

**Synthetic access to isoxazoline-functionalized isoquinolines via
microwave-assisted iminoxyl radical-participated cascade
cyclization of vinyl isocyanides**

Yulong Xu,^a Hao Chen,^a Wei Li,^a Qiong Xie,^a Linqian Yu^{*a} and Liming Shao^{*a,b}

*^aSchool of Pharmacy, Fudan University, 826 Zhangheng Road, Zhangjiang Hi-tech Park,
Pudong, Shanghai 201203, China*

*^bState Key Laboratory of Medical Neurobiology, Fudan University, 138 Yixueyuan Road,
Shanghai 200032, China*

*Corresponding author. Tel.: +86 21 5198 0201; fax: +86 21 5198 0201; e-mail:
limingshao@fudan.edu.cn (L. Shao), yulinqian@fudan.edu.cn (L. Yu).

Supporting Information

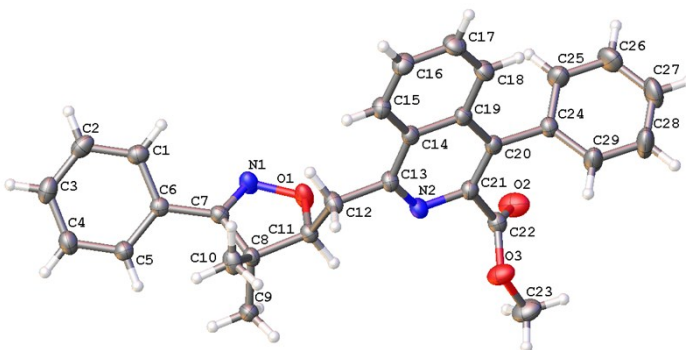
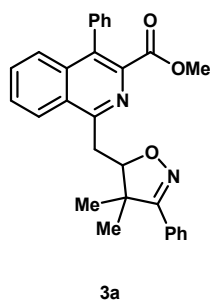
I . General information	2
II . Crystallographic data of 3a	3-4
III. Intermolecular competing kinetic isotope effect (KIE) experiment	5
IV. Radical trapping experiment	6-7
V. ¹ H and ¹³ C NMR	8-55

Supporting Information

I. General information

All reactions were carried out under an argon atmosphere. All commercially available reagents were used without further purification unless otherwise stated. All of the microwave-assisted reactions were performed in an Initiator+ microwave system (Biotage, Inc.) at the specified temperature using the standard mode of operation. Analytical thin layer chromatography (TLC) was performed using Silica Gel GF254 plates (Rushan Taiyang Desiccant co, .ltd, 0.2 mm thick). Compounds were purified using smart flash AI-580S (YAMAZEN co, .ltd). ^1H and ^{13}C spectra were recorded on Varian 400 MHz and Bruker 600 MHz, respectively. Chemical shifts in ^1H NMR spectra were reported in parts per million (ppm) on the δ scale from an internal standard of CDCl_3 (7.26 ppm). Data were reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = Broad), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra were reported in ppm from the central peak of CDCl_3 (77.0 ppm) on the δ scale. All melting points were taken on a WRS-1B Digital Melting Point Apparatus without correction. MS data was recorded on Agilent Technologies 6120 quadrupole mass spectrometer. ESI-HRMS (high resolution mass spectrometry) spectra were obtained on AB SCIEX TRIPLE TOF 5600+ mass spectrometer. X-Ray crystallography was measured on Bruker Apex Duo.

II. Crystallographic data of 3a

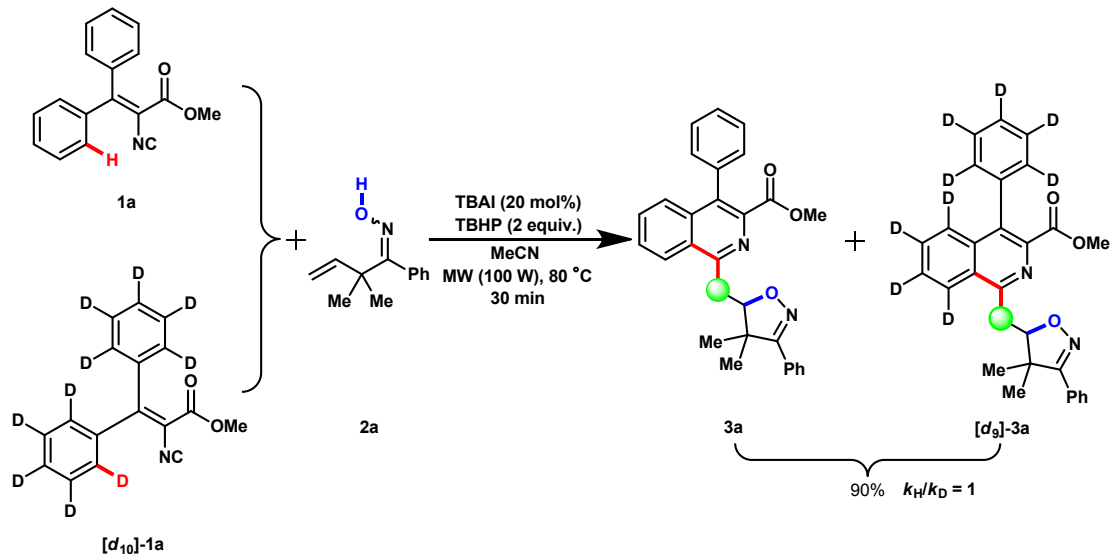


Datablock:

Bond precision:	C-C = 0.0029 Å	Wavelength=1.54178
Cell:	a=10.1449(2)	b=11.6133(3) c=40.0056(9)
	alpha=90	beta=90 gamma=90
Temperature:	302 K	
	Calculated	Reported
Volume	4713.29(19)	4713.29(19)
Space group	P b c a	P b c a
Hall group	-P 2ac 2ab	-P 2ac 2ab
Moiety formula	C ₂₉ H ₂₆ N ₂ O ₃	C ₂₉ H ₂₆ N ₂ O ₃
Sum formula	C ₂₉ H ₂₆ N ₂ O ₃	C ₂₉ H ₂₆ N ₂ O ₃
Mr	450.52	450.52
D _x , g cm ⁻³	1.270	1.270
Z	8	8
Mu (mm ⁻¹)	0.659	0.659
F ₀₀₀	1904.0	1904.0
F ₀₀₀ '	1909.58	

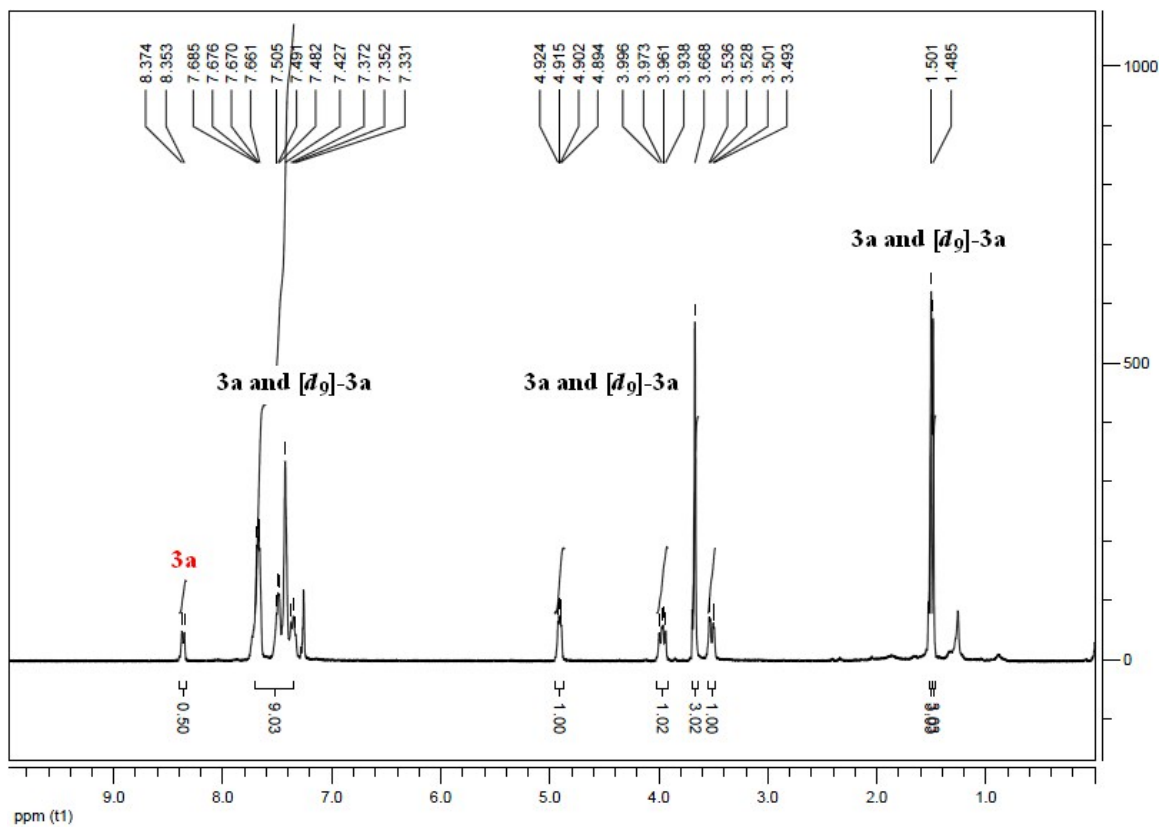
h,k,lmax	12,14,48	12,13,48
Nref	4485	4456
Tmin,Tmax	0.840,0.924	0.524,0.753
Tmin'	0.821	
Correction method= # Reported		T Limits: Tmin=0.524 Tmax=0.753
AbsCorr = MULTI-SCAN		
Data completeness= 0.994		Theta(max)= 70.084
R(reflections)= 0.0510(3452)		wR2(reflections)= 0.1408(4456)
S = 1.021		Npar= 310

III. Intermolecular competing kinetic isotope effect (KIE) experiment

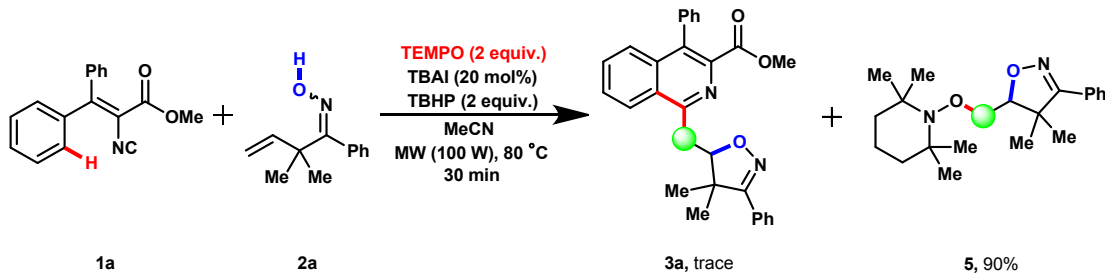


$k_H/k_D = 0.5/0.5 = 1/1$. (The KIE was determined by ^1H NMR spectroscopy by analyzing the ratio of 3a and $[d_9]$ -3a).

Proton NMR (CDCl_3)

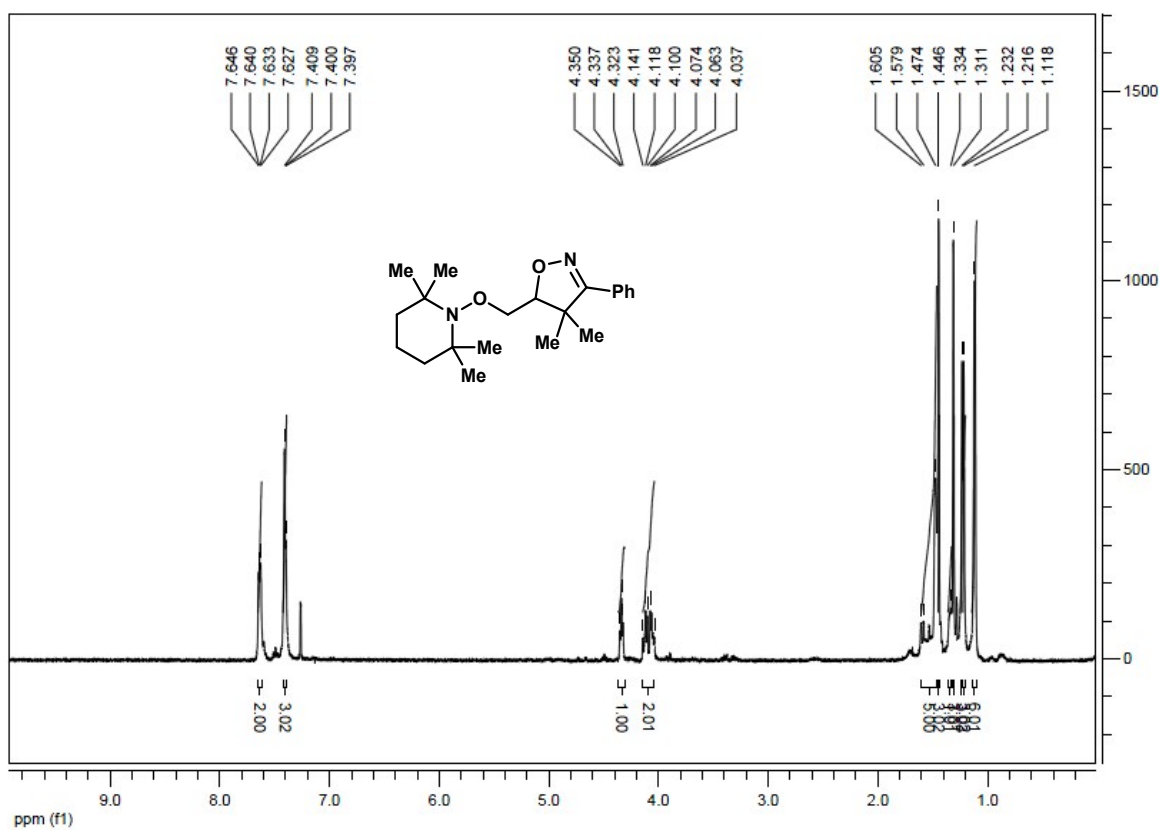


IV. Radical trapping experiment

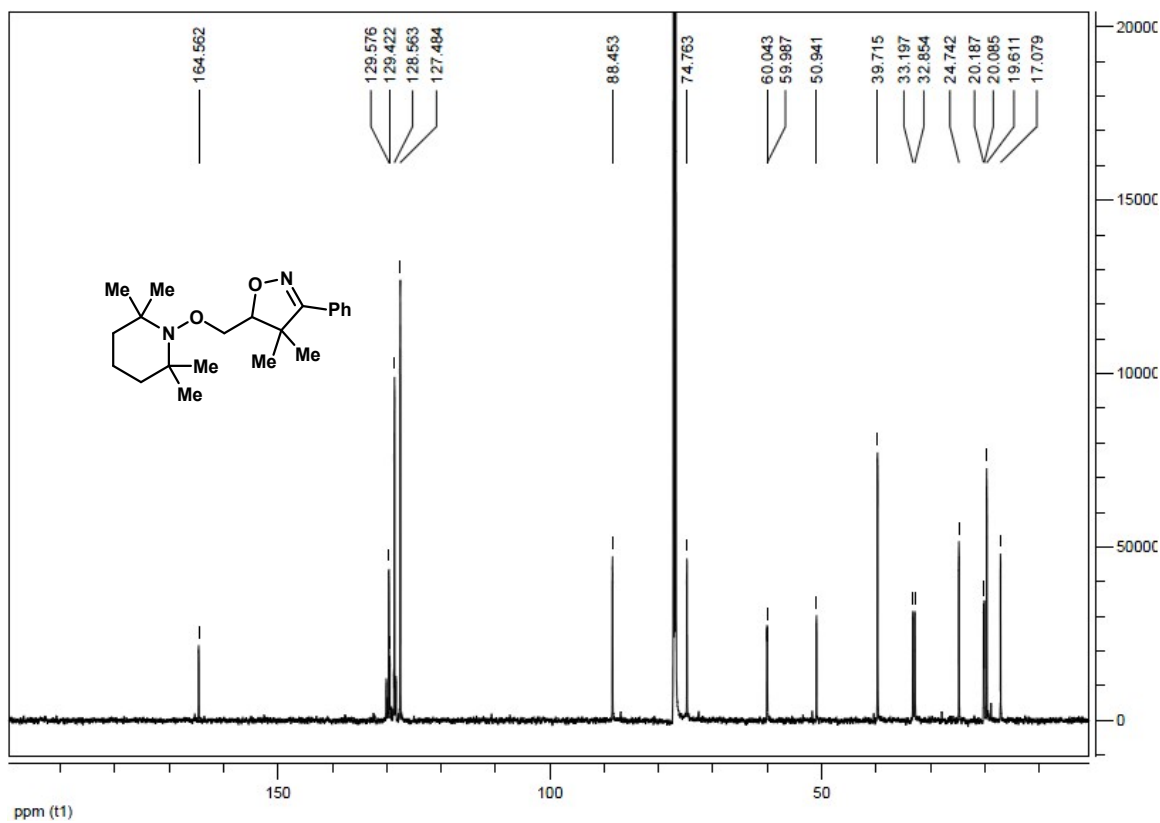


4,4-Dimethyl-3-phenyl-5-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)-4,5-dihydroisoxazole (5)

Proton NMR (CDCl₃)



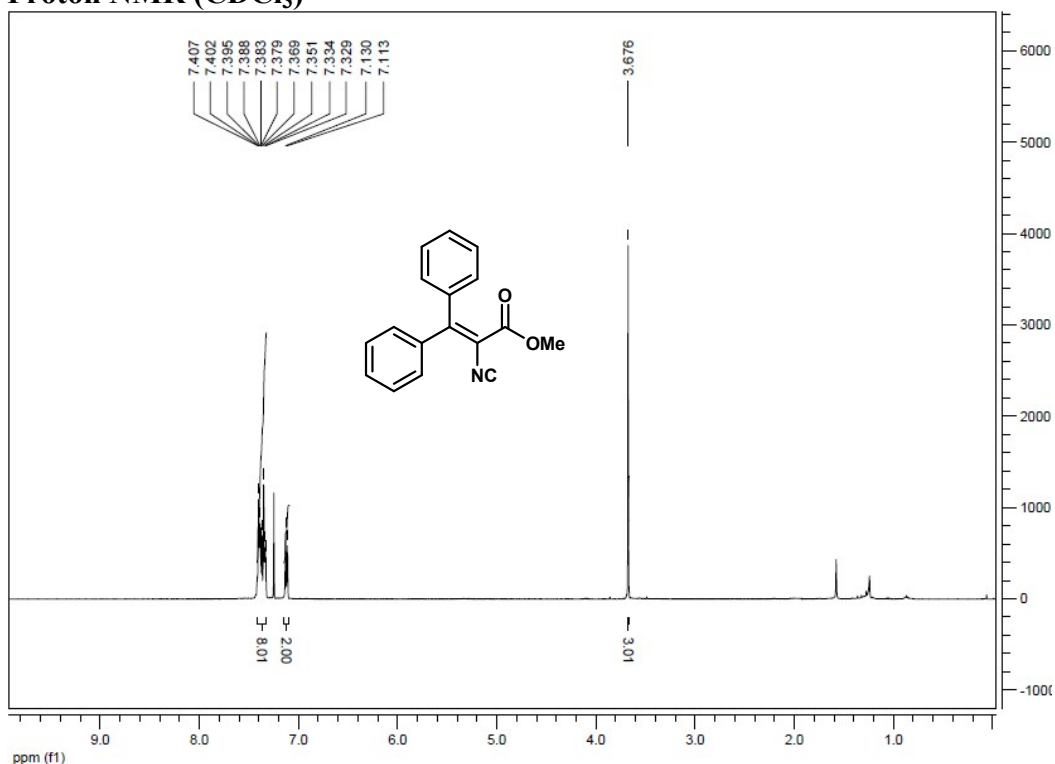
Carbon NMR (CDCl₃)



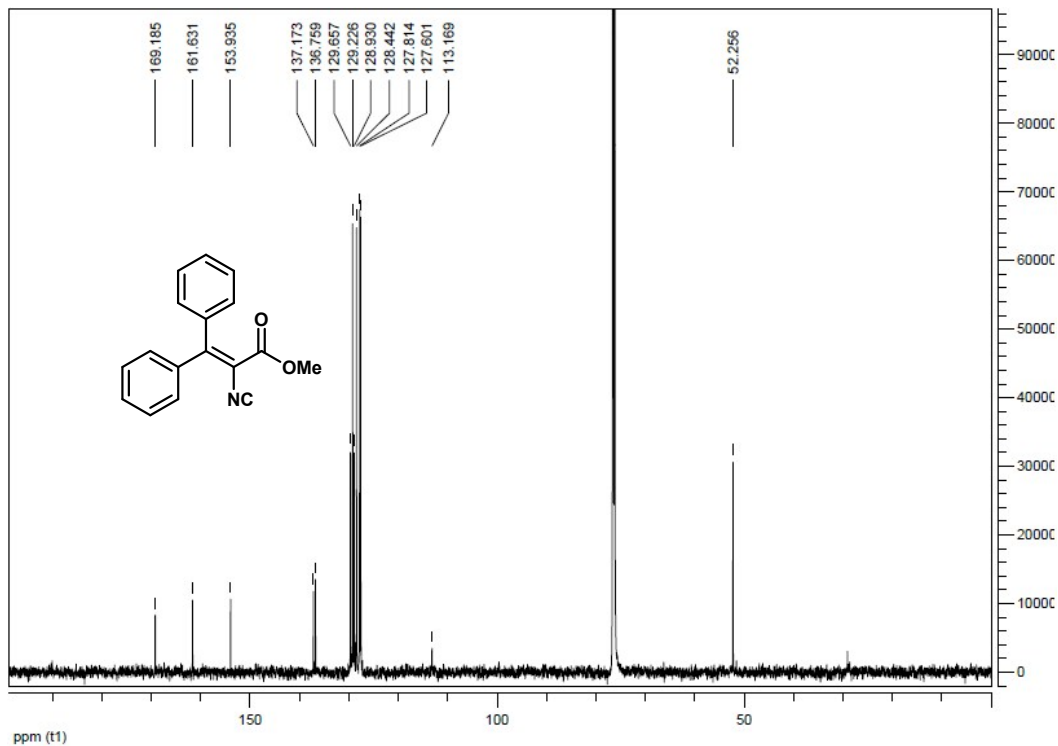
V. ¹H and ¹³C NMR

Methyl 2-isocyano-3,3-diphenylacrylate (1a)

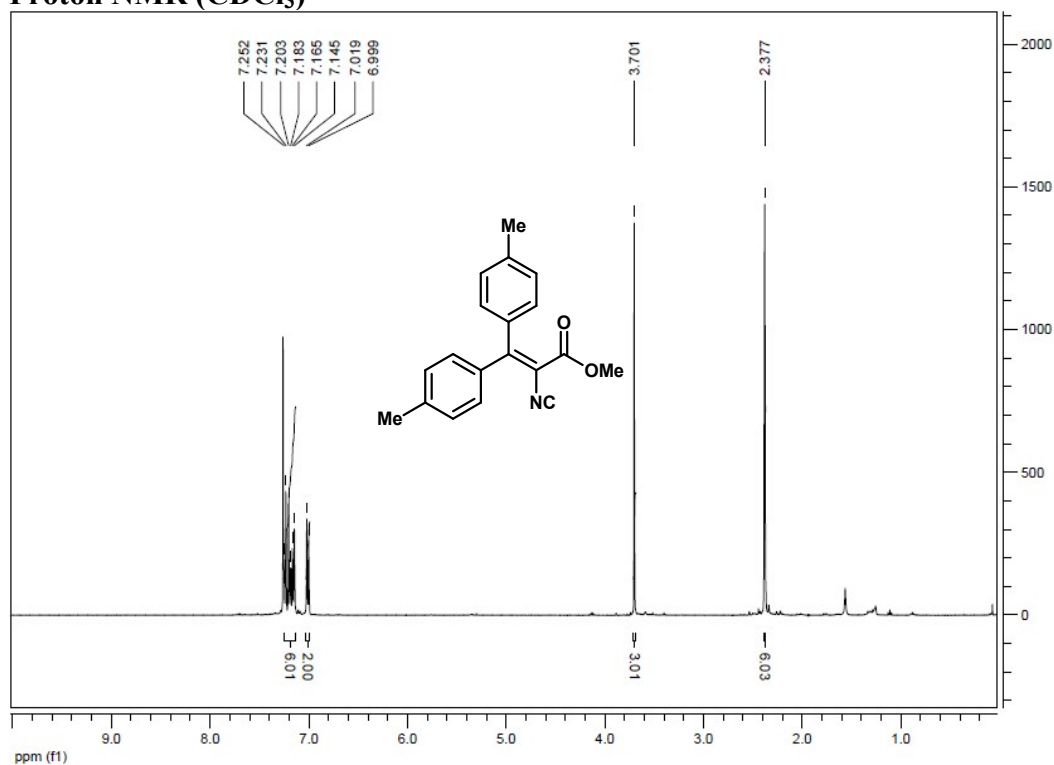
Proton NMR (CDCl₃)



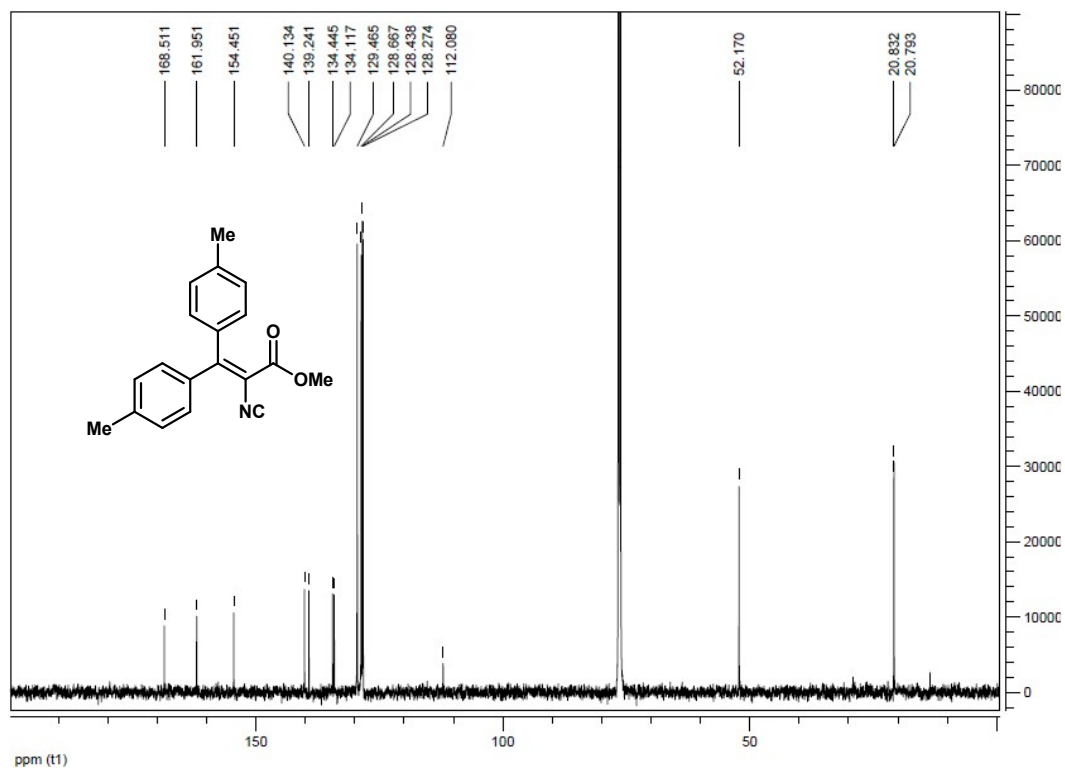
Carbon NMR (CDCl₃)



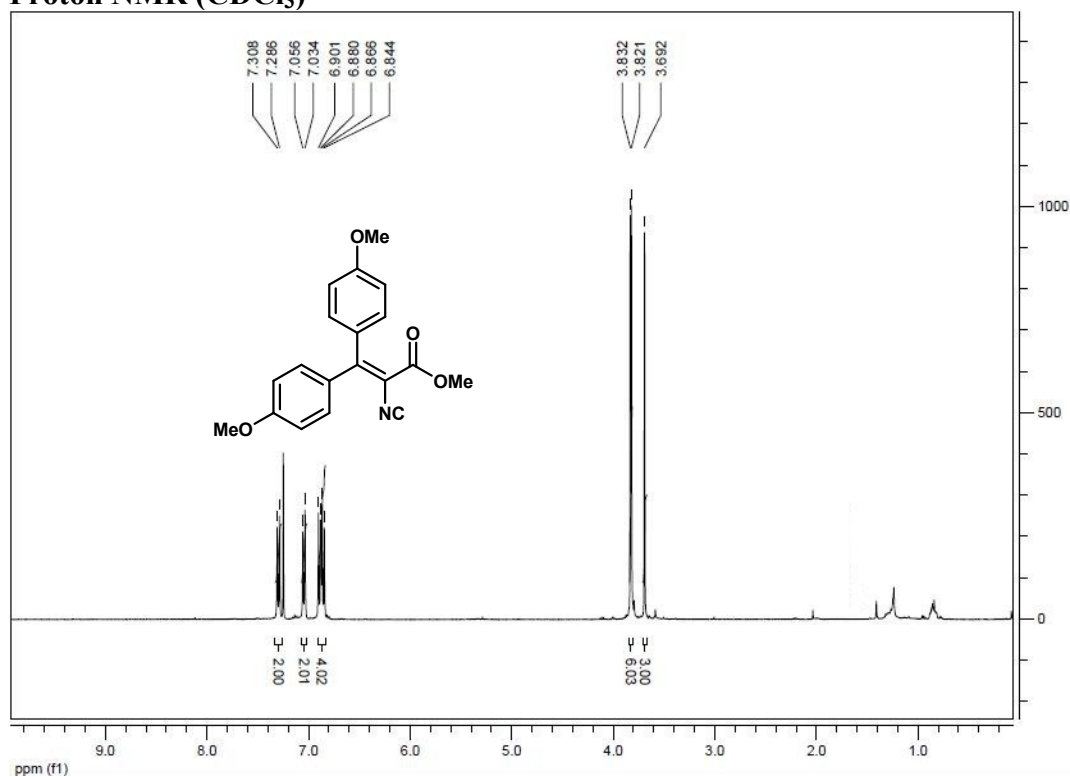
Methyl 2-isocyano-3,3-di-*p*-tolylacrylate (1b)
Proton NMR (CDCl₃)



