Decreasing HepG2 cytotoxicity by lowering the lipophilicity of benzo[d]oxazolephosphinate ester utrophin modulators

Maria Chatzopoulou,[a] Enrico Emer,[a] Cristina Lecci,[b] Jessica A. Rowley,[a] Anne-Sophie Casagrande,[d] Lee Moir,[e] Sarah E. Squire,[e] Stephen G. Davies,[a] Shawn Harriman,[c] Graham M. Wynne,[a] Francis X. Wilson,[c] Kay E. Davies,[e] Angela J. Russell[a,f*]

[a] Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, OX1 3TA, UK

[b] Evotec (UK) Ltd, 114 Innovation Dr, Milton Park, Milton, Abingdon OX14 4RZ

[c] Summit Therapeutics plc, 136a Eastern Avenue, Milton Park, Abingdon, Oxfordshire, OX14 4SB, UK

[d] Evotec (France) SAS, 195 Route d'Espagne, BP13669, 31036 TOULOUSE cedex (France)

[e] MDUK Oxford Neuromuscular Centre, Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford OX1 3PT, UK

[f] Department of Pharmacology, University of Oxford, Mansfield Road, Oxford, OX1 3PQ, UK

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Table S1. Molecular and physicochemical properties of phosphinate analogues. In blue are analogues that belong to the previous series of phosphinates most of which were reported previously[1], in orange are analogues of the new series. Analogues presented in this publication have their designated numbers. Predicted clogP values were generated with OSIRIS Datawarrior version 5.0.0 © 2002-2019 Idorsia Pharmaceuticals Ltd. logD (SF) was measured experimentally with the shaking flask method.

#	Molecular Formula	Total MW	cLogP	logD (SF)
2	C17H15NO3F3P	369.278	4.43	3.80
3	C16H15NO3FP	319.271	3.68	2.80
	C16H15NO3ClP	335.726	4.18	3.76
	C20H18NO3P	351.341	4.77	4.31
	C25H20NO3P	413.412	6.20	
	C16H14NO3Cl2P	370.171	4.79	
	C16H14NO3Cl2P	370.171	4.79	
	C19H17N2O3P	352.329	3.89	
	C18H18NO3P	327.319	4.03	
	C18H17NO3FP	345.309	4.03	
	C20H18NO3P	351.341	4.77	
	C16H14NO3Cl2P	370.171	4.79	3.96
	C18H18NO3P	327.319	4.03	
	C21H20NO3P	365.368	5.18	
	C18H18NO3P	327.319	4.03	
	C21H20NO3P	365.368	5.18	
	C17H16NO3Cl2P	384.198	5.20	
	C17H16NO3Cl2P	384.198	5.20	
	C21H20NO3P	365.368	5.18	
	C17H16NO3Cl2P	384.198	5.20	
	C20H18NO3P	351.341	4.77	
	C21H20NO3P	365.368	5.18	
	C17H16NO3Cl2P	384.198	5.20	
	C17H16NO3Cl2P	384.198	5.20	
	C17H16NO3Cl2P	384.198	5.20	
	C18H18NO3Cl2P	398.225	5.60	
	C16H13NO3Cl2FP	388.161	4.89	
	C19H20NO3P	341.346	4.44	
	C17H16NO3Cl2P	384.198	5.20	
	C21H20NO3P	365.368	5.18	
	C22H22NO3P	379.395	5.56	
	C18H18NO3Cl2P	398.225	5.58	
	C17H16NO3Cl2P	384.198	5.20	
	C17H16NO3Cl2P	384.198	5.20	
	C20H22NO3P	355.373	4.84	
	C20H22NO3P	355.373	4.82	
	C18H18NO3Cl2P	398.225	5.58	
	C18H18NO3Cl2P	398.225	5.60	
	C16H14NO3Cl2P	370.171	4.79	
	C21H16NO3Cl2P	432.242	6.22	
	C20H20NO3Cl2P	424.263	5.92	

C19H17N2O3P	352.329	3.89	2.95
C18H16NO3PS	357.369	4.42	
C19H17N2O3P	352.329	3.98	
C16H14NO3ClFP	353.716	4.28	
C17H16NO3Cl2P	384.198	5.13	
C16H15NO3FP	319.271	3.68	2.51
C16H15NO3FP	319.271	3.68	
C18H15NO3ClPS	391.814	5.26	
C16H12NO3Cl2P	368.155	3.96	
C16H15NO3FP	319.271	3.68	
C18H16NO4P	341.302	4.023	
C17H17N2O3P	328.307	3.03	
C16H13NO3ClF2P	371.706	4.38	
C14H13NO3ClPS	341.754	4.41	
C15H13NO4F3P	359.239	3.71	
C16H13NO3ClF2P	371.706	4.38	
C19H17N2O3P	352.329	3.89	
C21H20NO3P	365.368	5.23	
C17H16NO3Cl2P	384.198	5.24	
C17H16N3O3P	341.306	2.52	
C16H14NO2Cl2PS	386.238	4.97	
C14H13NO3ClPS	341.754	4.21	
C16H14NO3F2P	337.261	3.78	
C17H15NO3F3P	369.278	4.43	3.23
C17H15NO3F3P	369.278	4.43	3.53
C17H17NO3FP	333.298	4.08	3.48
C16H14NO3F2P	337.261	3.78	2.95
C16H14NO3F2P	337.261	3.78	
C17H15NO3F3P	369.278	4.43	
C16H15NO3FP	319.271	3.68	
C17H17NO3FP	333.298	4.08	
C16H14NO3F2P	337.261	3.78	
C17H17NO3FP	333.298	4.08	
C20H15NO3FP	367.315	4.70	
C17H15NO3F3P	369.278	4.43	
C17H17NO3FP	333.298	4.08	3.48
C17H15NO3F3P	369.278	4.43	
C19H17N2O3P	352.329	3.89	
C17H15NO3F3P	369.278	4.43	
C19H17N2O3P	352.329	3.77	
C20H19N2O3P	366.356	4.30	
C20H15NO3FP	367.315	4.70	
C16H15NO3FP	319.271	3.68	
C16H15NO3FP	319.271	3.68	
C19H17N2O3P	352.329	3.77	
C19H17N2O3P	352.329	3.77	
C19H17N2O3P	352.329	3.89	
C19H17N2O3P	352.329	3.98	

	C20H19N2O3P	366.356	4.30	
	C23H17N2O3P	400.373	4.92	
	C20H19N2O3P	366.356	4.30	
	C19H17N2O3P	352.329	3.89	
	C20H19N2O3P	366.356	4.30	
	C19H17N2O3P	352.329	3.89	
	C19H17N2O3P	352.329	3.77	
	C23H17N2O3P	400.373	4.92	
	C19H17N2O3P	352.329	3.89	
14	C17H16NO3F2P	351.288	4.27	2.80
15	C17H16NO3F2P	351.288	4.27	3.09
16	C17H15NO3F3P	369.278	4.38	3.40
17	C17H18NO4P	331.307	3.51	3.19
18	C17H16NO4F2P	367.287	3.75	2.45
19	C17H14NO5F2P	381.27	5.35	2.40
20	C16H15N2O4F2P	368.275	3.10	2.20
21	C16H14N2O3F3P	370.266	3.42	2.44
22	C16H15N2O3F2P	352.276	3.27	1.86
23	C17H15NO3F3P	369.278	4.38	3.59
24	C17H14NO5F2P	381.27	5.35	3.60
25	C16H15N2O4F2P	368.275	3.10	2.60
26	C16H14N2O3F3P	370.266	3.42	2.41
27	C16H15N2O3F2P	352.276	3.27	2.08
46	C17H16NO3F2P	351.288	4.27	3.06
47	C17H18NO4P	331.307	3.51	
48	C17H16NO4F2P	367.287	3.75	
49	C16H14N2O3F3P	370.266	3.48	
50	C16H14N2O3F3P	370.266	3.48	2.20
51	C17H16NO3F2P	351.288	4.27	3.33
52	C17H16NO3F2P	351.288	4.27	2.98
53	C17H16NO4F2P	367.287	3.75	3.20
54	C16H14N2O3F3P	370.266	3.48	1.98
	C21H21NO3F3P	423.37	5.64	4.50
	C19H19NO3F3P	397.332	5.19	
	C16H15NO3FP	319.271	3.68	
	C19H17NO3F3P	395.316	4.96	
	C16H15N2O3F2P	352.276	3.33	2.00
	C17H16NO4F2P	367.287	3.75	3.42
	C20H19NO3F3P	409.343	5.30	
	C20H24NO3P	357.389	5.16	
	C17H18NO4P	331.307	3.51	2.61
	C17H18NO4P	331.307	3.51	2.49
	C19H18NO4F2P	393.325	4.28	2.80
	C18H16N2O3F3P	396.304	4.01	2.80
	C19H18NO4F2P	393.325	4.28	3.60
	C19H17NO3F3P	395.316	4.96	4.20

Table S2. Calculated physicochemical properties and cytotoxicity of the compounds used for the clogP-cytotoxicity correlation. In orange are the data for the cpds that were considered outliers. clogP and topological polar surface area (TPSA) values were generated with generated with OSIRIS Datawarrior version 5.0.0 © 2002-2019 Idorsia Pharmaceuticals Ltd

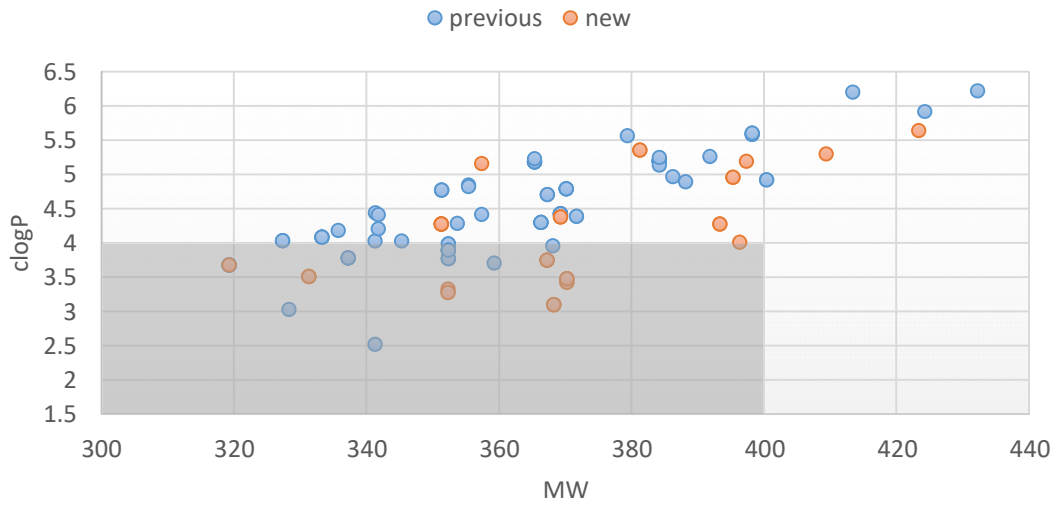
#	Molecular Formula	pIC_{50} (HepG2)	pEC_{50} (H2K)	ratio	ClogP	TPSA
2	$C_{17}H_{15}NO_3F_3P$	4.23	5.89	1.39	4.43	62.14
3(e2)	$C_{16}H_{15}NO_3FP$	3.70	6.91	1.87	3.68	62.14
20	$C_{16}H_{15}N_2O_4F_2P$	3.70	6.51	1.76	3.10	84.26
24	$C_{17}H_{14}NO_5F_2P$	4.16	4.00	0.96	5.35	80.60
47	$C_{17}H_{18}NO_4P$	3.70	6.29	1.70	3.51	71.37
49	$C_{16}H_{14}N_2O_3F_3P$	3.70	4.00	1.08	3.48	75.03
55	$C_{19}H_{19}NO_3F_3P$	7.67	4.00	0.52	5.19	62.14
56	$C_{19}H_{17}NO_3F_3P$	4.88	4.00	0.82	4.96	62.14
57	$C_{20}H_{19}NO_3F_3P$	5.30	4.00	0.75	5.30	62.14
	$C_{16}H_{15}NO_3ClP$	4.09	6.95	1.70	4.18	62.14
	$C_{19}H_{18}NO_4F_2P$	4.32	5.83	1.35	4.28	71.37
	$C_{19}H_{18}NO_4F_2P$	4.20	4.52	1.08	4.28	71.37
	$C_{16}H_{15}NO_3FP$	3.70	4.00	1.08	3.68	62.14
	$C_{18}H_{17}NO_3FP$	4.07	6.19	1.52	4.21	62.14

Table S3. Calculated clogP values with different software. From left to right: Dotmatics physicochemical properties calculator, Perkin Elmer ChemDraw version 19.1.0.8 © 1998-2020 PerkinElmer Informatics, Inc, and OSIRIS Datawarrior version 5.0.0 © 2002-2019 Idorsia Pharmaceuticals Ltd

		clogP		
Cpd	**Molecular Formula**	**Dotmatics**	**Chemdraw**	**DataWarrior**
2	$C_{17}H_{15}NO_3F_3P$	4.85	3.64	4.43
3(e2)	$C_{16}H_{15}NO_3FP$	3.96	2.89	3.68
20	$C_{16}H_{15}N_2O_4F_2P$	3.62	2.60	3.10
24	$C_{17}H_{14}NO_5F_2P$	4.57	4.35	5.35
47	$C_{17}H_{18}NO_4P$	3.82	2.75	3.51
49	$C_{16}H_{14}N_2O_3F_3P$	3.46	2.34	3.48
55	$C_{19}H_{19}NO_3F_3P$	5.77	4.48	5.19
56	$C_{19}H_{17}NO_3F_3P$	5.43	4.22	4.96
57	$C_{20}H_{19}NO_3F_3P$	5.30	4.55	5.30
	$C_{16}H_{15}NO_3ClP$	4.48	3.46	4.18
	$C_{19}H_{18}NO_4F_2P$	5.09	3.78	4.28
	$C_{19}H_{18}NO_4F_2P$	5.09	3.78	4.28
	$C_{16}H_{15}NO_3FP$	3.96	2.89	3.68
	$C_{18}H_{17}NO_3FP$	4.53	3.47	4.21

Figure S1. Physicochemical properties' plots a) MW-clogP b) MW-logD between previous (blue)[1] and new (orange) analogues showing decrease in lipophilicity and the move to optimal chemical space (grey area). Experimental logD (b) was measured with the shaking flask method for selected analogues. Predicted clogP (a) was generated with OSIRIS Datawarrior version 5.0.0 © 2002-2019 Idorsia Pharmaceuticals Ltd.

a)



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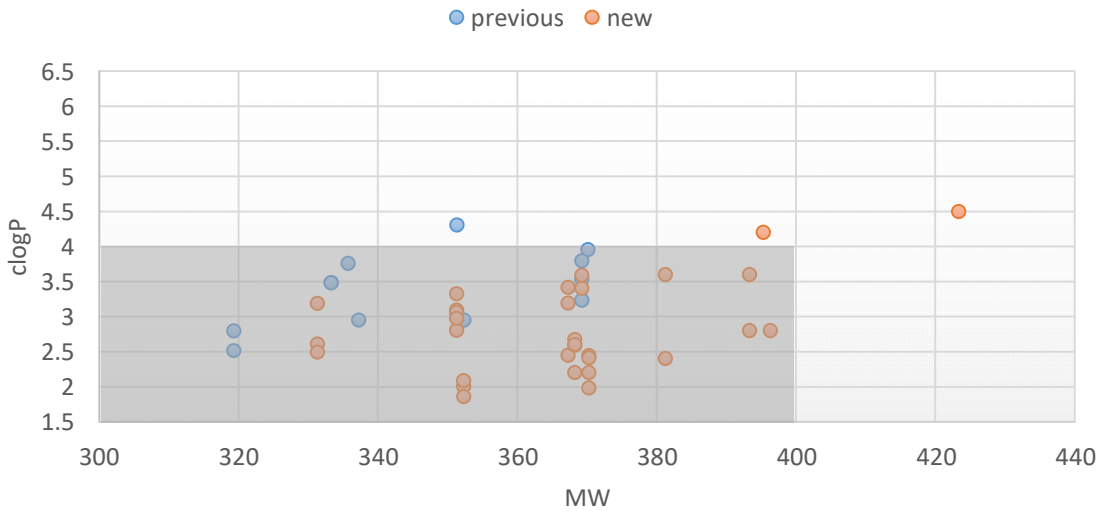


Equations S1 and S2

$$y = 0.9862x + 0.1893 \qquad (eq.1)$$

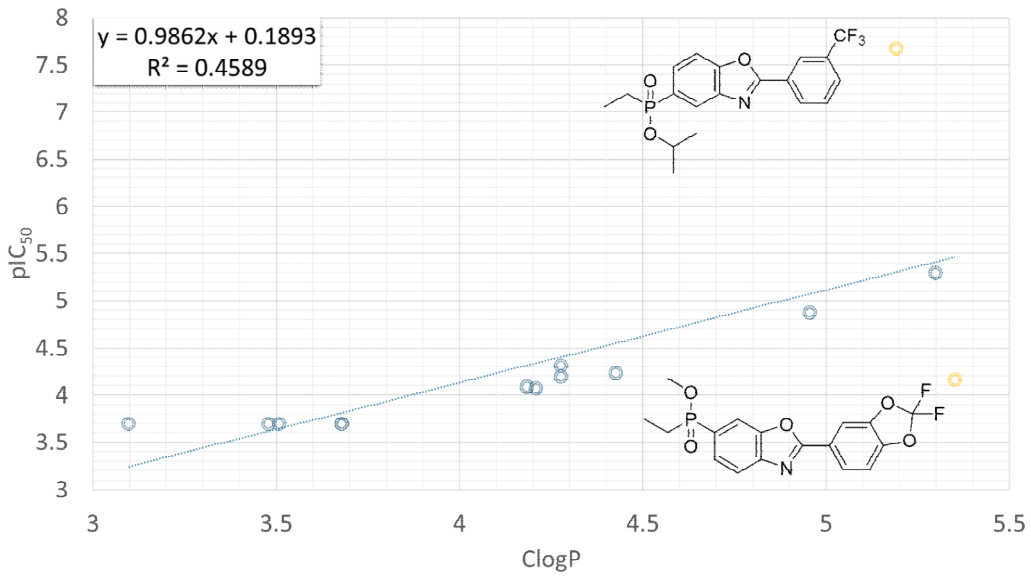
(n = 14, R^2 = 0.4589)

$$y = 0.7698x + 0.9853 \qquad (eq.2)$$

(n = 12, R^2 = 0.9081)

Figure S2. a) Correlation between cytotoxicity in HepG2 cells and lipophilicity as expressed from their pIC_{50} and clogP plot (n = 14). Predicted clogP (a) was generated with OSIRIS Datawarrior version 5.0.0 © 2002-2019 Idorsia Pharmaceuticals Ltd. In yellow are the two outliers b) Only a weak but negative correlation was shown when the ratio pEC_{50}[H2K]/pIC_{50}[HepG2] was plotted against ClogP.

a)



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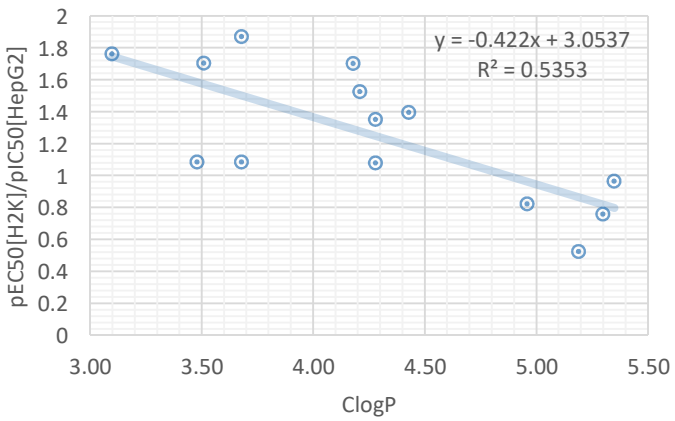


Analytical methods used for LCMS

Method A

MET/u-HPLC (MSQ1 low pH 7 min method)

Column: Phenomenex Kinetex-XB C18, 2.1 mm x 100 mm, 1.7 µm

Flow rate: 0.6 ml/min

Mobile Phase: A, Formic acid (aqueous) 0.1% and B, Formic acid (MeCN) 0.1%

Injection Vol: 3 µl

Temp.: 40 ºC

Detection: 215 nm (nominal)

Gradient Time (minutes) - % B

0.00 - 5

5.30 - 100

5.80 - 100

5.82 - 5

Method B

METCR 1410 (low pH Shimadzu 2min method) - IPC

Column: Kinetex Core-Shell C18, 2.1mmx50mm, 5µm column

Flow rate: 1.2 ml/min

Mobile Phase: A, Formic acid (aqueous) 0.1% and B, Formic acid (acetonitrile) 0.1%

Injection Vol: 3 µl

Temp.: 40 ºC

Detection: 215 nm (nominal)

Gradient Time (minutes) - % B

0.00 - 5

1.20 - 100

1.30 - 100

1.31 – 5

Experimental

Chemistry

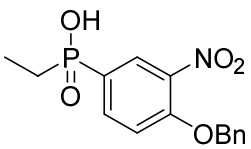
General Experimental. All reactions involving moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Water was purified by an Elix® UV-10 system. All other reagents were used as supplied (analytical or HPLC grade) without prior purification. Thin layer chromatography was performed on aluminium plates coated with 60 F254 silica. Flash column chromatography was performed either on Kieselgel 60 silica on a glass column, or on a Biotage SP4 automated flash column chromatography platform. Melting points were recorded on a EZ-Melt Automated Melting Point Apparatus (EZ Melt) and are uncorrected. NMR spectra were recorded on Bruker Avance III spectrometers (at 400 or 500 MHz) using the deuterated solvent stated and at RT. The field was locked by external referencing to the relevant deuteron resonance. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m $\times$ 0.25 mm) using amyl acetate as a lock mass. For preparative HPLC were the instrument used was a Waters Acquity H-Class consisting of an Acquity UPLC PDA Detector, an Acquity Quaternary Solvent Manager, and an Acquity QDa mass detector. Two general methods were used: 1) a basic method, where the column was an XBridge™ C18 10 µm particle size (30 × 100 mm); 5-95% gradient of MeCN (0.2% NH_4OH) in H_2O over 14 min, and the flow rate was 40 mL/min; 2) an acidic method, where the column was an Sunfire™ C18 10 µm particle size (30 × 100 mm); 5-95% gradient of MeCN (0.1% HCOOH) in H_2O over 14 min, and the flow rate was 40 mL/min. Experiments conducted at Contract Research Organisations used their standard equipment.

Acid chlorides

The acid chlorides used were either commercially available or synthesised from the respective carboxylic acids and oxalyl or sulfonyl chloride. The yield was assumed to be quantitative.

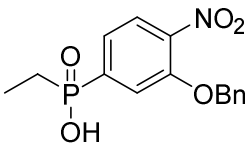
General procedure 1: Pd-catalysed C-P bond formation (6, 7, 37-45)

To a degassed solution of 2-arylbromobenzo[*d*]oxazole or bromophenyl derivative (1 eq), DIPEA (2.1 eq) and ethylphosphinic acid (2 eq) in DME (0.7 M) and toluene (0.3 M) $Pd(OAc)_2$ (0.06 eq) and xantphos (0.06 eq) were added under N_2 and the reaction was heated to 90°C for 2 h. The solvents were evaporated in vacuo, and the residue partitioned between EtOAc and NaOH (1M). The aqueous layer was extracted with EtOAc, acidified with 1M HCl (pH 3) and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford the title compounds.



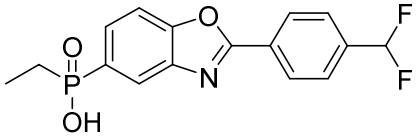
*(4-(Benzyloxy)-3-nitrophenyl)(ethyl)phosphinic acid (**6**)*

The title compound was prepared from **4** and isolated as a brown oil (715 mg, 71%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.13 (dd, *J* = 11.1, 1.8 Hz, 1H), 7.93 (ddd, *J* = 10.3, 8.6, 1.9 Hz, 1H), 7.58 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.48 – 7.45 (m, 2H), 7.45 – 7.39 (m, 2H), 7.39 – 7.28 (m, 1H), 5.38 (s, 2H), 1.78 (dq, *J* = 15.2, 7.6 Hz, 2H), 0.93 (dt, *J* = 18.7, 7.6 Hz, 4H). LC-MS (215 nm, 97%) R_T 1.04 min, MS (ESI): mass calculated for $C_{15}H_{16}NO_5P$, 321.08; *m/z* found 321.85 $[M + H]^+$, 319.90 ($[M - H]^-$.



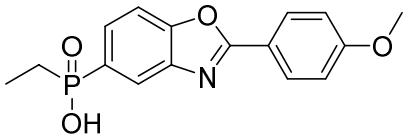
*(3-(Benzyloxy)-4-nitrophenyl)(ethyl)phosphinic acid (**7**)*

The title compound was prepared from **5** and isolated as a brown solid (3.5 g, 93%). ^{1}H NMR (500 MHz, DMSO-d_6) *δ* 7.98 (dd, *J* = 8.0, 3.2 Hz, 1H), 7.66 (dd, *J* = 12.2, 1.3 Hz, 1H), 7.48 – 7.37 (m, 5H), 7.37 – 7.32 (m, 1H), 5.37 (s, 2H), 1.79 (dq, *J* = 15.2, 7.7 Hz, 2H), 0.90 (dt, *J* = 18.7, 7.7 Hz, 3H). LC-MS (215 nm, 97%) R_T 1.01 min, MS (ESI): mass calculated for $C_{15}H_{16}NO_5P$, 321.08; *m/z* found 321.90 $[M + H]^+$.



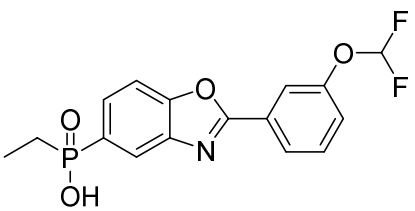
*(2-(4-(Difluoromethyl)phenyl)benzo[d]oxazol-5-yl)(ethyl)phosphinic acid (**37**)*

The title compound was prepared from **28** and isolated as a pink solid (170 mg, 71%). ^{1}H NMR (500 MHz, DMSO-d_6) *δ* 8.36 (d, *J* = 8.2 Hz, 2H), 8.12 (d, *J* = 11.4 Hz, 1H), 7.93 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.83 (d, *J* = 7.4 Hz, 2H), 7.81 – 7.78 (m, 1H), 7.17 (t, *J* = 55.6 Hz, 1H), 1.80 (dq, *J* = 15.2, 7.6 Hz, 2H), 0.95 (dt, *J* = 18.3, 7.6 Hz, 3H). LC-MS (215 nm, 96%) R_T 1.03 min, MS (ESI): mass calculated for $C_{16}H_{14}F_2NO_3P$, 337.07; *m/z* found 337.95 $[M + H]^+$.



*Ethyl(2-(4-methoxyphenyl)benzo[d]oxazol-5-yl)phosphinic acid (**38**)*

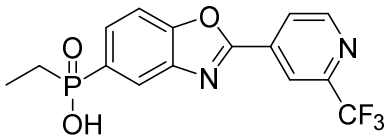
The title compound was prepared from **29** and isolated as a pink solid (411 mg, 83%). ^{1}H NMR (500 MHz, DMSO-d_6) *δ* 8.20 – 8.14 (m, 2H), 8.04 (dd, *J* = 11.5, 1.5 Hz, 1H), 7.87 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.73 (ddd, *J* = 10.9, 8.2, 1.4 Hz, 1H), 7.20 – 7.15 (m, 2H), 3.87 (s, 3H), 1.80 (dq, *J* = 15.2, 7.6 Hz, 2H), 0.95 (dt, *J* = 18.4, 7.6 Hz, 3H). LC-MS (215 nm, 99%) R_T 1.03 min, MS (ESI): mass calculated for $C_{16}H_{16}NO_4P$, 317.08; *m/z* found 317.85 $[M + H]^+$.



*(2-(3-(Difluoromethoxy)phenyl)benzo[d]oxazol-5-yl)(ethyl)phosphinic acid (**39**)*

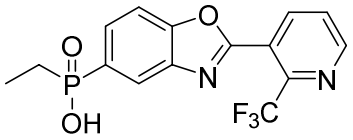
The title compound was prepared from **30** and isolated as pink oil (150 mg, 77%). ^{1}H NMR (250 MHz, DMSO-d_6) *δ* 8.13 (dt, *J* = 5.5, 1.1 Hz, 1H), 8.09 (q, *J* = 1.2 Hz, 1H), 7.98 – 7.89 (m, 2H), 7.84 – 7.77 (m, 1H), 7.77 – 7.63 (m, 1H), 7.52 – 7.43 (m, 1H), 7.43 (t, *J* = 73.6 Hz, 1H),

1.79 (dq, *J* = 15.1, 7.6 Hz, 2H), 0.94 (dt, *J* = 18.2, 7.6 Hz, 3H). LC-MS (215 nm, 94%) R_T 1.06 min, MS (ESI): mass calculated for $C_{16}H_{14}F_2NO_4P$, 353.06; *m/z* found 353.85 $[M + H]^+$.



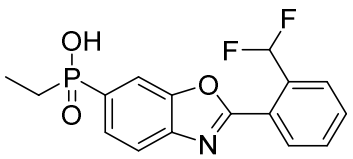
*Ethyl(2-(2-(trifluoromethyl)pyridin-4-yl)benzo[d]oxazol-5-yl)phosphinic acid (**40**)*

The title compound was prepared from **31** and isolated as pink oil (170 mg, 82%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.06 (d, *J* = 5.0 Hz, 1H), 8.47 (d, *J* = 1.0 Hz, 1H), 8.45 (dd, *J* = 5.0, 1.6 Hz, 1H), 8.20 (dd, *J* = 11.5, 1.2 Hz, 1H), 8.01 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.88 (ddd, *J* = 9.9, 8.3, 1.4 Hz, 1H), 1.80 (dt, *J* = 15.1, 7.6 Hz, 2H), 0.95 (dt, *J* = 18.4, 7.6 Hz, 3H). LC-MS (215 nm, 99%) R_T 1.01 min, MS (ESI): mass calculated for $C_{15}H_{12}F_3N_2O_3P$, 356.05; *m/z* found 356.80 $[M + H]^+$.



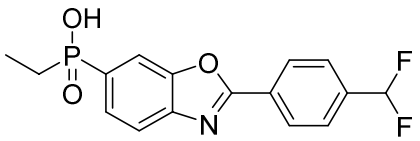
*Ethyl(2-(2-(trifluoromethyl)pyridin-3-yl)benzo[d]oxazol-5-yl)phosphinic acid (**41**)*

The title compound was prepared from **32** and isolated as a white solid (149 mg, 73%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.01 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.66 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.20 (d, *J* = 11.5 Hz, 1H), 8.04 – 7.96 (m, 2H), 7.87 (ddd, *J* = 10.3, 8.4, 1.4 Hz, 1H), 1.84 (dq, *J* = 15.1, 7.6 Hz, 2H), 0.96 (dt, *J* = 18.5, 7.7 Hz, 3H). LC-MS (215 nm, 98%) R_T 0.97 min, MS (ESI): mass calculated for $C_{15}H_{12}F_3N_2O_3P$, 356.05; *m/z* found 356.95 $[M + H]^+$, 354.95 $[M - H]^-$.



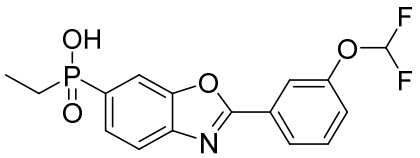
*(2-(2-(Difluoromethyl)phenyl)benzo[d]oxazol-6-yl)(ethyl)phosphinic acid (**42**)*

The title compound was prepared from **33** and isolated as a brown solid (180 mg, 91%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.31 – 8.25 (m, 1H), 8.08 (d, *J* = 11.4 Hz, 1H), 7.94 (dd, *J* = 8.2, 2.4 Hz, 2H), 7.92 (t, *J* = 54.6 Hz, 1H), 7.84 – 7.78 (m, 2H), 7.78 – 7.74 (m, 1H), 1.76 (dt, *J* = 15.2, 7.5 Hz, 3H), 0.93 (dt, *J* = 18.2, 7.6 Hz, 3H). LC-MS (215 nm, 95%) R_T 1.05 min, MS (ESI): mass calculated for $C_{16}H_{14}F_2NO_3P$, 337.07; *m/z* found 337.95 $[M + H]^+$.

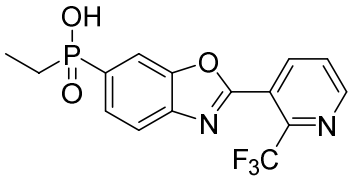


*(2-(4-(Difluoromethyl)phenyl)benzo[d]oxazol-6-yl)(ethyl)phosphinic acid (**43**)*

The title compound was prepared from **34** and isolated as a pink solid (150 mg, 72%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.36 (d, *J* = 8.1 Hz, 2H), 8.08 (d, *J* = 11.5 Hz, 1H), 7.94 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 2H), 7.80 – 7.73 (m, 1H), 7.18 (t, *J* = 55.6 Hz, 1H), 1.81 (dq, *J* = 15.2, 7.6 Hz, 2H), 0.95 (dt, *J* = 18.4, 7.6 Hz, 3H). LC-MS (215 nm, 97%) R_T 1.01 min, MS (ESI): mass calculated for $C_{16}H_{14}F_2NO_3P$, 337.07; *m/z* found 337.95 $[M + H]^+$.



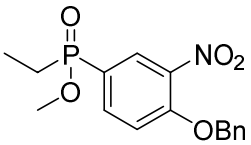
*(2-(3-(Difluoromethoxy)phenyl)benzo[d]oxazol-6-yl)(ethyl)phosphinic acid (**44**)*
The title compound was prepared from **35** and isolated as a brown oil (540 mg, 98%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.13 – 8.06 (m, 2H), 7.99 – 7.93 (m, 2H), 7.77 (ddd, *J* = 10.8, 8.1, 1.2 Hz, 1H), 7.71 (t, *J* = 8.0 Hz, 1H), 7.49 (dd, *J* = 8.2, 2.6 Hz, 1H), 7.43 (t, *J* = 73.6 Hz, 1H), 1.83 (dq, *J* = 15.2, 7.6 Hz, 2H), 0.95 (dt, *J* = 18.5, 7.6 Hz, 3H). LC-MS (215 nm, 97%) R_T 1.04 min, MS (ESI): mass calculated for $C_{16}H_{14}F_2NO_4P$, 353.06; *m/z* found 353.85 $[M + H]^+$, 351.85 $[M - H]^-$.



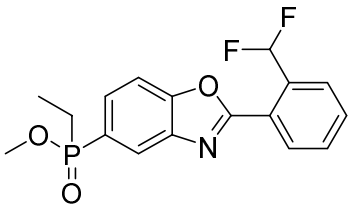
*Ethyl(2-(2-(trifluoromethyl)pyridin-3-yl)benzo[d]oxazol-6-yl)phosphinic acid (**45**)*
The title compound was prepared from **36** and isolated as a white solid (187 mg, 94%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.02 (dd, *J* = 4.7, 1.3 Hz, 1H), 8.66 (dd, *J* = 8.0, 1.1 Hz, 1H), 8.13 (d, *J* = 11.6 Hz, 1H), 8.04 (dd, *J* = 8.1, 2.4 Hz, 1H), 8.01 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.83 (ddd, *J* = 10.6, 8.1, 1.1 Hz, 1H), 1.91 – 1.77 (m, 2H), 0.96 (dt, *J* = 18.6, 7.6 Hz, 3H). LC-MS (215 nm, 100%) R_T 0.97 min, MS (ESI): mass calculated for $C_{15}H_{12}F_3N_2O_3P$, 356.05; *m/z* found 356.90 $[M + H]^+$, 354.95 ($[M - H]^-$.

General procedure 2: Formation of methyl phosphinates (8, 14, 46-54)

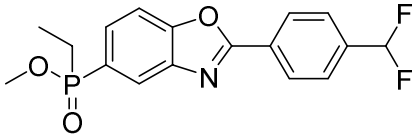
To a solution of ethylphosphinic acid derivative (1 eq) in $SOCl_2$ (0.15 M) catalytic DMF was added and the mixture was heated to 70 °C for 1 h. The solvents were evaporated in *vacuo*, the residue was dissolved in CH_2Cl_2 (0.1 M) and added dropwise to an ice-cold (0 °C) solution of DIPEA (3.5 eq) and DMAP (2 eq) in MeOH (0.3 M relative to DMAP) and CH_2Cl_2 (0.2 M relative to DMAP). The reaction mixture was stirred for 30 min at RT, concentrated in *vacuo* and the residue diluted with CH_2Cl_2, washed with aqueous HCl (1 M), sat. $NaHCO_3$, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by HPLC (acidic method) to afford the title compounds.



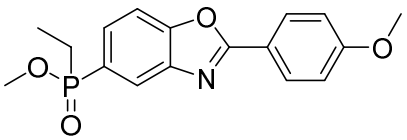
*Methyl (4-(benzyloxy)-3-nitrophenyl)(ethyl)phosphinate (**8**)*
The title compound was prepared from **6** and isolated as a yellow oil (3.46 g, 10.32 mmol, 81%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.17 (dd, *J* = 11.1, 1.9 Hz, 1H), 7.96 (ddd, *J* = 10.4, 8.6, 1.9 Hz, 1H), 7.63 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.51 – 7.45 (m, 2H), 7.45 – 7.41 (m, 2H), 7.39 – 7.32 (m, 1H), 5.40 (s, 2H), 3.52 (d, *J* = 11.0 Hz, 3H), 2.03 – 1.87 (m, 2H), 0.95 (dt, *J* = 19.2, 7.7 Hz, 3H). LCMS (215 nm, 100%) R_T 1.12 min, MS (ESI): mass calculated for $C_{16}H_{18}NO_5P$, 335.09; *m/z* found 335.85 $[M + H]^+$.



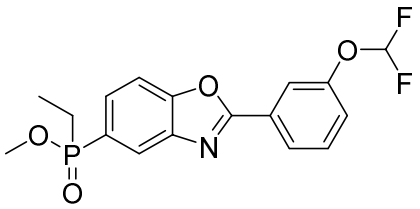
*Methyl (2-(2-(difluoromethyl)phenyl)benzo[d]oxazol-5-yl)(ethyl)phosphinate (**14**)*
The title compound was prepared from **14a** and isolated as a brown oil (45 mg, 85%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.33 – 8.27 (m, 1H), 8.22 (dd, J = 11.6, 1.4 Hz, 1H), 8.03 (dd, J = 8.3, 2.3 Hz, 1H), 7.97 – 7.93 (m, 1H), 7.92 (t, J = 54.7 Hz, 1H), 7.88 – 7.82 (m, 3H), 3.54 (d, J = 11.0 Hz, 3H), 2.08 – 1.96 (m, 2H), 0.98 (dt, J = 19.0, 7.6 Hz, 3H). ^{13}C NMR (125.5 MHz, DMSO-d_6) δ 161.5, 152.3, 141.5 (d, J = 17.1 Hz), 133.2 (t, J = 22.5 Hz), 132.5, 131.6, 130.1, 129.4 (d, J = 10.8 Hz), 127.1 (d, J = 121.1 Hz), 126.3 (t, J = 7.0 Hz), 124.4 (t, J = 5.7 Hz), 123.8 (d, J = 11.2 Hz), 112.3 (t, J = 235.7 Hz), 111.9 (d, J = 13.4 Hz), 50.8 (d, J = 6.6 Hz), 21.1 (d, J = 101.9 Hz), 5.8 (d, J = 4.6 Hz). ^{31}P NMR {H} (162 MHz, DMSO-d_6) δ 46.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.8 (d, J = 54.7 Hz). LC-MS (215 nm, 100%) R_T 1.15 min, MS (ESI): mass calculated for $C_{17}H_{16}F_2NO_3P$, 351.08; *m/z* found 351.90 $[M + H]^+$. HRMS (ESI): *m/z* calculated for $C_{17}H_{16}F_2NO_3P + H^+$ $[M + H]^+$: 352.09086. Found: 352.09021.



*Methyl (2-(4-(difluoromethyl)phenyl)benzo[d]oxazol-5-yl)(ethyl)phosphinate (**46**)*
The title compound was prepared from **37** and isolated as a white solid (100 mg, 56%). mp 60-63 ^{o}C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.37 (d, J = 8.0 Hz, 2H), 8.18 (dd, J = 11.6, 1.4 Hz, 1H), 8.02 (dd, J = 8.4, 2.3 Hz, 1H), 7.84 (d, J = 8.2 Hz, 2H), 7.83 (ddd, J = 10.8, 8.3, 1.4 Hz, 1H), 7.18 (t, J = 55.6 Hz, 1H), 3.54 (d, J = 10.9 Hz, 3H), 2.06 – 1.94 (m, 2H), 0.98 (dt, J = 18.9, 7.6 Hz, 3H). ^{13}C NMR (125.5 MHz, DMSO-d_6) δ 163.2, 153.2, 142.1 (d, J = 16.5 Hz), 137.8 (t, J = 22.4 Hz), 129.7 (d, J = 11.3 Hz), 128.7, 128.6, 127.6 (d, J = 121.1 Hz), 127.3 (t, J = 6.1 Hz), 124.2 (d, J = 10.8 Hz), 114.8 (t, J = 236.5 Hz), 112.3 (d, J = 14.1 Hz), 51.3 (d, J = 6.6 Hz), 21.7 (d, J = 101.3 Hz), 6.3 (d, J = 4.7 Hz). ^{31}P NMR {H} (162 MHz, DMSO-d_6) δ 46.8. ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.1 (d, J = 55.3 Hz). LC-MS (254 nm, 100%) R_T 3.05 min, MS (ESI): mass calculated for $C_{17}H_{16}F_2NO_3P$, 351.1; *m/z* found 352.1 $[M + H]^+$. HRMS (ESI): *m/z* calculated for $C_{17}H_{16}F_2NO_3P + H^+$ $[M + H]^+$: 352.09086. Found: 352.09017.

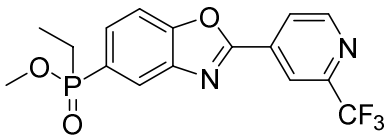


Methyl ethyl(2-(4-methoxyphenyl)benzo[d]oxazol-5-yl)phosphinate (**47**)
The title compound was prepared from **38** and isolated as a colourless oil (41 mg, 65%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.20 – 8.15 (m, 2H), 8.08 (dt, J = 11.6, 1.0 Hz, 1H), 7.94 (ddd, J = 8.3, 2.4, 0.6 Hz, 1H), 7.75 (ddd, J = 10.8, 8.3, 1.4 Hz, 1H), 7.22 – 7.15 (m, 2H), 3.88 (s, 3H), 3.53 (d, J = 10.9 Hz, 3H), 2.07 – 1.91 (m, 2H), 0.97 (dt, J = 18.9, 7.7 Hz, 3H). ^{13}C NMR (125.5 MHz, DMSO-d_6) δ 163.7, 162.6, 152.6, 142.0 (d, J = 17.2 Hz), 129.5, 128.4 (d, J = 11.4 Hz), 126.6 (d, J = 121.6 Hz), 122.9 (d, J = 11.5 Hz), 118.3, 114.9, 111.4 (d, J = 13.7 Hz), 55.6, 50.8 (d, J = 6.4 Hz), 21.2 (d, J = 101.7 Hz), 5.8 (d, J = 4.7 Hz). ^{31}P NMR {H} (162 MHz, DMSO-d_6) δ 43.9. LCMS (215 nm, 100%) R_T 1.31 min, MS (ESI): mass calculated for $C_{17}H_{18}NO_4P$, 331.10; *m/z* found 331.90 $[M + H]^+$. HRMS (ESI): *m/z* calculated for $C_{17}H_{18}NO_4P + H^+$ $[M + H]^+$: 332.1046. Found: 332.1048.



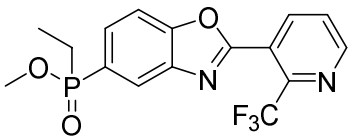
*Methyl (2-(3-(difluoromethoxy)phenyl)benzo[d]oxazol-5-yl)(ethyl)phosphinate (**48**)*

The title compound was prepared from **39** and isolated as a pale yellow oil (76 mg, 68%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.17 (dt, J = 11.5, 0.9 Hz, 1H), 8.11 (dt, J = 7.7, 1.3 Hz, 1H), 8.01 (dd, J = 8.3, 2.3 Hz, 1H), 7.96 (t, J = 2.1 Hz, 1H), 7.82 (ddd, J = 10.8, 8.3, 1.4 Hz, 1H), 7.72 (t, J = 8.0 Hz, 1H), 7.50 (dd, J = 8.0, 2.5 Hz, 1H), 7.43 (t, J = 73.6 Hz, 1H), 3.54 (d, J = 10.9 Hz, 3H), 2.07 – 1.93 (m, 2H), 0.98 (dt, J = 19.0, 7.7 Hz, 3H). ^{13}C NMR (125.5 MHz, DMSO-d_6) δ 162.5, 152.7, 151.4, 141.6 (d, J = 17.2 Hz), 131.5, 129.2 (d, J = 10.9 Hz), 127.8, 127.6, 126.6, 124.4, 123.6 (d, J = 11.3 Hz), 122.9, 117.2, 116.3 (t, J = 258.7 Hz), 111.8 (d, J = 13.5 Hz), 50.8 (d, J = 6.6 Hz), 21.2 (d, J = 101.9 Hz), 5.8 (d, J = 4.7 Hz). ^{31}P NMR {H} (162 MHz, DMSO-d_6) δ 46.8. ^{19}F NMR (376 MHz, DMSO-d_6) δ -82.6 (d, J = 73.8 Hz). LC-MS (215 nm, 100%) R_T 1.16 min, MS (ESI): mass calculated for $C_{17}H_{16}F_2NO_4P$, 367.08; *m/z* found 367.90 $[M + H]^+$. HRMS (ESI): *m/z* calculated for $C_{17}H_{16}F_2NO_4P + H^+$ $[M + H]^+$: 368.05878. Found: 368.05602.



*Methyl ethyl(2-(2-(trifluoromethyl)pyridin-4-yl)benzo[d]oxazol-5-yl)phosphinate (**49**)*

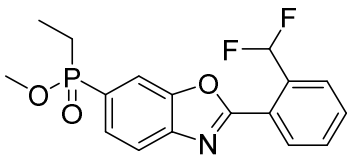
The title compound was prepared from **40** and isolated as a pale brown oil (95 mg, 68%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.08 (d, J = 5.0 Hz, 1H), 8.49 (t, J = 1.2 Hz, 1H), 8.46 (dd, J = 5.1, 1.5 Hz, 1H), 8.27 (dt, J = 11.7, 1.0 Hz, 1H), 8.08 (dd, J = 8.5, 2.3 Hz, 1H), 7.90 (ddd, J = 10.7, 8.3, 1.4 Hz, 1H), 3.54 (d, J = 10.9 Hz, 3H), 2.10 – 1.93 (m, 2H), 0.98 (dt, J = 19.0, 7.7 Hz, 3H). ^{13}C NMR (125.5 MHz, DMSO-d_6) δ 160.5, 152.8, 151.9, 147.7 (q, J = 34.7 Hz), 141.3 (d, J = 17.1 Hz), 135.5, 130.1 (d, J = 11.3 Hz), 127.7 (d, J = 120.6 Hz), 124.7, 124.4 (d, J = 11.3 Hz), 121.3 (q, J = 273.7 Hz), 117.9, 112.3 (d, J = 13.4 Hz), 50.9 (d, J = 6.6 Hz), 21.1 (d, J = 101.3 Hz), 5.8 (d, J = 4.8 Hz). ^{31}P NMR {H} (162 MHz, DMSO-d_6) δ 46.5. ^{19}F NMR (376 MHz, DMSO-d_6) δ -66.8. LCMS (254 nm, 100%) R_T 2.92 min, MS (ESI): mass calculated for $C_{16}H_{14}F_3N_2O_3P$, 370.1; *m/z* found 371.1 $[M + H]^+$. HRMS (ESI): *m/z* calculated for $C_{16}H_{14}F_3N_2O_3P + H^+$ $[M + H]^+$: 371.0767. Found: 371.0768.



*Methyl ethyl(2-(2-(trifluoromethyl)pyridin-3-yl)benzo[d]oxazol-5-yl)phosphinate (**50**)*

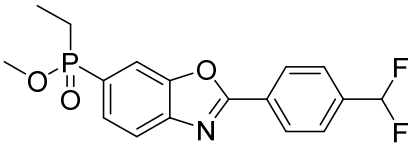
The title compound was prepared from **41** and isolated as a white solid (39 mg, 49%). mp 95-7 ^{o}C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.02 (dd, J = 4.8, 1.6 Hz, 1H), 8.66 (dd, J = 8.0, 1.6 Hz, 1H), 8.26 (dd, J = 11.6, 1.3 Hz, 1H), 8.06 (dd, J = 8.4, 2.3 Hz, 1H), 8.01 (dd, J = 8.0, 4.7 Hz, 1H), 7.89 (ddd, J = 10.7, 8.3, 1.4 Hz, 1H), 3.54 (d, J = 10.9 Hz, 3H), 2.09 – 1.97 (m, 2H), 0.98 (dt, J = 19.0, 7.6 Hz, 3H). ^{13}C NMR (125.5 MHz, DMSO-d_6) δ 159.8, 152.9 (d, J = 2.9 Hz), 151.7, 144.2 (q, J = 34.3 Hz), 141.3, 141.1, 129.8 (d, J = 11.3 Hz), 127.6, 127.5 (d, J = 120.3 Hz), 124.2 (d, J = 11.3 Hz), 122.0, 121.2 (q, J = 275.1 Hz), 112.0 (d, J = 13.4 Hz), 50.9 (d, J = 6.6 Hz), 21.1 (d, J = 101.9 Hz), 5.8 (d, J = 4.7 Hz). ^{31}P NMR {H} (162 MHz, DMSO-d_6) δ 46.6. ^{19}F NMR (376 MHz, DMSO-d_6) δ -63.0. LC-MS (215 nm, 100%) R_T 1.05 min, MS (ESI):

mass calculated for $C_{16}H_{14}F_3N_2O_3P$, 370.07; *m/z* found 370.95 $[M + H]^+$. HRMS (ESI): *m/z* calculated for $C_{16}H_{14}N_2O_3P + H^+$ $[M + H]^+$: 371.0767. Found: 371.0768.



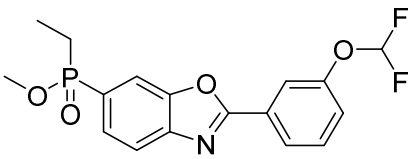
*Methyl (2-(2-(difluoromethyl)phenyl)benzo[d]oxazol-6-yl)(ethyl)phosphinate (**51**)*

The title compound was prepared from **42** and isolated as a white gum (73 mg, 41%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.31 (dd, J = 6.6, 2.5 Hz, 1H), 8.22 – 8.15 (m, 1H), 8.06 (dd, J = 8.1, 2.6 Hz, 1H), 7.97 – 7.93 (m, 1H), 7.92 (t, J = 54.7 Hz, 1H), 7.86 – 7.82 (m, 2H), 7.80 (ddd, J = 10.7, 8.1, 1.2 Hz, 1H), 3.54 (d, J = 10.9 Hz, 3H), 2.06 – 1.95 (m, 2H), 0.98 (dt, J = 19.0, 7.7 Hz, 3H). ^{13}C NMR (125.5 MHz, DMSO-d_6) δ 162.8, 150.4 (d, J = 19.1 Hz), 144.9, 133.7 (t, J = 22.5 Hz), 133.1, 132.1, 130.6, 128.7 (t, J = 10.7 Hz), 127.8, 126.8 (t, J = 7.1 Hz), 124.9 (t, J = 5.4 Hz), 121.2 (d, J = 13.5 Hz), 115.0 (d, J = 11.6 Hz), 112.7 (t, J = 236.0 Hz), 51.4 (d, J = 6.2 Hz), 21.6 (d, J = 102.0 Hz), 6.2 (d, J = 4.7 Hz). ^{31}P NMR {H} (162 MHz, DMSO-d_6) δ 46.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.8 (d, J = 54.5 Hz). LC-MS (254 nm, 100%) R_T 3.17 min, MS (ESI): mass calculated for $C_{17}H_{16}F_2NO_3P$, 351.1; *m/z* found 352.1 $[M + H]^+$. HRMS (ESI): *m/z* calculated for $C_{17}H_{16}F_2NO_3P + H^+$ $[M + H]^+$: 352.09086. Found: 352.09100.



*Methyl (2-(4-(difluoromethyl)phenyl)benzo[d]oxazol-6-yl)(ethyl)phosphinate (**52**)*

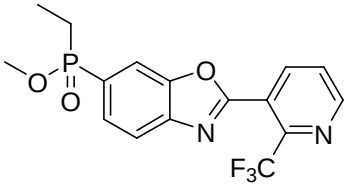
The title compound was prepared from **43** and isolated as a white solid (73 mg, 64%). mp 81-2 ^{o}C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.42 – 8.33 (m, 2H), 8.16 (dt, J = 11.7, 1.0 Hz, 1H), 8.02 (ddd, J = 8.1, 2.7, 0.6 Hz, 1H), 7.85 (d, J = 8.3 Hz, 2H), 7.79 (ddd, J = 10.8, 8.1, 1.3 Hz, 1H), 7.19 (t, J = 55.6 Hz, 1H), 3.54 (d, J = 11.0 Hz, 3H), 2.08 – 1.94 (m, 2H), 0.98 (dt, J = 19.0, 7.6 Hz, 3H). ^{13}C NMR (125.5 MHz, DMSO-d_6) δ 163.5, 150.2 (d, J = 19.1 Hz), 144.6, 137.5 (t, J = 22.4 Hz), 128.3, 128.2, 127.6 (d, J = 120.2 Hz), 126.8 (t, J = 6.2 Hz), 120.5 (d, J = 13.6 Hz), 114.5 (d, J = 11.6 Hz), 114.3 (t, J = 236.9 Hz), 50.9 (d, J = 6.6 Hz), 21.2 (d, J = 102.0 Hz), 5.8 (d, J = 4.8 Hz). ^{31}P NMR {H} (162 MHz, DMSO-d_6) δ 46.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.2 (d, J = 55.7 Hz). LC-MS (254 nm, 100%) R_T 3.03 min, MS (ESI): mass calculated for $C_{17}H_{16}F_2NO_3P$, 351.1; *m/z* found 352.1 $[M + H]^+$. HRMS (ESI): *m/z* calculated for $C_{17}H_{16}F_2NO_3P + H^+$ $[M + H]^+$: 352.09086. Found: 352.09054.



*Methyl (2-(3-(difluoromethoxy)phenyl)benzo[d]oxazol-6-yl)(ethyl)phosphinate (**53**)*

The title compound was prepared from **44** and isolated as a yellow oil (59 mg, 0.16 mmol, 48%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.16 (ddd, J = 11.6, 1.3, 0.7 Hz, 1H), 8.12 (ddd, J = 7.8, 1.6, 1.0 Hz, 1H), 8.01 (ddd, J = 8.1, 2.6, 0.7 Hz, 1H), 7.99 – 7.95 (m, 1H), 7.79 (ddd, J = 10.8, 8.1, 1.3 Hz, 1H), 7.72 (t, J = 8.0 Hz, 1H), 7.51 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 7.43 (t, J = 73.5 Hz, 1H), 3.54 (d, J = 11.0 Hz, 3H), 2.14 – 1.91 (m, 2H), 0.98 (dt, J = 19.0, 7.7 Hz, 3H). ^{13}C NMR (125.5 MHz, DMSO-d_6) δ 163.3, 151.4 (t, J = 3.3 Hz), 150.1 (d, J = 19.2 Hz), 144.5 (d, J = 2.6 Hz), 131.5, 128.2 (d, J = 10.4 Hz), 127.7, 127.6 (d, J = 120.6 Hz), 124.4, 123.0, 120.5 (d, J = 13.6 Hz), 117.3, 116.2 (t, J = 258.9 Hz), 114.5 (d, J = 11.7 Hz), 50.9 (d, J = 6.6

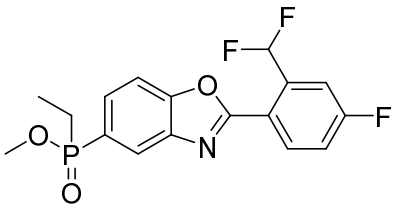
Hz), 21.2 (d, *J* = 101.8 Hz), 5.78 (d, *J* = 4.7 Hz). ^{31}P NMR {H} (162 MHz, DMSO-d_6) δ 46.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ -82.6 (d, *J* = 73.6 Hz). LC-MS (215 nm, 100%) R_T 4.13 min, MS (ESI): mass calculated for $C_{17}H_{16}F_2NO_4P$, 367.08; *m/z* found 367.85 $[M + H]^+$. HRMS (ESI): *m/z* calculated for $C_{17}H_{16}F_2NO_4P + H^+$ $[M + H]^+$: 368.08578. Found: 368.08655.



*Methyl ethyl(2-(2-(trifluoromethyl)pyridin-3-yl)benzo[d]oxazol-6-yl)phosphinate (**54**)*
The title compound was prepared from **45** and isolated as a white solid (42 mg, 46%). mp 82-3 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.02 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.66 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.21 (d, *J* = 11.6 Hz, 1H), 8.10 (dd, *J* = 8.1, 2.6 Hz, 1H), 8.02 (dd, *J* = 8.0, 4.7 Hz, 1H), 7.84 (ddd, *J* = 10.7, 8.1, 1.3 Hz, 1H), 3.54 (d, *J* = 10.9 Hz, 3H), 2.11 – 1.95 (m, 2H), 0.98 (dt, *J* = 19.1, 7.7 Hz, 3H). ^{13}C NMR (125.5 MHz, DMSO-d_6) δ 160.6, 151.8, 150.8 (d, *J* = 19.1 Hz), 144.2 (q, *J* = 34.1 Hz), 144.0 (d, *J* = 2.2 Hz), 141.1, 128.5 (d, *J* = 119.4 Hz), 128.4 (d, *J* = 10.3 Hz), 127.6, 122.0, 121.2 (q, *J* = 274.1 Hz), 121.0 (d, *J* = 13.5 Hz), 114.7 (d, *J* = 11.6 Hz), 50.9 (d, *J* = 6.7 Hz), 21.1 (d, *J* = 102.0 Hz), 5.8 (d, *J* = 4.7 Hz).^{31}P NMR {H} (162 MHz, DMSO-d_6) δ 46.5. ^{19}F NMR (376 MHz, DMSO-d_6) δ -63.0. LCMS (215 nm, 96%) R_T 1.04 min, MS (ESI): mass calculated for $C_{16}H_{14}F_3N_2O_3P$, 370.07; *m/z* found 370.90 $[M + H]^+$. HRMS (ESI): *m/z* calculated for $C_{16}H_{14}F_3N_2O_3P + H^+$ $[M + H]^+$: 371.0767. Found: 371.0770.

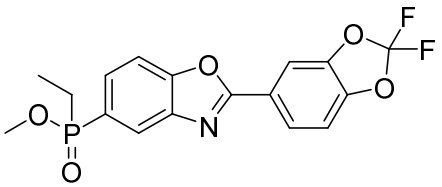
General procedure 3: Insertion of aryl and heteroaryl substituents via C-H activation (16, 19-27)

To a solution of methyl benzo[*d*]oxazolyl(ethyl)phosphinate (1 eq) and Cs_2CO_3 (2 eq) in anhydrous dioxane (0.15 M) under nitrogen $Pd(PPh_3)_2Cl_2$ (0.1 eq) and CuI (0.05 eq) were added. The reaction was stirred at RT for 5 min, before the addition of bromoaryl (1 eq) followed by heating at 100 °C for 12 h. The reaction was then diluted with water, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and the solvents were evaporated *in vacuo*. The residue was purified by HPLC (acidic method), unless otherwise stated, to afford the title compounds.

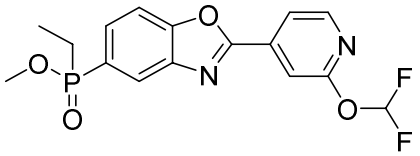


*Methyl (2-(2-(difluoromethyl)-4-fluorophenyl)benzo[d]oxazol-5-yl)(ethyl)phosphinate (**16**)*
The title compound was prepared from **12** and 1-bromo-2-(difluoromethyl)-4-fluorobenzene and isolated as a white solid (27 mg, 16%). mp 102-3 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.37 (dd, *J* = 8.8, 5.4 Hz, 1H), 8.21 (dt, *J* = 11.5, 1.0 Hz, 1H), 8.04 – 8.00 (m, 1H), 7.88 (td, *J* = 54.9, 0.9 Hz, 1H), 7.85 (ddd, *J* = 10.7, 8.3, 1.4 Hz, 1H), 7.78 (dd, *J* = 9.4, 2.6 Hz, 1H), 7.70 (td, *J* = 8.4, 2.7 Hz, 1H), 3.53 (d, *J* = 10.9 Hz, 3H), 2.07 – 1.97 (m, 2H), 0.97 (dt, *J* = 18.9, 7.6 Hz, 3H). ^{13}C NMR (125.5 MHz, DMSO-d_6) δ 164.0 (d, *J* = 252.7 Hz), 160.7, 152.4, 141.5 (d, *J* = 17.1 Hz), 136.0 (td, *J* = 23.0, 7.8 Hz), 133.2 (d, *J* = 9.4 Hz), 129.4 (d, *J* = 10.8 Hz), 127.6, 126.7, 123.8 (d, *J* = 11.4 Hz), 121.1 (q, *J* = 5.3 Hz), 118.9 (d, *J* = 21.9 Hz), 113.9 (dt, *J* = 24.8, 7.5 Hz), 111.9 (d, *J* = 13.6 Hz), 111.5 (t, *J* = 237.3 Hz), 50.8 (d, *J* = 6.4 Hz), 21.1 (d, *J* = 101.3 Hz), 5.8 (d, *J* = 4.7 Hz). ^{31}P NMR {H} (162 MHz, DMSO-d_6) δ 46.7. ^{19}F NMR (376 MHz, DMSO-

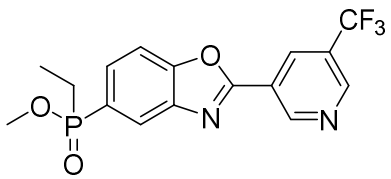
d$_6$) *δ* -105.5 (dd, *J* = 8.4, 6.1 Hz, 1F), -112.4 (d, *J* = 54.6 Hz, 2F). LC-MS (254 nm, 100%) R_T 3.26 min, MS (ESI): mass calculated for $C_{17}H_{15}F_3NO_3P$, 369.1; *m/z* found 370.1 $[M + H]^+$. HRMS (ESI): *m/z* calculated for $C_{17}H_{15}F_3NO_3P + H^+$ $[M + H]^+$: 370.08144. Found: 370.08074.



*Methyl (2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)benzo[d]oxazol-5-yl)(ethyl)phosphinate (**19**)*
The title compound was prepared from **12** and 5-bromo-2,2-difluorobenzo[*d*][1,3]dioxole and isolated as an off-white solid (17 mg, 8%). mp 103 °C. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) *δ* 8.21 (d, *J* = 1.7 Hz, 1H), 8.14 (dd, *J* = 11.7, 0.5 Hz, 2H), 8.13 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.98 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.81 (ddd, *J* = 10.7, 8.3, 1.4 Hz, 1H), 7.69 (d, *J* = 8.5 Hz, 1H), 3.53 (d, *J* = 10.9 Hz, 3H), 2.07 – 1.93 (m, 2H), 0.97 (dt, *J* = 18.9, 7.6 Hz, 3H). ^{13}C NMR (12.5 MHz, DMSO-*d*$_6$) *δ* 162.4, 152.7, 145.5, 143.5, 141.7 (d, *J* = 17.1 Hz), 131.3 (t, *J* = 254.7 Hz), 129.1 (d, *J* = 11.3 Hz), 127.1 (d, *J* = 121.1 Hz), 125.1, 123.5 (d, *J* = 10.9 Hz), 122.7, 111.7 (d, *J* = 13.5 Hz), 111.2, 109.3, 50.8 (d, *J* = 6.6 Hz), 21.2 (d, *J* = 101.8 Hz), 5.8 (d, *J* = 4.7 Hz). ^{31}P NMR {H} (162 MHz, DMSO-*d*$_6$) *δ* 46.8. ^{19}F NMR (376 MHz, DMSO-*d*$_6$) *δ* -48.9. LC-MS (215 nm, 98%) R_T 3.43 min, MS (ESI): mass calculated for $C_{17}H_{14}F_2NO_5P$, 381.1; *m/z* found 382.1 $[M + H]^+$. HRMS (ESI): *m/z* calculated for $C_{17}H_{14}F_2NO_5P + H^+$ $[M + H]^+$: 382.0650. Found: 382.0646.

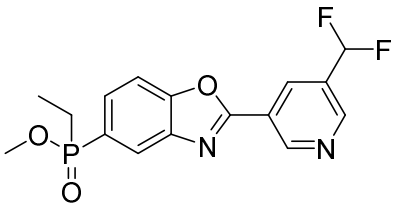


*Methyl (2-(2-(difluoromethoxy)pyridin-4-yl)benzo[d]oxazol-5-yl)(ethyl)phosphinate (**20**)*
The title compound was prepared from **12** and 4-bromo-2-(difluoromethoxy)pyridine and isolated as a white gum (63 mg, 31%). ^{1}H NMR (500 MHz, C*D*Cl$_3$) *δ* 8.55 (d, *J* = 5.2 Hz, 1H), 8.24 (dd, *J* = 11.6, 1.3 Hz, 1H), 8.04 (dd, *J* = 8.4, 2.3 Hz, 1H), 8.00 (dd, *J* = 5.3, 1.4 Hz, 1H), 7.88 (ddd, *J* = 10.0, 8.4, 1.4 Hz, 1H), 7.80 (t, *J* = 72.4 Hz, 1H), 7.77 – 7.71 (m, 1H), 3.54 (d, *J* = 10.9 Hz, 3H), 2.07 – 1.96 (m, 2H), 0.98 (dt, *J* = 19.0, 7.7 Hz, 3H). ^{13}C NMR (125.5 MHz, C*D*Cl$_3$) *δ* 161.1, 160.1 (t, *J* = 3.8 Hz), 153.4 (d, *J* = 2.9 Hz), 148.4, 142.1 (d, *J* = 17.1 Hz), 138.0, 130.3 (d, *J* = 11.3 Hz), 127.6 (d, *J* = 122.0 Hz), 125.2 (d, *J* = 10.7 Hz), 117.8, 114.1 (t, *J* = 256.4 Hz), 111.9 (d, *J* = 13.4 Hz), 109.6, 51.4 (d, *J* = 6.5 Hz), 22.9 (d, *J* = 103.1 Hz), 6.1 (d, *J* = 4.9 Hz). ^{31}P NMR {H} (162 MHz, C*D*Cl$_3$) *δ* 47.3. ^{19}F NMR (376 MHz, C*D*Cl$_3$) *δ* -89.1 (d, *J* = 72.3 Hz). LC-MS (215 nm, 97%) R_T 3.02 min, MS (ESI): mass calculated for $C_{16}H_{15}F_2N_2O_4P$, 368.1; *m/z* found 369.1 $[M + H]^+$. HRMS (ESI): *m/z* calculated for $C_{16}H_{15}N_2O_4P + H^+$ $[M + H]^+$: 369.0810. Found: 369.0816.



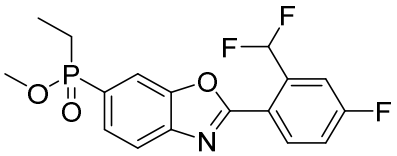
*Methyl ethyl(2-(5-(trifluoromethyl)pyridin-3-yl)benzo[d]oxazol-5-yl)phosphinate (**21**)*
The title compound was prepared from **12** and 3-bromo-5-(trifluoromethyl)pyridine. Purification with HPLC (basic method) derived the desired product as an off-white solid (66 mg, 40%). mp 134-5 °C. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) *δ* 9.65 (d, *J* = 2.0 Hz, 1H), 9.28 (dd, *J* = 2.1, 1.0 Hz, 1H), 8.84 (t, *J* = 2.3 Hz, 1H), 8.20 (dt, *J* = 11.6, 0.9 Hz, 1H), 8.07 (dd, *J* = 8.1, 2.5 Hz, 1H),

7.83 (ddd, *J* = 10.7, 8.1, 1.3 Hz, 1H), 3.55 (d, *J* = 10.9 Hz, 3H), 2.11 – 1.94 (m, 2H), 0.98 (dt, *J* = 19.1, 7.7 Hz, 3H). ^{13}C NMR (125.5 MHz, DMSO-d$_6$) *δ* 161.2, 152.0, 150.3 (d, *J* = 19.1 Hz), 149.2 (q, *J* = 3.6 Hz), 144.2, 132.2 (q, *J* = 3.7 Hz), 128.4 (d, *J* = 10.5 Hz), 128.3 (d, *J* = 120.1 Hz), 125.7 (q, *J* = 33.3 Hz), 123.2 (q, *J* = 272.8 Hz), 123.0, 120.8 (d, *J* = 13.5 Hz), 114.7 (d, *J* = 11.6 Hz), 50.9 (d, *J* = 6.7 Hz), 21.2 (d, *J* = 101.4 Hz), 5.8 (d, *J* = 4.8 Hz). ^{31}P NMR {H} (162 MHz, DMSO-*d*$_6$) *δ* 46.5. ^{19}F NMR (376 MHz, DMSO-*d*$_6$) *δ* -61.1. LC-MS (215 nm, 95%) R_T 1.07 min, MS (ESI): mass calcd for $C_{16}H_{14}F_3N_2O_3P$, 370.07; *m/z* found 370.90 $[M + H]^+$. HRMS (ESI): *m/z* calculated for $C_{16}H_{14}F_3N_2O_3P + H^+$ $[M + H]^+$: 371.0767. Found: 371.0768.



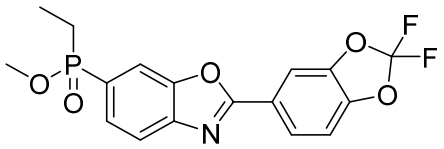
*Methyl (2-(5-(difluoromethyl)pyridin-3-yl)benzo[d]oxazol-5-yl)(ethyl)phosphinate (**22**)*

The title compound was prepared from **12** and 3-bromo-5-(difluoromethyl)pyridine and isolated as a pale brown solid (156 mg, 28%). mp 99-101 ^{o}C. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) *δ* 9.52 (d, *J* = 2.0 Hz, 1H), 9.10 – 9.01 (m, 1H), 8.73 (d, *J* = 2.3 Hz, 1H), 8.21 (dd, *J* = 11.6, 1.4 Hz, 1H), 8.04 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.85 (ddd, *J* = 10.7, 8.4, 1.4 Hz, 1H), 7.33 (t, *J* = 55.0 Hz, 1H), 3.54 (d, *J* = 10.9 Hz, 3H), 2.10 – 1.95 (m, 2H), 0.98 (dt, *J* = 19.0, 7.6 Hz, 3H). ^{13}C NMR (125.5 MHz, DMSO-*d*$_6$) *δ* 160.9, 152.7, 150.4, 149.9 (t, *J* = 6.1 Hz), 141.5 (d, *J* = 17.1 Hz), 132.5 (t, *J* = 5.9 Hz), 130.4 (t, *J* = 23.3 Hz), 129.5 (d, *J* = 10.8 Hz), 127.3 (d, *J* = 121.0 Hz), 123.9 (d, *J* = 11.3 Hz), 122.7, 113.4 (t, *J* = 237.3 Hz), 112.0 (d, *J* = 13.5 Hz), 50.9 (d, *J* = 6.6 Hz), 21.2 (d, *J* = 101.3 Hz), 5.8 (d, *J* = 4.7 Hz). ^{31}P NMR {H} (162 MHz, DMSO-*d*$_6$) *δ* 46.7. ^{19}F NMR (376 MHz, DMSO-*d*$_6$) *δ* -112.3 (d, *J* = 54.9 Hz). LC-MS (254 nm, 100%) R_T 2.49 min, MS (ESI): mass calculated for $C_{16}H_{15}F_2N_2O_3P$, 352.1; *m/z* found 353.1 $[M + H]^+$. HRMS (ESI): *m/z* calculated for $C_{16}H_{15}F_2N_2O_3P + H^+$ $[M + H]^+$: 353.0861. Found: 353.0862.

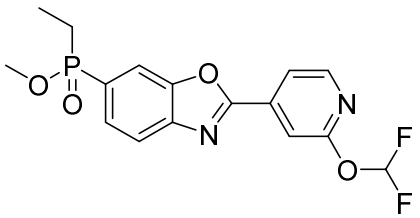


*Methyl (2-(2-(difluoromethyl)-4-fluorophenyl)benzo[d]oxazol-6-yl)(ethyl)phosphinate (**23**)*

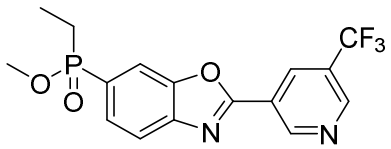
The title compound was prepared from **13** and 1-bromo-2-(difluoromethyl)-4-fluorobenzene and isolated as a white solid (66 mg, 39%). mp 132-4 ^{o}C. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) *δ* 8.38 (dd, *J* = 8.8, 5.4 Hz, 1H), 8.18 (d, *J* = 11.6 Hz, 1H), 8.05 (dd, *J* = 8.1, 2.6 Hz, 1H), 7.94 (t, *J* = 54.8 Hz, 1H), 7.84 – 7.75 (m, 2H), 7.71 (td, *J* = 8.4, 2.7 Hz, 1H), 3.54 (d, *J* = 10.9 Hz, 3H), 2.07 – 1.96 (m, 2H), 0.98 (dt, *J* = 19.0, 7.7 Hz, 3H). ^{13}C NMR (125.5 MHz, DMSO-*d*$_6$) *δ* 164.5 (d, *J* = 252.7 Hz), 162.0, 150.4 (d, *J* = 19.1 Hz), 144.8, 136.6 (td, *J* = 23.1, 8.6 Hz), 133.7 (d, *J* = 9.4 Hz), 128.7 (d, *J* = 10.4 Hz), 128.3 (d, *J* = 120.2 Hz), 121.6 (d, *J* = 4.5 Hz), 121.2 (d, *J* = 13.4 Hz), 119.4 (d, *J* = 22.0 Hz), 115.0 (d, *J* = 11.8 Hz), 114.4 (dt, *J* = 24.5, 7.4 Hz), 112.0 (t, *J* = 237.1 Hz), 51.4 (d, *J* = 6.5 Hz), 21.6 (d, *J* = 102.0 Hz), 6.2 (d, *J* = 4.7 Hz). ^{31}P NMR {H} (162 MHz, DMSO-*d*$_6$) *δ* 46.7. ^{19}F NMR (376 MHz, DMSO-*d*$_6$) *δ* -105.3 (dd *J*= 14.5, 8.4 Hz, 1F), -112.4 (d, *J* = 54.5 Hz, 2F). LC-MS (254 nm, 100%) R_T 3.29 min, MS (ESI): mass calculated for $C_{17}H_{15}$ F_3NO_3P, 369.1; *m/z* found 370.1 $[M + H]^+$. HRMS (ESI): *m/z* calculated for $C_{17}H_{15}$ $F_3NO_3P + H^+$ $[M + H]^+$: 370.08144. Found: 370.08112.



*Methyl (2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)benzo[d]oxazol-6-yl)(ethyl)phosphinate (**24**)*
The title compound was prepared from **13** and 5-bromo-2,2-difluorobenzo[*d*][1,3]dioxole and isolated as a white gum (14 mg, 7%). ^{1}H NMR (500 MHz, C*D*Cl3) *δ* 8.10 (dd, *J* = 8.4, 1.7 Hz, 1H), 8.07 (dt, *J* = 11.7, 0.9 Hz, 1H), 7.99 (d, *J* = 1.6 Hz, 1H), 7.86 (ddd, *J* = 8.0, 2.7, 0.6 Hz, 1H), 7.73 (ddd, *J* = 10.8, 8.1, 1.2 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 3.67 (d, *J* = 11.0 Hz, 3H), 2.08 – 1.86 (m, 2H), 1.14 (dt, *J* = 19.1, 7.7 Hz, 3H). ^{13}C NMR (125.5 MHz, C*D*Cl$_3$) *δ* 163.9, 150.9 (d, *J* = 19.1 Hz), 146.7, 145.5 (d, *J* = 2.8 Hz), 144.5, 131.9 (t, *J* = 257.5 Hz), 128.2 (d, *J* = 10.5 Hz), 127.2 (d, *J* = 122.0 Hz), 124.7, 123.0, 120.7 (d, *J* = 13.5 Hz), 115.0 (d, *J* = 11.4 Hz), 110.2, 109.3, 51.4 (d, *J* = 6.7 Hz), 22.9 (d, *J* = 103.8 Hz), 6.1 (d, *J* = 4.8 Hz). ^{31}P NMR {H} (162 MHz, C*D*Cl$_3$) *δ* 47.5. ^{19}F NMR (376 MHz, C*D*Cl$_3$) *δ* -49.8. LC-MS (215 nm, 100%) R_T 3.41 min, MS (ESI): mass calculated for $C_{17}H_{14}F_2NO_5P$, 381.1; *m/z* found 382.1 $[M + H]^+$. HRMS (ESI): *m/z* calculated for $C_{17}H_{14}NO_5P + H^+$ $[M + H]^+$: 382.0650. Found: 382.0649.

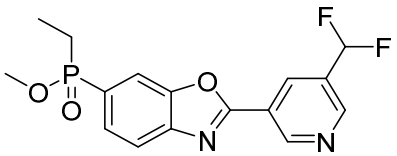


*Methyl (2-(2-(difluoromethoxy)pyridin-4-yl)benzo[d]oxazol-6-yl)(ethyl)phosphinate (**25**)*
The title compound was prepared from **13** and 4-bromo-2-(difluoromethoxy)pyridine and isolated as a white sticky solid (65 mg, 33%). mp 46-47 ^{o}C. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) *δ* 8.56 (dd, *J* = 5.2, 0.8 Hz, 1H), 8.20 (dt, *J* = 11.5, 0.9 Hz, 1H), 8.08 (dd, *J* = 8.1, 2.5 Hz, 1H), 8.01 (dd, *J* = 5.2, 1.4 Hz, 1H), 7.83 (ddd, *J* = 10.7, 8.1, 1.3 Hz, 1H), 7.81 (t, *J* = 72.4 Hz, 1H), 7.75 (t, *J* = 1.0 Hz, 1H), 3.54 (d, *J* = 11.0 Hz, 3H), 2.11 – 1.92 (m, 2H), 0.98 (dt, *J* = 19.0, 7.7 Hz, 3H). ^{13}C NMR (125.5 MHz, DMSO-*d*$_6$) *δ* 161.4 (d, *J* = 1.4 Hz), 159.2 (t, *J* = 3.8 Hz), 150.3 (d, *J* = 19.6 Hz), 149.0, 144.1, 137.6, 128.7 (d, *J* = 120.0 Hz), 128.5 (d, *J* = 10.4 Hz), 121.1 (d, *J* = 13.6 Hz), 118.2, 114.9 (d, *J* = 11.6 Hz), 114.8 (t, *J* = 255.7 Hz), 108.9, 50.9 (d, *J* = 6.6 Hz), 21.1 (d, *J* = 101.4 Hz), 5.7 (d, *J* = 4.7 Hz). ^{31}P NMR {H} (162 MHz, DMSO-*d*$_6$) *δ* 46.5. ^{19}F NMR (376 MHz, DMSO-*d*$_6$) *δ* -87.5 (d, *J* = 72.2 Hz). LC-MS (215 nm, 99%) R_T 3.01 min, MS (ESI): mass calculated for $C_{16}H_{15}F_2N_2O_4P$, 368.1; *m/z* found 369.1 $[M + H]^+$. HRMS (ESI): *m/z* calculated for $C_{16}H_{15}N_2O_4P + H^+$ $[M + H]^+$: 369.0810. Found: 369.0811.



*Methyl ethyl(2-(5-(trifluoromethyl)pyridin-3-yl)benzo[d]oxazol-6-yl)phosphinate (**26**)*
The title compound was prepared from **13** and 3-bromo-5-(trifluoromethyl)pyridine. Purification with HPLC (basic method) derived the desired product as an off-white solid (61 mg, 37%). mp 134-5 ^{o}C. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) *δ* 9.64 (d, *J* = 2.0 Hz, 1H), 9.27 (dd, *J* = 2.3, 1.0 Hz, 1H), 8.84 (dt, *J* = 2.6, 1.3 Hz, 1H), 8.23 (dt, *J* = 11.7, 1.0 Hz, 1H), 8.05 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.87 (ddd, *J* = 10.7, 8.3, 1.4 Hz, 1H), 3.54 (d, *J* = 10.9 Hz, 3H), 2.10 – 1.93 (m, 2H), 0.98 (dt, *J* = 19.0, 7.7 Hz, 3H). ^{13}C NMR (125.5 MHz, DMSO-*d*$_6$) *δ* 160.9, 153.2, 152.3, 149.6 (d, *J* = 4.1 Hz), 141.9 (d, *J* = 16.5 Hz), 132.6 (q, *J* = 2.9 Hz), 130.1 (d, *J* = 11.3 Hz), 127.9 (d, *J* = 120.4 Hz), 126.2 (q, *J* = 33.1 Hz), 124.4 (d, *J* = 11.1 Hz), 123.7 (q, *J* = 272.9 Hz), 123.4, 112.5 (d, *J* = 13.7 Hz), 51.3 (d, *J* = 6.6 Hz), 21.6 (d, *J* = 101.9 Hz), 6.3. ^{31}P NMR {H} (162 MHz,

DMSO-d_6) δ 46.6. ^{19}F NMR (376 MHz, DMSO-d_6) δ -61.1. LC-MS (215 nm, 100%) R_T 1.08 min, MS (ESI): mass calcd for $C_{16}H_{14}F_3N_2O_3P$, 370.07; *m/z* found 370.95 $[M + H]^+$. HRMS (ESI): *m/z* calculated for $C_{16}H_{14}F_3N_2O_3P + H^+$ $[M + H]^+$: 371.0767. Found: 371.0770.

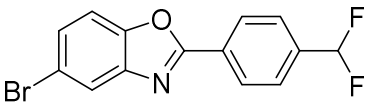


*Methyl (2-(5-(difluoromethyl)pyridin-3-yl)benzo[d]oxazol-6-yl)(ethyl)phosphinate (**27**)*

The title compound was prepared from **13** and 3-bromo-5-(difluoromethyl)pyridine and isolated as a yellow gum (11 mg, 7%). ^{1}H NMR (500 MHz, MeOH-d_4) δ 9.53 (d, *J* = 2.0 Hz, 1H), 9.07 (d, *J* = 1.9 Hz, 1H), 8.73 (t, *J* = 1.9 Hz, 1H), 8.22 – 8.15 (m, 1H), 8.06 (dd, *J* = 8.1, 2.6 Hz, 1H), 7.82 (ddd, *J* = 10.8, 8.1, 1.3 Hz, 1H), 7.34 (t, *J* = 55.0 Hz, 1H), 3.55 (d, *J* = 11.0 Hz, 3H), 2.12 – 1.95 (m, 2H), 0.98 (dt, *J* = 19.0, 7.6 Hz, 3H). ^{13}C NMR (125.5 MHz, DMSO-d_6) δ 162.2, 150.9, 150.7 (d, *J* = 19.2 Hz), 150.5 (t, *J* = 6.1 Hz), 144.8, 133.0 (t, *J* = 6.0 Hz), 130.8 (t, *J* = 23.5 Hz), 128.9 (d, *J* = 10.4 Hz), 128.5 (d, *J* = 120.1 Hz), 123.1, 121.2 (d, *J* = 13.4 Hz), 115.1 (d, *J* = 11.7 Hz), 113.9 (t, *J* = 237.0 Hz), 51.4 (d, *J* = 6.4 Hz), 21.6 (d, *J* = 101.6 Hz), 6.2 (d, *J* = 4.6 Hz). ^{31}P NMR {H} (162 MHz, DMSO-d_6) δ 46.6. ^{19}F NMR (376 MHz, DMSO-d_6) δ -112.4 (d, *J* = 54.9 Hz). LC-MS (254 nm, 96%) R_T 2.48 min, MS (ESI): mass calculated for $C_{16}H_{15}F_2N_2O_3P$, 352.1; *m/z* found 353.1 $[M + H]^+$. HRMS (ESI): *m/z* calculated for $C_{16}H_{15}F_2N_2O_3P + H^+$ $[M + H]^+$: 353.0861. Found: 353.0863.

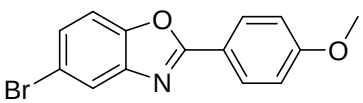
General procedure 4: Benzo[d]oxazole ring formation from o-aminophenols (28-36)

A suspension of bromoaminophenol (1 eq) and benzoyl chloride (1.25 eq) in xylenes (0.15 M) was heated to 155 °C for 1 h. Methanesulfonic acid (0.2 eq) was added and the reaction mixture was refluxed at 155 °C for 2-3 h. The solvents were evaporated in vacuo and the residue was purified by flash column chromatography to afford the title compounds.



