Supporting Information

Taming Photocatalysis in Flow: Easy and Speedy Preparation of α-Aminoamide Derivatives

Ricardo I. Rodríguez,[a] Marina Sicignano,[a] Montaña J. García,[a] Rodrigo G. Enríquez,[a] Silvia Cabrera,[b,c] and José Alemán*[a,c,d]

[a] Organic Chemistry Department, Módulo 1, Universidad Autónoma de Madrid, Madrid-28049, Spain.

[b] Inorganic Chemistry Department, Science Faculty, Universidad Autónoma de Madrid, Madrid-28049, Spain.

[c] Institute for Advanced Research in Chemical Sciences (IAdChem) Universidad Autónoma de Madrid, 28049 Madrid, Spain.

[d] Center for Innovation in Advanced Chemistry (ORFEO-CINQA), Universidad Autónoma de Madrid

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1. General Methods and Materials

NMR spectra were acquired on a BRUKER AVANCE 300 or 500 MHz spectrometer running at 300 or 500 MHz for ^{1}H and 76 or 126 MHz for ^{13}C and were internally referenced to residual solvent signals ($CDCl_3$ referenced at δ 7.26 ppm for ^{1}H-NMR and δ 77.2 ppm for ^{13}C-NMR; D_2O referenced at δ 4.79 ppm for ^{1}H-NMR; $(CD_3)_2SO$ referenced at δ 2.50 ppm for ^{1}H-NMR). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (*s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet, *br* = broad), coupling constant (Hz) and integration. Data for ^{1}H-decoupled and ^{13}C and are reported in terms of chemical shift. The diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixture through integration of diagnostic signals.

High-Resolution Mass Spectra (HRMS) were obtained on an Agilent Technologies 6120 Quadrupole LC/MS coupled with an SFC Agilent Technologies 1260 Infinity Series instrument for the MS (ESI) (Electrospray Ionization). *MassWorks* software version 4.0.0.0 (*Cerno Bioscience*) was used for the formula identification. *MassWorks* is an MS calibration software which calibrates isotope profiles to achieve high mass accuracy and enables elemental composition determination on conventional mass spectrometers of unit mass resolution allowing highly accurate comparisons between calibrated and theoretical spectra.

Optical rotations were recorded on a Perkin Elmer 241 MC Polarimeter in a 10 cm path length cell in HPLC grade $CHCl_3$ (concentration in g/100 mL).

Commercial grade reagents and solvents were purchased from *Acros Organics*, *Alfa Aesar*, *Fluorochem*, *Sigma-Aldrich*, *BLD Pharm*, and *TCI Chemicals*, and used as received without further purification, unless reagents containing radical inhibitors which were distilled before use. DCM, MeCN, PhMe and THF were purified by passing through a Pure SolvTM column drying system from Innovative Technology, Inc.

Analytical TLC was performed using pre-coated aluminum-backed plates (Merck TLC Silicagel 60 F254) and visualized by ultraviolet irradiation. Stain solutions are indicated in each case if employed, using heat as developing agent. Chromatographic purification of products was accomplished by flash chromatography using silica gel (Merck Geduran® Si 60). Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous material, unless otherwise stated.

1.1 Reactor configuration

-Flow setup

All continuous-flow experiments were carried out using a commercially available Vapourtec E-series device equipped with a UV-150 photoreactor (**Figure S1A**) including a 5 mL perfluoroalcoxy (PFA) reactor coil (inner diameter: 1.6 mm, external diameter 3.0 mm) and a lamp LED (60W, 420 nm).

When using both Vapourtec pumps A and B, a polyether ether ketone (PEEK) T-mixer (**Figure S1B**) and a second 8 mL reactor coil (inner diameter: 1.6 mm, external diameter 3.0 mm) were included into the *flow setup*.

Continuous extraction operations were performed with a Zaiput Flow Technologies Liquid-Liquid Separator (SEP-10) using an OB-900 Hydrophobic PTFE membrane (**Figure S1C**).

A

B **C**

Figure S1. A) Vapourtec 420 nm LED setup; B) T-mixer; C) Liquid-Liquid Separator (SEP-10)

-Batch setup

A custom-made photoreactor setup was used for the photocatalytic batch reactions. The vial is placed inside the fitted well in which irradiation takes place at the desired wavelengths (420 nm was employed during this project) using 380 mW single LEDs. Reaction temperature is easily controlled (operative range: -10-60 °C) using a recirculating system.

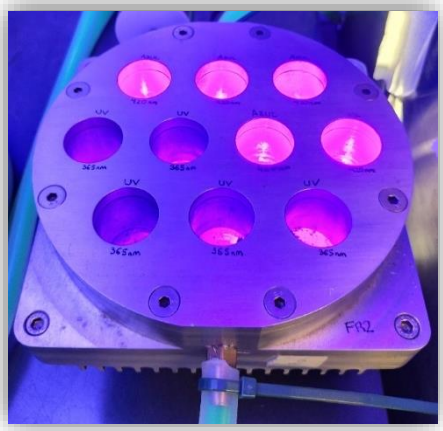
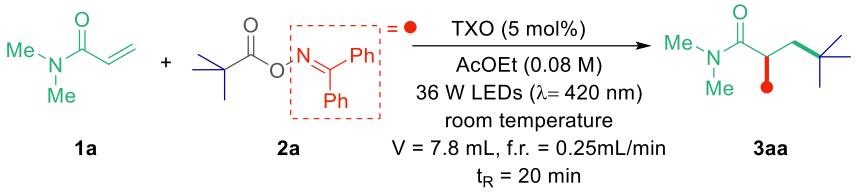


Figure S2. Photochemical batch setup

2. Optimization studies

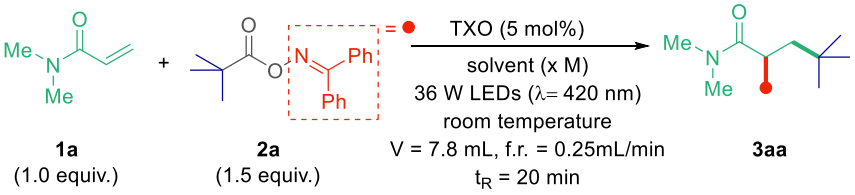
Table S1. Optimization of the reagents proportion



N,N-dimehtylacrylamide 1a (equiv.)	Oxime ester 2a (equiv.)	Yield (%)
2	1	51
1	1	70
1	**1.5**	75
1	2	75

Yield was calculated of the ^{1}H NMR of the crude mixture, using 1,3,5-trimethoxy benzene as I. S.

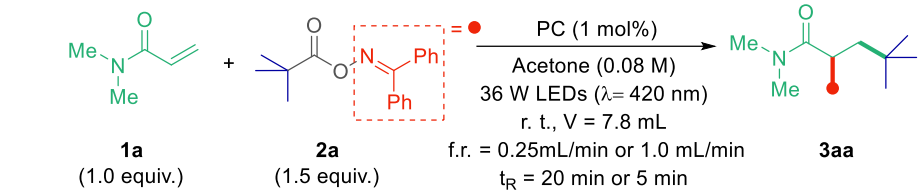
Table S2. Solvent and concentration screening

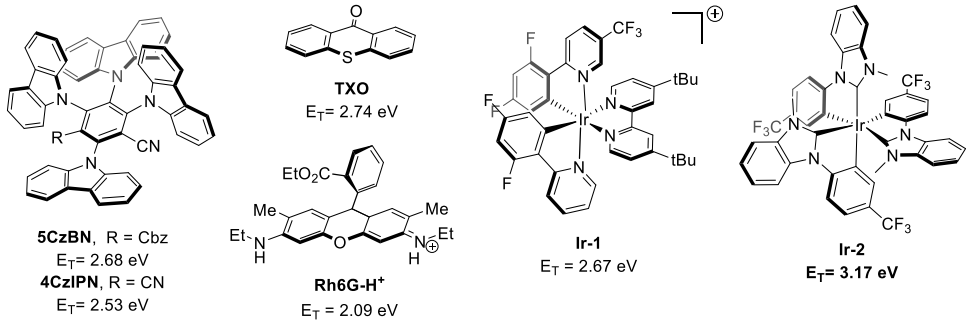


Solvent	Concentration (M)	Yield (%)
AcOEt	0.08	75
AcO*i*Pr	0.08	77
Acetone	**0.08**	**79**
Acetone:H_2O 2:1	0.08	<5
ACN	0.08	63
*i*PrOH	0.08	60
Acetone	0.17	68
Acetone	0.04	79

Yield was calculated of the ^{1}H NMR of the crude mixture, using 1,3,5-trimethoxy benzene as I. S.

Table S3. Optimization of the photosensitizer

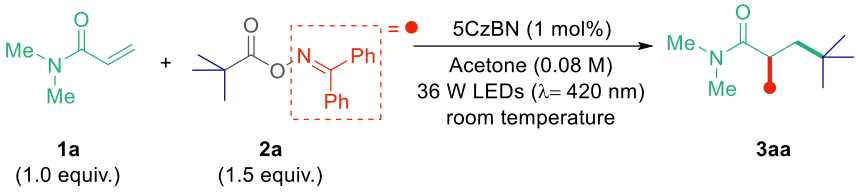




Photosensitizer	f.r. (mL/min)	t_R (min)	Yield (%)
5CzBN (1 mol%)	0.25	20	88
	1.0	**5**	**90**
4CzIPN (1 mol%)	0.25	20	75
	1.0	5	74
TXO (5 mol%)	0.25	20	79
	1.0	5	80
Rh6G-H^+ (1 mol%)	0.25	20	<5
	1.0	5	<5
Ir-1 (1 mol%)	0.25	20	88
	1.0	5	88
Ir-2 (1 mol%)	0.25	20	84
	1.0	5	85

Yield was calculated of the ^{1}H NMR of the crude mixture, using 1,3,5-trimethoxy benzene as I. S.

Table S4. Flow *vs* Batch reaction conditions



Flow

f.r.	t_R	Yield
0.12 mL/ min	40 min	85%
0.25 mL/min	20 min	89%
0.5 mL/min	10 min	90%
1.0 mL/min	**5 min**	**90%**
2.5 mL/min	2 min	42%

vs

Batch

t	Yield
20 h	49%
4 h	52%
5 min	<10%

Yield was calculated of the ^{1}H NMR of the crude mixture, using 1,3,5-trimethoxy benzene as I. S.

Table 5. Limitations

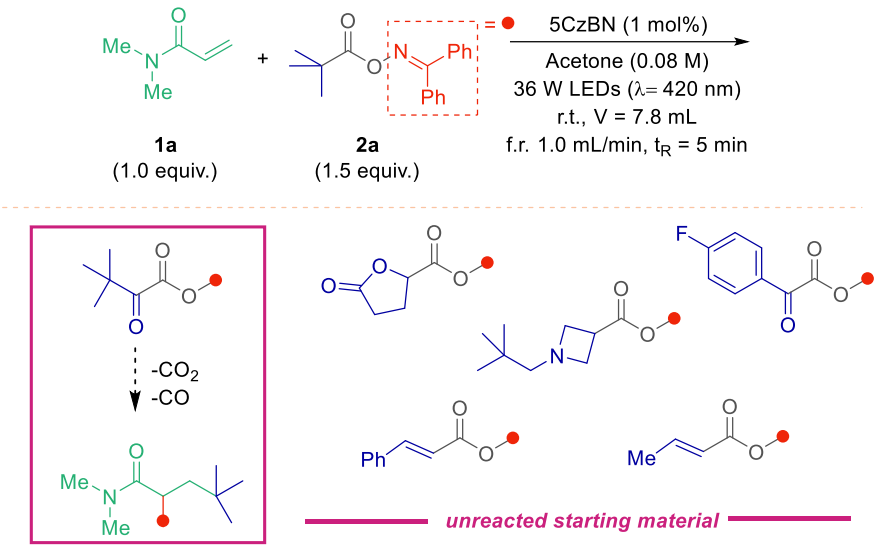
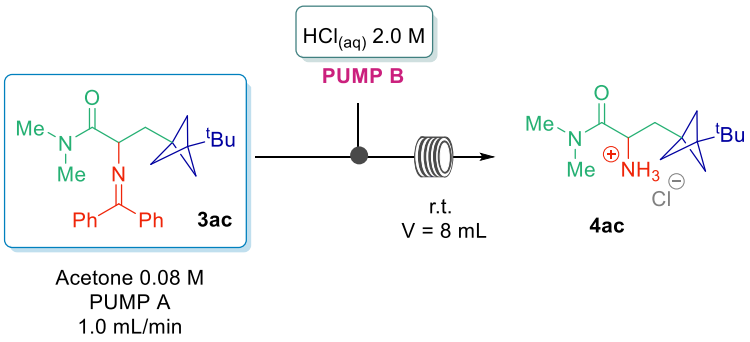
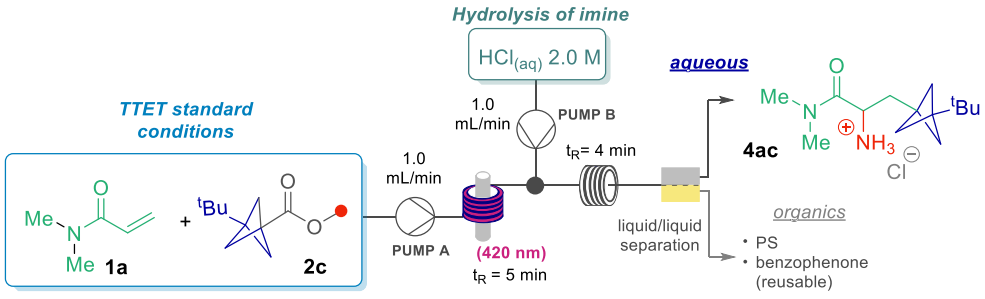


Table 6. Hydrolysis optimization



PUMP B f.r. (mL/min)	Total f.r. (mL/min)	t_R (min)	Yield 4ac (%)
0.25	1.25	6	85
0.5	1.5	5	85
1.0	**2.0**	**4**	**85**

Isolated yield.

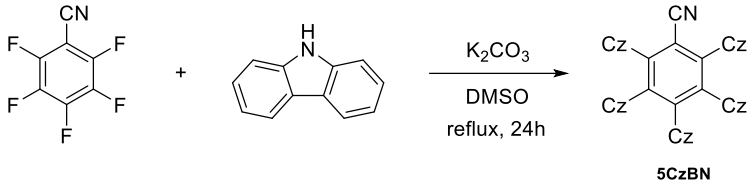


Once selected the best reaction conditions for the hydrolysis of **3ac**, the "one-operation" synthesis of **4ac** was tested starting from **1a** and **2c**. Since one of our principal goals was the design of a

fully automated assembly for the synthesis of **4ac**, a Zaiput liquid-liquid separator was installed aiming to separate the final aqueous and organic phases. However, when following the standard conditions, we observed some miscibility issues (acetone/water) which forbad a proper extraction. To solve this, it was necessary to replace acetone for AcOiPr (see **Table S2**), allowing an efficient isolation of both phases. The desired product **4ac** was isolated in pure form with 85% yield after water evaporation, without any further purification step.

3. Synthesis of photocatalyst 5CzBN

The photocatalyst 5CzBN was prepared following a known procedure.[1]



Scheme S1

In a 100 mL oven dried 3-neck round-bottom flask equipped with a magnetic bar, a mixture of carbazole (5.5 equiv., 10.0 mmol, 1.7 g), K_2CO_3 (19.0 equiv., 34.2 mmol, 4.7 g) and DMSO (15.0 mL) was bubbled with N_2 for 10 minutes. Then, pentafluorobenzonitrile (1.0 equiv., 1.8 mmol, 348 mg) was added and the reaction was heated at reflux and stirred for 24 hours under N_2 atmosphere. After cooled to room temperature, the reaction mixture was poured into 30.0 mL of water and the precipitate was collected by filtration and dried *in vacuo*. The solid was purified by refluxing in acetone/ethanol 1:1 for 24 hours, followed by filtration, obtaining the desired **5CzBN** as a yellow solid (987 mg, 59 % yield).

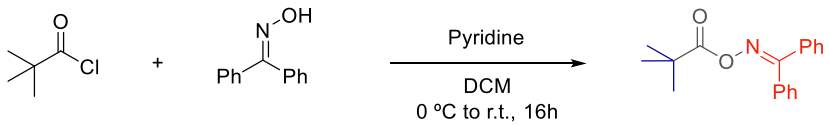
^{1}H NMR (300 MHz, DMSO) δ 7.91 – 7.79 (m, 8H), 7.77 – 7.68 (m, 6H), 7.38 (d, *J* = 7.9 Hz, 4H), 7.33 (d, *J* = 7.9 Hz, 2H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.81 – 6.53 (m, 10H).

4. Synthesis of oxime esters 2

The benzophenone oxime was prepared following a known procedure.[2]

The oxime esters **2b-h** were prepared modifying general procedures described in the literature.[3]

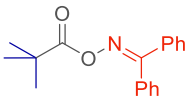
4.1 Synthesis of oxime ester 2a



Scheme S2

In a 50 mL round bottom flask equipped with a magnetic stirring bar, diphenylmethanone oxime (1.0 equiv., 10.0 mmol, 2.0 g), DCM (40.0 mL) and pyridine (2.1 equiv., 21.0 mmol, 1.7 mL) were added and cooled at 0 ºC. Pivaloyl chloride (2.0 equiv., 20.0 mmol, 2.5 mL) was added dropwise and the resulting solution was stirred at room temperature for 16 hours. Then, the mixture was diluted with water and the organic phase was washed twice with water and brine, dried over anhydrous Mg_2SO_4, filtered and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt 95:5) to obtain the desired product **2a** as a white solid (705 mg, 89% yield).

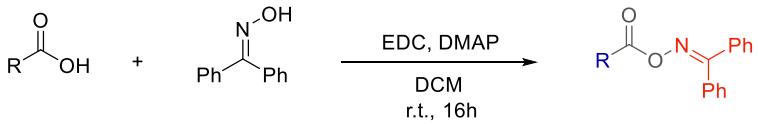
Spectroscopic data are in accordance with those reported in the literature.[3]



diphenylmethanone *O*-pivaloyl oxime (2a)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 – 7.59 (m, 1H), 7.52 – 7.41 (m, 2H), 7.40 – 7.28 (m, 2H), 1.09 (s, 5H).

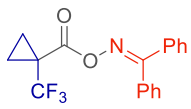
4.2 General procedure for the synthesis of oxime esters 2b, 2d-2h, 2q-2s



Scheme S3

In a 50 mL round bottom flask equipped with a stirring bar, the corresponding carboxylic acid (1.0 equiv., 2.0 mmol) and benzophenone oxime (1.0 equiv., 2.0 mmol) were dissolved in DCM (20.0 mL). Then, 4-dimethylaminopyridine (DMAP, 0.1 equiv., 0.2 mmol) and *N*-(3-Dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (EDC, 5.0 mmol, 2.5 equiv.) were added, and the resulting solution was stirred at room temperature for 16 hours. The mixture was diluted with water, then, the organic layer was washed twice with water and brine, dried over anhydrous Mg_2SO_4, filtered and concentrated *in vacuo*.

Note: these crude mixtures can be purified by consecutive pentane washing/sonication operations (3x10 mL for 10 mmol scale). The obtained product can be used like that for the photocatalyzed transformation without great yield diminishing. However, in order to meet the ^{1}H and ^{13}C NMR quality standards for publication, chromatographic purifications were conducted during these investigations for the isolation of products **2**.



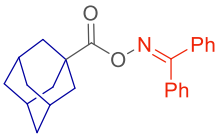
diphenylmethanone *O*-(1-(trifluoromethyl)cyclopropane-1-carbonyl) oxime (2b)

Prepared according to the general procedure **4.2** using 1-(trifluoromethyl)cyclopropane-1-carboxylic acid (2.0 mmol, 308 mg). The crude mixture was purified by flash column chromatography (Cyclohexane: AcOEt gradient from 95:5 to 85:15) to obtain the product **2b** as a white solid (327 mg, 49% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 – 7.60 (m, 2H), 7.52 – 7.44 (m, 4H), 7.43 – 7.30 (m, 4H), 1.43 – 1.37 (m, 2H), 1.35 – 1.28 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 165.7, 134.1, 132.2, 131.2, 129.6, 129.0, 128.4, 128.4, 128.1, 123.9 (q, *J* = 272.9 Hz), 26.0 (q, *J* = 35.0 Hz), 13.4 (q, *J* = 1.7 Hz).

HRMS (ESI) [M + H^+] calcd for $C_{18}H_{15}F_3NO_2^+$ 334.1049, found 334.1043.



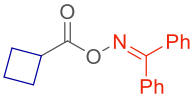
diphenylmethanone *O*-((1r,3R,5S)-adamantane-1-carbonyl) oxime (2d)

Prepared according to the general procedure **4.2** using adamantane-1-carboxylic acid (2.0 mmol, 360 mg). The crude mixture was purified by flash column chromatography (Cyclohexane: AcOEt gradient from 95:5 to 88:12) to obtain the product **2d** as a white solid (452 mg, 63% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 – 7.58 (m, 2H), 7.52 – 7.40 (m, 4H), 7.40 – 7.28 (m, 4H), 1.98 – 1.89 (m, 3H), 1.80 – 1.75 (m, 6H), 1.64 (q, *J* = 12.3 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 165.6, 134.7, 132.8, 130.8, 129.4, 129.0, 128.6, 128.3, 128.0, 40.5, 38.5, 36.3, 27.8.

HRMS (ESI) [M + H^+] calcd for $C_{24}H_{26}NO_2^+$ 360.1958, found 360.1963.



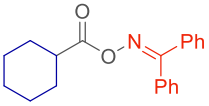
diphenylmethanone *O*-cyclobutanecarbonyl oxime (2e)

Prepared according to the general procedure **4.2** using cyclobutanecarboxylic acid (2.0 mmol, 200 mg). The crude mixture was purified by flash column chromatography (Cyclohexane: AcOEt gradient from 95:5 to 80:20) to obtain the product **2e** as a white solid (542 mg, 81% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 – 7.56 (m, 2H), 7.51 – 7.42 (m, 4H), 7.40 – 7.28 (m, 4H), 3.17 (p, *J* = 8.5 Hz, 1H), 2.42 – 2.05 (m, 4H), 2.05 – 1.78 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 165.0, 134.8, 132.6, 130.8, 129.5, 129.0, 128.7, 128.3, 128.1, 36.9, 25.1, 18.5.

HRMS (ESI) [M + H^+] calcd for $C_{18}H_{18}NO_2^+$ 280.1332, found 280.1339.



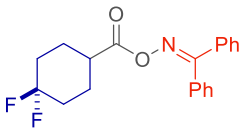
diphenylmethanone *O*-cyclohexanecarbonyl oxime (2f)

Prepared according to the general procedure **4.2** using cyclohexanecarboxylic acid (2.0 mmol, 252 mg). The crude mixture was purified by flash column chromatography (Cyclohexane: AcOEt gradient from 95:5 to 80:20) to obtain the product **2f** as a white solid (502 mg, 82% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 – 7.63 (m, 2H), 7.54 – 7.43 (m, 4H), 7.42 – 7.32 (m, 4H), 2.37 (tt, *J* = 11.0, 3.6 Hz, 1H), 1.89 – 1.84 (m, 2H), 1.79 – 1.60 (m, 3H), 1.55 – 1.38 (m, 2H), 1.28 – 1.23 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 164.8, 134.4, 132.3, 130.4, 129.1, 128.5, 128.2, 127.9, 127.7, 41.5, 28.2, 25.2, 24.8.

HRMS (ESI) [M + H^+] calcd for $C_{20}H_{22}NO_2^+$ 308.1645, found 308.1653.



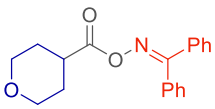
diphenylmethanone *O*-(4,4-difluorocyclohexanecarbonyl) oxime (2g)

Prepared according to the general procedure **4.2** using 4,4-difluorocyclohexanecarboxylic acid (2.0 mmol, 328 mg). The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 95:5 to 92:8) to obtain the product **2g** as a white solid (516 mg, 75% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 – 7.57 (m, 2H), 7.51 – 7.40 (m, 4H), 7.39 – 7.27 (m, 4H), 2.48 – 2.37 (m, 1H), 2.07 – 1.59 (m, 8H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 165.6, 134.1, 132.3, 130.8, 129.4, 128.7, 128.2, 128.1, 128.0, 122.2 (t, *J* = 241.1 Hz), 39.0, 31.9 (t, *J* = 24.5 Hz), 24.4 (t, *J* = 5.0 Hz).

HRMS (ESI) [M + H^+] calcd for $C_{20}H_{20}F_2NO_2^+$ 344.1457, found 344.1452.



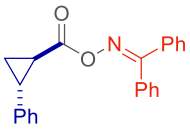
diphenylmethanone *O*-tetrahydro-2H-pyran-4-carbonyl oxime (2h)

Prepared according to the general procedure **4.2** using tetrahydro-2*H*-pyran-4-carboxylic acid (2.0 mmol, 260 mg). The crude mixture was purified by flash column chromatography (Cyclohexane: AcOEt gradient from 95:5 to 80:20) to obtain the product **2h** as a white solid (421 mg, 68% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 – 7.55 (m, 2H), 7.49 – 7.38 (m, 4H), 7.36 – 7.25 (m, 4H), 3.86 (t, *J* = 3.7 Hz, 1H), 3.82 (t, *J* = 3.7 Hz, 1H), 3.40 – 3.25 (m, 2H), 2.67 – 2.41 (m, 1H), 1.76 – 1.60 (m, *J* = 6.2, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 165.4, 134.2, 132.3, 130.7, 129.3, 128.7, 128.2, 128.1, 127.9, 66.5, 38.7, 28.0.

HRMS (ESI) [M + H^+] calcd for $C_{19}H_{20}NO_3^+$ 310.1438, found 310.1447.



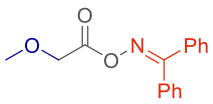
diphenylmethanone *O*-((1R,2R)-2-phenylcyclopropane-1-carbonyl) oxime (2i)

Prepared according to the general procedure **4.2** using (1*S*,2*S*)-2-phenylcyclopropane-1-carboxylic acid (2.0 mmol, 324 mg). The crude mixture was purified by flash column chromatography (Cyclohexane: AcOEt gradient from 95:5 to 80:20) to obtain the product **2i** as a white solid (512 mg, 75% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.1 Hz, 2H), 7.57 – 7.34 (m, *J* = 14.5, 6.5, 3.4 Hz, 8H), 7.32 – 7.18 (m, 3H), 7.08 (d, *J* = 7.1 Hz, 2H), 2.60 (ddd, *J* = 9.3, 6.6, 4.2 Hz, 1H), 1.92 – 1.82 (m, 1H), 1.66 (dt, *J* = 9.3, 4.2 Hz, 1H), 1.38 (ddd, *J* = 9.3, 6.6, 4.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 164.7, 139.6, 134.7, 132.6, 130.8, 129.5, 129.0, 128.7, 128.4, 128.3, 128.2, 126.6, 126.2, 26.7, 22.7, 17.1.

HRMS (ESI) [M + H^+] calcd for $C_{23}H_{20}NO_2^+$ 342.1489, found 342.1492.



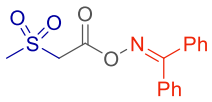
diphenylmethanone *O*-(2-methoxyacetyl) oxime (2j)

Prepared according to the general procedure **4.2** using methoxyacetic acid (2.0 mmol, 154 µL). The crude mixture was purified by flash column chromatography (Cyclohexane: AcOEt gradient from 90:10 to 80:20) to obtain the product **2j** as a white solid (374 mg, 70% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 – 7.54 (m, 2H), 7.47 – 7.41 (m, 4H), 7.39 – 7.26 (m, 4H), 4.12 (s, 2H), 3.38 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 165.3, 134.2, 131.9, 130.9, 129.6, 128.8, 128.5, 128.2, 128.0, 68.7, 59.2.

HRMS (ESI) [M + H^+] calcd for $C_{16}H_{16}NO_3^+$ 270.1125, found 270.1128.



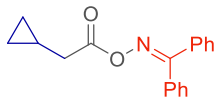
diphenylmethanone *O*-(2-(methylsulfonyl)acetyl) oxime (2k)

Prepared according to the general procedure **4.2** using methanesulfonylacetic acid (2.0 mmol, 276 mg). The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 95:5 to 80:20) to obtain the product **2k** as a white solid (258 mg, 41% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.53 – 7.44 (m, 4H), 7.44 – 7.30 (m, 4H), 4.01 (s, 2H), 2.98 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 160.7, 133.8, 131.8, 131.4, 130.0, 129.1, 128.7, 128.5, 128.4, 58.0, 41.5.

HRMS (ESI) [M + H^+] calcd for $C_{16}H_{16}NO_4S^+$ 318.0795, found 318.0792.



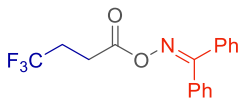
diphenylmethanone *O*-(2-cyclopropylacetyl) oxime (2l)

Prepared according to the general procedure **4.2** using 2-cyclopropylacetic acid (2.0 mmol, 186 µL). The crude mixture was purified by flash column chromatography (Cyclohexane: AcOEt gradient from 90:10 to 80:20) to obtain the product **2l** as a white solid (446 mg, 80% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 7.0, 1.6 Hz, 2H), 7.49 – 7.41 (m, 4H), 7.39 – 7.30 (m, 4H), 2.26 – 2.20 (m, 2H), 0.96 (m, 1H), 0.53 – 0.38 (m, 2H), 0.11 – 0.04 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 165.0, 134.7, 132.7, 130.9, 129.5, 129.0, 128.7, 128.3, 128.1, 38.3, 6.7, 4.5.

HRMS (ESI) [M + H^+] calcd for $C_{18}H_{18}NO_2^+$ 280.1332, found 280.2345.



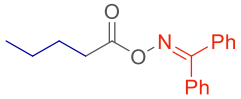
diphenylmethanone *O*-(4,4,4-trifluorobutanoyl) oxime (2m)

Prepared according to the general procedure **4.2** using 4,4,4-trifluorobutanoic acid (2.0 mmol, 284 mg). The crude mixture was purified by flash column chromatography (Cyclohexane: AcOEt gradient from 95:5 to 80:20) to obtain the product **2m** as a white solid (508 mg, 79% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 – 7.63 (m, 2H), 7.56 – 7.48 (m, 4H), 7.46 – 7.35 (m, 4H), 2.72 – 2.63 (m, 2H), 2.59 – 2.41 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 165.1, 134.2, 132.0, 130.8, 129.5, 128.7, 128.4, 128.2, 128.0, ^{13}C NMR (75 MHz, $CDCl_3$) δ 126.1 (q, *J* = 276.1 Hz), 28.7 (q, *J* = 30.1 Hz), 25.6 (q, *J* = 3.2 Hz).

HRMS (ESI) [M + H^+] calcd for $C_{17}H_{15}F_3NO_2^+$ 322.1049, found 322.1055.



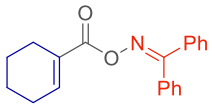
diphenylmethanone *O*-pentanoyl oxime (2n)

Prepared according to the general procedure **4.2** using pentanoic acid (2.0 mmol, 218 µL). The crude mixture was purified by flash column chromatography (Cyclohexane: AcOEt gradient from 95:5 to 90:10) to obtain the product **2n** as a white solid (503 mg, 90% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.48 (m, 2H), 7.39 – 7.31 (m, 4H), 7.27 – 7.16 (m, 4H), 2.22 (t, *J* = 7.4 Hz, 1H), 1.58 – 1.39 (m, 2H), 1.30 – 1.10 (m, 2H), 0.77 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 164.2, 134.3, 132.1, 130.3, 129.0, 128.4, 128.2, 127.9, 127.7, 32.1, 26.2, 21.6, 13.1.

HRMS (ESI) [M + H^+] calcd for $C_{18}H_{20}NO_2^+$ 282.1489, found 282.1491.



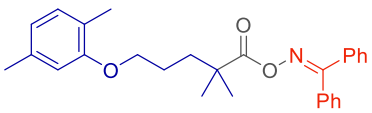
diphenylmethanone *O*-cyclohex-1-ene-1-carbonyl oxime (2q)

Prepared according to the general procedure **4.2** using cyclohex-1-ene-1-carboxylic acid (2.0 mmol, 252 mg). The crude mixture was purified by flash column chromatography (Cyclohexane: AcOEt gradient from 95:5 to 80:20) to obtain the product **2q** as a white solid (476 mg, 78% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 – 7.60 (m, 2H), 7.50 – 7.40 (m, 4H), 7.40 – 7.30 (m, 4H), 6.77 (m, 1H), 2.15 – 2.07 (m, 4H), 1.67 – 1.46 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 164.6, 141.0, 134.8, 132.9, 130.7, 129.4, 129.0, 128.9, 128.7, 128.3, 25.8, 23.8, 21.9, 21.2.

HRMS (ESI) [M + H^+] calcd for $C_{20}H_{20}NO_2^+$ 306.1489, found 306.1496.



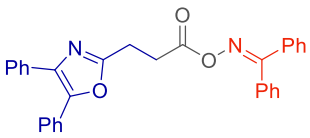
diphenylmethanone *O*-(5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoyl) oxime (2r)

Prepared according to the general procedure **4.2** using Gemfibrozil (2.0 mmol, 501 mg). The crude mixture was purified by flash column chromatography (Cyclohexane: AcOEt gradient from 95:5 to 80:20) to obtain the product **2r** as a white solid (507 mg, 59% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 – 7.54 (m, 2H), 7.42 – 7.37 (m, 4H), 7.36 – 7.28 (m, 2H), 7.25 – 7.22 (m, 2H), 6.95 (d, *J* = 7.5 Hz, 1H), 6.60 (d, *J* = 7.5 Hz, 1H), 6.53 (s, 1H), 3.73 (t, *J* = 6.0 Hz, 2H), 2.26 (s, 3H), 2.10 (s, 3H), 1.67 – 1.47 (m, 4H), 1.07 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 165.6, 156.8, 136.3, 134.4, 132.8, 130.8, 130.1, 129.3, 128.8, 128.3, 128.3, 128.1, 123.4, 120.6, 111.8, 67.7, 41.8, 36.9, 24.9, 24.9, 21.3, 15.6.

HRMS (ESI) [M + H^+] calcd for $C_{28}H_{32}NO_3^+$ 430.2377, found 430.2389.



diphenylmethanone *O*-(3-(4,5-diphenyloxazol-2-yl)propanoyl) oxime (2s)

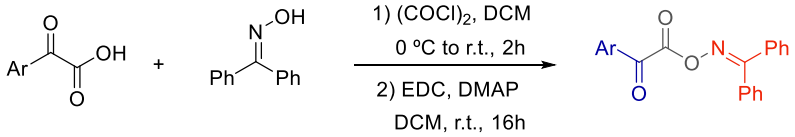
Prepared according to the general procedure **4.2** using Oxaprozin (2.0 mmol, 587 mg). The crude mixture was purified by flash column chromatography (Cyclohexane: AcOEt gradient from 95:5 to 80:20) to obtain the product **2s** as a white solid (537 mg, 57% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 – 7.54 (m, 6H), 7.48 – 7.27 (m, 14H), 3.18 (t, *J* = 7.5 Hz, 1H), 2.97 (t, *J* = 7.5 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 165.0, 161.3, 145.3, 135.0, 134.5, 132.3, 130.8, 129.5, 128.9, 128.8, 128.6, 128.5, 128.5, 128.4, 128.3, 128.3, 128.1, 128.0, 127.8, 126.3, 29.9, 23.1.

HRMS (ESI) [M + H^+] calcd for $C_{31}H_{25}N_2O_3^+$ 473.1860, found 473.1872.

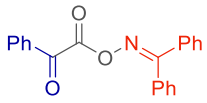
4.3 General procedure for the synthesis of oxime esters 2o and 2p



Scheme S4

In a 50 mL round bottom flask equipped with a magnetic stirring bar, the corresponding carboxylic acid (1.0 equiv., 4.0 mmol) was dissolved in DCM (20.0 mL) and the reaction mixture was cooled at 0 °C. A drop of DMF and oxalyl chloride (1.3 equiv., 5.2 mmol) were added dropwise and the resulting mixture was stirred for 2 hours under N_2. After removal of oxalyl chloride under reduced pressure, DCM, (20.0 mL) and DMAP (0.1 equiv., 0.4 mmol) and EDC (2.5 equiv., 10.0 mmol) were added, and the resulting reaction mixture was stirred at room

temperature for 16 hours. The mixture was diluted with water, then, the organic layer was washed twice with water and brine, dried over anhydrous Mg_2SO_4, filtered and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography to obtain the desired product **2**.



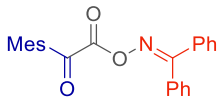
1-(((diphenylmethylene)amino)oxy)-2-phenylethane-1,2-dione (2o)

Prepared according to the general procedure **4.3** using phenylglyoxylic acid (4.0 mmol, 600 mg). The crude mixture was purified by flash column chromatography (Cyclohexane: AcOEt gradient from 95:5 to 90:10) to obtain the product **2o** as a white solid (1.11 g, 85% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 8.3, 1.0 Hz, 2H), 7.61 – 7.42 (m, 9H), 7.41 – 7.36 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 185.9, 166.6, 163.4, 134.9, 133.9, 132.4, 131.3, 130.1, 130.0, 129.7, 129.1, 128.9, 128.9, 128.4, 128.3.

HRMS (ESI) [M + H^+] calcd for $C_{21}H_{16}NO_3^+$ 330.1125, found 330.1129.



1-(((diphenylmethylene)amino)oxy)-2-mesitylethane-1,2-dione (2p)

Prepared according to the general procedure **4.3** using mesitylglyoxylic acid (4.0 mmol, 769 mg). The crude mixture was purified by flash column chromatography (Cyclohexane: AcOEt gradient from 95:5 to 92:8) to obtain the product **2p** as a white solid (1.07 g, 72% yield).

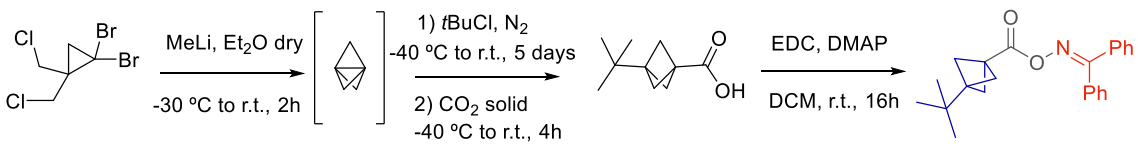
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 – 7.63 (m, 2H), 7.56 – 7.34 (m, 4H), 7.28 – 7.18 (m, 4H), 6.86 (bs, 2H), 2.36 (s, 3H), 2.22 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 190.5, 167.2, 159.6, 140.6, 135.7, 133.6, 132.8, 131.3, 131.2, 129.5, 128.9, 128.7, 128.3, 128.2, 127.8, 20.9, 19.2.

HRMS (ESI) [M + H^+] calcd for $C_{24}H_{22}NO_3^+$ 372.1594, found 372.1590.

4.4 Synthesis of oxime ester 2c

The oxime ester **2c** was prepared modifying a general procedure described in the literature.[4]

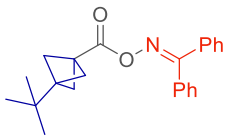


Scheme S5

MeLi (2.0 equiv., 67.6 mmol, 56 mL of a 1.2 M solution in diethyl ether) was added dropwise to a solution of 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane (1.0 equiv., 38.0 mmol, 10.0 g) in diethyl ether (38.0 mL, freshly distilled over sodium) at -30°C under stirring. This temperature

was kept for 15 additional minutes and further warmed to room temperature. The formation of a white precipitate indicated completion of the reaction (usually 1.5 h). The solvent and the volatile products were distilled from a 20°C bath into a three-neck RBF (Note 1: to have an effective distillation, the condenser liquid must be at 5°C or below) which was kept at -78°C under inert atmosphere. To the obtained clear solution, *tert*-butylmagnesium chloride (12.0 mL of 2.0 M solution in diethyl ether) was added dropwise at -40°C (dry ice/acetonitrile bath). The reaction was stirred for 5 days at room temperature under inert atmosphere. The resulting white suspension was bubbled with CO_2 (from dry ice, dried with calcium chloride. Note 2: try to use new dry ice for better yielding. Note 3: be careful with overpressure in the system) for 2.5 h at -40°C and 1 h at room temperature. Further, the resulting mixture was cooled to 0°C. Aqueous HCl (25.0 mL, 2.0 M) was added at this temperature. The organic phase was separated, and the aqueous layer was extracted with diethyl ether. Drying the combined organic layers with magnesium sulfate and evaporation of the solvent afforded carboxylic acid **2c'** as colorless needles. The product was used without further purification for next step.

The corresponding oxime ester **2c** was achieved as a white solid following the general procedure 4.2 (5.6 g, 42% overall yield).



diphenylmethanone *O*-(3-(tert-butyl)bicyclo[1.1.1]pentane-1-carbonyl) oxime (2c)

^{1}H NMR (300 MHz, CD_3CN) δ 7.69 – 7.59 (m, 2H), 7.53 – 7.43 (m, 4H), 7.42 – 7.32 (m, 4H), 1.81 (s, 6H), 0.85 (s, 9H).

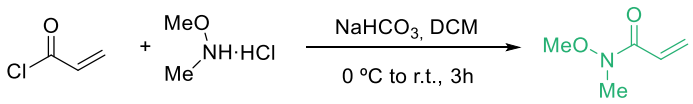
^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 165.2, 134.5, 132.2, 130.6, 129.4, 128.8, 128.7, 128.1, 127.7, 48.5, 47.9, 34.2, 29.1, 25.5.

HRMS (ESI) [M + H^+] calcd for $C_{23}H_{26}NO_2^+$ 348.1958, found 348.1961.

5. Synthesis of acrylamide derivatives 1

The Michael acceptors **1** were prepared modifying general procedures described in the literature.[5]

5.1 Synthesis of 1c

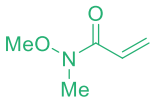


Scheme S6

To a solution of *N*,*O*-dimethylhydroxyamine hydrochloride (1.2 equiv., 11.9 mmol, 1.2 g) and $NaHCO_3$ (2.5 equiv., 24.8 mmol, 2.1 g) in DCM (8.0 mL) was added acryloyl chloride (1.0 equiv., 9.9 mmol, 0.8 mL) at 0 °C, and the mixture was stirred at room temperature for 3 h. The reaction

was quenched with 1 M aqueous HCl (10 mL) and extracted with Et_2O (3 x 10 mL). The organic layers were combined, dried over anhydrous Mg_2SO_4, filtered, and concentrated *in vacuo.*
and extracted with Et_2O (3 × 10 mL). The organic layer was combined, dried over Na_2SO4, and concentrated under reduced pressure. The residue was purified by Kugelrohr distillation (15 Torr, 70 °C) to give **1c** as a colorless oil (1.1 g, 95% yield).

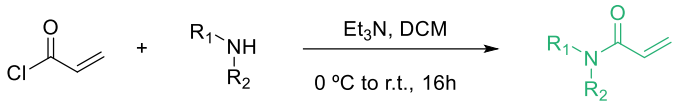
Spectroscopic data are in accordance with those reported in the literature.[6]



***N*-methoxy-*N*-methylacrylamide (1c)**

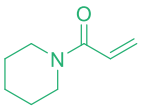
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74 (dd, *J* = 17.0, 10.4 Hz, 1H), 6.43 (dd, *J* = 17.0, 2.0 Hz, 1H), 5.76 (dd, *J* = 10.4, 2.0 Hz, 1H), 3.71 (s, 3H), 3.27 (s, 3H).

5.2 General procedure for the synthesis of 1d-1g



Scheme S7

In a 20 mL round bottom flask equipped with a magnetic stirring bar, the desired amine (1.0 equiv., 2.0 mmol) and Et_3N (1.2 equiv., 2.4 mmol) were dissolved in DCM (4.0 mL). At 0 ºC, acryloyl chloride (1.2 equiv., 2.4 mmol) was added dropwise and the reaction solution was stirred at room temperature for 16 hours. Then, the mixture was treated with aqueous $NaHCO_3$ (5.0 mL) and extracted with DCM (3 x 5 mL). The organic layer was washed with brine, dried over anhydrous Mg_2SO_4, filtered, and concentrated in vacuo to obtain the product **1** without any further purification, unless otherwise specified.

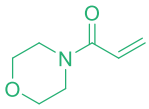


1-(piperidin-1-yl)prop-2-en-1-one (1d)

Prepared according to the general procedure **5.2** using piperidine (2.0 mmol, 198 µL) as amine. The desired compound **1d** (173 mg, 63% yield) was obtained as a colourless oil after purification by flash column chromatography (Cyclohexane: AcOEt gradient from 80:20 to 60:40).

Spectroscopic data are in accordance with those reported in the literature.[5b]

^{1}H NMR (300 MHz, $CDCl_3$-NEW) δ 6.53 (dd, *J* = 16.8, 10.6 Hz, 1H), 6.18 (dd, *J* = 16.8, 2.0 Hz, 1H), 5.59 (dd, *J* = 10.6, 2.0 Hz, 1H), 3.60 – 3.33 (m, 4H), 1.68 – 1.44 (m, 6H).



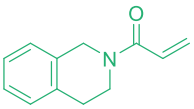
1-morpholinoprop-2-en-1-one (1e)

Prepared according to the general procedure **5.2** using morpholine (2.0 mmol, 173 µL) as amine. The desired compound **1e** (244 mg, 86% yield) was obtained as a

colourless oil after purification by flash column chromatography (Cyclohexane: AcOEt gradient from 80:20 to 60:40).

Spectroscopic data are in accordance with those reported in the literature.[5b]

^{1}H NMR (300 MHz, $CDCl_3$-NEW) δ 6.50 (dd, *J* = 16.8, 10.4 Hz, 1H), 6.27 (dd, *J* = 16.8, 2.0 Hz, 1H), 5.68 (dd, *J* = 10.4, 2.0 Hz, 1H), 3.71 – 3.40 (m, 8H).



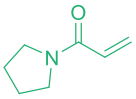
1-(3,4-dihydroisoquinolin-2(1*H*)-yl)prop-2-en-1-one (1f)

Prepared according to the general procedure **5.2** using 1,2,3,4-tetrahydroisoquinoline (2.0 mmol, 251 µL) as amine. The desired compound **1f** (236 mg, 63% yield) was obtained as a colourless oil after purification by flash column chromatography (Cyclohexane: AcOEt gradient from 80:20 to 60:40).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 – 7.07 (m, 4H), 6.66 (m, 1H), 6.34 (dd, *J* = 16.8, 1.8 Hz, 1H), 5.73 (dd, *J* = 10.5, 1.8 Hz, 1H), 4.76 (d, *J* = 21.0 Hz, 2H), 3.89 (t, *J* = 5.9 Hz, 1H), 3.78 (t, *J* = 5.9 Hz, 1H), 2.91 (dd, *J* = 12.4, 5.9 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 136.2, 133.0, 129.3, 128.3, 128.0, 127.6, 127.5, 126.3, 44.2, 43.2, 29.2.

HRMS (ESI) [M + H^+] calcd for $C_{12}H_{14}NO^+$ 188.1070, found 188.1078.



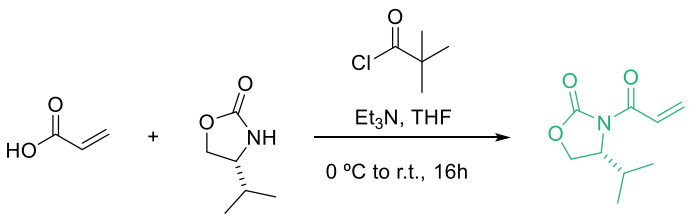
1-(pyrrolidin-1-yl)prop-2-en-1-one (1g)

Prepared according to the general procedure **5.2** using pyrrolidine (2.0 mmol, 166 µL) as amine. The desired compound **1g**, a yellow oil, was obtained in pure form without any further purification (250 mg, 98 % yield).

Spectroscopic data are in accordance with those reported in the literature.[7]

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 (dd, *J* = 16.8, 9.6 Hz, 1H), 6.36 (dd, *J* = 16.8, 2.8 Hz, 1H), 5.65 (dd, *J* = 9.6, 2.8 Hz, 1H), 3.54 (td, *J* = 6.9, 2.9 Hz, 4H), 1.92 (ddd, *J* = 19.1, 13.2, 6.9 Hz, 4H).

5.3 Synthesis of 1l

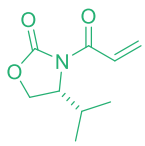


Scheme S8

To a solution of acrylic acid (1.3 equiv., 13.0 mmol, 870 µL) and triethylamine (2.5 equiv., 25.0 mmol, 3.5 mL) in THF (50.0 mL, 0.2 M) maintained at 0 °C, was added pivaloyl chloride (1.2 equiv., 12.0 mmol, 1.5 mL). The mixture was stirred for 1 h. Then lithium chloride (1.1 equiv.,

11.0 mmol, 466 mg) was added followed by (*R*)-4-isopropyl-2-oxazolidone (1.0 equiv., 10.0 mmol, 1.3 g). The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with aqueous ammonium chloride solution and extracted with AcOEt. The combined organic layers were dried with magnesium sulfate and evaporated under reduced pressure. The reaction crude was purified by flash column chromatography (cyclohexane:AcOEt 9:1) to give the desired product **1l** in 58% yield.

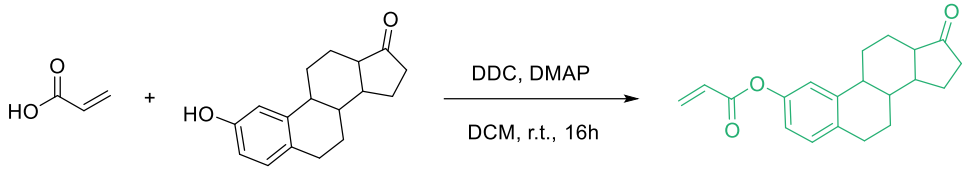
Spectroscopic data are in accordance with those reported in the literature.[8]



(*R*)-3-acryloyl-4-isopropyloxazolidin-2-one (1l)

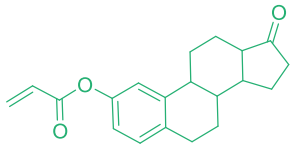
^{1}H NMR (300 MHz, $CDCl_3$-new) δ 7.51 (dd, *J* = 17.0, 10.4 Hz, 1H), 6.53 (dd, *J* = 17.0, 1.7 Hz, 1H), 5.89 (dd, *J* = 10.4, 1.7 Hz, 1H), 4.50 (dt, *J* = 7.5, 3.6 Hz, 1H), 4.29 (dd, *J* = 16.0, 7.5 Hz, 1H), 4.23 (dd, *J* = 9.1, 3.6 Hz, 1H), 2.42 (dtd, *J* = 13.9, 6.9, 3.6 Hz, 1H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H).

5.4 Synthesis of Estrone analogue 1q



Scheme S9

In a 50 mL round bottom flask equipped with a magnetic bar, acrylic acid (1.0 equiv., 2.0 mmol, 137 µL) and estrone (1.0 equiv., 2.0 mmol, 513 mg) were dissolved in DCM (20.0 mL). Then, 4-dimethylaminopyridine (DMAP, 0.1 equiv., 0.2 mmol, 24.4 mg) and *N,N'*-dicyclohexylcarbodiimide (DCC, 1.25 equiv., 1.6 mmol, 330 mg) were added, and the resulting solution was stirred at room temperature for 16 hours. The mixture was diluted with water, then, the organic layer was washed twice with water and brine, dried over anhydrous Mg_2SO_4, filtered and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (Cyclohexane: AcOEt gradient from 95:5 to 80:20) to obtain the desired product **1q** as a white solid (255 mg, 64 % yield).



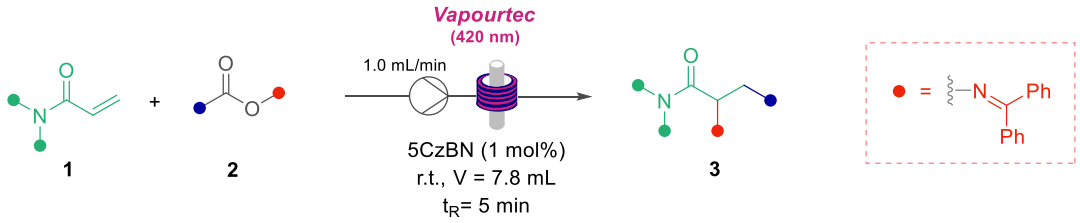
17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-2-yl acrylate (1q)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.4 Hz, 1H), 6.94 – 6.85 (m, 2H), 6.59 (dd, *J* = 17.3, 1.3 Hz, 1H), 6.31 (dd, *J* = 17.3, 10.4 Hz, 1H), 6.00 (dd, *J* = 10.4, 1.3 Hz, 1H), 2.92 (dd, *J* = 8.5, 3.9 Hz, 2H), 2.60 – 1.92 (m, 7H), 1.71 – 1.39 (m, 7H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 223.1, 164.8, 148.5, 138.0, 137.4, 132.4, 128.0, 126.4, 121.5, 118.7, 50.4, 47.9, 44.2, 38.0, 35.8, 31.6, 29.4, 26.3, 25.8, 21.6.

HRMS (ESI) [M + H^+] calcd for $C_{20}H_{23}O_3^+$ 311.1642, found 311.1646.

6. General procedure for the photo-flow synthesis of α-aminocarboxamides 3



Scheme S10

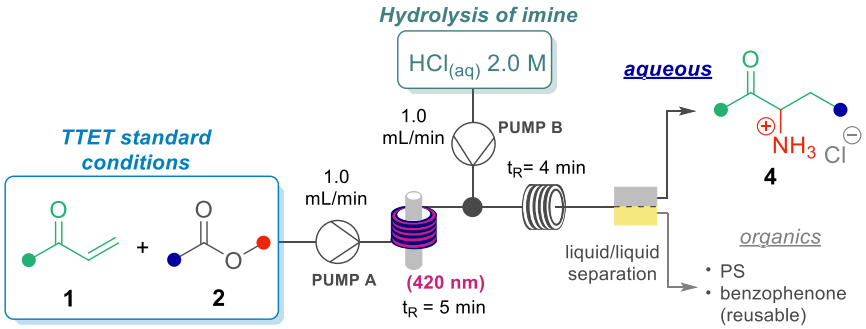
An oven-dried 5 mL glass vial was charged with catalyst 5CzBN (0.001 mmol), the corresponding Michael acceptor **1** (1.0 equiv., 0.1 mmol) and oxime ester **2** (1.5 equiv., 0.15 mmol). Then, 1.2 mL of acetone (0.08 M) were added. The vial was sealed with a PTFE/rubber septum and the reaction mixture was deoxygenated by three freeze-pump-thaw cycles.

Simultaneously, the *Vapourtec* setup was purged with degassed acetone to ensure inert atmosphere conditions. Once the system was conditioned (approximately 5 minutes), the reaction mixture was pumped by pump A with a 1.00 mL/min flow rate (5 min residence time) and collected at the end of the reactor. The solvent was removed under reduced pressure and the crude mixture was purified by flash column chromatography to afford the corresponding product.

Note1: All the products were rapidly prepared in continuous flow line, by carrying out the described procedure above, with a washing purge of degassed acetone (1.0 mL) between the injection of each reaction mixture.

Note2: During the optimization part of the investigation, some tests were carried out under batch conditions (see **Table S4**). Thus, after deoxygenation by three freeze-pump-thaw cycles, the reaction vial was irradiated with 420 nm purple LED using a custom-made photoreactor setup (see **Figure S2**).

7. General procedure for the photo-flow synthesis of α-aminocarboxamides 4



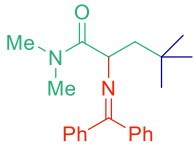
Scheme S11

An oven-dried 5 mL glass vial was charged with catalyst 5CzBN (0.001 mmol), the corresponding Michael acceptor **1** (1.0 equiv., 0.1 mmol) and oxime ester **2** (1.5 equiv., 0.15 mmol). Then, 1.2 mL of AcO*i*Pr (0.08 M) were added. The vial was sealed with a PTFE/rubber septum and the reaction mixture was deoxygenated by three freeze-pump-thaw cycles.

The *Vapourtec* setup was purged with degassed acetone to ensure inert atmosphere conditions. Once the system was conditioned (approximately 5 minutes), the reaction mixture was pumped by pump A with a 1.00 mL/min flow rate (5 min residence time). At the end of the photoreactor, the reaction mixture was fueled by a 2.0 M HCl aqueous solution (1.2 mL), simultaneously pumped (pump B) with a 1.00 mL/min flow rate, with a T mixer and passed through a second reactor coil (4 min residence time) with a total 2.00 mL/min flow rate. A continuous extraction of the crude mixture was performed with the Zaiput liquid-liquid separator, allowing the independent collection of both, organic (containing benzophenone, catalyst, and potential side products) and aqueous phases. After concentration of this latter *in vacuo* at 60 ºC, the desired hydrochloride salt **4** was achieved in pure form, without any additional purification step.

8. Analytical data of products 3 and 4

2-((diphenylmethylene)amino)-*N*,*N*,4,4-tetramethylpentanamide (3aa)



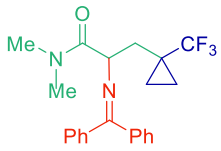
Prepared according to the general procedure **6** starting from *N*,*N*-dimethylacrylamide **1a** and oxime ester **2a**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 60:40) to obtain the product **3aa** as a white solid (30.3 mg, 90% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 8.2, 1.5 Hz, 2H), 7.48 – 7.43 (m, 3H), 7.38 – 7.27 (m, 3H), 7.15 (dd, *J* = 7.5, 1.9 Hz, 2H), 4.38 (dd, *J* = 7.0, 5.3 Hz, 1H), 2.89 (s, 3H), 2.83 (s, 3H), 1.95 (dd, *J* = 14.0, 7.1 Hz, 2H), 1.89 (dd, *J* = 14.0, 5.2 Hz, 1H), 0.82 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 167.9, 139.4, 137.1, 130.0, 128.7, 128.5, 128.4, 127.9, 127.5, 62.3, 47.2, 36.7, 36.0, 30.7, 29.8.

HRMS (ESI) [M + H^+] calcd for $C_{22}H_{29}N_2O^+$ 337.2274, found 337.2271.

2-((diphenylmethylene)amino)-*N*,*N*-dimethyl-3-(1-(trifluoromethyl)cyclopropyl)propenamide (3ab)



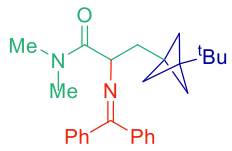
Prepared according to the general procedure **6** starting from *N*,*N*-dimethylacrylamide **1a** and oxime ester **2b**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 30:70) to obtain the product **3ab** as a white solid (29.9 mg, 77% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 8.0, 1.8 Hz, 2H), 7.51 – 7.43 (m, 3H), 7.39 – 7.28 (m, 3H), 7.15 (dd, *J* = 8.0, 1.8 Hz, 2H), 4.64 (dd, *J* = 7.6, 5.8 Hz, 1H), 2.88 (s, 3H), 2.57 (s, 3H), 2.36 (dd, *J* = 14.8, 5.8 Hz, 1H), 2.08 (dd, *J* = 14.8, 7.6 Hz, 1H), 1.02 – 0.93 (m, 1H), 0.92 – 0.81 (m, 2H), 0.77 – 0.68 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 169.7, 139.1, 137.1, 130.3, 128.8, 128.6, 128.6, 128.0, 127.5 (q, *J* = 274.0 Hz), 127.4, 60.5, 36.4, 36.4, 35.9, 20.0 (q, *J* = 32.1 Hz), 9.1 (dd, *J* = 5.1, 2.5 Hz), 8.6 (dd, *J* = 5.1, 2.5 Hz).

HRMS (ESI) [M + H^+] calcd for $C_{22}H_{24}F_3N_2O^+$ 389.1835, found 389.1841.

