Medicinal Chemistry Research

Supplementary material

The inhibition of monoamine oxidase by 2-methylbenzo[*d*]oxazole derivatives

Maryké Shaw[1] · Jacobus P. Petzer[1,2] · Theunis T. Cloete[1,2] · Anél Petzer[1,2]

[1] Centre of Excellence for Pharmaceutical Sciences, North-West University, Private Bag X6001, Potchefstroom 2520, South Africa

[2] Pharmaceutical Chemistry, School of Pharmacy, North-West University, Private Bag X6001, Potchefstroom 2520, South Africa

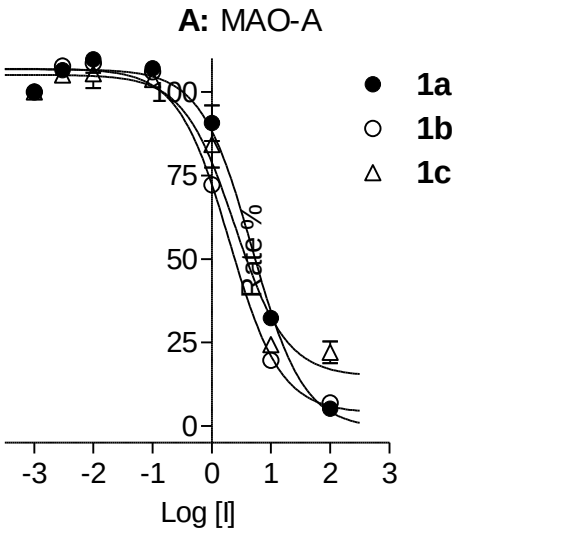
Corresponding author:

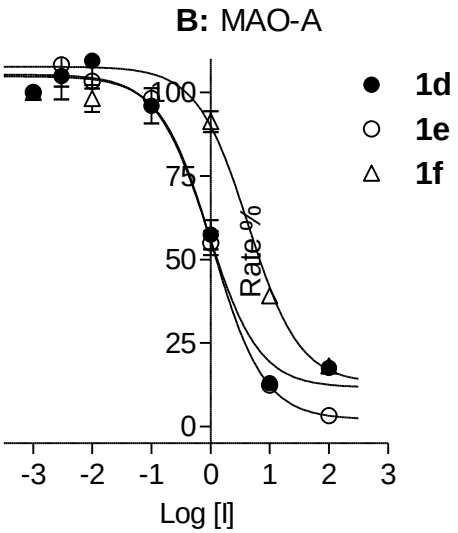
✉ Anél Petzer

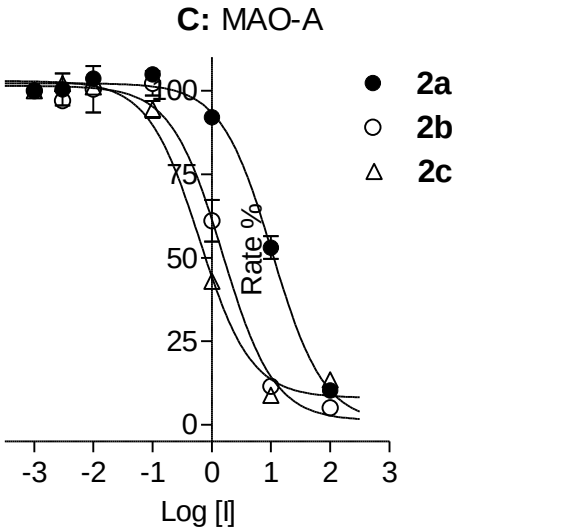
anel.petzer@nwu.ac.za

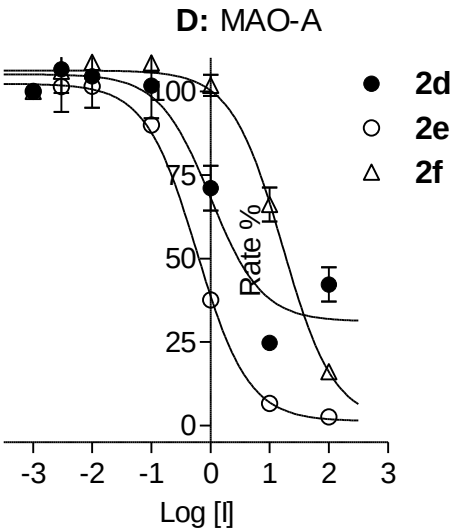
Tel.: +27 18 299 4464

ORCID: 0000-0001-8114-8223 (A Petzer)









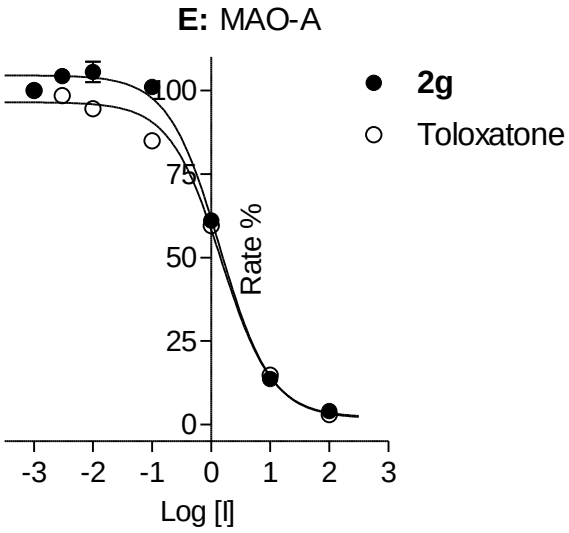


Fig S1. Sigmoidal plots for the inhibition of MAO-A by 2-methylbenzo[*d*]oxazole derivatives.

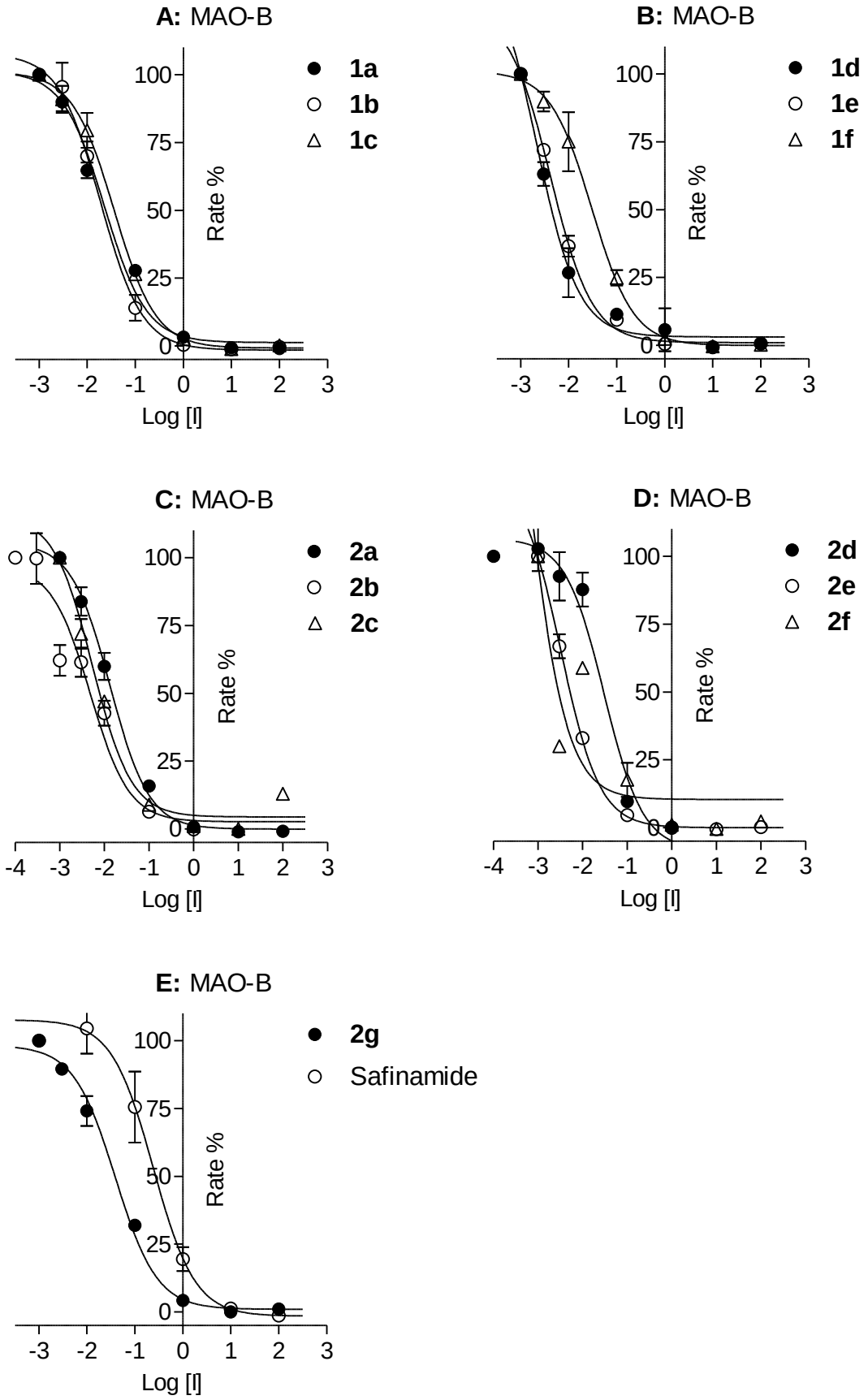
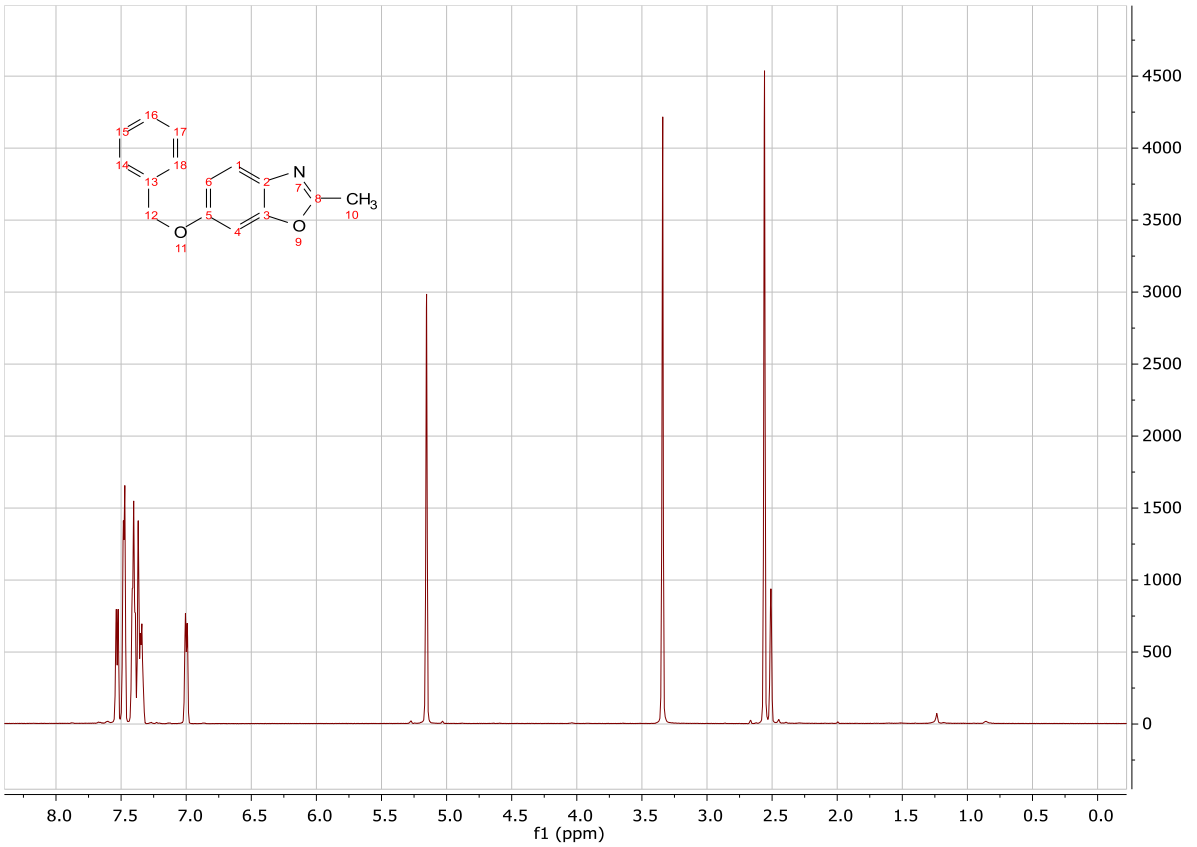
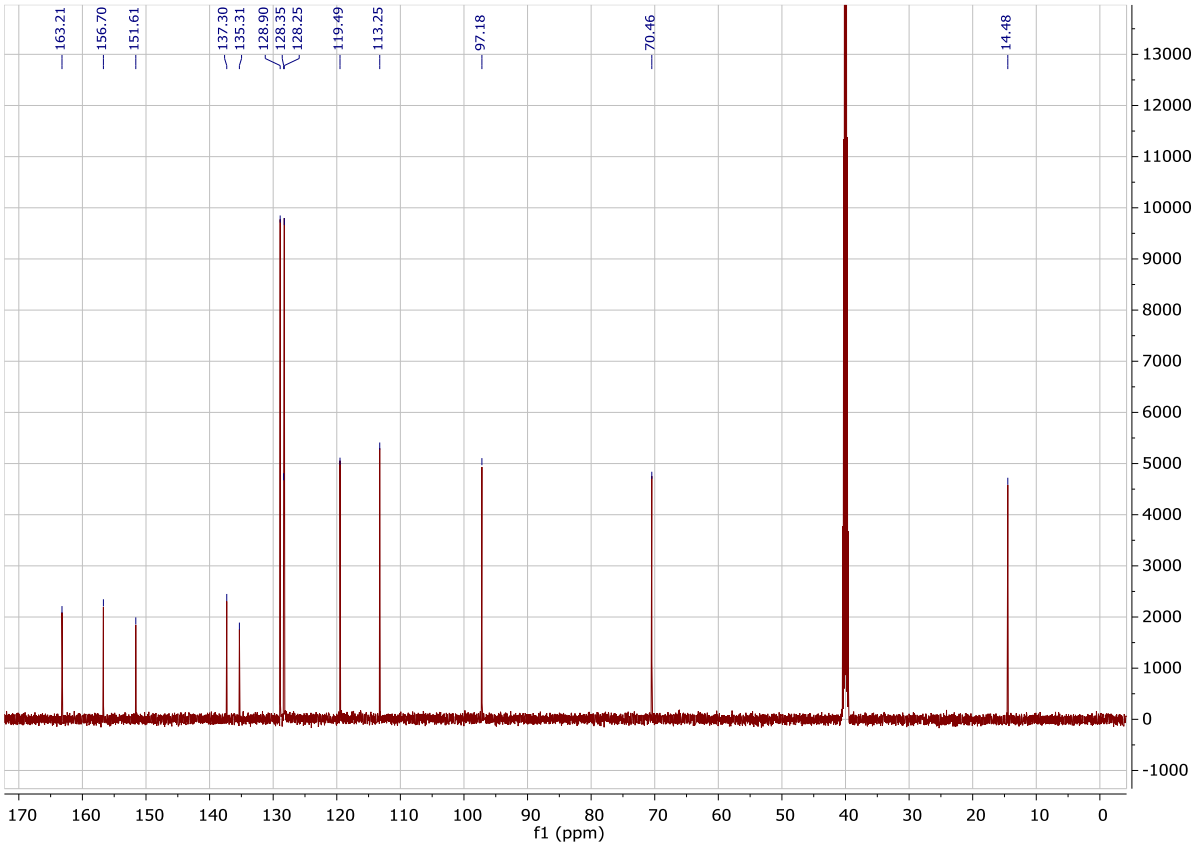


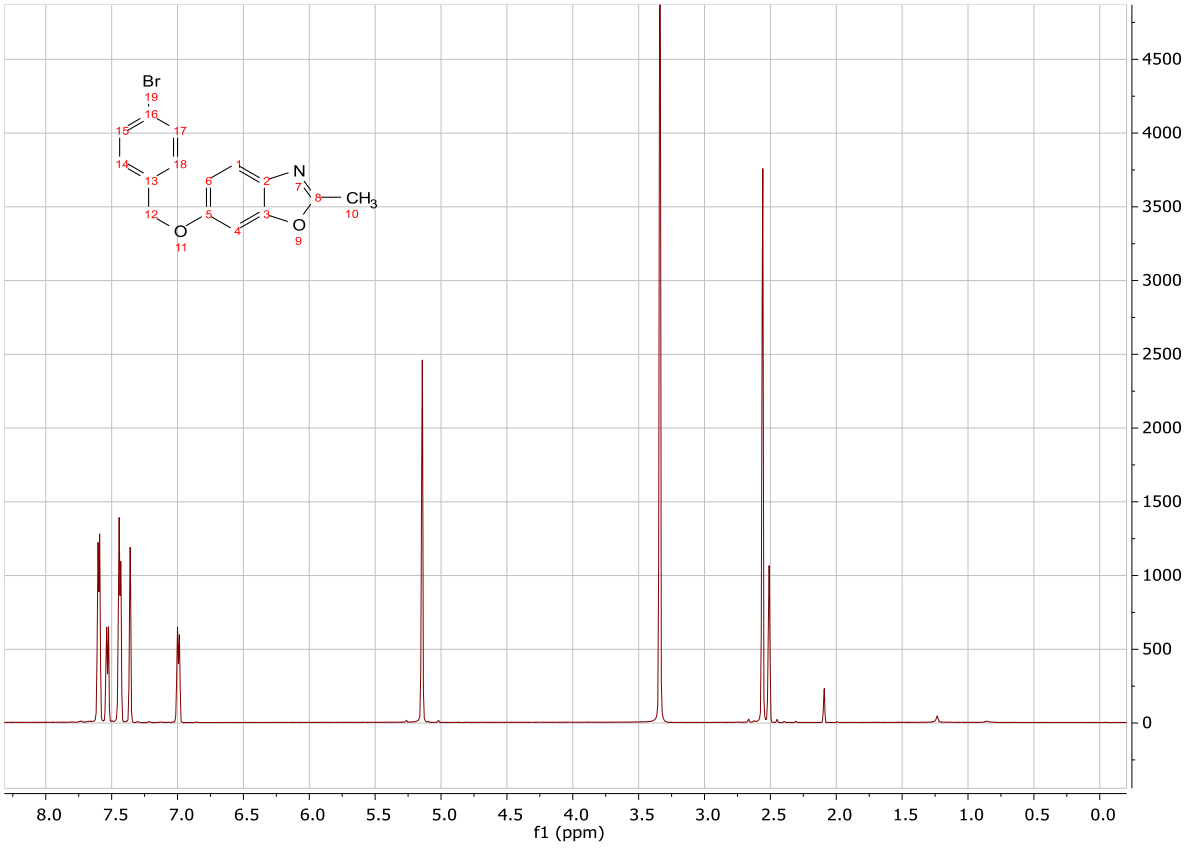
Fig. S2. Sigmoidal plots for the inhibition of MAO-B by 2-methylbenzo[*d*]oxazole derivatives.