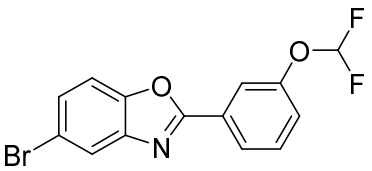
*5-Bromo-2-(4-(difluoromethyl)phenyl)benzo[d]oxazole (**28**)*

The title compound was prepared from 2-amino-4-bromophenol and 4-(difluoromethyl)benzoyl chloride followed by purification with flash column chromatography (gradient 0-50% EtOAc in hexane) to afford **28** as a pink solid (220 mg, 45%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.34 (d, *J* = 8.3 Hz, 2H), 8.10 (d, *J* = 1.8 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 2H), 7.64 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.17 (t, *J* = 55.6 Hz, 1H). LC-MS (215 nm, 96%) R_T 1.38 min, MS (ESI): mass calculated for $C_{14}H_8{}^{79}BrF_2NO$, 322.98; *m/z* found 323.85 $[M + H]^+$.



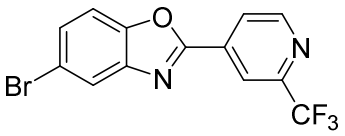
*5-Bromo-2-(4-methoxyphenyl)benzo[d]oxazole (**29**)*

The title compound was prepared from 2-amino-4-bromophenol and 4-methoxybenzoyl chloride followed by purification with flash column chromatography (gradient 0-40% EtOAc in heptane) to afford **29** as a pink solid (471 mg, 58%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.17 – 8.11 (m, 2H), 7.99 (d, *J* = 1.9 Hz, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.55 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.21 – 7.13 (m, 2H), 3.87 (s, 3H). LC-MS (215 nm, 98%) R_T 1.39 min, MS (ESI): mass calculated for $C_{14}H_{10}{}^{79}BrNO_2$, 302.99; *m/z* found 303.75 $[M + H]^+$.



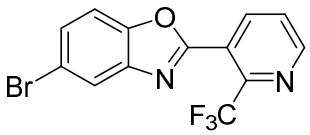
*5-Bromo-2-(3-(difluoromethoxy)phenyl)benzo[d]oxazole (**30**)*

The title compound was prepared from 2-amino-4-bromophenol and 3-(difluoromethoxy)benzoyl chloride followed by purification with flash column chromatography (gradient 0-100% EtOAc in heptane) to afford **30** as a pink solid (190 mg, 49%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.10 (d, J = 2.0 Hz, 1H), 8.08 (dt, J = 7.8, 1.3 Hz, 1H), 7.93 (t, J = 2.1 Hz, 1H), 7.82 (d, J = 8.7 Hz, 1H), 7.70 (t, J = 8.0 Hz, 1H), 7.63 (dd, J = 8.6, 2.0 Hz, 1H), 7.51 – 7.46 (m, 1H), 7.42 (t, J = 73.5 Hz, 1H). LC-MS (215 nm, 93%) R_T 1.40 min, MS (ESI): mass calculated for $C_{14}H_8{}^{79}BrF_2NO_2$, 338.97; *m/z* found 339.75 $[M + H]^+$.



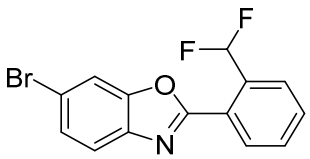
*5-Bromo-2-(2-(trifluoromethyl)pyridin-4-yl)benzo[d]oxazole (**31**)*

The title compound was prepared from 2-amino-4-bromophenol and 2-(trifluoromethyl)isonicotinoyl chloride followed by purification with flash column chromatography (gradient 0-50% EtOAc in heptane) to afford **31** as a pink solid (200 mg, 56%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.06 (d, J = 5.0 Hz, 1H), 8.46 (s, 1H), 8.42 (dd, J = 5.0, 1.2 Hz, 1H), 8.21 (d, J = 1.9 Hz, 1H), 7.90 (d, J = 8.7 Hz, 1H), 7.72 (dd, J = 8.7, 2.0 Hz, 1H). LC-MS (215 nm, 100%) R_T 1.36 min, MS (ESI): mass calculated for $C_{13}H_6{}^{79}BrF_3N_2O$, 341.96; *m/z* found 342.75 $[M + H]^+$.



*5-Bromo-2-(2-(trifluoromethyl)pyridin-3-yl)benzo[d]oxazole (**32**)*

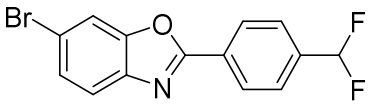
The title compound was prepared from 2-amino-4-bromophenol and 2-(trifluoromethyl)nicotinoyl chloride followed by purification with flash column chromatography (gradient 0-40% EtOAc in heptane) to afford **32** as a pink solid (498 mg, 66%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.01 (dd, J = 4.8, 1.6 Hz, 1H), 8.64 (dd, J = 8.0, 1.6 Hz, 1H), 8.20 (d, J = 1.9 Hz, 1H), 8.00 (dd, J = 7.9, 4.7 Hz, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.70 (dd, J = 8.7, 2.0 Hz, 1H). LC-MS (215 nm, 66%) R_T 0.94 min, MS (ESI): mass calculated for $C_{13}H_6{}^{81}BrF_2N_2O$, 343.96; *m/z* found 344.80 $[M + H]^+$.



*6-Bromo-2-(2-(difluoromethyl)phenyl)benzo[d]oxazole (**33**)*

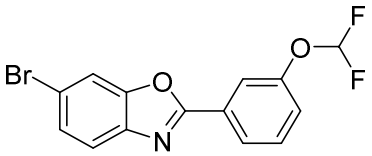
The title compound was prepared from 2-amino-5-bromophenol and 2-(difluoromethyl)benzoyl chloride followed by purification with flash column chromatography (gradient 0-100% EtOAc in hexane) to afford **33** as a pink solid (180 mg, 30%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.29 – 8.21 (m, 1H), 8.18 (d, J = 1.8 Hz, 1H), 7.95 – 7.91 (m, 1H), 7.90 (t, J = 54.8 Hz, 1H), 7.85 (d,

J = 8.5 Hz, 1H), 7.83 – 7.80 (m, 1H), 7.63 (dd, *J* = 8.5, 1.8 Hz, 1H). LC-MS (215 nm, 66%) R_T 1.38 min, MS (ESI): mass calculated for $C_{14}H_8{}^{81}BrF_2NO$, 324.97; *m/z* found 325.85 $[M + H]^+$.



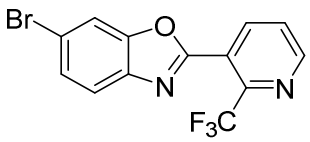
*6-Bromo-2-(4-(difluoromethyl)phenyl)benzo[d]oxazole (**34**)*

The title compound was prepared from 2-amino-5-bromophenol and 4-(difluoromethyl)benzoyl chloride followed by purification with flash column chromatography (gradient 0-50% EtOAc in hexane) to afford **34** as a pink solid (200 mg, 43%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.32 (d, *J* = 8.4 Hz, 2H), 8.16 (d, *J* = 1.8 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 2H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.62 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.17 (t, *J* = 55.6 Hz, 1H). LC-MS (215 nm, 100%) R_T 1.38 min, MS (ESI): mass calculated for $C_{14}H_8{}^{79}BrF_2NO$, 322.98; *m/z* found 323.80 $[M + H]^+$.



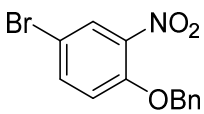
*6-Bromo-2-(3-(difluoromethoxy)phenyl)benzo[d]oxazole (**35**)*

The title compound was prepared from 2-amino-5-bromophenol and 3-(difluoromethoxy)benzoyl chloride followed by purification with flash column chromatography (gradient 0-30% EtOAc in hexane) to afford **35** as a red/brown solid (541 mg, 62%). ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.16 (d, *J* = 1.8 Hz, 1H), 8.06 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.94 – 7.89 (m, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.74 – 7.66 (m, 1H), 7.61 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.48 (dd, *J* = 8.0, 2.3 Hz, 1H), 7.41 (t, *J* = 73.6 Hz, 1H). LC-MS (215 nm, 98%) R_T 1.38 min, MS (ESI): mass calculated for $C_{14}H_8{}^{81}BrF_2NO_2$, 340.97; *m/z* found 341.75 $[M + H]^+$.



*6-Bromo-2-(2-(trifluoromethyl)pyridin-3-yl)benzo[d]oxazole (**36**)*

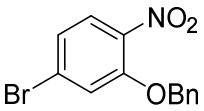
The title compound was prepared from 2-amino-5-bromophenol and 2-(trifluoromethyl)nicotinoyl chloride followed by purification with flash column chromatography (gradient 0-40% EtOAc in hexane) to afford **36** as a pink solid (545 mg, 75%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.29 – 8.21 (m, 1H), 8.18 (d, *J* = 1.8 Hz, 1H), 7.95 – 7.91 (m, 1H), 7.90 (t, *J* = 54.8 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.83 – 7.80 (m, 1H), 7.63 (dd, *J* = 8.5, 1.8 Hz, 1H). LC-MS (215 nm, 66%) R_T 0.94 min, MS (ESI): mass calculated for $C_{13}H_6{}^{81}BrF_3N_2O$, 343.96; *m/z* found 344.80 $[M + H]^+$.



*1-(Benzyloxy)-4-bromo-2-nitrobenzene (**4**)*

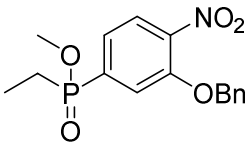
To a mixture of 4-bromo-2-nitrophenol (600 mg, 2.75 mmol) and K_2CO_3 (380 mg, 2.75 mmol) in acetone (10 mL) benzylbromide (0.36 mL, 3.03 mmol) was added and the resulting mixture was refluxed at 60 ˚C for 6 h. The reaction was cooled to RT and the solvent evaporated *in vacuo*. The residue was diluted with EtOAc, washed with water, brine, dried over Na_2SO_4, and the solvents were evaporated *in vacuo*. The title compound was obtained after purification with flash column chromatography (gradient 0-20% EtOAc in heptanes) as an off-white solid (1.37

g, 97%). ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.13 (d, J = 2.5 Hz, 1H), 7.84 (dd, J = 9.0, 2.5 Hz, 1H), 7.49 – 7.28 (m, 6H), 5.32 (s, 2H). LCMS (215 nm, 100%) R_T 1.34 min.



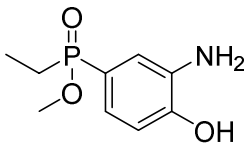
*2-(Benzyloxy)-4-bromo-1-nitrobenzene (**5**)*

The title compound was prepared from 5-bromo-2-nitrophenol (3.42 g, 15.7 mmol), benzyl bromide (2.05 mL, 17.3 mmol) and K_2CO_3 (2.17 g, 15.7 mmol) in acetone (25 mL) using a method analogous to the synthesis of **4**. Purification with flash column chromatography (gradient 0-15% EtOAc in heptanes) afforded **5** as a yellow solid (3.6 g, 74%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.87 (d, J = 8.6 Hz, 1H), 7.73 (d, J = 2.0 Hz, 1H), 7.48 – 7.39 (m, 4H), 7.38 – 7.33 (m, 2H), 5.35 (s, 2H). LCMS (215 nm, 97%) R_T 1.32 min.



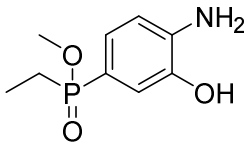
*Methyl (3-(benzyloxy)-4-nitrophenyl)(ethyl)phosphinate (**9**)*

A solution of **7** (3.5 g, 10.9 mmol) in $SOCl_2$ (12 mL) was heated at 70 °C for 2 h. The solvent was evaporated and the residue was dissolved in MeOH (30 mL) and stirred for 15 min, the solvents were evaporated *in vacuo* and the residue was diluted with CH_2Cl_2, washed with aqueous HCl (1 M), sat. $NaHCO_3$, dried over Na_2SO_4, and concentrated *in vacuo* to afford the title compound as a brown solid (3.46 g, 81%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.02 (dd, J = 8.0, 3.3 Hz, 1H), 7.66 (dd, J = 12.2, 1.3 Hz, 1H), 7.49 – 7.39 (m, 5H), 7.37 – 7.31 (m, 1H), 5.41 (s, 2H), 3.51 (d, J = 11.0 Hz, 3H), 2.06 – 1.91 (m, 2H), 0.93 (dt, J = 19.2, 7.6 Hz, 3H). LCMS (215 nm, 94%) R_T 1.13 min, MS (ESI): mass calculated for $C_{16}H_{18}NO_5P$, 335.09; *m/z* found 335.95 $[M + H]^+$.



*Methyl (3-amino-4-hydroxyphenyl)(ethyl)phosphinate (**10**)*

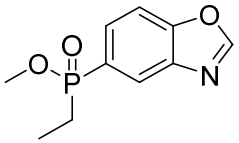
To a solution of **8** (820 mg, 2.69 mmol) in EtOH/CH_2Cl_2 (5:1, 30 mL) 10% Pd/C (286 mg, 0.27 mmol) was added and the resulting mixture was stirred at RT for 3 h under H_2. The reaction mixture was then filtered through Celite™, washed with MeOH and the solvents were evaporated *in vacuo* to give the title compound as a colourless oil (555 mg, 96%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.78 (br s, 1H), 6.99 – 6.87 (m, 1H), 6.82 – 6.70 (m, 2H), 4.78 (br s, 2H), 3.43 (d, J = 10.8 Hz, 3H), 1.85 – 1.65 (m, 2H), 0.93 (dt, J = 18.4, 7.7 Hz, 3H). LCMS (215 nm, 100%) R_T 0.34 min, MS (ESI): mass calculated for $C_9H_{14}NO_3P$, 215.07; *m/z* found 215.85 $[M + H]^+$, 213.85 $[M - H]^-$.



*Methyl (4-amino-3-hydroxyphenyl)(ethyl)phosphinate (**11**)*

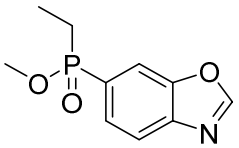
The title compound was prepared from **9** (3.45 g, 9.3 mmol) and 10% Pd/C (0.988 g, 0.93 mmol) in EtOH/CH_2Cl_2 (5:1, 90 mL), using a method analogous to the synthesis of **10**, and

isolated as a brown solid (2.0 g, 94%). ^{1}H NMR (250 MHz, DMSO-d_6) δ 9.39 (br s, 1H), 6.95 (dd, J = 11.8, 1.6 Hz, 1H), 6.97 – 6.81 (m, 1H), 6.66 (dd, J = 7.9, 4.0 Hz, 1H), 5.17 (br s, 2H), 3.42 (d, J = 10.9 Hz, 5H), 1.83 – 1.63 (m, 2H), 1.11 – 0.83 (m, 3H). LCMS (215 nm, 90%) R_T 0.64 min, MS (ESI): mass calculated for $C_9H_{14}NO_3P$, 215.07; *m/z* found 215.90 $[M + H]^+$.



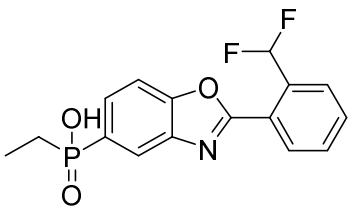
*Methyl benzo[d]oxazol-5-yl(ethyl)phosphinate (**12**)*

To a suspension of **10** (6.6 g, 30.7 mmol) in xylenes (100 mL) diethoxymethoxyethane (18 mL, 108 mmol) and pyridinium *p*-toluenesulfonate (771 mg, 3.07 mmol) were added and the resulting mixture was stirred at 140 °C for 3 h. The solvents were evaporated *in vacuo* and the desired product obtained after flash column chromatography (gradient 0-5% MeOH/CH_2Cl_2) as an orange oil (747 mg, 91%). ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.90 (s, 1H), 8.15 (dd, J = 11.6, 1.3 Hz, 1H), 7.97 (ddt, J = 8.3, 1.9, 0.9 Hz, 1H), 7.80 (ddt, J = 10.7, 8.4, 1.2 Hz, 1H), 3.51 (d, J = 10.9 Hz, 3H), 2.09 – 1.87 (m, 2H), 0.96 (dt, J = 18.9, 7.7 Hz, 3H). LCMS (215 nm, 92%) R_T 0. 80 min, MS (ESI): mass calculated for $C_{10}H_{12}NO_3P$, 225.06; *m/z* found 225.85 $[M + H]^+$.



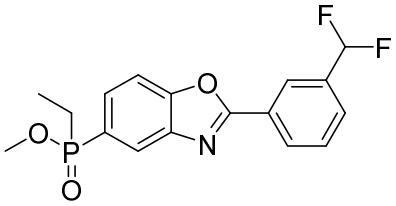
*Methyl benzo[d]oxazol-6-yl(ethyl)phosphinate (**13**)*

The title compound was prepared from **11** (724 mg, 2.86 mmol) diethoxymethoxyethane (1.67 mL, 10 mmol) and pyridinium *p*-toluenesulfonate (72 mg, 0.29 mmol) in xylenes (10 mL), using a method analogous to the synthesis of **12**. The desired product was obtained after flash column chromatography (gradient 0-15% MeOH/CH_2Cl_2) as a brown oil (677 mg, 95%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.93 (s, 1H), 8.13 (dt, J = 11.7, 1.0 Hz, 1H), 7.98 (ddd, J = 8.1, 2.7, 0.7 Hz, 1H), 7.76 (ddd, J = 10.7, 8.1, 1.3 Hz, 1H), 3.52 (d, J = 11.0 Hz, 3H), 2.05 – 1.92 (m, 2H), 0.96 (dt, J = 19.0, 7.7 Hz, 3H). LCMS (215 nm, 79%) R_T 0.78 min, MS (ESI): mass calculated for $C_{10}H_{12}NO_3P$, 225.06; *m/z* found 225.90 $[M + H]^+$.



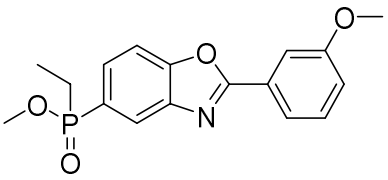
*(2-(2-(Difluoromethyl)phenyl)benzo[d]oxazol-5-yl)(ethyl)phosphinic acid (**14a**)*

In an oven-dried, nitrogen flushed pressure tube, **12** (150 mg, 0.67 mmol), $Pd(OAc)_2$ (7.5 mg, 0.03 mmol) and N-Xantphos (28 mg, 0.05 mmol) were suspended in DME (3 mL) and 1M LiHMDS (1.33 mL, 1.33 mmol) was added. The mixture was stirred at RT for 5 min. Bromo (difluoromethyl)benzene (166 mg, 0.80 mmol) was added and the reaction heated to 85 °C for 1 h. The solvent was evaporated *in vacuo* and the residue was purified by HPLC (acidic method) to afford the title compound as an orange solid (50 mg, 22%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.33 – 8.26 (m, 1H), 8.15 (d, J = 11.6 Hz, 1H), 7.95 (dd, J = 8.3, 2.4 Hz, 2H), 7.93 (t, J = 54.6 Hz, 1H), 7.86 – 7.80 (m, 3H), 1.82 (dq, J = 15.2, 7.6 Hz, 2H), 0.95 (dt, J = 18.4, 7.7 Hz, 3H). LC-MS (215 nm, 99%) R_T 1.06 min, MS (ESI): mass calculated for $C_{16}H_{14}F_2NO_3P$, 337.07; *m/z* found 337.90 $[M + H]^+$.



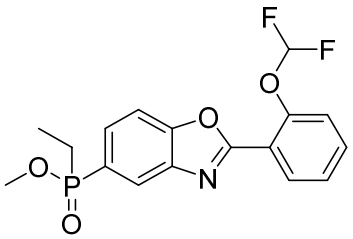
*Methyl (2-(3-(difluoromethyl)phenyl)benzo[d]oxazol-5-yl)(ethyl)phosphinate (**15**)*

The title compound was prepared from **12**, using a method analogous to the synthesis of **14a**. Purification with HPLC (acidic method) afforded **15** as a brown oil (19 mg, 12%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.44 – 8.37 (m, 2H), 8.18 (dd, J = 11.7, 1.4 Hz, 1H), 8.02 (dd, J = 8.3, 2.3 Hz, 1H), 7.89 (dd, J = 7.7, 1.7 Hz, 1H), 7.85 – 7.78 (m, 2H), 7.23 (t, J = 55.6 Hz, 1H), 3.54 (d, J = 10.9 Hz, 3H), 2.08 – 1.92 (m, 2H), 0.98 (dt, J = 18.9, 7.6 Hz, 3H). ^{13}C NMR (125.5 MHz, DMSO-d_6) δ 162.7, 152.7 (d, J = 3.8 Hz), 141.7 (d, J = 17.2 Hz), 135.3 (t, J = 22.8 Hz), 130.3, 129.9, 129.4 (d, J = 5.8 Hz), 129.1 (d, J = 11.3 Hz), 127.6, 126.6, 124.8 (t, J = 6.5 Hz), 123.6 (d, J = 11.3 Hz), 114.3 (t, J = 236.5 Hz), 111.8 (d, J = 13.5 Hz), 50.8 (d, J = 6.0 Hz), 21.2 (d, J = 101.3 Hz), 5.8 (d, J = 4.7 Hz). ^{31}P NMR {H} (162 MHz, DMSO-d_6) δ 46.8. ^{19}F NMR (376 MHz, DMSO-d_6) δ -110.6 (d, J = 55.9 Hz). LC-MS (254 nm, 100%) R_T 3.05 min, MS (ESI): mass calculated for $C_{17}H_{16}F_2NO_3P$, 352.1; *m/z* found 352.1 $[M + H]^+$. HRMS (ESI): *m/z* calculated for $C_{17}H_{16}F_2NO_3P + H^+$ $[M + H]^+$: 352.09086. Found: 352.09037.



*Methyl ethyl(2-(3-methoxyphenyl)benzo[d]oxazol-5-yl)phosphinate (**17**)*

3-methoxybenzoyl chloride (64.7 µl, 0.46 mmol) was added to a solution of **10** (90 mg, 0.42 mmol) in dioxane (4 mL) and stirred at RT for 1 h. $In(OTf)_3$ (23.51 mg, 0.04 mmol) was added and the reaction mixture was stirred at 100 °C overnight. The solvents were evaporated in vacuo, the residue was dissolved in CH_2Cl_2 and washed with 0.5 M aq. HCl, then sat. aq. $NaHCO_3$, dried over Na_2SO_4, and concentrated to give a yellow oil. The desired product was obtained after purification with HPLC (acidic method) as a white solid (36 mg, 26%). mp 102-3 ^{o}C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.15 (dd, J = 11.6, 1.3 Hz, 1H), 7.99 (dd, J = 8.4, 2.3 Hz, 1H), 7.86 – 7.76 (m, 2H), 7.75 – 7.66 (m, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.25 (dd, J = 8.2, 2.6 Hz, 1H), 3.89 (s, 3H), 3.53 (d, J = 10.9 Hz, 3H), 2.08 – 1.93 (m, 2H), 0.98 (dt, J = 18.9, 7.6 Hz, 3H). ^{13}C NMR (125.5 MHz, DMSO-d_6) δ 163.4, 159.7, 152.6, 141.7 (d, J = 16.6 Hz), 130.7, 128.9 (d, J = 10.9 Hz), 127.2, 126.9 (d, J = 120.8 Hz), 123.4 (d, J = 11.0 Hz), 119.9, 118.7, 112.1, 111.7 (d, J = 13.7 Hz), 55.5, 50.8 (d, J = 6.4 Hz), 21.2 (d, J = 101.7 Hz), 5.8 (d, J = 4.6 Hz). ^{31}P NMR {H} (162 MHz, DMSO-d_6) δ 46.8. LC-MS (215 nm, 100%) R_T 1.14 min, MS (ESI): mass calculated for $C_{17}H_{18}NO_4P$, 331.10; *m/z* found 331.95 $[M + H]^+$. HRMS (ESI): *m/z* calculated for $C_{17}H_{18}NO_4P + H^+$ $[M + H]^+$: 332.1046. Found: 332.1049.



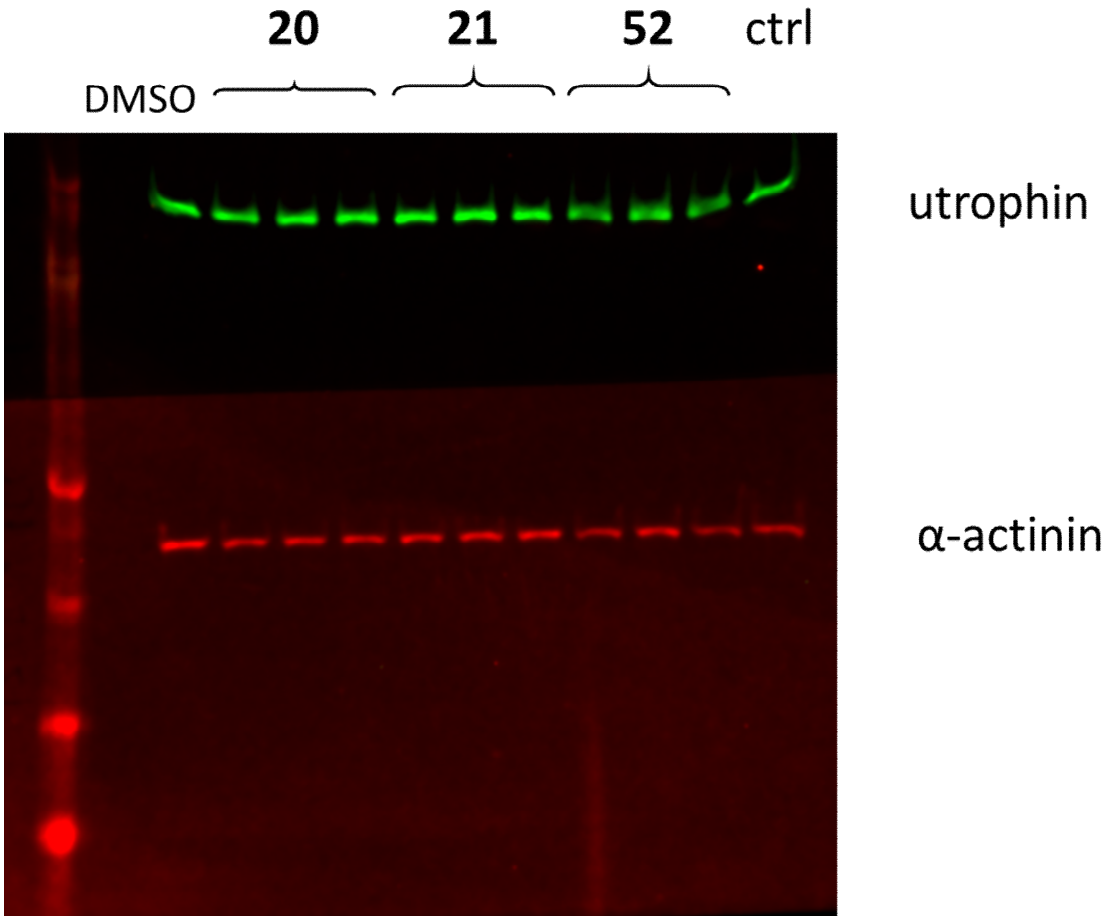
*Methyl (2-(2-(difluoromethoxy)phenyl)benzo[d]oxazol-5-yl)(ethyl)phosphinate (**18**)*

The title compound was prepared from **12** and 1-bromo-2-(difluoromethoxy)benzene with a similar method to general procedure 3, using $Pd(dppf)Cl_2$ as a catalyst and obtained as a brown gum (57 mg, 34%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.22 (dd, *J* = 7.8, 1.7 Hz, 1H), 8.18 (dd, *J* = 11.8, 1.5, 1H), 7.98 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.82 (ddd, *J* = 10.9, 8.3, 1.4 Hz, 1H), 7.74 (ddd, *J* = 8.3, 7.4, 1.8 Hz, 1H), 7.52 (td, *J* = 7.6, 1.1 Hz, 1H), 7.47 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.35 (t, *J* = 73.8 Hz, 1H), 3.52 (d, *J* = 11.0 Hz, 3H), 2.07 – 1.93 (m, 2H), 0.97 (dt, *J* = 18.9, 7.7 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) *δ* 161.0, 152.5 (d, *J* = 2.9 Hz), 149.0 (t, *J* = 3.4 Hz), 141.4 (d, *J* = 17.1 Hz), 133.8, 131.5, 129.1 (d, *J* = 11.2 Hz), 126.9 (d, *J* = 121.1 Hz), 126.3, 123.7 (d, *J* = 11.2 Hz), 121.3, 118.7, 116.0 (t, *J* = 259.3 Hz), 111.7 (d, *J* = 13.6 Hz), 50.8 (d, *J* = 6.6 Hz), 21.2 (d, *J* = 101.5 Hz), 5.8 (d, *J* = 4.7 Hz). ^{31}P NMR {H} (162 MHz, DMSO-d_6) *δ* 46.8. ^{19}F NMR (376 MHz, DMSO-d_6) *δ* -82.3 (d, *J* = 73.7 Hz). LC-MS (215 nm, 100%) R_T 1.11 min, MS (ESI): mass calculated for $C_{17}H_{16}F_2NO_4P$, 367.08; *m/z* found 367.95 $[M + H]^+$. HRMS (ESI): *m/z* calculated for $C_{17}H_{16}F_2NO_4P + H^+$ $[M + H]^+$: 368.08578. Found: 368.08634.

Biological evaluation

Utrophin quantification using Western blotting has previously been reported in detail.[1] OX01914 was used as positive control. An example of an uncropped blot is reported below.

Example of uncropped blot



H2K reporter gene assay

Cell culture: H2K-mdx utrnA-luc cells[2] were maintained in DMEM High glucose (Invitrogen) supplemented with 20% Fetal Bovine Serum Gold (PAA), 2% CEE (SLI), 2 mM l-Glutamine (Invitrogen), 1% Penicillin Streptomycin (Invitrogen) and 2 µg/500 mL Mouse Interferon-γ (Roche). Cells were maintained at 10% CO_2 at 33 °C. EC_{50} is the average from three or more biological replicates, 3 technical replicates each.

Utrophin firefly luciferase reporter gene assay: White flat bottomed 384 well plates (Corning) were seeded with 1500 H2K-mdx utrnA-luc cells. After 16 h at 10% CO_2 and 33 °C, the cells were dosed with compound in triplicate from 10 mM solution stocks in DMSO (final DMSO concentration was 0.1%). Compounds were diluted in the following concentration series: 0.0003 µM, 0.001 µM, 0.003 µM, 0.01 µM, 0.03 µM, 0.1 µM, 0.3 µM, 1 µM, 3 µM, 10 µM, 30 µM. The cells were incubated for a further 24 h, (10% CO_2, 33 °C). Relative luminescence readout after using the Luciferase Assay System (Promega, E1501) reagents was measured using an EnVision2103 plate reader (Perkin Elmer). The means from the biological triplicates were fitted with a four-parameter logistic function with least squares regression (Levenberg-Marquardt algorithm) to calculate EC_{50} values.

Firefly luciferase biochemical inhibition assay

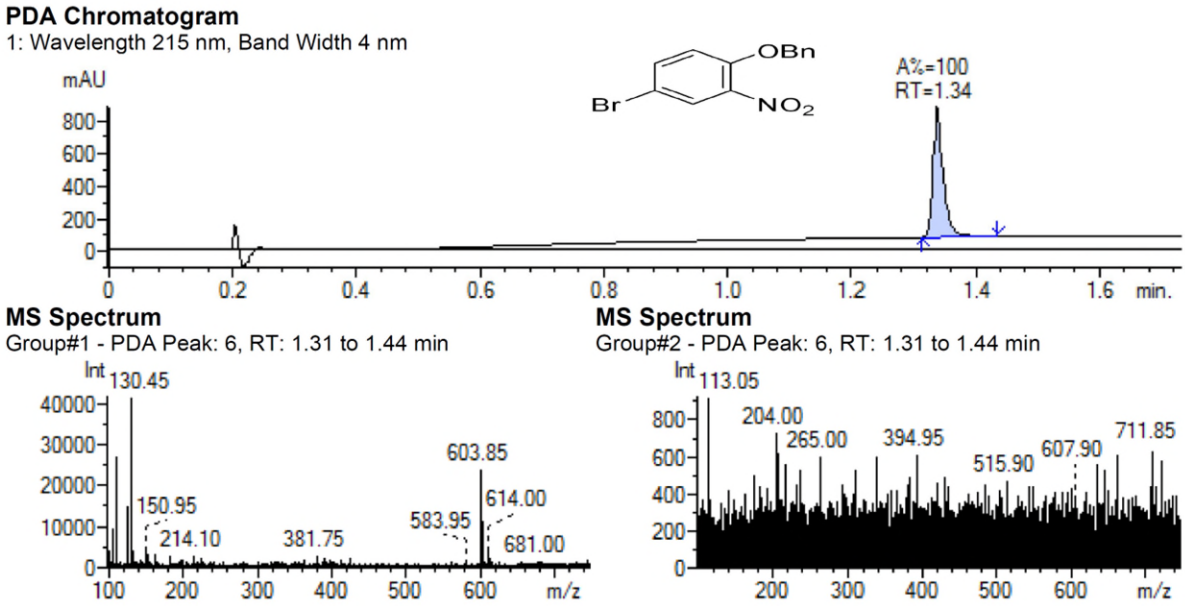
Recombinant firefly luciferase (QuantiLum Promega, E1701) was assayed at a final concentration of 0.6 nM in a buffer containing 25 mM HEPES, 5 mM $MgCl_2$, 1 mM EDTA, 5 mM DTT and 1 mg/mL BSA. Compounds were diluted in the following concentration series: 0.95 nM, 3 nM, 9.5 nM, 30 nM, 95 nM, 0.3 µM, 0.95 µM, 3 µM, 9.5 µM, 30 µM, from 10 mM stocks in DMSO (with a final assay concentration of DMSO at 0.3%). PTC124 was used as a positive control.[3] Luciferase substrates ATP (Sigma) and D-luciferin (Promega) were used in a final assay concentration of 10 µM, close to their K_M concentrations.[4] Luciferase was pre-incubated with ATP and the query compound at 0 °C for 15 min. D-Luciferin was dispensed and endpoint luminescence output immediately read using an EnSight plate reader (Perkin Elmer) FLUOstar Optima plate reader (BMG Labtech). Luminescence output was fitted with a four-parameter logistic function with least squares regression (Levenberg-Marquardt algorithm) to calculate IC_{50} values. IC_{50} is the average of three technical replicates.

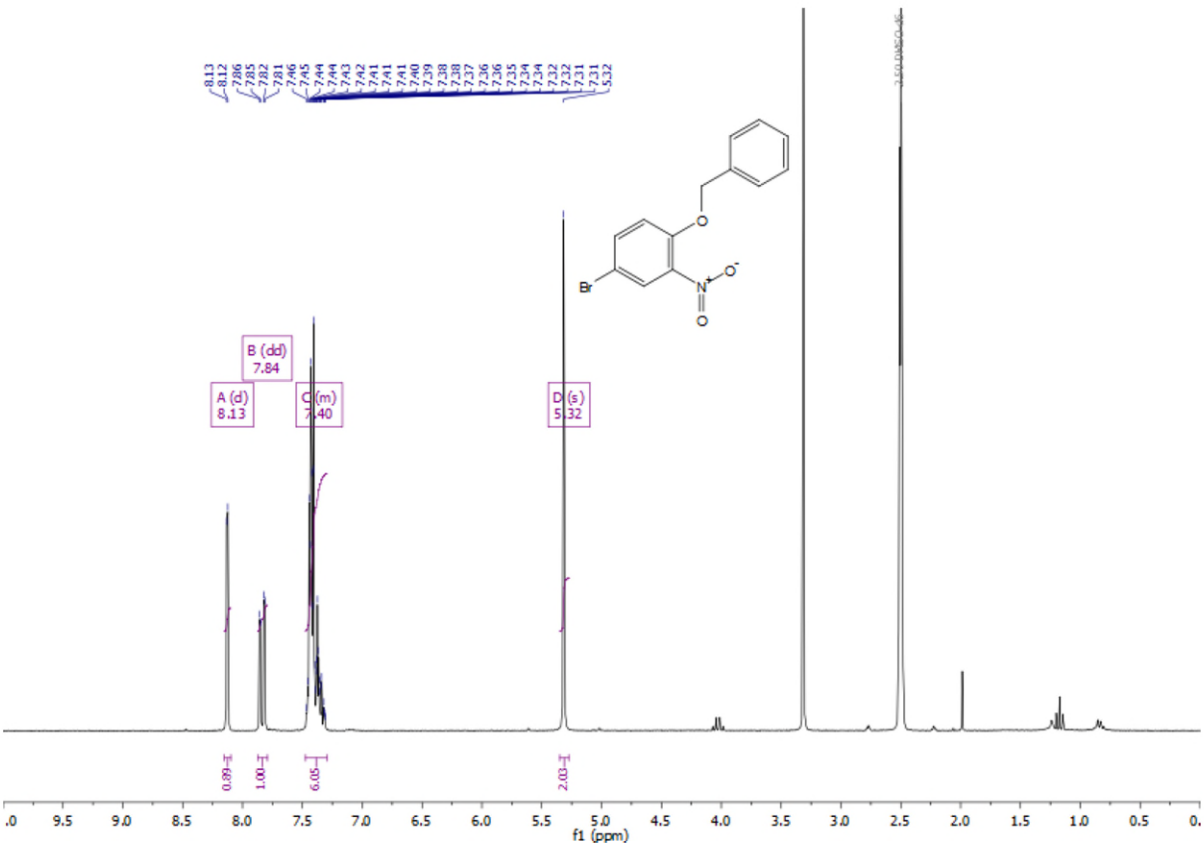
Cytotoxicity assay in HepG2 cells

Cell viability is based on ATP titration in intact cells using CellTiter-Glo® Reagent (provided by Promega) through the ATP–dependent oxydoreduction of luciferin by luciferase. Human hepatocarcinoma HepG2 cells (ATCC HB-8065) are plated at 2500 cells/well in 384-well plates (30µl/well). After 4 h of incubation at 37°C, compounds 100-fold concentrated are added to the cells. After an incubation of 40 h at 37°C, the medium is removed, and CellTiter-Glo® Reagent is added for luminescence reading. Compounds are tested in duplicate at ten concentrations (final top concentration of 30 µM, semi log dilution factor). Results are expressed as a percentage of inhibition of cell viability.

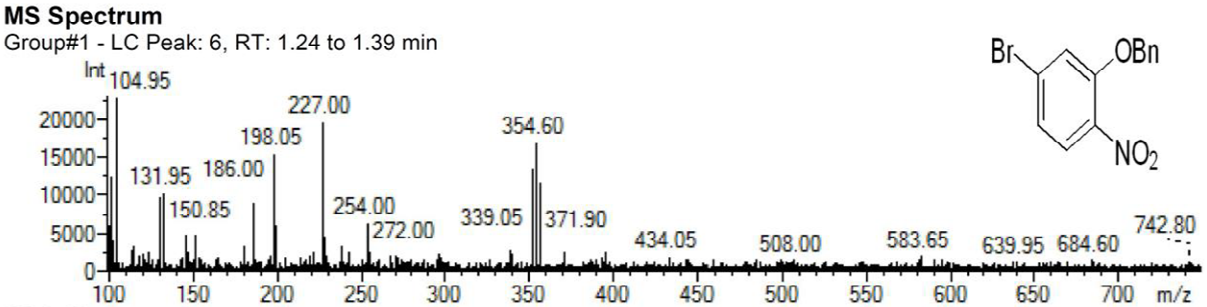
Characterization Data

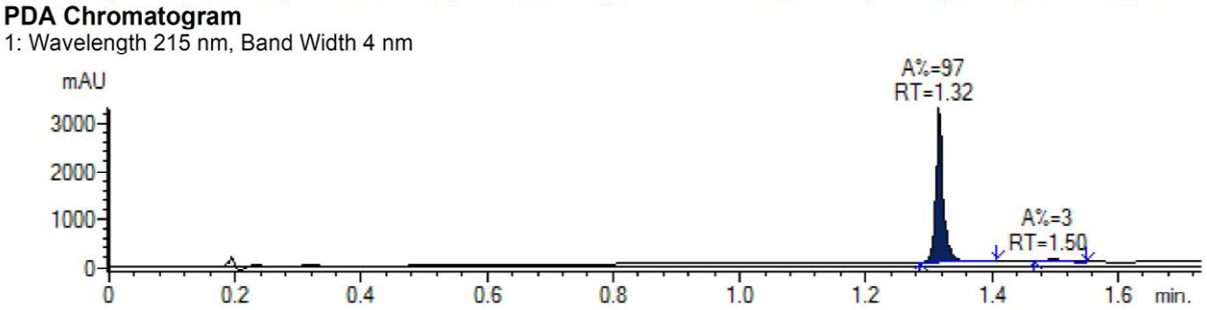
1-(benzyloxy)-4-bromo-2-nitrobenzene (4)

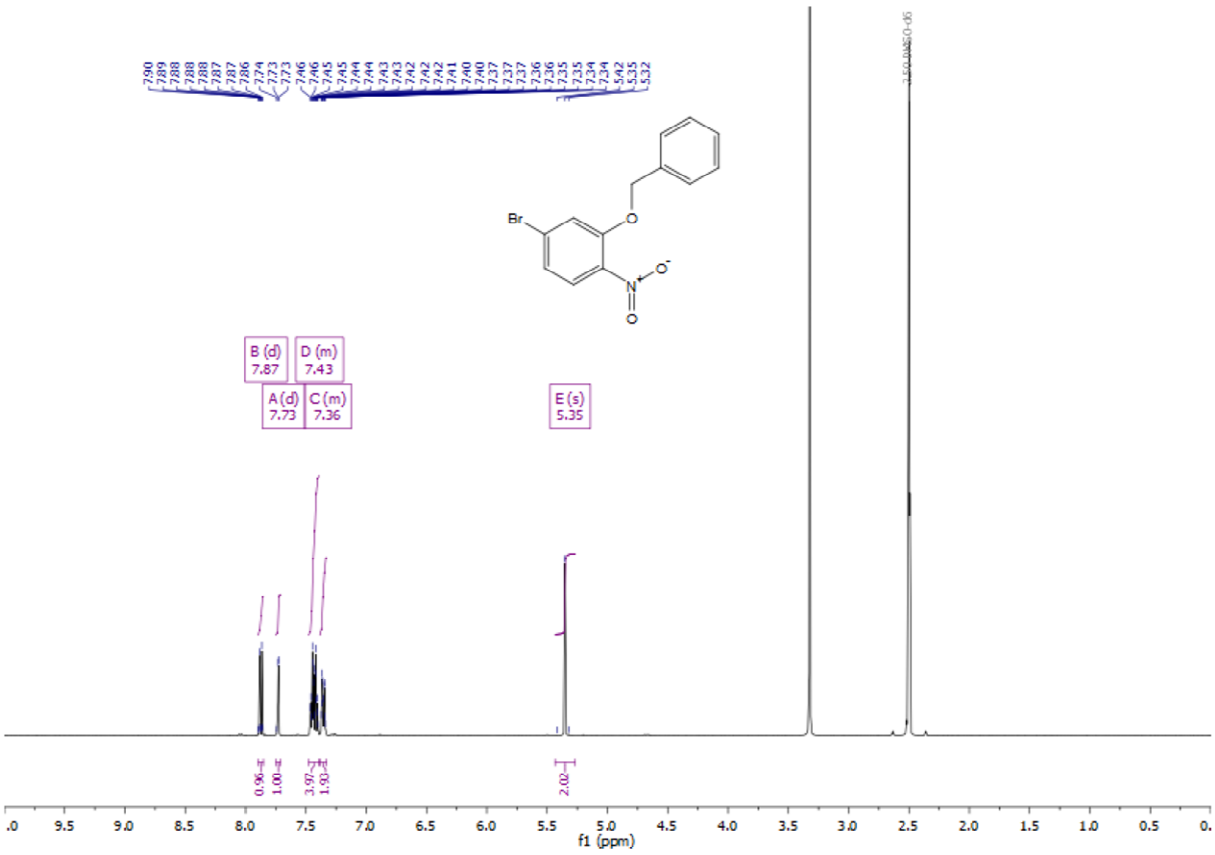




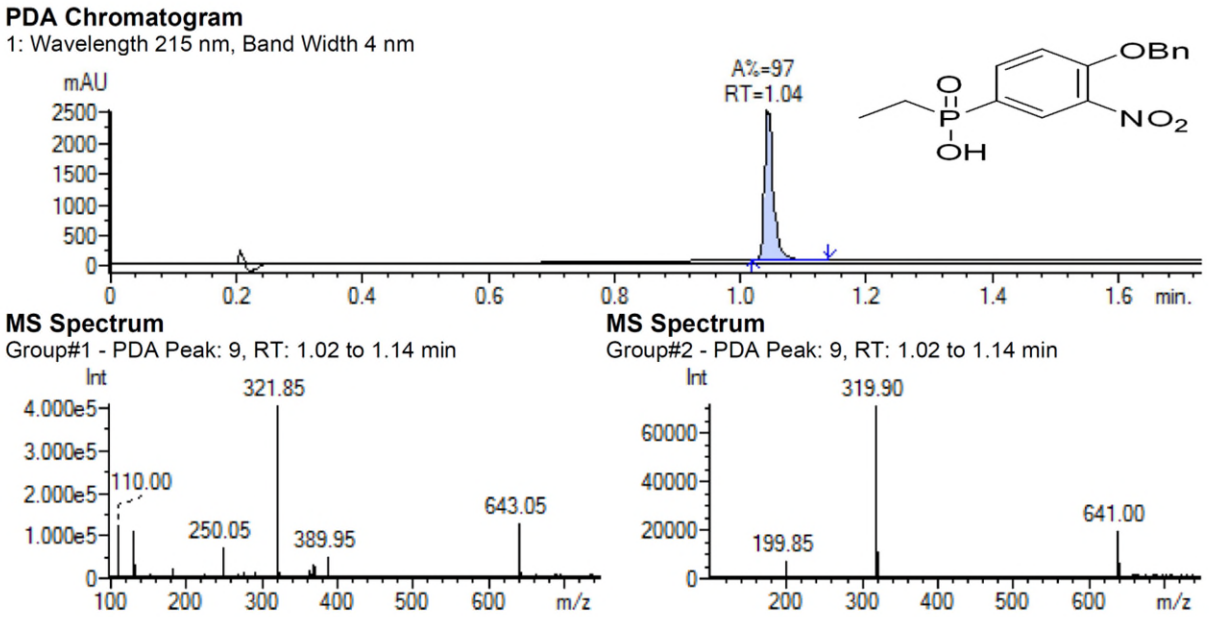
2-(benzyloxy)-4-bromo-1-nitrobenzene (5)

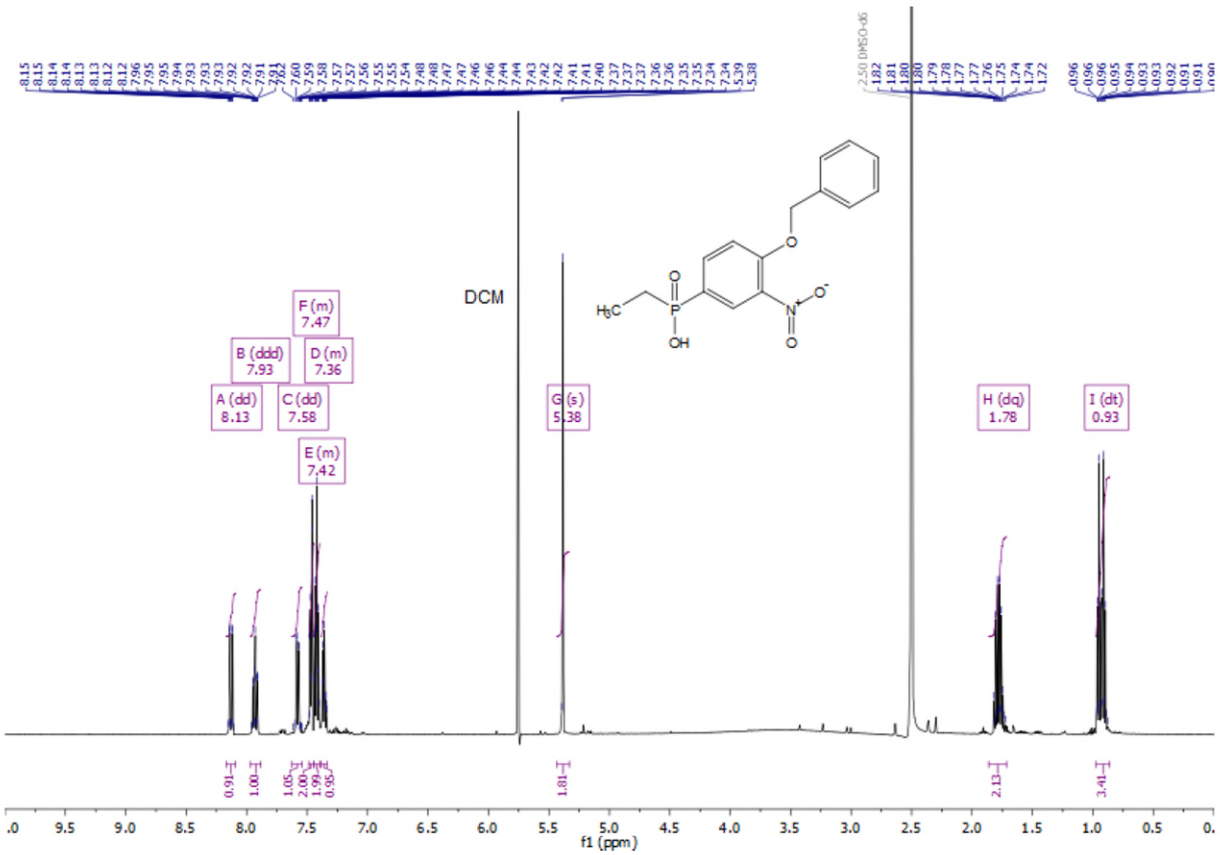




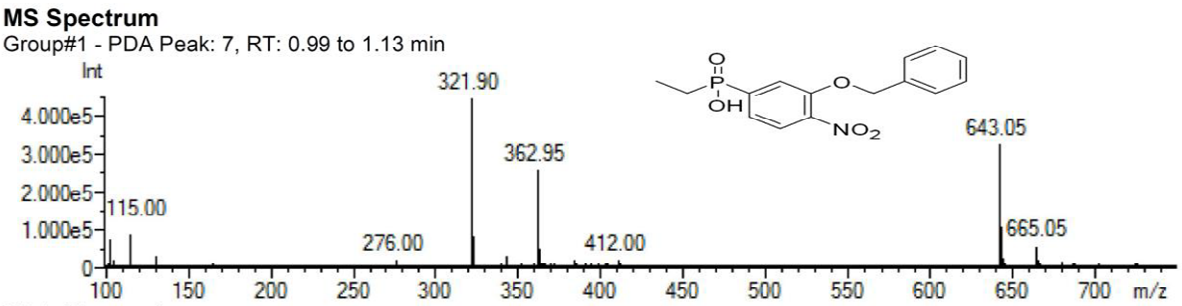


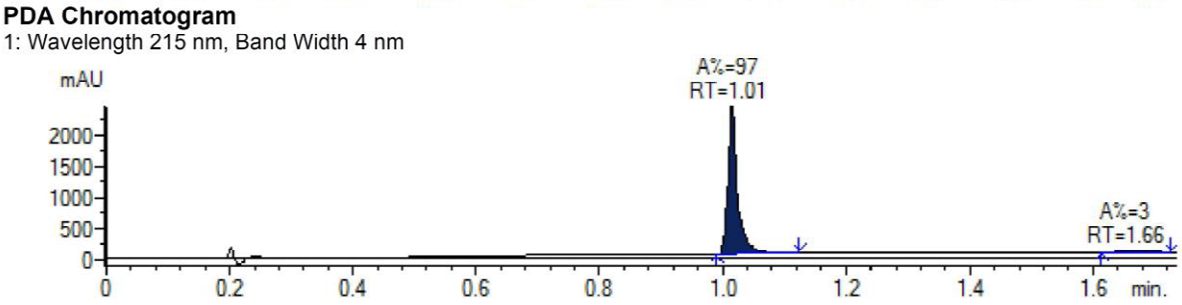
(4-(benzyloxy)-3-nitrophenyl)(ethyl)phosphinic acid (6)

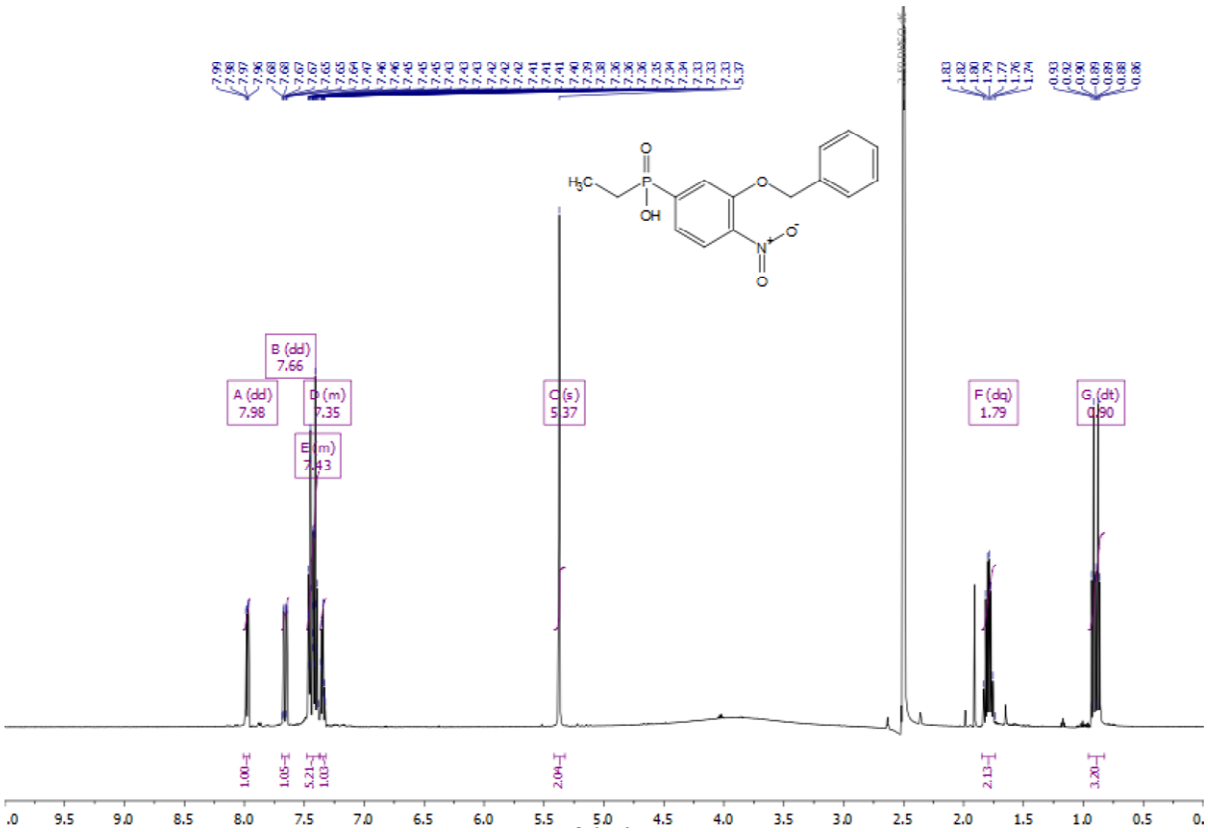




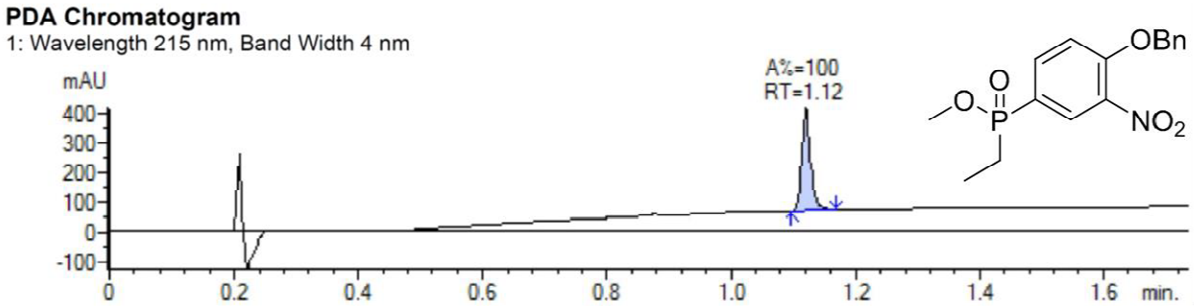
(3-(benzyloxy)-4-nitrophenyl)(ethyl)phosphinic acid (7)

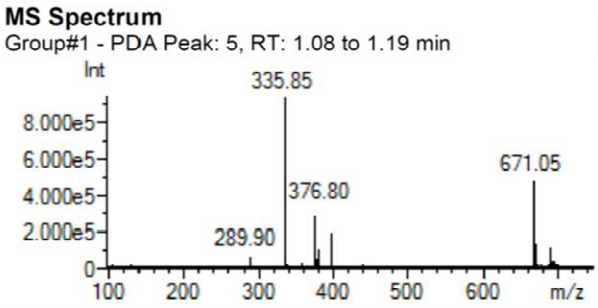


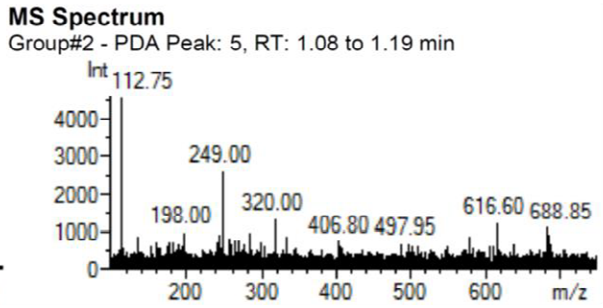


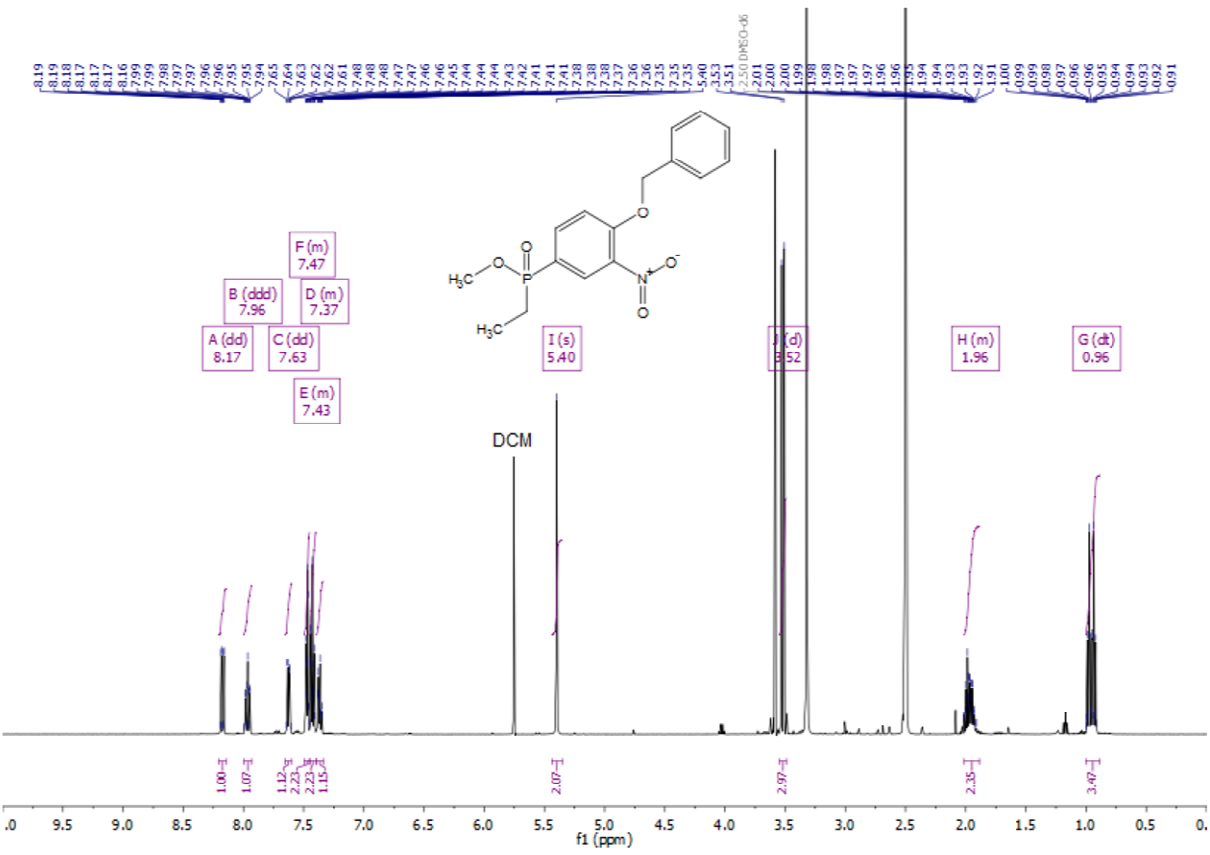


methyl (4-(benzyloxy)-3-nitrophenyl)(ethyl)phosphinate (8)

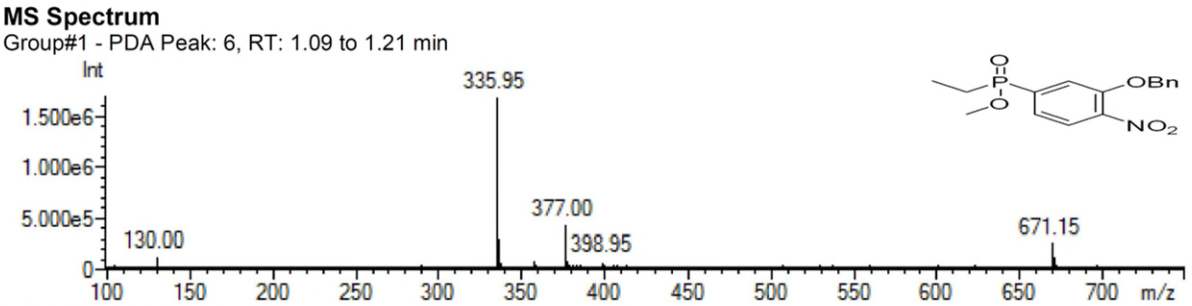


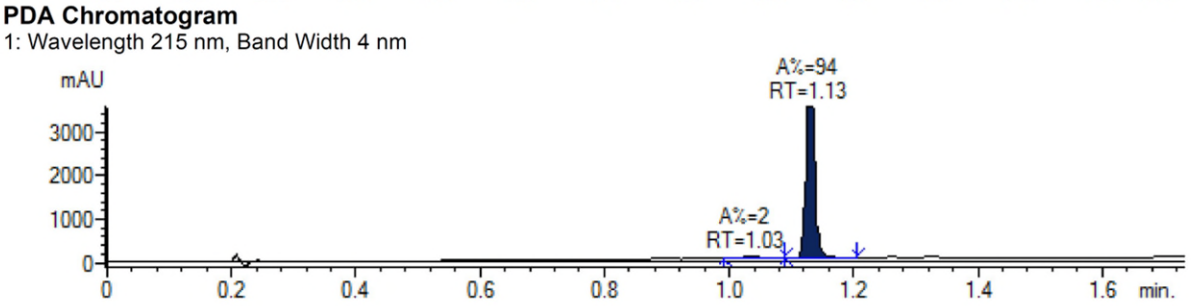


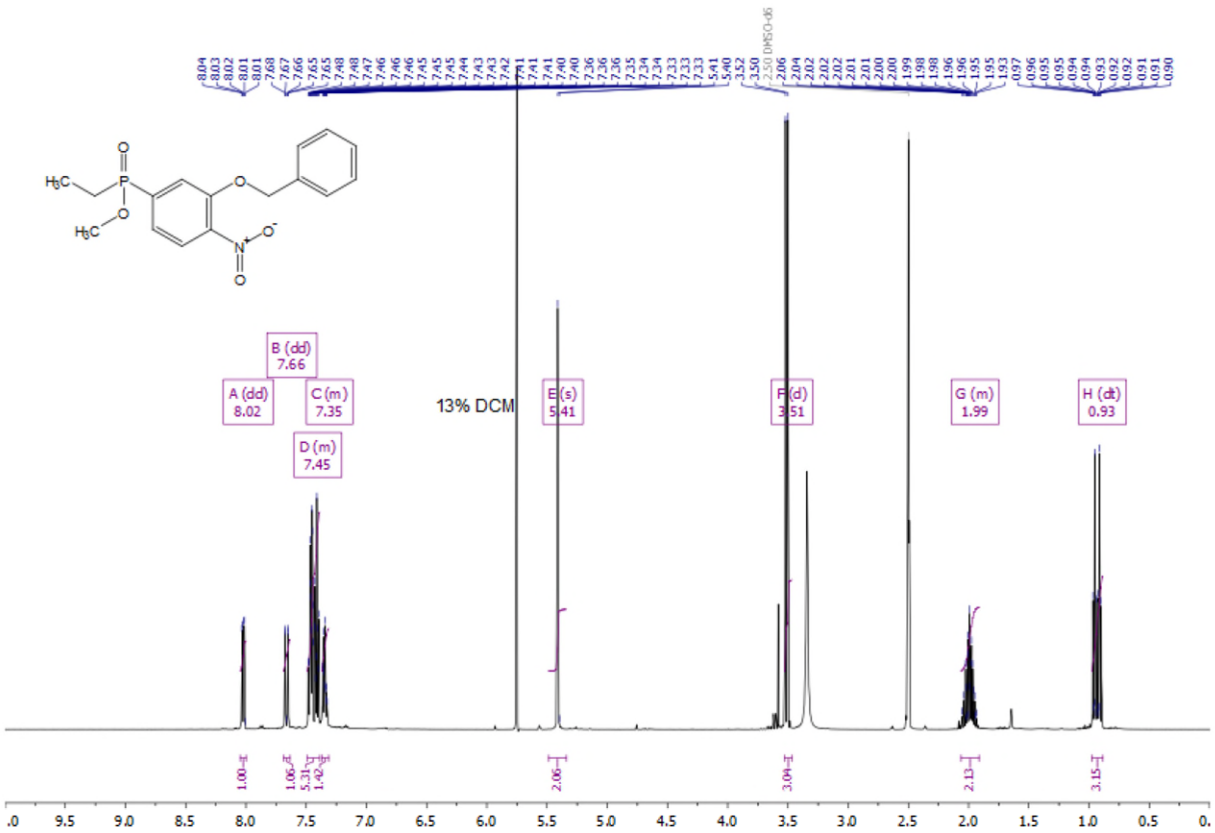




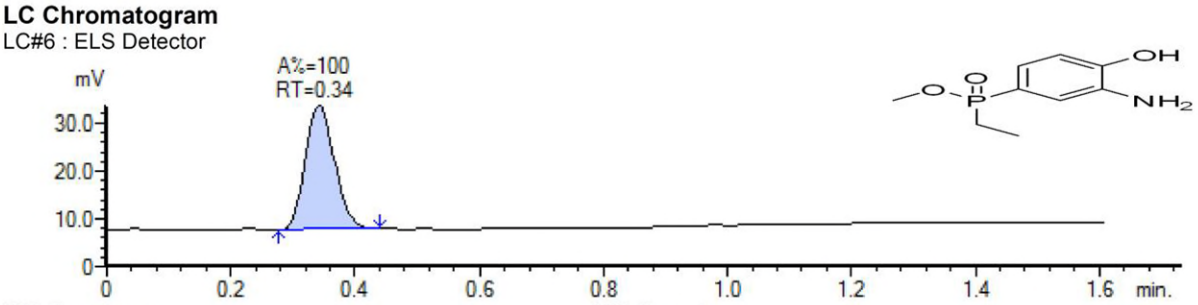
methyl (3-(benzyloxy)-4-nitrophenyl)(ethyl)phosphinate (9)

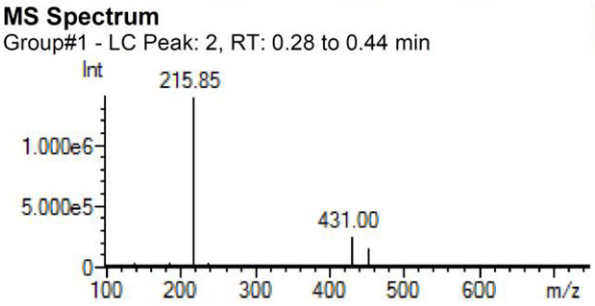


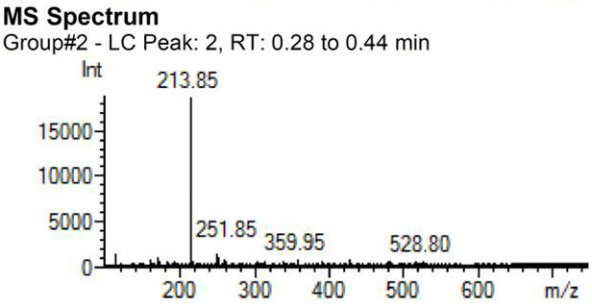


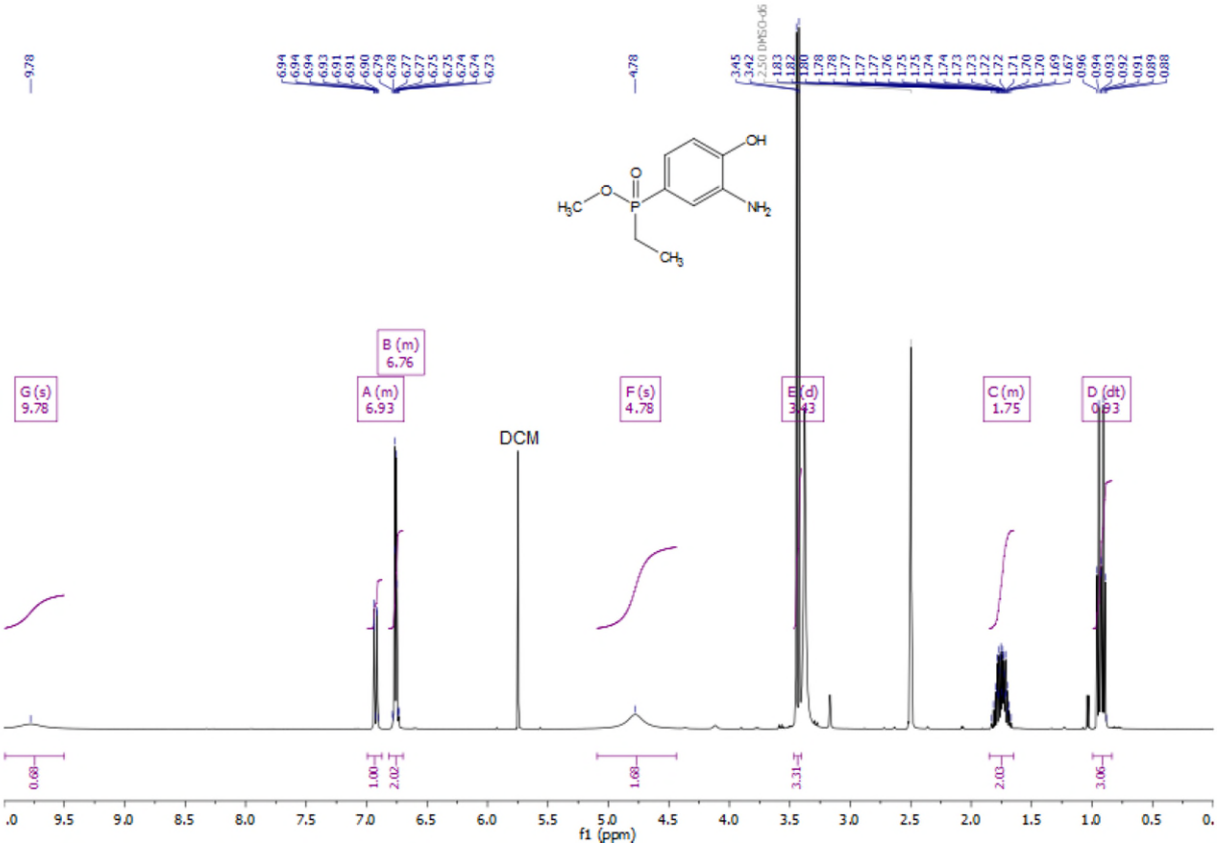


methyl (3-amino-4-hydroxyphenyl)(ethyl)phosphinate (10)

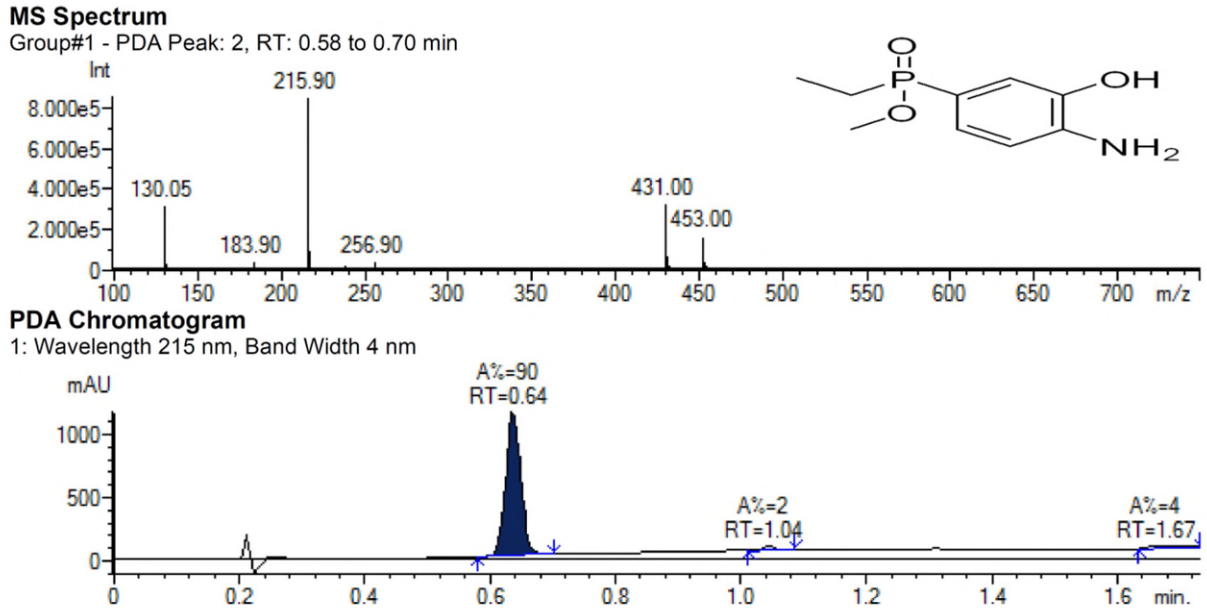


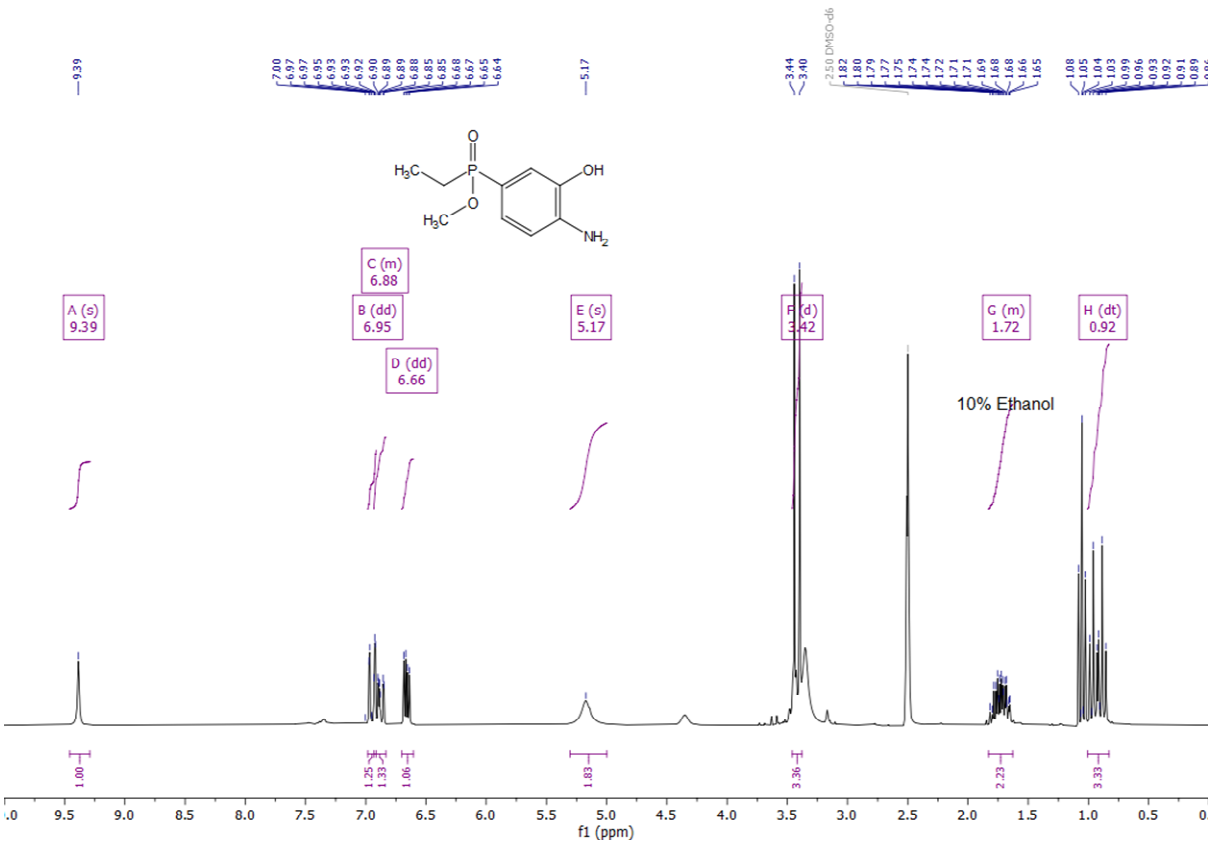




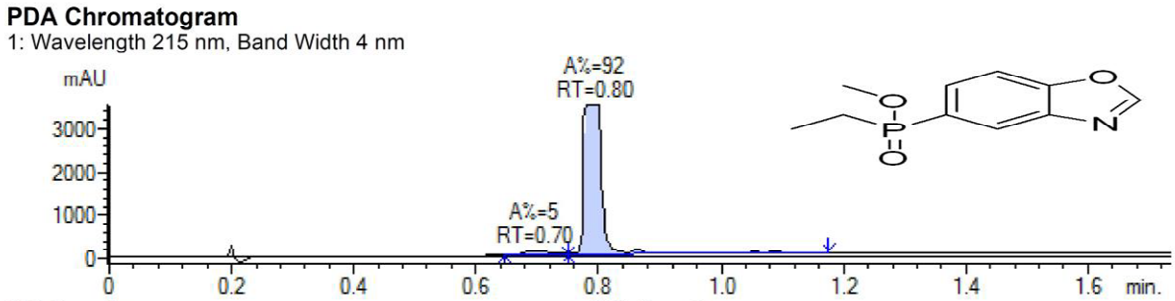


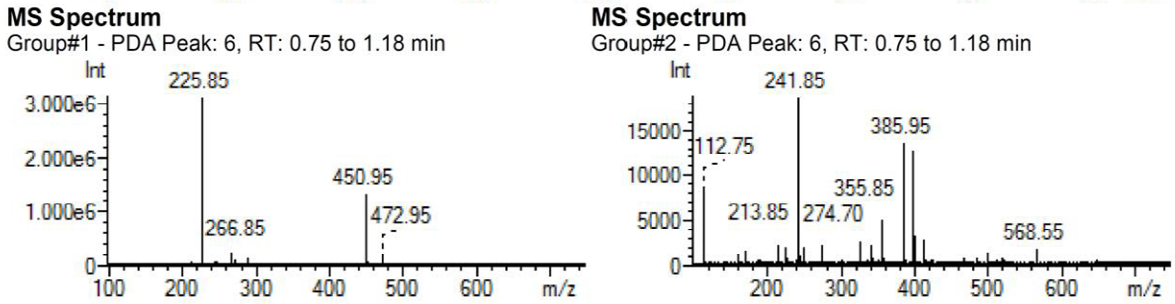
methyl (4-amino-3-hydroxyphenyl)(ethyl)phosphinate (11)

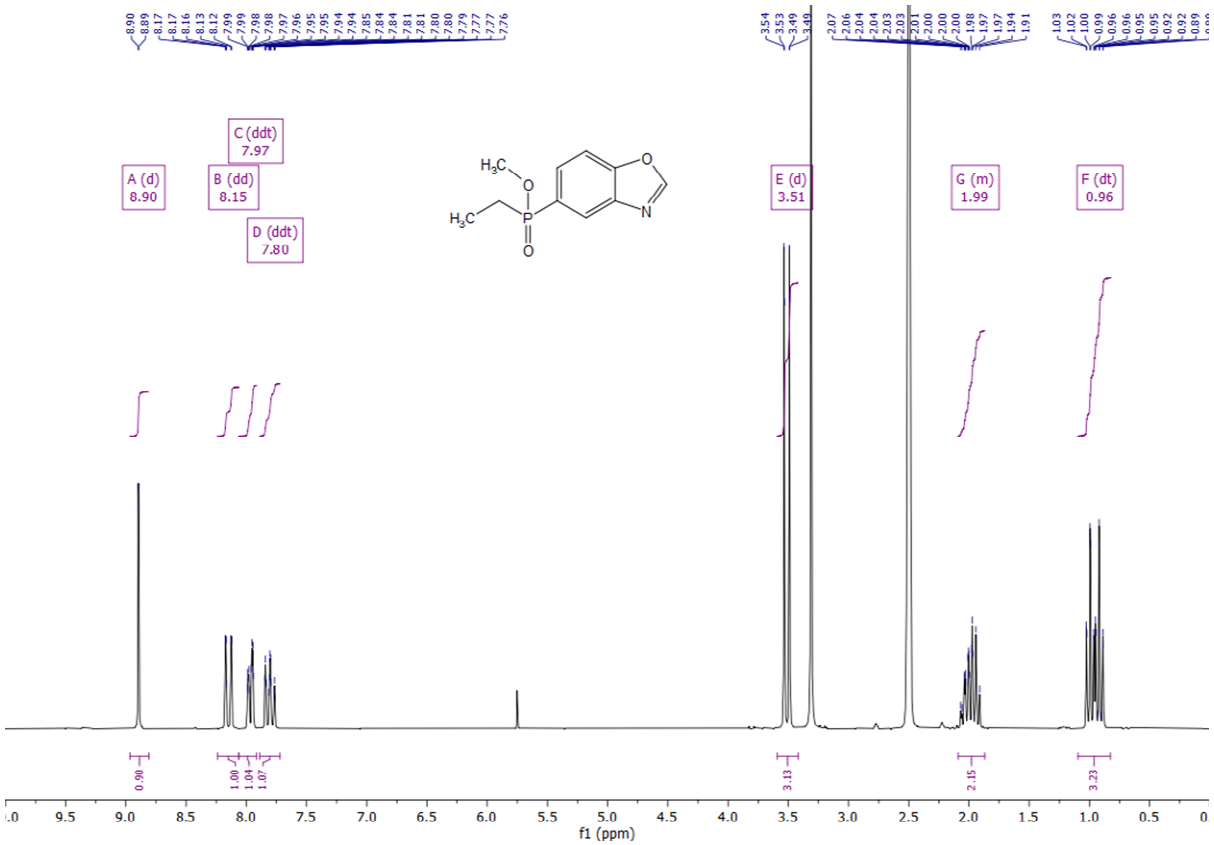




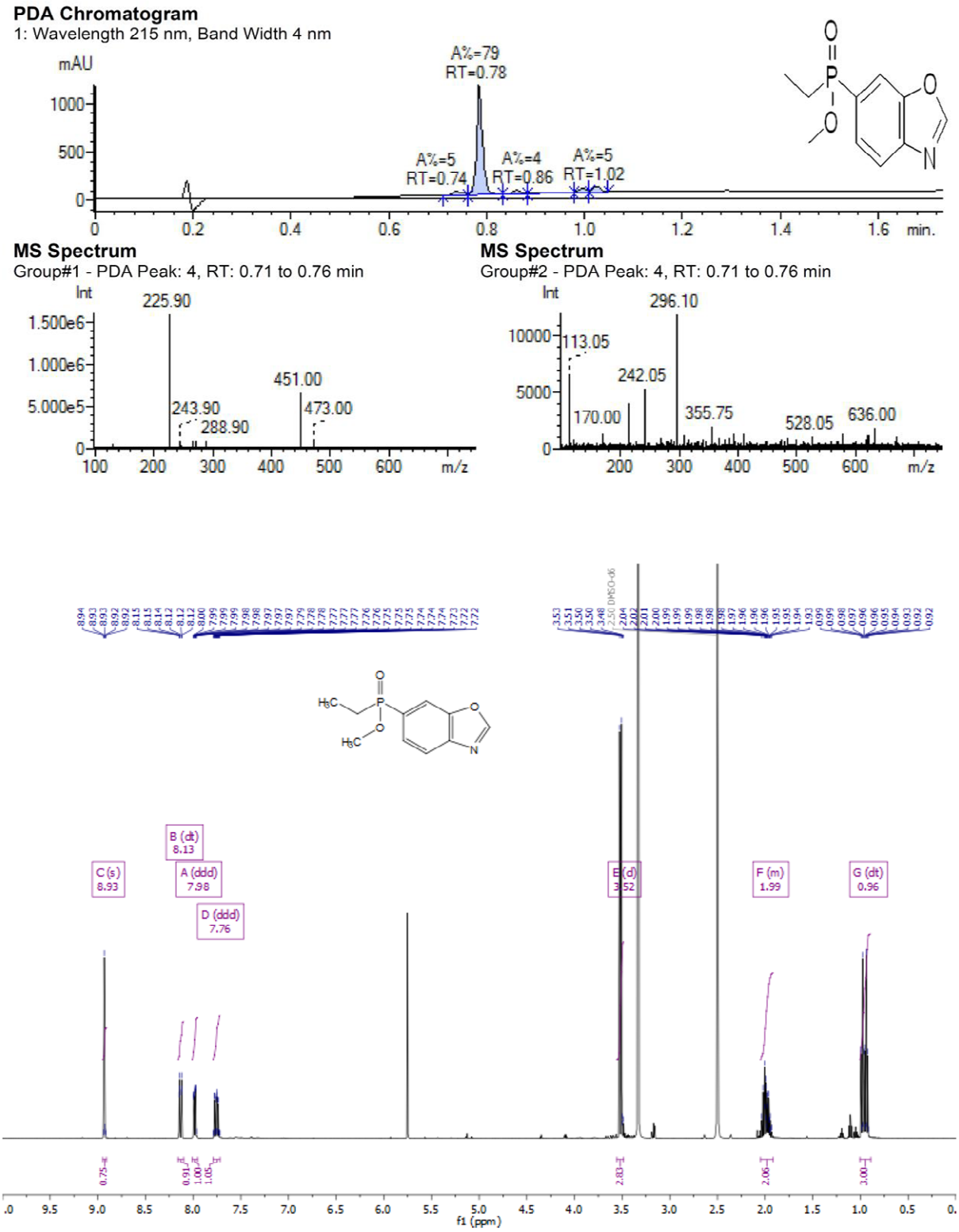
methyl benzo[d]oxazol-5-yl(ethyl)phosphinate (12)