2-(3-(*tert*-butyl)bicyclo[1.1.1]pentan-1-yl)-2-((diphenylmethylene)amino)-*N*,*N*-dimethylacetamide (3ac)



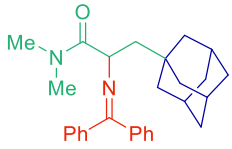
Prepared according to the general procedure **6** starting from *N*,*N*-dimethylacrylamide **1a** and oxime ester **2c**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 60:40) to obtain the product **3ac** as a white solid (31.1 mg, 80% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.49 – 7.43 (m, 3H), 7.39 – 7.30 (m, 3H), 7.16 (dd, *J* = 7.8, 1.6 Hz, 2H), 4.23 (t, *J* = 6.5 Hz, 1H), 2.90 (s, 3H), 2.80 (s, 3H), 2.24 (dd, *J* = 14.0, 6.5 Hz, 1H), 1.99 (dd, *J* = 14.0, 6.5 Hz, 1H), 1.30 (s, 6H), 0.75 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 168.6, 139.5, 136.8, 130.1, 128.8, 128.7, 128.4, 127.9, 127.7, 63.2, 48.3, 47.0, 36.7, 36.4, 36.1, 34.9, 29.4, 25.9.

HRMS (ESI) [M + H^+] calcd for $C_{26}H_{33}N_2O^+$ 389.2587, found 389.2593.

3-((1r,3R,5S)-adamantan-1-yl)-2-((diphenylmethylene)amino)-N,N-dimethylpropanamide (3ad)



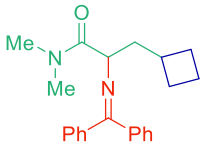
Prepared according to the general procedure **6** starting from *N*,*N*-dimethylacrylamide **1a** and oxime ester **2d**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 95:5 to 80:20) to obtain the product **3ad** as a white solid (26.5 mg, 64% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.50 – 7.43 (m, 3H), 7.38 – 7.30 (m, 3H), 7.16 (dd, *J* = 7.8, 1.6 Hz, 2H), 4.42 (dd, *J* = 7.3, 4.8 Hz, 1H), 2.89 (s, 3H), 2.80 (s, 3H), 1.92 – 1.75 (m, 4H), 1.69 – 1.50 (m, 9H), 1.48 – 1.32 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 167.7, 139.5, 137.3, 130.0, 128.8, 128.6, 128.5, 127.9, 127.6, 60.5, 48.3, 42.7, 37.0, 36.7, 36.1, 32.9, 28.6, 26.9.

HRMS (ESI) [M + H^+] calcd for $C_{28}H_{35}N_2O^+$ 415.2744, found 415.2773.

3-cyclobutyl-2-((diphenylmethylene)amino)-*N*,*N*-dimethylpropanamide (3ae)

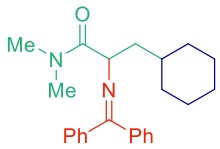


Prepared according to the general procedure **6** starting from *N*,*N*-dimethylacrylamide **1a** and oxime ester **2e**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 60:40) to obtain the product **3ae** as a white solid (32.1 mg, 96% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 6.9, 1.5 Hz, 2H), 7.49 – 7.41 (m, 3H), 7.38 – 7.28 (m, 3H), 7.14 (dd, *J* = 7.4, 1.9 Hz, 2H), 4.20 (t, *J* = 6.9 Hz, 1H), 2.89 (s, 3H), 2.88 (s, 3H), 2.25 (dq, *J* = 15.4, 7.6 Hz, 1H), 2.12 – 1.65 (m, 6H), 1.51 (dd, *J* = 17.8, 8.7 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 168.7, 139.5, 136.8, 130.1, 128.7, 128.5, 128.5, 127.9, 127.7, 63.6, 41.3, 36.8, 36.1, 33.2, 28.4, 28.1, 18.5.

HRMS (ESI) [M + H^+] calcd for $C_{22}H_{27}N_2O^+$ 335.2118, found 335.2223.



3-cyclohexyl-2-((diphenylmethylene)amino)-*N*,*N*-dimethylpropanamide (3af)

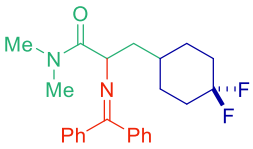
Prepared according to the general procedure **6** starting from *N*,*N*-dimethylacrylamide **1a** and oxime ester **2f**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 60:40) to obtain the product **3af** as a white solid (34.4 mg, 95% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.0 Hz, 2H), 7.49 – 7.42 (m, 3H), 7.39 – 7.27 (m, 3H), 7.14 (dd, *J* = 7.0, 1.9 Hz, 2H), 4.40 – 4.27 (m, 1H), 2.90 (s, 3H), 2.83 (s, 3H), 1.85 – 1.70 (m, 2H), 1.67 – 1.43 (m, 5H), 1.32 – 1.05 (m, 4H), 0.80 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 168.8, 139.5, 137.0, 130.1, 128.7, 128.6, 128.4, 127.9, 127.7, 62.2, 41.7, 36.7, 36.1, 34.4, 33.7, 32.7, 26.5, 26.2, 26.0.

HRMS (ESI) [M + H^+] calcd for $C_{24}H_{31}N_2O^+$ 363.2431, found 363.2458.

3-(4,4-difluorocyclohexyl)-2-((diphenylmethylene)amino)-*N*,*N*-dimethylpropanamide (3ag)



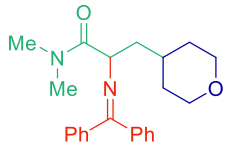
Prepared according to the general procedure **6** starting from *N*,*N*-dimethylacrylamide **1a** and oxime ester **2g**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 60:40) to obtain the product **3ag** as a white solid (37.9 mg, 95% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.1 Hz, 2H), 7.51 – 7.41 (m, 3H), 7.41 – 7.28 (m, 3H), 7.14 (dd, *J* = 7.0, 2.2 Hz, 2H), 4.31 (t, *J* = 7.0 Hz, 1H), 2.91 (s, 3H), 2.86 (s, 3H), 2.05 – 1.53 (m, 9H), 1.39 (s, 1H), 1.17 (t, *J* = 11.7 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 169.2, 139.2, 136.7, 130.3, 128.8, 128.7, 128.6, 128.0, 127.5, 123.6 (dd, *J* = 242.0, 239.4 Hz), 62.4, 39.9 (d, *J* = 2.3 Hz), 36.8, 36.1, 33.3 (ddd, *J* = 25.4, 22.6, 8.0 Hz), 32.6, 28.8 (dd, *J* = 37.6, 9.5 Hz).

HRMS (ESI) [M + H^+] calcd for $C_{22}H_{29}N_2O^+$ 399.2242, found 399.2273.

2-((diphenylmethylene)amino)-*N*,*N*-dimethyl-3-(tetrahydro-2*H*-pyran-4-yl)propenamide (3ah)



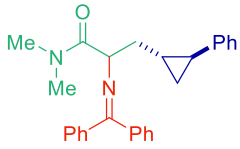
Prepared according to the general procedure **6** starting from *N*,*N*-dimethylacrylamide **1a** and oxime ester **2h**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 10:90) to obtain the product **3ah** as a white solid (31.0 mg, 85% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.1 Hz, 2H), 7.49 – 7.44 (m, 3H), 7.41 – 7.29 (m, 3H), 7.18 – 7.11 (m, 2H), 4.34 (t, *J* = 6.9 Hz, 1H), 3.86 (d, *J* = 8.9 Hz, 2H), 3.29 (dd, *J* = 20.2, 9.6 Hz, 2H), 2.92 (s, 3H), 2.86 (s, 3H), 1.92 – 1.72 (m, 2H), 1.62 – 1.33 (m, 3H), 1.26 – 1.10 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 169.2, 139.2, 136.7, 130.3, 128.7, 128.7, 128.5, 128.0, 127.5, 67.9, 61.7, 41.1, 36.8, 36.1, 33.2, 32.6, 31.8.

HRMS (ESI) [M + H^+] calcd for $C_{23}H_{29}N_2O_2^+$ 365.2224, found 365.2228.

2-((diphenylmethylene)amino)-*N*,*N*-dimethyl-3-(2-phenylcyclopropyl)propanamide (3ai/3ai')



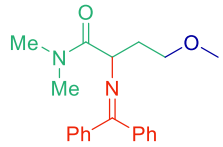
Prepared according to the general procedure **6** starting from *N*,*N*-dimethylacrylamide **1a** and oxime ester **2i**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 60:40) to obtain the product **3ai** as a white solid (23.8 mg, 60% yield, dr 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 – 7.59 (m, 4H), 7.49 – 7.28 (m, 12H), 7.23 – 6.99 (m, 10H), 6.93 (dd, *J* = 7.0, 1.4 Hz, 2H), 6.84 (dd, *J* = 7.0, 1.4 Hz, 2H), 4.45 (t, *J* = 6.8 Hz, 2H), 2.88 (s, 3H), 2.86 (s, 3H), 2.79 (s, 3H), 2.73 (s, 3H), 1.67 – 1.53 (m, 4H), 0.95 – 0.71 (m, 8H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 172.2, 169.0, 169.0, 143.3, 143.3, 139.4, 139.3, 136.8, 136.8, 130.2, 130.0, 128.7, 128.5, 128.1, 127.9, 127.6, 127.5, 125.5, 125.4, 65.0, 64.5, 39.3, 39.2, 36.8, 36.1, 29.7, 29.7, 23.2, 23.1, 21.4, 20.8, 16.2, 15.7.

HRMS (ESI) [M + H^+] calcd for $C_{27}H_{29}N_2O^+$ 397.2274, found 397.2279.

2-((diphenylmethylene)amino)-4-methoxy-*N*,*N*-dimethylbutanamide (3aj)



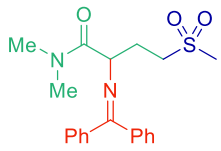
Prepared according to the general procedure **6** starting from *N*,*N*-dimethylacrylamide **1a** and oxime ester **2j**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 20:80) to obtain the product **3aj** as a white solid (26.2 mg, 77% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.48 – 7.42 (m, 3H), 7.38 – 7.28 (m, 3H), 7.15 (dd, *J* = 7.8, 1.8 Hz, 2H), 4.45 (dd, *J* = 7.5, 6.1 Hz, 1H), 3.41 (t, *J* = 6.1 Hz, 2H), 3.23 (s, 3H), 2.88 (s, 3H), 2.70 (s, 3H), 2.27 – 2.08 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 169.6, 139.4, 137.0, 130.2, 128.7, 128.5, 128.5, 127.9, 127.6, 69.4, 60.3, 58.4, 36.6, 35.9, 34.2.

HRMS (ESI) [M + H^+] calcd for $C_{21}H_{29}N_2O_2^+$ 341.2224, found 341.2265.

2-((diphenylmethylene)amino)-*N*,*N*-dimethyl-4-(methylsulfonyl)butanamide (3ak)



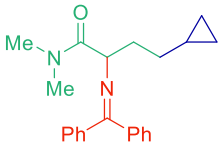
Prepared according to the general procedure **6** starting from *N*,*N*-dimethylacrylamide **1a** and oxime ester **2k**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 10:90) to obtain the product **3ak** as a white solid (29.8 mg, 80% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.0 Hz, 2H), 7.52 – 7.45 (m, 3H), 7.41 – 7.30 (m, 3H), 7.17 (dd, *J* = 7.0, 2.0 Hz, 2H), 4.43 (t, *J* = 6.1 Hz, 1H), 3.26 (t, *J* = 7.7 Hz, 2H), 2.92 (s, 3H), 2.89 (s, 3H), 2.71 (s, 3H), 2.50 – 2.23 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 171.0, 138.8, 136.3, 130.7, 129.0, 128.8, 128.7, 128.1, 127.3, 60.8, 51.4, 40.7, 36.8, 36.0, 27.0.

HRMS (ESI) [M + H^+] calcd for $C_{20}H_{25}N_2O_3^+$ 373.1580, found 373.1596

4-cyclopropyl-2-((diphenylmethylene)amino)-*N*,*N*-dimethylbutanamide (3al)



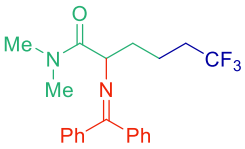
Prepared according to the general procedure **6** starting from *N*,*N*-dimethylacrylamide **1a** and oxime ester **2l**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 60:40) to obtain the product **3al** as a white solid (31.2 mg, 89% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.1 Hz, 2H), 7.49 – 7.42 (m, 3H), 7.40 – 7.29 (m, 3H), 7.12 (dd, *J* = 7.1, 2.2 Hz, 2H), 4.36 – 4.20 (m, 1H), 2.86 (s, 3H), 2.78 (s, 3H), 2.71 – 2.47 (m, 2H), 2.22 – 2.04 (m, 5H), 1.67 – 1.57 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 169.9, 139.2, 136.8, 130.3, 128.7, 128.6, 128.6, 128.0, 127.5, 62.6, 39.7, 36.7, 35.9, 30.0, 27.8, 15.6.

HRMS (ESI) [M + H^+] calcd for $C_{23}H_{31}N_2O^+$ 351.2431, found 351.2444.

2-((diphenylmethylene)amino)-6,6,6-trifluoro-*N*,*N*-dimethylhexanamide (3am)



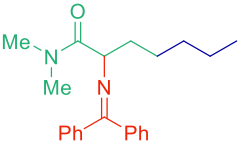
Prepared according to the general procedure **6** starting from *N*,*N*-dimethylacrylamide **1a** and oxime ester **2m**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 60:40) to obtain the product **3am** as a white solid (37.3 mg, 95% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.51 – 7.43 (m, 3H), 7.41 – 7.28 (m, 3H), 7.17 – 7.11 (m, 2H), 4.23 (dd, *J* = 7.4, 6.1 Hz, 1H), 2.90 (s, 3H), 2.85 (s, 3H), 2.14 – 1.85 (m, 4H), 1.67 – 1.46 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 169.6, 139.2, 136.6, 130.4, 129.0 (dd, *J* = 339.0, 204.4 Hz). 128.7, 128.6, 128.0, 127.5, 64.3, 36.8, 36.1, 33.4 (q, *J* = 28.7 Hz), 33.1, 18.9 (m).

HRMS (ESI) [M + H^+] calcd for $C_{22}H_{28}F_3N_2O^+$ 393.2148, found 393.2149.

2-((diphenylmethylene)amino)-*N*,*N*-dimethylheptanamide (3an)



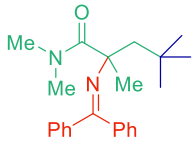
Prepared according to the general procedure **6** starting from *N*,*N*-dimethylacrylamide **1a** and oxime ester **2n**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 60:40) to obtain the product **3an** as a white solid (27.1 mg, 77% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.0 Hz, 2H), 7.51 – 7.41 (m, 3H), 7.41 – 7.28 (m, 3H), 7.14 (dd, *J* = 7.0, 2.0 Hz, 2H), 4.23 (dd, *J* = 7.5, 6.3 Hz, 1H), 2.90 (s, 3H), 2.88 (s, 3H), 2.01 – 1.76 (m, 2H), 1.37 – 1.09 (m, 6H), 0.84 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 168.8, 139.5, 136.9, 130.1, 128.7, 128.5, 128.5, 127.9, 127.7, 65.1, 36.8, 36.1, 34.2, 31.5, 26.0, 22.5, 14.0.

HRMS (ESI) [M + H^+] calcd for $C_{23}H_{33}N_2O^+$ 353.2587, found 353.2590.

2-((diphenylmethylene)amino)-*N*,*N*,2,4,4-pentamethylpentanamide (3ba)



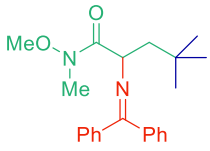
Prepared according to the general procedure **6** starting from **1b** and oxime ester **2a**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 60:40) to obtain the product **3ba** as a white solid (28.7 mg, 82% yield).

^{1}H NMR (300 MHz, CD_3CN) δ 7.61 – 7.56 (m, 4H), 7.49 – 7.29 (m, 8H), 7.01 (dd, *J* = 6.6, 3.0 Hz, 2H), 3.05 (s, 3H), 2.72 (s, 3H), 2.15 (d, *J* = 14.6 Hz, 1H), 1.89 (d, *J* = 14.6 Hz, 1H), 1.38 (s, 3H), 1.07 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 141.2, 137.6, 130.1, 129.8, 128.3, 128.3, 128.0, 127.7, 67.8, 54.1, 38.7, 36.7, 31.9, 31.6, 27.2.

HRMS (ESI) [M + H^+] calcd for $C_{23}H_{31}N_2O^+$ 351.2431, found 351.2439.

2-((diphenylmethylene)amino)-*N*-methoxy-*N*,4,4-trimethylpentanamide (3ca)



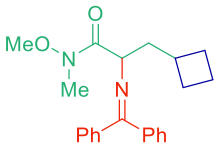
Prepared according to the general procedure **6** starting from **1c** and oxime ester **2a**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 50:50) to obtain the product **3ca** as a white solid (30.0 mg, 85% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.49 – 7.40 (m, 3H), 7.37 – 7.28 (m, 3H), 7.18 (dd, *J* = 8.0, 1.4 Hz, 2H), 4.42 (t, *J* = 5.9 Hz, 1H), 3.23 (bs, 3H), 3.13 (s, 3H), 2.08 (dd, *J* = 13.7, 5.9 Hz, 1H), 1.77 (dd, *J* = 13.7, 5.9 Hz, 1H), 0.80 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 139.5, 137.4, 130.0, 128.7, 128.4, 128.4, 128.3, 127.9, 127.6, 60.5, 46.5, 30.7, 29.8, 29.8, 28.8.

HRMS (ESI) [M + H^+] calcd for $C_{22}H_{29}N_2O_2^+$ 353.2224, found 353.2261.

3-cyclobutyl-2-((diphenylmethylene)amino)-*N*-methoxy-*N*-methylpropanamide (3ce)



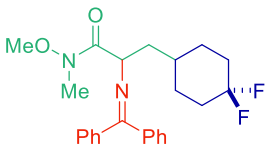
Prepared according to the general procedure **6** starting from **1c** and oxime ester **2e**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 50:50) to obtain the product **3ce** as a white solid (26.6 mg, 76% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.4 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 3H), 7.39 – 7.28 (m, 3H), 7.19 (d, *J* = 7.4 Hz, 2H), 4.27 (t, *J* = 6.6 Hz, 1H), 3.24 (s, 3H), 3.14 (s, 3H), 2.28 (dt, *J* = 14.7, 7.2 Hz, 1H), 2.13 (dt, *J* = 14.7, 7.2 Hz, 1H), 1.97 – 1.80 (m, 3H), 1.80 – 1.69 (m, 2H), 1.49 (dt, *J* = 19.0, 9.1 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 139.5, 137.1, 130.2, 128.8, 128.4, 128.4, 128.4, 128.0, 127.9, 60.8, 40.7, 33.1, 28.2, 28.1, 28.0, 18.5.

HRMS (ESI) [M + H^+] calcd for $C_{22}H_{27}N_2O_2^+$ 351.2067, found 351.2068.

3-(4,4-difluorocyclohexyl)-2-((diphenylmethylene)amino)-*N*-methoxy-*N*-methylpropanamide (3cg)



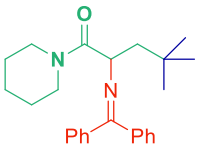
Prepared according to the general procedure **6** starting from **1c** and oxime ester **2g**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 50:50) to obtain the product **3cg** as a white solid (33.2 mg, 80% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 7.4, 1.5 Hz, 2H), 7.51 – 7.43 (m, 3H), 7.40 – 7.31 (m, 3H), 7.18 (dd, *J* = 7.4, 1.5 Hz, 2H), 4.41 (t, *J* = 6.7 Hz, 1H), 3.29 (s, 3H), 3.15 (s, 4H), 2.04 – 1.93 (m, 3H), 1.73 – 1.55 (m, 6H), 1.22 – 1.11 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 139.3, 136.9, 130.3, 128.7, 128.6, 128.5, 128.0, 127.7, 123.6 (t, *J* = 241.6, Hz), 60.9, 39.3, 33.3 (ddd, *J* = 25.4, 22.7, 6.6 Hz), 32.5, 32.5, 28.8 (dd, *J* = 29.5, 9.2 Hz), 28.70.

HRMS (ESI) [M + H^+] calcd for $C_{24}H_{29}F_2N_2O_2^+$ 415.2192, found 415.2199.

2-((diphenylmethylene)amino)-4,4-dimethyl-1-(piperidin-1-yl)pentan-1-one (3da)



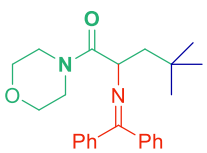
Prepared according to the general procedure **6** starting from **1d** and oxime ester **2a**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 60:40) to obtain the product **3da** as a white solid (32.8 mg, 87% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 7.8, 1.9 Hz, 2H), 7.49 – 7.41 (m, 3H), 7.38 – 7.27 (m, 3H), 7.16 (dd, *J* = 7.8, 1.9 Hz, 2H), 4.38 (t, *J* = 6.2 Hz, 1H), 3.64 – 3.30 (m, 4H), 1.95 – 1.87 (m, 2H), 1.63 – 1.44 (m, 4H), 1.42 – 1.34 (m, 2H), 0.82 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 167.6, 139.6, 136.9, 130.0, 128.7, 128.6, 128.4, 127.9, 127.7, 63.5, 47.5, 46.3, 43.4, 30.9, 29.9, 26.3, 25.6, 24.6.

HRMS (ESI) [M + H^+] calcd for $C_{25}H_{33}N_2O^+$ 377.2587, found 377.2588.

2-((diphenylmethylene)amino)-4,4-dimethyl-1-morpholinopentan-1-one (3ea)



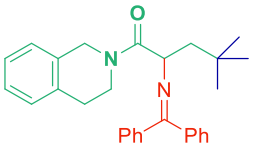
Prepared according to the general procedure **6** starting from **1e** and oxime ester **2a**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 20:80) to obtain the product **3ea** as a white solid (31.8 mg, 84% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.9, 1.4 Hz, 2H), 7.50 – 7.44 (m, 3H), 7.40 – 7.28 (m, 3H), 7.15 (dd, *J* = 7.9, 2.2 Hz, 2H), 4.39 (dd, *J* = 7.1, 5.9 Hz, 1H), 3.88 – 3.76 (m, 1H), 3.72 – 3.40 (m, 7H), 1.92 (dd, *J* = 12.7, 5.9 Hz, 1H), 1.86 (dd, *J* = 12.7, 5.9 Hz, 1H), 0.82 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 168.1, 139.4, 136.6, 130.2, 128.8, 128.6, 128.5, 128.0, 127.7, 66.9, 66.7, 63.9, 47.5, 46.1, 42.7, 30.9, 29.9.

HRMS (ESI) [M + H^+] calcd for $C_{24}H_{31}N_2O_2^+$ 379.2380, found 379.2383.

1-(3,4-dihydroisoquinolin-2(1*H*)-yl)-2-((diphenylmethylene)amino)-4,4-dimethylpentan-1-one (3fa)



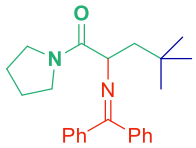
Prepared according to the general procedure **6** starting from **1f** and oxime ester **2a**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 60:40) to obtain the product **3fa** as a white solid (35.2 mg, 83% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (t, *J* = 6.7 Hz, 2H), 7.45 – 7.29 (m, 6H), 7.23 – 7.05 (m, 6H), 4.80 – 4.60 (m, 2H), 4.44 (dd, *J* = 12.7, 5.6 Hz, 1H), 4.06 – 3.43 (m, 2H), 3.04 – 2.55 (m, 2H), 2.10 – 1.86 (m, 2H), 0.84 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 168.2, 137.6, 136.8, 130.0, 128.7, 128.6, 128.5, 128.3, 128.0, 127.9, 127.7, 127.5, 126.7, 126.3, 64.1, 47.5, 44.9, 42.8, 40.5, 29.9, 29.1.

HRMS (ESI) [M + H^+] calcd for $C_{29}H_{33}N_2O^+$ 425.2587, found 425.2592.

2-((diphenylmethylene)amino)-4,4-dimethyl-1-(pyrrolidin-1-yl)pentan-1-one (3ga)



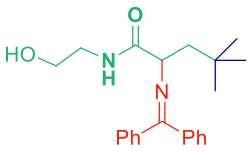
Prepared according to the general procedure **6** starting from **1g** and oxime ester **2a**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 60:40) to obtain the product **3ga** as a white solid (32.6 mg, 90% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.0, 1.9 Hz, 2H), 7.49 – 7.40 (m, 3H), 7.39 – 7.28 (m, 3H), 7.15 (dd, *J* = 7.0, 1.9 Hz, 2H), 4.19 (dd, *J* = 8.0, 4.4 Hz, 1H), 3.49 – 3.35 (m, 2H), 3.20 (dt, *J* = 9.5, 6.5 Hz, 1H), 2.77 (dt, *J* = 9.5, 6.5 Hz, 1H), 2.02 (dd, *J* = 14.0, 8.0 Hz, 1H), 1.83 (dd, *J* = 14.0, 4.4 Hz, 2H), 1.79 – 1.67 (m, 4H), 0.83 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 168.1, 139.4, 137.6, 130.0, 128.7, 128.5, 128.4, 127.9, 127.4, 63.1, 47.1, 46.0, 45.8, 30.8, 30.0, 26.1, 23.9.

HRMS (ESI) [M + H^+] calcd for $C_{24}H_{31}N_2O^+$ 363.2431, found 363.2436.

2-((diphenylmethylene)amino)-*N*-(2-hydroxyethyl)-4,4-dimethylpentanamide (3ia)



Prepared according to the general procedure **6** starting from **1i** and oxime ester **2a**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 10:90) to obtain the product **3ia** as a white solid (30.0 mg, 85% yield).

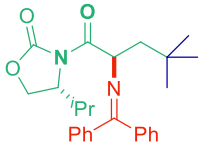
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.50 – 7.33 (m, 6H), 7.12 (dd, *J* = 7.8, 1.6 Hz, 2H), 6.86 (bs, 1H), 4.11 (dd, *J* = 8.6, 3.1 Hz, 1H), 3.75 – 3.71 (m, 2H), 3.56 – 3.37

(m, 2H), 3.06 (bs, 1H), 1.93 (dd, *J* = 13.9, 8.6 Hz, 1H), 1.82 (dd, *J* = 13.9, 3.1 Hz, 1H), 0.79 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 169.3, 139.5, 135.7, 130.5, 129.1, 128.9, 128.7, 128.2, 127.8, 65.3, 63.1, 49.2, 42.7, 30.9, 30.0.

HRMS (ESI) [M + H^+] calcd for $C_{22}H_{29}N_2O_2^+$ 353.2224, found 353.2272.

(*R*)-3-((*R*)-2-((diphenylmethylene)amino)-4,4-dimethylpentanoyl)-4-isopropyloxazolidin-2-one (3la)



Prepared according to the general procedure **6** starting from **1l** and oxime ester **2a**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 60:40) to obtain **3la/3la'** as a white solid (28.2 mg, 67% yield, d.r.=1:1).

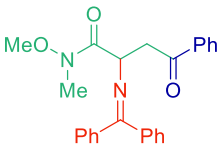
Enantioselective reprotonation: the diastereomeric mixture of **3la/3la'** (28.2 mg, 1 equiv) was dissolved in dry THF and cooled to -78 ºC. A freshly prepared solution of LDA (1.2 equiv) in THF was added dropwise. After 30 minutes of stirring at the same temperature, the reaction was quenched with a saturated aqueous solution of ammonium chloride. Percolate of the resulting mixture with cold AcOEt through a short plug of silica gel conducted to the enantioenriched product **3la** (27.1 mg, *ee* >99:1). $[\alpha]_D^{26}$= +20.4 (c =0.50, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 7.5, 1.9 Hz, 2H), 7.46 – 7.40 (m, 3H), 7.37 – 7.28 (m, 3H), 7.21 (dd, *J* = 7.5, 1.9 Hz, 2H), 5.45 (t, *J* = 6.2 Hz, 1H), 4.43 (dt, *J* = 8.0, 3.4 Hz, 1H), 4.27 – 4.12 (m, 2H), 2.06 (dd, *J* = 13.6, 6.2 Hz, 1H), 1.67 (dd, *J* = 13.6, 6.2 Hz, 1H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.76 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 170.0, 153.0, 139.5, 136.9, 130.2, 128.7, 128.6, 128.5, 127.9, 127.6, 63.0, 61.3, 58.7, 46.3, 30.7, 29.8, 28.1, 18.0, 14.5.

HRMS (ESI) [M + H^+] calcd for $C_{26}H_{33}N_2O_3^+$ 421.2486, found 421.2491.

2-((diphenylmethylene)amino)-*N*-methoxy-*N*-methyl-4-oxo-4-phenylbutanamide (3co)

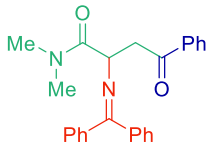


Prepared according to the general procedure **6** starting from **1c** and oxime ester **2o**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 50:50) to obtain the product **3co** as a white solid (31.2 mg, 78% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 8.6, 1.1 Hz, 2H), 7.64 (dd, *J* = 8.6, 1.1 Hz, 2H), 7.57 – 7.22 (m, 11H), 5.02 (dd, *J* = 8.6, 4.5 Hz, 1H), 4.08 (dd, *J* = 17.5, 8.6 Hz, 1H), 3.40 (s, 3H), 3.18 (s, 3H), 3.08 (dd, *J* = 17.5, 4.5 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 170.5, 139.4, 136.7, 136.5, 133.1, 130.4, 128.8, 128.7, 128.5, 128.5, 128.4, 128.2, 128.0, 127.7, 60.8, 59.2, 41.9, 32.4.

HRMS (ESI) [M + H^+] calcd for $C_{25}H_{25}N_2O_3^+$ 401.1860, found 401.1862.



2-((diphenylmethylene)amino)-*N*,*N*-dimethyl-4-oxo-4-phenylbutanamide (3ao)

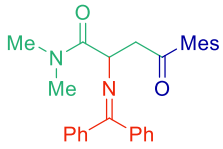
Prepared according to the general procedure **6** starting from *N*,*N*-dimethylacrylamide **1a** and oxime ester **2o**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 60:40) to obtain the product **3ao** as a white solid (31.1 mg, 81% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.2 Hz, 2H), 7.63 (d, *J* = 7.2 Hz, 2H), 7.58 – 7.28 (m, 9H), 7.23 – 7.18 (m, 2H), 5.00 (dd, *J* = 8.4, 4.8 Hz, 1H), 4.09 (dd, *J* = 17.3, 8.4 Hz, 1H), 3.16 (dd, *J* = 17.3, 4.8 Hz, 1H), 2.93 (s, 3H), 2.76 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 171.5, 170.0, 139.2, 136.7, 136.5, 133.1, 130.4, 128.9, 128.8, 128.8, 128.5, 128.2, 128.0, 127.4, 59.3, 43.0, 36.8, 36.1.

HRMS (ESI) [M + H^+] calcd for $C_{25}H_{25}N_2O_2^+$ 385.1911, found 385.1926.

2-((diphenylmethylene)amino)-4-mesityl-*N*,*N*-dimethyl-4-oxobutanamide (3ap)



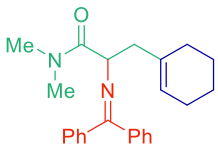
Prepared according to the general procedure **6** starting from *N*,*N*-dimethylacrylamide **1a** and oxime ester **2p**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 60:40) to obtain the product **3ap** as a white solid (36.2 mg, 85% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 8.0, 1.8 Hz, 2H), 7.53 – 7.27 (m, 6H), 7.21 (dd, *J* = 8.0, 1.8 Hz, 2H), 6.92 – 6.73 (m, 2H), 4.90 (dd, *J* = 8.1, 4.8 Hz, 1H), 3.71 (dd, *J* = 18.7, 8.1 Hz, 1H), 3.00 – 2.91 (m, 4H), 2.83 (s, 3H), 2.26 (s, 3H), 2.18 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 207.9, 171.3, 170.0, 139.0, 138.3, 136.5, 132.9, 130.4, 130.0, 128.9, 128.8, 128.7, 128.4, 128.0, 127.3, 58.4, 48.8, 36.8, 36.2, 21.0, 19.0.

HRMS (ESI) [M + H^+] calcd for $C_{28}H_{31}N_2O_2^+$ 427.2380, found 427.2388.

3-(cyclohex-1-en-1-yl)-2-((diphenylmethylene)amino)-*N*,*N*-dimethylpropanamide (3aq)



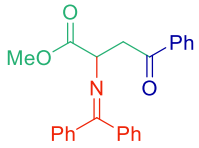
Prepared according to the general procedure **6** starting from *N*,*N*-dimethylacrylamide **1a** and oxime ester **2q**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 60:40) to obtain the product **3aq** as a white solid (13.3 mg, 37% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.9, 1.8 Hz, 2H), 7.52 – 7.41 (m, 3H), 7.40 – 7.28 (m, 3H), 7.12 (dd, *J* = 7.9, 1.8 Hz, 2H), 4.27 (dd, *J* = 7.3, 5.9 Hz, 1H), 2.98 (t, *J* = 8.1 Hz, 1H), 2.86 (s, 3H), 2.79 (s, 3H), 2.65 – 2.51 (m, 2H), 2.25 – 2.00 (m, 8H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 169.9, 139.2, 136.8, 132.4, 130.3, 130.0, 128.7, 128.6, 128.5, 128.0, 127.5, 62.6, 39.7, 36.7, 35.9, 30.0, 27.8.

HRMS (ESI) [M + H^+] calcd for $C_{24}H_{29}N_2O^+$ 361.2274, found 361.2279.

methyl 2-((diphenylmethylene)amino)-4-oxo-4-phenylbutanoate (3oo)



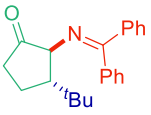
Prepared according to the general procedure **6** starting from **1o** and oxime ester **2o**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 95:5 to 80:20) to obtain the product **3oo** as a white solid (19.3 mg, 52% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.61 – 7.53 (m, 4H), 7.51 – 7.42 (m, 6H), 7.34 – 7.29 (m, 3H), 4.79 (t, *J* = 6.2 Hz, 1H), 3.79 (dd, *J* = 10.1, 6.2 Hz, 1H), 3.75 – 3.69 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 172.0, 159.9, 136.8, 133.2, 129.0, 128.9, 128.8, 128.6, 128.5, 128.5, 128.3, 128.2, 128.0, 127.9, 61.7, 52.4, 42.2.

HRMS (ESI) [M + H^+] calcd for $C_{24}H_{22}NO_3^+$ 372.1594, found 372.1590.

(2*S*,3*S*)-3-(tert-butyl)-2-((diphenylmethylene)amino)cyclopentan-1-one (3na)



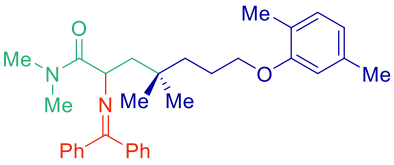
Prepared according to the general procedure **6** starting from **1n** and oxime ester **2a**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 95:5 to 80:20) to obtain the product **3na** as a white solid (23.3 mg, 73% yield, *anti*:*syn* >99:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 – 7.55 (m, 3H), 7.49 – 7.29 (m, 11H), 3.75 (d, *J* = 11.2 Hz, 1H), 2.52 (m, 1H), 2.43 – 2.31 (m, 2H), 2.05 (m, 1H), 1.51 (m, 1H), 0.82 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 214.8, 170.3, 140.0, 136.6, 130.0, 128.9, 128.8, 128.3, 128.1, 128.1, 72.7, 54.9, 37.0, 32.2, 27.8, 27.0.

HRMS (ESI) [M + H^+] calcd for $C_{22}H_{26}NO^+$ 320.2009, found 320.2013.

7-(2,5-dimethylphenoxy)-2-((diphenylmethylene)amino)-*N*,*N*,4,4-tetramethylheptanamide (3ap)



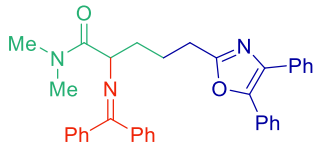
Prepared according to the general procedure **6** starting from *N*,*N*-dimethylacrylamide **1a** and oxime ester **2p**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 60:40) to obtain the product **3ap** as a white solid (42.2 mg, 87% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.8, 1.7 Hz, 2H), 7.48 – 7.40 (m, 3H), 7.37 – 7.27 (m, 3H), 7.15 (dd, *J* = 7.8, 1.7 Hz, 2H), 6.99 (d, *J* = 7.4 Hz, 1H), 6.65 (d, *J* = 7.4 Hz, 1H), 6.55 (s, 1H), 4.41 (dd, *J* = 7.5, 4.8 Hz, 1H), 3.81 (t, *J* = 6.8 Hz, 2H), 2.89 (s, 3H), 2.86 (s, 3H), 2.30 (s, 3H), 2.14 (s, 3H), 2.02 (dd, *J* = 14.1, 6.8 Hz, 1H), 1.90 (dd, *J* = 14.1, 4.8 Hz, 1H), 1.79 – 1.68 (m, 2H), 1.37 – 1.23 (m, 2H), 0.84 (s, 3H), 0.83 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 168.0, 157.1, 139.4, 137.0 136.4, 130.2, 130.1, 128.7, 128.6, 128.5, 127.9, 127.6, 123.5, 120.5, 112.0, 68.6, 62.3, 45.3, 39.0, 36.8, 36.1, 33.1, 27.4, 27.4, 24.2, 21.4, 15.8.

HRMS (ESI) [M + H^+] calcd for $C_{32}H_{41}N_2O_2^+$ 485.3163, found 485.3174.

2-((diphenylmethylene)amino)-5-(4,5-diphenyloxazol-2-yl)-*N*,*N*-dimethylpentanamide (3aq)

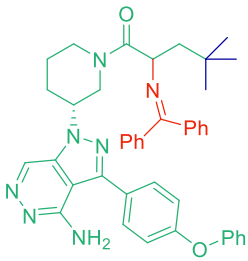


Prepared according to the general procedure **6** starting from *N*,*N*-dimethylacrylamide **1a** and oxime ester **2q**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 90:10 to 60:40) to obtain the product **3aq** as a white solid (49.1 mg, 93% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.46 – 7.19 (m, 14H), 7.07 (d, *J* = 8.0 Hz, 2H), 3.51 (t, *J* = 8.7 Hz, 1H), 3.09 (s, 3H), 2.90 (s, 3H), 2.24 – 1.63 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 166.8, 142.0, 138.4, 131.8, 130.3, 130.2, 130.2, 129.6, 129.5, 129.4, 129.4, 128.6, 128.4, 128.2, 128.1, 128.0, 127.9, 127.3, 127.1, 127.1, 49.5, 38.5, 37.9, 35.8, 28.0, 20.9.

HRMS (ESI) [M + H^+] calcd for $C_{35}H_{34}N_3O_2^+$ 528.2646, found 528.2650.



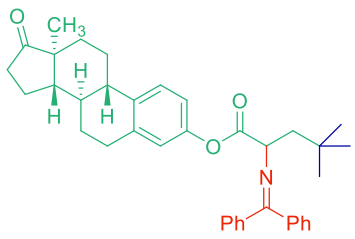
1-(3-(4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-((diphenylmethylene)amino)-4,4-dimethylpentan-1-one (3pa/3pa‘)

Prepared according to the general procedure **6** starting from **1p** and oxime ester **2a**. The crude mixture was purified by flash column chromatography (Cyclohexane: AcOEt gradient from 90:10 to 60:40) to obtain the product **3pa** as a white solid (54.9 mg, 81% yield, dr 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (t, *J* = 6.8 Hz, 1H), 7.72 – 7.60 (m, 3H), 7.58 – 7.45 (m, 2H), 7.44 – 7.28 (m, 6H), 7.23 – 7.03 (m, 8H), 5.60 (s, 2H), 4.92 – 4.51 (m, 3H), 4.43 (dd, *J* = 12.3, 6.1 Hz, 1H), 3.71 – 3.26 (m, 1H), 3.17 – 2.54 (m, 1H), 2.35 – 2.10 (m, 2H), 2.07 – 1.73 (m, 4H), 0.79 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 168.1, 158.4, 157.7, 156.4, 155.7, 154.1, 143.7, 139.5, 136.5, 130.0, 129.9, 128.7, 128.7, 128.5, 128.0, 127.9, 127.8, 119.5, 119.1, 98.5, 64.8, 63.2, 53.4, 52.9, 47.5, 30.9, 30.0, 29.8, 29.8.

HRMS (ESI) [M + H^+] calcd for $C_{42}H_{44}N_7O_2^+$ 678.3551, found 678.3556.



17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-2-yl 2-((diphenylmethylene)amino)-4,4-dimethylpentanoate (3qa)

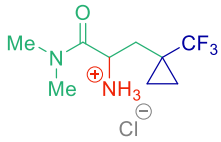
Prepared according to the general procedure **6** starting from **1q** and oxime ester **2a**. The crude mixture was purified by flash column chromatography (Cyclohexane:AcOEt gradient from 95:5 to 80:20) to obtain the product **3qa** as a white solid (50.4 mg, 92% yield, dr > 99:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.54 – 7.44 (m, 3H), 7.42 – 7.31 (m, 3H), 7.26 (dd, *J* = 10.2, 2.5 Hz, 3H), 6.89 – 6.75 (m, 2H), 4.37 (t, *J* = 6.1 Hz, 1H), 2.93 – 2.87 (m, 2H), 2.63 – 2.36 (m, 2H), 2.34 – 1.84 (m, 7H), 1.69 – 1.41 (m, 7H), 0.86 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 223.2, 171.8, 169.9, 148.7, 139.5, 137.9, 137.3, 136.6, 130.3, 128.8, 128.8, 128.5, 128.0, 127.7, 126.3, 121.4, 118.5, 63.8, 50.4, 47.9, 47.2, 44.1, 38.0, 35.8, 31.5, 30.6, 29.8, 29.4, 26.3, 25.7, 21.6.

HRMS (ESI) [M + H^+] calcd for $C_{37}H_{42}N_2O^+$ 548.3159, found 548.3166.

1-(dimethylamino)-1-oxo-3-(1-(trifluoromethyl)cyclopropyl)propan-2-aminium chloride (4ab)

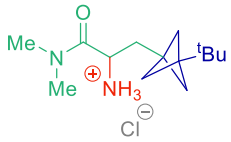


Prepared according to the general procedure **7** starting from *N*,*N*-dimethylacrylamide **1a** and oxime ester **2b**. After continuous extraction of the crude mixture and concentration *in vacuo* of the aqueous phase, the desired product **4ab** was obtained in pure form as a white solid (20.6 mg, 79% yield), without any further purification step.

^{1}H NMR (300 MHz, D_2O) δ 4.56 (dd, *J* = 9.3, 5.6 Hz, 1H), 3.00 (s, 3H), 2.84 (s, 3H), 2.32 (dd, *J* = 16.0, 5.6 Hz, 1H), 1.69 (dd, *J* = 16.0, 9.1 Hz, 1H), 1.10 – 0.94 (m, 2H), 0.73 (m, 1H), 0.53 (m, 1H).

^{13}C NMR (75 MHz, D_2O) δ 168.7, 118.9 (q, *J* = 271.4 Hz), 49.0, 36.9, 35.8, 32.5, 18.51 (dd, *J* = 60.3, 27.3 Hz), 9.2 (dd, *J* = 4.9, 2.9 Hz), 7.8 (dd, *J* = 4.9, 2.9 Hz).

HRMS (ESI) [M + H^+] calcd for $C_9H_{16}F_3N_2O^+$ 225.1209, found 225.1215.



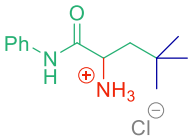
1-(3-(tert-butyl)bicyclo[1.1.1]pentan-1-yl)-2-(dimethylamino)-2-oxoethan-1-aminium chloride (4ac)

5 mmol scale: Prepared according to the general procedure **7** starting from *N*,*N*-dimethylacrylamide **1a** (5.0 mmol) and oxime ester **2c** (7.5 mmol). The *Vapourtec* device worked in continuous flow conditions for 9 hours (9 min total residence time). After continuous extraction of the crude mixture and concentration *in vacuo* of the aqueous phase, the desired product **4ac** was obtained in pure form as a white solid (1.2 g, 85% yield), without any further purification step.

^{1}H NMR (300 MHz, D_2O) δ 4.46 (t, *J* = 5.7 Hz, 1H), 3.11 (s, 3H), 2.98 (s, 3H), 2.11 (d, *J* = 5.9 Hz, 2H), 1.55 (s, 6H), 0.82 (s, 9H).

^{13}C NMR (75 MHz, D_2O) δ 169.1, 49.5, 48.2, 46.6, 37.0, 35.8, 32.6, 32.2, 28.7, 25.1.

HRMS (ESI) [M + H^+] calcd for $C_{13}H_{25}N_2O^+$ 225.1961, found 225.1969.



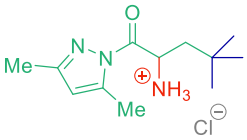
4,4-dimethyl-1-oxo-1-(phenylamino)pentan-2-aminium chloride (4ha)

Prepared according to the general procedure **7** starting from **1h** and oxime ester **2a**. After continuous extraction of the crude mixture and concentration *in vacuo* of the aqueous phase, the desired product **4ha** was obtained in pure form as a white solid (24.6 mg, 96% yield), without any further purification step.

^{1}H NMR (300 MHz, D_2O) δ 7.49 – 7.46 (m, 4H), 7.36 – 7.30 (m, 1H), 4.13 (dd, *J* = 8.9, 4.6 Hz, 1H), 2.09 (dd, *J* = 14.2, 8.9 Hz, 1H), 1.77 (dd, *J* = 14.2, 4.6 Hz, 1H), 1.02 (s, 9H).

^{13}C NMR (75 MHz, D_2O) δ 169.1, 135.7, 129.3, 126.4, 122.0, 52.0, 44.4, 29.3, 28.5.

HRMS (ESI) [M + H^+] calcd for $C_{13}H_{21}N_2O^+$ 221.1648, found 221.1640.



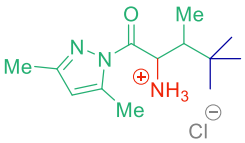
1-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4,4-dimethyl-1-oxopentan-2-aminium chloride (4ja)

Prepared according to the general procedure **7** starting from **1j** and oxime ester **2a**. After continuous extraction of the crude mixture and concentration *in vacuo* of the aqueous phase, the desired product **4ja** was obtained in pure form as a white solid (22.9 mg, 88% yield), without any further purification step.

^{1}H NMR (300 MHz, D_2O) δ 6.33 (s, 1H), 4.06 (t, *J* = 5.8 Hz, 1H), 2.31 (s, 6H), 2.05 (dd, *J* = 15.0, 5.8 Hz, 1H), 1.71 (dd, *J* = 15.0, 5.8 Hz, 1H), 1.02 (s, 9H).

^{13}C NMR (75 MHz, D_2O) δ 173.3, 145.9, 145.9, 106.7, 50.6, 43.9, 29.6, 28.3, 26.6, 10.0.

HRMS (ESI) [M + H^+] calcd for $C_{12}H_{22}N_3O^+$ 224.1757, found 224.1768.



1-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3,4,4-trimethyl-1-oxopentan-2-aminium chloride (4ka)

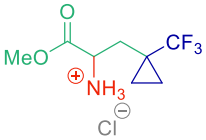
Prepared according to the general procedure **7** starting from **1k** and oxime ester **2a**. After continuous extraction of the crude mixture and concentration *in vacuo* of the aqueous phase, the desired product **4ka** was obtained in pure form as a white solid (17.2 mg, 63% yield, dr 4:1), without any further purification step.

^{1}H NMR (300 MHz, D_2O) δ 6.29 (s, 1H), 4.24 (bs, 1H), 2.35 (s, 6H), 2.18 (bs, 1H), 1.33 (s, 3H), 0.96 (s, 9H).

^{13}C NMR (75 MHz, D_2O) δ 173.4, 145.9, 145.8, 106.7, 54.8, 43.0, 32.4, 26.8, 26.6, 10.0.

HRMS (ESI) [M + H^+] calcd for $C_{13}H_{24}N_3O^+$ 238.1914, found 238.1918.

1-methoxy-1-oxo-3-(1-(trifluoromethyl)cyclopropyl)propan-2-aminium chloride (4ob)



Prepared according to the general procedure **7** starting from **1o** and oxime ester **2b**. After continuous extraction of the crude mixture and concentration

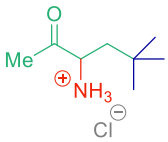
in vacuo of the aqueous phase, the desired product **4ob** was obtained in pure form as a white solid (17.3 mg, 70% yield), without any further purification step.

^{1}H NMR (300 MHz, D_2O) δ 4.42 (dd, *J* = 8.5, 6.5 Hz, 1H), 3.89 (s, 3H), 2.44 (dd, *J* = 15.9, 6.5 Hz, 1H), 2.17 (dd, *J* = 15.9, 8.5 Hz, 1H), 1.27 – 1.13 (m, 2H), 0.91 – 0.69 (m, 2H).

^{13}C NMR (75 MHz, D_2O) δ 170.1, 126.9 (q, *J* = 270.7 Hz), 53.7, 51.5, 32.2, 18.7 (q, *J* = 33.1 Hz), 9.2 (dd, *J* = 4.7, 2.3 Hz), 8.3 (dd, *J* = 4.8, 2.5 Hz).

HRMS (ESI) [M + H^+] calcd for $C_8H_{13}F_3NO_2^+$ 212.0893, found 212.0897.

4,5,5-trimethyl-2-oxohexan-3-aminium chloride (4ma)

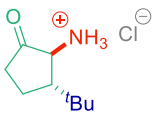


Prepared according to the general procedure **7** starting from **1m** and oxime ester **2a**. After continuous extraction of the crude mixture and concentration *in vacuo* of the aqueous phase, the desired product **4ma** was obtained in pure form as a white solid (15.7 mg, 81% yield), without any further purification step.

^{1}H NMR (300 MHz, D_2O) δ 4.23 (d, *J* = 7.2 Hz, 1H), 2.31 (s, 3H), 1.99 (d, *J* = 15.8 Hz, 1H), 1.52 (dd, *J* = 15.8, 7.2 Hz, 1H), 1.01 (s, 9H).

^{13}C NMR (75 MHz, D_2O) δ 206.8, 56.9, 30.0, 28.3, 25.6.

HRMS (ESI) [M + H^+] calcd for $C_9H_{20}NO^+$ 158.1539, found 158.1546.



(1*S*,2*S*)-2-(tert-butyl)-5-oxocyclopentan-1-aminium chloride (4na)

Prepared according to the general procedure **7** starting from **1n** and oxime ester **2a**. After continuous extraction of the crude mixture and concentration *in vacuo* of the aqueous phase, the desired product **4na** was obtained in pure form as a white solid (15.9 mg, 83% yield, *anti*:*syn* > 99:1), without any further purification step.

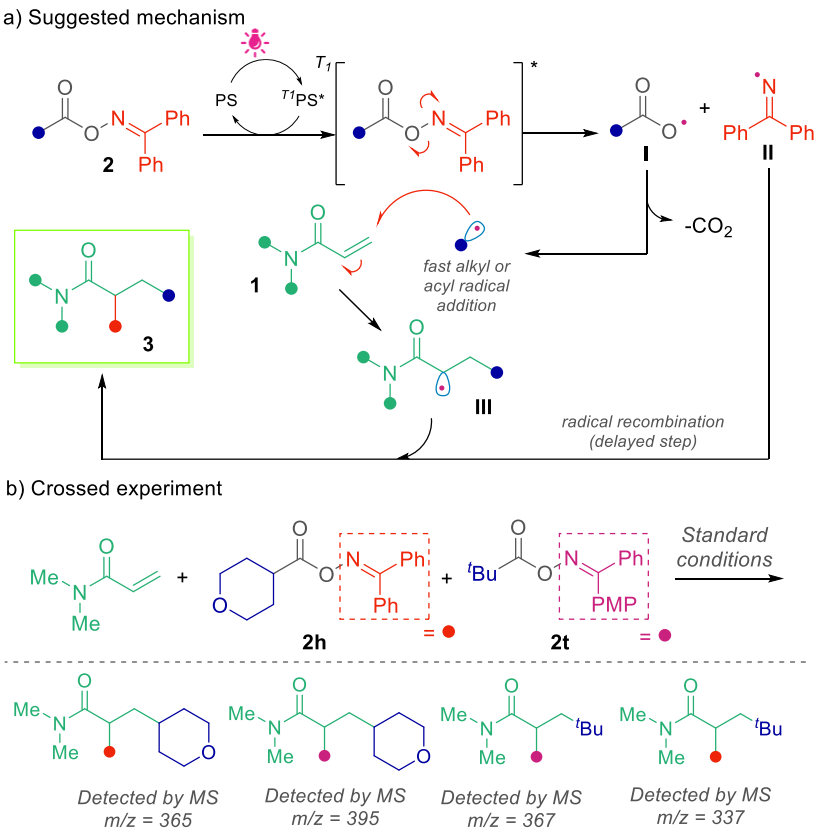
^{1}H NMR (300 MHz, D_2O) δ 3.73 (d, *J* = 11.6 Hz, 1H), 2.48 – 2.40 (m, 1H), 2.21 (dd, *J* = 19.9, 9.7 Hz, 1H), 2.08 – 1.95 (m, 2H), 1.73 (dd, *J* = 19.9, 9.7 Hz, 1H), 0.90 (s, 9H).

^{13}C NMR (75 MHz, D2O) δ 215.2, 58.2, 50.5, 34.2, 31.1, 26.5, 20.0.

HRMS (ESI) [M + H^+] calcd for $C_{12}H_{22}N_3O^+$ 224.1757, found 224.1768.

9. Mechanistic investigations

In the light of the experimental data obtained and drawing knowledge from previous reports, a plausible mechanism for the transformation in matter was proposed (**Scheme S10a**).



Scheme S12

Visible light excited **5CzBN** (T_1) (E_T = 2.68 eV) sensitizes oxime ester **2** via EnT, leading to the homolytic cleavage of the N-O bond. The latter is translated into the concomitant formation of both carboxyl- (**I**) and iminyl radical (**II**) intermediates. Unsurprisingly, the first one decomposes to the corresponding alkyl or acyl open-shell species upon carbon dioxide release. At this point, controlling the order in which both species might add to the expectant unsaturated carboxamide could result a major setback for the overall yield. In this case however, the high nucleophilic character of the alkyl/acyl radicals, joined to a delayed radical recombination (presumably due to a well-known persistent radical effect) between **1** and **II**, products **3** are generated with flawless regioselectivity.

A crossed functionalization experiment using **1a** and a mixture of two different oxime esters (**2h**, **2t**) under the standard conditions, conducted to the four possible adducts, concluding that a concerted functionalization is unlikely. Interestingly, the decarboxylative homocoupling or even the iminyl radical homocoupling byproducts are practically suppressed using the described flow setup in comparison to batch conditions, where the yield of compounds **3** is strongly diminished by the formation of these.

9.1 Procedure for the crossed experiment

An oven-dried 5 mL glass vial was charged with catalyst 5CzBN (0.001 mmol), *N*,*N*-dimethylacrylamide **1a** (1.0 equiv., 0.1 mmol, 9.9 mg) and oxime esters **2h** (1.0 equiv., 0.1 mmol, 30.9 mg) and **2t** (1.0 equiv., 0.1 mmol, 31.1 mg). Then, 1.2 mL of acetone (0.08 M) were added.

The vial was sealed with a PTFE/rubber septum and the reaction mixture was deoxygenated by three freeze-pump-thaw cycles.

Simultaneously, the *Vapourtec* setup was purged with degassed acetone to ensure inert atmosphere conditions. Once the system was conditioned (approximately 5 minutes), the reaction mixture was pumped by pump A with a 1.00 mL/min flow rate (5 min residence time) and collected at the end of the reactor. The solvent was removed under reduced pressure.

The crude mixture was subjected to High-Resolution Mass Spectroscopy (HRMS), determining the presence of the four expected adducts.

Any attempt to isolate each adduct in pure form by flash column chromatography failed due to the high complexity of the crude mixture.

9.2 Stern-Volmer luminescence quenching studies

The Stern-Volmer plots displayed in Figure **S3** show a linear correlation between the concentration of quencher [Q] and the ratio I_0/I according to the equation:

$$I_0/I = K_{SV} \times [Q] + 1$$

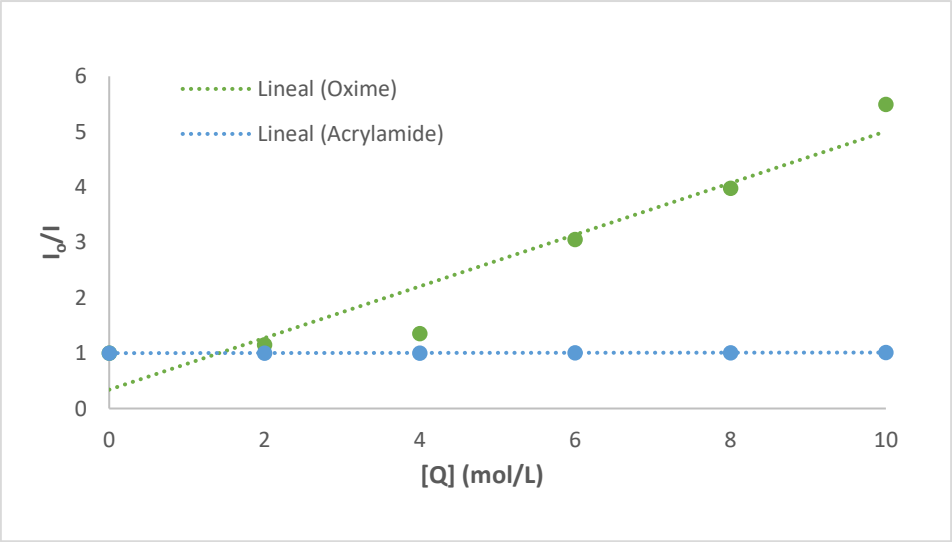


Figure **S3**

The data plotted in the chart confirms the lack of interaction between the unsaturated carboxamide **1** (blue line) and the **5CzBN**. Additionally, it presents the telescoped possibility of oxime **2a** (green line) quenching the triplet excited state of ***5CzBN**. Therefore, it is concluded that the initial step should involve the photosensitization of **2a** by populating its dark triple state through a TTET process by ***5CzBN**.

