Supporting Information

Copper-Catalyzed Oxidation of Azolines to Azoles

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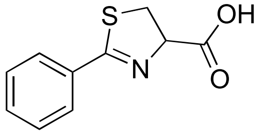
Contents

I. Experimental Details

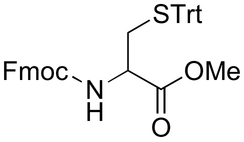
2-Phenyl-4,5-dihydrothiazole-4-carboxylic acid[1]



Procedure

Benzonitrile (8.24 mL, 80 mmol)[2] and L-cysteine (10.9 g, 90 mmol, 1.1 equiv.)[3] were dissolved in 1:1 methanol: pH 6.4 phosphate buffer (200 mL),[4] and the reaction was stirred at 40 °C for 3 days. A white precipitate was filtered out and the resulting clear yellow solution was acidified to ca. pH 4 with 1 M HCl and extracted three times with dichloromethane (25 mL). The solution was concentrated under reduced pressure, and crude product was obtained as a yellow solid upon its sonication in ethyl acetate. This solid was purified by recrystallization in ethyl acetate to yield product as white solid (4.97 g). Crude product was used in the next step without further purification.

Fmoc-Cys(trt)-OMe



Procedure

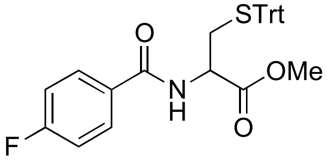
Fmoc-Cys(trt)-OH[5] (10.0 g, 17.1 mmol) was dissolved in DMF (30 mL) at 0 °C, to which K_2CO_3 (2.6 g, 18.8 mmol) was added. The reaction was allowed to stir for 30 minutes before iodomethane (2.13 mL, 34.1 mmol) was added to the reaction, which was then allowed to warm to room temperature and stirred until complete by TLC (80 minutes, TLC eluted with 1:1 hexanes: ethyl acetate). The solution was diluted with ethyl acetate (50 mL) then washed 5 times with 1:1 brine: H_2O (25 mL). Solvent was removed from the remaining organic fraction under reduced pressure to leave fluffy white crystals (9.69 g, 95%). Data are consistent with a previously characterized compound.[6]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (m, 2 H), 7.61 (m, 2 H), 7.41-7.19 (m, 19 H), 5.23 (d, 1 H, J = 8 Hz), 4.36 (m, 3 H), 4.23 (t, 1 H, J = 8 Hz), 3.72 (s, 3 H), 2.67 (d, 2 H, J = 5.2 Hz).

General Procedure for Preparation of Triphenylmethyl-Protected Cysteine Amides[7]

Fmoc-Cys(trt)-OMe was dissolved in acetonitrile (0.16 M solution), to which diethylamine (65 equiv.)[8] was added and the reaction was stirred at room temperature for 30 minutes. Completion of this reaction was verified by TLC, eluting with 3:1 hexanes: ethyl acetate. The solution was then concentrated under reduced pressure, and the residue was suspended in 1:1 dichloromethane: acetonitrile (20 mL). Diisopropylethylamine (2.1 equiv.)[3] and the appropriate acyl chloride (1.1 equiv.) were then added while stirring at room temperature, and the reaction was stirred overnight. The reaction mixture was concentrated under reduced pressure, diluted with ethyl acetate, washed twice with saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. The product was purified via flash chromatography on silica gel, eluting with an ethyl acetate/ hexanes mixture.

Methyl 2-(4-Fluorobenzamido)-3-(tritylthio)propanoate



Procedure

Prepared from Fmoc-Cys(trt)-OMe (4.6 g, 7.67 mmol) and 4-fluorobenzoyl chloride (1.34 g, 8.43 mmol)[2] according to the general procedure to give product as white crystals (1.66 g, 43%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (m, 2 H), 7.38 (m, 6 H), 7.23 (m, 9 H), 7.13 (m, 2 H), 6.59 (d, 1 H, J = 7.6 Hz), 4.81 (m, 1 H), 3.75 (s, 3 H), 2.80 (dd, 1 H, J_1 = 12.4 Hz, J_2 = 5.6 Hz), 2.74 (dd, 1 H, J_1 = 12.6 Hz, J_2 = 4.8 Hz).

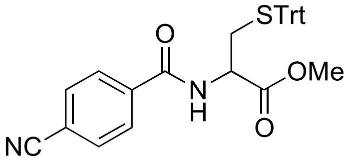
^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 166.4, 165.9, 163.9, 144.4, 129.7 (d, $J_{C\text{-}F}$ = 37.2 Hz), 129.6, 128.2, 127.1, 115.8 (d, $J_{C\text{-}F}$ = 86.8 Hz), 67.1, 53.0, 51.6, 34.2.

FT-IR (cm^{-1}): ν = 3031, 2933, 1746, 1812.

ESI-HRMS for $C_{30}H_{26}FNO_3S$: calculated $[MNa]^+$ 522.1617 g/mol, found 522.1510 g/mol.

M.P. 135-137 ºC

Methyl 2-(4-Cyanobenzamido)-3-(tritylthio)propanoate



Procedure

Prepared from Fmoc-Cys(trt)-OMe (5 g, 8.33 mmol) and 4-cyanobenzoyl chloride (1.52 g, 9.17 mmol)[2] to give product as white crystals (2.58 g, 56%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (m, 2 H, J_1 = 8 Hz), 7.75 (m, 2 H, J_1 = 8 Hz), 7.35-7.40 (m, 6 H), 7.17-7.26 (m, 9 H), 6.65 (d, 1 H, J = 8 Hz), 4.79 (dt, 1 H, J_1 = 8 Hz, J_2 = 5

Hz), 3.77 (s, 3 H), 2.83 (dd, 1 H, J_1 = 12 Hz, J_2 = 4 Hz), 2.75 (dd, 1 H, J_1 = 12 Hz, J_2 = 4 Hz).

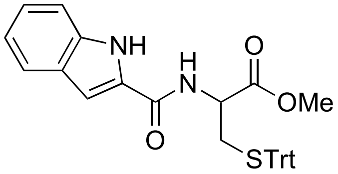
^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 165.2, 144.3, 137.7, 132.6, 129.6, 128.2, 128.1, 127.1, 118.1, 115.6, 67.2, 53.1, 51.8, 33.9.

FT-IR (cm^{-1}): ν = 3058, 2953, 2232, 1746, 1654.

ESI-HRMS for $C_{31}H_{26}N_2O_3S$: calculated [MNa]$^+$ 529.1664 g/mol, found 529.1556 g/mol.

M.P. 164-167 ºC

Methyl 2-(Indole-2-carboxamido)-3-(tritylthio)propanoate



Procedure:

Fmoc-Cys(Trt)-OMe (3.0 g, 5.0 mmol) was dissolved in 36 mL acetonitrile. Diethylamine (20.2 mL, 195 mmol) was added while stirring at room temperature. The reaction was stirred until complete by TLC (30 minutes, 3:1 hexanes: ethyl acetate) and the solvents were removed under reduced pressured. The residue was suspended in 8:1 dichloromethane: DMF (45 mL), to which indole-2-carboxylic acid (886 mg, 5.5 mmol)[3] and *N*-methylmorpholine (1.65 mL, 15 mmol)[9] were added. While stirring at 0 ºC, a solution of DCC (*N*,*N'*-dicyclohexylcarbodiimide, 1.24 g, 6.0 mmol)[10] and HOBt (1-hydroxybenzotriazole, 946 mg, 7 mmol)[11] in 8:1 dichloromethane: DMF solution (15 mL) was added. The resulting solution was brought to room temperature and allowed to stir for 15 hours. It was then filtered, and the filtrate was washed with saturated aqueous $NaHCO_3$ (30 mL x 3) and H_2O (30 mL) then dried over $MgSO_4$. The reaction mixture was then concentrated and purified via flash chromatography (gradient 5-30% ethyl acetate in hexanes) to give product as white crystals (1.39 g, 2.64 mmol, 53%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.33 (s, 1 H), 7.68 (dd, 1 H, J_1 = 8 Hz, J_2 = 0.8 Hz), 7.43 (dd, 1 H, J_1 = 8 Hz, J_2 = 0.8 Hz), 7.39 (m, 6 H), 7.30 (ddd, 1 H, J_1 = 8 Hz, J_2 = 8 Hz, J_3 = 0.8 Hz), 7.24-7.15 (m, 10 H), 6.93 (dd, 1 H, J_1 = 1.2 Hz, J_2 = 0.8 Hz), 6.78 (d, 1 H, J_1 = 8 Hz), 4.84 (dt, 1 H, J_1 = 8 Hz, J_2 = 4.8 Hz), 3.77 (s, 3 H), 2.84 (dd, 1 H, J_1 = 12 Hz, J_2 = 5.4 Hz), 2.74 (dd, 1 H, J_1 = 12 Hz, J_2 = 4.8 Hz).

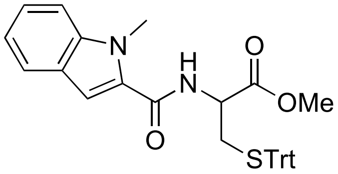
^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 161.1, 144.4, 136.6, 129.9, 129.6, 128.2, 127.8, 127.1, 124.9, 122.3, 120.9, 112.1, 103.4, 67.2, 53.6, 51.3, 34.3.

FT-IR (cm^{-1}): ν = 3057, 2949, 1741, 1645, 1541.

ESI-HRMS for $C_{32}H_{28}N_2O_3S$: calculated $[MNa]^+$ 543.1821 g/mol, found 543.1708 g/mol.

M.P. 145-148 ºC (Decomposition temperature)

Methyl 2-(1-Methylindole-2-carboxamido)-3-(tritylthio)propanoate



Procedure:

Fmoc-Cys(Trt)-OMe (3.0 g, 5.0 mmol) was dissolved in 36 mL acetonitrile. Diethylamine (20.2 mL, 195 mmol) was added while stirring at room temperature. The resulting solution was stirred until complete by TLC (30 minutes, 3:1 hexanes: ethyl acetate) and the solvents were removed under reduced pressured. The residue was suspended in 8:1 dichloromethane: DMF (45 mL), to which 1-methyl-indole-2-carboxylic acid (963 mg, 5.5 mmol)[12] and *N*-methylmorpholine (1.65 mL, 15 mmol) was added. While stirring at 0 ºC, a solution of DCC (1.24 g, 6.0 mmol) and HOBt (946 mg, 7 mmol) in 8:1 dichloromethane: DMF (15 mL) was added. The resulting solution was brought to room temperature and allowed to stir for 15 hours. The product mixture was then filtered, and the filtrate was washed with saturated aqueous $NaHCO_3$ (30 mL x 3) and H_2O (30 mL) then dried over $MgSO_4$. This was then concentrated and purified via flash chomatography (gradient 5-30% ethyl acetate in hexanes) to give product as a dark yellow solid (1.23 g, 2.3 mmol, 46%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, 1 H, J = 8 Hz), 7.41-7.15 (m, 18 H), 6.93 (s, 1 H), 6.69 (d, 1 H, J = 8 Hz), 4.79 (dt, 1 H, J_1 = 8 Hz, J_2 = 4.8 Hz), 4.02 (s, 3 H), 3.77 (s, 3 H), 2.80 (dd, 1 H, J_1 = 12 Hz, J_2 = 6 Hz), 2.74 (dd, 1 H, J_1 = 12 Hz, J_2 = 6 Hz).

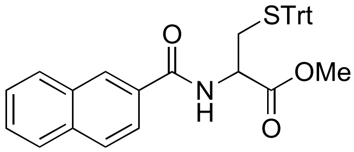
^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 161.9, 144.2, 139.1, 131.0, 129.5, 128.0, 126.9, 126.0, 124.3, 122.0, 120.5, 110.1, 104.8, 67.0, 52.8, 52.0, 34.1, 31.5.

FT-IR (cm^{-1}): ν = 3060, 2948, 1742, 1660, 1526.

MALDI for $C_{33}H_{30}N_2O_3S$: calculated $[MNa]^+$ 557.20 g/mol, found 557.02 g/mol.

M.P. 65-68 ºC

Methyl 2-(2-Naphthamido)-3-(tritylthio)propanoate



Procedure

L-Cys(Trt)-OH (727 mg, 2.0 mmol)[3] was dissolved in acetonitrile (10.0 mL) and dichloromethane (5.0 mL). Diisopropylethylamine (732 μL, 4.2 mmol) was added and the solution was stirred at room temperature for 14 hours until complete by TLC (eluting with methanol). The reaction was washed three times with saturated aqueous $NaHCO_3$ (10 mL) and dried over $MgSO_4$. Solvent was removed from the resulting organic fraction under reduced pressure to yield product as white crystals (727 mg), which were used for the next step without further purification.

Product prepared from previous step (400 mg, 0.77 mmol) was dissolved in DMF (1.36 mL). K_2CO_3 (117.1 g, 0.85 mmol, 1.1 equiv.) was added while stirring at 0 ºC. After stirring for 30 minutes, iodomethane (0.101 mL, 1.62 mmol, 1.9 equiv.) was added and the solution was brought to room temperature and stirred until complete by TLC (eluting with 1:1 hexanes: ethyl acetate). The reaction was diluted with ethyl acetate (10 mL) and washed with deionized water: brine (1:1) 3 times (10 mL), and the combined organic fractions were dried over $MgSO_4$. This was then concentrated and purified via flash chromatography (gradient 5-25% ethyl acetate in hexanes) to yield product as white crystals (203 mg, 35% over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (s, 1 H), 7.93 (m, 3 H), 7.82 (dd, 1 H, J_1 = 6.8 Hz, J_2 = 2 Hz), 7.58 (m, 2 H), 7.39 (d, 6 H, J = 7.2 Hz), 7.23 (d, 6 H, J = 8.0 Hz), 7.20 (t, 3 H, J = 8.0 Hz), 6.82 (d, 1 H, J = 8.0 Hz), 4.90 (dt, 1 H, J_1 = 8.0 Hz, J_2 = 4.8 Hz), 3.78 (s, 3 H), 2.84 (dd, 1 H, J_1 = 12 Hz, J_2 = 4 Hz), 2.78 (dd, 1 H, J_1 = 12 Hz, J_2 = 4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 167.0, 144.4, 135.1, 132.7, 131.0, 129.7, 129.6, 129.2, 128.6, 128.2, 127.9, 127.1, 127.0, 126.7, 123.8, 67.1, 52.9, 51.7, 34.3.