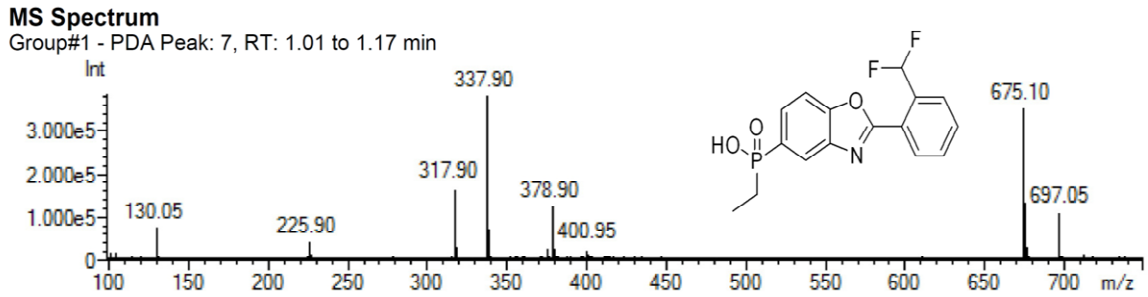


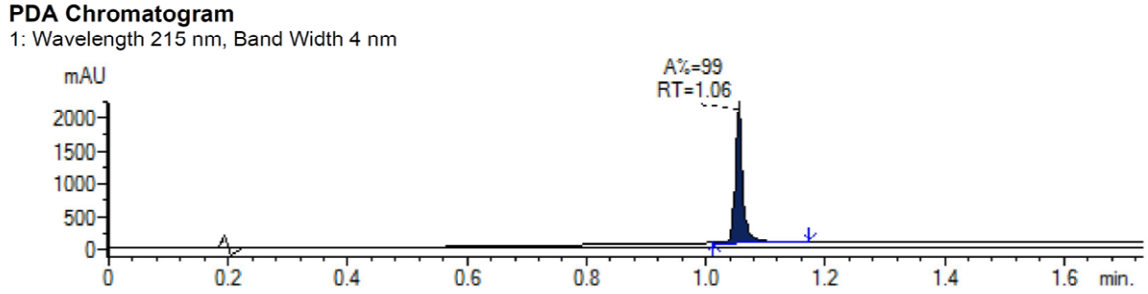


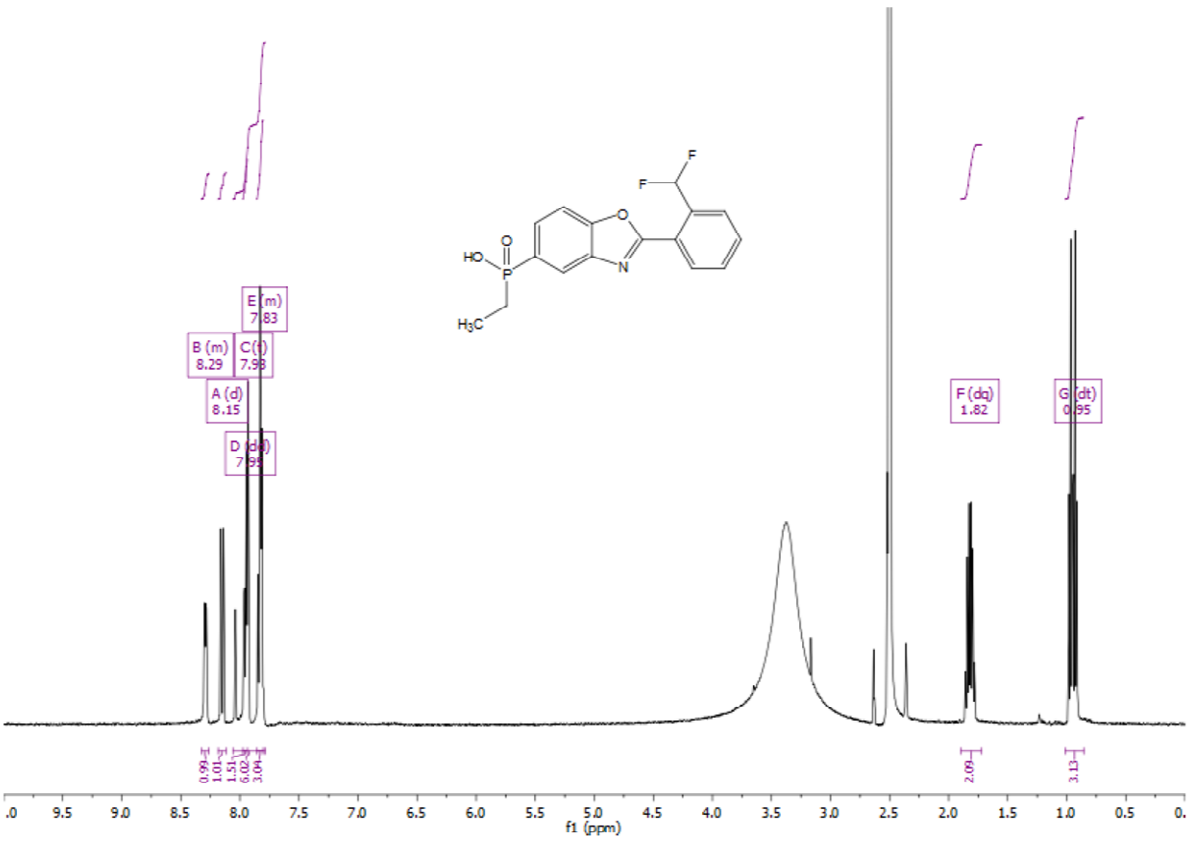
methyl benzo[*d*]oxazol-6-yl(ethyl)phosphinate (13)



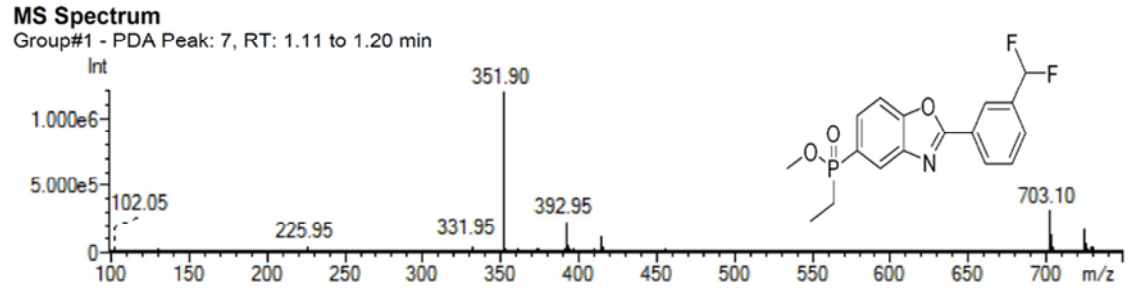
(2-(2-(difluoromethyl)phenyl)benzo[d]oxazol-5-yl)(ethyl)phosphinic acid (14a)

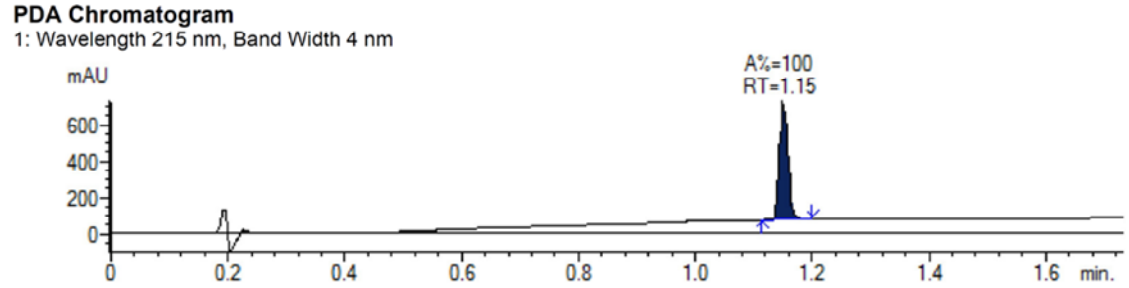


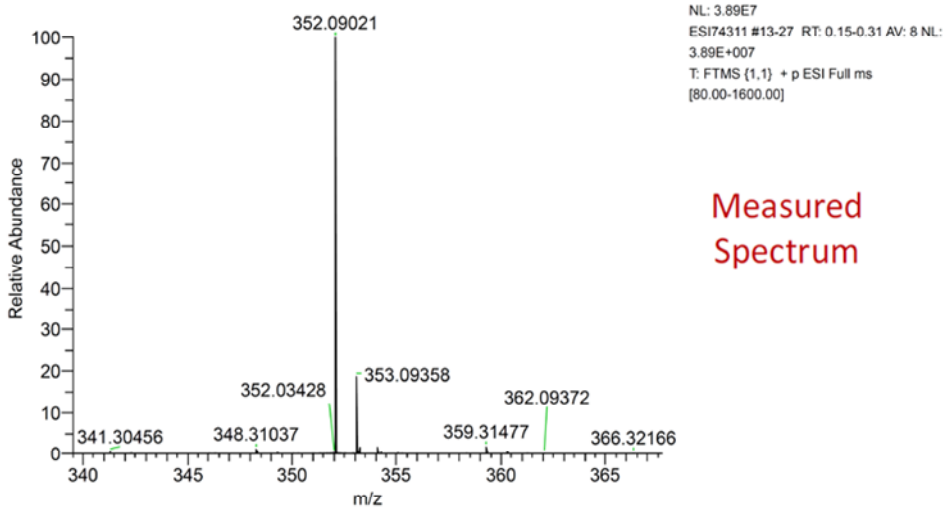


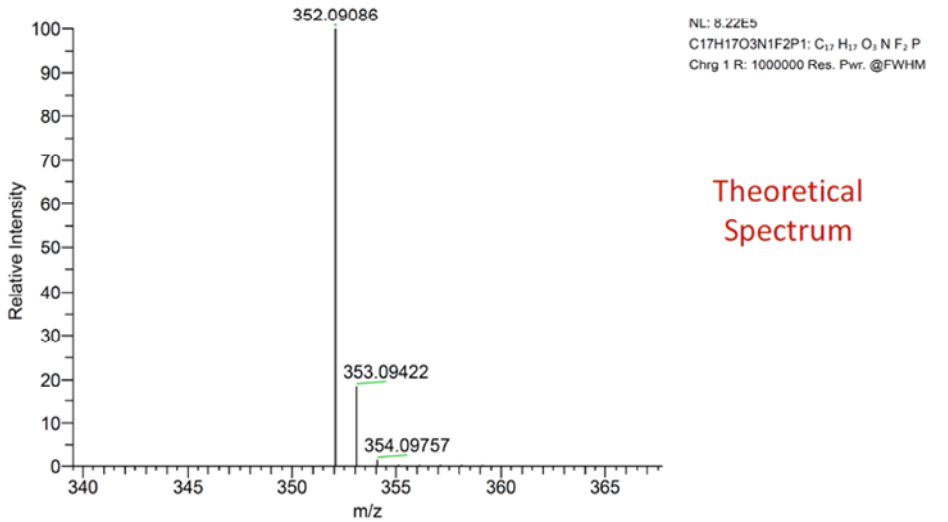


methyl (2-(2-(difluoromethyl)phenyl)benzo[*d*]oxazol-5-yl)(ethyl)phosphinate (14)

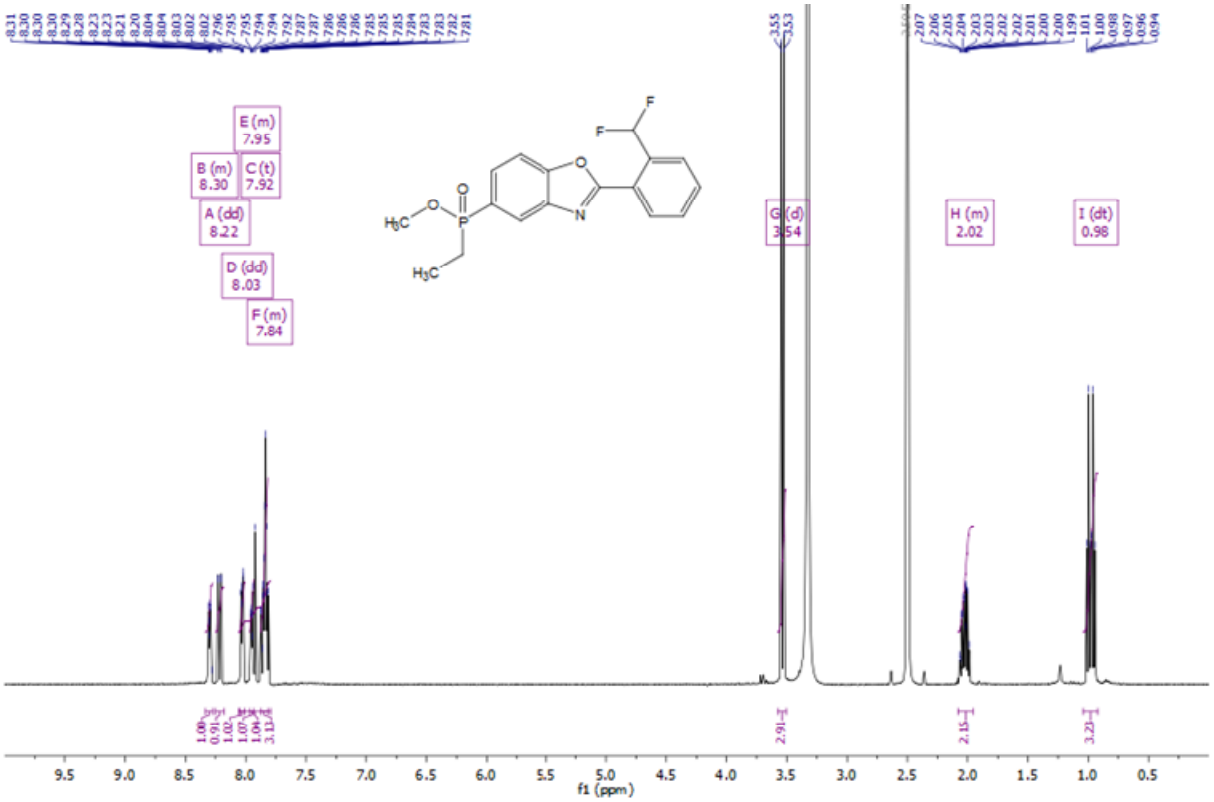


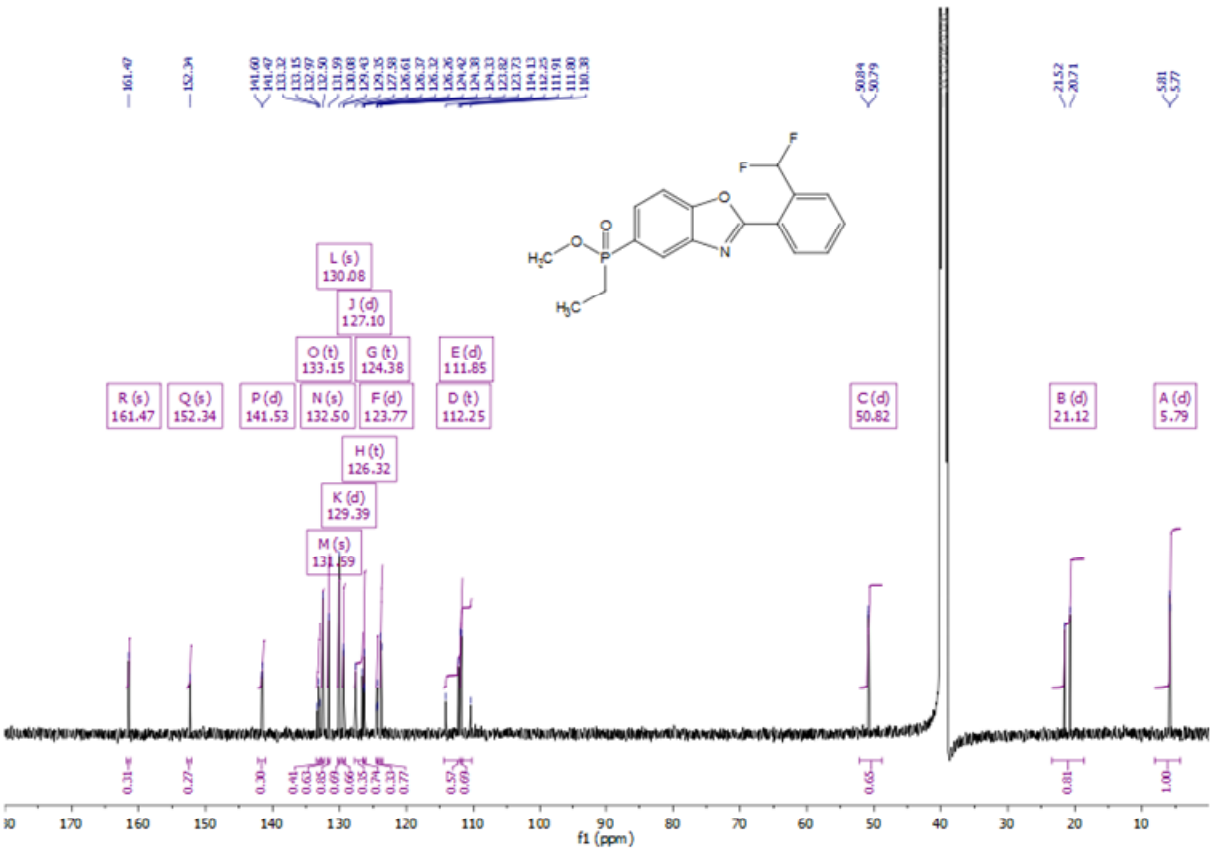




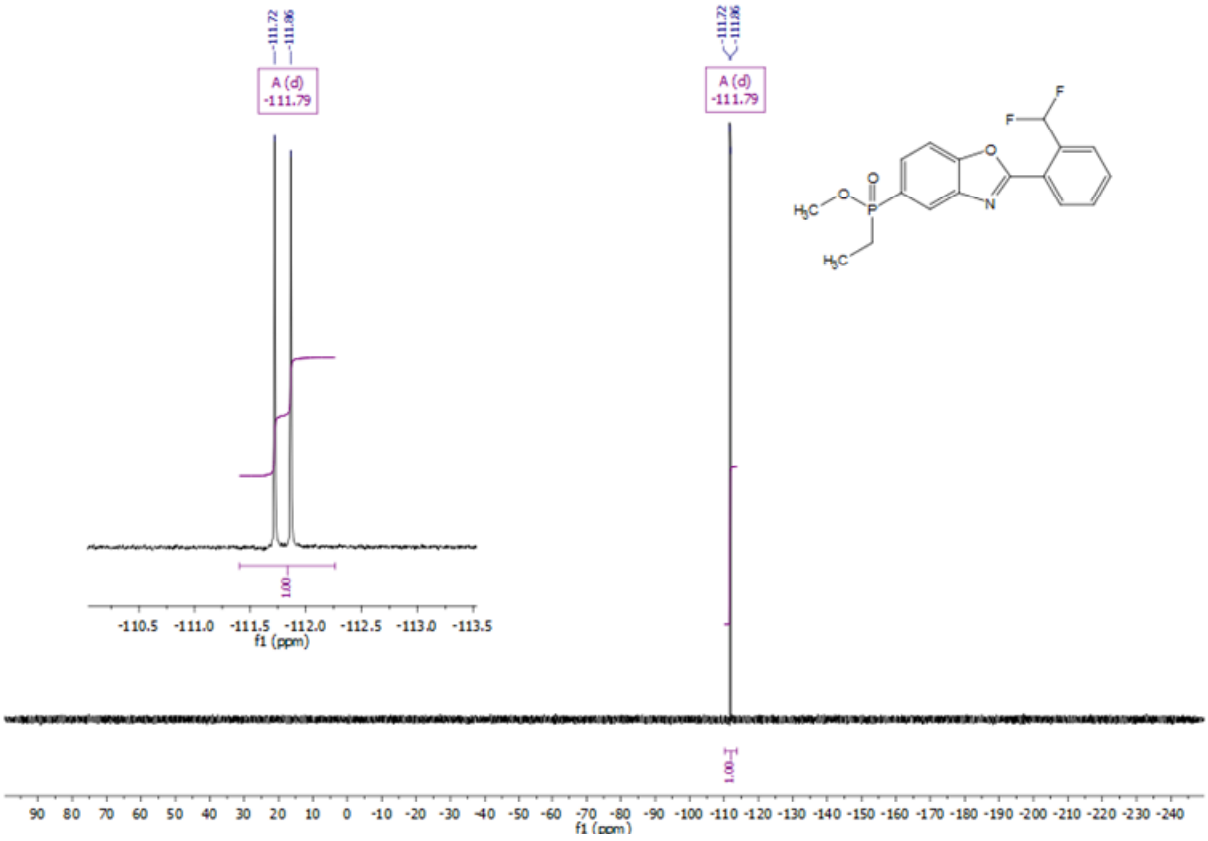


m/z	Formula	RDB	Delta ppm	Theo. Mass
352.09021	$C_{17}H_{17}O_3NF_2P$	9.5	-1.85	352.09086

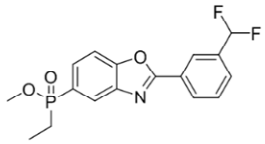

E (m)
7.95
B (m)
8.30
C (t)
7.92
A (dd)
8.22
D (dd)
8.03
F (m)
7.84
G (d)
3.54
H (m)
2.02
I (dt)
0.98
f1 (ppm)

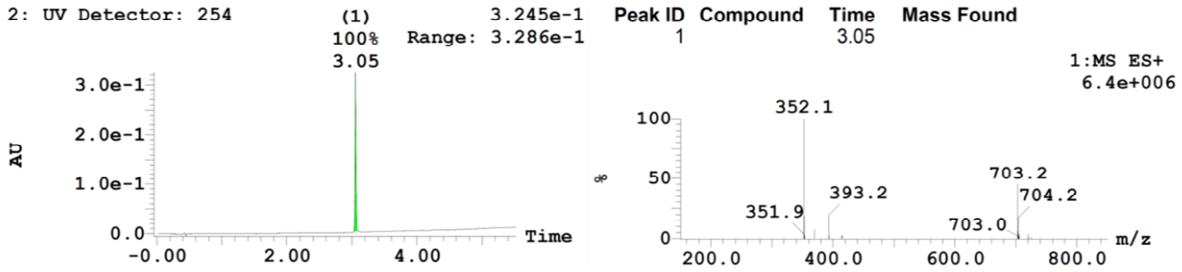

L (s)
130.08
J (d)
127.10
O (t)
133.15
G (t)
124.38
E (d)
111.85
R (s)
161.47
Q (s)
152.34
P (d)
141.53
N (s)
132.50
F (d)
123.77
D (t)
112.25
H (t)
126.32
K (d)
129.39
M (s)
131.59
C (d)
50.82
B (d)
21.12
A (d)
5.79
f1 (ppm)

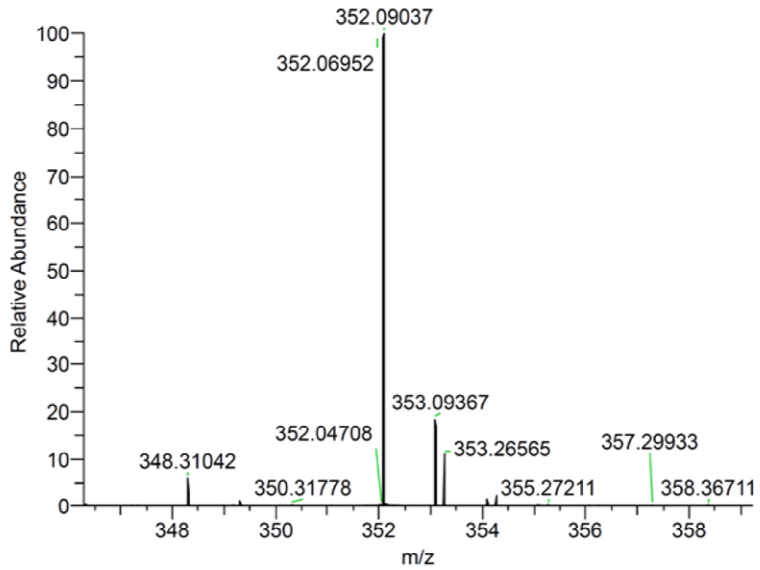

46.74
A (s)
46.74
F
F
O
N
O
P
O
H3C
H3C
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)


-111.72
-111.86
A (d)
-111.79
1.00
-110.5 -111.0 -111.5 -112.0 -112.5 -113.0 -113.5
f1 (ppm)
-111.72
-111.86
A (d)
-111.79
F
F
O
N
O
P
O
H3C
H3C
1.00
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

methyl (2-(3-(difluoromethyl)phenyl)benzo[d]oxazol-5-yl)(ethyl)phosphinate (15)

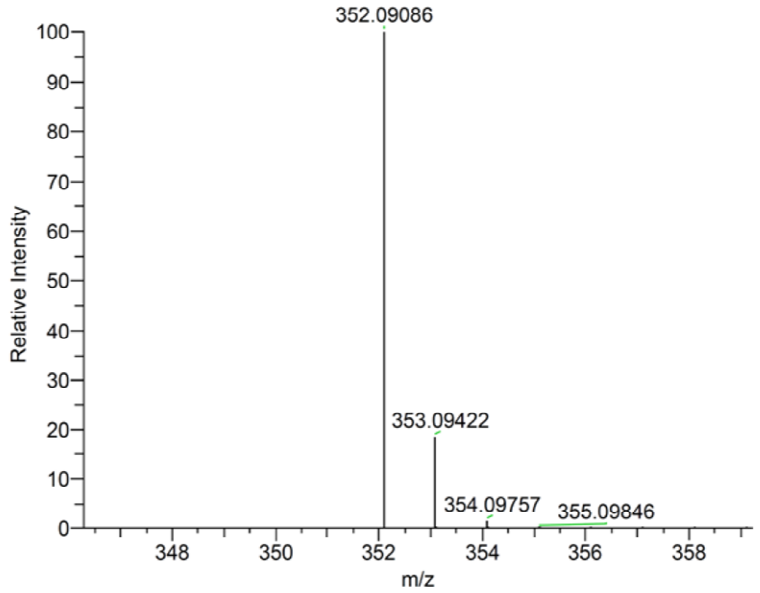






NL: 1.23E7
ESI74312 #13-27 RT: 0.15-0.31 AV: 8 NL: 1.23E+007
T: FTMS {1,1} + p ESI Full ms [80.00-1600.00]

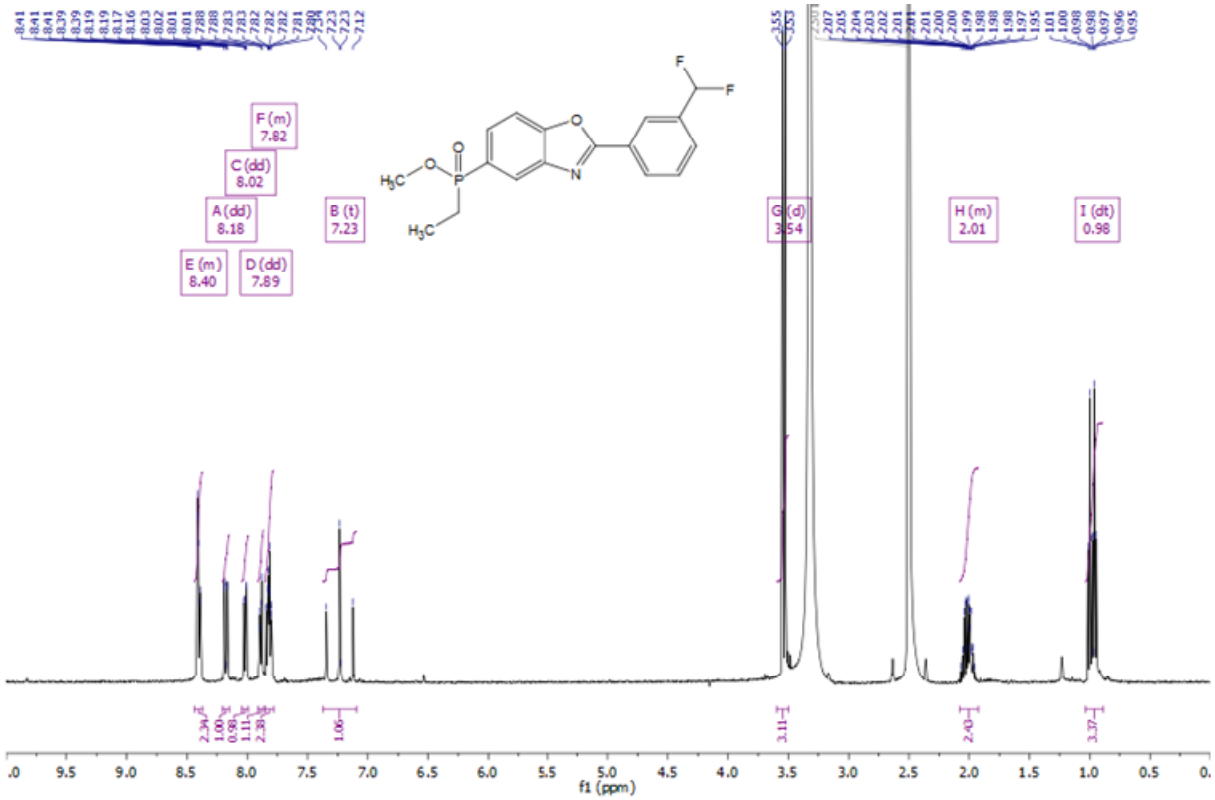
Measured Spectrum

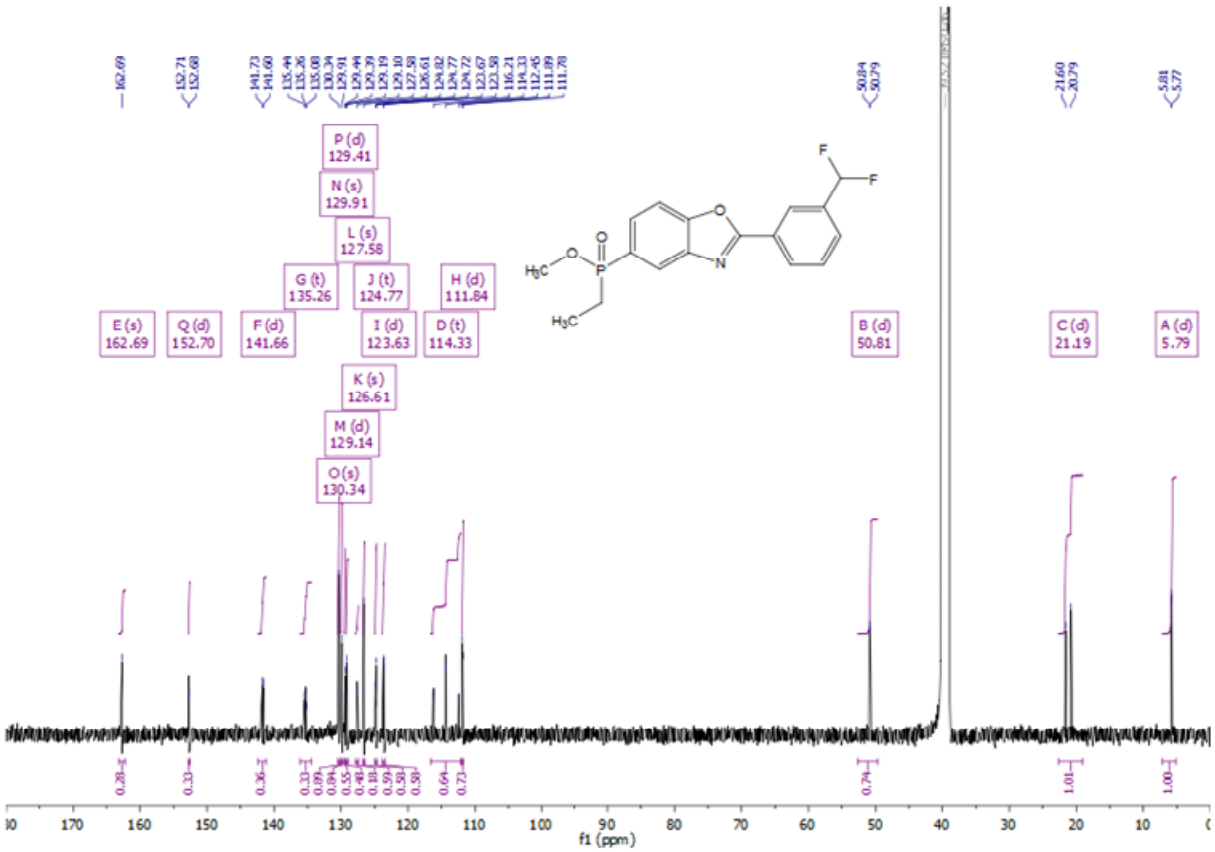


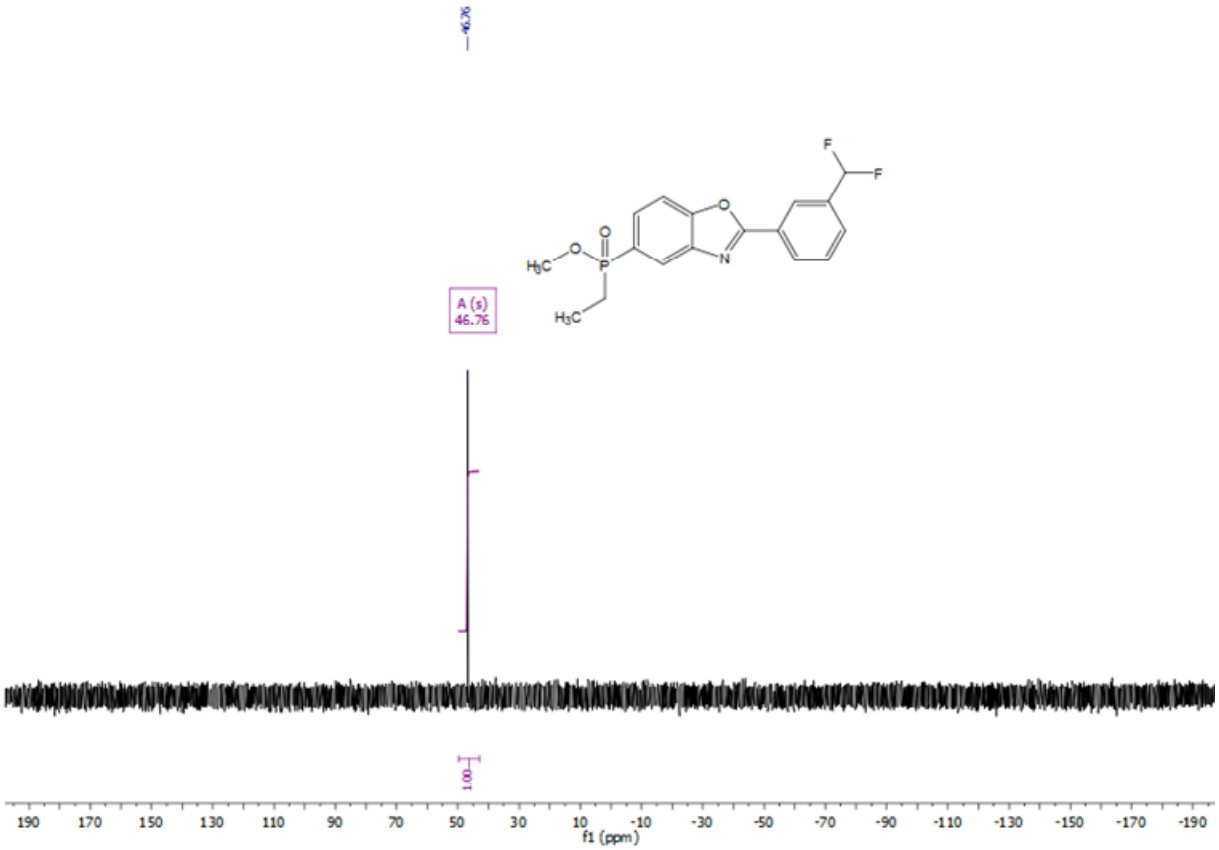
NL: 8.22E5
C17H17O3N1F2P1: $C_{17}H_{17}O_3NF_2P$
Chrg 1 R: 1000000 Res. Pwr. @FWHM

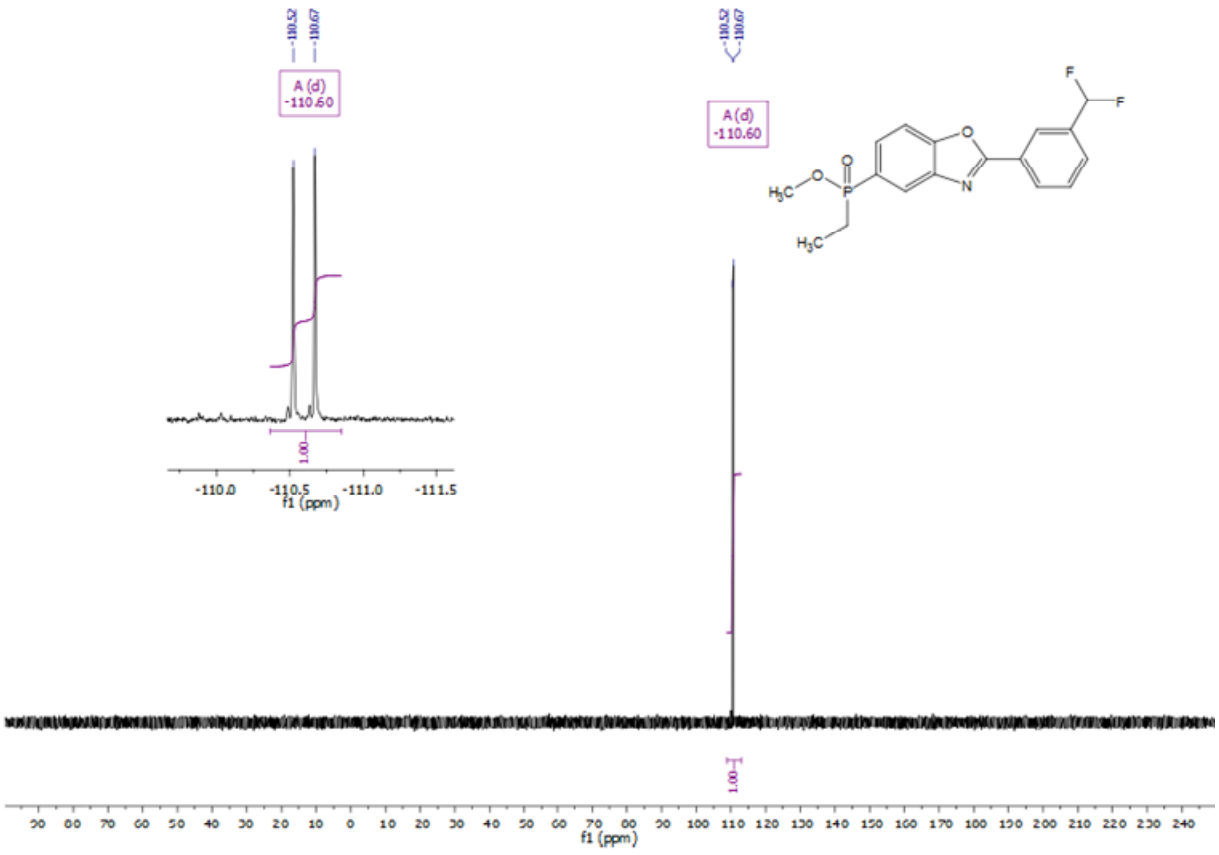
Theoretical Spectrum

m/z	Formula	RDB	Delta ppm	Theo. Mass
352.09036	$C_{17}H_{17}O_4NF_2P$	9.5	-1.42	352.09086

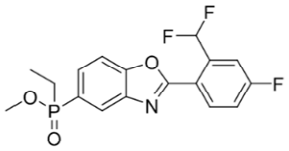

F (m)
7.82
C (dd)
8.02
A (dd)
8.18
E (m)
8.40
D (dd)
7.89
B (t)
7.23
G (d)
3.54
H (m)
2.01
I (dt)
0.98
f1 (ppm)

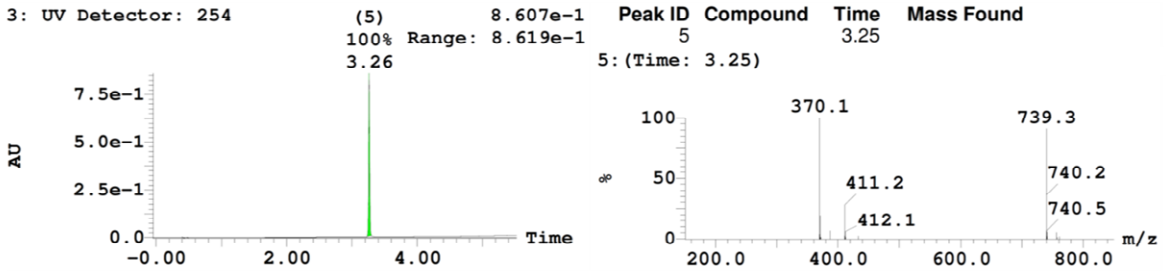

P (d)
129.41
N (s)
129.91
L (s)
127.58
G (t)
135.26
J (t)
124.77
H (d)
111.84
E (s)
162.69
Q (d)
152.70
F (d)
141.66
I (d)
123.63
D (t)
114.33
K (s)
126.61
M (d)
129.14
O (s)
130.34
B (d)
50.81
C (d)
21.19
A (d)
5.79
f1 (ppm)

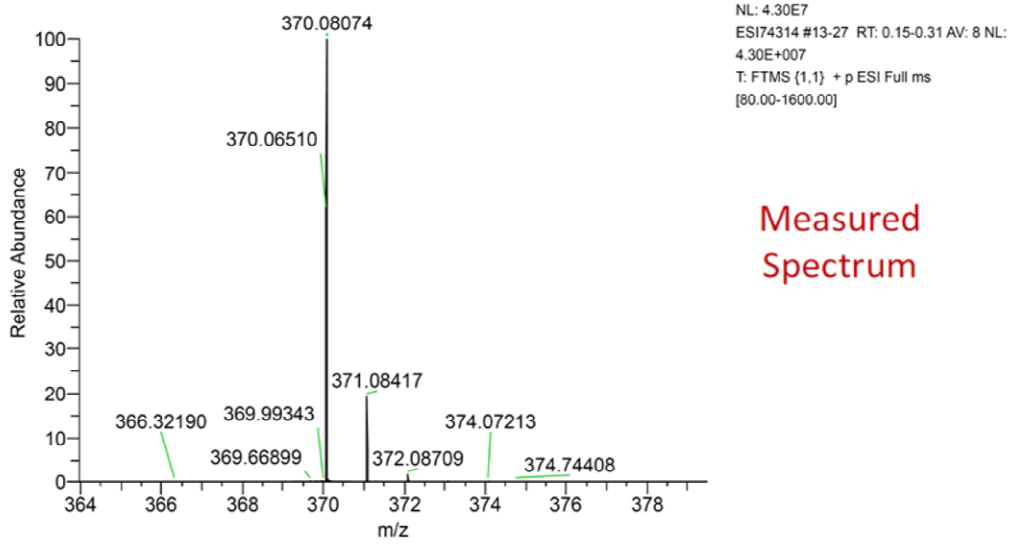

46.76
A (s)
46.76
F
F
O
O
N
P
O
H3C
H3C
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

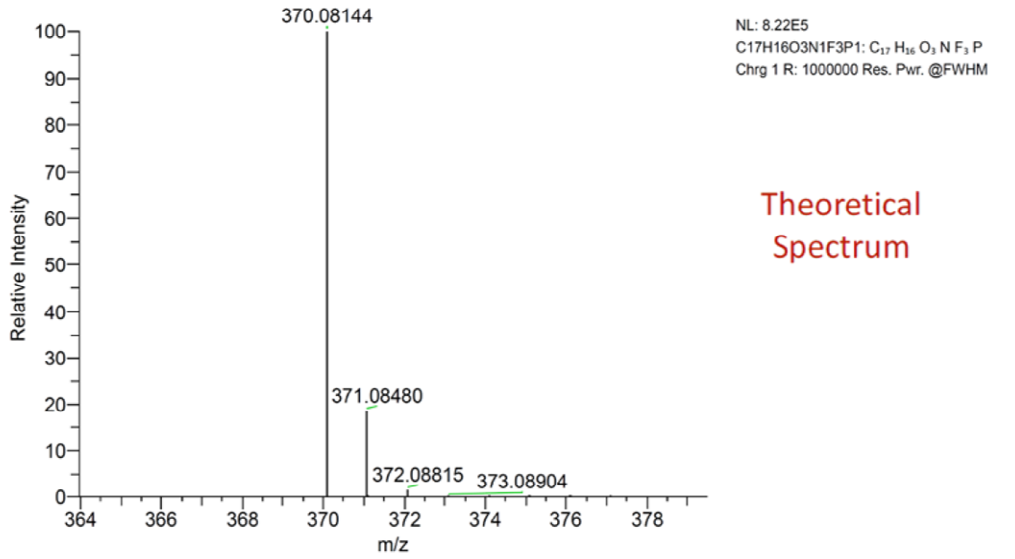

-110.52
-110.67
A (d)
-110.60
1.00
-110.0 -110.5 -111.0 -111.5
f1 (ppm)
-110.52
-110.67
A (d)
-110.60
F
F
O
O
N
P
O
H3C
H3C
1.00
50 60 70 60 50 40 30 20 10 0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240
f1 (ppm)

methyl (2-(2-(difluoromethyl)-4-fluorophenyl)benzo[d]oxazol-5-yl)(ethyl)phosphinate (16)

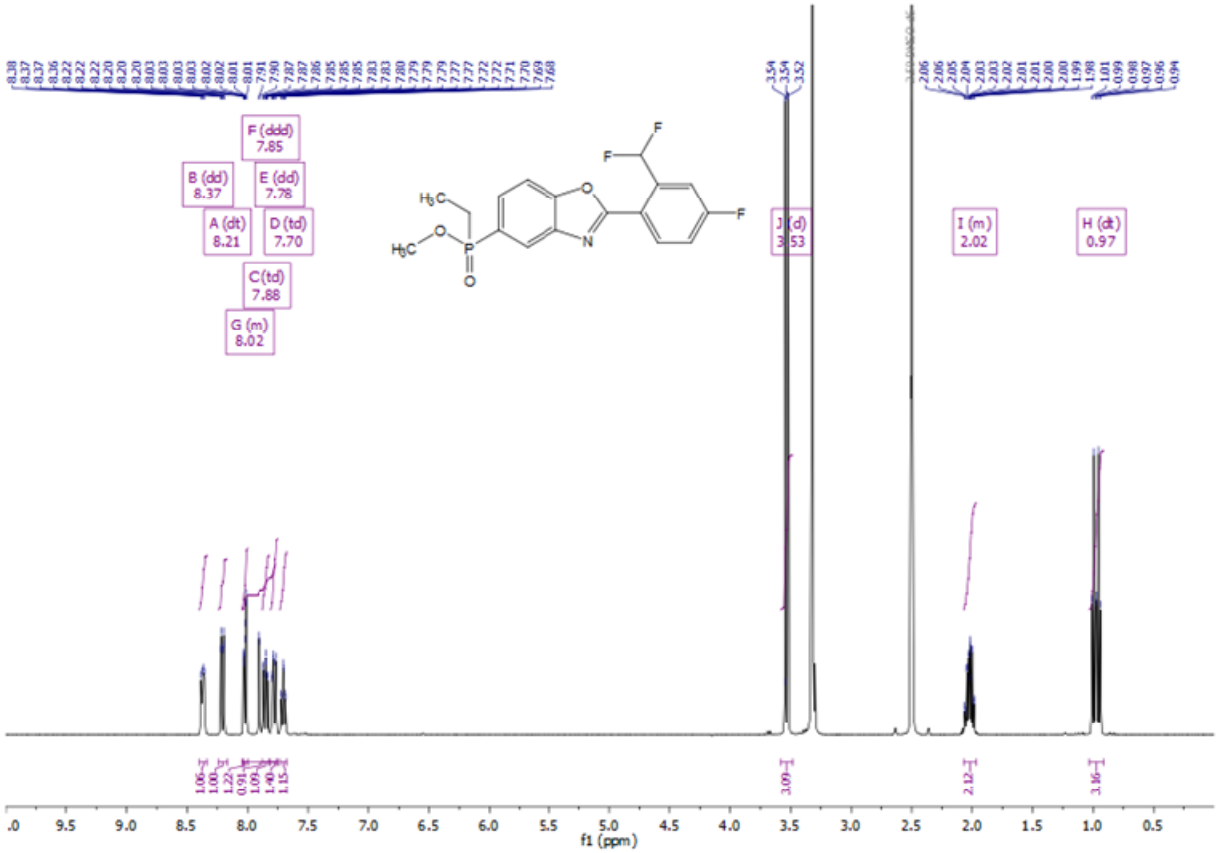


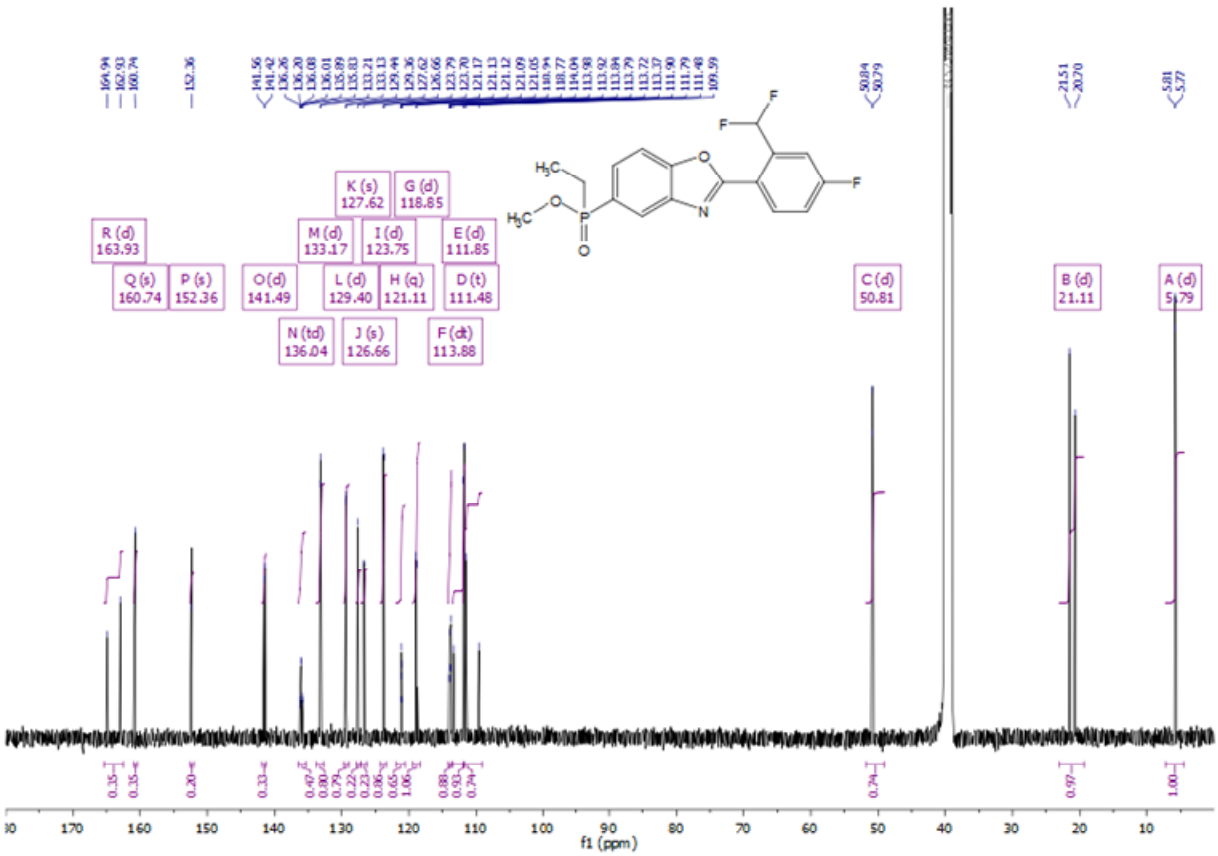


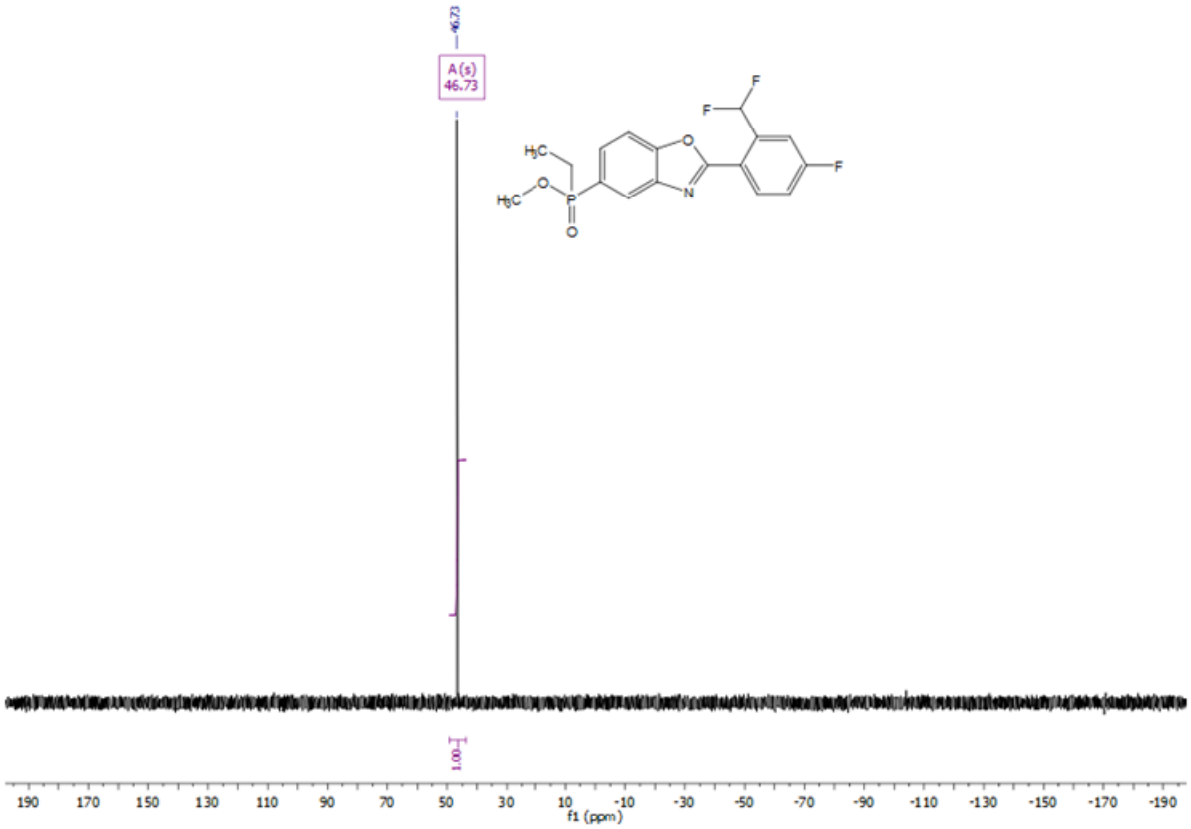


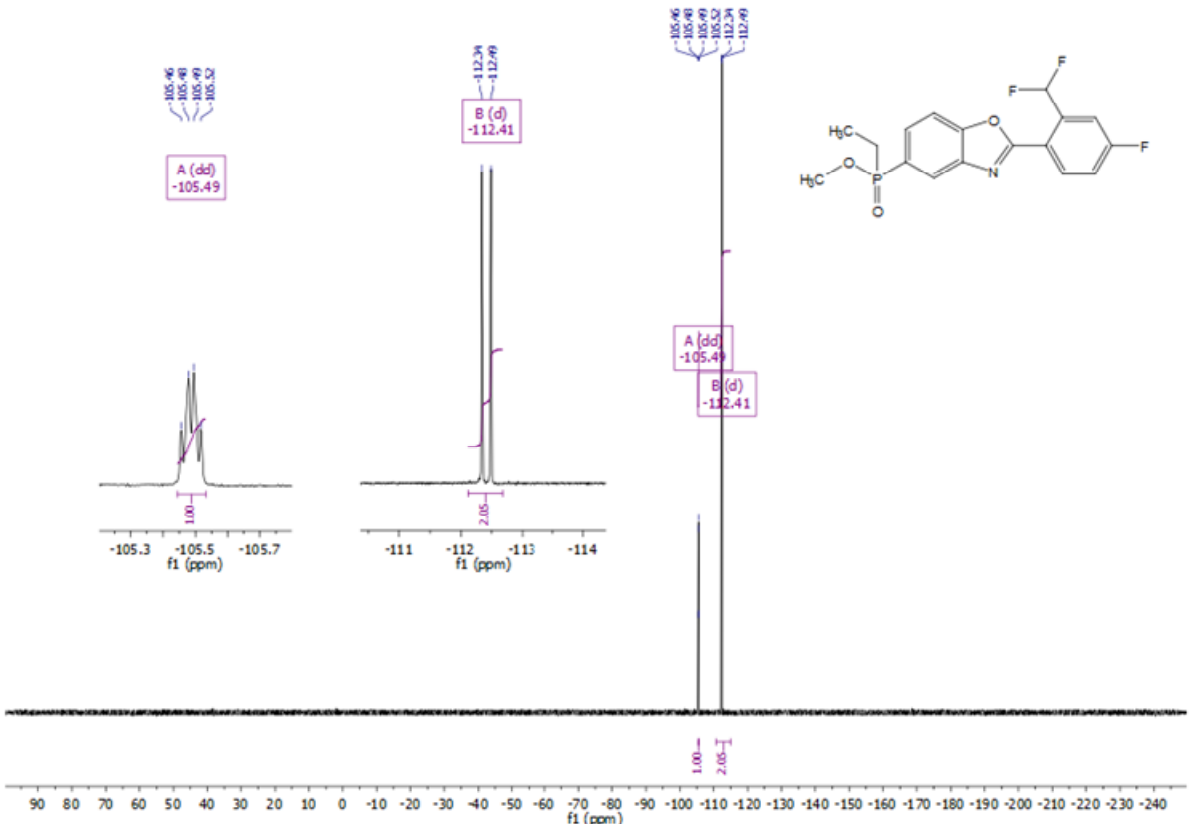


m/z	Formula	RDB	Delta ppm	Theo. Mass
370.08075	$C_{17}H_{16}O_3NF_3P$	9.5	-1.87	370.08144

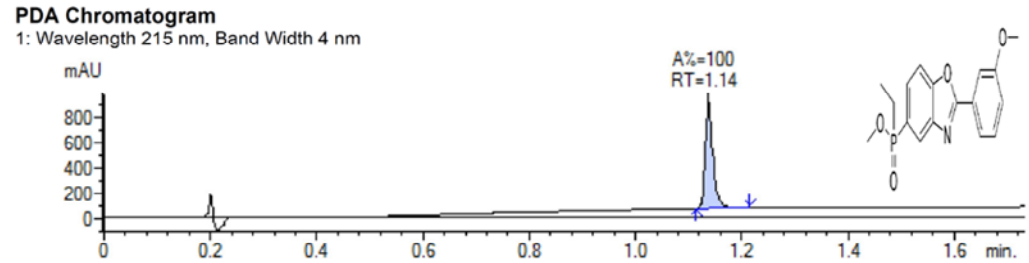

F (dddd) 7.85
B (dd) 8.37
E (dd) 7.78
A (dt) 8.21
D (td) 7.70
C (td) 7.88
G (m) 8.02
J (d) 3.53
I (m) 2.02
H (dt) 0.97
f1 (ppm)

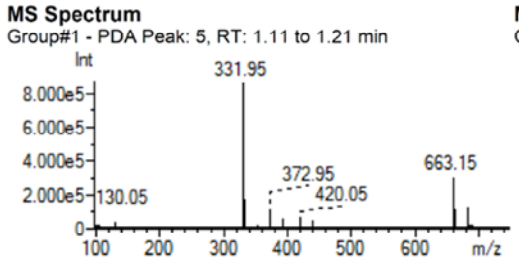

K (s) 127.62
G (d) 118.85
R (d) 163.93
M (d) 133.17
I (d) 123.75
E (d) 111.85
Q (s) 160.74
P (s) 152.36
O (d) 141.49
L (d) 129.40
H (q) 121.11
D (t) 111.48
N (td) 136.04
J (s) 126.66
F (dt) 113.88
C (d) 50.81
B (d) 21.11
A (d) 5.79
f1 (ppm)

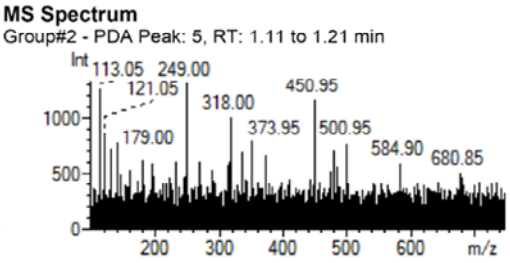

46.73
A (s)
46.73
F
F
F
H3C
O
H3C
P
O
O
N
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

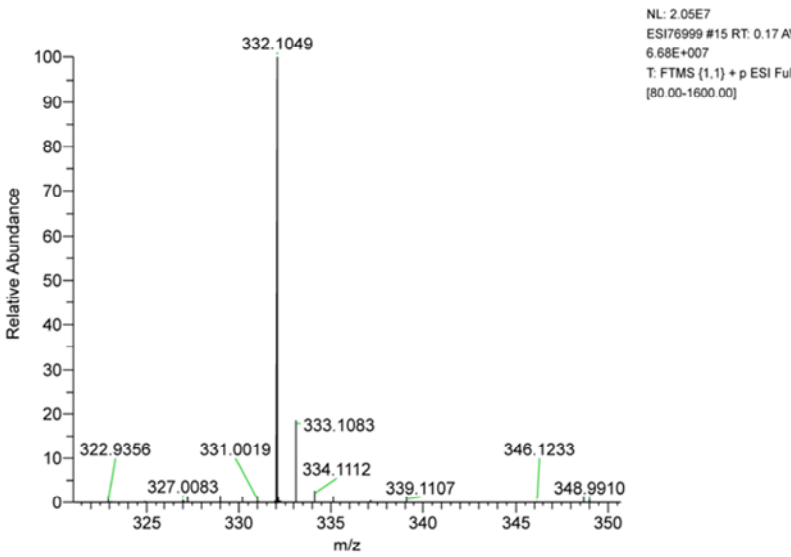

-105.46
-105.48
-105.49
-105.52
A (dd)
-105.49
-112.34
-112.49
B (d)
-112.41
1.00
2.05
-105.3 -105.5 -105.7
f1 (ppm)
-111 -112 -113 -114
f1 (ppm)
F
F
F
H3C
O
H3C
P
O
O
N
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

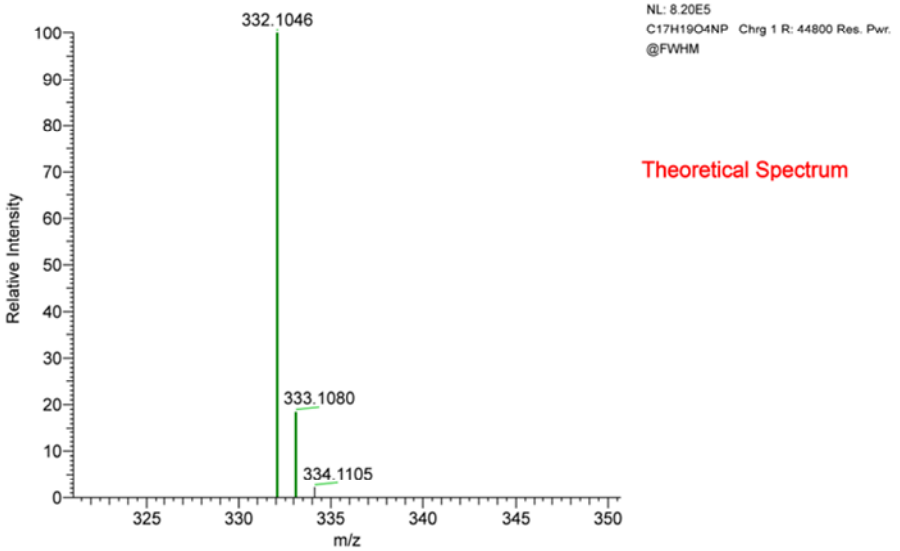
methyl ethyl(2-(3-methoxyphenyl)benzo[d]oxazol-5-yl)phosphinate (17)



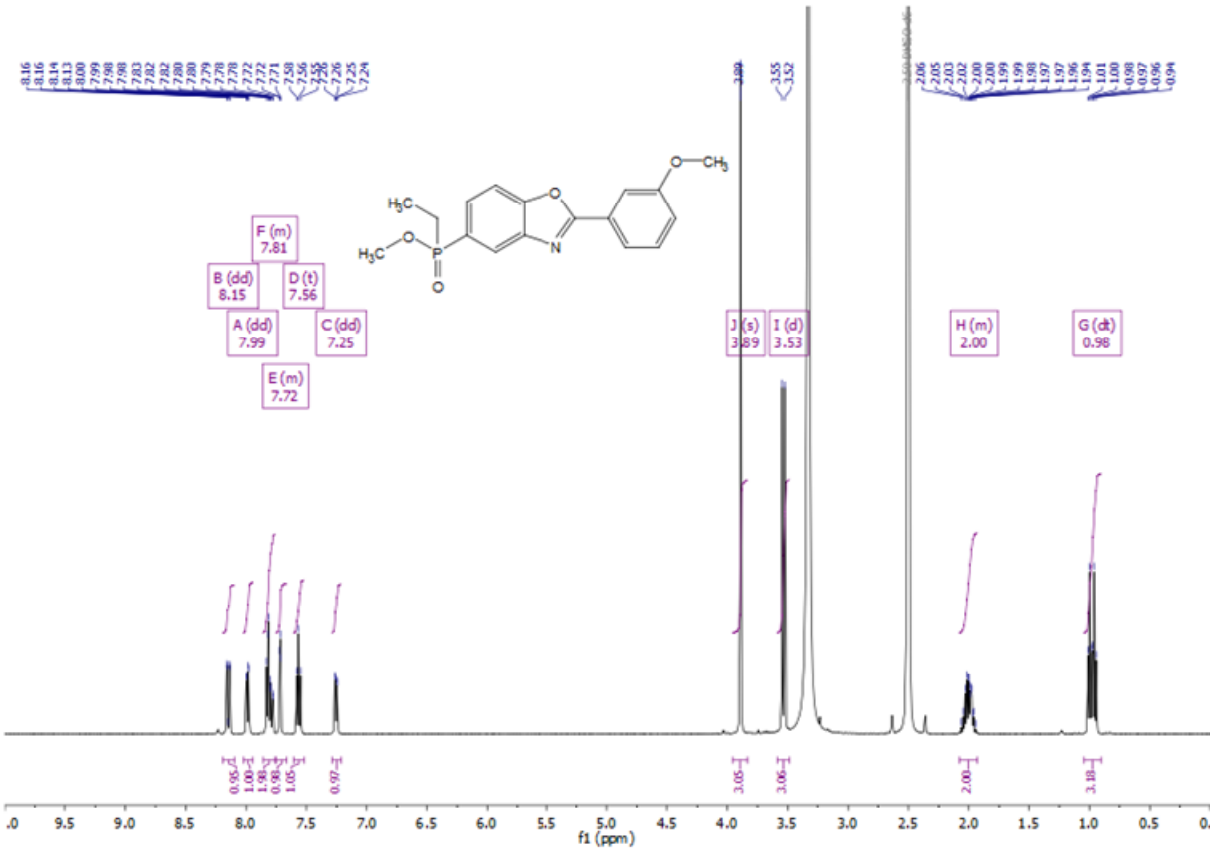


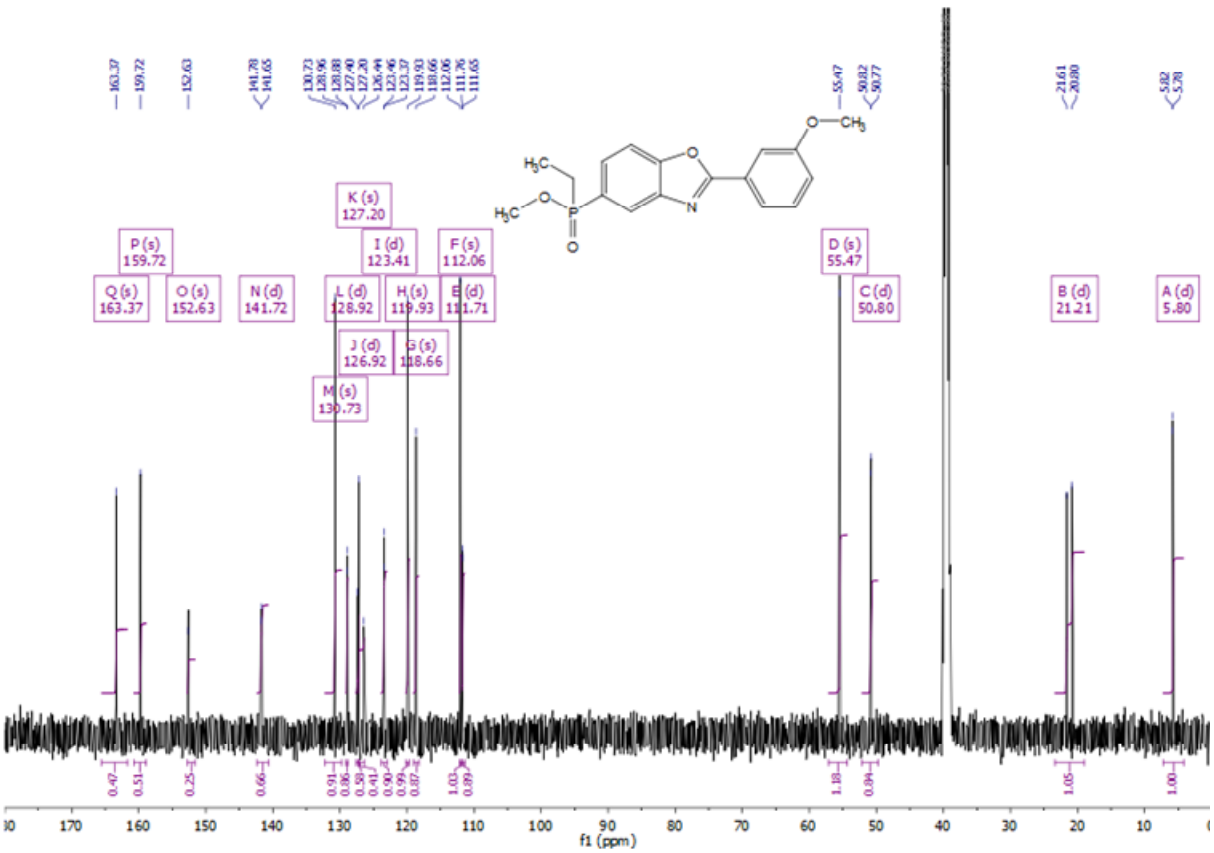






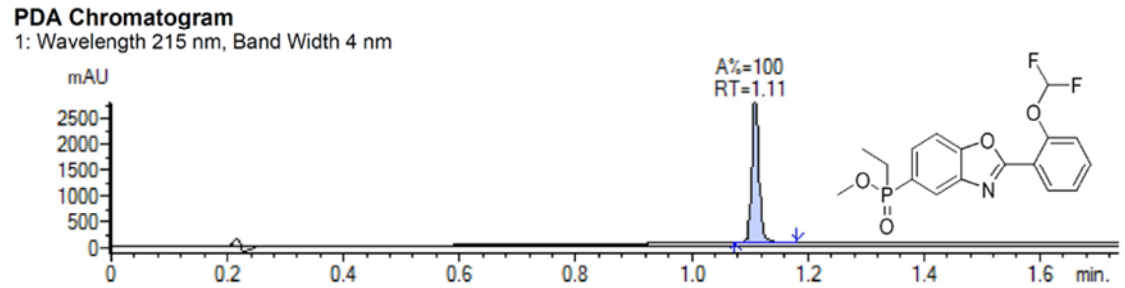
Peak Mass	Display...	Combin...	RDB	Delta [p...	Theo. m...	Rank	Combin...	# Match...	# Misse...	MS Cov....	Pattern...	MSMS...
332.1049	$C_{17}H_{19}$...	27.901...	9.50	0.99	332.10...	1	94.988...	4	0	98.715...	97.907...	(Collec...

