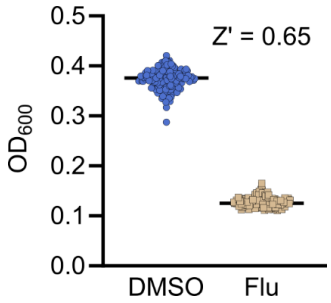
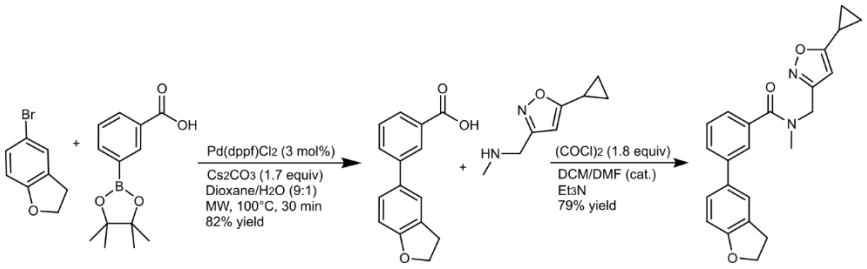
Supplementary Material

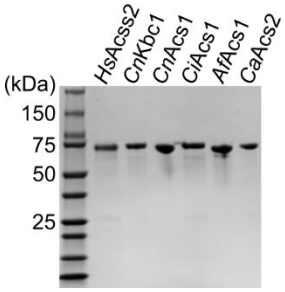
Supplemental Figures



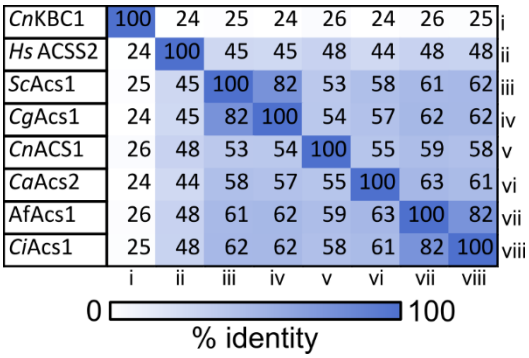
Supplemental Figure 1. The screening assay using the *acl1*Δ mutant was performed as described in materials and methods. Odd rows contained 1% DMSO solvent and even rows contained 64 µg/mL fluconazole in 1% DMSO. The OD600 of each well was corrected by subtraction of the optical density of cell free wells. The density of DMSO and fluconazole containing wells is shown as well as the Z' factor calculated from these data.



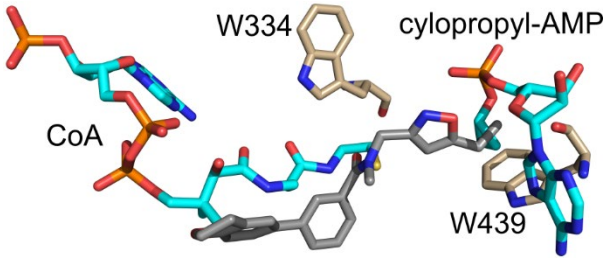
Supplemental Figure 2. Summary of synthetic route for isoxazole 1. See supplemental methods for full details and characterization of **1.**



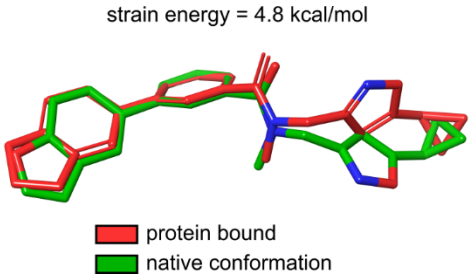
Supplemental Figure 3. SDS-PAGE gel of recombinant fungal ACS and human ACSS2 enzymes. The indicated enzymes were expressed and purified from E. coli as described in materials and methods. The purified proteins were fractionated on SDS-PAGE gels to assess purity which was greater than 90% by densitometry.



Supplemental Figure 4. Comparison of % identity for fungal ACSs, human ACSS2, and the acetoacetyl-CoA synthetase Kbc1. The alignments were performed with the Uniprot database.



Supplemental Figure 5. Overlay of the cyclopropyl moieties in structures of CnAcs1 bound to isoxazole 1 and cyclopropyl-AMP ester. The CoA, isoxazole 1 (grey), and cyclopropyl-AMP molecules bound to CnAcs1 were overlain. This revealed that the cyclopropyl moieties of both inhibitors overlap in the acetyl binding pocket between W334 and W349.



Supplemental Figure 6. Comparison of the conformations of free and CnAcs1-bound isoxazole 1. The predicted conformation of free isoxazole 1 was compared to the conformation present in the CnAcs1-bound form of **1** as described in materials and methods. The apparent strain energy of the bound form relative to free form of **1** was 4.8 kcal. The predicted free conformation of **1** is overlain with the bound conformation of **1**.

Supplemental Tables

Compound	Species	Biotransformation	Theoretical Mass	# Peaks	Total Area	Metabolite Fraction
Isoxazole 1	**Mouse**	Parent [M+H]+	375.1710	1	127,240,000	-
		Oxidation [M+H]+	391.1653	3	113,783,100	42.5%
		Oxidation and Methylation [M+H]+	405.1812	1	91,558,000	34.2%
		Di-Oxidation [M+H]+	407.1595	3	28,834,200	10.8%
		Internal Hydrolysis [M+H]+	393.1813	1	11,980,000	4.5%
		Oxidation and Internal Hydrolysis [M+H]+	409.1749	4	7,391,200	2.8%
		Desaturation [M+H]+	373.1545	2	6,638,800	2.5%
	Human	Parent [M+H]+	375.1710	1	206,600,000	-
		Oxidation [M+H]+	391.1644	5	101,628,500	36.8%
		Oxidation and Methylation [M+H]+	405.1811	1	47,220,000	17.1%
		Di-Oxidation [M+H]+	407.1592	3	37,944,000	13.7%
		Desaturation [M+H]+	373.1544	4	21,004,300	7.6%
		Internal Hydrolysis [M+H]+	393.1809	1	14,860,000	5.4%
		Demethylation and Oxidation [M+H]+	377.1482	3	9,561,600	3.5%
		Loss of CH2 [M+H]+	361.1545	2	8,971,000	3.2%
		Loss of C7H7NO [M+H]+	254.1177	1	5,966,000	2.2%
Isoxazole 2	**Mouse**	Parent [M+H]+	351.1507	1	382,300,000	-
		Loss of CH2 [M+H]+	337.1349	1	96,541,200	58.2%
		Desaturation [M+H]+	349.1355	1	21,099,000	12.7%
		Oxidation [M+H]+	367.1444	5	13,803,100	8.3%
		Demethylation and Oxidation [M+H]+	353.1292	4	12,332,200	7.4%
		Loss of C8H10N2O+Desaturation [M+H]+	199.0551	6	9,020,200	5.4%
		Loss of C7H7NO [M+H]+	230.0976	1	3,301,000	2.0%
	Human	Parent [M+H]+	351.1507	1	350,100,000	-
		Loss of CH2 [M+H]+	337.1349	1	67,290,000	53.9%
		Loss of C7H7NO [M+H]+	230.0976	1	28,260,000	22.7%
		Oxidation [M+H]+	367.1444	3	7,697,600	6.2%
		Loss of C8H10N2O+Desaturation [M+H]+	199.0551	5	5,635,200	4.5%
		Desaturation [M+H]+	349.1355	1	3,990,000	3.2%
		Demethylation and Oxidation [M+H]+	353.1292	1	2,537,900	2.0%

Supplemental Table 1. Metabolism of isoxazoles 1 & 2 in human and mouse liver microsomes.

Gene	Base Change	Amino Acid Change	Background (isolate)			
			H99 (H99^R)	*Δacl* (B4)	*Δacl* (E3)	*ΔaclΔkbc* (G4)
SAGA-associated factor 29 (CNAG_06392)	215C>T	Pro72Leu		x		
	216_217insT	Arg73fs	x			
	217_218insT	Arg73fs	x			x
	217C>T	Arg73Cys	x	x		
	218G>T	Arg73Leu	x			x
	219C>T	Arg73Arg		x		x
	220G>T	Ala74Ser		x		x
	224C>G	Thr75Arg				x
	875G>T	Gly292Val	x			
	878T>A	Met293Lys	x			
	879G>C	Met293Ile	x			x
	880T>A	Tyr294Asn	x			
	881A>C	Tyr294Ser	x		x	
	883A>T	Arg295*		x	x	
	884G>C	Arg295Thr	x	x	x	
	885A>C	Arg295Ser	x			
Rab guanyl-nucleotide exchange factor (VAM6, CNAG_05395)	293A>T	Asp98Val	x	x	x	
	334A>G	Asn112Asp	x	x	x	
	350A>G	Lys117Arg		x	x	
	365A>T	Asp122Val	x	x	x	
	382A>G	Ile128Val	x	x	x	
Hypothetical protein (CNAG_05343)	596C>G	X199X		x		
	597_598insGGGGG	Arg200fs		x		
	601G>A	Gly201Arg		x	x	
	606C>G	Ser202Arg		x		
Hypothetical protein (CNAG_08004)	440A>T	His147Leu				x
	446A>C	Ter149Ser+		x		
	447G>C	Ter149Tyr+		x		
Dihydroxyacetone kinase (CNAG_00826)	1130A>C	Glu377Ala		x	x	
Translation initiation factor 3 subunit D (CNAG_03641)	730A>T	Ile244Phe			x	x

Supplemental Table 2. Summary of mutations identified in the 4 isoxazole 1-resistant strains.

Supplemental Methods

Chemical synthesis and characterization

Materials and methods

All chemicals were purchased from either Aaron Chemicals, AmBeed Inc., or Enamine Ltd. and were used without further purification. All compounds have purity of >95% as judged by HPLC analysis (UV detection at 254 nm). HPLC was performed using an Agilent HPLC equipped with a C18 column (Avantor® Alltima C18, 5 µm, 4.6 mm x 150 mm) with the following method: Solvent A = H_2O (0.1% TFA), Solvent B = Acetonitrile; 0 to 10 min, (10% B), 10 to 25 min (10 to 100% B), 25 to 26 min (100 to 10% B), 26 to 29 min (10 to 100% B), 29 to 30 min (100% to 10% B). Detection was set at 254 nm. Analytical TLC was performed using aluminum-backed, pre-coated Alugram® SIL G/UV_{254} 0.20 mm TLC plates that were purchased from Macherey-Nagel through Fischer Scientific. TLC plates were visualized using UV light at 254 nm from a Spectroline® model ENF-280C 115 V UV-lamp. Purification was performed on normal phase silica gel (Millipore-Sigma 230-400 mesh ASTM) using a Biotage® Selekt Enkel. ^{1}H and ^{13}C NMR were recorded on a Bruker Avance III 500 outfitted with a 5 mm BBFO Z-gradient probe. Chemical shifts (δ) are in ppm, and the coupling constants (*J*) are expressed in hertz (Hz). The following abbreviations are used: singlet (s), doublet (d), triplet (t), multiplet (m), broad signal (br s). HRMS obtained on a Bruker Maxis Plus Quadrupole Time-of-Flight (QTOF).

Experimental Details for syntheses

N-((5-cyclopropylisoxazol-3-yl)methyl)-3-(2,3-dihydrobenzofuran-5-yl)-N-methylbenzamide (**1**)

To a 50 mL RBF was added 3-(2,3-dihydrobenzofuran-5-yl)benzoic acid (17.8 mg, 0.074 mmol, 1.00 eq), stir bar, 3 drops of anhydrous DMF, 3 mL DCM, and oxalyl chloride (17.1 mg, 0.135 mmol, 1.82 eq). Solution was stirred at RT for 30 min. Then [(5-cyclopropyl-1,2-oxazole-3-yl)methyl] (methyl)amine (15.2 mg, 0.099 mmol, 1.35 eq) was added to the flask along with 4

drops Et_3N. The reaction was stirred at RT overnight. Crude was then transferred to a separatory funnel with 25 mL DCM. Extracted twice with 35 mL of HCl (aq) at pH 2; aqueous layer discarded. Extracted twice with 30 mL of NaOH (aq) at pH 10; aqueous layer discarded. DCM layer was loaded onto silica gel and chromatographed in 0%-40% EtOAc/Hex. to afford the product as a colorless oil (21.6mg, 79% yield, HPLC = 95.6%). HR-MS data for $[C_{23}H_{22}N_2O_3]^+$: $[M+H]^+$ calculated 375.1703, found 375.1702; $[M+Na]^+$ calculated 397.1523, found 397.1522. ^1H NMR (500 MHz, $CDCl_3$, major rotamer (R1) 70% and minor rotamer (R2) 30%) δ 7.61 (m, 2H), 7.45 (m, 2H) , 7.36 (m, 2H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.06 (R1) and 5.80 (R2) (s, 1H), 4.74 (R1) and 4.52 (R2) (s, 2H), 4.64 (t, *J* = 8.7 Hz, 2H), 3.28 (t, *J* = 8.7 Hz, 2H), 2.04 (m, 1H), 1.09 (m, 2H), 0.99 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, major rotamer (R1) and minor rotamer (R2)) δ 175.6, 171.7, 160.3, 141.7, 136.1, 132.9, 129.1, 128.8, 128.2, 127.9, 127.1, 125.5, 125.1, 124.9, 123.8, 109.6, 98.6 (R1) and 97.5 (R2), 71.5, 47.4 (R2) and 42.8 (R1), 37.4 (R1) and 33.4 (R2), 29.7, 8.5, 8.2.

