Medicinal Chemistry Research

Supplementary material

Synthesis and evaluation of 2-methylbenzothiazole derivatives as monoamine oxidase inhibitors

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

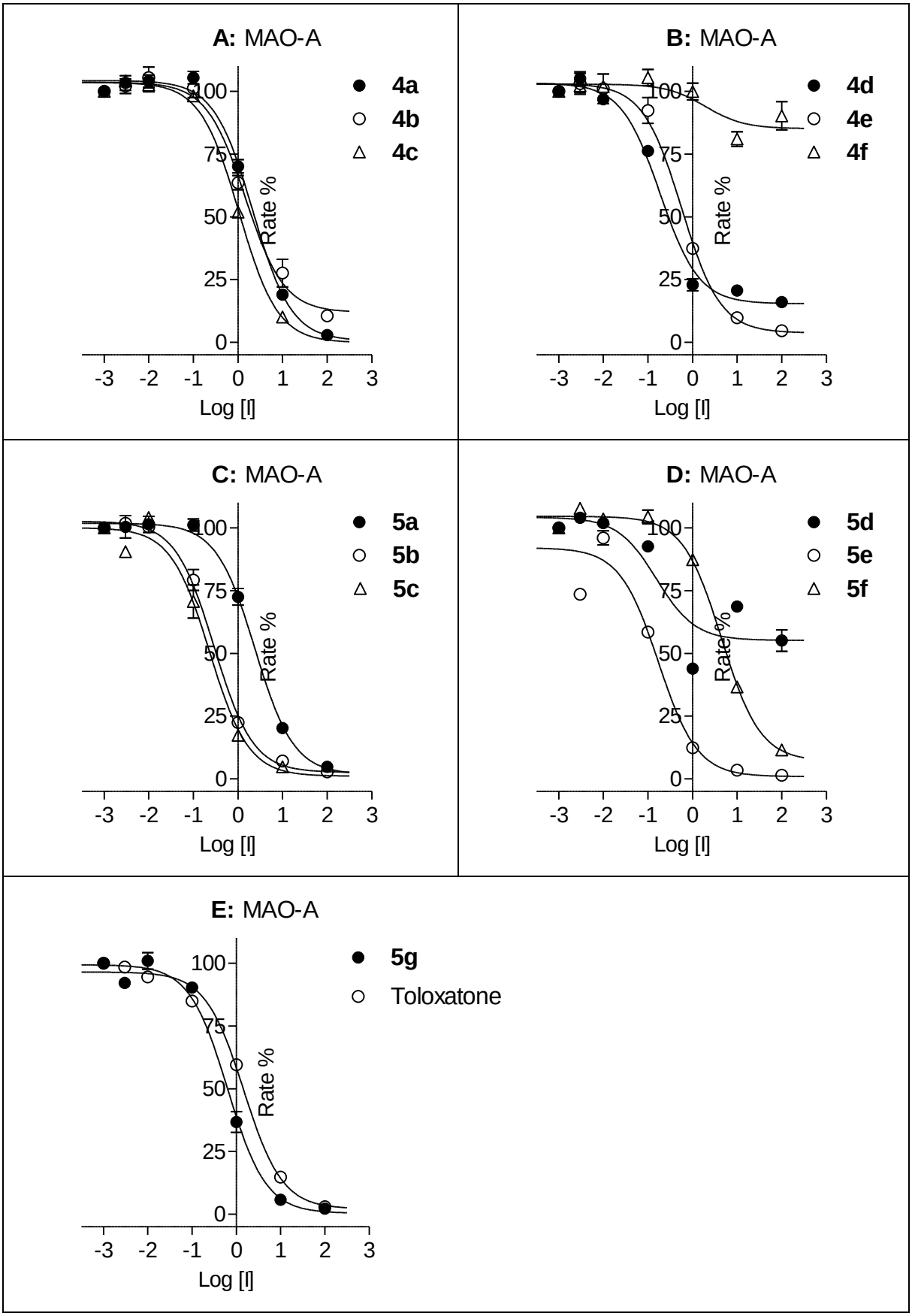


Fig. S1 Sigmoidal plots for the inhibition of MAO-A by the 2-methylbenzo[*d*]thiazole derivatives (**4a**–**f**, **5a**–**g**)