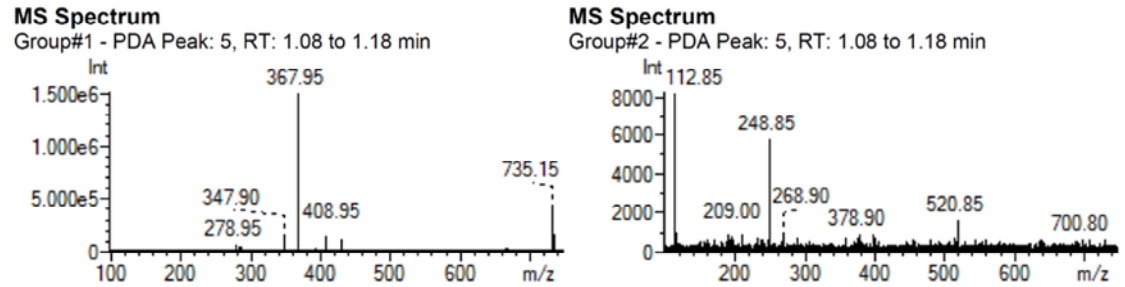

F (m) 7.81
B (dd) 8.15
D (t) 7.56
A (dd) 7.99
C (dd) 7.25
E (m) 7.72
J (s) 3.89
I (d) 3.53
H (m) 2.00
G (dt) 0.98
f1 (ppm)

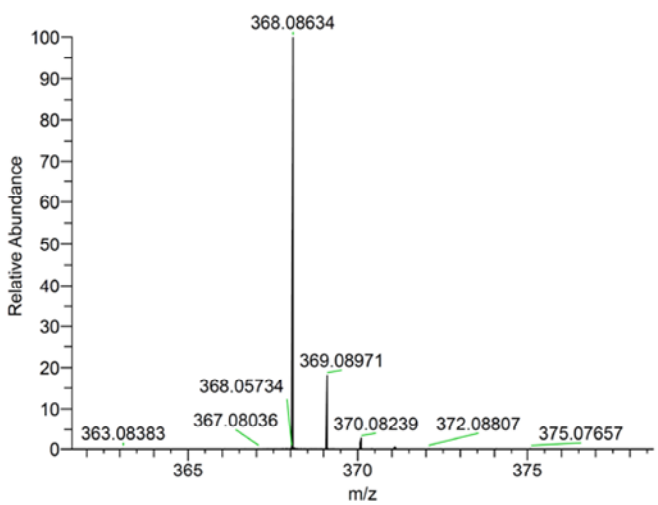

K (s) 127.20
I (d) 123.41
F (s) 112.06
P (s) 159.72
Q (s) 163.37
O (s) 152.63
N (d) 141.72
L (d) 128.92
H (s) 119.93
E (d) 111.71
J (d) 126.92
G (s) 118.66
M (s) 130.73
D (s) 55.47
C (d) 50.80
B (d) 21.21
A (d) 5.80
f1 (ppm)


46.77
A (s)
46.77
O—CH3
H3C
O
H3C
O
P
O
N
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

methyl (2-(2-(difluoromethoxy)phenyl)benzo[d]oxazol-5-yl)(ethyl)phosphinate (18)

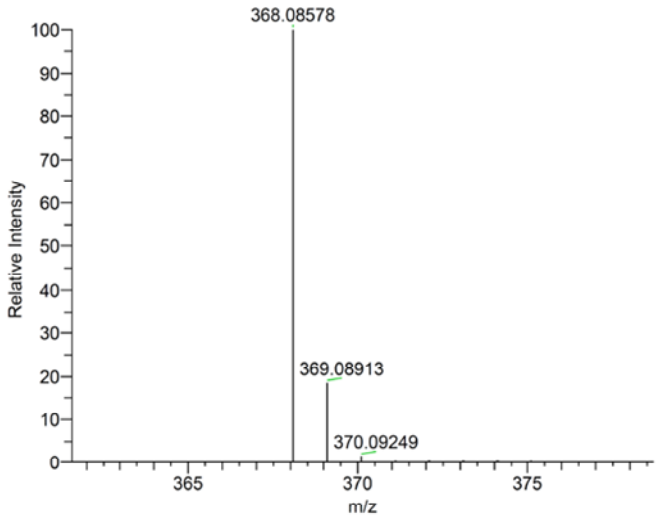






NL: 6.93E7
ESI74320 #13-27 RT: 0.15-0.31 AV: 8 NL: 6.93E+007
T: FTMS {1,1} + p ESI Full ms [80.00-1600.00]

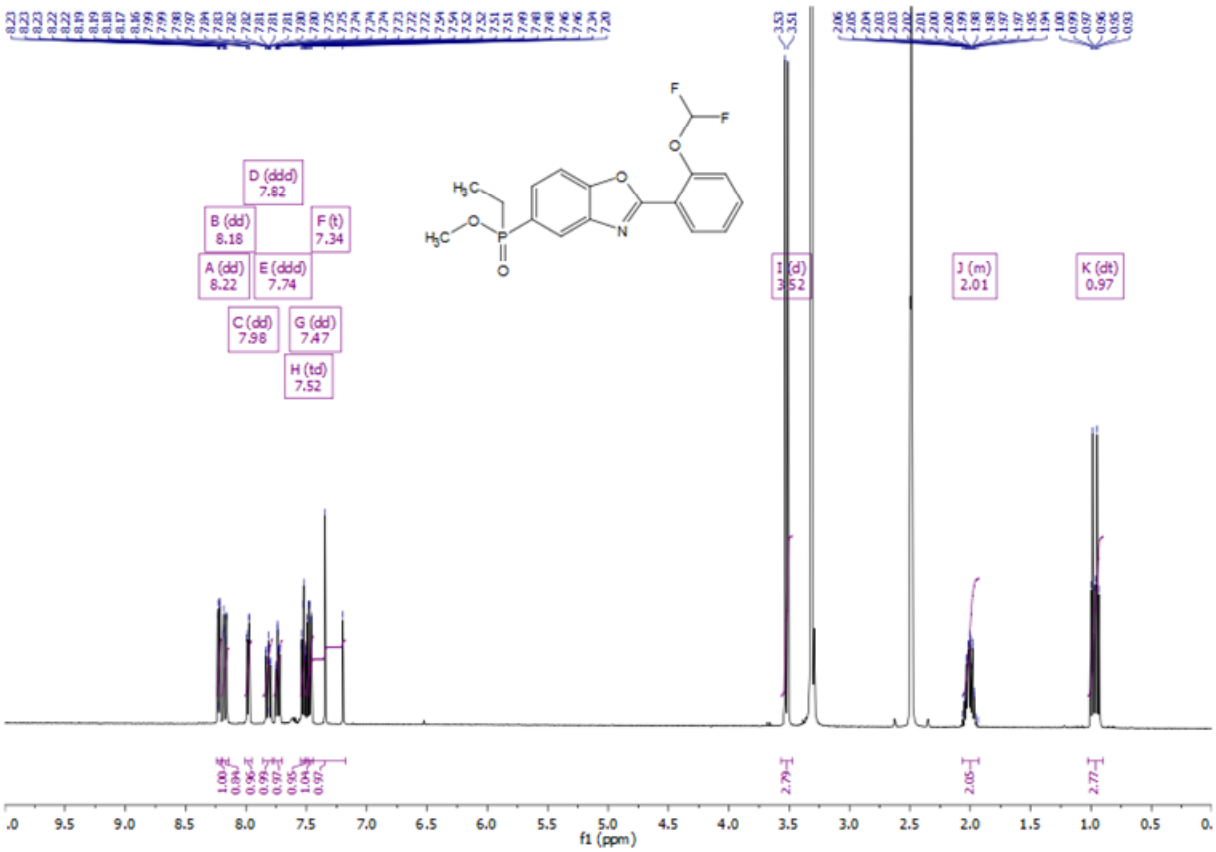
Measured Spectrum

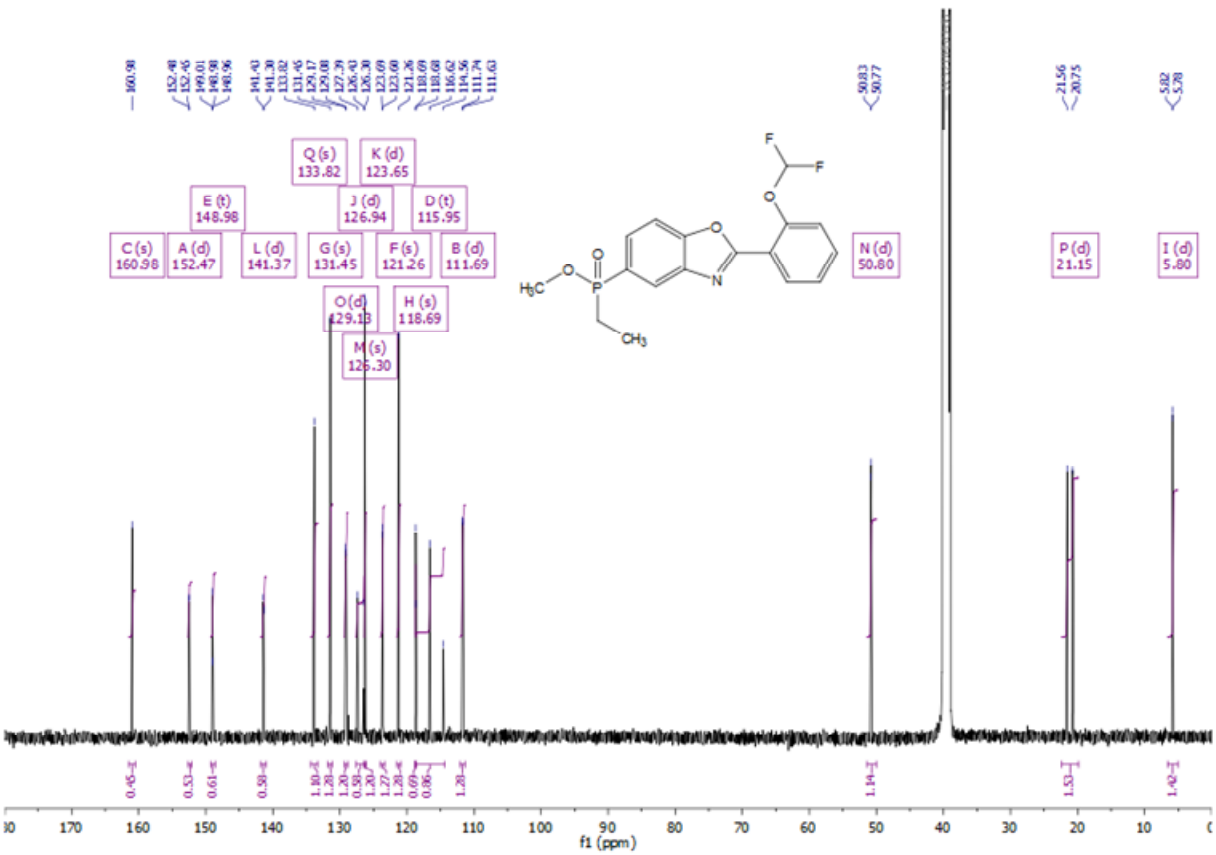


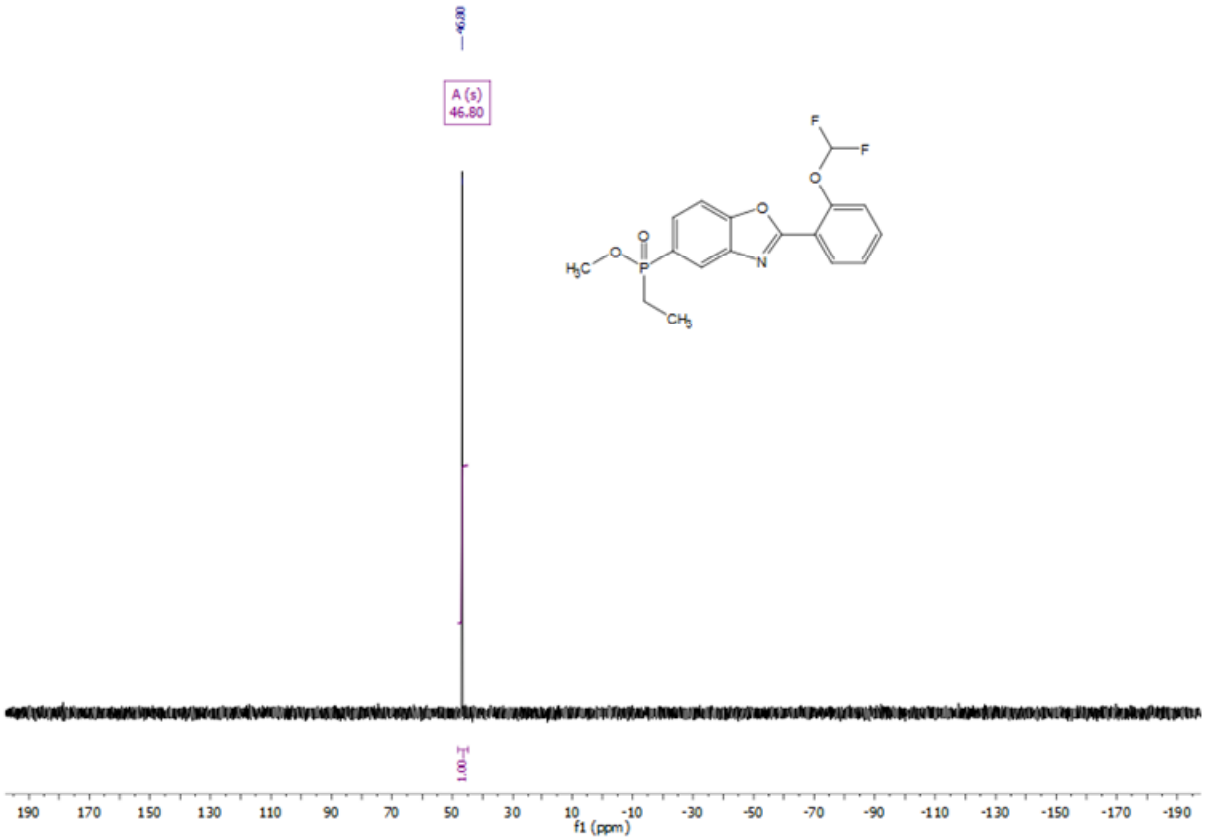
NL: 8.20E5
C17H17O4N1F2P1: $C_{17}H_{17}O_4NF_2P$
Chrg 1 R: 1000000 Res. Pwr. @FWHM

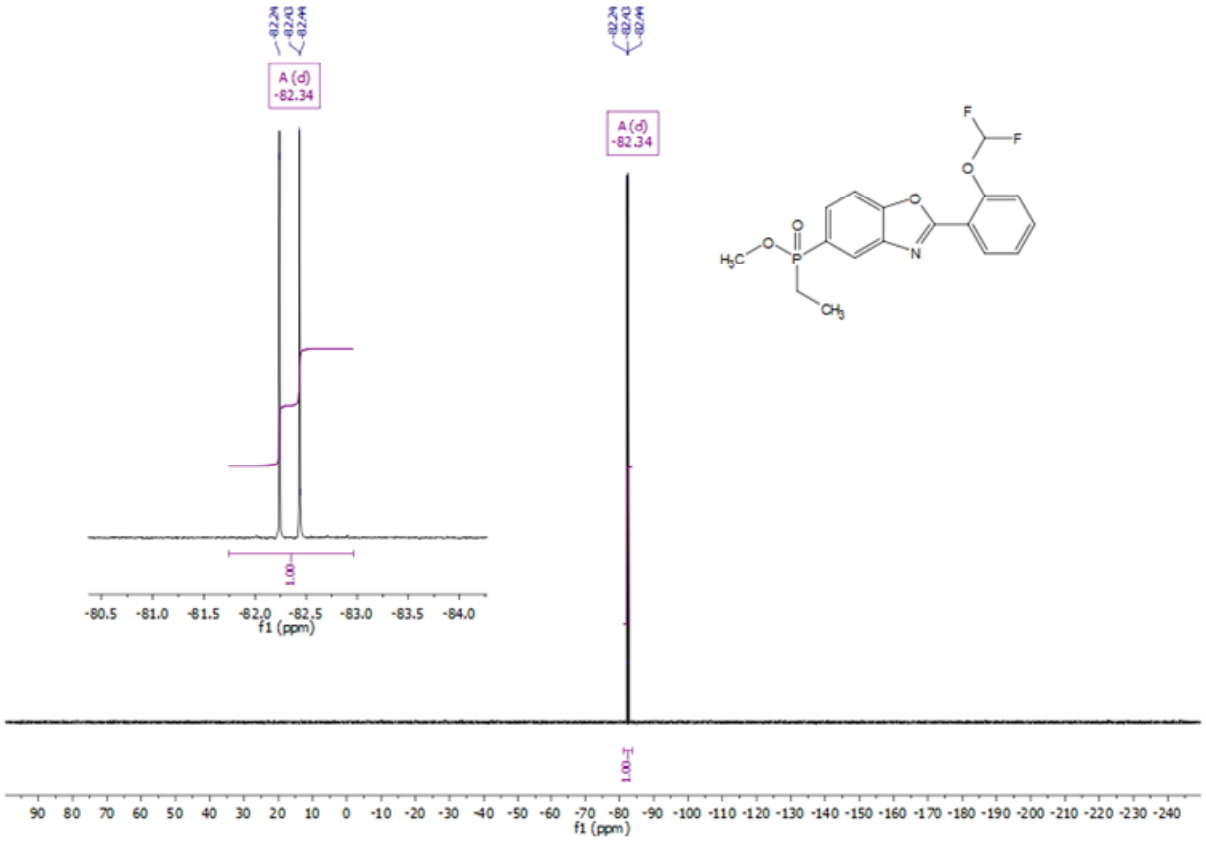
Theoretical Spectrum

m/z	Formula	RDB	Delta ppm	Theo. Mass
368.08633	$C_{17}H_{17}O_4NF_2P$	9.5	1.51	368.08578

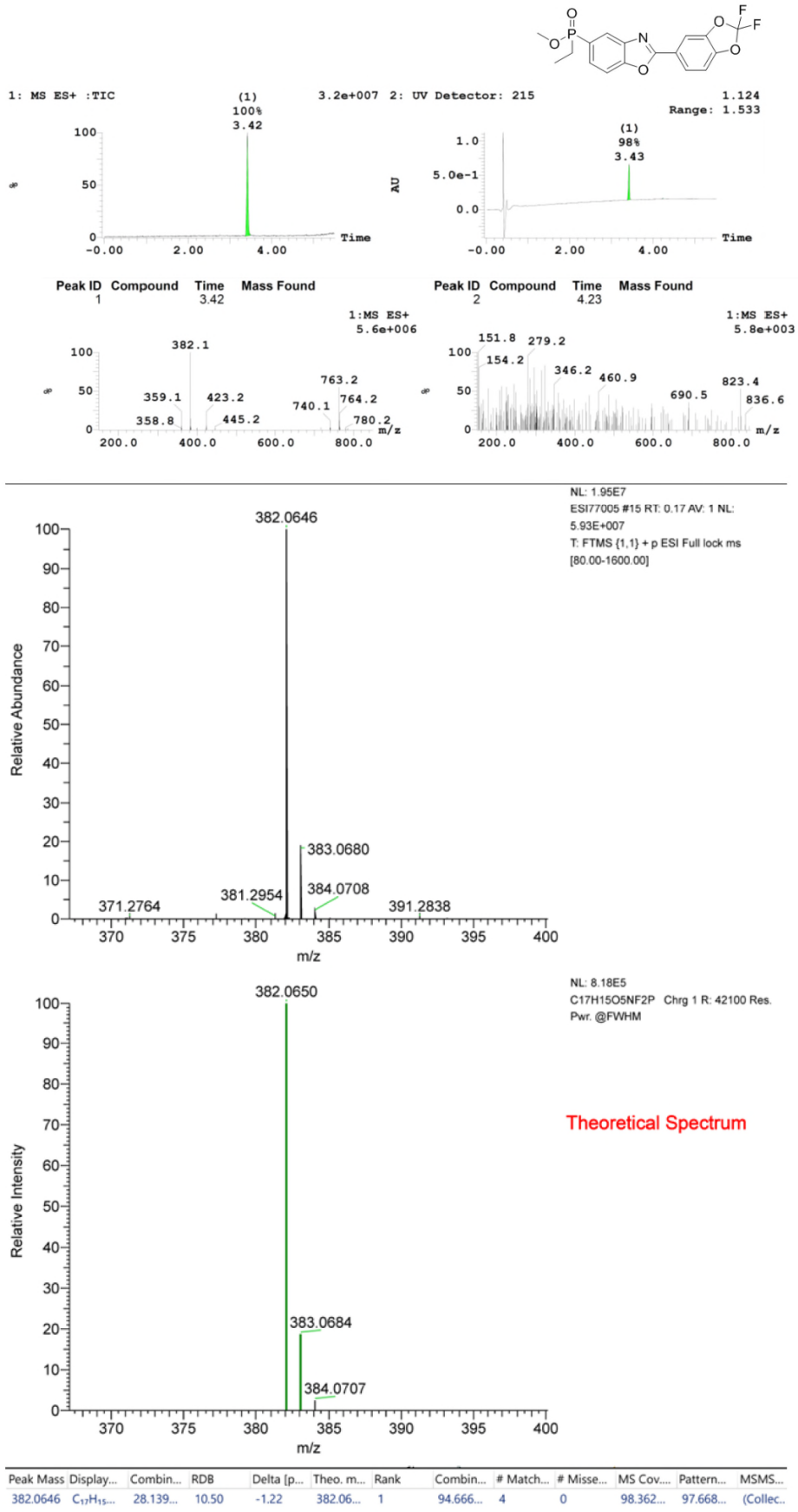

D (ddd) 7.82
B (dd) 8.18
F (t) 7.34
A (dd) 8.22
E (ddd) 7.74
C (dd) 7.98
G (dd) 7.47
H (td) 7.52
I (d) 3.52
J (m) 2.01
K (dt) 0.97
f1 (ppm)

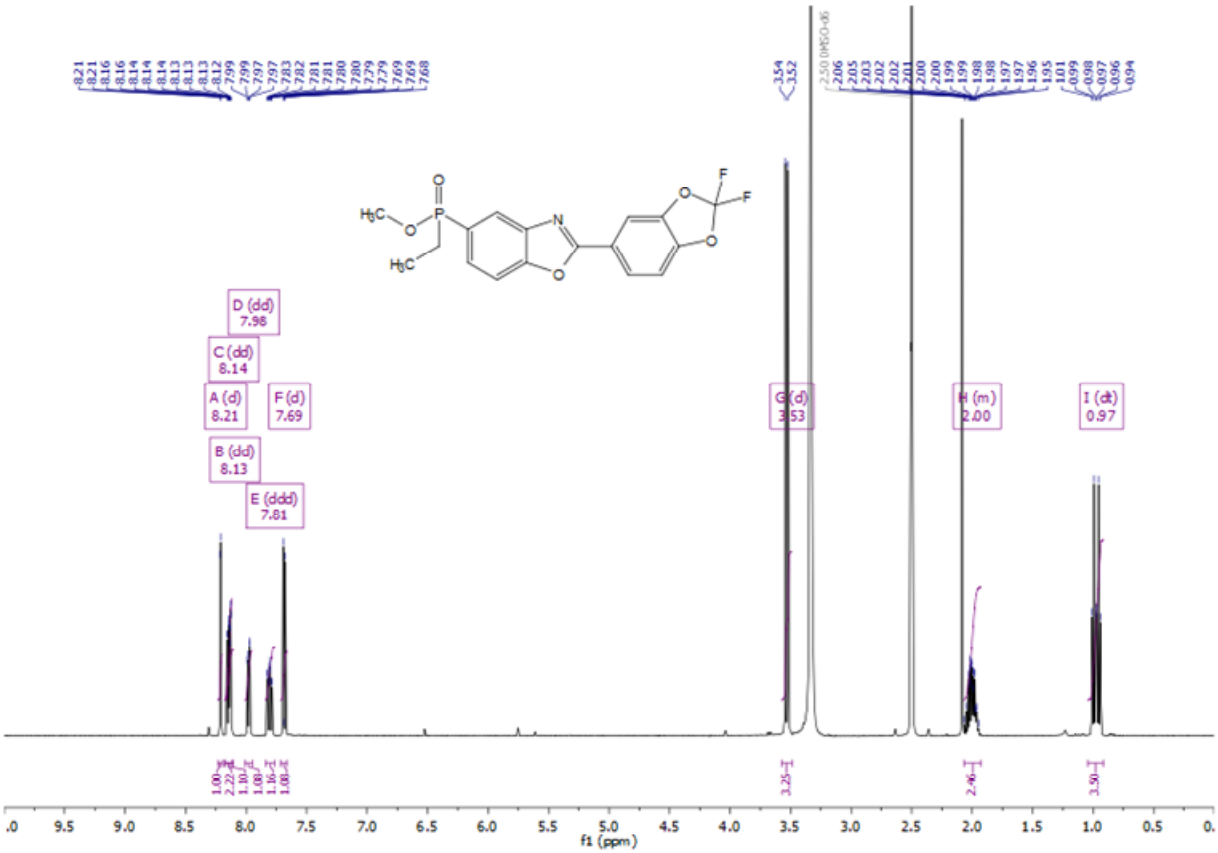

Q (s) 133.82
K (d) 123.65
E (t) 148.98
J (d) 126.94
D (t) 115.95
C (s) 160.98
A (d) 152.47
L (d) 141.37
G (s) 131.45
F (s) 121.26
B (d) 111.69
O (d) 129.13
H (s) 118.69
M (s) 126.30
N (d) 50.80
P (d) 21.15
I (d) 5.80
f1 (ppm)

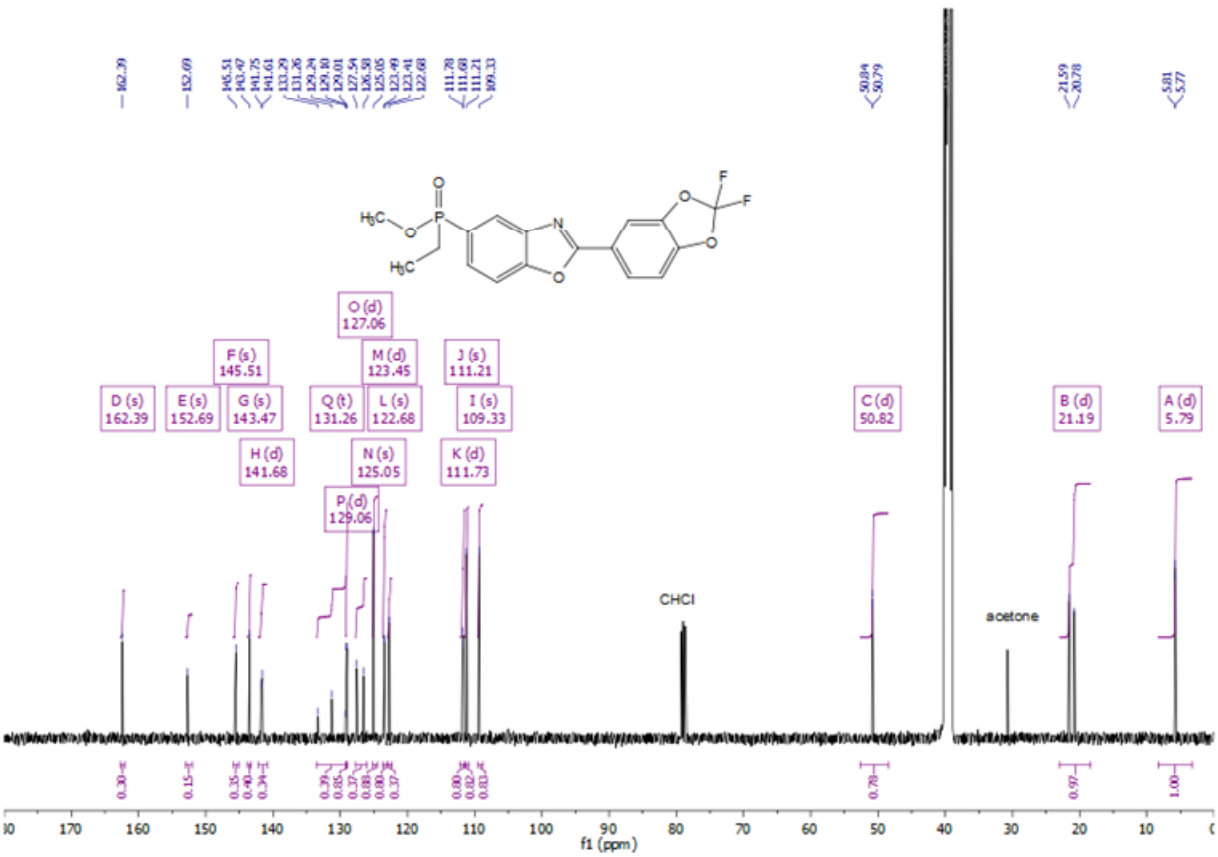

46.80
A (s)
46.80
F
F
O
O
O
P
N
H3C
CH3
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

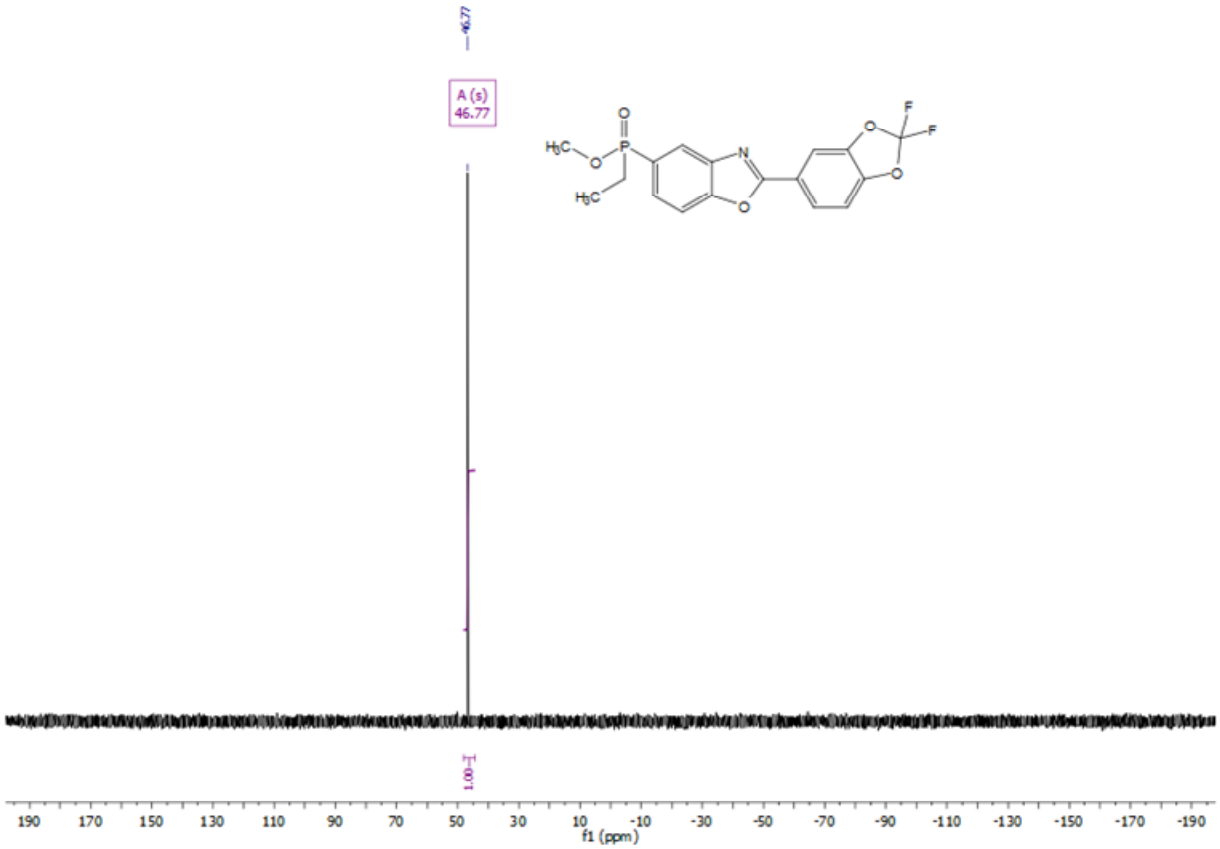

-82.24
-82.43
-82.44
A (d)
-82.34
1.00
-80.5 -81.0 -81.5 -82.0 -82.5 -83.0 -83.5 -84.0
f1 (ppm)
A (d)
-82.34
F
F
O
O
O
P
N
H3C
CH3
1.00
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

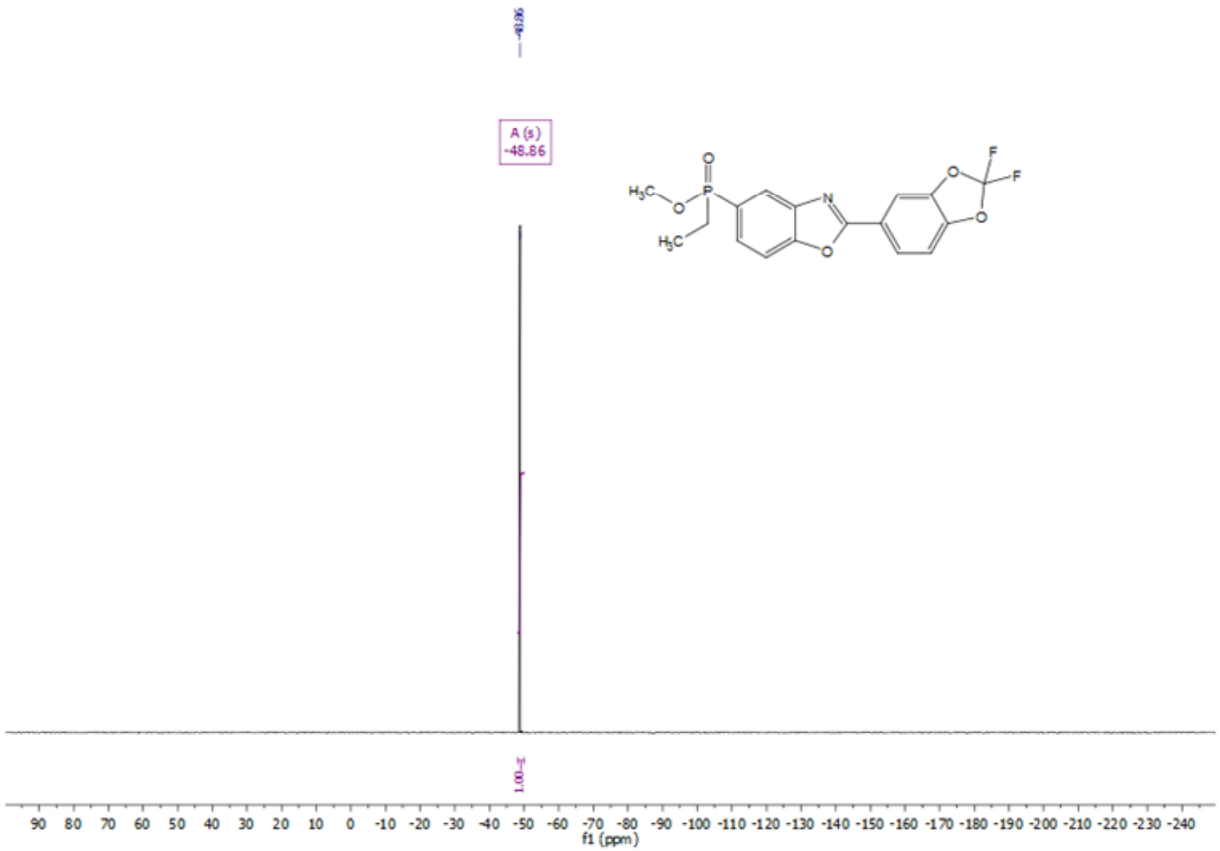
methyl (2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)benzo[d]oxazol-5-yl)(ethyl)phosphinate (19)



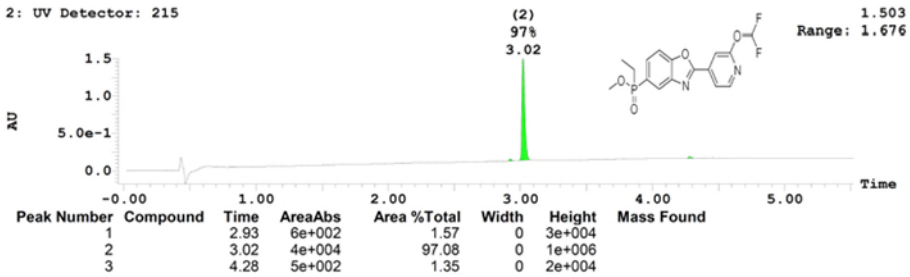

D (dd)
7.98
C (dd)
8.14
A (d)
8.21
F (d)
7.69
B (dd)
8.13
E (ddd)
7.81
G (d)
3.53
H (m)
2.00
I (dt)
0.97
f1 (ppm)


O (d)
127.06
F (s)
145.51
M (d)
123.45
J (s)
111.21
D (s)
162.39
E (s)
152.69
G (s)
143.47
Q (t)
131.26
L (s)
122.68
I (s)
109.33
H (d)
141.68
N (s)
125.05
K (d)
111.73
P (d)
129.06
C (d)
50.82
B (d)
21.19
A (d)
5.79
CHCl
acetone
f1 (ppm)


46.77
A (s)
46.77
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

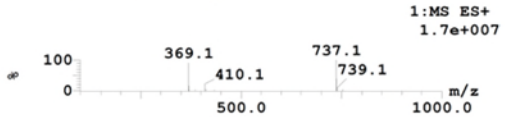

-48.86
A (s)
-48.86
1.00
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

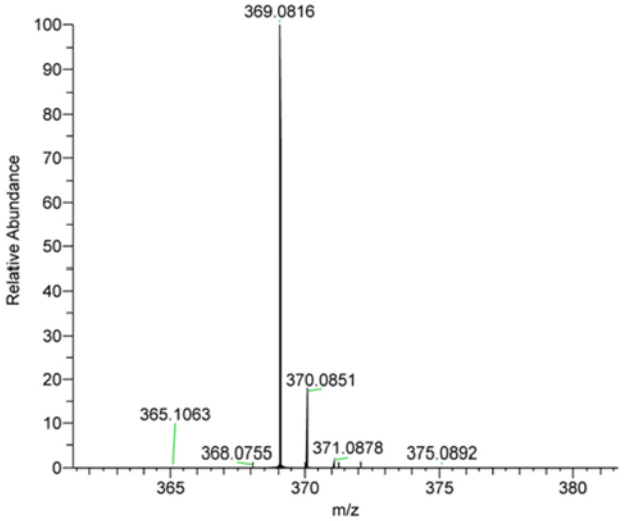
methyl (2-(2-(difluoromethoxy)pyridin-4-yl)benzo[d]oxazol-5-yl)(ethyl)phosphinate (20)

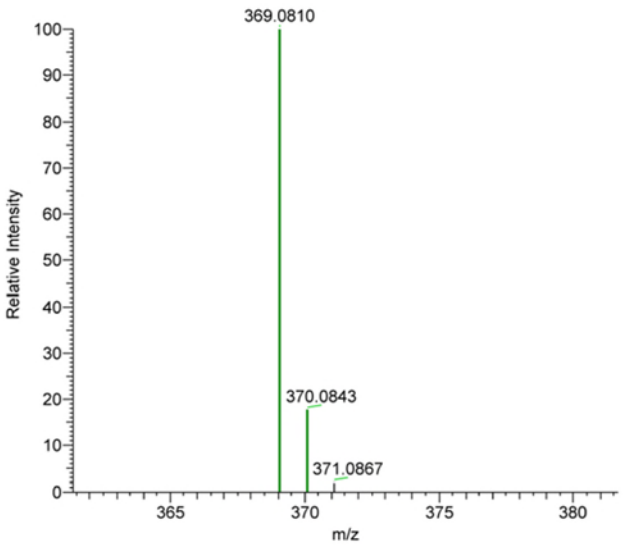


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		2.93	6e+002	1.57	0	3e+004	
2		3.02	4e+004	97.08	0	1e+006	
3		4.28	5e+002	1.35	0	2e+004	

Peak ID	Compound	Time	Mass Found
2		3.02	

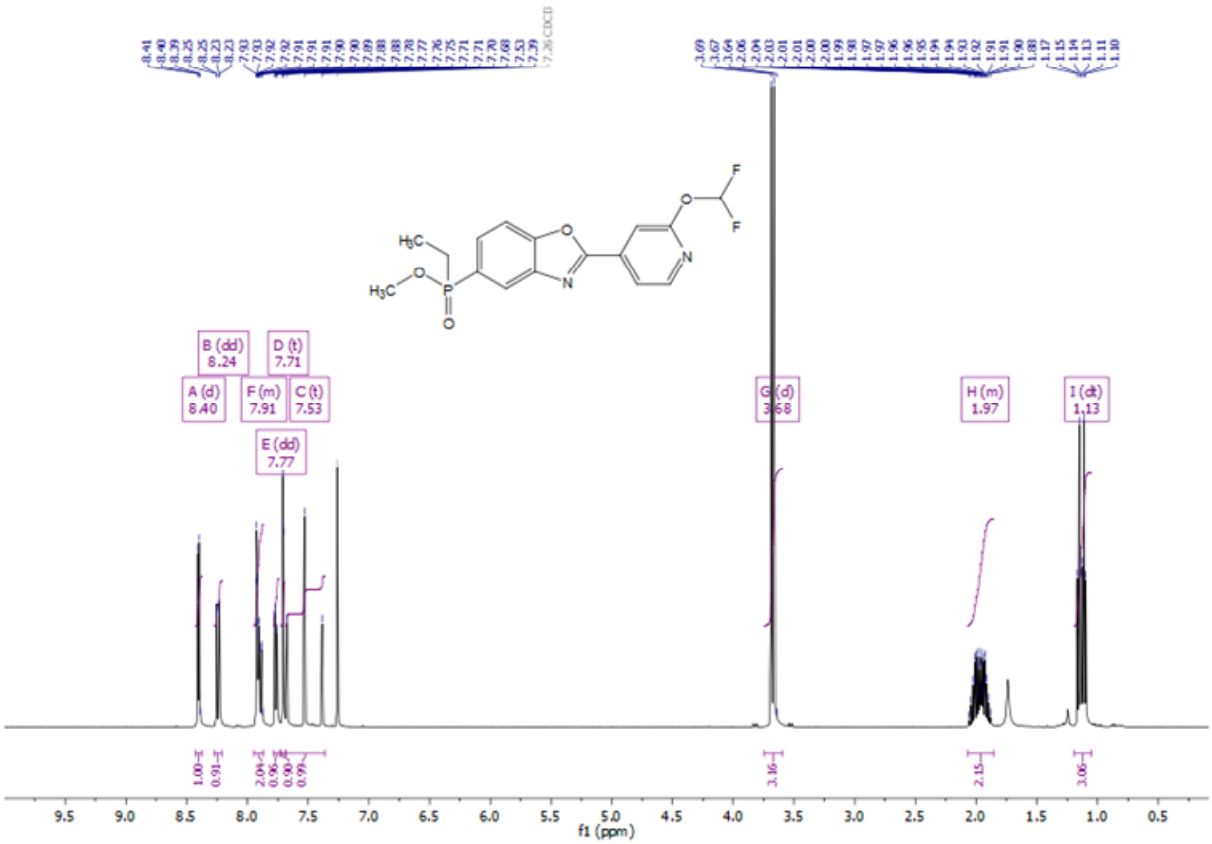




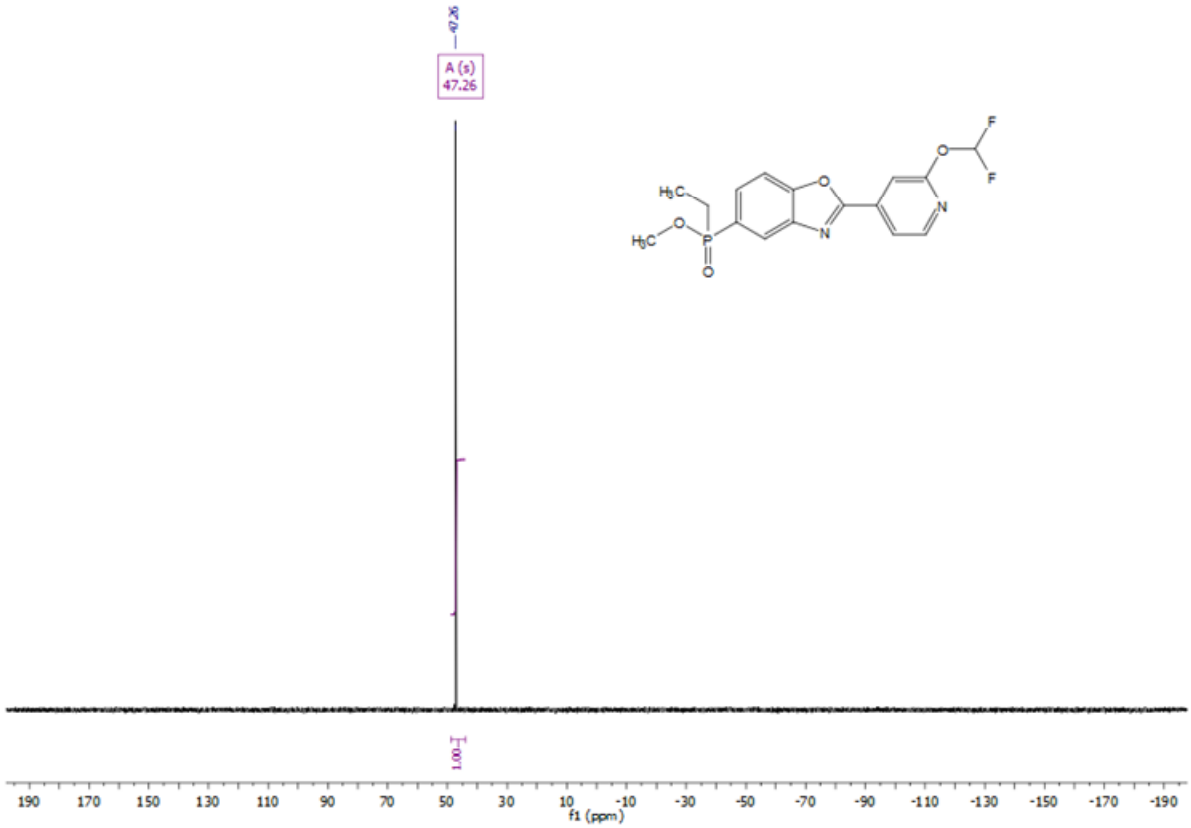


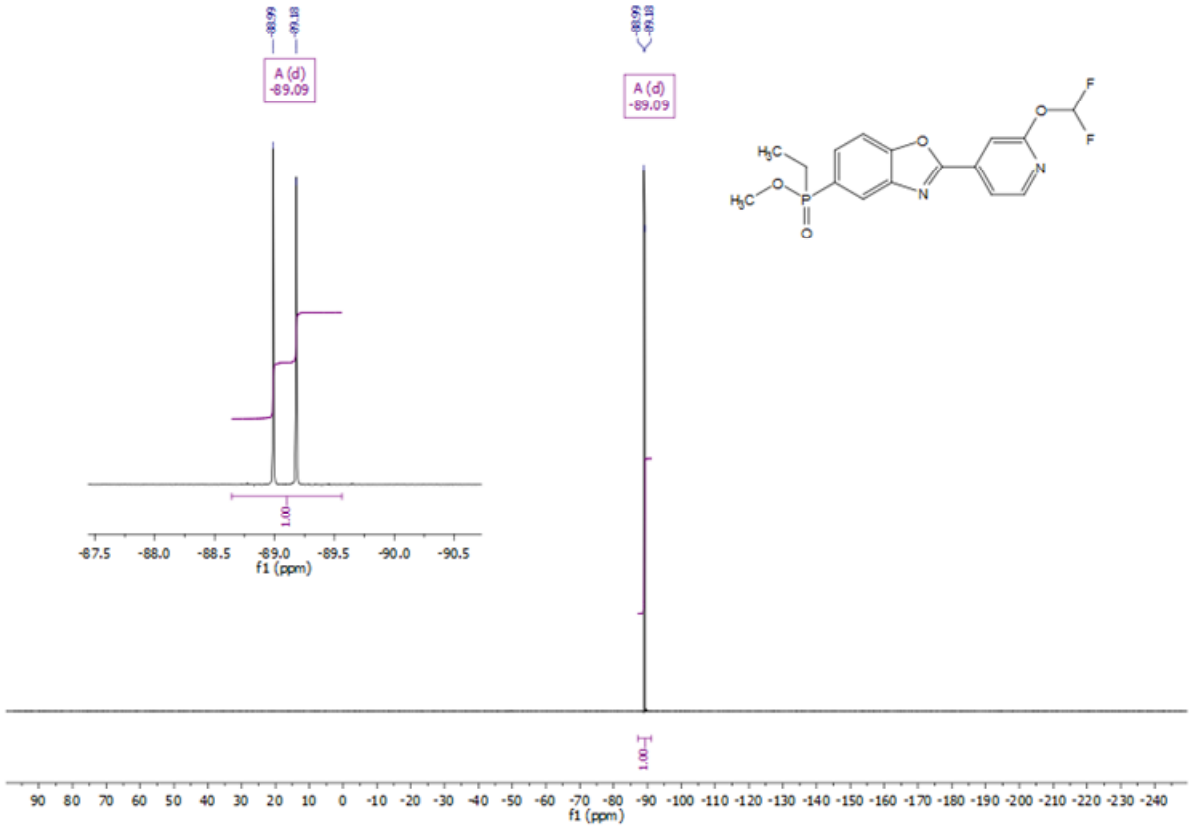
Theoretical Spectrum

Peak Mass	Display...	Combin...	RDB	Delta [p...	Theo. m...	Rank	Combin...	# Match...	# Misse...	MS Cov....	Pattern...	MSMS...
369.0816	$C_{16}H_{16}$...	26.855...	9.50	1.48	369.08...	1	94.843...	4	0	98.620...	97.992...	(Collec...

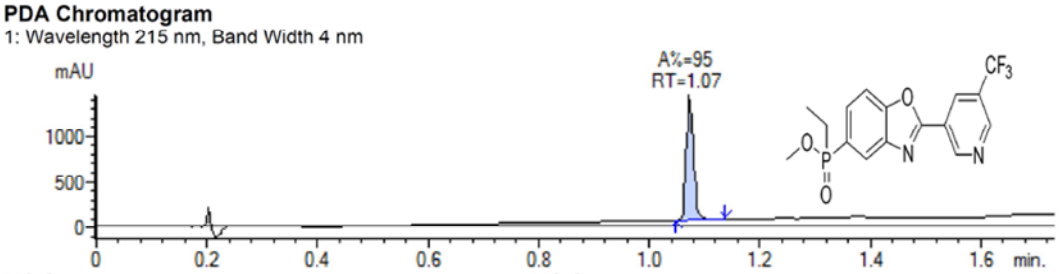

B (dd) 8.24
D (t) 7.71
A (d) 8.40
F (m) 7.91
C (t) 7.53
E (dd) 7.77
G (d) 3.68
H (m) 1.97
I (dt) 1.13
f1 (ppm)

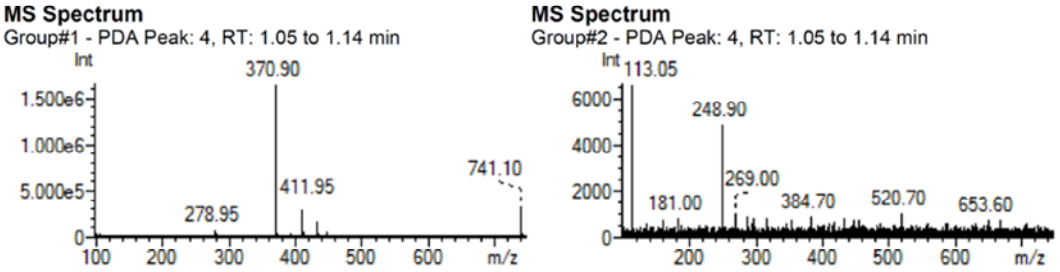

O (d) 153.36
M (d) 142.13
H (d) 125.18
E (d) 111.87
P (t) 160.11
N (s) 148.44
L (s) 137.99
I (d) 127.59
G (s) 117.82
D (s) 109.60
Q (s) 161.12
K (d) 130.34
F (t) 114.06
C (d) 51.40
B (d) 22.88
A (d) 6.05
f1 (ppm)

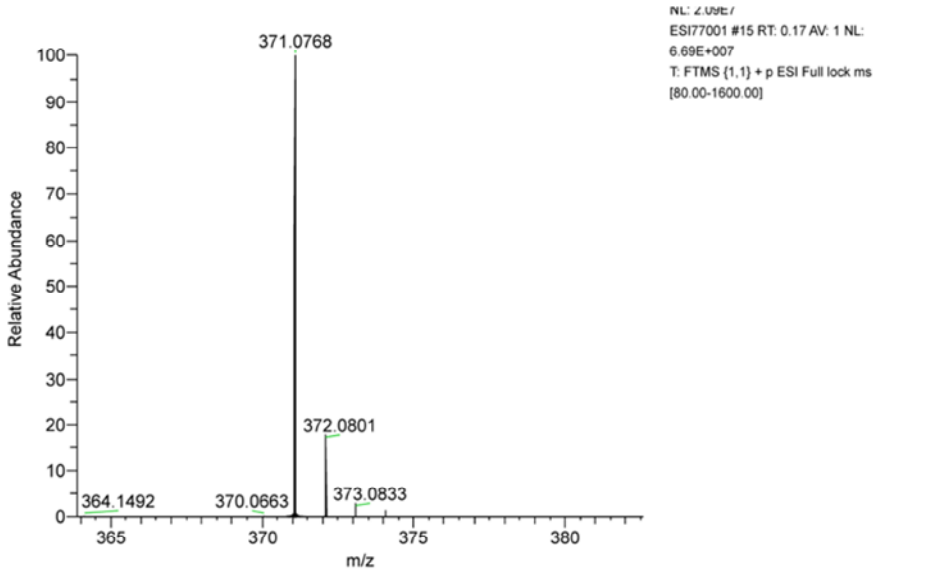

47.26
A (s)
47.26
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

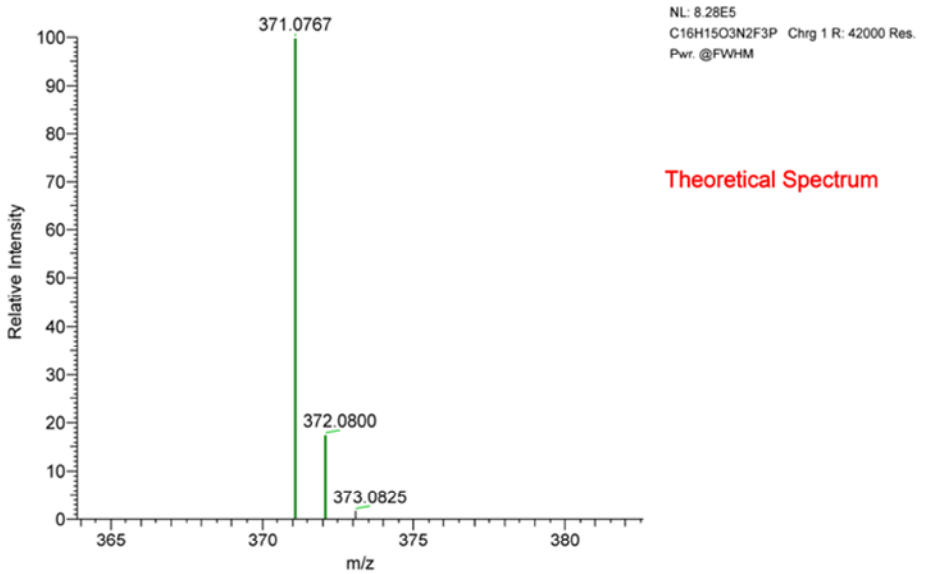

-88.99
-89.18
A (d)
-89.09
1.00
-87.5 -88.0 -88.5 -89.0 -89.5 -90.0 -90.5
f1 (ppm)
-88.99
-89.18
A (d)
-89.09
1.00
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

methyl ethyl(2-(5-(trifluoromethyl)pyridin-3-yl)benzo[*d*]oxazol-5-yl)phosphinate (21)

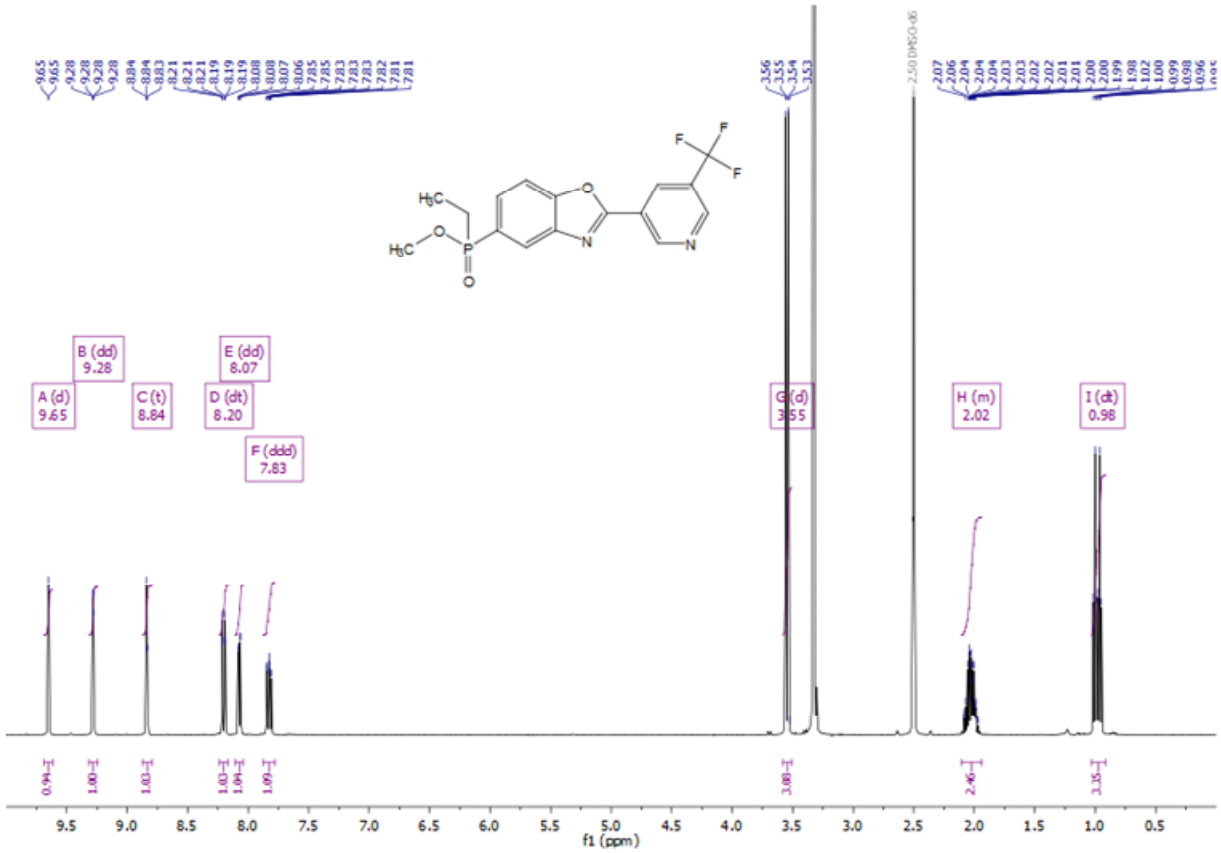


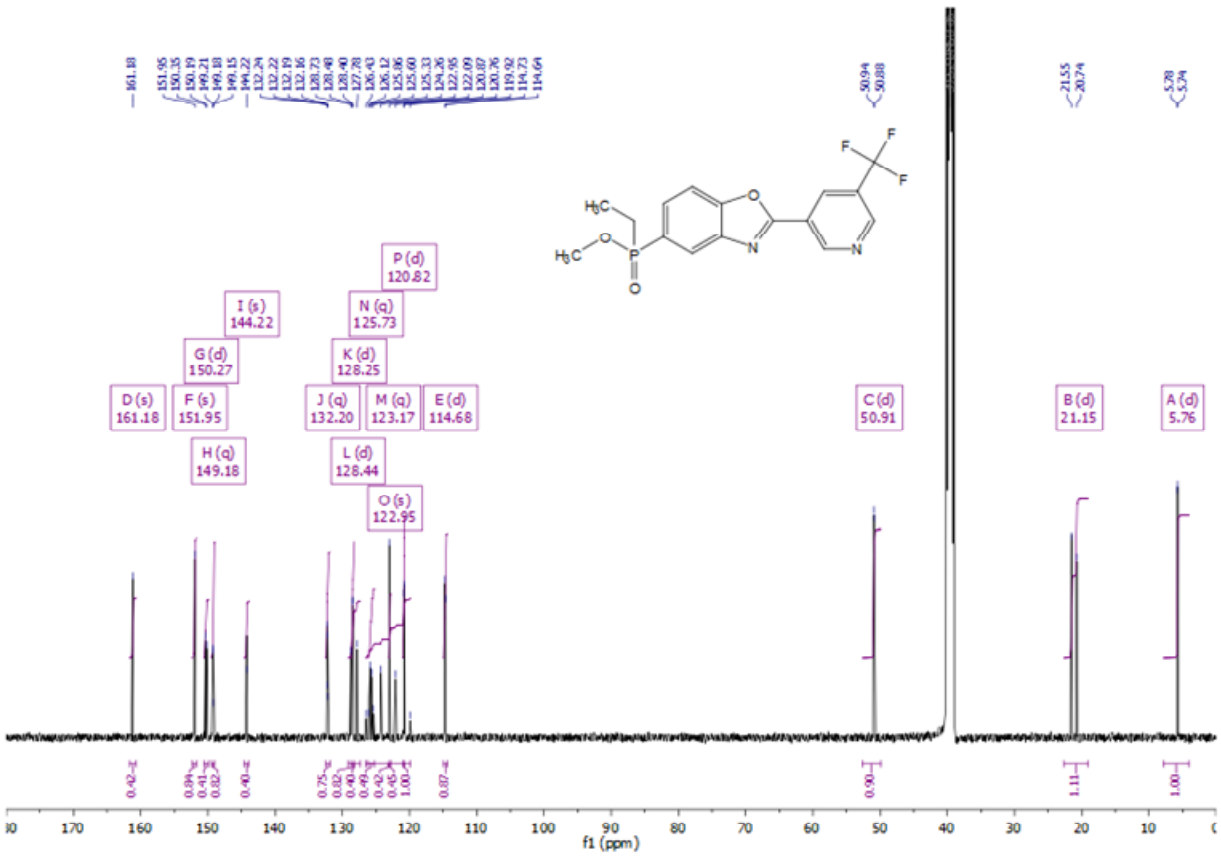


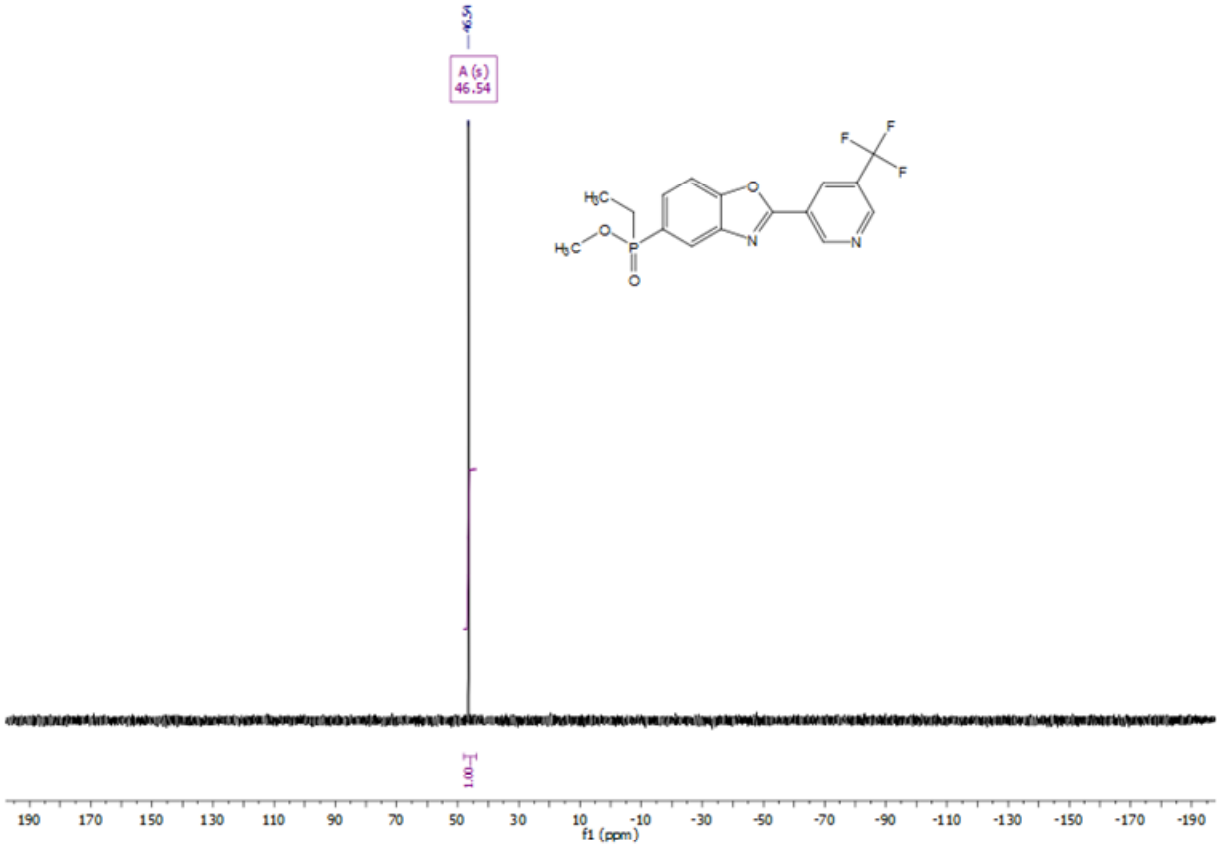


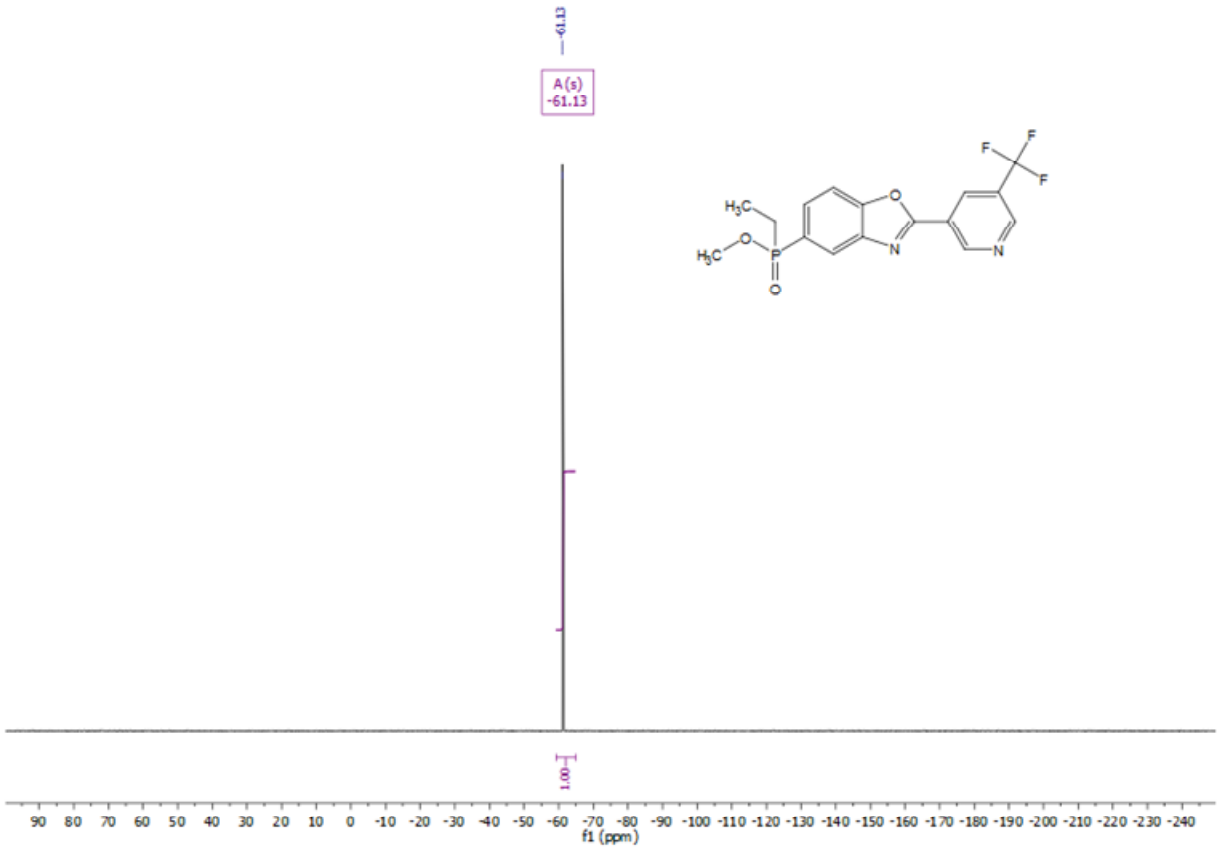


Peak Mass	Display...	Combin...	RDB	Delta [p...	Theo. m...	Rank	Combin...	# Match...	# Misse...	MS Cov....	Pattern...	MSMS...
371.0768	$C_{16}H_{15}$...	40.278...	9.50	0.33	371.07...	1	96.856...	3	1	100	99.855...	(Collec...

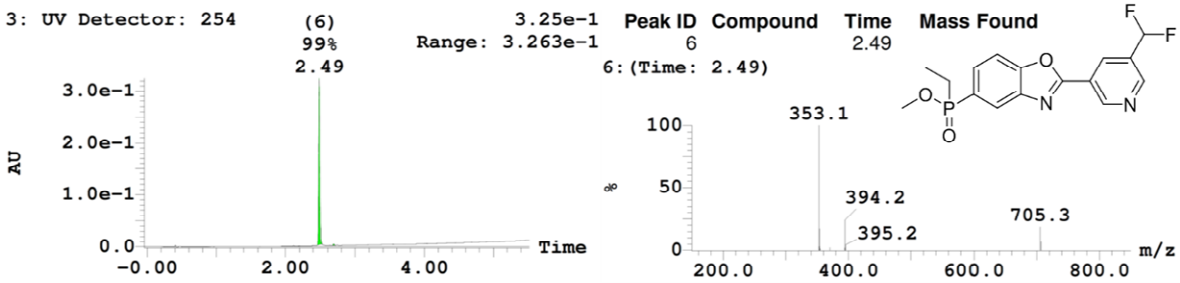

A (d) 9.65
B (dd) 9.28
C (t) 8.84
D (dt) 8.20
E (dd) 8.07
F (ddd) 7.83
G (d) 3.55
H (m) 2.02
I (dt) 0.98
f1 (ppm)

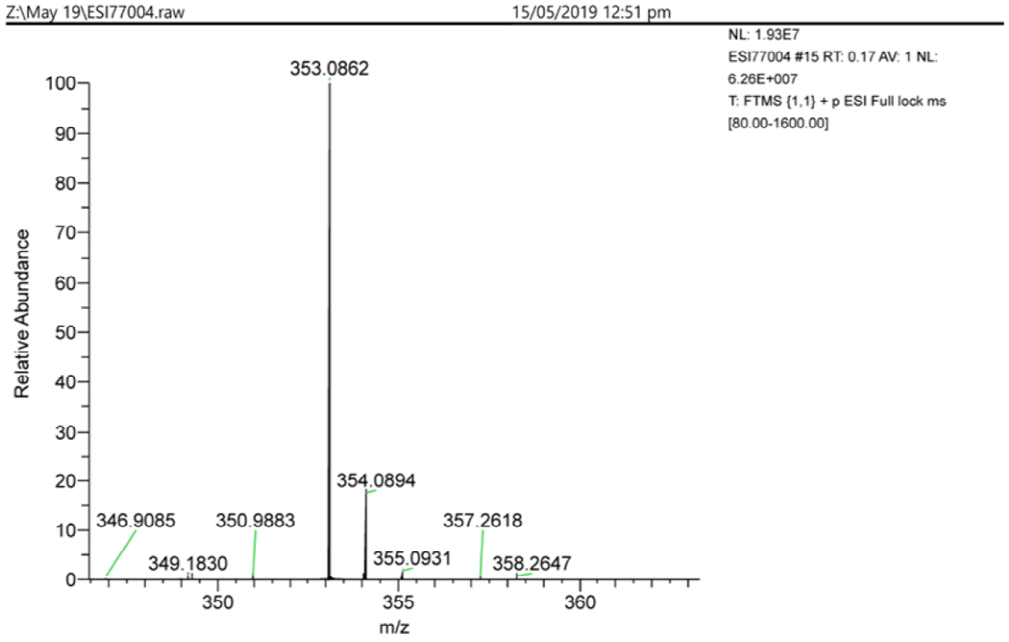

D (s) 161.18
F (s) 151.95
H (q) 149.18
G (d) 150.27
I (s) 144.22
J (q) 132.20
K (d) 128.25
L (d) 128.44
M (q) 123.17
N (q) 125.73
O (s) 122.95
P (d) 120.82
E (d) 114.68
C (d) 50.91
B (d) 21.15
A (d) 5.76
f1 (ppm)

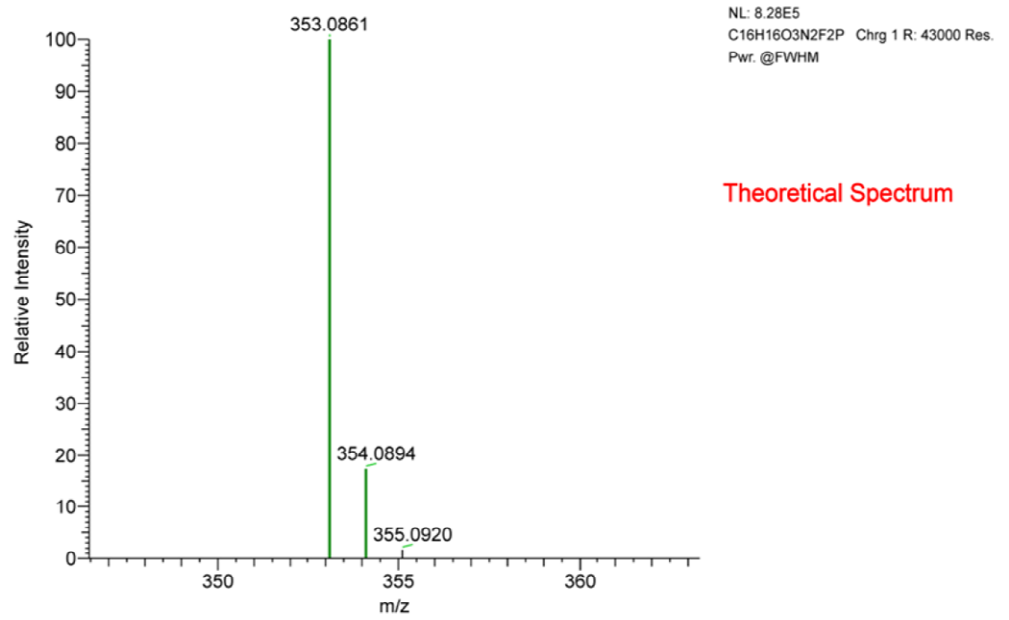

A (s)
46.54
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)


A (s)
-61.13
1.00
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

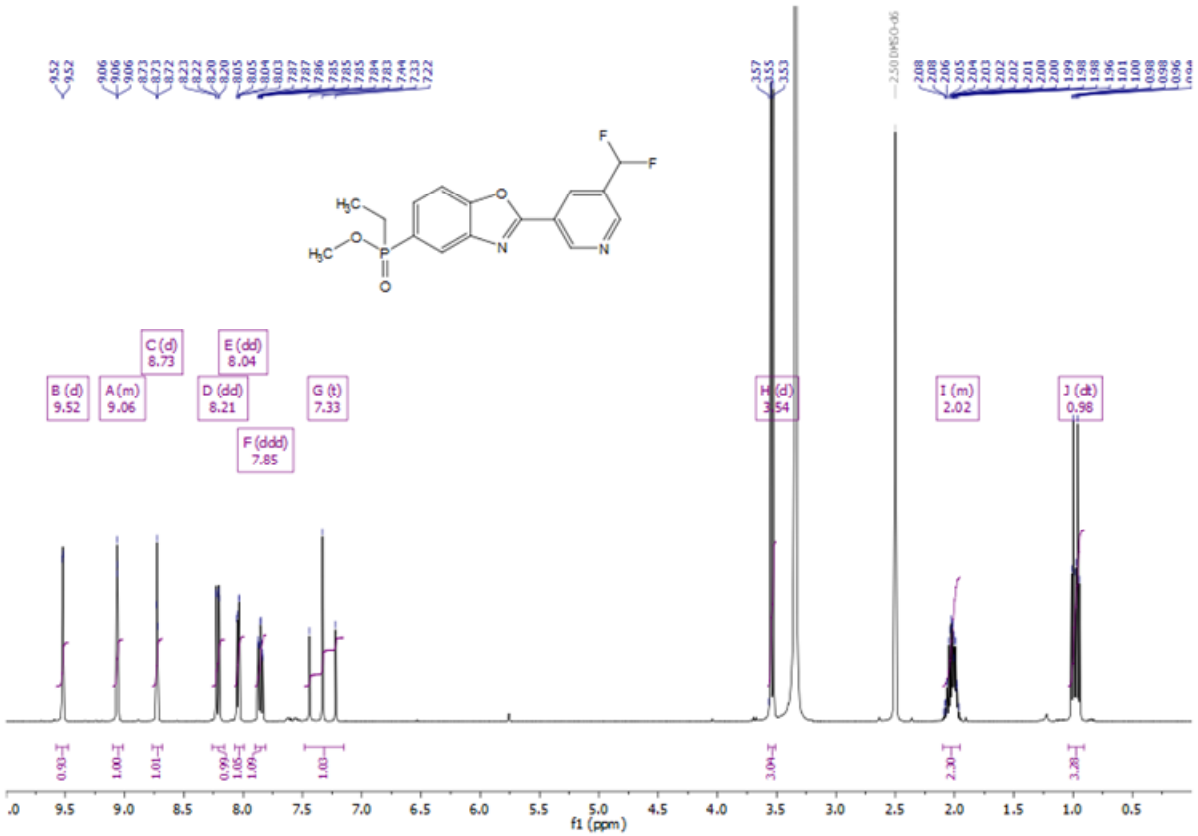
methyl (2-(5-(difluoromethyl)pyridin-3-yl)benzo[*d*]oxazol-5-yl)(ethyl)phosphinate (22)

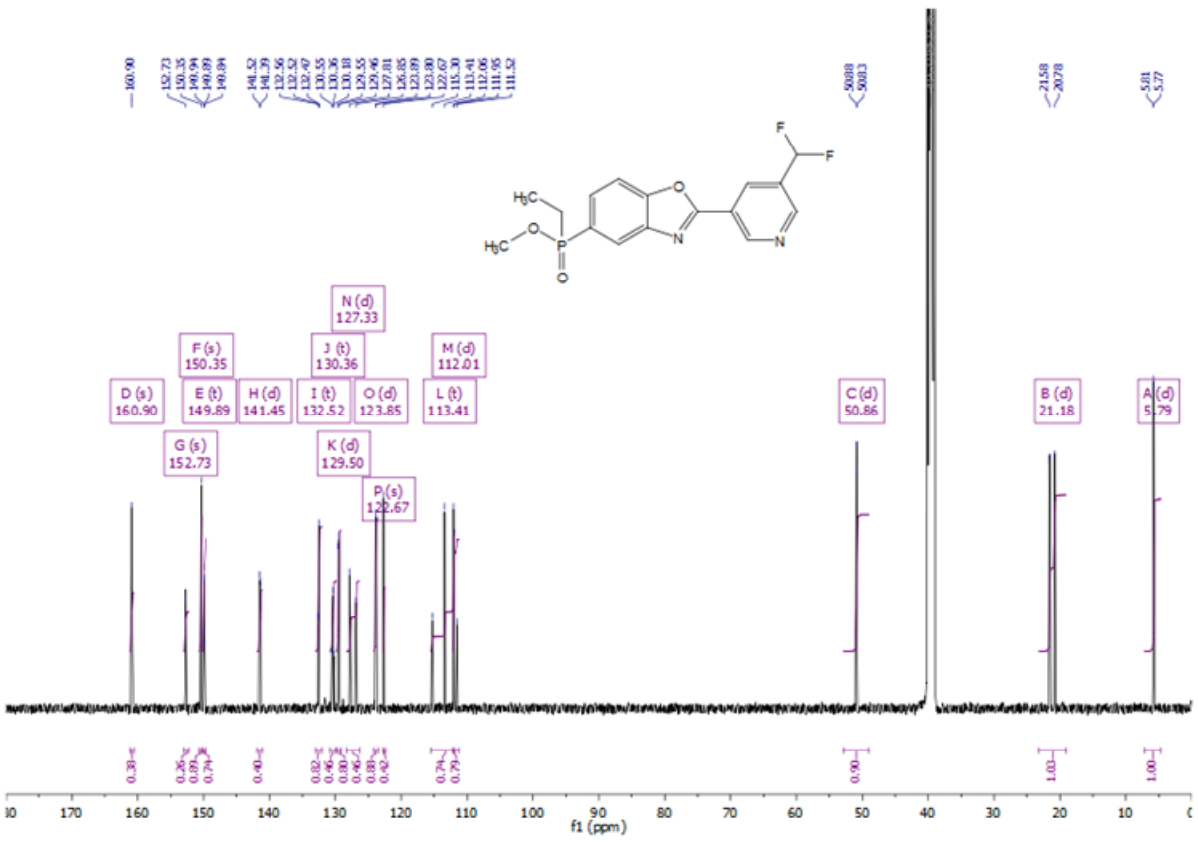


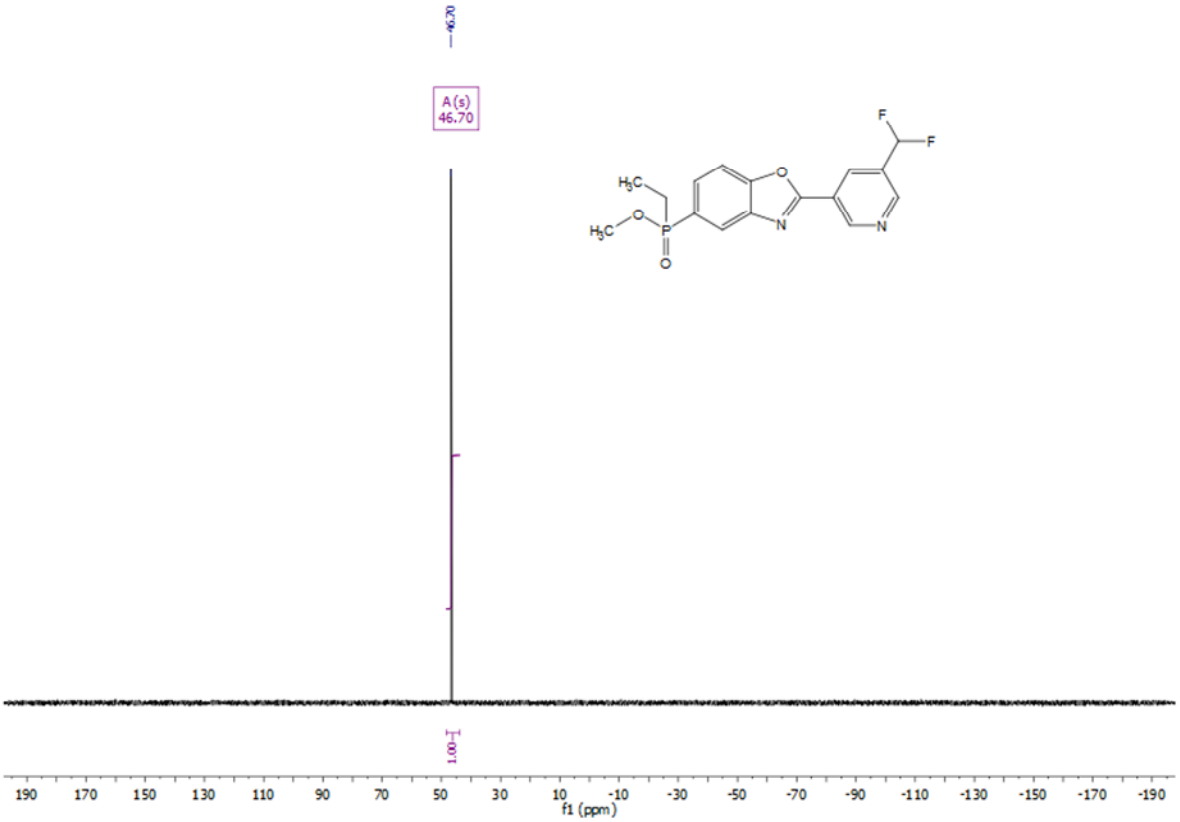


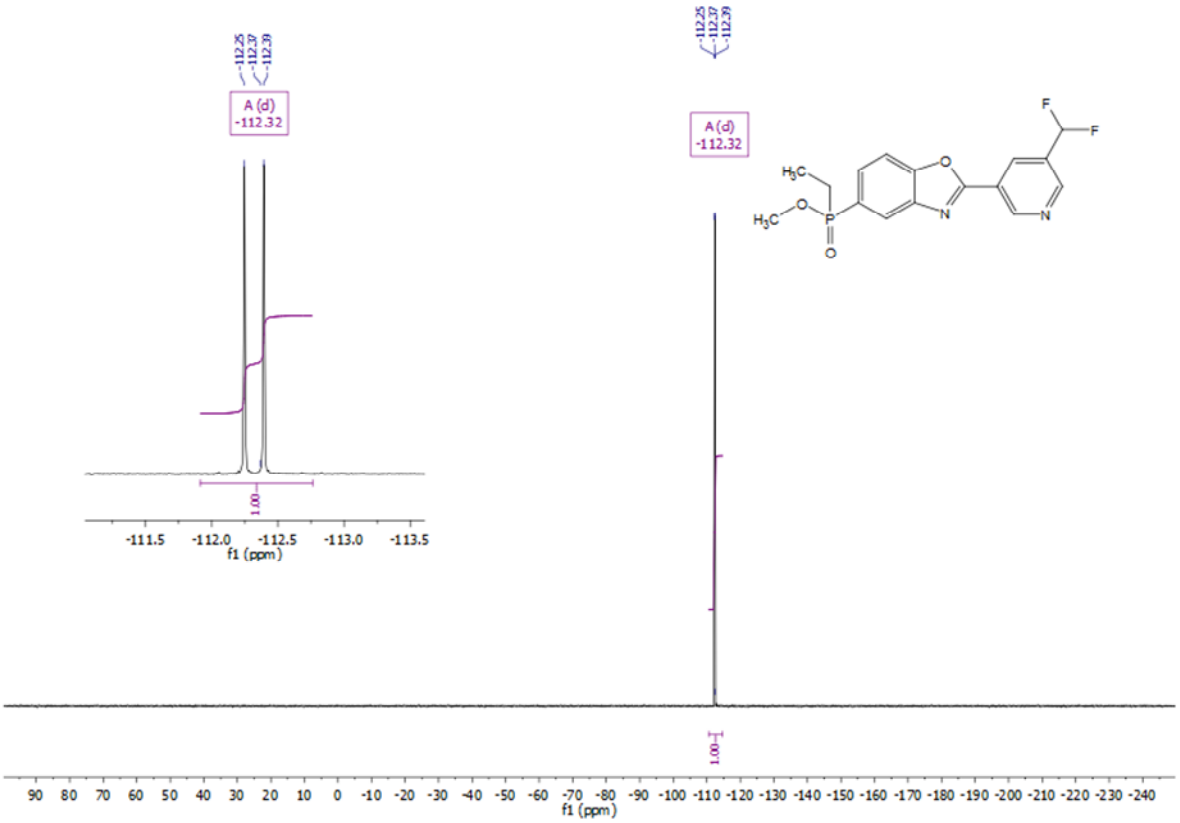


Peak Mass	Display...	Combin...	RDB	Delta [p...	Theo. m...	Rank	Combin...	# Match...	# Misse...	MS Cov....	Pattern...	MSMS...
353.0862	$C_{16}H_{16}$...	28.902...	9.50	0.20	353.08...	1	95.194...	3	1	98.877...	98.194...	(Collec...