10. References

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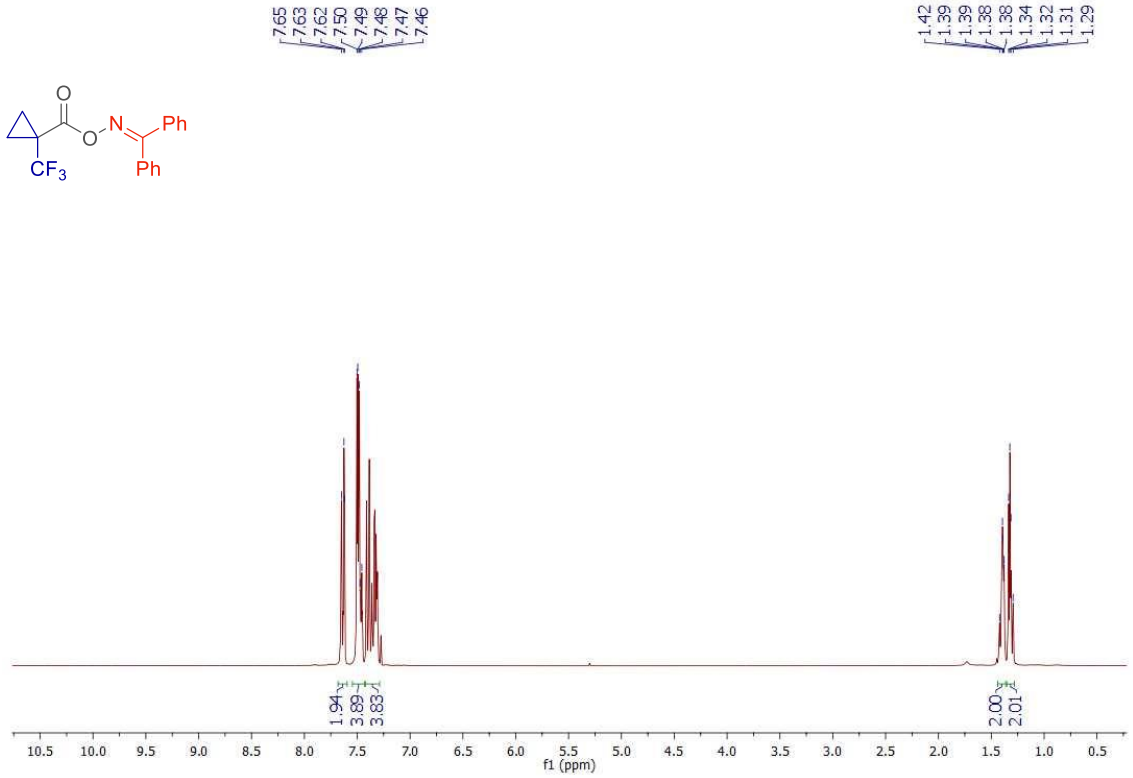
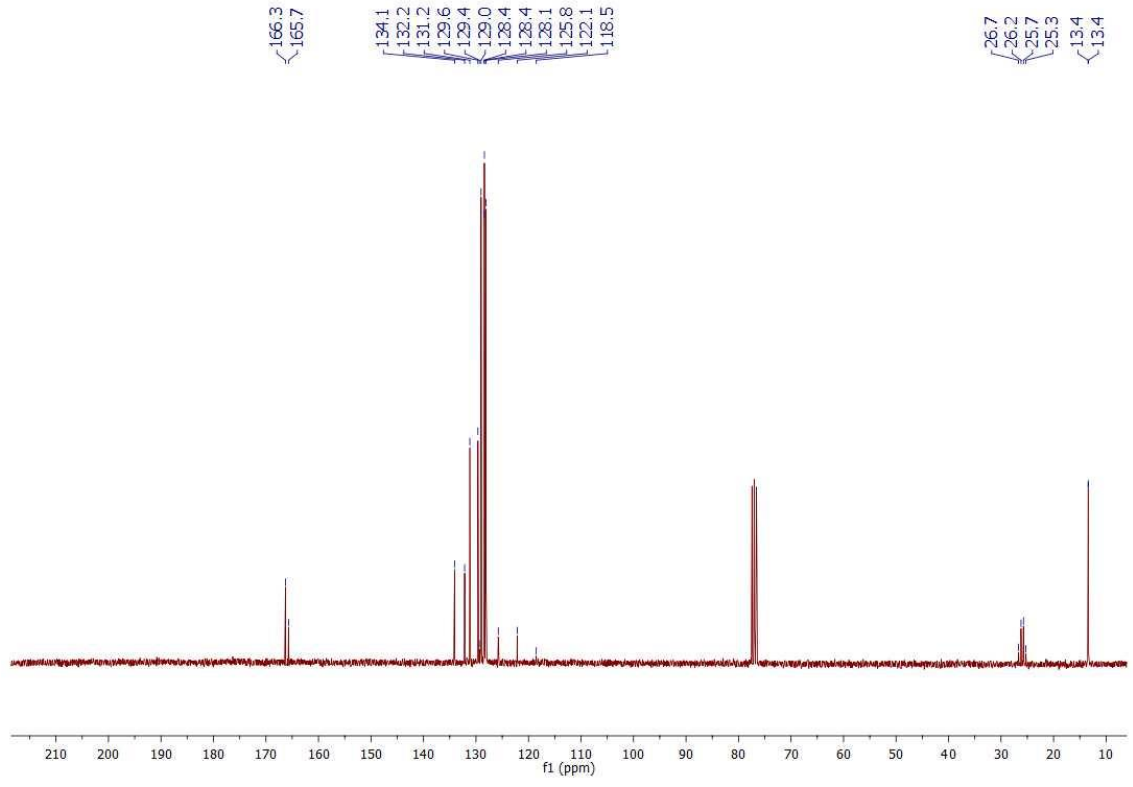
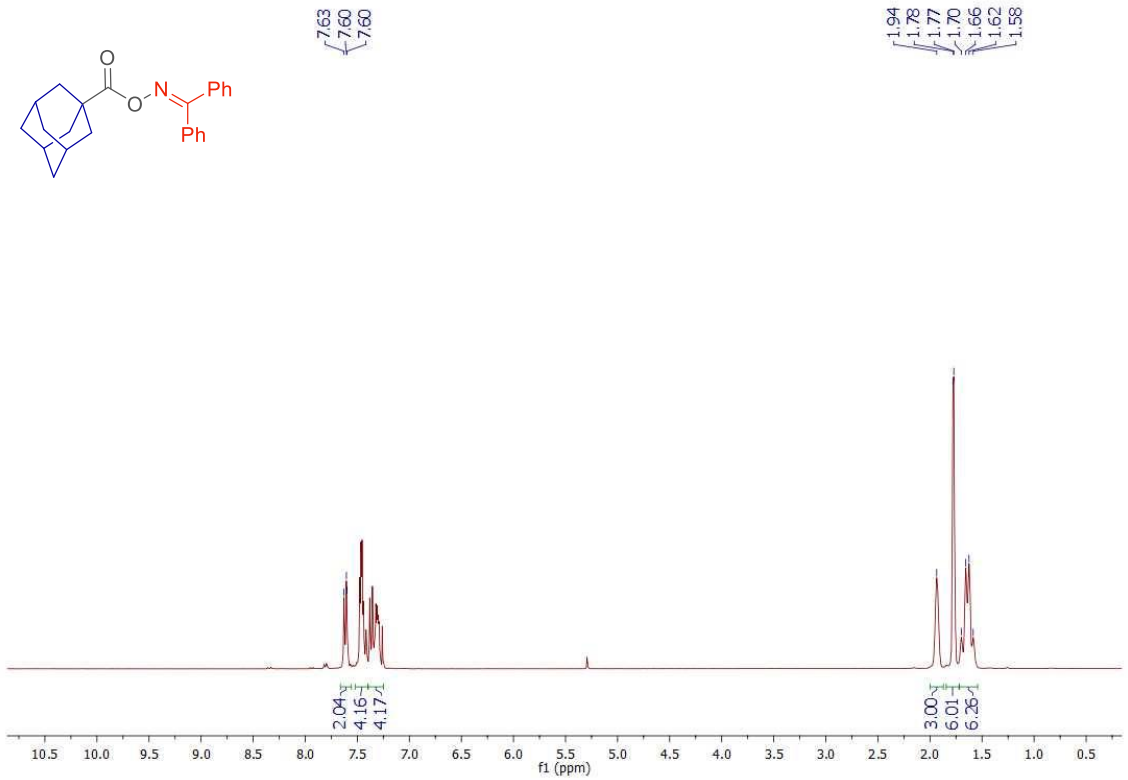
11. NMR Spectral Data



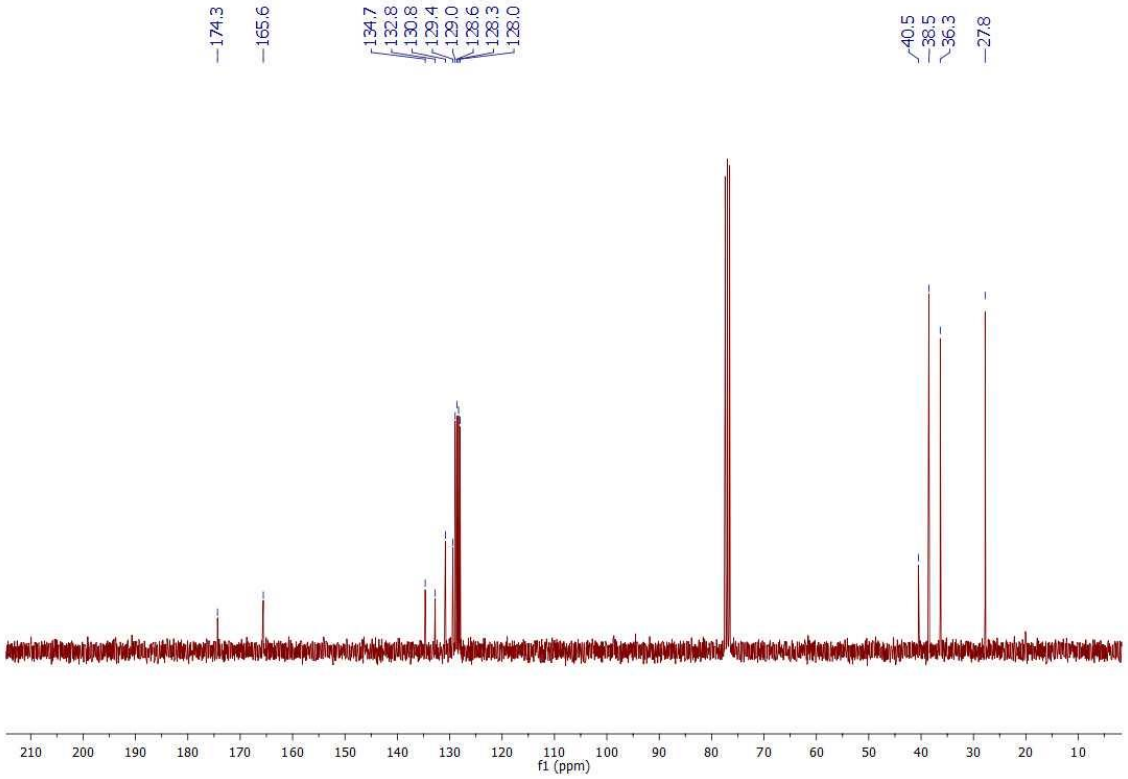
^{1}H NMR of compound **2b** (300 MHz, $CDCl_3$)



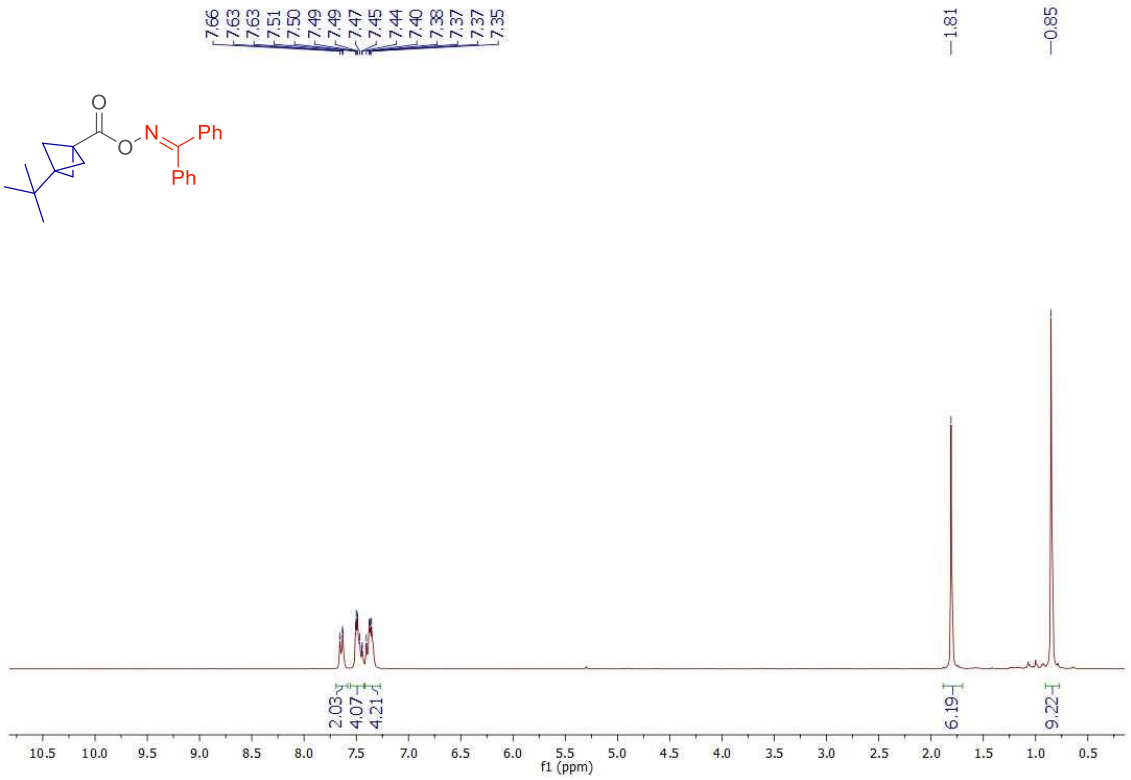
^{13}C NMR of compound **2b** (75 MHz, $CDCl_3$)



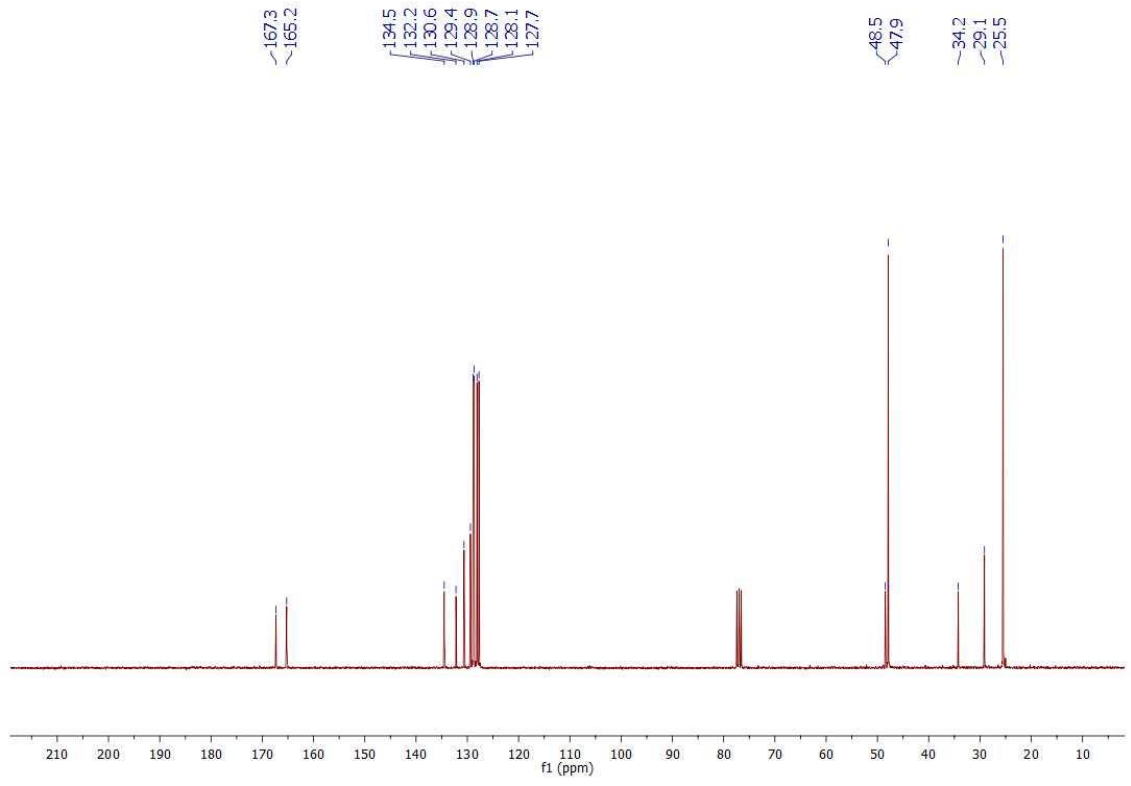
^{1}H NMR of compound **2d** (300 MHz, $CDCl_3$)



^{13}C NMR of compound **2d** (75 MHz, $CDCl_3$)



^{1}H NMR of compound **2c** (300 MHz, $CDCl_3$)



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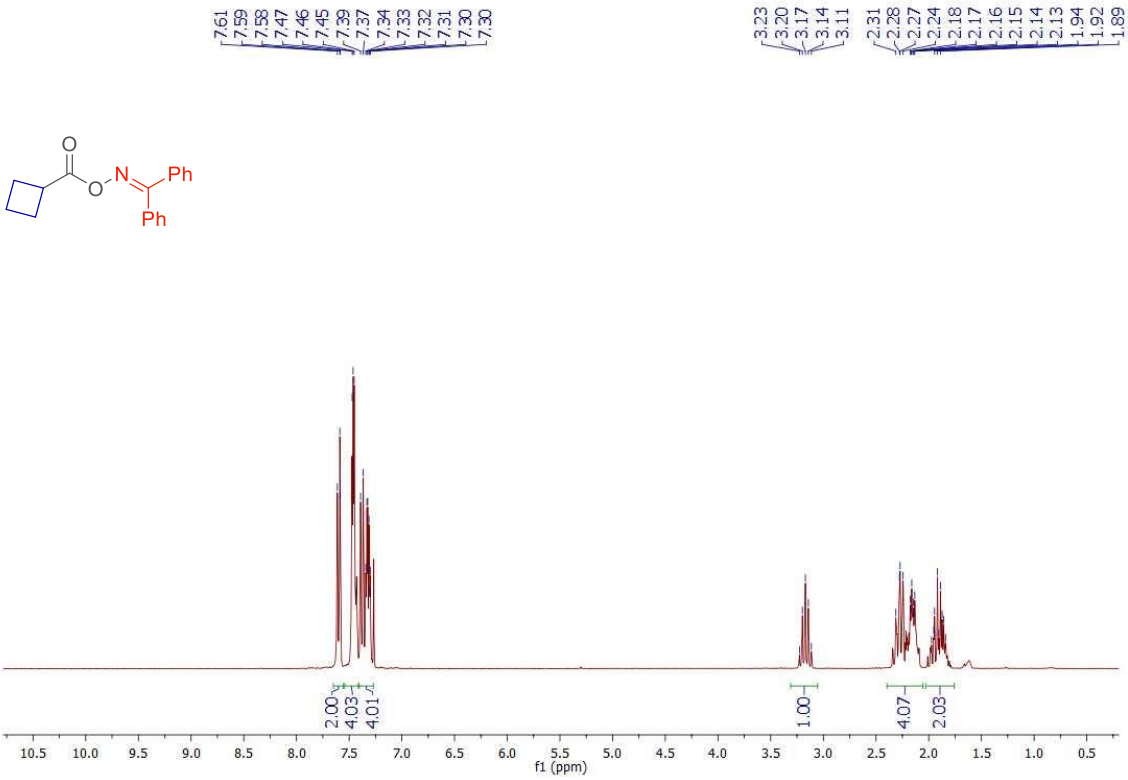
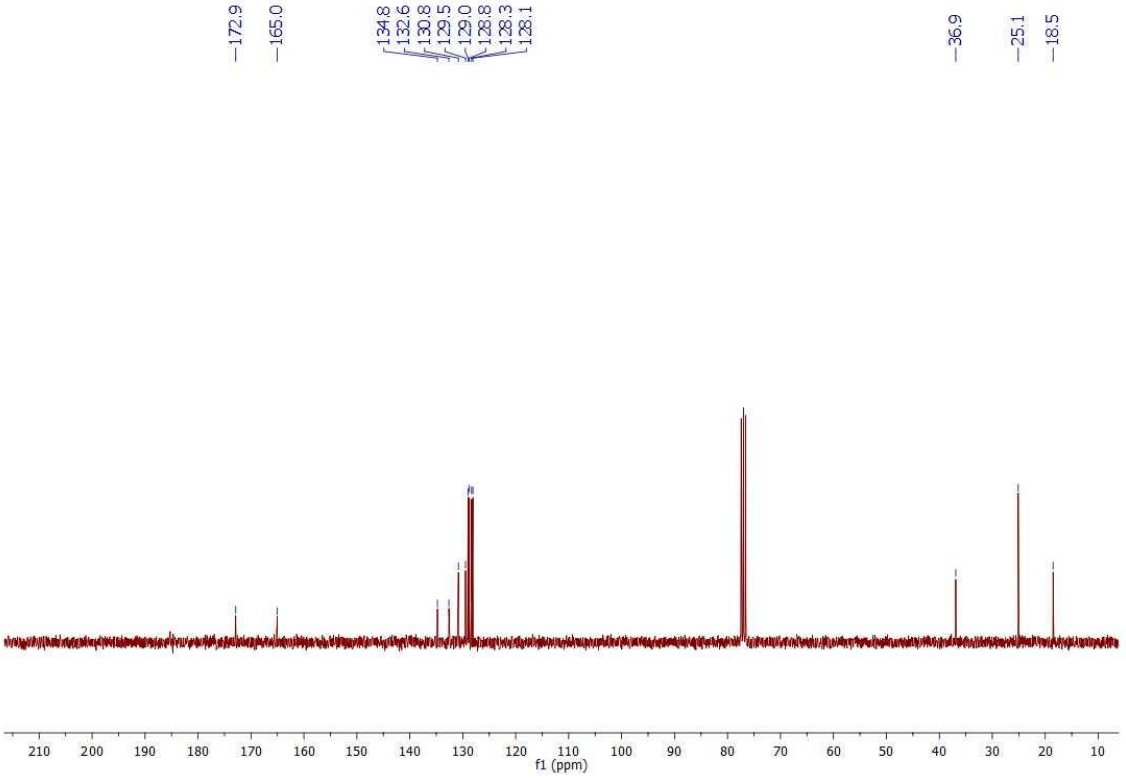
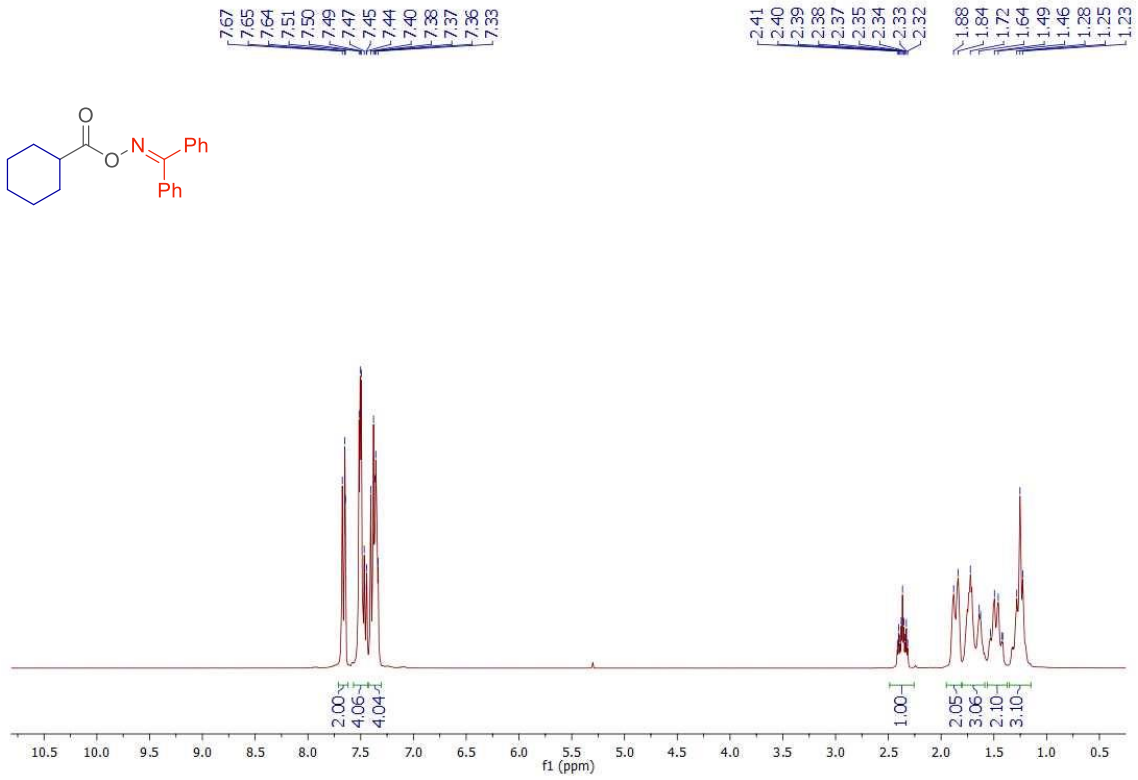


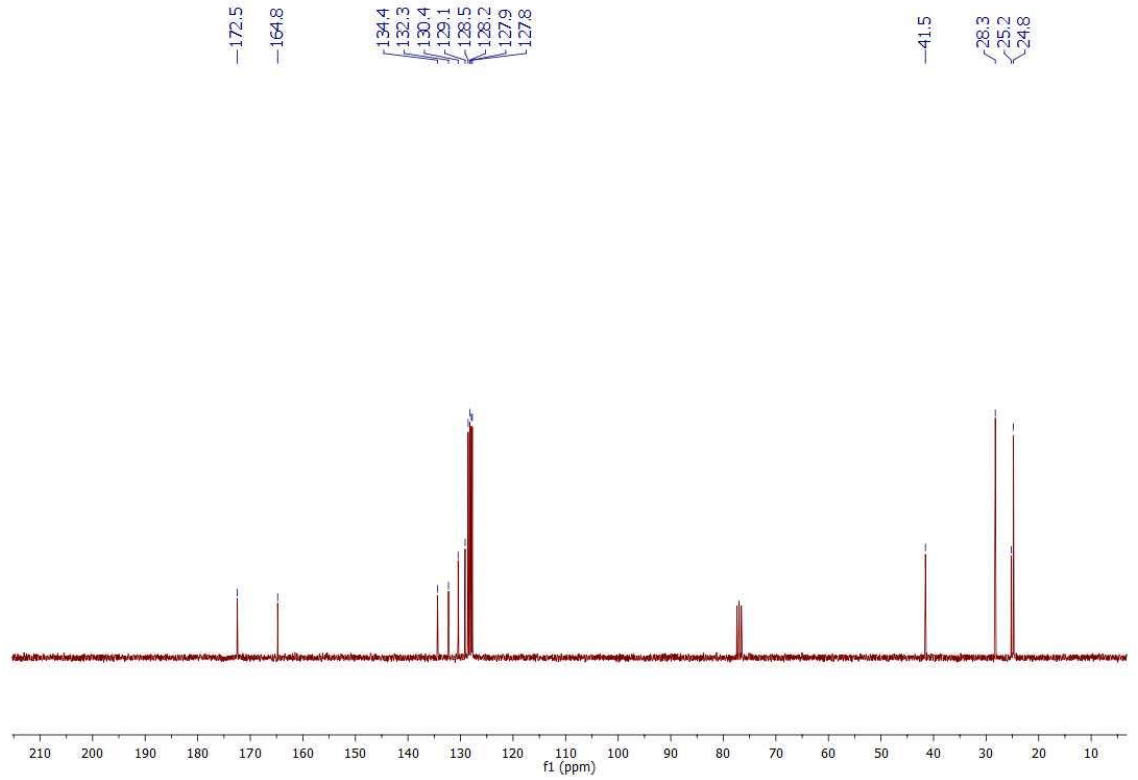
^{1}H NMR of compound **2e** (300 MHz, $CDCl_3$)



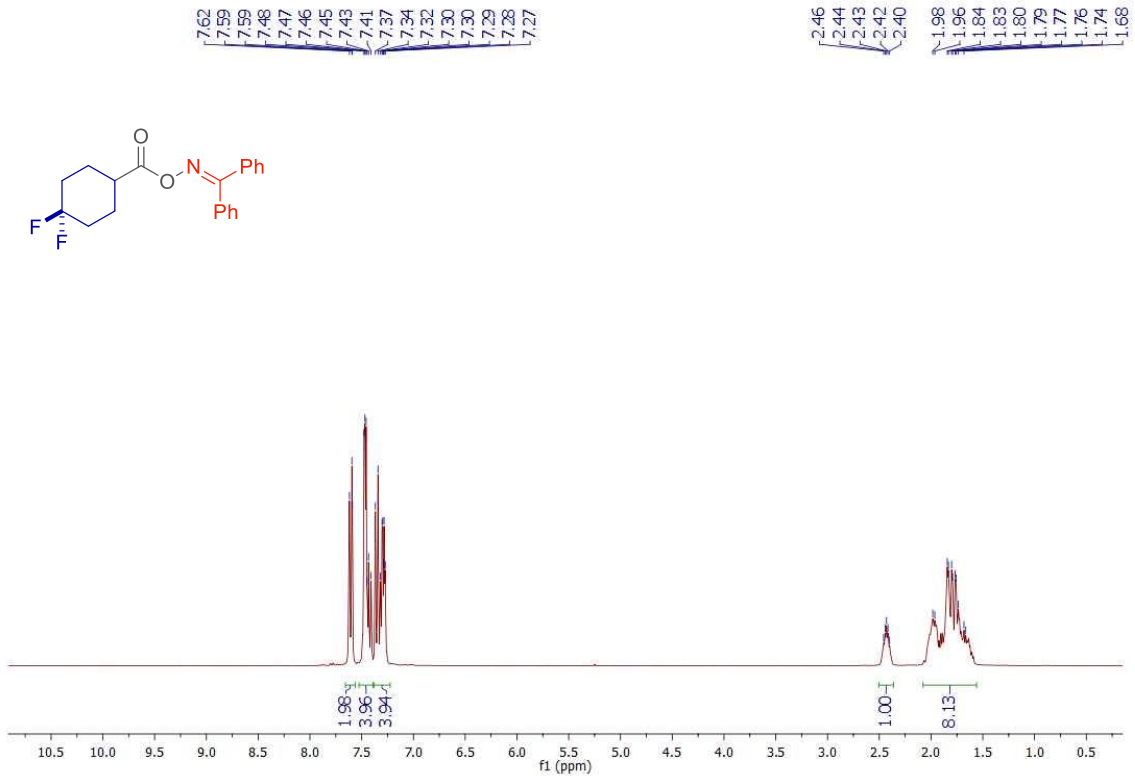
^{13}C NMR of compound **2e** (75 MHz, $CDCl_3$)



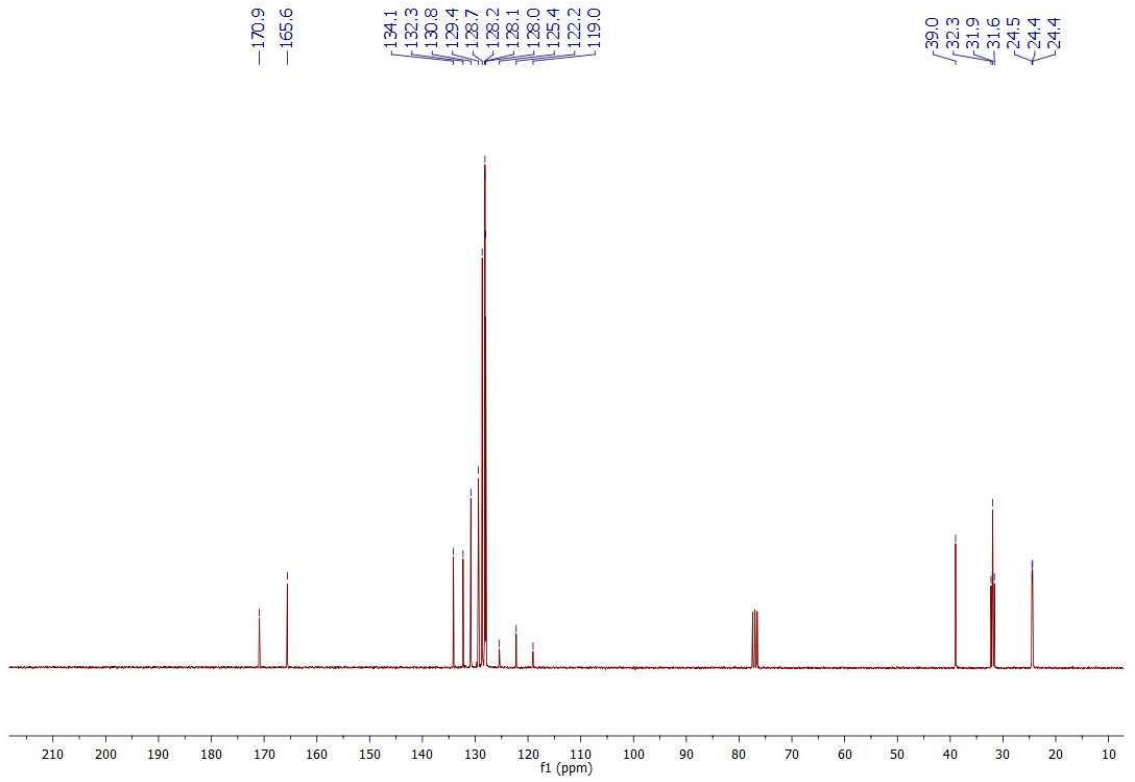
^{1}H NMR of compound **2f** (300 MHz, $CDCl_3$)



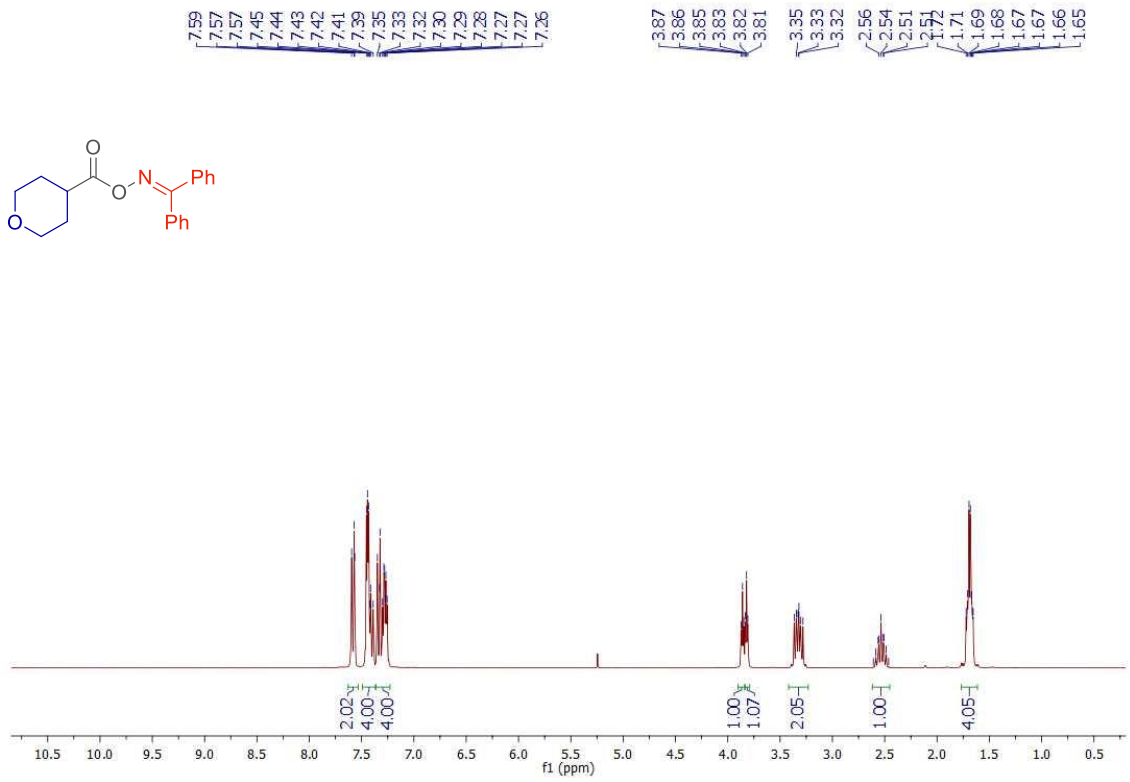
^{13}C NMR of compound **2f** (75 MHz, $CDCl_3$)



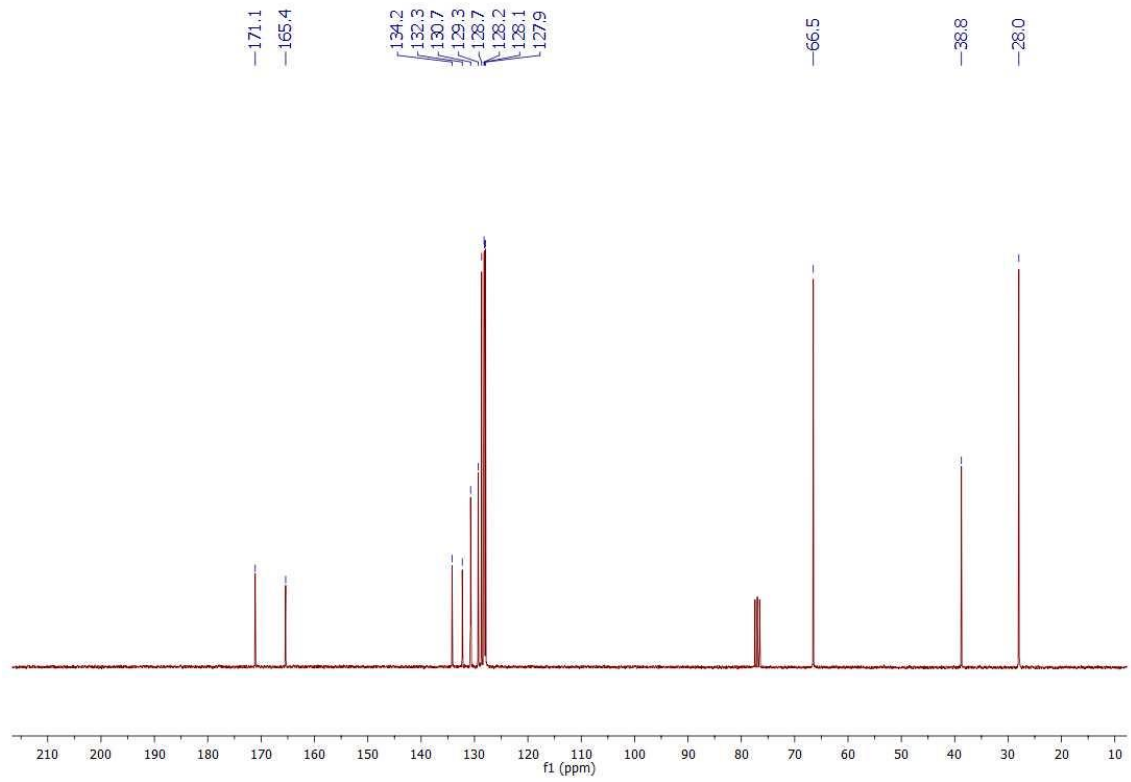
^{1}H NMR of compound **2g** (300 MHz, $CDCl_3$)



^{13}C NMR of compound **2g** (75 MHz, $CDCl_3$)



^{1}H NMR of compound **2h** (300 MHz, $CDCl_3$)



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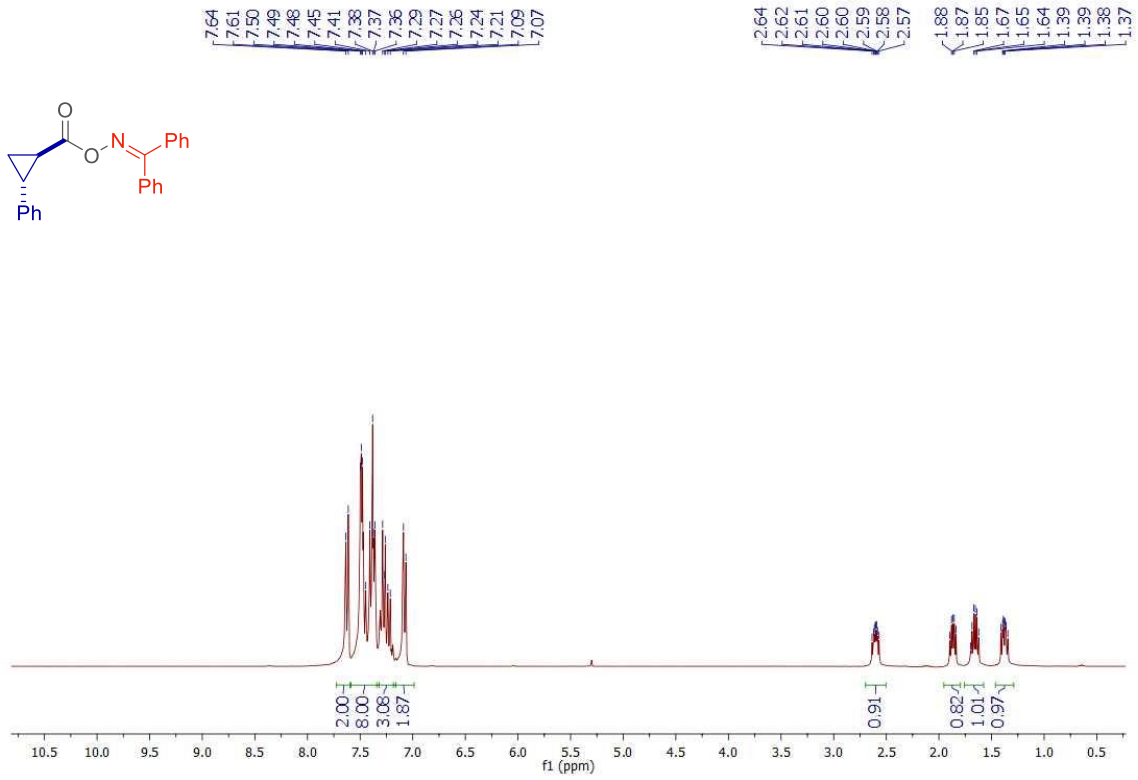
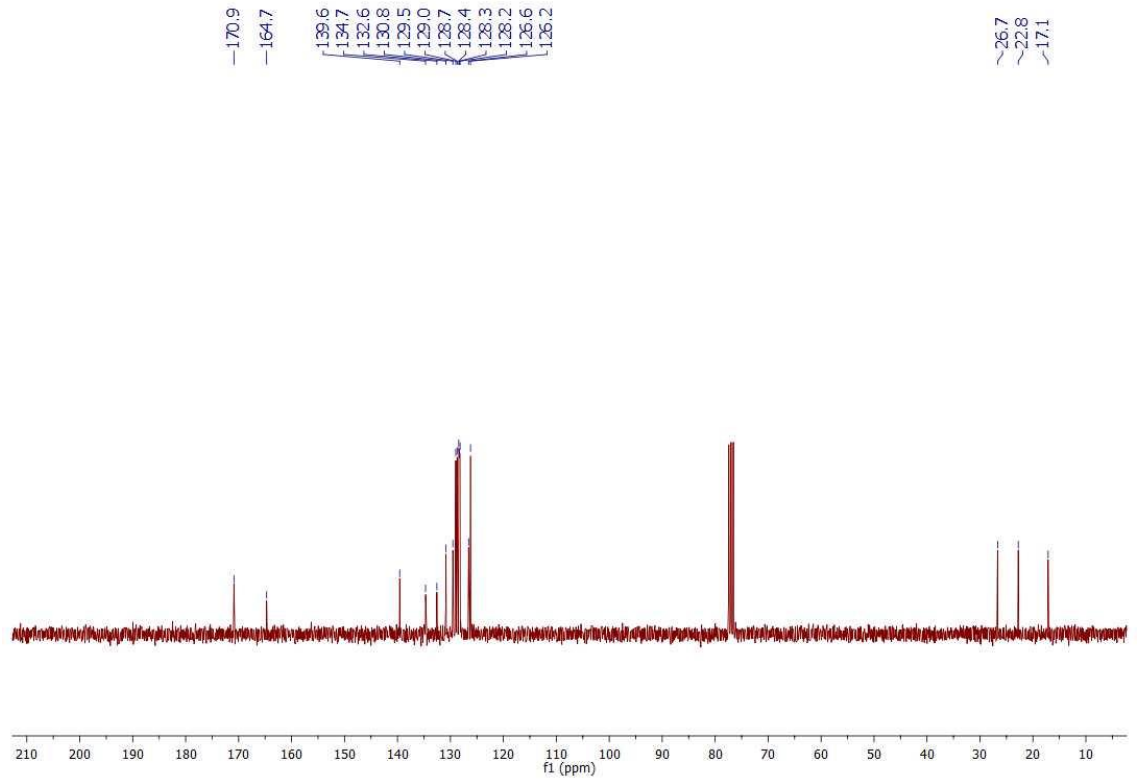
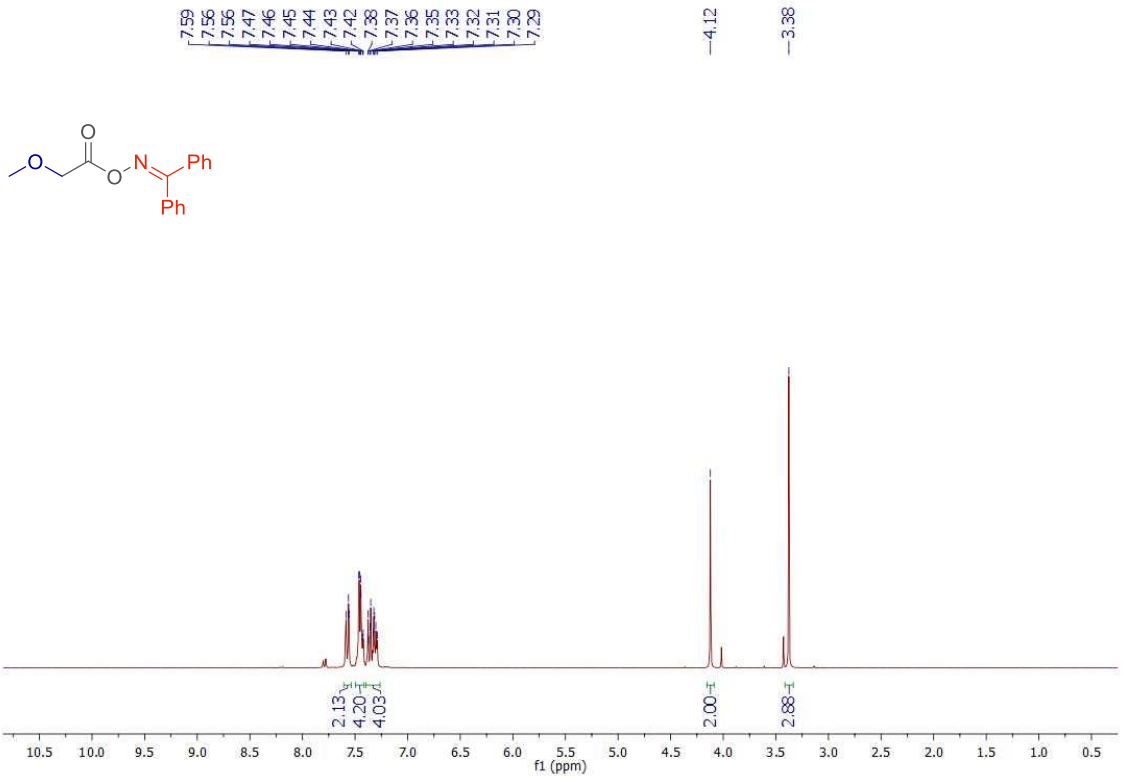


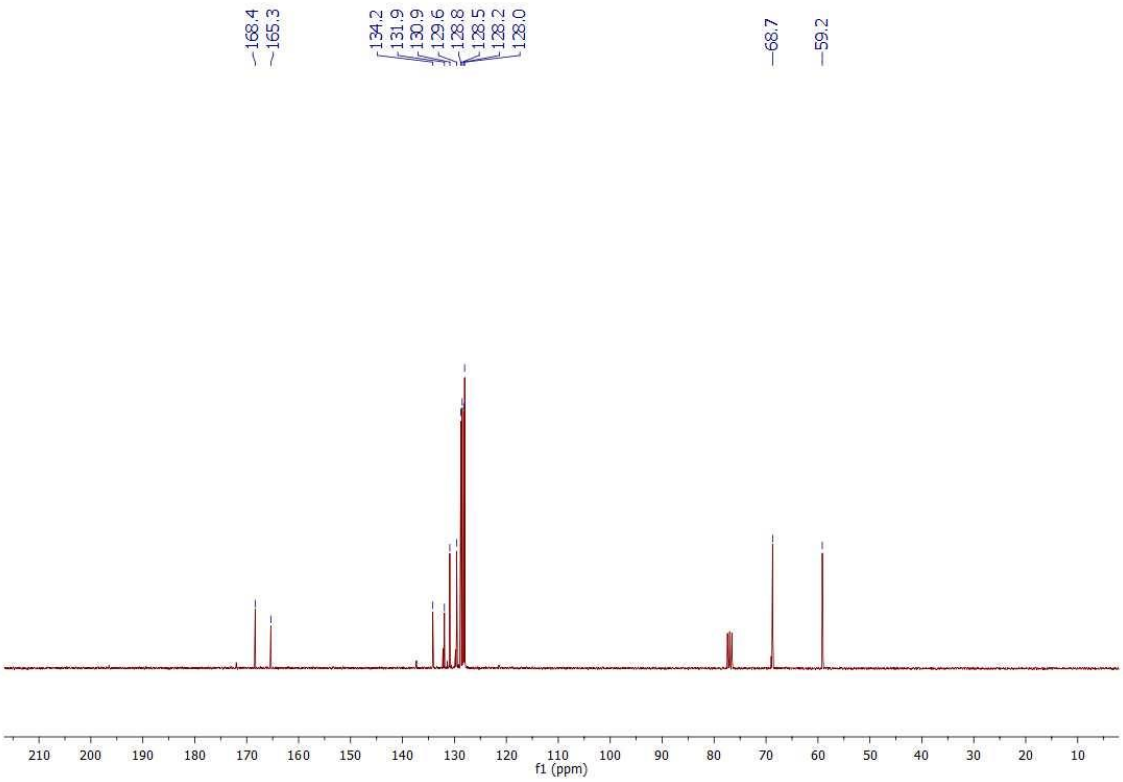
^{1}H NMR of compound **2i** (300 MHz, $CDCl_3$)



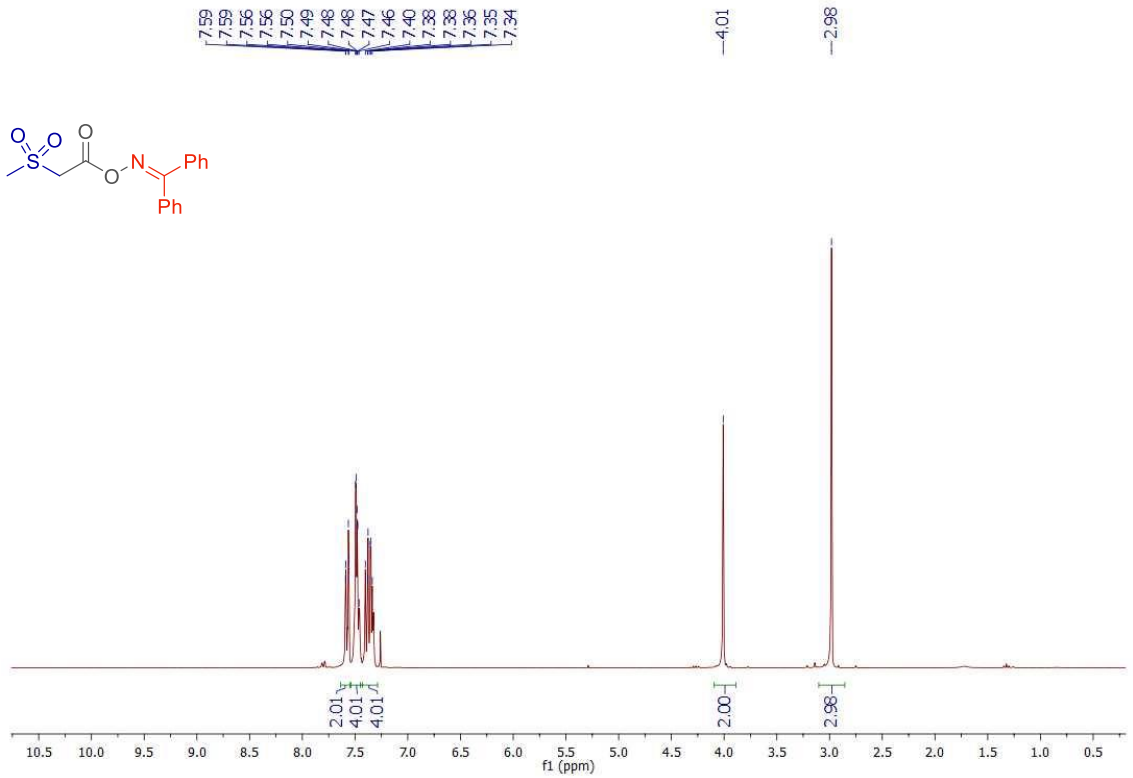
^{13}C NMR of compound **2i** (75 MHz, $CDCl_3$)



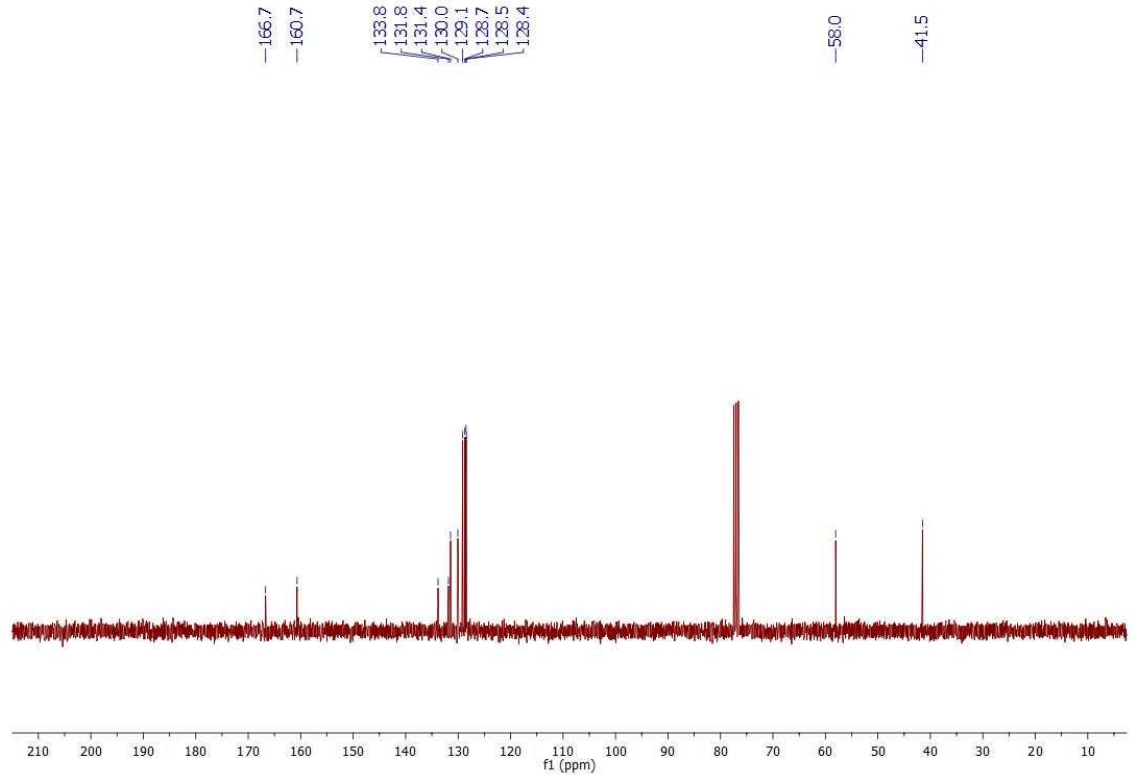
^{1}H NMR of compound **2j** (300 MHz, $CDCl_3$)



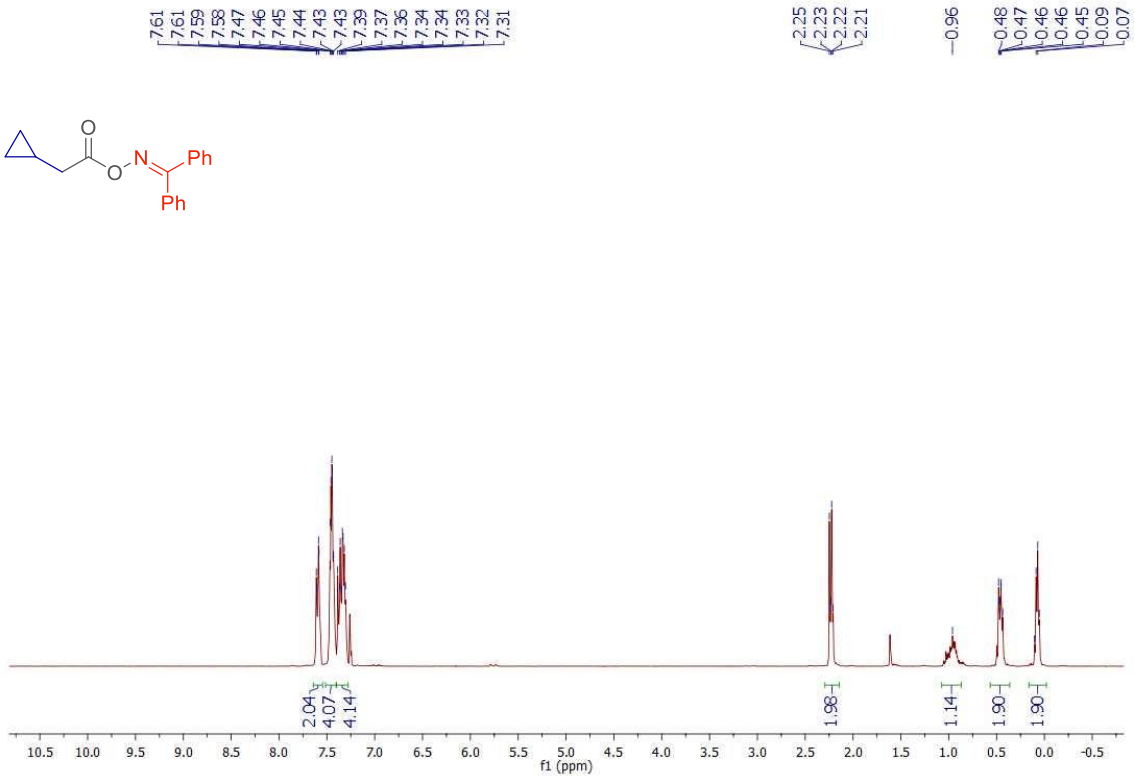
^{13}C NMR of compound **2j** (75 MHz, $CDCl_3$)



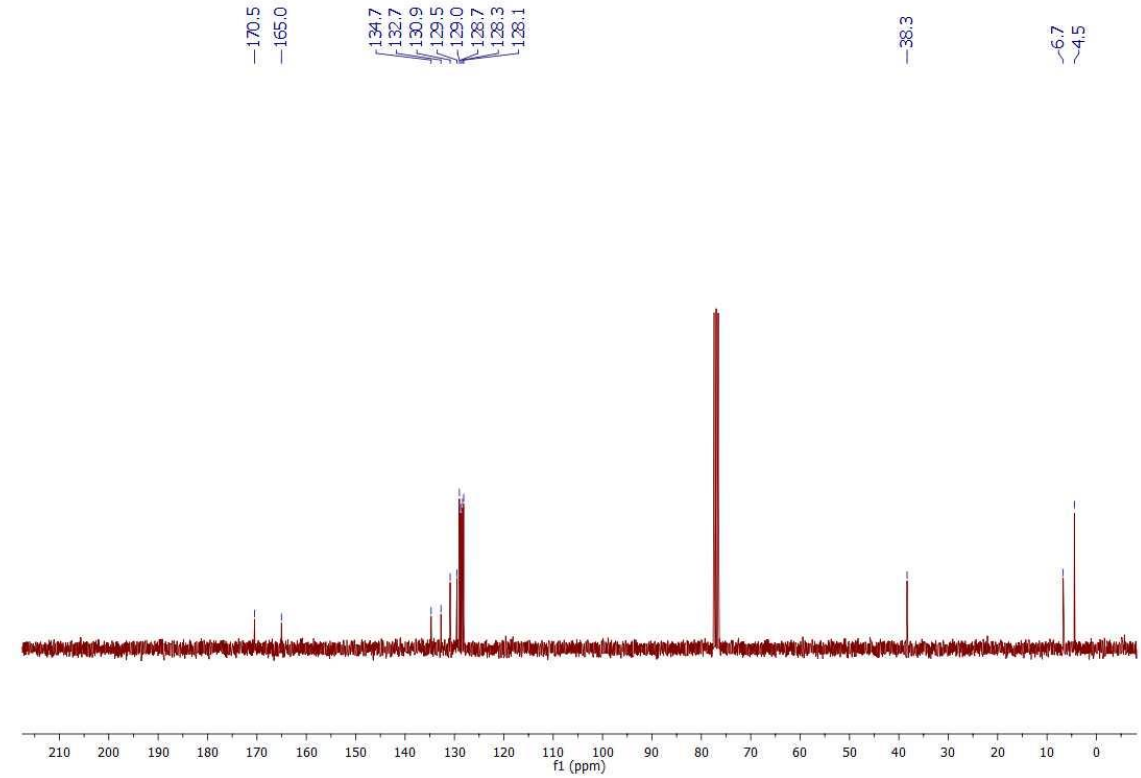
^{1}H NMR of compound **2k** (300 MHz, $CDCl_3$)



