Electron donor−acceptor complex of aryl sulfonium salt enabled hydrogen/halogen atom transfer: C(sp^3)−H alkylation of glycine derivatives and late-stage modification of peptides

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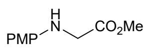
1. General information

All commercially available reagents were used without further purification unless otherwise stated. All solvents were purified and dried according to standard methods prior to use. NMR spectra were recorded on Bruker 400 M and 600 M instrument spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as internal standard unless otherwise stated. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, and brs = broad signal, coupling constant (s) in Hz, integration). Data for ^{13}C NMR and ^{19}F NMR are reported in terms of chemical shift (δ, ppm). Reactions were monitored by thin layer chromatography (TLC). Column chromatography purifications were carried out using silica gel. Melting points were measured on a SCW X-4 and values are uncorrected. UV-Vis absorption spectra were recorded by using BIOMATE 3S UV-Visible Spectrophotometer. All new compounds were characterized by high resolution mass spectra (HRMS, ESI source).

2. Synthesis of substrates

2.1 Glycine derivatives and peptides



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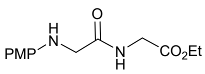

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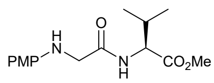

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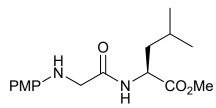

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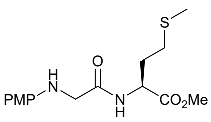

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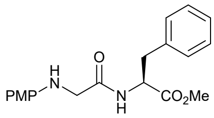

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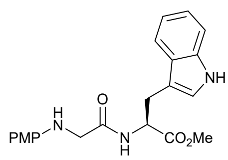

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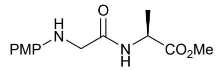

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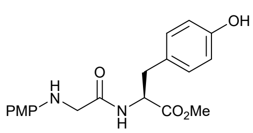

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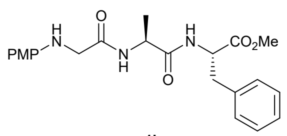

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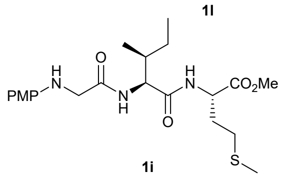
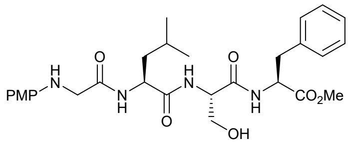


1i



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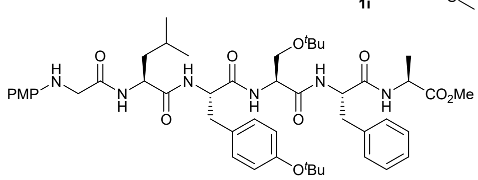
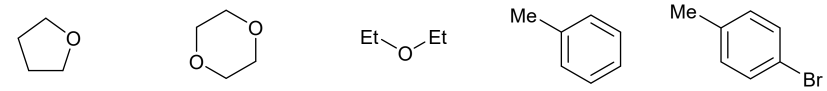


1k

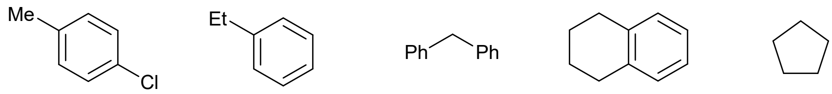
Esters of *N*-aryl-substituted glycine,[1] dipeptides[2] and tripeptides[2] were all prepared according to previous reports. Other peptides were synthesized via solid phase synthesis.

2.2 HAT reaction substrates

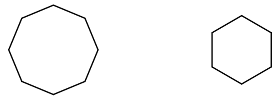
2a-2l were commercially available reagents.



2a 2b 2c 2d 2e



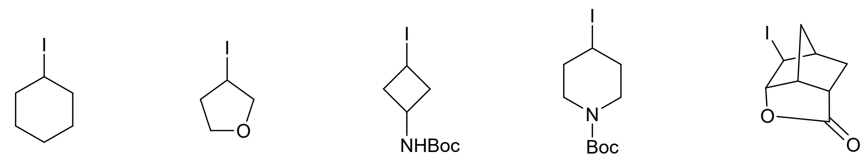
2f 2g 2h 2i 2j



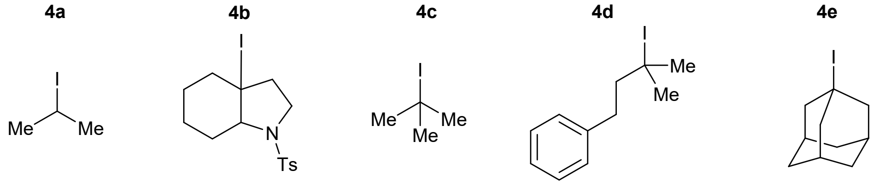
2k 2l

2.3 Alkyl Iodides

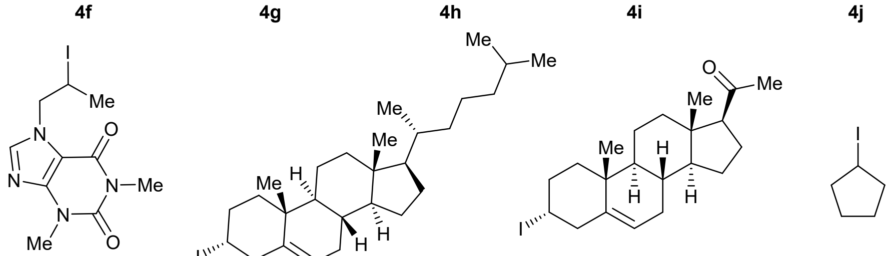
4a-4d, 4f, 4h, 4j, 4n were commercially available, **4e, 4g, 4k-4m** were prepared according to previous reports,[3] **4i** was prepared according to previous report.[4]



4a 4b 4c 4d 4e



4f 4g 4h 4i 4j



4k 4l 4m 4n

2.4 Aryl sulfonium salt

Aryl sulfonium salt (Tol)DBT·OTf was prepared according to previous report.[5]

3. General procedures

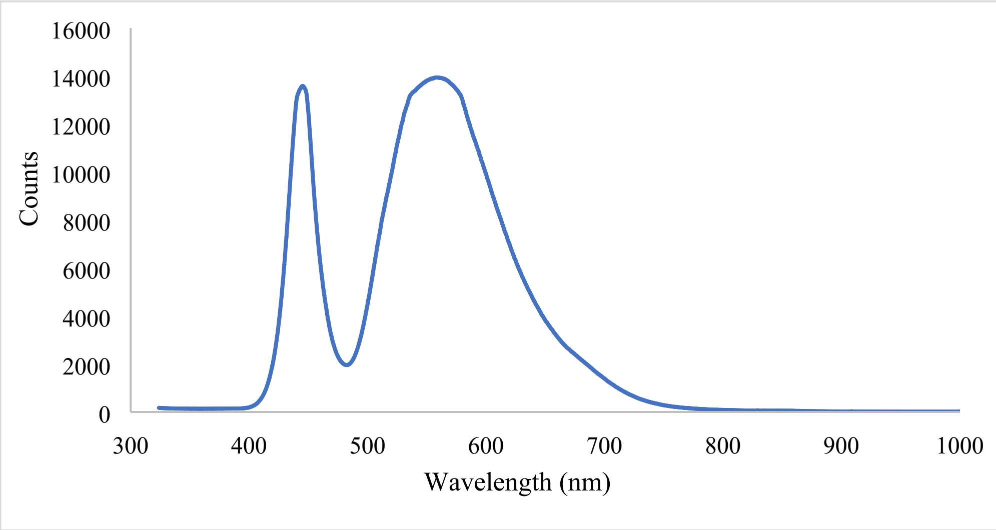
Procedure A: To an oven-dried 10 mL quartz test tube with a stirring bar was added derivative of glycine or peptide **1** (0.1 mmol), (Tol)DBT·OTf (0.2 mmol) and DABCO (0.3 mmol). Then, air was withdrawn and backfilled with Ar (three times), acetone (0.5 mL) and alkanes (0.5 ml) were added. The reaction mixture was irradiated with white LED (27 W) for 12 h under continuous cooling via a fan. Then, the reaction was quenched with water (4 mL), extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate, concentrated in vacuo, and purified by column chromatography (hexane/ethyl acetate) to afford the product **3aa-3ak, 3ba-3ja, 5aa**.

Procedure B: To an oven-dried 10 mL quartz test tube with a stirring bar was added derivative of glycine or peptide **1** (0.1 mmol), (Tol)DBT·OTf (0.2 mmol) and DABCO (0.3 mmol). Then, air was withdrawn and backfilled with Ar (three times), DMSO (0.5 mL) and alkanes (0.5 ml) were added. The reaction mixture was irradiated with white LED (27 W) for 12 h under continuous cooling via a fan. Then, the reaction was quenched with water (4 mL), extracted with CH_2Cl_2, washed with brine, dried over anhydrous sodium sulfate, concentrated in vacuo, and purified by column chromatography (CH_2Cl_2/MeOH) to afford the product **3ka**.

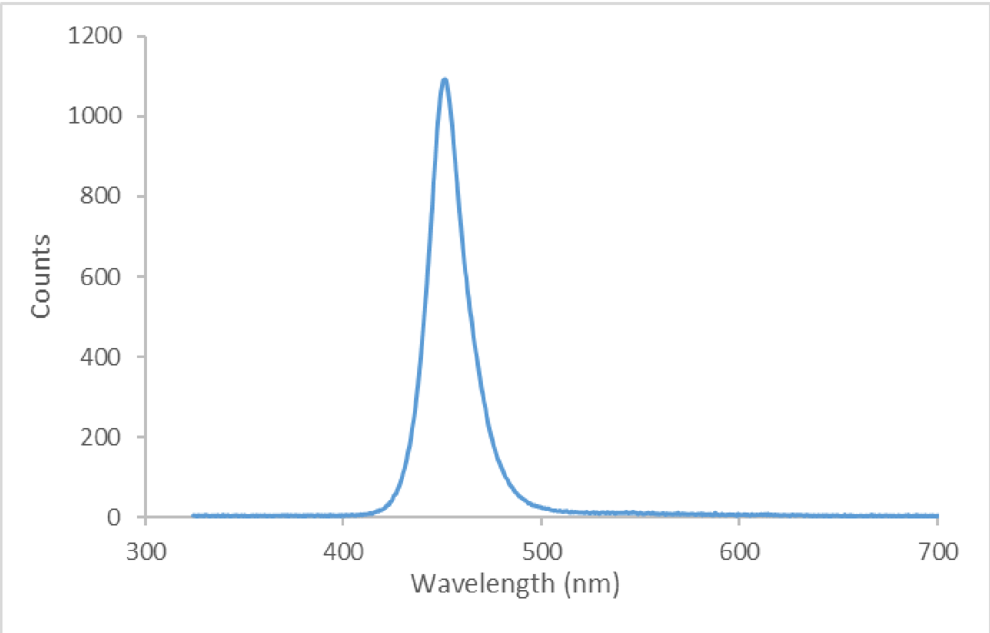
Procedure C: To an oven-dried 10 mL quartz test tube with a stirring bar was added derivative of glycine or peptide **1** (0.1 mmol), (Tol)DBT·OTf (0.2 mmol), alkyl iodides (0.3 mmol, if solid) and DABCO (0.3 mmol). Then, air was withdrawn and backfilled with Ar (three times), acetone (1.0 mL) and alkyl iodides (0.3 mmol, if liquid) were added. The reaction mixture was irradiated with blue LED (27 W) for 12 h under continuous cooling via a fan. Then, the reaction was quenched with water (4 mL), extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate, concentrated in vacuo, and purified by column chromatography (hexane/ethyl acetate) to afford the product **5aa-5am, 5ba-5ia, 5la-5ma**.

Procedure D: To an oven-dried 10 mL quartz test tube with a stirring bar was added derivative of glycine or peptide **1** (0.1 mmol), (Tol)DBT·OTf (0.2 mmol) and DABCO (0.3 mmol). Then, air was withdrawn and backfilled with Ar (three times), DMSO (1.0 mL) and alkyl iodide (0.3 mmol) were added. The reaction mixture was irradiated with blue LED (27 W) for 12 h under continuous cooling via a fan. Then, the reaction was quenched with water (4 mL), extracted with CH_2Cl_2, washed with brine, dried over anhydrous sodium sulfate, concentrated in vacuo, and purified by column chromatography (CH_2Cl_2/MeOH) to afford the product **5ka**.

The white LED (27 W) was purchased from Yihua Company. We measured the spectral profile of the white LED light by ourselves (recorded on an AVANTES®AvaSpec-ULS2048 spectrometer instrument). The result was shown as follows:



The blue LED (27 W) was purchased from Yihua Company. We measured the spectral profile of the blue LED light by ourselves (recorded on an AVANTES®AvaSpec-

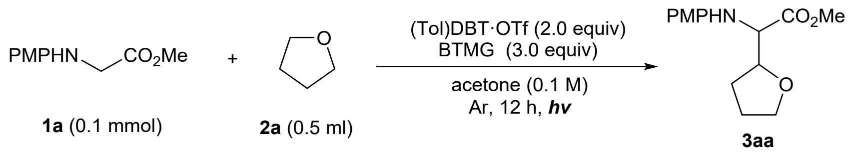


ULS2048 spectrometer instrument). The result was shown as follows:

4. Optimization of reaction conditions

4.1 Optimization of reaction conditions of HAT reactions

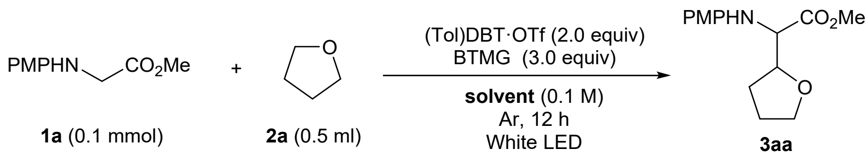
Table S1 Light source screening[a]



Entry	light source	yield (%)
1	Green LED	63
2	***White LED***	***76***
3	Blue LED	53
4	420-430 nm	48
5	410-420 nm	46
6	400-410 nm	39
7	395-400 nm	33
8	380-385 nm	33

[a] Yield was determined by ^{1}H NMR using 4-bromobenzaldehyde as an internal standard.

Table S2 Solvent screening[a]

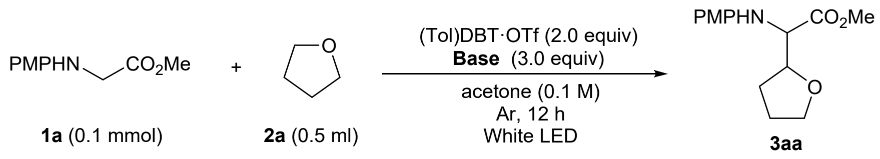


Entry	solvent	yield (%)
1	MeCN	58
2	DMSO	60
3	DMF	62
4	THF	50
5	toluene	25
6	1,4-dioxane	25
7	Et_2O	30
8	***acetone***	***76***
9	EA	35
10	MeOH	41
11	DCM	47
12	DMPU	30
13	HFIP	20

14	DMAc	44
15	DME	30

[a] Yield was determined by ^{1}H NMR using 4-bromobenzaldehyde as an internal standard.

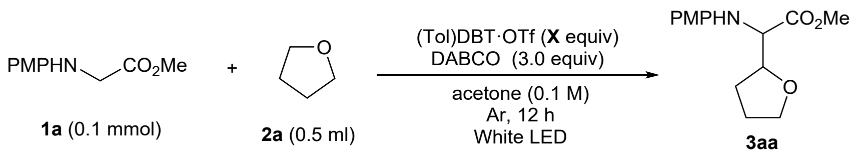
Table S3 Base screening[a]



Entry	base	yield (%)	Entry	base	yield (%)
1	BTMG	76	12	NaOH	trace
2	Cs_2CO_3	37	13	KH_2PO_4	trace
3	***DABCO***	***84***	14	KOMe	28
4	DMAP	45	15	piperazine	trace
5	K_3PO_4	34	16	DBU	55
6	KO^{t}Bu	20	17	PPh_3	trace
7	$NaHCO_3$	22	18	DIEA	10
8	NaOAc	25	19	TMG	46
9	CsF	26	20	Et_3N	30
10	K_2HPO_4	25	21	Imidazole	25
11	KF	25	22	2,6-lutidine	trace

[a] Yield was determined by ^{1}H NMR using 4-bromobenzaldehyde as an internal standard.

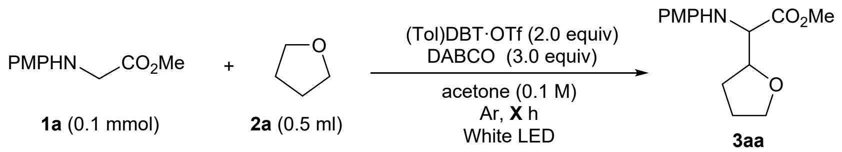
Table S4 Screening the loading of (Tol)DBT·OTf[a]



Entry	X	yield (%)
1	1.0	28
2	1.5	50
3	***2.0***	***84***

[a] Yield was determined by ^{1}H NMR using 4-bromobenzaldehyde as an internal standard.

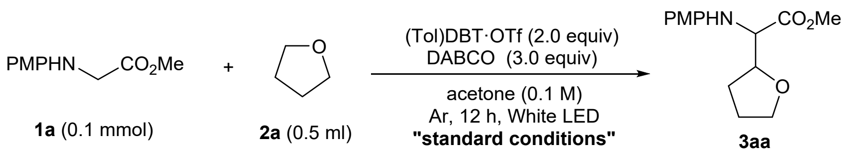
Table S5 Reaction time screening[a]



Entry	X	yield (%)
1	9	70
2	***12***	***84***

[a] Yield was determined by ^{1}H NMR using 4-bromobenzaldehyde as an internal standard.

Table S6 Control experiments under standard reaction conditions[a]

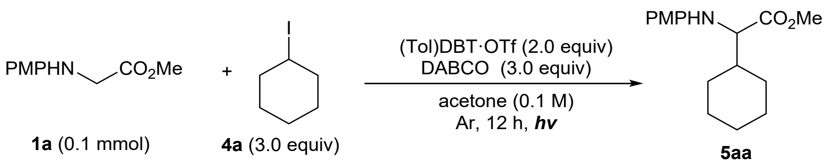


Entry	deviation from the "standard conditions"	NMR yield (%)
1	**none**	**84 (80)**
2	other bases instead of DABCO	< 76
5	other solvents instead of acetone	< 65
9	without base	0
10	without light	0
11	without light and heated to 80 °C	0

[a] 0.1 mmol scale. Yield was determined by ^{1}H NMR using 4-bromobenzaldehyde as an internal standard. Isolated yield in parentheses.

4.2 Optimization of reaction conditions of XAT reactions

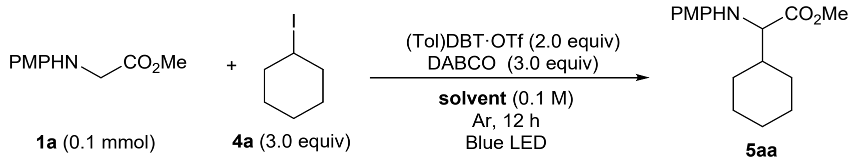
Table S7 Light source screening[a]



Entry	light source	yield (%)
1	Green LED	N.R.
2	White LED	40
3	***Blue LED***	***88***
4	420-430 nm	68
5	410-420 nm	68
6	400-410 nm	64
7	395-400 nm	65
8	380-385 nm	65

[a] Yield was determined by ^{1}H NMR using 4-bromobenzaldehyde as an internal standard.

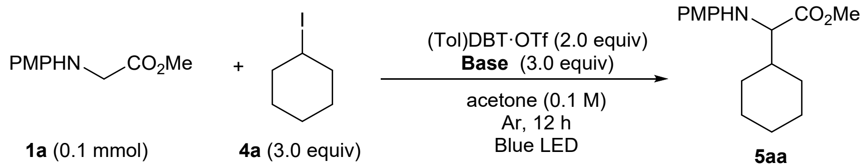
Table S8 Solvent screening[a]



Entry	solvent	yield (%)
1	MeCN	70
2	DMSO	50
3	DMF	61
4	THF	66
5	DMAc	65
6	DCM	63
7	MeOH	50
8	***acetone***	***88***

[a] Yield was determined by ^{1}H NMR using 4-bromobenzaldehyde as an internal standard.

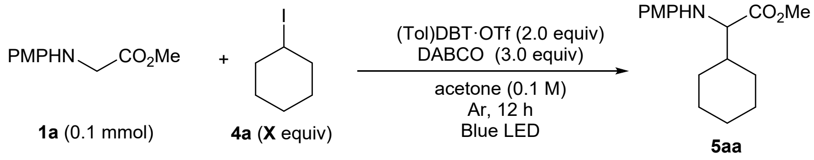
Table S9 Base screening[a]



Entry	solvent	yield (%)
1	BTMG	60
2	Cs_2CO_3	42
3	***DABCO***	***88***
4	DMAP	53
5	K_3PO_4	20
6	KO^{t}Bu	20
7	Et_3N	63
8	Imidazole	25
9	$NaHCO_3$	18
10	K_2HPO_4	25

[a] 0.1 mmol scale. Yield was determined by ^{1}H NMR using 4-bromobenzaldehyde as an internal standard.

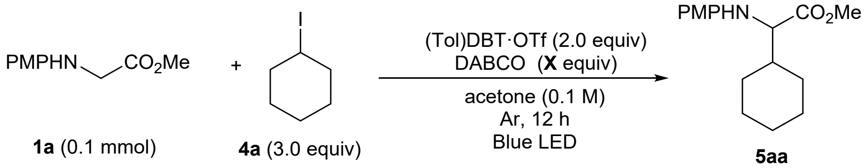
Table S10 Screening the loading of alkyl iodide[a]



Entry	X	yield (%)
1	2	72
2	***3***	***88***
3	4	88

[a] 0.1 mmol scale. Yield was determined by ^{1}H NMR using 4-bromobenzaldehyde as an internal standard.

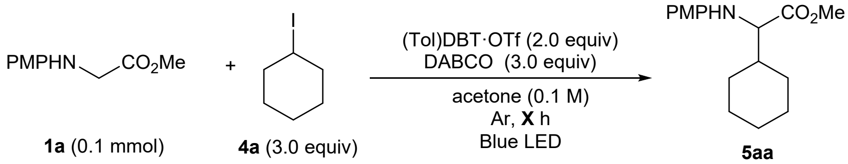
Table S11 Screening the loading of base[a]



Entry	X	yield (%)
1	2	65
2	***3***	***88***
3	4	88

[a] 0.1 mmol scale. Yield was determined by ^{1}H NMR using 4-bromobenzaldehyde as an internal standard.

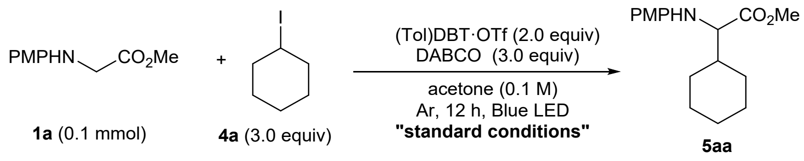
Table S12 Reaction time screening[a]



Entry	X	yield (%)
1	9	76
2	***12***	***88***

[a] 0.1 mmol scale. Yield was determined by ^{1}H NMR using 4-bromobenzaldehyde as an internal standard.

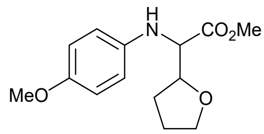
Table S13 Control experiments under standard reaction conditions[a]



Entry	deviation from the "standard conditions"	NMR yield (%)
1	**none**	**88 (83)**
2	other bases instead of DABCO	< 63
5	other solvents instead of acetone	< 70
9	without DABCO	0
10	without light	0
11	without light and heated to 80 °C	0

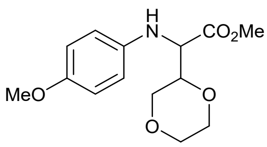
[a] 0.1 mmol scale. Yield was determined by ^{1}H NMR using 4-bromobenzaldehyde as an internal standard. Isolated yield in parentheses.

5. Characterization of products



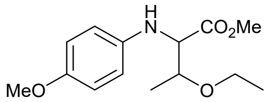
3aa

methyl 2-((4-methoxyphenyl)amino)-2-(tetrahydrofuran-2-yl)acetate (3aa): 21.2 mg, yield: 80%, Yellow oil. d.r. = 1.5:1 (determined by ^{1}H NMR). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.81 – 6.71 (m, 2H), 6.65 (d, *J* = 8.9 Hz, 1.2H), 6.60 (d, *J* = 8.9 Hz, 0.8H), 4.41 – 4.02 (m, 2H), 4.02 – 3.96 (m, 1H), 3.96 – 3.85 (m, 1H), 3.83 – 3.68 (m, 7H), 2.07 – 1.88 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.35, 173.05, 152.97, 152.83, 141.41, 140.89, 115.46, 115.21, 114.90, 114.84, 79.82, 79.34, 69.30, 68.74, 61.89, 60.92, 55.72, 55.69, 52.31, 52.19, 28.38, 28.25, 26.05, 25.55. HRMS (ESI) $C_{14}H_{20}NO_4^+$ $[M+H]^+$ calcd: 266.1387, found: 266.1396.



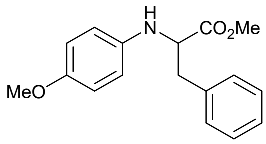
3ab

methyl 2-(1,4-dioxan-2-yl)-2-((4-methoxyphenyl)amino)acetate (3ab): 22.8 mg, yield: 81%, Yellow oil. d.r. = 1:1 (determined by ^{1}H NMR). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.81 – 6.70 (m, 2H), 6.62 (d, *J* = 8.9 Hz, 1H), 6.57 (d, *J* = 8.9 Hz, 1H), 4.32 – 3.99 (m, 2H), 3.94 (dd, *J* = 11.5, 2.6 Hz, 1H), 3.89 – 3.75 (m, 3H), 3.73 (d, *J* = 1.1 Hz, 6H), 3.72 – 3.47 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.44, 172.39, 153.25, 152.94, 140.96, 140.23, 115.70, 115.12, 114.91, 76.04, 75.56, 68.73, 68.41, 67.19, 66.93, 66.49, 66.22, 59.33, 58.88, 55.69, 55.66, 52.49, 52.31. HRMS (ESI) $C_{14}H_{20}NO_5^+$ $[M+H]^+$ calcd: 282.1336, found: 282.1343.



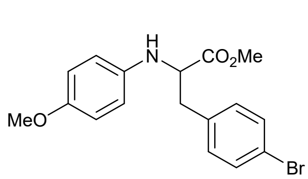
3ac

methyl 3-ethoxy-2-((4-methoxyphenyl)amino)butanoate (3ac): 21.4 mg, yield: 80%, Yellow oil. d.r. = 1:1 (determined by ^{1}H NMR). **3ac-1** ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 6.76 (d, *J* = 8.9 Hz, 2H), 6.58 (d, *J* = 8.9 Hz, 2H), 4.26 – 4.16 (m, 1H), 3.97 (qd, *J* = 6.3, 3.2 Hz, 1H), 3.91 (d, *J* = 3.2 Hz, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.59 (dq, *J* = 9.4, 7.0 Hz, 1H), 3.42 (dq, *J* = 9.4, 7.0 Hz, 1H), 1.29 (d, *J* = 6.3 Hz, 3H), 1.16 (t, *J* = 7.0 Hz, 3H).^{13}**C NMR** (151 MHz, $CDCl_3$) δ 173.49, 152.58, 141.64, 114.87, 114.86, 75.54, 64.76, 62.36, 55.73, 52.12, 17.15, 15.42. **3ac-2** ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 6.76 (d, *J* = 8.8 Hz, 2H), 6.62 (d, *J* = 8.9 Hz, 2H), 4.01 (d, *J* = 5.4 Hz, 2H), 3.90 – 3.68 (m, 7H), 3.62 (dq, *J* = 9.2, 7.0 Hz, 1H), 3.44 (dq, *J* = 9.3, 7.0 Hz, 1H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.18 (t, *J* = 7.0 Hz, 3H). ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 174.74, 152.92, 141.30, 137.99, 135.65, 129.47, 128.21, 126.62, 125.62, 115.47, 114.81, 62.37, 55.69, 51.85, 41.50, 29.24, 24.49, 20.24. HRMS (ESI) $C_{14}H_{22}NO_4^+$ $[M+H]^+$ calcd: 268.1543, found: 268.1546.



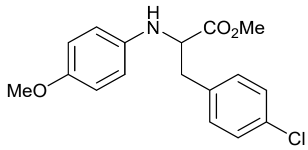
3ad

methyl (4-methoxyphenyl)phenylalaninate (3ad): 16.8 mg, yield: 59%, Yellow oil. ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 8.0, 6.2 Hz, 2H), 7.26 – 7.21 (m, 1H), 7.20 – 7.14 (m, 2H), 6.76 (d, *J* = 8.9 Hz, 2H), 6.57 (d, *J* = 8.9 Hz, 2H), 4.27 (t, *J* = 6.4 Hz, 1H), 3.87 (s, 1H), 3.73 (s, 3H), 3.65 (s, 3H), 3.16 – 3.05 (m, 2H). ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 173.96, 152.85, 140.49, 136.49, 129.24, 128.54, 126.99, 115.26, 114.92, 59.00, 55.71, 52.00, 38.91. HRMS (ESI) $C_{17}H_{20}NO_3^+$ $[M+H]^+$ calcd: 286.1438, found: 286.1442.



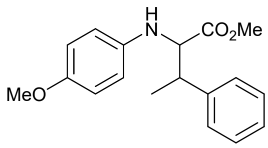
3ae

methyl 3-(4-bromophenyl)-2-((4-methoxyphenyl)amino)propanoate (3ae): 23.6 mg, yield: 65%, Yellow solid. M. p. 92.3 – 94.7 ^{o}C. ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.3 Hz, 2H), 7.04 (d, *J* = 8.3 Hz, 2H), 6.76 (d, *J* = 8.9 Hz, 2H), 6.57 (d, *J* = 8.9 Hz, 2H), 4.28 – 4.23 (m, 1H), 3.88 (s, 1H), 3.73 (s, 3H), 3.66 (s, 3H), 3.08 (dd, *J* = 13.7, 6.2 Hz, 1H), 3.03 (dd, *J* = 13.7, 6.3 Hz, 1H). ^{13}**C NMR** (151 MHz, $CDCl_3$) δ 173.62, 152.92, 140.23, 135.52, 131.59, 131.00, 120.96, 115.29, 114.94, 58.72, 55.69, 52.12, 38.16. HRMS (ESI) $C_{17}H_{19}BrNO_3^+$ $[M+H]^+$ calcd: 364.0543, found: 364.0536.



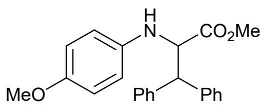
3af

methyl 3-(4-chlorophenyl)-2-((4-methoxyphenyl)amino)propanoate (3af): 20.1 mg, yield: 63%, Yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.28 – 7.25 (m, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 8.9 Hz, 2H), 6.57 (d, *J* = 8.9 Hz, 2H), 4.26 (t, *J* = 6.2 Hz, 1H), 3.91 (s, 1H), 3.73 (s, 3H), 3.66 (s, 3H), 3.10 (dd, *J* = 13.7, 6.1 Hz, 1H), 3.04 (dd, *J* = 13.7, 6.3 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.66, 152.92, 140.25, 135.00, 132.87, 130.62, 128.65, 115.29, 114.94, 58.81, 55.69, 52.11, 38.11. HRMS (ESI) $C_{17}H_{19}ClNO_3^+$ $[M+H]^+$ calcd: 320.1048, found: 320.1044.



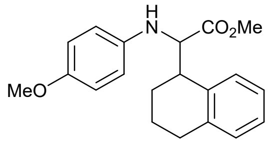
3ag

methyl 2-((4-methoxyphenyl)amino)-3-phenylbutanoate (3ag): 18.8 mg, yield: 63%, Colorless oil. d.r. = 1:1 (determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.31 (q, *J* = 7.6 Hz, 2H), 7.26 – 7.19 (m, 3H), 6.72 (d, *J* = 8.9 Hz, 2H), 6.52 (dd, *J* = 17.4, 9.0 Hz, 2H), 4.12 – 4.04 (m, 1H), 3.92 (s, 0.5H), 3.71 (d, *J* = 2.4 Hz, 3H), 3.67 (s, 1.45H), 3.64 (s, 0.46H), 3.48 (s, 1.48H), 3.27 (p, *J* = 7.0 Hz, 0.52H), 3.18 (p, *J* = 7.0 Hz, 0.52H), 1.44 (d, *J* = 7.2 Hz, 1.5H), 1.39 (d, *J* = 7.3 Hz, 1.5H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.17, 173.82, 152.85, 152.81, 142.22, 141.80, 141.23, 141.15, 128.61, 128.41, 127.82, 127.63, 127.14, 127.03, 115.49, 115.35, 114.82, 114.79, 64.49, 63.90, 55.69, 51.92, 51.73, 43.09, 42.72, 18.47, 17.16. HRMS (ESI) $C_{18}H_{22}NO_3^+$ $[M+H]^+$ calcd: 300.1594, found: 300.1592.



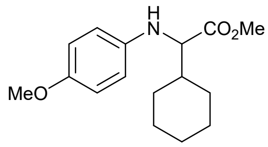
3ah

methyl 2-((4-methoxyphenyl)amino)-3,3-diphenylpropanoate (3ah): 22.0 mg, yield: 61%, White solid. M. p. 81.2 – 83.4 °C. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.34 – 7.18 (m, 10H), 6.74 (d, *J* = 8.9 Hz, 2H), 6.57 (d, *J* = 8.9 Hz, 2H), 4.67 (d, *J* = 8.9 Hz, 1H), 4.39 (d, *J* = 8.9 Hz, 1H), 3.72 (s, 3H), 3.44 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.98, 152.94, 140.83, 140.70, 139.85, 128.74, 128.56, 128.53, 128.42, 127.12, 115.19, 114.84, 61.98, 55.68, 54.30, 51.90. HRMS (ESI) $C_{23}H_{24}NO_3^+$ $[M+H]^+$ calcd: 362.1751, found: 362.1752.



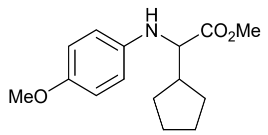
3ai

methyl 2-((4-methoxyphenyl)amino)-2-(1,2,3,4-tetrahydronaphthalen-1-yl)acetate (3ai): 19.5 mg, yield: 60%, White solid. M. p. 62.3 – 64.7 °C. d.r. = 2.2:1 (determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.16 – 7.04 (m, 4H), 6.75 – 6.69 (m, 2H), 6.56 – 6.52 (m, 2H), 4.29 (d, *J* = 6.8 Hz, 1H), 3.83 (s, 1H), 3.72 (s, 3H), 3.58 (s, 3H), 3.28 (q, *J* = 6.2 Hz, 1H), 2.87 (t, *J* = 6.3 Hz, 0.34H), 2.84 (t, *J* = 6.3 Hz, 0.75H), 2.79 (t, *J* = 6.3 Hz, 0.74H), 2.76 (t, *J* = 6.3 Hz, 0.35H), 2.13 – 2.07 (m, 1H), 1.97 (m, 1H), 1.83 – 1.72 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.74, 152.91, 141.30, 137.99, 135.65, 129.47, 128.21, 126.62, 125.62, 115.47, 114.81, 62.37, 55.69, 51.85, 41.50, 29.24, 24.49, 20.24. HRMS (ESI) $C_{20}H_{24}NO_3^+$ $[M+H]^+$ calcd: 326.1751, found: 326.1749.



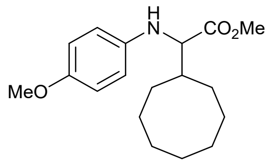
5aa

methyl 2-cyclohexyl-2-((4-methoxyphenyl)amino)acetate (5aa): 22.7 mg, yield of HAT condition :82%, 23.0 mg, yield of XAT condition: 83%, Yellow solid. M. p. 36.9 – 37.7 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.75 (d, *J* = 8.9 Hz, 2H), 6.59 (d, *J* = 8.9 Hz, 2H), 3.78 (d, *J* = 6.2 Hz, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 1.86 (d, *J* = 12.8 Hz, 1H), 1.80 – 1.62 (m, 5H), 1.31 (d, *J* = 3.1 Hz, 1H), 1.24 – 1.08 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.57, 152.69, 141.54, 115.18, 114.89, 63.41, 55.73, 51.76, 41.33, 29.72, 29.26, 26.20, 26.10, 26.08. HRMS (ESI) $C_{16}H_{24}NO_3^+$ $[M+H]^+$ calcd: 278.1751, found: 278.1755.



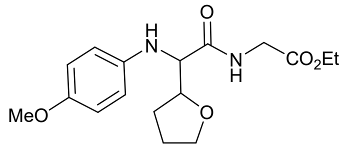
3aj

methyl 2-cyclopentyl-2-((4-methoxyphenyl)amino)acetate (3aj): 20.3 mg, yield of HAT condition: 77%, 22.9 mg, yield of XAT condition: 87%, Yellow solid. M. p. 51.2 – 53.4 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.76 (d, *J* = 7.6 Hz, 2H), 6.60 (d, *J* = 7.7 Hz, 2H), 3.91 (s, 1H), 3.79 (d, *J* = 8.0 Hz, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 2.20 (h, *J* = 8.1 Hz, 1H), 1.83 (dp, *J* = 11.8, 3.6 Hz, 1H), 1.73 – 1.53 (m, 5H), 1.50 – 1.39 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.08, 152.67, 141.38, 115.01, 114.86, 62.05, 55.72, 51.88, 43.22, 29.51, 29.10, 25.33, 25.13. HRMS (ESI) $C_{15}H_{22}NO_3^+$ $[M+H]^+$ calcd: 264.1594, found: 264.1594.



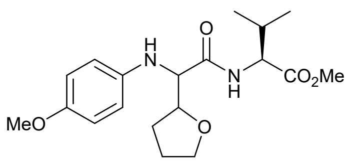
3ak

methyl 2-cyclooctyl-2-((4-methoxyphenyl)amino)acetate (3ak): 24.4 mg, yield: 80%, Yellow solid. M. p. 52.1 – 53.4 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.75 (d, *J* = 8.9 Hz, 2H), 6.59 (d, *J* = 8.9 Hz, 2H), 3.77 (d, *J* = 6.3 Hz, 2H), 3.72 (s, 3H), 3.67 (s, 3H), 1.99 (dq, *J* = 8.6, 4.3 Hz, 1H), 1.82 – 1.67 (m, 3H), 1.65 – 1.40 (m, 11H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.77, 152.67, 141.50, 115.14, 114.89, 64.08, 55.72, 51.78, 40.75, 30.17, 28.44, 26.94, 26.46, 26.38, 25.14. HRMS (ESI) $C_{18}H_{28}NO_3^+$ $[M+H]^+$ calcd: 306.2064, found: 306.2065.



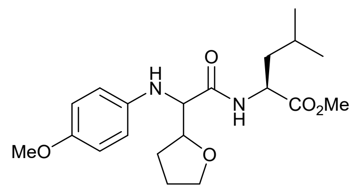
3ba

ethyl (2-((4-methoxyphenyl)amino)-2-(tetrahydrofuran-2-yl)acetyl)glycinate (3ba): 27.2 mg, yield:81%, Yellow solid. M. p. 67.2 – 69.3 °C. d.r. = 1:1 (determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.33 (t, J = 5.6 Hz, 1H), 6.77 (d, J = 8.9 Hz, 2H), 6.61 (d, J = 9.0 Hz, 2H), 4.28 – 4.24 (m, 1H), 4.23 – 4.10 (m, 4H), 3.99 – 3.94 (m, 1H), 3.88 (dd, *J* = 4.8, 2.4 Hz, 1.52H), 3.85 (d, *J* = 4.9 Hz, 0.49H), 3.81 (td, *J* = 7.9, 5.7 Hz, 1H), 3.73 (d, J = 4.2 Hz, 3H), 2.03 – 1.89 (m, 4H), 1.24 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.82, 169.52, 153.17, 141.02, 115.25, 114.80, 79.44, 68.84, 62.45, 61.36, 55.69, 41.06, 27.02, 25.67, 14.11. HRMS (ESI) $C_{17}H_{25}N_2O_5^+$ $[M+H]^+$ calcd: 337.1758, found: 337.1747.



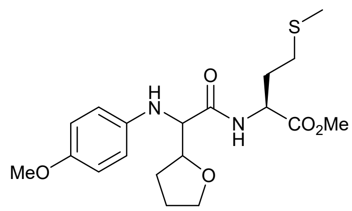
3ca

methyl (2-((4-methoxyphenyl)amino)-2-(tetrahydrofuran-2-yl)acetyl)-*L*-valinate (3ca): 30.2 mg, yield: 83%, Yellow oil. d.r. = 1.3:1 (determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.42 – 7.21 (m, 1H), 6.80 – 6.73 (m, 2H), 6.65 – 6.62 (m, 0.86H), 6.62 – 6.60 (m, 1.12H), 4.54 – 4.48 (m, 1H), 4.29 – 4.22 (m, 1H), 4.10 – 3.75 (m, 4H), 3.75 – 3.68 (m, 5H), 3.61 (d, *J* = 19.0 Hz, 1H), 2.19 – 2.07 (m, 1H), 2.04 – 1.89 (m, 4H), 0.91 (d, *J* = 6.8 Hz, 1.12H), 0.88 (dd, *J* = 6.9, 0.9 Hz, 1.12H), 0.80 (dd, *J* = 10.2, 6.9 Hz, 1.88H), 0.71 (dd, *J* = 18.7, 6.9 Hz, 1.88H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.14, 172.07, 171.77, 171.63, 171.38, 171.24, 153.21, 153.13, 153.07, 153.06, 141.35, 141.08, 141.04, 140.75, 115.60, 115.29, 115.25, 115.04, 114.82, 114.79, 114.71, 114.63, 79.54, 79.26, 79.16, 78.89, 68.77, 68.73, 68.54, 68.47, 63.11, 62.98, 62.96, 62.30, 57.18, 57.06, 56.81, 56.71, 55.67, 55.65, 55.63, 52.07, 52.02, 51.91, 31.07, 31.02, 30.96, 30.91, 28.46, 28.08, 27.18, 26.76, 25.71, 25.63, 25.56, 25.50, 19.01, 18.99, 18.94, 17.81, 17.73, 17.48, 17.33. HRMS (ESI) $C_{19}H_{29}N_2O_5^+$ $[M+H]^+$ calcd: 365.2071, found: 365.2064.



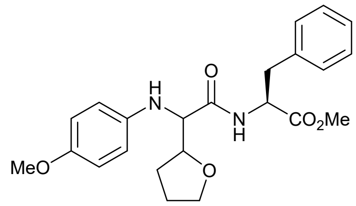
3da

methyl (2-((4-methoxyphenyl)amino)-2-(tetrahydrofuran-2-yl)acetyl)-*L*-leucinate (3da): 29.1 mg, yield: 77%, Yellow oil. d.r. = 1.6:1 (determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.29 – 7.01 (m, 1H), 6.81 – 6.71 (m, 2H), 6.67 – 6.62 (m, 0.76H), 6.61 – 6.56 (m, 1.24H), 4.63 – 4.56 (m, 1H), 4.48 – 4.11 (m, 2H), 4.01 – 3.77 (m, 3H), 3.75 – 3.71 (m, 3H), 3.71 – 3.61 (m, 3H), 2.04 – 1.88 (m, 4H), 1.63 – 1.51 (m, 1.68H), 1.48 – 1.27 (m, 1.34H), 0.91 (td, *J* = 7.2, 6.2, 2.4 Hz, 2.4H), 0.84 (d, *J* = 6.5 Hz, 0.6H), 0.80 (dd, *J* = 6.6, 4.5 Hz, 1.82H), 0.76 (d, *J* = 6.6 Hz, 1.25H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.08, 173.03, 172.66, 171.75, 171.31, 171.18, 153.22, 153.11, 141.15, 141.06, 140.76, 115.61, 115.13, 115.03, 114.79, 114.69, 114.62, 79.57, 79.23, 78.93, 68.77, 68.74, 68.43, 63.19, 62.86, 62.31, 55.68, 55.62, 52.19, 52.11, 52.05, 50.48, 50.33, 50.16, 41.11, 41.00, 40.89, 28.43, 26.99, 26.75, 25.73, 25.64, 25.51, 24.73, 24.63, 24.45, 22.87, 22.84, 22.77, 21.51, 21.32. HRMS (ESI) $C_{20}H_{31}N_2O_5^+$ $[M+H]^+$ calcd: 379.2227, found: 379.2214.



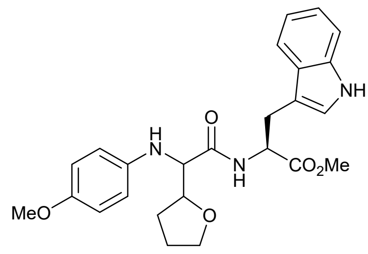
3ea

methyl (2-((4-methoxyphenyl)amino)-2-(tetrahydrofuran-2-yl)acetyl)-*L*-methioninate (3ea): 26.5 mg, yield: 67%, Yellow oil. d.r. = 1.5:1 (determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.55 – 7.29 (m, 1H), 6.77 (td, *J* = 8.1, 1.7 Hz, 2H), 6.66 – 6.61 (m, 0.8H), 6.59 (dd, *J* = 8.9, 1.6 Hz, 1.2H), 4.76 – 4.65 (m, 1H), 4.47 – 4.12 (m, 2H), 4.01 – 3.75 (m, 3H), 3.74 – 3.61 (m, 6H), 2.60 – 2.32 (m, 1H), 2.26 – 1.89 (m, 10H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.13, 172.06, 172.00, 171.85, 171.82, 171.73, 171.41, 171.26, 171.11, 153.21, 153.13, 141.26, 140.97, 140.91, 140.62, 115.49, 115.19, 115.02, 114.91, 114.89, 114.83, 114.80, 114.68, 79.63, 79.17, 78.87, 68.79, 68.57, 68.50, 63.08, 62.82, 62.28, 60.36, 55.69, 55.67, 55.65, 52.46, 52.39, 52.34, 52.32, 51.24, 51.04, 50.86, 31.31, 29.84, 29.67, 29.62, 28.44, 27.28, 26.90, 25.71, 25.63, 25.52, 21.02, 15.43, 15.31, 15.24, 15.18, 14.19. HRMS (ESI) $C_{19}H_{29}N_2O_5S^+$ $[M+H]^+$ calcd: 397.1792, found: 397.1784.



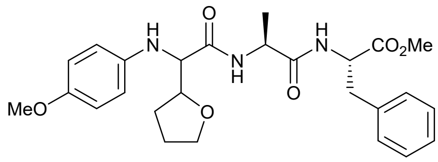
3fa

methyl (2-((4-methoxyphenyl)amino)-2-(tetrahydrofuran-2-yl)acetyl)-*L*-phenylalaninate (3fa): 32.2 mg, yield: 78%, Yellow oil. d.r. = 1.1:1 (determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.41 – 7.18 (m, 2.56H), 7.15 – 7.03 (m, 2.52H), 6.87 – 6.72 (m, 3H), 6.60 (d, *J* = 8.9 Hz, 1H), 6.51 (dd, *J* = 9.0, 3.7 Hz, 1H), 4.94 (dt, *J* = 8.6, 5.7 Hz, 0.48H), 4.89 – 4.82 (m, 0.52H), 4.44 – 3.97 (m, 2H), 3.92 – 3.56 (m, 9H), 3.17 (dd, *J* = 14.1, 5.4 Hz, 0.45H), 3.06 – 2.90 (m, 1.58H), 1.97 – 1.62 (m, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.65, 171.56, 171.47, 171.41, 171.05, 153.18, 153.07, 153.04, 141.10, 141.05, 140.79, 136.17, 135.52, 135.40, 129.27, 129.14, 129.06, 128.51, 128.47, 128.46, 128.43, 126.93, 126.88, 115.62, 114.91, 114.86, 114.79, 114.73, 114.62, 79.34, 79.22, 78.84, 68.69, 68.60, 68.42, 62.90, 62.83, 62.11, 55.70, 55.68, 55.62, 53.04, 52.55, 52.29, 52.22, 52.15, 37.90, 37.84, 37.67, 28.37, 26.85, 26.75, 25.67, 25.52, 25.47.HRMS (ESI) $C_{23}H_{29}N_2O_5^+$ $[M+H]^+$ calcd: 413.2071, found: 413.2059.



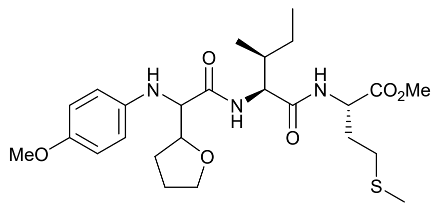
3ga

methyl (2-((4-methoxyphenyl)amino)-2-(tetrahydrofuran-2-yl)acetyl)-*L*-tryptophanate (3ga): 28.9 mg, yield: 64%, White solid. M. p. 62.9 – 63.8 ^{o}C. d.r. = 1.2:1 (determined by 1H NMR). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.47 (d, *J* = 17.6 Hz, 0.45H), 8.29 – 8.13 (m, 0.55H), 7.57 – 7.27 (m, 2.55H), 7.23 (d, *J* = 4.6 Hz, 0.46H), 7.17 – 6.98 (m, 2H), 6.88 (d, *J* = 11.5 Hz, 0.45H), 6.77 – 6.64 (m, 2H), 6.55 (d, *J* = 8.9 Hz, 0.55H), 6.46 (dd, *J* = 16.3, 8.8 Hz, 1.6H), 6.36 (s, 0.37H), 4.97 – 4.84 (m, 1H), 4.32 – 4.03 (m, 2H), 3.90 – 3.53 (m, 9H), 3.31 – 3.07 (m, 2H), 1.95 – 1.60 (m, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.12, 172.09, 171.97, 171.92, 171.87, 171.54, 171.19, 153.10, 153.01, 152.95, 152.88, 141.22, 141.11, 140.92, 136.19, 136.11, 136.08, 127.56, 127.46, 127.27, 127.14, 123.25, 123.12, 123.03, 122.87, 122.05, 122.02, 121.95, 119.47, 119.44, 119.35, 118.66, 118.46, 118.42, 118.40, 115.60, 115.08, 114.97, 114.83, 114.75, 114.65, 111.29, 111.20, 109.87, 109.69, 109.26, 109.12, 109.10, 79.45, 79.19, 78.99, 78.86, 68.72, 68.61, 68.53, 68.44, 63.15, 62.75, 62.52, 62.28, 55.73, 55.71, 55.67, 52.90, 52.85, 52.32, 52.25, 52.22, 52.19, 51.88, 29.68, 28.37, 28.03, 27.69, 27.51, 26.92, 26.74, 25.67, 25.61, 25.53, 25.49. HRMS (ESI) $C_{25}H_{30}N_3O_5^+$ $[M+H]^+$ calcd: 452.2180, found: 452.2171.



