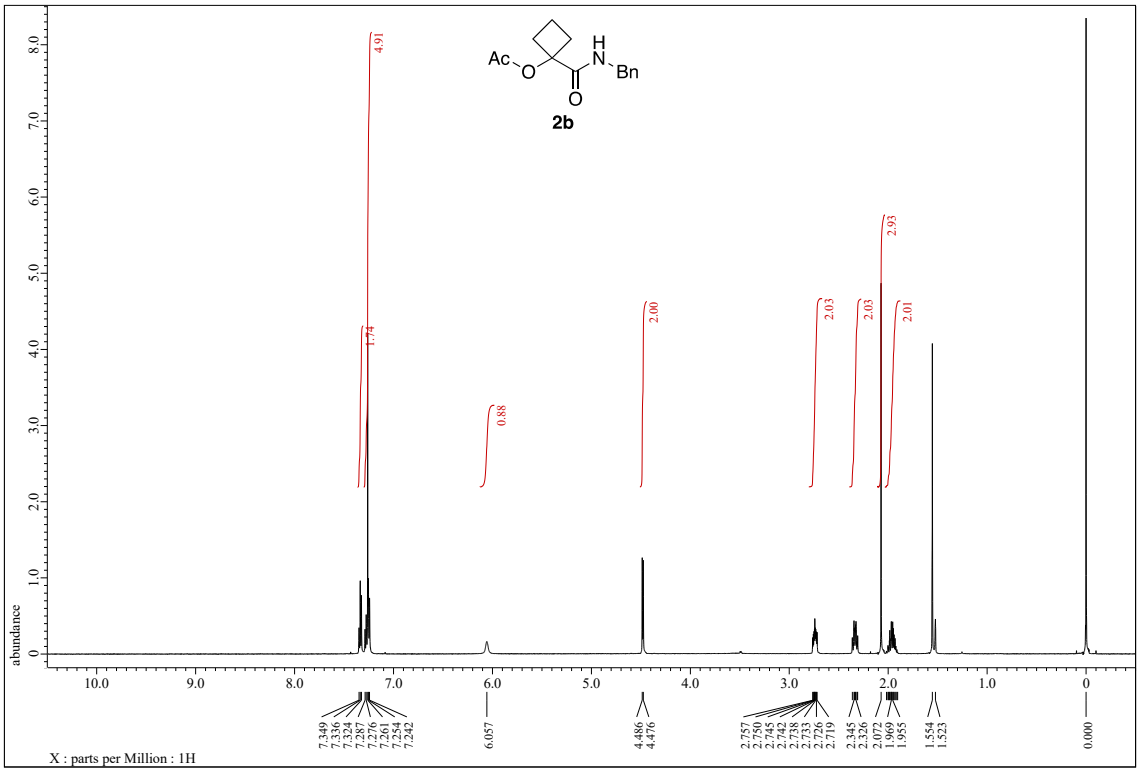

Figure S9. ^{1}H NMR spectrum (600 MHz) of **2b** in $CDCl_3$.

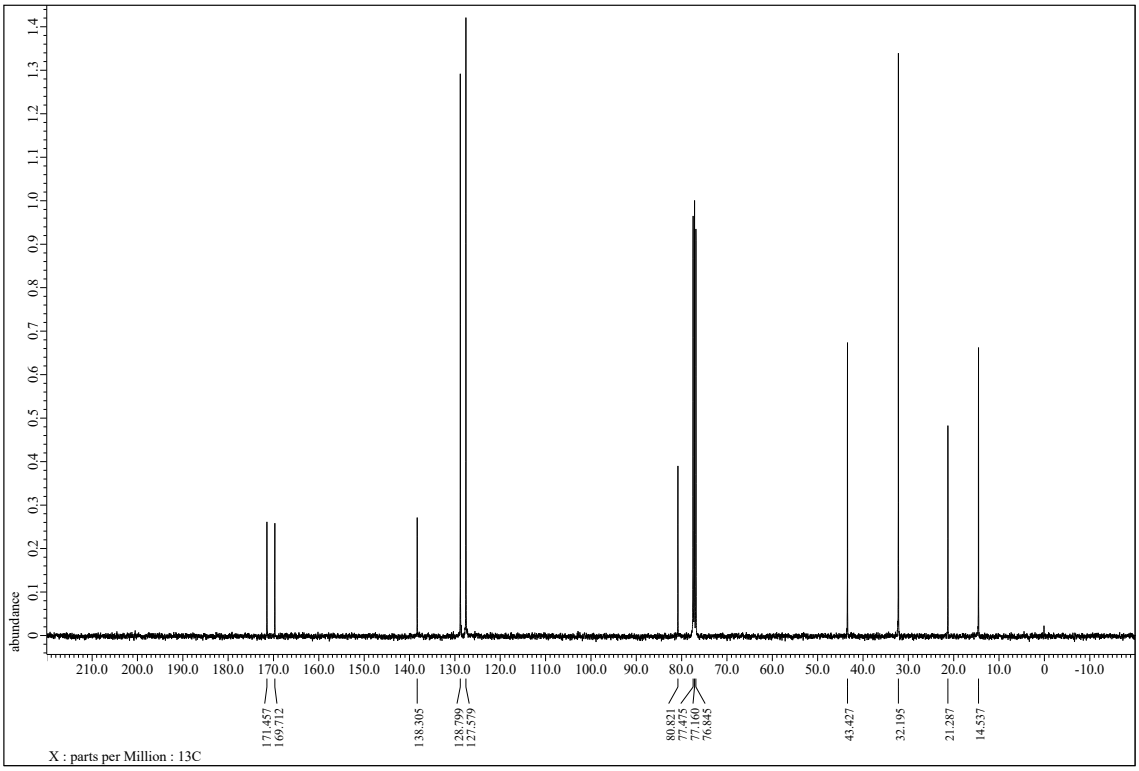

Figure S10. ^{13}C NMR spectrum (101 MHz) of **2b** in $CDCl_3$.

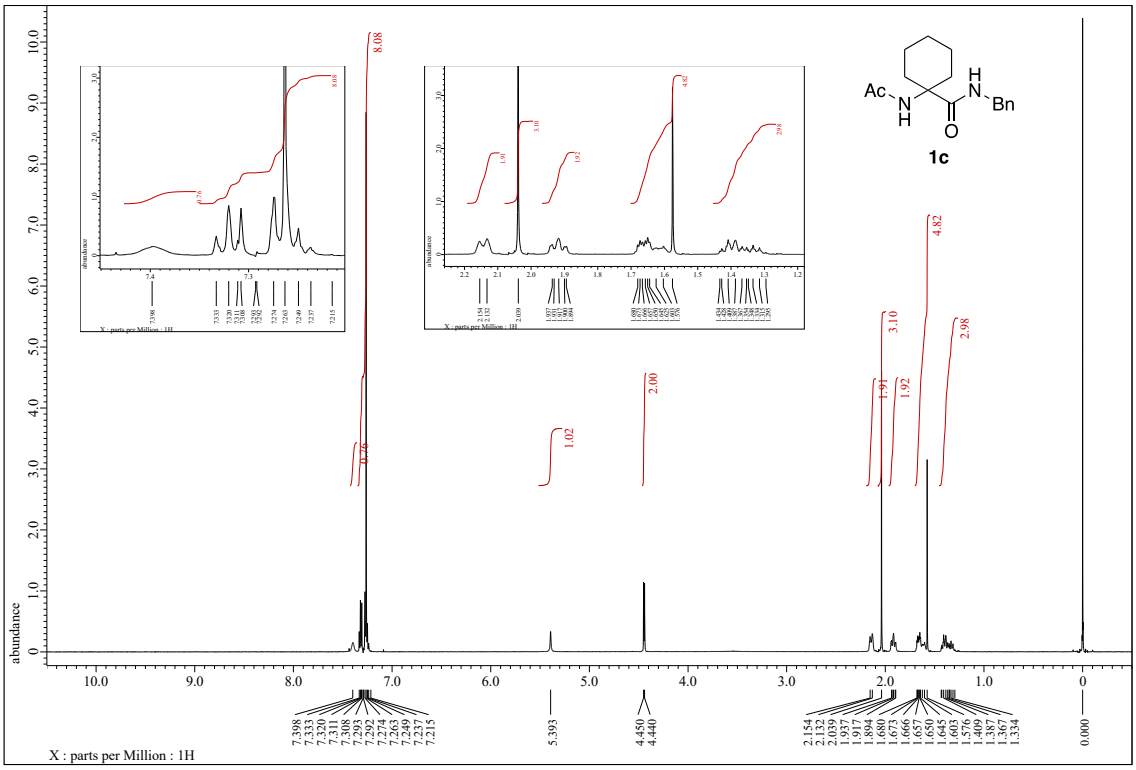

Figure S11. ^{1}H NMR spectrum (600 MHz) of **1c** in $CDCl_3$.

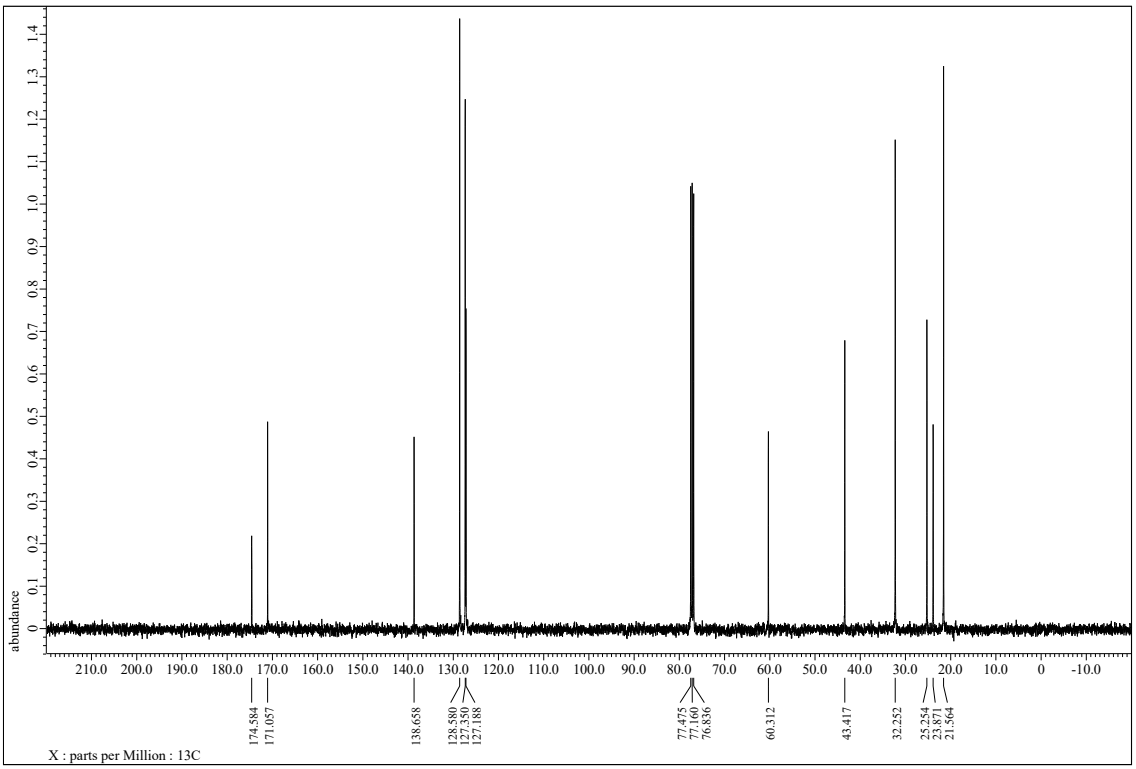

Figure S12. ^{13}C NMR spectrum (101 MHz) of **1c** in $CDCl_3$.

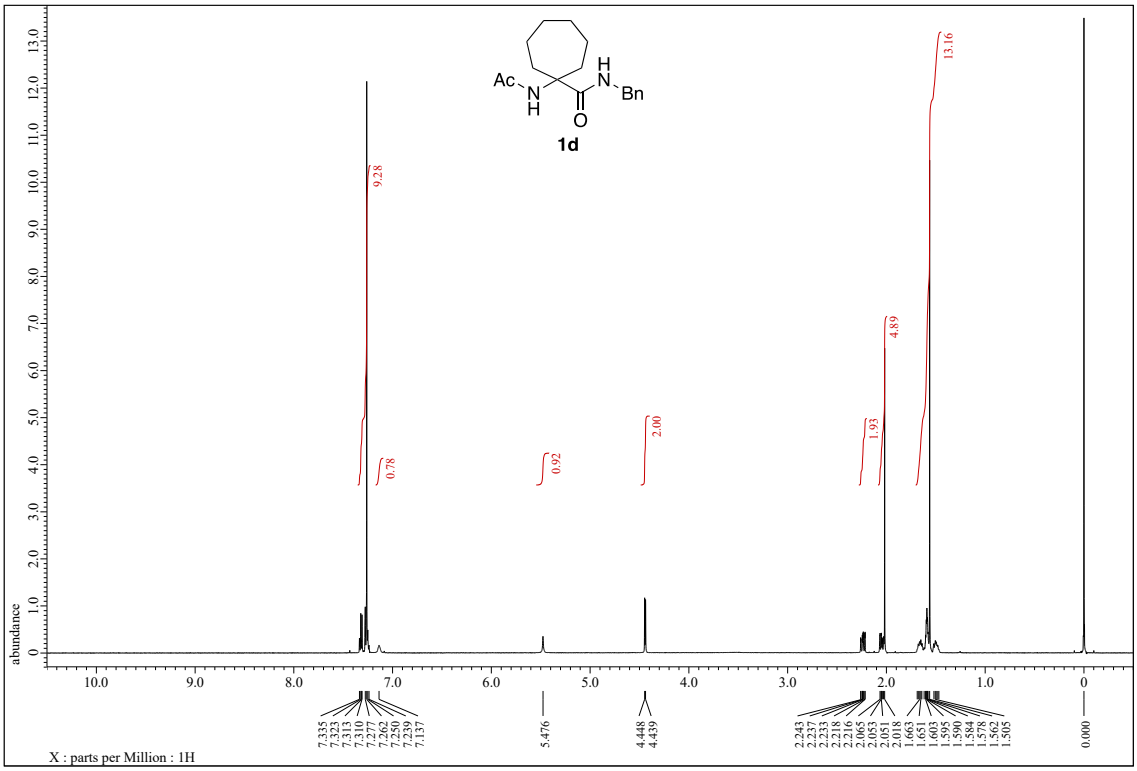

Figure S13. ^{1}H NMR spectrum (600 MHz) of **1d** in $CDCl_3$.

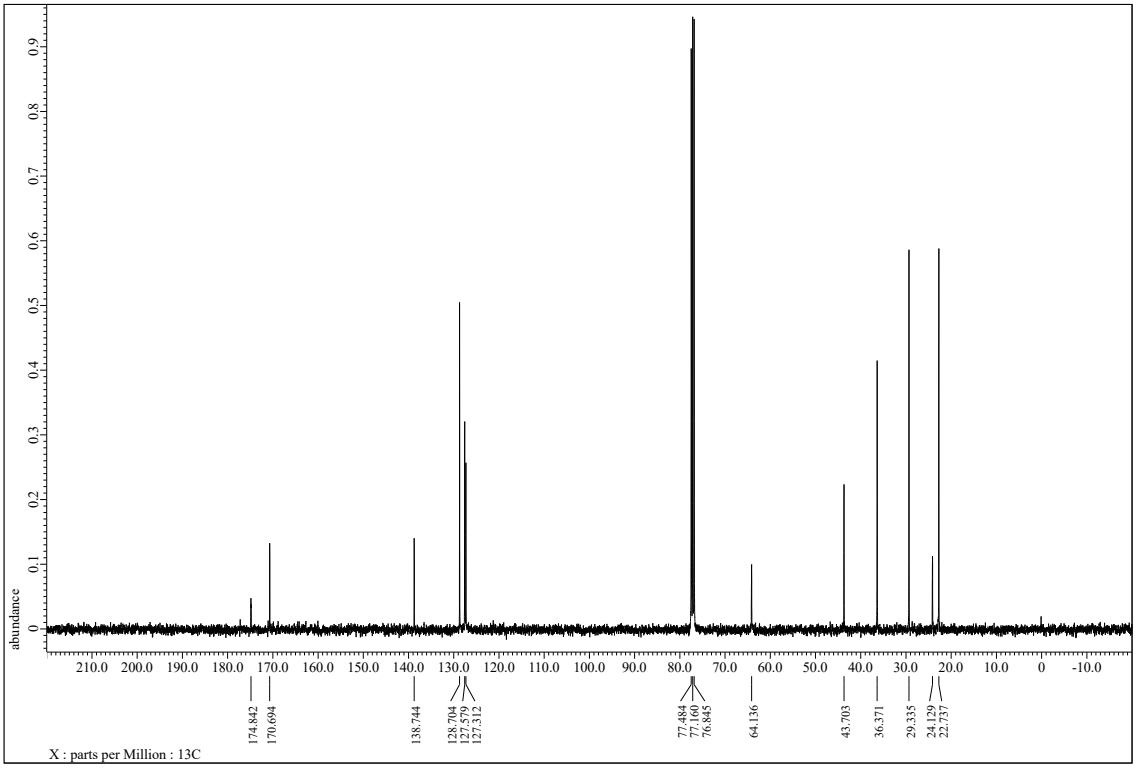

Figure S14. ^{13}C NMR spectrum (101 MHz) of **1d** in $CDCl_3$.

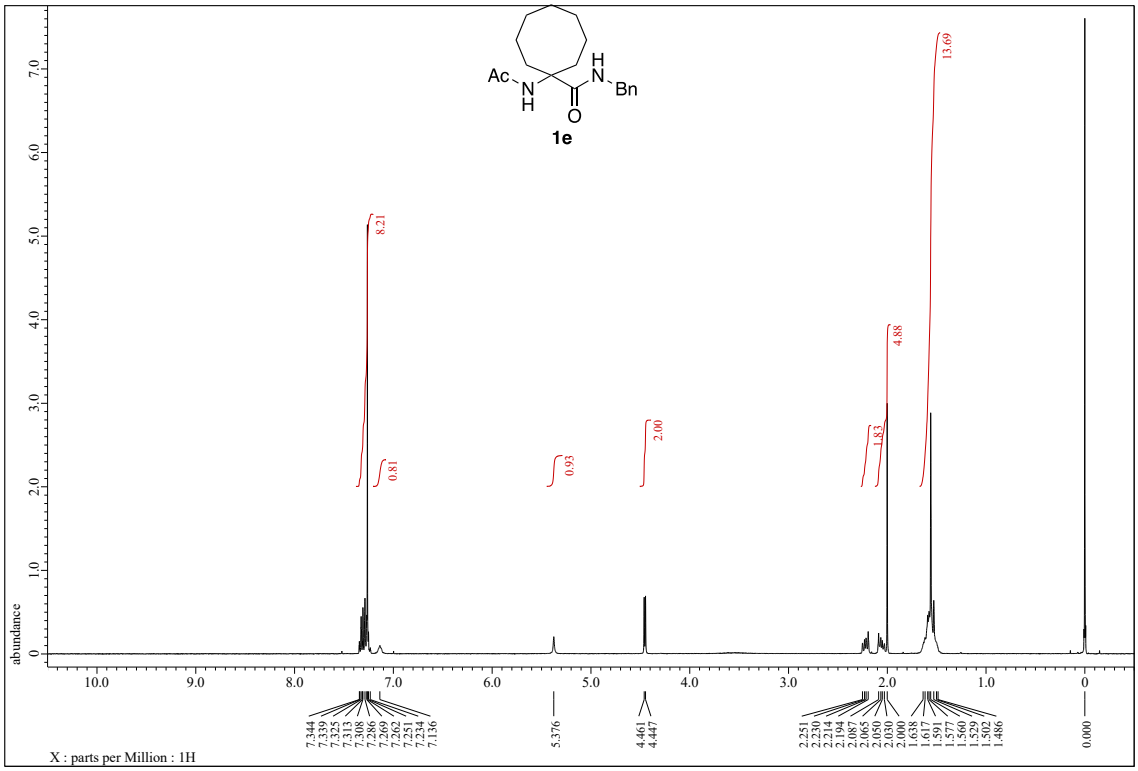

Figure S15. ^{1}H NMR spectrum (400 MHz) of **1e** in $CDCl_3$.

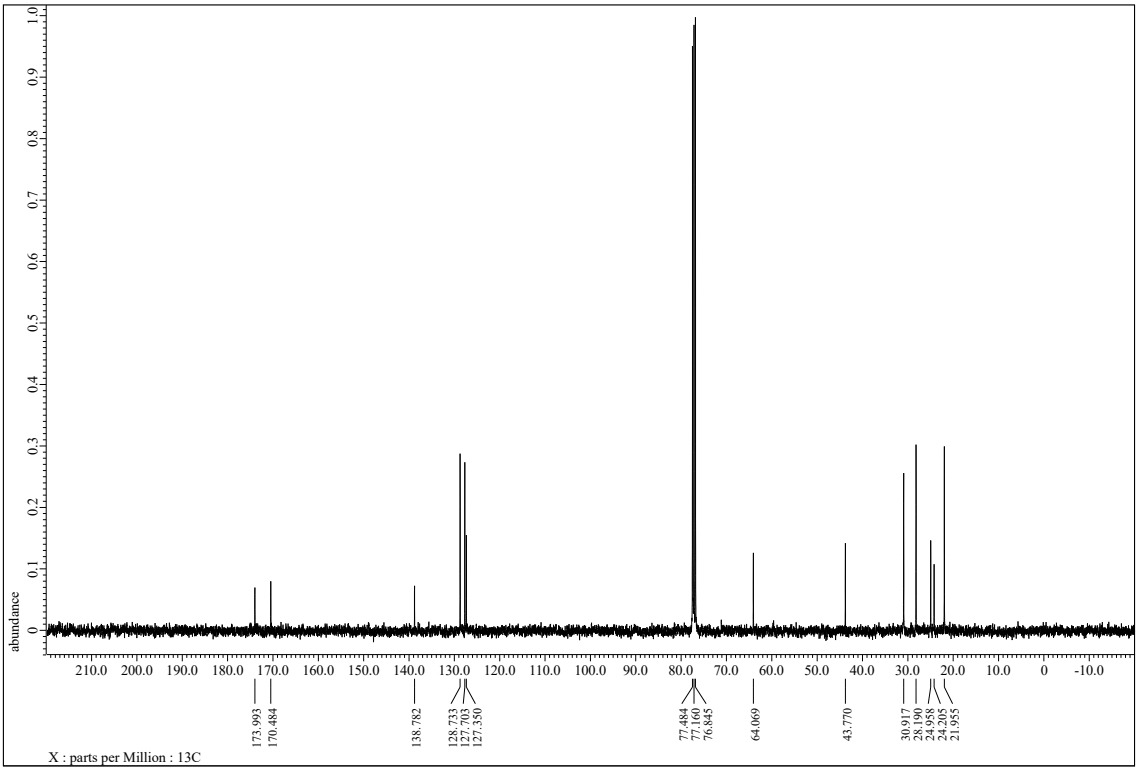

Figure S16. ^{13}C NMR spectrum (101 MHz) of **1e** in $CDCl_3$.

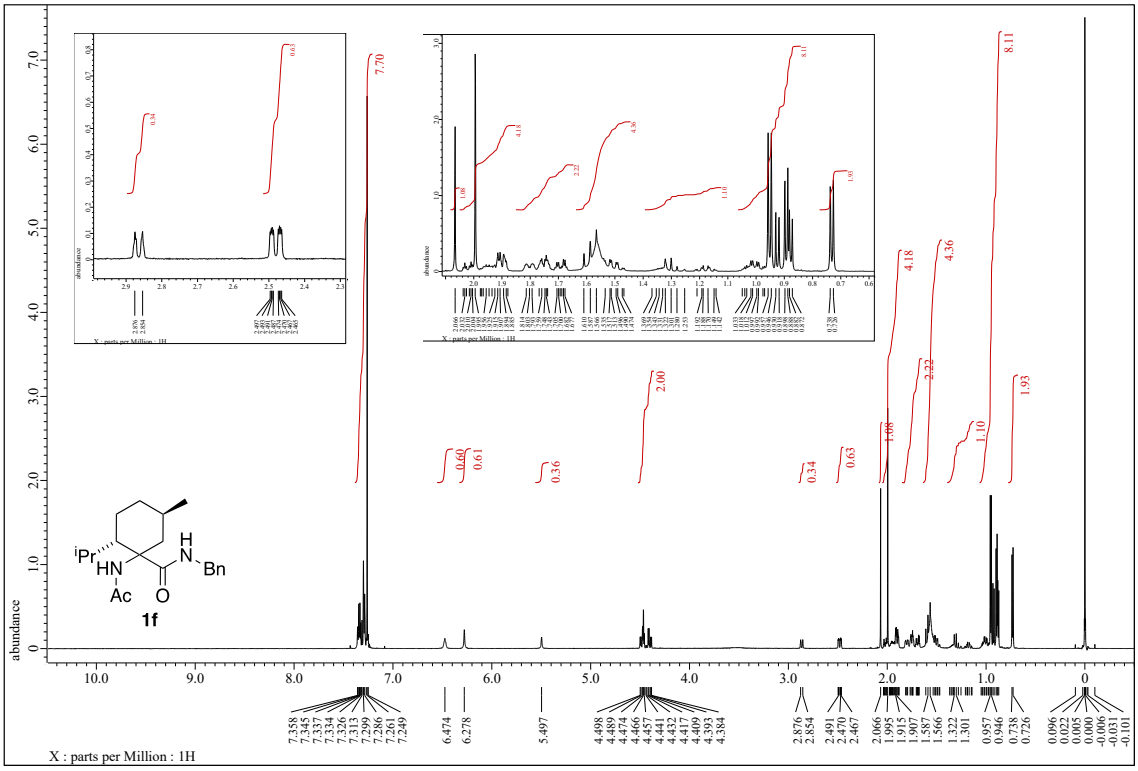

Figure S17. ^{1}H NMR spectrum (600 MHz) of **1f** in $CDCl_3$.

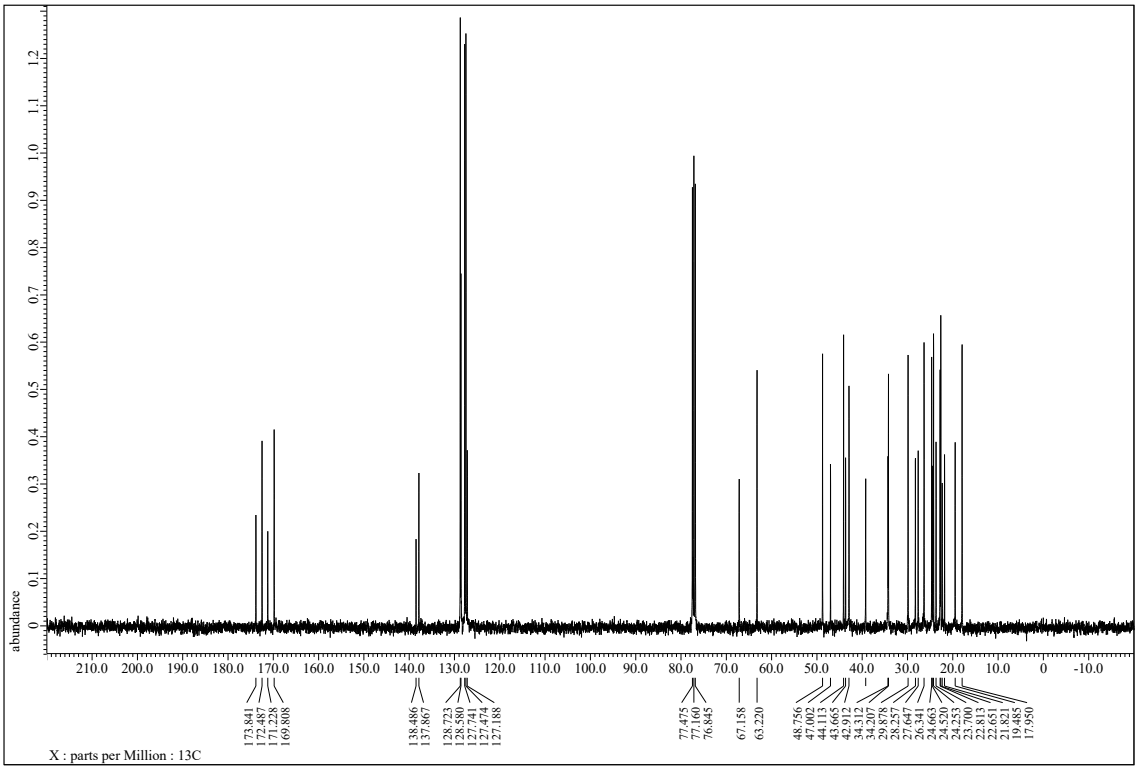

Figure S18. ^{13}C NMR spectrum (101 MHz) of **1f** in $CDCl_3$.

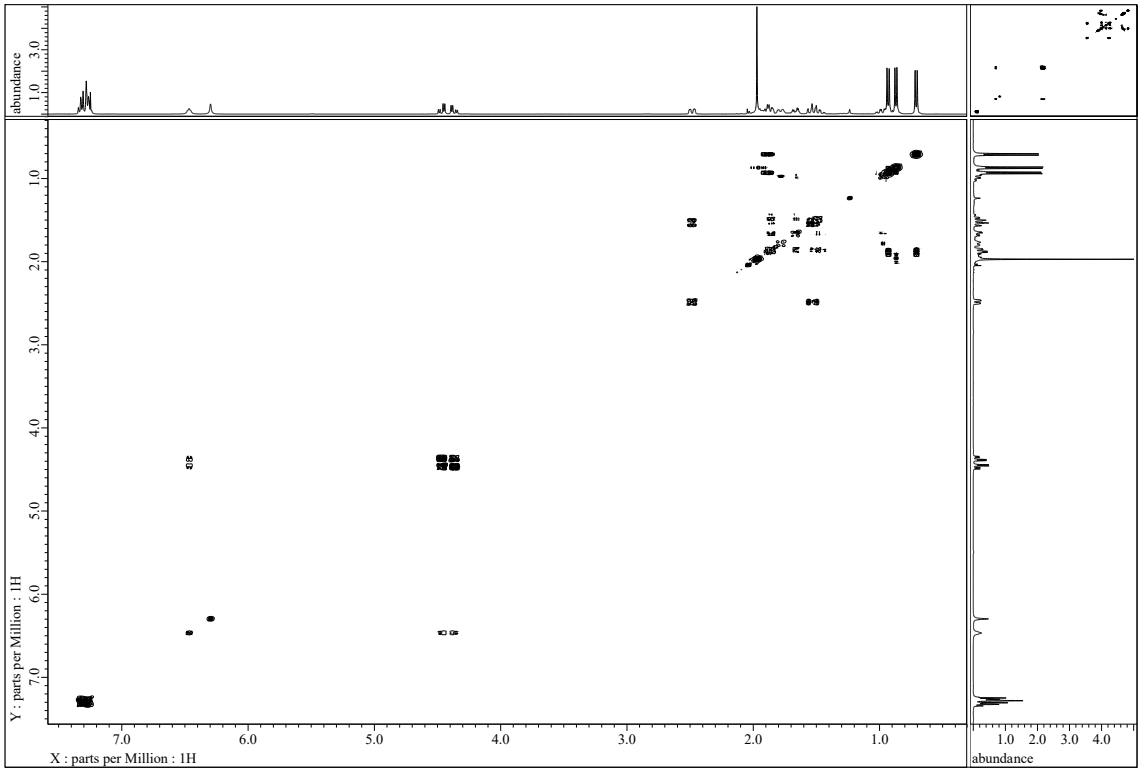

Figure S19. ^{1}H ^{1}H COSY spectrum (400 MHz) of (1*R*,2*S*,5*R*)-**1f** in $CDCl_3$.

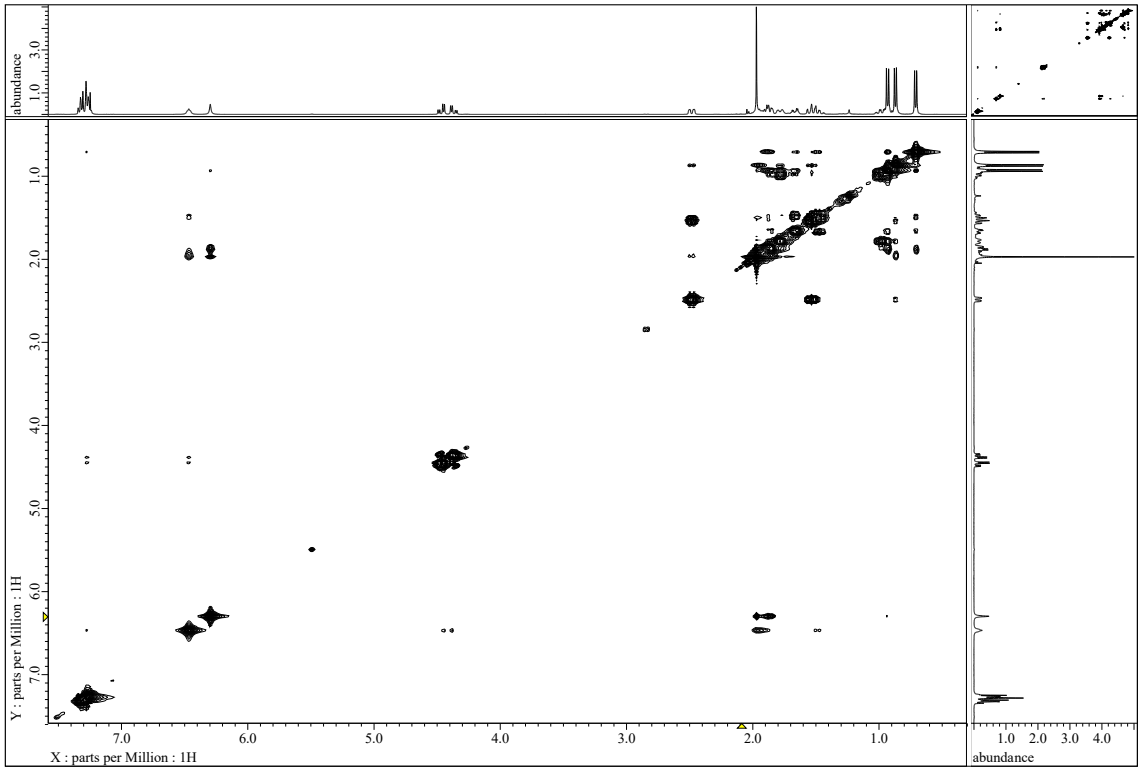

Figure S20. NOESY spectrum (400 MHz) of (1*R*,2*S*,5*R*)-**1f** in $CDCl_3$.

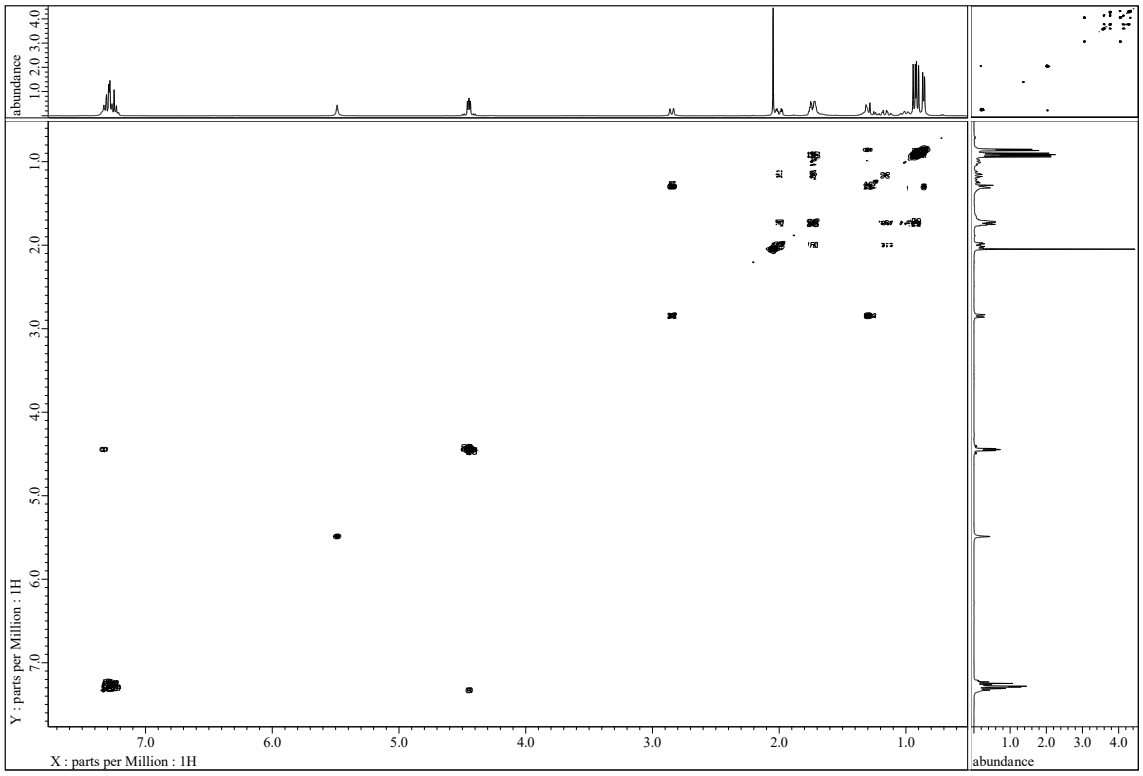

Figure S21. ^{1}H ^{1}H COSY spectrum (400 MHz) of (1*S,2S,5R*)-**1f** in $CDCl_3$.

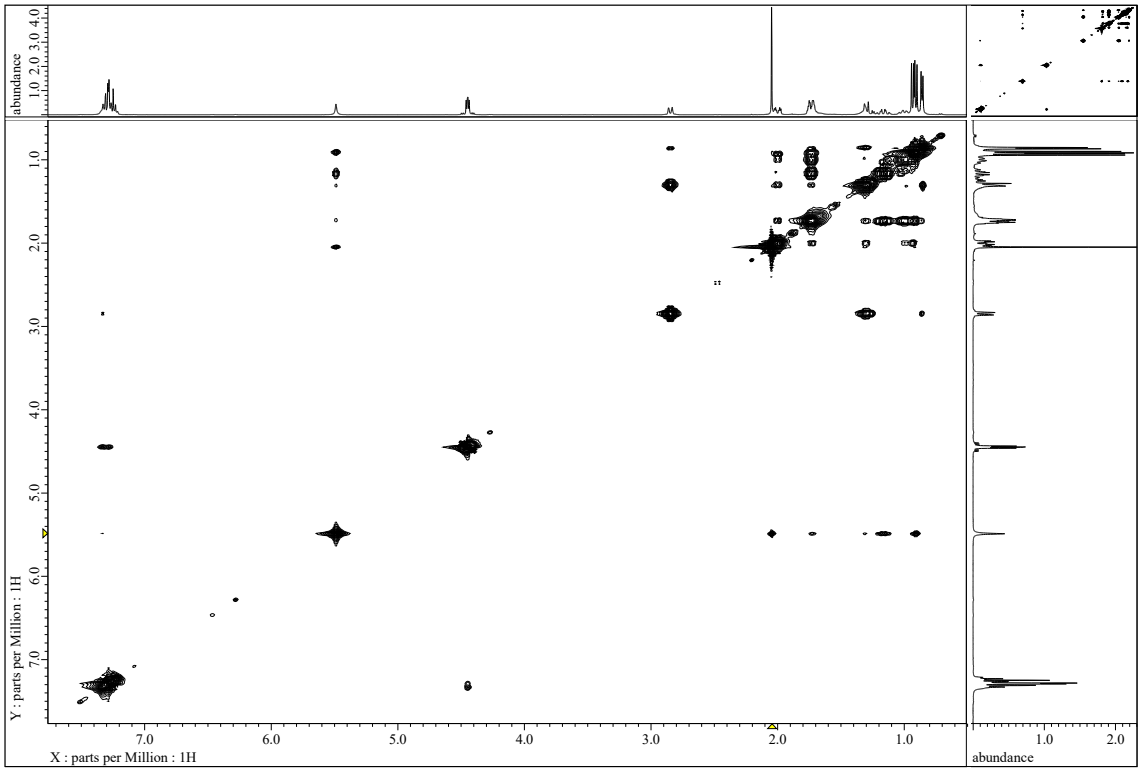

Figure S22. NOESY spectrum (400 MHz) of (1*S*,2*S*,5*R*)-**1f** in $CDCl_3$.

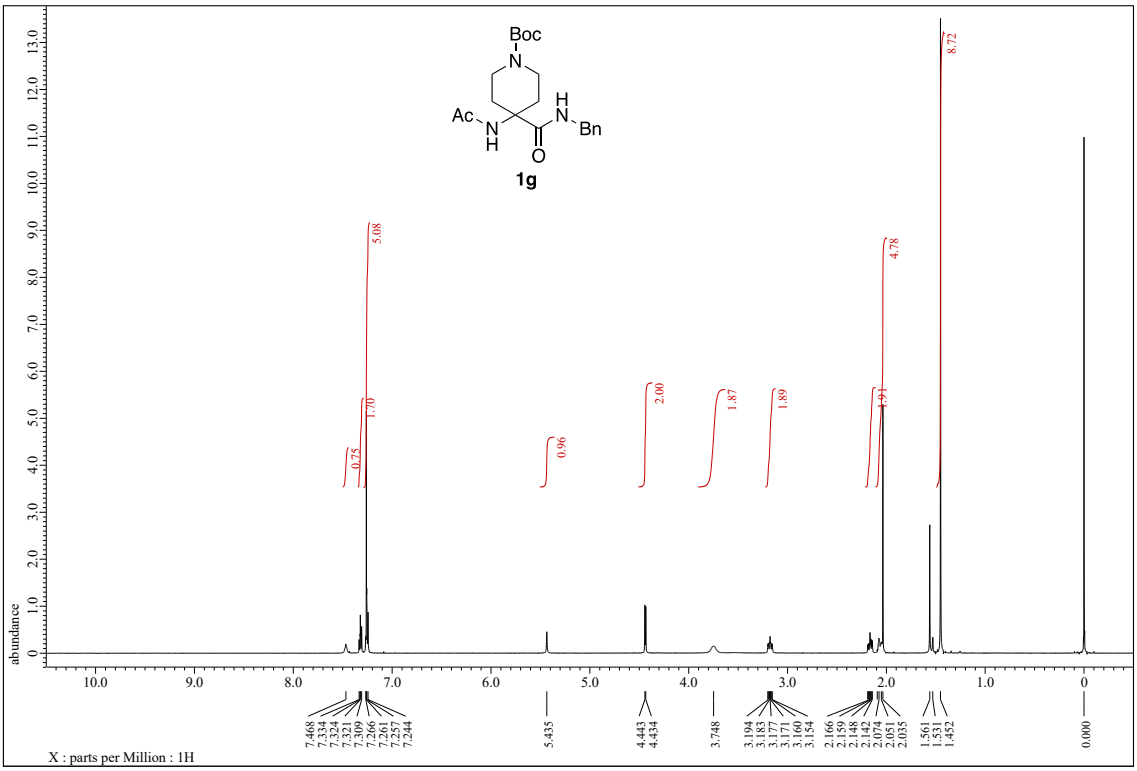

Figure S23. ^{1}H NMR spectrum (600 MHz) of **1g** in $CDCl_3$.

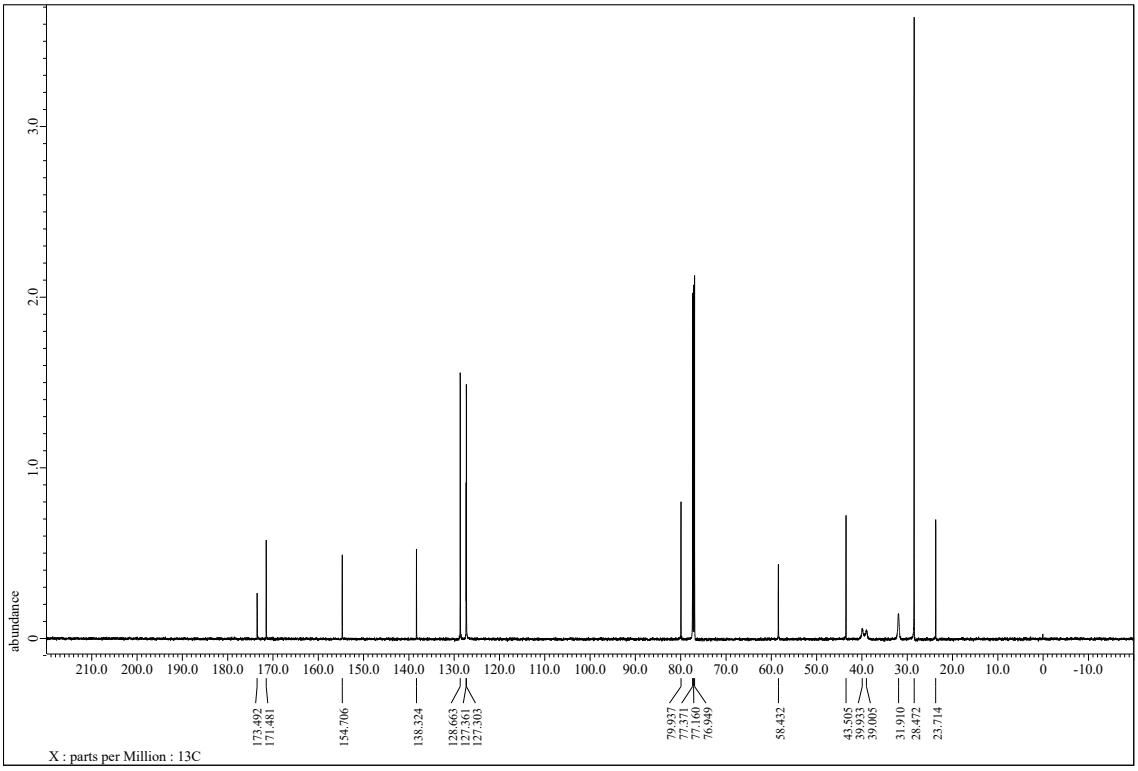

Figure S24. ^{13}C NMR spectrum (151 MHz) of **1g** in $CDCl_3$.

