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Electronic Supplementary Information

Photo-induced Preparation of Unnatural α-Amino Acids: Synthesis and Characterization of Novel Leu^5-Enkephalin Analogues

Hongxiang Xue, Mengzhun Guo, Chao Wang,* Yuxuan Shen, Rupeng Qi, Yifei Wu, Zhaoqing Xu* and Min Chang*

Contents

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 a Bruker 300 and a Bruker 400 instrument spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as internal standard unless otherwise stated. Data for ^1H 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 br = 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) and column chromatography purifications were carried out using silica gel GF254. 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 further characterized by high resolution mass spectra (HRMS, ESI source).

Animals

Male Kunming strain mice (Experimental Animal Centre of Lanzhou University, Lanzhou, China) weighing approximately 22 g were housed in groups (4–6 per cage) in an environment with a controlled temperature (22 ± 1°C) and a 12 h light/dark cycle. All the animals had access to food and water ad libitum. All the experimental protocols were approved by the Ethics Committee of Lanzhou University (No.: SYXK Gan 2009-0005) and followed the guidelines formulated by the European Community (2010/63/EU). Animal studies are reported in compliance with the ARRIVE guidelines (Kilkenny et al., 2010). The mice were divided randomly into groups on the day of the experiment. The studies were blinded to treatment assignment and outcome assessment.

Tail-flick test

Nociceptive responses in mice were confirmed using the tail-flick test as previously described (Li et al., 2016a). Briefly, the tail of the mouse was positioned in a groove underneath a radiant heat source. The intensity of the heat source was adjusted to the baseline of naïve mice between 3–5 s, and a cut-off time of 10 s was set in this study. The latency was recorded before and at 15, 30, 45, 60, 90, 120, and 240 min post-injection. Maximal possible effect (MPE) was used to quantify the antinociceptive effects as follows: MPE(%) = 100 × [(post-drug response-baseline response)/(cut-off response-baseline response)].

2. Synthesis of substrates

Preparation of alkyl chlorides

Esters, amides of *N*-aryl-substituted glycine,[1] dipeptides,[2] tripeptides[2] and *N*-aryl tetrahydroisoquinoline[3] were all prepared according to previous reports. Other peptides were synthesized via solid phase synthesis. Alkyl chlorides and alkyl iodides were prepared according to the previous reported literatures.[4] **2h, 2k** and **2m** were purchased from Energy and Innochem.

Preparation of **2l**: PCl_3 (0.42 equiv) was added dropwise to a solution of 2-methyl-1-phenyl-2-propanol and pyridine (0.42 equiv) in anhydrous hexanes (0.5 M in alcohol) at 0 °C. After stirring

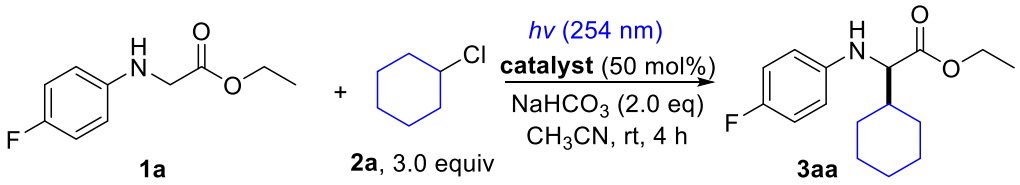
at 0 °C for 2 h, the reaction mixture was allowed to warm to room temperature, and it was stirred for an additional 3 h. Next, the reaction mixture was diluted with Et_2O, washed (water, saturated $NaHCO_3$, and brine), dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was purified by column chromatography (hexane) and the title compound **2k** was obtained. The NMR data are consistent with a previous report.[5]

3. General procedures of C(sp^3)-H alkylation

3.1 Optimization of reaction conditions

3.1.1 Optimization for the coupling of 1a and cyclohexyl chloride

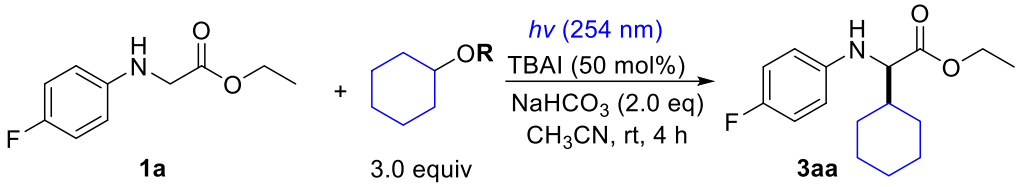
Table S1. Catalyst screening for the coupling of 1a and 2a[a]



Entry	Catalyst	Yield (%)[b]	Entry	Catalyst	Yield (%)[b]
1	LiI	0	***4***	***TBAI***	***25***
2	NaI	0	5	TBAB	0
3	KI	0	6	--	0

[a] 0.1 mmol scale. [b] Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

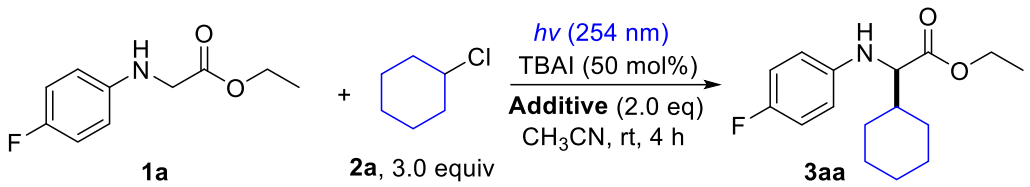
Table S2. Cyclohexyl alcohol and cyclohexyl esters screening for the coupling of 1a and 2a[a]



Entry	R	Yield (%)[b]	Entry	R	Yield (%)[b]
1	H	0	3	Ts	0
2	Ac	0	4	Boc	0

[a] 0.1 mmol scale. [b] Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

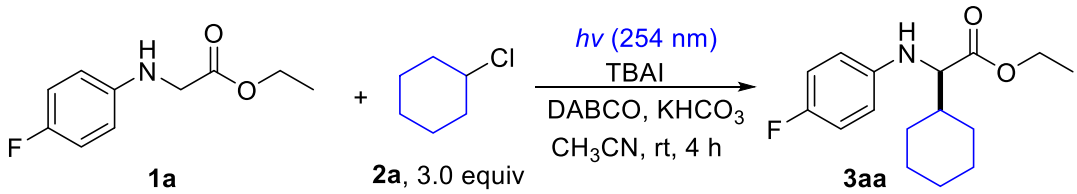
Table S3. Base screening for the coupling of 1a and 2a[a]



Entry	Additive	Yield (%)[b]	Entry	Additive	Yield (%)[b]
1	$NaHCO_3$	25	9	CsF	16
2	Cs_2CO_3	9	10	KF	17
3	K_2CO_3	12	11	Et_3N	17
4	Na_2CO_3	21	12	*i*-Pr_2NH	21
5	KOAc	18	13	Et_2NH	16
6	***$KHCO_3$***	***28***	***14***	***DABCO***	***31***
7	K_2HPO_4	17	***15[c]***	***DABCO/$KHCO_3$***	***40***
8	K_3PO_4	20			

[a] 0.1 mmol scale. [b] Yield was determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c] 2.0 equiv DABCO and 2.0 equiv $KHCO_3$ were added.

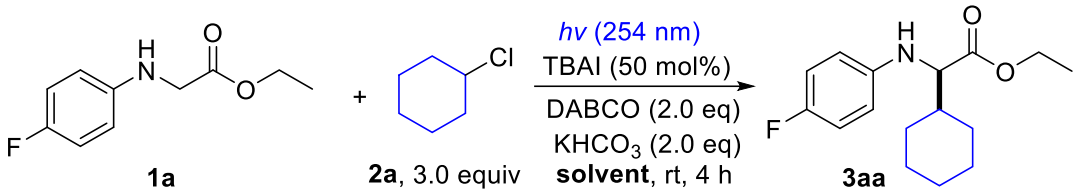
Table S4. Catalyst and additive loading screening for the coupling of 1a and 2a[a]



Entry	TBAI (eq)	DABCO (eq)	$KHCO_3$ (eq)	Yield (%)[b]
1	***0.5***	***2.0***	***2.0***	***40***
2	0.4	2.0	2.0	31
3	0.5	2.0	3.0	40
4	0.5	3.0	2.0	40
5	0.5	1.0	2.0	34
6	0.5	2.0	1.0	35
7	--	2.0	2.0	<5
8	0.5	--	2.0	28
9	0.5	2.0	--	31
10	--	--	2.0	0
11	--	2.0	--	trace
12	0.5	--	--	0

[a] 0.1 mmol scale. [b] Yield was determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

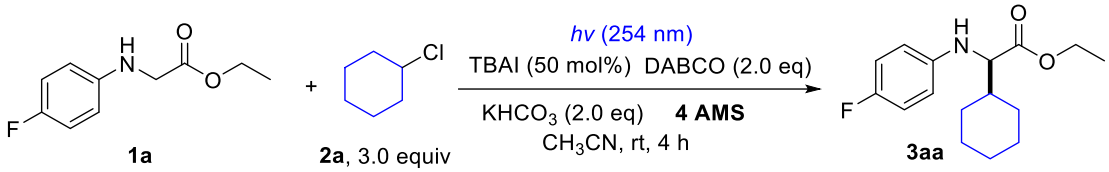
Table S5. Solvent screening for the coupling of 1a and 2a[a]



Entry	Solvent	Yield (%)[b]	Entry	Solvent	Yield (%)[b]
1	DMF	19	6	MeOH	trace
2	DCM	trace	7	THF	29
3	acetone	trace	***8***	***CH$_3$CN***	***40***
4	DMSO	28	9	1,4-dioxane	27
5	toluene	trace			

[a] 0.1 mmol scale. [b] Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

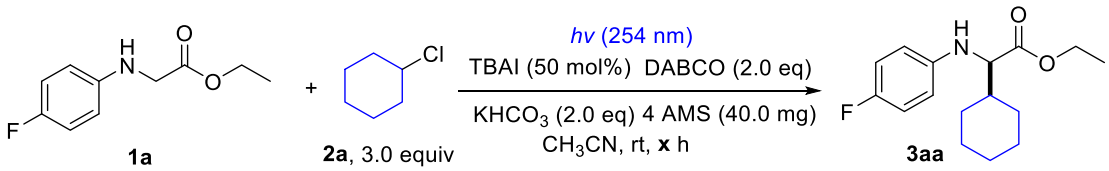
Table S6. 4 ÅMS loading screening for the coupling of 1a and 2a[a]



Entry	4ÅMS dosage	Yield(%)[b]
1	20.0 mg	42
2	***40.0 mg***	***45***
3	60.0 mg	45

[a] 0.1 mmol scale. [b] Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

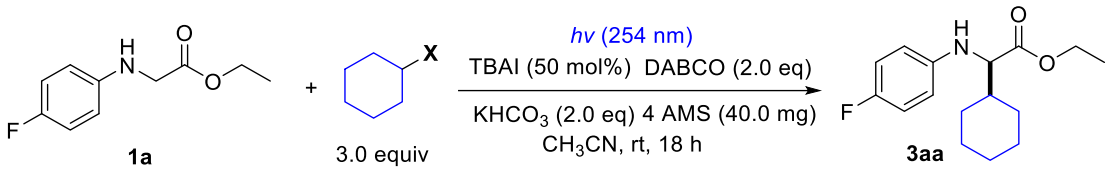
Table S7. Reaction time screening for the coupling of 1a and 2a[a]



Entry	**x**	Yield(%)[b]
1	4	45
2	12	58
3	***18***	***72***
4	24	71

[a] 0.1 mmol scale. [b] Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

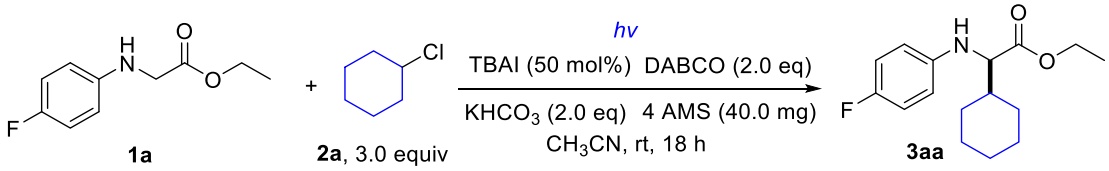
Table S8. Other alkyl halides screening for the coupling of 1a and 2a[a]



Entry	X	Yield(%)[b]
1	X = Br	35
2	X = I	48

[a] 0.1 mmol scale. [b] Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Table S9. Light sources screening for the coupling of 1a and 2a[a]

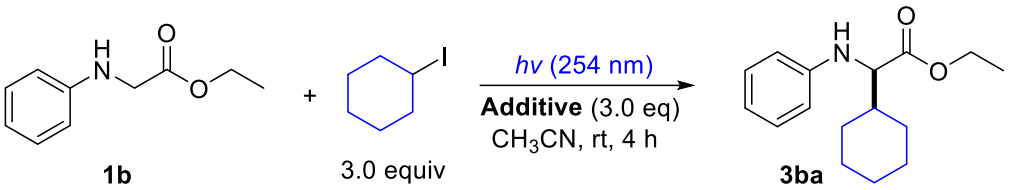


Entry	Light sources	Yield(%)[b]
1	***100 W UVC compact fluorescent light bulbs***	***72***
2	50 W UVC compact fluorescent light bulbs	37
3	80 W low-pressure mercury lamp (365 nm)	0
4	80 W UVB CFL (280-320 nm)	0
5	30 W blue LED	0
6	30 W white LED	0

[a] 0.1 mmol scale. [b] Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

3.1.2 Optimization for the coupling of 1b and cyclohexyl iodide

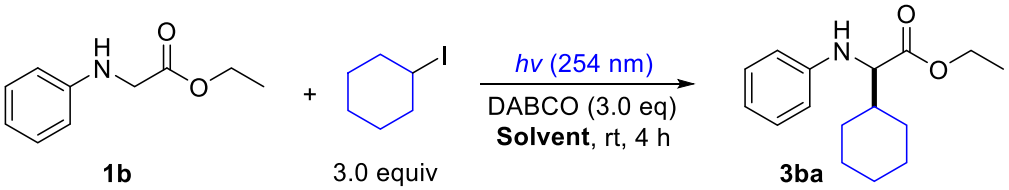
Table S10. Base screening for the coupling of 1b and cyclohexyl iodide[a]



Entry	Additive	Yield (%)[b]	Entry	Additive	Yield (%)[b]
1	$NaHCO_3$	0	***9***	***DABCO***	***40***
2	KH_2PO_4	0	10	DBU	trace
3	NaOH	0	11	2,6-lutidine	trace
4	Na_2CO_3	0	12	TMEDA	trace
5	NaOAc	0	13	HMPA	trace
6	LiO^{t}Bu	0	14	DIPEA	trace
7	K_2HPO_4	0	15	Et_3N	trace
8	K_3PO_4	0	16	DMAP	trace

[a] 0.1 mmol scale. [b] Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

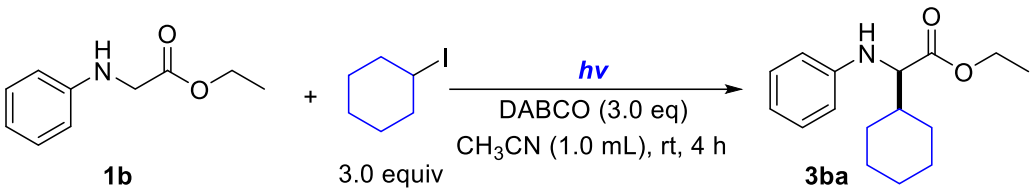
Table S11. Solvent screening for the coupling of 1b and cyclohexyl iodide[a]



Entry	Solvent	Yield (%)[b]	Entry	Solvent	Yield (%)[b]
1	DMF	0	6	MeOH	0
2	DCM	0	7	THF	0
3	acetone	0	***8***	***CH$_3$CN***	***40***
4	DMSO	trace	9	1,4-dioxane	0
5	toluene	0			

[a] 0.1 mmol scale. [b] Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

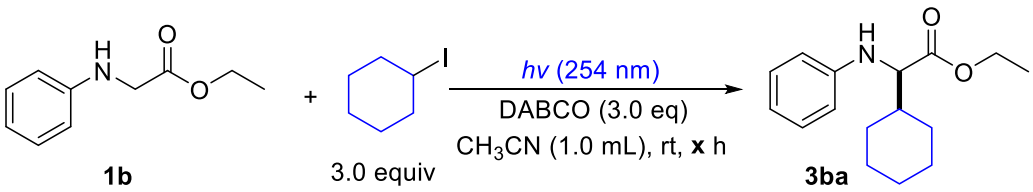
Table S12. Light source screening for the coupling of 1b and cyclohexyl iodide[a]



Entry	Light sources	Yield(%)[b]
1	100 W UVC compact fluorescent light bulbs	40
2	***50 W UVC compact fluorescent light bulbs***	***46***
3	25 W UVC compact fluorescent light bulbs	42
4	80 W low-pressure mercury lamp (365 nm)	0
5	80 W UVB CFL (280-320 nm)	0
6	30 W blue LED	0
7	30 W white LED	0

[a] 0.1 mmol scale. [b] Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

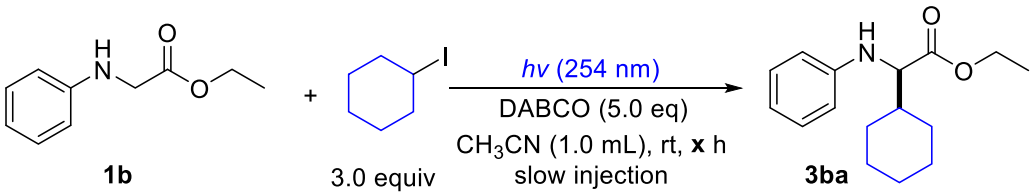
Table S13. Reaction time screening for the coupling of 1b and cyclohexyl iodide[a]



Entry	**x**	Yield(%)[b]
1	4	40
2	8	44
3	12	47
4	***18***	***53***
5	24	48

[a] 0.1 mmol scale. [b] Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Table S14. Slow injection for the coupling of 1b and cyclohexyl iodide[a]



Entry	Conditions	Yield(%)[b]
1	UVC CFL 50-W, 12 h	65
2	UVC CFL 50-W, 18 h	70
3	UVC CFL 25-W, 12 h	45
4	***UVC CFL 25-W, 18 h***	***80***
5	UVC CFL 25-W, 24 h	67

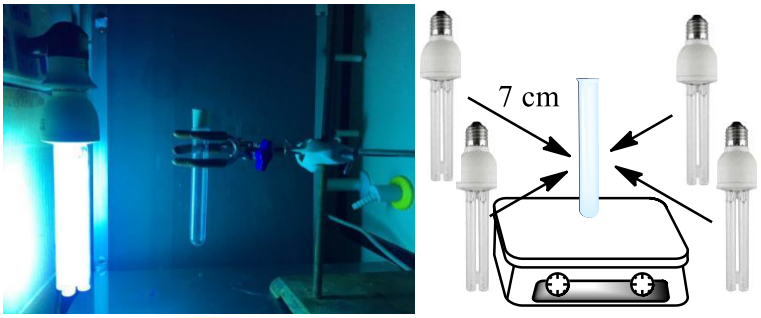
[a] 0.1 mmol scale. [b] Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

3.2 General procedure for the synthesis of 3

General procedure of Method A: To an oven-dried 10 mL quartz test tube with a stirring bar was added derivatives of glycine or peptide (0.2 mmol), TBAI (0.1 mmol, 37 mg), $KHCO_3$ (0.4 mmol, 40 mg), DABCO (0.4 mmol, 44.8 mg) and 4ÅMS (80.0 mg). Then, air was withdrawn and backfilled with Ar (three times). CH_3CN (1.0 mL) and alkyl chloride (0.6 mmol) were added in turn by syringe. Thereafter, the test tube was transferred to a UV photoreactor (4×25 W, see Scheme S1 for details), where it was irradiated at 254 nm for 18 h. Eighteen hours later, the reaction was quenched with water (2.0 mL), extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated in *vacuo* and purified by column chromatography (hexane/ethyl acetate) to afford the product **3**.

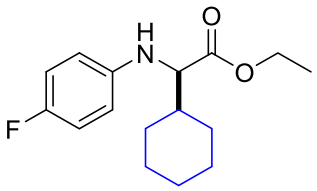
General procedure of Method B: To an oven-dried 10 mL quartz test tube with a stirring bar was added derivatives of glycine or peptide (0.2 mmol), DABCO (1.0 mmol, 112.0 mg). Then, air was withdrawn and backfilled with Ar (three times). CH_3CN (0.8 mL) was added by syringe. Thereafter, the test tube was transferred to a UV photoreactor (25 W, see Scheme S1 for details), alkyl iodide (0.6 mmol) was dissolved in CH_3CN (1.2 mL) and slowly added 18 h by syringe pump. Eighteen hours later, the reaction was quenched with water (2.0 mL), extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated in *vacuo* and purified by column chromatography (hexane/ethyl acetate) to afford the product.

Scheme S1. Placement of CFL around quartz test tube



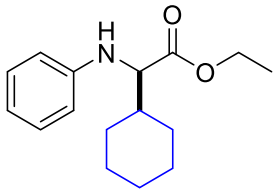
Instructions on placement of CFL: Four 25 W UVC compact fluorescent light bulbs were placed around the quartz test tube and the distance was about 7 cm. A cardboard box lined with tin foil was placed over the lamps and stir plate. In one side of the cardboard box, part of the side was cut out, and a high-speed fan was setup into for dissipating heat.

4. Characterization of products



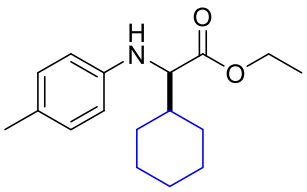
3aa

ethyl 2-cyclohexyl-2-((4-fluorophenyl)amino)acetate (3aa): 38.0 mg, yield: 68%. Yellow solid. M. p. 52 – 53 °C. Known compound.[2] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.93 – 6.80 (m, 2H), 6.62 – 6.51 (m, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.00 (d, *J* = 9.7 Hz, 1H), 3.77 (dd, *J* = 9.7, 6.1 Hz, 1H), 1.89 – 1.64 (m, 6H), 1.36 – 1.06 (m, 8H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.68, 156.15 (d, *J* = 235.7 Hz), 143.80, 115.65 (d, *J* = 22.3 Hz), 114.60 (d, *J* = 7.5 Hz), 62.92, 60.81, 41.21, 29.61, 29.15, 26.14, 26.04, 26.01, 14.27. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -127.12. HRMS (ESI) $C_{16}H_{22}FNNaO_2$ [M + Na]$^+$calcd: 302.1527, found: 302.1524.



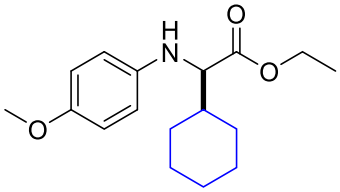
3ba

ethyl 2-cyclohexyl-2-(phenylamino)acetate (3ba): 36.0 mg, yield: 69%. Yellow solid. M. p. 48 – 49 °C. Known compound.[2] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.16 (t, *J* = 7.9 Hz, 2H), 6.72 (t, *J* = 7.3 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 3H), 3.86 (d, *J* = 6.0 Hz, 1H), 1.89 – 1.65 (m, 6H), 1.35 – 1.06 (m, 8H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.63, 147.39, 129.22, 118.03, 113.47, 61.98, 60.76, 41.25, 29.56, 29.15, 26.15, 26.06, 26.01, 14.26. HRMS (ESI) $C_{16}H_{23}NNaO_2$ [M + Na]$^+$calcd: 284.1621, found: 284.1629.



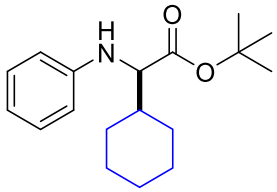
3ca

ethyl 2-cyclohexyl-2-(p-tolylamino)acetate (3ca): 39.0 mg, yield: 71%. Yellow oil. Known compound.[2] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.96 (d, *J* = 8.2 Hz, 2H), 6.54 (d, *J* = 8.4 Hz, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 4.02 (d, *J* = 9.3 Hz, 1H), 3.82 (dd, *J* = 9.3, 6.1 Hz, 1H), 2.22 (s, 3H), 1.89 – 1.64 (m, 6H), 1.27 – 1.05 (m, 8H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.76, 145.12, 129.65, 127.17, 113.62, 62.34, 60.62, 41.21, 29.54, 29.11, 26.13, 26.02, 25.98, 20.28, 14.22. HRMS (ESI) $C_{17}H_{25}NNaO_2$ $[M + Na]^+$calcd: 298.1778, found: 298.1781.



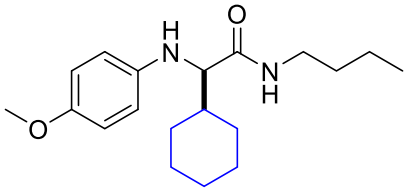
3da

ethyl 2-cyclohexyl-2-((4-methoxyphenyl)amino)acetate (3da):38.0 mg, yield: 65%. Yellow solid. M. p. 55 –56 °C. Known compound.[2] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.79 – 6.72 (m, 2H), 6.64 – 6.57 (m, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.87 (br, 1H), 3.79 – 3.71 (m, 4H), 1.90 – 1.64 (m, 6H), 1.32 – 1.06 (m, 8H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.00, 152.55, 141.61, 115.14, 114.79, 63.34, 60.68, 55.69, 41.26, 29.64, 29.18, 26.18, 26.07, 26.05, 14.28. HRMS (ESI) $C_{17}H_{25}NNaO_3$ $[M + Na]^+$calcd: 314.1727, found: 314.1731.



3ea

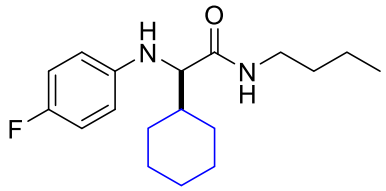
***tert*-butyl 2-cyclohexyl-2-(phenylamino)acetate (3ea):** 36.0 mg, yield: 62%. Yellow solid. M. p. 73 – 74 °C. Known compound.[2] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.15 (t, *J* = 7.8 Hz, 2H), 6.70 (t, *J* = 7.3 Hz, 1H), 6.62 (d, *J* = 8.2 Hz, 2H), 4.14 (d, *J* = 8.1 Hz, 1H), 3.80 – 3.71 (m, 1H), 1.87 – 1.63 (m, 6H), 1.42 (s, 9H), 1.35 – 1.10 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.76, 147.62, 129.11, 117.77, 113.49, 81.33, 62.38, 41.25, 29.46, 29.10, 28.03, 26.22, 26.12, 26.06. HRMS (ESI) $C_{18}H_{27}NNaO_2$ $[M + Na]^+$calcd: 312.1934, found: 312.1937.



3fa

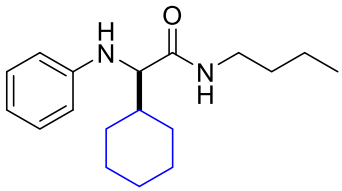
***N*-butyl-2-cyclohexyl-2-((4-methoxyphenyl)amino)acetamide (3fa):** 32.0 mg, yield: 50%. Yellow oil. Known compound.[6] **^{1}H NMR** (300 MHz, CDCl3) δ 6.90 (br, 1H), 6.78 (d, J = 8.8 Hz,

2H), 6.56 (d, J = 8.8 Hz, 2H), 3.75 (s, 3H), 3.69 (br, 1H),3.46 (d, J = 3.3 Hz, 1H), 3.36 – 3.13 (m, 2H), 2.07 – 1.96 (m, 1H), 1.80 – 1.65 (m, 5H), 1.49 – 1.07 (m, 9H), 0.87 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.65, 152.85, 141.48, 114.71, 114.64, 65.73, 55.67, 41.04, 38.73, 31.61, 30.33, 27.93, 26.12, 19.96, 13.66. HRMS (ESI) $C_{19}H_{30}N_2NaO_2$ $[M + Na]^+$calcd: 341.2199, found: 341.2201.



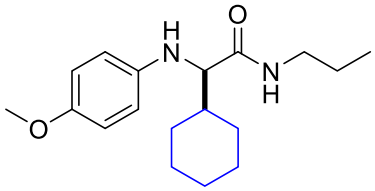
3ga

***N*-butyl-2-cyclohexyl-2-((4-fluorophenyl)amino)acetamide (3ga):** 33.0 mg, yield: 54%. Yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.95 – 6.86 (m, 3H), 6.64 – 6.59 (m, 2H), 3.51 (d, *J* = 3.9 Hz, 1H), 3.29 – 3.19 (m, 2H), 2.02 (t,*J* = 10.3 Hz, 1H), 1.82 – 1.69 (m, 5H), 1.48 – 1.06 (m, 10H), 0.86 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.86, 156.93 (d, *J* = 237.8 Hz), 142.92, 115.83 (d, *J* = 22.5 Hz), 115.23, 65.98, 40.88, 38.88, 31.60, 30.17, 28.28, 26.17, 26.16, 26.07, 19.97, 13.63. HRMS (ESI) $C_{18}H_{27}FN_2NaO$ $[M + Na]^+$calcd: 329.2000, found: 329.2002.



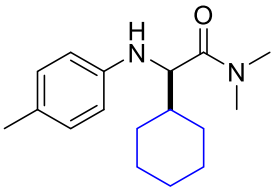
3ha

***N*-butyl-2-cyclohexyl-2-(phenylamino)acetamide (3ha):** 33.0 mg, yield: 57%. Colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.12 (dd, *J* = 8.3, 7.5 Hz, 2H), 6.72 (t, *J* = 7.3 Hz, 2H), 6.54 (d, *J* = 7.7 Hz, 2H), 3.85 (d, *J* = 2.9 Hz, 1H), 3.48 (t, *J* = 3.7 Hz, 1H), 3.28 – 3.05 (m, 2H), 2.02 – 1.91 (m, 1H), 1.85 – 1.59 (m, 5H), 1.41 – 1.28 (m, 2H), 1.26 – 1.00 (m, 7H), 0.79 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.39, 147.40, 129.30, 118.86, 113.64, 64.92, 40.99, 38.80, 31.61, 30.31, 28.00, 26.15, 19.96, 13.64. HRMS (ESI) $C_{18}H_{28}N_2NaO$ $[M + Na]^+$calcd: 311.2094, found: 311.2097.



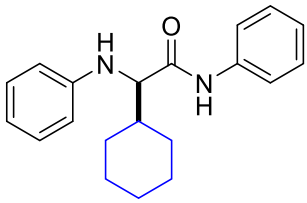
3ia

2-cyclohexyl-2-((4-methoxyphenyl)amino)-*N*-propylacetamide (3ia): 34.0 mg, yield: 56%. Colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.87 (s, 1H), 6.70 (d, *J* = 8.8 Hz, 2H), 6.50 (d, *J* = 8.8 Hz, 2H), 3.67 (s, 3H), 3.57 (br, 1H), 3.40 (d, *J* = 4.0 Hz, 1H), 3.14 (qt, *J* = 13.6, 7.0 Hz, 2H), 1.99 – 1.89 (m, 1H), 1.75 – 1.58 (m, 5H), 1.39 (dq, *J* = 14.6, 7.3 Hz, 2H), 1.29 – 1.00 (m, 5H), 0.77 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.71, 152.99, 141.38, 114.76, 65.84, 55.75, 41.00, 40.75, 30.34, 28.00, 26.13, 22.84, 11.30. HRMS (ESI) $C_{18}H_{28}N_2NaO_2$ $[M + Na]^+$calcd: 327.2043, found: 327.2048.



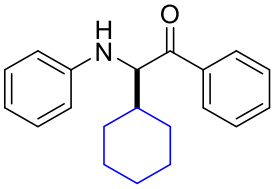
3ja

2-cyclohexyl-*N*,*N*-dimethyl-2-(*p*-tolylamino)acetamide (3ja): 34.0 mg, yield: 62%. White solid. M. p. 138–139°C. Known compound.[2] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.88 (d, *J* = 8.2 Hz, 2H), 6.49 (d, *J* = 8.3 Hz, 2H), 4.28 (br, 1H), 4.02 (br, 1H), 3.01 (s, 3H), 2.87 (s, 3H), 2.14 (s, 3H), 1.85 – 1.77 (m, 1H),1.69 – 1.58 (m, 5H),1.23 – 0.94 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.38, 146.09, 129.70, 127.02, 114.02, 58.95, 41.95, 37.27, 35.61, 30.20, 28.71, 26.21, 20.28. HRMS (ESI) $C_{17}H_{26}N_2NaO$ $[M + Na]^+$calcd: 297.1937, found: 297.1942.



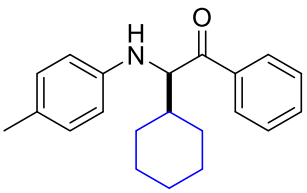
3ka

2-cyclohexyl-N-phenyl-2-(phenylamino)acetamide (3ka): 36.0 mg, yield: 58%. Yellow solid. M. p. 176 – 1 77 °C. Known compound.[2] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.69 (br, 1H), 7.53 (d, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 7.9 Hz, 2H), 7.22 (t, *J* = 7.9 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.84 (t, *J* = 7.3 Hz, 1H), 6.70 (d, *J* = 7.9 Hz, 2H), 4.03 (d, *J* = 2.1 Hz, 1H), 3.68 – 3.61 (m, 1H), 2.15 – 2.07 (m, 1H), 1.80 – 1.67 (m, 5H), 1.38 – 1.12 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.17, 147.24, 137.34, 129.51, 128.93, 124.35, 119.84, 119.60, 114.03, 65.90, 41.45, 30.30, 28.22, 26.23, 26.20, 26.05. HRMS (ESI) $C_{20}H_{24}N_2NaO$ $[M + Na]^+$calcd: 331.1781, found: 331.1783.



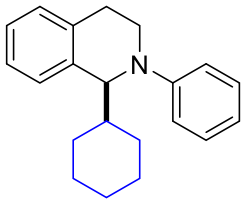
3la

2-cyclohexyl-1-phenyl-2-(phenylamino)ethanone (3la): 24.2 mg, yield: 41%. Yellow solid. M. p. 83 – 84 °C. Known compound.[2] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.01 – 7.94 (m, 2H), 7.61 (t, J = 7.3 Hz, 1H), 7.50 (t, J = 7.5 Hz, 2H), 7.15 (dd, J = 8.7, 7.2 Hz, 2H), 6.69 (t, J = 7.7 Hz, 3H), 4.90 (dd, J = 8.3, 4.1 Hz, 1H), 4.66 (d, J = 8.0 Hz, 1H), 1.89 – 1.57 (m, 6H), 1.44 – 1.04 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 201.21, 148.19, 136.06, 133.46, 129.27, 128.82, 128.33, 117.89, 113.85, 63.02, 41.97, 30.85, 27.71, 26.36, 26.13, 25.99. HRMS (ESI) $C_{20}H_{23}NNaO$ $[M + Na]^+$calcd: 316.1672, found: 316.1676.



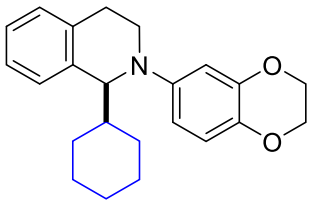
3ma

2-cyclohexyl-1-phenyl-2-(*p*-tolylamino)ethanone (3ma): 28.0 mg, yield: 46%. Yellow solid. M. p.78–79 °C. Known compound.[7] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.7 Hz, 2H), 7.50 (t, *J* = 7.0 Hz, 1H), 7.40 (t, *J* = 7.3 Hz, 2H), 6.88 (d, *J* = 7.8 Hz, 2H), 6.56 (d, *J* = 8.0 Hz, 2H), 4.77 (br, 1H), 4.43 (br, 1H), 2.13 (s, 3H), 1.78 – 1.61 (m, 4H), 1.53 (br, 2H), 1.36 – 1.24 (m, 1H), 1.24 – 0.99 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 201.46, 145.91, 136.07, 133.35, 129.71, 128.75, 128.22, 127.12, 114.02, 63.49, 41.90, 30.84, 27.71, 26.00, 20.37. HRMS (ESI) $C_{21}H_{26}NO$ $[M + H]^+$calcd: 308.2009, found: 308.2013.



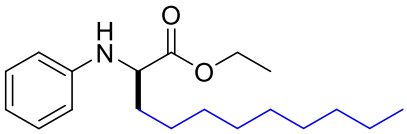
3na

1-cyclohexyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline (3na): 26.1 mg, yield: 45%. Yellow solid. M. p. 63 – 64 °C. Known compound.[8] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27 – 7.04 (m, 6H),, 6.85 (d, *J* = 8.4 Hz, 2H), 6.67 (t, *J* = 7.2 Hz, 1H), 4.42 (d, *J* = 8.1 Hz, 1H), 3.72 (dt, *J* = 12.0, 6.0 Hz, 1H), 3.52 – 3.39 (m, 1H), 3.11 – 2.91 (m, 2H), 2.01 – 1.93 (m, 1H), 1.75 – 1.60 (m, 5H), 1.22 – 1.00 (m, 5H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.85, 137.74, 135.21, 129.04, 128.27, 128.09, 126.49, 125.10, 116.16, 112.78, 63.65, 44.07, 42.91, 30.89, 30.62, 27.30, 26.62, 26.41, 26.30.



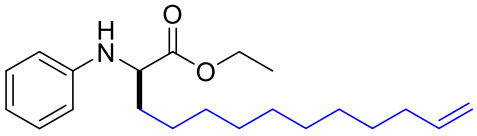
3oa

1-cyclohexyl-2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1,2,3,4-tetrahydroisoquinoline (3oa): 34.0 mg, yield: 48%. Colorless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.11 – 6.94 (m, 4H), 6.69 – 6.61 (m, 1H), 6.33 – 6.27 (m, 2H), 4.12 (dt, *J* = 13.6, 6.7 Hz, 5H), 3.58 (dt, *J* = 12.6, 6.4 Hz, 1H), 3.38 – 3.26 (m, 1H), 2.96 – 2.76 (m, 2H), 1.91 (d, *J* = 10.4 Hz, 1H), 1.66 – 1.53 (m, 5H), 1.15 – 0.90 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 145.54, 143.64, 137.68, 135.21, 134.91, 128.42, 128.27, 126.40, 125.00, 117.29, 107.11, 102.60, 64.75, 64.41, 64.21, 43.92, 43.22, 30.78, 26.92, 26.64, 26.42. HRMS (ESI) $C_{23}H_{28}NO_2$ $[M + H]^+$calcd: 350.2115, found: 350.2118.



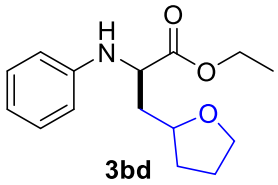
3bb

ethyl 2-(phenylamino)undecanoate (3bb): Method A: 33.0 mg, yield: 54%. Method B: 36.5 mg, yield: 60%. Yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.17 (t, *J* = 7.9 Hz, 2H), 6.73 (t, *J* = 7.3 Hz, 1H), 6.62 (d, *J* = 7.8 Hz, 2H), 4.23 – 3.98 (m, 4H), 1.91 – 1.66 (m, 2H), 1.46 – 1.37 (m, 2H), 1.29 – 1.20 (m, 15H), 0.88 (t, *J* = 6.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.29, 146.95, 129.28, 118.15, 113.40, 60.95, 56.65, 33.08, 31.85, 29.47, 29.41, 29.32, 29.26, 25.53, 22.66, 14.24, 14.10. HRMS (ESI) $C_{19}H_{31}NNaO_2$ $[M + Na]^+$calcd: 328.2247, found: 328.2246.



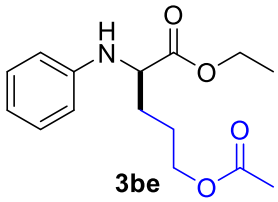
3bc

ethyl 2-(phenylamino)tridec-12-enoate (3bc): Method A: 34.0 mg, yield: 51%. Method B: 35.0 mg, yield: 53%. Yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.17 (t, *J* = 7.9 Hz, 2H), 6.73 (t, *J* = 7.3 Hz, 1H), 6.62 (d, *J* = 7.8 Hz, 2H), 5.81 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.04 – 4.89 (m, 2H), 4.23 – 4.01 (m, 4H), 2.03 (dd, *J* = 14.1, 6.8 Hz, 2H), 1.91 – 1.66 (m, 2H), 1.43 – 1.20 (m, 17H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.26, 146.96, 139.21, 129.28, 118.16, 114.10, 113.42, 60.94, 56.66, 33.78, 33.08, 29.44, 29.41, 29.38, 29.31, 29.09, 28.91, 25.52, 14.24. HRMS (ESI) $C_{21}H_{33}NNaO_2$ $[M + Na]^+$calcd: 354.2404, found: 354.2404.



3bd

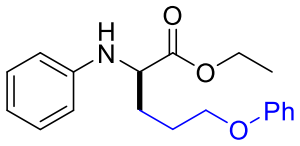
ethyl 2-(phenylamino)-3-(tetrahydrofuran-2-yl)propanoate (3bd): 27 mg, yield: 51%. d.r. > 20:1. Yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.17 (t, *J* = 7.8 Hz, 2H), 6.77 – 6.62 (m, 3H), 4.57 (d, *J* = 9.2 Hz, 1H), 4.30 – 4.14 (m, 3H), 4.05 – 3.98 (m, 1H), 3.91 (dd, *J* = 14.6, 7.4 Hz, 1H), 3.76 (dd, *J* = 14.8, 7.3 Hz, 1H), 2.11 – 1.80 (m, 5H), 1.59 – 1.40 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.16, 147.32, 129.19, 118.12, 113.53, 75.85, 67.77, 61.01, 55.23, 38.75, 31.69, 25.54, 14.20. HRMS (ESI) $C_{15}H_{21}NNaO_3$ $[M + Na]^+$calcd: 286.1414, found: 286.1417.



3be

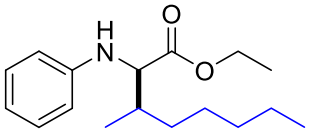
ethyl 5-acetoxy-2-(phenylamino)pentanoate (3be): Method A: 34.0 mg, yield: 61%. Method B: 36.4 mg, yield: 65%. Yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.9 Hz, 2H), 6.75 (t, *J* = 7.3 Hz, 1H), 6.63 (d, *J* = 7.7 Hz, 2H), 4.25 – 4.06 (m, 6H), 2.04 (s, 3H), 1.99 – 1.71 (m, 4H), 1.25

(t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.76, 171.06, 146.68, 129.32, 118.41, 113.49, 63.82, 61.19, 56.21, 29.49, 24.81, 20.91, 14.21. HRMS (ESI) $C_{15}H_{21}NNaO_4$ [M + Na]$^+$calcd: 302.1363, found: 302.1372.



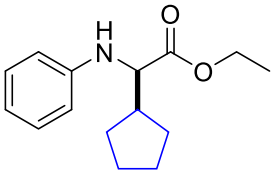
3bf

ethyl 5-phenoxy-2-(phenylamino)pentanoate (3bf): Method A: 34 mg, yield: 54%. Method B: 39.0 mg, yield: 62% yield. Yellow solid. M. p. 29 – 30 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28 (t, J = 8.3 Hz, 2H), 7.18 (t, J = 7.9 Hz, 2H), 6.99 – 6.85 (m, 3H), 6.74 (t, J = 7.3 Hz, 1H), 6.63 (d, J = 7.8 Hz, 2H), 4.24 – 4.07 (m, 4H), 3.99 (t, J = 5.3 Hz, 2H), 2.11 – 1.86 (m, 4H), 1.25 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.94, 158.78, 146.79, 129.44, 129.32, 120.71, 118.32, 114.45, 113.48, 67.01, 61.16, 56.36, 29.66, 25.48, 14.22. HRMS (ESI) $C_{19}H_{23}NNaO_3$ [M + Na]$^+$calcd: 336.1570, found: 336.1577.