N-((5-cyclopropylisoxazol-3-yl)methyl)-4'-fluoro-N-methyl-[1,1'-biphenyl]-3-carboxamide (**2**)

To a 50 mL RBF was added 4'-fluoro-[1,1'-biphenyl]-3-carboxylic acid (342.8 mg, 1.585 mmol, 1.00 eq), stir bar, 0.1 mL anhydrous DMF, 20 mL DCM, and oxalyl chloride (311.1 mg, 0.135 mmol, 1.55 eq). Solution was stirred at RT for 30 min. Then [(5-cyclopropyl-1,2-oxazole-3-yl)methyl] (methyl)amine (282.4 mg, 1.856 mmol, 1.17 eq) was added to the flask along with 0.2 mL NEt_3. The reaction was stirred at RT for 16 hr. Crude was then transferred to a separatory funnel with 25 mL DCM. Extracted twice with 35 mL of HCl (aq) at pH 2; aqueous layer discarded. Extracted twice with 30 mL of NaOH (aq) at pH 10; aqueous layer discarded. DCM layer was loaded onto silica gel and chromatographed in 0%-50% EtOAc/Hex. to afford the product as a colorless oil (180.3 mg, 33% yield, HPLC = 99.1%). HR-MS data for $[C_{21}H_{19}N_2O_2F]^+$: $[M+H]^+$ calculated 351.1503, found 351.1502; $[M+Na]^+$ calculated 373.1323,

found 373.1322. ^{1}H NMR (500 MHz, $CDCl_3$, major rotamer (R1) 70% and minor rotamer (R2) 30%) δ 7.63 (br s, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.55 (br s, 2H(, 7.48 (t, J = 8.6 Hz, 1H), 7.42 (br s, 1H), 7.14 (t, J = 8.6 Hz, 2H), 6.05 (R1) and 5.80 (R2) (s, 1H), 4.75 (R1) and 4.51 (R2) (s, 2H), 3.12 (R2) and 3.01 (R1) (s, 3H), 2.04 (m, 1H), 1.07 (m, 2H), 0.99 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, major rotamer (R1) and minor rotamer (R2)) δ 175.6, 171.5, 163.7, 161.7, 160.2, 140.6, 136.3, 128.9, 128.8, 128.7, 128.5, 125.9, 125.8, 115.9, 115.7, 98.6 (R1) and 97.5 (R2), 47.5 (R2) and 42.8 (R1), 37.4 (R1) and 33.5 (R2), 8.5, 8.2; ^{19}F NMR (470 MHz, $CDCl_3$): δ -114.9.

1-(5-cyclopropylisoxazol-3-yl)-N-((4'-fluoro-[1,1'-biphenyl]-3-yl)methyl)-N-methylmethanamine (**3**)

To a 50 mL RBF was added N-((5-cyclopropylisoxazol-3-yl)methyl)-4'-fluoro-N-methyl-[1,1'-biphenyl]-3-carboxamide (121.7 mg, 0.347 mmol, 1.0 eq). Flask was placed into an ice bath and purged with N_2 (g) for 5 min. Then 7 mL anhydrous THF was added followed by 0.35 mL of 2.4 M $LiAlH_4$ solution in THF (31.9 mg, 0.840 mmol, 2.42 eq). Solution was allowed to warm to RT while stirring over 14 hr. Flask was then placed over a fresh ice bath and neutralized with the slow addition of 15 mL EtOAc. Then the septum was removed and Rochelle's salt (2,486.7 mg, 8.811 mmol, 25.39 eq) was added along with 5 mL H_2O. Flask stirred for 45 min before the contents were transferred to a separatory funnel with 45 mL EtOAc. Organic layer was extracted with 20 mL H_2O. The organic layer was then loaded onto silica gel and chromatographed in 0-100% DCM/Hex. followed by a final elution with EtOAc to afford the product as a colorless oil (48.6 mg, 42% yield, HPLC = 100%). HR-MS data for $[C_{21}H_{21}N_2OF]^+$: $[M+H]^+$ calculated 337.1711, found 337.1706;

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (t, *J* = 4.6 Hz, 2H), 7.54 (s, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.5 Hz), 7.35 (d, *J* = 7.4 Hz, 1H), 7.14 (t, *J* = 8.6 Hz, 2H), 5.97 (s, 1H), 3.63 (d, *J* = 9.8 Hz, 4H), 2.30 (t, 3H), 2.04 (m, 1H), 1.07 (m, 2H), 0.98 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8,

163.5, 162.1, 161.5, 140.3, 139.3, 137.3, 137.3, 128.8, 128.8, 128.7, 127.9, 127.6, 125.8, 115.7, 115.5, 114.0, 98.8, 61.6, 52.1, 42.4, 8.4, 8.2; ^{19}F NMR (470 MHz, $CDCl_3$): δ -115.7.

N-((5-cyclopropylisoxazol-3-yl)methyl)-4'-fluoro-N-methyl-[1,1'-biphenyl]-3-sulfonamide (**4**)

In a 5 mL microwave vial was added 3-bromo-N-((5-cyclopropylisoxazol-3-yl)methyl)-N-methylbenzenesulfonamide (90 mg, 0.242 mmol, 1.00 eq), 4-fluorophenyl boronic acid (30 mg, 0.242 mmol, 1.00 eq), cesium carbonate (90 mg, 0.291 mmol, 1.20 eq), and 1 mL of 9:1 (v/v) 1,4-Dioxane/H_2O. Vial was sealed and purged with N_2 (g) for 5 min. Then $Pd(dppf)Cl_2$ (4 mg, 0.006 mmol, 6.0 mol%) was added. The vial was sealed and microwaved at 100°C for 25 min. Upon completion of the reaction, the solvent was evaporated under reduced pressure and dissolved into 30 mL EtOAc and then extracted with 30 mL H_2O. Organic layer was loaded onto silica gel and chromatographed over 0-30% EtOAc/Hex. to afford the product as a white solid(76 mg, 81% yield, HPLC = 100%, MP 85-87°C) HR-MS data for $[C_{20}H_{19}N_2O_3SF]^+$: $[M+Na]^+$ calculated 409.0993, found 409.0988; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.81 (dd, *J* = 7.8 Hz, 1.8 Hz 2H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.59 (m, 2H), 7.20 (t, *J* = 8.6 Hz, 2H) 6.00 (s, 1H), 4.26 s, 2H), 2.75 (s, 3H), 2.03 (m, 1H), 1.09 (m, 2H), 0.96 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 164.0, 162.0, 159.8, 141.6, 138.0, 135.3, 131.4, 129.8, 129.0, 129.0, 126.0, 116.2, 116.0, 98.2, 45.7, 34.9, 8.6, 8.1; ^{19}F NMR (470 MHz, $CDCl_3$): δ -113.8.

4'-fluoro-N-((5-isopropylisoxazol-3-yl)methyl)-N-methyl-[1,1'-biphenyl]-3-carboxamide (**5**)

To a 20 mL vial was added 4'-fluoro-[1,1'-biphenyl]-3-carboxylic acid (120.9 mg, 0.559 mmol, 1.00 eq), stir bar, 5 drops of anhydrous DMF, 7 mL DCM, and oxalyl chloride (76.9 mg, 0.606 mmol, 1.08 eq). Solution was stirred at RT for 1 hr. Then methyl({[5-(propan-2-yl)-1,2-oxazol-3-yl]methyl}]amine hydrochloride (106.9 mg, 0.561 mmol, 1.00 eq) was added to the flask along with 0.1 mL NEt_3. The reaction was stirred at RT for 2 days. Crude was then transferred to a

separatory funnel with 30 mL DCM. Extracted twice with 30 mL of HCl (aq) at pH 2; aqueous layer discarded. Extracted twice with 30 mL of NaOH (aq) at pH 10; aqueous layer discarded. DCM layer dried through Na_2SO_4 and concentrated under reduced pressure to yield the product as a colorless oil (107.5mg, 55% yield, HPLC=100%). HR-MS data for $[C_{21}H_{21}N_2O_2F]^+$: $[M+H]^+$ calculated 353.1660, found 353.1661; $[M+Na]^+$ calculated 375.1479, found 375.1480. ^1H NMR (500 MHz, $CDCl_3$, major rotamer (R1) 70% and minor rotamer (R2) 30%) δ 7.63 (s, 1H), 7.58 (d, *J* = 7.6, 1H), 7.53 (br s, 2H), 7.46 (t, *J* = 7.6, 1H), 7.42 (br s, 1H), 7.11 (t, *J* = 8.3, 2H), 6.09 (R1) and 5.83 (R2) (s, 1H), 4.75 (R1) and 4.52 (R2) (s, 2H), 3.11 (R2) and 3.01 (R1) (s, 3H), 3.06 (m, 1H), 1.3 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, major rotamer (R1) and minor rotamer (R2)) δ 179.5, 171.4, 163.7, 161.7, 159.9, 140.6, 136.3, 129.9, 129.2, 128.9, 128.8, 128.7, 128.4, 125.9, 125.8, 115.9, 115.7, 98.9 (R1) and 97.7 (R2), 47.5 (R2) and 42.9 (R1), 37.5 (R1) and 33.5 (R2), 27.2, 20.8; ^{19}F NMR (470 MHz, $CDCl_3$): δ -114.9

4'-fluoro-N-methyl-N-((5-methylisoxazol-3-yl)methyl)-[1,1'-biphenyl]-3-carboxamide (**6**)
To a 20 mL vial was added 4'-fluoro-[1,1'-biphenyl]-3-carboxylic acid (117 mg, 0.541 mmol, 1.00 eq), stir bar, 5 drops of anhydrous DMF, 7 mL DCM, and oxalyl chloride (78.5 mg, 0.619 mmol, 1.14 eq). Solution was stirred at RT for 1 hr. Then methyl[(5-methyl-1,2-oxazol-3-yl)methyl]amine (66.2 mg, 0.525 mmol, 0.97 eq) was added to the flask along with 0.1 mL NEt_3. The reaction was stirred at RT for 2 days. Crude was then transferred to a separatory funnel with 30 mL DCM. Extracted twice with 30 mL of HCl (aq) at pH 2; aqueous layer discarded. Extracted twice with 30 mL of NaOH (aq) at pH 10; aqueous layer discarded. Compound was then loaded onto silica gel and chromatographed over 0%-40% EtOAc/Hex. to yield the product as a colorless oil (91.2 mg, 52% yield, HPLC=98.5%). HR-MS data for $[C_{17}H_{19}N_2O_2F]^+$: $[M+H]^+$ calculated 325.1347, found 325.1347; $[M+Na]^+$ calculated 347.1166, found 347.1166. ^1H NMR (500 MHz, $CDCl_3$, major rotamer (R1) 70% and minor rotamer (R2) 30%) δ 7.62, (br s, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.54 (br s, 2H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.42 (br s, 1H), 7.13 (t, *J* = 8.6 Hz,

2H) , 6.13 (R1) and 5.88 (R2) (s, 1H), 4.75 (R1) and 4.53 (R2) (s, 2H), 3.11 (R2) and 3.01 (R1) (s, 3H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, major rotamer (R1) and minor rotamer (R2)) δ 171.5, 170.2, 163.7, 161.7, 160.3, 140.6, 136.3,128.9, 128.8, 128.7, 128.4, 125.8, 125.8, 125.6,115.9, 115.7, 101.5 (R1) and 100.4 (R2), 47.4 (R2) and 42.8 (R1), 37.4 (R1) and 33.4 (R2), 12.3; ^{19}F NMR (470 MHz, $CDCl_3$): δ -114.9

4'-fluoro-N-(isoxazol-3-ylmethyl)-N-methyl-[1,1'-biphenyl]-3-carboxamide (**7**)

