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

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Supporting Information

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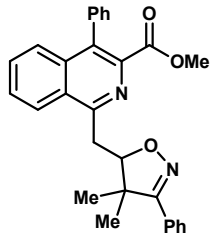
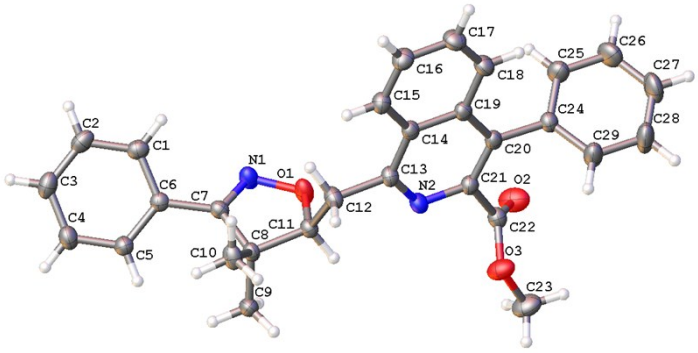
I. General information

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). ^{1}H and ^{13}C spectra were recorded on Varian 400 MHz and Bruker 600 MHz, respectively. Chemical shifts in ^{1}H 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



3a



Datablock:

Bond precision:	C-C = 0.0029 A		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	C29 H26 N2 O3		C29 H26 N2 O3
Sum formula	C29 H26 N2 O3		C29 H26 N2 O3
Mr	450.52		450.52
Dx,g cm-3	1.270		1.270
Z	8		8
Mu (mm-1)	0.659		0.659
F000	1904.0		1904.0
F000’	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

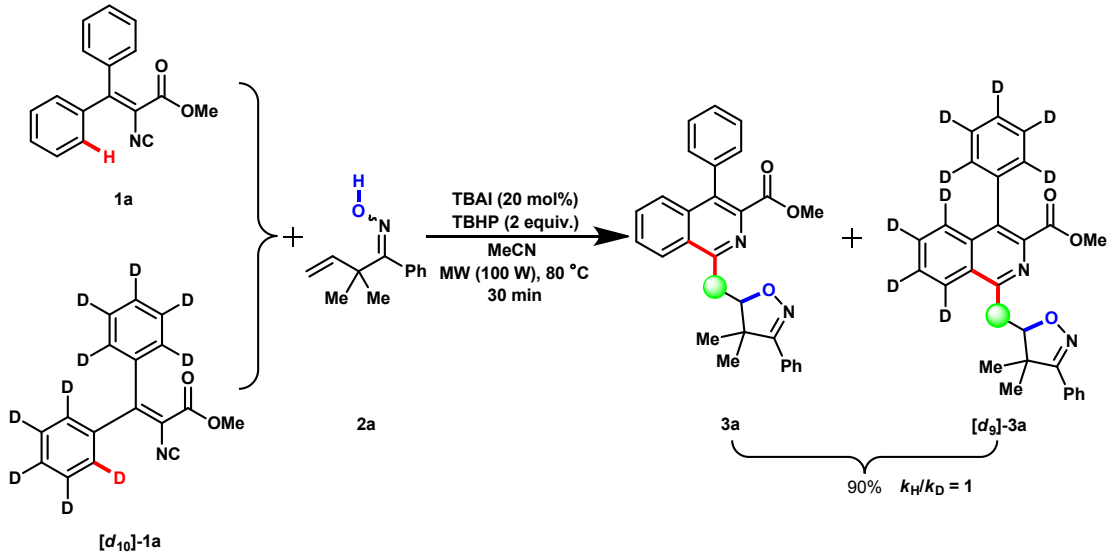
AbsCorr = MULTI-SCAN

Data completeness= 0.994 Theta(max)= 70.084

R(reflections)= 0.0510(3452) wR2(reflections)= 0.1408(4456)

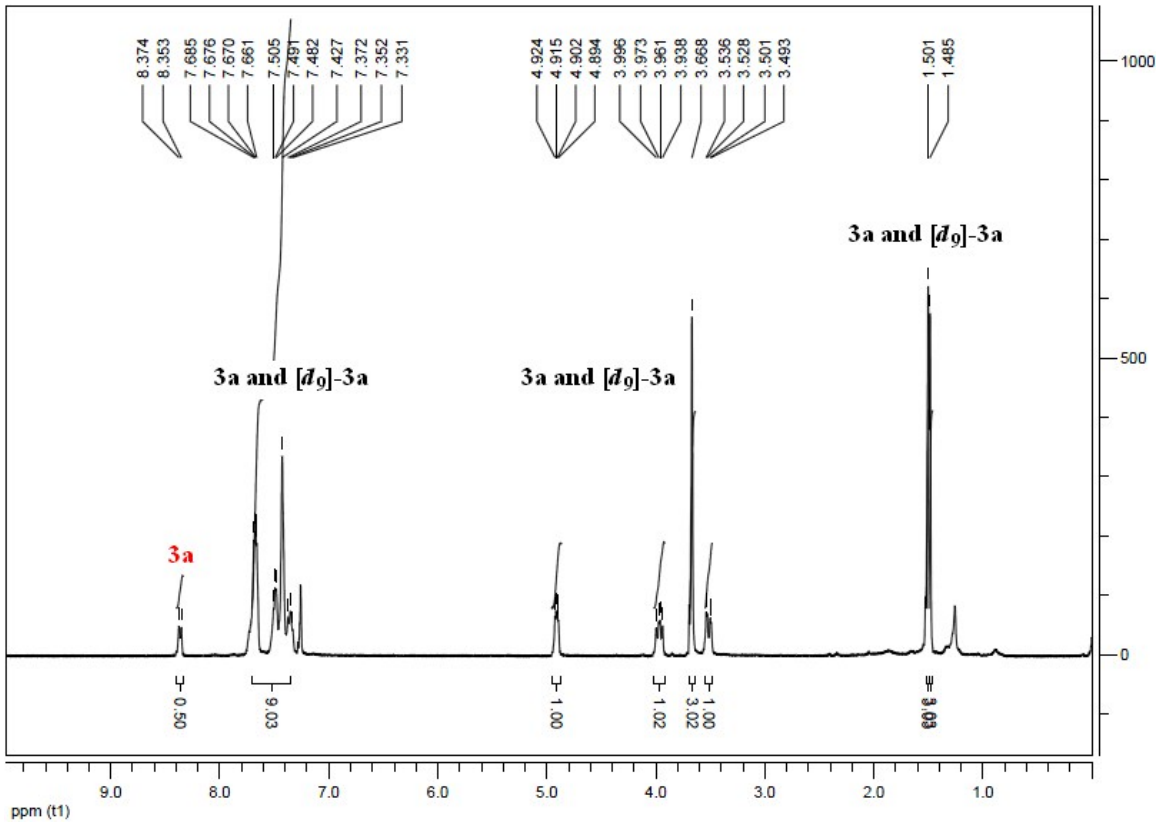
S = 1.021 Npar= 310

III. Intermolecular competing kinetic isotope effect (KIE) experiment

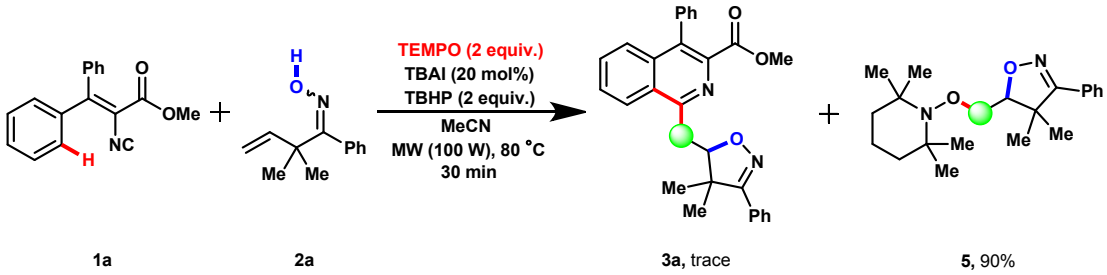


k_H/k_D = 0.5/0.5 = 1/1. (The KIE was determined by ^{1}H NMR spectroscopy by analyzing the ratio of **3a** and **[d_9]-3a**).

Proton NMR ($CDCl_3$)



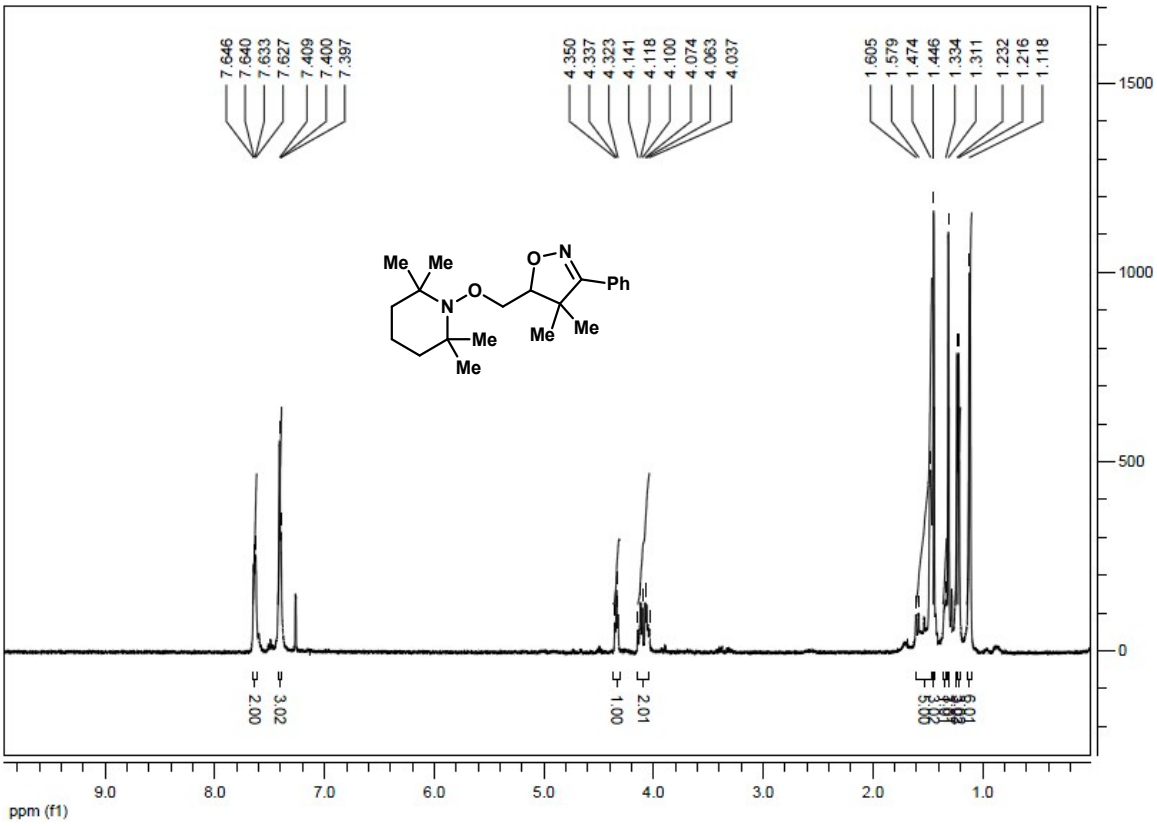
IV. Radical trapping experiment



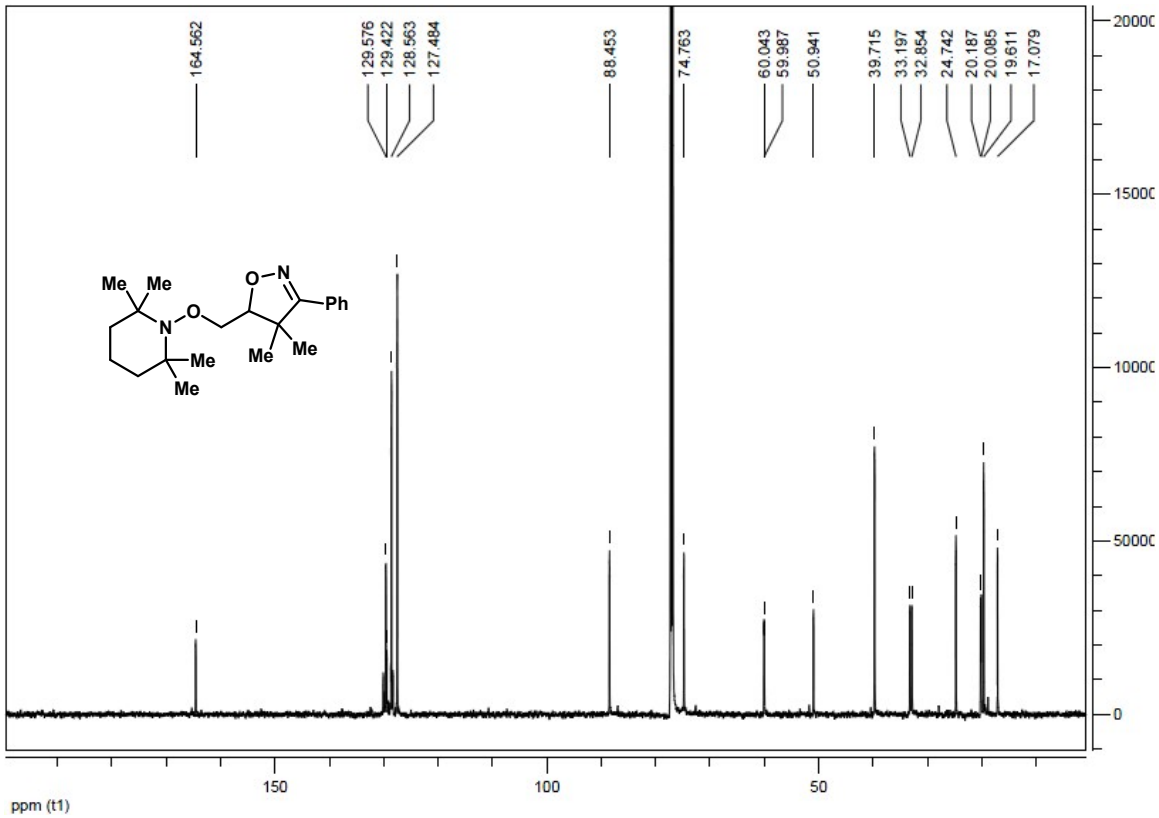
1a 2a **3a**, trace **5**, 90%

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

Proton NMR ($CDCl_3$)



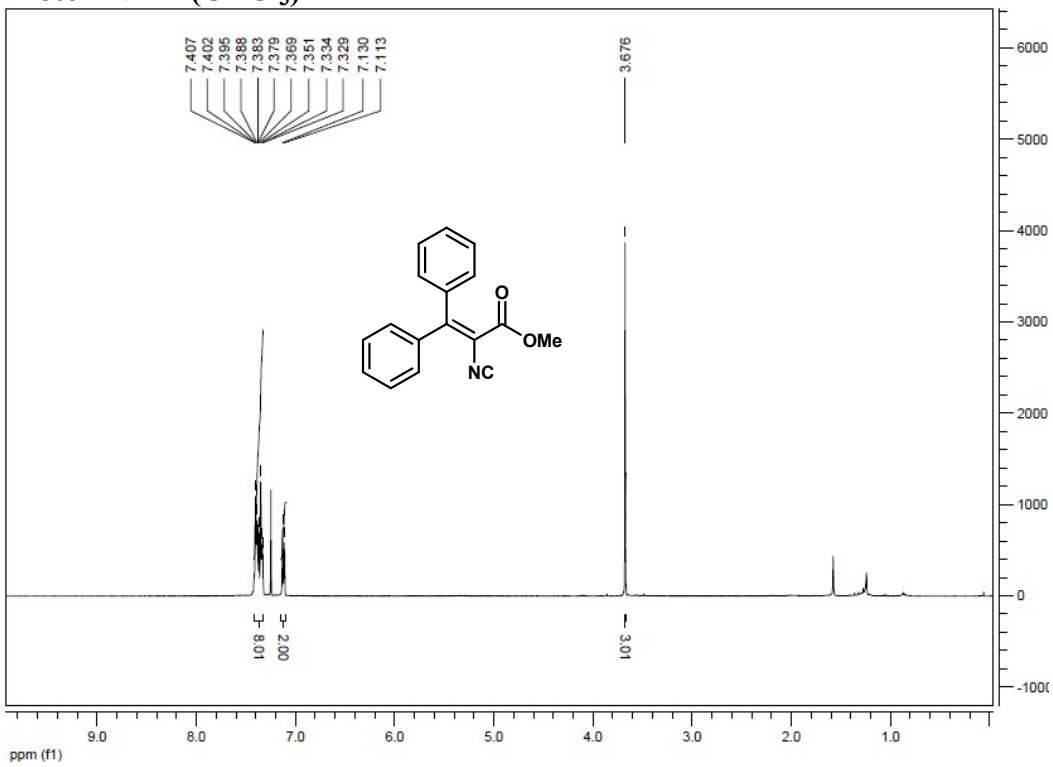
Carbon NMR ($CDCl_3$)



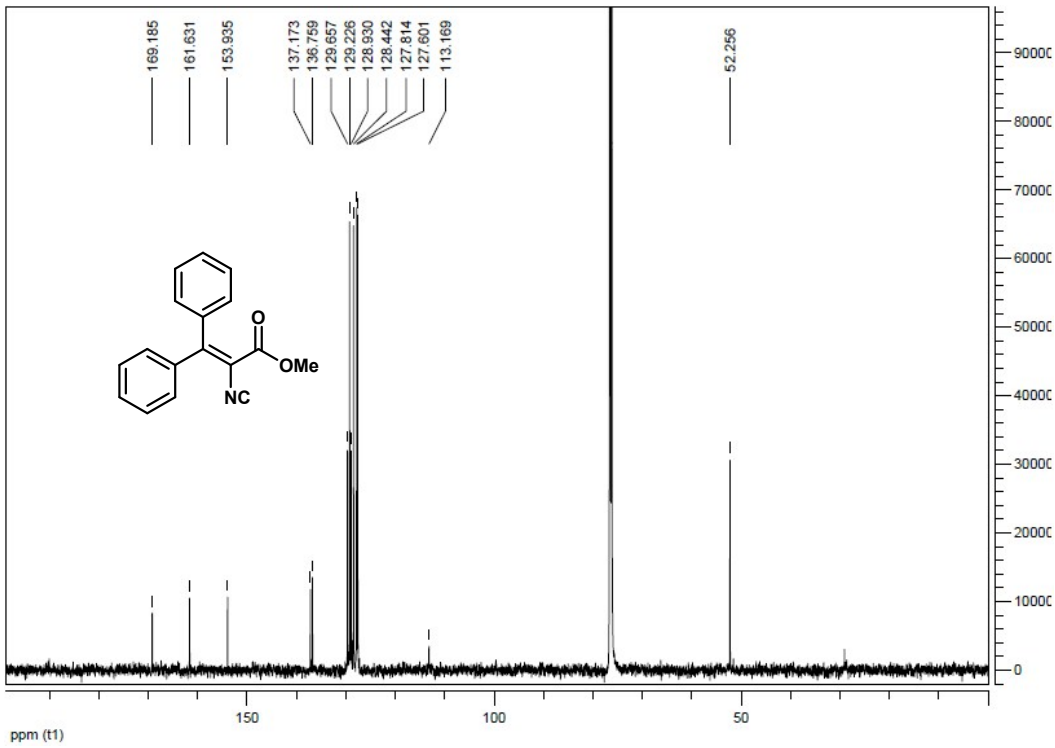
V. ^{1}H and ^{13}C NMR

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

Proton NMR ($CDCl_3$)

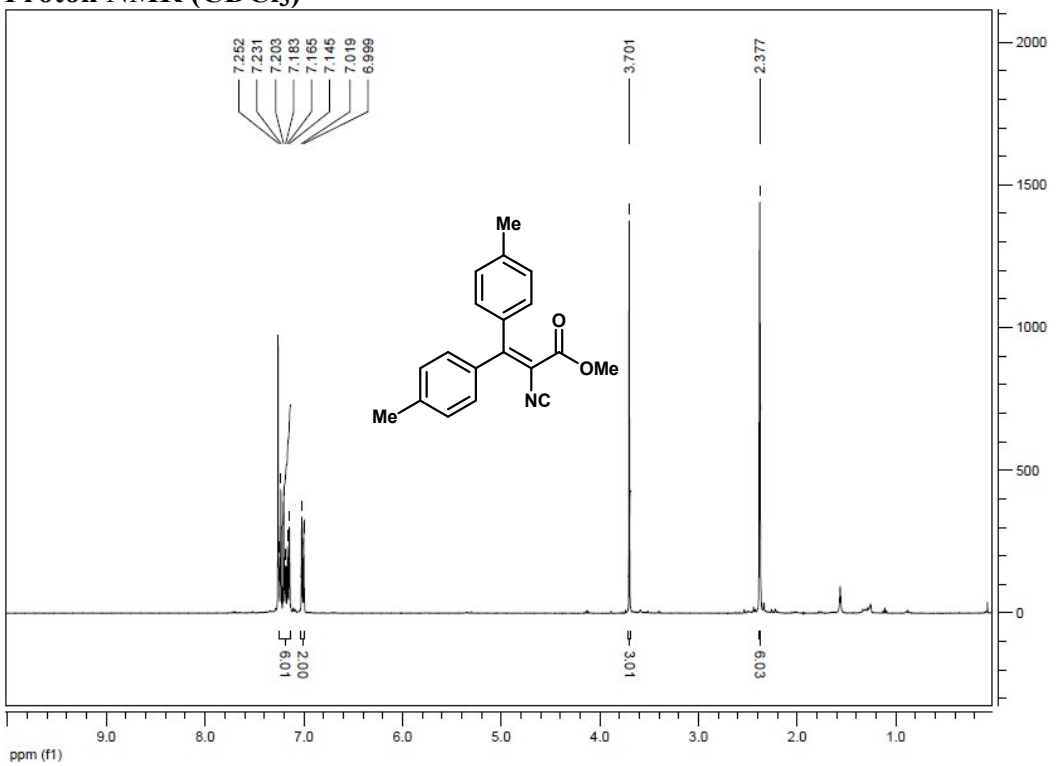


Carbon NMR ($CDCl_3$)

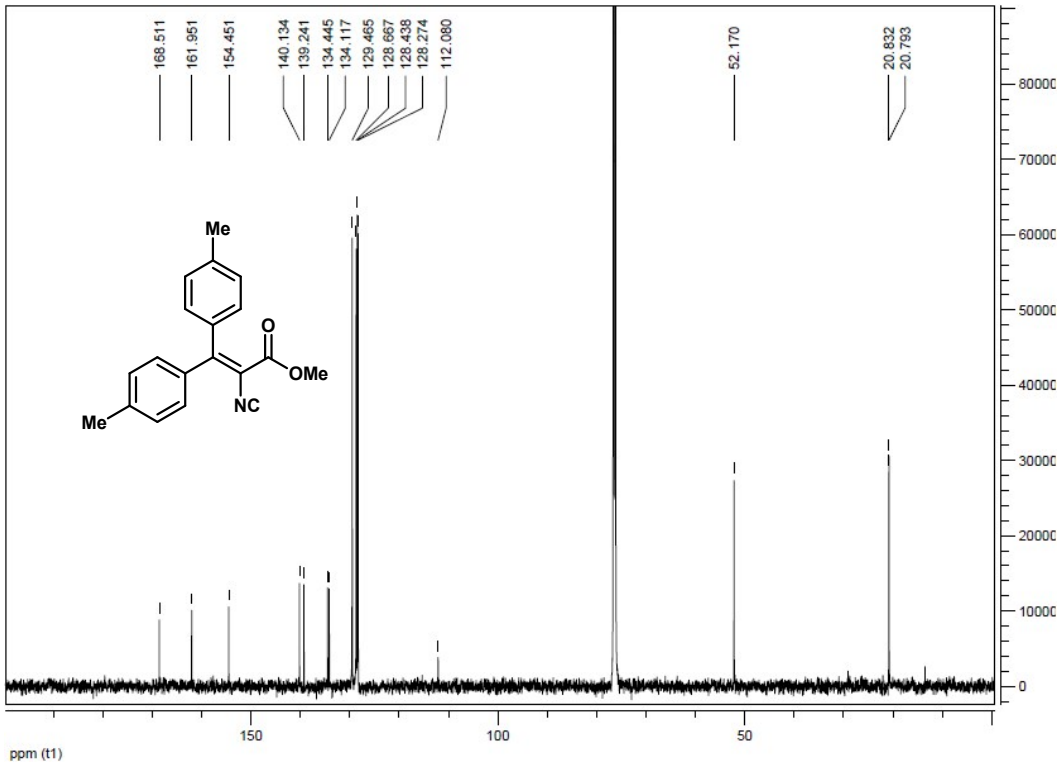


Methyl 2-isocyano-3,3-di-*p*-tolylacrylate (1b)

Proton NMR ($CDCl_3$)

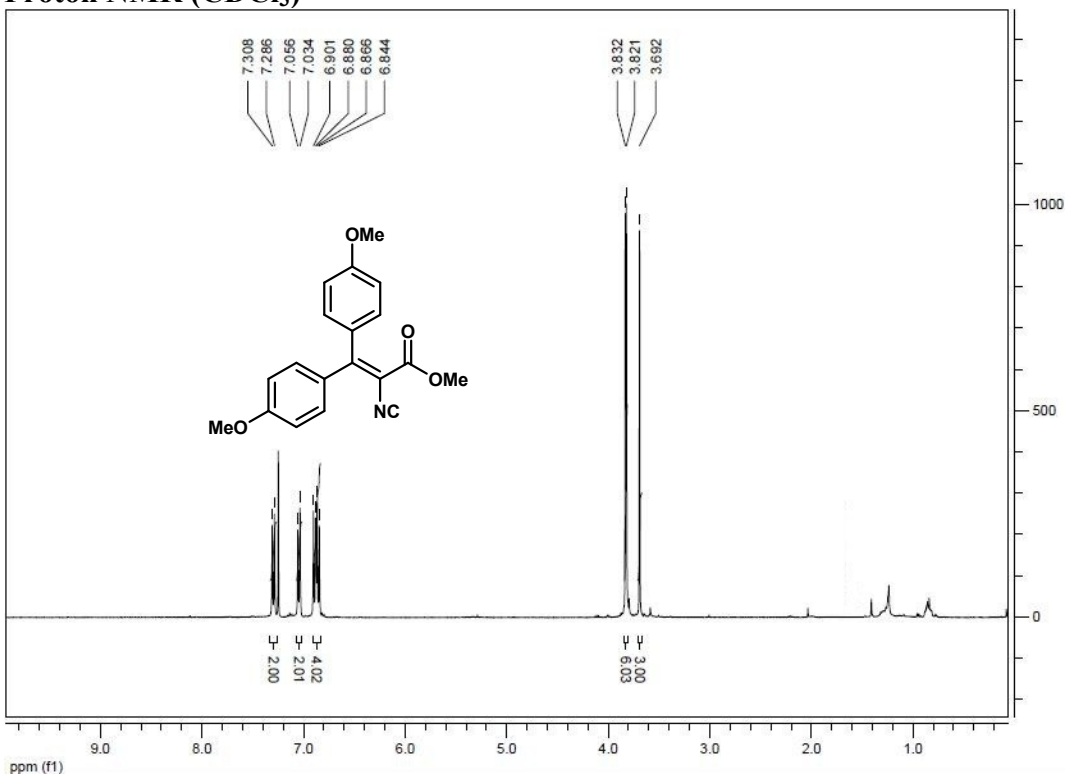


Carbon NMR ($CDCl_3$)

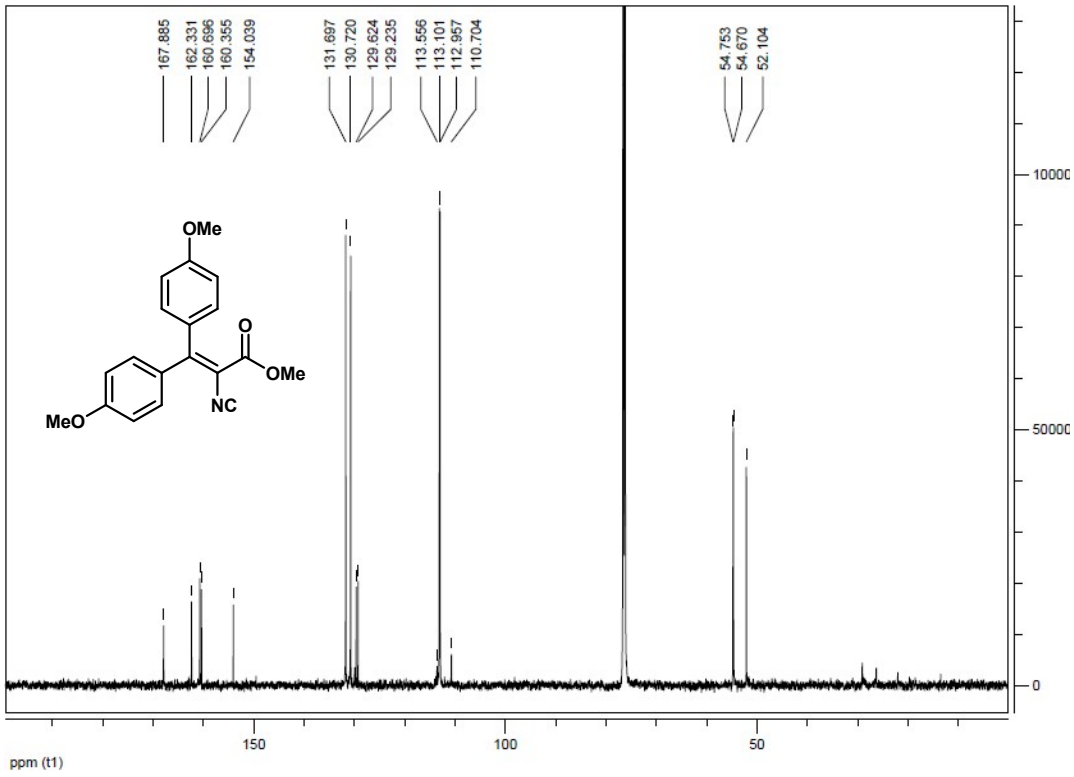


Methyl 2-isocyano-3,3-bis(4-methoxyphenyl)acrylate (1c)

Proton NMR ($CDCl_3$)

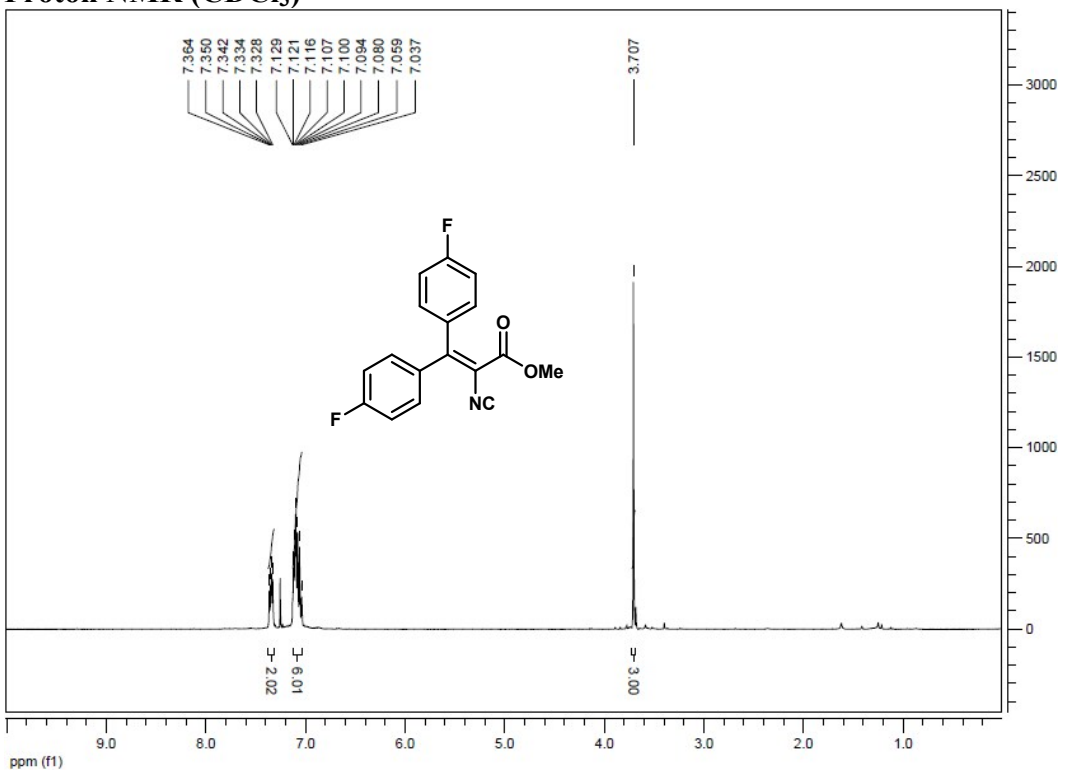


Carbon NMR ($CDCl_3$)

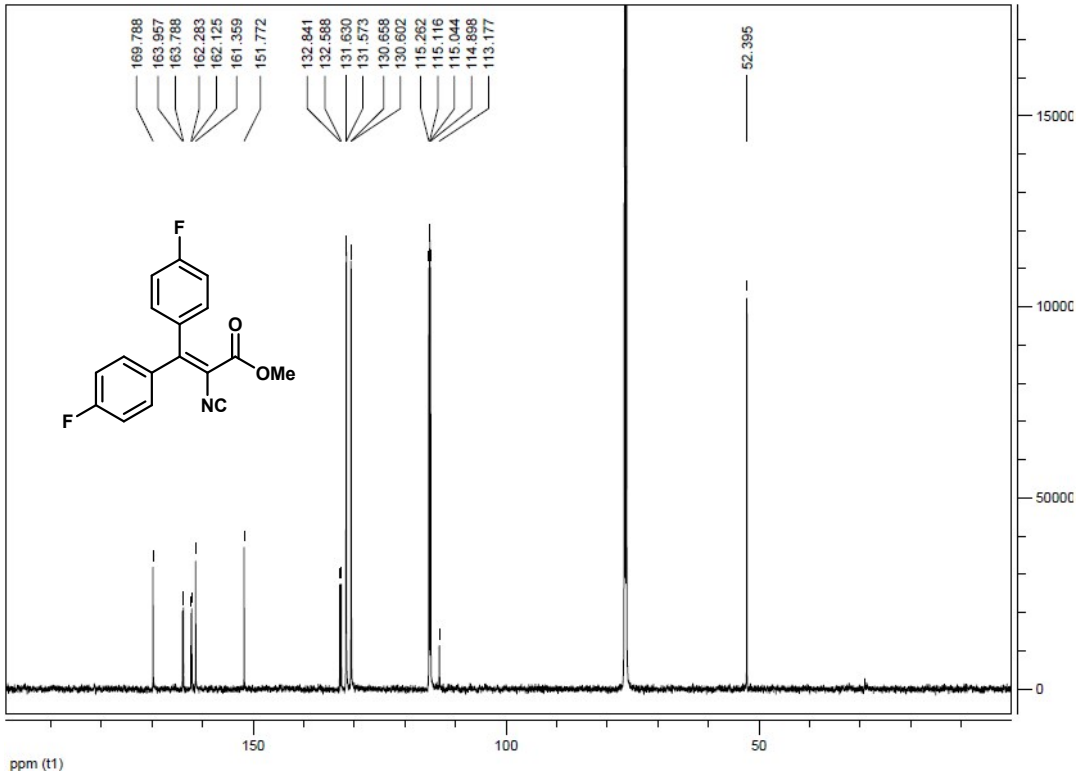


Methyl 3,3-bis(4-fluorophenyl)-2-isocyanoacrylate (1d)