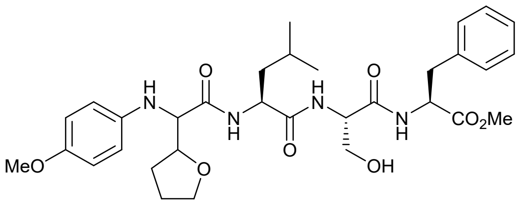
3ha

methyl (2-((4-methoxyphenyl)amino)-2-(tetrahydrofuran-2-yl)acetyl)-*L*-alanyl-*L*-phenylalaninate (3ha): 30.9 mg, yield: 64%, Yellow solid. M. p. 45.2 – 46.8 ^{o}C. d.r. = 2.1:1 (determined by ^{1}H NMR). **^{1}H NMR** (400 MHz, MeOD) δ 7.29 – 6.98 (m, 5H), 6.81 – 6.66 (m, 2H), 6.65 – 6.48 (m, 2H), 4.61 (dtd, J = 16.9, 8.8, 5.7 Hz, 1H), 4.42 – 4.34 (m, 0.68H), 4.31 (q, J = 7.2 Hz, 0.32H), 4.21 – 4.07 (m, 0.71H), 4.05 – 3.97 (m, 0.3H), 3.94 – 3.81 (m, 1H), 3.81 – 3.69 (m, 2H), 3.69 – 3.57 (m, 6H), 3.17 – 2.78 (m, 2H), 2.13 – 1.76 (m, 4H), 1.28 – 1.15 (m, 3H). **^{13}C NMR** (101 MHz, MeOD) δ 173.77, 173.61, 173.15, 173.07, 172.87, 172.85, 171.70, 171.62, 171.46, 152.76, 152.72, 141.61, 141.34, 141.28, 141.22, 136.65, 136.57, 136.54, 128.95, 128.92, 128.88, 128.16, 128.13, 126.52, 126.50, 114.89, 114.68, 114.56, 114.53, 114.44, 114.38, 114.33, 114.27, 79.95, 79.49, 79.39, 79.25, 68.39, 68.33, 68.26, 68.24, 62.69, 62.38, 62.25, 62.23, 54.68, 54.66, 53.82, 53.72, 53.48, 51.33, 51.30, 48.98, 48.76, 48.60, 37.12, 37.06, 37.01, 36.97, 28.96, 28.00, 27.84, 27.64, 25.38, 25.32, 25.00, 24.92, 23.09, 16.98, 16.74, 16.60, 16.42. HRMS (ESI) $C_{26}H_{34}N_3O_6^+$ $[M+H]^+$ calcd: 484.2442, found: 484.2427.



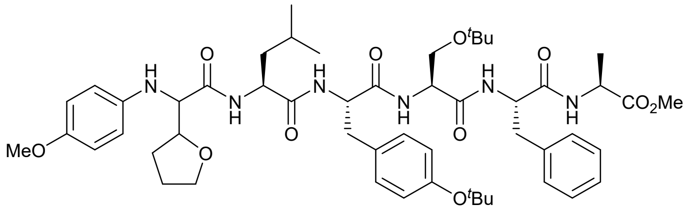
3ia

methyl (2-((4-methoxyphenyl)amino)-2-(tetrahydrofuran-2-yl)acetyl)-*L*-isoleucyl-*L*-methioninate (3ia): 30.6 mg, yield: 60%, Yellow solid. M. p. 91.7 – 92.3 ^{o}C. d.r. = 1:1 (determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.32 – 6.92 (m, 1H), 6.78 (d, *J* = 8.9 Hz, 1H), 6.76 (d, *J* = 8.9 Hz, 1H), 6.64 – 6.52 (m, 2H), 4.72 – 4.60 (m, 1H), 4.46 – 4.04 (m, 3H), 3.98 – 3.89 (m, 1.51H), 3.82 – 3.69 (m, 7.46H), 2.52 – 2.34 (m, 2H), 2.23 – 1.76 (m, 10H), 1.32 – 1.26 (m, 1H), 0.96 – 0.64 (m, 7H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.56, 172.49, 172.02, 172.00, 171.94, 171.92, 171.35, 171.28, 170.95, 170.87, 170.84, 170.77, 153.19, 153.14, 140.63, 140.53, 115.11, 114.98, 114.78, 79.78, 79.41, 79.06, 68.87, 68.69, 62.61, 62.59, 62.32, 62.30, 57.64, 57.61, 57.49, 55.75, 55.73, 52.47, 52.42, 51.44, 51.42, 51.34, 51.32, 36.50, 35.81, 35.79, 31.44, 31.41, 31.37, 31.35, 29.98, 29.68, 28.10, 27.28, 25.64, 25.59, 24.41, 24.37, 15.64, 15.47, 15.40, 15.38, 11.29, 11.00. HRMS (ESI) $C_{25}H_{40}N_3O_6S^+$ $[M+H]^+$ calcd: 510.2632, found: 510.2617.



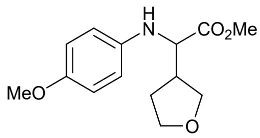
3ja

methyl (2-((4-methoxyphenyl)amino)-2-(tetrahydrofuran-2-yl)acetyl)-*L*-leucyl-*L*-seryl-*L*-phenylalaninate (3ja): 39.8 mg, yield: 65%, White solid. M. p. 68.2 – 70.5 °C, d.r. = 1.7:1 (determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 8.53 – 8.08 (m, 1H), 8.06 – 7.86 (m, 1H), 7.84 – 7.54 (m, 1H), 7.27 (q, J = 7.4 Hz, 2H), 7.23 – 7.14 (m, 3H), 6.73 – 6.64 (m, 2H), 6.63 – 6.55 (m, 2H), 5.30 – 5.07 (m, 1H), 4.84 (q, J = 5.6 Hz, 0.63H), 4.80 (t, J = 5.6 Hz, 0.37H), 4.50 – 4.43 (m, 1H), 4.35 – 4.21 (m, 2H), 4.10 – 3.96 (m, 1H), 3.89 – 3.70 (m, 2H), 3.62 (d, J = 2.8 Hz, 4H), 3.58 – 3.42 (m, 5H), 3.04 – 2.90 (m, 2H), 1.99 – 1.73 (m, 4H), 1.62 – 1.48 (m, 1H), 1.40 – 1.22 (m, 2H), 0.85 (dd, J = 13.4, 6.6 Hz, 1.48H), 0.72 (dq, J = 13.5, 5.9 Hz, 4.52H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 172.93, 172.19, 172.11, 172.02, 171.93, 171.83, 171.80, 171.72, 170.17, 170.12, 170.09, 170.02, 169.94, 151.75, 151.65, 151.61, 142.22, 142.16, 137.24, 137.21, 129.41, 129.37, 128.59, 126.91, 114.73, 114.68, 114.61, 114.55, 114.46, 79.77, 79.53, 79.40, 68.07, 68.05, 67.91, 62.09, 61.95, 61.83, 61.64, 61.38, 55.65, 55.61, 55.51, 55.14, 55.06, 55.02, 53.93, 53.89, 53.84, 53.80, 53.77, 53.67, 52.14, 51.39, 51.08, 41.20, 41.10, 37.11, 37.07, 29.06, 28.24, 28.02, 25.63, 25.29, 25.16, 24.39, 24.14, 24.04, 23.61, 23.60, 23.50, 21.74, 21.57, 21.50, 21.21. HRMS (ESI) $C_{32}H_{45}N_4O_8^+$ [M+H]$^+$ calcd: 613.3232, found: 613.3215.



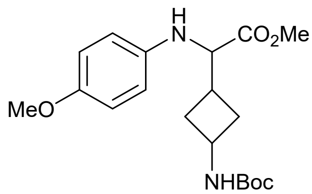
3ka

methyl N-((2*S*)-3-(4-(tert-butoxy)phenyl)-2-((2*S*)-2-(2-((4-methoxyphenyl)amino)-2-(tetrahydrofuran-2-yl)acetamido)-4-methylpentanamido)propanoyl)-*O*-(*tert*-butyl)-*L*-seryl-*L*-phenylalanyl-*L*-alaninate (3ka): 67.1 mg, yield: 70%, White solid. M. p. 243 – 244 °C. d.r. = 1.5:1 (determined by ^{1}H NMR). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.42 (qd, J = 4.9, 3.1 Hz, 1H), 8.28 – 7.63 (m, 4H), 7.57 – 6.91 (m, 8H), 6.89 – 6.72 (m, 2H), 6.72 – 6.58 (m, 3H), 5.36 – 5.00 (m, 1H), 4.69 – 4.44 (m, 2H), 4.27 (p, J = 7.3 Hz, 3H), 4.03 (tt, J = 12.0, 5.6 Hz, 1H), 3.88 – 3.52 (m, 8H), 3.45 – 3.37 (m, 1H), 3.31 (dd, J = 9.1, 5.2 Hz, 1H), 3.05 (d, J = 4.9 Hz, 0.43H), 3.01 (d, J = 4.9 Hz, 0.63H), 3.00 – 2.88 (m, 1H), 2.82 (dd, J = 14.0, 8.3 Hz, 1H), 2.65 (ddt, J = 18.2, 14.0, 8.7 Hz, 1H), 2.01 – 1.49 (m, 4H), 1.44 – 1.13 (m, 15H), 1.08 (dd, J = 4.9, 1.9 Hz, 9H), 0.90 – 0.62 (m, 6H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 173.19, 172.61, 172.19, 172.17, 172.06, 171.93, 171.67, 171.62, 171.43, 171.36, 171.33, 171.14, 170.88, 169.58, 169.56, 160.06, 158.05, 156.56, 153.83, 153.79, 151.94, 151.85, 151.81, 151.77, 151.72, 142.61, 142.40, 142.24, 142.22, 137.83, 132.84, 132.76, 132.71, 132.68, 130.25, 130.11, 130.08, 130.04, 130.01, 129.95, 129.71, 128.58, 128.42, 127.71, 126.67, 123.82, 123.74, 123.70, 122.29, 115.02, 114.84, 114.77, 114.74, 114.71, 114.63, 114.59, 114.24, 80.04, 79.68, 79.64, 79.46, 77.99, 77.93, 77.91, 73.42, 73.40, 73.38, 68.15, 68.09, 62.52, 62.22, 62.07, 61.61, 61.40, 55.73, 55.70, 55.67, 55.62, 53.94, 53.80, 53.73, 53.64, 53.62, 52.39, 52.33, 51.61, 51.44, 51.29, 51.09, 48.01, 41.56, 41.40, 41.22, 40.64, 38.18, 37.18, 37.08, 29.02, 28.99, 28.16, 28.12, 27.56, 27.54, 25.74, 25.71, 25.45, 25.33, 24.70, 24.50, 24.43, 24.24, 24.13, 23.63, 23.57, 23.51, 23.43, 22.58, 22.00, 21.90, 21.68, 21.64, 21.35, 17.38. HRMS (ESI) $C_{52}H_{75}N_6O_{11}^+$ $[M+H]^+$ calcd: 959.5488, found: 959.5474.



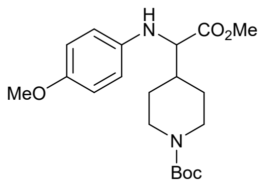
5ab

methyl 2-((4-methoxyphenyl)amino)-2-(tetrahydrofuran-3-yl)acetate (5ab): 22.5 mg, yield: 85%, Yellow oil. d.r. = 1:1 (determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.76 (dd, *J* = 8.9, 3.5 Hz, 2H), 6.60 (dd, *J* = 8.9, 3.8 Hz, 2H), 3.98 – 3.71 (m, 8H), 3.70 (d, *J* = 3.9 Hz, 3H), 2.66 – 2.54 (m, 1H), 2.13 – 2.05 (m, 0.52H), 2.00 (dtd, *J* = 12.7, 8.1, 4.8 Hz, 0.53H), 1.97 – 1.90 (m, 0.52H), 1.89 – 1.82 (m, 0.53H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.26, 174.17, 153.04, 152.99, 140.82, 140.77, 115.37, 115.25, 114.90, 114.88, 70.79, 69.90, 68.03, 67.91, 60.70, 59.97, 55.68, 55.67, 52.18, 52.09, 42.48, 42.37, 29.07, 28.83. HRMS (ESI) $C_{14}H_{20}NO_4^+$ $[M+H]^+$ calcd: 266.1387, found: 266.1384.



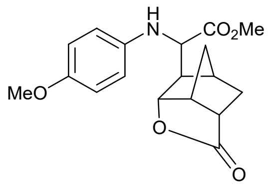
5ac

methyl 2-(3-((tert-butoxycarbonyl)amino)cyclobutyl)-2-((4-methoxyphenyl)amino)acetate (5ac): 29.1 mg, yield: 80%, Yellow oil. d.r. = 1.1:1 (determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.76 (d, *J* = 8.9 Hz, 2H), 6.60 (d, *J* = 8.9 Hz, 1.05H), 6.57 (d, *J* = 8.9 Hz, 0.95H), 4.86 (s, 0.55H), 4.77 (s, 0.45H), 4.38 – 3.91 (m, 2H), 3.87 (d, *J* = 7.0 Hz, 1H), 3.73 (d, *J* = 1.0 Hz, 3H), 3.67 (d, *J* = 6.0 Hz, 3H), 2.55 – 2.29 (m, 3H), 2.03 (tt, *J* = 15.2, 7.0 Hz, 1H), 1.90 – 1.68 (m, 1H), 1.43 (d, *J* = 7.4 Hz, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.30, 173.80, 154.96, 154.82, 152.90, 152.84, 141.25, 141.10, 115.27, 115.13, 114.87, 79.36, 79.30, 61.45, 61.32, 55.68, 55.67, 52.06, 51.99, 43.82, 41.79, 33.90, 33.78, 32.98, 32.52, 32.44, 31.07, 28.38. HRMS (ESI) $C_{19}H_{29}N_2O_5^+$ $[M+H]^+$ calcd: 365.2071, found: 365.2060.



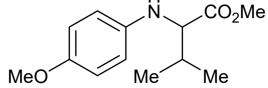
5ad

***tert*-butyl 4-(2-methoxy-1-((4-methoxyphenyl)amino)-2-oxoethyl)piperidine-1-carboxylate (5ad):** 31.0 mg, yield: 82%. Yellow oil. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.76 (d, *J* = 9.0 Hz, 2H), 6.60 (d, *J* = 8.9 Hz, 2H), 4.12 (s, 2H), 3.99 – 3.80 (m, 2H), 3.73 (s, 3H), 3.69 (s, 3H), 2.68 (s, 2H), 1.92 – 1.78 (m, 2H), 1.61 – 1.55 (m, 1H), 1.45 (s, 11H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.06, 154.68, 152.83, 141.12, 115.29, 114.86, 79.49, 62.59, 55.66, 52.00, 43.36, 39.74, 28.68, 28.44. HRMS (ESI) $C_{20}H_{31}N_2O_5^+$ $[M+H]^+$ calcd: 379.2227, found: 379.2230.



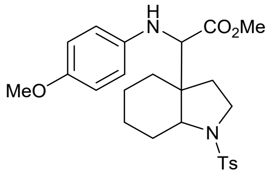
5ae

methyl 2-((4-methoxyphenyl)amino)-2-(2-oxohexahydro-2*H*-3,5-methanocyclopenta[*b*]furan-6-yl)acetate (5ae): 24.8 mg, yield: 75%, Yellow oil. d.r. = 1:1 (determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.79 – 6.73 (m, 2H), 6.63 – 6.58 (m, 2H), 4.77 (s, 0.5H), 4.71 – 4.59 (m, 0.5H), 3.88 (s, 1H), 3.76 – 3.68 (m, 6H), 3.66 (d, *J* = 10.9 Hz, 0.5H), 3.60 (d, *J* = 11.5 Hz, 0.5H), 3.21 (s, 1H), 2.73 (s, 0.5H), 2.62 – 2.55 (m, 1H), 2.29 (s, 0.5H), 2.11 – 2.00 (m, 1H), 1.96 – 1.78 (m, 2H), 1.72 (t, *J* = 13.7 Hz, 1H), 1.68 – 1.57 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 180.57, 180.52, 173.62, 173.43, 153.19, 140.49, 140.40, 115.40, 114.94, 114.92, 83.22, 82.29, 59.02, 58.72, 55.67, 53.07, 52.98, 52.42, 52.22, 46.41, 46.30, 38.93, 38.80, 38.78, 38.74, 35.43, 35.07, 35.02, 34.79. HRMS (ESI) $C_{18}H_{21}NNaO_5{}^+$ $[M+Na]^+$ calcd: 354.1312, found: 354.1297.



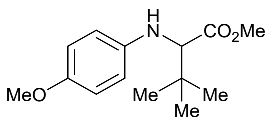
5af

methyl (4-methoxyphenyl)valinate (5af): 19.0 mg, yield: 80%, Yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.76 (d, *J* = 8.9 Hz, 2H), 6.61 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 1.09H), 3.76 (d, *J* = 6.0 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 2.08 (dq, *J* = 13.3, 6.7 Hz, 1H), 1.03 (dd, *J* = 9.6, 6.9 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.58, 152.70, 141.48, 115.22, 114.88, 63.79, 55.73, 51.81, 31.61, 19.19, 18.73. HRMS (ESI) $C_{13}H_{20}NO_3^+$ $[M+H]^+$ calcd: 238.1438, found: 238.1435.



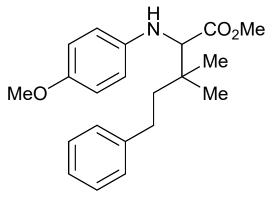
5ag

methyl 2-((4-methoxyphenyl)amino)-2-(1-tosyloctahydro-3aH-indol-3a-yl)acetate (5ag): 34.5 mg, yield: 73%, Yellow oil. d.r. = 1.4:1 (determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 0.83H), 7.67 (d, *J* = 8.3 Hz, 1.17H), 7.29 (d, *J* = 8.4 Hz, 0.84H), 7.17 (d, *J* = 8.4 Hz, 1.17H), 6.79 – 6.62 (m, 2H), 6.50 (d, *J* = 8.9 Hz, 1.17H), 6.29 (d, *J* = 8.9 Hz, 0.83H), 3.91 (dd, *J* = 7.4, 5.2 Hz, 0.43H), 3.73 (d, *J* = 1.3 Hz, 4.80H), 3.68 (s, 1.20H), 3.62 (s, 0.74H), 3.56 (s, 1.58H), 3.48 (dddt, *J* = 14.8, 11.7, 6.6, 2.7 Hz, 1.57H), 3.26 (ddd, *J* = 10.5, 8.5, 6.5 Hz, 0.42H), 2.44 (s, 1.25H), 2.37 (s, 1.75H), 2.03 – 1.58 (m, 6.59H), 1.56 – 1.51 (m, 1H), 1.49 – 1.36 (m, 2H), 1.32 – 1.22 (m, 0.41H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.37, 173.35, 153.31, 153.13, 143.18, 143.04, 141.02, 140.91, 135.82, 135.22, 129.60, 129.52, 127.70, 127.24, 116.36, 115.61, 114.78, 114.72, 61.43, 60.90, 60.50, 60.48, 55.67, 55.63, 51.97, 51.79, 47.68, 47.55, 45.11, 44.83, 29.35, 29.26, 28.88, 28.12, 27.48, 21.80, 21.77, 21.60, 21.56, 21.15, 21.01. HRMS (ESI) $C_{25}H_{33}N_2O_5S^+$ $[M+H]^+$ calcd: 473.2105, found: 473.2091.



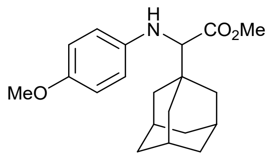
5ah

methyl 2-((4-methoxyphenyl)amino)-3,3-dimethylbutanoate (5ah): 20.6 mg, yield: 82%, White solid. M. p. 42.6 – 44.3 °C. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.76 (d, *J* = 8.9 Hz, 2H), 6.63 (d, *J* = 8.9 Hz, 2H), 3.90 (s, 1H), 3.73 (s, 3H), 3.68 (s, 1H), 3.66 (s, 3H), 1.05 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.27, 152.80, 141.72, 115.53, 114.84, 67.01, 55.70, 51.43, 34.29, 26.74. HRMS (ESI) $C_{14}H_{22}NO_3^+$ $[M+H]^+$ calcd: 252.1594, found: 252.1592.



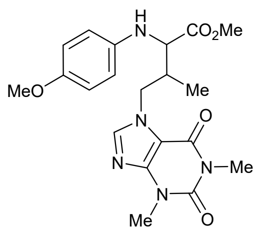
5ai

methyl 2-((4-methoxyphenyl)amino)-3,3-dimethyl-5-phenylpentanoate (5ai): 27.6 mg, yield: 81%, Colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 2H), 7.17 (dd, J = 8.0, 4.8 Hz, 3H), 6.76 (d, J = 8.9 Hz, 2H), 6.64 (d, J = 8.9 Hz, 2H), 3.98 – 3.88 (m, 1H), 3.86 (s, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 2.73 – 2.56 (m, 2H), 1.77 – 1.63 (m, 2H), 1.11 (s, 3H), 1.09 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.22, 152.91, 142.72, 141.59, 128.42, 128.40, 125.78, 115.71, 114.86, 65.54, 55.71, 51.61, 42.16, 37.00, 30.47, 24.13, 23.59. HRMS (ESI) $C_{21}H_{28}NO_3^+$ $[M+H]^+$ calcd: 342.2064, found: 342.2056.



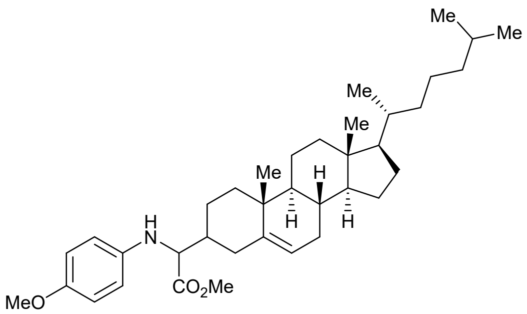
5aj

methyl 2-((3r,5r,7r)-adamantan-1-yl)-2-((4-methoxyphenyl)amino)acetate (5aj): 28.0 mg, yield: 85%, White solid. M. p. 91.3 – 92.8 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.75 (d, J = 9.0 Hz, 2H), 6.62 (d, J = 10.0 Hz, 2H), 3.90 (s, 1H), 3.72 (s, 3H), 3.66 (s, 3H), 3.56 (s, 1H), 2.02 (s, 3H), 1.80 (d, J = 11.5 Hz, 3H), 1.69 (q, J = 12.2 Hz, 6H), 1.55 (d, J = 13.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.81, 152.70, 141.89, 115.48, 114.83, 67.99, 55.71, 51.43, 39.05, 36.88, 36.14, 28.39. HRMS (ESI) $C_{20}H_{28}NO_3^+$ $[M+H]^+$ calcd: 330.2064, found: 330.2058.



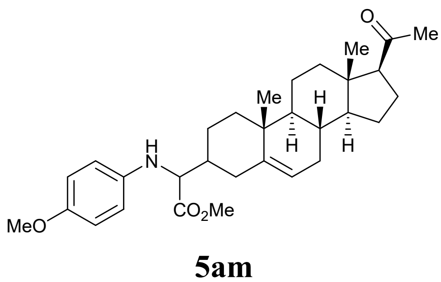
5ak

methyl 4-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)-2-((4-methoxyphenyl)amino)-3-methylbutanoate (5ak): 30.3 mg, yield: 73%, Yellow oil. d.r. = 1.2:1 (determined by ^{1}H NMR). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (s, 0.45H), 7.50 (s, 0.55H), 6.75 (dd, J = 9.0, 3.4 Hz, 2H), 6.60 (dd, J = 13.1, 8.9 Hz, 2H), 4.81 – 4.37 (m, 1.5H), 4.28 – 3.97 (m, 1.5H), 3.83 (d, J = 7.6 Hz, 1H), 3.77 – 3.65 (m, 6H), 3.59 (d, J = 3.9 Hz, 3H), 3.42 (s, 3H), 2.80 (qd, J = 7.2, 3.4 Hz, 0.55H), 2.60 – 2.49 (m, 0.46H), 0.99 (t, J = 7.8 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.46, 173.19, 155.11, 155.09, 153.19, 152.73, 151.58, 151.55, 149.13, 149.01, 141.87, 141.75, 140.64, 140.55, 115.68, 114.92, 114.83, 114.78, 106.94, 106.80, 60.48, 58.23, 55.61, 55.56, 52.30, 52.19, 50.01, 49.82, 37.68, 36.54, 29.82, 29.79, 28.04, 28.01, 14.19, 12.34. HRMS (ESI) $C_{20}H_{26}N_5O_5^+$ $[M+H]^+$ calcd: 416.1928, found: 416.1926.



5al

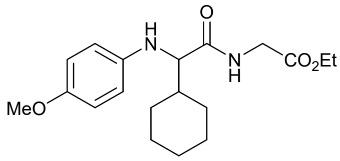
methyl 2-((8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl)-2-((4-methoxyphenyl)amino)acetate (5al): 39.4 mg, yield: 70%, White solid. M. p. 155.2 – 157.4 °C. d.r. = 1:1 (determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.76 (d, *J* = 8.9 Hz, 2H), 6.61 (d, *J* = 8.9 Hz, 2H), 5.33 (d, *J* = 5.3 Hz, 0.51H), 5.31 (d, *J* = 4.1 Hz, 0.51H), 3.99 – 3.86 (m, 1H), 3.80 (t, *J* = 5.6 Hz, 1H), 3.73 (s, 3H), 3.69 (d, *J* = 1.5 Hz, 3H), 2.36 – 1.69 (m, 8H), 1.58 – 1.25 (m, 12H), 1.17 – 0.95 (m, 12H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.86 (dd, *J* = 6.6, 2.7 Hz, 6H), 0.67 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.43, 174.38, 152.74, 141.82, 141.78, 141.58, 141.50, 120.61, 115.33, 115.31, 114.87, 63.29, 63.16, 56.79, 56.15, 55.71, 51.82, 51.80, 50.34, 50.33, 42.66, 42.63, 42.31, 39.79, 39.52, 39.04, 37.12, 36.19, 35.95, 35.79, 35.41, 31.89, 31.83, 28.24, 28.02, 25.62, 24.86, 24.28, 23.83, 22.83, 22.57, 20.93, 19.44, 19.42, 18.72, 11.87.HRMS (ESI) $C_{37}H_{58}NO_3^+$ $[M+H]^+$ calcd: 564.4411, found: 564.4399.



5am

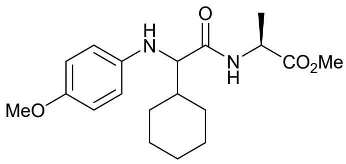
methyl 2-((8*S*,9*S*,10*R*,13*S*,14*S*,17*S*)-17-acetyl-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-3-yl)-2-((4-methoxyphenyl)amino)acetate (5am): 33.5 mg, yield: 68%, White solid. M. p. 86.2 – 88.4 °C. d.r. = 2:1(determined by ^{1}H NMR). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 6.75 (t, *J* = 7.3 Hz, 2H), 6.61 (dd, *J* = 8.3, 5.6 Hz, 2H), 5.31 (q, *J* = 6.0, 5.6 Hz, 1H), 4.07 – 3.74 (m, 2H), 3.73 (s, 3H), 3.70 – 3.62

(m, 3H), 2.57 – 2.17 (m, 3H), 2.14 (s, 1H), 2.12 (s, 2H), 2.06 – 1.88 (m, 3H), 1.86 – 1.32 (m, 10.74H), 1.29 – 0.94 (m, 7.37H), 0.63 (d, *J* = 3.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 209.69, 175.69, 175.49, 174.46, 174.40, 152.73, 152.71, 152.65, 141.78, 141.75, 141.58, 141.54, 141.45, 141.28, 139.44, 139.06, 122.67, 122.35, 120.34, 115.52, 115.33, 115.30, 115.04, 114.84, 114.76, 63.74, 63.72, 63.22, 63.09, 58.96, 57.62, 56.93, 55.70, 51.90, 51.88, 51.71, 51.63, 50.33, 50.26, 50.16, 44.02, 42.60, 42.56, 39.04, 38.84, 38.02, 37.31, 37.25, 37.13, 35.91, 35.38, 34.75, 34.25, 33.44, 31.88, 31.80, 31.78, 31.64, 25.59, 24.83, 24.50, 24.36, 22.80, 22.65, 20.95, 20.82, 20.76, 19.57, 19.55, 19.47, 19.45, 13.27. HRMS (ESI) $C_{31}H_{44}NO_4^+$ $[M+H]^+$ calcd: 494.3265, found: 494.3261.



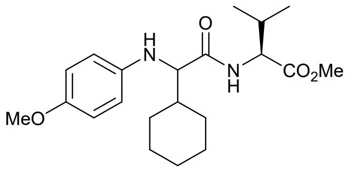
5ba

ethyl (2-cyclohexyl-2-((4-methoxyphenyl)amino)acetyl)glycinate (5ba): 29.6 mg, yield: 85%, Colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.41 (t, *J* = 5.7 Hz, 1H), 6.76 (d, *J* = 8.9 Hz, 2H), 6.59 (d, *J* = 8.9 Hz, 2H), 4.18 – 4.08 (m, 3H), 3.92 – 3.84 (m, 2H), 3.72 (s, 3H), 3.53 (d, *J* = 4.4 Hz, 1H), 2.00 (tdd, *J* = 11.7, 6.4, 3.6 Hz, 1H), 1.78 (td, *J* = 8.1, 3.4 Hz, 3H), 1.73 – 1.65 (m, 2H), 1.32 – 1.13 (m, 8H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.58, 169.65, 152.95, 141.63, 114.86, 114.83, 65.62, 61.28, 55.66, 41.28, 41.01, 30.16, 28.07, 26.28, 26.25, 26.12, 14.09. HRMS (ESI) $C_{19}H_{29}N_2O_4^+$ $[M+H]^+$ calcd:349.2122, found: 349.2105.



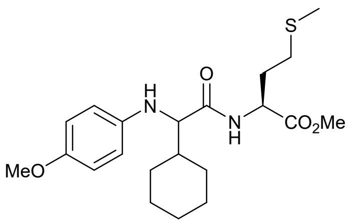
5la

methyl (2-cyclohexyl-2-((4-methoxyphenyl)amino)acetyl)-*L*-alaninate (5la): 28.9 mg, yield: 83%, Yellow solid. M. p. 89.2 – 92.3 °C. d.r. = 1:1 (determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.40 – 7.31 (m, 1H), 6.81 – 6.72 (m, 2H), 6.65 – 6.60 (m, 1H), 6.59 – 6.54 (m, 1H), 4.67 – 4.55 (m, 1H), 3.84 (s, 1H), 3.77 – 3.68 (m, 4.54H), 3.67 – 3.62 (m, 1.51H), 3.52 – 3.47 (m, 1H), 2.04 – 1.94 (m, 1H), 1.82 – 1.64 (m, 5H), 1.41 – 1.11 (m, 8H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.19, 172.92, 172.89, 172.69, 153.01, 152.92, 141.72, 141.55, 115.21, 114.80, 114.72, 65.84, 65.62, 55.65, 52.30, 52.23, 47.74, 47.54, 41.26, 41.24, 30.19, 30.16, 28.16, 28.02, 26.29, 26.26, 26.23, 26.13, 18.23, 18.11. HRMS (ESI) $C_{19}H_{29}N_2O_4^+$ $[M+H]^+$ calcd:349.2122, found: 349.2114.



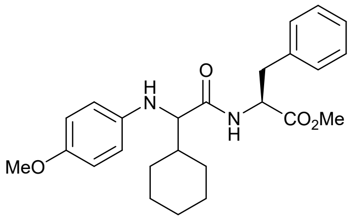
5ca

methyl (2-cyclohexyl-2-((4-methoxyphenyl)amino)acetyl)-*L*-valinate (5ca): 30.9 mg, yield: 82%, White solid. M. p. 81.2 – 82.8 ^{o}C. d.r. = 1.1:1 (determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.35 (t, *J* = 9.3 Hz, 1H), 6.76 (dd, *J* = 8.9, 2.4 Hz, 2H), 6.66 – 6.57 (m, 2H), 4.53 (ddd, *J* = 10.5, 9.0, 5.0 Hz, 1H), 3.93 (s, 1H), 3.72 (d, *J* = 1.3 Hz, 3H), 3.70 (s, 1.56H), 3.60 (s, 1.44H), 3.57 – 3.50 (m, 1H), 2.19 – 2.09 (m, 1H), 2.04 – 1.94 (m, 1H), 1.83 – 1.65 (m, 5H), 1.36 – 1.29 (m, 1H), 1.25 – 1.11 (m, 3H), 0.91 (d, *J* = 6.9 Hz, 1.45H), 0.87 (d, *J* = 6.9 Hz, 1.45H), 0.81 (d, *J* = 6.9 Hz, 1.55H), 0.71 (d, *J* = 6.9 Hz, 1.55H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.28, 172.94, 172.23, 171.76, 153.04, 152.93, 141.73, 141.33, 115.39, 114.77, 114.66, 66.27, 65.42, 57.12, 56.63, 55.62, 55.59, 51.96, 51.84, 41.23, 41.14, 30.94, 30.83, 30.21, 28.34, 27.94, 26.31, 26.25, 26.23, 26.20, 26.12, 19.08, 19.01, 17.87, 17.43. HRMS (ESI) $C_{21}H_{33}N_2O_4^+$ [M+H]$^+$ calcd:377.2435, found: 377.2416.



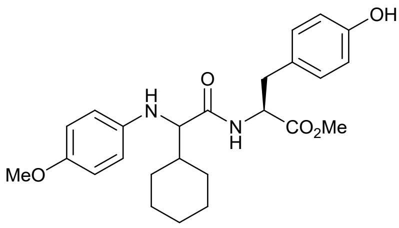
5ea

methyl (2-cyclohexyl-2-((4-methoxyphenyl)amino)acetyl)-*L*-methioninate (5ea): 29.8 mg, yield: 73%, Yellow oil .d.r. = 1:1 (determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 12.4, 8.4 Hz, 1H), 6.77 (d, *J* = 8.6 Hz, 2H), 6.61 (d, *J* = 8.9 Hz, 1H), 6.56 (d, *J* = 8.9 Hz, 1H), 4.75 (td, *J* = 8.2, 4.7 Hz, 0.5H), 4.69 (td, *J* = 8.0, 5.0 Hz, 0.52H), 3.83 – 3.63 (m, 7H), 3.53 (d, *J* = 4.2 Hz, 0.5H), 3.49 (d, *J* = 4.6 Hz, 0.52H), 2.44 (dd, *J* = 7.9, 7.1 Hz, 1H), 2.31 – 2.21 (m, 1H), 2.18 – 2.04 (m, 2.64H), 2.02 – 1.84 (m, 3.52H), 1.82 – 1.67 (m, 5H), 1.33 – 1.13 (m, 5H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.23, 172.90, 172.23, 171.87, 153.17, 153.07, 141.53, 141.14, 115.36, 114.89, 114.76, 114.63, 66.10, 65.31, 55.73, 55.69, 52.42, 52.34, 51.30, 50.85, 41.20, 41.17, 31.47, 31.37, 30.25, 30.23, 30.06, 29.75, 28.33, 28.04, 26.30, 26.25, 26.22, 26.18, 26.12, 15.41, 15.24. HRMS (ESI) $C_{21}H_{33}N_2O_4S^+$ [M+H]$^+$ calcd: 409.2156, found: 409.2143.



5fa

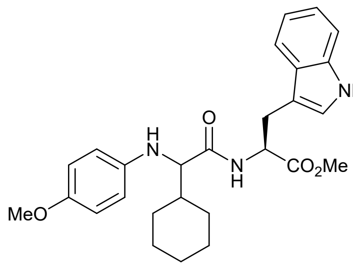
methyl (2-cyclohexyl-2-((4-methoxyphenyl)amino)acetyl)-*L*-phenylalaninate (5fa): 33.5 mg, yield: 79%, Yellow solid. M. p. 104.2 – 106.3 ^{o}C. d.r. = 1.2:1 (determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.28 – 7.11 (m, 3H), 7.10 – 7.02 (m, 2H), 6.88 – 6.63 (m, 3H), 6.59 – 6.55 (m, 1.1H), 6.51 – 6.43 (m, 0.88H), 4.96 (ddd, *J* = 8.9, 6.5, 5.3 Hz, 0.45H), 4.91 (td, *J* = 8.4, 5.3 Hz, 0.55H), 3.85 – 3.56 (m, 7H), 3.48 (d, *J* = 4.3 Hz, 0.46H), 3.40 (d, *J* = 4.6 Hz, 0.56H), 3.19 (dd, *J* = 14.1, 5.3 Hz, 0.58H), 3.03 (dd, *J* = 13.9, 6.5 Hz, 0.46H), 2.98 – 2.89 (m, 1H), 1.99 – 1.58 (m, 5H), 1.55 – 1.47 (m, 0.58H), 1.41 – 1.33 (m, 0.58H), 1.29 – 0.91 (m, 5H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.02, 172.78, 171.80, 171.70, 153.13, 152.98, 141.66, 141.37, 136.20, 135.54, 129.17, 129.11, 128.52, 126.96, 126.92, 115.41, 114.90, 114.72, 114.67, 66.16, 65.26, 55.76, 55.68, 52.82, 52.25, 52.19, 41.23, 41.13, 38.01, 37.88, 30.22, 30.01, 28.07, 27.94, 26.32, 26.27, 26.25, 26.22, 26.14, 26.08. HRMS (ESI) $C_{25}H_{33}N_2O_4^+$ $[M+H]^+$ calcd: 425.2435, found: 425.2419.



5ma

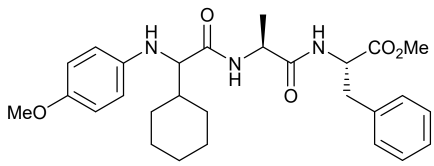
methyl (2-cyclohexyl-2-((4-methoxyphenyl)amino)acetyl)-*L*-tyrosinate (5ma): 29.9 mg, yield: 68%, White solid. M. p. 61.8 – 63.4 ^{o}C. d.r. = 1.2:1 (determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.41 (d, *J* = 8.1 Hz, 0.46H), 7.32 (d, *J* = 3.4 Hz, 0.57H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.79 – 6.68 (m, 3H), 6.65 (d, *J* = 8.2 Hz, 1H), 6.57 (t, *J* = 8.3 Hz, 2H), 6.44 (d, *J* = 8.9 Hz, 1H), 5.00 – 4.92 (m, 0.45H), 4.92 – 4.87 (m, 0.55H), 3.71 (t, *J* = 12.8 Hz, 5H), 3.61 (s, 2H), 3.48 (d, *J* = 3.5 Hz, 0.45H), 3.43 (d, *J* = 4.6 Hz, 0.55H), 3.13 (dd, *J* = 14.2, 5.2 Hz, 0.54H), 2.98 – 2.82 (m, 1.47H), 1.95 (td, *J* = 12.0, 3.6 Hz, 0.46H), 1.85 – 1.78 (m, 0.60H), 1.78 – 1.53 (m, 4H), 1.51 (d, *J* = 12.0 Hz, 0.56H), 1.34 (d, *J* = 12.8 Hz, 0.5H), 1.27 – 0.85 (m, 5H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.85, 173.60, 172.12, 171.82, 155.80, 155.66, 153.12, 152.95, 141.47, 141.19, 130.16, 130.12, 126.96, 126.37, 115.69, 115.60, 115.42, 115.00, 114.80, 114.70, 66.14, 65.24, 55.82, 55.73, 53.13, 52.47, 52.38, 52.33, 41.21, 41.07, 37.21, 37.17, 30.21, 30.02, 28.04, 27.87, 26.26, 26.21, 26.15, 26.08, 26.03. HRMS

(ESI) $C_{25}H_{33}N_2O_5^+$ $[M+H]^+$ calcd: 441.2384, found: 441.2367.



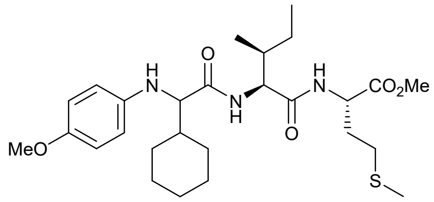
5ga

methyl (2-cyclohexyl-2-((4-methoxyphenyl)amino)acetyl)-*L*-tryptophanate (5ga): 30.1 mg, yield: 65%, Yellow oil. d.r. = 1.2:1 (determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 8.58 (s, 0.53H), 8.28 (s, 0.46H), 7.50 (d, *J* = 8.0 Hz, 0.57H), 7.38 (dd, *J* = 10.9, 8.2 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 0.59H), 7.24 – 7.21 (m, 1H), 7.17 – 7.04 (m, 1.64H), 6.97 (td, *J* = 7.5, 7.0, 1.0 Hz, 0.51H), 6.82 (d, *J* = 2.4 Hz, 0.59H), 6.73 – 6.67 (m, 2H), 6.54 – 6.35 (m, 2.59H), 4.94 (dtd, *J* = 27.9, 8.1, 5.5 Hz, 1H), 3.81 – 3.55 (m, 7H), 3.44 (dd, *J* = 27.7, 4.5 Hz, 1H), 3.30 – 3.10 (m, 2H), 1.86 (dddd, *J* = 73.6, 12.5, 7.9, 3.9 Hz, 1H), 1.74 – 1.58 (m, 4H), 1.50 (d, *J* = 12.5 Hz, 0.58H), 1.35 (d, *J* = 12.9 Hz, 0.59H), 1.26 – 0.85 (m, 5H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.26, 173.07, 172.35, 172.17, 152.99, 152.89, 141.62, 141.52, 136.24, 136.19, 127.60, 127.26, 123.25, 122.91, 122.06, 121.98, 119.50, 119.42, 118.47, 118.43, 115.32, 114.88, 114.75, 114.70, 111.43, 111.28, 109.90, 109.22, 65.87, 65.49, 55.79, 55.73, 52.90, 52.30, 52.25, 51.96, 41.22, 41.08, 30.22, 30.03, 28.01, 27.96, 27.76, 27.64, 26.31, 26.25, 26.22, 26.21, 26.14, 26.10. HRMS (ESI) $C_{27}H_{34}N_3O_4^+$ $[M+H]^+$ calcd: 464.2544, found: 464.2534.



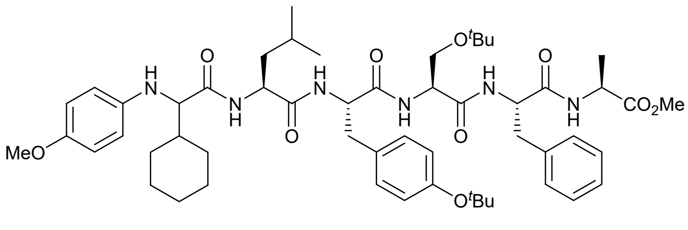
5ha

methyl (2-cyclohexyl-2-((4-methoxyphenyl)amino)acetyl)-*L*-alanyl-*L*-phenylalaninate (5ha): 37.1 mg, yield: 75%, White solid. M. p. 146 – 155 °C. d.r. = 1.3:1 (determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, MeOD) δ 7.26 – 7.21 (m, 2H), 7.20 – 7.16 (m, 1H), 7.15 – 7.08 (m, 2H), 6.71 (dd, *J* = 8.9, 1.9 Hz, 2H), 6.59 (dd, *J* = 11.5, 8.9 Hz, 2H), 4.62 – 4.55 (m, 1H), 4.42 – 4.35 (m, 1H), 3.66 (d, *J* = 5.8 Hz, 3H), 3.64 (d, *J* = 9.2 Hz, 3H), 3.51 (d, *J* = 6.3 Hz, 0.55H), 3.48 (d, *J* = 6.2 Hz, 0.44H), 3.03 (ddd, *J* = 13.8, 6.1, 2.0 Hz, 1H), 2.92 (dd, *J* = 13.9, 7.9 Hz, 0.48H), 2.84 (dd, *J* = 13.9, 8.3 Hz, 0.55H), 1.89 – 1.82 (m, 1H), 1.80 – 1.71 (m, 3H), 1.70 – 1.61 (m, 2H), 1.32 – 1.15 (m, 8H). **^{13}C NMR** (151 MHz, MeOD) δ 174.57, 172.91, 171.67, 152.57, 152.50, 141.90, 136.49, 136.45, 128.88, 128.83, 128.10, 126.52, 126.50, 114.51, 114.44, 114.36, 114.27, 64.80, 64.77, 54.69, 53.76, 53.70, 51.27, 51.25, 48.37, 48.25, 41.11, 36.97, 29.56, 28.92, 26.05, 26.03, 26.01, 25.95, 17.15, 17.00. HRMS (ESI) $C_{28}H_{38}N_3O_5^+$ $[M+H]^+$ calcd: 496.2806, found: 496.2797.



5ia

methyl (2-cyclohexyl-2-((4-methoxyphenyl)amino)acetyl)-*L*-isoleucyl-*L*-methioninate (5ia): 33.9 mg, yield: 65%, White solid. M. p. 176 – 180 °C. d.r. = 1.3:1 (determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.8 Hz, 0.54H), 7.24 (d, *J* = 8.8 Hz, 0.4H), 6.77 (dd, *J* = 8.8, 5.5 Hz, 2H), 6.65 – 6.53 (m, 3H), 4.69 (td, *J* = 7.6, 5.1 Hz, 0.58H), 4.64 (td, *J* = 7.9, 5.1 Hz, 0.44H), 4.29 (dd, *J* = 8.8, 6.5 Hz, 0.45H), 4.23 (dd, *J* = 8.8, 7.5 Hz, 0.57H), 3.79 – 3.67 (m, 7H), 3.52 (dd, *J* = 12.4, 4.5 Hz, 1H), 2.49 (t, *J* = 7.4 Hz, 1.14H), 2.42 – 2.35 (m, 0.89H), 2.18 – 2.03 (m, 4H), 2.01 – 1.93 (m, 2H), 1.84 – 1.63 (m, 6H), 1.41 (ddq, *J* = 15.0, 7.4, 3.8 Hz, 0.52H), 1.33 – 1.13 (m, 5.55H), 1.09 – 0.86 (m, 4H), 0.82 (d, *J* = 6.8 Hz, 1.58H), 0.75 (t, *J* = 7.4 Hz, 1.54H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.35, 173.22, 172.00, 171.96, 170.97, 170.65, 153.22, 153.05, 141.38, 141.09, 115.04, 114.84, 114.75, 66.02, 65.29, 57.78, 57.41, 55.76, 55.67, 52.53, 52.48, 51.43, 51.26, 41.31, 41.15, 36.42, 36.33, 31.52, 31.45, 30.32, 30.30, 29.92, 29.89, 28.44, 28.19, 26.25, 26.23, 26.20, 26.17, 26.11, 24.84, 24.62, 15.65, 15.43, 15.41, 15.38, 11.26, 10.82. HRMS (ESI) $C_{27}H_{44}N_3O_5S^+$ $[M+H]^+$ calcd: 522.2996, found: 522.2977.

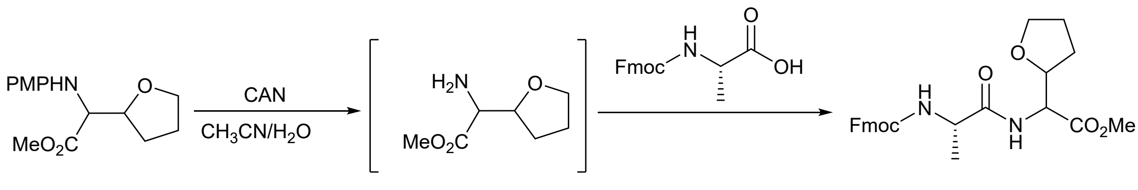


5ka

methyl N-((2*S*)-3-(4-(*tert*-butoxy)phenyl)-2-((2*S*)-2-(2-cyclohexyl-2-((4-methoxyphenyl)amino)acetamido)-4-methylpentanamido)propanoyl)-*O*-(*tert*-butyl)-*L*-seryl-*L*-phenylalanyl-*L*-alaninate (5ka): 69.9 mg, yield: 72%, White solid. d.r. = 1.4:1. (determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 8.70 (d, *J* = 9.2 Hz, 0.47H), 8.52 – 8.38 (m, 1.12H), 8.21 (d, *J* = 8.7 Hz, 0.52H), 8.05 – 7.74 (m, 3H), 7.48 – 7.00 (m, 8H), 6.93 – 6.49 (m, 5H), 5.32 (t, *J* = 5.0 Hz, 1H), 5.20 (d, *J* = 7.8 Hz, 0.41H), 5.04 (d, *J* = 9.1 Hz, 0.57H), 4.67 – 4.47 (m, 2H), 4.38 – 4.12 (m, 3H), 3.88

– 3.42 (m, 6H), 3.39 (t, *J* = 7.4 Hz, 1H), 3.31 – 3.18 (m, 1H), 3.02 (dd, *J* = 15.0, 4.8 Hz, 1H), 2.92 (ddt, *J* = 24.3, 14.6, 4.3 Hz, 1H), 2.82 (ddd, *J* = 12.2, 8.5, 3.2 Hz, 1H), 2.68 (tt, *J* = 17.6, 9.4 Hz, 1H), 1.99 (dq, *J* = 12.7, 6.9, 6.5 Hz, 2H), 1.85 – 1.41 (m, 5H), 1.39 – 0.93 (m, 28H), 0.87 – 0.58 (m, 6H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 174.73, 173.20, 172.28, 171.50, 171.12, 170.90, 169.56, 156.55, 153.79, 137.82, 132.76, 131.13, 130.23, 130.12, 129.72, 129.70, 128.43, 127.58, 126.68, 125.98, 123.69, 122.30, 115.20, 114.70, 114.27, 77.93, 73.38, 62.08, 55.70, 55.65, 53.84, 53.61, 52.36, 47.99, 38.16, 35.58, 31.75, 29.74, 29.55, 29.49, 29.44, 29.34, 29.30, 29.21, 29.16, 29.04, 29.01, 28.99, 27.63, 27.57, 27.02, 25.58, 24.68, 24.37, 23.59, 23.44, 22.56, 21.91, 21.64, 17.38, 14.42. HRMS (ESI) $C_{54}H_{79}N_6O_{10}^+$ [M+H]$^+$ calcd: 971.5852, found: 971.5804.