To a 20 mL vial was added 4'-fluoro-[1,1'-biphenyl]-3-carboxylic acid (154.2 mg, 0.714 mmol, 1.00 eq), stir bar, 5 drops of anhydrous DMF, 7 mL DCM, and oxalyl chloride (115.1 mg, 0.907 mmol, 1.27 eq). Solution was stirred at RT for 1 hr. Then methyl[(1,2-oxazol-3-yl)methyl]amine (79.0 mg, 0.705 mmol, 0.99 eq) was added to the flask along with 0.1 mL NEt_3. The reaction was stirred at RT for 2 days. Crude was then transferred to a separatory funnel with 30 mL DCM. Extracted twice with 30 mL of HCl (aq) at pH 2; aqueous layer discarded. Extracted twice with 30 mL of NaOH (aq) at pH 10; aqueous layer discarded. DCM layer dried through Na_2SO_4 and concentrated under reduced pressure to yield the product as a colorless oil (90.4 mg, 41% yield, HPLC=98.5%). HR-MS data for $[C_{18}H_{15}N_2O_2F]^+$: $[M+H]^+$ calculated 311.1190, found 311.1191; $[M+Na]^+$ calculated 333.1010, found 333.1010.; ^{1}H NMR (500 MHz, $CDCl_3$, major rotamer (R1) 70% and minor rotamer (R2) 30%) δ 8.43 (s, 1H), 7.62 (br s, 2H), 7.55 (br s, 2H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.42 (br s, 1H), 7.15 (t, *J* = 8.6 Hz, 2H), 6.52 (R1) and 6.26 (R2) (s, 1H), 4.86 (R1) and 4.63 (R2) (s, 2H), 3.13 (R2) and 3.04 (R1) (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, major rotamer (R1) and minor rotamer (R2)) δ 171.6, 163.7, 161.7, 159.1, 140.7, 136.3, 136.2, 129.0, 128.8, 128.7, 128.5, 125.8, 115.9, 115.7, 104.3 (R1) and 103.2 (R2), 47.2 (R2) and 42.6 (R1), 37.5 (R1) and 33.4 (R2); ^{19}F NMR (470 MHz, $CDCl_3$): δ -114.9.

3-(2,3-dihydrobenzofuran-5-yl)benzoic acid

To a 20 mL microwave vial was added 5-bromo-2,3-dihydrobenzofuran (441.4 mg, 2.218 mmol, 1.0 eq), 3-(4,4,5,5)-tetramehtyl-1,3,2-dioxaborolan-2-yl)benzoic acid (608.9 mg, 2.454 mg, 1.1 eq), cesium carbonate (1263.8 mg, 3.855 mmol, 1.74 eq), and 10 mL of 9:1 (v/v) 1,4-Dioxane/H_2O. Vial was sealed and purged with N_2 (g) for 5 min. Then Pd(dppf)Cl_2 (54.9 mg, 0.067 mmol, 3.0 mol%) was added. The vial was sealed and microwaved at 100°C for 30 min. The crude was filtered through a pad of Celite with excess DCM. Organic layer transferred to a separatory funnel and extracted with 40 mL of pH 11 NaOH (aq). The aqueous layer was then acidified to pH 2 using 37% HCl and extracted 3x30 mL with DCM. Combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to afford the product as a white solid (436.1 mg, 82% yield, HPLC = 95%, MP = 165-169°C). ^{1}H NMR (500 MHz, $CDCl_3$) 8.13 (s, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.56 (s, 1H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 4.58 (t, *J* = 8.7 Hz, 2H), 3.25 (t, *J* = 8.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 160.2, 141.7, 132.6, 132.0, 129.8, 128.9, 128.4, 128.2, 127.9, 127.2, 123.8, 109.7, 71.6, 29.7.

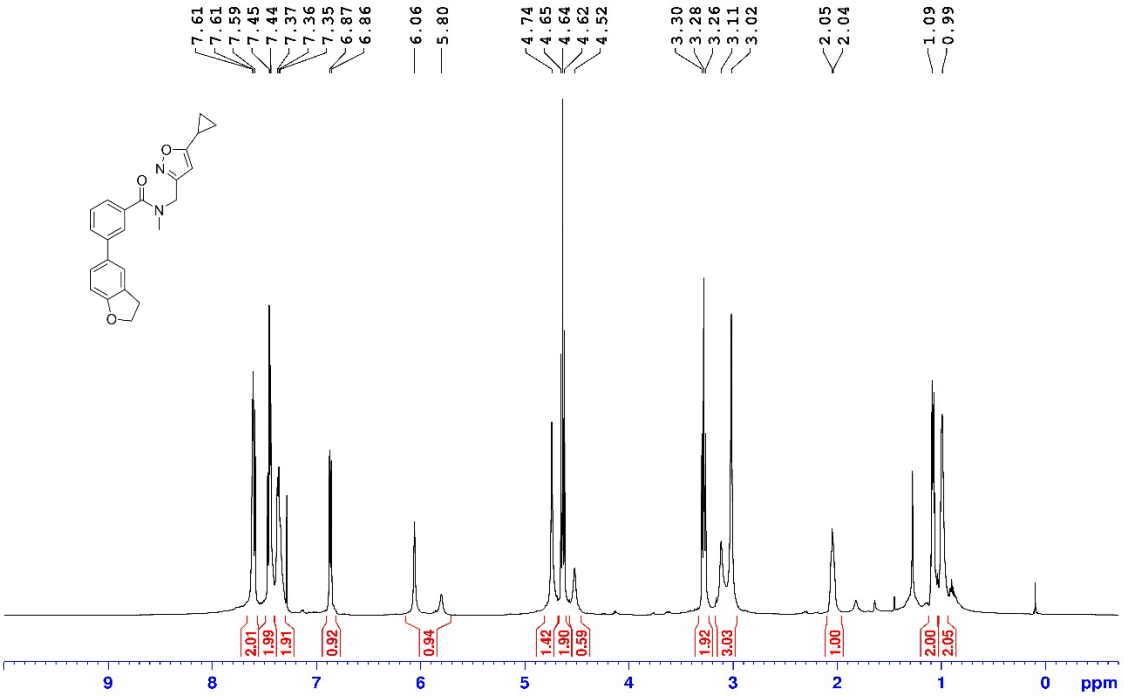
3-bromo-N-((5-cyclopropylisoxazol-3-yl)methyl)-N-methylbenzenesulfonamide

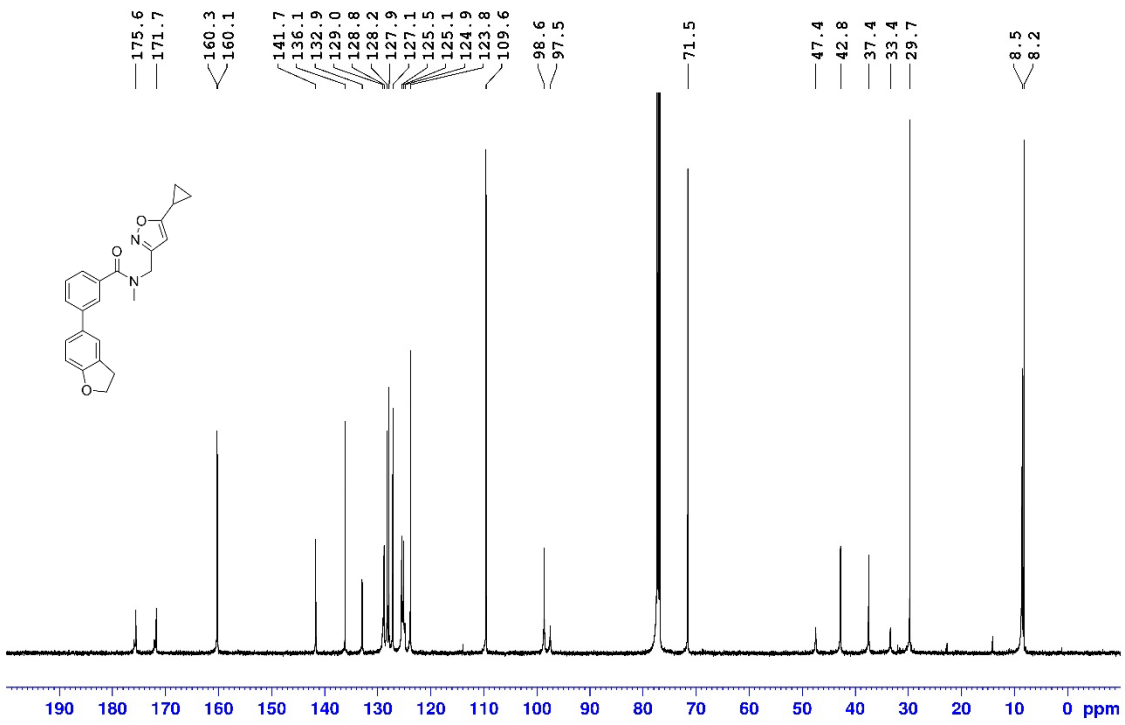
In a 25 mL RBF, 3-bromobenzene-1-sulfonyl chloride (0.200 g, 0.782 mmol, 1.0 eq) was dissolved in THF (2.0 mL) and stirred at 0-5°C. Triethylamine (0.094 g, 0.939 mmol, 1.2 eq) and [(5-cyclopropyl-1,2-oxazole-3-yl)methyl] (methyl)amine (0.119 g, 0.782 mmol, 1.0 eq) were added to the reaction solution and stirred at RT for 3 hr. After completion of the reaction, the mixture was concentrated under reduced pressure. The crude was then loaded onto silica gel and purified by normal phase column chromatography over 0-40% EtOAc/Hex. to yield the product as white solid (0.180g, 82% yield, HPLC = 100%, MP = 68 °C) ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.97 (1H, t, *J* = 2 Hz), 7.78-7.76 (2H, m), 7.45 (1H, t, *J* = 7.5 Hz), 5.98 (1H, s), 4.24

(2H, s), 2.74 (3H, q), 2.07-2.01 (1H, m), 1.10-1.07 (2H, m), 0.99-0.96 (2H, m); ^{13}C NMR: (125 MHz, $CDCl_3$) δ 176.0, 159.6, 139.3, 136.0, 130.8, 130.2, 125.9, 123.3, 45.6, 34.8, 8.6, 8.2.