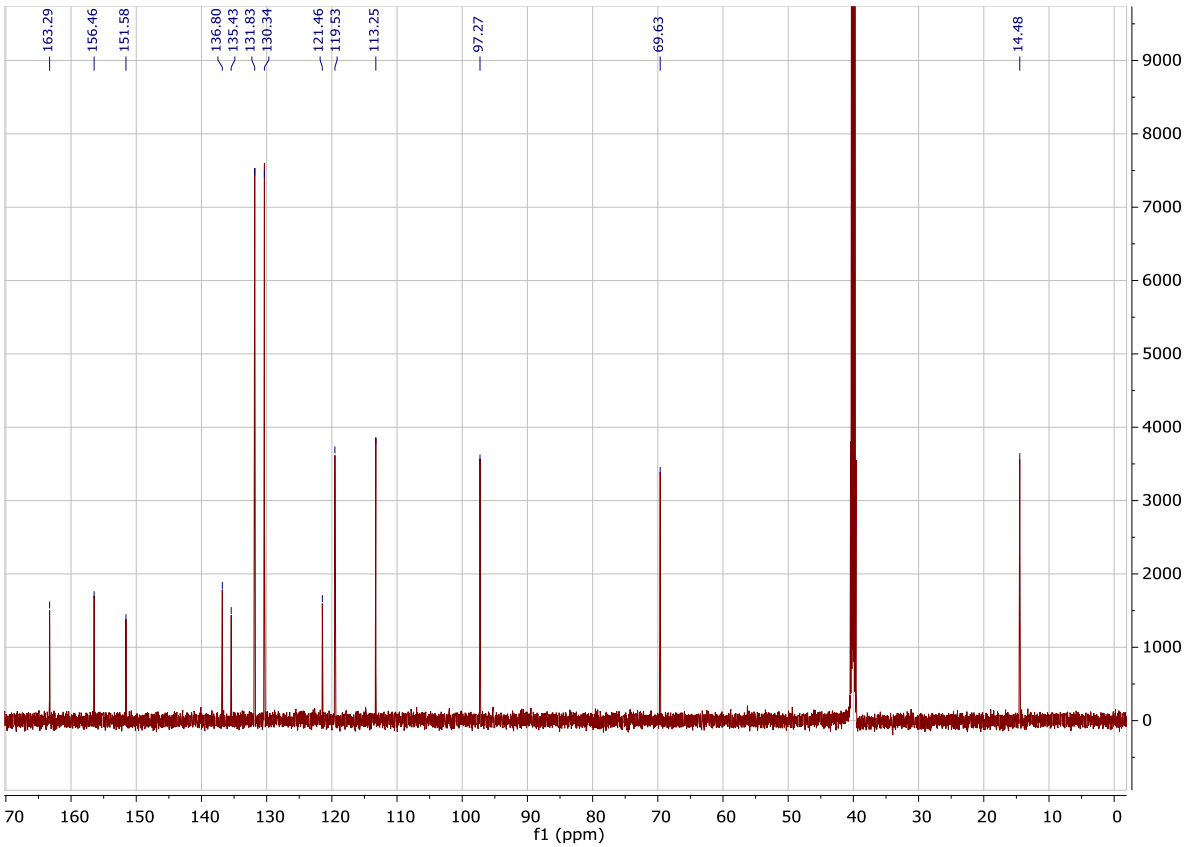
6-(Benzyloxy)-2-methylbenzo[*d*]oxazole (1a)



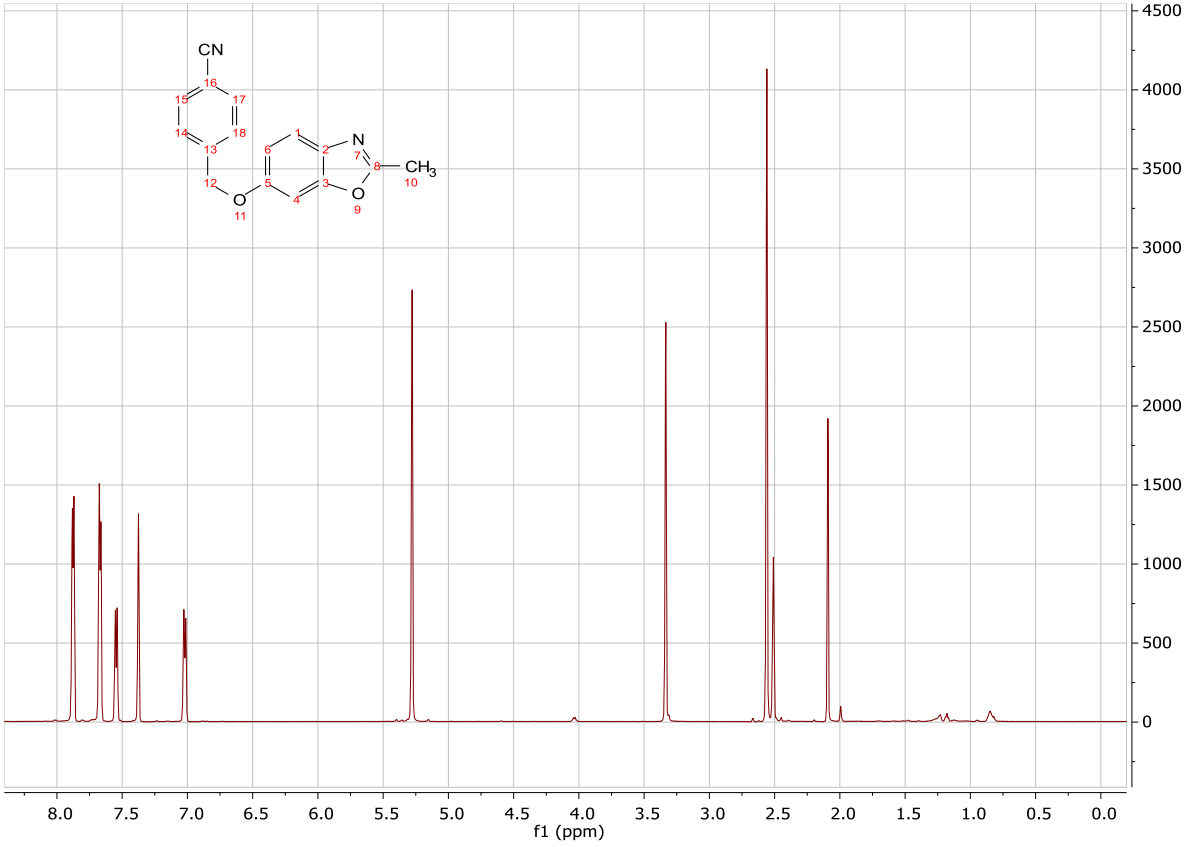


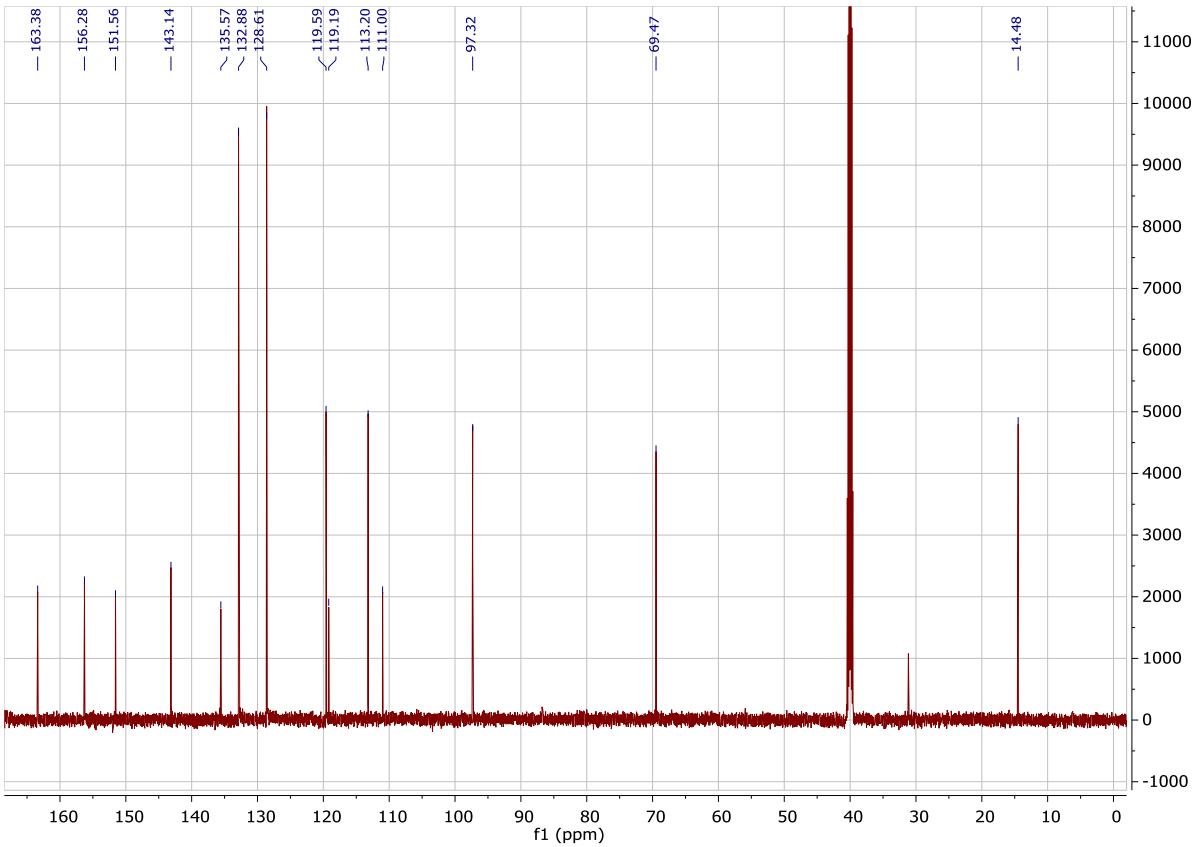
6-((4-Bromobenzyl)oxy)-2-methylbenzo[*d*]oxazole (1b)



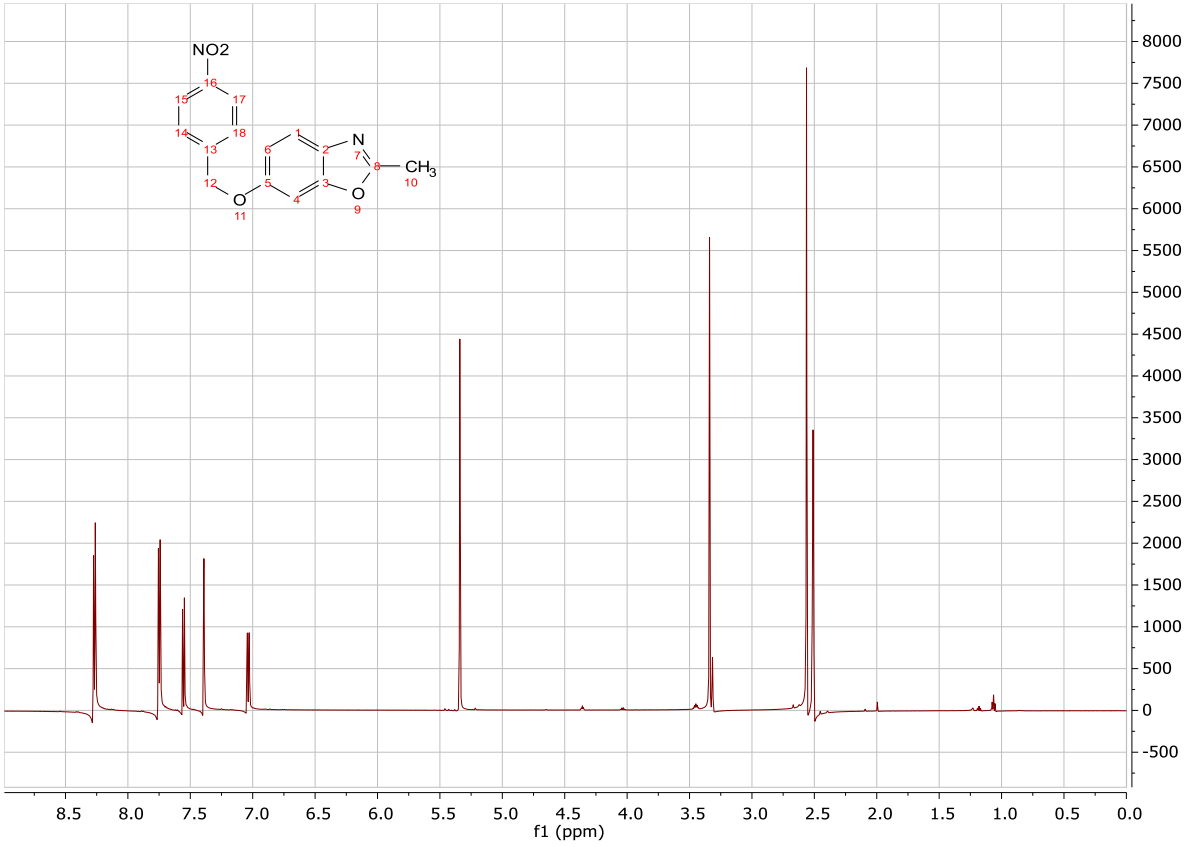


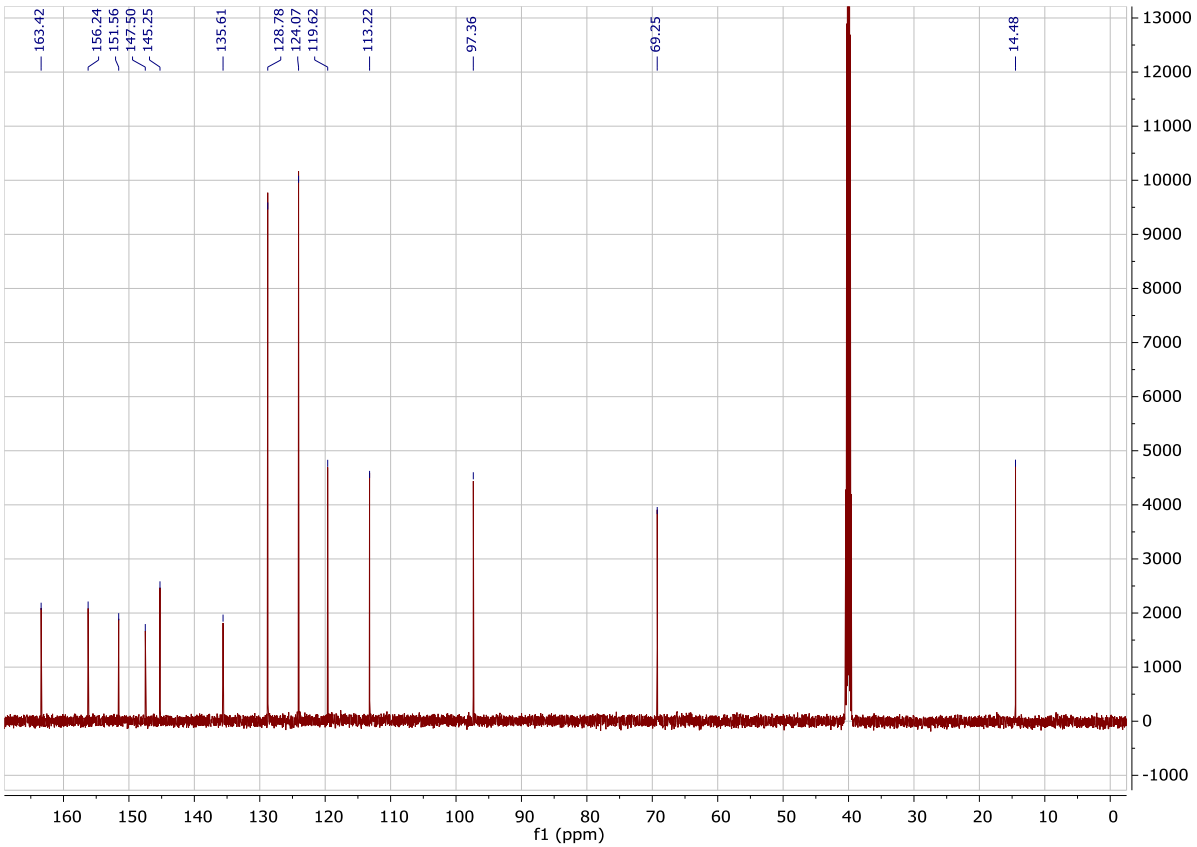
4-(((2-Methylbenzo[*d*]oxazol-6-yl)oxy)methyl)benzonitrile (1c)