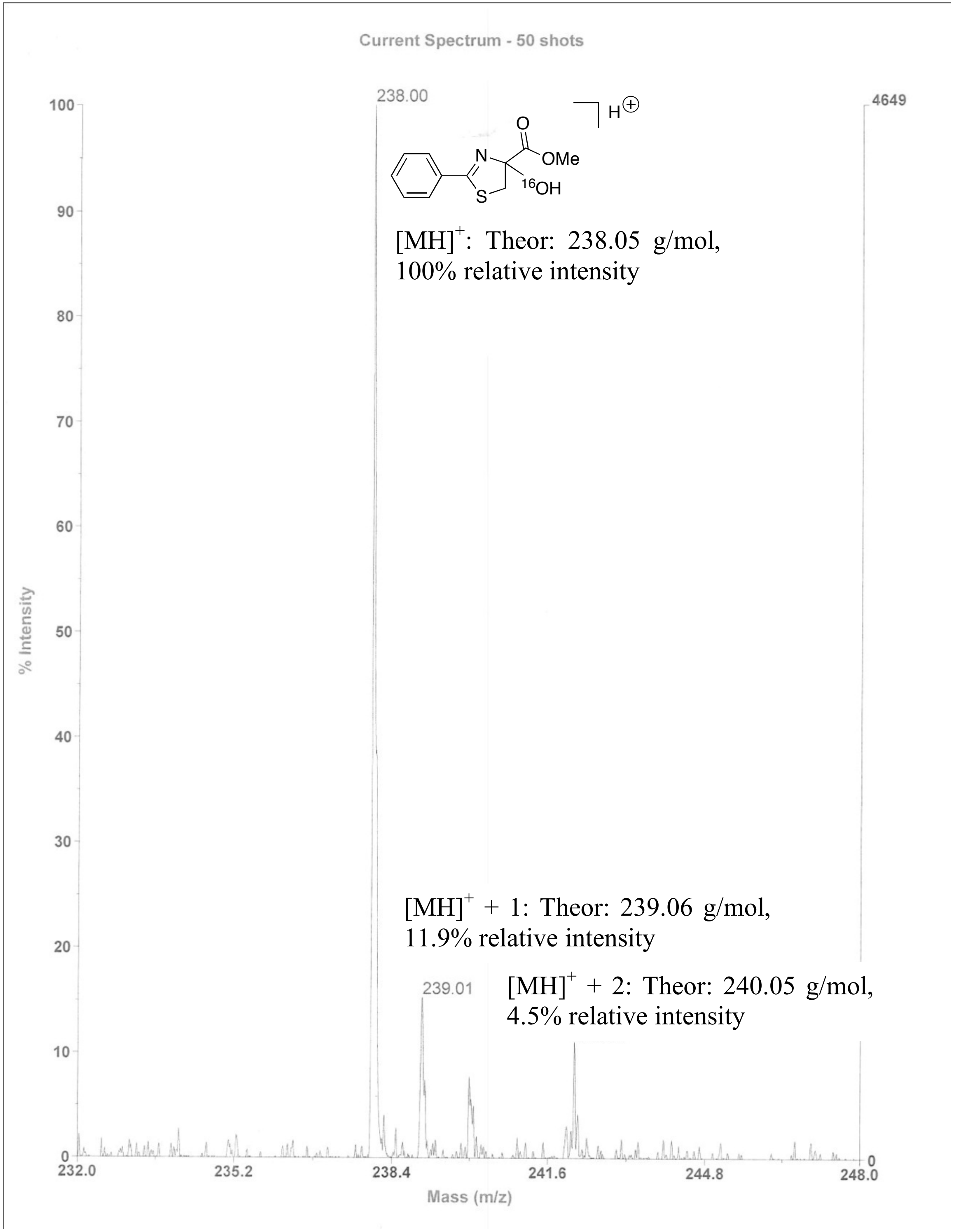
FT-IR (cm^{-1}): ν = 3057, 2951, 1813, 1744.

ESI-HRMS for $C_{34}H_{29}NO_3S$: calculated $[MNa]^+$ 554.1868 g/mol, found 554.1760 g/mol.

M.P. 75-80 ºC

Graphical MALDI:

With no $H_2{}^{18}O$ added

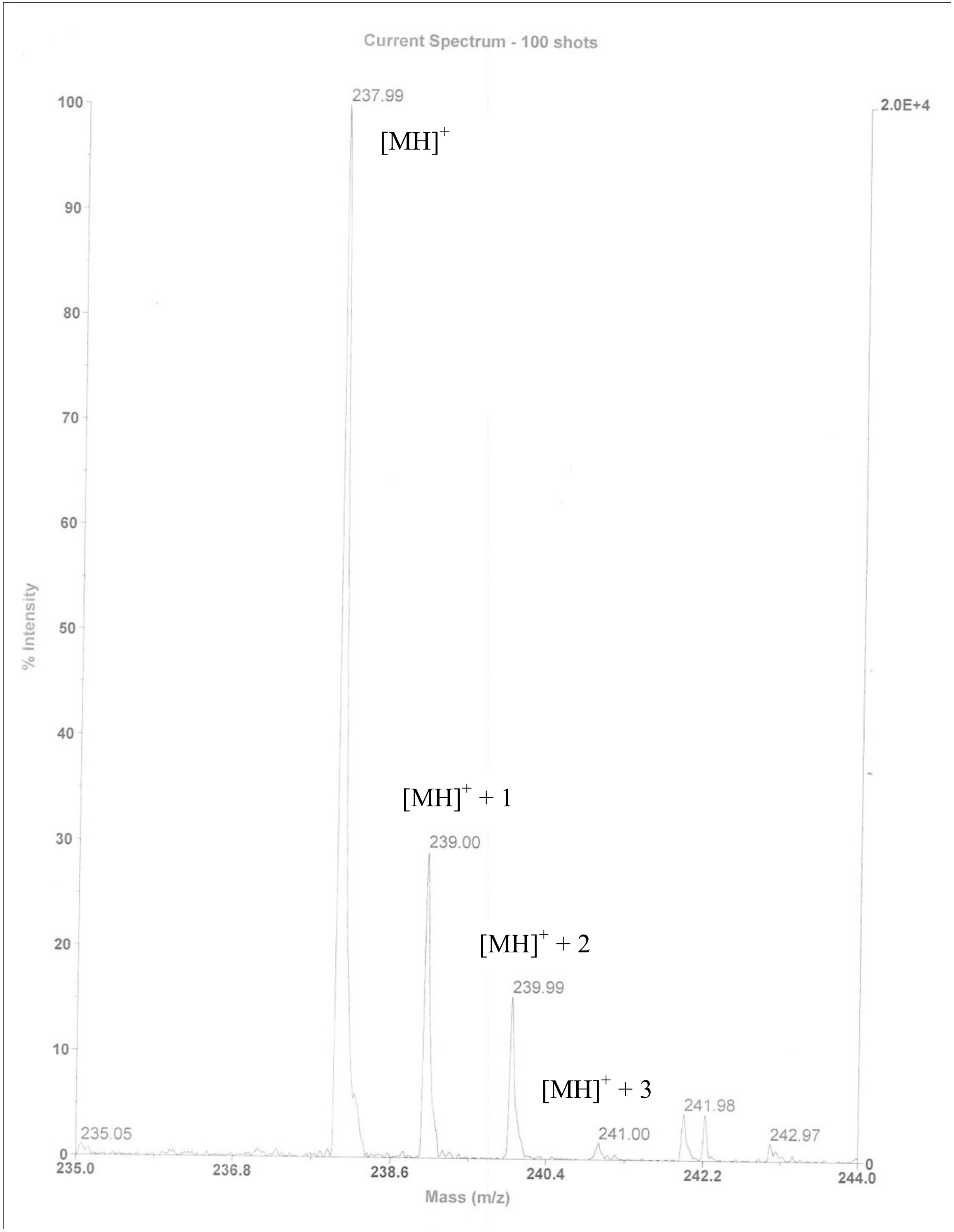


$[MH]^+$: Theor: 238.05 g/mol, 100% relative intensity

$[MH]^+ + 1$: Theor: 239.06 g/mol, 11.9% relative intensity

$[MH]^+ + 2$: Theor: 240.05 g/mol, 4.5% relative intensity

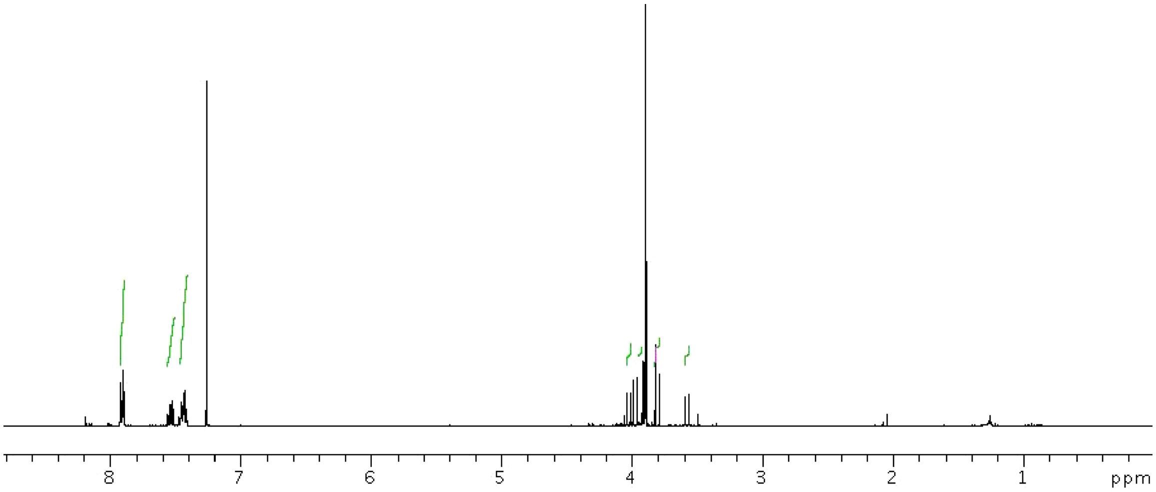
With $H_2{}^{18}O$ added



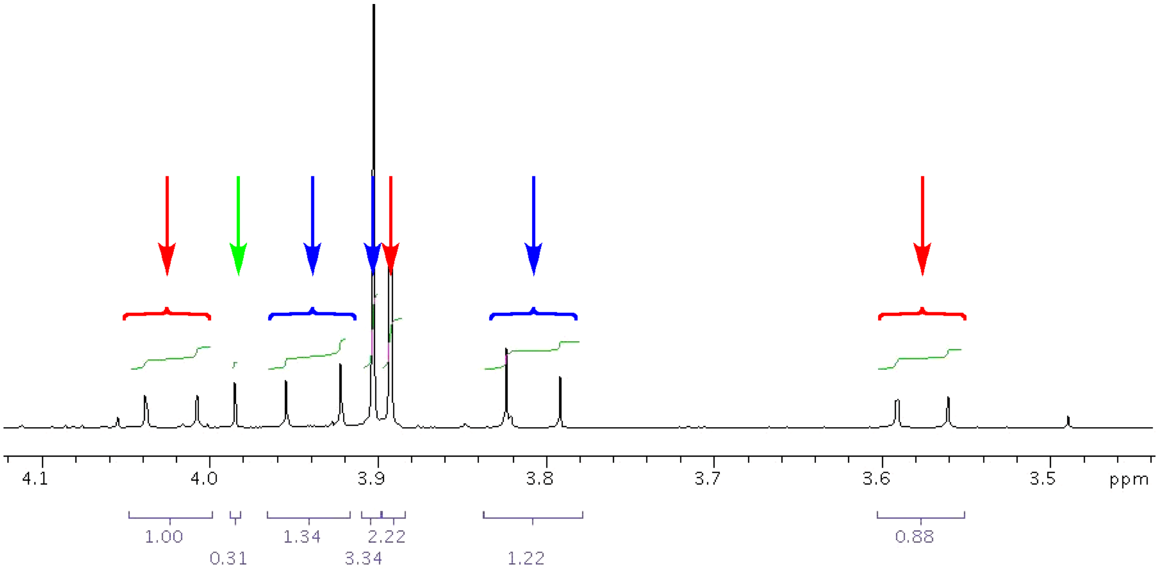
Oxidation of **2** with K_2CO_3

Reaction of thiazoline **2** with K_2CO_3 (1 equiv.) and catalyst **1** in DMF (2 mL) produced thiazole **2a** in 30% yield as well as a mixture of angular hydroxide **15** and an unknown intermediate, which is purportedly an angular peroxide,[13] in a ratio of ca. 1:1.3 ratio, 22% and ca. 26% isolated yields respectively. A MALDI MS of this mixture contains a weak signal at 254.00 g/mol, which could correspond to an angular hydroperoxide + H^+. We consider this weak signal inconclusive, however, because such a peroxide should be susceptible to photodecomposition in the MALDI spectrometer.

^{1}H NMR:



^{1}H NMR Zoomed in:



Green: product **2** (-CO_2Me); Red: hydroxythiazoline **15**; Blue: purportedly an angular peroxide.

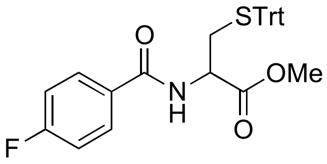
II. Cost Analysis

Table S1. Cost Analysis for the Synthesis of 1 Gram of Methyl 2-Phenylthiazole-4-Carboxylate.

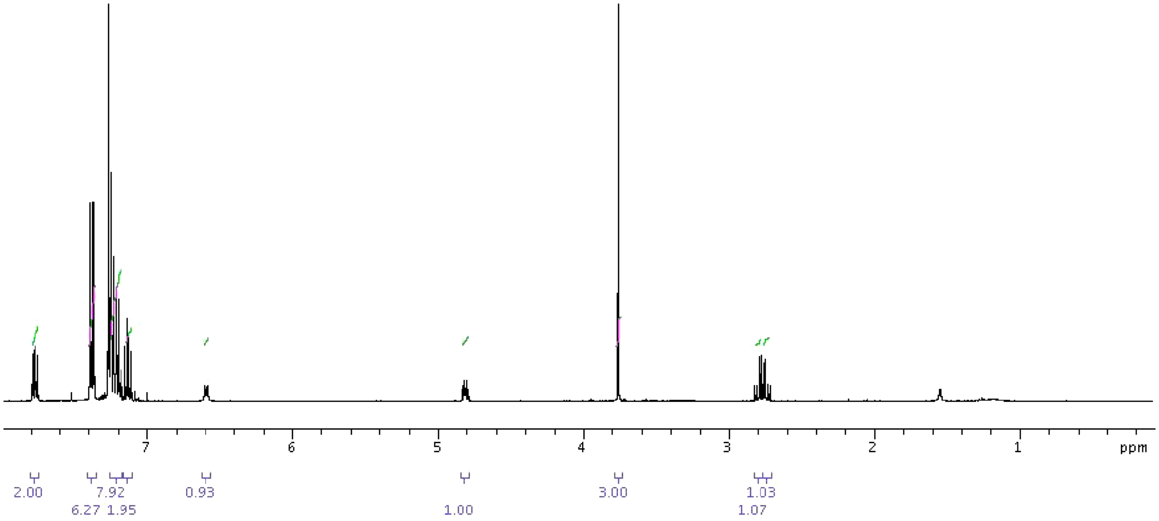
Reagent	List Price	List Quantity	Unit Price	Amt. Needed	Cost
Butanedione	$90.60	500 g	$\$0.18\ \text{g}^{-1}$	43 mg	$0.01
Copper Triflate	$190.00	25 g	$\$7.60\ \text{g}^{-1}$	165 mg	$1.25
2,4,6-dimethylaniline	$530.00	2.5 kg	$\$0.21\ \text{g}^{-1}$	134 mg	$0.03
L-Cysteine	$318.00	1 kg	$\$0.32\ \text{g}^{-1}$	2.28 g	$0.73
Benzonitrile	$98.00	2.5 kg	$\$0.04\ \text{g}^{-1}$	2.14 g	$0.90
Iodomethane	$455.16	500 g	$\$0.87\ \text{g}^{-1}$	1.56 g	$1.36
DBU	$184.00	500 g	$\$0.37\ \text{g}^{-1}$	69 mg	$0.03
Phosphate Buffer 6.4	$74.38	4 L	$\$18.60\ \text{L}^{-1}$	20.91 mL	$0.39
MeOH	$614.00	204 L	$\$3.01\ \text{L}^{-1}$	20.91 mL	$0.06
DMF	$3,446.82	204 L	$\$16.90\ \text{L}^{-1}$	232 mL	$3.92
EtOAc	$1,648.44	204 L	$\$8.08\ \text{L}^{-1}$	1 L	$8.08
Hexanes	$916.12	204 L	$\$4.49\ \text{L}^{-1}$	2.5 L	$11.23
				Total:	$27.99

All prices are based on the VWR list price.