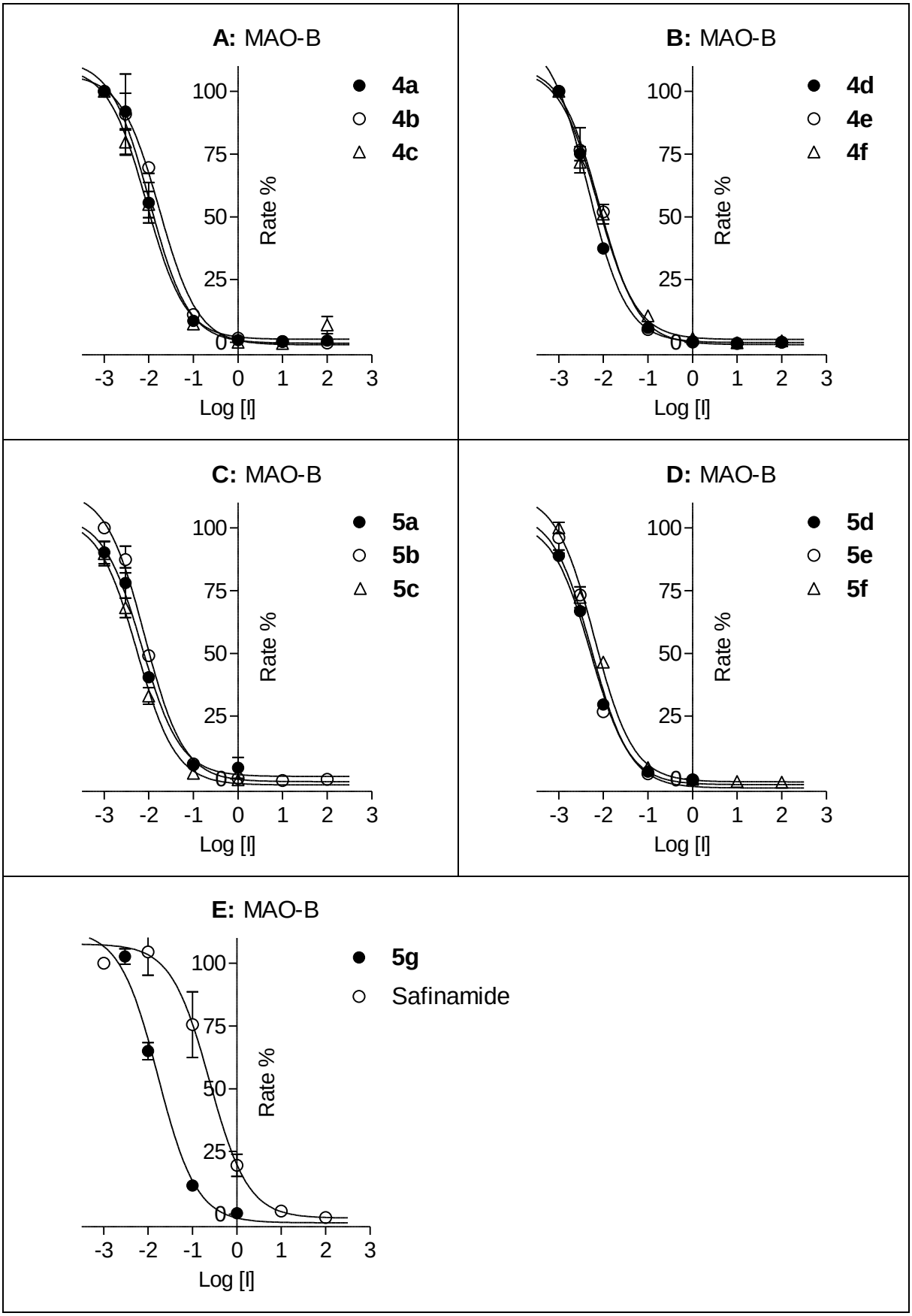
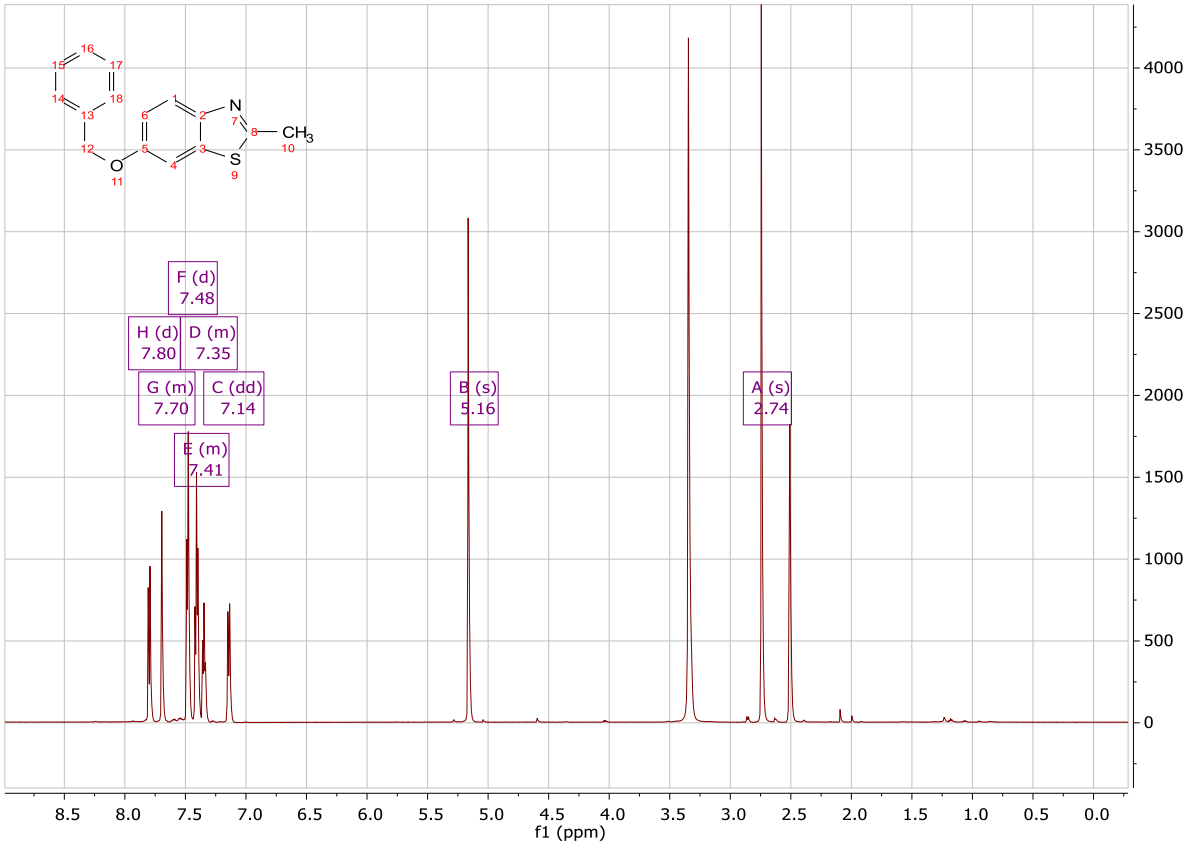
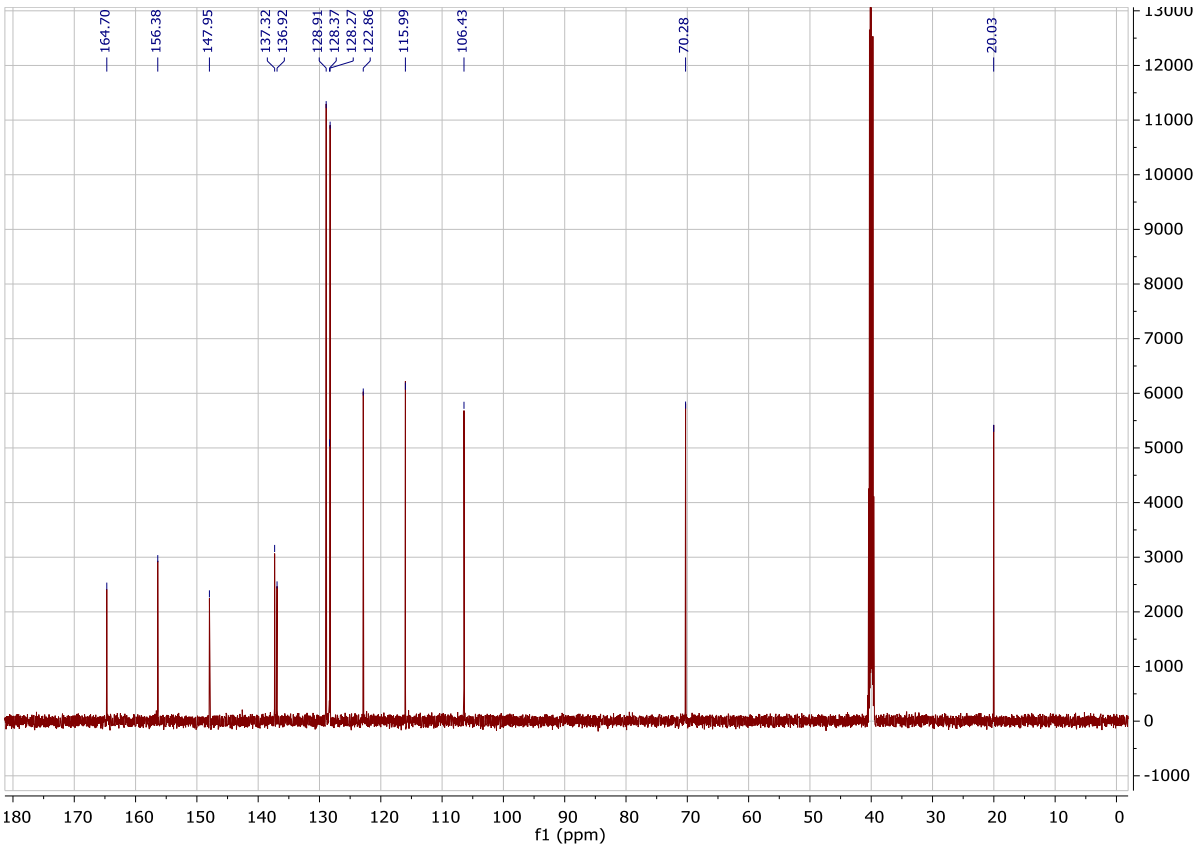