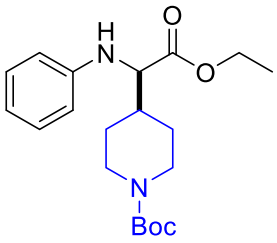
3bg

ethyl 3-methyl-2-(phenylamino)octanoate (3bg): 36 mg, yield: 65%. Yellow oil. d.r. = 1:1. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.17 (dd, J = 8.4, 7.4 Hz, 2H), 6.77 – 6.68 (m, 1H), 6.63 (d, J = 8.1 Hz, 2H), 4.24 – 4.06 (m, 3H), 4.00 – 3.88 (m, 1H),2.07 – 1.92 (m, 1H), 1.52 – 1.20 (m, 11H), 0.99 (t, J = 7.1 Hz, 3H), 0.88 (td, J = 6.7, 3.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.85, 173.51, 147.49, 147.23, 129.26, 118.12, 118.06, 113.59, 113.50, 61.42, 61.02, 60.83, 60.79, 36.33, 36.22, 33.25, 32.77, 31.93, 31.89, 26.86, 26.73, 22.58, 16.00, 15.39, 14.28, 14.04. HRMS (ESI) $C_{17}H_{27}NNaO_2$ [M + Na]$^+$calcd: 300.1934, found: 300.1937.



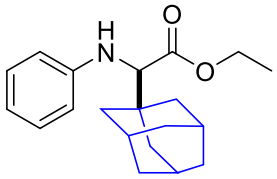
3bh

ethyl 2-cyclopentyl-2-(phenylamino)acetate (3bh): 34 mg, yield: 69%. Yellow solid. M. p. 76 – 77 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.16 (t, J = 7.9 Hz, 2H), 6.73 (t, J = 7.3 Hz, 1H), 6.63 (d, J = 7.9 Hz, 2H), 4.22 – 4.07 (m, 3H), 3.86 (t, J = 8.5 Hz, 1H), 2.33 – 2.15 (m, 1H), 1.88 – 1.39 (m, 8H), 1.23 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.15, 147.33, 129.24, 118.17, 113.45, 60.83, 60.79, 43.17, 29.34, 29.04, 25.32, 25.09, 14.26. HRMS (ESI) $C_{15}H_{21}NNaO_2$ [M + Na]$^+$calcd: 270.1465, found: 270.1469.



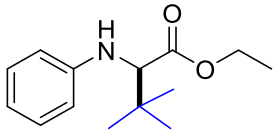
3bi

***tert*-butyl 4-(2-ethoxy-2-oxo-1-(phenylamino)ethyl)piperidine-1-carboxylate (3bi):** 46 mg, yield: 63%. White solid. M. p. 104 – 105 °C. Known compound.[2] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.17 (t, *J* = 7.6 Hz, 2H), 6.74 (t, *J* = 7.1 Hz, 1H), 6.62 (d, *J* = 7.9 Hz, 2H), 4.23 – 4.12 (m, 5H), 3.96 – 3.86 (m, 1H), 2.68 (br, 2H), 1.91 – 1.77 (m, 2H), 1.63 (d, *J* = 13.3 Hz, 1H), 1.47 – 1.33 (m, 11H), 1.25 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.08, 154.59, 146.96, 129.27, 118.30, 113.48, 79.43, 61.27, 61.07, 43.32, 39.66, 28.40, 28.28, 14.20. HRMS (ESI) $C_{20}H_{30}N_2NaO_4$ [M + Na]$^+$calcd: 385.2098, found: 385.2101.



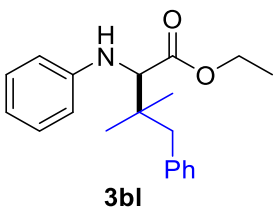
3bj

ethyl 2-((*3r*,*5r*,*7r*)-adamantan-1-yl)-2-(phenylamino)acetate (3bj): Method A: 44 mg, yield: 70%. Method B: 53.4 mg, yield: 85%. Yellow solid. M. p. 72 – 73 °C. Known compound.[2] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.16 (dd, *J* = 8.4, 7.4 Hz, 2H), 6.76 – 6.62 (m, 3H), 4.23 – 4.09 (m, 3H), 3.66 (d, *J* = 10.0 Hz, 1H), 2.02 (br, 3H), 1.84 – 1.56 (m, 12H), 1.24 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.82, 147.85, 129.23, 118.08, 113.73, 66.40, 60.50, 39.01, 36.84, 36.34, 28.35, 14.34. HRMS (ESI) $C_{20}H_{27}NNaO_2$ [M + Na]$^+$calcd: 336.1934, found: 336.1934.



3bk

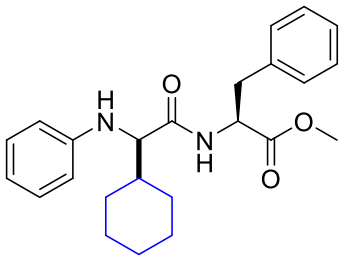
ethyl 3,3-dimethyl-2-(phenylamino)butanoate (3bk): Method A: 26.0 mg, yield: 55%. Method B: 33.0 mg, yield: 70%. Yellow oil. Known compound.[2] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.17 (t, *J* = 7.9 Hz, 2H), 6.73 (t, *J* = 7.3 Hz, 1H), 6.66 (d, *J* = 7.8 Hz, 2H), 4.20 – 4.09 (m, 3H), 3.79 (d, *J* = 10.5 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.07 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.32, 147.68, 129.24, 118.25, 113.80, 65.47, 60.56, 34.46, 26.75, 14.27. HRMS (ESI) $C_{14}H_{21}NNaO_2$ [M + Na]$^+$calcd: 258.1465, found: 258.1471.



3bl

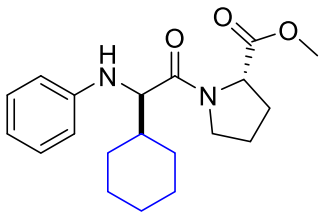
ethyl 3,3-dimethyl-4-phenyl-2-(phenylamino)butanoate (3bl): Method A: 36 mg, yield: 58%.

Method B: 37.5mg, yield: 60%. Yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31 – 7.13 (m, 7H), 6.76 (t, *J* = 7.3 Hz, 1H), 6.66 (d, *J* = 7.8 Hz, 2H), 4.25 (d, *J* = 11.2 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.83 (d, *J* = 11.2 Hz, 1H), 2.87 (d, *J* = 13.0 Hz, 1H), 2.64 (d, *J* = 13.0 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.06 (s, 3H), 0.99 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.38, 147.29, 137.84, 130.87, 129.28, 127.89, 126.25, 118.55, 114.04, 63.27, 60.62, 45.53, 37.93, 24.27, 23.21, 14.27. HRMS (ESI) $C_{20}H_{25}NNaO_2$ $[M + Na]^+$calcd: 334.1778, found: 334.1781.



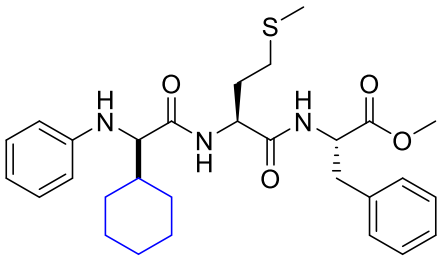
3pa

(2*S*)-methyl 2-(2-cyclohexyl-2-(phenylamino)acetamido)-3-phenylpropanoate (3pa): 35 mg, yield: 44%. d.r. = 1.2:1. White solid. M. p. 126 – 127 °C. Known compound.[2] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28 – 6.99 (m, 7H), 6.87 – 6.71 (m, 2H), 6.58 (dd, *J* = 17.6, 7.7 Hz, 2H), 5.04 – 4.86 (m, 1H), 3.91 (d, *J* = 3.4 Hz, 0.53H), 3.82 (d, *J* = 3.6 Hz, 0.41H), 3.70 (s, 1.65H), 3.62 (s, 1.23H), 3.58 (t, *J* = 3.8 Hz, 0.58H), 3.49 (t, *J* = 4.1 Hz, 0.43H), 3.21 (dd, *J* = 14.1, 5.3 Hz, 0.47H), 3.06 (dd, *J* = 13.8, 6.1 Hz, 0.55H), 2.93 (ddd, *J* = 13.7, 6.8, 3.9 Hz, 1H), 2.07 – 1.93 (m, 0.57H), 1.89 – 1.62 (m, 5H), 1.53 (d, *J* = 13.2 Hz, 0.49H), 1.37 – 0.84 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.64, 172.37, 171.65, 171.53, 147.28, 147.00, 136.00, 135.20, 129.27, 129.08, 128.97, 128.40, 126.84, 126.82, 118.90, 118.73, 113.86, 113.43, 64.98, 64.27, 52.68, 52.20, 52.00, 40.89, 37.86, 37.70, 30.04, 27.83, 26.07, 14.05. HRMS (ESI) $C_{24}H_{30}N_2NaO_3$ $[M + Na]^+$calcd: 417.2149, found: 417.2149.



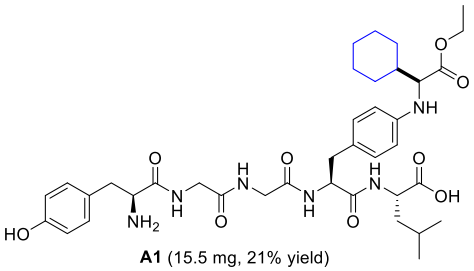
3qa

(2*S*)-methyl 1-(2-cyclohexyl-2-(phenylamino)acetyl)pyrrolidine-2-carboxylate (3qa): 26 mg, yield: 38%. d.r. = 2:1. Brown oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.20 – 7.09 (m, 2H), 6.74 – 6.59 (m, 3H), 4.61 – 4.31 (m, 2H), 3.99 (d, *J* = 5.3 Hz, 1H), 3.80 – 3.70 (m, 1.65H), 3.71 – 3.54 (m, 3.39H), 2.25 – 1.89 (m, 5H), 1.74 – 1.63 (m, 5H), 1.34 – 1.05 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.44, 172.37, 172.02, 171.99, 148.18, 147.88, 129.21, 129.11, 117.75, 117.65, 113.77, 113.66, 60.74, 60.43, 59.05, 58.81, 52.09, 51.99, 47.07, 46.94, 41.77, 41.69, 30.05, 29.86, 28.98, 28.88, 26.25, 26.19, 26.16, 26.11, 24.97, 24.80. HRMS (ESI) $C_{20}H_{28}N_2NaO_3$ $[M + Na]^+$calcd: 367.1992, found: 367.1994.

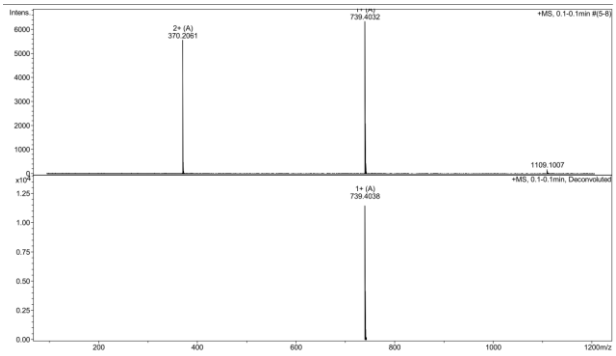


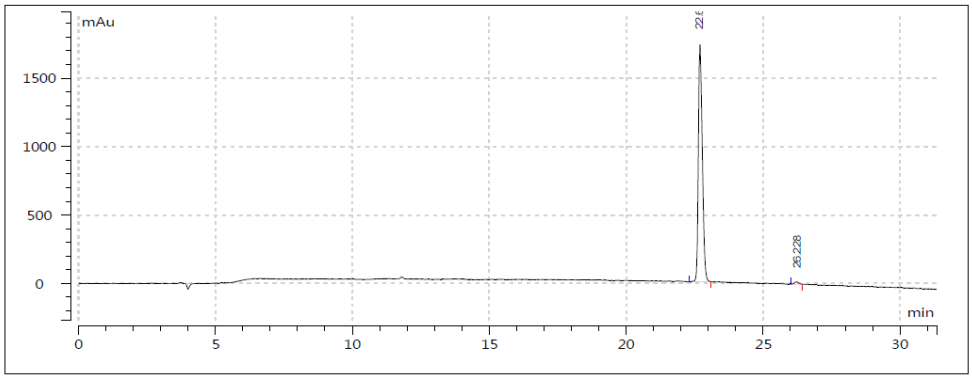
3ra

(2S)-methyl-2-((2S)-2-(2-cyclohexyl-2-(phenylamino)acetamido)-4-(methylthio)butanamido)-3-phenylpropanoate (3ra): 48 mg, yield: 46%. d.r. = 1.5:1. White solid. M. p. 156– 157 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.47 – 7.36 (m, 1H), 7.32 – 7.07 and 7.00 – 6.94 (m, 7H), 6.82 – 6.70 and 6.64 – 6.55 (m, 4H), 4.85 – 4.54 (m, 2H), 4.07 – 3.98 (m, 1H), 3.71 and 3.69 (s, 3H), 3.61 (br, 1H), 3.11 – 2.99 (m, 1.58H), 2.76 (dd, *J* = 13.7, 8.0 Hz, 0.40H), 2.39 – 2.25 (m, 2H), 2.07 – 1.67 (m, 11H), 1.27 – 1.08 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.84, 171.44, 171.36, 170.42, 170.21, 147.19, 146.96, 135.79, 135.47, 129.56, 129.34, 129.15, 129.04, 128.60, 128.51, 127.15, 127.00, 119.01, 118.92, 113.43, 113.37, 64.42, 64.37, 53.24, 53.21, 52.25, 51.99, 51.52, 41.07, 40.99, 37.71, 30.86, 30.53, 30.13, 29.78, 29.60, 28.37, 28.27, 26.12, 25.98, 14.94, 14.74. HRMS (ESI) $C_{29}H_{39}N_3NaO_4S$ [M + Na]$^+$calcd: 548.2553, found: 548.2549.

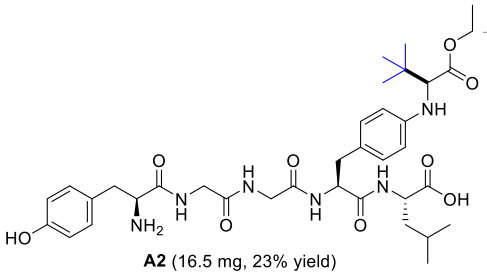


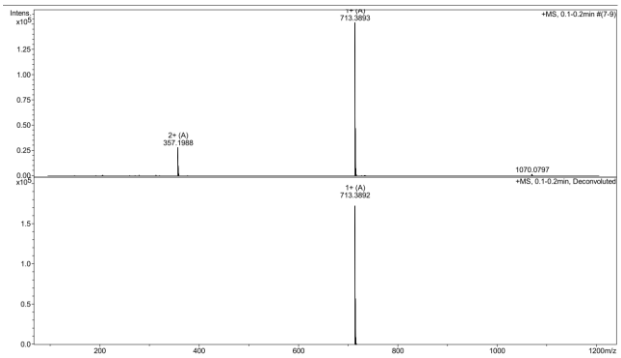
A1 (15.5 mg, 21% yield)
Exact Mass: 738.3952
Molecular Weight: 738.8830
m/z: 738.3952 (100.0%), 739.3986 (41.1%), 740.4019 (8.2%), 739.3923 (2.2%), 740.3995 (1.8%)
Elemental Analysis: C, 61.77; H, 7.37; N, 11.37; O, 19.49



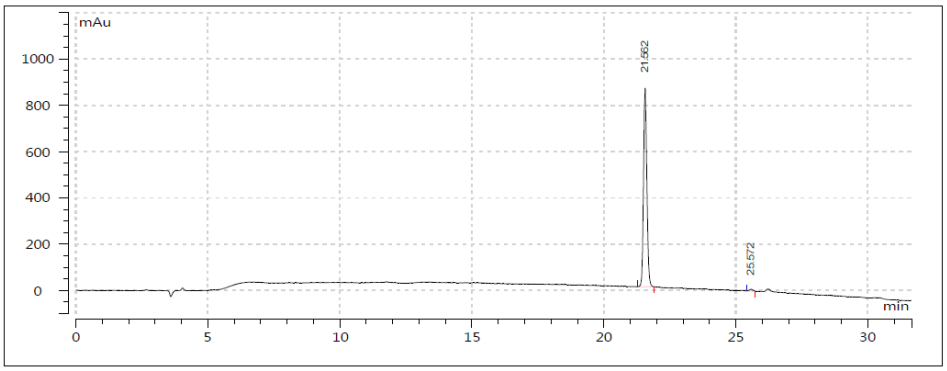


		(min)	(mAu*s)	(min)	(min)	(mAu)	(%)	
1	N. A.	22. 693	17479. 72927	0. 267	0. 156	1742. 957	98. 988	BB
2	N. A.	26. 228	178. 68634	0. 251	0. 158	17. 304	1. 012	BB

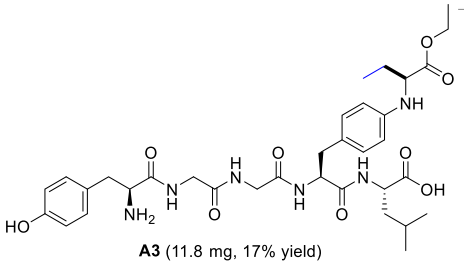


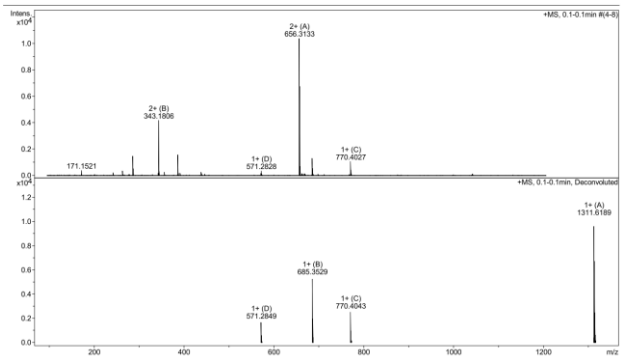


A2 (16.5 mg, 23% yield)
Exact Mass: 712.3796
Molecular Weight: 712.8450
m/z: 712.3796 (100.0%), 713.3829 (38.9%), 714.3863 (7.4%), 713.3766 (2.2%), 714.3838 (1.8%)
Elemental Analysis: C, 60.66; H, 7.35; N, 11.79; O, 20.20

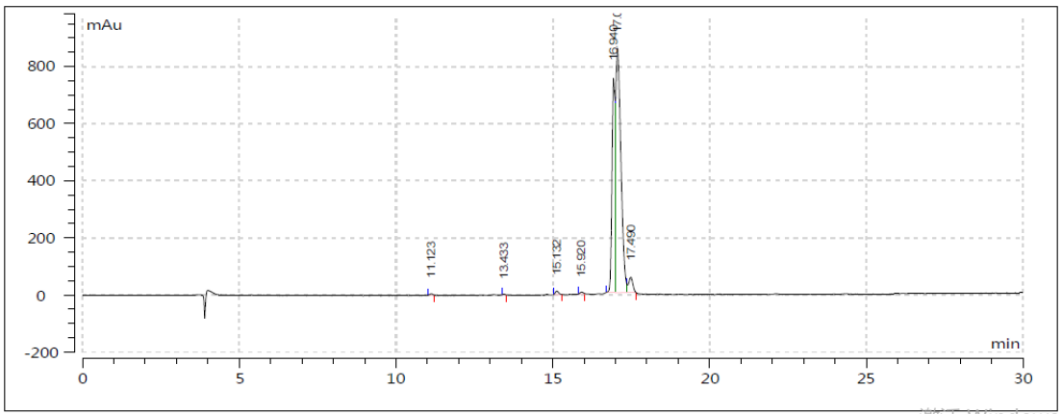


		(min)	(mAu*s)	(min)	(min)	(mAu)	(%)	
1	N. A.	21. 562	7497. 77867	0. 226	0. 133	863. 098	99. 088	BB
2	N. A.	25. 572	69. 00570	0. 210	0. 147	7. 576	0. 912	BB

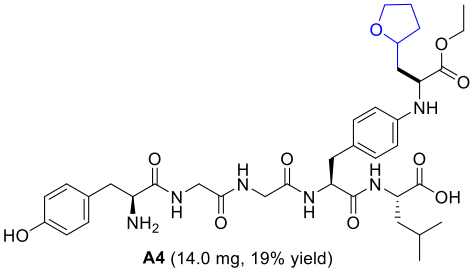


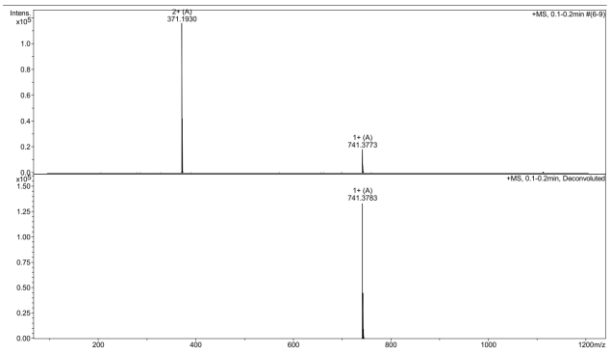


A3 (11.8 mg, 17% yield)
Exact Mass: 684.3483
Molecular Weight: 684.7910
m/z: 684.3483 (100.0%), 685.3516 (36.8%), 686.3550 (6.6%), 685.3453 (2.2%), 686.3525 (1.8%)
Elemental Analysis: C, 59.63; H, 7.07; N, 12.27; O, 21.03

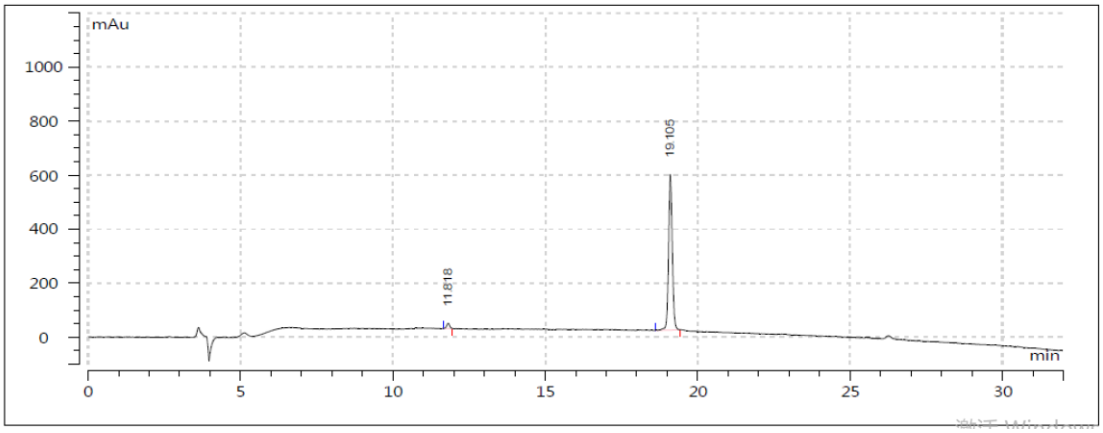


		(min)	(mAu*s)	(min)	(min)	(mAu)	(%)	
1	N. A.	11. 123	31. 85033	0. 169	0. 101	5. 201	0. 206	BB
2	N. A.	13. 433	13. 67494	0. 139	0. 085	2. 714	0. 088	BB
3	N. A.	15. 132	83. 94287	0. 180	0. 107	12. 658	0. 543	BB
4	N. A.	15. 920	46. 37690	0. 190	0. 114	6. 739	0. 300	BB
5	N. A.	16. 940	4760. 41051	0. 354	0. 000	757. 246	30. 802	BB
6	N. A.	17. 065	10007. 10228	0. 430	0. 000	856. 483	64. 751	BB
7	N. A.	17. 490	511. 38144	0. 258	0. 155	55. 208	3. 309	BB

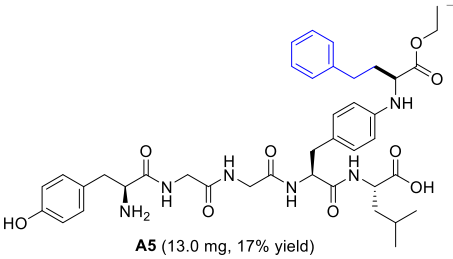


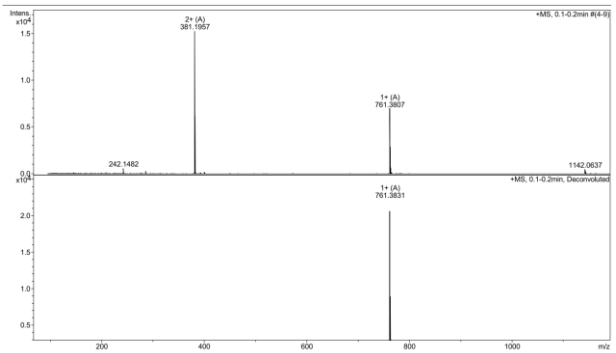


A4 (14.0 mg, 19% yield)
Exact Mass: 740.3745
Molecular Weight: 740.8550
m/z: 740.3745 (100.0%), 741.3778 (40.0%), 742.3812 (7.8%), 741.3715 (2.2%), 742.3787 (2.1%)
Elemental Analysis: C, 59.99; H, 7.08; N, 11.34; O, 21.60

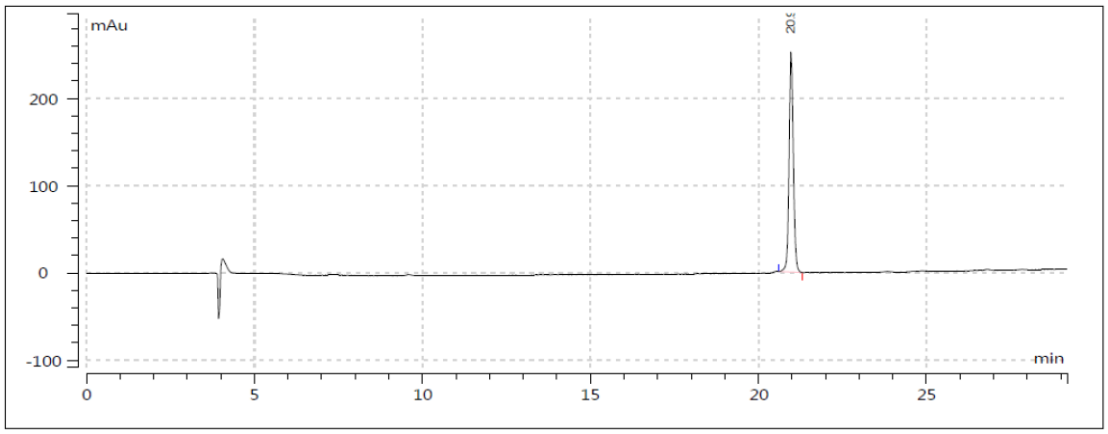


		(min)	(mAu*s)	(min)	(min)	(mAu)	(%)	
1	N. A.	11. 818	134. 77136	0. 164	0. 100	20. 221	2. 707	BB
2	N. A.	19. 105	4842. 97447	0. 213	0. 125	579. 871	97. 293	BB

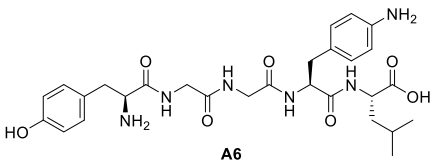




A5 (13.0 mg, 17% yield)
Exact Mass: 760.3796
Molecular Weight: 760.8890
m/z: 760.3796 (100.0%), 761.3829 (43.3%), 762.3863 (9.1%), 761.3766 (2.2%), 762.3838 (1.8%)
Elemental Analysis: C, 63.14; H, 6.89; N, 11.05; O, 18.92

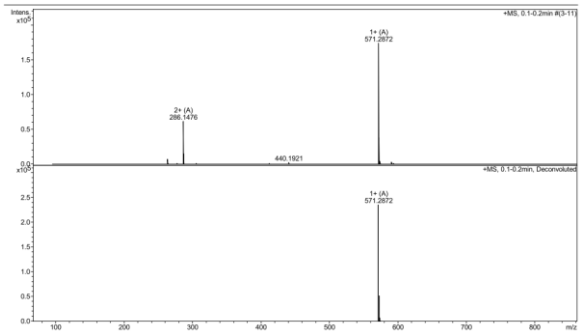


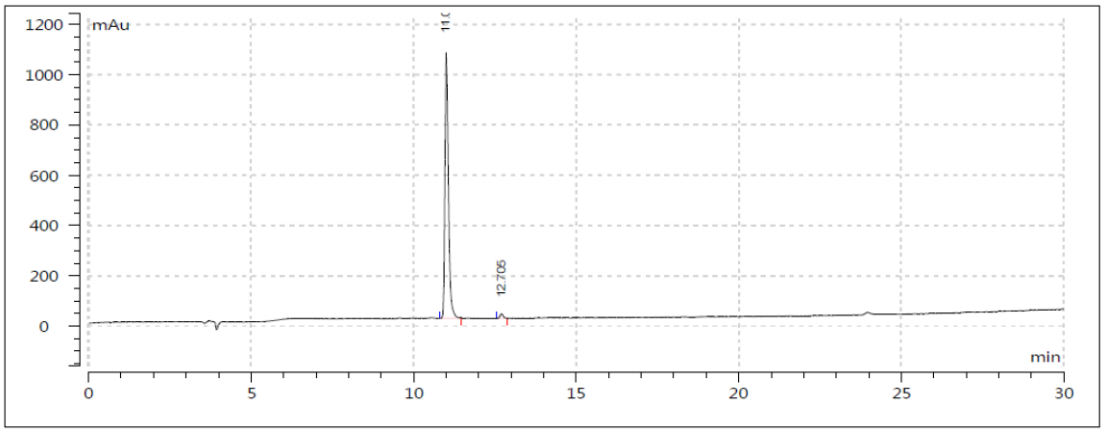
		(min)	(mAu*s)	(min)	(min)	(mAu)	(%)	
1	N. A.	20. 973	2213. 45316	0. 222	0. 130	254. 929	100. 000	BB



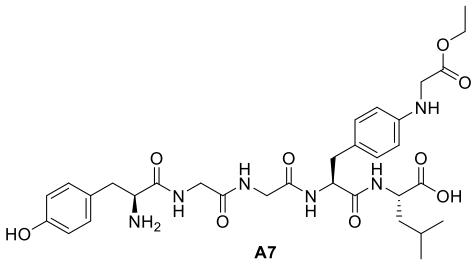
A6

Exact Mass: 570.2802
Molecular Weight: 570.6470
m/z: 570.2802 (100.0%), 571.2836 (30.3%), 572.2869 (2.7%), 571.2772 (2.2%), 572.2869 (1.7%), 572.2844 (1.4%)
Elemental Analysis: C, 58.93; H, 6.71; N, 14.73; O, 19.63



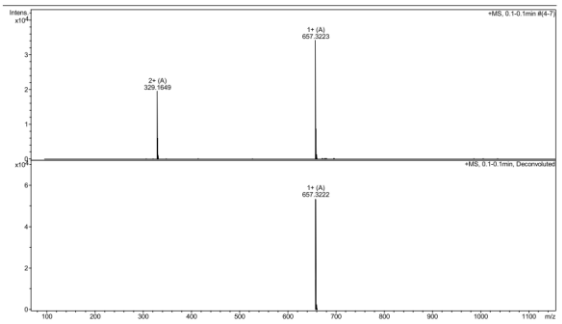


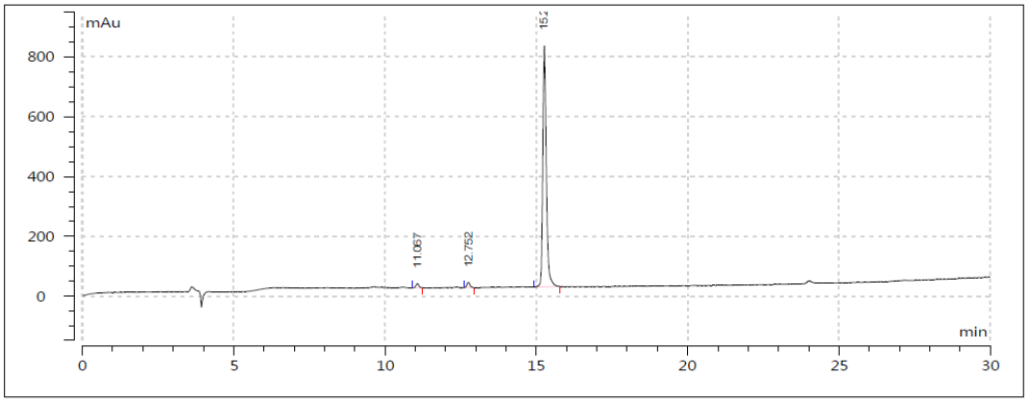
		(min)	(mAu*s)	(min)	(min)	(mAu)	(%)	
1	N. A.	11. 007	7753. 58767	0. 184	0. 108	1070. 952	98. 420	BB
2	N. A.	12. 705	124. 47556	0. 168	0. 101	18. 643	1. 580	BB



A7

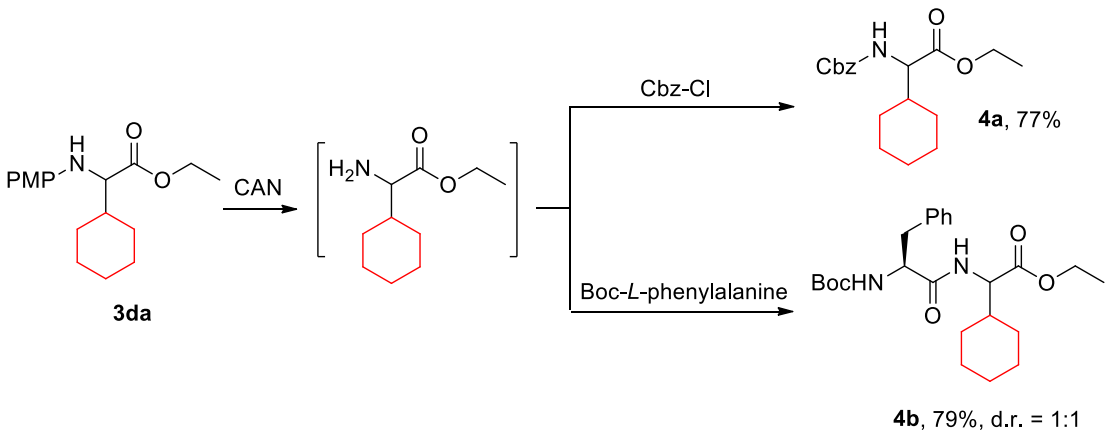
Exact Mass: 656.3170
Molecular Weight: 656.7370
m/z: 656.3170 (100.0%), 657.3203 (34.6%), 658.3237 (5.8%), 657.3140 (2.2%), 658.3212 (1.8%)
Elemental Analysis: C, 58.52; H, 6.75; N, 12.80; O, 21.93





		(min)	(mAu*s)	(min)	(min)	(mAu)	(%)	
1	N. A.	11. 067	95. 11904	0. 171	0. 100	14. 562	1. 426	BB
2	N. A.	12. 752	120. 41519	0. 167	0. 101	17. 955	1. 805	BB
3	N. A.	15. 263	6454. 34114	0. 201	0. 118	806. 188	96. 769	BB

5. Synthetic applications



3da

Preparation of 4a

A mixture of **3da** (0.3 mmol, 87.4 mg) and CAN (cerium ammonium, 1.8 mmol, 986.8 mg) in 5:2 solution of H_2O/CH_3CN (3.0 mL) was 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 3 mL DCM. Benzyloxycarbonyl chloride (0.34 mmol, 0.056 mL) was added. The

resulting solution was cooled to 0 °C and TEA (0.34 mmol, 0.052 mL) was then added dropwise. After 5 min, the ice bath was removed and the mixture was allowed to stir for 2 h at room temperature. 10 mL DCM was added and the mixture was washed with H_2O (10 mL) and brine (10 mL). The resulting solution was dried over Na_2SO_4 and evaporated in *vacuo*. The product **4a** was purified by silica gel column chromatography using hexane-EtOAc as eluents. Yield: 77%, 74.0 mg. Colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.45 – 7.30 (m, 5H), 5.33 – 5.25 (m, 1H), 5.11 (s, 2H), 4.32 – 4.14 (m, 3H), 1.79 – 1.54 (m, 6H), 1.32 – 0.97 (m, 8H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ171.98, 156.13, 136.28, 128.50, 128.11, 121.96, 66.96, 61.18, 58.70, 41.08, 29.37, 27.96, 25.95, 14.20. HRMS (ESI) $C_{18}H_{25}NNaO_4$ $[M + Na]^+$calcd: 342.1676, found: 342.1680.

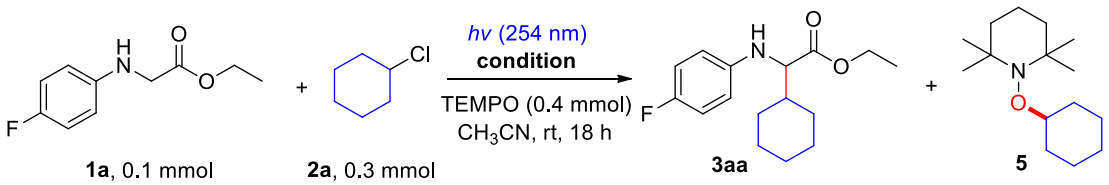
Preparation of 4b

A mixture of **3da** (0.3 mmol, 87.4 mg) and CAN (cerium ammonium, 1.8 mmol, 986.8 mg) in 5:2 solution of H_2O/CH_3CN (3.0 mL) was 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 and *N*-Boc-L-phenylalanine were dissolved in dry DCM (3 mL). The reaction mixture was cooled to 0 °C before addition of HOBt hydrate (0.45 mmol, 60.8 mg) and TEA (1.5 mmol, 0.21 mL). The reaction mixture was kept at 0 °C for 15 min before EDCI (0.375 mmol, 72 mg) was added. The mixture was stirred at room temperature for 24 h. An additional DCM (10 mL) was added, and the organic layer was washed successively with citric acid (1.6 M), saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated in *vacuo*. The product **4b** was purified by silica gel column chromatography using hexane-EtOAc as eluents. Yield: 79%, 102.0 mg. Yellow oil. d.r. = 1:1. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.29 – 7.20 (m, 5H), 6.46 – 6.35 (m, 1H), 5.08 (d, J = 5.5 Hz, 1H), 4.47 – 4.34 (m, 2H), 4.26 – 4.09 (m, 2H), 3.08 (d, J = 6.5 Hz, 2H), 1.71 – 1.61 (m, 6H), 1.41 (s, 9H), 1.32 – 0.96 (m, 8H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.47, 171.24, 170.91, 155.32, 136.54, 129.28, 129.17, 128.64, 128.53, 126.85, 80.08, 61.10, 56.88, 56.72, 56.56, 55.72, 40.89, 38.39, 37.90, 29.12, 28.22, 28.11, 25.86, 14.18, 14.11. HRMS (ESI) $C_{24}H_{36}N_2NaO_5$ $[M + Na]^+$calcd: 455.2516, found: 455.2516.

6. The mechanistic study

6.1 Radical trapping with TEMPO

Table S15. Radical inhibition experiments



	Condition	Yield of **3aa**	Yield of **5**[a]
A	0.05 mmol TBAI, 0.2 mmol DABCO, 0.2 mmol $KHCO_3$	0	42
B	0.05 mmol TBAI, 0.2 mmol $KHCO_3$	0	15
C	0.2 mmol DABCO, 0.2 mmol $KHCO_3$	0	trace

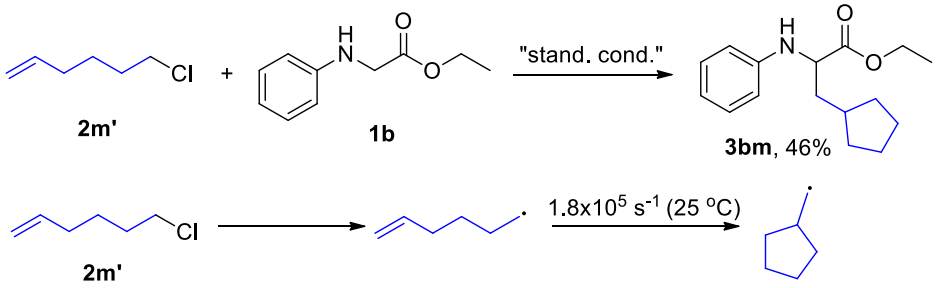
[a] The yield was based on alkyl chloride **2a**.

In order to gain some information on reaction mechanism, a series of alkyl radical inhibition reaction were carried out (Table S15). Under condition A, the reaction was completely suppressed and TEMPO-Cy product **5** was isolated in 42% yield, which suggested that a radical pathway was involved in this reaction. Under condition B and C, the absence of DABCO or TBAI caused an obvious yield decreasing of the product **5**, which demonstrated the importance of TBAI and DABCO for generation of alkyl radical.

Procedure of Condition A, B and C:

To an oven-dried 10 mL quartz test tube with a stirring bar was added **1a** (0.1 mmol, 19.7 mg), TBAI (0.05 mmol, 18.5 mg, A and B), DABCO (0.2 mmol, 22.4 mg, A and C), $KHCO_3$ (0.2 mmol, 20.0 mg), TEMPO (0.4 mmol, 62.5 mg) and 4ÅMS (40 mg). Then, air was withdrawn and backfilled with Ar (three times). CH_3CN (0.5 mL) and alkyl chloride **2a** (0.3 mmol, 35.6 mg) were added in turn by syringe. Thereafter, the test tube was transferred to a UV photoreactor (4×25 W, see Scheme S1 for details), where it was irradiated at 254 nm for 18 h. Eighteen hours later, the reaction was quenched with water (2 mL), extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated in *vacuo* and purified by column chromatography (hexane/ethyl acetate = 50:1) to afford the product **5** as a colorless oil (no product **3aa** was detected). Known compound.[2] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.63 – 3.53 (m, 1H), 2.05 (br, 2H), 1.76 – 1.71 (m, 2H), 1.56 – 1.44 (m, 6H), 1.34 – 1.09 (m, 18H).

6.2 Radical clock experiment



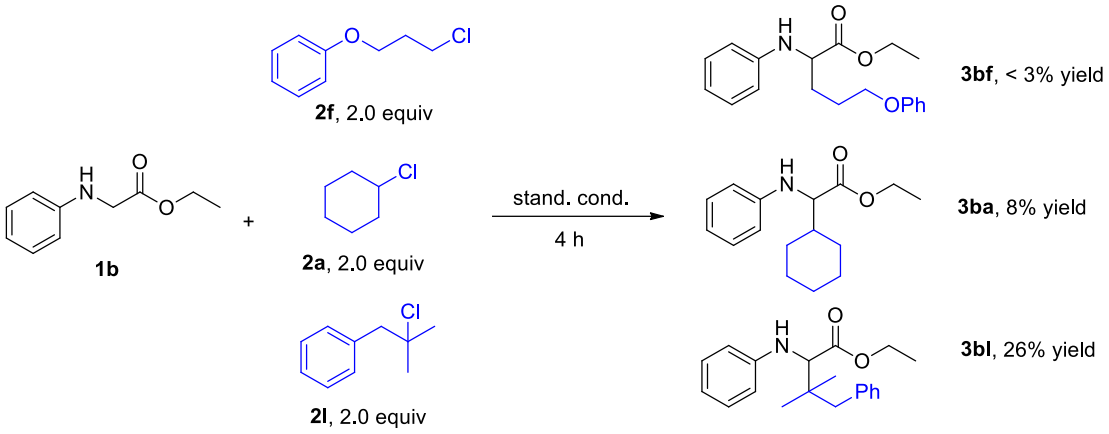
When 6-chlorohex-1-ene **2m'** was applied, once an alkyl radical was formed, it undergoes a fast ring-forming coupling reaction and **3bm** was obtained.[9]

Procedure of radical clock experiment:

To an oven-dried 10 mL quartz test tube with a stirring bar was added derivatives of glycine (0.2 mmol, 35.8 mg), TBAI (0.1 mmol, 37 mg), $KHCO_3$ (0.4 mmol, 40 mg), DABCO (0.4 mmol, 44.8 mg) and 4ÅMS (80 mg). Then, air was withdrawn and backfilled with Ar (three times). CH_3CN (1.0 mL) and 6-chlorohex-1-ene **2m'** (0.6 mmol, 70.8 mg) were added in turn by syringe. Thereafter, the test tube was transferred to a UV photoreactor (4×25 W, see Scheme S1 for details), where it was irradiated at 254 nm for 18 h. Eighteen hours later, the reaction was quenched with water (2 mL), extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated in *vacuo* and purified by column chromatography (hexane/ethyl acetate) to afford the product **3bm**. **ethyl 3-cyclopentyl-2-(phenylamino)propanoate:** 24.0 mg, 46% yield. White solid. M. p. 52 – 53 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.17 (dd, J = 8.4, 7.5 Hz, 2H), 6.73 (t, J = 7.3 Hz, 1H), 6.62 (d, J = 7.7 Hz, 2H), 4.16 (q, J = 7.1 Hz, 2H), 4.04 (br, 2H), 2.03 – 1.77 (m, 5H), 1.71 – 1.39 (m, 4H), 1.28 – 1.09 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.55, 146.98, 129.25, 118.16, 113.39, 60.87, 56.34,

39.53, 36.70, 32.80, 32.59, 25.13, 24.90, 14.19. HRMS (ESI) $C_{16}H_{23}NNaO_2$ [M + Na]$^+$calcd: 284.1621, found: 284.1628.