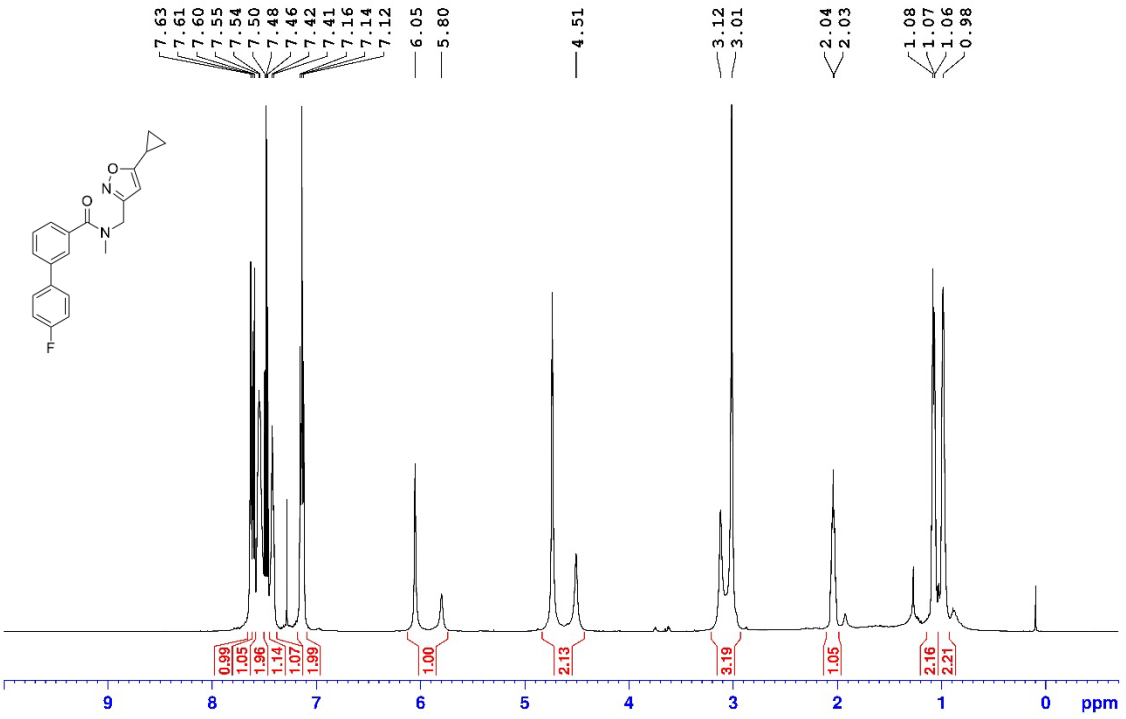
^{1}H/^{13}C NMR Spectra

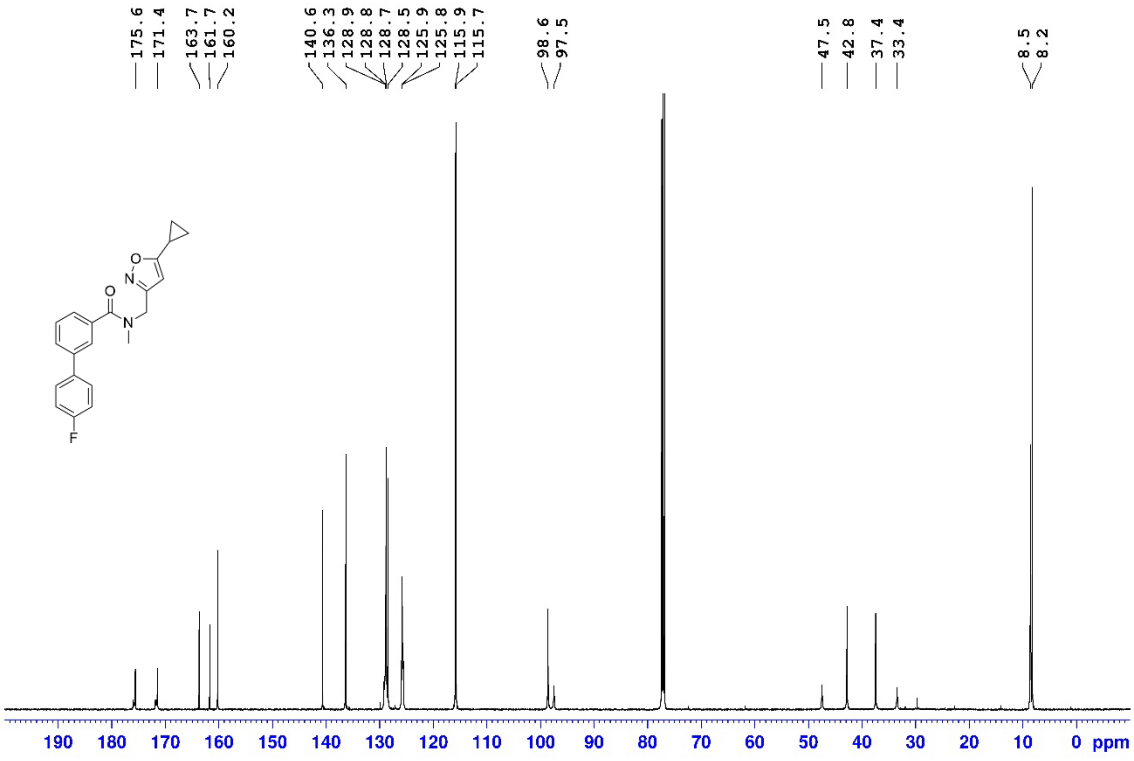
N-((5-cyclopropylisoxazol-3-yl)methyl)-3-(2,3-dihydrobenzofuran-5-yl)-N-methylbenzamide

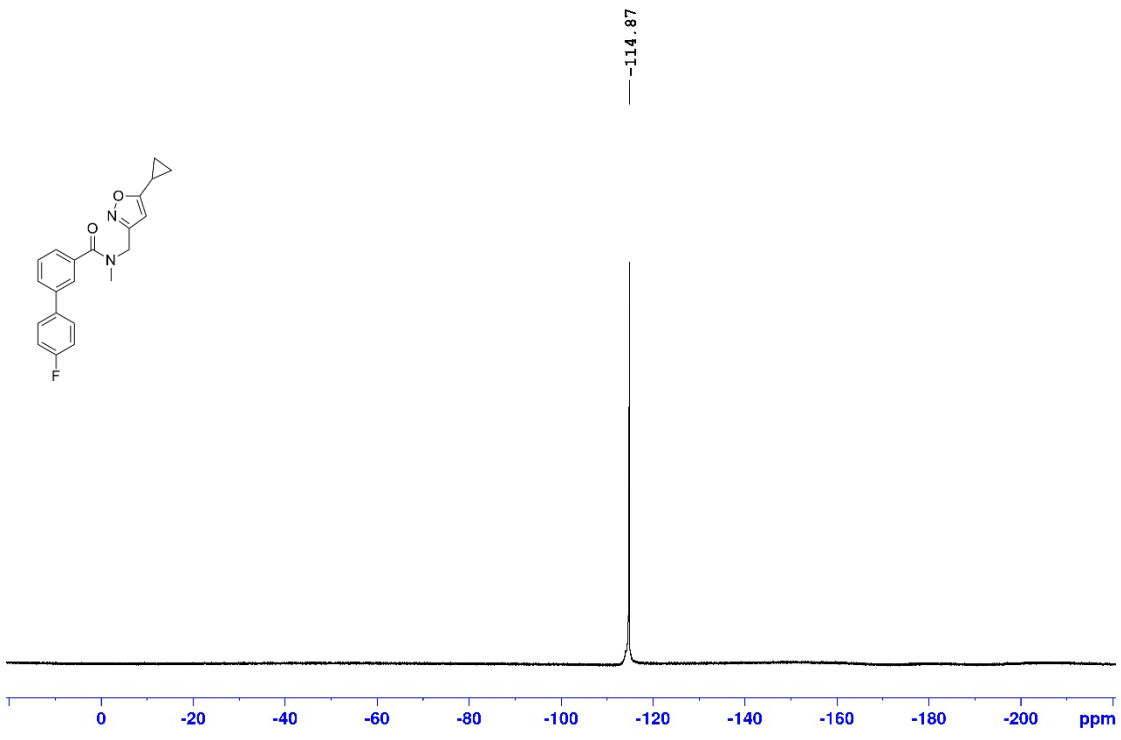




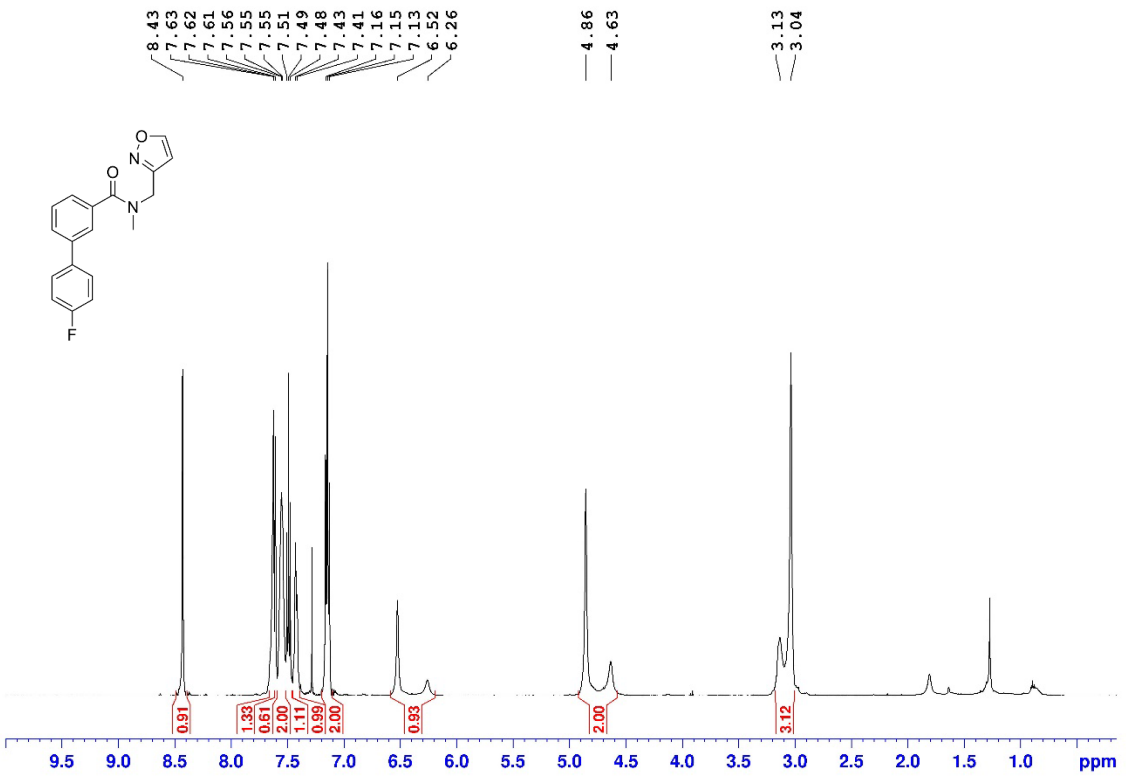
N-((5-cyclopropylisoxazol-3-yl)methyl)-4'-fluoro-N-methyl-[1,1'-biphenyl]-3-carboxamide

