Supporting Information

Base- and metal-free visible-light driven site-selective α-C(sp^3)-H functionalization reaction of glycine derivatives with hydroxamic acid derivatives

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1.General Information

Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. All manipulations were performed in a dried sealed tube equipped with a magnetic stir bar under a nitrogen atmosphere. Except for the specially mentioned dry solvent, all the solvents were treated according to general methods. All the reactions were monitored by TLC and were visualized using UV light. The product purification was done using silica gel column chromatography. TLC characterization was performed with precoated silica gel GF254 (0.2 mm), while column chromatography characterization was performed with silica gel (100−200 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded with tetramethylsilane (TMS, δ = 0.00 ppm) as the internal standard. ^{1}H NMR spectra were recorded at 400 or 600 MHz (Varian), and ^{13}C NMR spectra were recorded at 100 or 150 MHz (Varian). ^{19}F NMR spectra were recorded at 376 MHz. Chemical shifts are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) for ^{1}H NMR, and chemical shifts for ^{13}C NMR spectra are reported in ppm relative to the central $CDCl_3$ (δ = 77.0 ppm) Coupling constants were given in Hz. The following notations were used: br-broad, s-singlet, d-doublet, t-triplet, q-quartet, m-multiplet, dd-doublet of doublet, dt-doublet of triplet, td-triplet of doublet, and ddd-doublet of doublet of doublet. Melting points were measured with a YRT-3 melting point apparatus (Shantou Keyi Instrument & Equipment Co., Ltd., Shantou, China). The blue light source (455nm) was provided by Shanghai 3S Technology Co., Ltd SSSTECH-LAL1CV 1.0 parallel reactor (Figure S1). The volume of the reaction tube is 10 ml.

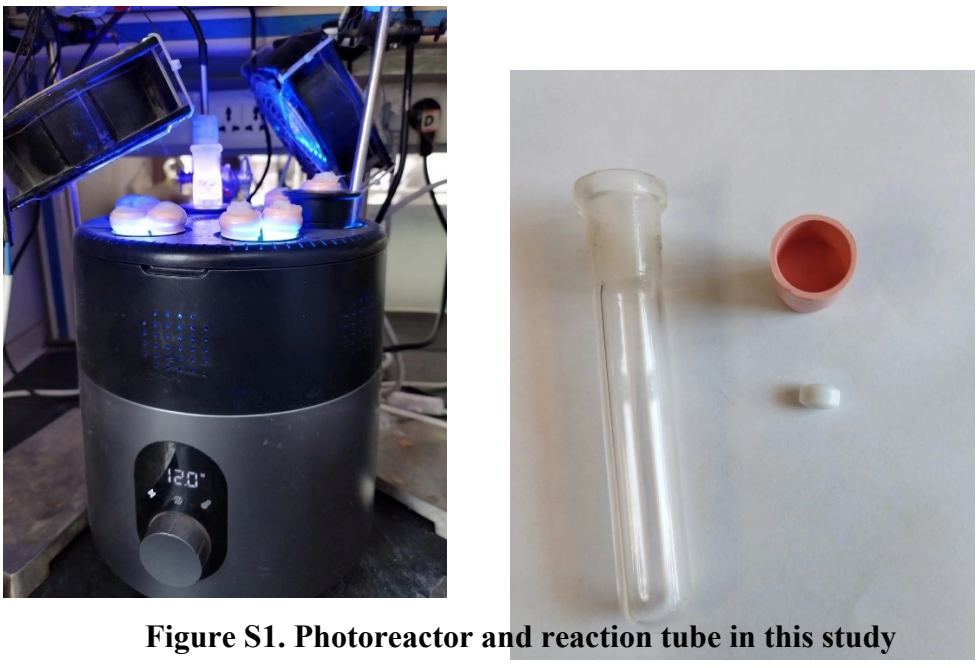
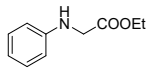


Figure S1. Photoreactor and reaction tube in this study

2. Starting Materials

N-aryl protected derivatives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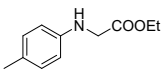
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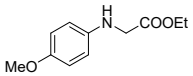
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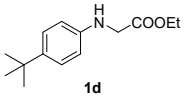
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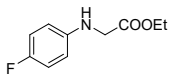
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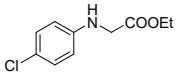
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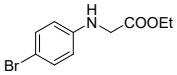
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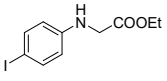
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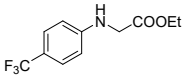
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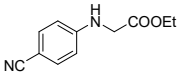
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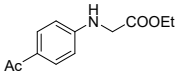
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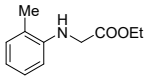
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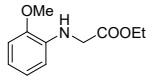
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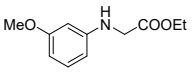
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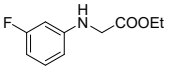
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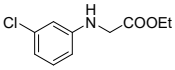
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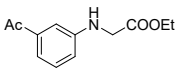
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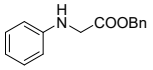
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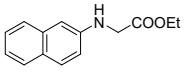
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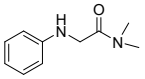
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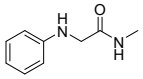
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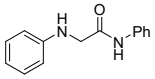
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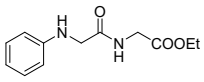
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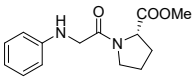
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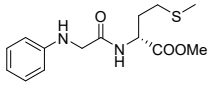
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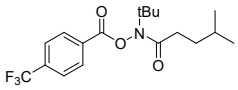
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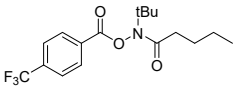
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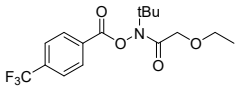
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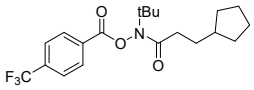
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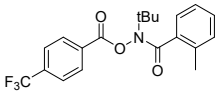
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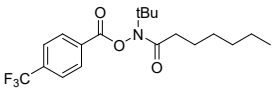
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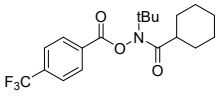
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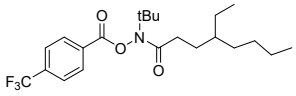
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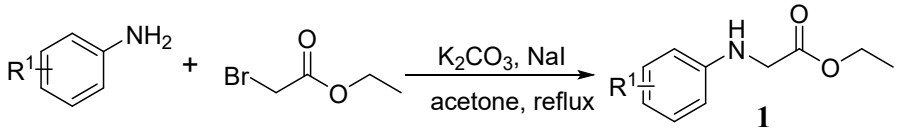
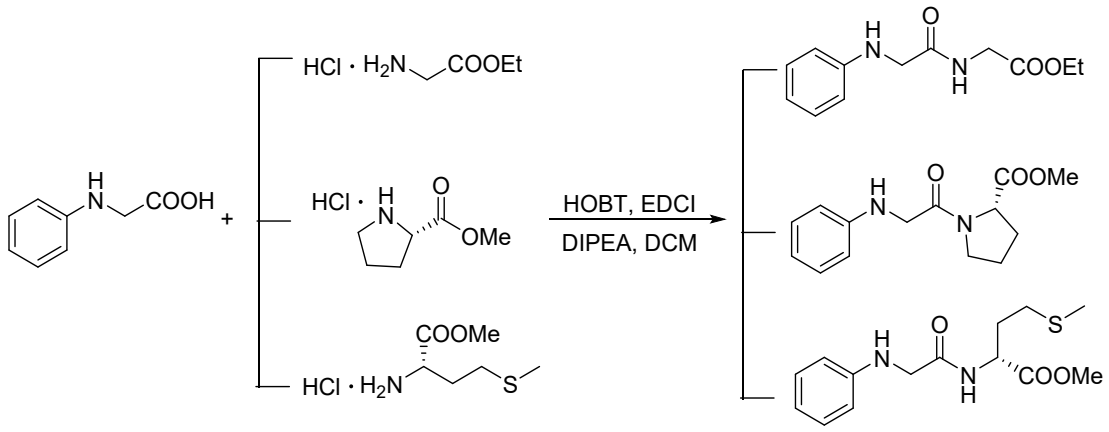
2.1 Preparation of Glycine Derivatives 1



1

Following the literature procedure:[1]a mixture of aniline (10 mmol), the corresponding bromoacetate-ester (1.1 equiv), potassium carbonate anhydrous (1.2 equiv) and sodium iodide (1.2 equiv) in 30 mL of dry acetone was refluxed for 12 h. The resulting mixture was cooled to room temperature, and filtered through a celite. The celite was washed with CH_2Cl_2, the combined organic layer was evaporated to

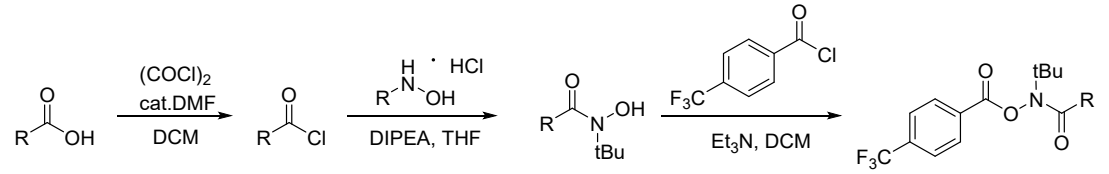
remove the solvent and the crude product was then purified by column chromatography. The pure product was obtained as solid or liquid.



Following the literature procedure[2]: In round-bottom flask, phenylglycine (1.0 equiv) were dissolved in DCM (0.33 M), HOBT (1.45 equiv) and EDCI (1.6 equiv) were added in turn. The mixture was stirred at room temperature. After 30 min, DIEA (4.0 equiv) and ester-protected amino acids (1.0 equiv) were added at 0℃. The reaction mixture was warmed to room temperature and stirred overnight. The resulting mixture was washed by citric acid solution, saturated sodium bicarbonate solution and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography and the title compounds were obtained.

2.2 Preparation of hydroxamide compounds 2

Hydroxamide compounds **2** are known compounds, and they were synthesized according to the literature procedure[3]



Step 1:

To a solution of carboxylic acid (1.0 equiv.) and 3-5 drops of anhydrous DMF in anhydrous CH_2Cl_2 (0.5 M) at 0 ℃, oxalyl chloride (1.5 equiv.) was added dropwise over 10 minutes. The reaction was vigorously stirred at room temperature for 3 h. The solvent was removed in vacuum. Anhydrous CH_2Cl_2 was added to remove the residual of oxalyl chloride in vacuum. Then the resulting acyl chloride was redissolved in anhydrous acetonitrile and used directly for the next step without further purification.

Step 2:

A solution of the N-(tert-butyl)hydroxylamine hydrochloride in anhydrous THF (0.4 M) was cooled to 0 ℃, treated with DIPEA (2.0 equiv.) and stirred for 15 minutes. The acyl chloride (1.0 equiv.) in anhydrous acetonitrile was added dropwise over 15 minutes and the mixture was allowed to warm to room temperature overnight. The mixture was diluted with saturated $NaHCO_3$ and EtOAc and the layers were separated. The aqueous layer was extracted twice with EtOAc and the combined organic layers

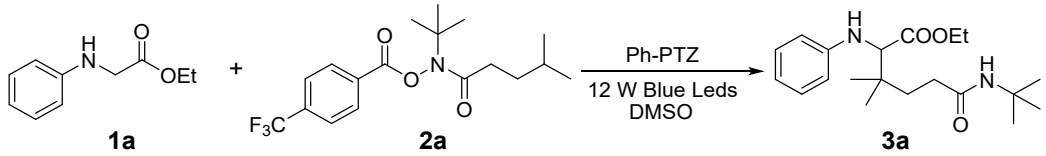
were washed with 1 M HCl, saturated $NaHCO_3$ and brine, successively, and then evaporated. Purification by column chromatography on silica gel eluting with petroleum ether and EtOAc gave the hydroxylamine.

Step 3:

To a solution of hydroxylamine (1.1 equiv.) in anhydrous CH_2Cl_2 (0.35 M) at 0 ℃, Et_3N (1.5 equiv.) was added dropwise. 4-trifluoromethyl-benzoyl chloride (1.0 equiv.) was then added dropwise over 5 minutes. The reaction was vigorously stirred at room temperature for 2 h. The mixture was diluted with saturated $NaHCO_3$ and CH_2Cl_2 and the layers were separated. The aqueous layer was extracted twice with CH_2Cl_2 and the combined organic layers were washed with 1 M HCl, saturated $NaHCO_3$ and brine, successively, and then evaporated. Purification by column chromatography on silica gel eluting with petroleum ether and EtOAc gave the hydroxamide compounds 2.

3. Optimization of Reaction conditions

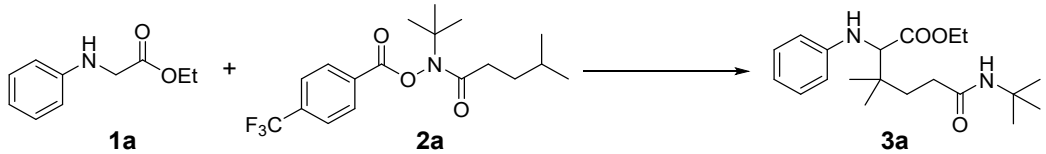
3.1 General Procedure for the synthesis of products 3 (3a as an example).



1a 2a 3a

In a dry 10 ml sealed glass tube, add **1a** (0.10 mmol, 1.0 equiv.), **2a** (0.15 mmol, 1.5 equiv.) and photocatalyst Ph-PTZ (5 mol%). Then, the tube was evacuated and backfilled with nitrogen (three times). Subsequently, add solvent DMSO (1 mL). After irradiating the reaction mixture with 12W Blue LEDs for 24h. After that, the resulting mixture was quenched with H_2O and extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography to obtain the products **3a**.

3.2 Optimization of the Reaction 1a, 2a

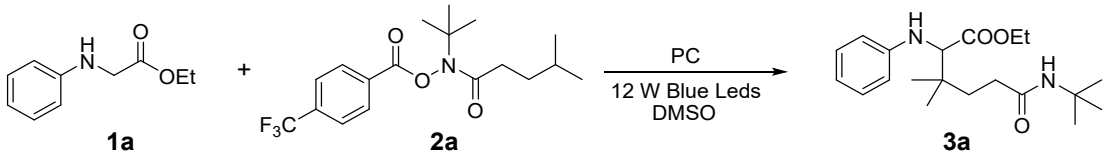


1a 2a 3a

Entry	Photocatalyst	Base	Slovent	Yields(%)[a]
1	4CzIPN	$NaHCO_3$	DMSO	71..5
2	4CzIPN	DABCO	DMSO	77.5
3	4CzIPN	DABCO	MeCN	trace
4	**4CzIPN**	**None**	**DMSO**	**74.0**

[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.15 mmol, 1.5 equiv.), Slovent (1.0 mL), PC (5 mol%), Base (2.0 equiv), Blue LEDs 12 W, for 24 h, under N_2, isolated yield.

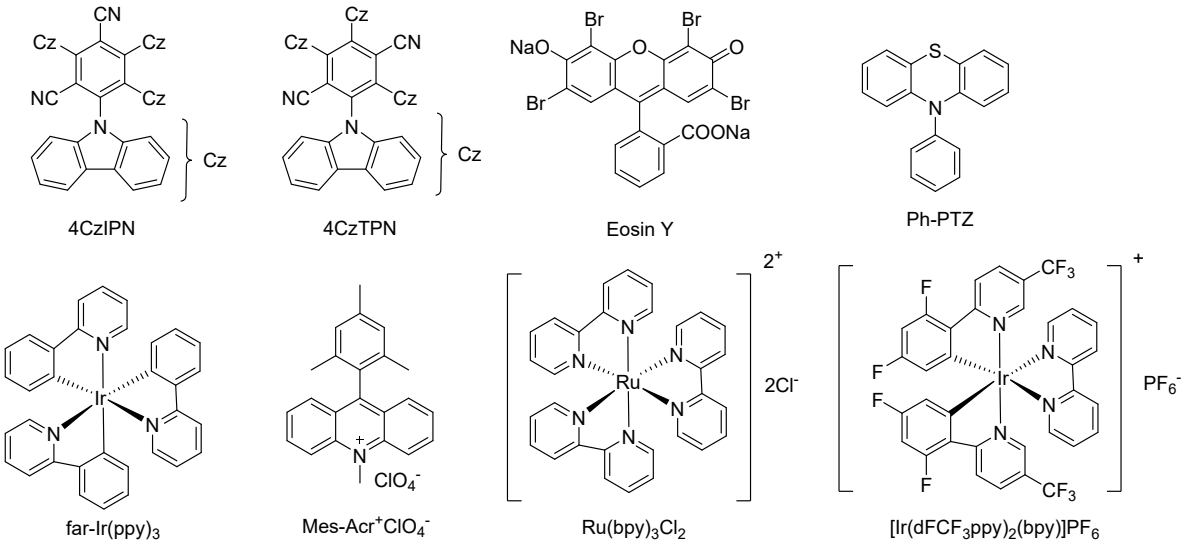
Photocatalyst



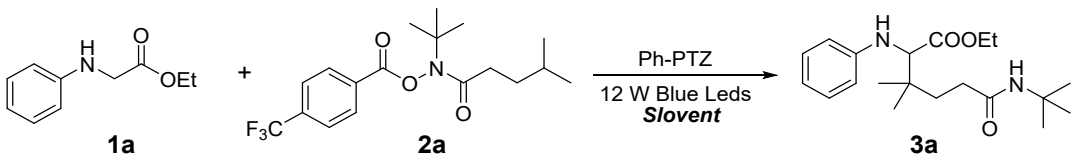
1a **2a** **3a**

Entry	Photocatalyst	Yields(%)[a]
1	4CzIPN	74.0
2	4CzTPN	72.0
3	Eosin Y	68.3
4	**Ph-PTZ**	**94.0**
5	fac-Ir(ppy)$_3$	trace
6	Mes-Acr$^+$ClO$_4^-$	0
7	Ru(bpy)$_3$Cl$_2$	0
8	[Ir(dFCF$_3$ppy)$_2$(bpy)]PF$_6$	trace
9	none	0

[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.15 mmol, 1.5 equiv.), DMSO (1.0 mL), PC (5 mol%), Blue LEDs 12 W, for 24 h, under N_2, isolated yield.



Solvent



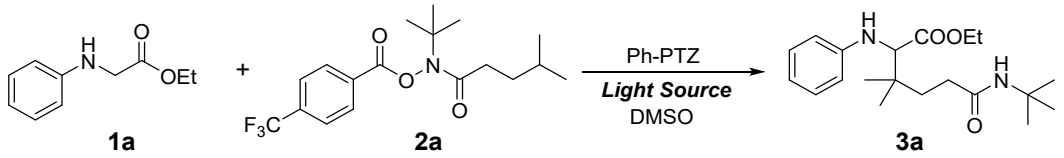
1a **2a** **3a**

Entry	Solvent	Yields(%)[a]
1	**DMSO**	**94.0**
2	DMF	50.5
3	DMA	44.7
4	NMP	0
5	THF	trace
6	Dioxane	0

7	Acetone	trace
8	EA	0
9	MeCN	trace
10	MeOH	0

[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.15 mmol, 1.5 equiv.), Solvent (1.0 mL), Ph-PTZ (5 mol%), Blue LEDs 12 W, for 24 h, under N_2, isolated yield.

Light source

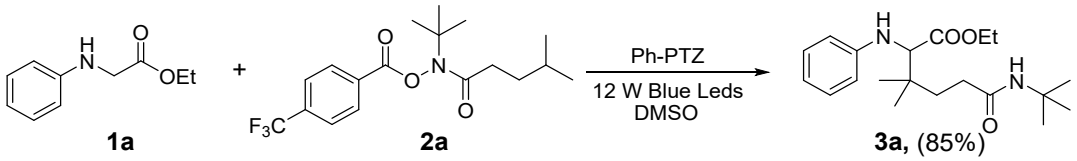


1a **2a** **3a**

Entry	Light source	Yields(%)[a]
1	425nm 12W	53.9
2	**Blue LEDs 12W**	**94.0**
3	390nm 12W	41.3
4	White LEDs 12W	60.0
5	525nm 12W	trace
6	425nm 2*40W Kessil lamp	65.0
7	455nm 2*40W Kessil lamp	78.5

[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.15 mmol, 1.5 equiv.), DMSO (1.0 mL), Ph-PTZ (5 mol%), Light source , for 24 h, under N_2, isolated yield.

4. Scale-up preparation



1a **2a** **3a,** (85%)

To a flame-dried 50 ml thick-walled pressure bottle equipped with magnetic stirrer, add **1a** (6.0 mmol, 1.0 equiv.), **2a** (9.0 mmol, 1.5 equiv.), photocatalyst Ph-PTZ (5 mol%) and 35 mL dry DMSO. The flask was charged with argon (three times).After irradiating the reaction mixture with 12W Blue LEDs for 24h (Figure S2). Tthe resulting mixture was quenched with H_2O and extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel to give the pure product **3a.**

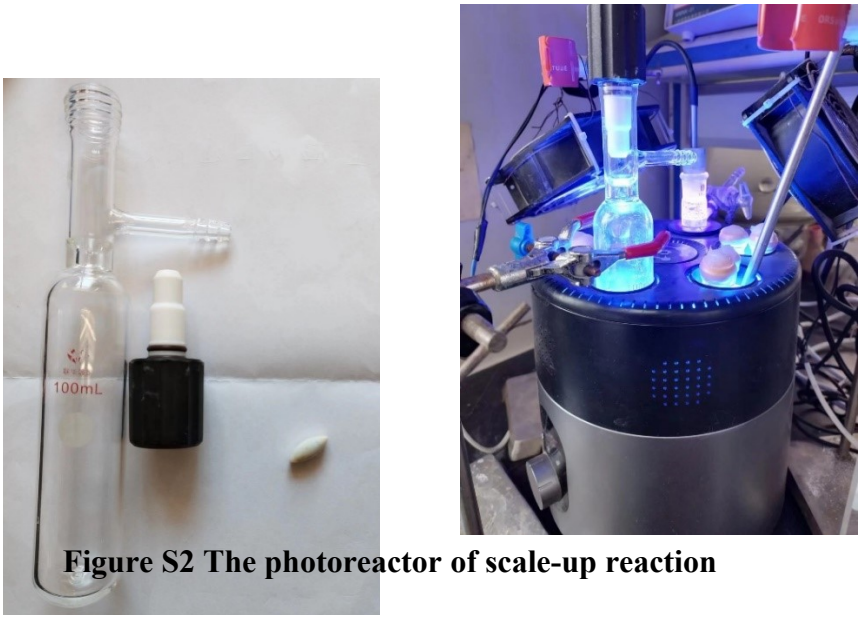
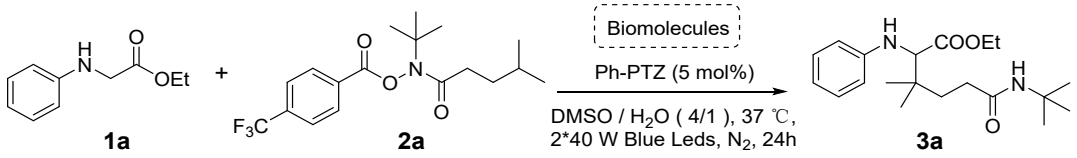
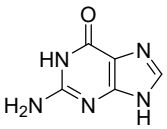
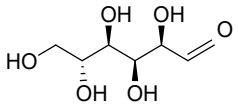
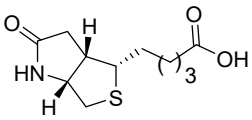
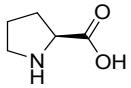


Figure S2 The photoreactor of scale-up reaction

5. Compatibility with biomolecules



Entry	Biomolecules	Yields[a]	Entry	Biomolecules	Yields[a]
1	none	65%	4	10 mg ml^{-1} Lysozyme	47%
2	 Guanine 1.0 equiv	41%	5	 D-(+)-Glucose 1.0 equiv	44%
3	 D-Biotin 1.0 equiv	51%	6	 L-Proline 1.0 equiv	40%

In a dry 10 ml sealed glass tube, add **1a** (0.10 mmol, 1.0 equiv.), **2a** (0.15 mmol, 1.5 equiv.), photocatalyst Ph-PTZ (5 mol%) and biomolecules. Then, the tube was evacuated and backfilled with nitrogen (three times). Subsequently, add solvent DMSO (0.8 ml) and H_2O (0.2 ml). The vial was sealed and exposed to Blue LEDs at 37 ℃ for 24 h (Figure S3).

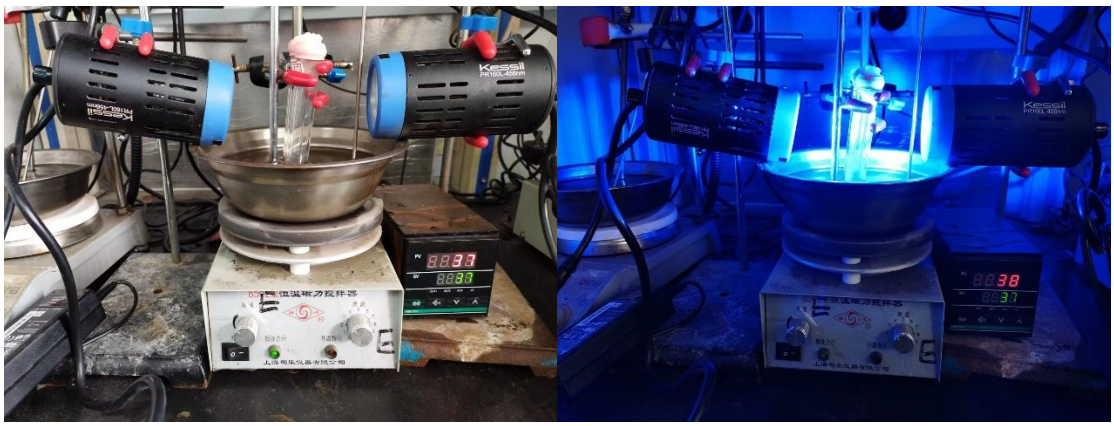
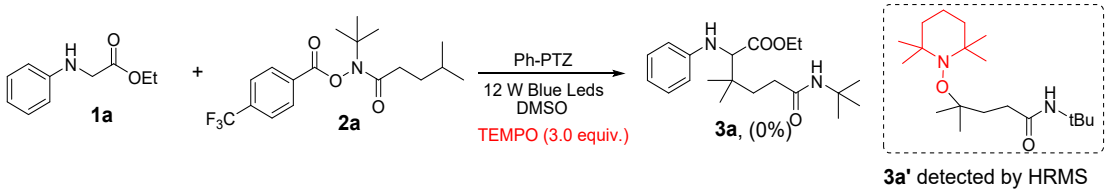


Figure S3 The photoreactor of biomolecules reaction

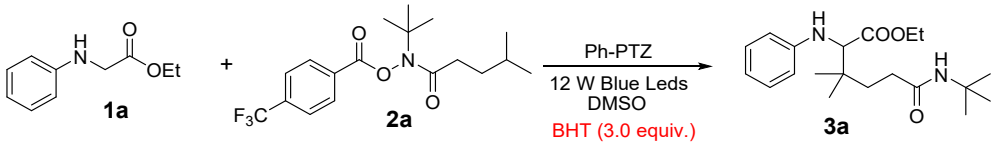
6. The mechanistic studies

6.1 Radical trapping experiments



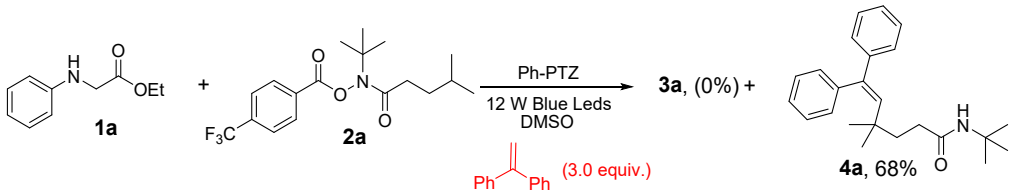
In a dry 10 ml sealed glass tube, **1a** (0.10 mmol, 1.0 equiv.), **2a** (0.15 mmol, 1.5 equiv.), photocatalyst Ph-PTZ (5 mol%) and TEMPO (0.30 mmol, 3.0 equiv) were added. Then, the tube was evacuated and backfilled with nitrogen (three times). Subsequently, add solvent DMSO (1 mL). After irradiating the reaction mixture with 12W Blue LEDs (λ = 455 nm) for 24h. After that, the resulting mixture was quenched with H_2O and extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo.

When 3.0 equiv. of TEMPO was subjected into the reaction of 1a with 2a under the standard conditions, only a trace amount of **3a** was observed, along with the TEMPO adduct **3a'** was detected by LC-HRMS (327.3).



1a (0.10 mmol, 1.0 equiv.), **2a** (0.15 mmol, 1.5 equiv.), photocatalyst Ph-PTZ (5 mol%) were added in a dry 10 ml sealed glass tube. Then, the tube was evacuated and backfilled with nitrogen (three times). Then BHT (0.3 mmol, 3.0 equiv.), and 1 mL DMSO were injected. The reaction mixture with 12W Blue LEDs (λ = 455 nm) for 24h. After that, the resulting mixture was quenched with H_2O and extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The radical trapping product **4a** (68%) was obtained by column chromatography on silica gel.

Only a trace amount of 3a was observed. This result indicates that a radical pathway might be involved in this transformation.



In a dry 10 ml sealed glass tube, **1a** (0.10 mmol, 1.0 equiv.), **2a** (0.15 mmol, 1.5 equiv.), photocatalyst Ph-PTZ (5 mol%) were added. Then, the tube was evacuated and backfilled with nitrogen (three times). Then 1,1-diphenylene (0.3 mmol, 3.0 equiv.), and 1 mL dry DMSO were injected. The reaction mixture with 12W Blue LEDs (λ = 455 nm) for 24h. After that, the resulting mixture was quenched with H_2O and extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The radical trapping product **4a** (68%) was obtained by column chromatography on silica gel.

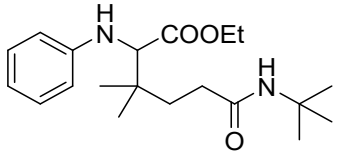
7.References

[1] A. V. Jerezano, E. M. Labarrios and F. E. Jiménez. Iodine-mediated one-pot synthesis of indoles and 3-dimethylaminoindoles via annulation of enaminones. *Arkivoc*, 2014, 318-53.

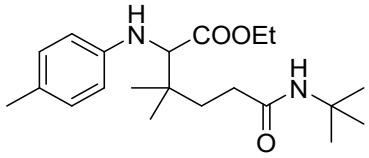
[2] W. Chao, G. Meng, Qi. Ru. Visible-light-driven, copper-catalyzed decarboxylative C (sp^3)-H alkylation of glycine and peptides. *Angewandte Chemie*, 2018, **130(48)**, 16067-16072.

[3] H. Chen, L. Guo, S. Yu. Primary, Secondary, and Tertiary gamma-C(sp^3)-H Vinylation of Amides via Organic Photoredox-Catalyzed Hydrogen Atom Transfer. *Org Lett*, 2018, **20 (19)**, 6255-6259.

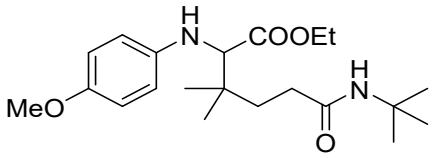
8.Characterization of Products



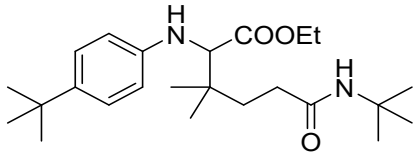
Ethyl 6-(tert-butylamino)-3,3-dimethyl-6-oxo-2-(phenylamino)hexanoate (3a). Yellow solid (94%, 32.6 mg); m.p.: 115-120 °C; R_f= 0.30 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.20 – 7.12 (m, 2H), 6.76 – 6.72 (m, 1H), 6.69 – 6.61 (m, 2H), 5.26 (s, 1H), 4.17 – 4.12 (m, 2H), 3.83 (s, 1H), 2.23 – 2.04 (m, 2H), 1.79 – 1.70 (m, 2H), 1.31 (s, 9H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.03 (d, *J* = 4.5 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.22, 172.36, 147.57, 129.48, 118.72, 114.06, 64.01, 60.93, 51.24, 36.83, 35.68, 32.58, 28.93, 24.29, 23.59, 14.42. **HRMS (ESI)** calcd for $C_{20}H_{33}N_2O_3$ $[M+H]^+$ 349.4945, found 349.4940.