6.3 Competitive of 3º, 2º, 1º alkyl chloride

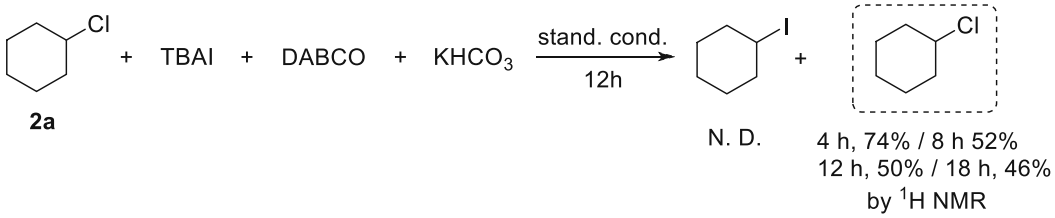


Procedure of competing reaction:

To an oven-dried 10 mL quartz test tube with a stirring bar was added **1b** (0.2 mmol, 35.8 mg), TBAI (0.1 mmol, 37 mg), $KHCO_3$ (0.4 mmol, 40 mg), DABCO (0.4 mmol, 44.8 mg) and 4ÅMS (80 mg). Then, air was withdrawn and backfilled with Ar (three times). **2f** (0.4 mmol, 68.0 mg), **2a** (0.4 mmol, 47.2 mg), **2l** (0.4 mmol, 67.2 mg) and CH_3CN (1.0 mL) were added in turn by syringe. Thereafter, the test tube was transferred to a UV photoreactor (4×25 W, see Scheme S1 for details), where it was irradiated at 254 nm for 4 h. Four hours later, the reaction was quenched with water (2 mL), extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated in *vacuo* and purified by column chromatography.

NOTE: We studied the relative reactivity of alkyl chlorides via competing reactions of 3º, 2º, and 1º alkyl chlorides. The results indicated that more substituted tertiary alkyl chloride **2l** proceeded smoothly with the best result (26% yield) due to the greater stability of themore highly substituted radical, and the reactivity order was tertiary alkyl chloride > secondary alkyl chloride > primary alkyl chloride.

6.4 Control experiment



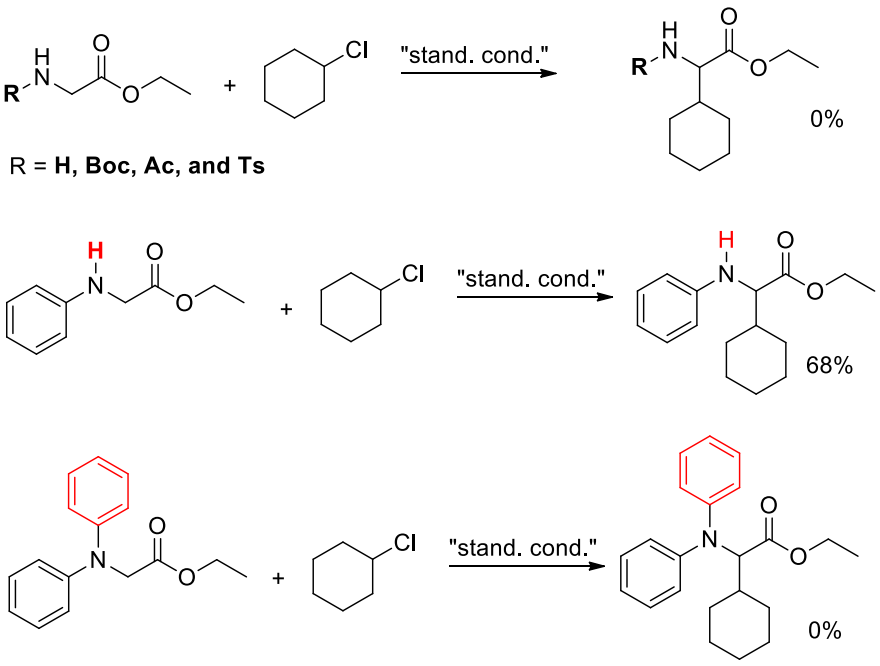
To an oven-dried 10 mL quartz test tube with a stirring bar was added TBAI (0.1 mmol, 37 mg), $KHCO_3$ (0.4 mmol, 40 mg) and DABCO (0.4 mmol, 44.8 mg). Then, air was withdrawn and backfilled with Ar (three times).**2a** (0.6 mmol, 71.0 mg) and CH_3CN (1.0 mL) were added in turn

by syringe. Thereafter, the test tube was transferred to a UV photoreactor (4×25 W, see Scheme S1 for details), where it was irradiated at 254 nm. The reaction was quenched with water (2 mL), extracted with ethyl acetate, dried over anhydrous sodium sulfate and concentrated in *vacuo*. The recycled yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

NOTE: Some control experiments were performed. When alkyl chloride **2a** was combined with TBAI under standard conditions and irradiated at 254 nm, no cyclohexyl iodide was detected (the reaction was monitored each an hour) and the cyclohexyl chloride was recycled in 46% yield after 12 h (in the absence of TBAI, cyclohexyl chloride was recovered quantitatively after 12 h). Previous report (*J. Am. Chem. Soc.*, 2015, **137**, 13902) and our results indicated that the alkyl iodide was not likely in situ generated and act as an intermediate, which then underwent a C-I bond homolysis upon photo irradiation.

6.5 The *N*-protecting group studies

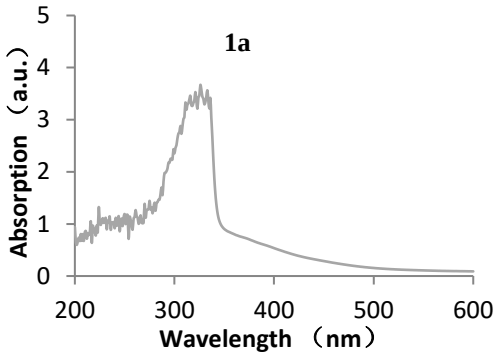
When the substrates with -*N*-Boc, -*N*-Ac, and -*N*-Ts were tested, no desired product was observed. Importantly, the substrates with free NH_2, *N*-mono-aryl, and *N*-di-aryl were applied under the standard conditions, respectively, only mono-arylated substrate gave the desired alkylation product. The results indicated that the a single free hydrogen atom and aryl protection in Ar-*N*-H are both crucial for this transformation.

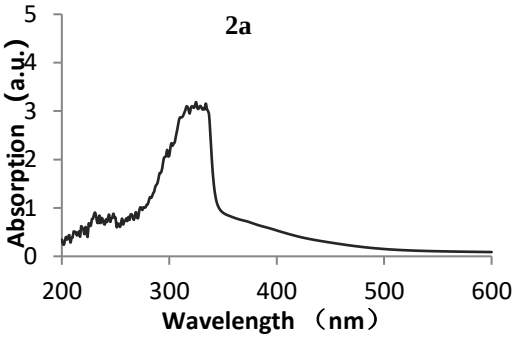


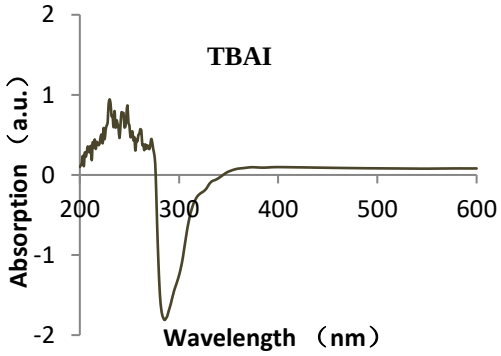
Discussion: In previous report (*J. Am. Chem. Soc.*, 1972, **94**, 7114) and our previous research (*Angew. Chem., Int. Ed.*, 2018, **57**, 15841), the radical cation of DABCO ($E_{1/2}$ = 0.6 V vs. SCE) is sufficient to oxidize *N*-phenyl glycine derivative ($E_p^{0/+1}$ (**1b**) = 0.31 V versus SCE in MeCN) due to its suitable redox potential. However, the single electron oxidization of BocNH-R or AcNH-R requires relatively strong oxidants (corresponding reports including *ACS Catal.*, 2020, **10**, 4671; *Nature*, 2016, **539**, 272; *Nature*, 2016, **539**, 268; *Nat. Chem.*, 2018, **10**, 1037 et.al.). Thus, *N*-arylated

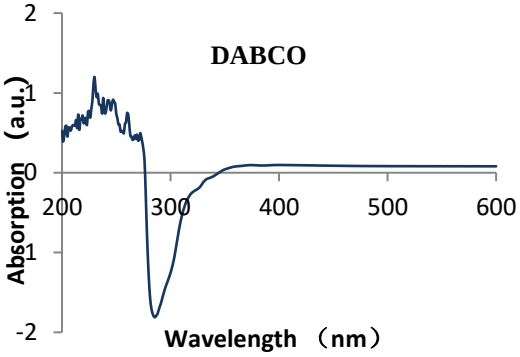
protected glycine derivatives are more easily to oxidize under our reaction conditions.

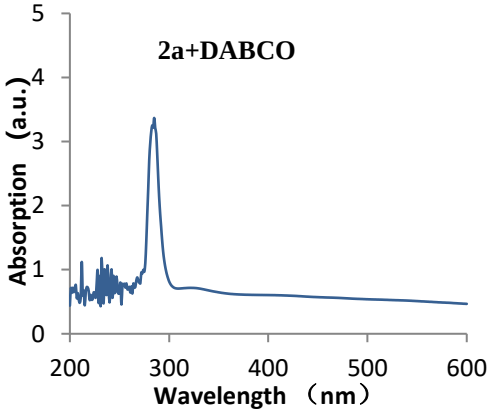
6.6 UV-Vis absorption spectra between 200 nm to 600 nm

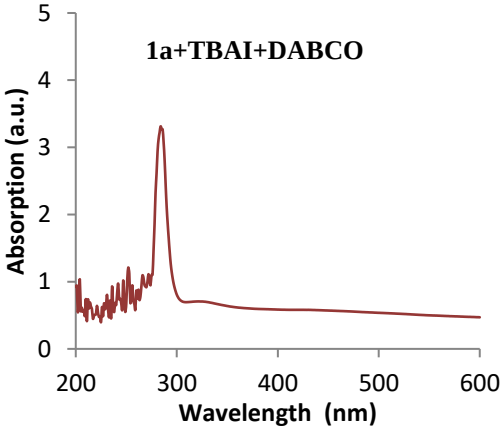


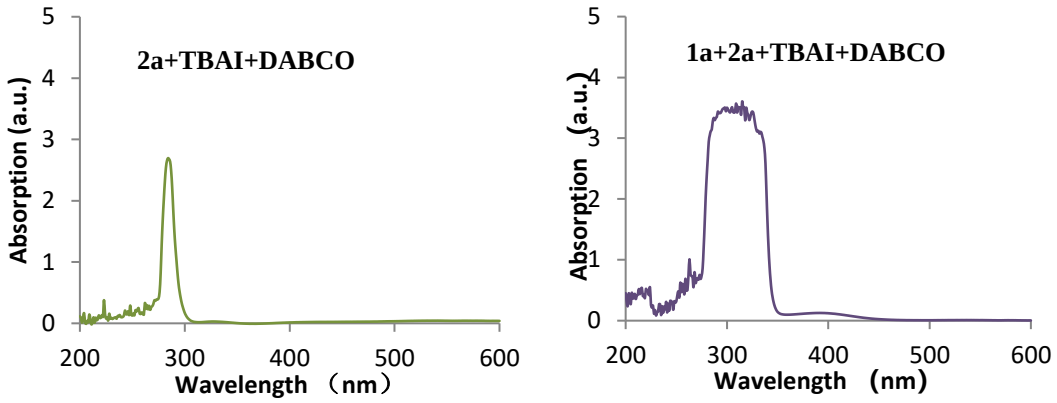












Discussion

a): The maximum absorption peak of **1a** and **2a** were at about 330 nm. Meanwhile, **TBAI** and **DABCO** all have obvious UV absorption between 210 nm with 270 nm.

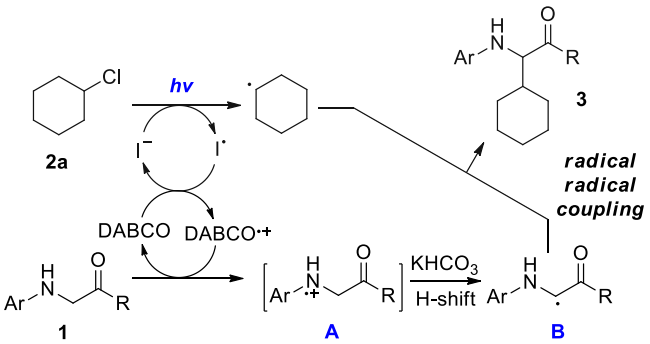
b): The blue shift of **2a** in the presence of DABCO was observed, which was possibly caused by the formation of halogen bond between alkyl chloride and tertiary amine.[10]

c): Furthermore, the mixture of **1a**, **DABCO** and **TBAI** or mixture of **2a**, **DABCO** and **TBAI** analogously all promoted hypochromatic shift of maximum absorption wavelength.

d): Notably, the mixture of **1a**, **2a**, **DABCO** and **TBAI** not only promoted hypochromatic shift of maximum absorption wavelength but also provided a much broader absorption region.

6.7 A possible reaction mechanism

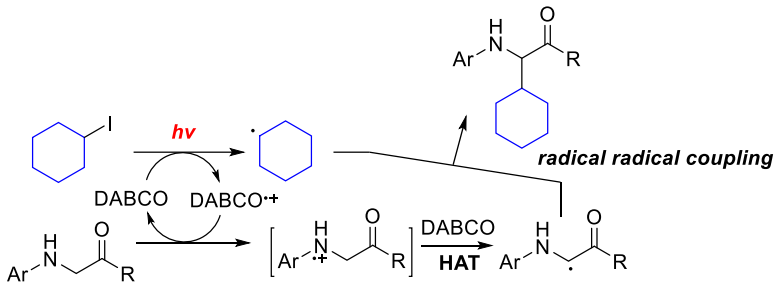
6.7.1 Possible reaction mechanism using alkyl chlorides as alkylation reagents



Although the completely understanding of the reaction mechanism is still difficult at this stage, based on the radical inhibition experiments, radical clock experiment, and competitive experiment, we proposed a possible mechanism. Firstly, the UV-light promoted a single electron transfer (SET) between alkyl chloride and iodide (I^-), which reduced the alkyl chloride to alkyl radical and chloride along with an iodine radical. Then, the SET between tertiary amine and iodine radical was happened to give an amine radical cation and regenerated the iodide catalyst. **1** was oxidized by the tertiary amine radical cation to form the radical cation intermediate **A**, which underwent a deprotonation

and 1,2-H shift process under basic conditions to give a stable α-carbon radical **B**. The subsequent radical-radical cross coupling of alkyl radical with **B** provided the final alkylation product **3**

6.7.2 Possible reaction mechanism using alkyl iodides as alkylation reagents



When alkyl iodides were used as alkylation reagents, a single electron transfer between alkyl iodide and DABCO might possibly happen upon the irradiation. The radical cation of DABCO abstracted one electron on nitrogen atom of glycine derivative. The radical cation of glycine derivative underwent a deprotonation and HAT process under basic conditions to give the stable α-carbon radical. The subsequent radical-radical cross coupling provided the final alkylation product.

7. Metabolic stability

Degradation of Leu^5-enkephalin and analogue **A2** in mouse brain and spinal cord homogenates. The Degradation analysis was performed as described in our previous report.[11] The homogenate was prepared from brain and spinal cords obtained from ten mice and homogenized in phosphate buffer (100 μM, pH 7.4). 10 μL Leu^5-enkephalin (10 mM) was incubated in 190 μL homogenate (final protein concentration of 2.3 mg/ml) for 0, 5, 10, 15, 20, 30, 45 and 60 min at 37 °C, while analogue **A2** was incubated in homogenate for 0, 10, 20, 30, 60, 120 and 180 min at 37 °C. 20 μL of the mixture was extracted at each time, immediately 90 μL of acetonitrile was added, and maintaining for 5 min in an ice bath. Then, 90 μL of acetic acid solution (0.5%) was added to prevent further degradation. The mixtures were centrifuged at 15000g for 15 min, and the supernatants were collected for HPLC analysis. Linear regression was used to calculate the half-life of Leu^5-enkephalin and analogue **A2** incubated in the mouse brain and spinal cord homogenates.

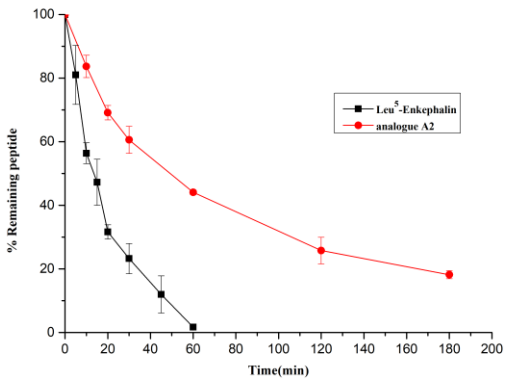


Figure S1. In vitro homogenate stability assessment of Leu^5-enkephalin and analogue **A2** in mouse brain and

spinal cord homogenate. Each data point represents the mean ± SEM, n = 3 independent experiments.

8. References

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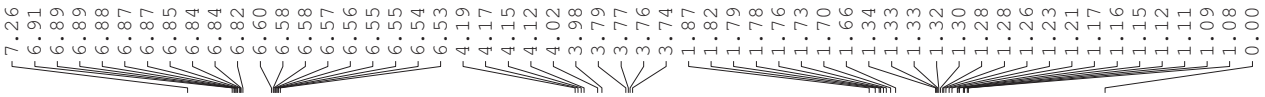
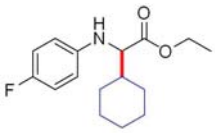
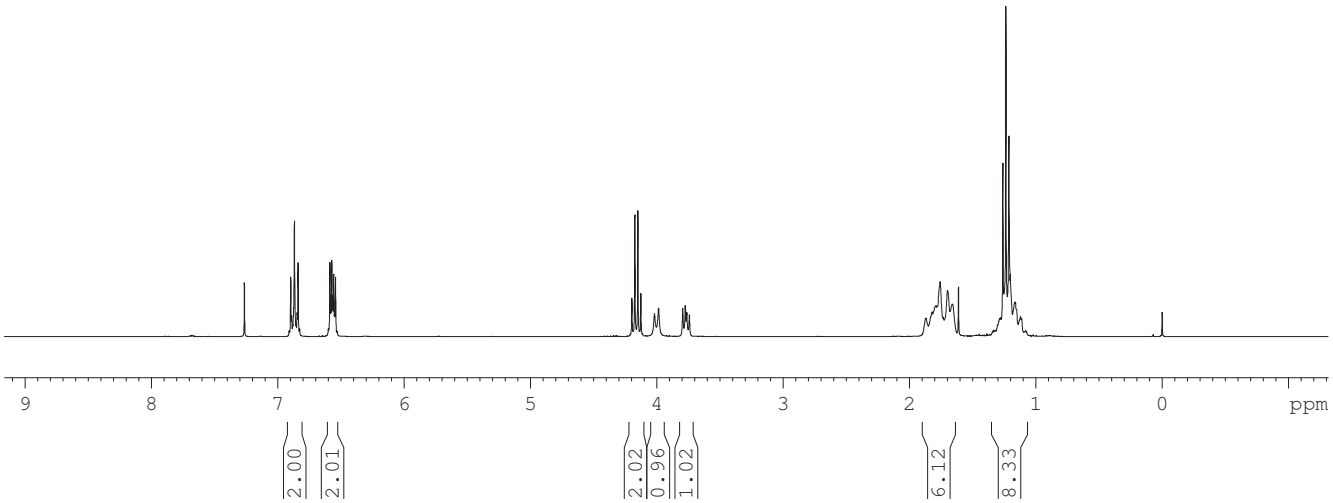
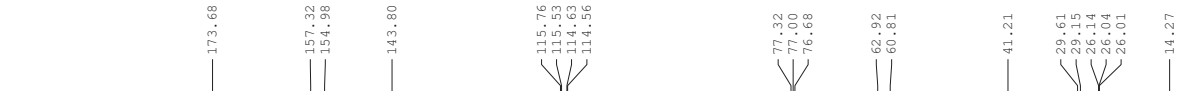


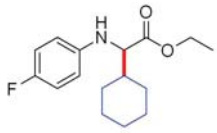


3aa

^{1}H NMR (300 MHz, $CDCl_3$)

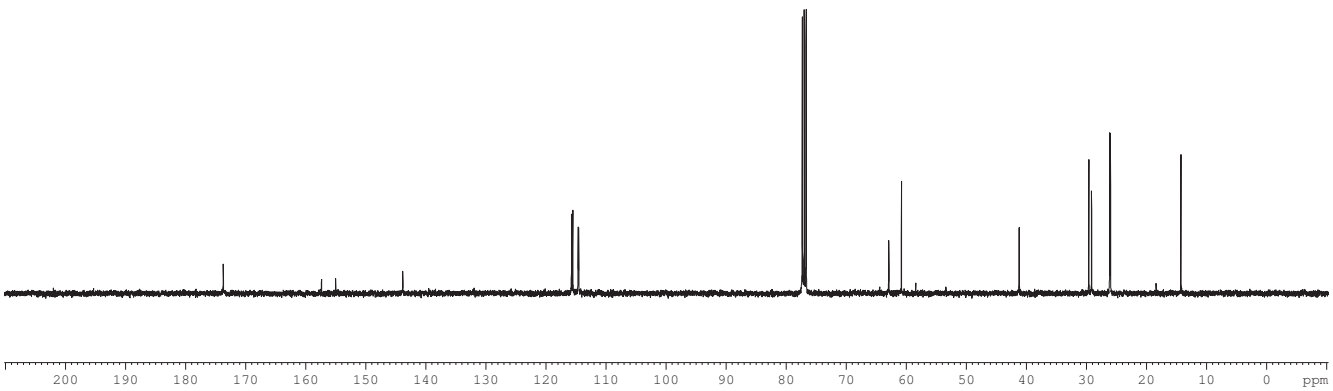


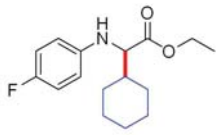




3aa

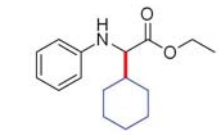
^{13}C NMR (101 MHz, $CDCl_3$)





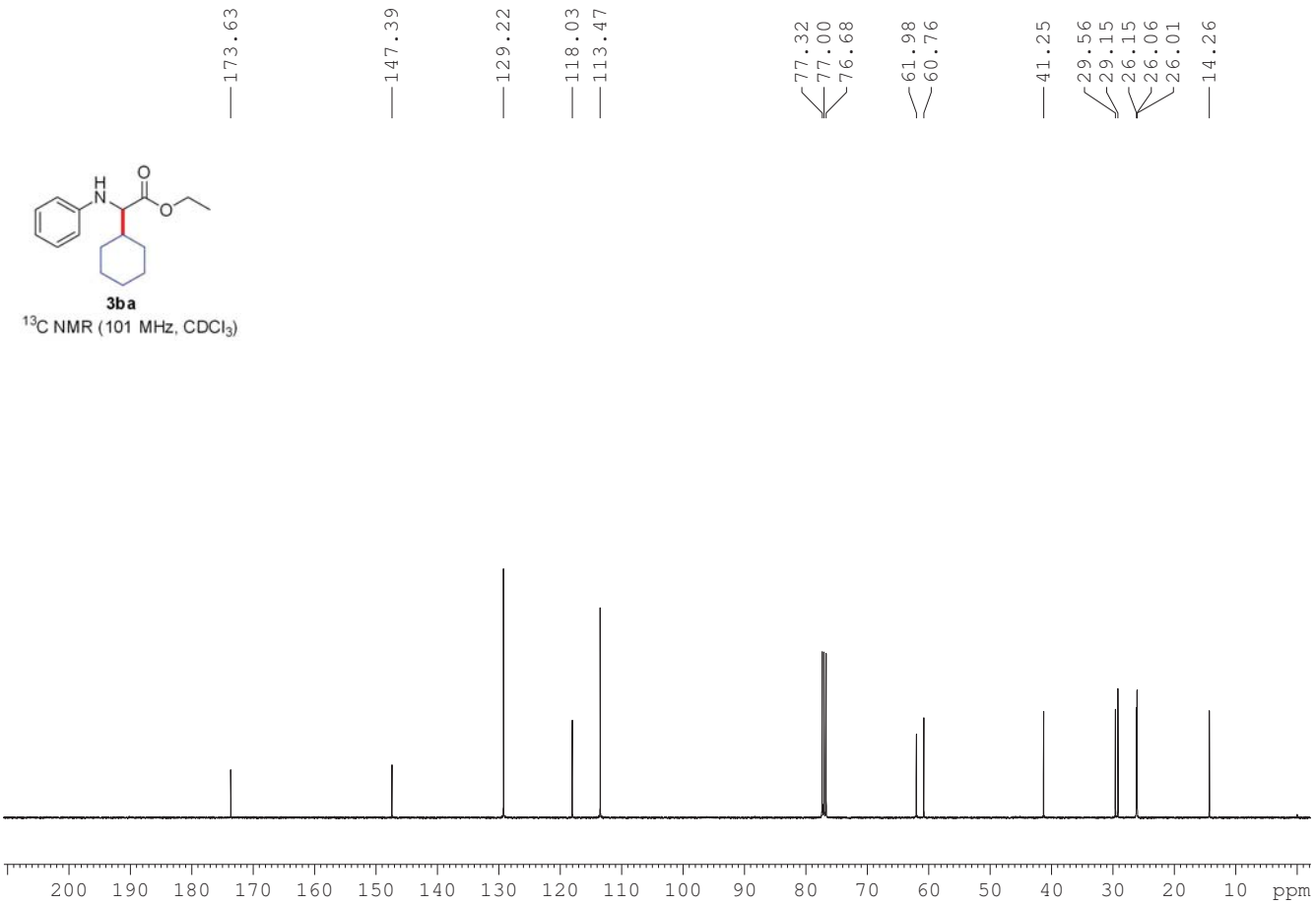
3aa

^{19}F NMR (376 MHz, $CDCl_3$)



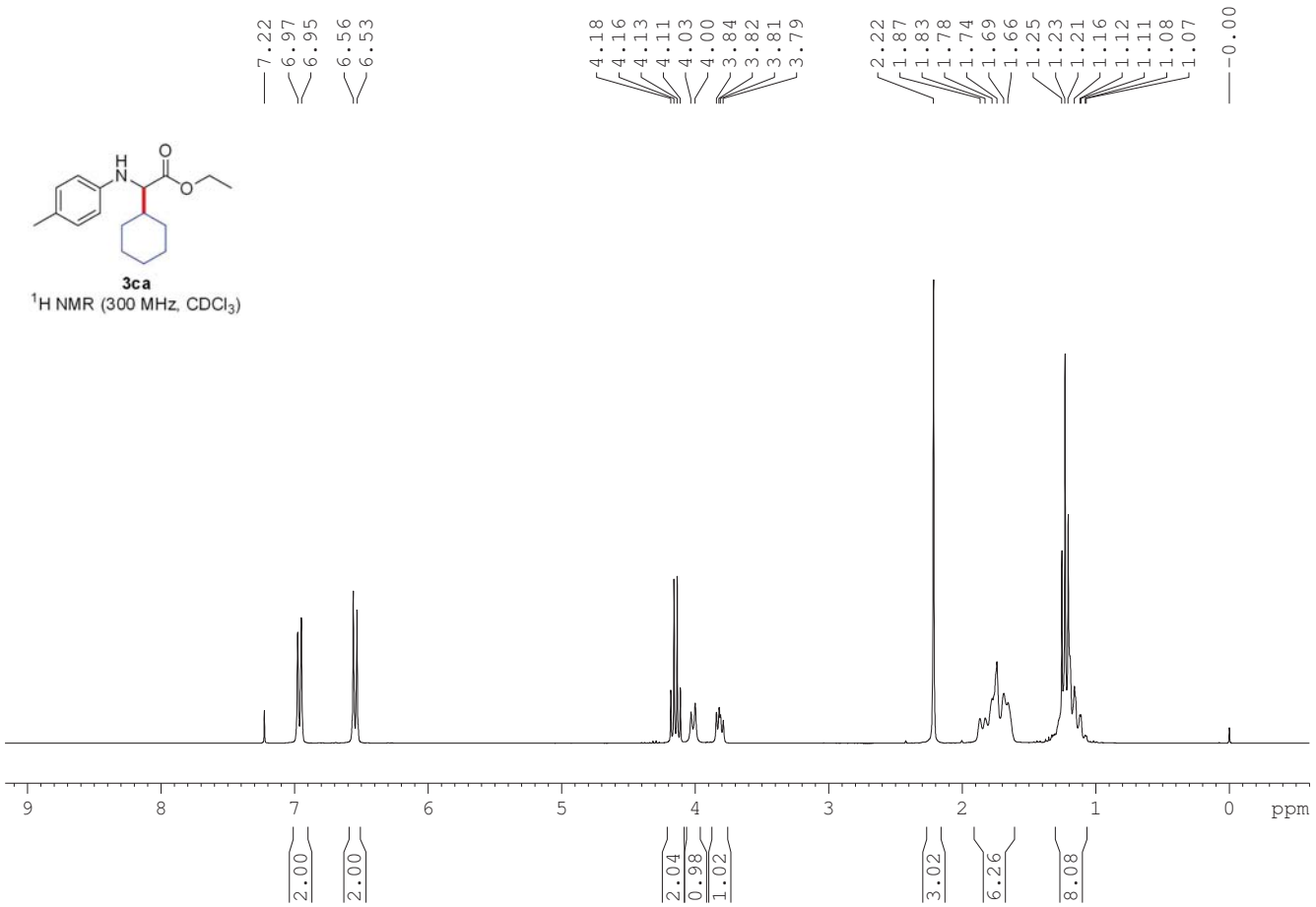
3ba

^{1}H NMR (300 MHz, $CDCl_3$)



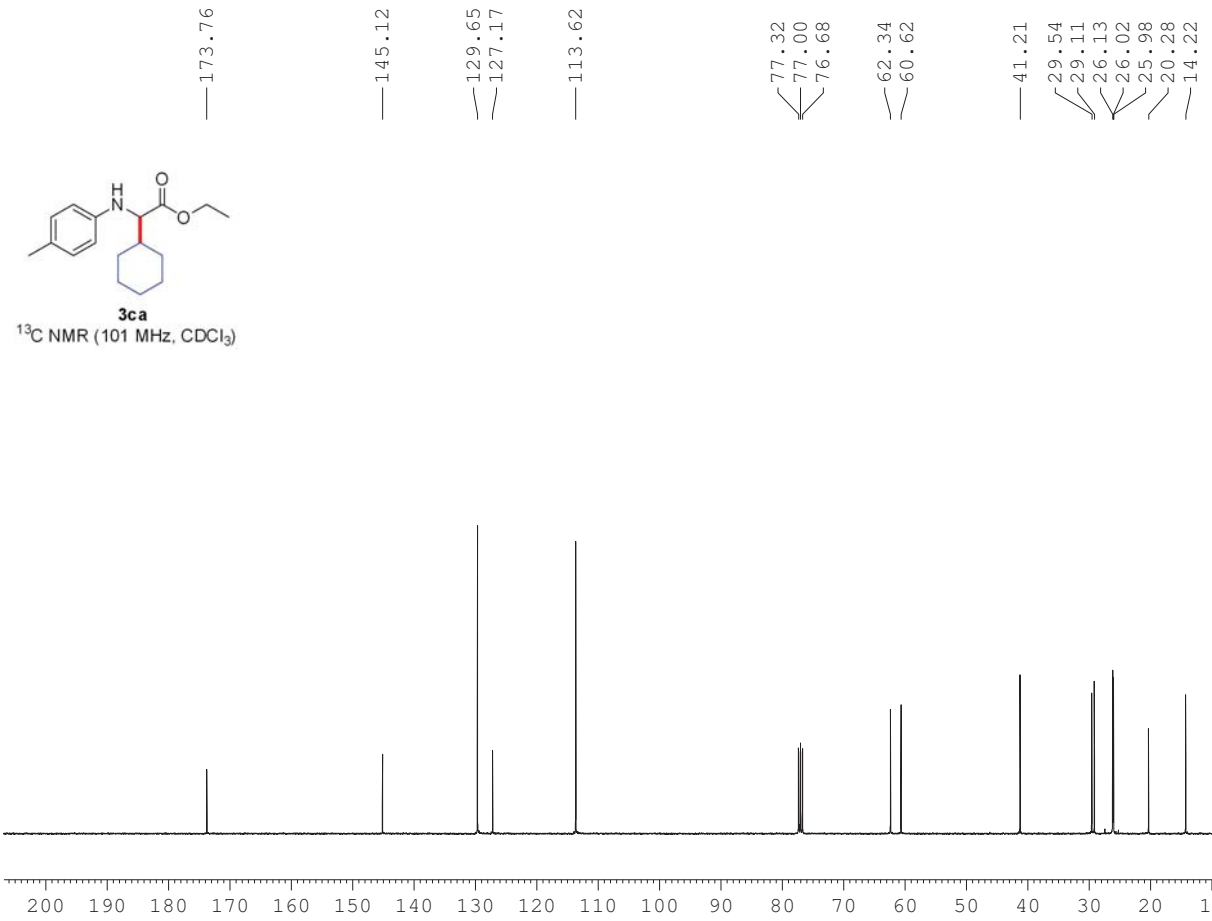
3ba

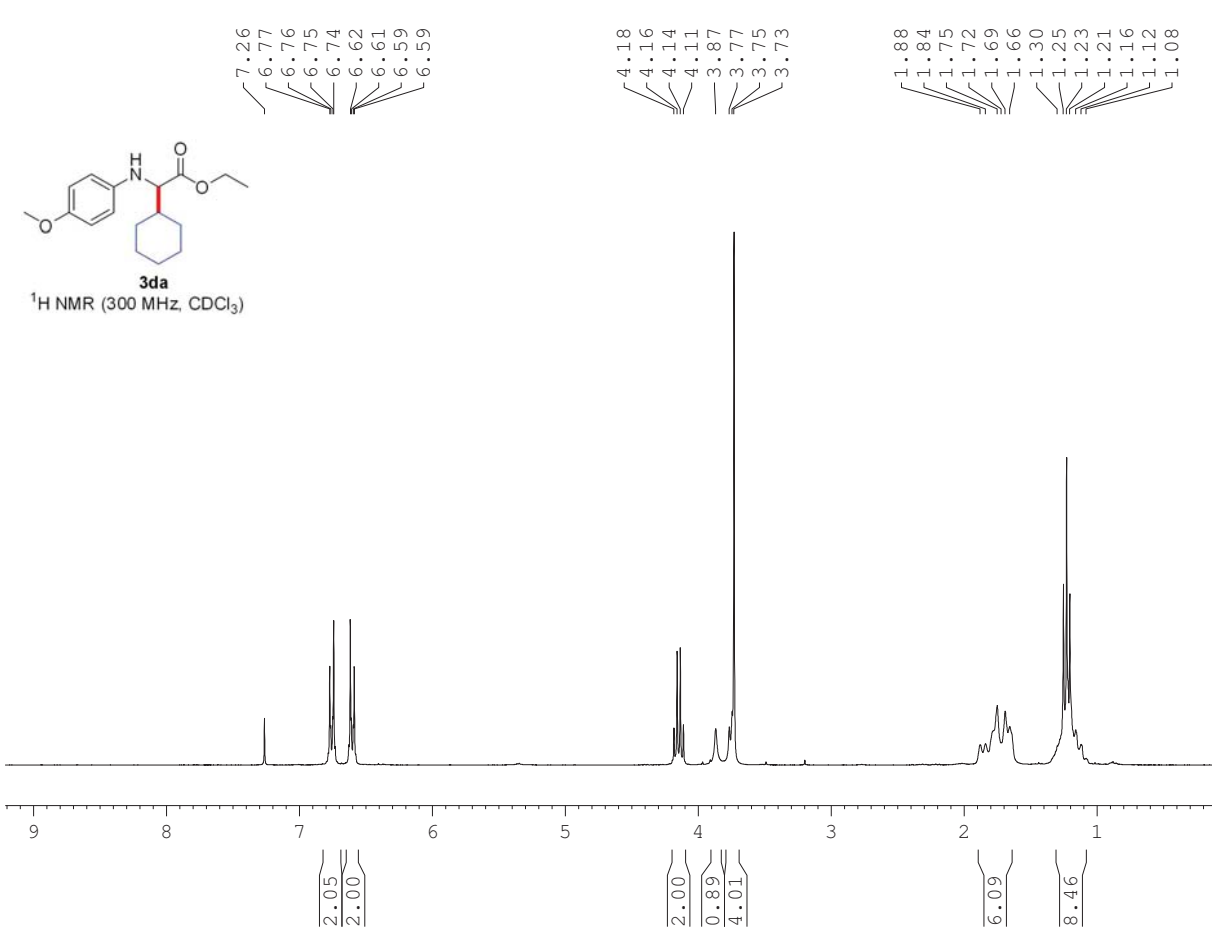
^{13}C NMR (101 MHz, $CDCl_3$)