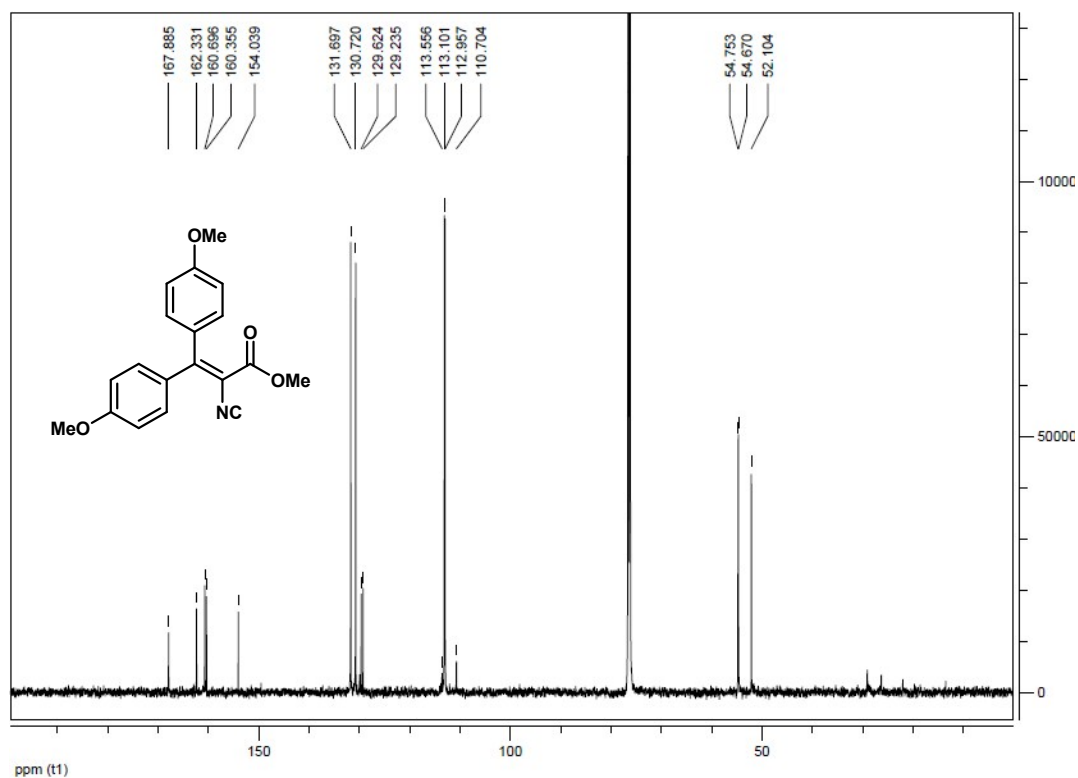
Carbon NMR (CDCl₃)



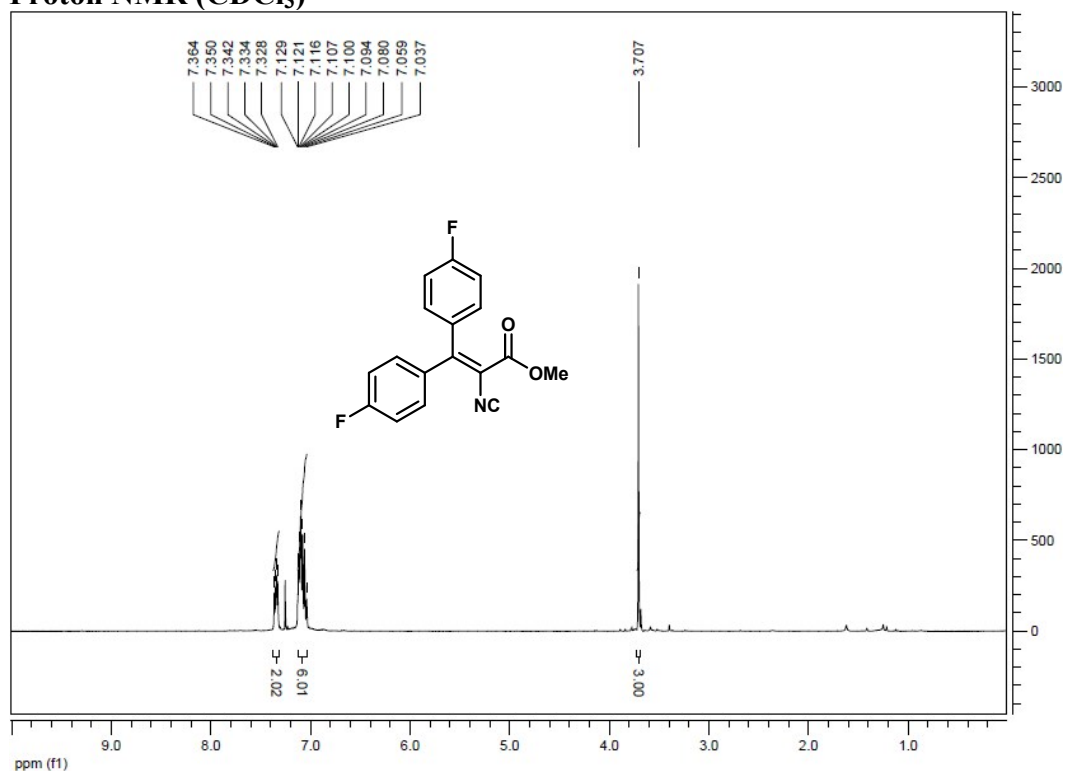
Methyl 2-isocyano-3,3-bis(4-methoxyphenyl)acrylate (1c)
Proton NMR (CDCl₃)



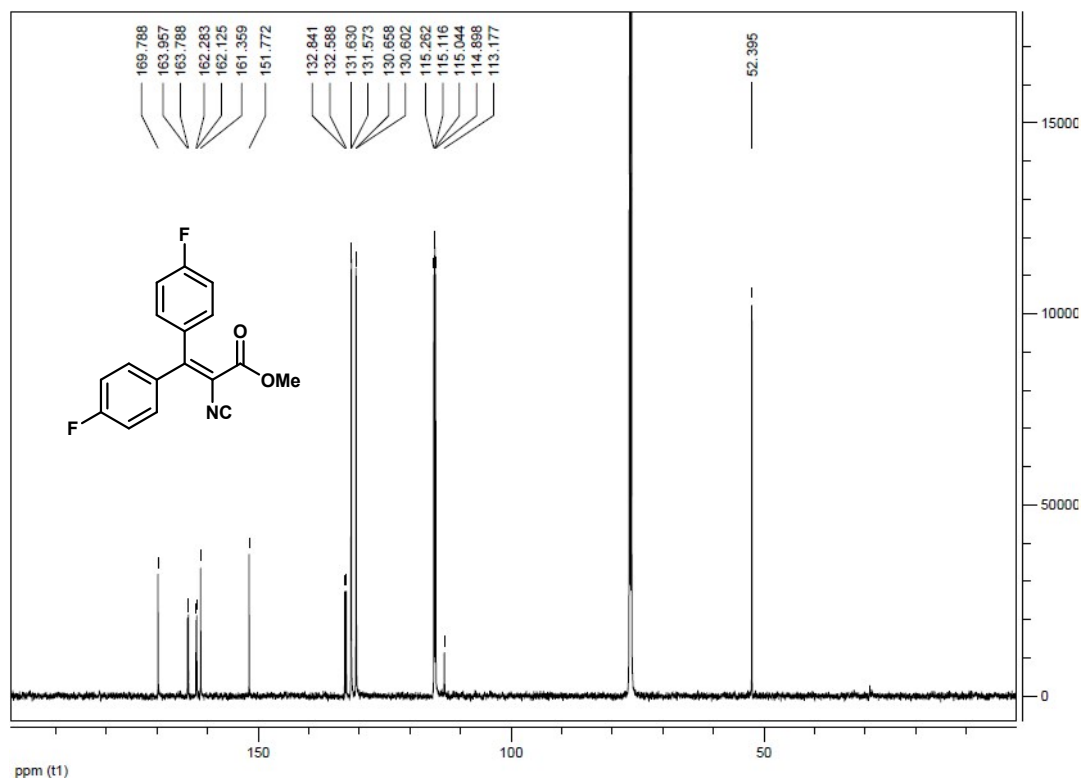
Carbon NMR (CDCl₃)



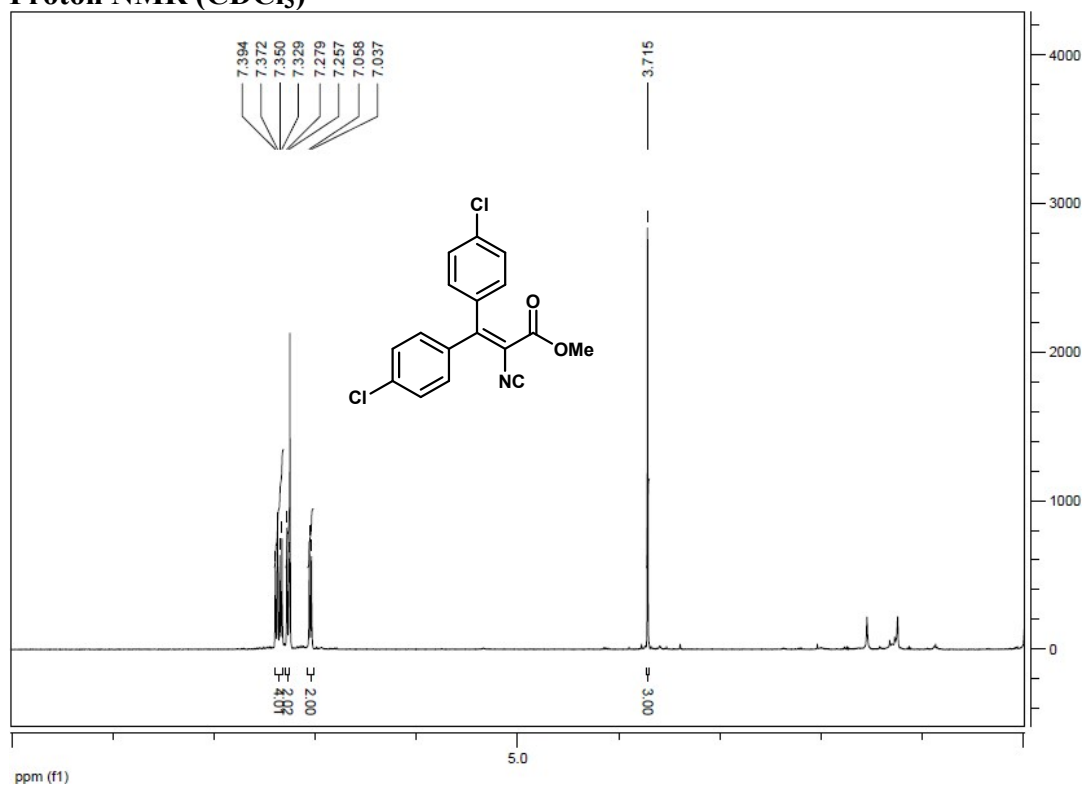
Methyl 3,3-bis(4-fluorophenyl)-2-isocyanoacrylate (1d)
Proton NMR (CDCl₃)



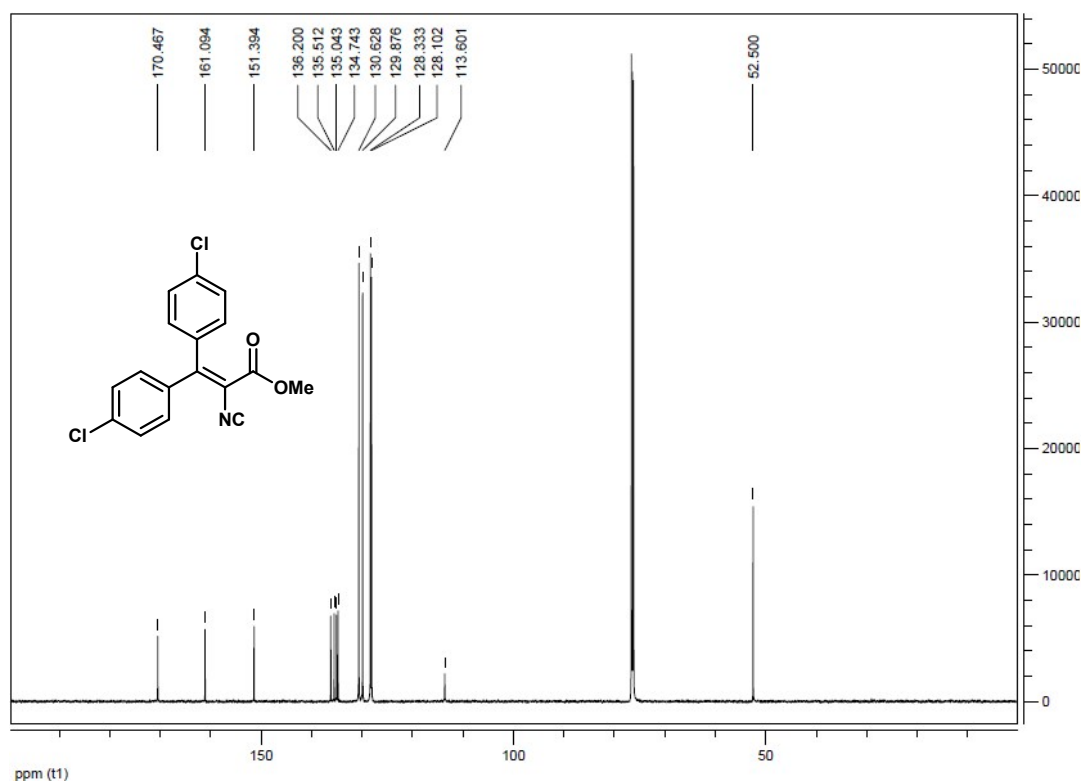
Carbon NMR (CDCl₃)



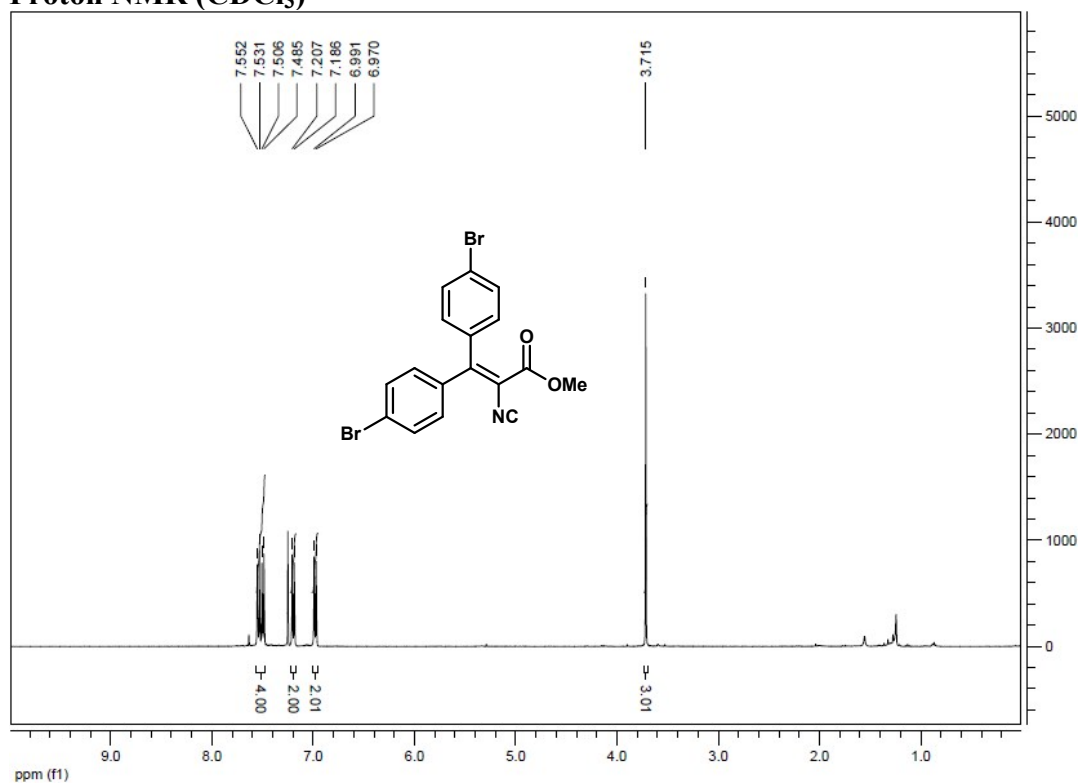
Methyl 3,3-bis(4-chlorophenyl)-2-isocyanoacrylate (1e)
Proton NMR (CDCl₃)



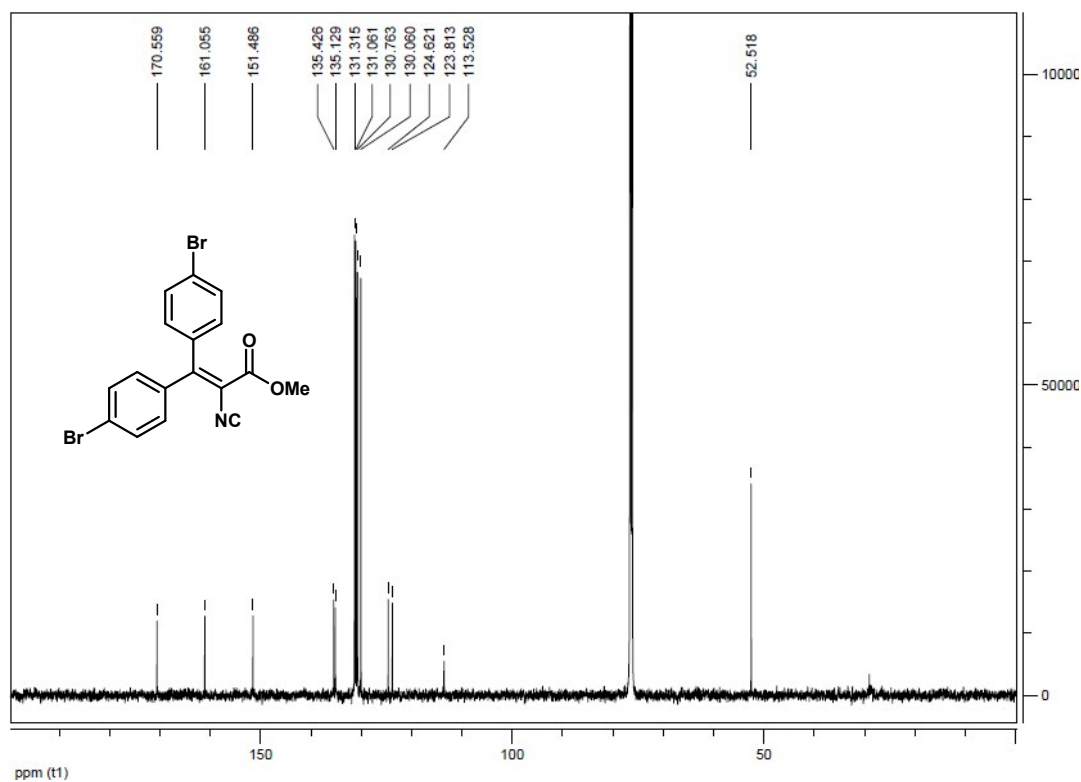
Carbon NMR (CDCl₃)



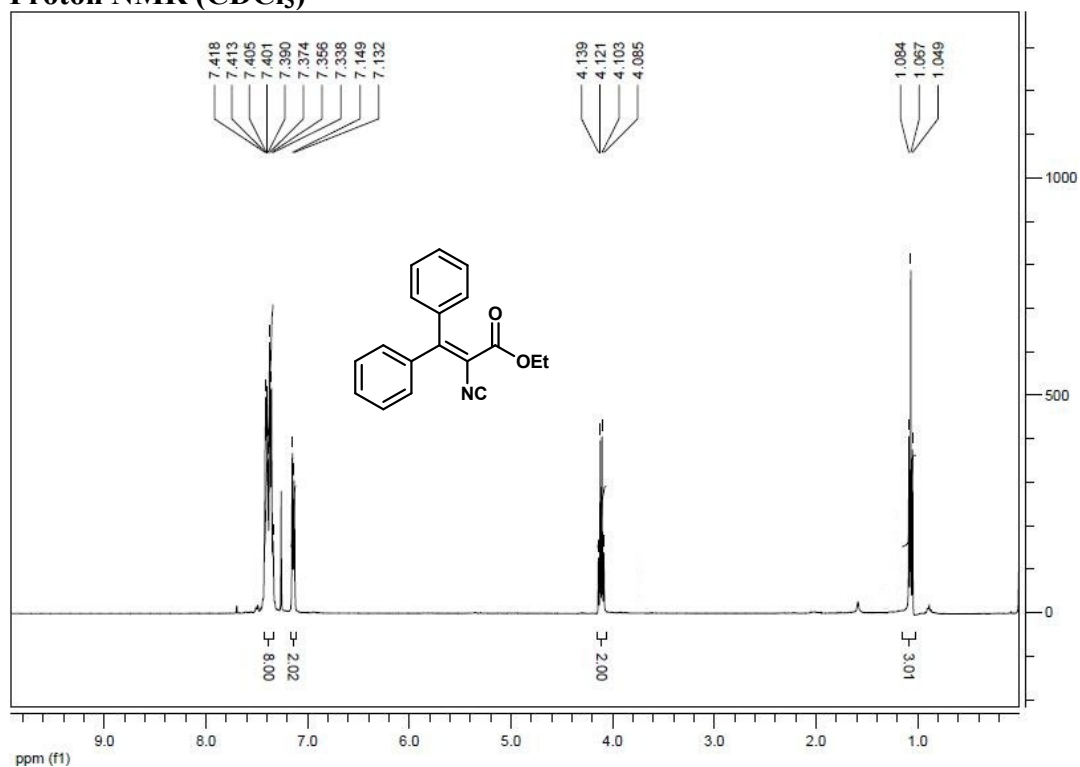
Methyl 3,3-bis(4-bromophenyl)-2-isocyanoacrylate (1f)
Proton NMR (CDCl₃)



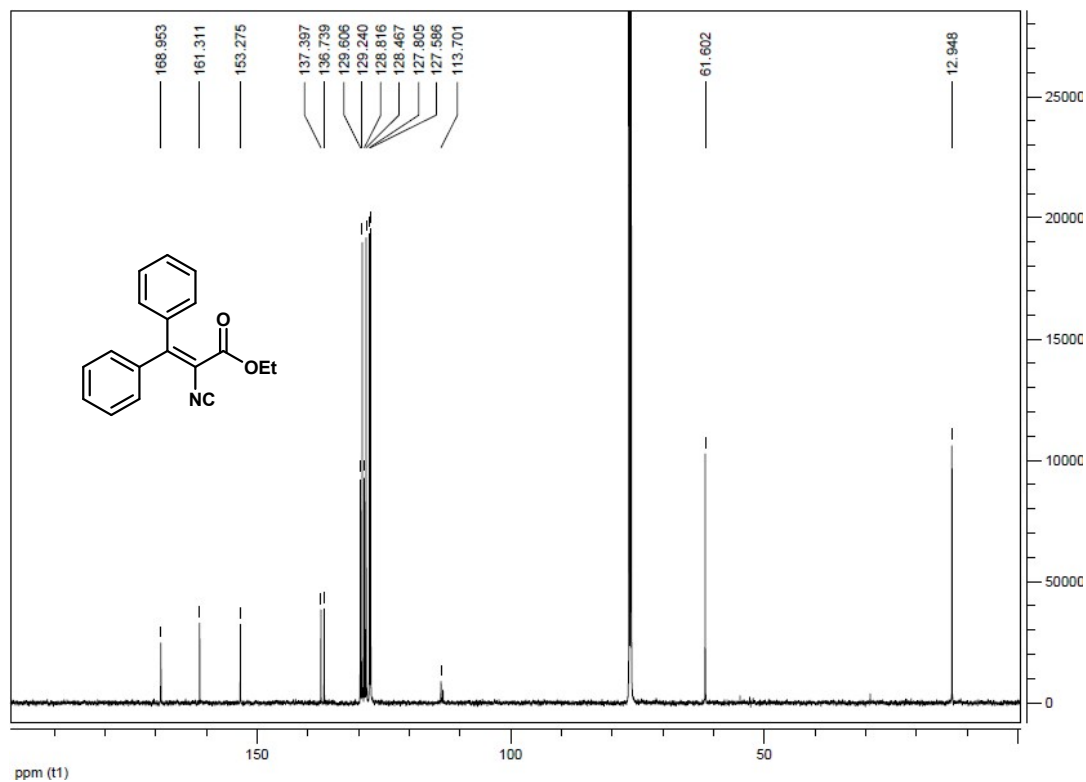
Carbon NMR (CDCl₃)



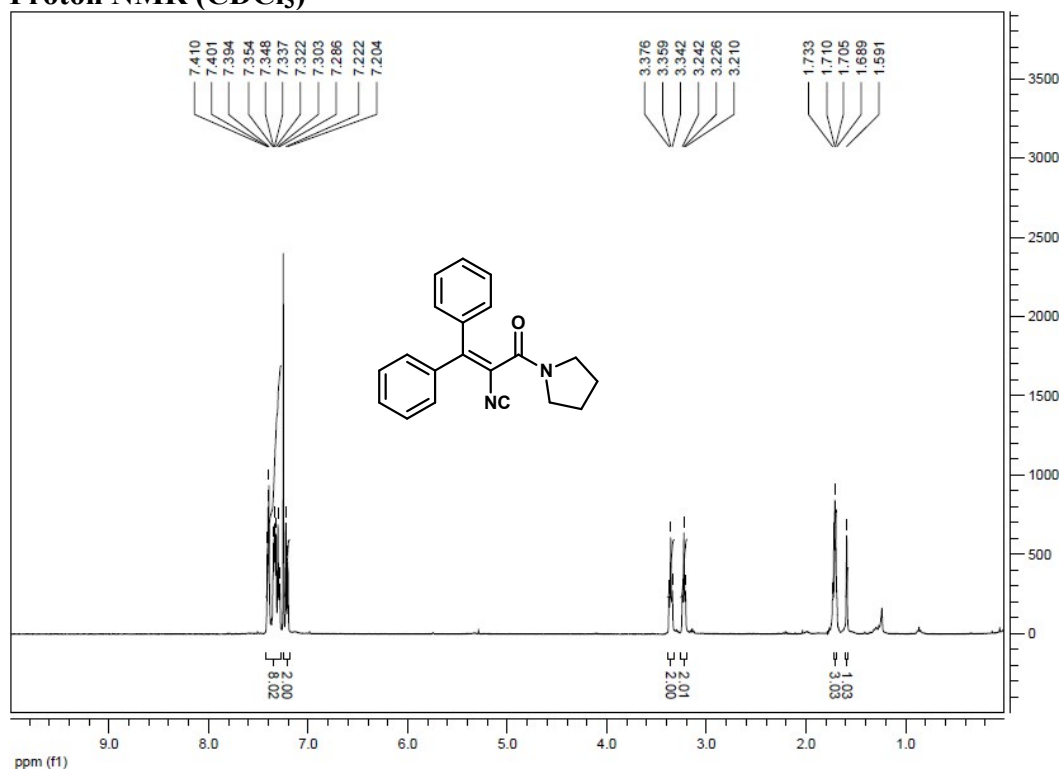
Ethyl 2-isocyano-3,3-diphenylacrylate (1g)
Proton NMR (CDCl₃)



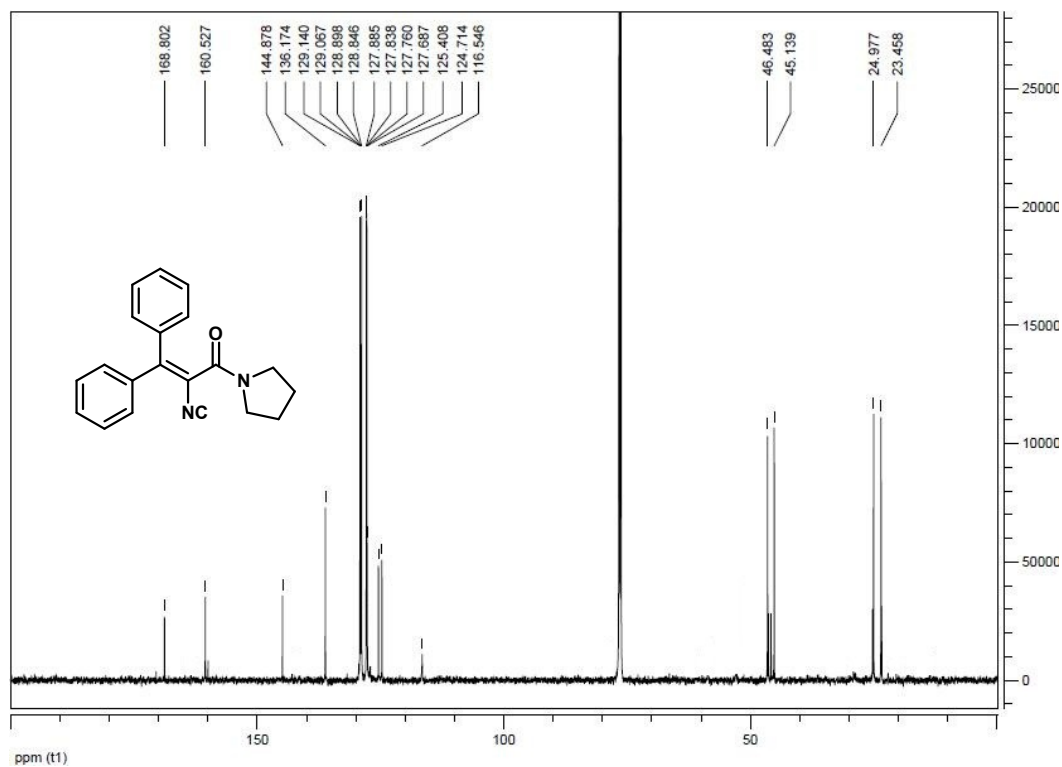
Carbon NMR (CDCl₃)