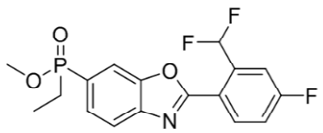

B (d) 9.52
A (m) 9.06
C (d) 8.73
D (dd) 8.21
E (dd) 8.04
F (ddd) 7.85
G (t) 7.33
H (d) 3.54
I (m) 2.02
J (dt) 0.98
f1 (ppm)

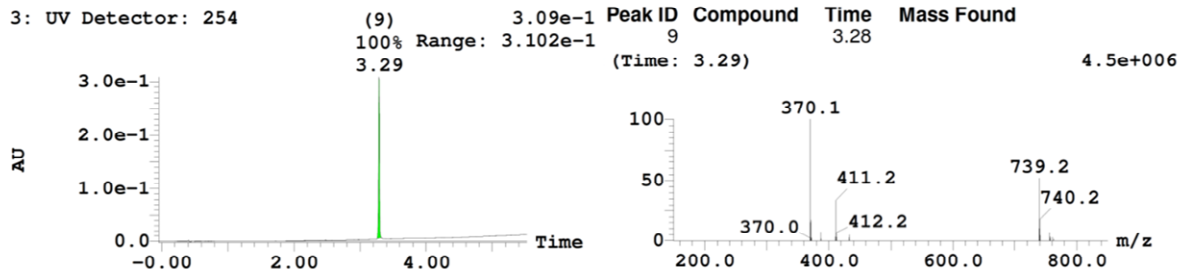

D (s) 160.90
G (s) 152.73
F (s) 150.35
E (t) 149.89
H (d) 141.45
N (d) 127.33
J (t) 130.36
I (t) 132.52
O (d) 123.85
K (d) 129.50
P (s) 122.67
M (d) 112.01
L (t) 113.41
C (d) 50.86
B (d) 21.18
A (d) 5.79
f1 (ppm)

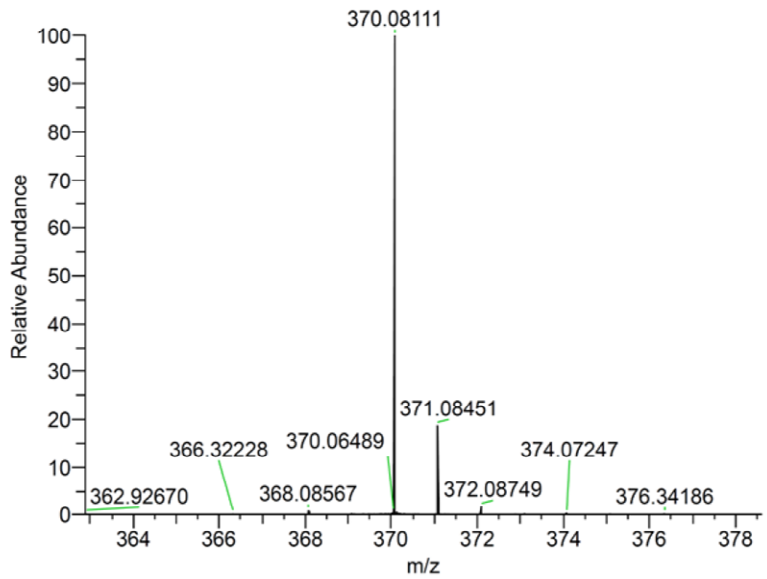

46.70
A (s)
46.70
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)


-112.25
-112.37
-112.39
A (d)
-112.32
1.00
-111.5 -112.0 -112.5 -113.0 -113.5
f1 (ppm)
1.00
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

methyl (2-(2-(difluoromethyl)-4-fluorophenyl)benzo[d]oxazol-6-yl)(ethyl)phosphinate (23)

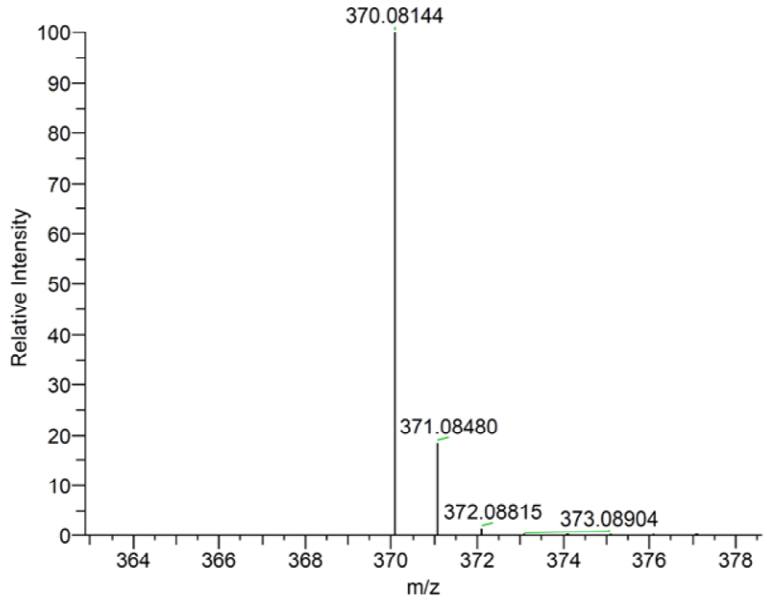






NL: 1.73E7
ESI74318 #13-27 RT: 0.15-0.31 AV: 8 NL
1.73E+007
T: FTMS {1,1} + p ESI Full lock ms
[80.00-1600.00]

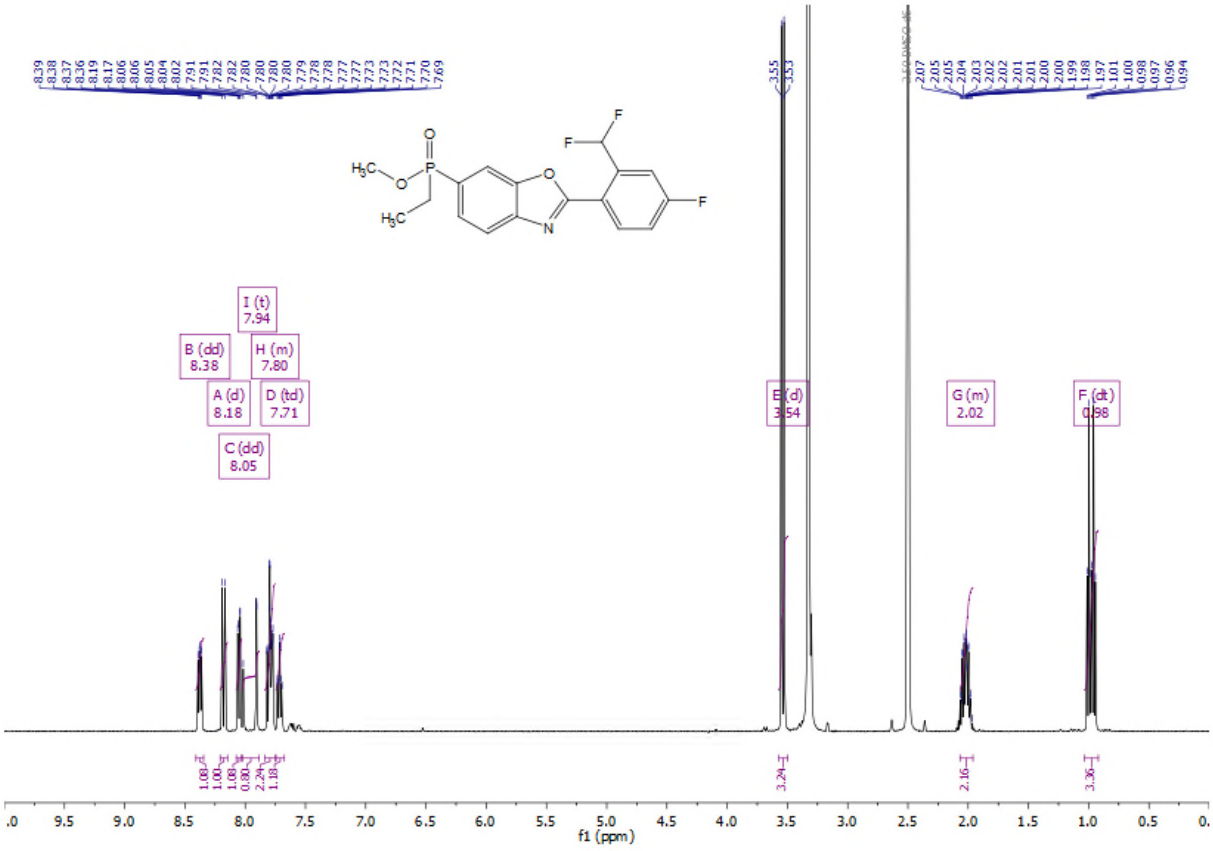
Measured Spectrum

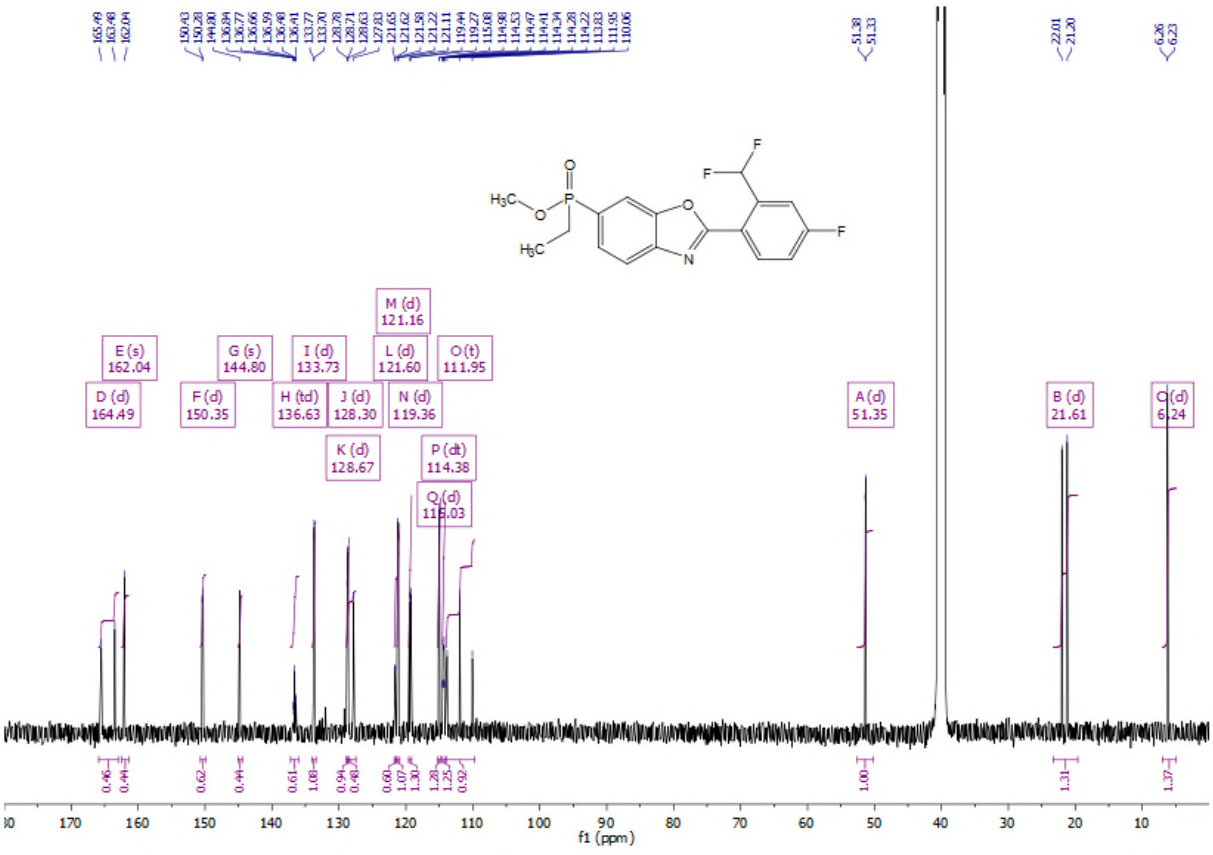


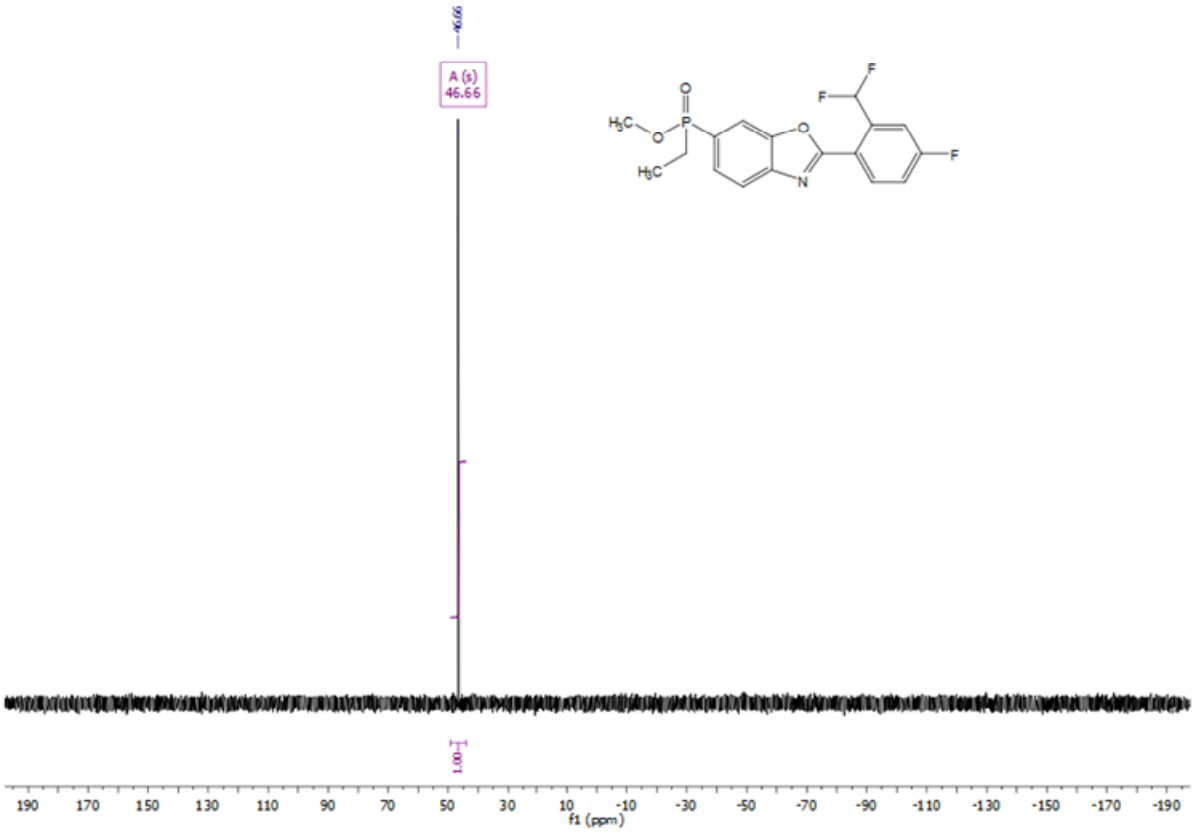
NL: 8.22E5
C17H16O3N1F3P1: $C_{17}H_{16}O_3NF_3P$
Chrg 1 R: 1000000 Res. Pwr. @FWHM

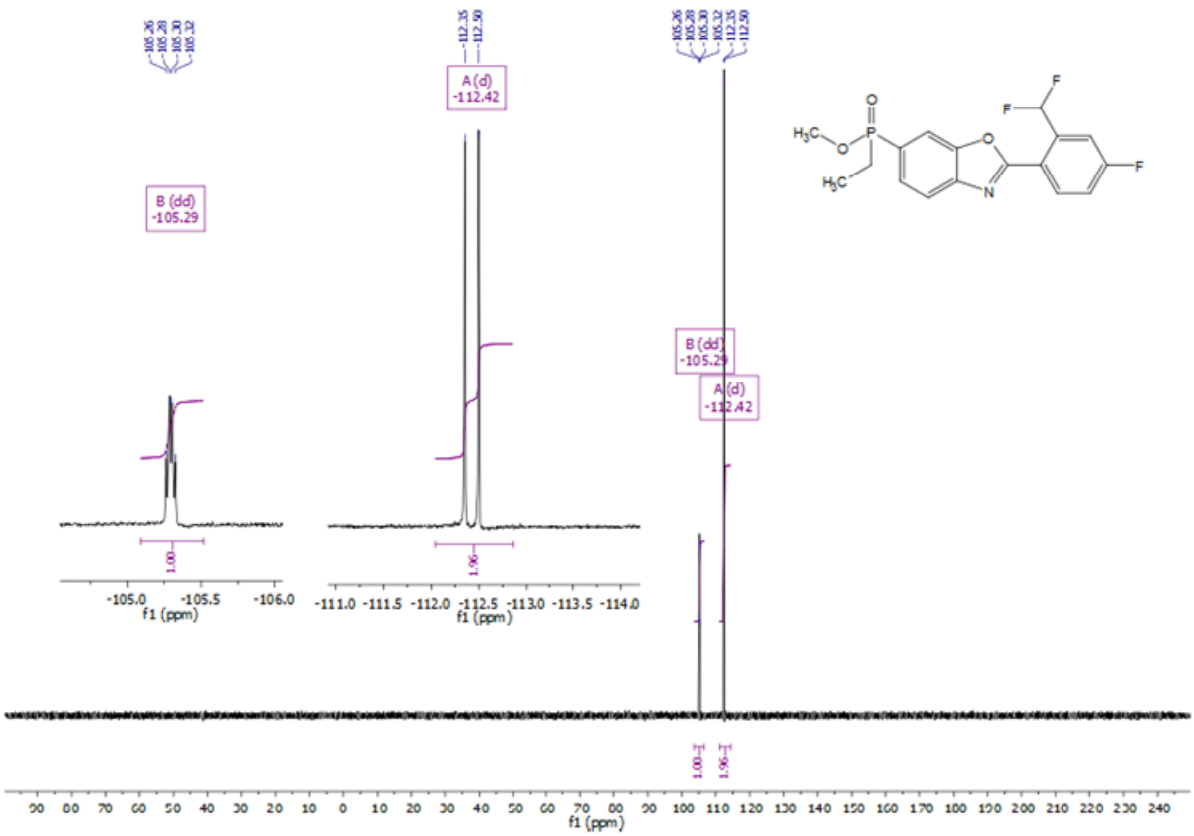
Theoretical Spectrum

m/z	Formula	RDB	Delta ppm	Theo. Mass
370.08112	$C_{17}H_{16}O_3NF_3P$	9.5	-0.88	370.08144

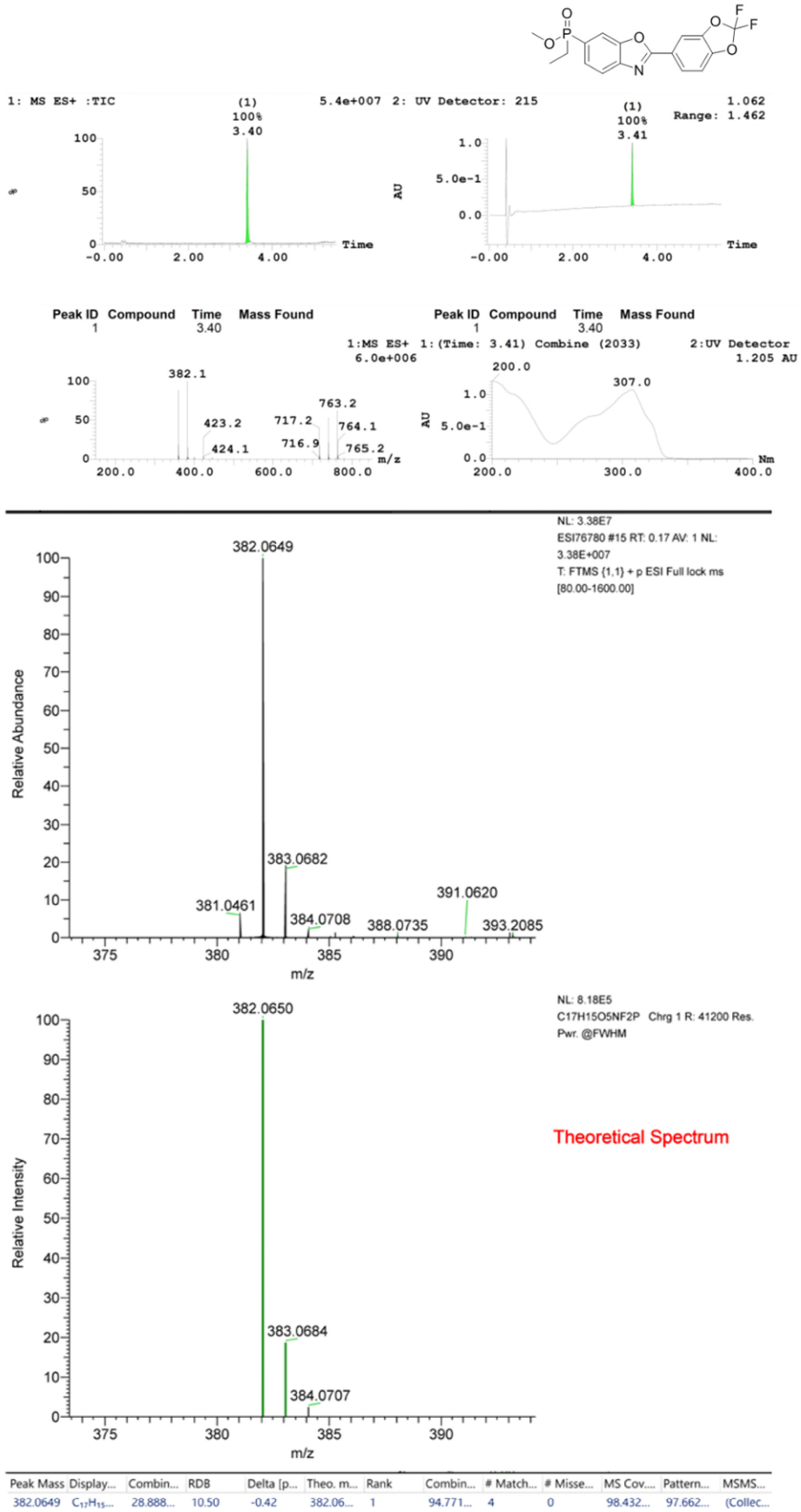

I (t)
7.94
B (dd)
8.38
H (m)
7.80
A (d)
8.18
D (td)
7.71
C (dd)
8.05
E (d)
3.54
G (m)
2.02
F (dt)
0.98
f1 (ppm)

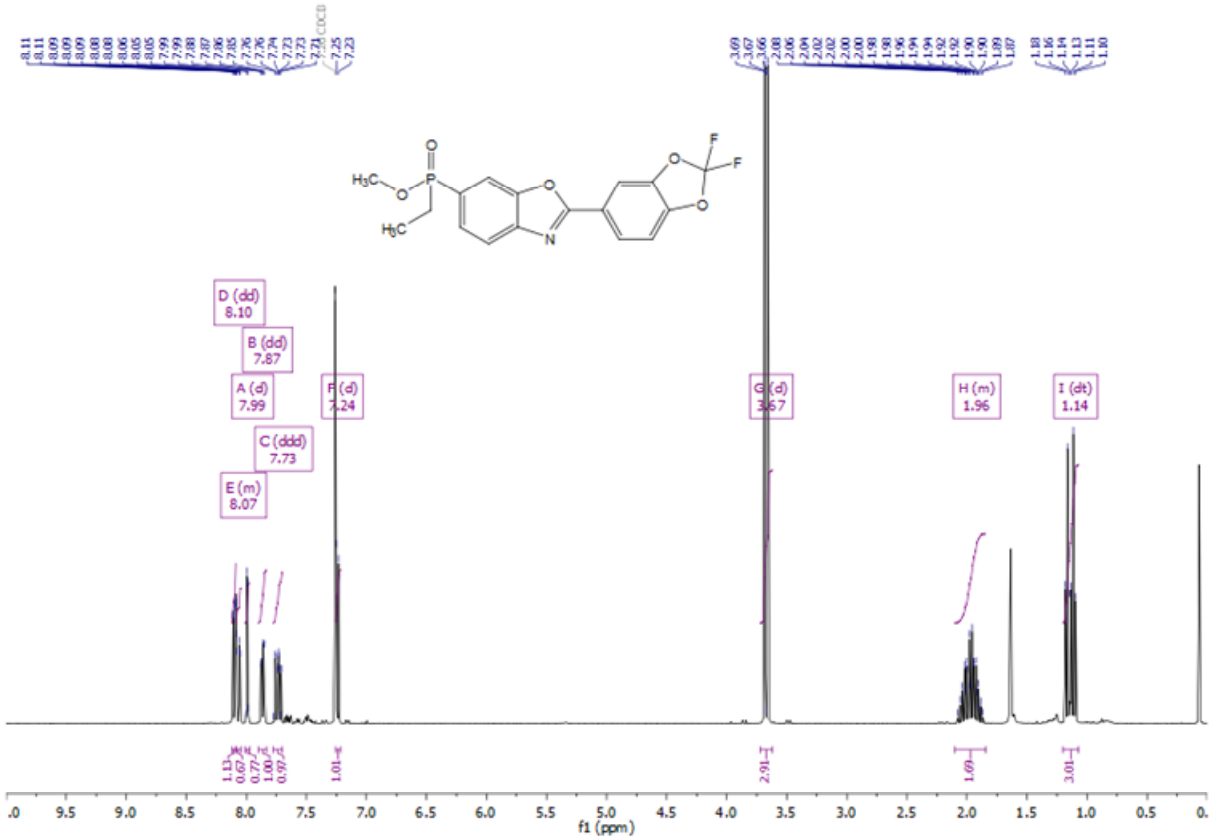

M (d)
121.16
E (s)
162.04
G (s)
144.80
I (d)
133.73
L (d)
121.60
O (t)
111.95
D (d)
164.49
F (d)
150.35
H (td)
136.63
J (d)
128.30
N (d)
119.36
K (d)
128.67
P (dt)
114.38
Q (d)
118.03
A (d)
51.35
B (d)
21.61
C (d)
6.24
f1 (ppm)

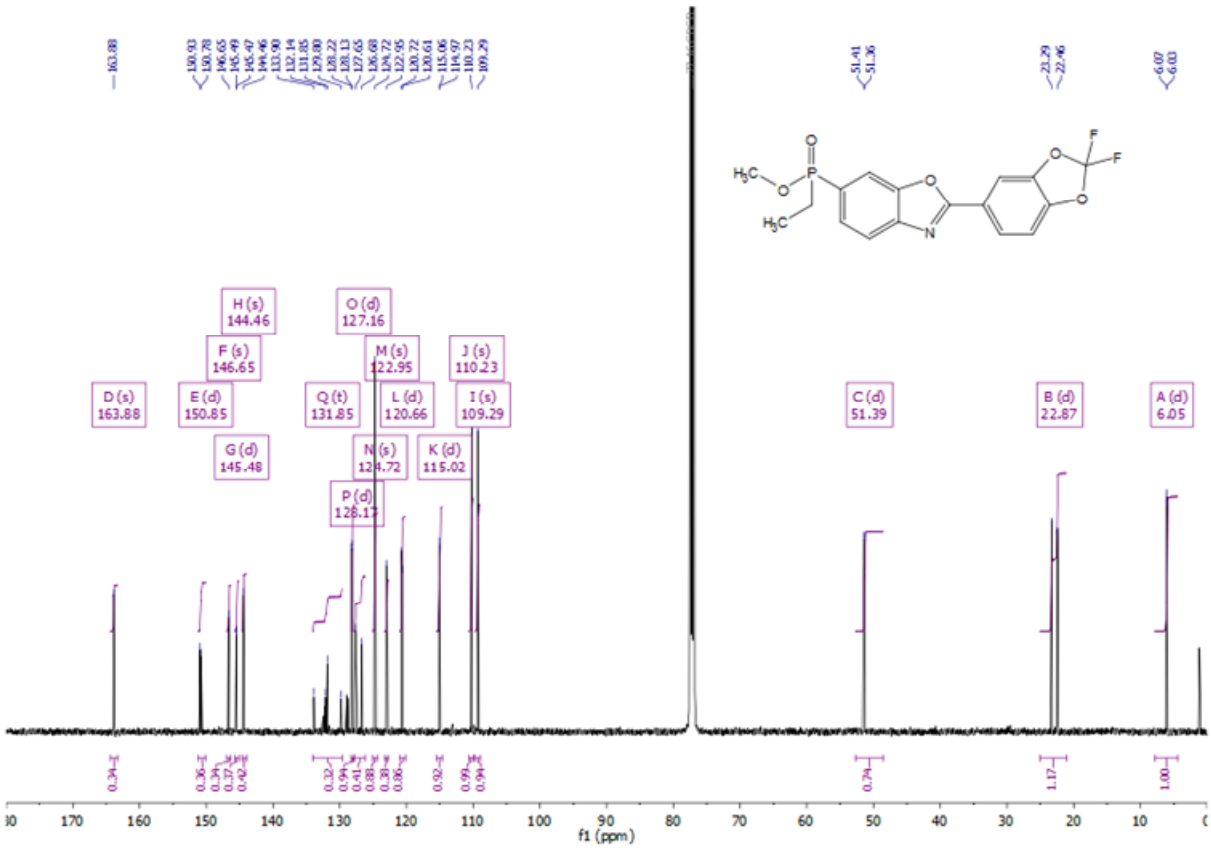

46.66
A (s)
46.66
1.00
f1 (ppm)

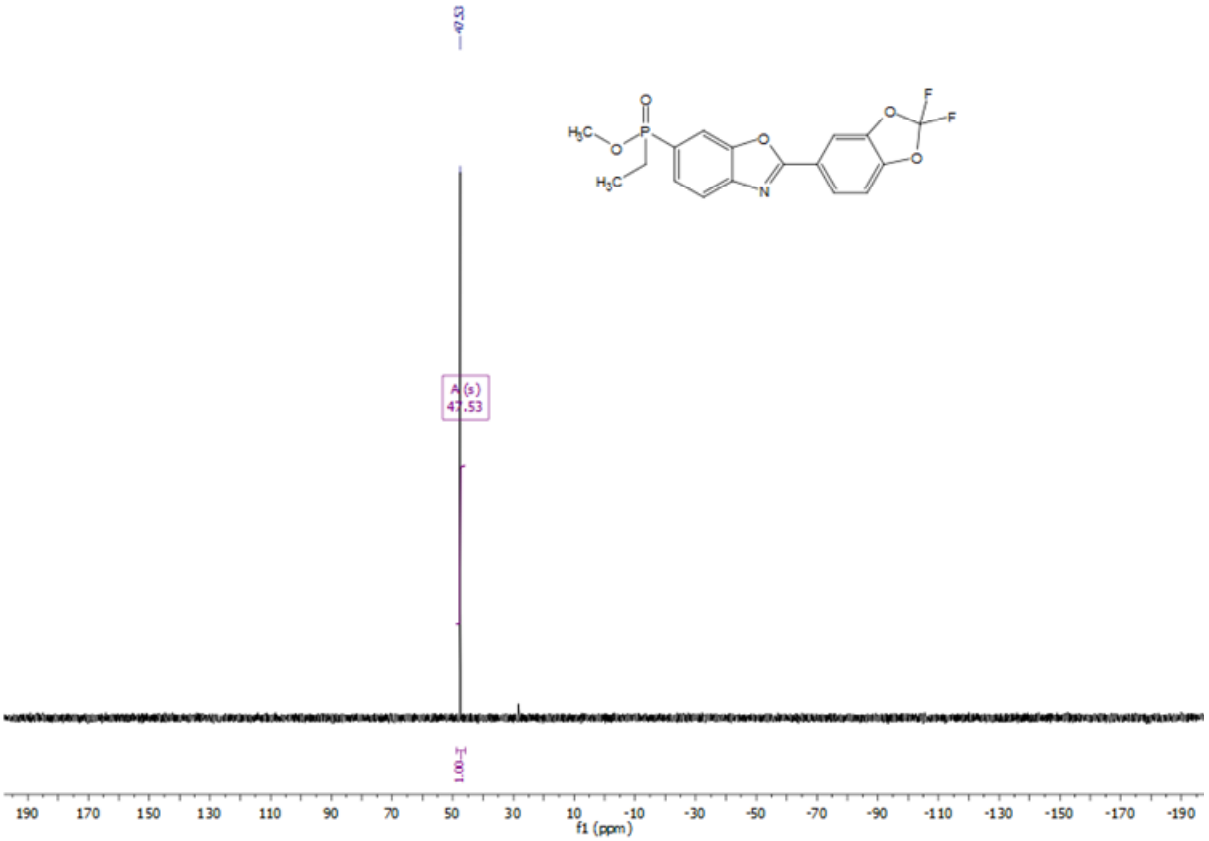

105.26
105.28
105.30
105.32
112.35
112.50
A (d)
-112.42
B (dd)
-105.29
1.00
1.96
f1 (ppm)

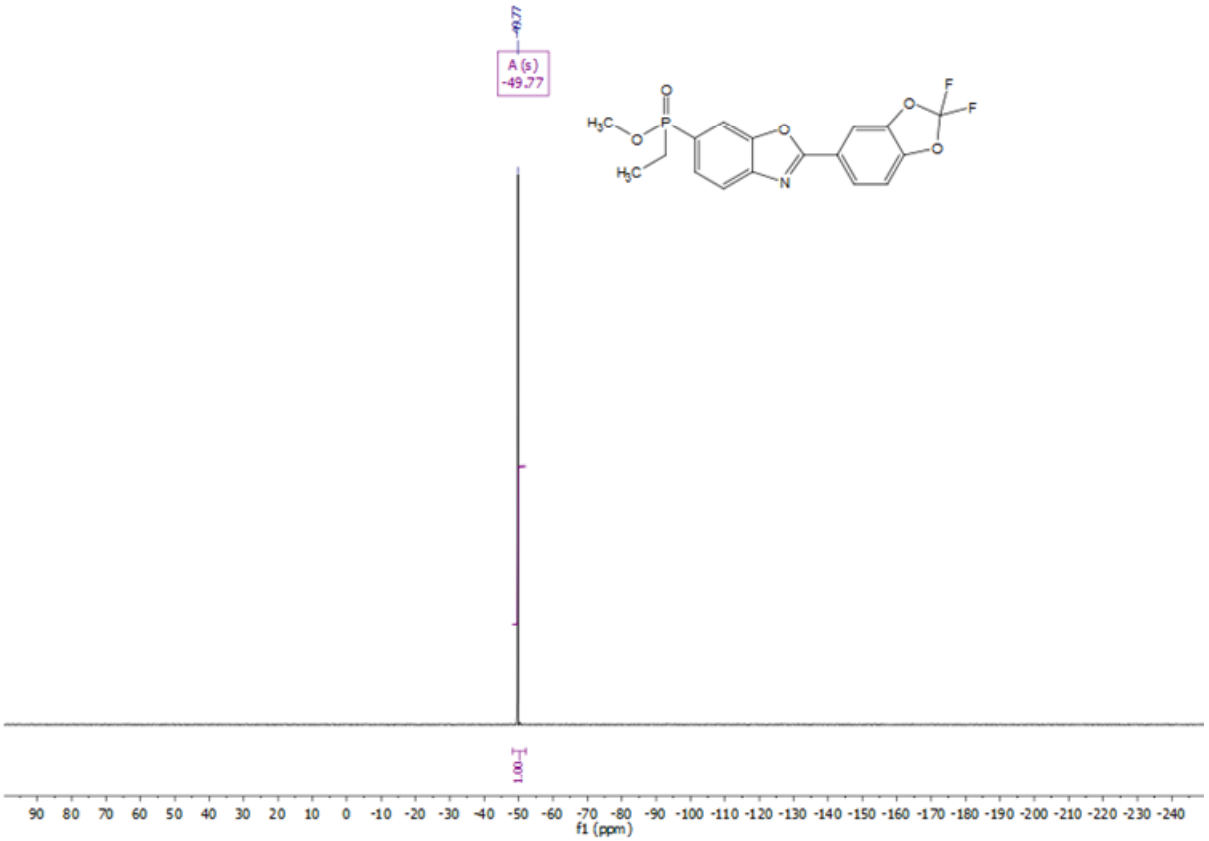
methyl (2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)benzo[d]oxazol-6-yl)(ethyl)phosphinate (24)



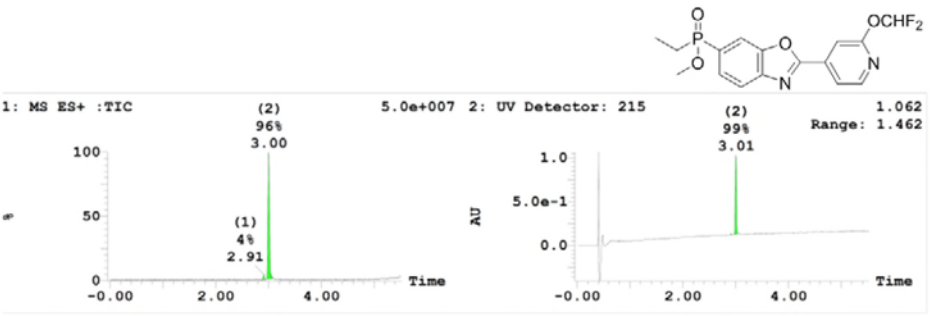

D (dd)
8.10
B (dd)
7.87
A (d)
7.99
C (ddd)
7.73
E (m)
8.07
F (d)
7.24
G (d)
3.67
H (m)
1.96
I (dt)
1.14
f1 (ppm)

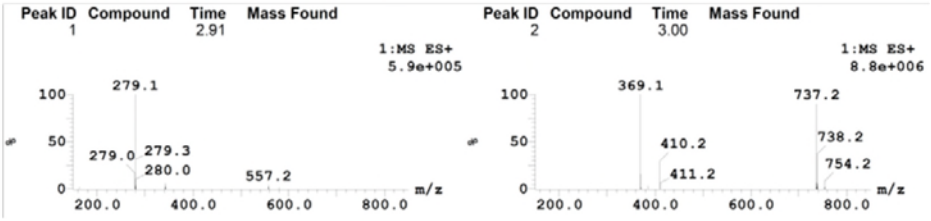

H (s)
144.46
O (d)
127.16
F (s)
146.65
M (s)
122.95
J (s)
110.23
D (s)
163.88
E (d)
150.85
Q (t)
131.85
L (d)
120.66
I (s)
109.29
G (d)
145.48
N (s)
124.72
K (d)
115.02
P (d)
128.17
C (d)
51.39
B (d)
22.87
A (d)
6.05
f1 (ppm)

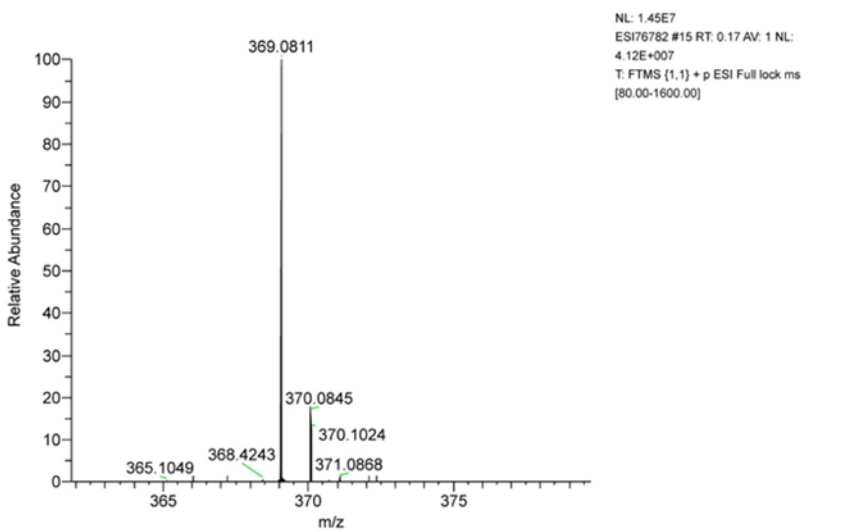

-47.53
A (s)
47.53
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

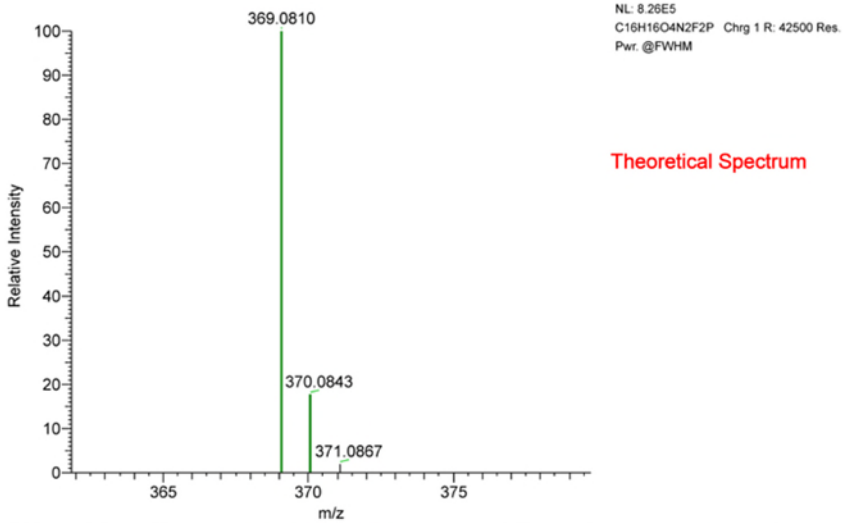

-49.77
A (s)
-49.77
1.00
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

methyl (2-(2-(difluoromethoxy)pyridin-4-yl)benzo[*d*]oxazol-6-yl)(ethyl)phosphinate (25)

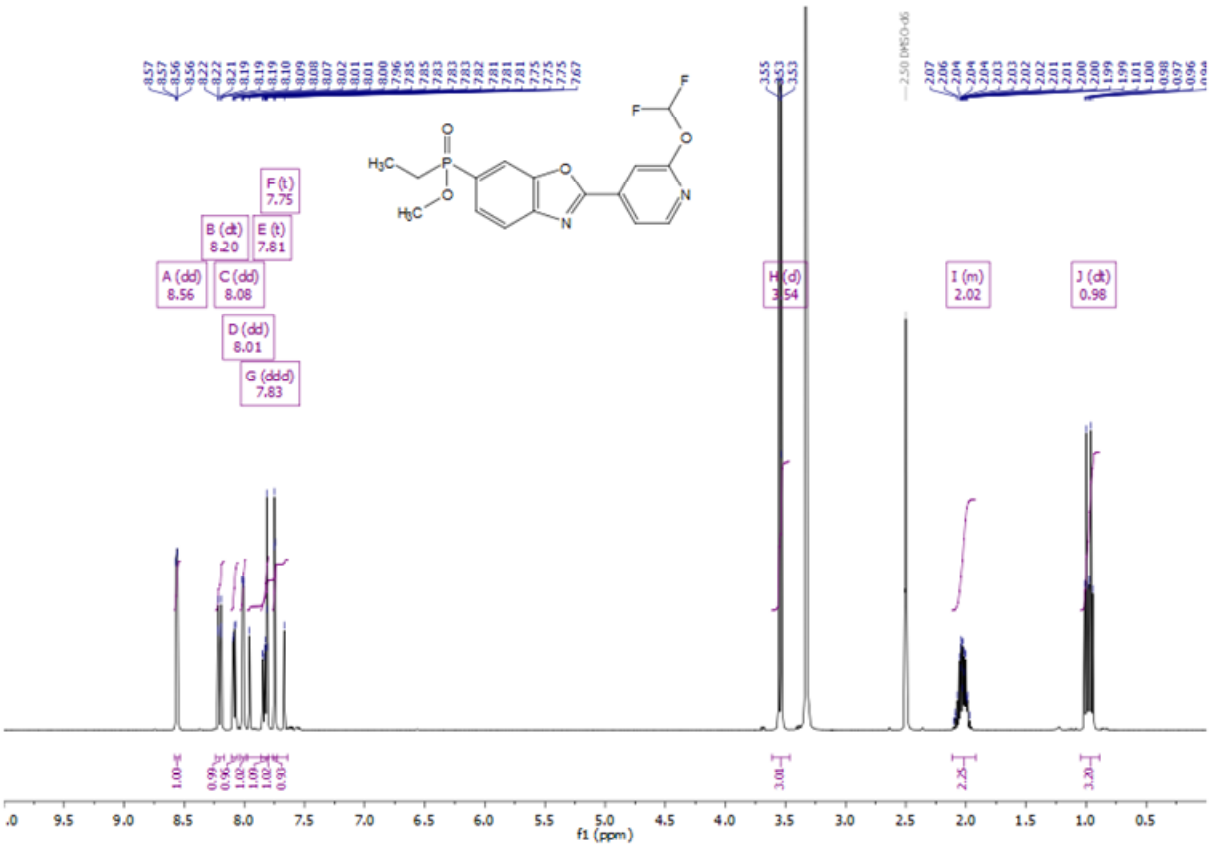


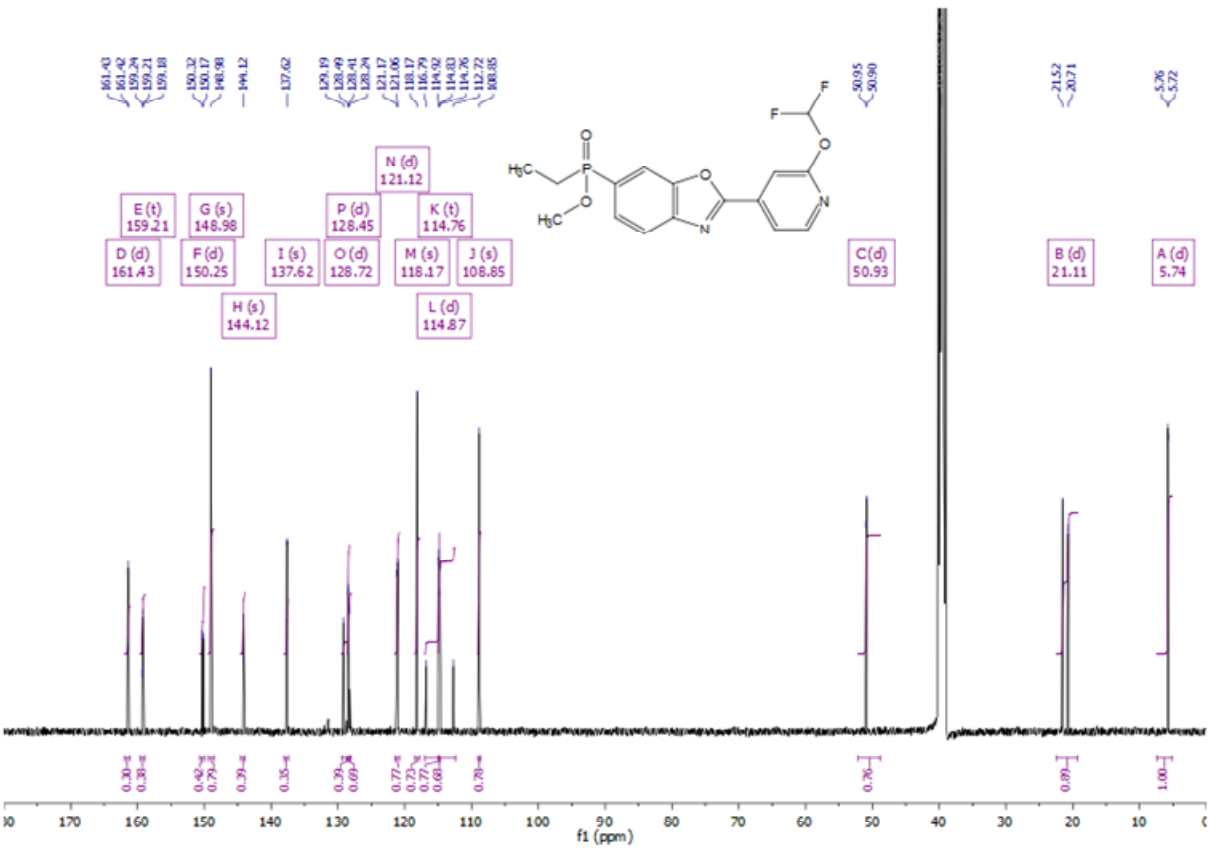




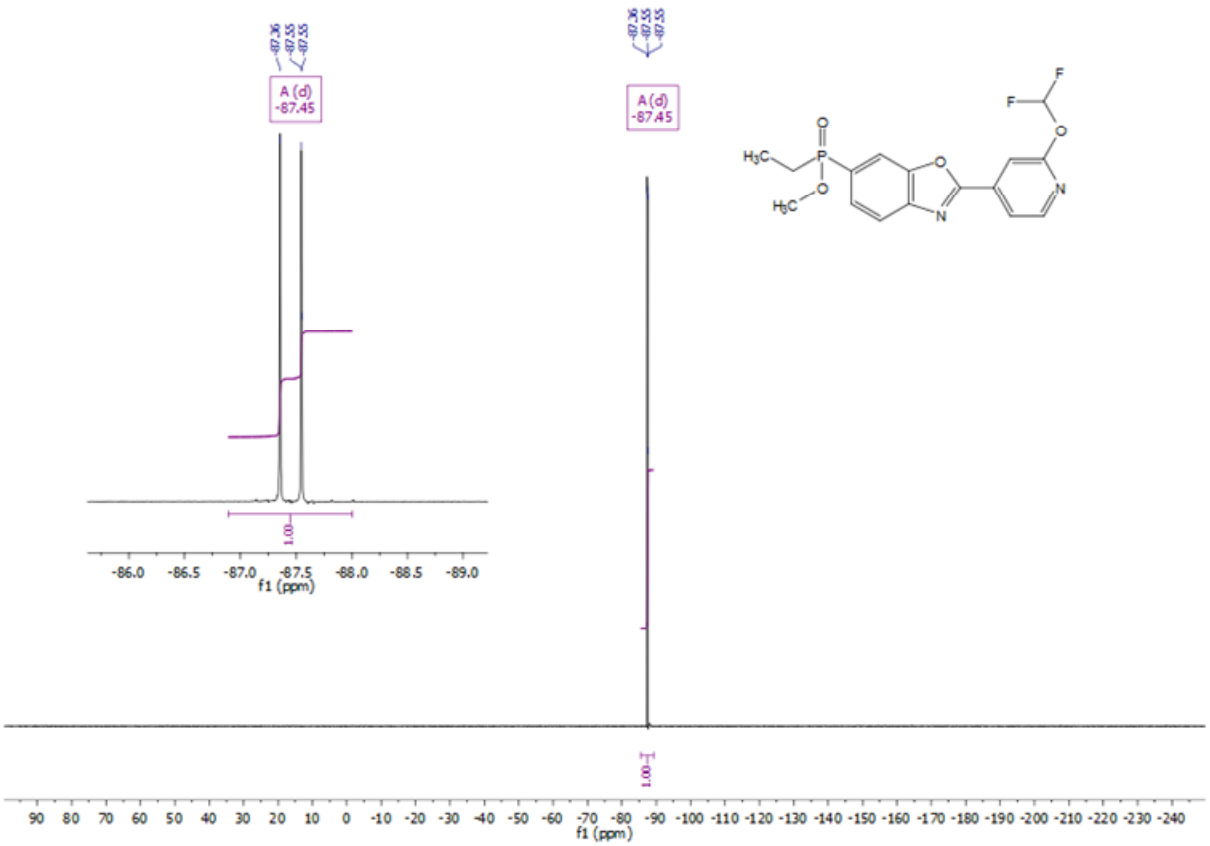


Peak Mass	Display...	Combin...	RDB	Delta [p...	Theo. m...	Rank	Combin...	# Match...	# Misse...	MS Cov....	Pattern...	MSMS...
369.0811	$C_{16}H_{16}$...	38.696...	9.50	0.32	369.08...	1	95.632...	4	0	98.795...	98.168...	(Collec...

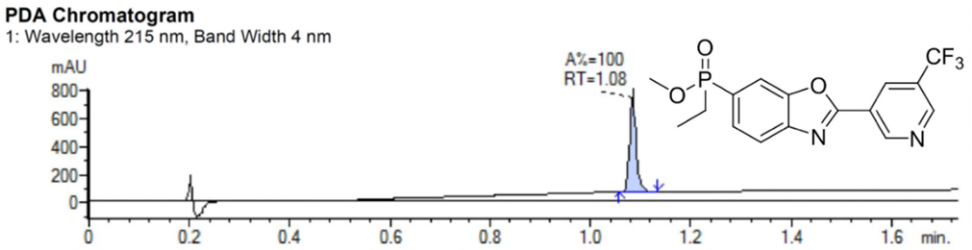

F (t) 7.75
B (dt) 8.20
E (t) 7.81
A (dd) 8.56
C (dd) 8.08
D (dd) 8.01
G (ddd) 7.83
H (d) 3.54
I (m) 2.02
J (dt) 0.98
f1 (ppm)

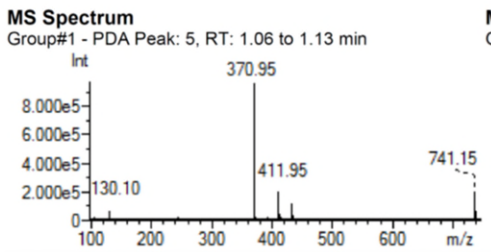

N (d) 121.12
E (t) 159.21
G (s) 148.98
P (d) 128.45
K (t) 114.76
D (d) 161.43
F (d) 150.25
I (s) 137.62
O (d) 128.72
M (s) 118.17
J (s) 108.85
H (s) 144.12
L (d) 114.87
C (d) 50.93
B (d) 21.11
A (d) 5.74
f1 (ppm)

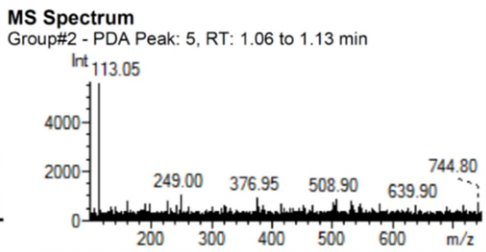

46.51
A (s)
46.51
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

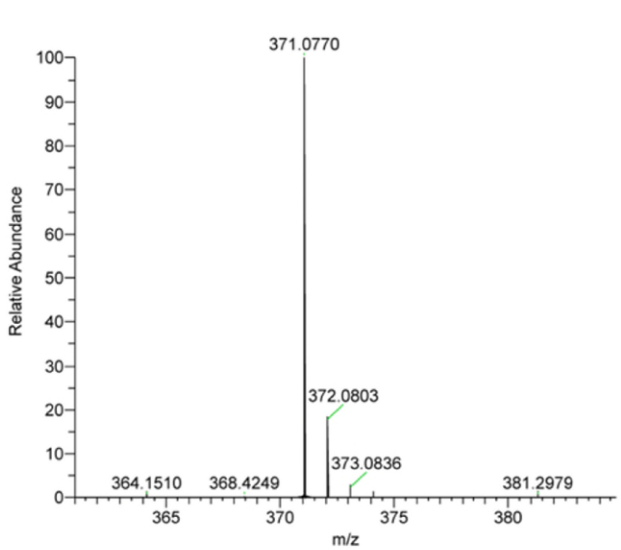

-87.36
-87.55
-87.55
A (d)
-87.45
1.00
-86.0 -86.5 -87.0 -87.5 -88.0 -88.5 -89.0
f1 (ppm)
-87.36
-87.55
-87.55
A (d)
-87.45
1.00
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

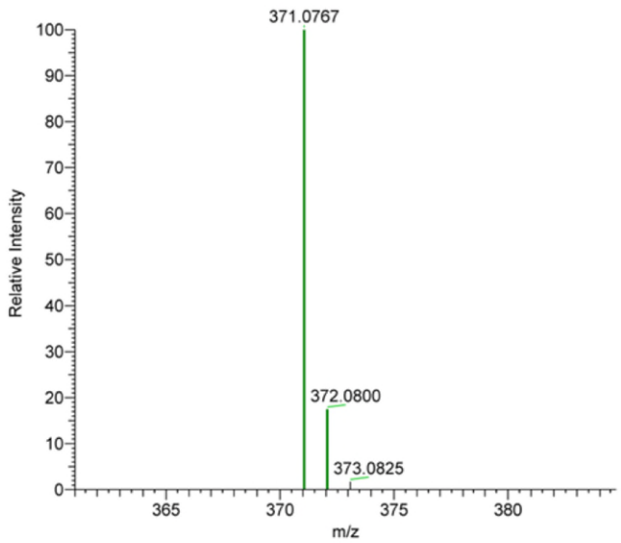
methyl ethyl(2-(5-(trifluoromethyl)pyridin-3-yl)benzo[*d*]oxazol-6-yl)phosphinate (26)



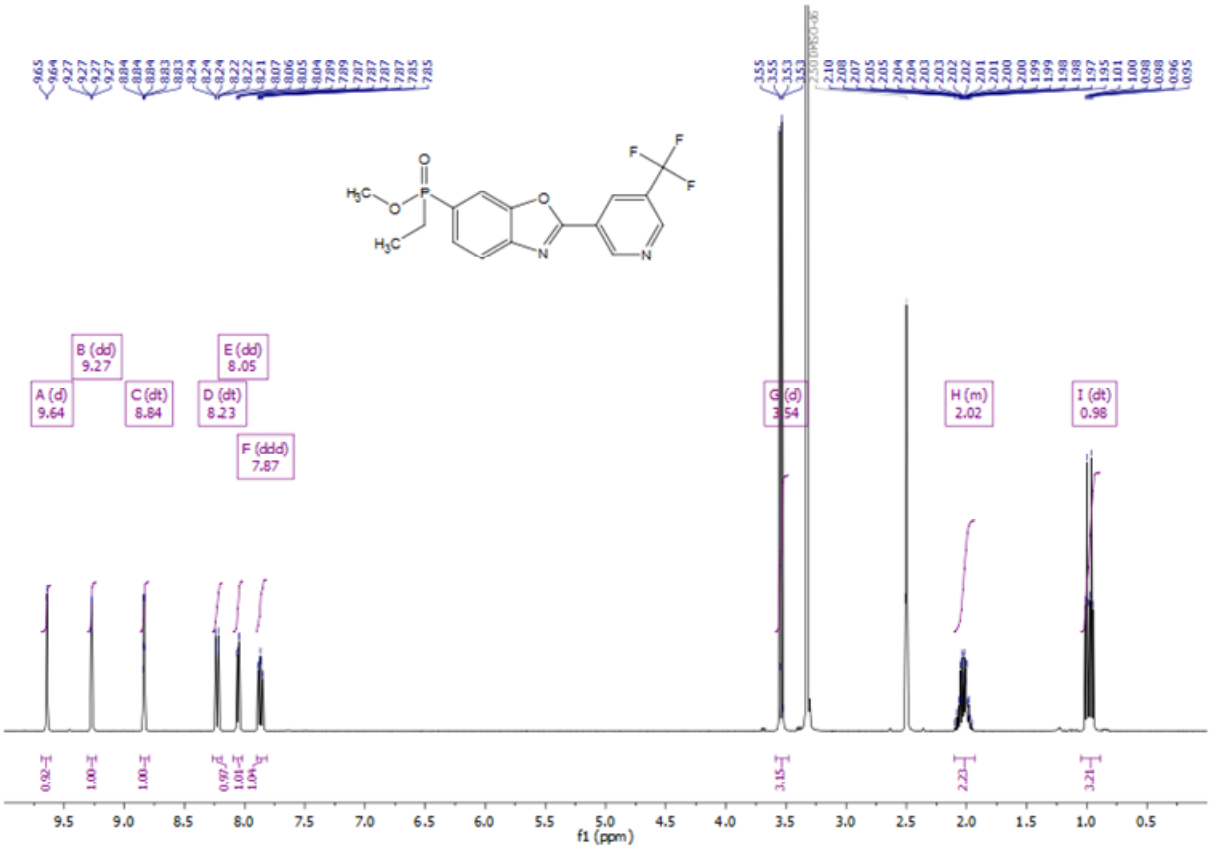


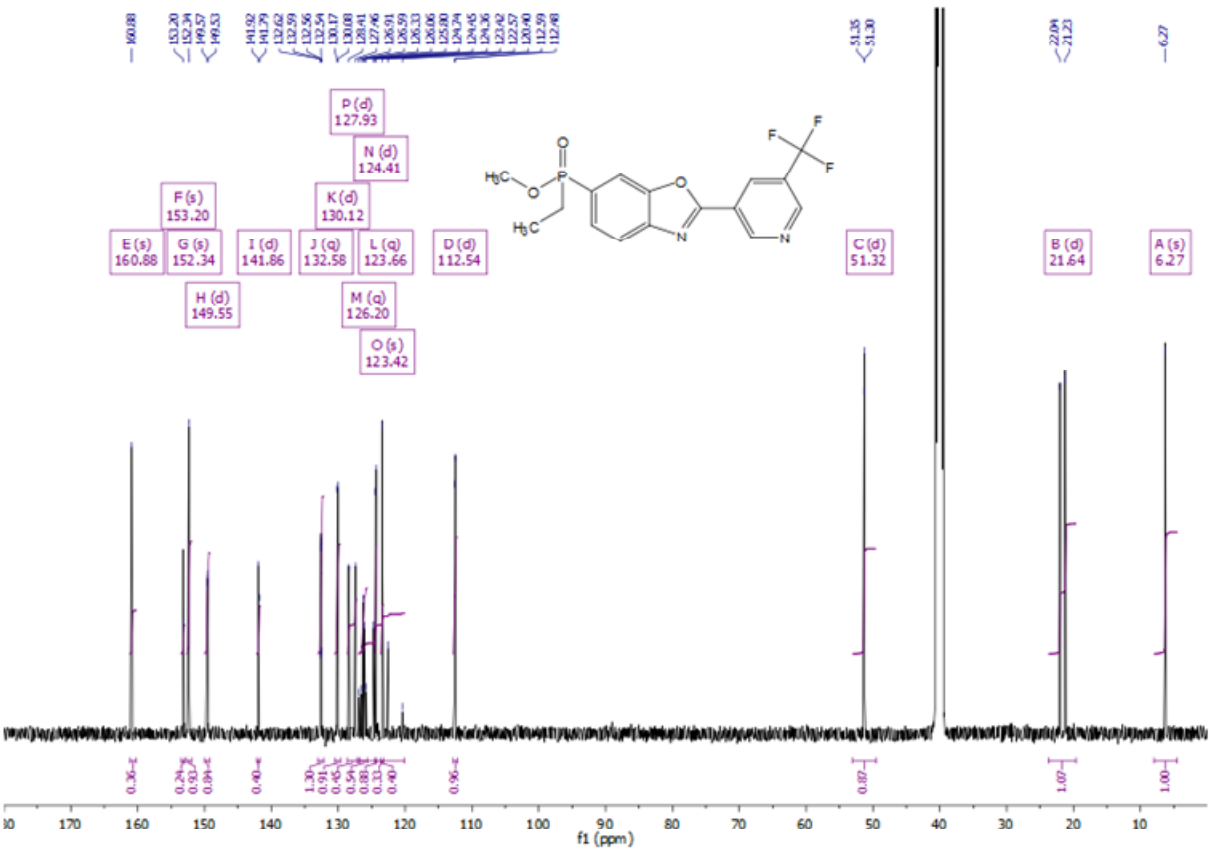




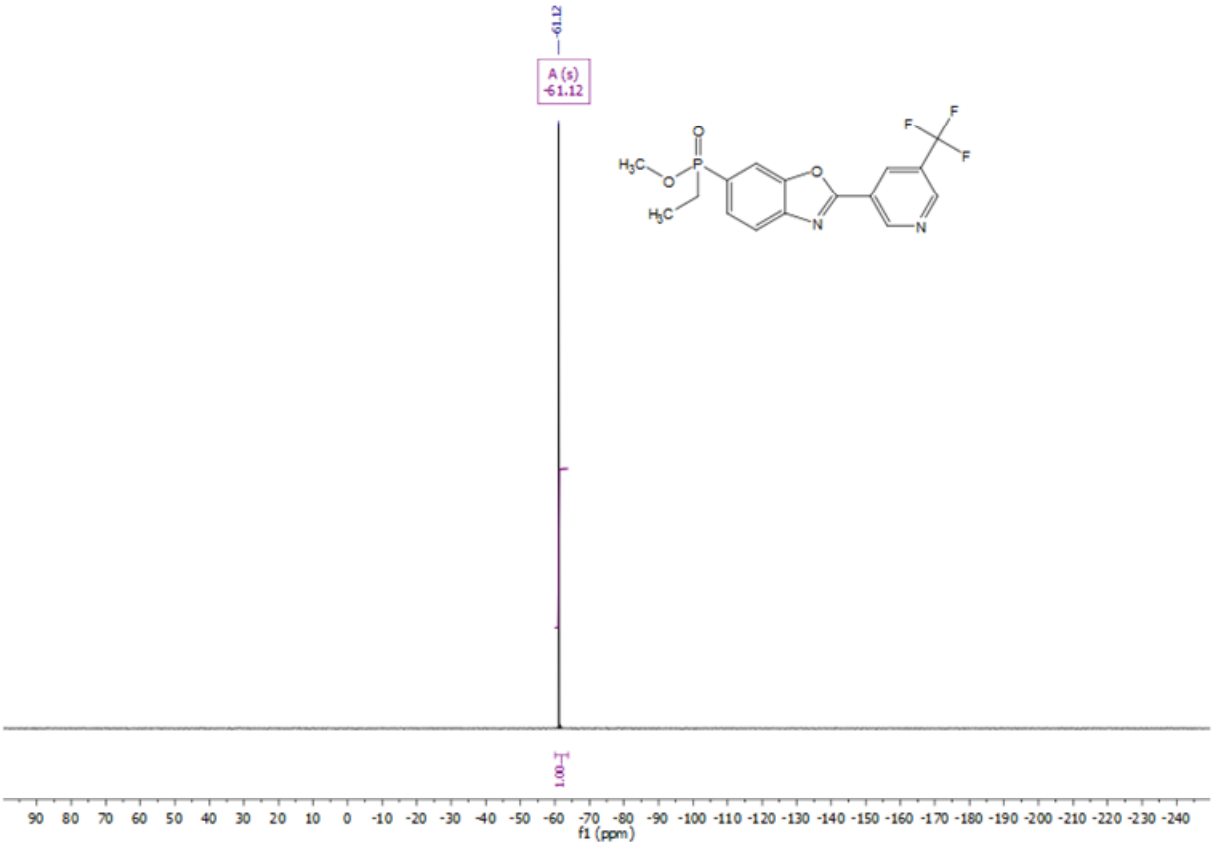


Peak Mass	Display...	Combin...	RDB	Delta (p...	Theo. m...	Rank	Combin...	# Match...	# Misse...	MS Cov....	Pattern...	MSMS.
371.0770	$C_{16}H_{15}$...	40.435...	9.50	0.82	371.07...	1	96.457...	3	1	99.569...	99.855...	(Collec

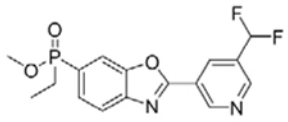

A (d) 9.64
B (dd) 9.27
C (dt) 8.84
D (dt) 8.23
E (dd) 8.05
F (ddd) 7.87
G (d) 3.54
H (m) 2.02
I (dt) 0.98
f1 (ppm)

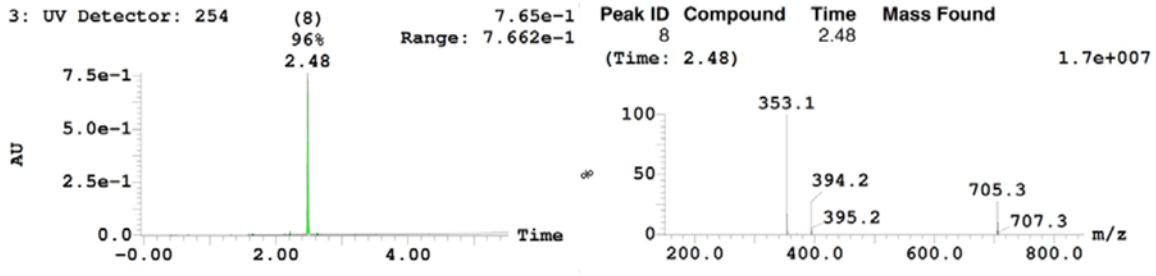

P (d) 127.93
N (d) 124.41
F (s) 153.20
K (d) 130.12
E (s) 160.88
G (s) 152.34
I (d) 141.86
J (q) 132.58
L (q) 123.66
D (d) 112.54
H (d) 149.55
M (q) 126.20
O (s) 123.42
C (d) 51.32
B (d) 21.64
A (s) 6.27
f1 (ppm)

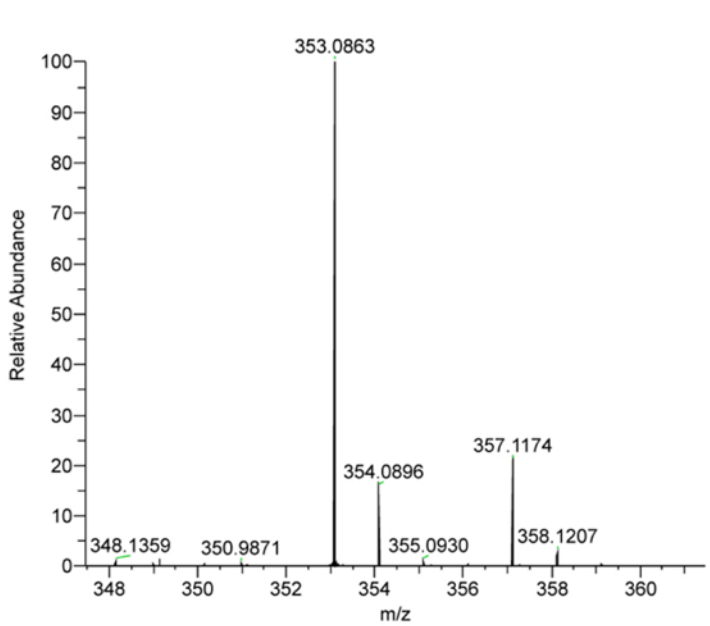

46.61
A (s)
46.61
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

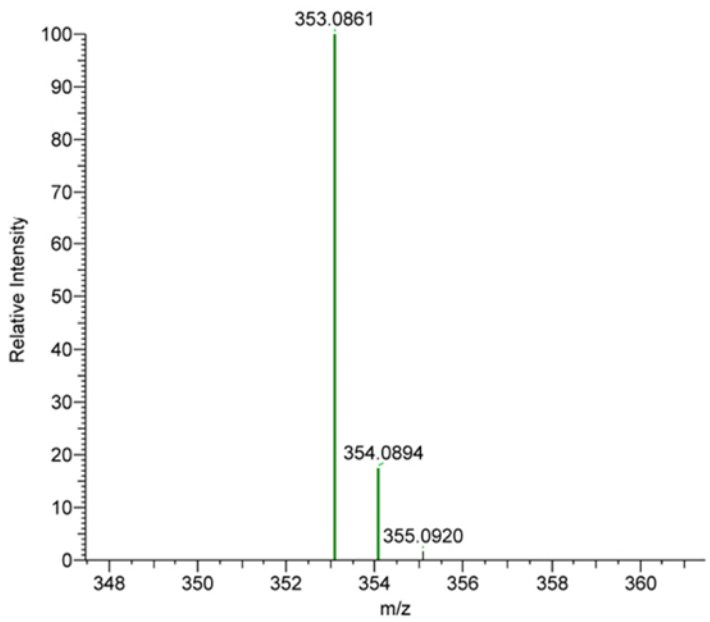

-61.12
A (s)
-61.12
1.00
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

methyl (2-(5-(difluoromethyl)pyridin-3-yl)benzo[d]oxazol-6-yl)(ethyl)phosphinate (27)

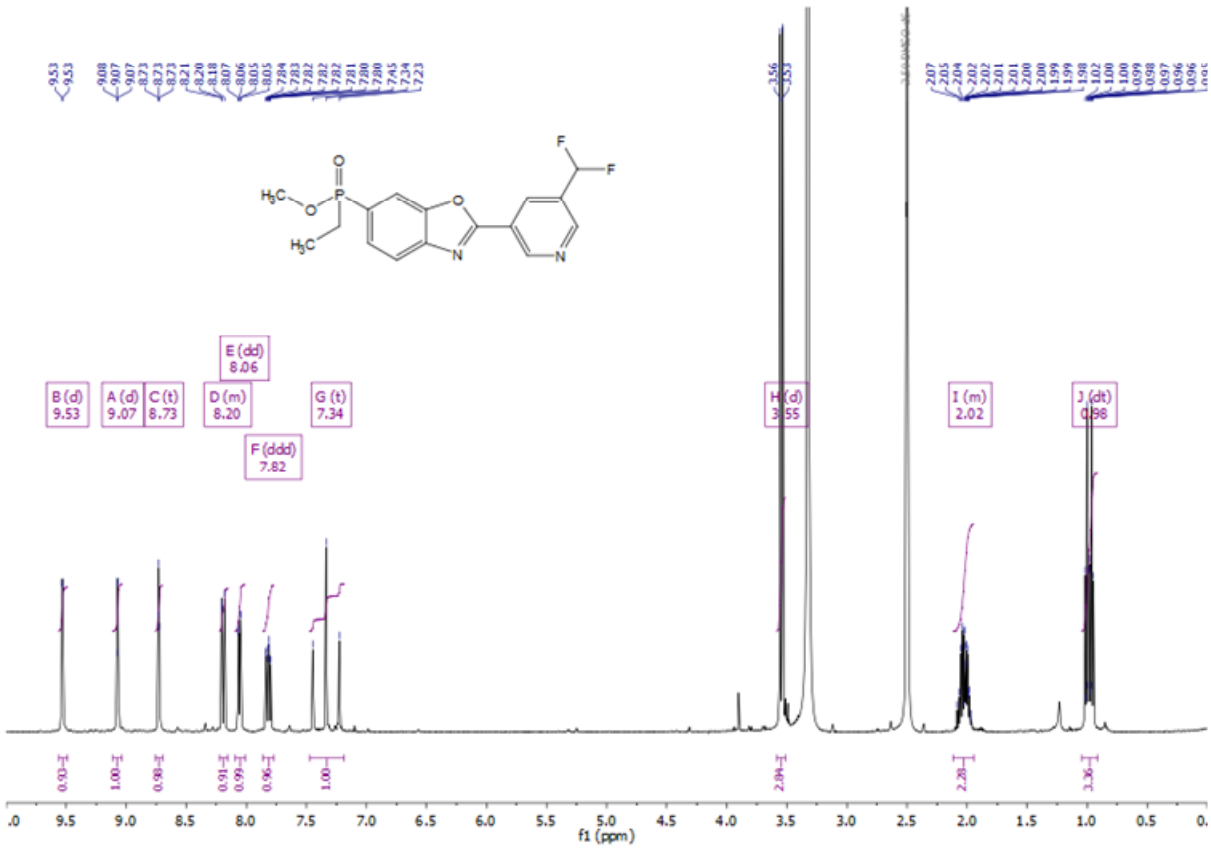


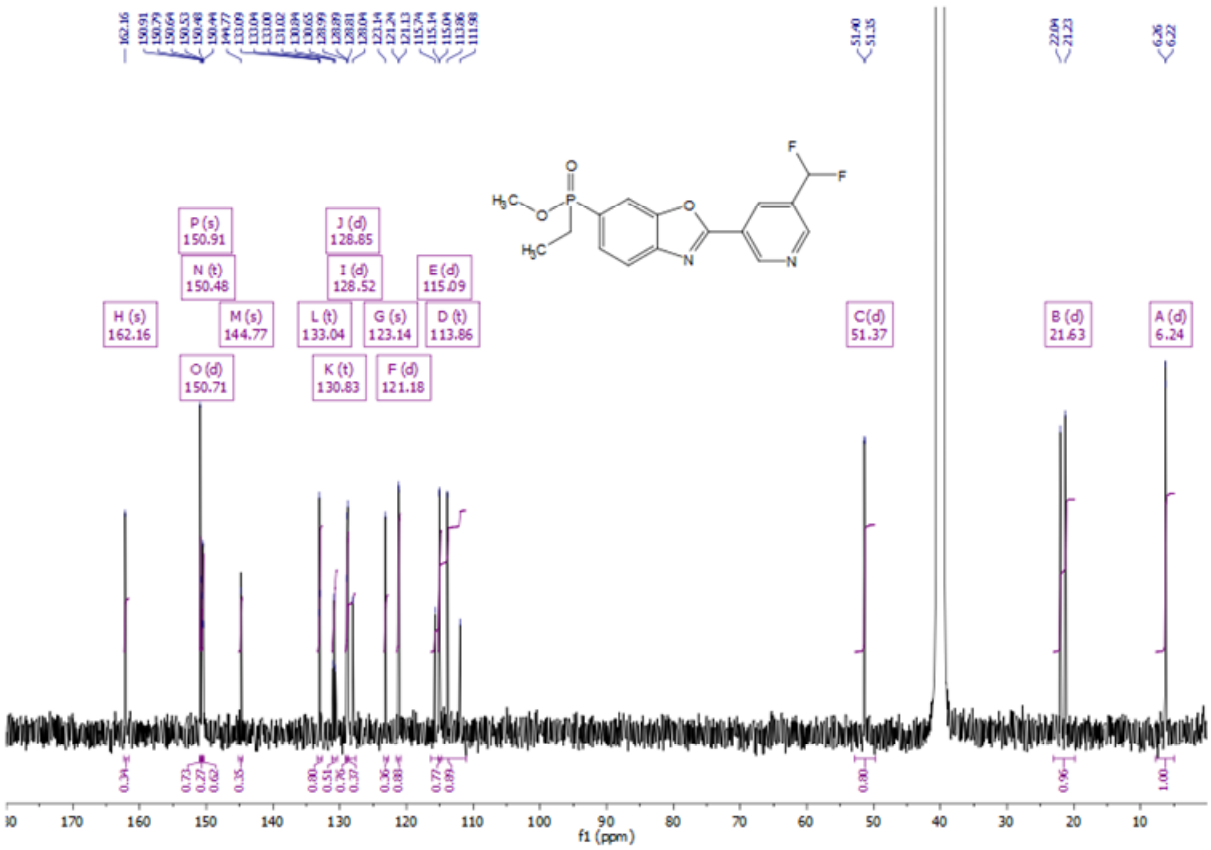


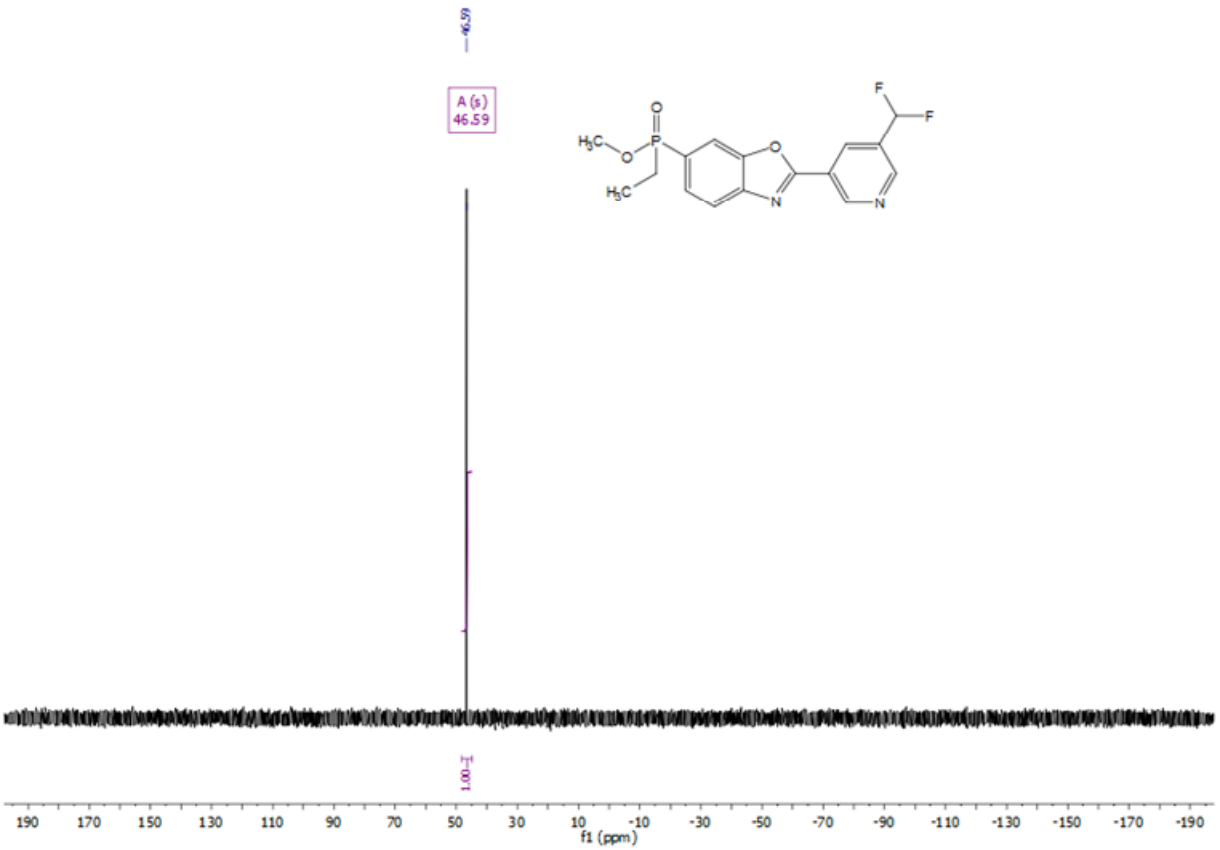


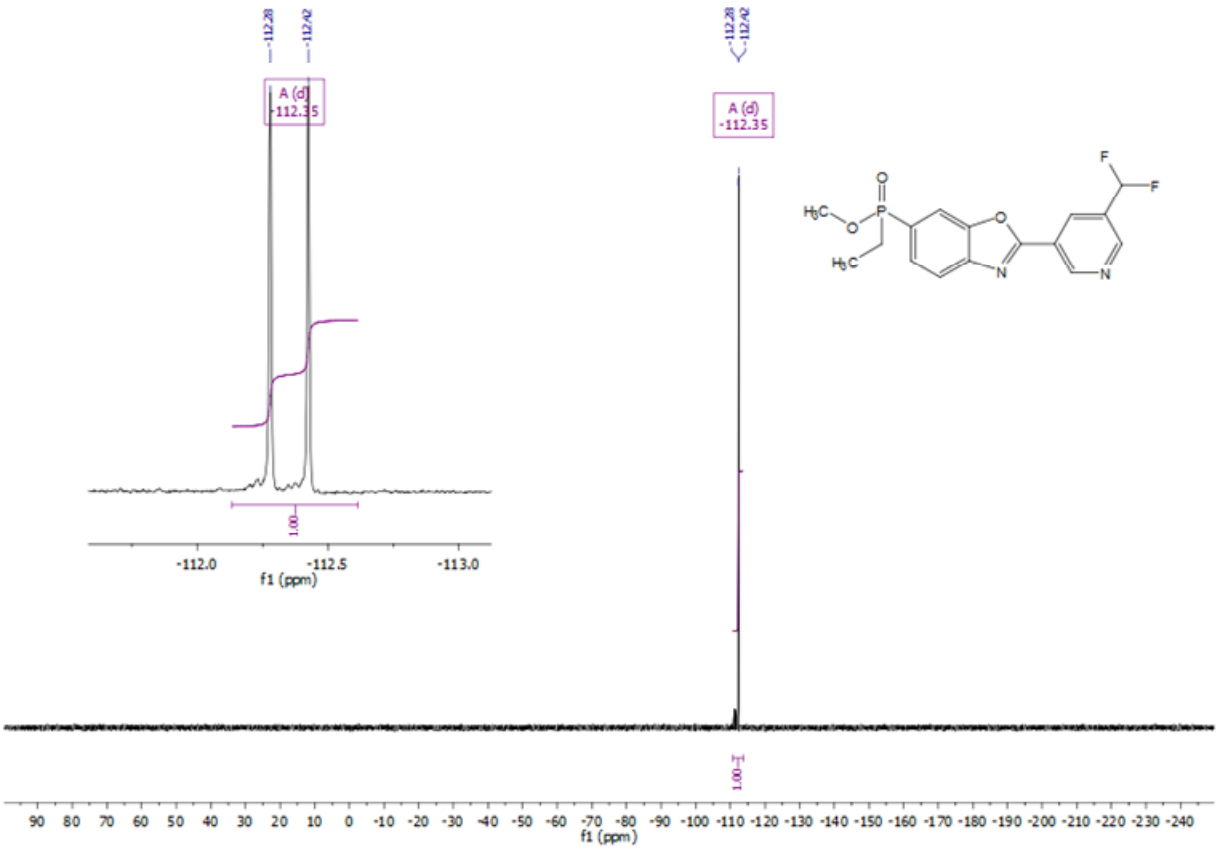


Peak Mass	Display...	Combin...	RDB	Delta [p...	Theo. m...	Rank	Combin...	# Match...	# Misse...	MS Cov....	Pattern...	MSMS...
353.0863	$C_{16}H_{16}$...	27.433...	9.50	0.46	353.08...	1	95.088...	3	1	98.846...	98.199...	(Collec.