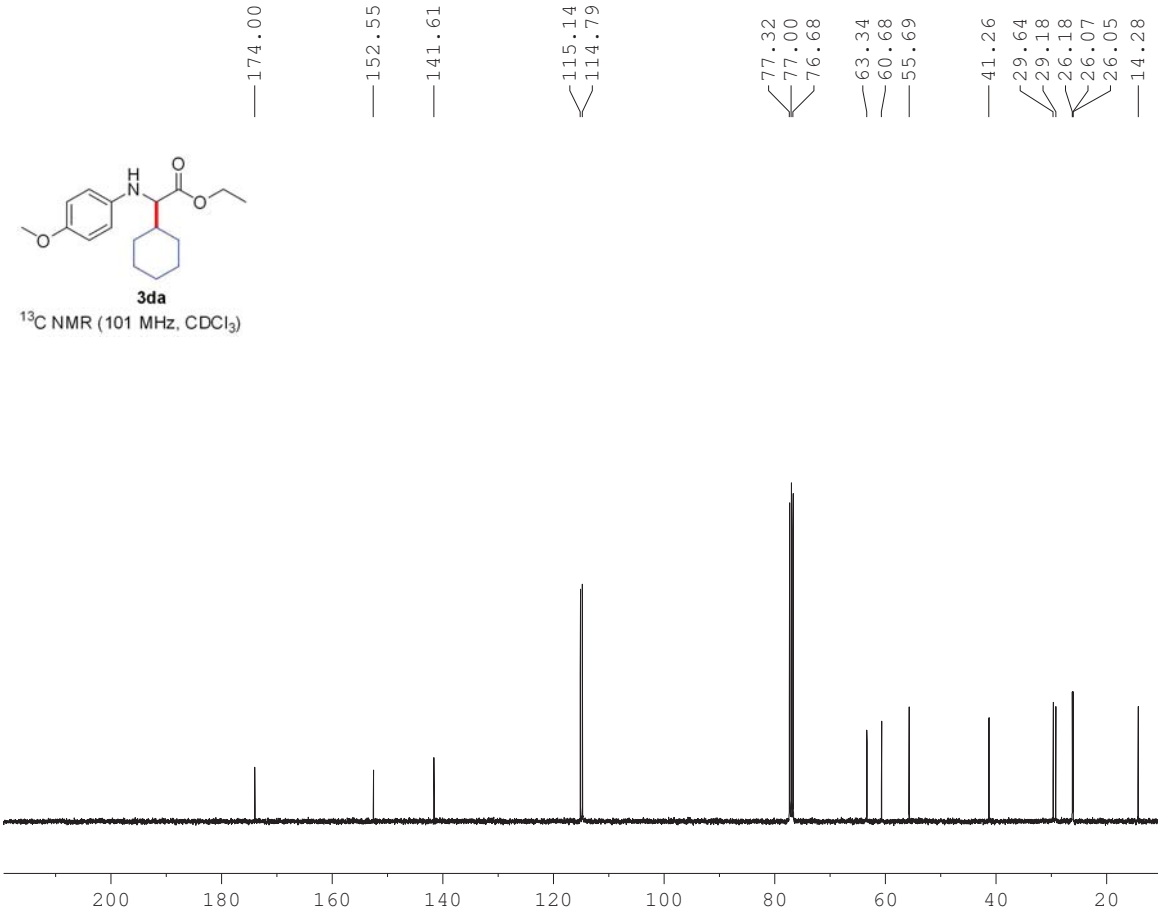


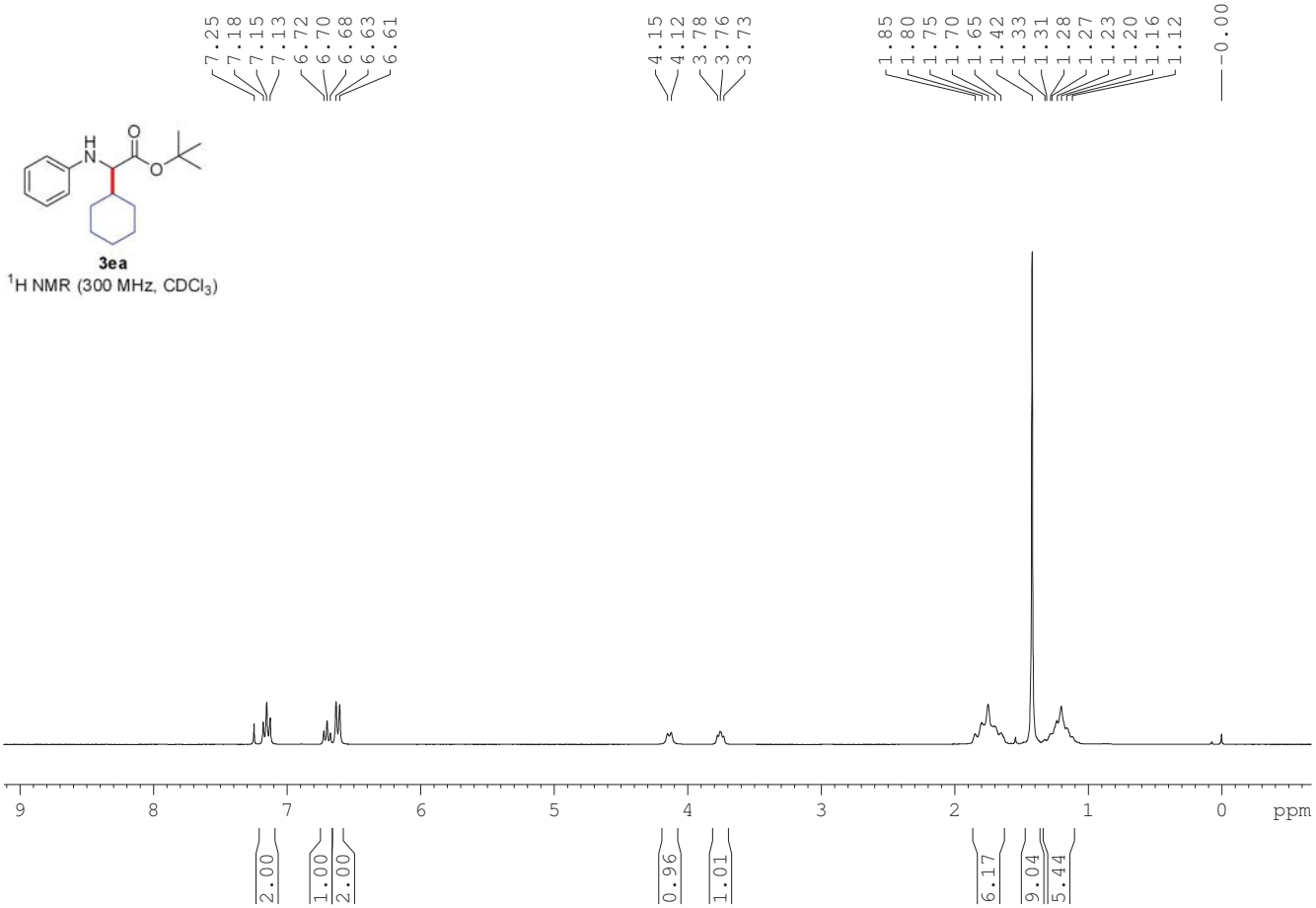
3ca

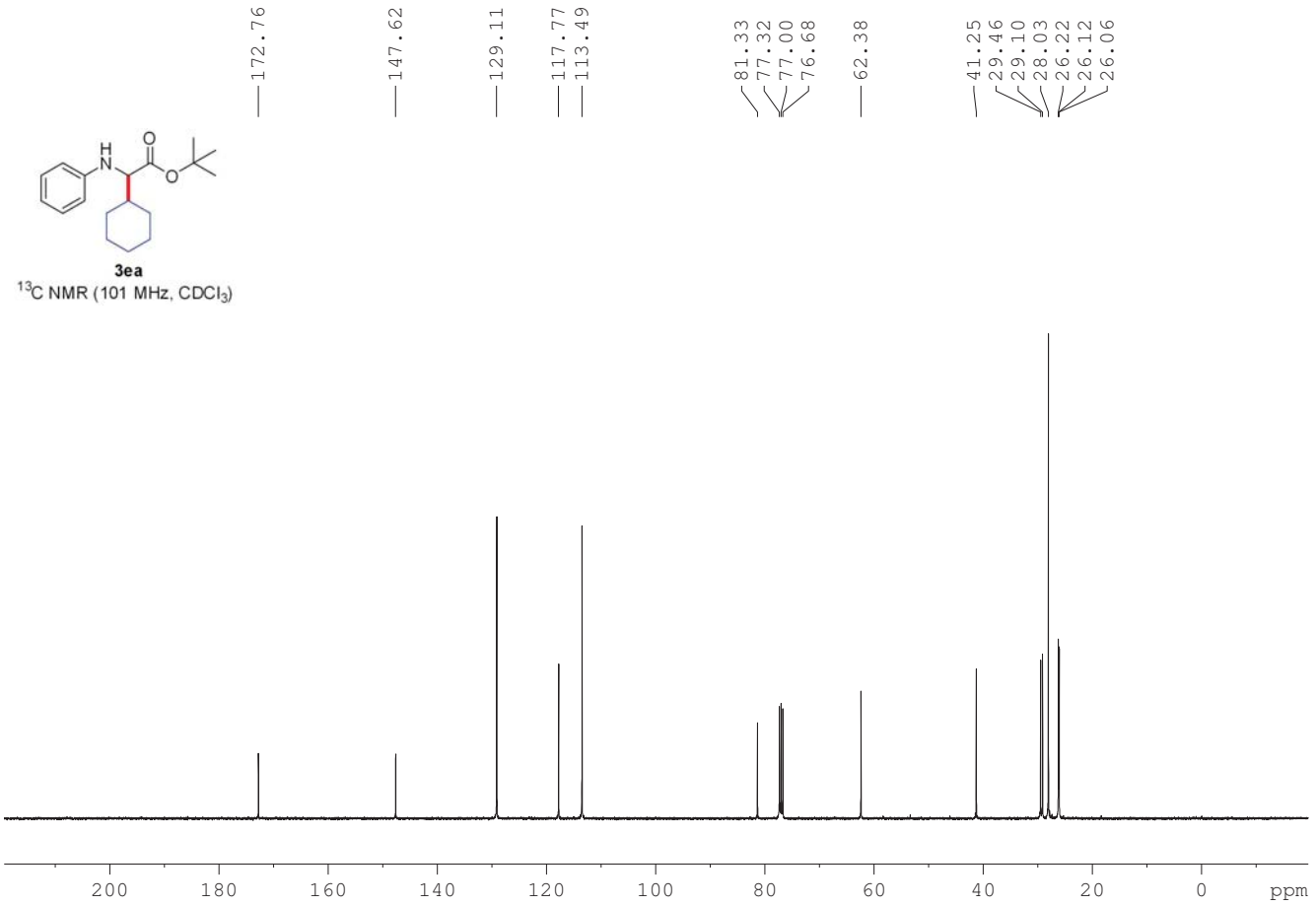
^{1}H NMR (300 MHz, $CDCl_3$)


173.76
145.12
129.65
127.17
113.62
77.32
77.00
76.68
62.34
60.62
41.21
29.54
29.11
26.13
26.02
25.98
20.28
14.22
3ca
13C NMR (101 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


7.26
6.77
6.76
6.75
6.74
6.62
6.61
6.59
6.59
4.18
4.16
4.14
4.11
3.87
3.77
3.75
3.73
1.88
1.84
1.75
1.72
1.69
1.66
1.30
1.25
1.23
1.21
1.16
1.12
1.08
0.00
3da
1H NMR (300 MHz, CDCl3)
9 8 7 6 5 4 3 2 1 0 ppm
2.05
2.00
2.00
0.89
4.01
6.09
8.46

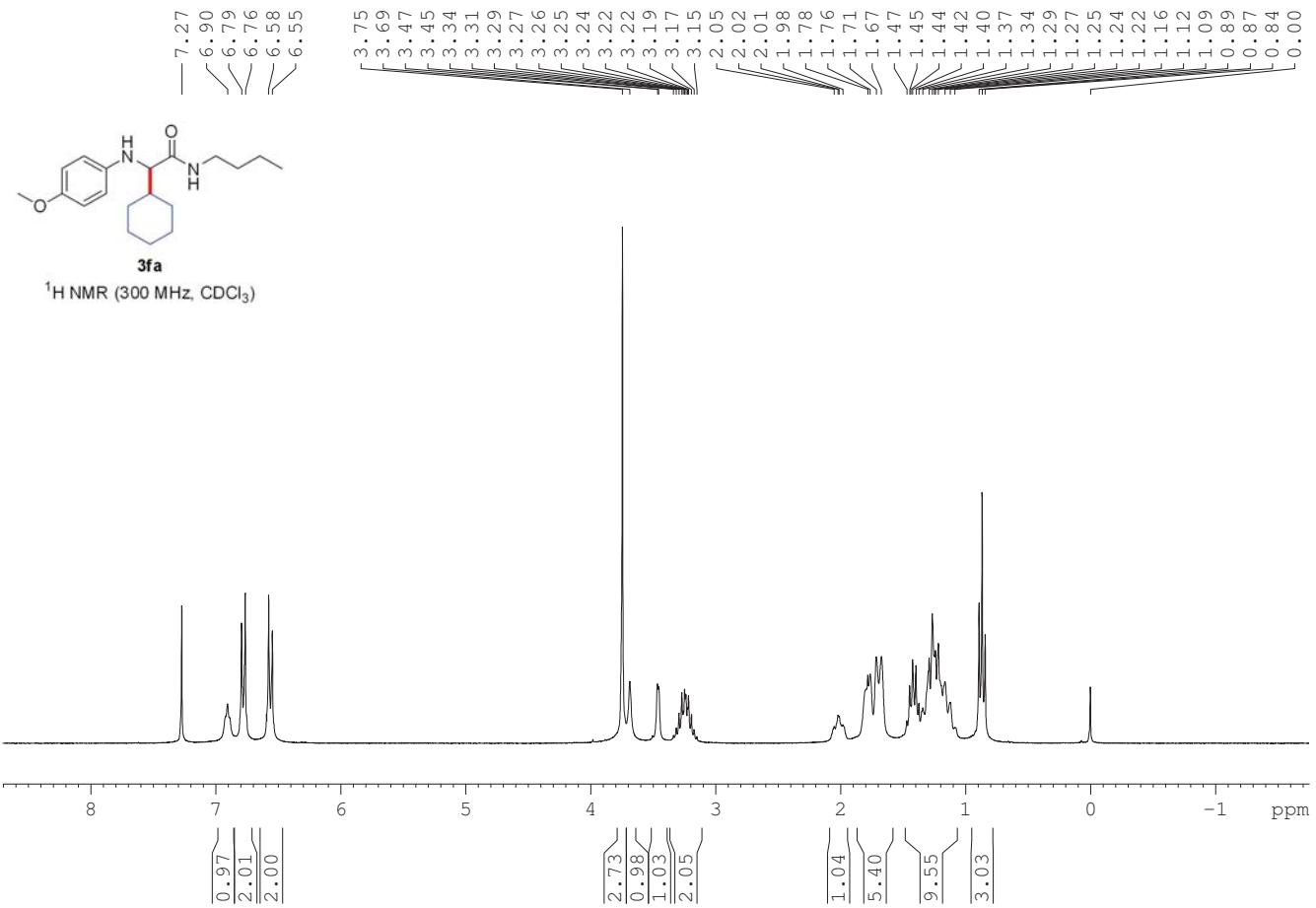

174.00
152.55
141.61
115.14
114.79
77.32
77.00
76.68
63.34
60.68
55.69
41.26
29.64
29.18
26.18
26.07
26.05
14.28
3da
13C NMR (101 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm


7.25
7.18
7.15
7.13
6.72
6.70
6.68
6.63
6.61
4.15
4.12
3.78
3.76
3.73
1.85
1.80
1.75
1.70
1.65
1.42
1.33
1.31
1.28
1.27
1.23
1.20
1.16
1.12
0.00
3ea
1H NMR (300 MHz, CDCl3)
9
8
7
6
5
4
3
2
1
0
ppm
2.00
1.00
2.00
0.96
1.01
6.17
9.04
5.44



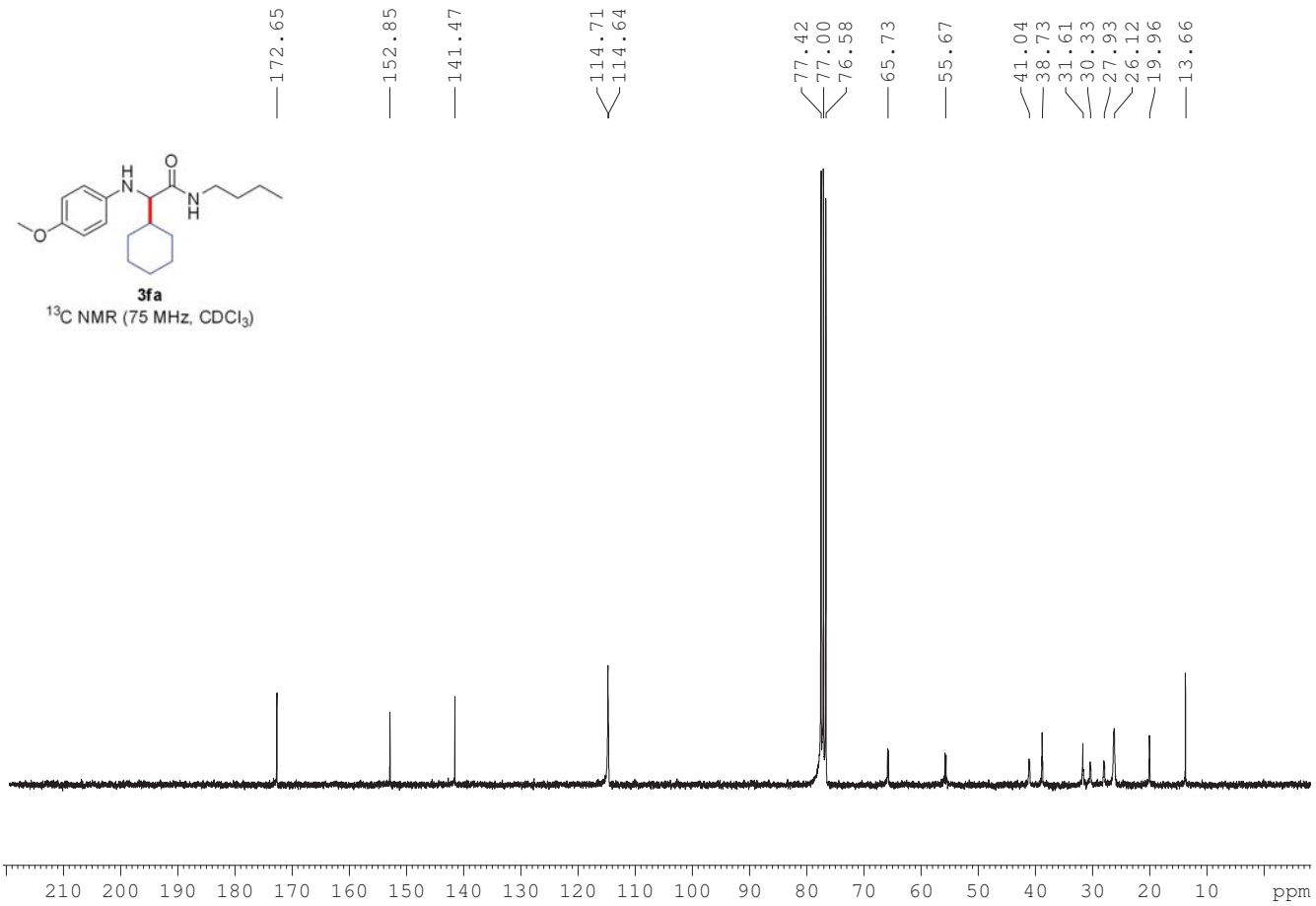
3ea

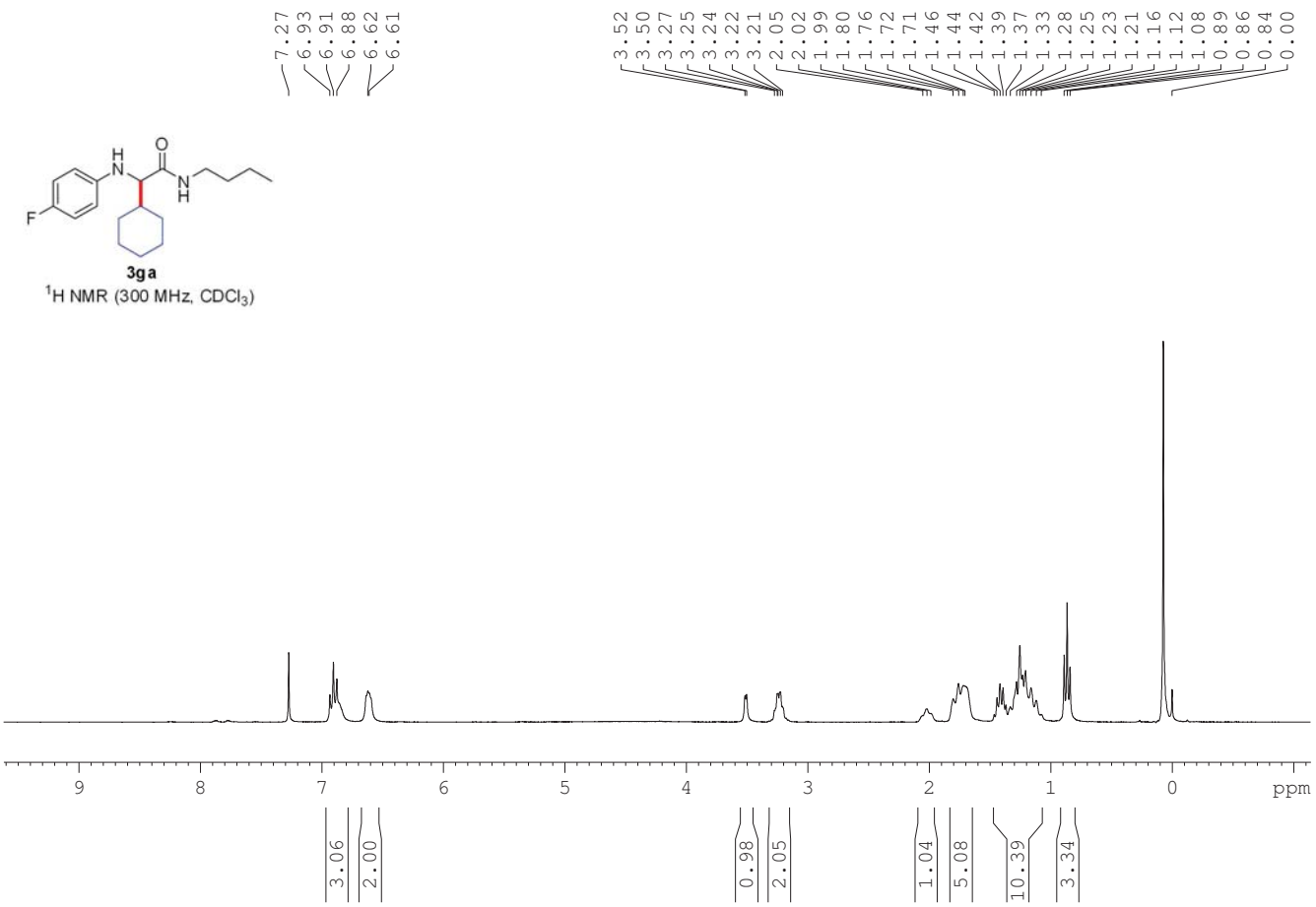
^{13}C NMR (101 MHz, $CDCl_3$)

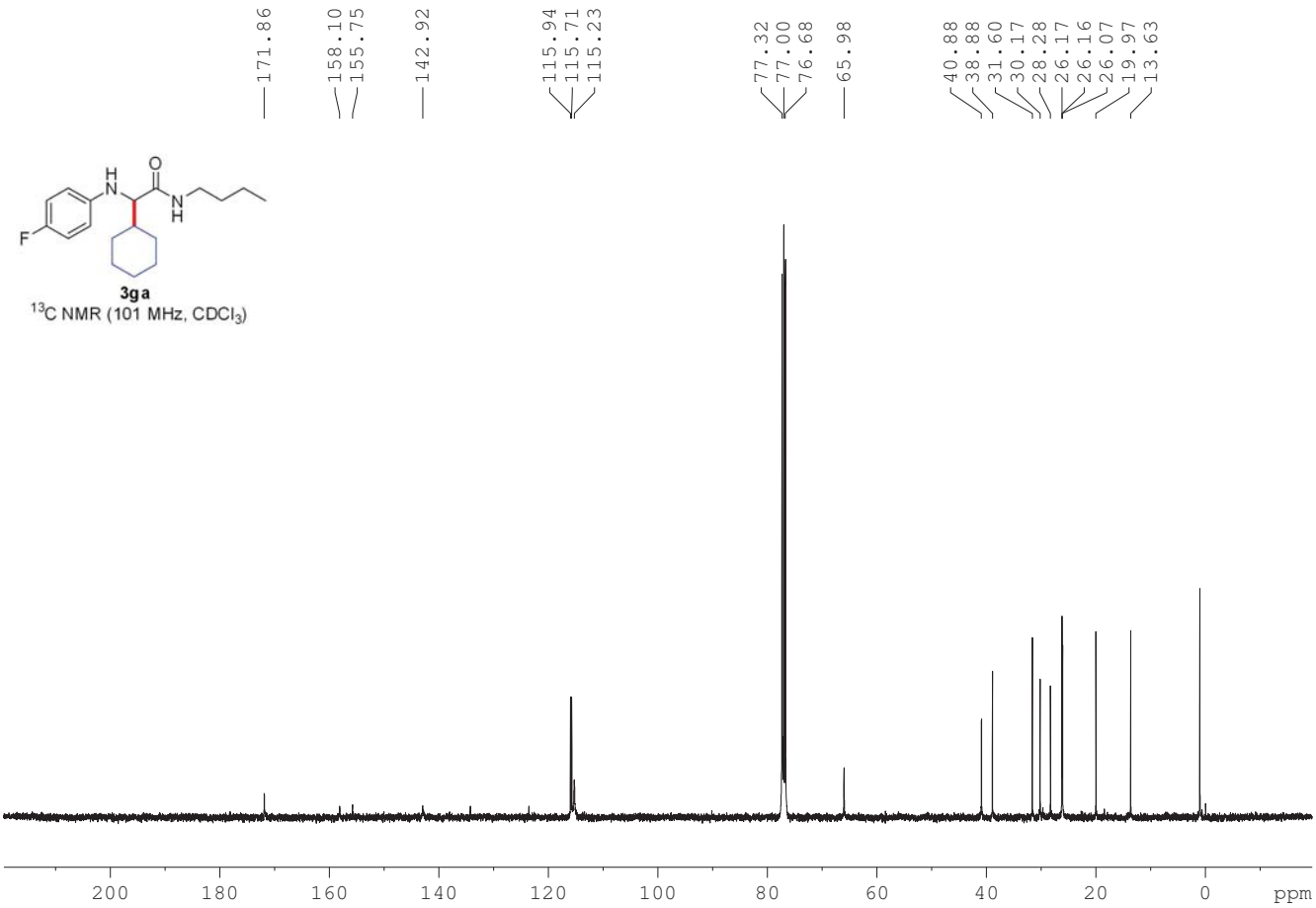


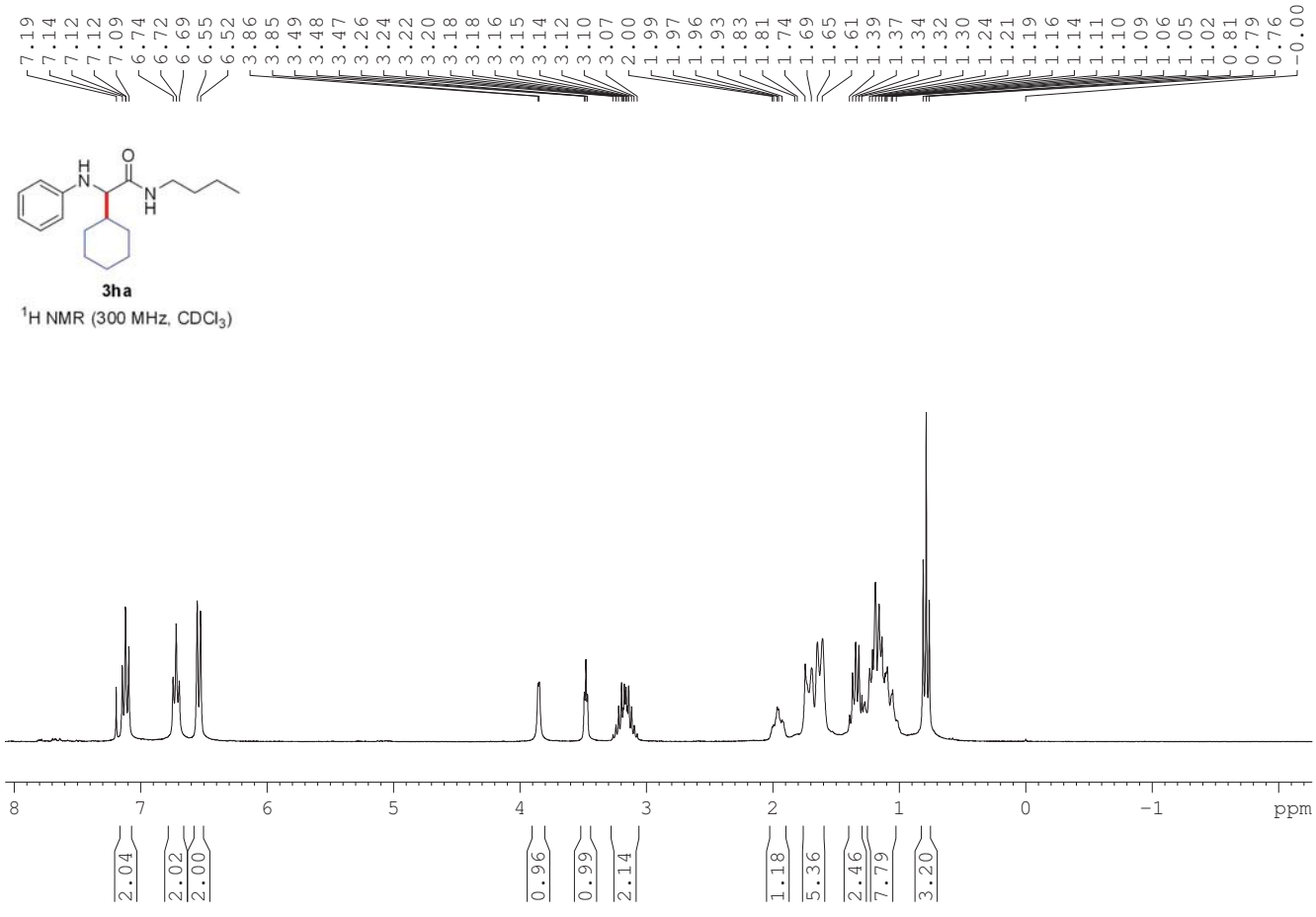
3fa

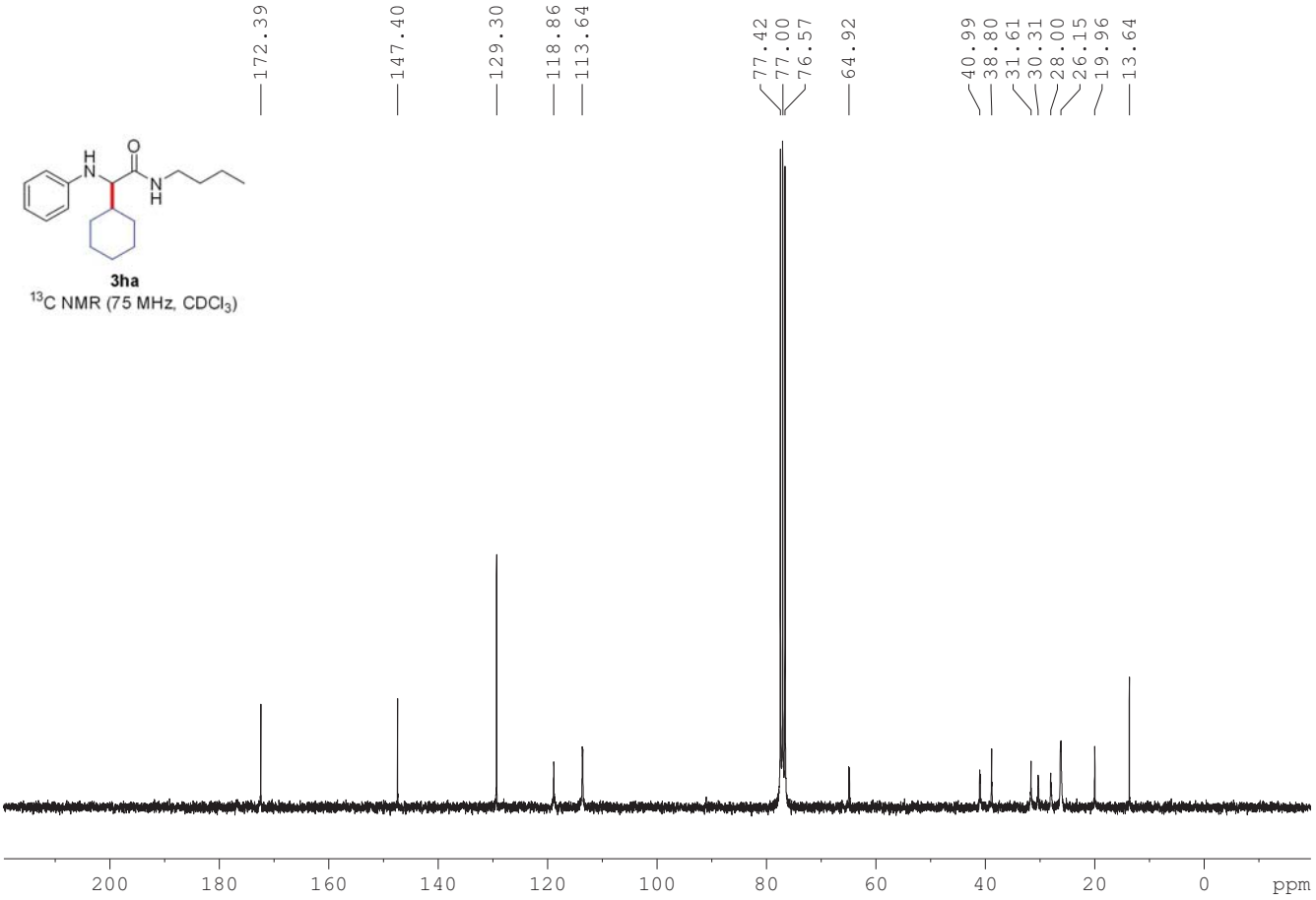
^{1}H NMR (300 MHz, $CDCl_3$)


172.65
152.85
141.47
114.71
114.64
77.42
77.00
76.58
65.73
55.67
41.04
38.73
31.61
30.33
27.93
26.12
19.96
13.66
3fa
13C NMR (75 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.27
6.93
6.91
6.88
6.62
6.61
3.52
3.50
3.27
3.25
3.24
3.22
3.21
2.05
2.02
1.99
1.80
1.76
1.72
1.71
1.46
1.44
1.42
1.39
1.37
1.33
1.28
1.25
1.23
1.21
1.16
1.12
1.08
0.89
0.86
0.84
0.00
3ga
1H NMR (300 MHz, CDCl3)
9 8 7 6 5 4 3 2 1 0 ppm
3.06
2.00
0.98
2.05
1.04
5.08
10.39
3.34

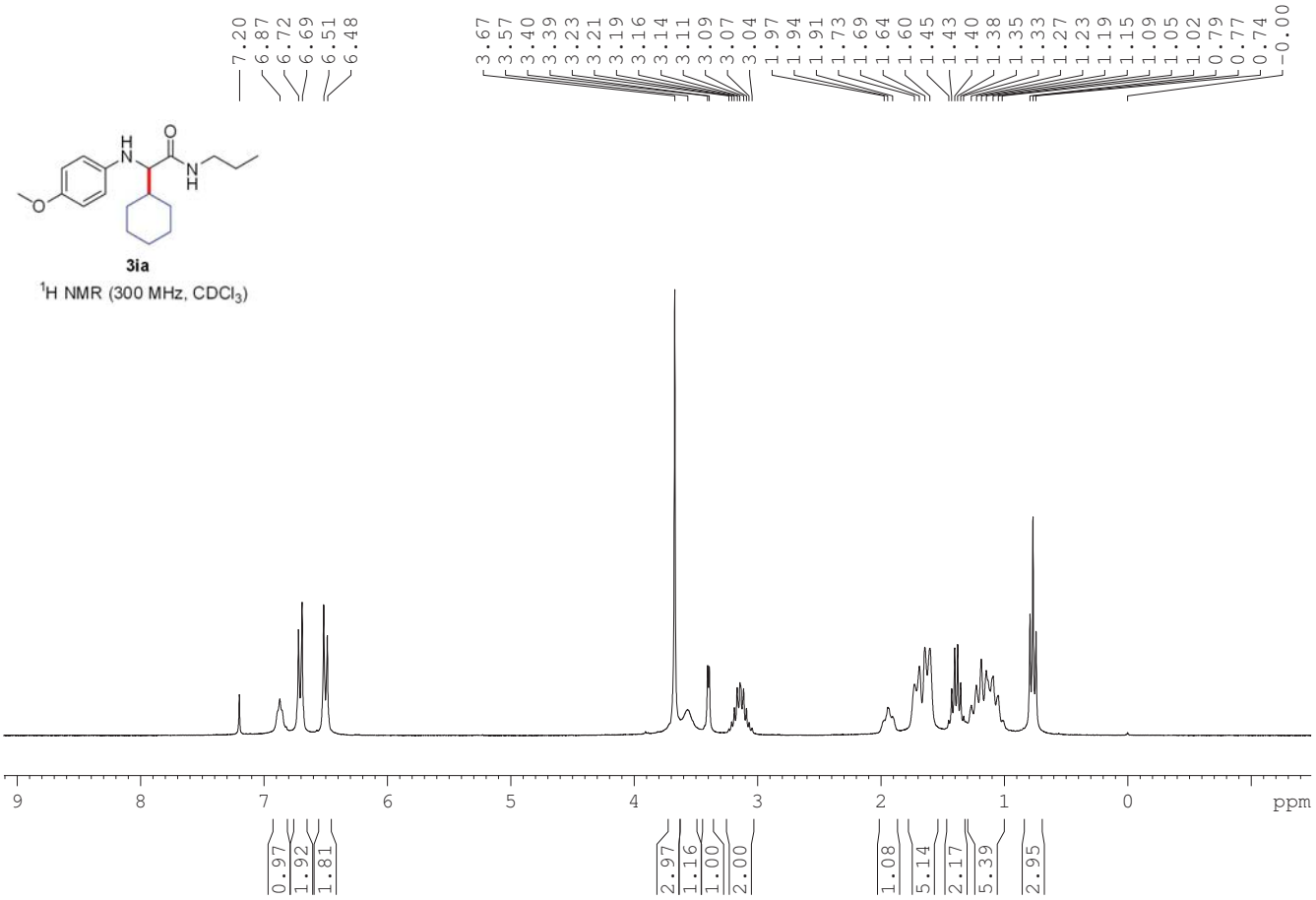

171.86
158.10
155.75
142.92
115.94
115.71
115.23
77.32
77.00
76.68
65.98
40.88
38.88
31.60
30.17
28.28
26.17
26.16
26.07
19.97
13.63
3ga
13C NMR (101 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm


7.19
7.14
7.12
7.12
7.09
6.74
6.72
6.69
6.55
6.52
3.86
3.85
3.49
3.48
3.47
3.26
3.24
3.22
3.20
3.18
3.18
3.16
3.15
3.14
3.12
3.10
3.07
2.00
1.99
1.97
1.96
1.93
1.83
1.81
1.74
1.69
1.65
1.61
1.39
1.37
1.34
1.32
1.30
1.24
1.21
1.19
1.16
1.14
1.11
1.10
1.09
1.06
1.05
1.02
0.81
0.79
0.76
0.00
3ha
1H NMR (300 MHz, CDCl3)
8
7
6
5
4
3
2
1
0
−1
ppm
2.04
2.02
2.00
0.96
0.99
2.14
1.18
5.36
2.46
7.79
3.20



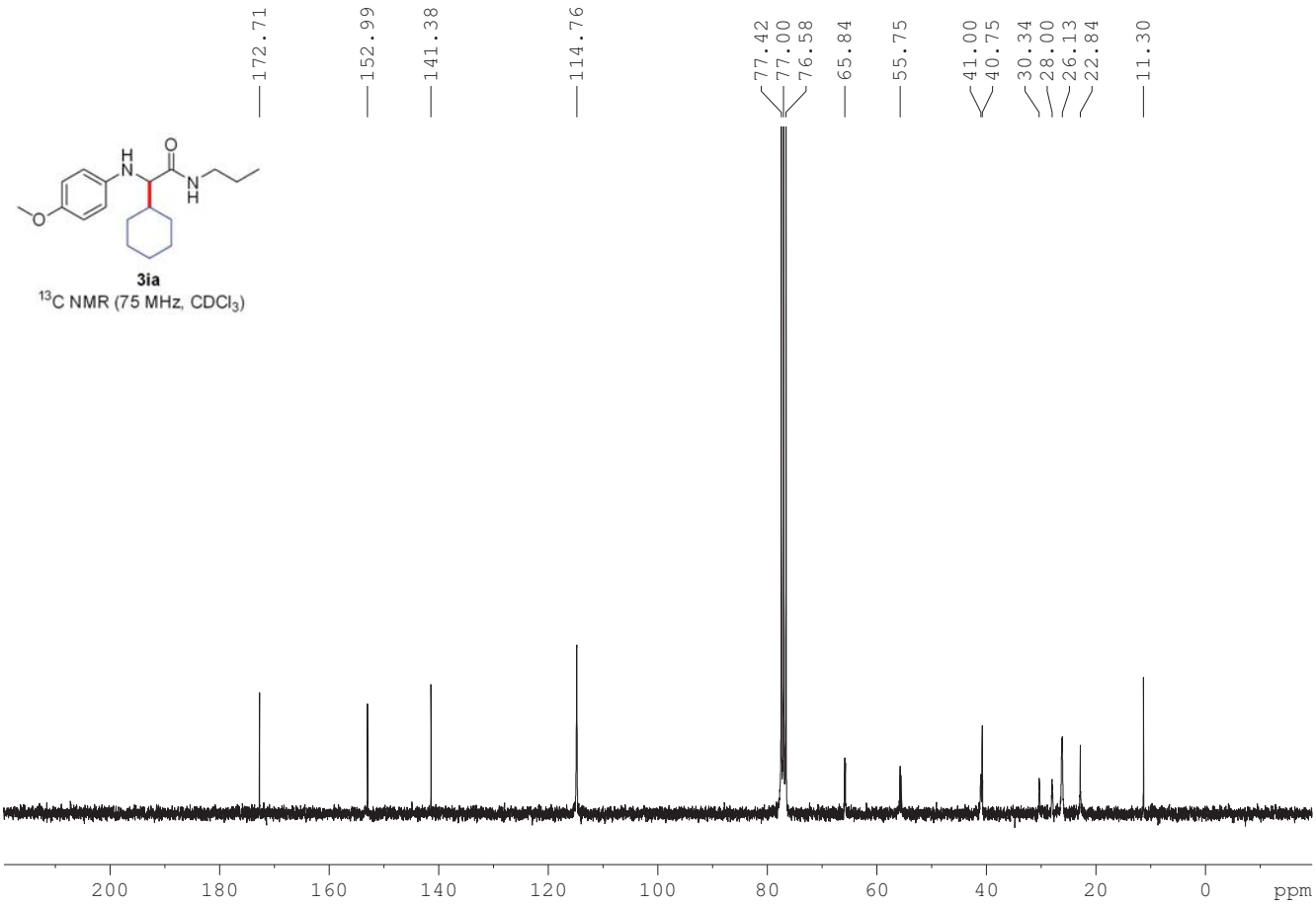
3ha

^{13}C NMR (75 MHz, $CDCl_3$)



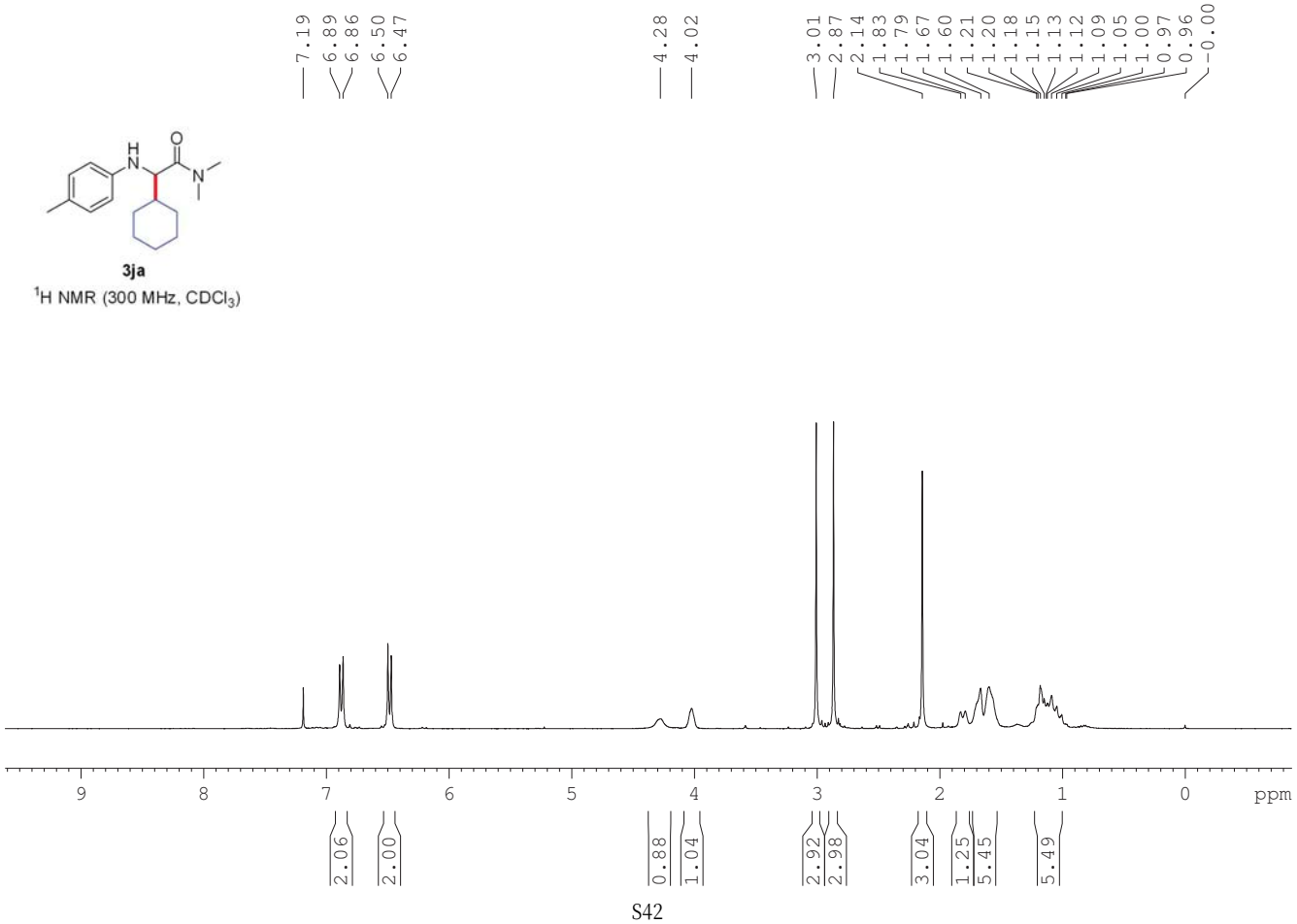
3ia

^{1}H NMR (300 MHz, $CDCl_3$)