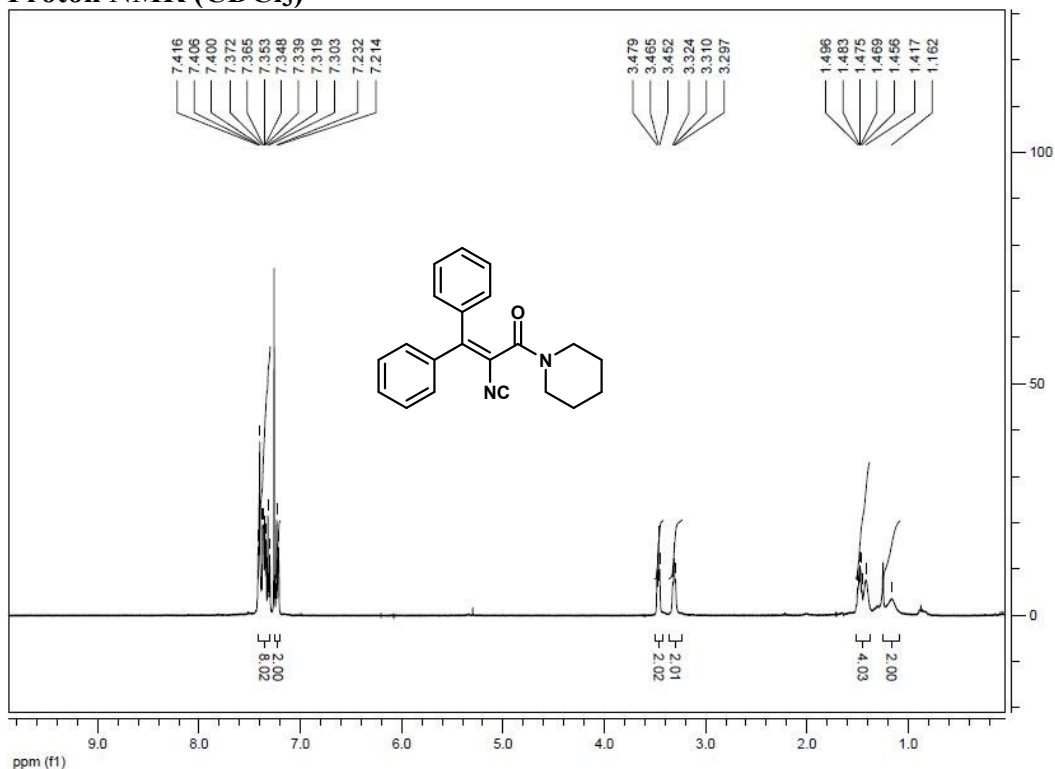
2-Isocyano-3,3-diphenyl-1-(pyrrolidin-1-yl)prop-2-en-1-one (1h)
Proton NMR (CDCl₃)



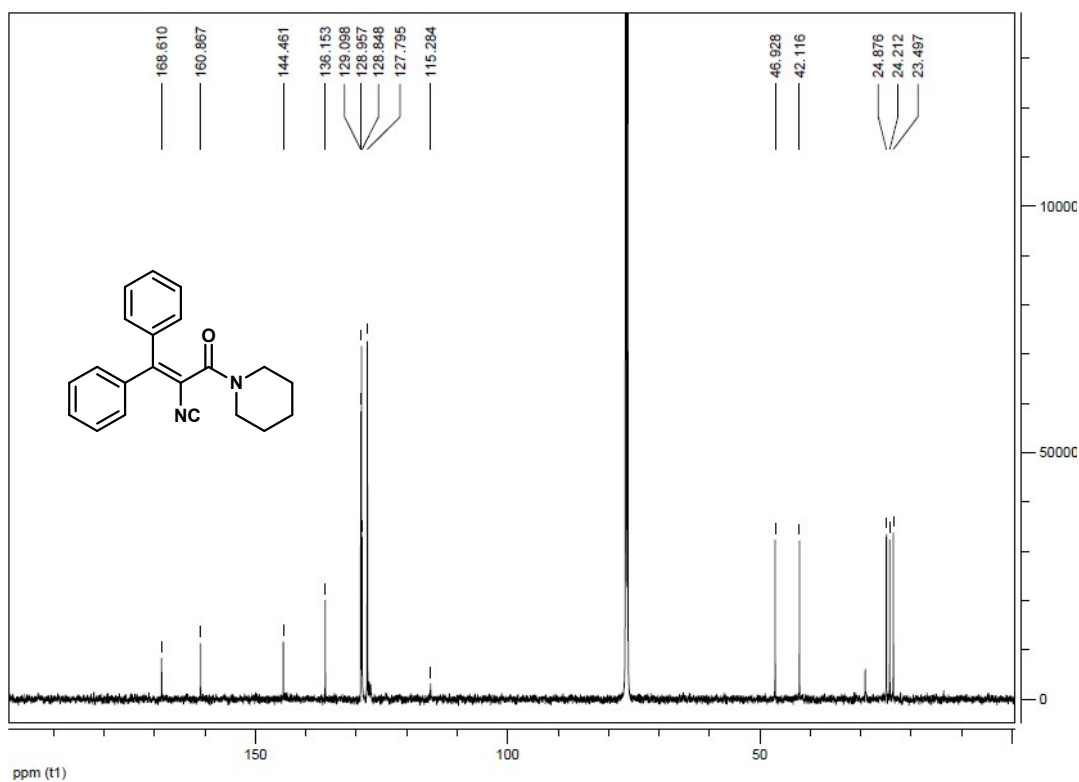
Carbon NMR (CDCl₃)



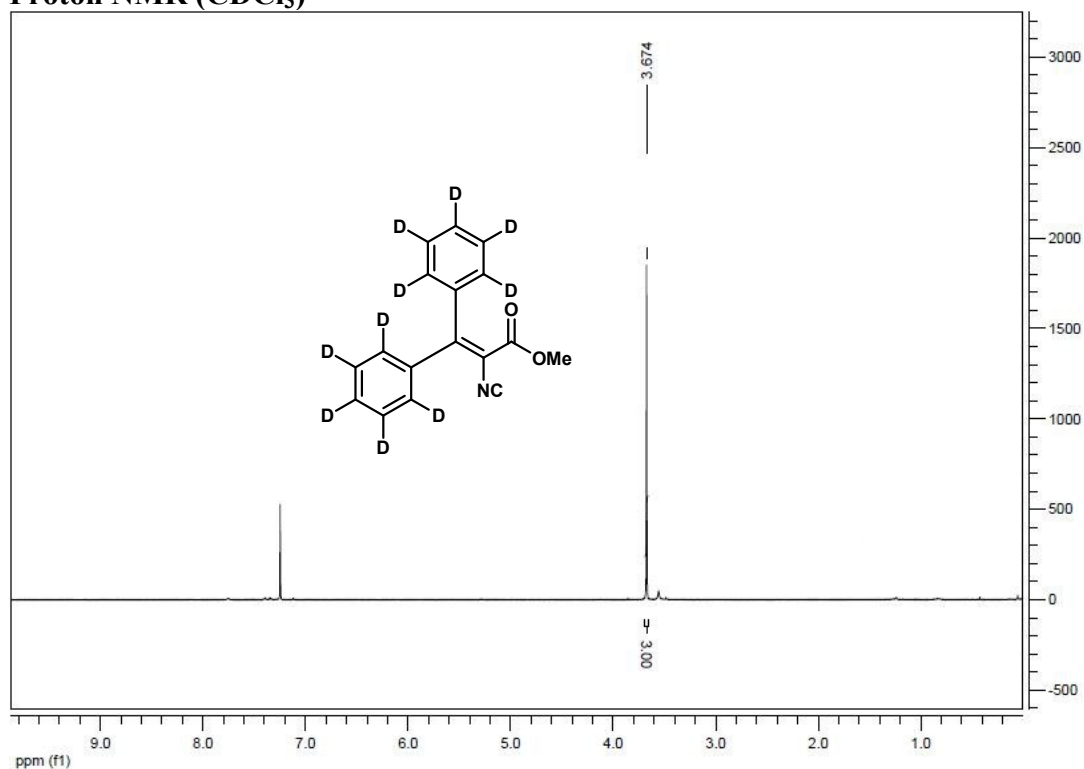
2-Isocyano-3,3-diphenyl-1-(piperidin-1-yl)prop-2-en-1-one (1i)
Proton NMR (CDCl₃)



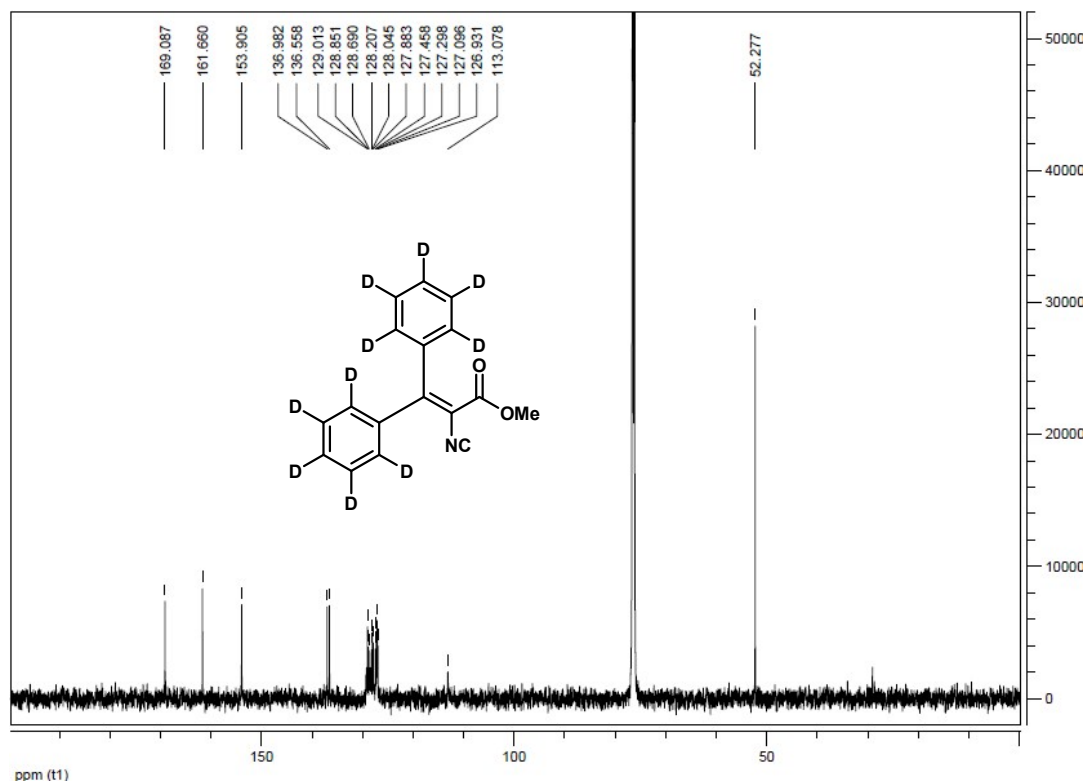
Carbon NMR (CDCl₃)



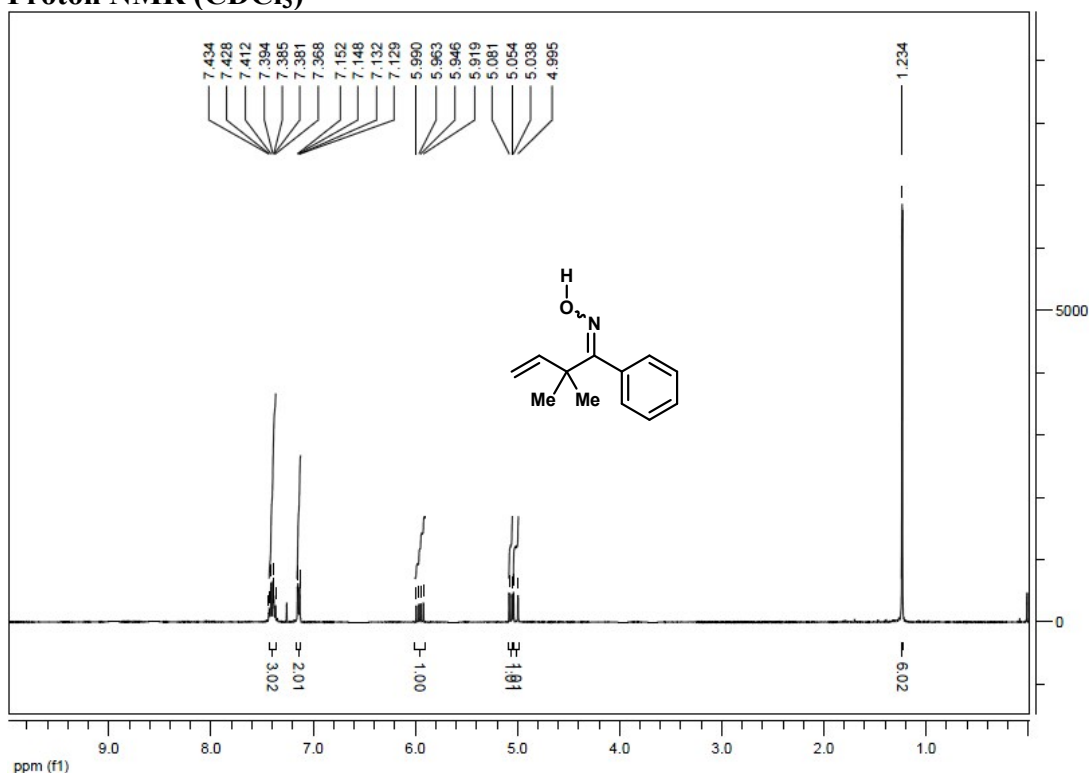
[d₁₀]-Methyl 2-isocyano-3,3-diphenylacrylate ([d₁₀]-1a)
Proton NMR (CDCl₃)



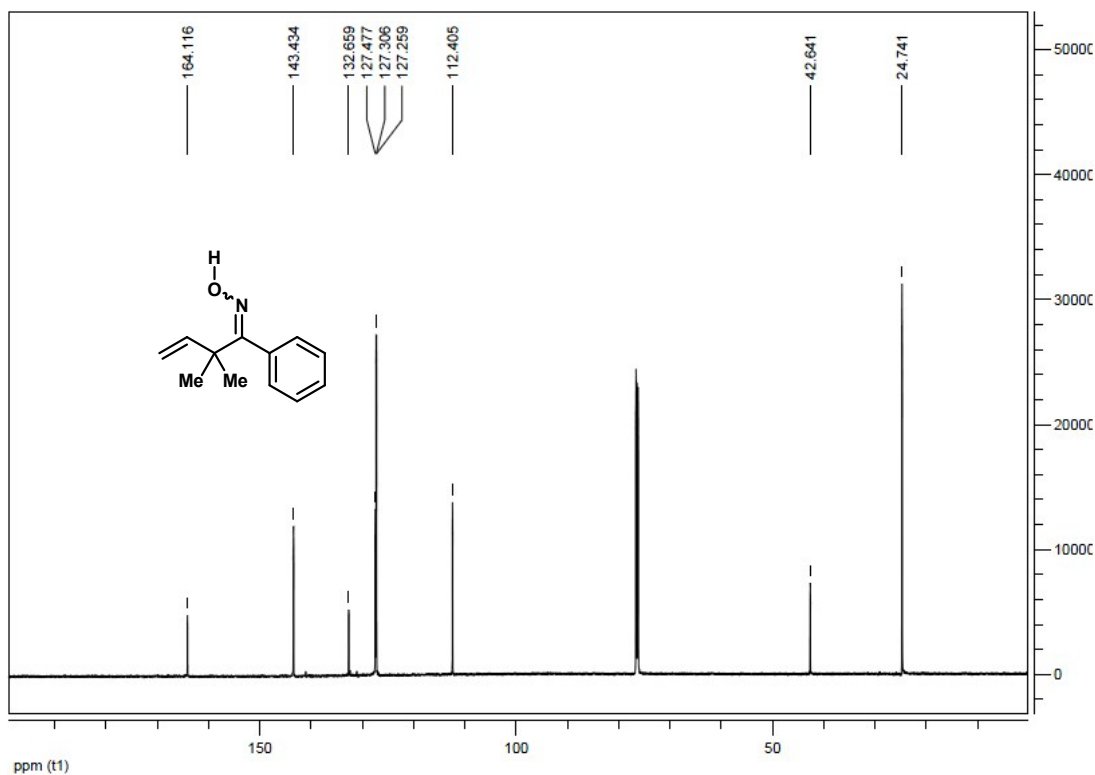
Carbon NMR (CDCl₃)



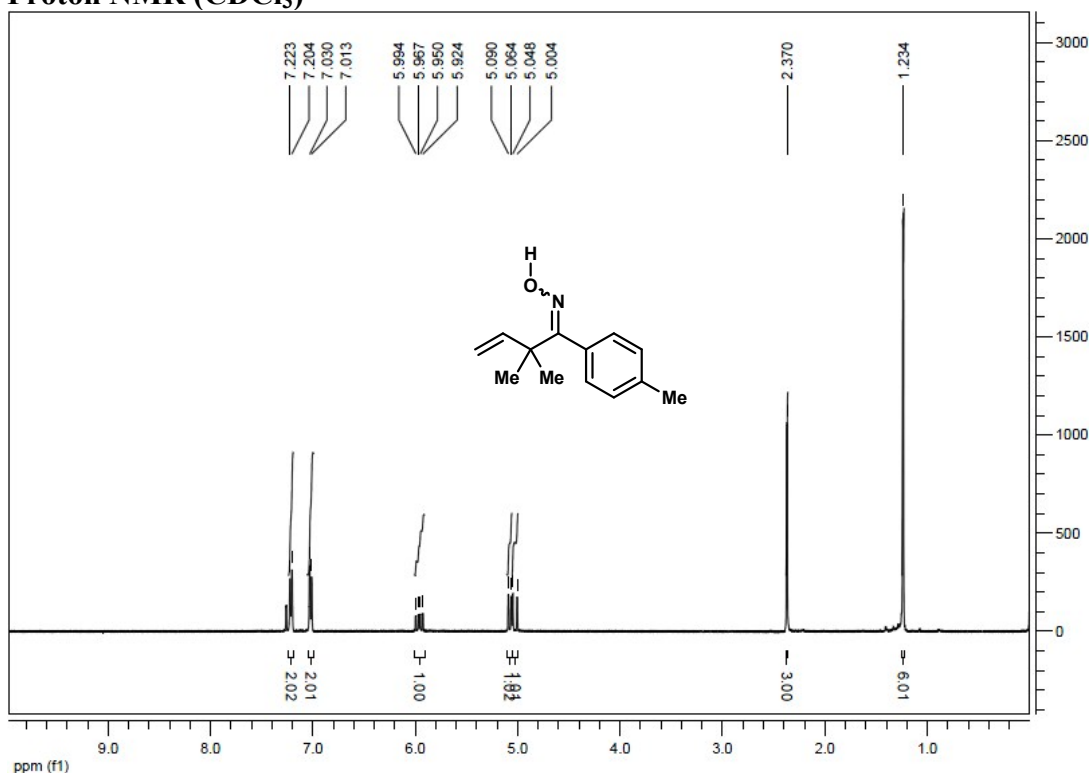
2,2-Dimethyl-1-phenylbut-3-en-1-one oxime (2a)
Proton NMR (CDCl₃)



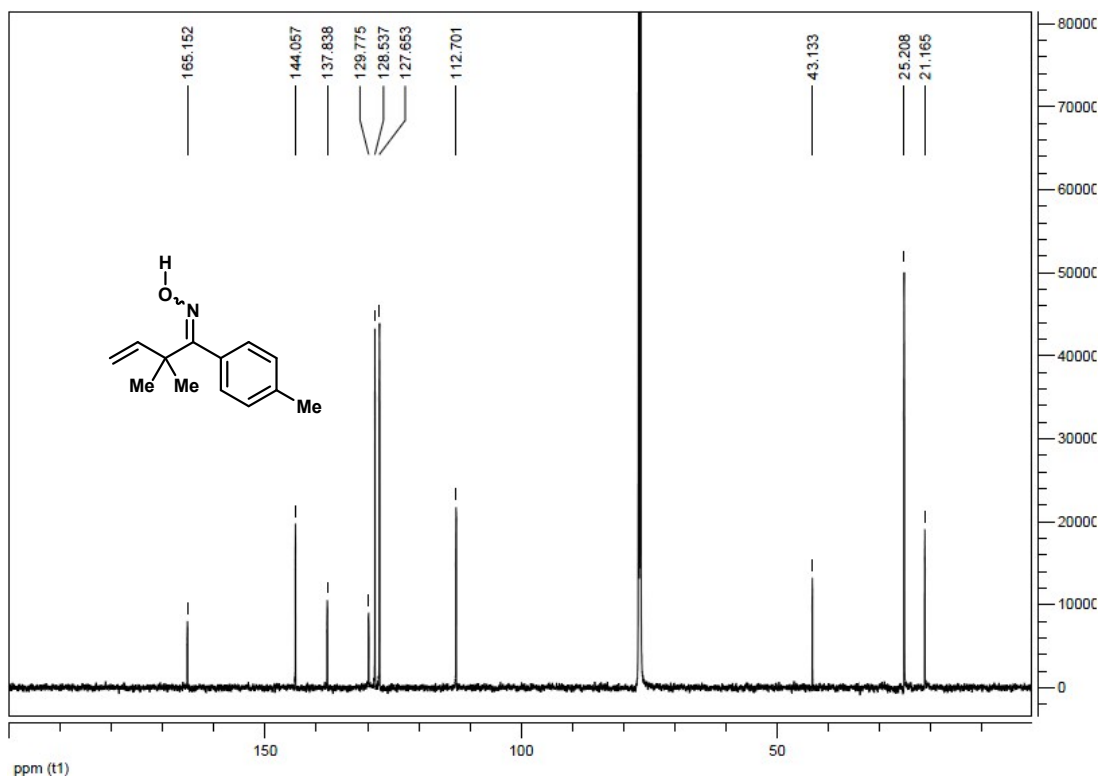
Carbon NMR (CDCl₃)



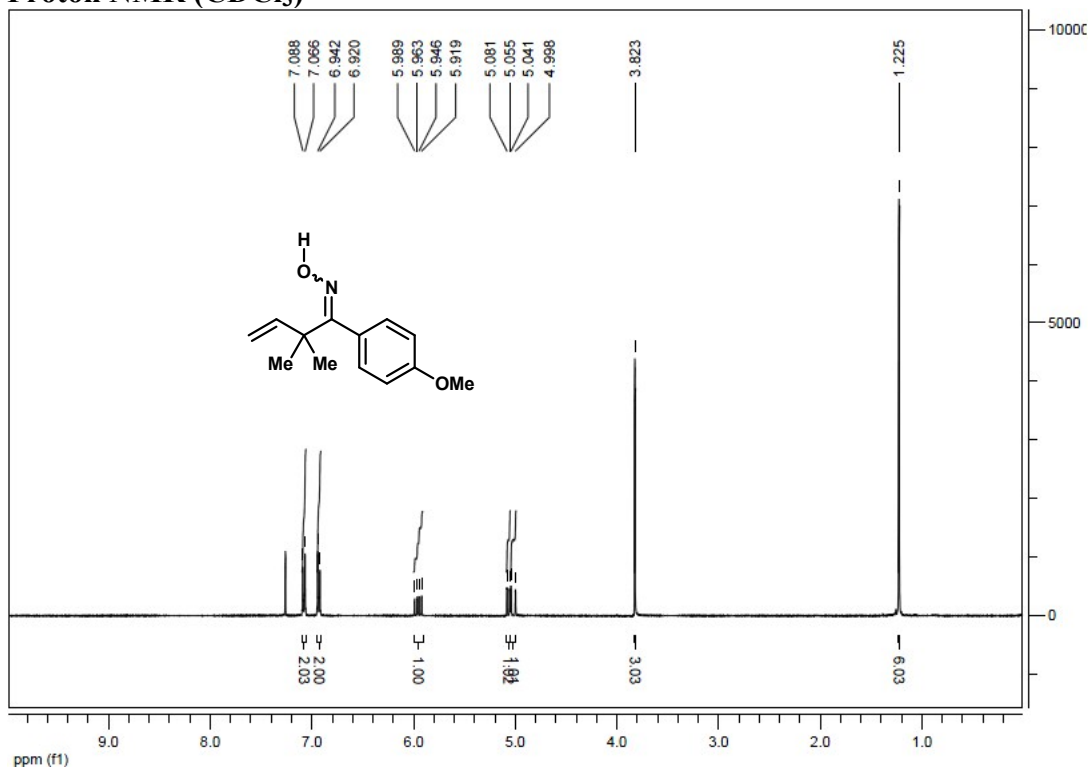
2,2-Dimethyl-1-(*p*-tolyl)but-3-en-1-one oxime (2b)
Proton NMR (CDCl₃)



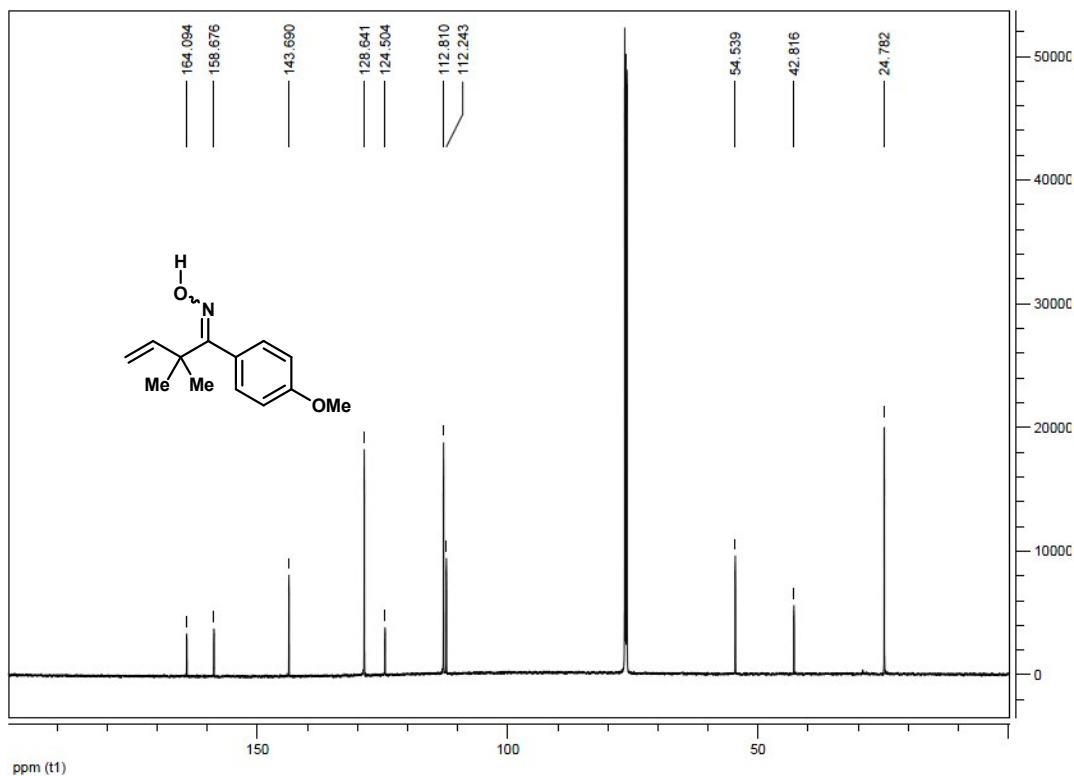
Carbon NMR (CDCl₃)



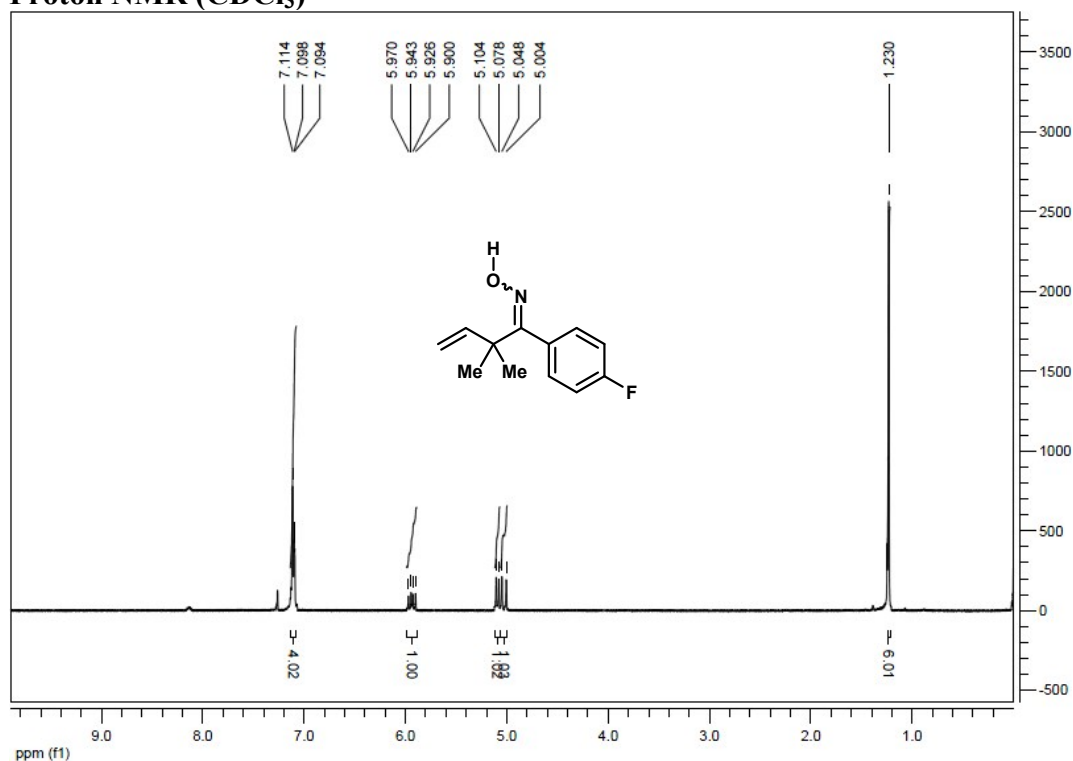
1-(4-Methoxyphenyl)-2,2-dimethylbut-3-en-1-one oxime (2c)
Proton NMR (CDCl₃)