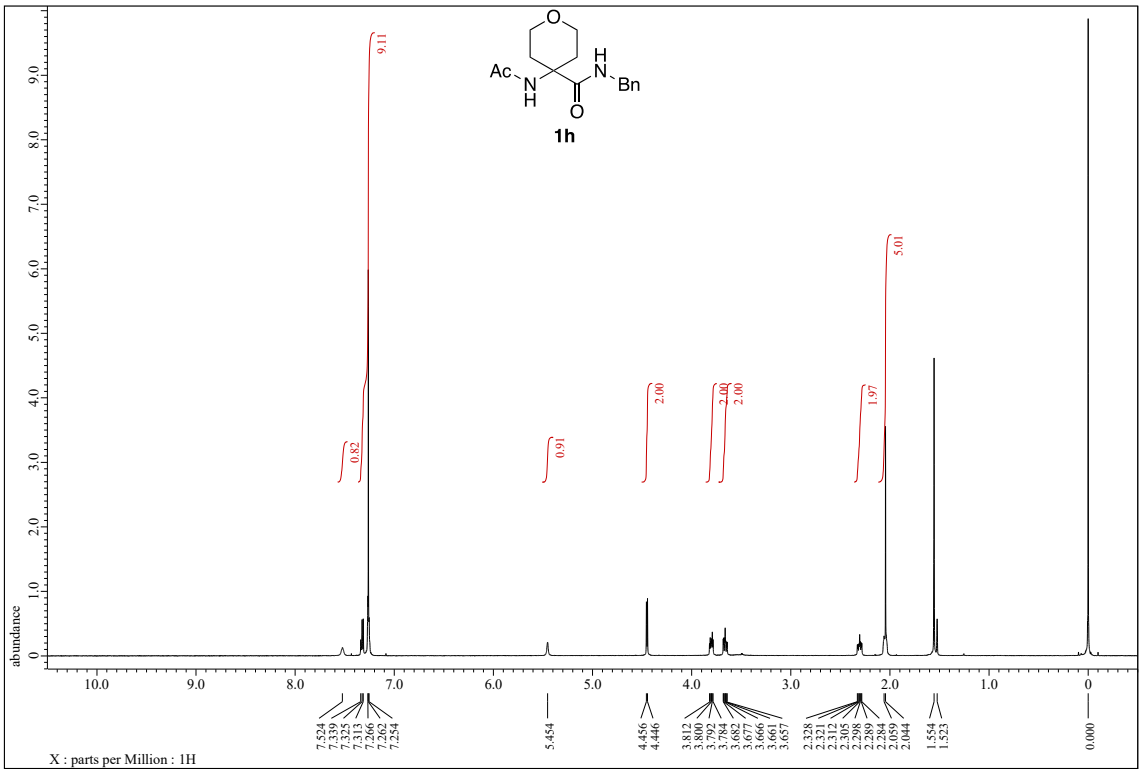

Figure S25. ^{1}H NMR spectrum (600 MHz) of **1h** in $CDCl_3$.

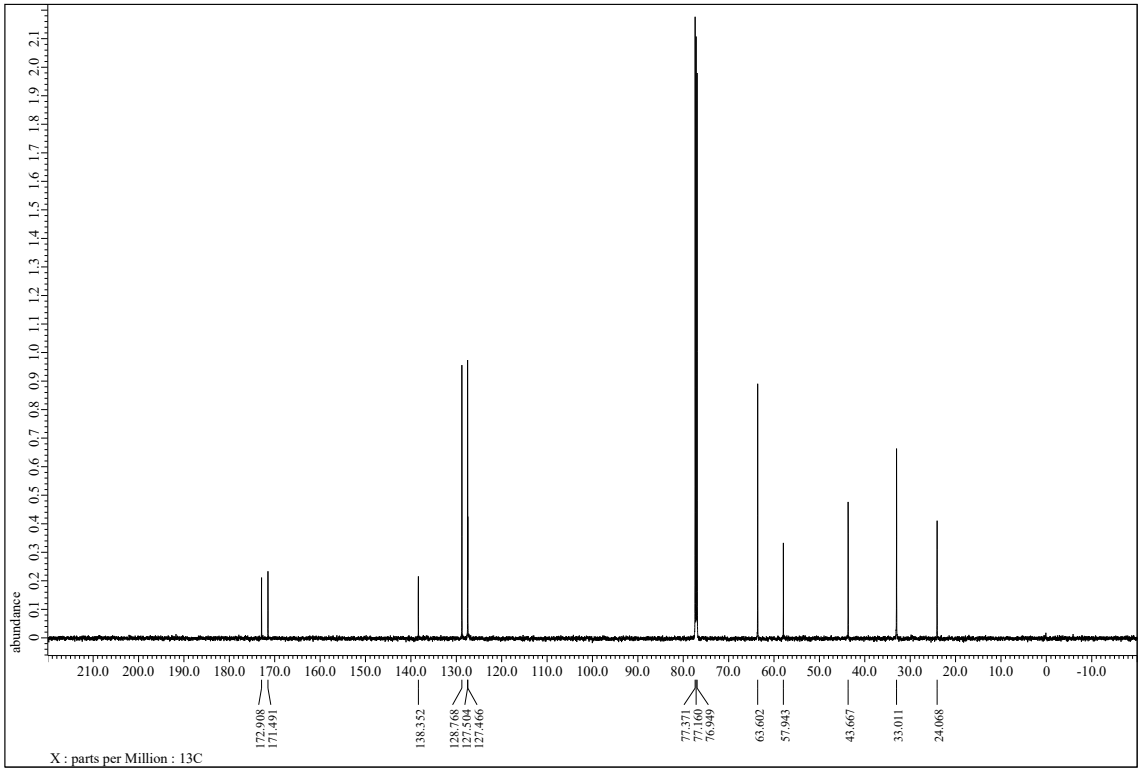

Figure S26. ^{13}C NMR spectrum (151 MHz) of **1h** in $CDCl_3$.

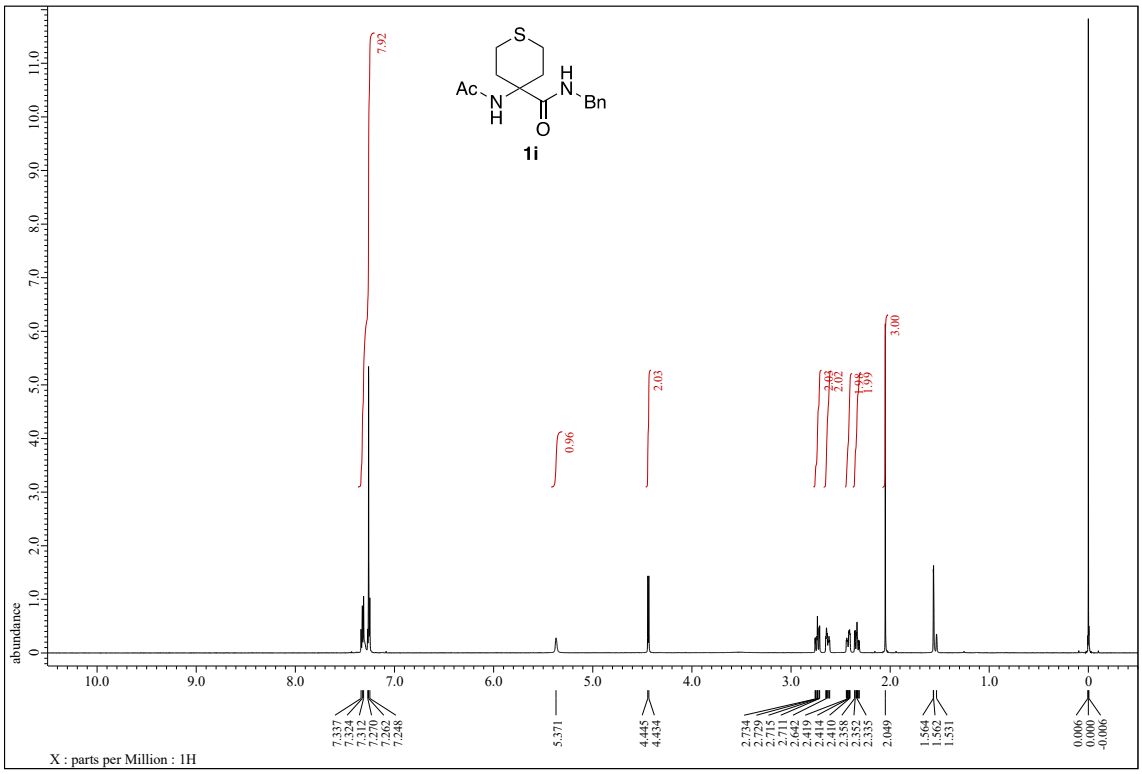

Figure S27. ^{1}H NMR spectrum (600 MHz) of **1i** in $CDCl_3$.

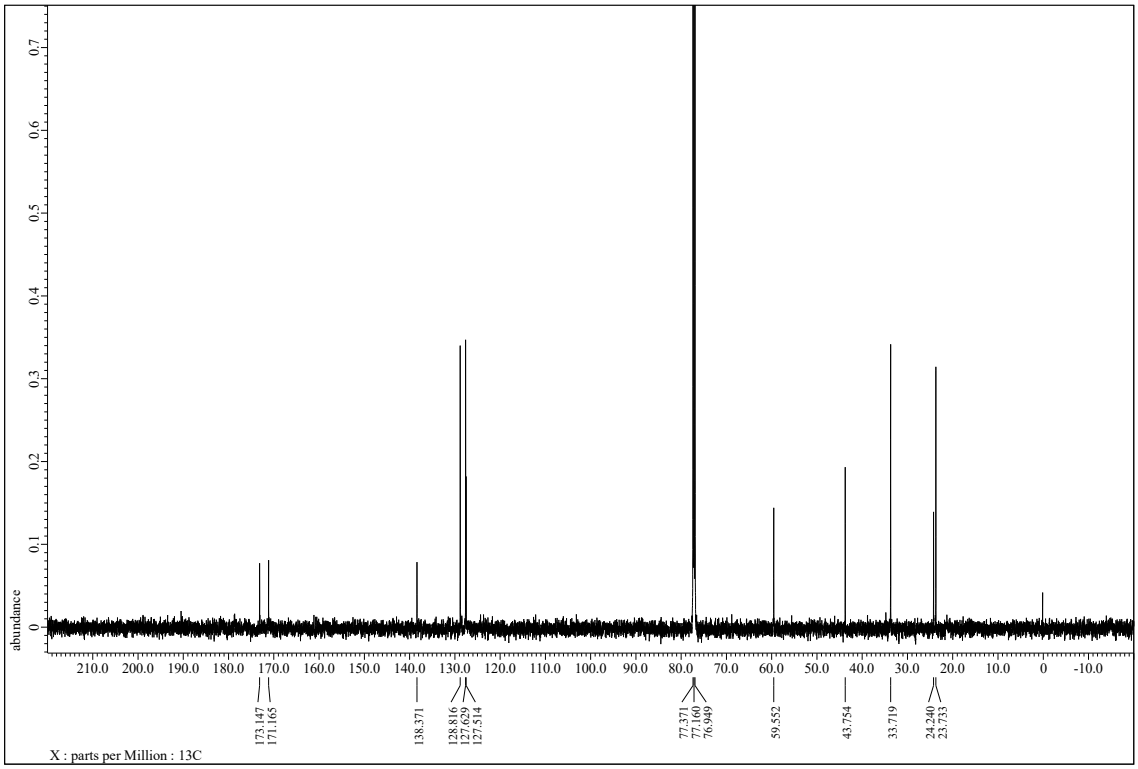

Figure S28. ^{13}C NMR spectrum (151 MHz) of **1i** in $CDCl_3$.

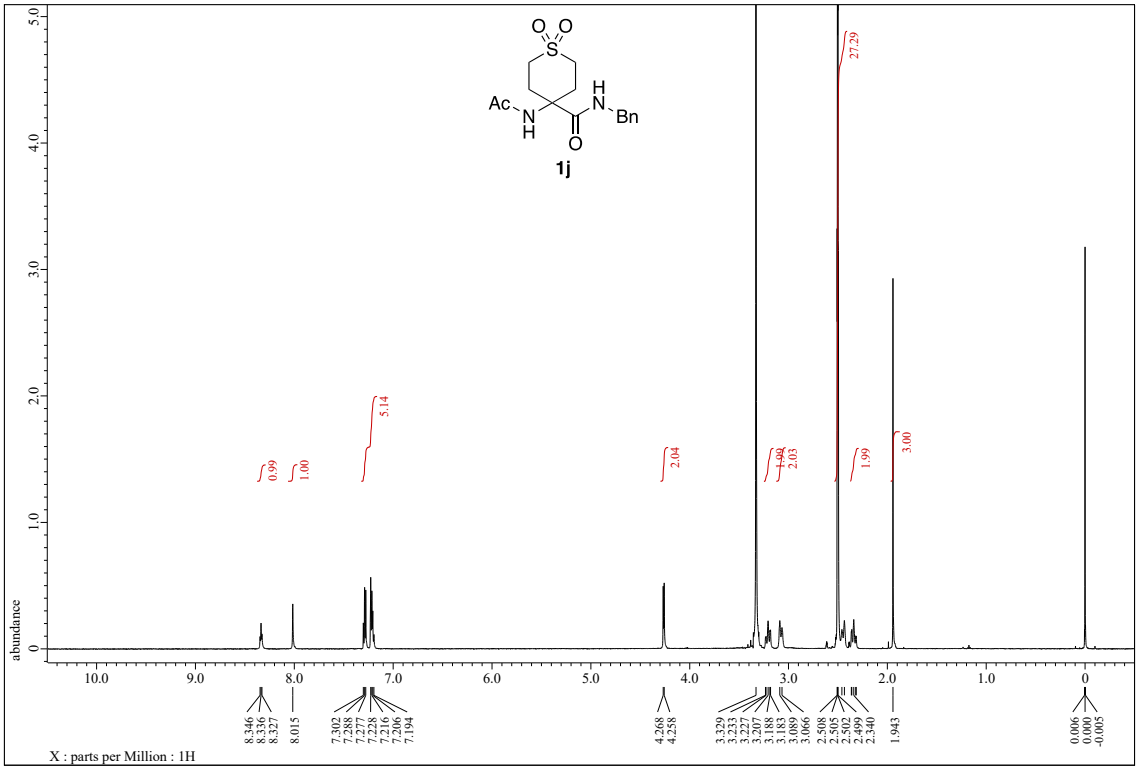

Figure S29. ^{1}H NMR spectrum (600 MHz) of **1j** in DMSO-d_6.

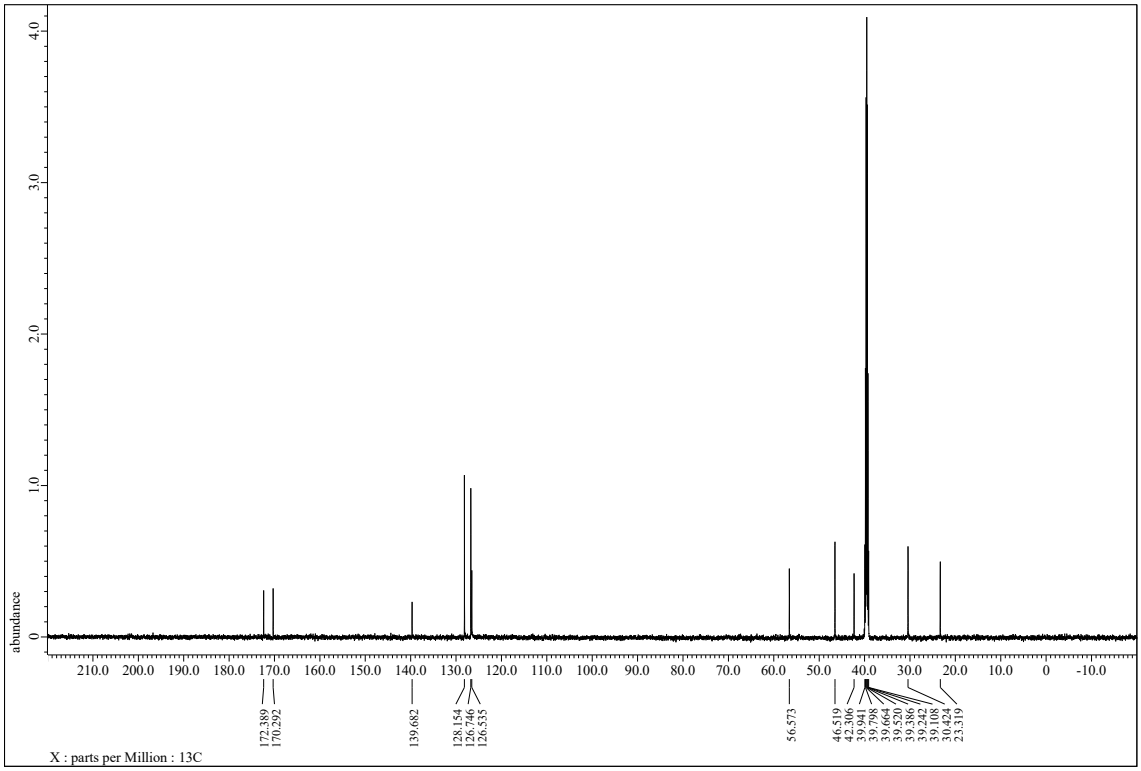

Figure S30. ^{13}C NMR spectrum (151 MHz) of **1j** in DMSO-d_6.

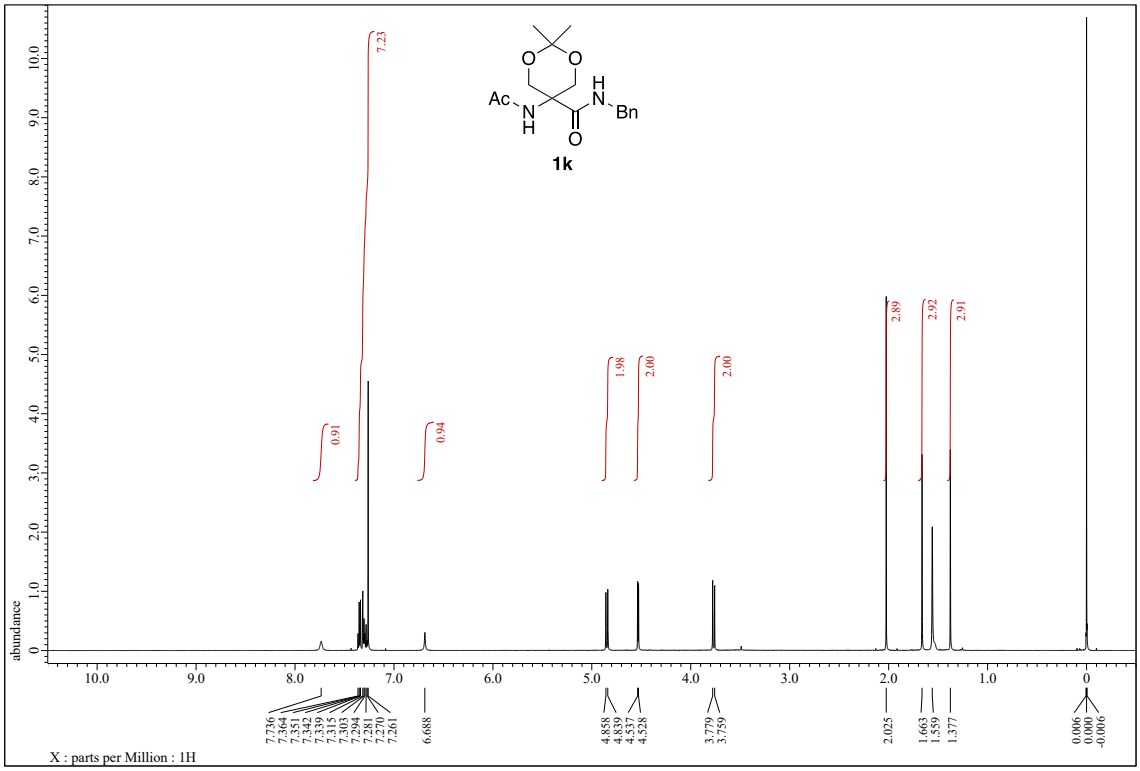

Figure S31. ^{1}H NMR spectrum (600 MHz) of **1k** in $CDCl_3$.

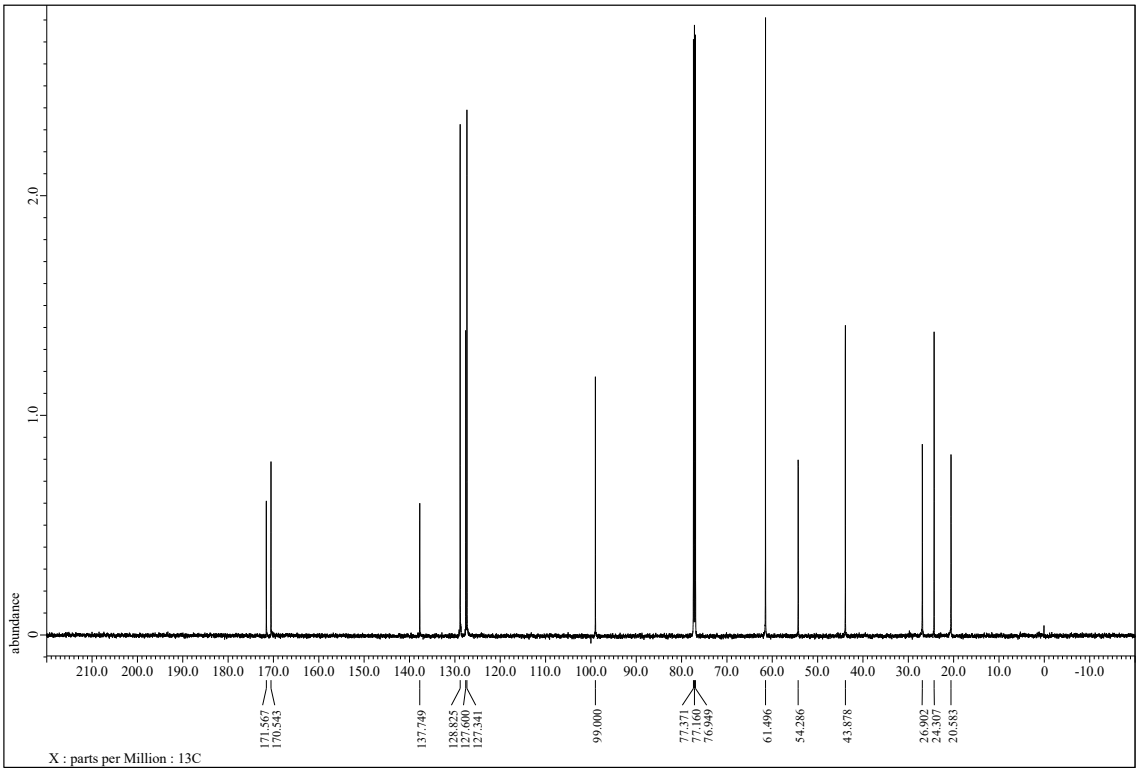

Figure S32. ^{13}C NMR spectrum (151 MHz) of **1k** in $CDCl_3$.

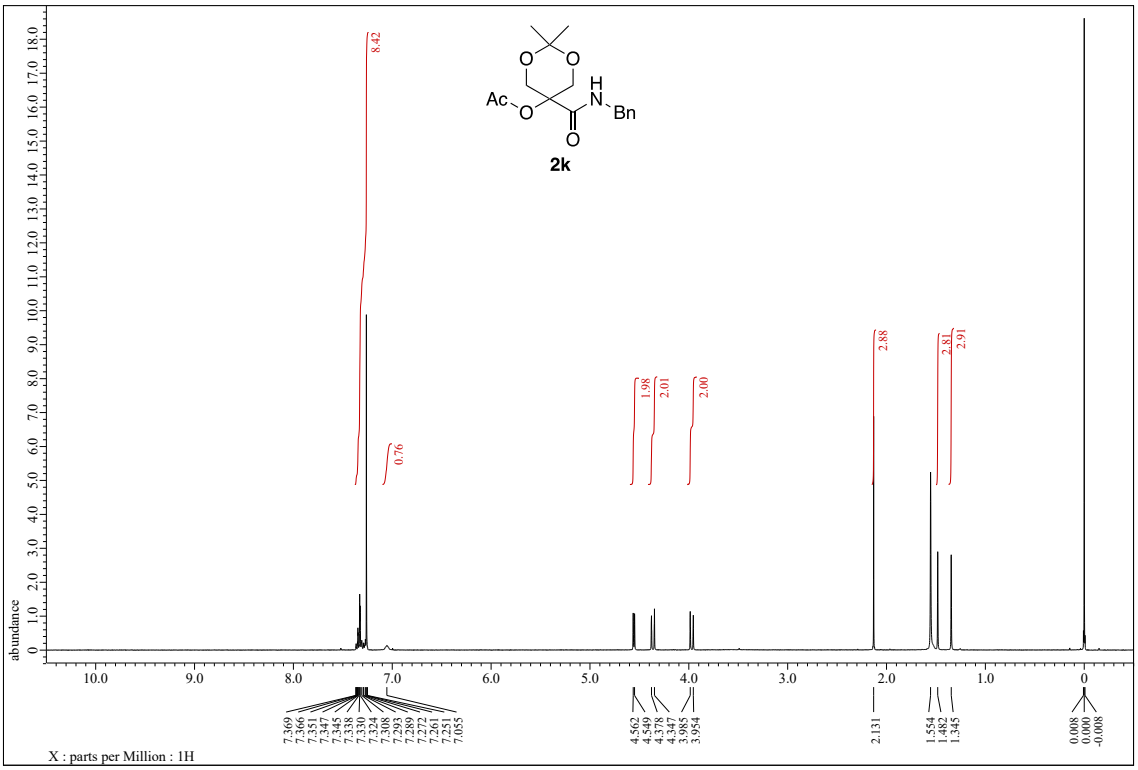

Figure S33. ^{1}H NMR spectrum (400 MHz) of **2k** in $CDCl_3$.

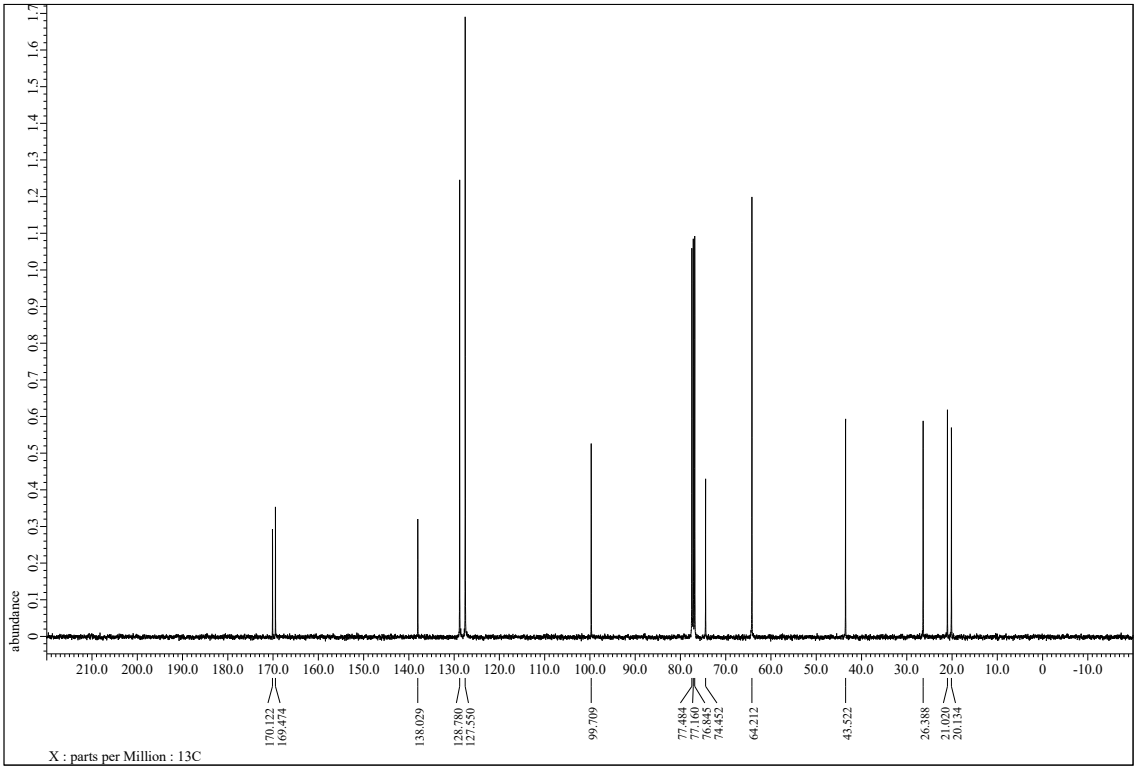

Figure S34. ^{13}C NMR spectrum (101 MHz) of **2k** in $CDCl_3$.

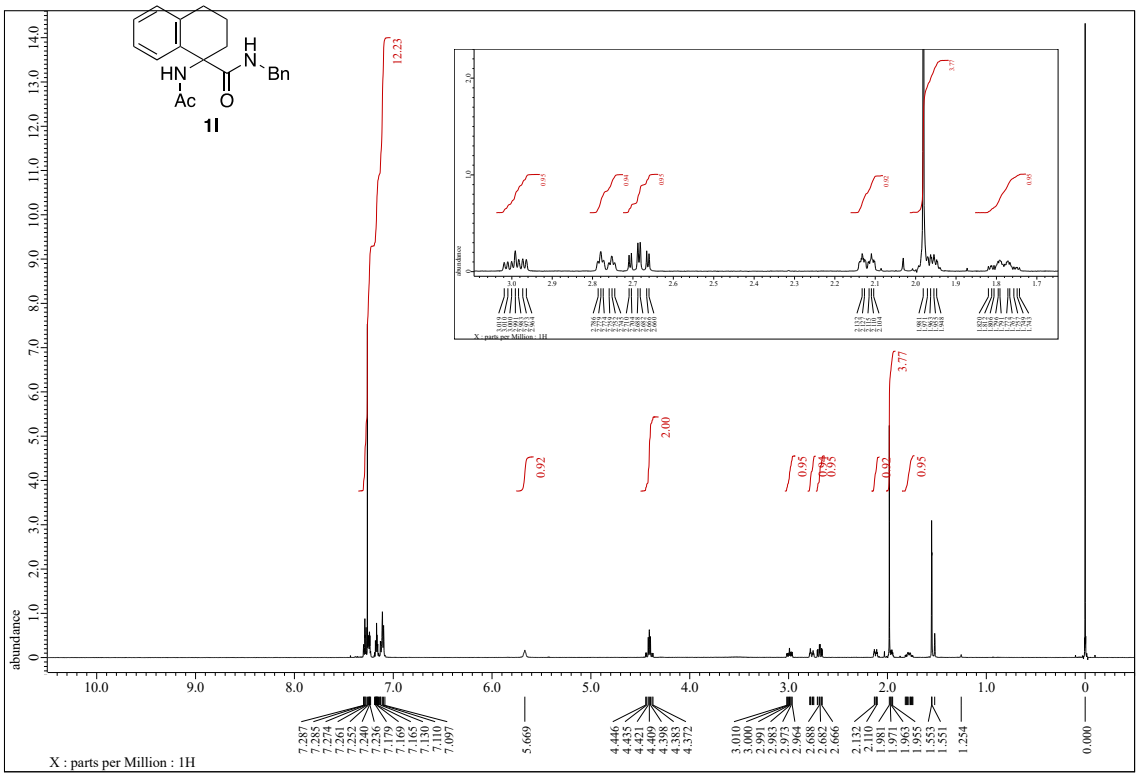

Figure S35. ^{1}H NMR spectrum (600 MHz) of **1l** in $CDCl_3$.

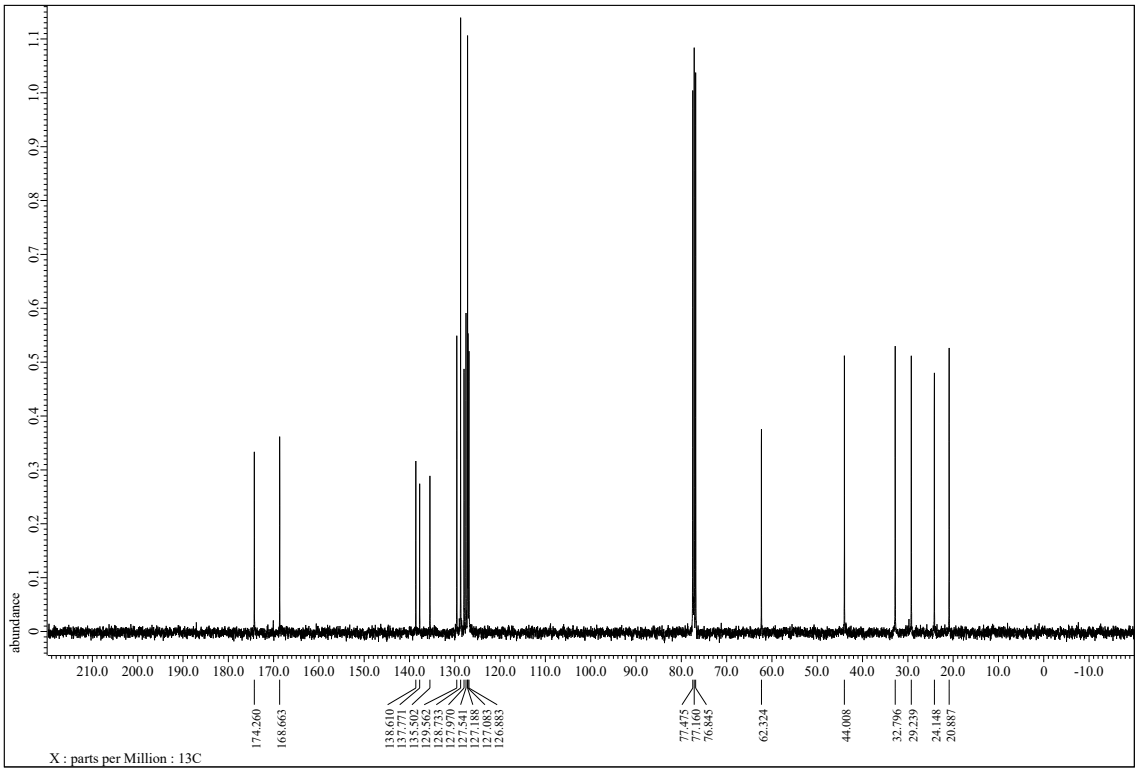

Figure S36. ^{13}C NMR spectrum (101 MHz) of **1l** in $CDCl_3$.

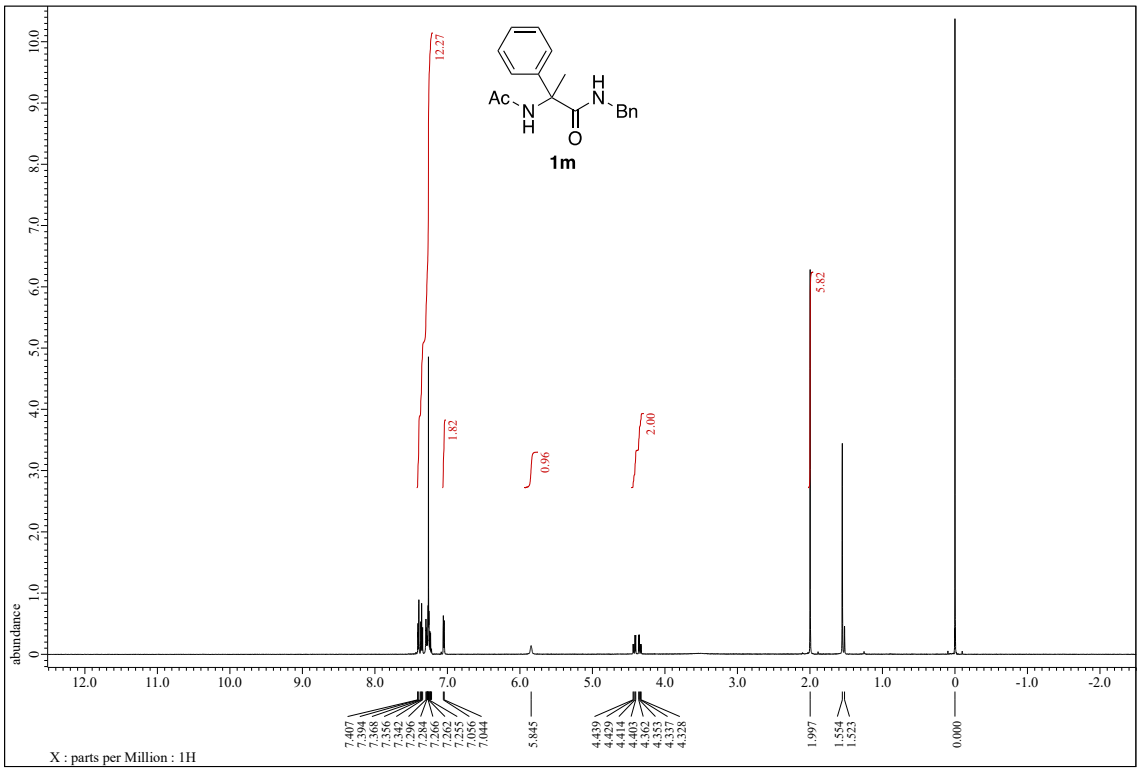

Figure S37. ^{1}H NMR spectrum (600 MHz) of **1m** in $CDCl_3$.

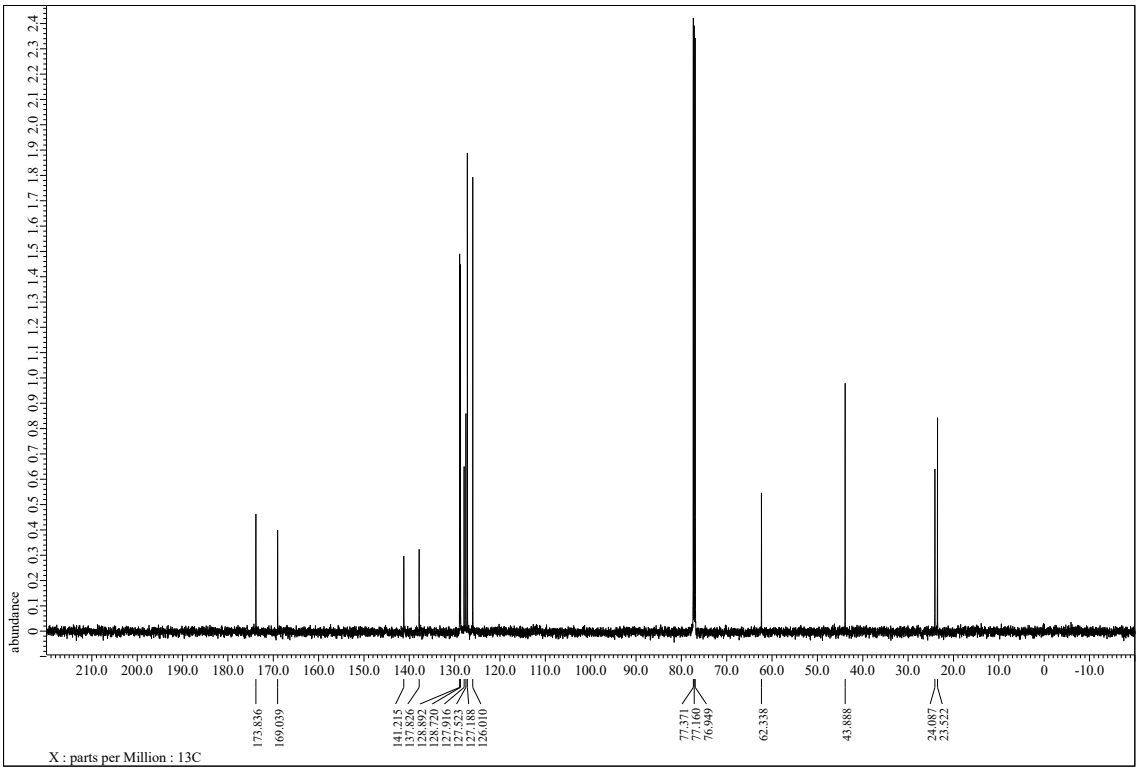

Figure S38. ^{13}C NMR spectrum (151 MHz) of **1m** in $CDCl_3$.

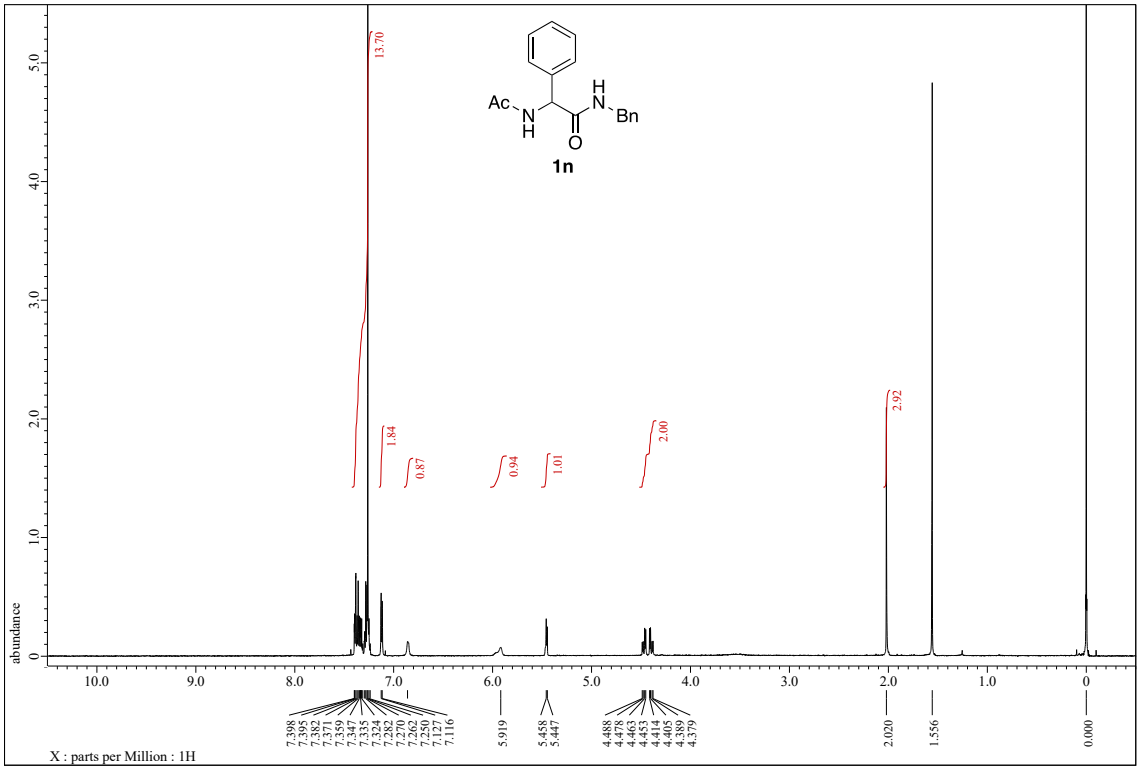

Figure S39. ^{1}H NMR spectrum (600 MHz) of **1n** in $CDCl_3$.

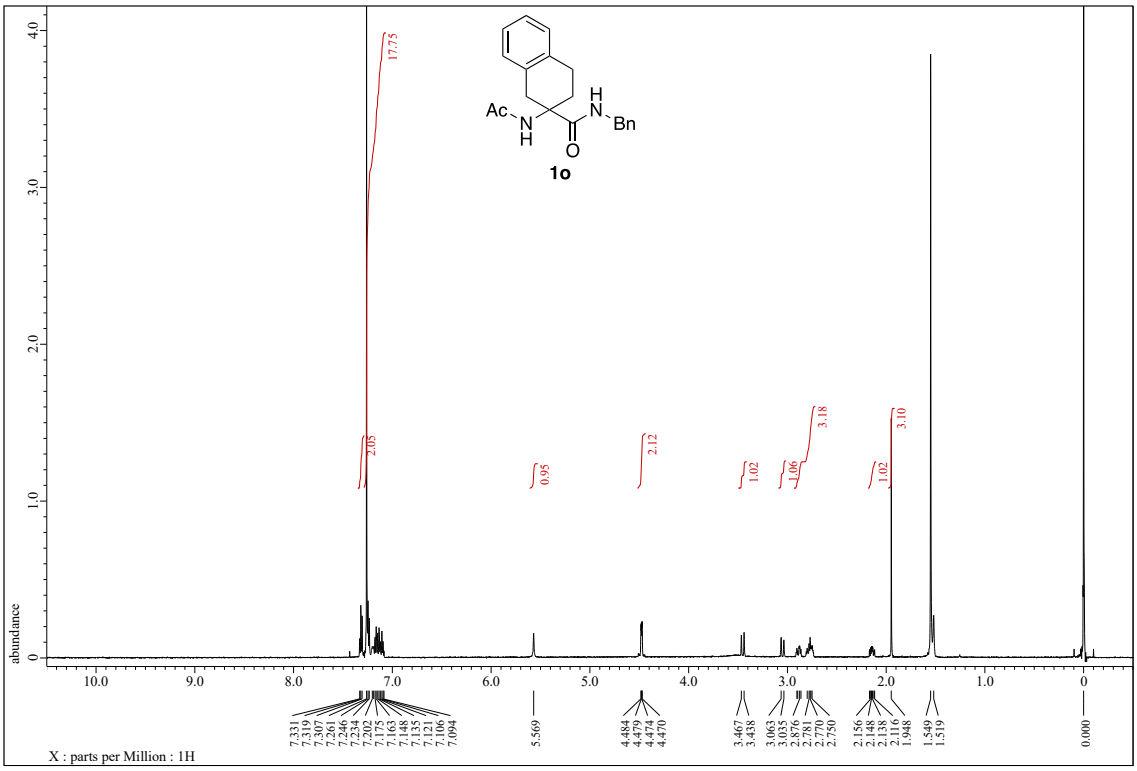

Figure S40. ^{1}H NMR spectrum (600 MHz) of **1o** in $CDCl_3$.