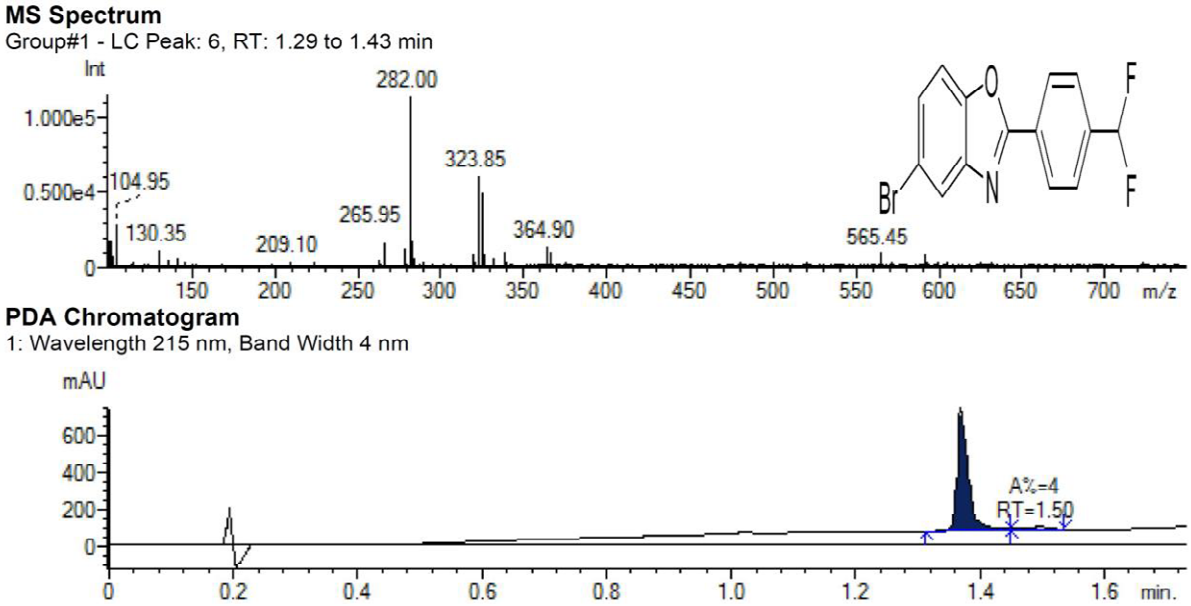

B (d) 9.53
A (d) 9.07
C (t) 8.73
D (m) 8.20
E (dd) 8.06
F (ddd) 7.82
G (t) 7.34
H (d) 3.55
I (m) 2.02
J (dt) 0.98
f1 (ppm)

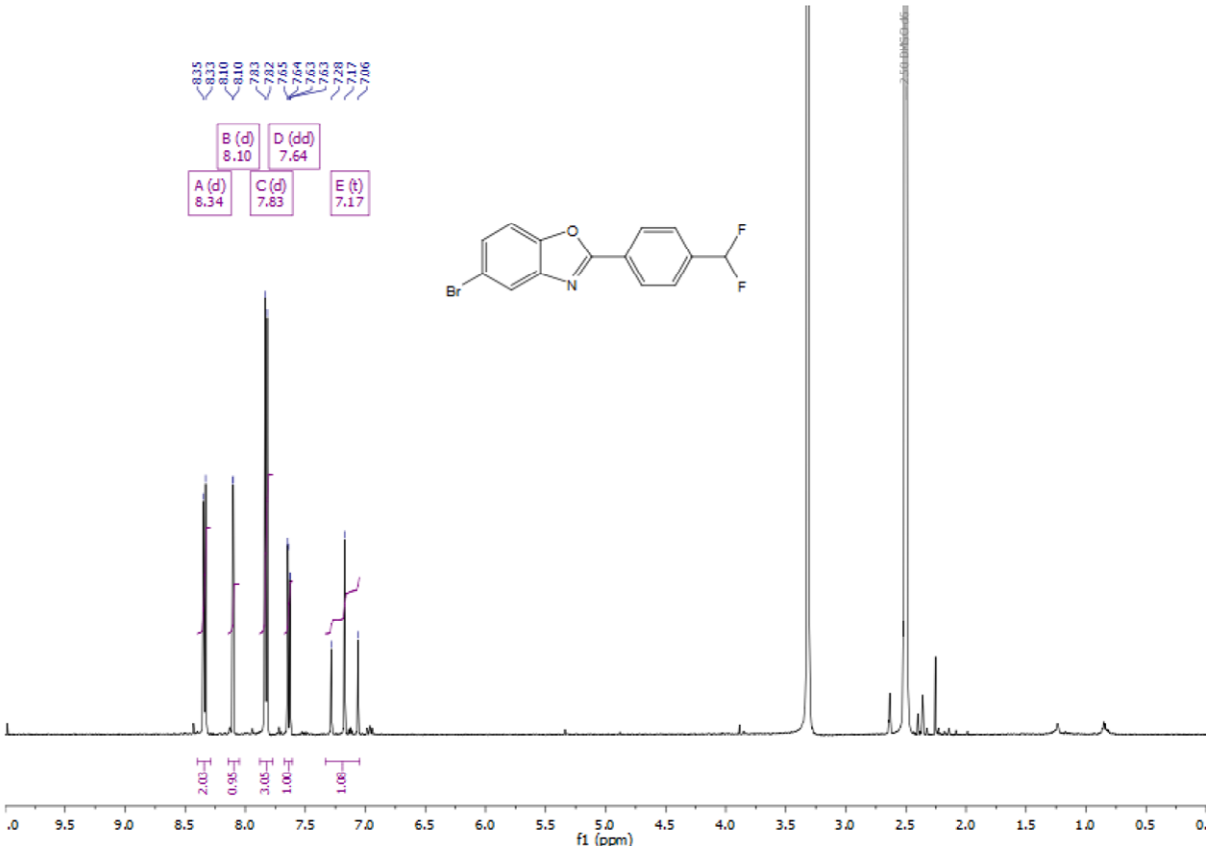

P (s) 150.91
N (t) 150.48
H (s) 162.16
M (s) 144.77
O (d) 150.71
J (d) 128.85
I (d) 128.52
E (d) 115.09
L (t) 133.04
G (s) 123.14
D (t) 113.86
K (t) 130.83
F (d) 121.18
C (d) 51.37
B (d) 21.63
A (d) 6.24
f1 (ppm)


46.59
A (s)
46.59
F
F
O
P
H3C
O
CH3
O
N
N
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

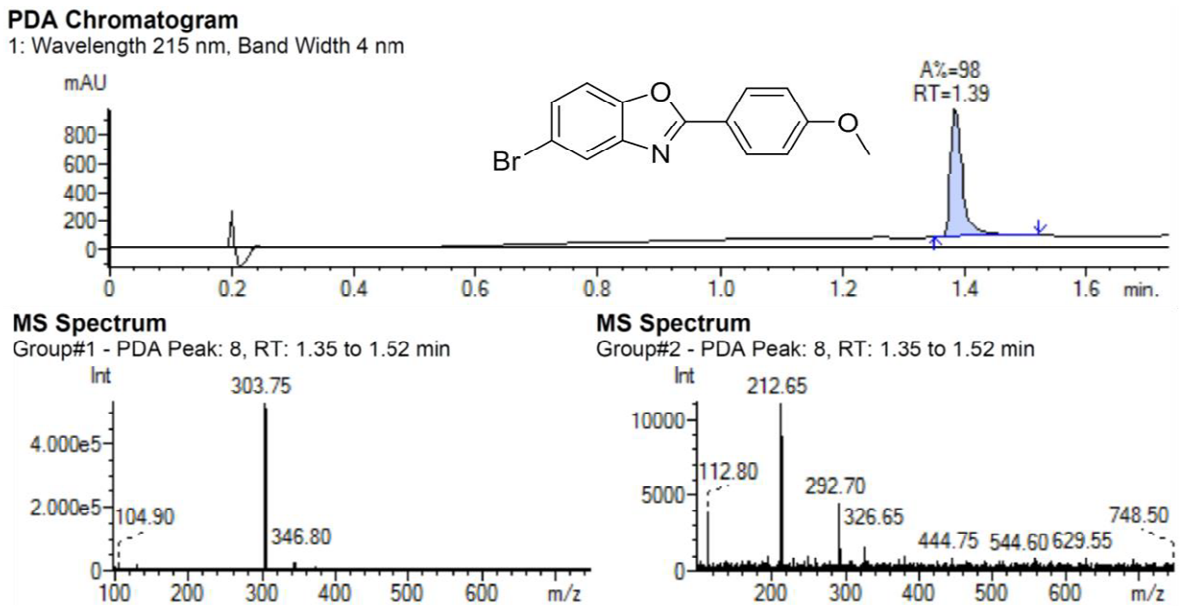

-112.28
-112.42
A (d)
-112.35
1.00
-112.0
-112.5
-113.0
f1 (ppm)
-112.28
-112.42
A (d)
-112.35
F
F
O
P
H3C
O
CH3
O
N
N
1.00
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

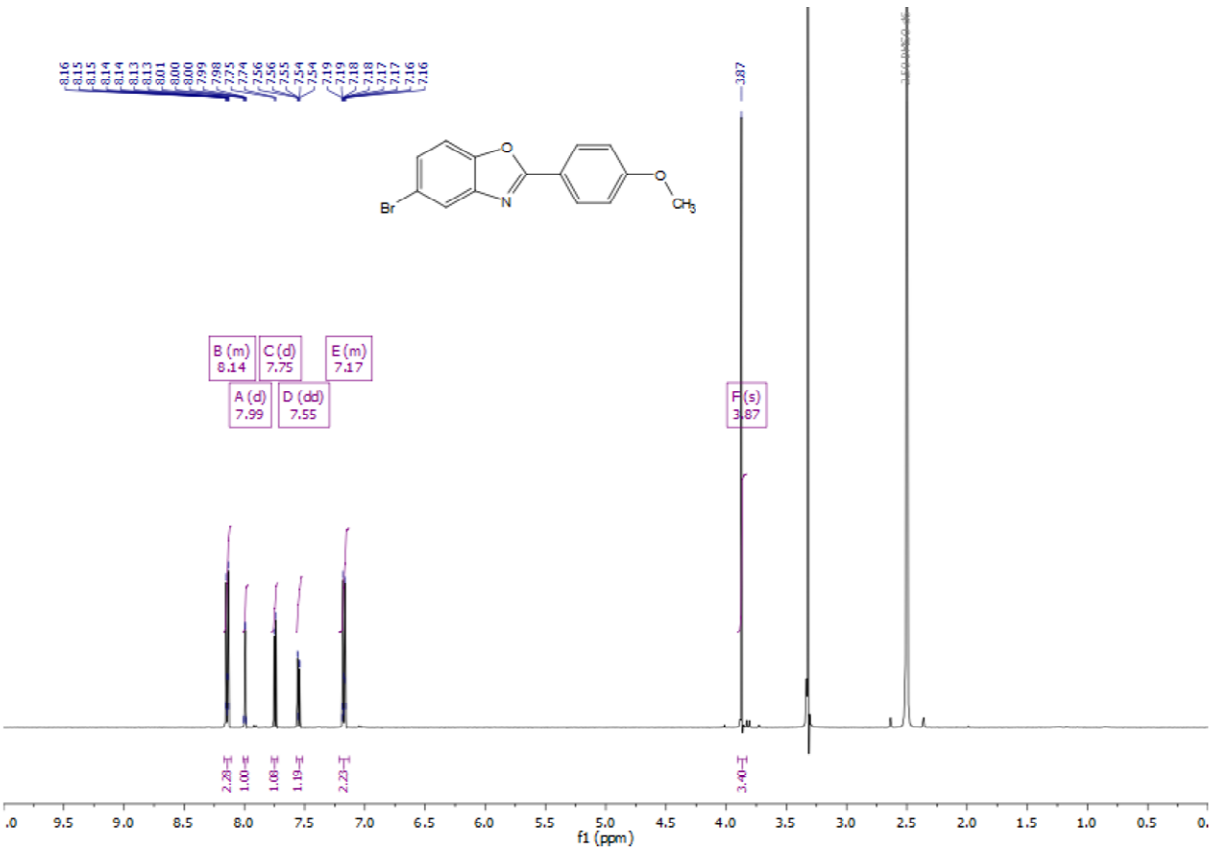
5-bromo-2-(4-(difluoromethyl)phenyl)benzo[d]oxazole (28)



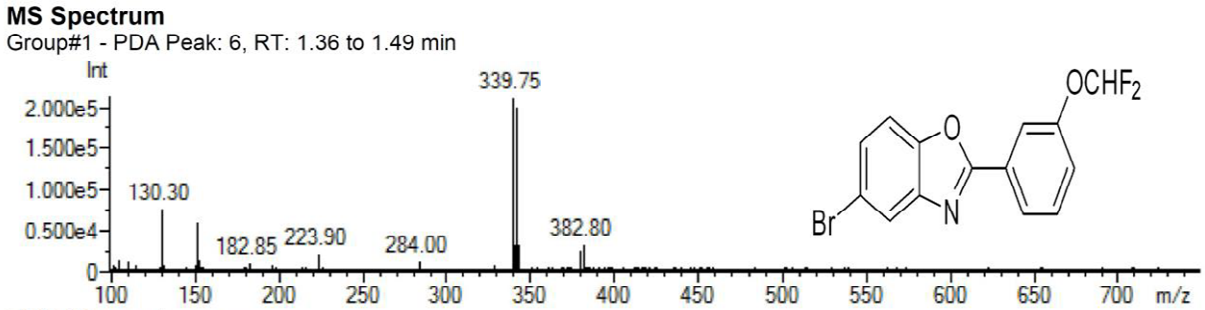


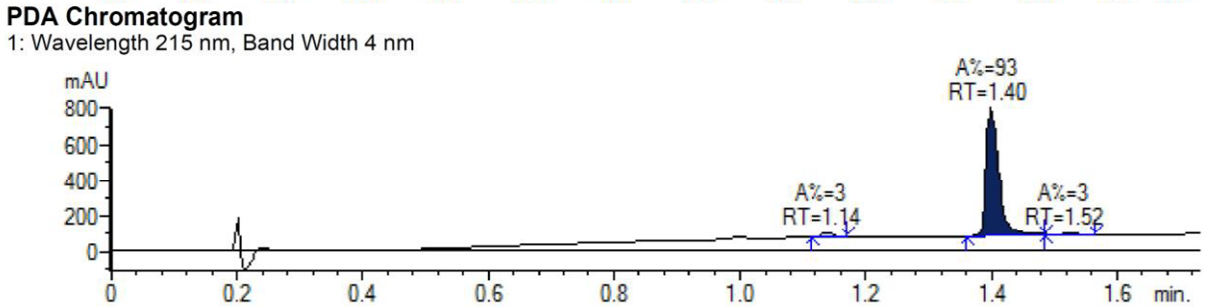
5-bromo-2-(4-methoxyphenyl)benzo[*d*]oxazole (29)

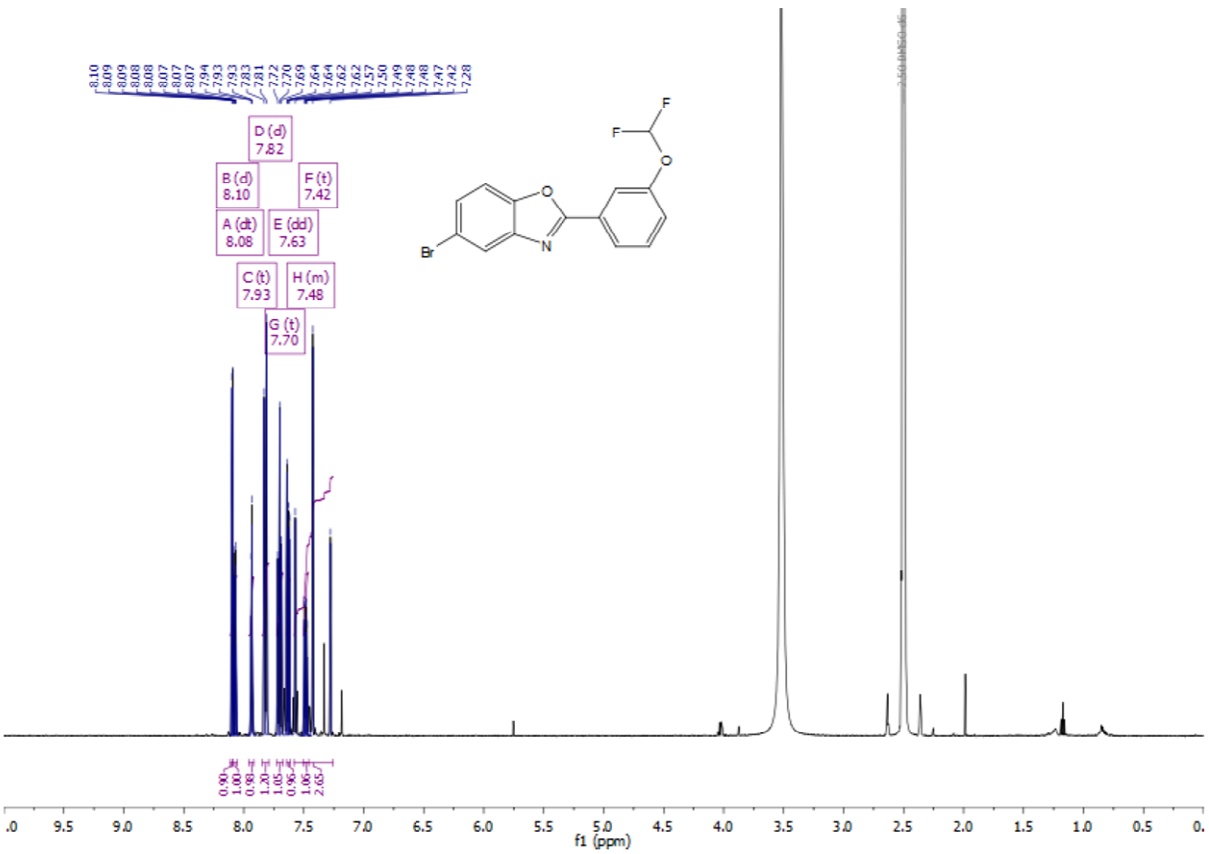




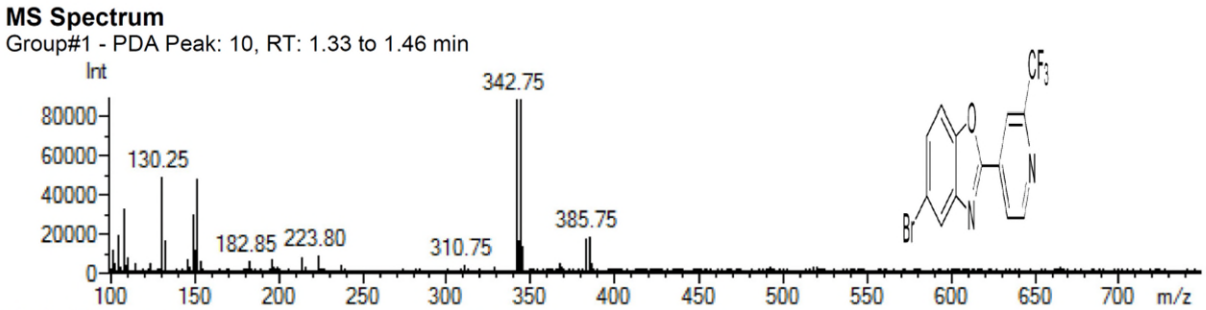
5-bromo-2-(3-(difluoromethoxy)phenyl)benzo[*d*]oxazole (30)

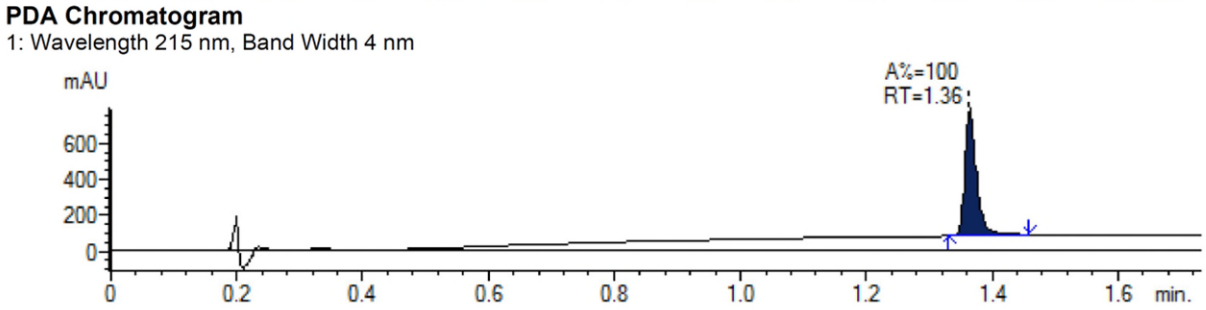


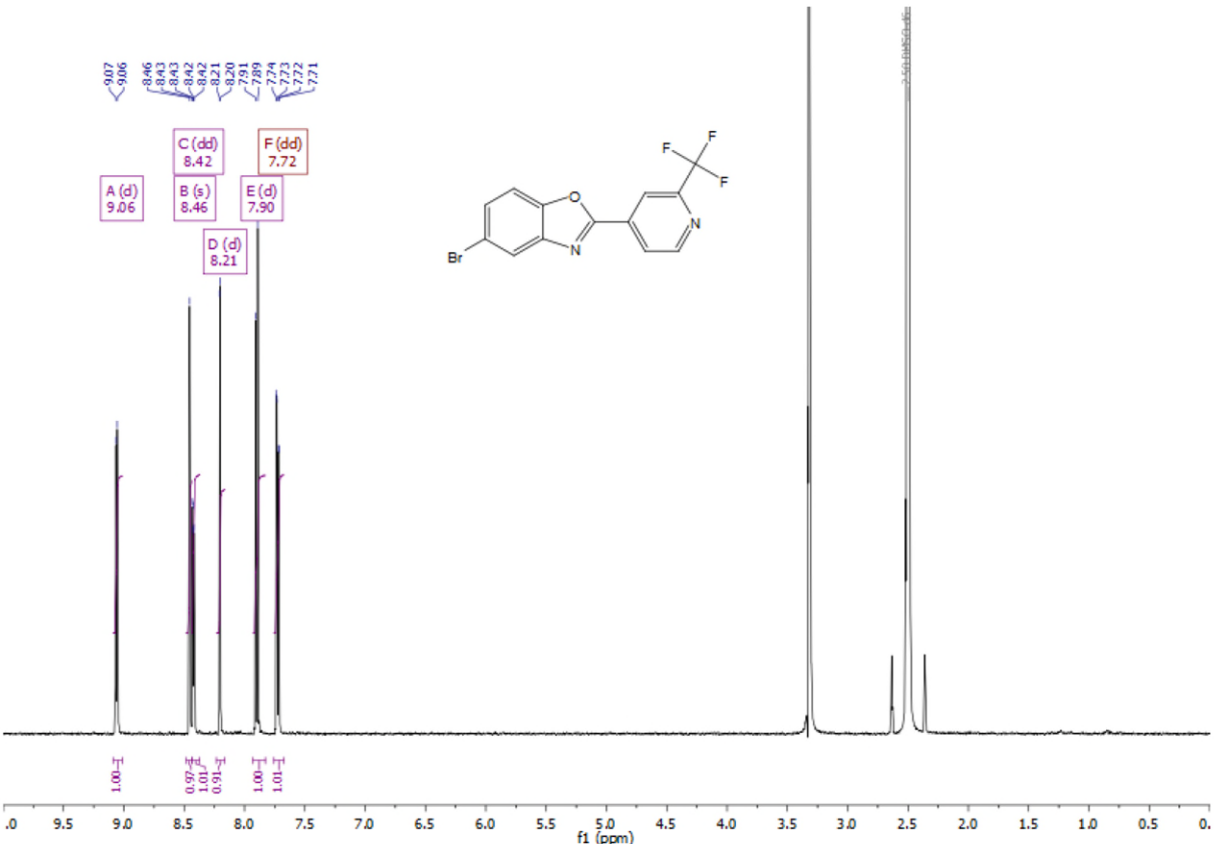




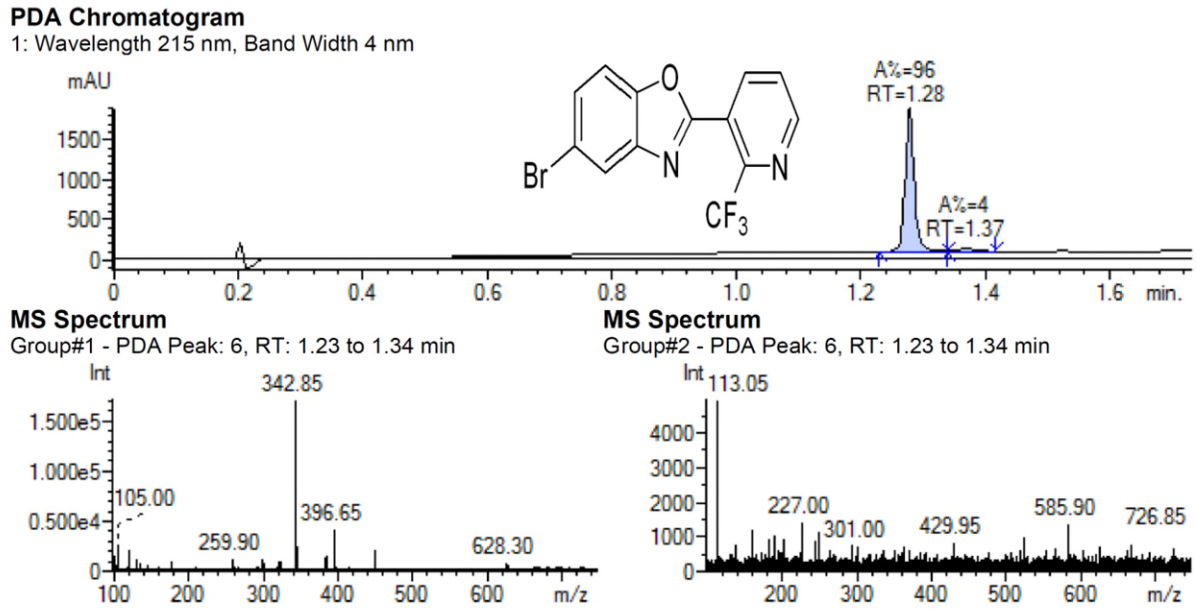
5-bromo-2-(2-(trifluoromethyl)pyridin-4-yl)benzo[*d*]oxazole (31)

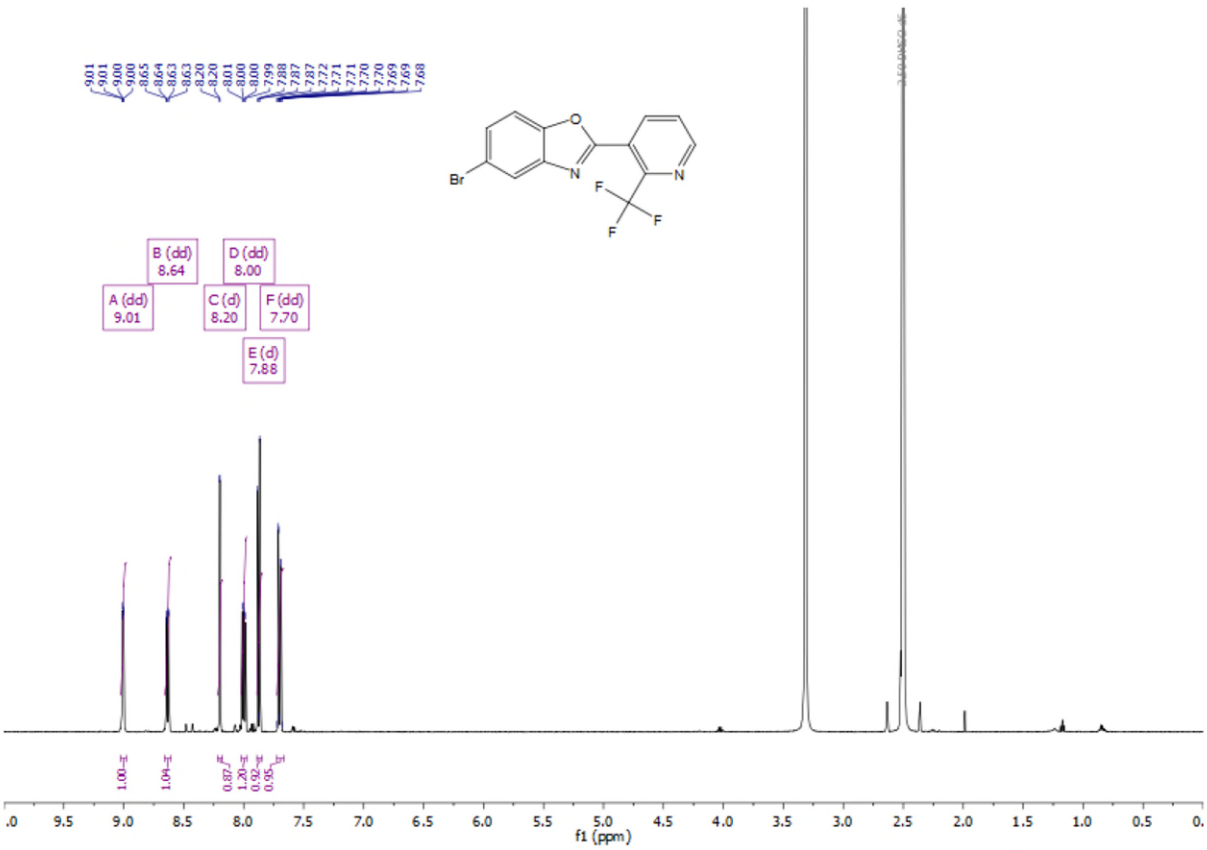






5-bromo-2-(2-(trifluoromethyl)pyridin-3-yl)benzo[d]oxazole (32)

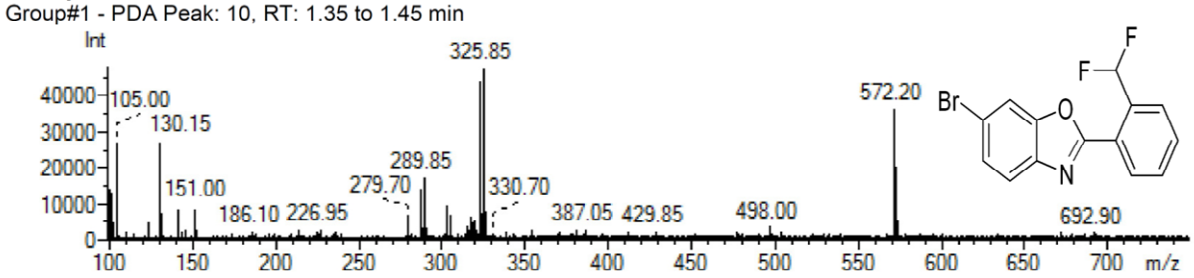




6-bromo-2-(2-(difluoromethyl)phenyl)benzo[d]oxazole (33)

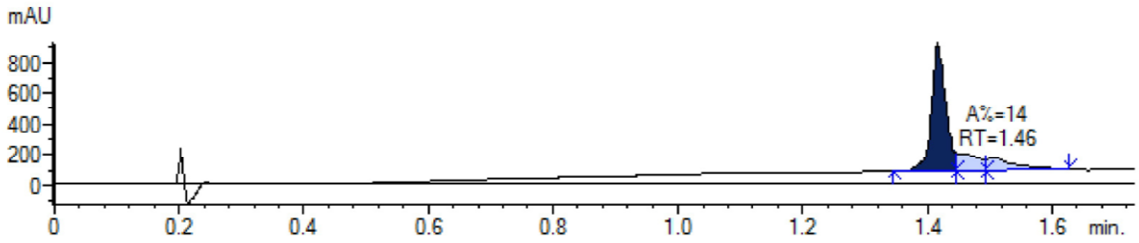
MS Spectrum

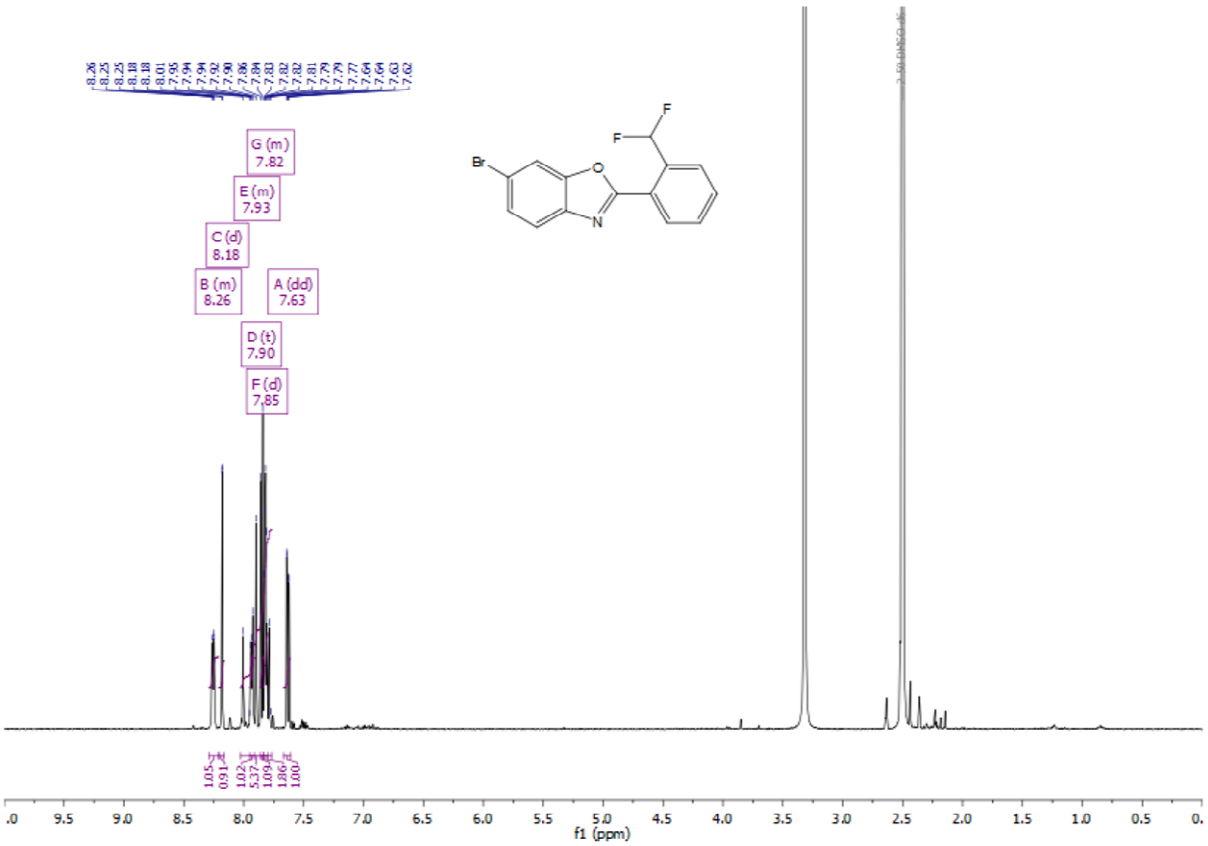
Group#1 - PDA Peak: 10, RT: 1.35 to 1.45 min



PDA Chromatogram

1: Wavelength 215 nm, Band Width 4 nm

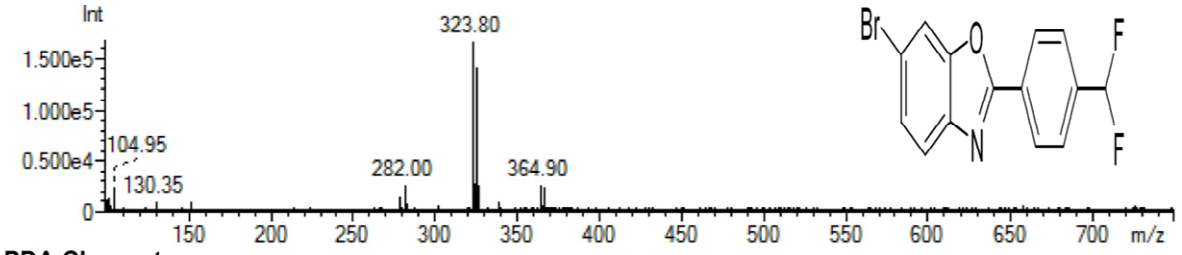




6-bromo-2-(4-(difluoromethyl)phenyl)benzo[*d*]oxazole (34)

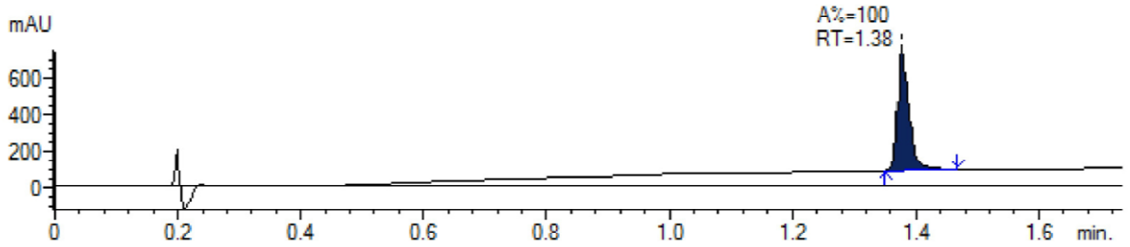
MS Spectrum

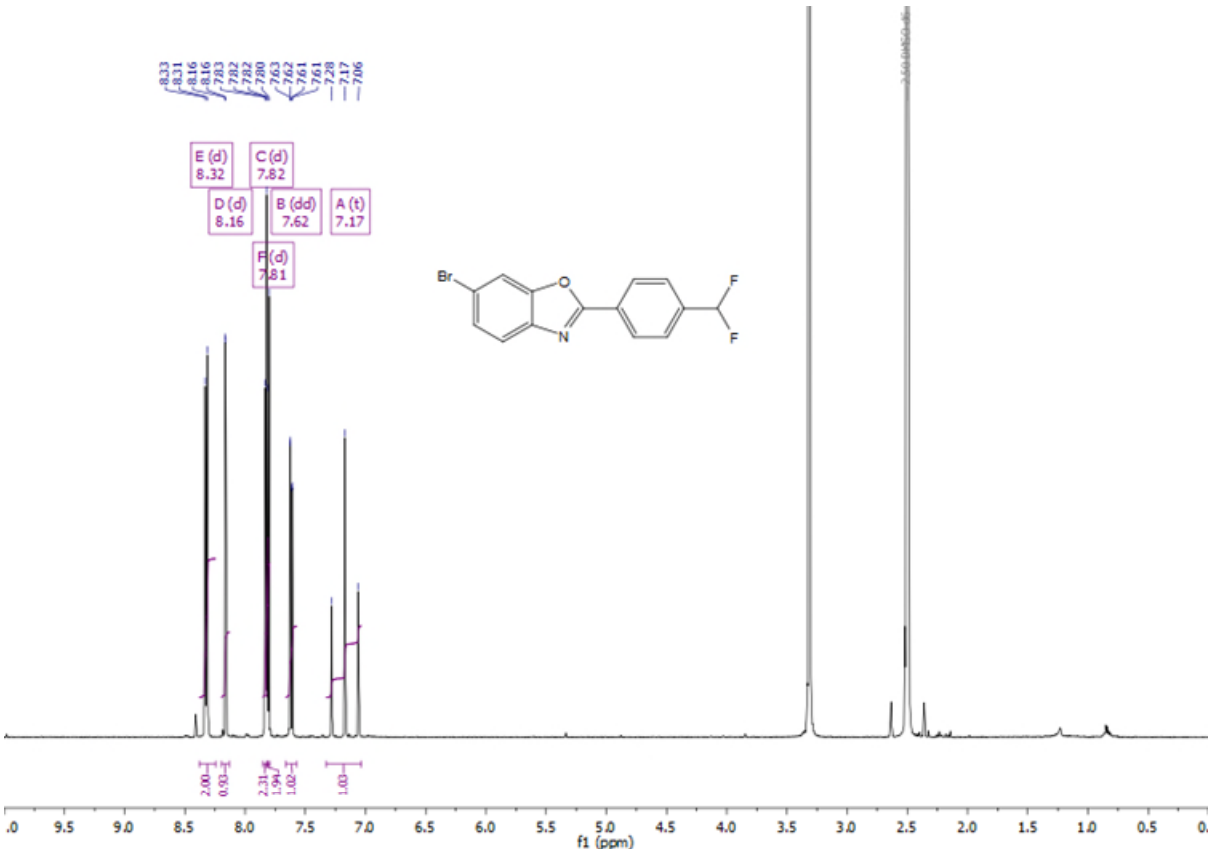
Group#1 - PDA Peak: 9, RT: 1.35 to 1.47 min



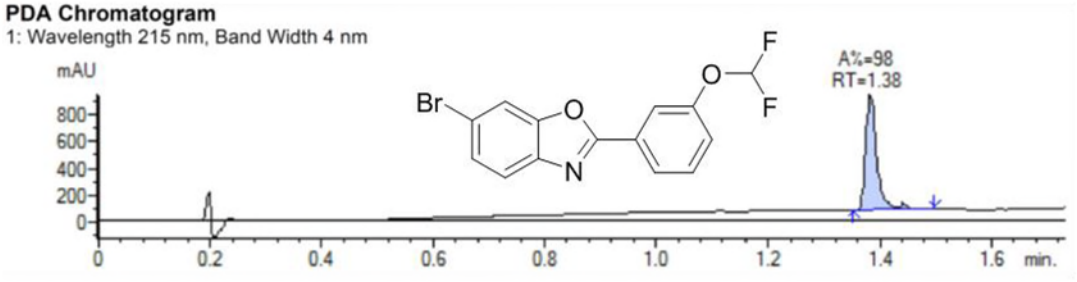
PDA Chromatogram

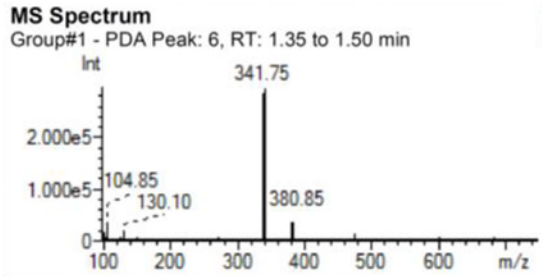
1: Wavelength 215 nm, Band Width 4 nm

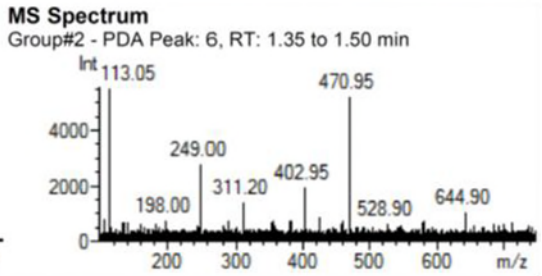


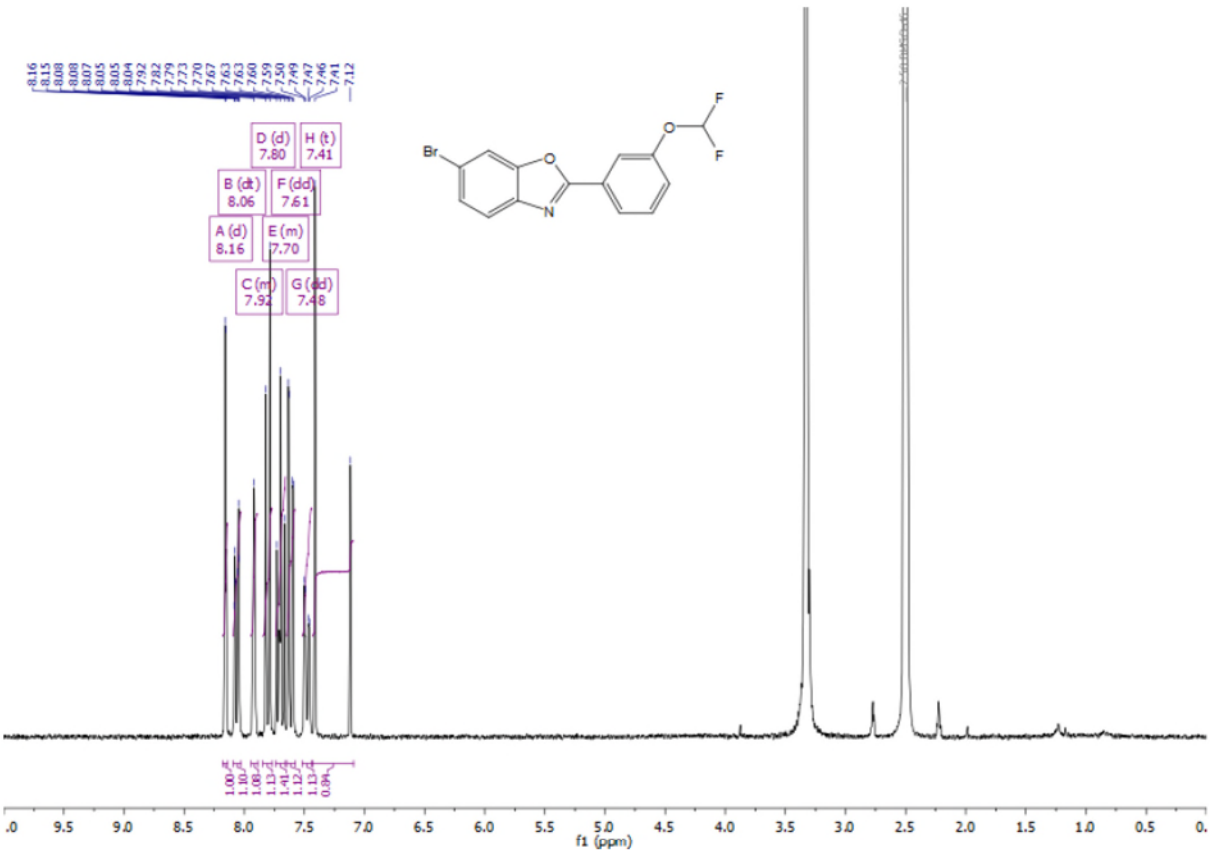


6-bromo-2-(3-(difluoromethoxy)phenyl)benzo[d]oxazole (35)

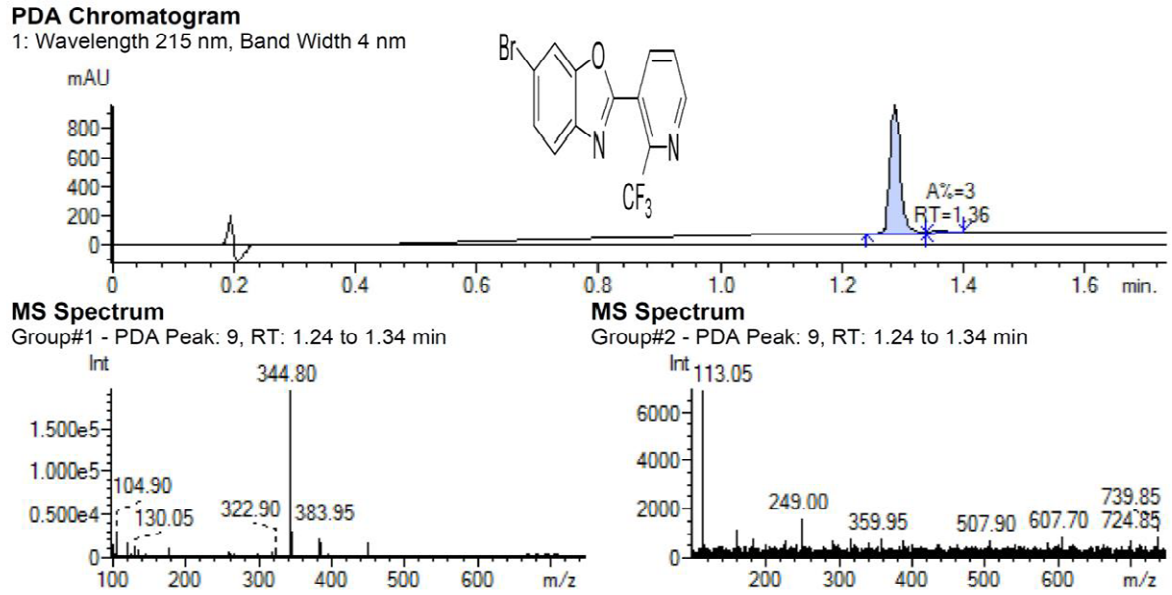


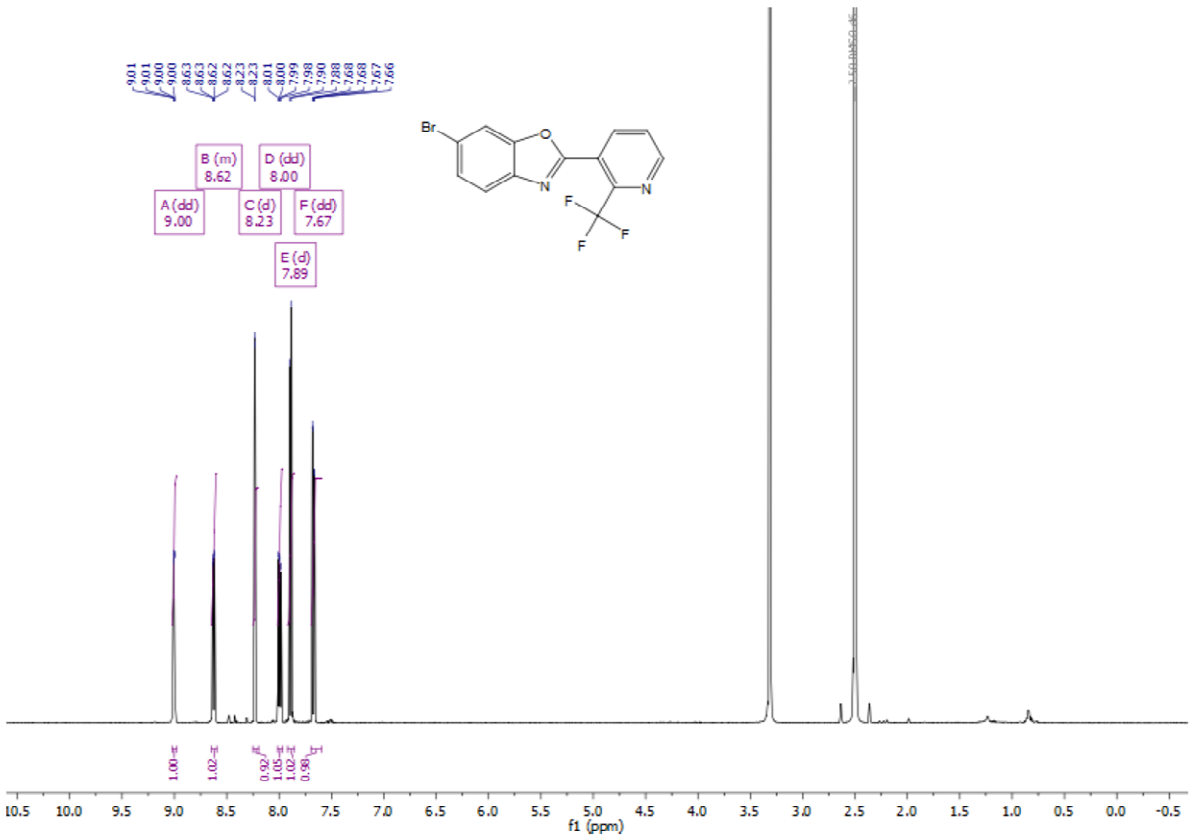




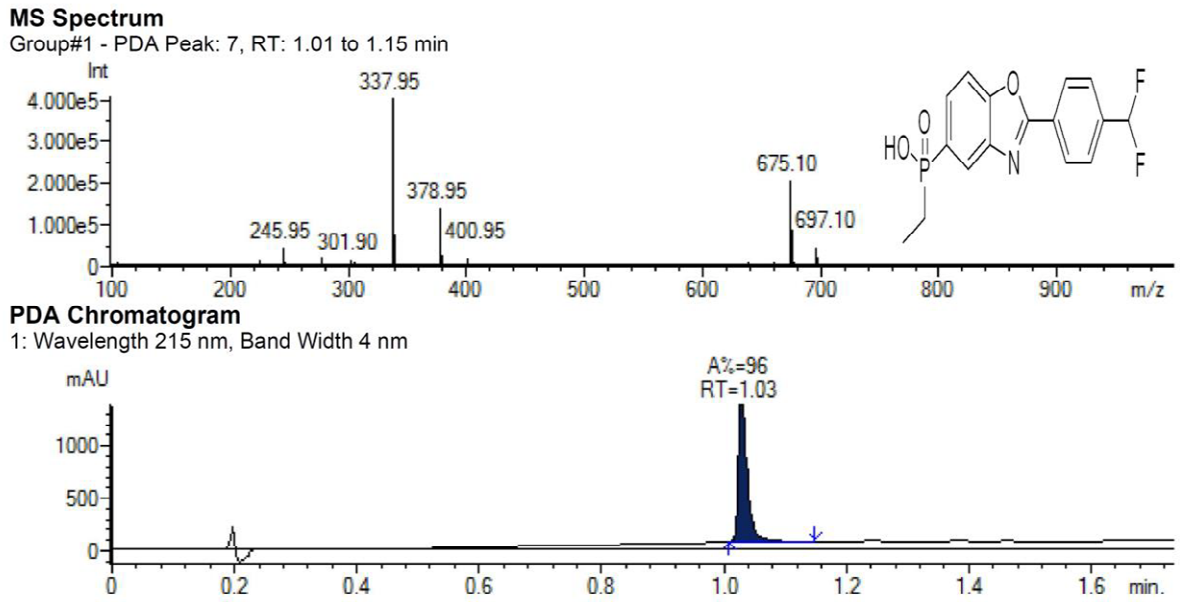


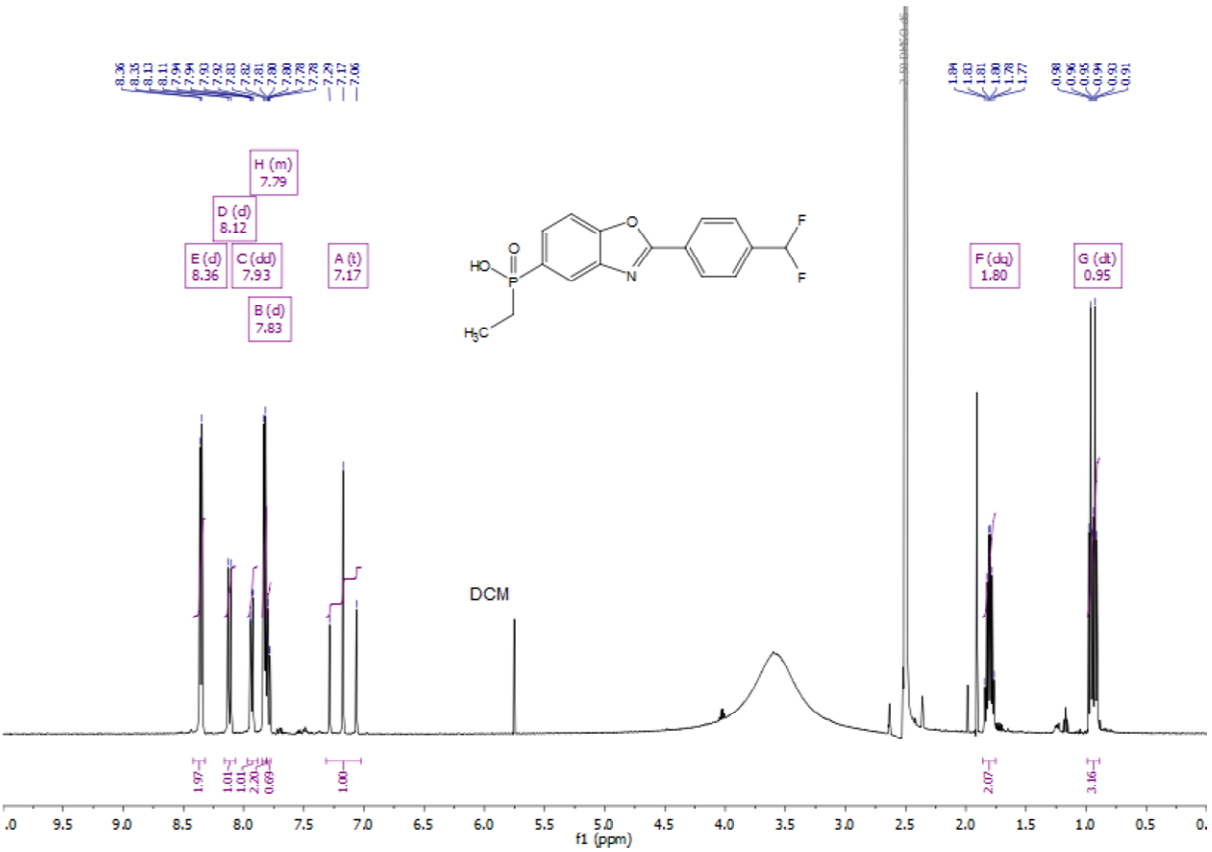
6-bromo-2-(2-(trifluoromethyl)pyridin-3-yl)benzo[d]oxazole (36)



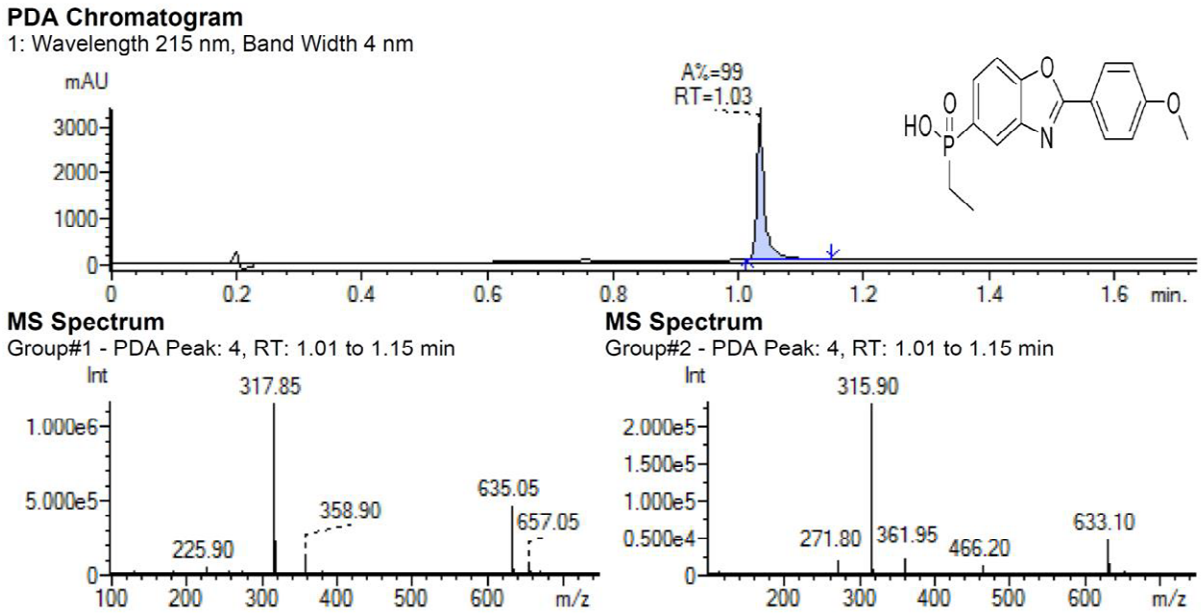


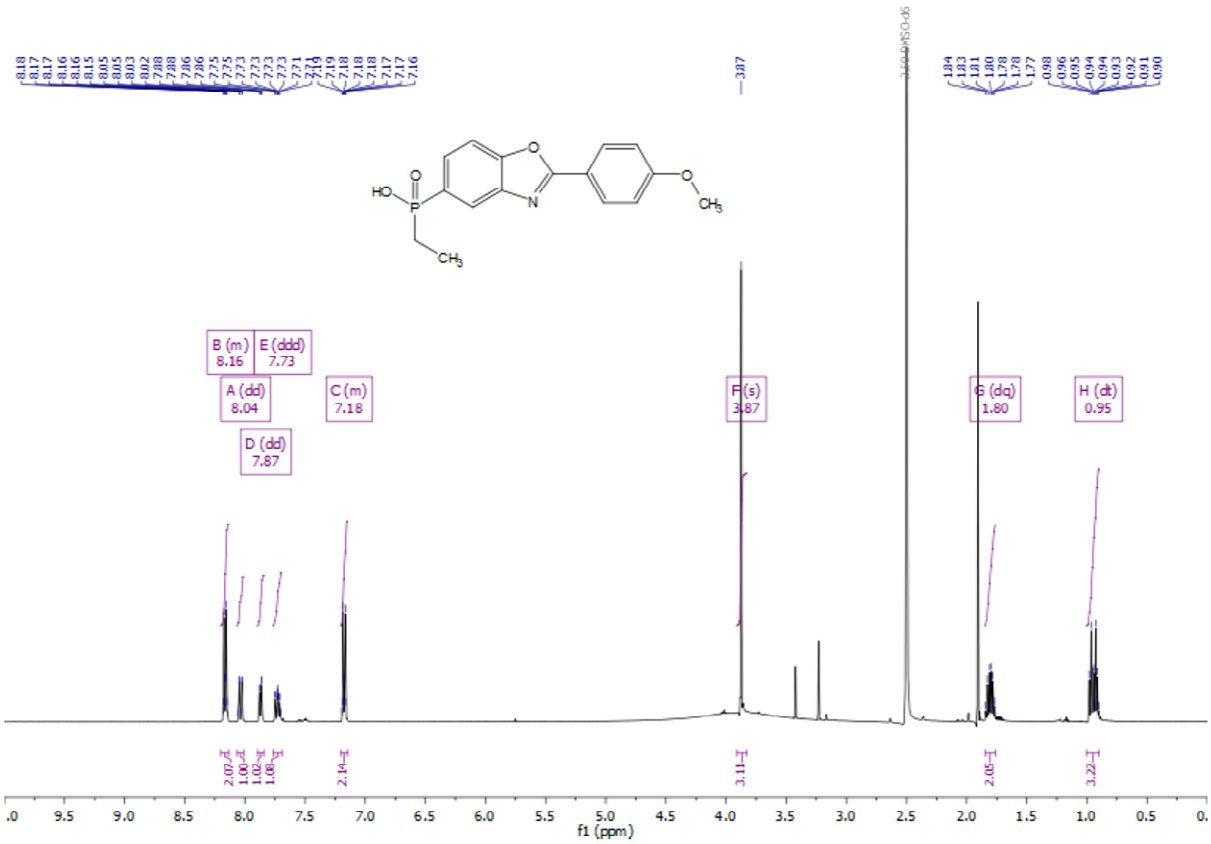
(2-(4-(difluoromethyl)phenyl)benzo[d]oxazol-5-yl)(ethyl)phosphinic acid (37)



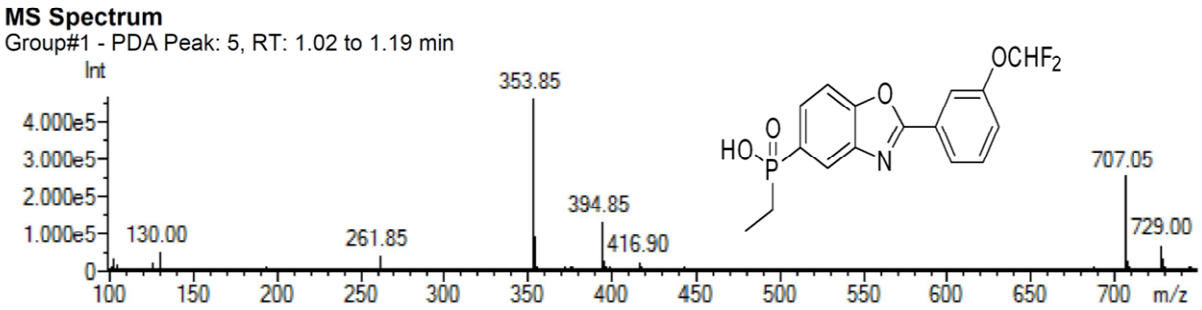


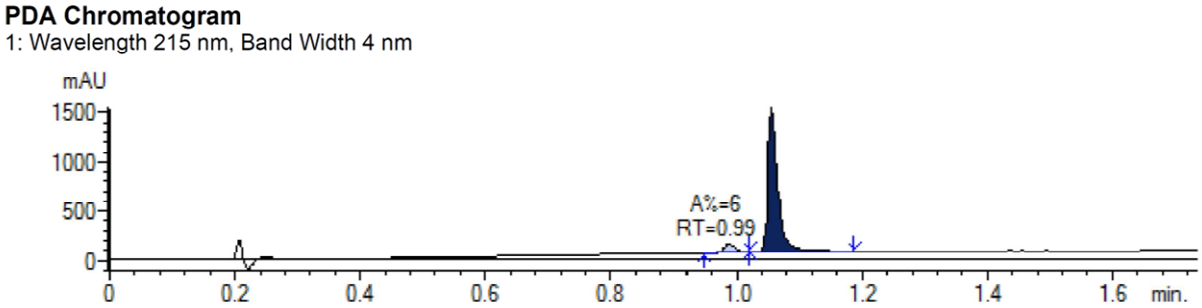
ethyl(2-(4-methoxyphenyl)benzo[d]oxazol-5-yl)phosphinic acid (38)

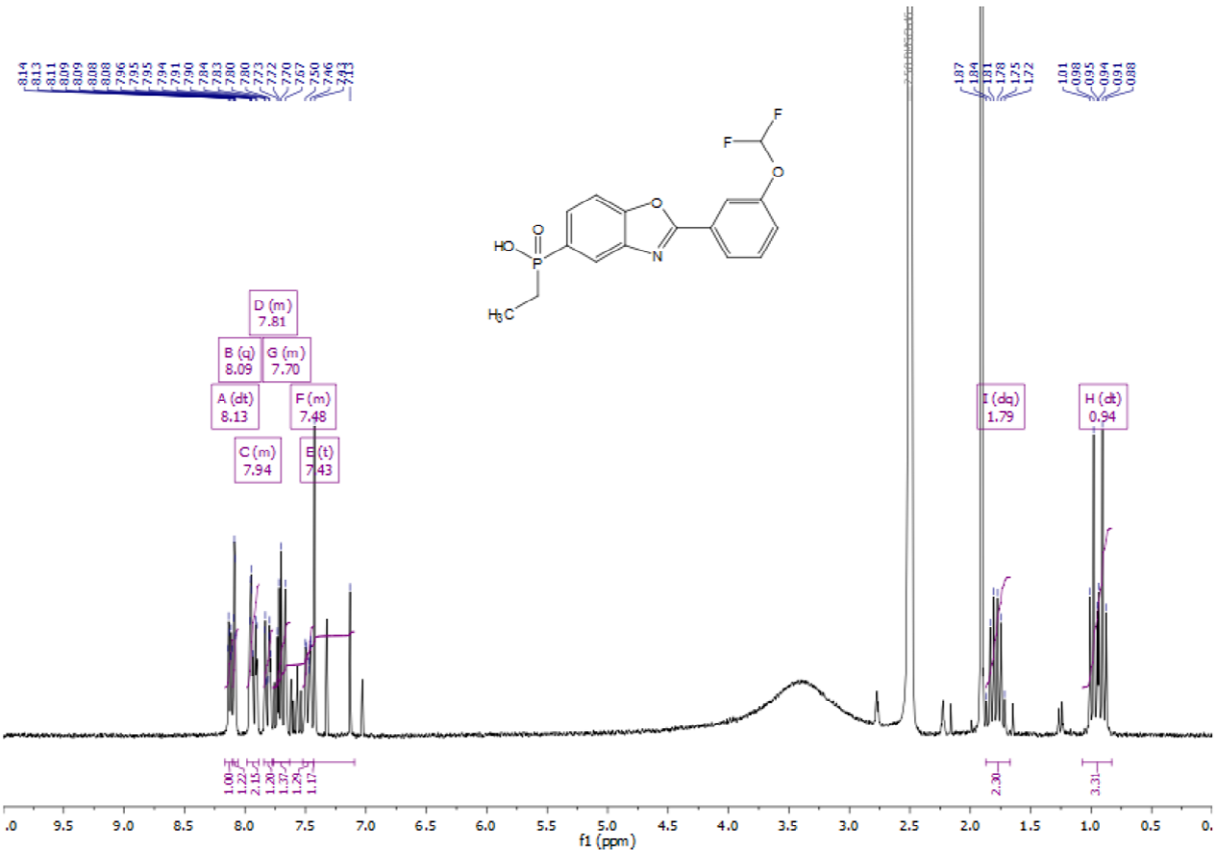




(2-(3-(difluoromethoxy)phenyl)benzo[d]oxazol-5-yl)(ethyl)phosphinic acid (39)



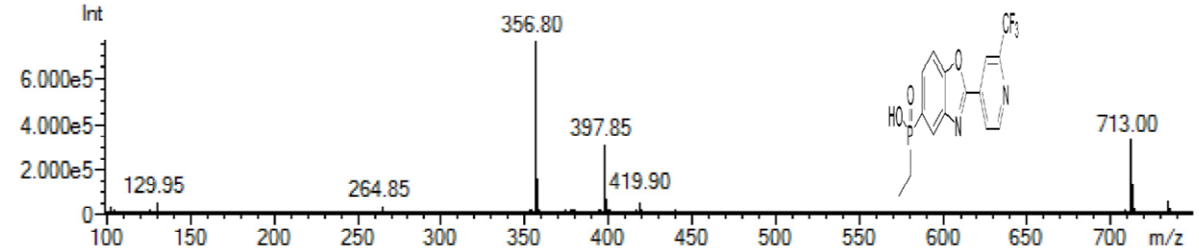




ethyl(2-(2-(trifluoromethyl)pyridin-4-yl)benzo[d]oxazol-5-yl)phosphinic acid (40)

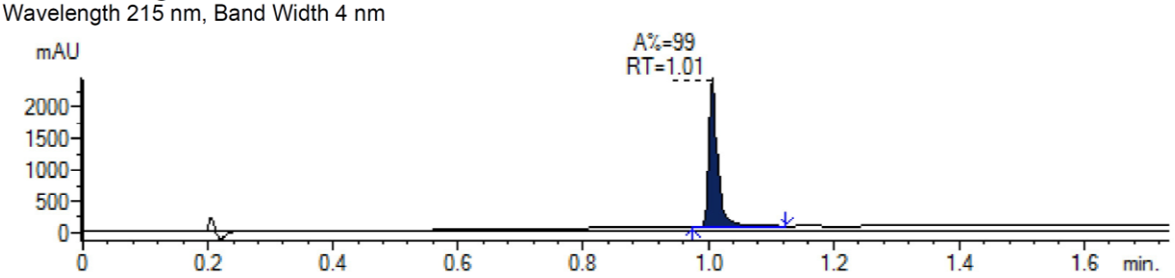
MS Spectrum

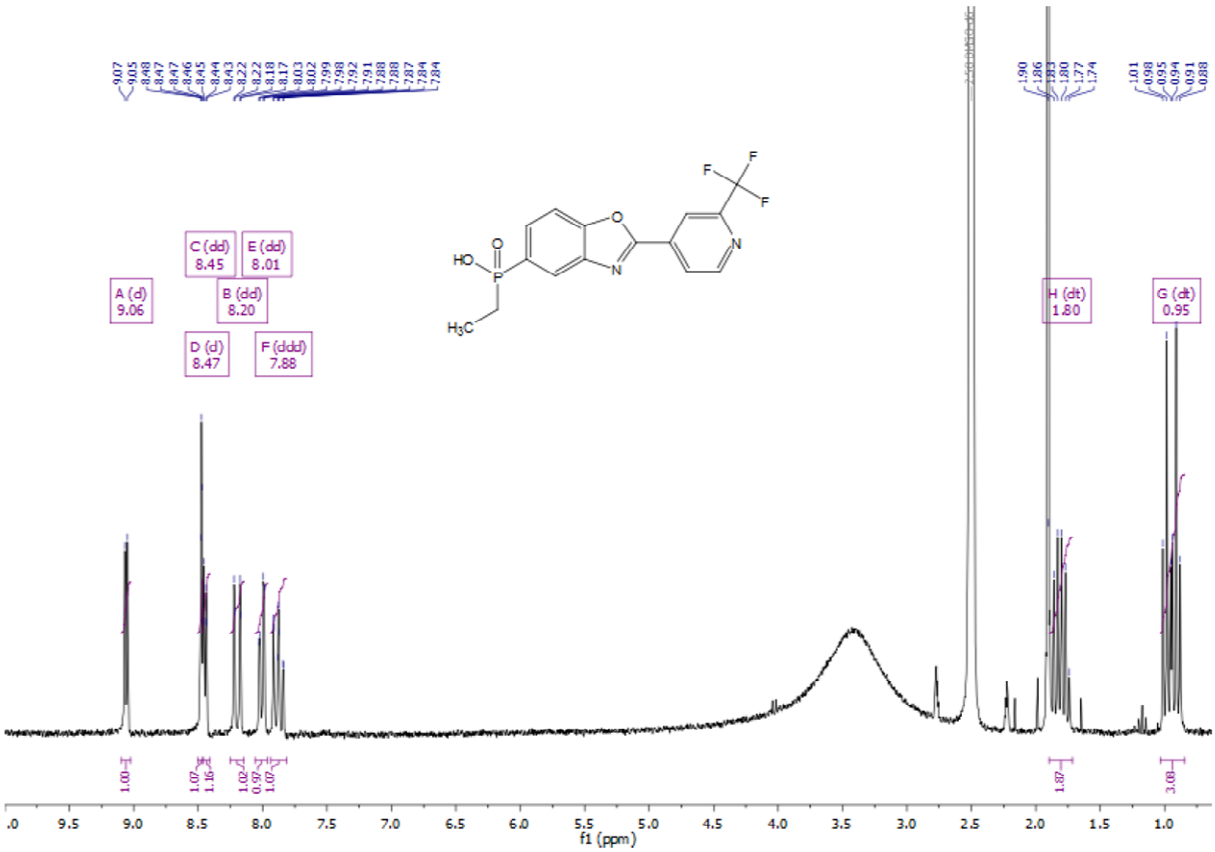
Group#1 - PDA Peak: 3, RT: 0.98 to 1.12 min



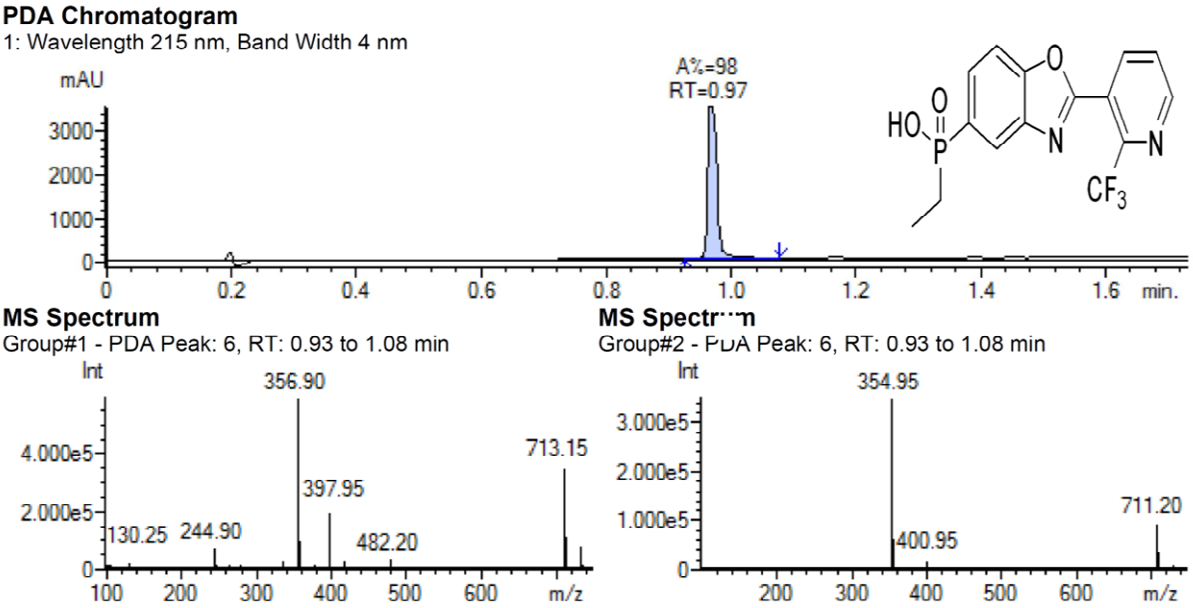
PDA Chromatogram

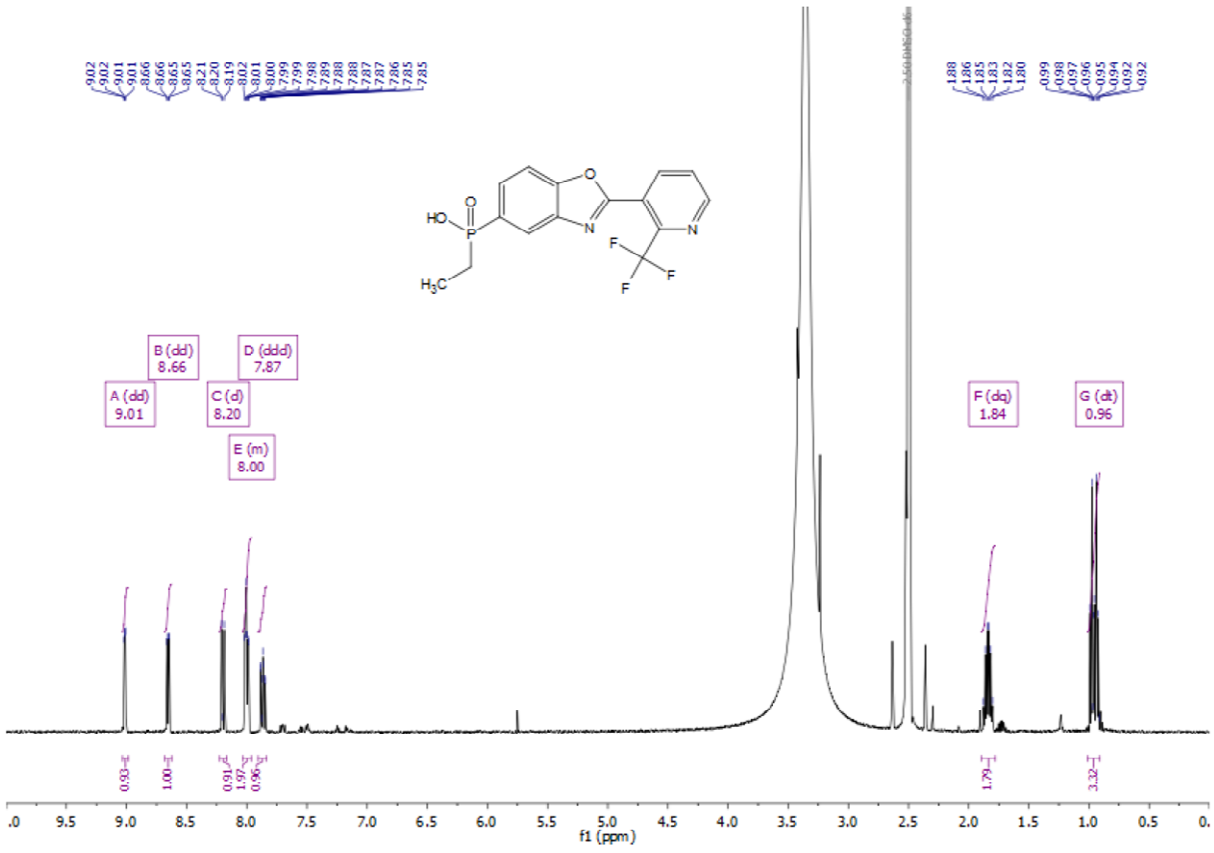
1: Wavelength 215 nm, Band Width 4 nm



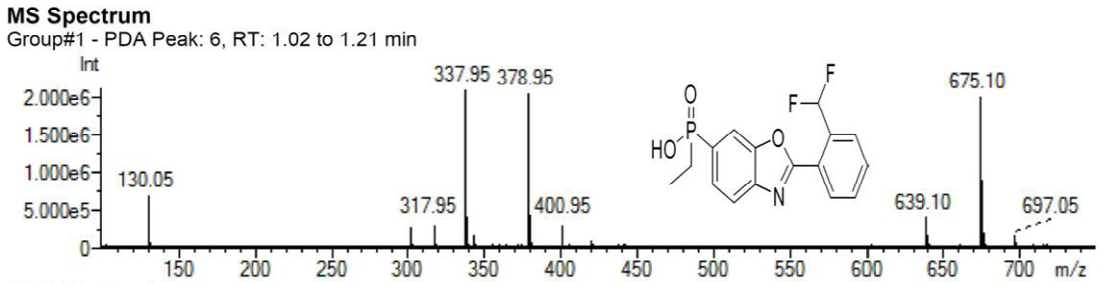


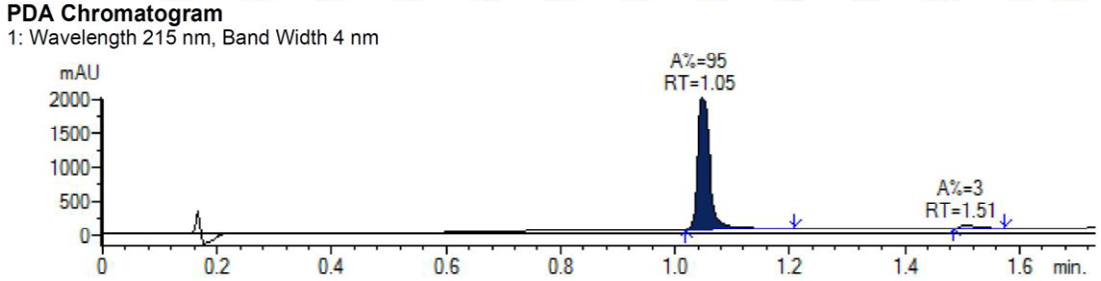
ethyl(2-(2-(trifluoromethyl)pyridin-3-yl)benzo[*d*]oxazol-5-yl)phosphinic acid (41)

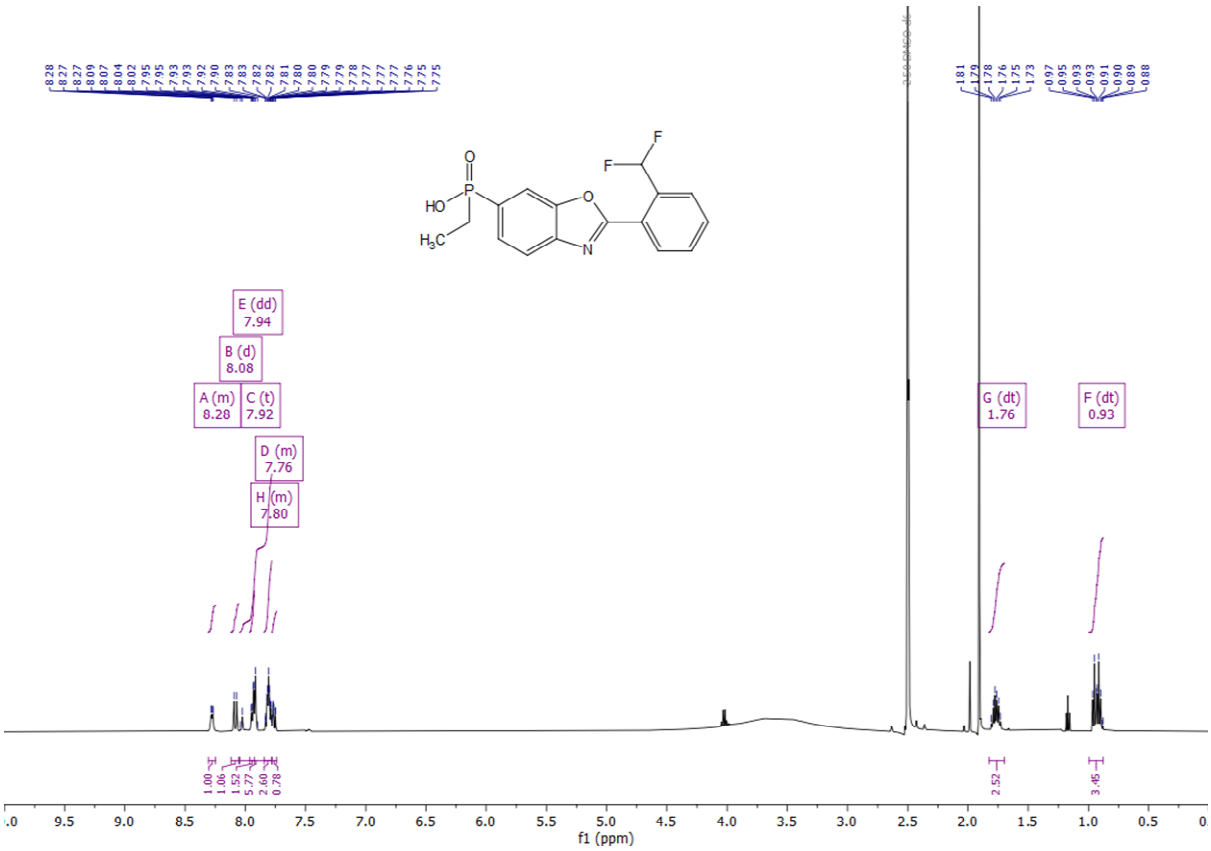




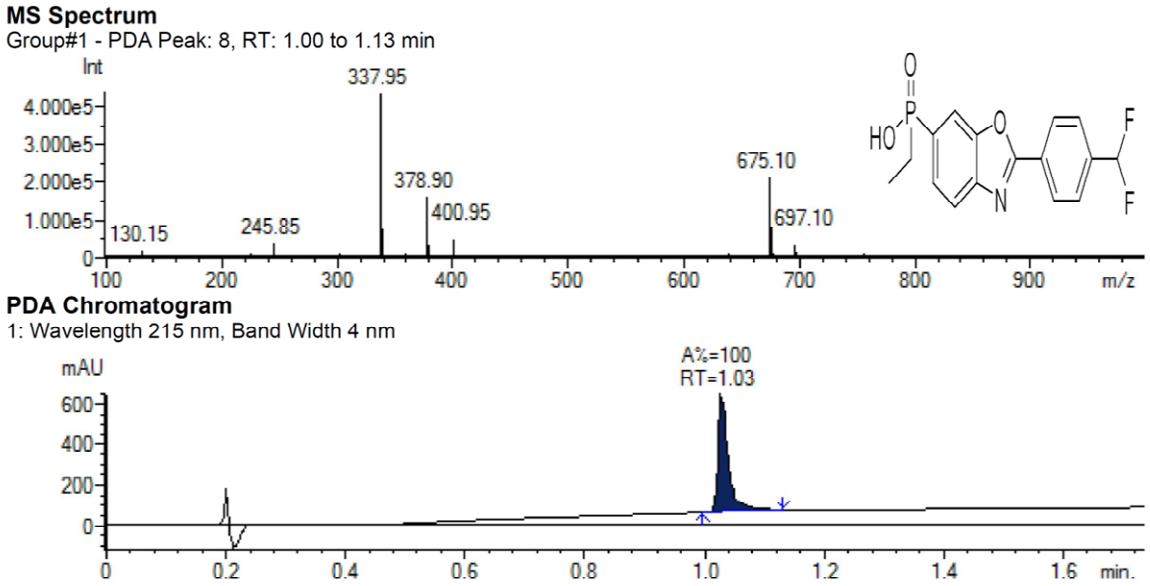
(2-(2-(difluoromethyl)phenyl)benzo[d]oxazol-6-yl)(ethyl)phosphinic acid (42)