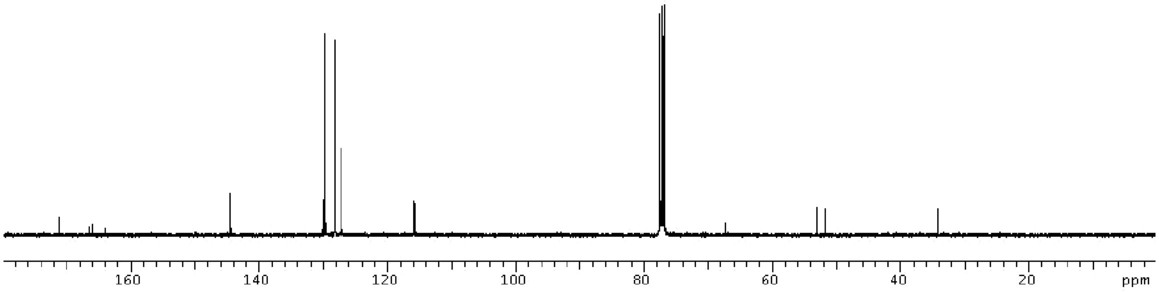
III. Graphical ^{1}H and ^{13}C NMR Spectra for New Compounds

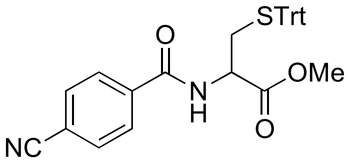


^{1}H NMR, 400 MHz, CDCl$_3$, 25 °C

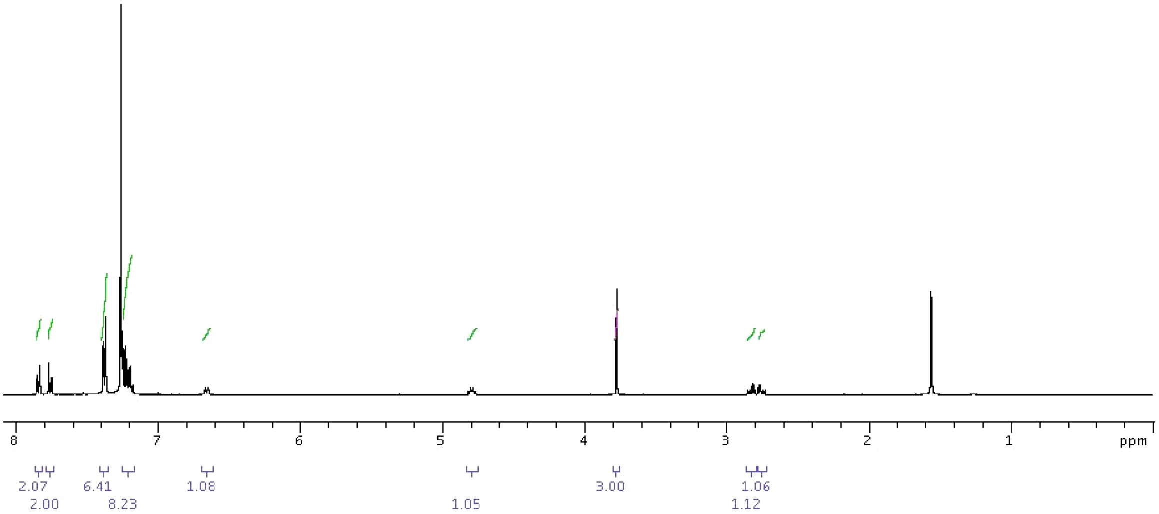


^{13}C NMR, 100 MHz, CDCl$_3$, 25 °C

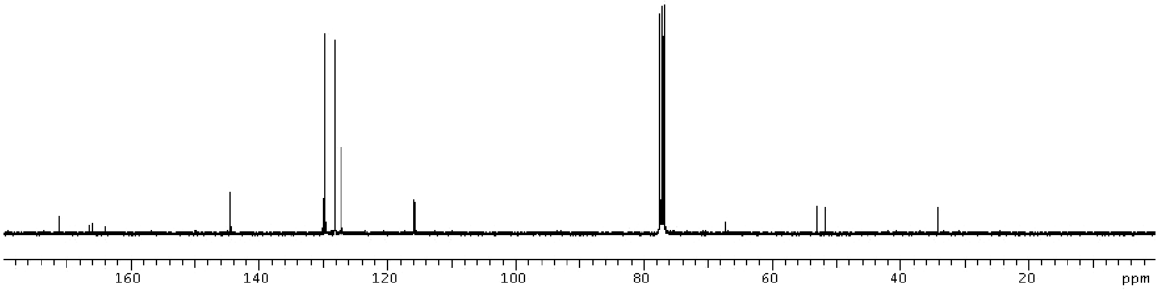


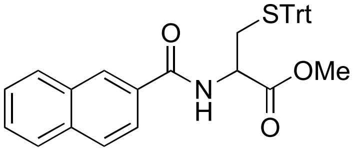


^{1}H NMR, 400 MHz, CDCl$_3$, 25 °C

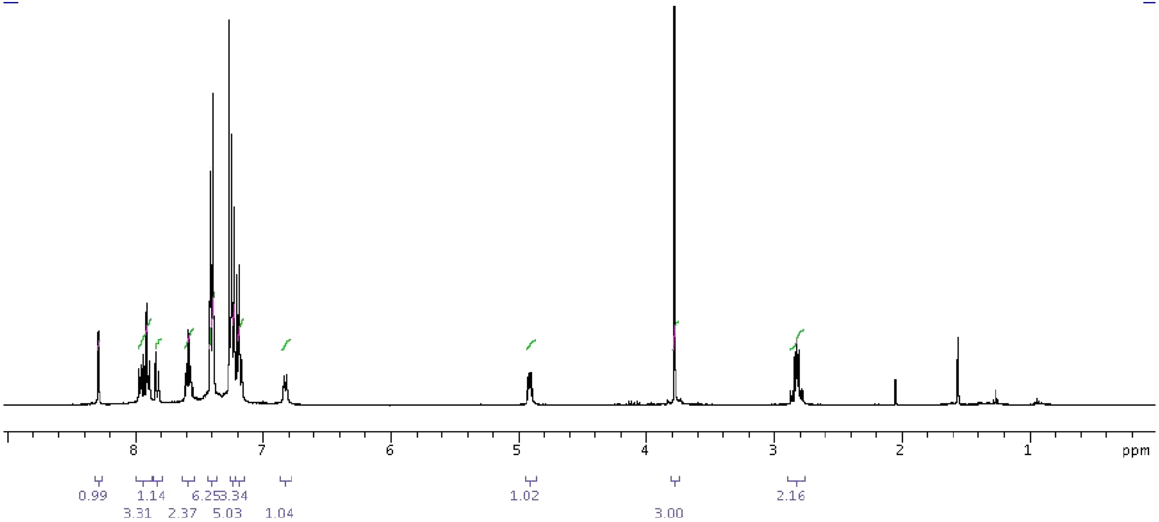


^{13}C NMR, 100 MHz, CDCl$_3$, 25 °C





^{1}H NMR, 400 MHz, CDCl$_3$, 25 °C



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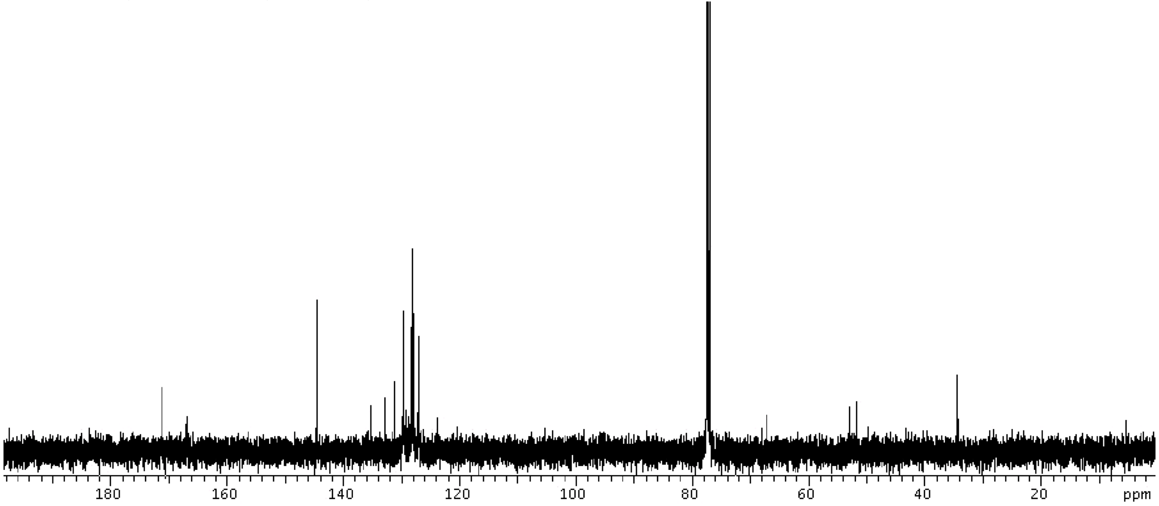

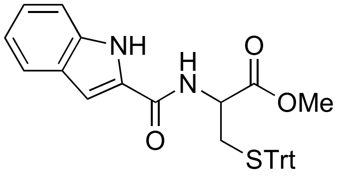

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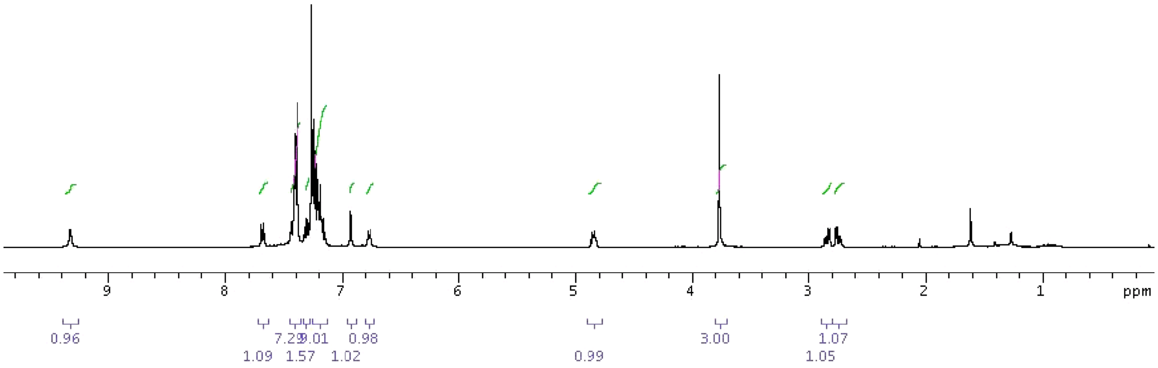

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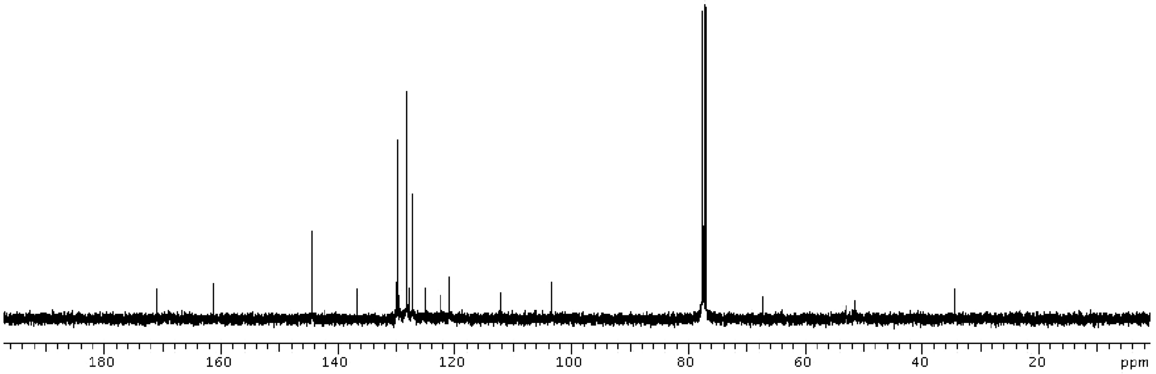
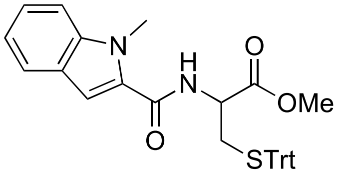
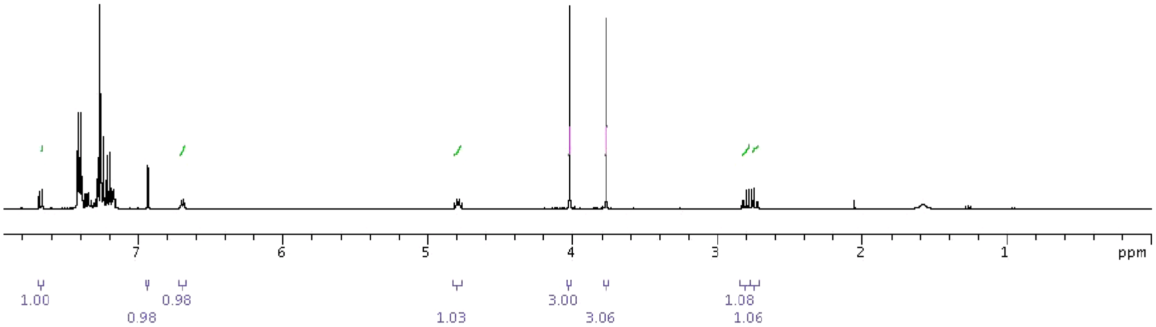




^{1}H NMR, 400 MHz, $CDCl_3$, 25 °C



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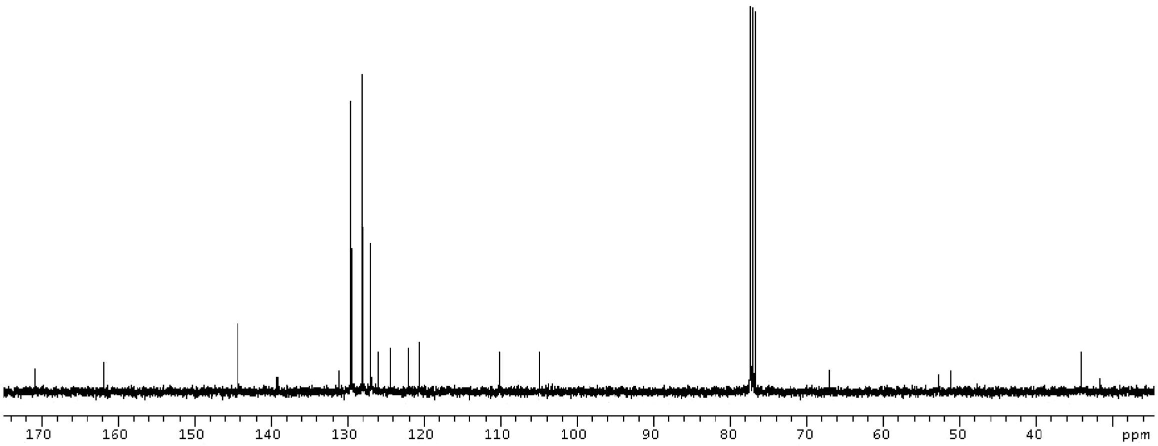
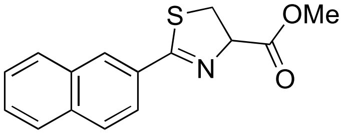
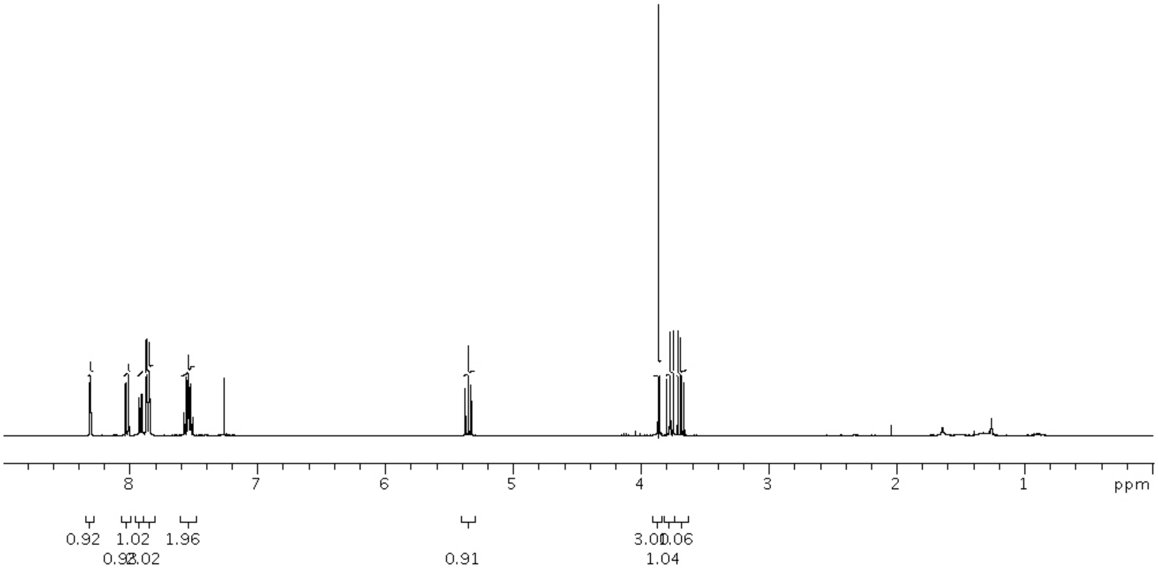
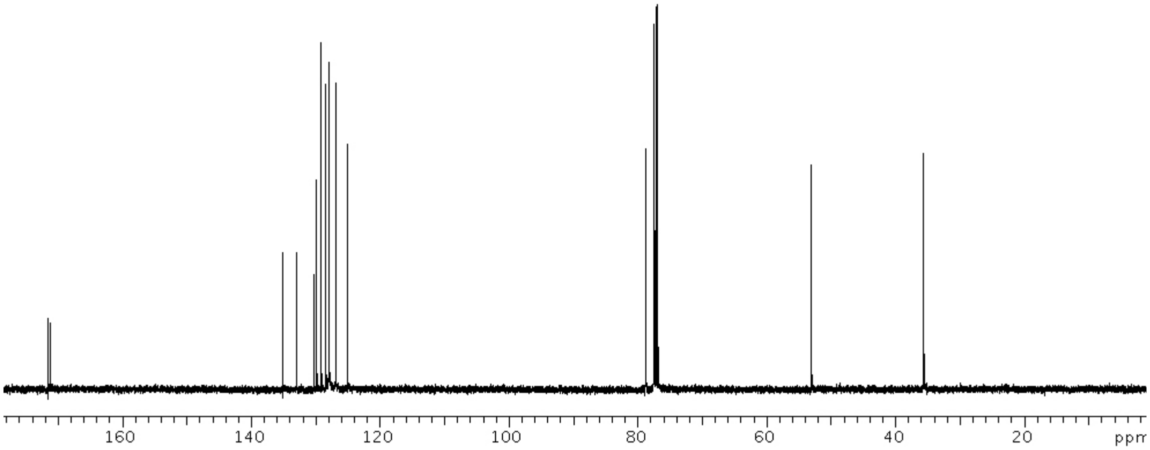