Proton NMR ($CDCl_3$)

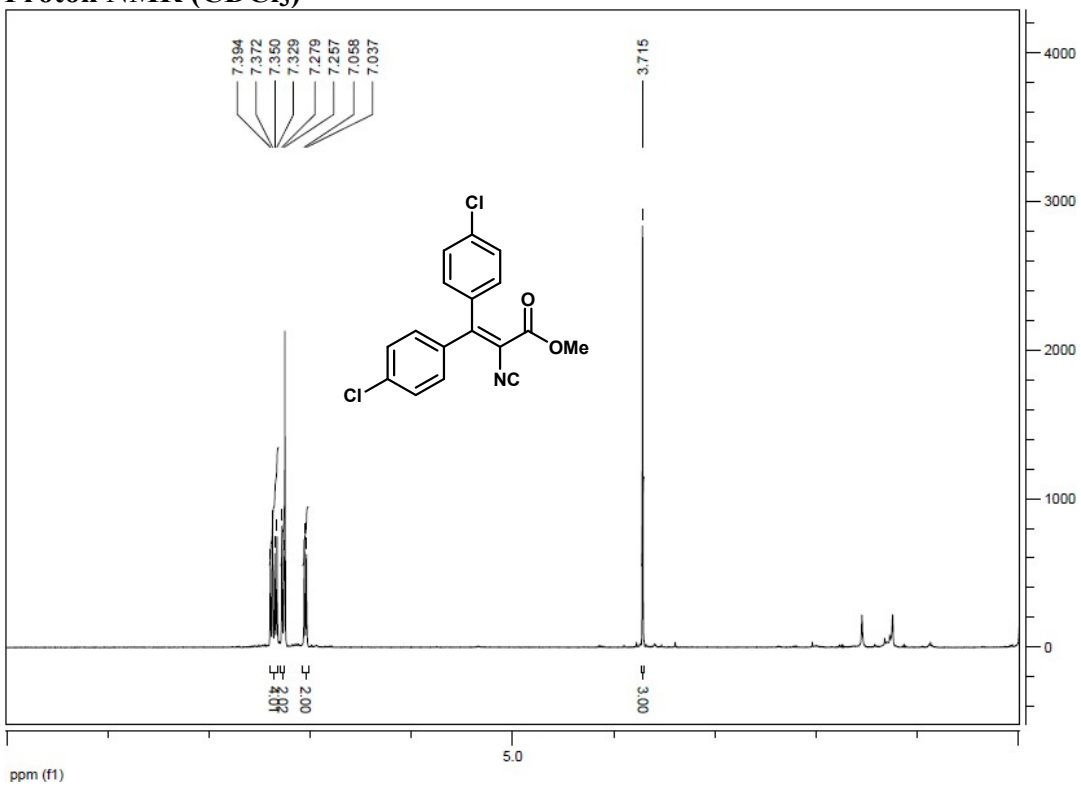


Carbon NMR ($CDCl_3$)

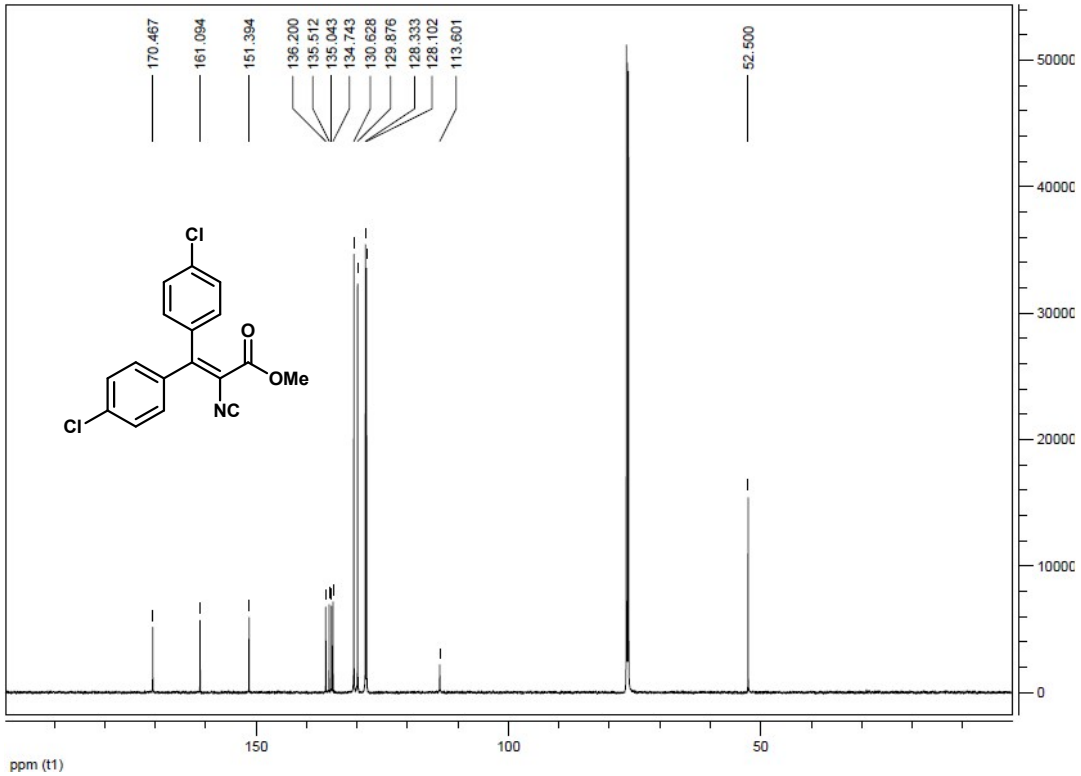


Methyl 3,3-bis(4-chlorophenyl)-2-isocyanoacrylate (1e)

Proton NMR ($CDCl_3$)

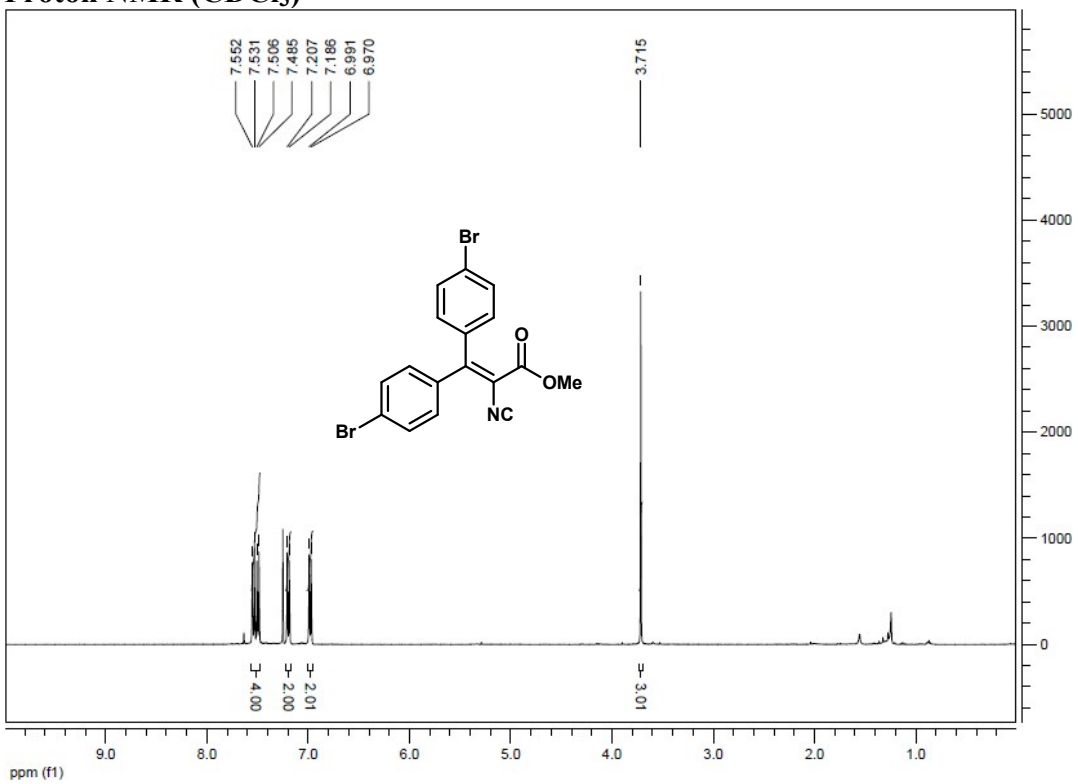


Carbon NMR ($CDCl_3$)

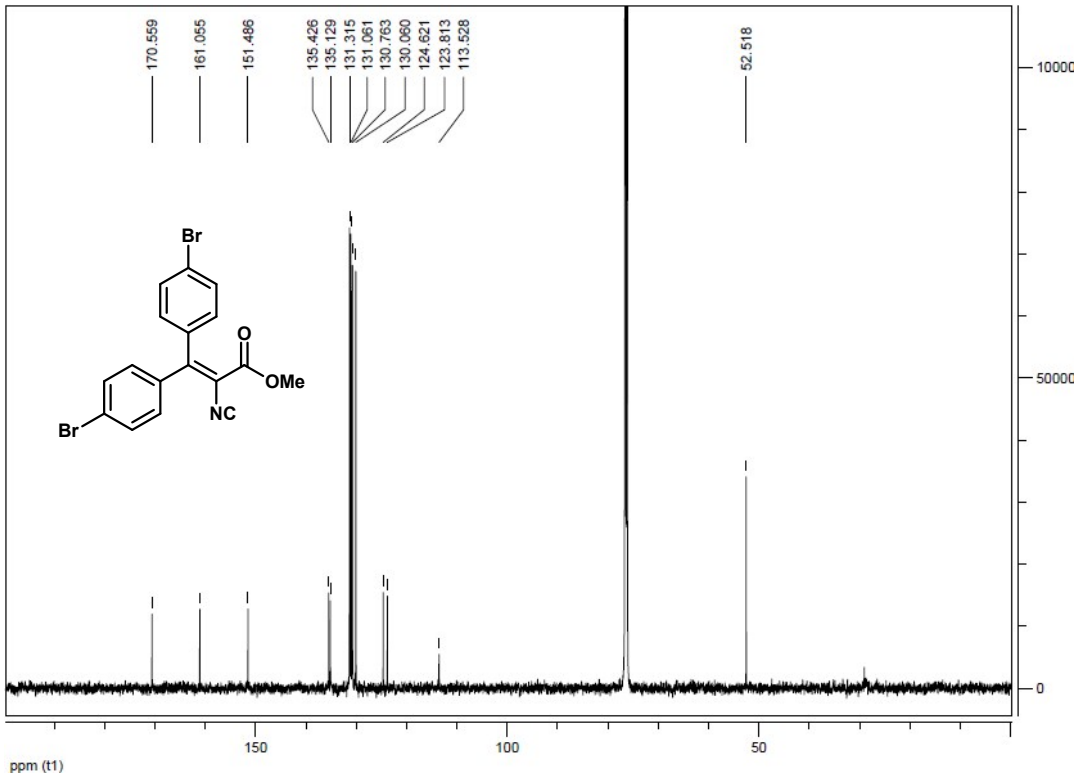


Methyl 3,3-bis(4-bromophenyl)-2-isocyanoacrylate (1f)

Proton NMR ($CDCl_3$)

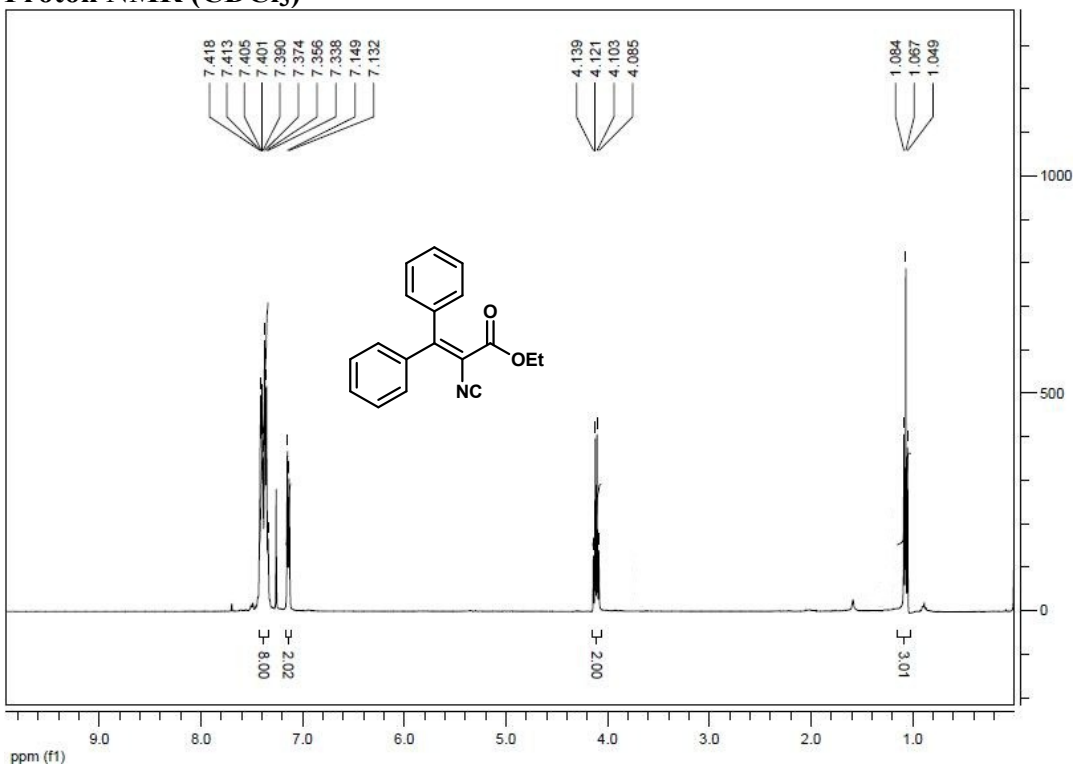


Carbon NMR ($CDCl_3$)

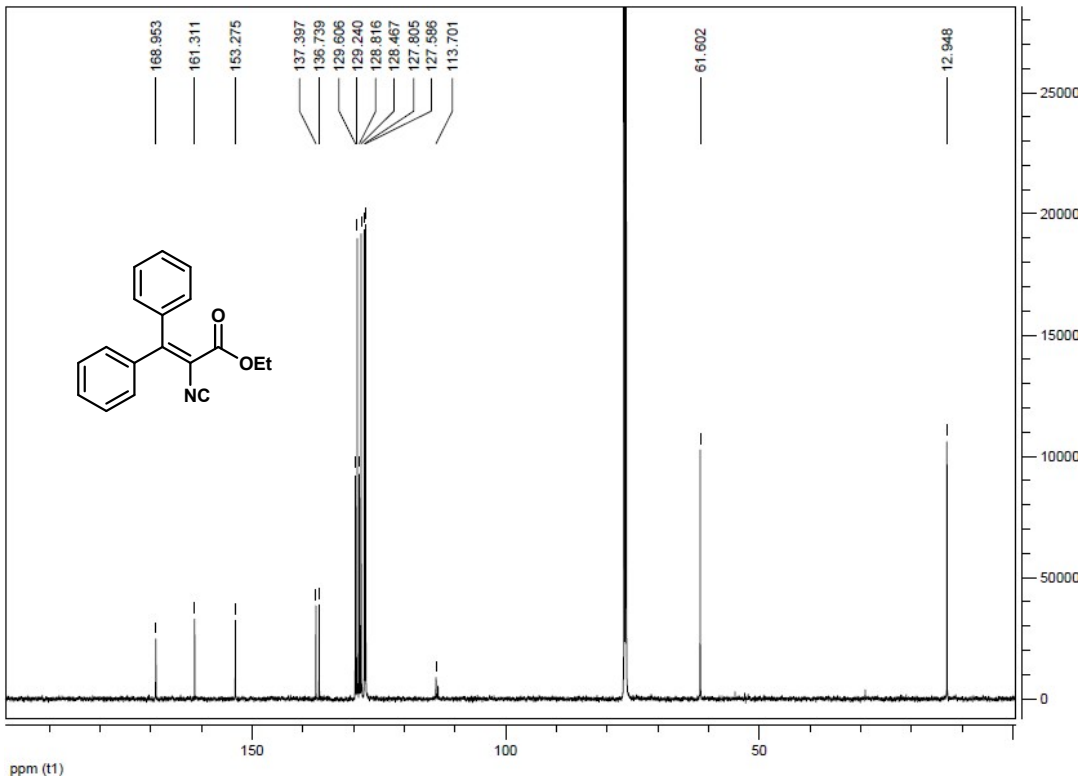


Ethyl 2-isocyano-3,3-diphenylacrylate (1g)

Proton NMR ($CDCl_3$)

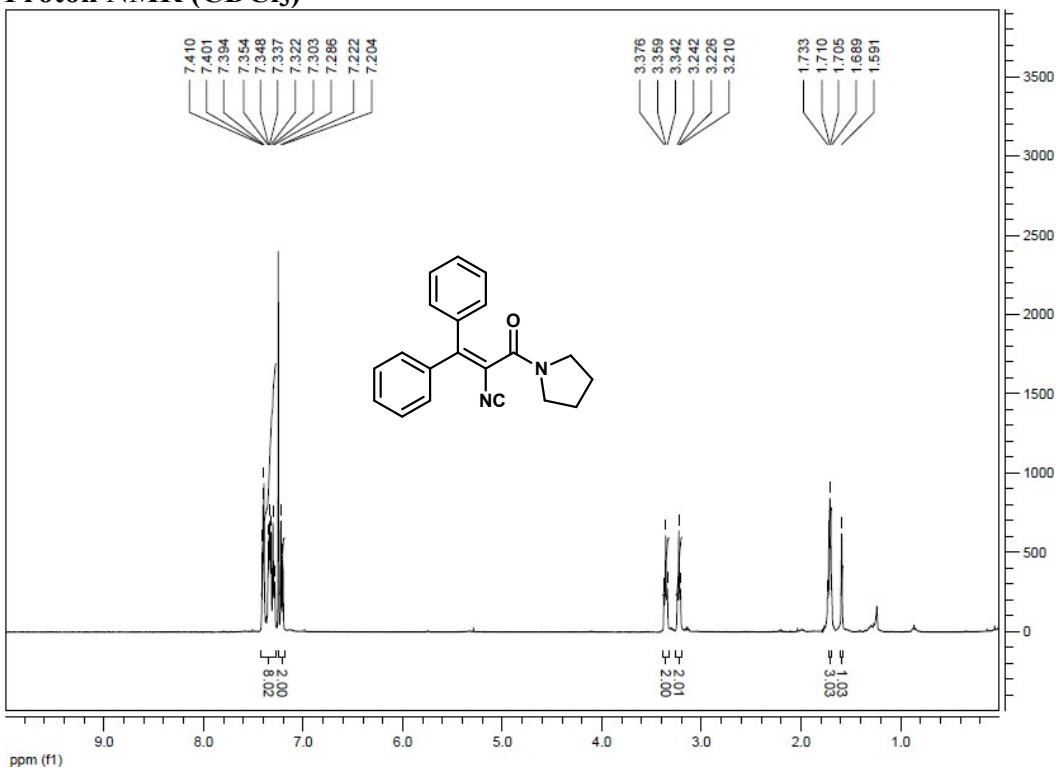


Carbon NMR ($CDCl_3$)

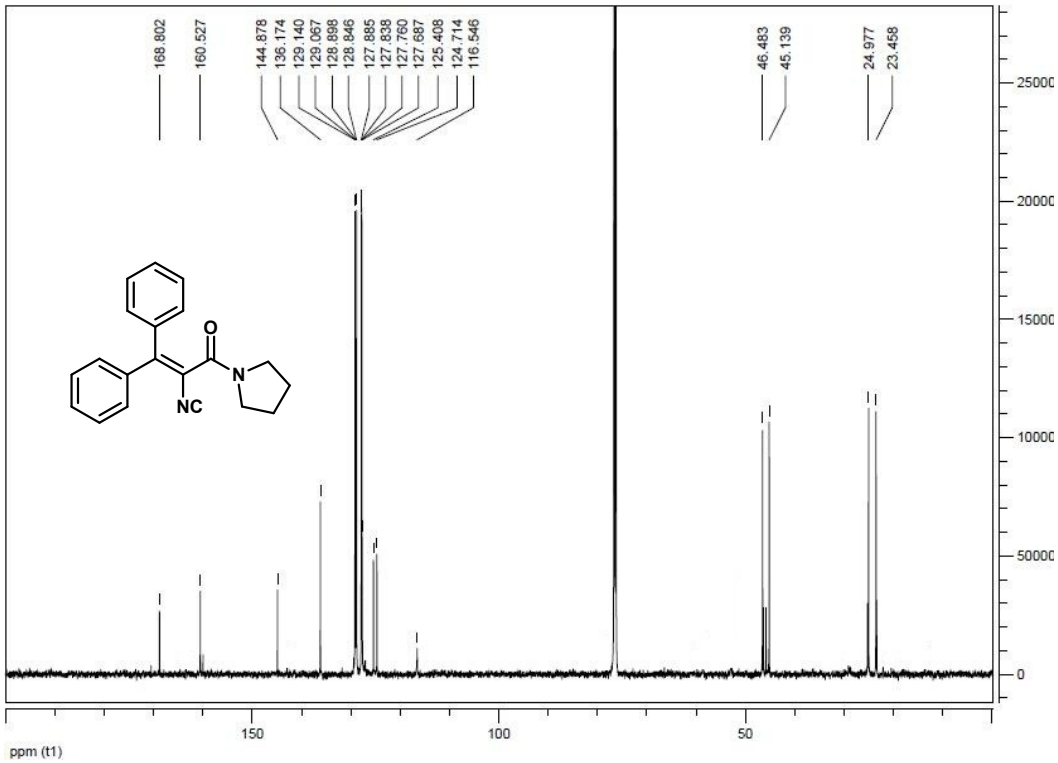


2-Isocyano-3,3-diphenyl-1-(pyrrolidin-1-yl)prop-2-en-1-one (1h)

Proton NMR ($CDCl_3$)

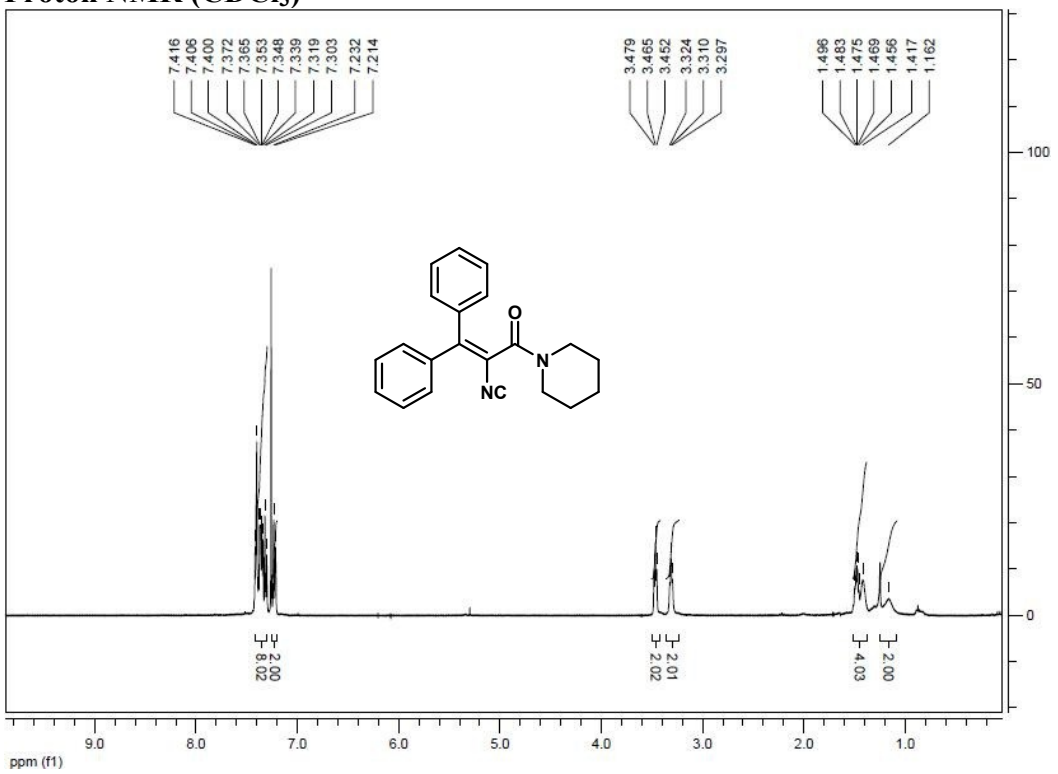


Carbon NMR ($CDCl_3$)

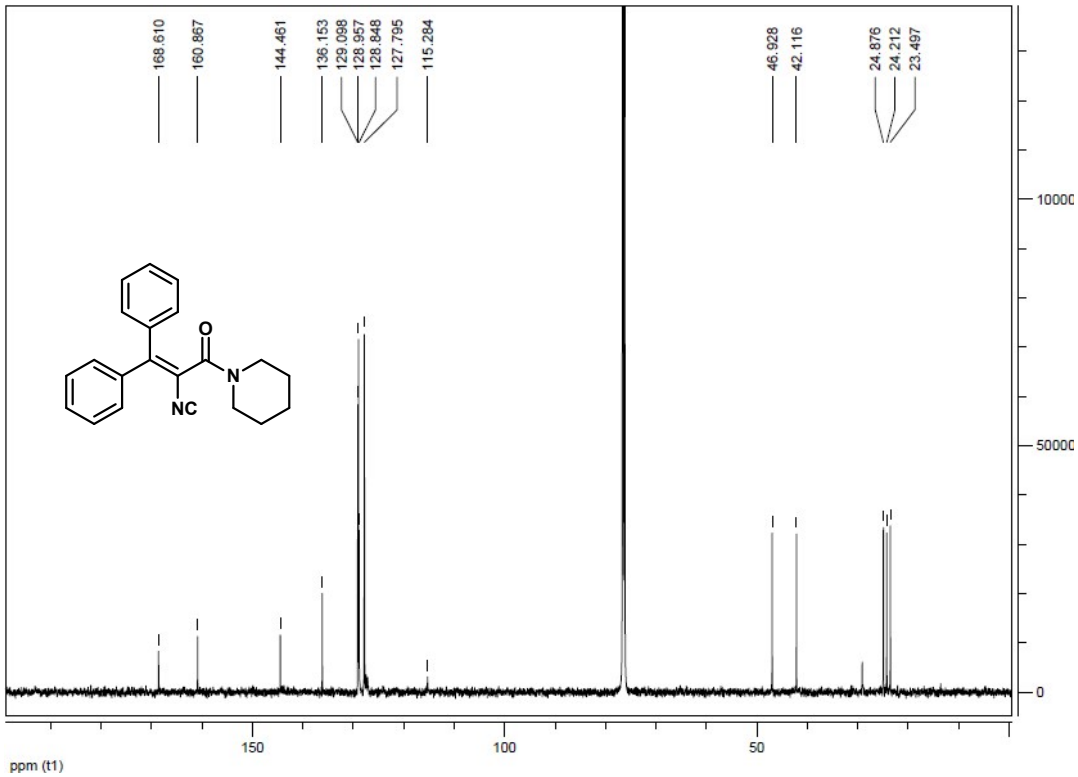


2-Isocyano-3,3-diphenyl-1-(piperidin-1-yl)prop-2-en-1-one (1i)

Proton NMR ($CDCl_3$)

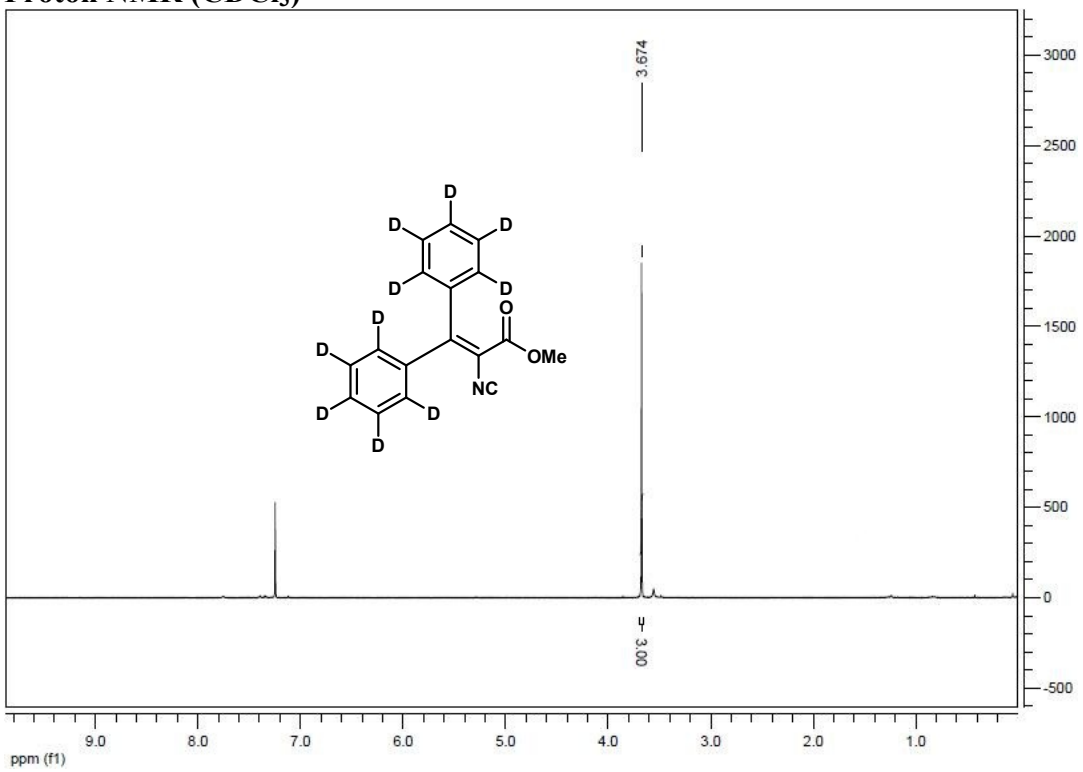


Carbon NMR ($CDCl_3$)

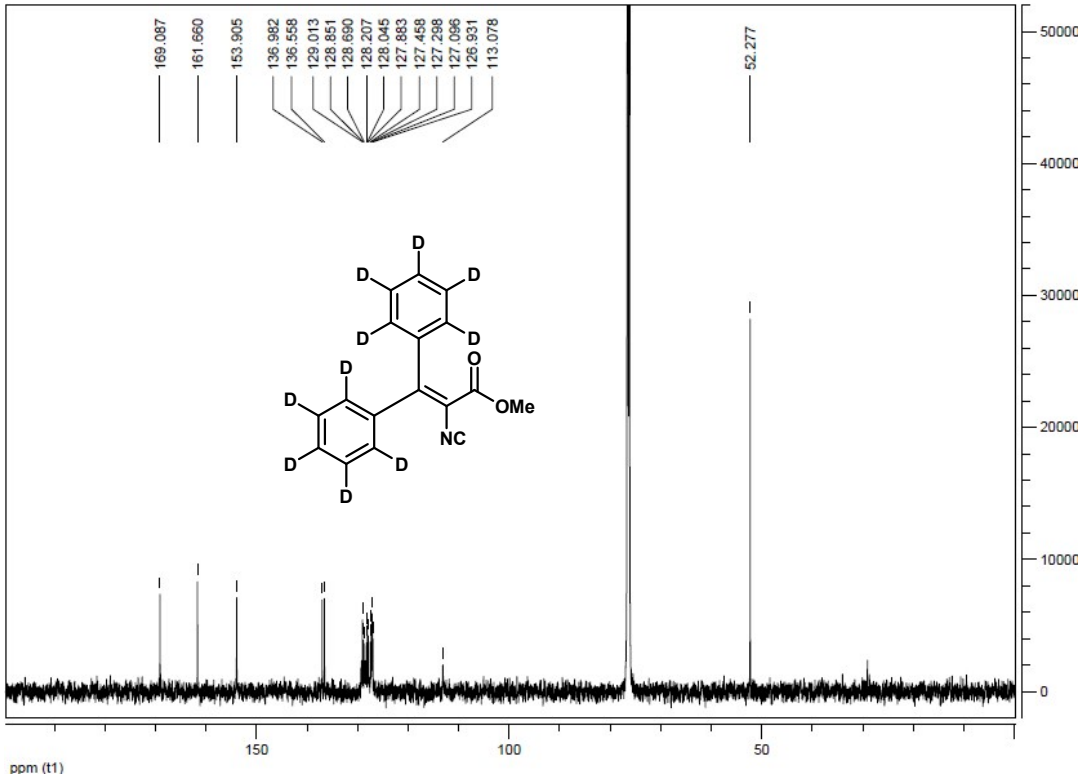


[d_{10}]-Methyl 2-isocyano-3,3-diphenylacrylate ([d_{10}]-1a)

Proton NMR ($CDCl_3$)