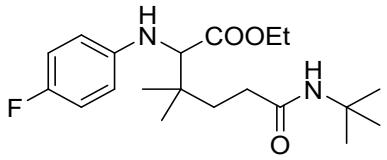
Ethyl 6-(tert-butylamino)-3,3-dimethyl-6-oxo-2-(p-tolylamino)hexanoate (3b).
Yellow solid (99%, 35.9 mg) ; m.p.: 120-125 ℃; R_f = 0.35 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$)δ 6.97 (d, *J* = 8.3 Hz, 2H), 6.60 – 6.54 (m, 2H), 5.29 (s, 1H), 4.16 – 4.09 (m, 2H), 3.78 (s, 1H), 2.22 (s, 3H), 2.18 – 2.02 (m, 2H), 1.80 – 1.65 (m, 2H), 1.31 (s, 9H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 4.6 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.24, 171.30, 144.11, 128.79, 126.81, 113.09, 63.22, 59.69, 50.04, 35.60, 34.59, 31.42, 27.75, 23.15, 22.42, 19.35, 13.27. **HRMS (ESI)** calcd for $C_{21}H_{35}N_2O_3$ $[M+H]^+$ 363.5215, found 363.5211.



Ethyl 6-(tert-butylamino)-2-((4-methoxyphenyl)amino)-3,3-dimethyl-6-oxohexanoate (3c).
Colorless oil (98%, 36.9 mg) ; R_f = 0.35 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.78 – 6.70 (m, 2H), 6.66 – 6.56 (m, 2H), 5.33 (s, 1H), 4.13 – 4.09 (m, 2H), 3.72 (s, 3H), 3.70 (s, 1H), 2.21 – 2.03 (m, 2H), 1.76 – 1.70 (m, 2H), 1.30 (s, 9H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.01 (d, *J* = 6.7 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.37, 171.33, 151.89, 140.47, 114.65, 113.82, 64.34, 59.67, 54.67, 50.04, 35.52, 34.57, 31.42, 27.76, 23.14, 22.40, 13.27. **HRMS (ESI)** calcd for $C_{21}H_{35}N_2O_4$ $[M+H]^+$ 379.5205, found 379.5210.

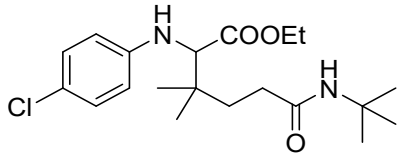


Ethyl 2-((4-(tert-butyl)phenyl)amino)-6-(tert-butylamino)-3,3-dimethyl-6-oxohexanoate (3d).
Yellow oil (76%, 30.7 mg) ; R_f = 0.30 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21 – 7.14 (m, 2H), 6.63 – 6.54 (m, 2H), 5.29 (s, 1H), 4.16 – 4.11 (m, 3H), 3.80 (s, 1H), 2.24 – 2.03 (m, 2H), 1.80 – 1.66 (m, 2H), 1.31 (s, 9H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.03 (d, *J* = 4.4 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.42, 172.41, 145.12, 141.40, 126.22, 113.70, 64.13, 60.84, 51.18, 36.82, 35.67, 33.99, 32.59, 31.61, 28.90, 24.25, 23.58, 14.39. **HRMS (ESI)** calcd for $C_{24}H_{41}N_2O_3$ $[M+H]^+$ 405.6025, found 405.6026.



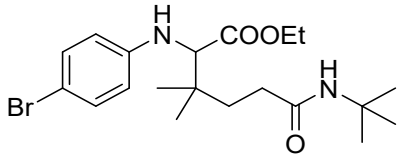
Ethyl 6-(tert-butylamino)-2-((4-fluorophenyl)amino)-3,3-dimethyl-6-oxohexanoate (3e).

Yellow oil (99%, 33.0 mg) ; R_f = 0.25 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.96 – 6.82 (m, 2H), 6.64 – 6.53 (m, 2H), 5.28 (s, 1H), 4.15 – 4.12 (m, 2H), 3.72 (s, 1H), 2.22 – 2.01 (m, 2H), 1.76 – 1.71 (m, 2H), 1.32 (s, 8H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 5.4 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.21, 172.32, 156.57 (d, *J* = 236.4 Hz), 143.90 (d, *J* = 2.0 Hz), 115.88 (d, *J* = 22.3 Hz), 115.29 (d, *J* = 7.5 Hz), 65.17, 60.95, 51.26, 36.72, 35.54, 32.50, 28.92, 24.26, 23.51, 14.41. **^{19}F NMR (376 MHz, CDCl3)** δ -126.02. **HRMS (ESI)** calcd for $C_{20}H_{32}FN_2O_3$ $[M+H]^+$ 367.4849, found 367.4845.



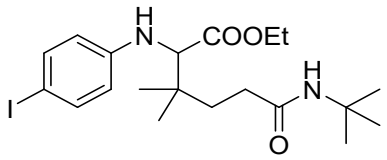
Ethyl 6-(tert-butylamino)-2-((4-chlorophenyl)amino)-3,3-dimethyl-6-oxohexanoate (3f).

Yellow oil (85%, 32.5 mg) ; R_f = 0.25 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.17 – 7.05 (m, 2H), 6.60 – 6.53 (m, 2H), 5.26 (s, 1H), 4.17 – 4.11 (m, 2H), 3.76 (s, 1H), 2.19 – 2.05 (m, 2H), 1.73 (dd, *J* = 9.2, 6.0 Hz, 3H), 1.31 (s, 9H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.02 (d, *J* = 3.4 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.94, 172.22, 146.19, 129.29, 123.32, 115.18, 64.33, 61.06, 51.28, 36.81, 35.46, 32.46, 28.92, 24.24, 23.52, 14.42. **HRMS (ESI)** calcd for $C_{20}H_{32}ClN_2O_3$ $[M+H]^+$ 383.9365, found 383.9360.



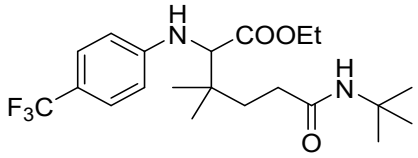
Ethyl 2-((4-bromophenyl)amino)-6-(tert-butylamino)-3,3-dimethyl-6-oxohexanoate(3g)

Yellow oil (89%, 38.0 mg) ; R_f = 0.25 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.17 (d, *J* = 8.3 Hz, 2H), 6.46 (d, *J* = 8.8 Hz, 2H), 5.21 (s, 1H), 4.12 – 4.04 (m, 2H), 3.69 (s, 1H), 2.13 – 1.96 (m, 2H), 1.70 – 1.63 (m, 2H), 1.29 – 1.23 (m, 9H), 1.17 – 1.12 (m, 3H), 0.95 (d, *J* = 3.1 Hz, 6H). **^{13}C NMR** (100 MHz, CDCl3) δ 172.86, 172.20, 146.61, 132.17, 115.63, 110.37, 64.18, 61.07, 51.28, 36.81, 35.44, 32.44, 28.92, 24.24, 23.52, 14.42. **HRMS (ESI)** calcd for $C_{20}H_{32}BrN_2O_3$ $[M+H]^+$ 428.3905, found 428.3912.



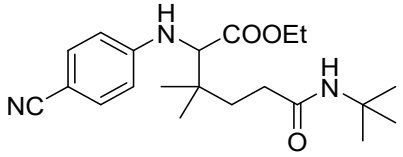
Ethyl 6-(tert-butylamino)-2-((4-iodophenyl)amino)-3,3-dimethyl-6-oxohexanoate (3h).

Yellow oil (81%, 38.0 mg) ; R_f = 0.25 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.36 (m, 2H), 6.47 – 6.41 (m, 2H), 5.25 (s, 1H), 4.20 (s, 1H), 4.17 – 4.11 (m, 2H), 3.76 (d, *J* = 10.1 Hz, 1H), 2.20 – 2.03 (m, 2H), 1.74 – 1.68 (m, 2H), 1.31 (s, 9H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.01 (d, *J* = 2.6 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.83, 172.17, 147.23, 138.03, 116.16, 79.51, 63.92, 61.08, 51.27, 36.82, 35.42, 32.42, 28.92, 24.23, 23.52, 14.42. **HRMS (ESI)** calcd for $C_{20}H_{32}IN_2O_3$ $[M+H]^+$ 475.3910, found 475.3915.



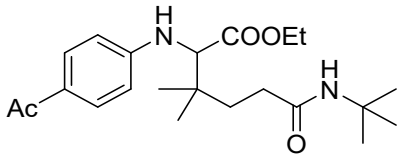
Ethyl 6-(tert-butylamino)-3,3-dimethyl-6-oxo-2-((4-(trifluoromethyl)phenyl)amino)hexanoate (3i)

Yellow oil (50%, 20.8 mg) ; R_f = 0.25 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.4 Hz, 2H), 6.66 (d, J = 8.4 Hz, 2H), 5.26 (s, 1H), 4.50 (d, *J* = 10.0 Hz, 1H), 4.19 – 4.14 (m , 2H), 3.86 (d, *J* = 9.2 Hz, 1H), 2.26 – 2.02 (m, 2H), 1.78 – 1.69 (m, 2H), 1.32 (s, 9H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.03 (d, *J* = 2.3 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.54, 172.09, 150.13, 126.83 (q, *J* = 3.7 Hz), 124.87 (d, *J* = 270.5 Hz), 120.15 (q, *J* = 32.7 Hz), 112.98, 63.55, 61.22, 51.30, 36.97, 35.25, 32.36, 28.90, 24.19, 23.53, 14.39. **^{19}F NMR** (376 MHz, CDCl3) δ -61.23. **HRMS (ESI)** calcd for $C_{21}H_{32}F_3N_2O_3$ $[M+H]^+$ 417.4927, found 417.4928.



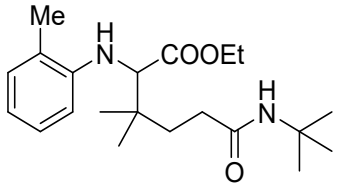
Ethyl 6-(tert-butylamino)-2-((4-cyanophenyl)amino)-3,3-dimethyl-6-oxohexanoate (3j).

Yellow oil (57%, 21.3mg) ; R_f = 0.30 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 2H), 6.64 – 6.58 (m, 2H), 5.29 (s, 1H), 4.20 – 4.15 (m, 2H), 3.86 (s, 1H), 2.22 – 2.02 (m, 3H), 1.73 (t, *J* = 8.2 Hz, 2H), 1.32 (s, 9H), 1.25 – 1.24 (m, 3H), 1.02 (d, *J* = 2.0 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.06, 171.97, 150.85, 133.89, 120.15, 113.26, 100.25, 63.37, 61.37, 51.34, 37.10, 34.94, 32.23, 28.90, 24.17, 23.52, 14.38. **HRMS (ESI)** calcd for $C_{21}H_{32}N_3O_3$ $[M+H]^+$ 374.5045, found 374.5040.



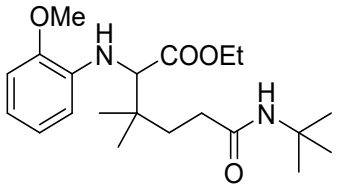
Ethyl 2-((4-acetylphenyl)amino)-6-(tert-butylamino)-3,3-dimethyl-6-oxohexanoate (3k).

Yellow oil (78%, 30.5mg) ; R_f = 0.25 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 – 7.75 (m, 2H), 6.65 – 6.56 (m, 2H), 5.35 (s, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.92 (d, *J* = 8.4 Hz, 1H), 2.48 (s, 3H), 2.25 – 2.02 (m, 3H), 1.79 – 1.71 (m, 2H), 1.31 (s, 9H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.03 (d, *J* = 2.2 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 196.50, 172.28, 172.19, 151.60, 130.88, 127.84, 112.46, 63.31, 61.25, 51.32, 37.08, 35.14, 32.31, 28.88, 26.15, 24.15, 23.52, 14.38. **HRMS (ESI)** calcd for $C_{22}H_{35}N_2O_4$ $[M+H]^+$ 391.5315, found 391.5319.



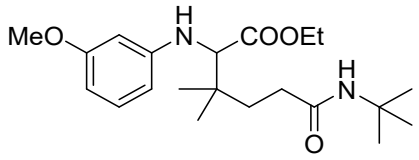
Ethyl 6-(tert-butylamino)-3,3-dimethyl-6-oxo-2-(o-tolylamino)hexanoate (3l).

Yellow oil (70%, 25.4mg) ; R_f = 0.30 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.0 Hz, 2H), 6.68 (t, *J* = 7.4 Hz, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 5.27 (s, 1H), 4.17 – 4.11 (m, 2H), 3.89 (s, 1H), 2.21 (s, 3H), 2.13 – 2.04 (m, 2H), 1.79 – 1.69 (m, 2H), 1.31 (s, 9H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.06 (d, *J* = 7.6 Hz, 6H). **^{13}C NMR** (100MHz, $CDCl_3$) δ 173.35, 172.33, 145.53, 130.54, 127.21, 123.39, 118.20, 110.74, 63.51, 60.91, 51.19, 36.91, 35.87, 32.55, 28.90, 24.23, 23.66, 17.59, 14.38. **HRMS (ESI)** calcd for $C_{21}H_{35}N_2O_3$ $[M+H]^+$ 363.5215, found 363.5220.



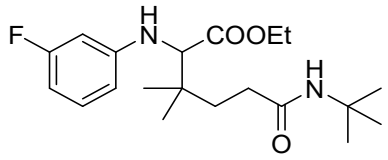
Ethyl 6-(tert-butylamino)-2-((2-methoxyphenyl)amino)-3,3-dimethyl-6-oxohexanoate (3m).

Yellow oil (84%, 31.8mg) ; R_f = 0.30 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.84 – 6.80 (m, 1H), 6.77 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.68 (td, *J* = 7.7, 1.5 Hz, 1H), 6.57 (dd, *J* = 7.9, 1.5 Hz, 1H), 5.30 (s, 1H), 4.17 – 4.09 (m, 2H), 3.85 (s, 3H), 2.25 – 2.03 (m, 2H), 1.78 – 1.74 (m, 2H), 1.30 (s, 9H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.06 (d, *J* = 7.3 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.20, 172.46, 147.41, 137.40, 121.21, 117.58, 110.44, 109.97, 63.41, 60.76, 55.69, 51.12, 36.82, 35.90, 32.60, 28.85, 24.26, 23.58, 14.36. **HRMS (ESI)** calcd for $C_{21}H_{35}N_2O_4$ $[M+H]^+$ 379.2594, found 379.2593.



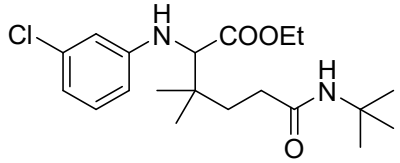
Ethyl 6-(tert-butylamino)-2-((3-methoxyphenyl)amino)-3,3-dimethyl-6-oxohexanoate (3n).

Yellow oil (88%, 33.3mg) ; R_f = 0.35 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.06 (t, *J* = 8.1 Hz, 1H), 6.27 (ddd, *J* = 15.8, 8.1, 2.3 Hz, 2H), 6.20 (d, *J* = 2.4 Hz, 1H), 5.29 (s, 1H), 4.14 (qd, *J* = 7.2, 2.0 Hz, 2H), 3.81 (s, 1H), 3.75 (s, 3H), 2.22 – 2.04 (m, 2H), 1.75 –1.69 (m, 2H), 1.31 (s, 9H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.02 (d, *J* = 4.3 Hz, 6H). **^{13}C NMR** (100MHz, $CDCl_3$)) δ 173.12, 172.33, 160.91, 148.96, 130.21, 106.82, 103.87, 99.98, 63.80, 60.91, 55.20, 51.19, 36.80, 35.60, 32.50, 28.88, 24.26, 23.58, 14.39. **HRMS (ESI)** calcd for $C_{21}H_{35}N_2O_4$ $[M+H]^+$ 379.5205, found 379.5211.



Ethyl 6-(tert-butylamino)-2-((3-fluorophenyl)amino)-3,3-dimethyl-6-oxohexanoate (3o).

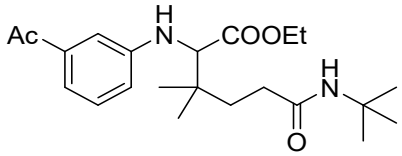
Yellow oil (65%, 23.8mg) ; R_f = 0.25 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.08 (td, *J* = 8.1, 6.7 Hz, 1H), 6.43 – 6.39 (m, 2H), 6.35 – 6.31 (m, 1H), 5.29 (s, 1H), 4.18 – 4.13 (m, 2H), 3.78 (s, 1H), 2.19 – 2.08 (m, 2H), 1.75 – 1.70 (m, 2H), 1.32 (s, 9H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.02 (d, *J* = 3.5 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.81, 172.24, 164.10 (d, *J* = 243.5 Hz), 149.38 (d, *J* = 10.5 Hz), 130.55 (d, *J* = 10.2 Hz), 109.82 (d, *J* = 2.3 Hz), 105.09 (d, *J* = 21.5 Hz), 100.64 (d, *J* = 25.5 Hz), 63.91, 61.08, 51.28, 36.85, 35.42, 32.42, 28.90, 24.22, 23.55, 14.39. **^{19}F NMR** (376 MHz, CDCl3) δ -112.52 (dt, J = 11.6, 7.6 Hz). **HRMS (ESI)** calcd for $C_{20}H_{32}FN_2O_3$ $[M+H]^+$ 367.4849, found 367.4851.



Ethyl 6-(tert-butylamino)-2-((3-chlorophenyl)amino)-3,3-dimethyl-6-oxohexanoate (3p).

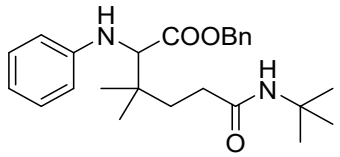
Yellow oil (54%, 20.7mg) ; R_f = 0.30 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.06 (t, *J* = 8.0 Hz, 1H), 6.69 (dd, *J* = 7.9, 1.9 Hz, 1H), 6.62 (t, *J* = 2.2 Hz, 1H), 6.52 (dd, *J* = 8.2, 2.4 Hz, 1H), 5.27 (s, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 1H), 2.22 – 2.04 (m, 2H), 1.75 – 1.70 (m, 2H), 1.32 (s, 9H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 3.3 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.77, 172.18, 148.75, 135.19, 130.44, 118.56, 113.61, 112.34, 63.81, 61.11, 51.28, 36.87, 35.43, 32.44, 28.92,

24.22, 23.56, 14.42. **HRMS (ESI)** calcd for $C_{20}H_{32}ClN_2O_3$ $[M+H]^+$ 383.9365, found 383.9562.



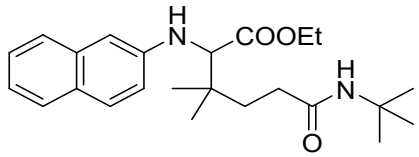
Ethyl 2-((3-acetylphenyl)amino)-6-(tert-butylamino)-3,3-dimethyl-6-oxohexanoate (3q)

Yellow oil (70%, 27.3mg) ; R_f = 0.25 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 7.6 Hz, 1H), 7.24 (s, 1H), 7.23 (d, *J* = 2.9 Hz, 1H), 6.85 (dd, *J* = 8.0, 2.6 Hz, 1H), 5.31 (s, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 1H), 2.56 (s, 3H), 2.21 – 2.08 (m, 2H), 1.77 – 1.72 (m, 2H), 1.31 (s, 9H), 1.22 (d, *J* = 7.1 Hz, 3H), 1.04 (d, *J* = 4.0 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.58, 172.93, 172.23, 147.85, 138.31, 129.61, 119.08, 118.90, 112.45, 63.72, 61.08, 51.27, 36.91, 35.43, 32.46, 28.91, 26.85, 24.25, 23.60, 14.41. **HRMS (ESI)** calcd for $C_{22}H_{35}N_2O_4$ $[M+H]^+$ 391.5315, found 391.5309.



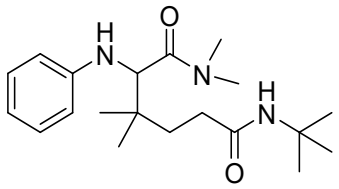
Benzyl 6-(tert-butylamino)-3,3-dimethyl-6-oxo-2-(phenylamino)hexanoate (3r).

Yellow oil (78%, 32.0mg) ; R_f = 0.40 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 4.8, 2.0 Hz, 3H), 7.17 (dt, *J* = 6.0, 2.5 Hz, 2H), 7.08 (t, *J* = 7.7 Hz, 2H), 6.68 (t, *J* = 7.3 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 2H), 5.21 (s, 1H), 5.02 (s, 2H), 3.82 (s, 1H), 3.54 (s, 1H), 2.13 – 1.97 (m, 2H), 1.72 – 1.60 (m, 2H), 1.23 (s, 9H), 0.94 (d, *J* = 7.9 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.18, 172.32, 147.41, 135.48, 129.48, 128.65, 128.54, 128.44, 118.81, 114.08, 66.82, 64.06, 51.19, 36.82, 35.61, 32.46, 28.86, 24.32, 23.55. **HRMS (ESI)** calcd for $C_{25}H_{35}N_2O_3$ $[M+H]^+$ 411.5655, found 411.5653.

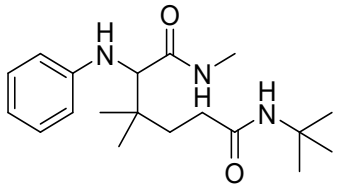


Ethyl 6-(tert-butylamino)-3,3-dimethyl-2-(naphthalen-2-ylamino)-6-oxohexanoate (3s).

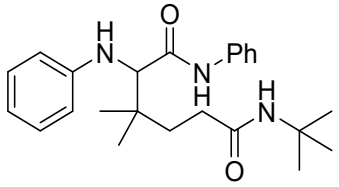
Yellow oil (65%, 26.0mg) ; R_f = 0.35 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 – 7.48 (m, 3H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.20 – 7.07 (m, 1H), 6.88 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.77 (d, *J* = 2.4 Hz, 1H), 5.20 (s, 1H), 4.13 – 4.04 (m, 2H), 3.90 (s, 1H), 2.19 – 1.95 (m, 2H), 1.74 – 1.66 (m, 2H), 1.22 (s, 9H), 1.15 (t, *J* = 7.1 Hz, 3H), 1.01 (d, *J* = 3.7 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.15, 172.39, 145.18, 135.02, 129.26, 128.16, 127.72, 126.54, 126.17, 122.66, 118.68, 105.92, 63.83, 60.99, 51.24, 36.80, 35.72, 32.53, 28.87, 24.36, 23.64, 14.43. **HRMS (ESI)** calcd for $C_{24}H_{35}N_2O_3$ $[M+H]^+$ 399.5545, found 399.5552.



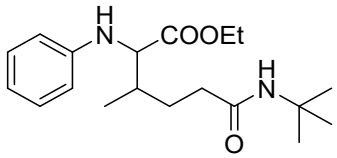
N^6-(tert-butyl)-N^1,N^1,3,3-tetramethyl-2-(phenylamino)hexanediamide (3t).
Yellow oil (74%, 25.7mg) ; R_f = 0.40 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19 – 7.08 (m, 2H), 6.70 (d, *J* = 7.3 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 2H), 5.28 (s, 1H), 4.23 (s, 1H), 3.10 (d, *J* = 1.9 Hz, 3H), 2.91 (d, *J* = 1.9 Hz, 3H), 2.17 – 2.07 (m, 2H), 1.88 – 1.69 (m, 2H), 1.31 (d, *J* = 1.9 Hz, 9H), 1.02 (d, *J* = 17.2 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.06, 172.63, 148.23, 129.52, 118.43, 114.27, 59.64, 51.22, 38.43, 38.38, 35.79, 35.50, 32.87, 28.92, 23.29, 23.16. **HRMS (ESI)** calcd for $C_{20}H_{34}N_3O_2$ $[M+H]^+$ 348.5105, found 348.5110.



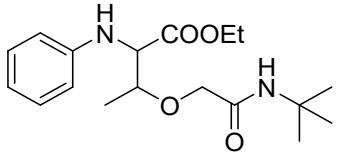
N^6-(tert-butyl)-N^1,3,3-trimethyl-2-(phenylamino)hexanediamide (3u).
Yellow oil (99%, 33.0mg) ; R_f = 0.40 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.17 (t, *J* = 7.7 Hz, 2H), 6.97 (q, *J* = 5.0 Hz, 1H), 6.78 (t, *J* = 7.3 Hz, 1H), 6.62 (d, *J* = 7.9 Hz, 2H), 5.91 (s, 1H), 4.95 (s, 2H), 3.52 (s, 1H), 2.76 (d, *J* = 4.9 Hz, 3H), 2.41 – 2.26 (m, 1H), 2.09 – 2.00 (m, 1H), 1.81 – 1.73 (m, 2H), 1.32 (s, 9H), 1.05 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.33, 172.79, 147.22, 129.50, 119.17, 113.89, 65.98, 51.28, 36.77, 36.25, 32.56, 28.81, 26.13, 24.92, 24.68. **HRMS (ESI)** calcd for $C_{19}H_{32}N_3O_2$ $[M+H]^+$ 334.4835, found 334.4830.



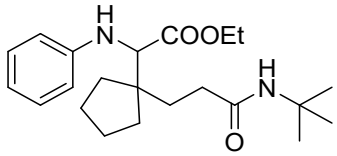
N^6-(tert-butyl)-3,3-dimethyl-N^1-phenyl-2-(phenylamino)hexanediamide (3v).
Yellow oil (78%, 30.9mg) ; R_f = 0.30 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.49 – 7.40 (m, 2H), 7.26 – 7.16 (m, 2H), 7.16 – 7.08 (m, 2H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.73 (t, *J* = 7.3 Hz, 1H), 6.67 – 6.58 (m, 2H), 5.73 (s, 1H), 3.54 (s, 1H), 2.37 – 1.98 (m, 2H), 1.86 – 1.67 (m, 2H), 1.27 (s, 9H), 1.04 (d, *J* = 3.8 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.96, 170.61, 147.28, 137.59, 129.58, 129.01, 124.49, 120.15, 119.55, 114.19, 66.58, 51.30, 37.31, 36.07, 32.64, 28.86, 25.20, 24.78. **HRMS (ESI)** calcd for $C_{24}H_{34}N_3O_2$ $[M+H]^+$ 396.5545, found 396.5543.



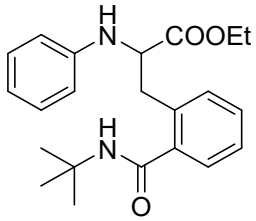
Ethyl 6-(tert-butylamino)-3-methyl-6-oxo-2-(phenylamino)hexanoate (3w).
Yellow oil (91%, 30.4mg) ; 1:1 d.r ; R_f = 0.35 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.15 (ddd, *J* = 9.0, 7.2, 1.9 Hz, 2H), 6.74 – 6.69 (m, 1H), 6.65 – 6.58 (m, 2H), 5.39 – 5.21 (m, 1H), 4.20 – 4.13 (m, 2H), 3.98 – 3.88 (m, 1H), 2.24 – 2.06 (m, 2H), 2.02 – 1.78 (m, 2H), 1.62 – 1.51 (m, 1H), 1.32 (d, *J* = 10.7 Hz, 9H), 1.25 – 1.21 (m, 3H), 1.03 – 0.97 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.54, 171.94 (d, *J* = 2.6 Hz), 147.27 (d, *J* = 22.1 Hz), 129.40 (d, *J* = 2.0 Hz), 118.32 (d, *J* = 15.4 Hz), 113.66 (d, *J* = 8.0 Hz), 61.36 (d, *J* = 43.5 Hz), 60.93 (d, *J* = 25.5 Hz), 51.25 (d, *J* = 4.6 Hz), 35.85 (d, *J* = 20.6 Hz), 35.13 (d, *J* = 22.8 Hz), 29.19 (d, *J* = 15.9 Hz), 28.89 (d, *J* = 5.1 Hz), 15.77 (d, *J* = 48.6 Hz), 14.37 (d, *J* = 1.4 Hz). **HRMS (ESI)** calcd for $C_{19}H_{31}N_2O_3$ $[M+H]^+$ 335.4675, found 335.4680.



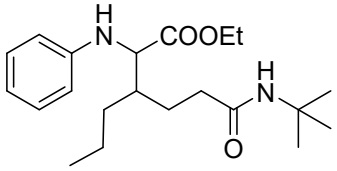
Ethyl 3-(2-(tert-butylamino)-2-oxoethoxy)-2-(phenylamino)butanoate (3x).
Yellow oil (81%, 27.3mg) ; 1:1 d.r ; R_f = 0.35 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21 – 7.14 (m, 2H), 6.81 – 6.71 (m, 1H), 6.65 (d, *J* = 8.0 Hz, 2H), 6.59 – 6.49 (m, 1H), 4.26 – 4.17 (m, 2H), 4.12 – 3.97 (m, 2H), 3.91 – 3.70 (m, 2H), 1.32 (d, *J* = 3.2 Hz, 9H), 1.28 – 1.24 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.00 (d, *J* = 67.0 Hz), 168.67 (d, *J* = 6.3 Hz), 146.91 (d, *J* = 66.2 Hz), 129.52 (d, *J* = 3.3 Hz), 119.00 (d, *J* = 13.8 Hz), 113.94 (d, *J* = 9.8 Hz), 77.75 (d, J = 44.0 Hz),69.22, 68.98, 61.56 (dd, *J* = 9.5, 4.8 Hz), 51.02 (d, *J* = 3.5 Hz), 28.82 (d, *J* = 3.2 Hz), 16.42 (d, *J* = 43.2 Hz), 14.38. **HRMS (ESI)** calcd for $C_{18}H_{29}N_2O_4$ $[M+H]^+$ 337.4395, found 337.4400.



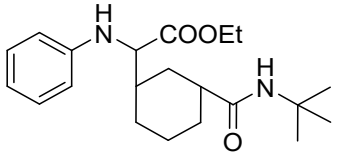
Ethyl 2-(1-(3-(tert-butylamino)-3-oxopropyl)cyclopentyl)-2-(phenylamino)acetate (3y).
Yellow oil (92%, 34.5mg) ; R_f = 0.40 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.18 – 7.13 (m, 2H), 6.73 (t, *J* = 7.3 Hz, 1H), 6.66 – 6.59 (m, 2H), 5.33 (s, 1H), 4.16 – 4.11 (m, 2H), 3.95 (s, 1H), 2.26 – 2.06 (m, 2H), 1.94 – 1.79 (m, 3H), 1.72 – 1.58 (m, 5H), 1.47 – 1.42 (m, 2H), 1.31 (s, 9H), 1.21 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.56, 172.39, 147.54, 129.44, 118.56, 113.73, 61.83, 60.98, 51.19, 48.24, 34.17, 33.97, 33.70, 33.01, 28.88, 25.56, 25.45, 14.36. **HRMS (ESI)** calcd for $C_{22}H_{35}N_2O_3$ $[M+H]^+$ 375.5325, found 375.5327.



Ethyl 3-(2-(tert-butylcarbamoyl)phenyl)-2-(phenylamino)propanoate (3z). Yellow oil (68%, 25.1mg) ; R_f = 0.25 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 3H), 7.25 – 7.19 (m, 1H), 7.12 – 7.04 (m, 2H), 6.67 – 6.61 (m, 1H), 6.57 – 6.51 (m, 2H), 5.86 (s, 1H), 4.31 – 4.27 (m, 1H), 4.20 – 4.12 (m, 2H), 3.32 – 3.13 (m, 2H), 1.48 (s, 9H), 1.19 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.07, 169.70, 147.32, 138.33, 135.58, 130.74, 129.98, 129.17, 126.99, 126.92, 117.71, 113.30, 61.19, 59.09, 52.09, 36.19, 28.93, 14.27. **HRMS (ESI)** calcd for $C_{22}H_{29}N_2O_3$ $[M+H]^+$ 369.4845, found 369.4850.