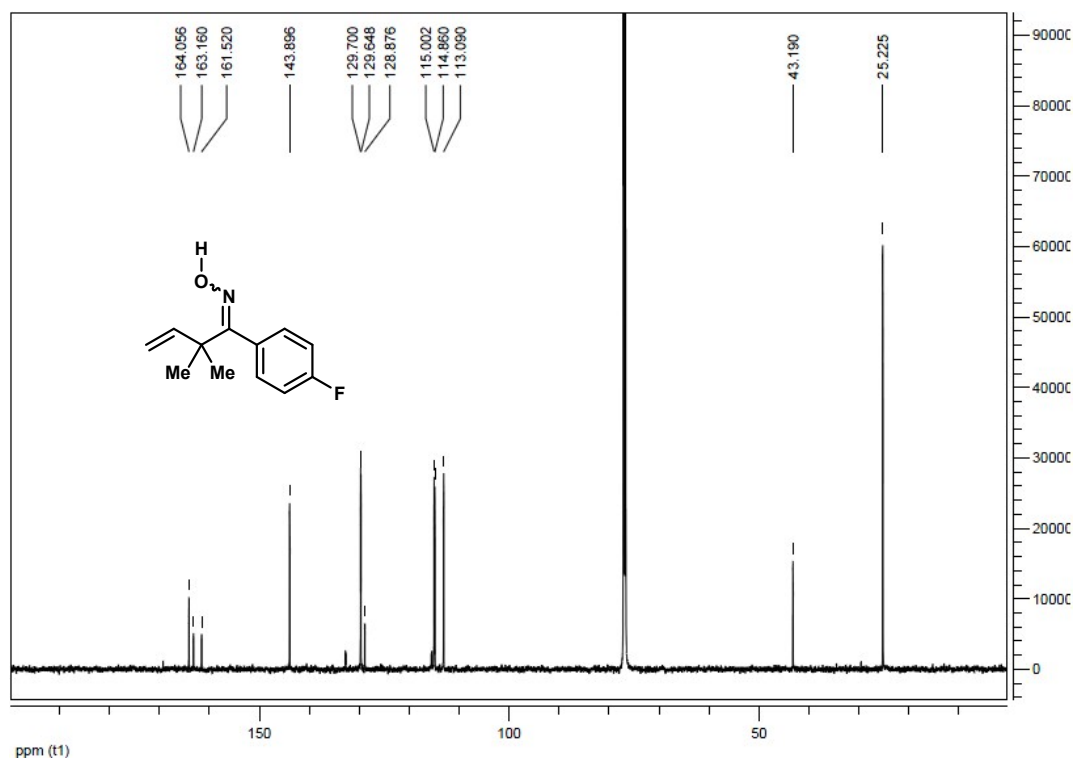
Carbon NMR (CDCl₃)



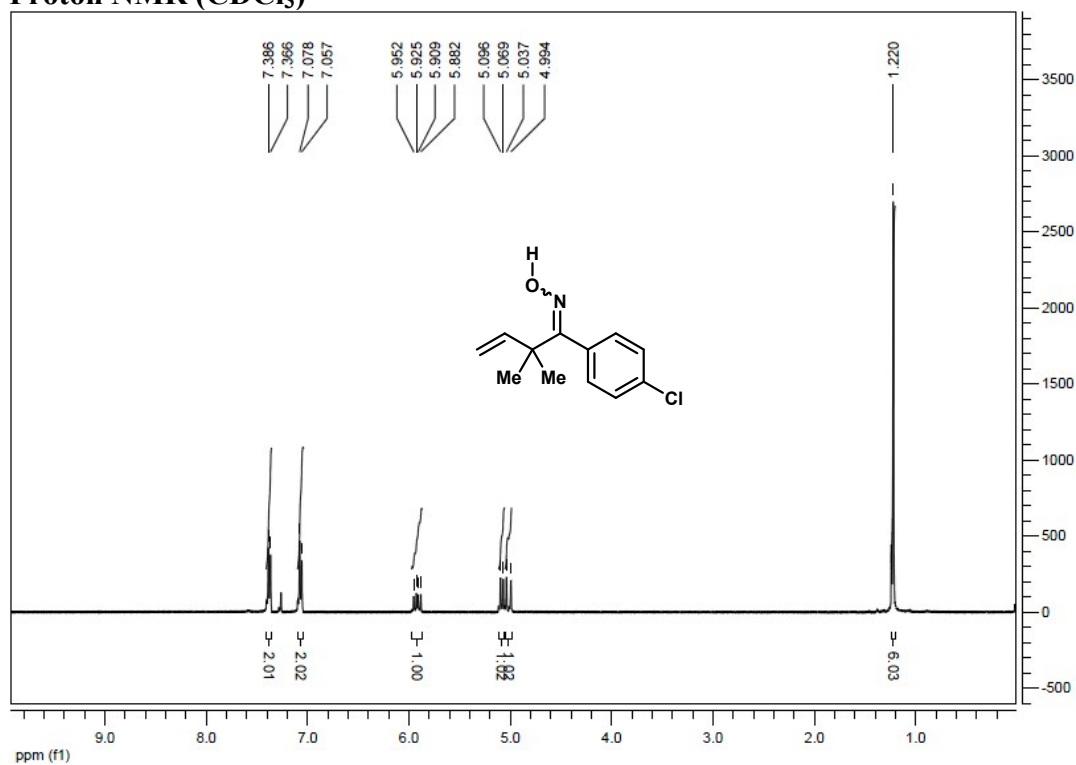
1-(4-Fluorophenyl)-2,2-dimethylbut-3-en-1-one oxime (2d)
Proton NMR (CDCl₃)



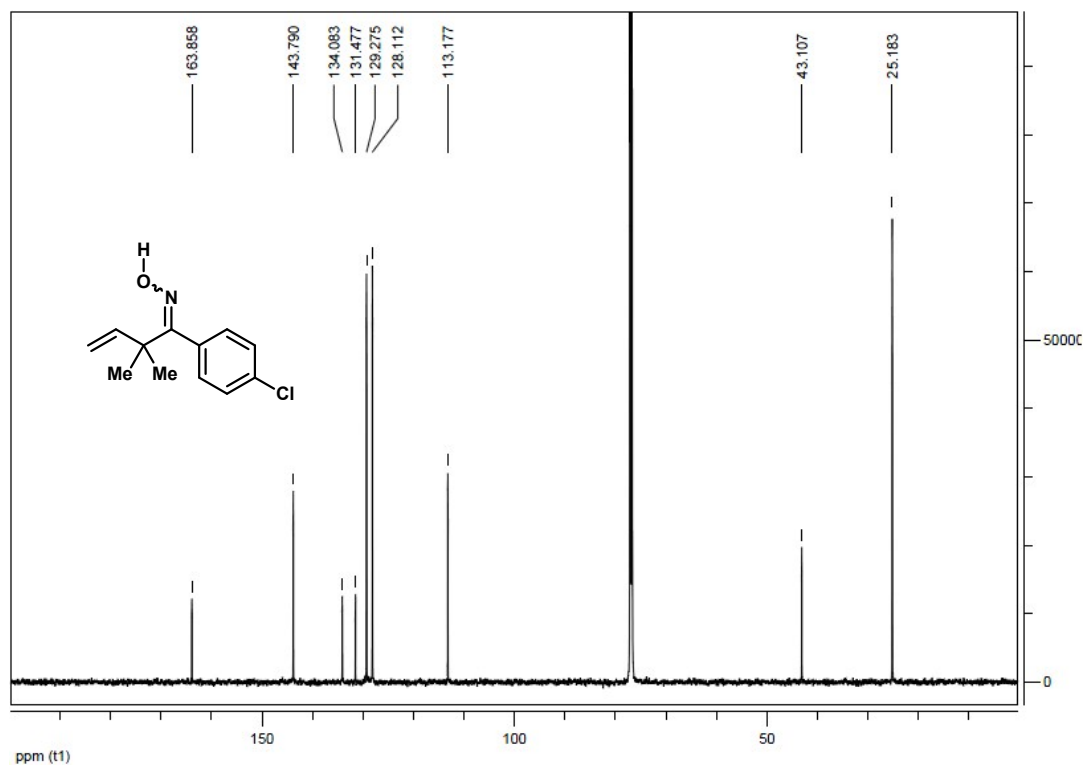
Carbon NMR (CDCl₃)



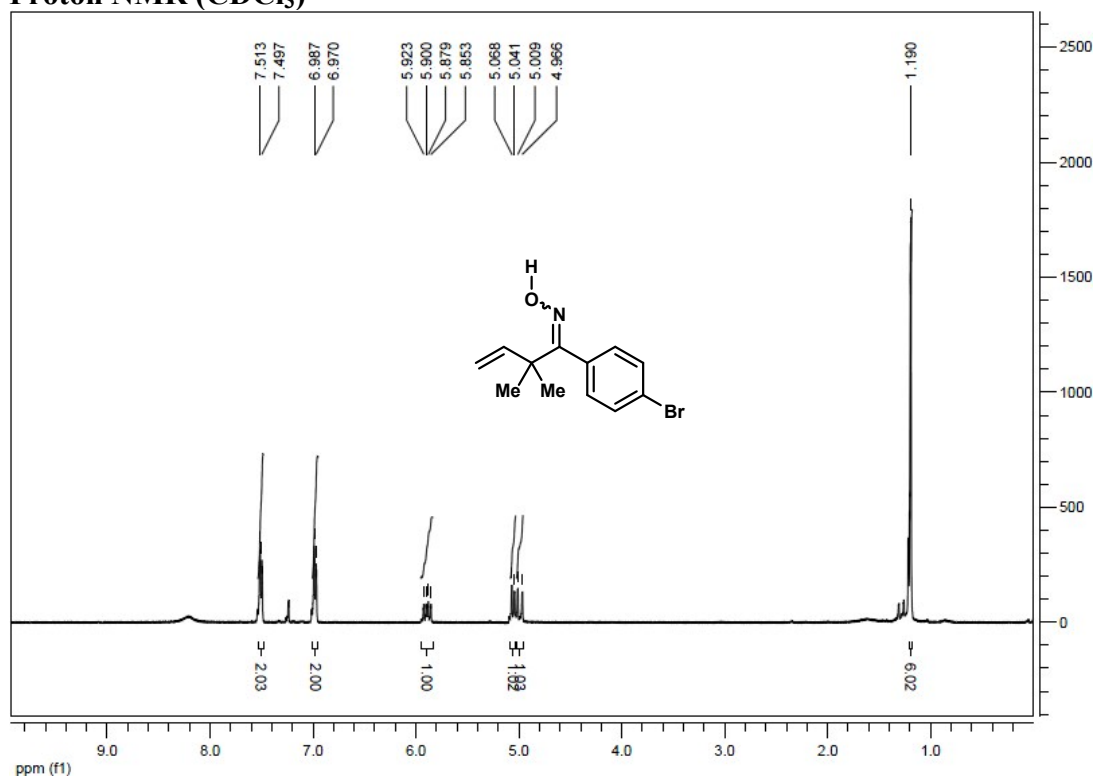
1-(4-Chlorophenyl)-2,2-dimethylbut-3-en-1-one oxime (2e)
Proton NMR (CDCl₃)



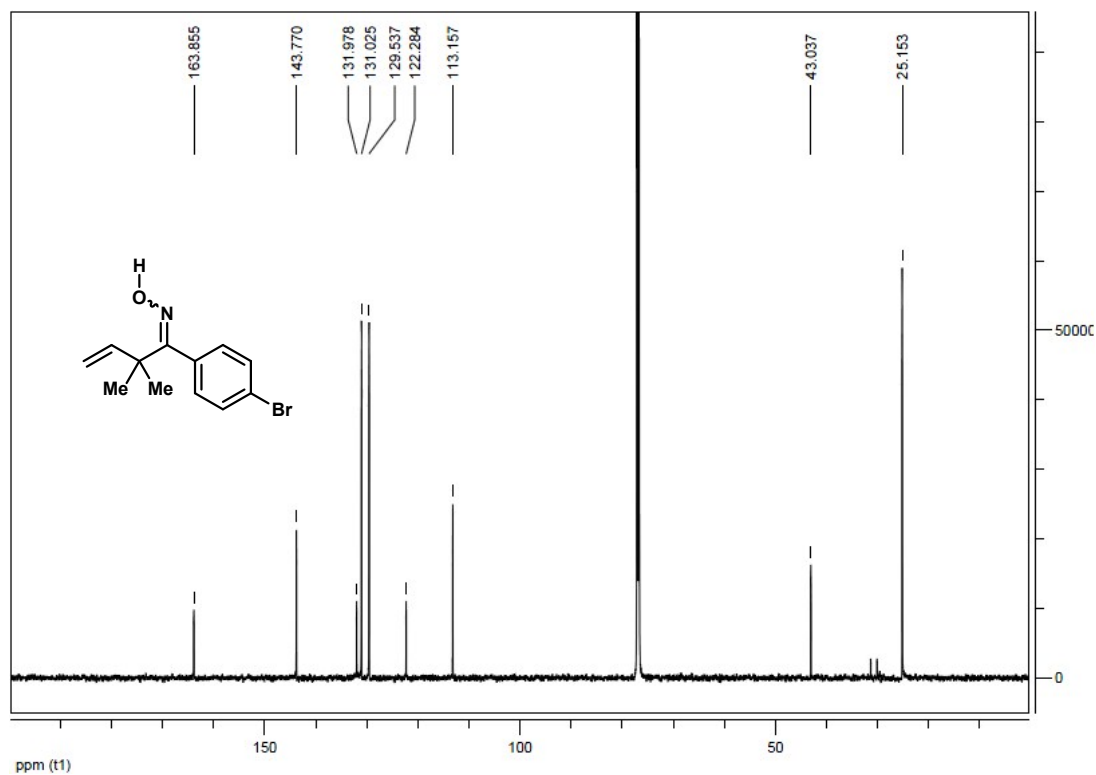
Carbon NMR (CDCl₃)



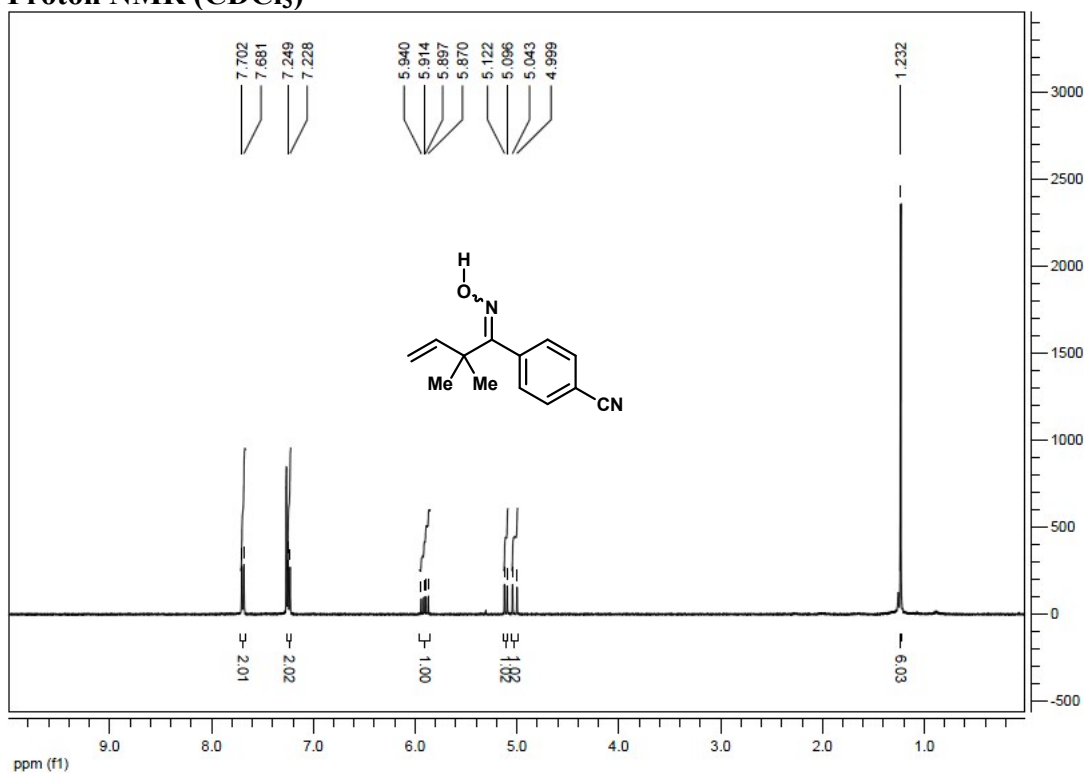
1-(4-Bromophenyl)-2,2-dimethylbut-3-en-1-one oxime (2f)
Proton NMR (CDCl₃)



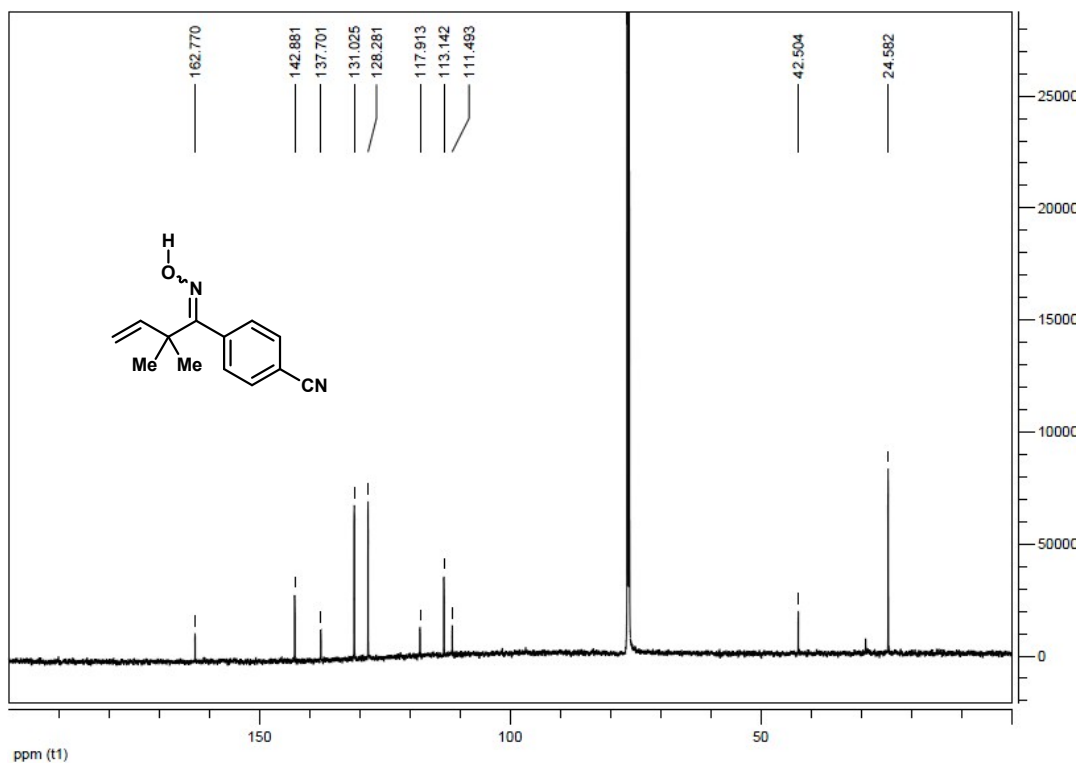
Carbon NMR (CDCl₃)



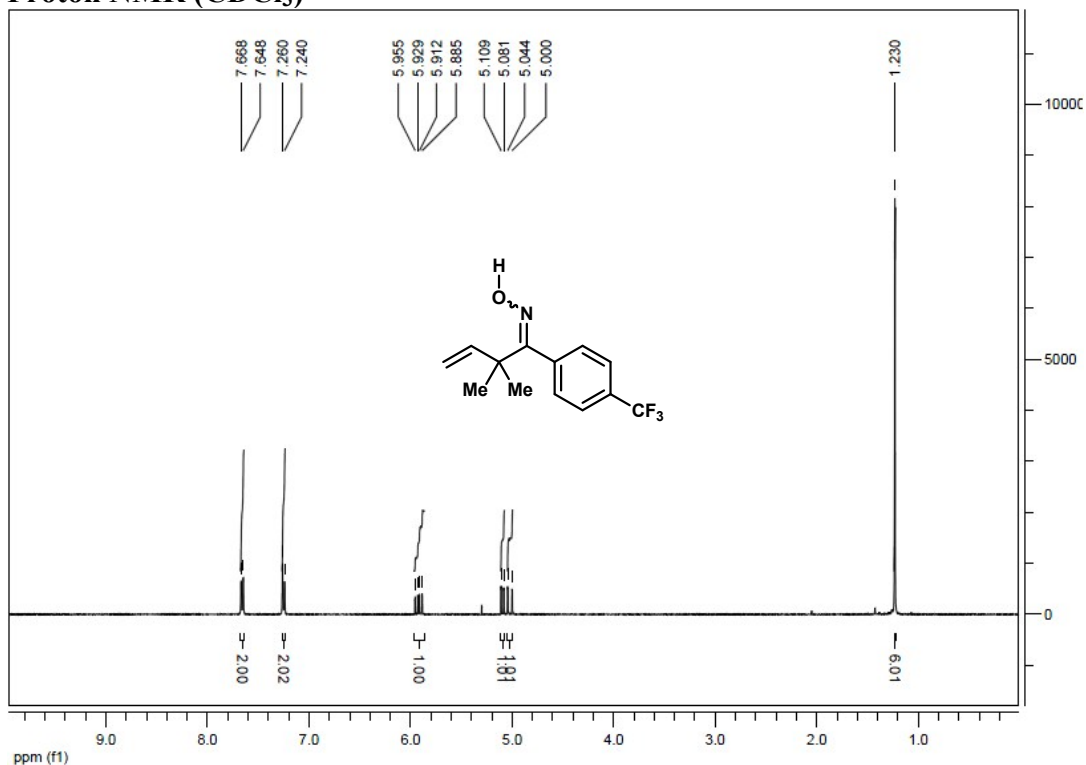
4-(1-(Hydroxyimino)-2,2-dimethylbut-3-en-1-yl)benzonitrile (2g)
Proton NMR (CDCl₃)



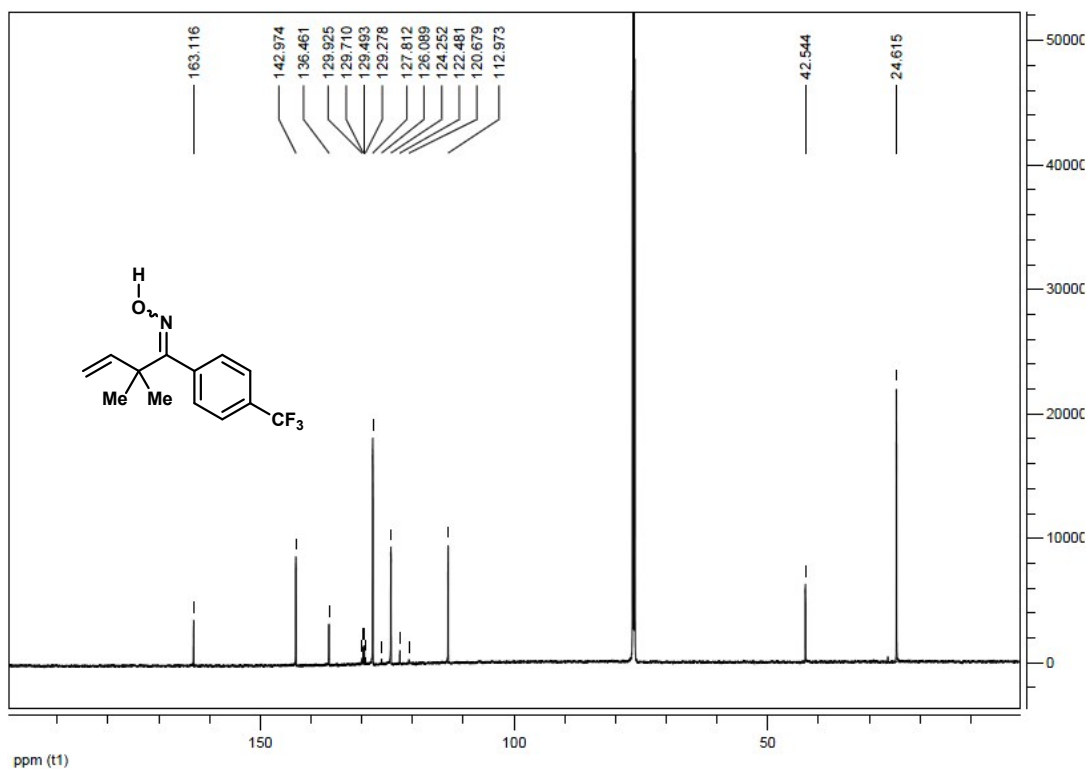
Carbon NMR (CDCl₃)



2,2-Dimethyl-1-(4-(trifluoromethyl)phenyl)but-3-en-1-one oxime (2h)
Proton NMR (CDCl₃)



Carbon NMR (CDCl₃)

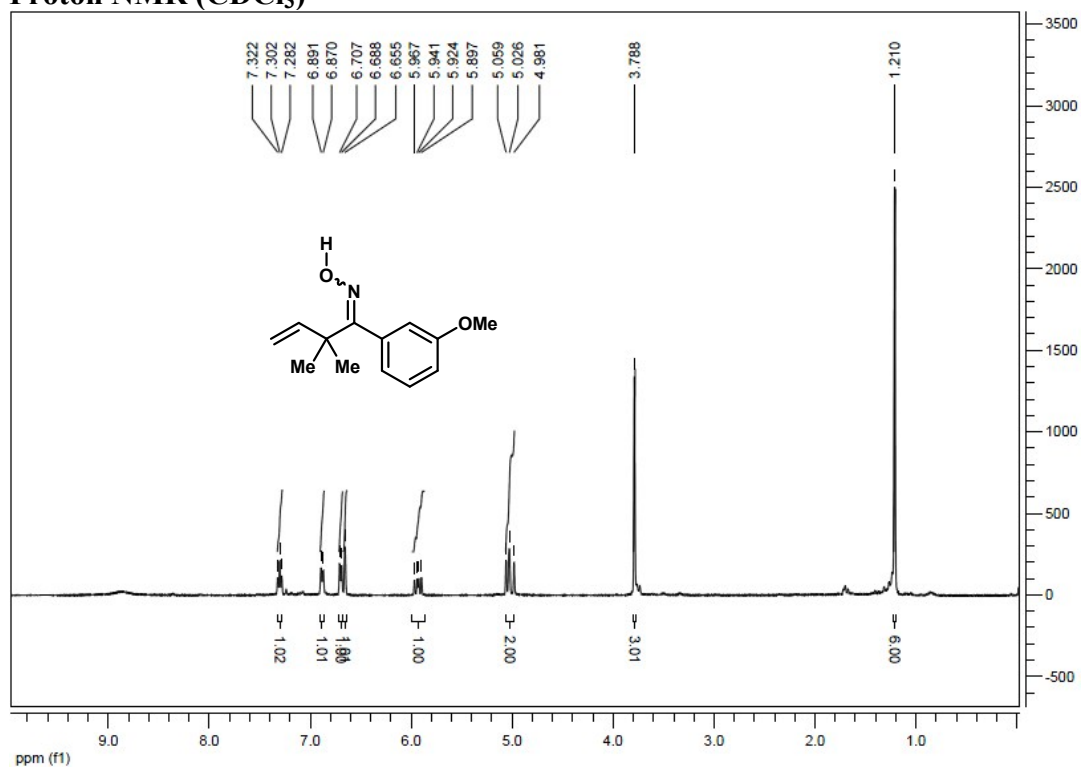


Proton NMR (CDCl₃)

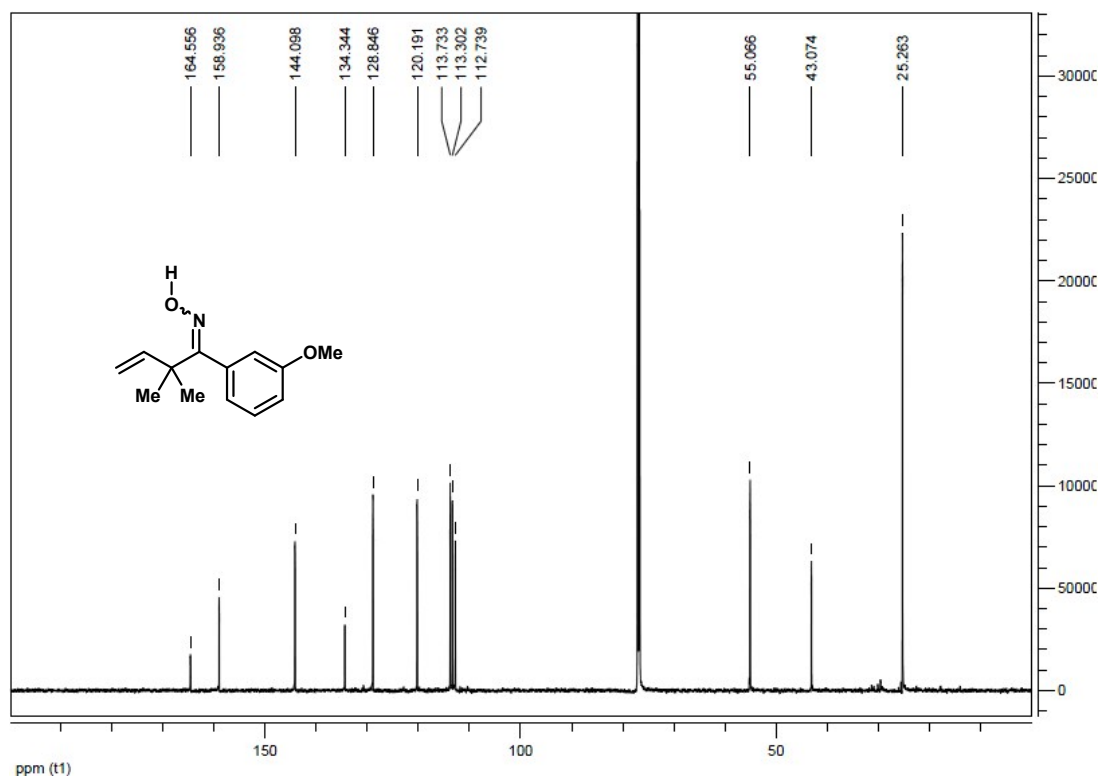




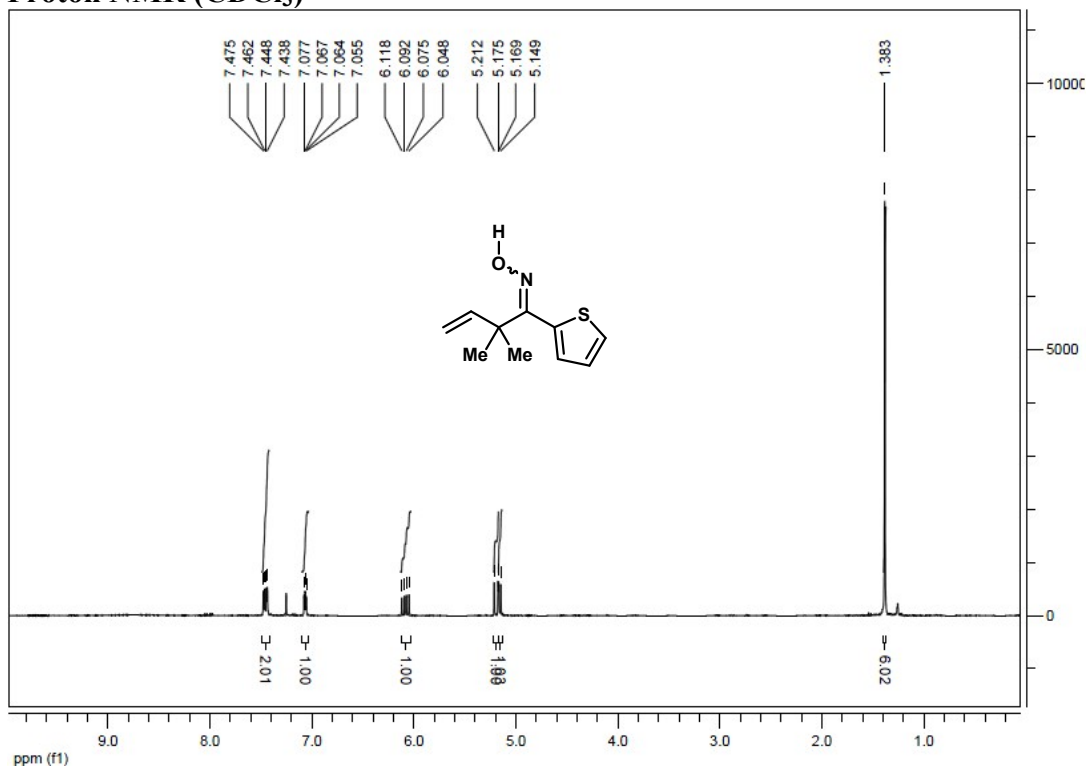
1-(3-Methoxyphenyl)-2,2-dimethylbut-3-en-1-one oxime (2j)
Proton NMR (CDCl₃)