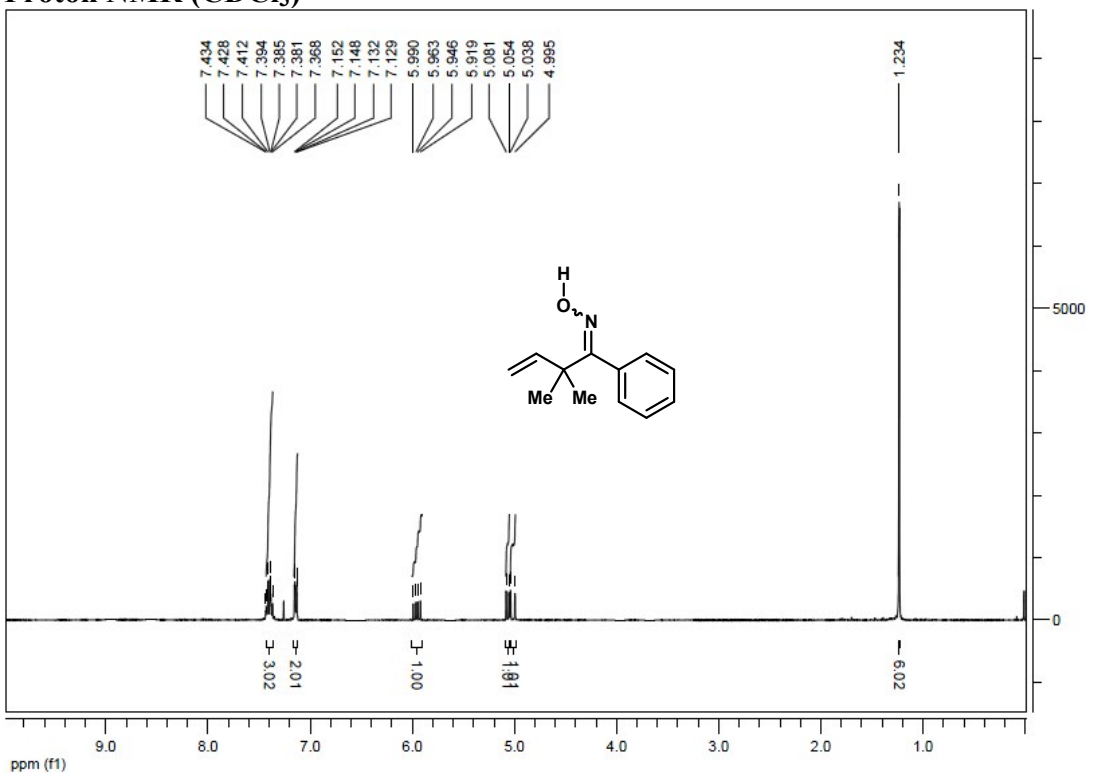


Carbon NMR ($CDCl_3$)

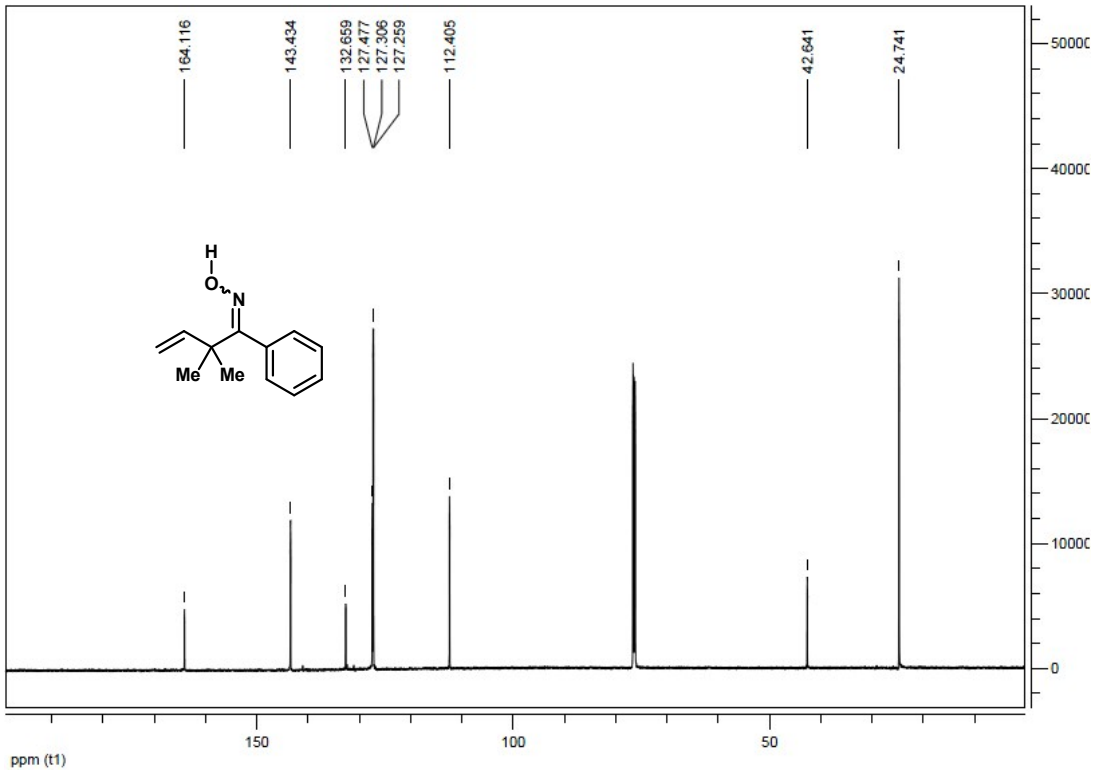


2,2-Dimethyl-1-phenylbut-3-en-1-one oxime (2a)

Proton NMR ($CDCl_3$)

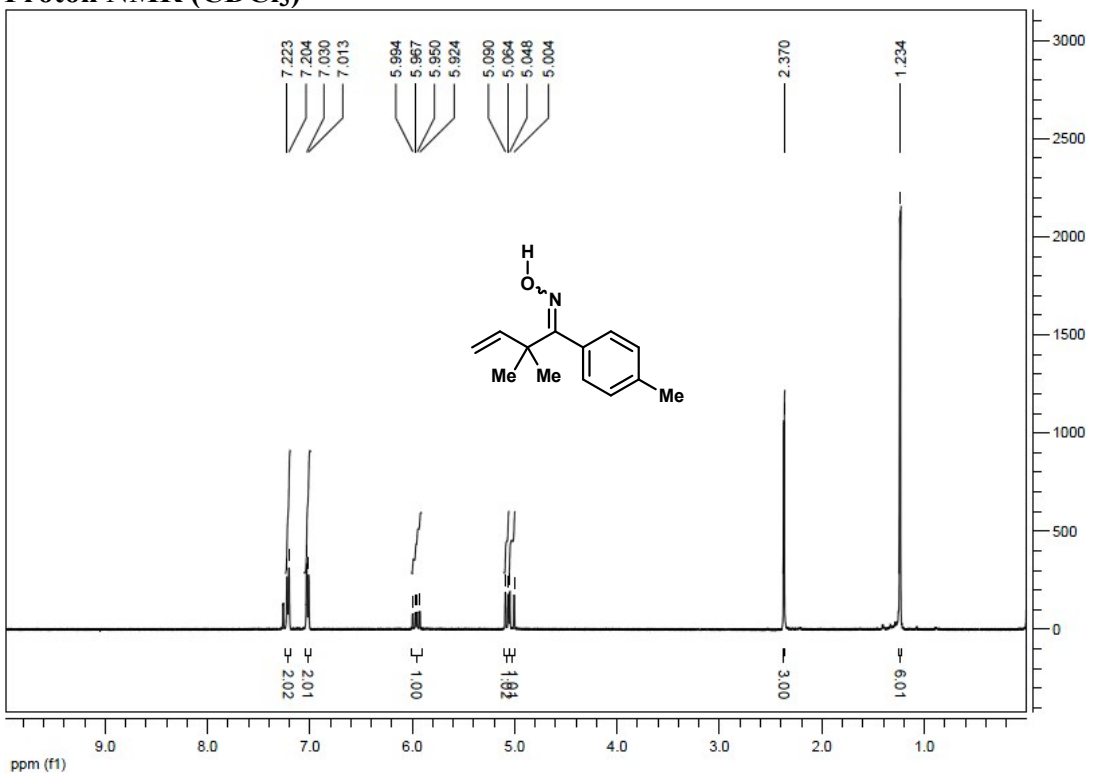


Carbon NMR ($CDCl_3$)

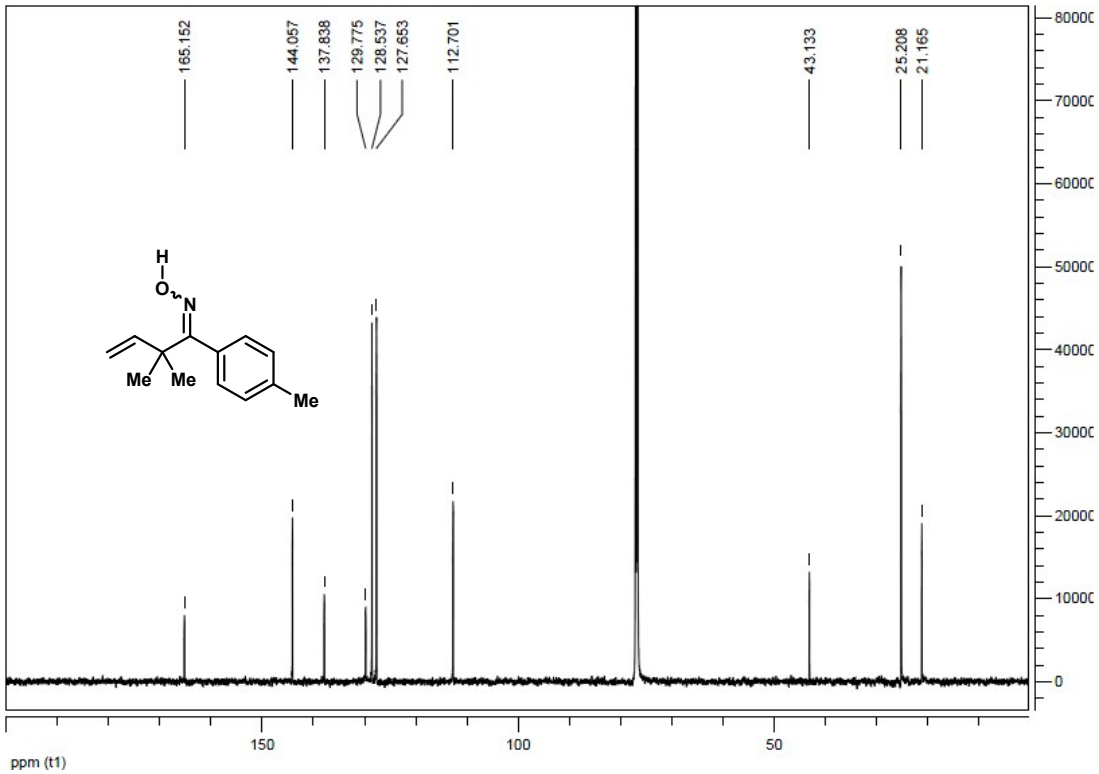


2,2-Dimethyl-1-(*p*-tolyl)but-3-en-1-one oxime (2b)

Proton NMR ($CDCl_3$)

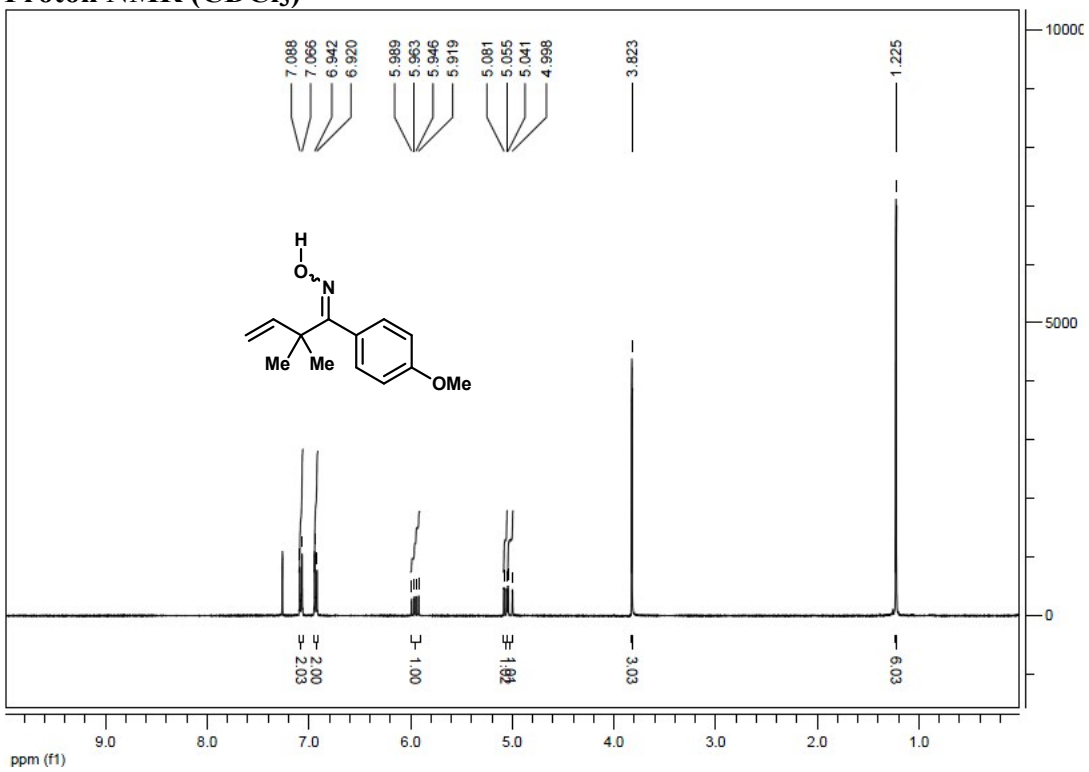


Carbon NMR ($CDCl_3$)

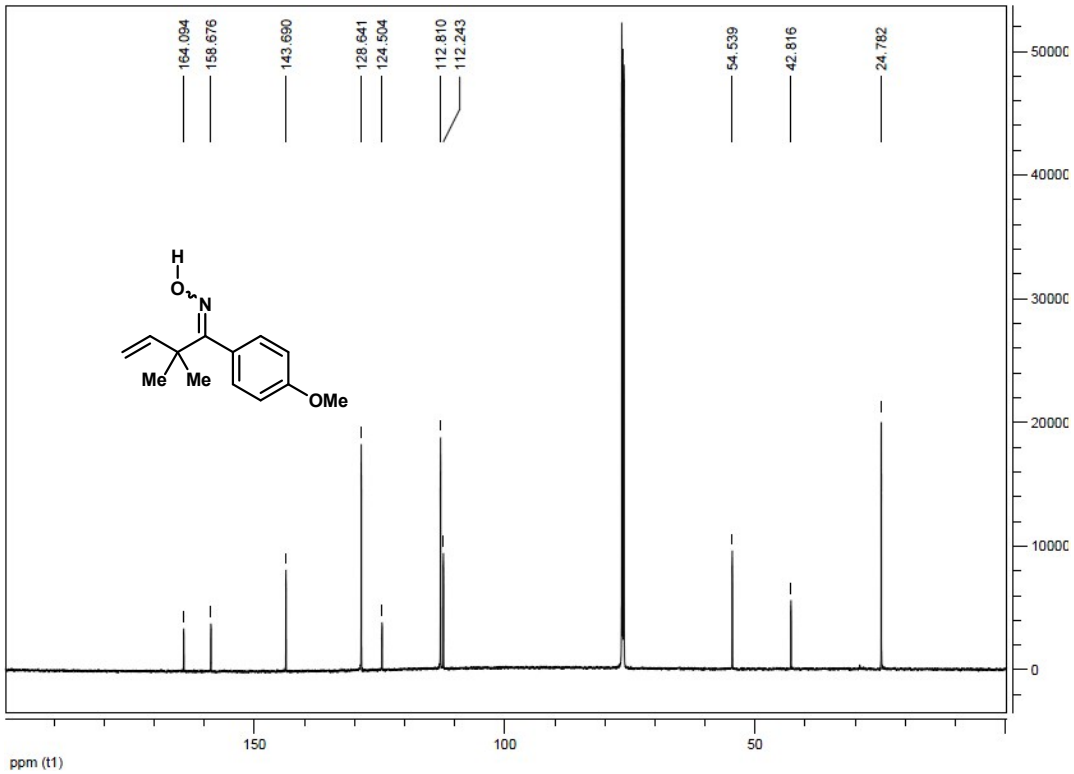


1-(4-Methoxyphenyl)-2,2-dimethylbut-3-en-1-one oxime (2c)

Proton NMR ($CDCl_3$)

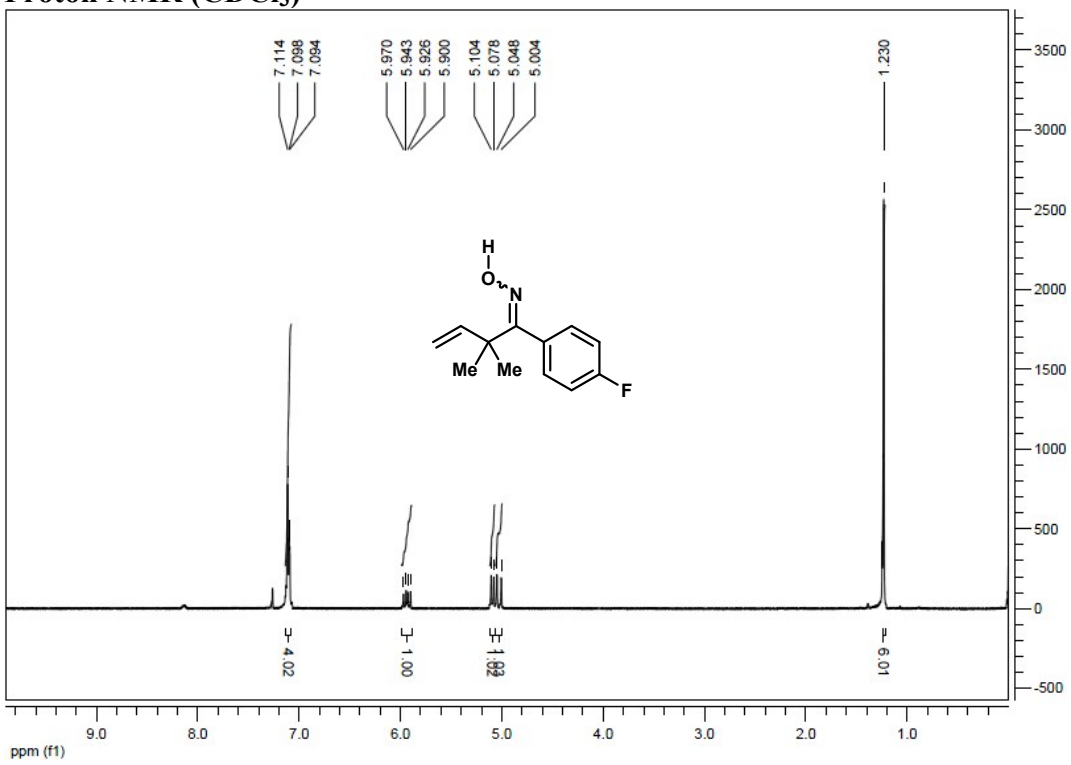


Carbon NMR ($CDCl_3$)

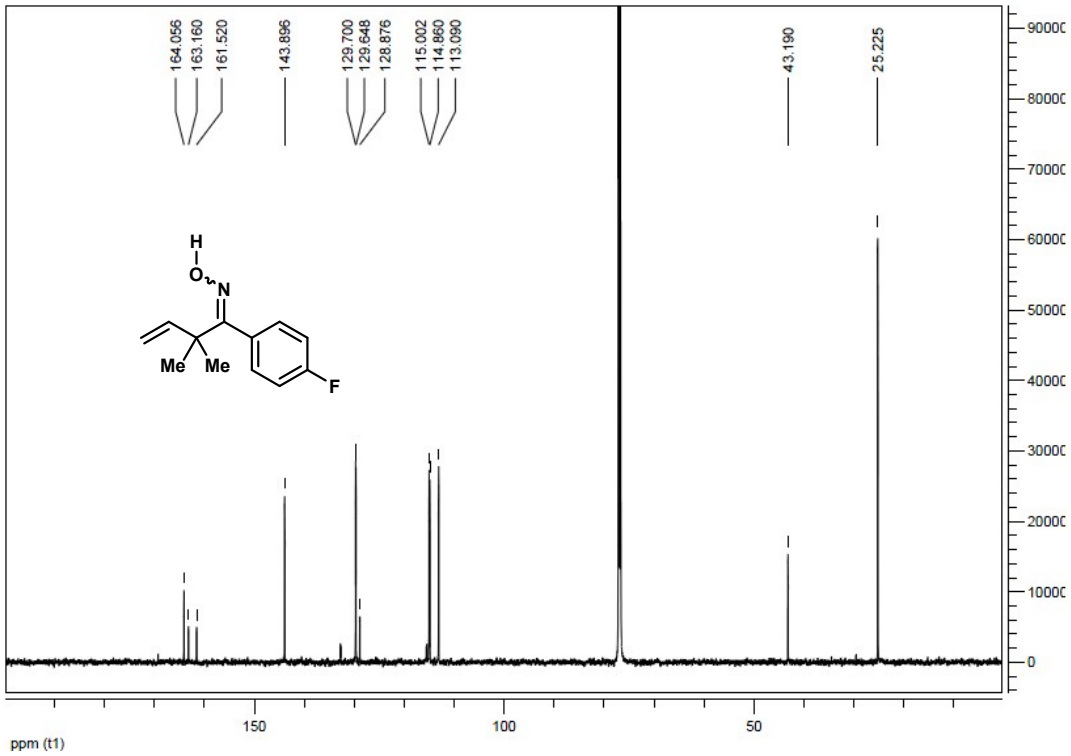


1-(4-Fluorophenyl)-2,2-dimethylbut-3-en-1-one oxime (2d)

Proton NMR ($CDCl_3$)

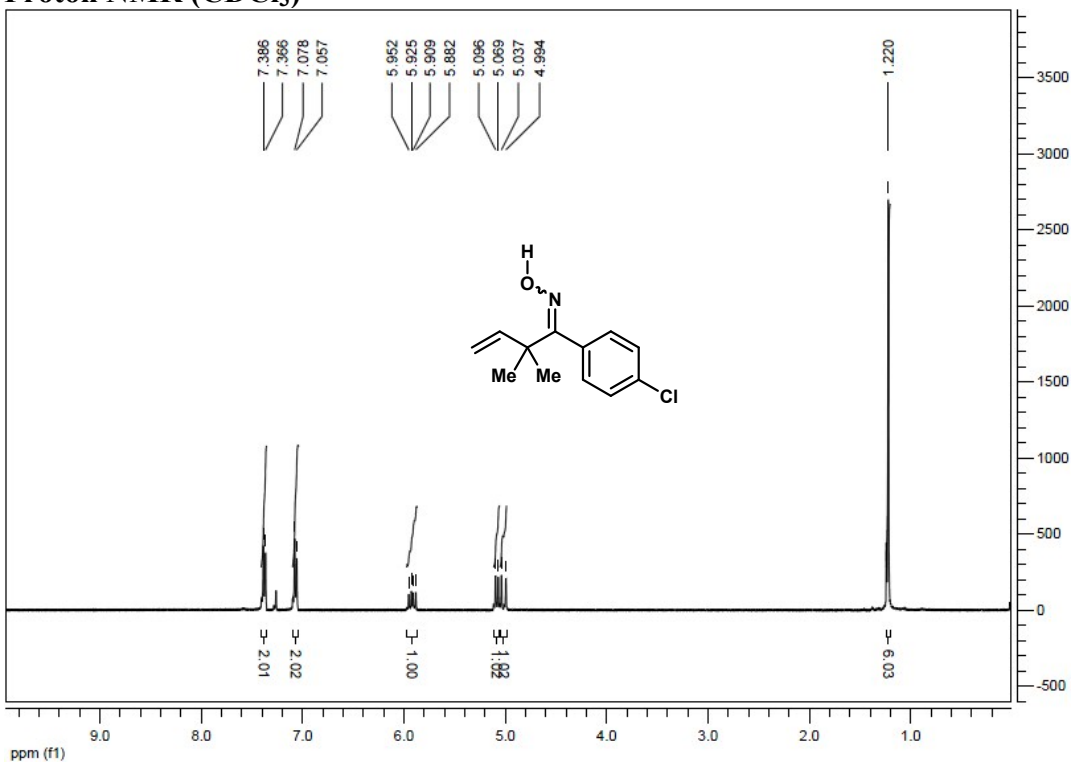


Carbon NMR ($CDCl_3$)

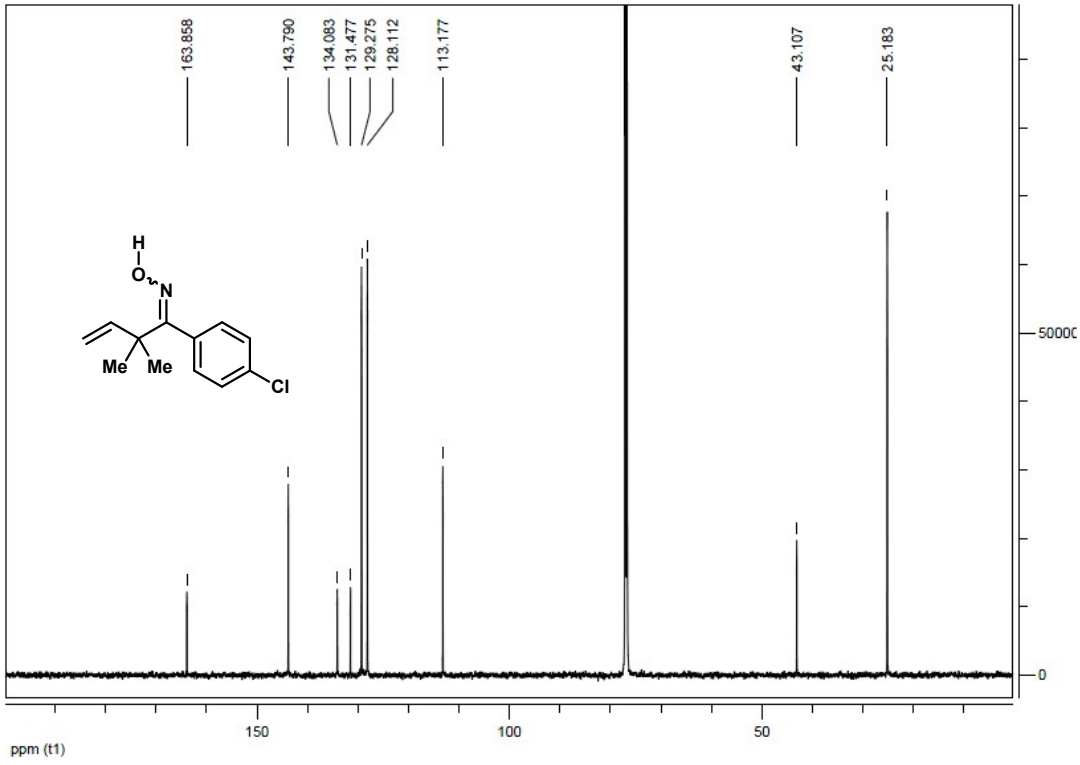


1-(4-Chlorophenyl)-2,2-dimethylbut-3-en-1-one oxime (2e)

Proton NMR ($CDCl_3$)

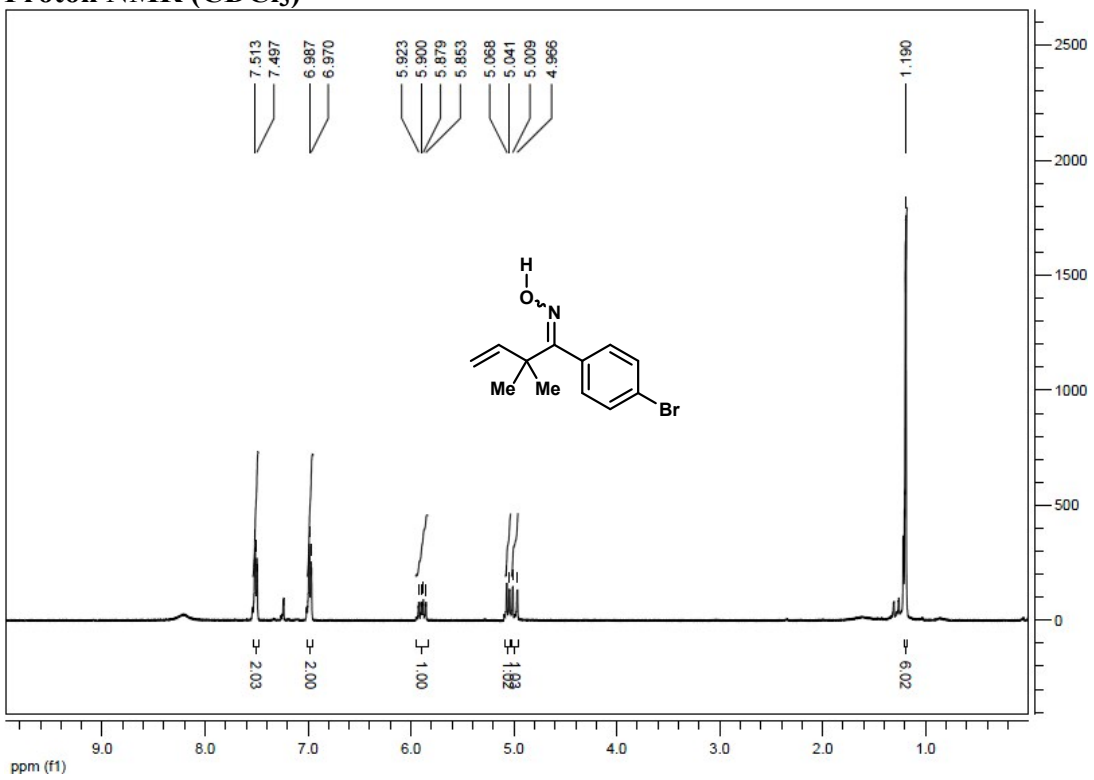


Carbon NMR ($CDCl_3$)

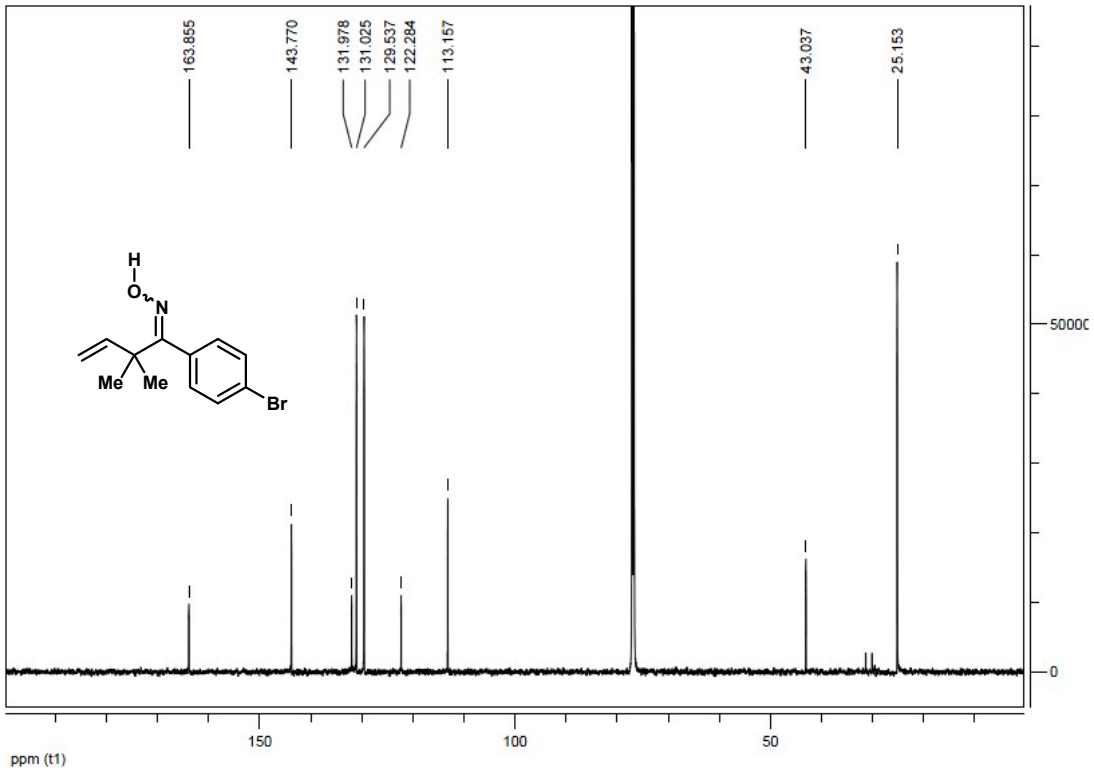


1-(4-Bromophenyl)-2,2-dimethylbut-3-en-1-one oxime (2f)

Proton NMR ($CDCl_3$)

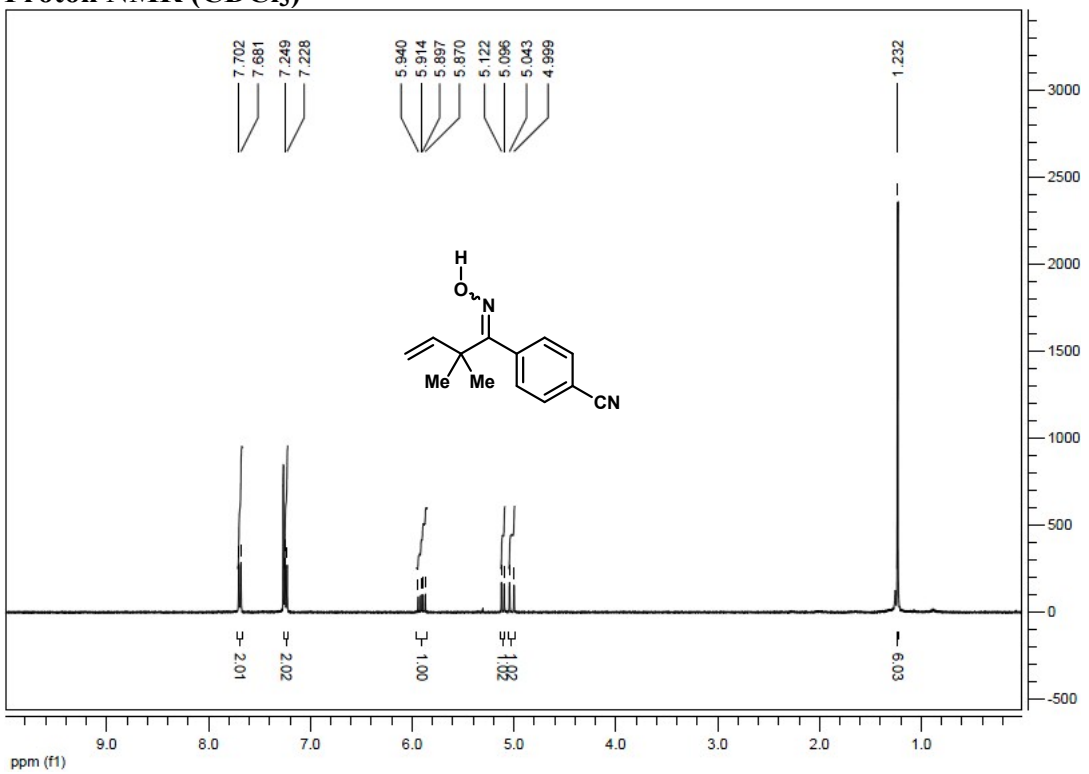


Carbon NMR ($CDCl_3$)