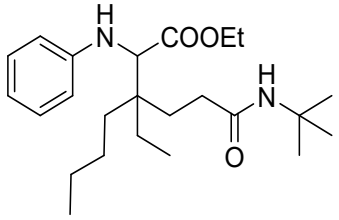
Ethyl 6-(tert-butylamino)-6-oxo-2-(phenylamino)-3-propylhexanoate (3aa). Yellow oil (80%, 29.0 mg) ; 1:1 d.r ; R_f = 0.30 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.20 – 7.11 (m, 2H), 6.72 (t, *J* = 7.3 Hz, 1H), 6.66 – 6.58 (m, 2H), 5.25 (s, 1H), 4.20 – 4.14 (m, 2H), 4.01 (d, *J* = 5.4 Hz, 1H), 2.18 – 2.15 (m, 2H), 1.91 – 1.79 (m, 2H), 1.73 – 1.71 (m, 2H), 1.49 – 1.38 (m, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 6.7 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.86, 172.01, 147.40, 129.45, 118.38, 113.71, 61.14, 59.40, 51.33, 40.55, 35.11, 32.77, 28.96, 26.26, 20.34, 14.40, 14.37. **HRMS (ESI)** calcd for $C_{21}H_{35}N_2O_3$ $[M+H]^+$ 363.5215, found 363.5210.



Ethyl 2-(3-(tert-butylcarbamoyl)cyclohexyl)-2-(phenylamino)acetate (3ab). Yellow oil (86%, 31.0mg); R_f = 0.35 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.16 (t, *J* = 7.7 Hz, 2H), 6.72 (t, *J* = 7.3 Hz, 1H), 6.68 – 6.55 (m, 2H), 5.32 – 5.13 (m, 1H), 4.22 – 4.13 (m, 2H), 3.94 – 3.88 (m, 1H), 2.59 – 2.17 (m, 1H), 2.15 – 1.94 (m, 2H), 1.93 – 1.78 (m, 3H), 1.77 – 1.59 (m, 2H), 1.45 (d, *J* = 29.4 Hz, 2H), 1.32 (dd, *J* = 5.9, 3.2 Hz, 9H), 1.24 – 1.18 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.80 (d, *J* = 8.2 Hz), 174.21 (dd, *J* = 51.5, 13.4 Hz), 173.46 (d, *J* = 11.7 Hz), 147.61 – 147.10 (m), 129.45 (d, *J* = 2.9 Hz), 118.55 – 118.28 (m), 113.70 (dd, *J* = 7.4, 5.0 Hz), 61.85 (d, *J* = 15.7 Hz), 61.17, 51.10 (d, *J* = 4.3 Hz), 46.26, 40.78 (d, *J* = 2.8 Hz), 32.28 (d, *J* = 38.8 Hz), 30.94 (d, *J* = 88.5 Hz), 29.52 (d, *J* = 13.5 Hz), 28.95

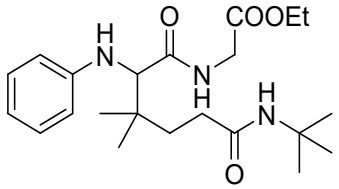
(d, J = 2.5 Hz), 25.41 (d, J = 6.9 Hz), 14.42. **HRMS (ESI)** calcd for $C_{21}H_{33}N_2O_3$ $[M+H]^+$ 361.5055, found 361.5050.

Note: d.r. cannot be determined by NMR and chiral HPLC (CHIRALCEL O-DH, CHIRALPAK IA, IB, IC, and AD-H columns).



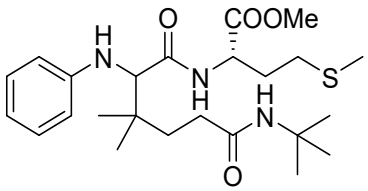
Ethyl 3-(3-(tert-butylamino)-3-oxopropyl)-3-ethyl-2-(phenylamino)heptanoate (3ac).

Yellow oil (32%, 13.0mg) ; 1:1 d.r ; R_f = 0.40 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19 – 7.12 (m, 2H), 6.73 (t, J = 7.3 Hz, 1H), 6.66 – 6.60 (m, 2H), 5.30 (s, 1H), 4.17 – 4.09 (m, 2H), 3.96 (s, 1H), 2.23 – 2.04 (m, 2H), 1.79 – 1.71 (m, 2H), 1.55 – 1.41 (m, 4H), 1.31 (s, 9H), 1.22 (t, J = 7.1 Hz, 3H), 0.93 – 0.88 (m, 6H).**^{13}C NMR** (100MHz, $CDCl_3$) δ 173.82 (d, J = 2.9 Hz), 172.72, 147.66, 129.47, 118.58, 113.88 (d, J = 1.8 Hz), 62.76 (d, J = 4.8 Hz), 60.97, 51.19, 41.82, 34.67 (d, J = 15.0 Hz), 32.52 (d, J = 3.7 Hz), 28.94, 27.73, 27.44, 25.85 (d, J = 2.7 Hz), 23.80 (d, J = 3.5 Hz), 14.33, 14.20, 8.43 (d, J = 3.2 Hz). **HRMS (ESI)** calcd for $C_{24}H_{41}N_2O_3$ $[M+H]^+$ 405.6025, found 405.6021.



Ethyl (6-(tert-butylamino)-3,3-dimethyl-6-oxo-2(phenylamino)hexanoyl)glycinate (3ad).

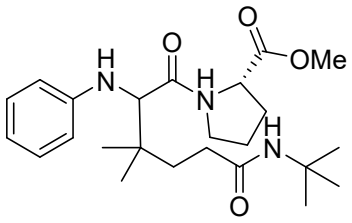
Yellow oil (80%, 32.4mg); R_f = 0.35 (petroleum ether/ethyl acetate = 1:1); **^{1}H NMR**(400 MHz, $CDCl_3$) δ 7.32 (t, J = 5.8 Hz, 1H), 7.22 – 7.14 (m, 2H), 6.79 (t, J = 7.3 Hz, 1H), 6.69 – 6.57 (m, 2H), 5.73 (s, 1H), 4.18 – 4.12 (m, 3H), 3.87 – 3.81 (m, 1H), 3.53 (s, 1H), 2.40 – 2.28 (m, 1H), 2.07 – 2.00 (m, 1H), 1.84 – 1.72 (m, 2H), 1.32 (s, 9H), 1.25 – 1.21 (m, 3H), 1.10 (d, J = 2.4 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.89, 172.60, 169.79, 147.36, 129.53, 119.24, 113.90, 66.02, 61.52, 51.16, 41.29, 37.03, 36.16, 32.80, 28.87, 25.03, 24.81, 14.25. **HRMS (ESI)** calcd for $C_{22}H_{36}N_3O_4$ $[M+H]^+$ 405.5465, found 405.5470.



Methyl (6-(tert-butylamino)-3,3-dimethyl-6-oxo-2-(phenylamino)hexanoyl)-L-

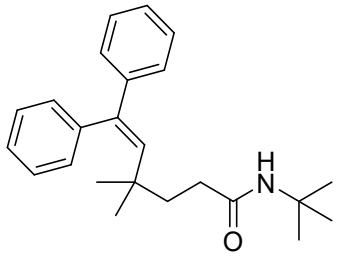
methioninate (3ae).

Yellow oil (48%, 22.3 mg) ; 3:1 d.r R_f = 0.30 (petroleum ether/ethyl acetate = 1:1); **^{1}H NMR**(400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.4 Hz, 1H), 7.22 – 7.15 (m, 2H), 6.79 (t, *J* = 7.2 Hz, 1H), 6.65 – 6.59 (m, 2H), 5.73 (s, 1H), 4.75 – 4.69 (m, 1H), 3.72 (s, 3H), 3.55 – 3.53 (m, 1H), 2.48 – 2.27 (m, 2H), 2.21 – 2.17 (m, 2H), 2.05 – 2.01 (m, 2H), 1.87 (s, 3H), 1.81 – 1.76 (m, 2H), 1.32 (s, 9H), 1.10 (d, *J* = 1.6 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.80, 172.40, 172.05, 146.90, 129.56, 119.38, 113.70, 65.94, 52.58, 51.71, 51.16, 36.77, 36.35, 32.72, 31.12, 29.84, 28.88, 25.06, 24.88, 15.33. **HRMS (ESI)** calcd for $C_{24}H_{40}N_3O_4S$ $[M+H]^+$ 466.6605 , found 466.6598.



Methyl (2S)-1-(6-(tert-butylamino)-3,3-dimethyl-6-oxo-2-(phenylamino)hexanoyl)-1l4-pyrrolidine-2-carboxylate (3af).

Yellow oil (30%, 13.0mg) ; 10:1 d.r R_f = 0.30 (petroleum ether/ethyl acetate = 1:1);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.17 – 7.12 (m, 2H), 6.74 – 6.70 (m, 1H), 6.66 (d, *J* = 8.0 Hz, 2H), 5.58 (s, 1H), 4.45 – 4.42 (m, 1H), 4.02 (s, 1H), 3.72 (s, 3H), 3.67 – 3.54 (m, 2H), 2.18 – 2.14 (m, 2H), 2.07 – 1.98 (m, 2H), 1.95 – 1.89 (m, 2H), 1.85 – 1.79 (m, 2H), 1.32 (s, 9H), 1.11 (s, 3H), 1.07 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.97, 172.91, 171.95, 148.08, 129.55, 118.45, 114.20, 62.16, 59.00, 52.37, 51.15, 48.14, 38.84, 35.58, 33.08, 29.84, 28.89, 25.25, 23.76, 22.87. **HRMS (ESI)** calcd for $C_{24}H_{39}N_3O_4$ $[M+H]^+$ 433.5925 , found 433.5922.

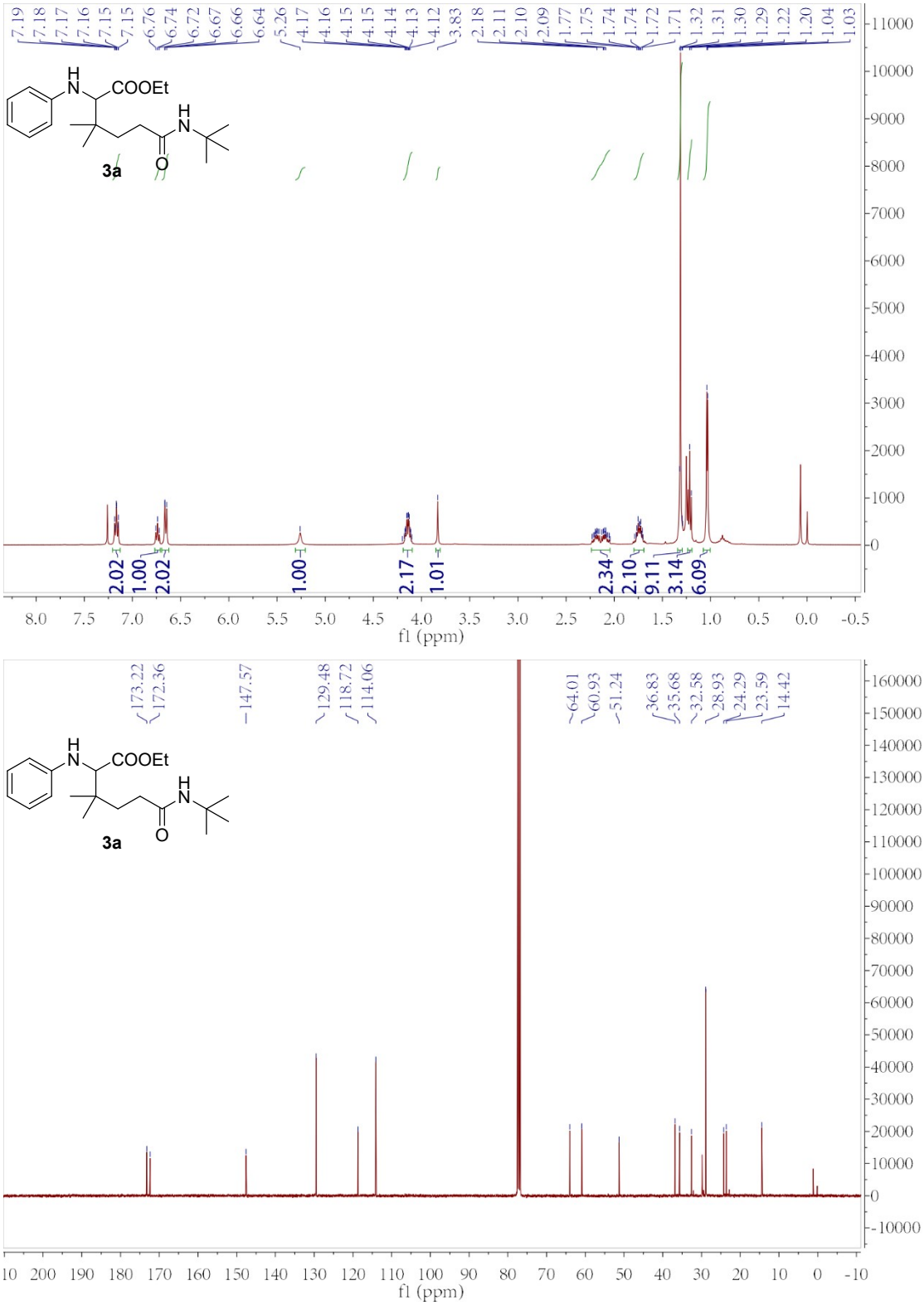


N-(tert-butyl)-4,4-dimethyl-6,6-diphenylhex-5-enamide (4a).

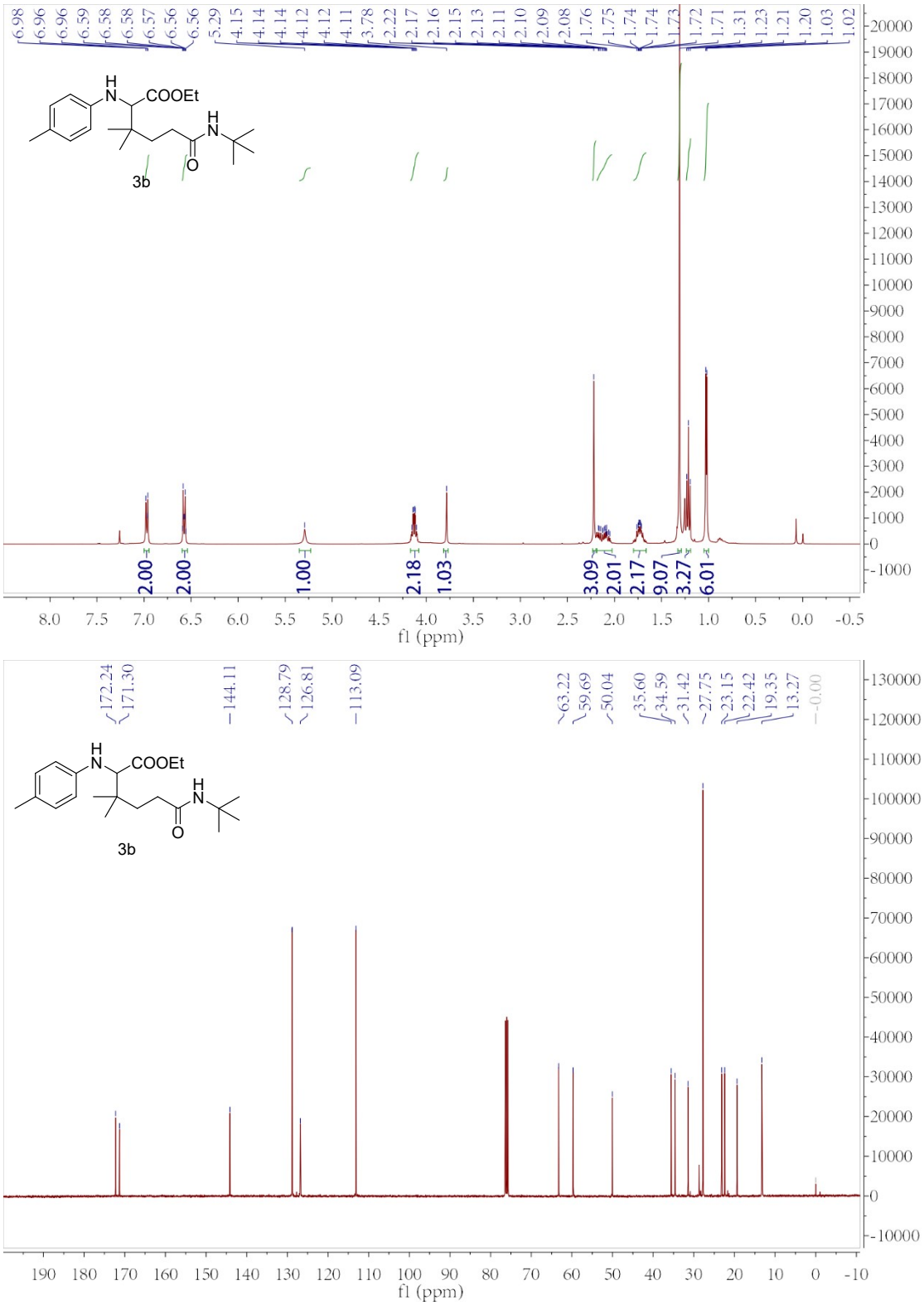
White solid (90%, 31.4mg); m.p.: 94-97 °C; R_f = 0.60 (petroleum ether/ethyl acetate = 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 3H), 7.24 – 7.15 (m, 7H), 5.96 (s, 1H), 5.13 (s, 1H), 2.14 – 2.07 (m, 2H), 1.65 – 1.58 (m, 2H), 1.32 (s, 9H), 0.91 (s, 6H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.75, 144.03, 140.67, 140.46, 138.11, 130.27, 128.16, 127.99, 127.09, 127.02, 126.91, 51.18, 40.02, 36.96, 33.86, 29.14, 28.95. **HRMS (ESI)** calcd for $C_{24}H_{32}NO$ $[M+H]^+$ 350.5255, found 350.5260.

9.NMR Spectra

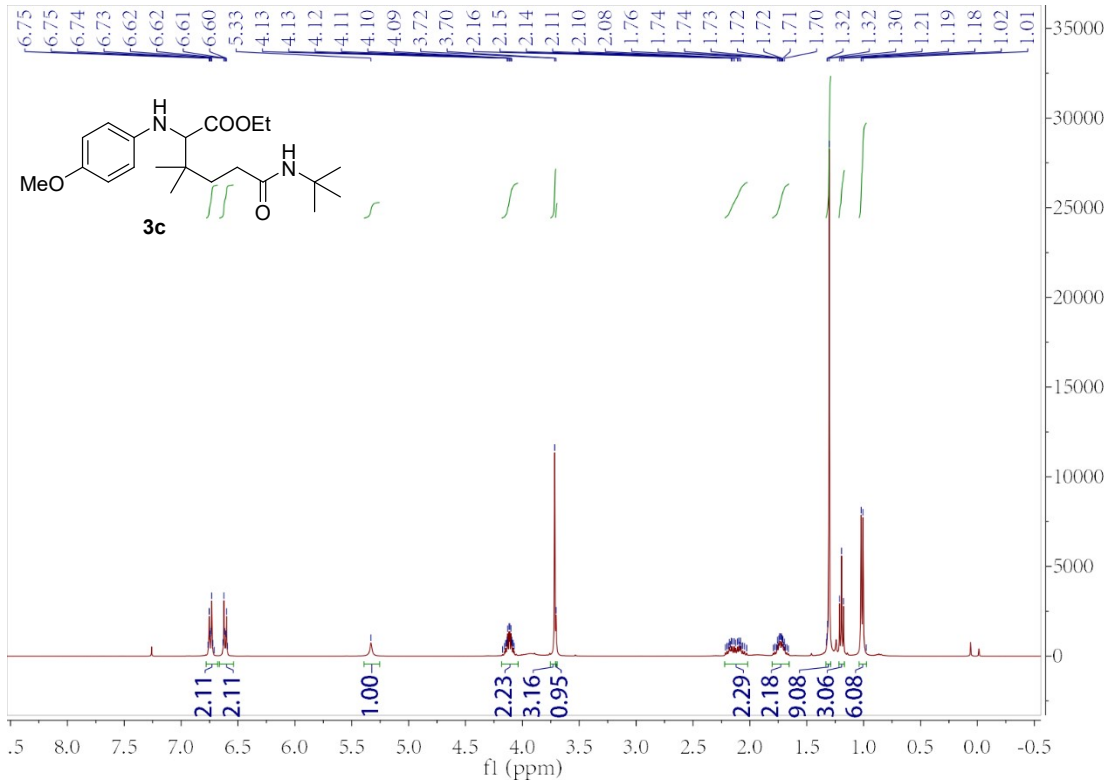
^{1}H NMR and ^{13}C NMR spectra for compound 3a ($CDCl_3$).

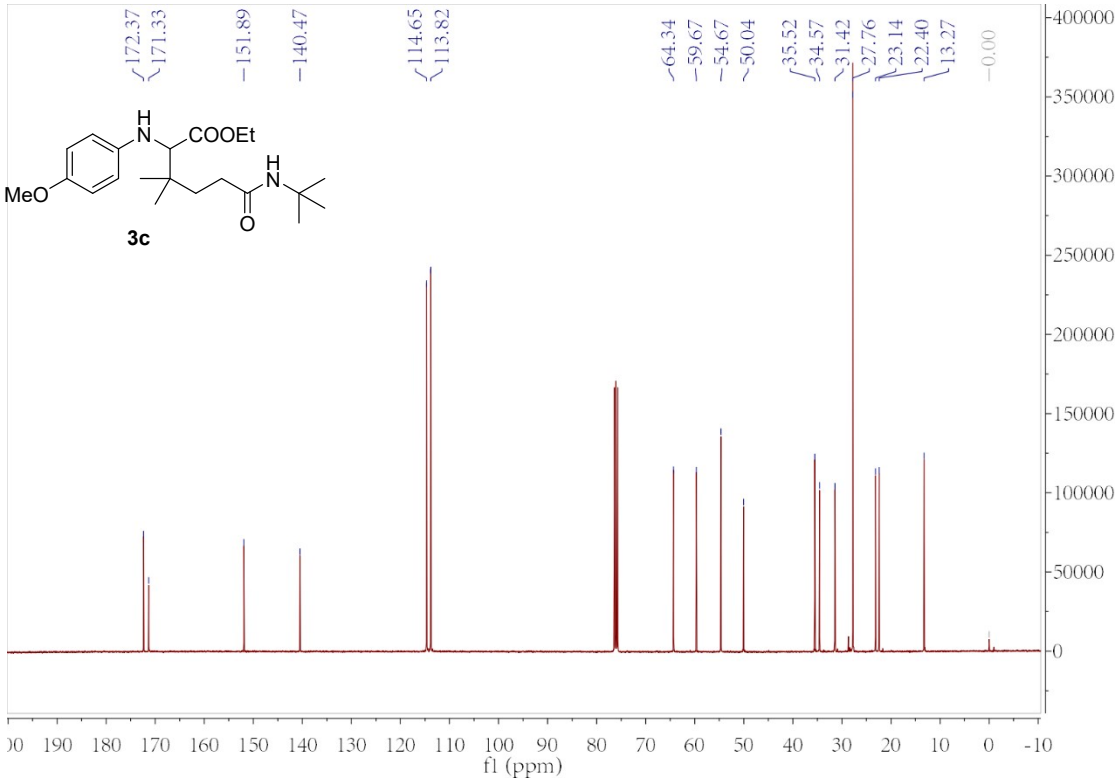


^{1}H NMR and ^{13}C NMR spectra for compound 3b ($CDCl_3$).

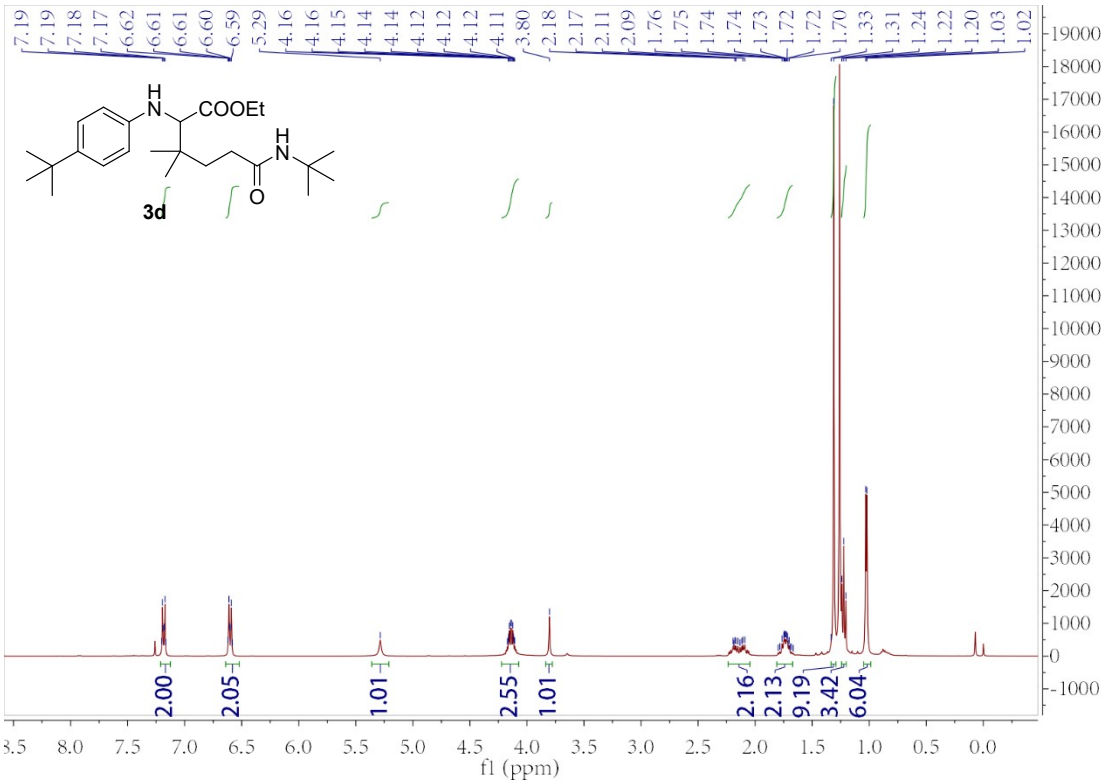


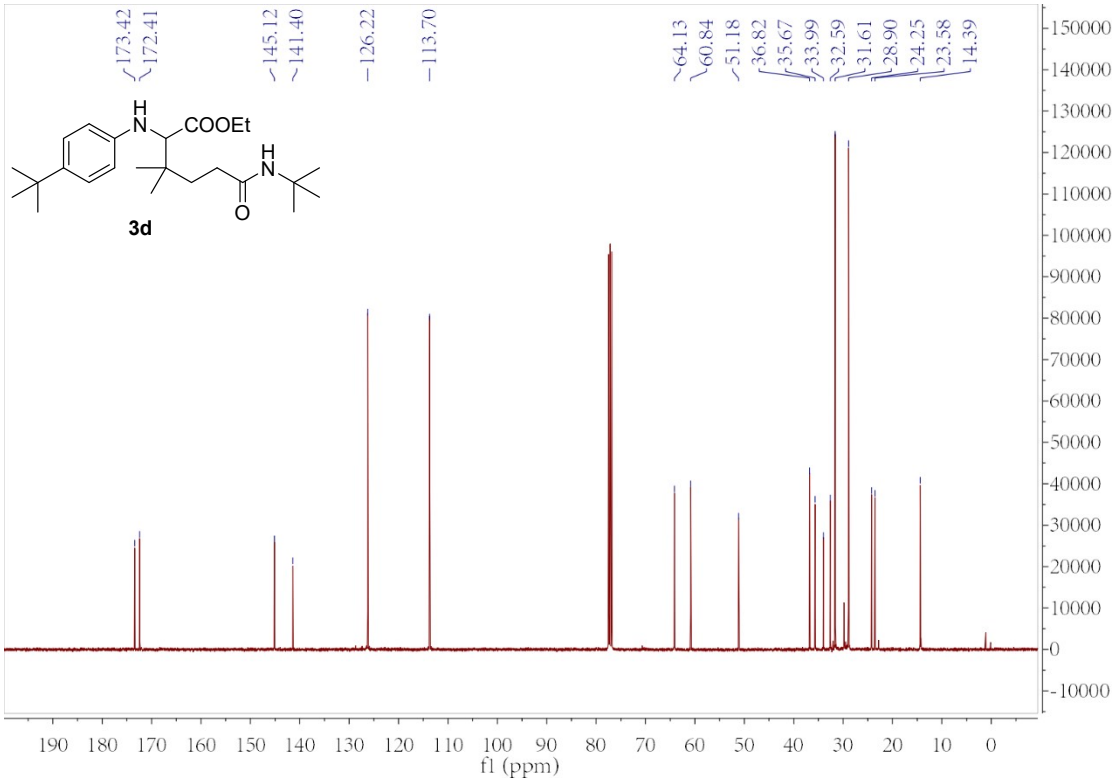
^{1}H NMR and ^{13}C NMR spectra for compound 3c ($CDCl_3$).



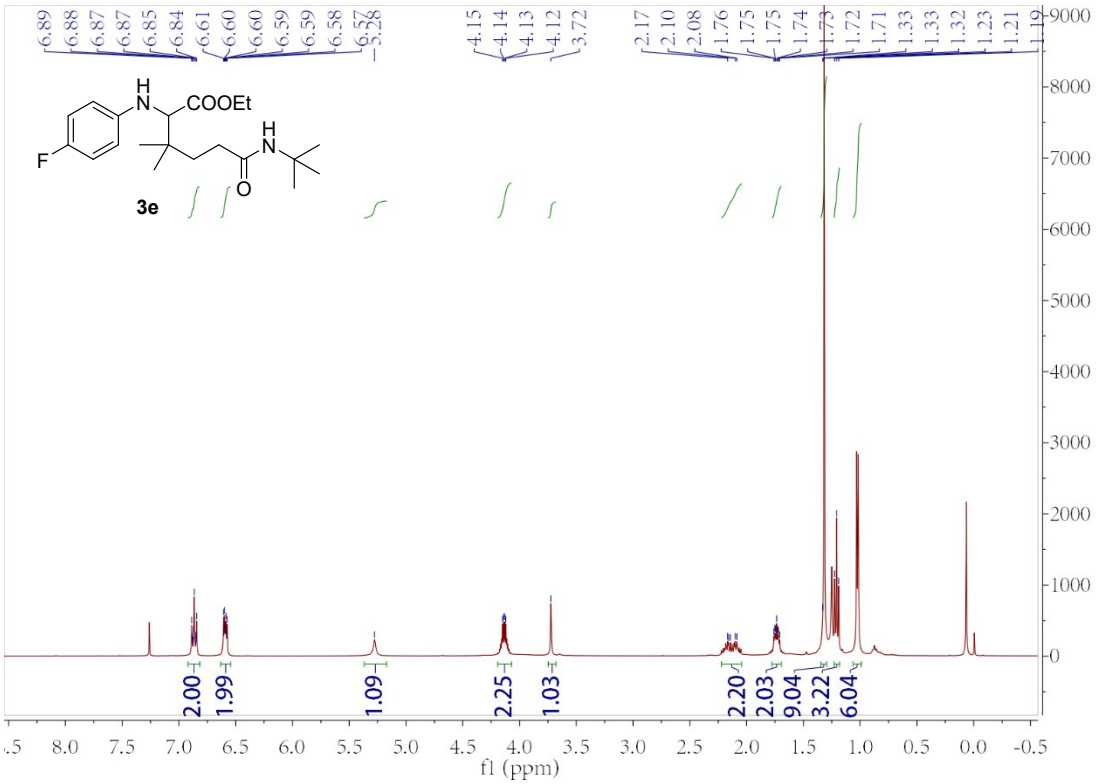


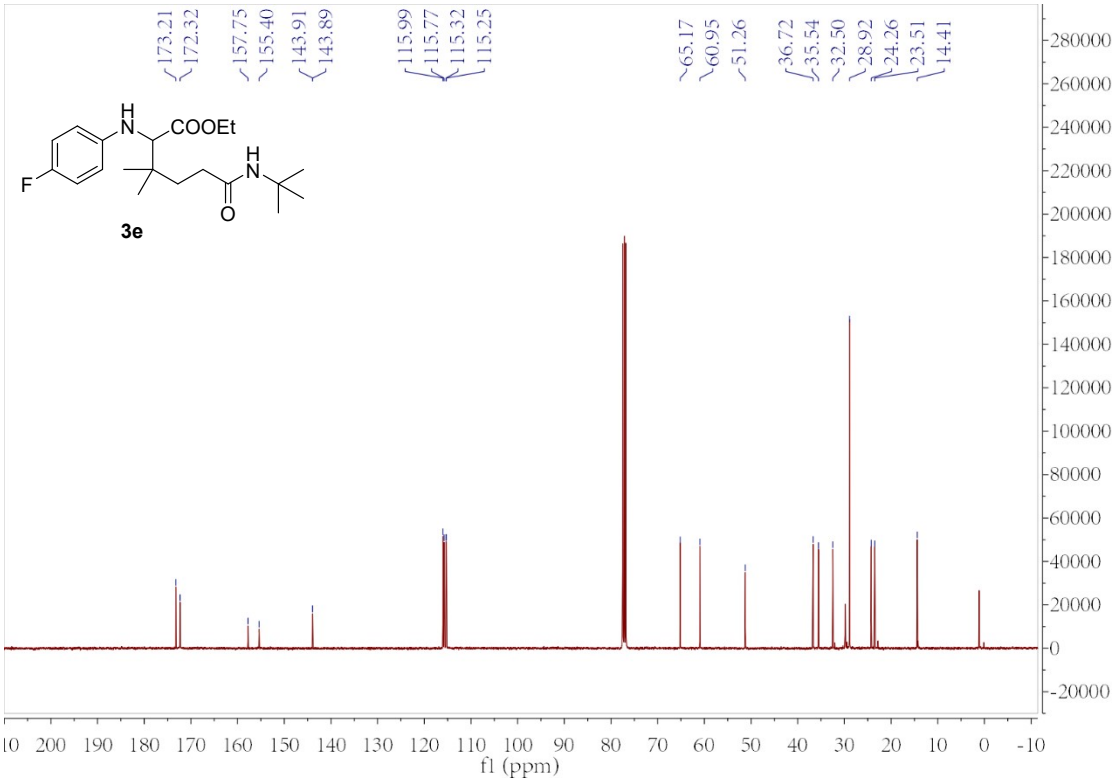
^{1}H NMR and ^{13}C NMR spectra for compound 3d ($CDCl_3$).