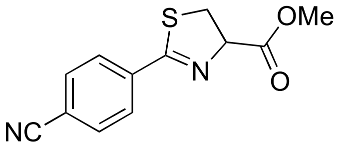


^{1}H NMR, 400 MHz, CDCl$_3$, 25 °C

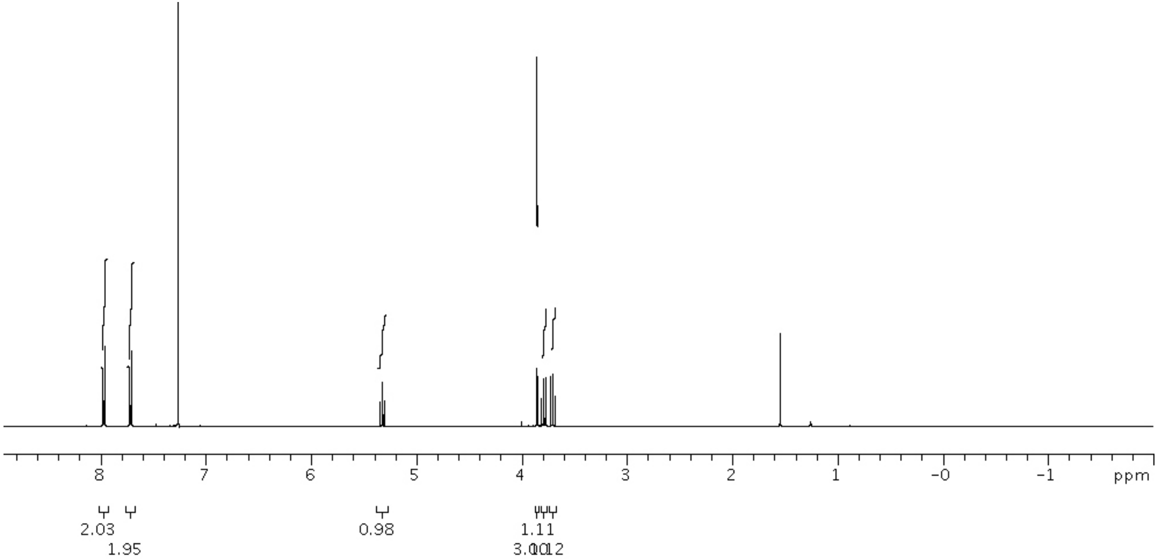


^{13}C NMR, 100 MHz, CDCl$_3$, 25 °C

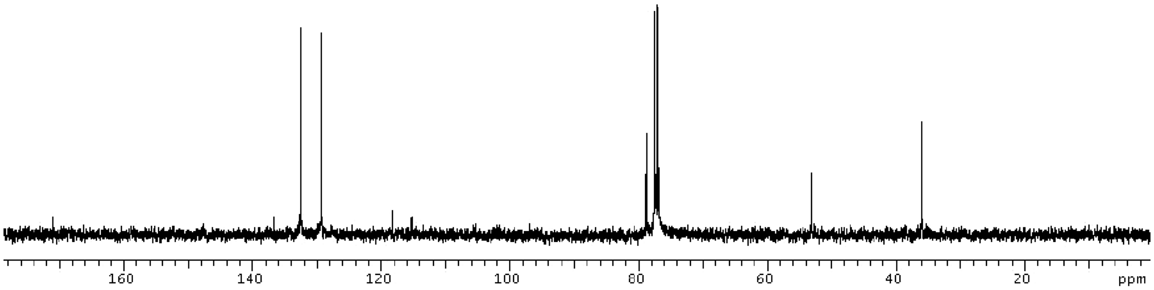


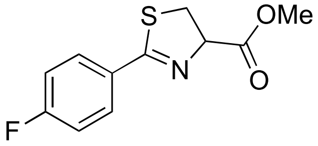


^{1}H NMR, 500 MHz, CDCl$_3$, 25 °C

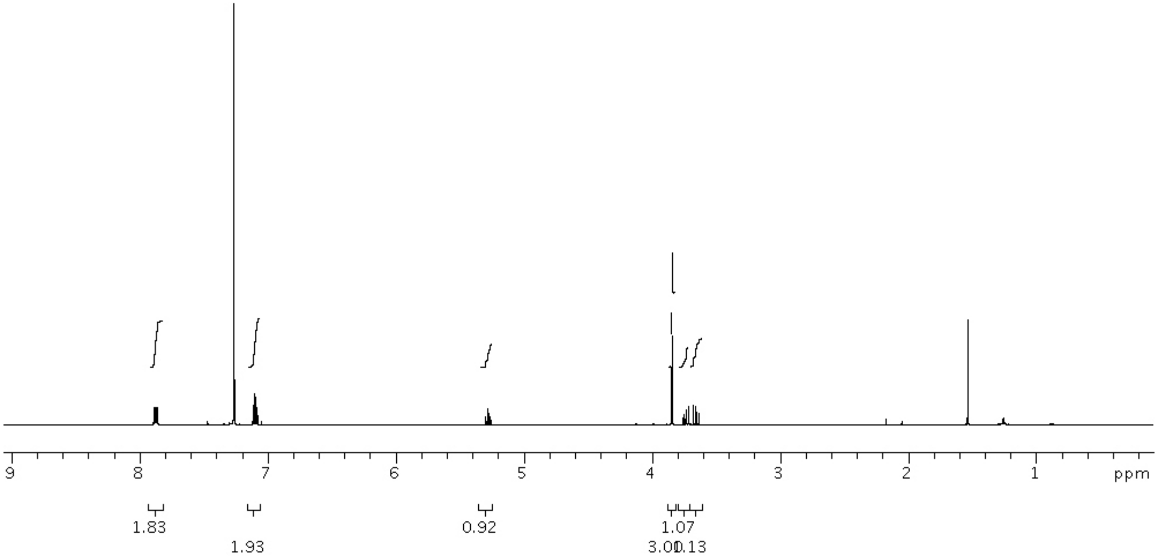


^{13}C NMR, 100 MHz, CDCl$_3$, 25 °C

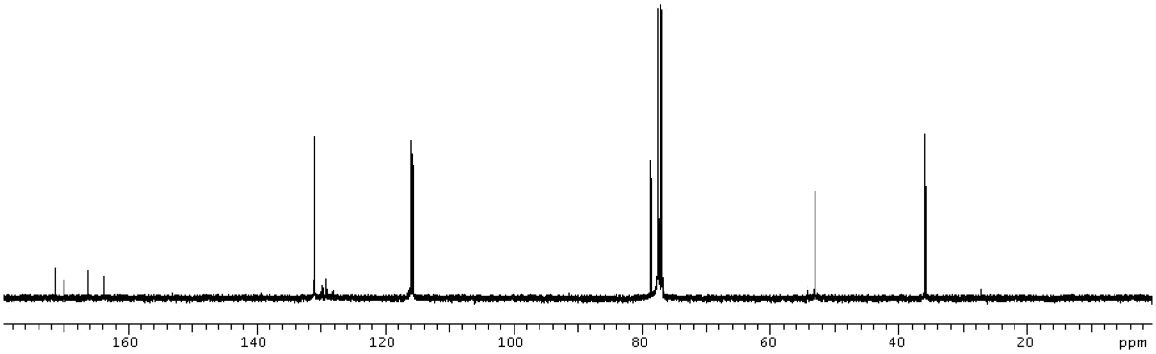


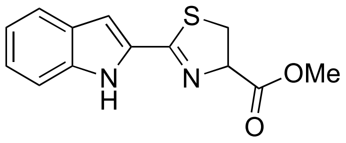


^{1}H NMR, 500 MHz, CDCl$_3$, 25 °C

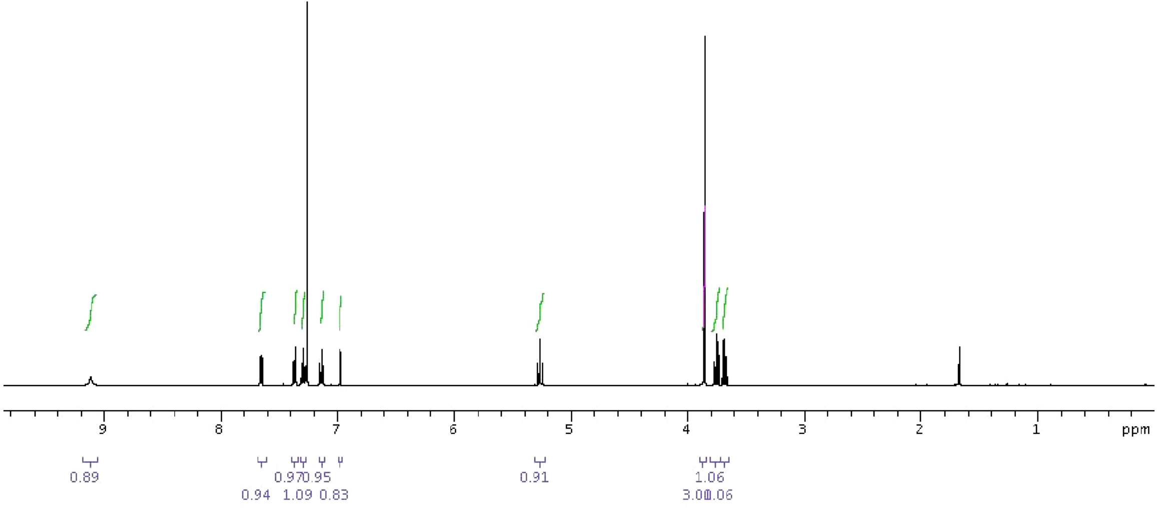


^{13}C NMR, 100 MHz, CDCl$_3$, 25 °C

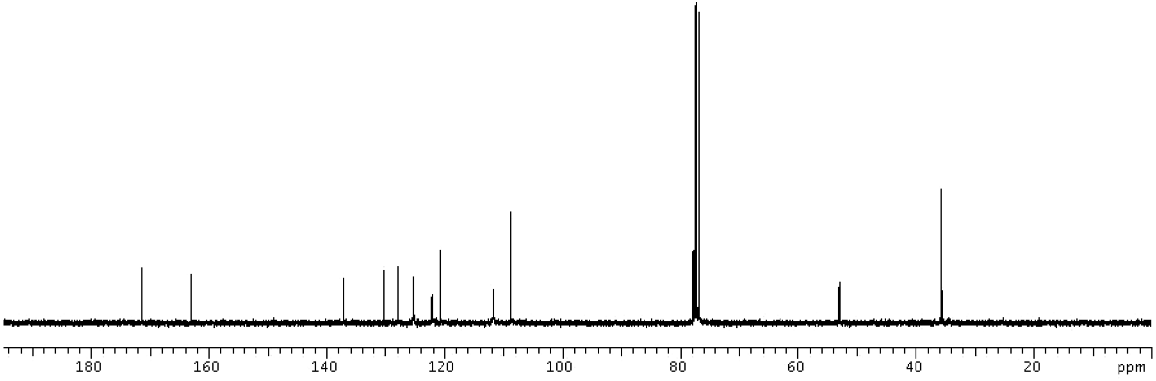


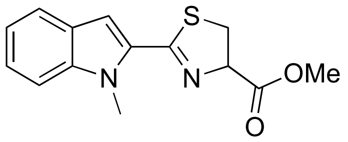


^{1}H NMR, 400 MHz, CDCl$_3$, 25 °C

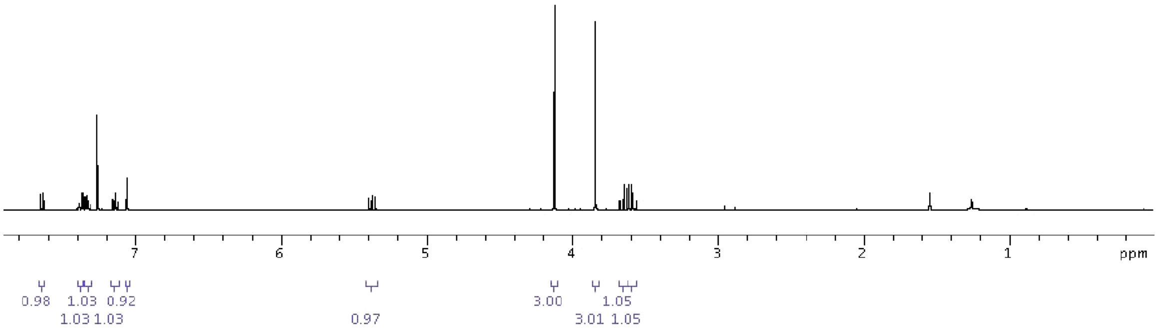


^{13}C NMR, 100 MHz, CDCl$_3$, 25 °C

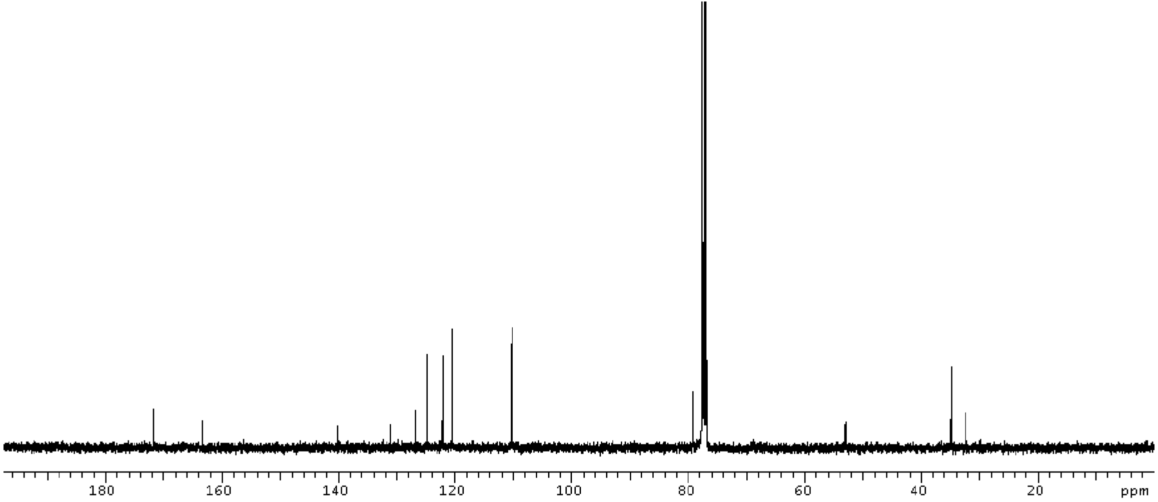


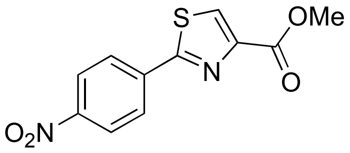


^{1}H NMR, 400 MHz, $CDCl_3$, 25 °C

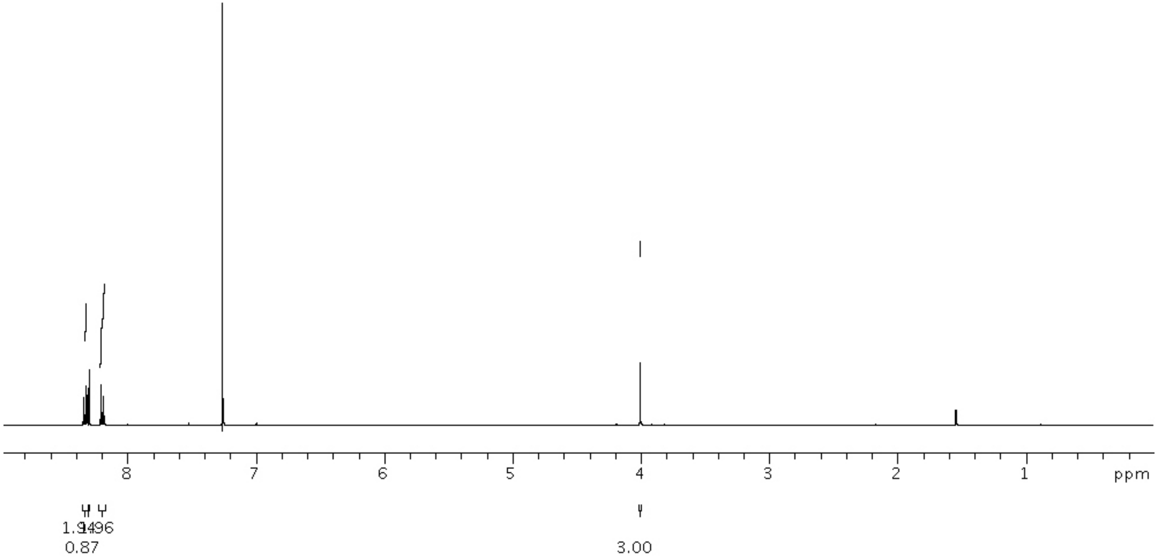