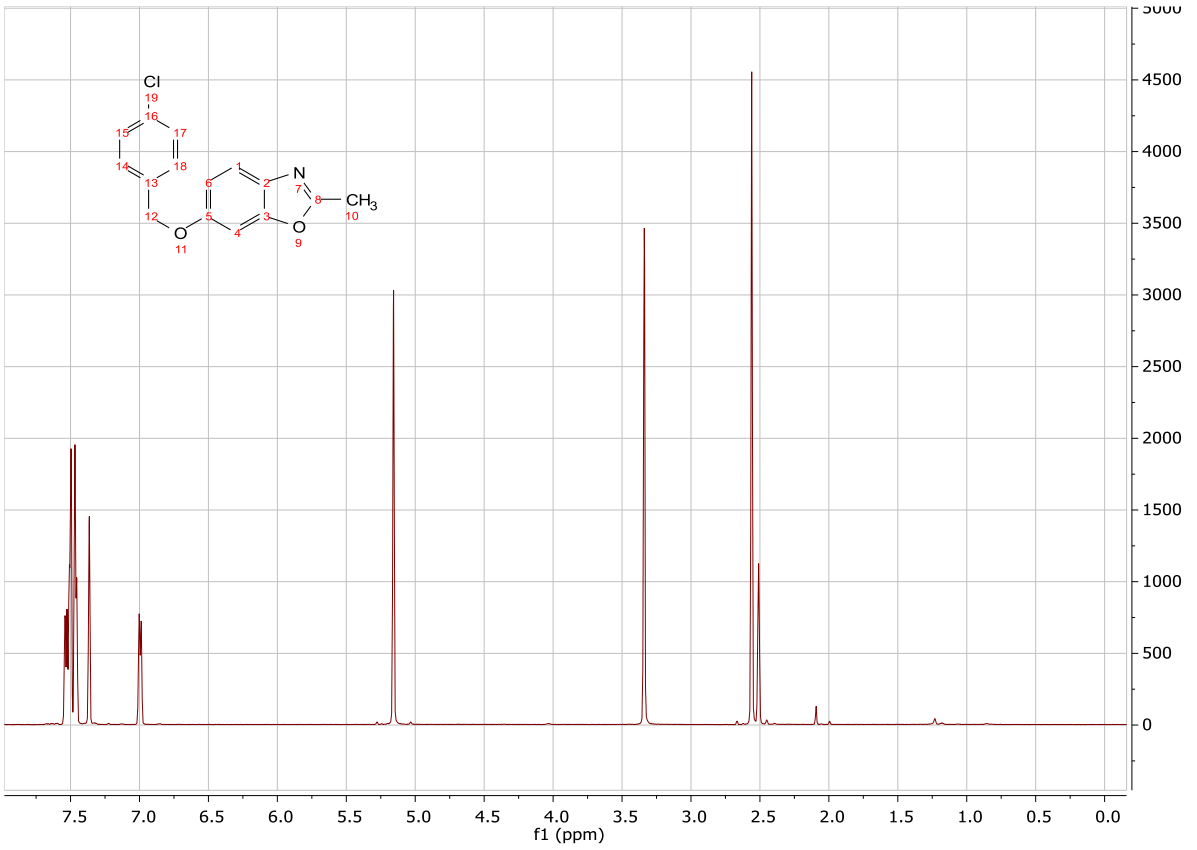


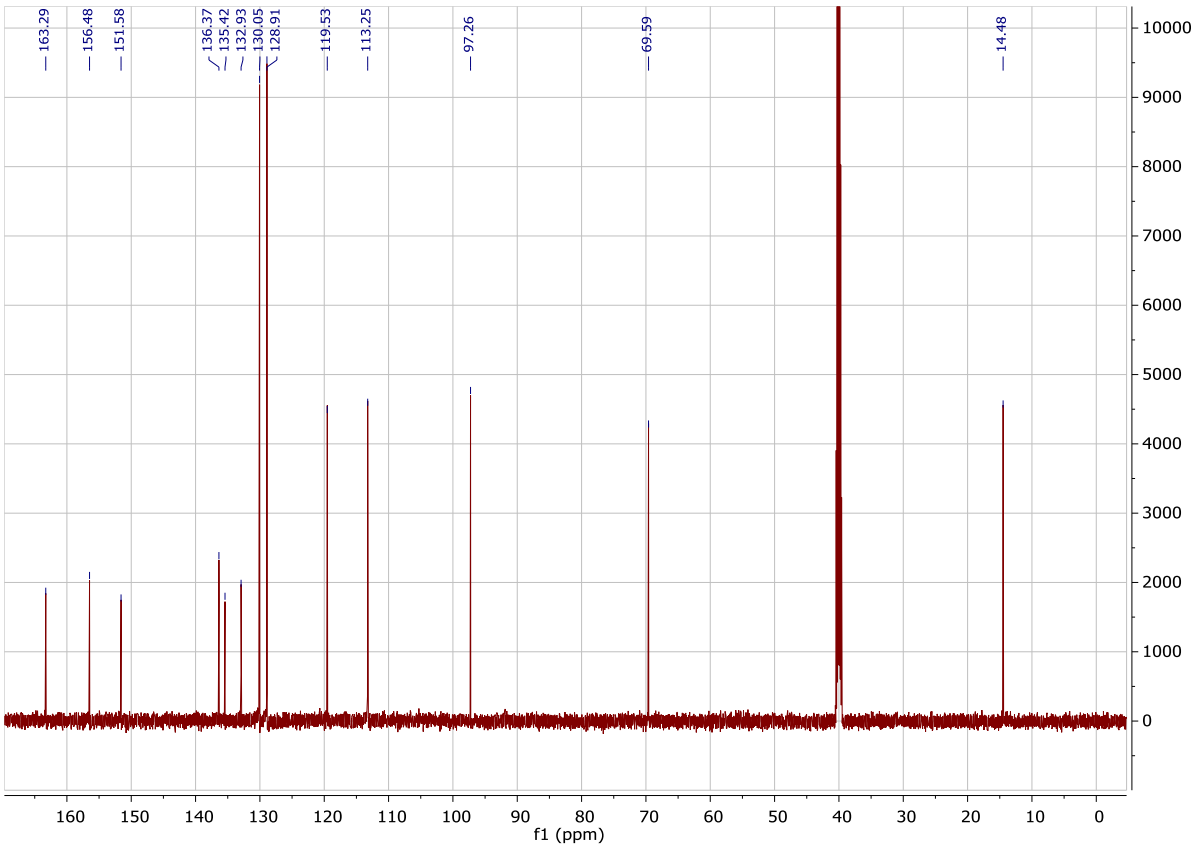
2-Methyl-6-((4-nitrobenzyl)oxy)benzo[*d*]oxazole (1d)



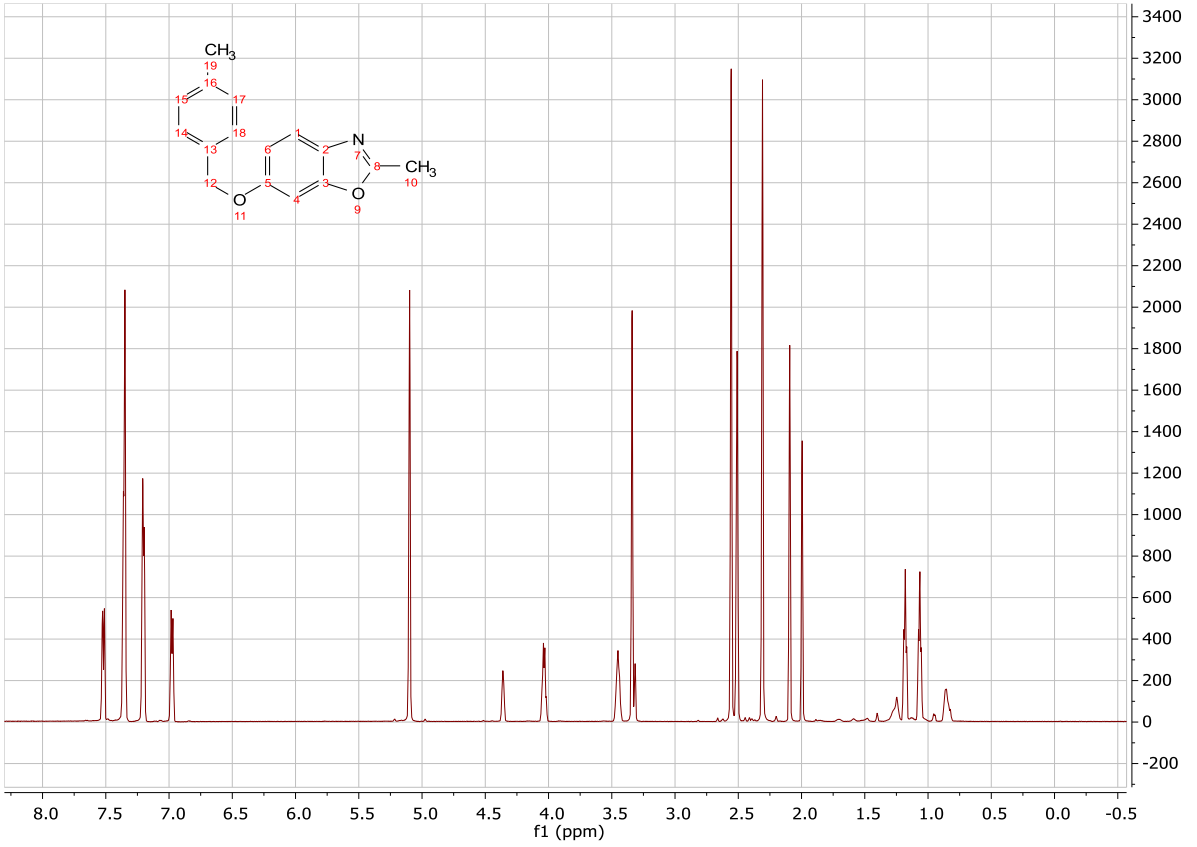


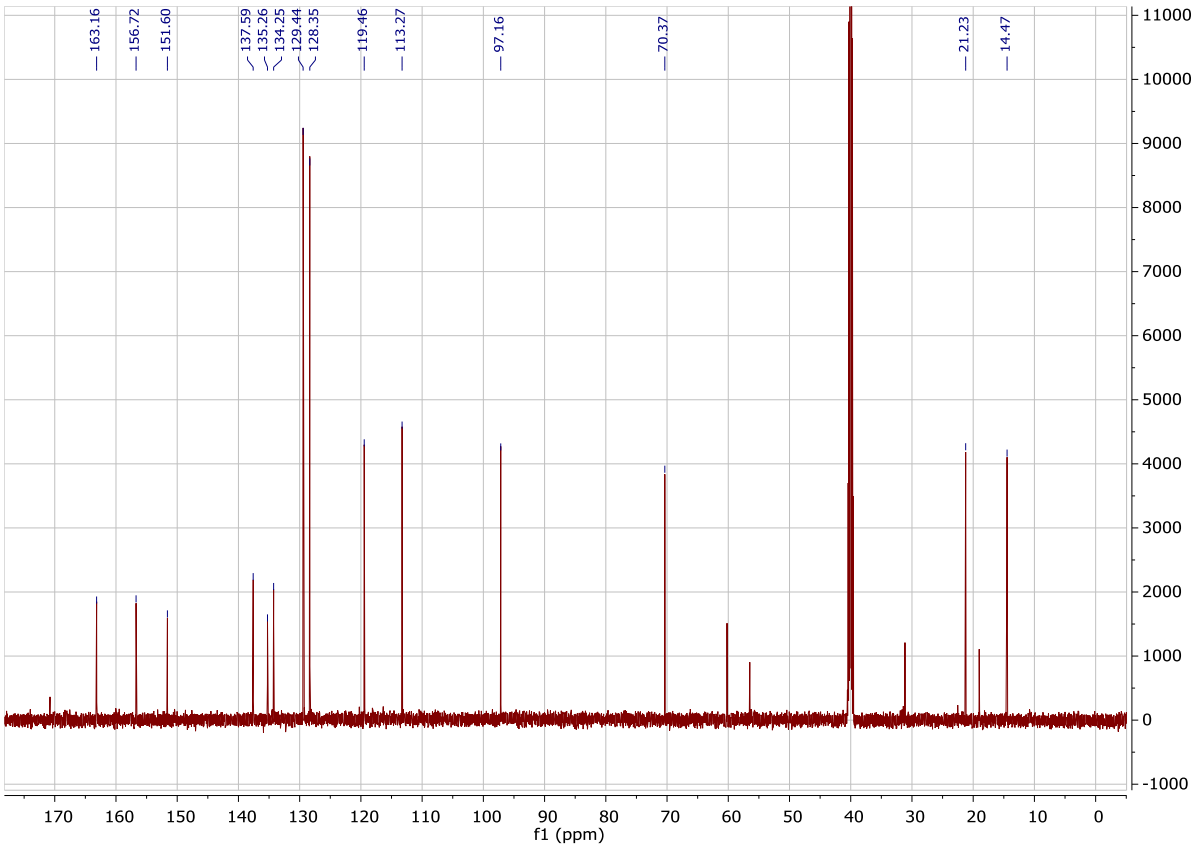
6-((4-Chlorobenzyl)oxy)-2-methylbenzo[*d*]oxazole (1e)



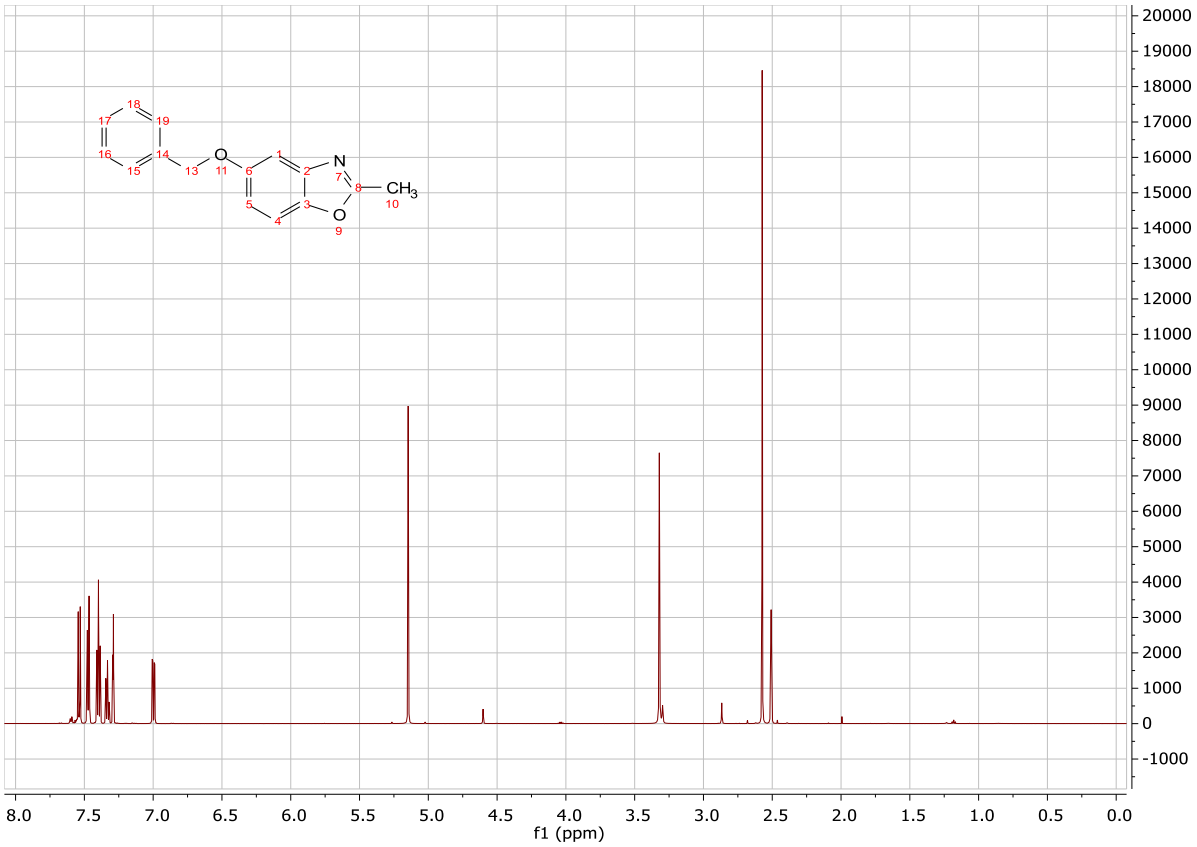


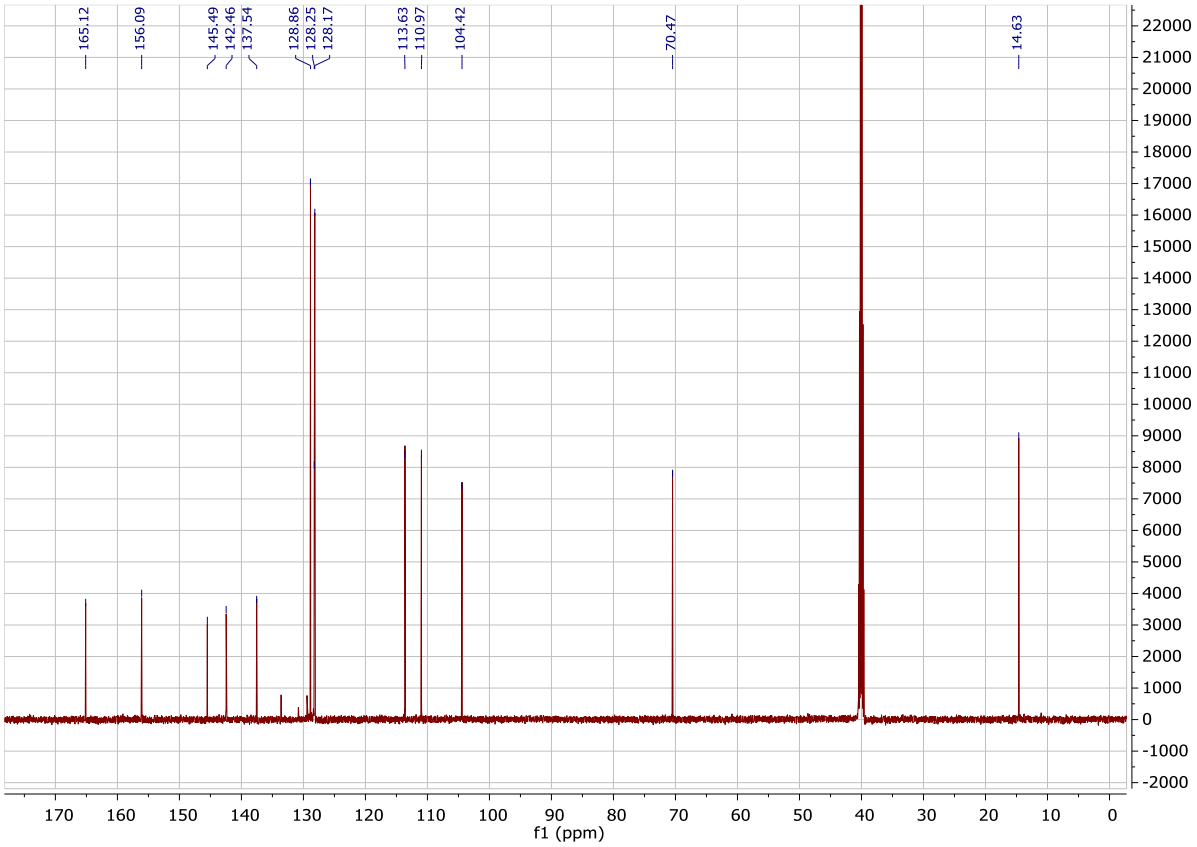
2-Methyl-6-((4-methylbenzyl)oxy)benzo[*d*]oxazole (1f)