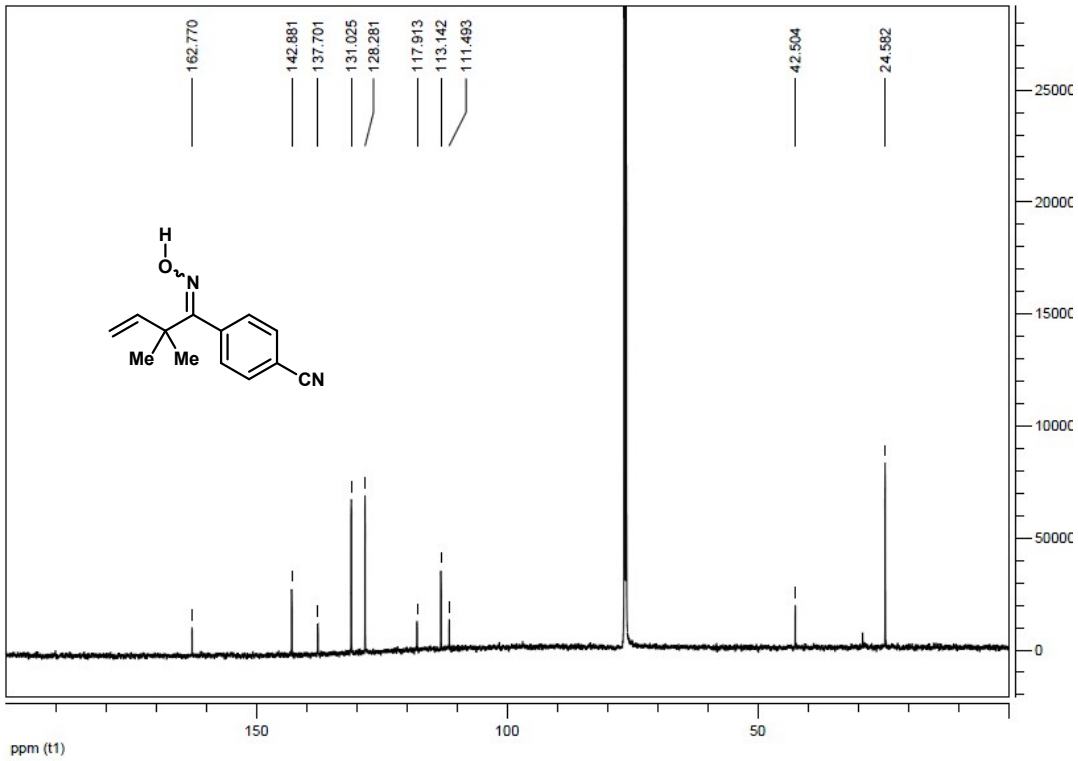


4-(1-(Hydroxyimino)-2,2-dimethylbut-3-en-1-yl)benzonitrile (2g)

Proton NMR ($CDCl_3$)

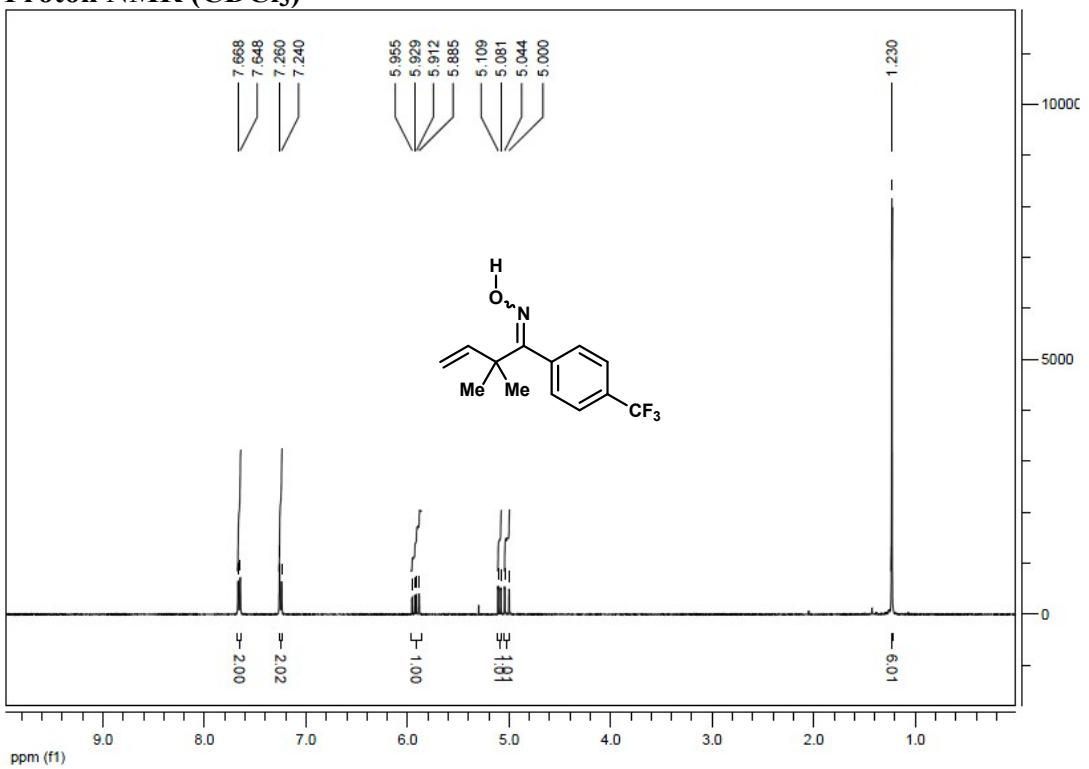


Carbon NMR ($CDCl_3$)

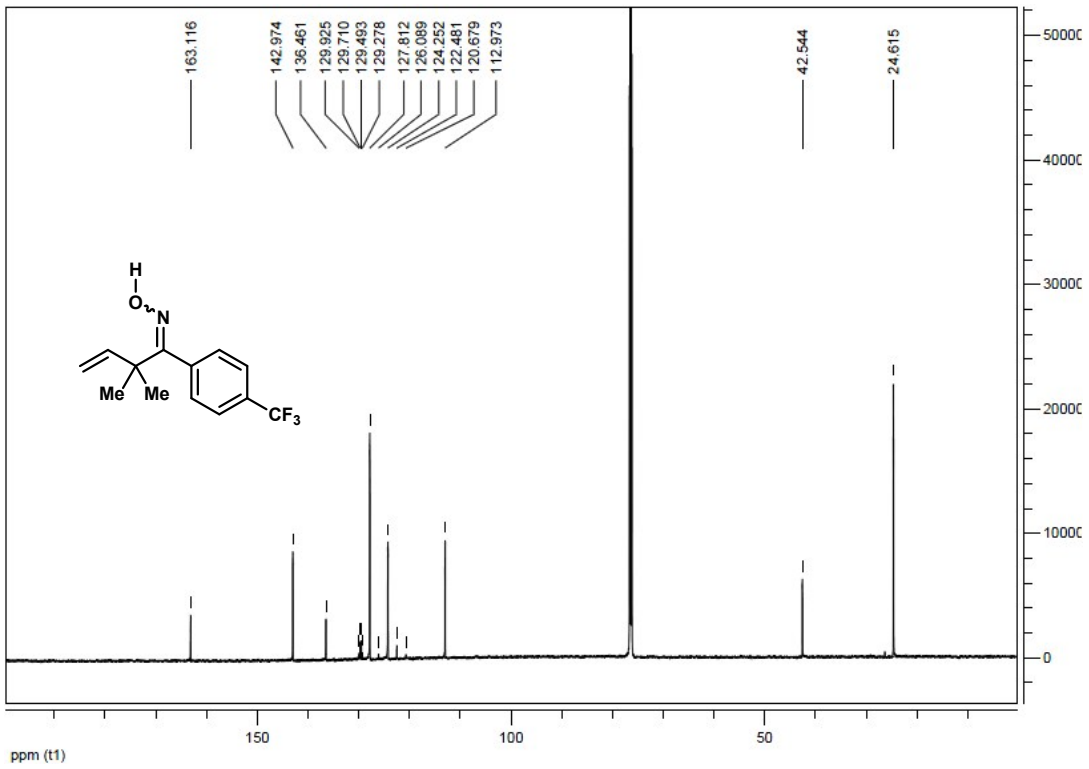


2,2-Dimethyl-1-(4-(trifluoromethyl)phenyl)but-3-en-1-one oxime (2h)

Proton NMR ($CDCl_3$)

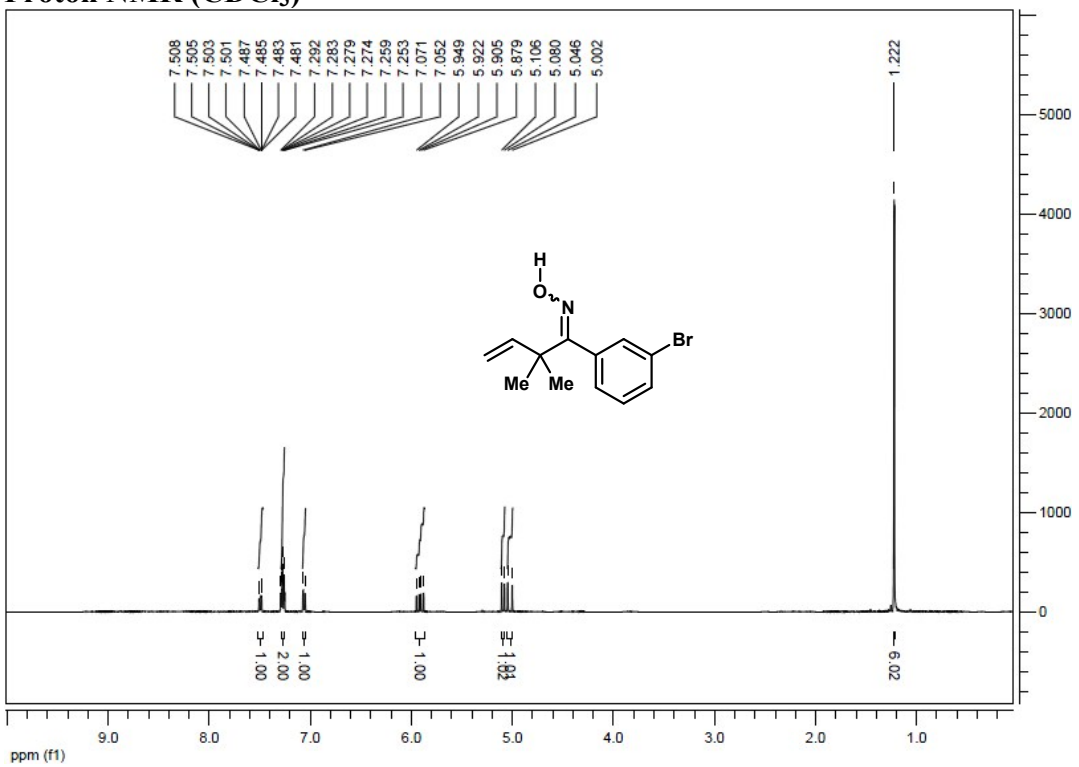


Carbon NMR ($CDCl_3$)

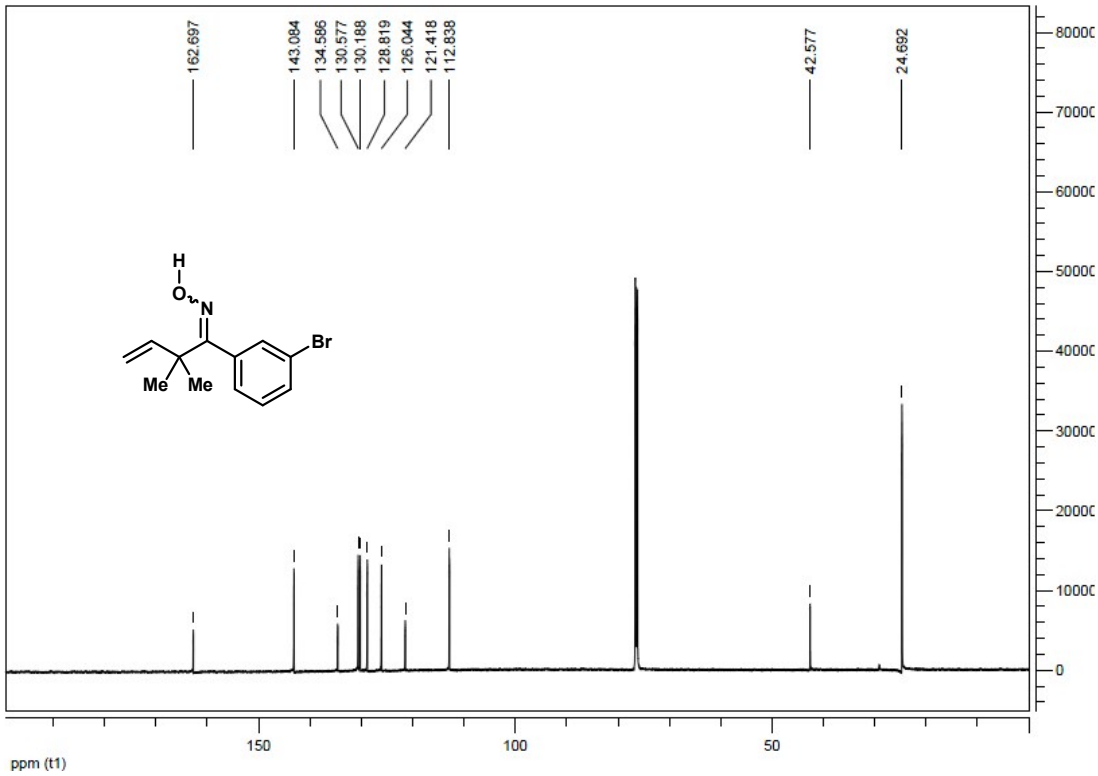


1-(3-Bromophenyl)-2,2-dimethylbut-3-en-1-one oxime (2i)

Proton NMR ($CDCl_3$)

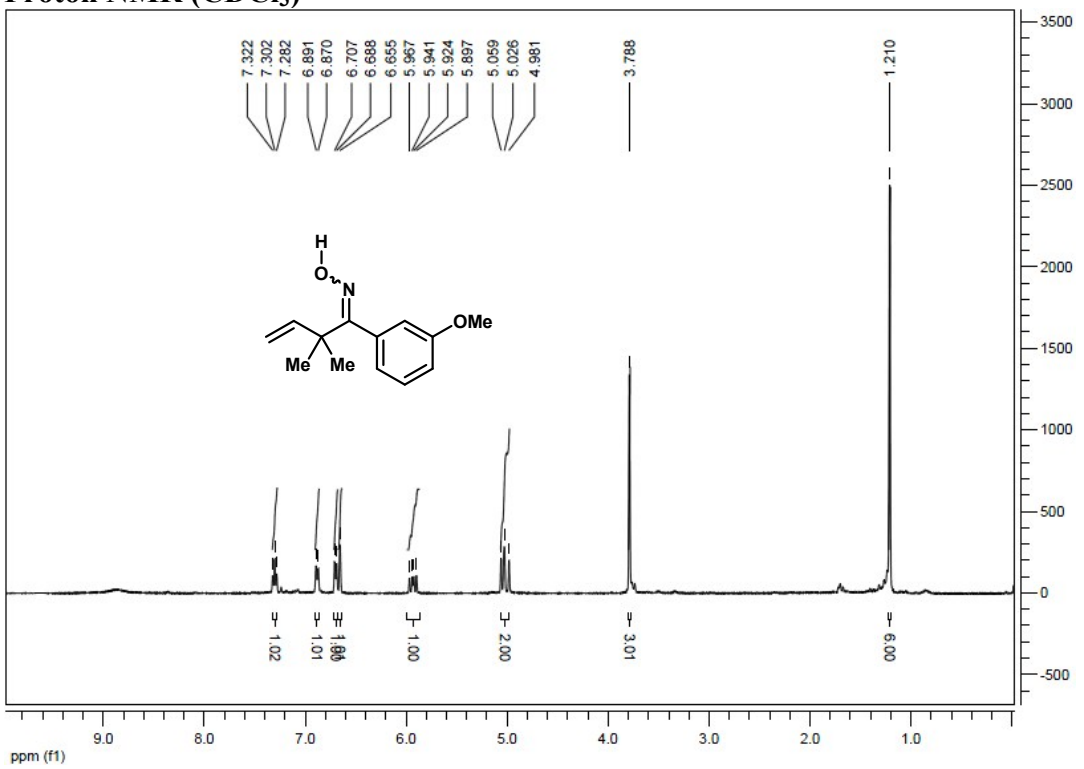


Carbon NMR ($CDCl_3$)

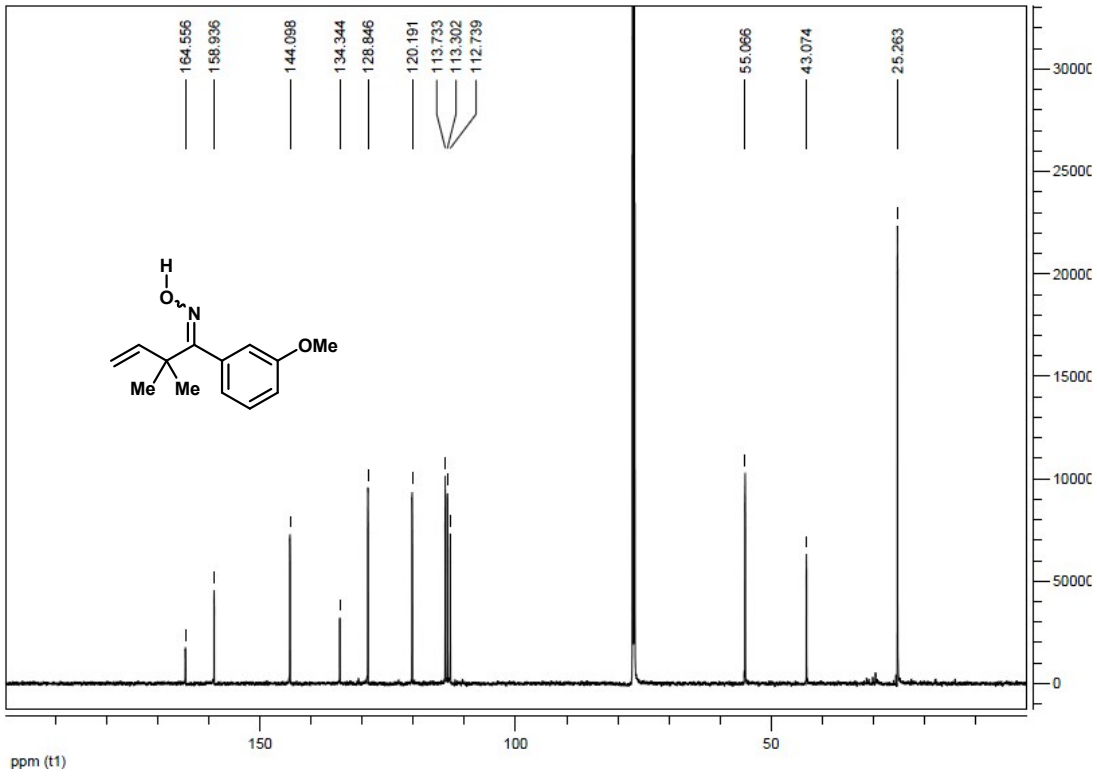


1-(3-Methoxyphenyl)-2,2-dimethylbut-3-en-1-one oxime (2j)

Proton NMR ($CDCl_3$)

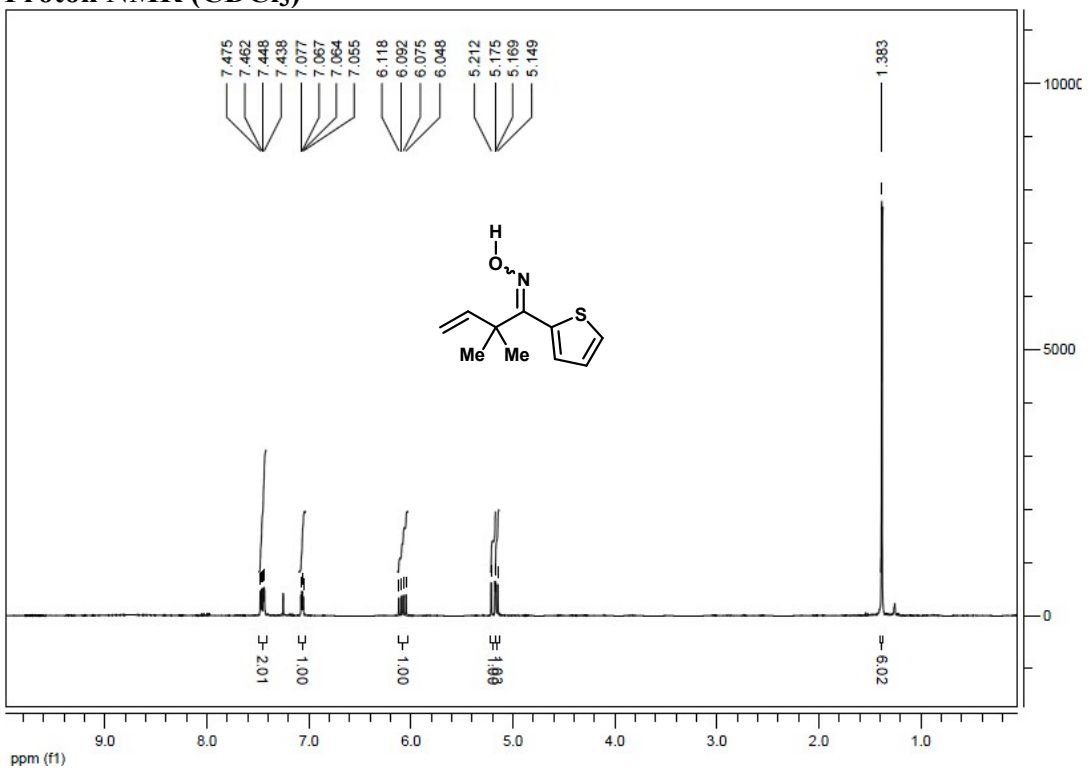


Carbon NMR ($CDCl_3$)

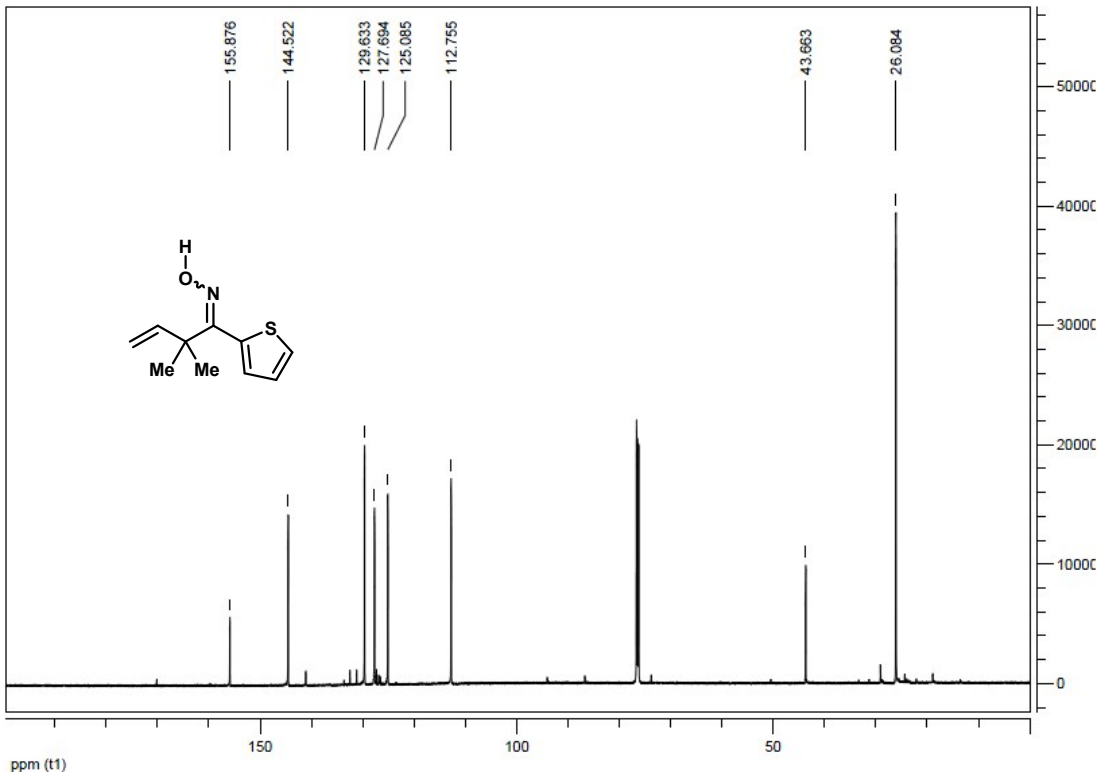


2,2-Dimethyl-1-(thiophen-2-yl)but-3-en-1-one oxime (2k)

Proton NMR ($CDCl_3$)

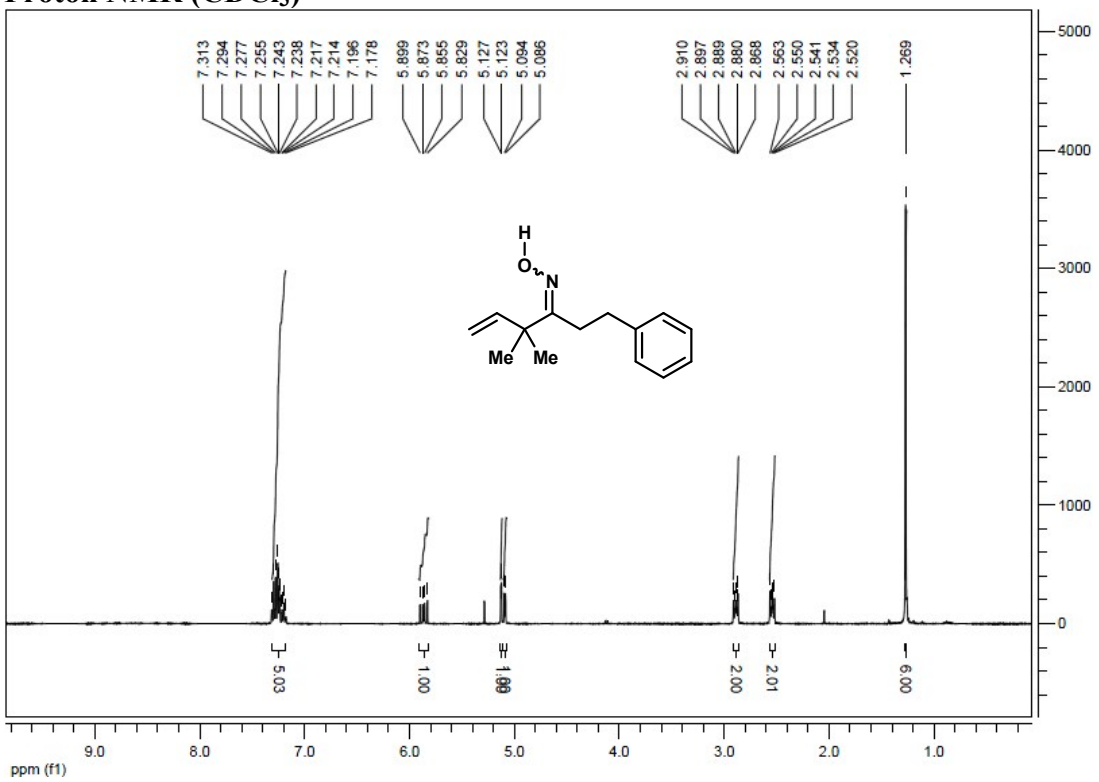


Carbon NMR ($CDCl_3$)

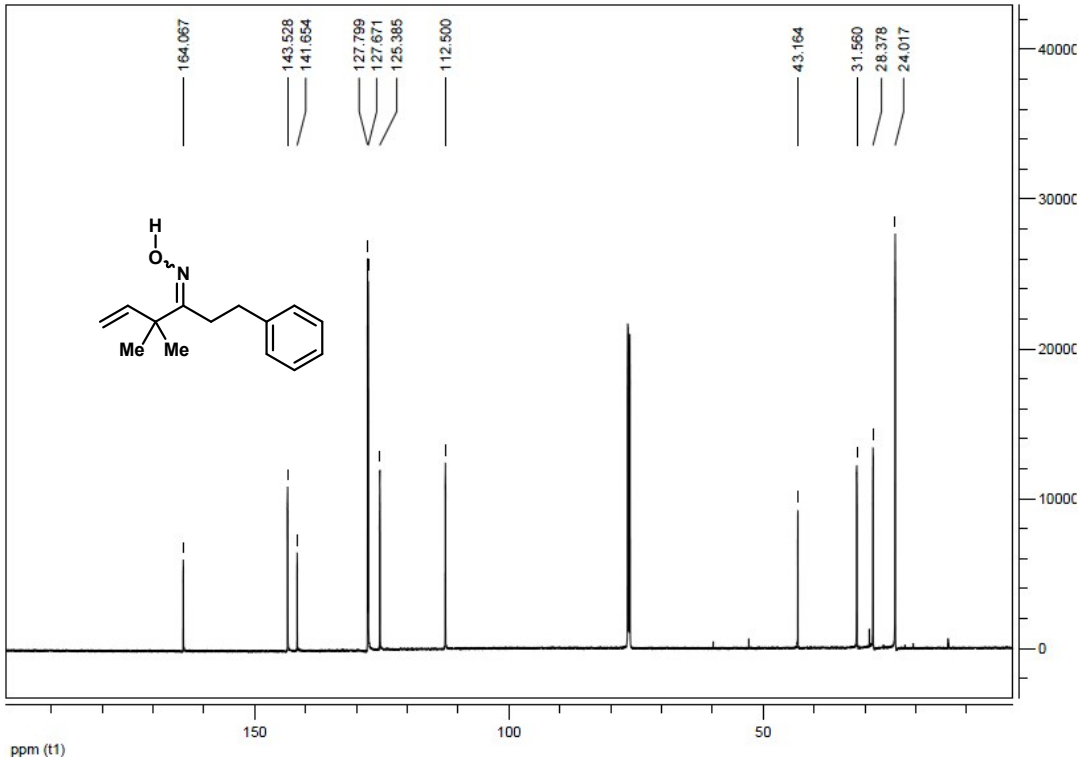


4,4-Dimethyl-1-phenylhex-5-en-3-one oxime (2l)

Proton NMR ($CDCl_3$)

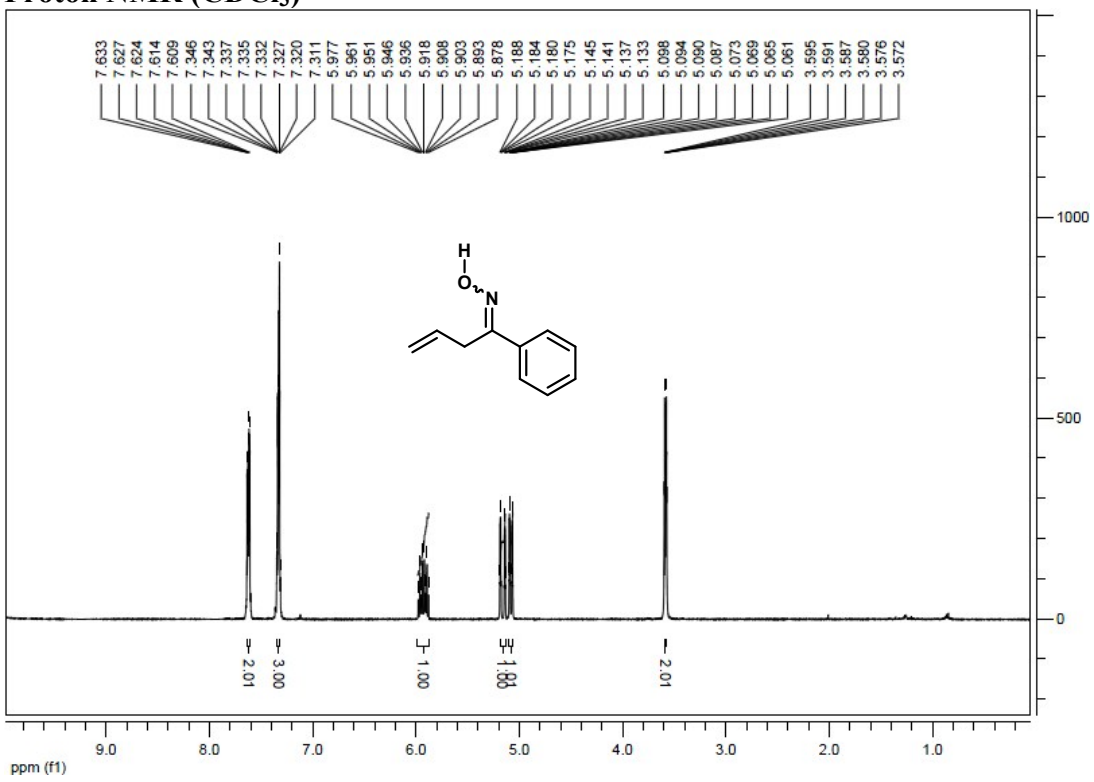


Carbon NMR ($CDCl_3$)