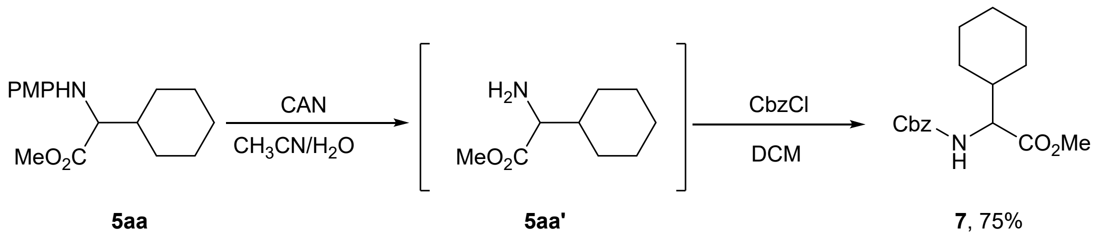
6. Synthetic applications



Preparation of 6:

A mixture of **3aa** (0.1 mmol, 26.5 mg) and CAN (cerium ammonium, 0.6 mmol, 318.1 mg) in 5:2 solution of H_2O/CH_3CN (1.0 mL) were stirred at 0 °C for 2 h. The mixture was modulated to alkalescence with saturated aqueous sodium carbonate. Then, the mixture was extracted by DCM for three times, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was dissolved in 1.0 mL DCM, followed by the addition of EDCI (0.16 mmol, 30.7 mg), HOBT (0.16 mmol, 21.6 mg), Fmoc-Ala-OH (0.12 mmol, 37.4 mg), and DIPEA (0.4 mmol, 70 μL). The mixture was stirred under argon atmosphere for 12 h. After completion of the reaction monitored by TLC, the resulting mixture was washed by citric acid solution (three times), saturated sodium bicarbonate solution (three times) and brine (two times). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The product **6** was purified by silica gel column chromatography using hexane-EtOAc as eluents. **methyl 2-((*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)propanamido)-2-(tetrahydrofuran-2-yl)acetate:** 31.7 mg, yield: 70%, Yellow solid. M. p. 135.7 – 138.2 °C. d.r. = 1:1 (determined by ^{1}H NMR). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.5 Hz, 2H), 7.58 (d, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 6.7 Hz, 2H), 7.32 – 7.27 (m, 2H), 7.11 – 7.04 (m, 0.25H), 7.01 (d, *J* = 8.3 Hz, 0.25H), 6.96 – 6.89 (m, 0.25H), 6.87 – 6.76 (m, 0.25H), 5.70 – 5.60 (m, 1H), 4.78 – 4.72 (m, 0.53H), 4.71 – 4.61 (m, 0.52H), 4.39 (d, *J* = 15.8 Hz, 3.5H), 4.20 (t, *J* = 6.6 Hz, 1H), 4.12 – 4.04 (m, 0.5H), 3.83 – 3.64 (m, 5H), 2.01 – 1.63 (m, 4 H), 1.47 – 1.36 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.07, 172.99, 172.31, 172.22, 170.89, 170.58, 170.46, 155.94, 143.83, 127.74, 127.09, 125.14, 125.11, 119.99, 79.46, 78.59, 78.53, 69.16, 69.11, 68.83, 68.81, 67.14, 55.39, 55.34, 54.56, 54.50, 52.64, 52.46, 52.44, 50.75, 50.49, 50.40, 47.09, 28.06, 28.05, 28.02, 27.99, 26.02, 25.91, 25.43, 19.04, 18.86. HRMS (ESI) $C_{25}H_{29}N_2O_6^+$ $[M+H]^+$ calcd: 453.2020, found: 453.2018.

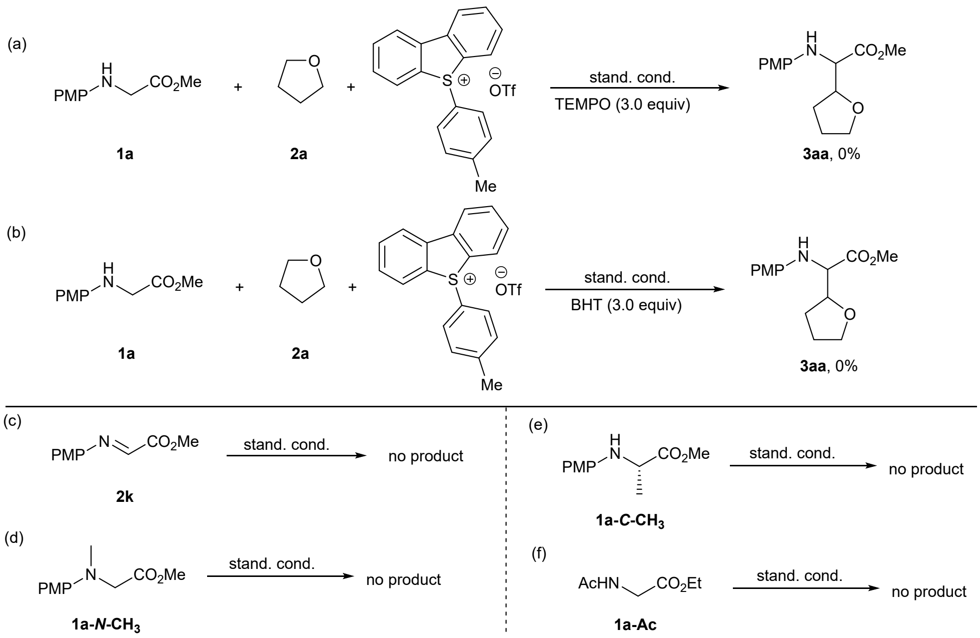
Preparation of 7:



A mixture of **5aa** (0.1 mmol, 27.7 mg) and CAN (cerium ammonium, 0.6 mmol, 318.1 mg) in 5:2 solution of H_2O/CH_3CN (1.0 mL) were stirred at 0 °C for 2 h. The mixture was modulated to alkalescence with saturated aqueous sodium carbonate. Then, the mixture was extracted by DCM for three times, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was dissolved in 1.0 mL DCM. Benzyloxycarbonyl chloride (0.12 mmol, 16.9 µL) was added. The resulting solution was cooled to 0 °C and TEA (0.12 mmol, 16.6 µL) was then added dropwise. After 5 min, the ice bath was removed and the mixture was allowed to stir for 2 h at roomtemperature. 10 mL DCM was added and the mixture was washed with H_2O (10 mL) and brine (10mL). The resulting solution was dried over Na_2SO_4 and evaporated in vacuo. The product **7** was purified by silica gel column chromatography using hexane-EtOAc as eluents. **methyl 2-(((benzyloxy)carbonyl)amino)-2-cyclohexylacetate:**22.9 mg, yield: 75%, Yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 5H), 5.28 (d, *J* = 8.9 Hz, 1H), 5.10 (s, 2H), 4.29 (dd, *J* = 9.1, 5.2 Hz, 1H), 3.73 (s, 3H), 1.81 – 1.56 (m, 7H), 1.23 – 1.19 (m, 1H), 1.13 – 1.02 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.56, 156.16, 136.27, 128.55, 128.21, 128.17, 67.05, 58.75, 52.15, 41.03, 29.42, 28.04, 25.95. HRMS (ESI) $C_{17}H_{24}NO_4^+$ $[M+H]^+$ calcd: 306.1700, found: 306.1702.

7. The mechanistic studies

7.1 Radical inhibition experiments and control experiments of HAT reaction



To an oven-dried 10 mL quartz test tube with a stirring bar was added derivative of glycine or peptide **1a** (0.1 mmol, 19.5 mg), (Tol)DBT·OTf (0.2 mmol, 84.8 mg), DABCO (0.3 mmol, 33.7 mg), TEMPO (0.3 mmol, 46.9 mg) or BHT (0.3 mmol, 66.1 mg). Then, air was withdrawn and backfilled with Ar (three times). acetone (0.5 mL) and THF (0.5 ml) were added. The reaction mixture was irradiated with white LED for 12 h under continuous cooling via fan. Then, the reaction was quenched with water (4 mL), extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate, concentrated in vacuo, and the yields of **3aa** were determined by ^{1}H NMR using 4-bromobenzaldehyde as an internal standard. In the presence of TEMPO or BHT, the reaction was completely suppressed and the yield of **3aa** was 0%. But the alkyl or aryl radicals were not captured.

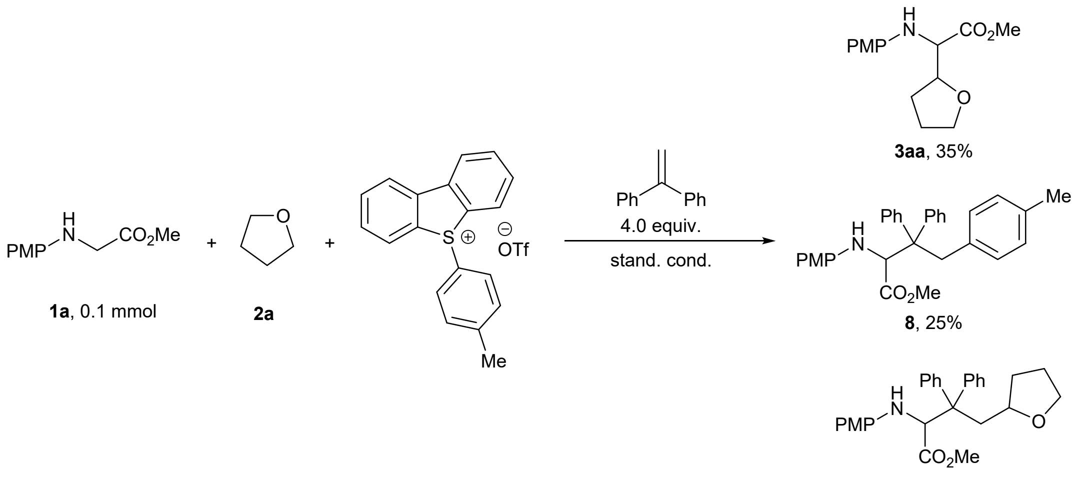
Imine did not give any desired product under standard reaction conditions, revealing that the two electron-oxidation pathway was unlikely happened and imine was not a potential intermediate.

The negative performance with **1a-*N*-CH$_3$** as the substrate indicated that the presence of hydrogen on the nitrogen atom is critical. The formation of glycine derivative secondary nitrogen radical is a key intermediate that promoted the formation of glycine *C*-centered radical via intermolecular hydrogen atom transfer. Furthermore, **1a-*C*-CH$_3$**

failed to participate in coupling maybe attributed to the instability of tertiary radical in the presence of C_α-methyl influenced by unfavorable nonbonding interaction. Distinguished from C_α-substituted amino acids, glycine *C*-centered radical possesses a favorable conformation, which is relatively free of nonbonding interactions and allowing maximum delocalization of the unpaired electron.

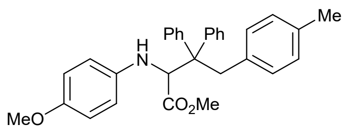
When the protecting group on *N* atom of **1a** was replaced by -Ac (**1a-Ac**), no corresponding product was obtained. It indicated that aryl protection on *N* atom is crucial for this reaction.

7.2 Radical capture experiment



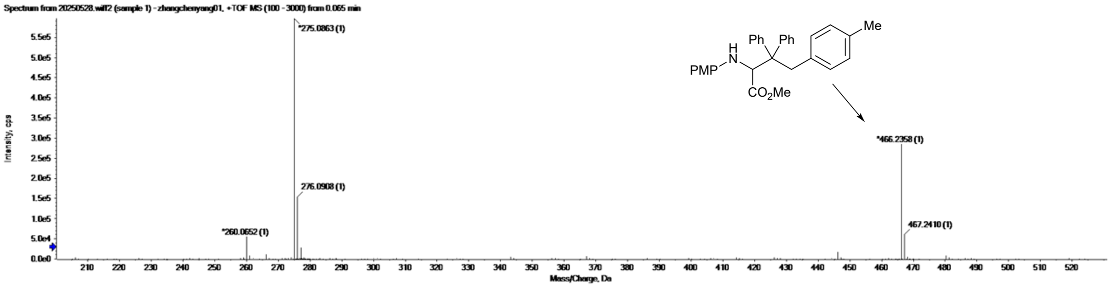
To further verify that the reaction occurs through the radical pathway, we used 1,1-diphenylethylene as a radical capture reagent to capture the radicals generated during the reaction. In the presence of 1,1-diphenylethylene, the yield of **3aa** decreased to 35%. Furthermore, the glycinate radical-alkene-aryl radical adduct **8** was obtained in 25% yield, and the glycinate radical-alkene-alkyl radical adduct **9** was detected by HRMS.

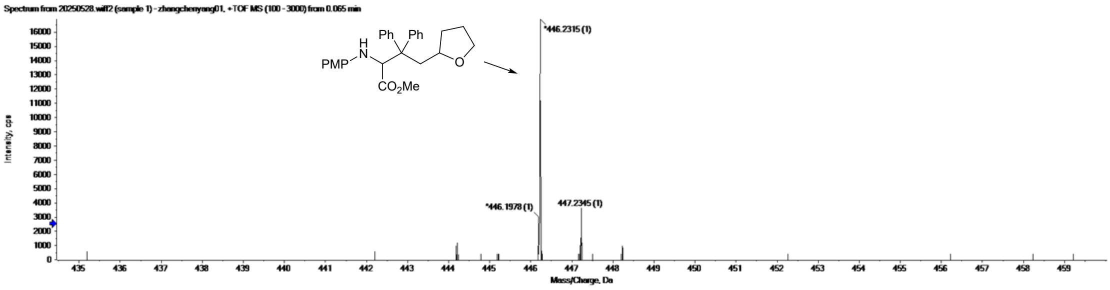
To an oven-dried 10 mL quartz test tube with a stirring bar was added derivative of glycine or peptide **1a** (0.1 mmol, 19.5 mg), (Tol)DBT·OTf (0.2 mmol, 84.8 mg), DABCO (0.3 mmol, 33.7 mg). Then, air was withdrawn and backfilled with Ar (three times). acetone (0.5 mL), THF (0.5 ml) and 1,1-Diphenylethylene (0.4 mmol, 71 μL) were added. The reaction mixture was irradiated with white LED for 12 h under continuous cooling via fan. Then, the reaction was quenched with water (4 mL), extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate, concentrated in vacuo and purified by column chromatography (hexane/ethyl acetate) to afford the **3aa** and **8.**



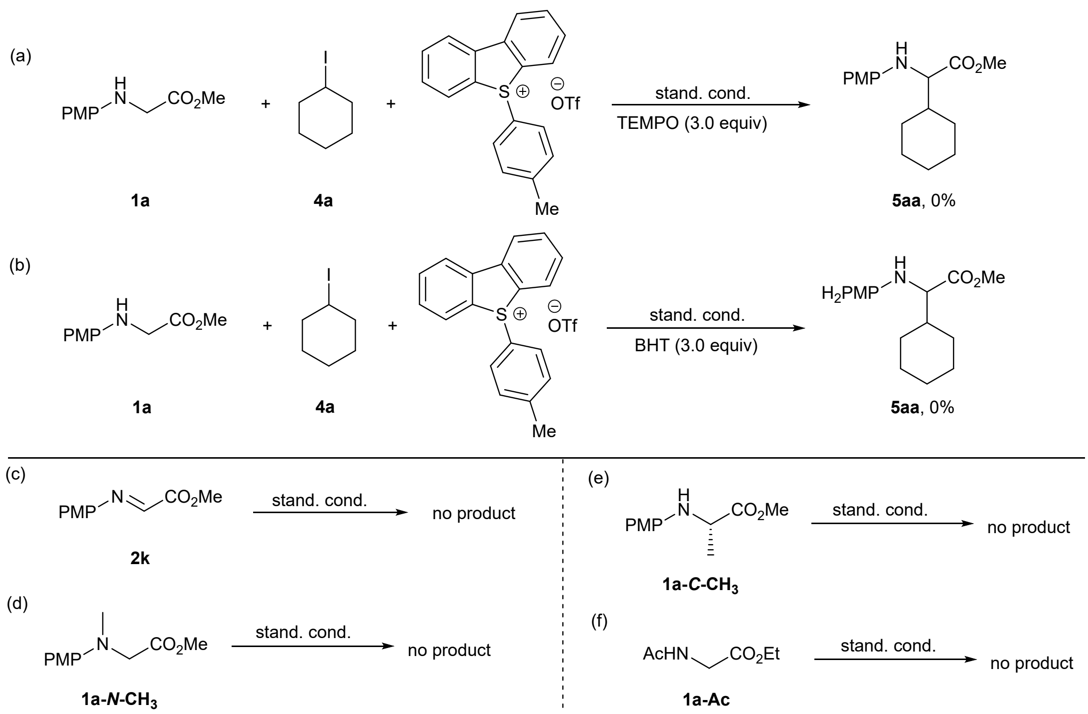
8

methyl 2-((4-methoxyphenyl)amino)-3,3-diphenyl-4-(*p*-tolyl)butanoate (8): Colorless oil. 11.6 mg, yield 25%. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.30 (d, *J* = 3.7 Hz, 5H), 7.22 – 7.16 (m, 3H), 6.95 (dd, *J* = 6.5, 3.1 Hz, 2H), 6.83 (d, *J* = 7.7 Hz, 2H), 6.73 (d, J = 8.7 Hz, 2H), 6.58 – 6.50 (m, 4H), 4.76 (d, J = 11.2 Hz, 1H), 4.26 (d, J = 11.3 Hz, 1H), 3.63 (s, 3H), 3.62 – 3.45 (m, 2H), 3.31 (s, 3H), 2.18 (s, 3H). **^{13}C NMR** (101 MHz, DMSO) δ 172.91, 152.47, 143.80, 143.61, 140.92, 135.50, 134.39, 131.05, 130.04, 129.78, 128.40, 127.97, 127.62, 127.15, 126.78, 115.17, 114.77, 60.58, 55.64, 55.55, 51.94, 44.10, 21.05. HRMS (ESI) $C_{31}H_{32}NO_3^+$ $[M+H]^+$ calcd: 466.2377, found: 466.2358.





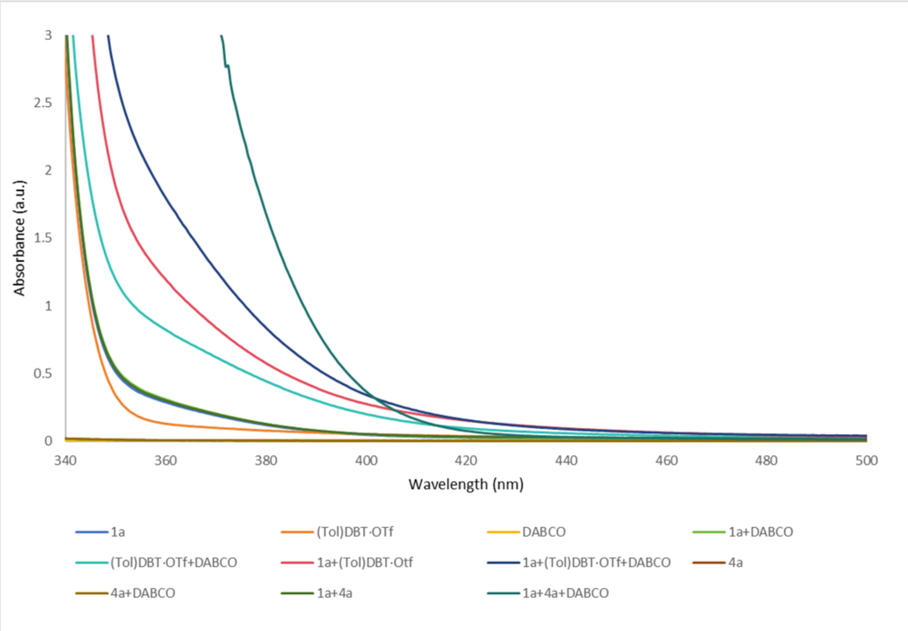
7.3 Radical inhibition experiments and control experiments of XAT reaction



To an oven-dried 10 mL quartz test tube with a stirring bar was added derivative of glycine or peptide **1a** (0.1 mmol, 19.5 mg), (Tol)DBT·OTf (0.2 mmol, 84.8 mg) and

DABCO (0.3 mmol, 33.7 mg). Then, air was withdrawn and backfilled with Ar (three times). acetone (1.0 mL) and **4a** (0.3 mmol, 38.8 μL) were added. The reaction mixture was irradiated with Blue LED for 12 h under continuous cooling via fan. Then, the reaction was quenched with water (4 mL), extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate, concentrated in vacuo, and the yields of **5aa** were determined by ^{1}H NMR using 4-bromobenzaldehyde as an internal standard. The results of XAT reaction were similar to HAT reation.

7.4 Analysis of UV-Vis absorption spectra



The UV-Vis absorption spectrum was performed on UV visible spectrophotometer (recorded in acetone in 1 mm path quartz cuvettes using BIOMATE 3S UV-Visible Spectrophotometer). **1a** (2×10^{-2} M), (Tol)DBT·OTf (2×10^{-2} M), DABCO (2×10^{-2} M), [**1a** + DABCO] (2×10^{-2} M, **1a**:DABCO = 1:1), [(Tol)DBT·OTf + DABCO] (2×10^{-2} M, (Tol)DBT·OTf:DABCO = 1:1), [**1a** + (Tol)DBT·OTf] (2×10^{-2} M, **1a**:(Tol)DBT·OTf = 1:1), [**1a** + (Tol)DBT·OTf + DABCO] (2×10^{-2} M, **1a**:(Tol)DBT·OTf:DABCO = 1:1:1), **4a** (2×10^{-2} M), [**4a** + DABCO] (2×10^{-2} M, **4a**:DABCO = 1:1), [**1a** + **4a**] (2×10^{-2} M, **1a**:**4a** = 1:1), [**1a** + **4a** + DABCO] (2×10^{-2} M, **1a**: **4a**:DABCO = 1:1:1)in acetone were provided, respectively. We observed the [**1a** + (Tol)DBT·OTf] mixture displayed an obviously red-shift in absorbance, diagnostic of an EDA complex. Furthermore, we also collected the UV/Vis spectrum of DABCO and the mixture of [**1a** + (Tol)DBT·OTf + DABCO], respectively. DABCO showed almost no absorption. Combining **1a**, (Tol)DBT·OTf, and DABCO, the absorption of mixture showed further red-shifted, which suggesting that the addition of DABCO enhanced the formation of EDA complex. An obvious color change of the mixture solution also explained the formation of EDA complex to some extent. Although the combination of **1a**, **4a** and DABCO showed an obvious red-shift in absorbance, compared with **1a** and the mixture of **1a** and **4a**. When (Tol)DBT·OTf was absent, the product of **5aa** could not be obtained.

7.5 Quantum yield determination

7.5.1 HAT reaction

To an oven-dried 20 mL round-bottom flask with a stirring bar was added derivative of glycine **1a** (1.5 mmol, 292.7 mg), (Tol)DBT·OTf (3.0 mmol, 1.2721 g), DABCO (4.5 mmol, 504.8 mg), Then, air was withdrawn and backfilled with Ar (three times). acetone (7.5 mL) and THF (7.5 mL) were added. The reaction mixture was irradiated with white LED for 6.38 h. After irradiation, the solution was measured the unit area photon flux (TBQ-5 photosynthetic active radiation meter, TRM-SCY). And the yield of product formed was determined by ^{1}H NMR using 4-bromobenzaldehyde as an internal standard. The quantum yield is calculated using the following equation:

$$\Phi = \frac{mol\,product}{flux \cdot S \cdot t}$$

Where, **Φ** is quantum yield, **S** (m^2) is the irradiation area and **t** (s) is the photoreaction time.

Experiment: the unit photon flux was 3058 μmol·s^{-1}·m^{-2} (average of three experiments), the irradiation area was 1.043×10^{-3} m^2, and the product yield was 41% after 383 min (22980 s).

Quantum yield calculation:

$$\Phi = \frac{mol\,product}{flux \cdot S \cdot t} = \frac{0.41 \times 1.5 \times 10^{3}}{3058 \times 1.043 \times 10^{-3} \times 22980} = 0.0084$$

7.5.2 XAT reaction

To an oven-dried 25 mL round-bottom flask with a stirring bar was added derivative of glycine **1a** (1.5 mmol, 292.7 mg), (Tol)DBT·OTf (3.0 mmol, 1.2721 g), DABCO (4.5 mmol, 504.8 mg), Then, air was withdrawn and backfilled with Ar (three times). acetone (15 mL) and **4a** (4.5 mmol, 582 μL) were added. The reaction mixture was irradiated with white LED for 6.8 h. After irradiation, the solution was measured the unit area photon flux (TBQ-5 photosynthetic active radiation meter, TRM-SCY). And the yield of product formed was determined by ^{1}H NMR using 4-bromobenzaldehyde as an internal standard. The quantum yield is calculated using the following equation:

$$\Phi = \frac{mol\,product}{flux \cdot S \cdot t}$$

Where, **Φ** is quantum yield, **S** (m^2) is the irradiation area and **t** (s) is the photoreaction time.

Experiment: the unit photon flux was 453 μmol·s^{-1}·m^{-2} (average of three experiments), the irradiation area was 1.043×10^{-3} m^2, and the product yield was 68% after 408 min (24480s).

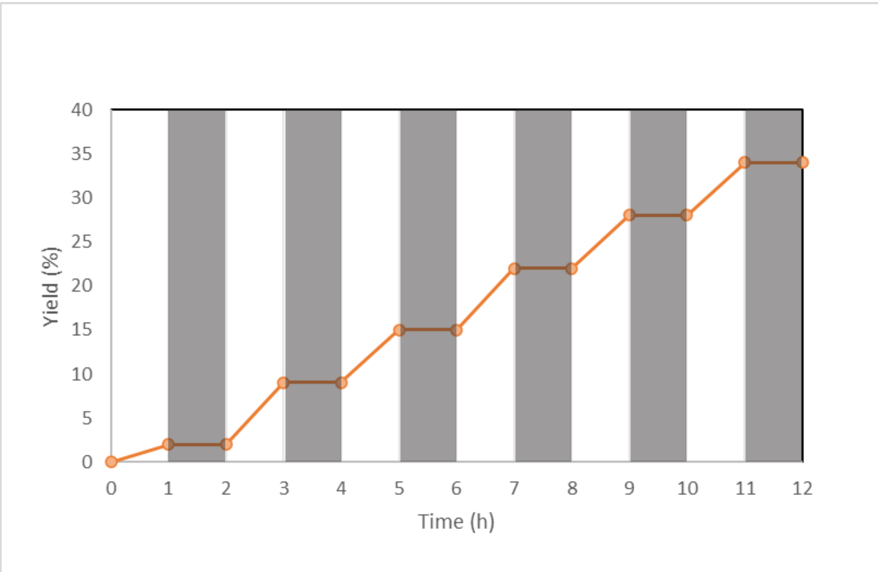
Quantum yield calculation:

$$\Phi = \frac{mol\, product}{flux \cdot S \cdot t} = \frac{0.68 \times 1.5 \times 10^3}{453 \times 1.043 \times 10^{-3} \times 24480} = 0.088$$

7.6 Light/dark experiment

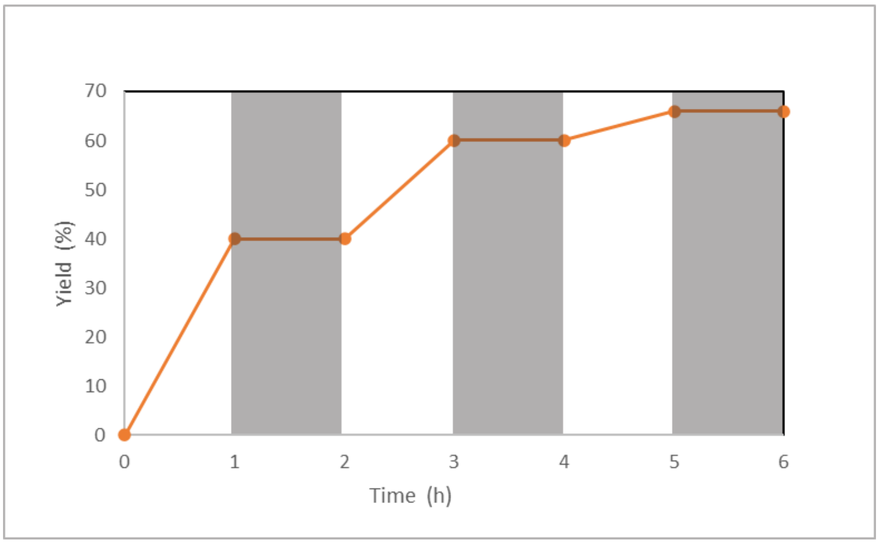
7.6.1 HAT reaction

To an oven-dried 25 mL round-bottom flask with a stirring bar was added derivative of glycine **1a** (0.5 mmol, 97.6 mg), (Tol)DBT·OTf (1.0 mmol, 424.1 mg), DABCO (1.5 mmol, 183.3 mg), Then, air was withdrawn and backfilled with Ar (three times). acetone (2.5 mL) and THF (2.5 mL) were added. The reaction mixture was irradiated with white LED and kept in the dark in one-hour intervals. The yield was determined by ^{1}H NMR.



7.6.2 XAT reaction

To an oven-dried 10 mL quartz test tube with a stirring bar was added derivative of glycine or peptide **1a** (0.5 mmol, 97.6 mg), (Tol)DBT·OTf (1.0 mmol, 424.1 mg) and DABCO (1.5 mmol, 183.3 mg). Then, air was withdrawn and backfilled with Ar (three times). acetone (5.0 mL) and **4a** (1.5 mmol, 194.0 μL) were added. The reaction mixture was irradiated with blue LED and kept in the dark in one-hour intervals. The yield was determined by ^{1}H NMR.



8. References

1 Nithinchandra, B. Kalluraya, S. Aamir and A. R. Shabaraya, *Eur. J. Med. Chem.*, 2012, **54**, 597−604.

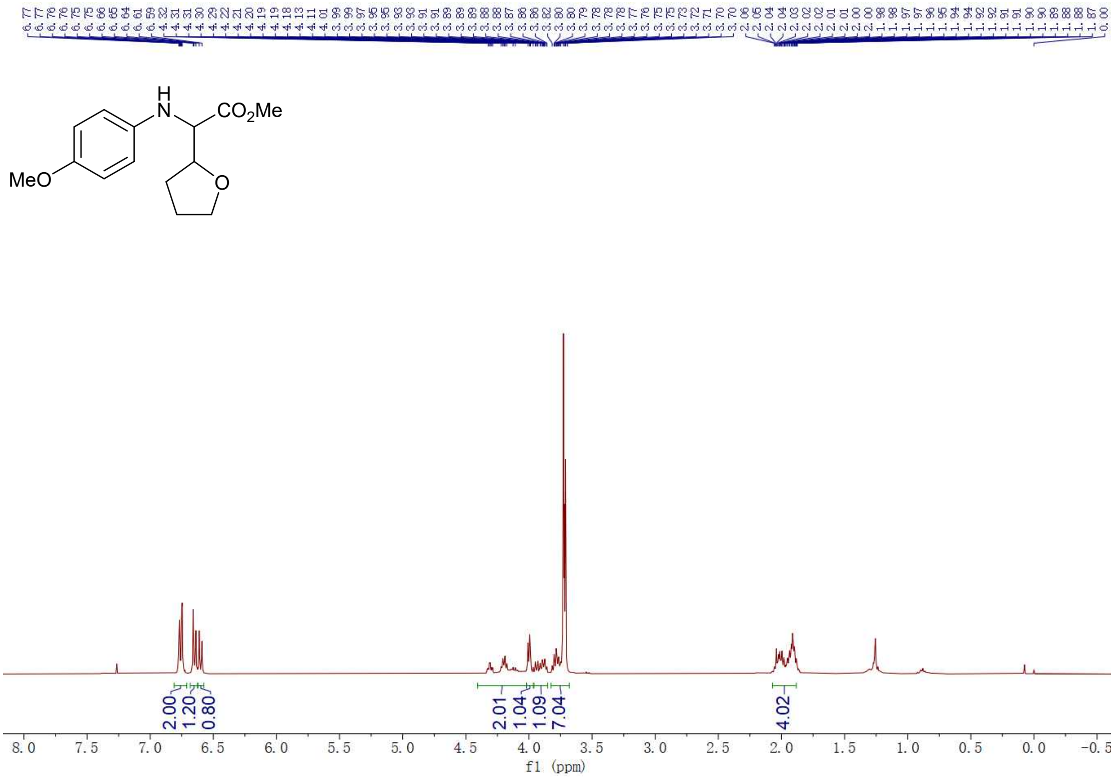
2 C. Wang, M. Guo, R. Qi, Q. Shang, Q. Liu, S. Wang, L. Zhao, R, Wang and Z. Xu, *Angew. Chem. Int. Ed.*, 2018, **57**, 15841−15846.

3 H. Zhao, V. Cuomo, J. Rossi-Ashton and D. Procter, *Chem.*, 2024, **10**, 1240−1251.

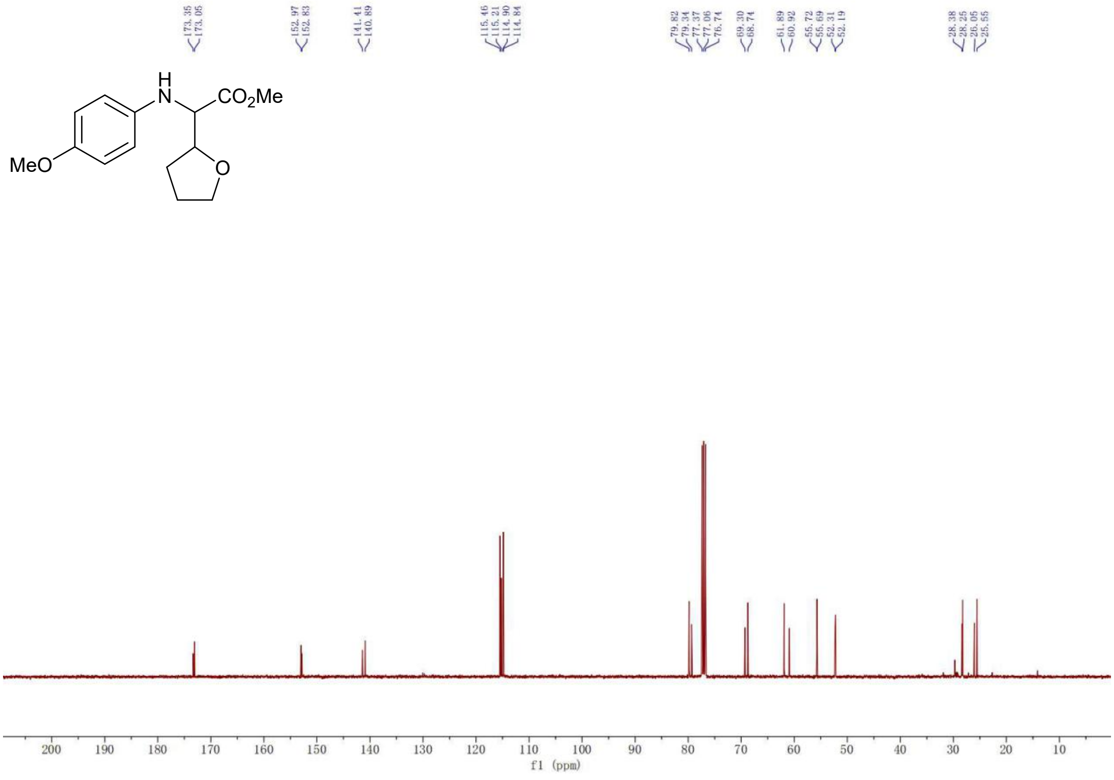
4 P. Kong, Y. Ye, X. Zhang, X. Bao and C. Huo, *Org. Lett.*, 2024, **26**, 7507−7513.

5 X. Dang, Z. Li, J. Shang, C. Zhang, C. Wang and Z. Xu, *Angew. Chem. Int. Ed.*, 2024, **63**, e202400494.

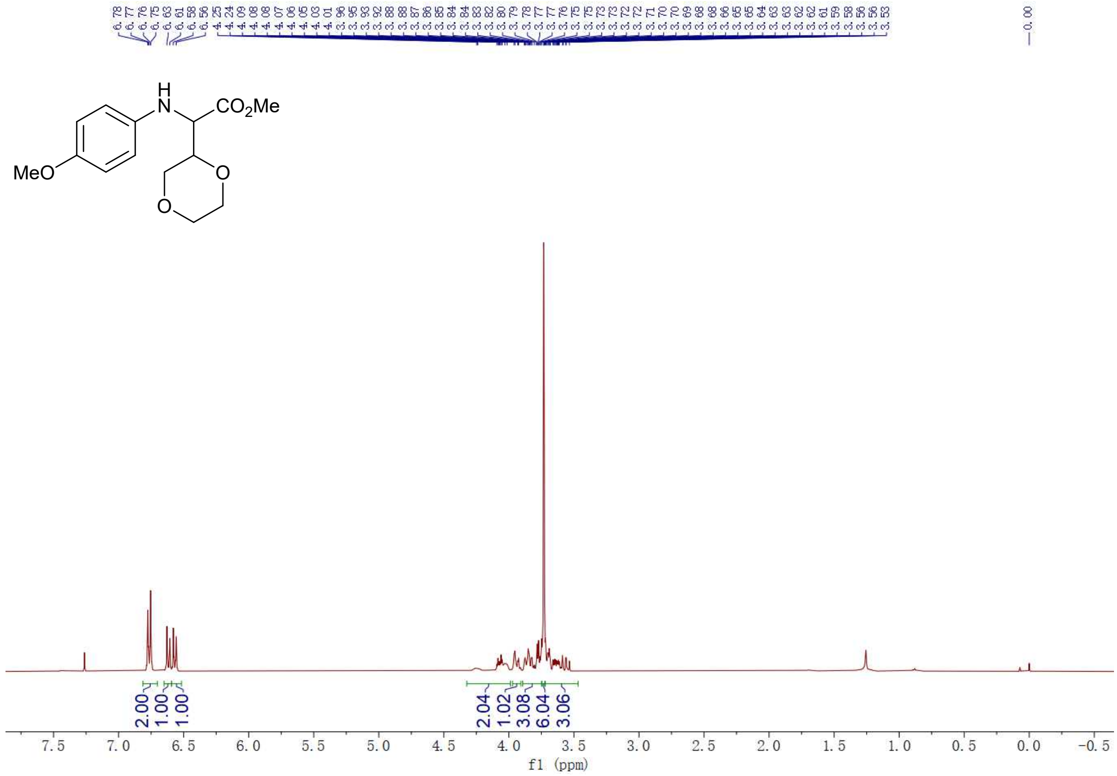
9. NMR spectra of products



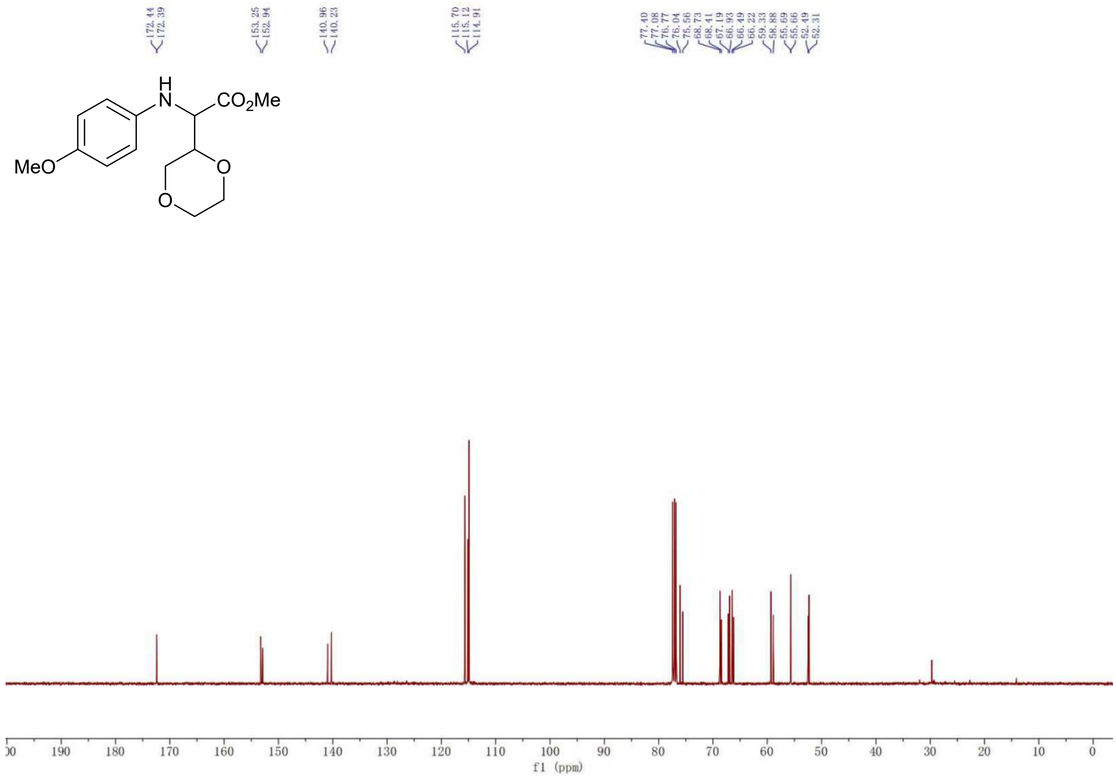
^{1}H NMR of **3aa** (400 MHz, $CDCl_3$)



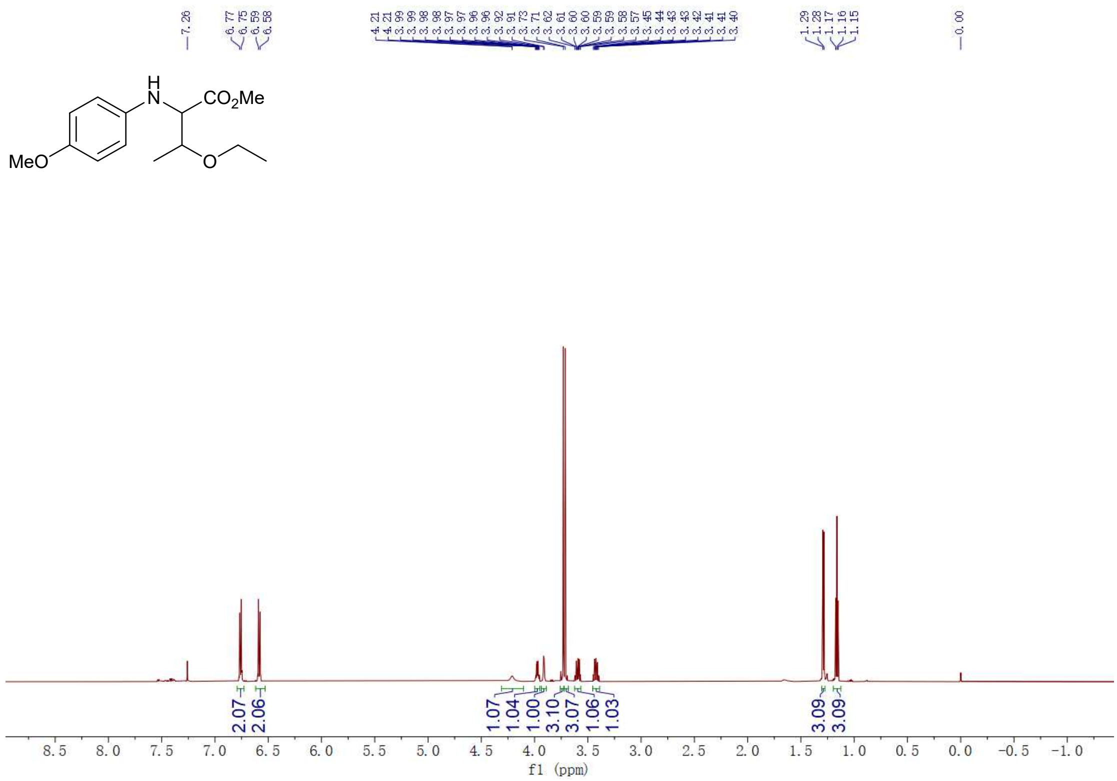
^{13}C NMR of **3aa** (101 MHz, $CDCl_3$)



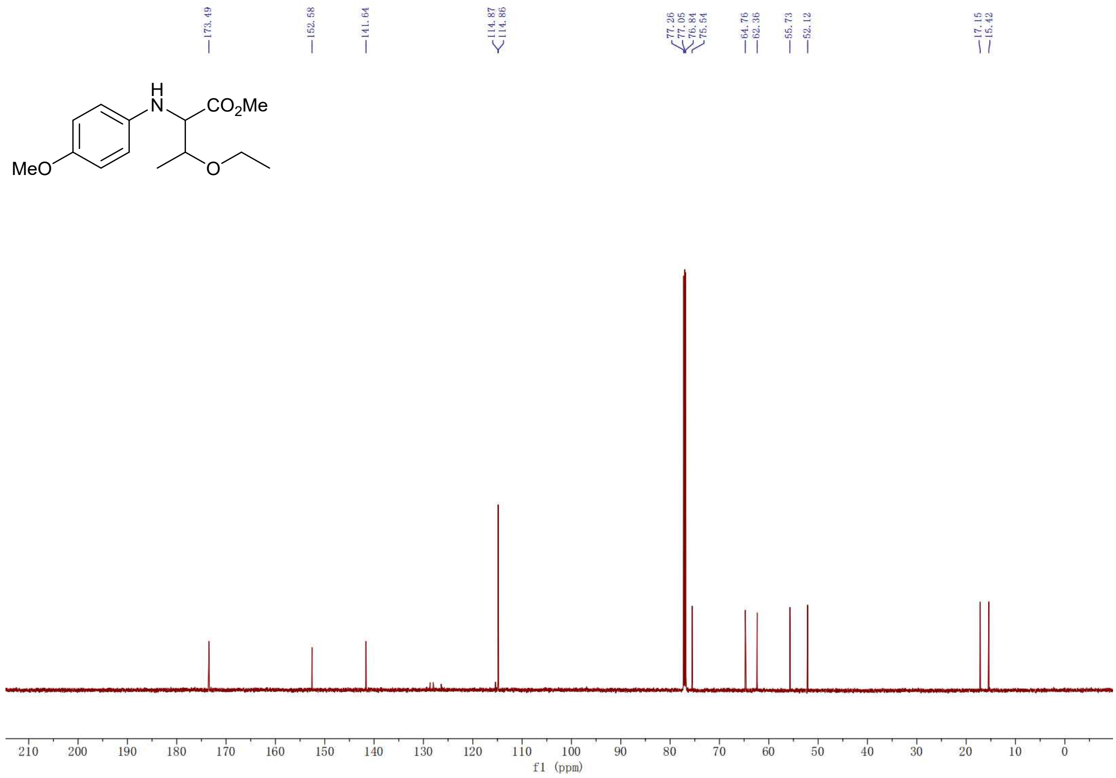
^{1}H NMR of **3ab** (400 MHz, $CDCl_3$)



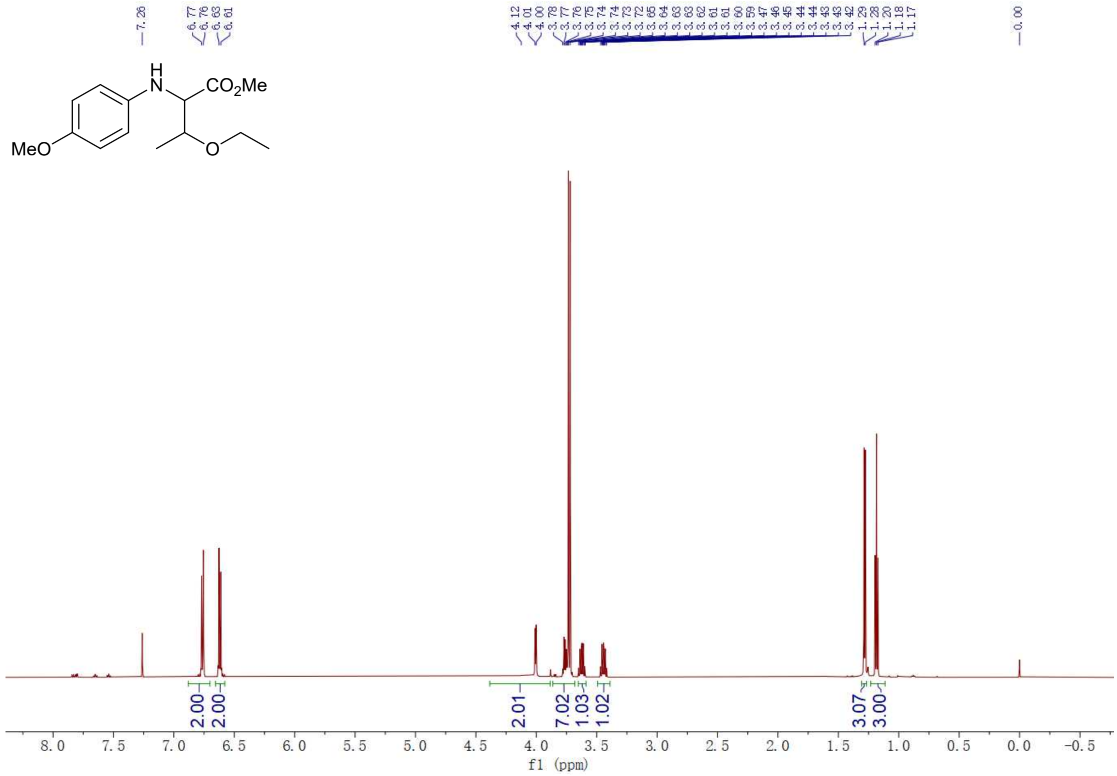
^{13}C NMR of **3ab** (101 MHz, $CDCl_3$)