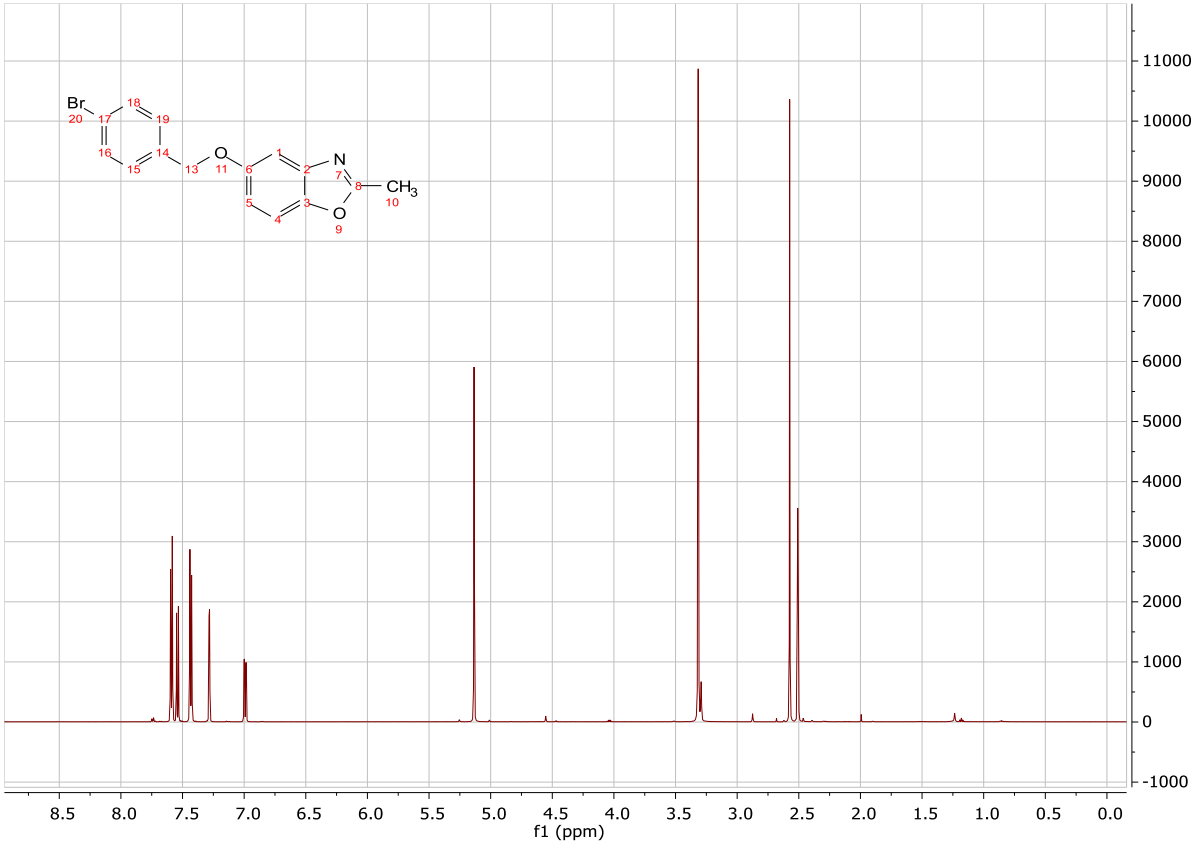


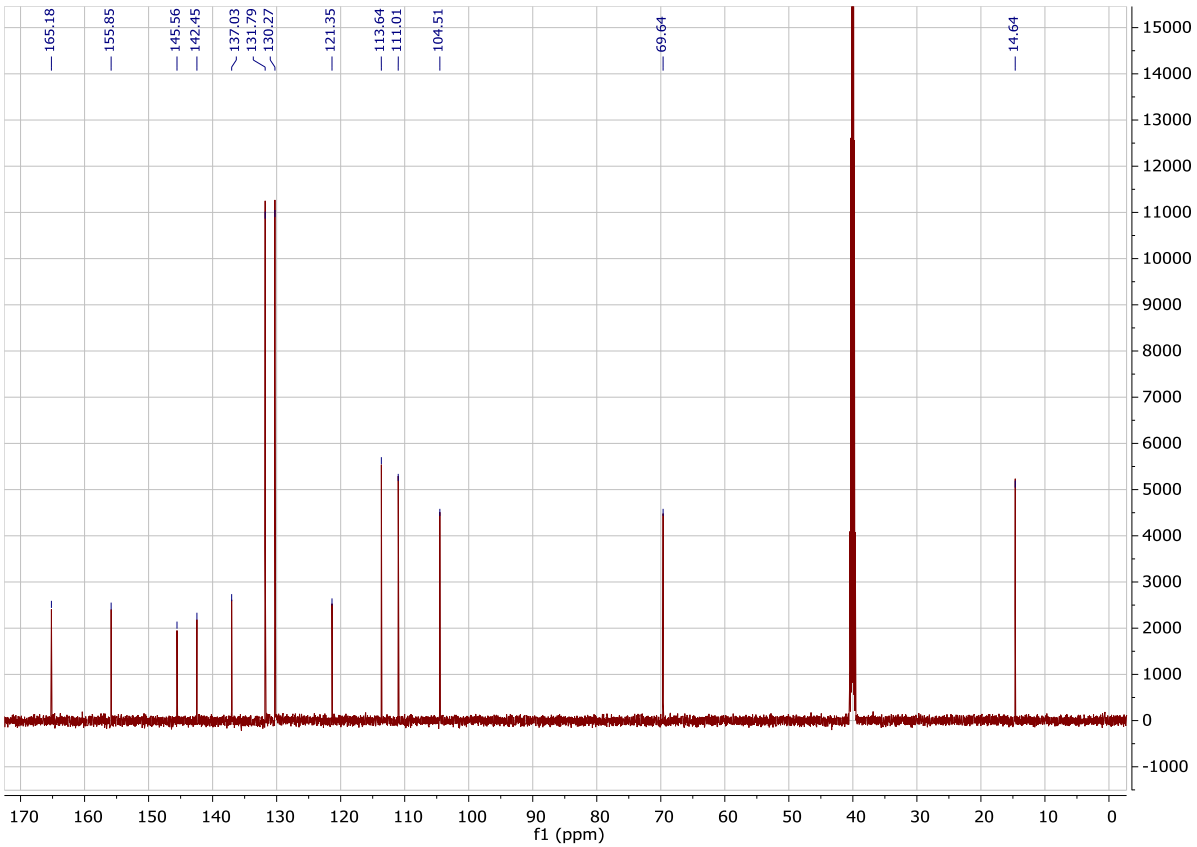
5-(Benzyloxy)-2-methylbenzo[*d*]oxazole (2a)



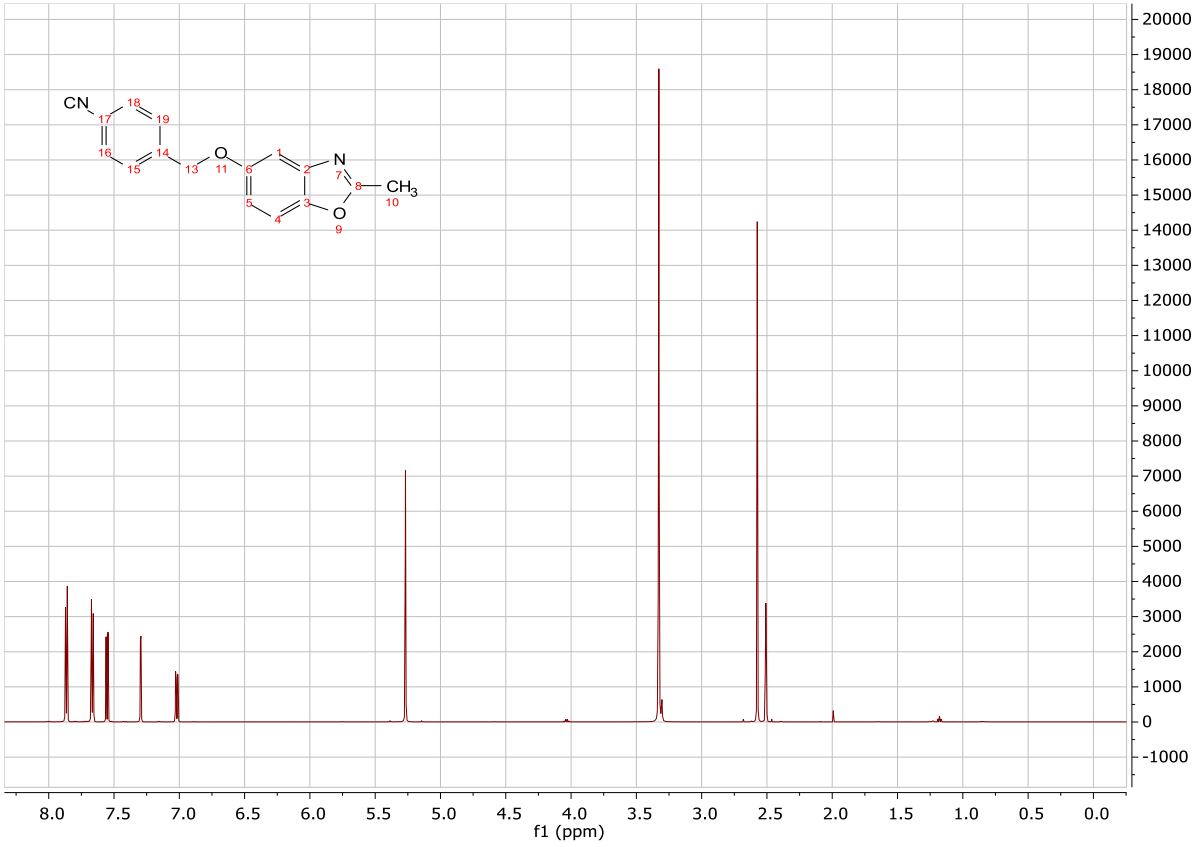


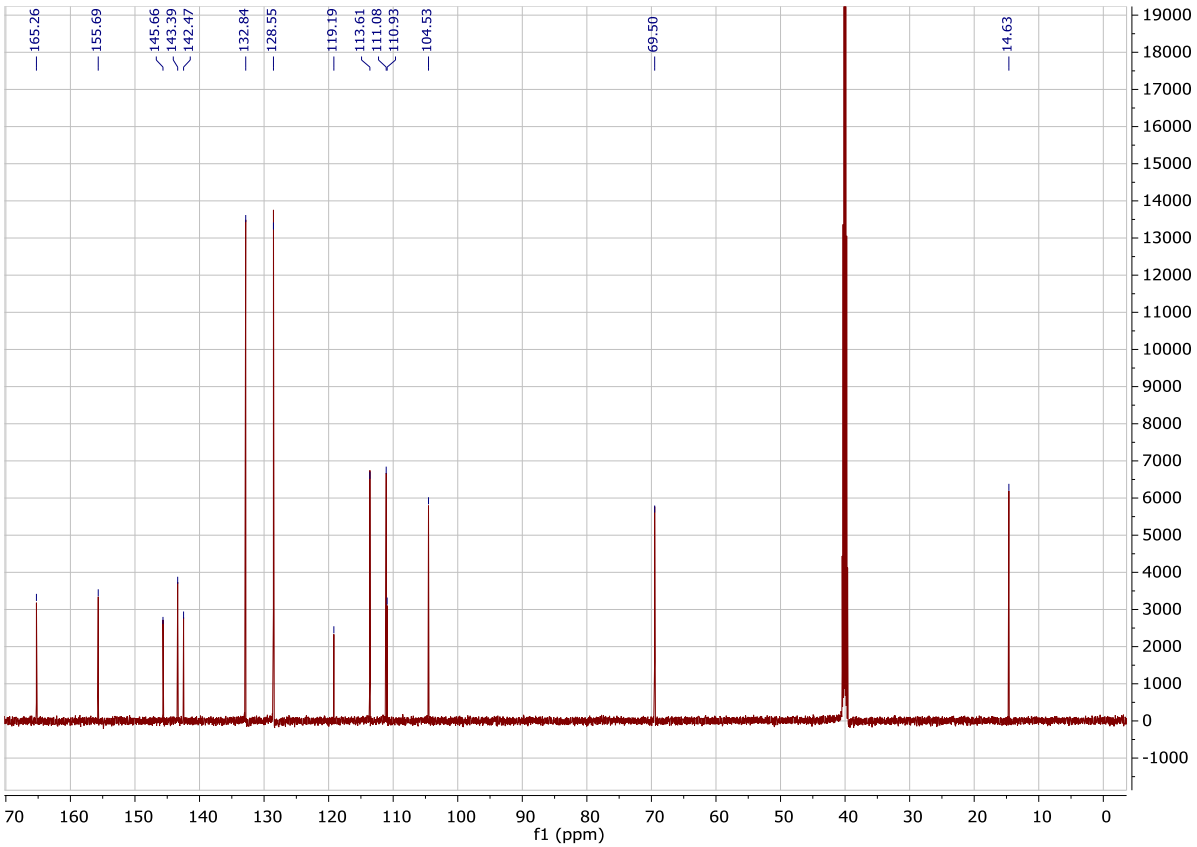
5-((4-Bromobenzyl)oxy)-2-methylbenzo[*d*]oxazole (2b)



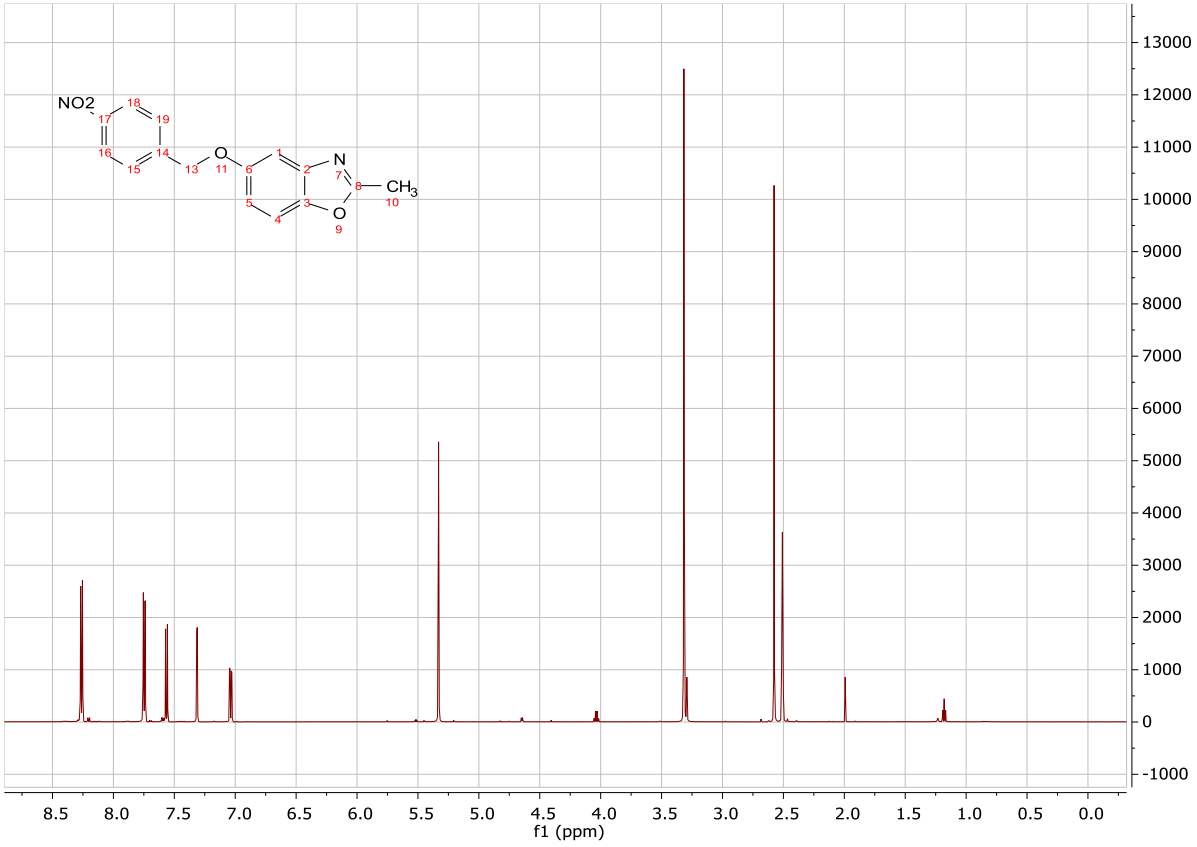


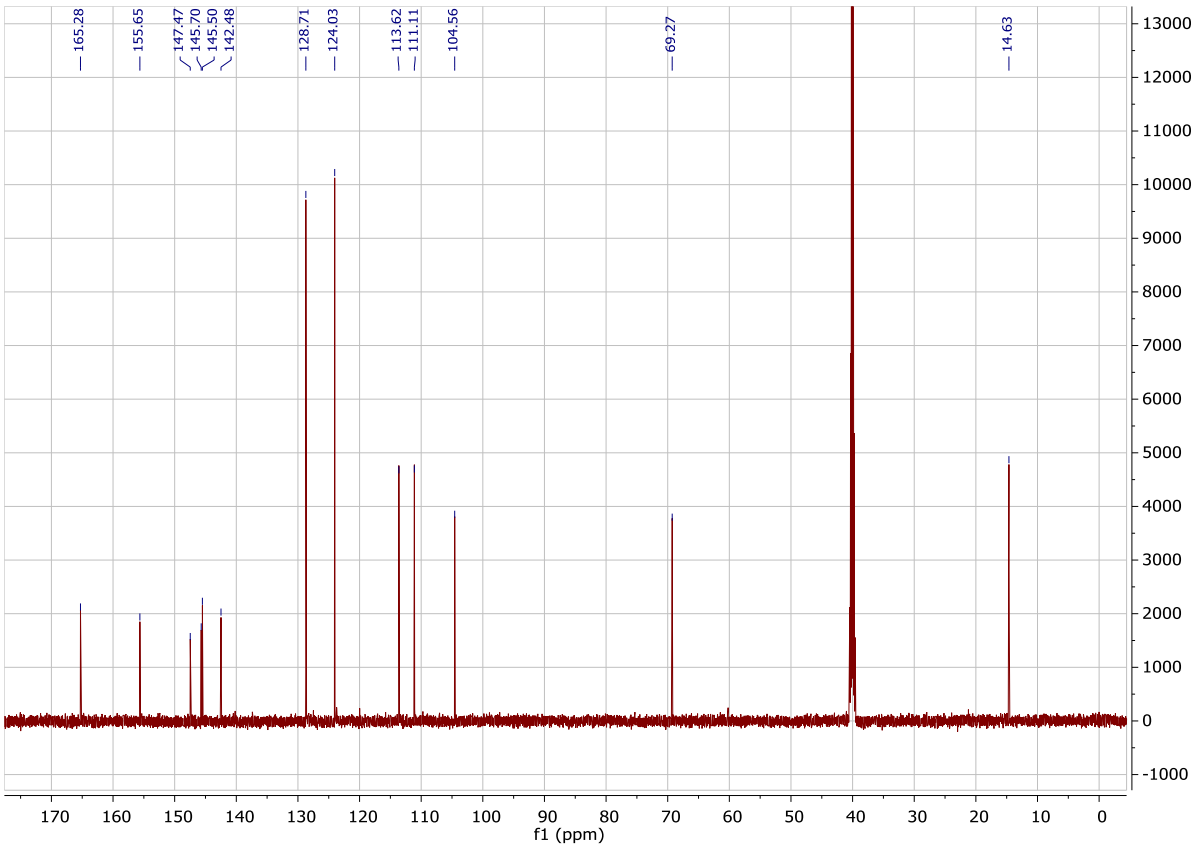
4-(((2-Methylbenzo[*d*]oxazol-5-yl)oxy)methyl)benzonitrile (2c)