Fig. S2 Sigmoidal plots for the inhibition of MAO-B by the 2-methylbenzo[*d*]thiazole derivatives (**4a**–**f**, **5a**–**g**)

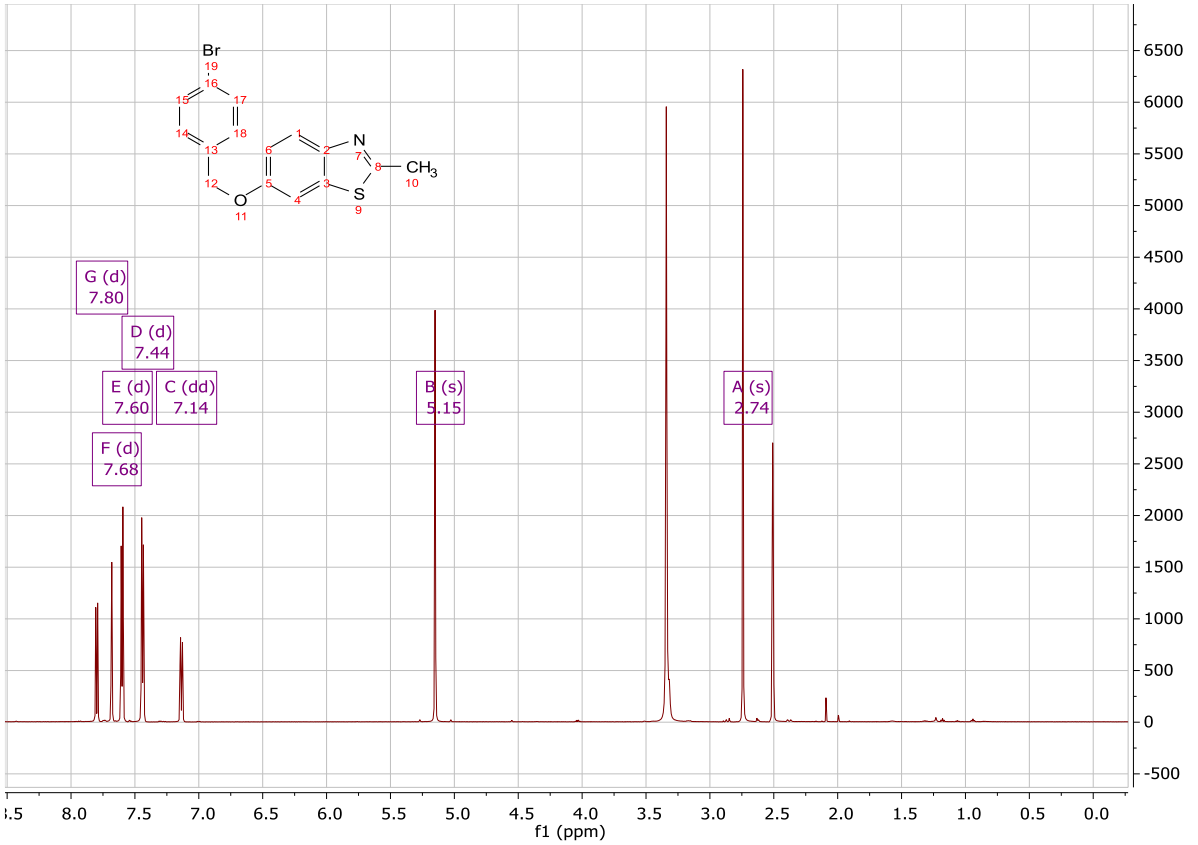
NMR spectra

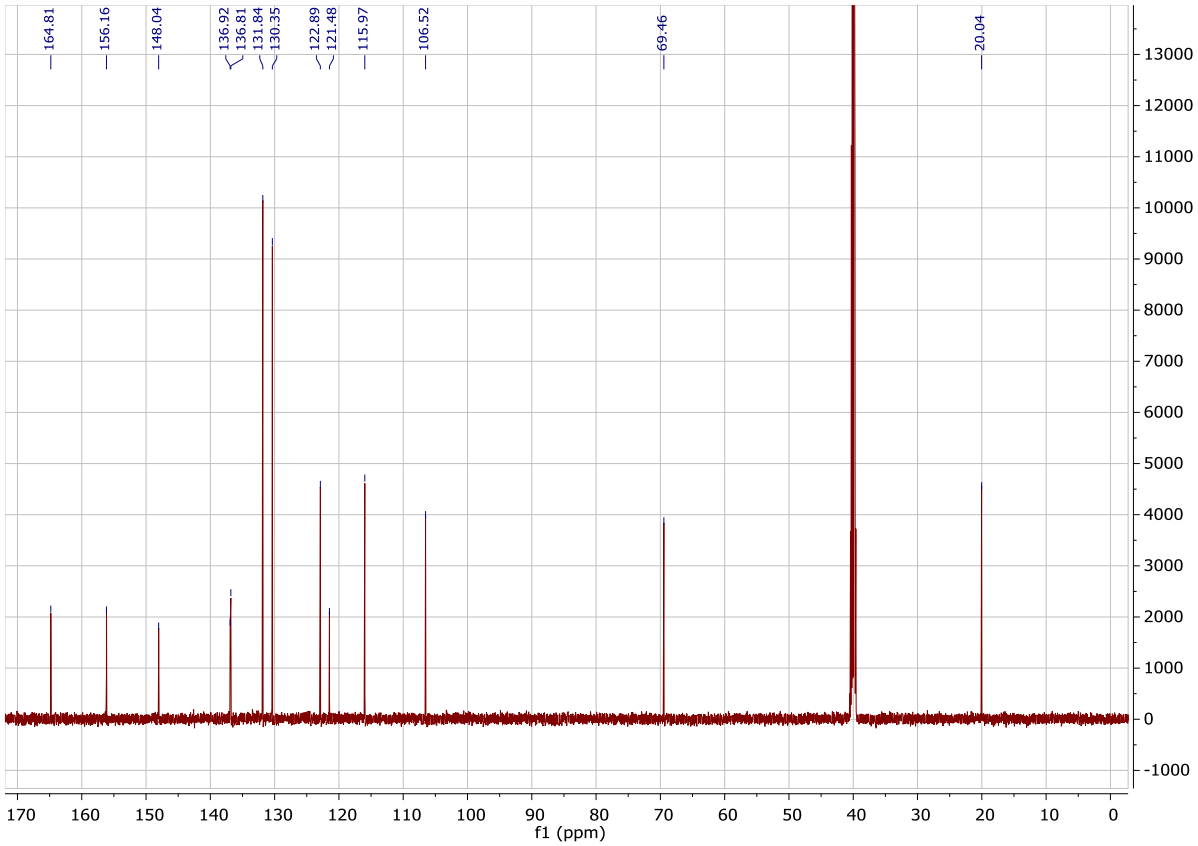
6-(Benzyloxy)-2-methylbenzo[*d*]thiazole **(4a)**