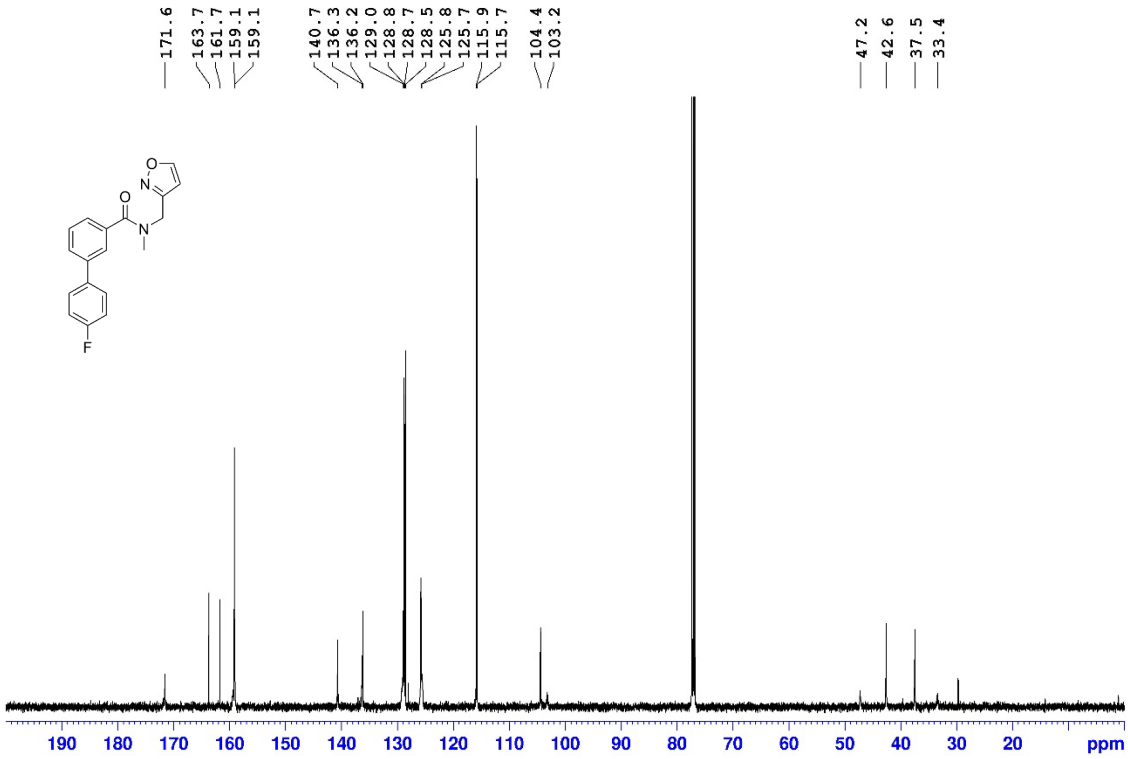


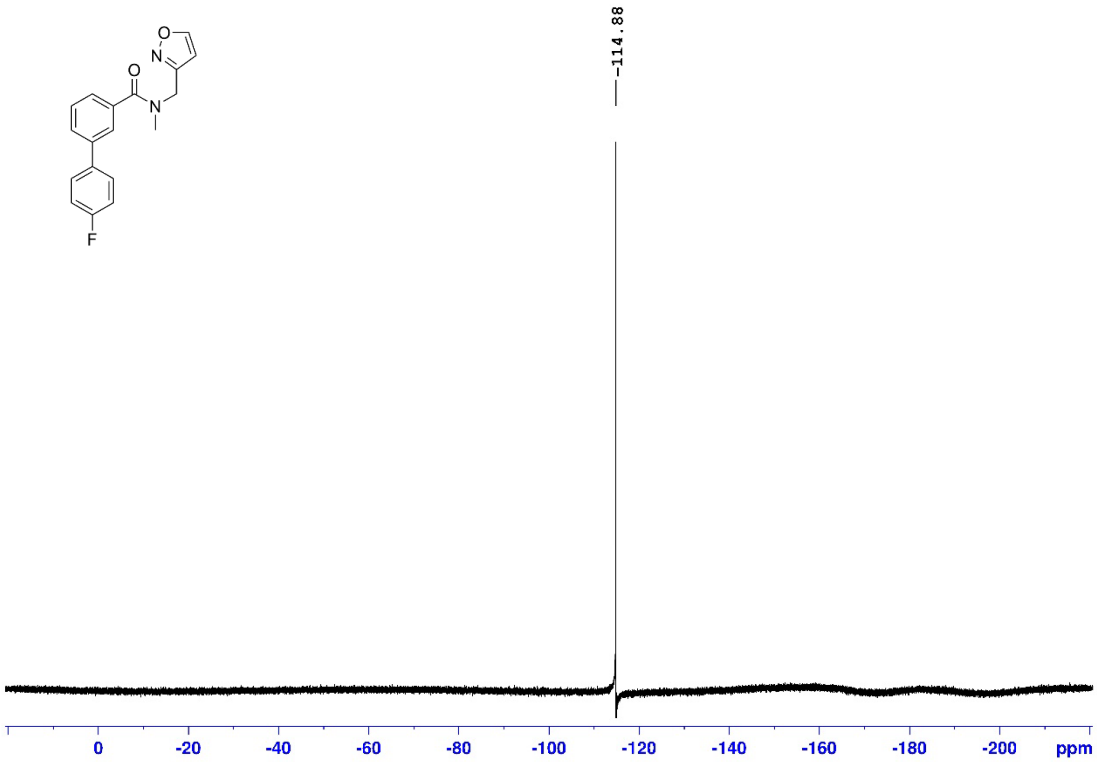

175.6
171.4
163.7
161.7
160.2
140.6
136.3
128.9
128.8
128.7
128.5
125.9
125.8
115.9
115.7
98.6
97.5
47.5
42.8
37.4
33.4
8.5
8.2
O
N
O
N
F
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


-114.87
O
N
O
N
F
0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 ppm

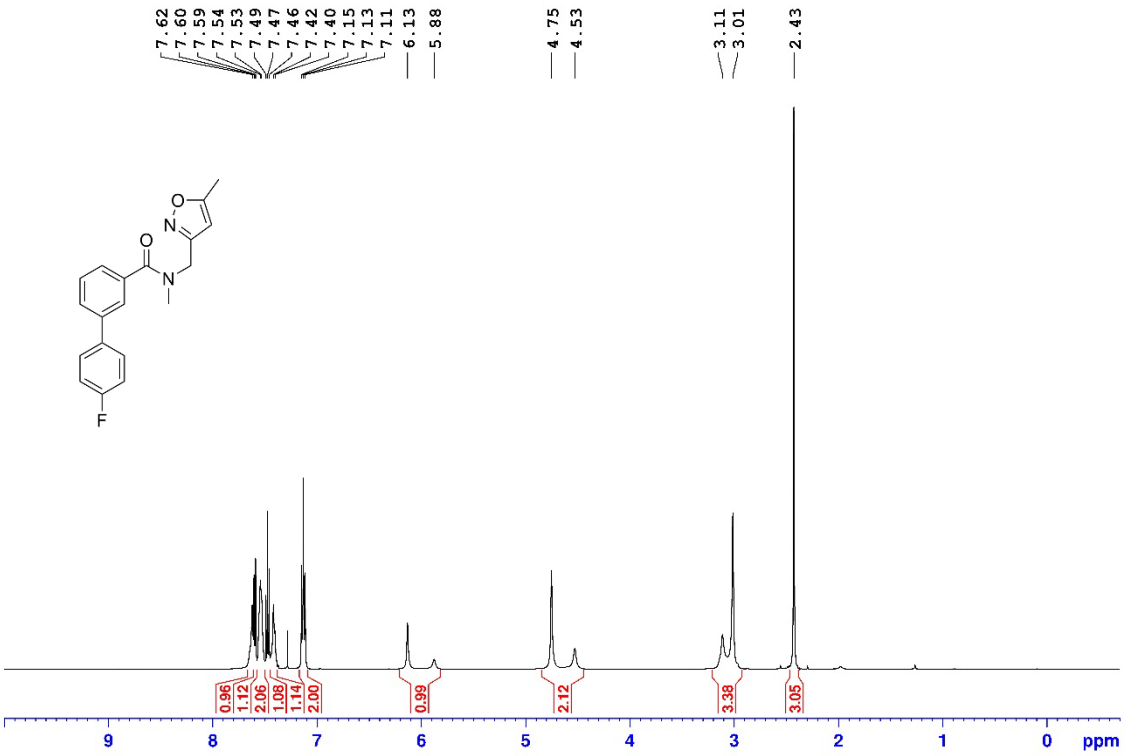
4'-fluoro-N-(isoxazol-3-ylmethyl)-N-methyl-[1,1'-biphenyl]-3-carboxamide

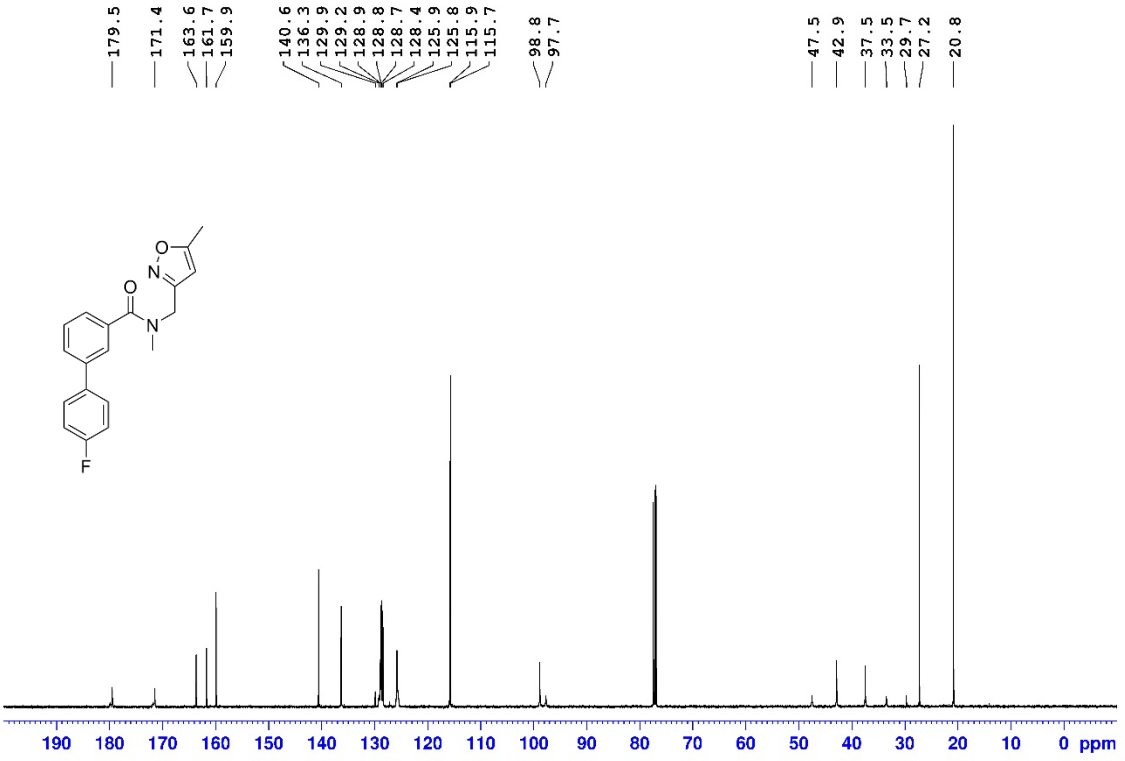


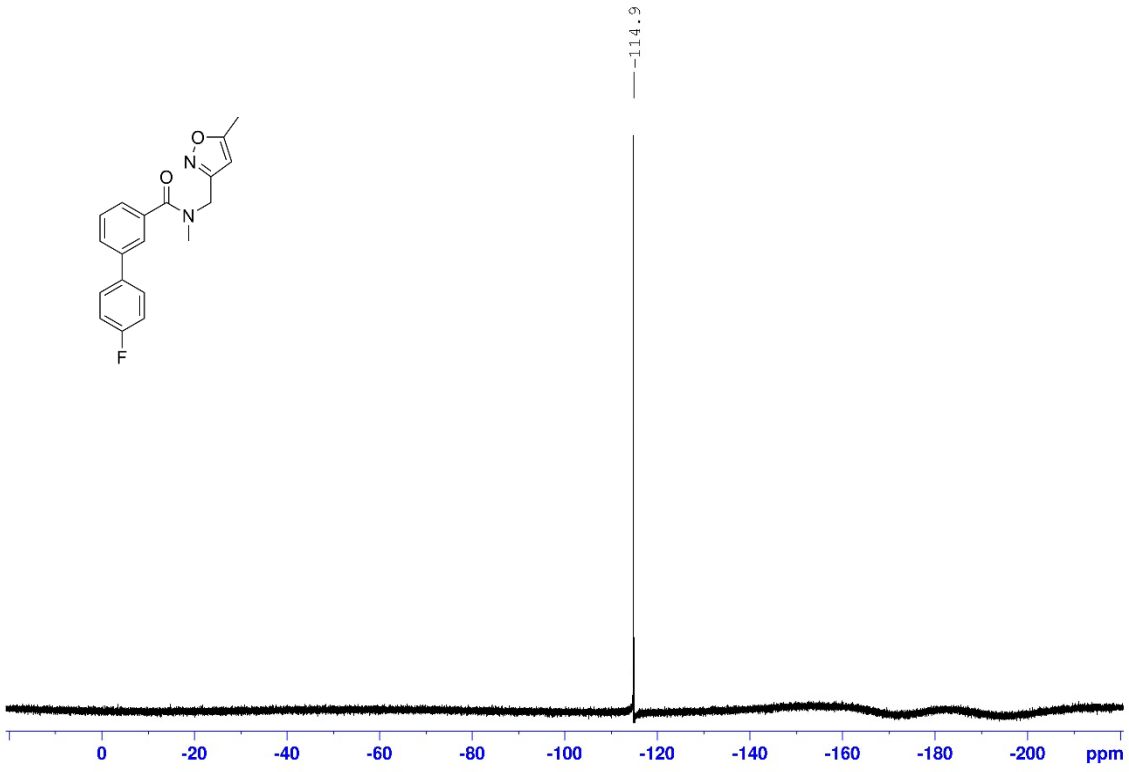




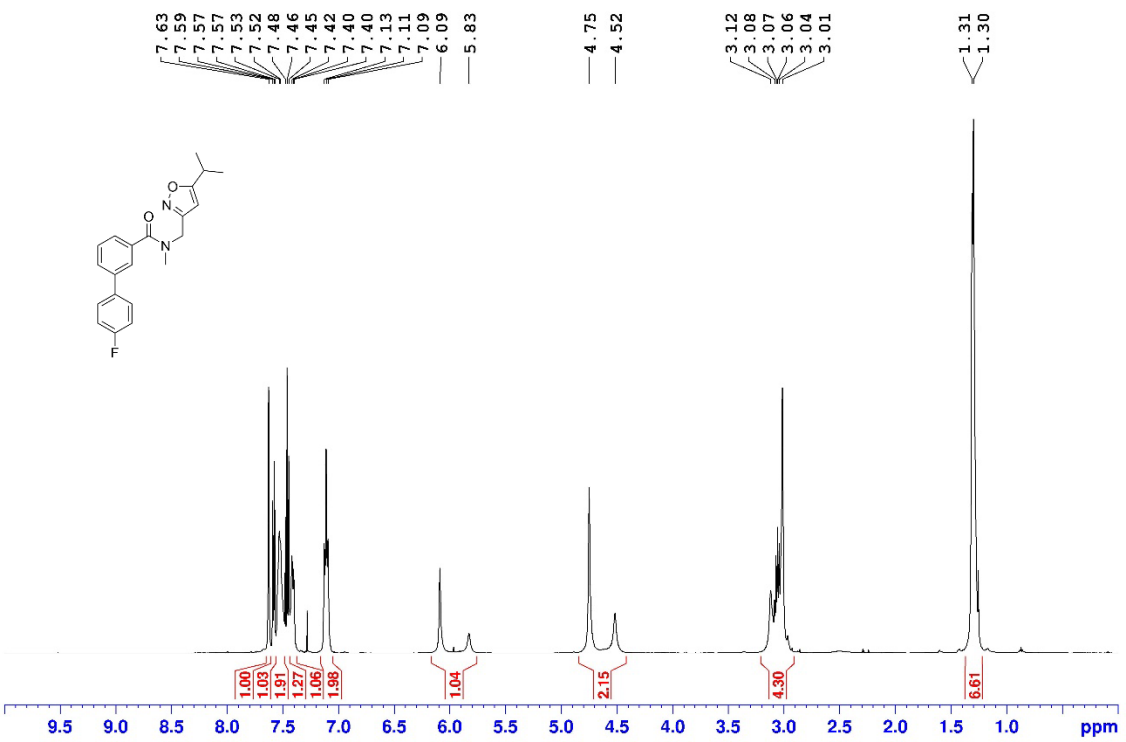
4'-fluoro-N-methyl-N-((5-methylisoxazol-3-yl)methyl)-[1,1'-biphenyl]-3-carboxamide