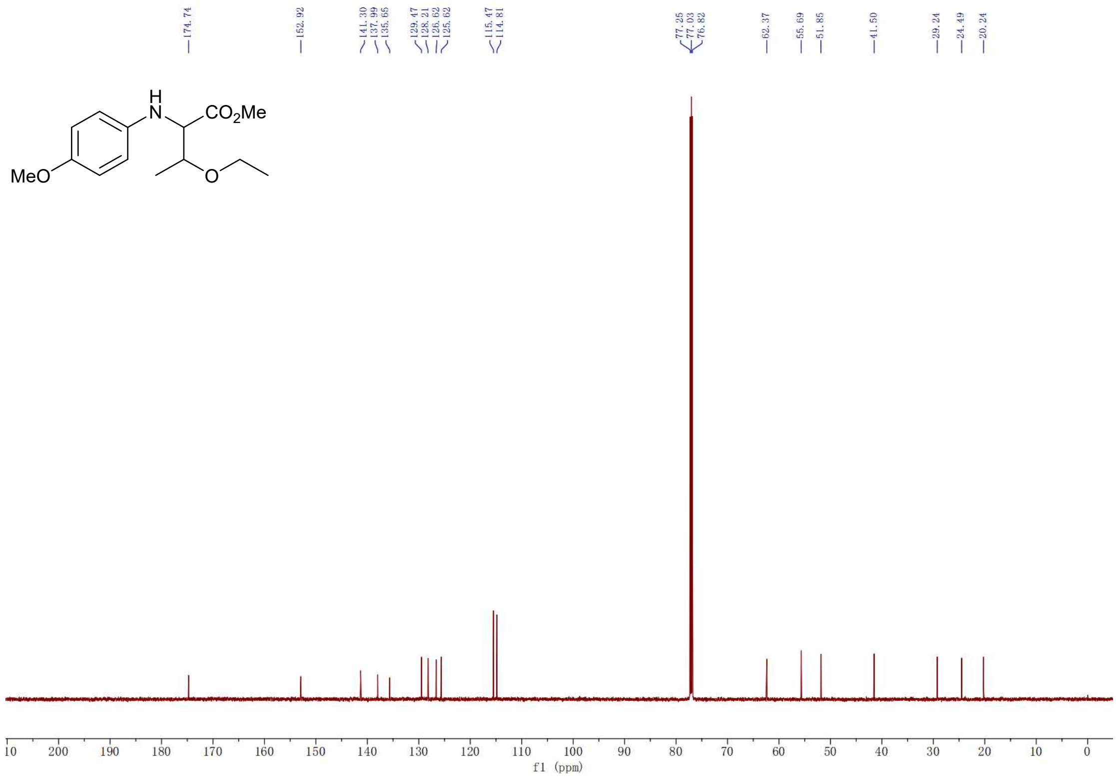
^{1}**H NMR** of **3ac-1** (600 MHz, $CDCl_3$)



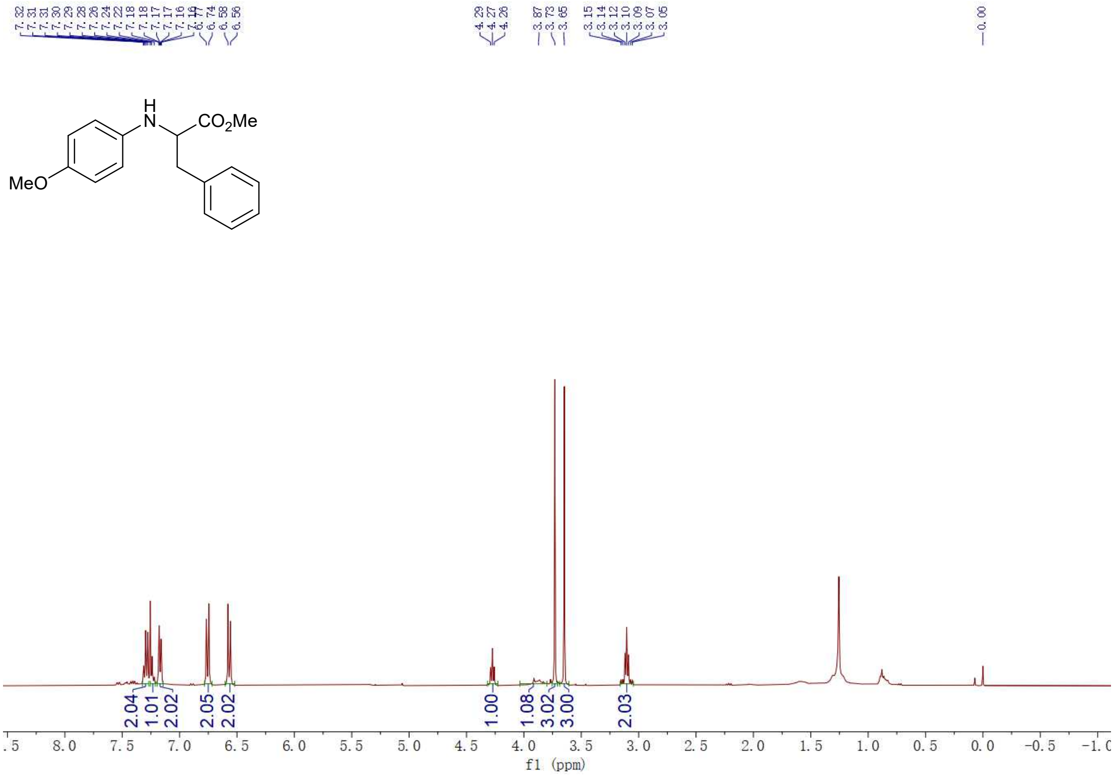
^{13}**C NMR** of **3ac-1** (151 MHz, $CDCl_3$)



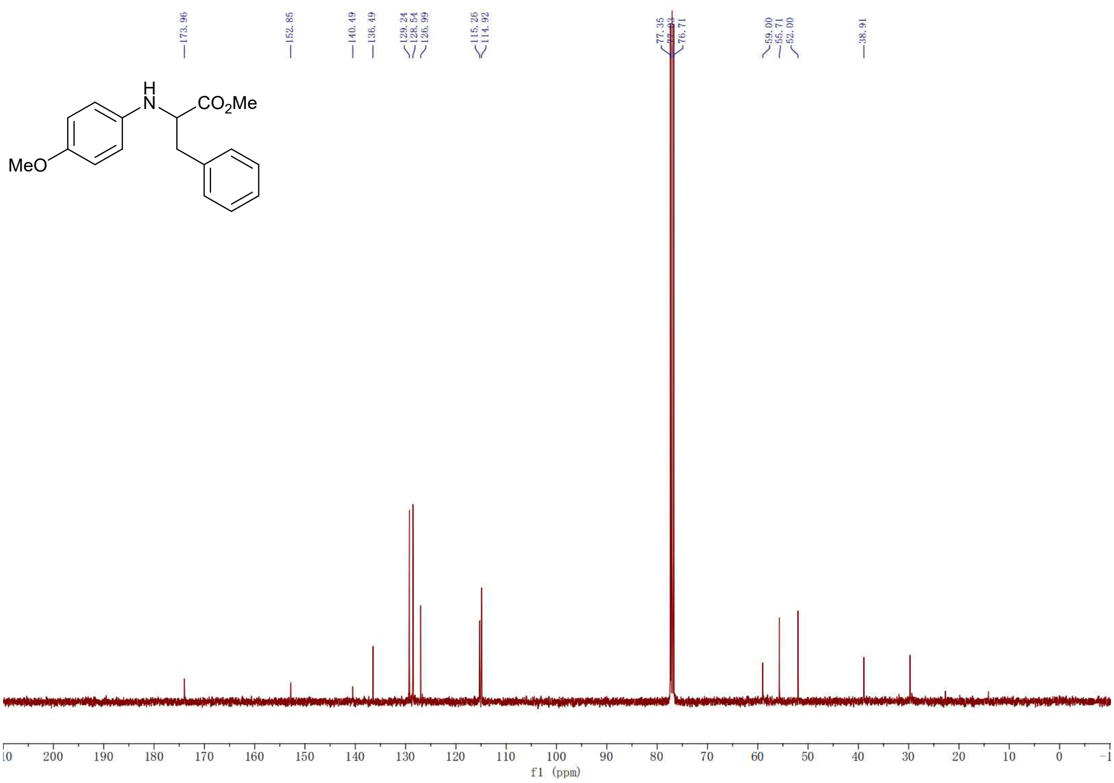
¹H NMR of **3ac-2** (600 MHz, $CDCl_3$)



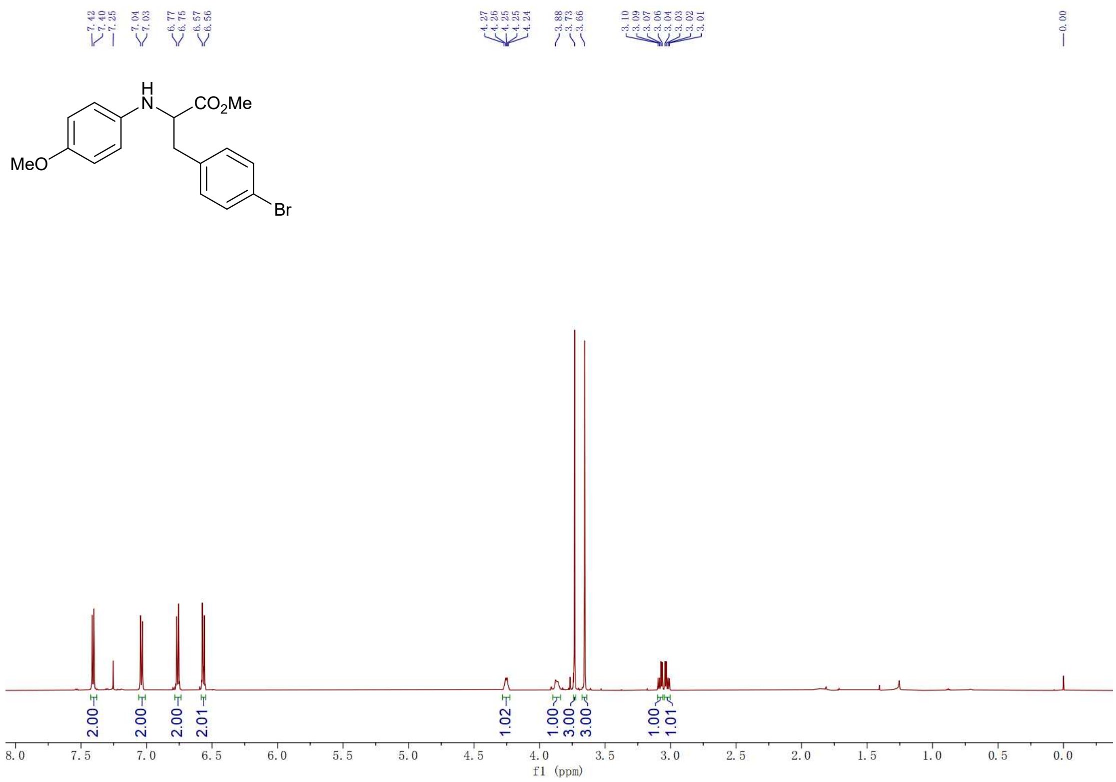
¹³C NMR of **3ac-2** (151 MHz, $CDCl_3$)



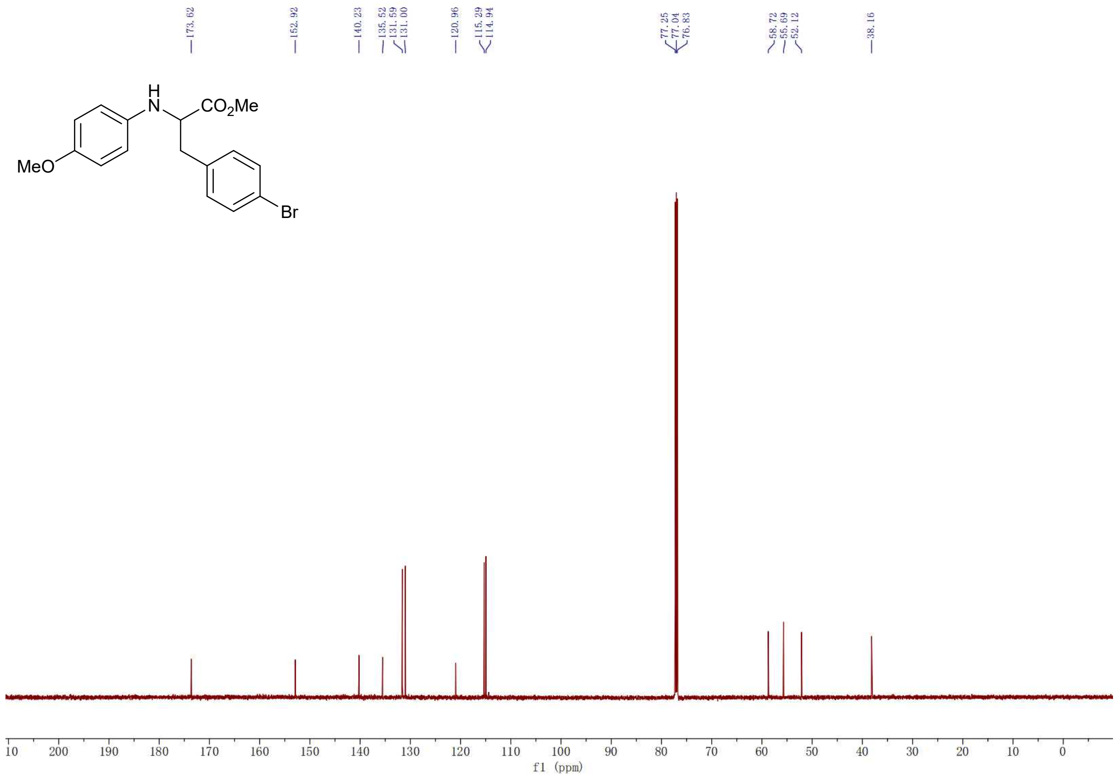
¹H NMR of **3ad** (400 MHz, $CDCl_3$)



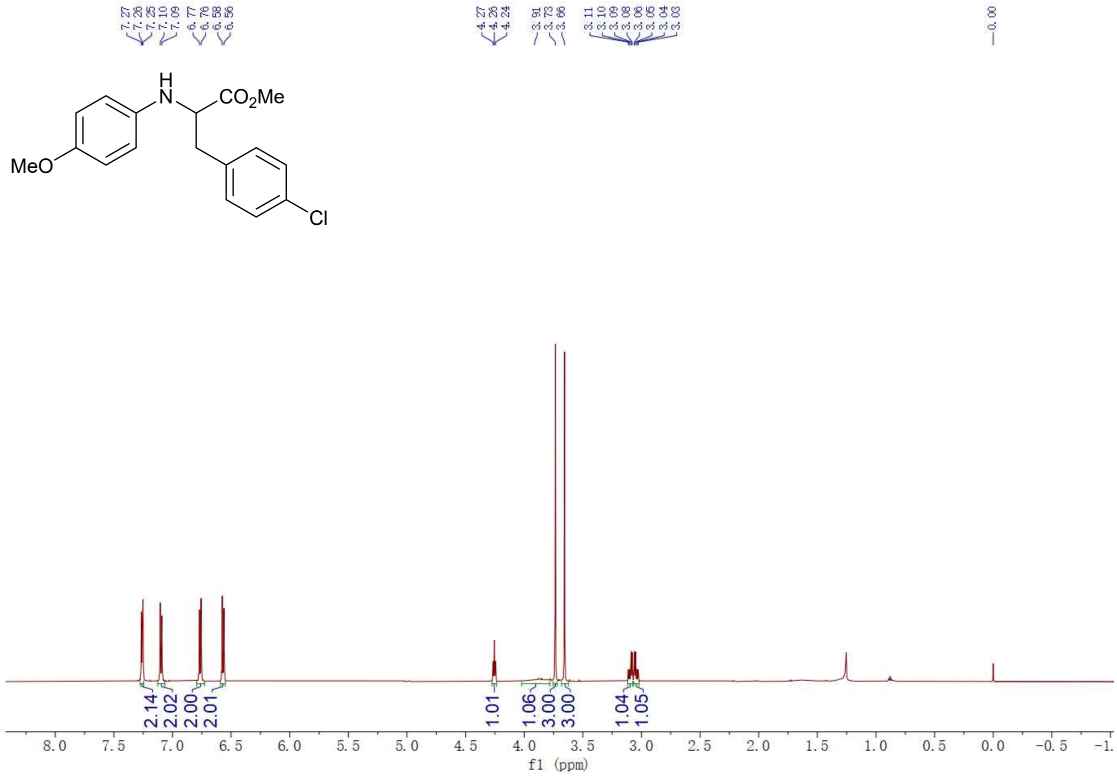
¹³C NMR of **3ad** (101 MHz, $CDCl_3$)



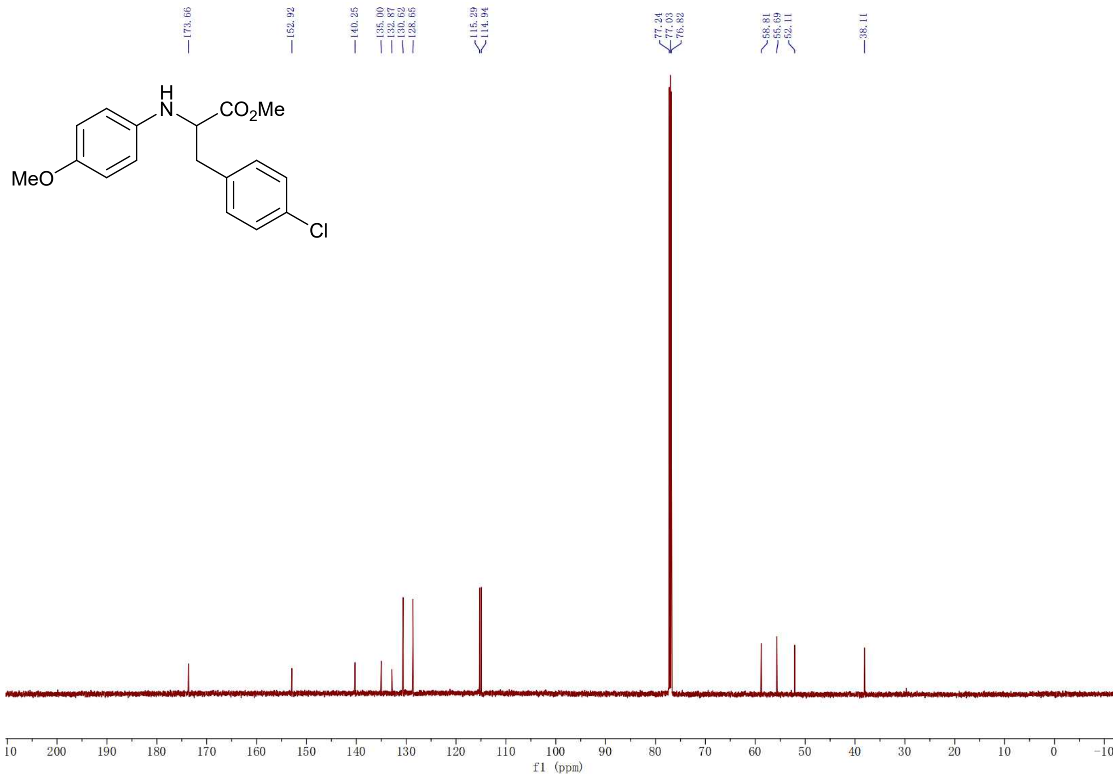
^{1}H NMR of **3ae** (600 MHz, $CDCl_3$)



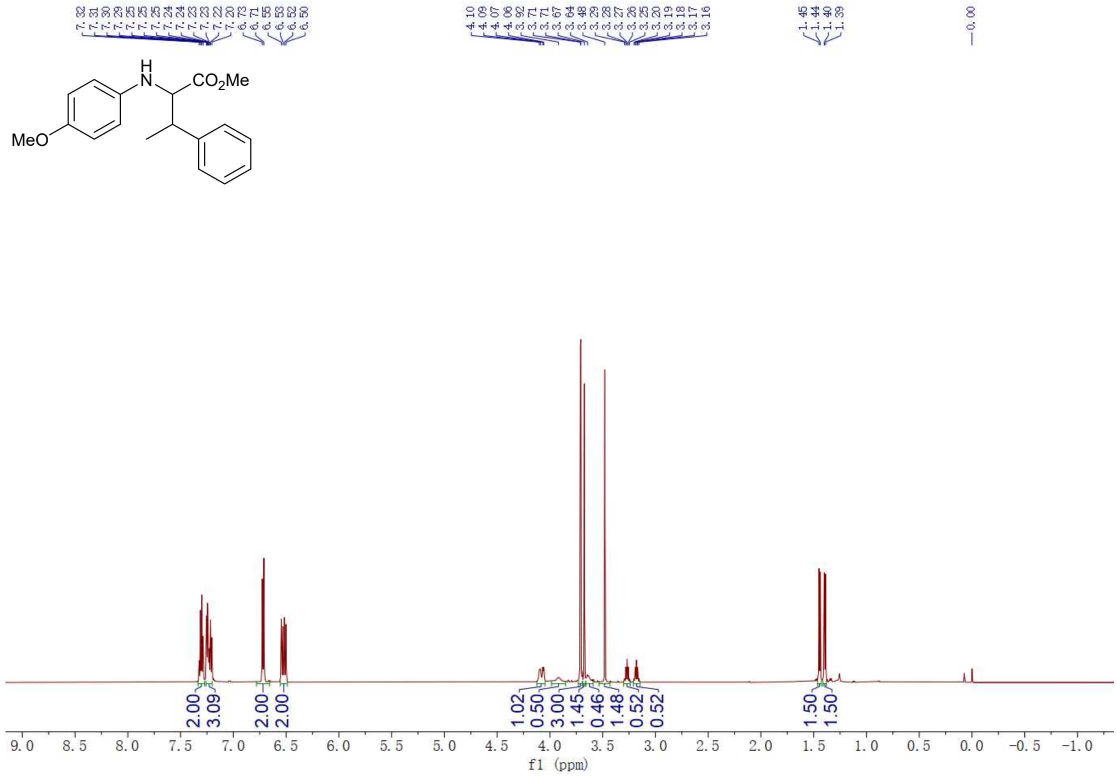
^{13}C NMR of **3ae** (151 MHz, $CDCl_3$)



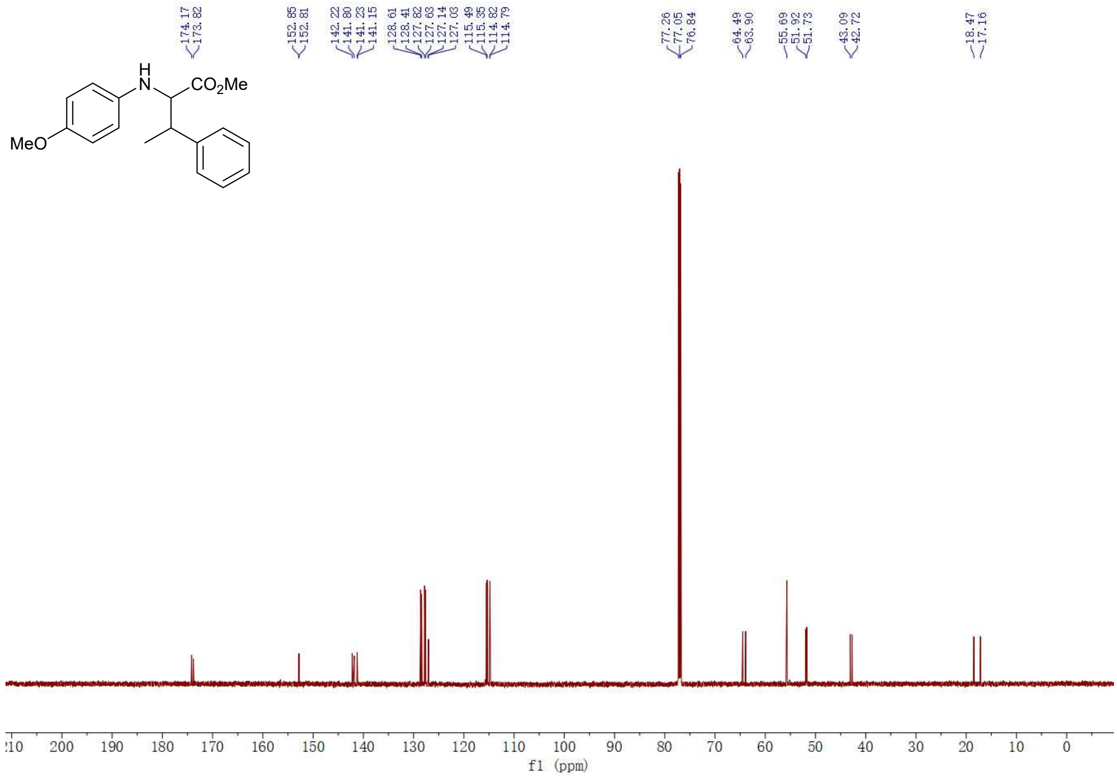
¹H NMR of **3af** (600 MHz, $CDCl_3$)



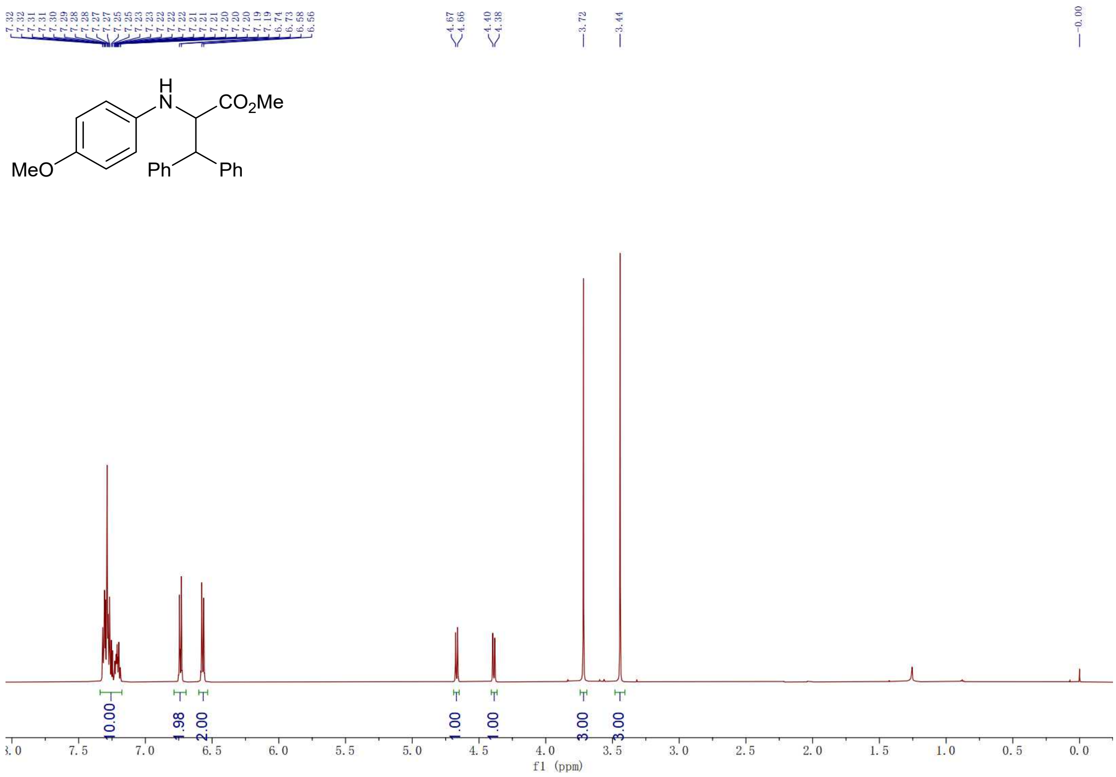
¹³C NMR of **3af** (151 MHz, $CDCl_3$)



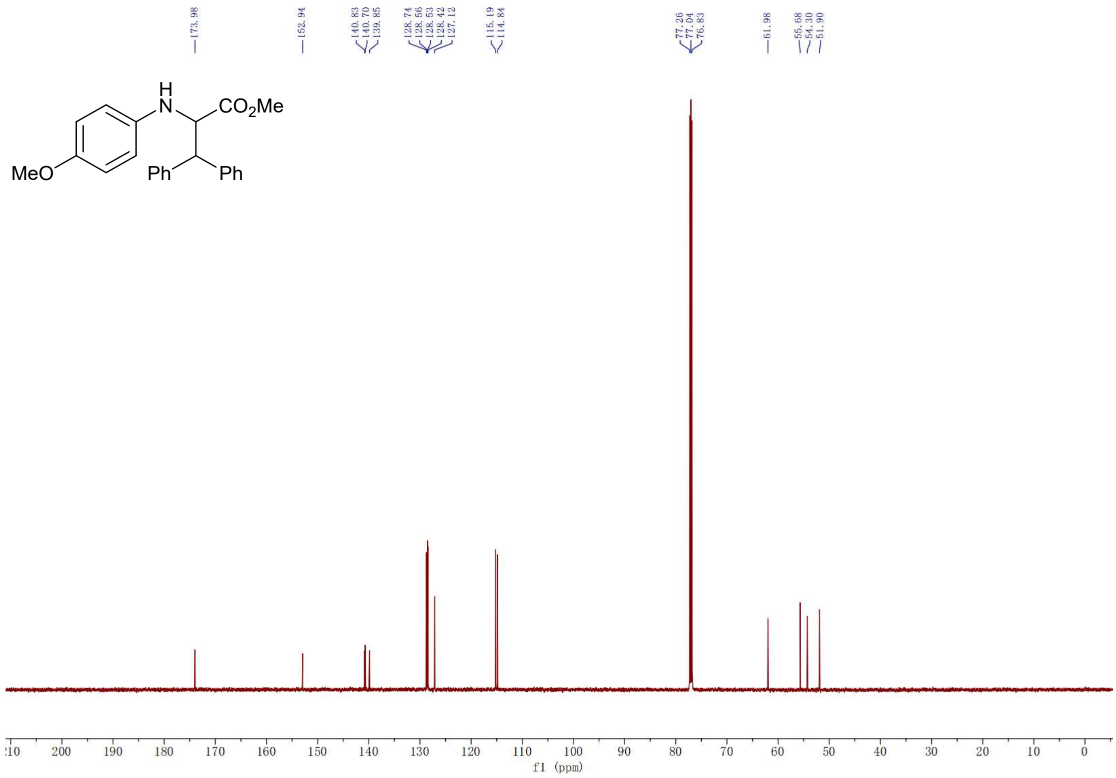
¹H NMR of **3ag** (600 MHz, $CDCl_3$)



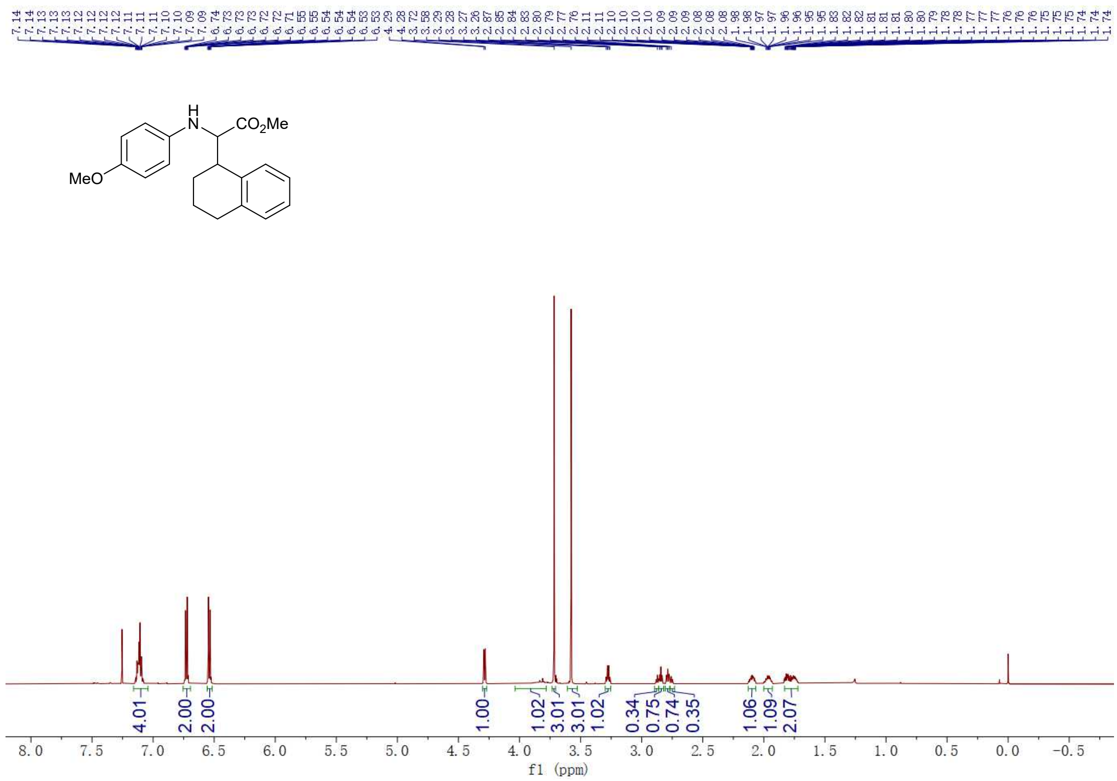
¹³C NMR of **3ag** (151 MHz, $CDCl_3$)



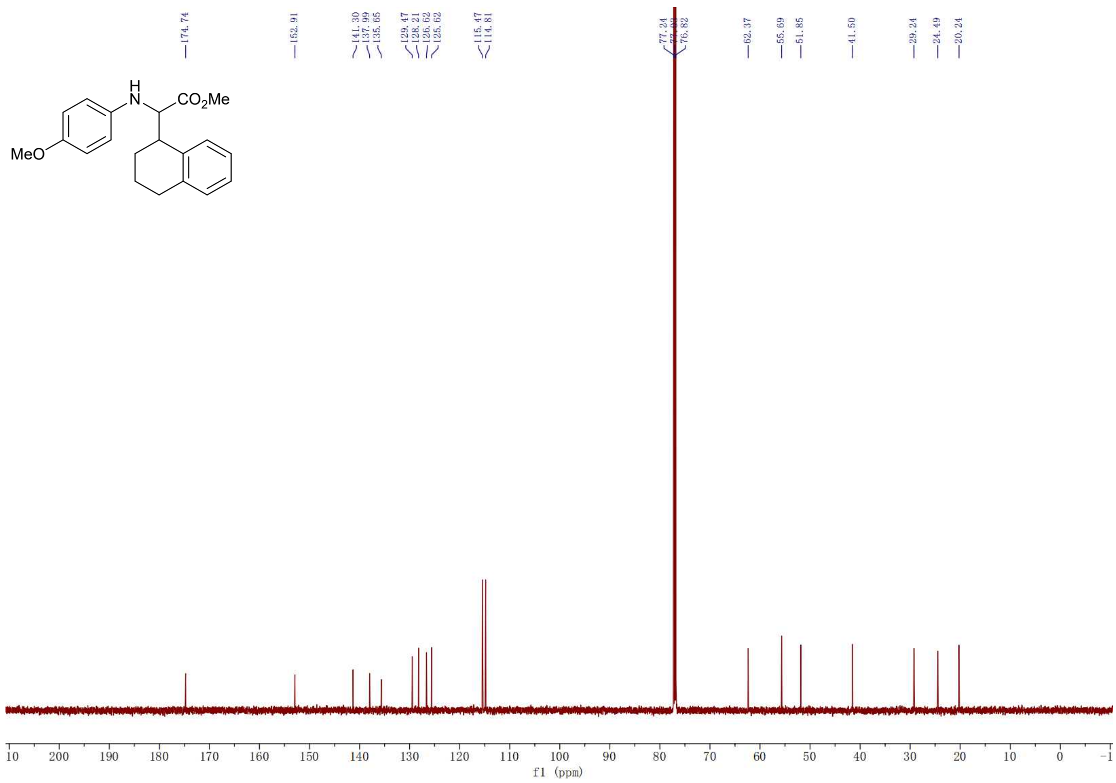
^{1}H NMR of **3ah** (600 MHz, $CDCl_3$)



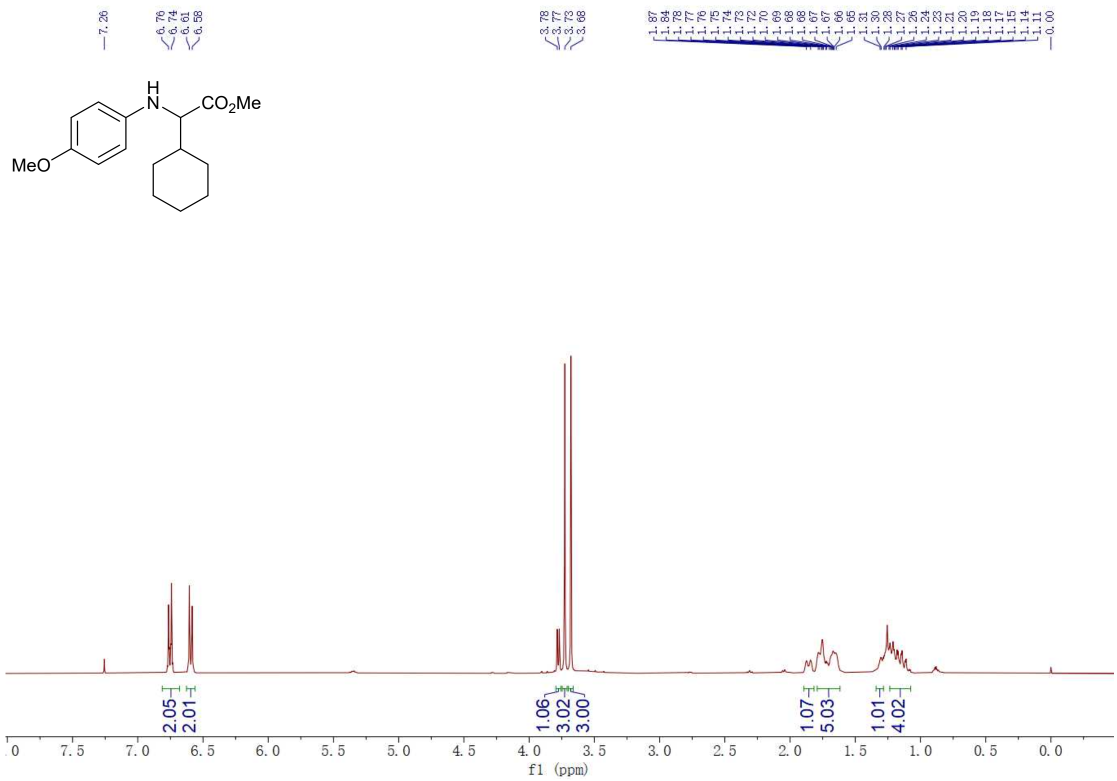
^{13}C NMR of **3ah** (151 MHz, $CDCl_3$)



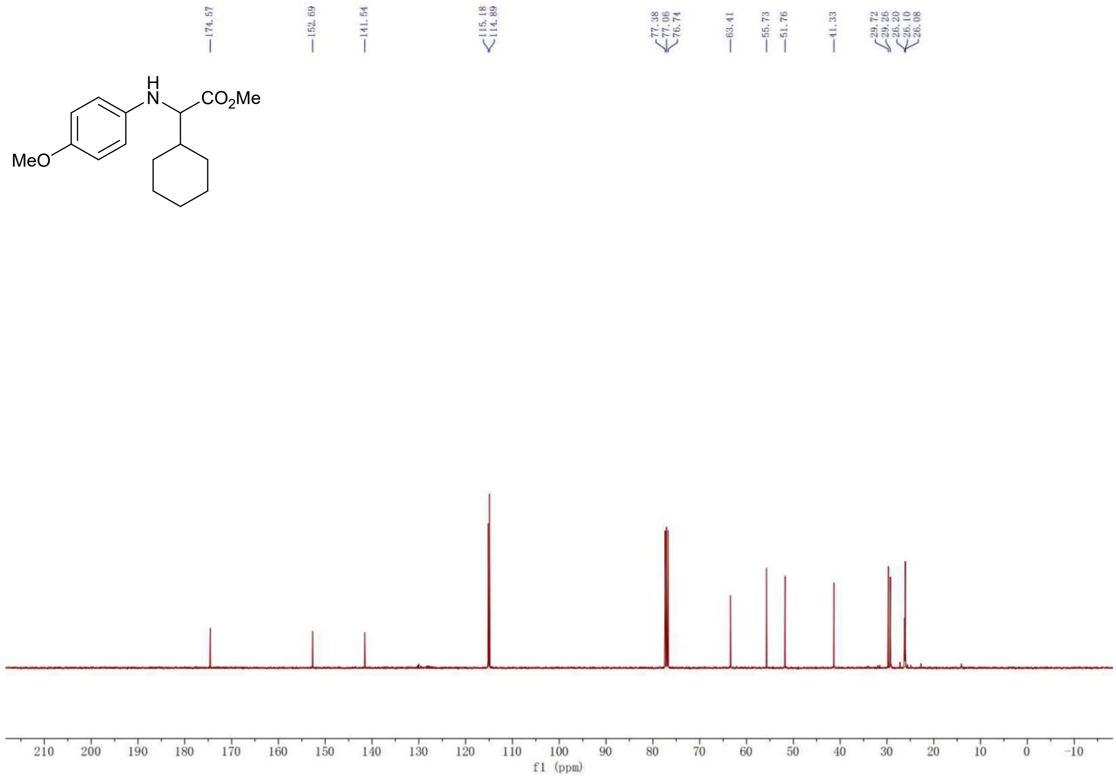
^{1}H NMR of **3ai** (600 MHz, $CDCl_3$)



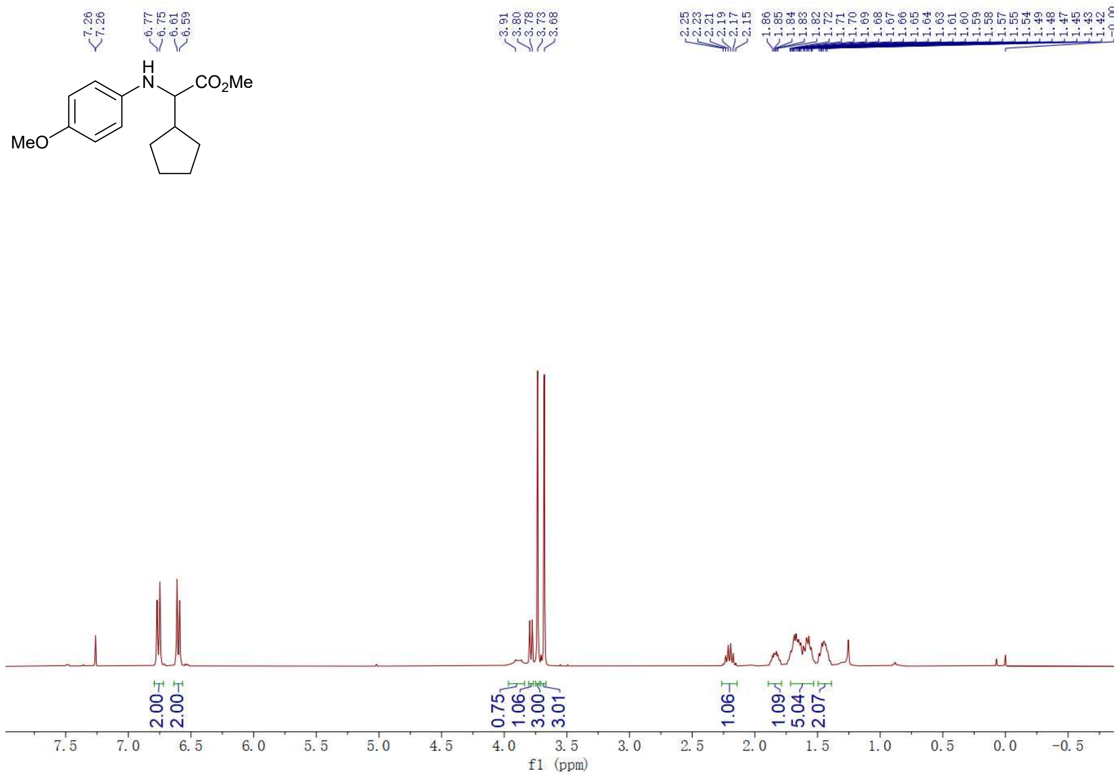
^{13}C NMR of **3ai** (151 MHz, $CDCl_3$)



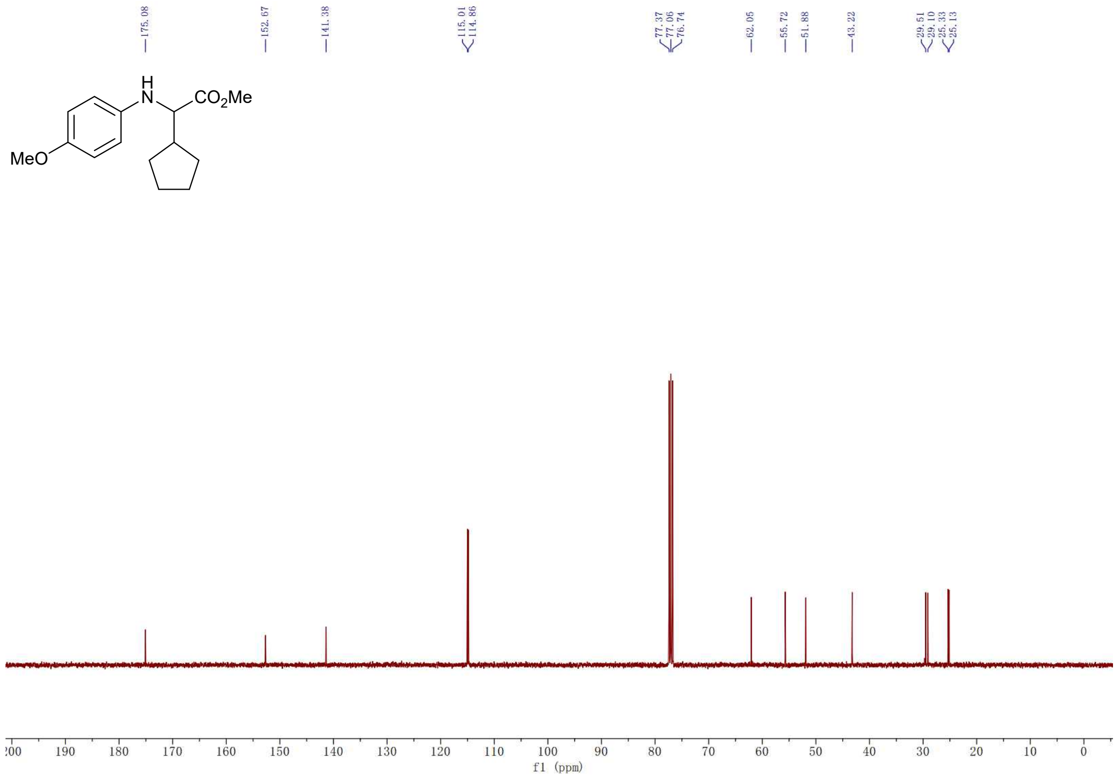
^{1}H NMR of **5aa** (400 MHz, $CDCl_3$)



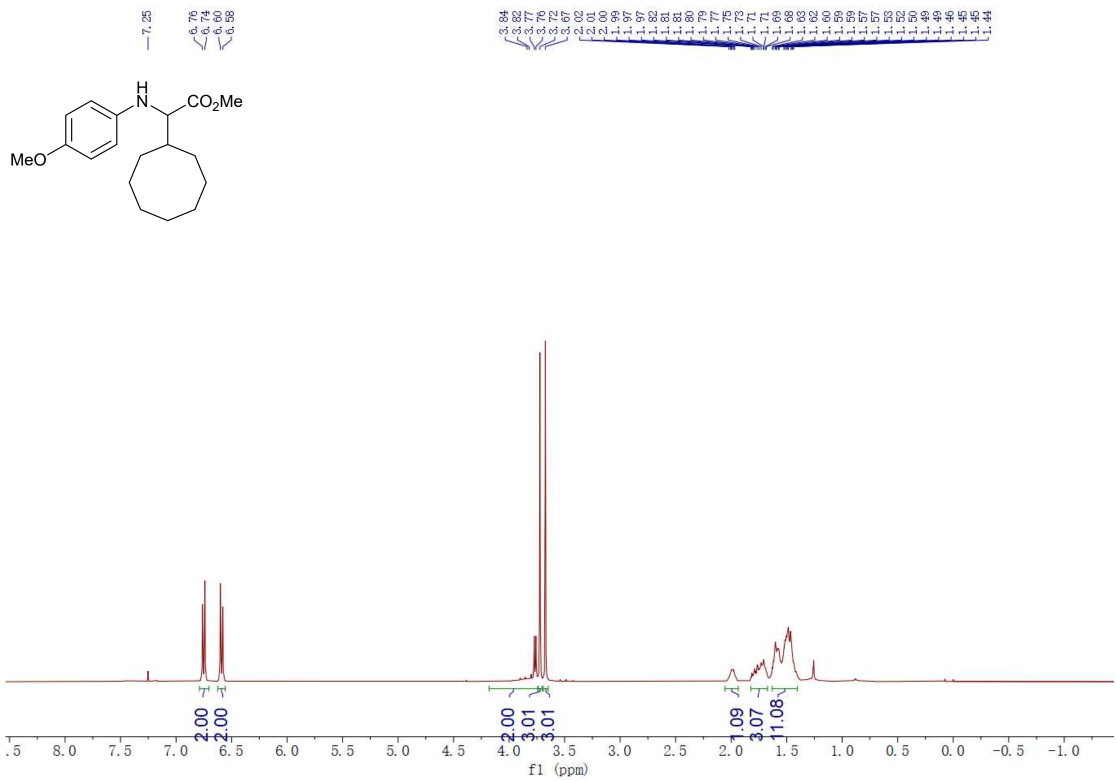
^{13}C NMR of **5aa** (101 MHz, $CDCl_3$)