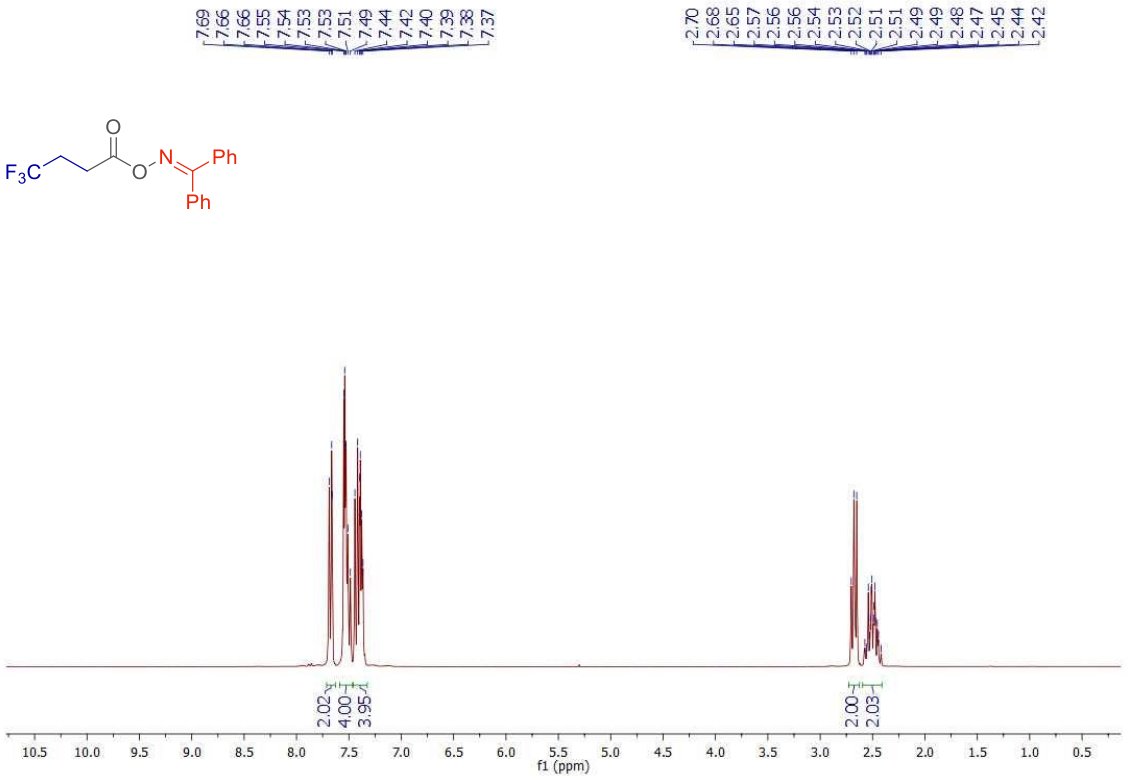
^{13}C NMR of compound **2k** (75 MHz, $CDCl_3$)



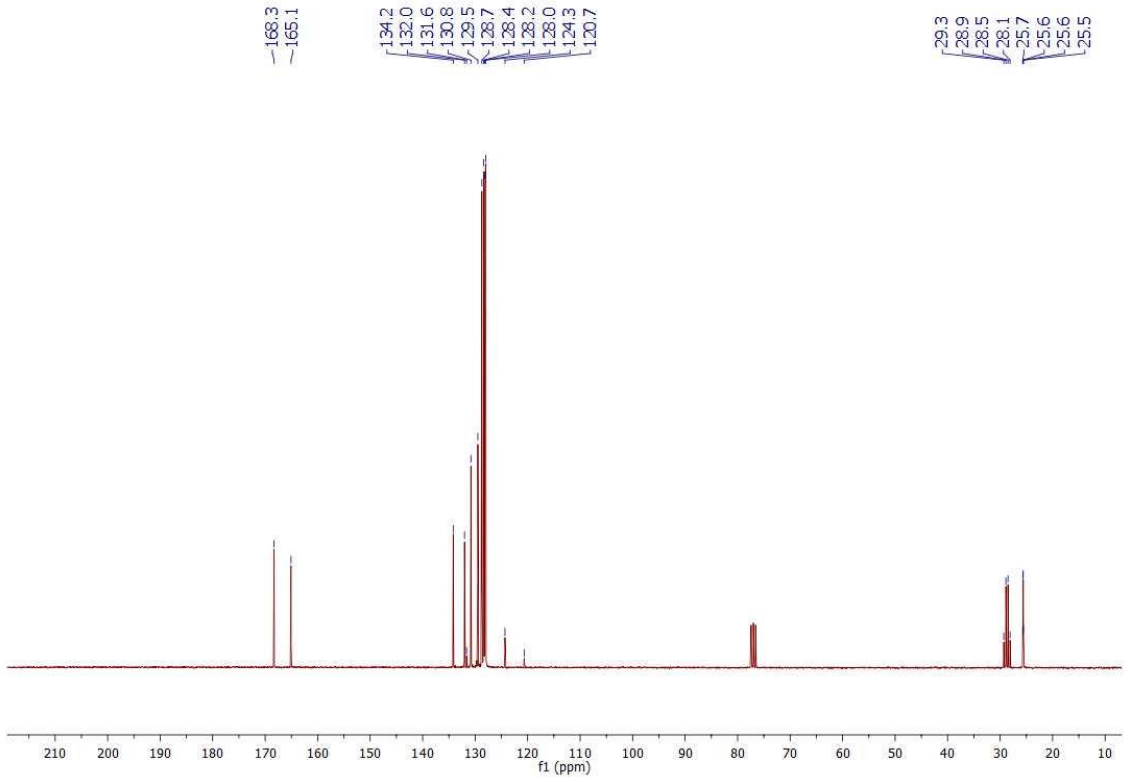
^{1}H NMR of compound **2l** (300 MHz, $CDCl_3$)



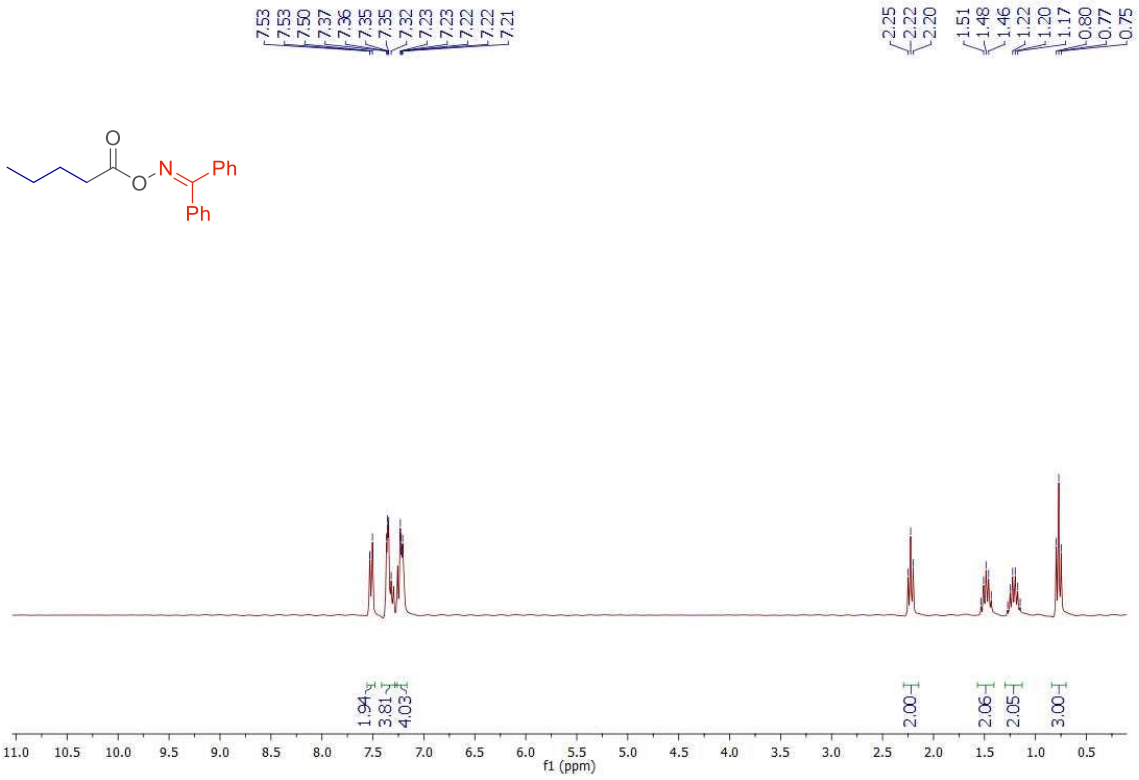
^{13}C NMR of compound **2l** (75 MHz, $CDCl_3$)



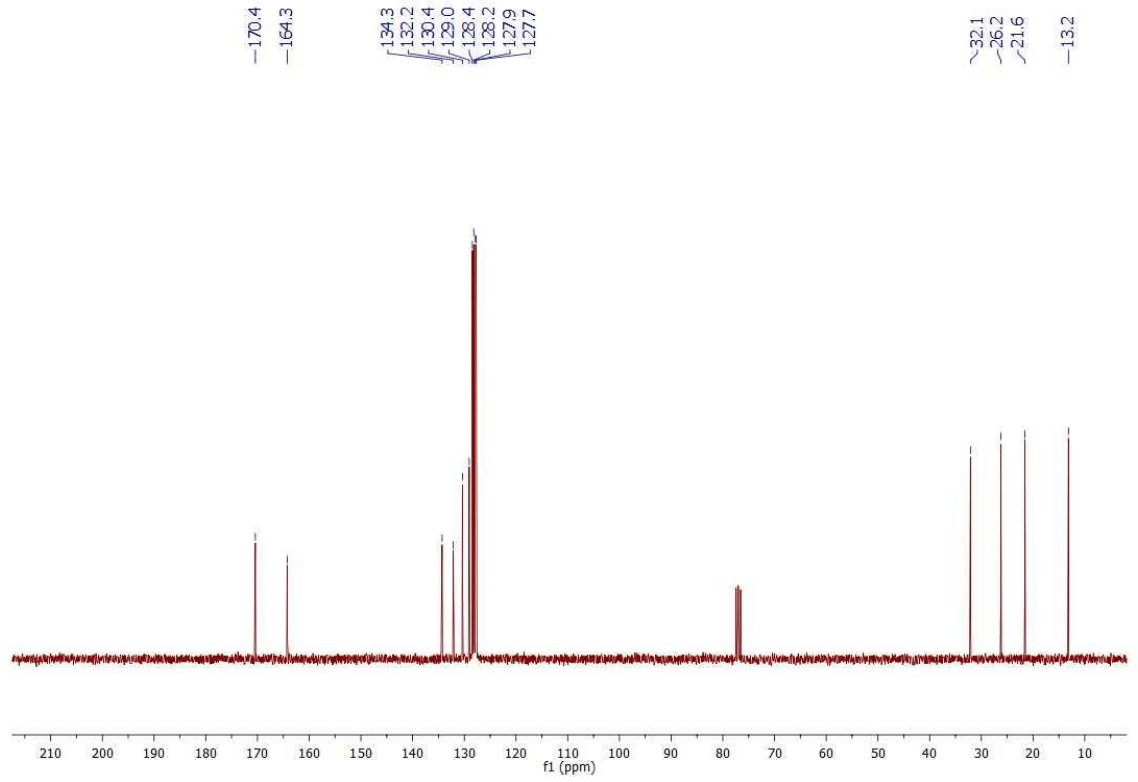
^{1}H NMR of compound **2m** (300 MHz, $CDCl_3$)



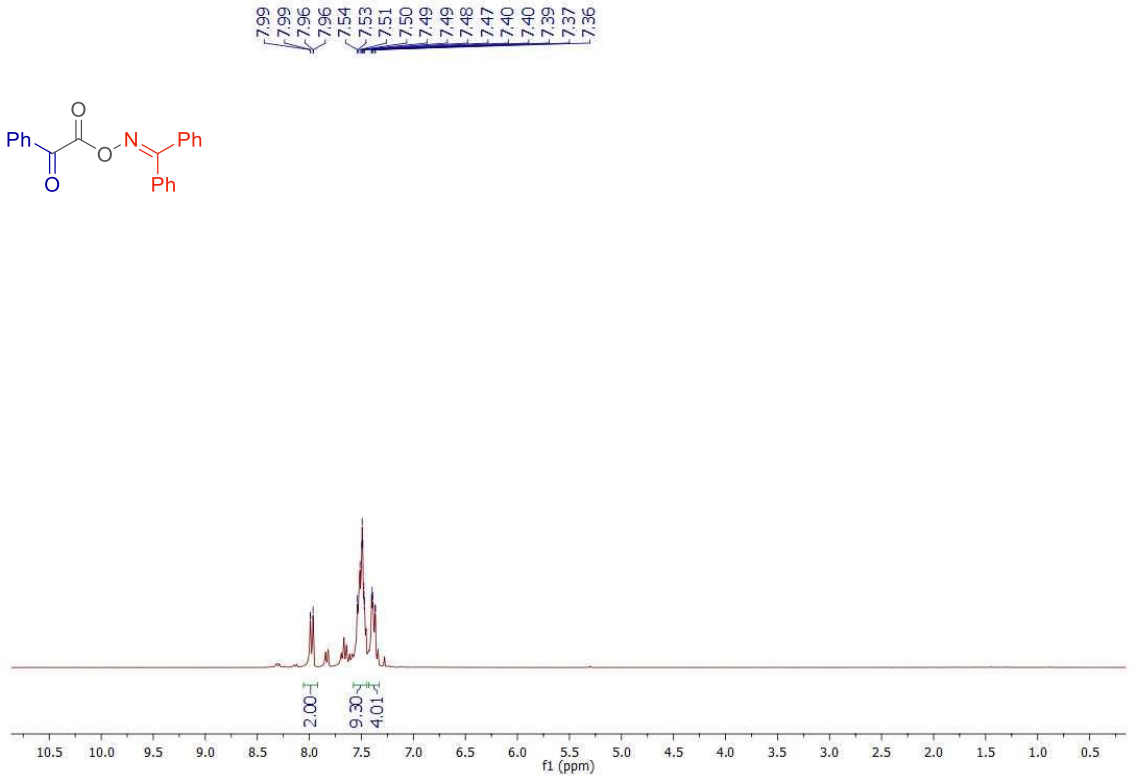
^{13}C NMR of compound **2m** (75 MHz, $CDCl_3$)



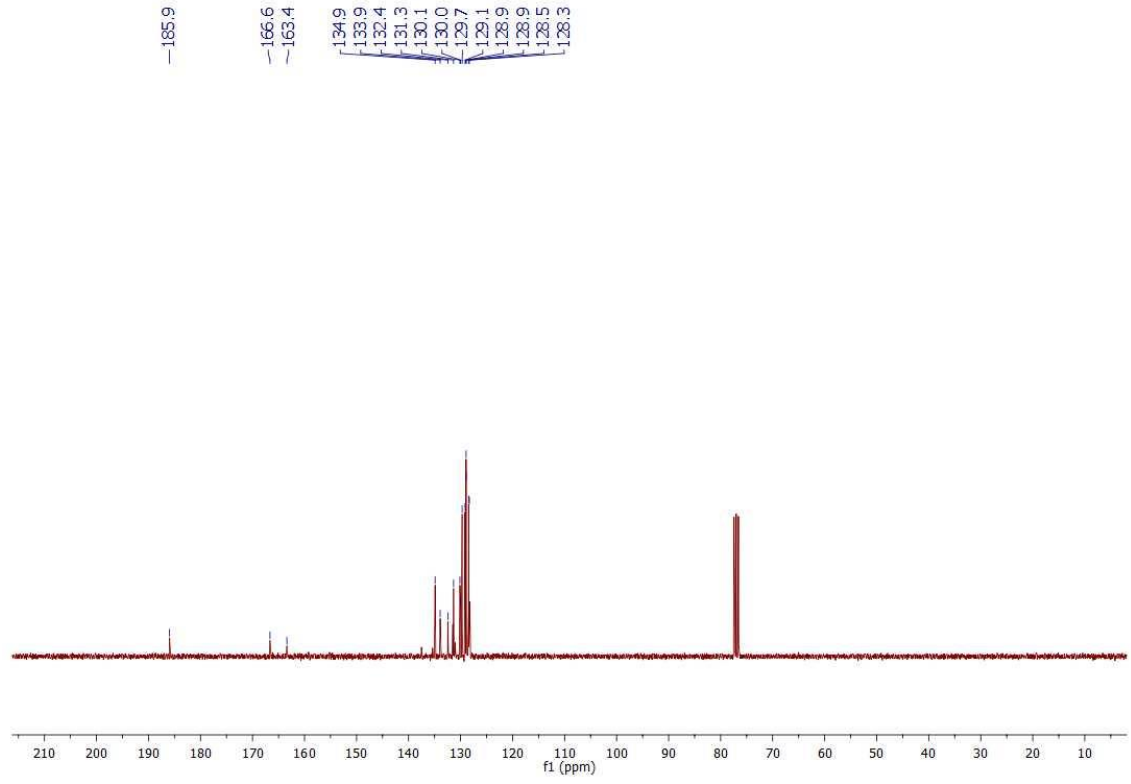
^{1}H NMR of compound **2n** (300 MHz, $CDCl_3$)



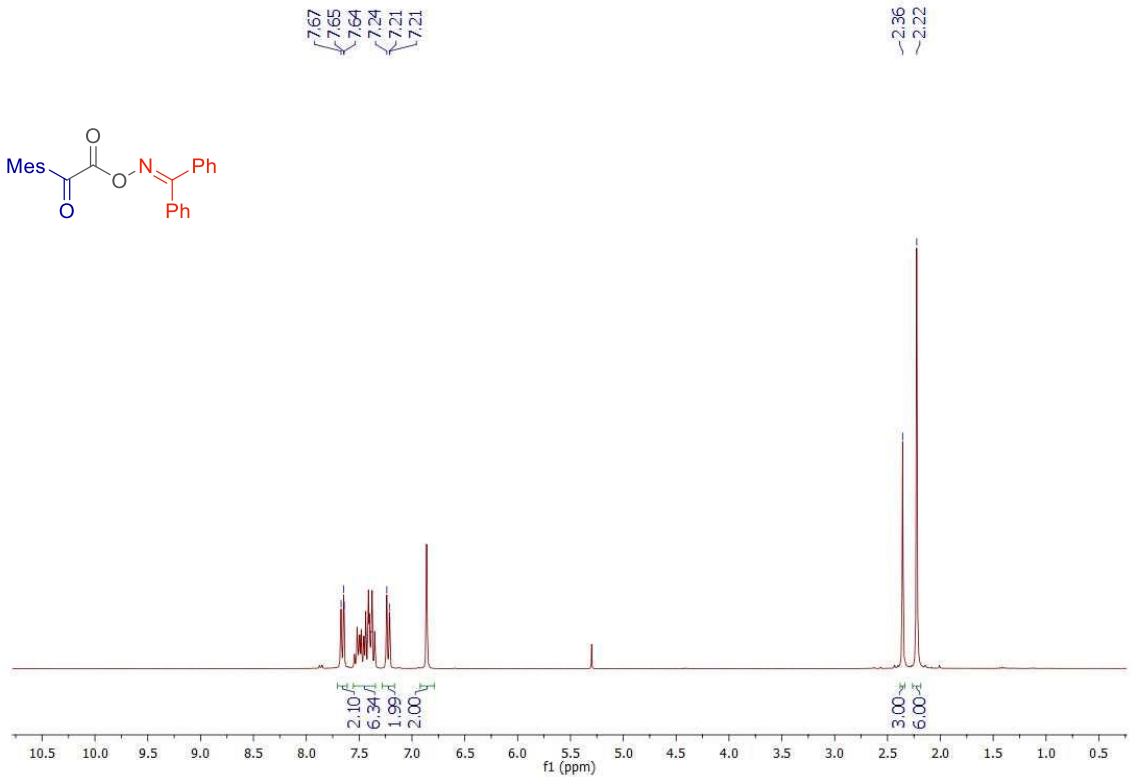
^{13}C NMR of compound **2n** (75 MHz, $CDCl_3$)



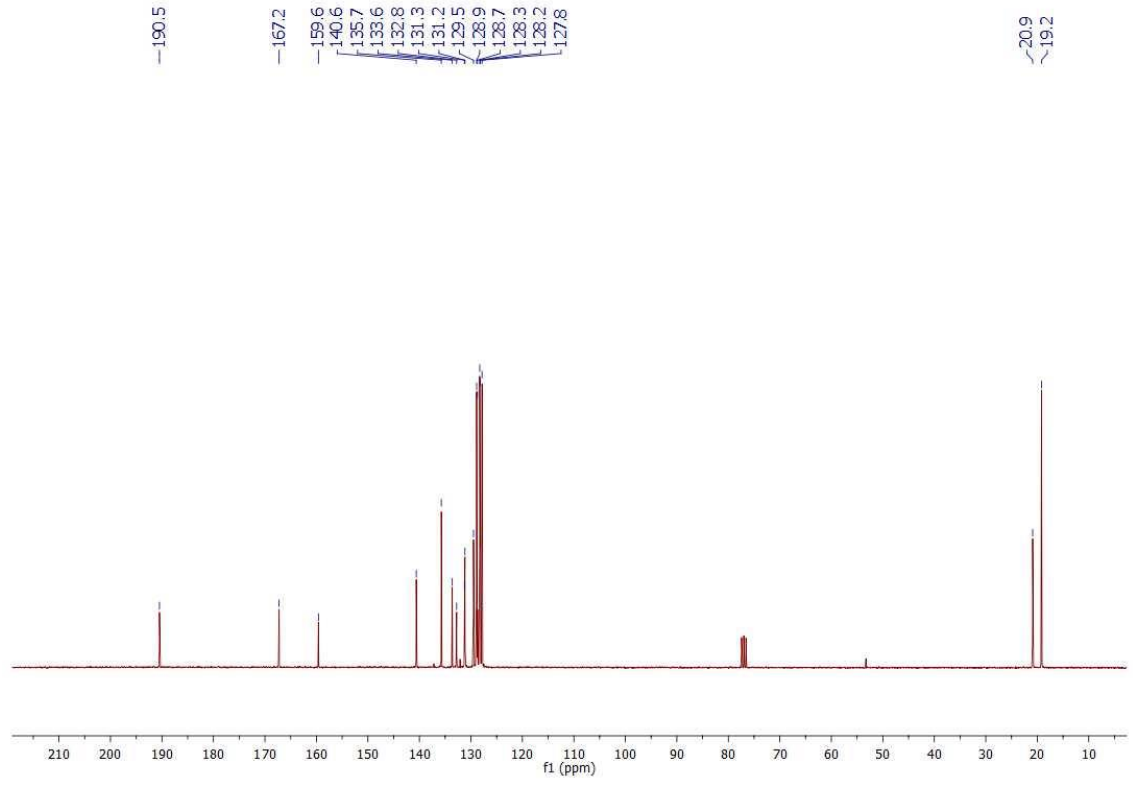
^{1}H NMR of compound **2o** (300 MHz, $CDCl_3$)



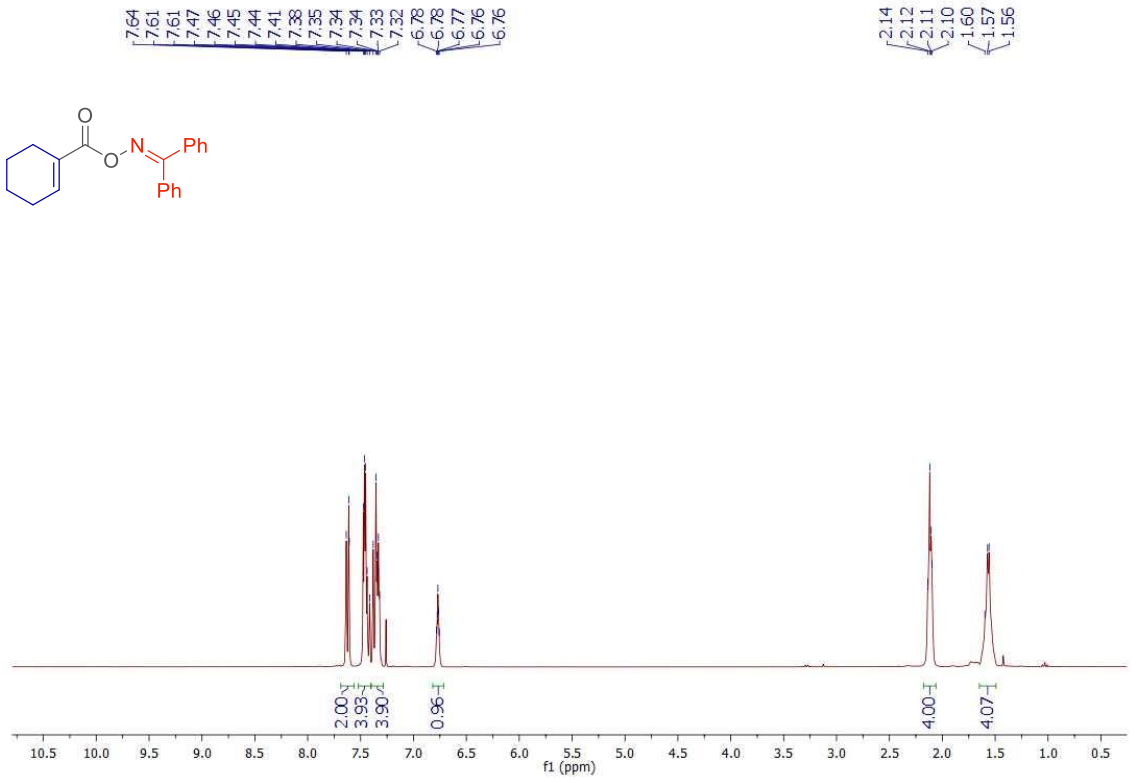
^{13}C NMR of compound **2o** (75 MHz, $CDCl_3$)



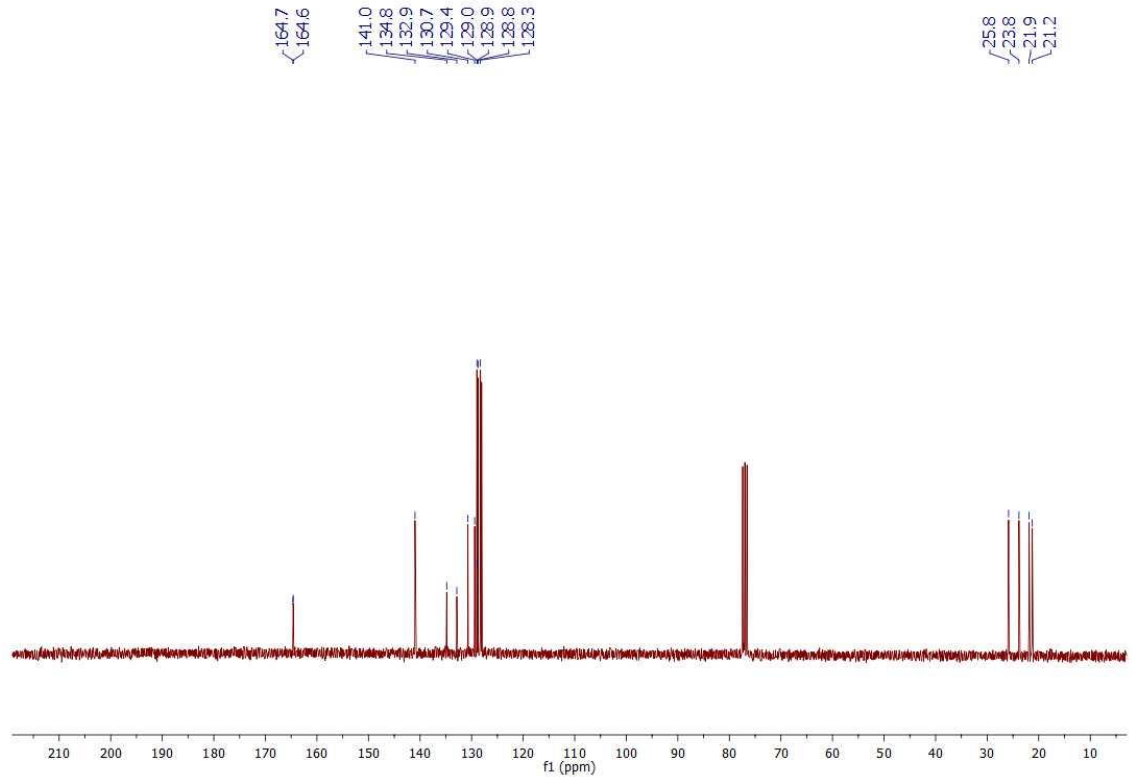
^{1}H NMR of compound **2p** (300 MHz, $CDCl_3$)



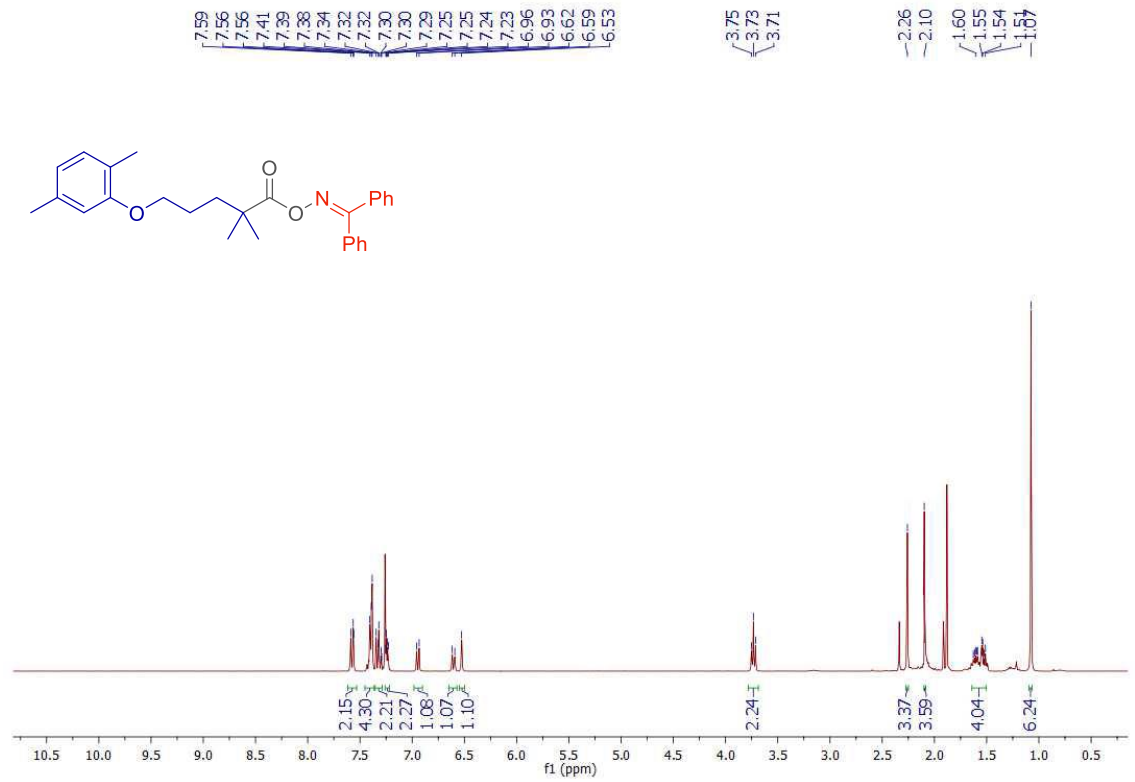
^{13}C NMR of compound **2p** (75 MHz, $CDCl_3$)



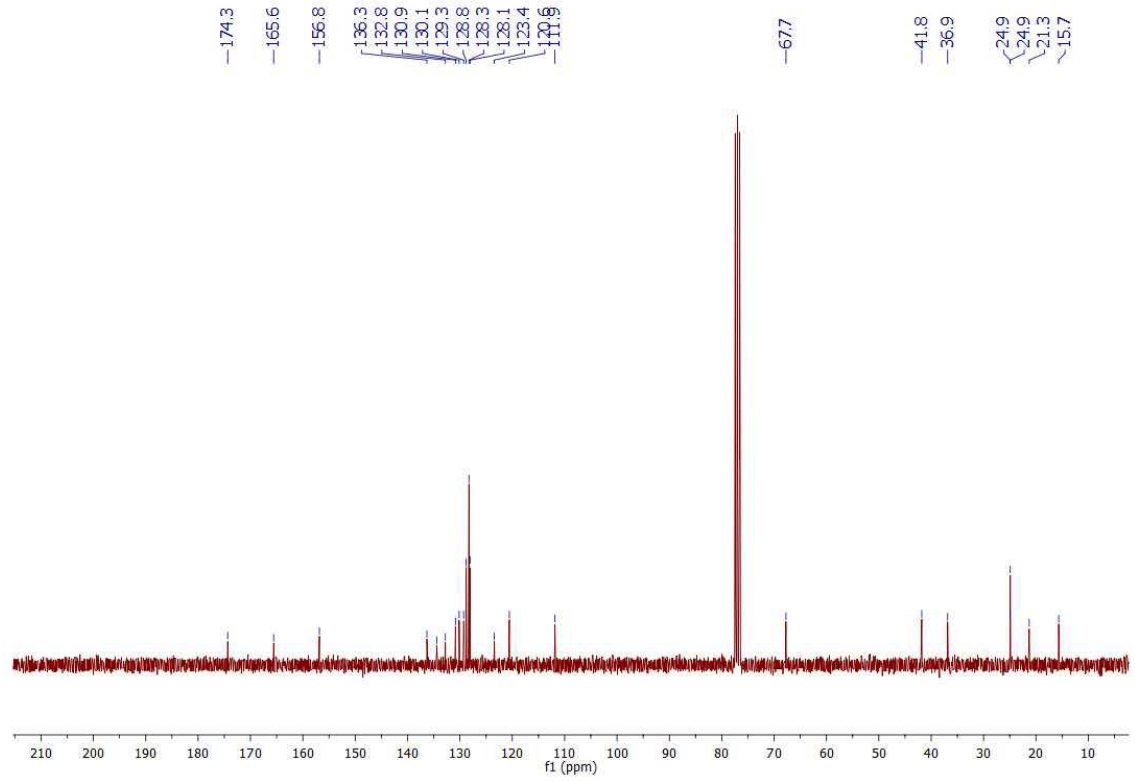
^{1}H NMR of compound **2q** (300 MHz, $CDCl_3$)



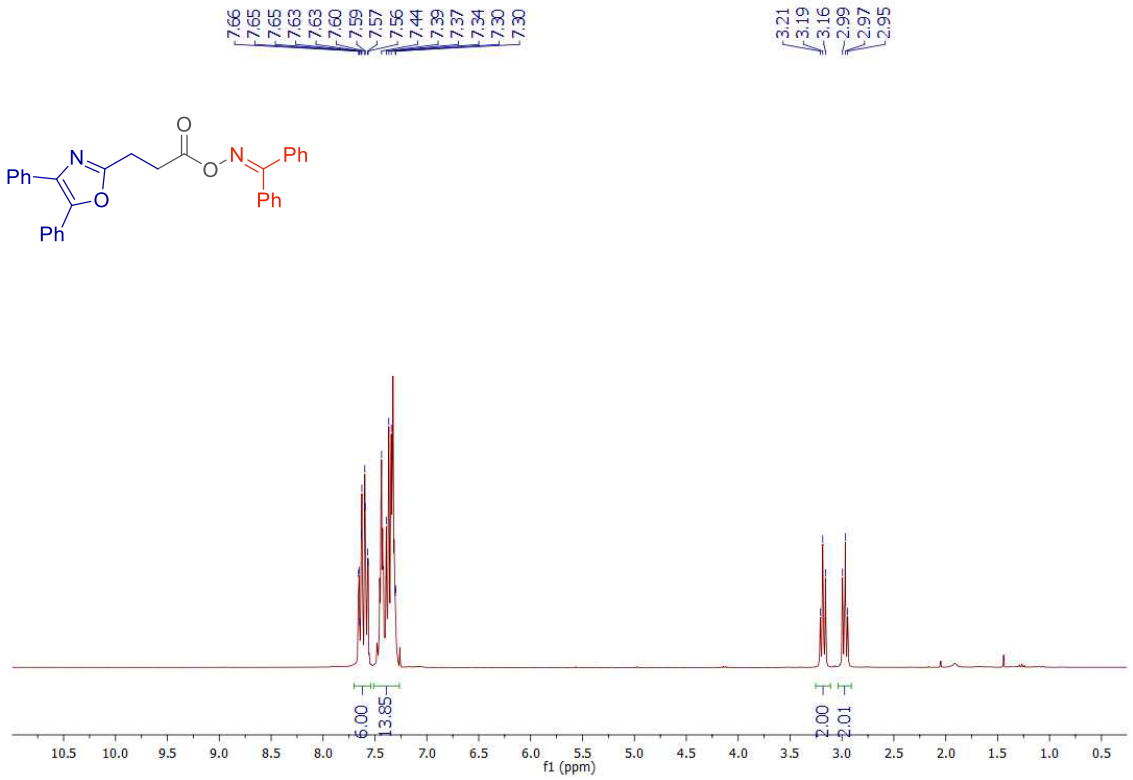
^{13}C NMR of compound **2q** (75 MHz, $CDCl_3$)



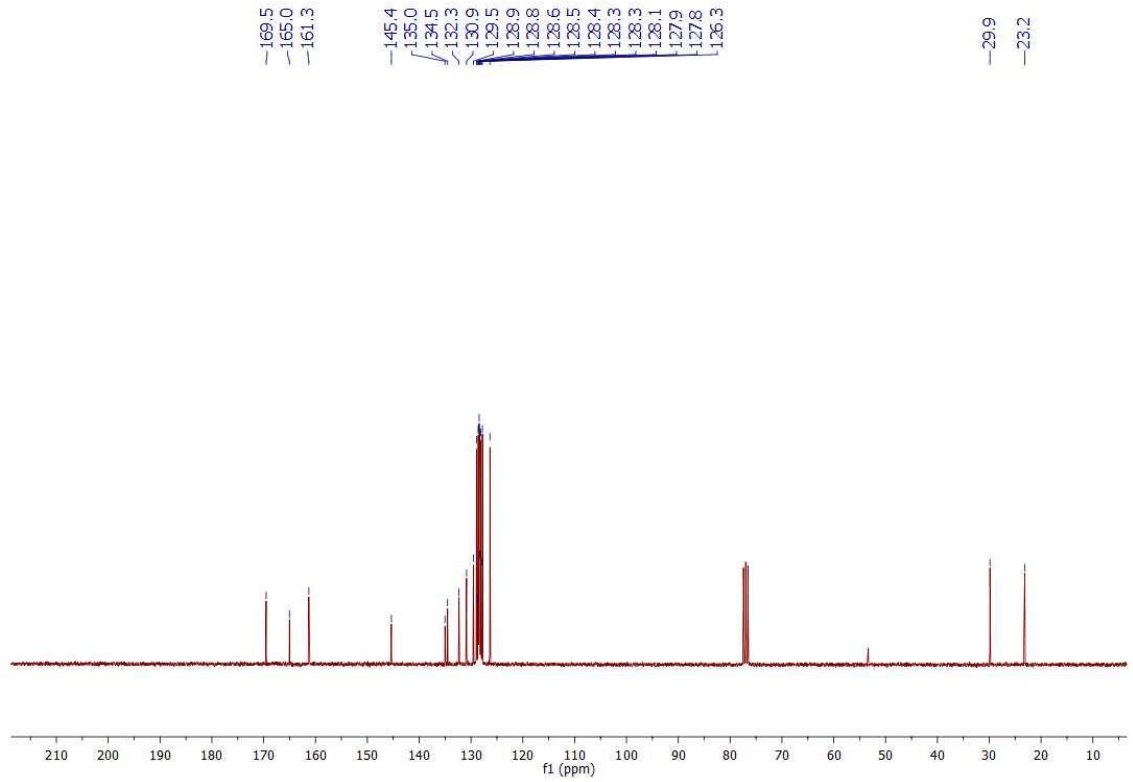
^{1}H NMR of compound **2r** (300 MHz, $CDCl_3$)



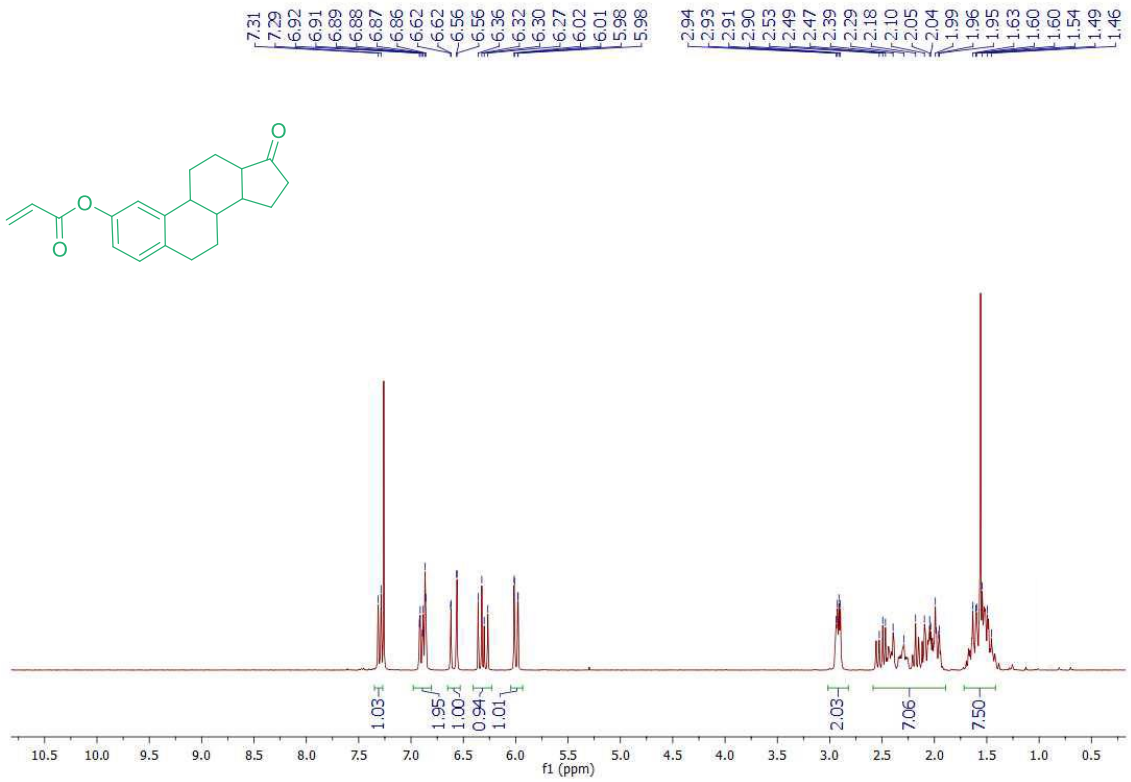
^{13}C NMR of compound **2r** (75 MHz, $CDCl_3$)



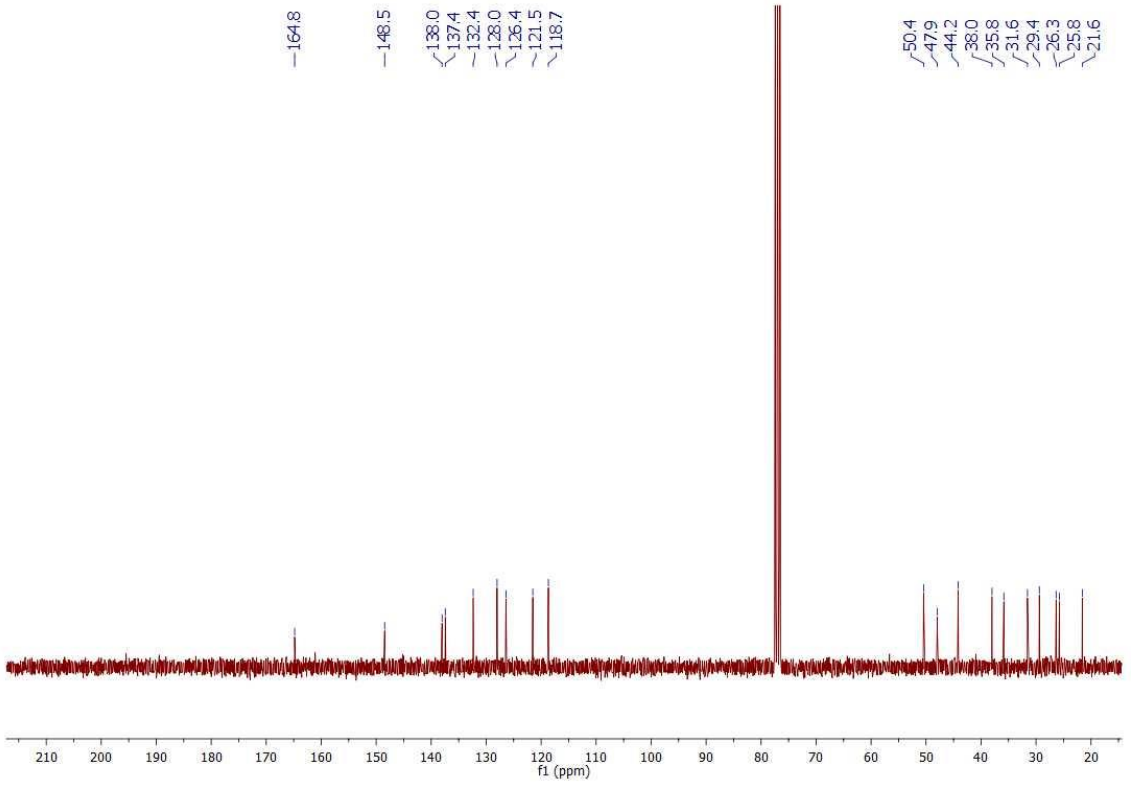
^{1}H NMR of compound **2s** (300 MHz, $CDCl_3$)



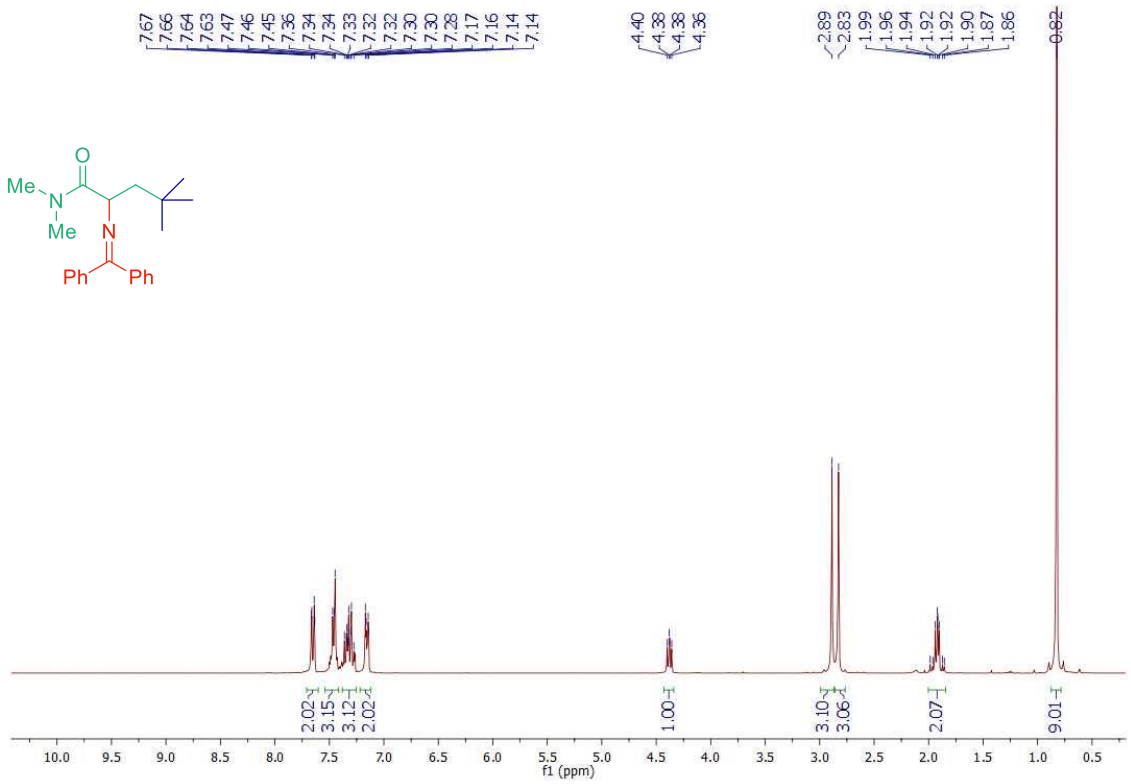
^{13}C NMR of compound **2s** (75 MHz, $CDCl_3$)



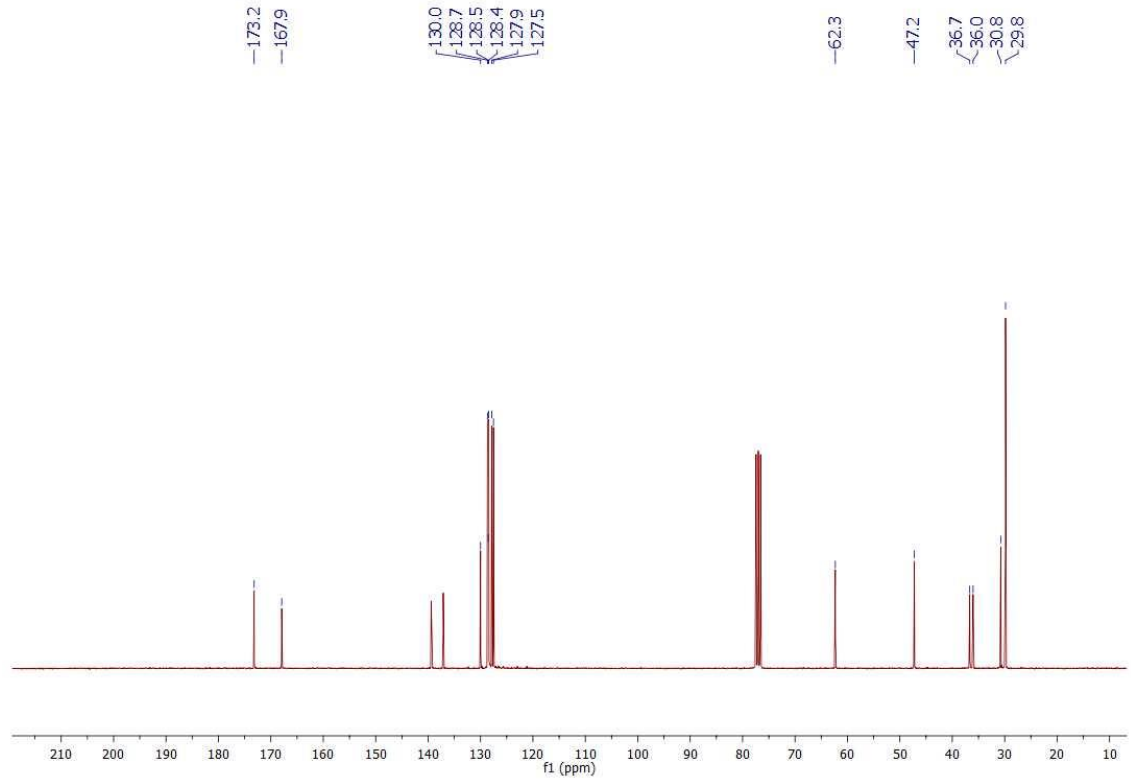
^{1}H NMR of compound **1q** (300 MHz, $CDCl_3$)



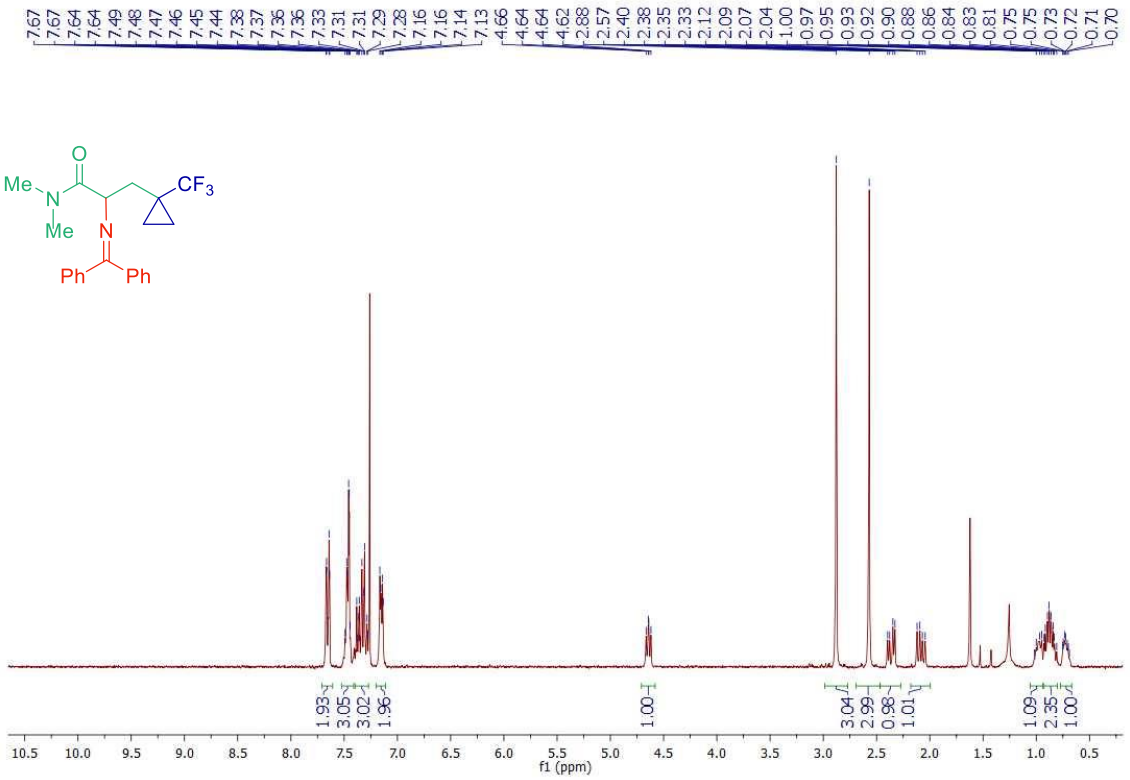
^{13}C NMR of compound **1q** (75 MHz, $CDCl_3$)



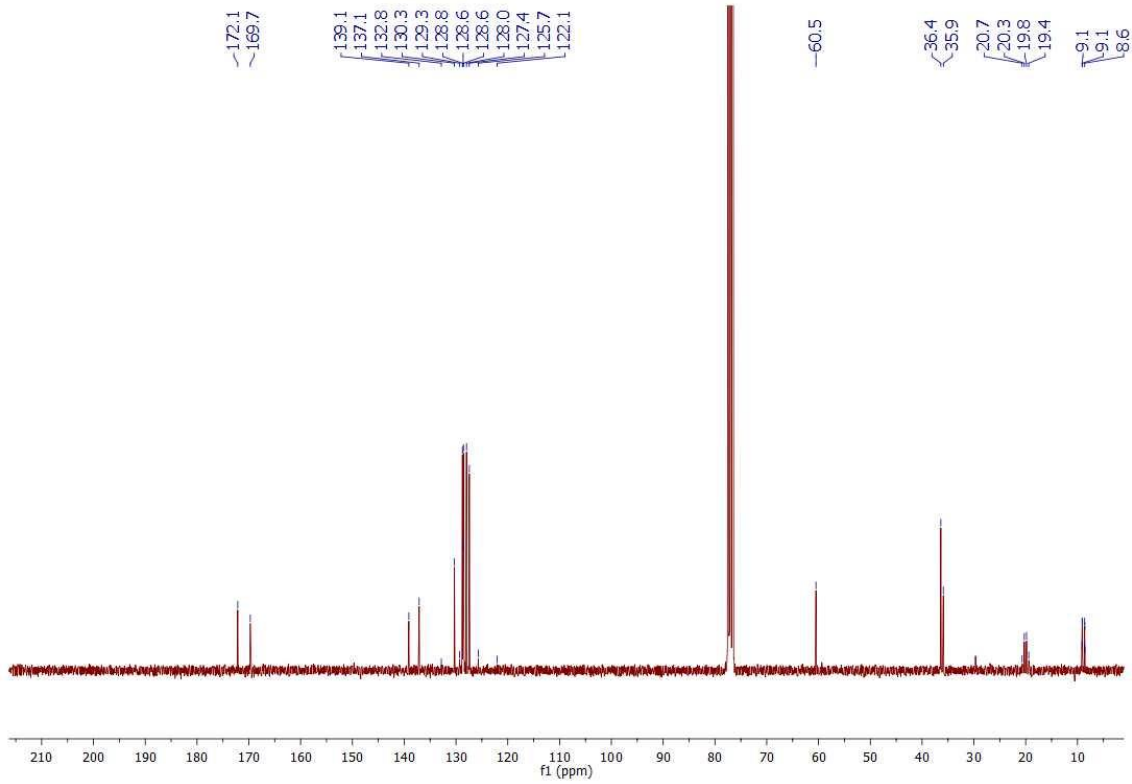
^{1}H NMR of compound **3aa** (300 MHz, $CDCl_3$)



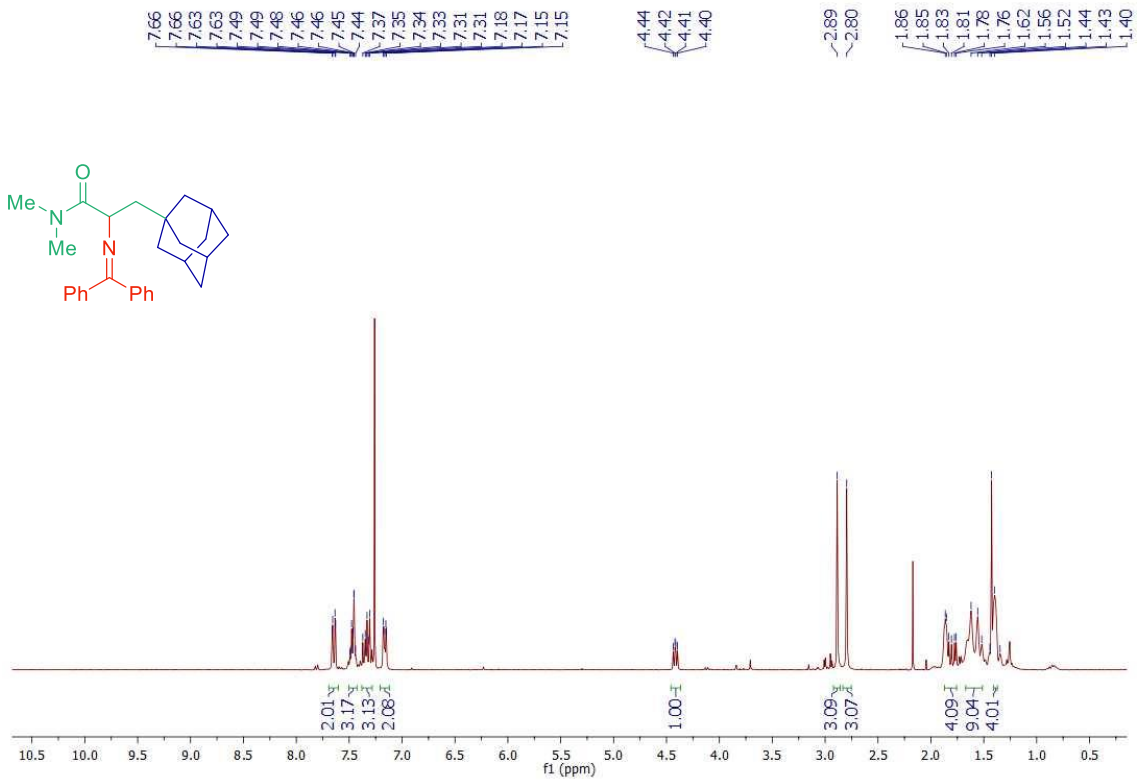
^{13}C NMR of compound **3aa** (75 MHz, $CDCl_3$)