^{1}H, ^{13}C NMR and ^{19}F spectra for compound 3e ($CDCl_3$).


6.89 6.88 6.87 6.87 6.85 6.84 6.61 6.60 6.60 6.59 6.59 6.58 6.57 5.28
4.15 4.14 4.13 4.12 3.72
2.17 2.10 2.08 1.76 1.75 1.75 1.74 1.73 1.72 1.71 1.33 1.33 1.32 1.23 1.21 1.19
H
N
COOEt
F
H
N
O
3e
2.00 1.99 1.09 2.25 1.03 2.20 2.03 9.04 3.22 6.04
f1 (ppm)


173.21 172.32 157.75 155.40 143.91 143.89 115.99 115.77 115.32 115.25
65.17 60.95 51.26 36.72 35.54 32.50 28.92 24.26 23.51 14.41
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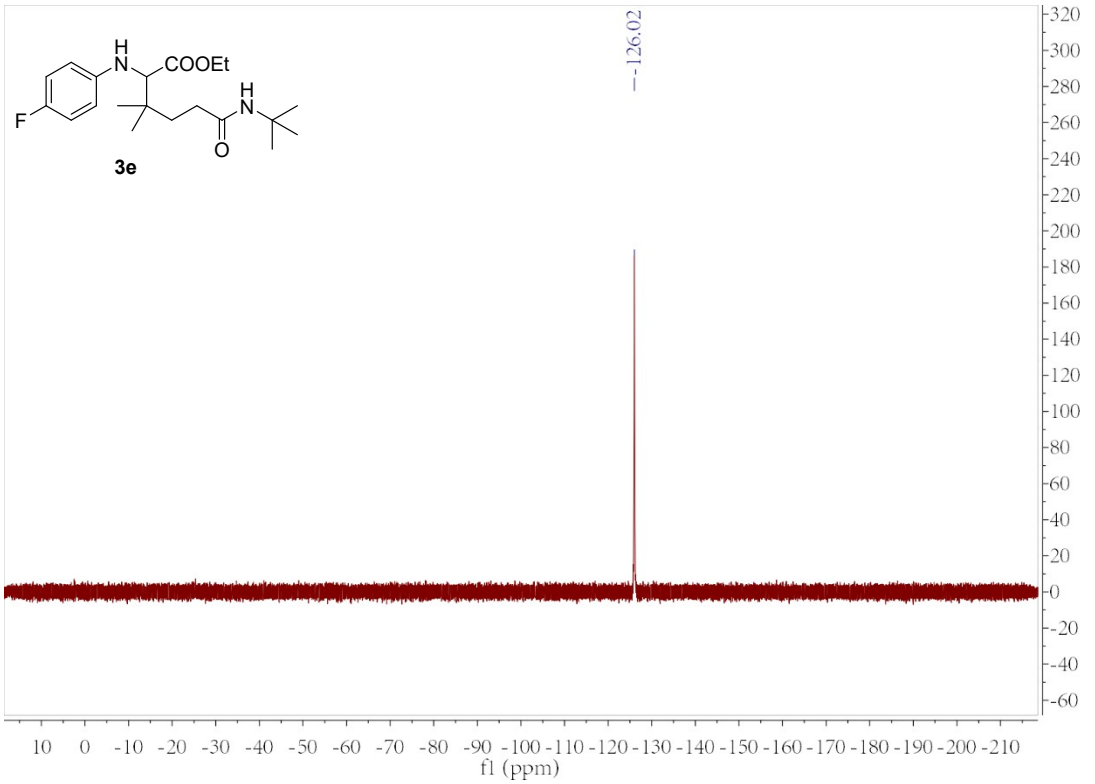
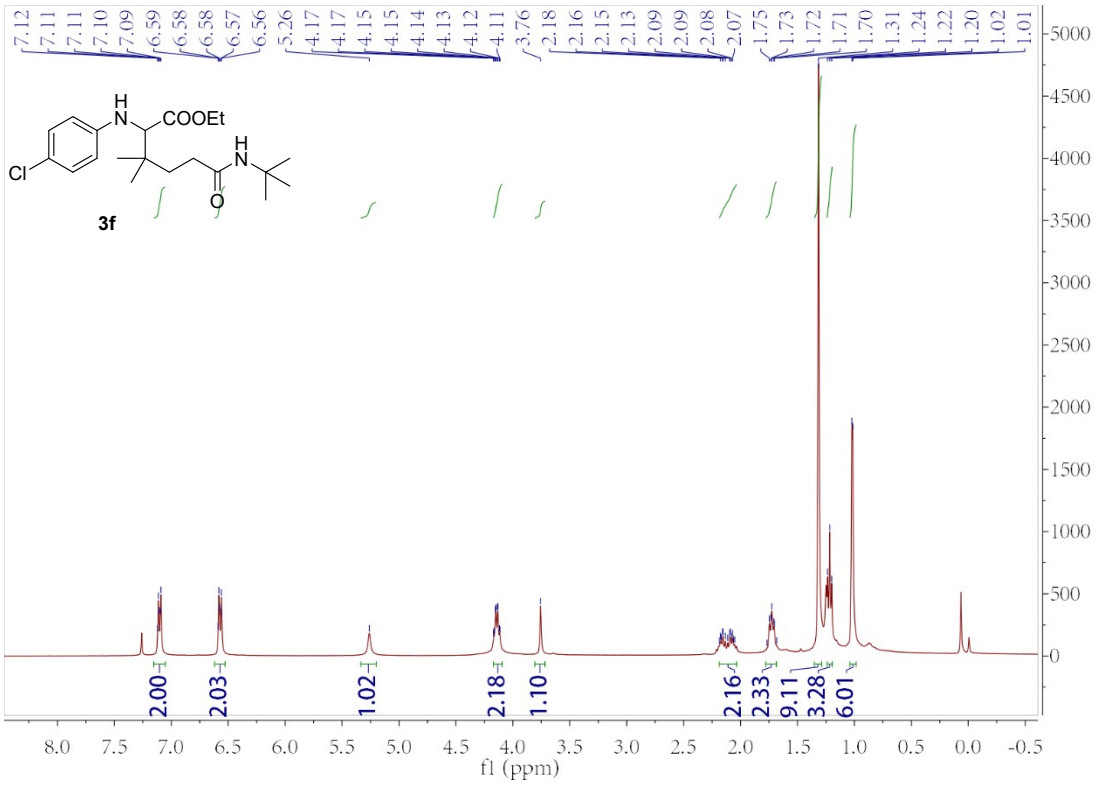
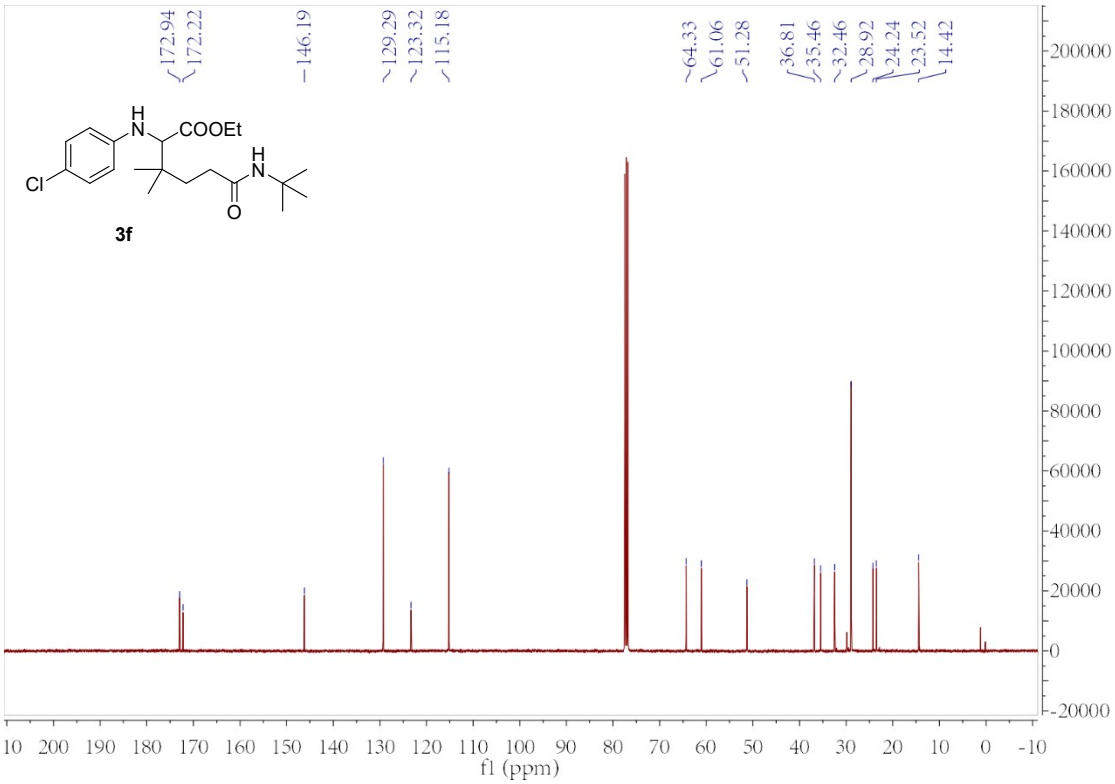
COOEt
F
H
N
O
3e
f1 (ppm)

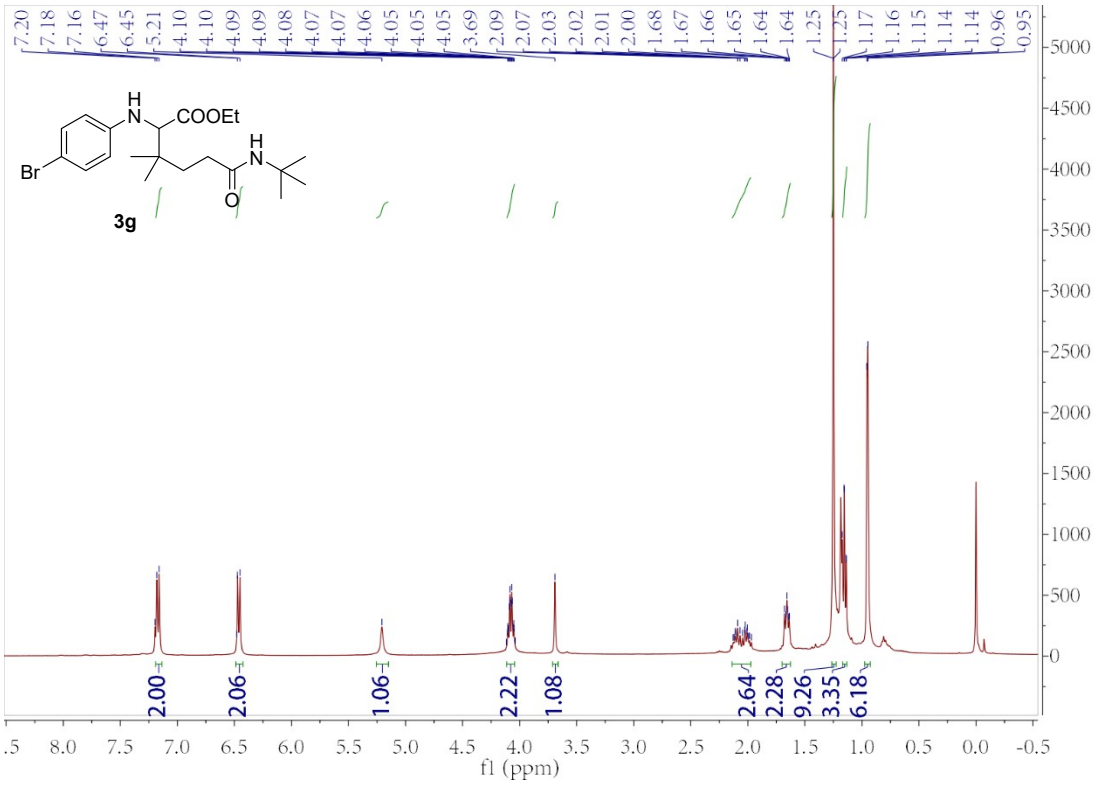


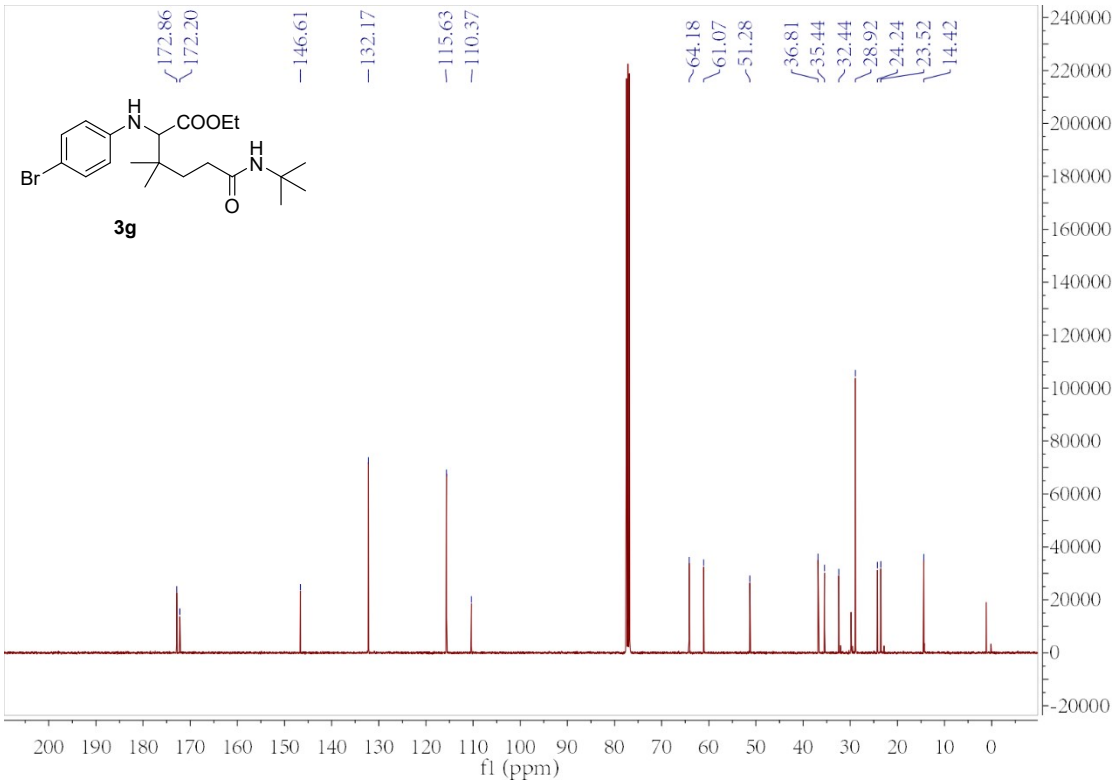
^{1}H NMR and ^{13}C NMR spectra for compound 3f ($CDCl_3$).



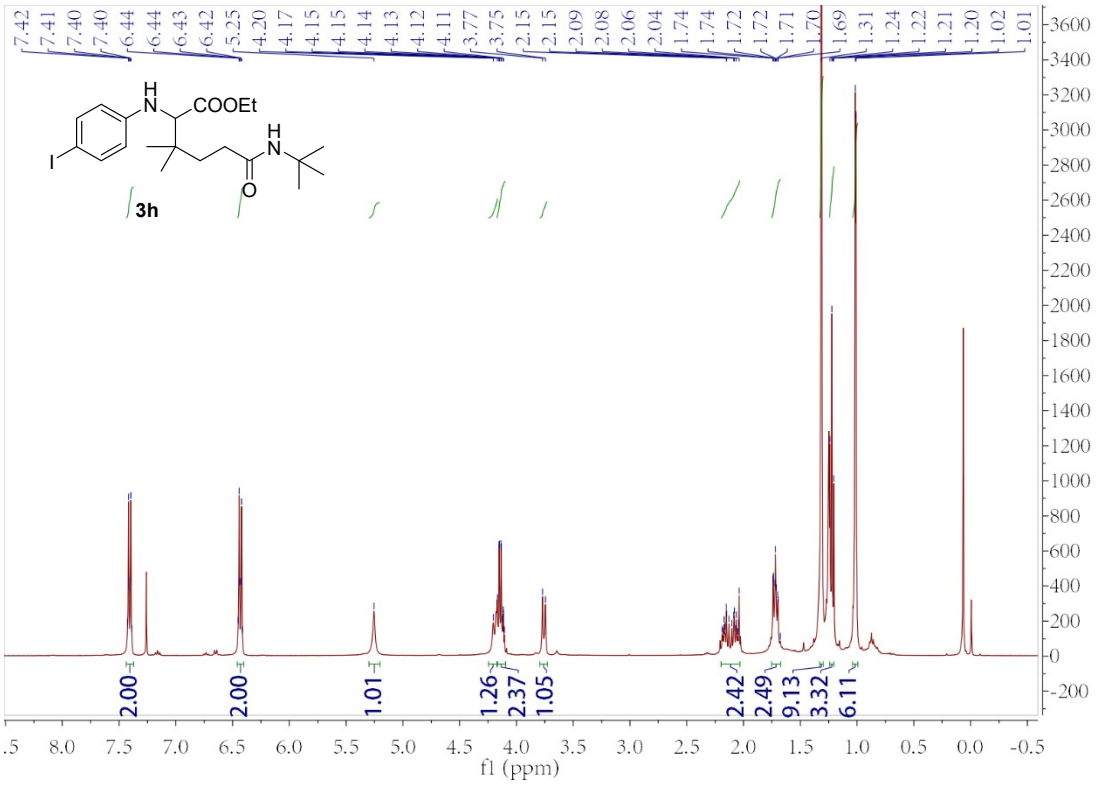


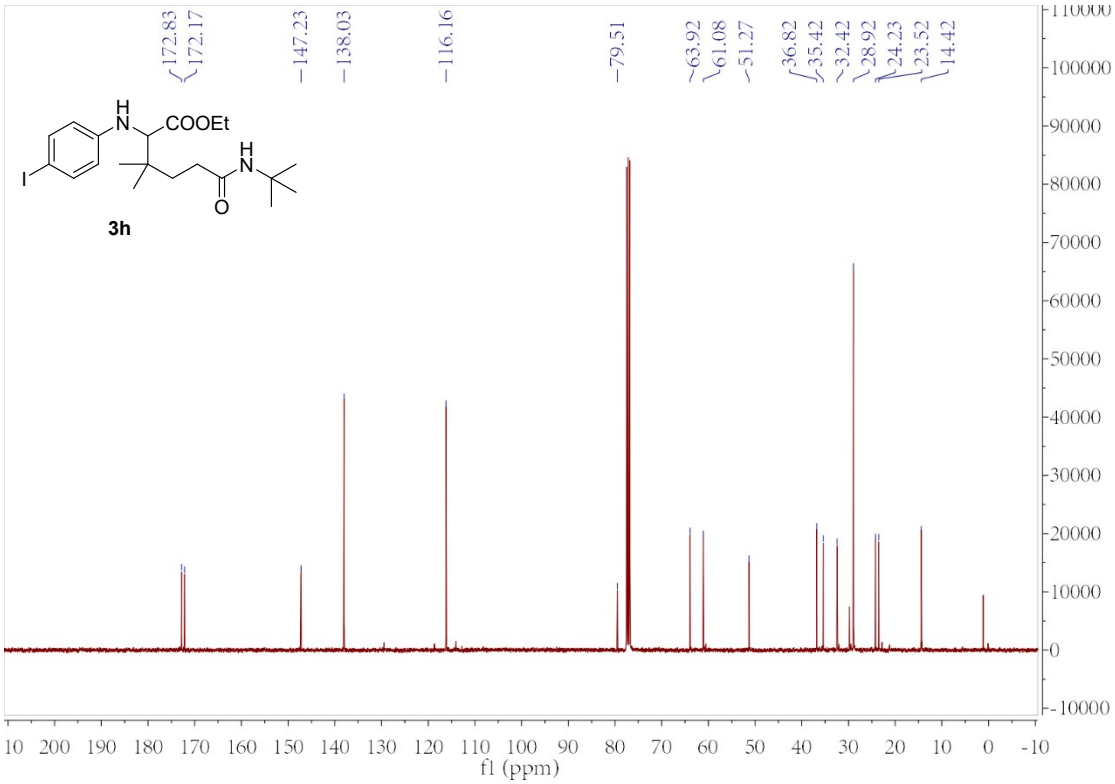
^{1}H NMR and ^{13}C NMR spectra for compound 3g ($CDCl_3$).



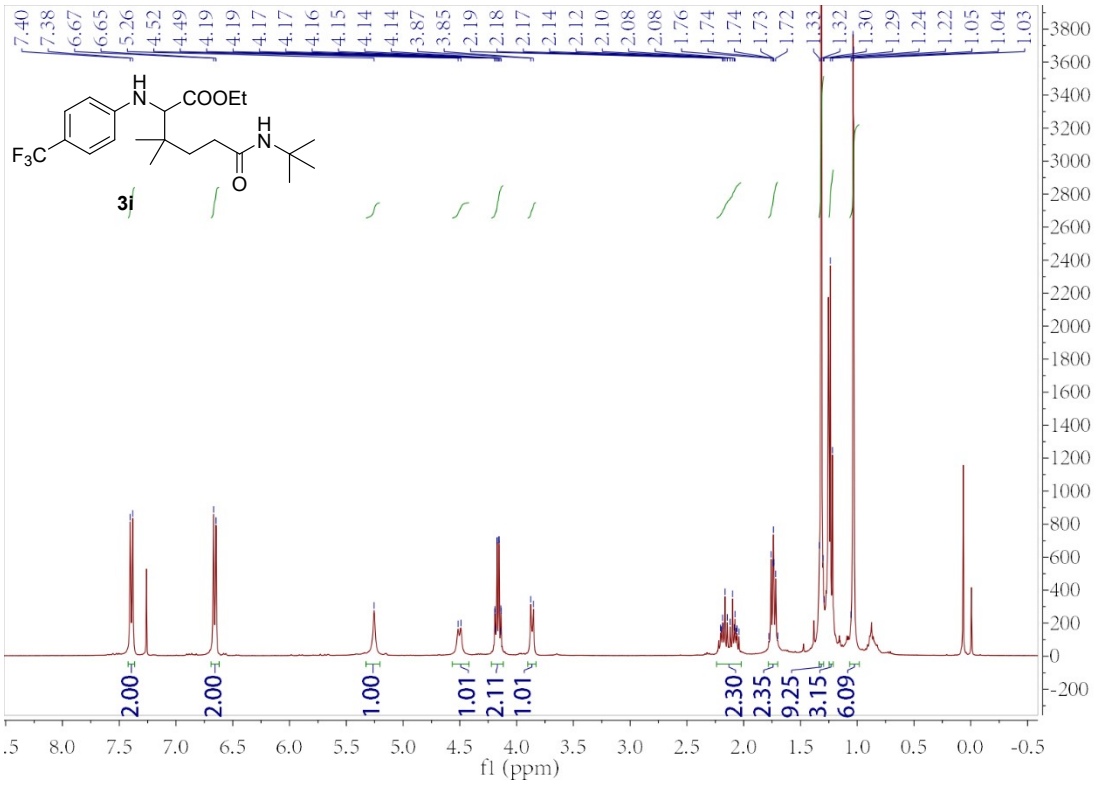


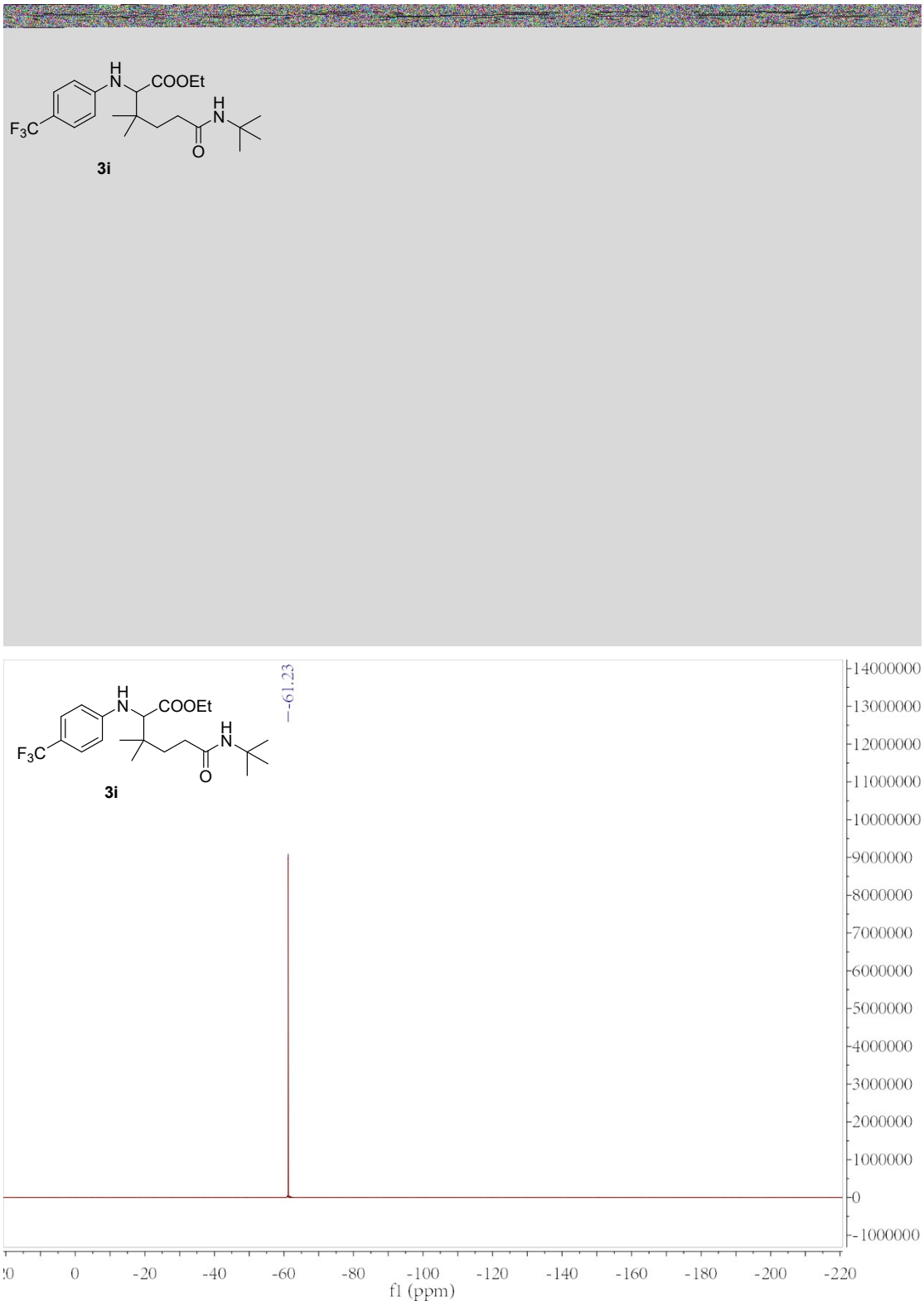
^{1}H NMR and ^{13}C NMR spectra for compound 3h ($CDCl_3$).



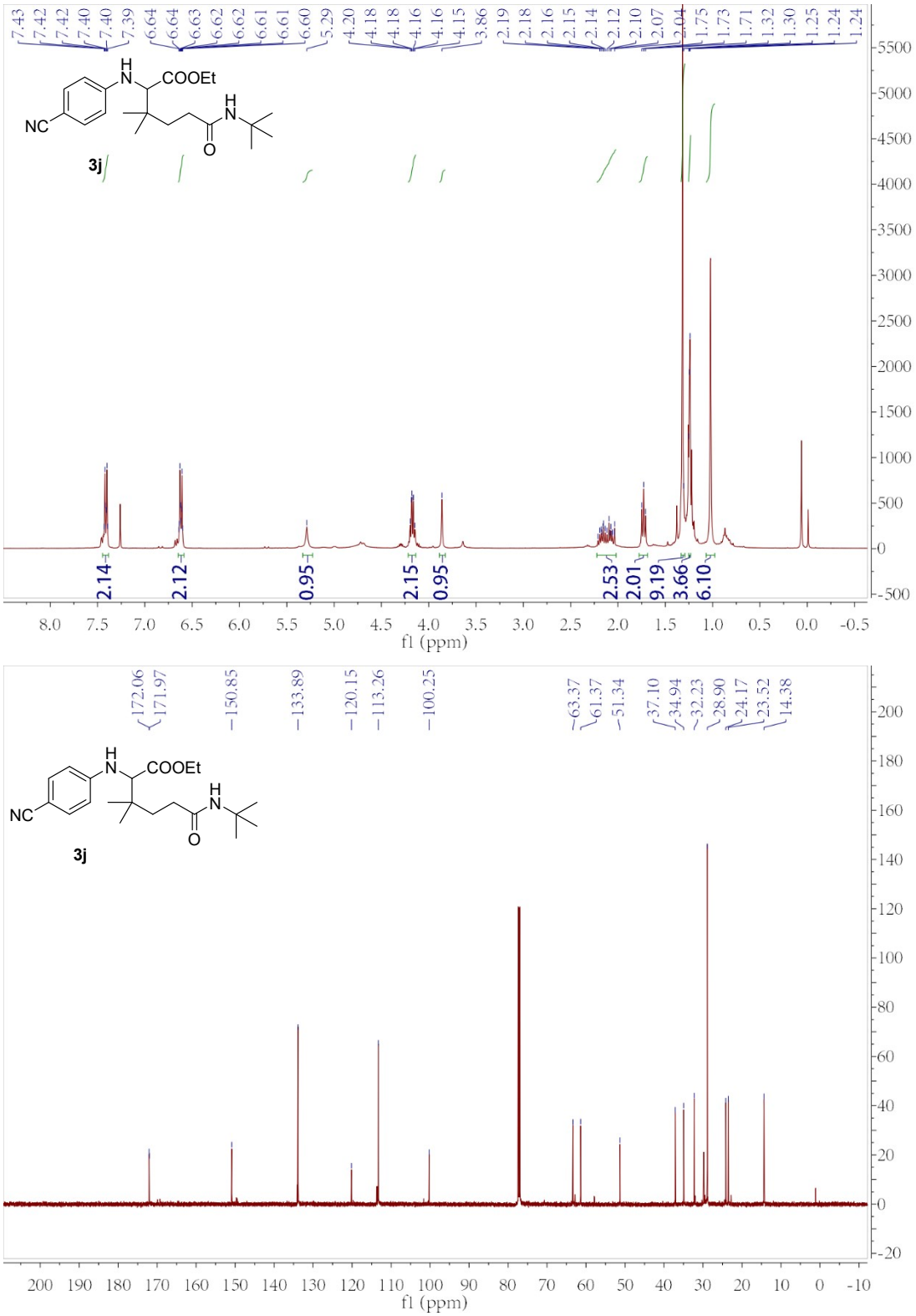


^{1}H, ^{13}C NMR and ^{19}F spectra for compound 3i ($CDCl_3$).