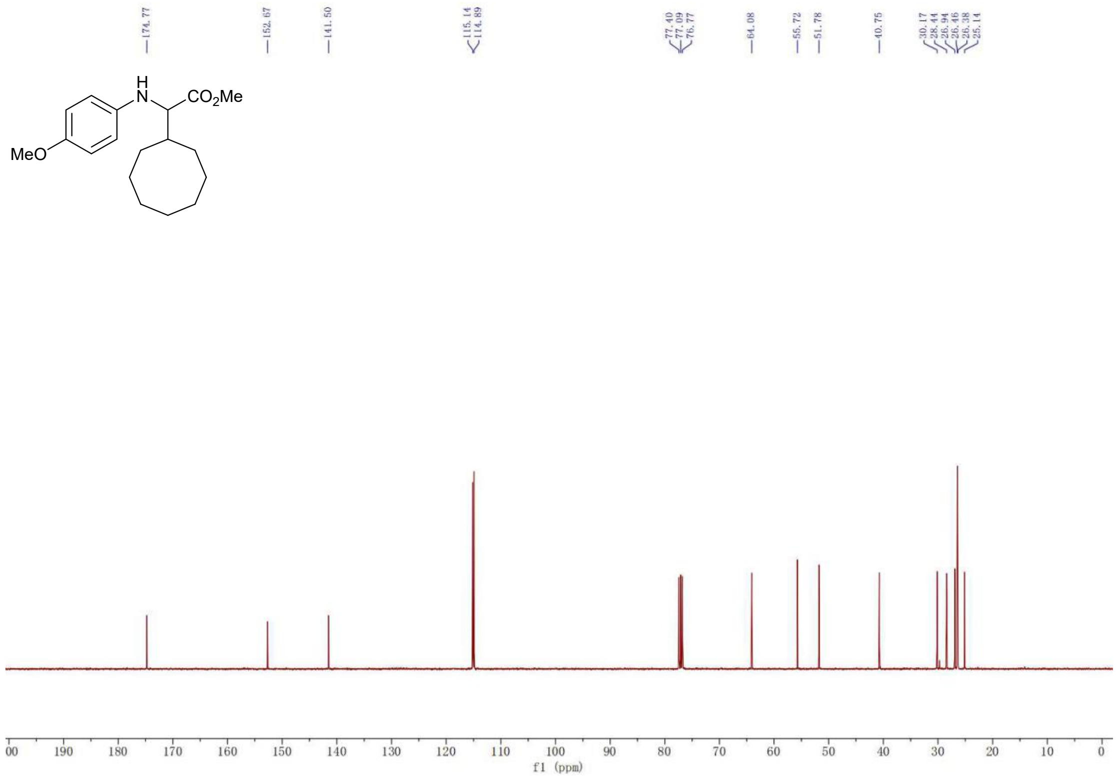
^{1}**H NMR** of **3aj** (400 MHz, $CDCl_3$)



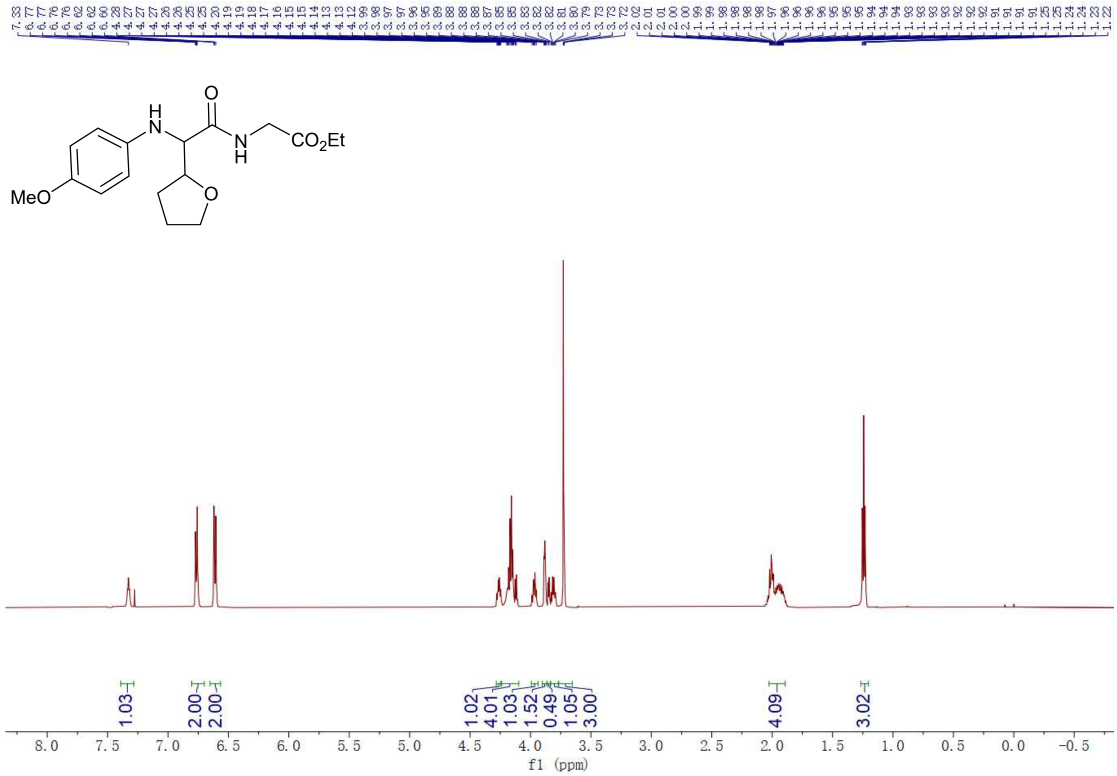
^{13}**C NMR** of **3aj** (101 MHz, $CDCl_3$)



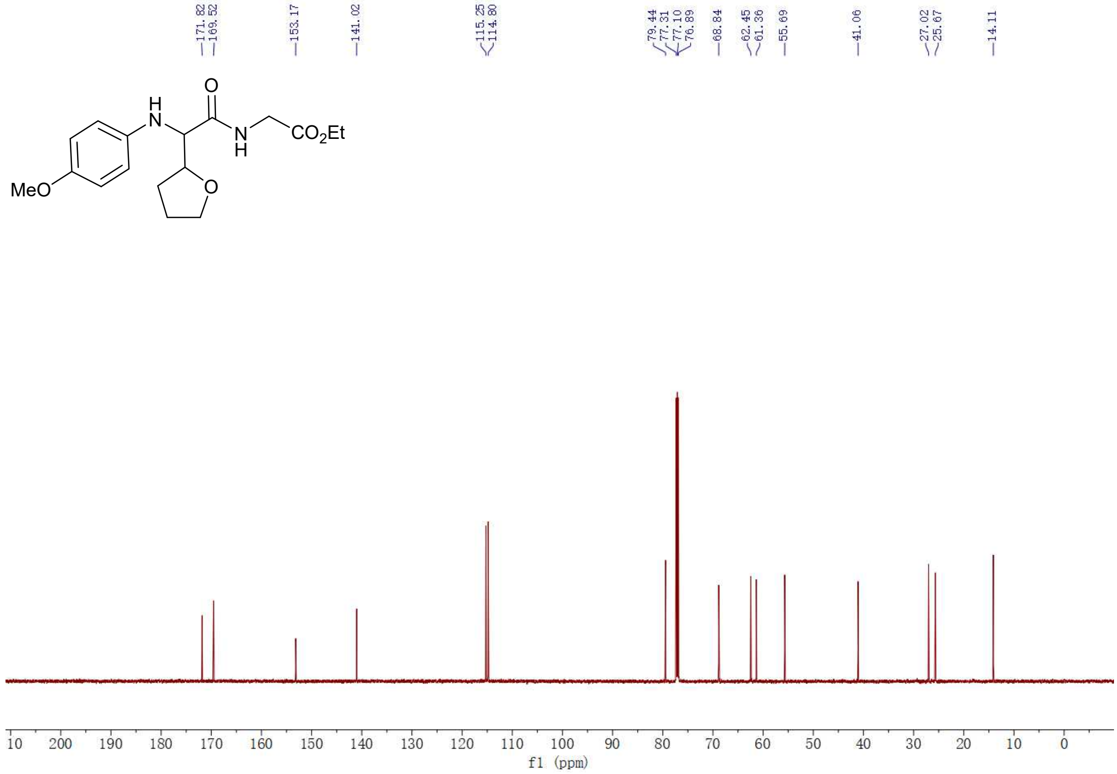
^{1}**H NMR** of **3ak** (400 MHz, $CDCl_3$)



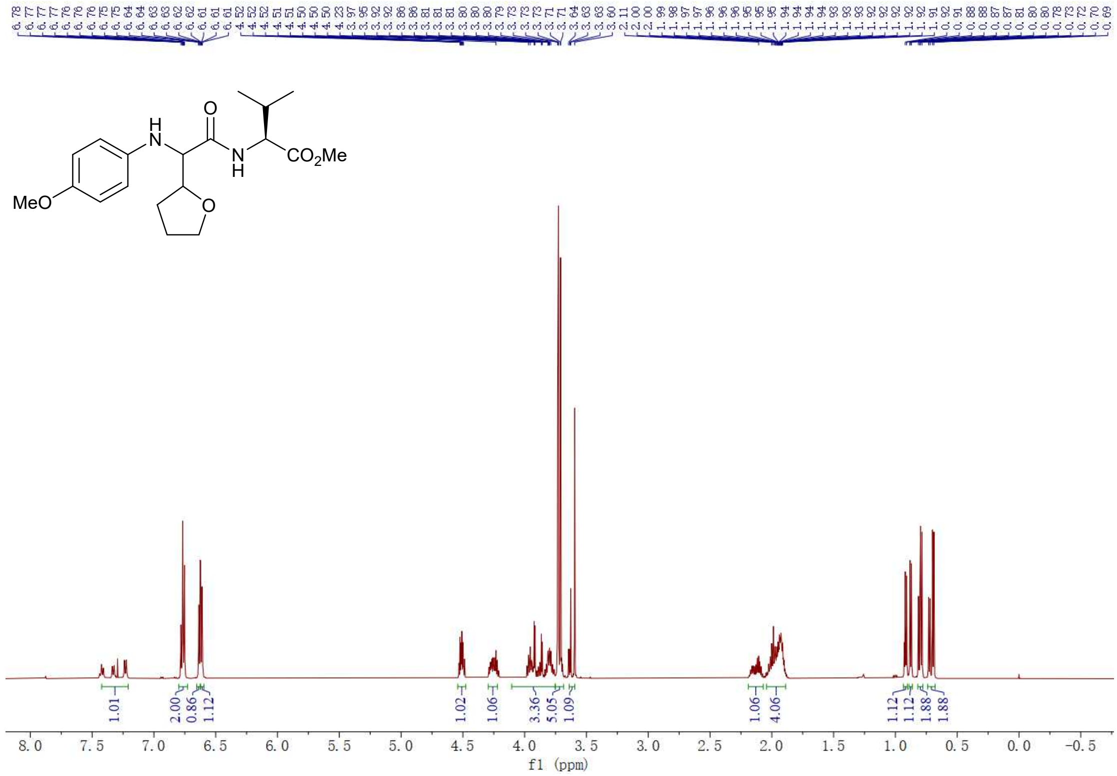
^{13}**C NMR** of **3ak** (101 MHz, $CDCl_3$)



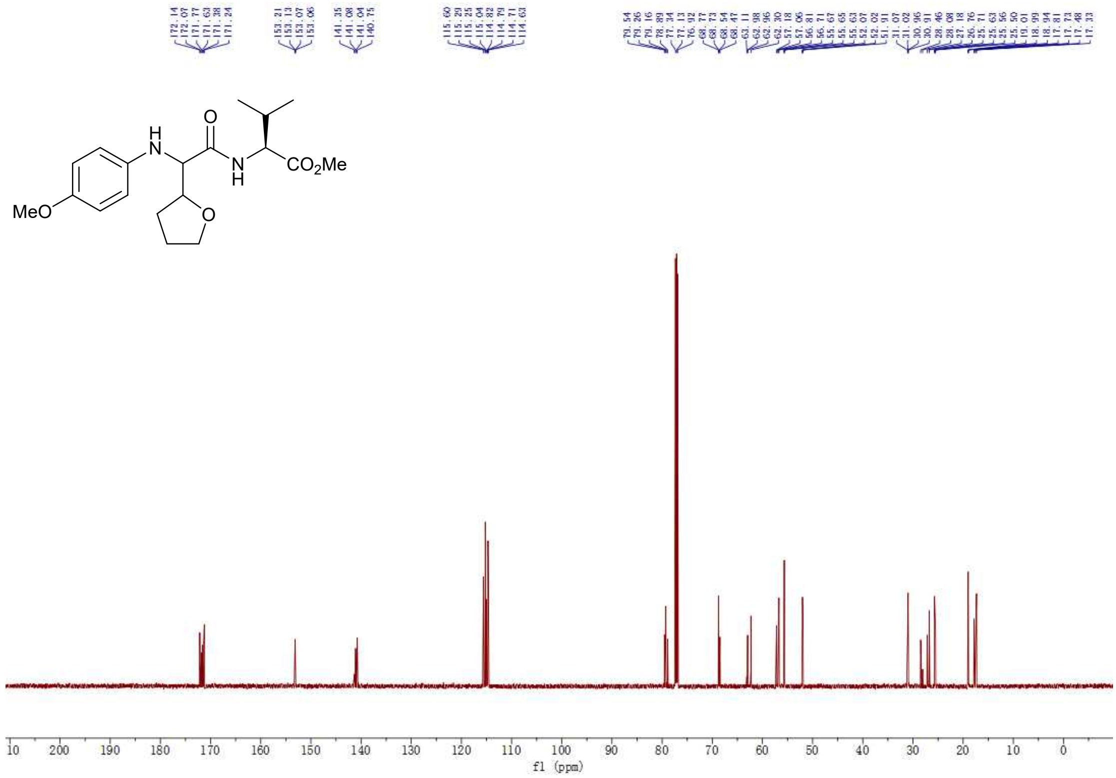
^{1}H NMR of **3ba** (600 MHz, CDCl3)



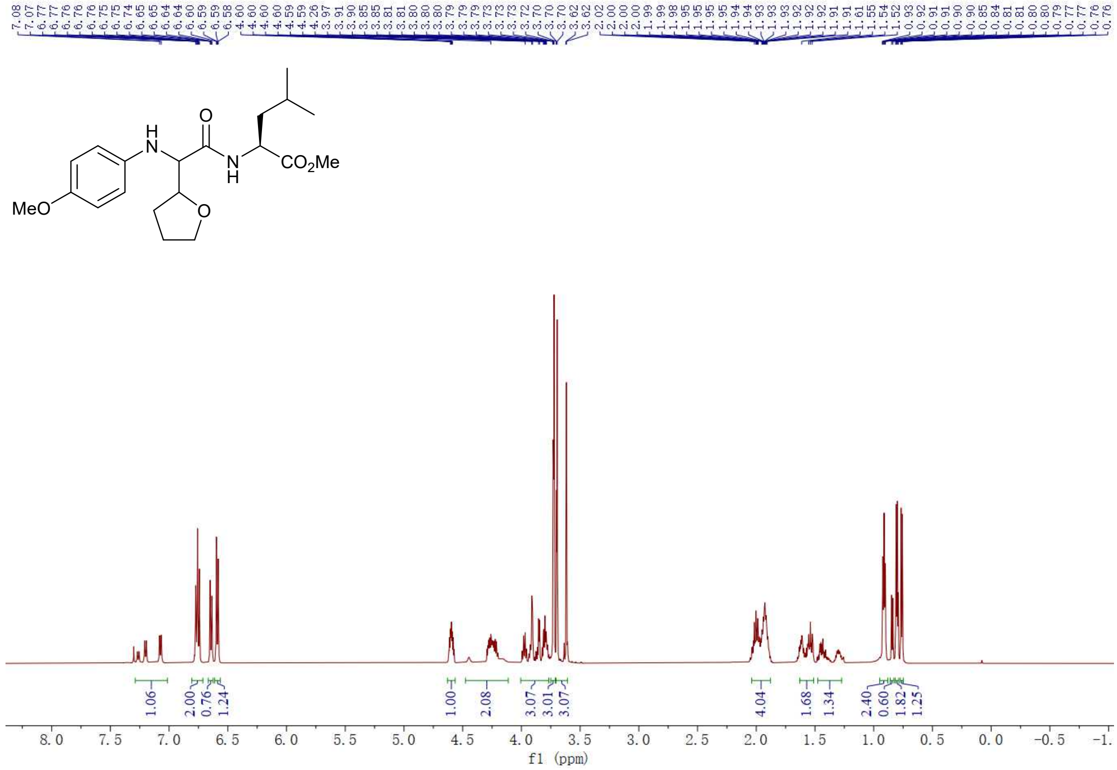
^{13}C NMR of **3ba** (151 MHz, $CDCl_3$)



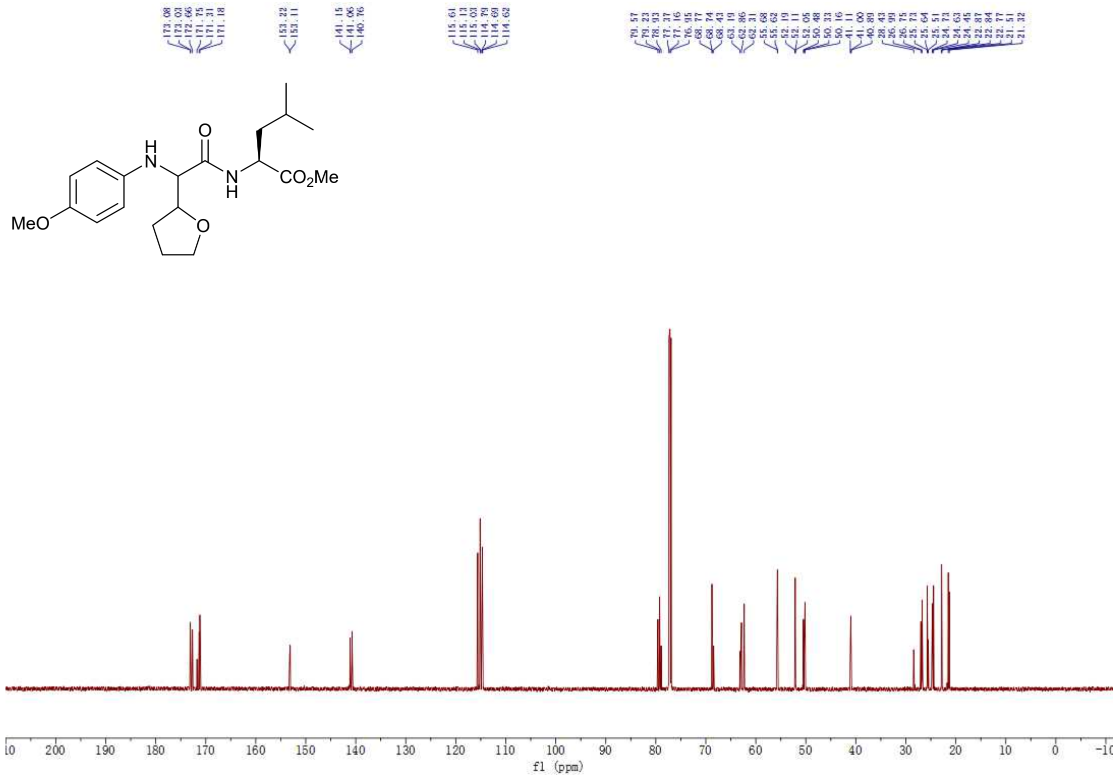
^{1}H NMR of **3ca** (600 MHz, $CDCl_3$)



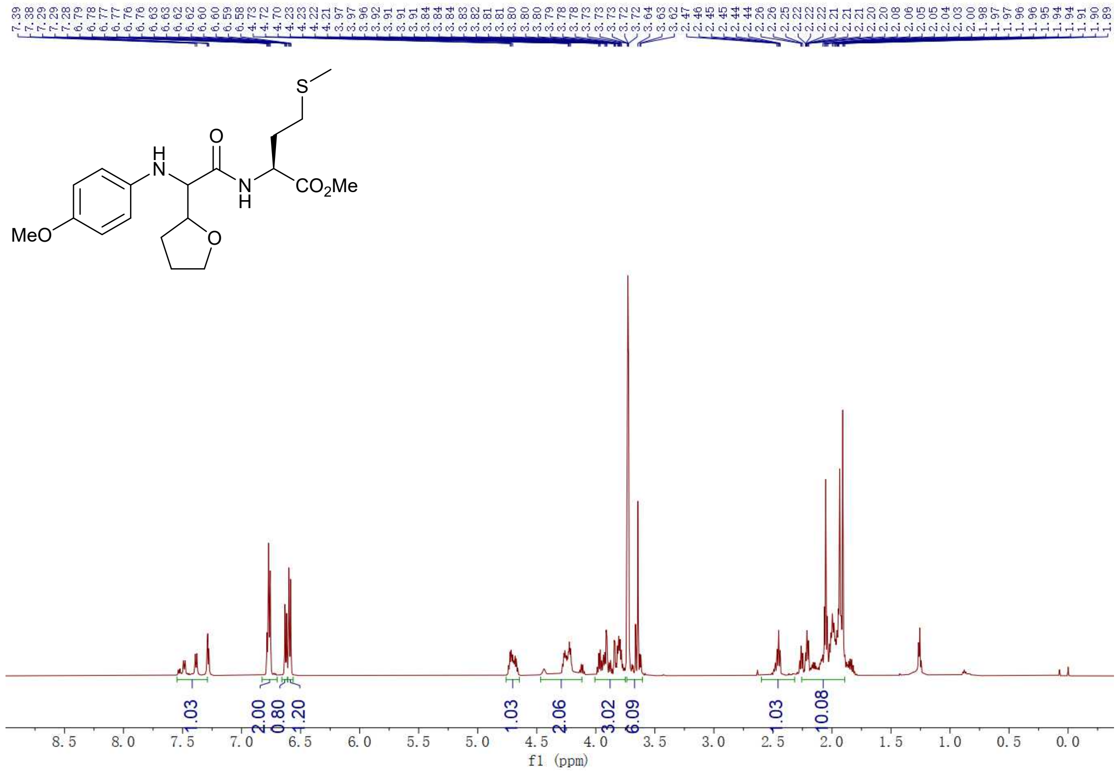
^{13}C NMR of **3ca** (151 MHz, $CDCl_3$)



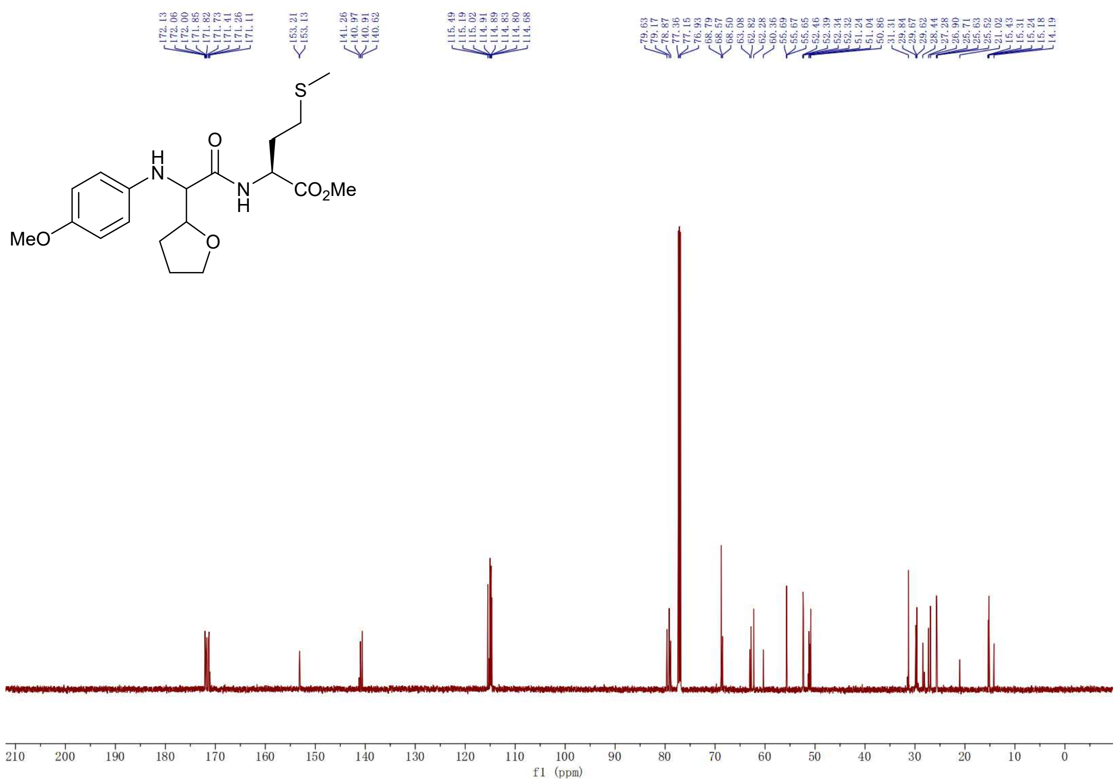
^{1}H NMR of **3da** (600 MHz, $CDCl_3$)



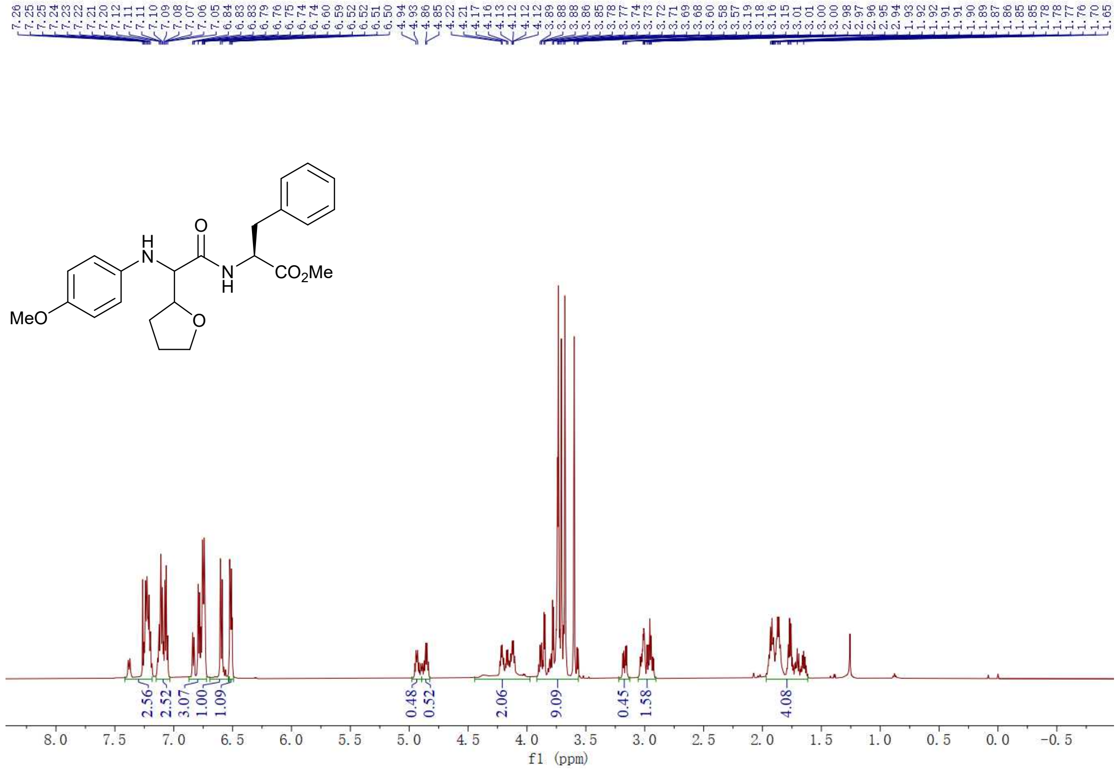
^{13}C NMR of **3da** (151 MHz, $CDCl_3$)



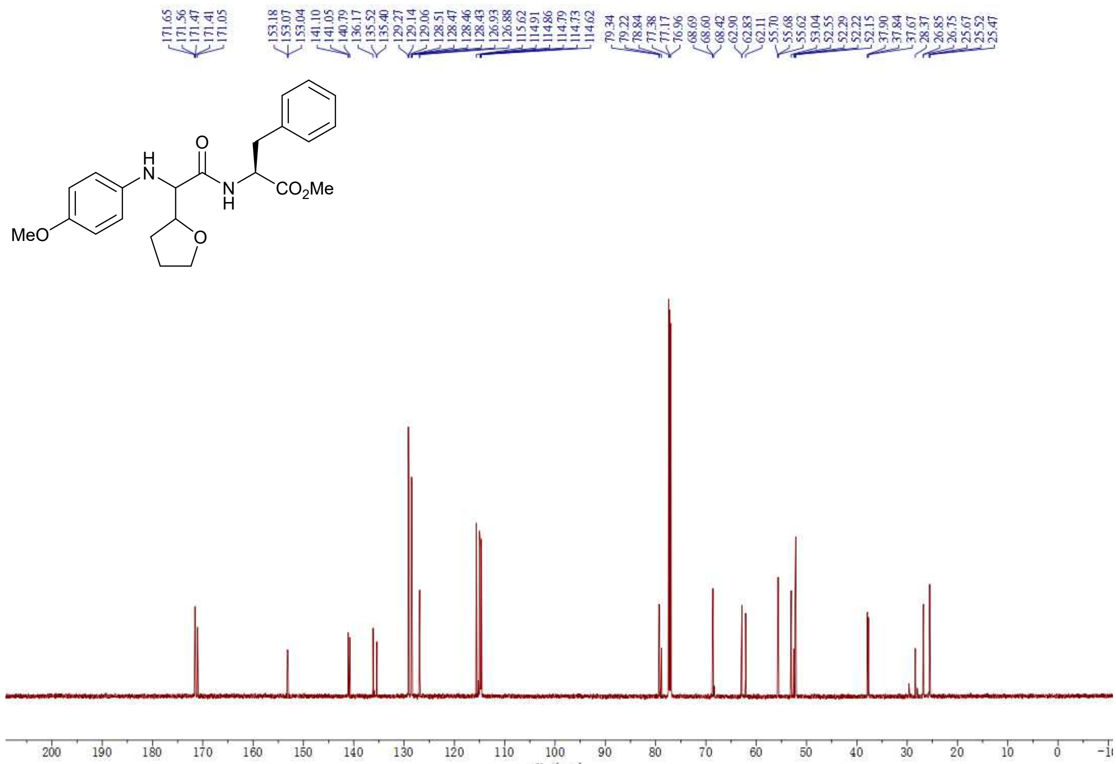
^{1}H NMR of **3ea** (600 MHz, $CDCl_3$)



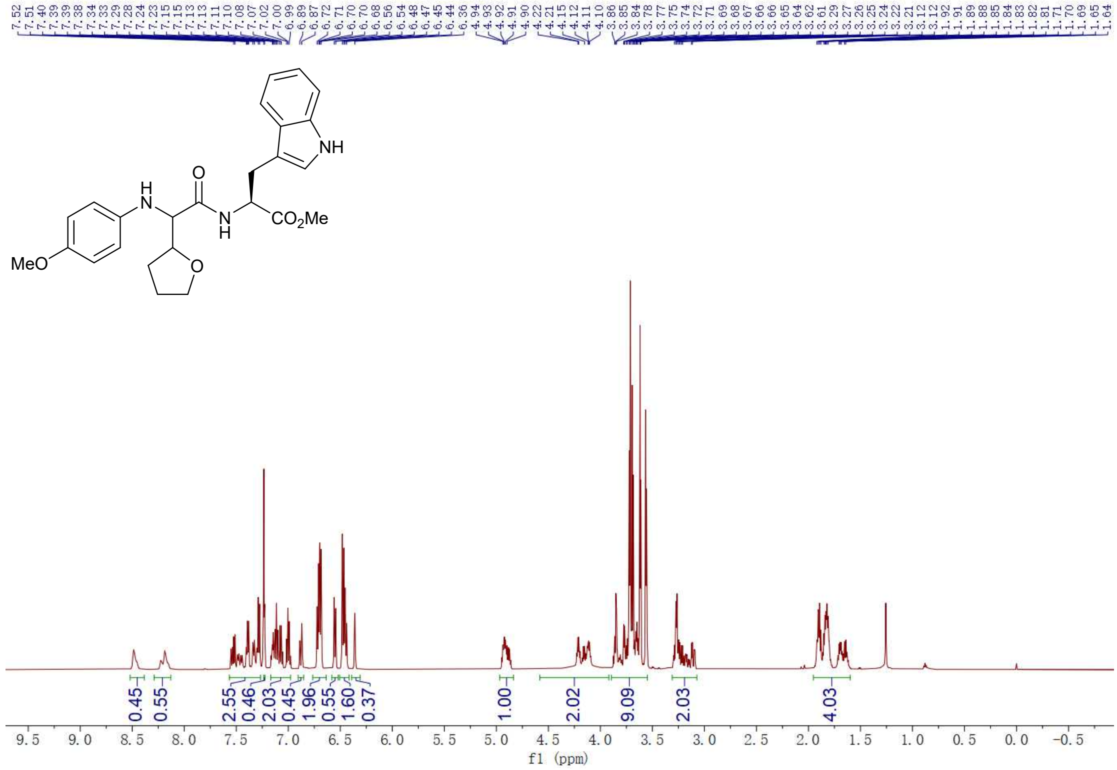
^{13}C NMR of **3ea** (151 MHz, $CDCl_3$)



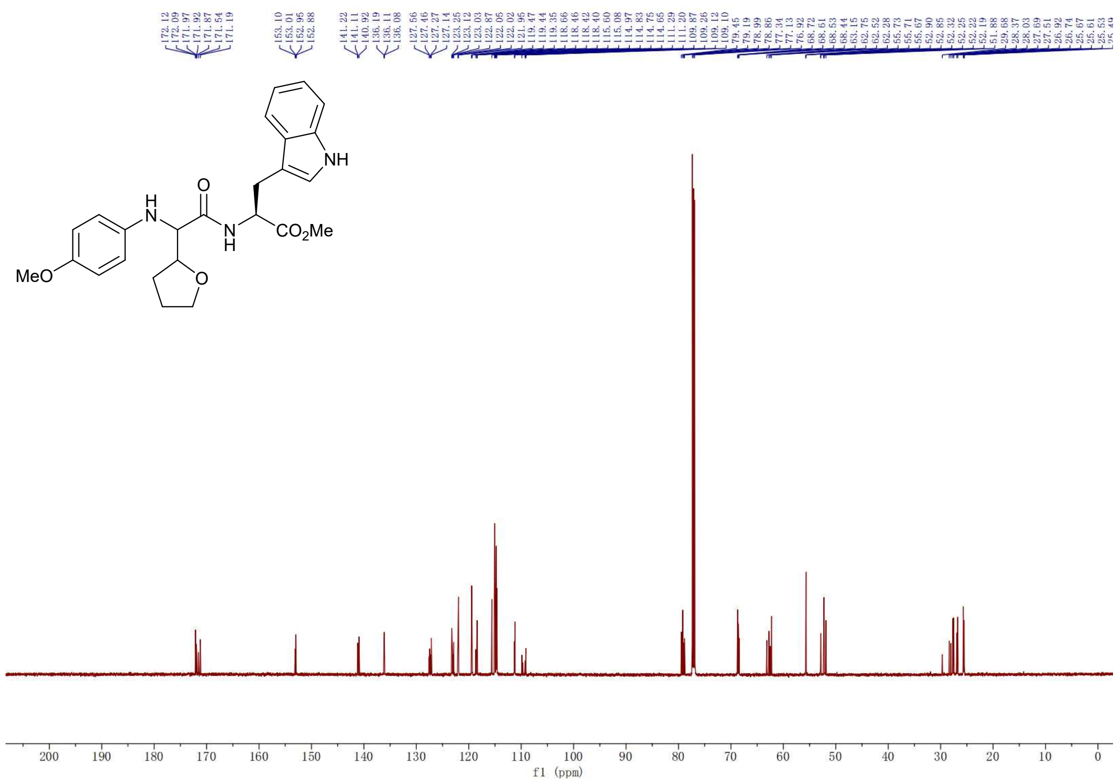
^{1}H NMR of **3fa** (600 MHz, $CDCl_3$)



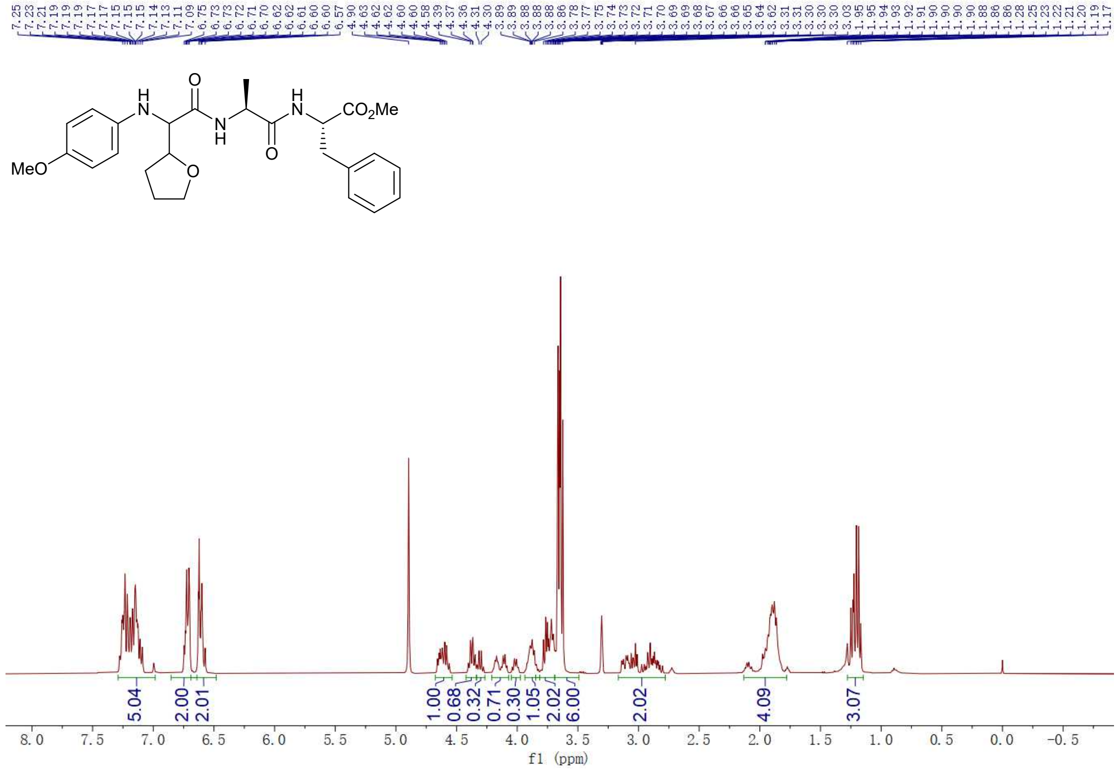
^{13}C NMR of **3fa** (151 MHz, $CDCl_3$)



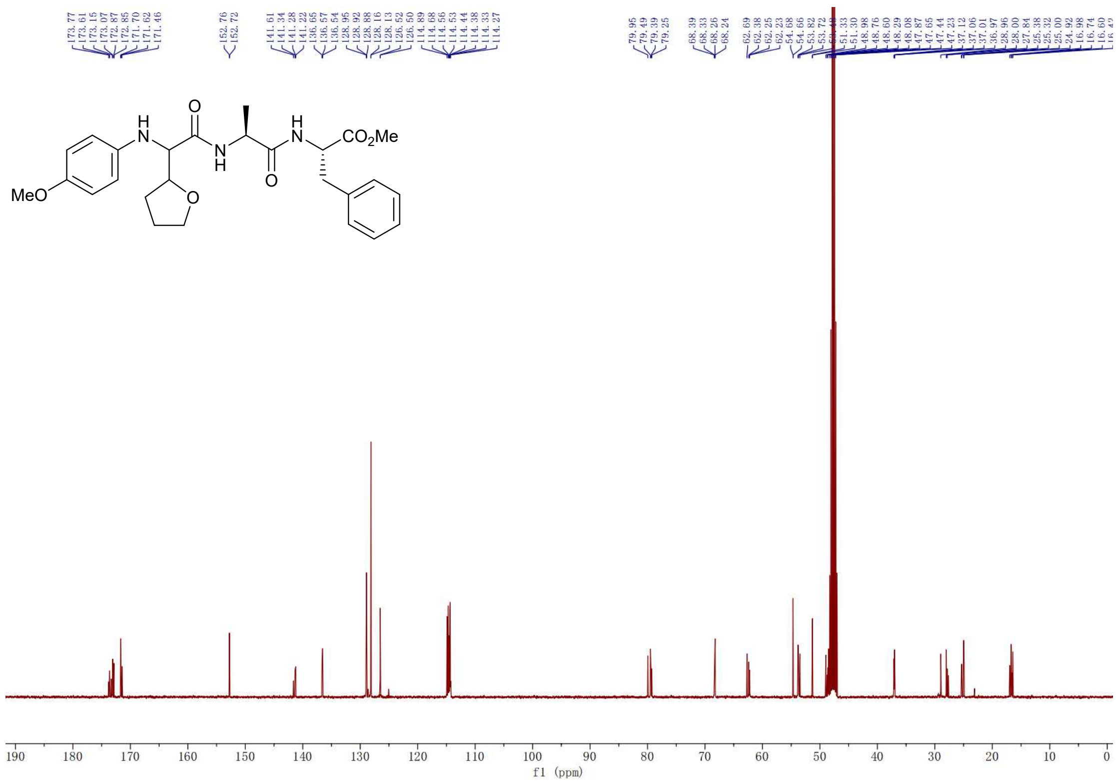
^{1}H NMR of **3ga** (600 MHz, $CDCl_3$)



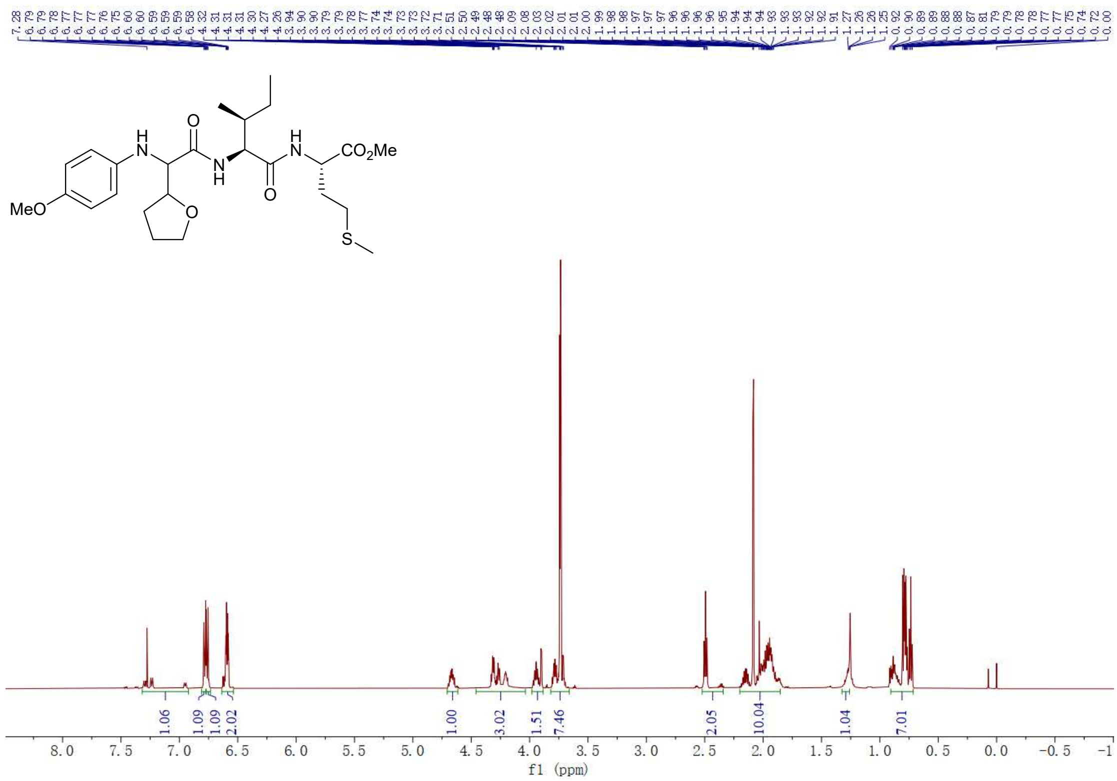
^{13}C NMR of **3ga** (151 MHz, $CDCl_3$)



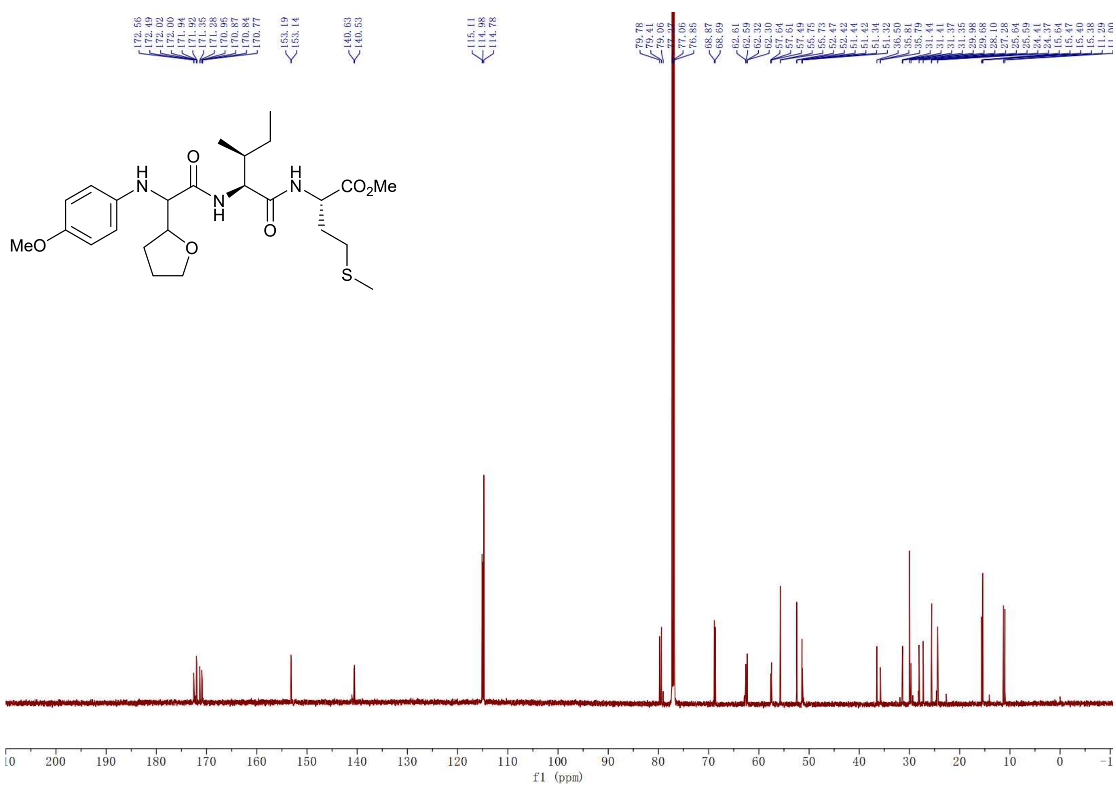
^{1}H NMR of **3ha** (400 MHz, MeOD)