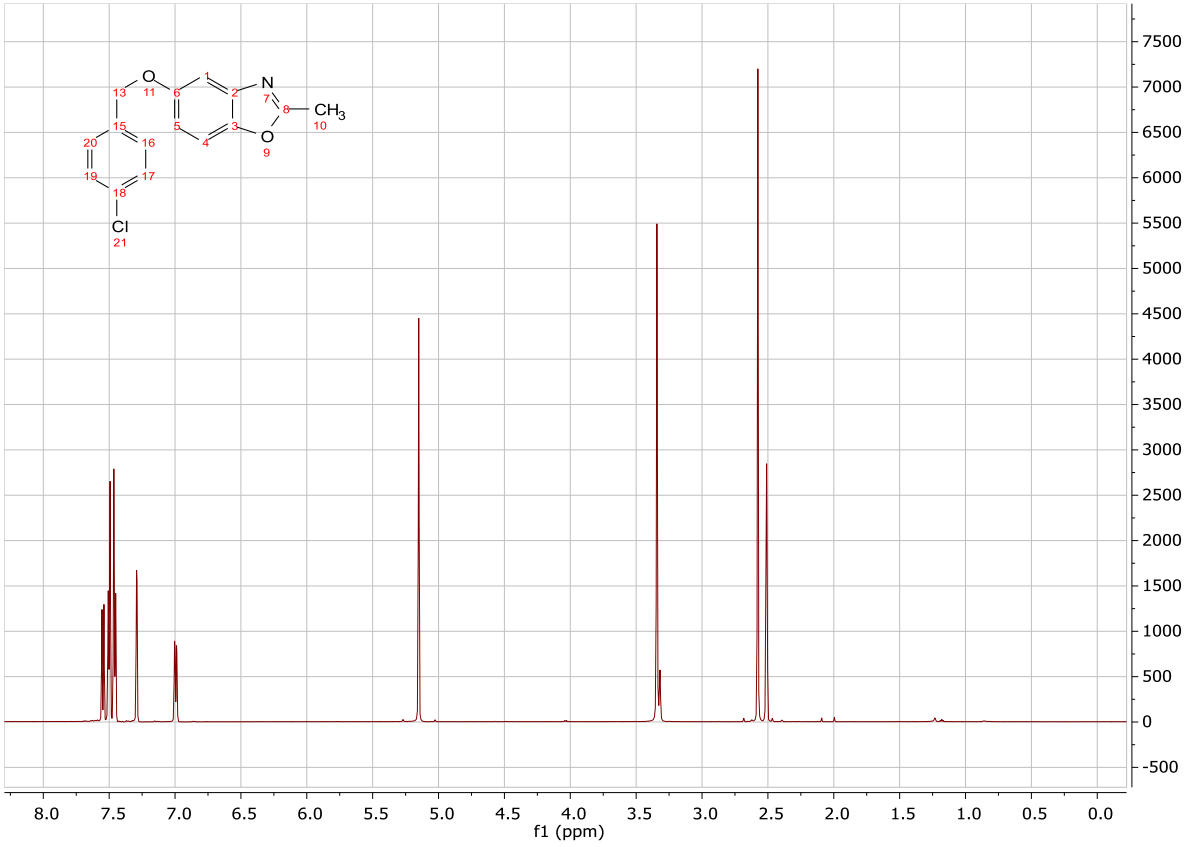


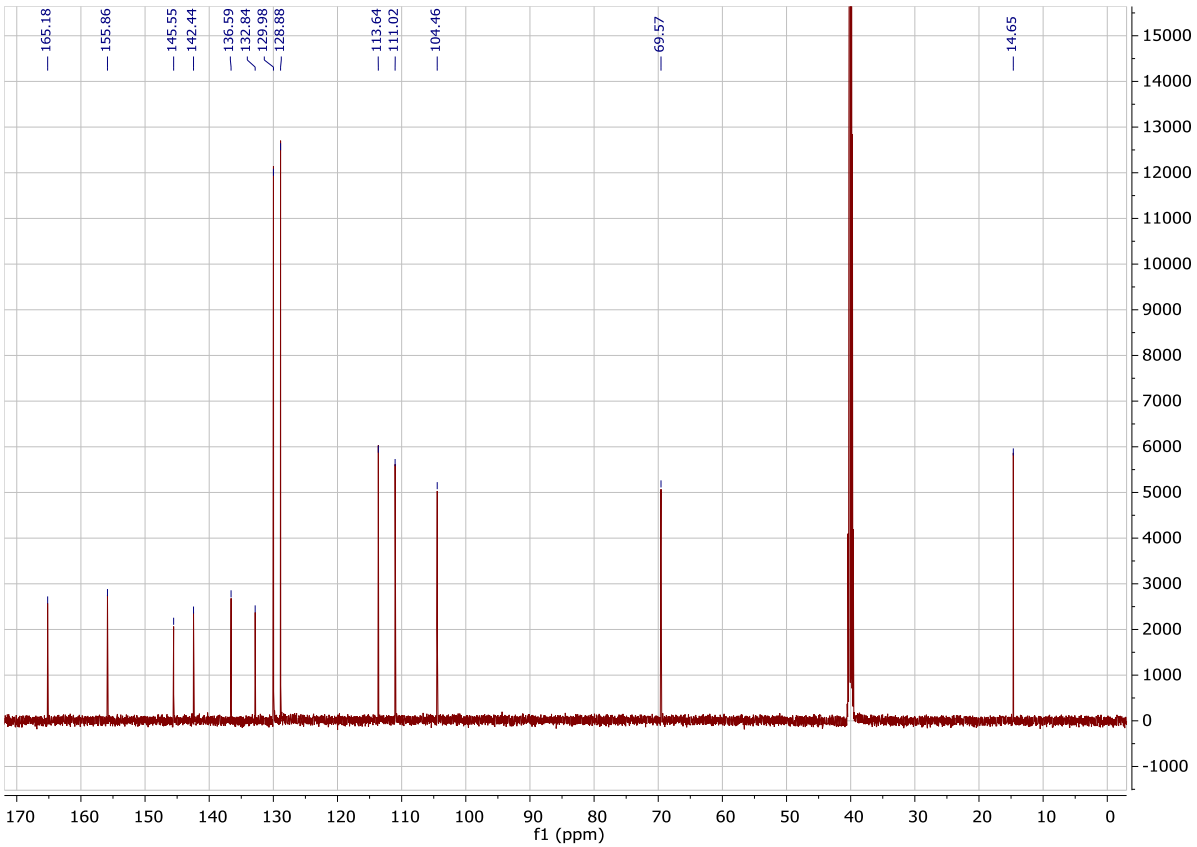
2-Methyl-5-((4-nitrobenzyl)oxy)benzo[*d*]oxazole (2d)



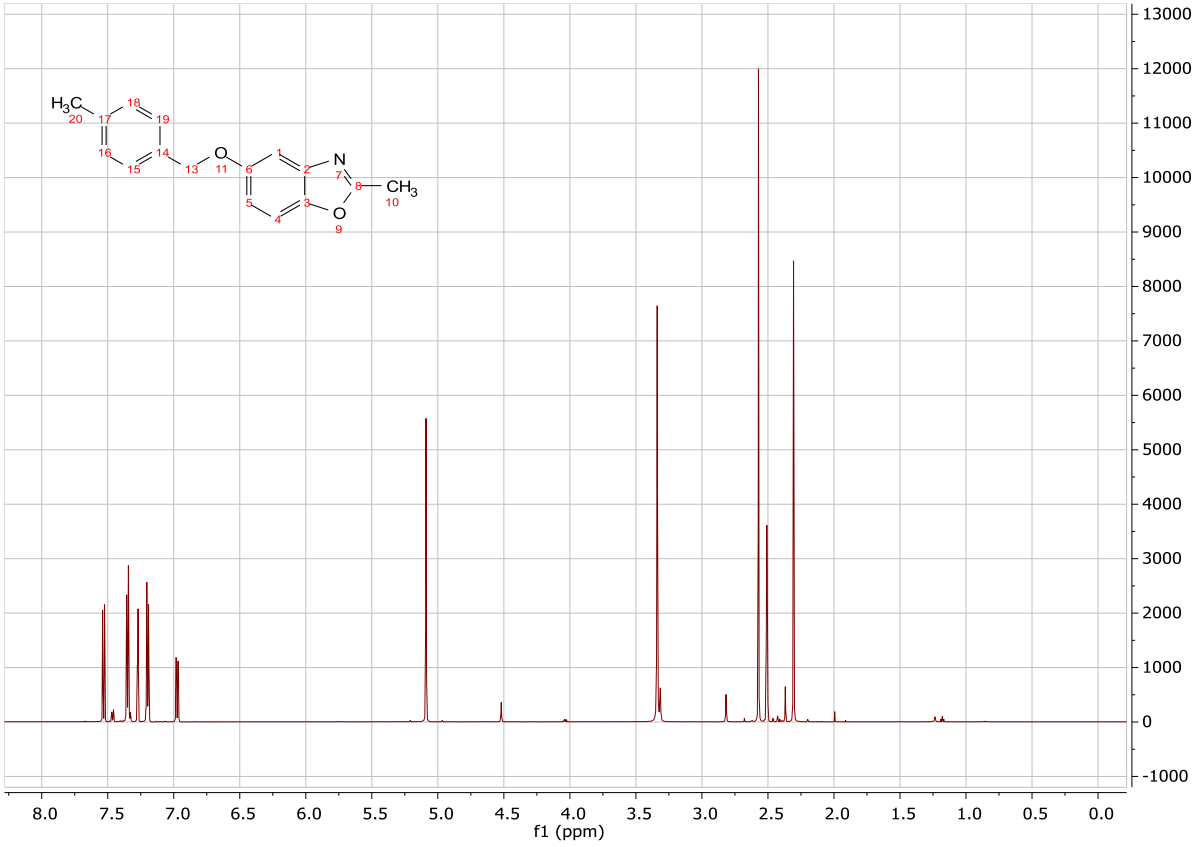


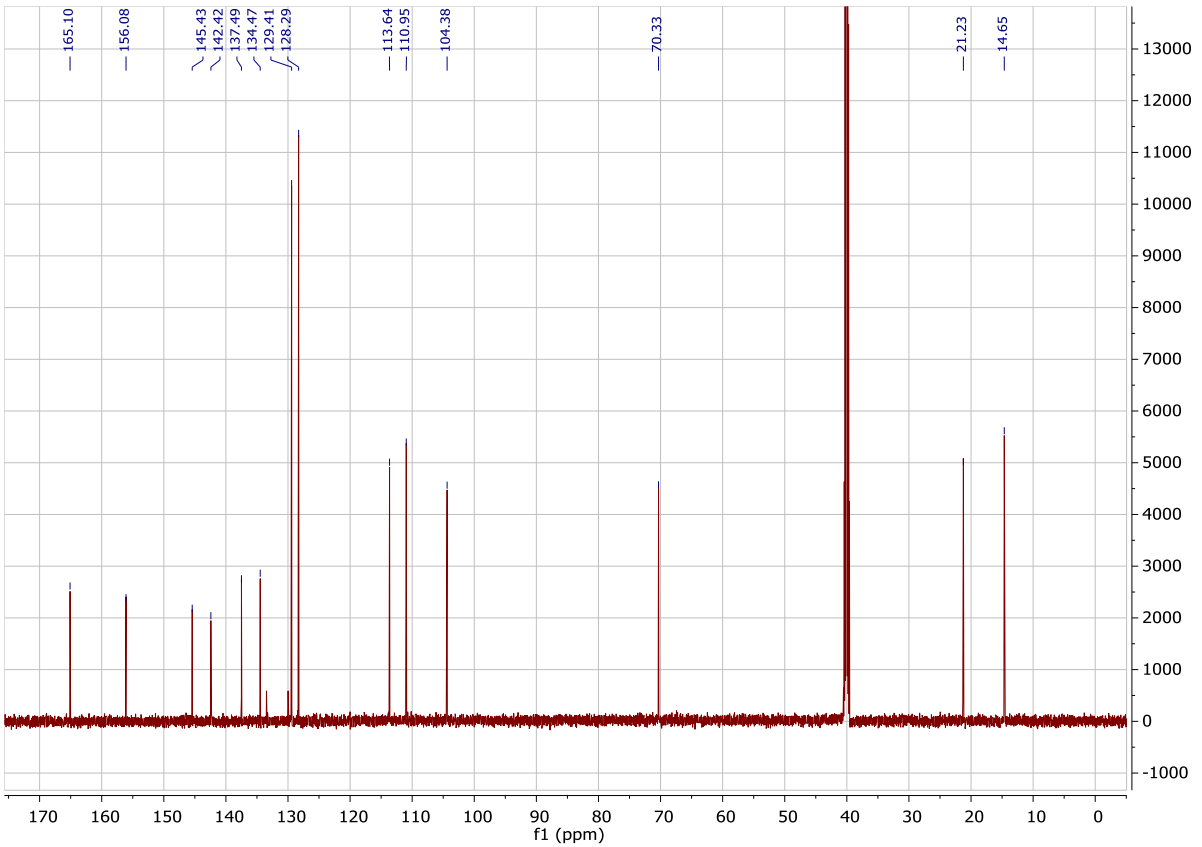
5-((4-Chlorobenzyl)oxy)-2-methylbenzo[*d*]oxazole (2e)



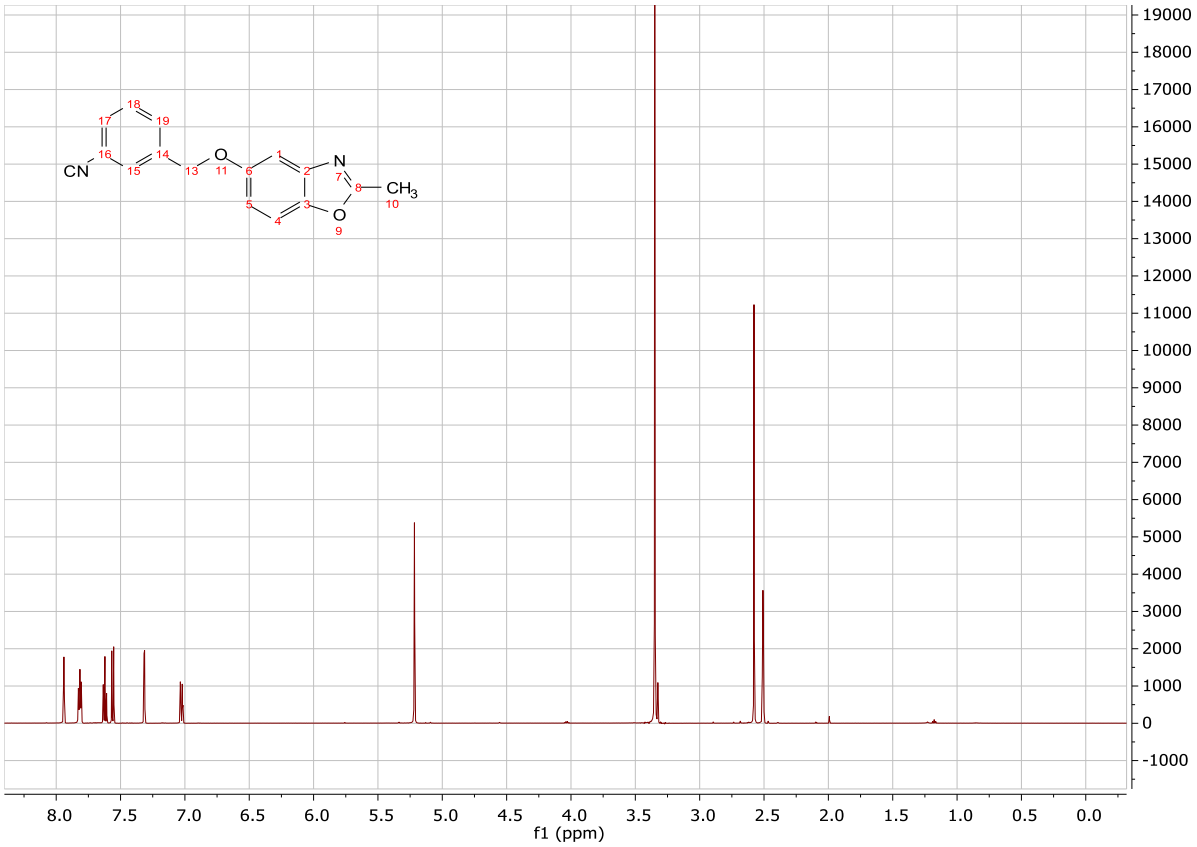


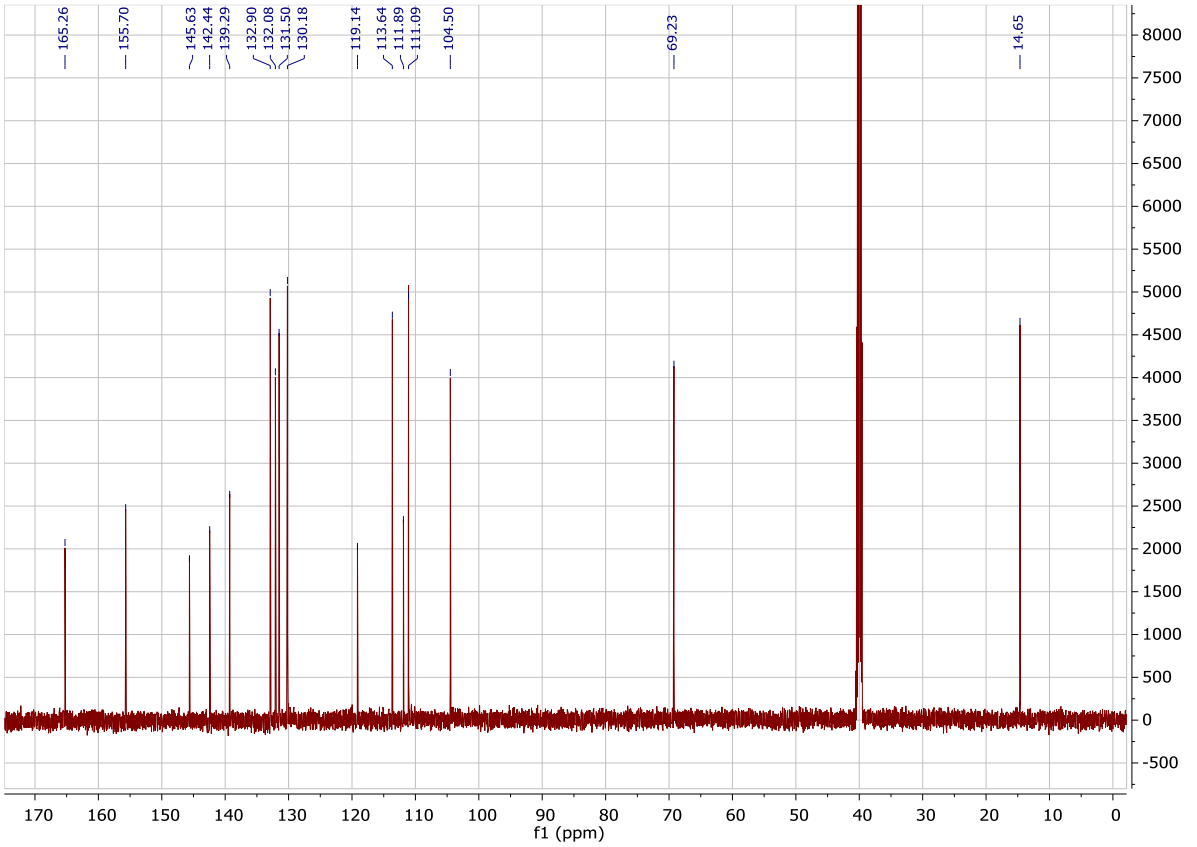
2-Methyl-5-((4-methylbenzyl)oxy)benzo[*d*]oxazole (2f)