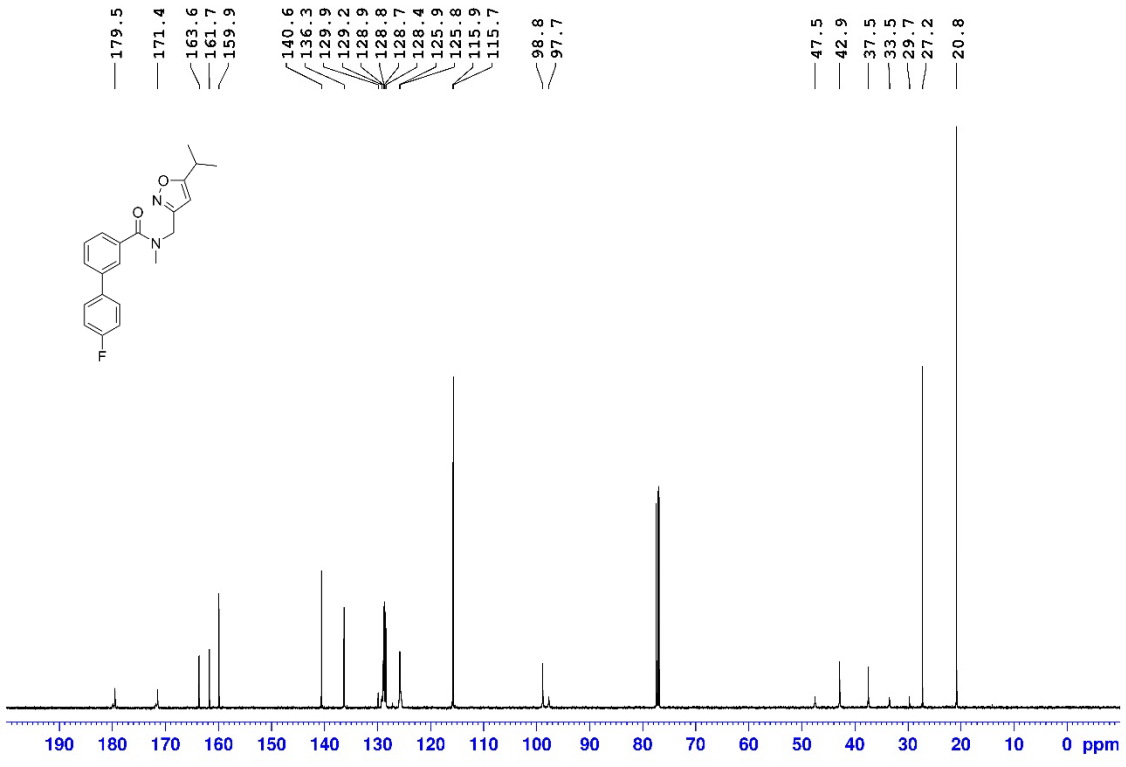

7.62
7.60
7.59
7.54
7.53
7.49
7.47
7.46
7.42
7.40
7.15
7.13
7.11
6.13
5.88
4.75
4.53
3.11
3.01
2.43
O
N
O
N
F
0.96
1.12
2.06
1.08
1.14
2.00
0.99
2.12
3.38
3.05
9
8
7
6
5
4
3
2
1
0
ppm

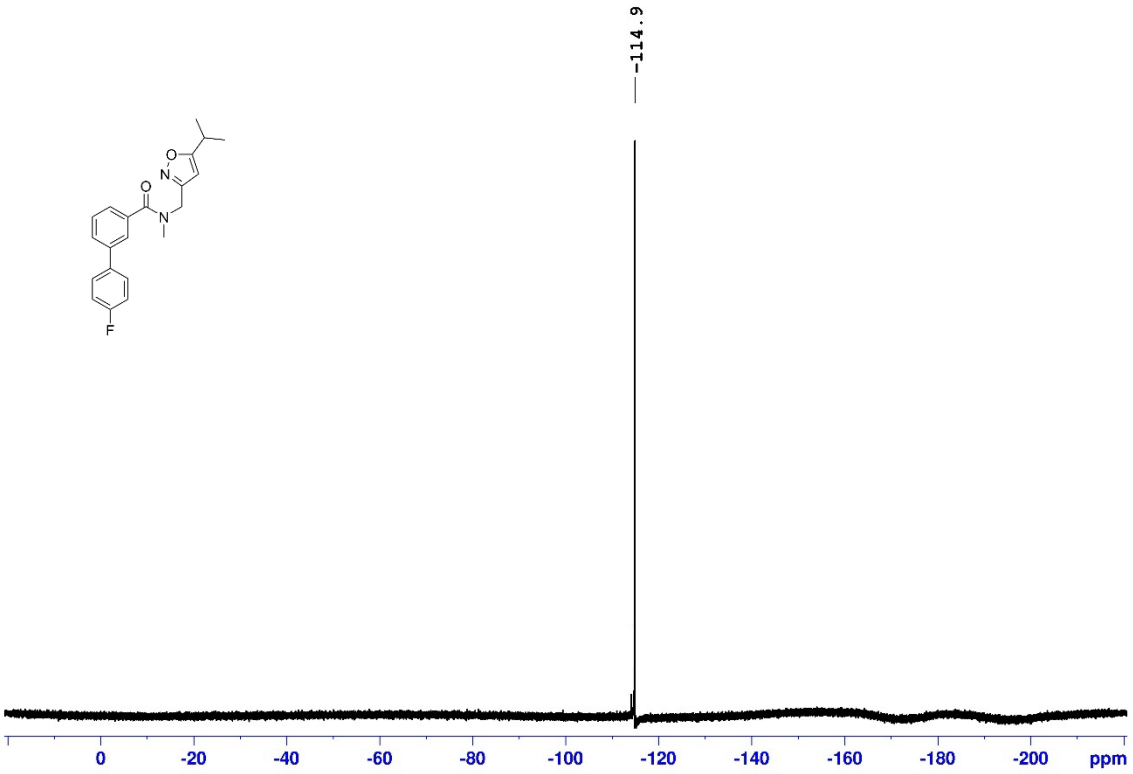

179.5
171.4
163.6
161.7
159.9
140.6
136.3
129.9
129.2
128.9
128.8
128.7
128.4
125.9
125.8
115.9
115.7
98.8
97.7
47.5
42.9
37.5
33.5
29.7
27.2
20.8
O
N
O
N
F
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



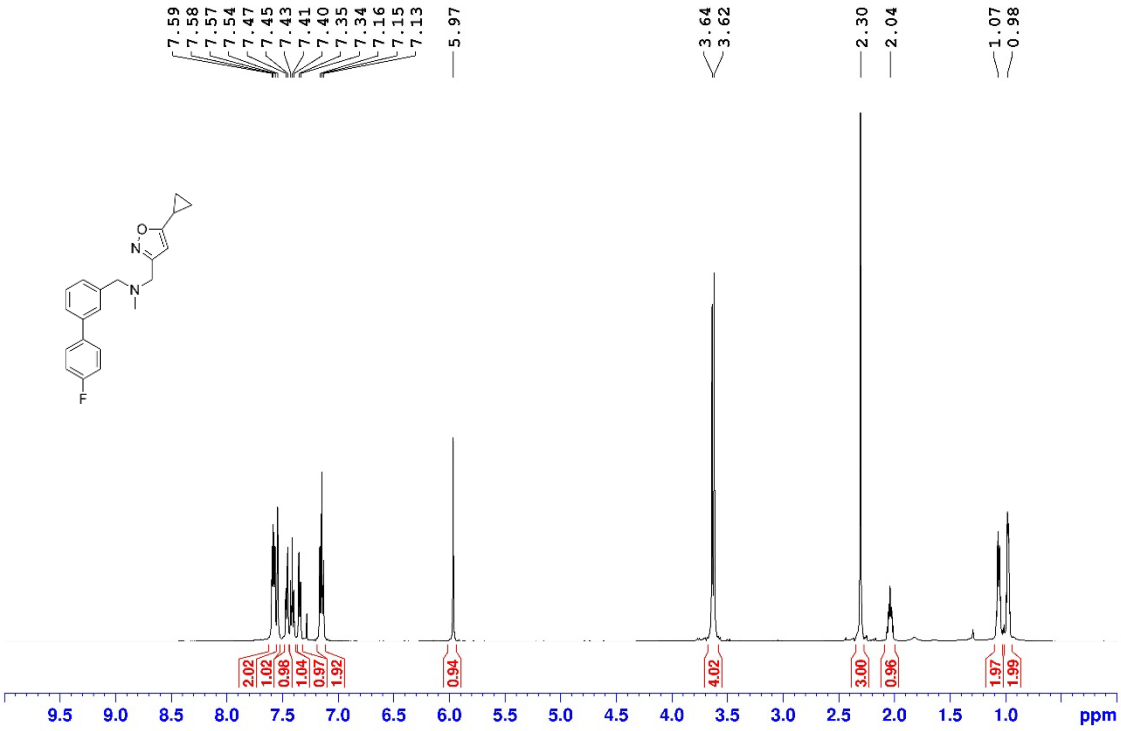
4'-fluoro-N-((5-isopropylisoxazol-3-yl)methyl)-N-methyl-[1,1'-biphenyl]-3-carboxamide

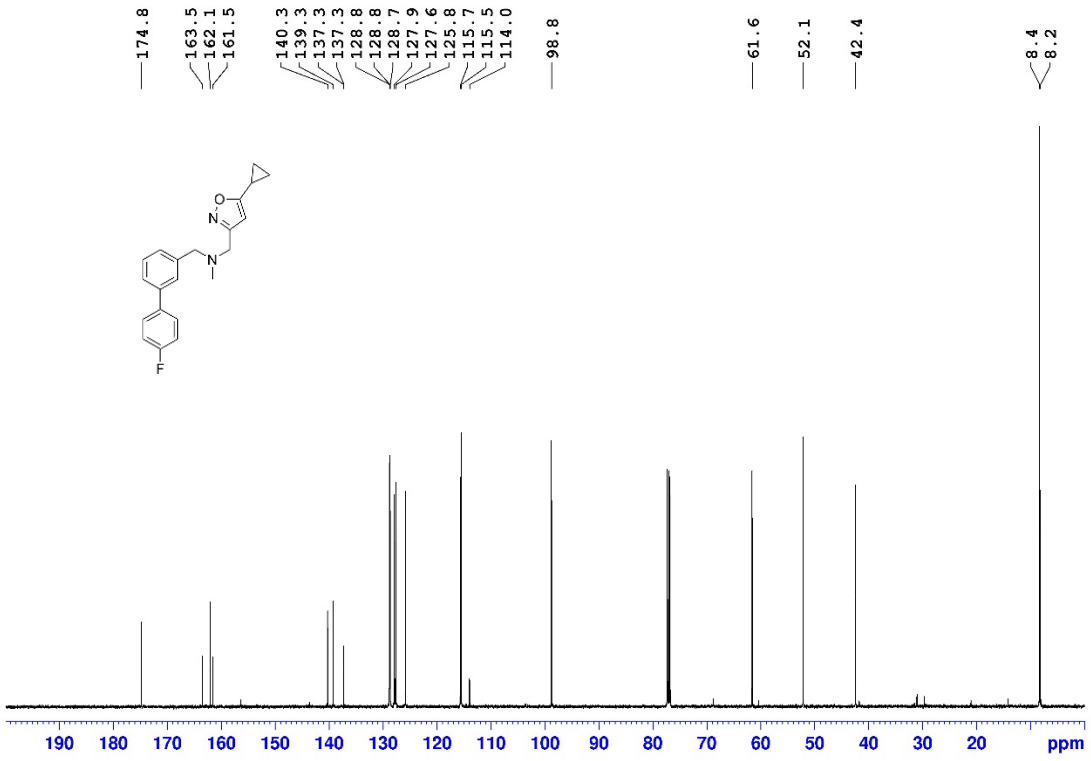

7.63
7.59
7.57
7.57
7.53
7.52
7.48
7.46
7.45
7.42
7.40
7.40
7.13
7.11
7.09
6.09
5.83
4.75
4.52
3.12
3.08
3.07
3.06
3.04
3.01
1.31
1.30
O
N
O
N
F
1.00
1.03
1.91
1.27
1.06
1.98
1.04
2.15
4.30
6.61
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm