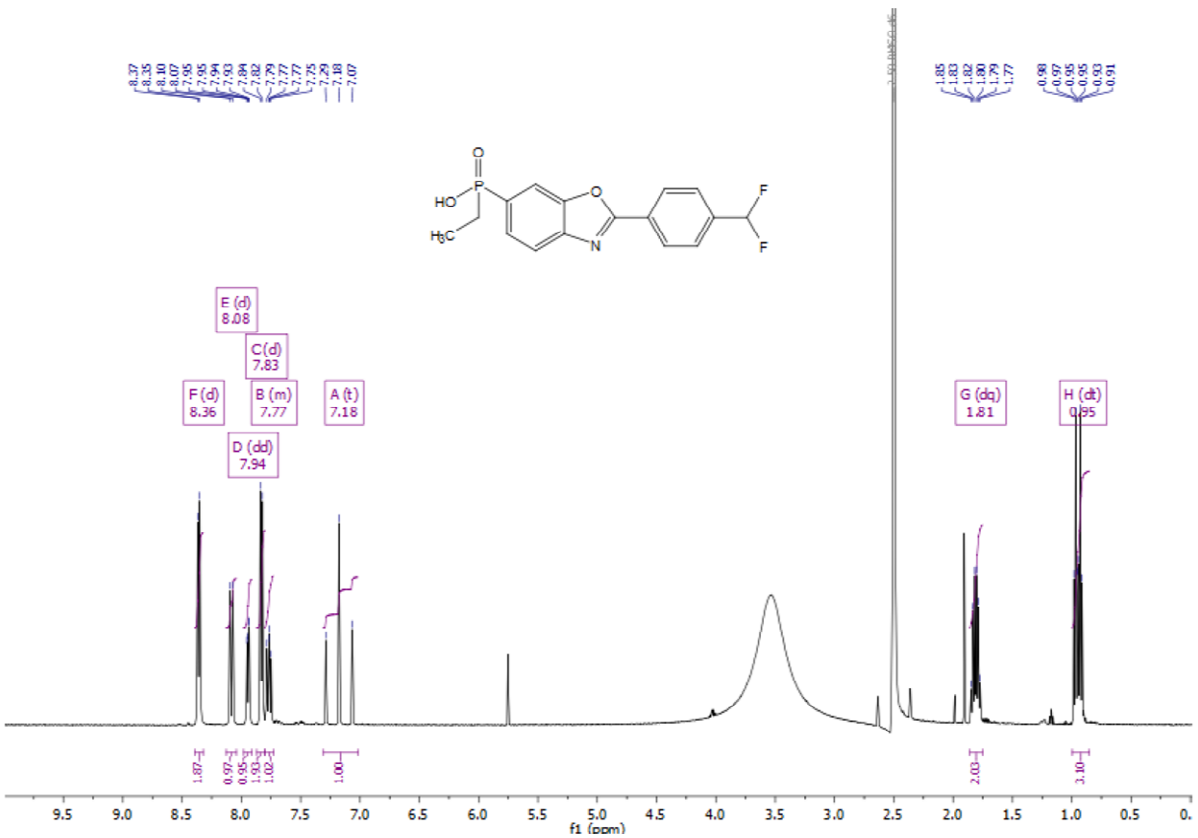




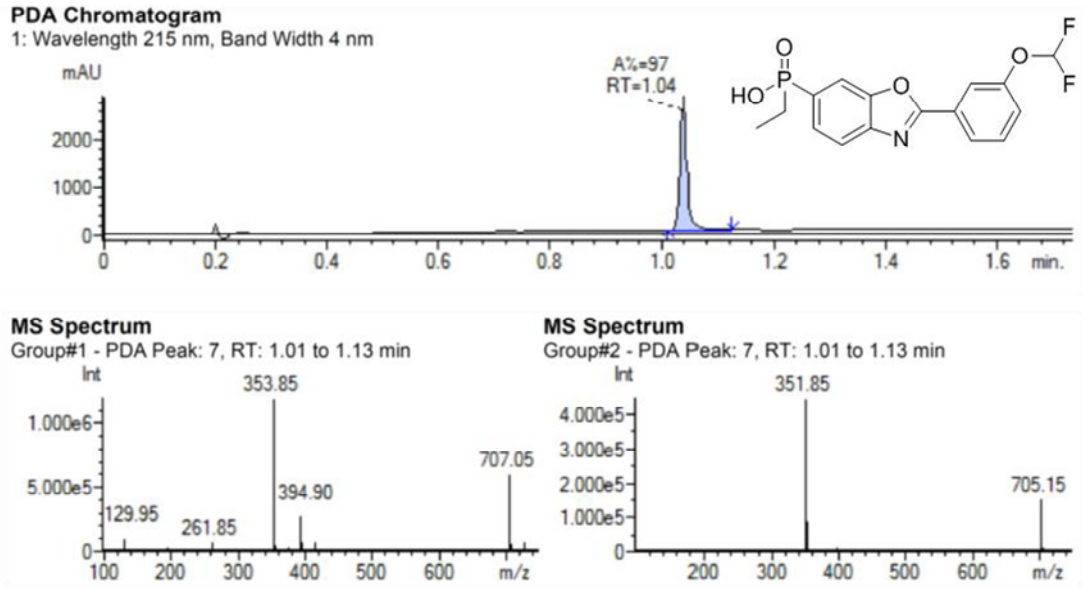


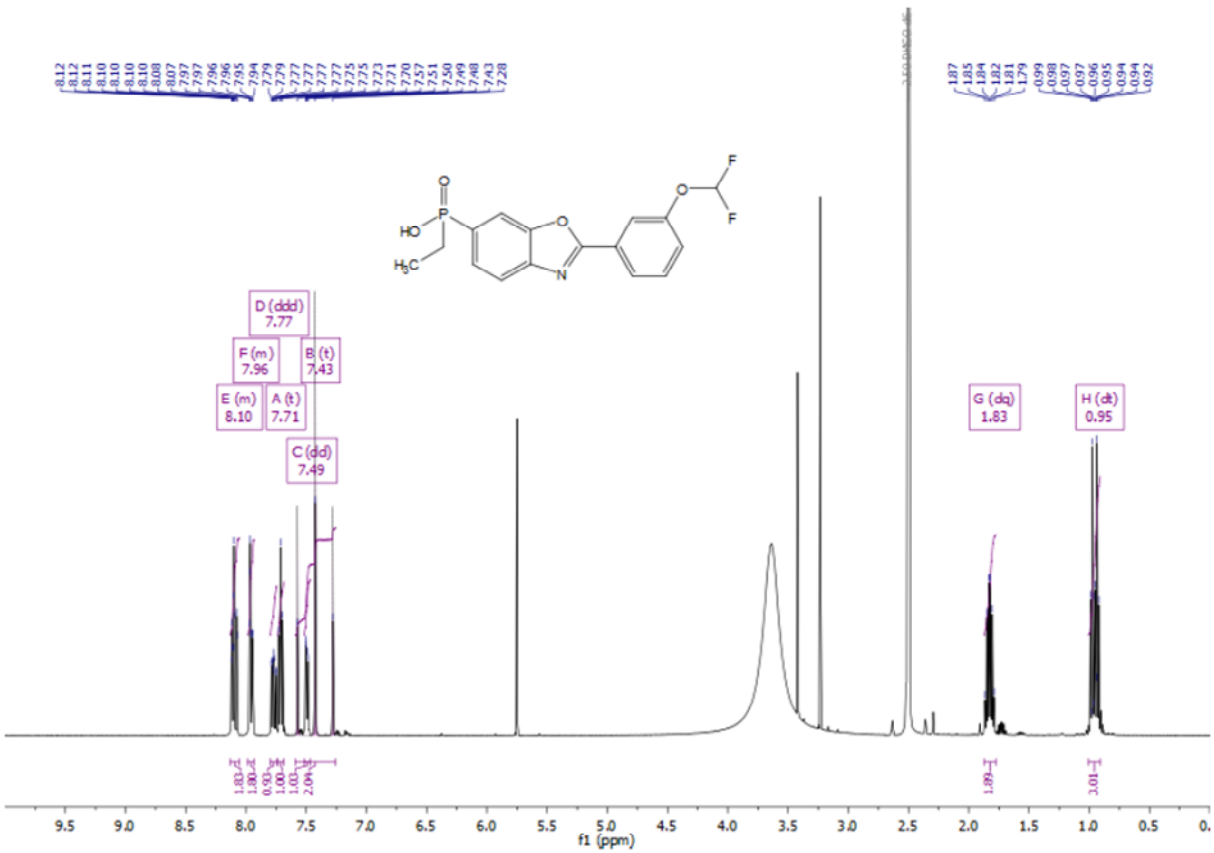
(2-(4-(difluoromethyl)phenyl)benzo[d]oxazol-6-yl)(ethyl)phosphinic acid (43)



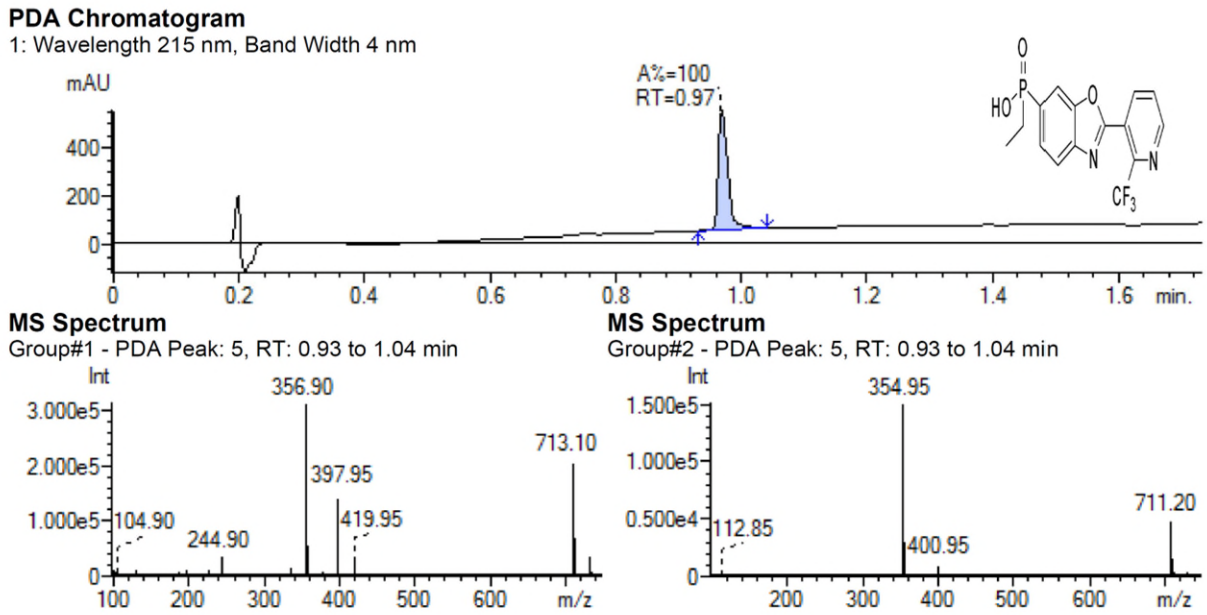


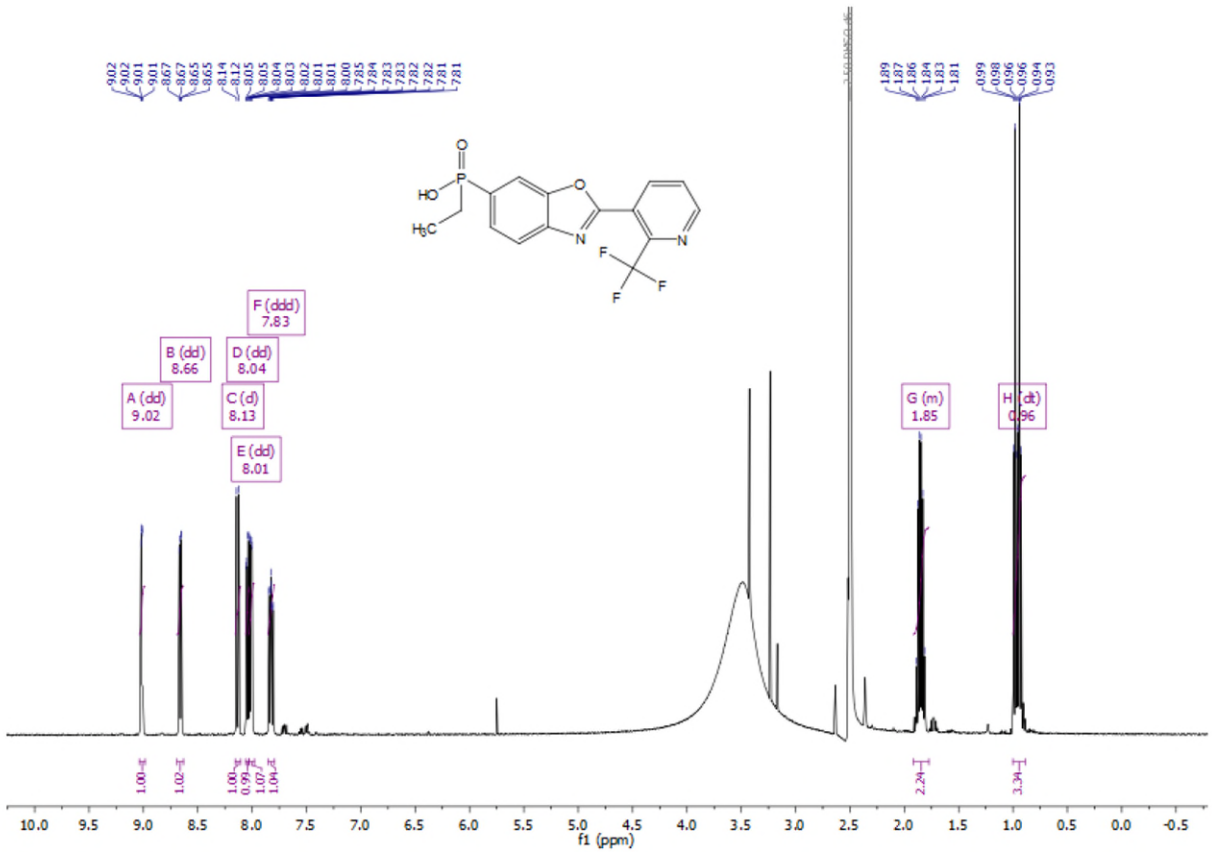
(2-(3-(difluoromethoxy)phenyl)benzo[d]oxazol-6-yl)(ethyl)phosphinic acid (44)



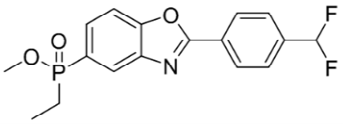


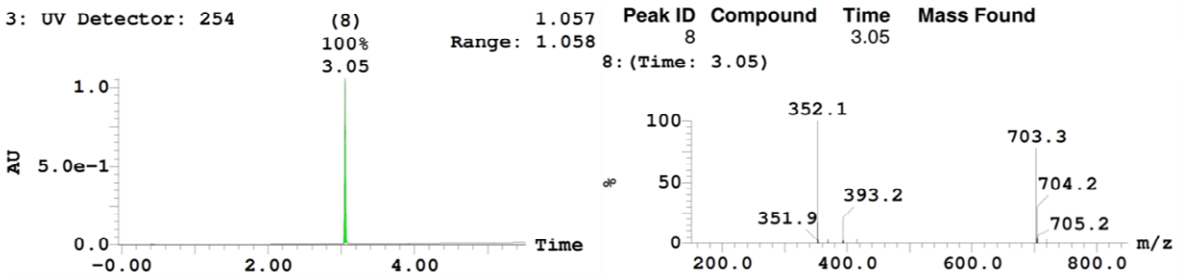
ethyl(2-(2-(trifluoromethyl)pyridin-3-yl)benzo[*d*]oxazol-6-yl)phosphinic acid (45)

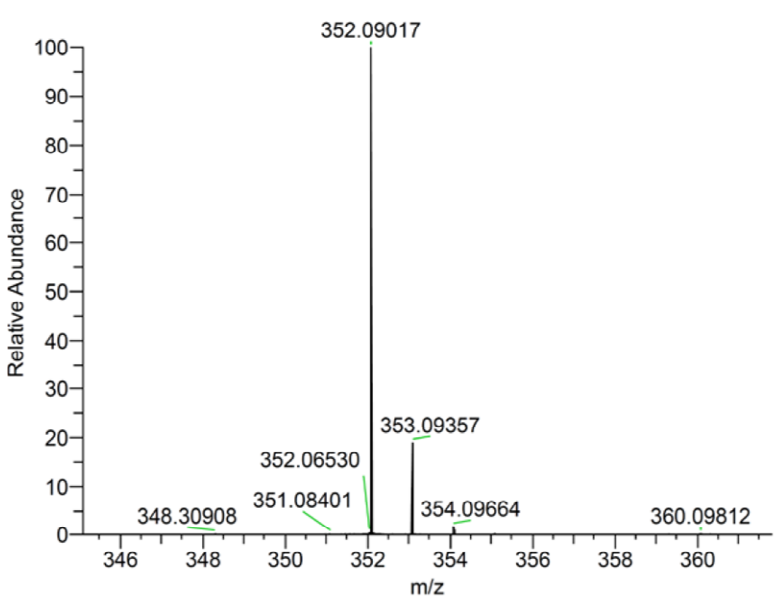




methyl (2-(4-(difluoromethyl)phenyl)benzo[d]oxazol-5-yl)(ethyl)phosphinate (46)

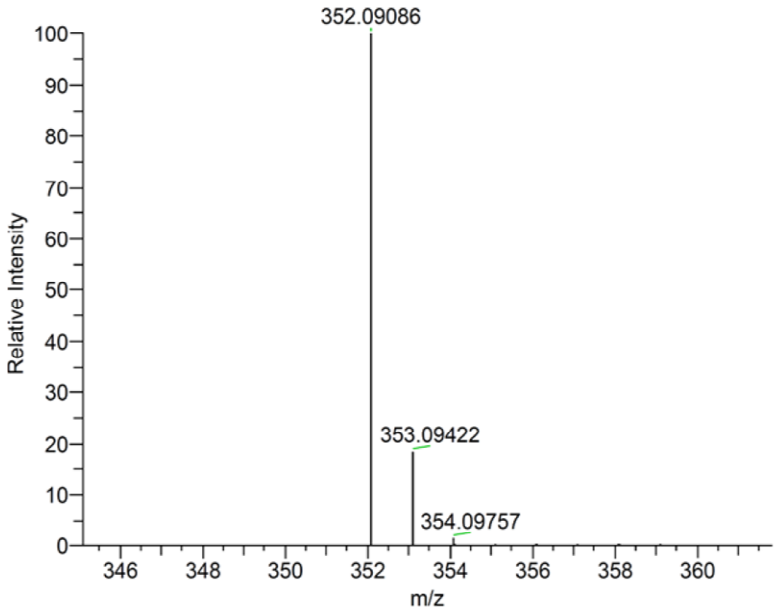






NL: 5.74E7
ESI74313 #13-27 RT: 0.15-0.31 AV: 8 NL: 5.74E+007
T: FTMS {1,1} + p ESI Full ms [80.00-1600.00]

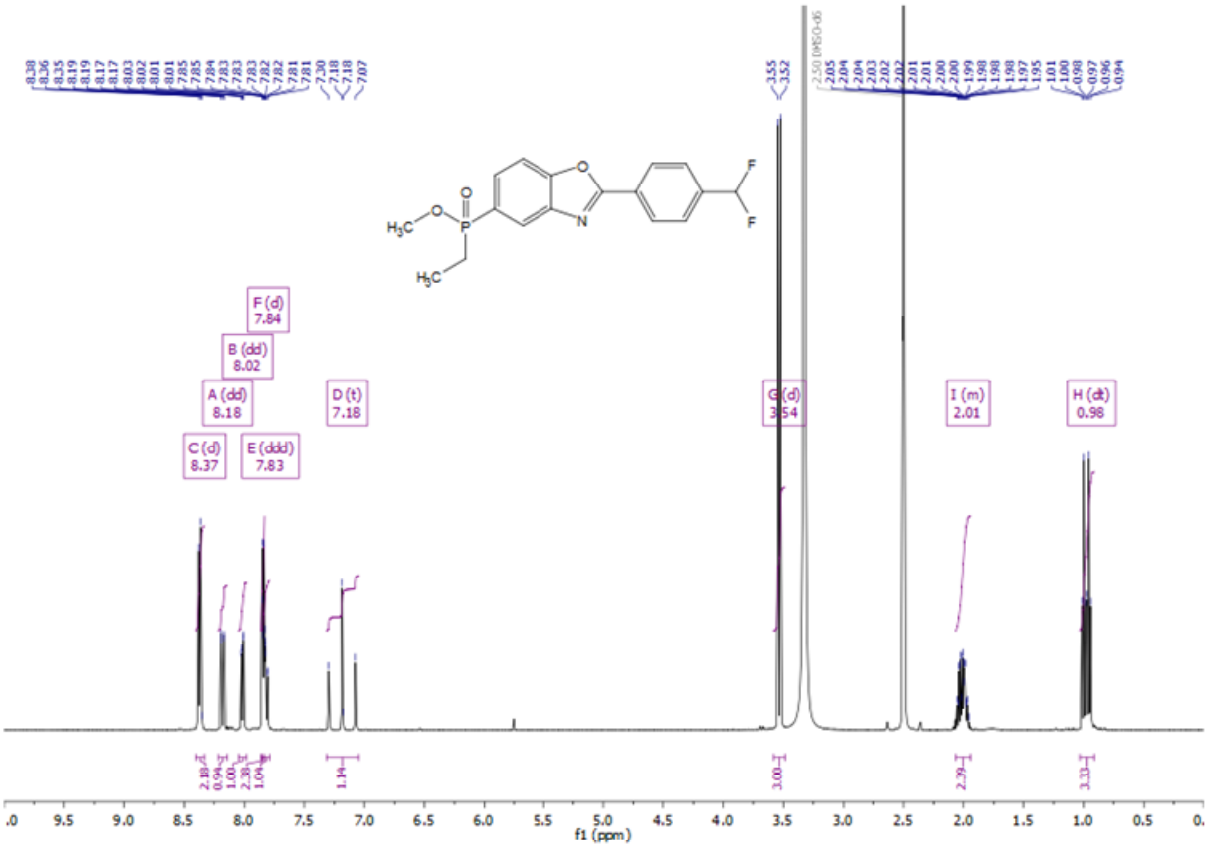
Measured Spectrum

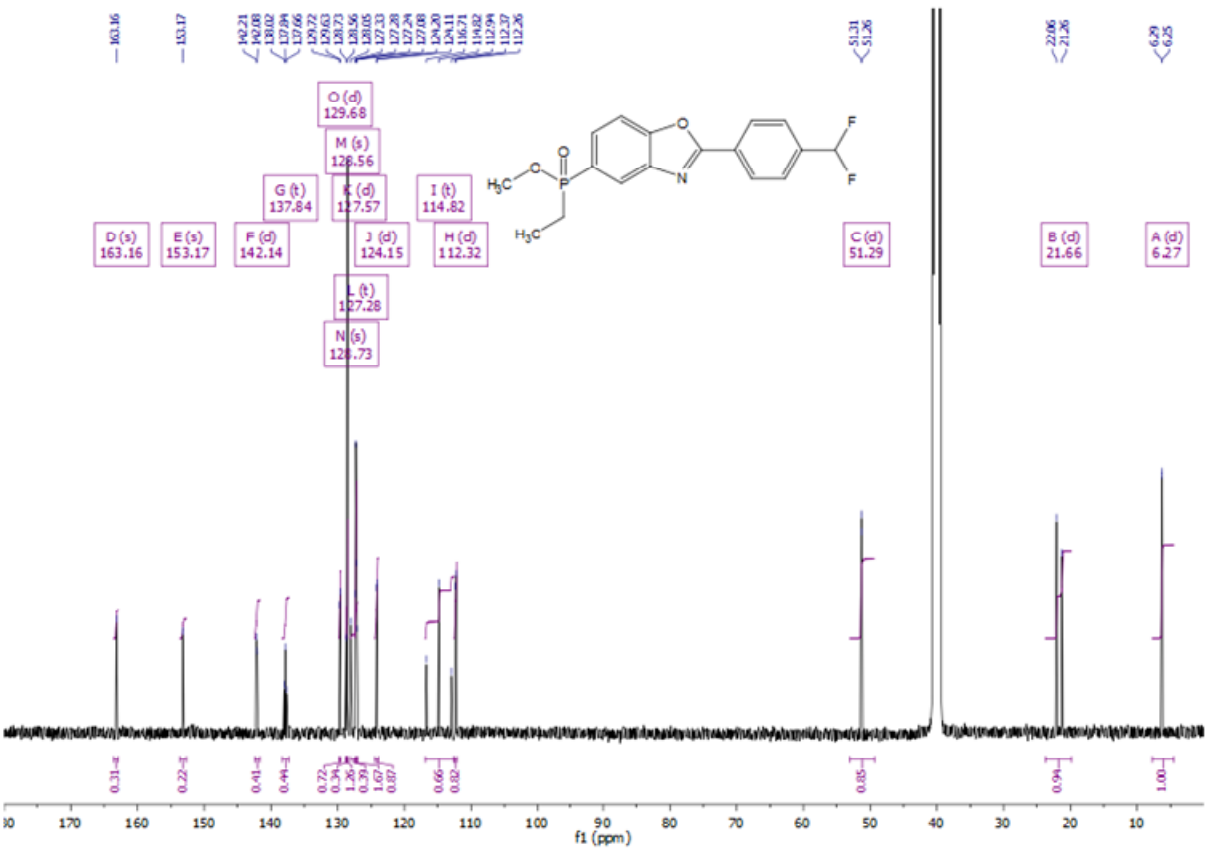


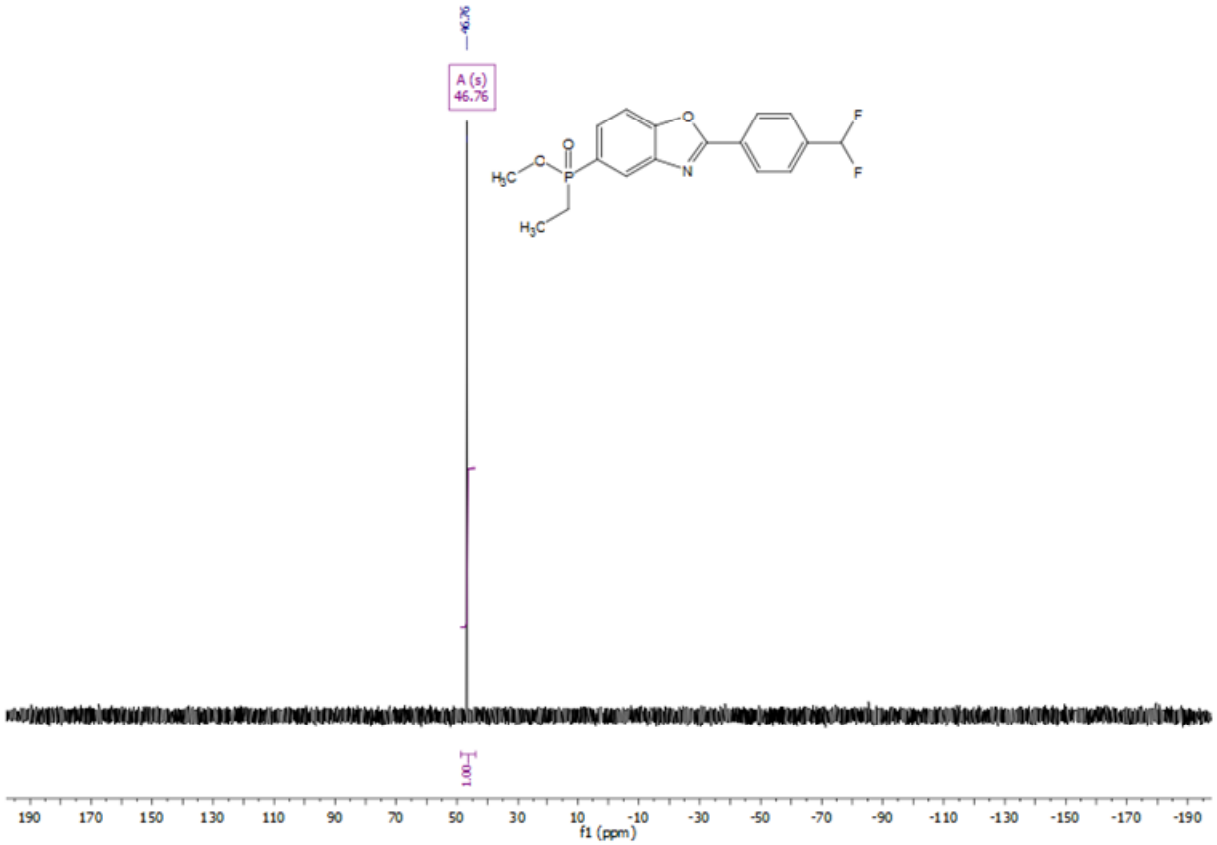
NL: 8.22E5
C17H17O3N1F2P1: $C_{17}H_{17}O_3NF_2P$
Chrg 1 R: 1000000 Res. Pwr. @FWHM

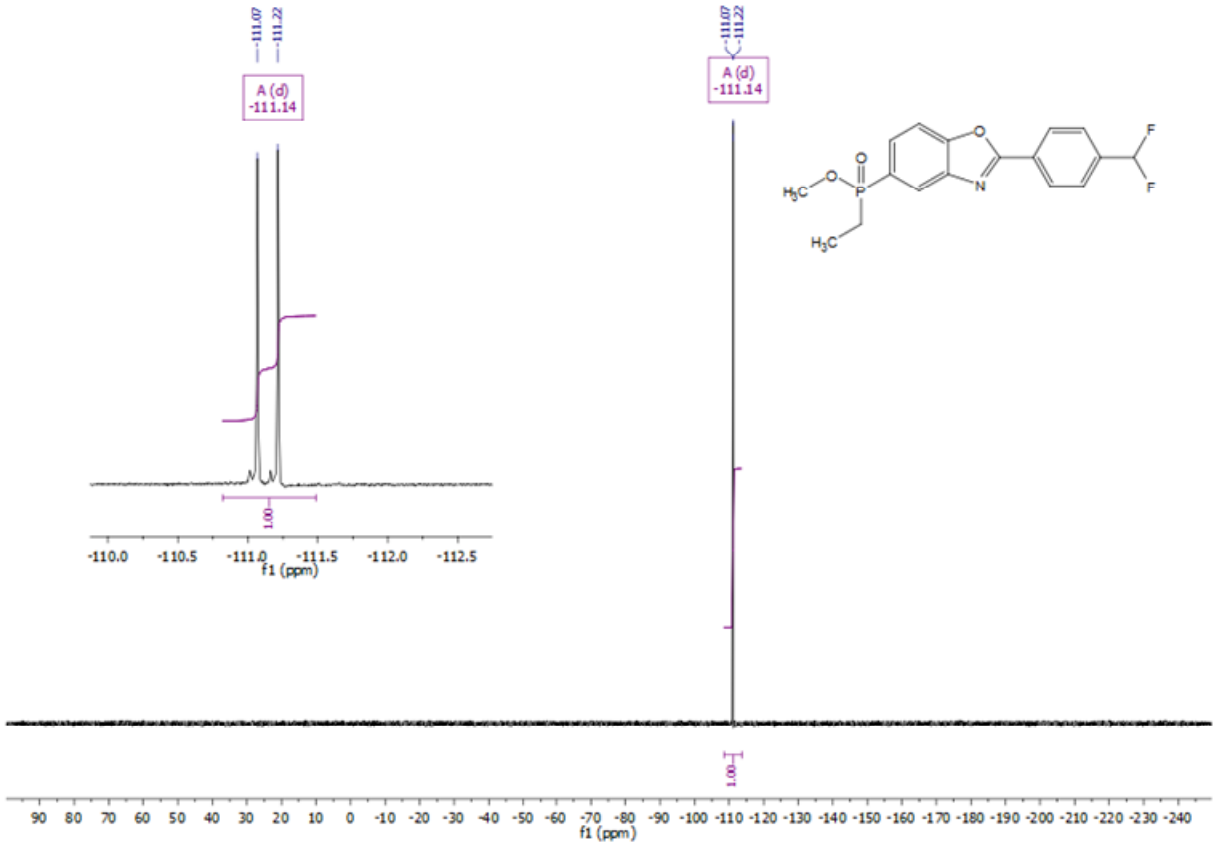
Theoretical Spectrum

m/z	Formula	RDB	Delta ppm	Theo. Mass
352.09018	$C_{17}H_{17}O_3NF_2P$	9.5	-1.94	352.09086

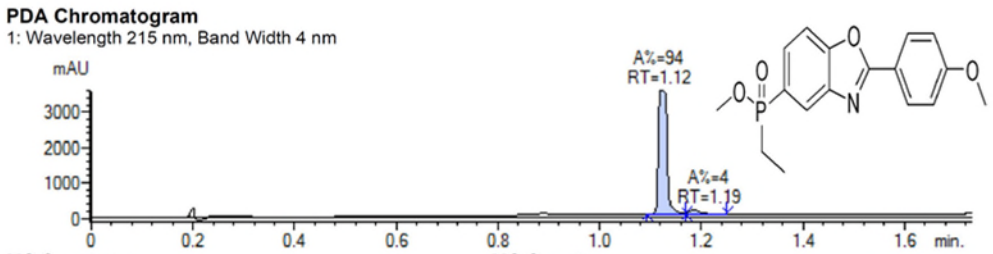

F (d) 7.84
B (dd) 8.02
A (dd) 8.18
C (d) 8.37
E (ddd) 7.83
D (t) 7.18
G (d) 3.54
I (m) 2.01
H (dt) 0.98
f1 (ppm)

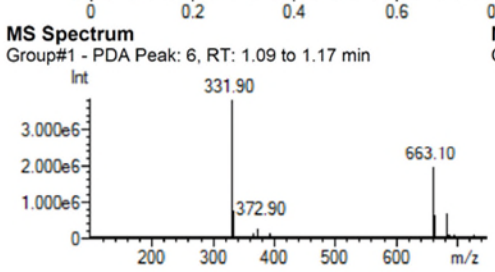

O (d) 129.68
M (s) 128.56
G (t) 137.84
K (d) 127.57
I (t) 114.82
D (s) 163.16
E (s) 153.17
F (d) 142.14
J (d) 124.15
H (d) 112.32
L (t) 127.28
N (s) 128.73
C (d) 51.29
B (d) 21.66
A (d) 6.27
f1 (ppm)

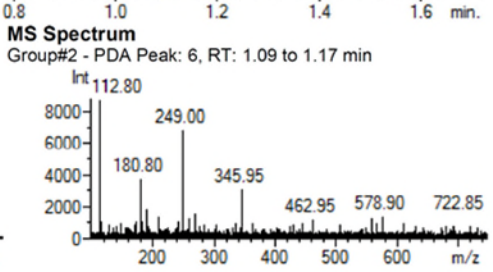

46.76
A (s)
46.76
O
O
N
F
F
H3C
O
P
H3C
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

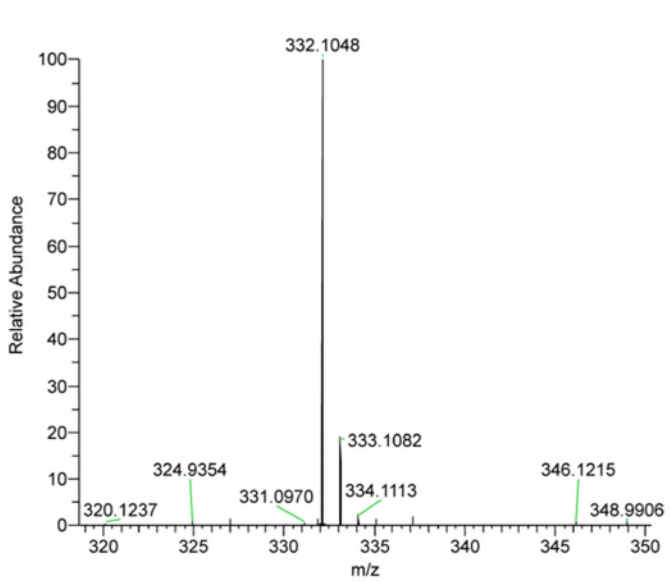

-111.07
-111.22
A (d)
-111.14
1.00
-110.0 -110.5 -111.0 -111.5 -112.0 -112.5
f1 (ppm)
-111.07
-111.22
A (d)
-111.14
O
O
N
F
F
H3C
O
P
H3C
1.00
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

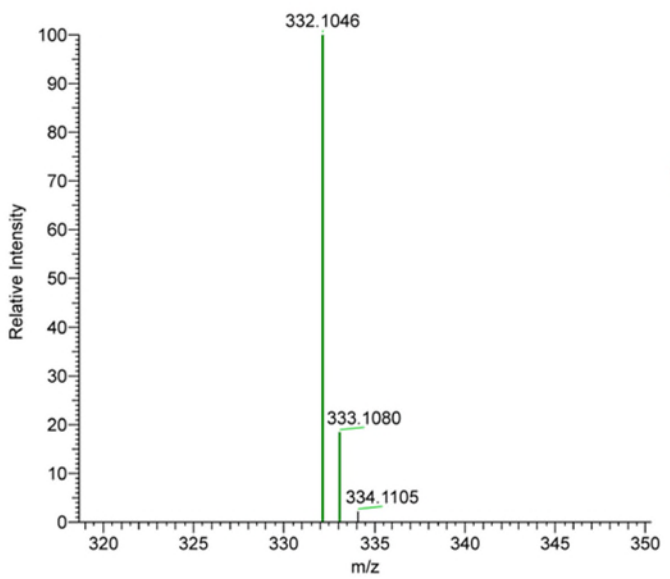
methyl ethyl(2-(4-methoxyphenyl)benzo[d]oxazol-5-yl)phosphinate (47)



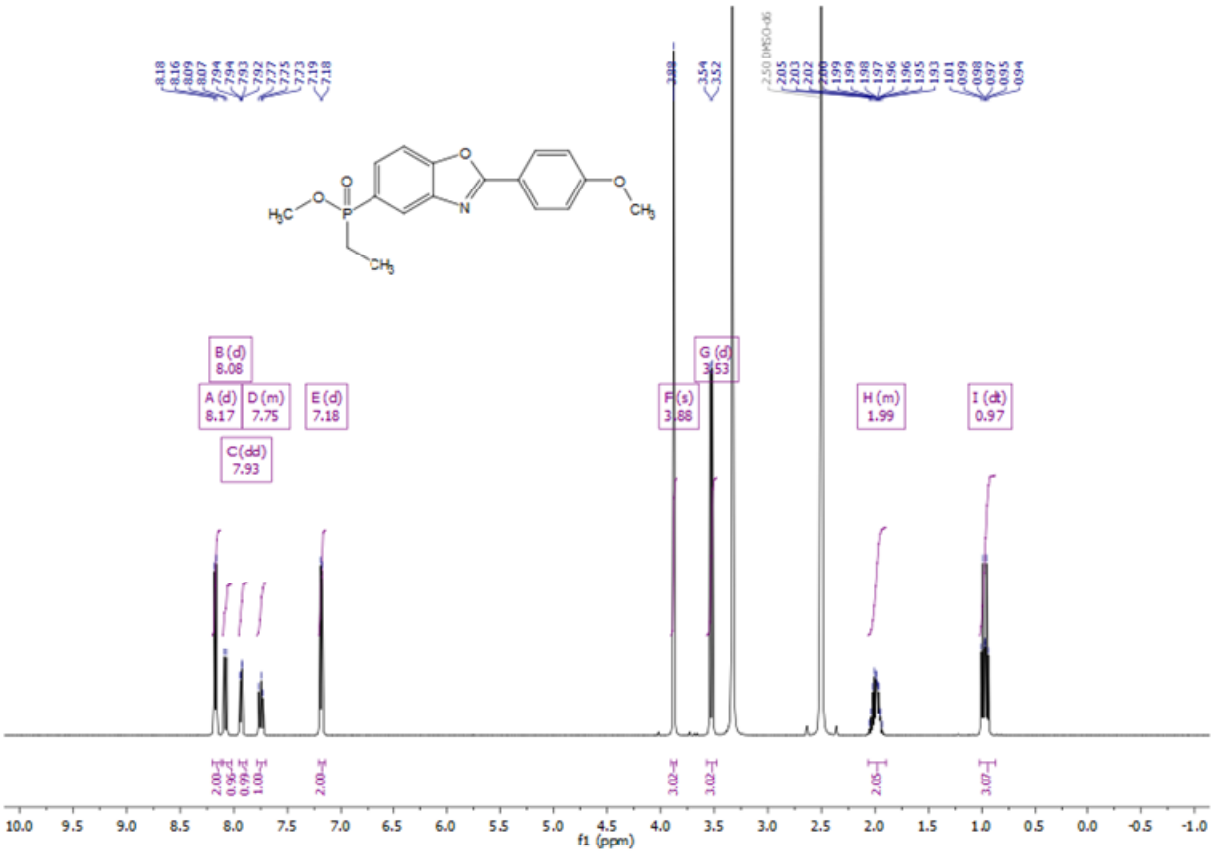


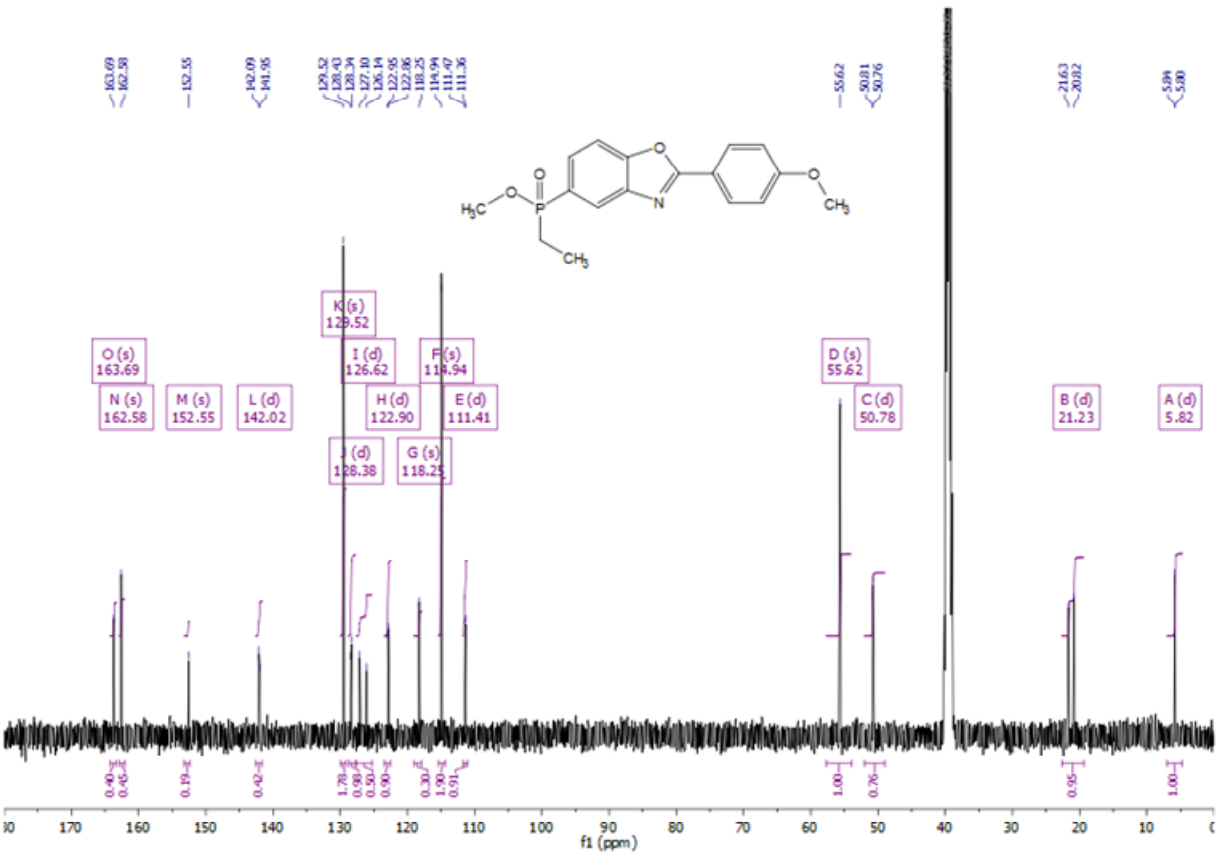






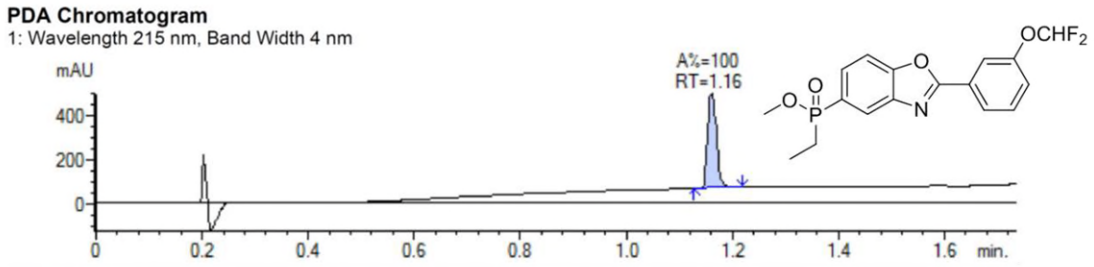
Peak Mass	Display...	Combin...	RDB	Delta [p...	Theo. m...	Rank	Combin...	# Match...	# Misse...	MS Cov....	Pattern...	MSMS...
332.1048	$C_{17}H_{19}$...	28.787...	9.50	0.62	332.10...	1	95.042...	4	0	98.723...	97.907...	(Collec.

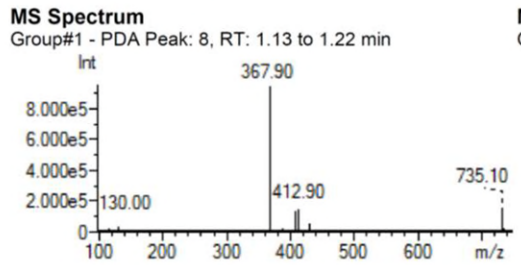

B (d) 8.08
A (d) 8.17
D (m) 7.75
E (d) 7.18
C (dd) 7.93
F (s) 3.88
G (d) 3.53
H (m) 1.99
I (dt) 0.97
f1 (ppm)

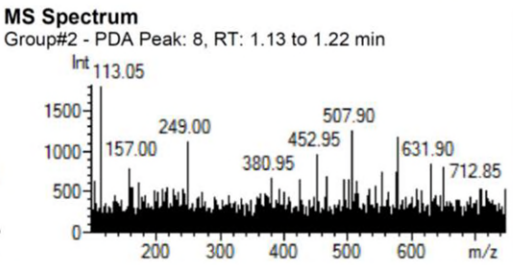

K (s) 129.52
I (d) 126.62
F (s) 118.94
O (s) 163.69
N (s) 162.58
M (s) 152.55
L (d) 142.02
H (d) 122.90
E (d) 111.41
J (d) 128.38
G (s) 118.25
D (s) 55.62
C (d) 50.78
B (d) 21.23
A (d) 5.82
f1 (ppm)

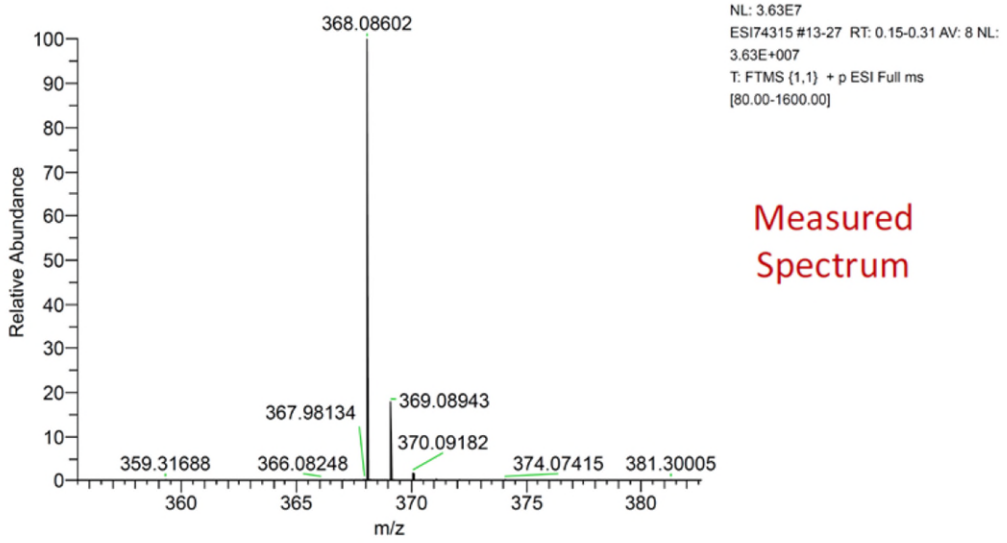

46.93
A (s)
46.93
O
O
P
O
CH3
H3C
O
N
O
CH3
1.00
190
170
150
130
110
90
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
f1 (ppm)

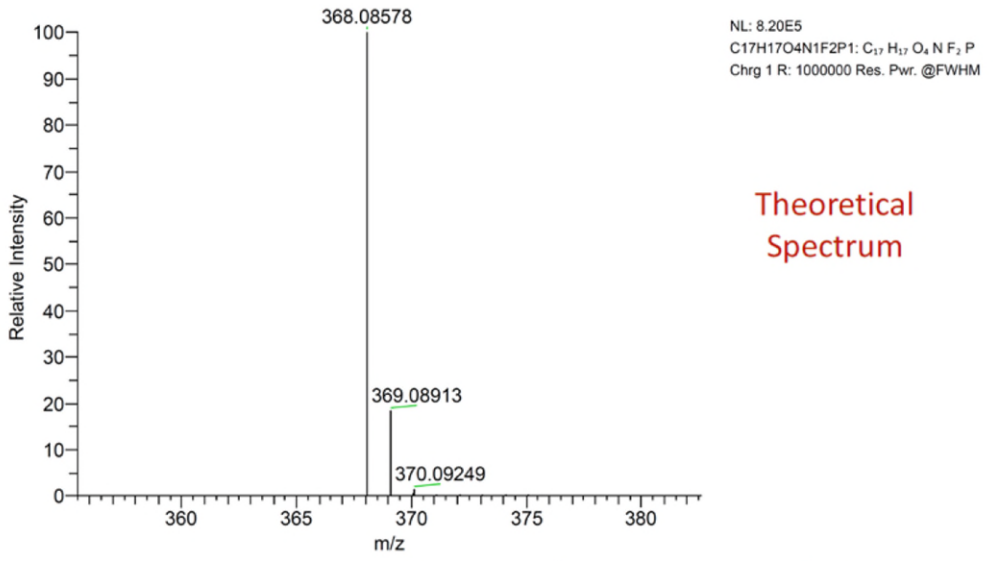
methyl (2-(3-(difluoromethoxy)phenyl)benzo[d]oxazol-5-yl)(ethyl)phosphinate (48)



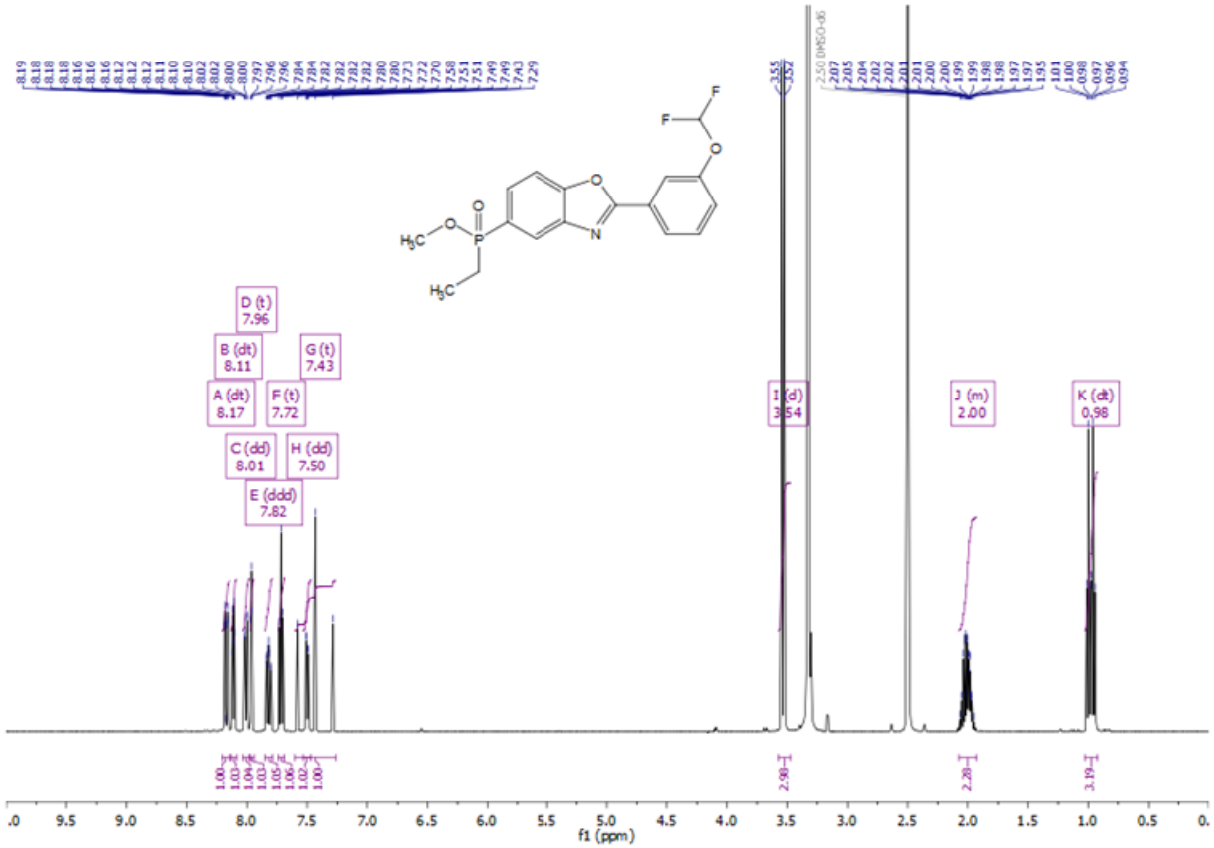


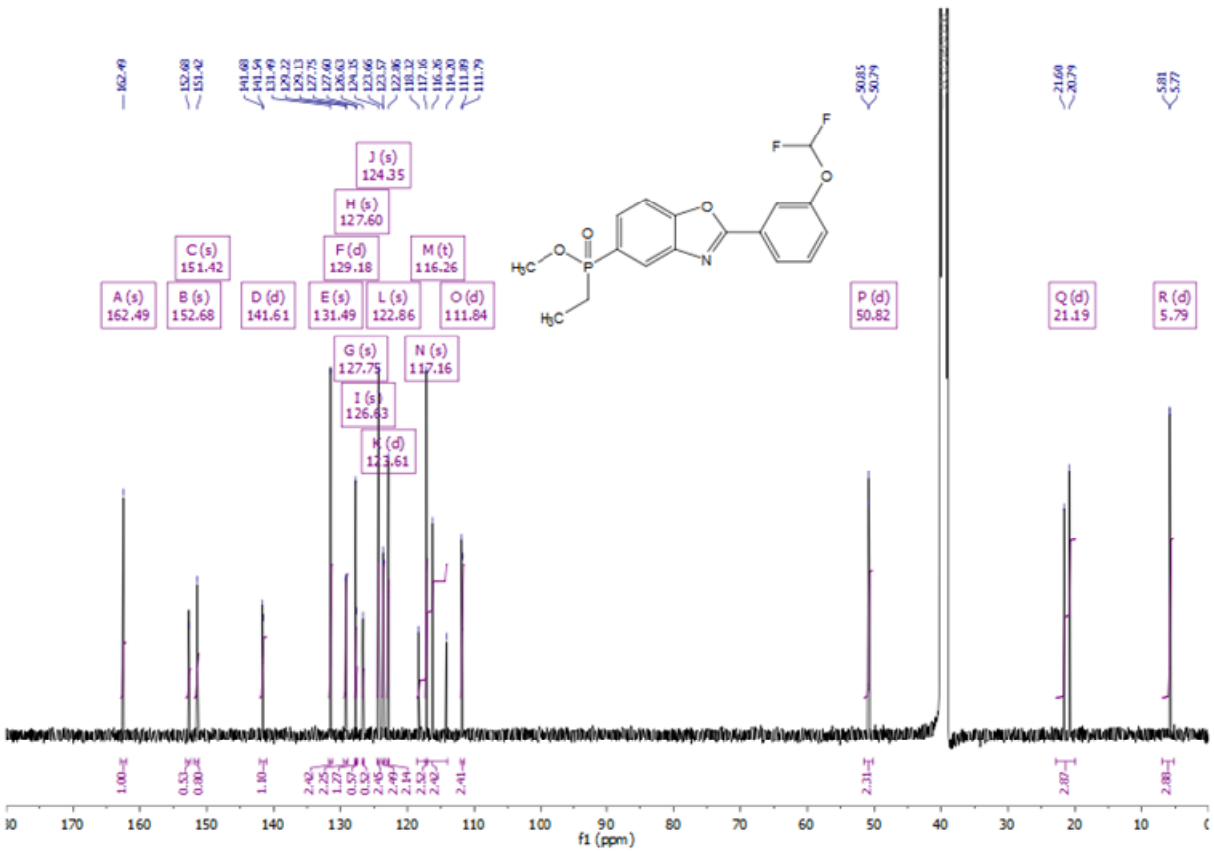


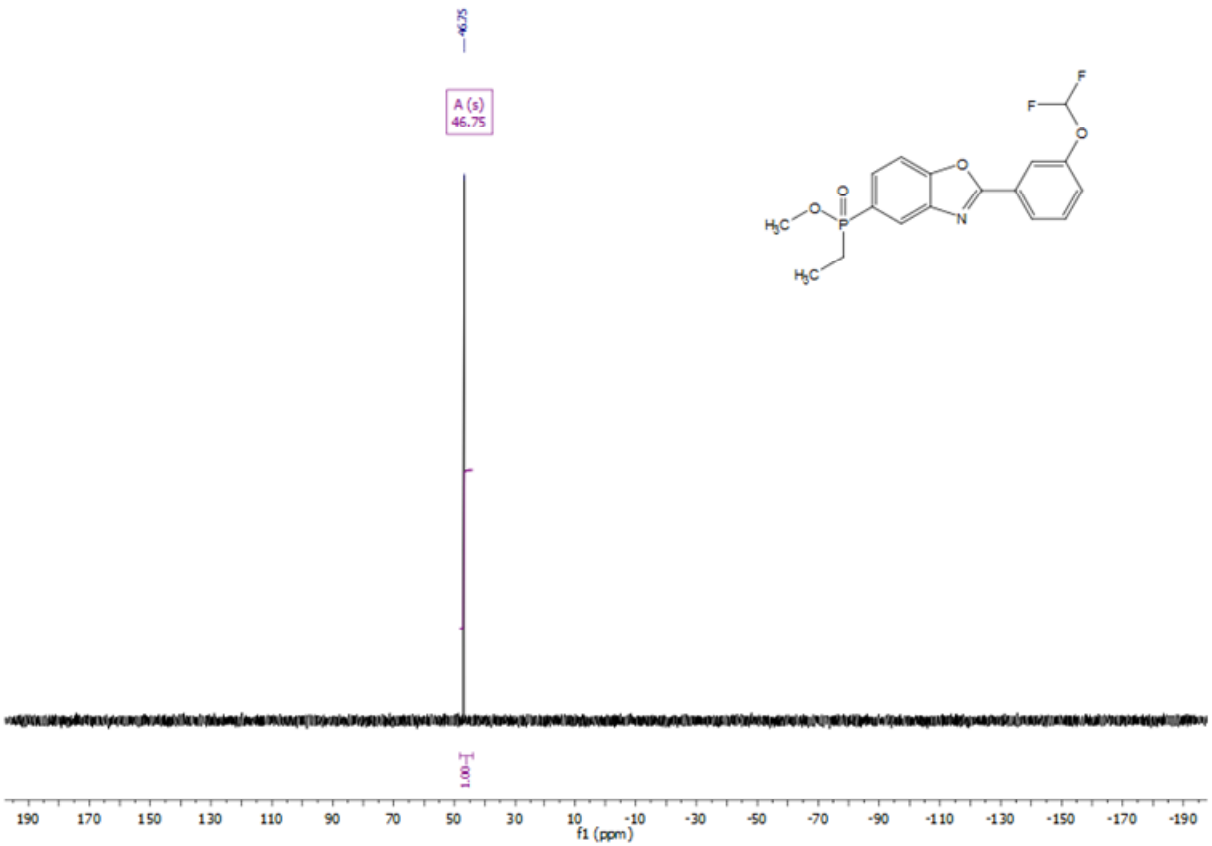


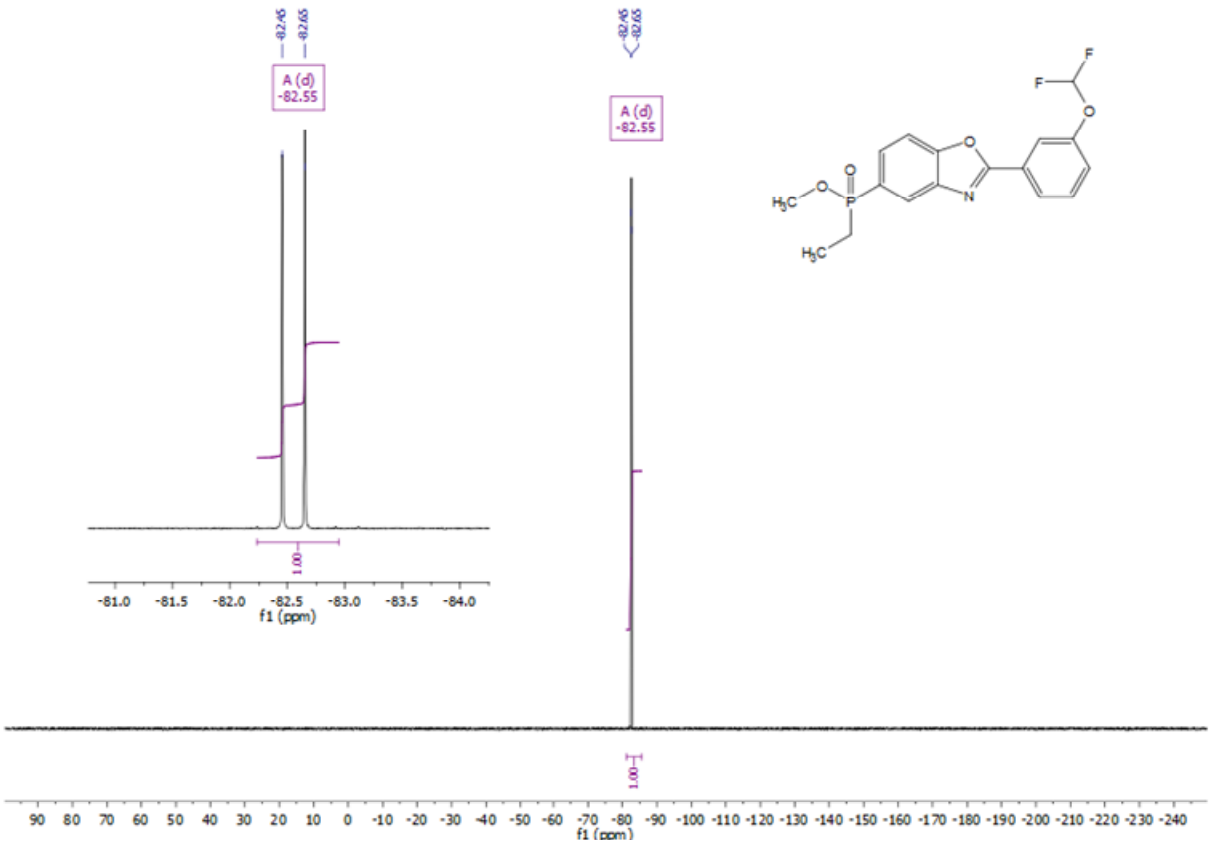


m/z	Formula	RDB	Delta ppm	Theo. Mass
368.08603	$C_{17}H_{17}O_4NF_2P$	9.5	0.68	368.08578

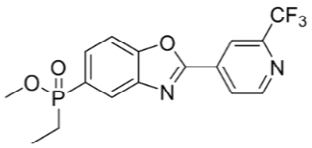

D (t)
7.96
B (dt)
8.11
G (t)
7.43
A (dt)
8.17
F (t)
7.72
C (dd)
8.01
H (dd)
7.50
E (ddd)
7.82
I (d)
3.54
J (m)
2.00
K (dt)
0.98
f1 (ppm)

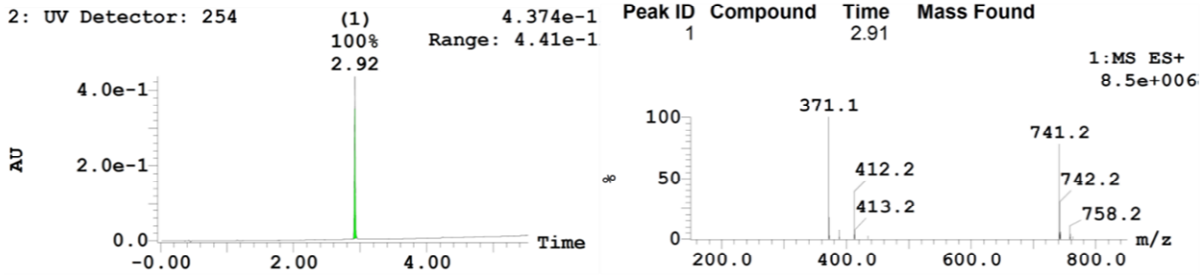

J (s)
124.35
H (s)
127.60
C (s)
151.42
F (d)
129.18
M (t)
116.26
A (s)
162.49
B (s)
152.68
D (d)
141.61
E (s)
131.49
L (s)
122.86
O (d)
111.84
G (s)
127.75
N (s)
117.16
I (s)
126.43
K (d)
123.61
P (d)
50.82
Q (d)
21.19
R (d)
5.79
f1 (ppm)

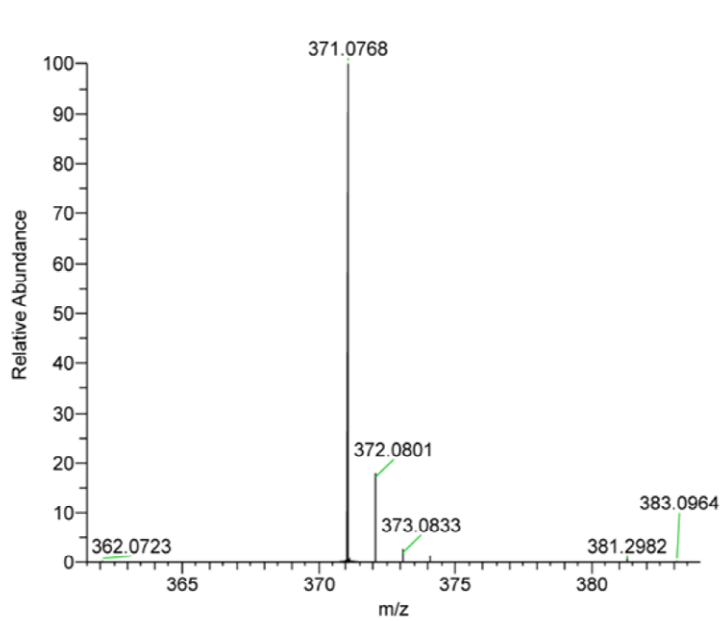

46.75
A (s)
46.75
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

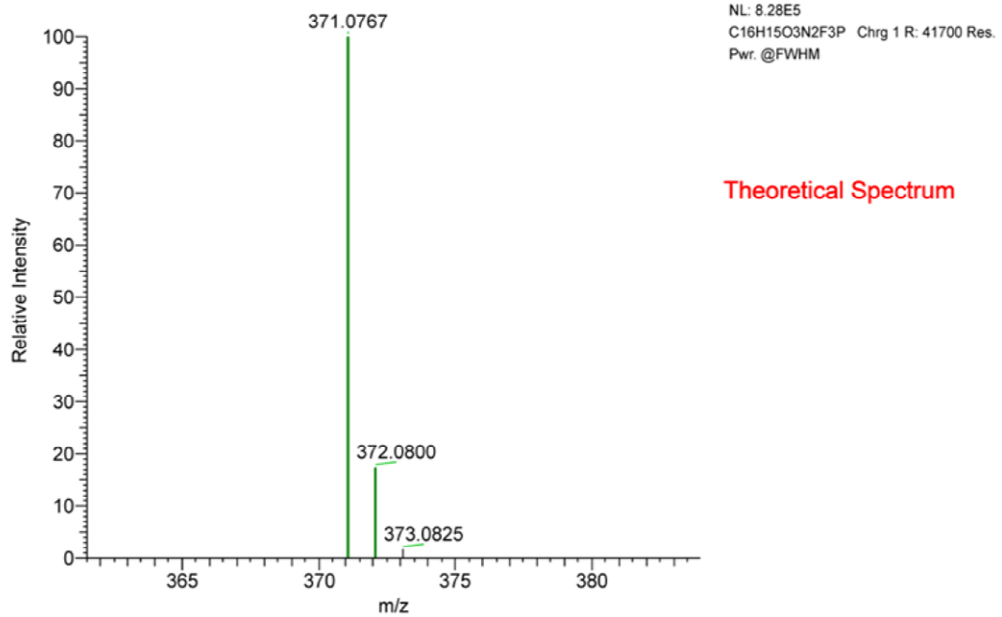

-82.45
-82.65
A (d)
-82.55
1.00
-81.0 -81.5 -82.0 -82.5 -83.0 -83.5 -84.0
f1 (ppm)
-82.45
-82.65
A (d)
-82.55
1.00
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

methyl ethyl(2-(2-(trifluoromethyl)pyridin-4-yl)benzo[d]oxazol-5-yl)phosphinate (49)

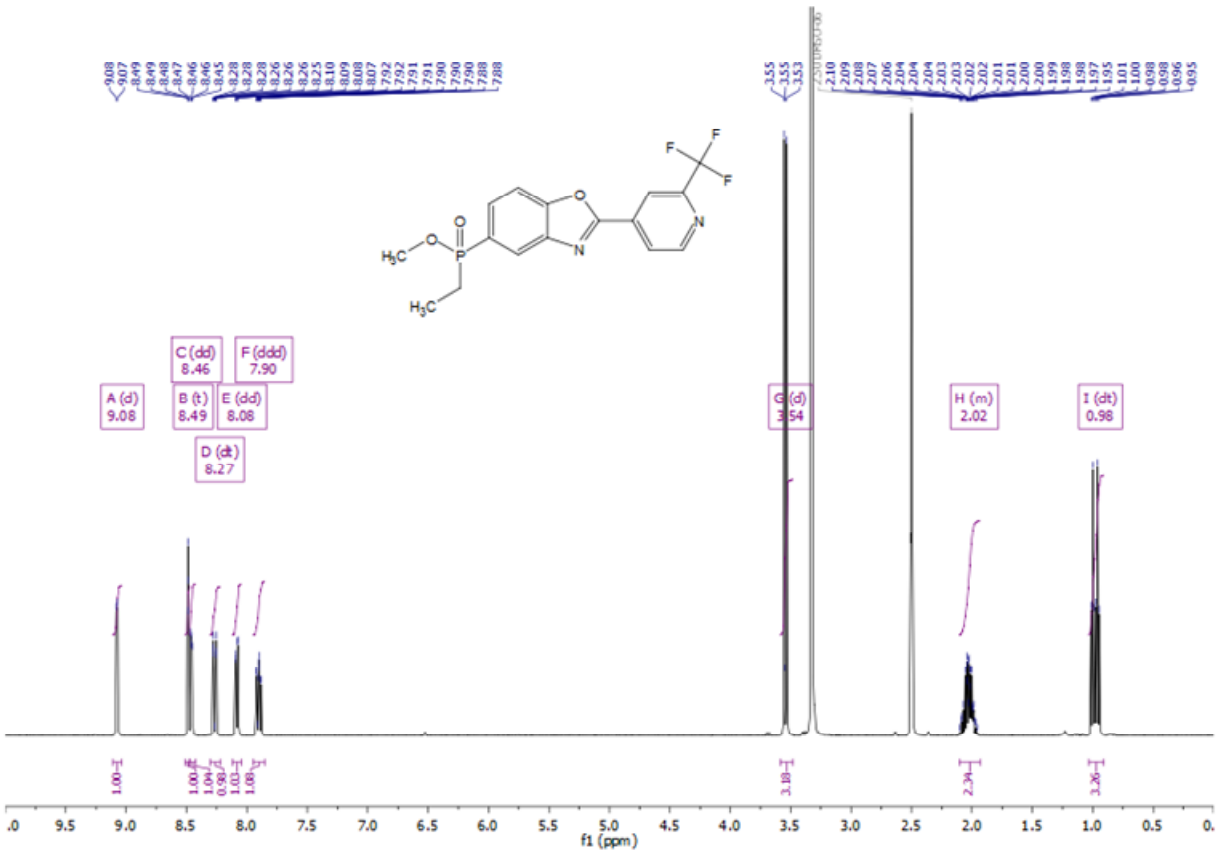


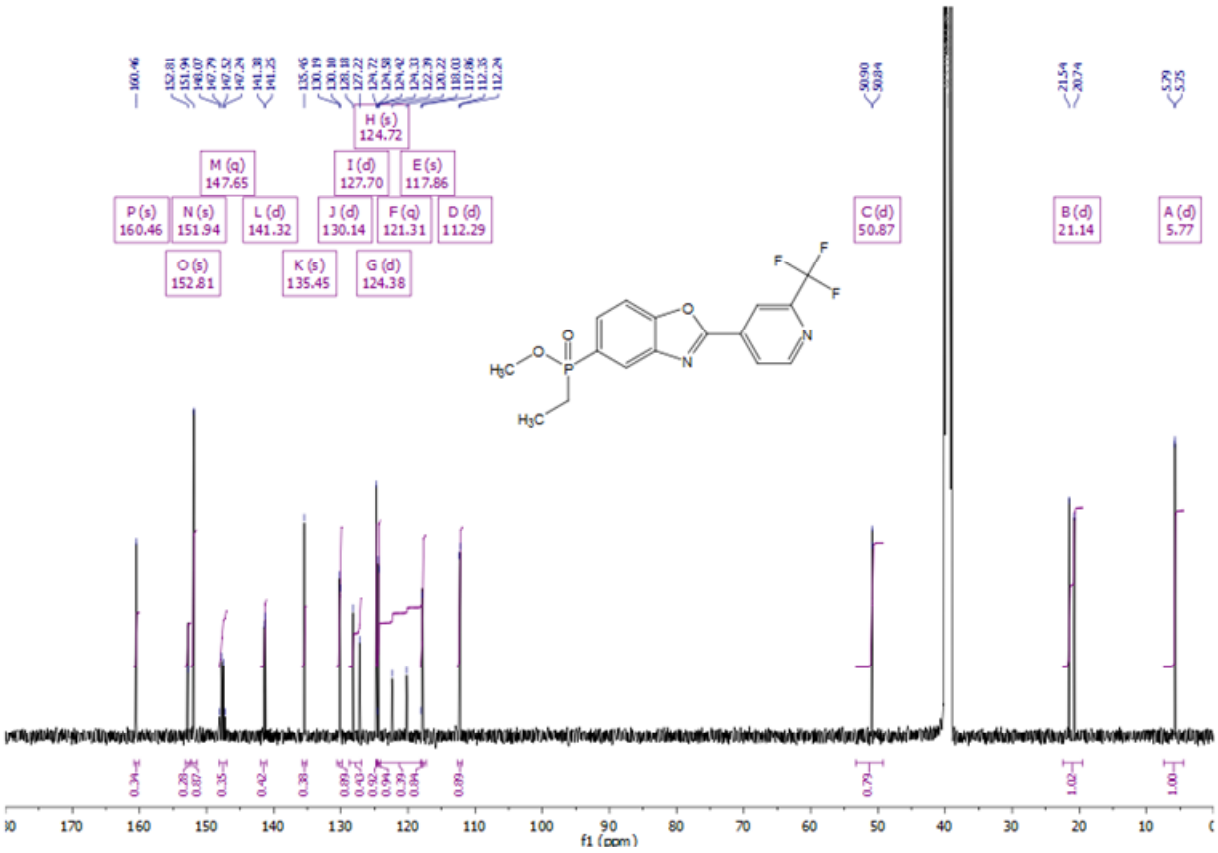




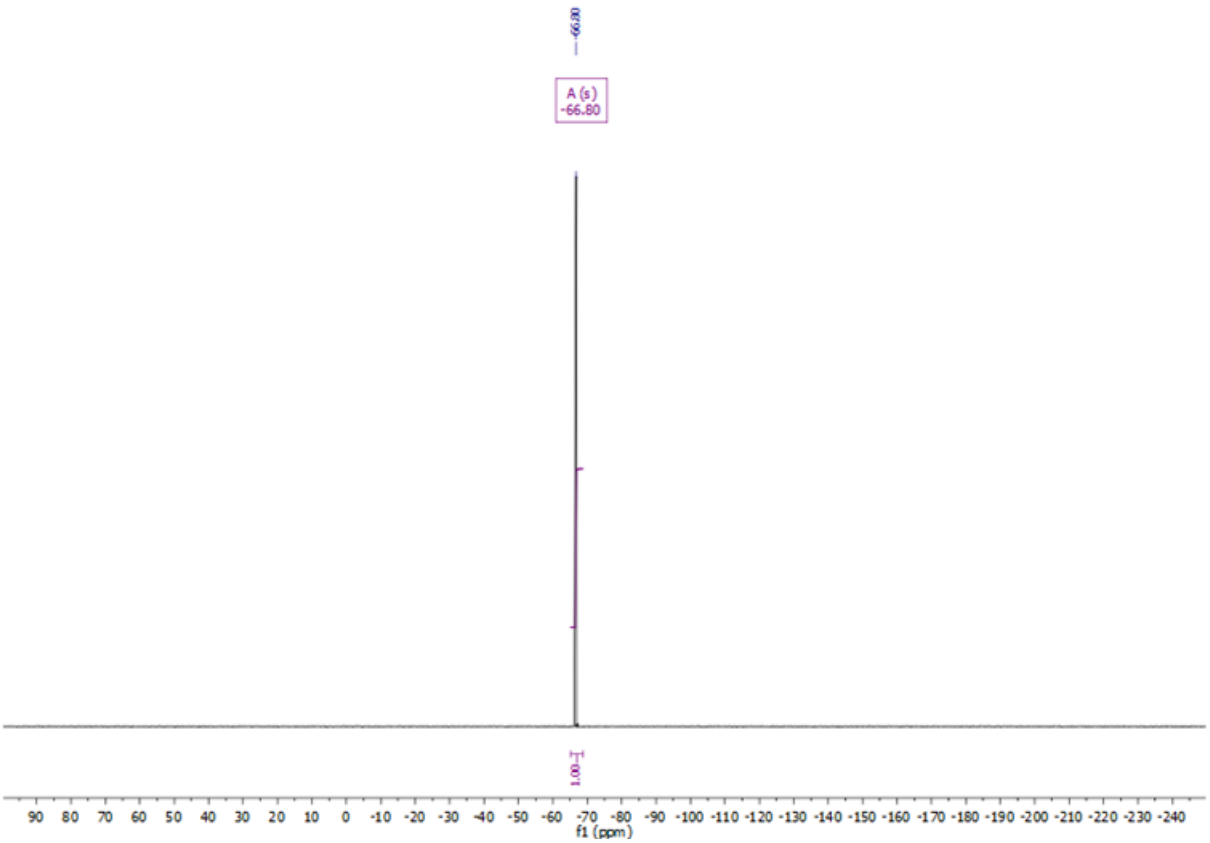


Peak Mass	Display...	Combin...	RDB	Delta [p...	Theo. m...	Rank	Combin...	# Match...	# Misse...	MS Cov....	Pattern...	MSMS...
371.0768	$C_{16}H_{15}$...	28.353...	9.50	0.25	371.07...	1	95.032...	3	1	98.736...	98.176...	(Collec

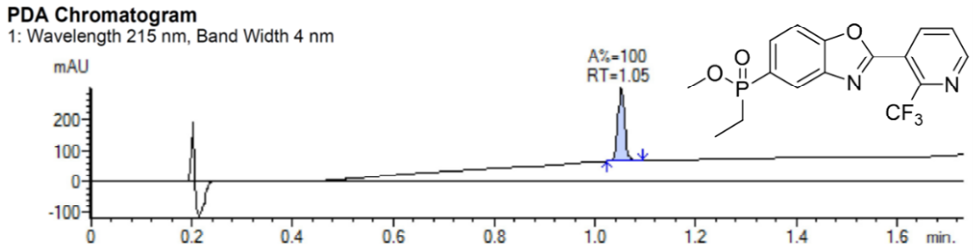

A (d) 9.08
B (t) 8.49
C (dd) 8.46
D (dt) 8.27
E (dd) 8.08
F (ddd) 7.90
G (d) 3.54
H (m) 2.02
I (dt) 0.98
f1 (ppm)

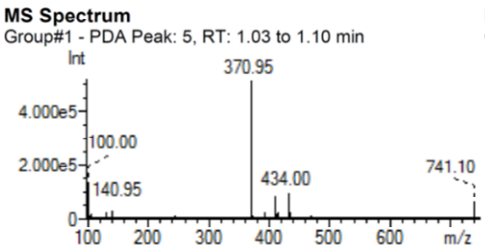

H (s) 124.72
M (q) 147.65
I (d) 127.70
E (s) 117.86
P (s) 160.46
N (s) 151.94
L (d) 141.32
J (d) 130.14
F (q) 121.31
D (d) 112.29
O (s) 152.81
K (s) 135.45
G (d) 124.38
C (d) 50.87
B (d) 21.14
A (d) 5.77
f1 (ppm)

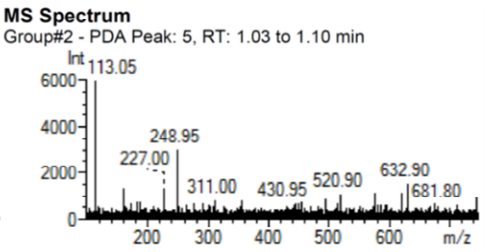

46.53
A (s)
46.53
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

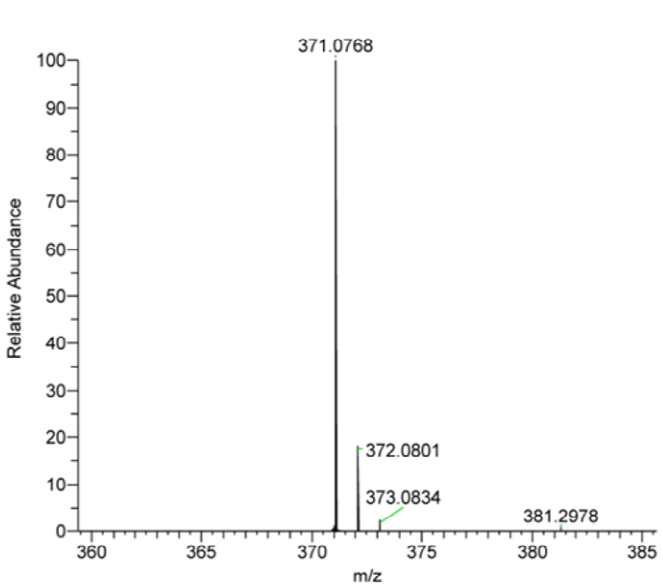

-66.80
A (s)
-66.80
1.00
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

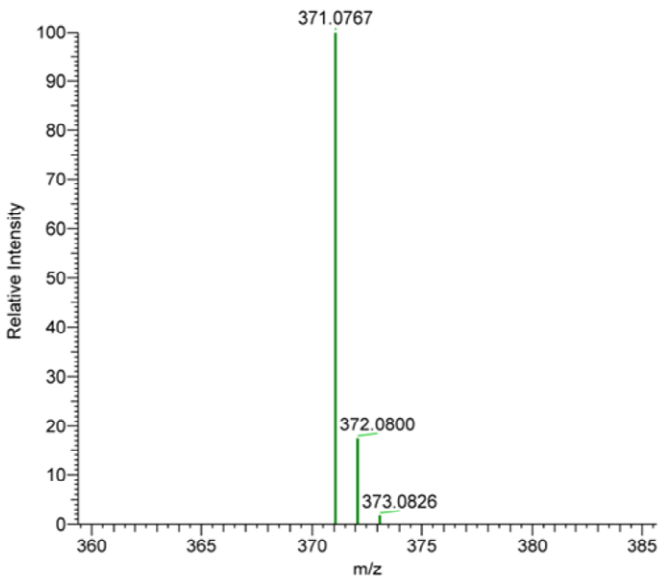
methyl ethyl(2-(2-(trifluoromethyl)pyridin-3-yl)benzo[d]oxazol-5-yl)phosphinate (50)



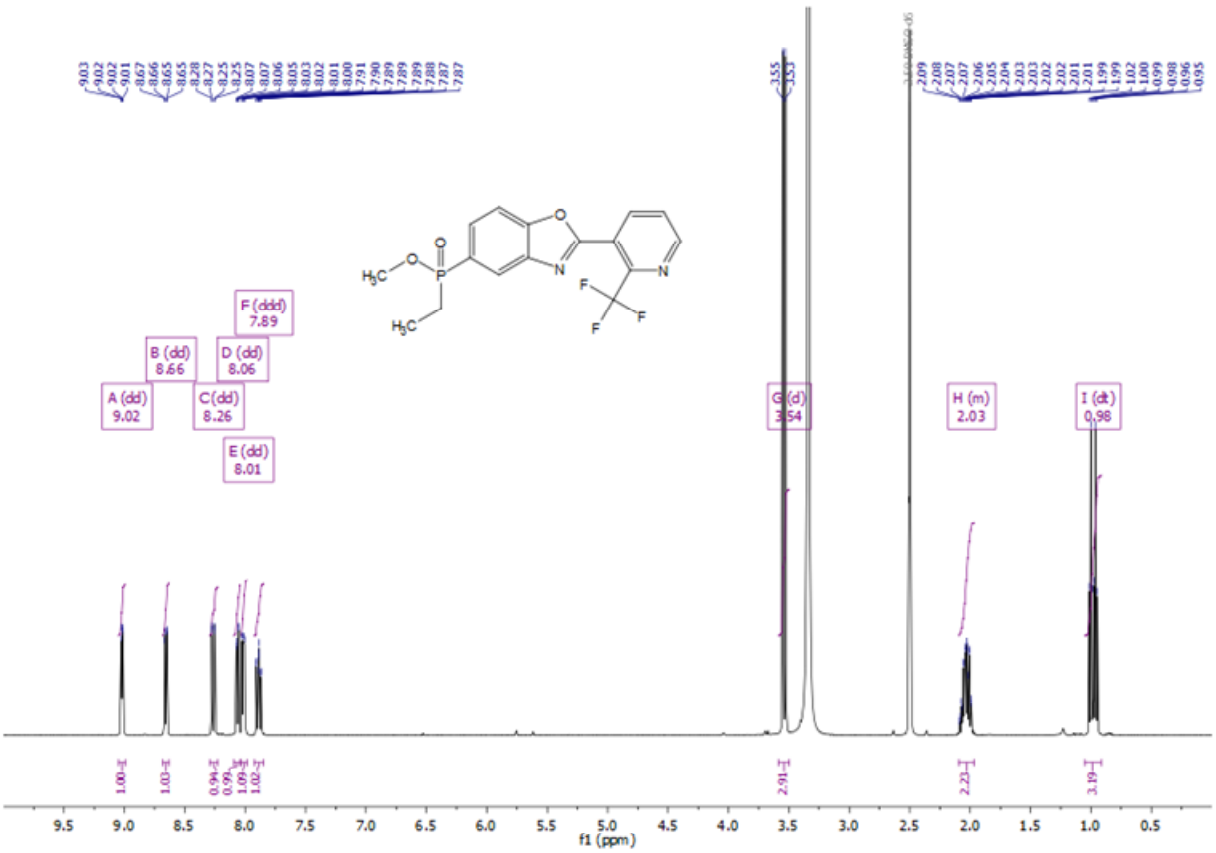


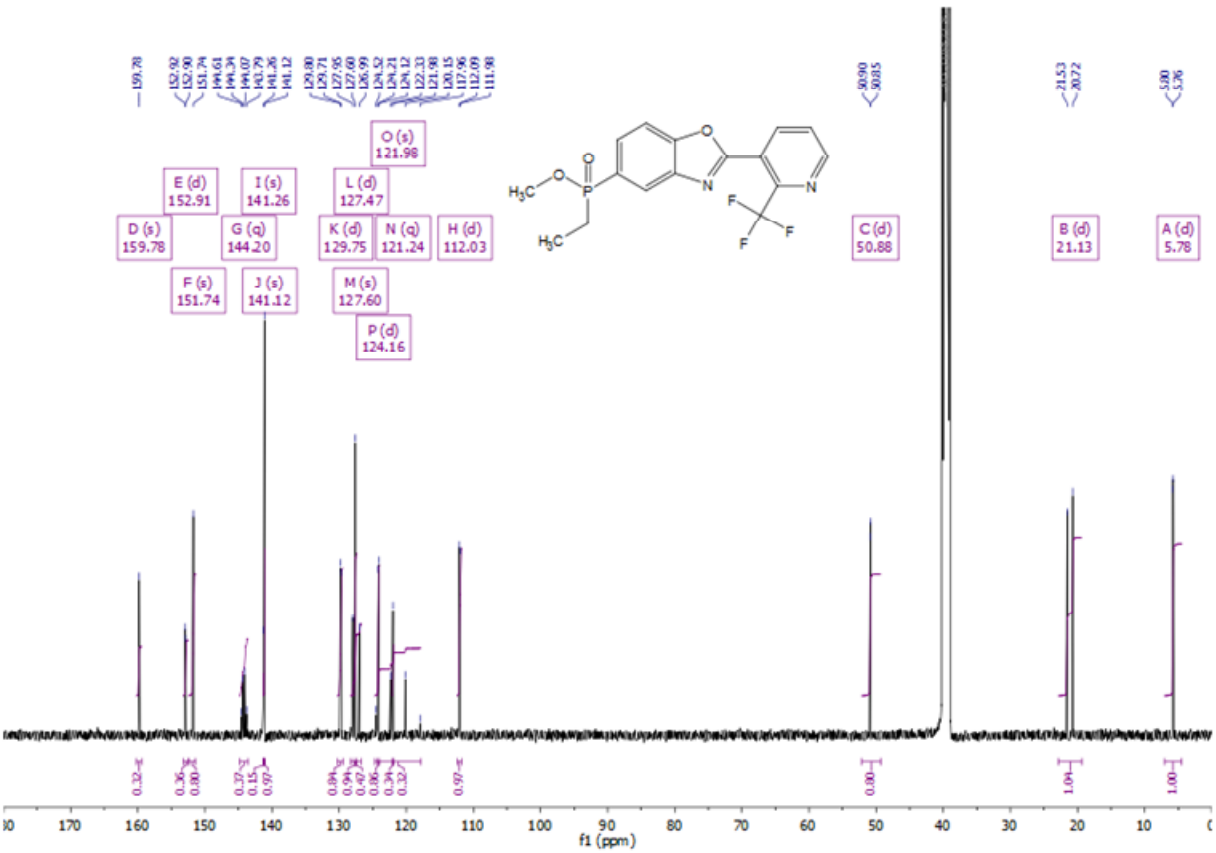


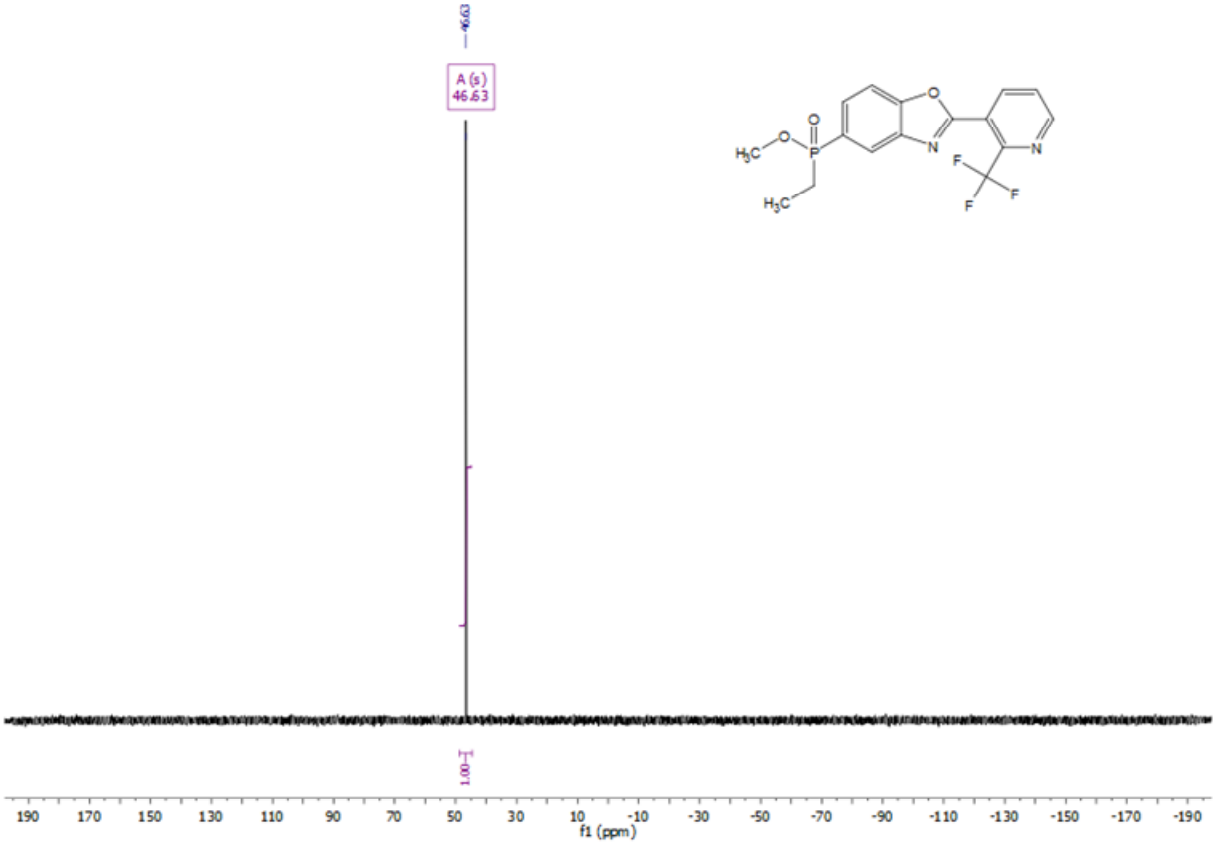


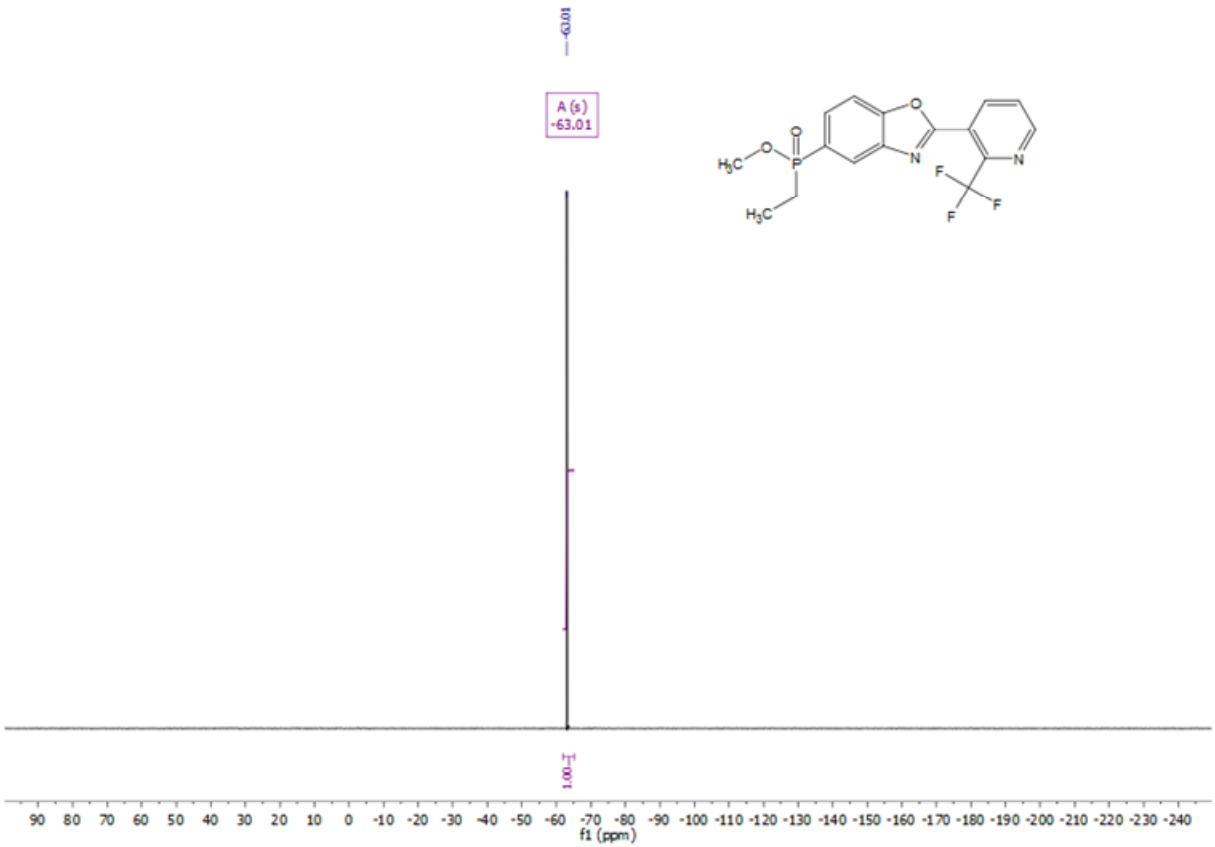


Peak Mass	Display...	Combin...	RDB	Delta [p...	Theo. m...	Rank	Combin...	# Match...	# Misse...	MS Cov....	Pattern...	MSMS...
371.0768	$C_{16}H_{15}$...	29.061...	9.50	0.25	371.07...	1	95.362...	3	1	99.045...	98.179...	(Collec...