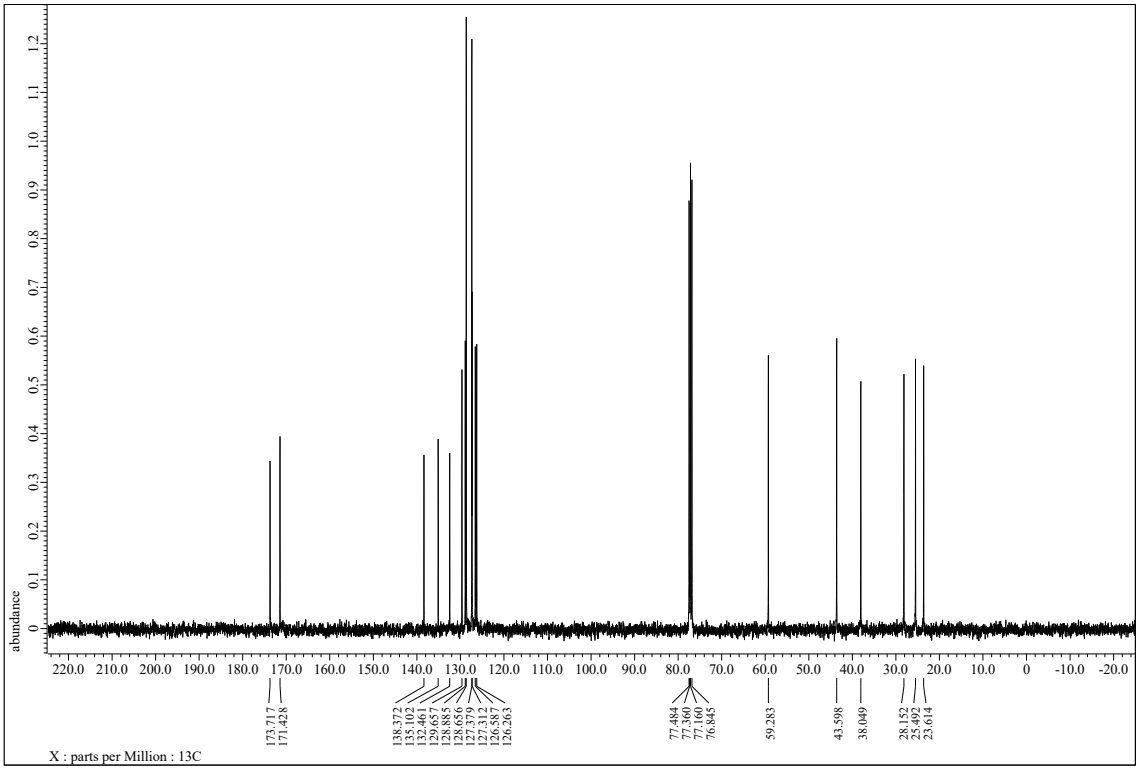

Figure S41. ^{13}C NMR spectrum (101 MHz) of **1o** in $CDCl_3$.

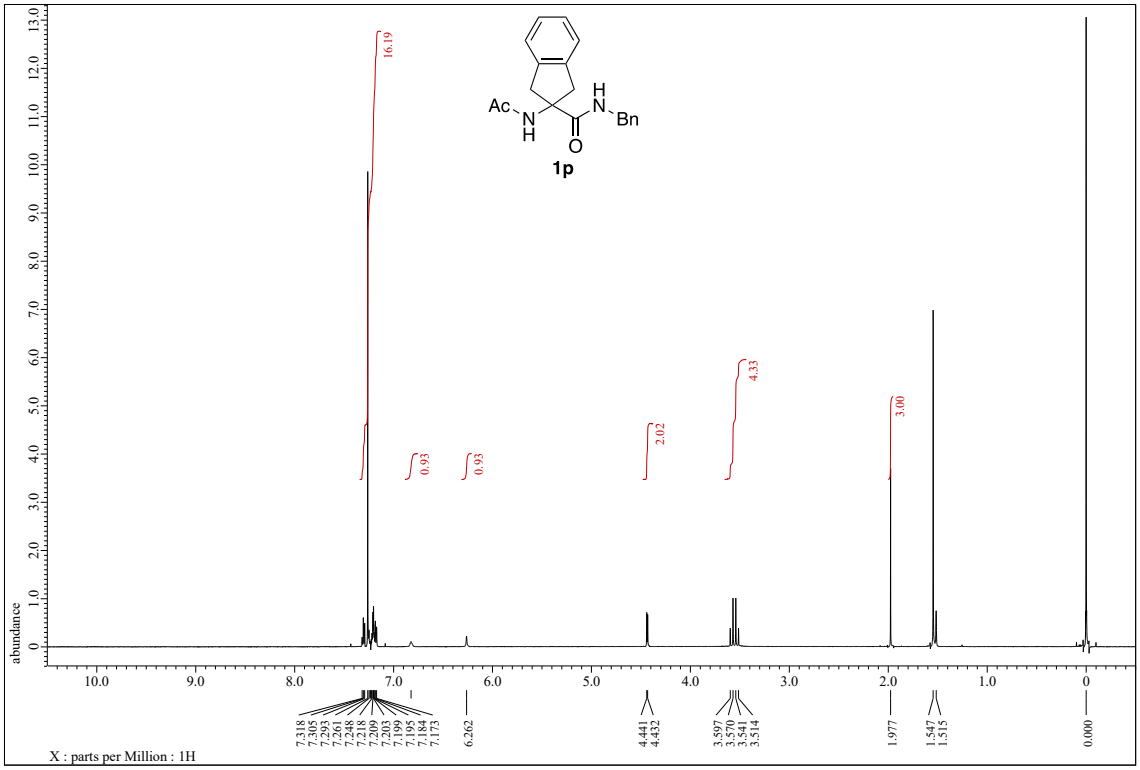

Figure S42. ^{1}H NMR spectrum (600 MHz) of **1p** in $CDCl_3$.

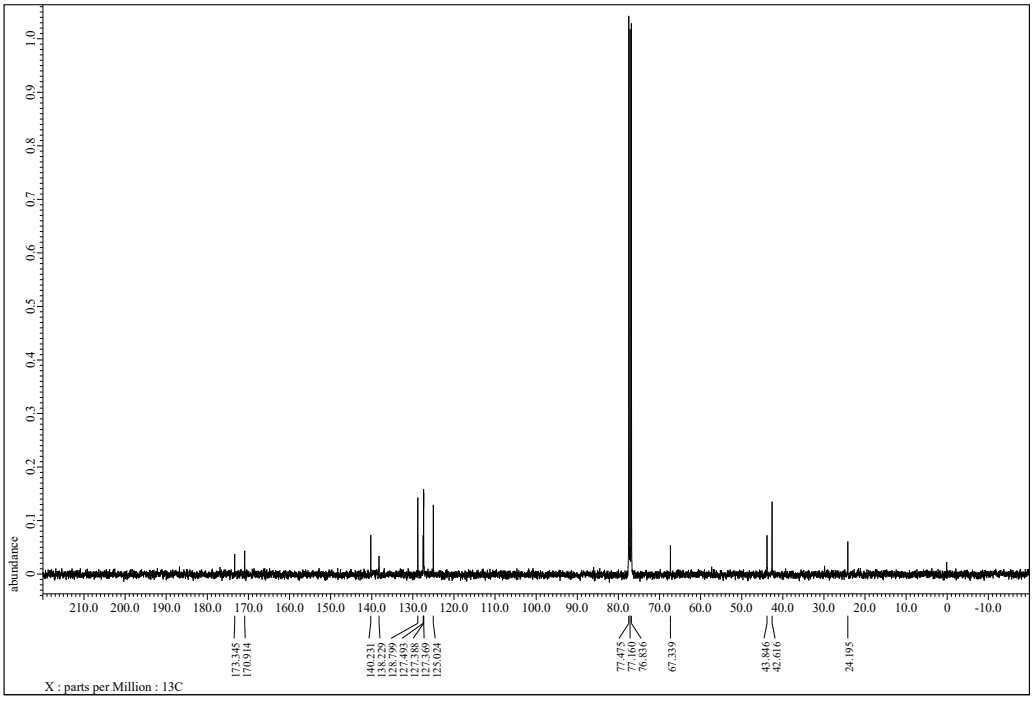

Figure S43. ^{13}C NMR spectrum (101 MHz) of **1p** in $CDCl_3$.

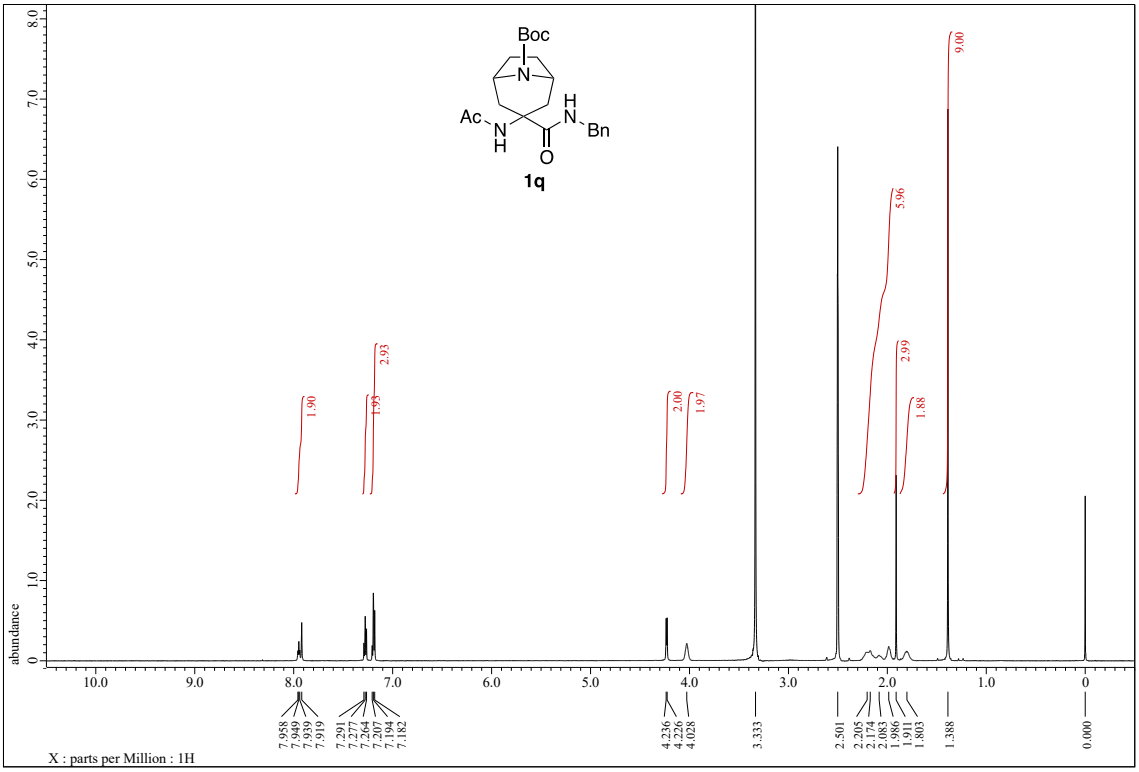

Figure S44. ^{1}H NMR spectrum (600 MHz) of **1q** in DMSO-d_6.

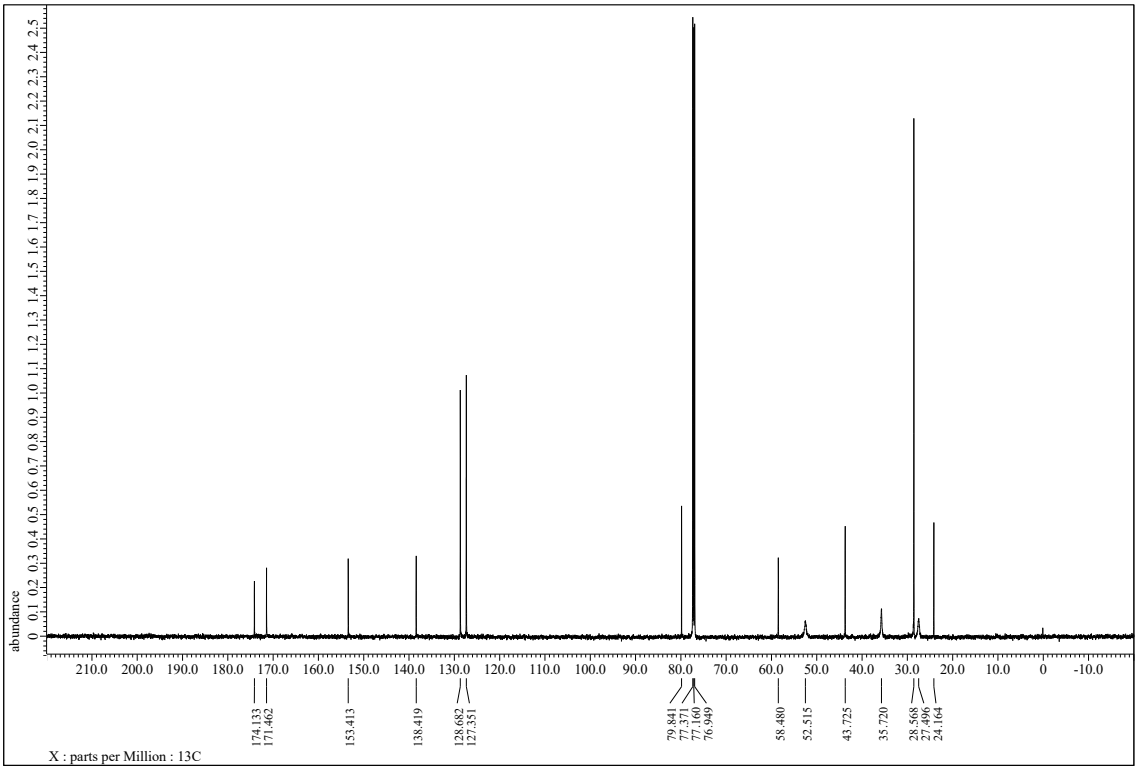

Figure S45. ^{13}C NMR spectrum (151 MHz) of **1q** in $CDCl_3$.

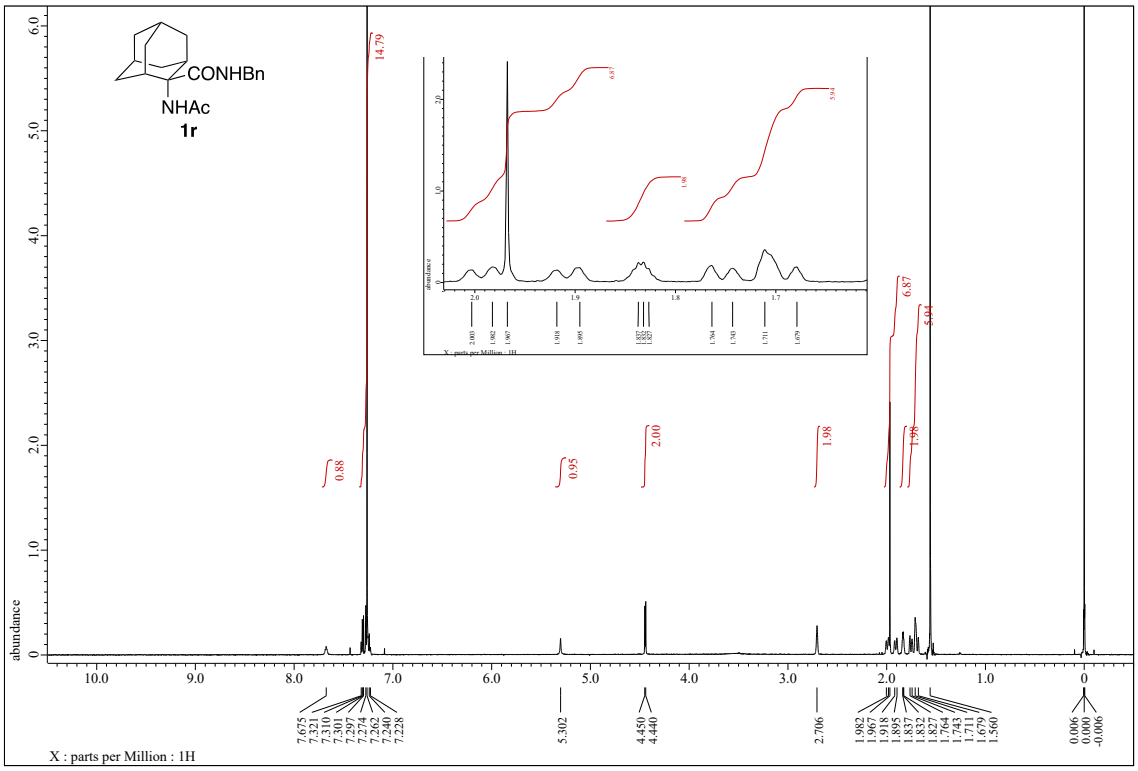

Figure S46. ^{1}H NMR spectrum (600 MHz) of **1r** in $CDCl_3$.

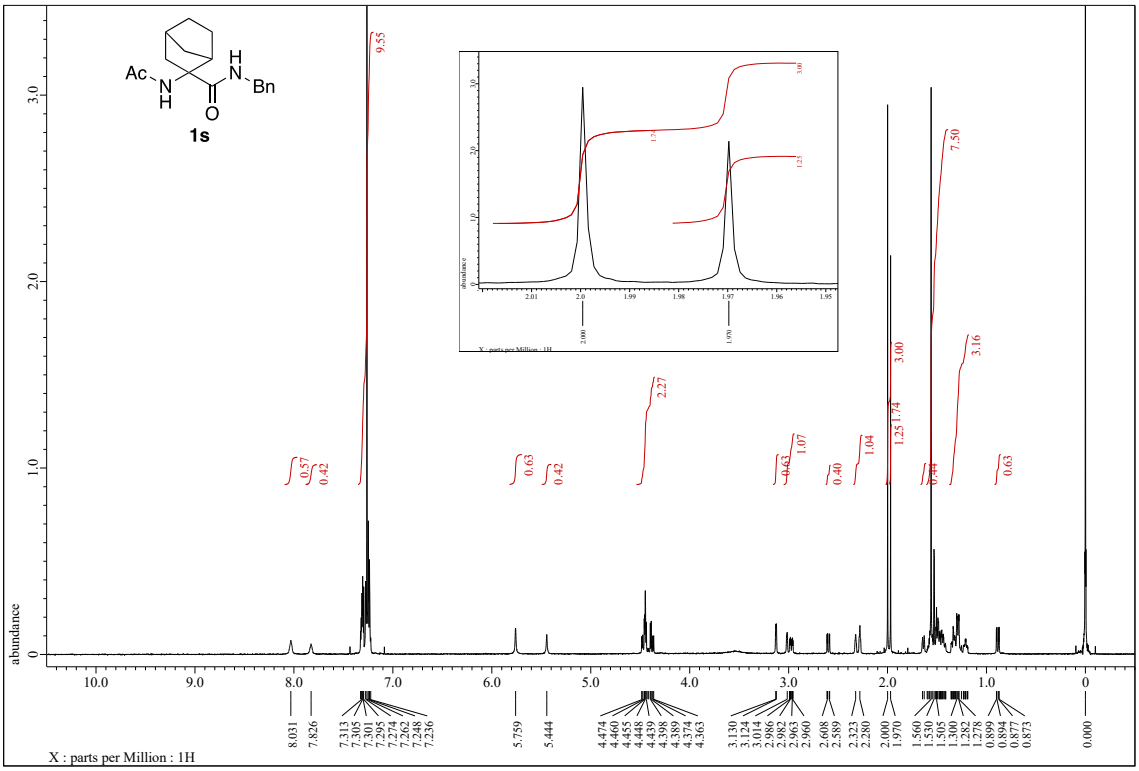

Figure S47. ^{1}H NMR spectrum (600 MHz) of **1s** in $CDCl_3$.

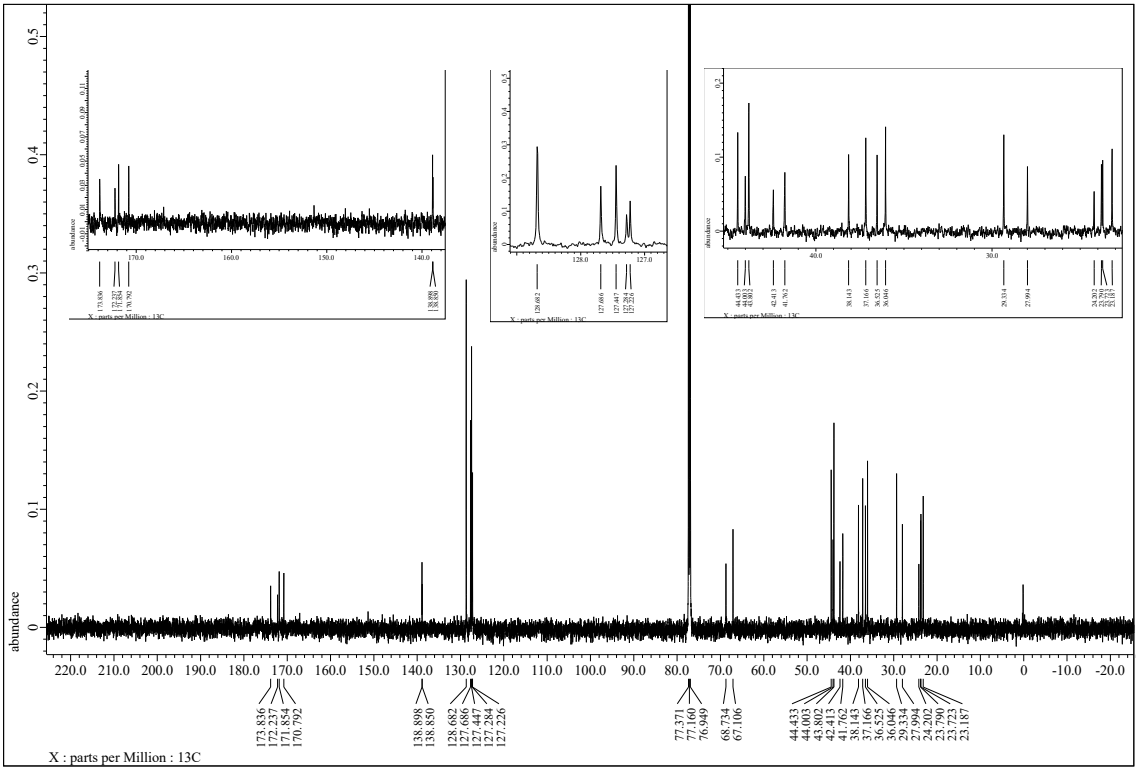

Figure S48. ^{13}C NMR spectrum (151 MHz) of **1s** in $CDCl_3$.

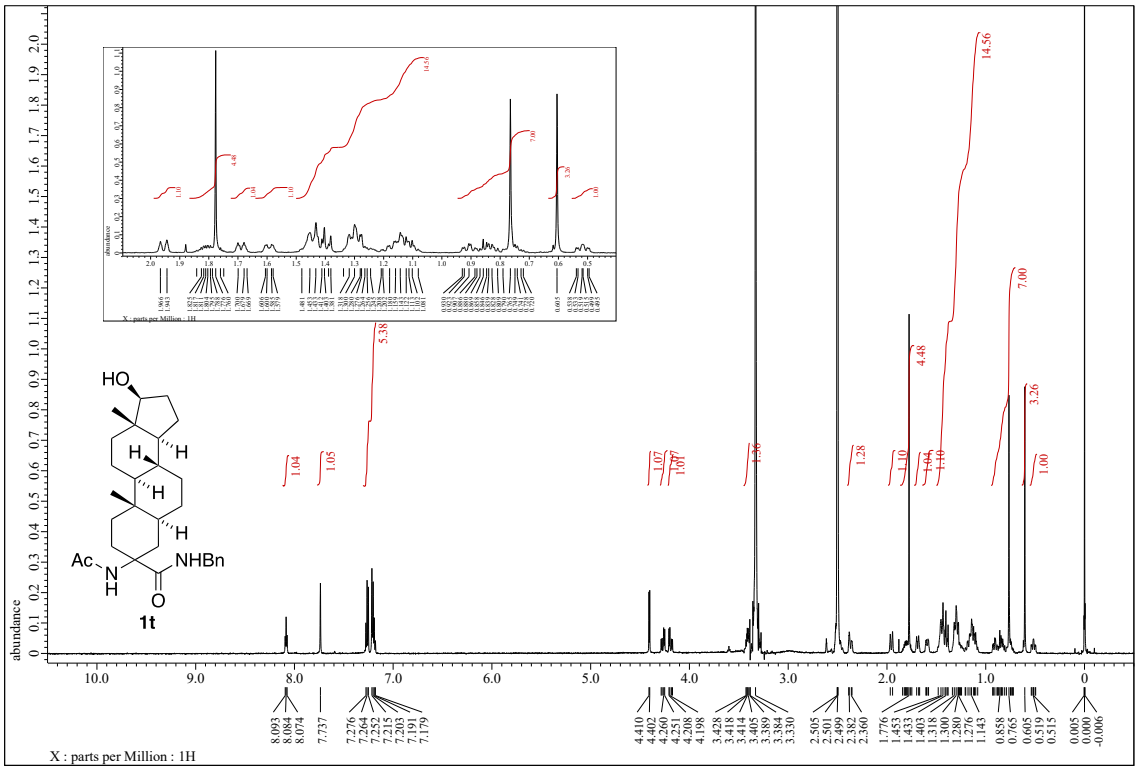

Figure S49. ^{1}H NMR spectrum (600 MHz) of **1t** in DMSO-d_6.

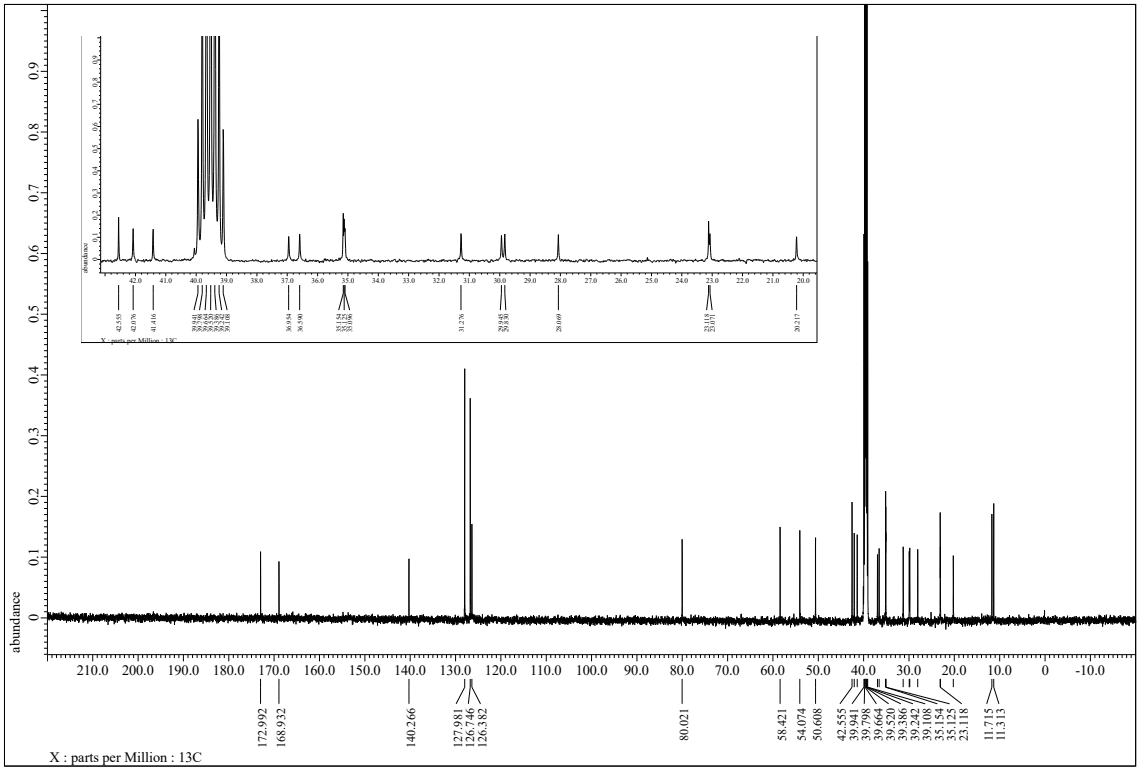

Figure S50. ^{13}C NMR spectrum (151 MHz) of **1t** in DMSO-d_6.

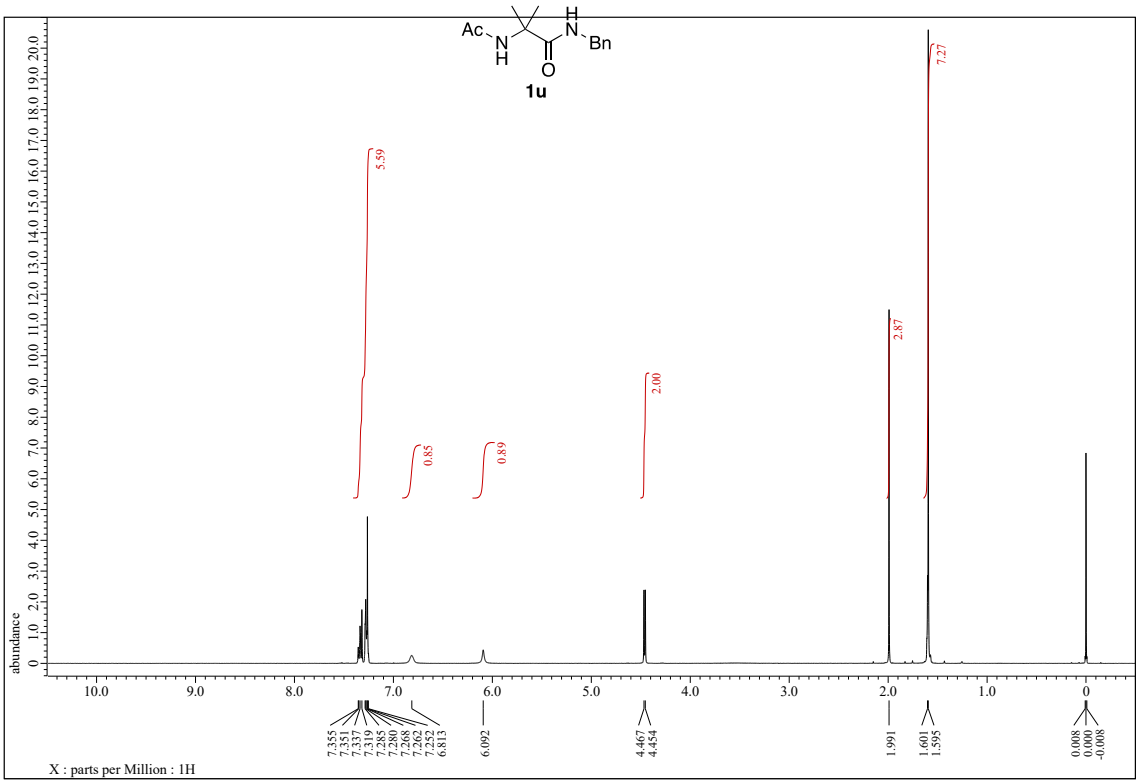

Figure S51. ^{1}H NMR spectrum (400 MHz) of **1u** in $CDCl_3$.

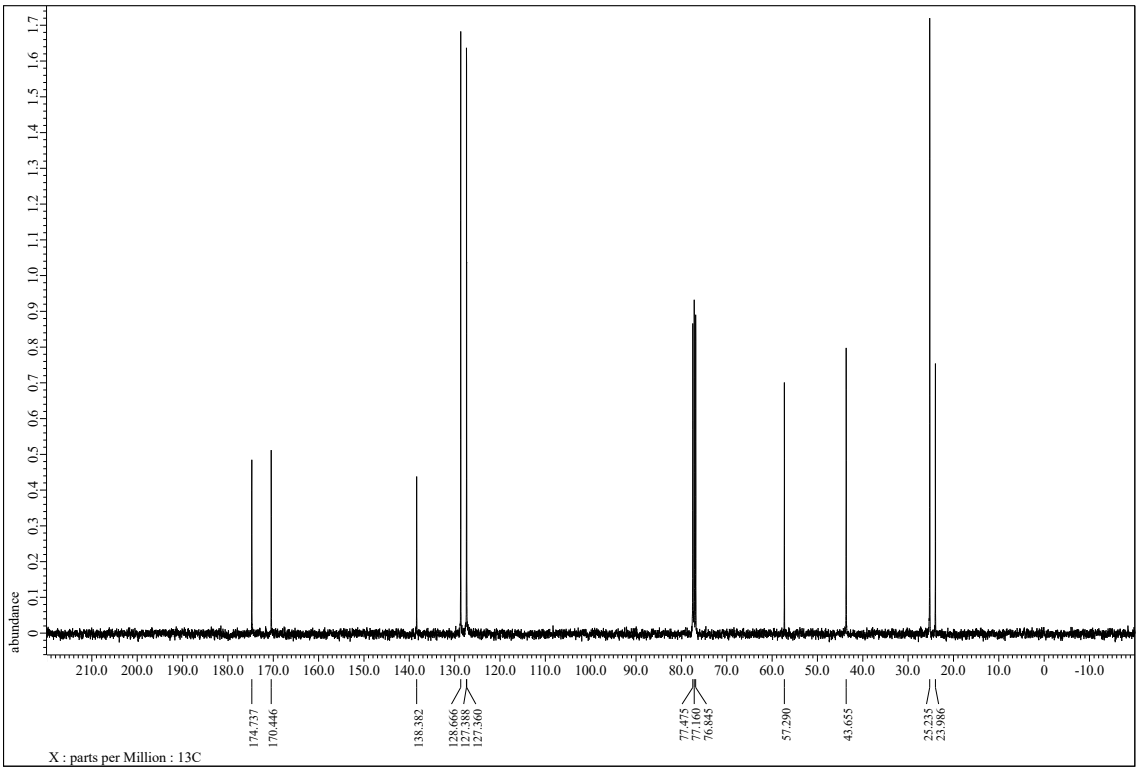

Figure S52. ^{13}C NMR spectrum (101 MHz) of **1u** in $CDCl_3$.

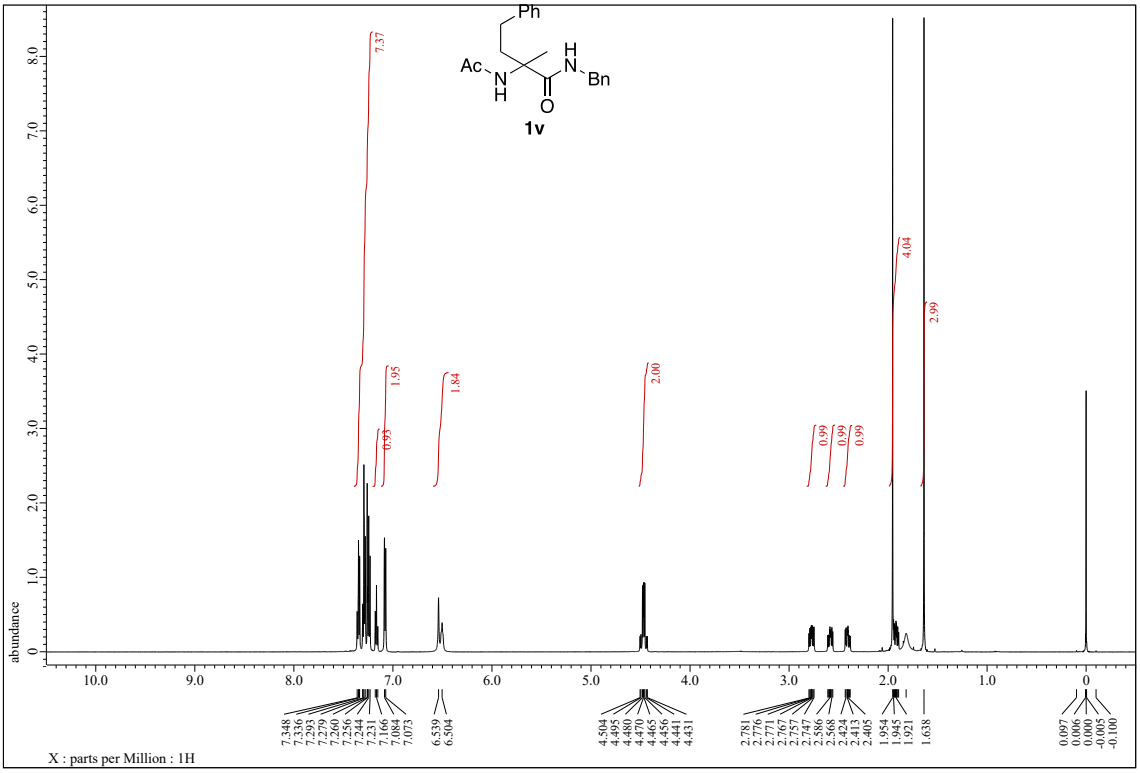

Figure S53. ^{1}H NMR spectrum (600 MHz) of **1v** in $CDCl_3$.

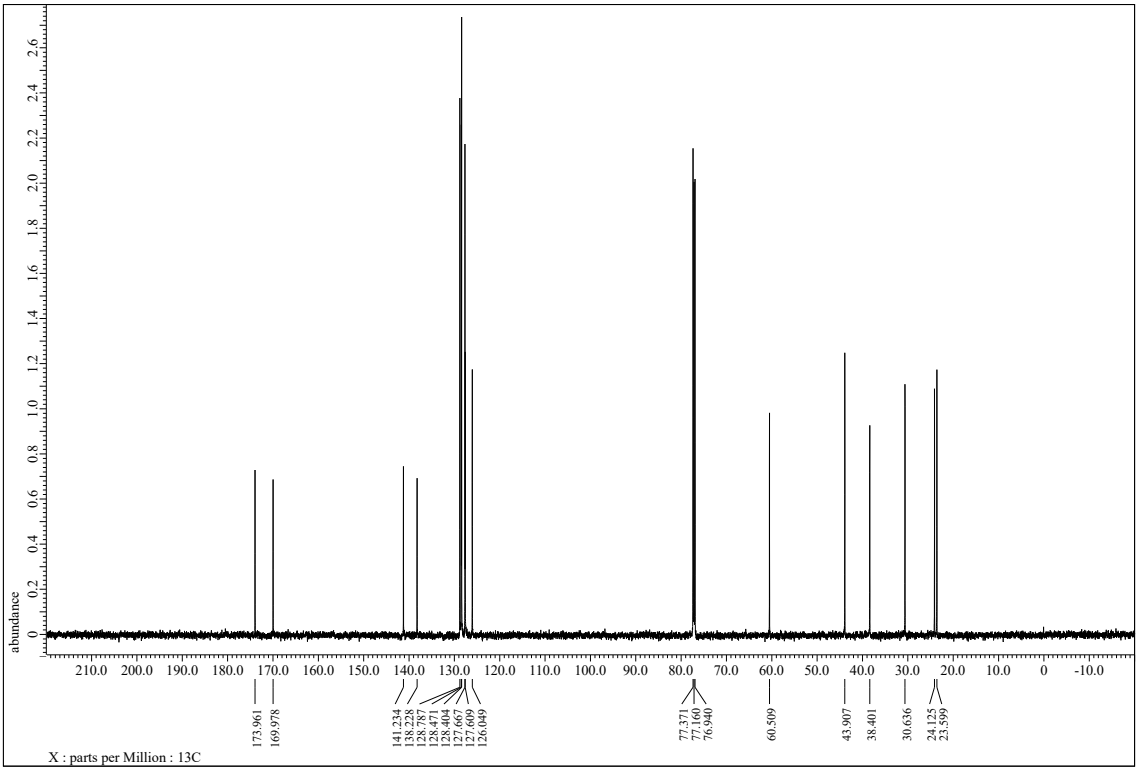

Figure S54. ^{13}C NMR spectrum (151 MHz) of **1v** in $CDCl_3$.

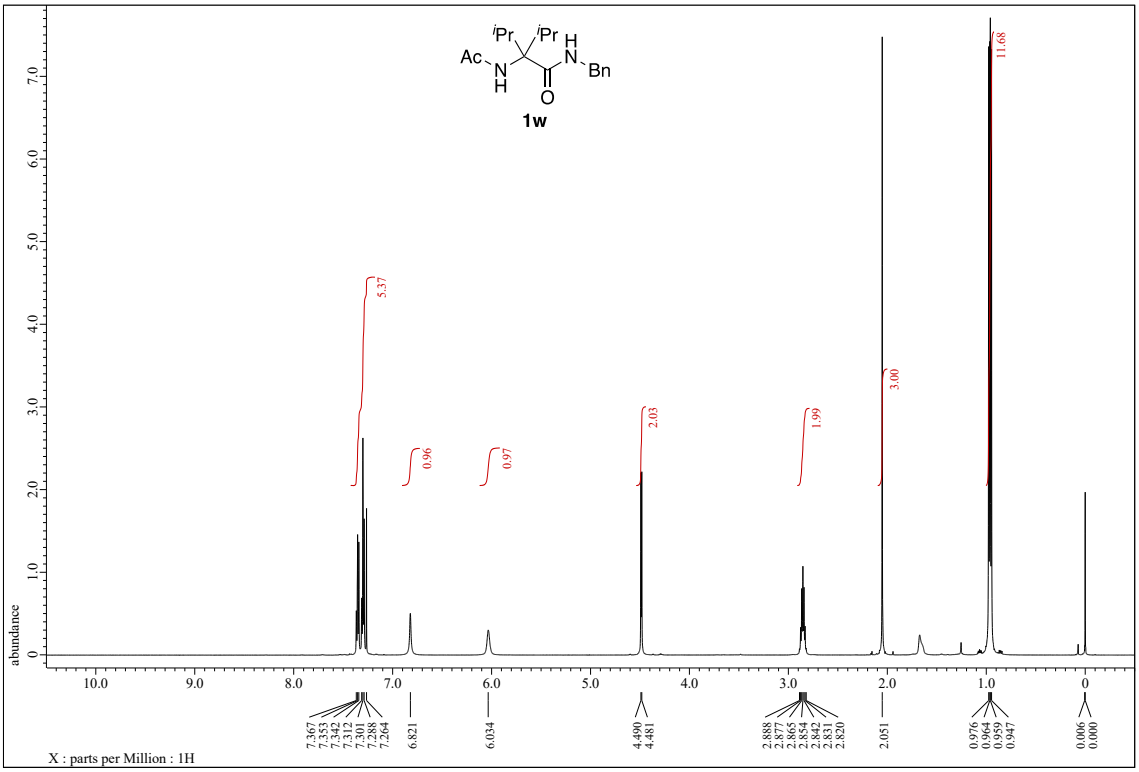

Figure S55. ^{1}H NMR spectrum (600 MHz) of **1w** in $CDCl_3$.

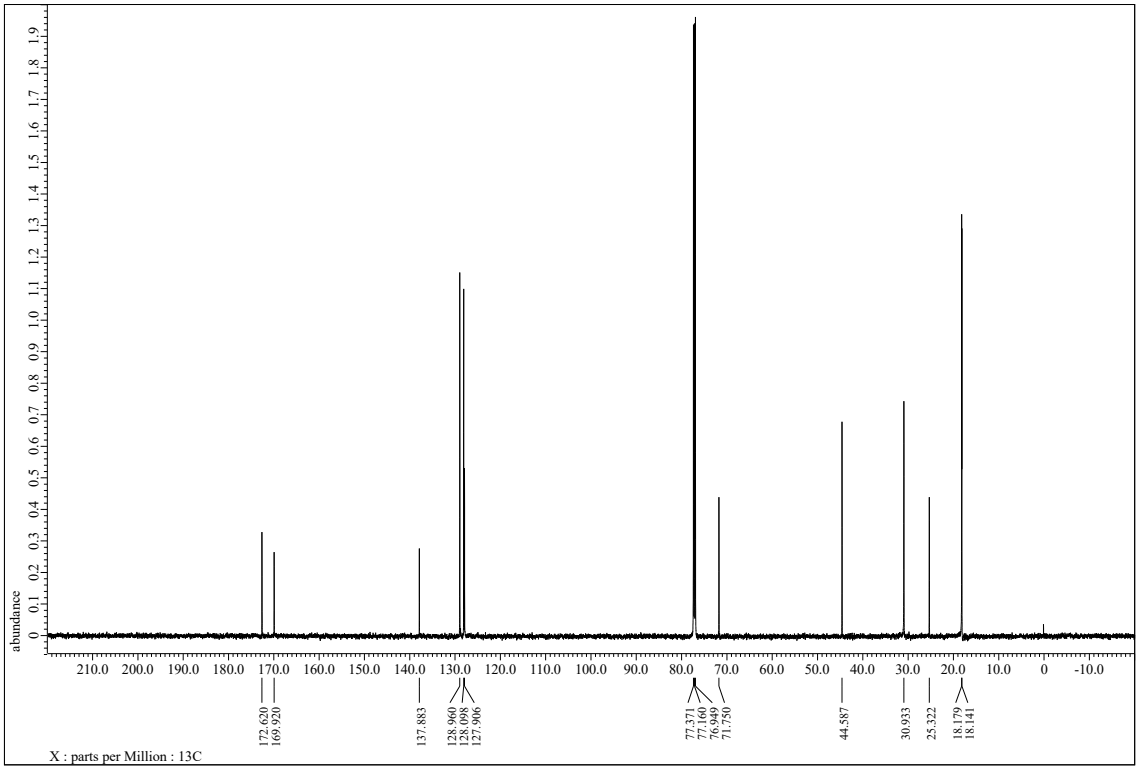

Figure S56. ^{13}C NMR spectrum (151 MHz) of **1w** in $CDCl_3$.

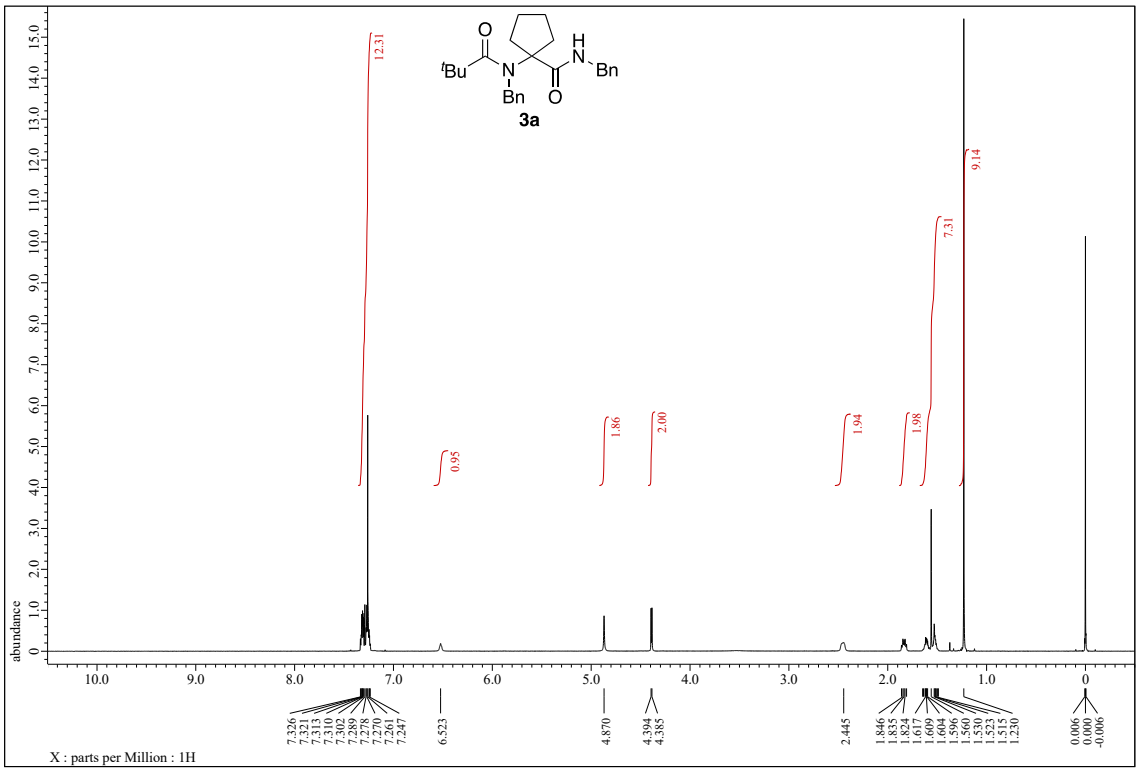

Figure S57. ^{1}H NMR spectrum (600 MHz) of *N*-benzyl-*N*-pivaroyl-Ac$_5$c-NHBn (**3a**) in $CDCl_3$.