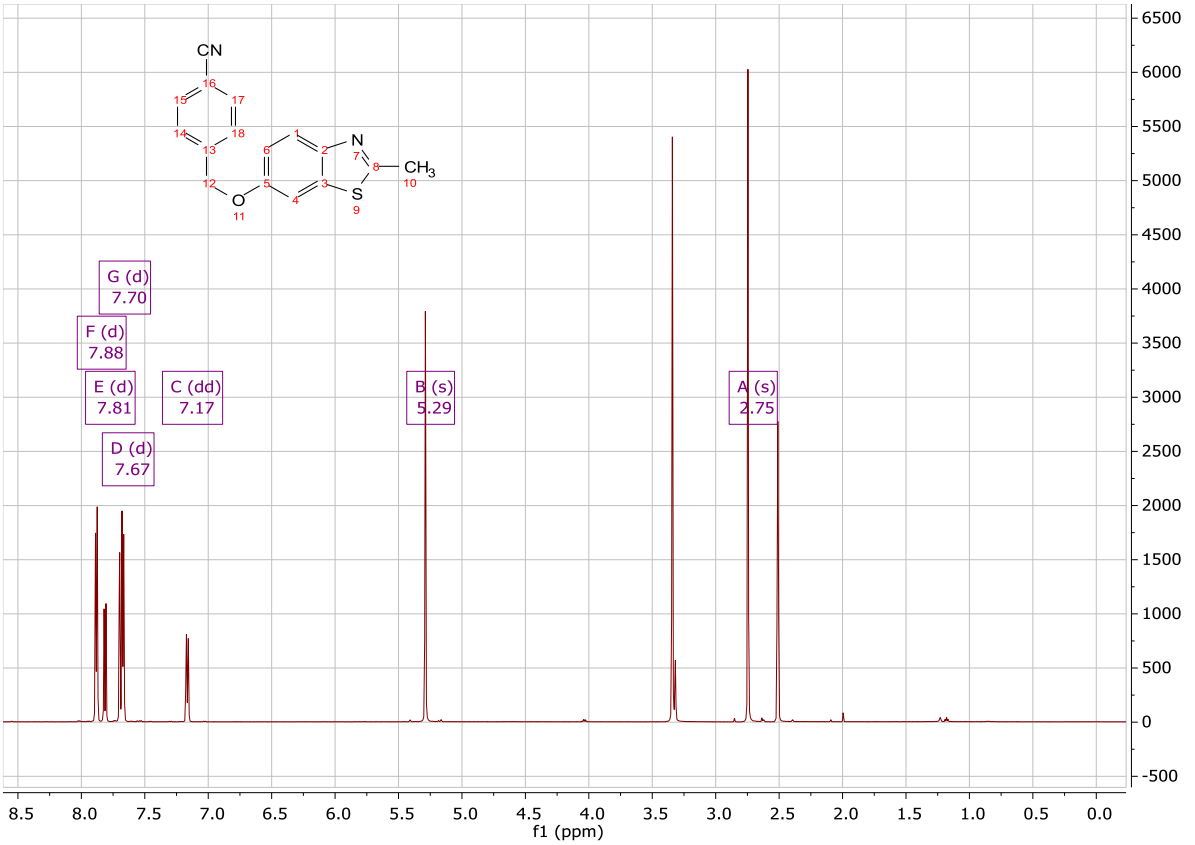


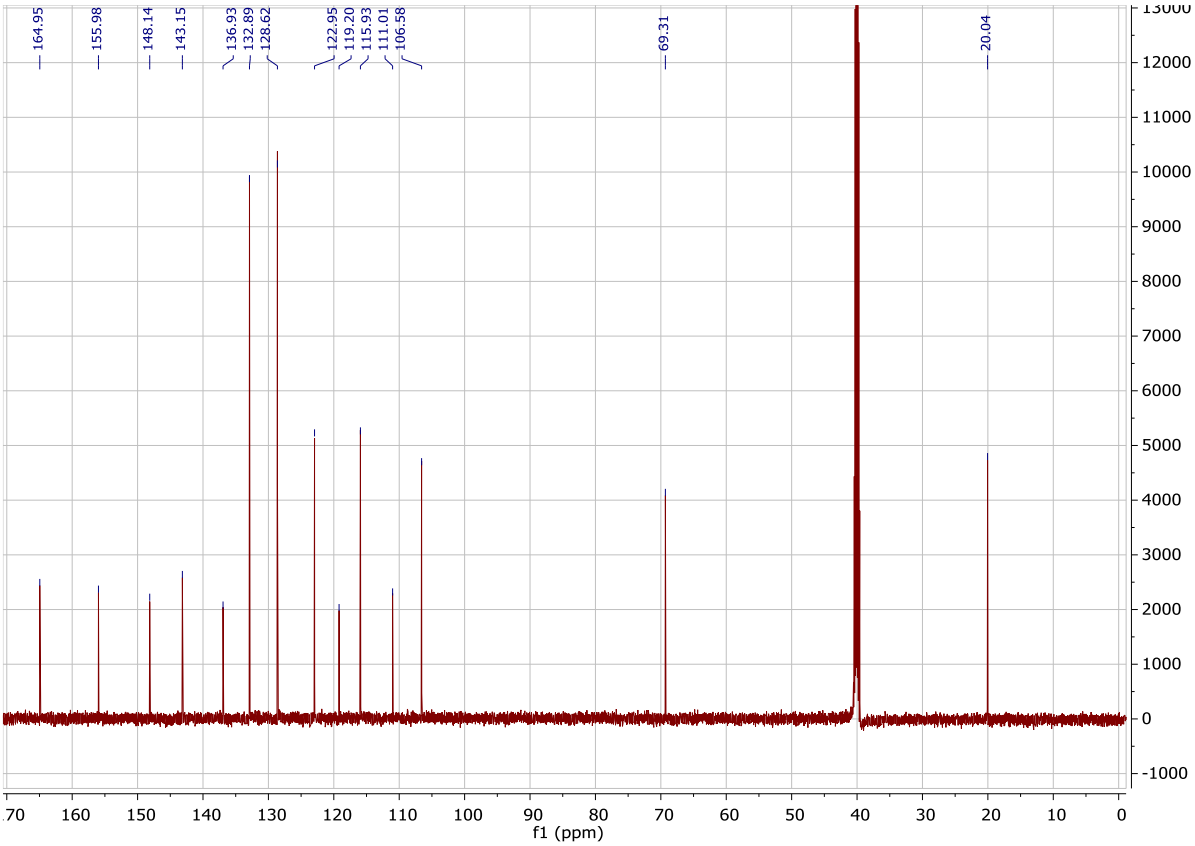
6-((4-Bromobenzyl)oxy)-2-methylbenzo[*d*]thiazole **(4b)**