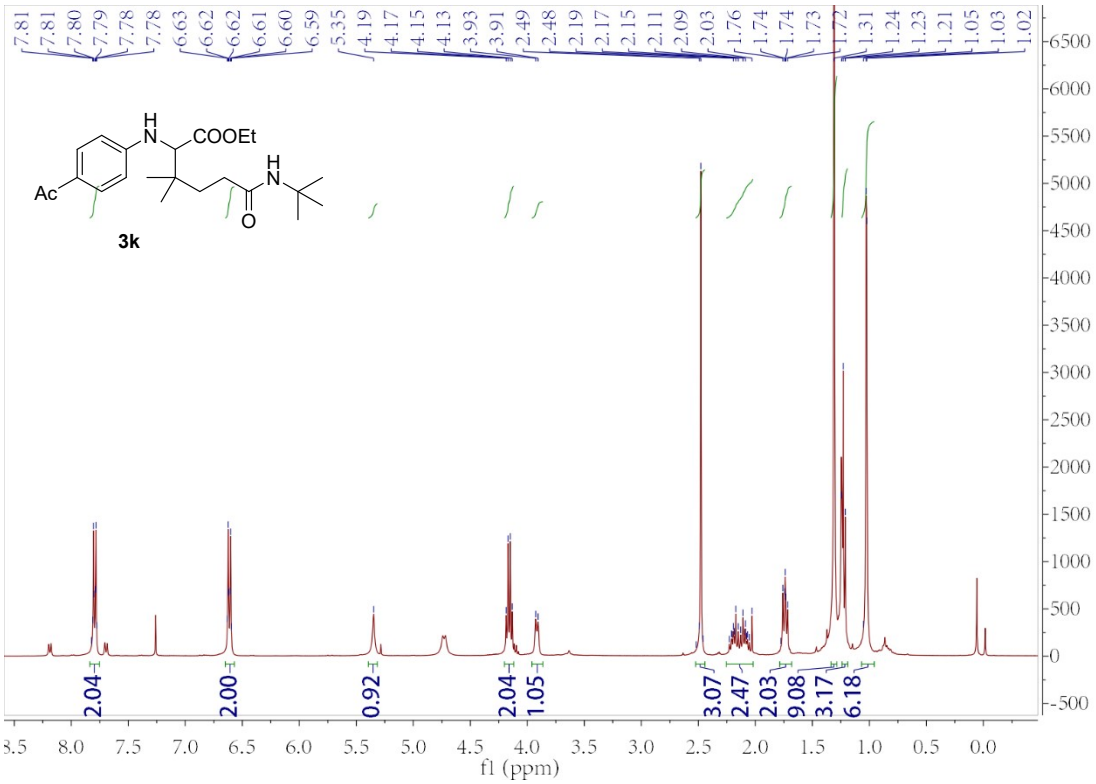


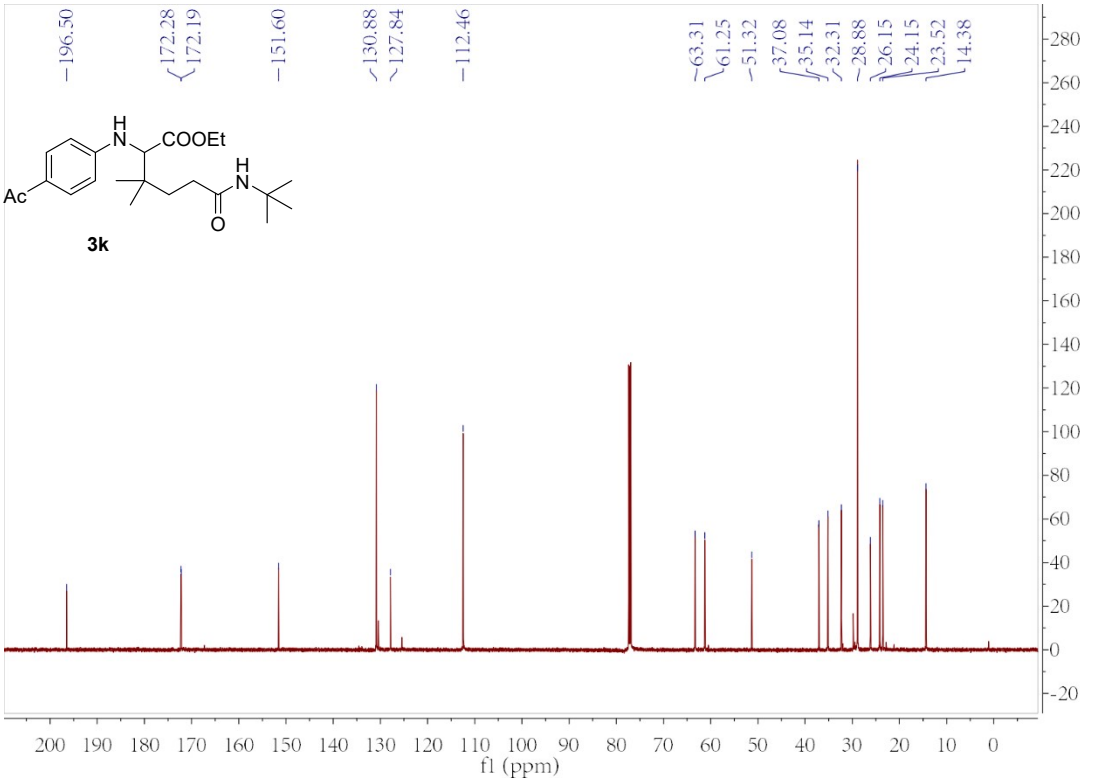


^{1}H NMR and ^{13}C NMR spectra for compound 3j ($CDCl_3$).

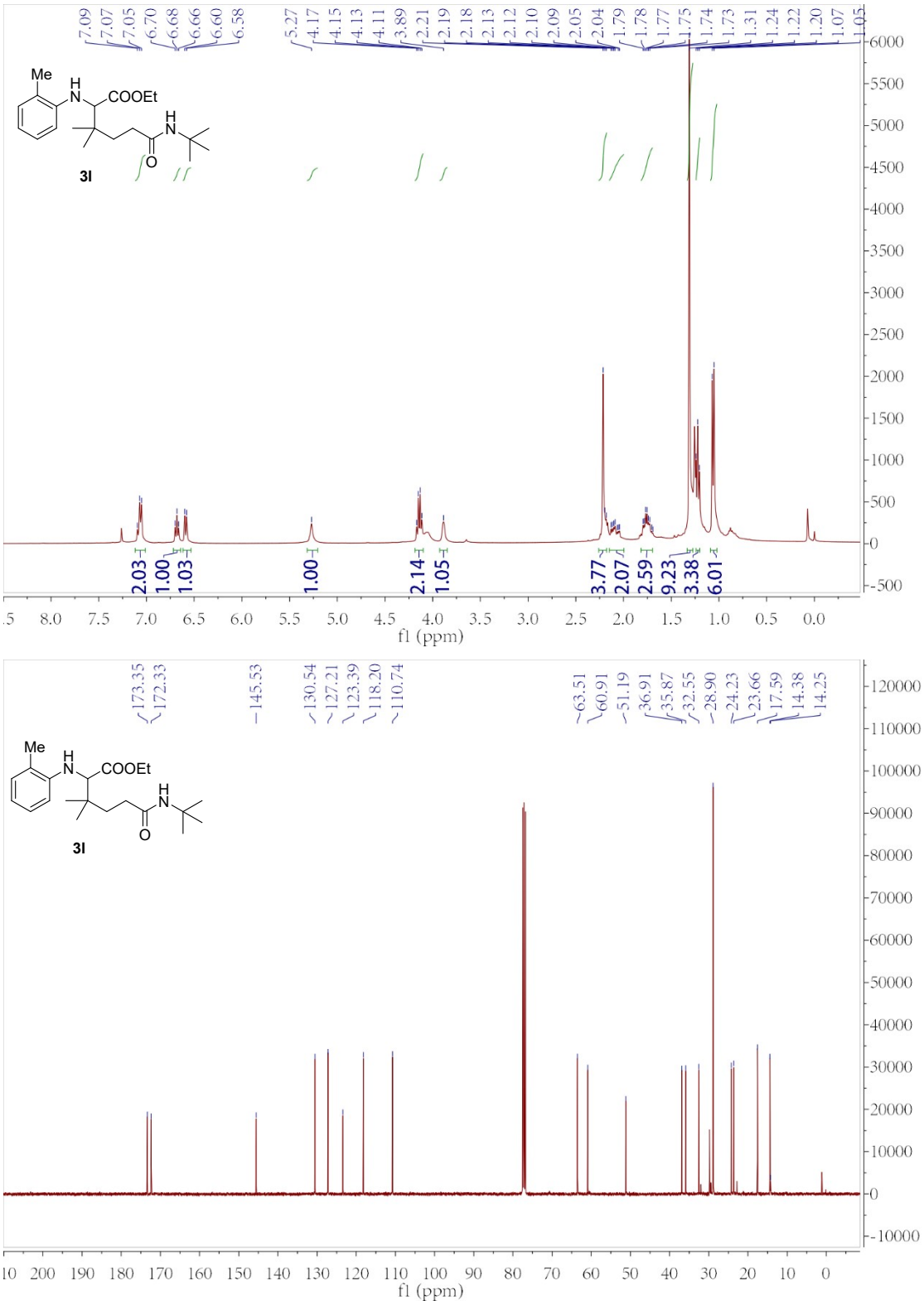


^{1}H NMR and ^{13}C NMR spectra for compound 3k ($CDCl_3$).

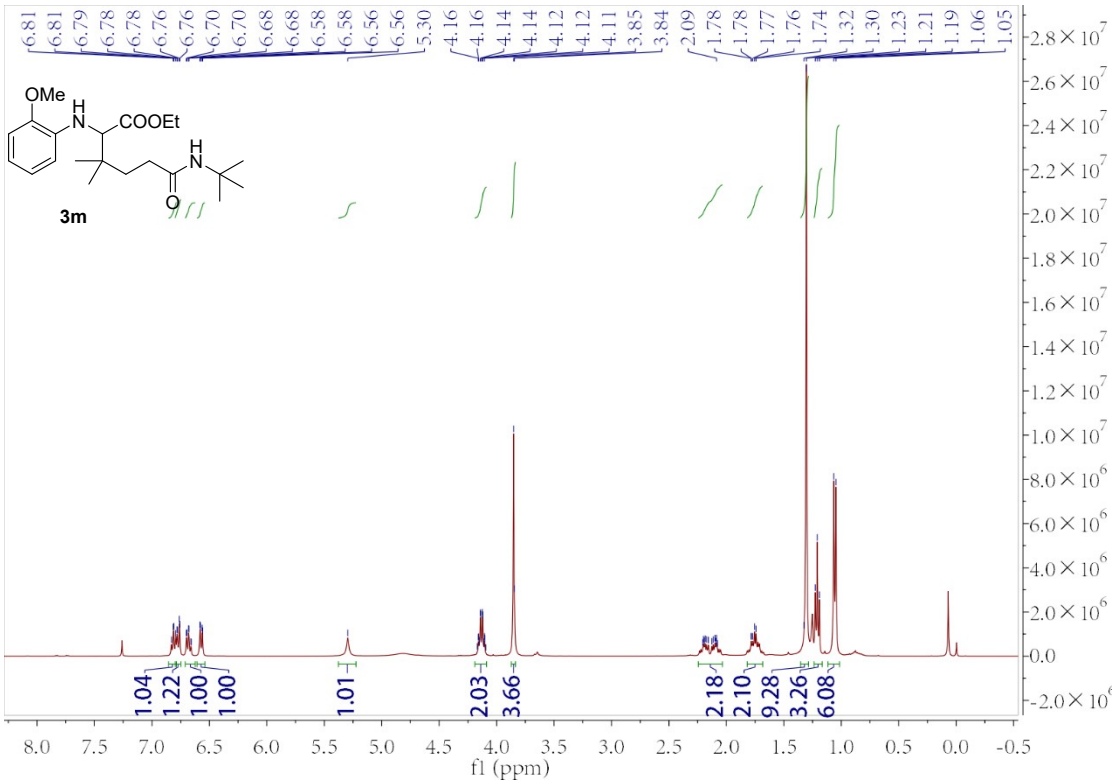


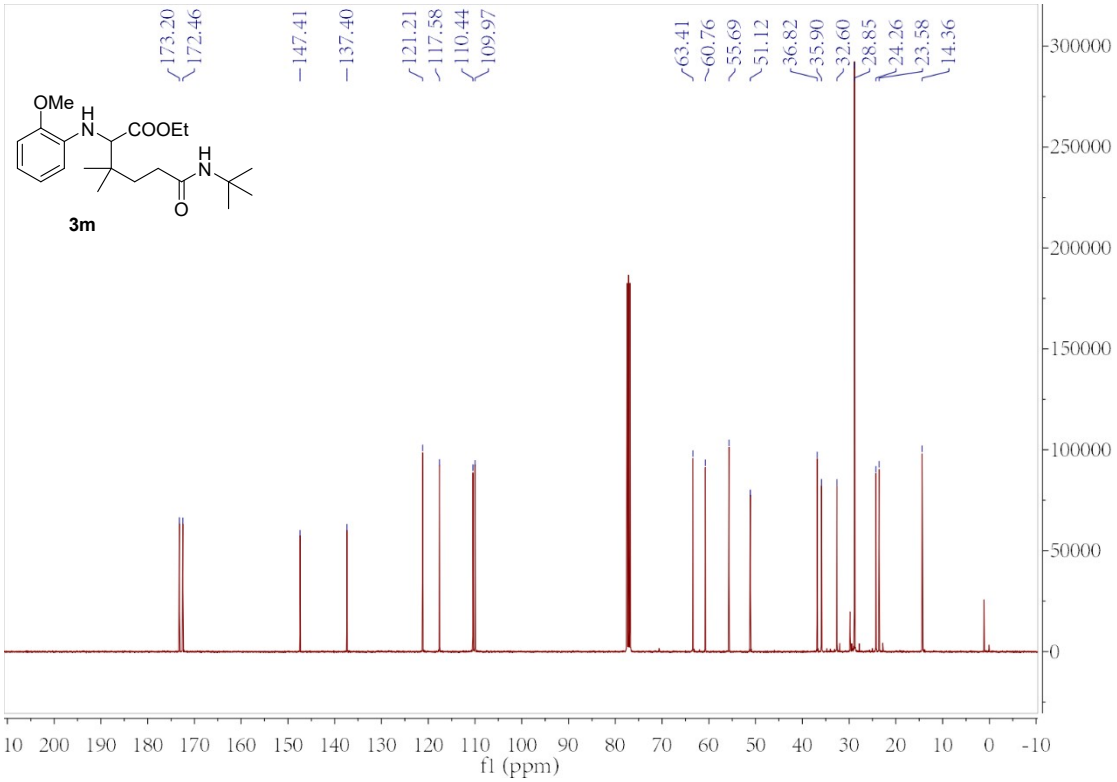


^{1}H NMR and ^{13}C NMR spectra for compound 3l ($CDCl_3$).

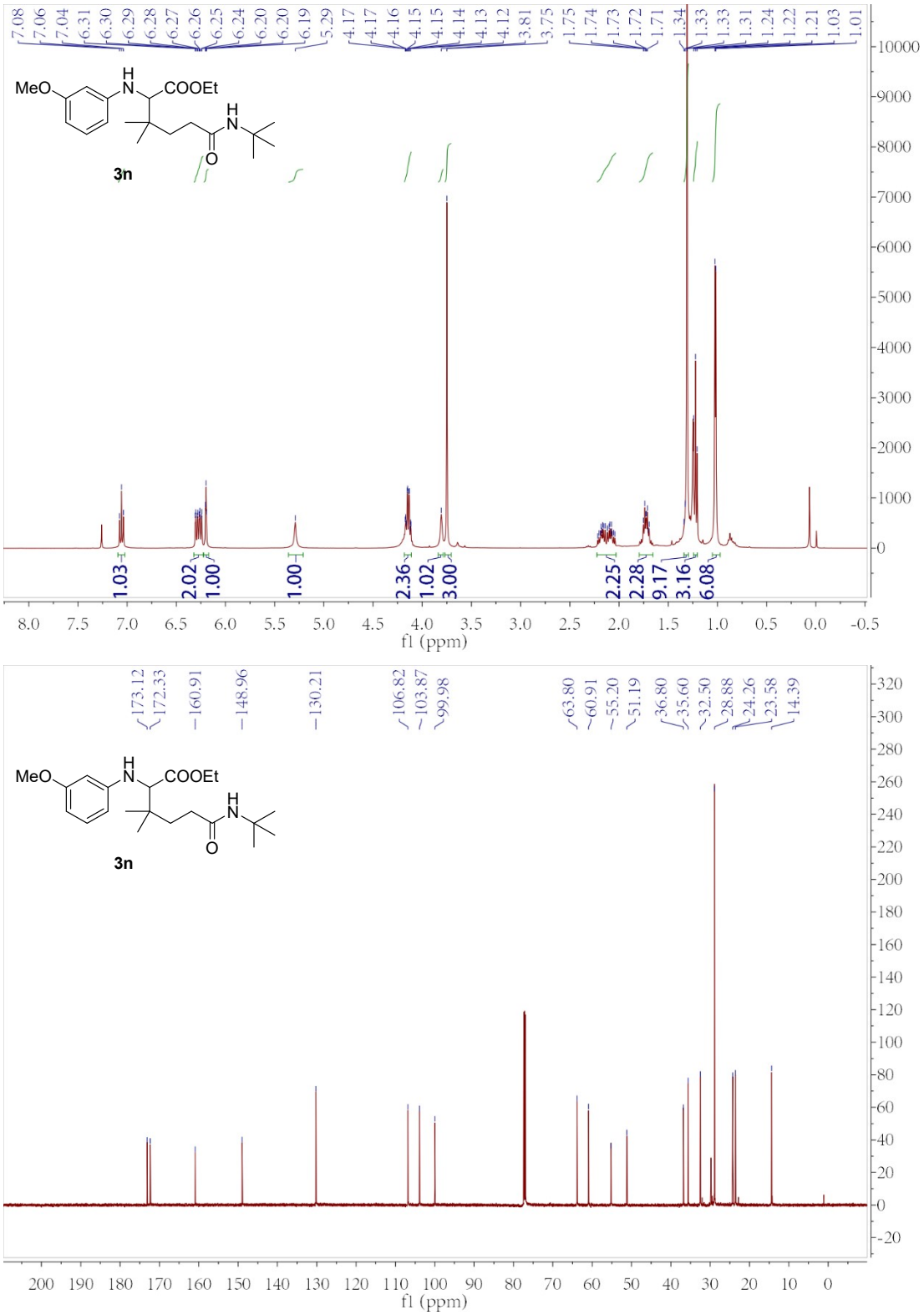


^{1}H NMR and ^{13}C NMR spectra for compound 3m ($CDCl_3$).

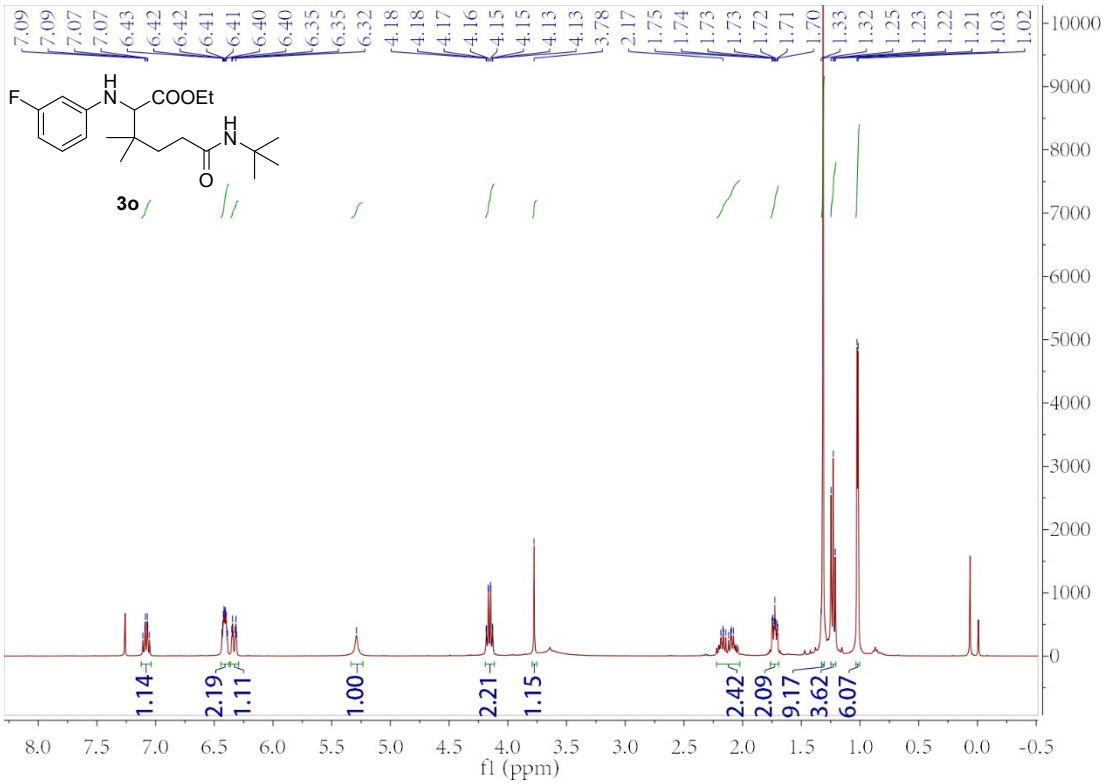


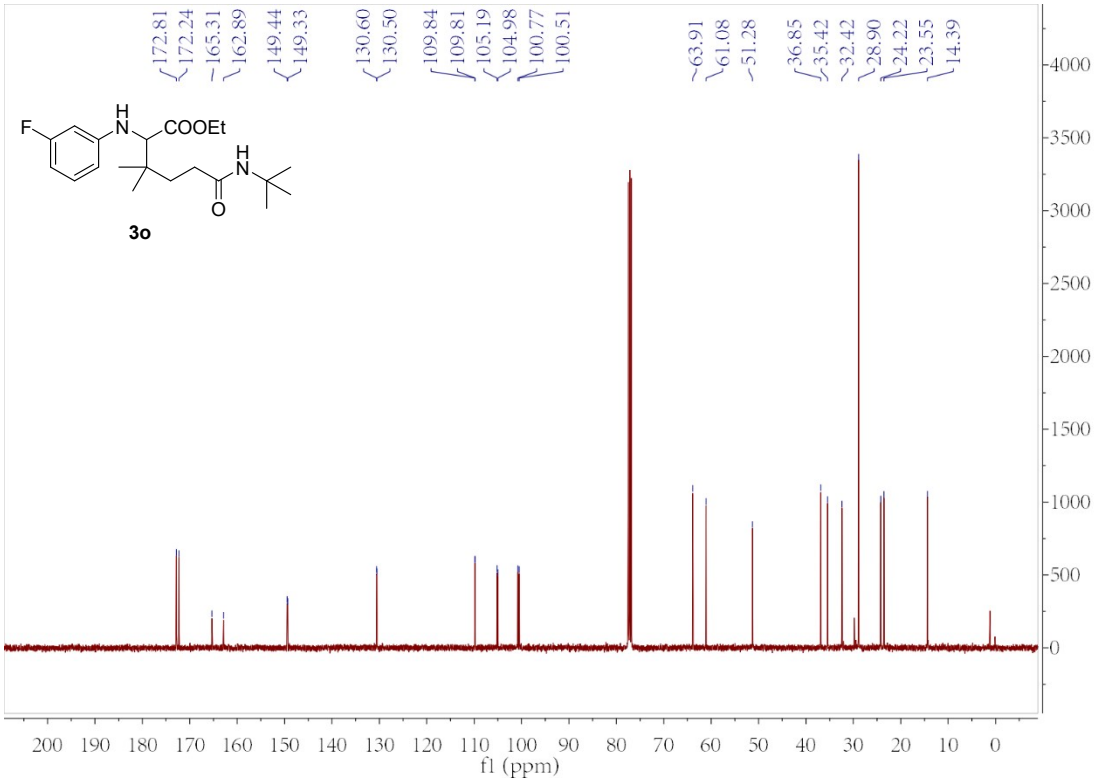


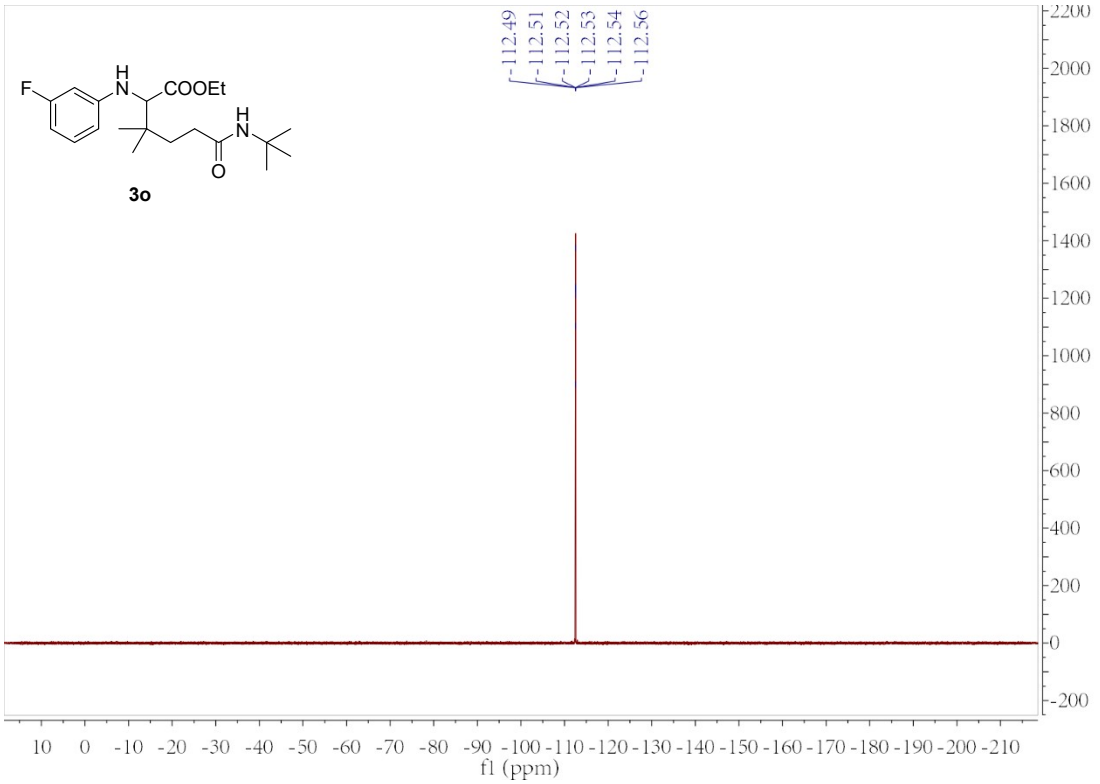
^{1}H NMR and ^{13}C NMR spectra for compound 3n ($CDCl_3$).



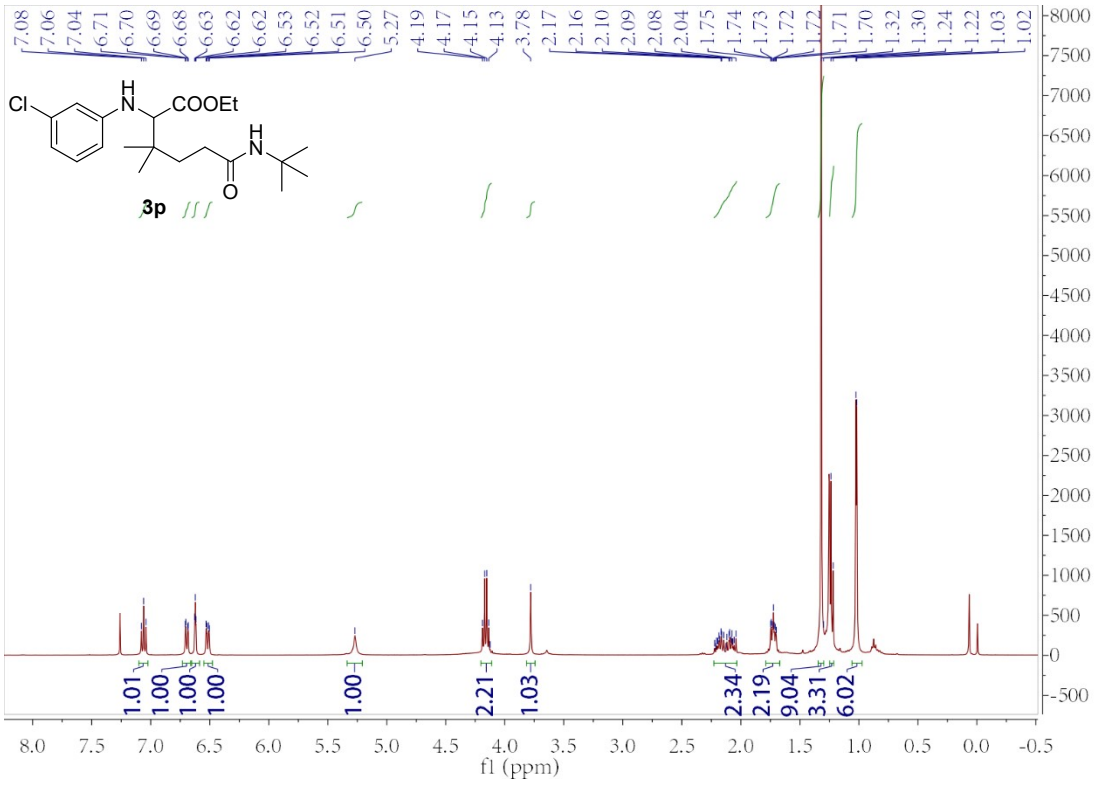
^{1}H, ^{13}C NMR and ^{19}F spectra for compound 3o ($CDCl_3$).