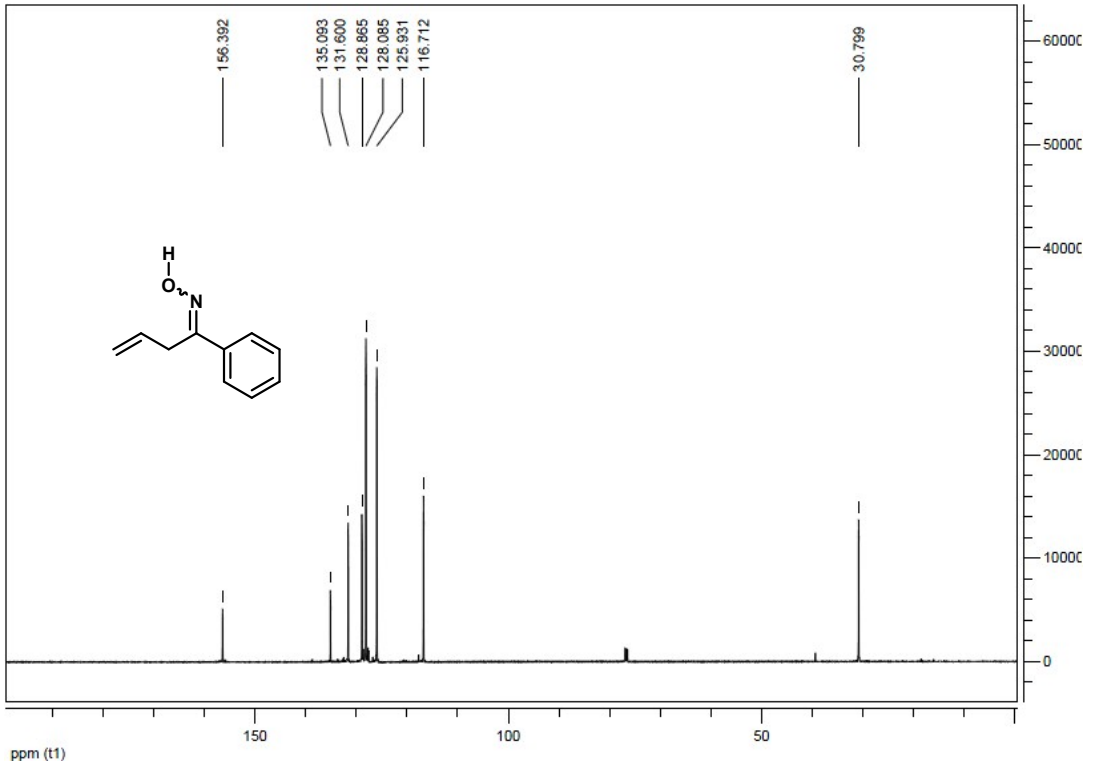


1-Phenylbut-3-en-1-one oxime (2m)

Proton NMR ($CDCl_3$)

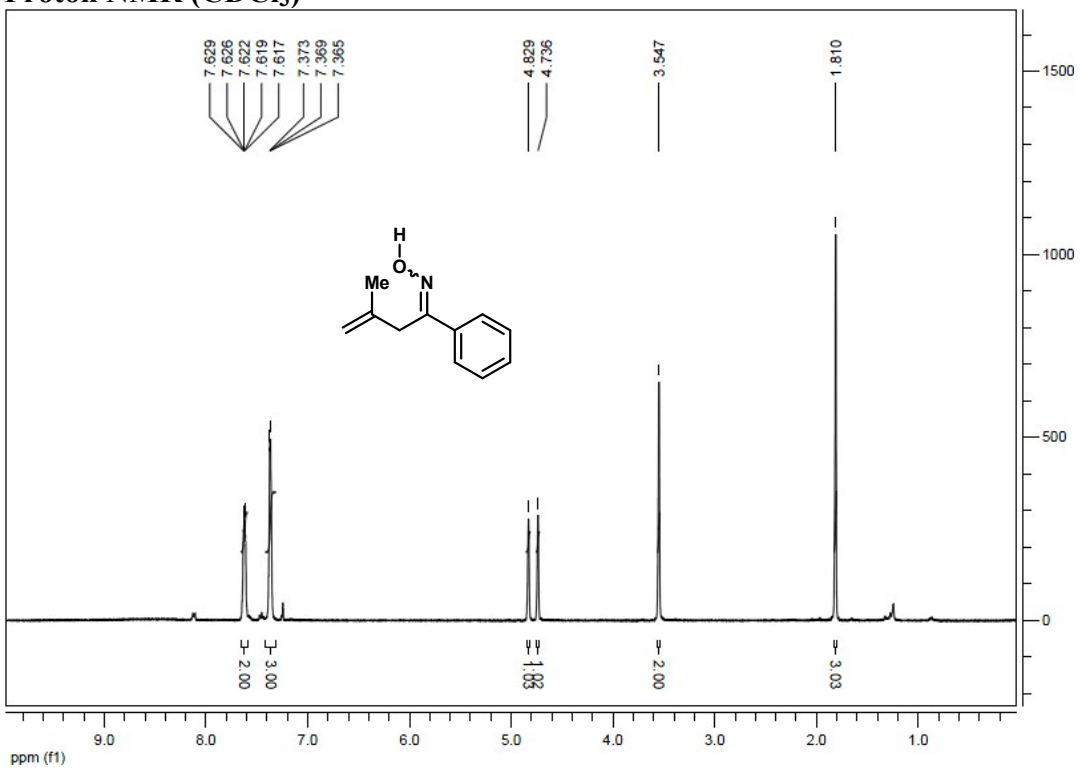


Carbon NMR ($CDCl_3$)

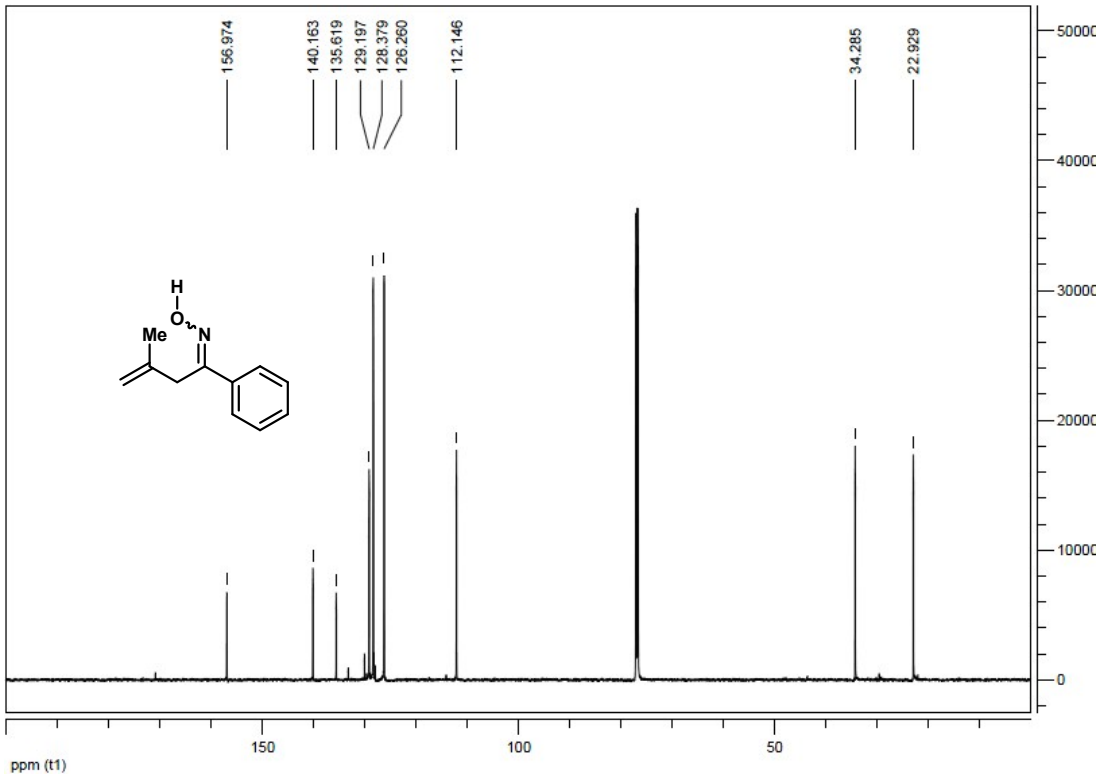


3-Methyl-1-phenylbut-3-en-1-one oxime (2n)

Proton NMR ($CDCl_3$)

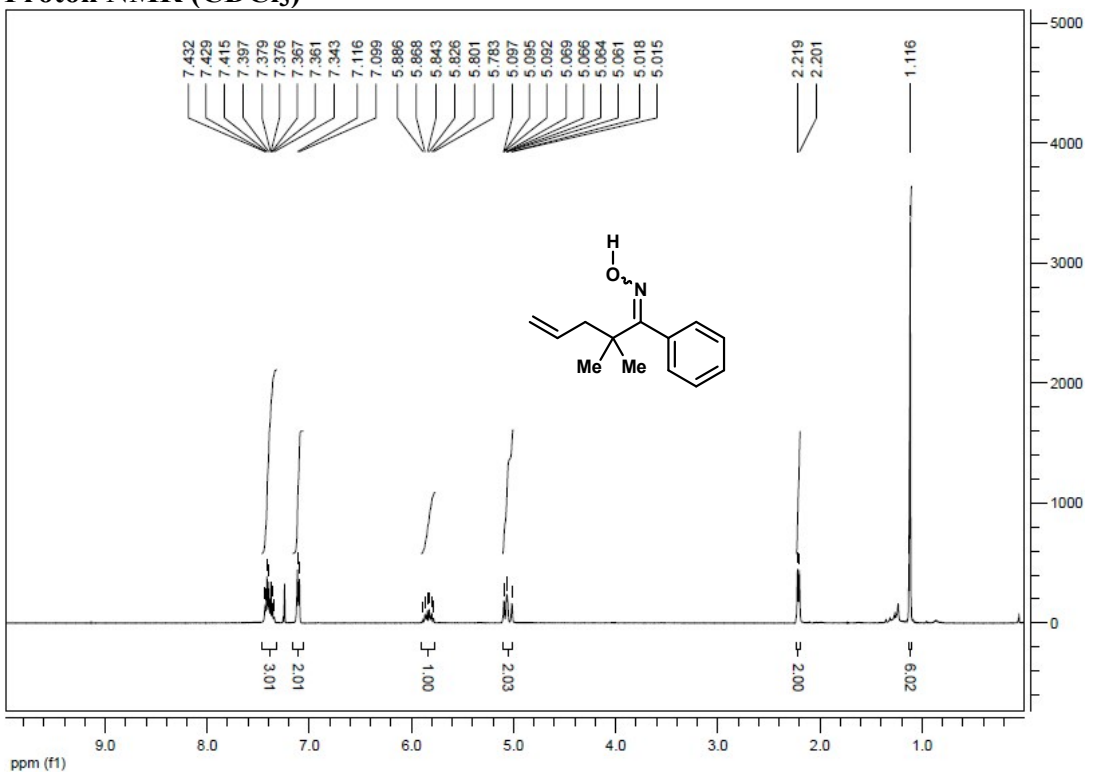


Carbon NMR ($CDCl_3$)

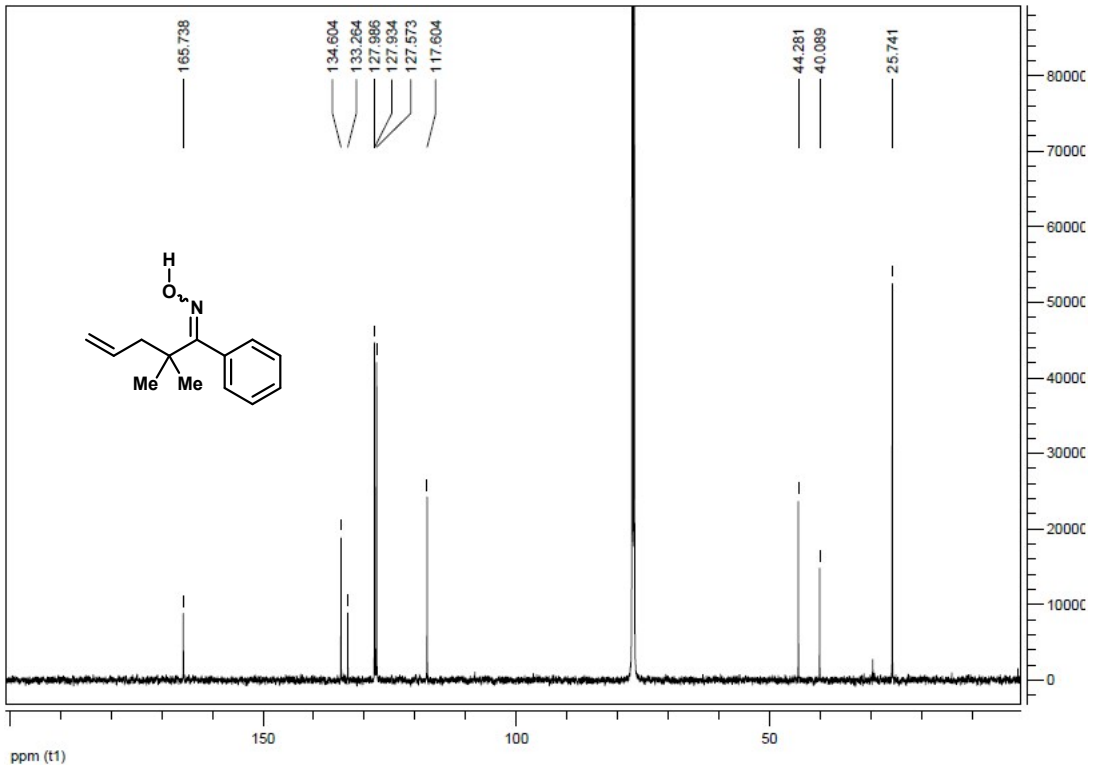


2,2-Dimethyl-1-phenylpent-4-en-1-one oxime (2o)

Proton NMR ($CDCl_3$)

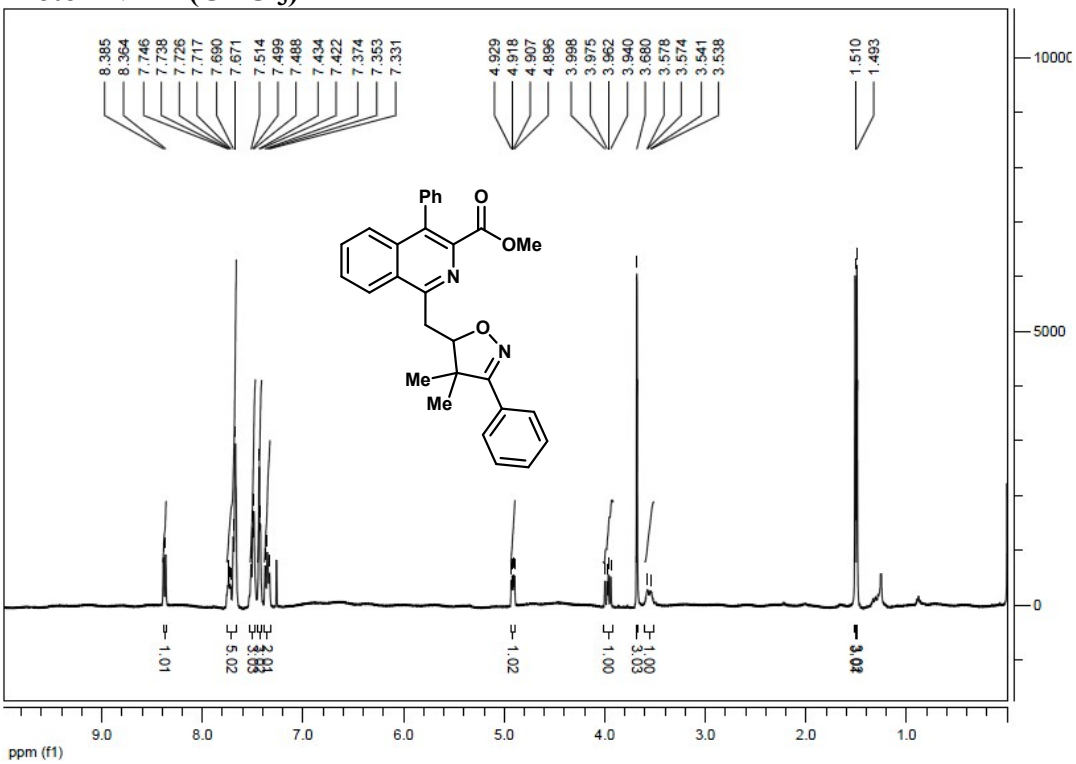


Carbon NMR ($CDCl_3$)

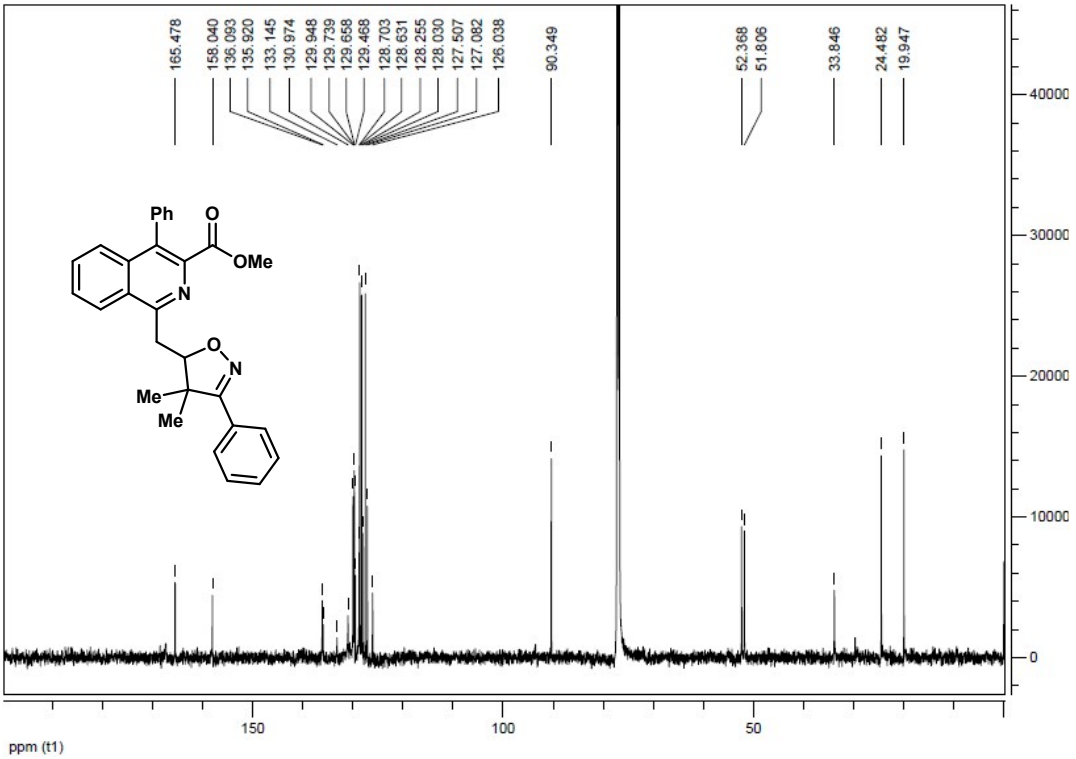


Methyl 1-((4,4-dimethyl-3-phenyl-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinoline-3-carboxylate (3a)

Proton NMR ($CDCl_3$)



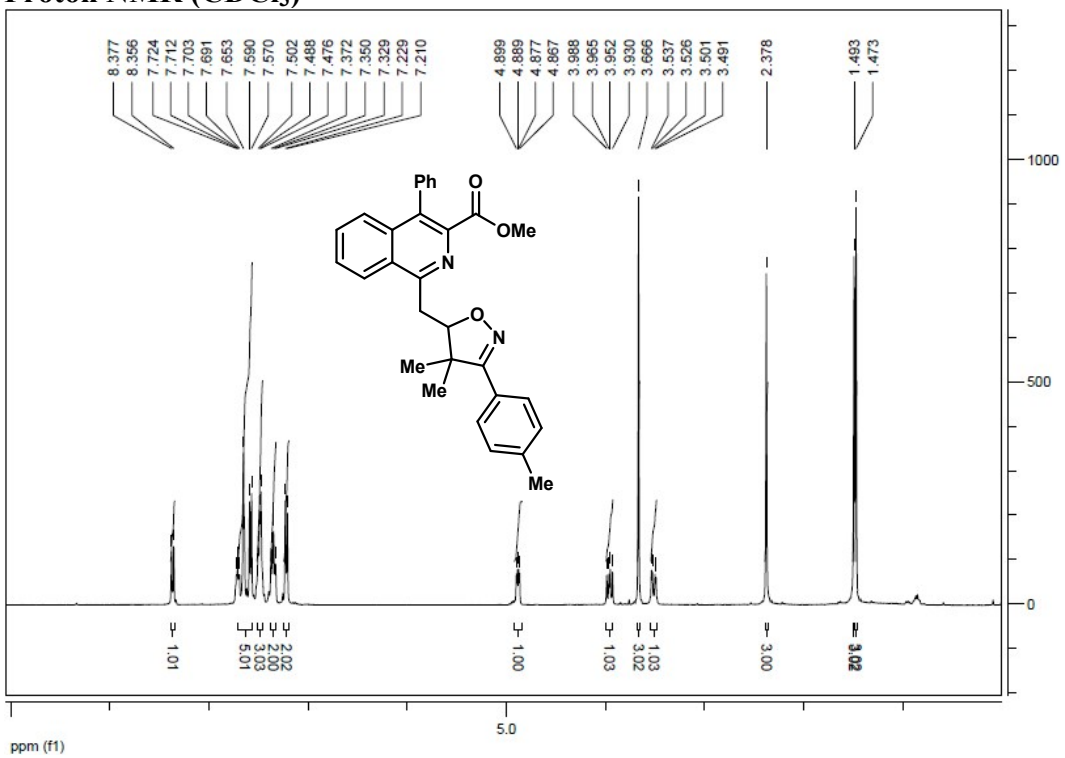
Carbon NMR ($CDCl_3$)



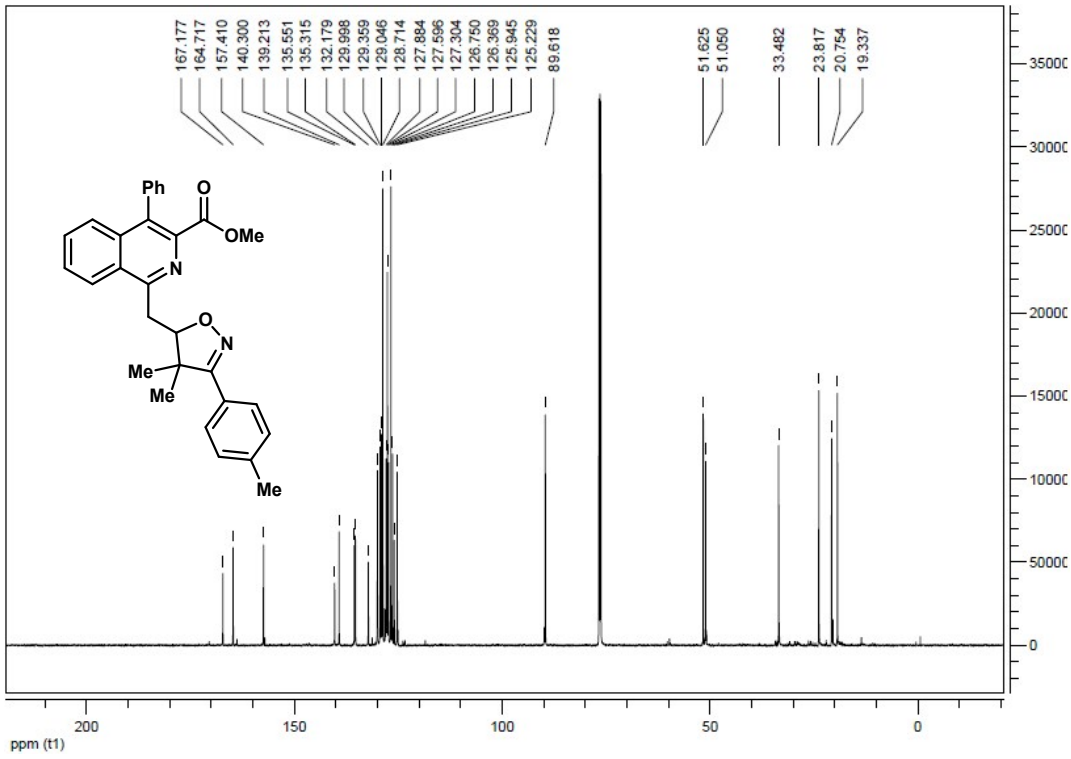
Methyl 1-((4,4-dimethyl-3-(*p*-tolyl)-4,5-dihydroisoxazol-5-yl)methyl)-4-

phenylisoquinoline-3-carboxylate (3b)

Proton NMR ($CDCl_3$)

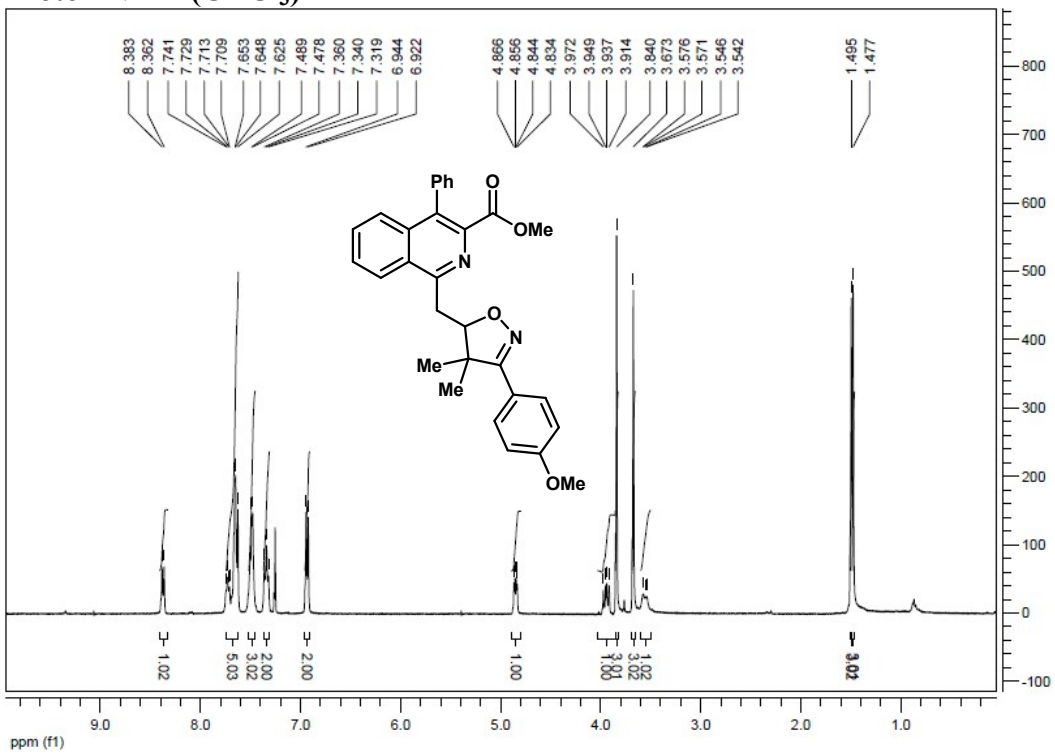


Carbon NMR ($CDCl_3$)

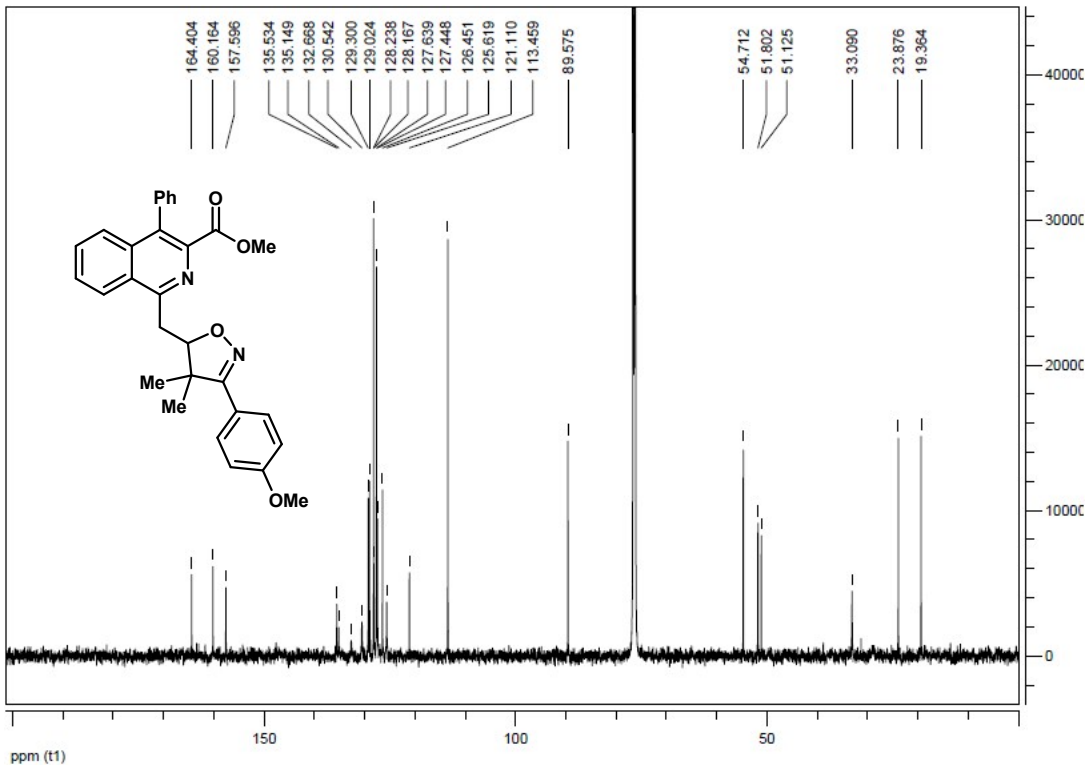


Methyl 1-((3-(4-methoxyphenyl)-4,4-dimethyl-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinoline-3-carboxylate (3c)

Proton NMR ($CDCl_3$)

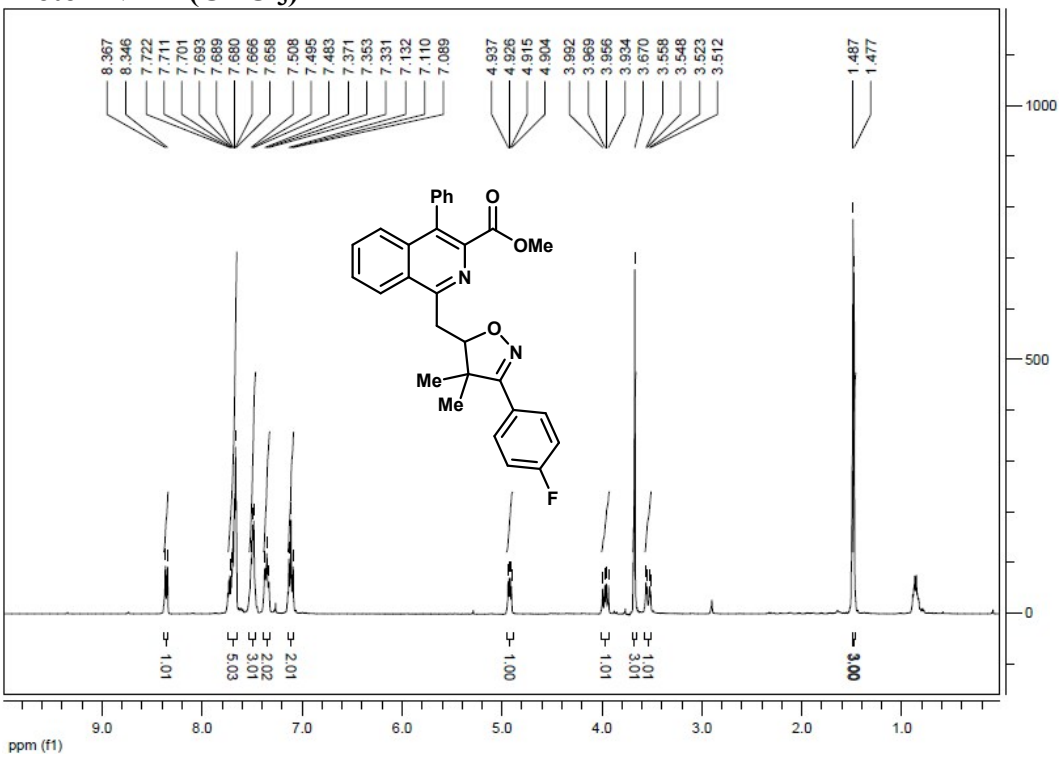


Carbon NMR ($CDCl_3$)

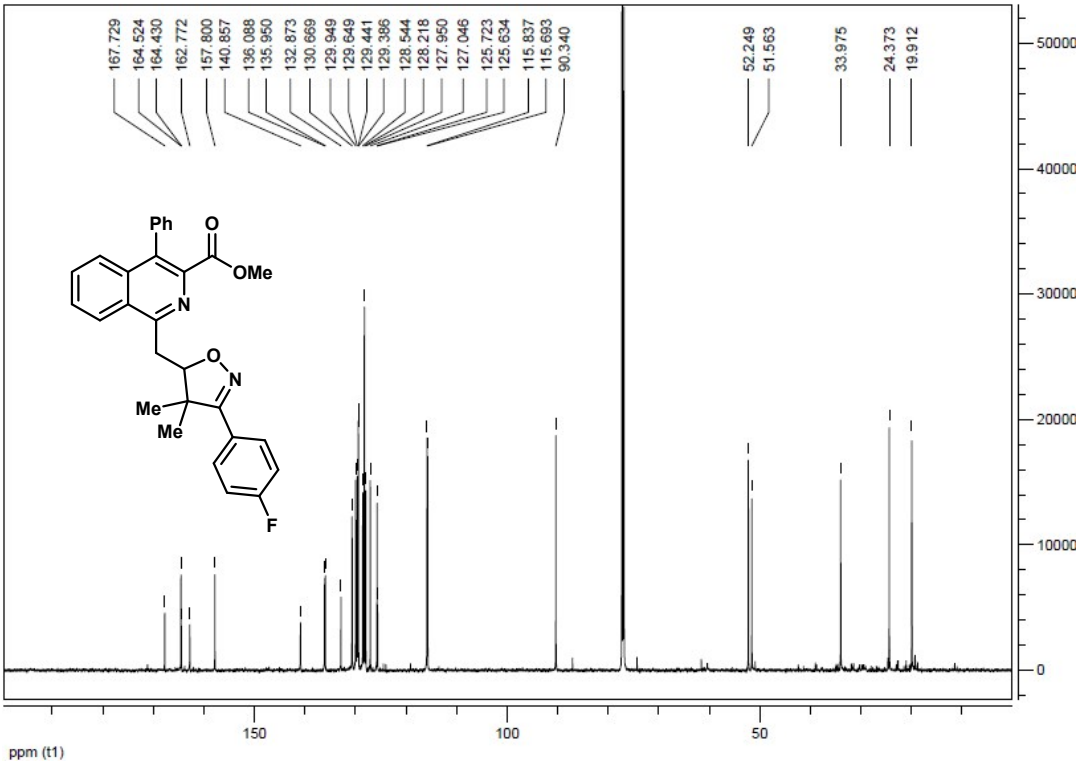


Methyl 1-((3-(4-fluorophenyl)-4,4-dimethyl-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinoline-3-carboxylate (3d)

Proton NMR ($CDCl_3$)