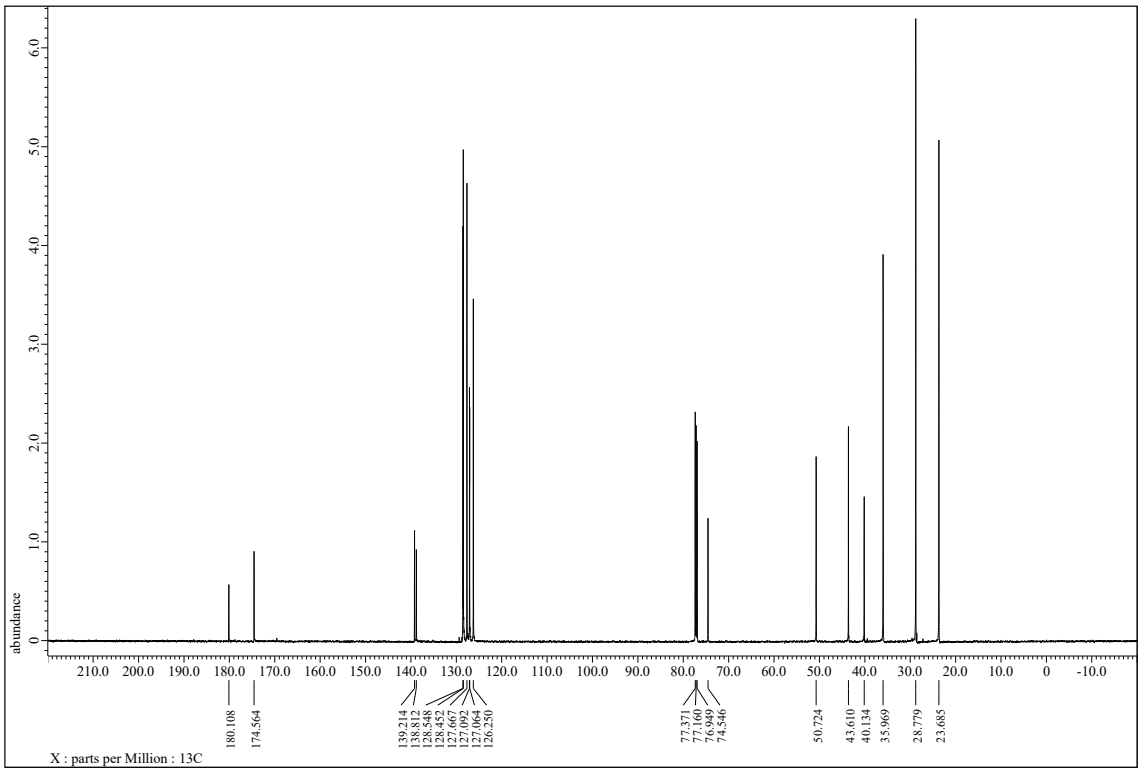

Figure S58. ^{13}C NMR spectrum (151 MHz) of *N*-benzyl-*N*-pivaroyl-Ac$_5$c-NHBn (**3a**) in $CDCl_3$.

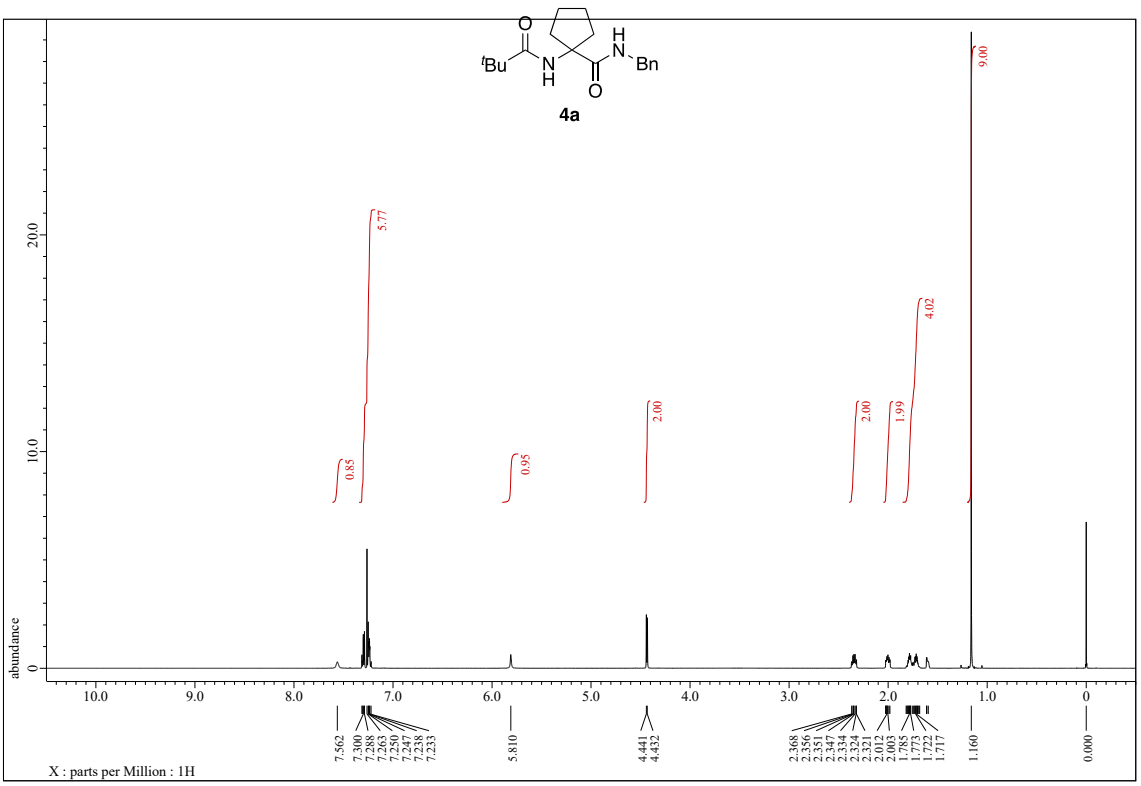

Figure S59. ^{1}H NMR spectrum (600 MHz) of *N*-pivaroyl-Ac$_5$c-NH-Bn (**4a**) in $CDCl_3$.

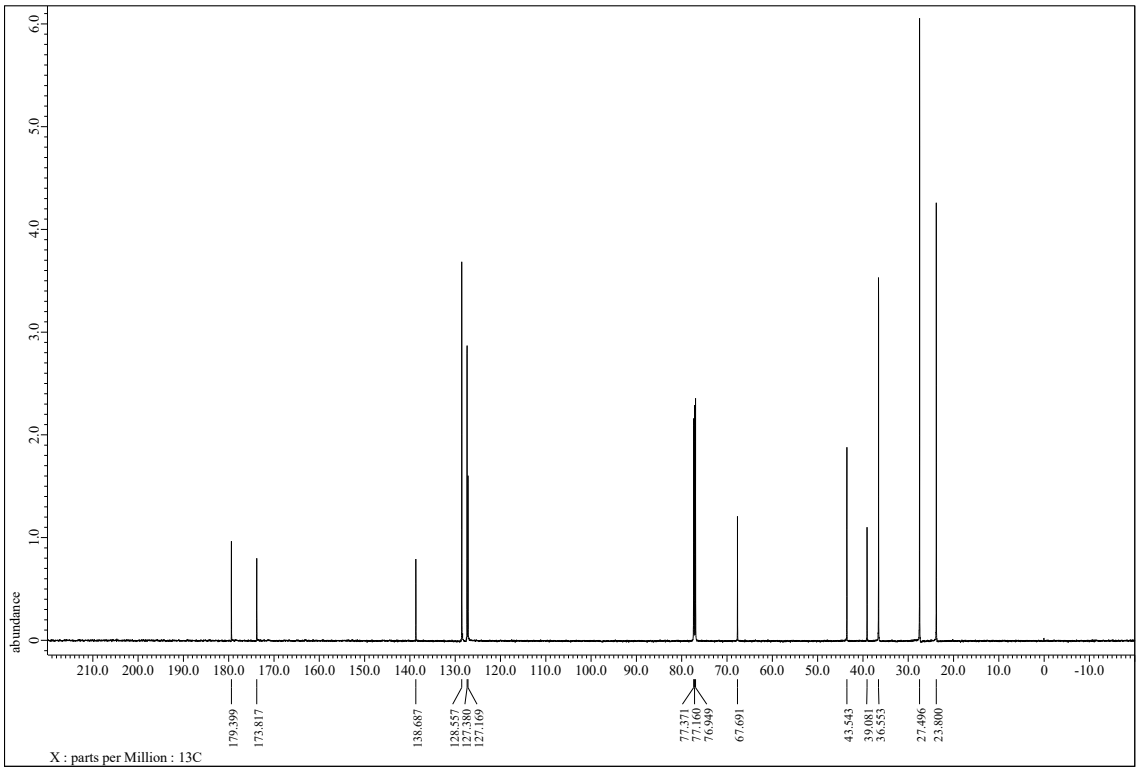

Figure S60. ^{13}C NMR spectrum (151 MHz) of *N*-pivaroyl-Ac$_5$c-NH-Bn (**4a**) in $CDCl_3$.

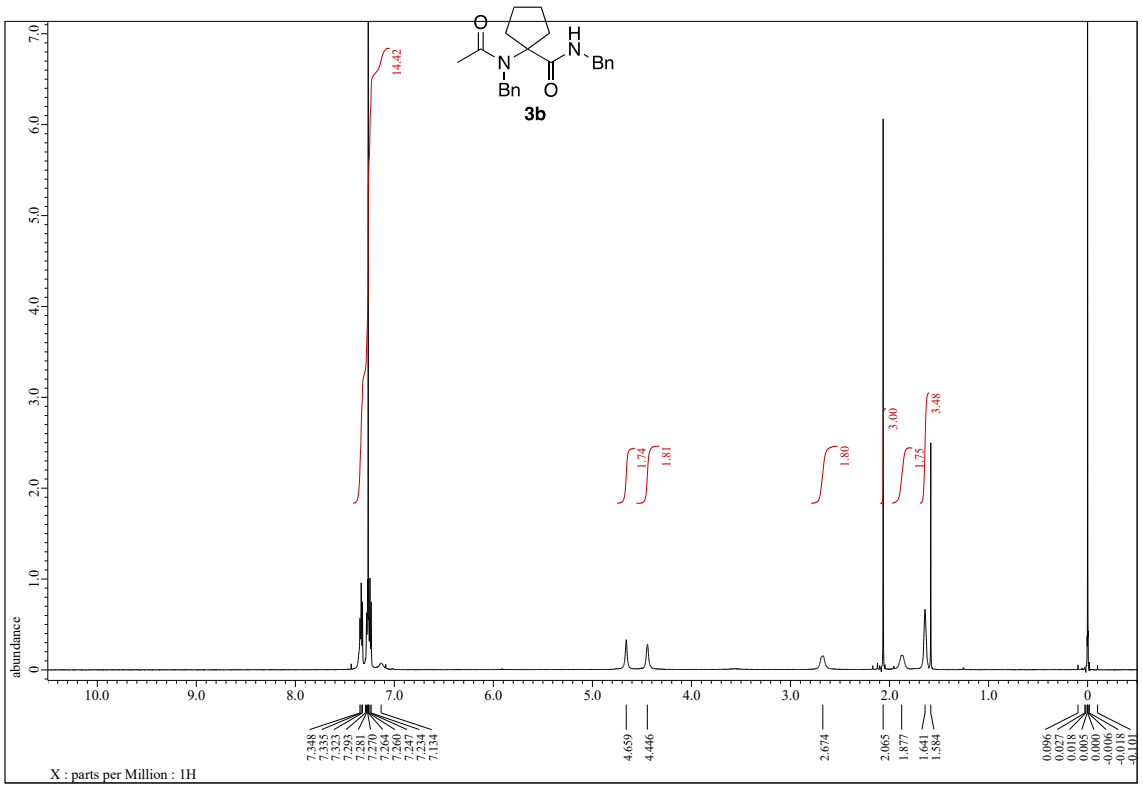

Figure S61. ^{1}H NMR spectrum (600 MHz) of *N*-acetyl-*N*-benzyl-Ac$_5$c-NH-Bn (**3b**) in $CDCl_3$.

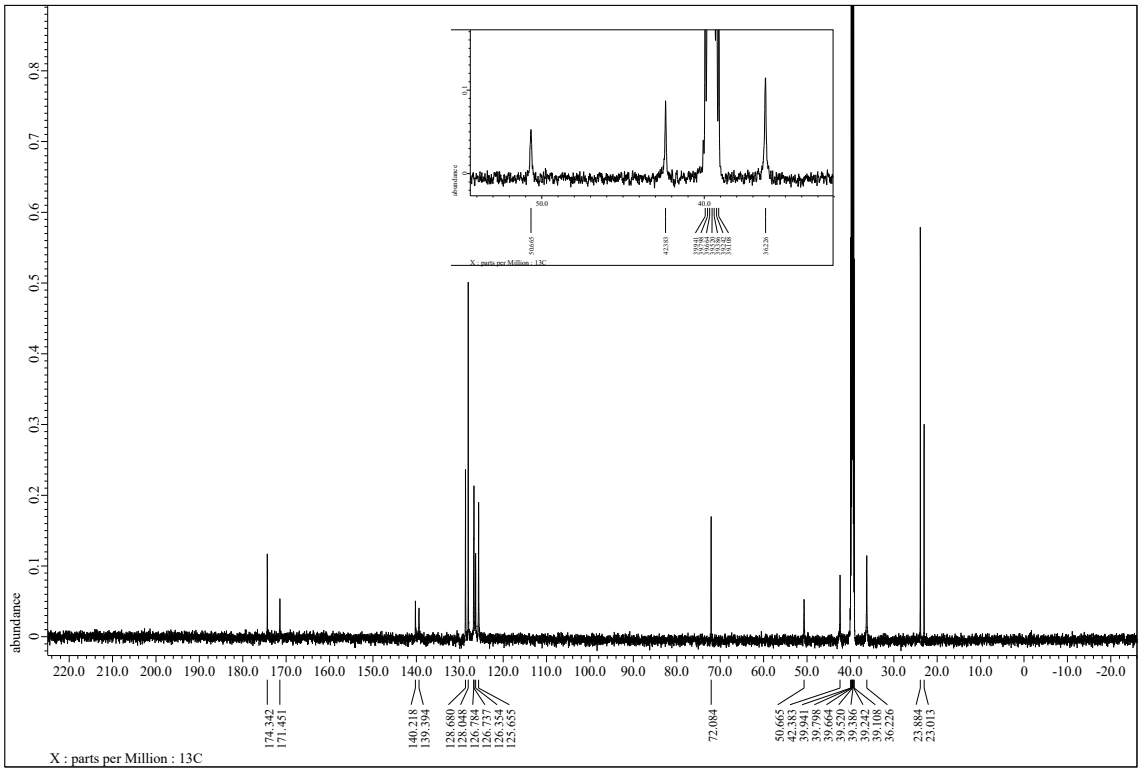

Figure S62. ^{13}C NMR spectrum (151 MHz) of *N*-acetyl-*N*-benzyl-Ac$_5$c-NH-Bn (**3b**) in DMSO-d_6.

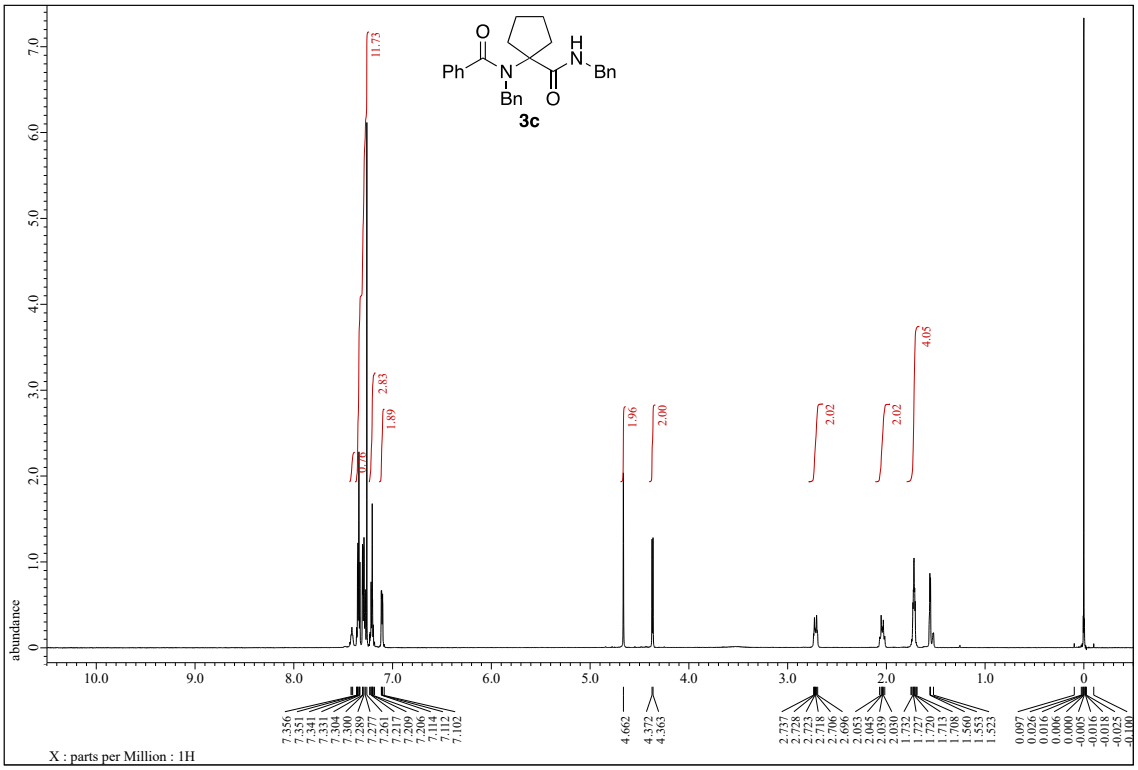

Figure S63. ^{1}H NMR spectrum (600 MHz) of *N*-benzoyl-*N*-benzyl-Ac$_5$c-NH-Bn (**3c**) in $CDCl_3$.

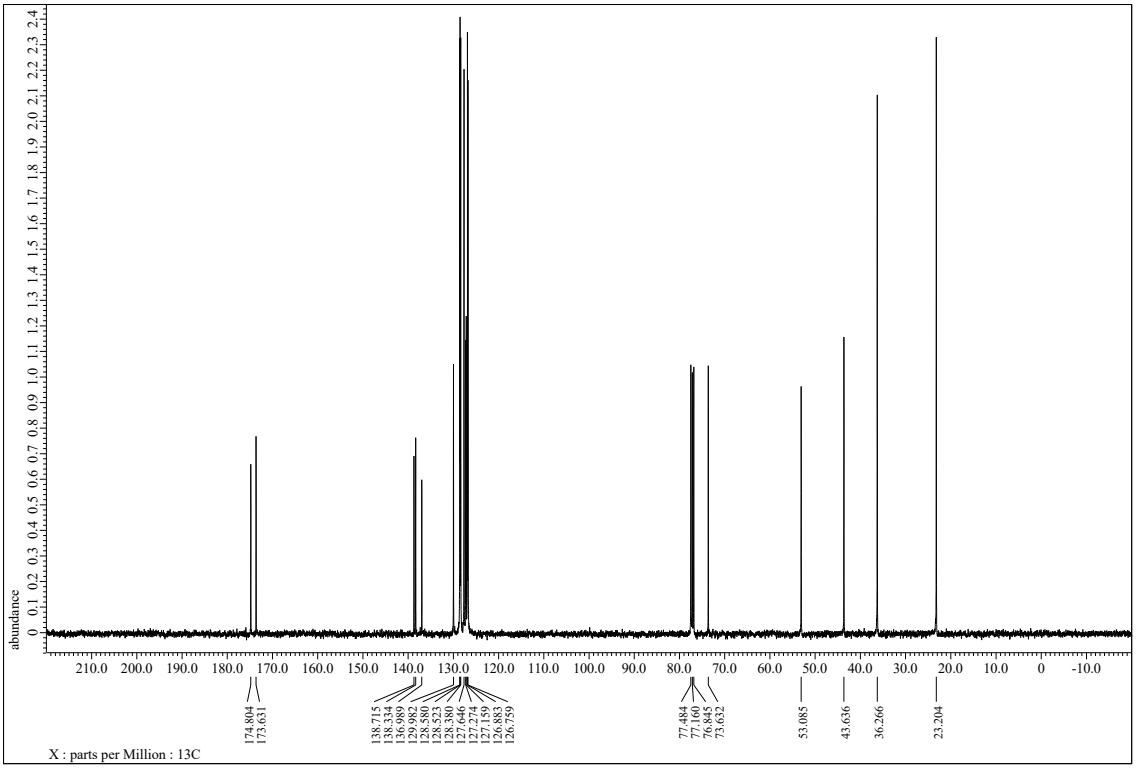

Figure S64. ^{13}C NMR spectrum (101 MHz) of *N*-benzoyl-*N*-benzyl-Ac$_5$c-NH-Bn (**3c**) in $CDCl_3$.

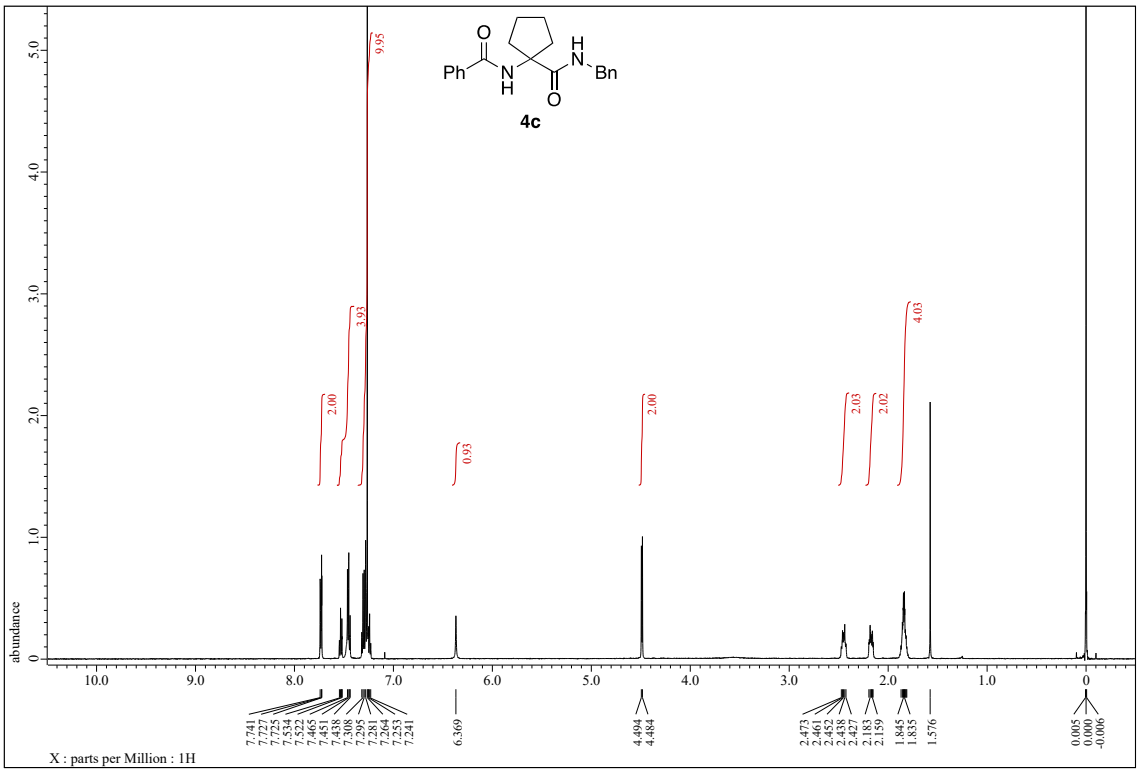

Figure S65. ^{1}H NMR spectrum (600 MHz) of *N*-benzoyl-Ac$_5$c-NH-Bn (**4c**) in $CDCl_3$.

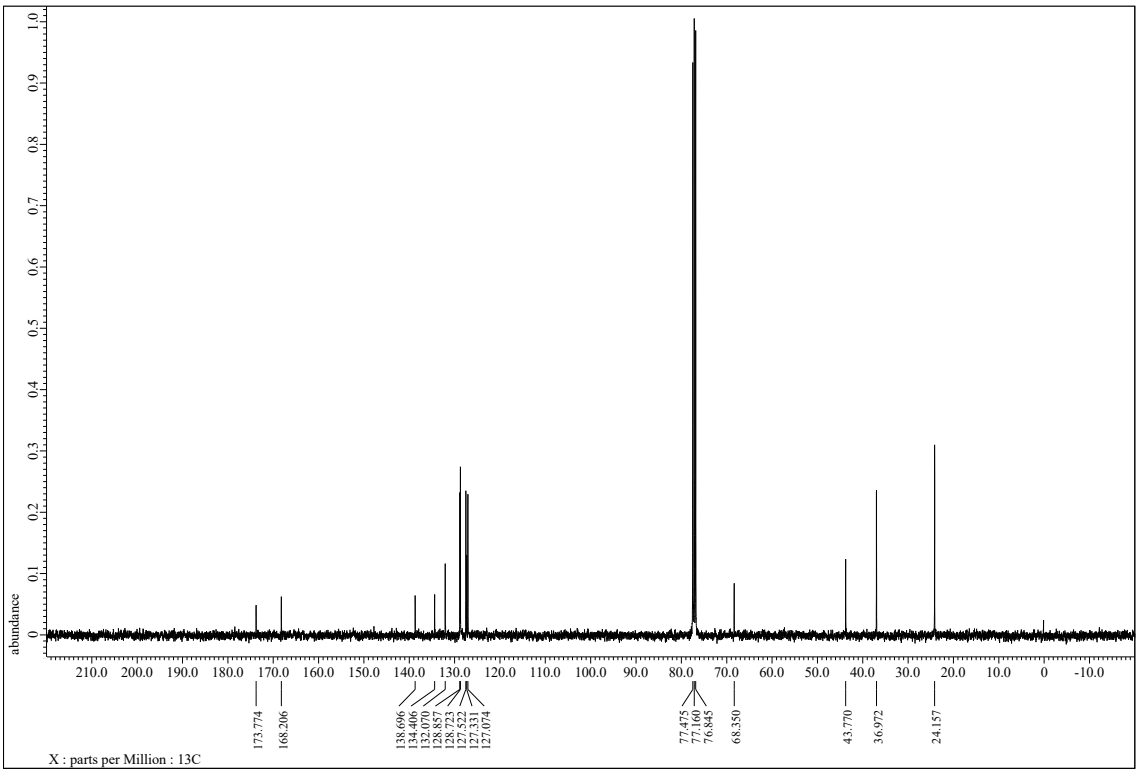

Figure S66. ^{13}C NMR spectrum (101 MHz) of *N*-benzoyl-Ac$_5$c-NH-Bn (**4c**) in $CDCl_3$.

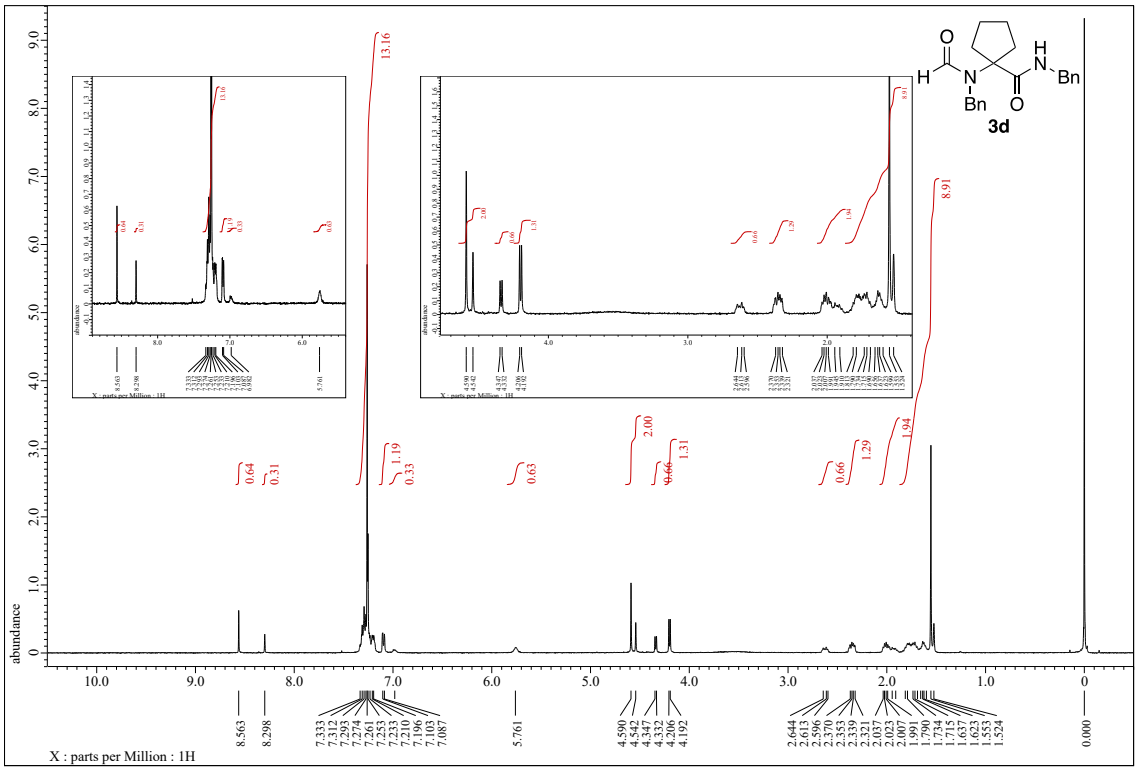

Figure S67. ^{1}H NMR spectrum (400 MHz) of *N*-benzyl-*N*-formyl Ac$_5$c NH-Bn (**3d**) in $CDCl_3$.

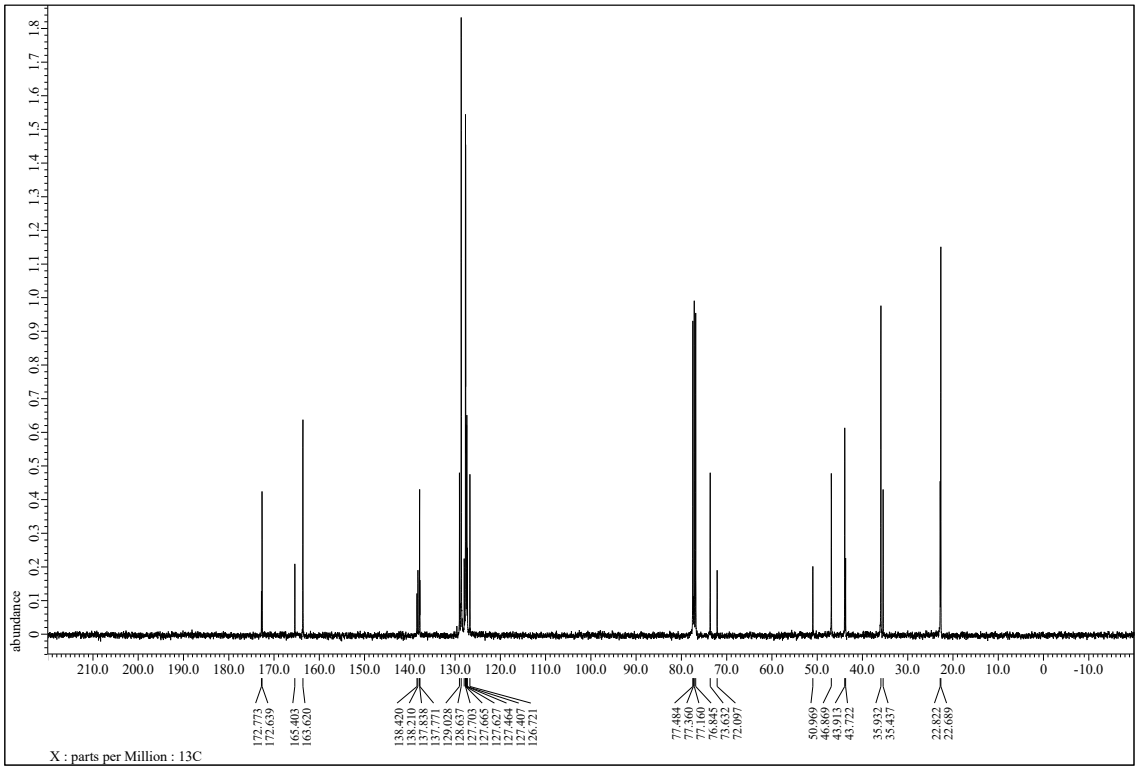

Figure S68. ^{13}C NMR spectrum (101 MHz) of *N*-benzyl-*N*-formyl-Ac$_5$c-NH-Bn (**3d**) in $CDCl_3$.

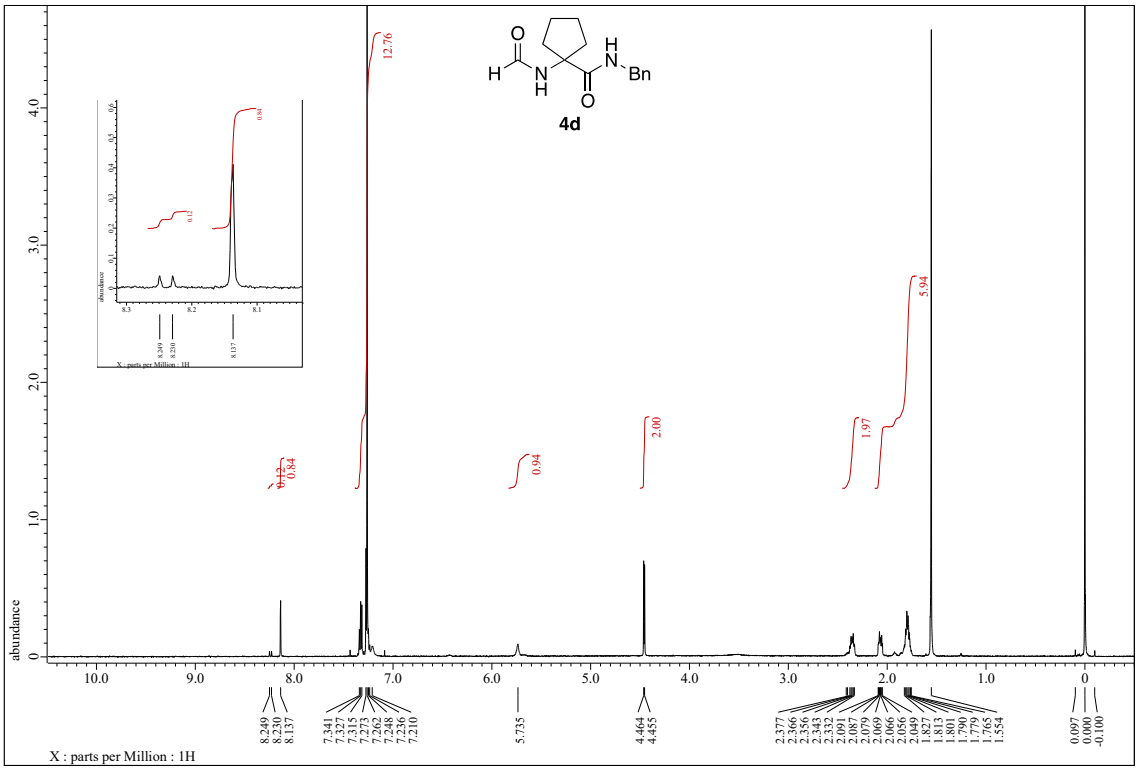

Figure S69. ^{1}H NMR spectrum (600 MHz) of *N*-formyl-Ac$_5$c-NH-Bn (**4d**) in $CDCl_3$.

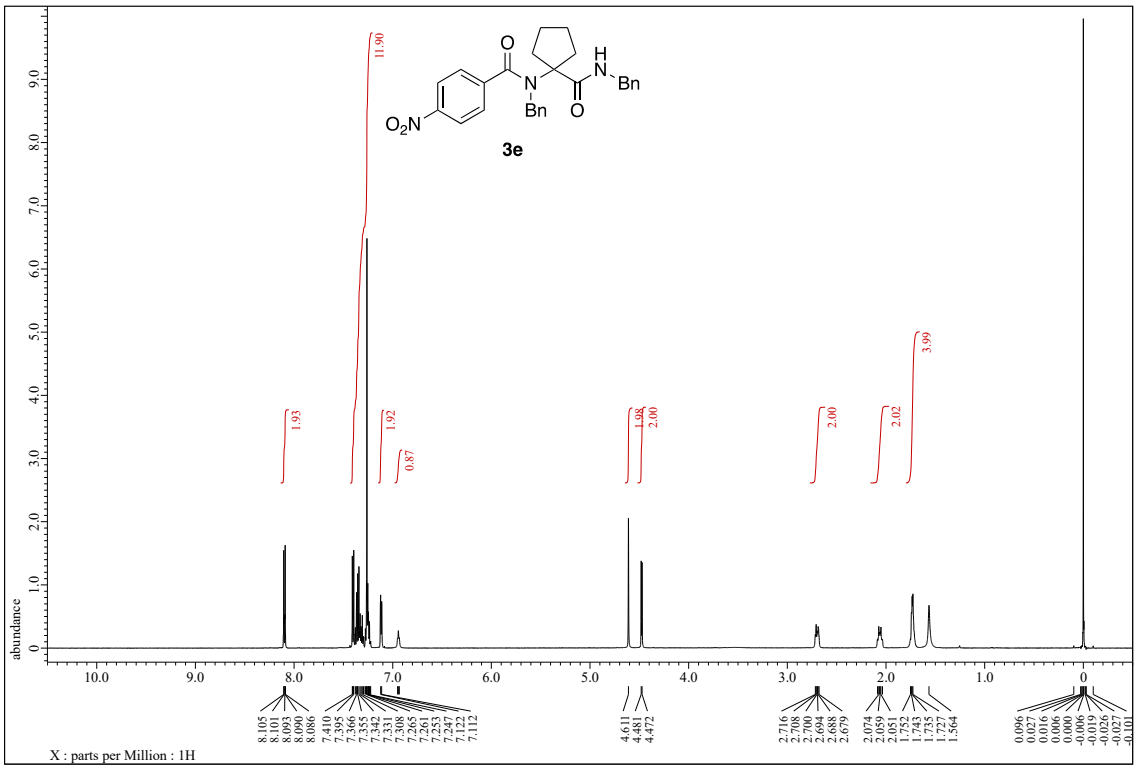

Figure S70. ^{1}H NMR spectrum (600 MHz) of *N*-benzyl-*N*-*p*-nitrobenzoyl-Ac$_5$c-NHBn (**3e**) in $CDCl_3$.

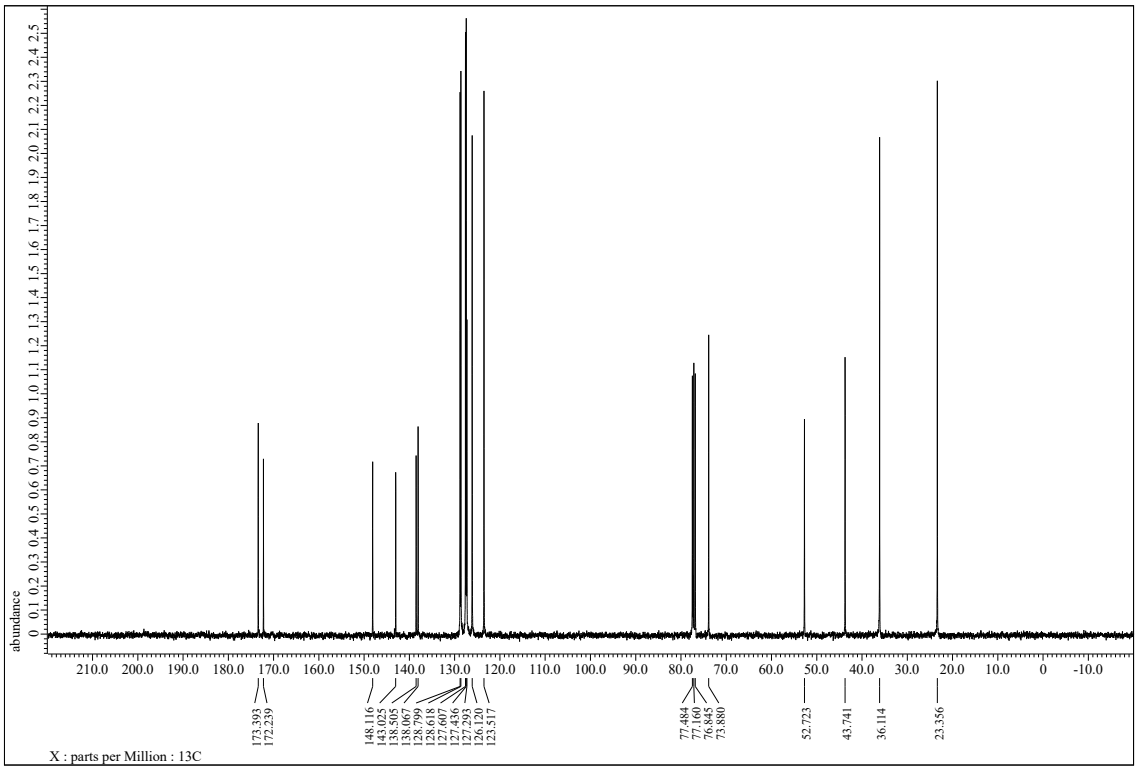

Figure S71. ^{13}C NMR spectrum (101 MHz) of *N*-benzyl-*N*-*p*-nitrobenzoyl-Ac$_5$c-NHBn (**3e**) in $CDCl_3$.

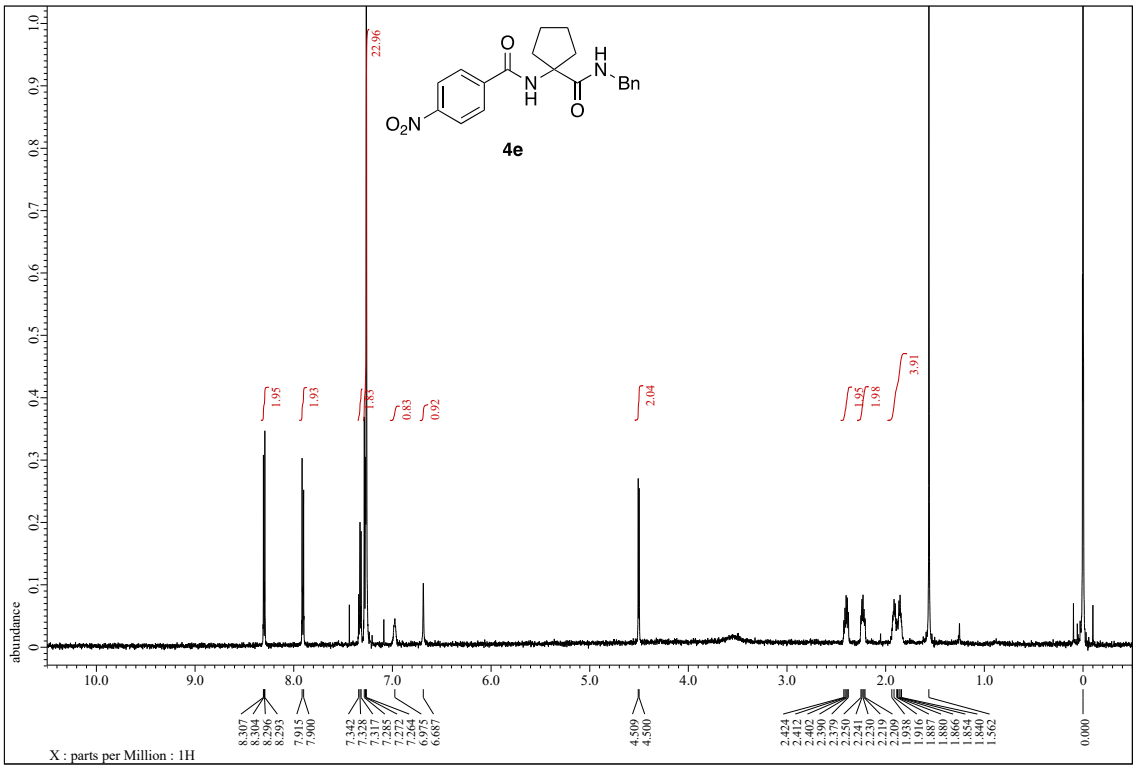

Figure S72. ^{1}H NMR spectrum (600 MHz) of *N*-*p*-nitrobenzoyl-Ac$_5$c-NH-Bn (**4e**) in $CDCl_3$.

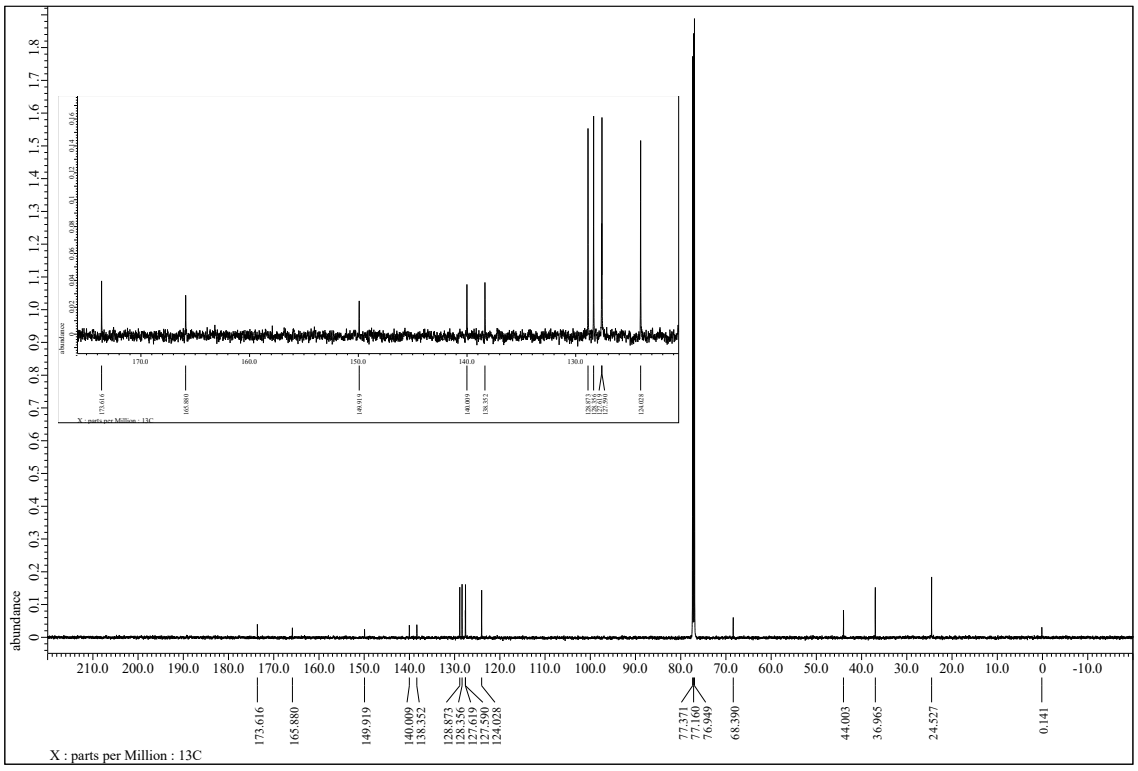

Figure S73. ^{13}C NMR spectrum (151 MHz) of *N*-*p*-nitrobenzoyl-Ac$_5$c-NH-Bn (**4e**) in $CDCl_3$.