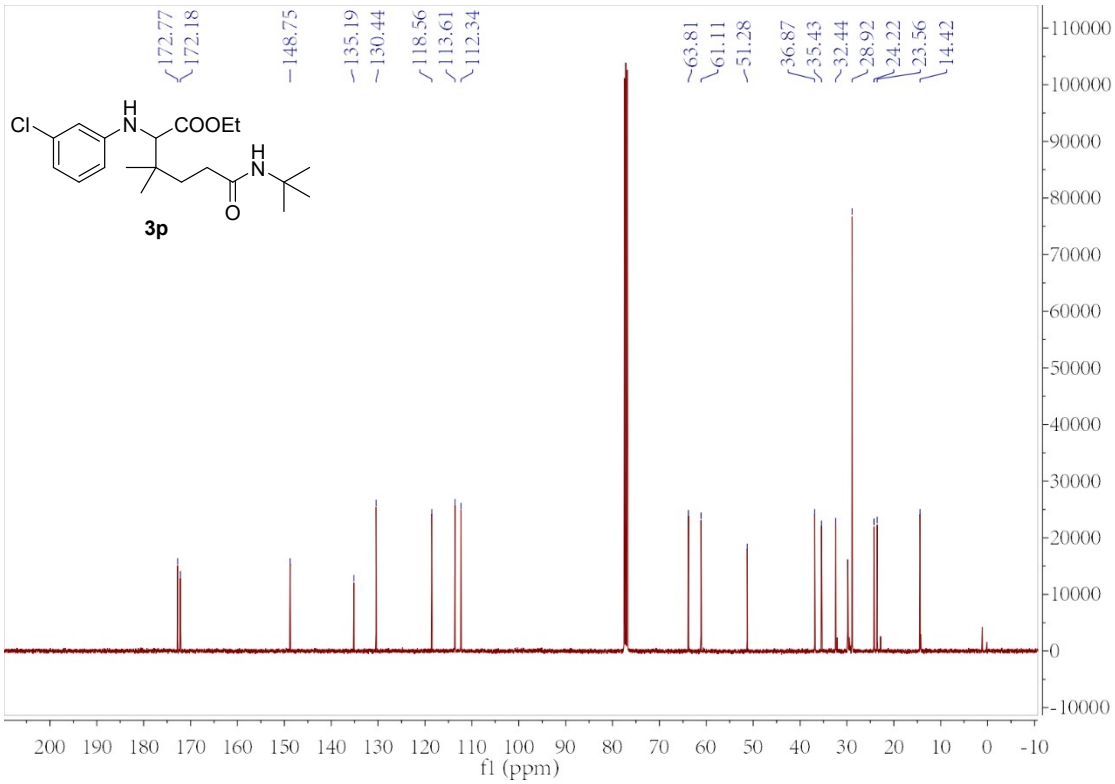

7.09 7.09 7.07 7.07 6.43 6.42 6.42 6.41 6.41 6.40 6.40 6.35 6.35 6.32 4.18 4.18 4.17 4.16 4.15 4.15 4.13 4.13 3.78 2.17 1.75 1.74 1.73 1.73 1.72 1.71 1.70 1.33 1.32 1.25 1.23 1.22 1.21 1.03 1.02
F
H
N
COOEt
H
N
O
3o
1.14 2.19 1.11 1.00 2.21 1.15 2.42 2.09 9.17 3.62 6.07
f1 (ppm)


172.81 172.24 165.31 162.89 149.44 149.33 130.60 130.50 109.84 109.81 105.19 104.98 100.77 100.51 63.91 61.08 51.28 36.85 35.42 32.42 28.90 24.22 23.55 14.39
F
H
N
COOEt
H
N
O
3o
f1 (ppm)

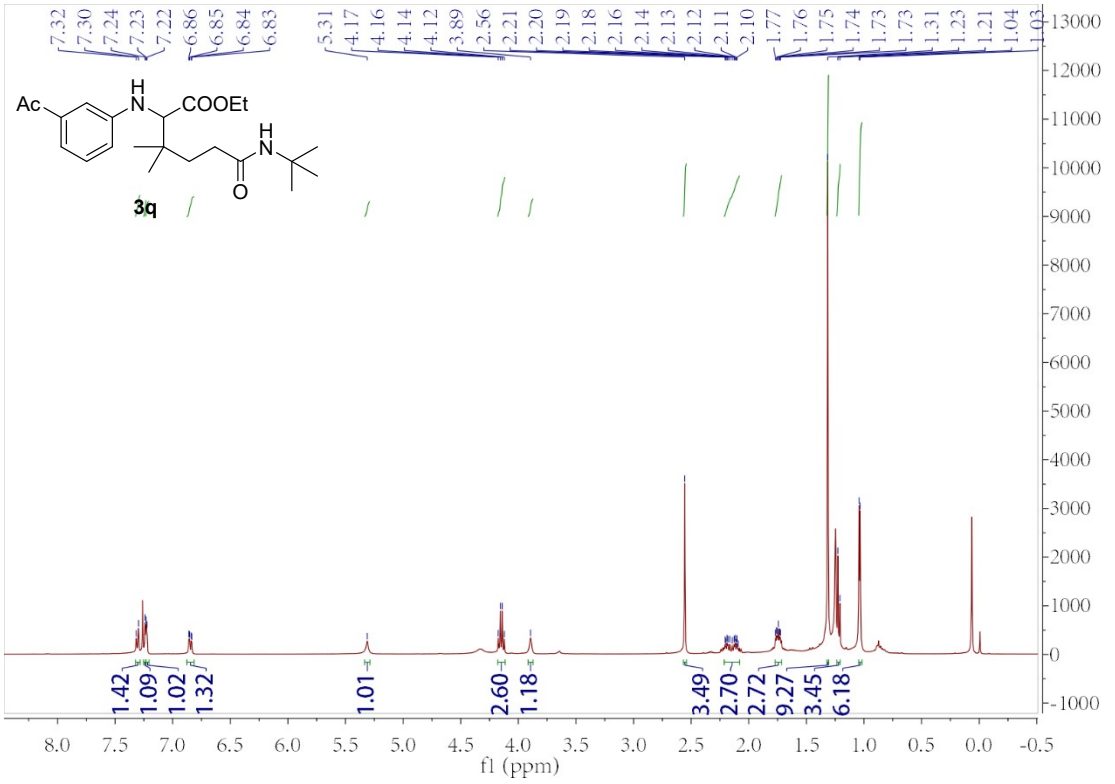


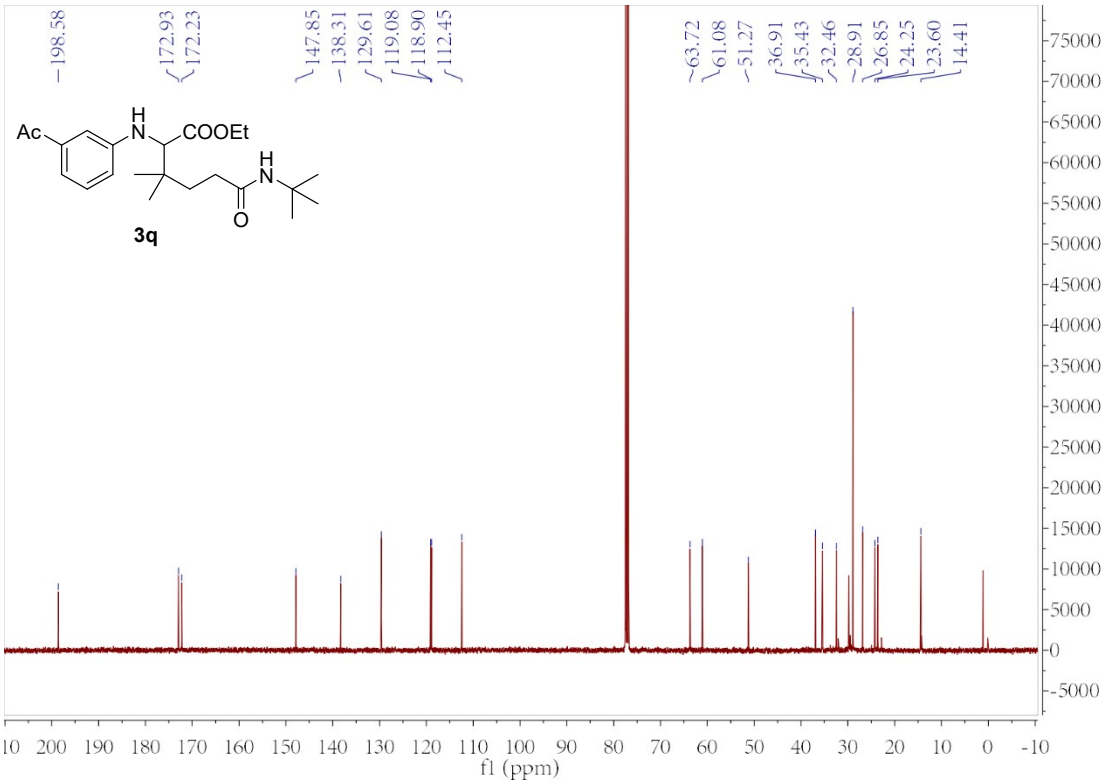
^{1}H NMR and ^{13}C NMR spectra for compound 3p ($CDCl_3$).



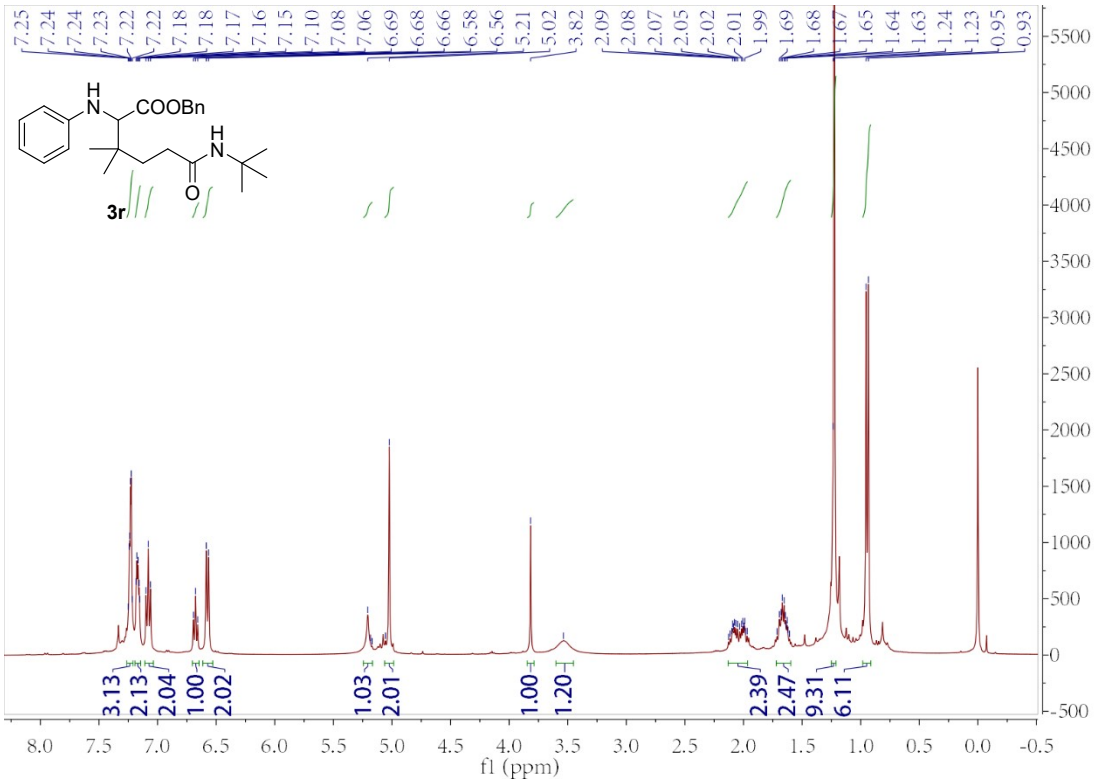


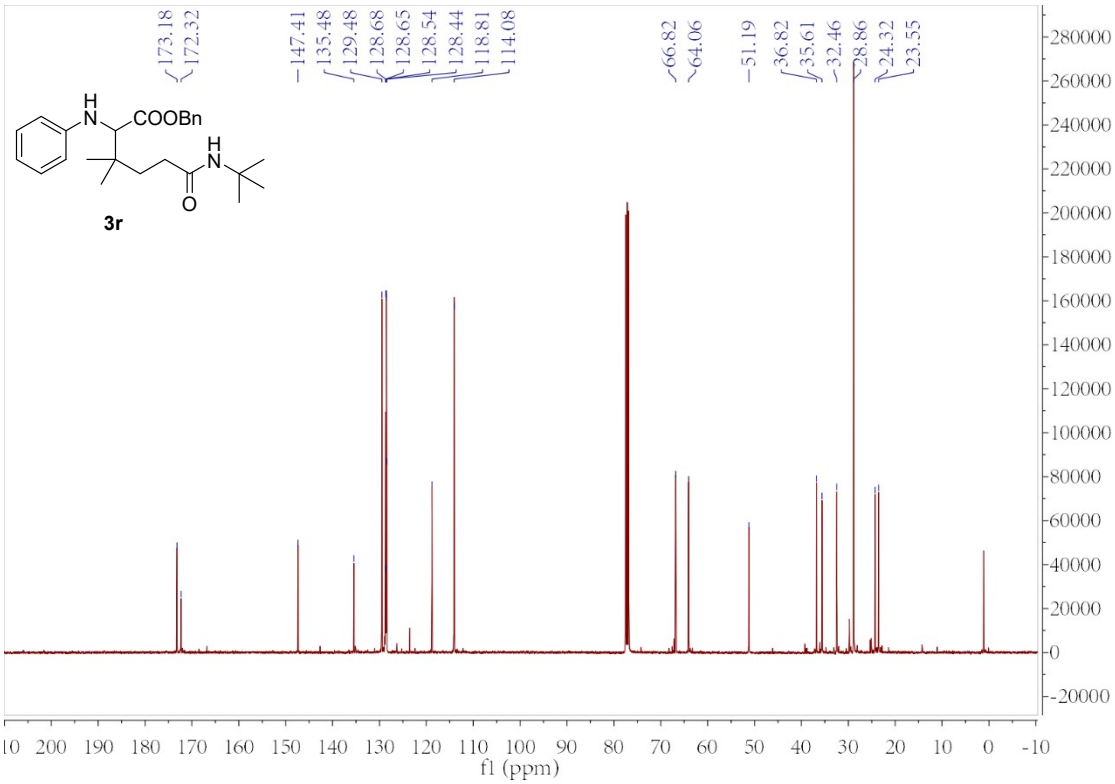
^{1}H NMR and ^{13}C NMR spectra for compound 3q ($CDCl_3$).



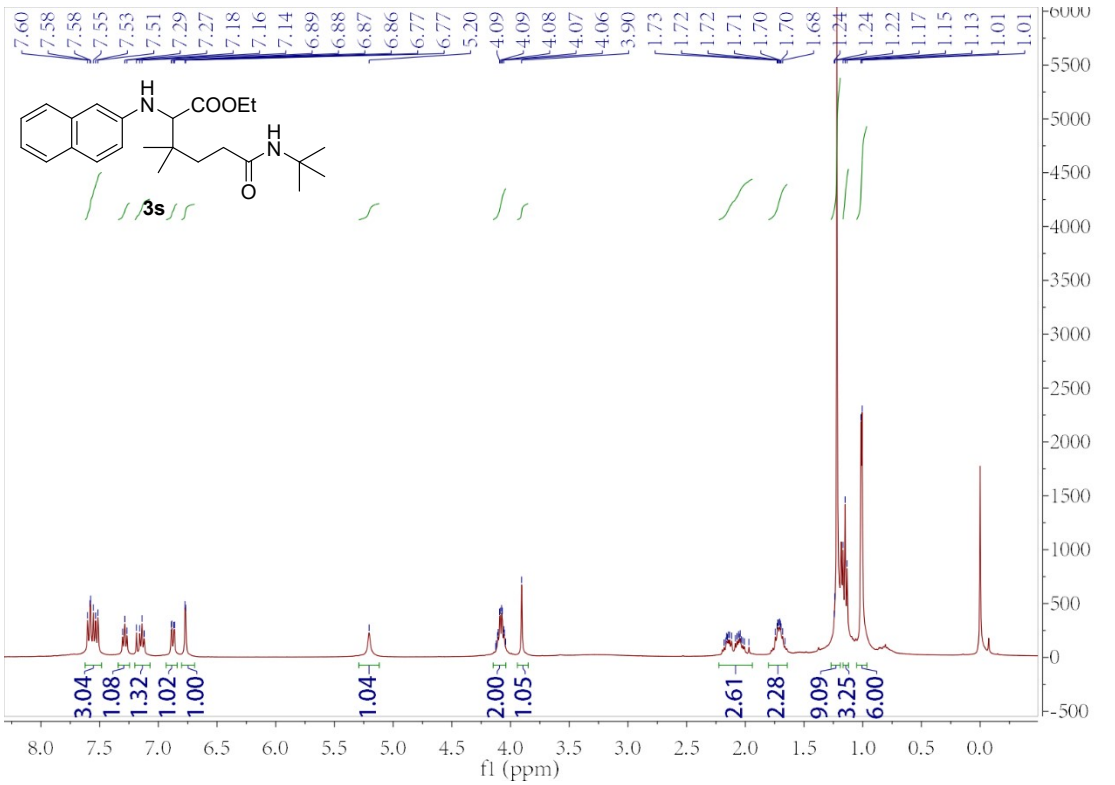


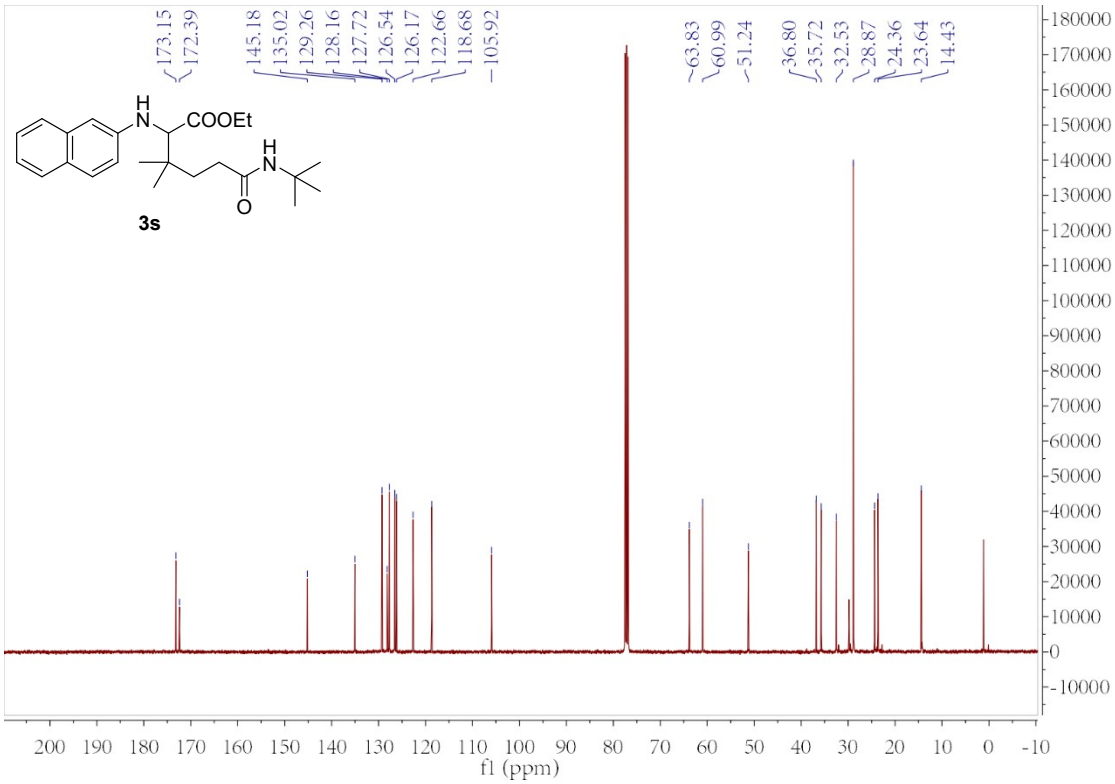
^{1}H NMR and ^{13}C NMR spectra for compound 3r ($CDCl_3$).



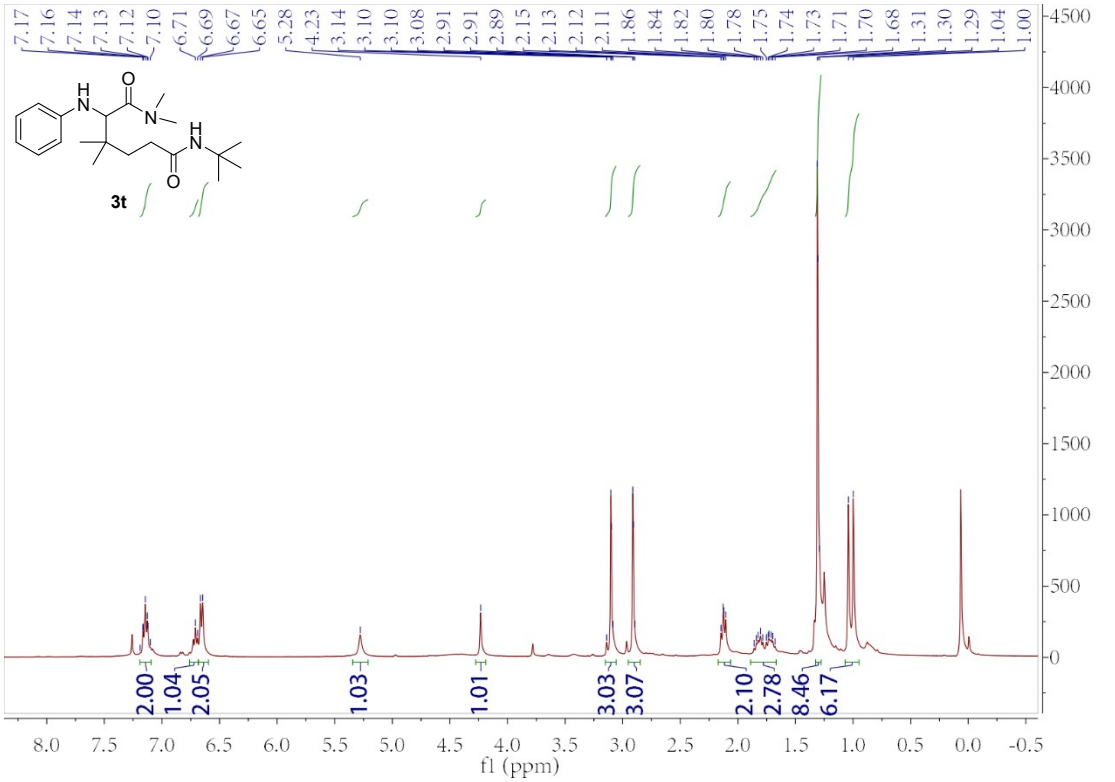


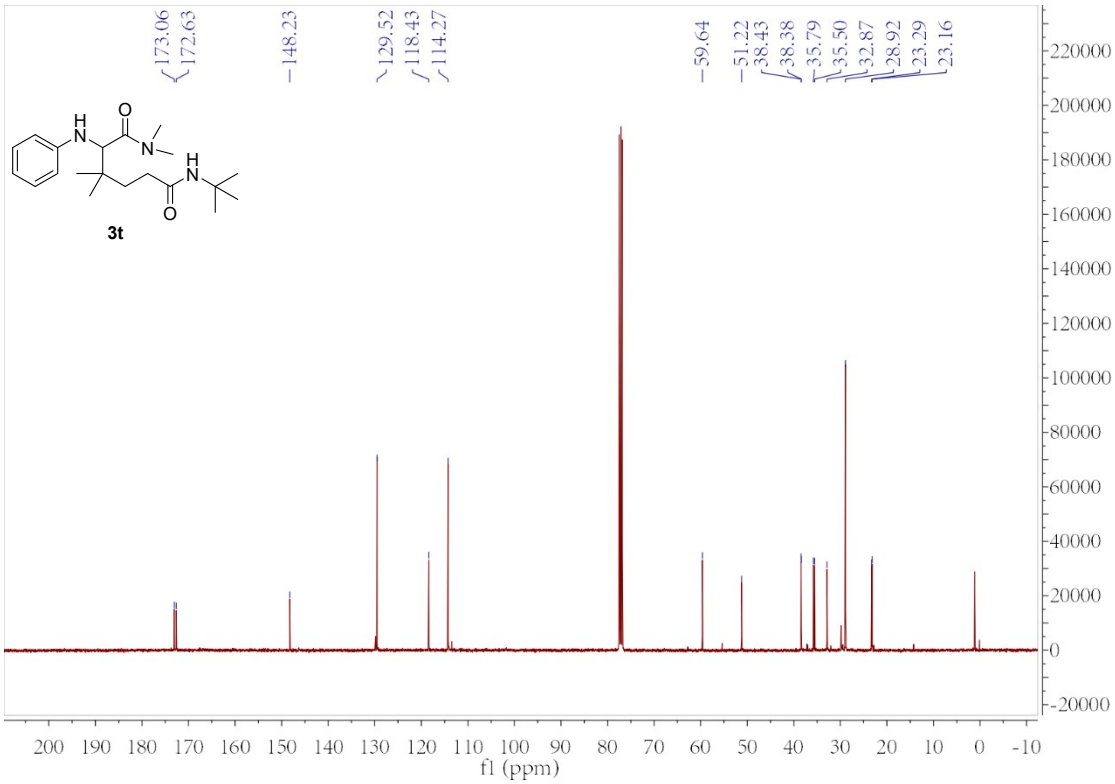
^{1}H NMR and ^{13}C NMR spectra for compound 3s ($CDCl_3$).



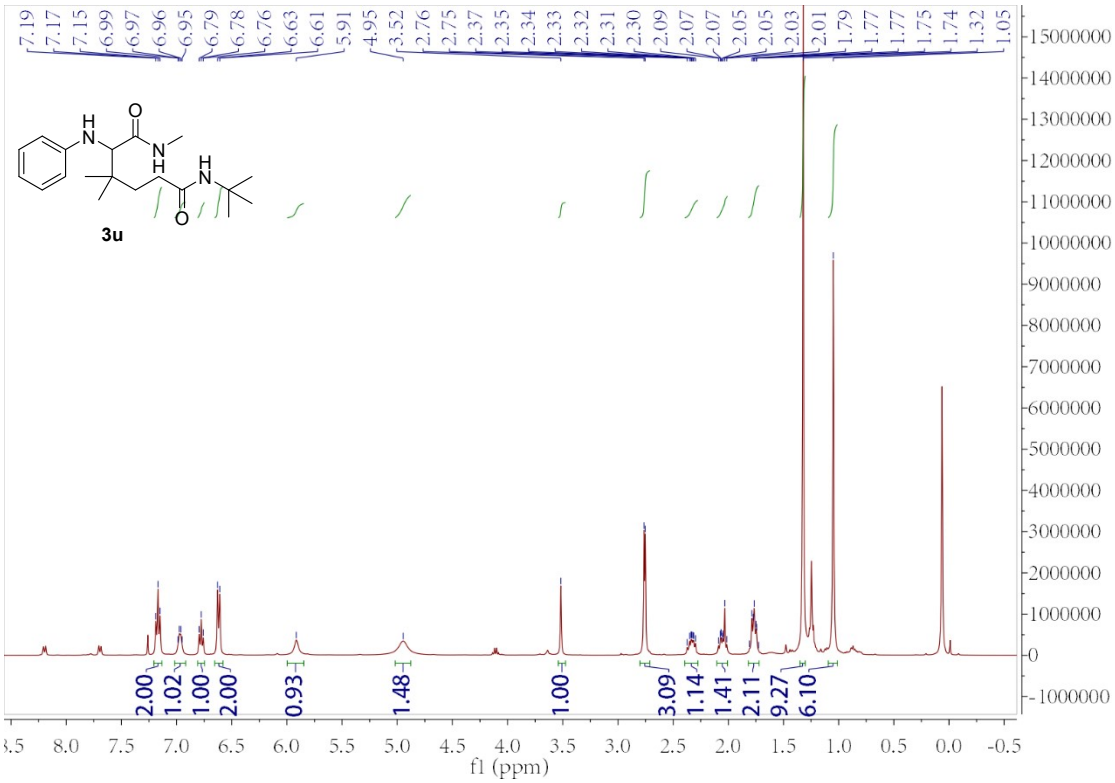


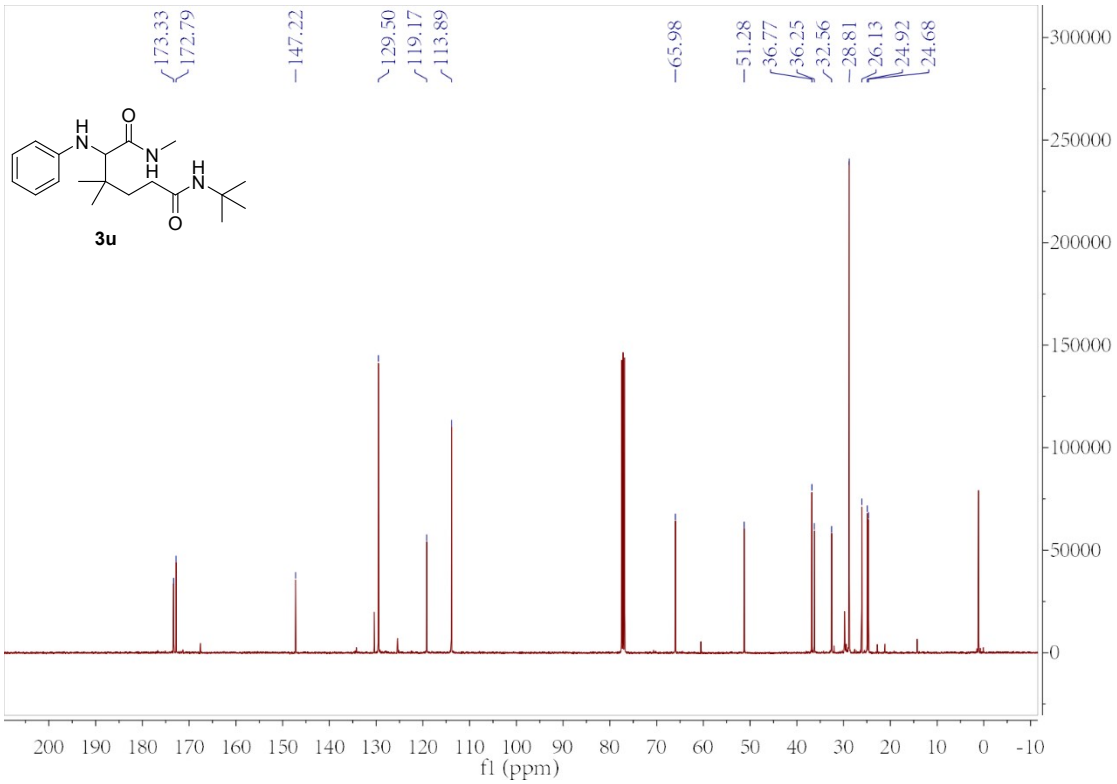
^{1}H NMR and ^{13}C NMR spectra for compound 3t ($CDCl_3$).