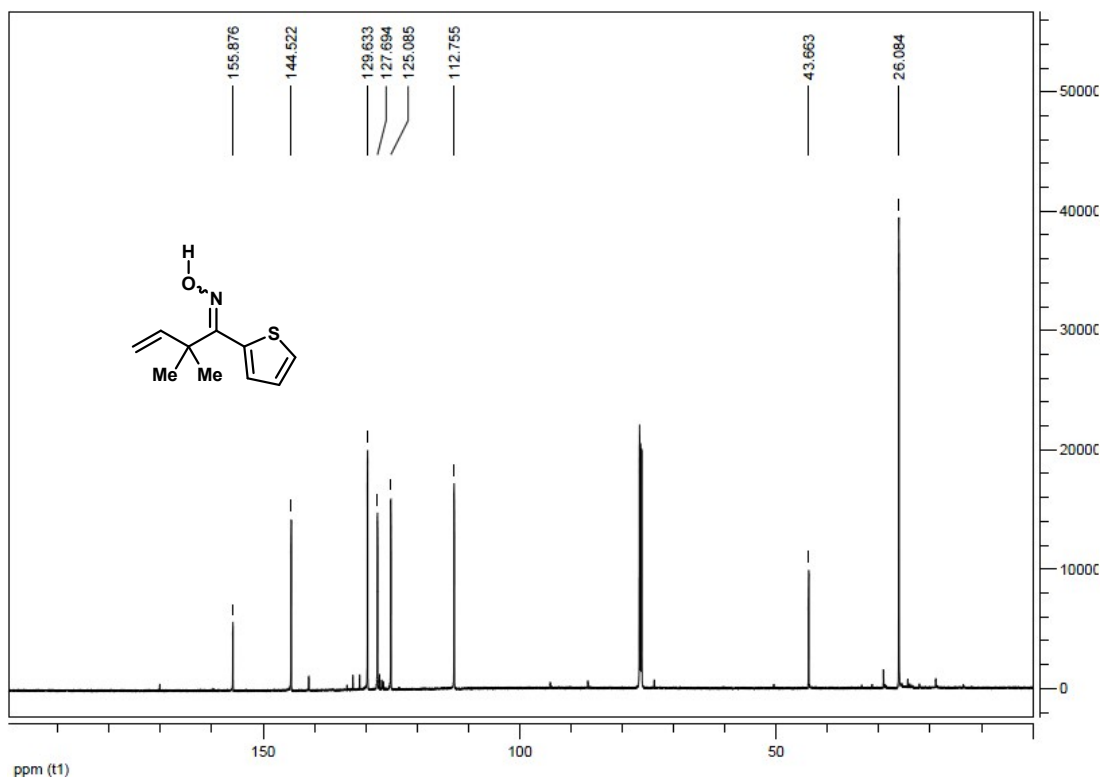
Carbon NMR (CDCl₃)



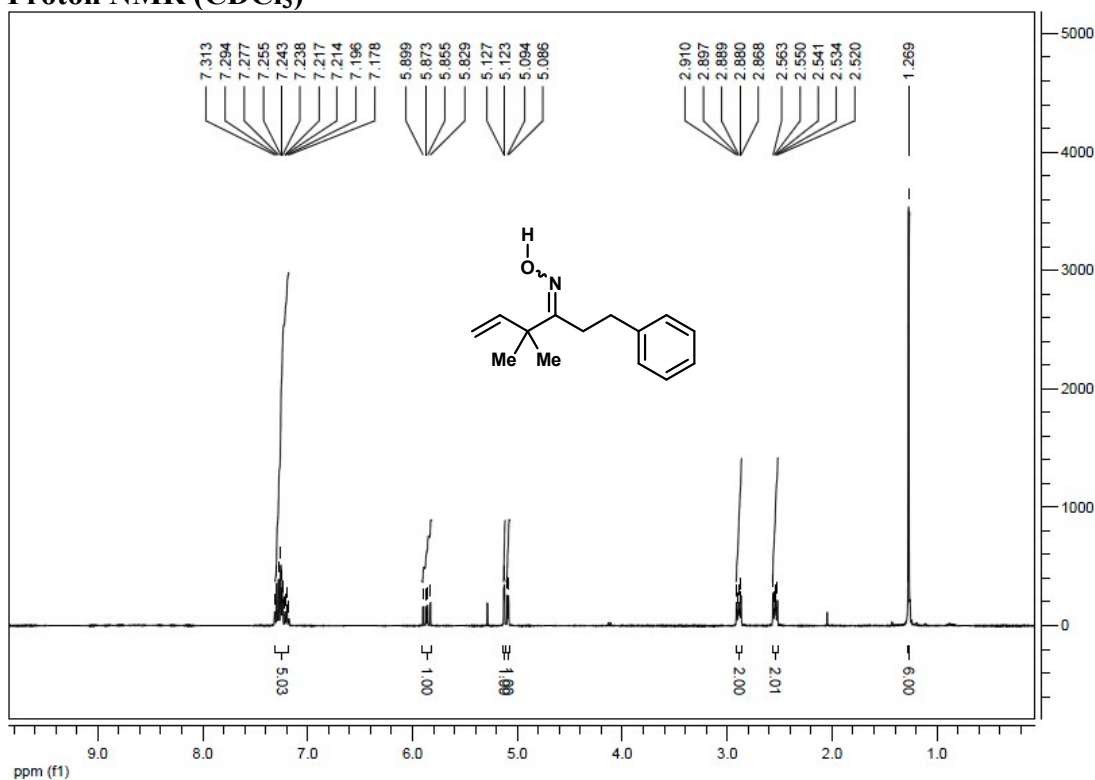
2,2-Dimethyl-1-(thiophen-2-yl)but-3-en-1-one oxime (2k)
Proton NMR (CDCl₃)



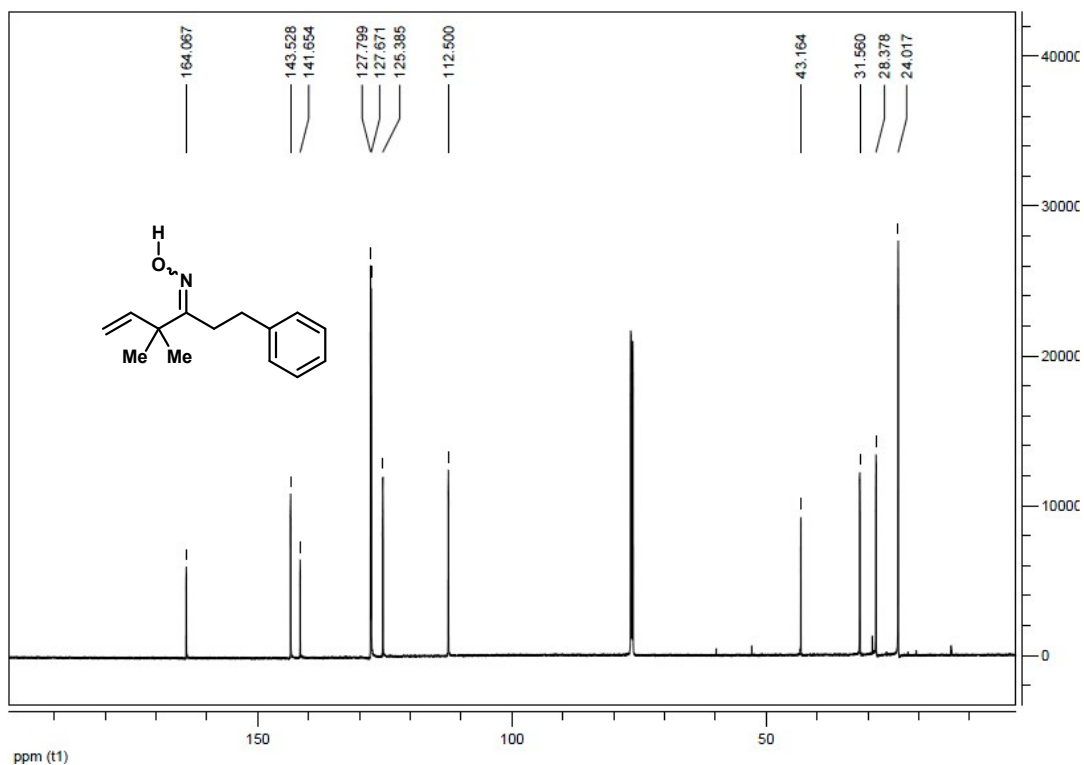
Carbon NMR (CDCl₃)



4,4-Dimethyl-1-phenylhex-5-en-3-one oxime (2l)
Proton NMR (CDCl₃)

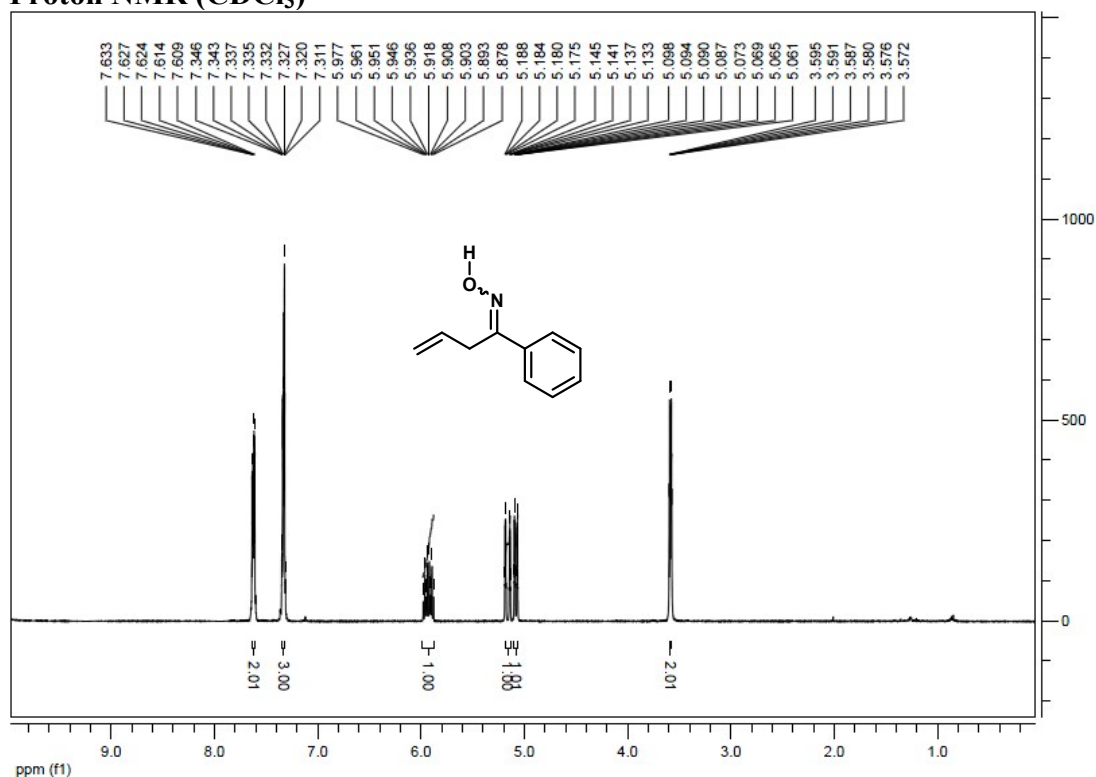


Carbon NMR (CDCl₃)

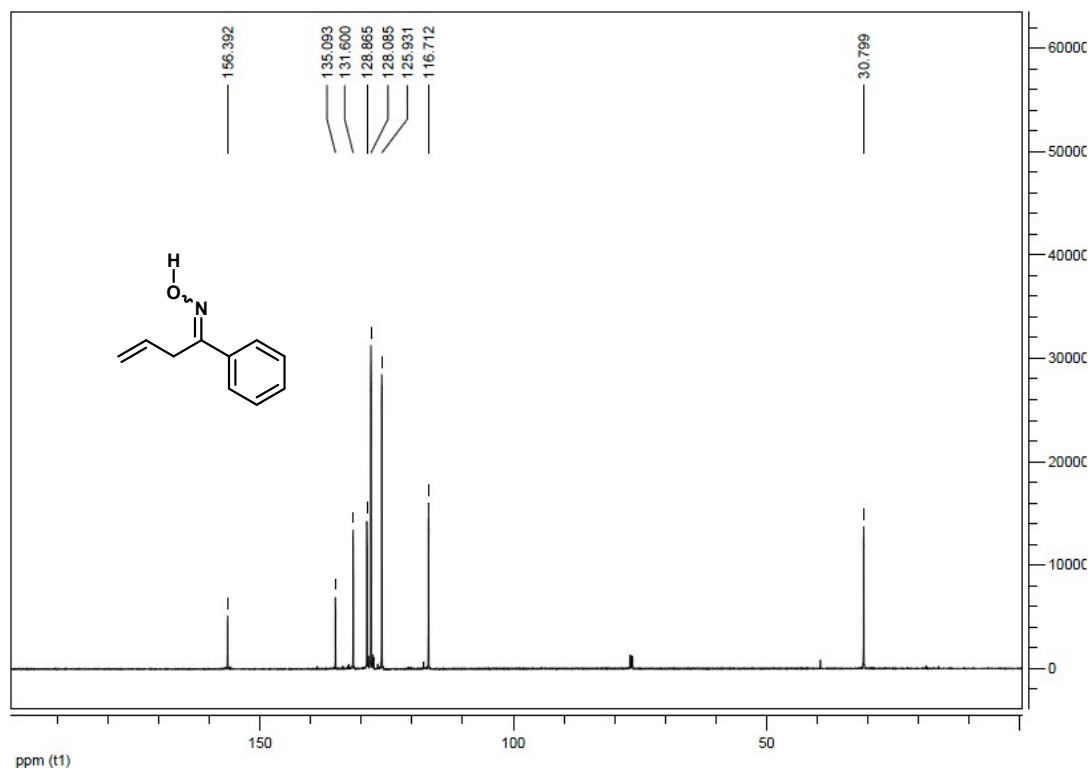


1-Phenylbut-3-en-1-one oxime (2m)

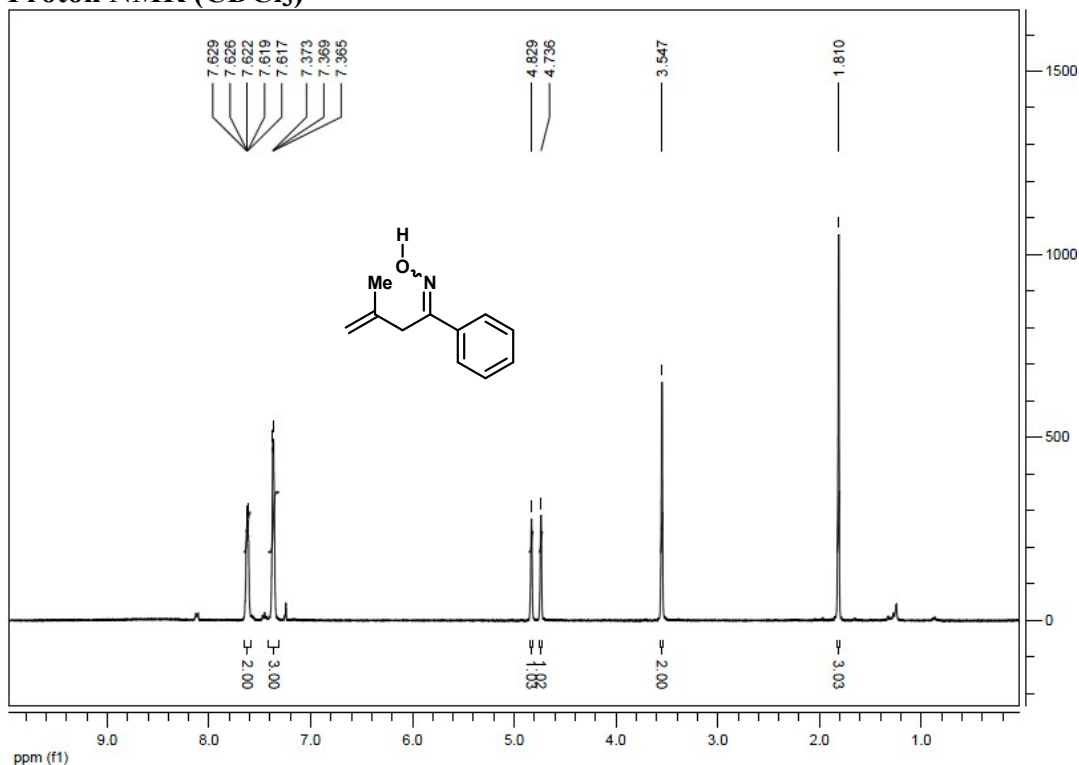
Proton NMR (CDCl₃)



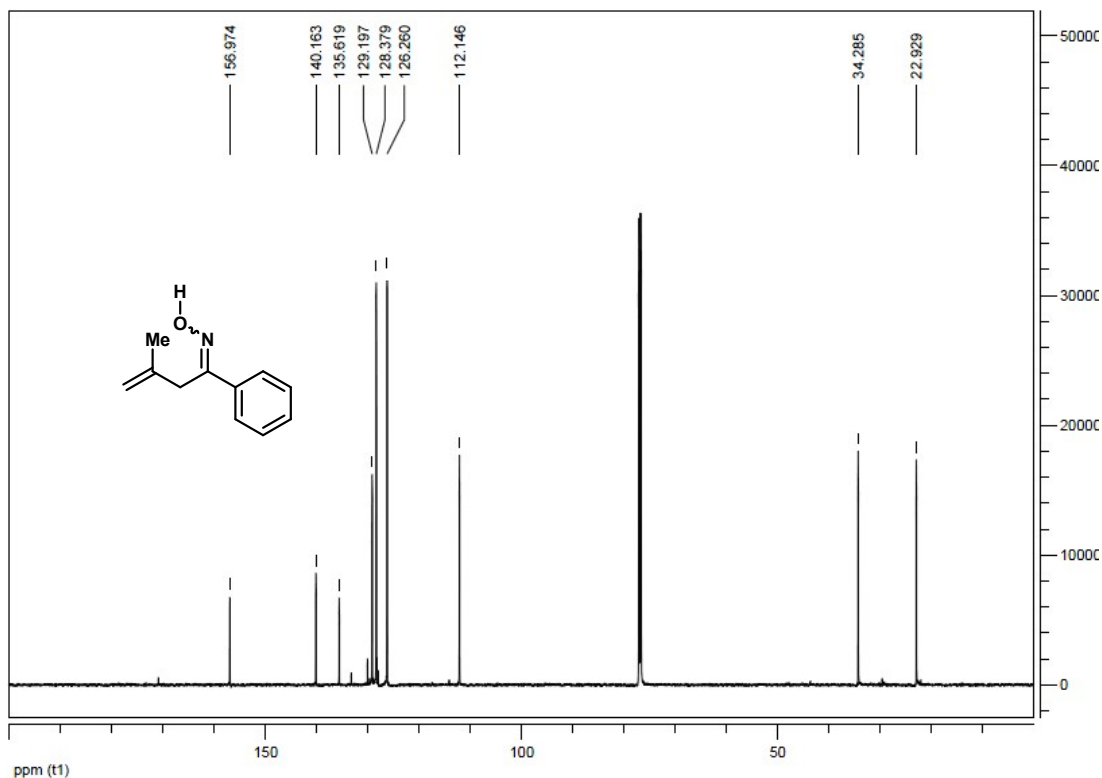
Carbon NMR (CDCl₃)



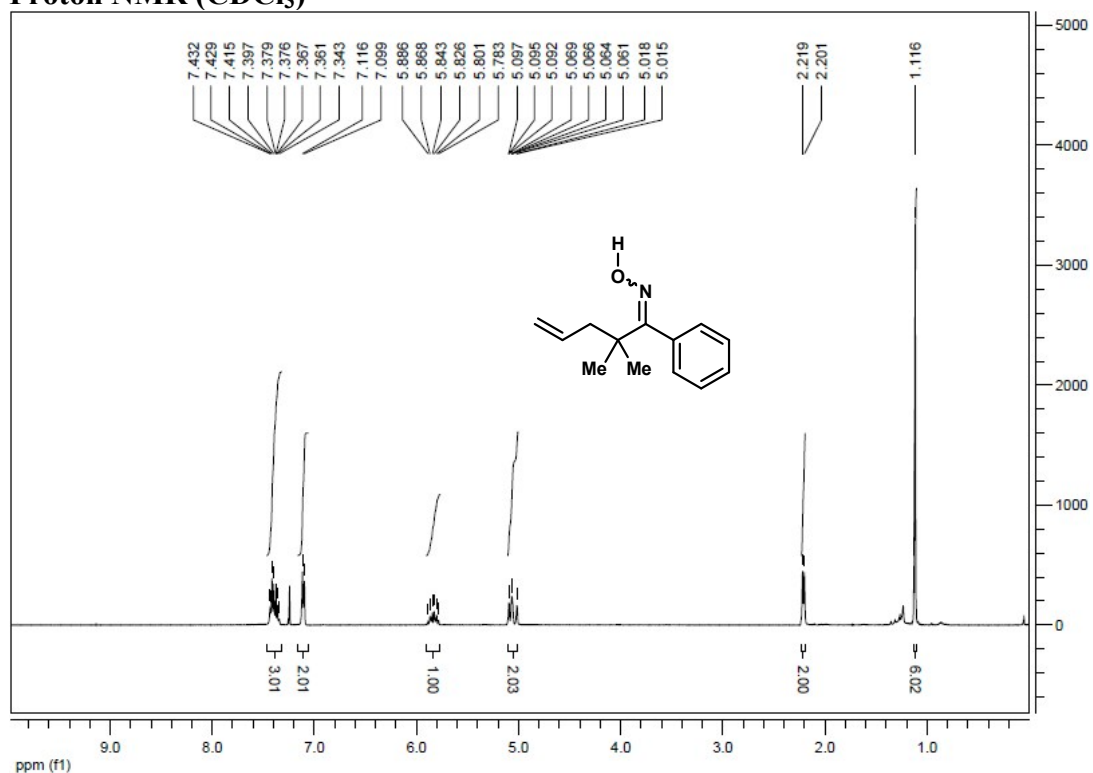
3-Methyl-1-phenylbut-3-en-1-one oxime (2n)
Proton NMR (CDCl₃)



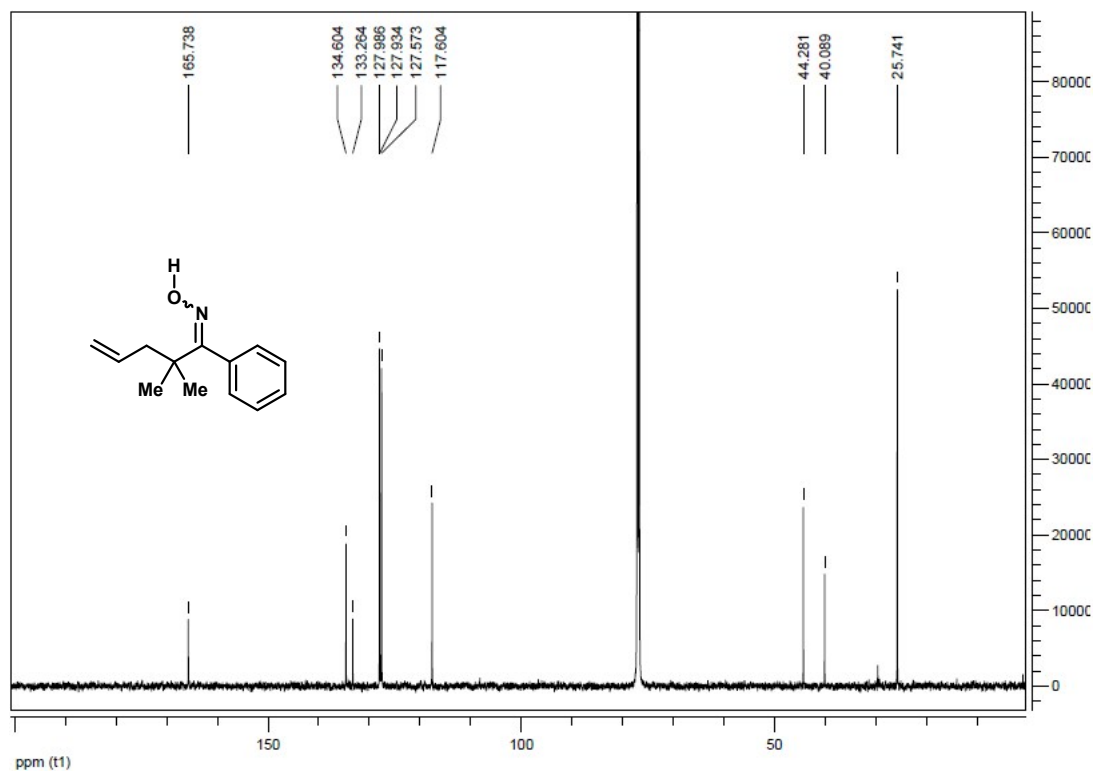
Carbon NMR (CDCl₃)



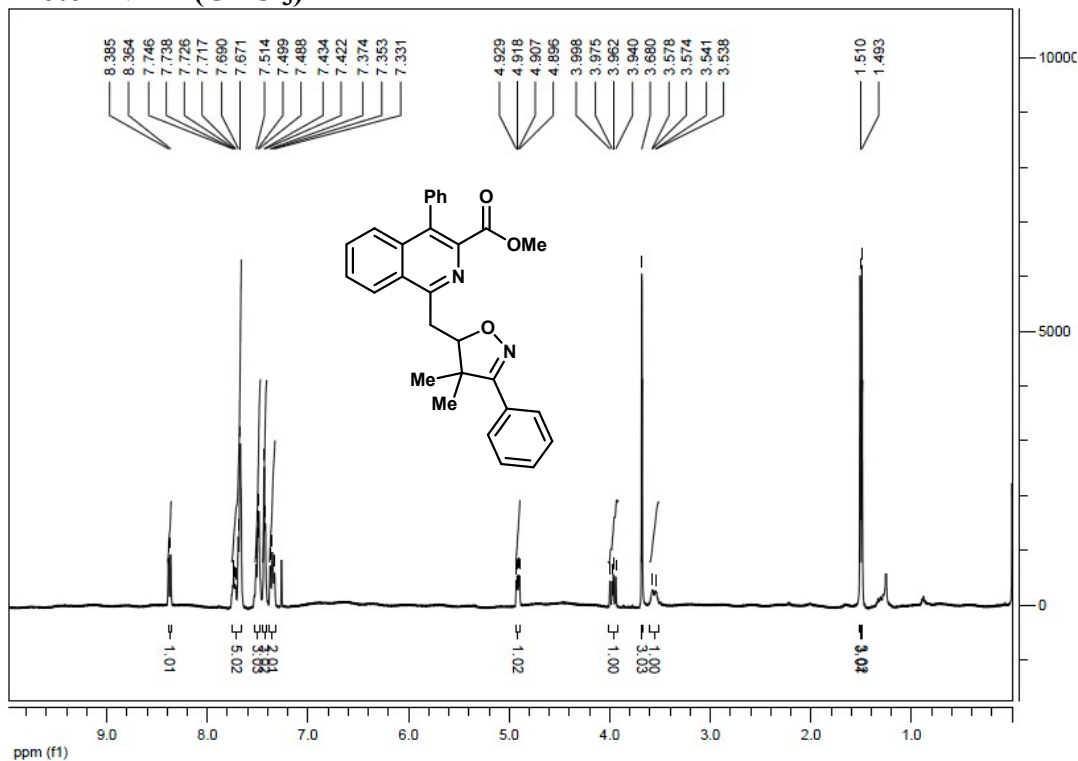
2,2-Dimethyl-1-phenylpent-4-en-1-one oxime (2o)
Proton NMR (CDCl₃)