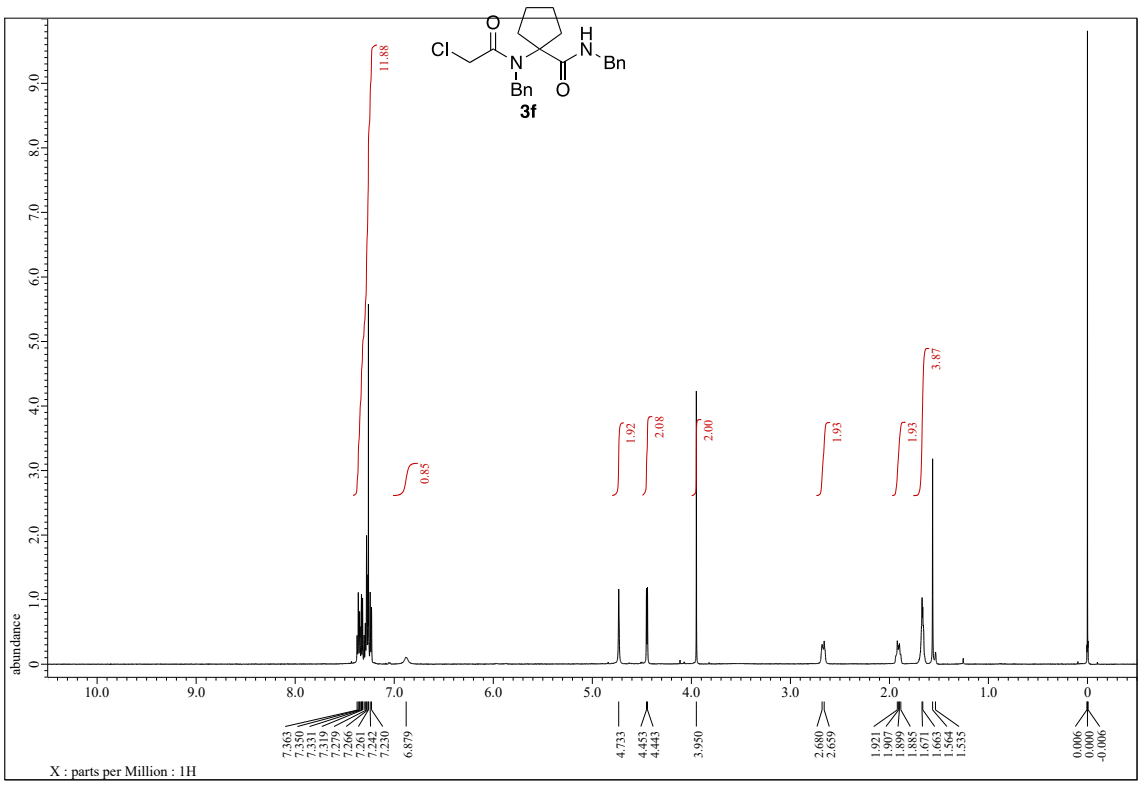

Figure S74. ^{1}H NMR spectrum (600 MHz) of *N*-benzyl-*N*-chloroacetyl-Ac$_5$c-NH-Bn (**3f**) in $CDCl_3$.

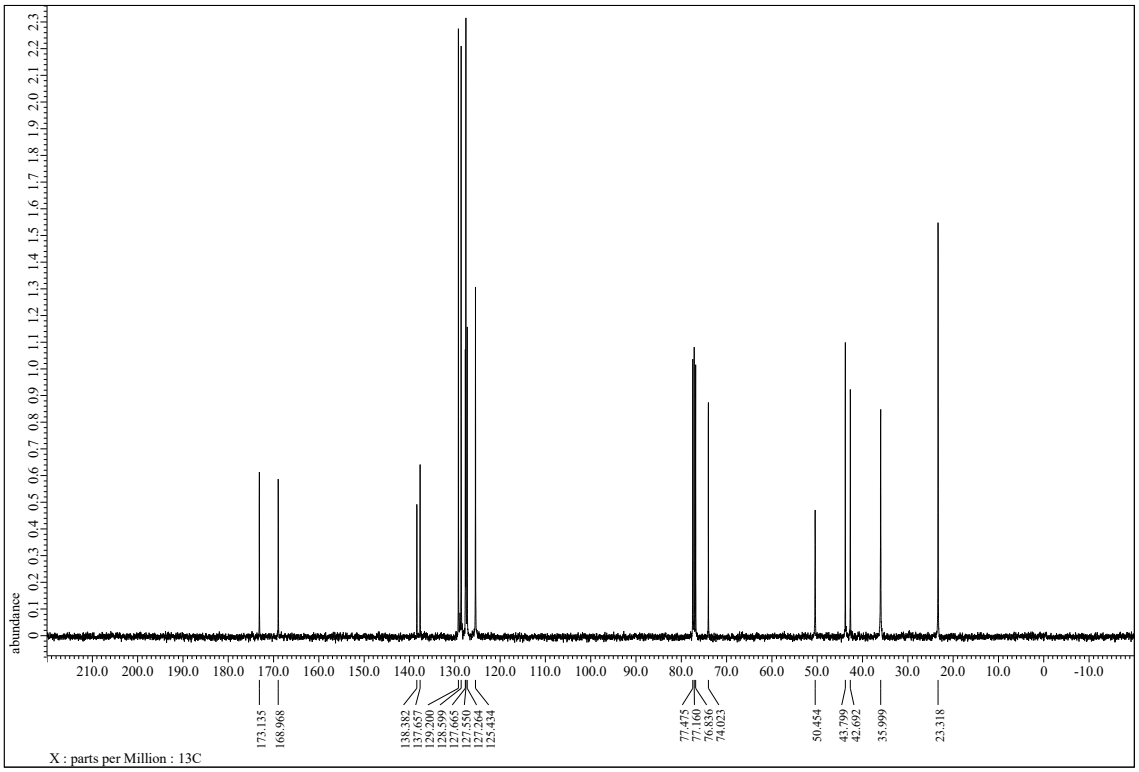

Figure S75. ^{13}C NMR spectrum (101 MHz) of *N*-benzyl-*N*-chloroacetyl-Ac$_5$c-NH-Bn (**3f**) in $CDCl_3$.

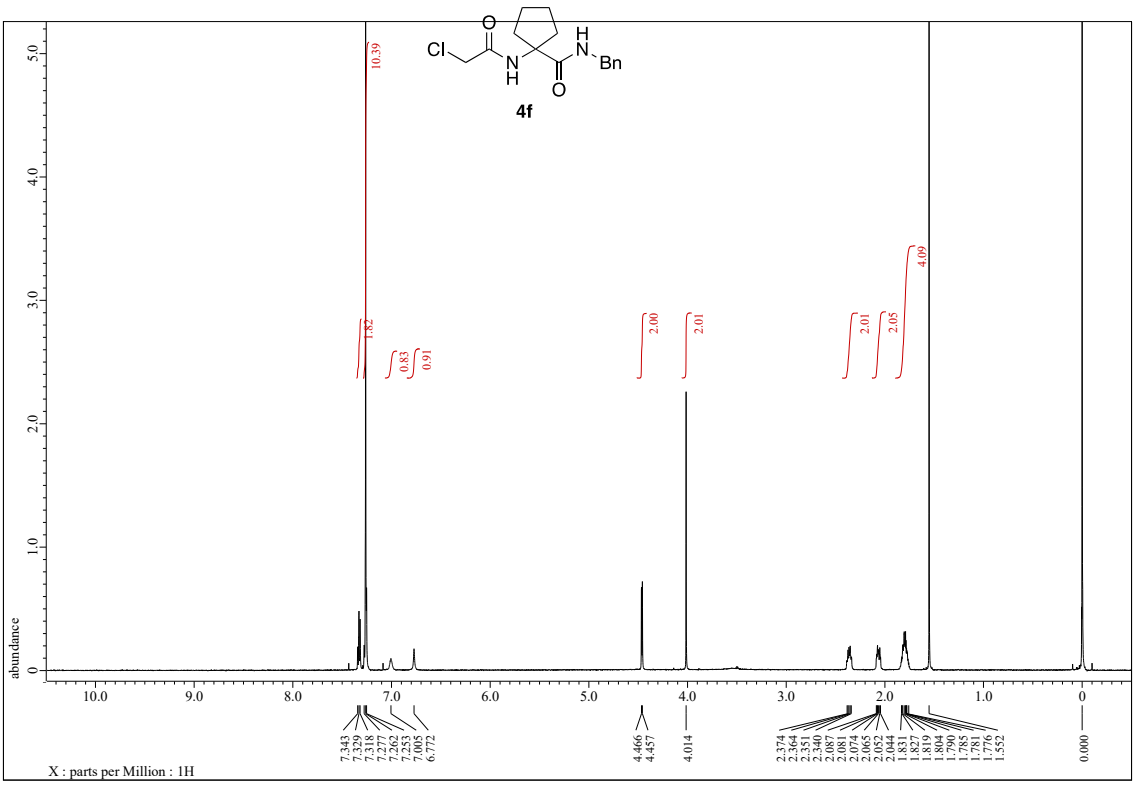

Figure S76. ^{1}H NMR spectrum (600 MHz) of *N*-chloroacetyl-Ac$_5$c-NH-Bn (**4f**) in $CDCl_3$.

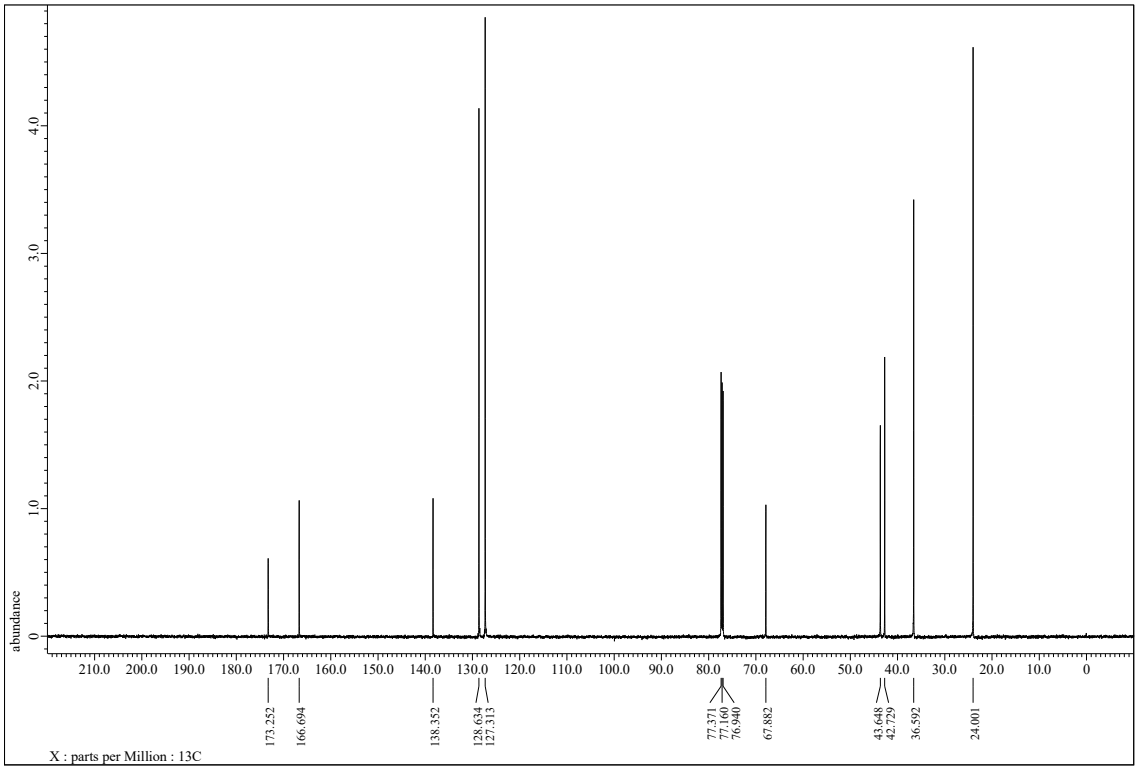

Figure S77. ^{13}C NMR spectrum (151 MHz) of *N*-chloroacetyl-Ac$_5$c-NH-Bn (**4f**) in $CDCl_3$.

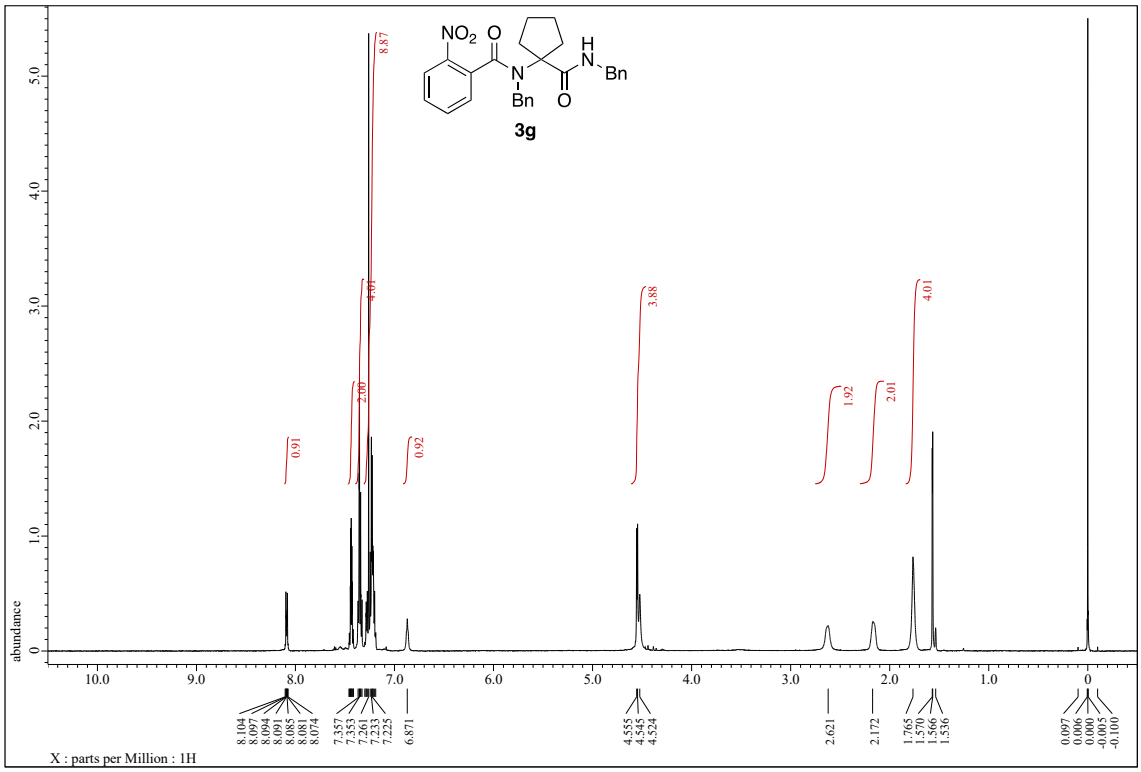

Figure S78. ^{1}H NMR spectrum (600 MHz) of *N*-benzyl-*N*-o-Nitrobenzoyl-Ac$_5$c-NH-Bn (**3g**) in $CDCl_3$.

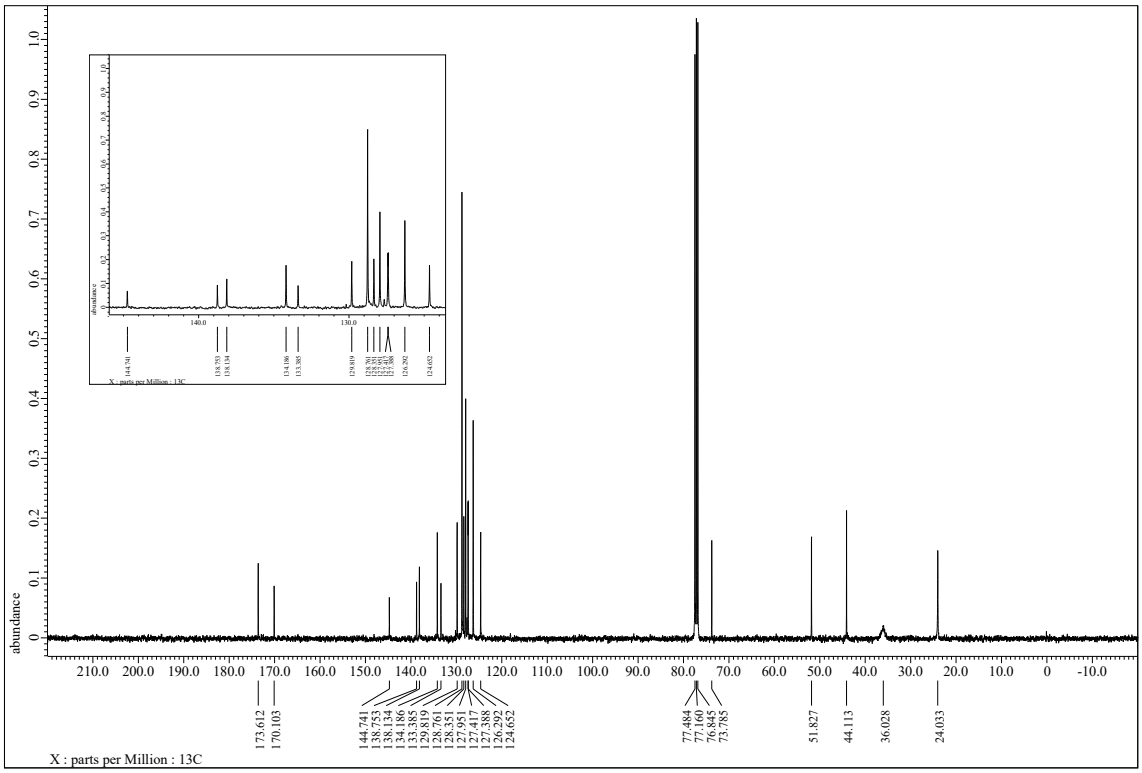

Figure S79. ^{13}C NMR spectrum (101 MHz) of *N*-benzyl-*N*-o-Nitrobenzoyl-Ac$_5$c-NH-Bn (**3g**) in $CDCl_3$.

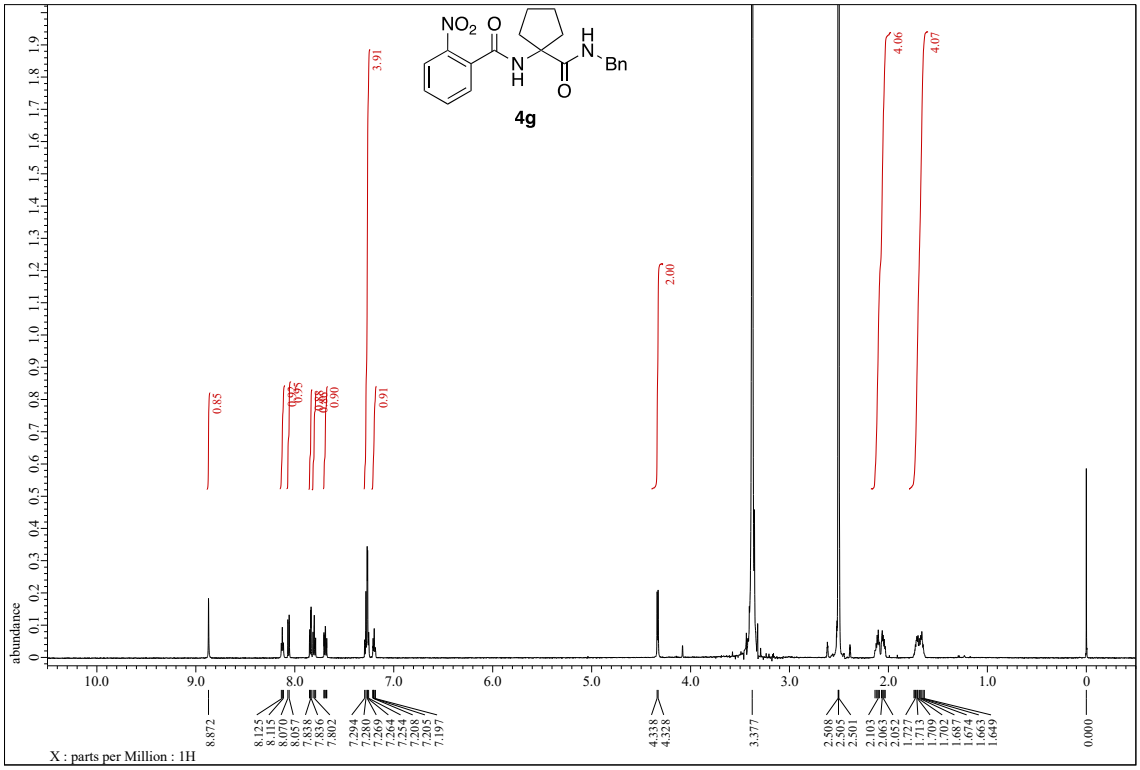

Figure S80. ^{1}H NMR spectrum (600 MHz) of *N*-o-nitrobenzoyl-Ac$_5$c-NH-Bn (**4g**) in DMSO-d_6.

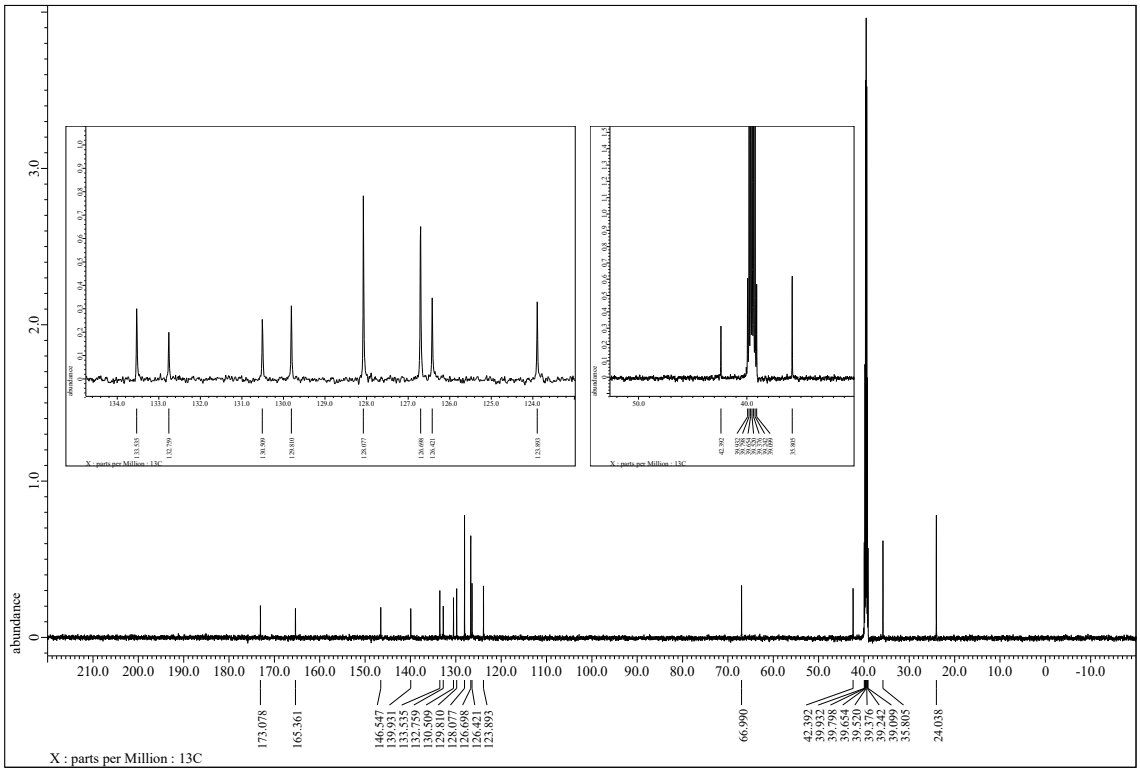

Figure S81. ^{13}C NMR spectrum (151 MHz) of *N*-o-nitrobenzoyl-Ac$_5$c-NH-Bn (**4g**) in DMSO-d_6.

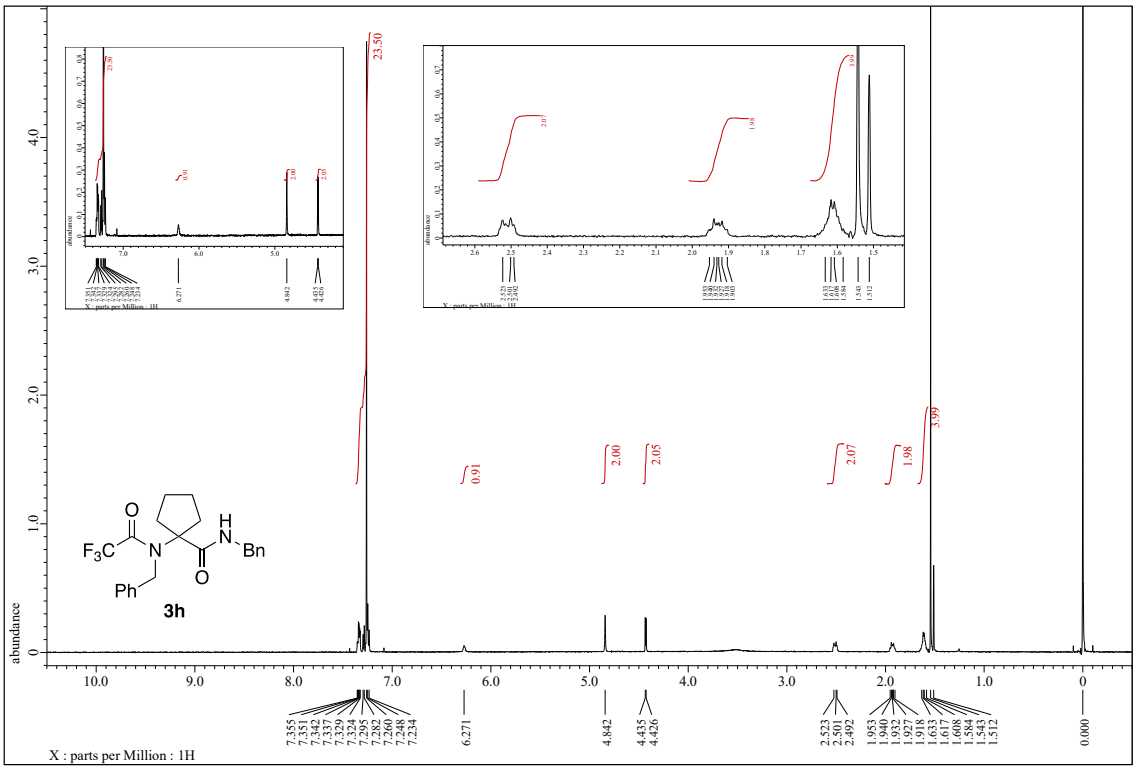

Figure S82. ^{1}H NMR spectrum (600 MHz) of *N*-benzyl-*N*-trifluoroacetyl-Ac$_5$c-NH-Bn **(3h)** in $CDCl_3$.

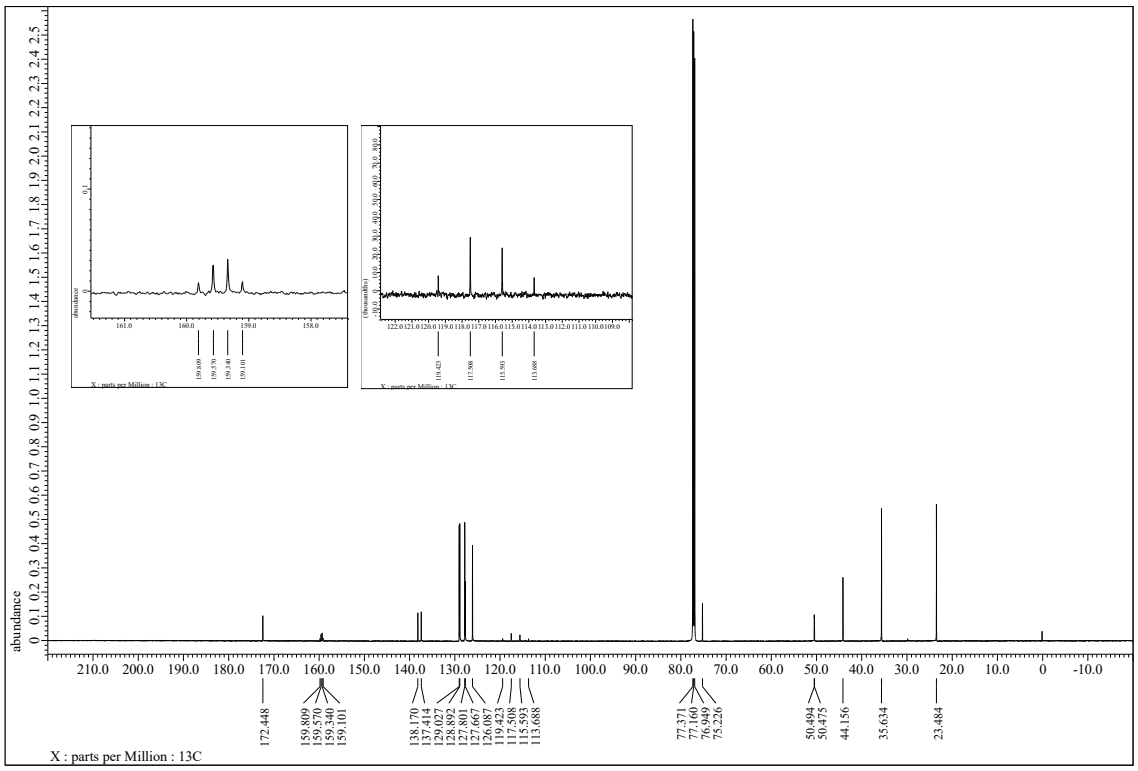

Figure S83. ^{13}C NMR spectrum (151 MHz) of *N*-benzyl-*N*-trifluoroacetyl-Ac$_5$c-NH-Bn (**3h**) in $CDCl_3$.

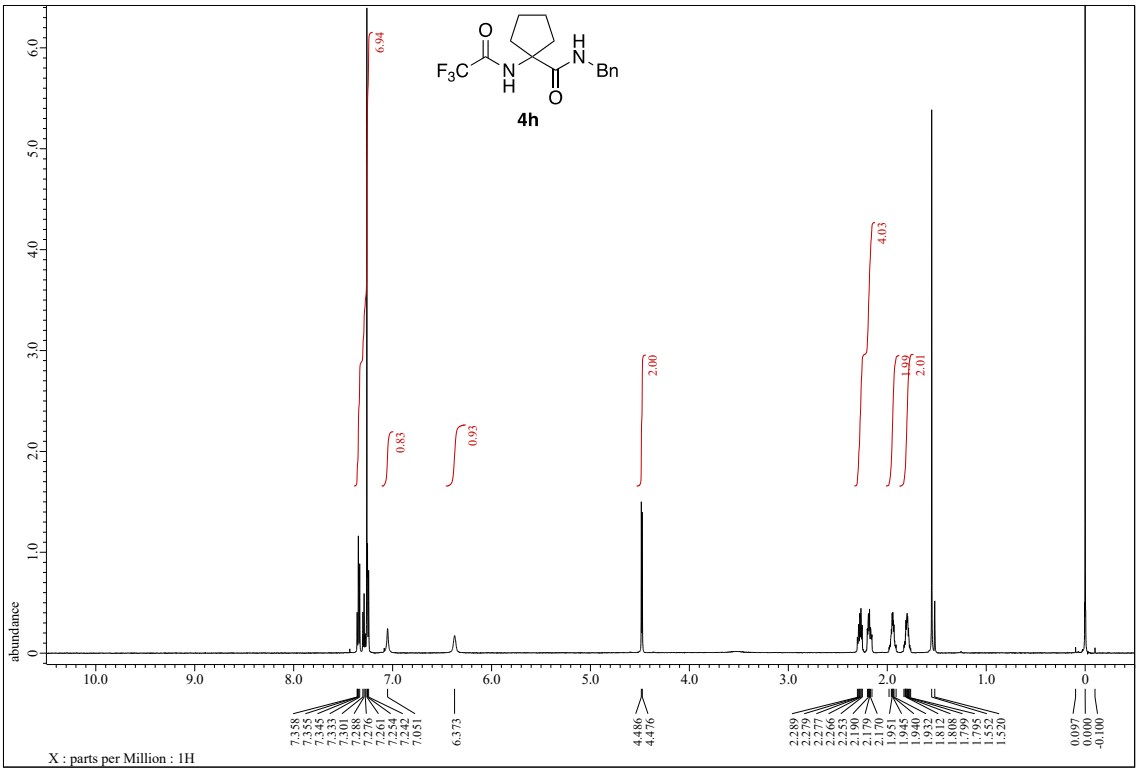

Figure S84. ^{1}H NMR spectrum (600 MHz) of *N*-trifluoroacetyl-Ac$_5$c-NH-Bn (**4h**) in $CDCl_3$.

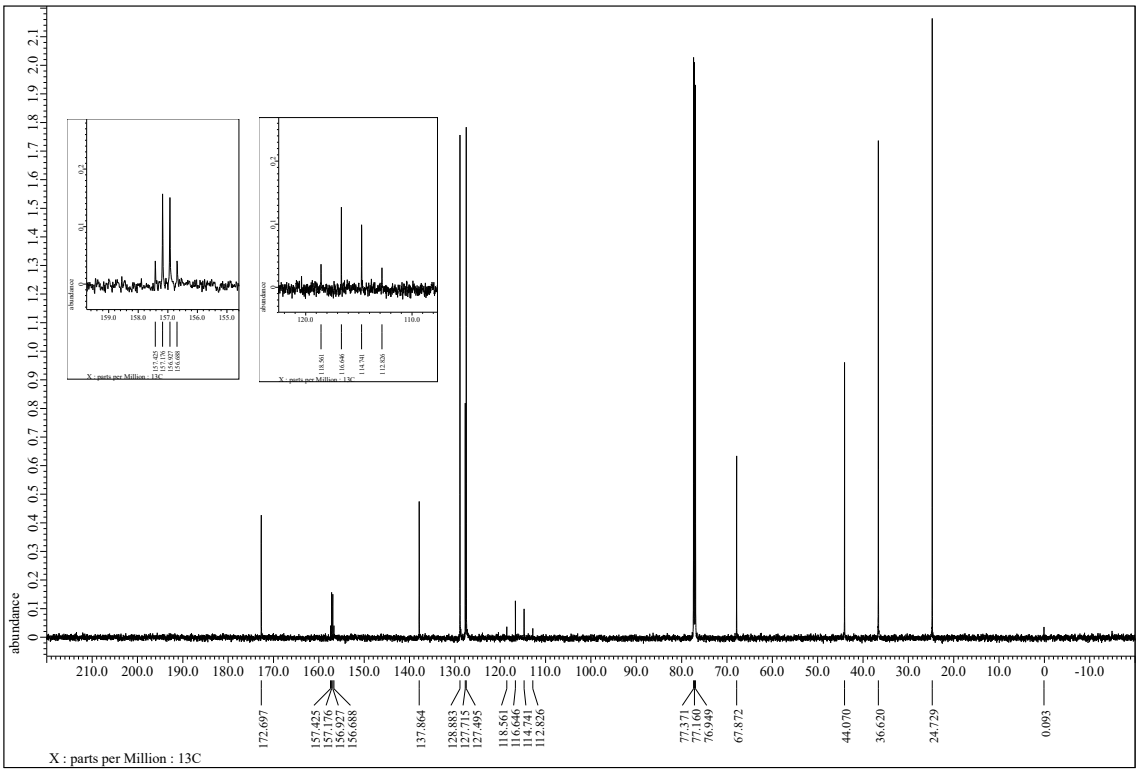

Figure S85. ^{13}C NMR spectrum (151 MHz) of *N*-trifluoroacetyl-Ac$_5$c-NH-Bn (**4h**) in $CDCl_3$.

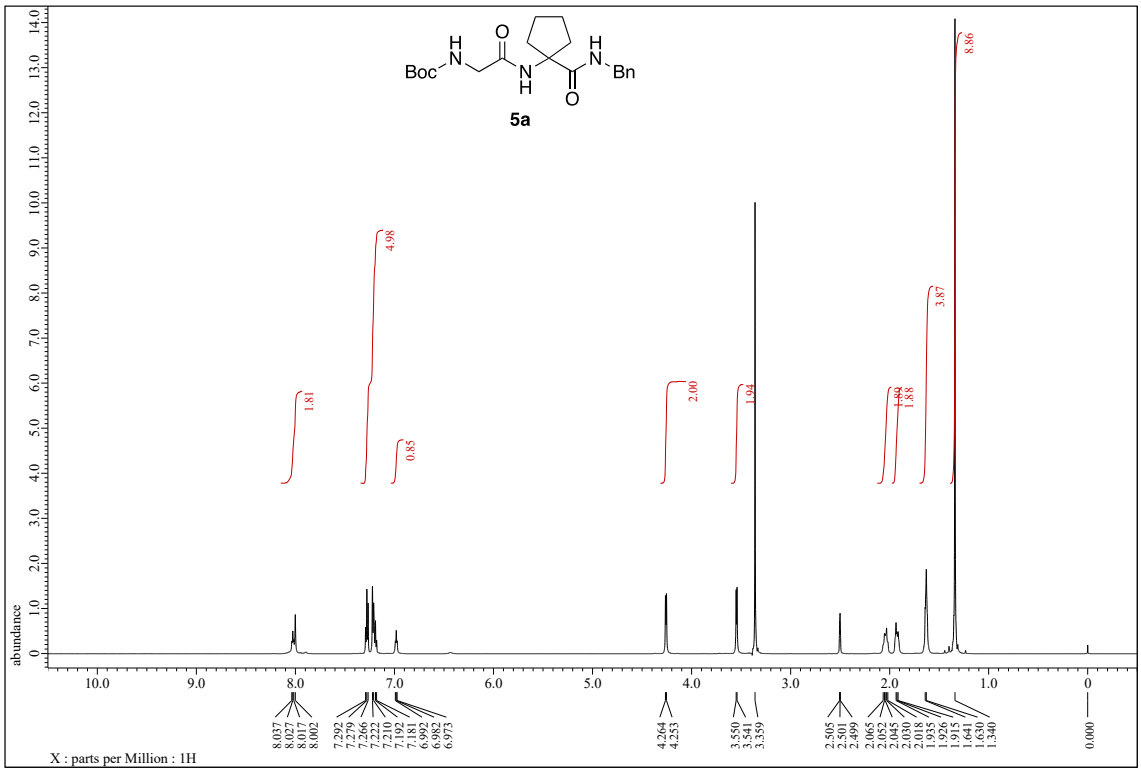

Figure S86. ^{1}H NMR spectrum (600 MHz) of Boc-Gly-Ac$_5$c-NH-Bn (**5a**) in DMSO-d_6.

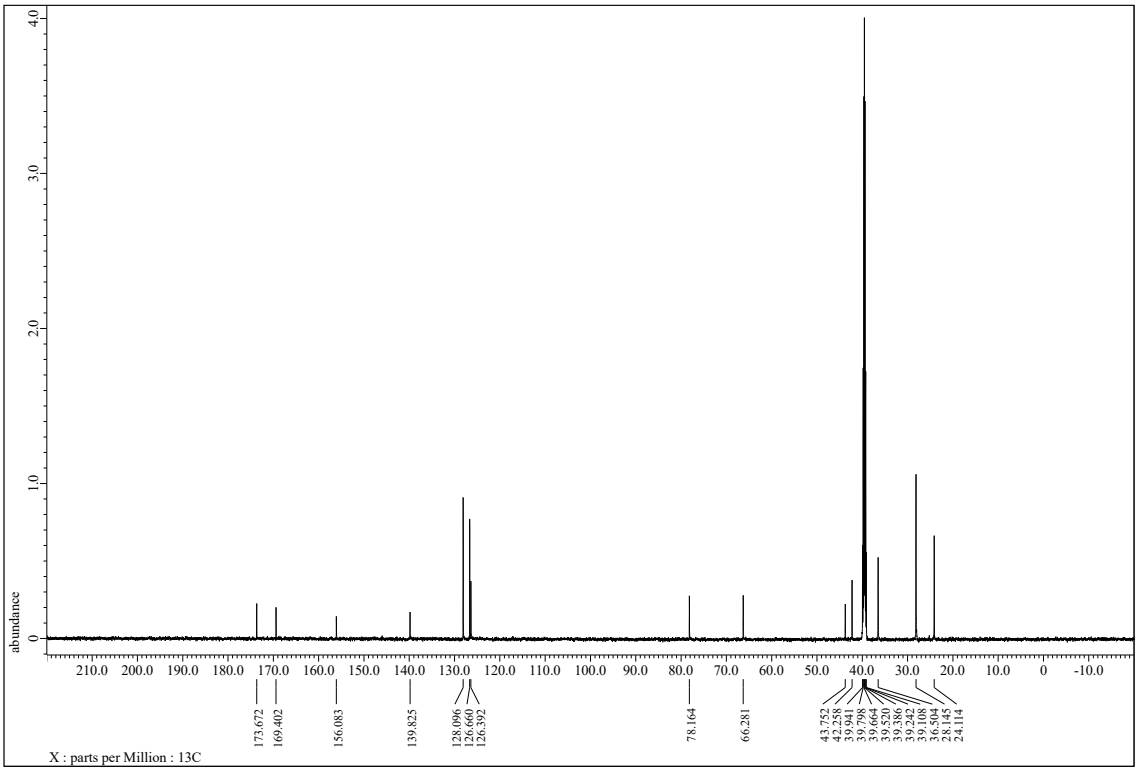

Figure S87. ^{13}C NMR spectrum (151 MHz) of Boc-Gly-Ac$_5$c-NH-Bn (**5a**) in DMSO-d_6.

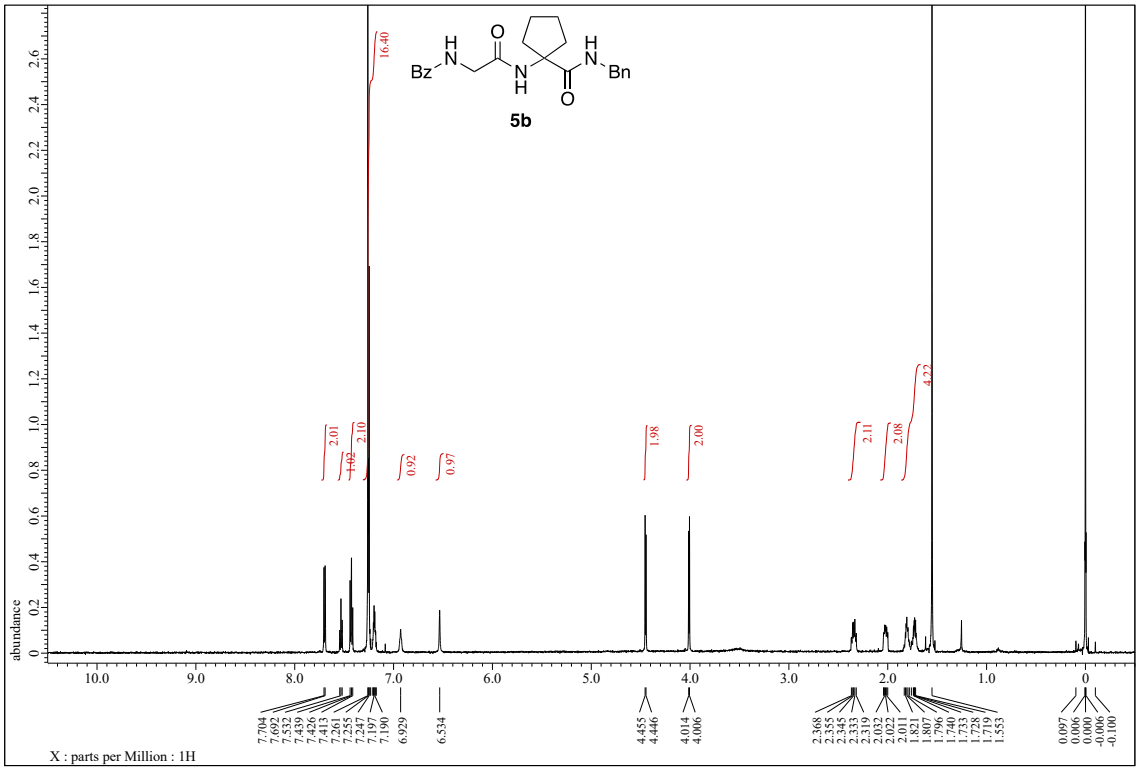

Figure S88. ^{1}H NMR spectrum (600 MHz) of Bz-Gly-Ac$_5$c-NH-Bn (**5b**) in $CDCl_3$.