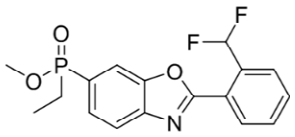

A (dd) 9.02
B (dd) 8.66
C (dd) 8.26
D (dd) 8.06
E (dd) 8.01
F (dddd) 7.89
G (d) 3.54
H (m) 2.03
I (dt) 0.98
f1 (ppm)

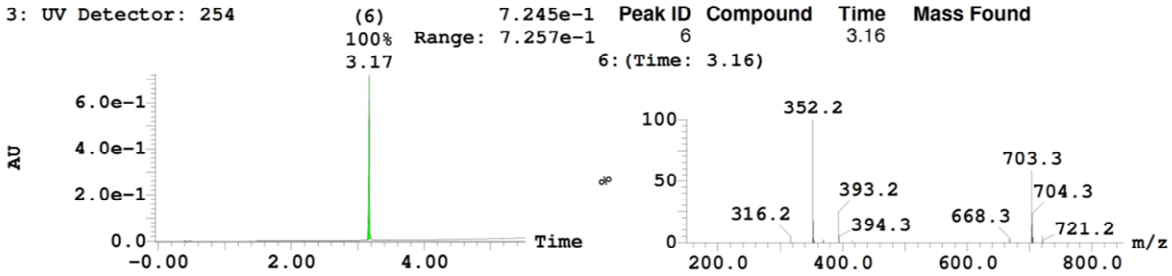

O (s) 121.98
E (d) 152.91
I (s) 141.26
L (d) 127.47
D (s) 159.78
G (q) 144.20
K (d) 129.75
N (q) 121.24
H (d) 112.03
F (s) 151.74
J (s) 141.12
M (s) 127.60
P (d) 124.16
C (d) 50.88
B (d) 21.13
A (d) 5.78
f1 (ppm)

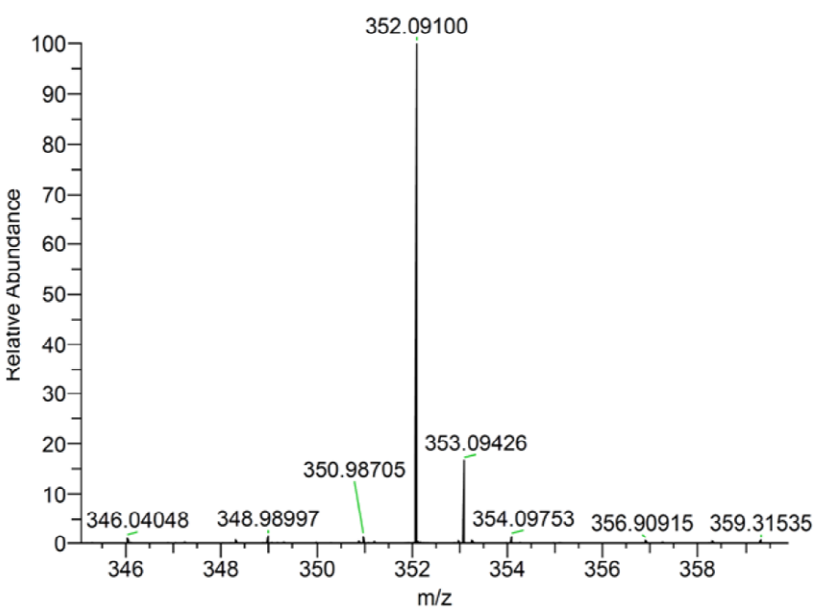

46.63
A (s)
46.63
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

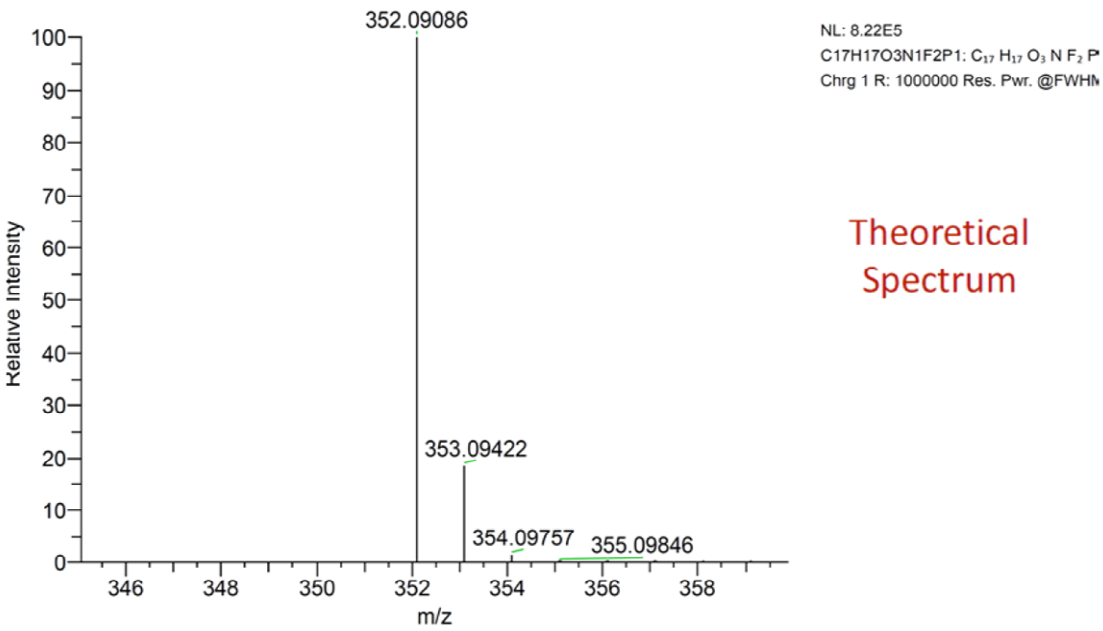

-63.01
A (s)
-63.01
1.00
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

methyl (2-(2-(difluoromethyl)phenyl)benzo[d]oxazol-6-yl)(ethyl)phosphinate (51)

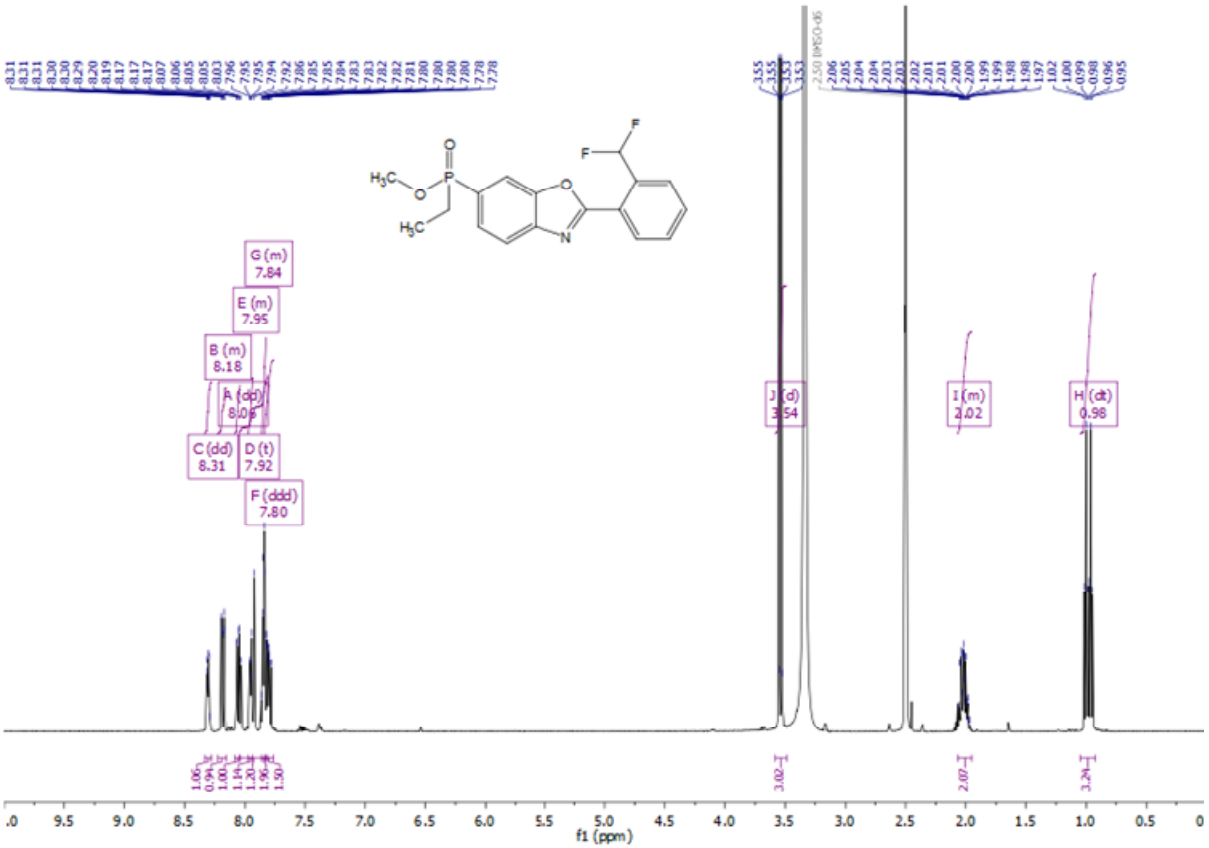


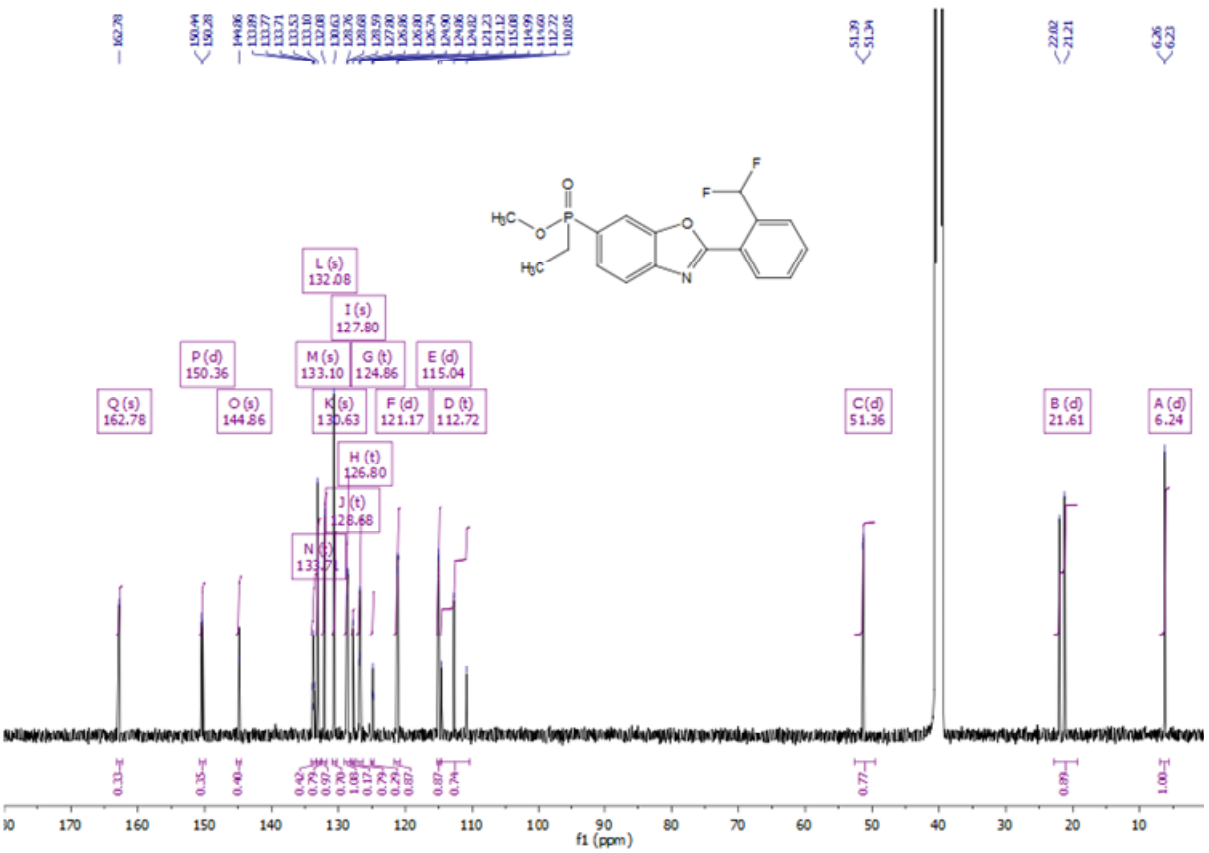


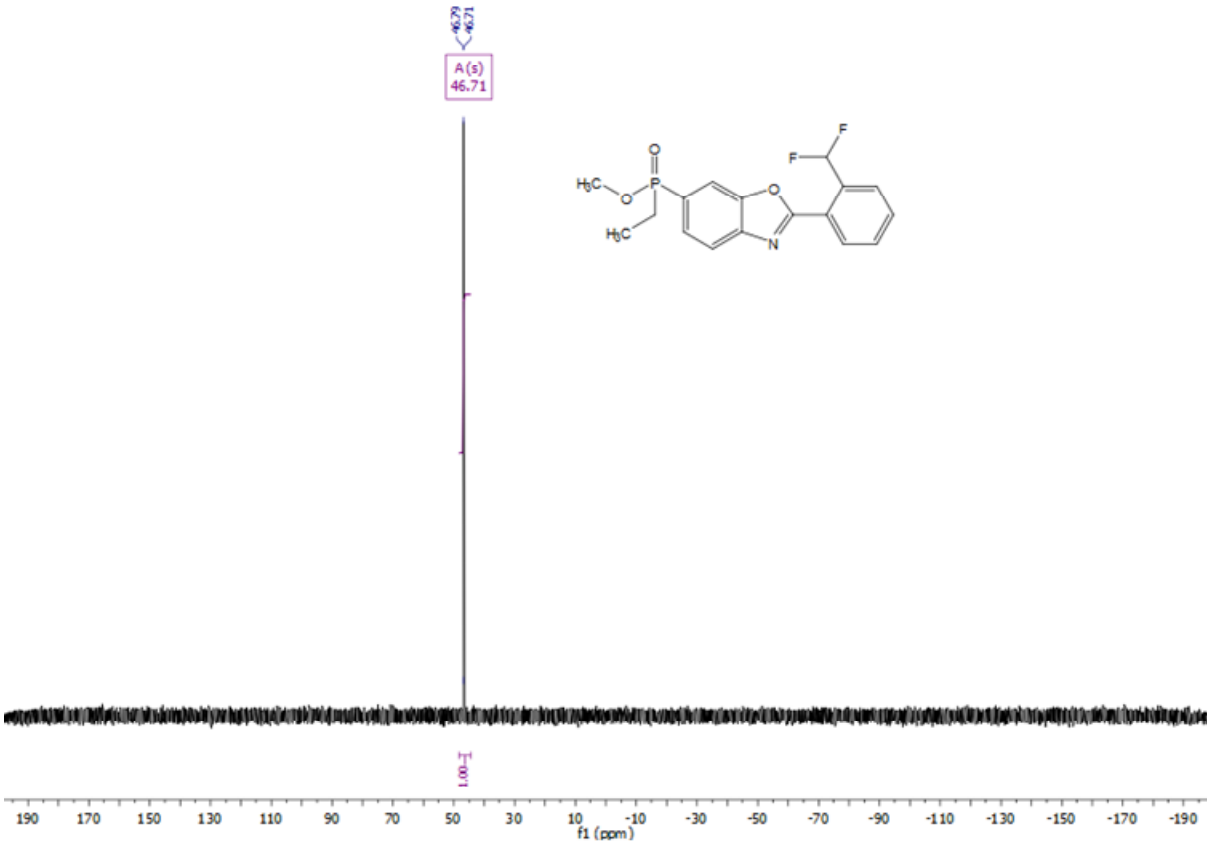


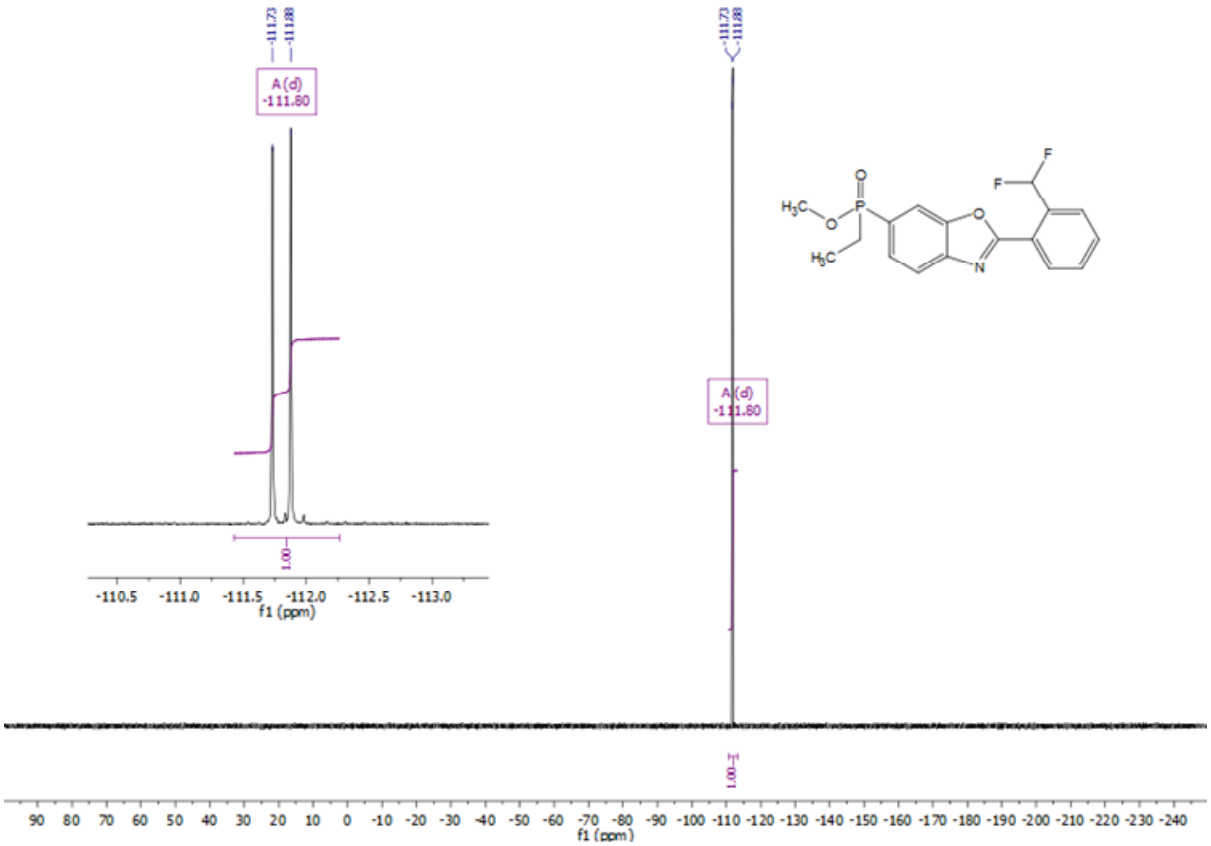


m/z	Formula	RDB	Delta ppm	Theo. Mass
352.09100	$C_{17}H_{17}O_3NF_2P$	9.5	0.4	352.09086

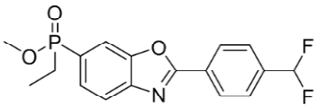

G (m) 7.84
E (m) 7.95
B (m) 8.18
A (dd) 8.06
C (dd) 8.31
D (t) 7.92
F (ddd) 7.80
J (d) 3.54
I (m) 2.02
H (dt) 0.98
f1 (ppm)

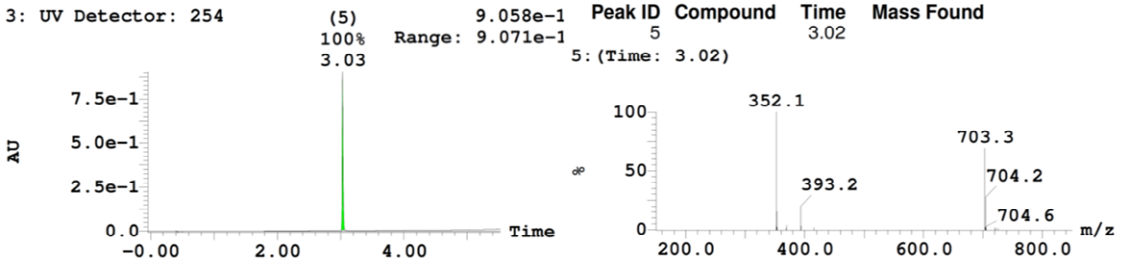

L (s) 132.08
I (s) 127.80
P (d) 150.36
M (s) 133.10
G (t) 124.86
E (d) 115.04
Q (s) 162.78
O (s) 144.86
K (s) 130.63
F (d) 121.17
D (t) 112.72
H (t) 126.80
J (t) 128.68
N (s) 133.07
C (d) 51.36
B (d) 21.61
A (d) 6.24
f1 (ppm)

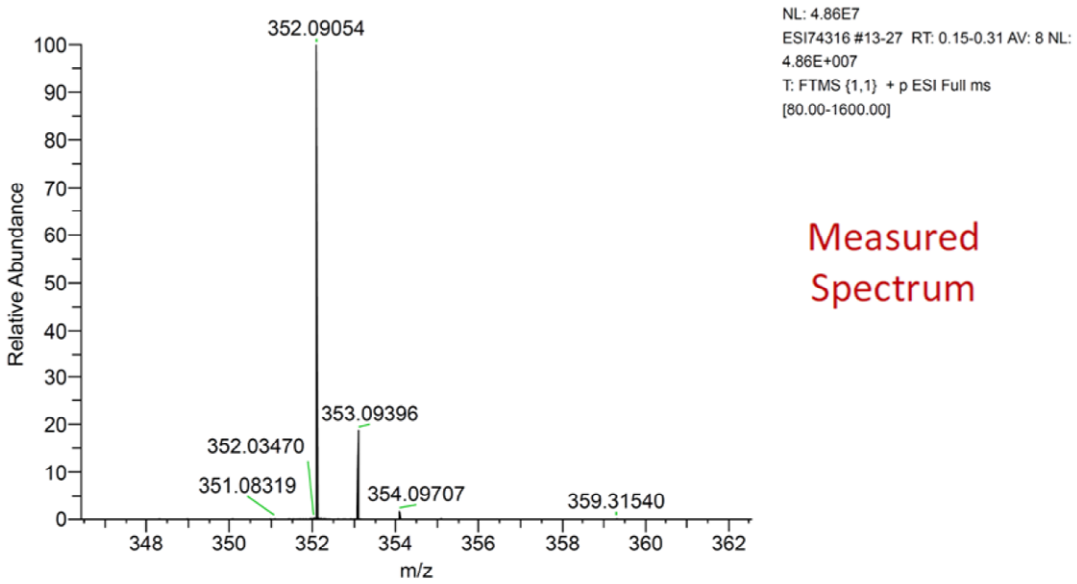

46.29
46.71
A(s)
46.71
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

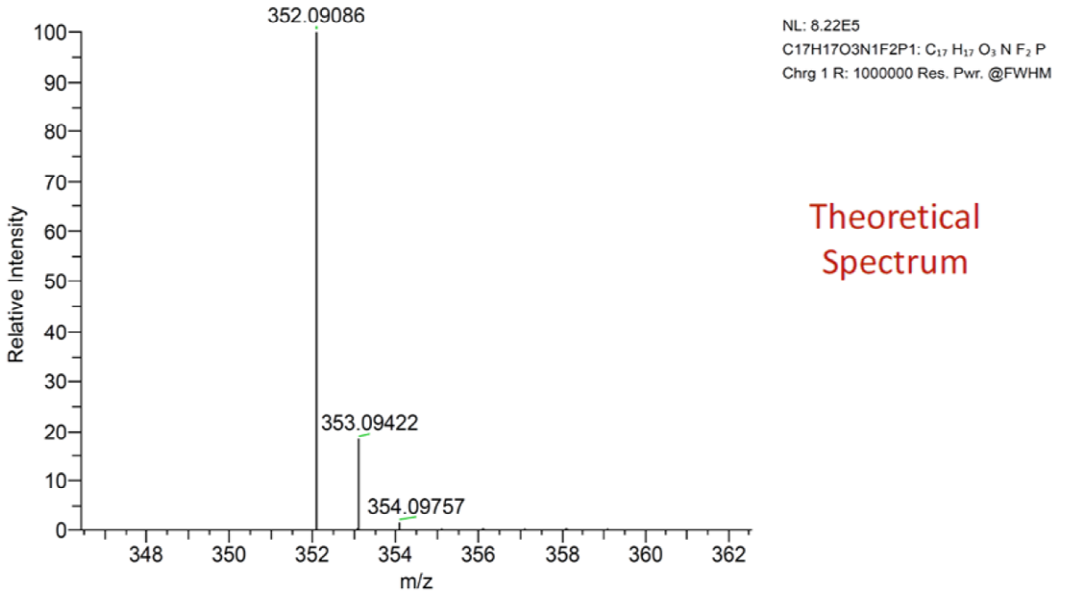

-111.73
-111.88
A(d)
-111.80
1.00
-110.5 -111.0 -111.5 -112.0 -112.5 -113.0
f1 (ppm)
-111.73
-111.88
A(d)
-111.80
1.00
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

methyl (2-(4-(difluoromethyl)phenyl)benzo[d]oxazol-6-yl)(ethyl)phosphinate (52)

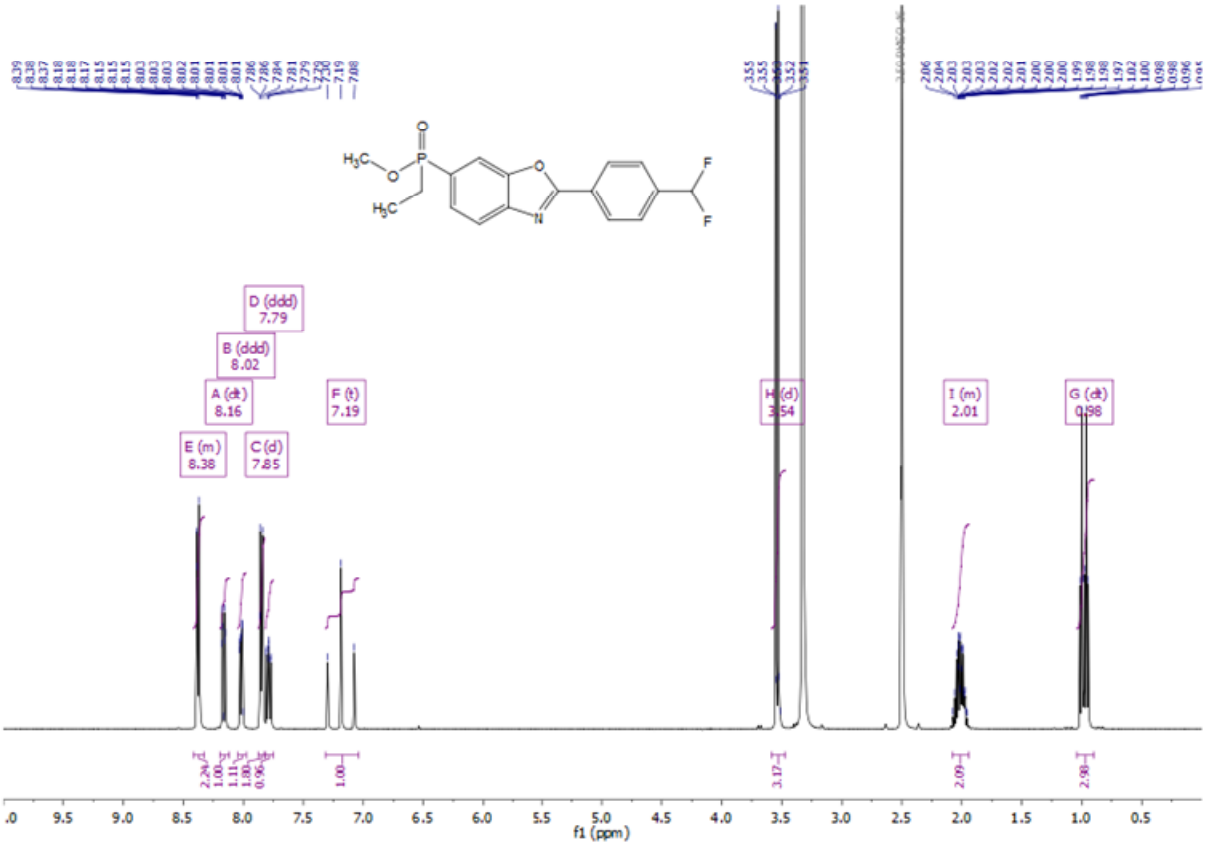


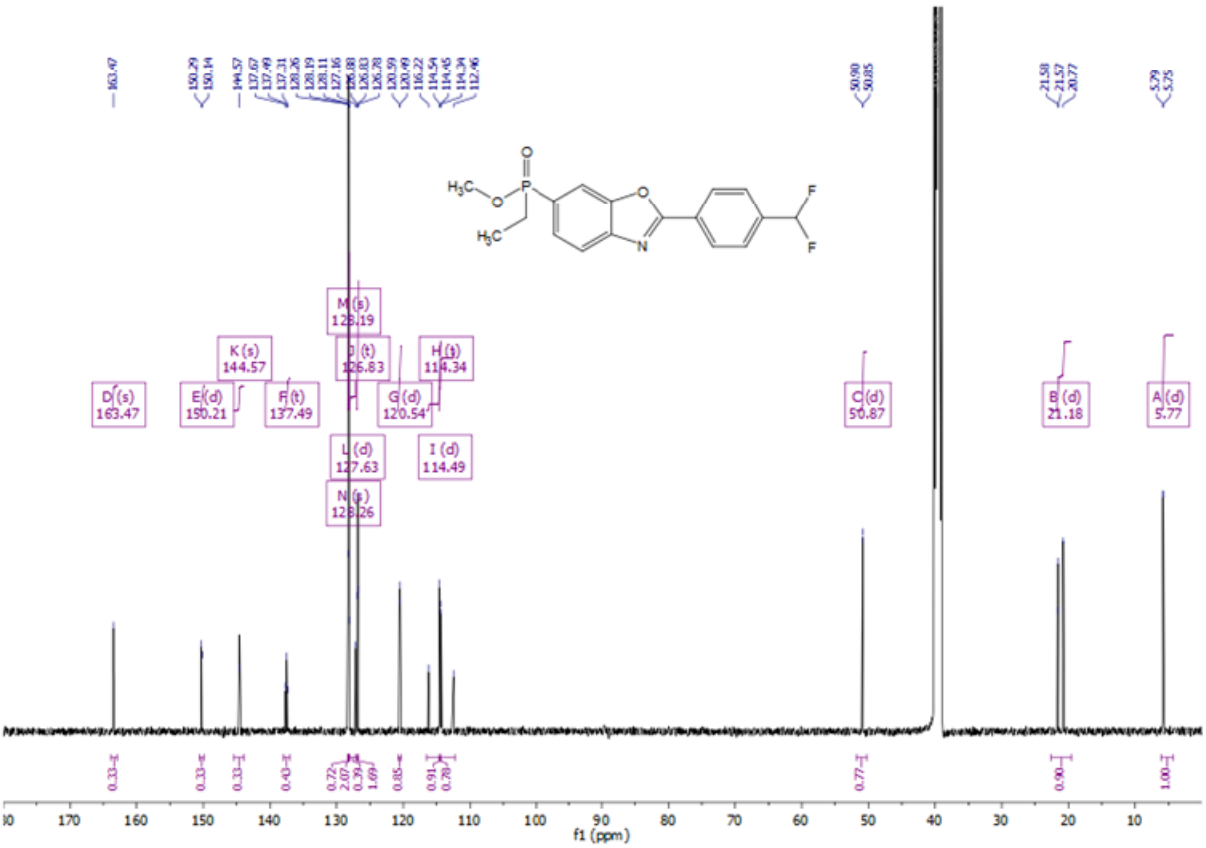




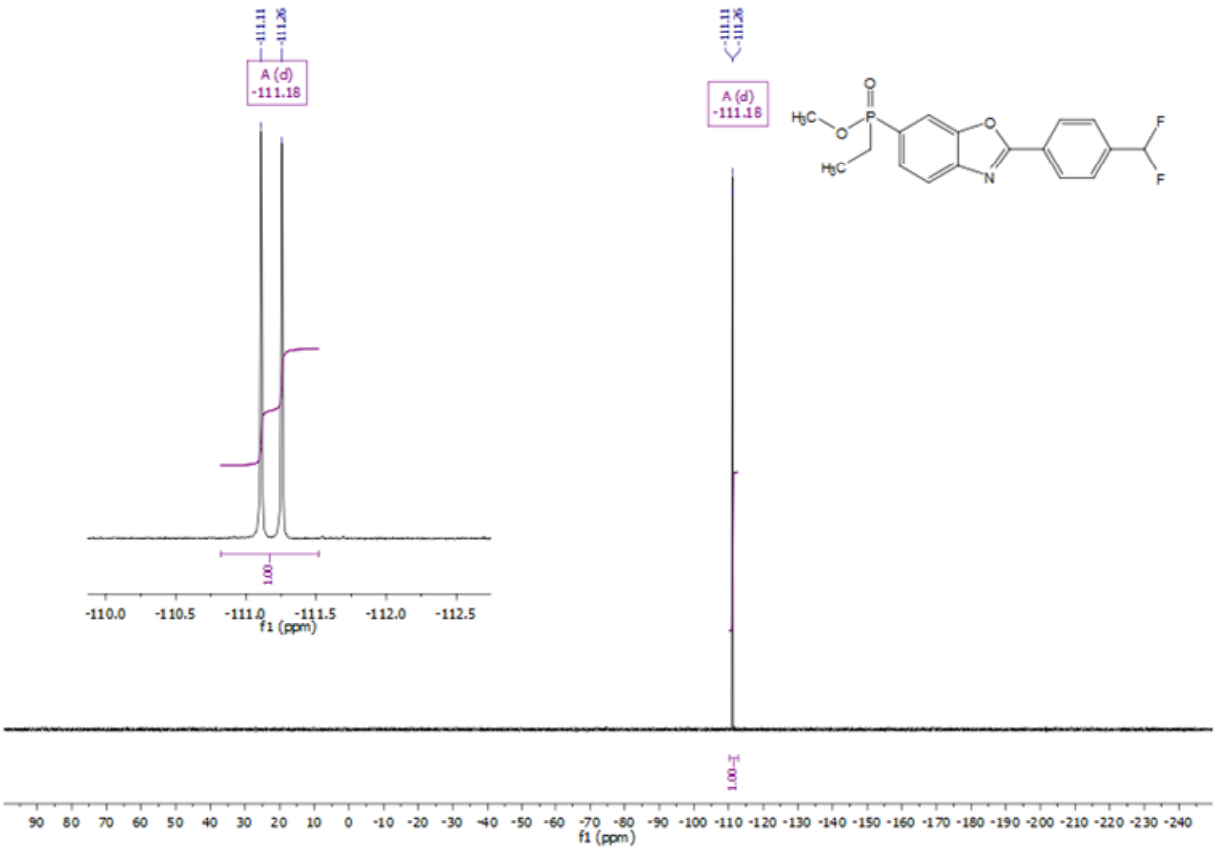


m/z	Formula	RDB	Delta ppm	Theo. Mass
352.09055	$C_{17}H_{17}O_3NF_2P$	9.5	-0.9	352.09086

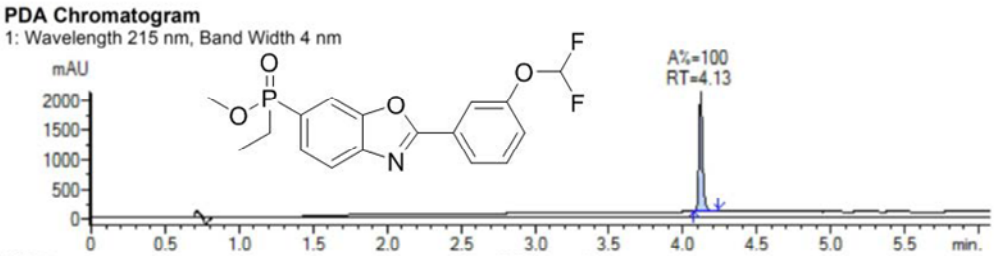

D (ddd)
7.79
B (ddd)
8.02
A (dt)
8.16
E (m)
8.38
C (d)
7.85
F (t)
7.19
H (d)
3.54
I (m)
2.01
G (dt)
0.98
f1 (ppm)

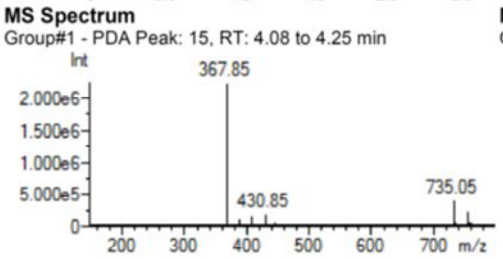

M (s)
128.19
K (s)
144.57
J (t)
126.83
H (s)
114.34
D (s)
163.47
E (d)
150.21
F (t)
137.49
G (d)
120.54
L (d)
127.63
I (d)
114.49
N (s)
128.26
C (d)
50.87
B (d)
21.18
A (d)
5.77
f1 (ppm)

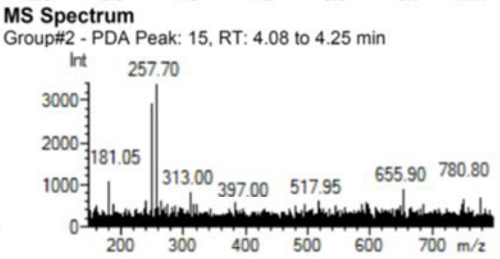

46.70
A (s)
46.70
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

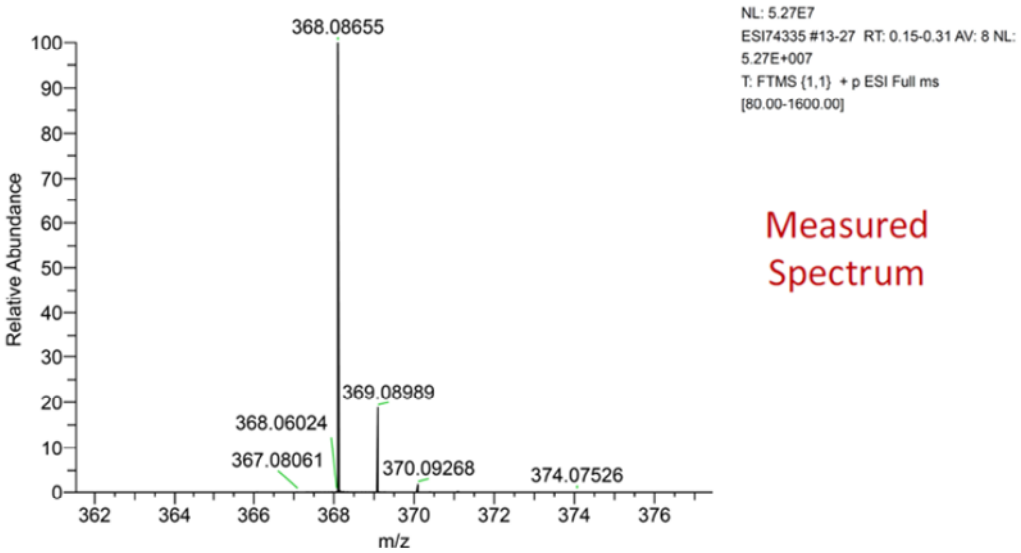

-111.11
-111.26
A (d)
-111.18
1.00
-110.0 -110.5 -111.0 -111.5 -112.0 -112.5
f1 (ppm)
-111.11
-111.26
A (d)
-111.18
1.00
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

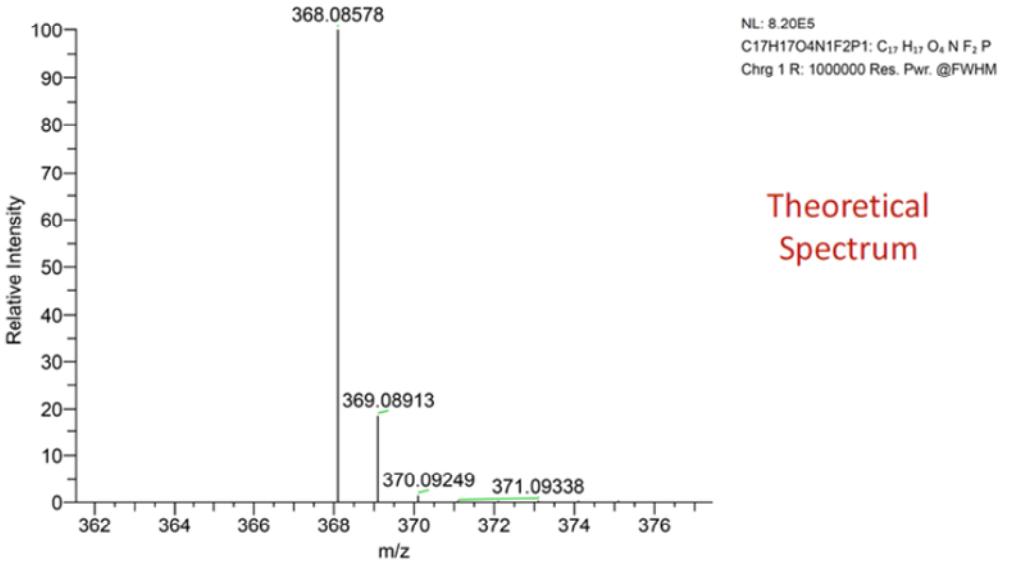
methyl (2-(3-(difluoromethoxy)phenyl)benzo[d]oxazol-6-yl)(ethyl)phosphinate (53)



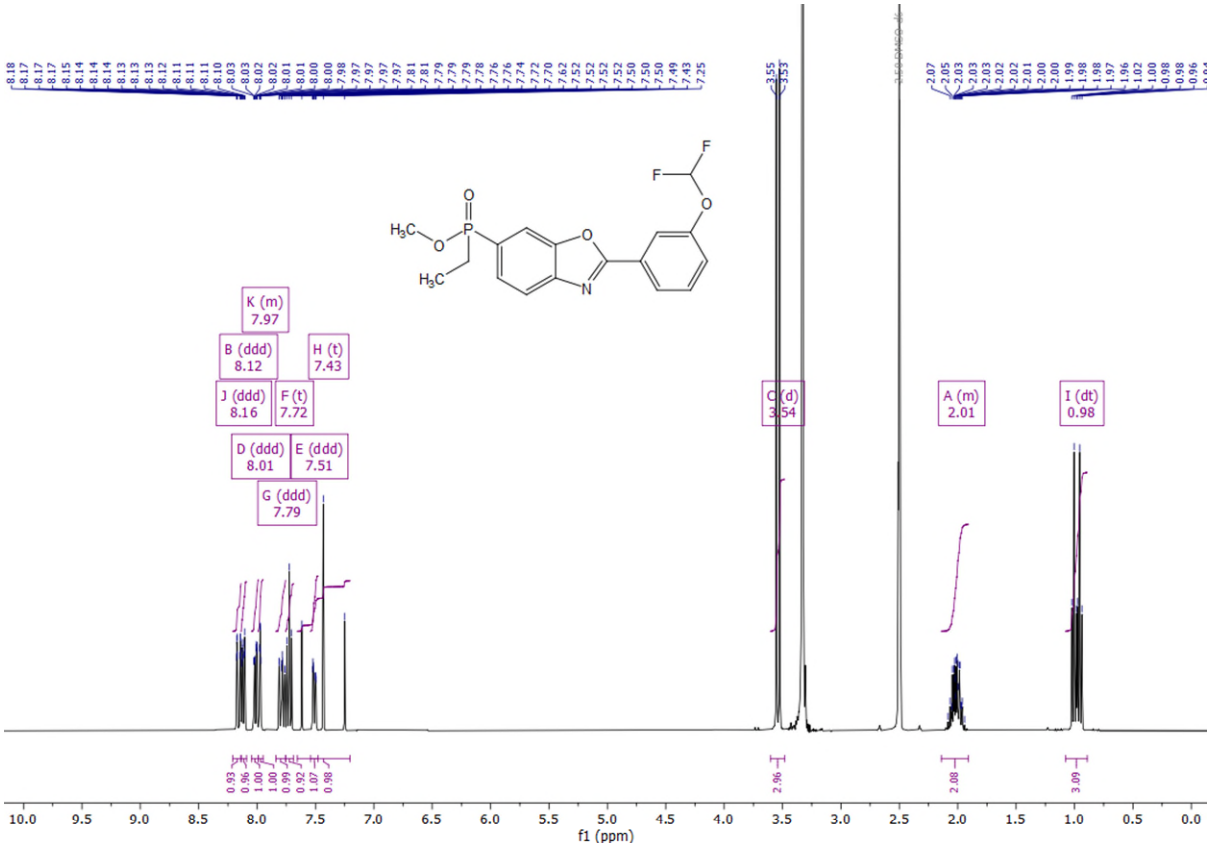


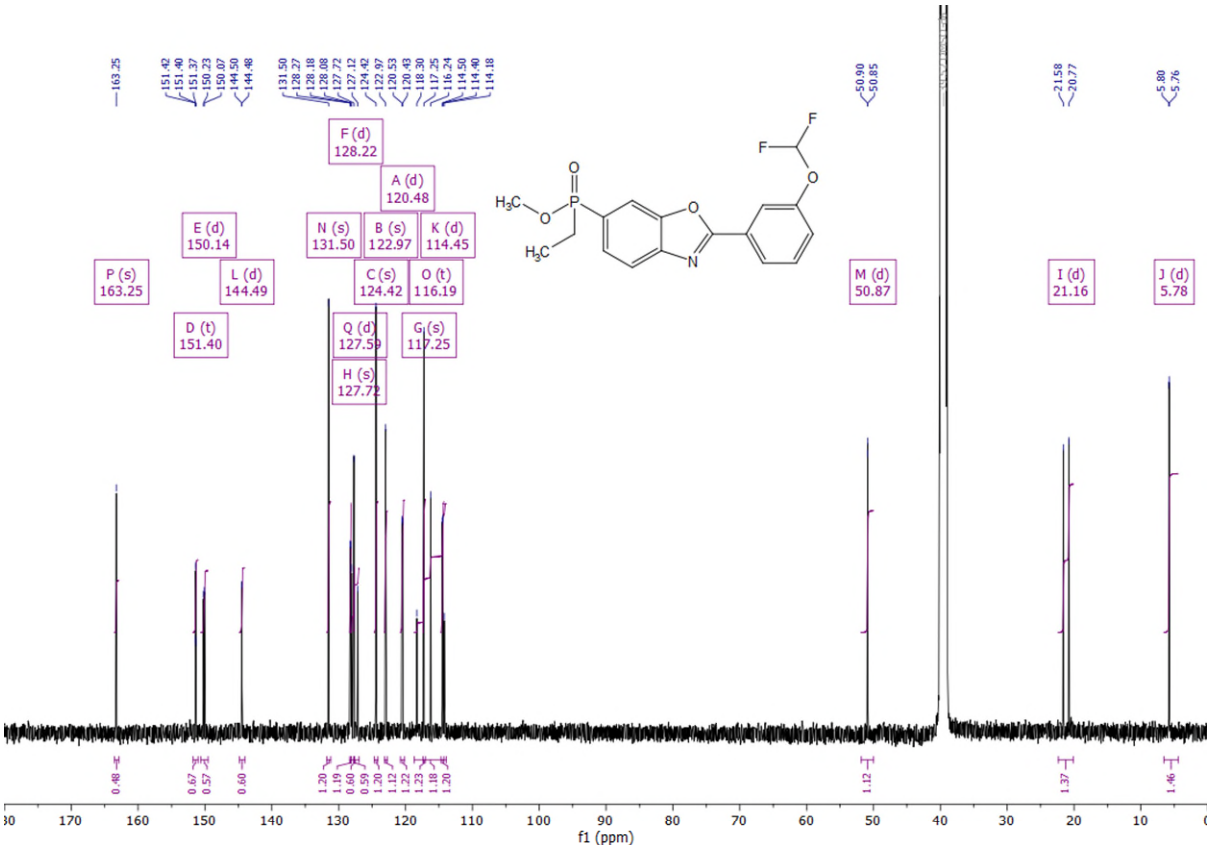


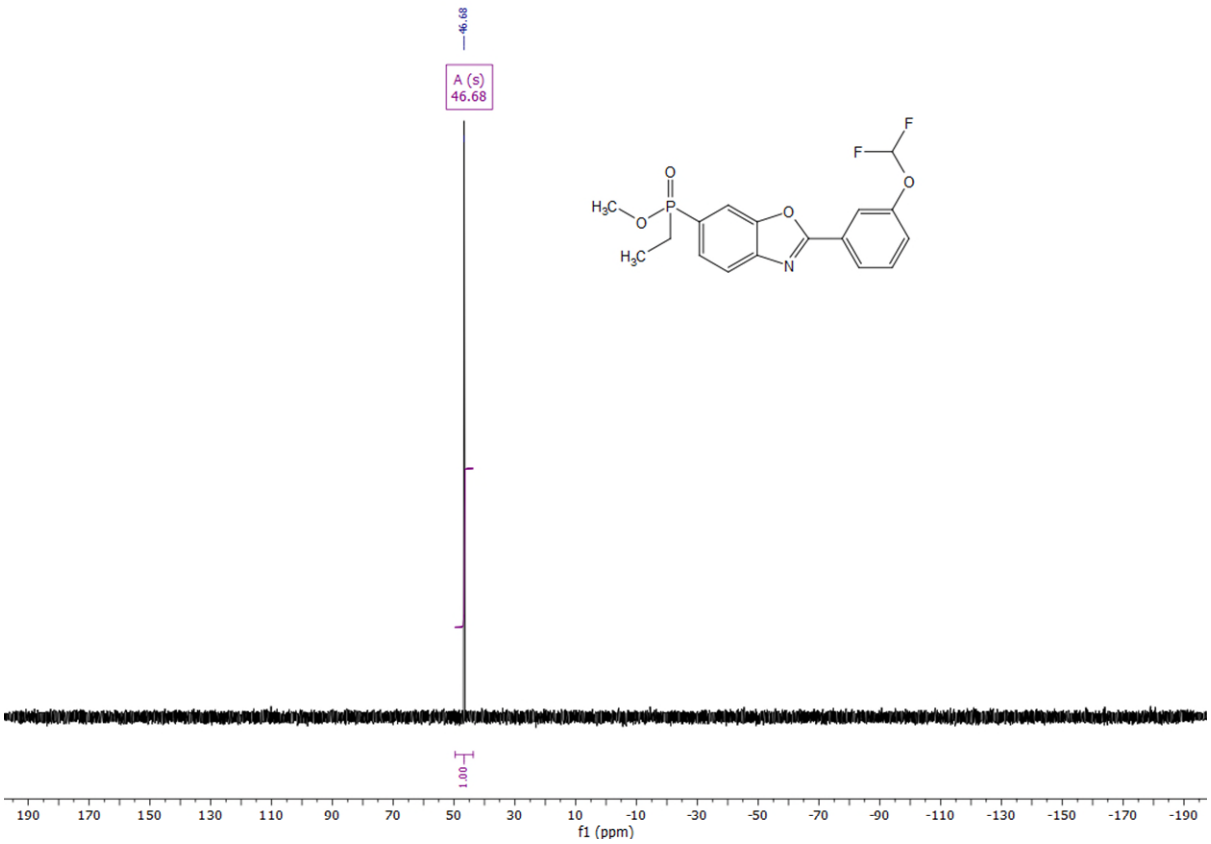


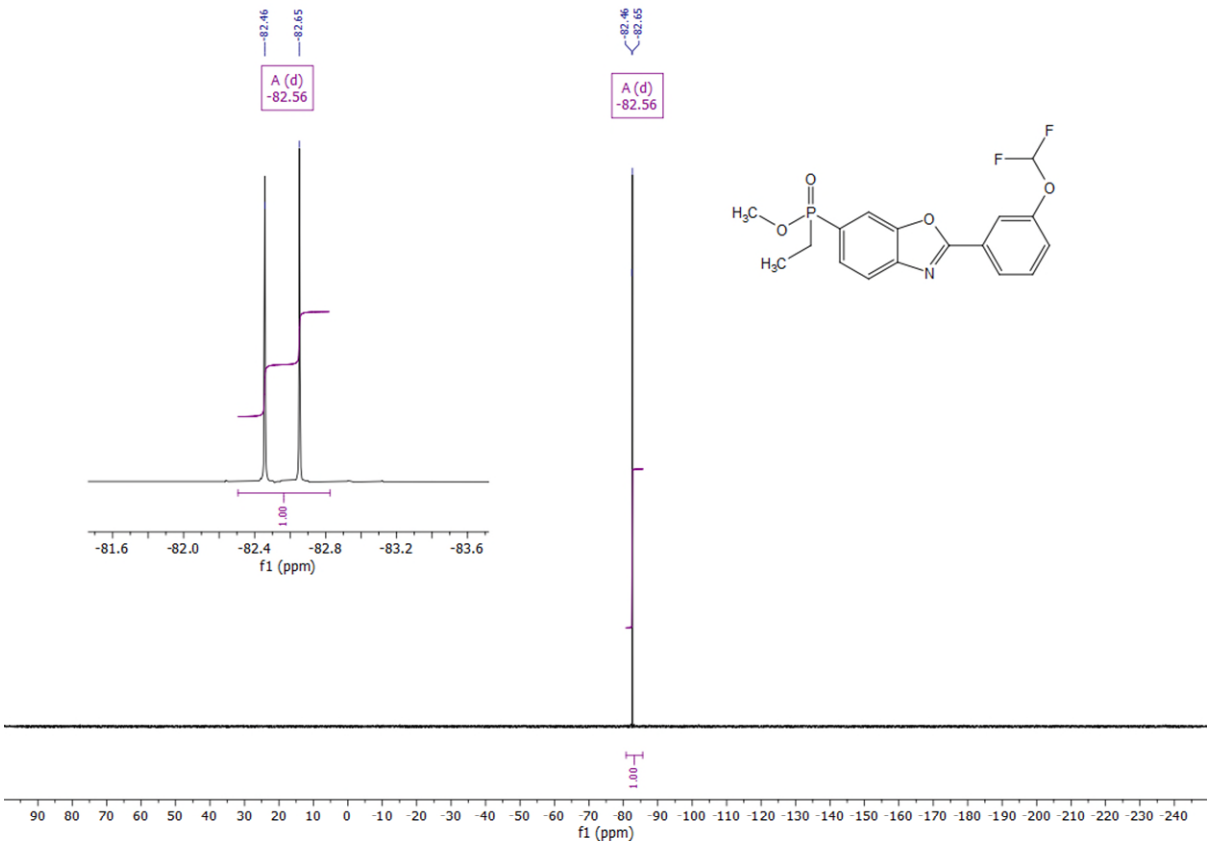


m/z	Formula	RDB	Delta ppm	Theo. Mass
368.08655	$C_{17}H_{17}O_4NF_2P$	9.5	2.09	368.08578

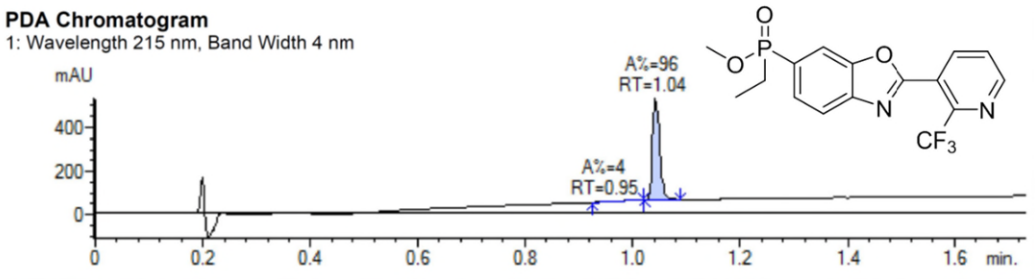

K (m)
7.97
B (ddd)
8.12
H (t)
7.43
J (ddd)
8.16
F (t)
7.72
D (ddd)
8.01
E (ddd)
7.51
G (ddd)
7.79
C (d)
3.54
A (m)
2.01
I (dt)
0.98
f1 (ppm)

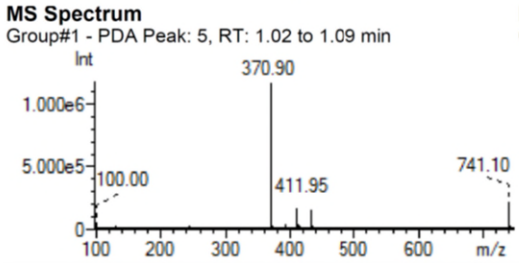

F (d)
128.22
A (d)
120.48
E (d)
150.14
N (s)
131.50
B (s)
122.97
K (d)
114.45
P (s)
163.25
L (d)
144.49
C (s)
124.42
O (t)
116.19
M (d)
50.87
I (d)
21.16
J (d)
5.78
D (t)
151.40
Q (d)
127.59
G (s)
117.25
H (s)
127.72
f1 (ppm)

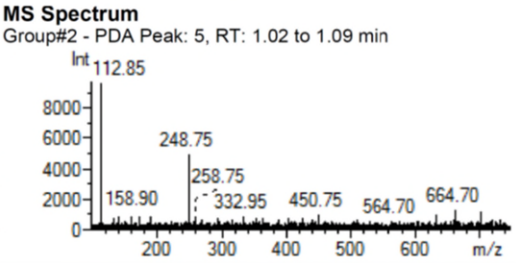

46.68
A (s)
46.68
F
F
O
O
P
O
H3C
H3C
O
N
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

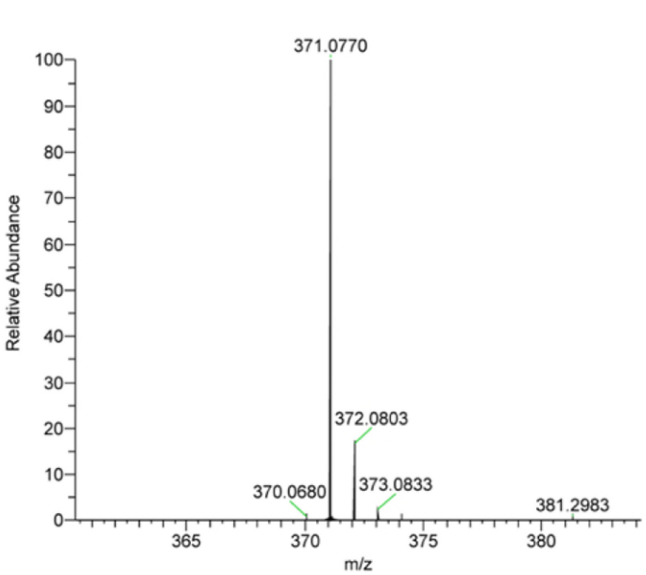

-82.46
-82.65
A (d)
-82.56
1.00
-81.6 -82.0 -82.4 -82.8 -83.2 -83.6
f1 (ppm)
-82.46
-82.65
A (d)
-82.56
F
F
O
O
P
O
H3C
H3C
O
N
1.00
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

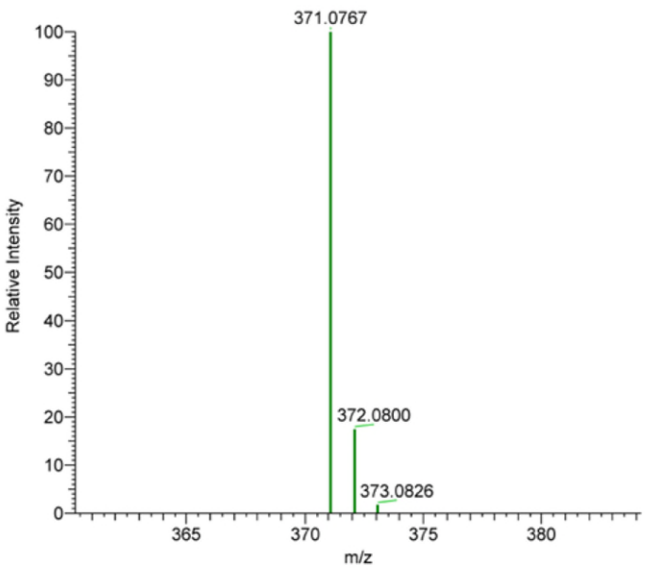
methyl ethyl(2-(2-(trifluoromethyl)pyridin-3-yl)benzo[*d*]oxazol-6-yl)phosphinate (54)



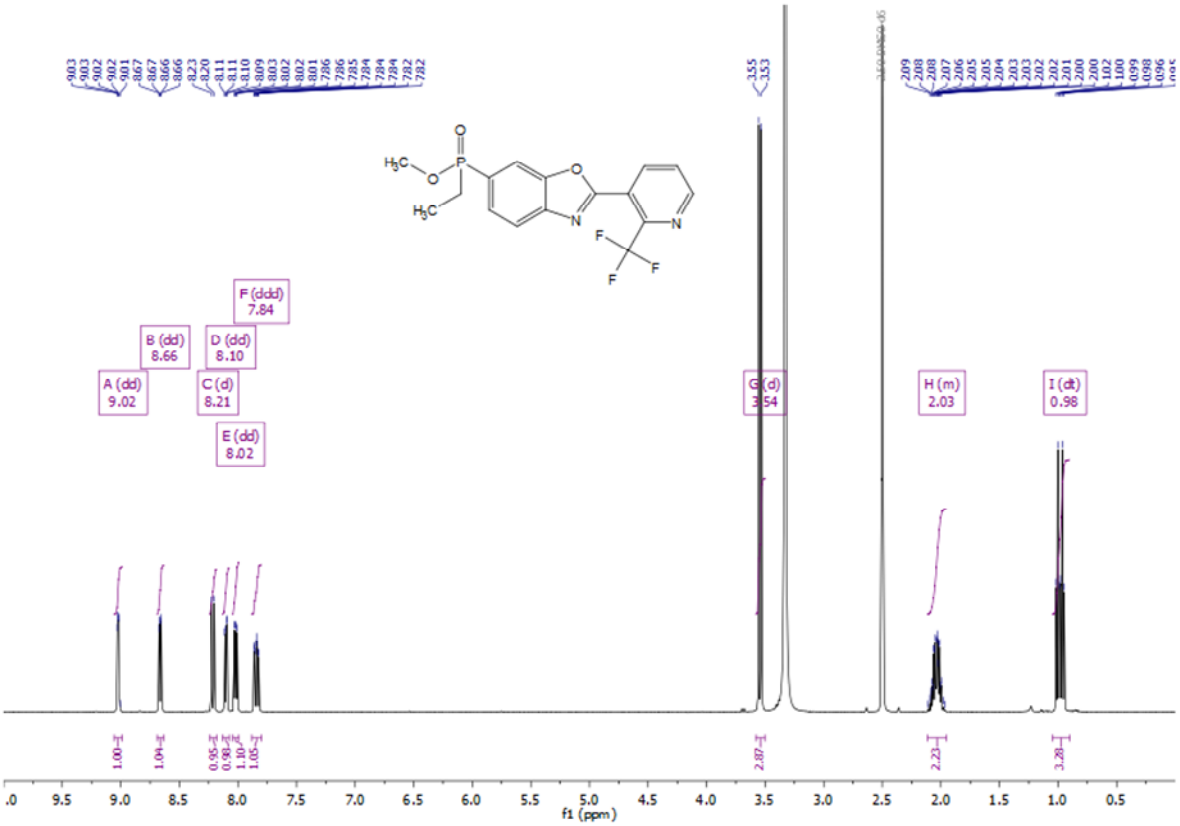


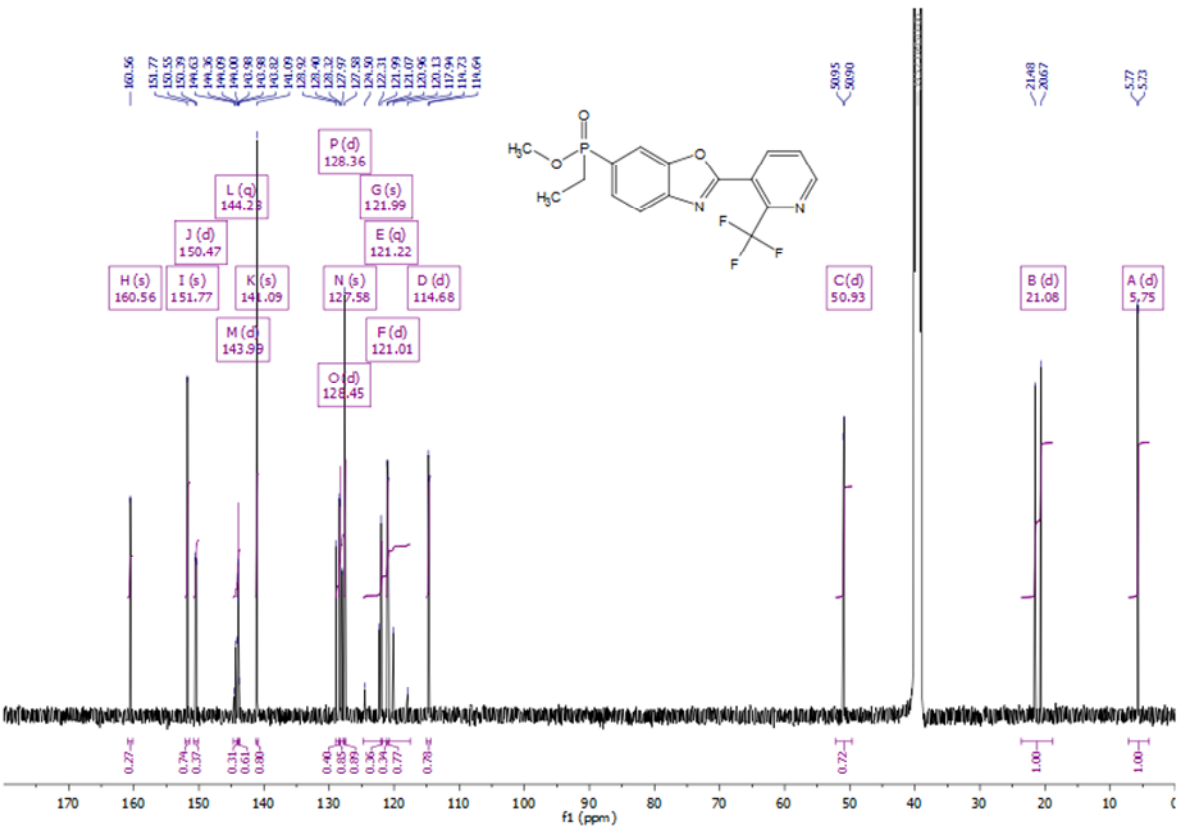


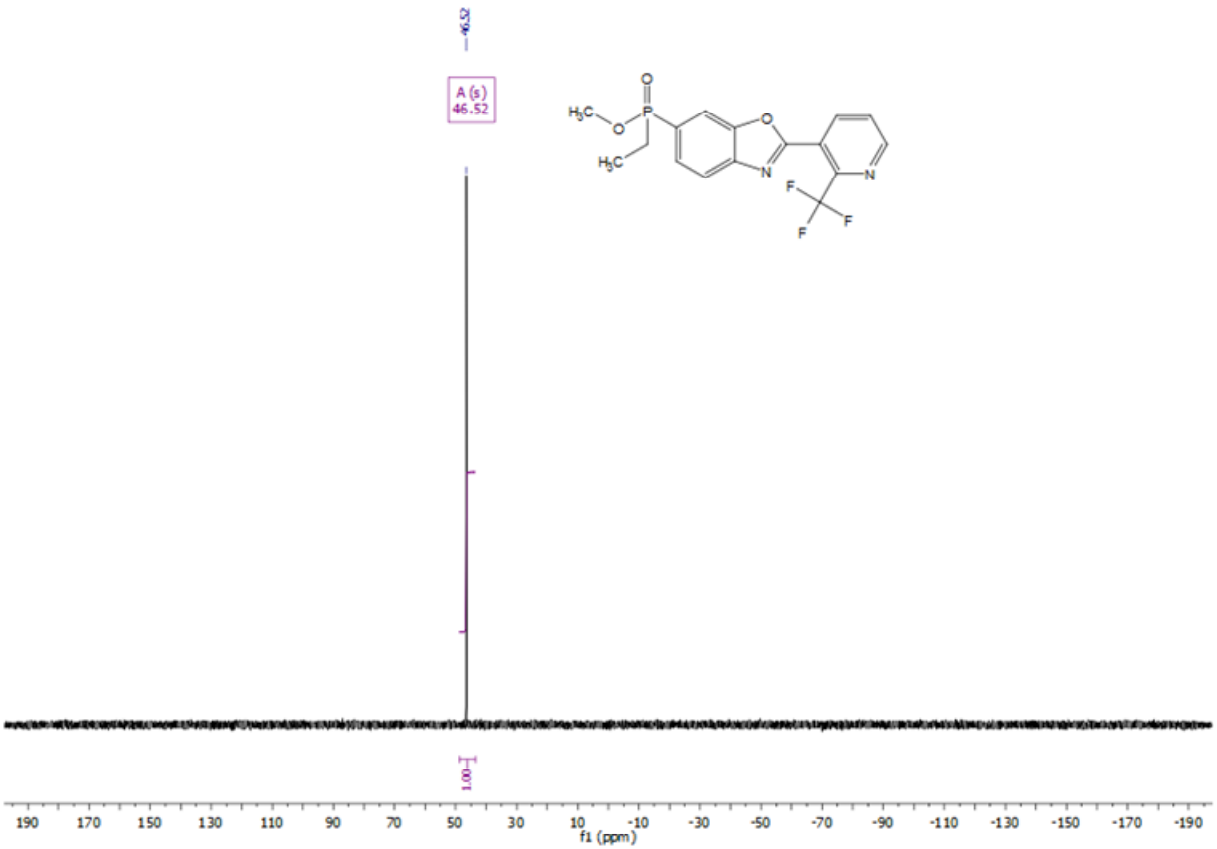


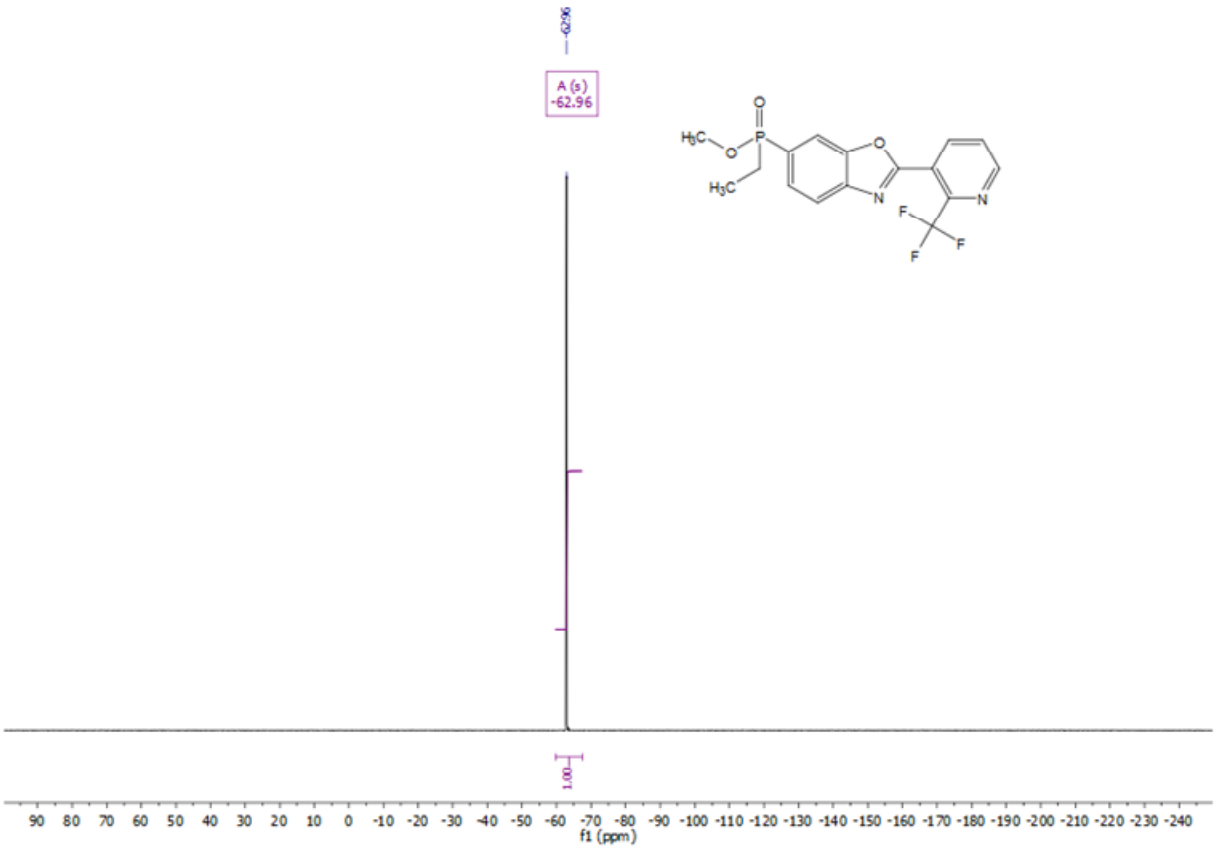


Peak Mass	Display...	Combin...	RDB	Delta [p...	Theo. m...	Rank	Combin...	# Match...	# Misse...	MS Cov....	Pattern...	MSMS...
371.0770	$C_{16}H_{15}$...	43.114...	9.50	0.74	371.07...	1	96.931...	4	0	99.921...	99.855...	(Collec...


A (dd) 9.02
B (dd) 8.66
C (d) 8.21
D (dd) 8.10
E (dd) 8.02
F (ddd) 7.84
G (d) 3.54
H (m) 2.03
I (dt) 0.98
f1 (ppm)


A (d) 5.75
B (d) 21.08
C (d) 50.93
D (d) 114.68
E (q) 121.22
F (d) 121.01
G (s) 121.99
H (s) 160.56
I (s) 151.77
J (d) 150.47
K (s) 141.09
L (q) 144.28
M (d) 143.99
N (s) 127.58
O (d) 128.45
P (d) 128.36
f1 (ppm)


46.52
A (s)
46.52
1.00
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)


-62.96
A (s)
-62.96
1.00
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

References

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2. Wynne, G. M.; Wren, S. P.; Johnson, P. D.; Price, D.; De Moor, O.; Nugent, G.; Tinsley, J. M.; Storer, R.; Mulvaney, A.; Pye, R. J.; Dorgan, C. R. Preparation of benzimidazoles, benzoxazoles, benzothiazoles, indoles and their analogs for the treatment of muscular dystrophy and cachexia. WO2007091106A2, 2007.

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4. Feeney, K. A.; Putker, M.; Brancaccio, M.; O'Neill, J. S., In-depth Characterization of Firefly Luciferase as a Reporter of Circadian Gene Expression in Mammalian Cells. Journal of Biological Rhythms 2016, 31, 540-550, https://doi.org/10.1177/0748730416668898.