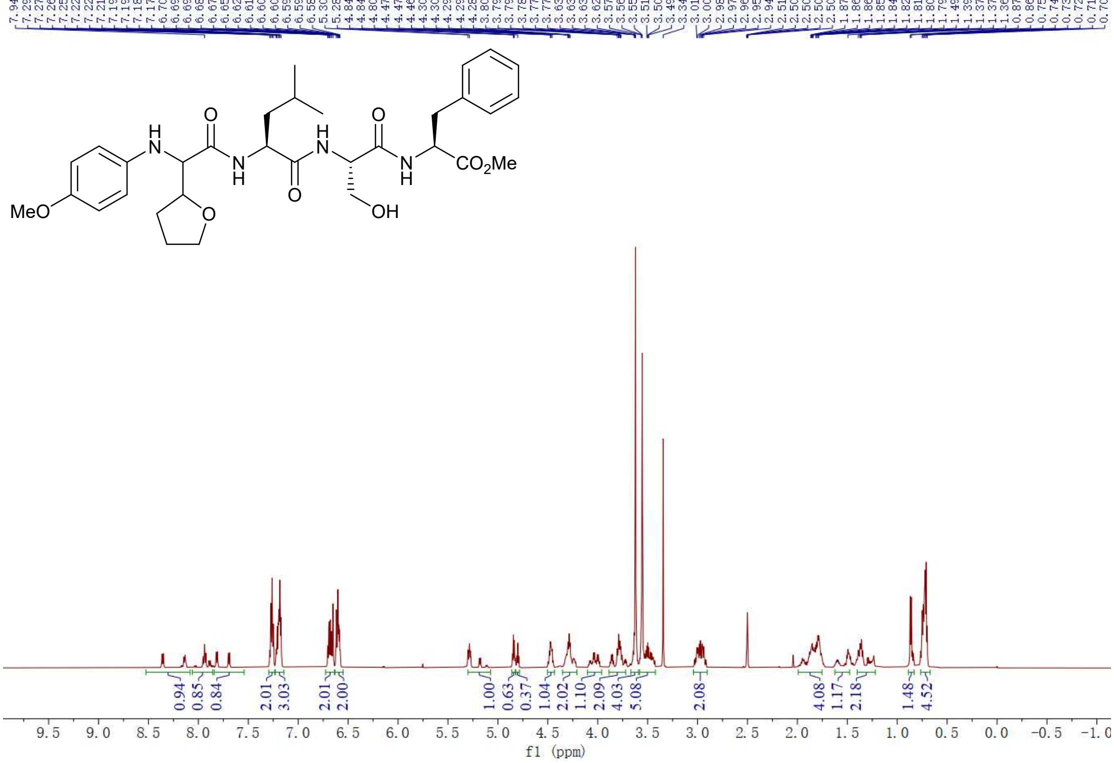
^{13}C NMR of **3ha** (101 MHz, MeOD)



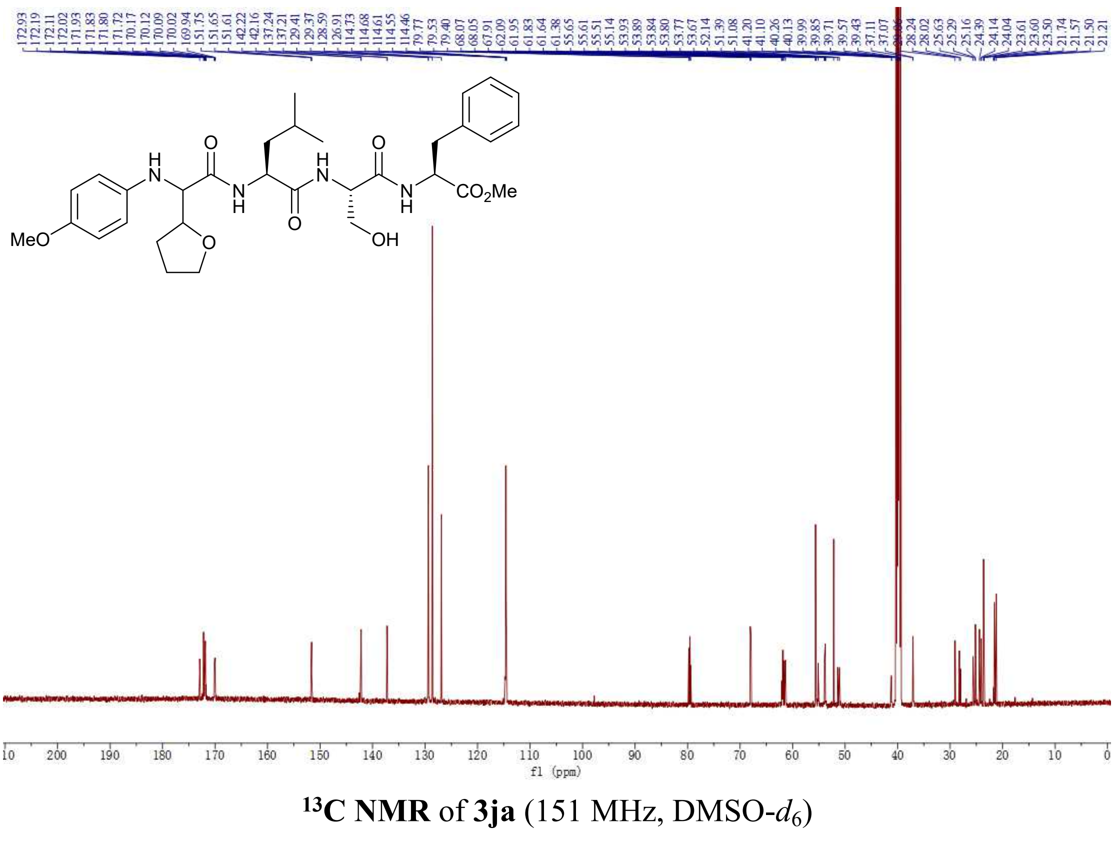
^{1}H NMR of **3ia** (600 MHz, $CDCl_3$)



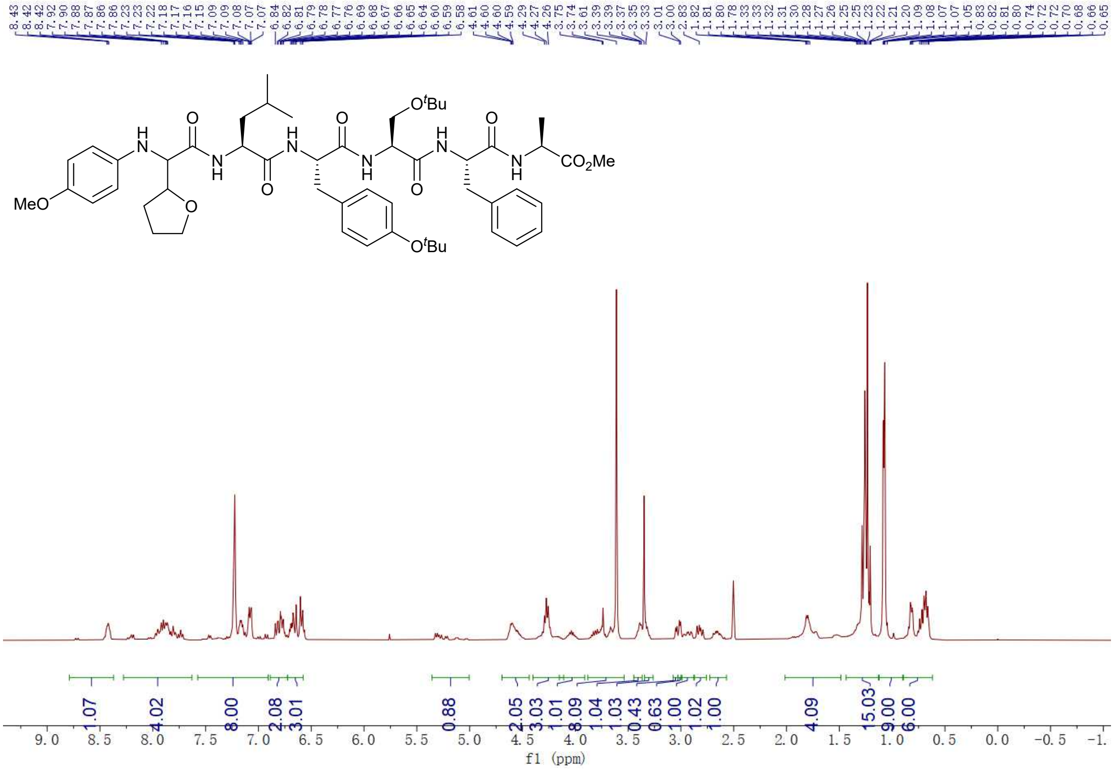
^{13}C NMR of **3ia** (151 MHz, $CDCl_3$)



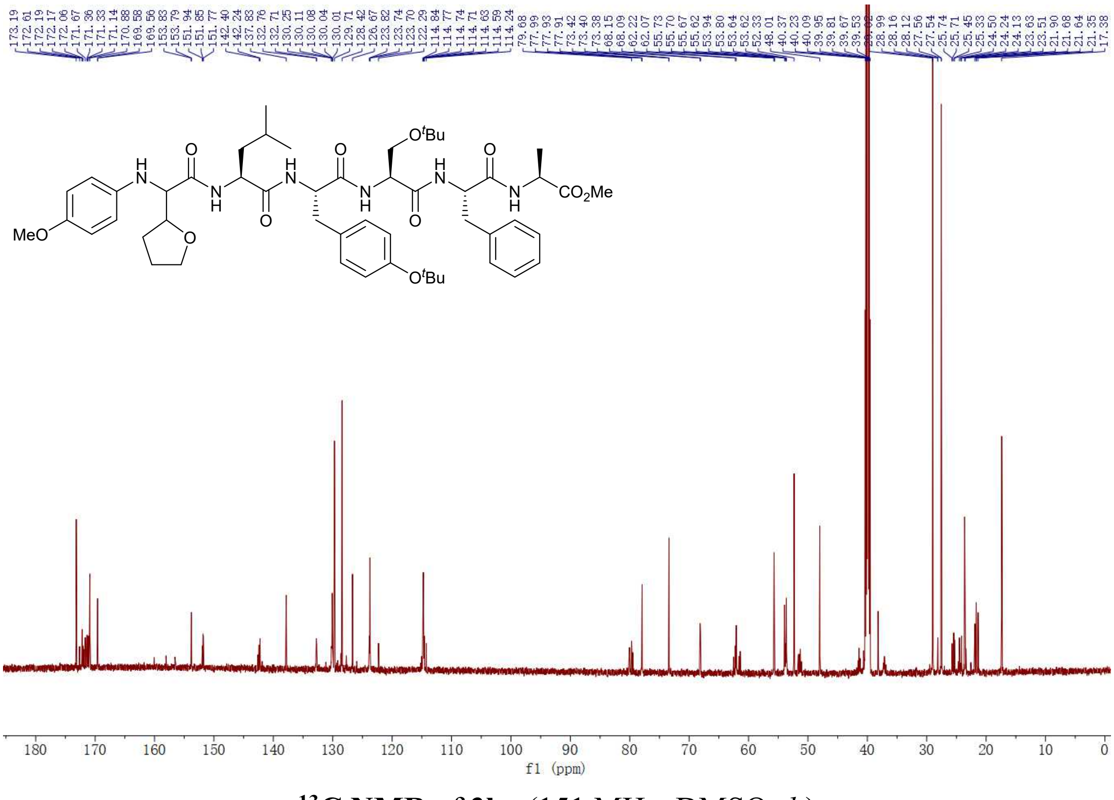
^{1}H NMR of **3ja** (600 MHz, DMSO-d_6)



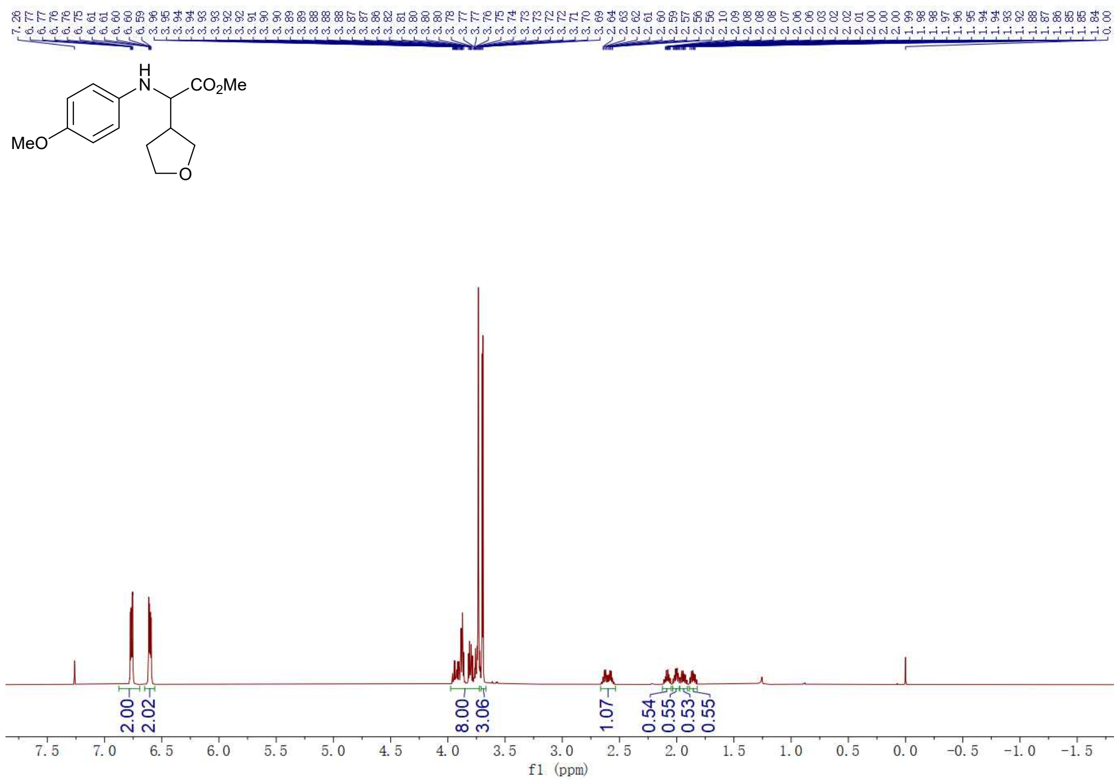
^{13}C NMR of **3ja** (151 MHz, DMSO-d_6)



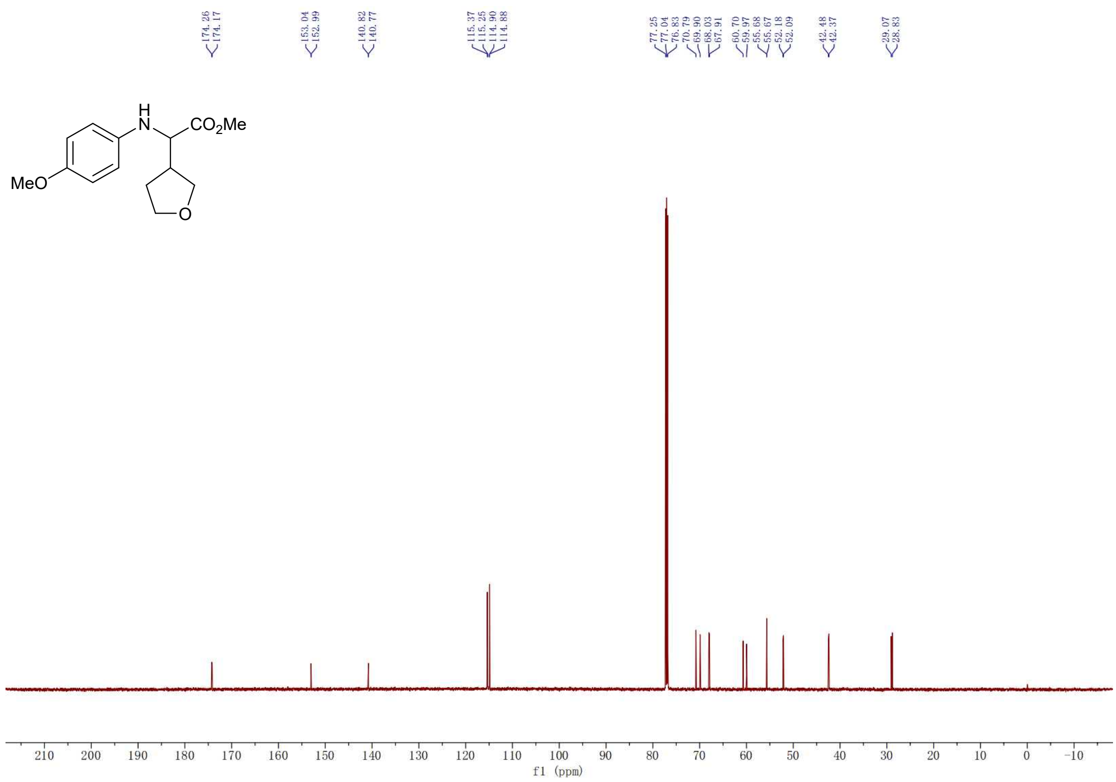
^{1}H NMR of **3ka** (600 MHz, DMSO-d_6)



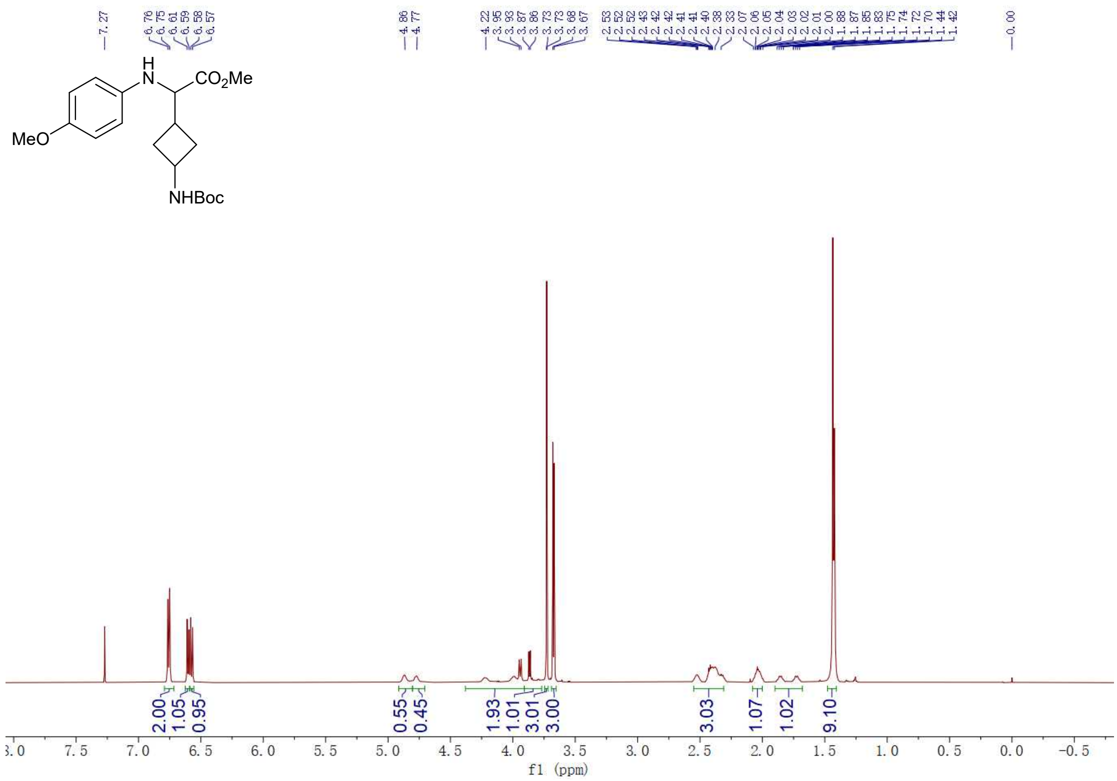
^{13}C NMR of **3ka** (151 MHz, DMSO-d_6)



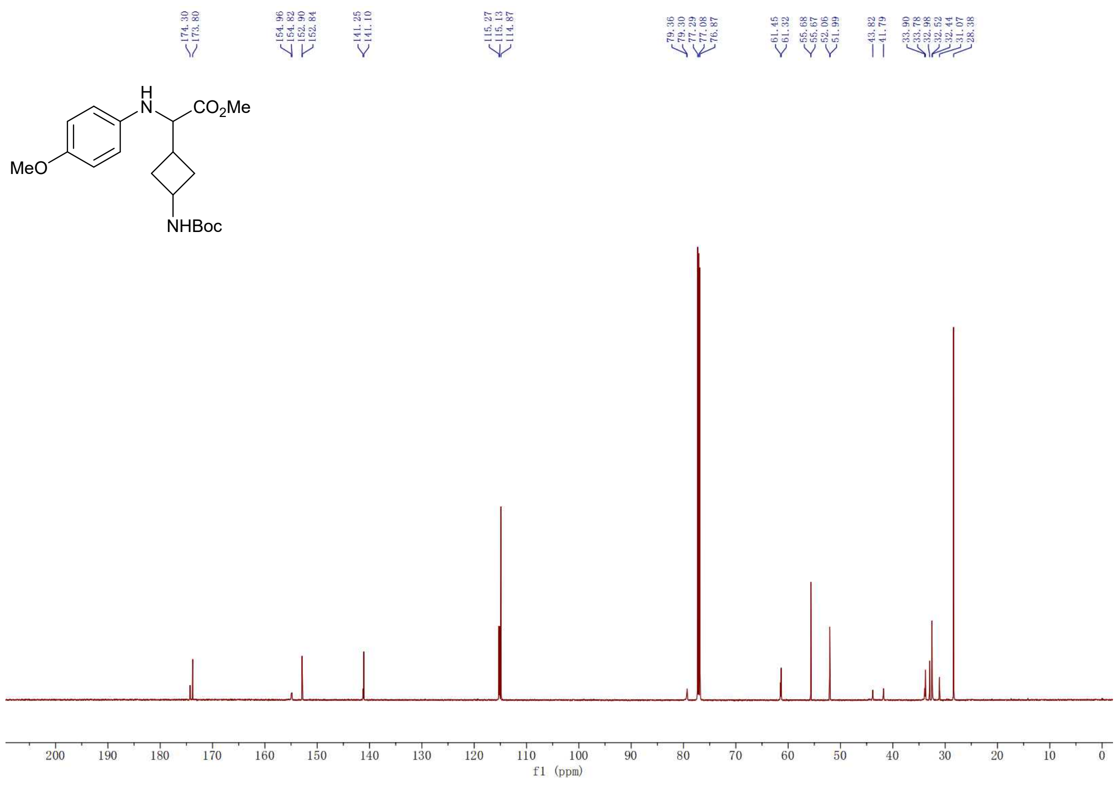
^{1}**H NMR** of **5ab** (600 MHz, $CDCl_3$)



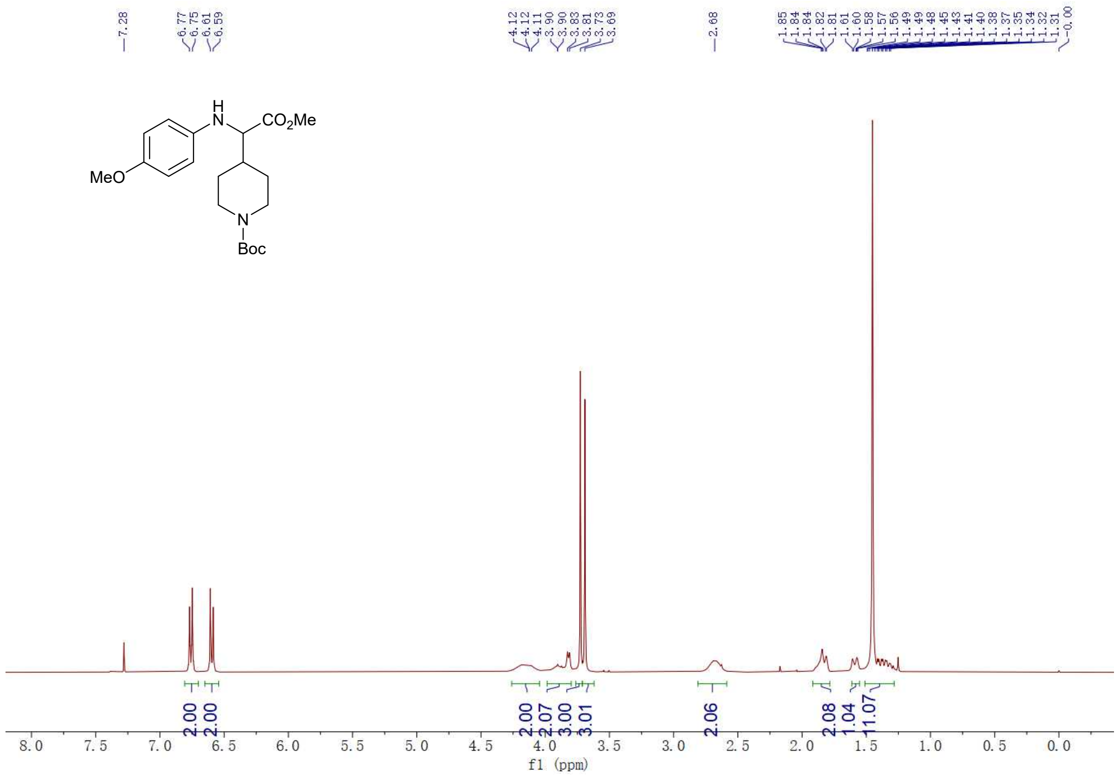
^{13}**C NMR** of **5ab** (151 MHz, $CDCl_3$)



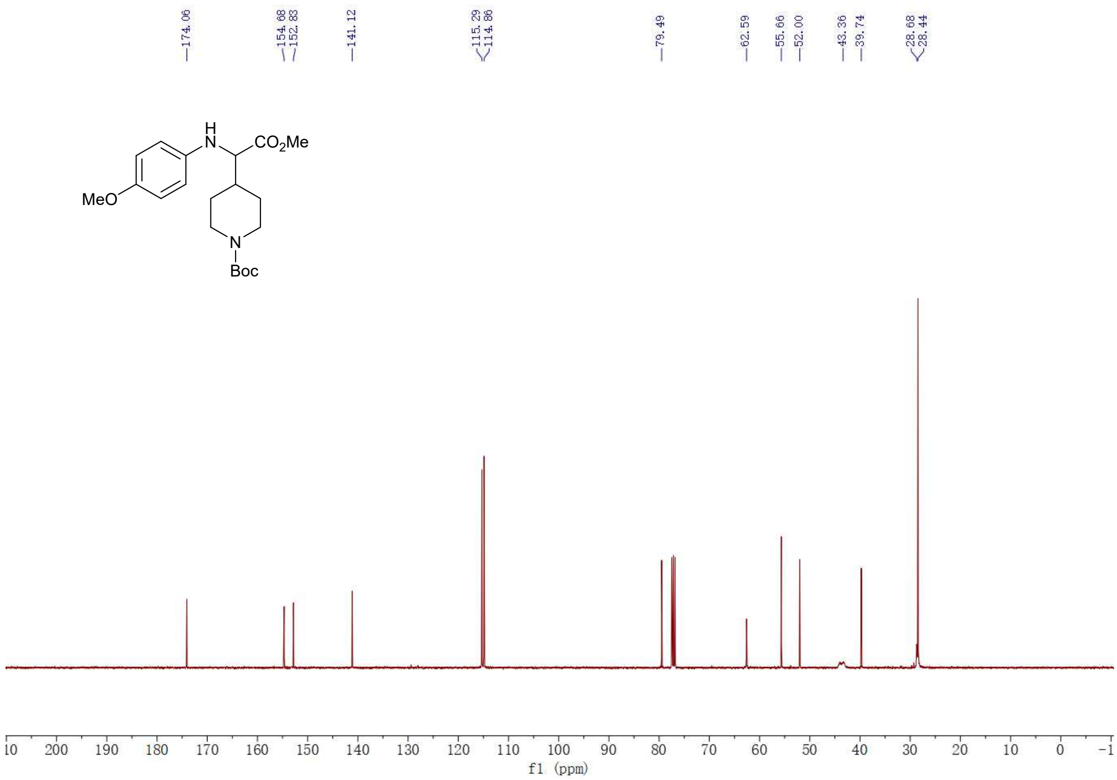
^{1}H NMR of **5ac** (600 MHz, $CDCl_3$)



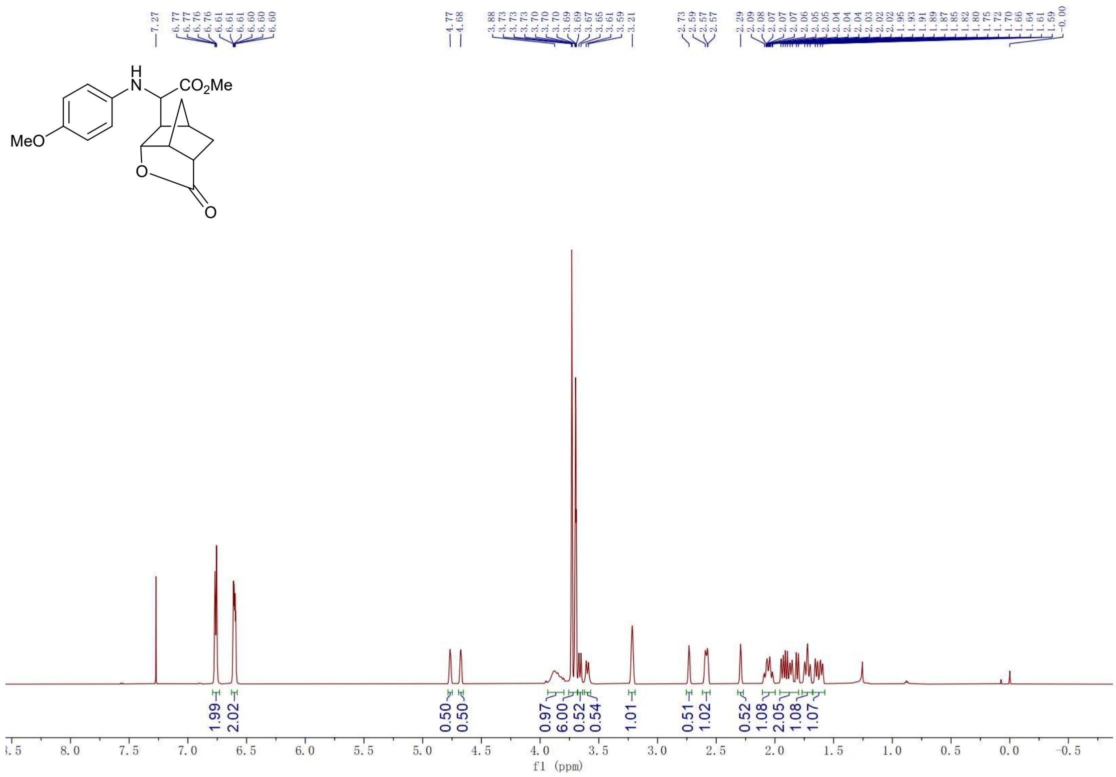
^{13}C NMR of **5ac** (151 MHz, $CDCl_3$)



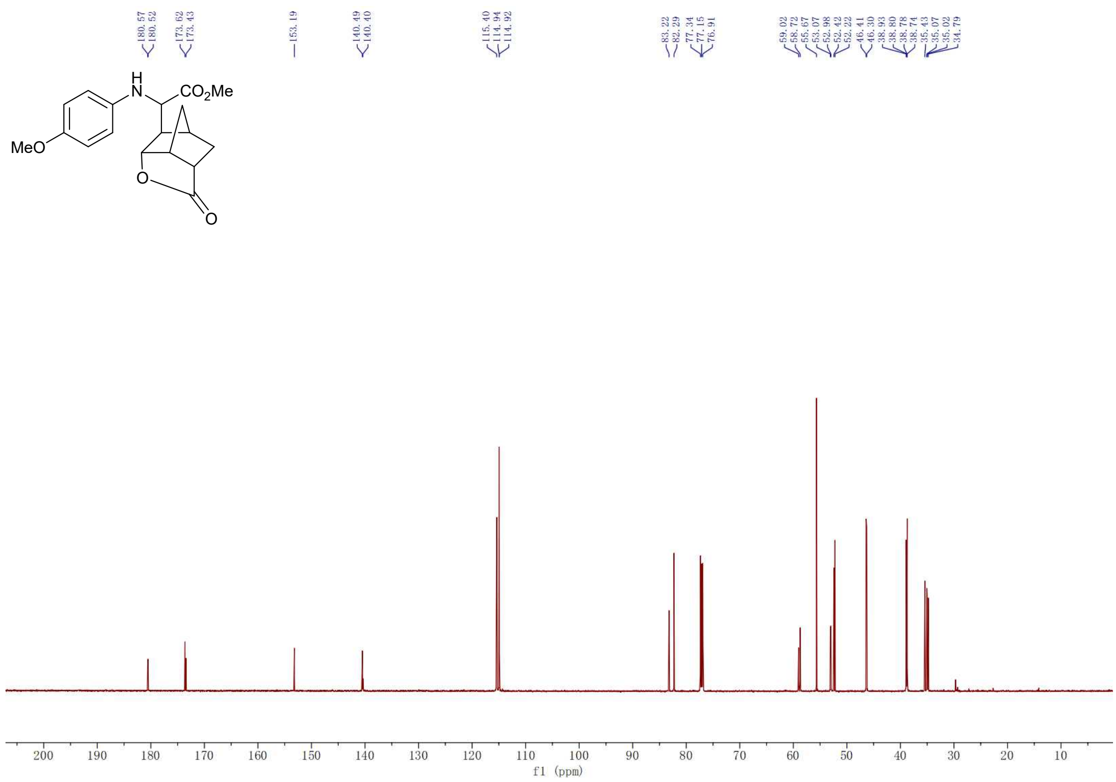
^{1}**H NMR** of **5ad** (400 MHz, $CDCl_3$)



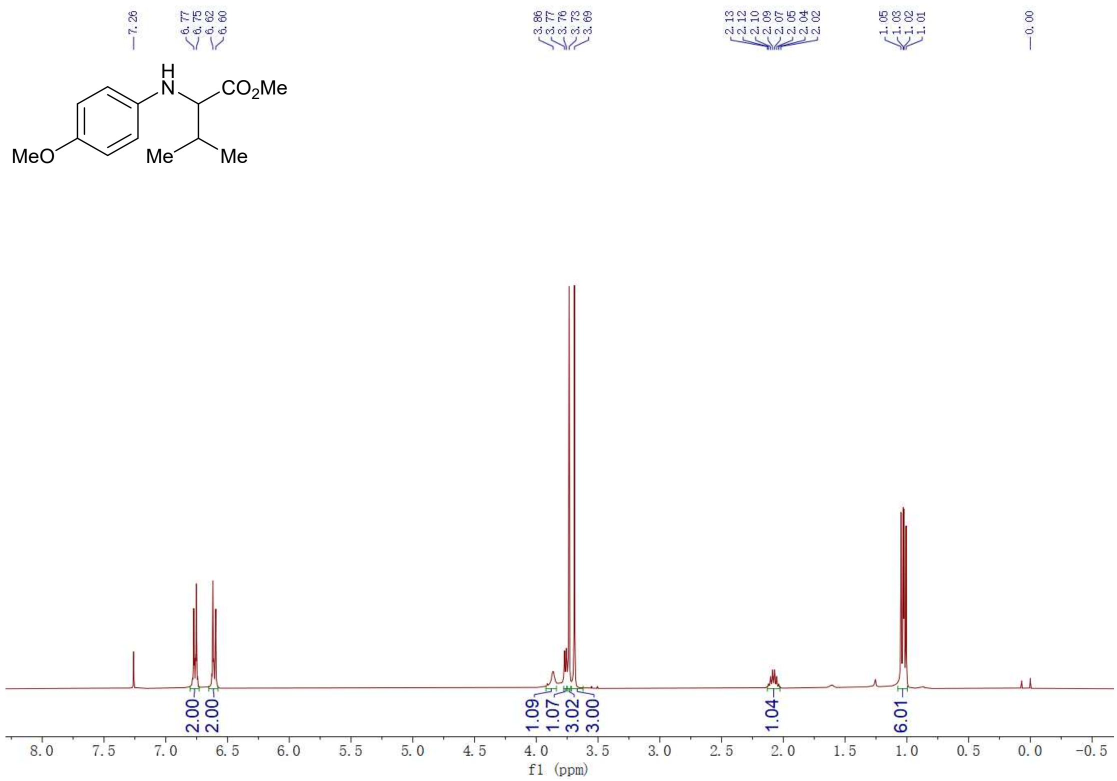
^{13}**C NMR** of **5ad** (101 MHz, $CDCl_3$)



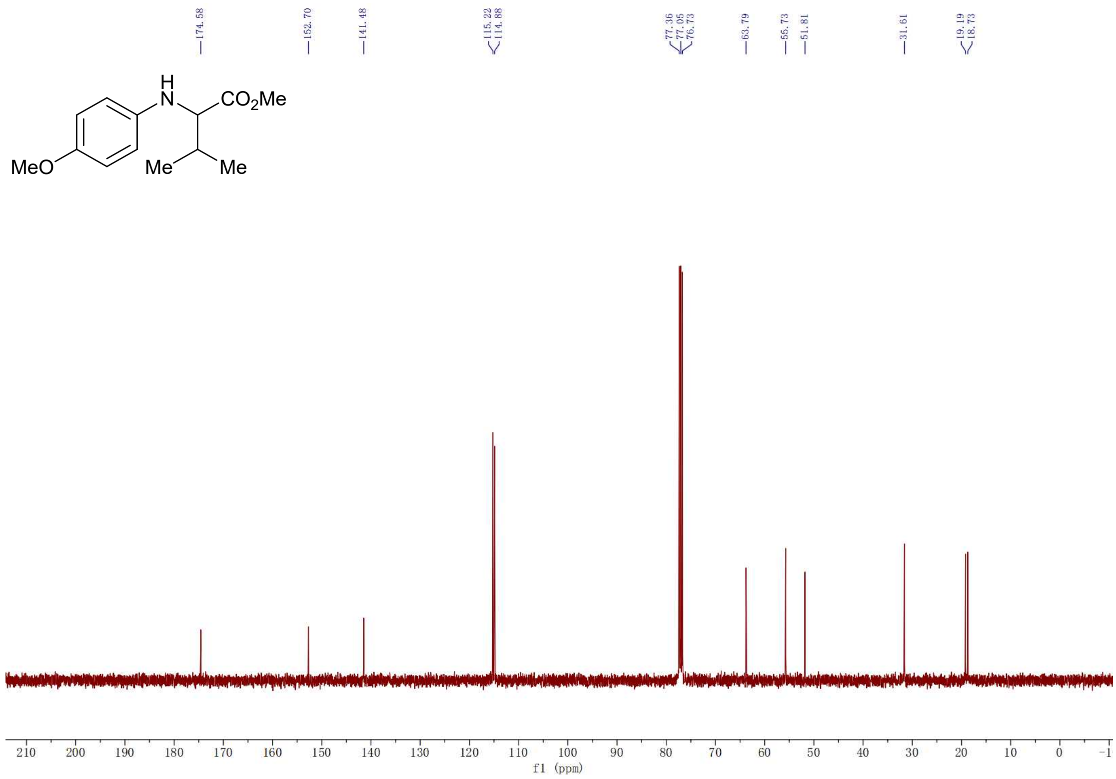
^{1}H NMR of **5ae** (600 MHz, $CDCl_3$)



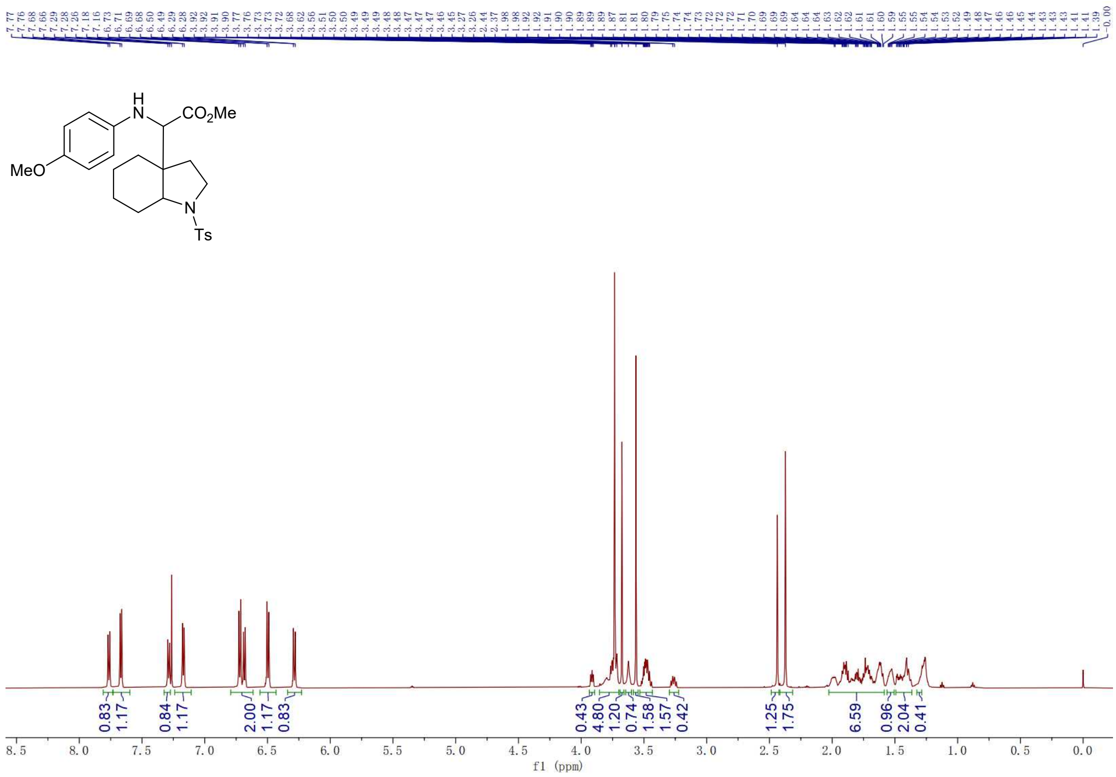
^{13}C NMR of **5ae** (151 MHz, $CDCl_3$)



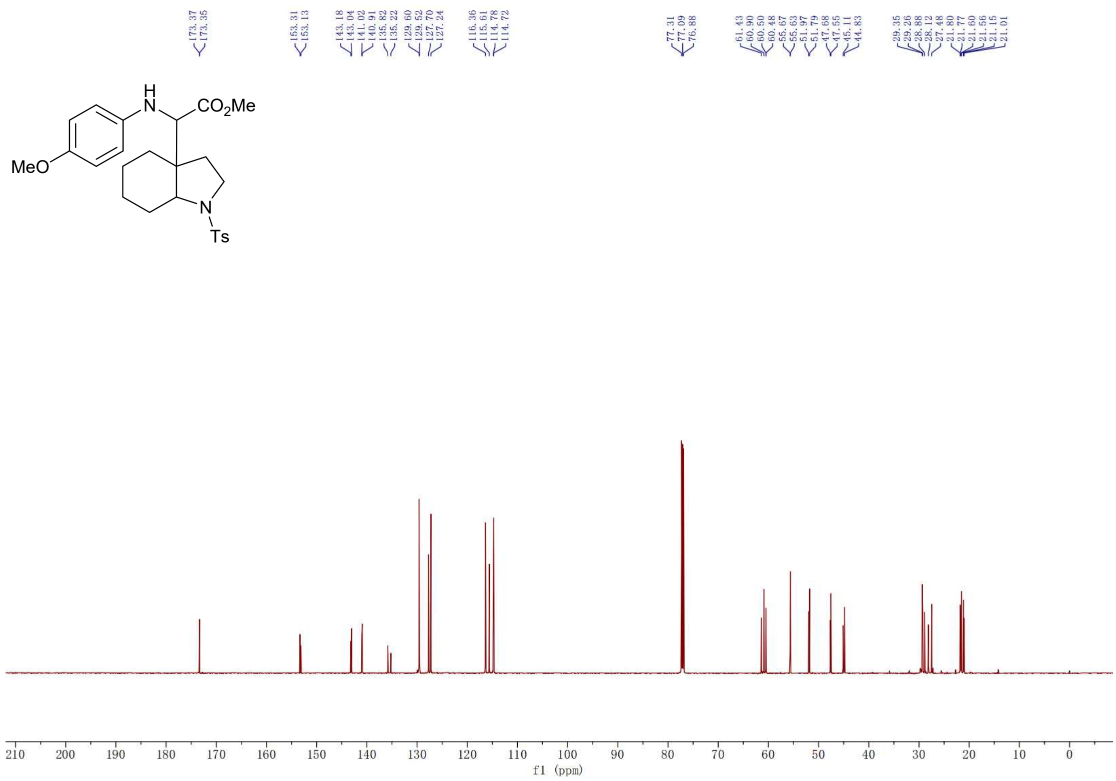
^{1}**H NMR** of **5af** (400 MHz, $CDCl_3$)



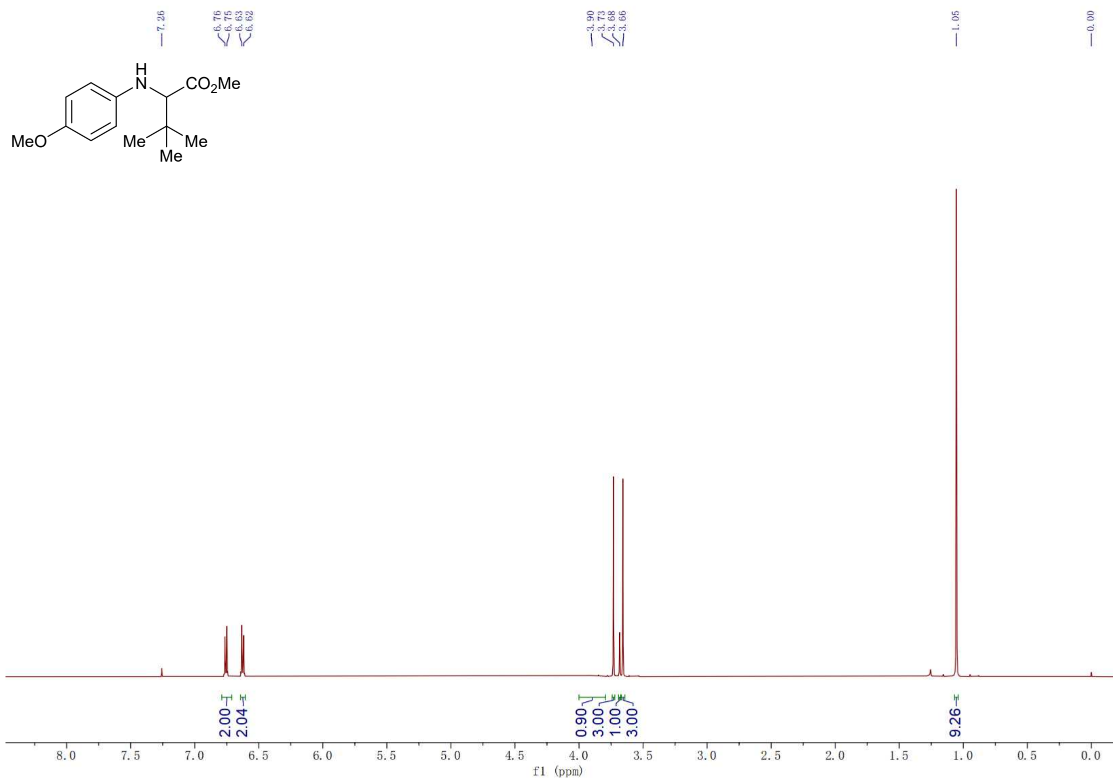
^{13}**C NMR** of **5af** (101 MHz, $CDCl_3$)



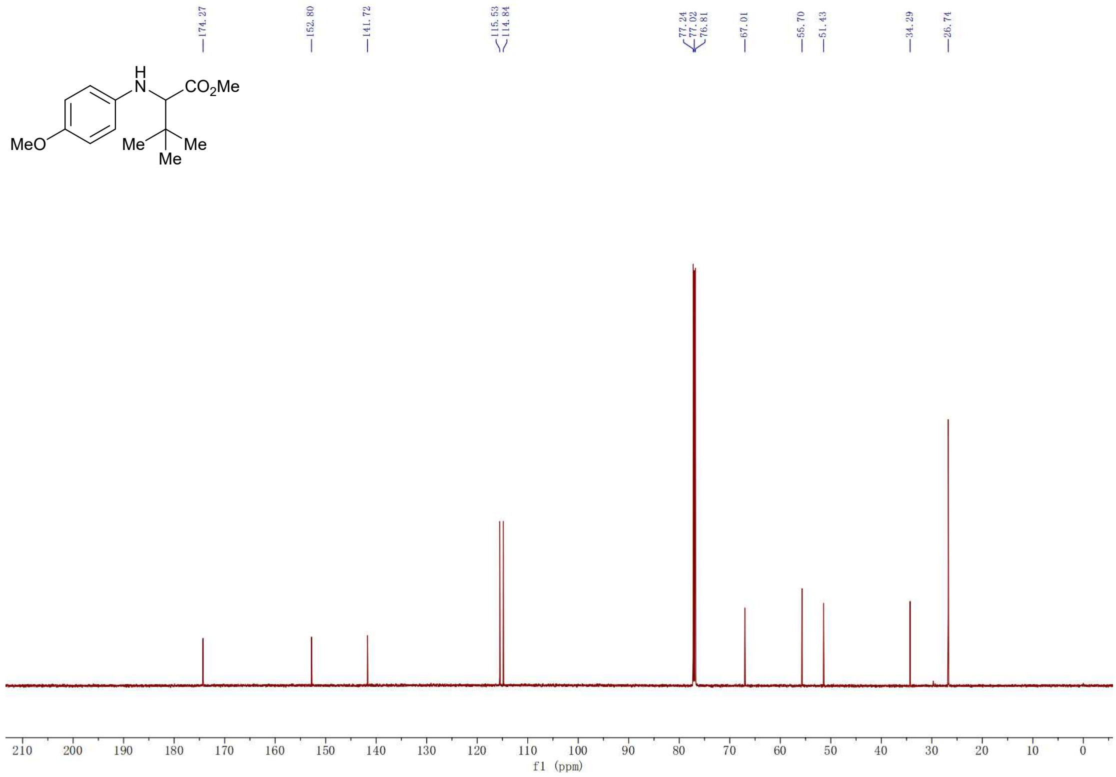
^{1}H NMR of **5ag** (600 MHz, $CDCl_3$)