^{13}C NMR, 100 MHz, $CDCl_3$, 25 °C

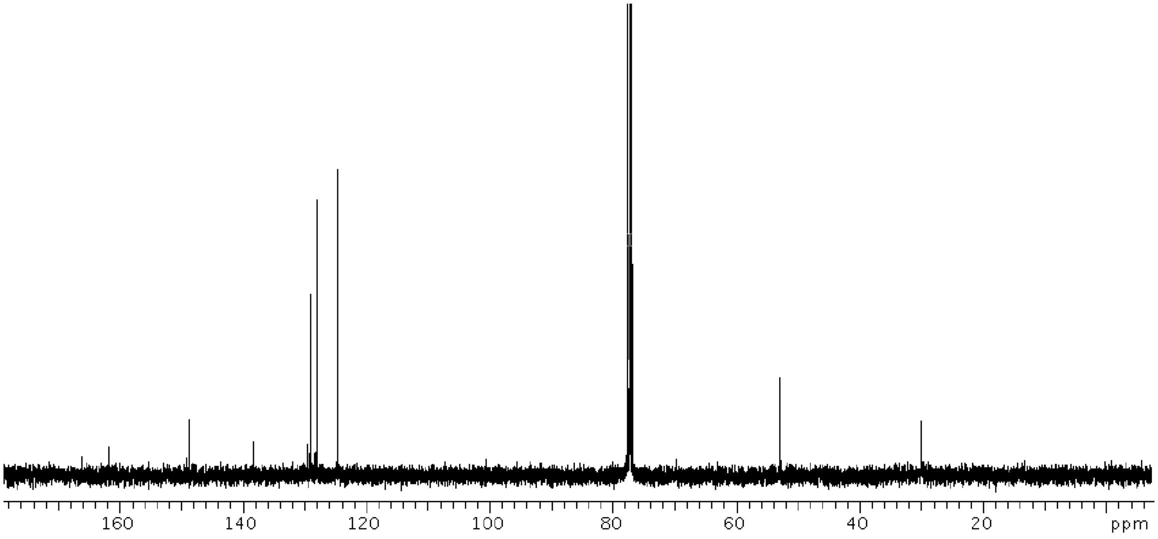


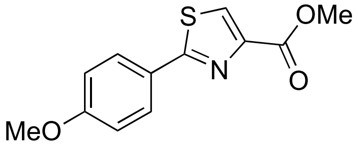


^{1}H NMR, 400 MHz, $CDCl_3$, 25 °C

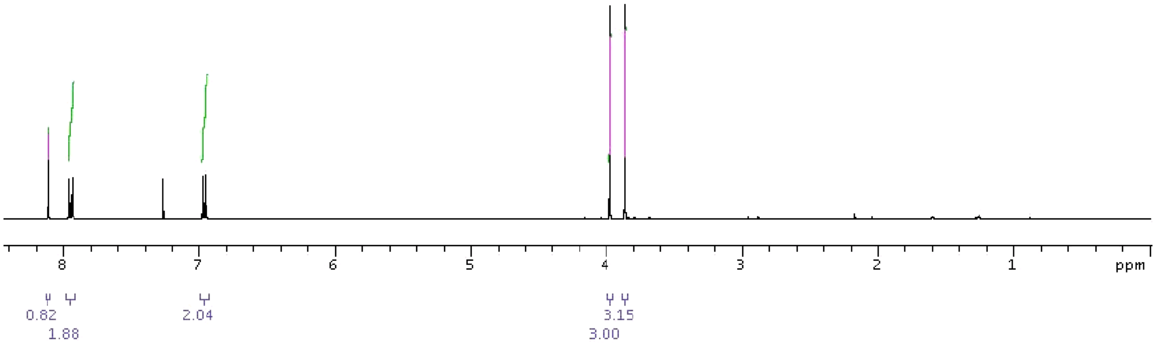


^{13}C NMR, 100 MHz, $CDCl_3$, 25 °C

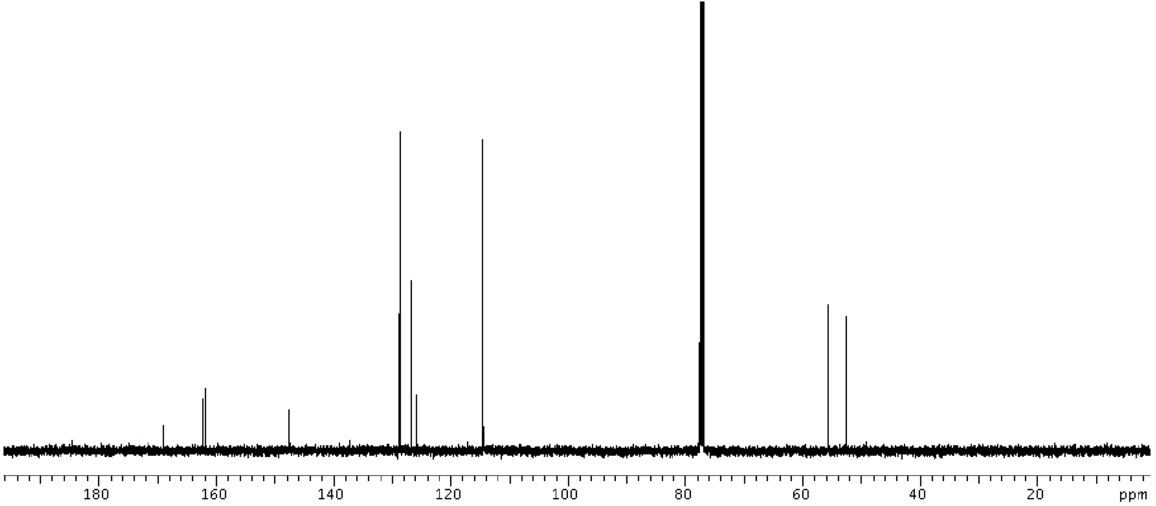


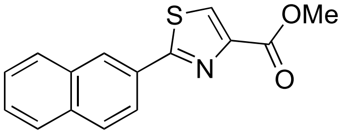


^{1}H NMR, 400 MHz, CDCl$_3$, 25 °C

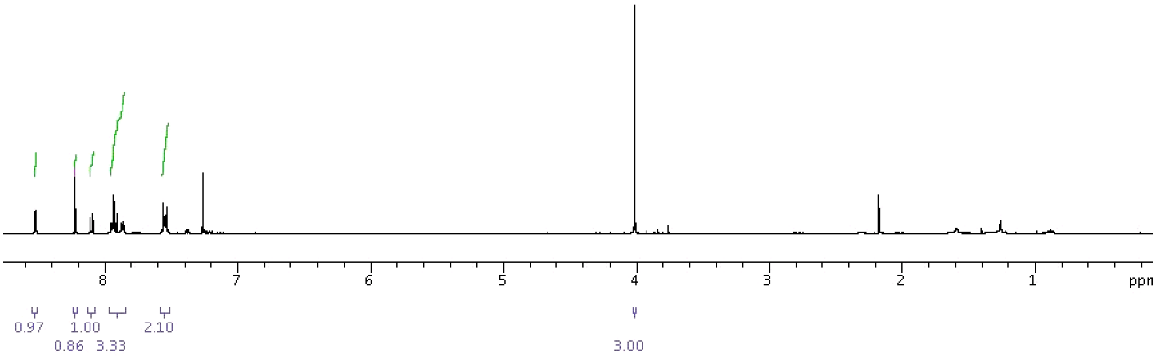


^{13}C NMR, 100 MHz, CDCl$_3$, 25 °C

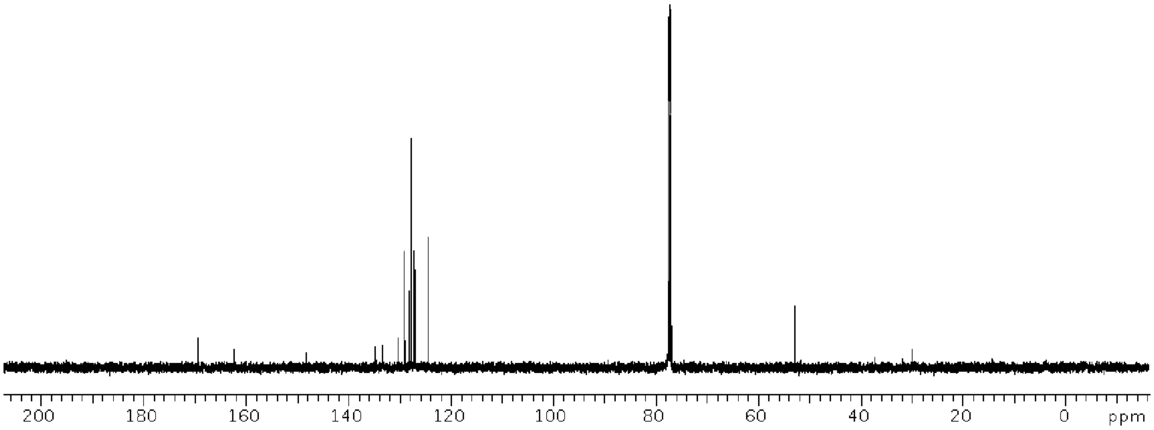


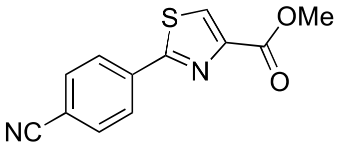


^{1}H NMR, 400 MHz, CDCl$_3$, 25 °C

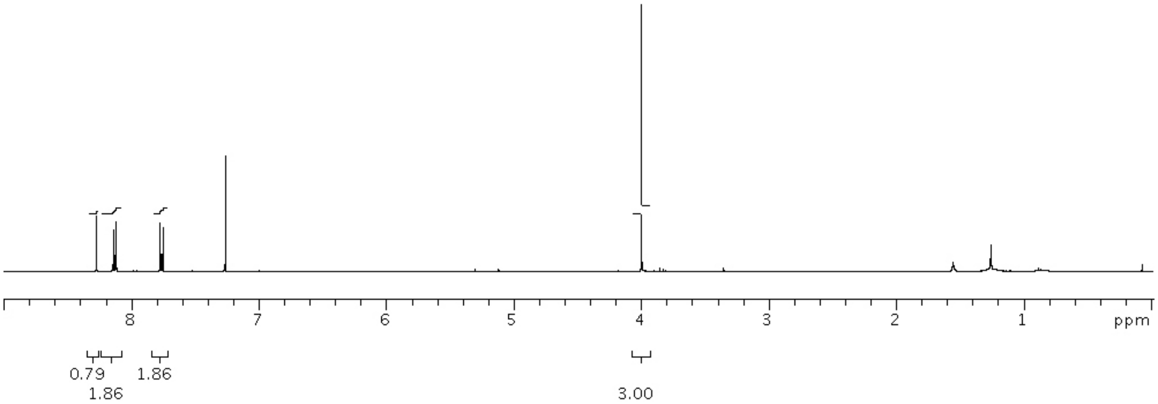


^{13}C NMR, 100 MHz, CDCl$_3$, 25 °C

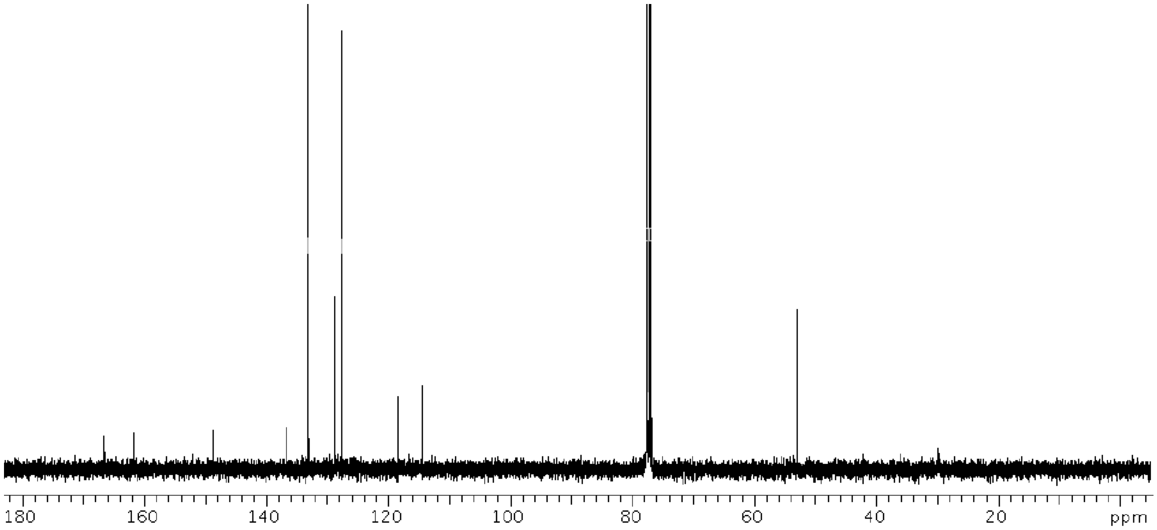


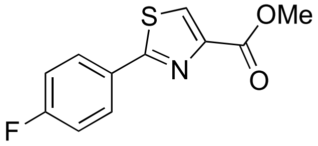


^{1}H NMR, 500 MHz, $CDCl_3$, 25 °C

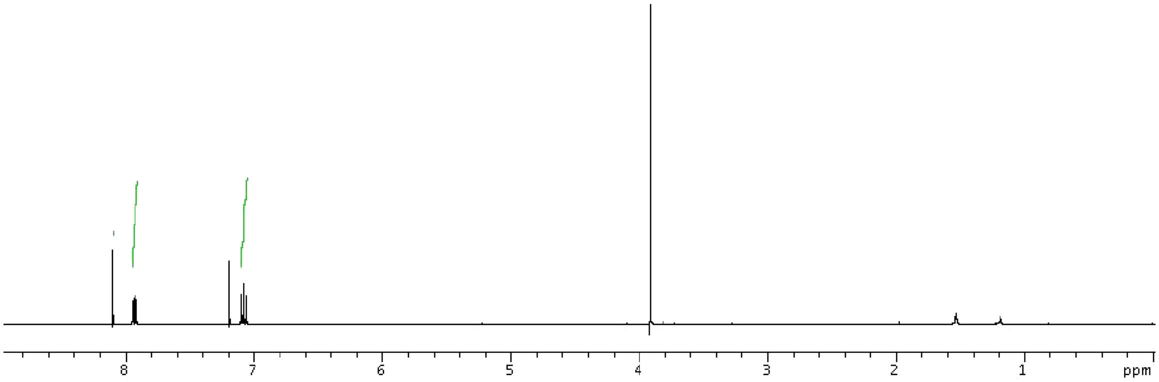


^{13}C NMR, 100 MHz, $CDCl_3$, 25 °C

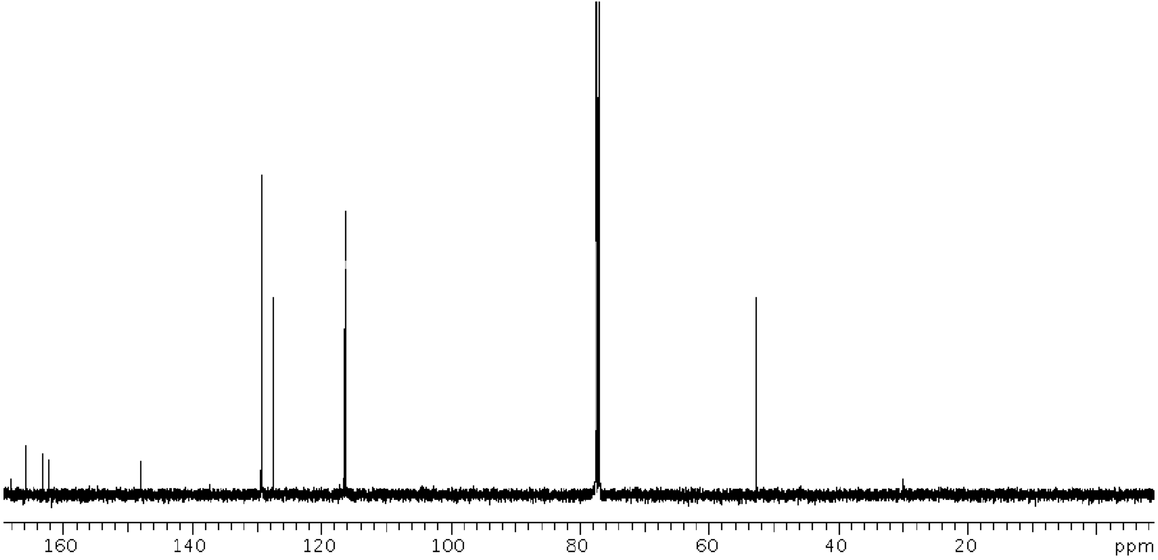


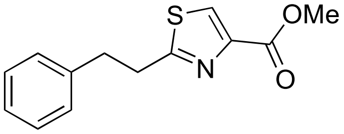