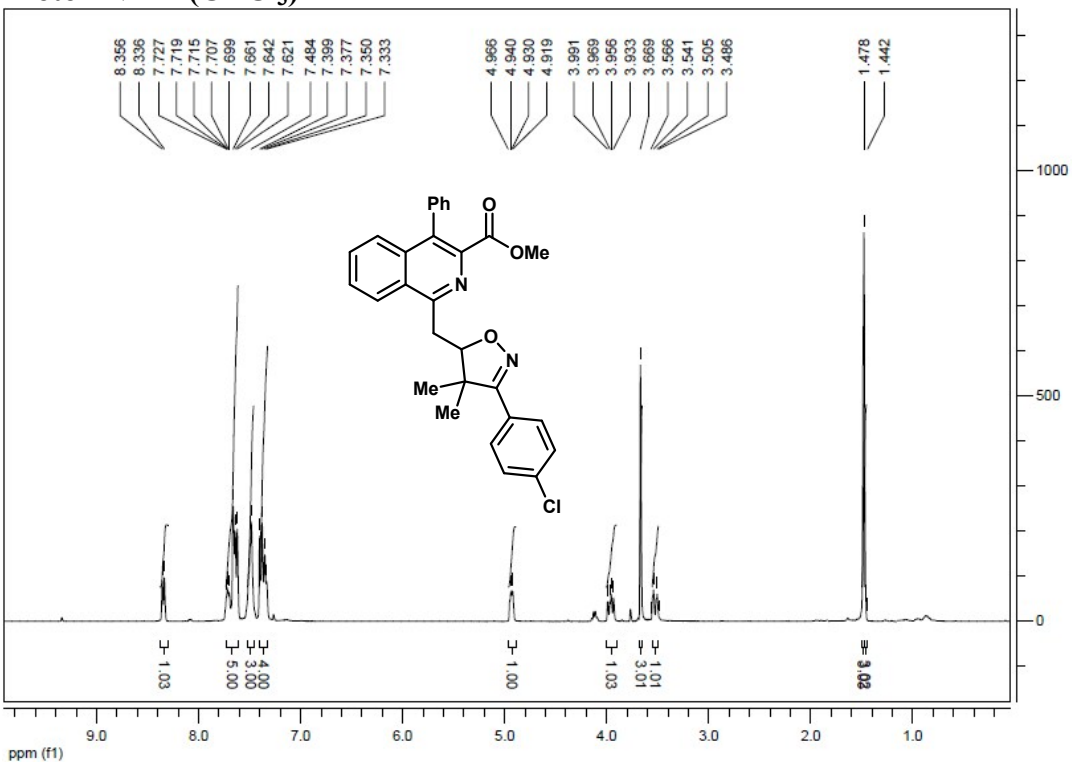


Carbon NMR ($CDCl_3$)

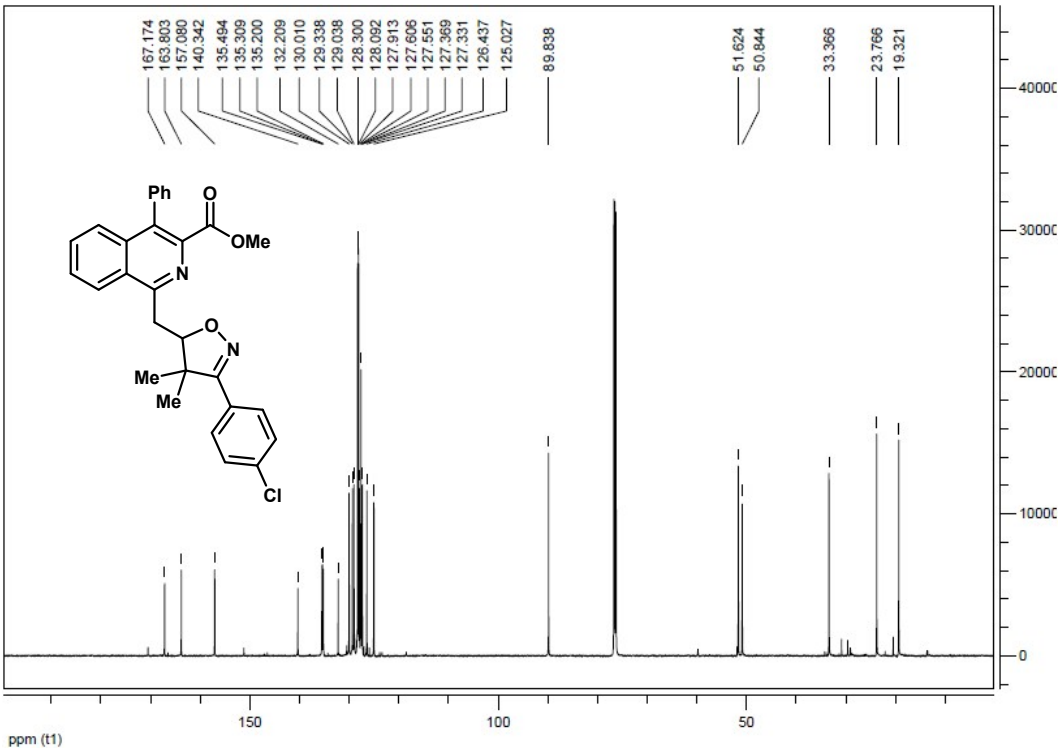


Methyl 1-((3-(4-chlorophenyl)-4,4-dimethyl-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinoline-3-carboxylate (3e)

Proton NMR ($CDCl_3$)

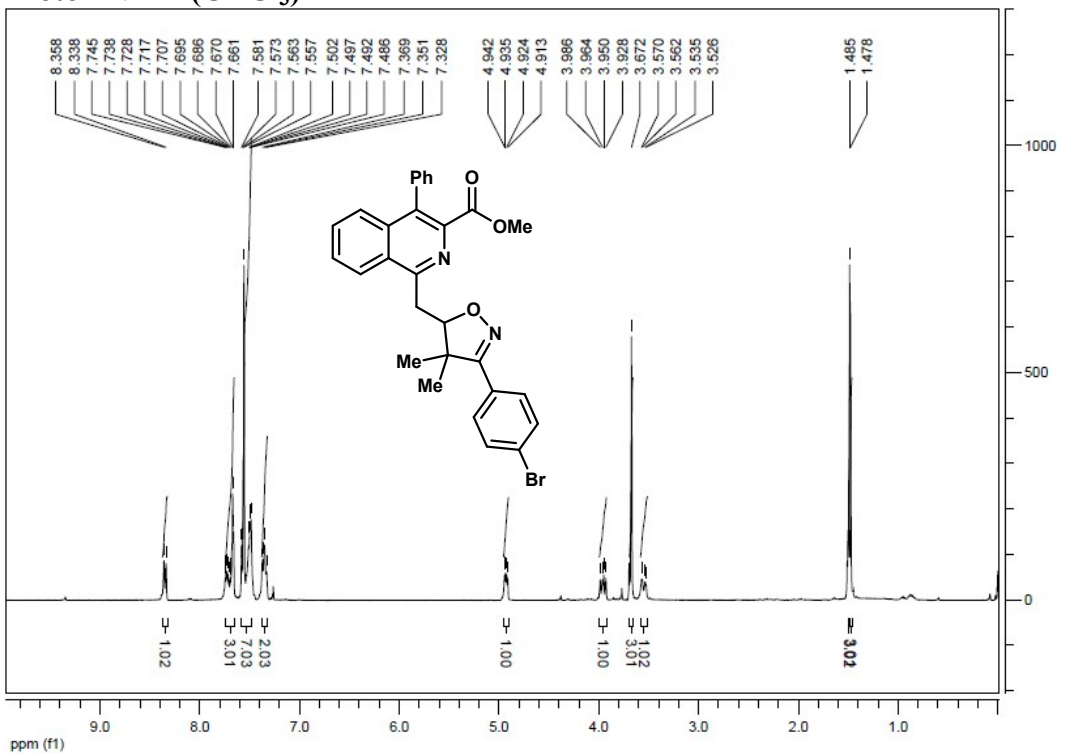


Carbon NMR ($CDCl_3$)

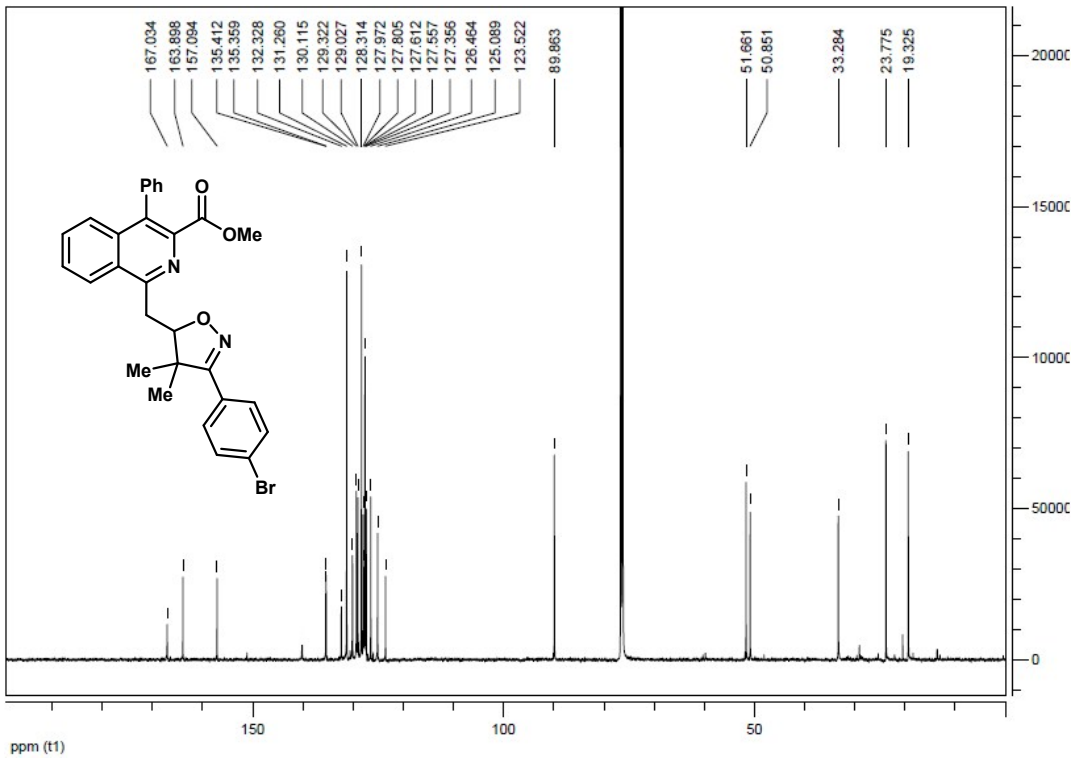


Methyl 1-((3-(4-bromophenyl)-4,4-dimethyl-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinoline-3-carboxylate (3f)

Proton NMR ($CDCl_3$)

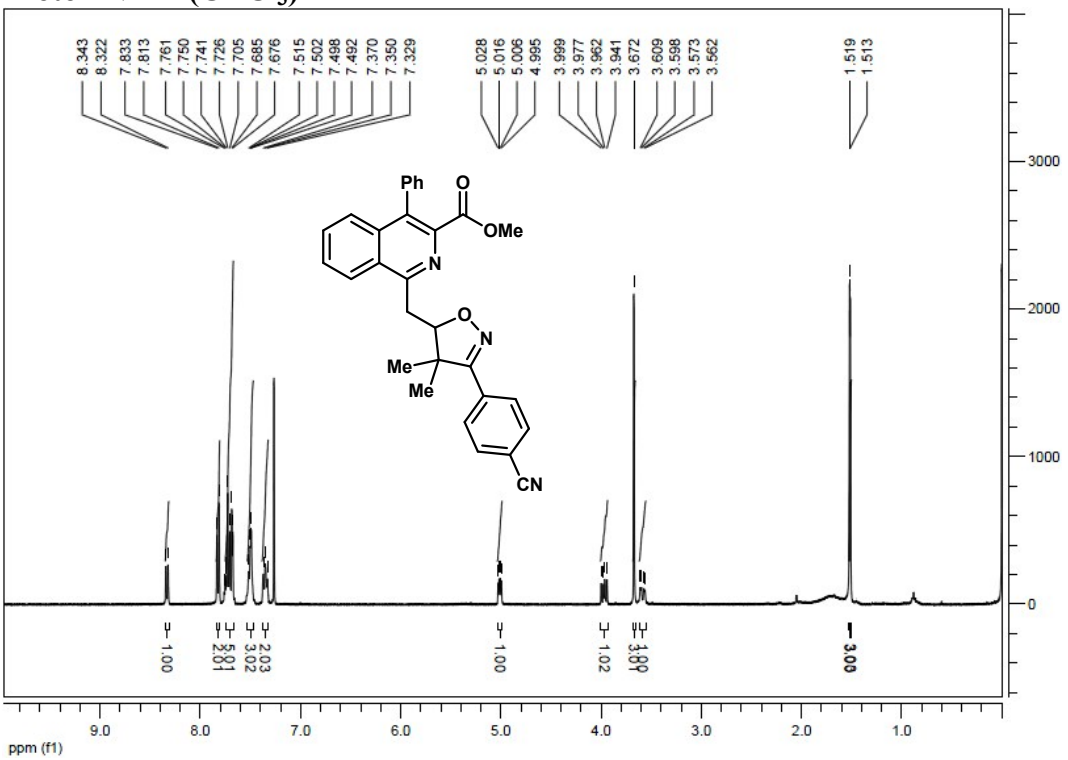


Carbon NMR ($CDCl_3$)

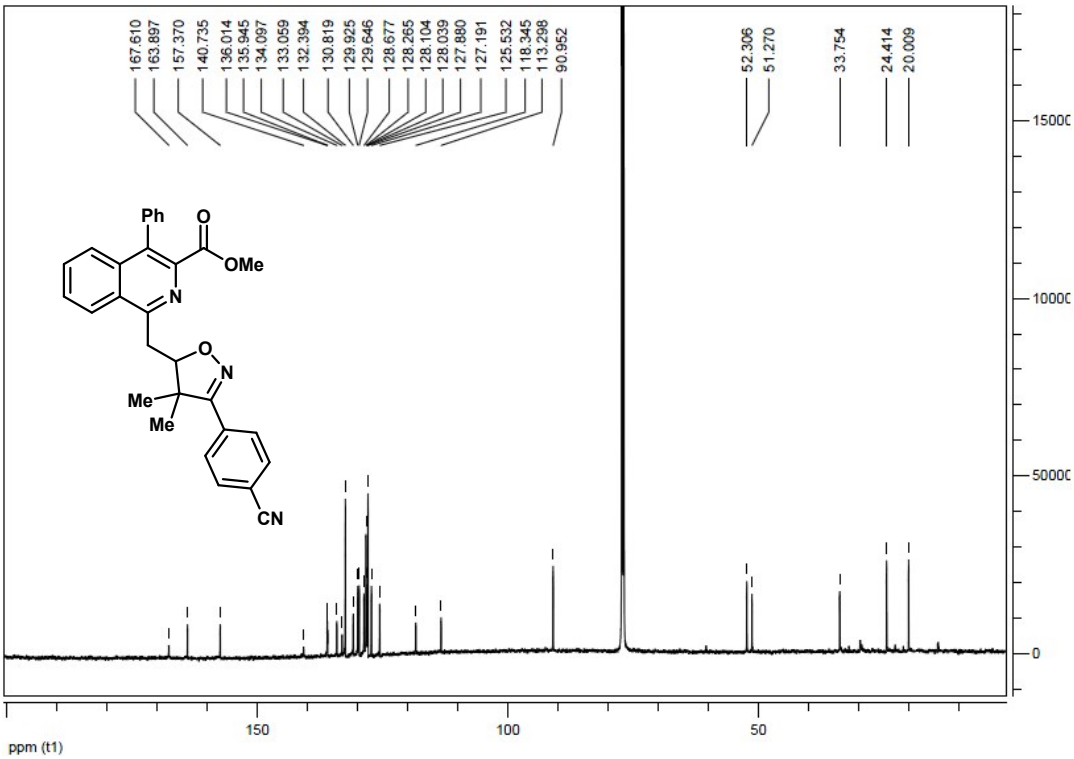


Methyl 1-((3-(4-cyanophenyl)-4,4-dimethyl-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinoline-3-carboxylate (3g)

Proton NMR ($CDCl_3$)

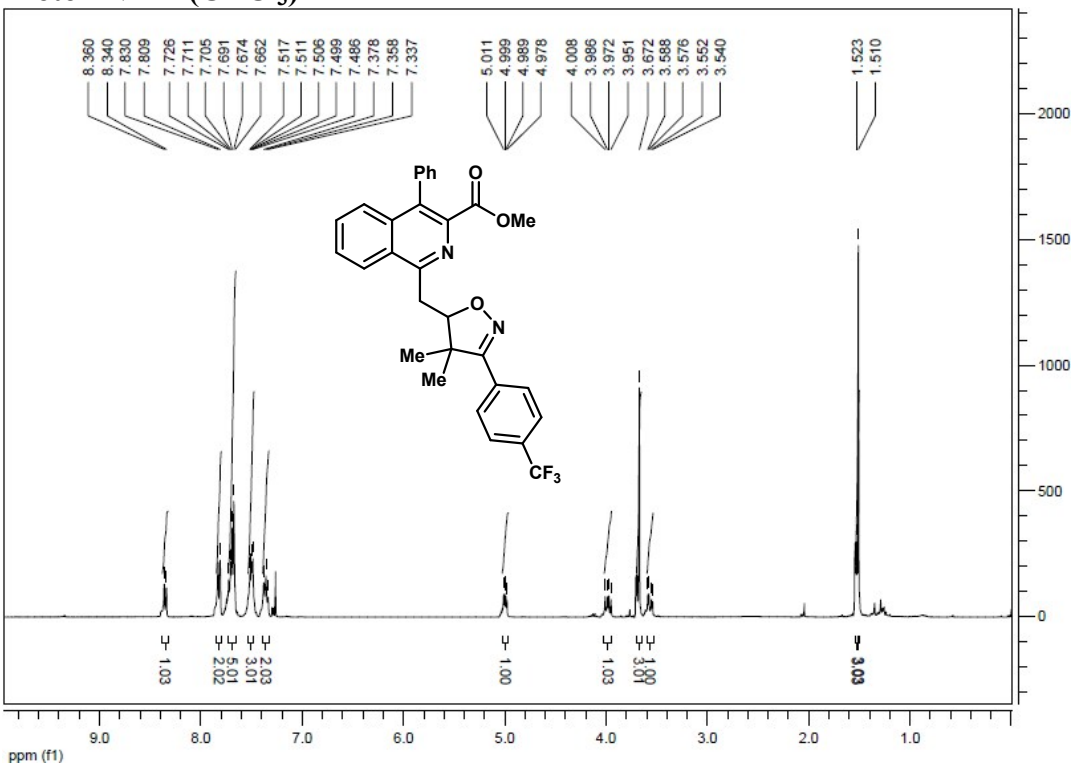


Carbon NMR ($CDCl_3$)

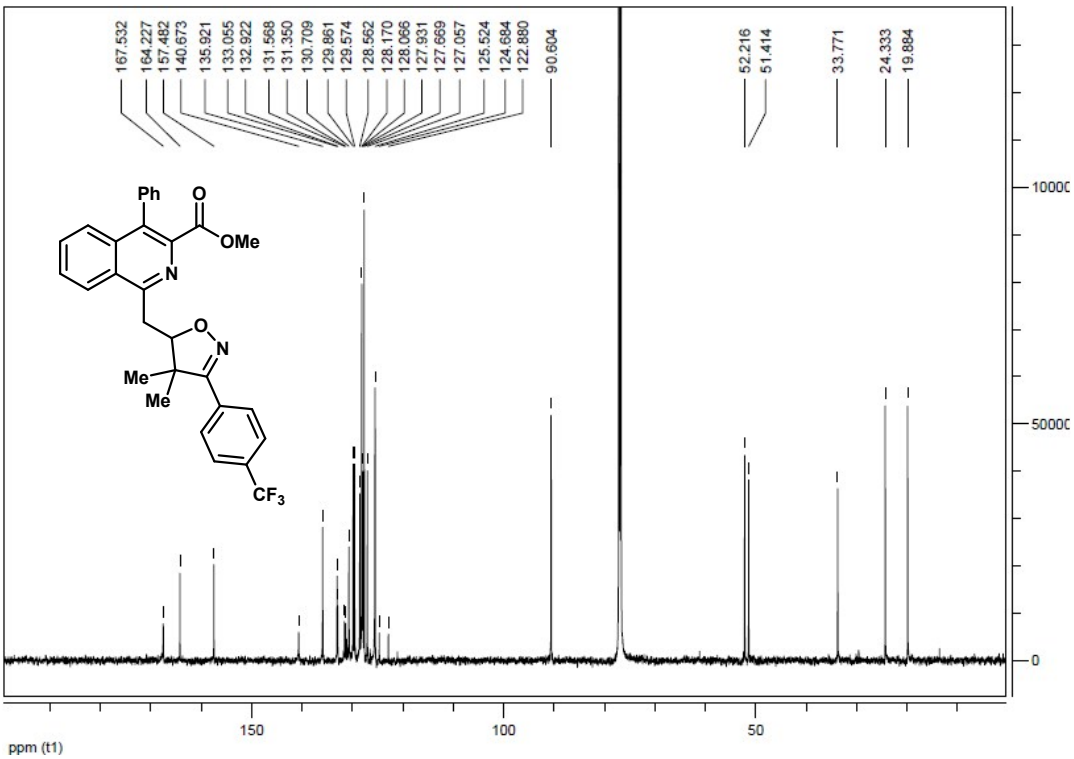


Methyl 1-((4,4-dimethyl-3-(4-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinoline-3-carboxylate (3h)

Proton NMR ($CDCl_3$)

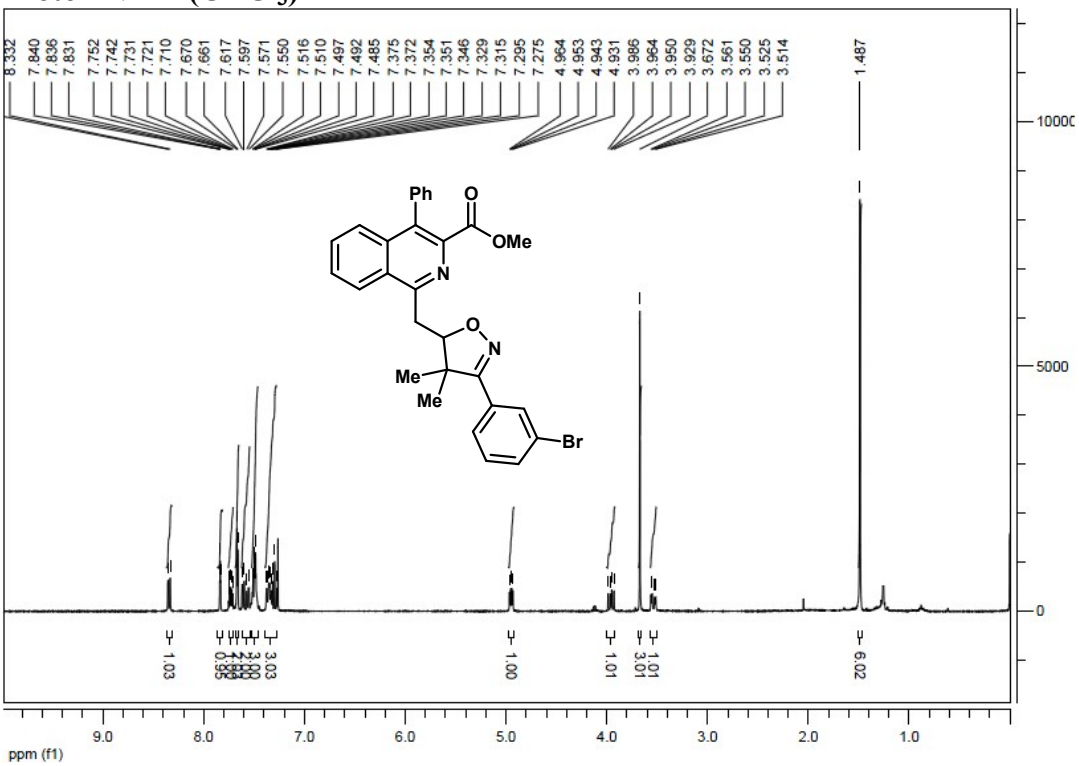


Carbon NMR ($CDCl_3$)

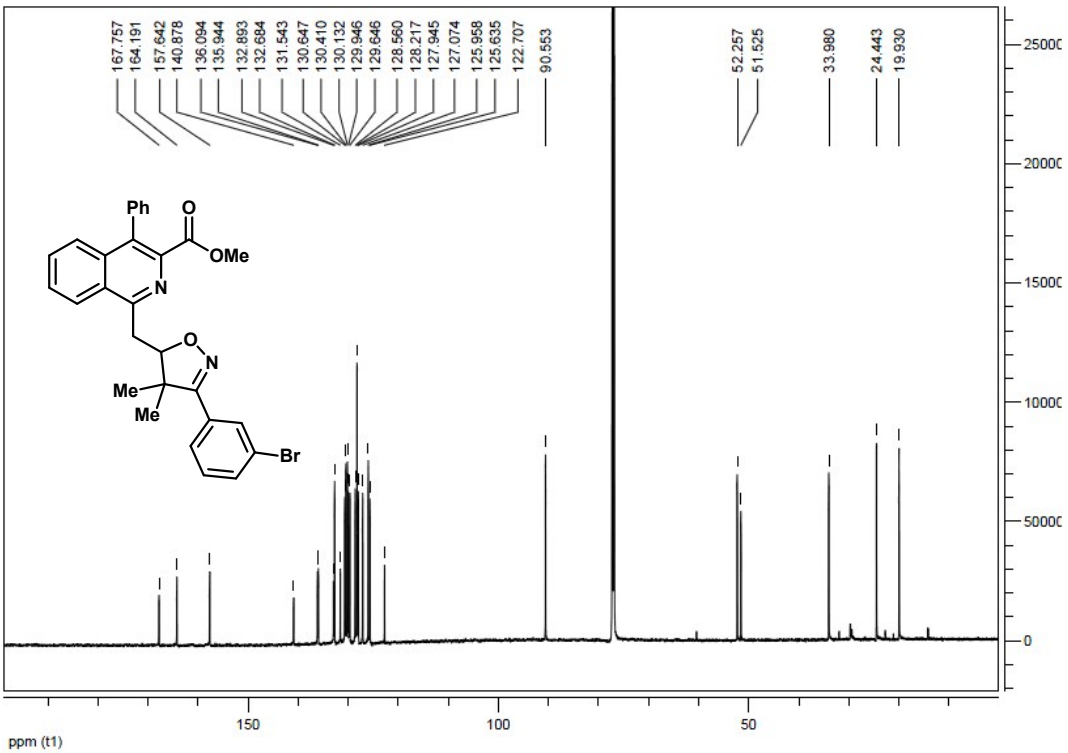


Methyl 1-((3-(3-bromophenyl)-4,4-dimethyl-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinoline-3-carboxylate (3i)

Proton NMR ($CDCl_3$)

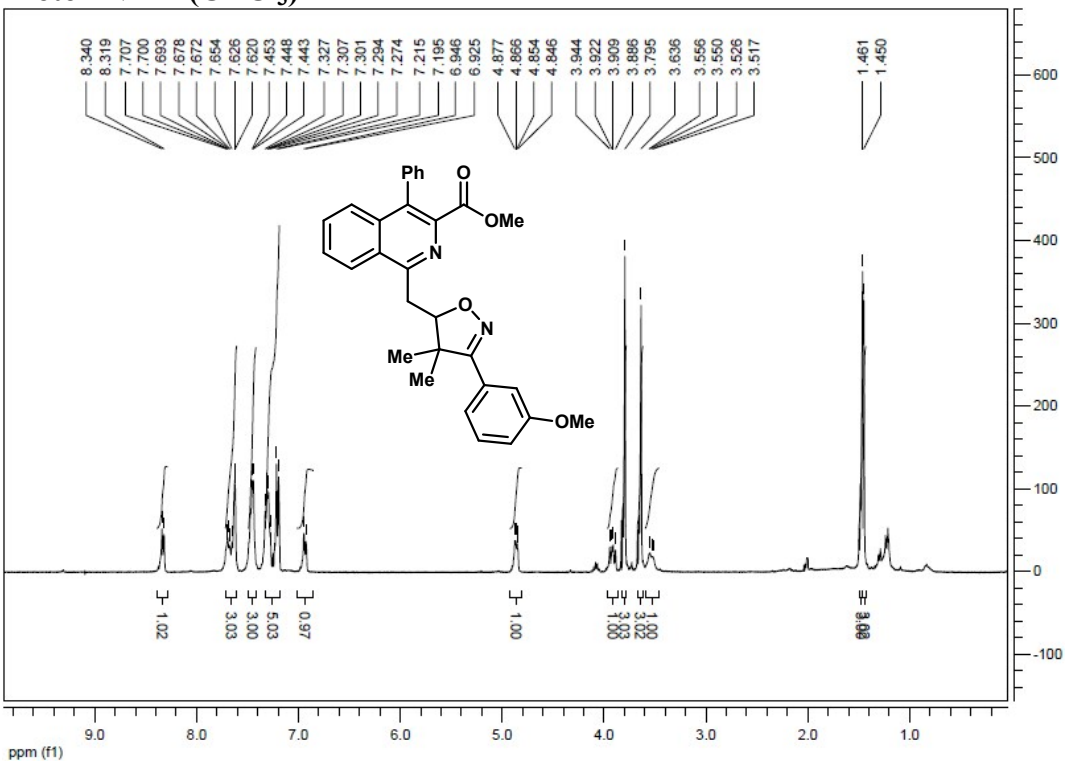


Carbon NMR ($CDCl_3$)

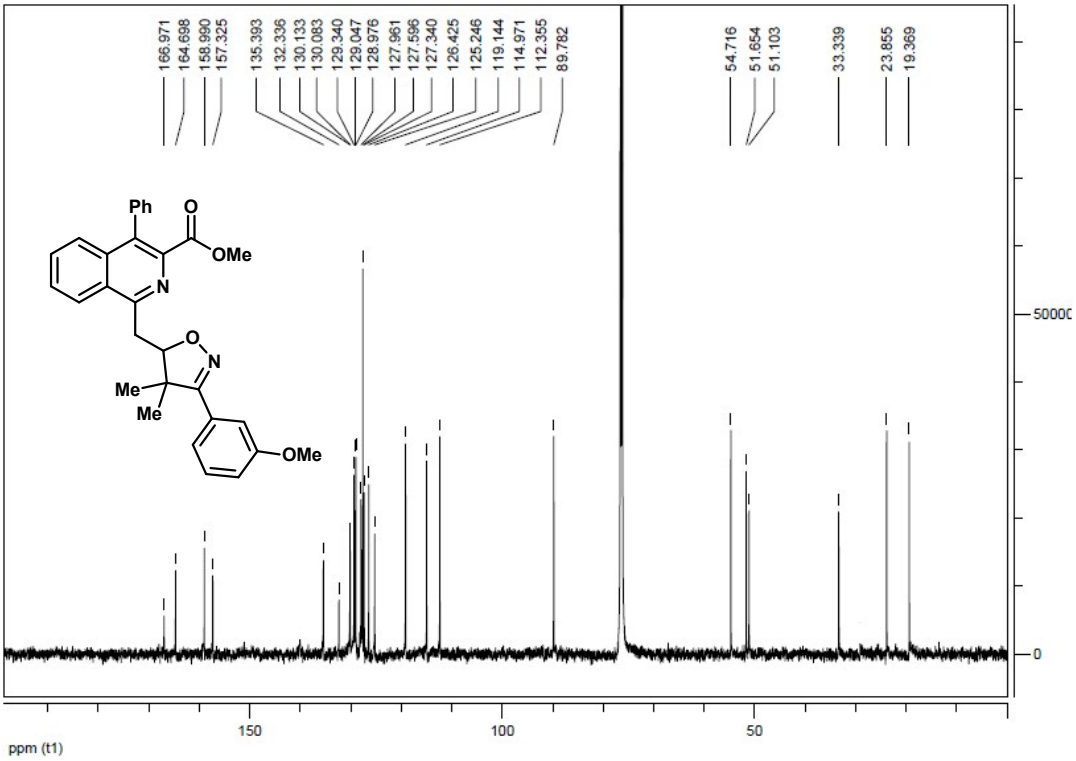


Methyl 1-((3-(3-methoxyphenyl)-4,4-dimethyl-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinoline-3-carboxylate (3j)

Proton NMR ($CDCl_3$)

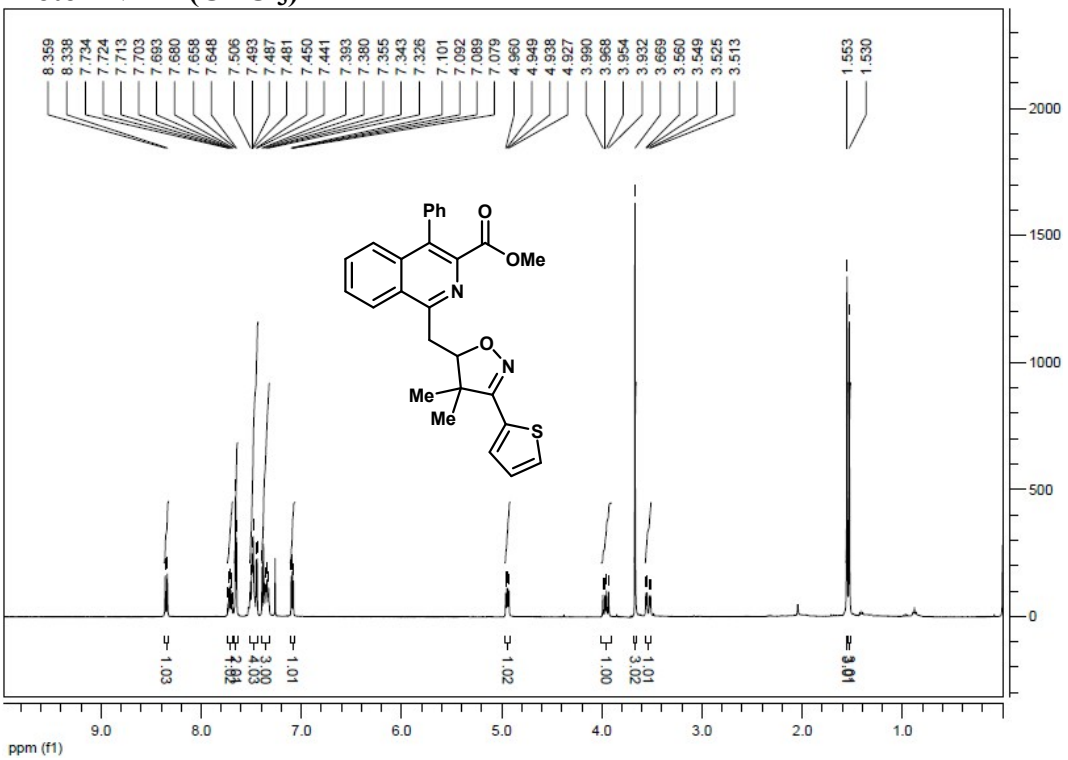


Carbon NMR ($CDCl_3$)