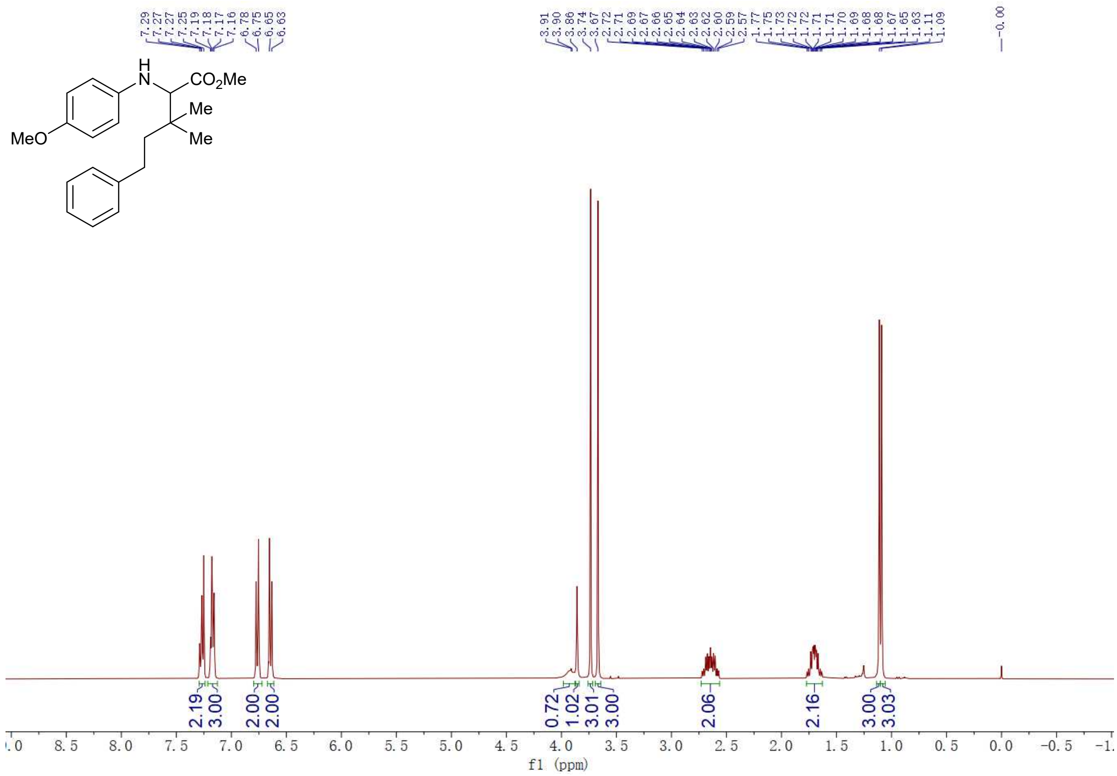
^{13}C NMR of **5ag** (151 MHz, $CDCl_3$)



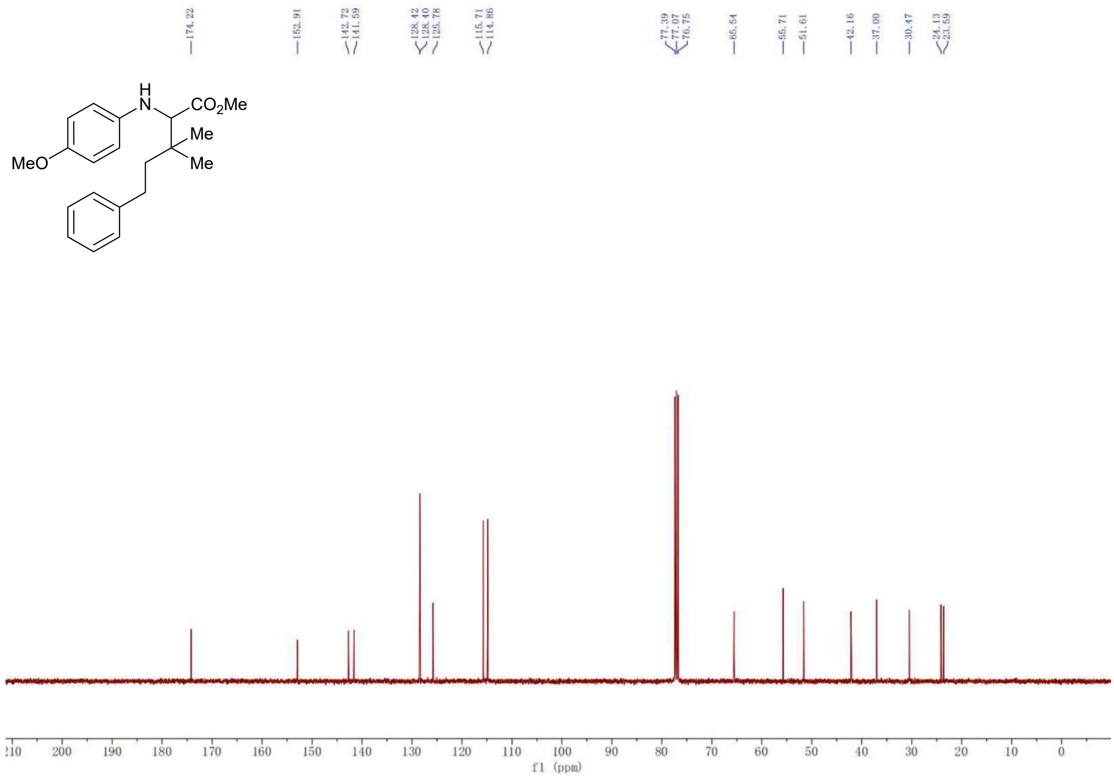
^{1}H NMR of **5ah** (600 MHz, $CDCl_3$)



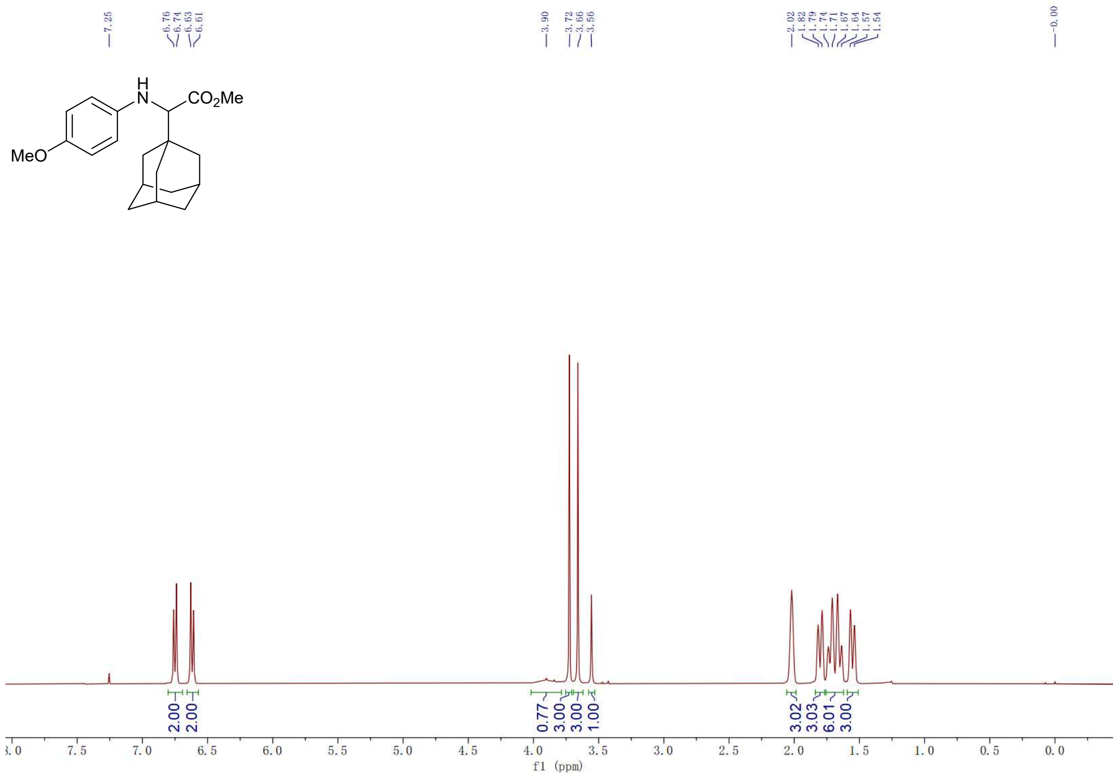
^{13}C NMR of **5ah** (151 MHz, $CDCl_3$)



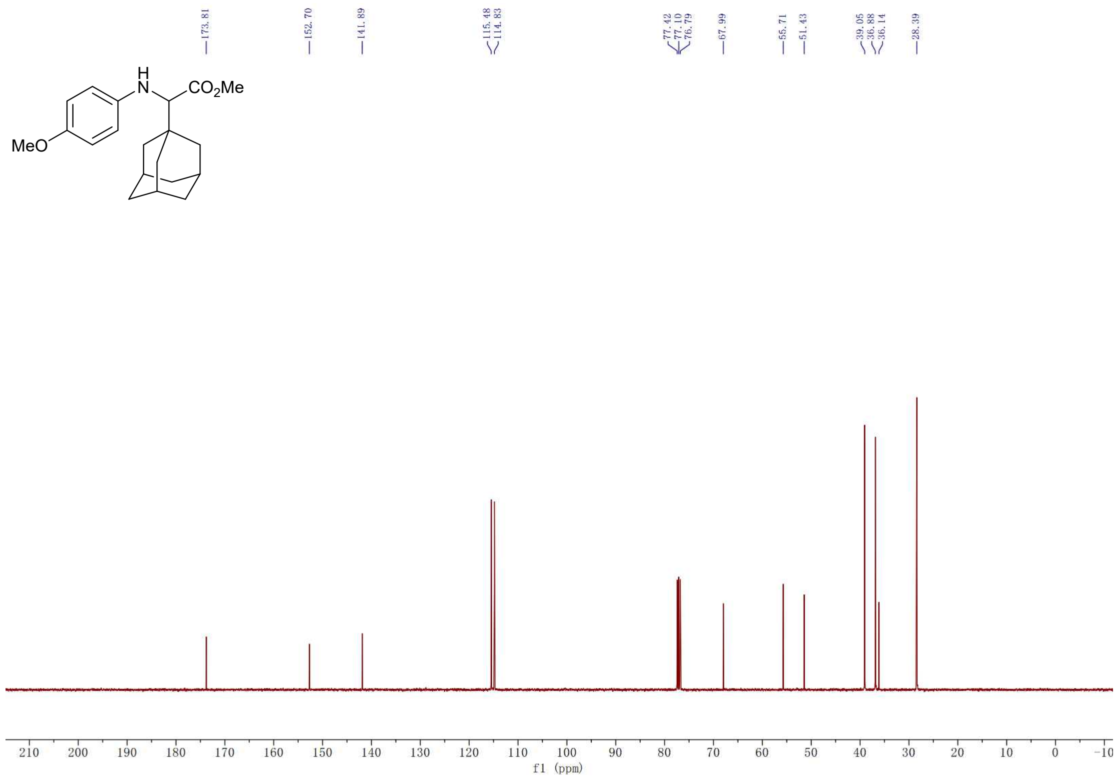
^{1}H NMR of **5ai** (400 MHz, $CDCl_3$)



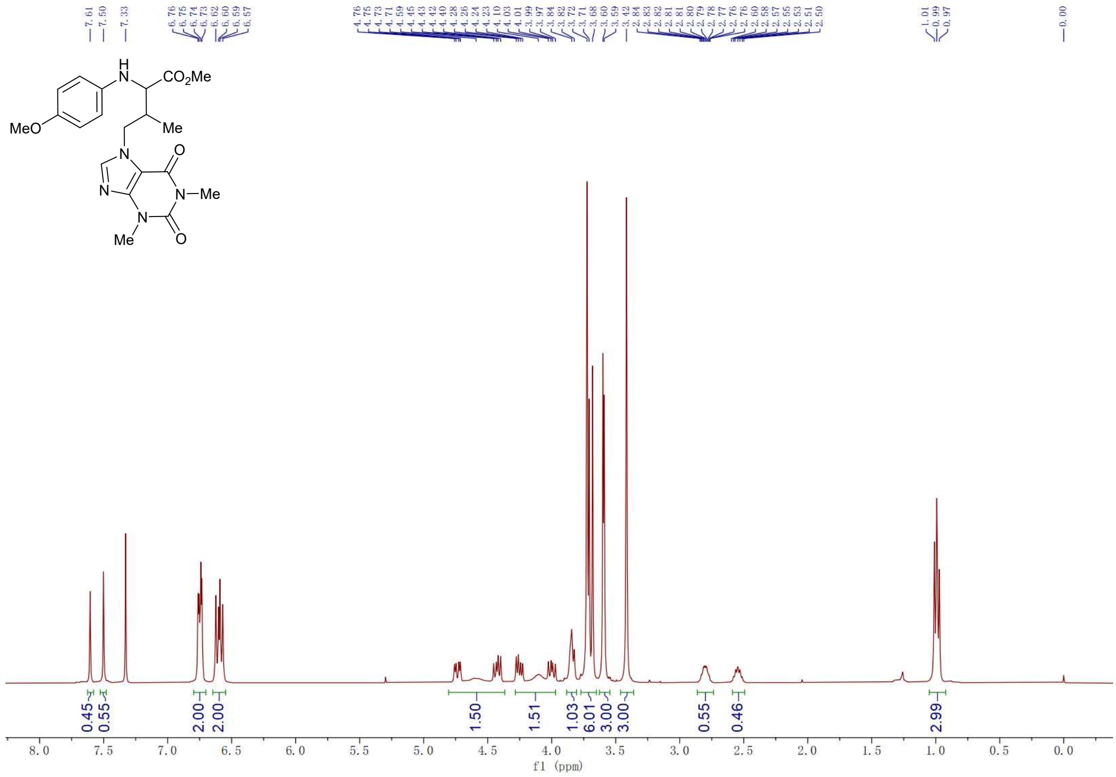
^{13}C NMR of **5ai** (101 MHz, $CDCl_3$)



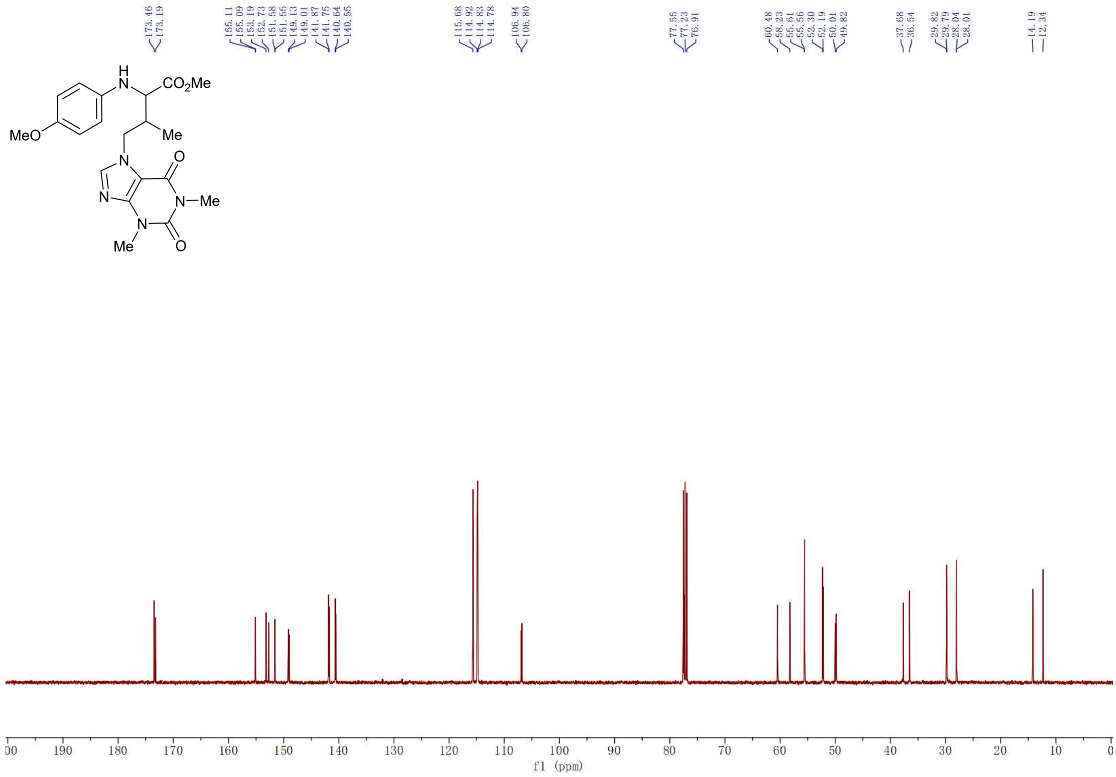
^{1}H NMR of **5aj** (400 MHz, $CDCl_3$)



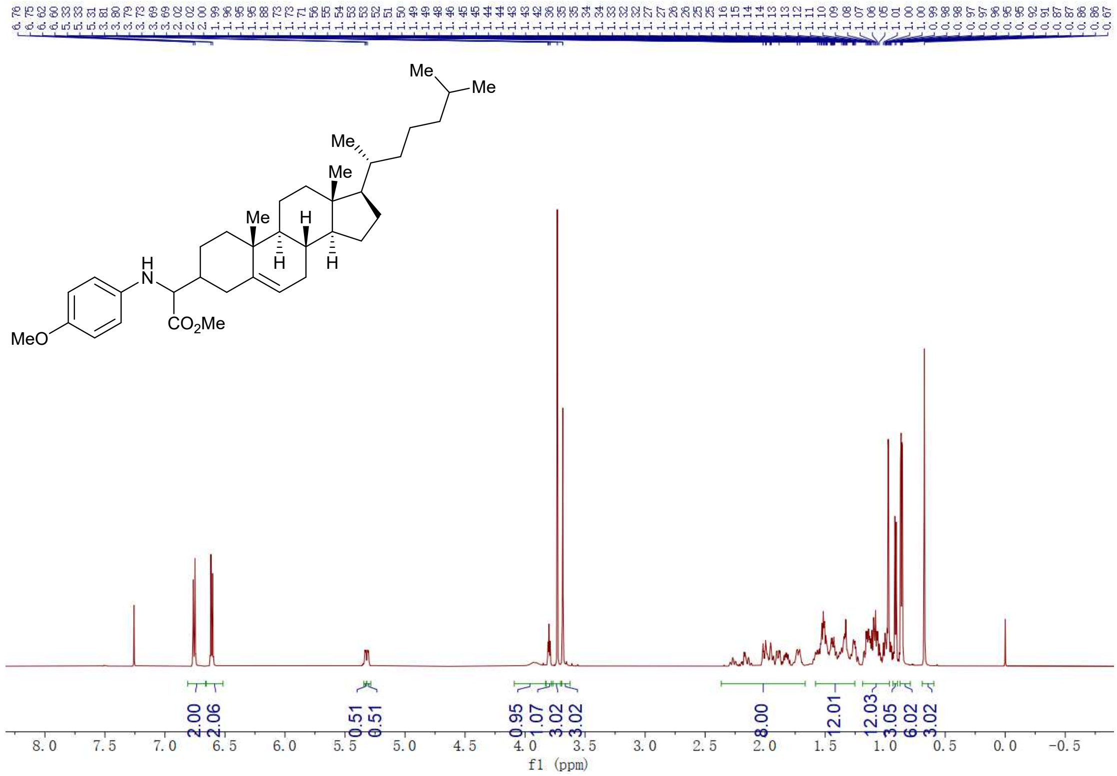
^{13}C NMR of **5aj** (101 MHz, $CDCl_3$)



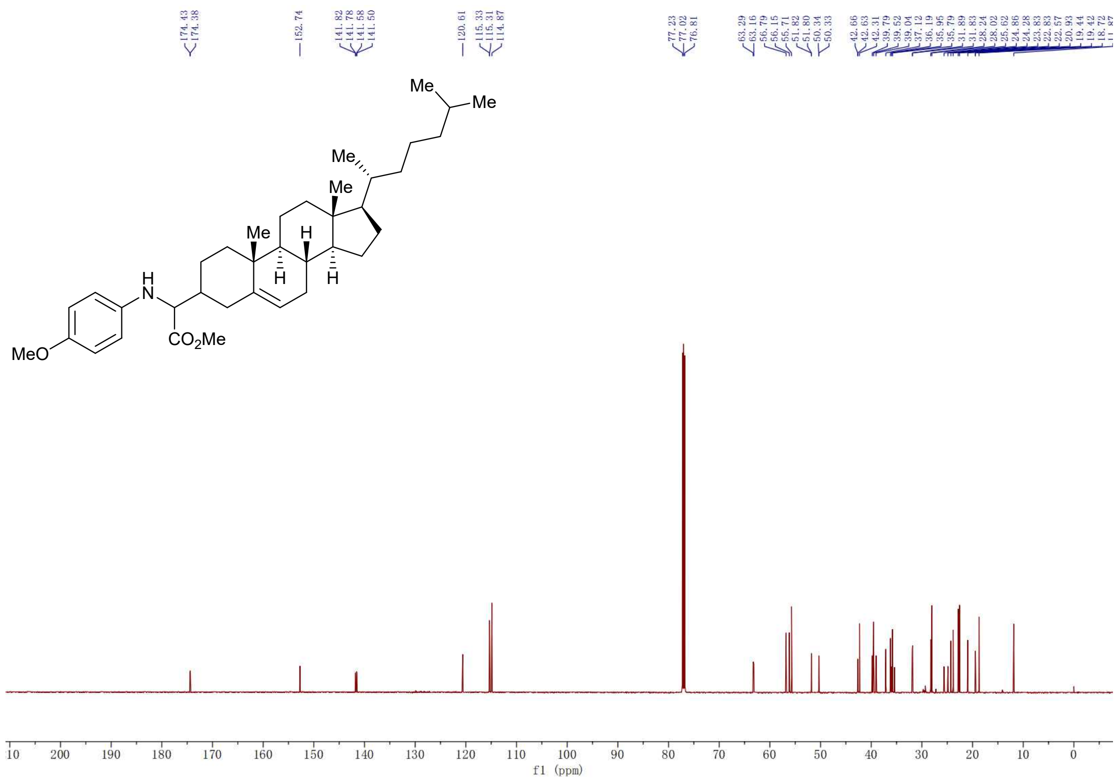
^{1}H NMR of **5ak** (400 MHz, $CDCl_3$)



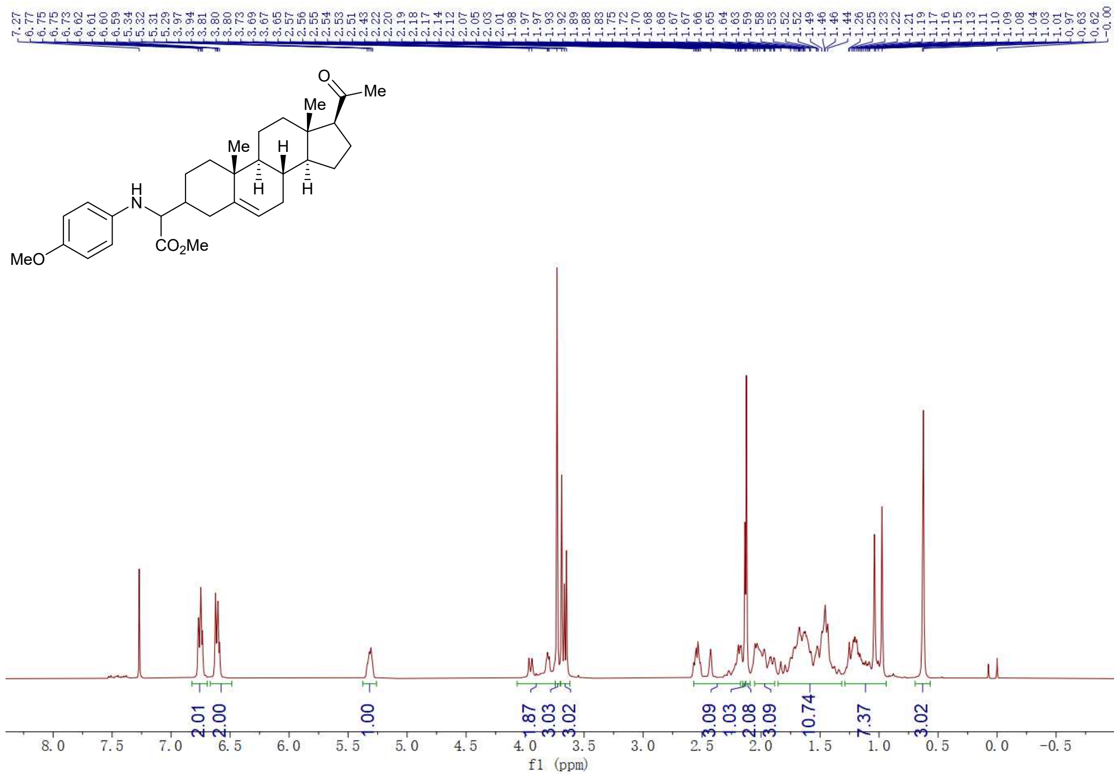
^{13}C NMR of **5ak** (101 MHz, $CDCl_3$)



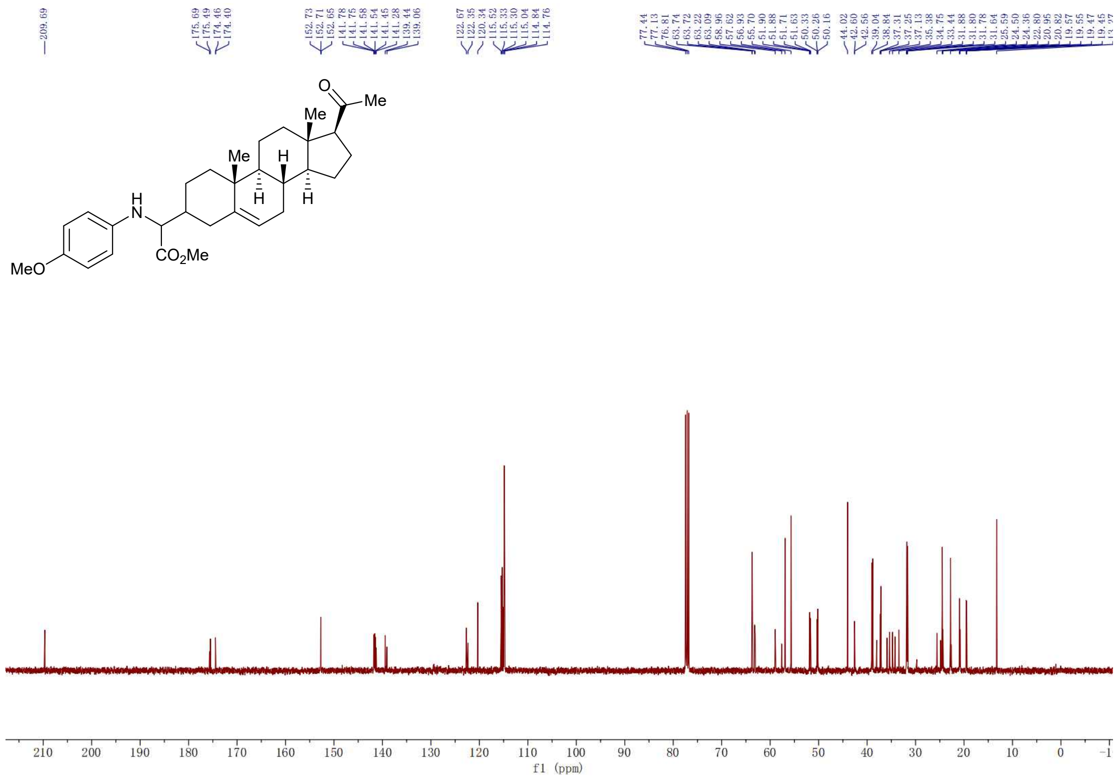
^{1}H NMR of **5al** (600 MHz, $CDCl_3$)



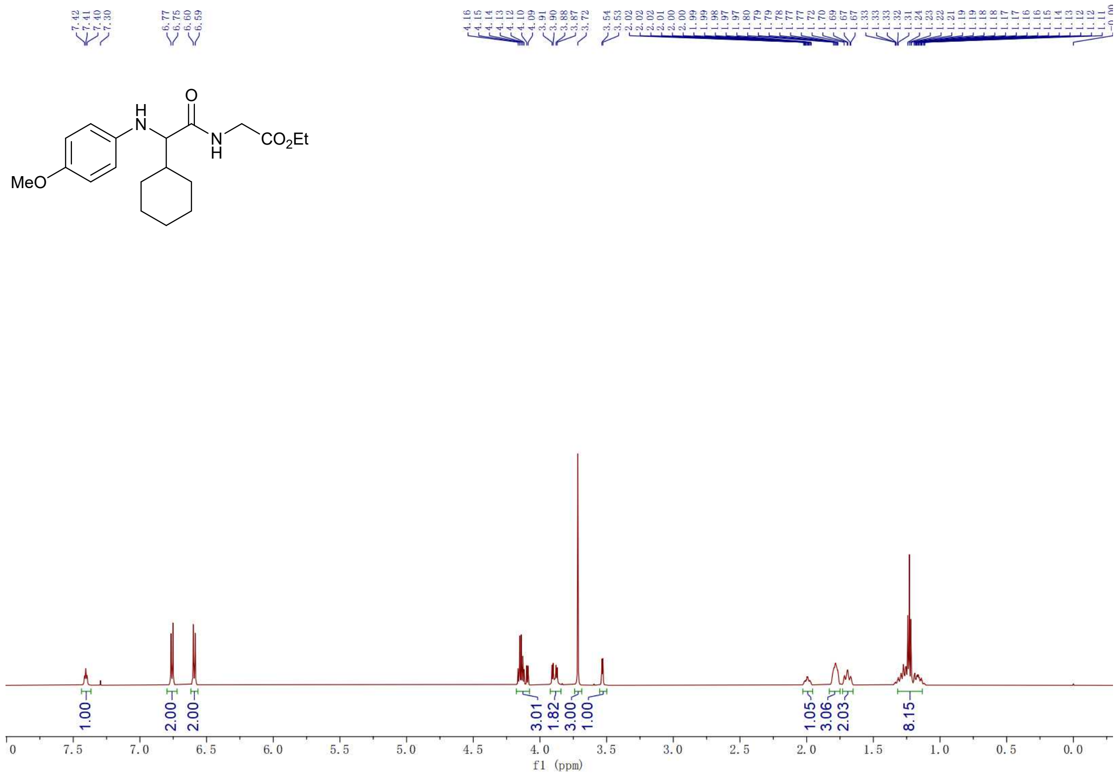
^{13}C NMR of **5al** (151 MHz, $CDCl_3$)



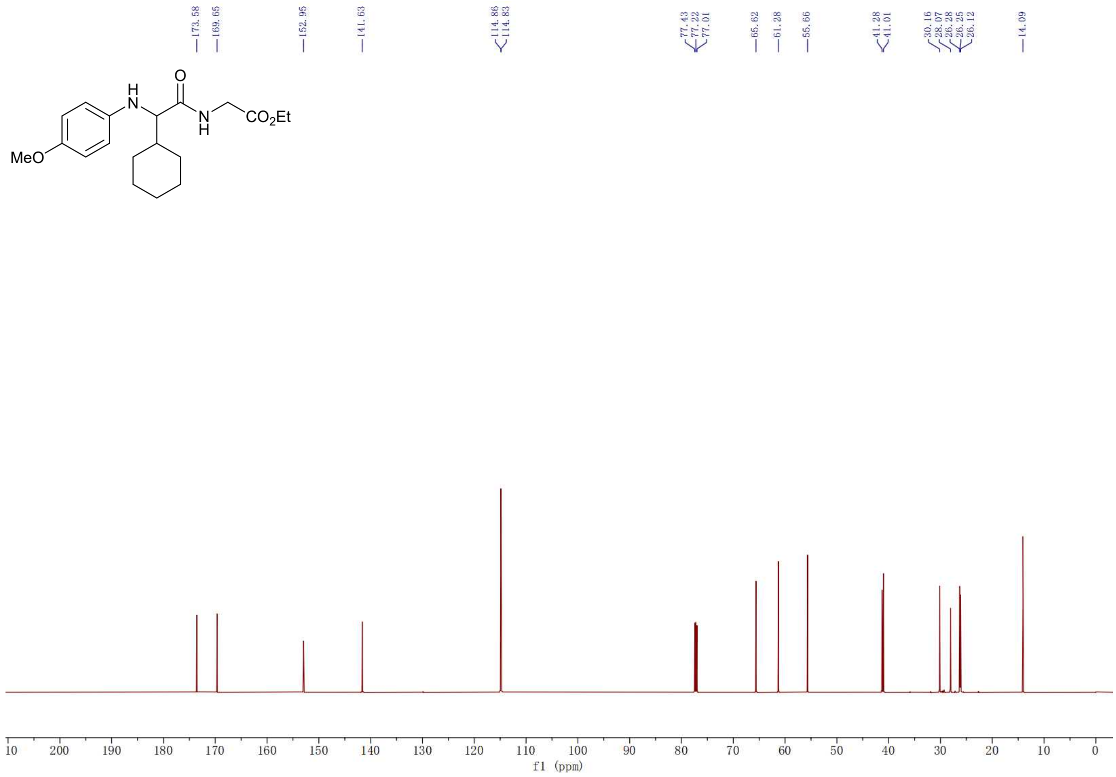
^{1}H NMR of **5am** (400 MHz, $CDCl_3$)



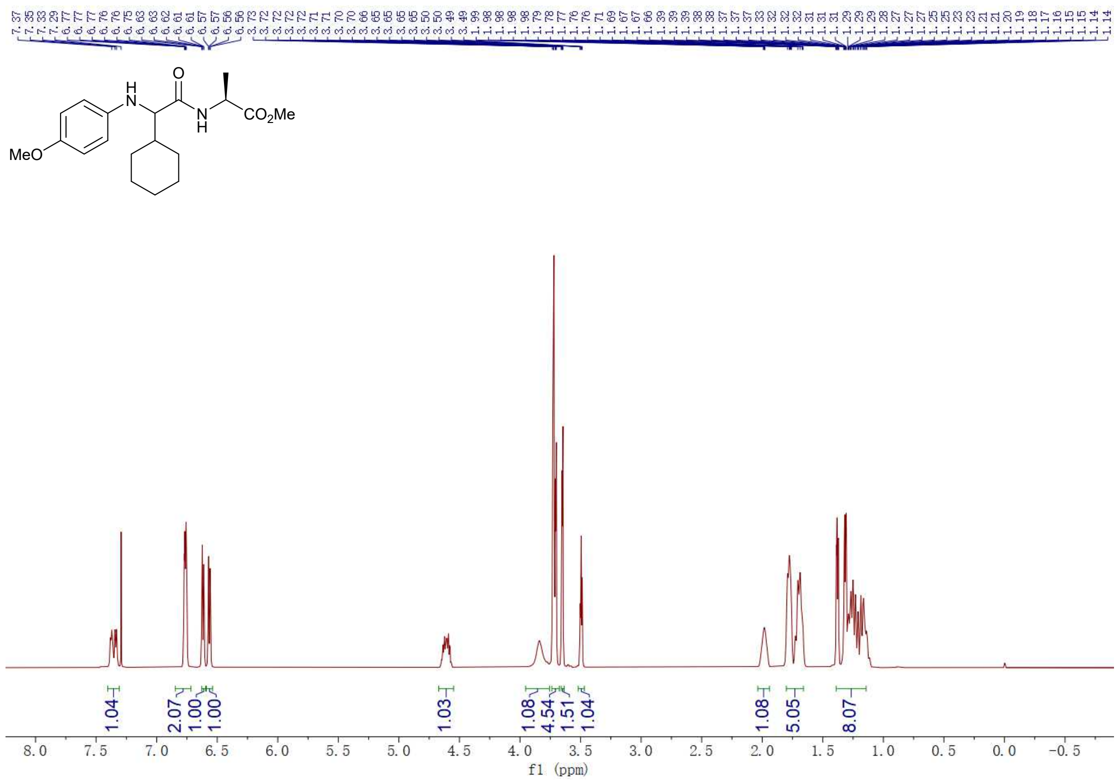
^{13}C NMR of **5am** (101 MHz, $CDCl_3$)



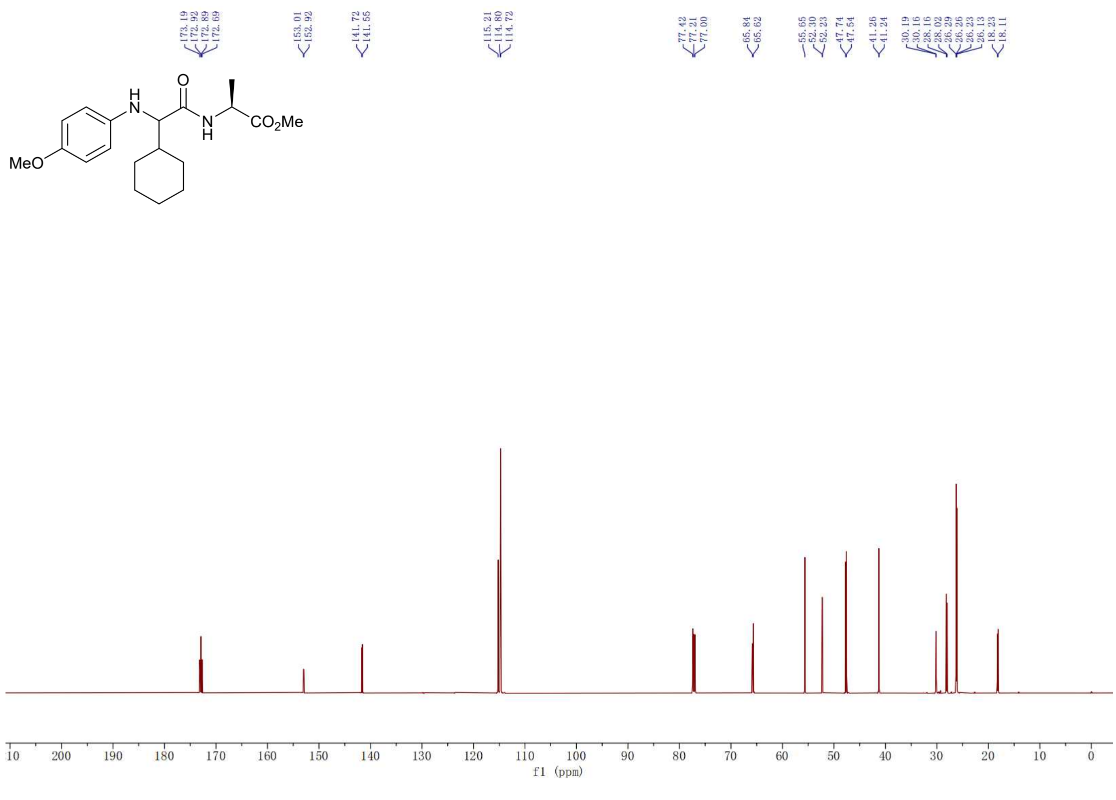
^{1}H NMR of **5ba** (600 MHz, $CDCl_3$)



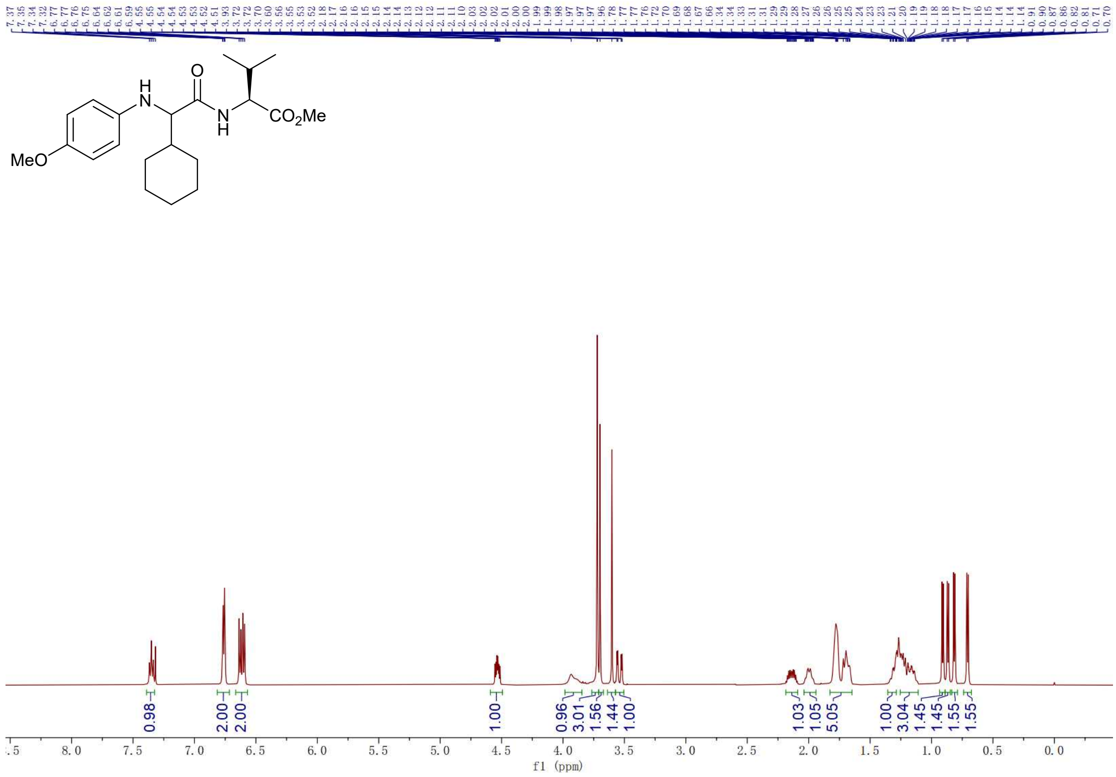
^{13}C NMR of **5ba** (151 MHz, $CDCl_3$)



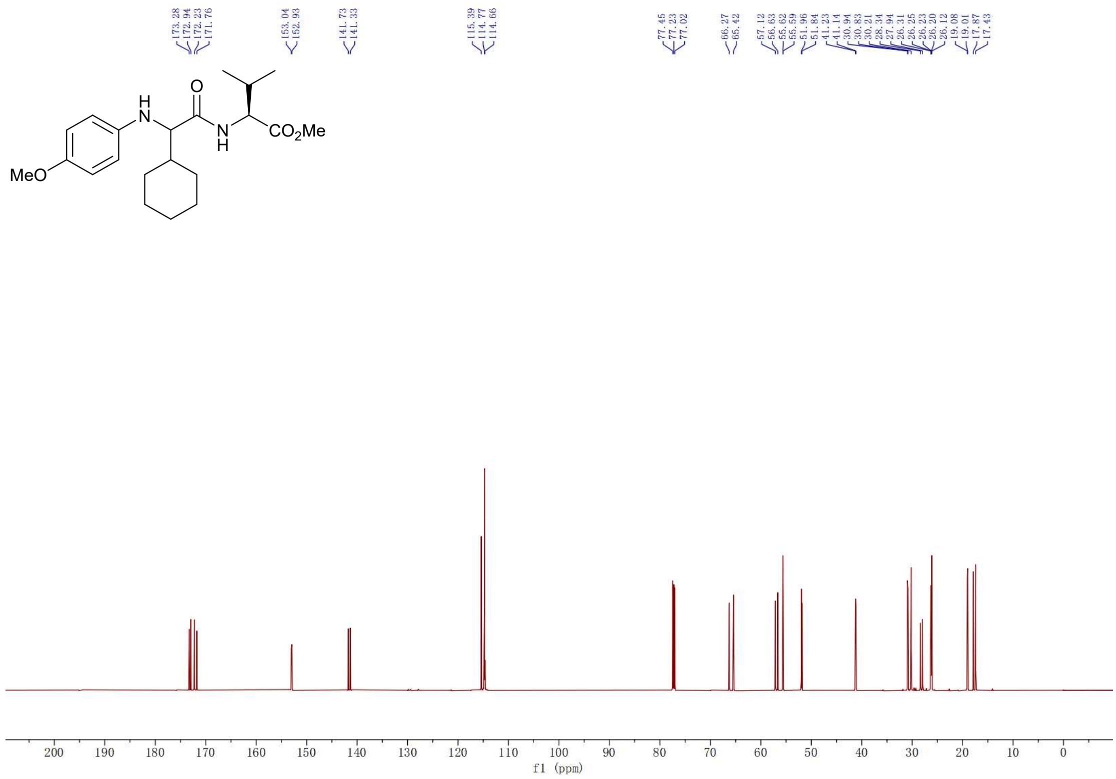
^{1}H NMR of **5la** (600 MHz, $CDCl_3$)



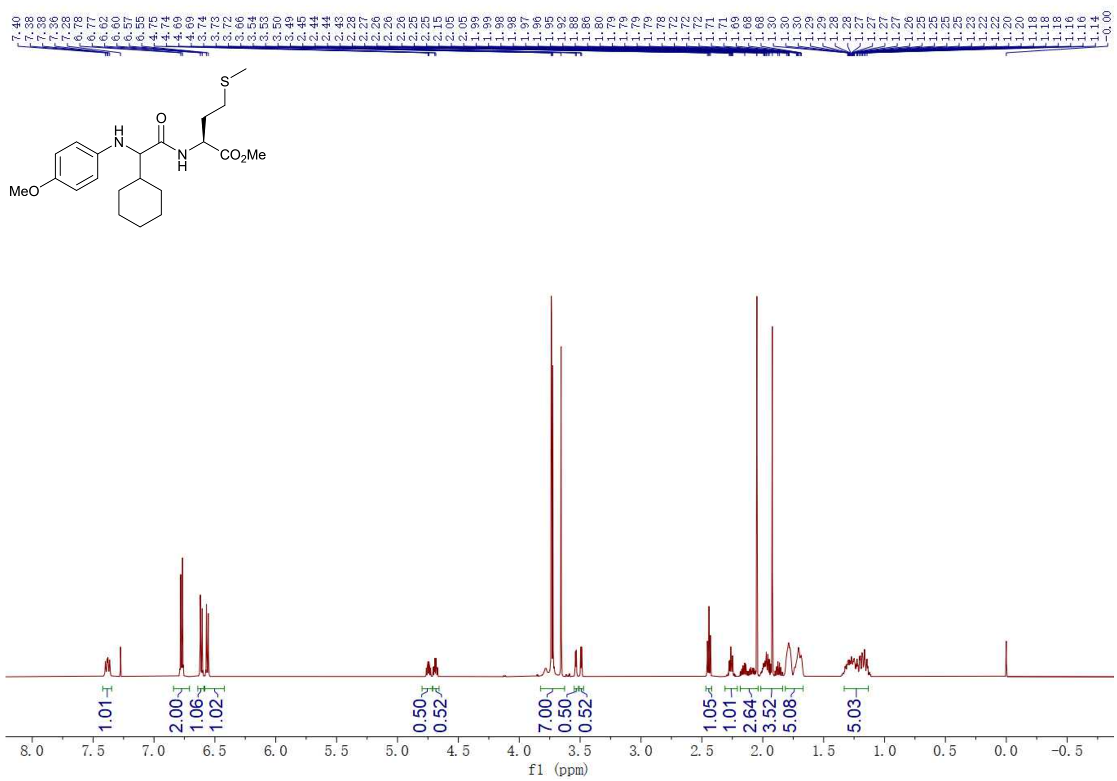
^{13}C NMR of **5la** (151 MHz, $CDCl_3$)



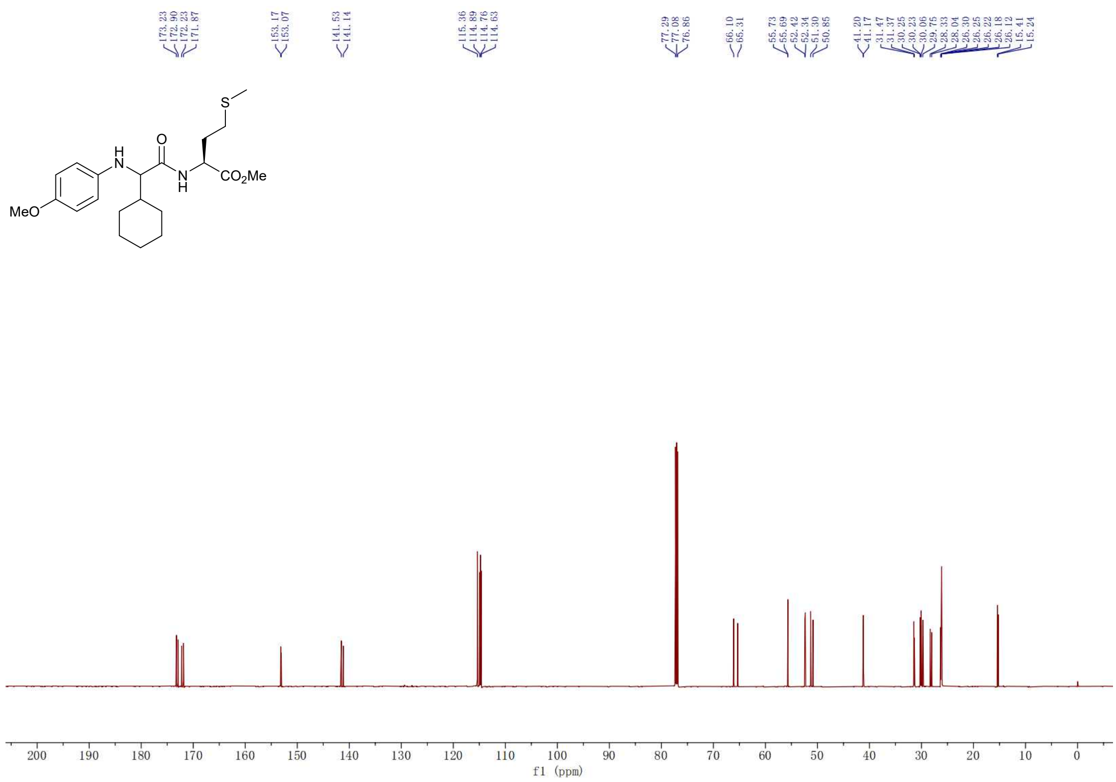
^{1}H NMR of **5ca** (600 MHz, $CDCl_3$)