3-(((2-Methylbenzo[*d*]oxazol-5-yl)oxy)methyl)benzonitrile (2g)

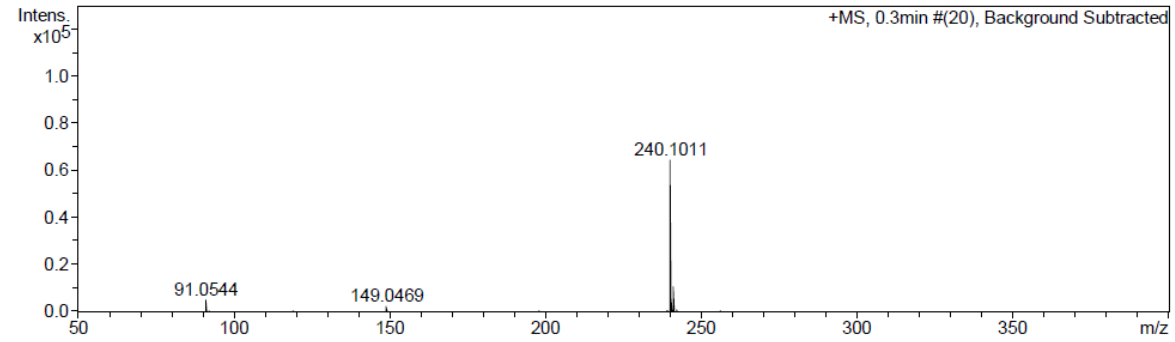




6-(Benzyloxy)-2-methylbenzo[*d*]oxazole **(1a)**

Acquisition Parameter

Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.8 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1600 m/z	Set Collision Cell RF	150.0 Vpp	Set Divert Valve	Waste

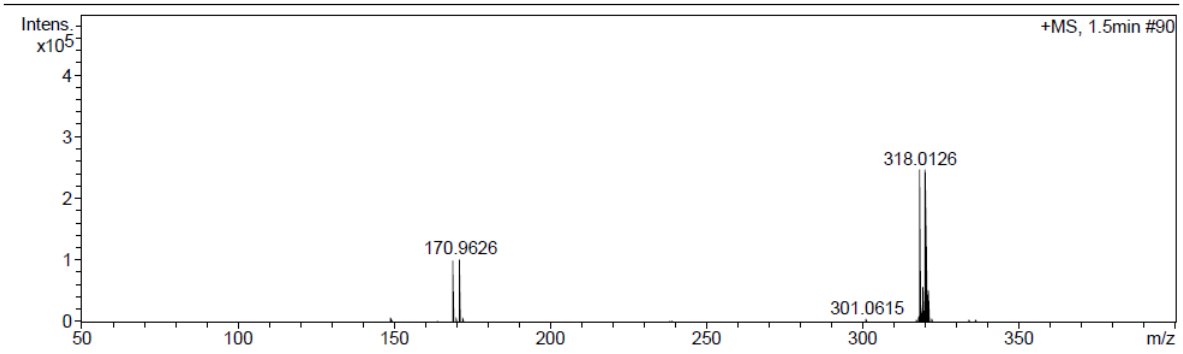


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
240.1011	1	C 15 H 14 N O 2	100.00	240.1019	0.8	3.2	0.4	9.5	even	ok

6-((4-Bromobenzyl)oxy)-2-methylbenzo[*d*]oxazole **(1b)**

Acquisition Parameter

Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.8 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1600 m/z	Set Collision Cell RF	150.0 Vpp	Set Divert Valve	Waste

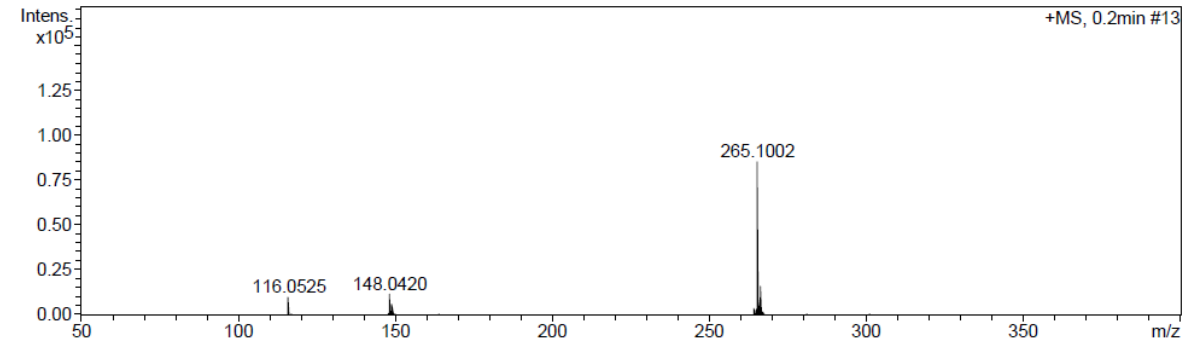


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
168.9645	1	C 7 H 6 Br	100.00	168.9647	0.2	1.3	14.6	4.5	even	ok
	2	C 3 H 8 Br N O 2	0.00	168.9733	8.8	51.9	27.6	0.0	odd	ok
318.0126	1	C 15 H 13 Br N O 2	100.00	318.0124	-0.1	-0.4	35.3	9.5	even	ok

4-(((2-Methylbenzo[*d*]oxazol-6-yl)oxy)methyl)benzonitrile **(1c)**

Acquisition Parameter

Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.8 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1600 m/z	Set Collision Cell RF	150.0 Vpp	Set Divert Valve	Waste

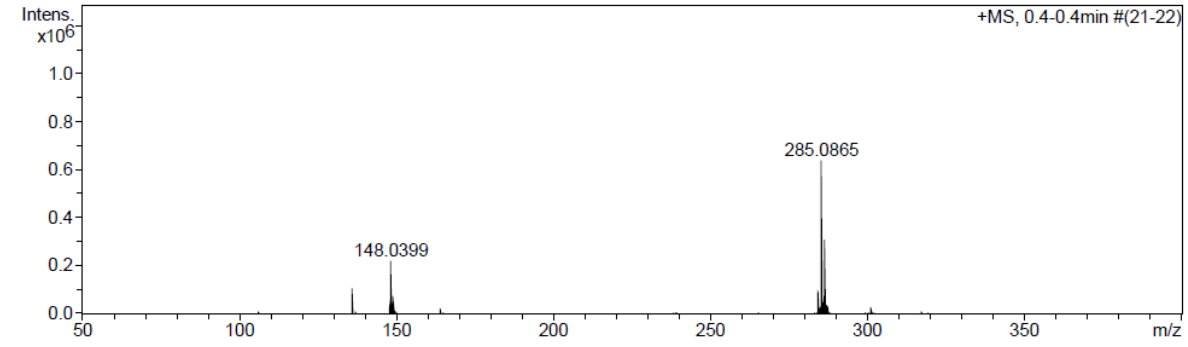


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
265.1002	1	C 15 H 18 Cl O 2	100.00	265.0990	-1.2	-4.5	143.1	6.5	even	ok

2-Methyl-6-((4-nitrobenzyl)oxy)benzo[*d*]oxazole **(1d)**

Acquisition Parameter

Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.8 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1600 m/z	Set Collision Cell RF	150.0 Vpp	Set Divert Valve	Waste

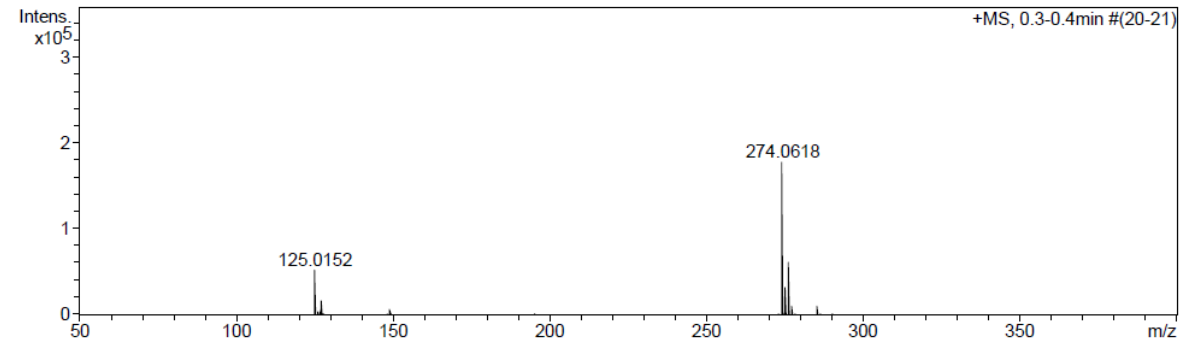


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
285.0865	1	C 15 H 13 N 2 O 4	100.00	285.0870	0.4	1.5	181.2	10.5	even	ok

6-((4-Chlorobenzyl)oxy)-2-methylbenzo[*d*]oxazole **(1e)**

Acquisition Parameter

Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.8 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1600 m/z	Set Collision Cell RF	150.0 Vpp	Set Divert Valve	Waste

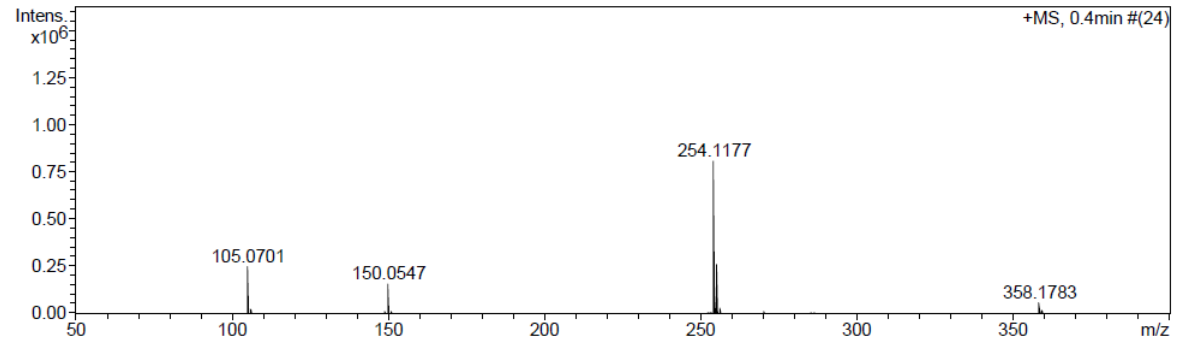


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e¯ Conf	N-Rule
125.0152	1	C 7 H 6 Cl	100.00	125.0153	0.1	0.8	6.1	4.5	even	ok
	2	C 2 H 6 Cl N 2 O 2	3.48	125.0112	-3.9	-31.4	25.6	0.5	even	ok
	3	C 8 H N 2	0.01	125.0134	-1.7	-13.9	191.8	9.5	even	ok
274.0618	1	C 15 H 13 Cl N O 2	100.00	274.0629	1.1	4.2	7.6	9.5	even	ok

2-Methyl-6-((4-methylbenzyl)oxy)benzo[*d*]oxazole **(1f)**

Acquisition Parameter

Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.8 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1600 m/z	Set Collision Cell RF	150.0 Vpp	Set Divert Valve	Waste

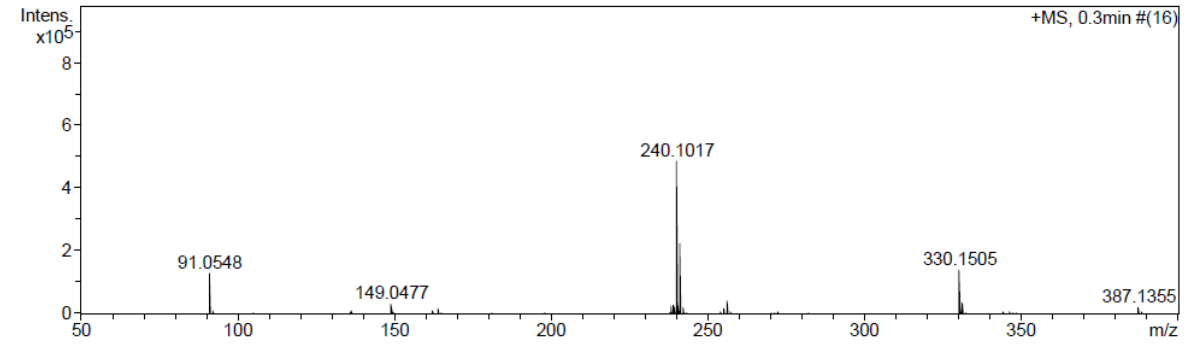


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e¯ Conf	N-Rule
105.0701	1	C 8 H 9	100.00	105.0699	-0.2	-2.2	3.6	4.5	even	ok
150.0547	1	C 8 H 8 N O 2	100.00	150.0550	0.2	1.4	3.7	5.5	even	ok
254.1177	1	C 16 H 16 N O 2	100.00	254.1176	-0.1	-0.4	84.4	9.5	even	ok

5-(Benzyloxy)-2-methylbenzo[*d*]oxazole **(2a)**

Acquisition Parameter

Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.8 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1600 m/z	Set Collision Cell RF	150.0 Vpp	Set Divert Valve	Waste

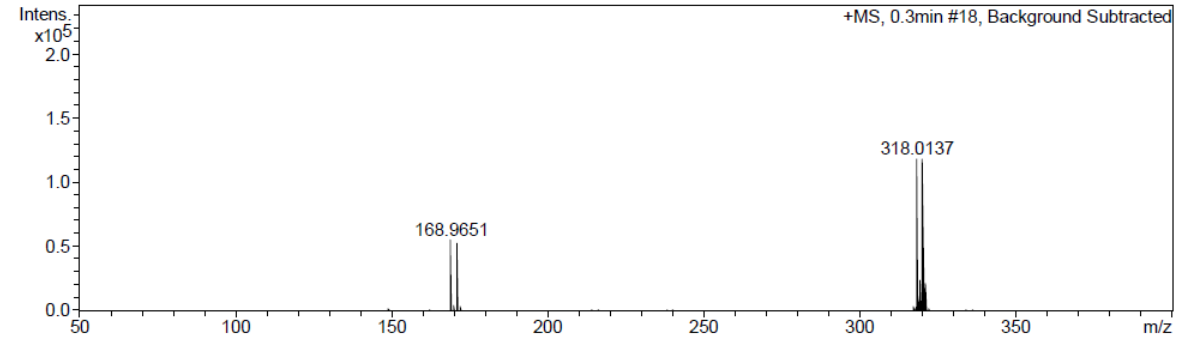


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
91.0548	1	C 7 H 7	100.00	91.0542	-0.6	-6.1	4.4	4.5	even	ok
240.1017	1	C 15 H 14 N O 2	100.00	240.1019	0.2	0.8	171.2	9.5	even	ok
330.1505	1	C 22 H 20 N O 2	100.00	330.1489	-1.7	-5.1	2.7	13.5	even	ok
	2	C 20 H 18 N 4 O	28.76	330.1475	-3.0	-9.1	9.9	14.0	odd	ok

5-((4-Bromobenzyl)oxy)-2-methylbenzo[*d*]oxazole **(2b)**

Acquisition Parameter

Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.8 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1600 m/z	Set Collision Cell RF	150.0 Vpp	Set Divert Valve	Waste

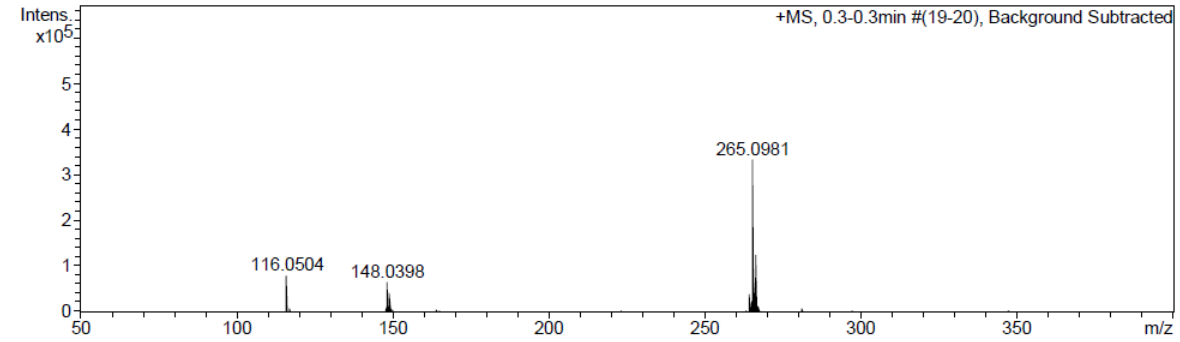


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
168.9651	1	C 7 H 6 Br	100.00	168.9647	-0.3	-1.9	9.5	4.5	even	ok
318.0137	1	C 15 H 13 Br N O 2	100.00	318.0124	-1.3	-4.0	20.2	9.5	even	ok