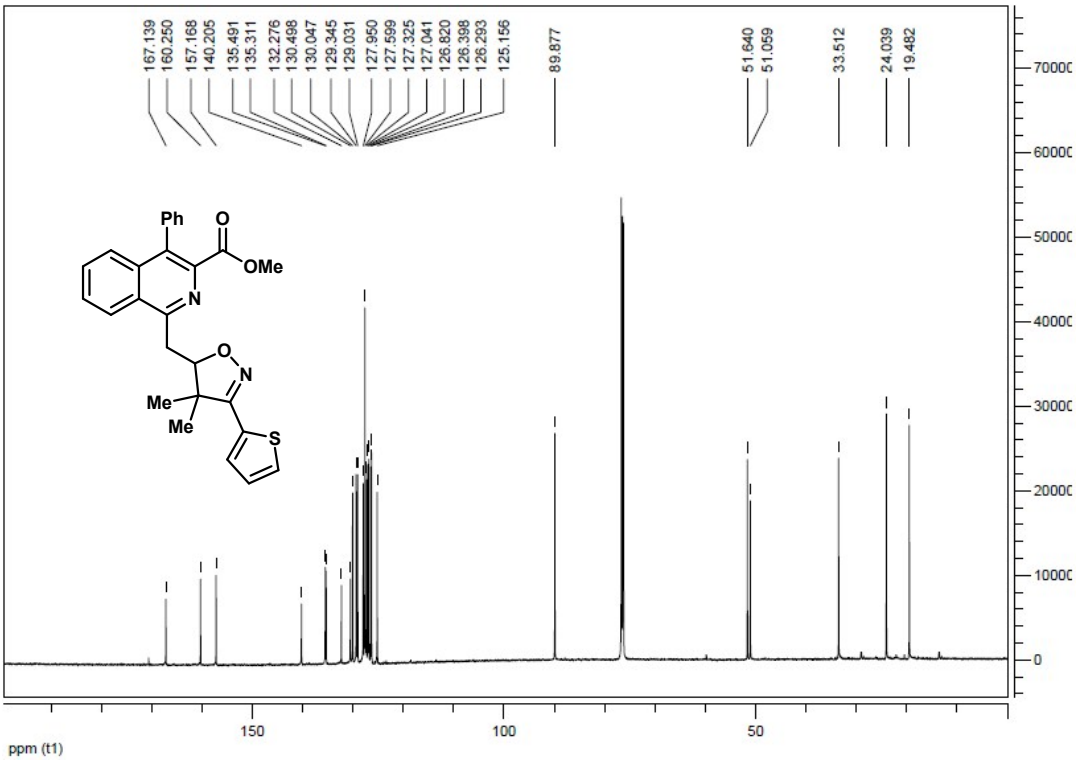


Methyl 1-((4,4-dimethyl-3-(thiophen-2-yl)-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinoline-3-carboxylate (3k)

Proton NMR ($CDCl_3$)

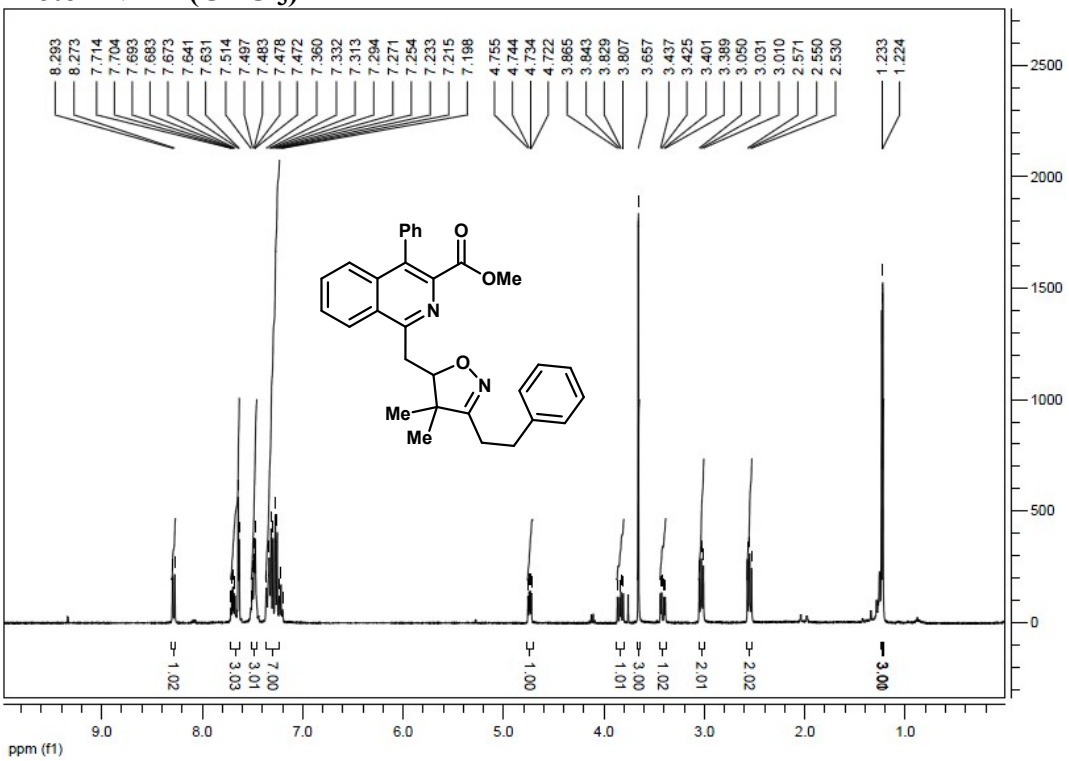


Carbon NMR ($CDCl_3$)

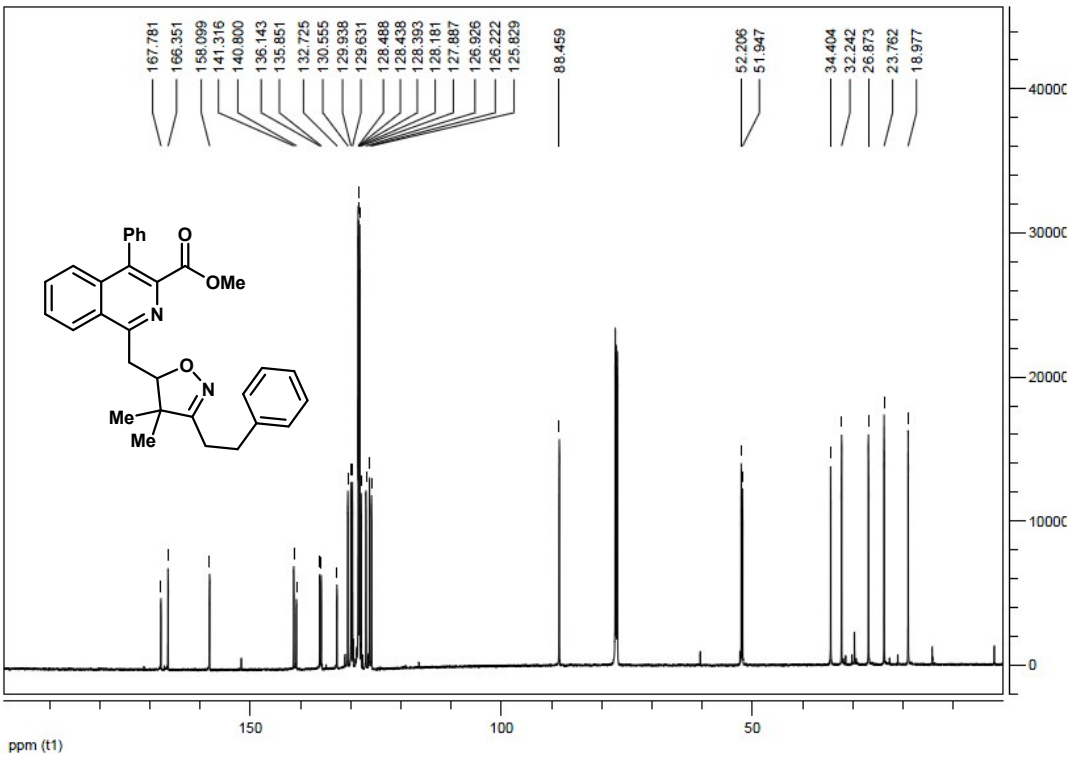


Methyl 1-((4,4-dimethyl-3-phenethyl-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinoline-3-carboxylate (3l)

Proton NMR ($CDCl_3$)

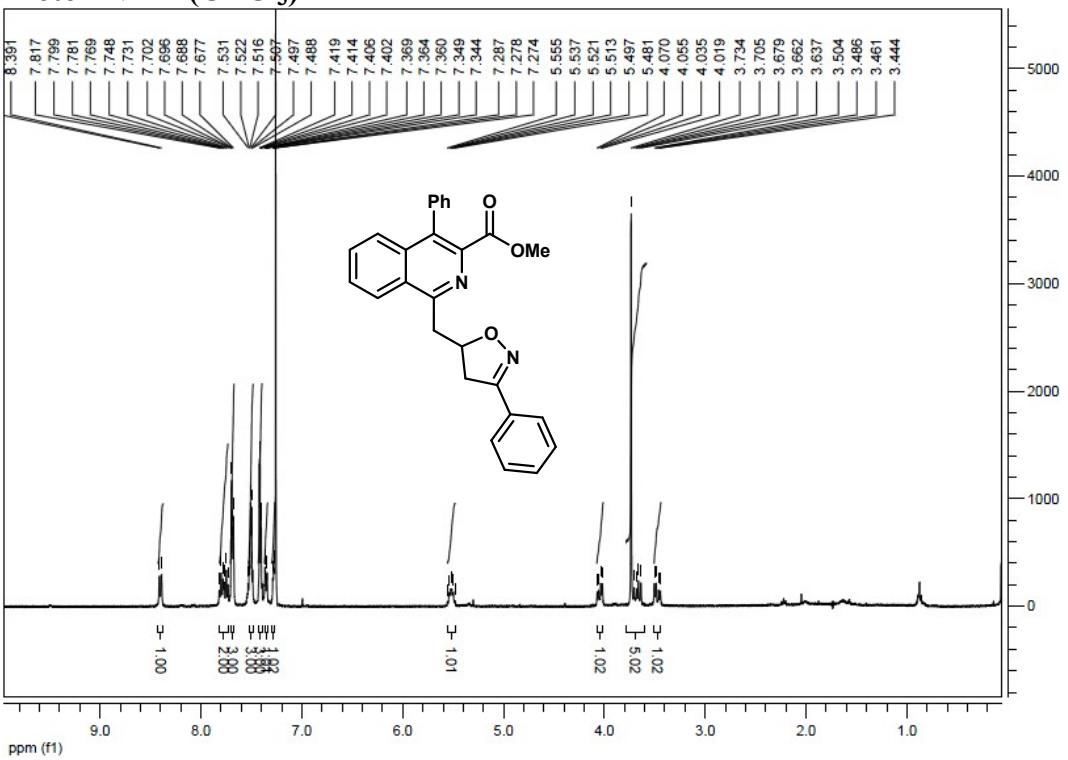


Carbon NMR ($CDCl_3$)

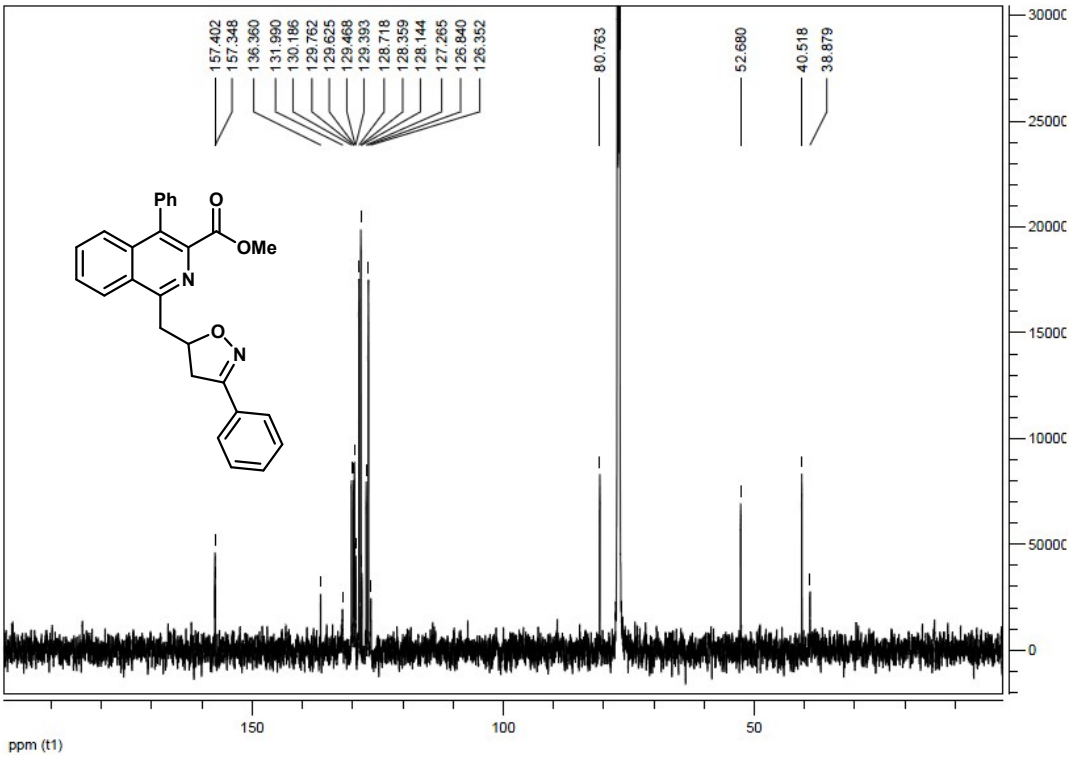


Methyl 4-phenyl-1-((3-phenyl-4,5-dihydroisoxazol-5-yl)methyl)isoquinoline-3-carboxylate (3m)

Proton NMR ($CDCl_3$)

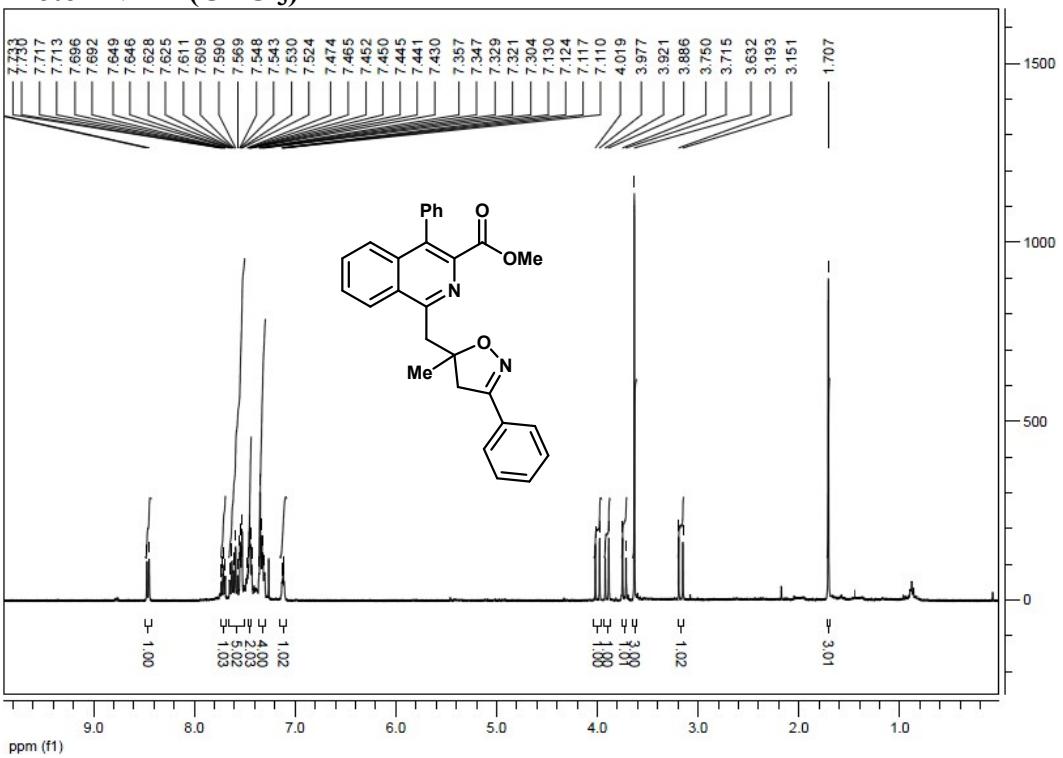


Carbon NMR ($CDCl_3$)

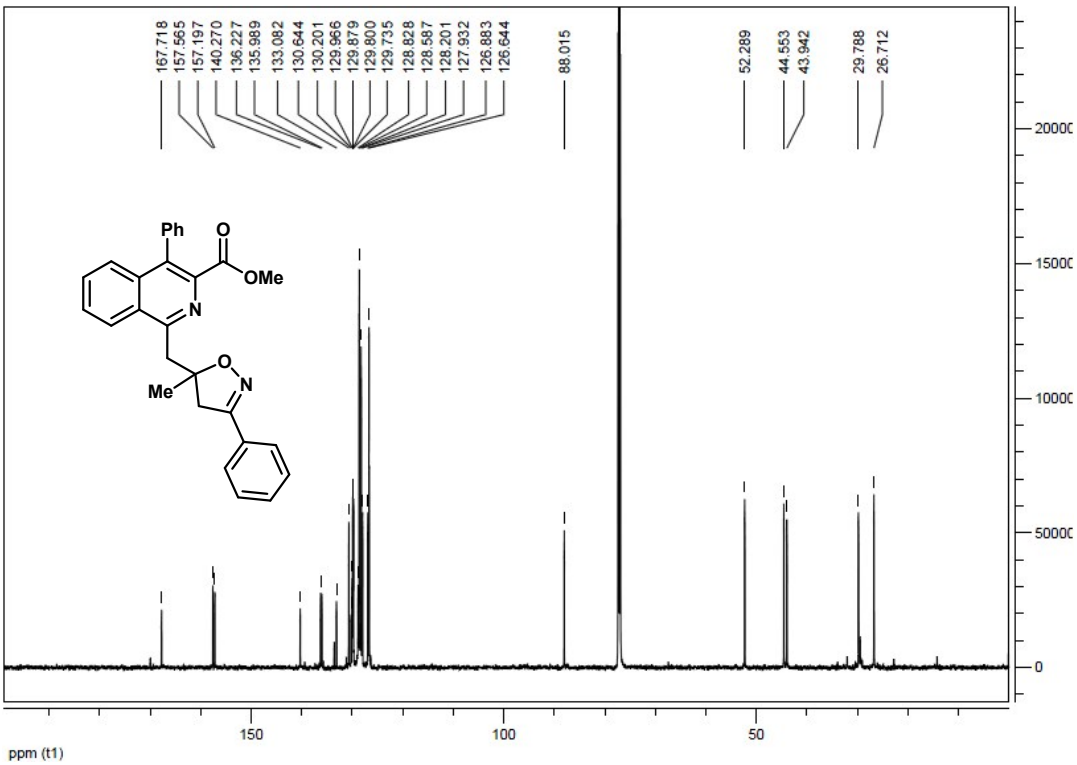


Methyl 1-((5-methyl-3-phenyl-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinoline-3-carboxylate (3n)

Proton NMR ($CDCl_3$)

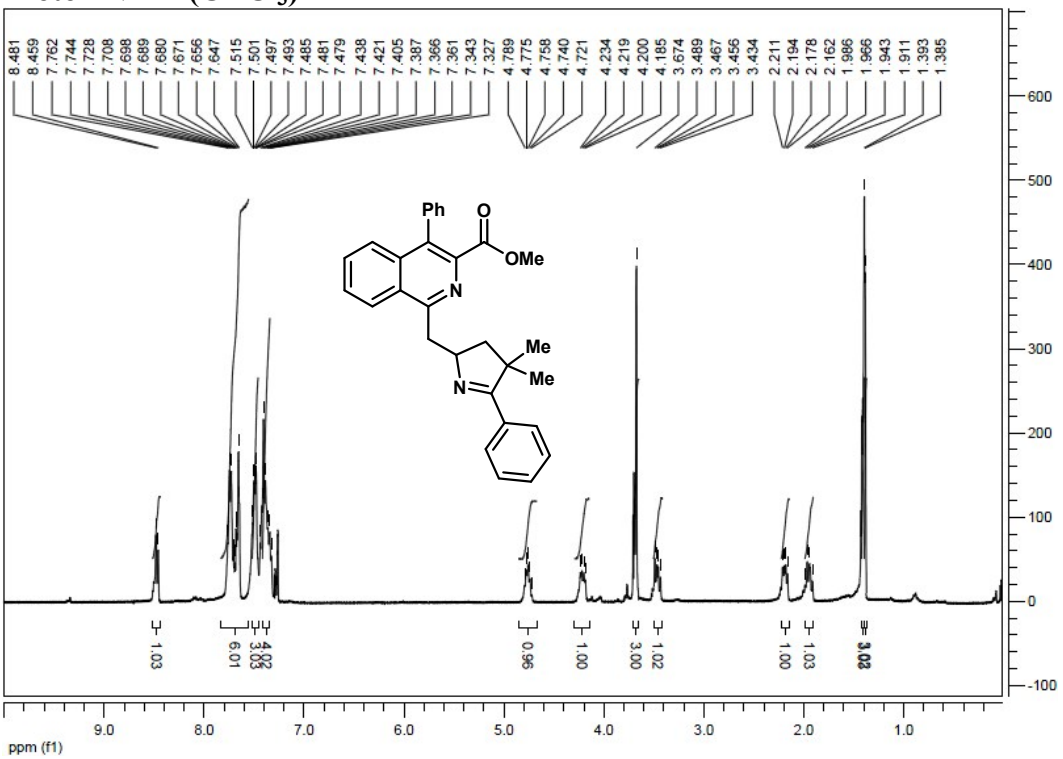


Carbon NMR ($CDCl_3$)

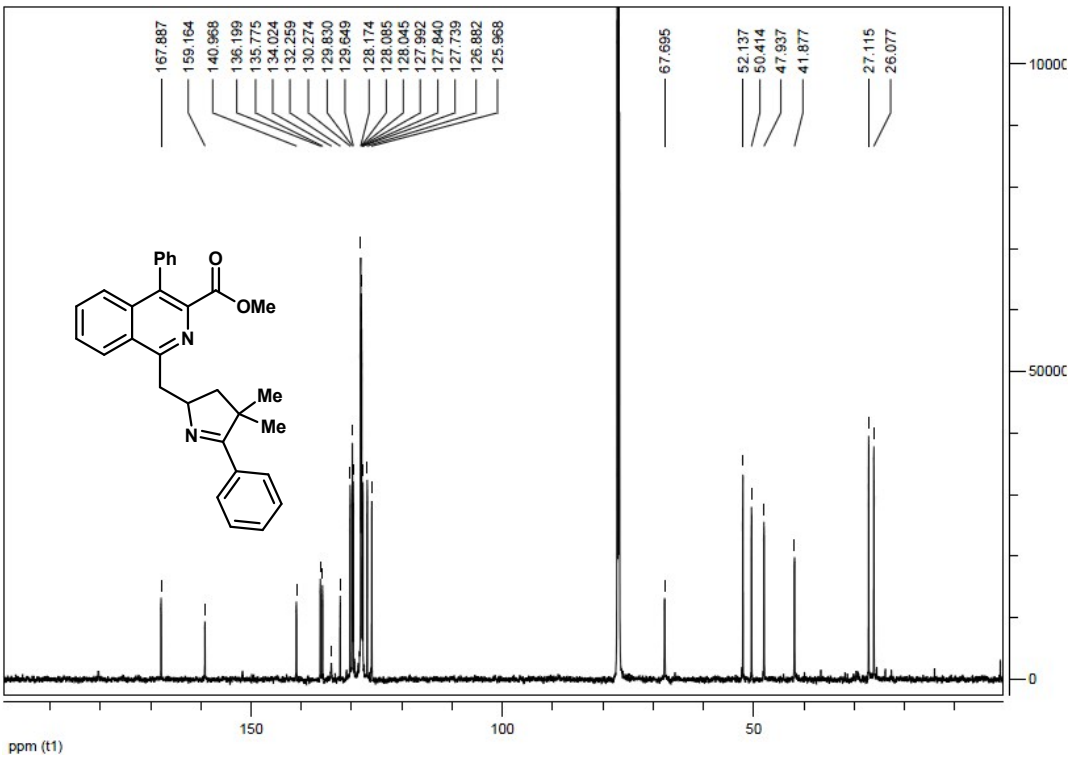


Methyl 1-((4,4-dimethyl-5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)methyl)-4-phenylisoquinoline-3-carboxylate (3o)

Proton NMR ($CDCl_3$)

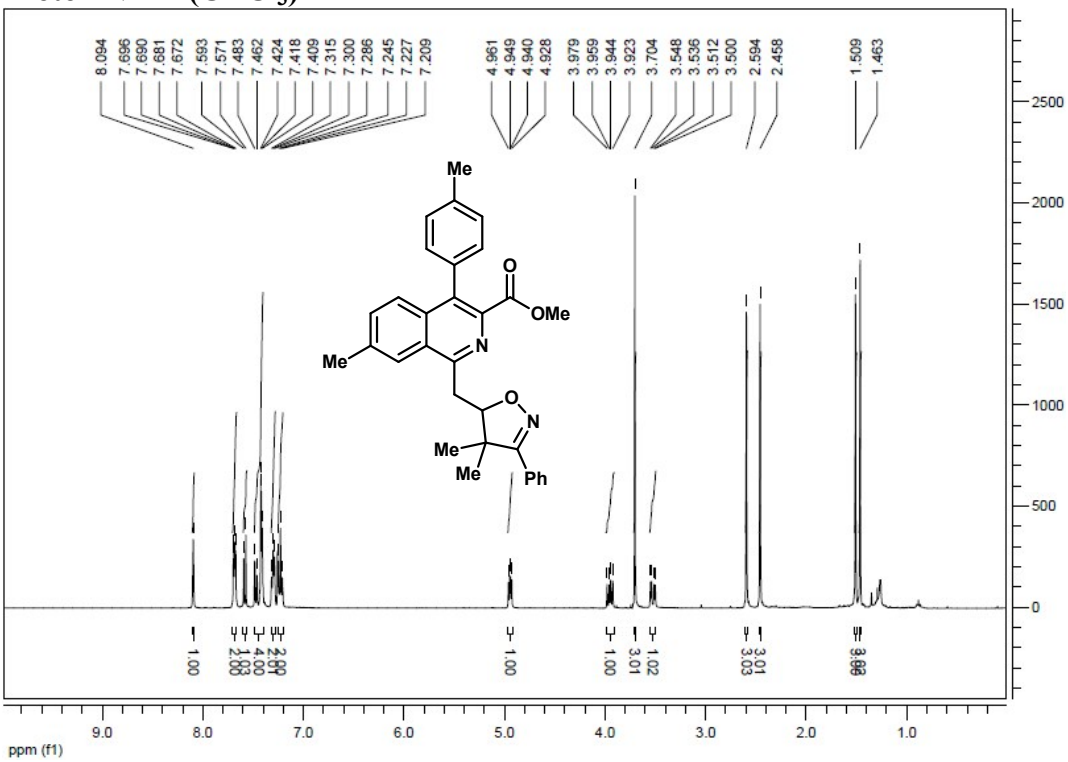


Carbon NMR ($CDCl_3$)

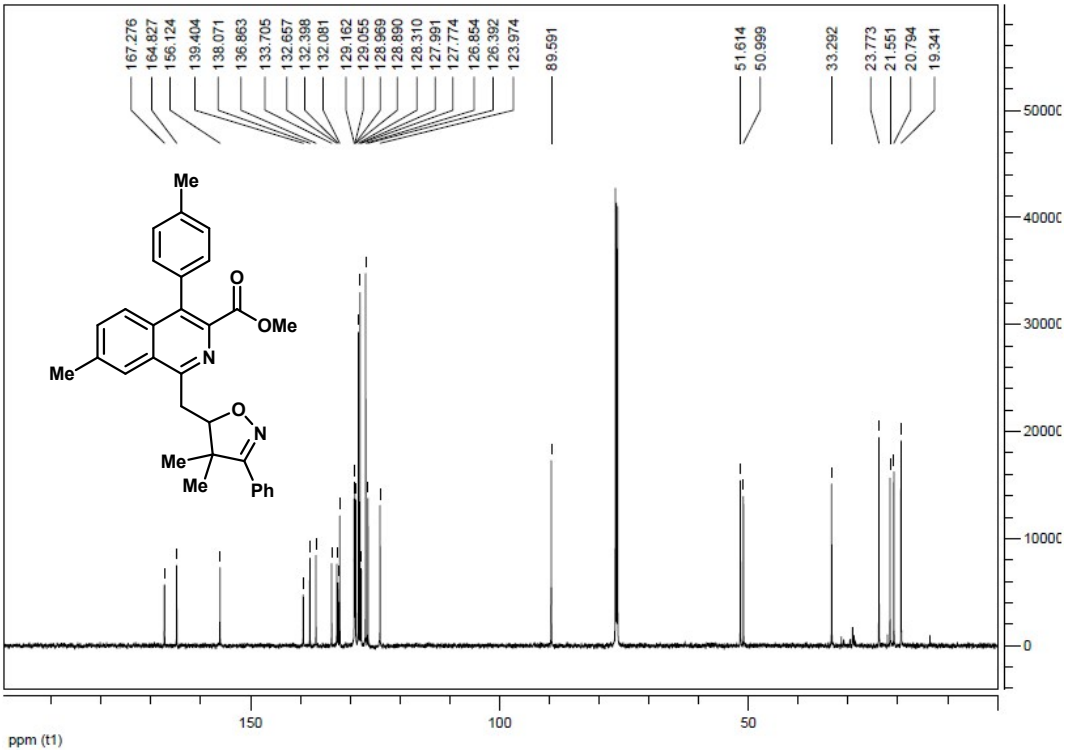


Methyl 1-((4,4-dimethyl-3-phenyl-4,5-dihydroisoxazol-5-yl)methyl)-7-methyl-4-(*p*-tolyl)isoquinoline-3-carboxylate (4b)

Proton NMR ($CDCl_3$)

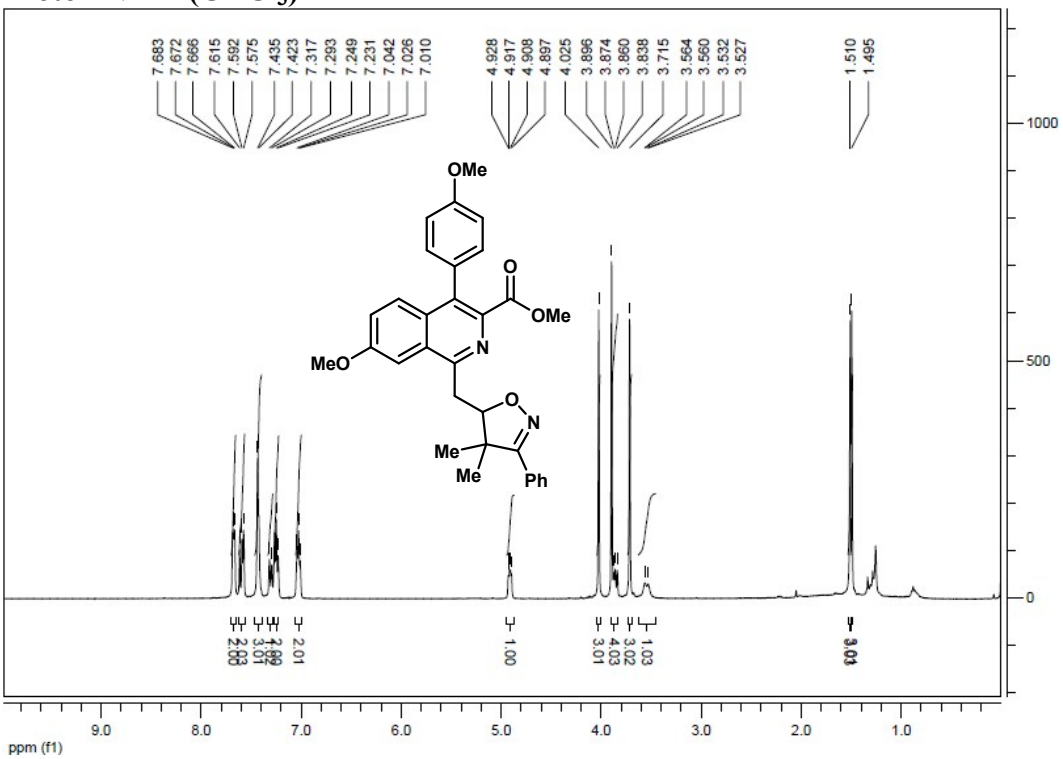


Carbon NMR ($CDCl_3$)

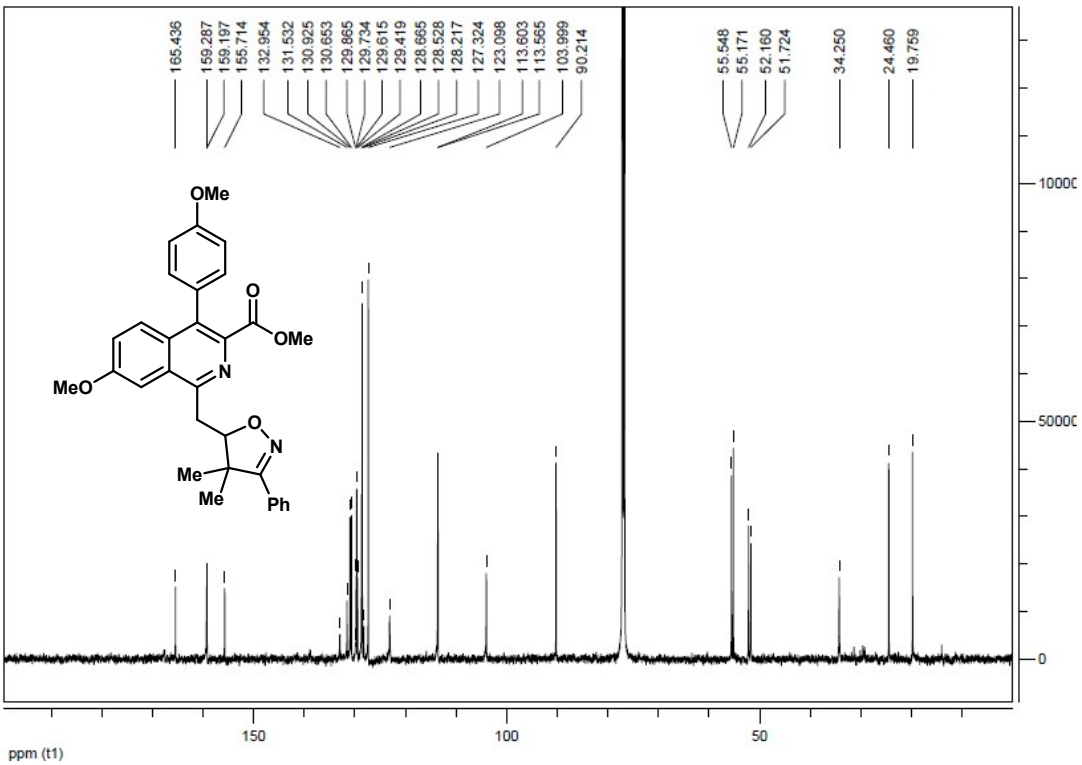


Methyl 1-((4,4-dimethyl-3-phenyl-4,5-dihydroisoxazol-5-yl)methyl)-7-methoxy-4-(4-methoxyphenyl)isoquinoline-3-carboxylate (4c)