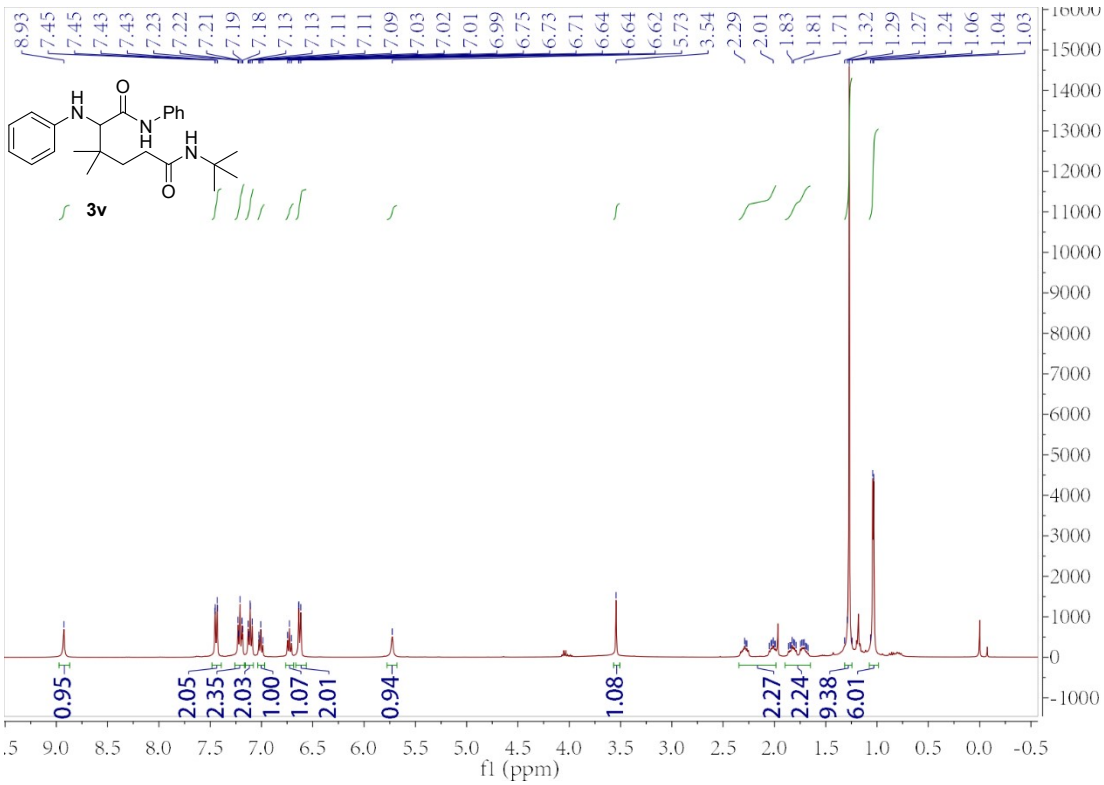


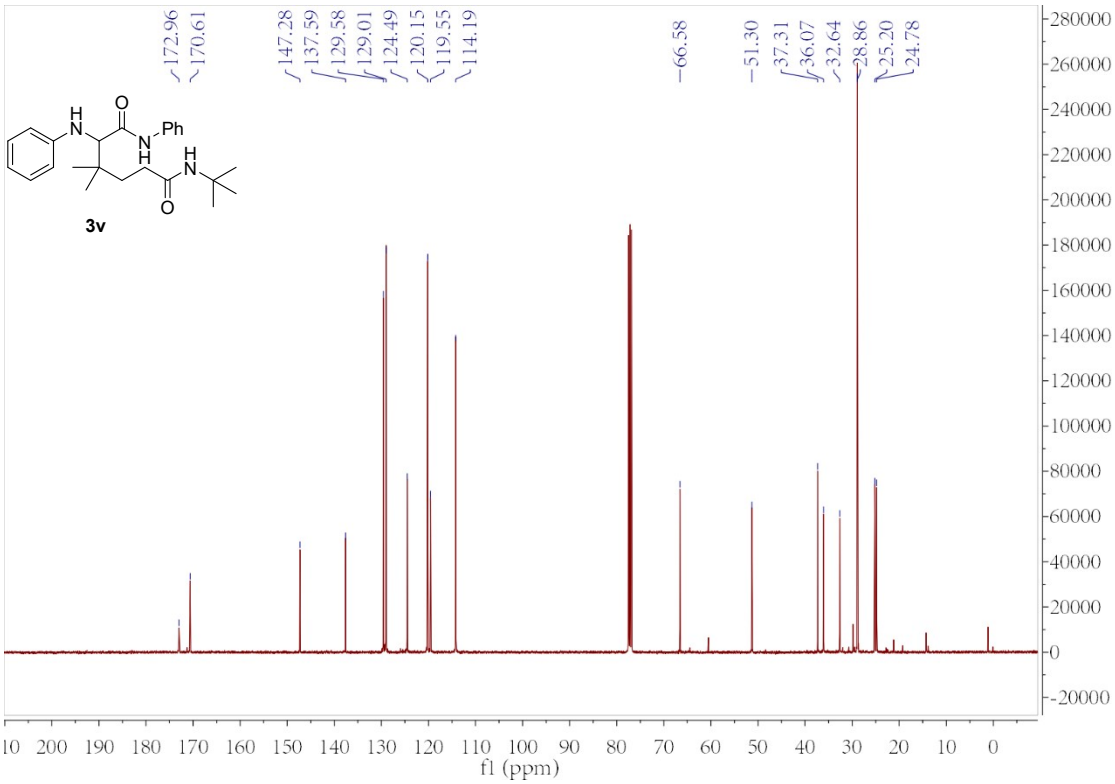
^{1}H NMR and ^{13}C NMR spectra for compound 3u ($CDCl_3$).



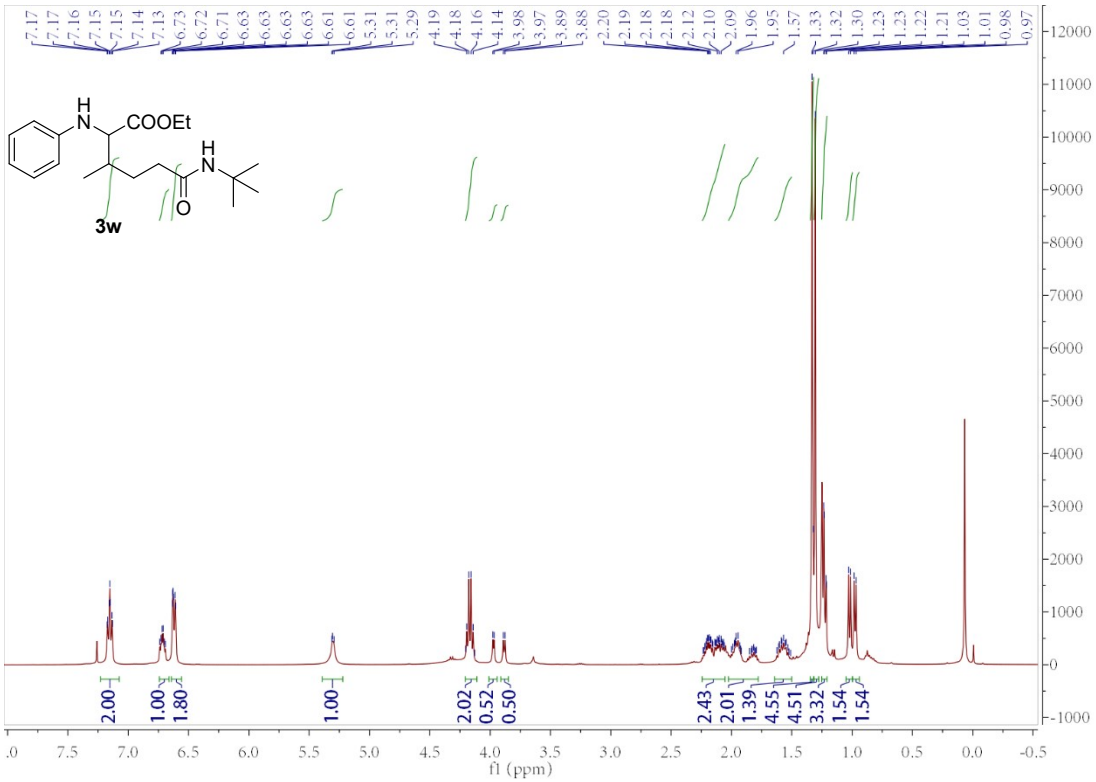


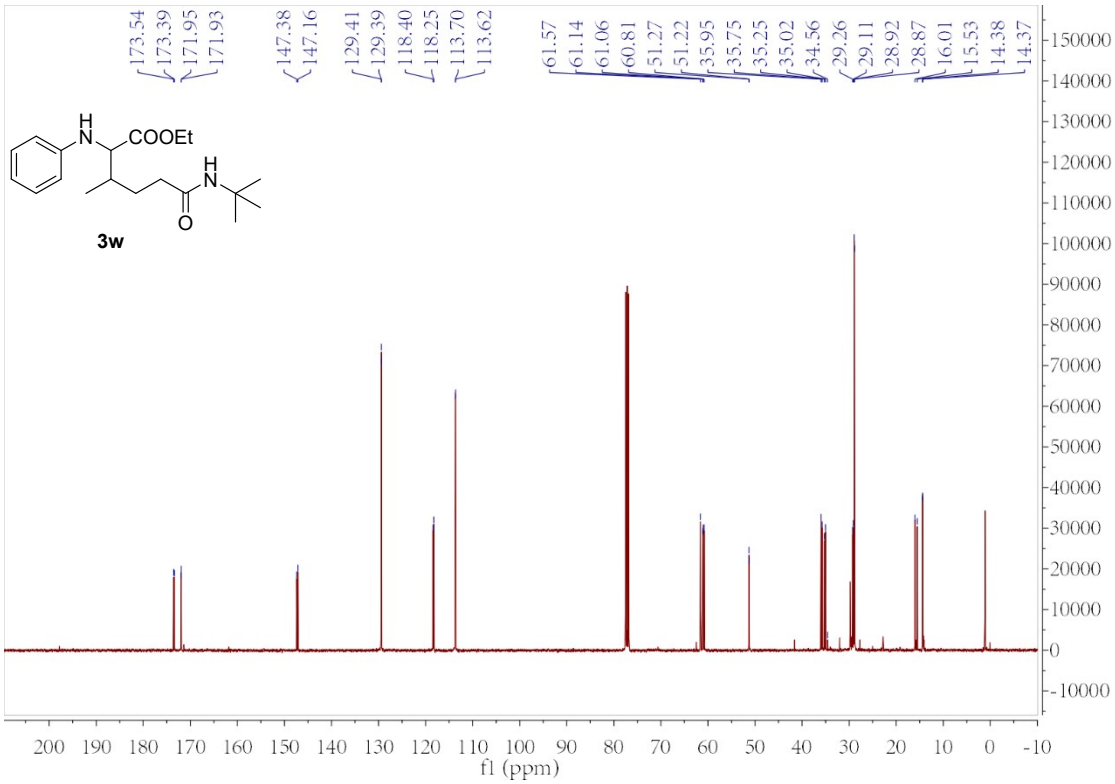
^{1}H NMR and ^{13}C NMR spectra for compound 3v ($CDCl_3$).



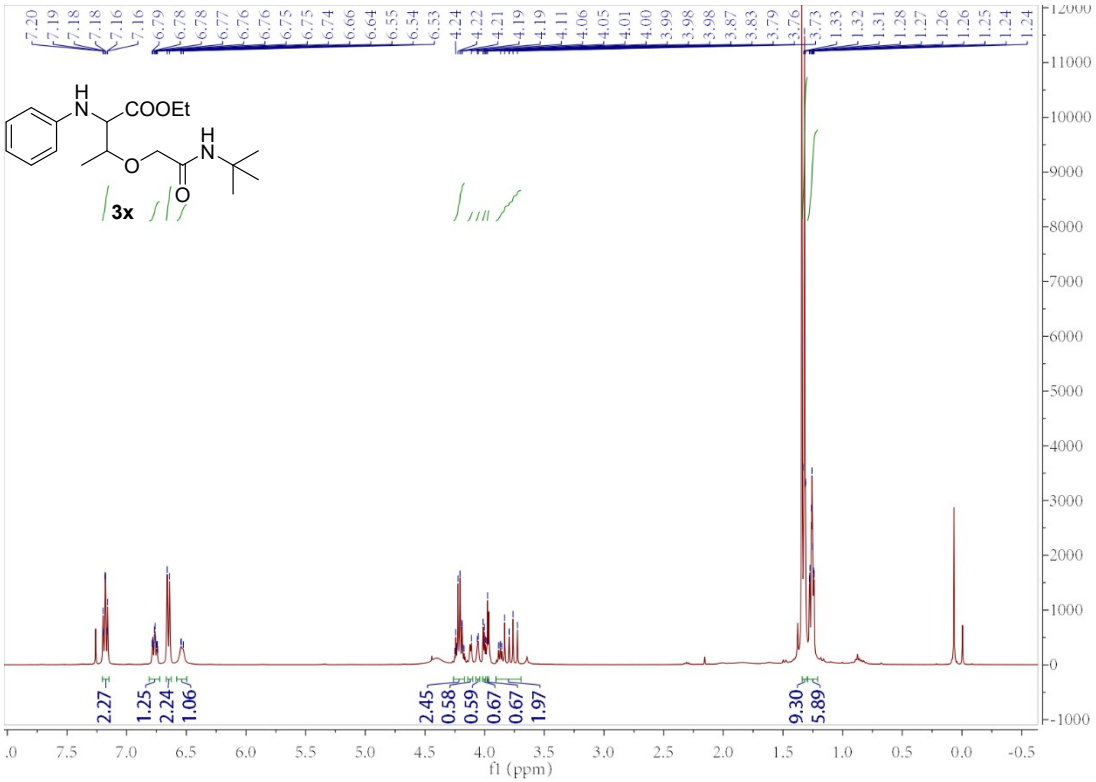


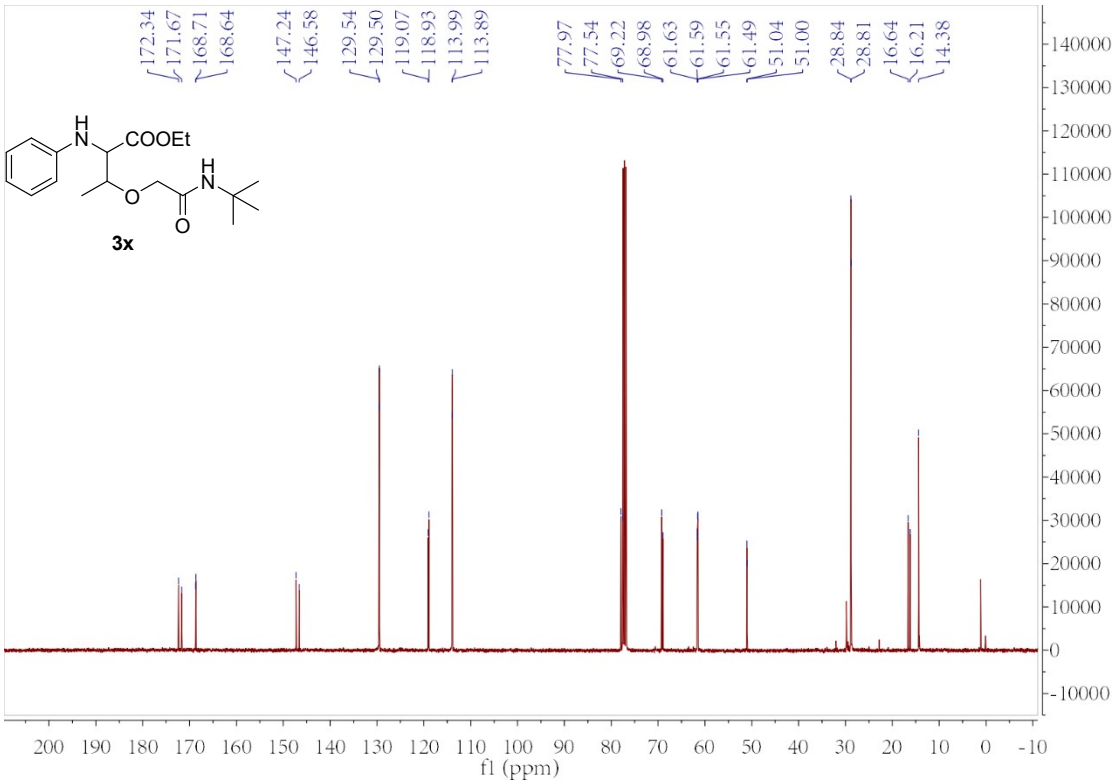
^{1}H NMR and ^{13}C NMR spectra for compound 3w ($CDCl_3$).



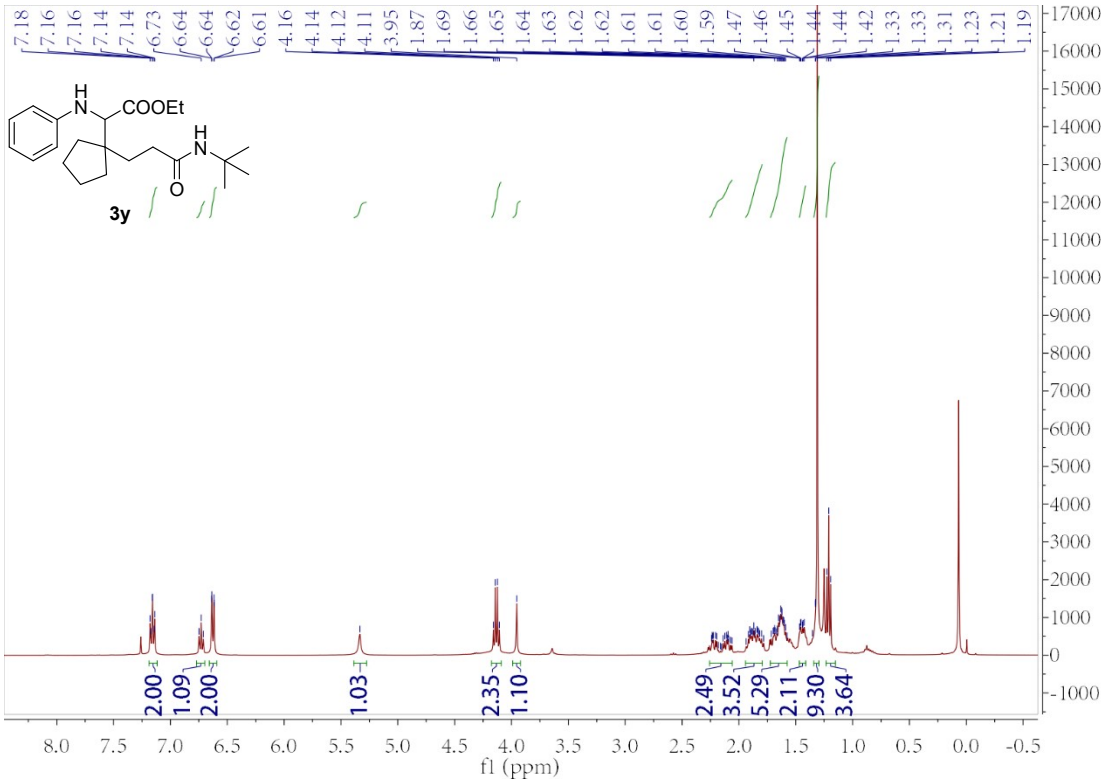


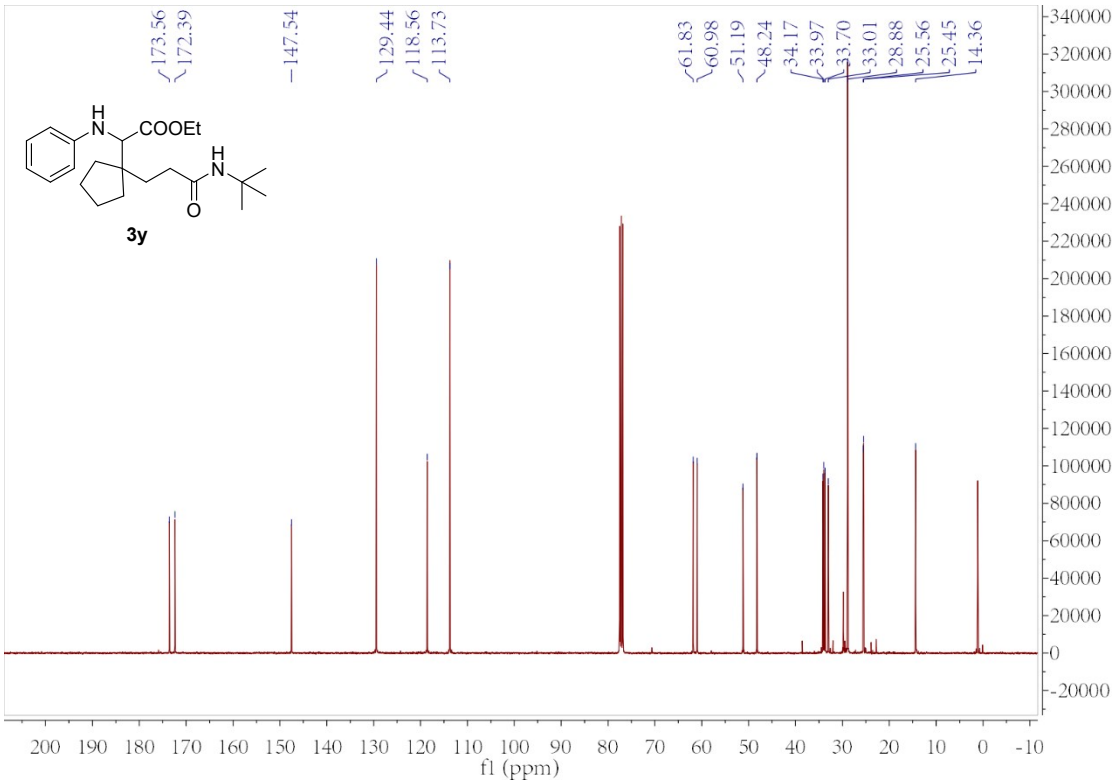
^{1}H NMR and ^{13}C NMR spectra for compound 3x ($CDCl_3$).



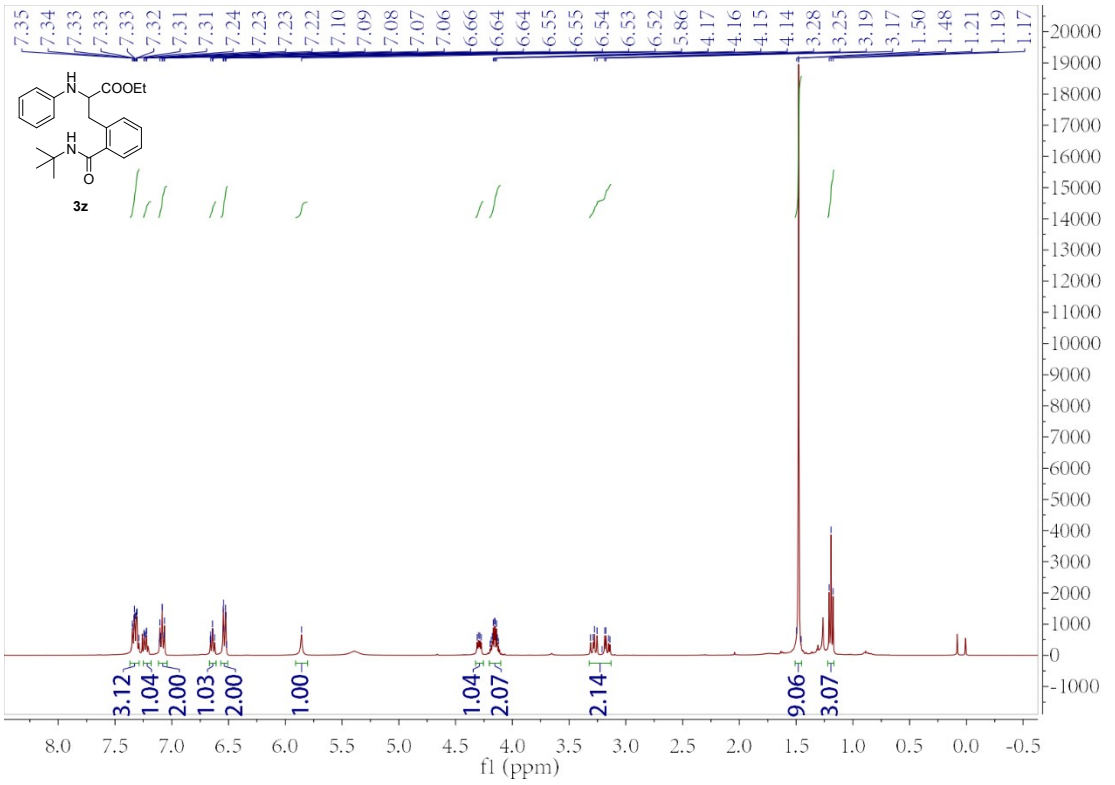


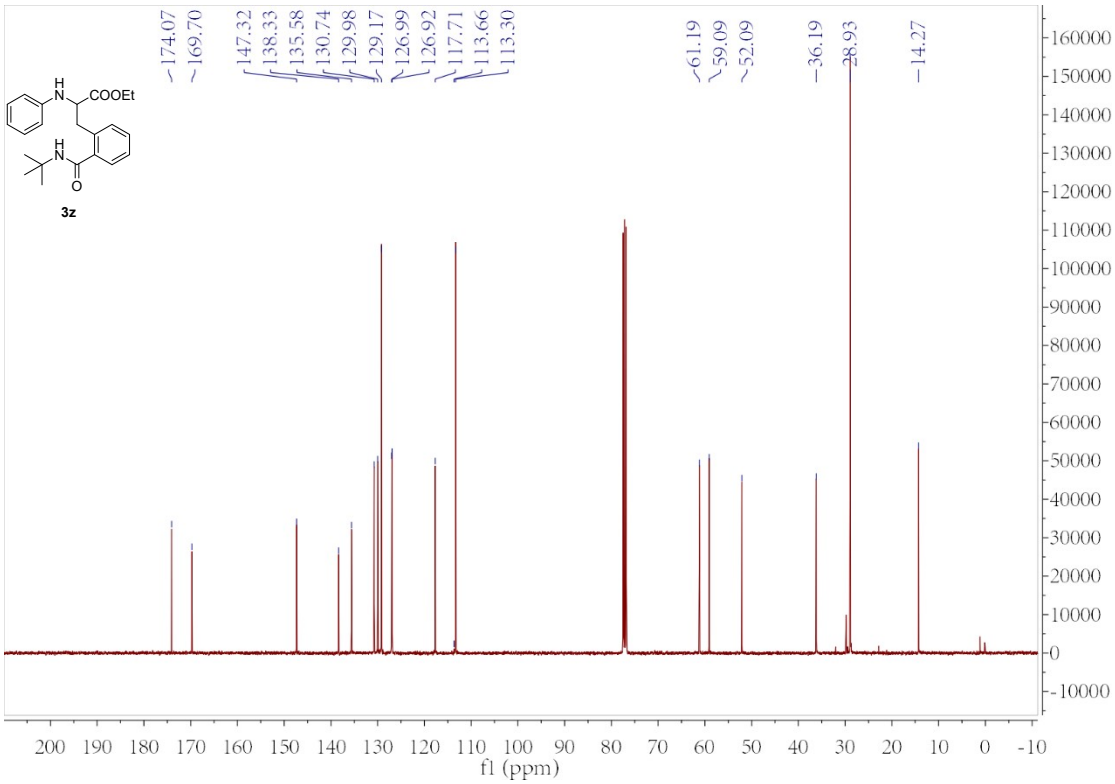
^{1}H NMR and ^{13}C NMR spectra for compound 3y ($CDCl_3$).



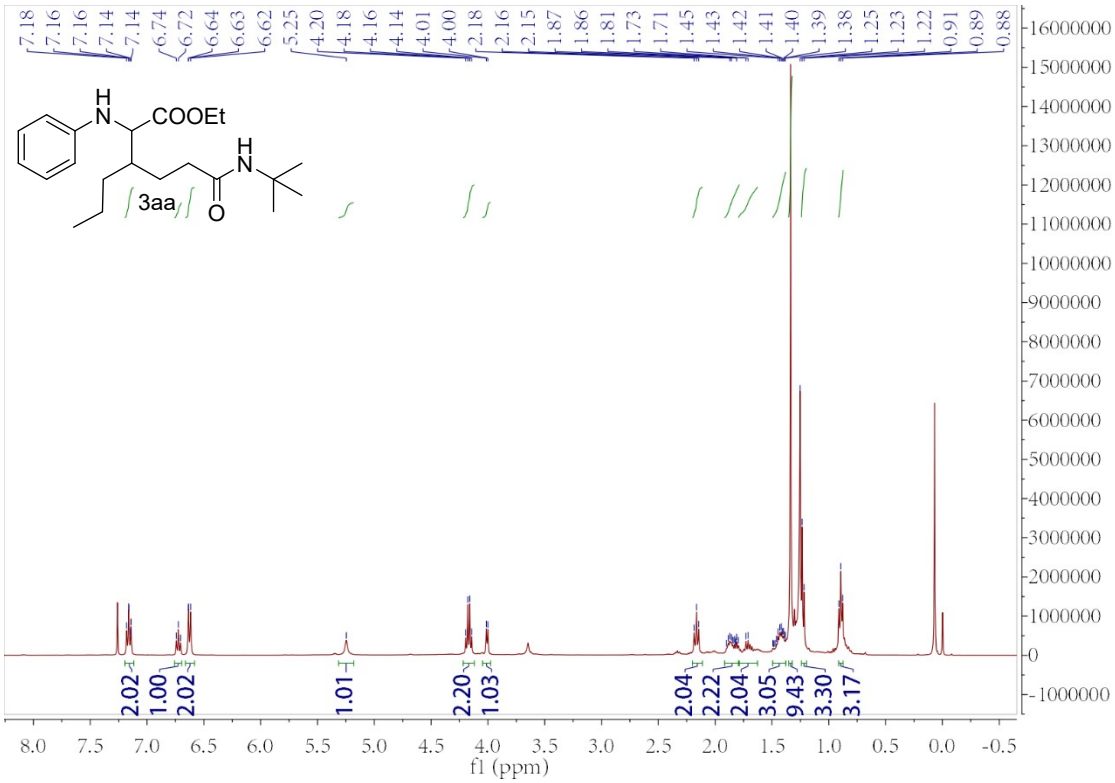


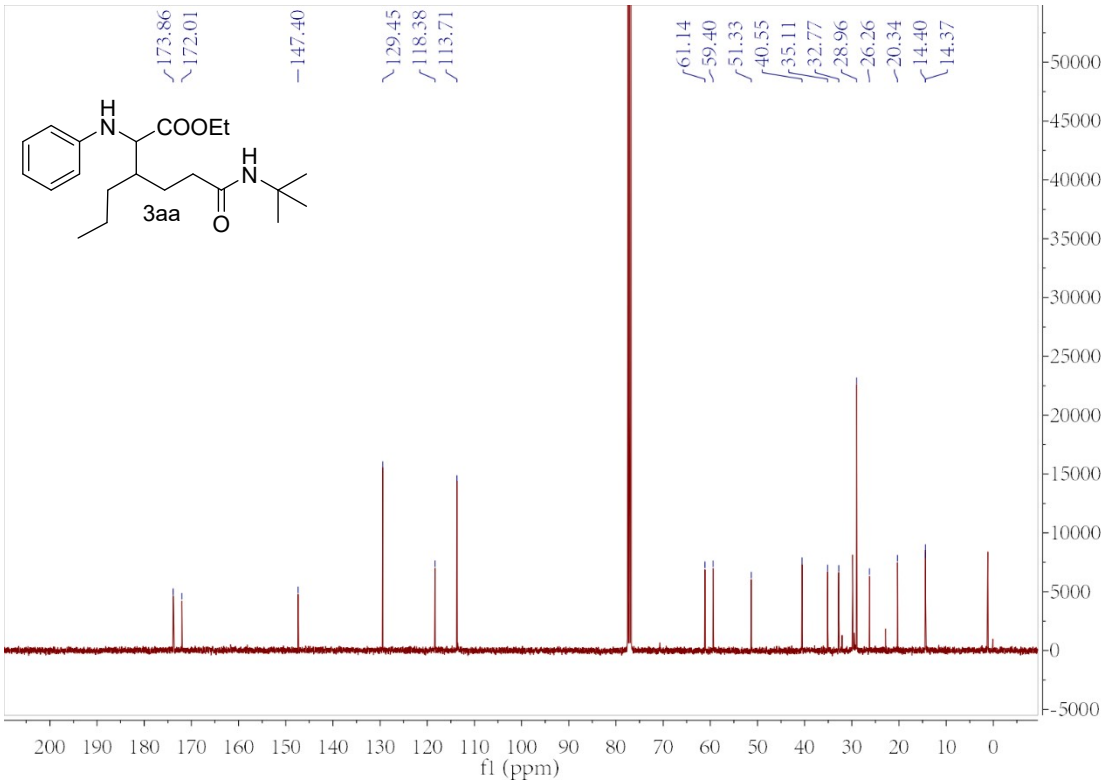
^{1}H NMR and ^{13}C NMR spectra for compound 3z ($CDCl_3$).