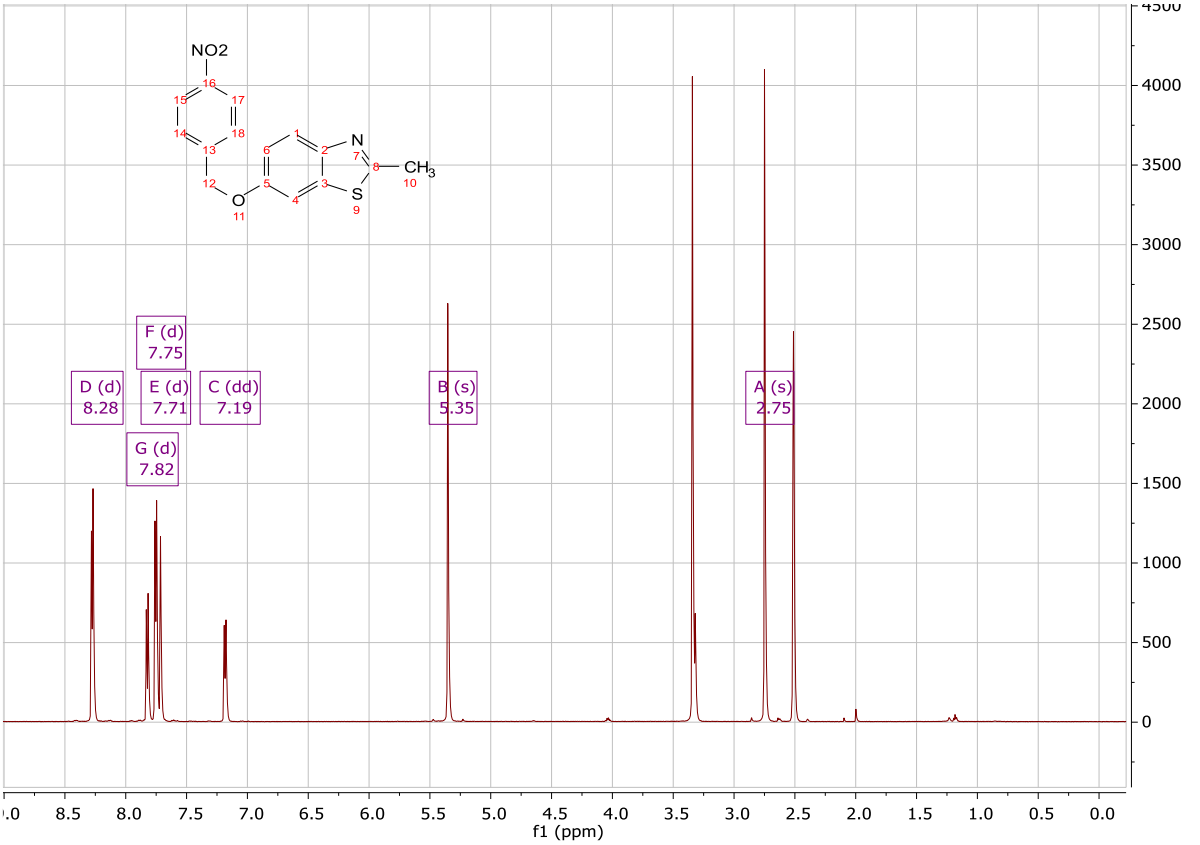


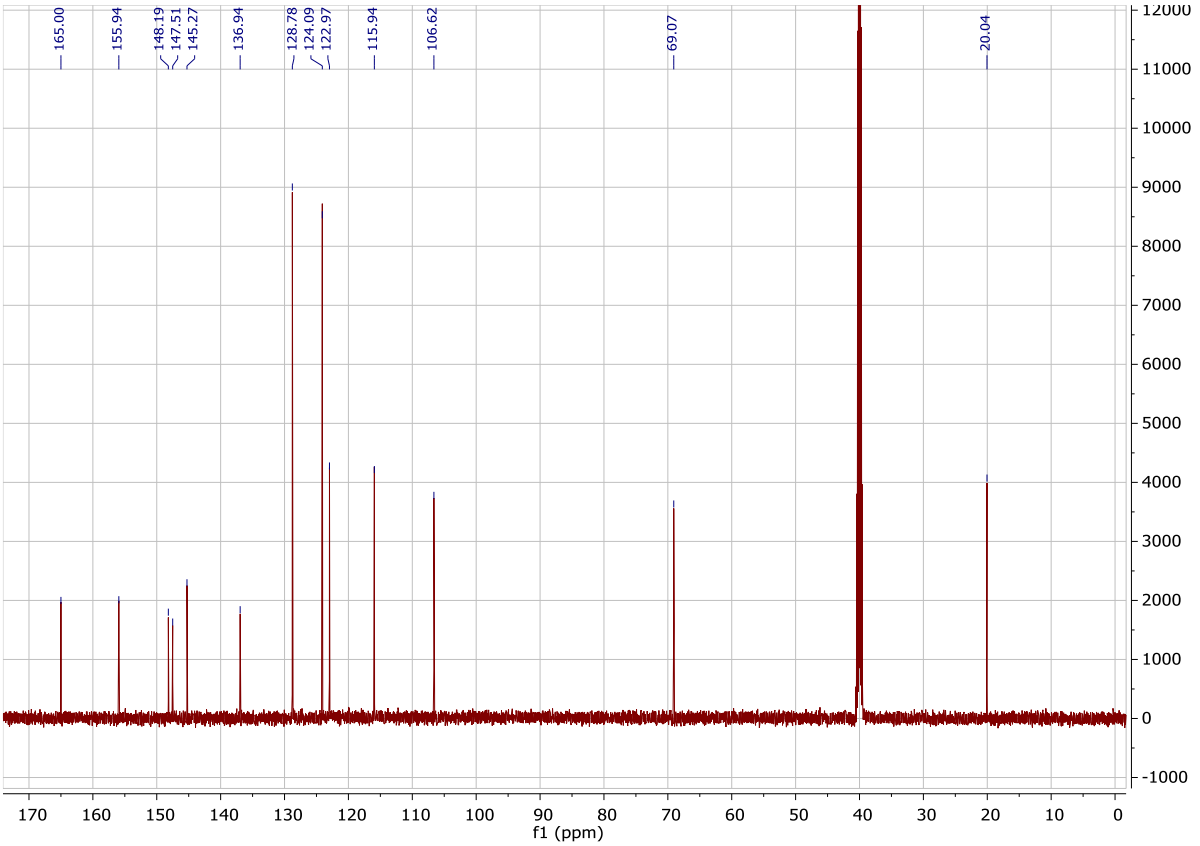
4-(((2-Methylbenzo[*d*]thiazol-6-yl)oxy)methyl)benzonitrile **(4c)**