^{1}H NMR, 400 MHz, $CDCl_3$, 25 °C

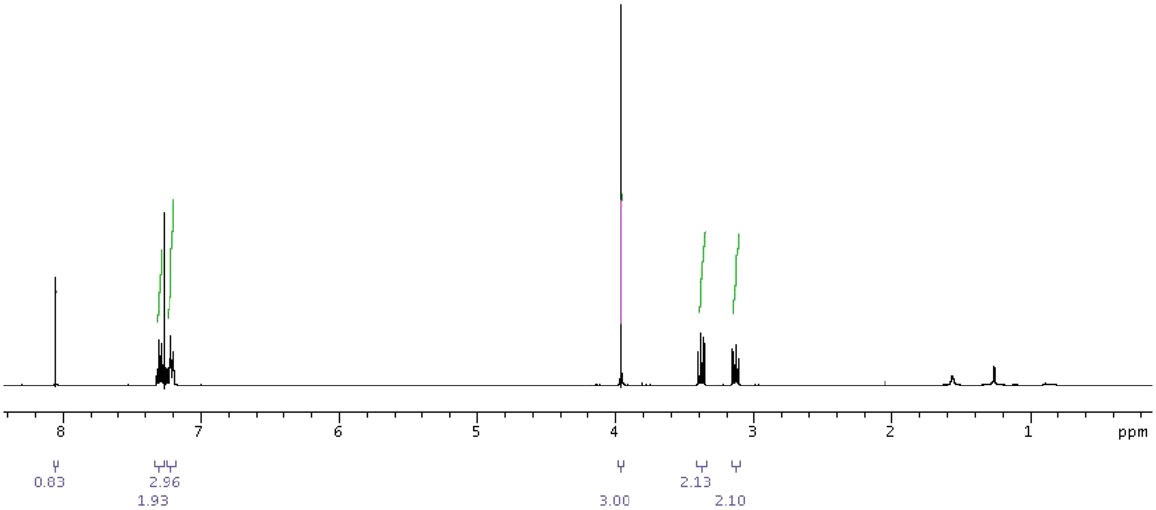


^{13}C NMR, 100 MHz, $CDCl_3$, 25 °C

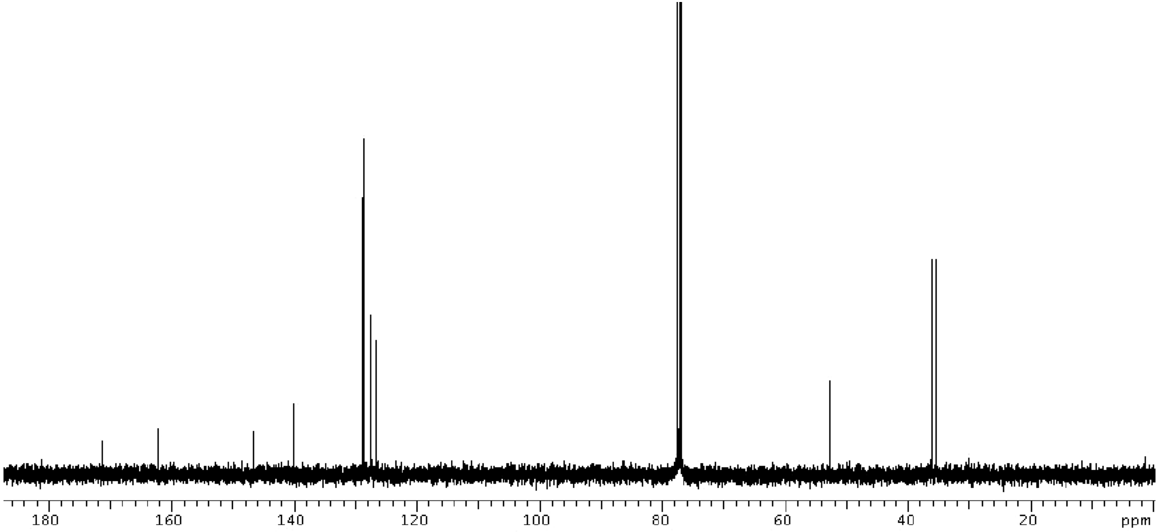


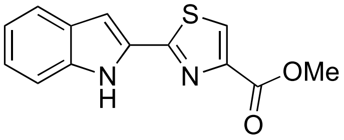


^{1}H NMR, 400 MHz, $CDCl_3$, 25 °C

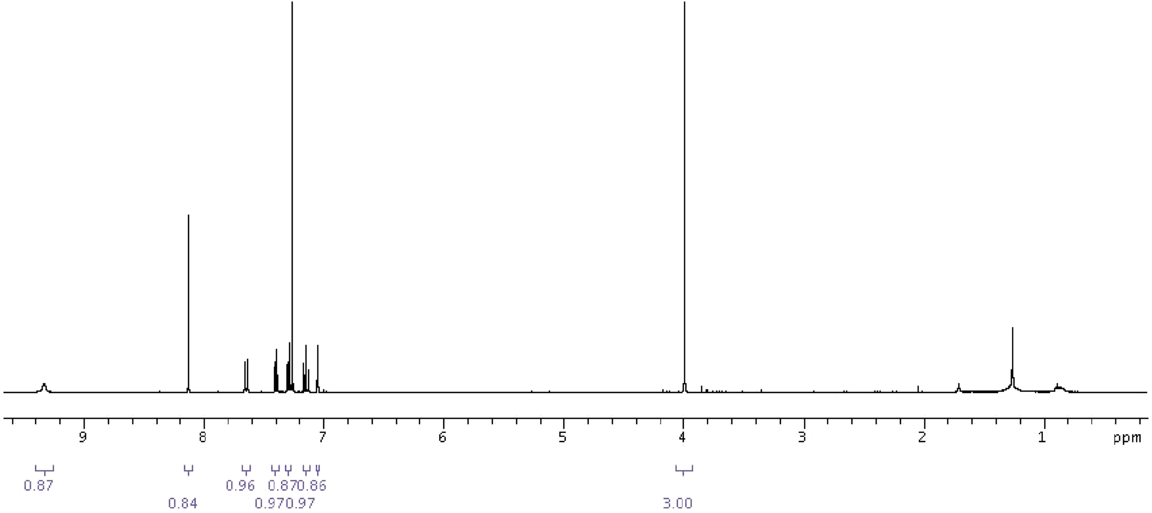


^{13}C NMR, 100 MHz, $CDCl_3$, 25 °C

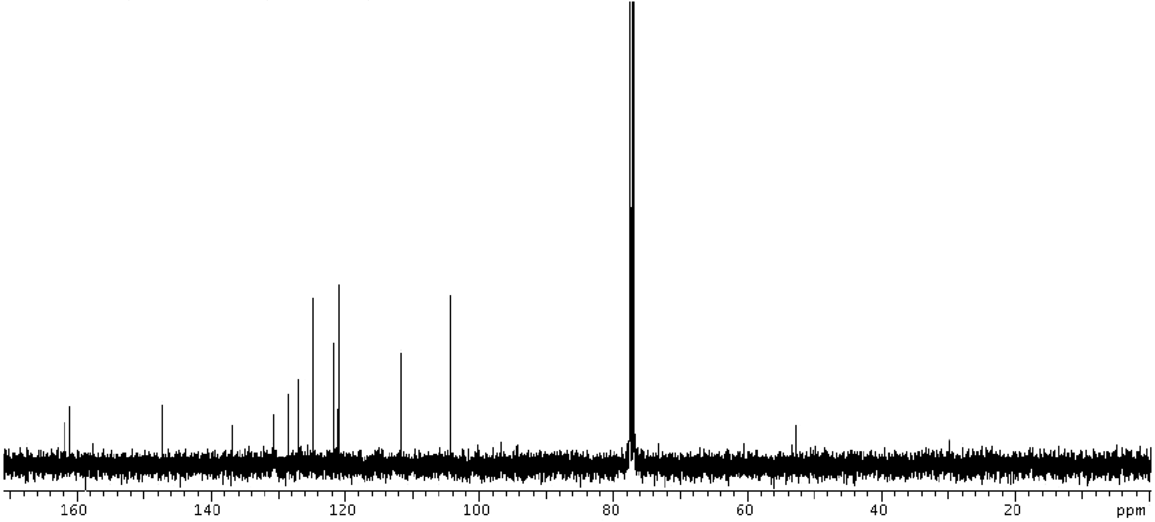


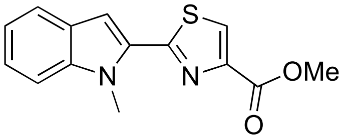


^{1}H NMR, 400 MHz, $CDCl_3$, 25 °C

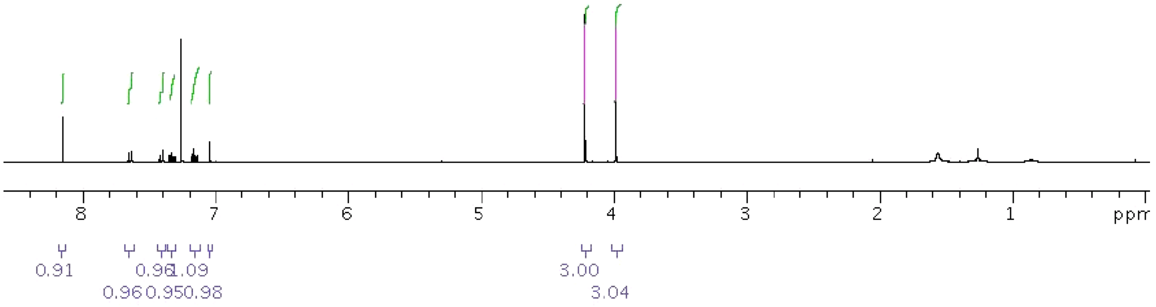


^{13}C NMR, 100 MHz, $CDCl_3$, 25 °C

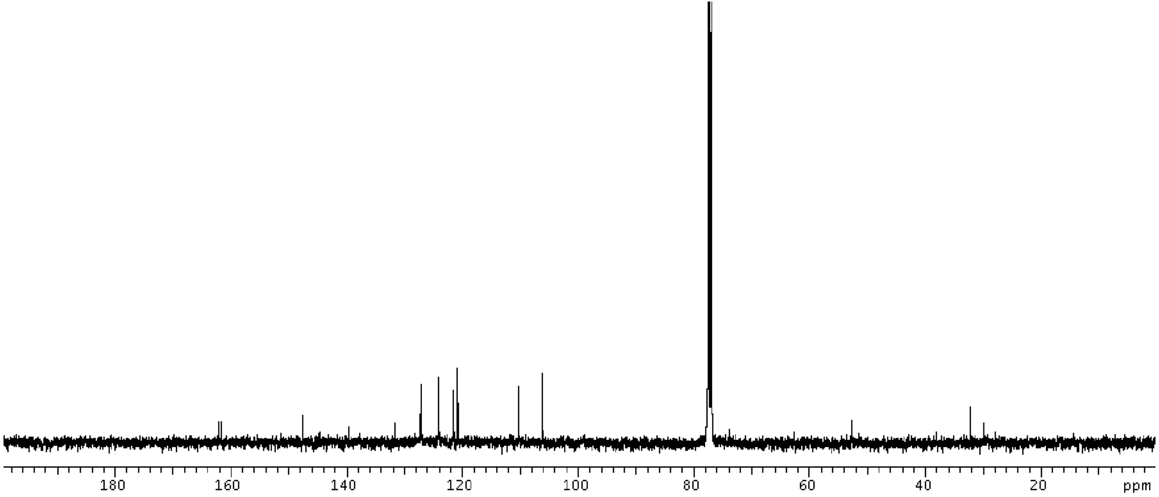


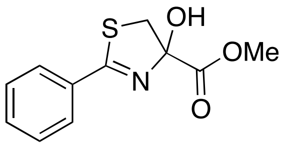


^{1}H NMR, 400 MHz, CDCl$_3$, 25 °C

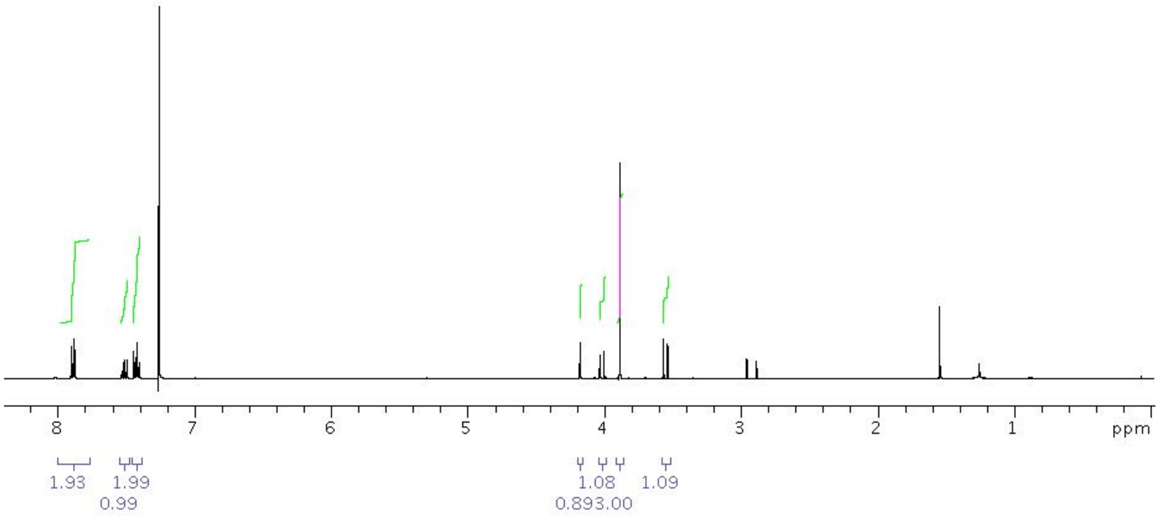


^{13}C NMR, 100 MHz, CDCl$_3$, 25 °C





^{1}H NMR, 400 MHz, $CDCl_3$, 25 °C



IV. X-Ray Crystal Structure Solutions of 1 and 1a

Figure S1. ORTEP Diagram of Complex **1**. Ellipsoids are Drawn at the 50% Probability Level.