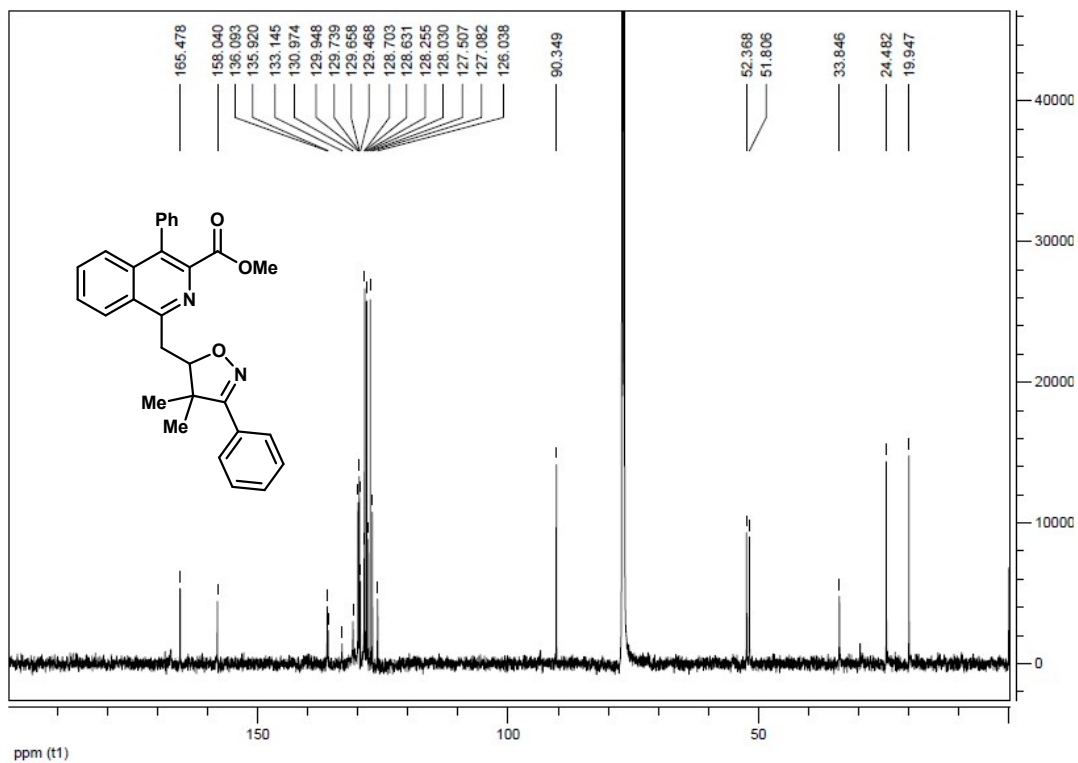
Carbon NMR (CDCl₃)



Methyl 1-((4,4-dimethyl-3-phenyl-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinoline-3-carboxylate (3a)
Proton NMR (CDCl₃)

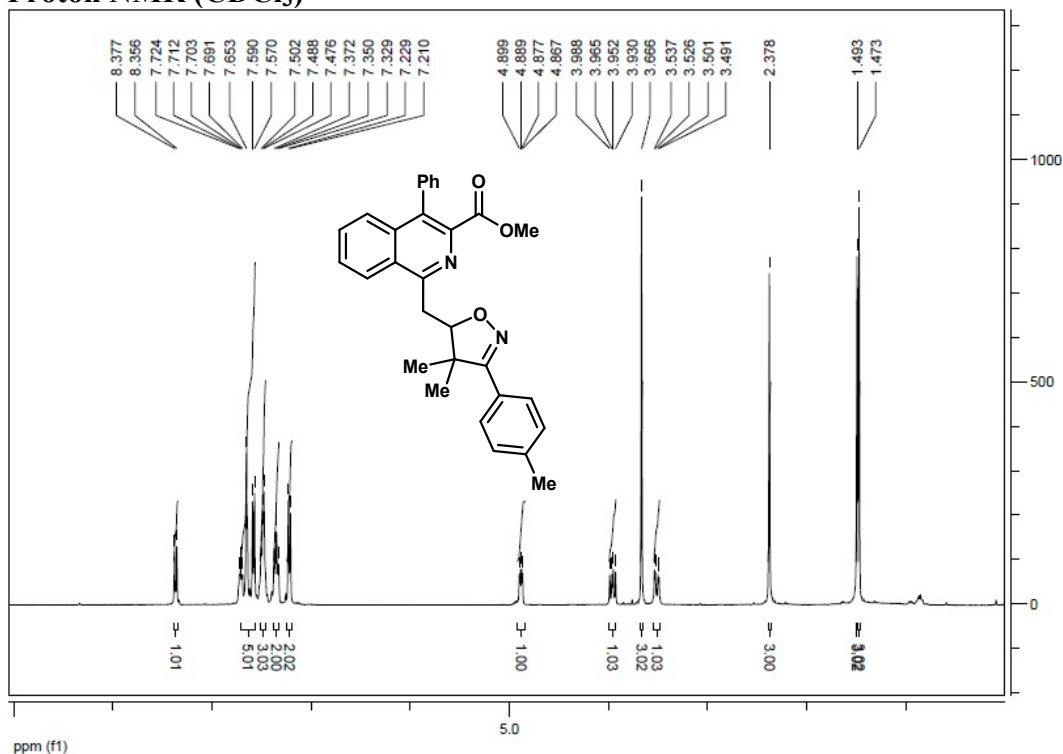


Carbon NMR (CDCl₃)

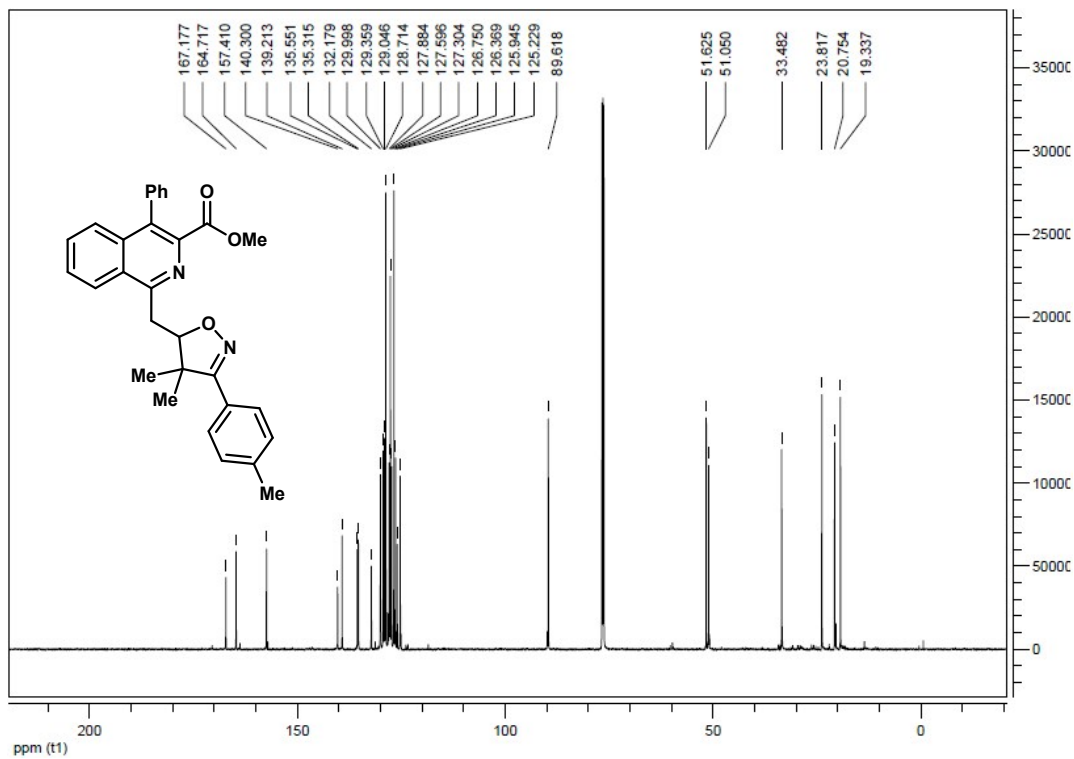


Methyl 1-((4,4-dimethyl-3-(*p*-tolyl)-4,5-dihydroisoxazol-5-yl)methyl)-4-

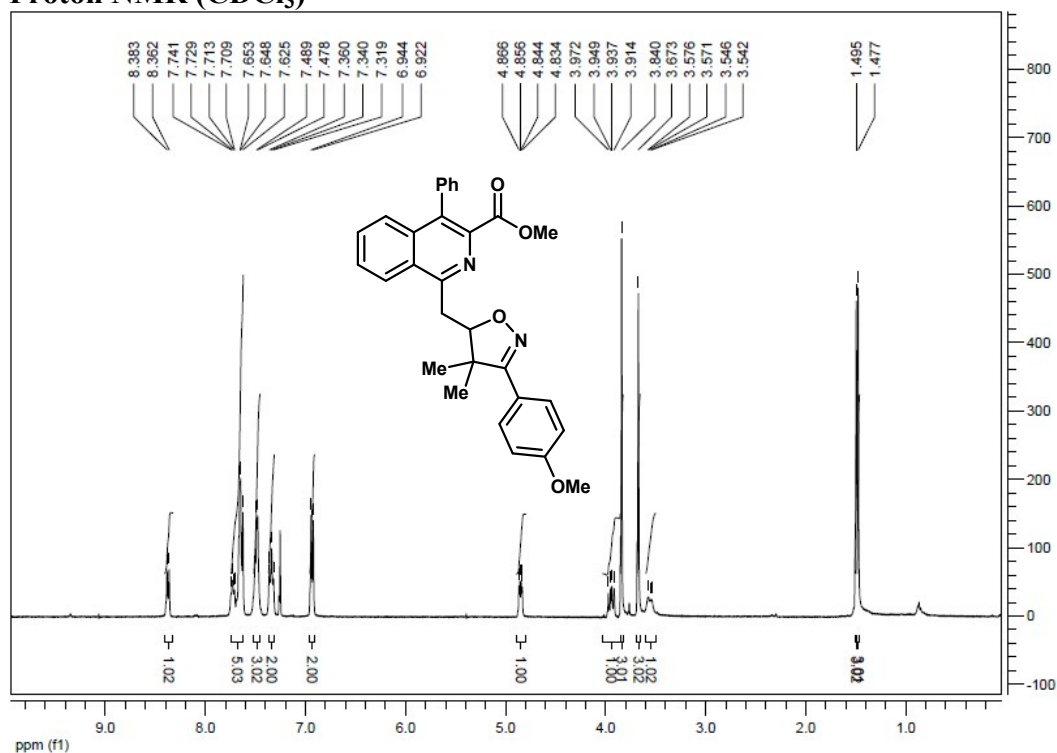
phenylisoquinoline-3-carboxylate (3b)
Proton NMR (CDCl₃)



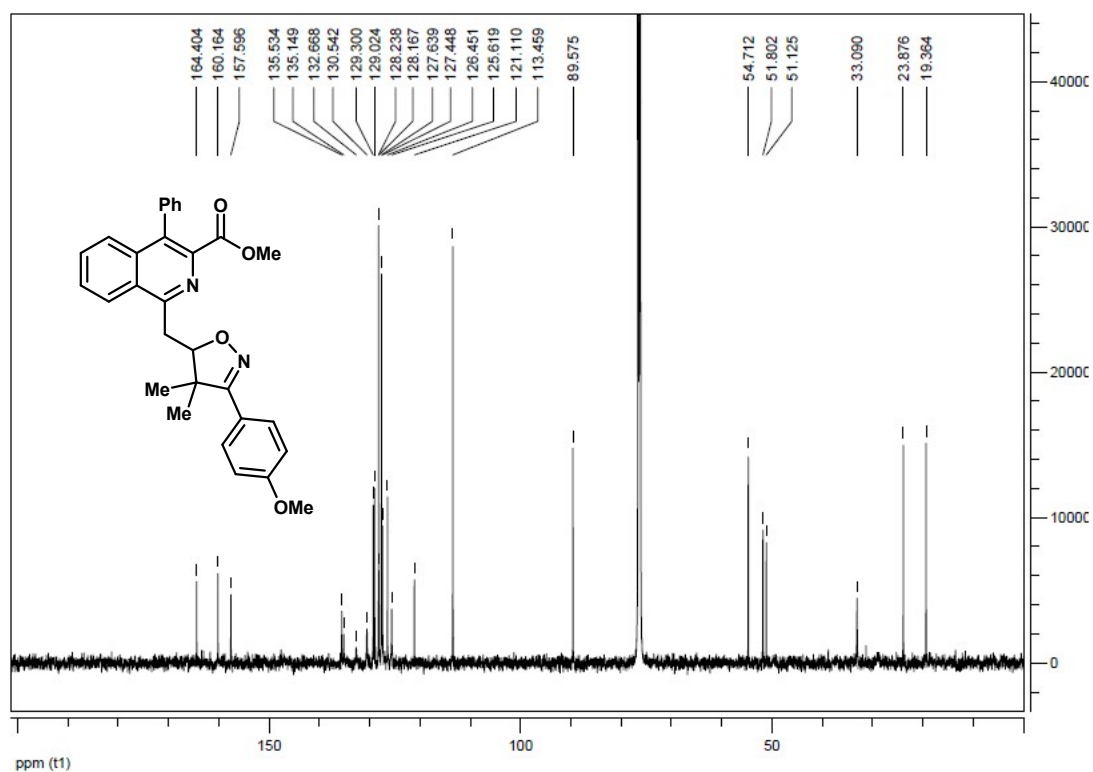
Carbon NMR (CDCl₃)



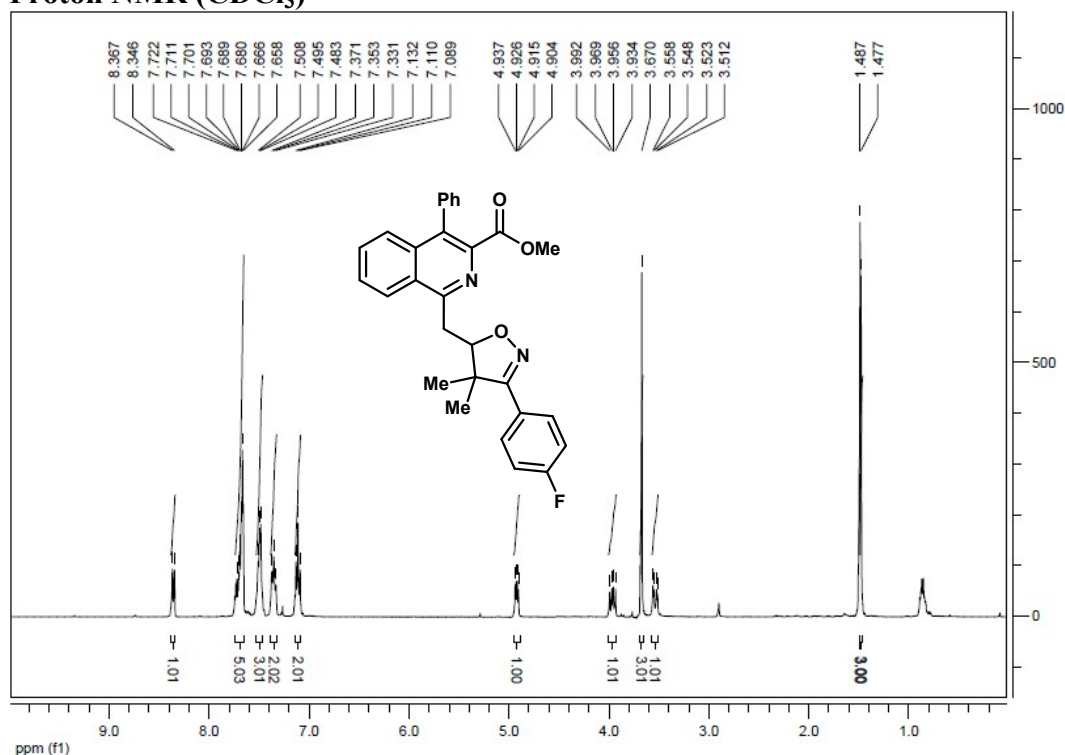
Methyl 1-((3-(4-methoxyphenyl)-4,4-dimethyl-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinoline-3-carboxylate (3c)
Proton NMR (CDCl₃)



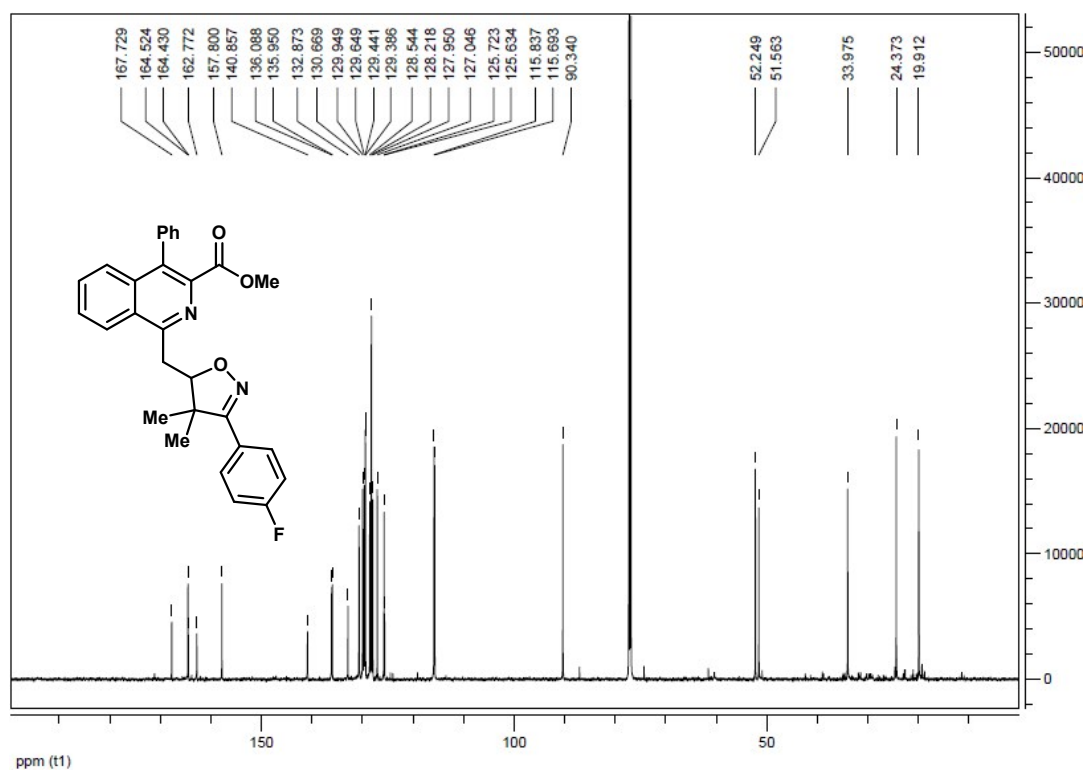
Carbon NMR (CDCl₃)



Methyl 1-((3-(4-fluorophenyl)-4,4-dimethyl-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinoline-3-carboxylate (3d)
Proton NMR (CDCl₃)

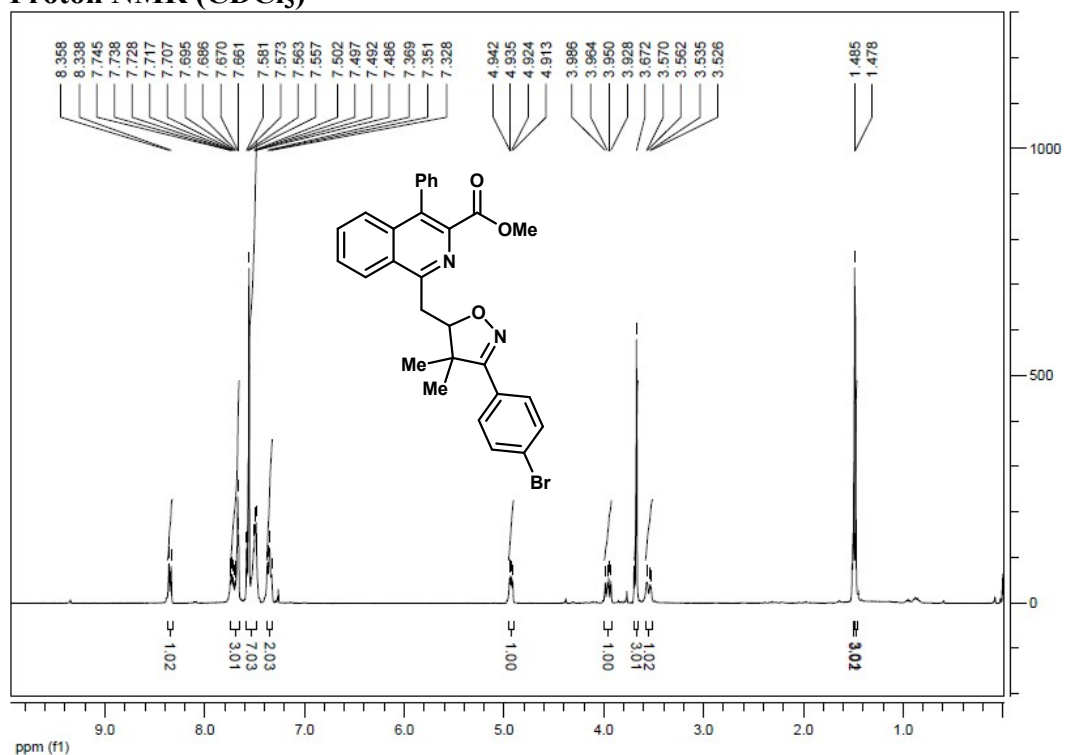


Carbon NMR (CDCl₃)

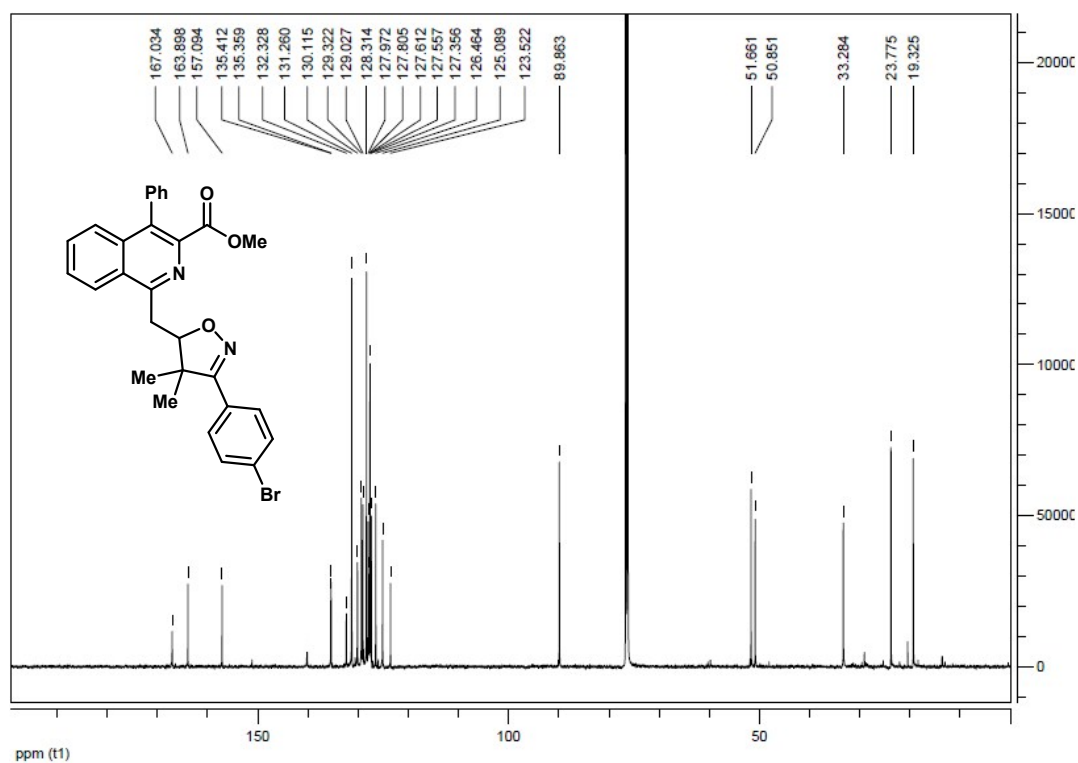




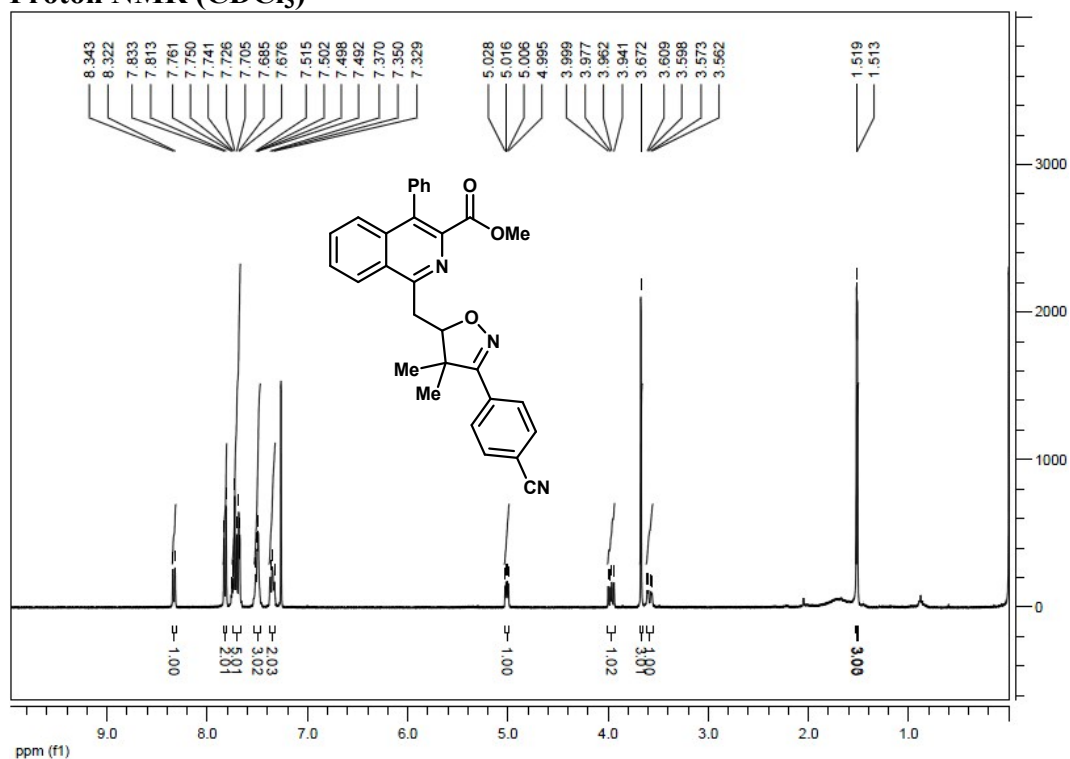
Methyl 1-((3-(4-bromophenyl)-4,4-dimethyl-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinoline-3-carboxylate (3f)
Proton NMR (CDCl₃)



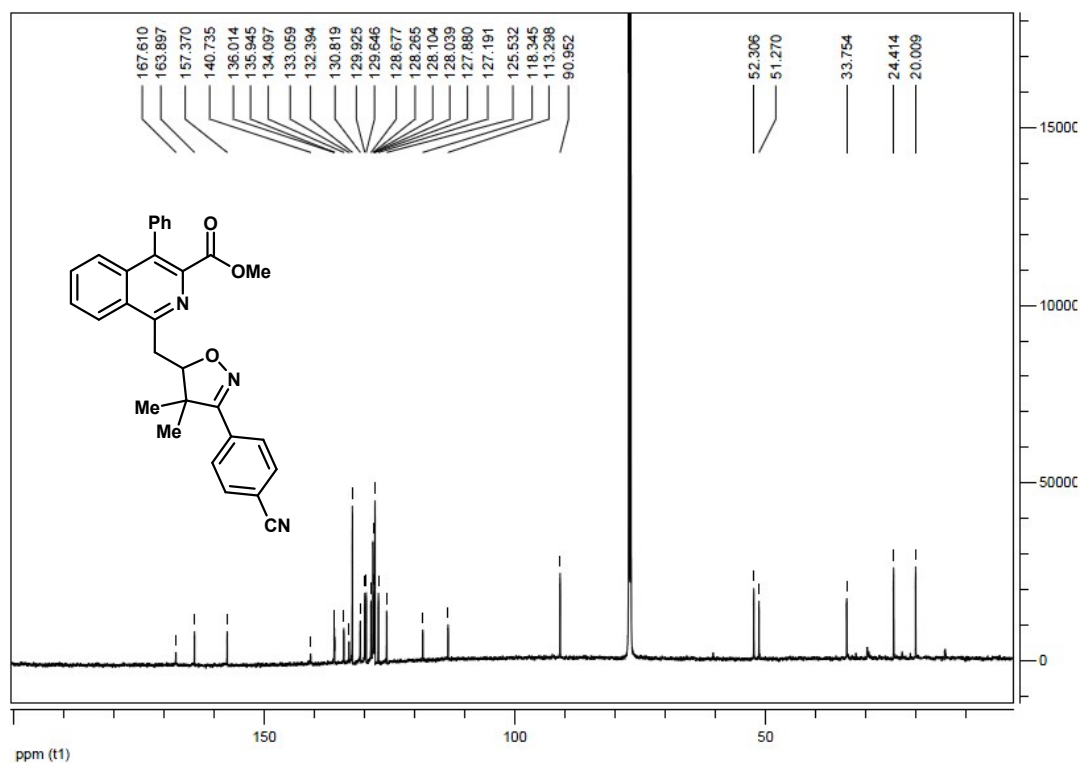
Carbon NMR (CDCl₃)



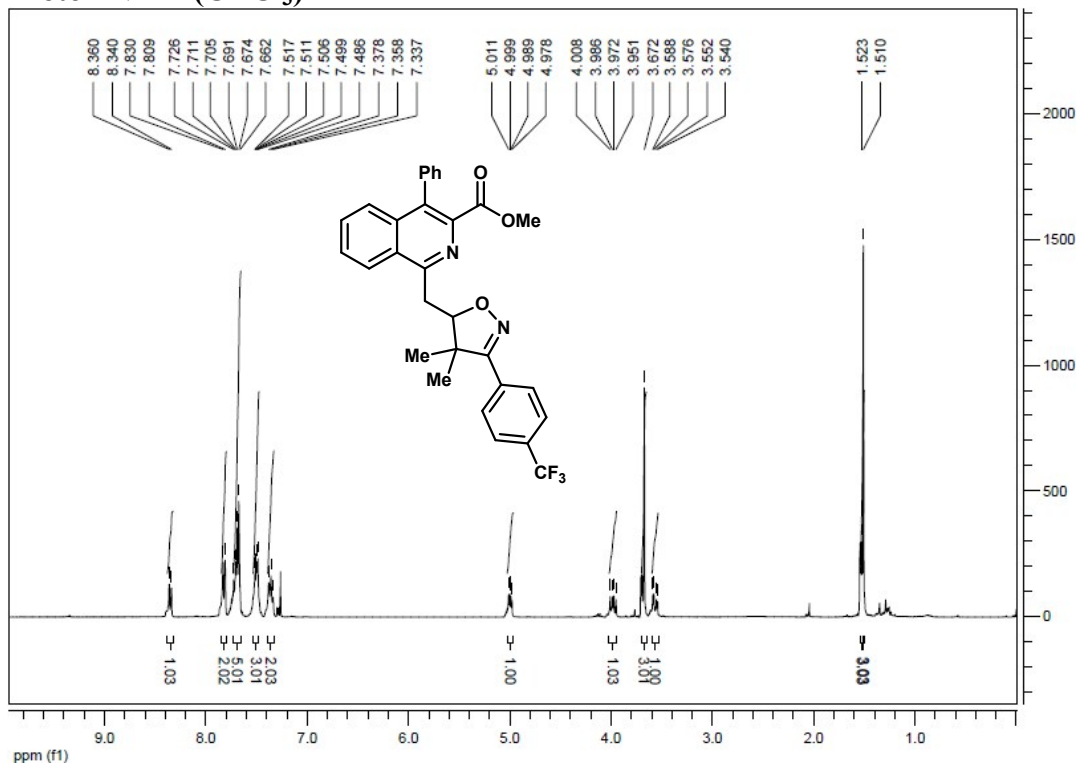
Methyl 1-((3-(4-cyanophenyl)-4,4-dimethyl-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinoline-3-carboxylate (3g)
Proton NMR (CDCl₃)