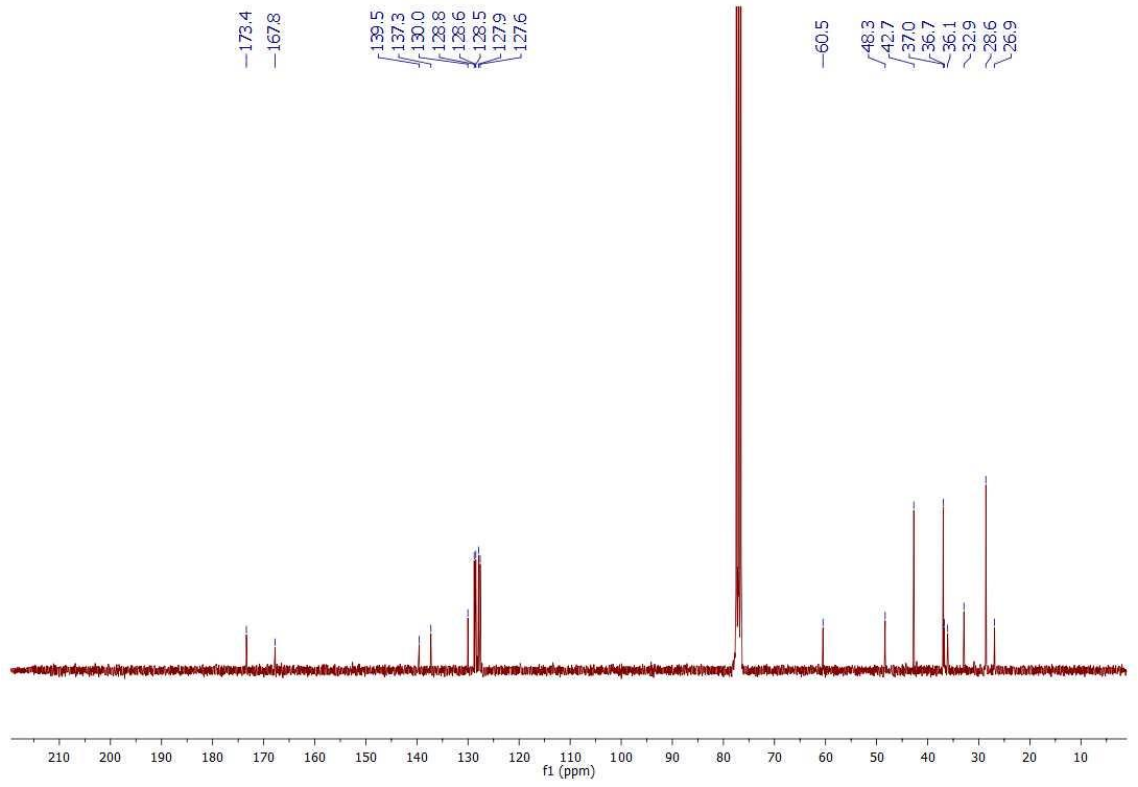
^{1}H NMR of compound **3ab** (300 MHz, $CDCl_3$)



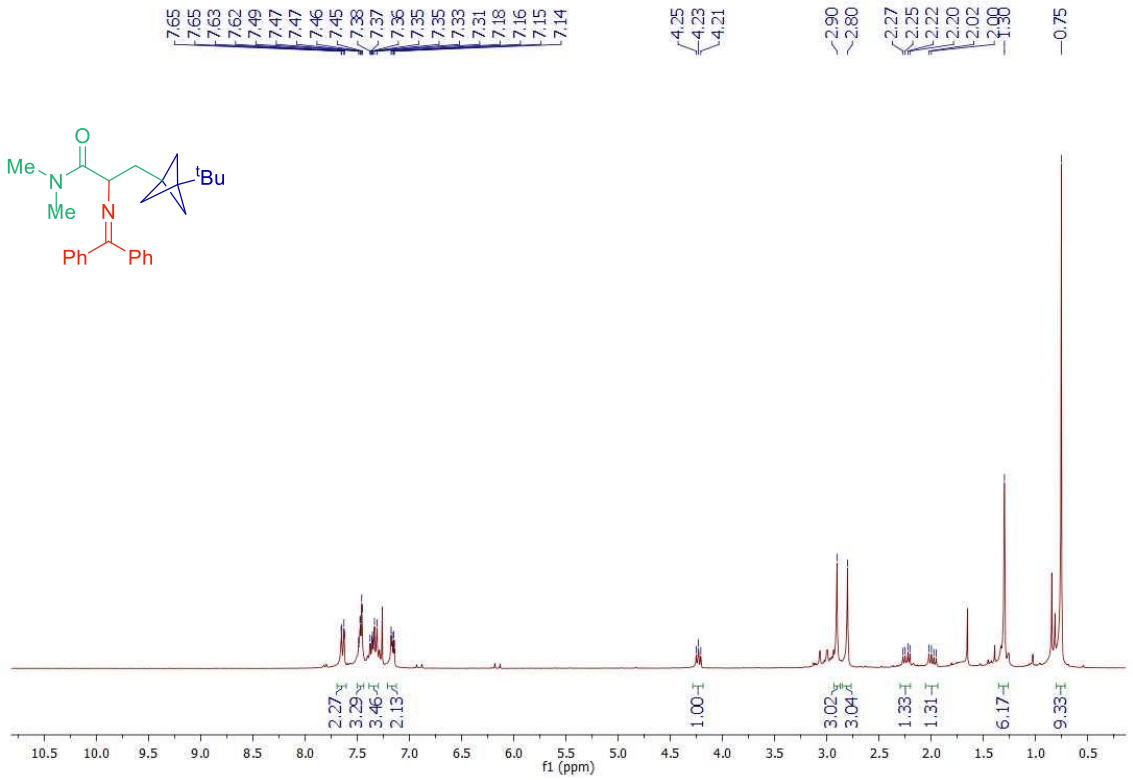
^{13}C NMR of compound **3ab** (75 MHz, $CDCl_3$)



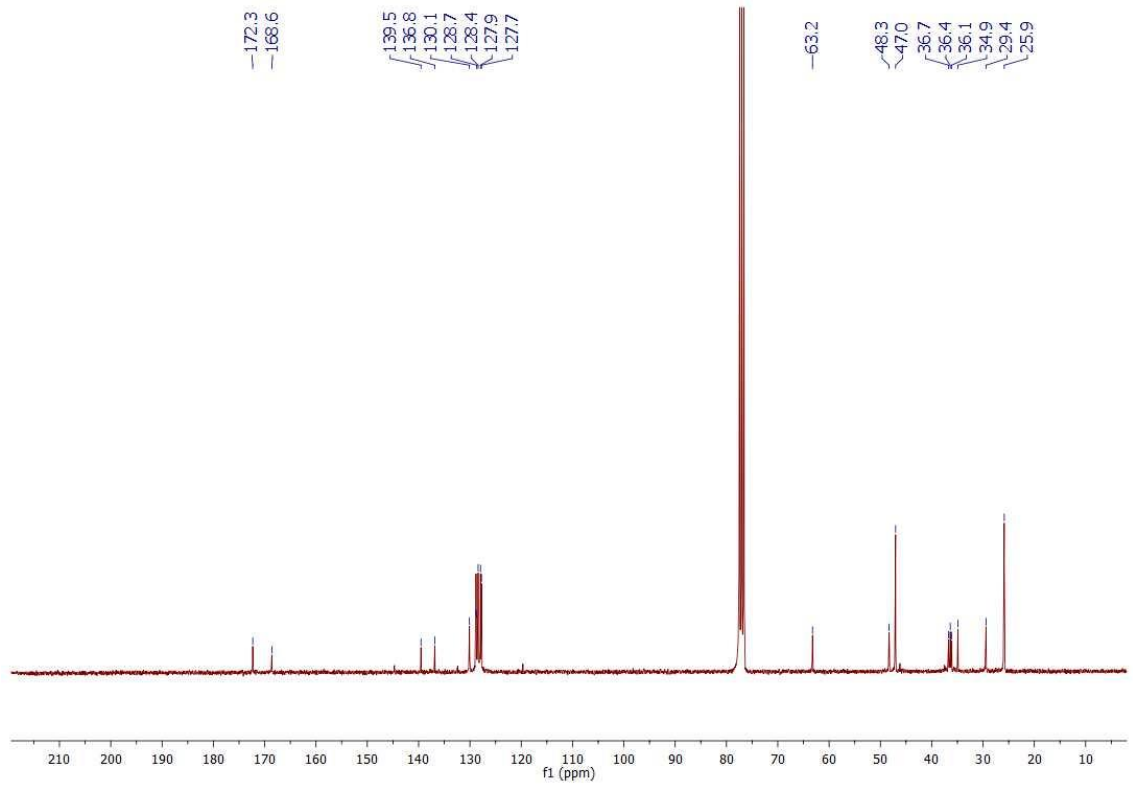
^{1}H NMR of compound **3ad** (300 MHz, $CDCl_3$)



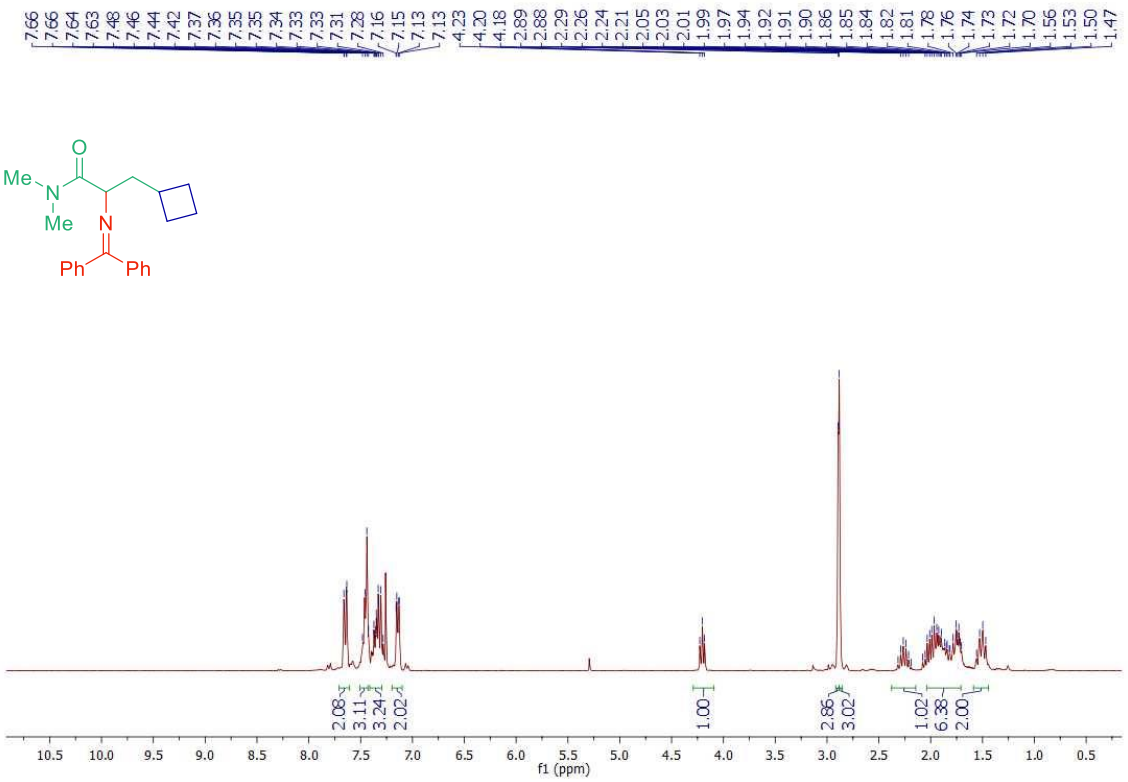
^{13}C NMR of compound **3ad** (75 MHz, $CDCl_3$)



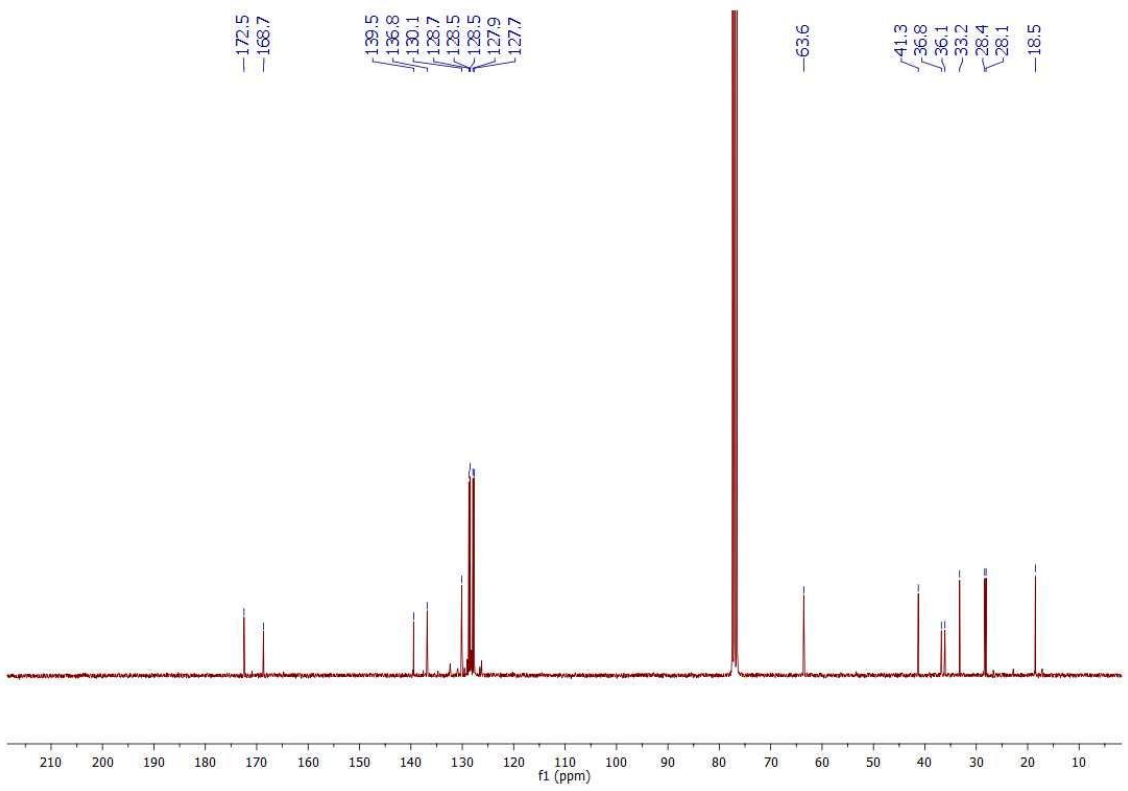
^{1}H NMR of compound **3ac** (300 MHz, $CDCl_3$)



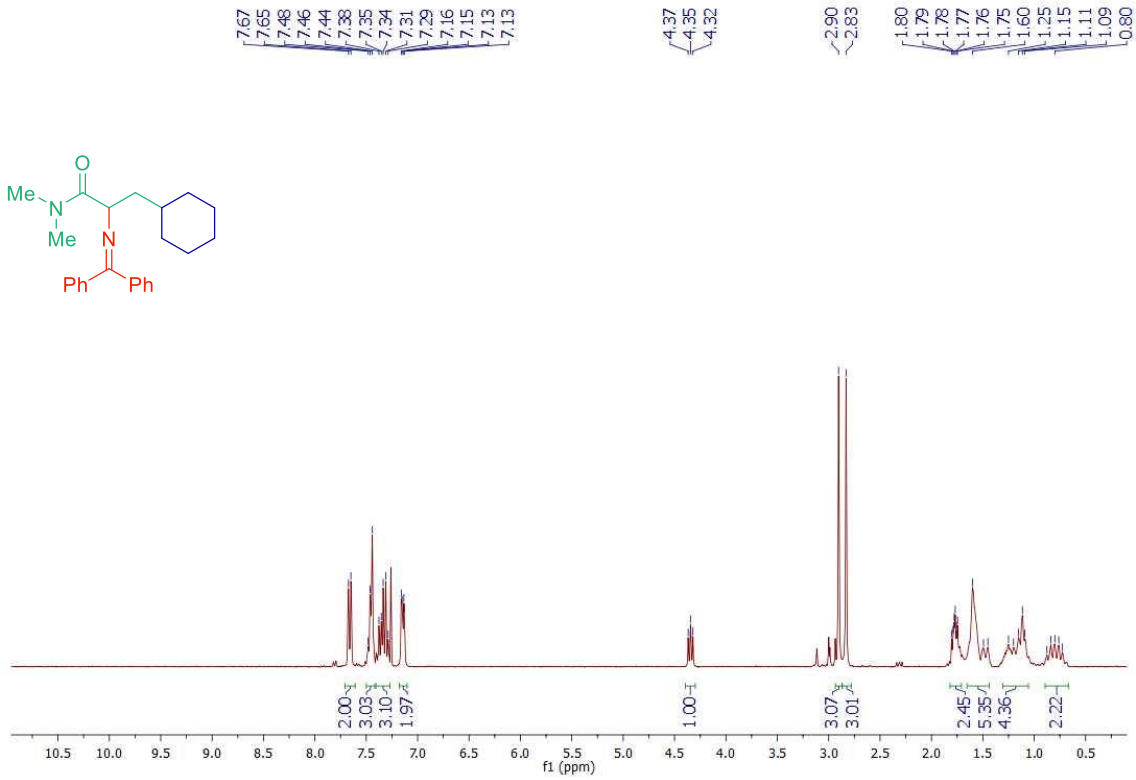
^{13}C NMR of compound **3ac** (75 MHz, $CDCl_3$)



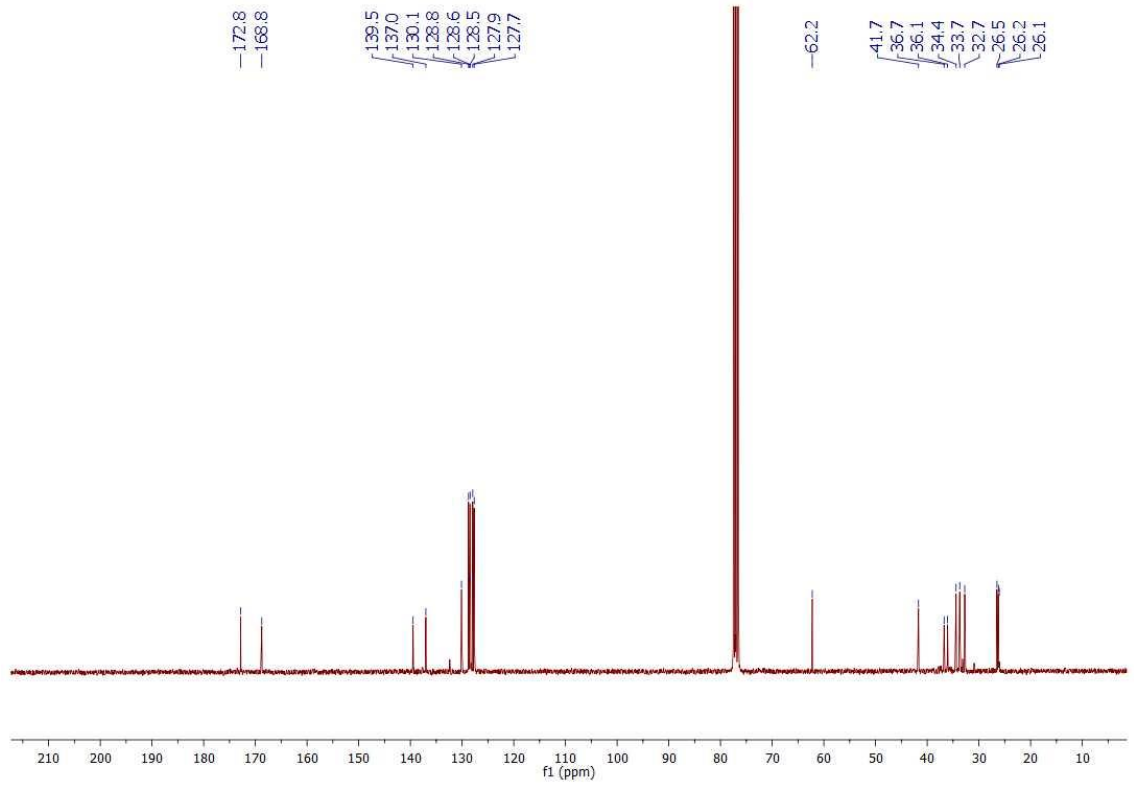
^{1}H NMR of compound **3ae** (300 MHz, $CDCl_3$)



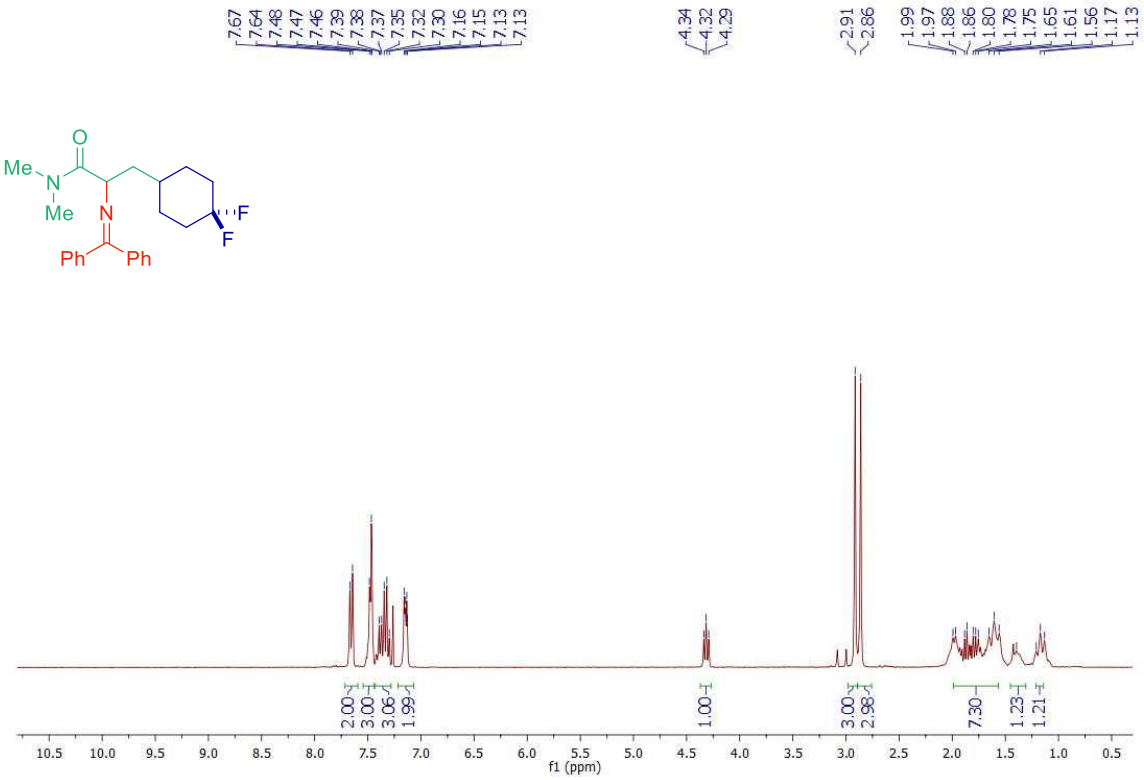
^{13}C NMR of compound **3ae** (75 MHz, $CDCl_3$)



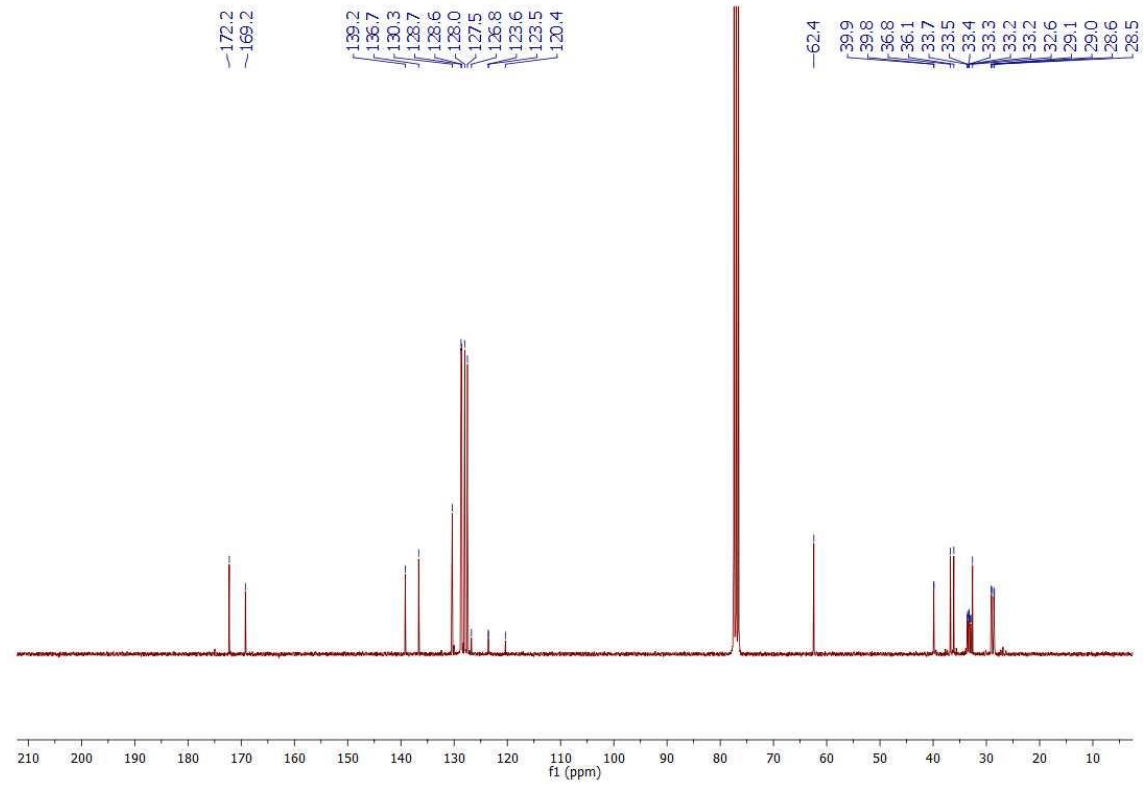
^{1}H NMR of compound **3af** (300 MHz, $CDCl_3$)



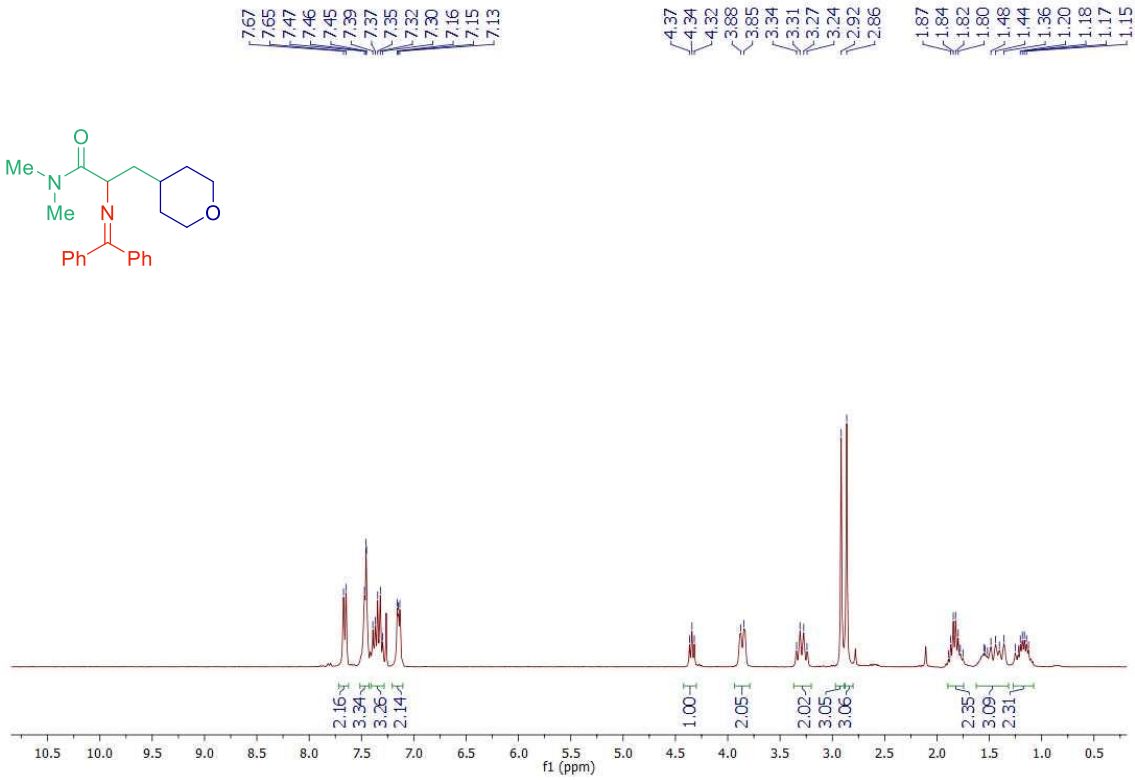
^{13}C NMR of compound **3af** (75 MHz, $CDCl_3$)



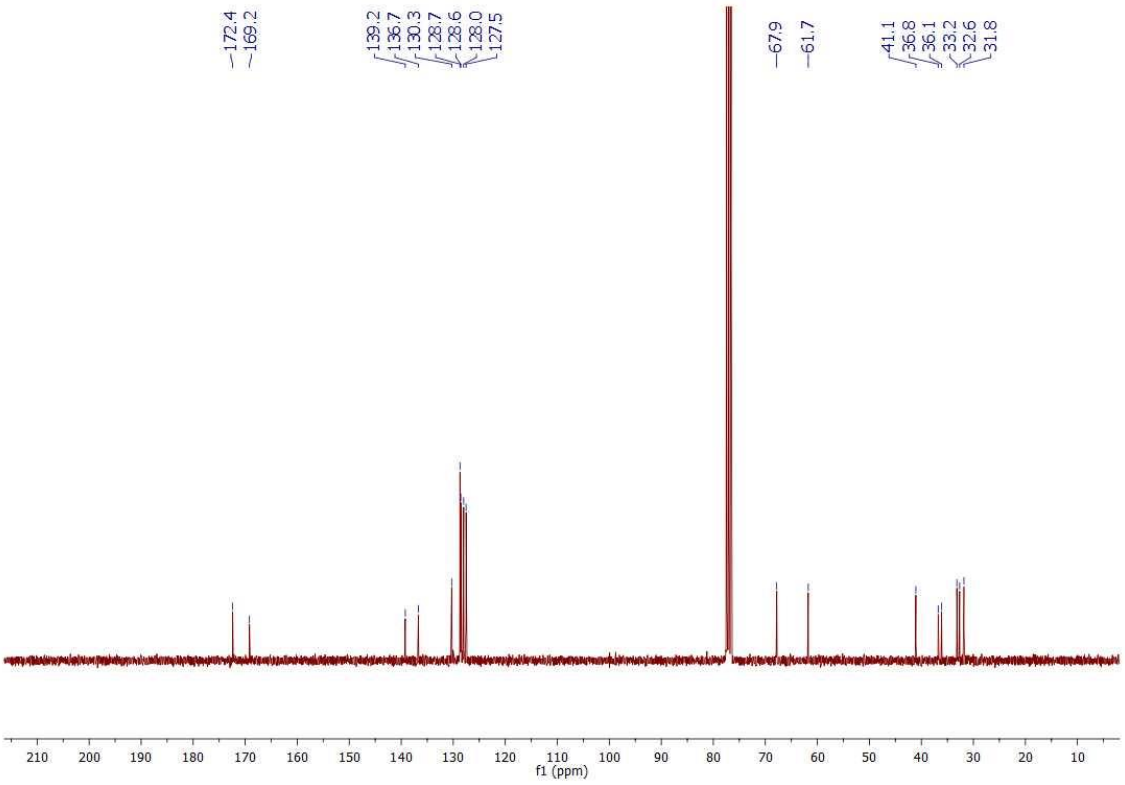
^{1}H NMR of compound **3ag** (300 MHz, $CDCl_3$)



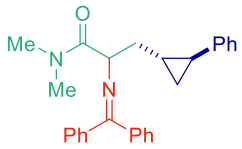
^{13}C NMR of compound **3ag** (75 MHz, $CDCl_3$)



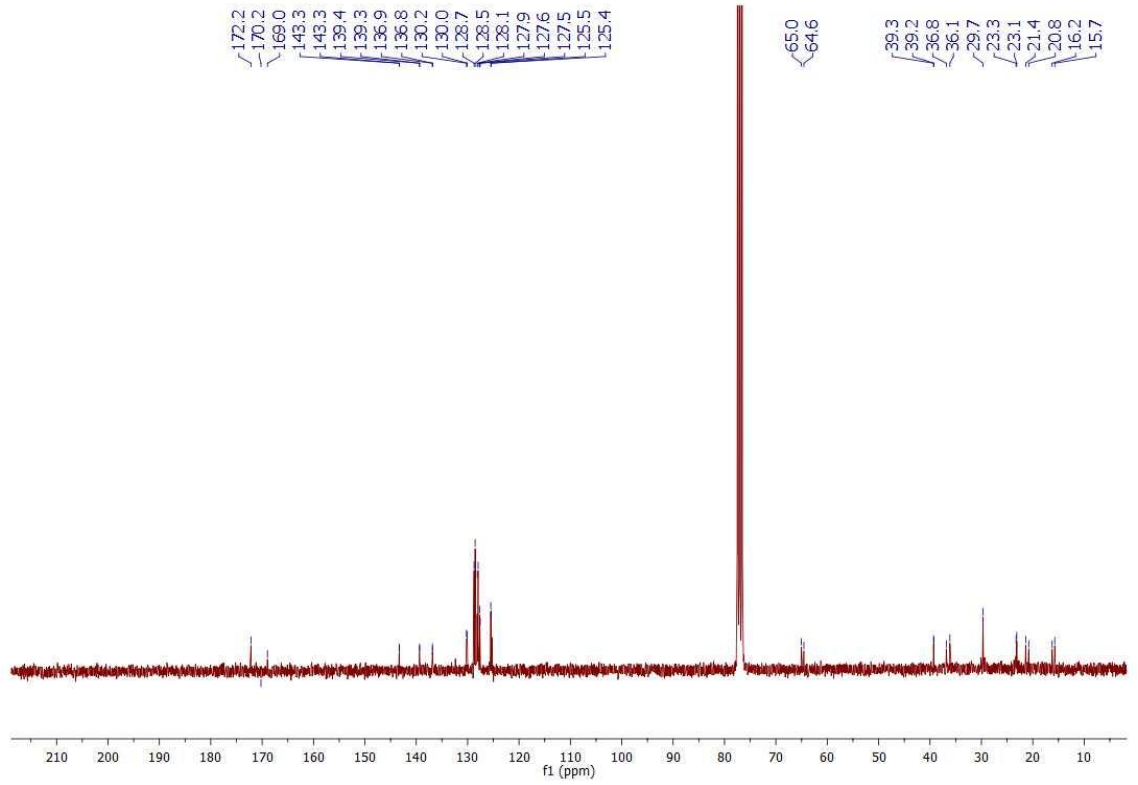
^{1}H NMR of compound **3ah** (300 MHz, $CDCl_3$)



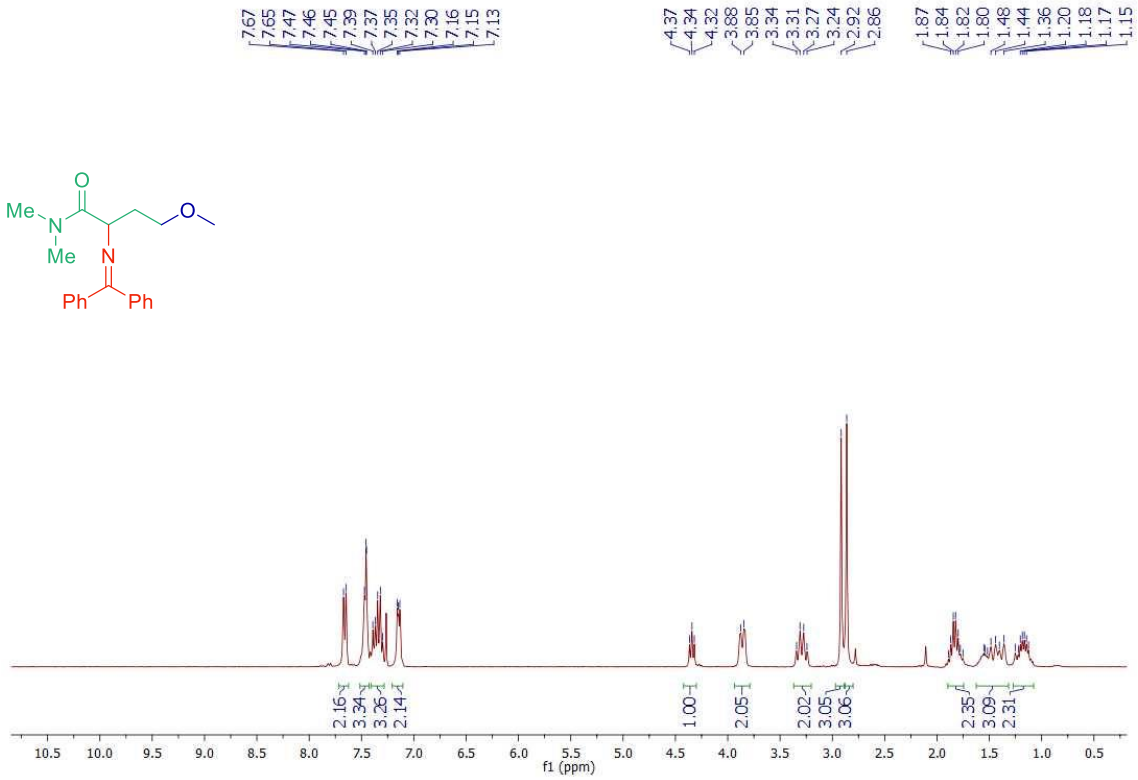
^{13}C NMR of compound **3ah** (75 MHz, $CDCl_3$)



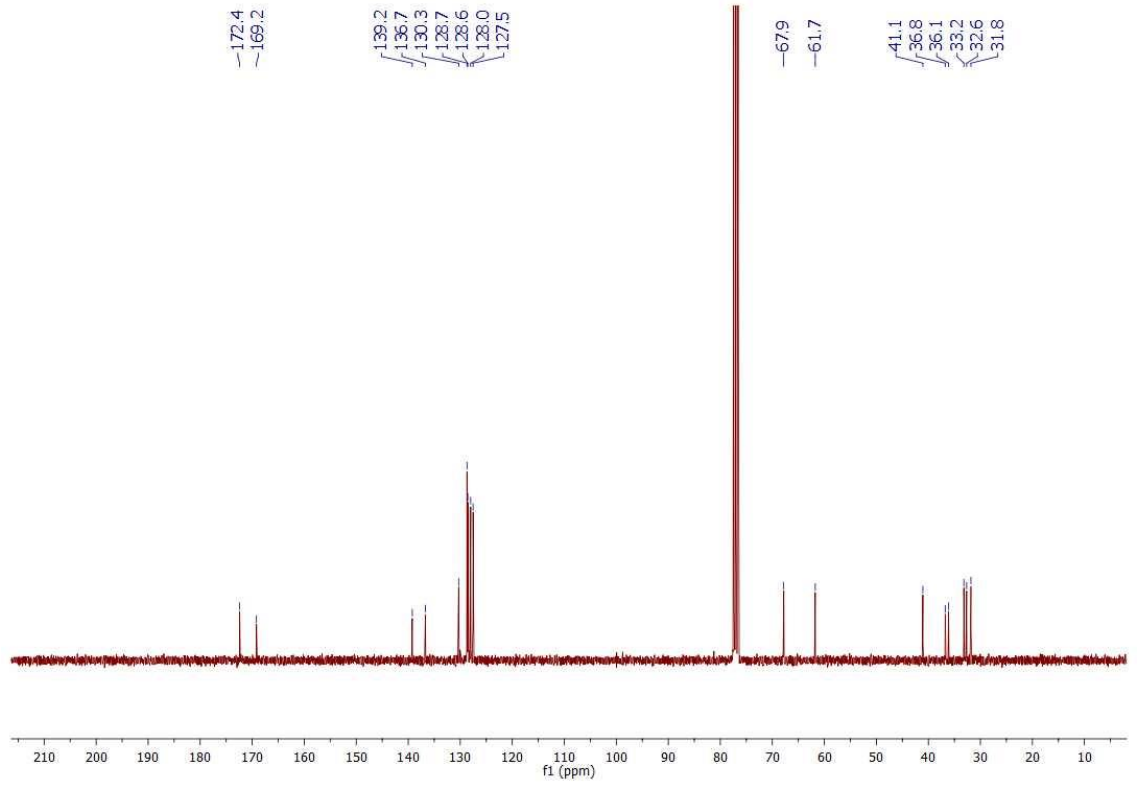
^{1}H NMR of compound **3ai/3ai'** (300 MHz, $CDCl_3$)



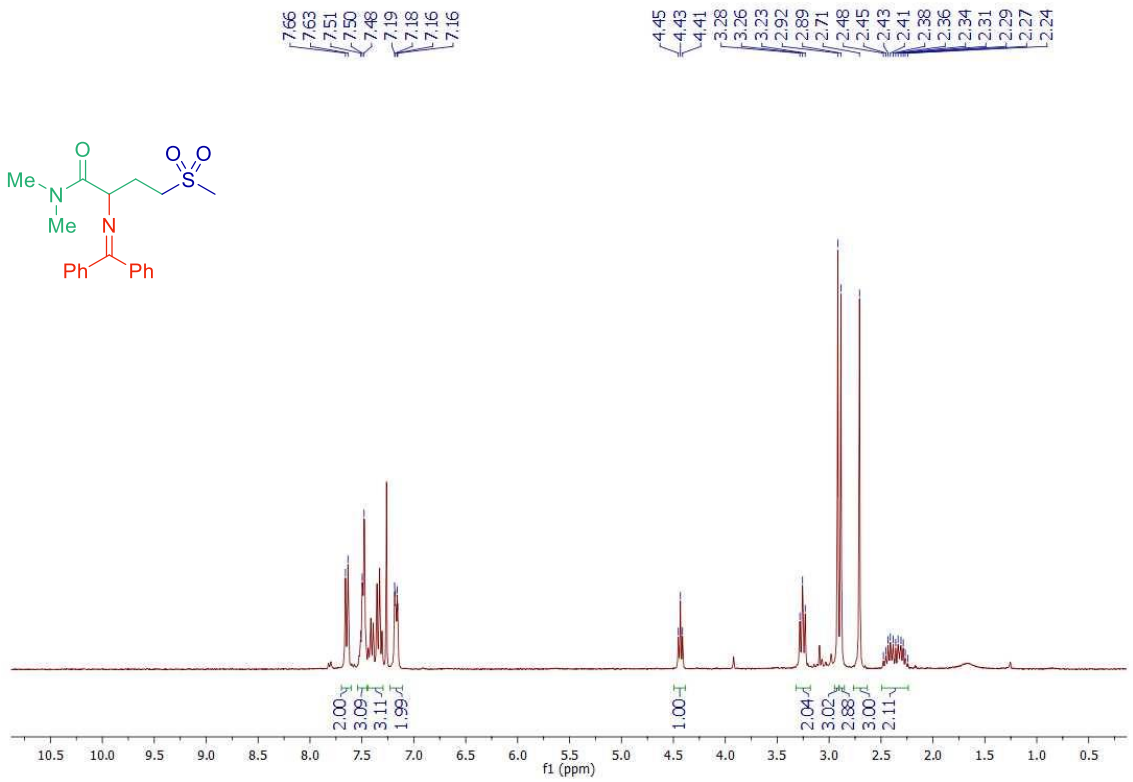
^{13}C NMR of compound **3ai/3ai'** (75 MHz, $CDCl_3$)



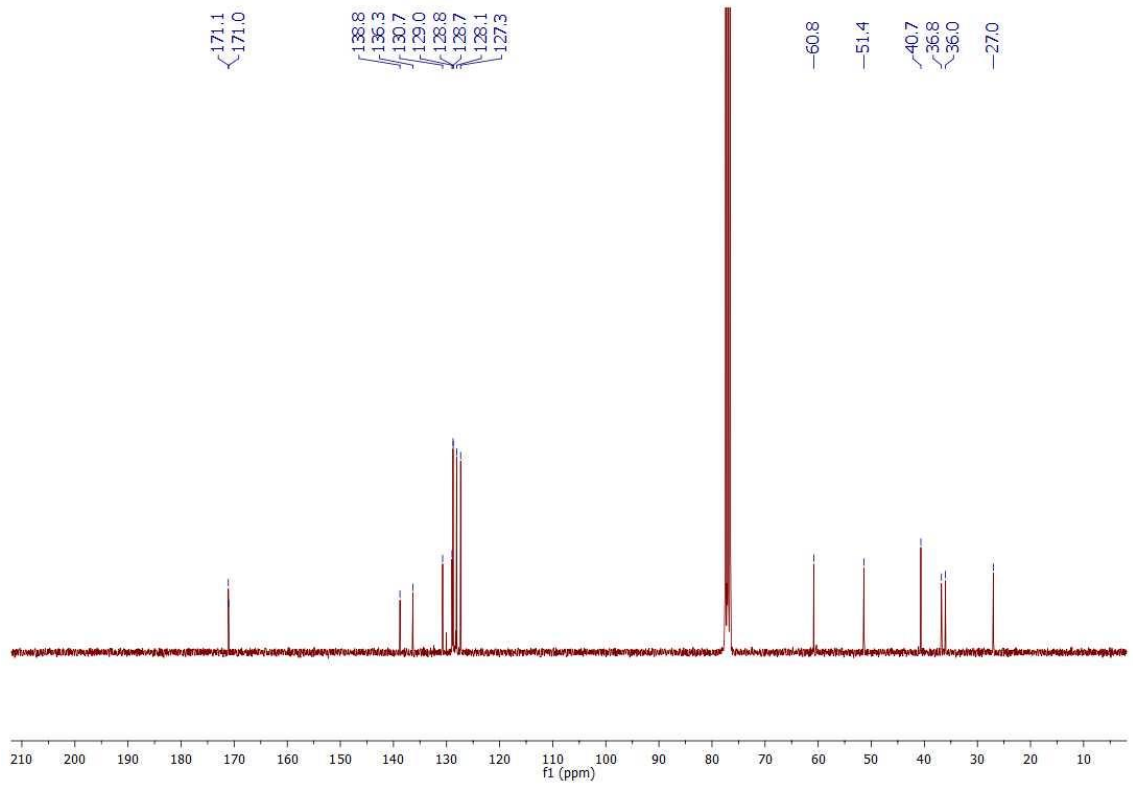
^{1}H NMR of compound **3aj** (300 MHz, $CDCl_3$)



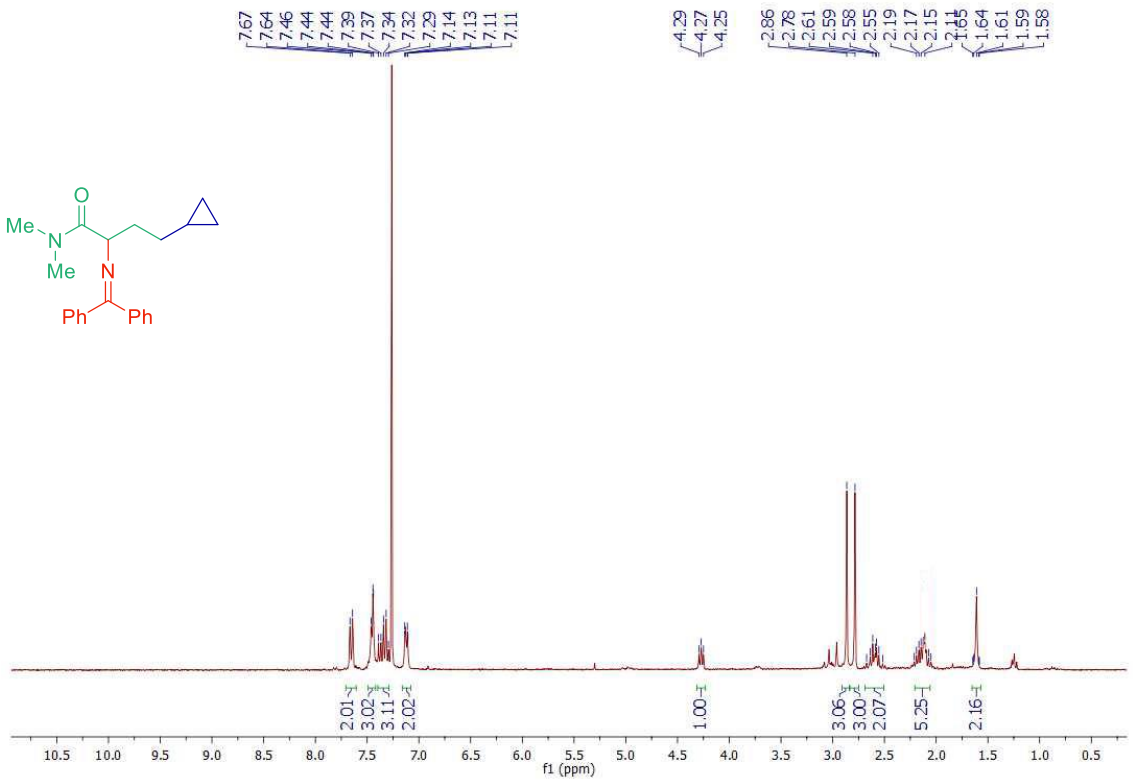
^{13}C NMR of compound **3aj** (75 MHz, $CDCl_3$)



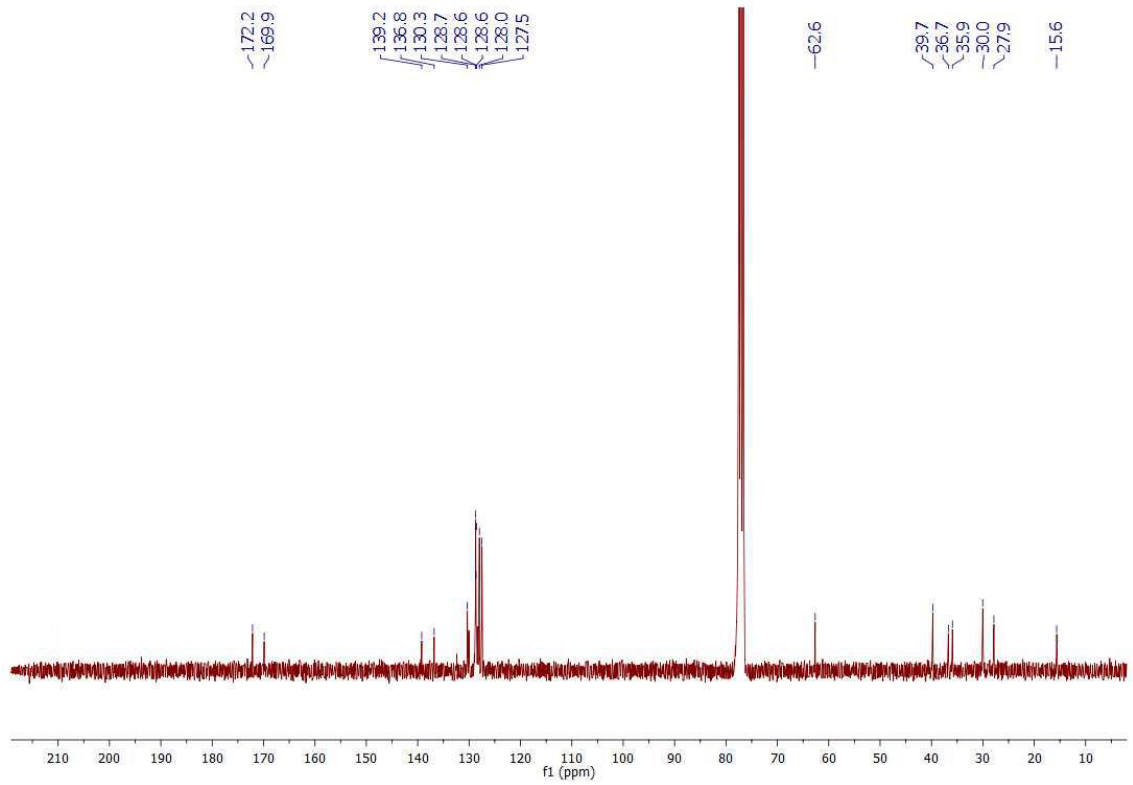
^{1}H NMR of compound **3ak** (300 MHz, $CDCl_3$)



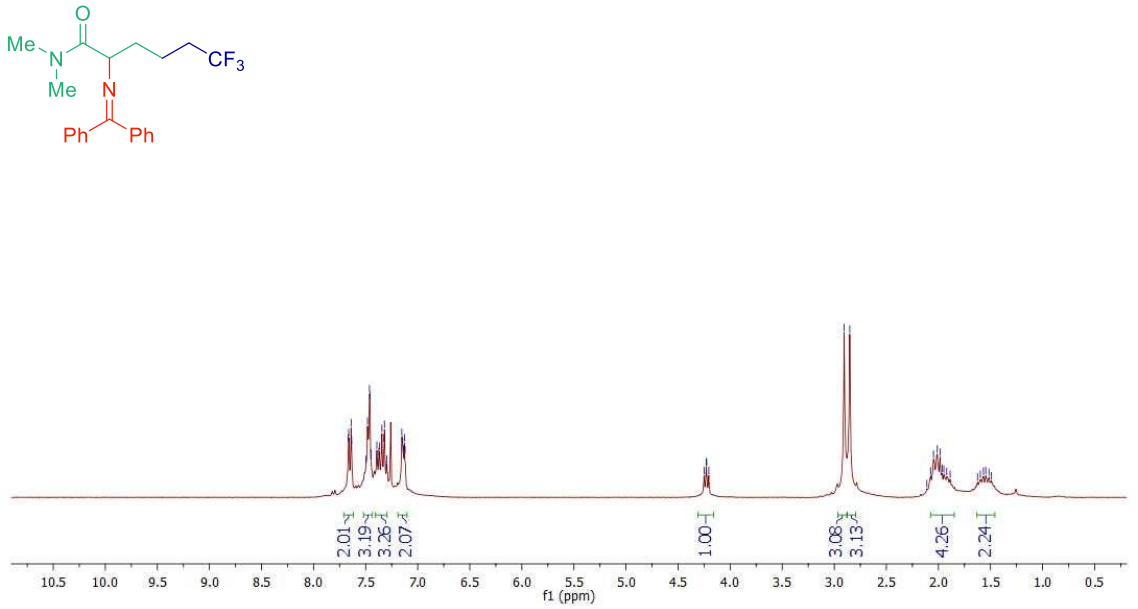
^{13}C NMR of compound **3ak** (75 MHz, $CDCl_3$)



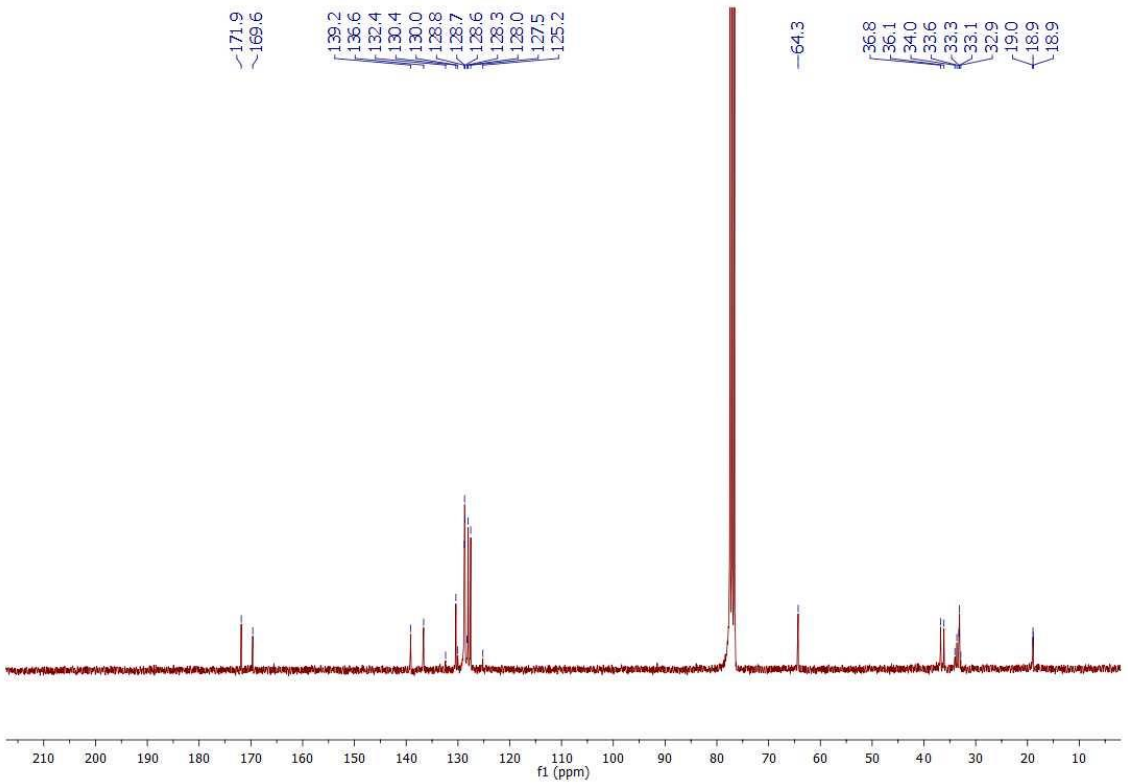
^{1}H NMR of compound **3al** (300 MHz, $CDCl_3$)