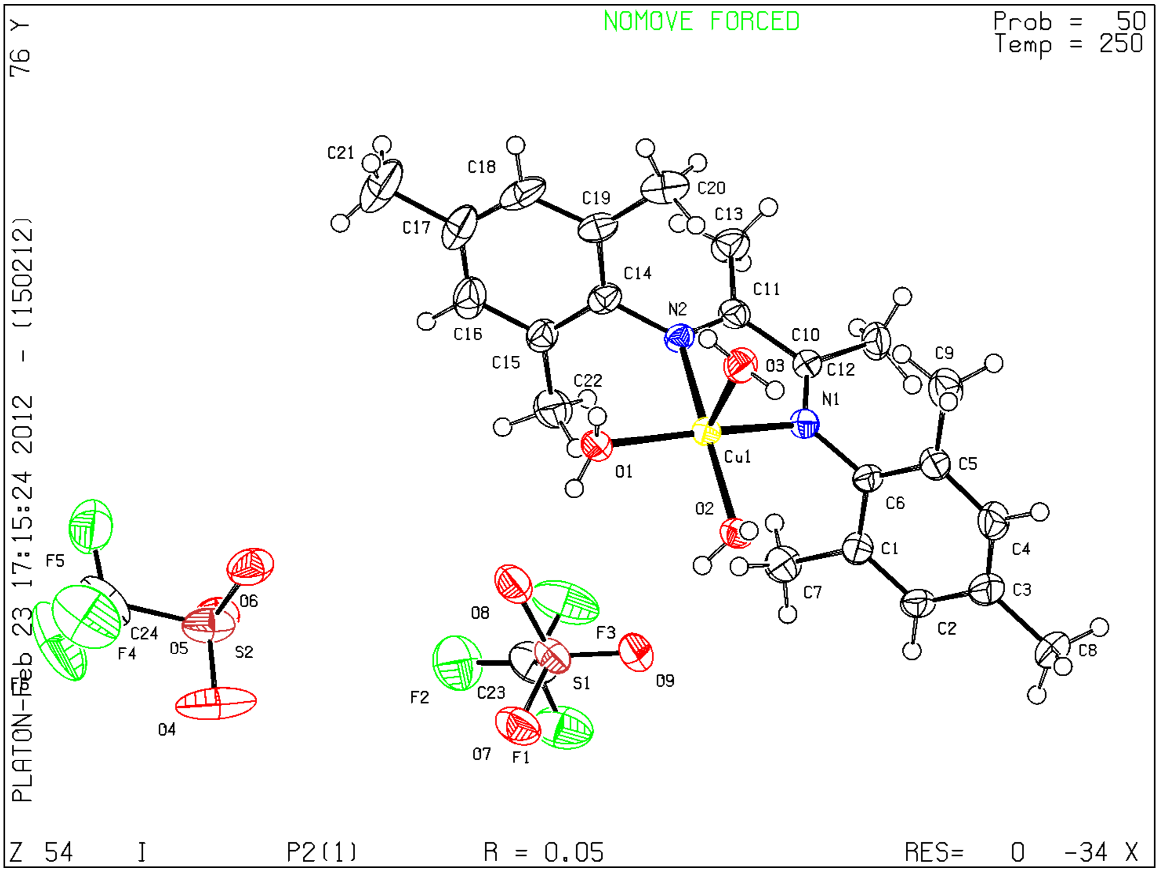


Table S2. Crystal Data and Structure Refinement **1**.

Empirical formula	$C_{24}\ H_{34}\ Cu\ F_6\ N_2\ O_9\ S_2$	
Formula weight	736.19	
Temperature	250(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 10.4067(13) Å	α= 90°
	b = 12.5305(15) Å	β= 91.443(2)°
	c = 12.5733(16) Å	γ = 90°
Volume	1639.1(4) $Å^3$	
Z	2	
Density (calculated)	1.492 Mg/m^3	
Absorption coefficient	0.876 mm^{-1}	
F(000)	758	
Theta range for data collection	1.62 to 27.49°	
Index ranges	$-13 \le h \le 13, -12 \le k \le 5, -15 \le l \le 6$	
Reflections collected	10158	
Independent reflections	5429 [R(int) = 0.0389]	
Completeness to theta = 27.49°	97.5%	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.150 and 0.801	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5429 / 1 / 405	
Goodness-of-fit on F^2	1.038	
Final R indices [I>2sigma(I)]	R1 = 0.0453, wR2 = 0.0983	
R indices (all data)	R1 = 0.0609, wR2 = 0.1051	
Absolute structure parameter	0.000(14)	
Largest diff. peak and hole	0.562 and -0.291 e.$Å^{-3}$	

Table S3. Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters ($Å^2 x 10^3$) for **1**. U(eq) is Defined as One Third of the Trace of the Orthogonalized U^{ij} Tensor.

	x	y	z	U(eq)
C(1)	7483(5)	5853(4)	304(3)	34(1)
C(2)	7788(5)	5453(4)	-692(3)	36(1)
C(3)	8537(5)	6038(4)	-1382(4)	43(1)
C(4)	9008(5)	7015(4)	-1055(3)	42(1)
C(5)	8740(4)	7454(4)	-63(3)	34(1)
C(6)	7955(3)	6863(5)	597(3)	27(1)
C(7)	6664(5)	5206(4)	1049(4)	40(1)

C(8)	8849(6)	5591(5)	-2478(4)	58(2)
C(9)	9279(5)	8534(4)	258(4)	46(1)
N(1)	7624(3)	7243(3)	1630(2)	27(1)
C(10)	6736(4)	7924(4)	1737(3)	29(1)
C(11)	6402(4)	8202(4)	2869(3)	30(1)
N(2)	7086(3)	7715(3)	3573(3)	26(1)
C(14)	6845(4)	7857(4)	4692(3)	30(1)
C(15)	6233(4)	7016(4)	5211(3)	33(1)
C(16)	6031(5)	7148(5)	6297(3)	45(1)
C(17)	6395(5)	8060(6)	6835(3)	51(2)
C(18)	7004(5)	8866(5)	6293(4)	49(2)
C(19)	7256(4)	8791(4)	5198(4)	36(1)
C(20)	7879(5)	9697(4)	4637(4)	50(1)
C(21)	6100(6)	8204(7)	8003(4)	74(2)
C(22)	5754(5)	6064(4)	4631(4)	49(1)
C(13)	5331(5)	8946(4)	3076(4)	41(1)
C(12)	5986(5)	8454(4)	837(3)	40(1)
C(23)	7329(6)	2858(5)	3892(5)	57(2)
C(24)	7179(5)	1667(6)	9691(5)	65(2)
Cu(1)	8476(1)	6786(1)	2999(1)	28(1)
F(1)	7107(3)	2129(3)	3154(3)	76(1)
F(2)	6962(4)	2464(3)	4808(3)	82(1)
F(3)	6605(3)	3705(3)	3657(4)	81(1)
F(4)	8364(4)	1515(4)	10058(4)	106(2)
F(5)	6732(5)	2511(4)	10168(3)	88(1)
F(6)	6505(5)	857(4)	9973(4)	124(2)
O(1)	8883(3)	6148(2)	4412(2)	35(1)
O(2)	9550(3)	5727(3)	2288(2)	34(1)
O(3)	10029(3)	7980(3)	3145(2)	37(1)
O(4)	7897(5)	930(4)	7880(5)	93(2)
O(5)	5825(3)	1795(4)	7954(3)	54(1)
O(6)	7774(4)	2845(3)	8089(3)	57(1)
O(7)	9649(4)	2235(3)	4171(3)	55(1)
O(8)	9081(4)	3988(3)	4834(3)	50(1)
O(9)	9239(4)	3686(3)	2945(3)	51(1)
S(1)	9014(1)	3231(1)	3965(1)	39(1)

Table S4. Bond lengths [Å] for **1**.

C(1)-C(2)	1.393(6)
C(1)-C(6)	1.403(7)
C(1)-C(7)	1.517(7)
C(2)-C(3)	1.390(7)
C(3)-C(4)	1.378(7)
C(3)-C(8)	1.530(7)
C(4)-C(5)	1.397(6)
C(5)-C(6)	1.392(6)
C(5)-C(9)	1.517(7)
C(6)-N(1)	1.434(5)
N(1)-C(10)	1.268(5)
N(1)-Cu(1)	1.999(3)
C(10)-C(12)	1.512(6)
C(10)-C(11)	1.514(6)
C(11)-N(2)	1.277(5)
C(11)-C(13)	1.481(7)
N(2)-C(14)	1.447(5)
N(2)-Cu(1)	2.004(4)
C(14)-C(19)	1.394(7)
C(14)-C(15)	1.402(6)
C(15)-C(16)	1.396(6)
C(15)-C(22)	1.479(7)
C(16)-C(17)	1.376(8)
C(17)-C(18)	1.382(8)
C(17)-C(21)	1.518(7)
C(18)-C(19)	1.412(7)
C(19)-C(20)	1.493(7)
C(23)-F(2)	1.318(7)
C(23)-F(1)	1.318(7)
C(23)-F(3)	1.331(7)
C(23)-S(1)	1.815(6)
C(24)-F(6)	1.289(7)
C(24)-F(5)	1.307(8)
C(24)-F(4)	1.319(6)
C(24)-S(2)	1.837(7)
Cu(1)-O(2)	1.965(3)
Cu(1)-O(1)	1.985(3)
Cu(1)-O(3)	2.206(3)
O(4)-S(2)	1.441(5)
O(5)-S(2)	1.427(3)
O(6)-S(2)	1.439(4)
O(7)-S(1)	1.433(4)
O(8)-S(1)	1.447(4)
O(9)-S(1)	1.428(3)

Symmetry transformations used to generate equivalent atoms.

Table S5. Bond angles [°] for **1**.

C(2)-C(1)-C(6)	118.3(4)	C(14)-C(19)-C(18)	116.0(5)
C(2)-C(1)-C(7)	120.5(5)	C(14)-C(19)-C(20)	123.7(4)
C(6)-C(1)-C(7)	121.2(4)	C(18)-C(19)-C(20)	120.3(4)
C(3)-C(2)-C(1)	121.0(5)	F(2)-C(23)-F(1)	107.9(5)
C(4)-C(3)-C(2)	118.9(4)	F(2)-C(23)-F(3)	108.5(5)
C(4)-C(3)-C(8)	120.8(5)	F(1)-C(23)-F(3)	108.0(5)
C(2)-C(3)-C(8)	120.3(5)	F(2)-C(23)-S(1)	110.7(4)
C(3)-C(4)-C(5)	122.6(5)	F(1)-C(23)-S(1)	111.5(4)
C(6)-C(5)-C(4)	117.2(5)	F(3)-C(23)-S(1)	110.3(4)
C(6)-C(5)-C(9)	122.3(4)	F(6)-C(24)-F(5)	108.0(6)
C(4)-C(5)-C(9)	120.5(4)	F(6)-C(24)-F(4)	107.5(5)
C(5)-C(6)-C(1)	122.0(4)	F(5)-C(24)-F(4)	107.3(6)
C(5)-C(6)-N(1)	121.5(5)	F(6)-C(24)-S(2)	111.6(5)
C(1)-C(6)-N(1)	116.5(4)	F(5)-C(24)-S(2)	111.8(4)
C(10)-N(1)-C(6)	120.8(3)	F(4)-C(24)-S(2)	110.5(5)
C(10)-N(1)-Cu(1)	114.2(3)	O(2)-Cu(1)-O(1)	91.39(14)
C(6)-N(1)-Cu(1)	125.0(3)	O(2)-Cu(1)-N(1)	92.66(14)
N(1)-C(10)-C(12)	125.5(4)	O(1)-Cu(1)-N(1)	165.05(15)
N(1)-C(10)-C(11)	116.1(4)	O(2)-Cu(1)-N(2)	168.43(15)
C(12)-C(10)-C(11)	118.5(4)	O(1)-Cu(1)-N(2)	92.96(14)
N(2)-C(11)-C(13)	126.1(4)	N(1)-Cu(1)-N(2)	80.53(14)
N(2)-C(11)-C(10)	113.8(4)	O(2)-Cu(1)-O(3)	94.11(15)
C(13)-C(11)-C(10)	120.1(4)	O(1)-Cu(1)-O(3)	93.39(14)
C(11)-N(2)-C(14)	120.5(4)	N(1)-Cu(1)-O(3)	100.66(13)
C(11)-N(2)-Cu(1)	115.0(3)	N(2)-Cu(1)-O(3)	96.32(14)
C(14)-N(2)-Cu(1)	124.5(3)	O(9)-S(1)-O(7)	115.1(2)
C(19)-C(14)-C(15)	123.8(4)	O(9)-S(1)-O(8)	114.2(2)
C(19)-C(14)-N(2)	119.2(4)	O(7)-S(1)-O(8)	114.9(2)
C(15)-C(14)-N(2)	116.9(4)	O(9)-S(1)-C(23)	103.7(3)
C(16)-C(15)-C(14)	116.6(4)	O(7)-S(1)-C(23)	103.0(3)
C(16)-C(15)-C(22)	121.4(5)	O(8)-S(1)-C(23)	103.6(3)
C(14)-C(15)-C(22)	121.9(4)	O(5)-S(2)-O(6)	115.2(3)
C(17)-C(16)-C(15)	122.2(5)	O(5)-S(2)-O(4)	114.9(3)
C(16)-C(17)-C(18)	119.2(4)	O(6)-S(2)-O(4)	114.2(3)
C(16)-C(17)-C(21)	120.9(6)	O(5)-S(2)-C(24)	103.4(2)
C(18)-C(17)-C(21)	119.8(6)	O(6)-S(2)-C(24)	103.5(3)
C(17)-C(18)-C(19)	122.1(5)	O(4)-S(2)-C(24)	103.5(4)

Symmetry transformations used to generate equivalent atoms.

Figure S2. ORTEP Diagram of Complex **1a**. Ellipsoids are Drawn at the 50% Probability Level.