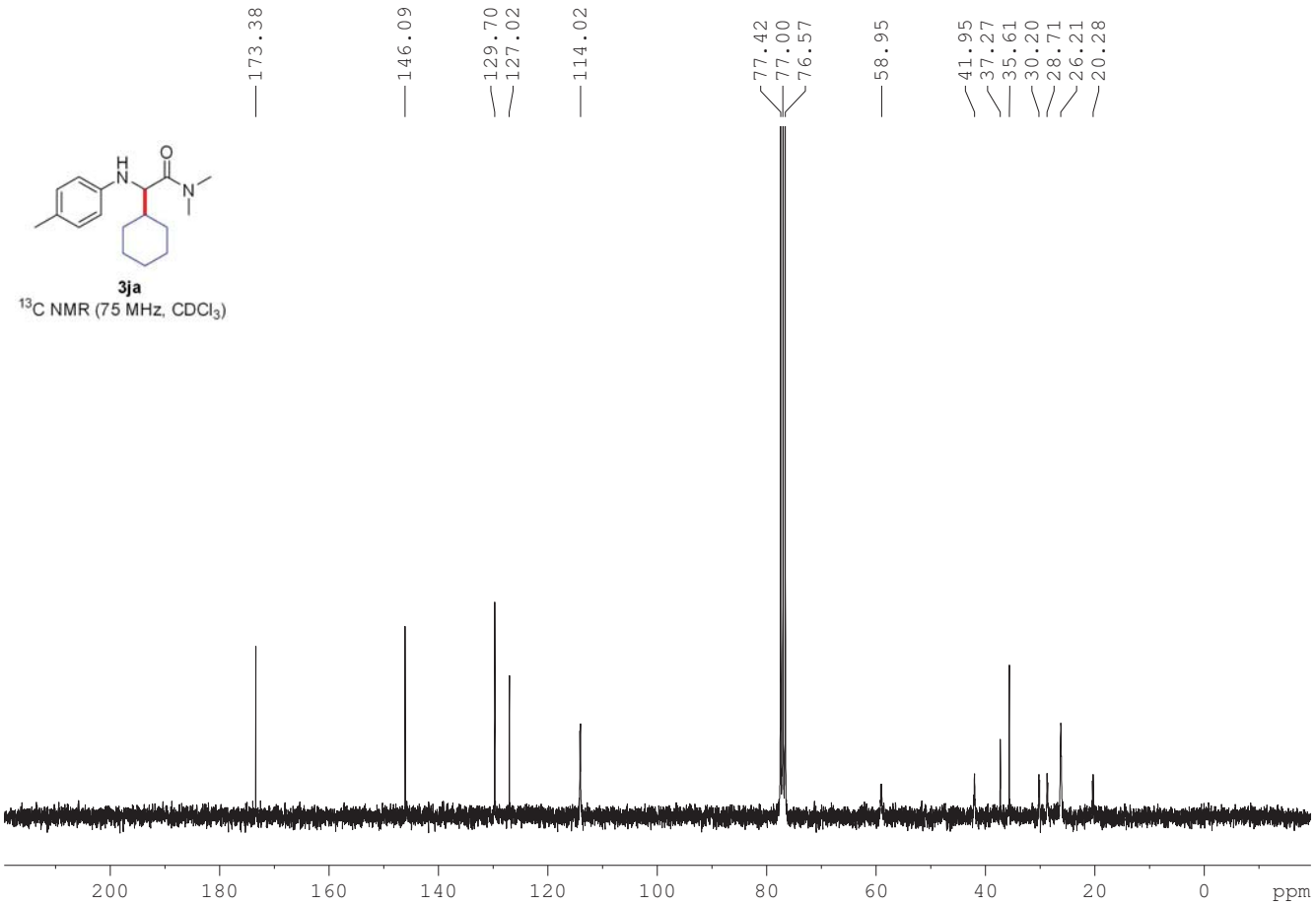
3ia

^{13}C NMR (75 MHz, $CDCl_3$)



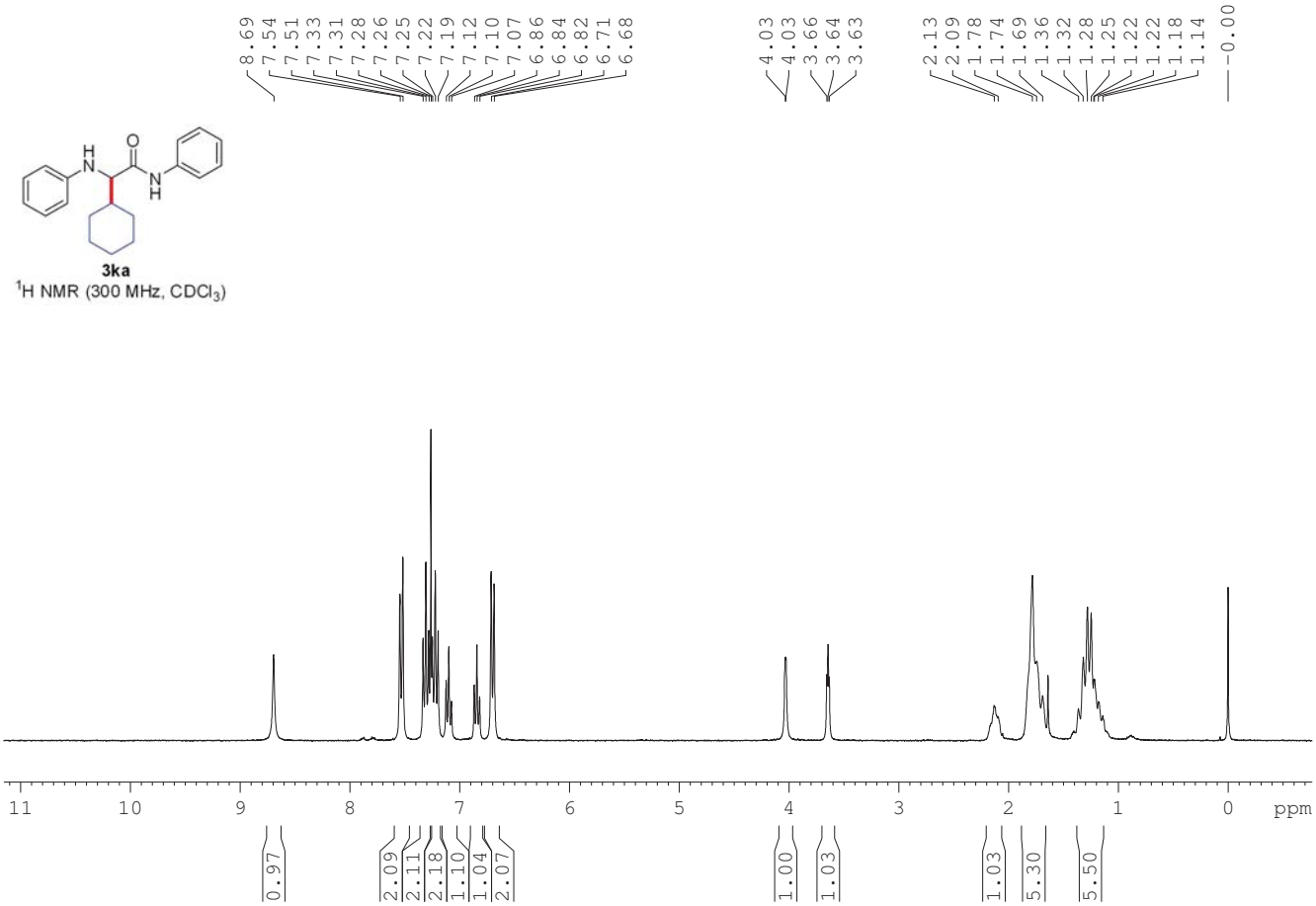
3ja

^{1}H NMR (300 MHz, $CDCl_3$)



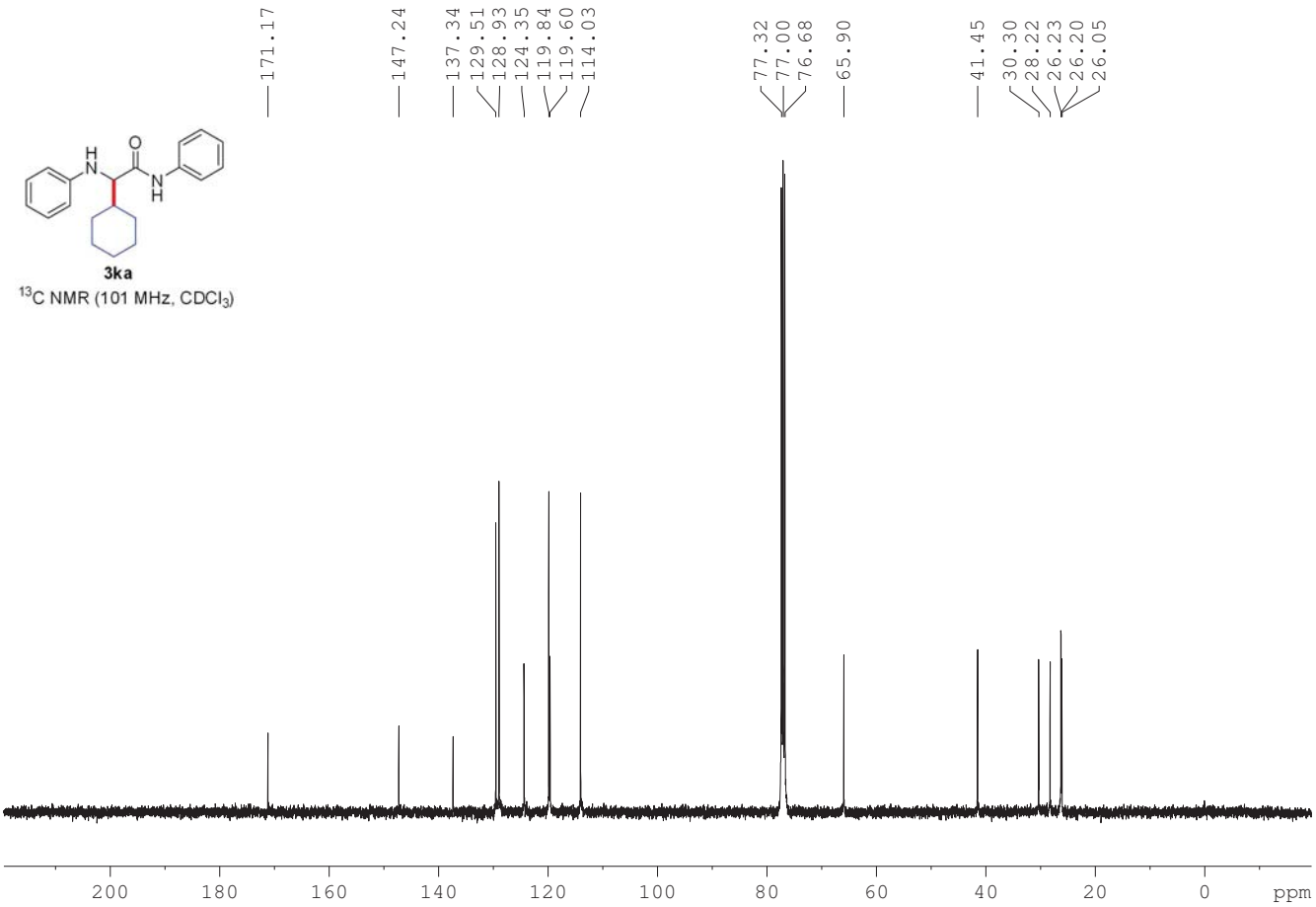
3ja

^{13}C NMR (75 MHz, $CDCl_3$)



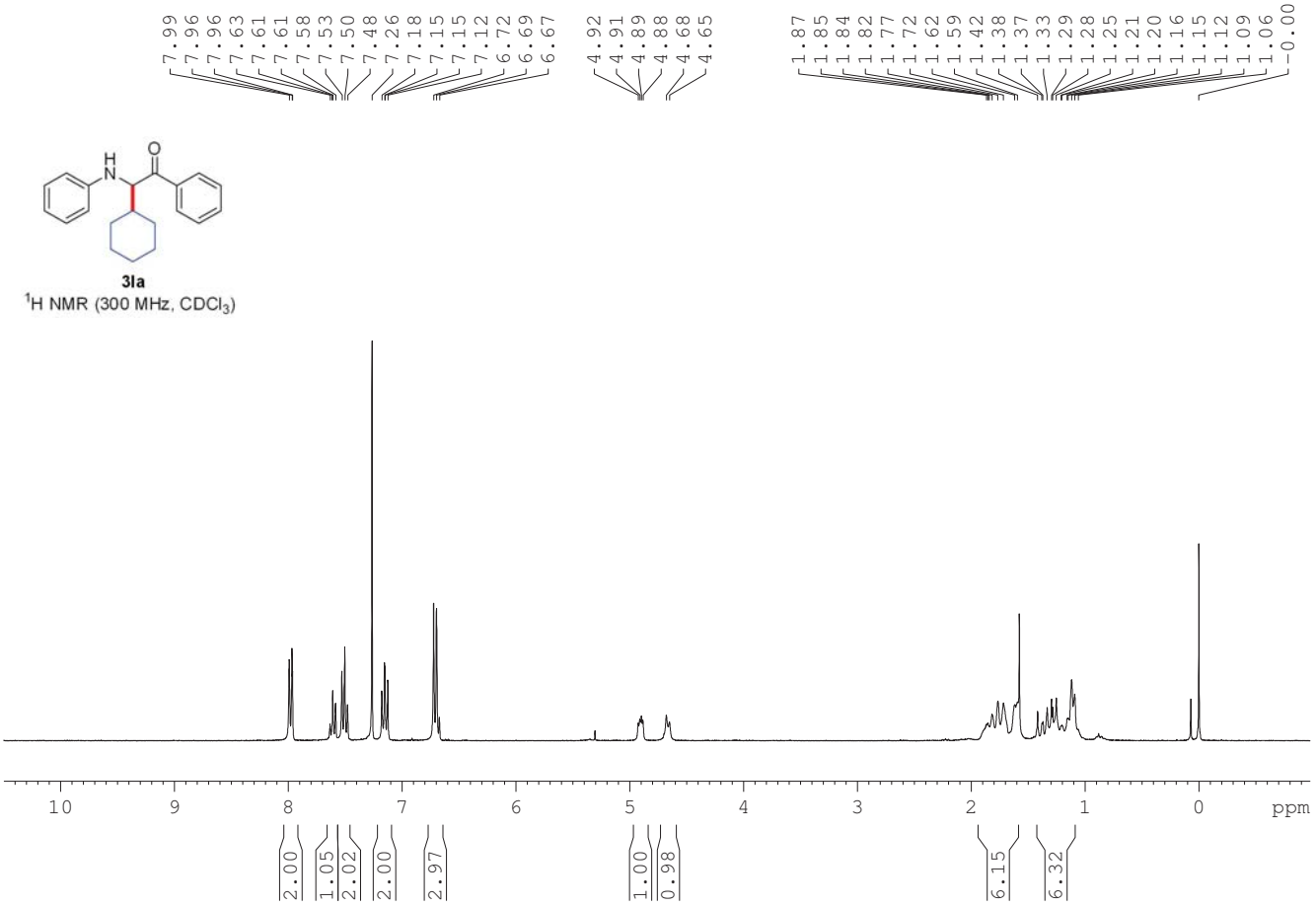
3ka

^{1}H NMR (300 MHz, $CDCl_3$)



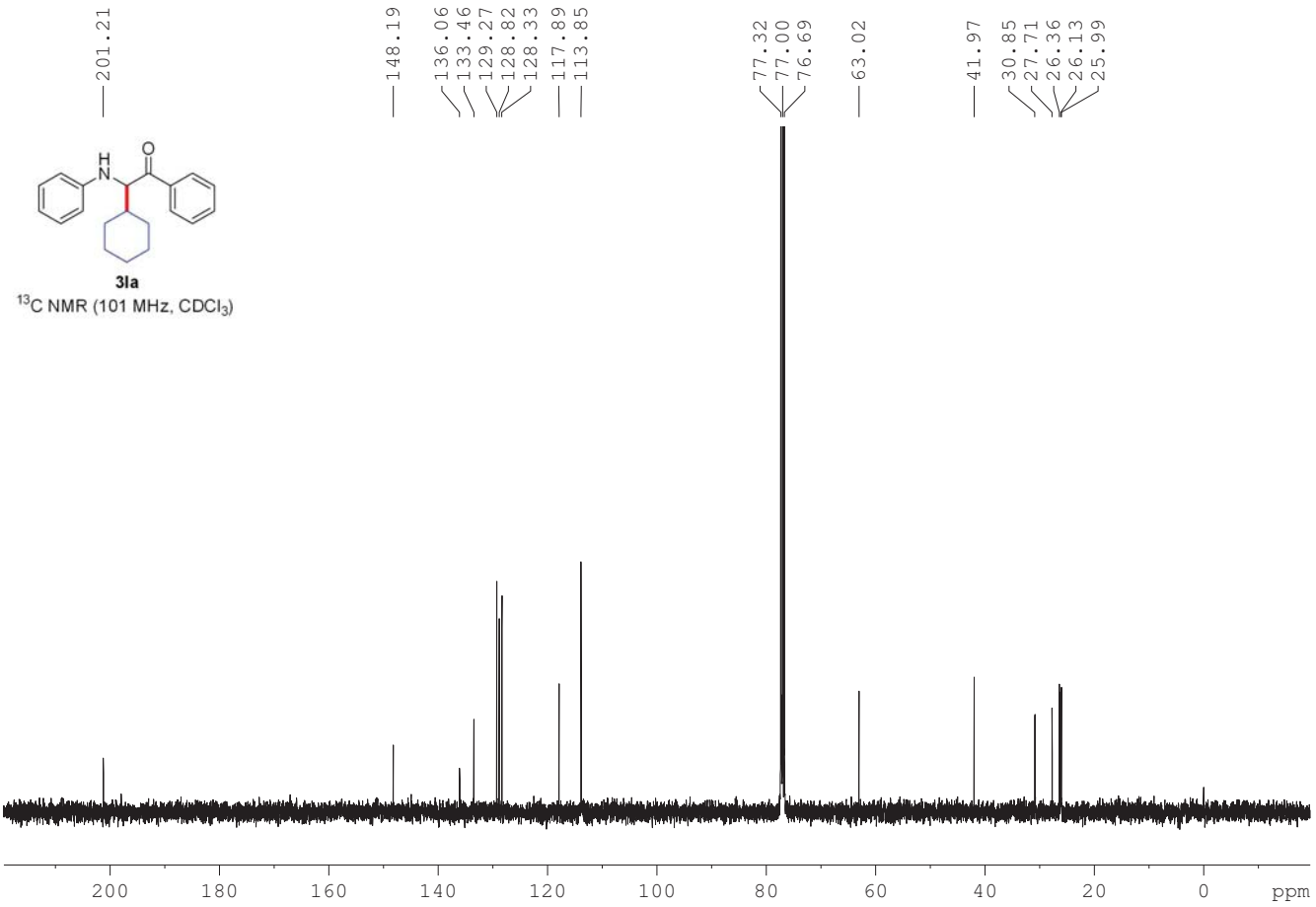
3ka

^{13}C NMR (101 MHz, $CDCl_3$)



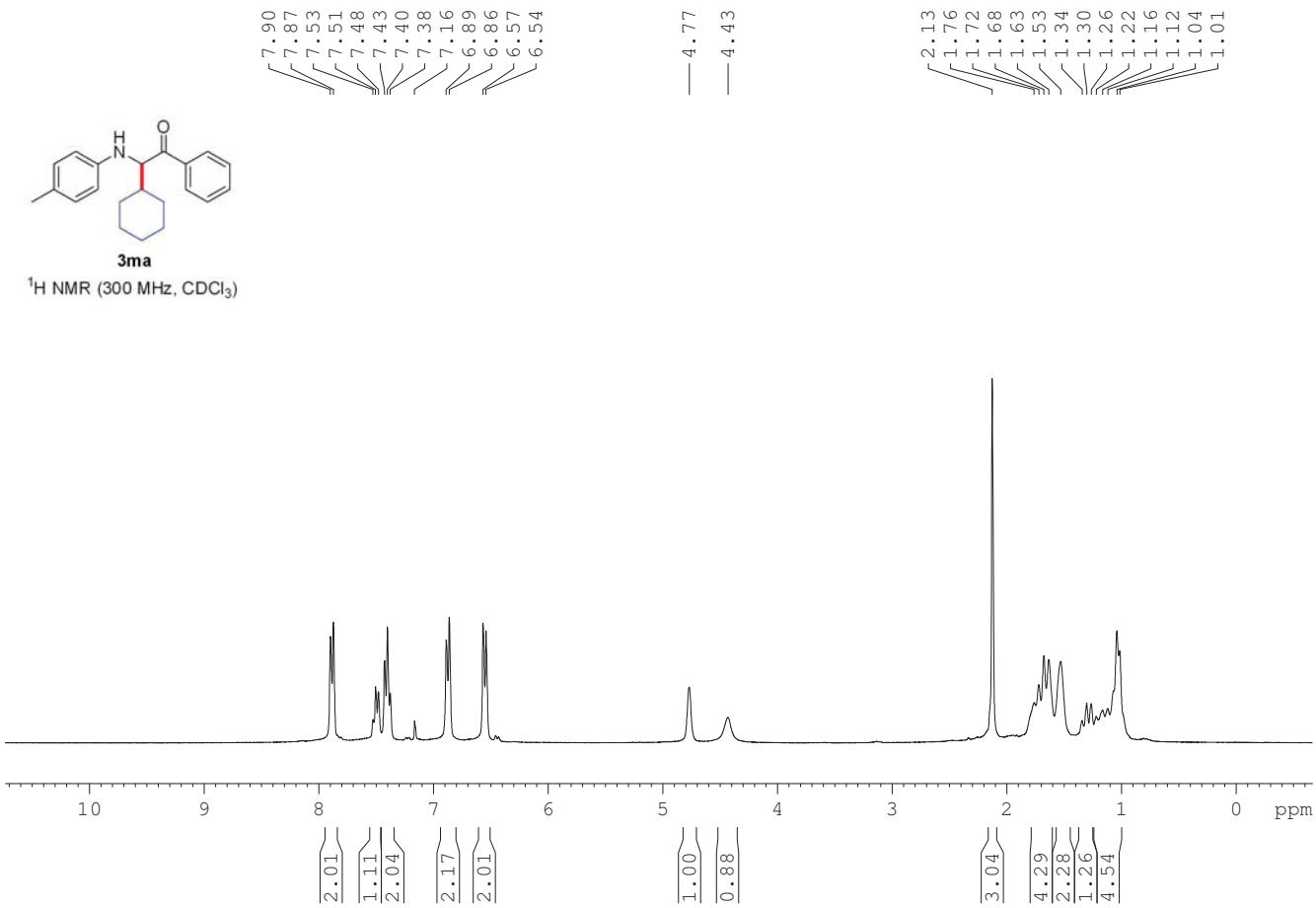
3la

^{1}H NMR (300 MHz, $CDCl_3$)



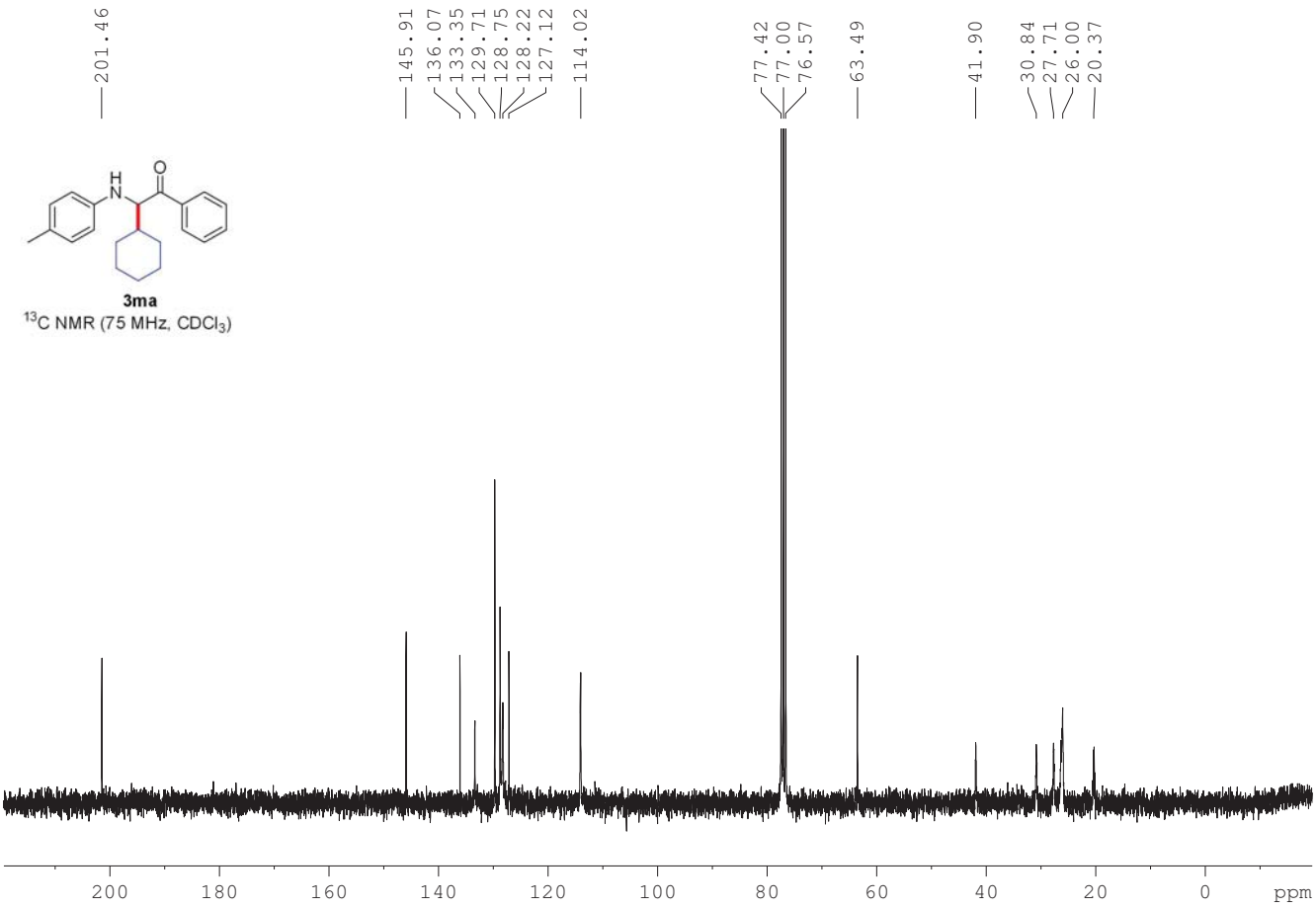
3la

^{13}C NMR (101 MHz, $CDCl_3$)



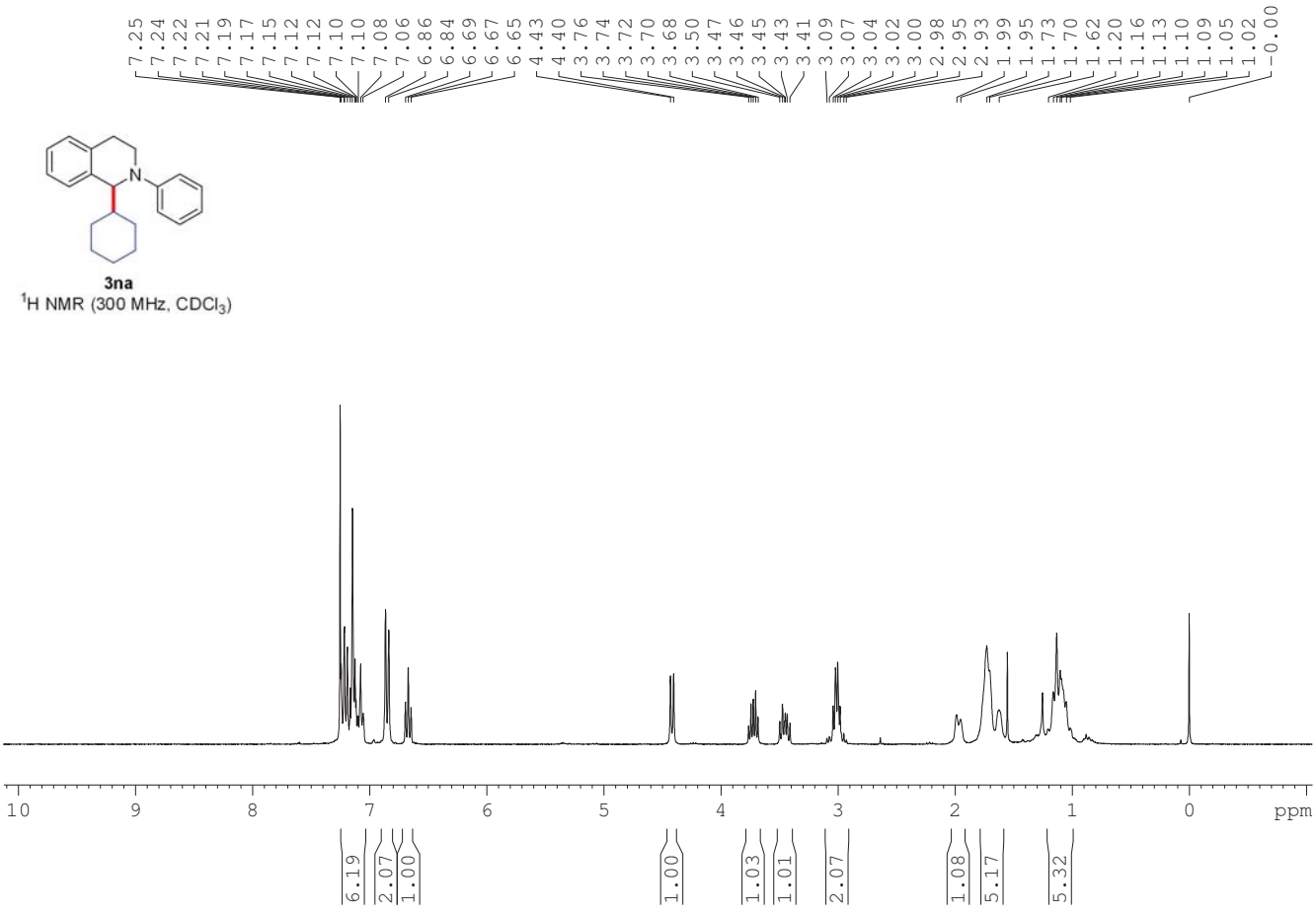
3ma

^{1}H NMR (300 MHz, $CDCl_3$)



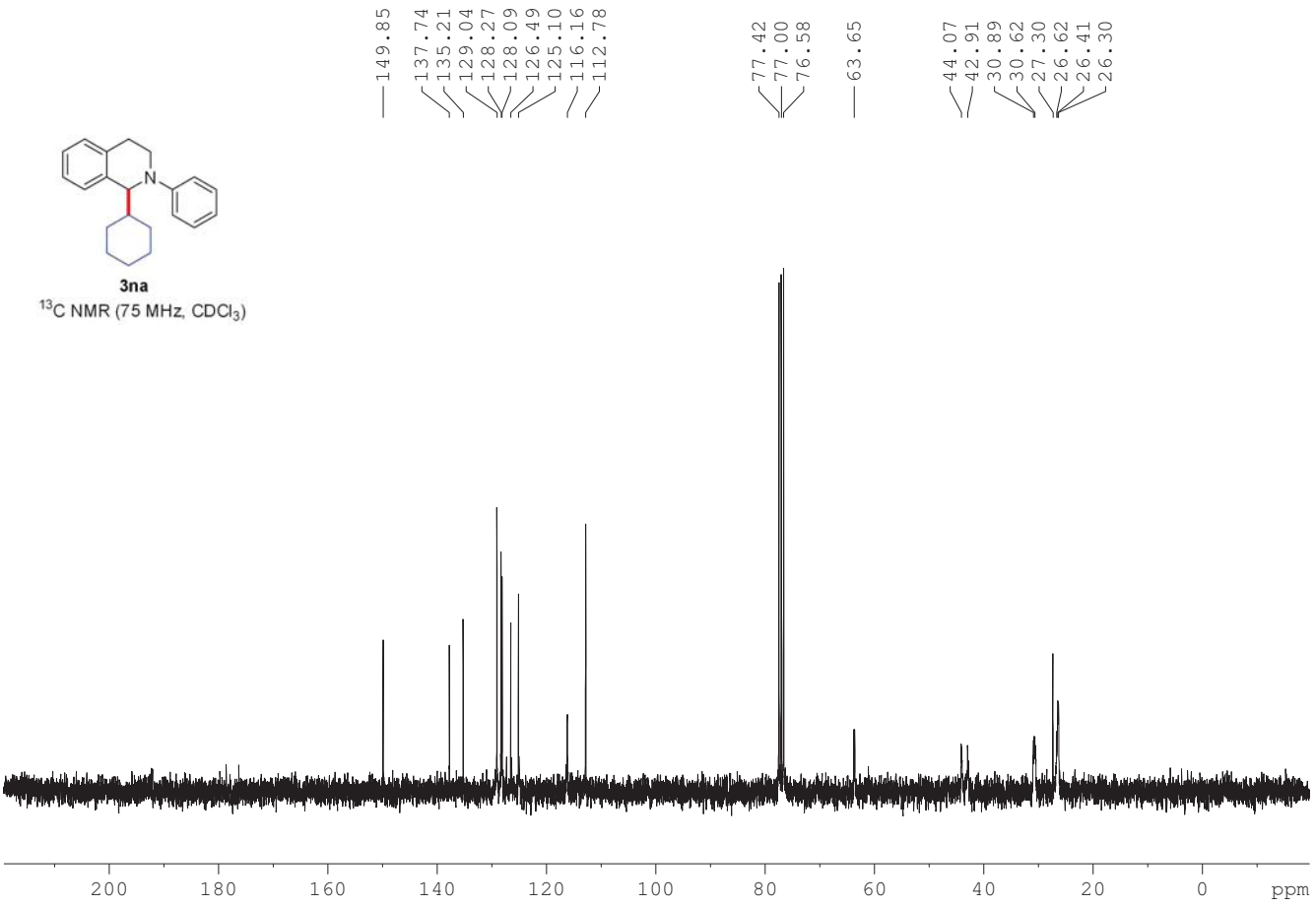
3ma

^{13}C NMR (75 MHz, $CDCl_3$)



3na

^{1}H NMR (300 MHz, $CDCl_3$)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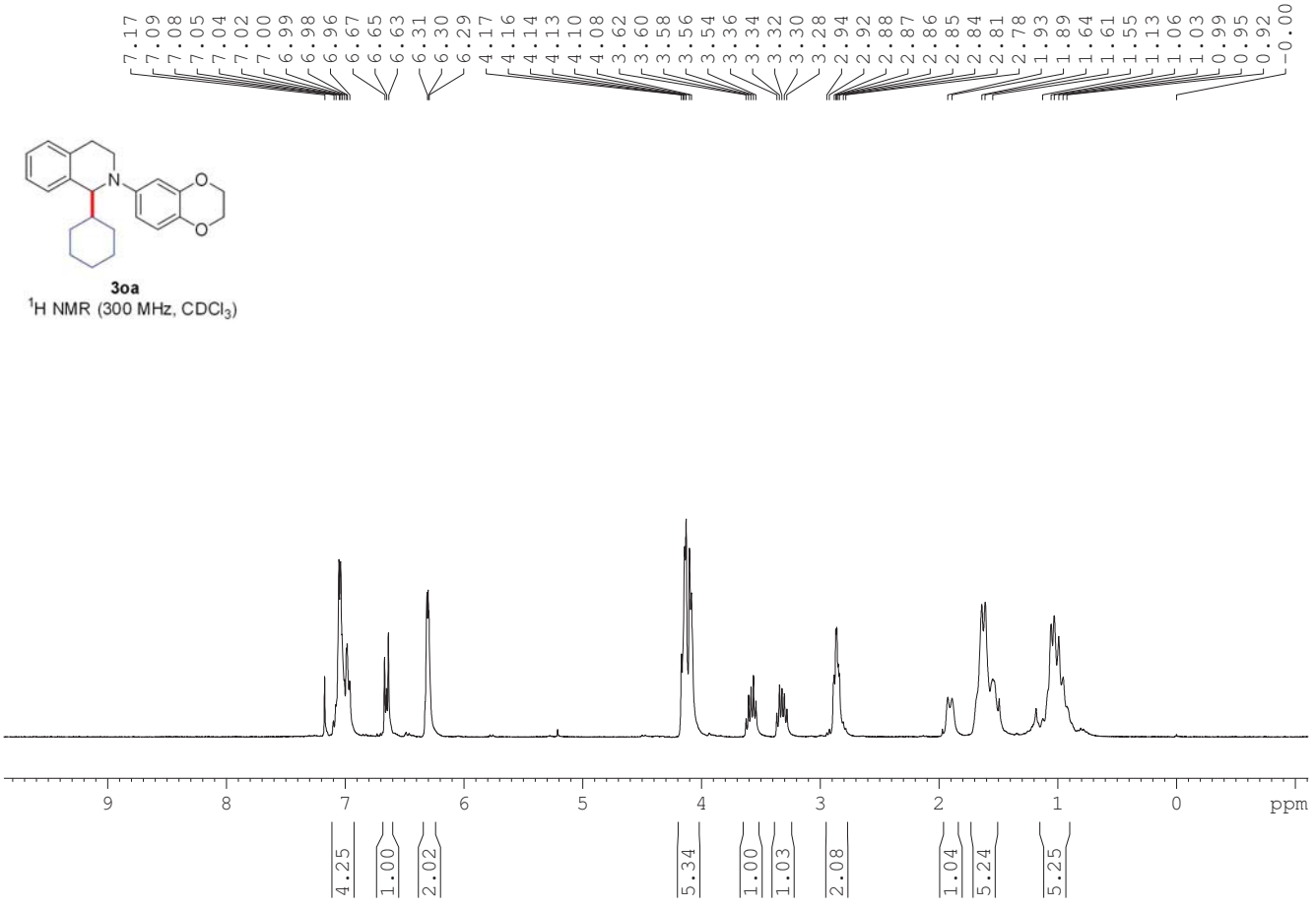
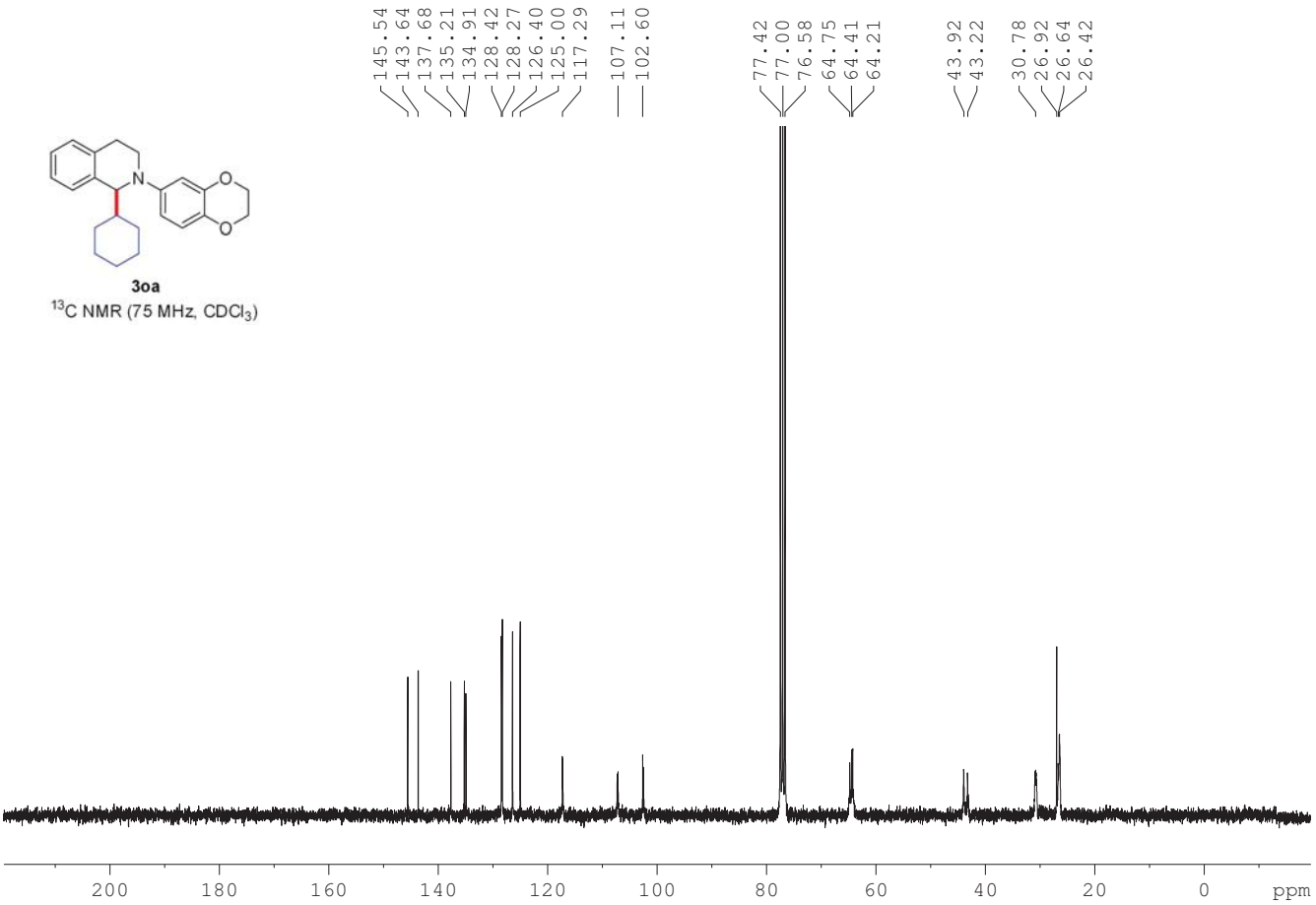
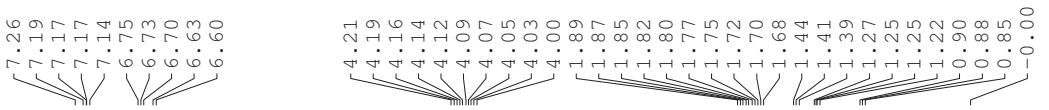
137.74
135.21
129.04
128.27
128.09
126.49
125.10
116.16
112.78
77.42
77.00
76.58
63.65
44.07
42.91
30.89
30.62
27.30
26.62
26.41
26.30
3na
13C NMR (75 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm


7.17
7.09
7.08
7.05
7.04
7.02
7.00
6.99
6.98
6.96
6.67
6.65
6.63
6.31
6.30
6.29
4.17
4.16
4.14
4.13
4.10
4.08
3.62
3.60
3.58
3.56
3.54
3.36
3.34
3.32
3.30
3.28
2.94
2.92
2.88
2.87
2.86
2.85
2.84
2.81
2.78
1.93
1.89
1.64
1.61
1.55
1.13
1.06
1.03
0.99
0.95
0.92
0.00
3oa
1H NMR (300 MHz, CDCl3)
9
8
7
6
5
4
3
2
1
0
ppm
4.25
1.00
2.02
5.34
1.00
1.03
2.08
1.04
5.24
5.25