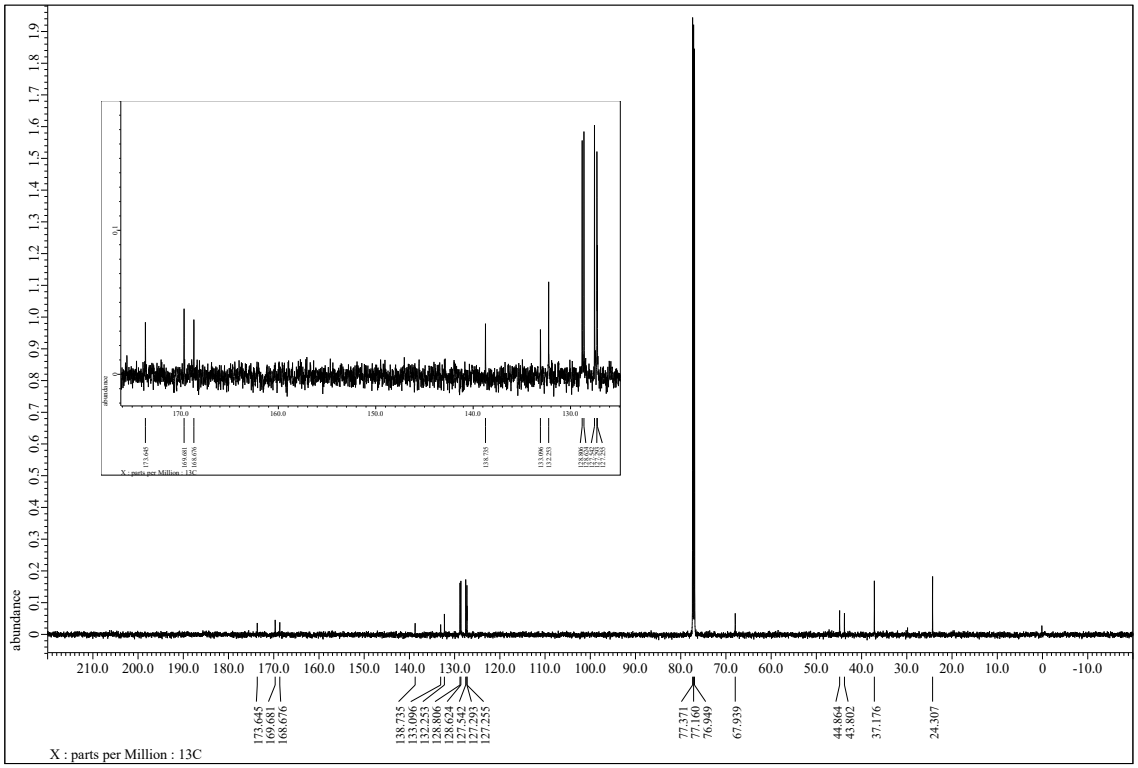

Figure S89. ^{13}C NMR spectrum (151 MHz) of Bz-Gly-Ac$_5$c-NH-Bn (**5b**) in $CDCl_3$.

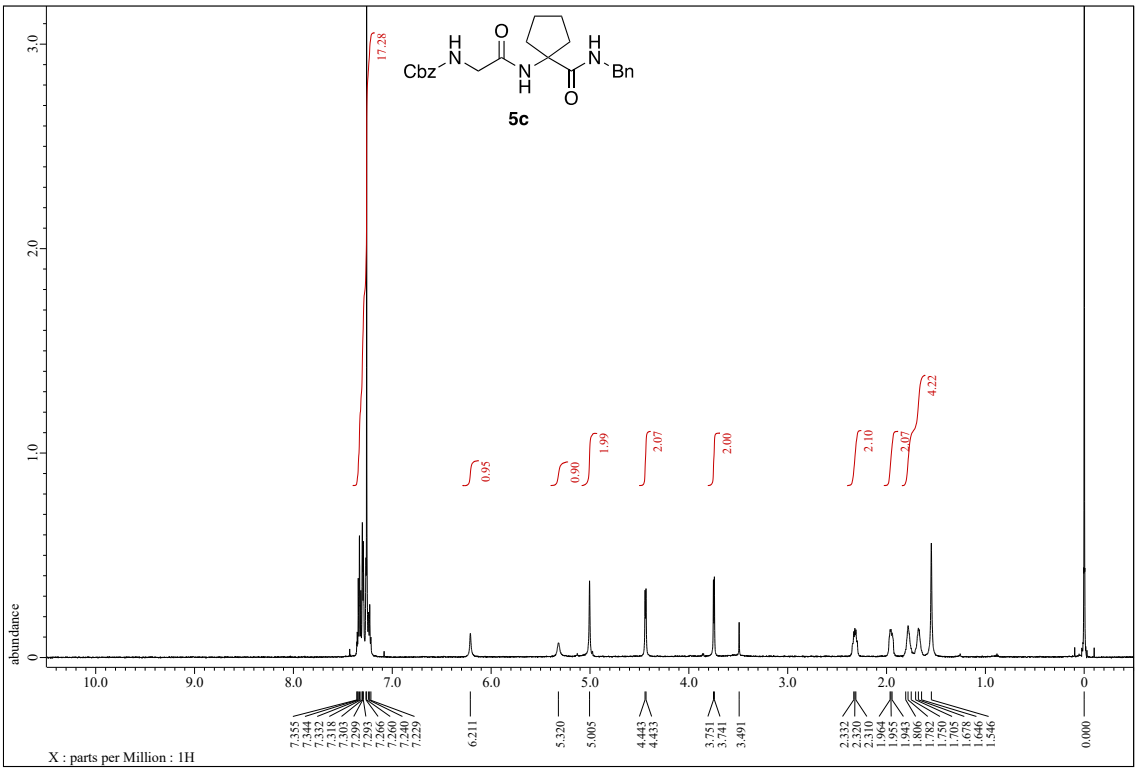

Figure S90. ^{1}H NMR spectrum (600 MHz) of Cbz-Gly-Ac$_5$c-NH-Bn (**5c**) in $CDCl_3$.

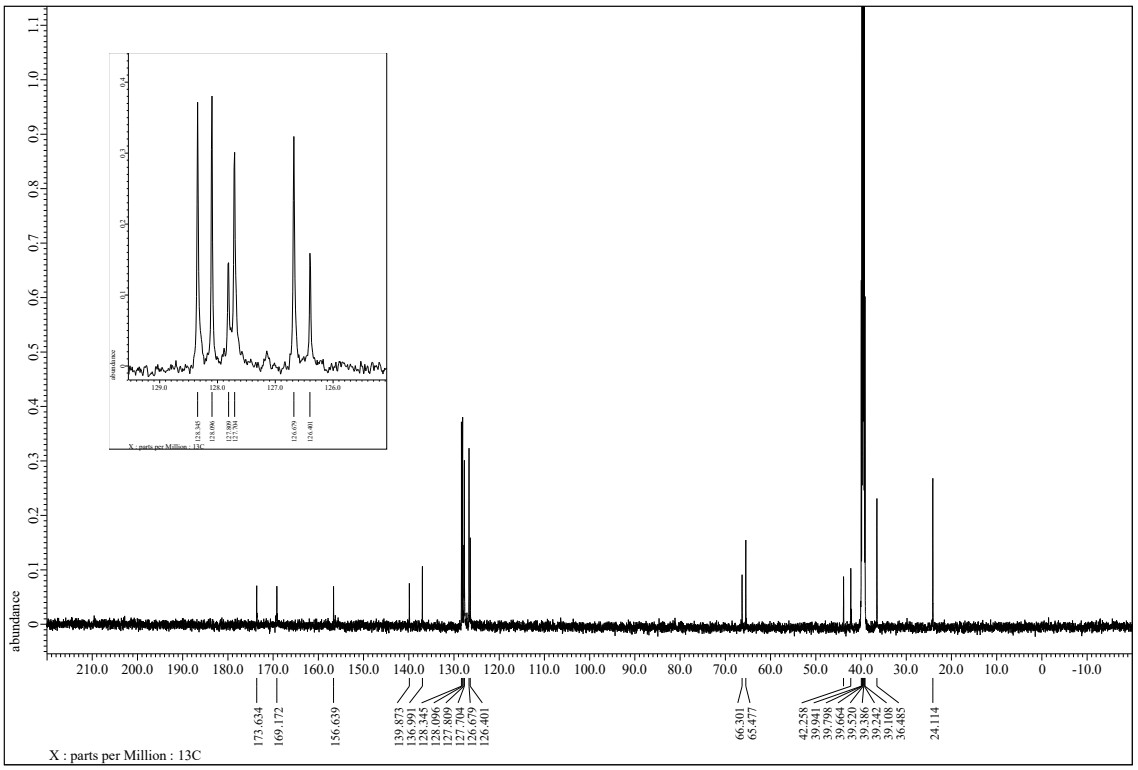

Figure S91. ^{13}C NMR spectrum (151 MHz) of Cbz-Gly-Ac$_5$c-NH-Bn (**5c**) in DMSO-d_6.

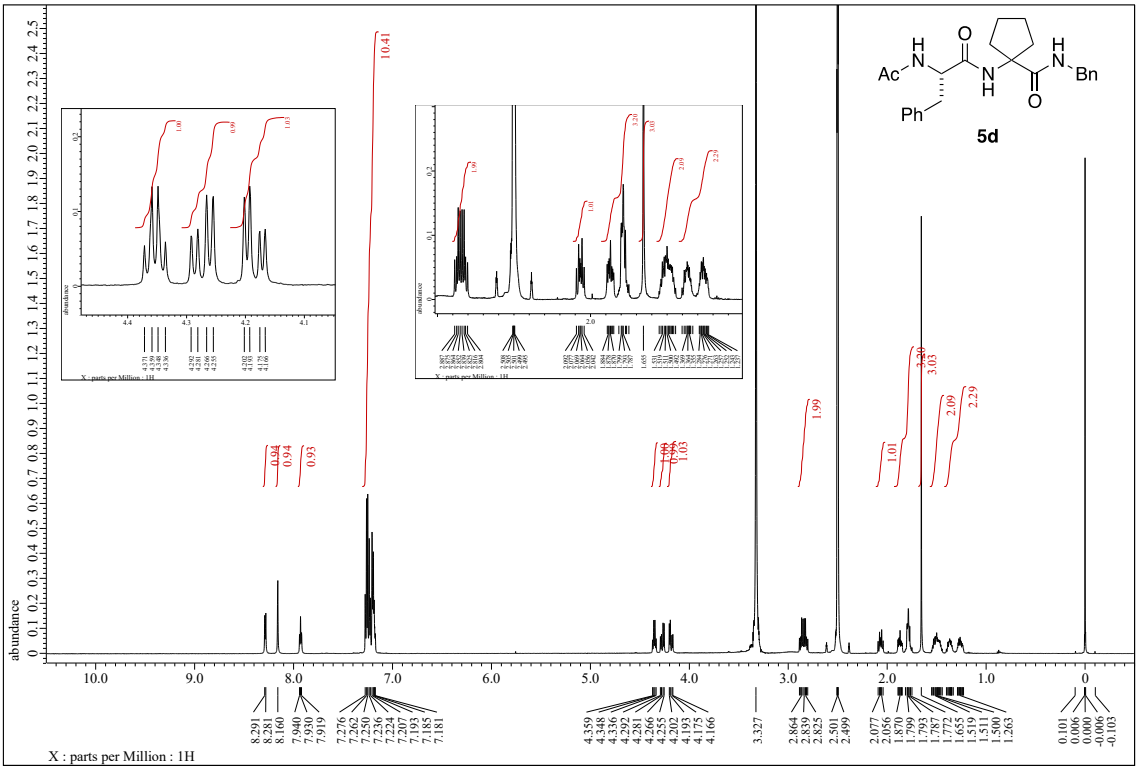

Figure S92. ^{1}H NMR spectrum (600 MHz) of Ac-Phe-Ac$_5$c-NH-Bn (**5d**) in DMSO-d_6.

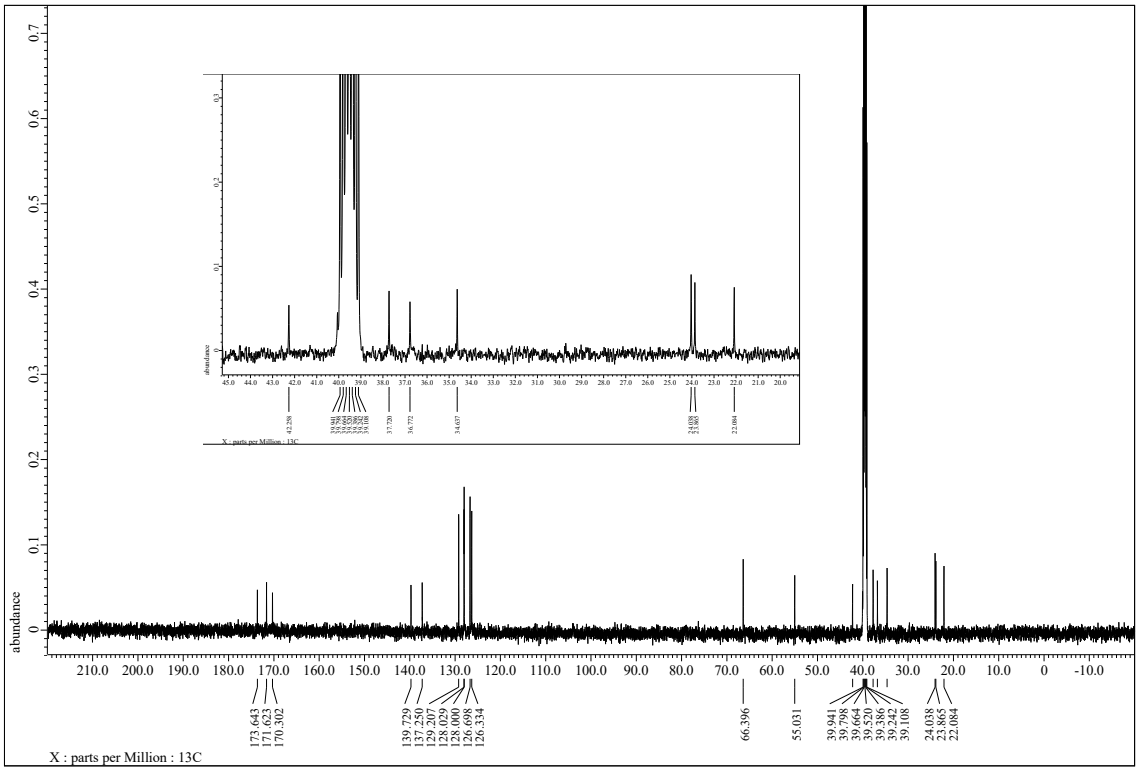

Figure S93. ^{13}C NMR spectrum (151 MHz) of Ac-Phe-Ac$_5$c-NH-Bn (**5d**) in DMSO-d_6.

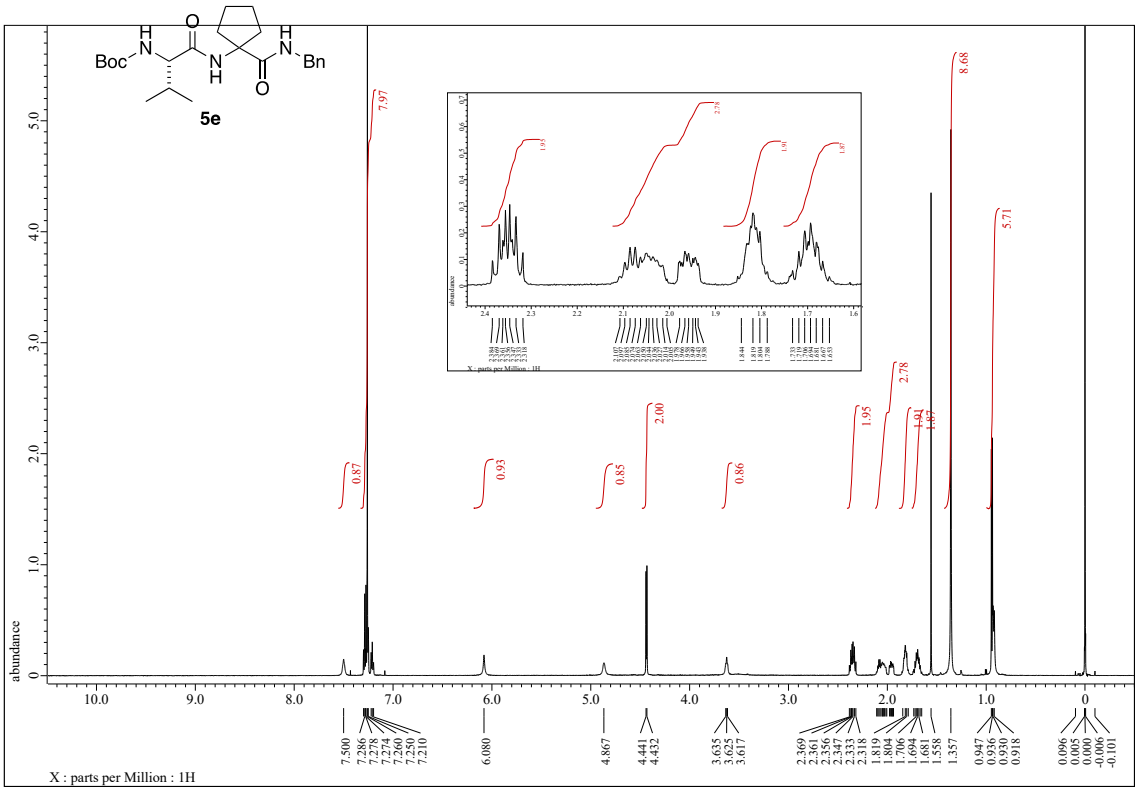

Figure S94. ^{1}H NMR spectrum (600 MHz) of Boc-Val-Ac$_5$c-NH-Bn (**5e**) in $CDCl_3$.

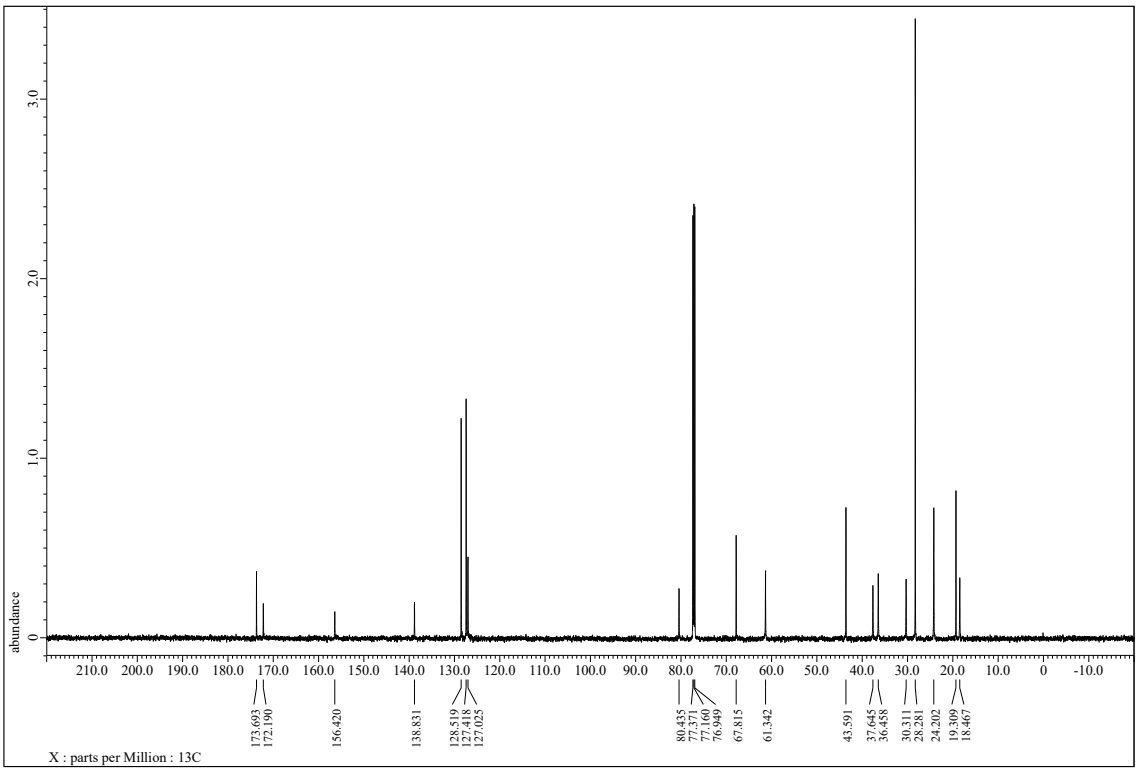

Figure S95. ^{13}C NMR spectrum (151 MHz) of Boc-Val-Ac$_5$c-NH-Bn (**5e**) in $CDCl_3$.

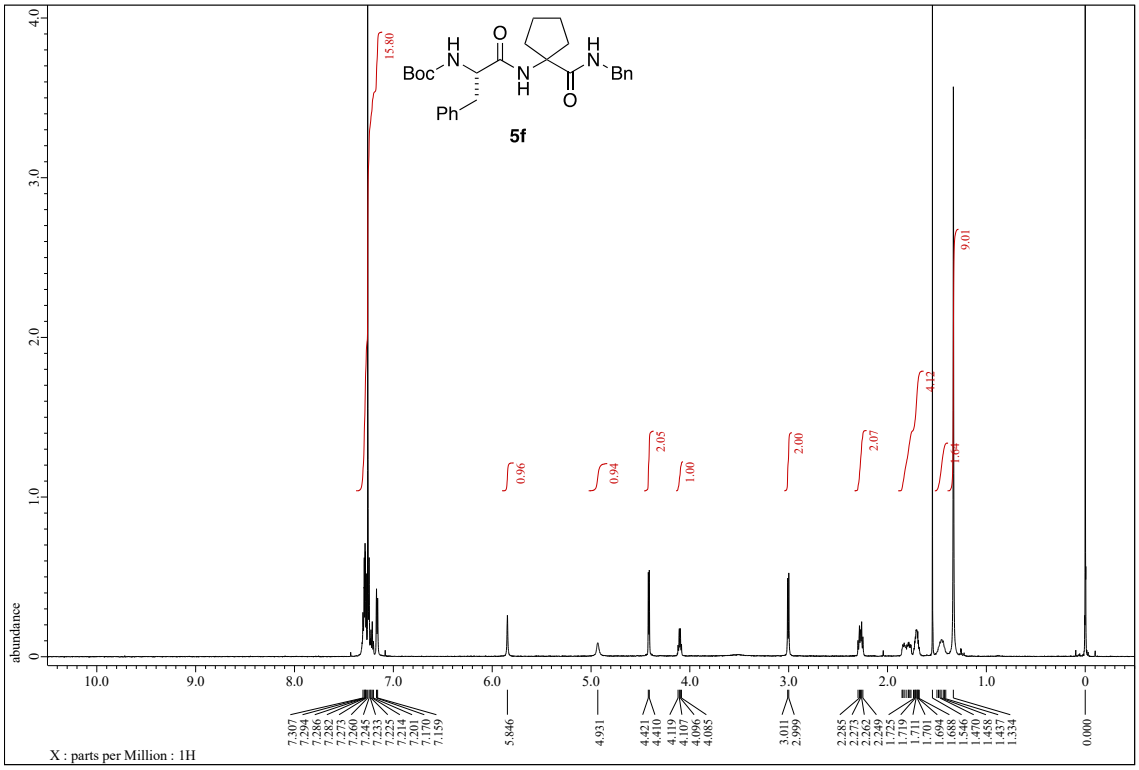

Figure S96. ^{1}H NMR spectrum (600 MHz) of Boc-Phe-Ac$_5$c-NH-Bn (**5f**) in $CDCl_3$.

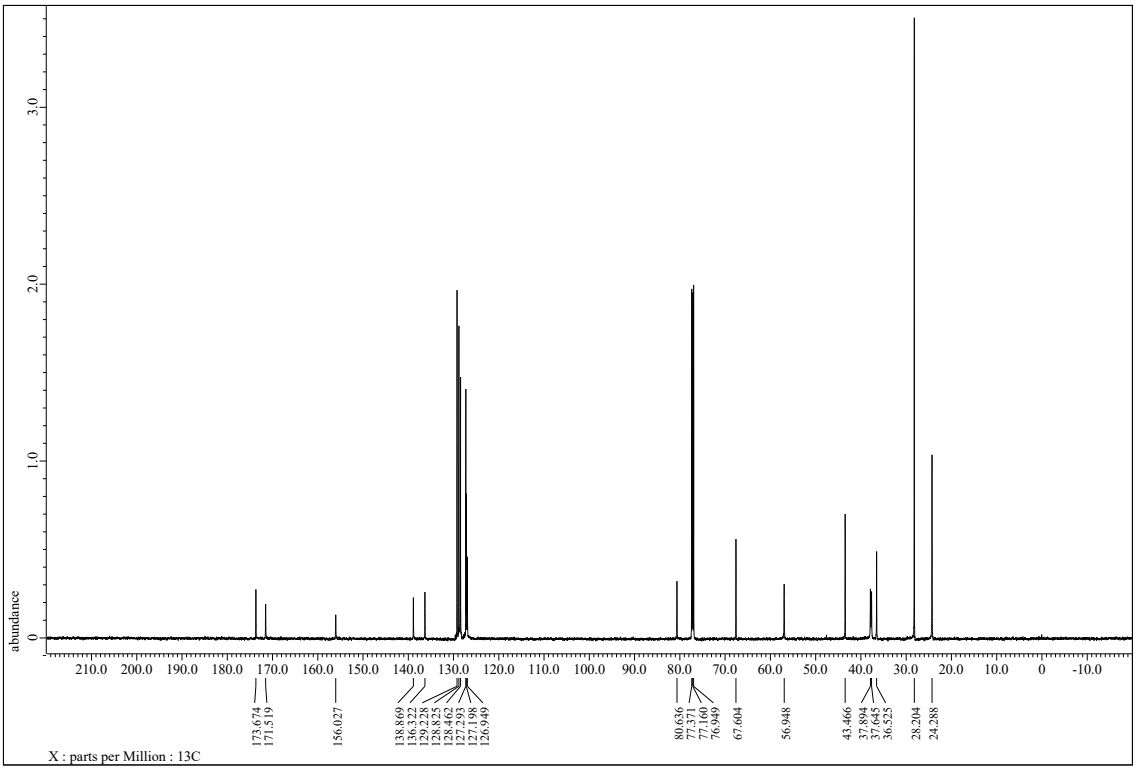

Figure S97. ^{13}C NMR spectrum (151 MHz) of Boc-Phe-Ac$_5$c-NH-Bn (**5f**) in $CDCl_3$.

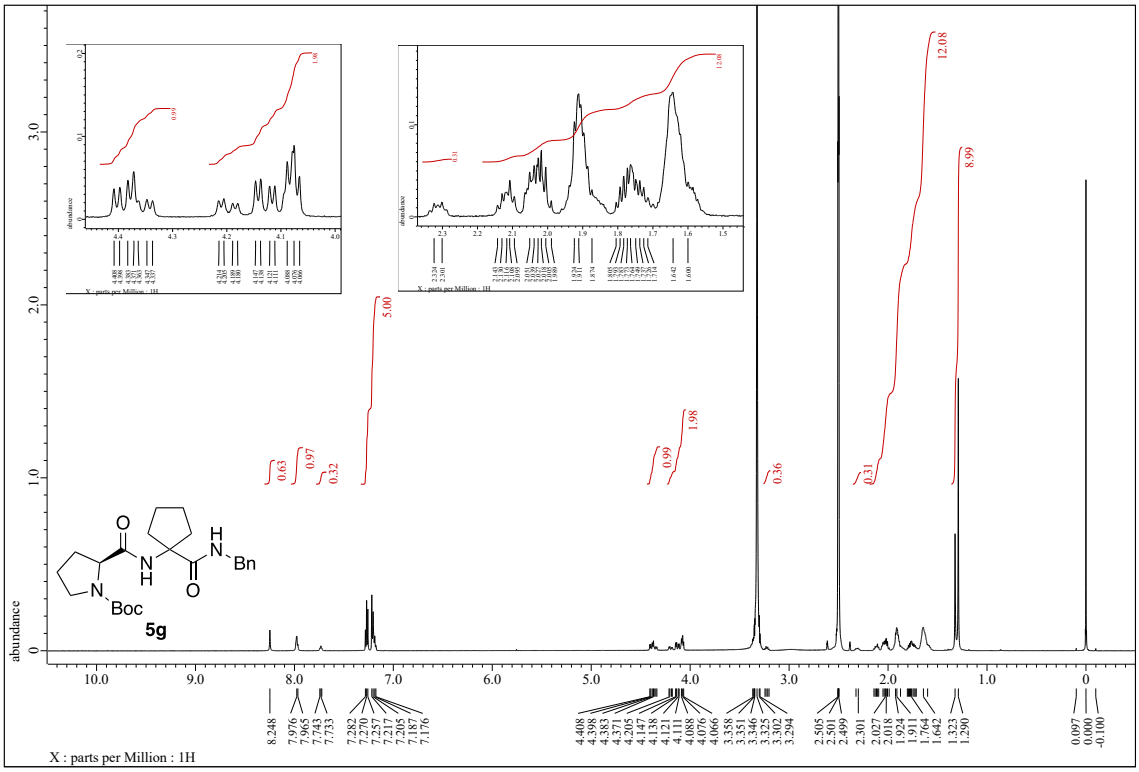

Figure S98. ^{1}H NMR spectrum (600 MHz) of Boc-Pro-Ac$_5$c-NH-Bn (**5g**) in DMSO-d_6.

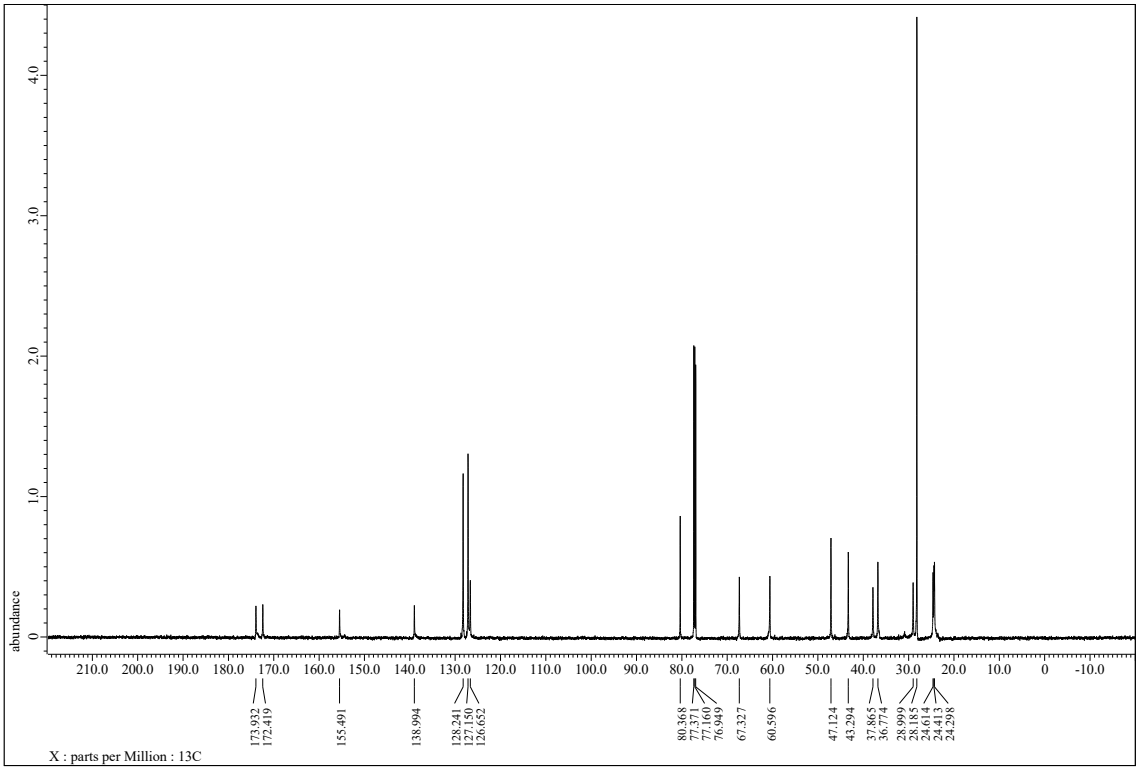

Figure S99. ^{13}C NMR spectrum (151 MHz) of Boc-Pro-Ac$_5$c-NH-Bn (**5g**) in $CDCl_3$.

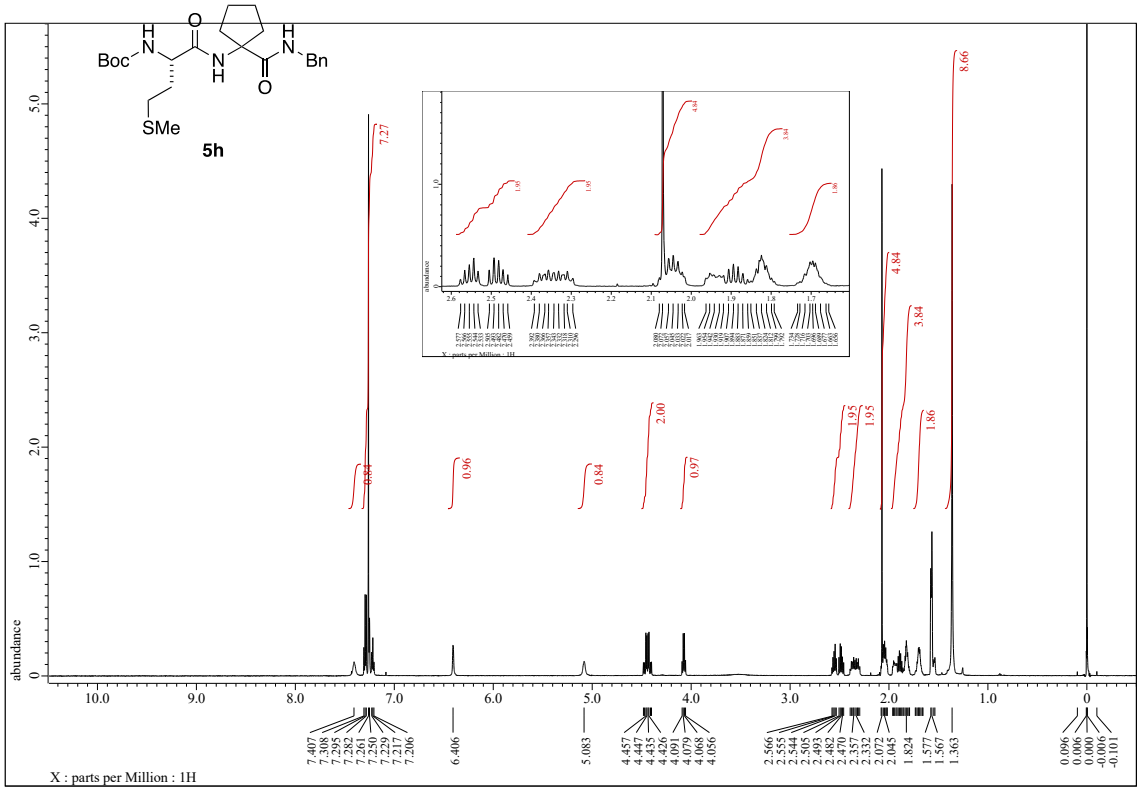

Figure S100. ^{1}H NMR spectrum (600 MHz) of Boc-Met-Ac$_5$c-NH-Bn (**5h**) in $CDCl_3$.

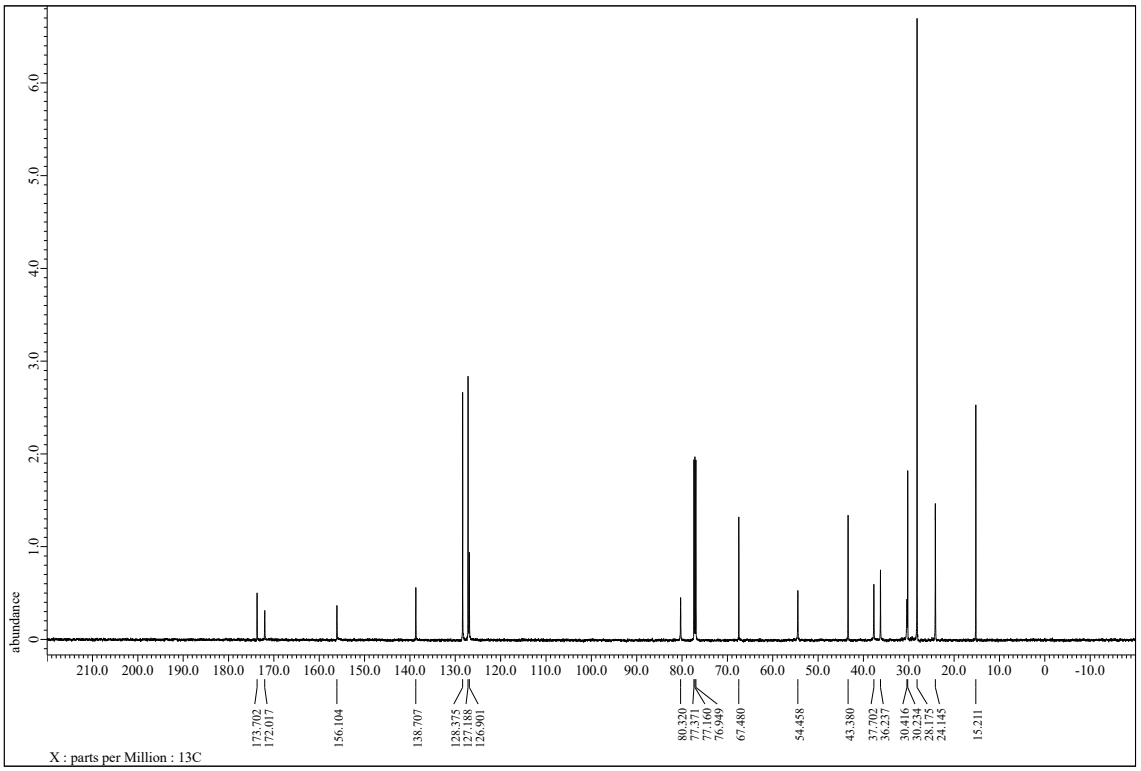

Figure S101. ^{13}C NMR spectrum (151 MHz) of Boc-Met-Ac$_5$c-NH-Bn (**5h**) in $CDCl_3$.

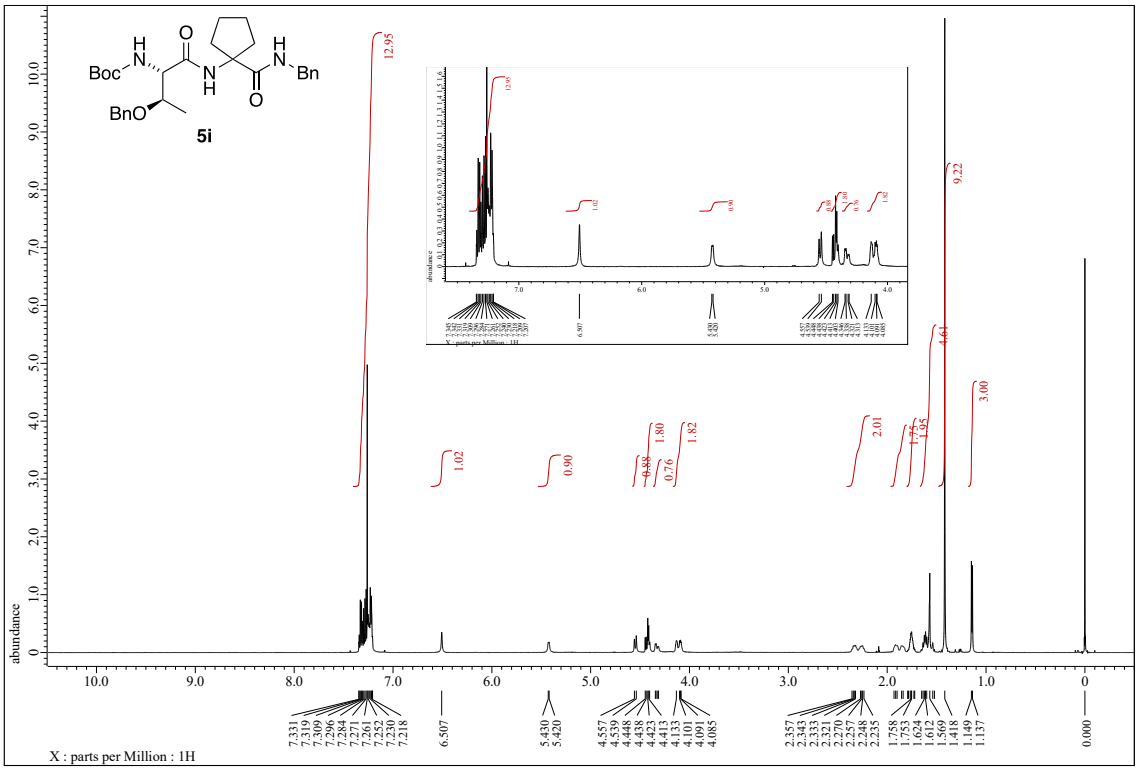

Figure S102. ^{1}H NMR spectrum (600 MHz) of Boc-Thr(Bn)-Ac$_5$c-NH-Bn (**5i**) in $CDCl_3$.

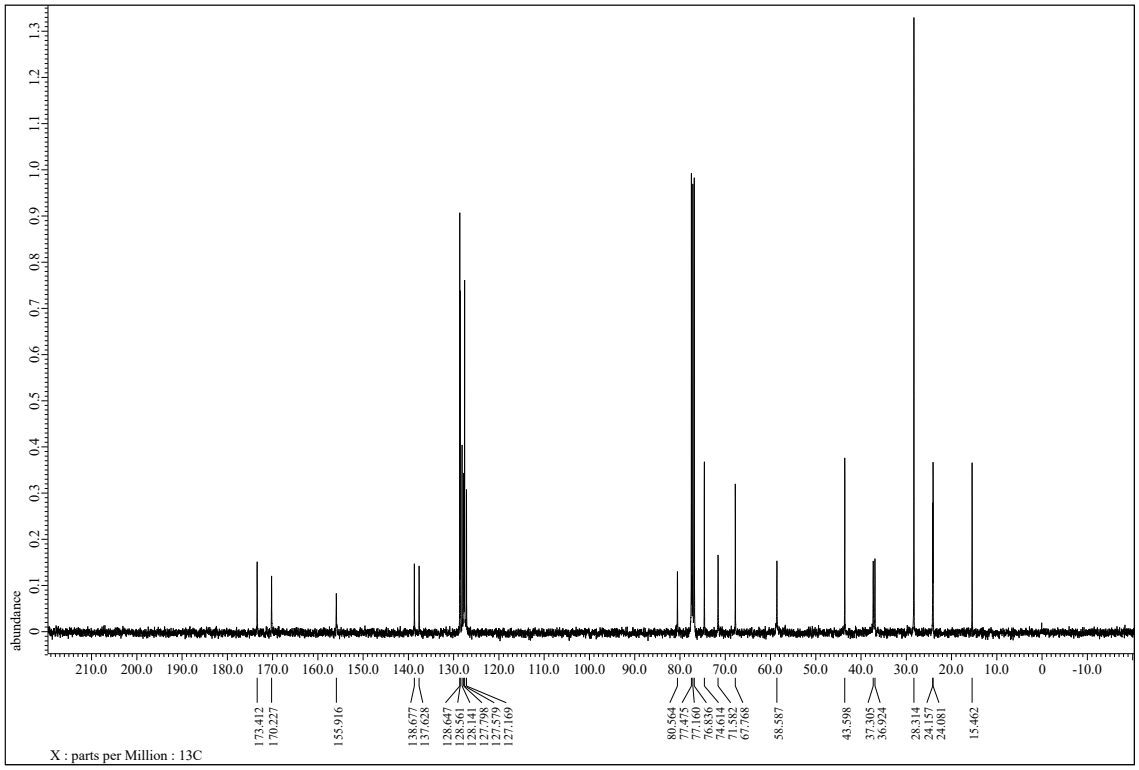

Figure S103. ^{13}C NMR spectrum (101 MHz) of Boc-Thr(Bn)-Ac$_5$c-NH-Bn (**5i**) in $CDCl_3$.

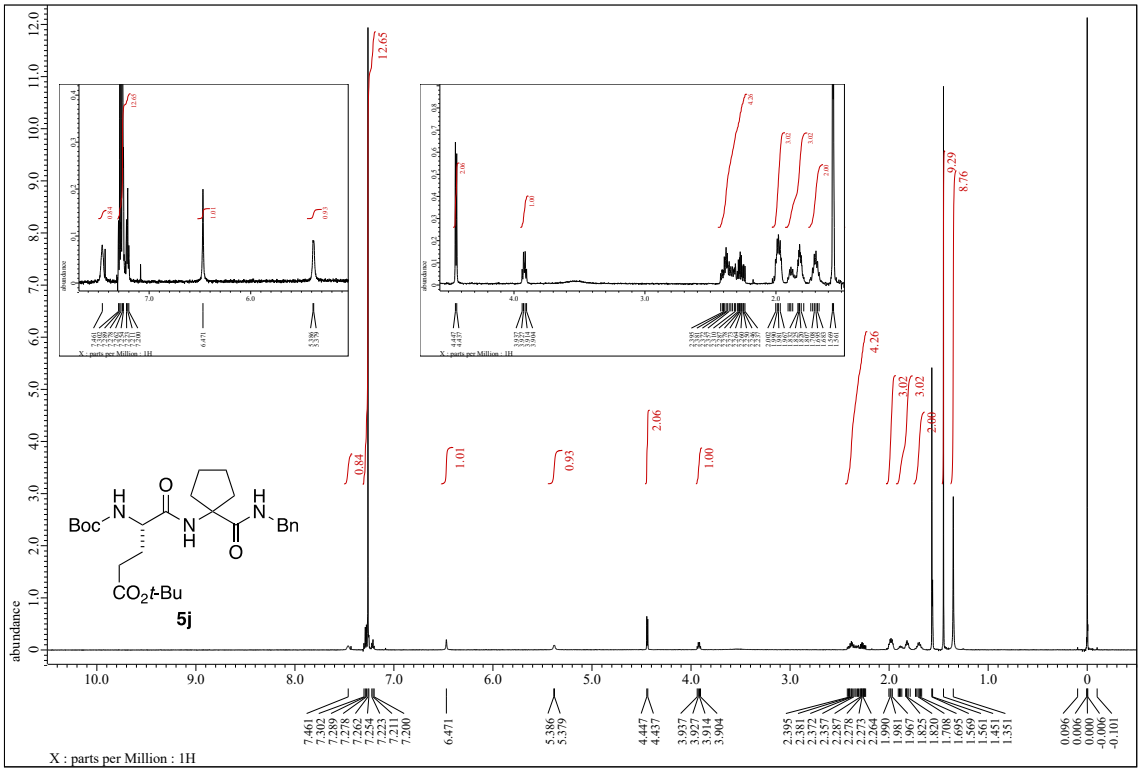

Figure S104. ^{1}H NMR spectrum (600 MHz) of Boc-Glu(O*t*-Bu)-Ac$_5$c-NH-Bn (**5j**) in $CDCl_3$.