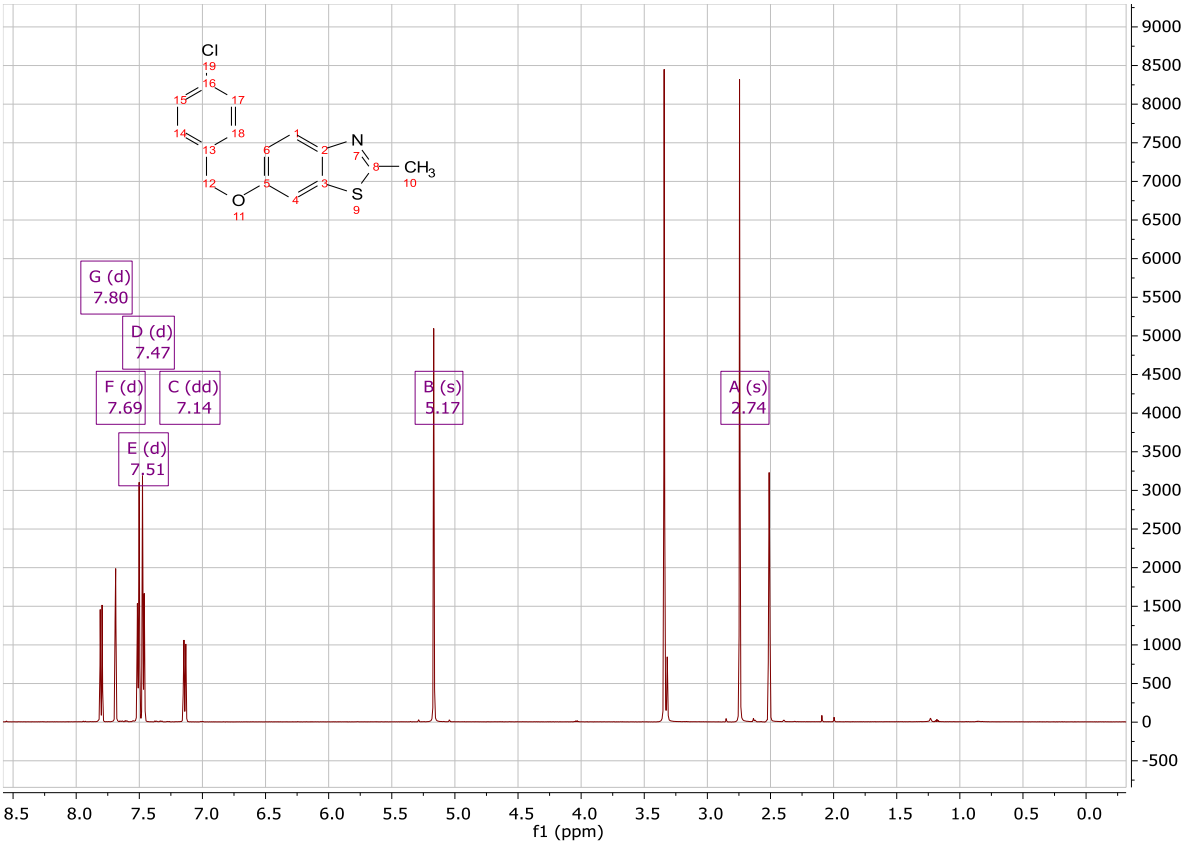


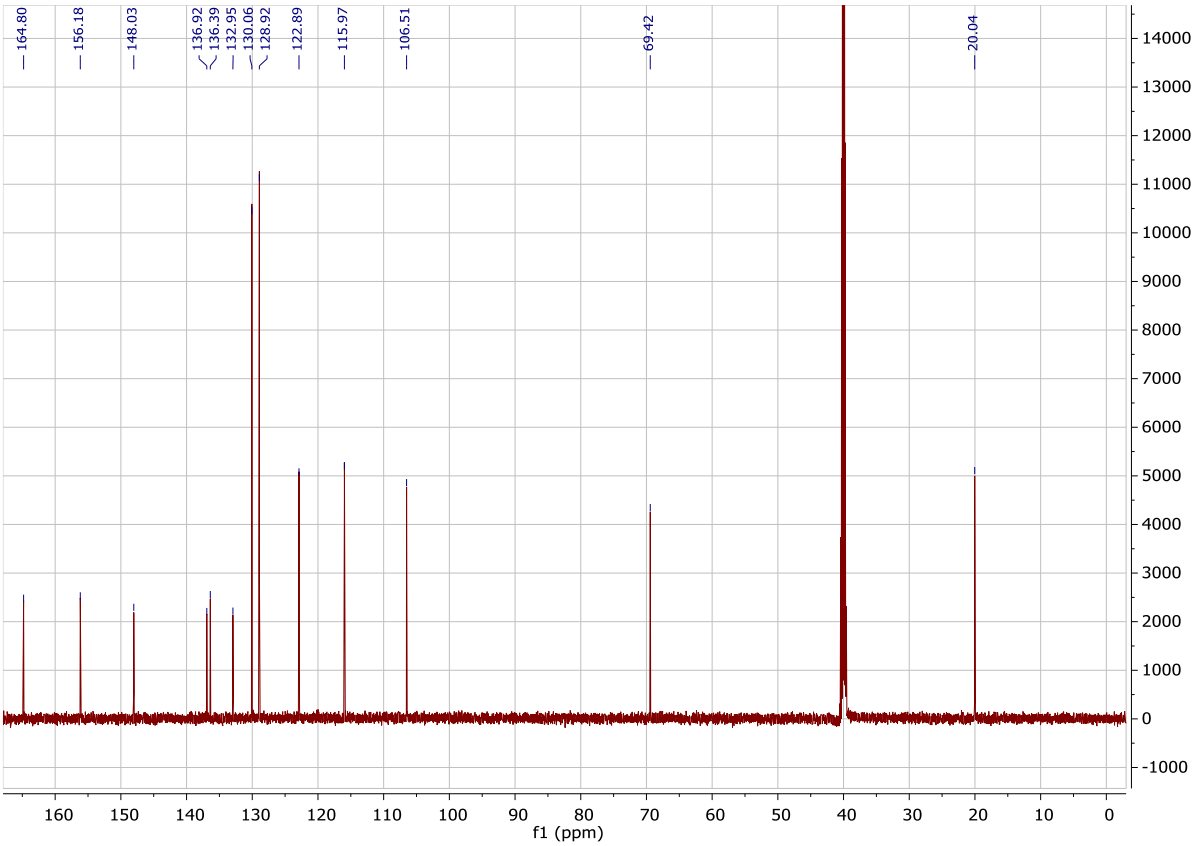
2-Methyl-6-((4-nitrobenzyl)oxy)benzo[*d*]thiazole **(4d)**