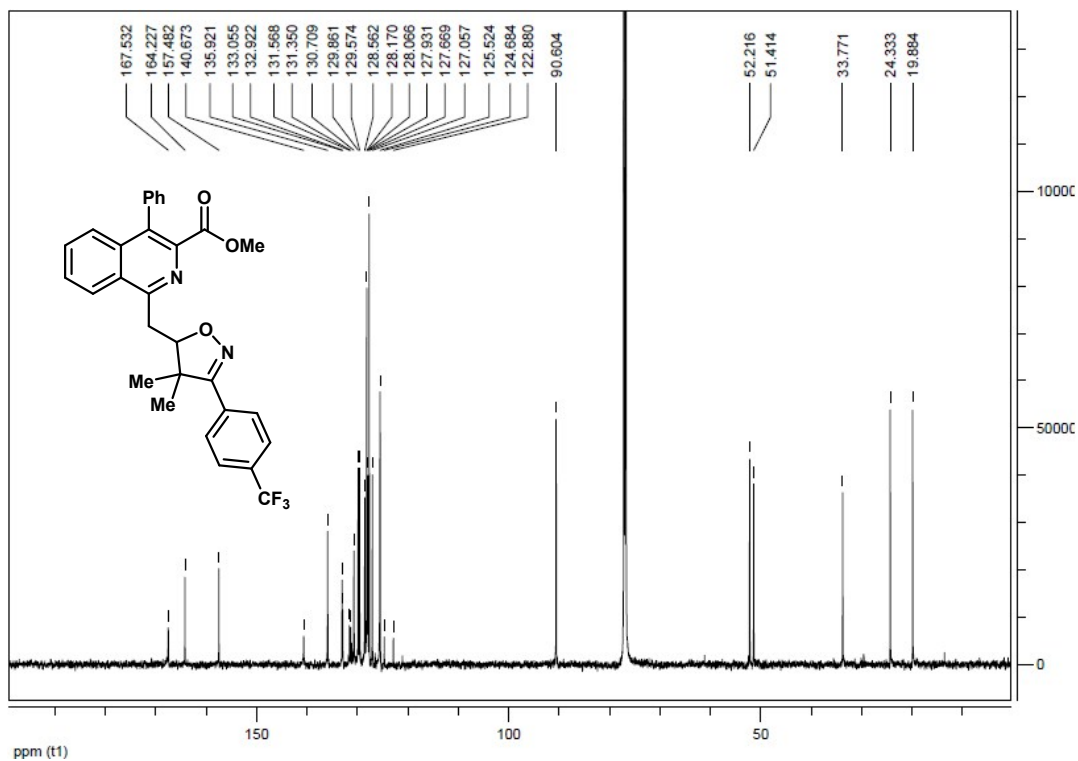
Carbon NMR (CDCl₃)



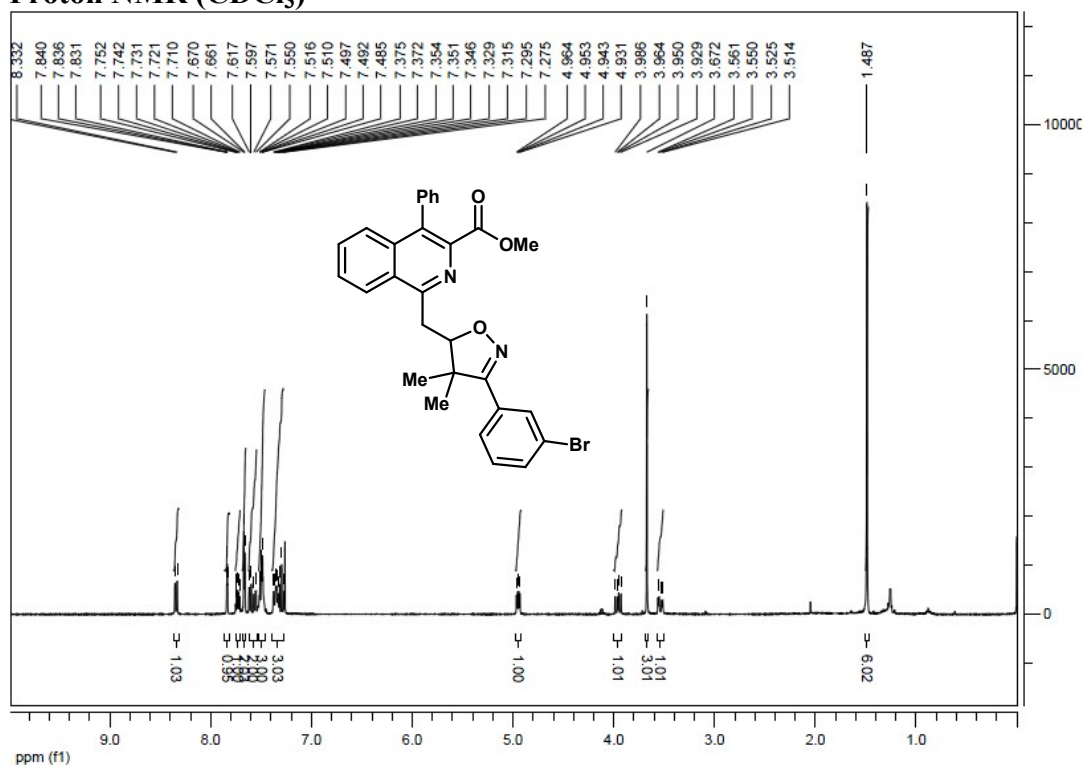
Methyl 1-((4,4-dimethyl-3-(4-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinoline-3-carboxylate (3h)
Proton NMR (CDCl₃)



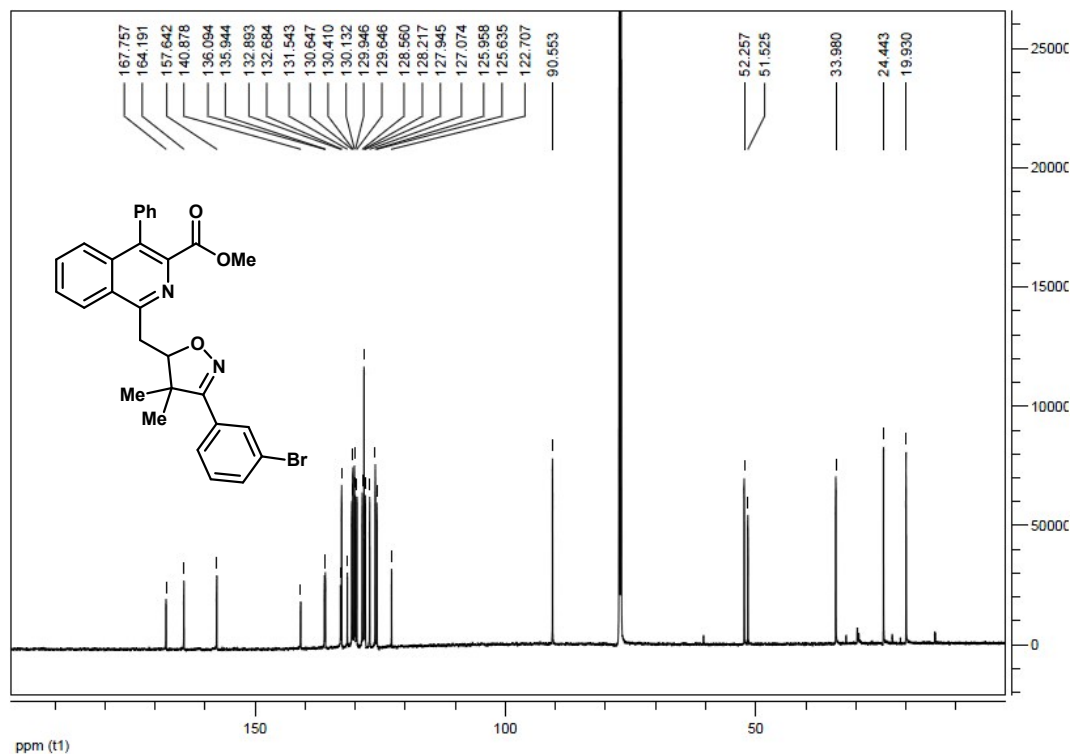
Carbon NMR (CDCl₃)



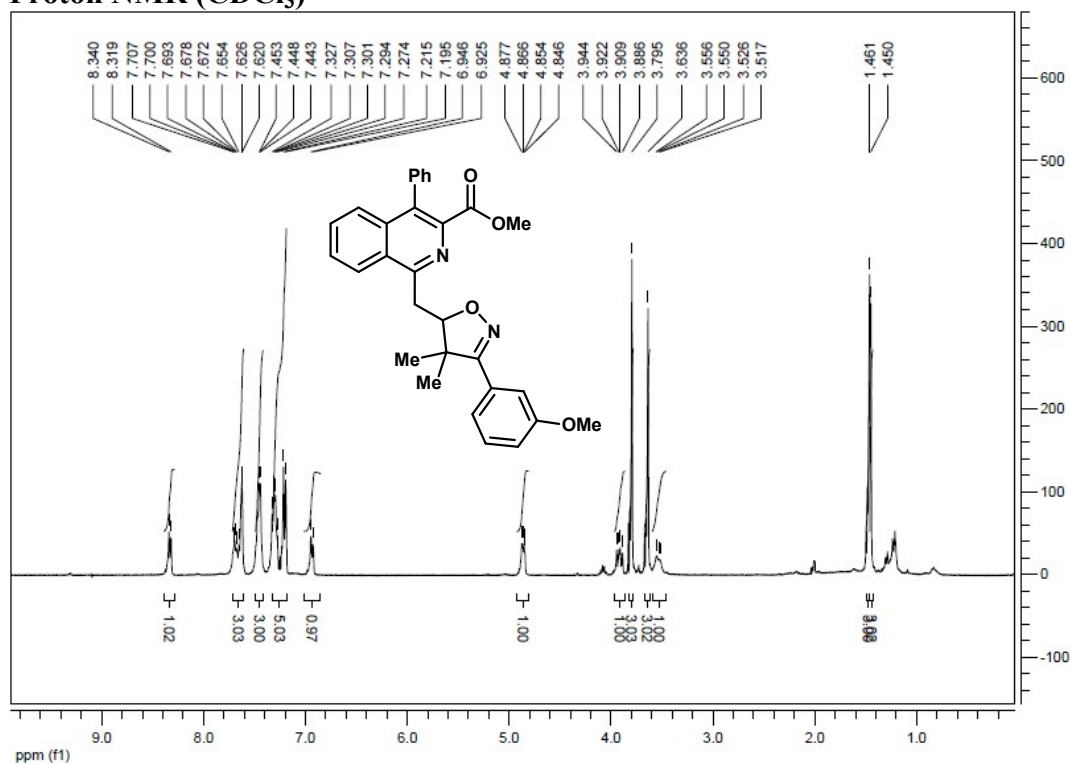
Methyl 1-((3-(3-bromophenyl)-4,4-dimethyl-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinoline-3-carboxylate (3i)
Proton NMR (CDCl₃)



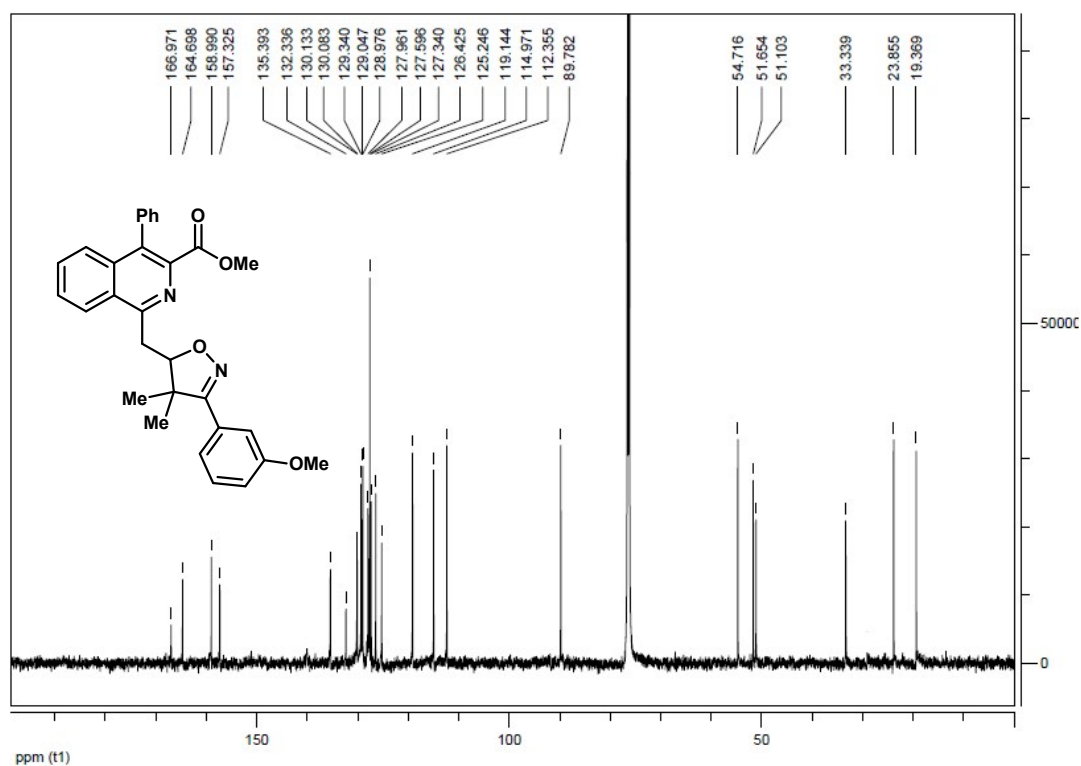
Carbon NMR (CDCl₃)



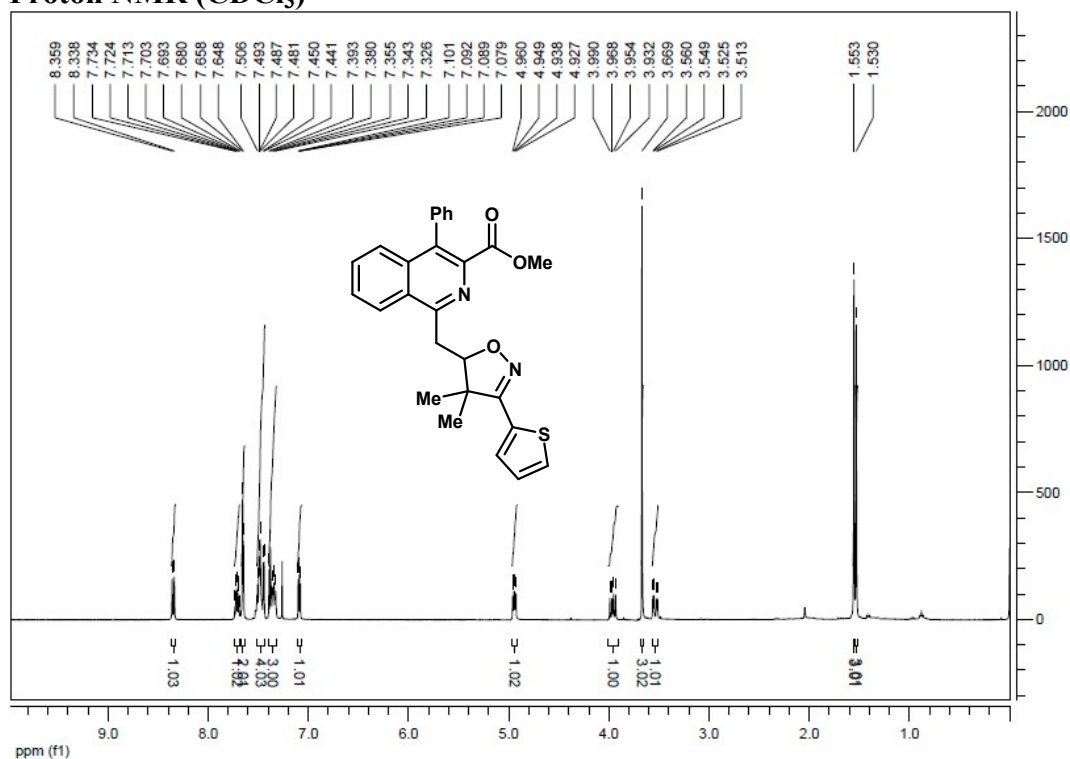
Methyl 1-((3-(3-methoxyphenyl)-4,4-dimethyl-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinoline-3-carboxylate (3j)
Proton NMR (CDCl₃)



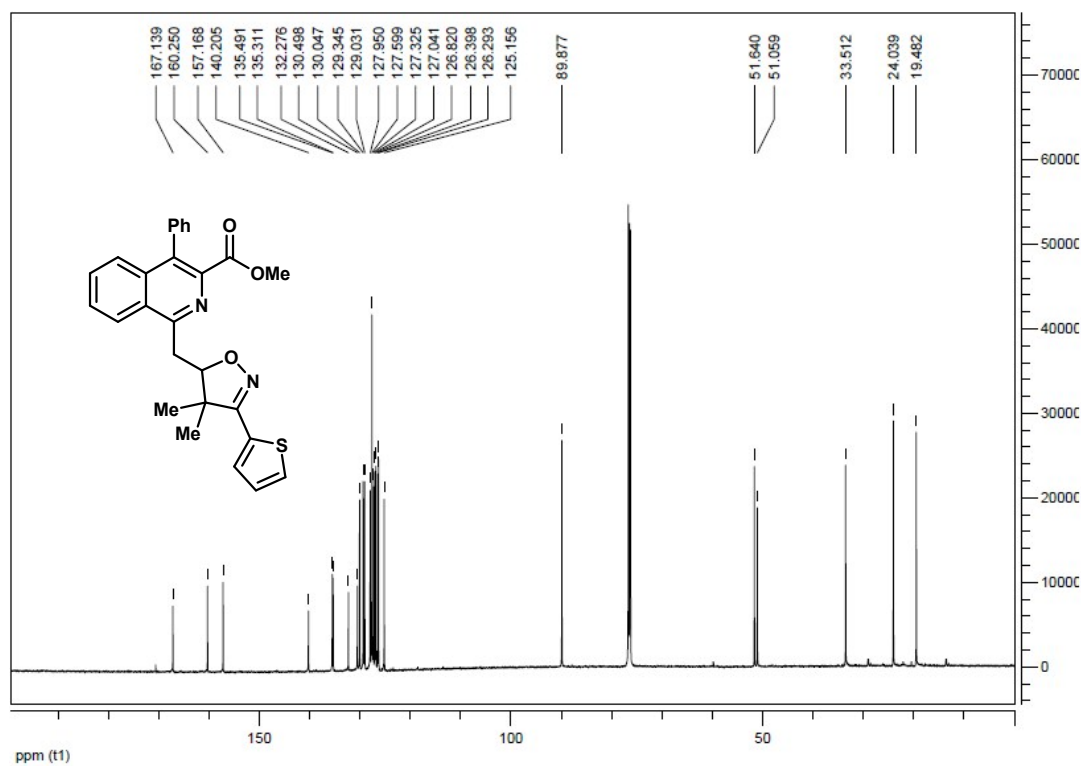
Carbon NMR (CDCl₃)



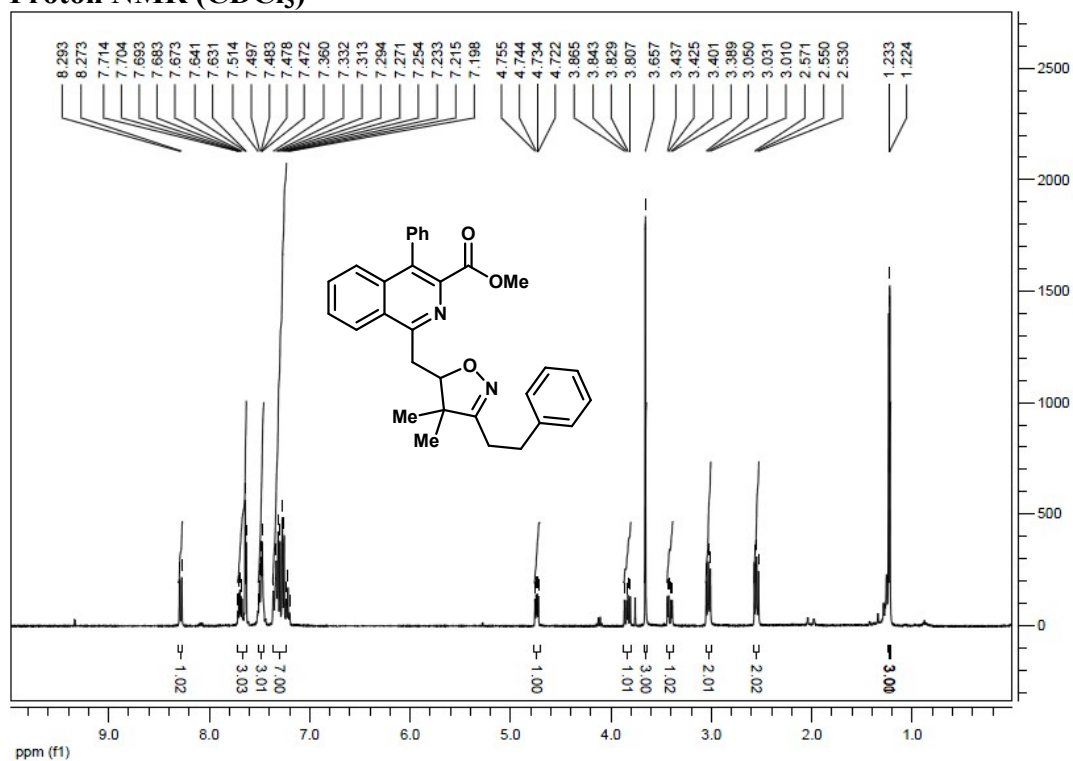
Methyl 1-((4,4-dimethyl-3-(thiophen-2-yl)-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinoline-3-carboxylate (3k)
Proton NMR (CDCl₃)



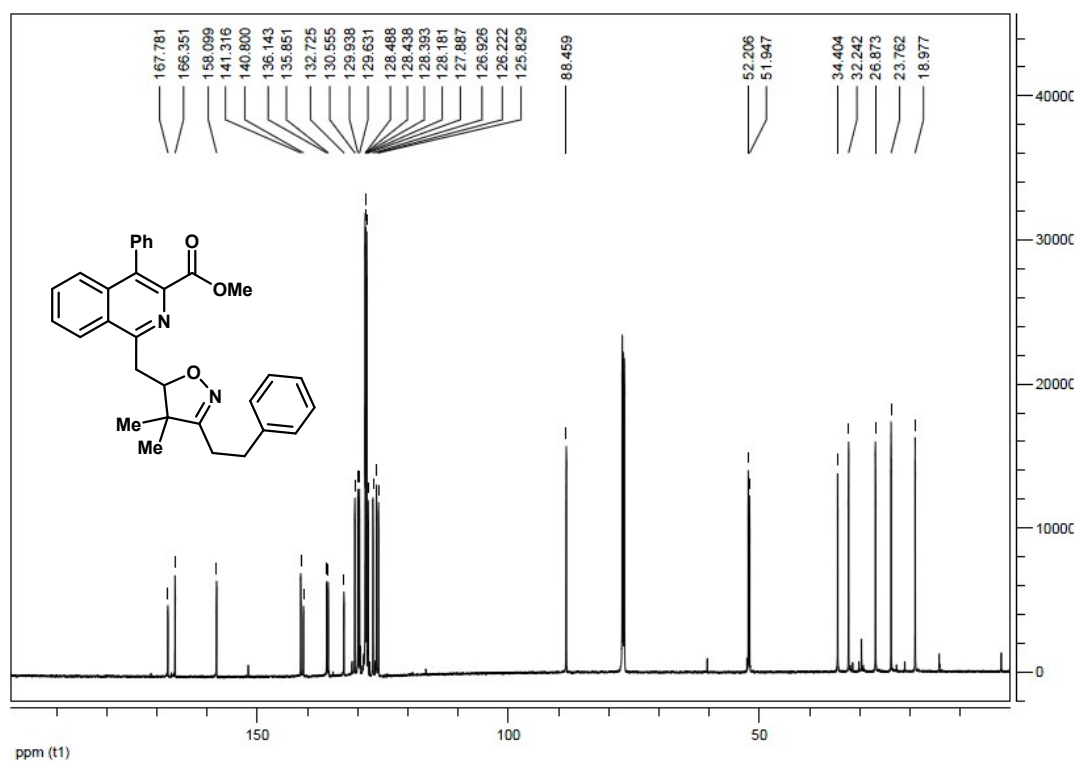
Carbon NMR (CDCl₃)



Methyl 1-((4,4-dimethyl-3-phenethyl-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinoline-3-carboxylate (3l)
Proton NMR (CDCl₃)



Carbon NMR (CDCl₃)



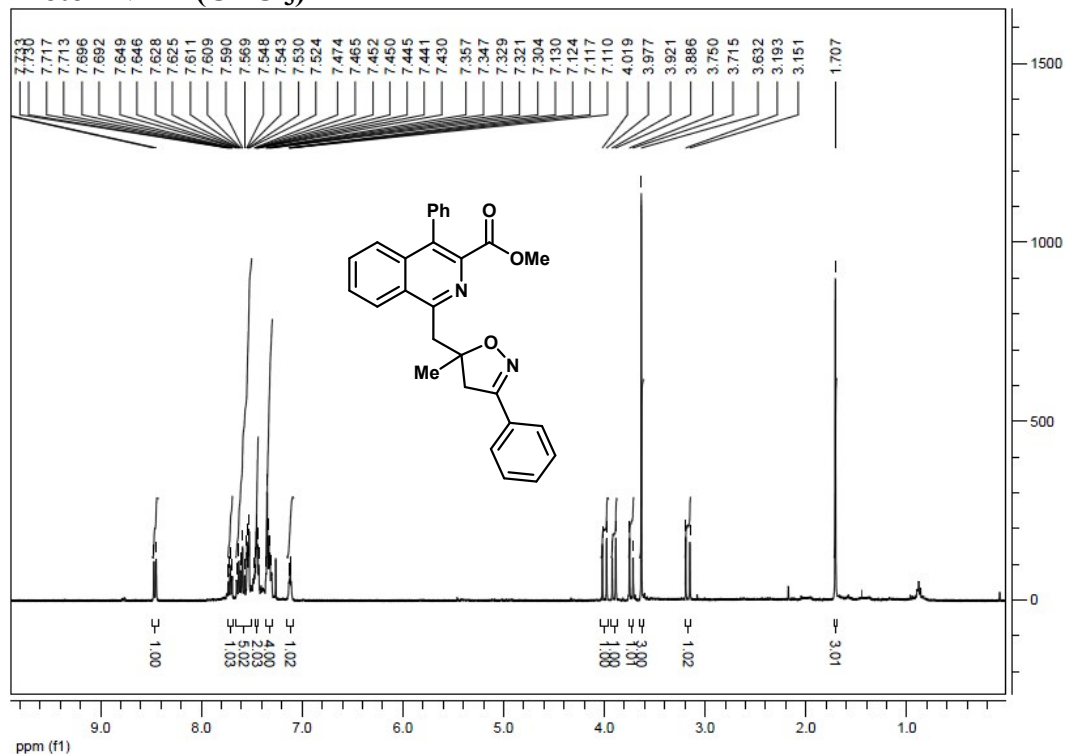
Chemical structure: COC(=O)c1nc(Cc2cc(C(=O)c3ccccc3)cc2)c4ccccc14

¹H NMR spectrum (ppm):

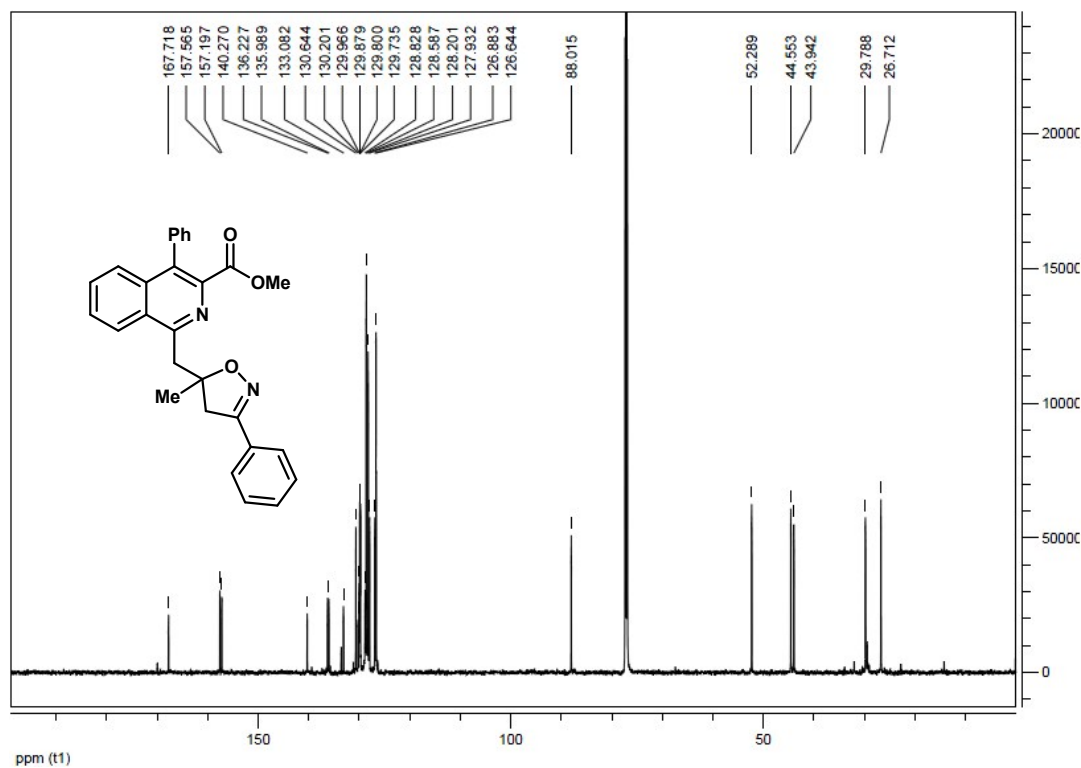
Chemical Shift (ppm)	Integration
8.391	
7.817	
7.799	
7.781	
7.769	
7.748	
7.731	
7.702	
7.696	
7.688	
7.677	
7.531	
7.522	
7.516	
7.507	
7.497	
7.488	
7.419	
7.414	
7.406	
7.402	
7.369	
7.364	
7.360	
7.349	
7.344	
7.287	
7.278	
7.274	
5.555	
5.537	
5.521	
5.513	
5.497	
5.481	
4.070	
4.055	
4.035	
4.019	
3.734	
3.705	
3.679	
3.662	
3.637	
3.504	
3.486	
3.461	
3.444	

Chemical structure of compound 10 is shown in the top left. The spectrum displays peaks corresponding to the structure, with the following chemical shifts (ppm) labeled: 157.402, 157.348, 136.360, 131.990, 130.186, 129.762, 129.625, 129.468, 129.393, 128.718, 128.359, 128.144, 127.265, 126.840, 126.352, 80.763, 52.680, 40.518, and 38.879.