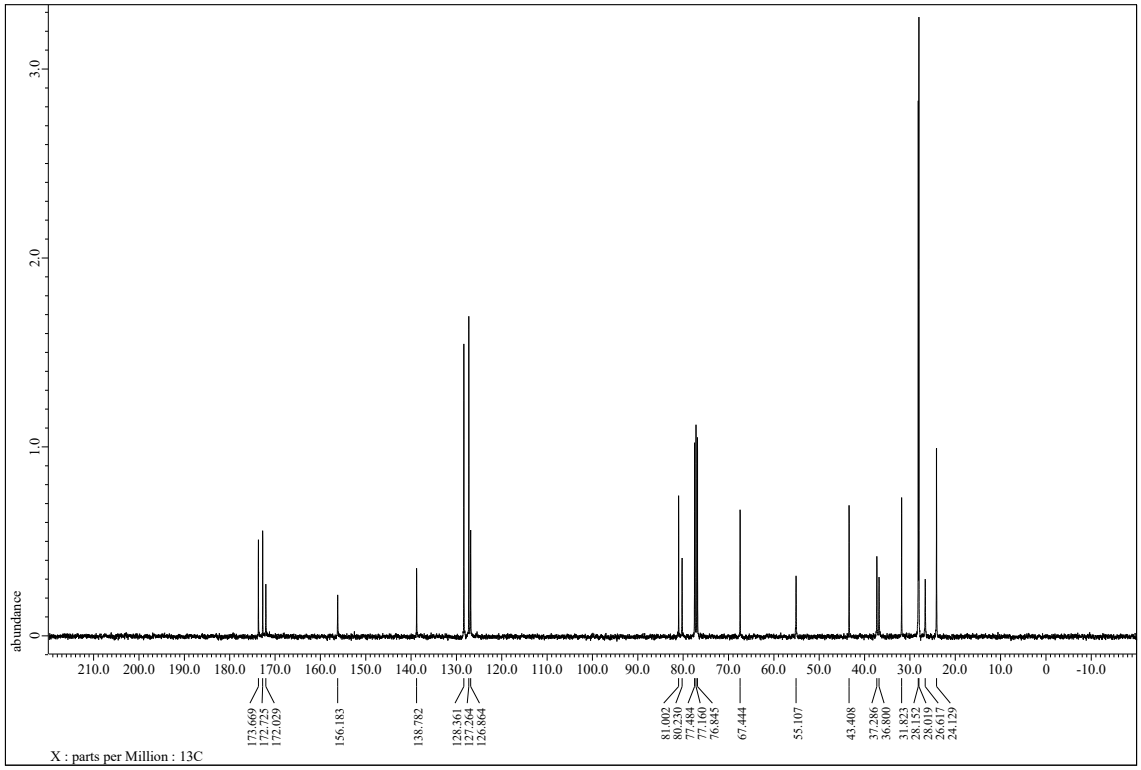

Figure S105. ^{13}C NMR spectrum (101 MHz) of Boc-Glu(O*t*-Bu)-Ac$_5$c-NH-Bn (**5j**) in $CDCl_3$.

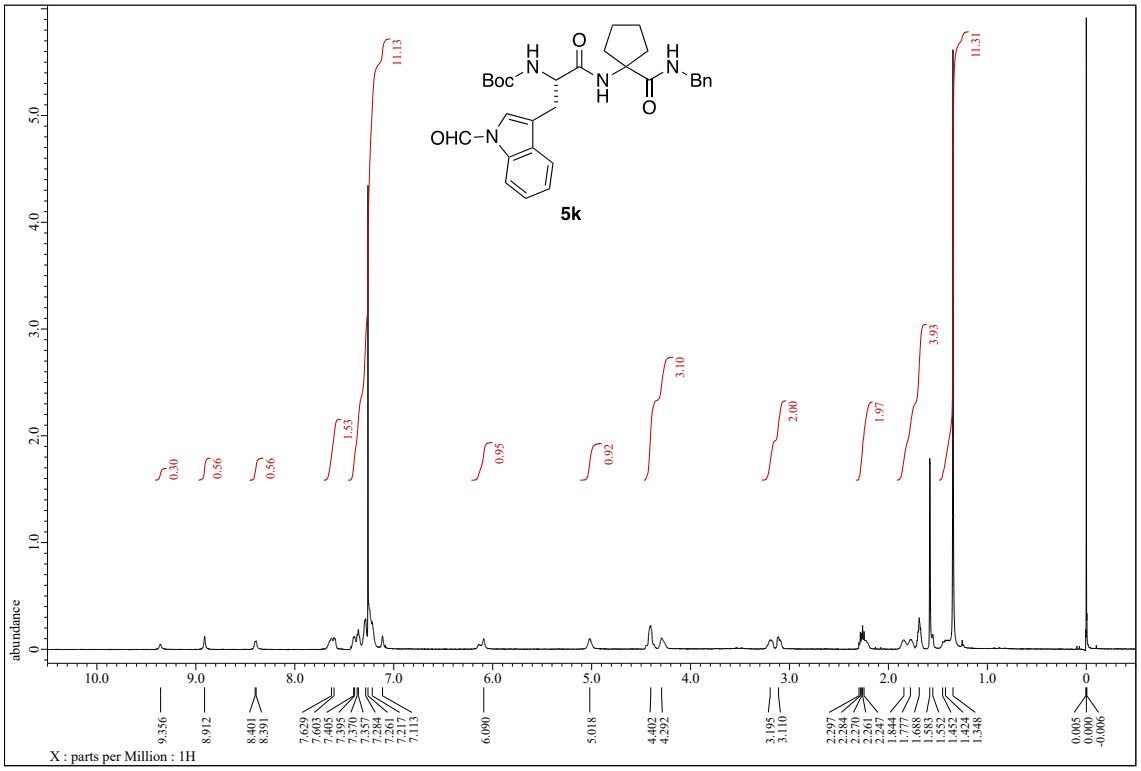

Figure S106. ^{1}H NMR spectrum (600 MHz) of Boc-Trp(CHO)-Ac$_5$c-NH-Bn (**5k**) in $CDCl_3$.

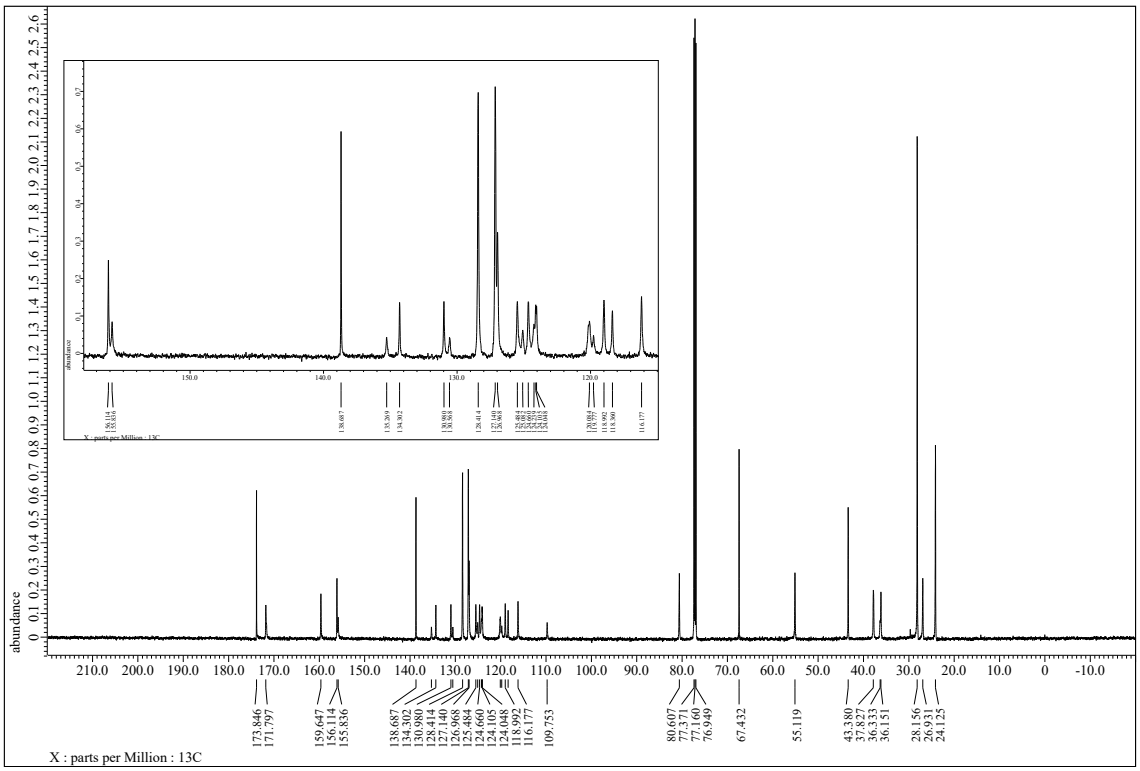

Figure S107. ^{13}C NMR spectrum (151 MHz) of Boc-Trp(CHO)-Ac$_5$c-NH-Bn (**5k**) in $CDCl_3$.

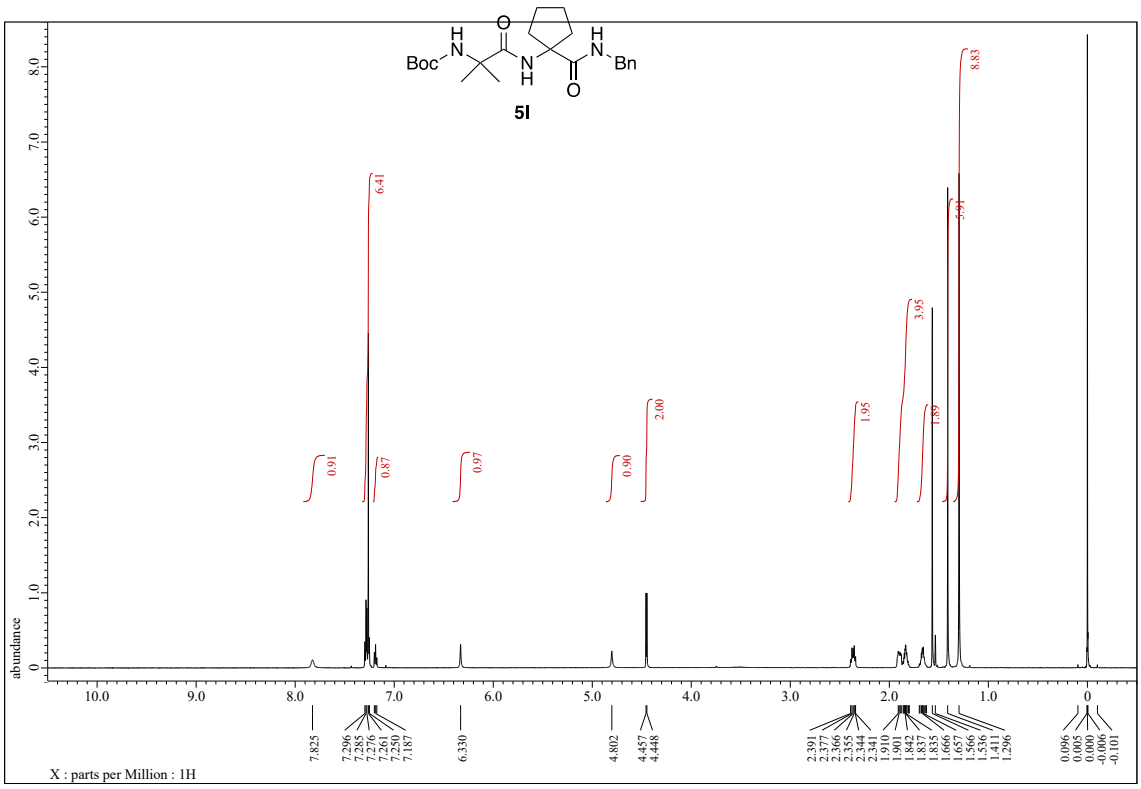

Figure S108. ^{1}H NMR spectrum (600 MHz) of Boc-Aib-Ac$_5$c-NH-Bn (**5l**) in $CDCl_3$.

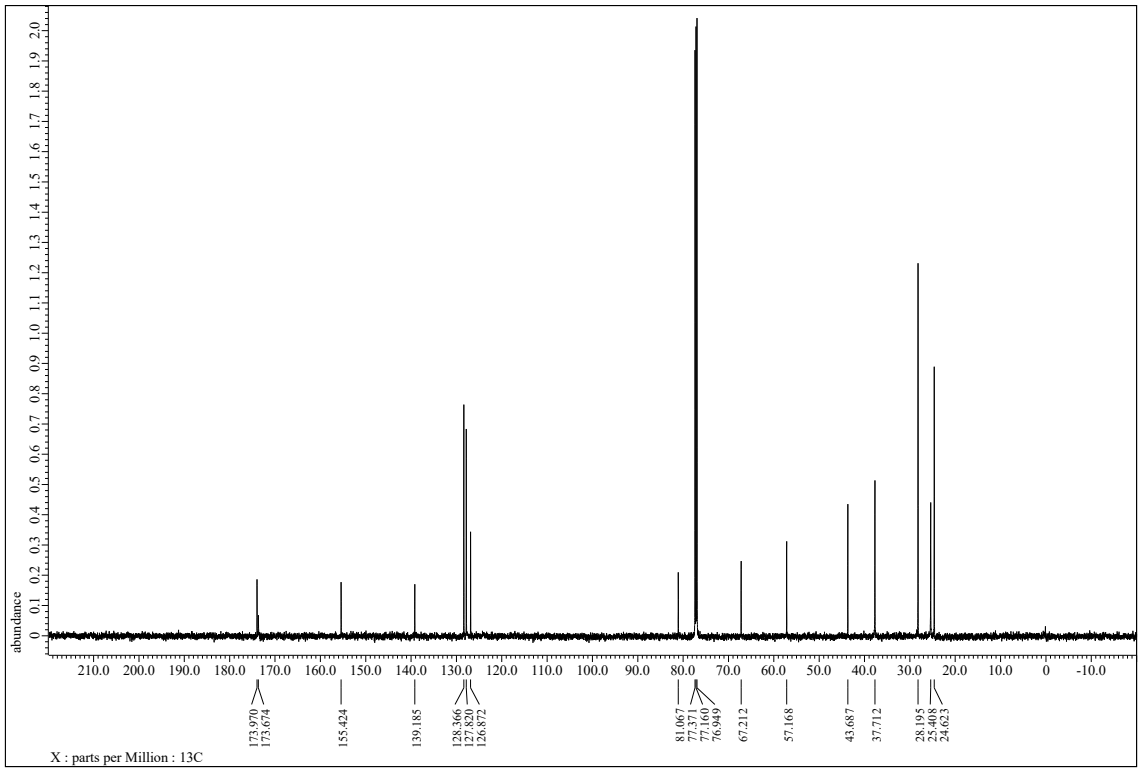

Figure S109. ^{13}C NMR spectrum (151 MHz) of Boc-Aib-Ac$_5$c-NH-Bn (**5l**) in $CDCl_3$.

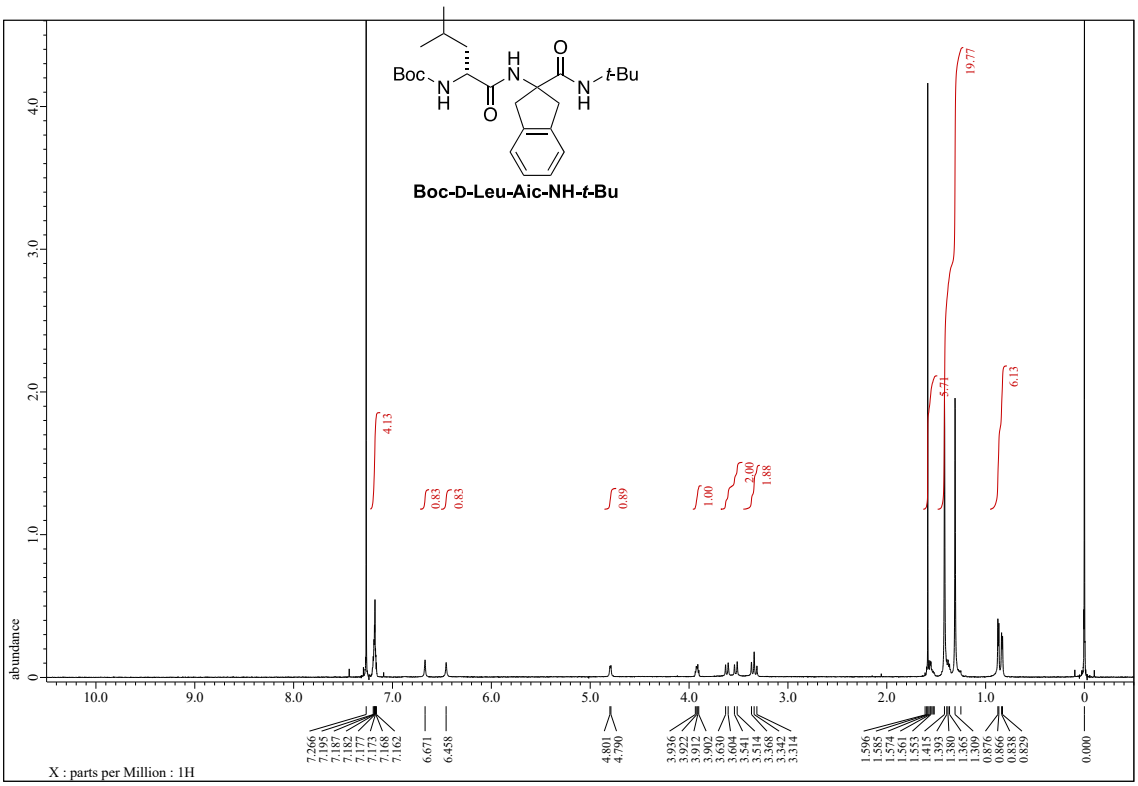

Figure S110. ^{1}H NMR spectrum (600 MHz) of Boc-D-Leu-Aic-NH-*t*-Bu in $CDCl_3$.

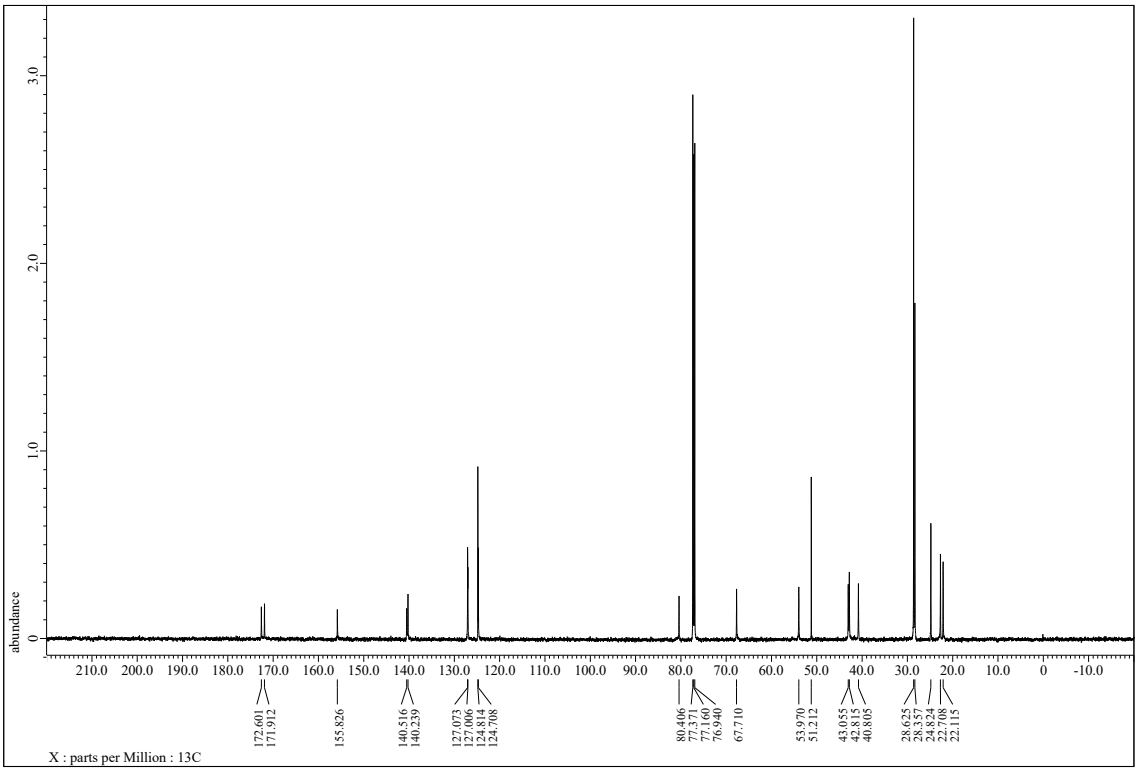

Figure S111. ^{13}C NMR spectrum (151 MHz) of Boc-D-Leu-Aic-NH-*t*-Bu in $CDCl_3$.

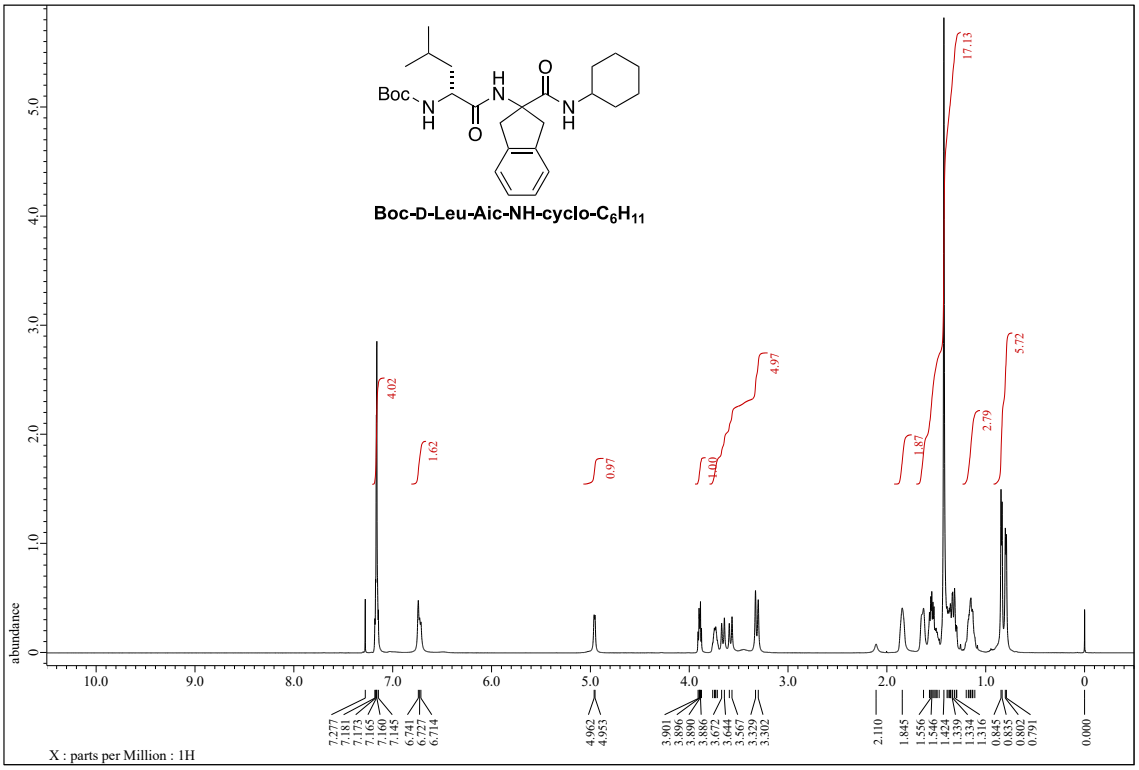

Figure S112. ^{1}H NMR spectrum (600 MHz) of Boc-D-Leu-Aic-NH-cyclo-C_6H_{11} in $CDCl_3$.

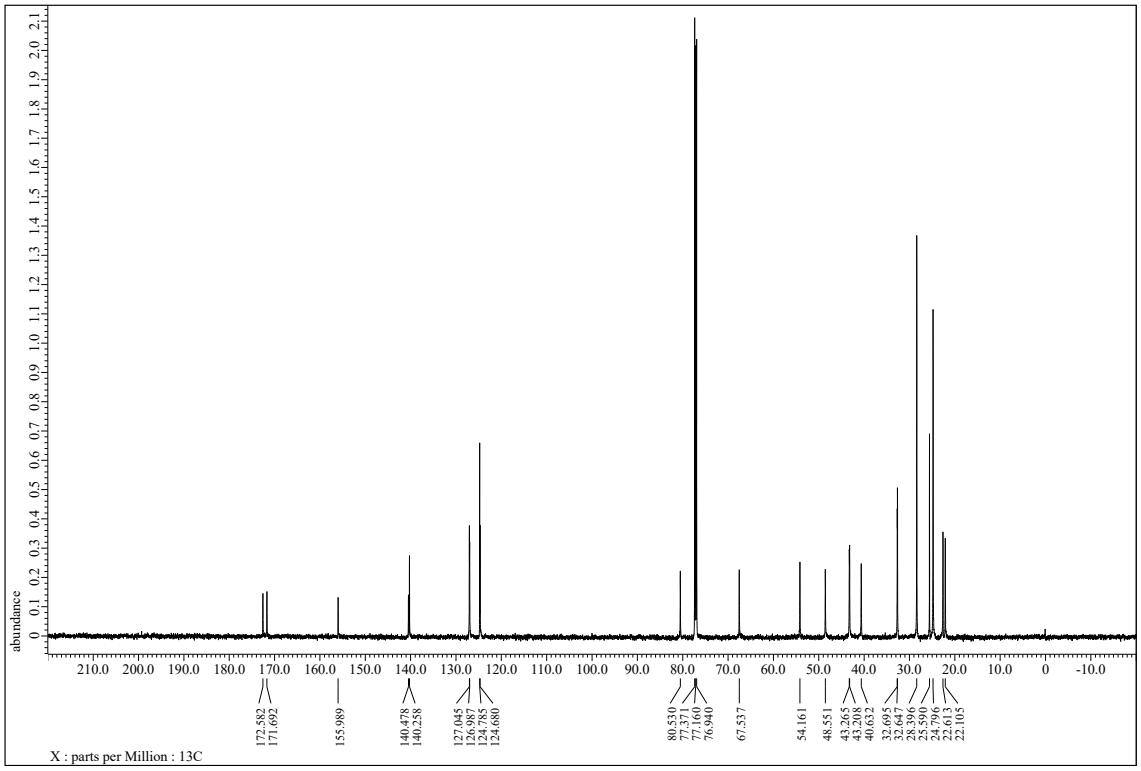

Figure S113. ^{13}C NMR spectrum (151 MHz) of Boc-D-Leu-Aic-NH-cyclo-C_6H_{11} in $CDCl_3$.

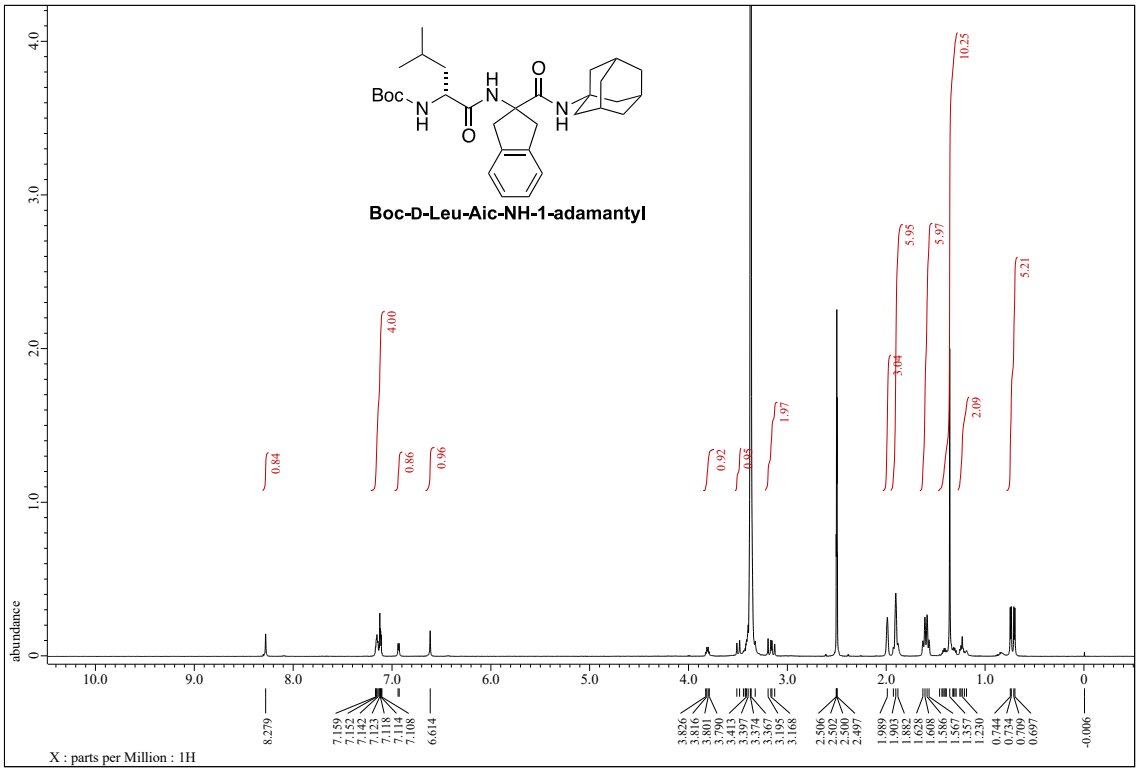

Figure S114. ^{1}H NMR spectrum (600 MHz) of Boc-D-Leu-Aic-NH-1-adamantyl in DMSO-d_6.

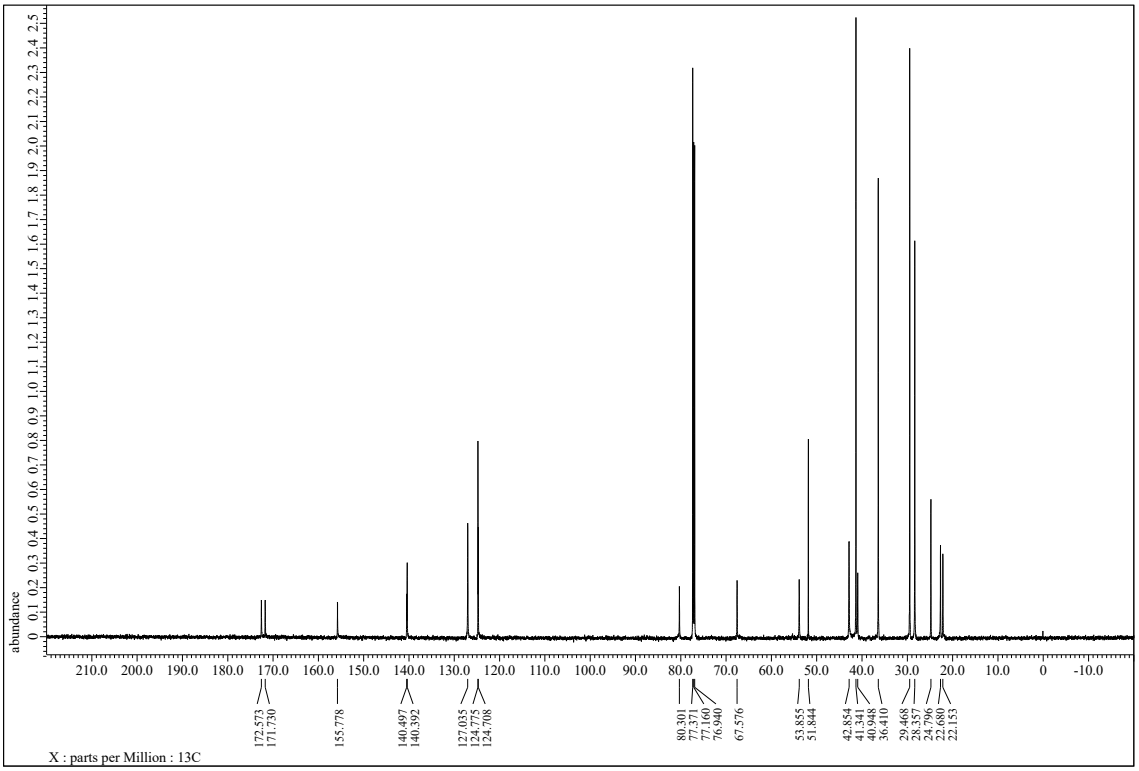

Figure S115. ^{13}C NMR spectrum (151 MHz) of Boc-D-Leu-Aic-NH-1-adamantyl in $CDCl_3$.

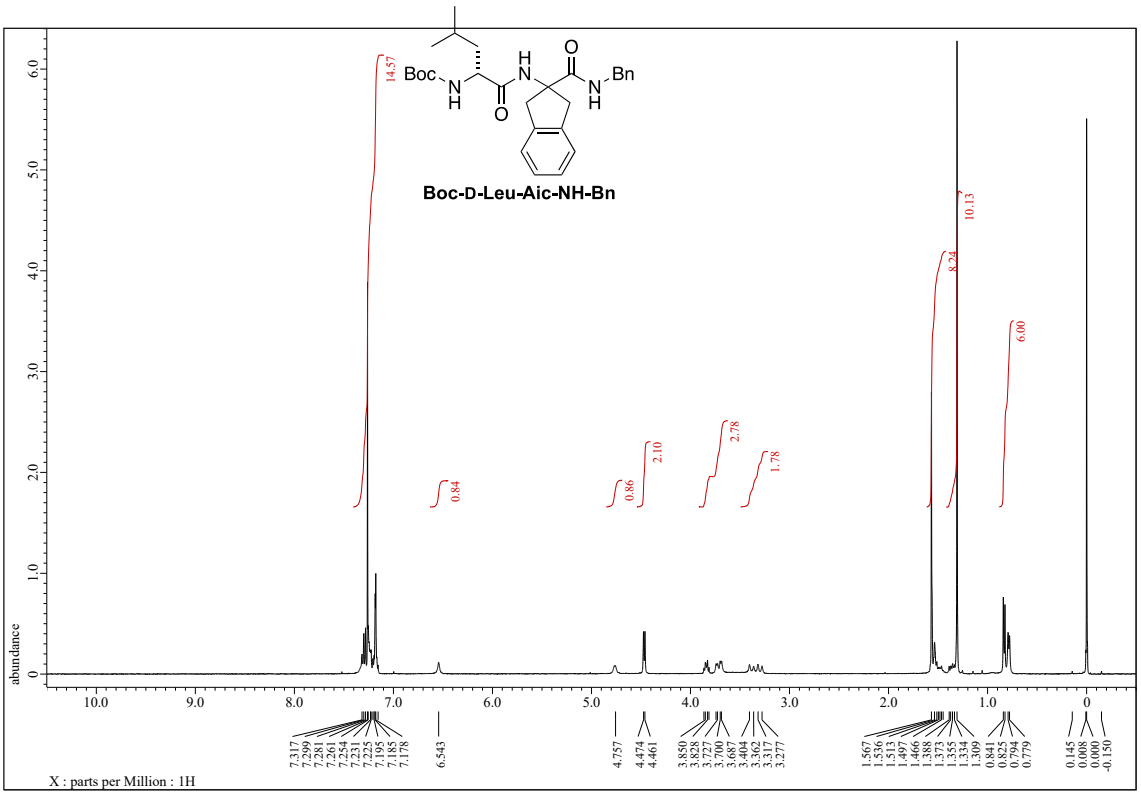

Figure S116. ^{1}H NMR spectrum (400 MHz) of Boc-D-Leu-Aic-NH-Bn in $CHCl_3$.

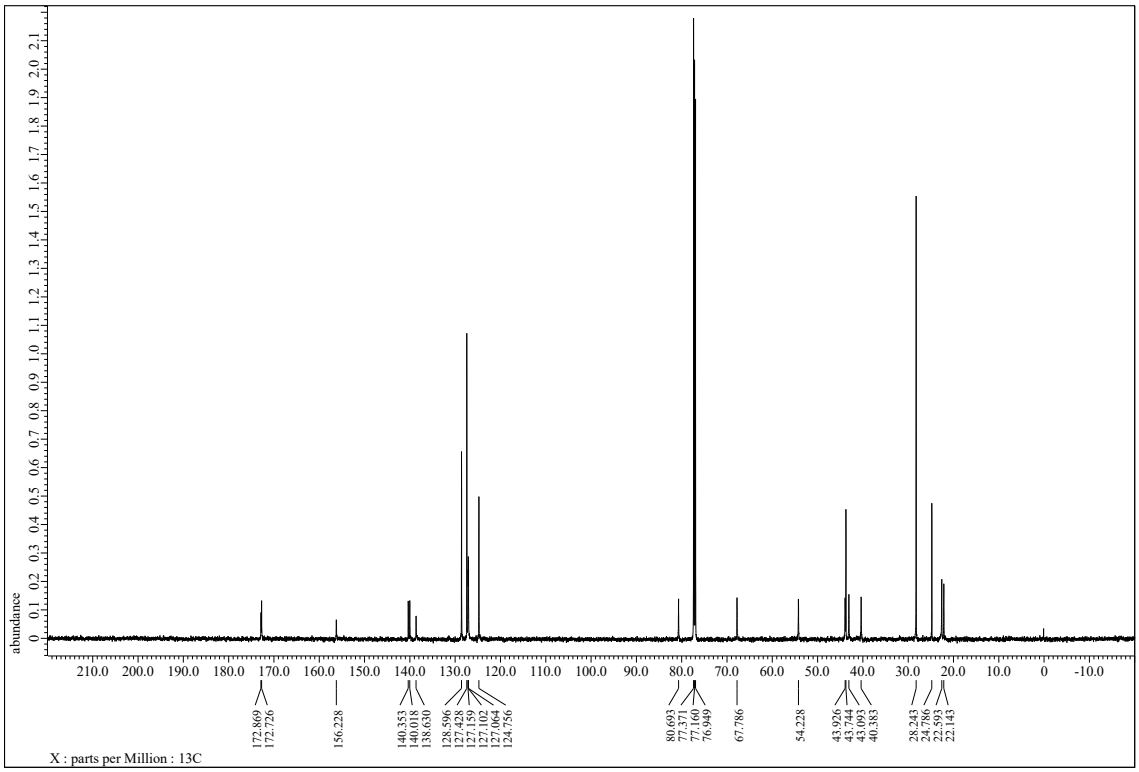

Figure S117. ^{13}C NMR spectrum (151 MHz) of Boc-D-Leu-Aic-NH-Bn in $CHCl_3$.

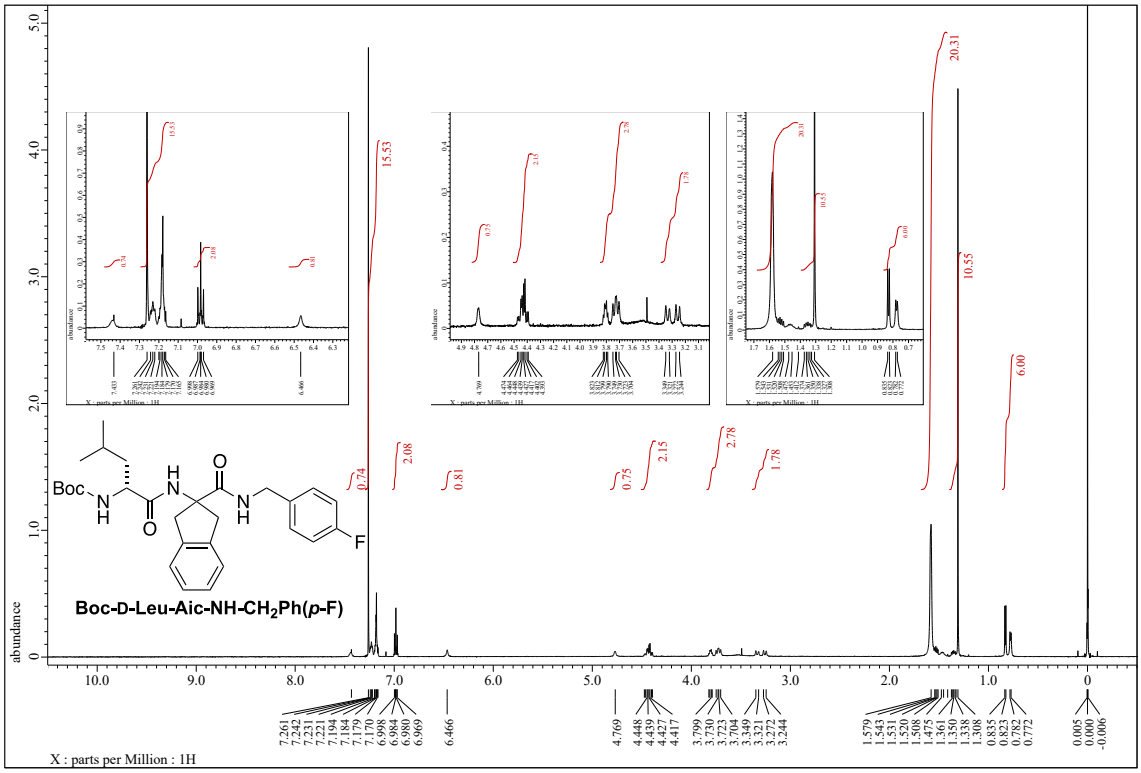

Figure S118. ^{1}H NMR spectrum (600 MHz) of Boc-D-Leu-Aic-NH-CH_2Ph(*p*-F) in $CHCl_3$.

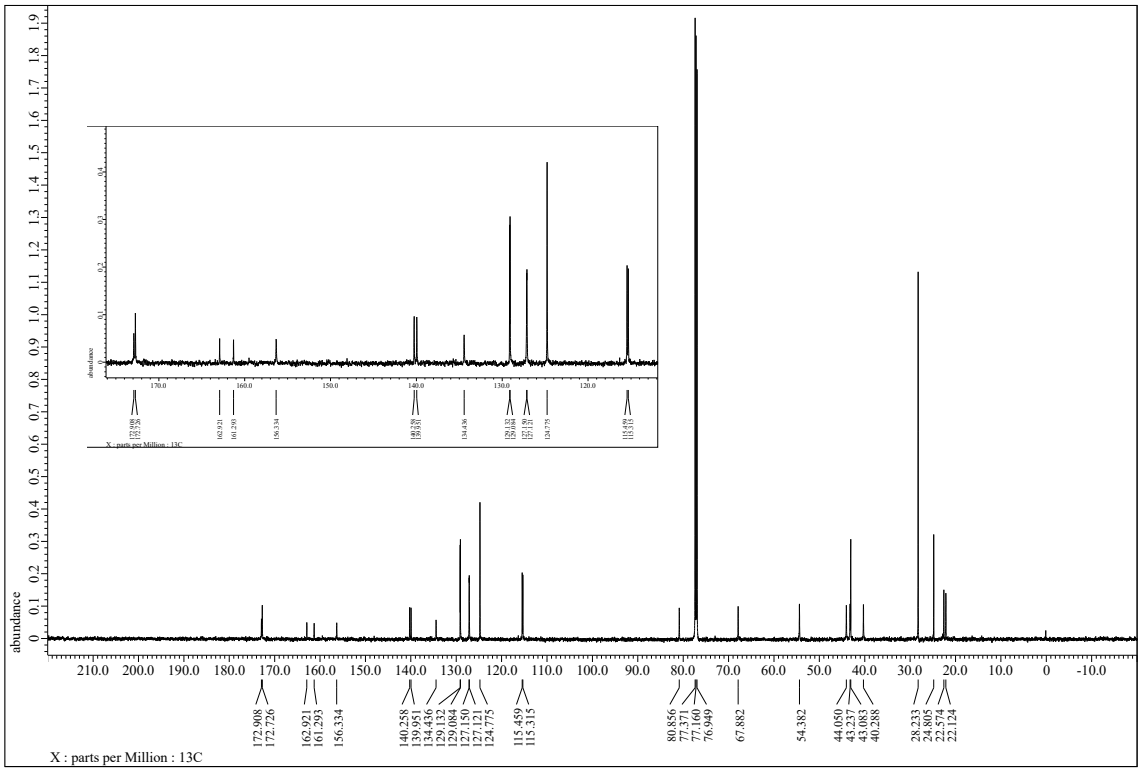

Figure S119. ^{13}C NMR spectrum (151 MHz) of Boc-D-Leu-Aic-NH-CH_2Ph(*p*-F) in $CDCl_3$.

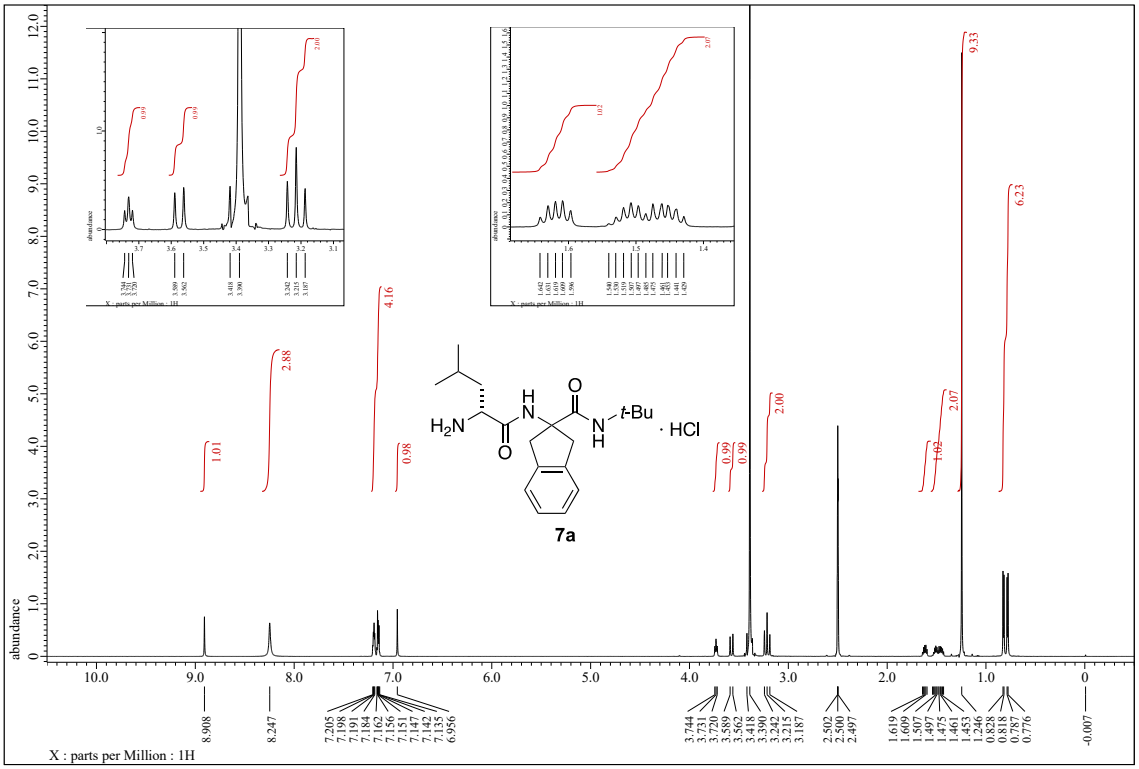

Figure S120. ^{1}H NMR spectrum (600 MHz) of D-Leu-Aic-NH-*t*-Bu·HCl (**7a**) in DMSO-d_6.