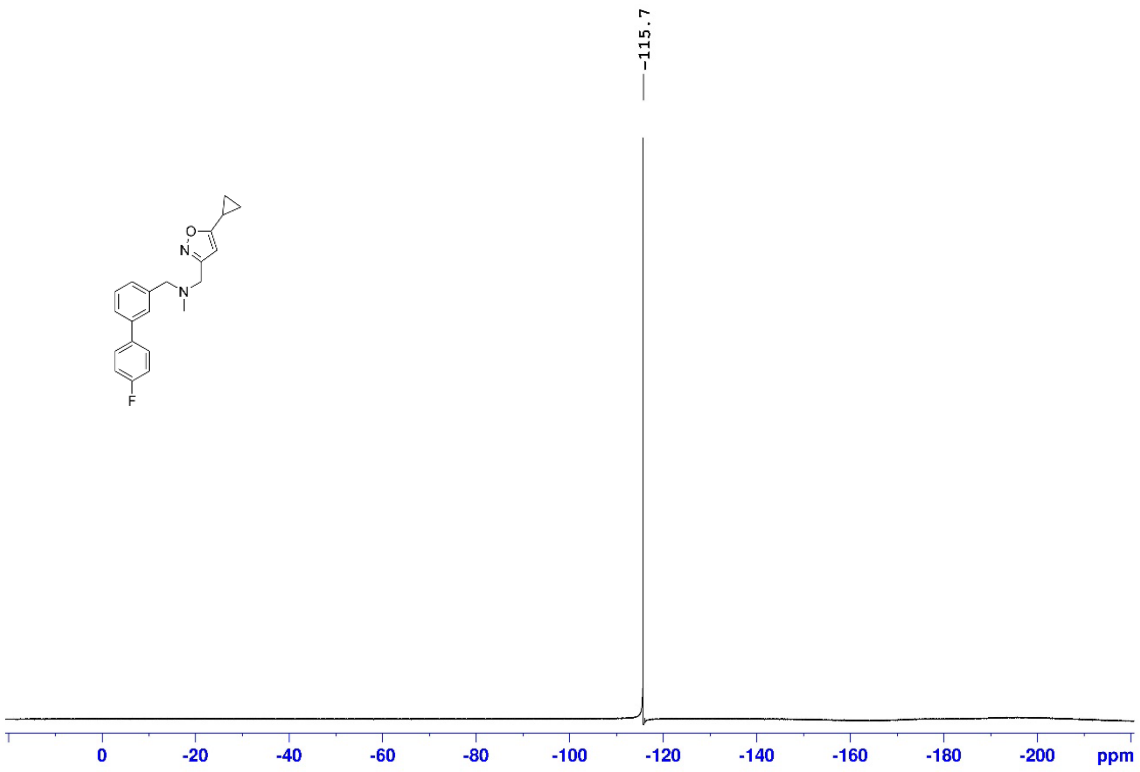

179.5
171.4
163.6
161.7
159.9
140.6
136.3
129.9
129.2
128.9
128.8
128.7
128.4
125.9
125.8
115.9
115.7
98.8
97.7
47.5
42.9
37.5
33.5
29.7
27.2
20.8
O
N
O
N
F
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



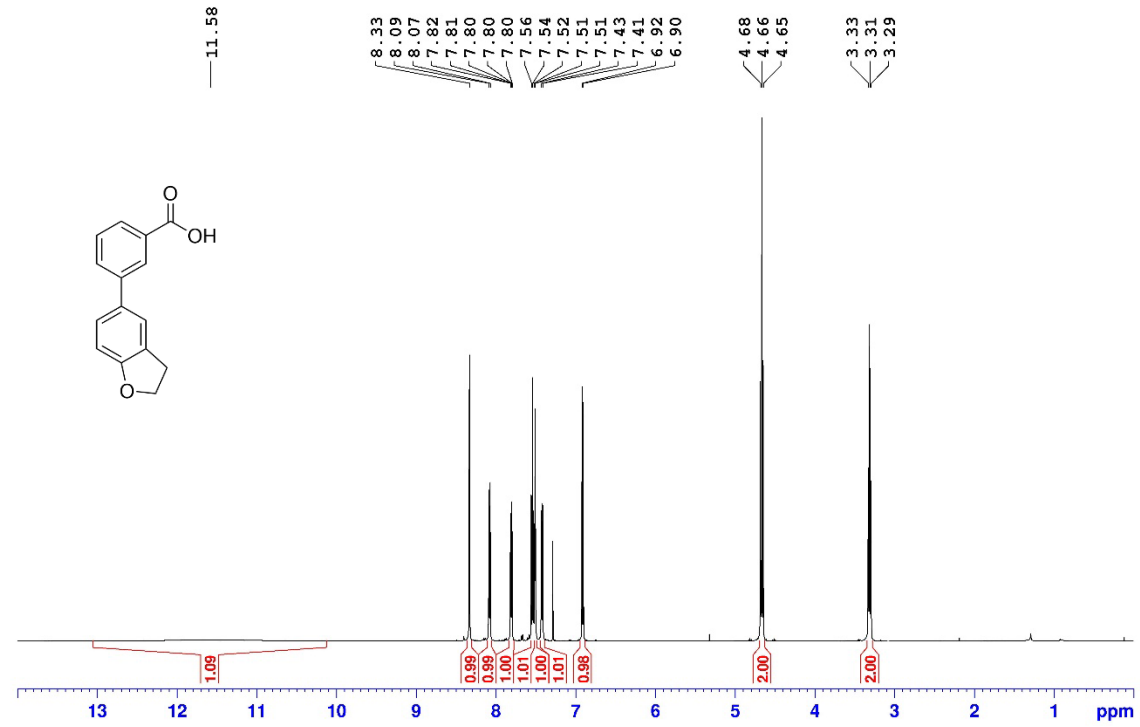
Tertiary Amine **1-(5-cyclopropylisoxazol-3-yl)-N-((4'-fluoro-[1,1'-biphenyl]-3-yl)methyl)-N-methylmethanamine**

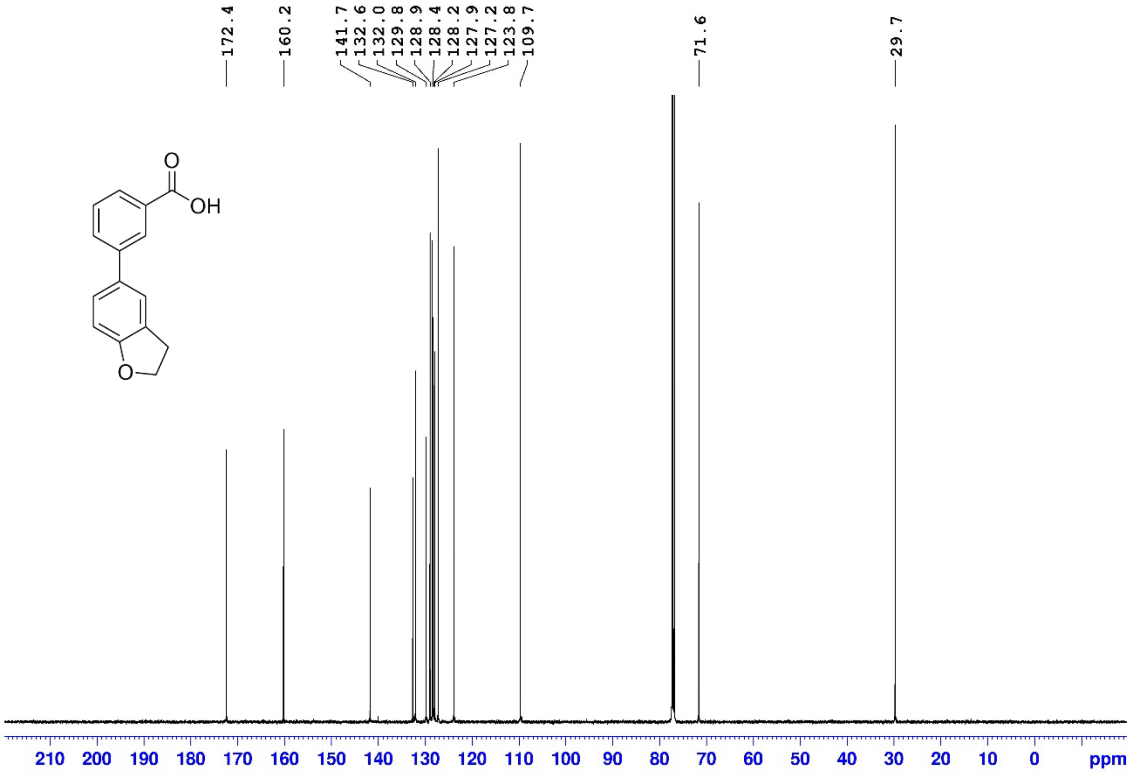

7.59
7.58
7.57
7.54
7.47
7.45
7.43
7.41
7.40
7.35
7.34
7.16
7.15
7.13
5.97
3.64
3.62
2.30
2.04
1.07
0.98
2.02
1.02
0.98
1.04
0.97
1.92
0.94
4.02
3.00
0.96
1.97
1.99
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm


174.8
163.5
162.1
161.5
140.3
139.3
137.3
137.3
128.8
128.8
128.7
127.9
127.6
125.8
115.7
115.5
114.0
98.8
61.6
52.1
42.4
8.4
8.2
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