4-(((2-Methylbenzo[*d*]oxazol-5-yl)oxy)methyl)benzonitrile **(2c)**

Acquisition Parameter

Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.8 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1600 m/z	Set Collision Cell RF	150.0 Vpp	Set Divert Valve	Waste

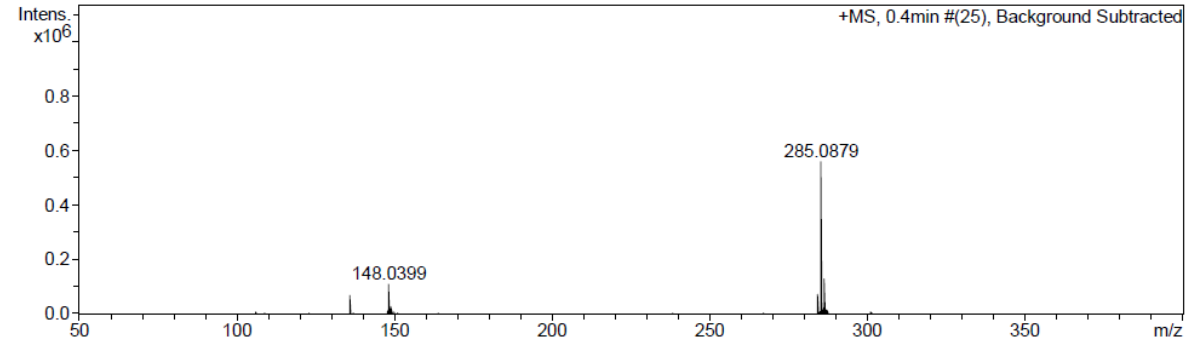


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e¯ Conf	N-Rule
116.0504	1	C 8 H 6 N	100.00	116.0495	-0.9	-7.6	1.1	6.5	even	ok
148.0398	1	C 8 H 6 N O 2	100.00	148.0393	-0.5	-3.4	308.6	6.5	even	ok
	2	C 6 H 4 N 4 O	19.73	148.0380	-1.8	-12.5	315.0	7.0	odd	ok
265.0981	1	C 16 H 13 N 2 O 2	100.00	265.0972	-1.0	-3.6	114.3	11.5	even	ok

2-Methyl-5-((4-nitrobenzyl)oxy)benzo[*d*]oxazole **(2d)**

Acquisition Parameter

Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.8 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1600 m/z	Set Collision Cell RF	150.0 Vpp	Set Divert Valve	Waste

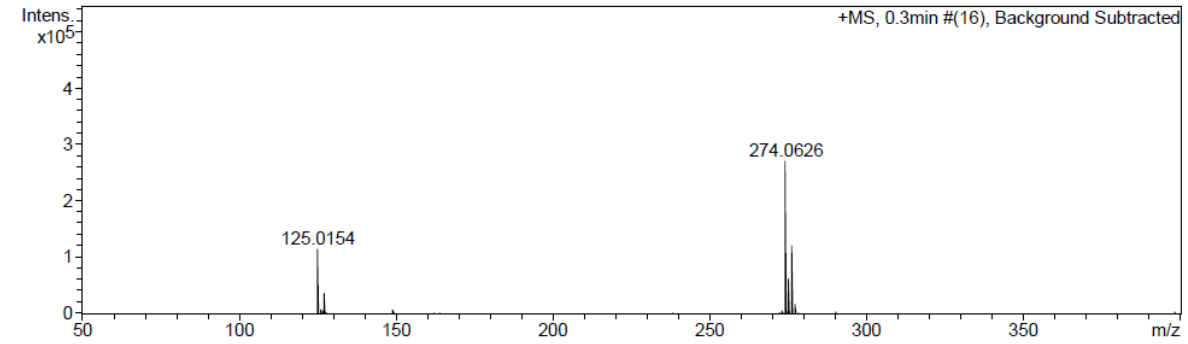


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e¯ Conf	N-Rule
136.0400	1	C 7 H 6 N O 2	100.00	136.0393	-0.7	-5.3	9.5	5.5	even	ok
	2	C 5 H 4 N 4 O	37.69	136.0380	-2.1	-15.1	15.2	6.0	odd	ok
148.0399	1	C 8 H 6 N O 2	100.00	148.0393	-0.6	-3.9	111.7	6.5	even	ok
	2	C 6 H 4 N 4 O	30.80	148.0380	-1.9	-12.9	118.3	7.0	odd	ok
285.0879	1	C 15 H 13 N 2 O 4	100.00	285.0870	-0.9	-3.2	38.1	10.5	even	ok

5-((4-Chlorobenzyl)oxy)-2-methylbenzo[*d*]oxazole **(2e)**

Acquisition Parameter

Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.8 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1600 m/z	Set Collision Cell RF	150.0 Vpp	Set Divert Valve	Waste

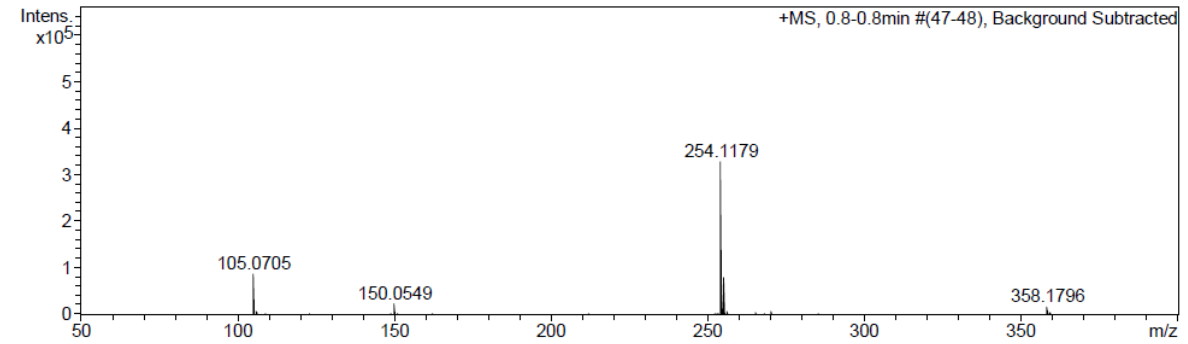


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e¯ Conf	N-Rule
125.0154	1	C 7 H 6 Cl	100.00	125.0153	-0.1	-0.8	7.3	4.5	even	ok
274.0626	1	C 15 H 13 Cl N O 2	100.00	274.0629	0.3	1.2	56.1	9.5	even	ok

2-Methyl-5-((4-methylbenzyl)oxy)benzo[*d*]oxazole **(2f)**

Acquisition Parameter

Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.8 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1600 m/z	Set Collision Cell RF	150.0 Vpp	Set Divert Valve	Waste

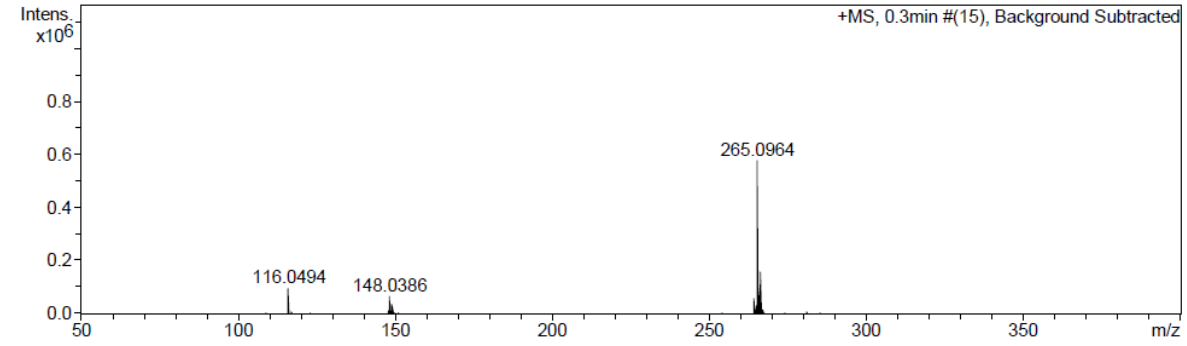


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e¯ Conf	N-Rule
105.0705	1	C 8 H 9	100.00	105.0699	-0.6	-5.5	3.4	4.5	even	ok
254.1179	1	C 16 H 16 N O 2	100.00	254.1176	-0.4	-1.4	40.5	9.5	even	ok

3-(((2-Methylbenzo[*d*]oxazol-5-yl)oxy)methyl)benzonitrile **(2g)**

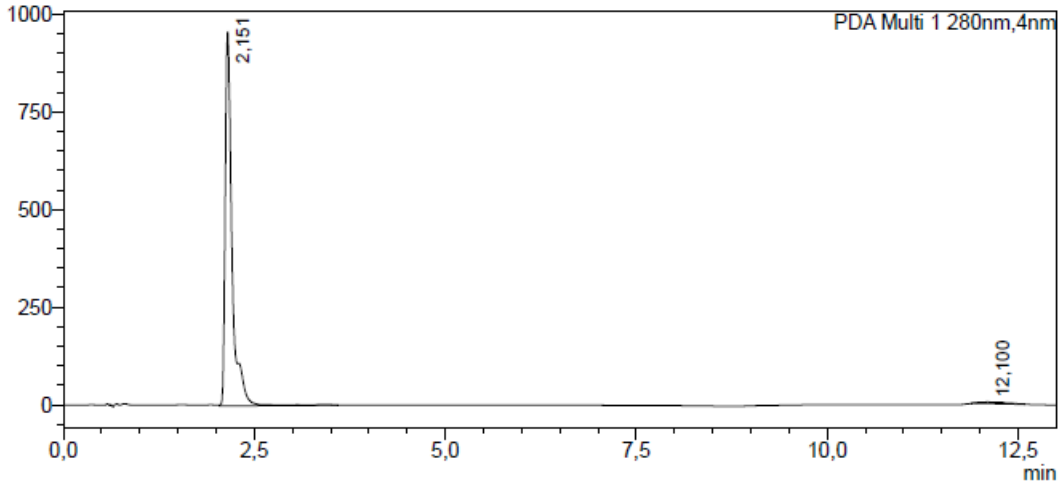
Acquisition Parameter

Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.8 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1600 m/z	Set Collision Cell RF	150.0 Vpp	Set Divert Valve	Waste



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e¯ Conf	N-Rule
116.0494	1	C 8 H 6 N	100.00	116.0495	0.1	0.5	2.7	6.5	even	ok
148.0386	1	C 8 H 6 N O 2	100.00	148.0393	0.7	5.0	292.9	6.5	even	ok
265.0964	1	C 16 H 13 N 2 O 2	100.00	265.0972	0.8	3.0	53.3	11.5	even	ok

6-(Benzyloxy)-2-methylbenzo[*d*]oxazole **(1a)**

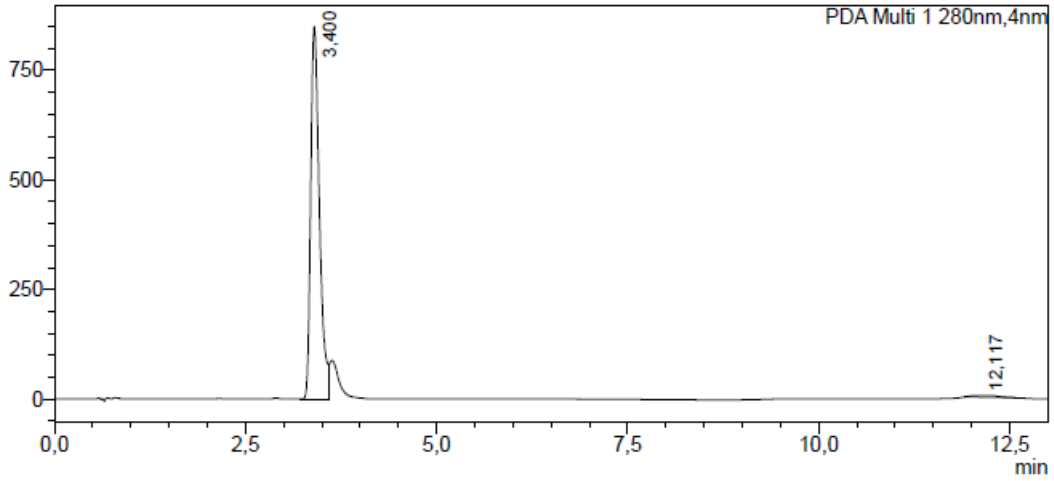


<Peak Table>

PDA Ch1 280nm

Peak#	Ret. Time	Area	Area%
1	2,151	5994429	98,226
2	12,100	108268	1,774
Total		6102696	100,000

6-((4-Bromobenzyl)oxy)-2-methylbenzo[*d*]oxazole **(1b)**

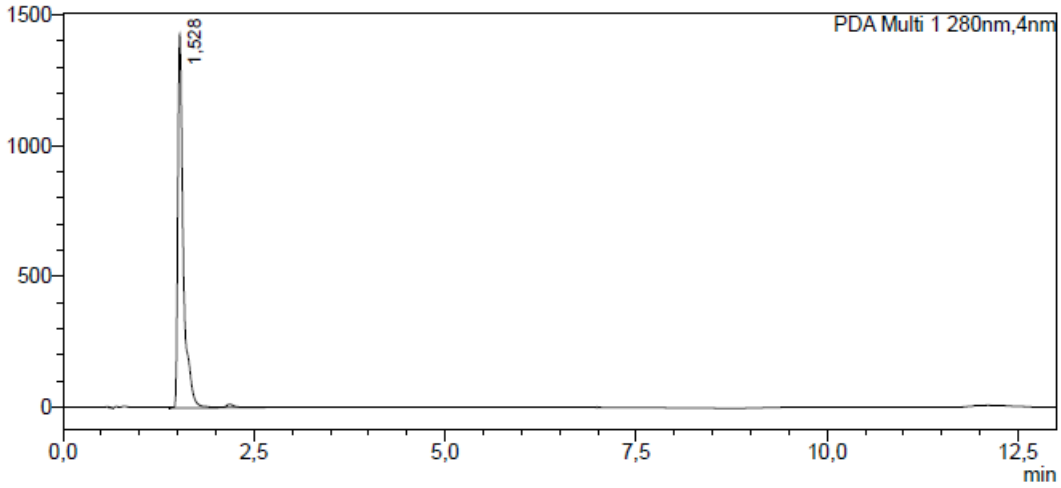


<Peak Table>

PDA Ch1 280nm

Peak#	Ret. Time	Area	Area%
1	3,400	6744437	98,576
2	12,117	97435	1,424
Total		6841873	100,000

4-(((2-Methylbenzo[*d*]oxazol-6-yl)oxy)methyl)benzonitrile **(1c)**

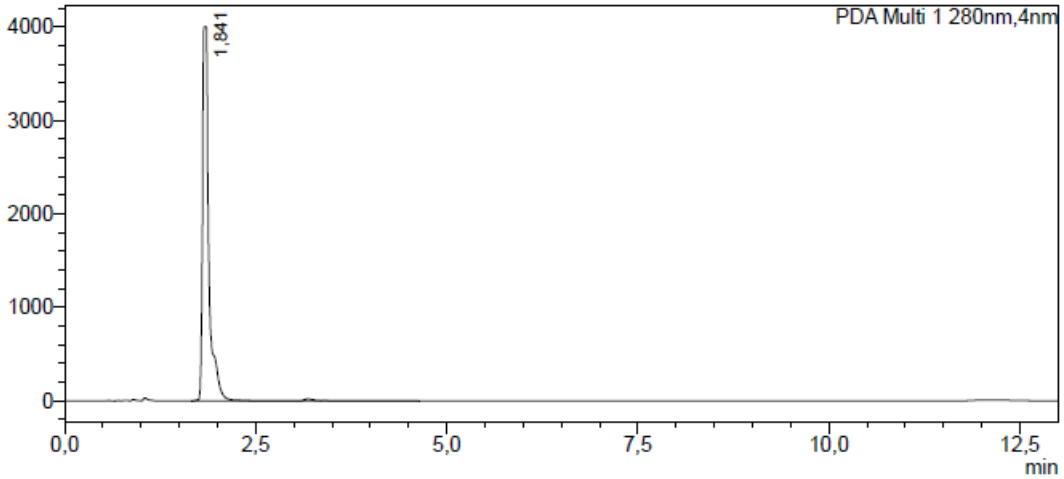


<Peak Table>

PDA Ch1 280nm

Peak#	Ret. Time	Area	Area%
1	1,528	7340296	100,000
Total		7340296	100,000

2-Methyl-6-((4-nitrobenzyl)oxy)benzo[*d*]oxazole **(1d)**

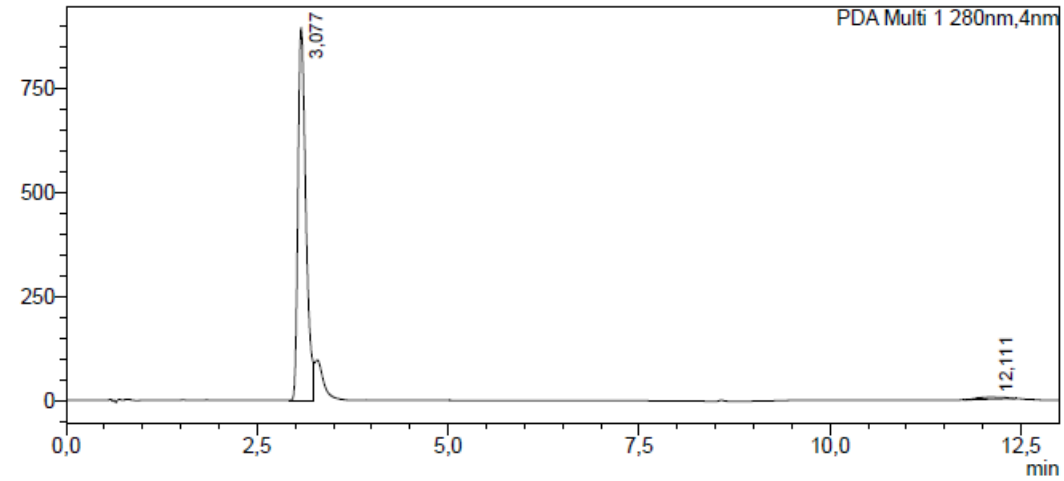


<Peak Table>

PDA Ch1 280nm

Peak#	Ret. Time	Area	Area%
1	1,841	23644682	100,000
Total		23644682	100,000

6-((4-Chlorobenzyl)oxy)-2-methylbenzo[*d*]oxazole **(1e)**

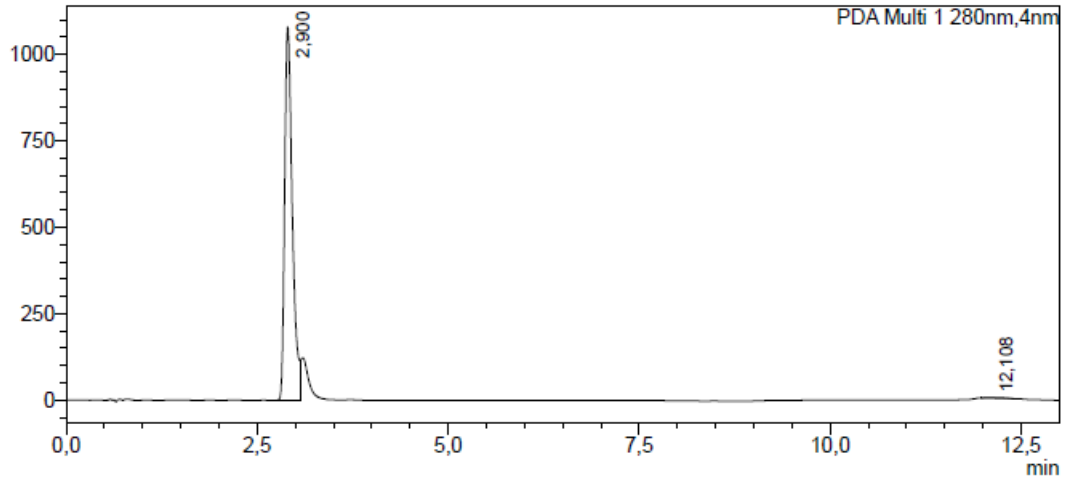


<Peak Table>

PDA Ch1 280nm

Peak#	Ret. Time	Area	Area%
1	3,077	6527390	98,219
2	12,111	118357	1,781
Total		6645747	100,000