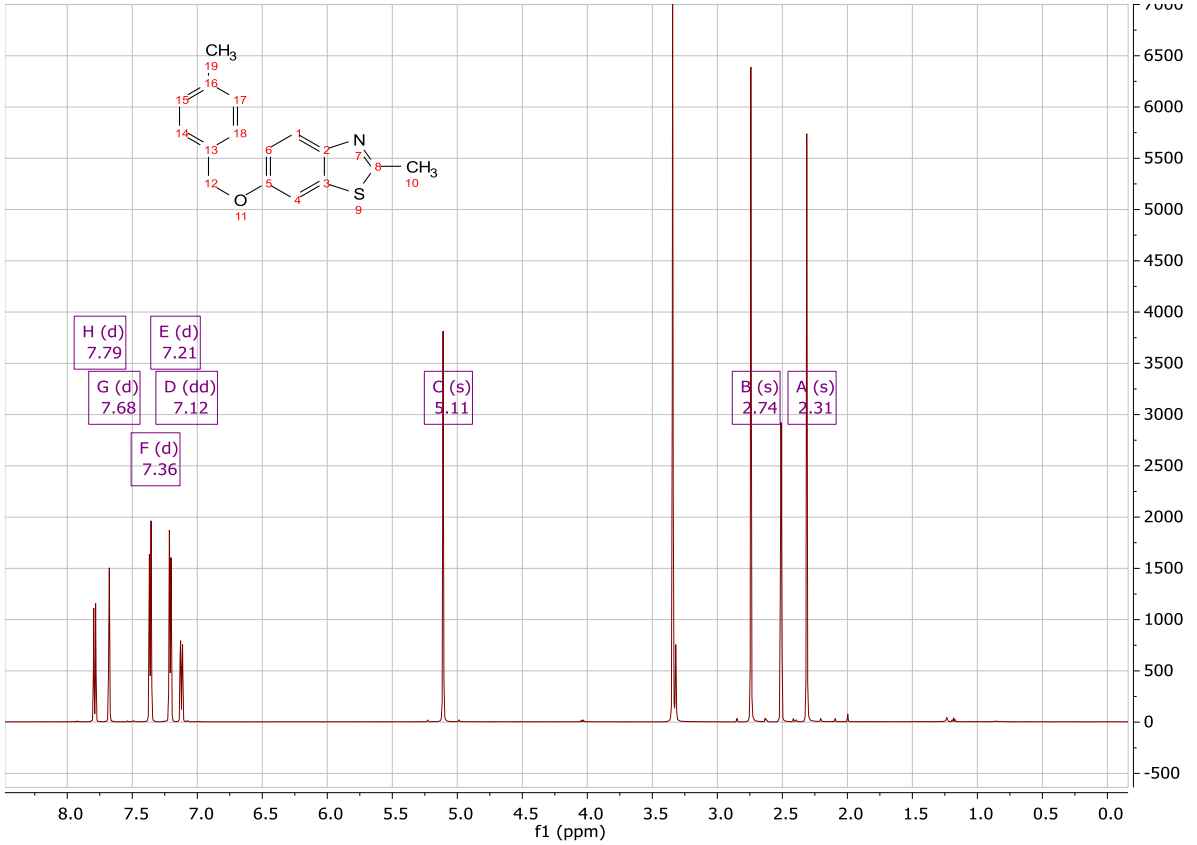


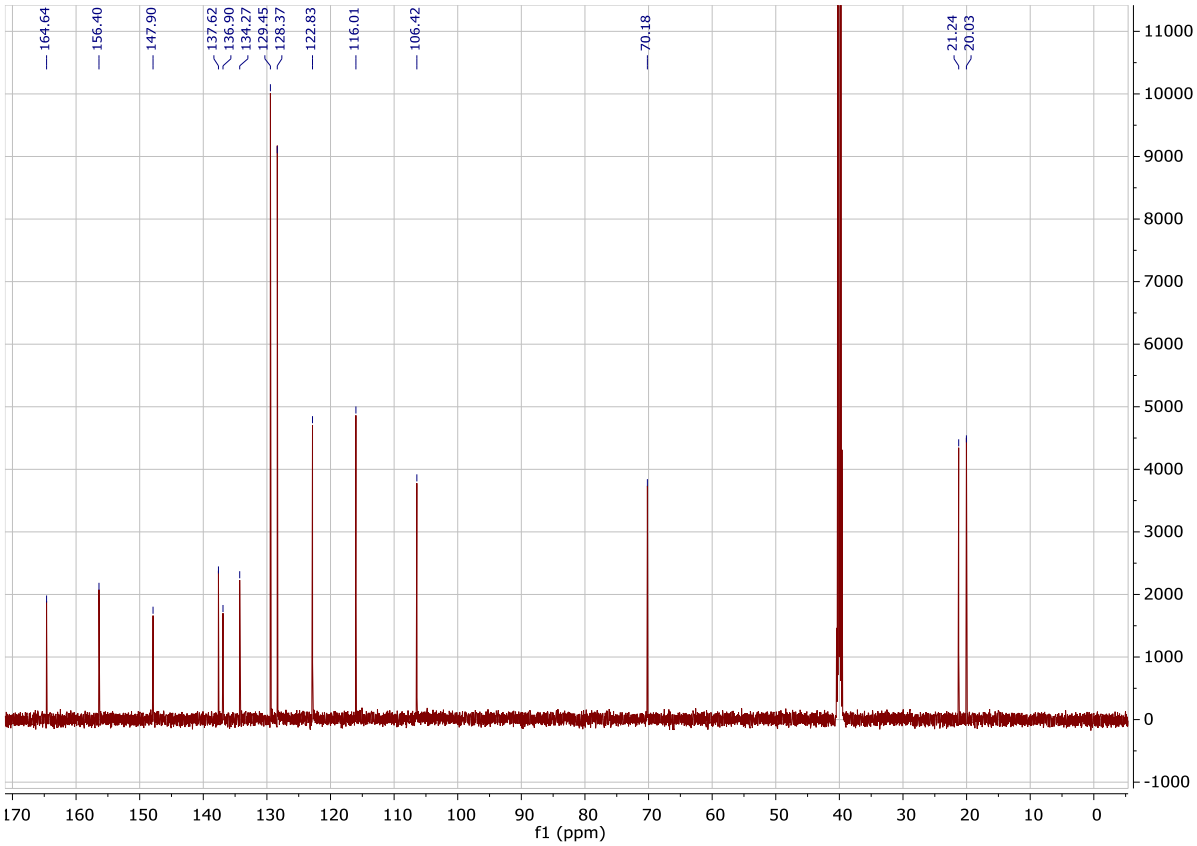
6-((4-Chlorobenzyl)oxy)-2-methylbenzo[*d*]thiazole **(4e)**