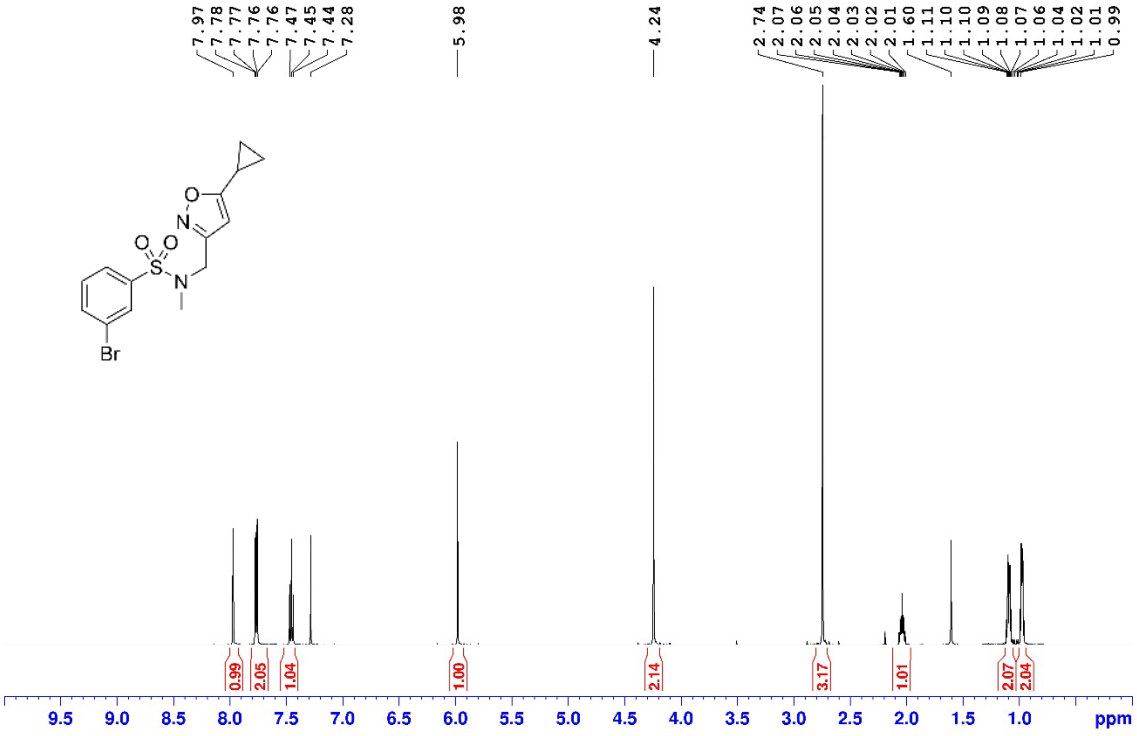


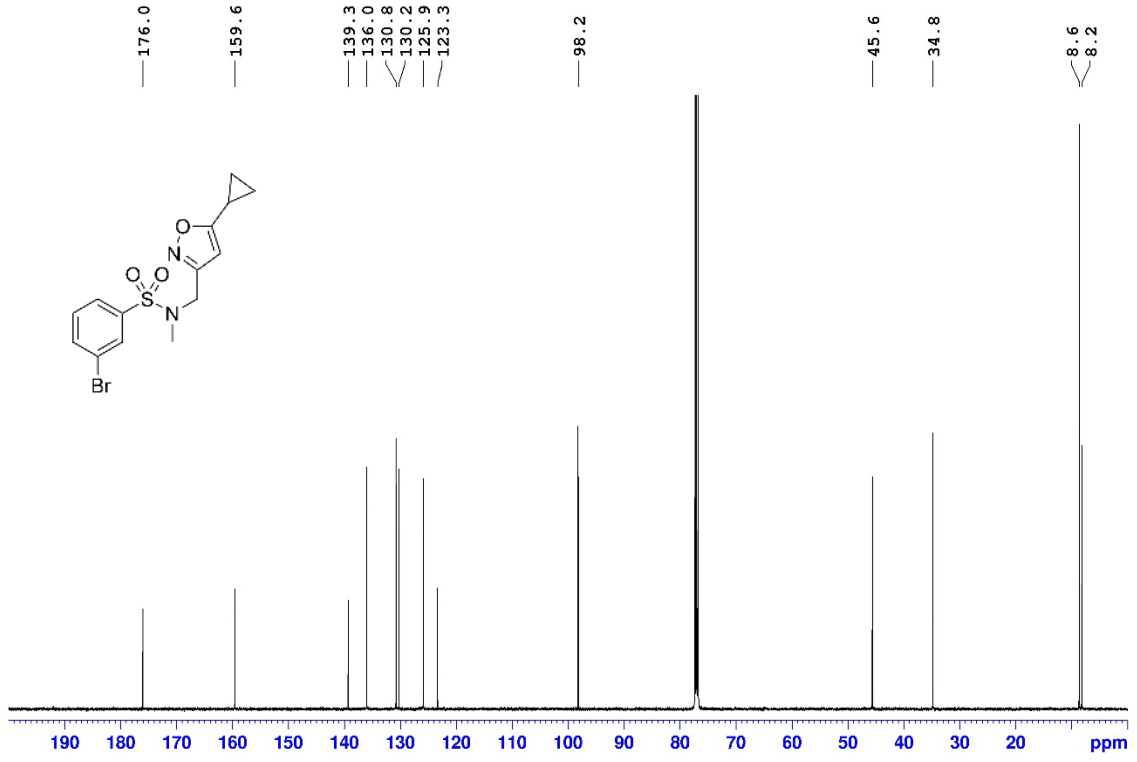
3-(2,3-dihydrobenzofuran-5-yl)benzoic acid


11.58
8.33
8.09
8.07
7.82
7.81
7.80
7.80
7.80
7.56
7.54
7.52
7.51
7.51
7.43
7.41
6.92
6.90
4.68
4.66
4.65
3.33
3.31
3.29
O
OH
O
1.09
0.99
0.99
1.00
1.01
1.00
1.01
0.98
2.00
2.00
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm

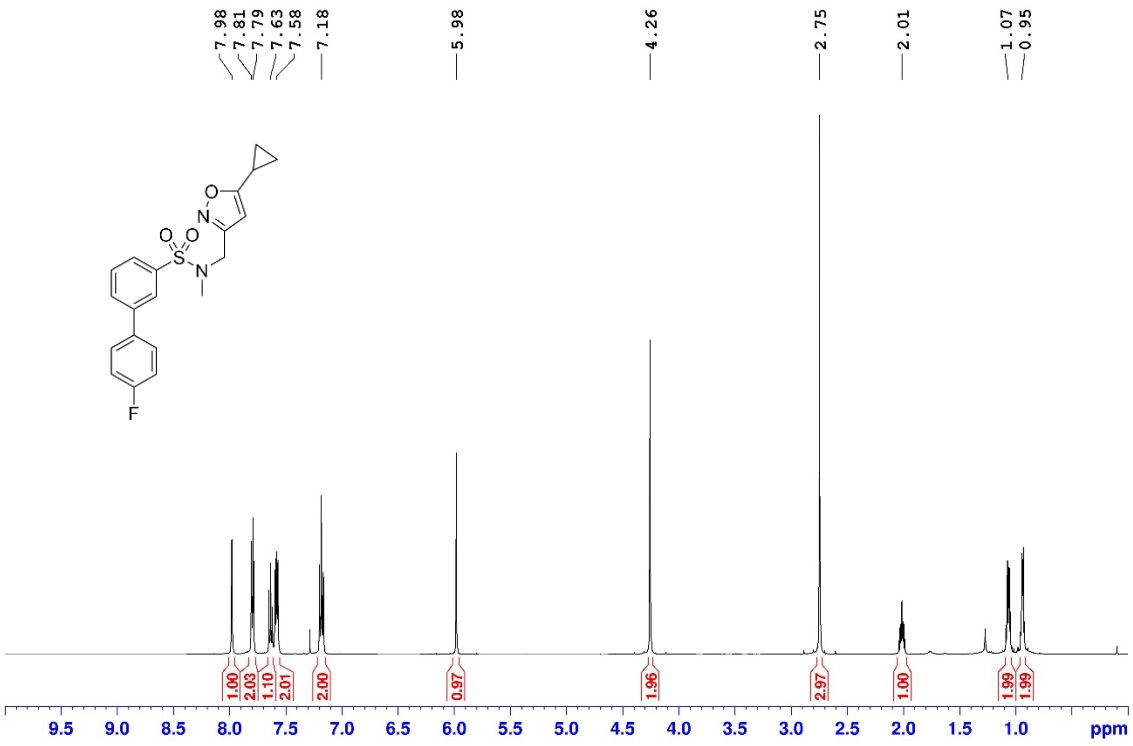

172.4
160.2
141.7
132.6
132.0
129.8
128.9
128.4
128.2
127.9
127.2
123.8
109.7
71.6
29.7
O
OH
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

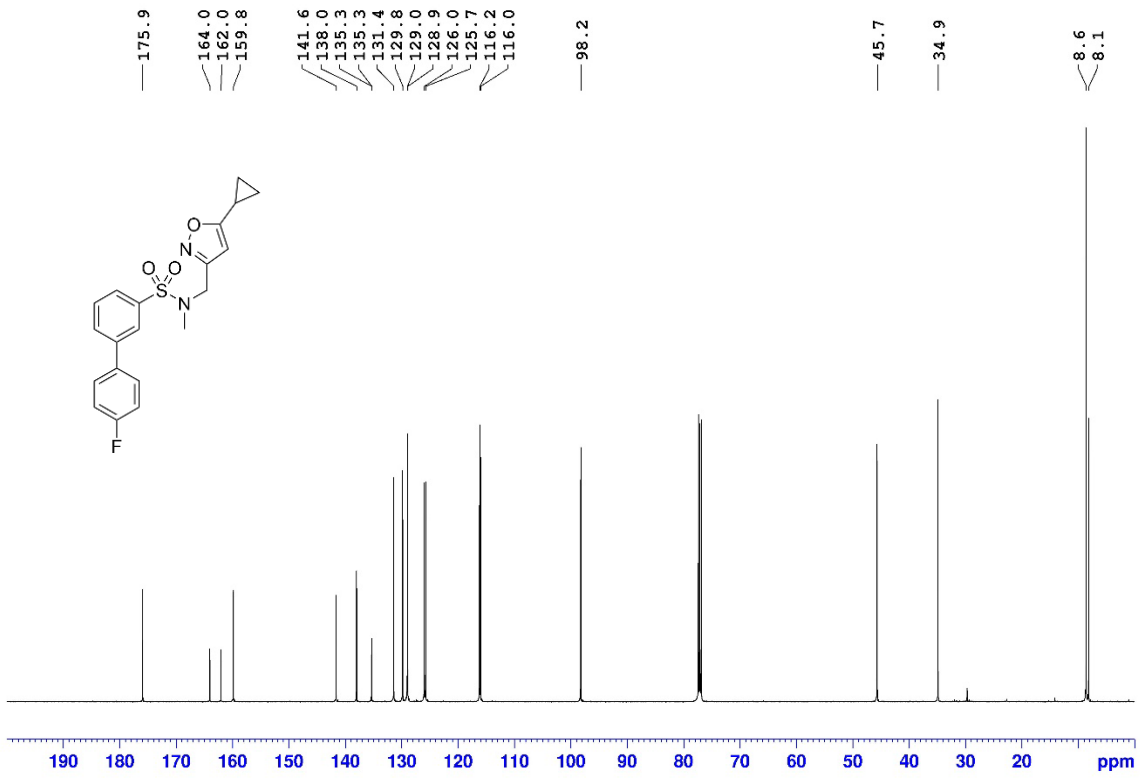
3-bromo-N-((5-cyclopropylisoxazol-3-yl)methyl)-N-methylbenzenesulfonamide

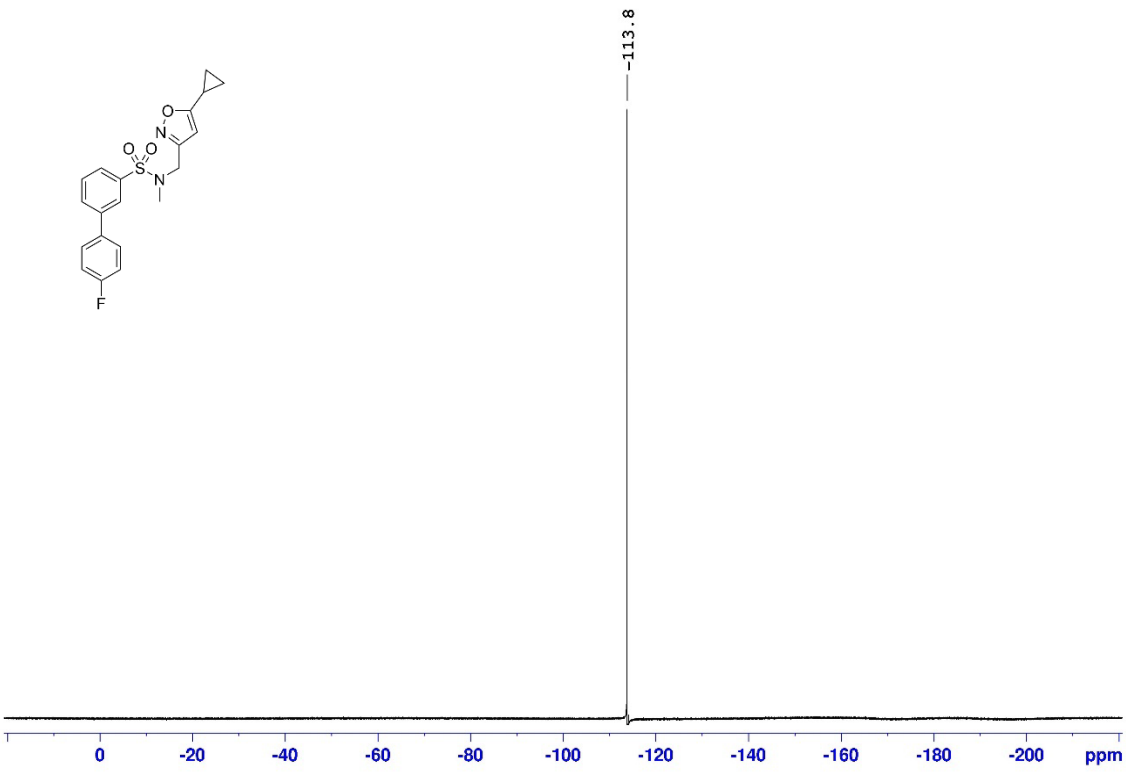




N-((5-cyclopropylisoxazol-3-yl)methyl)-4'-fluoro-N-methyl-[1,1'-biphenyl]-3-sulfonamide




175.9
164.0
162.0
159.8
141.6
138.0
135.3
135.3
131.4
129.8
129.0
128.9
126.0
125.7
116.2
116.0
98.2
45.7
34.9
8.6
8.1
O
N
O
O
S
N
F
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


-113.8
O
N
O
O
S
N
F
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
ppm