2-Methyl-6-((4-methylbenzyl)oxy)benzo[*d*]oxazole **(1f)**

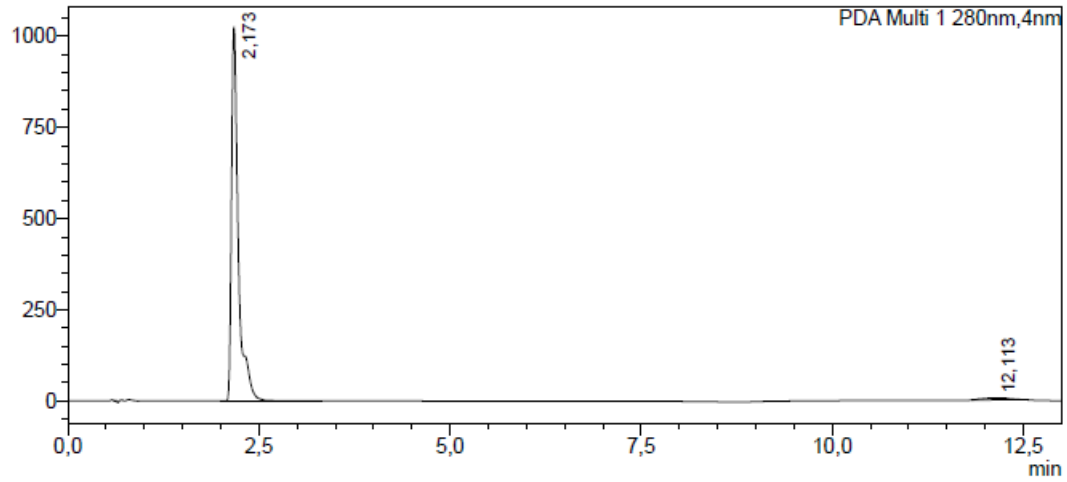


<Peak Table>

PDA Ch1 280nm

Peak#	Ret. Time	Area	Area%
1	2,900	7544732	99,554
2	12,108	33802	0,446
Total		7578534	100,000

5-(Benzyloxy)-2-methylbenzo[*d*]oxazole **(2a)**

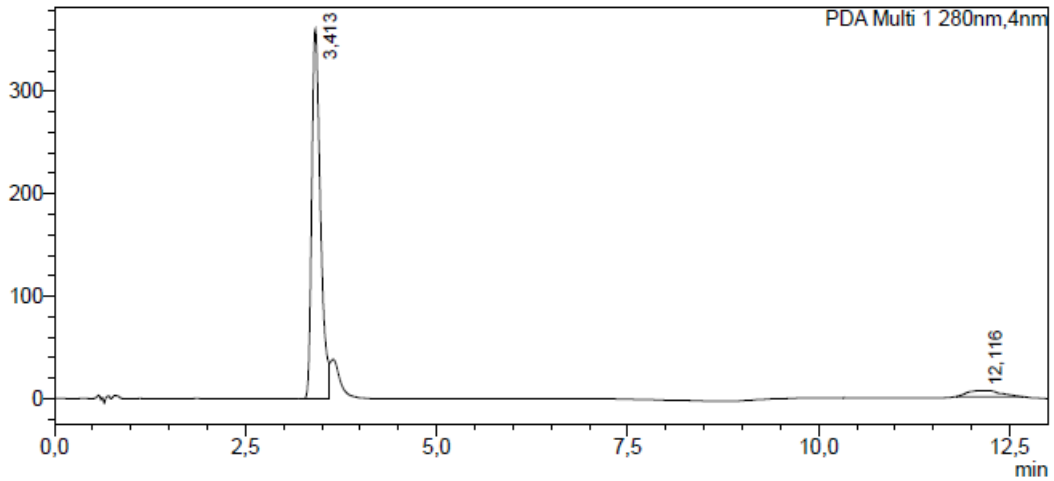


<Peak Table>

PDA Ch1 280nm

Peak#	Ret. Time	Area	Area%
1	2,173	6388513	98,312
2	12,113	109692	1,688
Total		6498205	100,000

5-((4-Bromobenzyl)oxy)-2-methylbenzo[*d*]oxazole **(2b)**

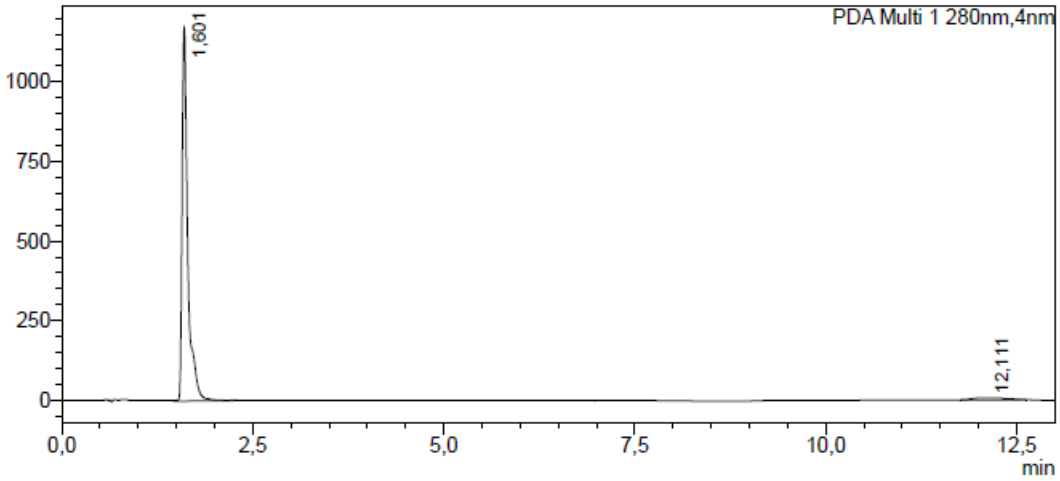


<Peak Table>

PDA Ch1 280nm

Peak#	Ret. Time	Area	Area%
1	3,413	2860474	94,084
2	12,116	179868	5,916
Total		3040342	100,000

4-(((2-Methylbenzo[*d*]oxazol-5-yl)oxy)methyl)benzonitrile **(2c)**

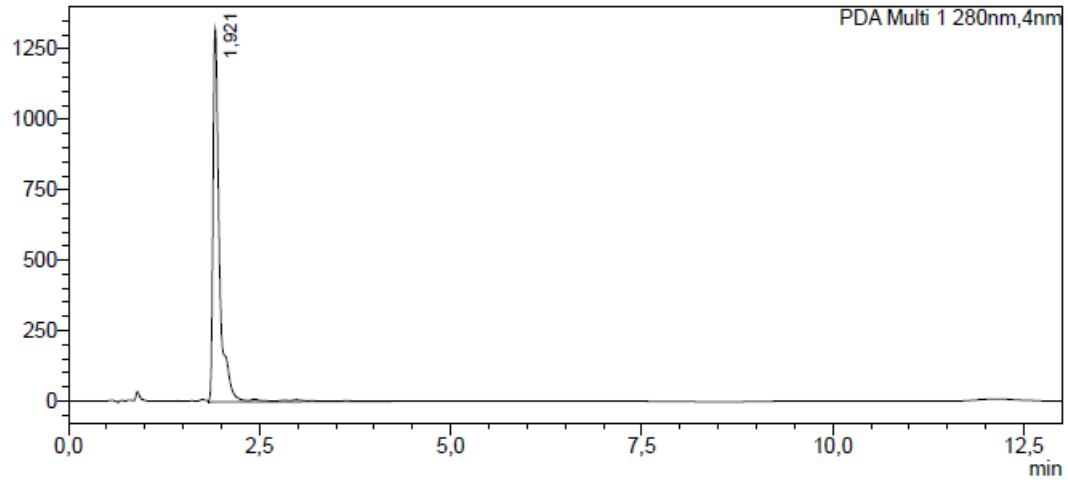


<Peak Table>

PDA Ch1 280nm

Peak#	Ret. Time	Area	Area%
1	1,601	6099449	97,178
2	12,111	177125	2,822
Total		6276574	100,000

2-Methyl-5-((4-nitrobenzyl)oxy)benzo[*d*]oxazole **(2d)**

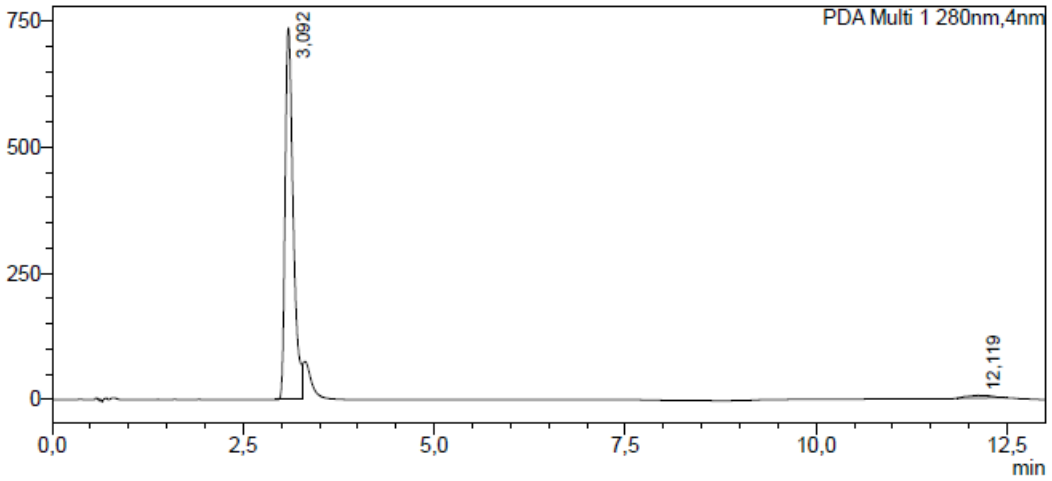


<Peak Table>

PDA Ch1 280nm

Peak#	Ret. Time	Area	Area%
1	1,921	7819251	100,000
Total		7819251	100,000

5-((4-Chlorobenzyl)oxy)-2-methylbenzo[*d*]oxazole **(2e)**

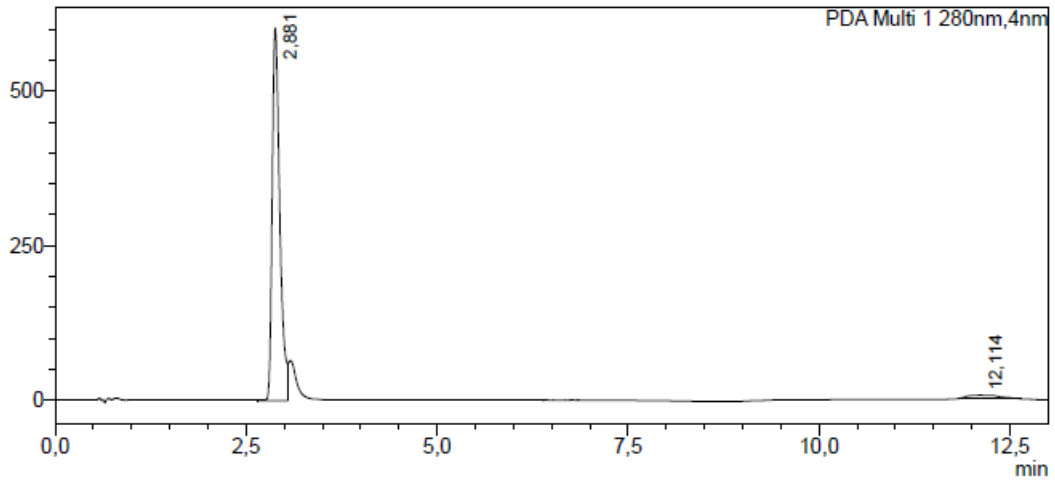


<Peak Table>

PDA Ch1 280nm

Peak#	Ret. Time	Area	Area%
1	3,092	5397085	97,908
2	12,119	115339	2,092
Total		5512424	100,000

2-Methyl-5-((4-methylbenzyl)oxy)benzo[*d*]oxazole **(2f)**

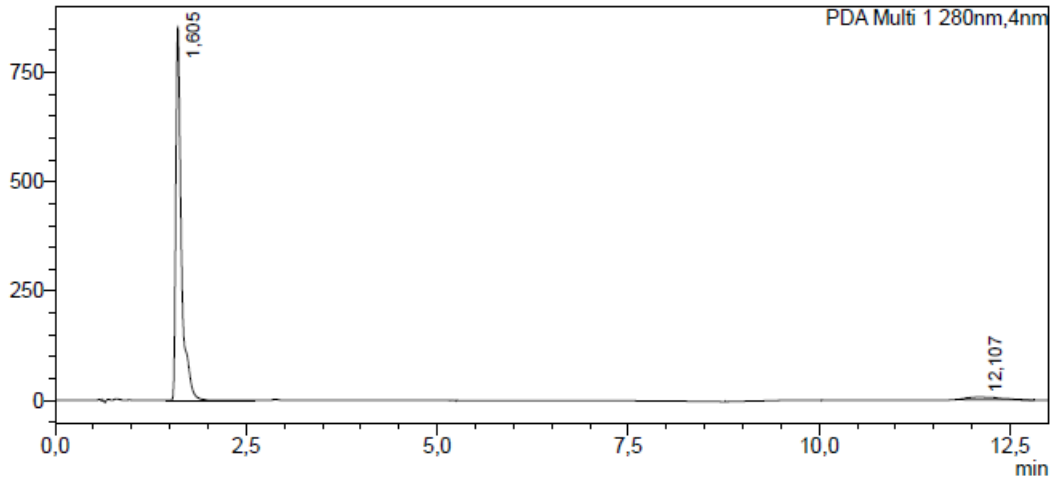


<Peak Table>

PDA Ch1 280nm

Peak#	Ret. Time	Area	Area%
1	2,881	4189707	96,257
2	12,114	162901	3,743
Total		4352607	100,000

3-(((2-Methylbenzo[*d*]oxazol-5-yl)oxy)methyl)benzonitrile **(2g)**



<Peak Table>

PDA Ch1 280nm

Peak#	Ret. Time	Area	Area%
1	1,605	4369560	95,651
2	12,107	198681	4,349
Total		4568242	100,000

Single crystal X-ray diffraction data for 2b

Table S1. Sample and crystal data for **2b**

CCDC no.	2408388	
Chemical formula	$C_{15}H_{12}BrNO_2$	
M_r	318 g/mol	
Temperature	293(2) K	
Wavelength	0.71076 Å	
Crystal size	0.200 × 0.200 × 0.200 mm	
Crystal system	triclinic	
Space group	P -1	
Unit cell dimensions	a = 7.4433(12) Å	α = 79.667(9)°
	b = 7.7961(13) Å	β = 79.791(8)°
	c = 12.024(2) Å	γ = 82.934(8)°
Volume	672.5(2) $Å^3$	
Z	8	
Density (calculated)	1.571 g/cm^3	
Absorption coefficient	3.052 mm^{-1}	
F(000)	320	

Table S2. Data collection and structure refinement for **2b**.

Theta range for data collection	2.67 to 25.21°	
Index ranges	-8<=h<=8, -9<=k<=9, -14<=l<=14	
Reflections collected	19298	
Independent reflections	2408 [R(int) = 0.0920]	
Coverage of independent reflections	99.0%	
Absorption correction	Multi-Scan	
Max. and min. transmission	0.5800 and 0.5800	
Structure solution technique	direct methods	
Structure solution program	XT, VERSION 2018/2	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2019/1 (Sheldrick, 2019)	
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	2408 / 0 / 173	
Goodness-of-fit on F^2	1.112	
Δ/σ_{max}	0.031	
Final R indices	1485 data; I>2σ(I)	R1 = 0.0808, wR2 = 0.2127
	all data	R1 = 0.1405, wR2 = 0.2562

Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0979P)^2+3.8668P]$ where $P=(F_o^2+2F_c^2)/3$
Largest diff. peak and hole	0.939 and -0.936 $eÅ^{-3}$
R.M.S. deviation from mean	0.107 $eÅ^{-3}$