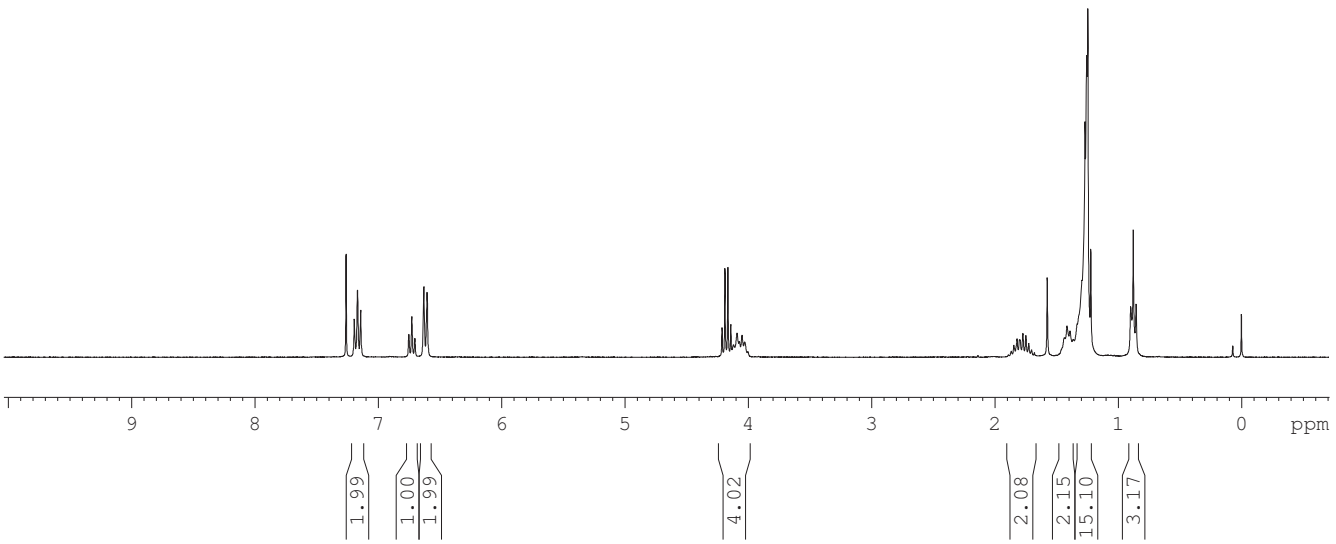
3oa

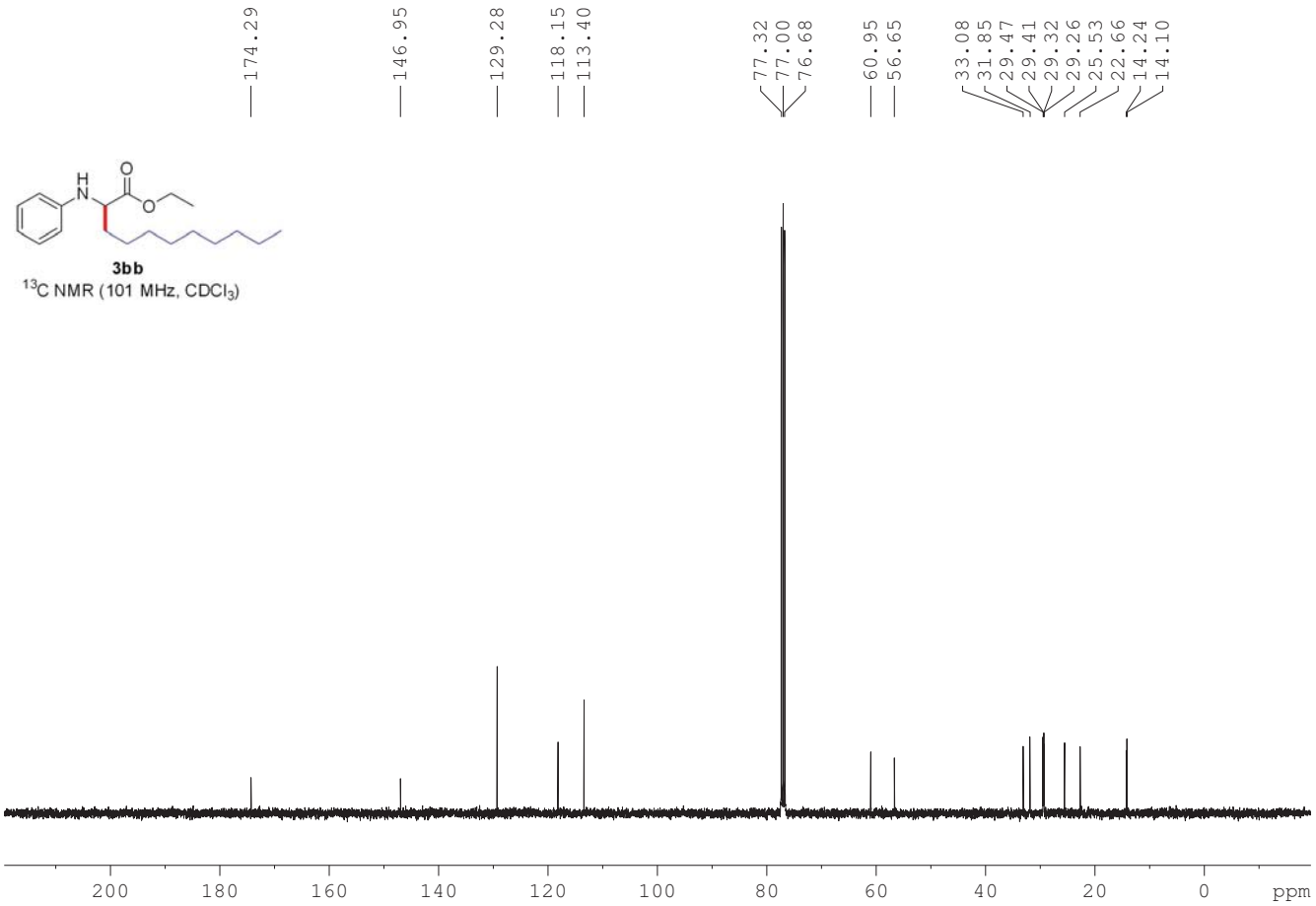
^{13}C NMR (75 MHz, $CDCl_3$)



3bb

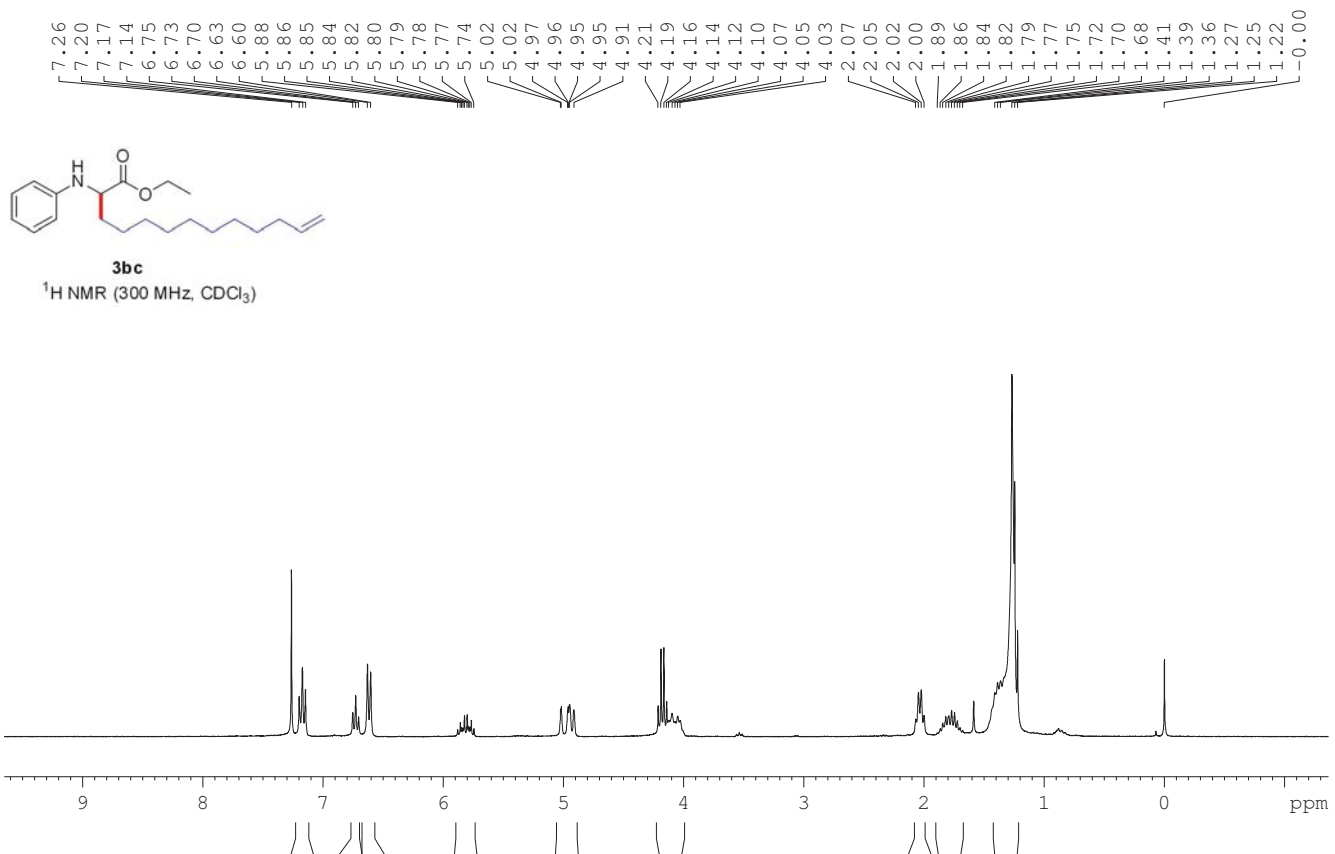
^{1}H NMR (300 MHz, $CDCl_3$)





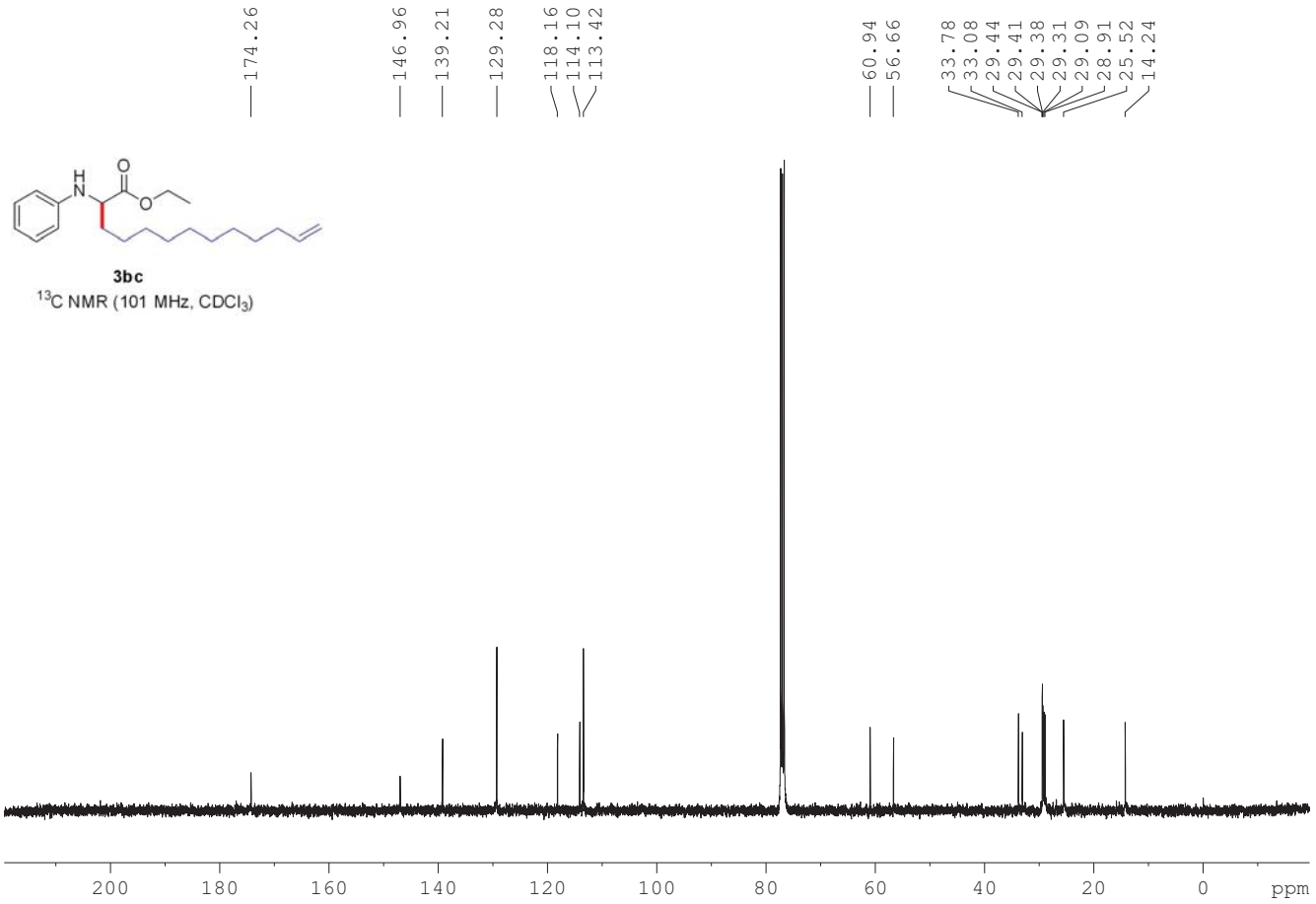
3bb

^{13}C NMR (101 MHz, $CDCl_3$)



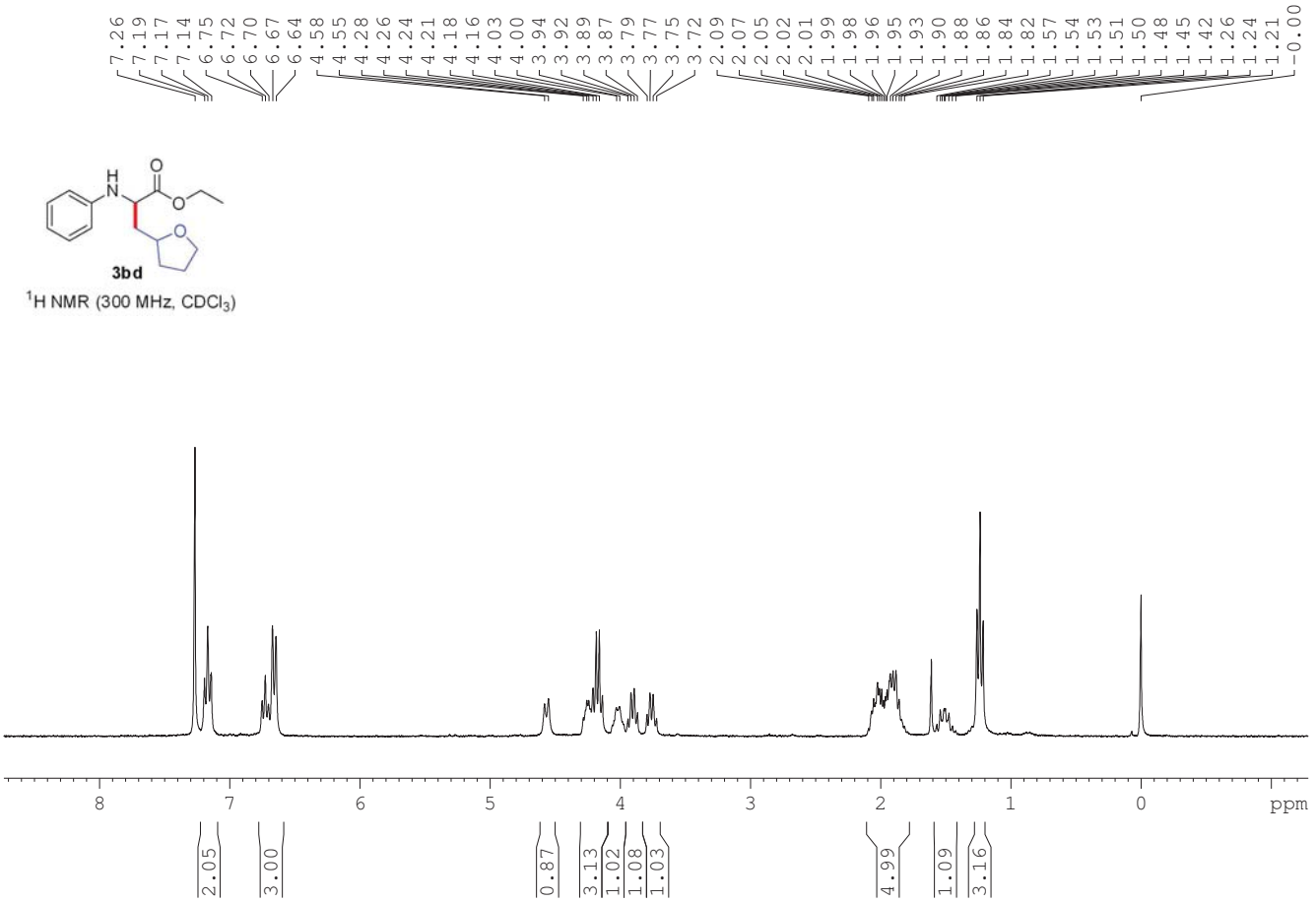
3bc

^{1}H NMR (300 MHz, $CDCl_3$)



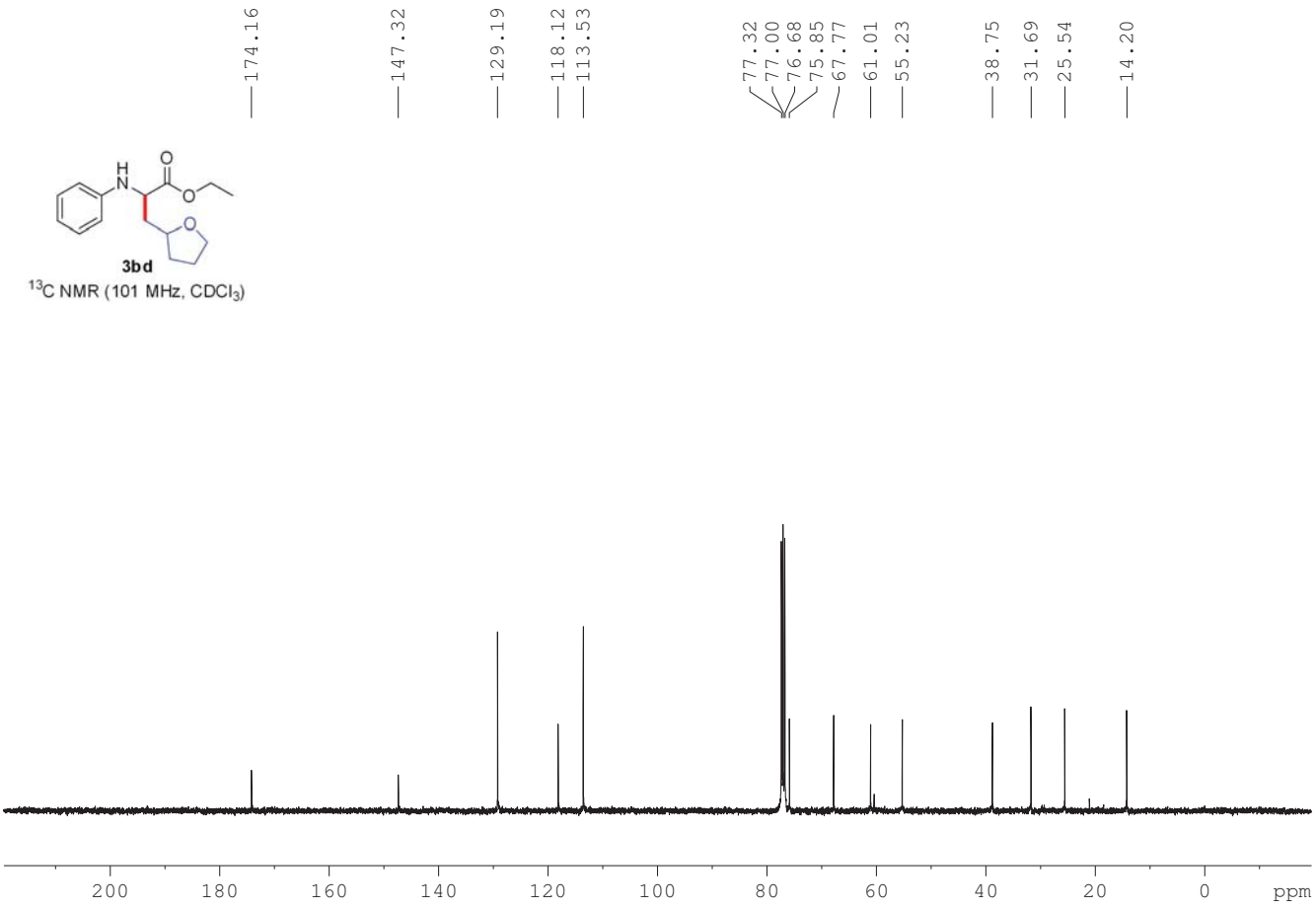
3bc

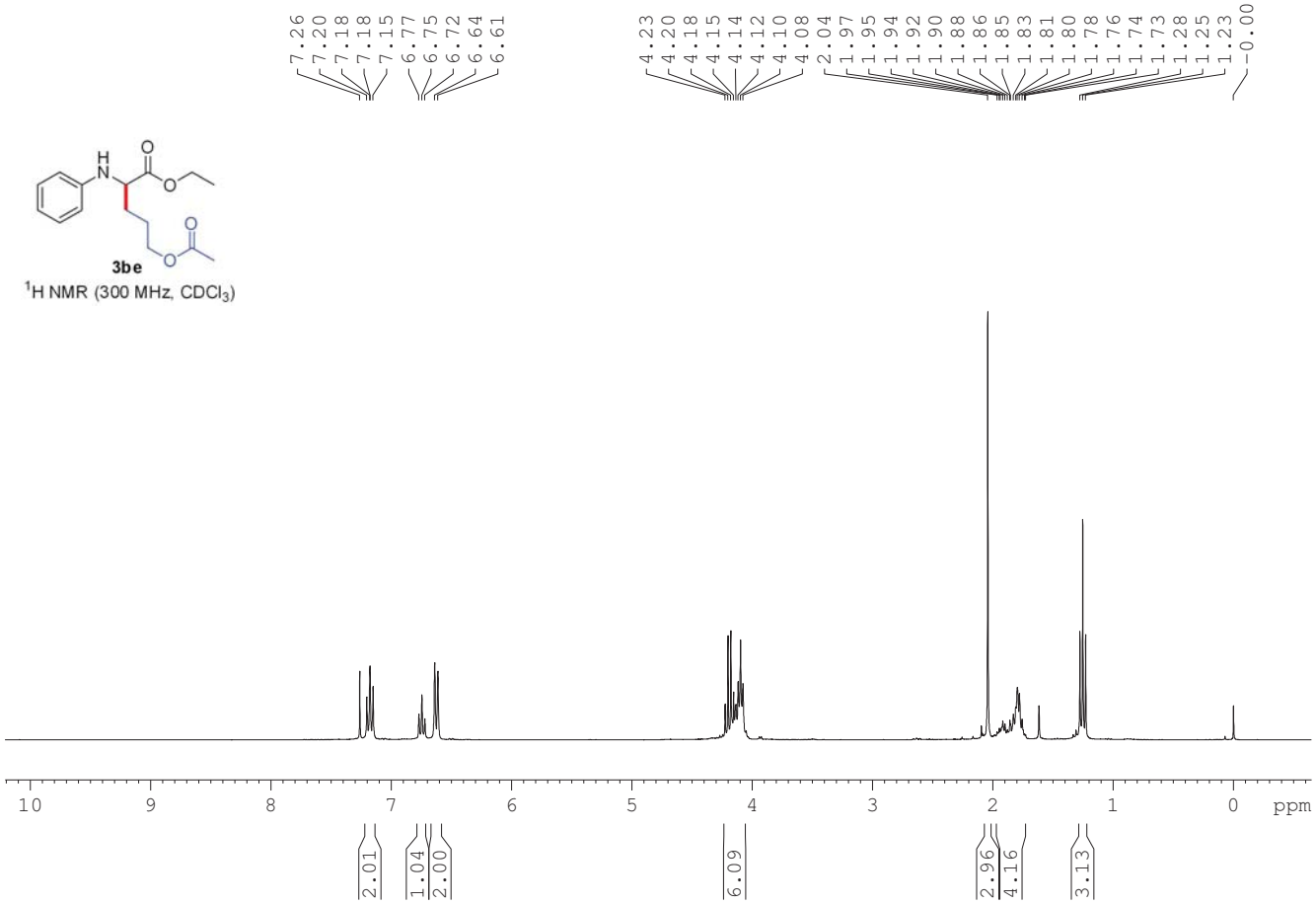
^{13}C NMR (101 MHz, $CDCl_3$)

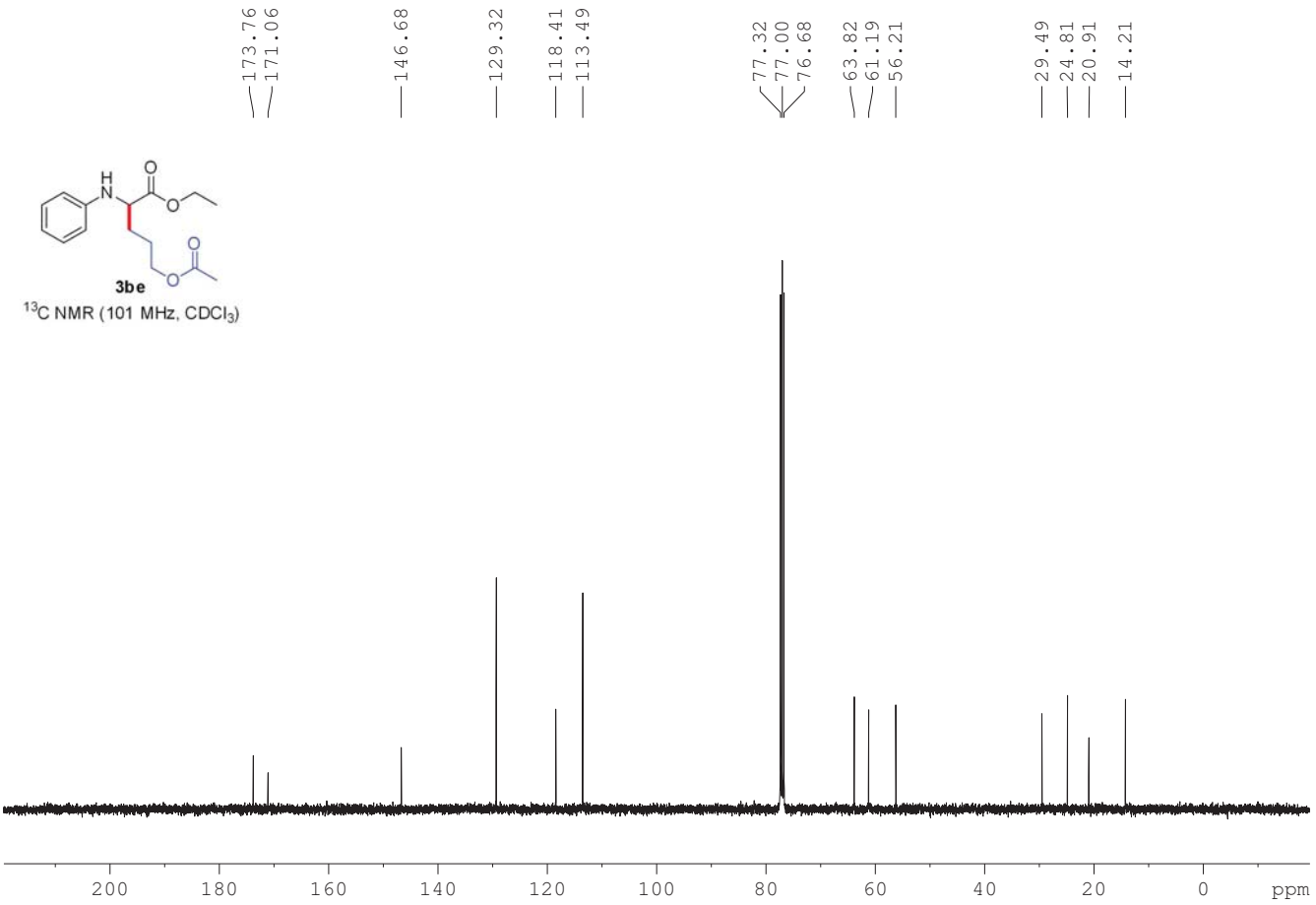


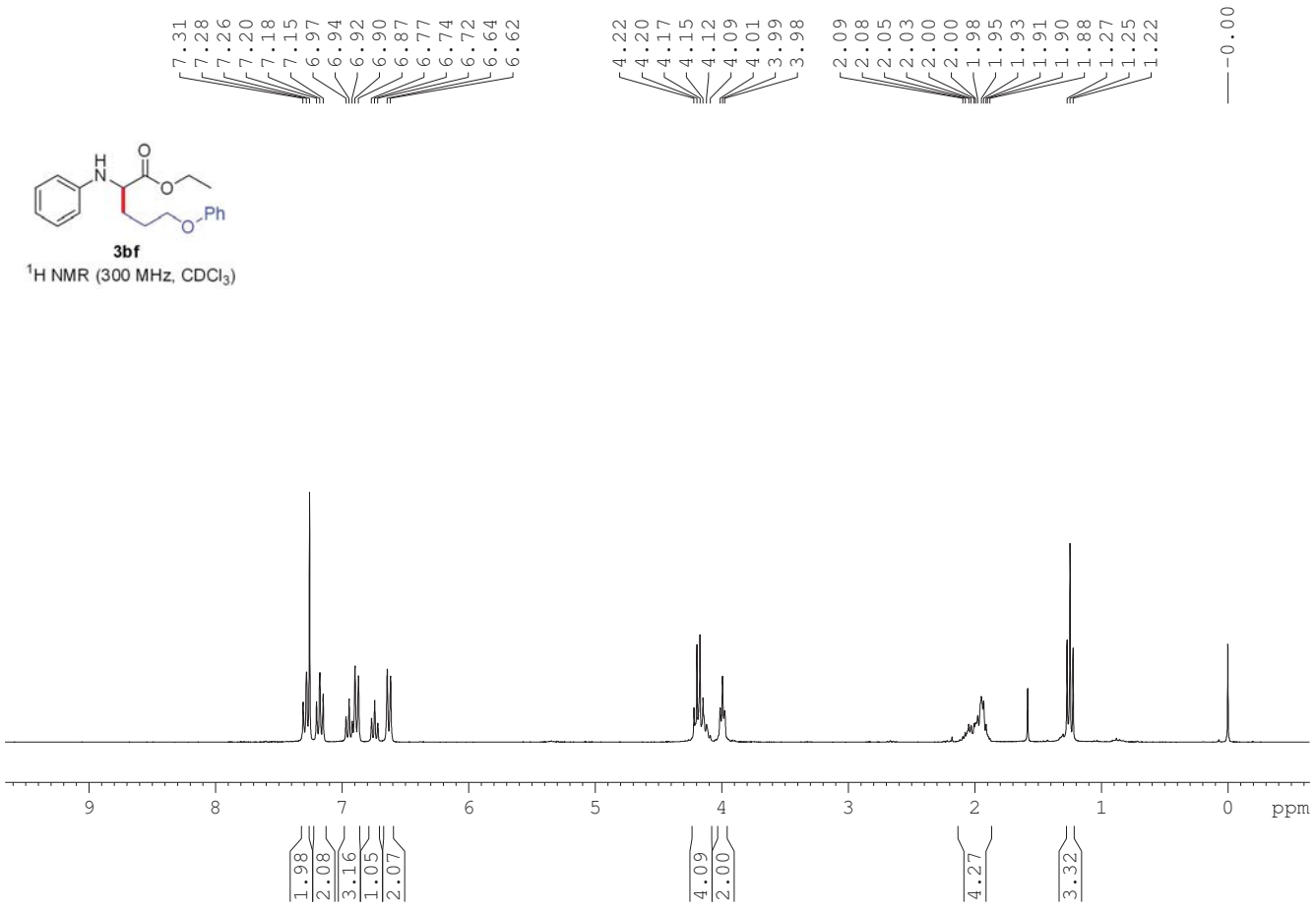
3bd

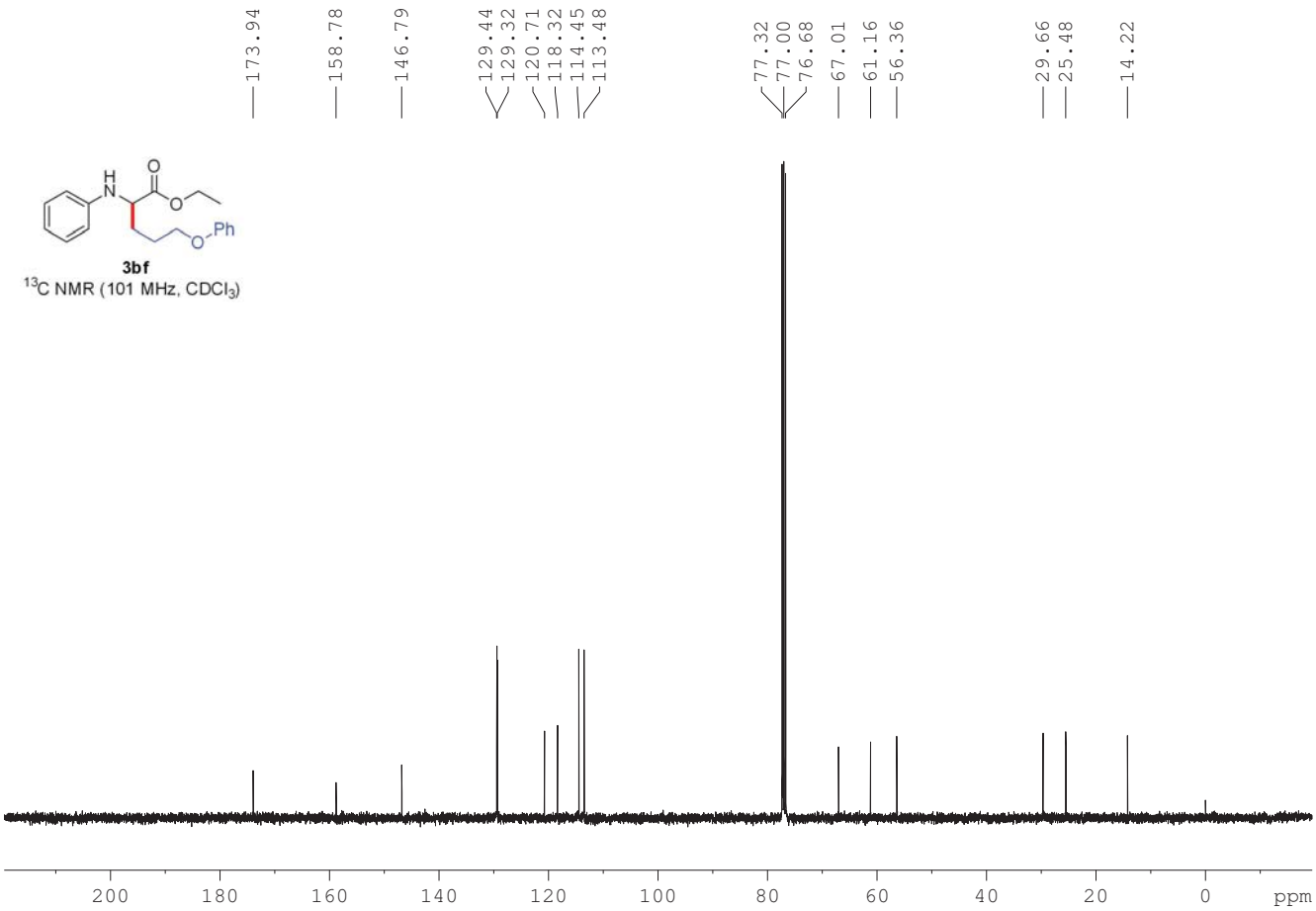
^{1}H NMR (300 MHz, $CDCl_3$)

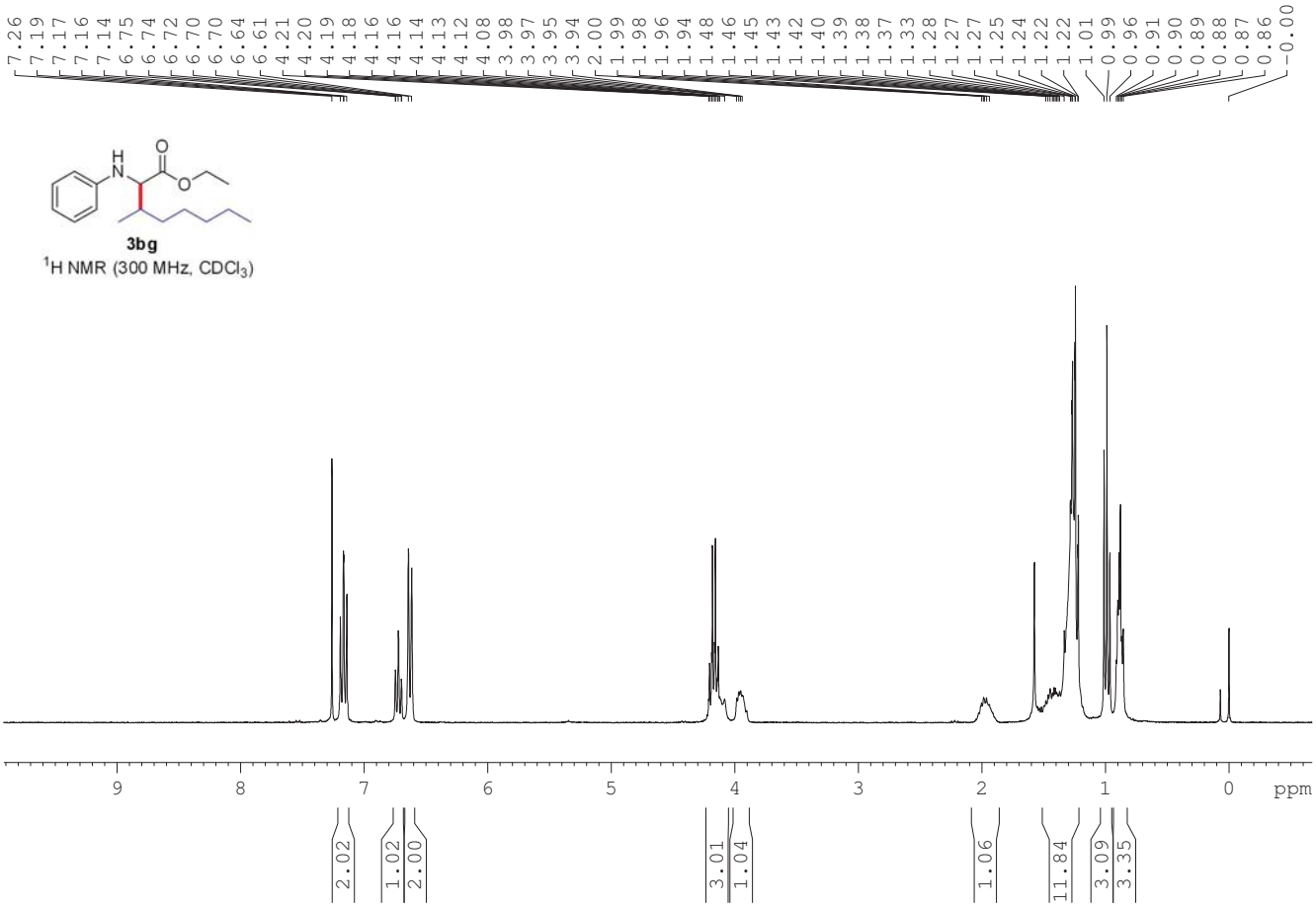

174.16
147.32
129.19
118.12
113.53
77.32
77.00
76.68
75.85
67.77
61.01
55.23
38.75
31.69
25.54
14.20
3bd
13C NMR (101 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm

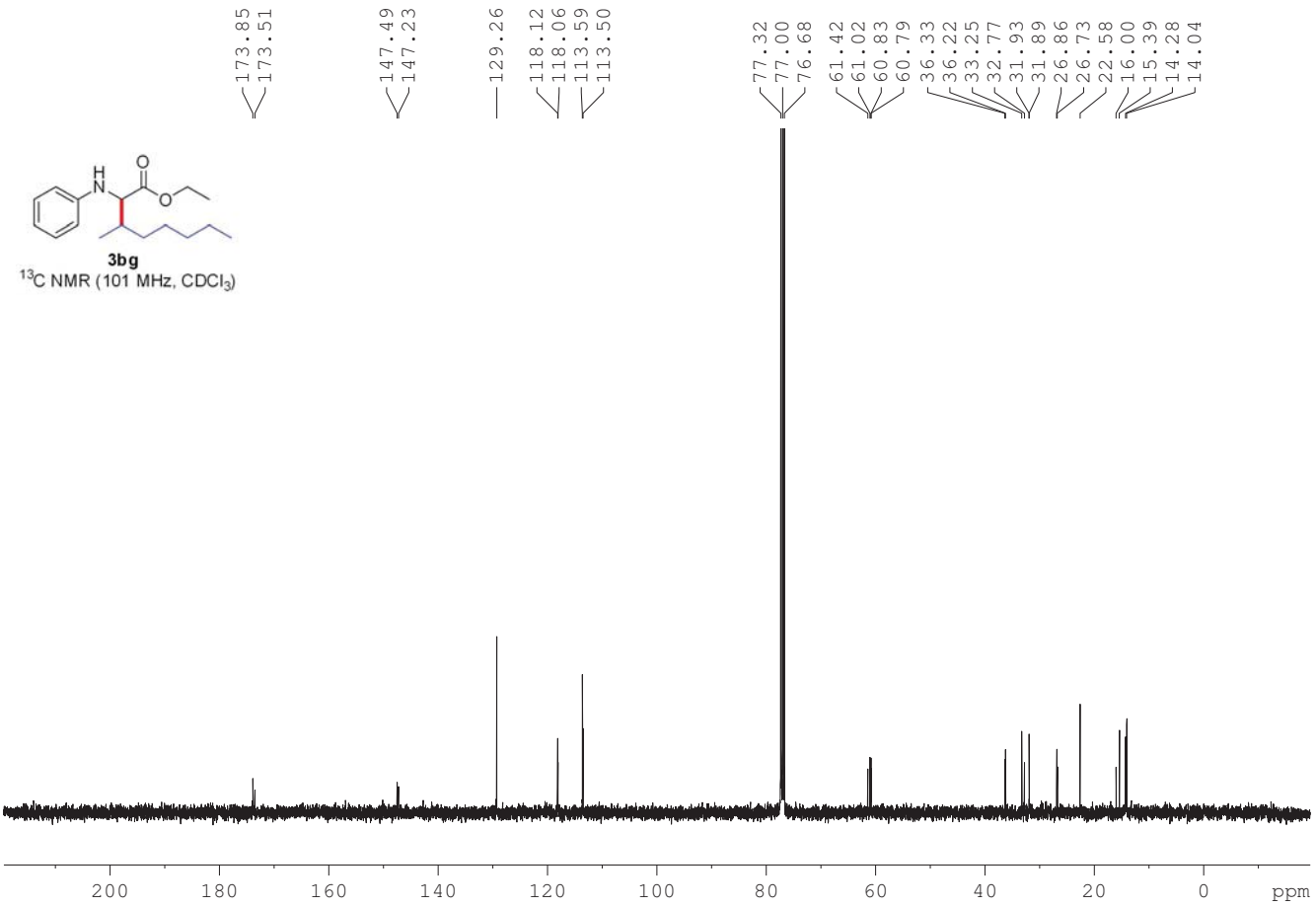

7.26
7.20
7.18
7.18
7.15
6.77
6.75
6.72
6.64
6.61
4.23
4.20
4.18
4.15
4.14
4.12
4.10
4.08
2.04
1.97
1.95
1.94
1.92
1.90
1.88
1.86
1.85
1.83
1.81
1.80
1.78
1.76
1.74
1.73
1.28
1.25
1.23
0.00
3be
1H NMR (300 MHz, CDCl3)
10
9
8
7
6
5
4
3
2
1
0
ppm
2.01
1.04
2.00
6.09
2.96
4.16
3.13


173.76
171.06
146.68
129.32
118.41
113.49
77.32
77.00
76.68
63.82
61.19
56.21
29.49
24.81
20.91
14.21
3be
13C NMR (101 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm