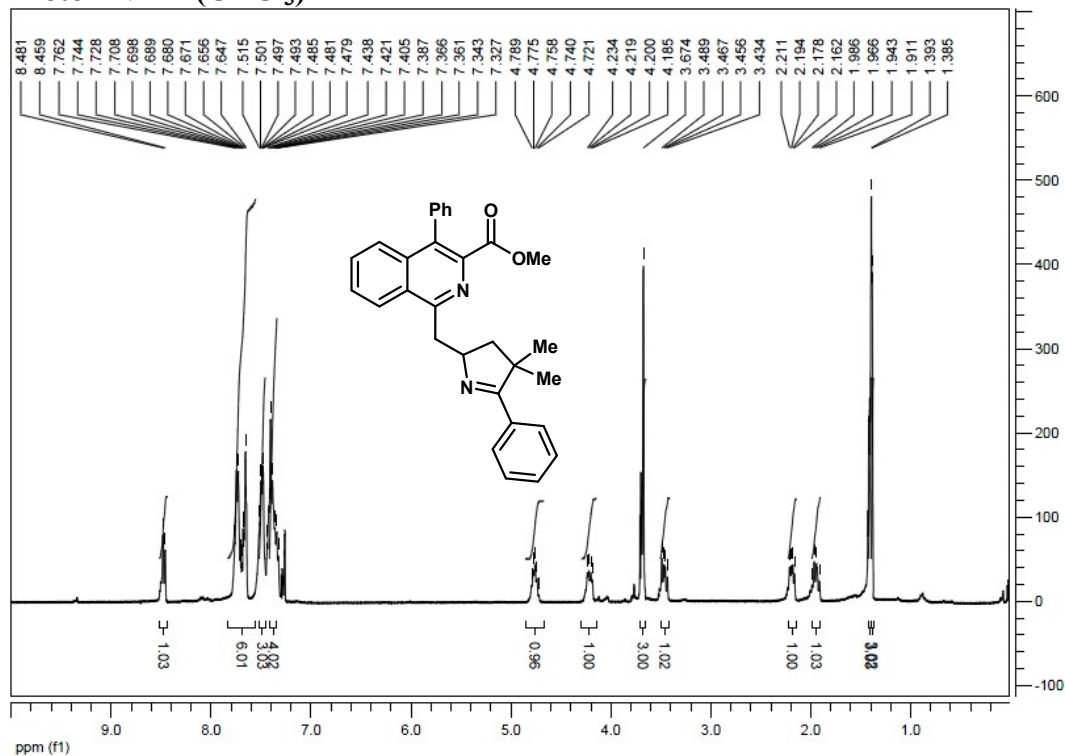
Methyl 1-((5-methyl-3-phenyl-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinoline-3-carboxylate (3n)
Proton NMR (CDCl₃)



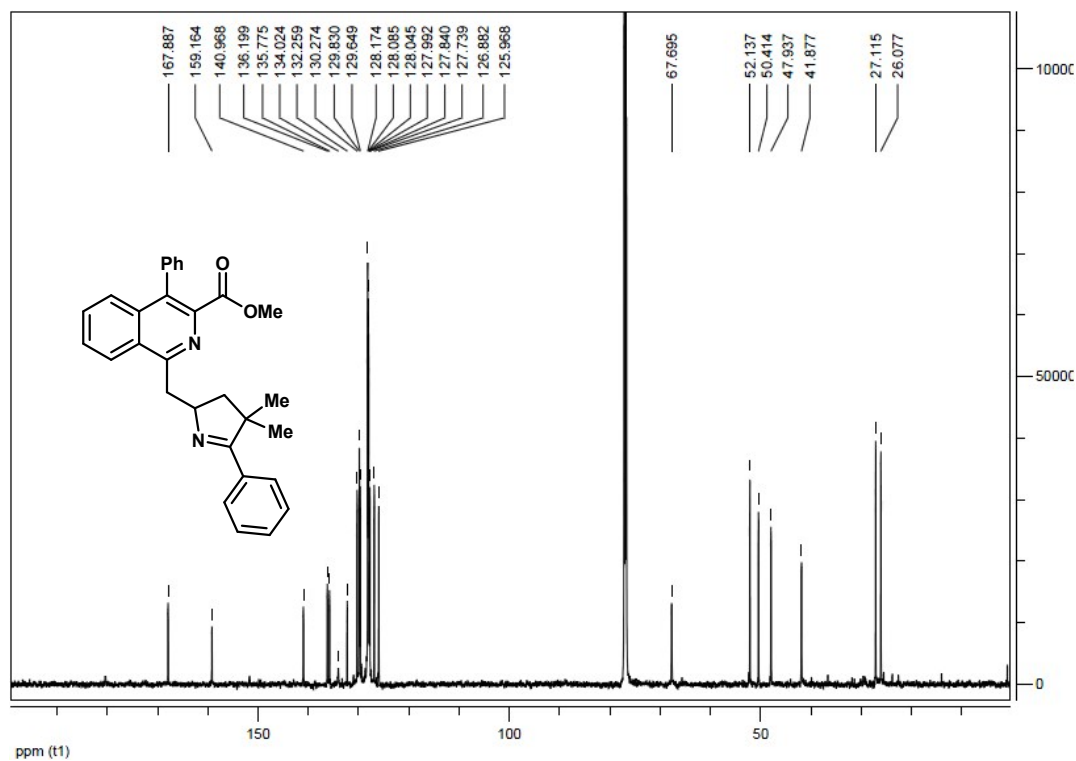
Carbon NMR (CDCl₃)



Methyl 1-((4,4-dimethyl-5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)-4-phenylisoquinoline-3-carboxylate (3o)
Proton NMR (CDCl₃)



Carbon NMR (CDCl₃)



Proton NMR (CDCl₃)



Chemical structure of compound 10 is shown above the spectrum. The structure is a quinoline derivative with a 4-methoxyphenyl group at position 2, a methoxycarbonyl group at position 3, and a 2-methyl-2-phenyl-1,3-oxazolidin-5-ylmethyl group at position 4.

¹H NMR spectrum (CDCl₃) of compound 10. The x-axis represents chemical shift in ppm (f1) from 0 to 10. The y-axis represents intensity. The spectrum shows several peaks corresponding to the structure, with integration values provided below the peaks.

Chemical shift values (ppm) labeled above the peaks:

- 7.683, 7.672, 7.666, 7.615, 7.592, 7.575, 7.435, 7.423, 7.317, 7.293, 7.249, 7.231, 7.042, 7.026, 7.010
- 4.928, 4.917, 4.908, 4.897, 4.025, 3.896, 3.874, 3.860, 3.838, 3.715, 3.564, 3.560, 3.532, 3.527
- 1.510, 1.495

Integration values (labeled below the peaks):

- 2.01, 1.89, 1.31, 2.68
- 1.00
- 1.03, 3.02, 4.03, 3.01
- 3.03

Chemical structure of compound 10 is shown. The ¹³C NMR spectrum (ppm (t1)) is displayed below the structure, with peaks labeled with their chemical shifts (ppm):

165.436, 159.287, 159.197, 155.714, 132.954, 131.532, 130.925, 130.653, 129.865, 129.734, 129.615, 129.419, 128.665, 128.528, 128.217, 127.324, 123.098, 113.603, 113.565, 103.999, 90.214, 55.548, 55.171, 52.160, 51.724, 34.250, 24.460, 19.759.

Chemical structure of compound 10 is shown above the spectrum. The structure is a 6-fluoro-2-(4-fluorophenyl)-3-((2-methyl-2-phenyl-1,3-oxazol-5-yl)methyl)quinoline-4-carboxylate.

¹H NMR spectrum (CDCl₃) showing peaks (ppm) and integration values:

Peak (ppm)	Integration
7.976, 7.971, 7.952, 7.946, 7.689, 7.684, 7.676, 7.665, 7.649, 7.635, 7.626, 7.612, 7.459, 7.453, 7.429, 7.424, 7.415, 7.411, 7.401, 7.332, 7.318, 7.310, 7.297, 7.288, 7.274, 7.227, 7.209, 7.188, 7.171, 4.881, 4.872, 4.858, 4.849, 3.855, 3.831, 3.819, 3.796, 3.698, 3.471, 3.462, 3.436, 3.426	1.00, 1.00, 2.02, 2.02, 2.02, 3.01, 1.00, 1.00, 1.02, 1.02, 3.02

Chemical structure of compound 10 is shown in the top left corner of the spectrum. The structure is a quinoline derivative with a 6-fluoro group, a 2-(2-methyl-2-phenyl-1,3-oxazolidin-5-yl) group, and a 3-methoxycarbonyl group.

The ^{13}C NMR spectrum (ppm (t1)) shows the following chemical shifts (ppm) for the peaks:

- 166.813
- 164.761
- 162.634
- 161.976
- 161.193
- 160.307
- 157.051
- 157.018
- 140.026
- 132.474
- 131.174
- 131.117
- 131.046
- 130.994
- 130.695
- 130.642
- 129.179
- 129.119
- 128.978
- 128.921
- 128.736
- 128.036
- 126.845
- 120.589
- 120.423
- 114.939
- 114.890
- 114.795
- 114.747
- 109.331
- 109.186
- 89.605
- 51.764
- 51.103
- 33.541
- 23.824
- 19.280

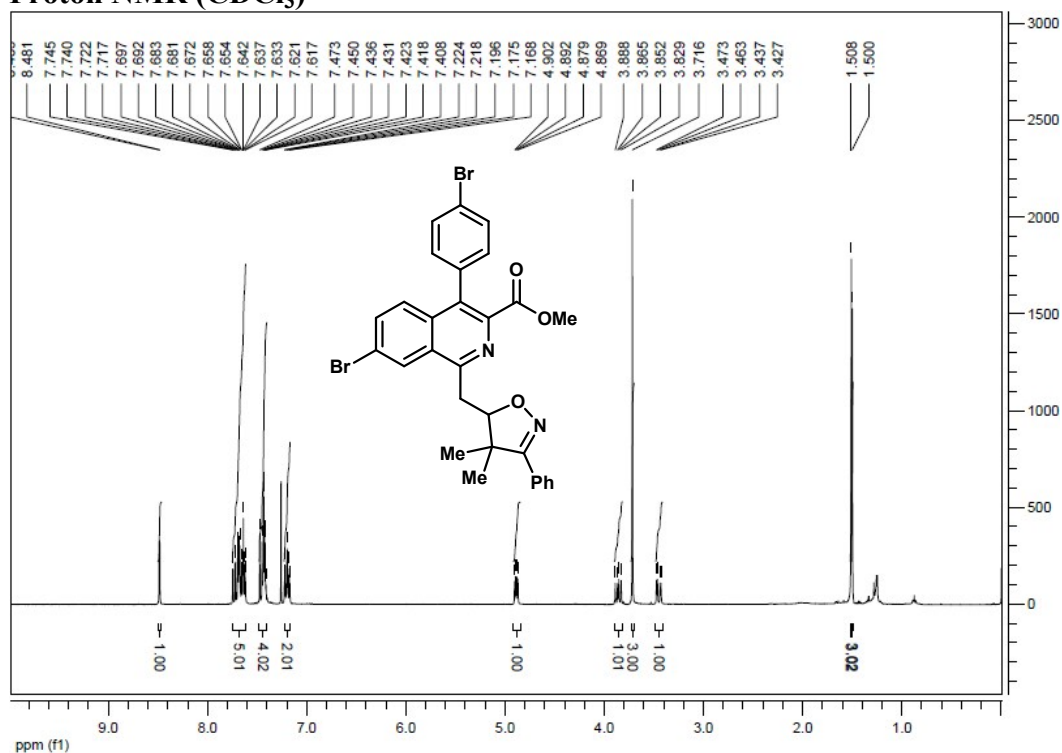
Proton NMR (CDCl₃)



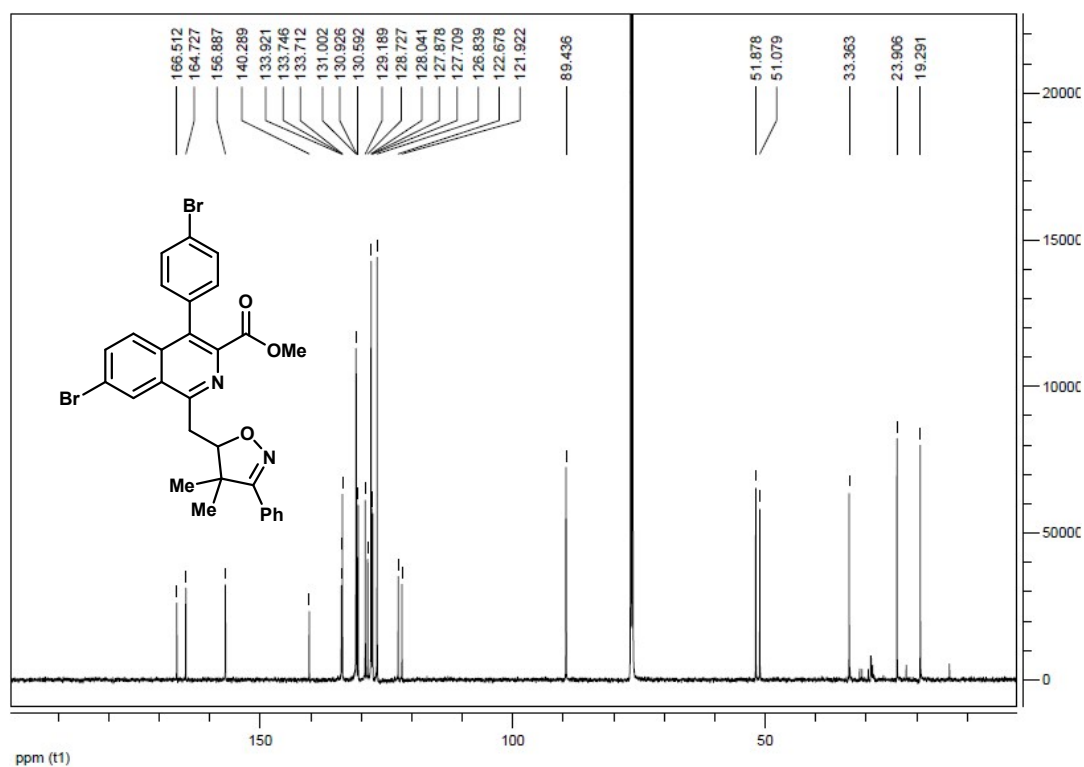
Carbon NMR (CDCl₃)



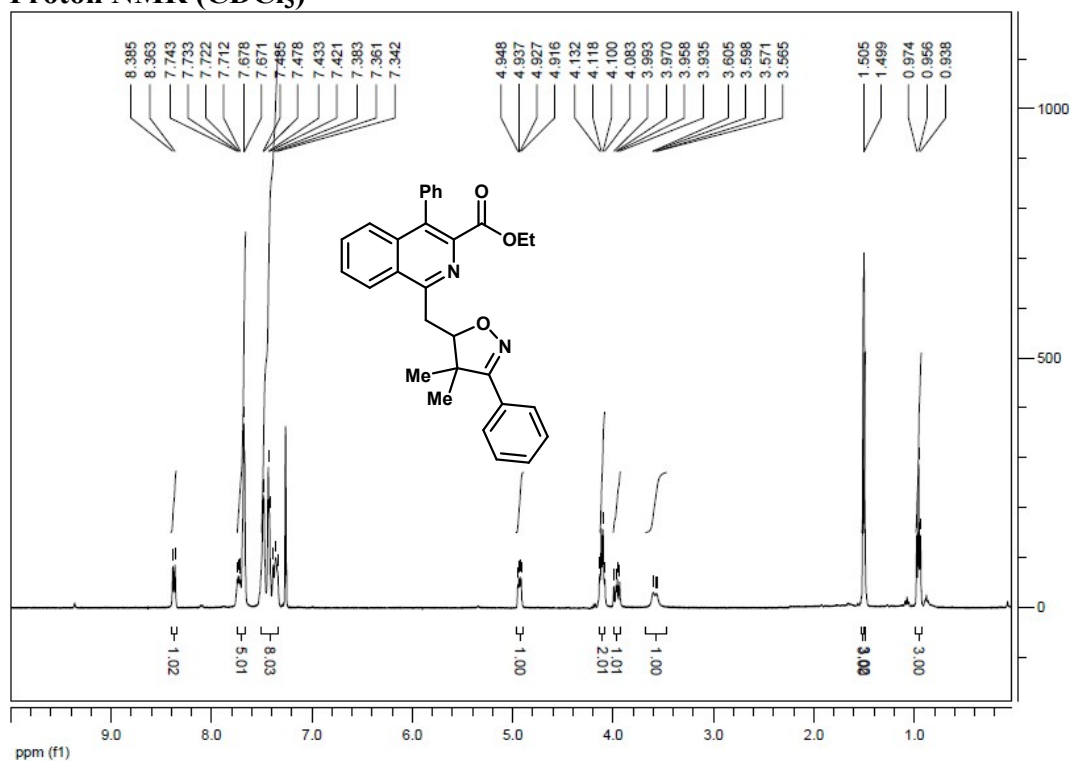
Methyl 7-bromo-4-(4-bromophenyl)-1-((4,4-dimethyl-3-phenyl-4,5-dihydroisoxazol-5-yl)methyl)isoquinoline-3-carboxylate (4f)
Proton NMR (CDCl₃)



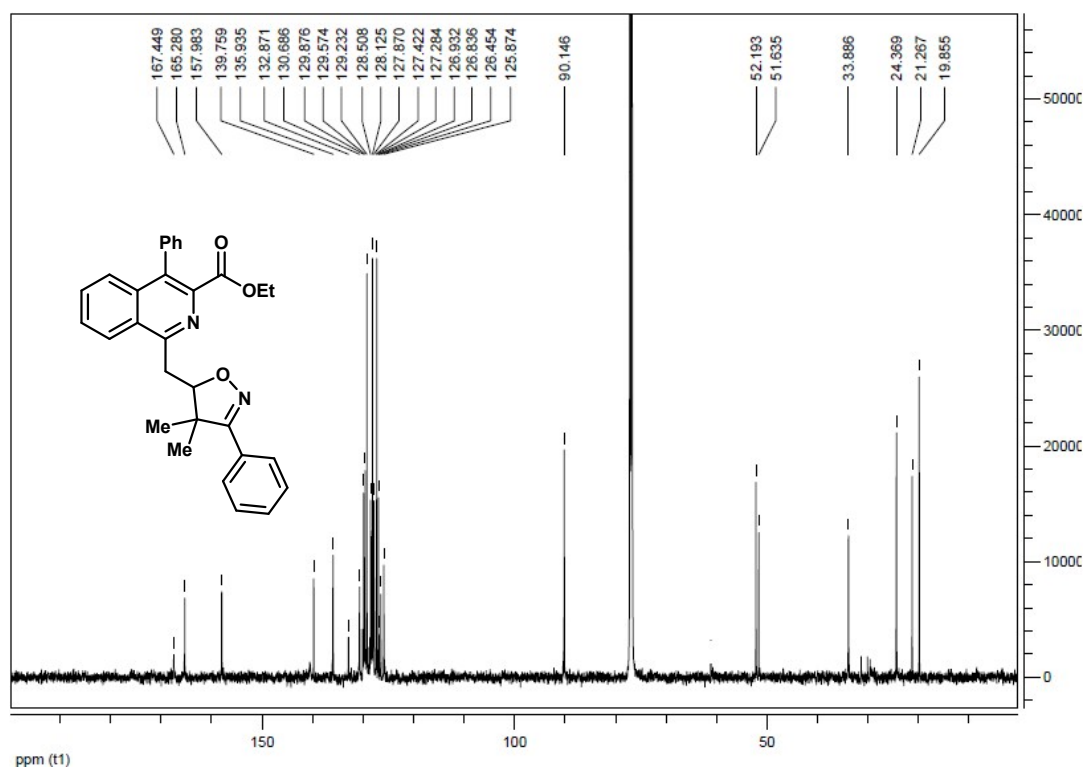
Carbon NMR (CDCl₃)



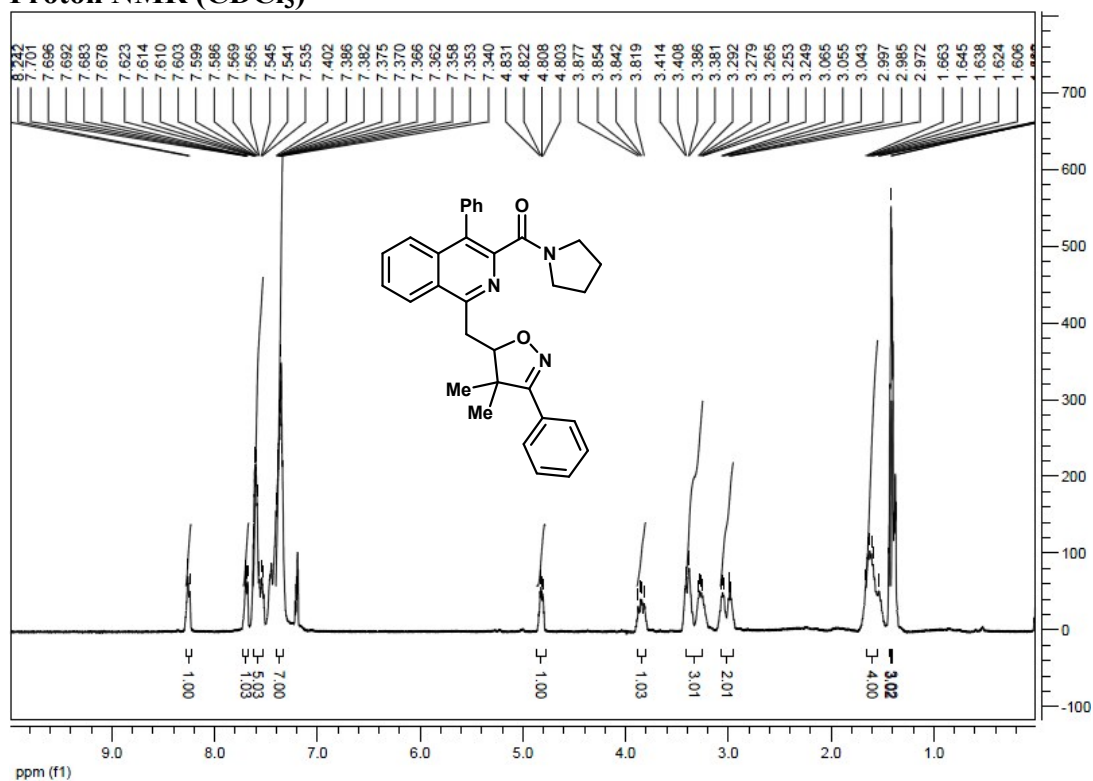
Ethyl 1-((4,4-dimethyl-3-phenyl-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinoline-3-carboxylate (4g)
Proton NMR (CDCl₃)



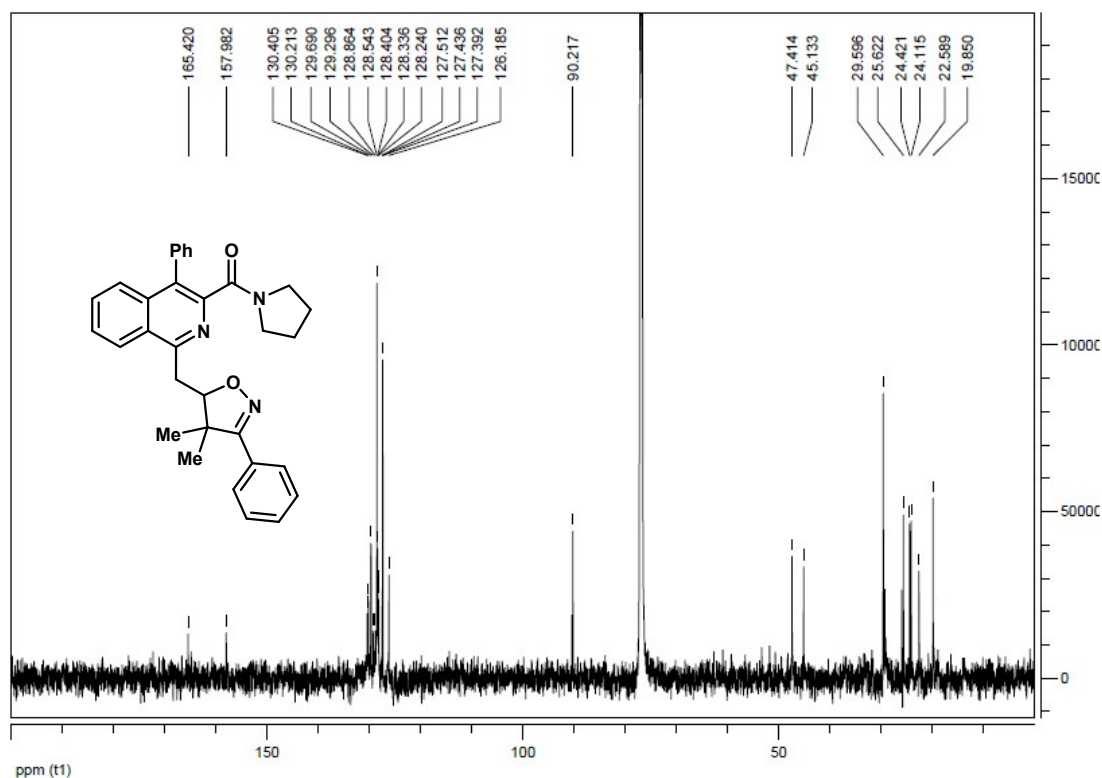
Carbon NMR (CDCl₃)



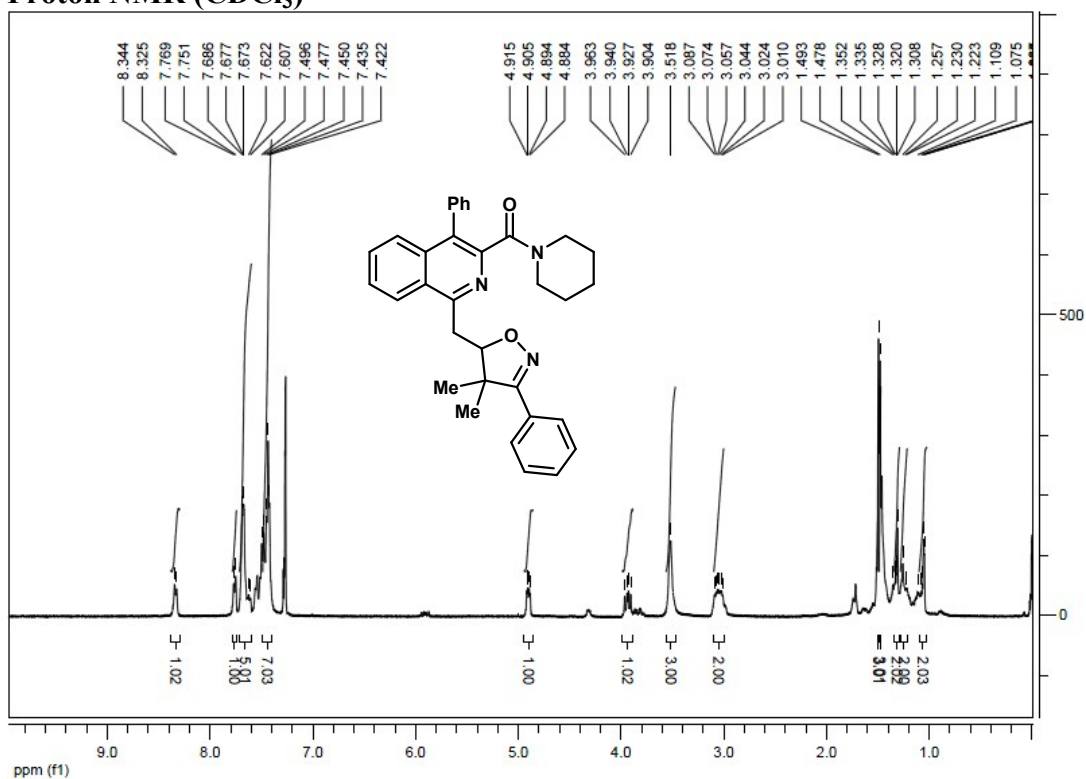
(1-((4,4-Dimethyl-3-phenyl-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinolin-3-yl)(pyrrolidin-1-yl)methanone (4h)
Proton NMR (CDCl₃)



Carbon NMR (CDCl₃)



(1-((4,4-dimethyl-3-phenyl-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinolin-3-yl)(piperidin-1-yl)methanone (4i)
Proton NMR (CDCl₃)



Carbon NMR (CDCl₃)