Proton NMR ($CDCl_3$)

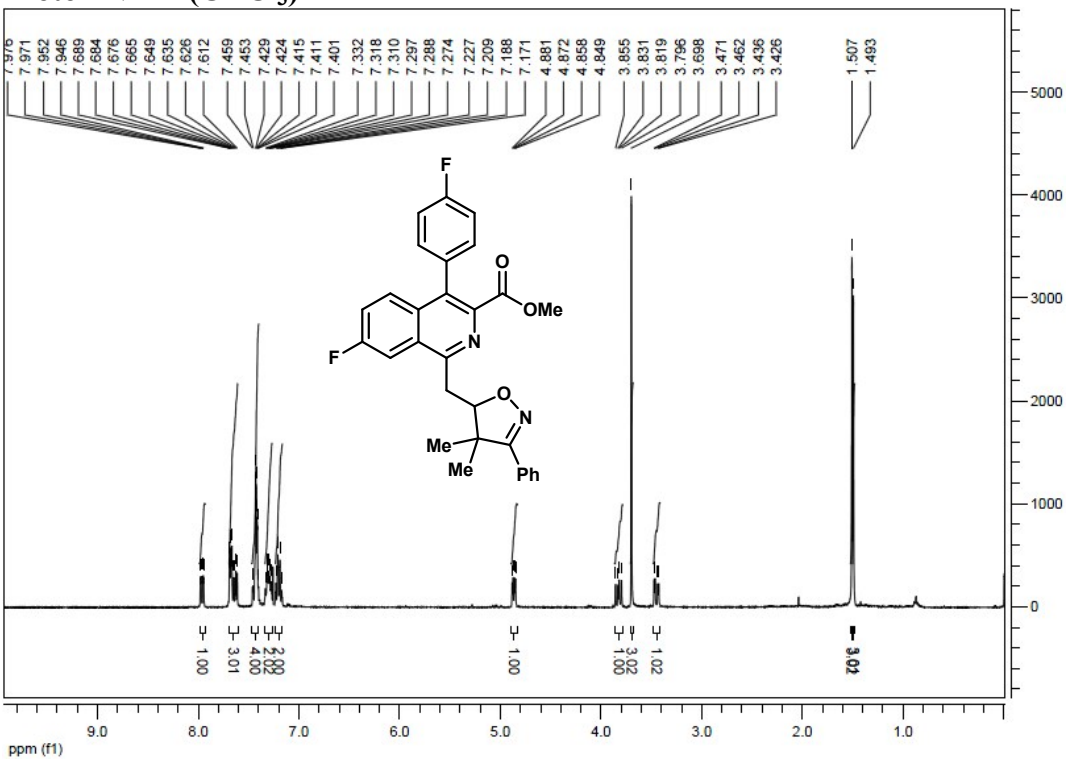


Carbon NMR ($CDCl_3$)

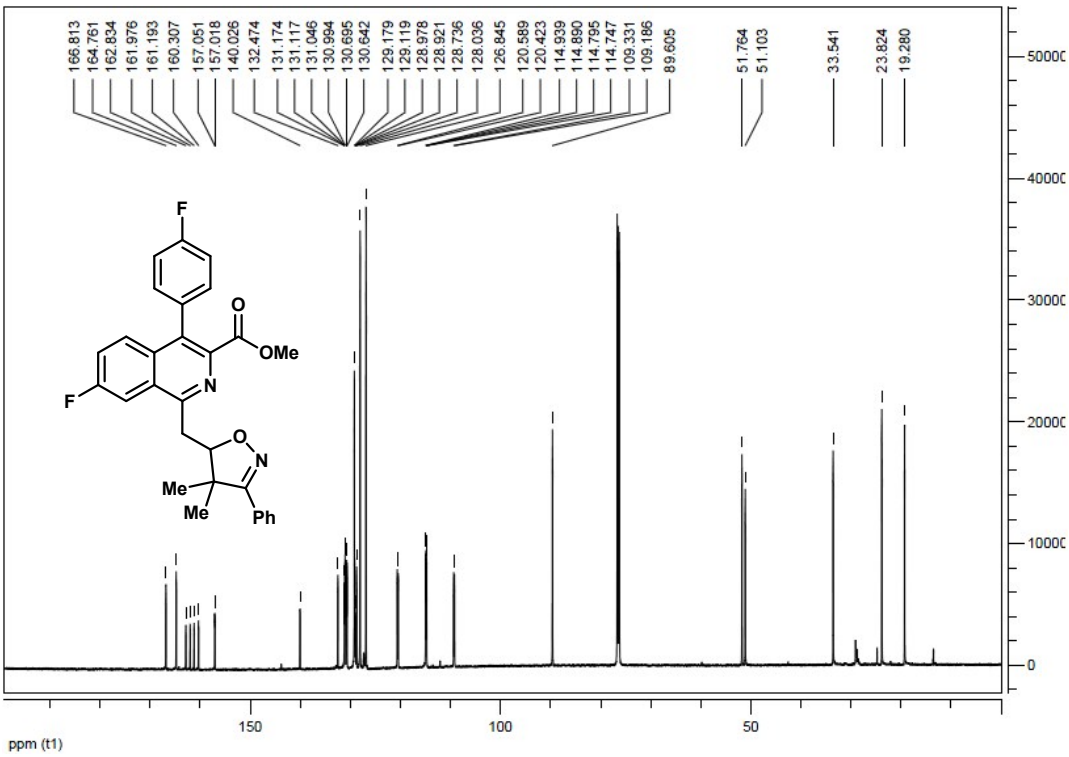


Methyl 1-((4,4-dimethyl-3-phenyl-4,5-dihydroisoxazol-5-yl)methyl)-7-fluoro-4-(4-fluorophenyl)isoquinoline-3-carboxylate (4d)

Proton NMR ($CDCl_3$)

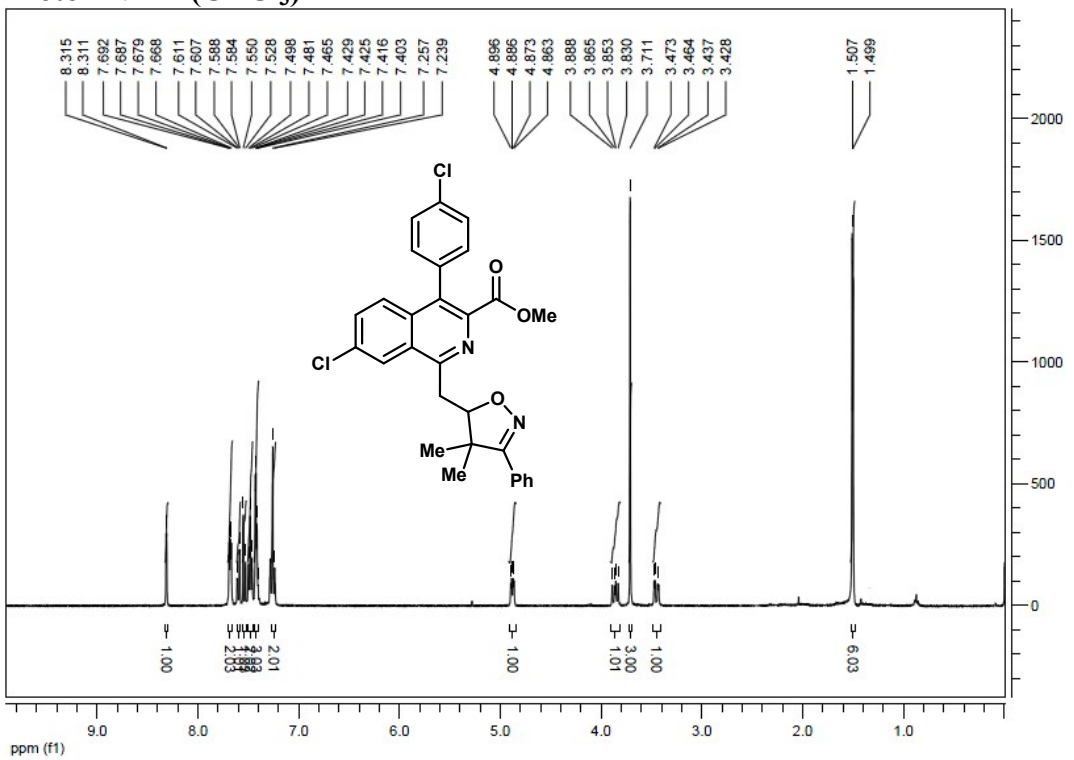


Carbon NMR ($CDCl_3$)

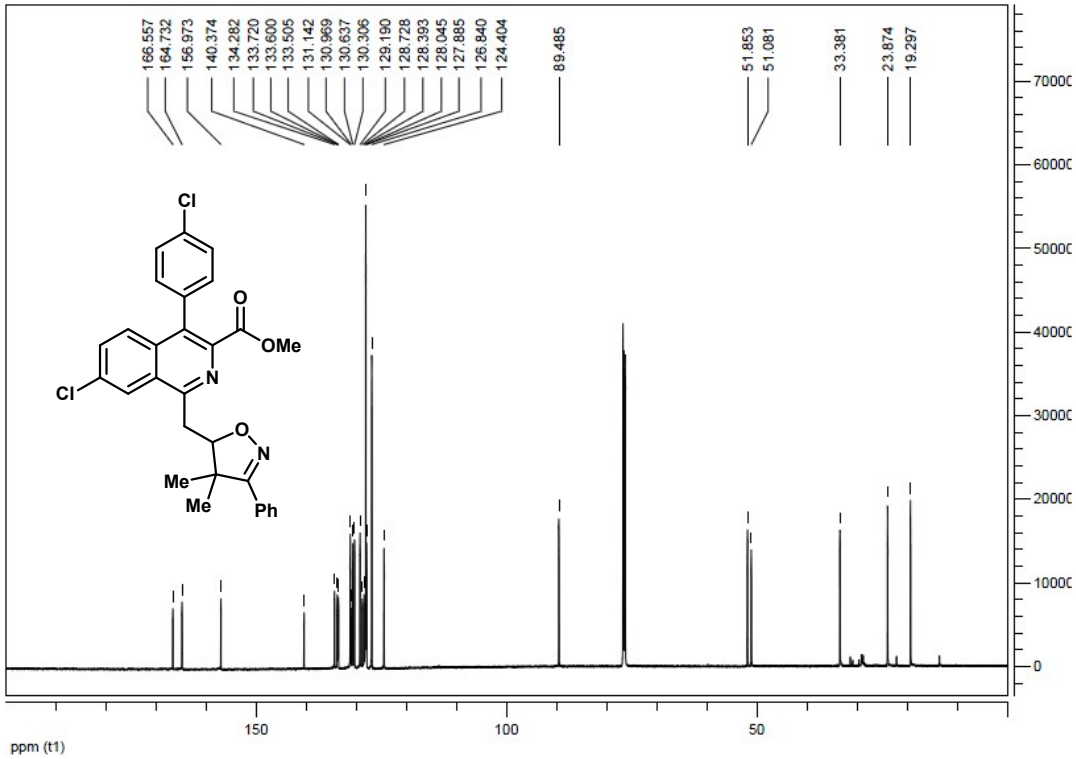


Methyl 7-chloro-4-(4-chlorophenyl)-1-((4,4-dimethyl-3-phenyl-4,5-dihydroisoxazol-5-yl)methyl)isoquinoline-3-carboxylate (4e)

Proton NMR ($CDCl_3$)

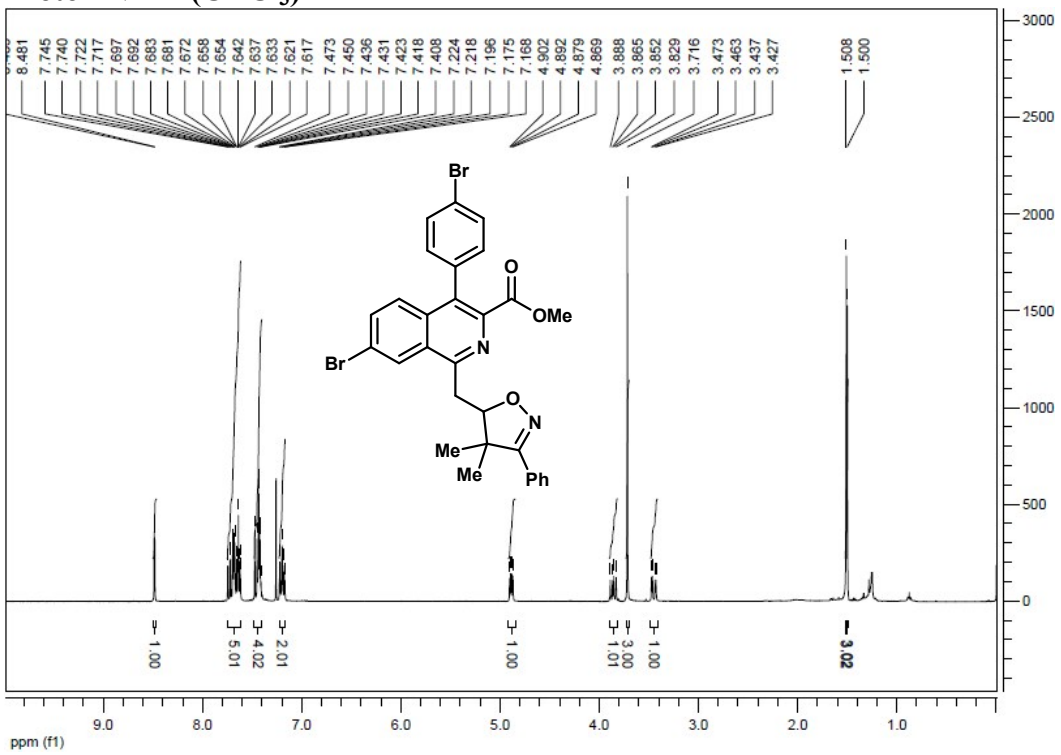


Carbon NMR ($CDCl_3$)

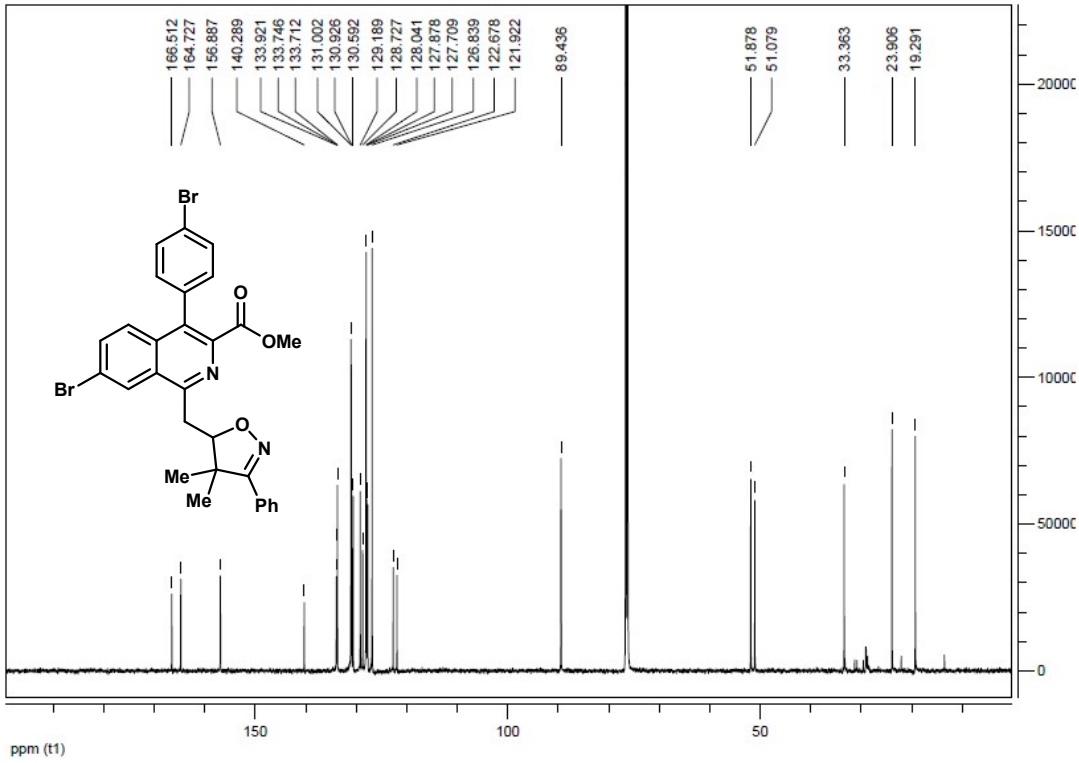


Methyl 7-bromo-4-(4-bromophenyl)-1-((4,4-dimethyl-3-phenyl-4,5-dihydroisoxazol-5-yl)methyl)isoquinoline-3-carboxylate (4f)

Proton NMR ($CDCl_3$)

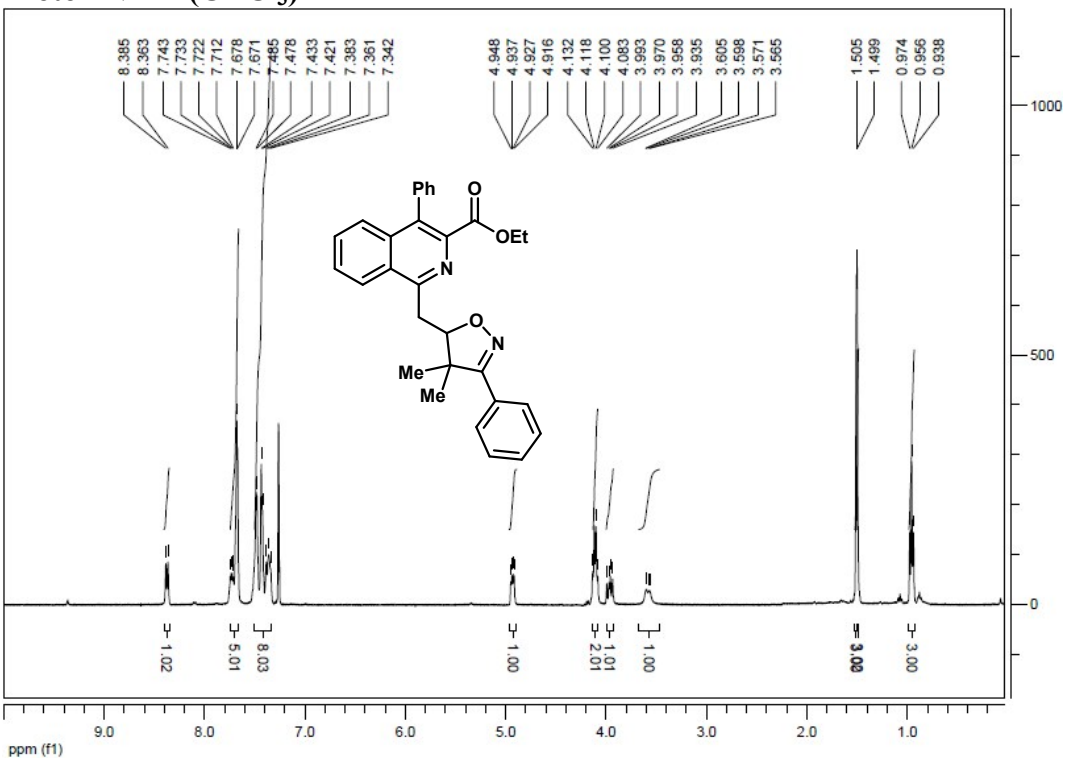


Carbon NMR ($CDCl_3$)

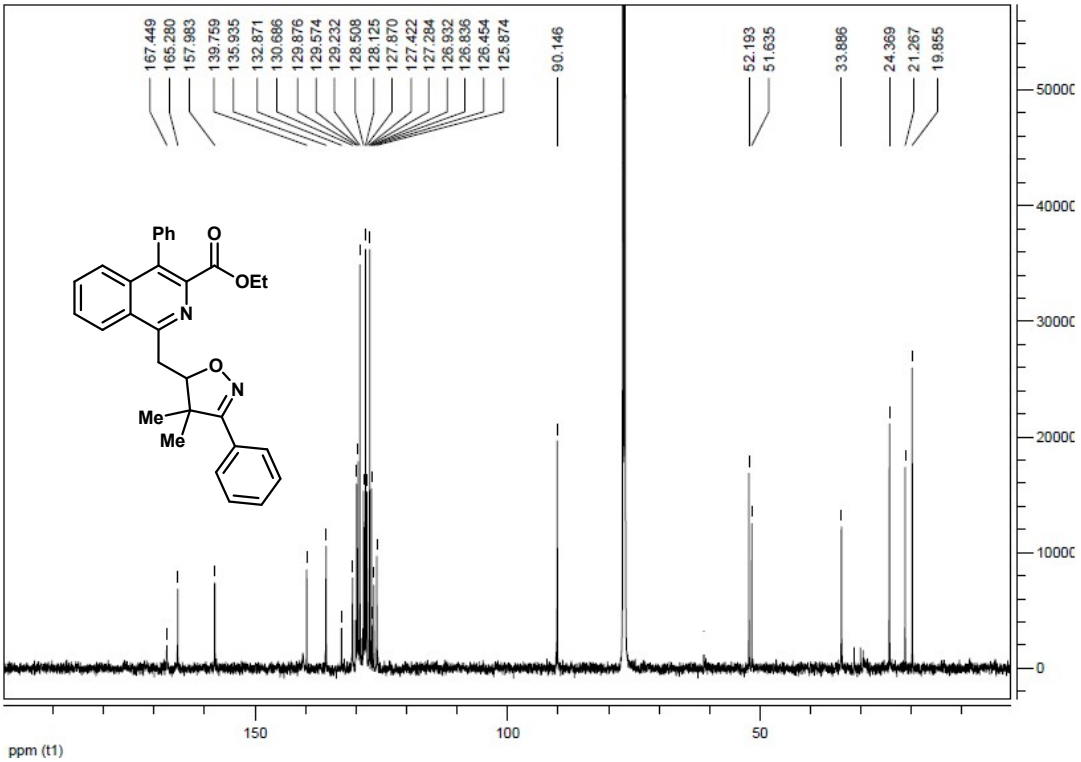


Ethyl 1-((4,4-dimethyl-3-phenyl-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinoline-3-carboxylate (4g)

Proton NMR ($CDCl_3$)

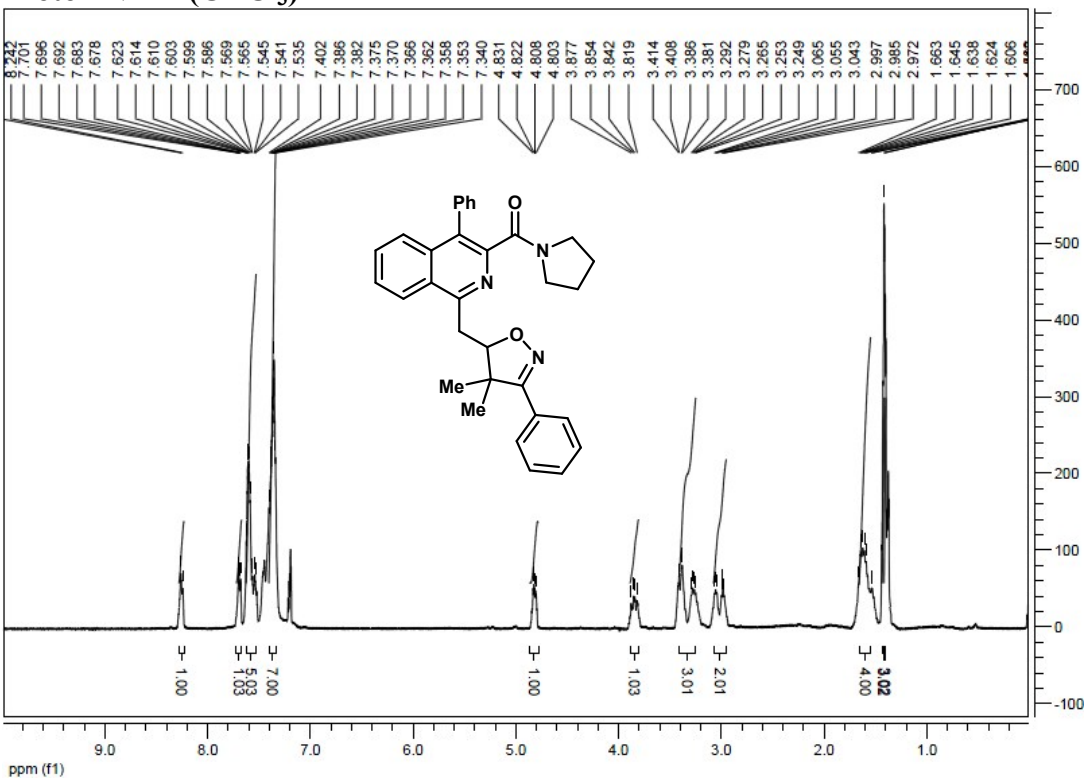


Carbon NMR ($CDCl_3$)

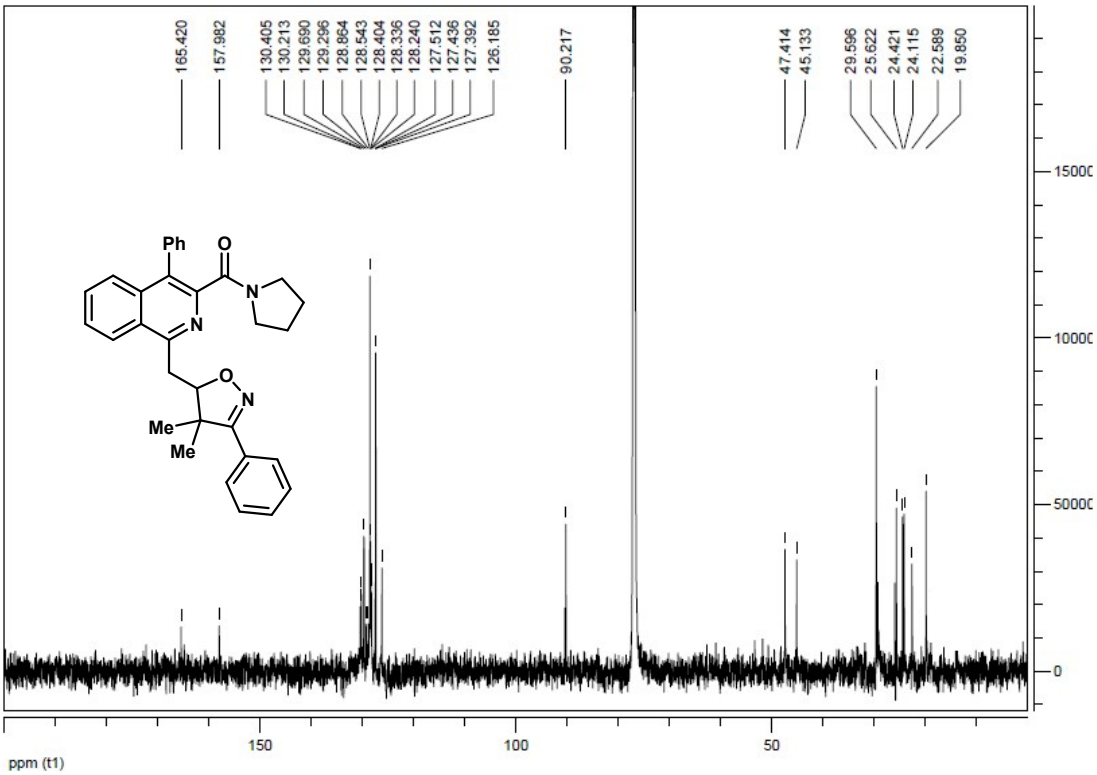


(1-((4,4-Dimethyl-3-phenyl-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinolin-3-yl)(pyrrolidin-1-yl)methanone (4h)

Proton NMR ($CDCl_3$)

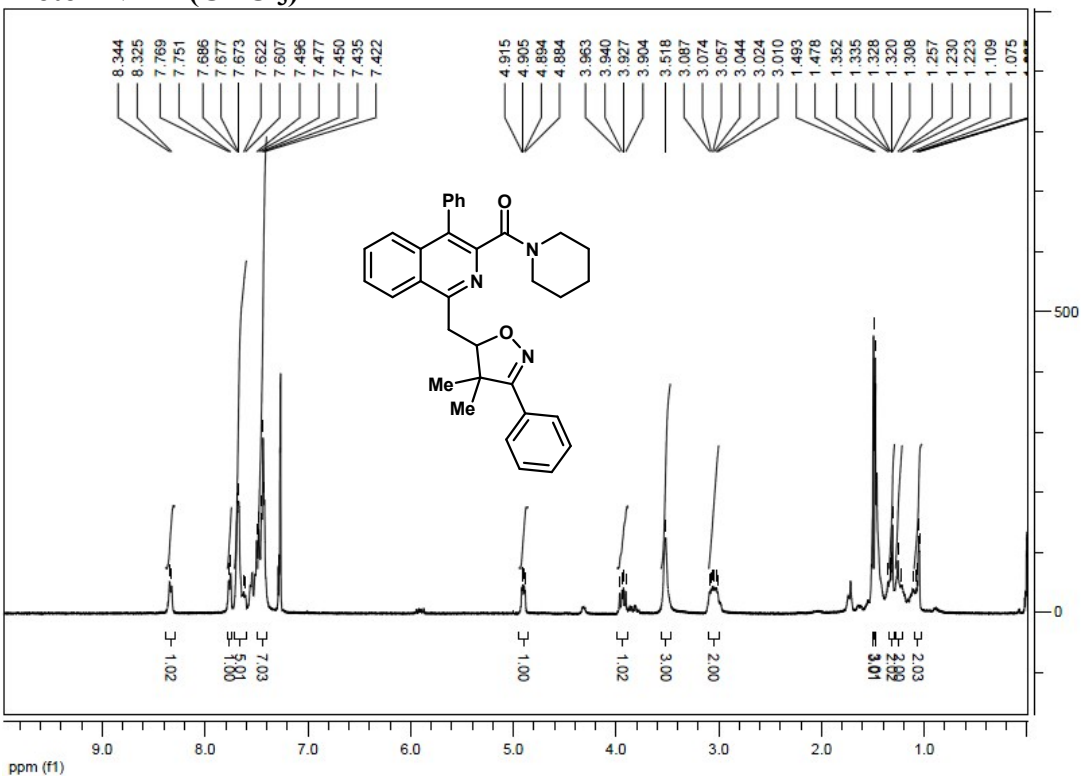


Carbon NMR ($CDCl_3$)

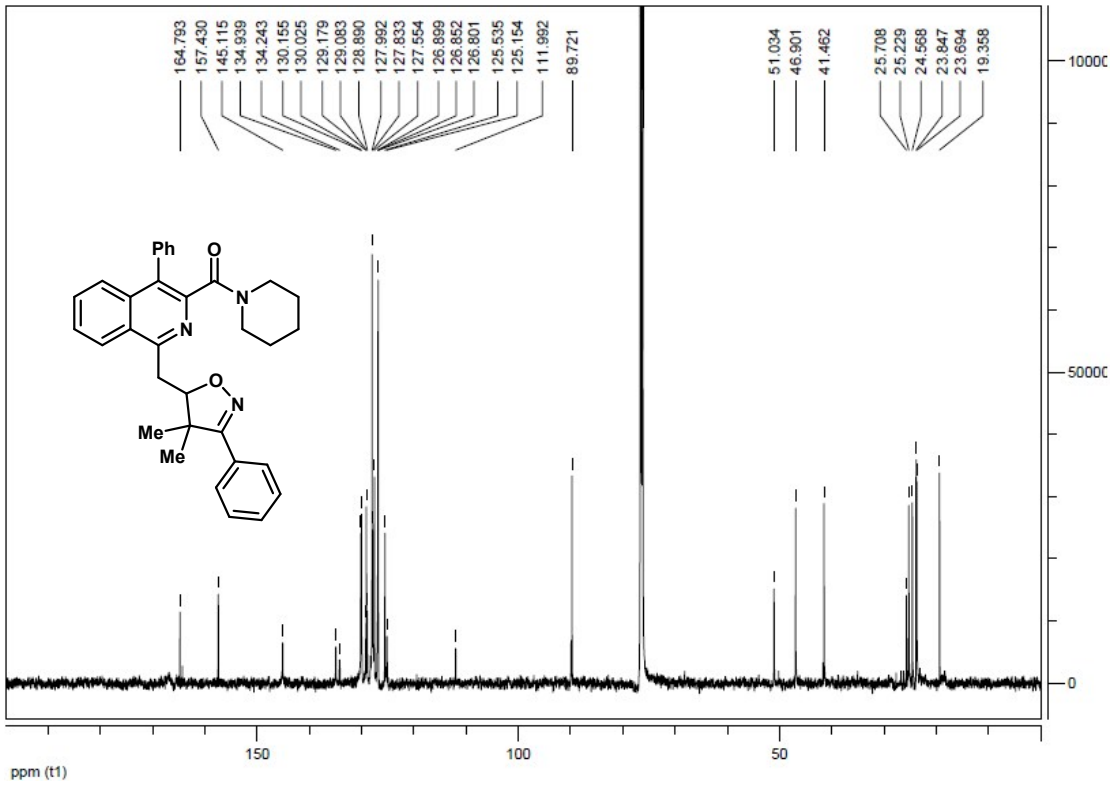


(1-((4,4-dimethyl-3-phenyl-4,5-dihydroisoxazol-5-yl)methyl)-4-phenylisoquinolin-3-yl)(piperidin-1-yl)methanone (4i)

Proton NMR ($CDCl_3$)



Carbon NMR ($CDCl_3$)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134.243
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130.025
129.179
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128.890
127.992
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126.899
126.852
126.801
125.535
125.154
111.992
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24.568
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Me
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