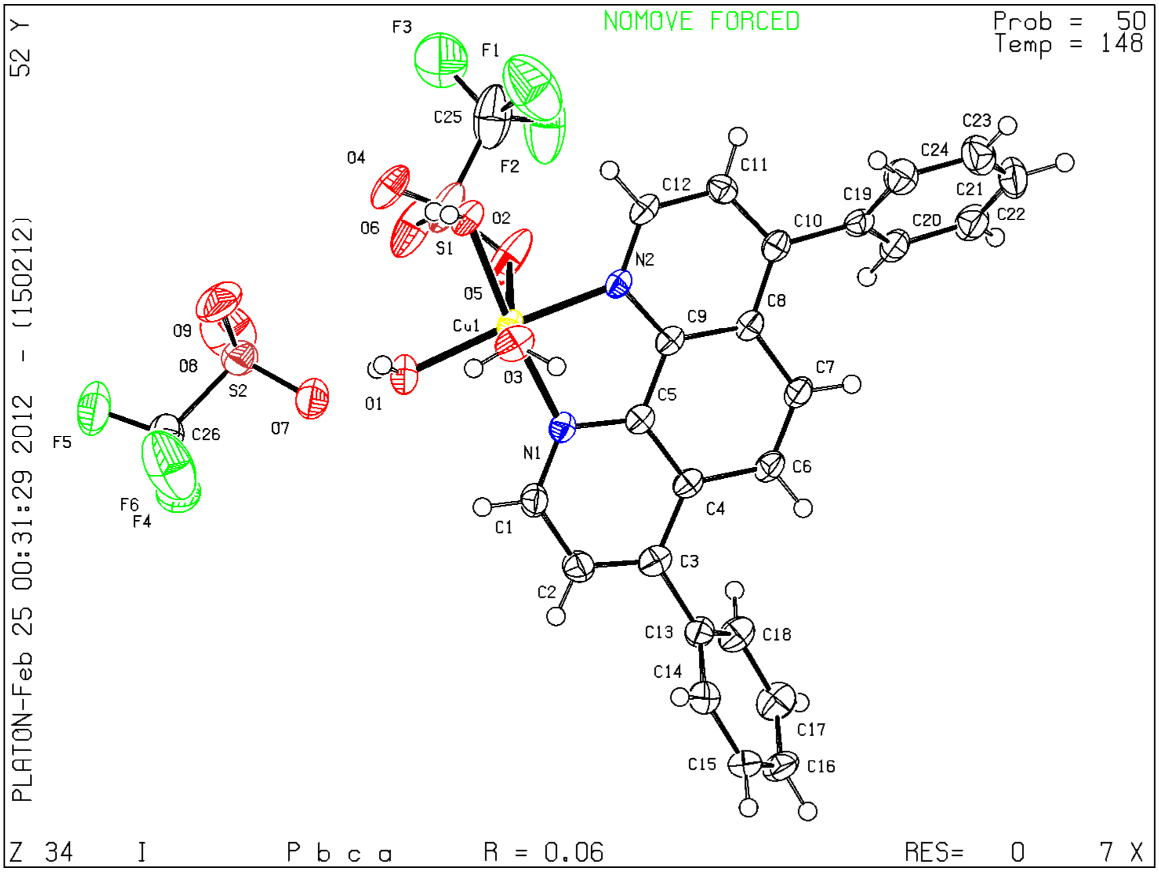


Table S6. Crystal Data and Structure Refinement for **1a**.

Empirical formula	$C_{26}H_{22}CuF_6N_2O_9S_2$	
Formula weight	748.12	
Temperature	148(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 8.5620(12) Å	α= 90°.
	b = 26.689(4) Å	β= 90°.
	c = 26.774(4) Å	γ = 90°.
Volume	6118.3(15) Å3	
Z	8	
Density (calculated)	1.624 Mg/m3	
Absorption coefficient	0.941 mm-1	
F(000)	3032	
Crystal size	0.21 x 0.11 x 0.03 mm3	
Theta range for data collection	1.52 to 28.43°.	
Index ranges	-11<=h<=10, -35<=k<=34, -35<=l<=31	
Reflections collected	36207	
Independent reflections	7239 [R(int) = 0.1122]	
Completeness to theta = 27.50°	99.4 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.75 and 0.62	
Refinement method	Full-matrix least-squares on F2	
Data / restraints / parameters	7239 / 47 / 439	
Goodness-of-fit on F2	1.010	
Final R indices [I>2sigma(I)]	R1 = 0.0588, wR2 = 0.1210	
R indices (all data)	R1 = 0.1327, wR2 = 0.1452	
Largest diff. peak and hole	0.871 and -0.708 e $Å^{-3}$	

Table S7. Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$x10^3) for **1a**. U(eq) is Defined as One Third of the Trace of the Orthogonalized U^{ij} Tensor.

	x	y	z	U(eq)
C(1)	9368(5)	816(2)	823(2)	30(1)
C(2)	9986(5)	678(2)	366(2)	32(1)
C(3)	10290(4)	1025(2)	-3(1)	28(1)
C(4)	10052(4)	1539(2)	124(1)	24(1)
C(5)	9448(4)	1650(1)	598(1)	22(1)
C(6)	10489(5)	1955(2)	-185(1)	28(1)
C(7)	10311(5)	2433(2)	-32(1)	29(1)
C(8)	9659(4)	2556(1)	446(1)	24(1)
C(9)	9245(4)	2154(1)	760(1)	22(1)
C(10)	9475(4)	3048(1)	638(1)	25(1)

C(11)	8903(5)	3098(2)	1120(1)	27(1)
C(12)	8539(4)	2679(2)	1405(1)	27(1)
C(13)	10827(5)	870(2)	-506(1)	28(1)
C(14)	12082(5)	541(2)	-558(2)	32(1)
C(15)	12561(5)	391(2)	-1027(2)	35(1)
C(16)	11793(5)	558(2)	-1451(2)	37(1)
C(17)	10550(5)	881(2)	-1402(2)	39(1)
C(18)	10075(5)	1040(2)	-933(2)	35(1)
C(19)	9864(5)	3502(2)	339(1)	29(1)
C(20)	9280(5)	3565(2)	-143(2)	32(1)
C(21)	9649(5)	3995(2)	-410(2)	41(1)
C(22)	10595(6)	4354(2)	-203(2)	46(1)
C(23)	11184(5)	4293(2)	269(2)	44(1)
C(24)	10813(5)	3870(2)	548(2)	36(1)
C(25)	3451(7)	2617(3)	1554(2)	72(2)
C(26)	3386(6)	-278(2)	1949(2)	42(1)
Cu(1)	8205(1)	1569(1)	1570(1)	25(1)
F(1)	4628(5)	2887(1)	1746(2)	107(1)
F(2)	3081(4)	2830(2)	1115(2)	112(2)
F(3)	2228(4)	2697(1)	1856(1)	87(1)
F(4)	3103(4)	-487(1)	1509(1)	72(1)
F(5)	2277(4)	-434(1)	2251(1)	67(1)
F(6)	4721(4)	-452(1)	2105(2)	100(1)
N(1)	9054(4)	1290(1)	937(1)	24(1)
N(2)	8707(3)	2215(1)	1233(1)	22(1)
O(1)	7418(4)	905(1)	1779(1)	34(1)
O(2)	7348(3)	1913(1)	2162(1)	29(1)
O(3)	10418(3)	1435(1)	1998(1)	36(1)
O(4)	4145(3)	1823(1)	2002(1)	41(1)
O(5)	5325(4)	1969(2)	1198(1)	64(1)
O(6)	2534(4)	1776(2)	1260(1)	62(1)
O(7)	4683(4)	479(1)	1546(1)	43(1)
O(8)	1898(4)	517(2)	1716(2)	82(1)
O(9)	3778(5)	559(1)	2392(1)	71(1)
S(1)	3919(1)	1978(1)	1492(1)	46(1)
S(2)	3412(1)	396(1)	1887(1)	40(1)

Table S8. Bond Lengths [Å] for **1a**.

C(1)-N(1)	1.328(5)	C(19)-C(20)	1.394(5)
C(1)-C(2)	1.381(5)	C(20)-C(21)	1.390(6)
C(2)-C(3)	1.380(5)	C(21)-C(22)	1.370(6)
C(3)-C(4)	1.429(5)	C(22)-C(23)	1.371(7)
C(3)-C(13)	1.480(5)	C(23)-C(24)	1.390(6)
C(4)-C(5)	1.402(5)	C(25)-F(3)	1.339(6)
C(4)-C(6)	1.434(5)	C(25)-F(1)	1.339(7)
C(5)-N(1)	1.365(5)	C(25)-F(2)	1.345(6)
C(5)-C(9)	1.423(5)	C(25)-S(1)	1.761(7)
C(6)-C(7)	1.349(5)	C(26)-F(6)	1.302(5)
C(7)-C(8)	1.435(5)	C(26)-F(5)	1.314(5)
C(8)-C(9)	1.408(5)	C(26)-F(4)	1.325(5)
C(8)-C(10)	1.418(5)	C(26)-S(2)	1.809(5)
C(9)-N(2)	1.358(4)	Cu(1)-O(2)	1.974(3)
C(10)-C(11)	1.387(5)	Cu(1)-O(1)	1.976(3)
C(10)-C(19)	1.490(5)	Cu(1)-N(1)	1.989(3)
C(11)-C(12)	1.390(5)	Cu(1)-N(2)	1.994(3)
C(12)-N(2)	1.330(5)	Cu(1)-O(3)	2.243(3)
C(13)-C(18)	1.389(5)	O(4)-S(1)	1.441(3)
C(13)-C(14)	1.394(6)	O(5)-S(1)	1.438(3)
C(14)-C(15)	1.381(5)	O(6)-S(1)	1.442(3)
C(15)-C(16)	1.386(6)	O(7)-S(2)	1.436(3)
C(16)-C(17)	1.374(6)	O(8)-S(2)	1.412(4)
C(17)-C(18)	1.385(6)	O(9)-S(2)	1.453(4)
C(19)-C(24)	1.392(6)		

Symmetry transformations used to generate equivalent atoms

Table S9. Bond Angles [°] for **1a**.

N(1)-C(1)-C(2)	122.3(4)	F(3)-C(25)-F(1)	105.9(6)
C(3)-C(2)-C(1)	122.0(4)	F(3)-C(25)-F(2)	106.0(5)
C(2)-C(3)-C(4)	116.4(4)	F(1)-C(25)-F(2)	106.6(5)
C(2)-C(3)-C(13)	121.6(4)	F(3)-C(25)-S(1)	112.9(4)
C(4)-C(3)-C(13)	122.0(4)	F(1)-C(25)-S(1)	112.7(4)
C(5)-C(4)-C(3)	118.1(3)	F(2)-C(25)-S(1)	112.2(5)
C(5)-C(4)-C(6)	117.1(3)	F(6)-C(26)-F(5)	108.9(4)
C(3)-C(4)-C(6)	124.6(3)	F(6)-C(26)-F(4)	107.3(4)
N(1)-C(5)-C(4)	123.0(3)	F(5)-C(26)-F(4)	106.4(4)
N(1)-C(5)-C(9)	115.7(3)	F(6)-C(26)-S(2)	111.9(3)
C(4)-C(5)-C(9)	121.3(3)	F(5)-C(26)-S(2)	112.3(3)
C(7)-C(6)-C(4)	121.9(4)	F(4)-C(26)-S(2)	109.8(3)
C(6)-C(7)-C(8)	122.0(4)	O(2)-Cu(1)-O(1)	93.60(12)
C(9)-C(8)-C(10)	117.5(3)	O(2)-Cu(1)-N(1)	174.13(12)
C(9)-C(8)-C(7)	117.2(3)	O(1)-Cu(1)-N(1)	91.70(13)
C(10)-C(8)-C(7)	125.3(3)	O(2)-Cu(1)-N(2)	92.37(12)
N(2)-C(9)-C(8)	123.4(3)	O(1)-Cu(1)-N(2)	167.78(13)
N(2)-C(9)-C(5)	116.1(3)	N(1)-Cu(1)-N(2)	81.96(12)
C(8)-C(9)-C(5)	120.5(3)	O(2)-Cu(1)-O(3)	88.73(11)
C(11)-C(10)-C(8)	117.8(3)	O(1)-Cu(1)-O(3)	90.00(13)
C(11)-C(10)-C(19)	119.9(3)	N(1)-Cu(1)-O(3)	93.81(12)
C(8)-C(10)-C(19)	122.3(3)	N(2)-Cu(1)-O(3)	100.79(13)
C(10)-C(11)-C(12)	120.8(4)	C(1)-N(1)-C(5)	117.9(3)
N(2)-C(12)-C(11)	122.3(4)	C(1)-N(1)-Cu(1)	128.8(3)
C(18)-C(13)-C(14)	118.7(4)	C(5)-N(1)-Cu(1)	113.1(2)
C(18)-C(13)-C(3)	120.9(4)	C(12)-N(2)-C(9)	118.3(3)
C(14)-C(13)-C(3)	120.4(4)	C(12)-N(2)-Cu(1)	128.7(3)
C(15)-C(14)-C(13)	120.1(4)	C(9)-N(2)-Cu(1)	113.0(2)
C(14)-C(15)-C(16)	120.7(4)	O(5)-S(1)-O(4)	113.64(19)
C(17)-C(16)-C(15)	119.4(4)	O(5)-S(1)-O(6)	116.6(2)
C(16)-C(17)-C(18)	120.4(4)	O(4)-S(1)-O(6)	114.2(2)
C(17)-C(18)-C(13)	120.7(4)	O(5)-S(1)-C(25)	105.0(3)
C(24)-C(19)-C(20)	119.7(4)	O(4)-S(1)-C(25)	102.5(2)
C(24)-C(19)-C(10)	119.3(4)	O(6)-S(1)-C(25)	102.5(3)
C(20)-C(19)-C(10)	120.9(4)	O(8)-S(2)-O(7)	117.0(2)
C(21)-C(20)-C(19)	119.6(4)	O(8)-S(2)-O(9)	115.5(3)
C(22)-C(21)-C(20)	120.3(4)	O(7)-S(2)-O(9)	112.4(2)
C(21)-C(22)-C(23)	120.4(4)	O(8)-S(2)-C(26)	104.2(2)
C(22)-C(23)-C(24)	120.5(5)	O(7)-S(2)-C(26)	102.8(2)
C(23)-C(24)-C(19)	119.4(4)	O(9)-S(2)-C(26)	102.4(2)

Symmetry transformations used to generate equivalent atoms

V. References

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1. Lu, Y.; Li, C.; Wang, Z.; Ross II, C. R.; Chen, J.; Dalton, J. T.; Li, W.; Miller, D. D. *J. Med. Chem.* **2009**, 52, 1701-1711.
2. Purchased from Sigma Aldrich and was used as received.
3. Purchased from Alfa Aesar and was used as received.
4. Purchased from EM Science and was used as received
5. Purchased from BA Chem and was used as received.
6. Osawa, T.; Ando, S.; Akiba, M.; Kakimoto, N. *PCT Int Appl.* (**1999**).
7. Raman, P; Razavi, H.; Kelly, J.W. *Org. Lett.* **2000**, *2*, 3289-3292.
8. Purchased from J.T. Baker and was used as received.
9. Purchased from TCI America and was used as received.
10. Purchased from Lancaster and was used as received.
11. Purchased from Chem-Impex International and was used as received.
12. (a) Shieh, W.; Dell, S.; Bach, A.; Repic, O.; Blacklock, T. J. *J. Org. Chem*. **2002**, *68*, 1954-1957. (b) Sechi, M.; Derudas, M.; Dallocchio, R.; Dessi, A.; Bacchi, A.; Sannia, L.; Carta, F.; Palomba, M.; Ragab, O.; Chan, C.; Shoemaker, R.; Sei, S.; Dayam, R.; Neamai, N. *J. Med. Chem.* **2004**, *47*, 5298-5310.
13. Purportedly observed by TLC: Huang, Y.; Gan, H.; Li, S.; Xu, J.; Wu, X.; Yao, H. *Tetrahedron Lett*. **2010**, *51*, 1751.