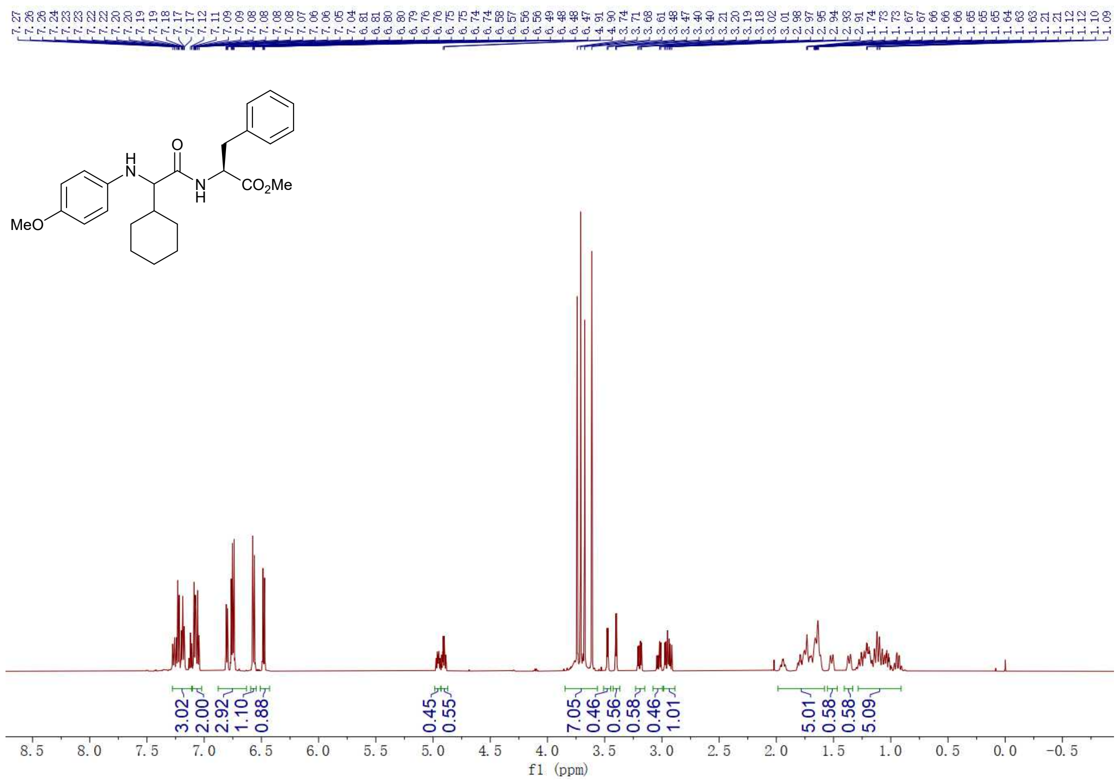
^{13}C NMR of **5ca** (151 MHz, $CDCl_3$)



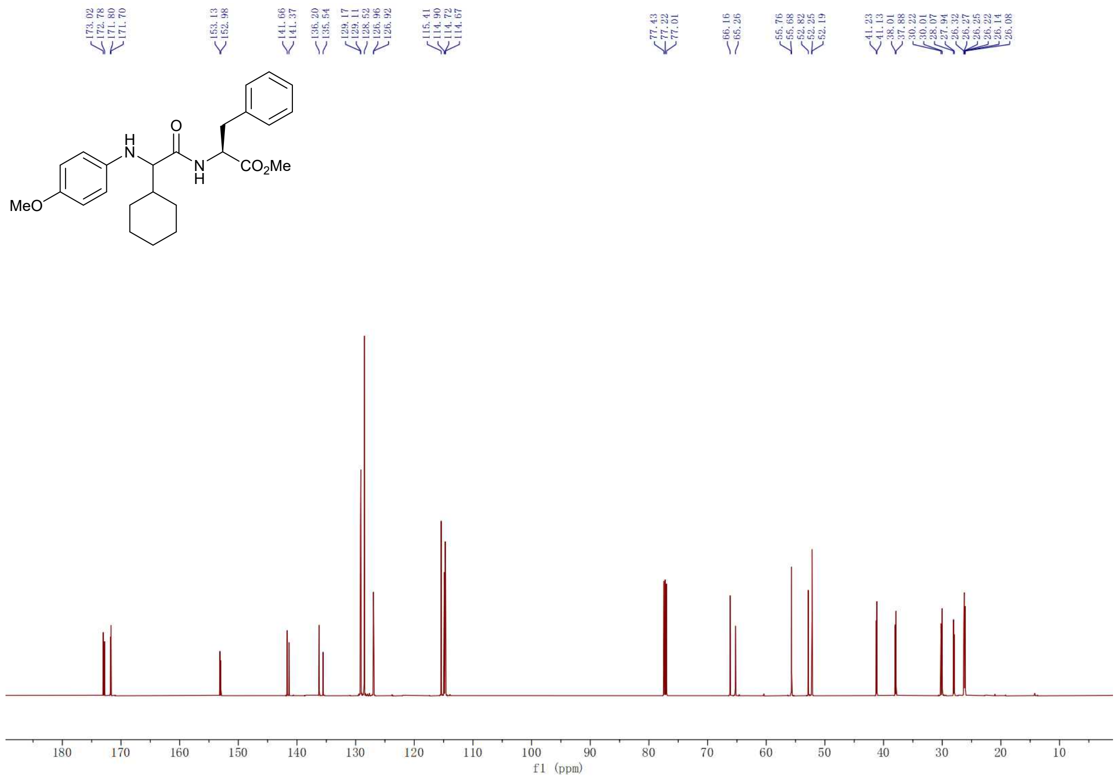
^{1}**H NMR** of **5ea** (600 MHz, $CDCl_3$)



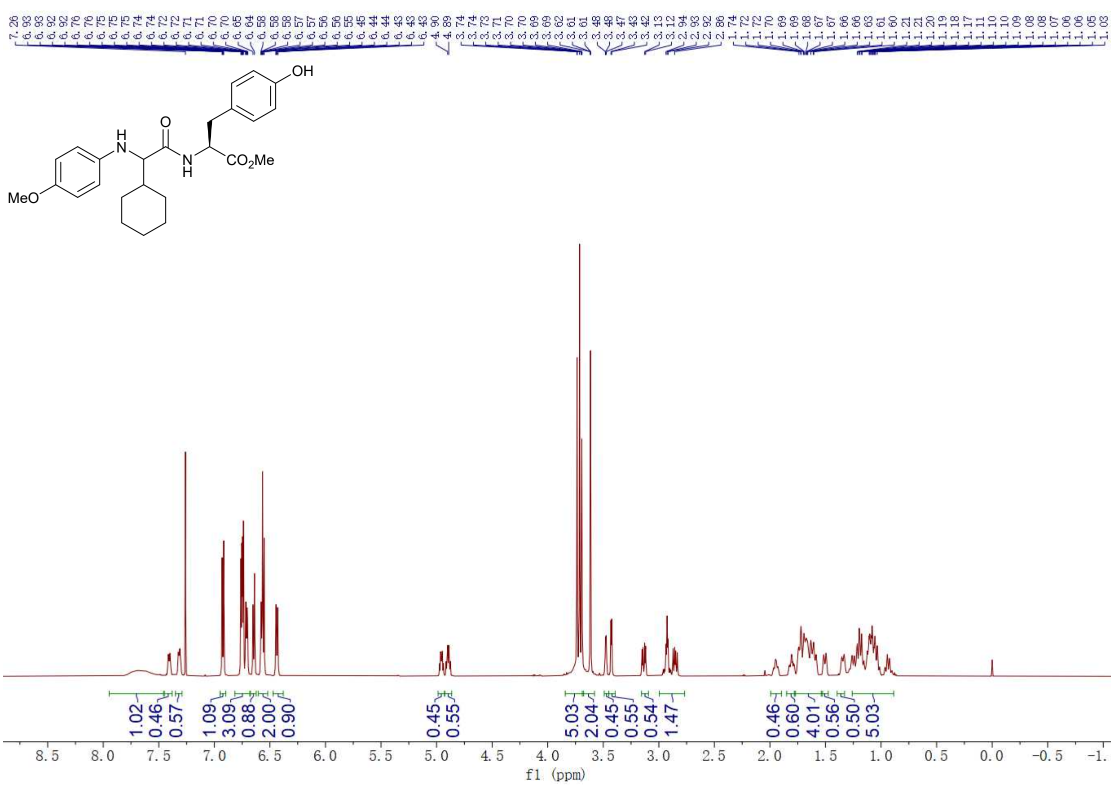
^{13}**C NMR** of **5ea** (151 MHz, $CDCl_3$)



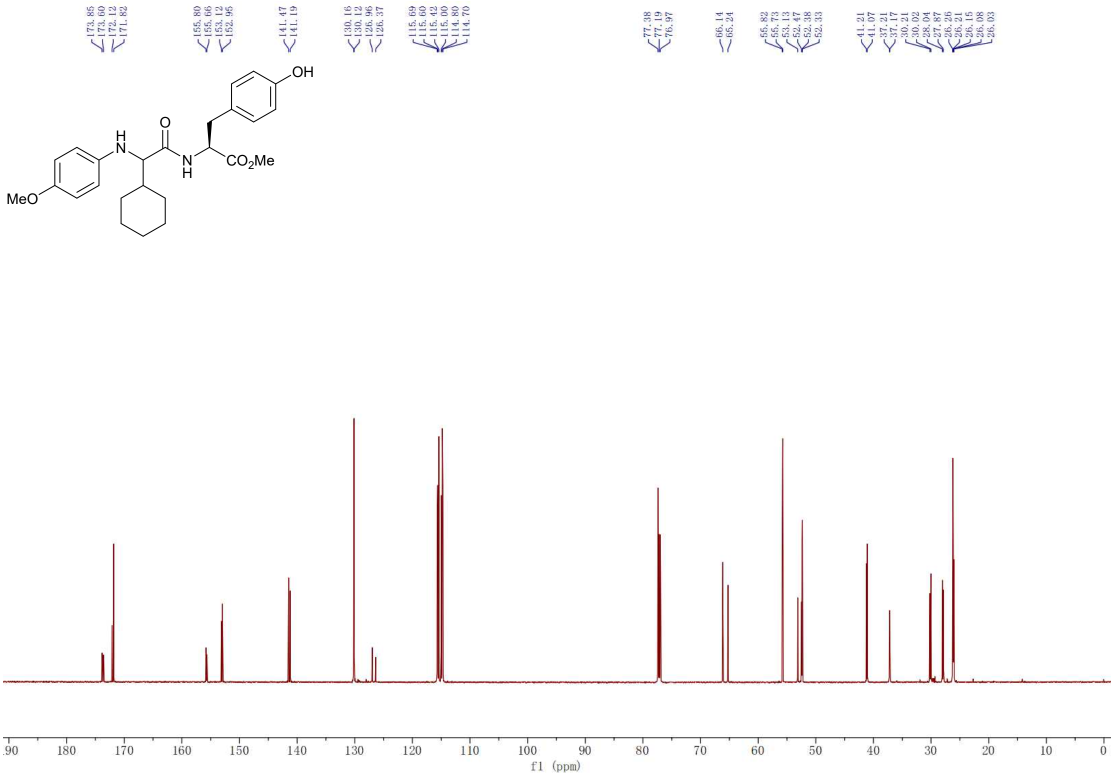
^{1}H NMR of **5fa** (600 MHz, $CDCl_3$)



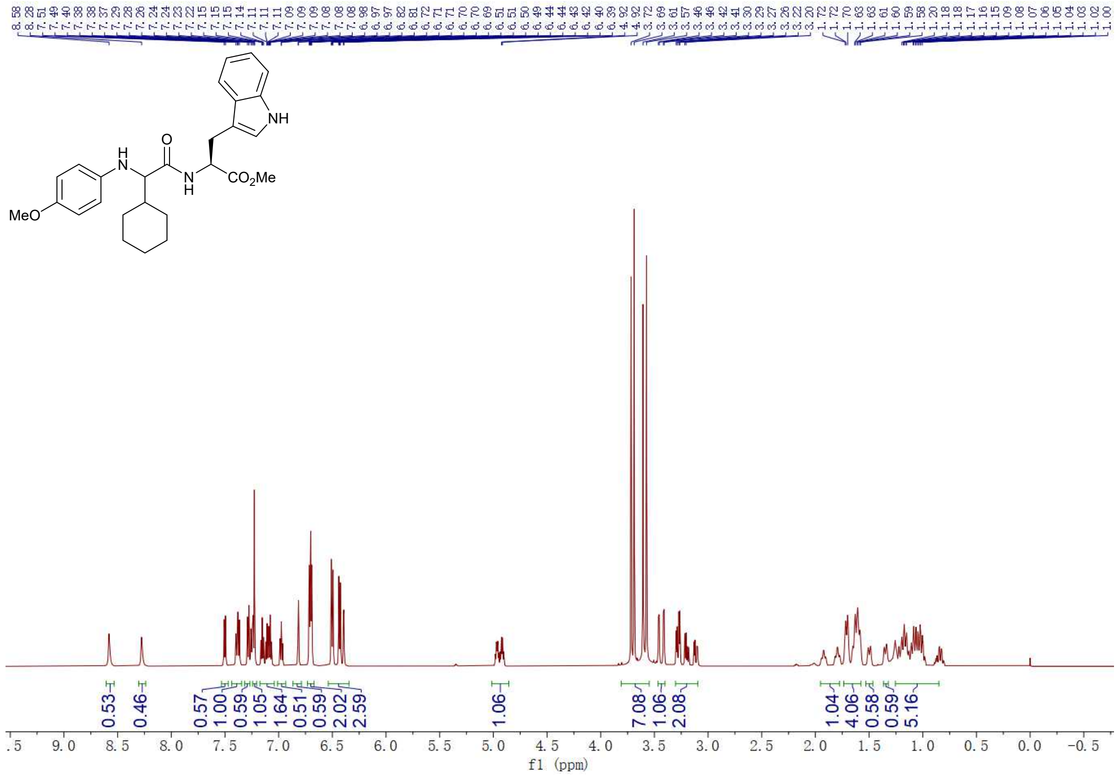
^{13}C NMR of **5fa** (151 MHz, $CDCl_3$)



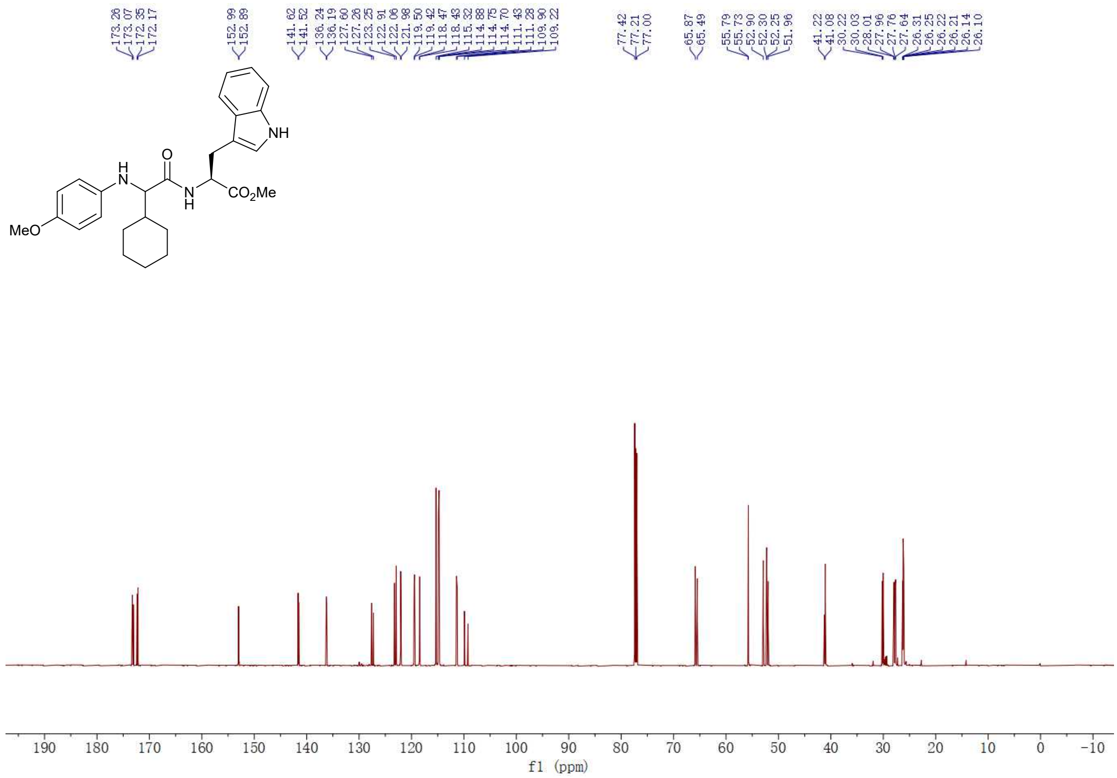
^{1}H NMR of **5ma** (600 MHz, $CDCl_3$)



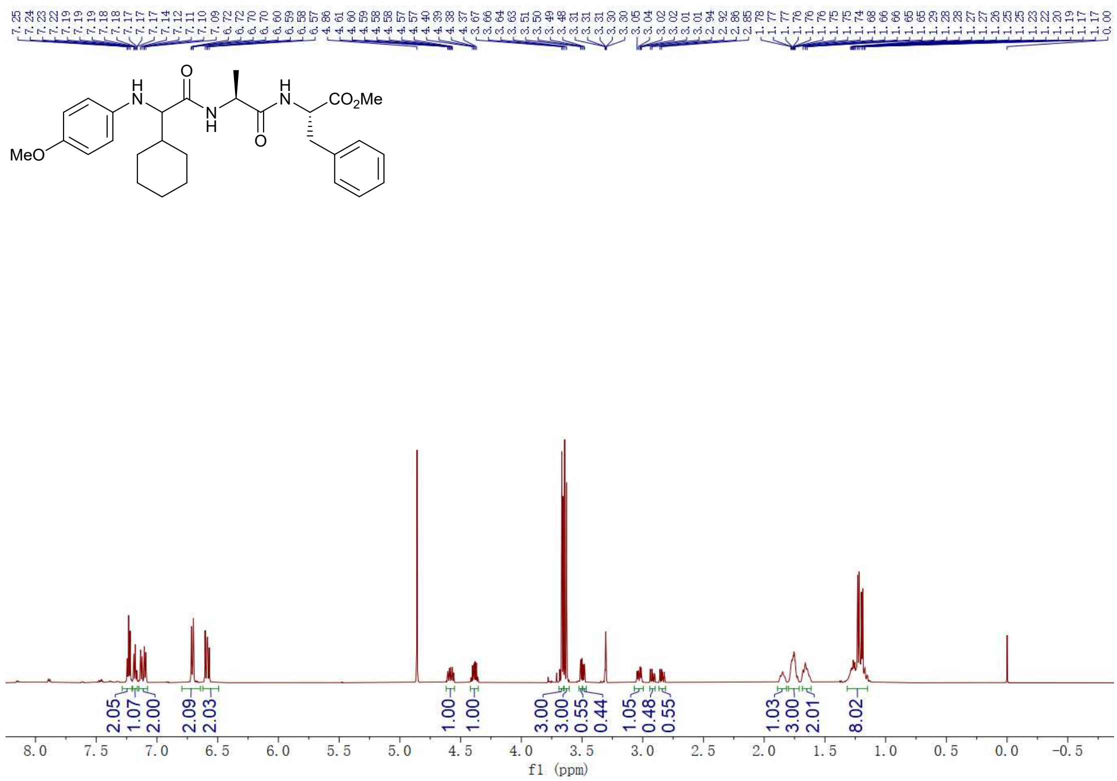
^{13}C NMR of **5ma** (151 MHz, $CDCl_3$)



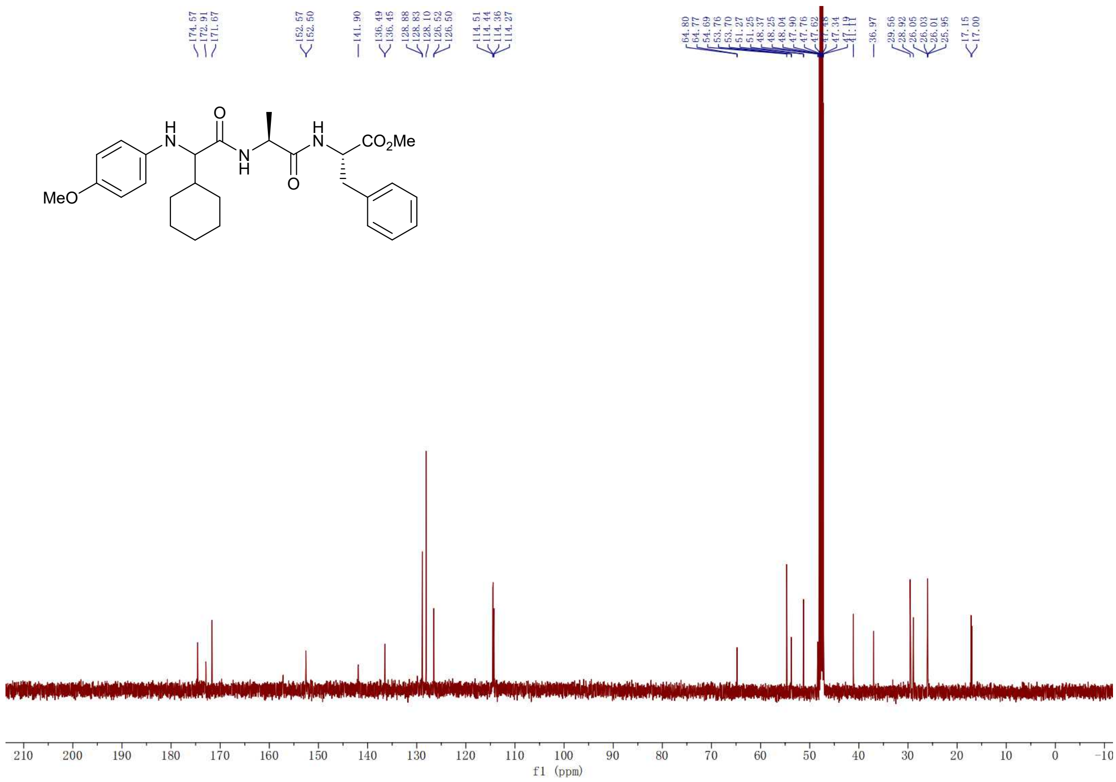
^{1}**H NMR** of **5ga** (600 MHz, $CDCl_3$)



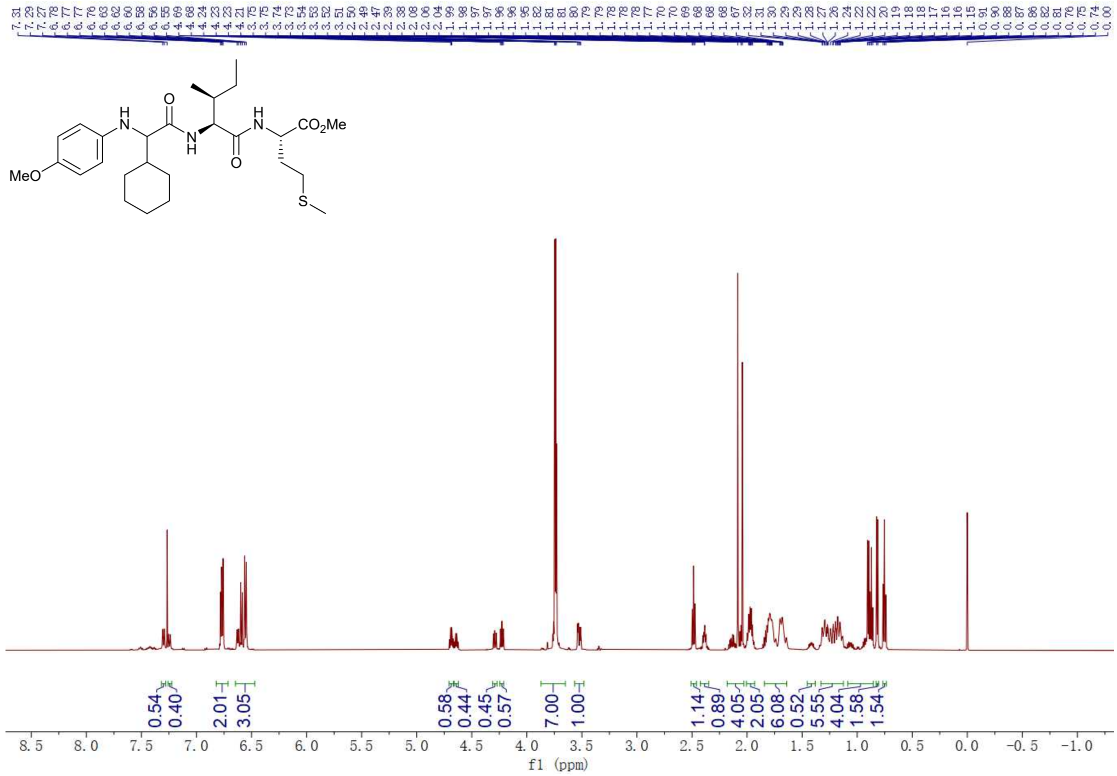
^{13}**C NMR** of **5ga** (151 MHz, $CDCl_3$)



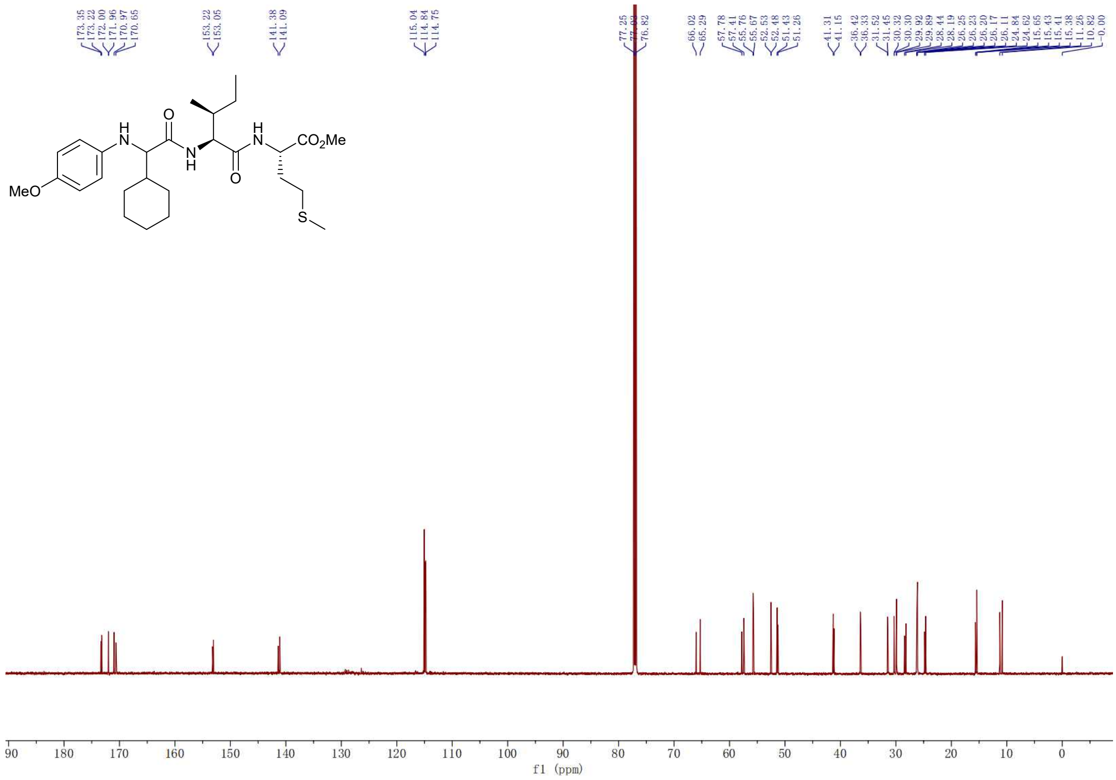
^{1}H NMR of **5ha** (600 MHz, MeOD)



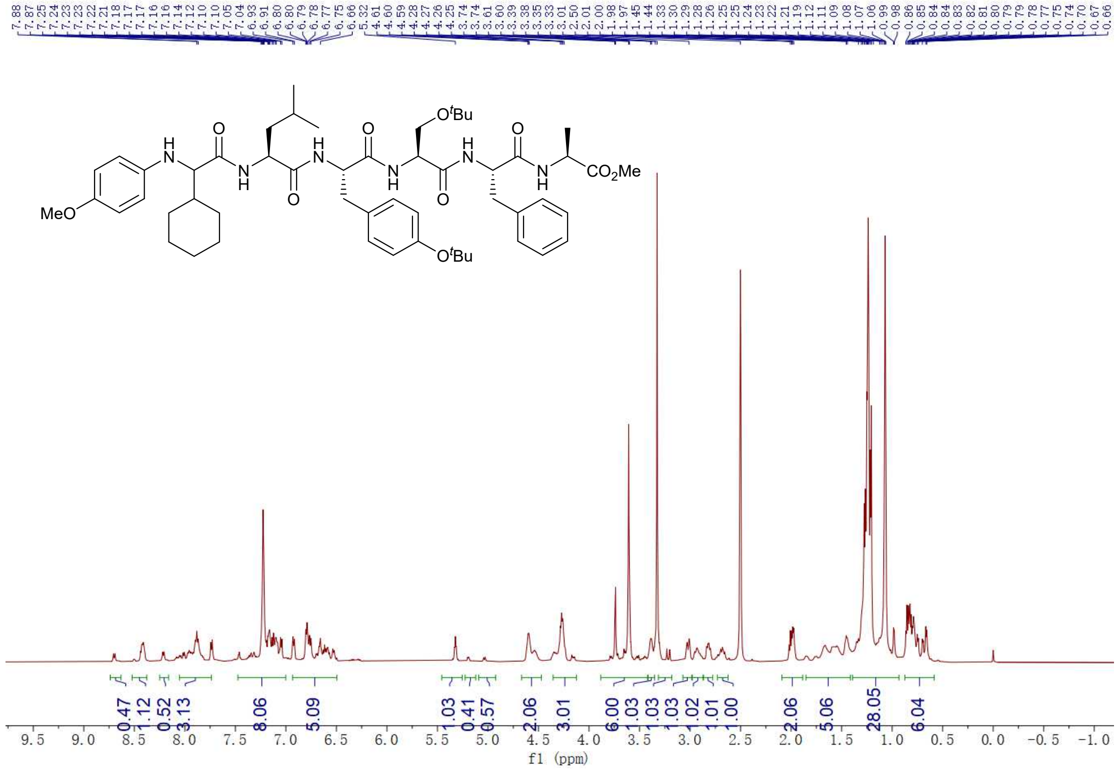
^{13}C NMR of **5ha** (151 MHz, $CDCl_3$)



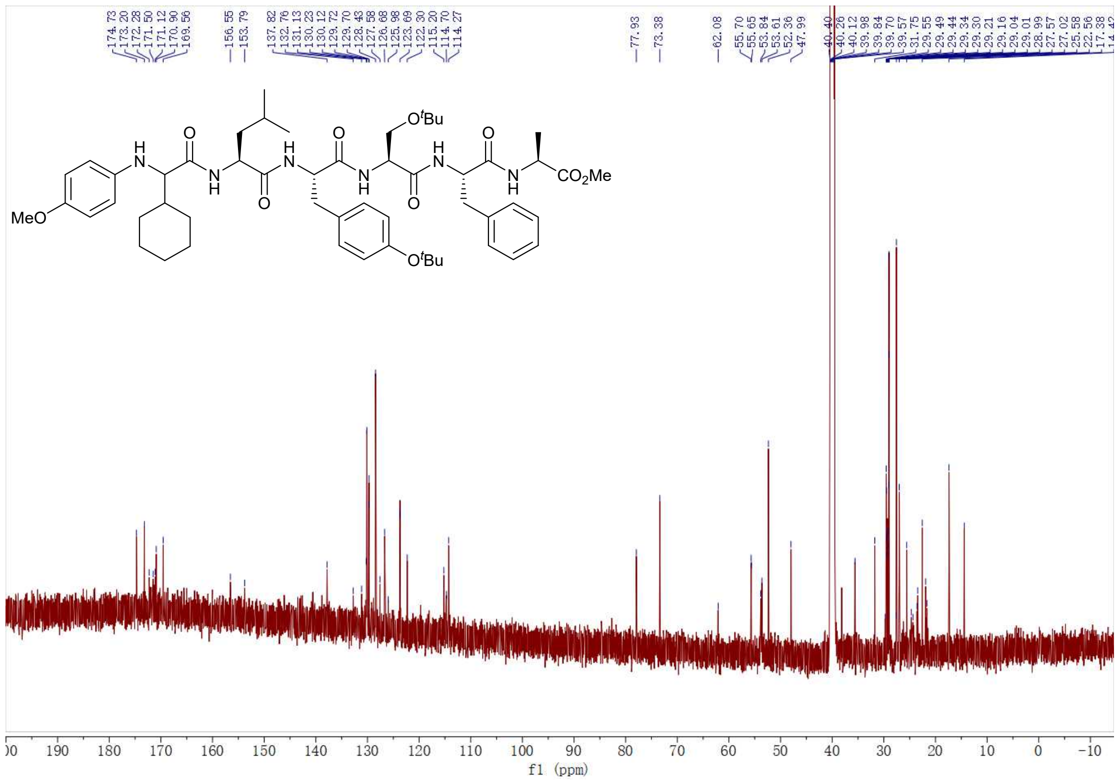
^{1}H NMR of **5ia** (600 MHz, $CDCl_3$)



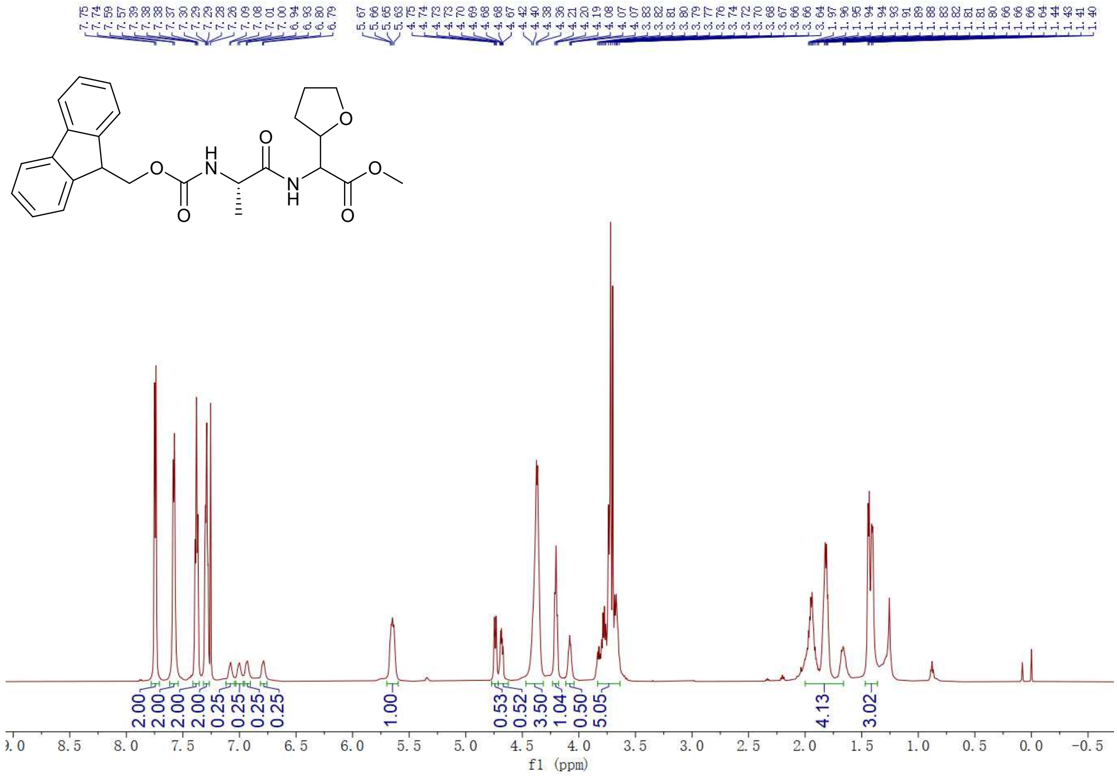
^{13}C NMR of **5ia** (151 MHz, $CDCl_3$)



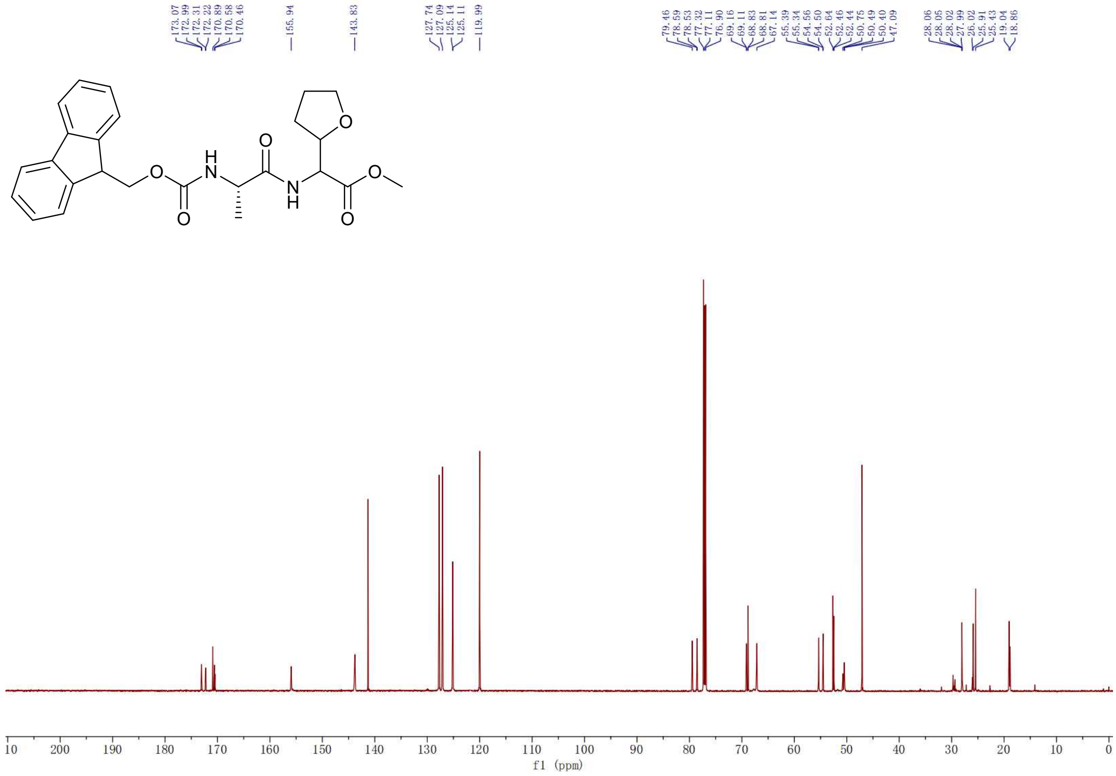
^{1}**H NMR** of **5ka** (600 MHz, DMSO-d_6)



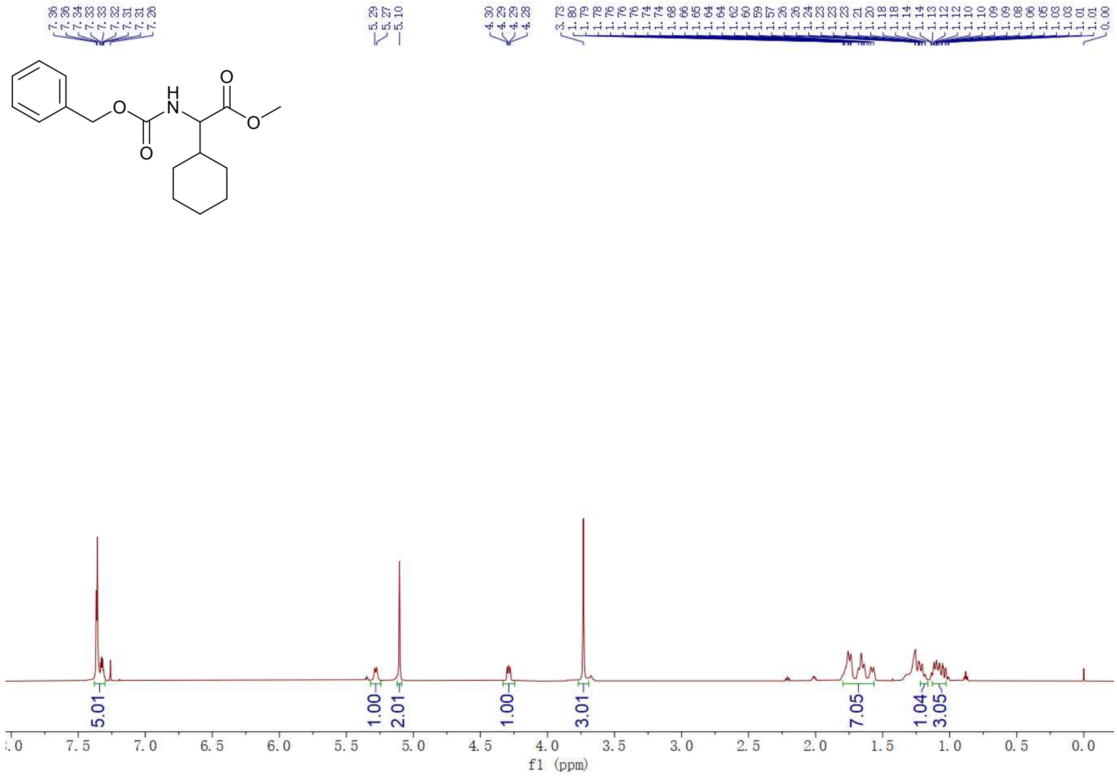
^{13}**C NMR** of **5ka** (151 MHz, DMSO-d_6)



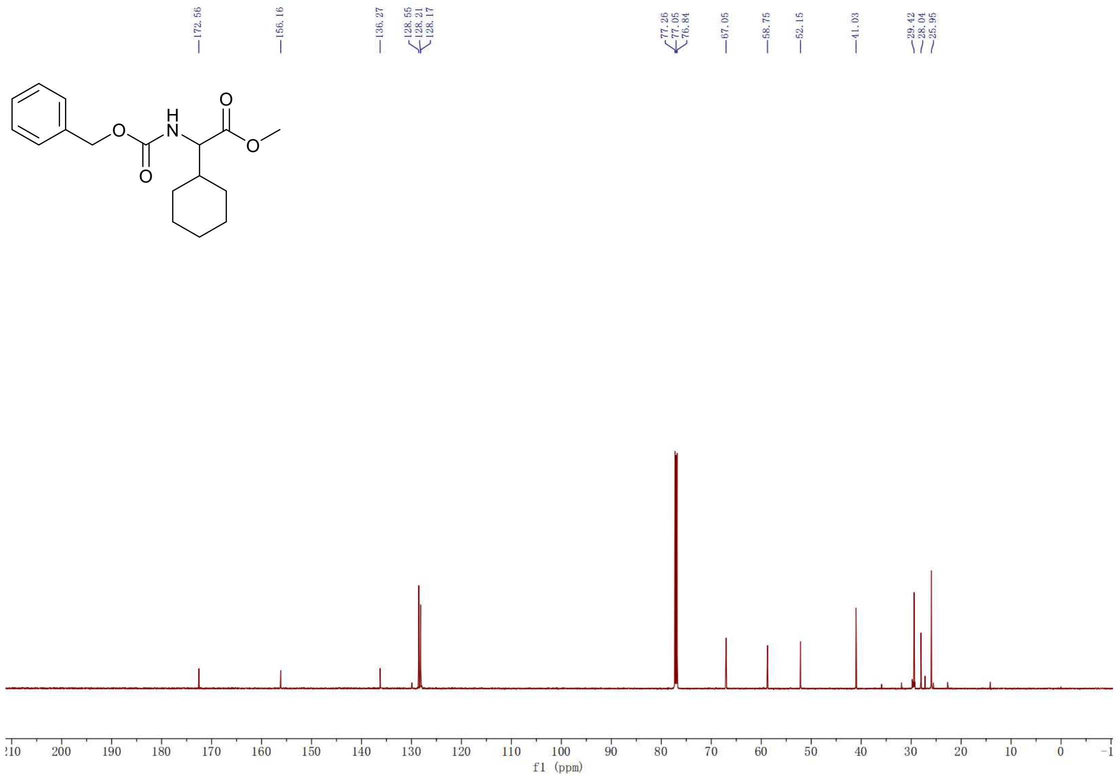
^{1}H NMR of **6** (600 MHz, $CDCl_3$)



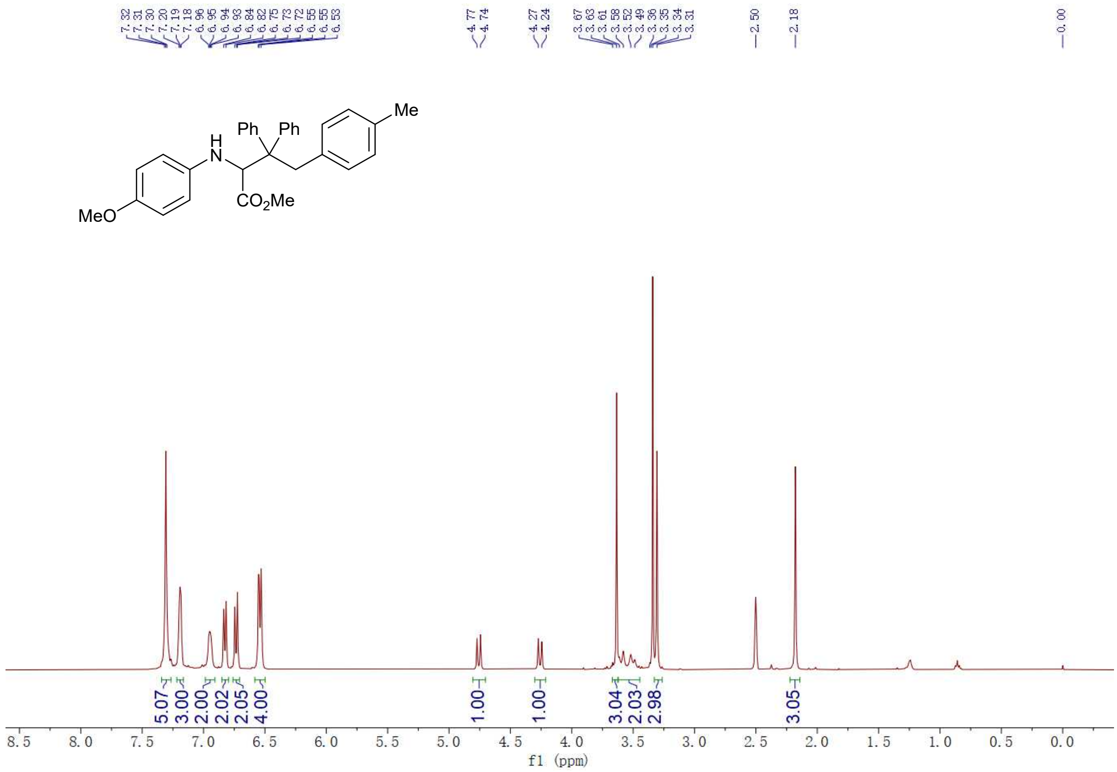
^{13}C NMR of **6** (151 MHz, $CDCl_3$)



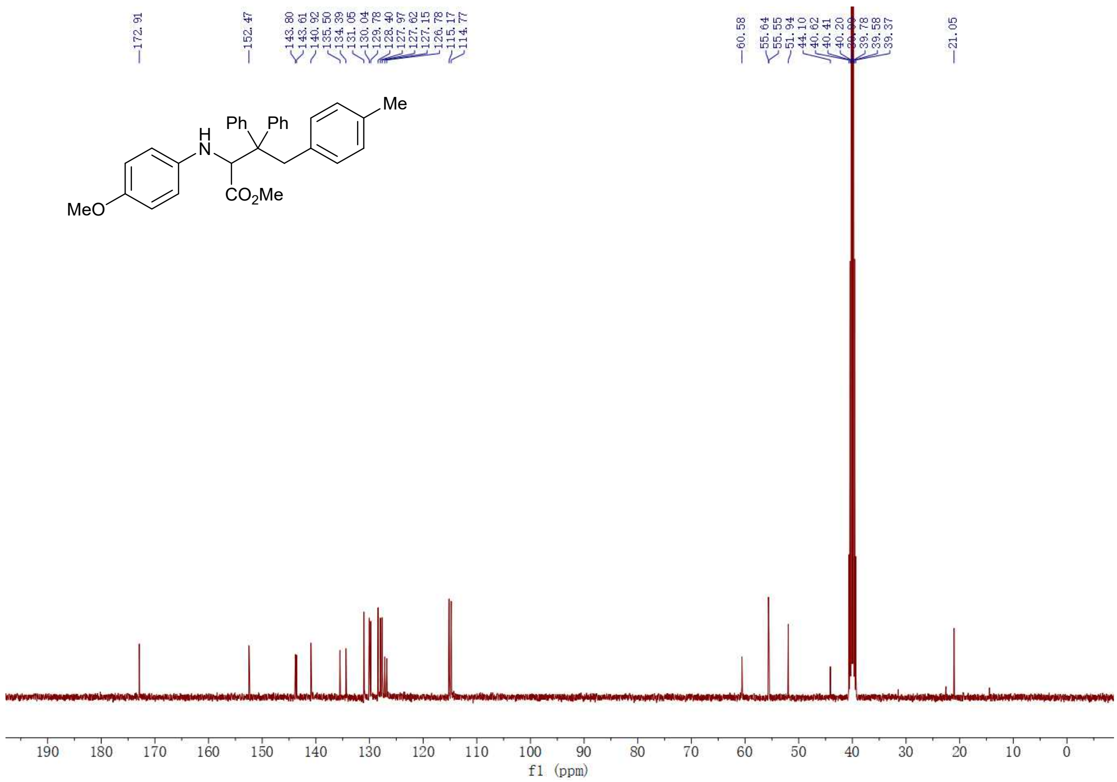
^{1}H NMR of **7** (600 MHz, $CDCl_3$)



^{13}C NMR of **7** (151 MHz, $CDCl_3$)



^{1}**H NMR** of **8** (400 MHz, DMSO-d_6)



^{13}**C NMR** of **8** (101 MHz, DMSO-d_6)