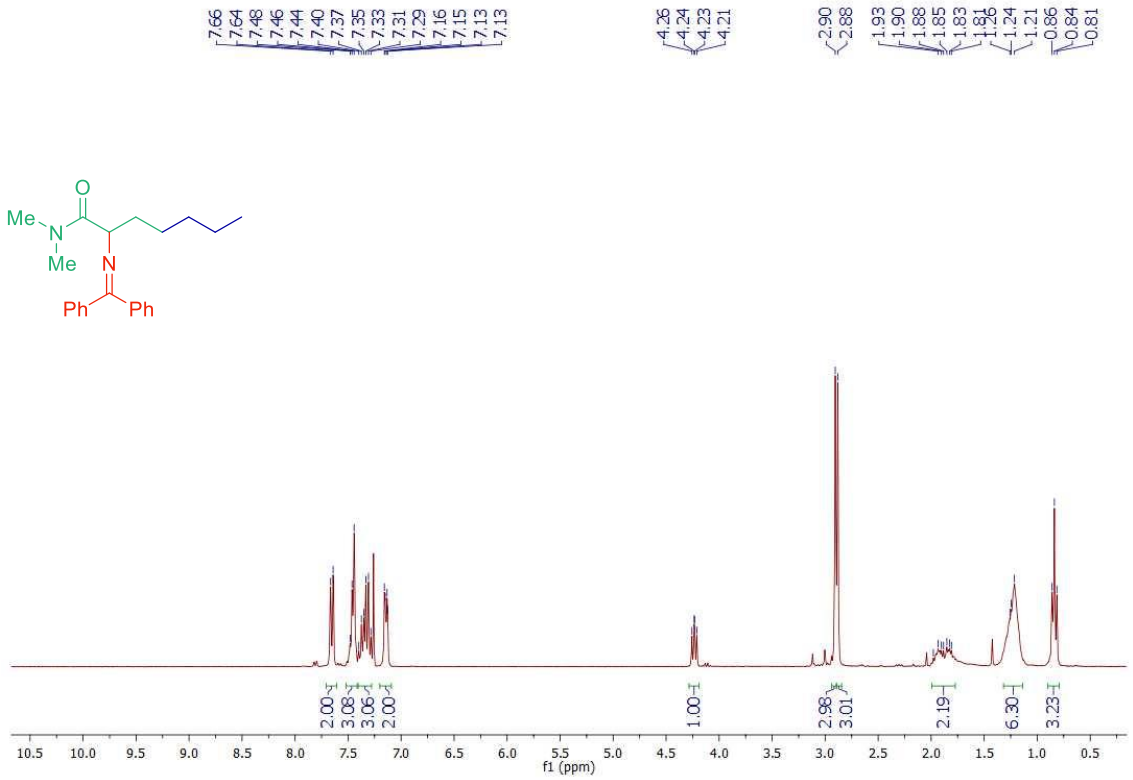
^{13}C NMR of compound **3al** (75 MHz, $CDCl_3$)



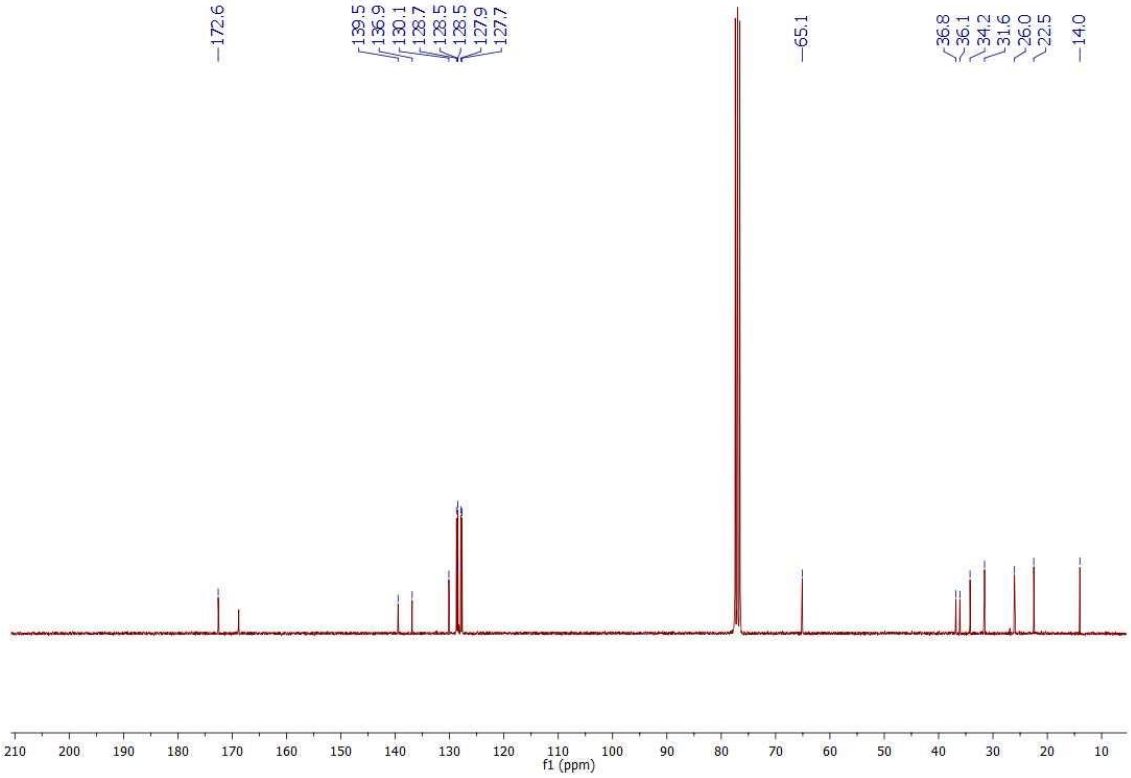
^{1}H NMR of compound **3am** (300 MHz, $CDCl_3$)



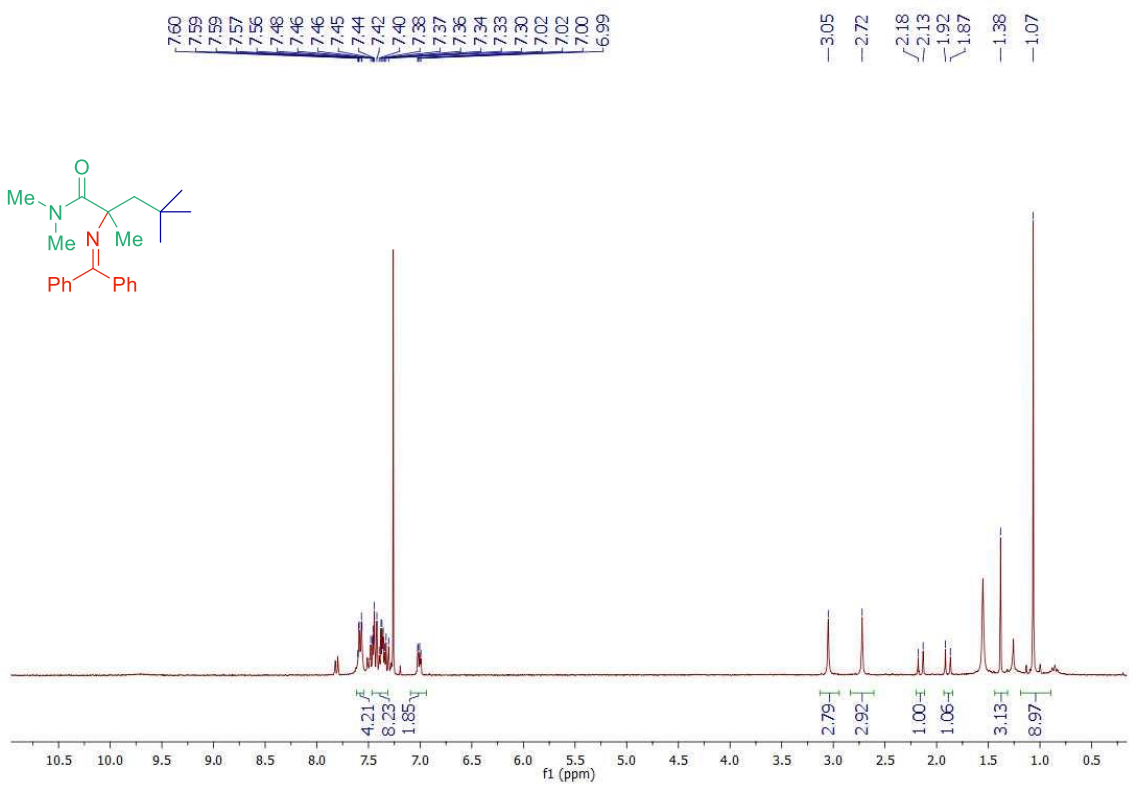
^{13}C NMR of compound **3am** (75 MHz, $CDCl_3$)



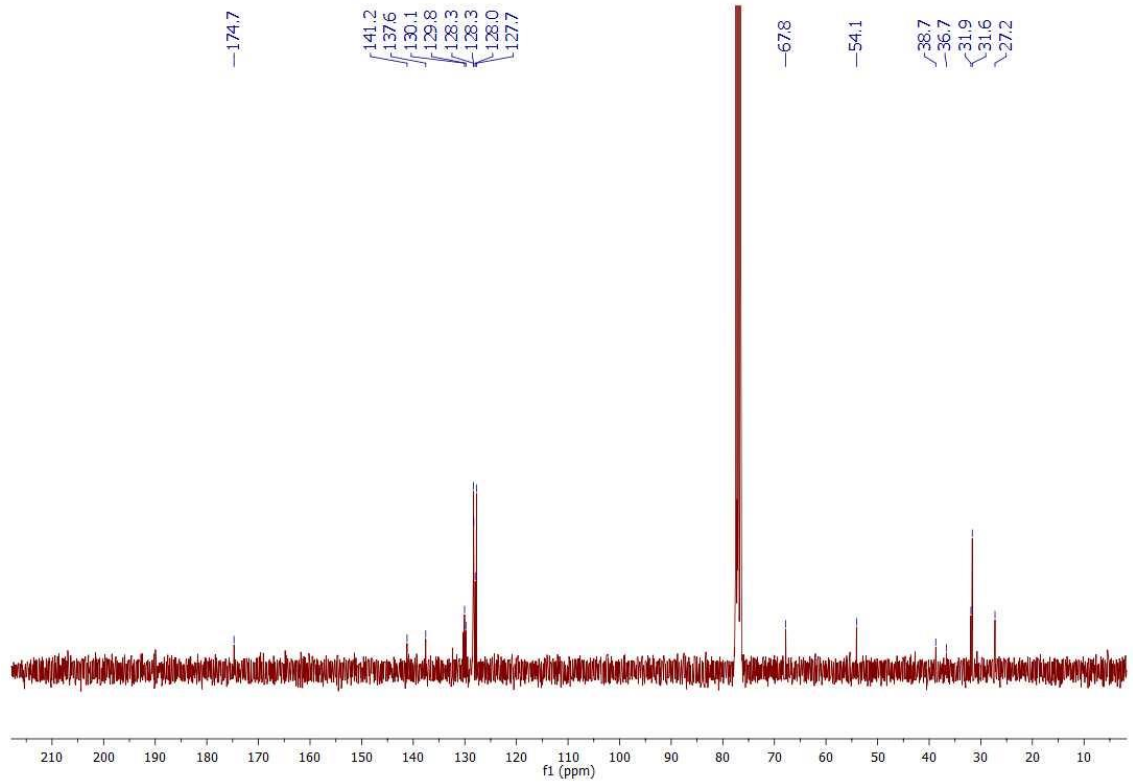
^{1}H NMR of compound **3an** (300 MHz, $CDCl_3$)



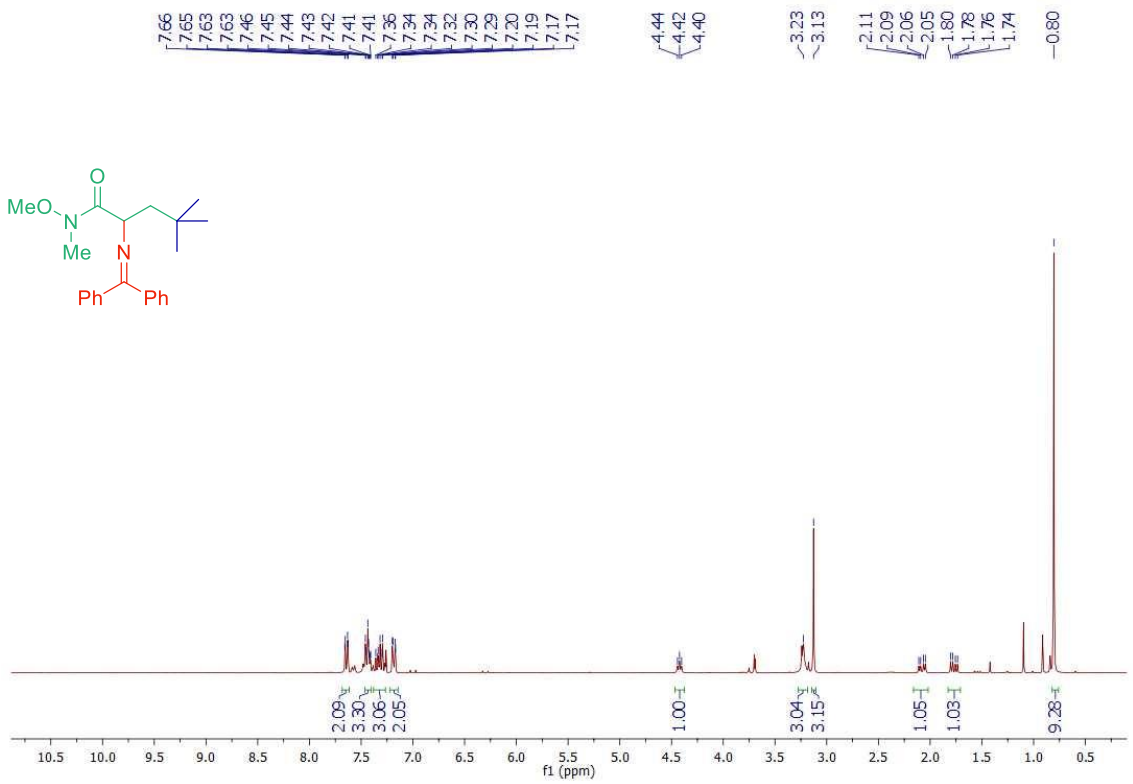
^{13}C NMR of compound **3an** (75 MHz, $CDCl_3$)



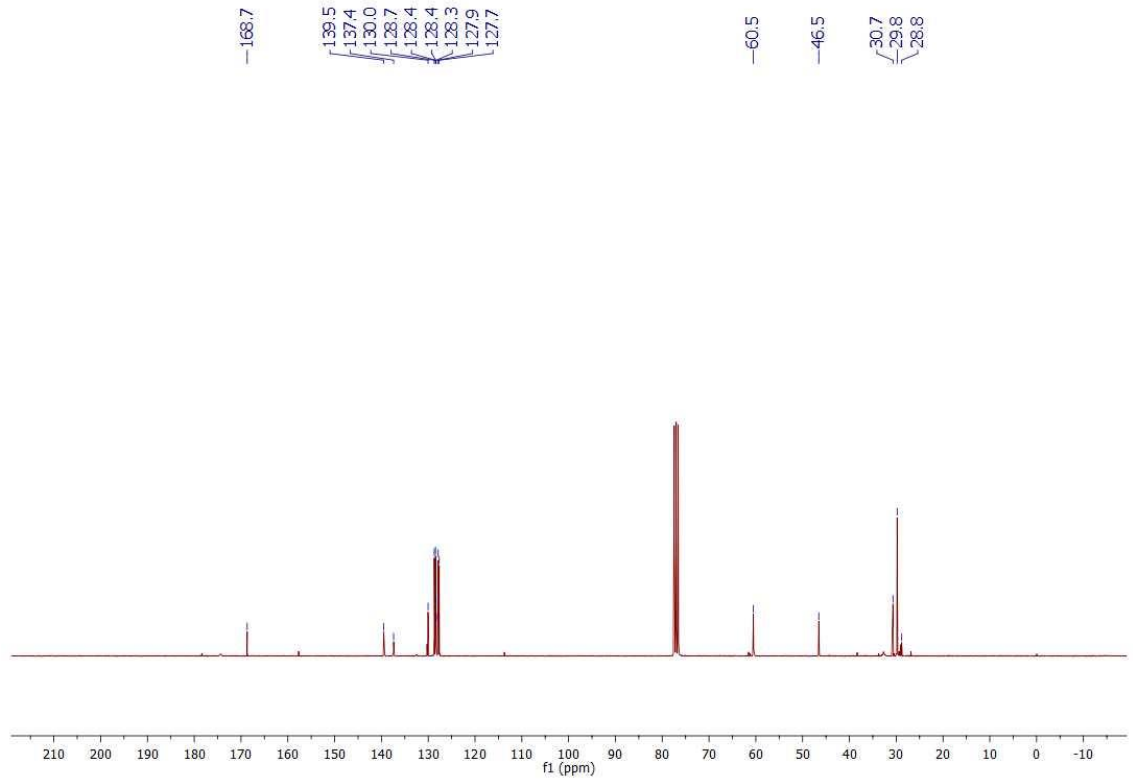
^{1}H NMR of compound **3ba** (300 MHz, $CDCl_3$)



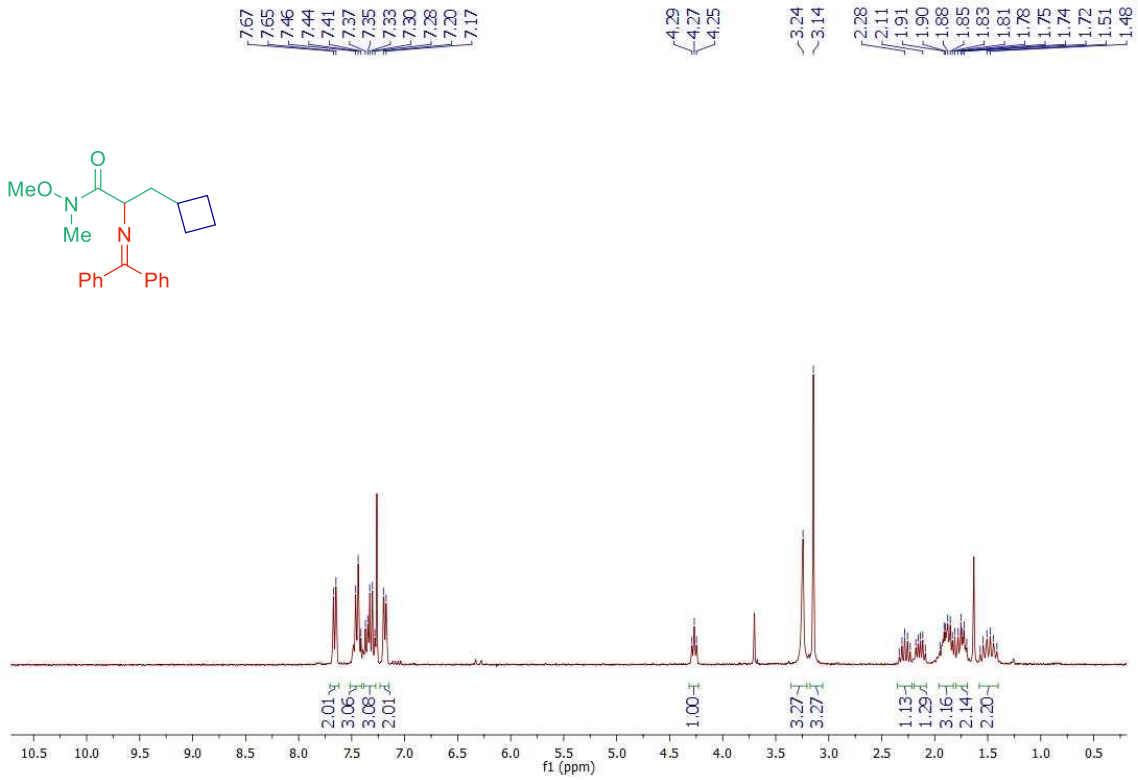
^{13}C NMR of compound **3ba** (75 MHz, $CDCl_3$)



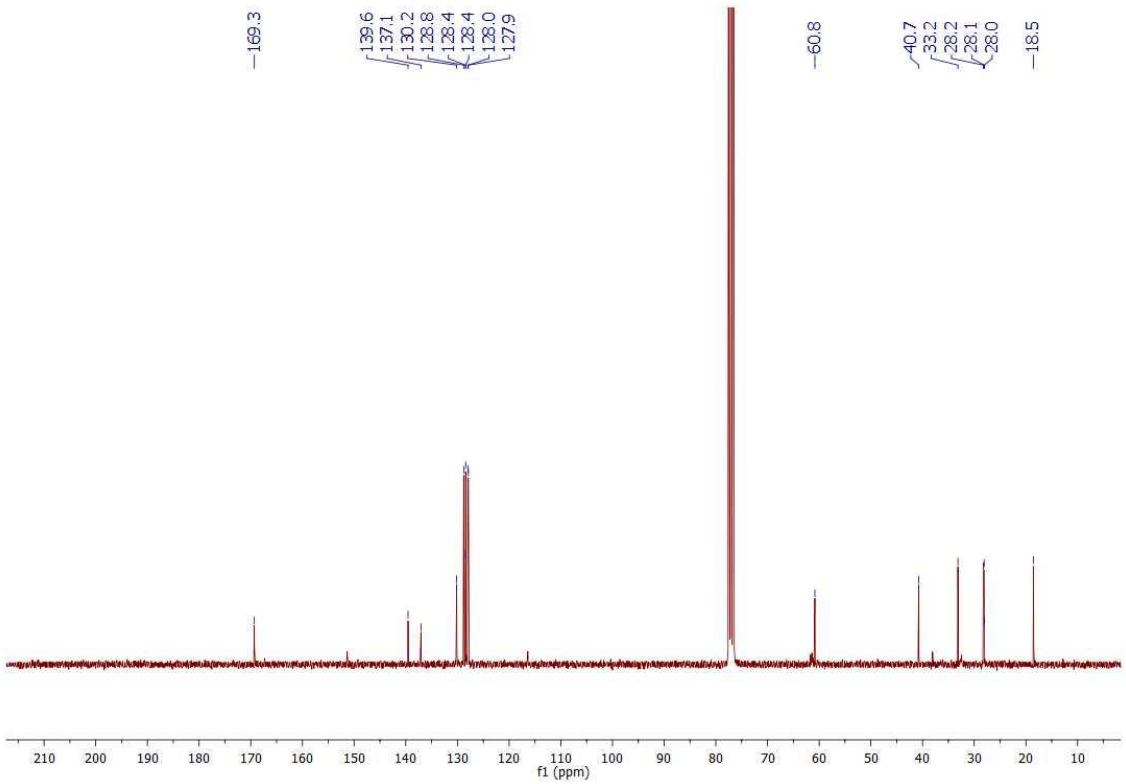
^{1}H NMR of compound **3ca** (300 MHz, $CDCl_3$)



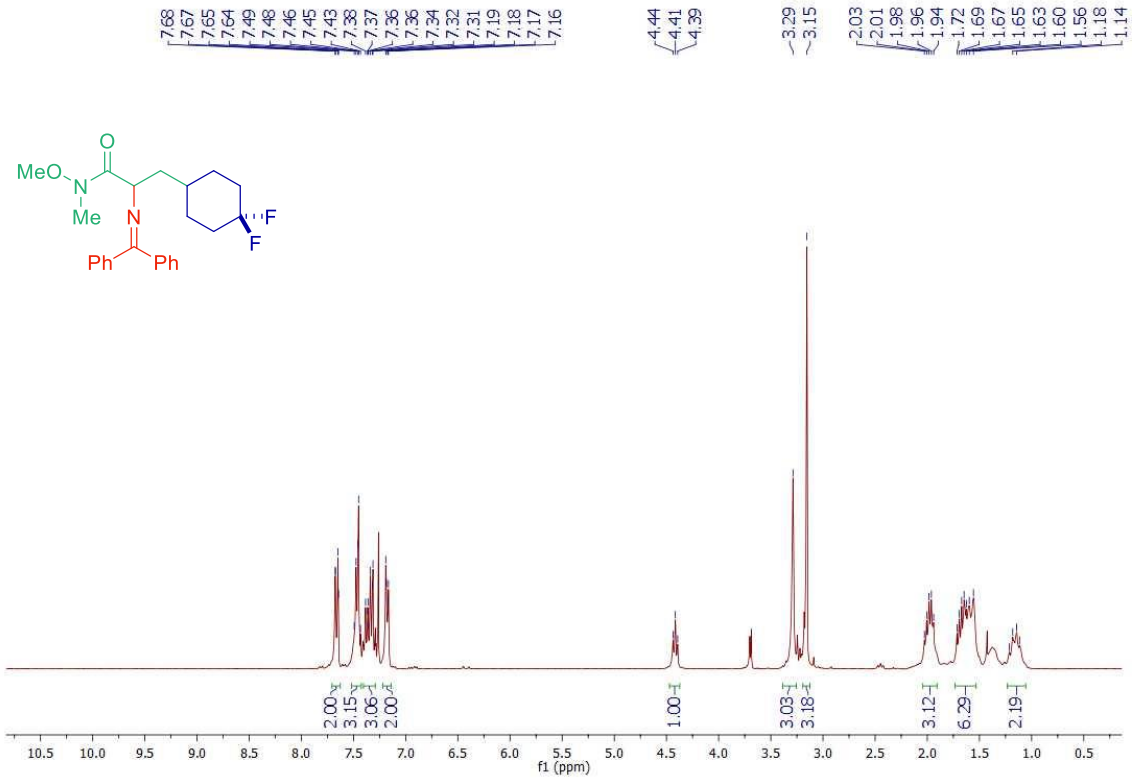
^{13}C NMR of compound **3ca** (75 MHz, $CDCl_3$)



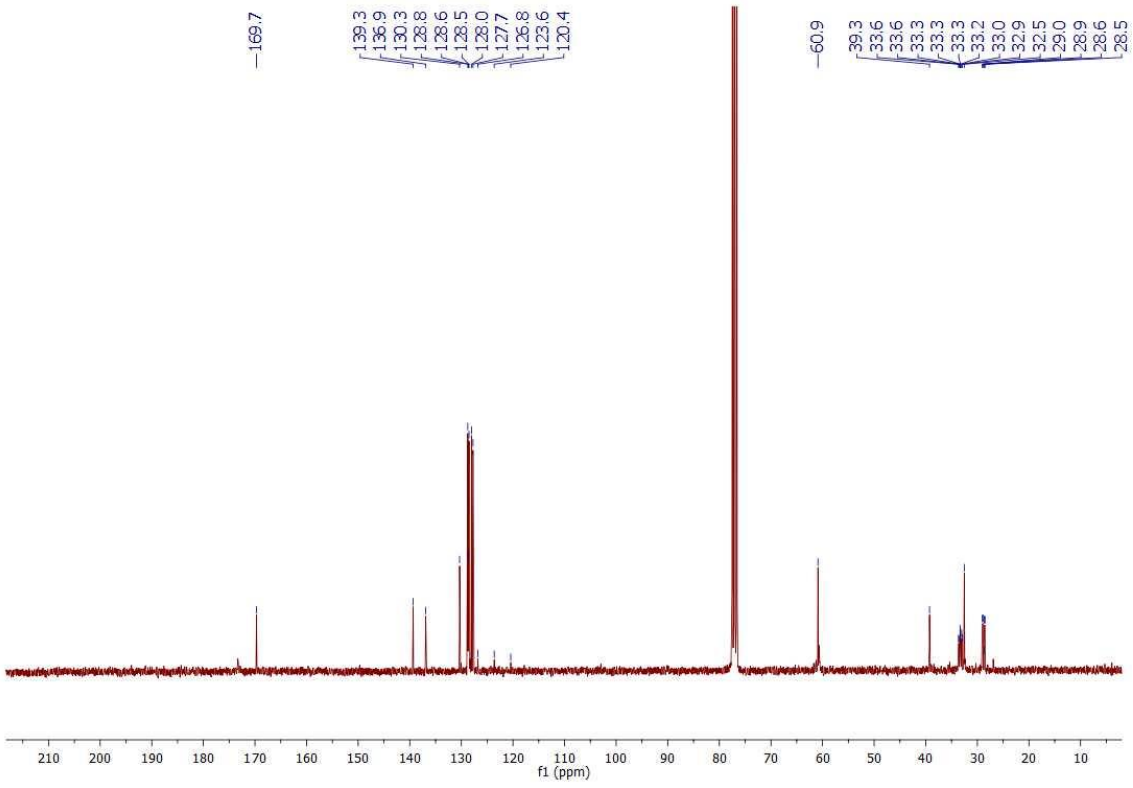
^{1}H NMR of compound **3ce** (300 MHz, $CDCl_3$)



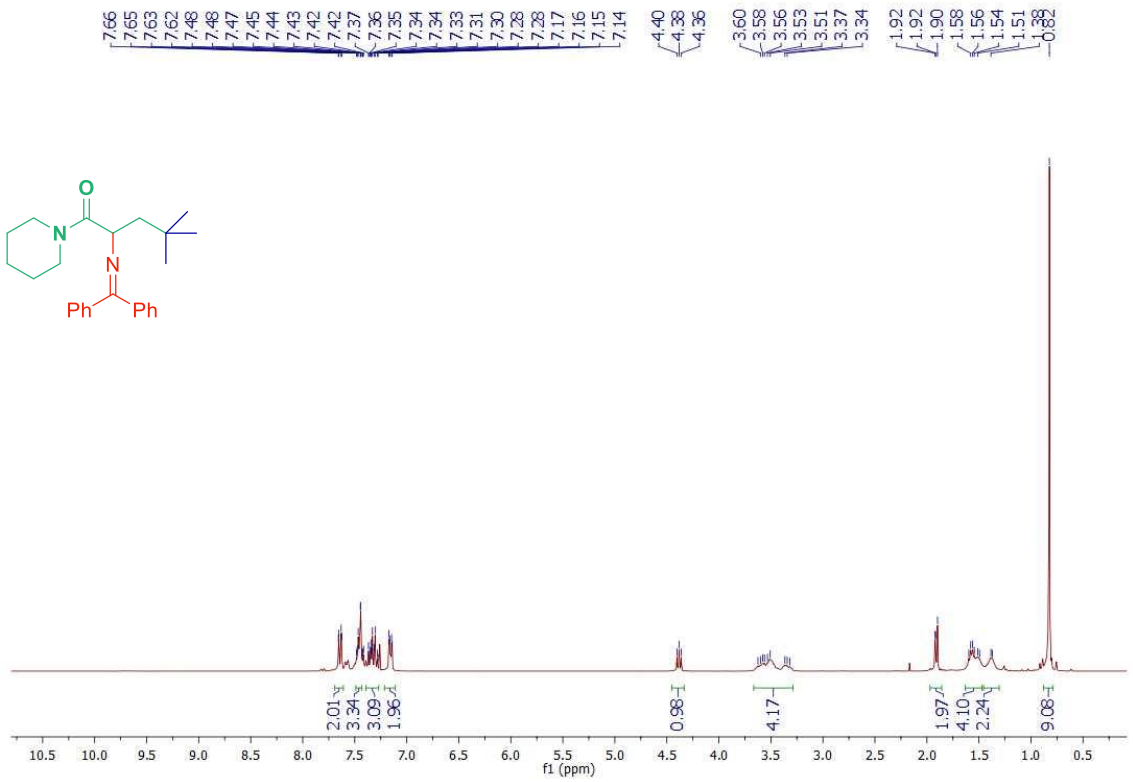
^{13}C NMR of compound **3ce** (75 MHz, $CDCl_3$)



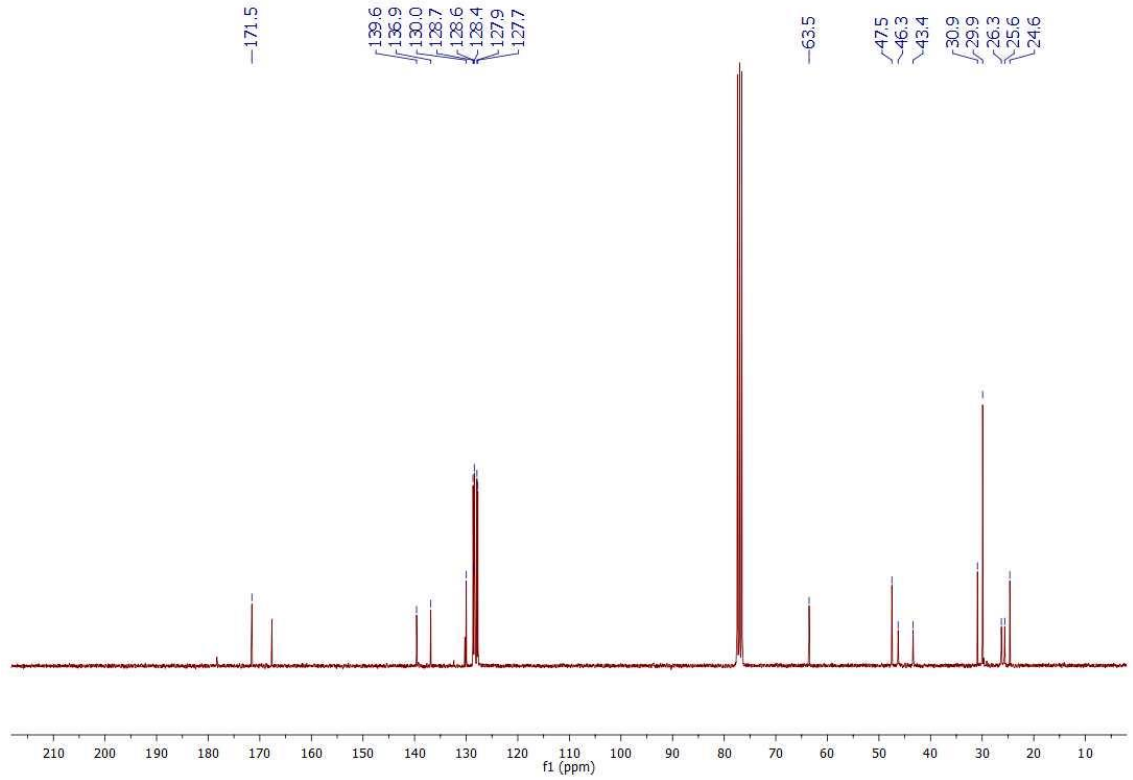
^{1}H NMR of compound **3cg** (300 MHz, $CDCl_3$)



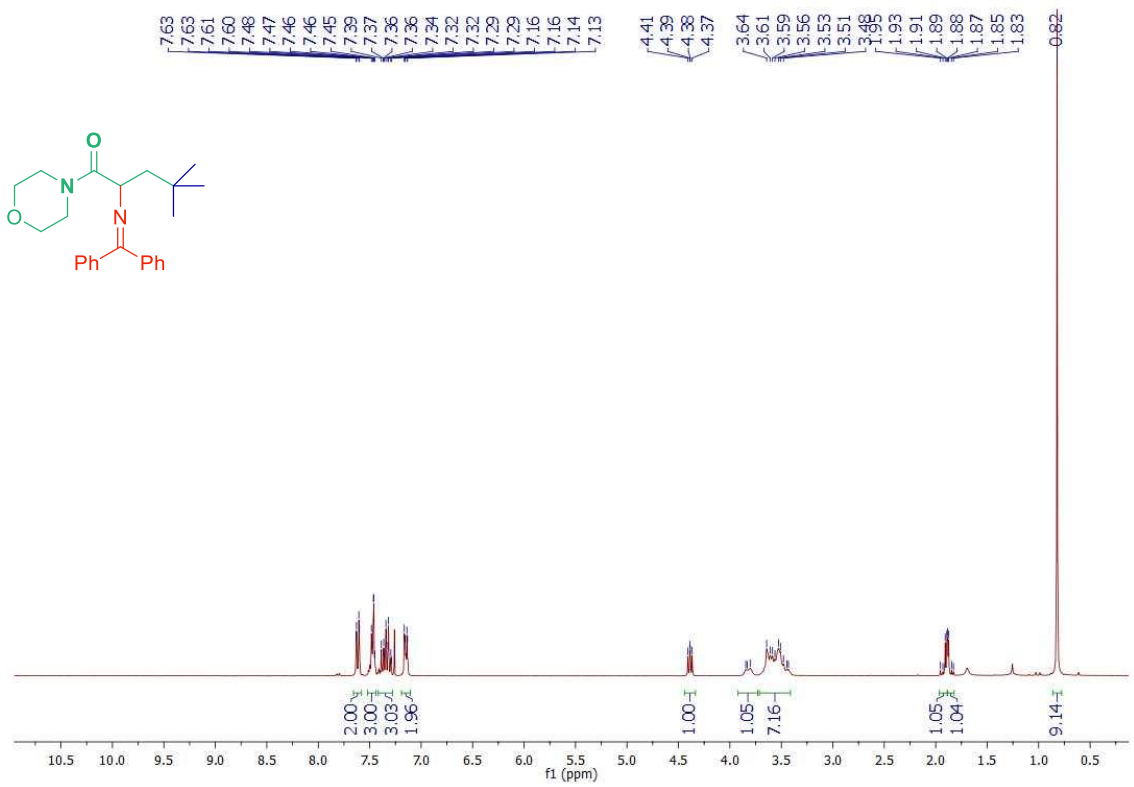
^{13}C NMR of compound **3cg** (75 MHz, $CDCl_3$)



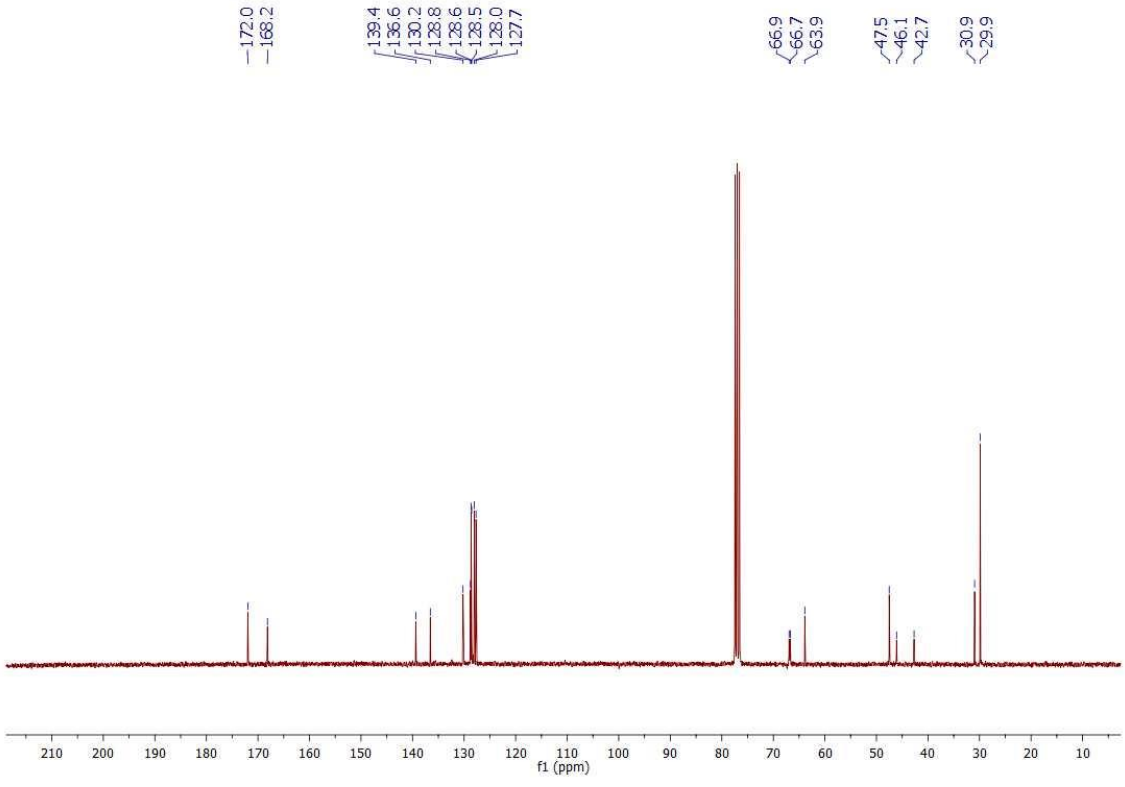
^{1}H NMR of compound **3da** (300 MHz, $CDCl_3$)



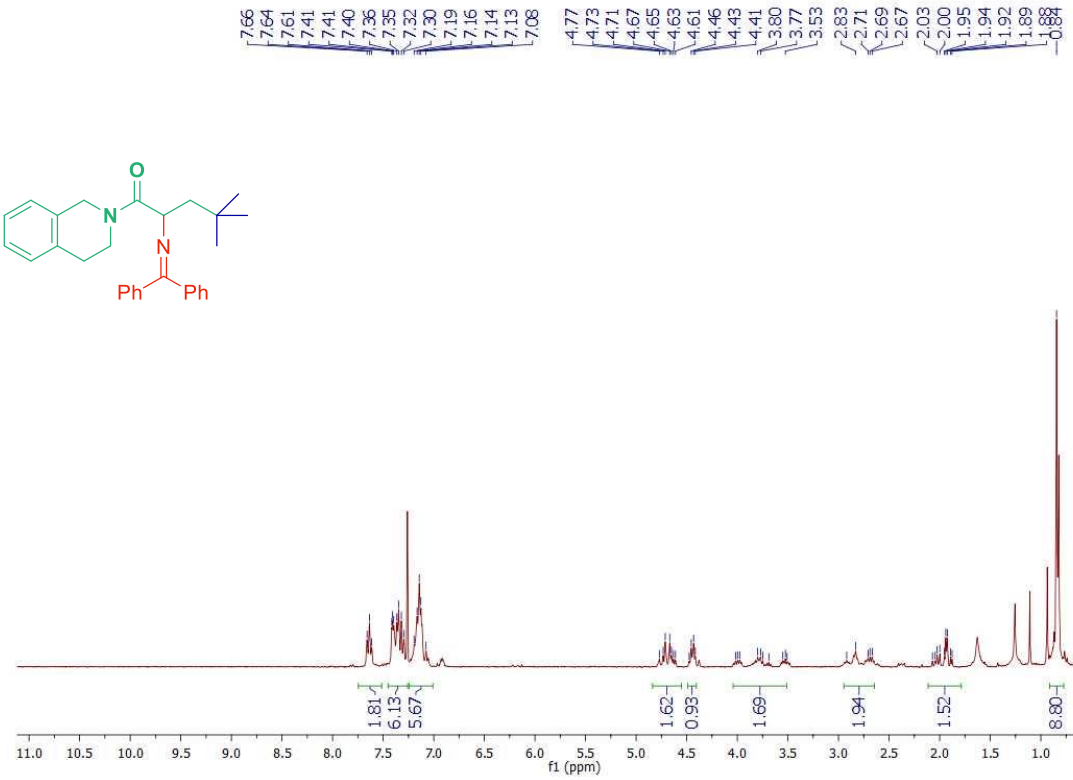
^{13}C NMR of compound **3da** (75 MHz, $CDCl_3$)



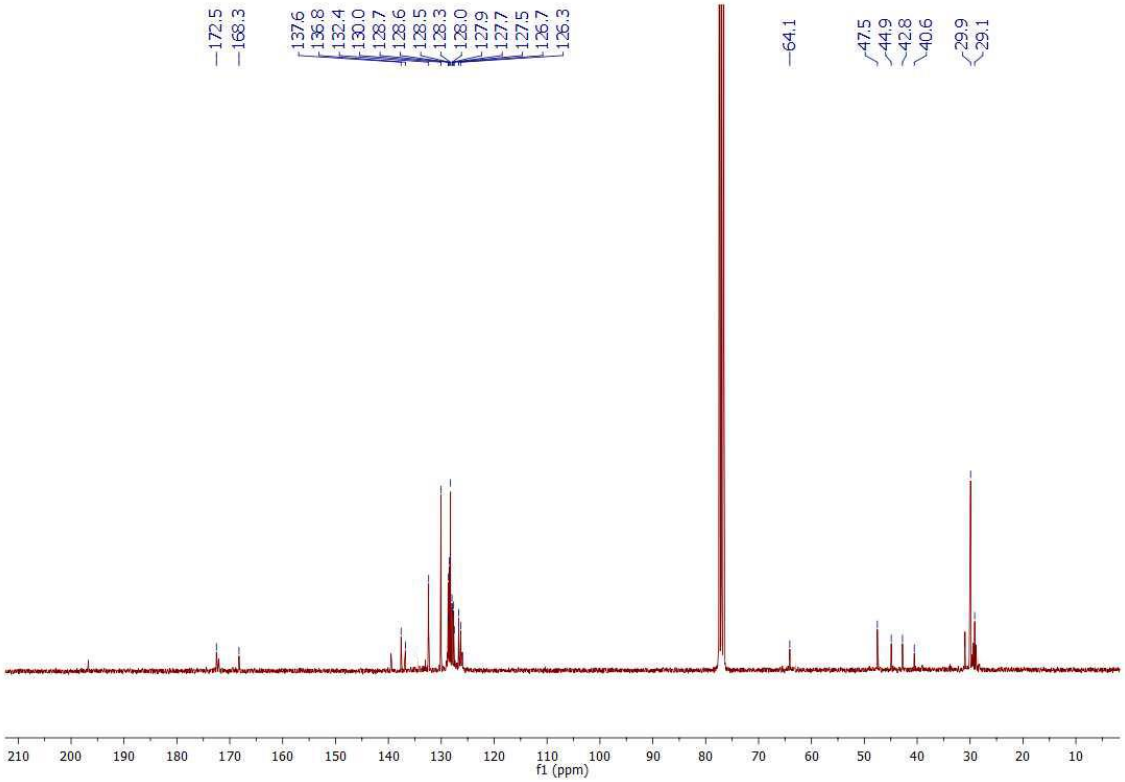
^{1}H NMR of compound **3ea** (300 MHz, $CDCl_3$)



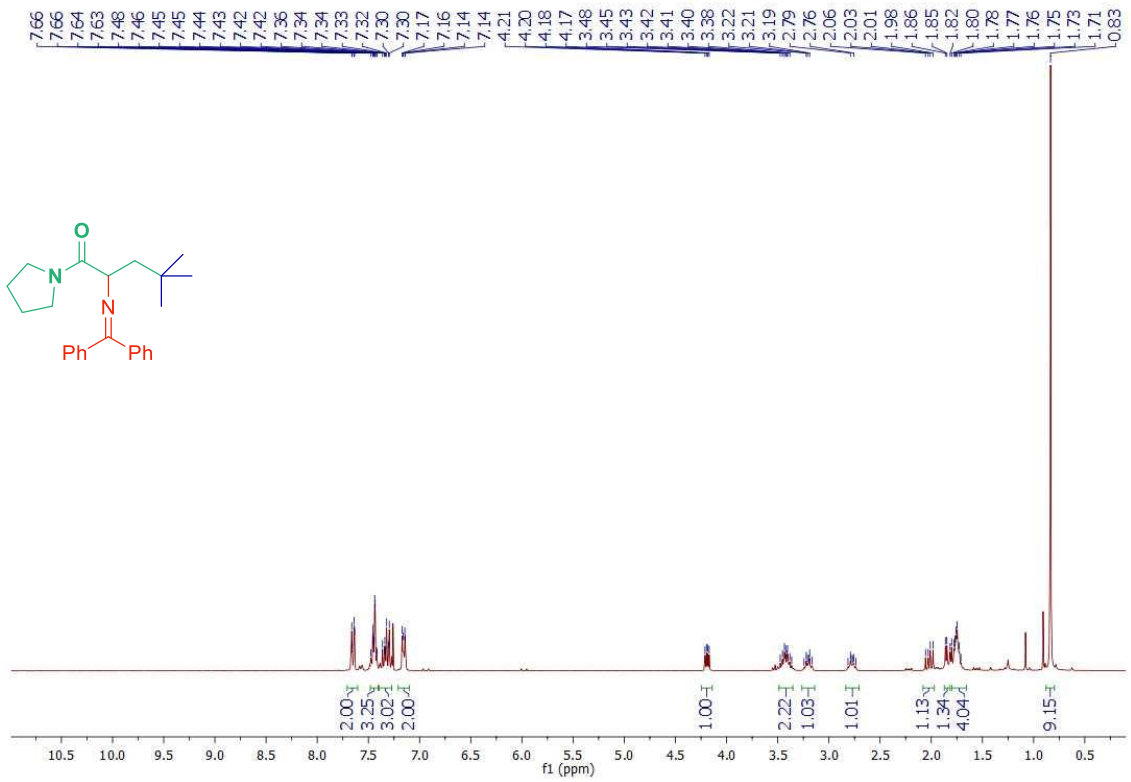
^{13}C NMR of compound **3ea** (75 MHz, $CDCl_3$)



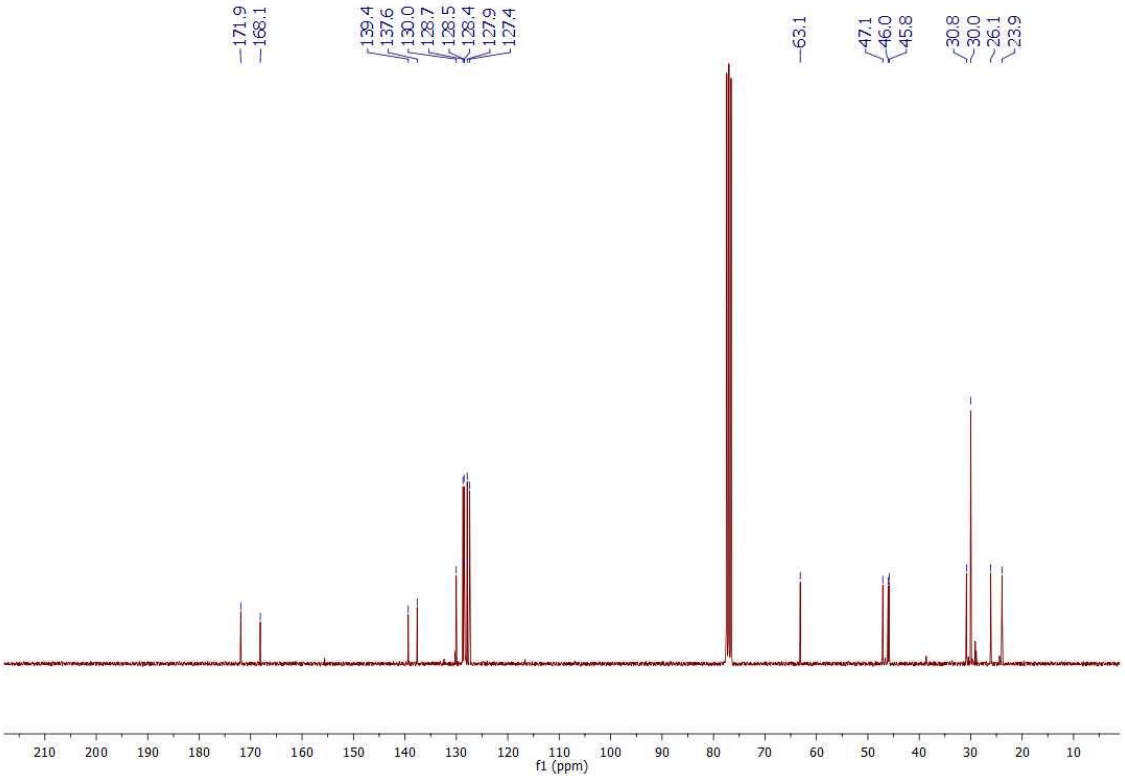
^{1}H NMR of compound **3fa** (300 MHz, $CDCl_3$)



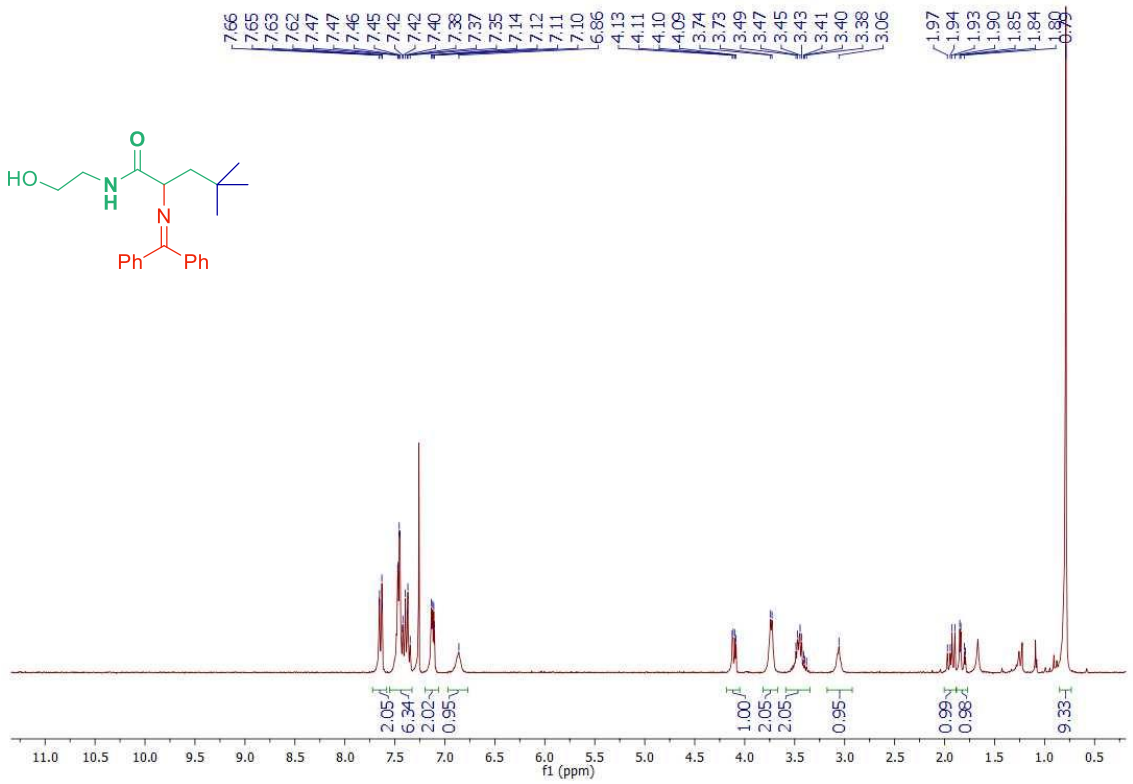
^{13}C NMR of compound **3fa** (75 MHz, $CDCl_3$)



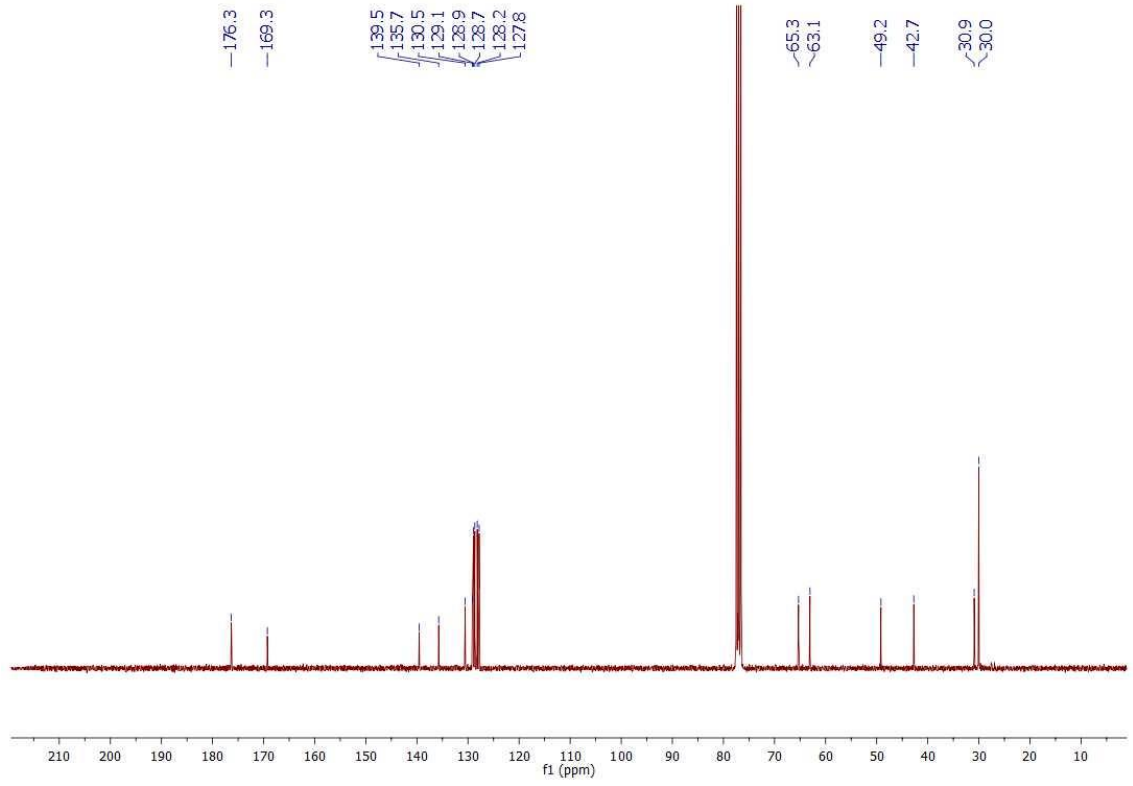
^{1}H NMR of compound **3ga** (300 MHz, $CDCl_3$)



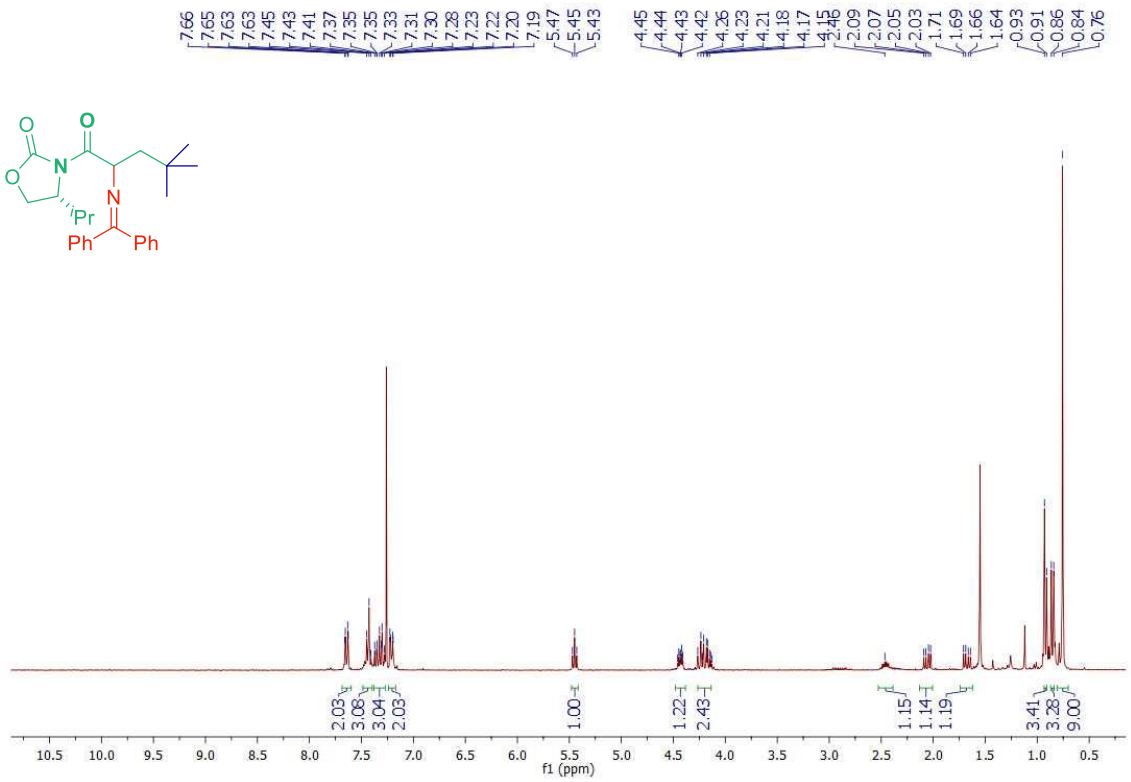
^{13}C NMR of compound **3ga** (75 MHz, $CDCl_3$)