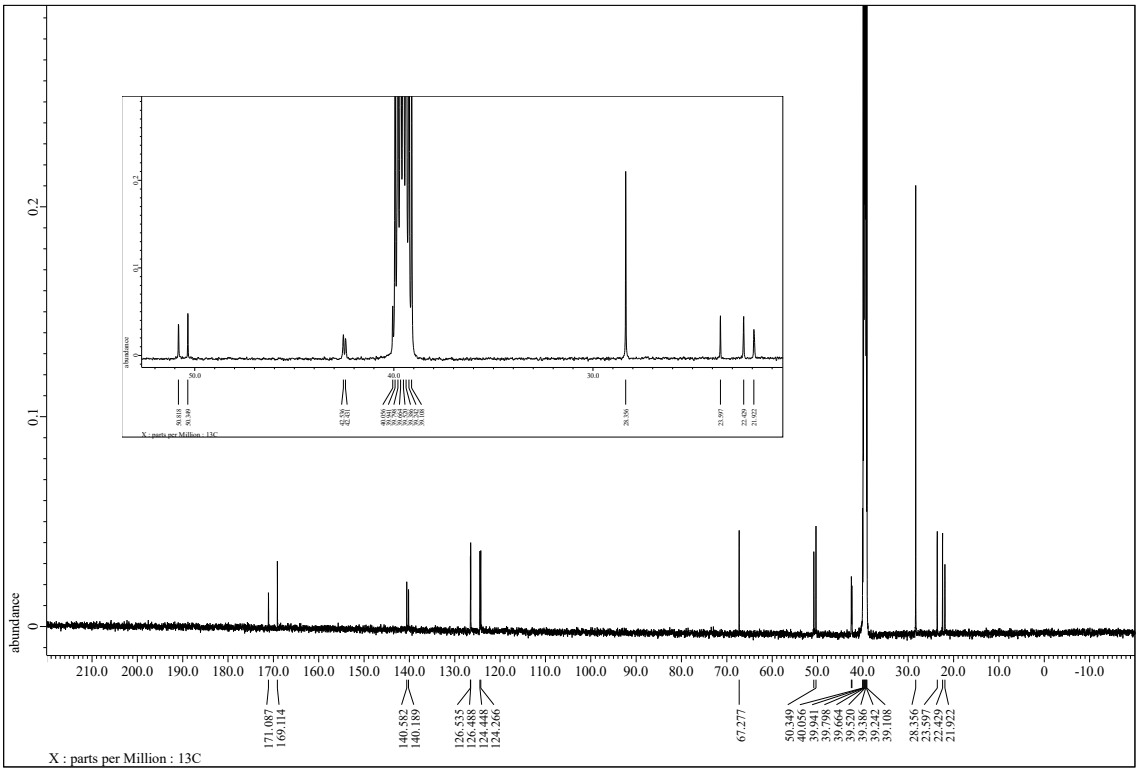

Figure S121. ^{13}C NMR spectrum (151 MHz) of D-Leu-Aic-NH-*t*-Bu·HCl (**7a**) in DMSO-d_6.

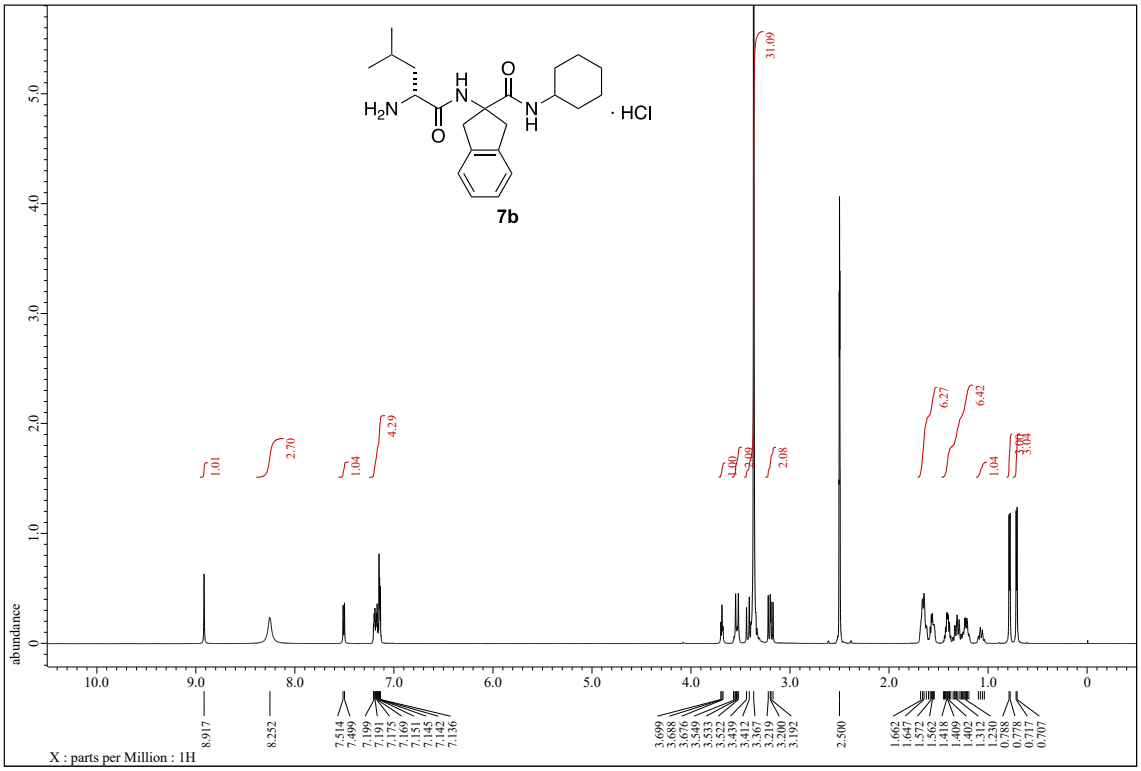

Figure S122. ^{1}H NMR spectrum (600 MHz) of D-Leu-Aic-NH-cyclohexyl-C_6H_{11}·HCl (**7b**) in DMSO-d_6.

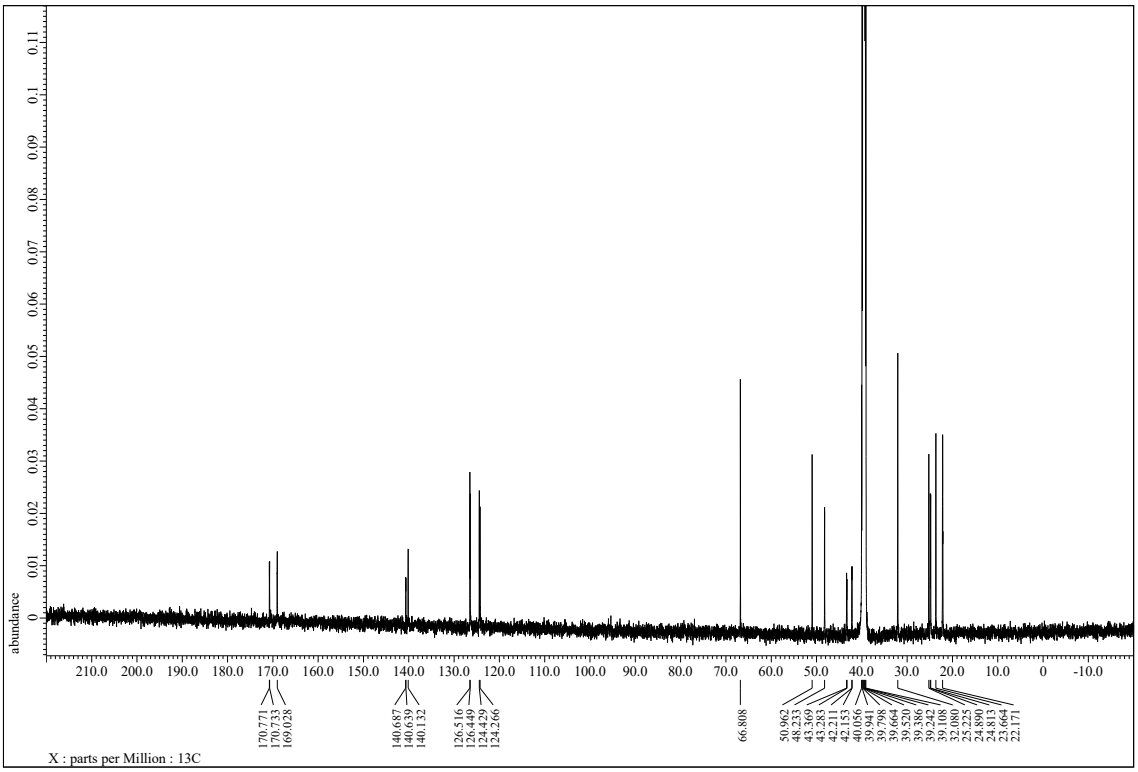

Figure S123. ^{13}C NMR spectrum (151 MHz) of D-Leu-Aic-NH-cyclo-C_6H_{11}·HCl (**7b**) in DMSO-d_6.

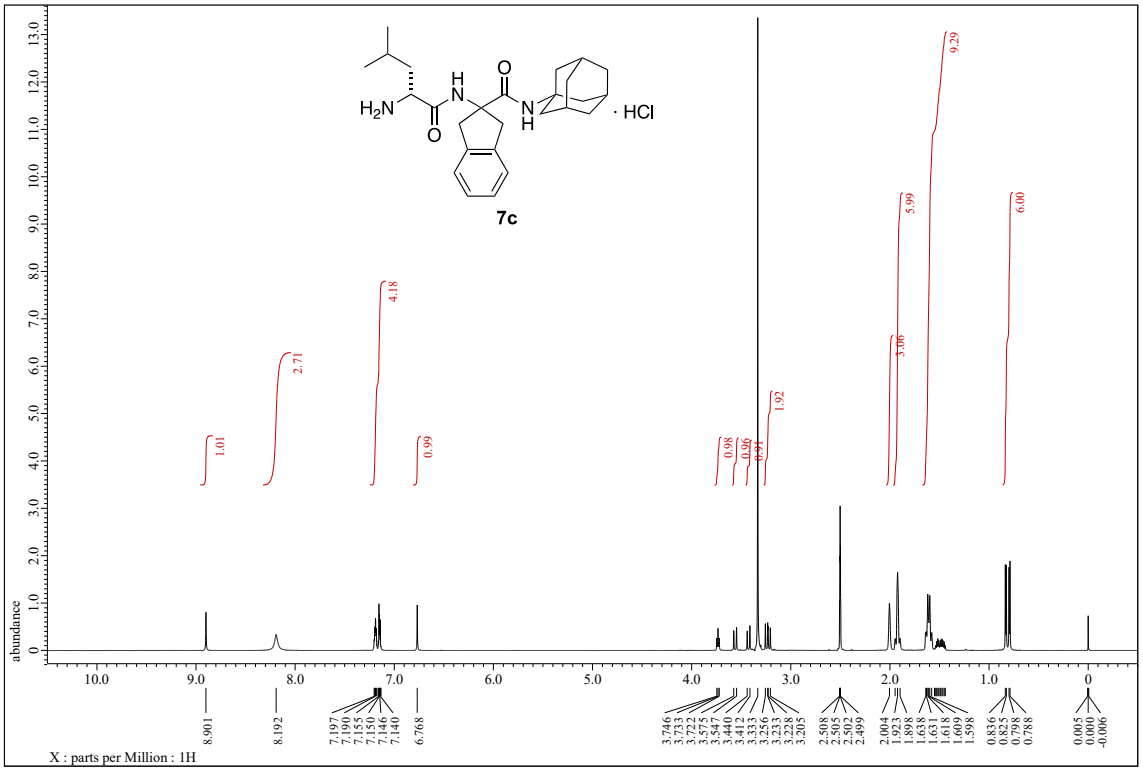

Figure S124. ^{1}H NMR spectrum (600 MHz) of D-Leu-Aic-NH-1-adamantyl·HCl (**7c**) in DMSO-d_6.

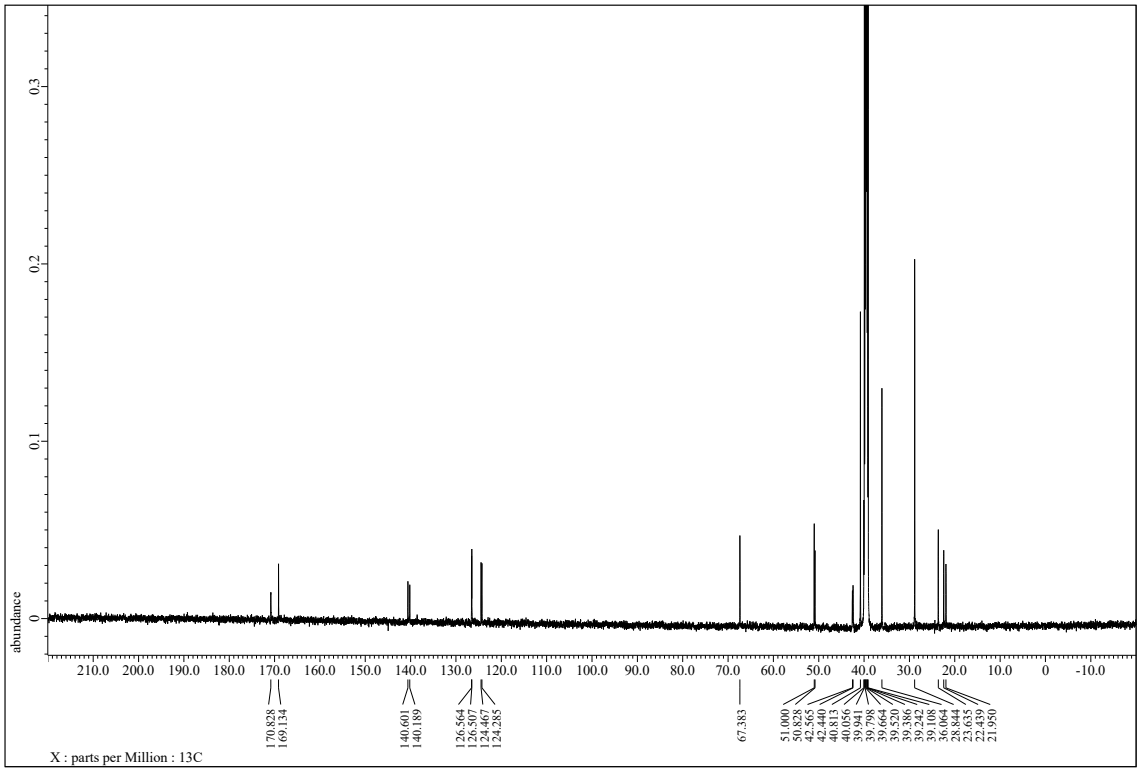

Figure S125. ^{13}C NMR spectrum (151 MHz) of D-Leu-Aic-NH-1-adamantyl·HCl (**7c**) in DMSO-d_6.

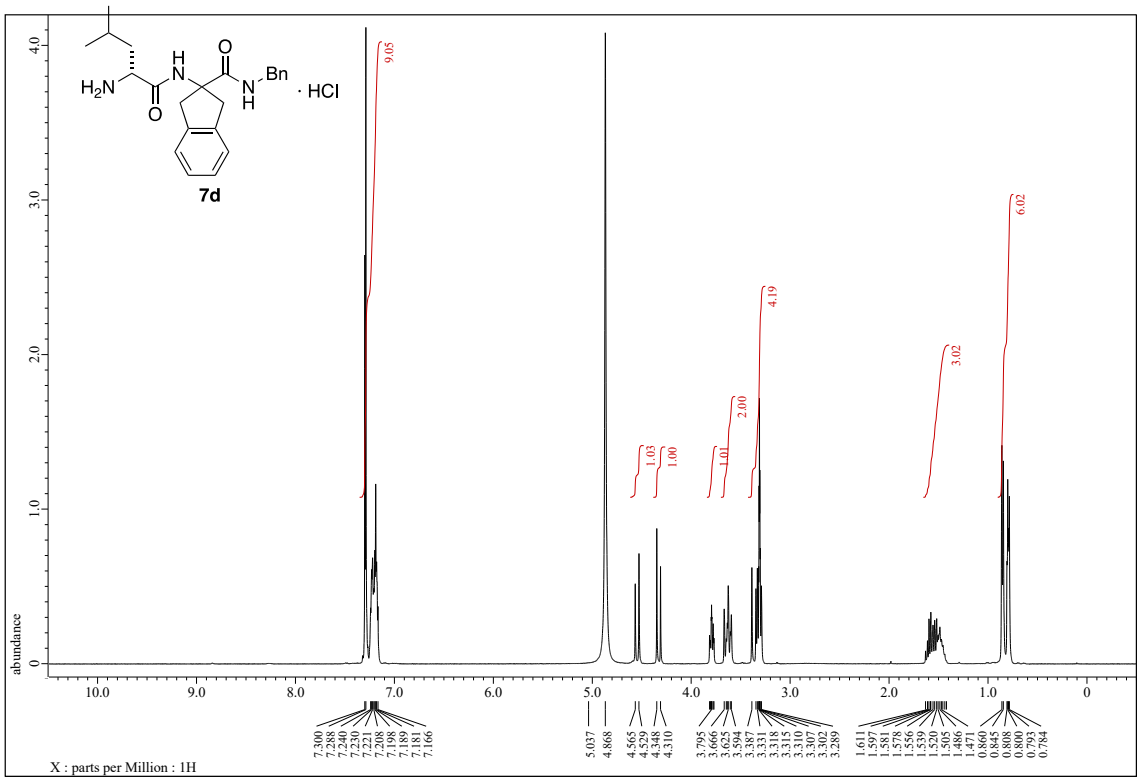

Figure S126. [1]H NMR spectrum (400 MHz) of D-Leu-Aic-NH-Bn·HCl (**7d**) in MeOD.

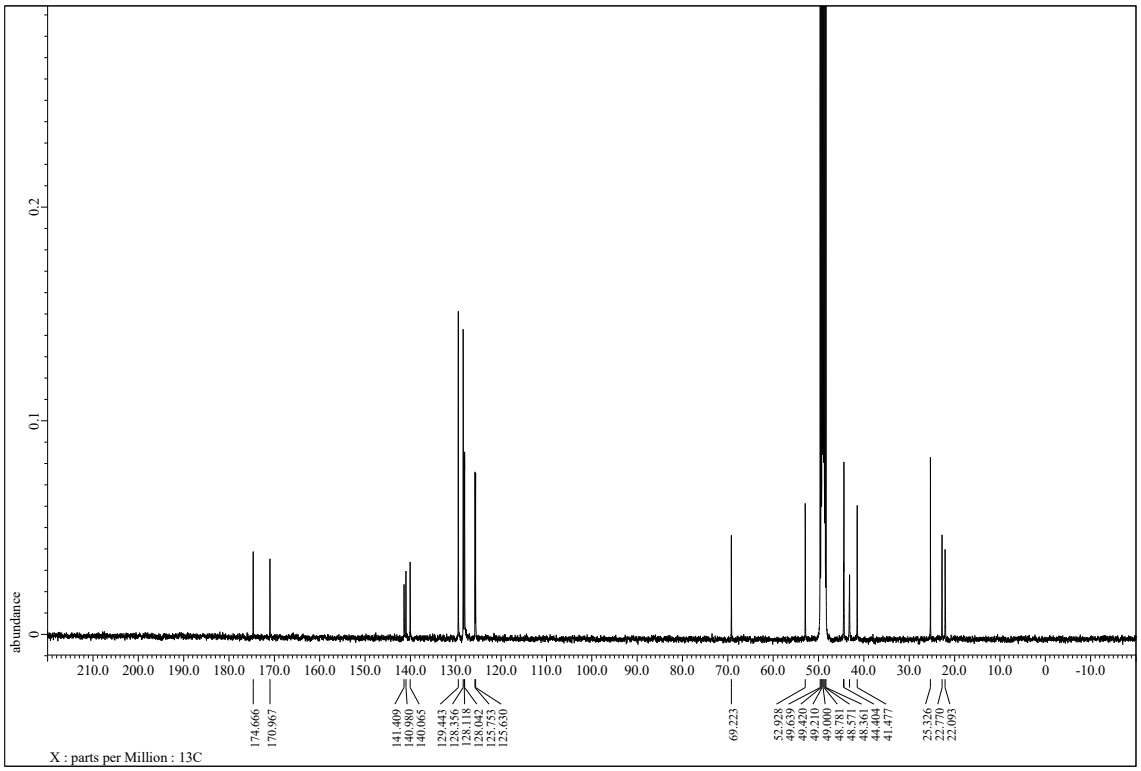

Figure S127. [13]C NMR spectrum (101 MHz) of D-Leu-Aic-NH-Bn·HCl (**7d**) in MeOD.

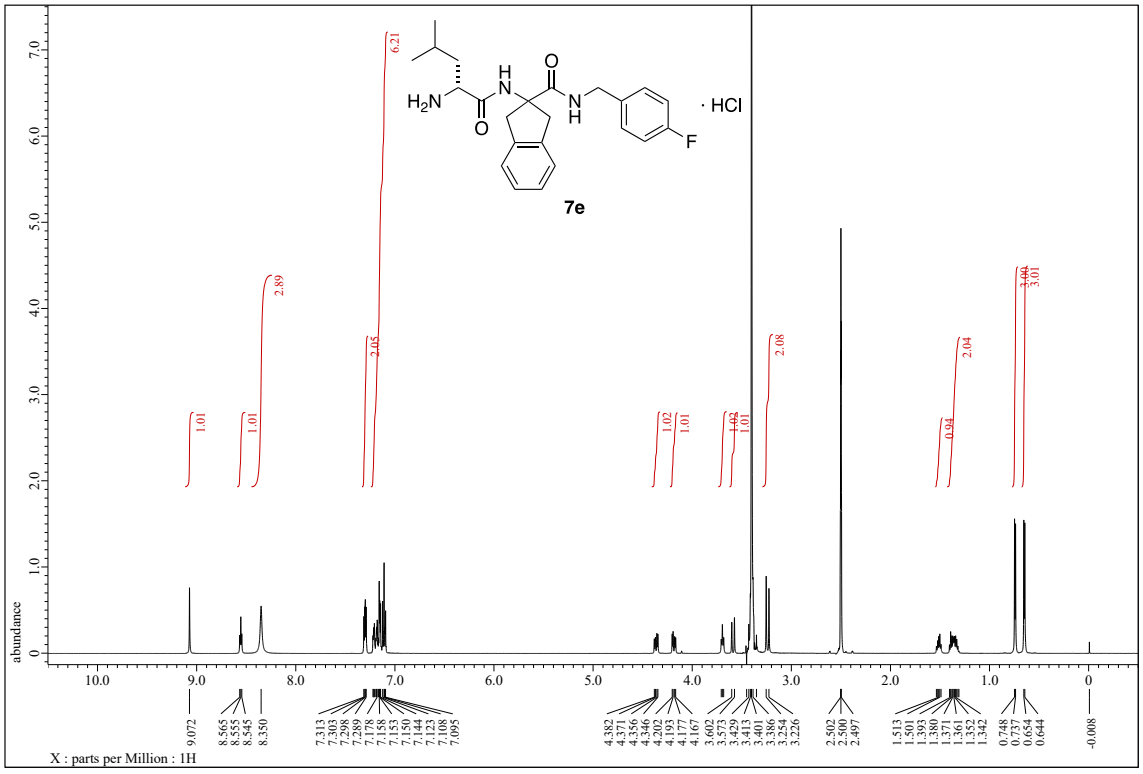

Figure S128. ^{1}H NMR spectrum (600 MHz) of D-Leu-Aic-NH-CH_2Ph(*p*-F)·HCl (**7e**) in DMSO-d_6.

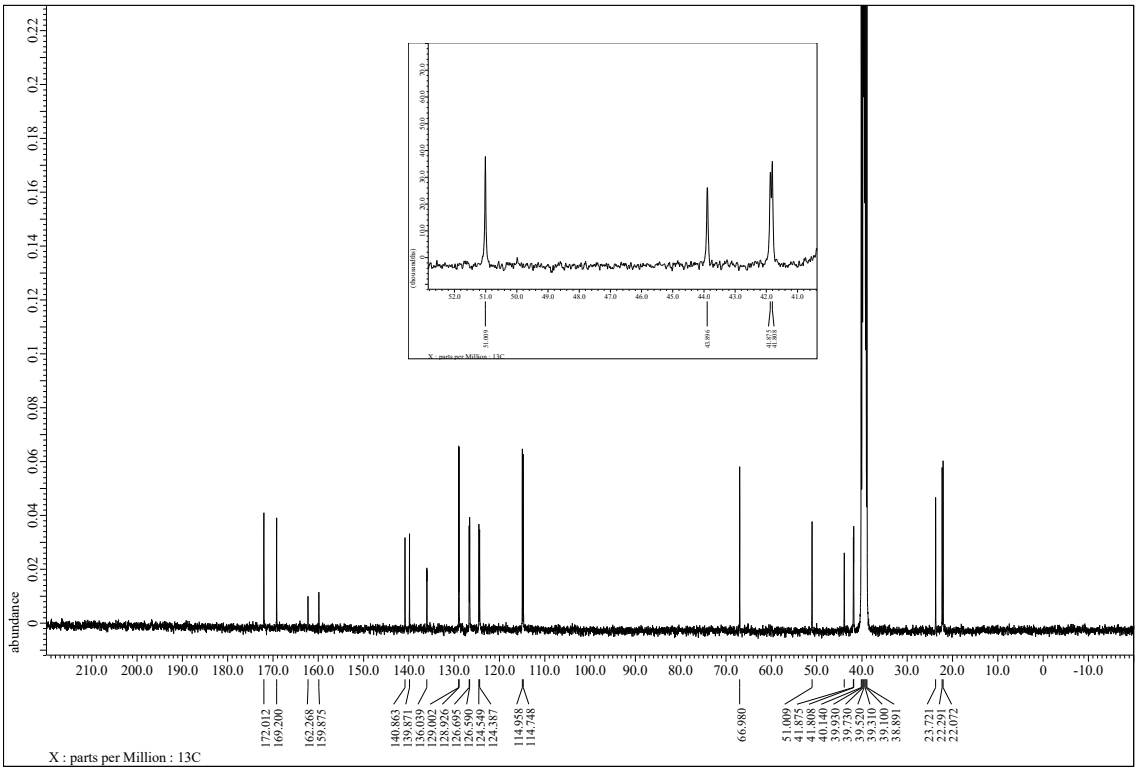

Figure S129. ^{13}C NMR spectrum (101 MHz) of D-Leu-Aic-NH-CH_2Ph(*p*-F)·HCl (**7e**) in DMSO-d_6.

15. Supplementary Figures S130–143 (HPLC Charts)

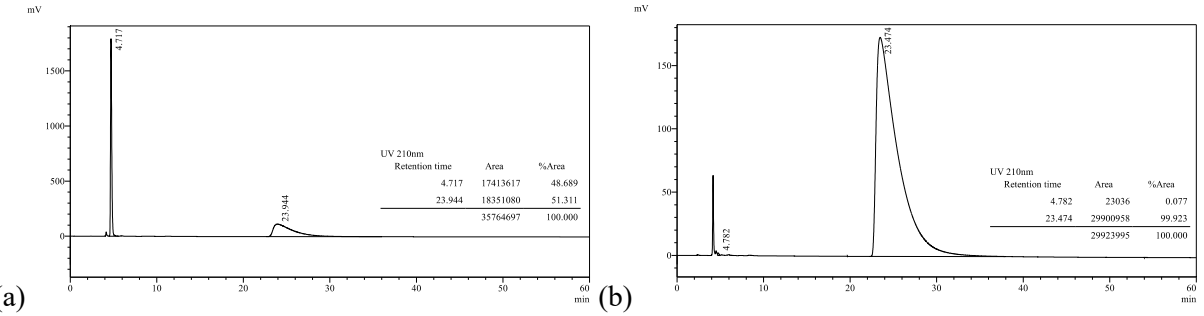

Figure S130. HPLC charts of Ac-DL-Phe-Ac_5c-NH-Bn (a), Ac-L-Phe-Ac_5c-NH-Bn (**5d**) (b).

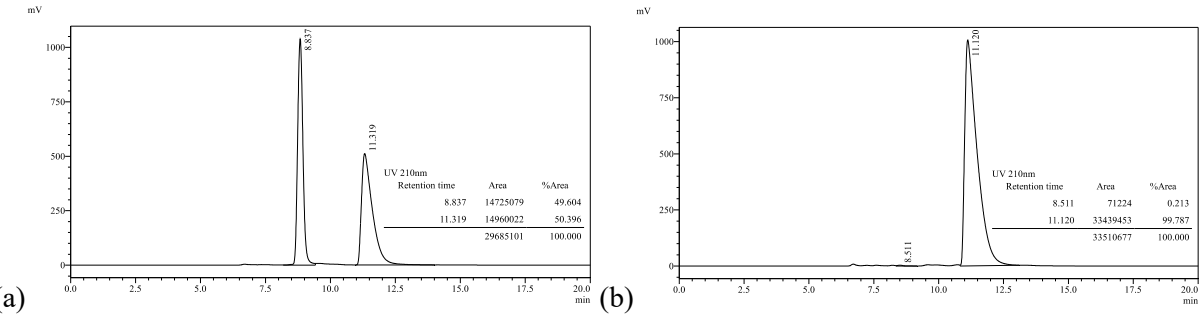

Figure S131. HPLC charts of Boc-DL-Val-Ac_5c-NH-Bn (a), Boc-L-Val-Ac_5c-NH-Bn (**5e**) (b).

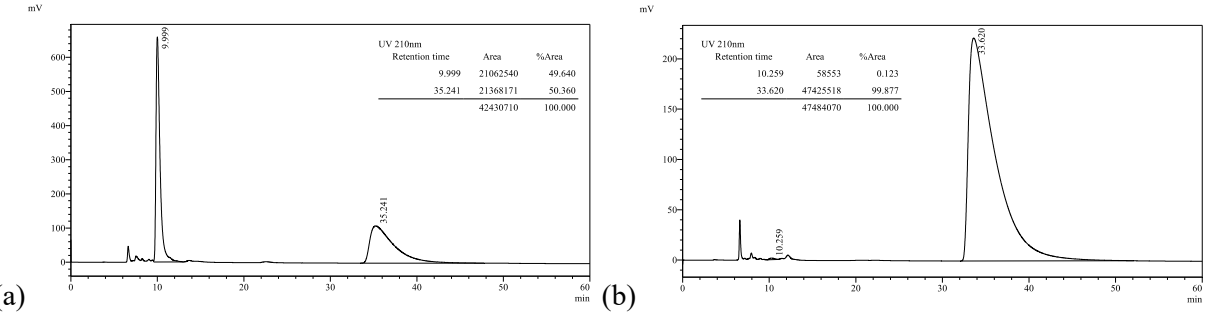

Figure S132. HPLC charts of Boc-DL-Phe-Ac_5c-NH-Bn (a), Boc-L-Phe-Ac_5c-NH-Bn (**5f**) (b).

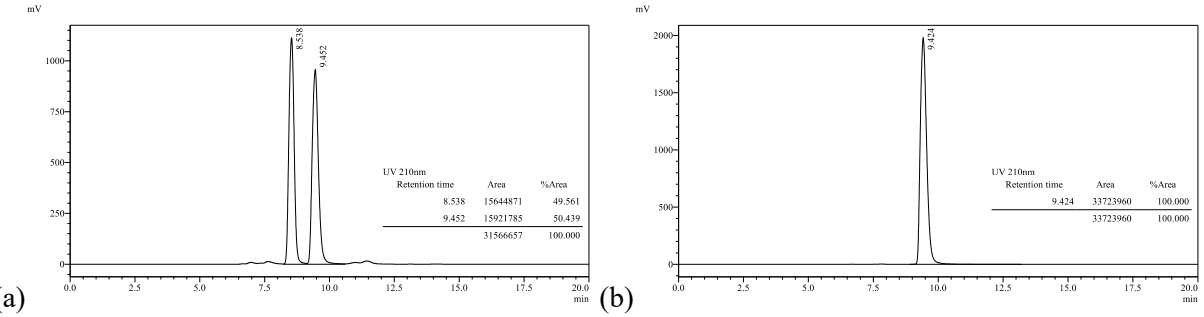

Figure S133. HPLC charts of Boc-DL-Pro-Ac_5c-NH-Bn (a), Boc-L-Pro-Ac_5c-NH-Bn (**5g**) (b).

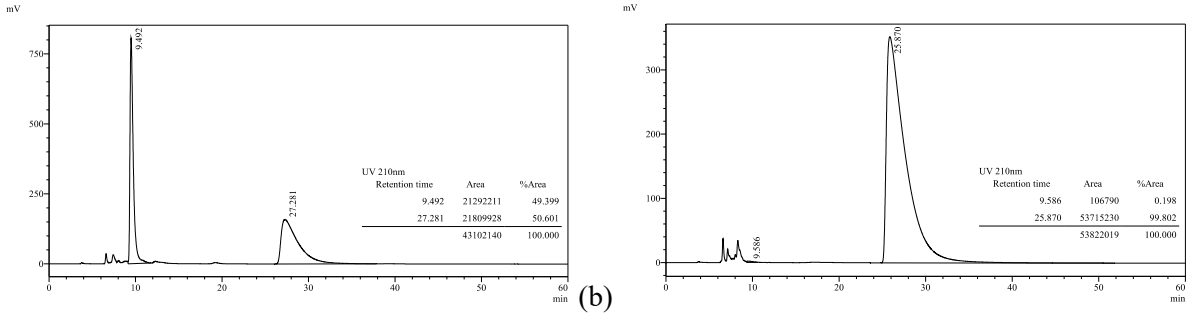

Figure S134. HPLC charts of Boc-DL-Pro-Ac$_5$c-NH-Bn (a), Boc-L-Pro-Ac$_5$c-NH-Bn (**5g**) (b). **5g** was synthesized at 60 °C.

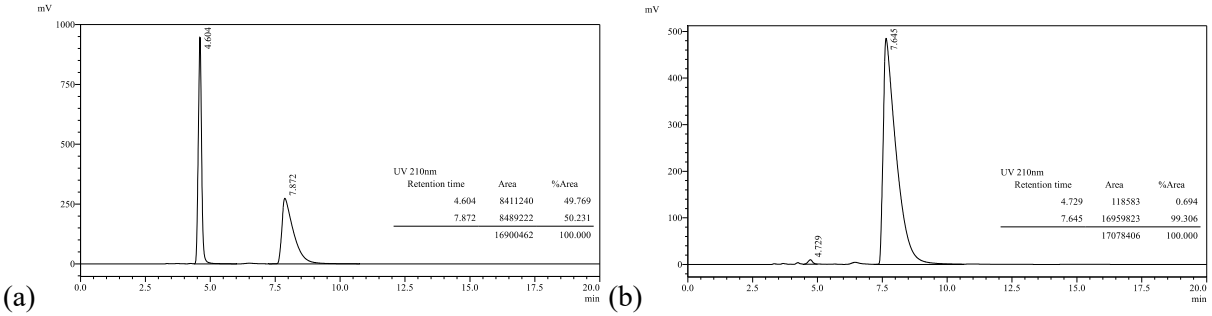

Figure S135. HPLC charts of Boc-DL-Met-Ac$_5$c-NH-Bn (a), Boc-L-Met-Ac$_5$c-NH-Bn (**5h**) (b).

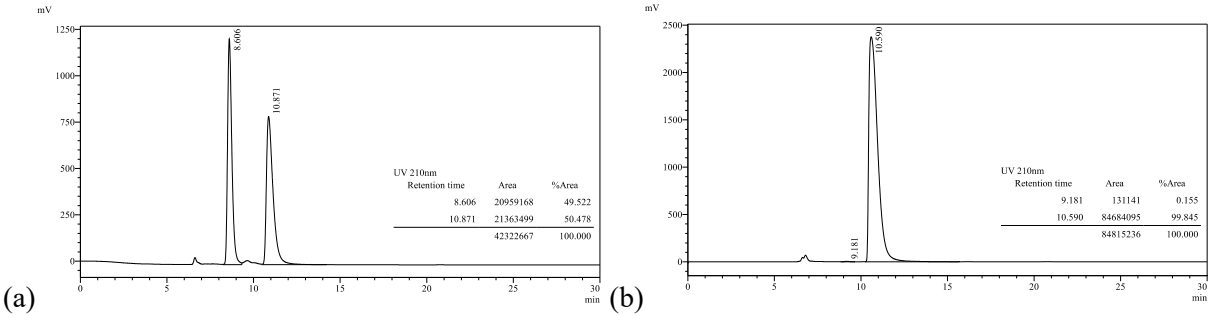

Figure S136. HPLC charts of Boc-DL-Thr(OBn)-Ac$_5$c-NH-Bn (a), Boc-L-Thr(OBn)-Ac$_5$c-NH-Bn (**5i**) (b).

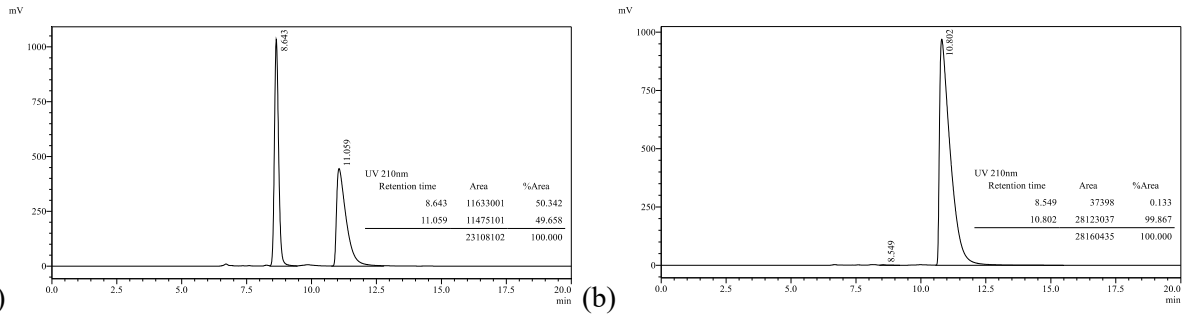

Figure S137. HPLC charts of Boc-DL-Glu(O*t*-Bu)-Ac$_5$c-NH-Bn (a), Boc-L-Glu(O*t*-Bu)-Ac$_5$c-NH-Bn (**5j**) (b).

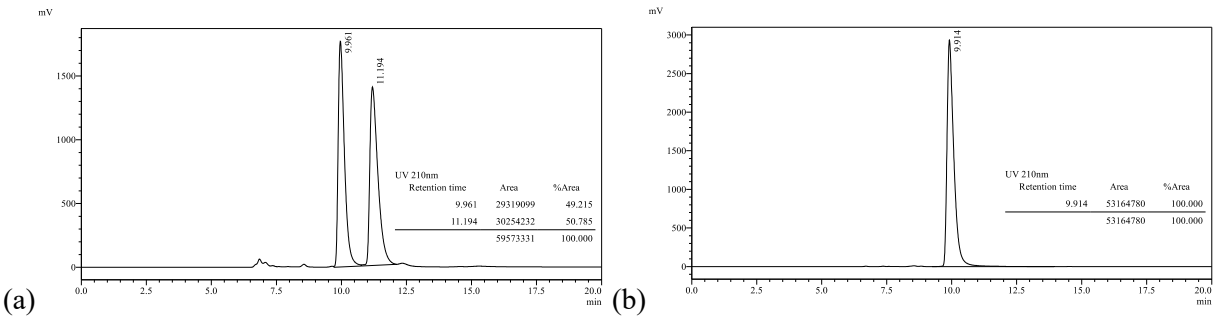

Figure S138. HPLC charts of Boc-DL-Trp(CHO)-Ac_5c-NH-Bn (a), Boc-L-Trp(CHO)-Ac_5c-NH-Bn (**5k**) (b).

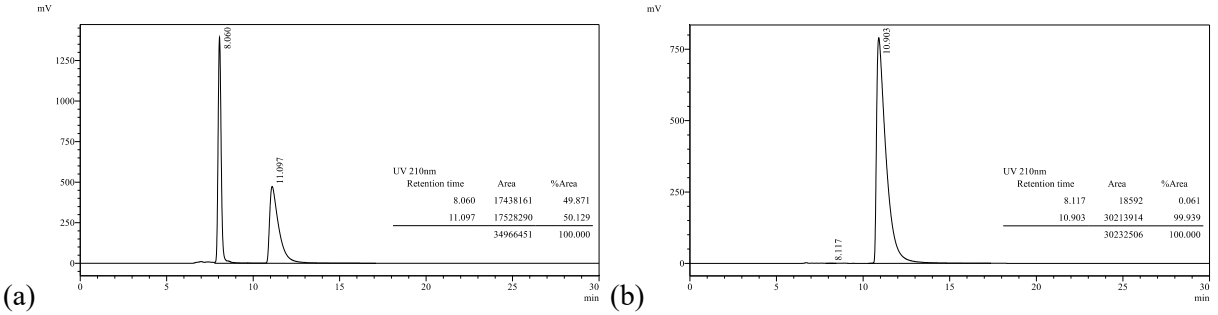

Figure S139. HPLC charts of Boc-DL-Leu-Aic-NH-*t*-Bu (a), Boc-D-Leu-Aic-NH-*t*-Bu (b).

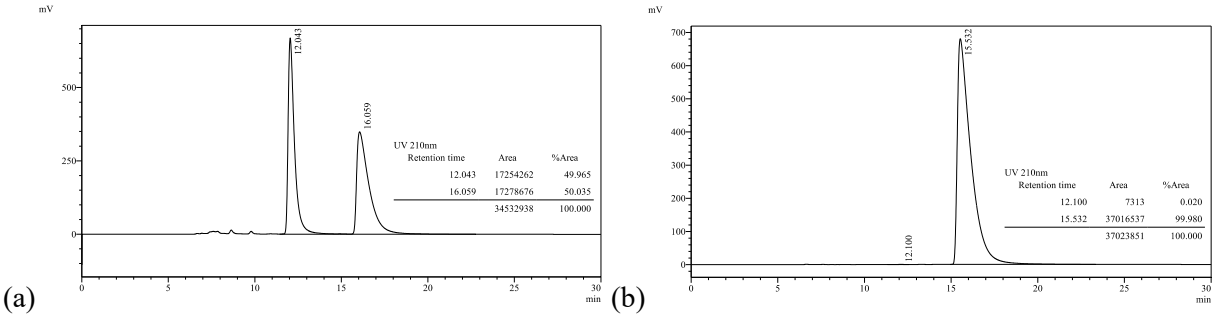

Figure S140. HPLC charts of Boc-DL-Leu-Aic-NH-cyclo-C_6H_{11} (a), Boc-D-Leu-Aic-NH-cyclo-C_6H_{11} (b).

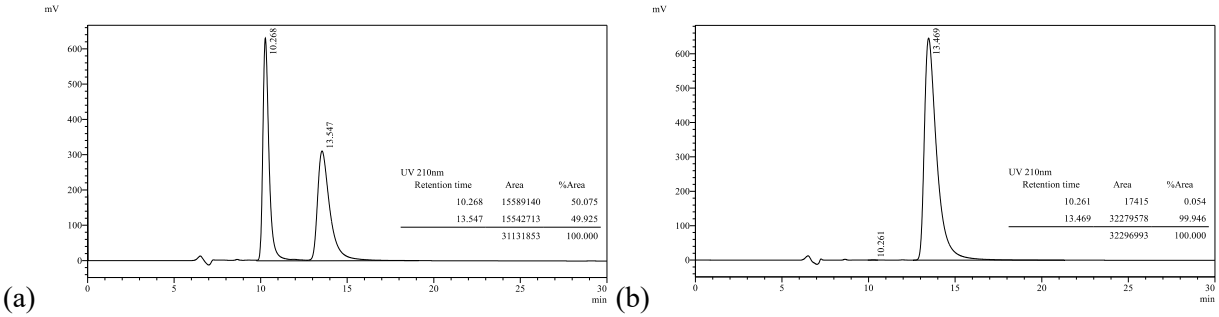

Figure S141. HPLC charts of Boc-DL-Leu-Aic-NH-1-adamantyl (a), Boc-D-Leu-Aic-NH-1-adamantyl (b).

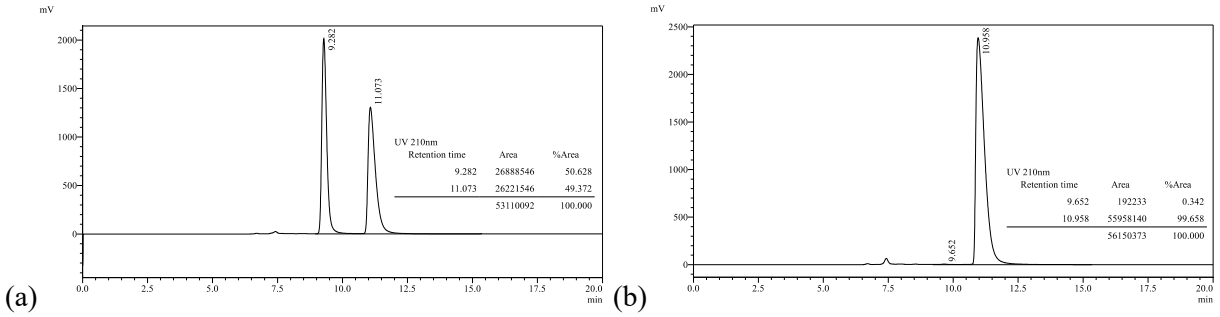

Figure S142. HPLC charts of Boc-DL-Leu-Aic-NH-Bn (a), Boc-D-Leu-Aic-NH-Bn (b).

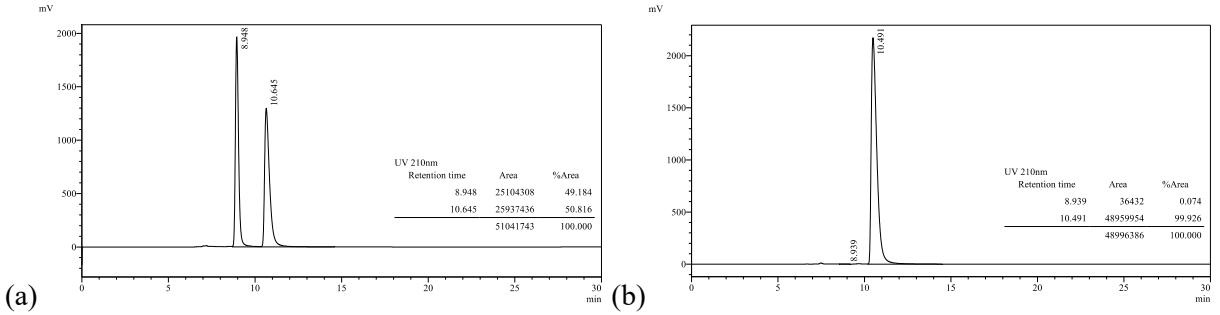

Figure S143. HPLC charts of Boc-DL-Leu-Aic-NH-CH_2-Ph(*p*-F) (a), Boc-D-Leu-Aic-NH-CH_2-Ph(*p*-F) (b).