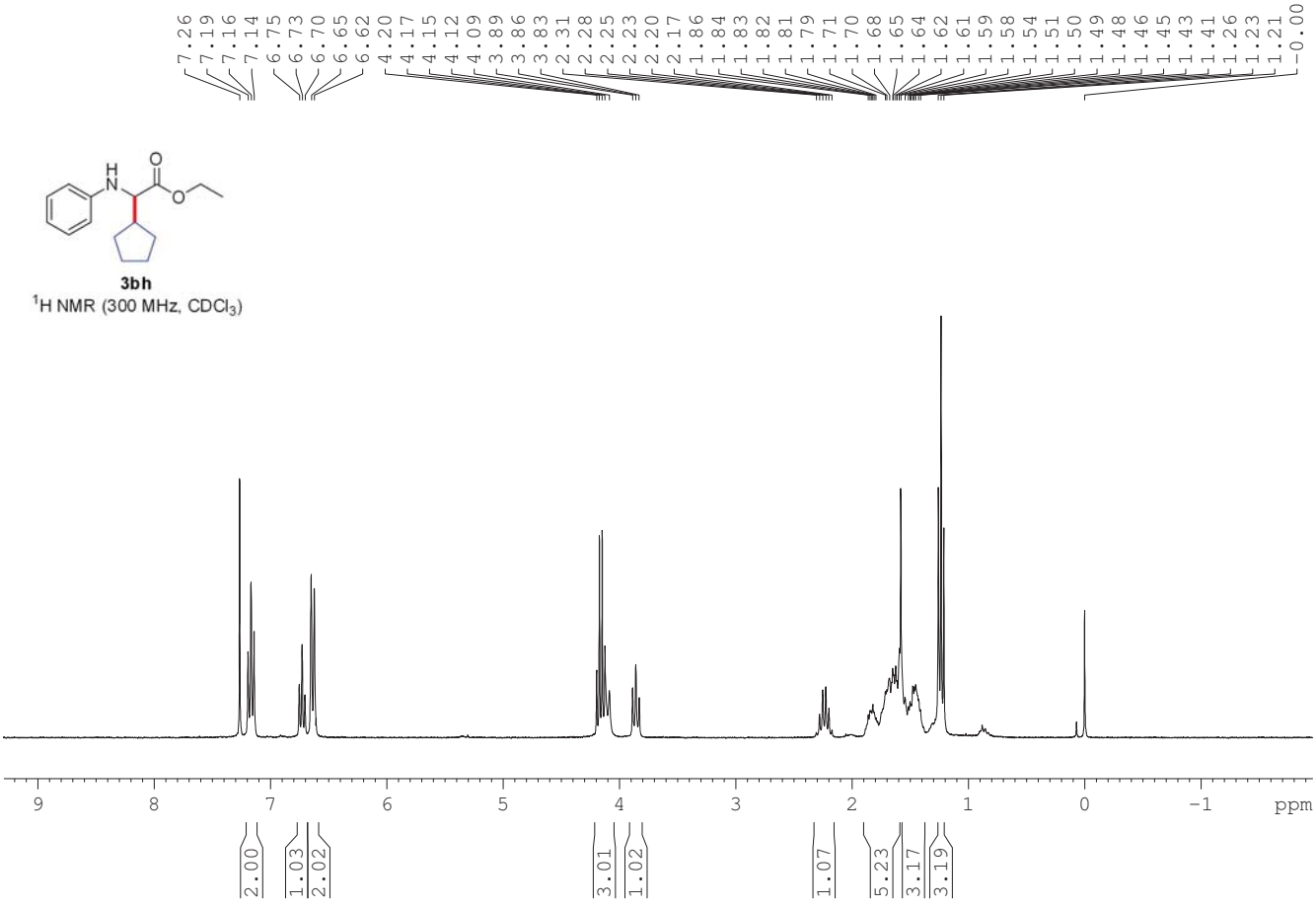

7.31
7.28
7.26
7.20
7.18
7.15
6.97
6.94
6.92
6.90
6.87
6.77
6.74
6.72
6.64
6.62
4.22
4.20
4.17
4.15
4.12
4.09
4.01
3.99
3.98
2.09
2.08
2.05
2.03
2.00
2.00
1.98
1.95
1.93
1.91
1.90
1.88
1.27
1.25
1.22
0.00
Ph
3bf
1H NMR (300 MHz, CDCl3)
9
8
7
6
5
4
3
2
1
0
ppm
1.98
2.08
3.16
1.05
2.07
4.09
2.00
4.27
3.32


173.94
158.78
146.79
129.44
129.32
120.71
118.32
114.45
113.48
77.32
77.00
76.68
67.01
61.16
56.36
29.66
25.48
14.22
Ph
3bf
13C NMR (101 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm

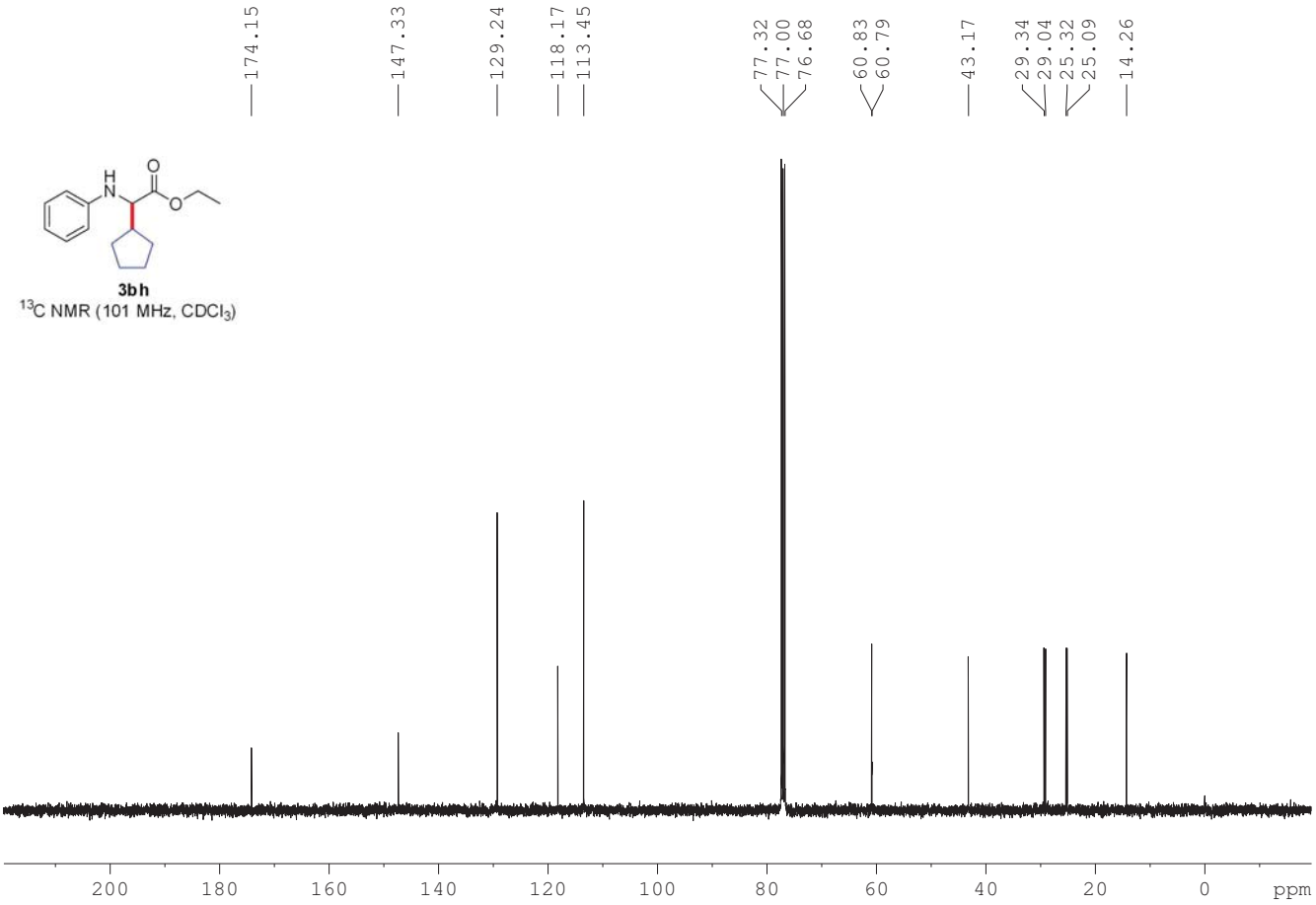

7.26
7.19
7.17
7.16
7.14
6.75
6.74
6.72
6.70
6.70
6.64
6.61
4.21
4.20
4.19
4.18
4.16
4.16
4.14
4.13
4.12
4.08
3.98
3.97
3.95
3.94
2.00
1.99
1.98
1.96
1.94
1.48
1.46
1.45
1.43
1.42
1.40
1.39
1.38
1.37
1.33
1.28
1.27
1.27
1.25
1.24
1.22
1.22
1.01
0.99
0.96
0.91
0.90
0.89
0.88
0.87
0.86
0.00
3bg
1H NMR (300 MHz, CDCl3)
9
8
7
6
5
4
3
2
1
0
ppm
2.02
1.02
2.00
3.01
1.04
1.06
11.84
3.09
3.35



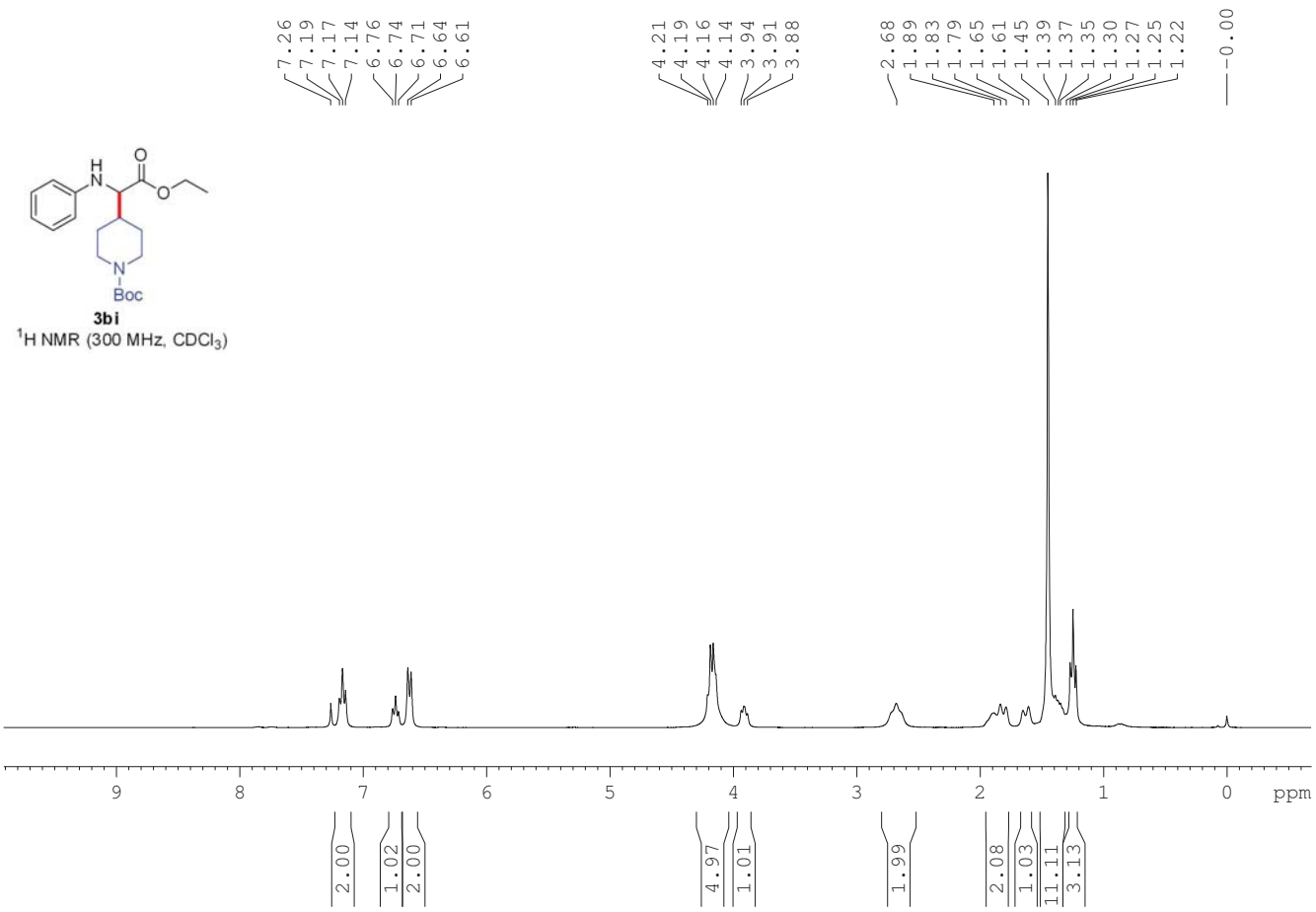
3bg
^{13}C NMR (101 MHz, $CDCl_3$)



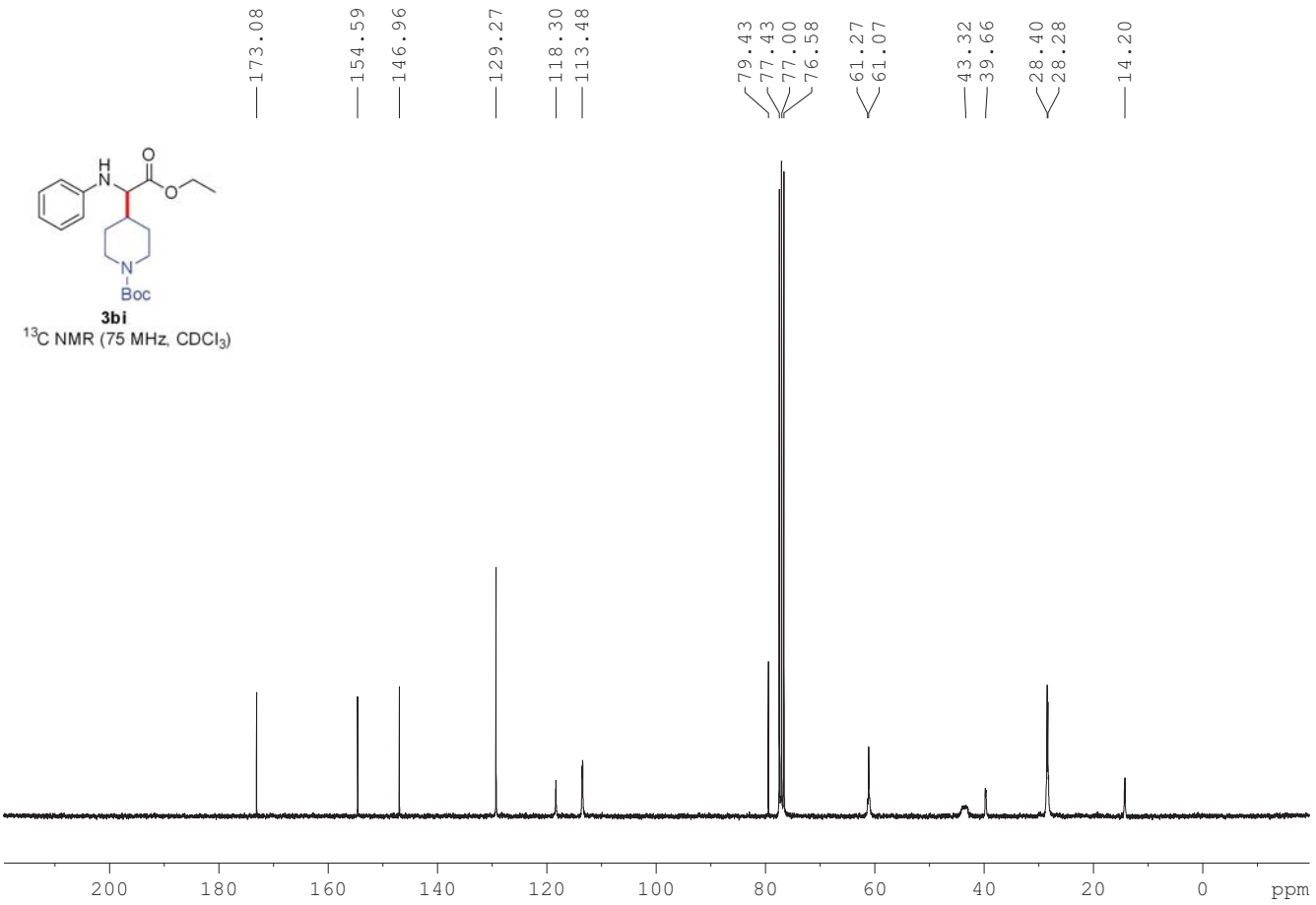
3bh
^{1}H NMR (300 MHz, $CDCl_3$)



3bh
^{13}C NMR (101 MHz, $CDCl_3$)

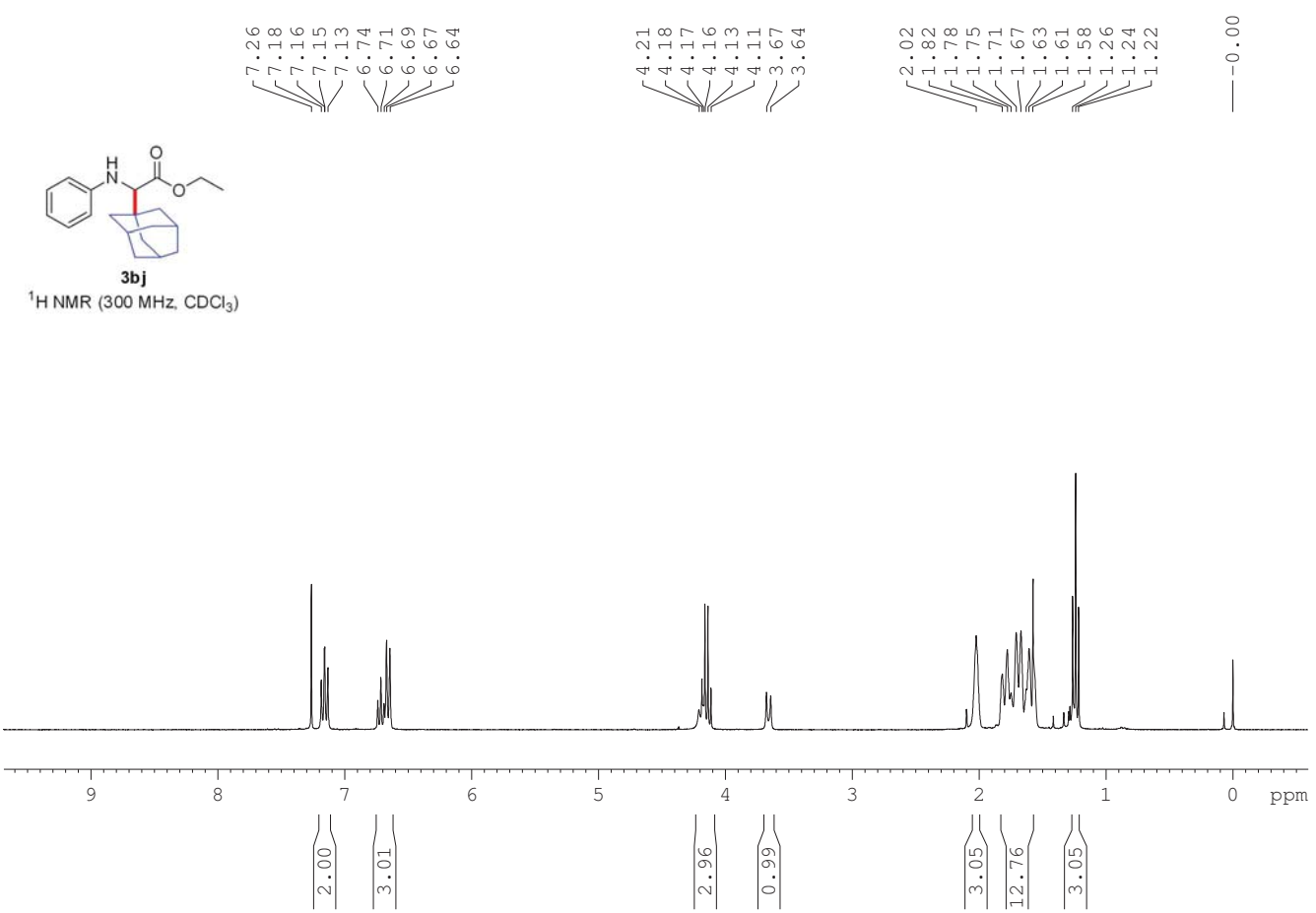


3bi
^{1}H NMR (300 MHz, $CDCl_3$)



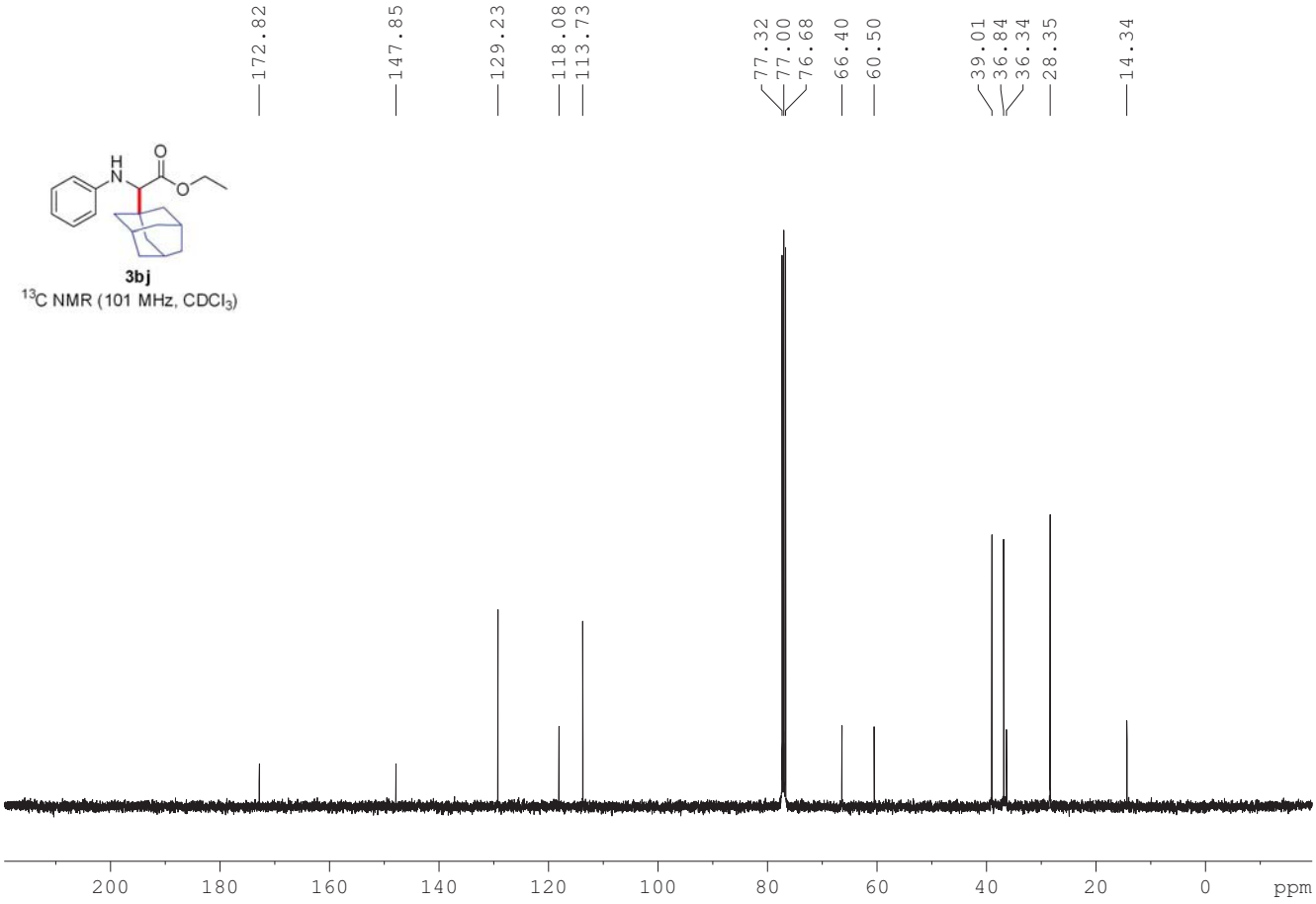
3bi

^{13}C NMR (75 MHz, $CDCl_3$)



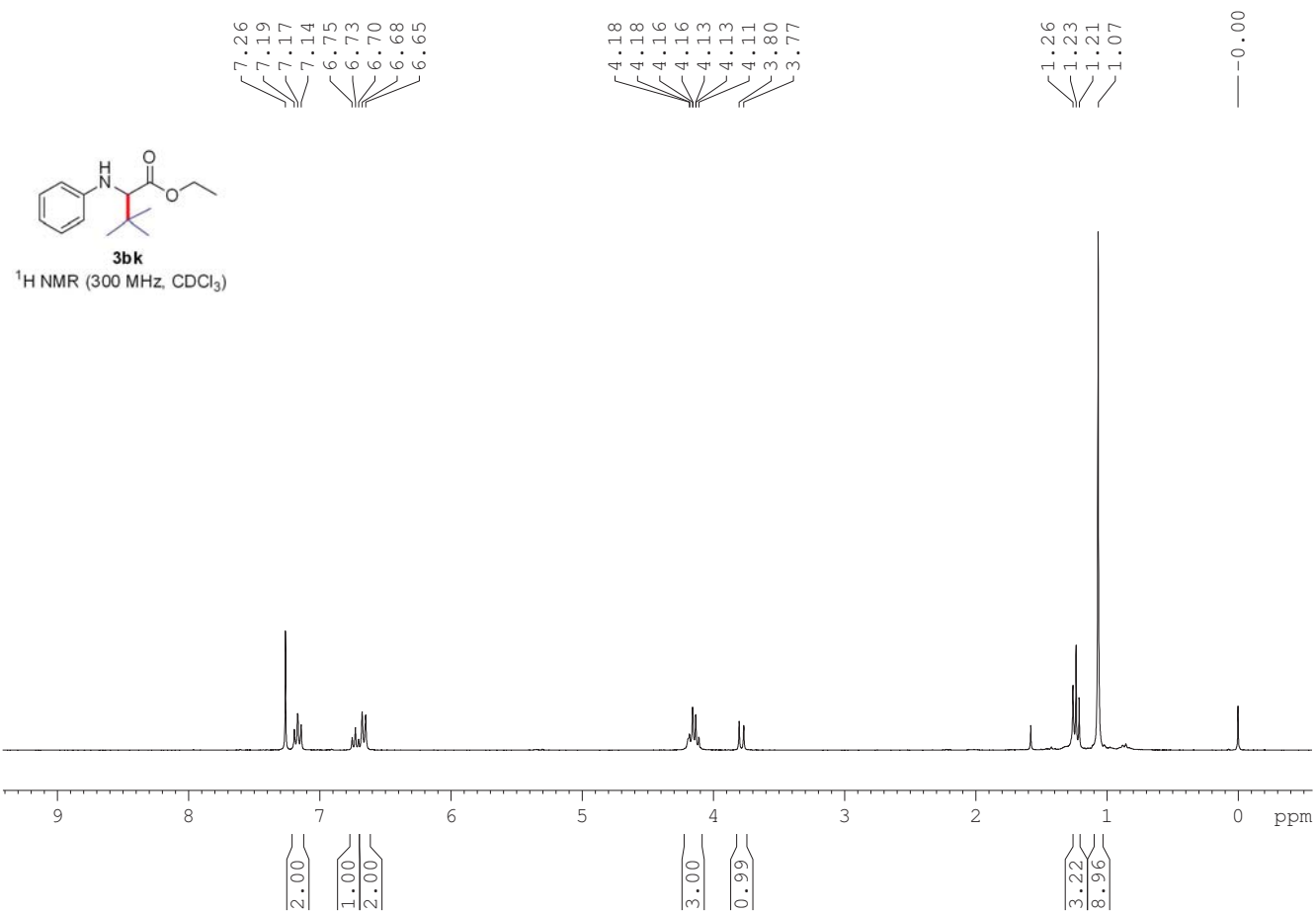
3bj

^{1}H NMR (300 MHz, $CDCl_3$)



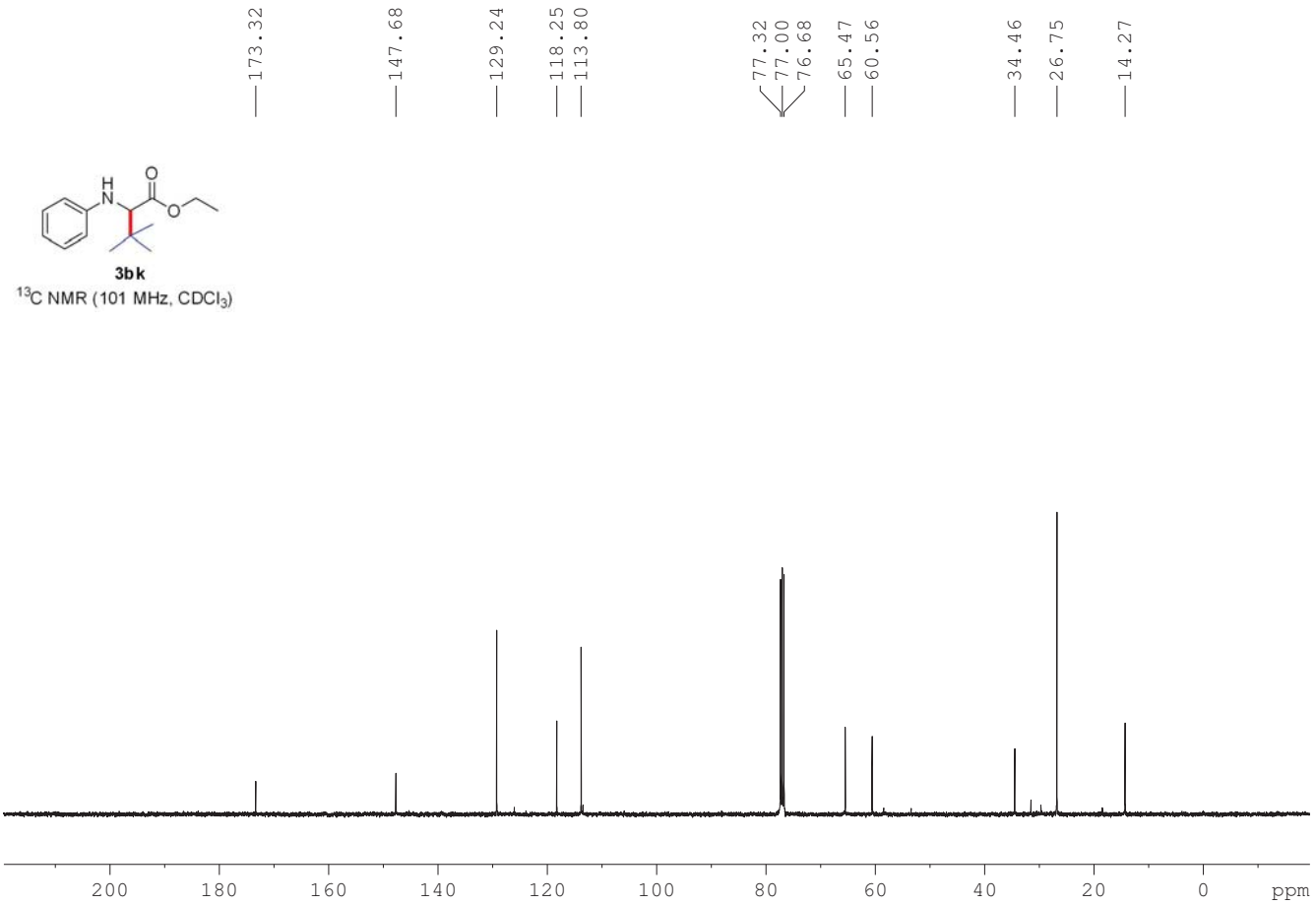
3bj

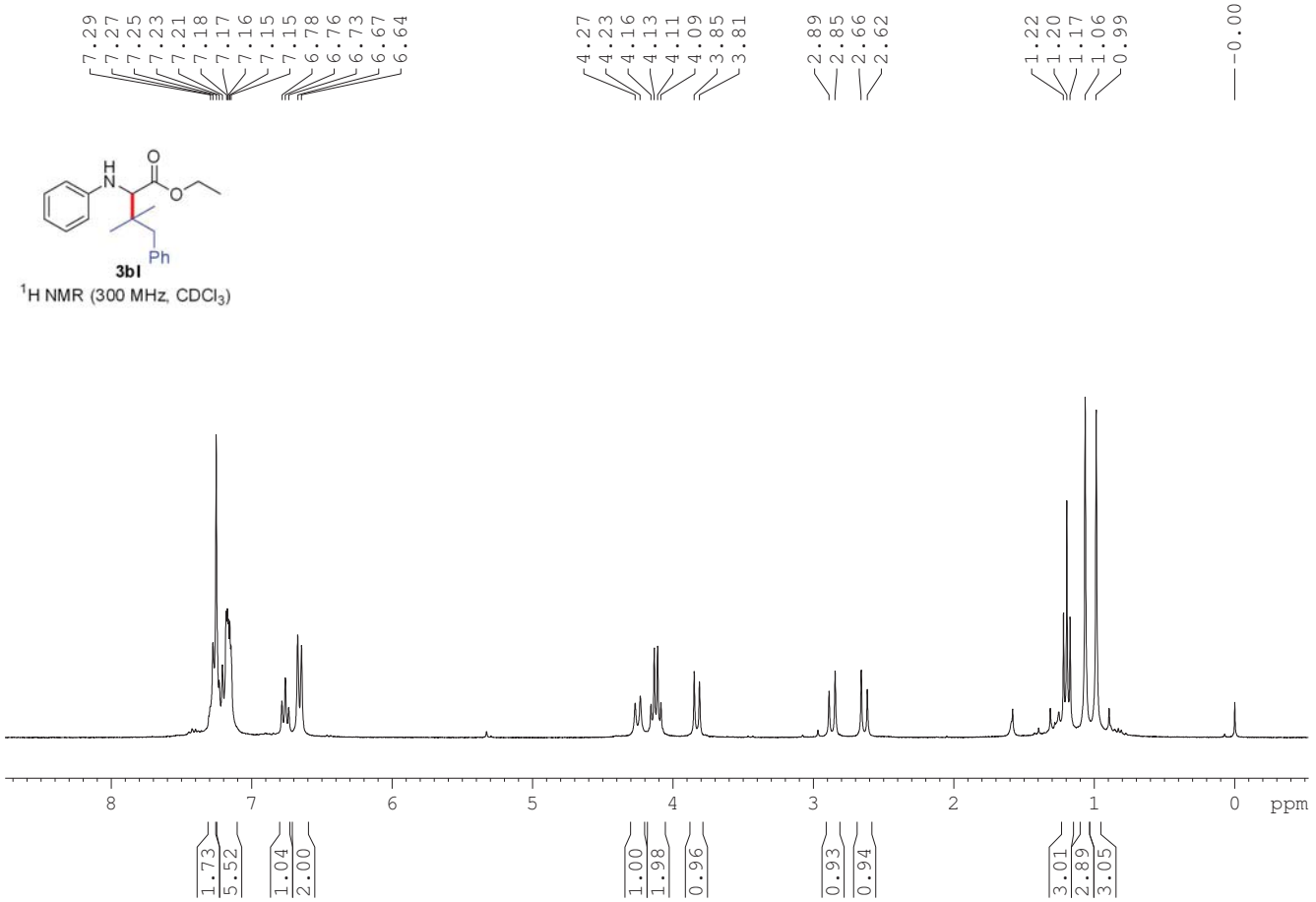
^{13}C NMR (101 MHz, $CDCl_3$)

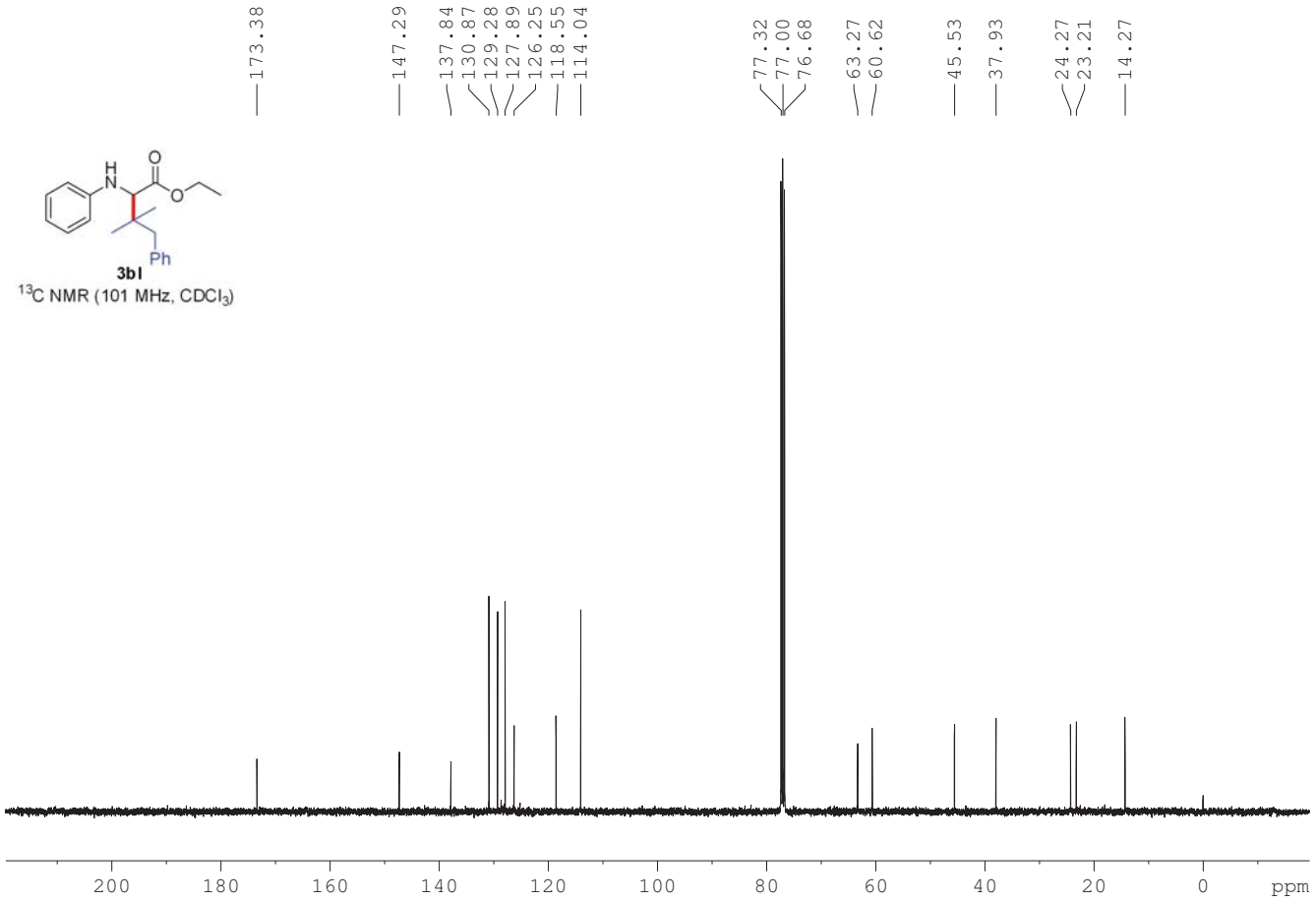


3bk

^{1}H NMR (300 MHz, $CDCl_3$)

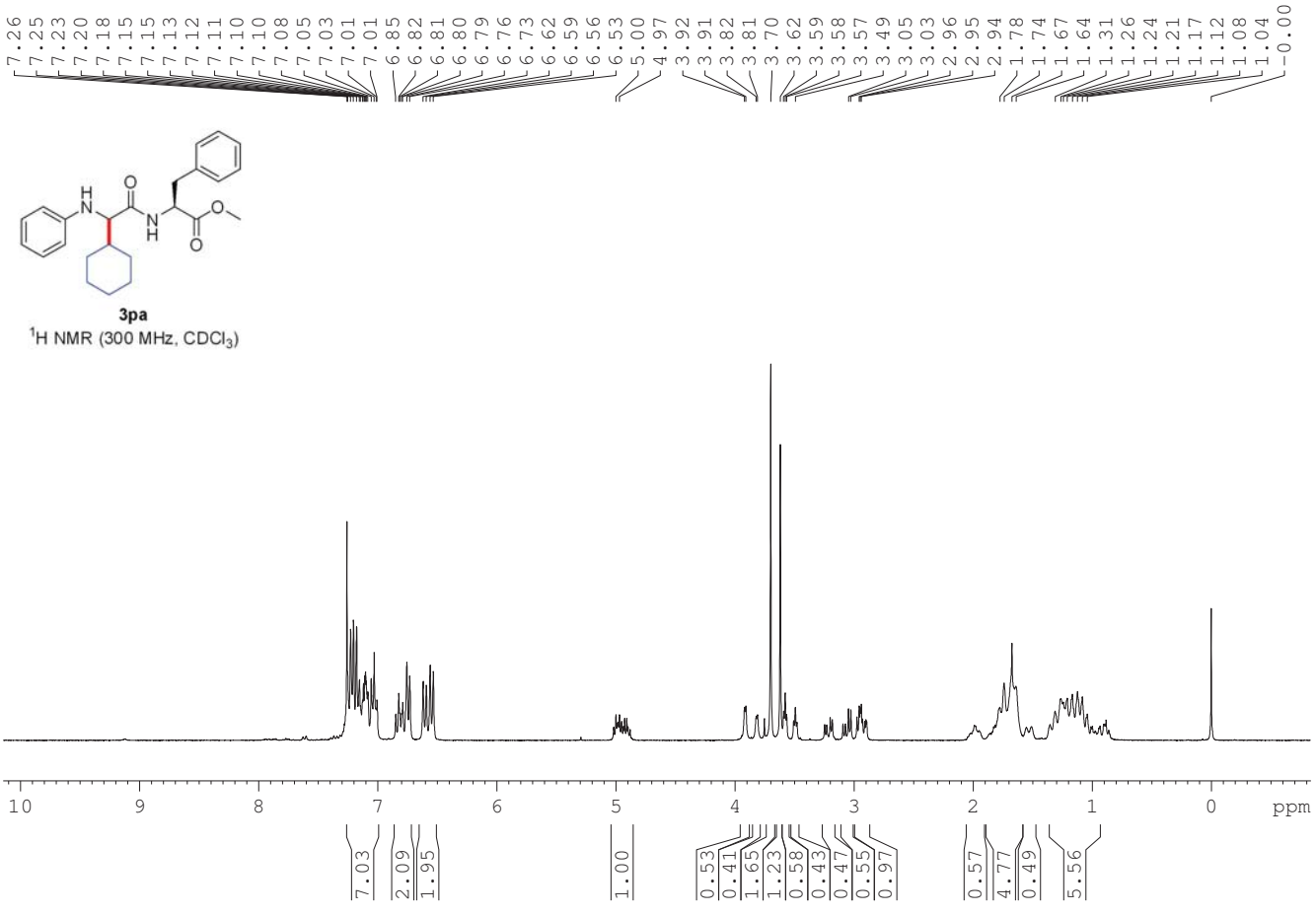

173.32
147.68
129.24
118.25
113.80
77.32
77.00
76.68
65.47
60.56
34.46
26.75
14.27
3bk
13C NMR (101 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm


7.29
7.27
7.25
7.23
7.21
7.18
7.17
7.16
7.15
6.78
6.76
6.73
6.67
6.64
4.27
4.23
4.16
4.13
4.11
4.09
3.85
3.81
2.89
2.85
2.66
2.62
1.22
1.20
1.17
1.06
0.99
0.00
Ph
3bl
1H NMR (300 MHz, CDCl3)
8
7
6
5
4
3
2
1
0
ppm
1.73
5.52
1.04
2.00
1.00
1.98
0.96
0.93
0.94
3.01
2.89
3.05