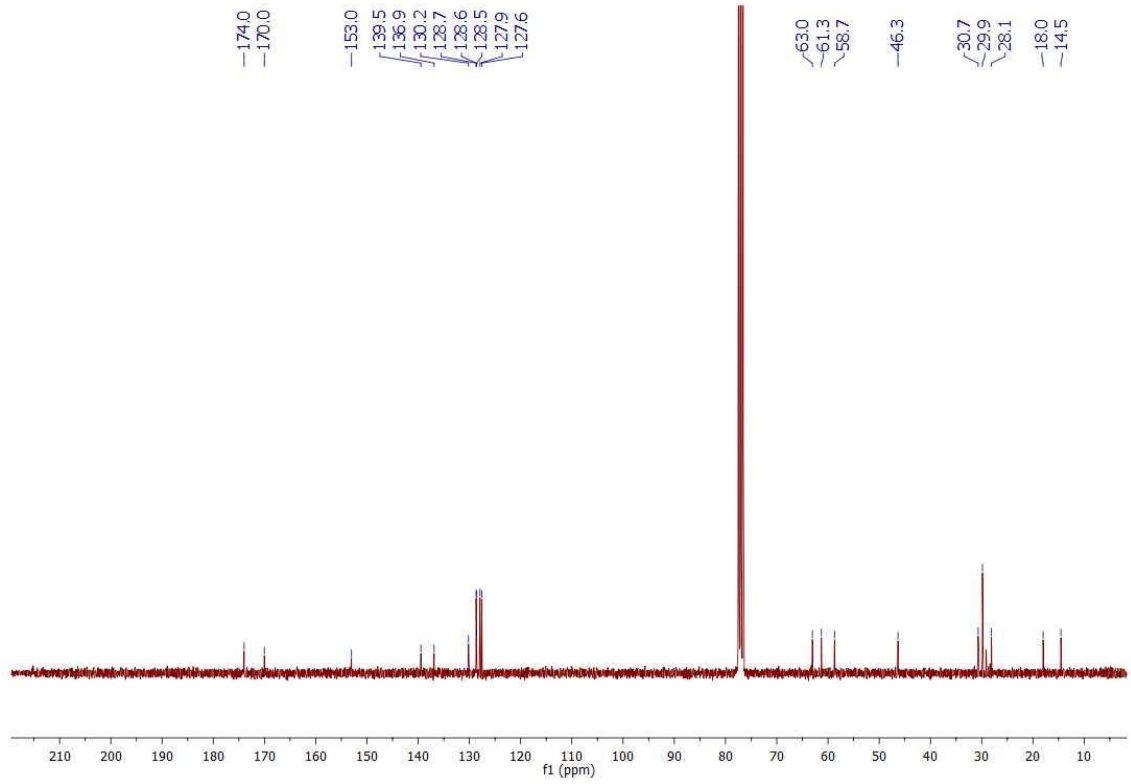
^{1}H NMR of compound **3ia** (300 MHz, $CDCl_3$)



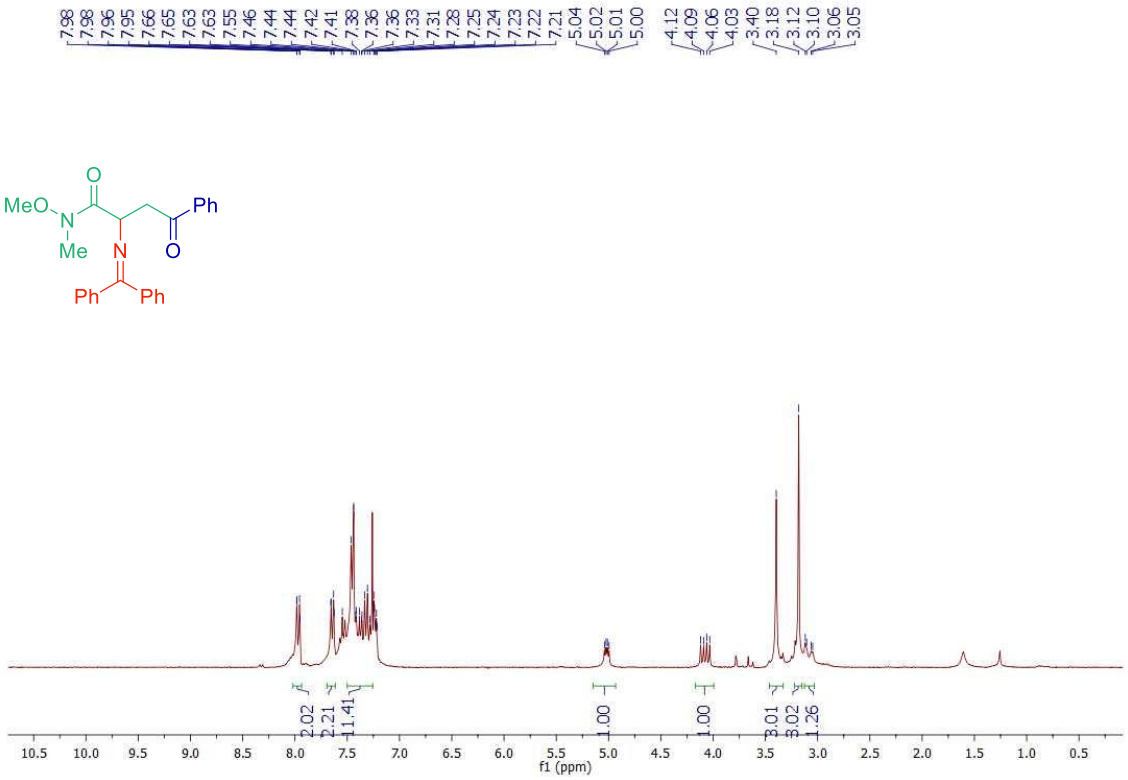
^{13}C NMR of compound **3ia** (75 MHz, $CDCl_3$)



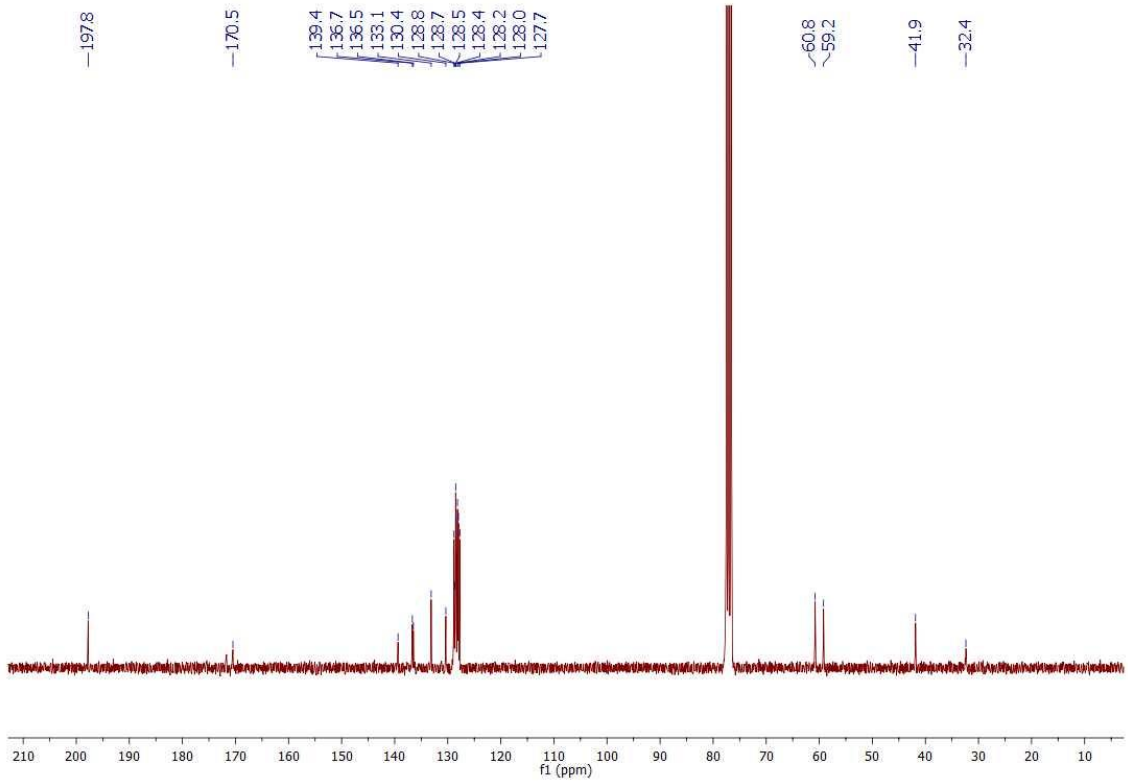
^{1}H NMR of compound **3la** (300 MHz, $CDCl_3$)



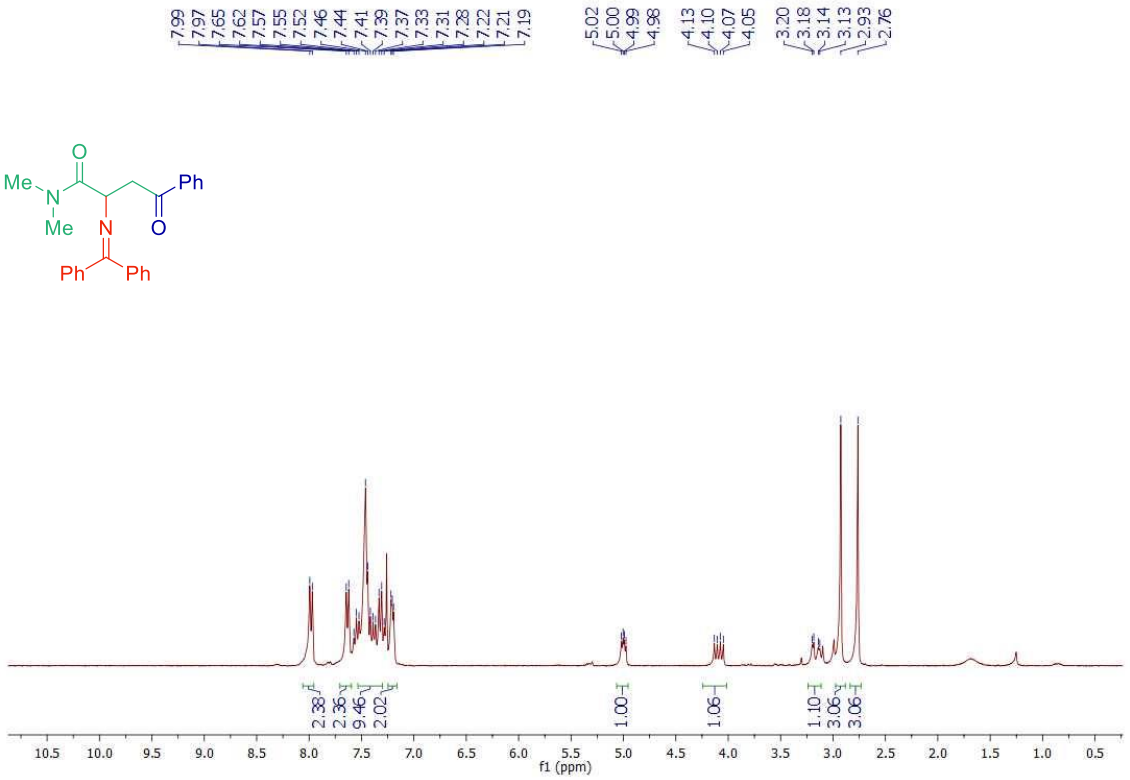
^{13}C NMR of compound **3la** (75 MHz, $CDCl_3$)



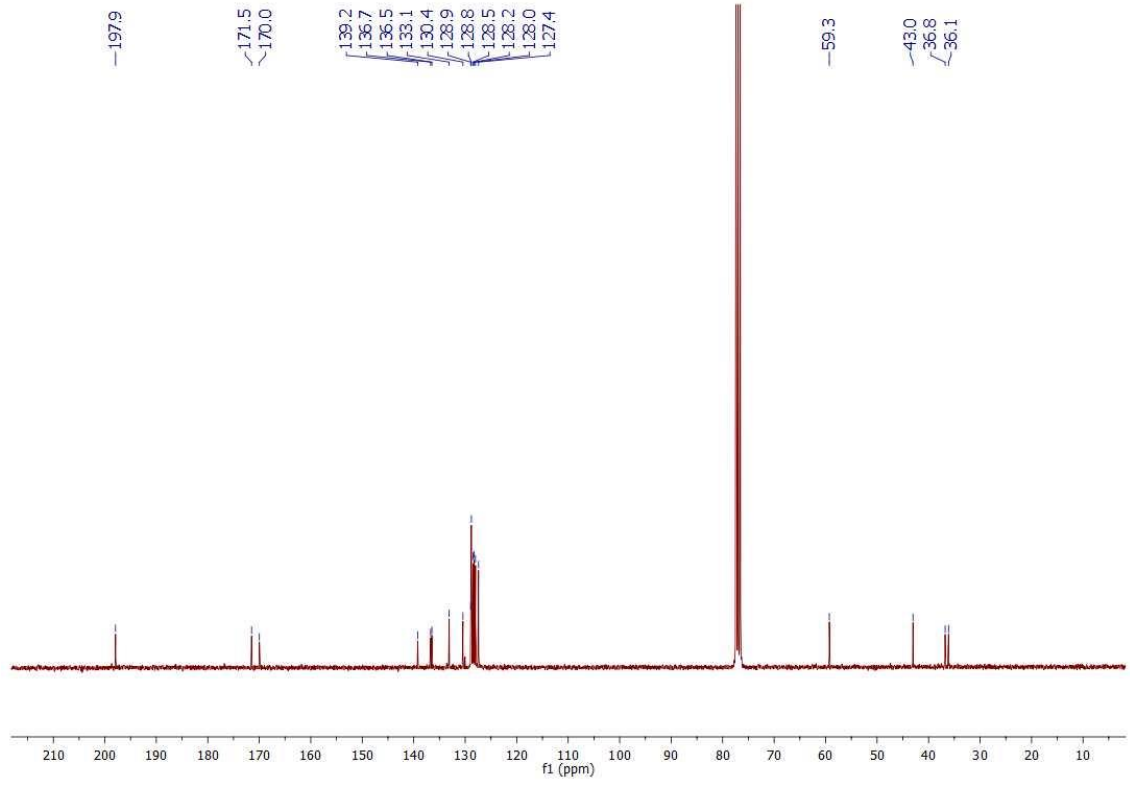
^{1}H NMR of compound **3co** (300 MHz, $CDCl_3$)



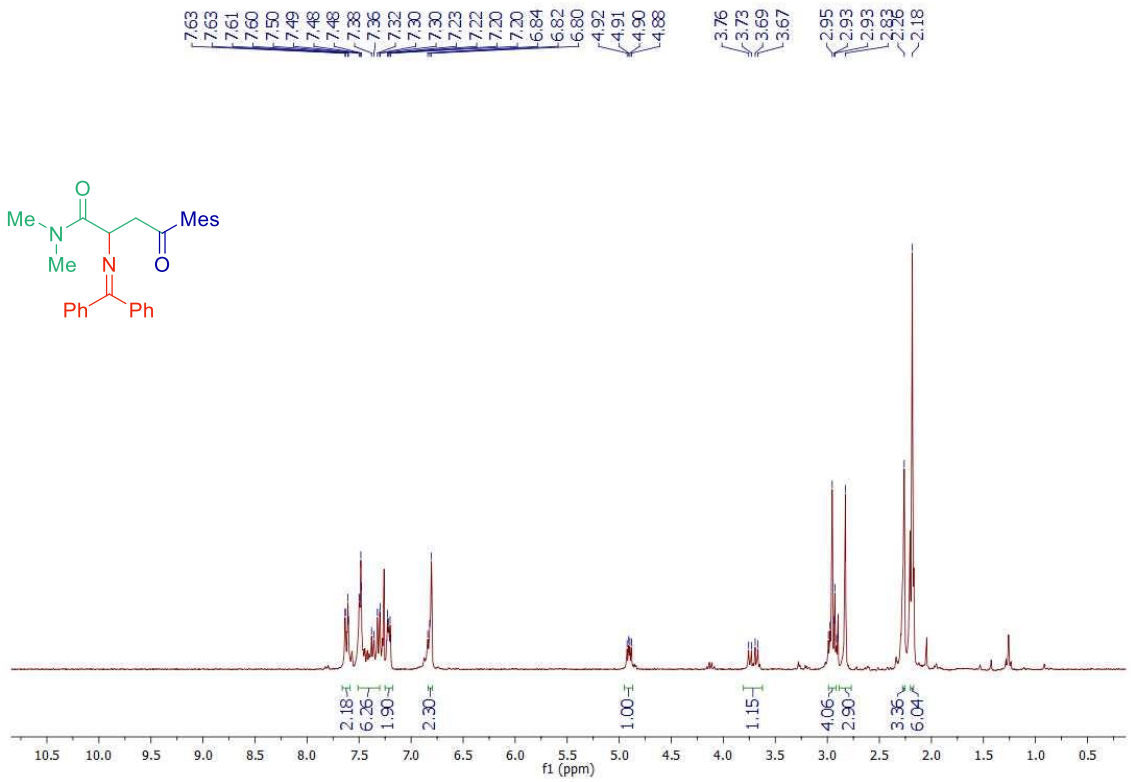
^{13}C NMR of compound **3co** (75 MHz, $CDCl_3$)



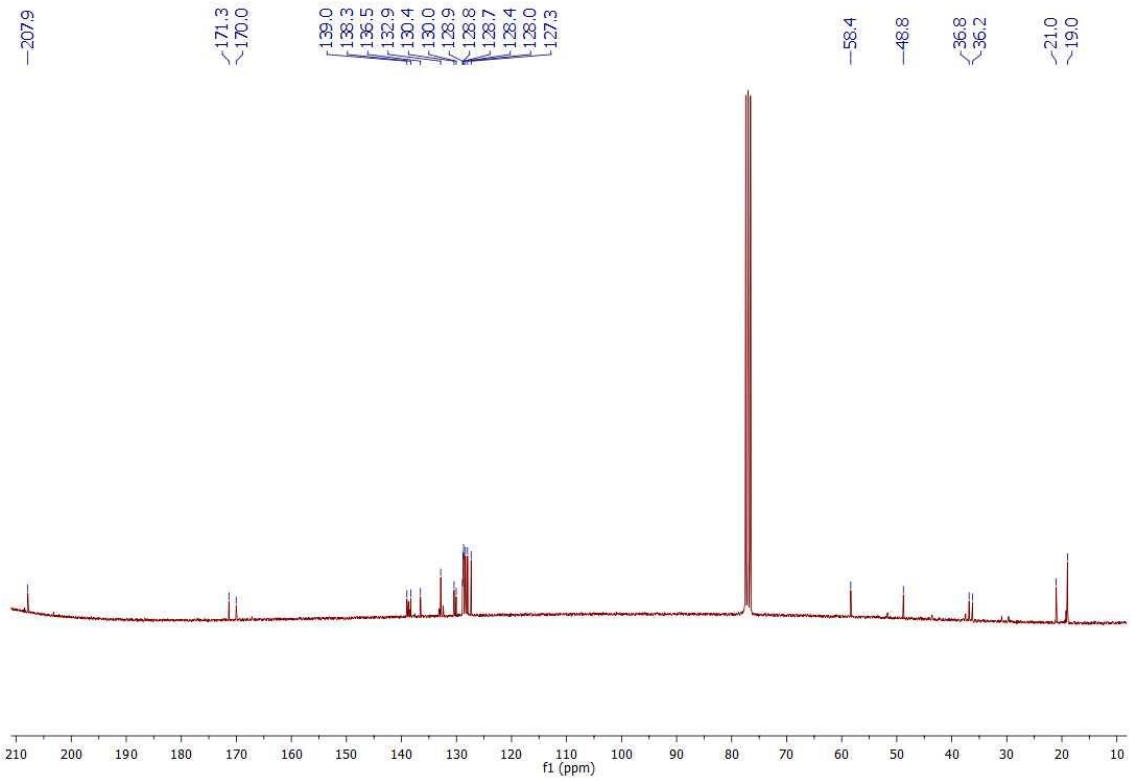
^{1}H NMR of compound **3ao** (300 MHz, $CDCl_3$)



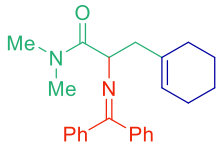
^{13}C NMR of compound **3ao** (75 MHz, $CDCl_3$)

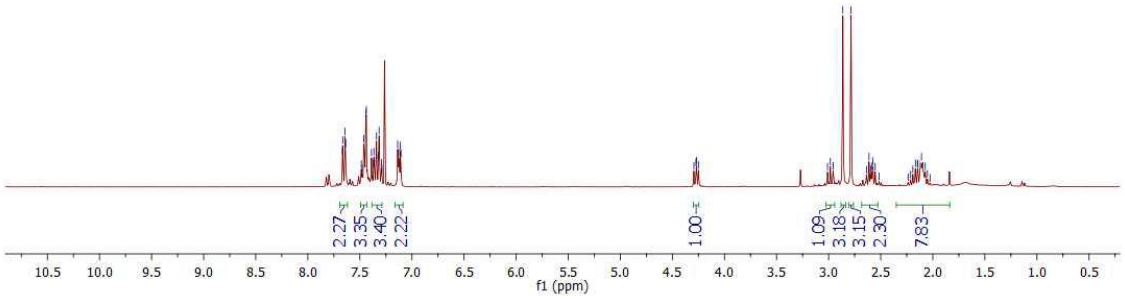


^{1}H NMR of compound **3ap** (300 MHz, $CDCl_3$)

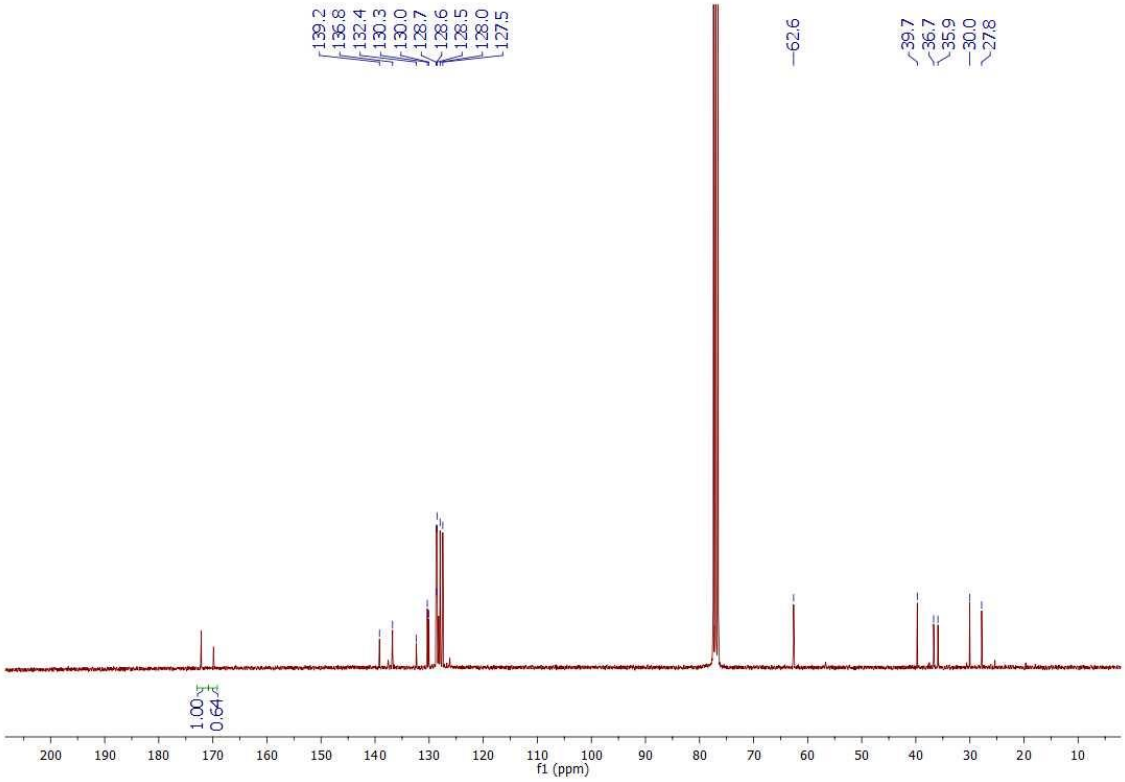


^{13}C NMR of compound **3ap** (75 MHz, $CDCl_3$)

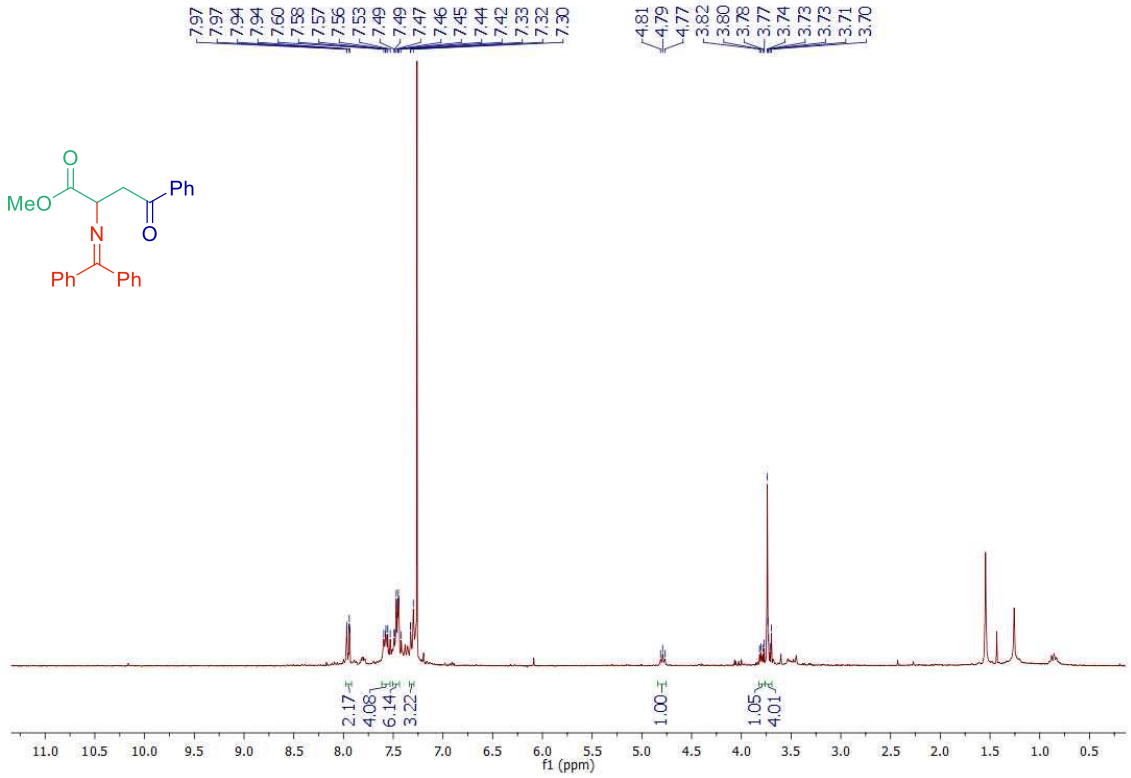




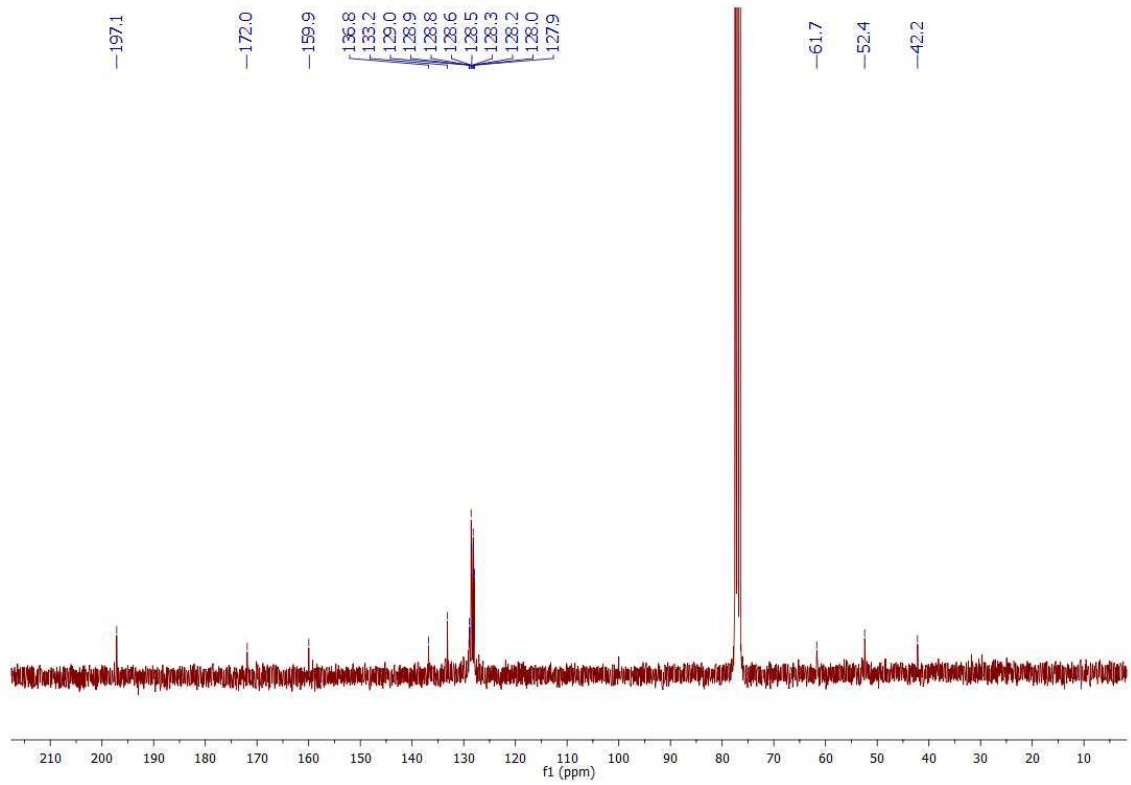
^{1}H NMR of compound **3aq** (300 MHz, $CDCl_3$)



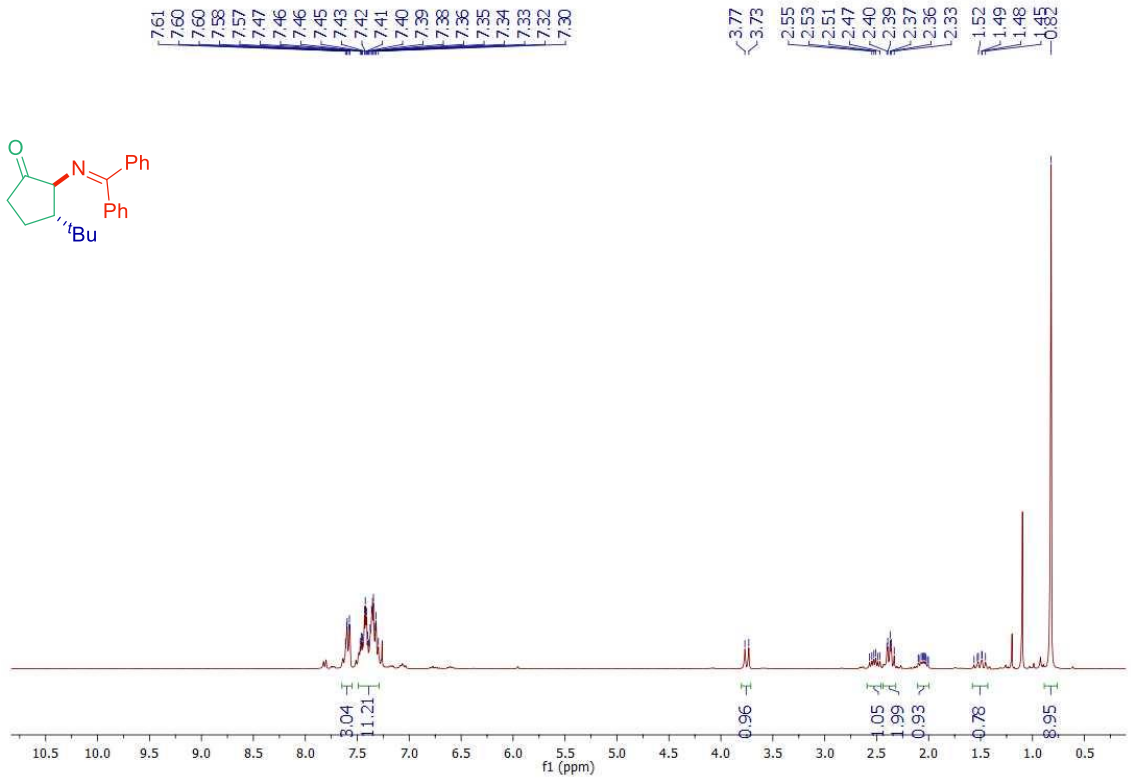
^{13}C NMR of compound **3aq** (75 MHz, $CDCl_3$)



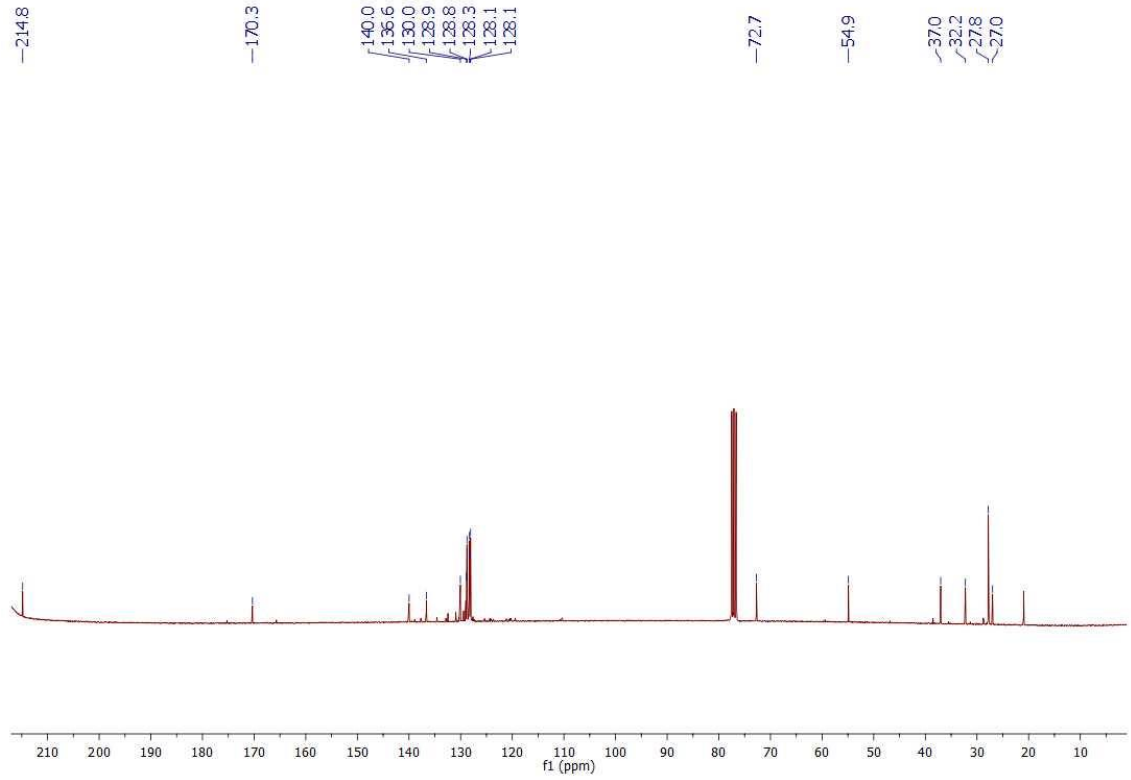
^{1}H NMR of compound **3oo** (300 MHz, $CDCl_3$)



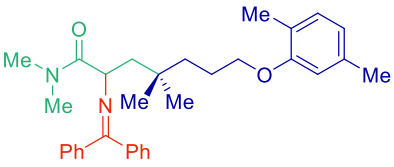
^{13}C NMR of compound **3oo** (75 MHz, $CDCl_3$)

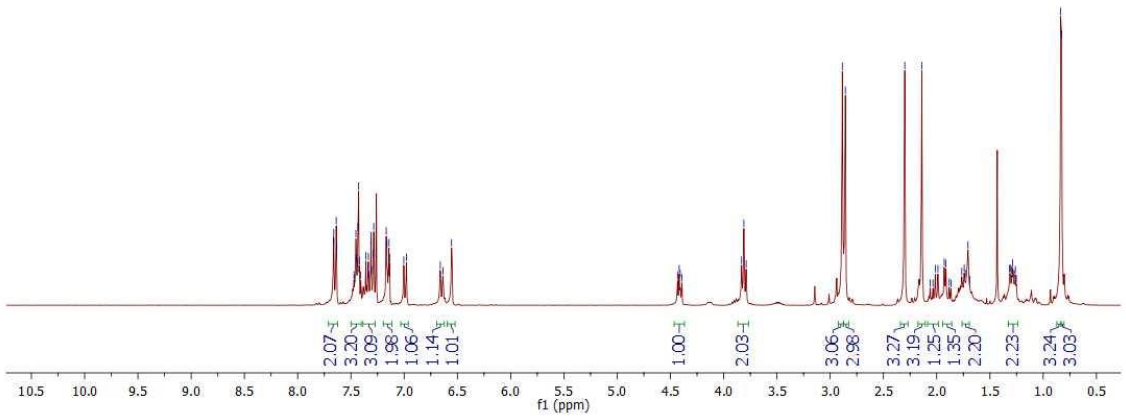


^{1}H NMR of compound **3na** (300 MHz, $CDCl_3$)

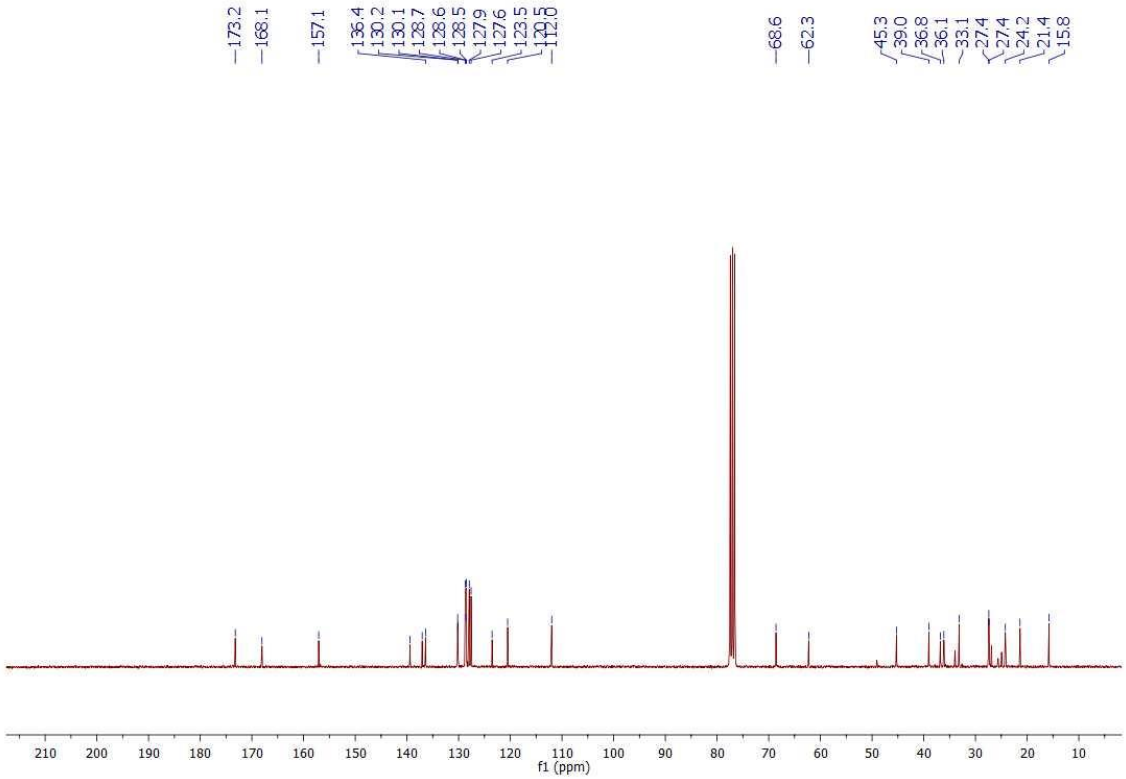


^{13}C NMR of compound **3na** (75 MHz, $CDCl_3$)

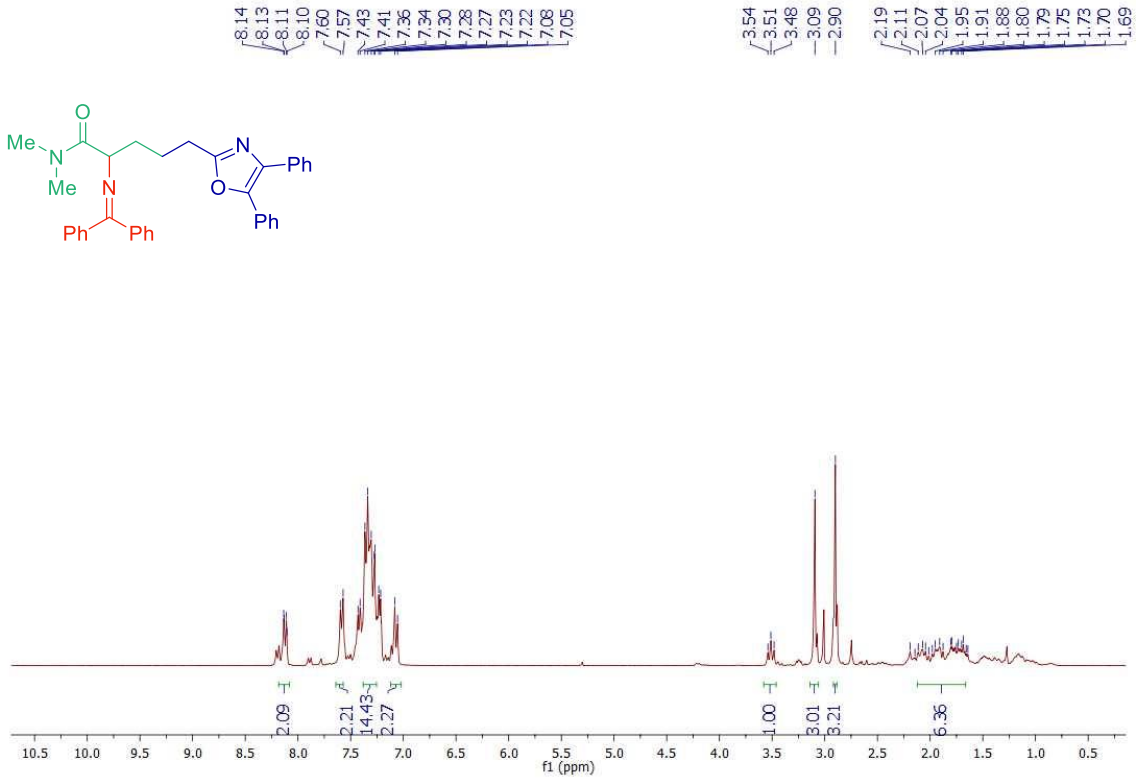




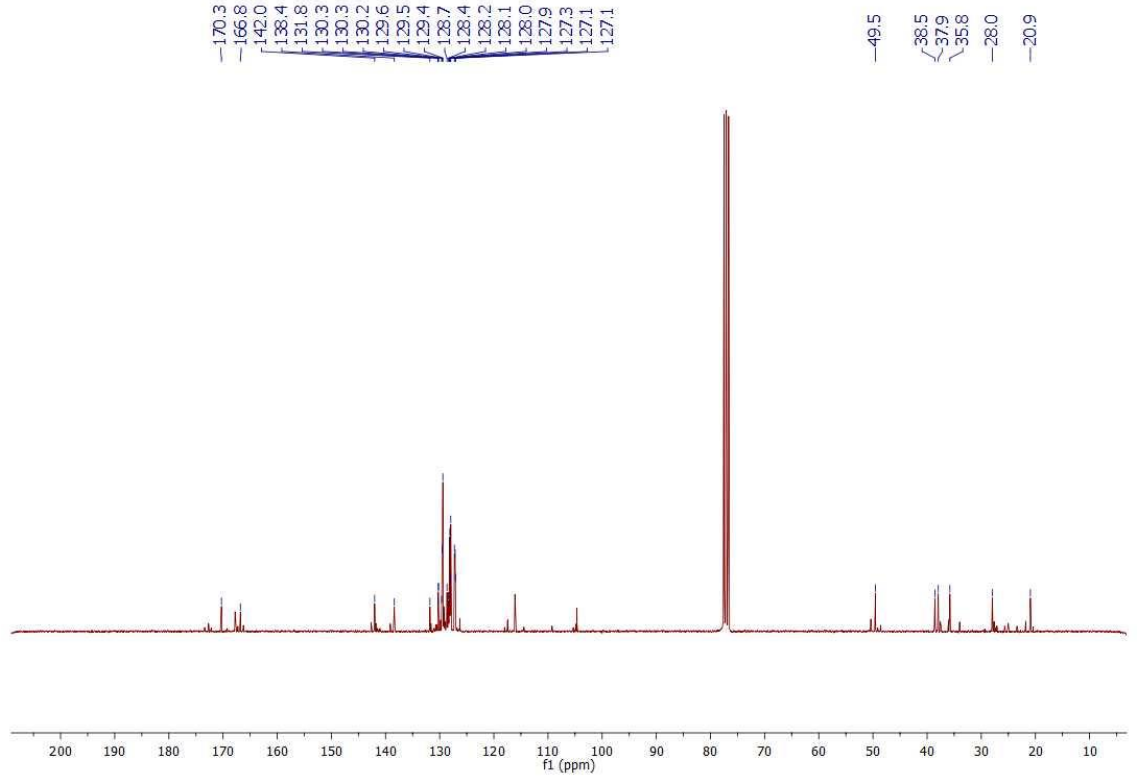
^{1}H NMR of compound **3ap** (300 MHz, $CDCl_3$)



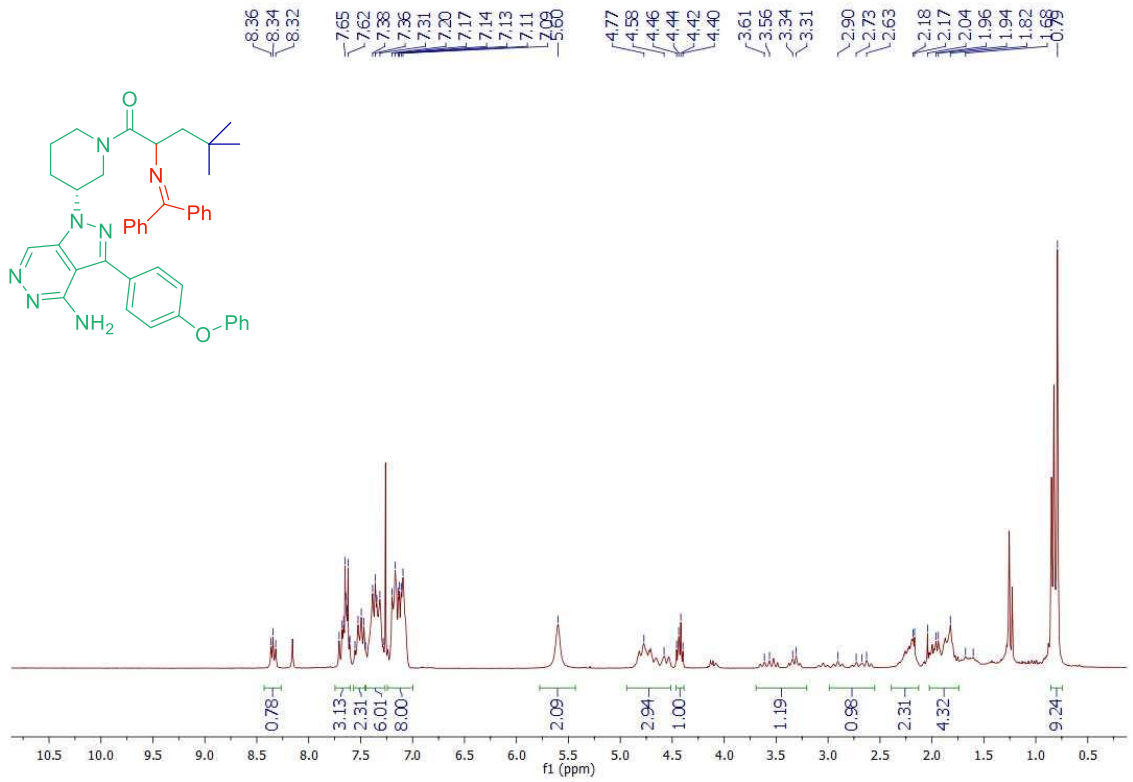
^{13}C NMR of compound **3ap** (75 MHz, $CDCl_3$)



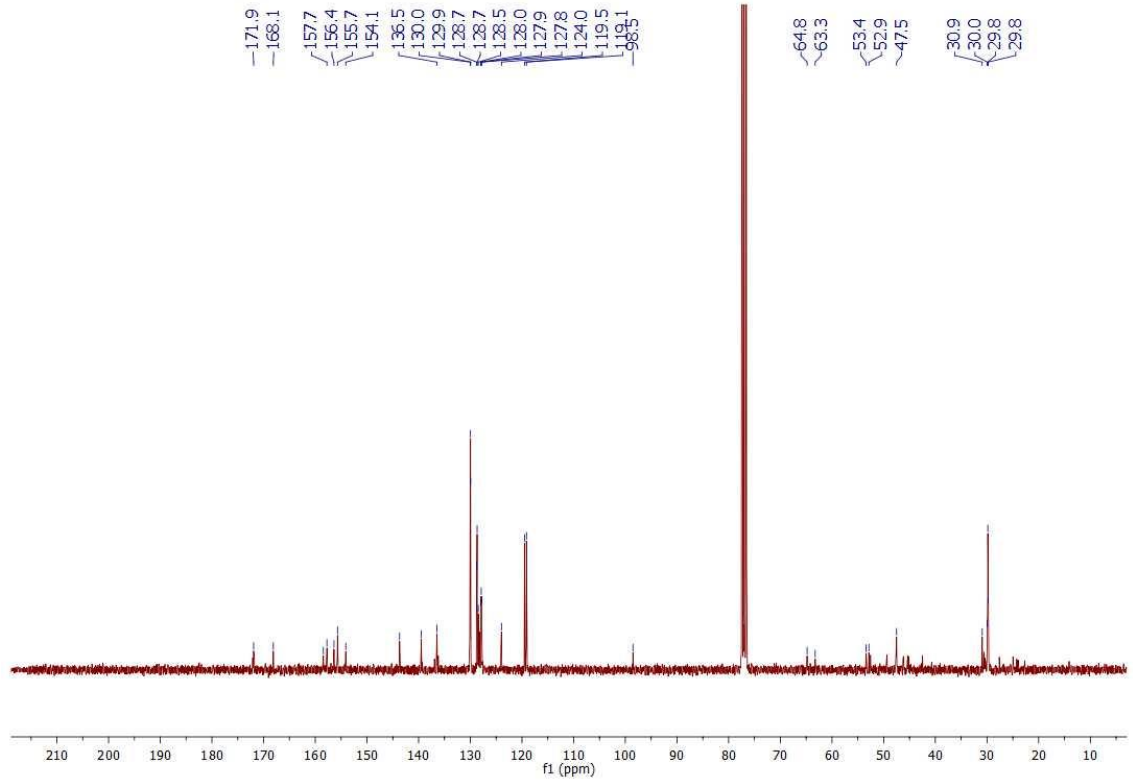
^{1}H NMR of compound **3aq** (300 MHz, $CDCl_3$)



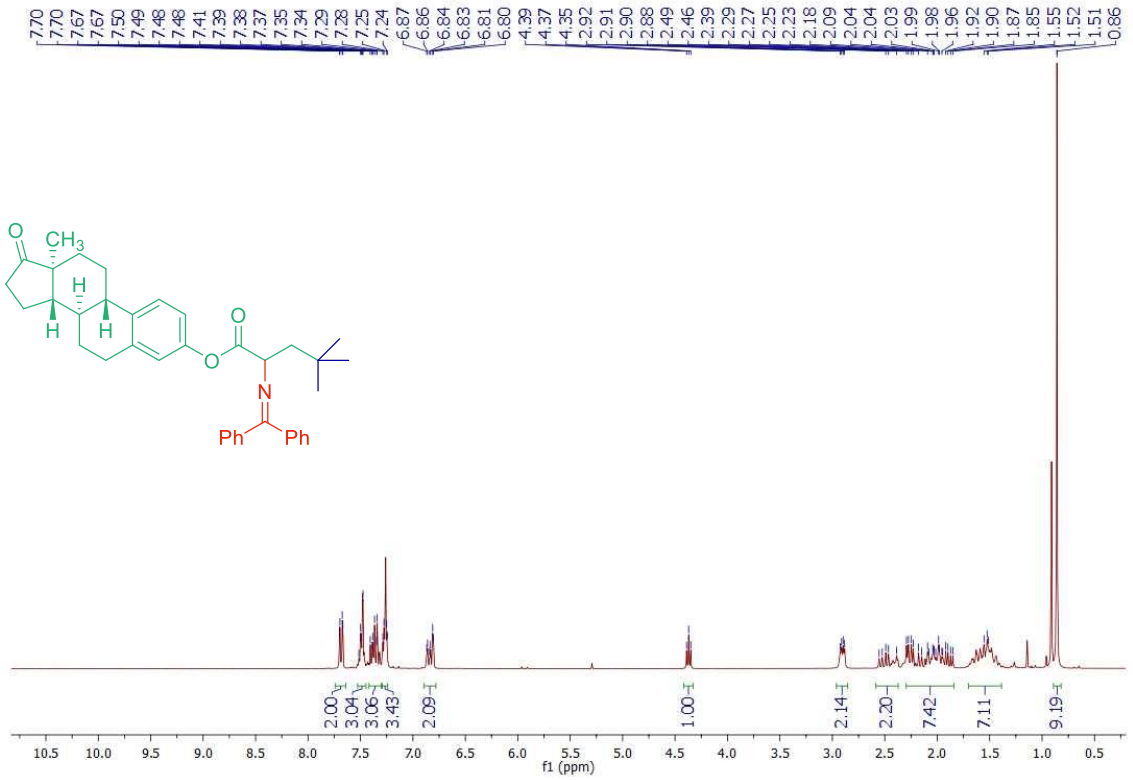
^{13}C NMR of compound **3aq** (75 MHz, $CDCl_3$)



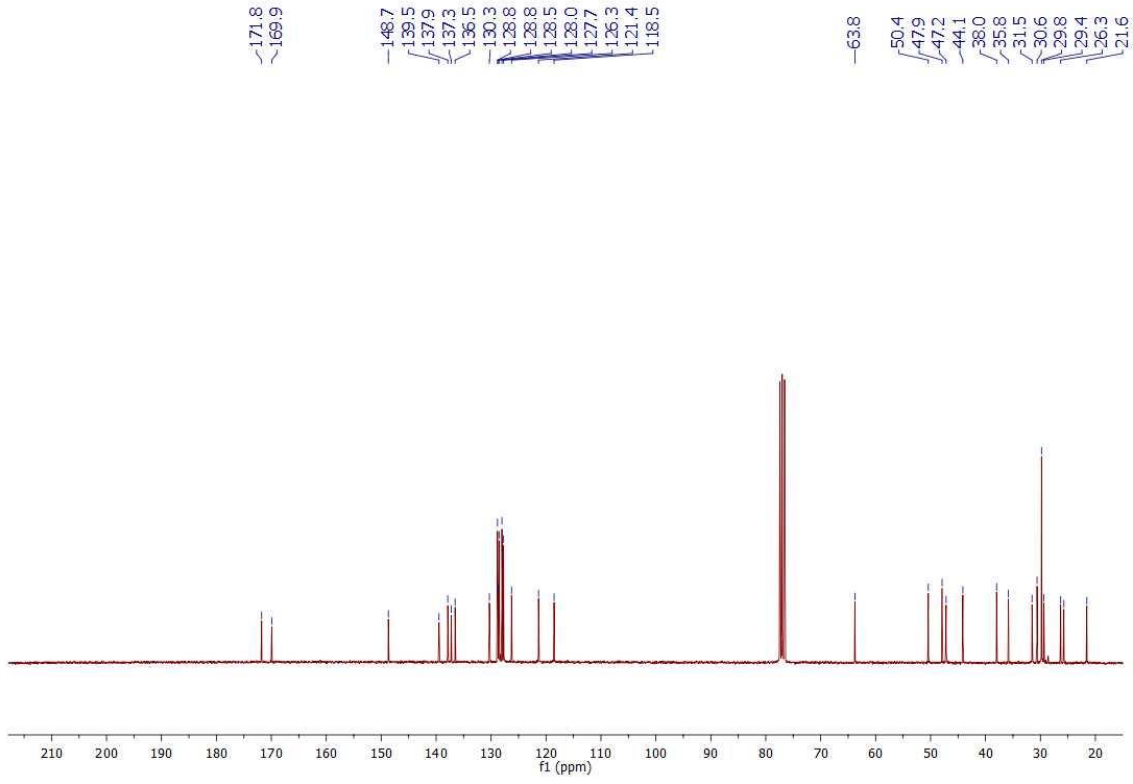
^{1}H NMR of compound **3pa**/**3pa'** (300 MHz, $CDCl_3$)



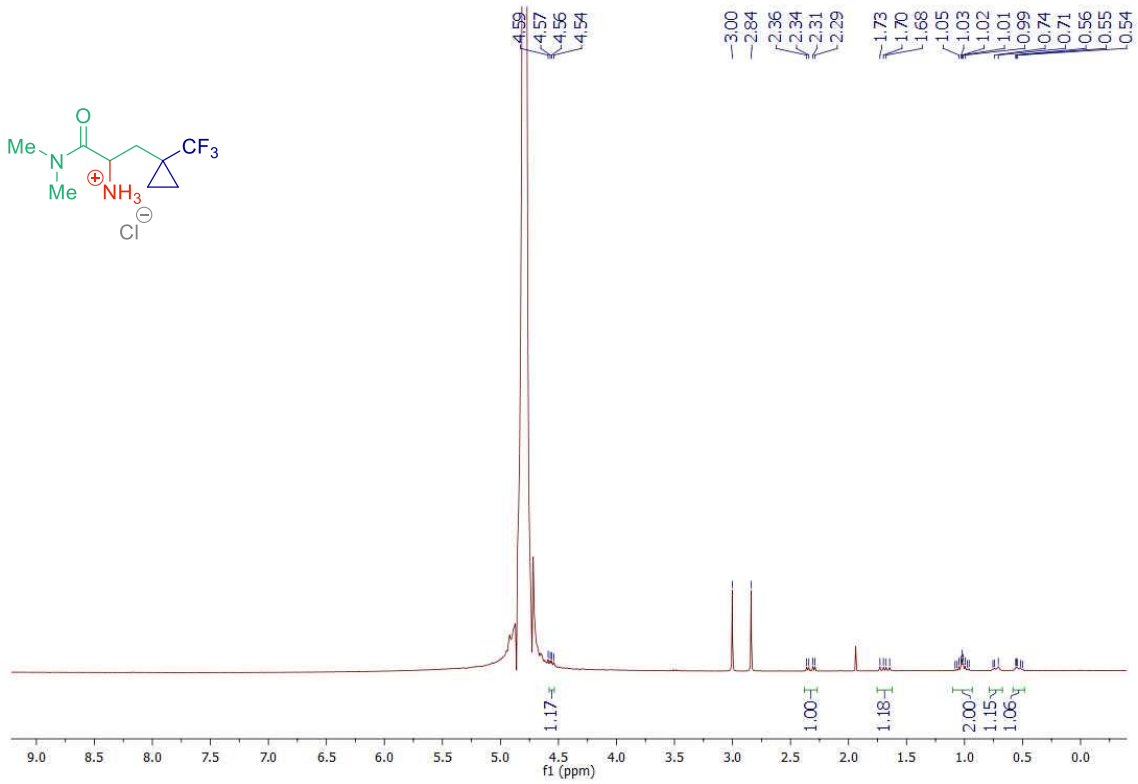
^{13}C NMR of compound **3pa**/**3pa'** (75 MHz, $CDCl_3$)