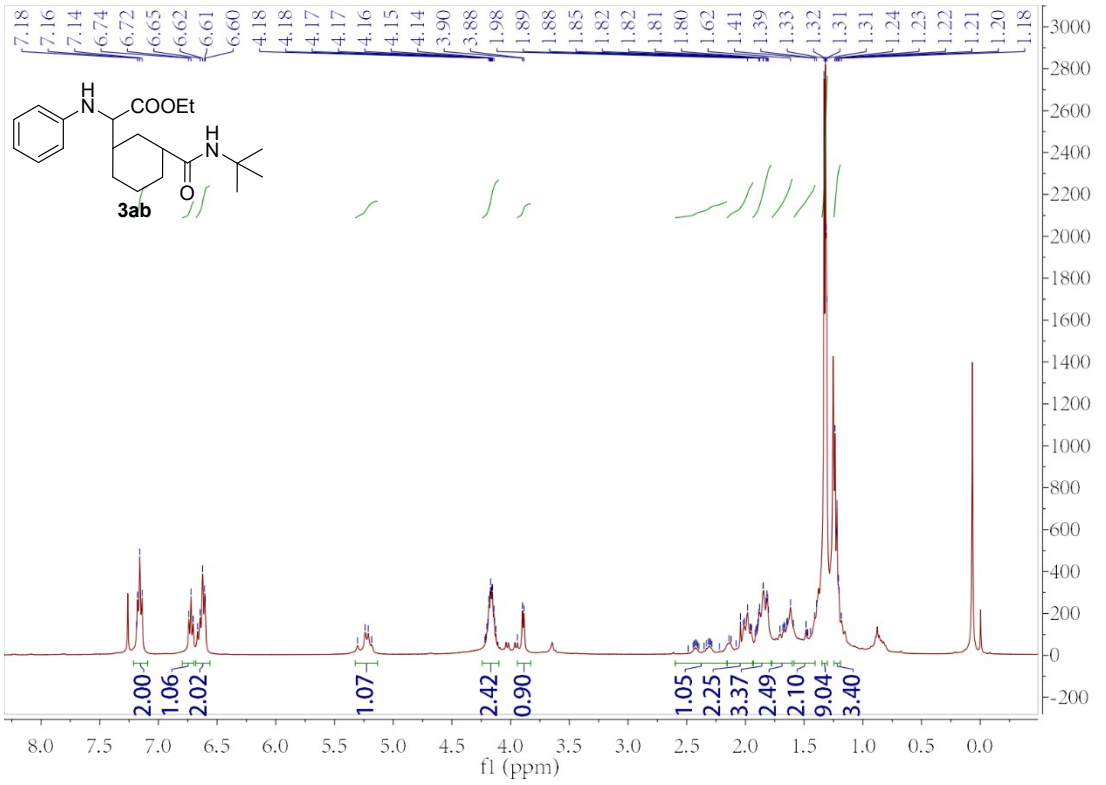


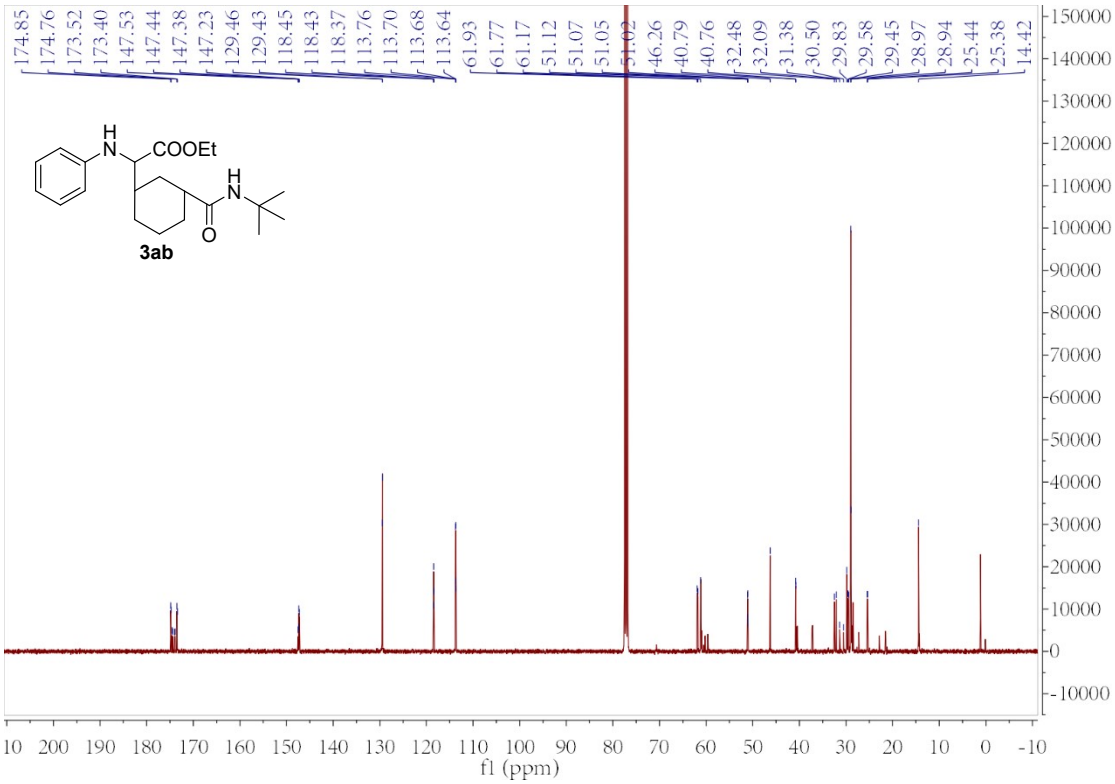
^{1}H NMR and ^{13}C NMR spectra for compound 3aa ($CDCl_3$).



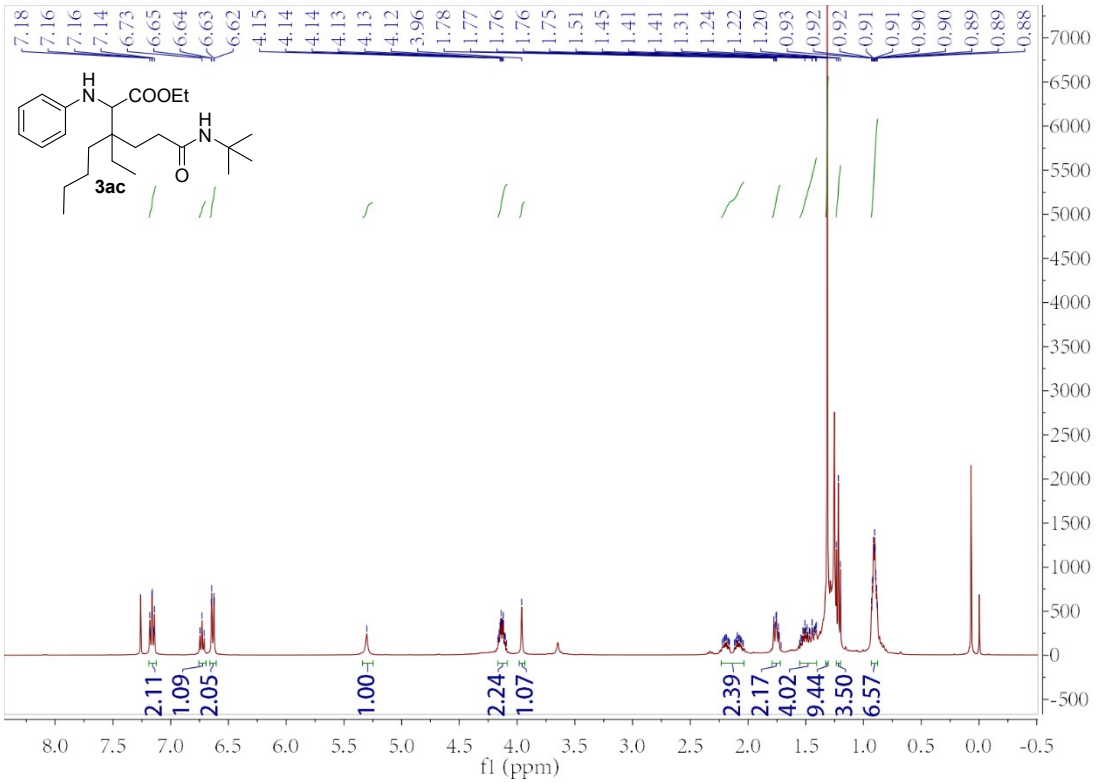


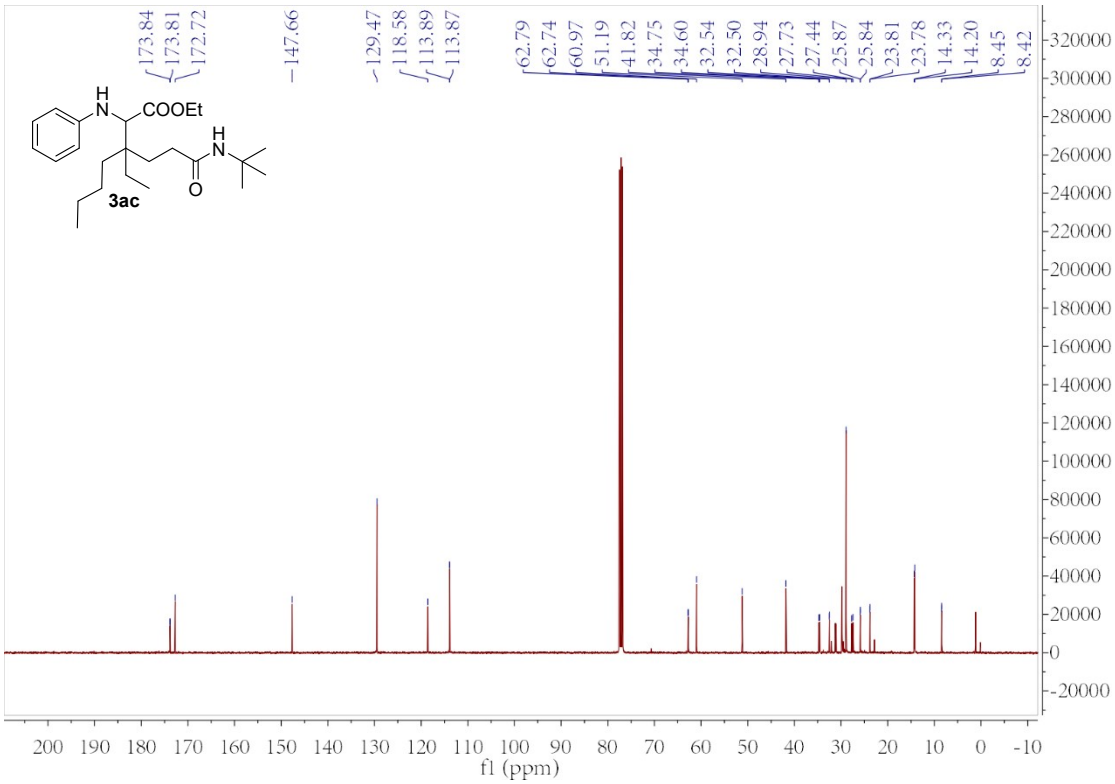
^{1}H NMR and ^{13}C NMR spectra for compound 3ab ($CDCl_3$).



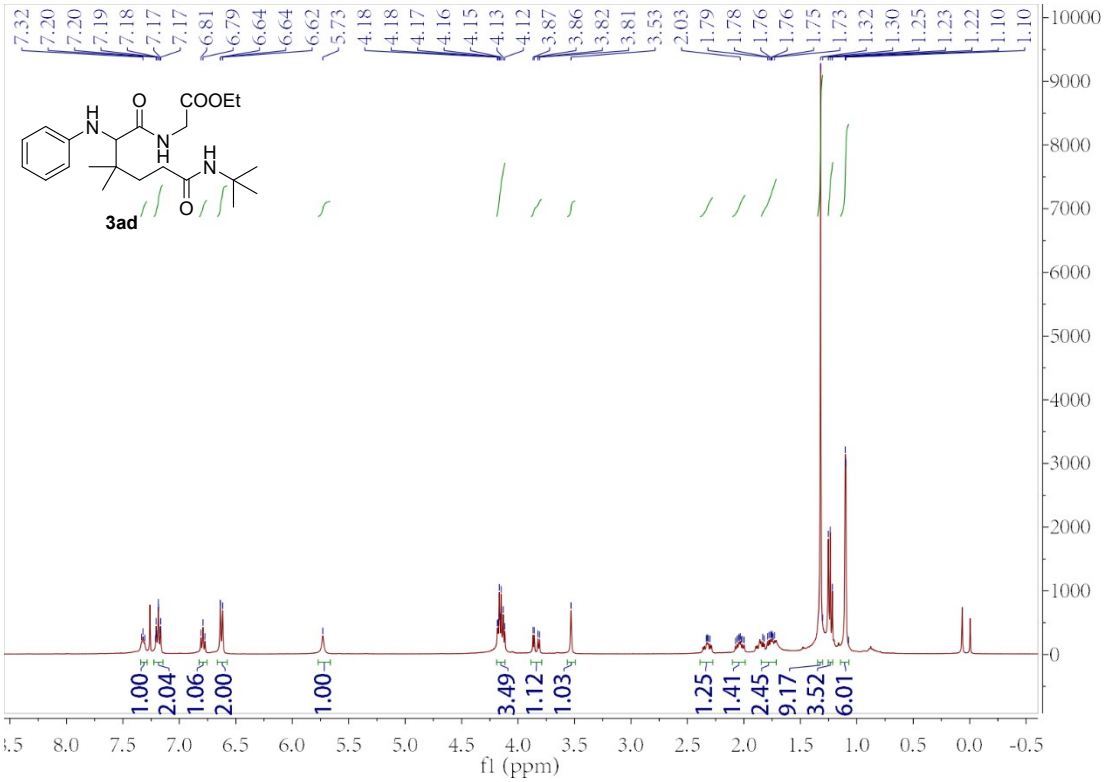


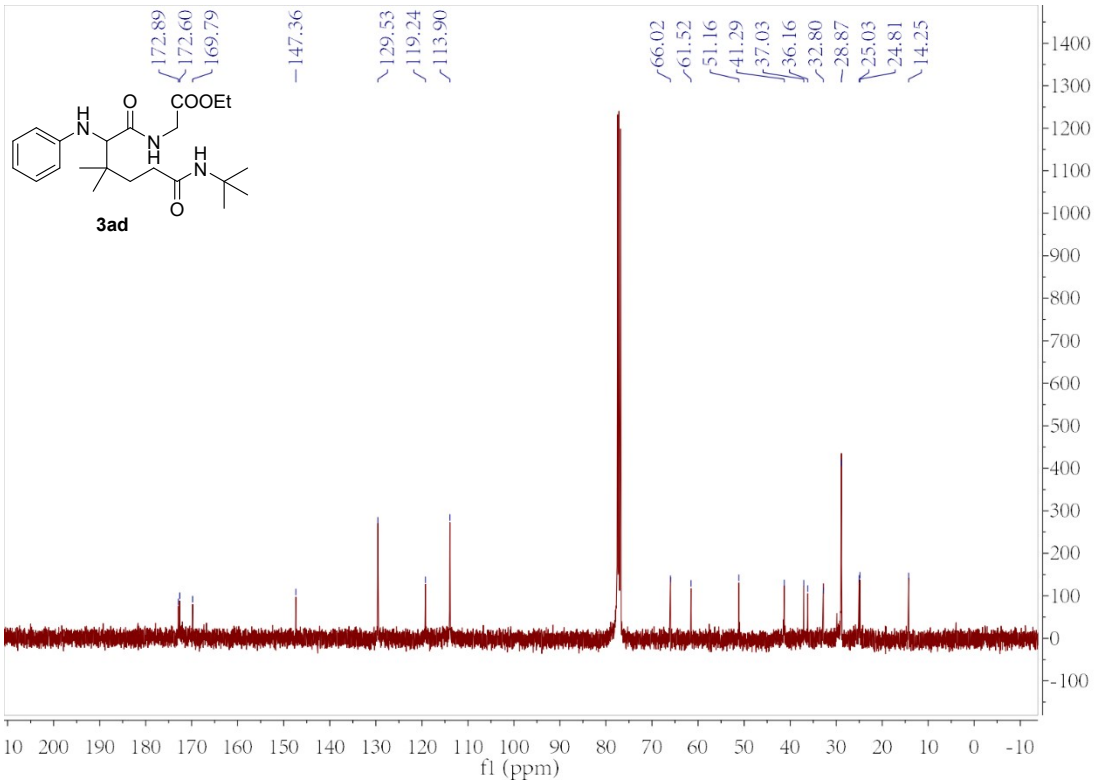
^{1}H NMR and ^{13}C NMR spectra for compound 3ac ($CDCl_3$).



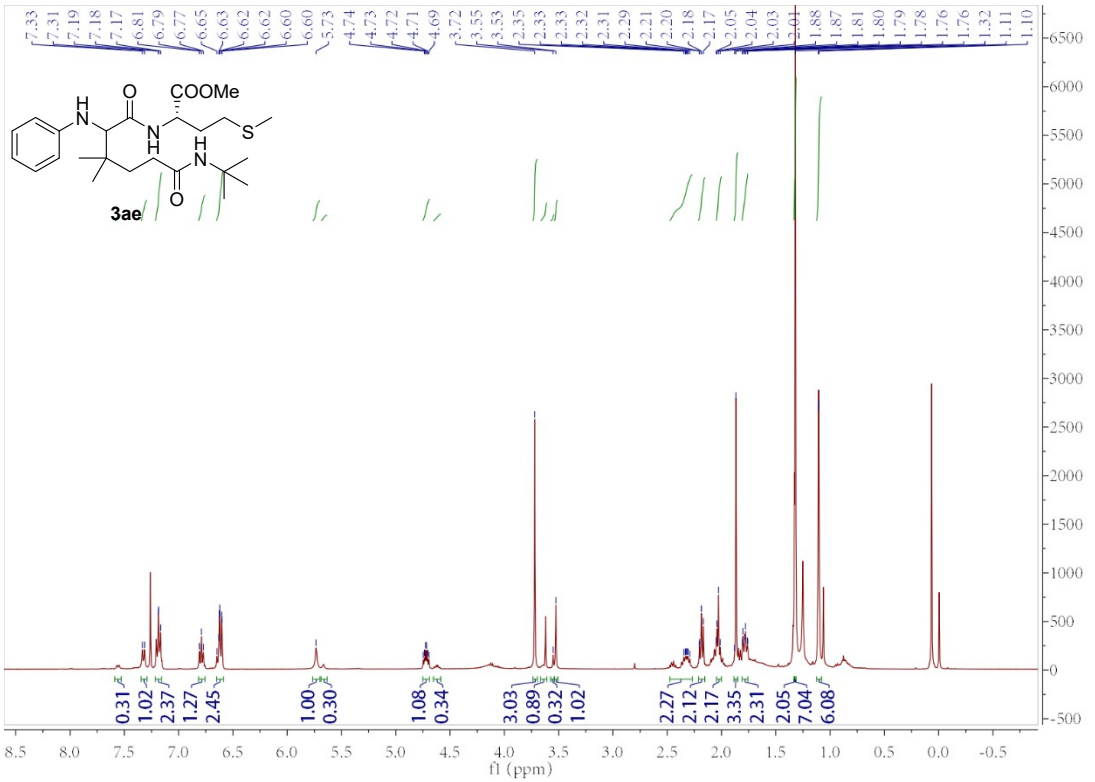


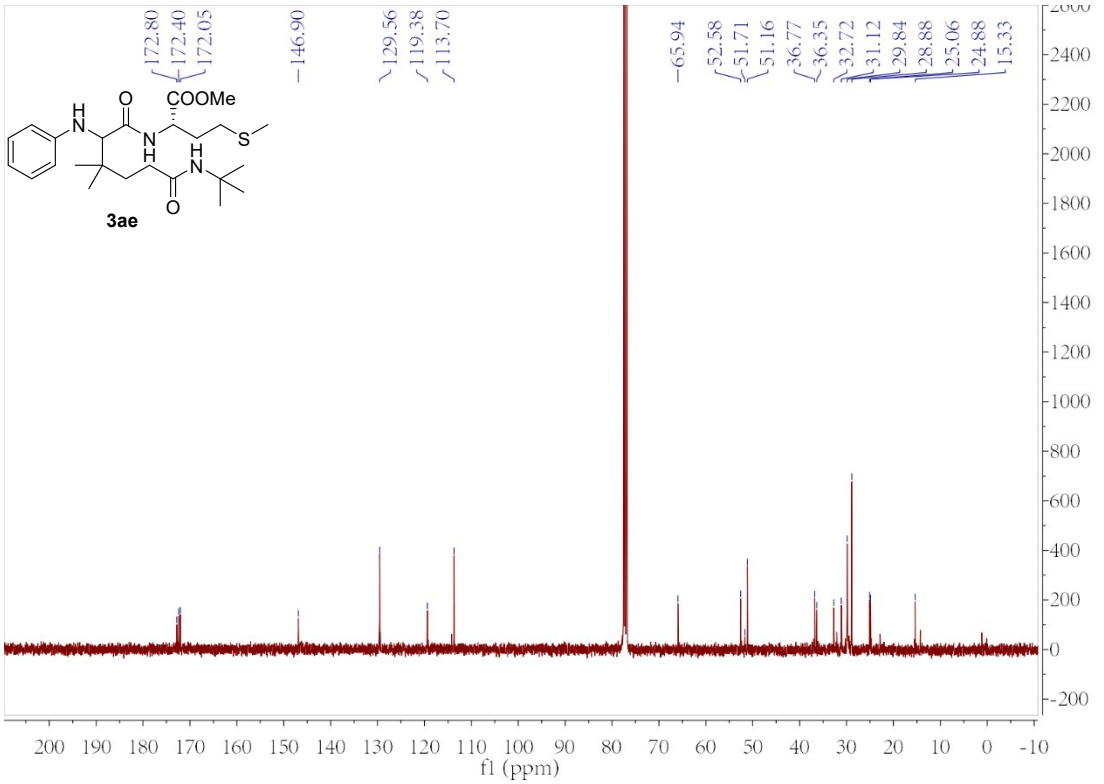
^{1}H NMR and ^{13}C NMR spectra for compound 3ad ($CDCl_3$).



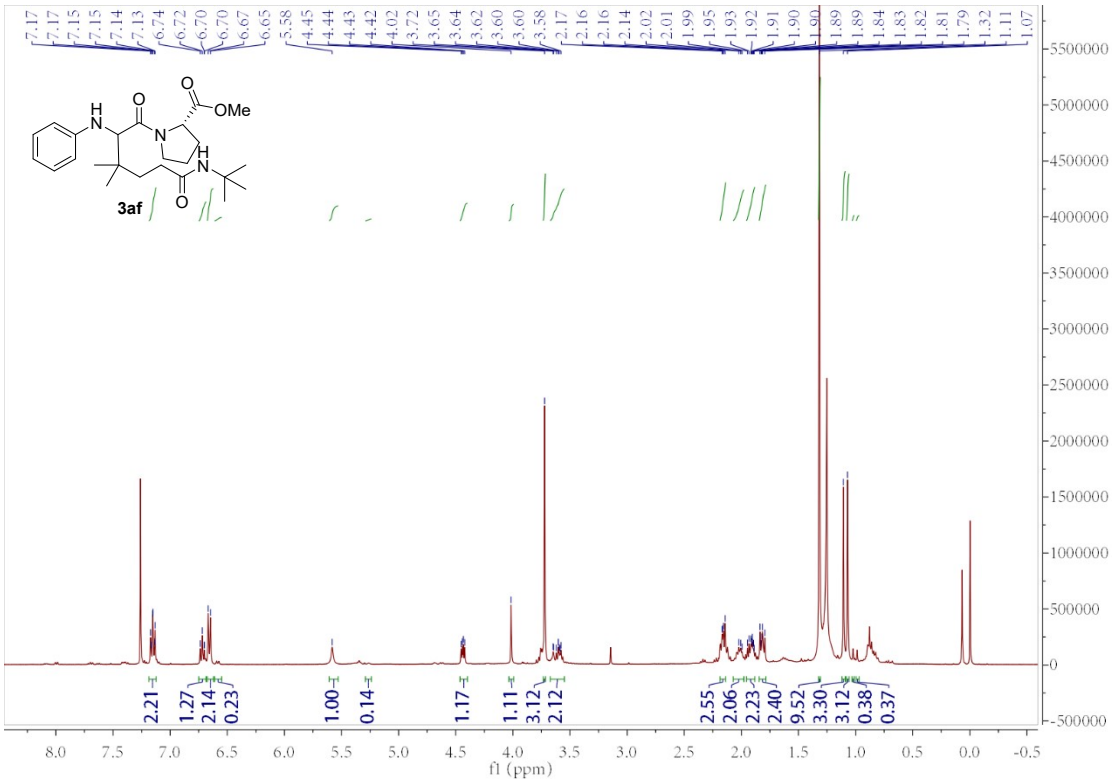


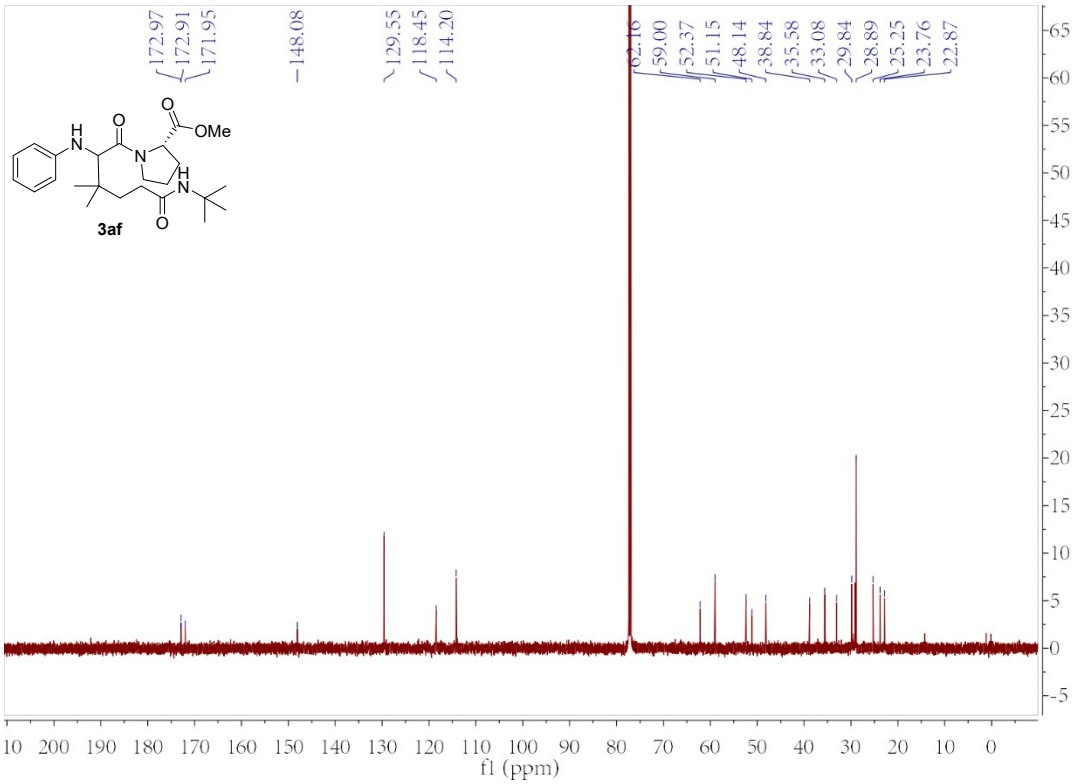
^{1}H NMR and ^{13}C NMR spectra for compound 3ae ($CDCl_3$).



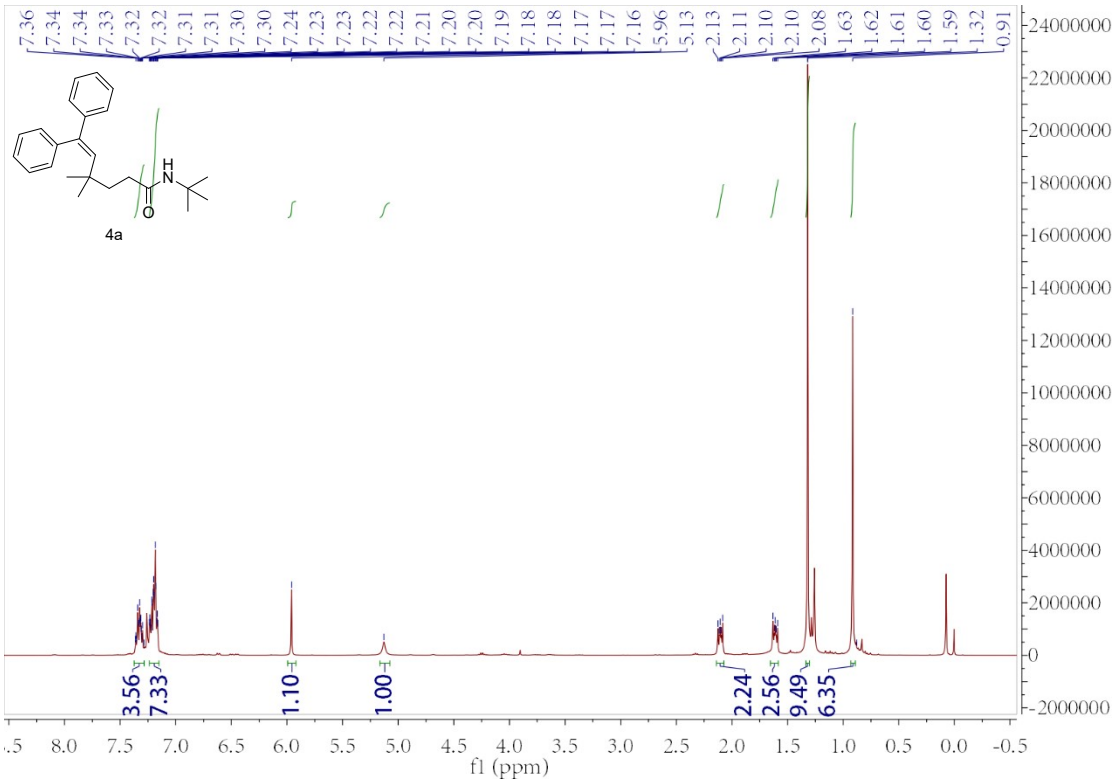


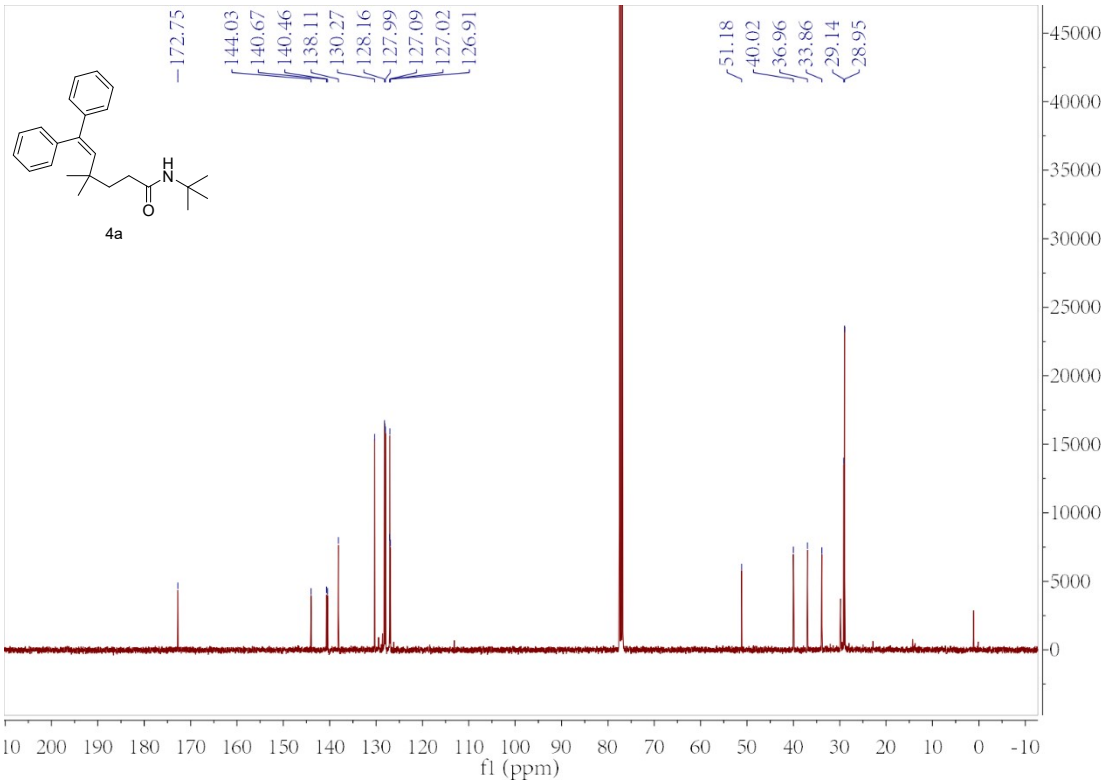
^{1}H NMR and ^{13}C NMR spectra for compound 3af ($CDCl_3$).





^{1}H NMR and ^{13}C NMR spectra for compound 4a ($CDCl_3$).

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127.99
127.09
127.02
126.91
51.18
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36.96
33.86
29.14
28.95
H
N
O
4a
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)