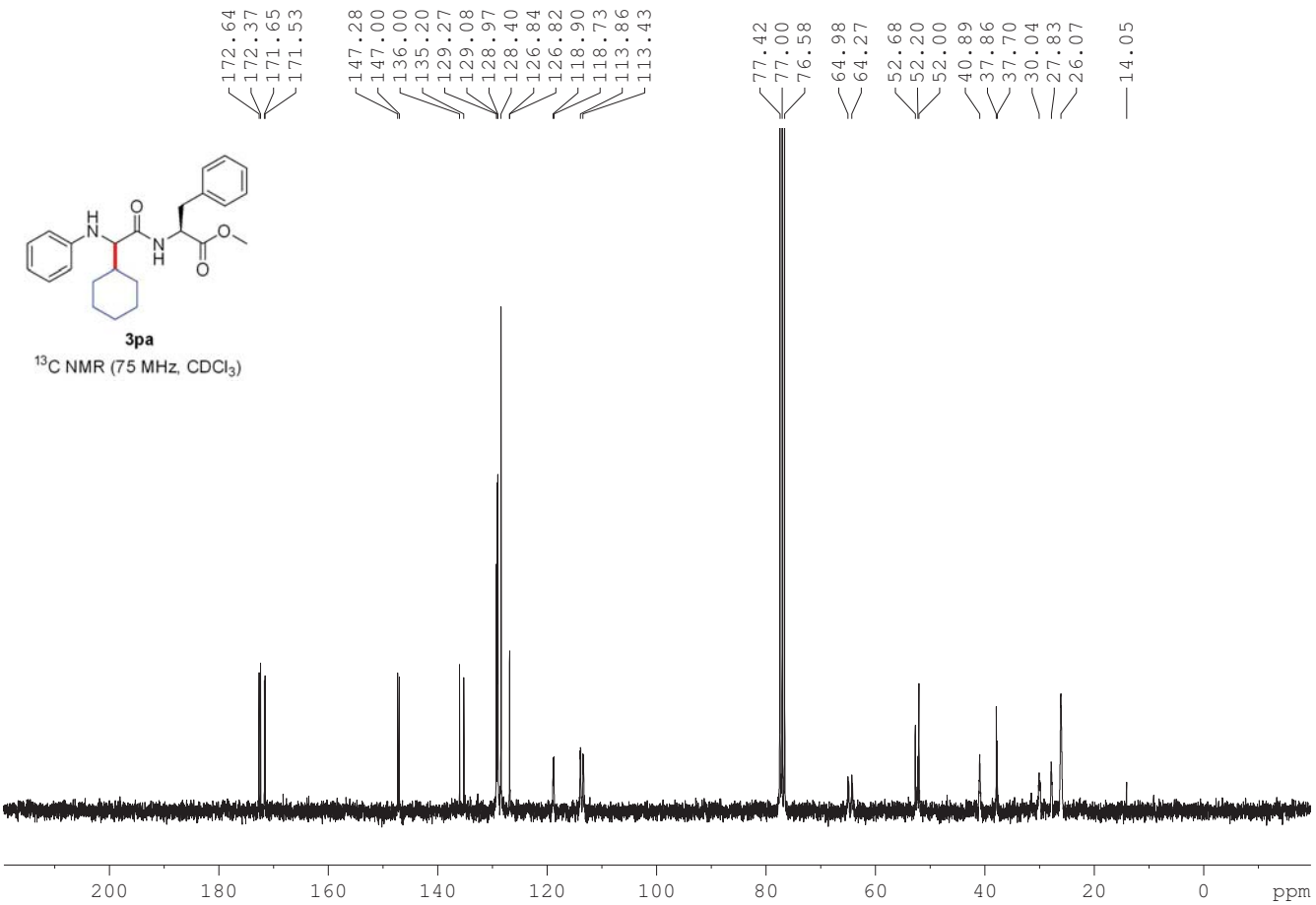
3bl

^{13}C NMR (101 MHz, $CDCl_3$)



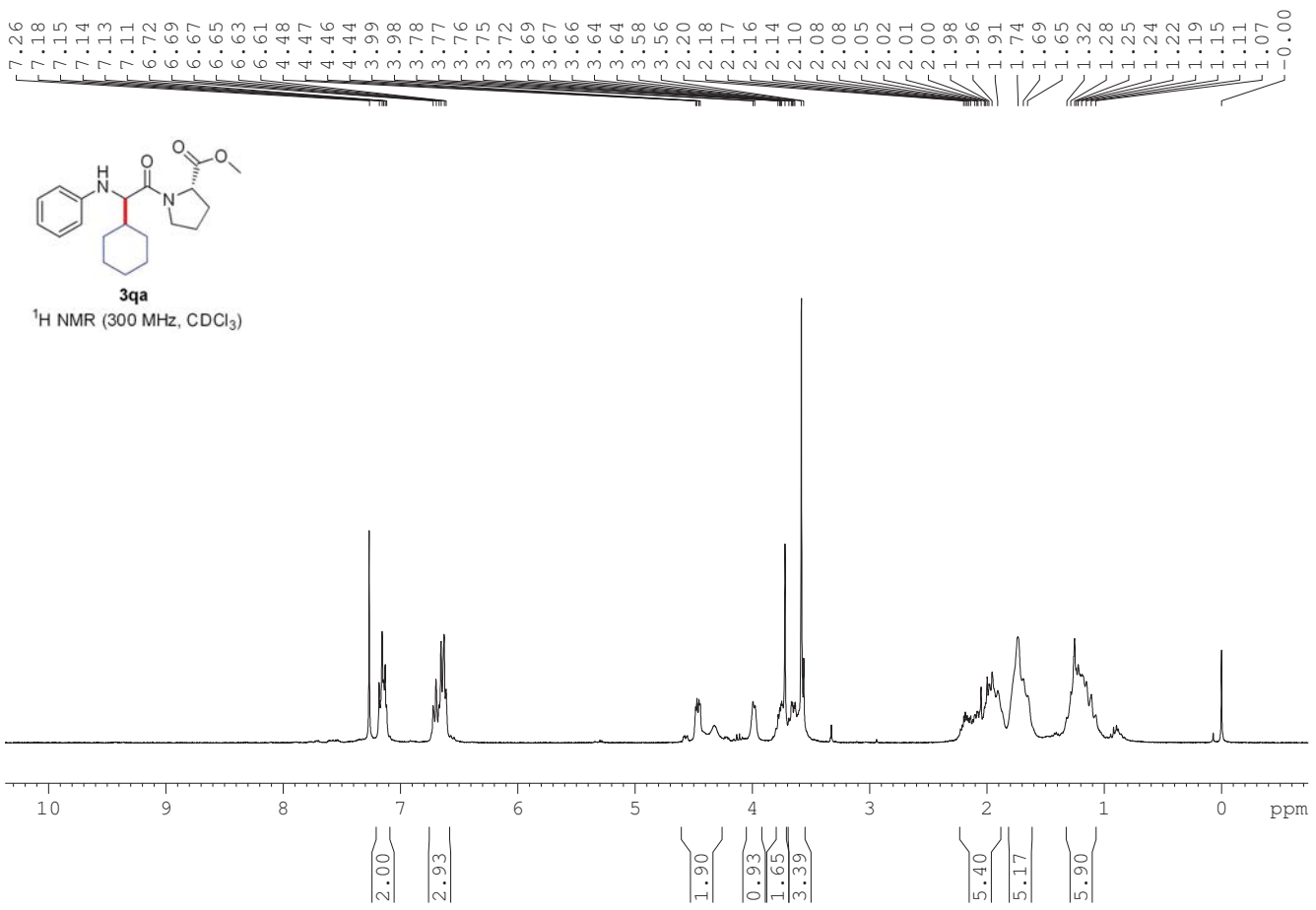
3pa

^{1}H NMR (300 MHz, $CDCl_3$)



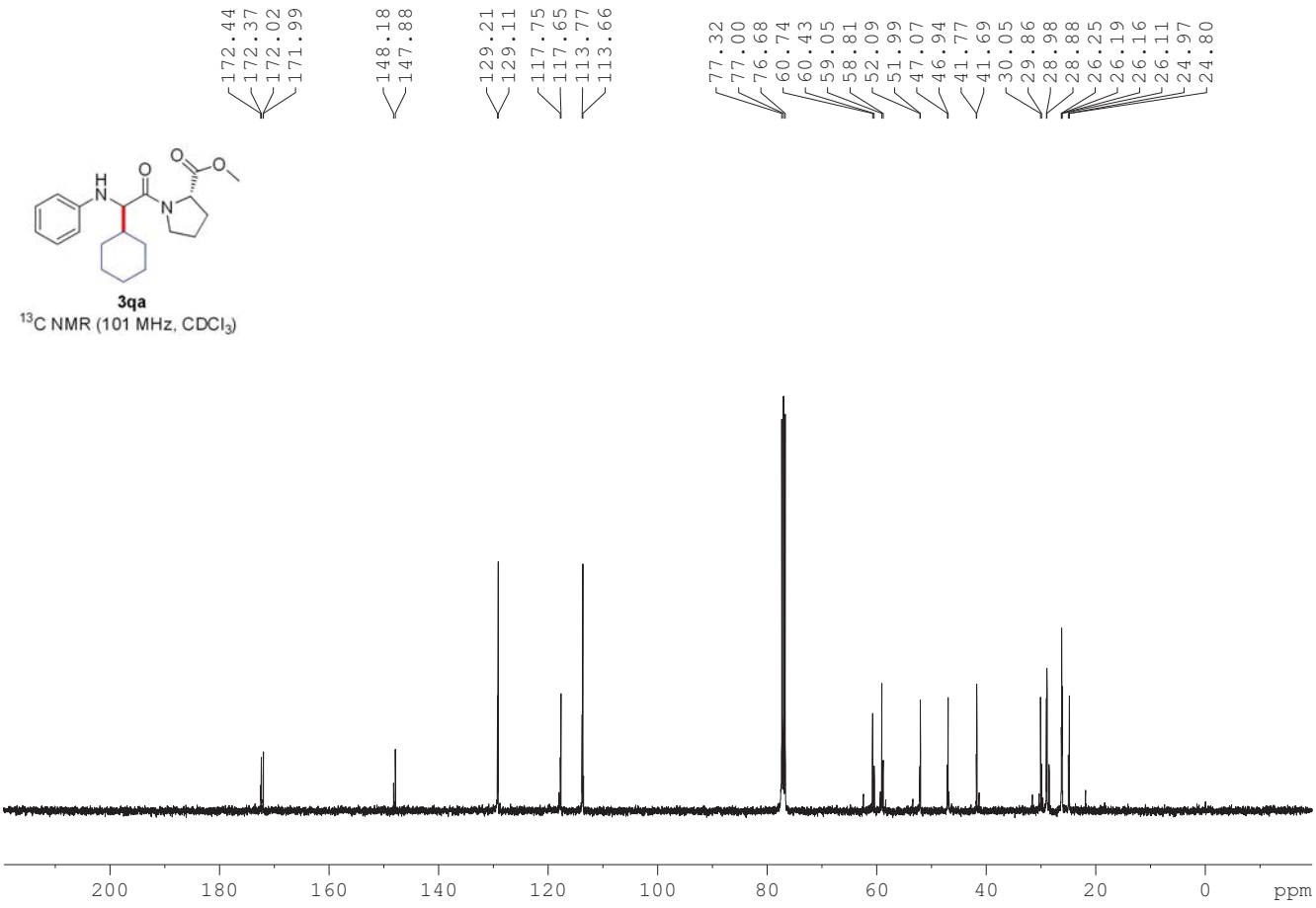
3pa

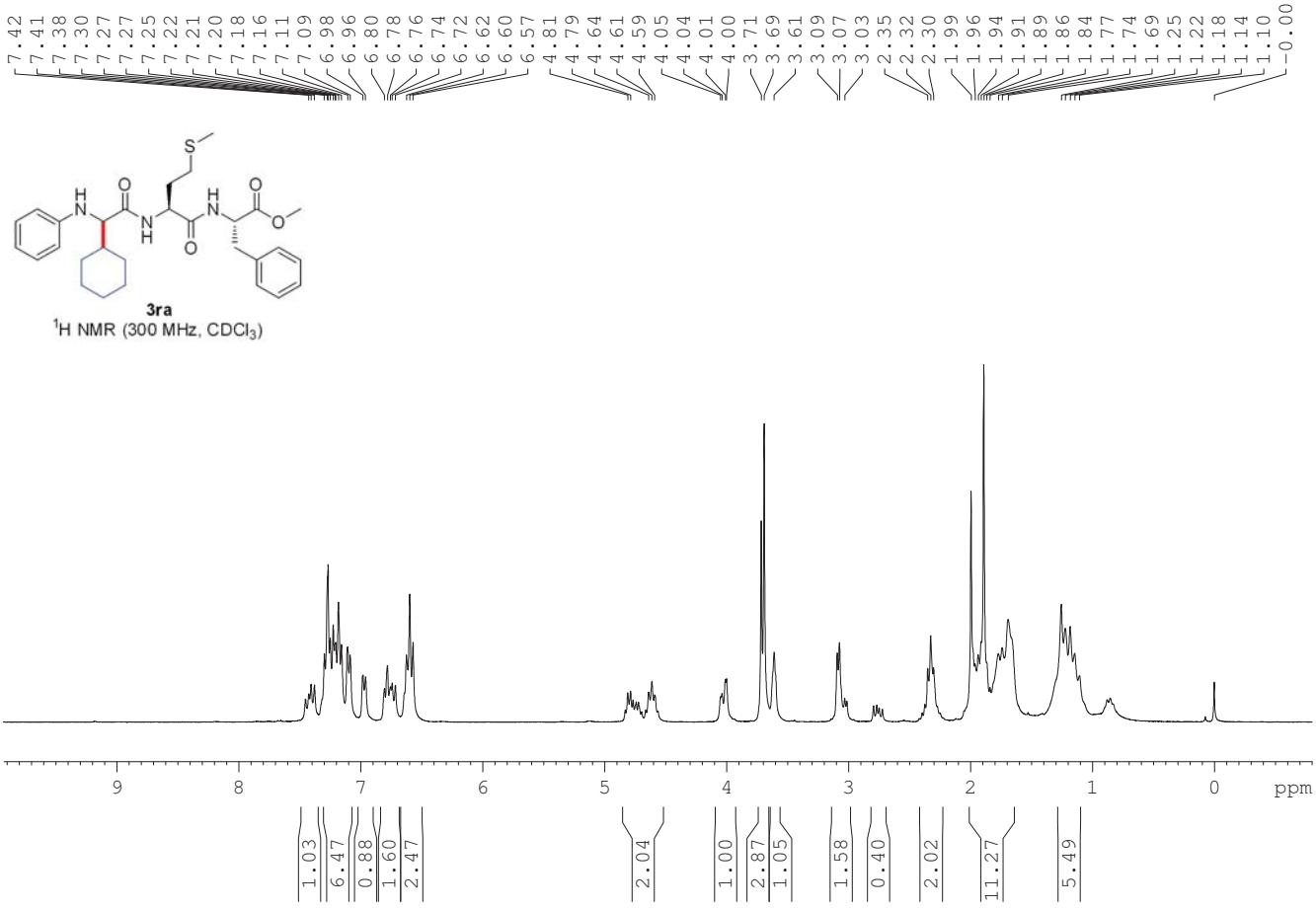
^{13}C NMR (75 MHz, $CDCl_3$)

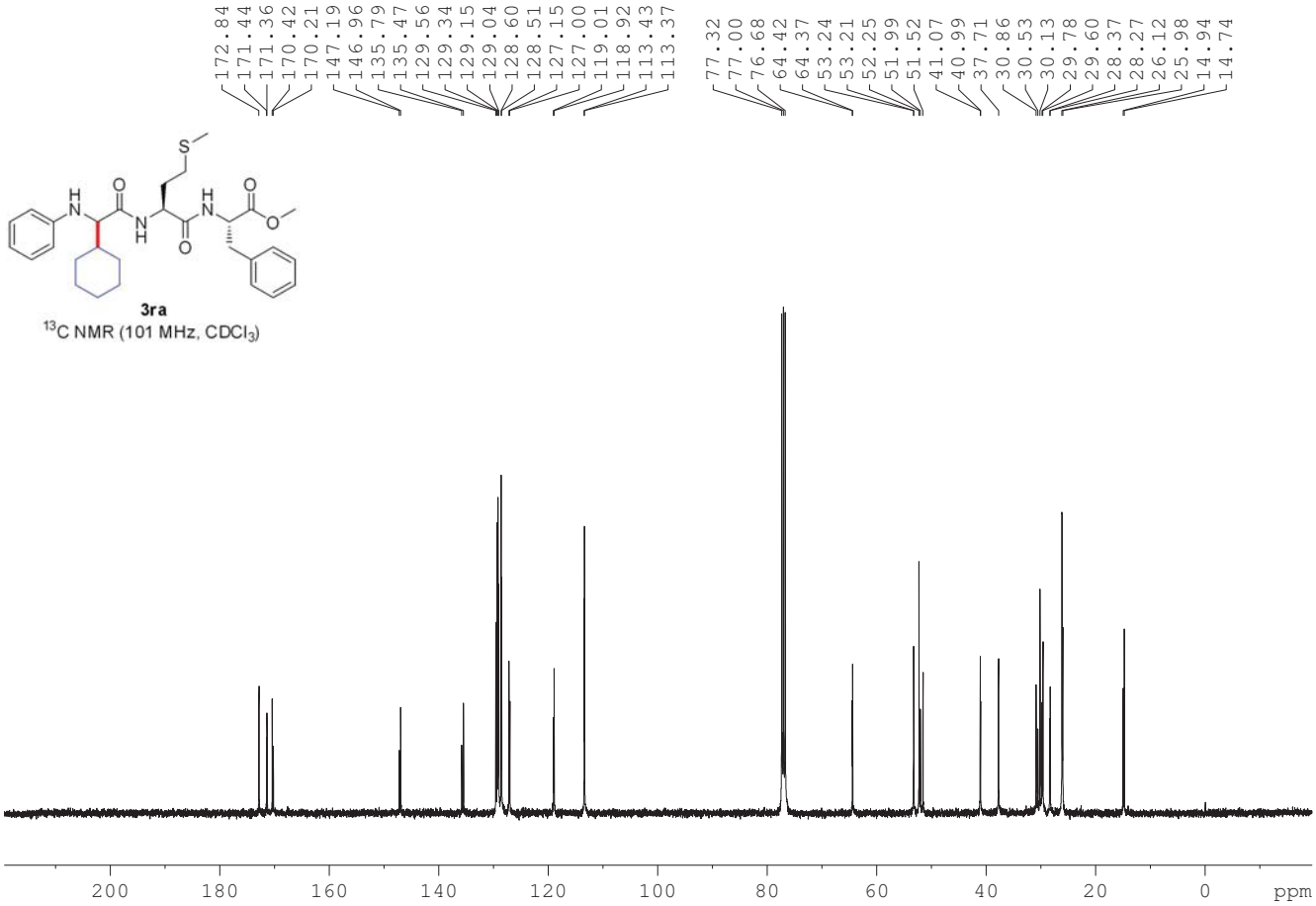


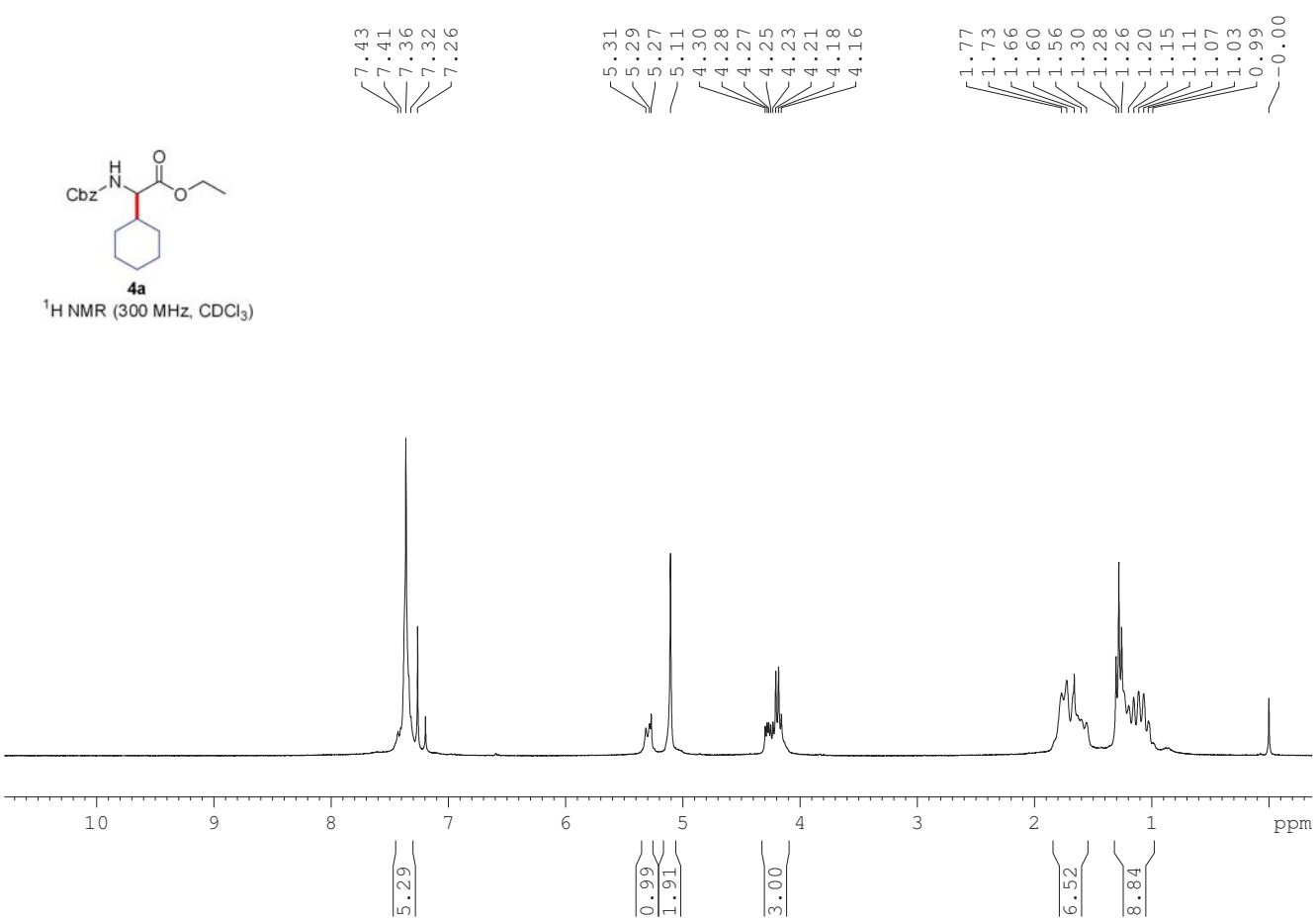
3qa

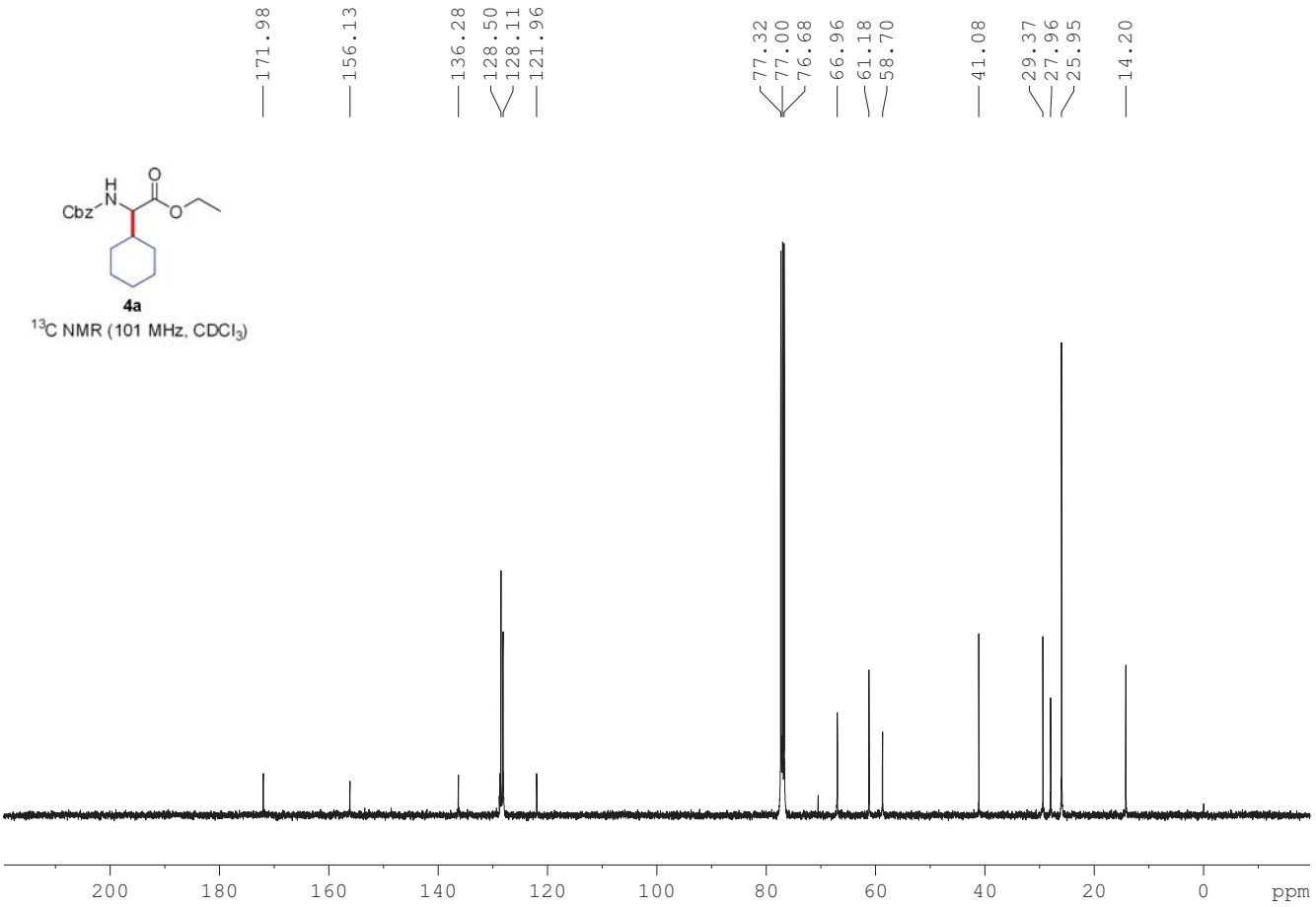
^{1}H NMR (300 MHz, $CDCl_3$)

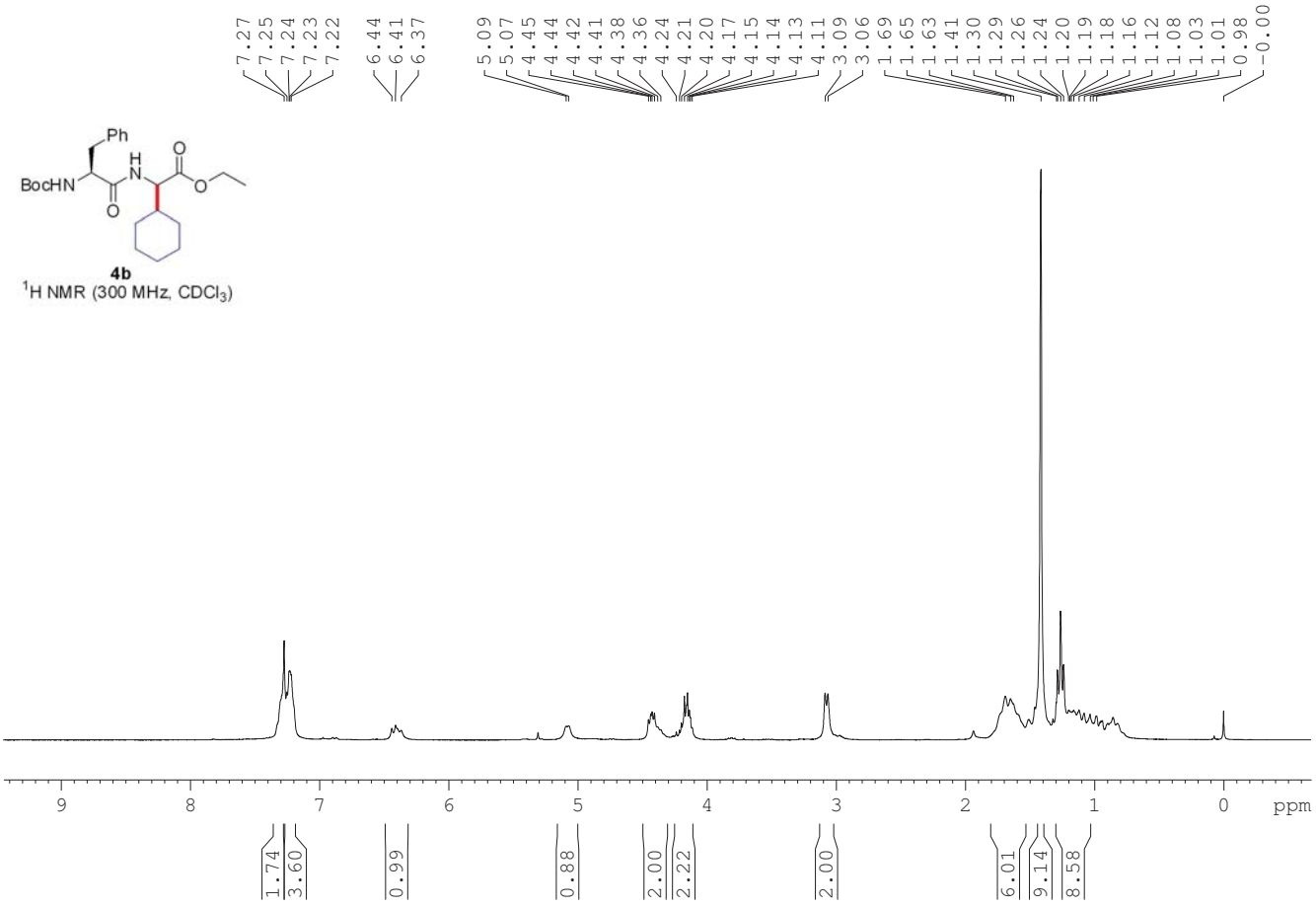

172.44
172.37
172.02
171.99
148.18
147.88
129.21
129.11
117.75
117.65
113.77
113.66
77.32
77.00
76.68
60.74
60.43
59.05
58.81
52.09
51.99
47.07
46.94
41.77
41.69
30.05
29.86
28.98
28.88
26.25
26.19
26.16
26.11
24.97
24.80
3qa
13C NMR (101 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm

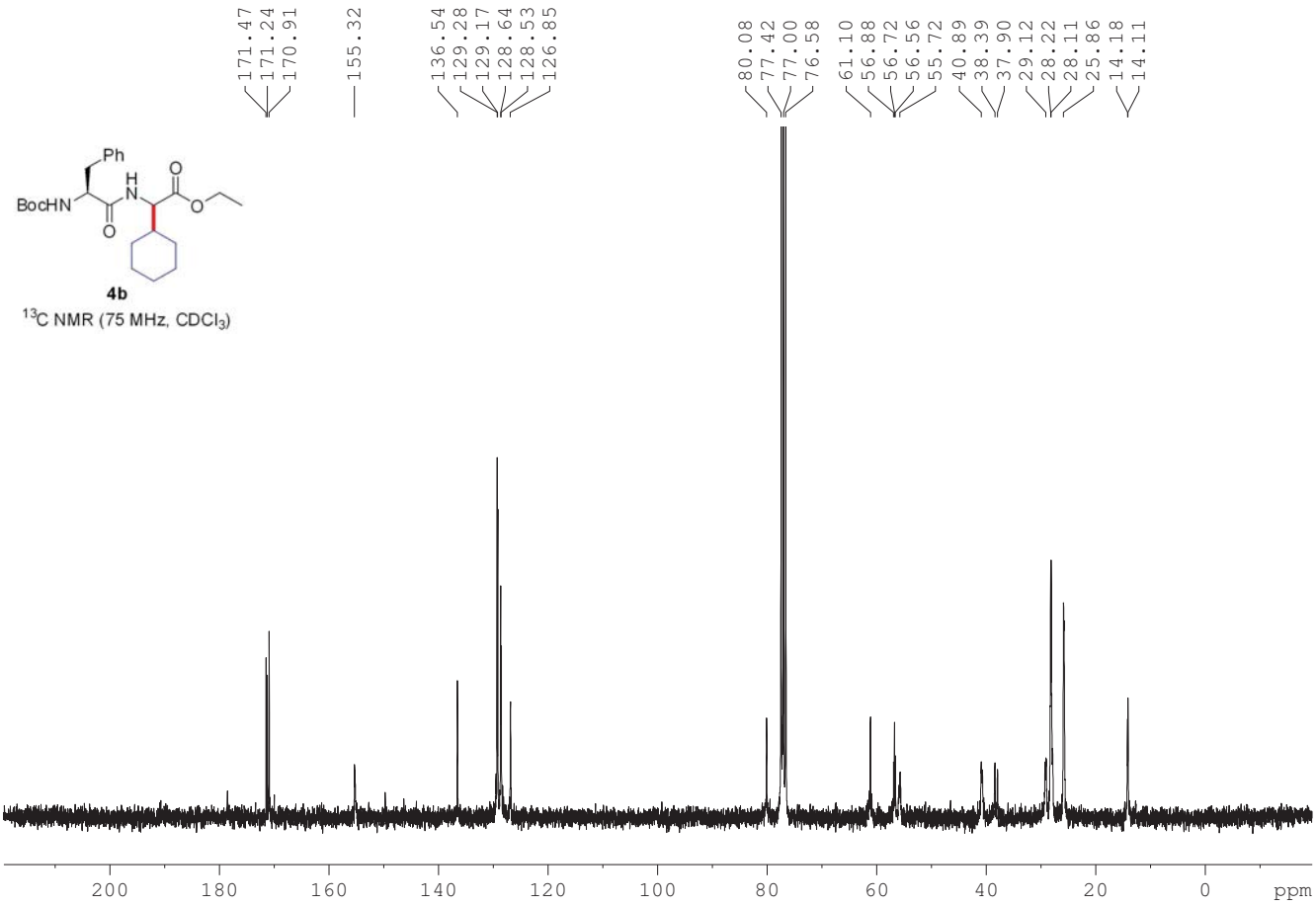

7.42
7.41
7.38
7.30
7.27
7.27
7.25
7.22
7.21
7.20
7.18
7.16
7.11
7.09
6.98
6.96
6.80
6.78
6.76
6.74
6.72
6.62
6.60
6.57
4.81
4.79
4.64
4.61
4.59
4.05
4.04
4.01
4.00
3.71
3.69
3.61
3.09
3.07
3.03
2.35
2.32
2.30
1.99
1.96
1.94
1.91
1.89
1.86
1.84
1.77
1.74
1.69
1.25
1.22
1.18
1.14
1.10
0.00
3ra
1H NMR (300 MHz, CDCl3)
9
8
7
6
5
4
3
2
1
0
ppm
1.03
6.47
0.88
1.60
2.47
2.04
1.00
2.87
1.05
1.58
0.40
2.02
11.27
5.49


172.84
171.44
171.36
170.42
170.21
147.19
146.96
135.79
135.47
129.56
129.34
129.15
129.04
128.60
128.51
127.15
127.00
119.01
118.92
113.43
113.37
77.32
77.00
76.68
64.42
64.37
53.24
53.21
52.25
51.99
51.52
41.07
40.99
37.71
30.86
30.53
30.13
29.78
29.60
28.37
28.27
26.12
25.98
14.94
14.74
3ra
13C NMR (101 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm


7.43
7.41
7.36
7.32
7.26
5.31
5.29
5.27
5.11
4.30
4.28
4.27
4.25
4.23
4.21
4.18
4.16
1.77
1.73
1.66
1.60
1.56
1.30
1.28
1.26
1.20
1.15
1.11
1.07
1.03
0.99
-0.00
Cbz
4a
1H NMR (300 MHz, CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
5.29
0.99
1.91
3.00
6.52
8.84

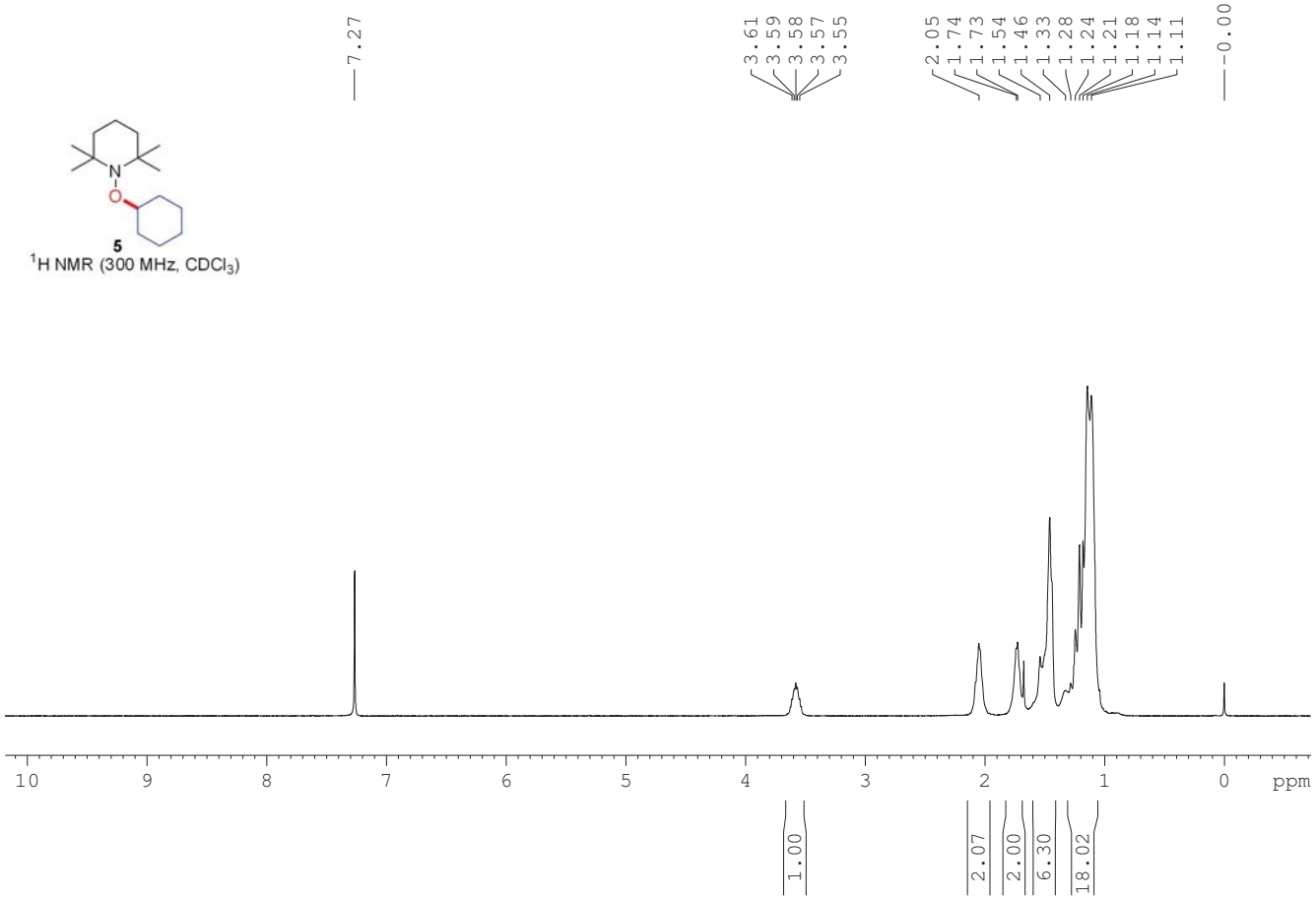

171.98
156.13
136.28
128.50
128.11
121.96
77.32
77.00
76.68
66.96
61.18
58.70
41.08
29.37
27.96
25.95
14.20
Cbz
H
N
O
O
4a
13C NMR (101 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm


7.27
7.25
7.24
7.23
7.22
6.44
6.41
6.37
5.09
5.07
4.45
4.44
4.42
4.41
4.38
4.36
4.24
4.21
4.20
4.17
4.15
4.14
4.13
4.11
3.09
3.06
1.69
1.65
1.63
1.41
1.30
1.29
1.26
1.24
1.20
1.19
1.18
1.16
1.12
1.08
1.03
1.01
0.98
0.00
Ph
BocHN
H
N
O
O
O
4b
1H NMR (300 MHz, CDCl3)
9
8
7
6
5
4
3
2
1
0
ppm
1.74
3.60
0.99
0.88
2.00
2.22
2.00
6.01
9.14
8.58



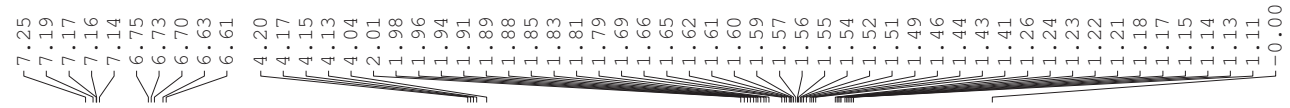
4b

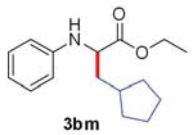
^{13}C NMR (75 MHz, $CDCl_3$)



5

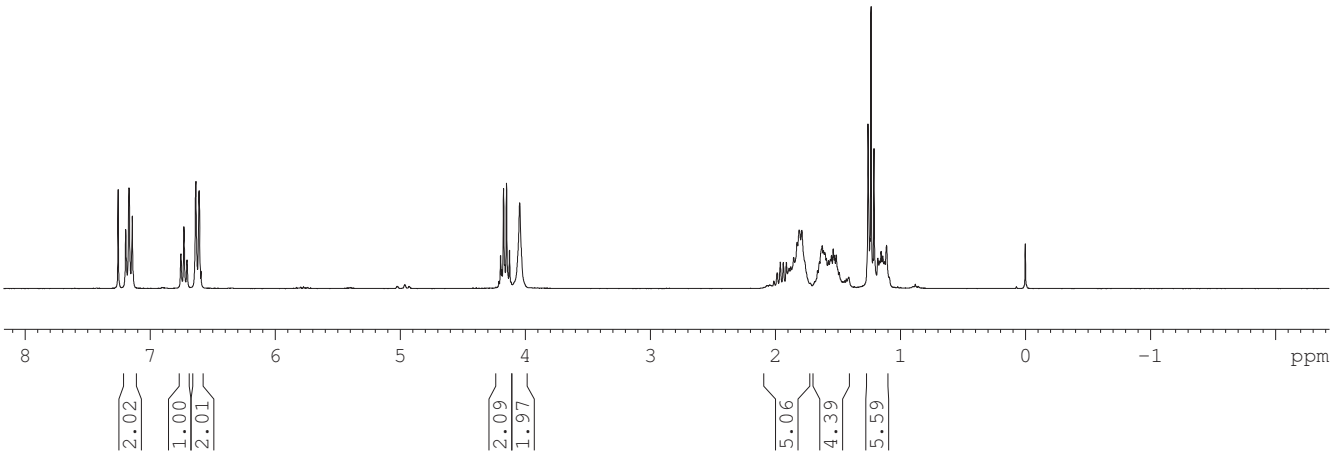
^{1}H NMR (300 MHz, $CDCl_3$)

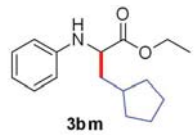




3bm

^{1}H NMR (300 MHz, $CDCl_3$)





3bm

^{13}C NMR (101 MHz, $CDCl_3$)