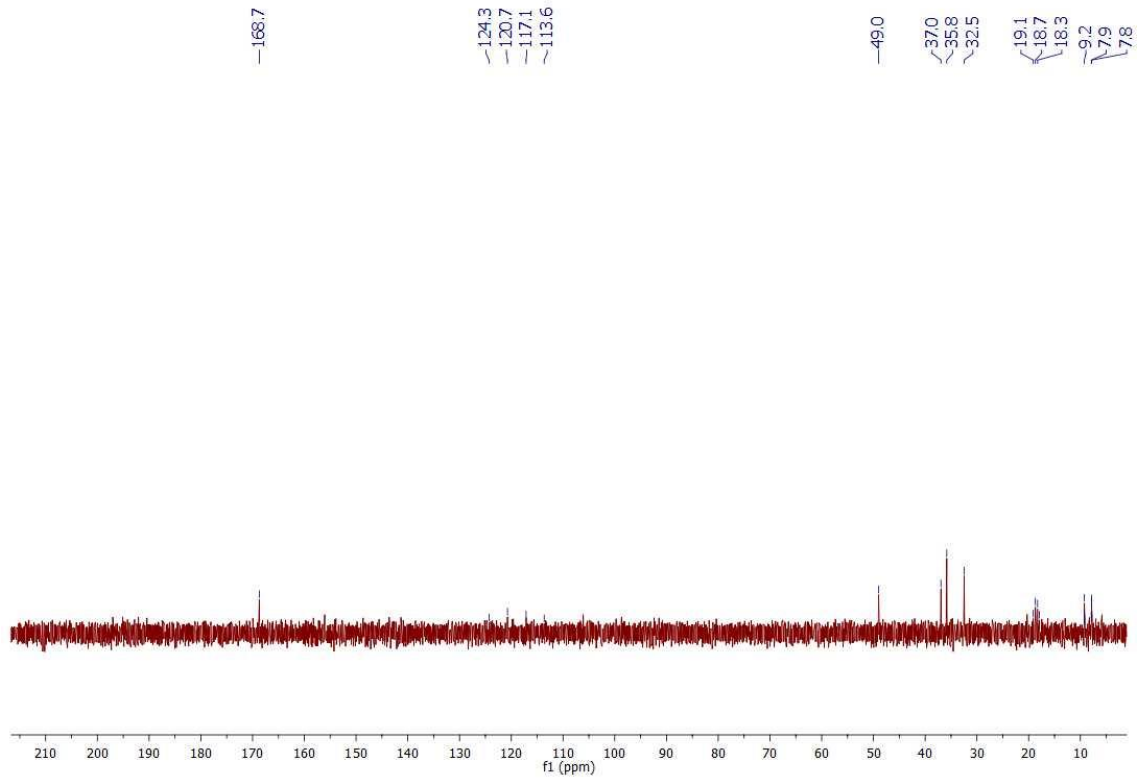
^{1}H NMR of compound **3qa** (300 MHz, $CDCl_3$)



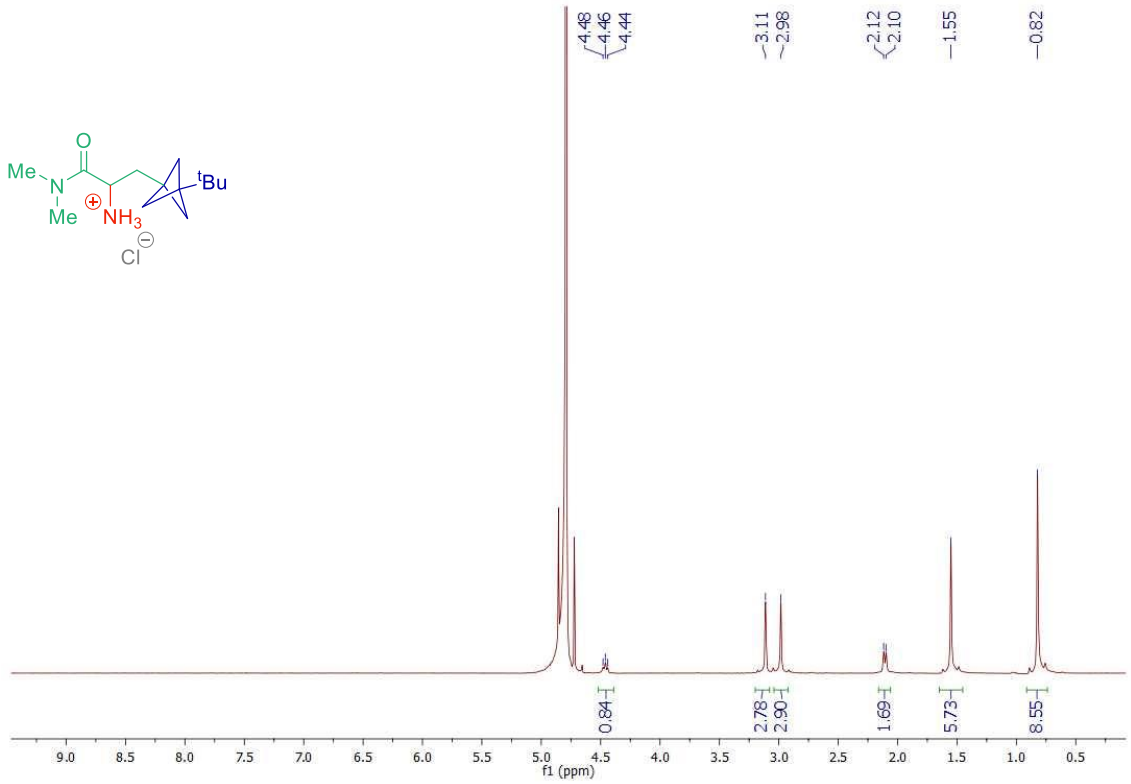
^{13}C NMR of compound **3qa** (75 MHz, $CDCl_3$)



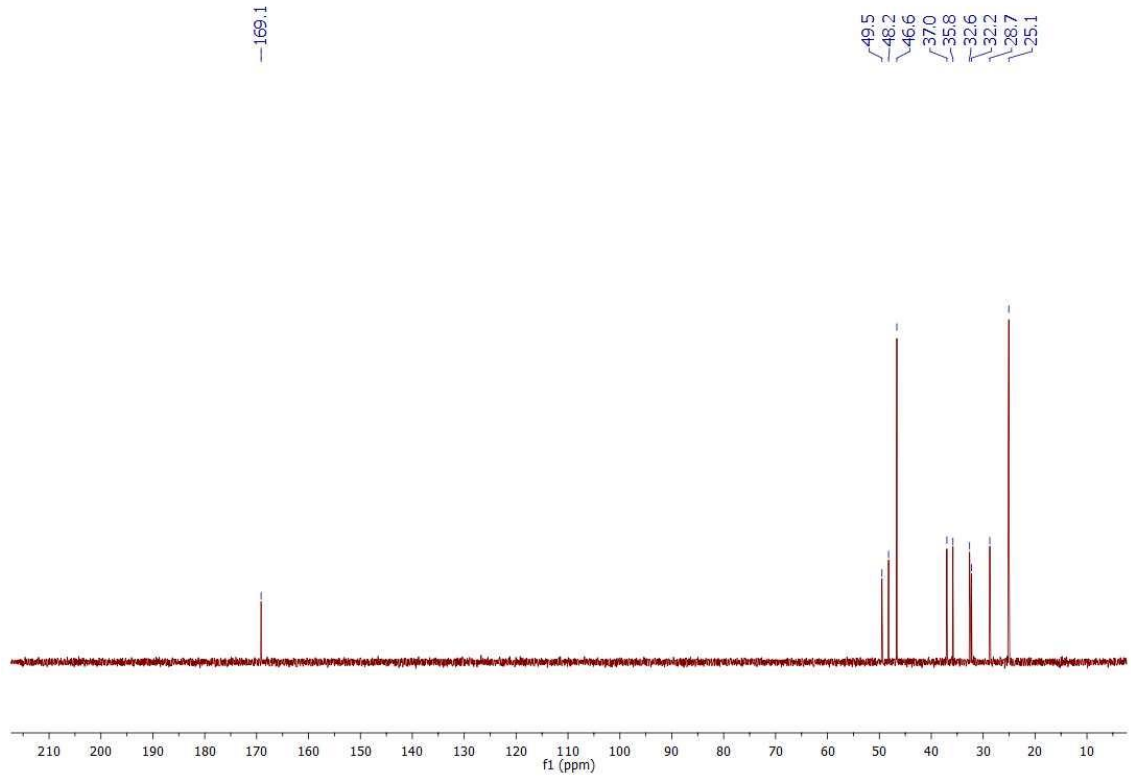
^{1}H NMR of compound **4ab** (300 MHz, D_2O)



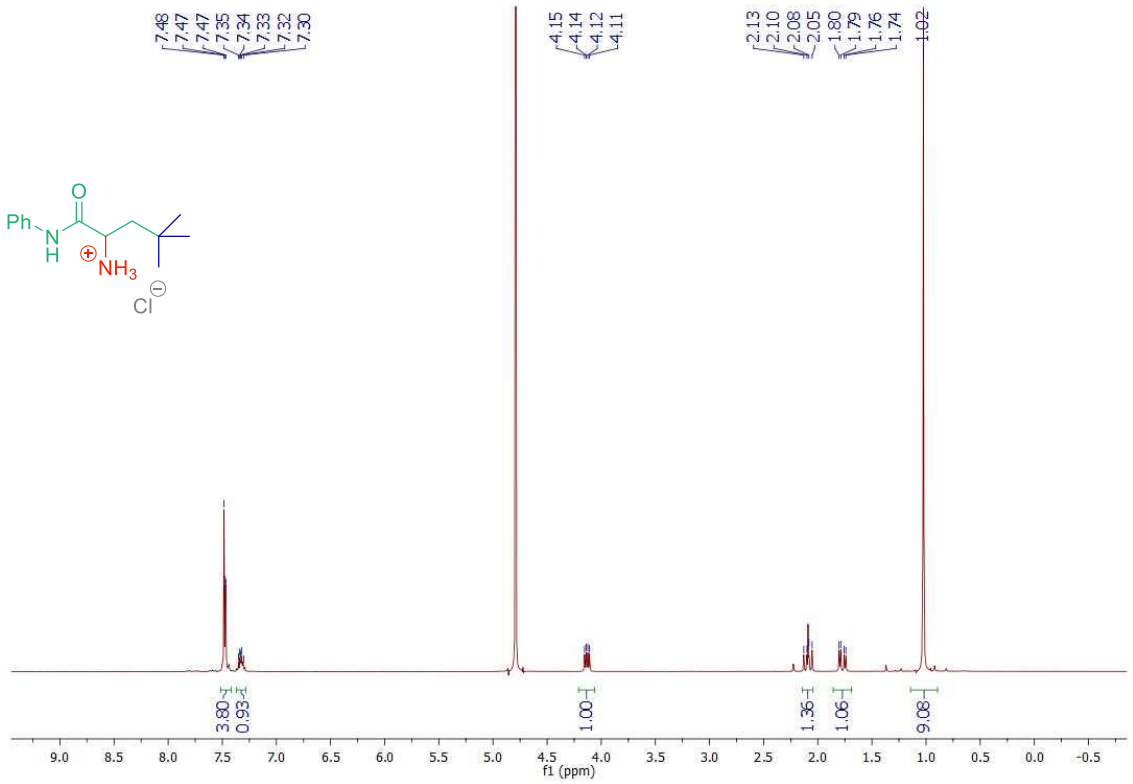
^{13}C NMR of compound **4ab** (75 MHz, D_2O)



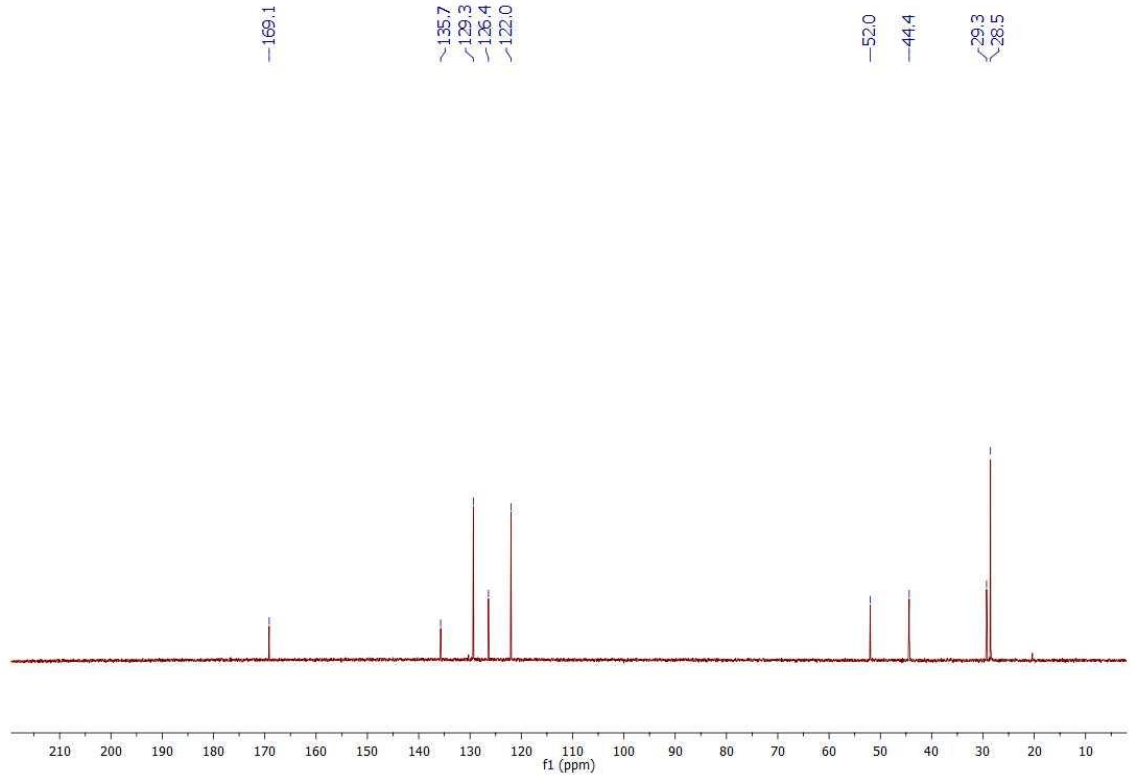
^{1}H NMR of compound **4ac** (300 MHz, D_2O)



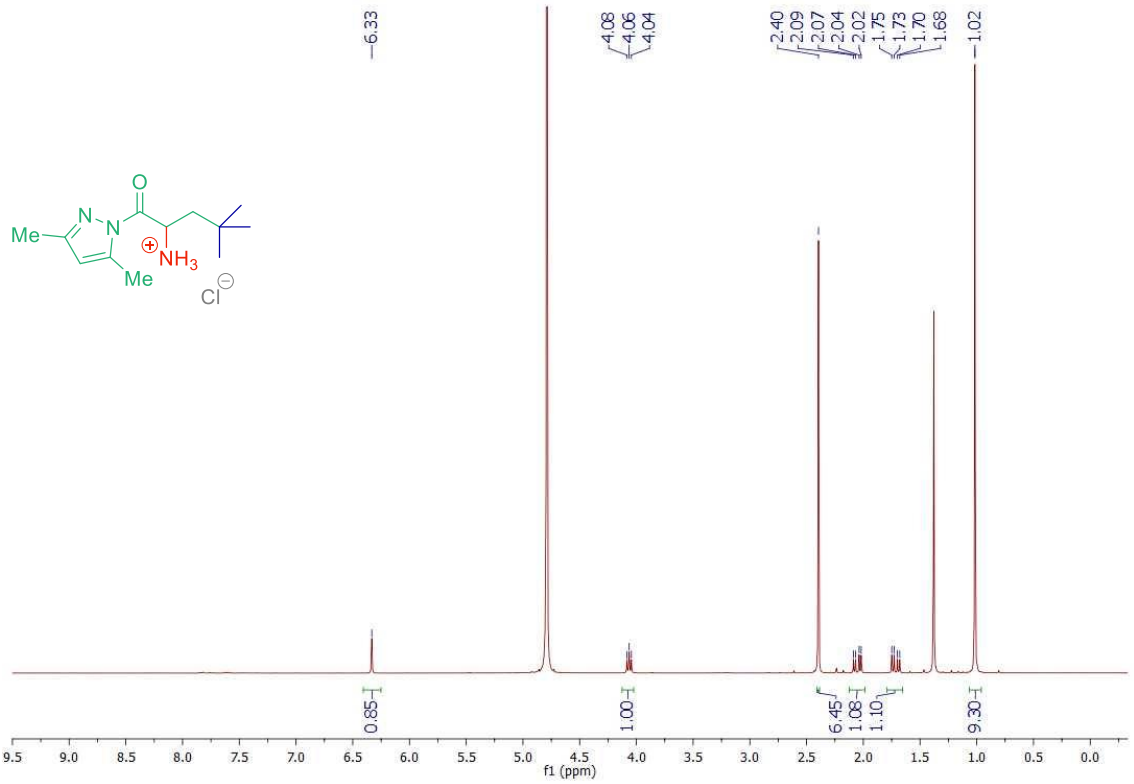
^{13}C NMR of compound **4ac** (75 MHz, D_2O)



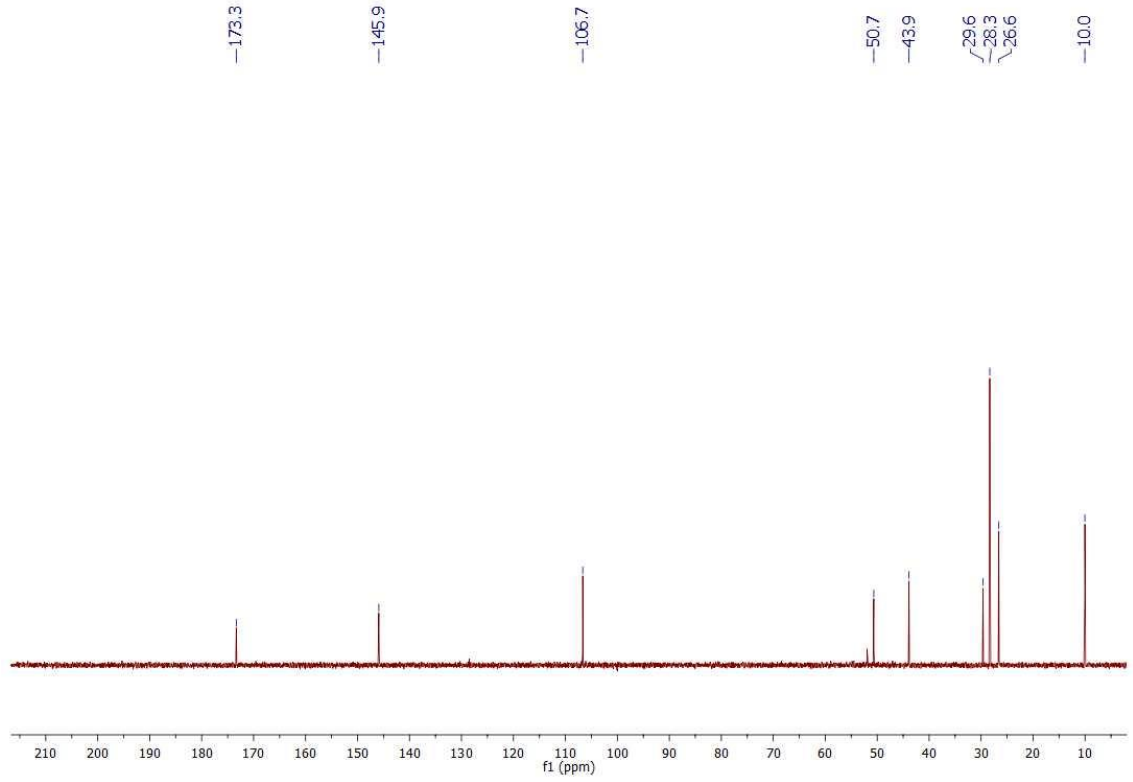
^{1}H NMR of compound **4ha** (300 MHz, D_2O)



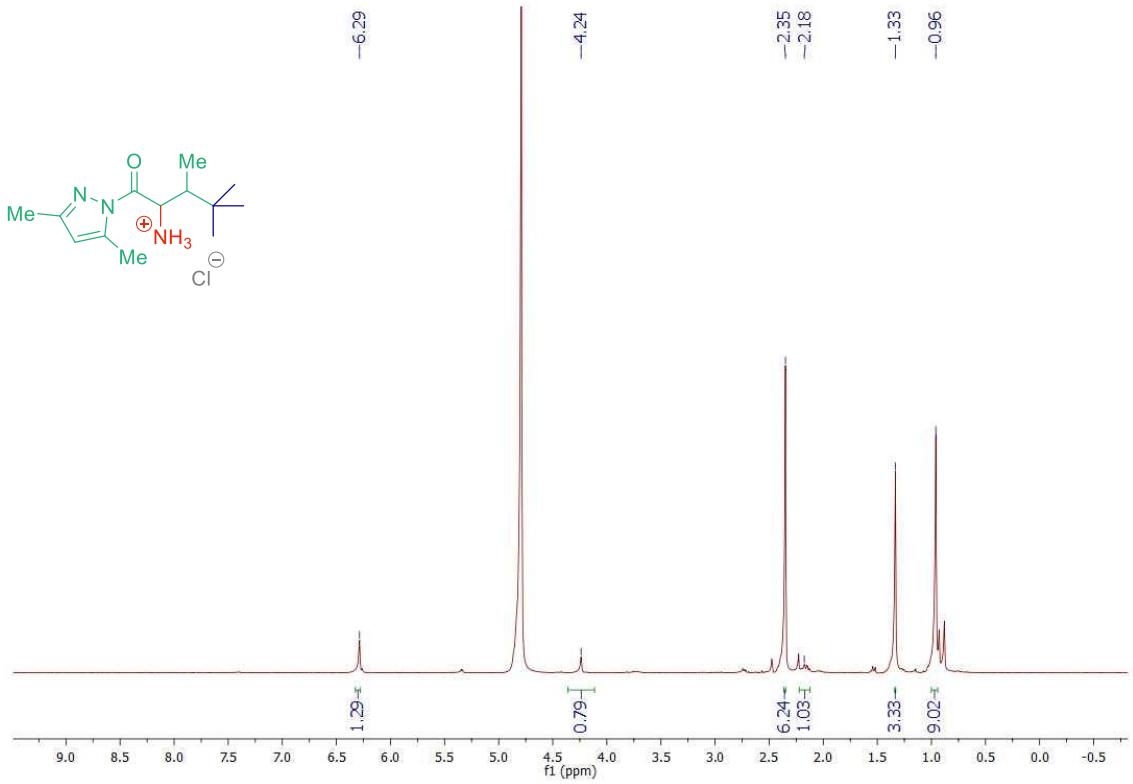
^{13}C NMR of compound **4ha** (75 MHz, D_2O)



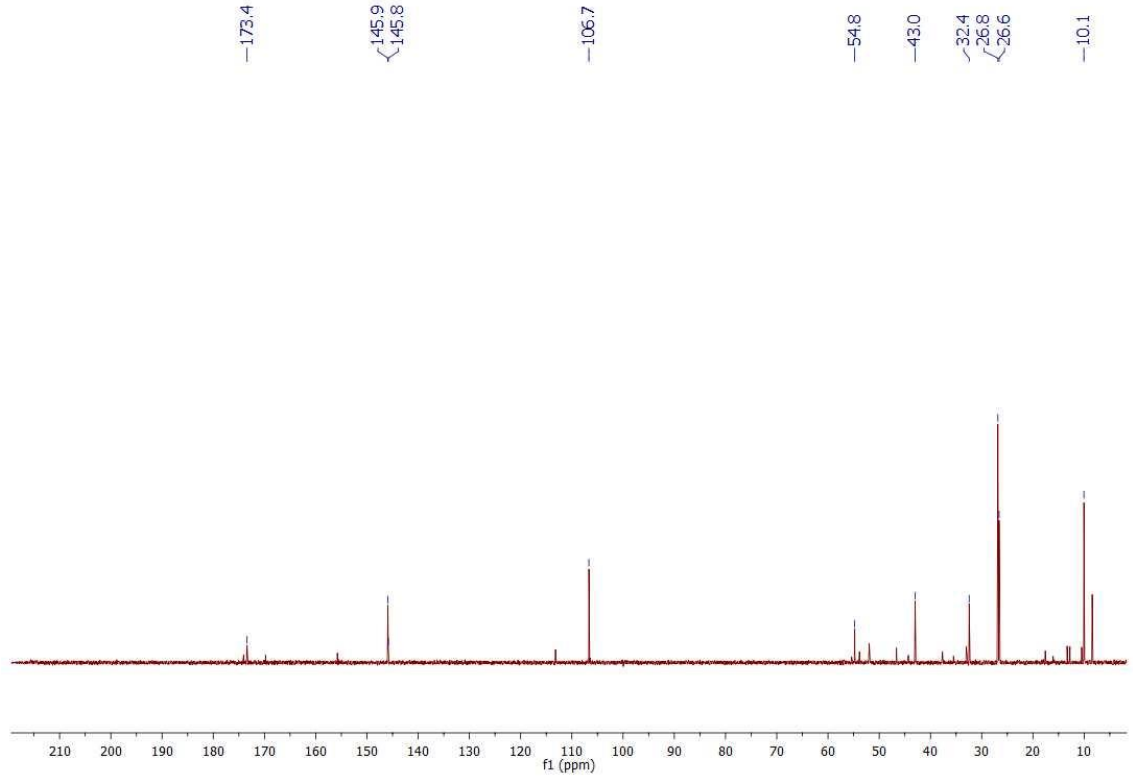
^{1}H NMR of compound **4ja** (300 MHz, D_2O)



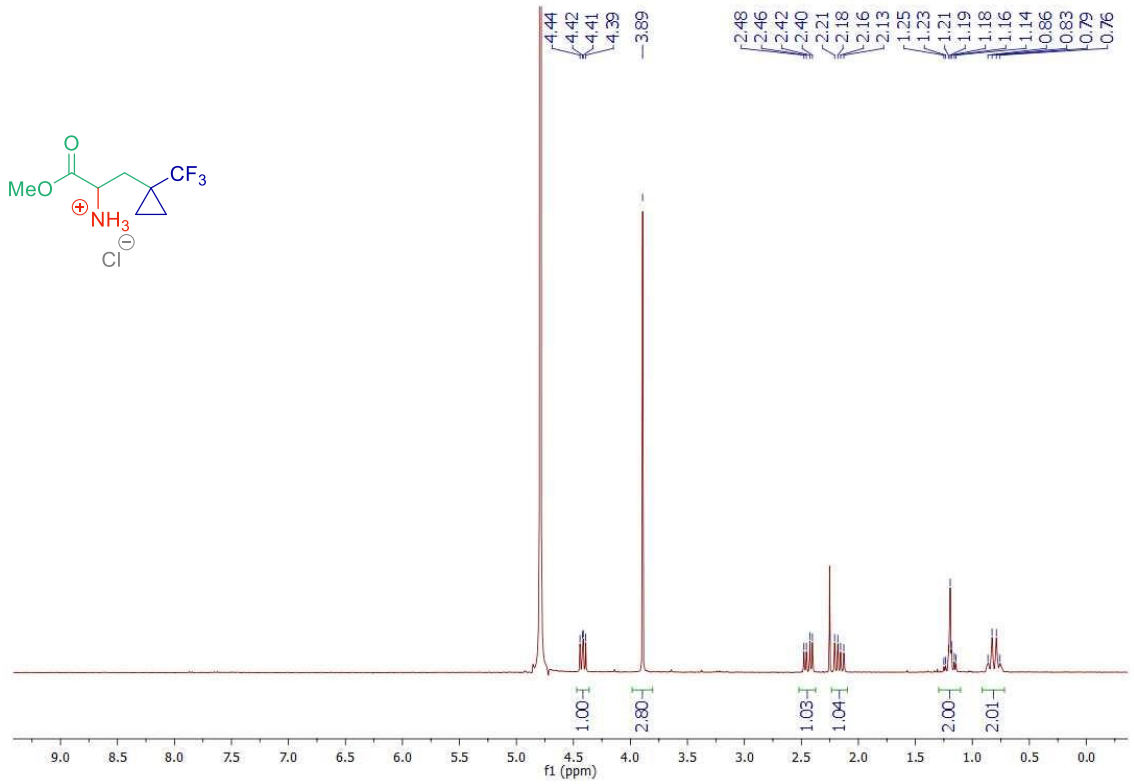
^{13}C NMR of compound **4ja** (75 MHz, D_2O)



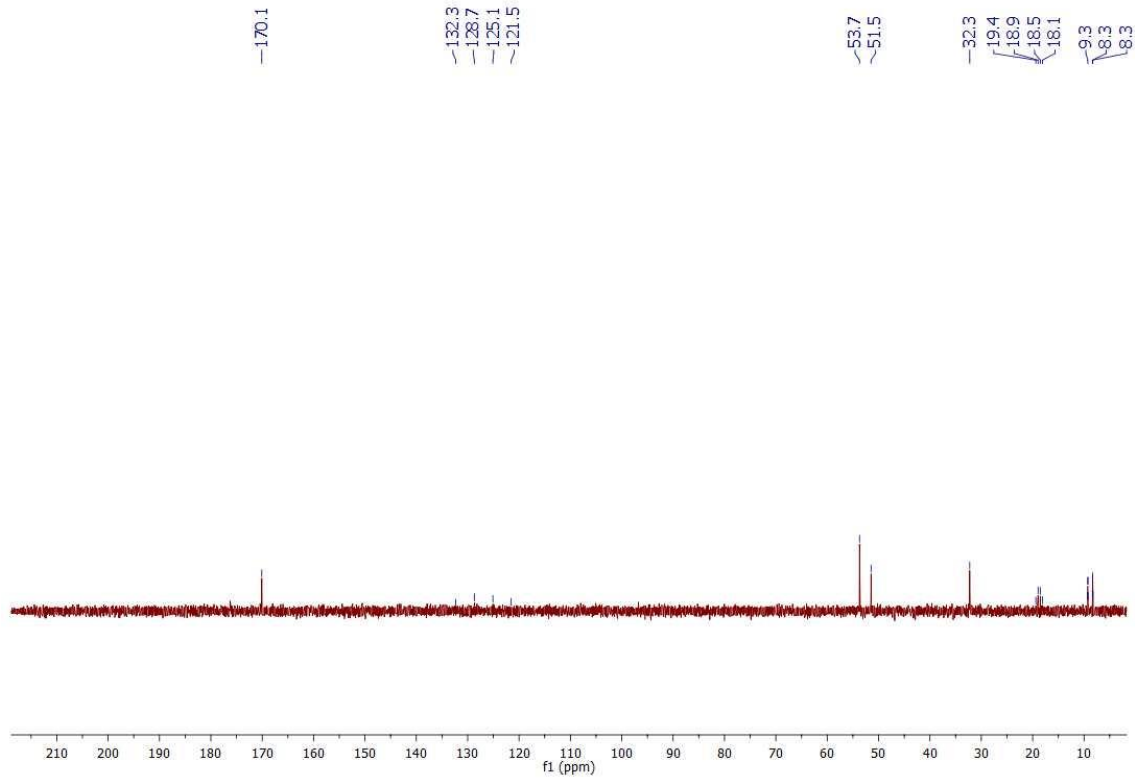
^{1}H NMR of compound **4ka** (300 MHz, D_2O)



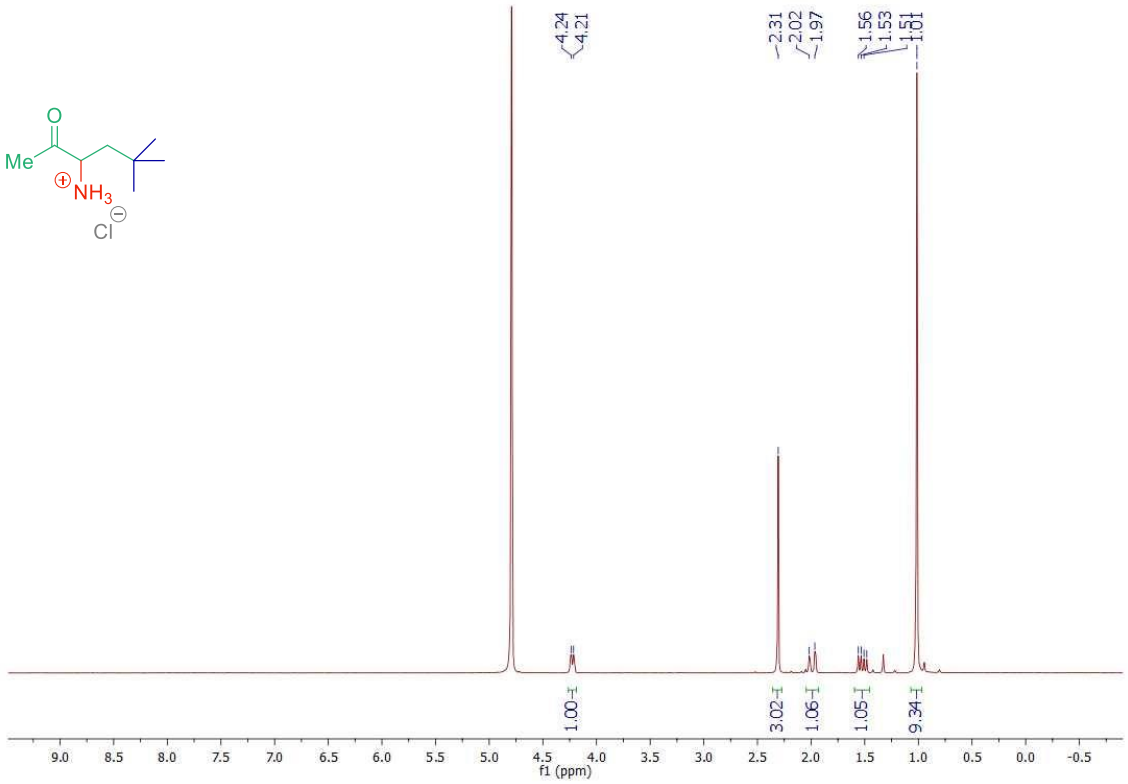
^{13}C NMR of compound **4ka** (75 MHz, D_2O)



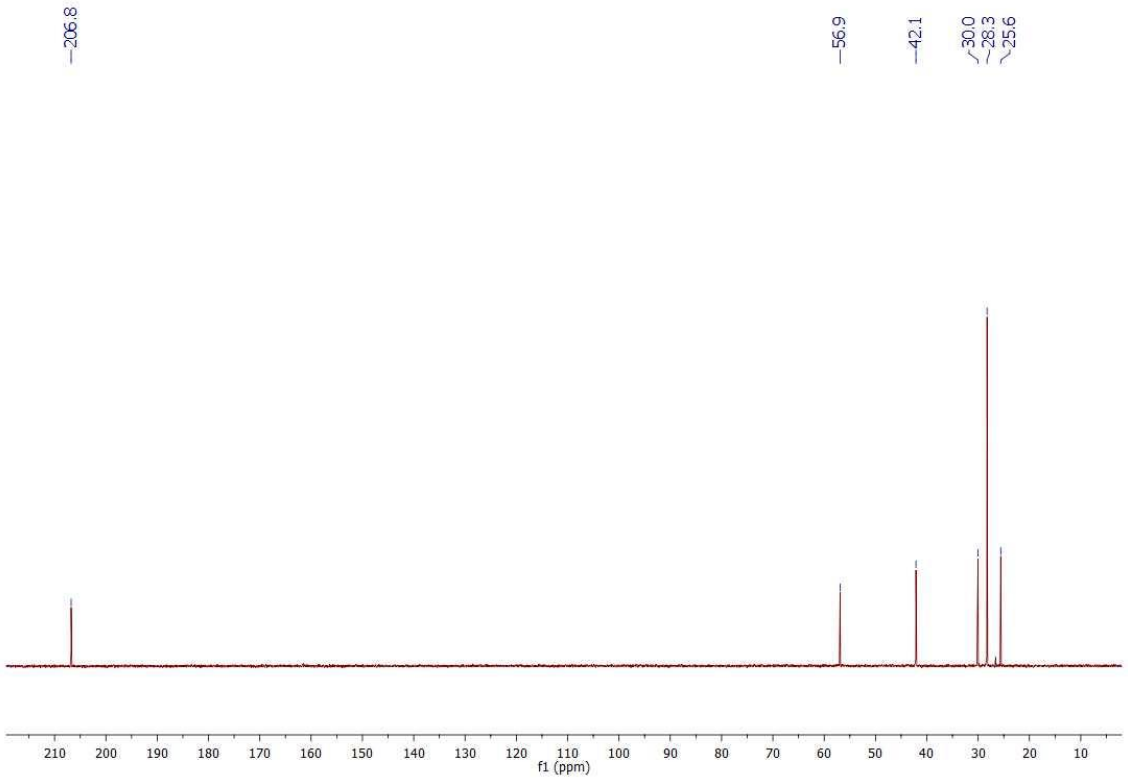
^{1}H NMR of compound **4ob** (300 MHz, D_2O)



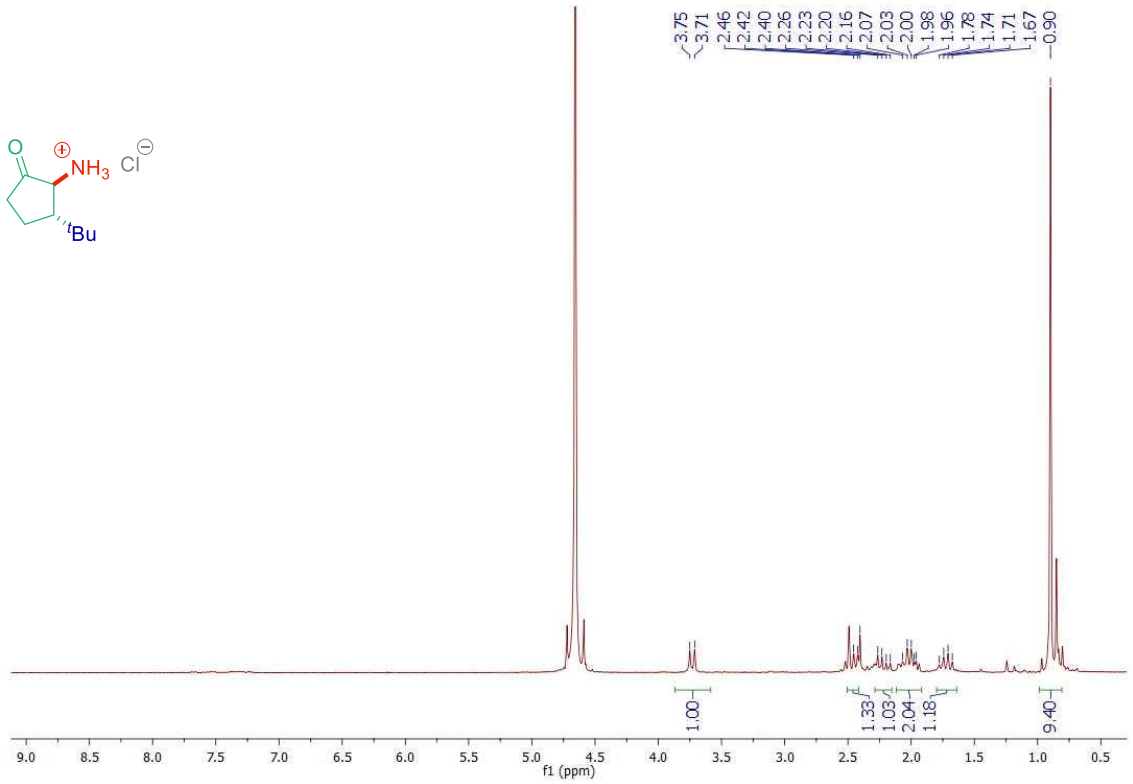
^{13}C NMR of compound **4ob** (75 MHz, D_2O)



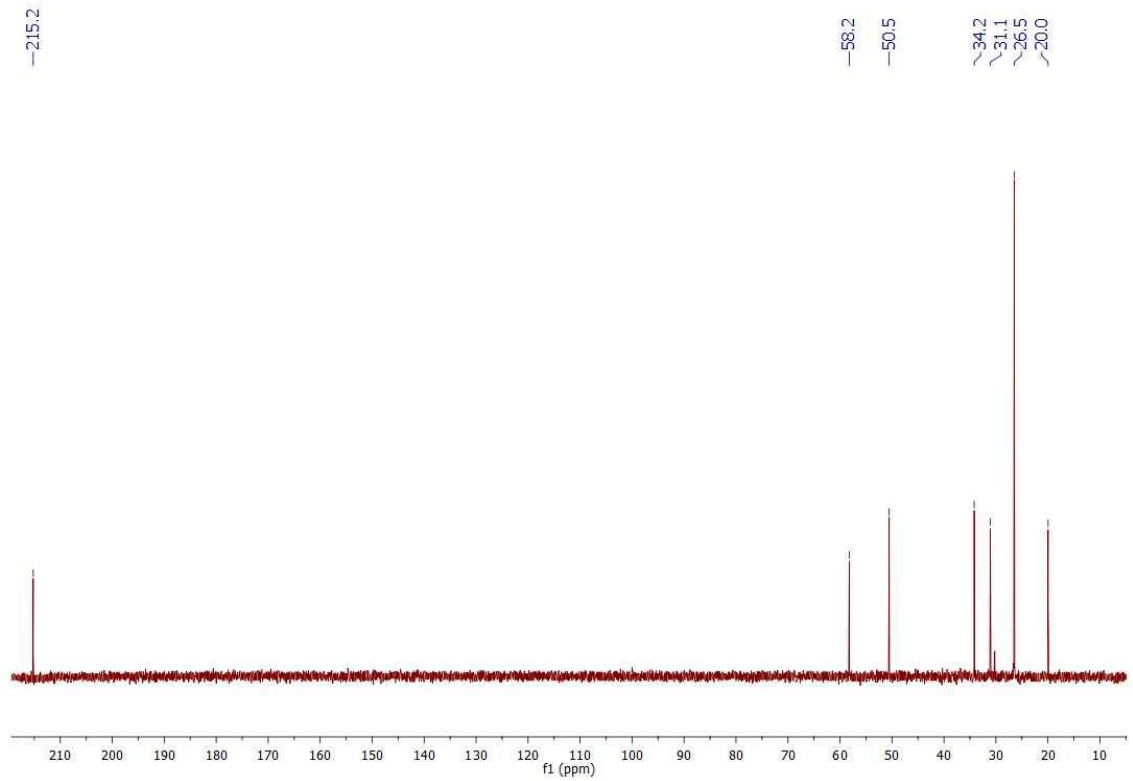
^{1}H NMR of compound **4ma** (300 MHz, D_2O)



^{13}C NMR of compound **4ma** (75 MHz, D_2O)



^{1}H NMR of compound **4na** (300 MHz, D_2O)



^{13}C NMR of compound **4na** (75 MHz, D_2O)

12. X-Ray Crystallographic Data of 3ag

A clear colourless, needle-like specimen of $C_{24}H_{28}F_2N_2O$, approximate dimensions 0.056 mm x 0.067 mm x 0.217 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured (λ = 0.71073 Å).

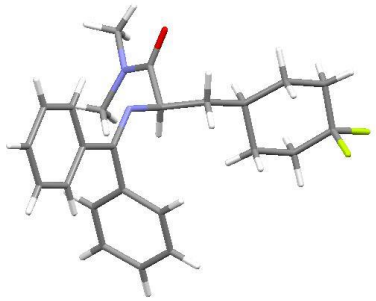


Figure S4. X-Ray structure of **3ag**

The total exposure time was 11.53 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using an orthorhombic unit cell yielded a total of 31693 reflections to a maximum θ angle of 25.34° (0.83 Å resolution), of which 3954 were independent (average redundancy 8.015, completeness = 99.2%, R_{int} = 8.15%, R_{sig} = 4.94%) and 2388 (60.39%) were greater than $2\sigma(F^2)$. The final cell constants of a = 10.1227(17) Å, b = 19.823(2) Å, c = 21.730(5) Å, volume = 4360.4(14) $Å^3$, are based upon the refinement of the XYZ-centroids of 3428 reflections above 20 σ(I) with 6.053° < 2θ < 40.41°. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.924. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9820 and 0.9950.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P b c a, with Z = 8 for the formula unit, $C_{24}H_{28}F_2N_2O$. The final anisotropic full-matrix least-squares refinement on F^2 with 264 variables converged at R1 = 5.04%, for the observed data and wR2 = 14.45% for all data. The goodness-of-fit was 1.042. The largest peak in the final difference electron density synthesis was 0.162 $e^-/Å^3$ and the largest hole was -0.172 $e^-/Å^3$ with an RMS deviation of 0.042 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.214 g/cm^3 and F(000), 1696 e^-.

Table S7. Sample and crystal data

Identification code	03526
Chemical formula	$C_{24}H_{28}F_2N_2O$
Formula weight	398.48 g/mol
Temperature	250(2) K
Wavelength	0.71073 Å
Crystal size	0.056 x 0.067 x 0.217 mm
Crystal habit	clear colourless needle
Crystal system	orthorhombic

Space group	P b c a	
Unit cell dimensions	a = 10.1227(17) Å	α = 90°
	b = 19.823(2) Å	β = 90°
	c = 21.730(5) Å	γ = 90°
Volume	4360.4(14) $Å^3$	
Z	8	
Density (calculated)	1.214 g/cm^3	
Absorption coefficient	0.086 mm^{-1}	
F(000)	1696	

Table S8. Data collection and structure refinement

Theta range for data collection	3.48 to 25.34°	
Index ranges	-12<=h<=12, -23<=k<=18, -26<=l<=26	
Reflections collected	31693	
Independent reflections	3954 [R(int) = 0.0815]	
Coverage of independent reflections	99.2%	
Absorption correction	Multi-Scan	
Max. and min. transmission	0.9950 and 0.9820	
Structure solution technique	direct methods	
Structure solution program	XT, VERSION 2018/2	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2019/1 (Sheldrick, 2019)	
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	3954 / 0 / 264	
Goodness-of-fit on F^2	1.042	
Final R indices	2388 data; I>2σ(I)	R1 = 0.0504, wR2 = 0.1215
	all data	R1 = 0.1001, wR2 = 0.1445
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0760P)^2+0.0063P]$ where $P=(F_o^2+2F_c^2)/3$	
Largest diff. peak and hole	0.162 and -0.172 $eÅ^{-3}$	
R.M.S. deviation from mean	0.042 $eÅ^{-3}$	

Table S9. Atomic coordinates and equivalent isotropic atomic displacement parameters (Å2)

	x/a	y/b	z/c	U(eq)
C1	0.8779(2)	0.72949(12)	0.52228(11)	0.0513(6)
C2	0.8794(2)	0.77613(11)	0.57535(11)	0.0508(6)

	x/a	y/b	z/c	U(eq)
C3	0.8311(2)	0.74125(10)	0.63376(10)	0.0415(5)
C4	0.6971(2)	0.70725(9)	0.62486(9)	0.0330(5)
C5	0.6996(2)	0.66078(10)	0.56929(9)	0.0406(6)
C6	0.7485(2)	0.69583(12)	0.51108(10)	0.0513(6)
C7	0.6571(2)	0.66992(10)	0.68343(9)	0.0371(5)
C8	0.5098(2)	0.65635(10)	0.68980(9)	0.0365(5)
C9	0.4379(2)	0.72396(11)	0.69953(10)	0.0381(5)
C10	0.2526(3)	0.79810(13)	0.68108(13)	0.0676(8)
C11	0.2380(3)	0.67928(13)	0.64680(13)	0.0660(7)
C12	0.4684(2)	0.55160(10)	0.74083(10)	0.0367(5)
C13	0.4581(2)	0.51441(10)	0.68104(10)	0.0403(6)
C14	0.5689(2)	0.49556(11)	0.64851(12)	0.0522(7)
C15	0.5576(3)	0.46469(12)	0.59188(13)	0.0675(8)
C16	0.4357(4)	0.45147(13)	0.56789(14)	0.0744(9)
C17	0.3245(3)	0.46844(13)	0.59999(15)	0.0748(9)
C18	0.3355(3)	0.49970(12)	0.65649(13)	0.0600(7)
C19	0.4555(2)	0.51159(10)	0.79881(11)	0.0394(5)
C20	0.4419(3)	0.44207(11)	0.79779(12)	0.0564(7)
C21	0.4316(3)	0.40583(12)	0.85212(15)	0.0693(8)
C22	0.4342(3)	0.43804(13)	0.90781(13)	0.0629(7)
C23	0.4478(2)	0.50713(12)	0.90946(12)	0.0545(7)
C24	0.4594(2)	0.54344(10)	0.85577(11)	0.0431(6)
F1	0.91825(16)	0.76227(9)	0.46976(7)	0.0842(5)
F3	0.97435(14)	0.68064(7)	0.53083(7)	0.0691(5)
N1	0.31638(19)	0.73196(9)	0.67583(8)	0.0480(5)
N2	0.48882(18)	0.61531(8)	0.74564(8)	0.0384(4)
O1	0.49311(16)	0.76949(7)	0.72754(8)	0.0519(4)

Table S10. Bond lengths (Å)

C1-F1	1.375(2)	C1-F3	1.388(3)
C1-C2	1.478(3)	C1-C6	1.490(3)
C2-C3	1.526(3)	C3-C4	1.527(3)
C4-C5	1.519(3)	C4-C7	1.527(3)
C5-C6	1.526(3)	C7-C8	1.522(3)
C8-N2	1.476(2)	C8-C9	1.539(3)
C9-O1	1.224(2)	C9-N1	1.343(3)
C10-N1	1.466(3)	C11-N1	1.456(3)
C12-N2	1.284(2)	C12-C19	1.495(3)
C12-C13	1.498(3)	C13-C14	1.378(3)
C13-C18	1.381(3)	C14-C15	1.379(4)
C15-C16	1.364(4)	C16-C17	1.366(4)
C17-C18	1.380(4)	C19-C20	1.385(3)

C19-C24	1.390(3)	C20-C21	1.386(4)
C21-C22	1.369(4)	C22-C23	1.377(3)
C23-C24	1.376(3)		

Table S11. Bond angles (°)

F1-C1-F3	103.40(18)	F1-C1-C2	110.41(19)
F3-C1-C2	108.95(19)	F1-C1-C6	109.71(19)
F3-C1-C6	109.2(2)	C2-C1-C6	114.6(2)
C1-C2-C3	111.23(17)	C2-C3-C4	112.30(17)
C5-C4-C3	110.71(17)	C5-C4-C7	111.91(16)
C3-C4-C7	110.12(17)	C4-C5-C6	112.85(17)
C1-C6-C5	110.71(19)	C8-C7-C4	114.91(17)
N2-C8-C7	108.23(16)	N2-C8-C9	107.40(16)
C7-C8-C9	108.77(16)	O1-C9-N1	121.5(2)
O1-C9-C8	119.6(2)	N1-C9-C8	118.9(2)
N2-C12-C19	117.86(19)	N2-C12-C13	124.48(19)
C19-C12-C13	117.65(17)	C14-C13-C18	118.4(2)
C14-C13-C12	121.4(2)	C18-C13-C12	120.1(2)
C13-C14-C15	120.7(2)	C16-C15-C14	120.1(3)
C15-C16-C17	120.2(3)	C16-C17-C18	119.9(3)
C17-C18-C13	120.7(2)	C20-C19-C24	118.0(2)
C20-C19-C12	121.5(2)	C24-C19-C12	120.48(18)
C19-C20-C21	120.6(2)	C22-C21-C20	120.7(2)
C21-C22-C23	119.3(2)	C24-C23-C22	120.4(2)
C23-C24-C19	121.0(2)	C9-N1-C11	125.51(19)
C9-N1-C10	118.6(2)	C11-N1-C10	115.8(2)
C12-N2-C8	119.88(18)		

Table S12. Torsion angles (°)

F1-C1-C2-C3	178.36(18)	F3-C1-C2-C3	-68.7(2)
C6-C1-C2-C3	53.9(3)	C1-C2-C3-C4	-52.8(3)
C2-C3-C4-C5	52.6(2)	C2-C3-C4-C7	176.86(17)
C3-C4-C5-C6	-52.8(2)	C7-C4-C5-C6	-176.03(18)
F1-C1-C6-C5	-178.35(18)	F3-C1-C6-C5	69.0(2)
C2-C1-C6-C5	-53.5(3)	C4-C5-C6-C1	52.6(3)
C5-C4-C7-C8	-77.9(2)	C3-C4-C7-C8	158.47(17)
C4-C7-C8-N2	175.33(15)	C4-C7-C8-C9	-68.3(2)
N2-C8-C9-O1	84.1(2)	C7-C8-C9-O1	-32.8(3)
N2-C8-C9-N1	-97.2(2)	C7-C8-C9-N1	145.92(18)
N2-C12-C13-C14	80.4(3)	C19-C12-C13-C14	-99.0(2)
N2-C12-C13-C18	-98.0(3)	C19-C12-C13-C18	82.6(3)

C18-C13-C14-C15	2.1(3)	C12-C13-C14-C15	-176.3(2)
C13-C14-C15-C16	-1.1(4)	C14-C15-C16-C17	-0.3(4)
C15-C16-C17-C18	0.7(4)	C16-C17-C18-C13	0.3(4)
C14-C13-C18-C17	-1.7(4)	C12-C13-C18-C17	176.8(2)
N2-C12-C19-C20	-175.8(2)	C13-C12-C19-C20	3.6(3)
N2-C12-C19-C24	3.0(3)	C13-C12-C19-C24	-177.64(19)
C24-C19-C20-C21	0.5(4)	C12-C19-C20-C21	179.2(2)
C19-C20-C21-C22	0.2(4)	C20-C21-C22-C23	-0.3(4)
C21-C22-C23-C24	-0.3(4)	C22-C23-C24-C19	1.0(4)
C20-C19-C24-C23	-1.1(3)	C12-C19-C24-C23	-179.9(2)
O1-C9-N1-C11	-174.1(2)	C8-C9-N1-C11	7.2(3)
O1-C9-N1-C10	3.4(3)	C8-C9-N1-C10	-175.31(18)
C19-C12-N2-C8	176.56(17)	C13-C12-N2-C8	-2.8(3)
C7-C8-N2-C12	-101.8(2)	C9-C8-N2-C12	141.0(2)

Table S13. Anisotropic atomic displacement parameters (Å2)
The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	0.0399(14)	0.0736(15)	0.0404(14)	0.0130(12)	0.0049(11)	-0.0013(13)
C2	0.0402(14)	0.0503(13)	0.0618(17)	0.0100(12)	0.0005(12)	-0.0109(11)
C3	0.0412(13)	0.0437(12)	0.0396(13)	-0.0029(10)	-0.0023(11)	-0.0073(10)
C4	0.0331(12)	0.0340(10)	0.0318(12)	0.0023(9)	-0.0002(9)	0.0020(9)
C5	0.0373(13)	0.0499(12)	0.0345(13)	-0.0051(10)	-0.0012(10)	-0.0046(10)
C6	0.0441(15)	0.0764(15)	0.0335(13)	-0.0017(12)	-0.0009(11)	-0.0051(12)
C7	0.0385(13)	0.0403(11)	0.0326(12)	0.0035(9)	-0.0005(10)	0.0015(9)
C8	0.0411(14)	0.0384(11)	0.0299(12)	0.0012(9)	0.0003(9)	-0.0044(9)
C9	0.0382(13)	0.0442(13)	0.0319(12)	0.0082(10)	0.0095(10)	-0.0016(11)
C10	0.0555(18)	0.0712(16)	0.076(2)	0.0289(14)	0.0111(15)	0.0210(14)

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C11	0.0469(16)	0.0898(18)	0.0613(18)	0.0143(15)	-0.0118(14)	-0.0124(14)
C12	0.0313(12)	0.0354(12)	0.0433(14)	-0.0015(10)	0.0037(10)	-0.0019(9)
C13	0.0395(14)	0.0340(11)	0.0475(14)	-0.0037(10)	0.0057(11)	-0.0037(10)
C14	0.0466(15)	0.0498(13)	0.0602(17)	-0.0154(12)	0.0077(12)	-0.0025(11)
C15	0.072(2)	0.0613(16)	0.069(2)	-0.0235(14)	0.0209(16)	-0.0088(14)
C16	0.102(3)	0.0604(16)	0.0608(19)	-0.0227(14)	-0.0037(19)	-0.0100(17)
C17	0.068(2)	0.0702(18)	0.086(2)	-0.0215(16)	-0.0243(18)	-0.0069(15)
C18	0.0426(15)	0.0608(15)	0.0767(19)	-0.0212(14)	-0.0017(14)	-0.0057(12)
C19	0.0355(13)	0.0334(12)	0.0494(15)	0.0028(10)	0.0097(10)	0.0009(9)
C20	0.0685(18)	0.0381(13)	0.0625(17)	-0.0020(12)	0.0174(14)	-0.0037(11)
C21	0.090(2)	0.0327(13)	0.085(2)	0.0128(15)	0.0214(17)	0.0008(13)
C22	0.0702(19)	0.0542(16)	0.0643(19)	0.0223(14)	0.0144(14)	0.0098(13)
C23	0.0661(18)	0.0506(15)	0.0469(16)	0.0107(12)	0.0019(12)	0.0069(12)
C24	0.0452(14)	0.0363(12)	0.0479(15)	0.0056(11)	0.0039(11)	0.0040(10)
F1	0.0617(11)	0.1383(14)	0.0525(9)	0.0328(9)	0.0123(8)	-0.0233(9)
F3	0.0453(9)	0.0932(10)	0.0687(11)	-0.0057(8)	0.0093(7)	0.0143(8)
N1	0.0393(12)	0.0566(11)	0.0483(12)	0.0149(9)	0.0010(10)	0.0008(9)
N2	0.0423(11)	0.0386(10)	0.0342(10)	0.0030(8)	0.0062(8)	-0.0032(8)
O1	0.0551(11)	0.0417(9)	0.0588(11)	-0.0070(8)	0.0005(9)	0.0010(8)

Table S14. Hydrogen atomic coordinates and isotropic atomic displacement parameters (Å2)

	x/a	y/b	z/c	U(eq)
H2A	0.8226	0.8150	0.5665	0.061000
H2B	0.9695	0.7928	0.5818	0.061000
H3A	0.8242	0.7746	0.6669	0.050000
H3B	0.8960	0.7073	0.6463	0.050000
H4	0.6308	0.7429	0.6171	0.040000
H5A	0.6103	0.6434	0.5620	0.049000
H5B	0.7571	0.6222	0.5782	0.049000
H6A	0.7581	0.6626	0.4780	0.062000
H6B	0.6834	0.7295	0.4979	0.062000
H7A	0.7040	0.6267	0.6847	0.045000

x/a	y/b	z/c	U(eq)	
H7B	0.6863	0.6964	0.7190	0.045000
H8	0.4753	0.6328	0.6529	0.044000
H10A	0.1731	0.7940	0.7057	0.101000
H10B	0.2298	0.8145	0.6404	0.101000
H10C	0.3128	0.8296	0.7006	0.101000
H11A	0.1531	0.6759	0.6673	0.099000
H11B	0.2841	0.6365	0.6500	0.099000
H11C	0.2244	0.6903	0.6038	0.099000
H14	0.6531	0.5038	0.6651	0.063000
H15	0.6339	0.4528	0.5698	0.081000
H16	0.4283	0.4306	0.5292	0.089000
H17	0.2407	0.4588	0.5836	0.090000
H18	0.2588	0.5111	0.6785	0.072000
H20	0.4397	0.4193	0.7599	0.068000
H21	0.4227	0.3587	0.8507	0.083000
H22	0.4267	0.4133	0.9445	0.075000
H23	0.4493	0.5296	0.9475	0.065000
H24	0.4700	0.5905	0.8576	0.052000

Table 15. Hydrogen bond distances (Å) and angles (°)

Donor-H	Acceptor-H	Donor-Acceptor	Angle
C10-H10A···O1#1	0.97	2.38	3.342(3) 171.5

Symmetry transformations used to generate equivalent atoms:
#1 x-1/2, y, -z+3/2