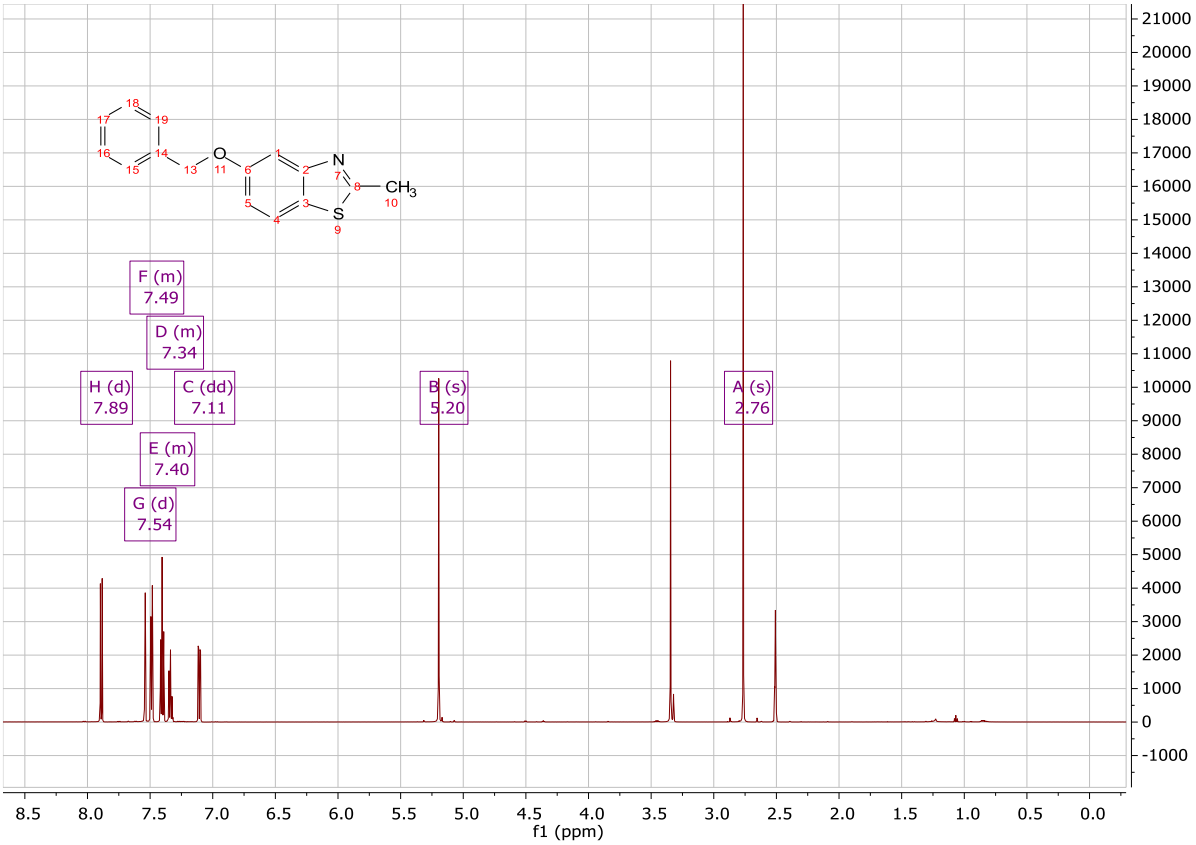


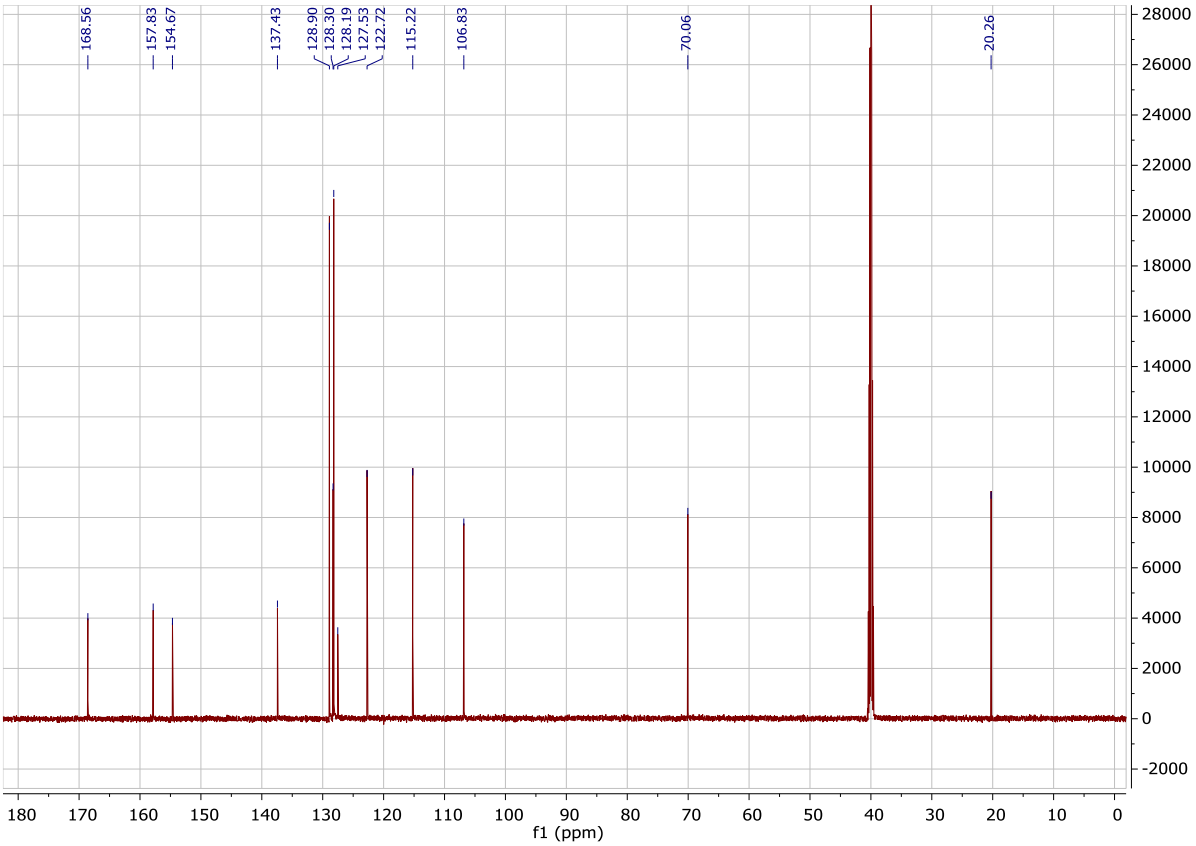
2-Methyl-6-((4-methylbenzyl)oxy)benzo[*d*]thiazole **(4f)**



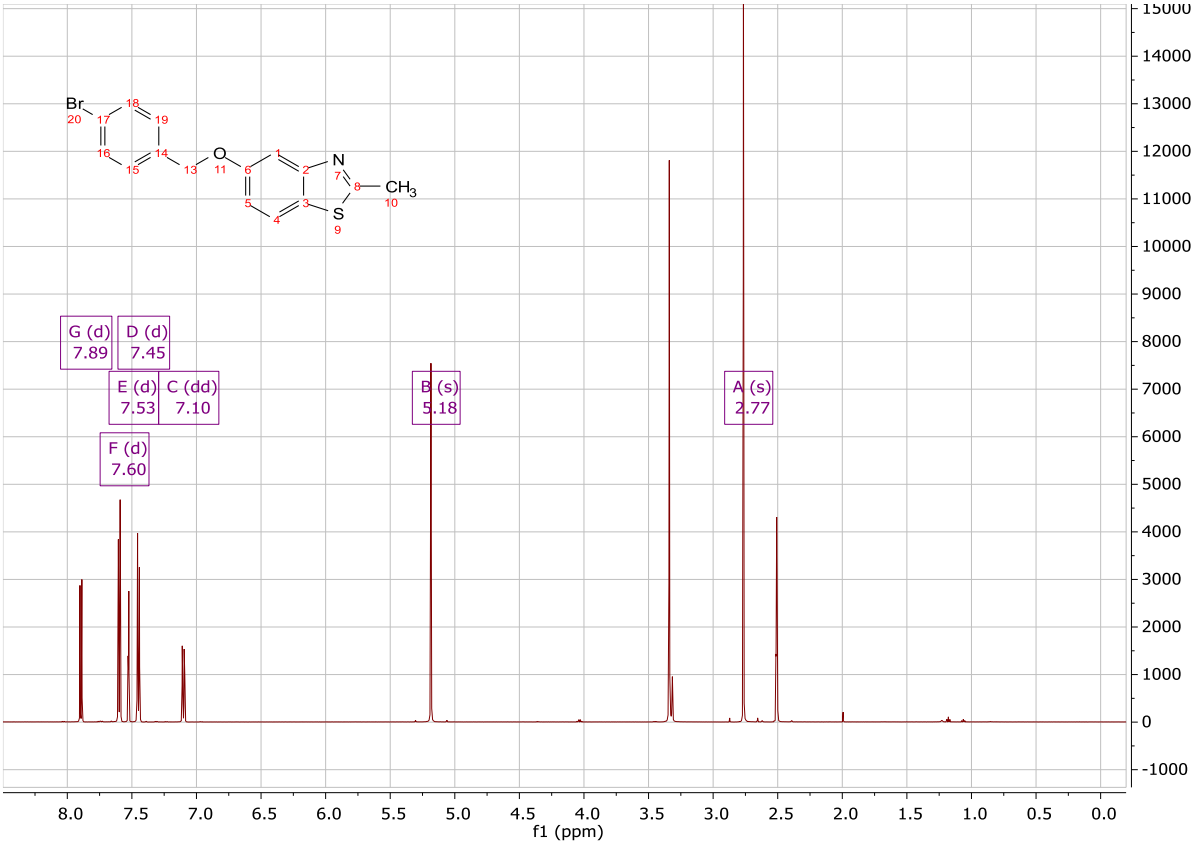


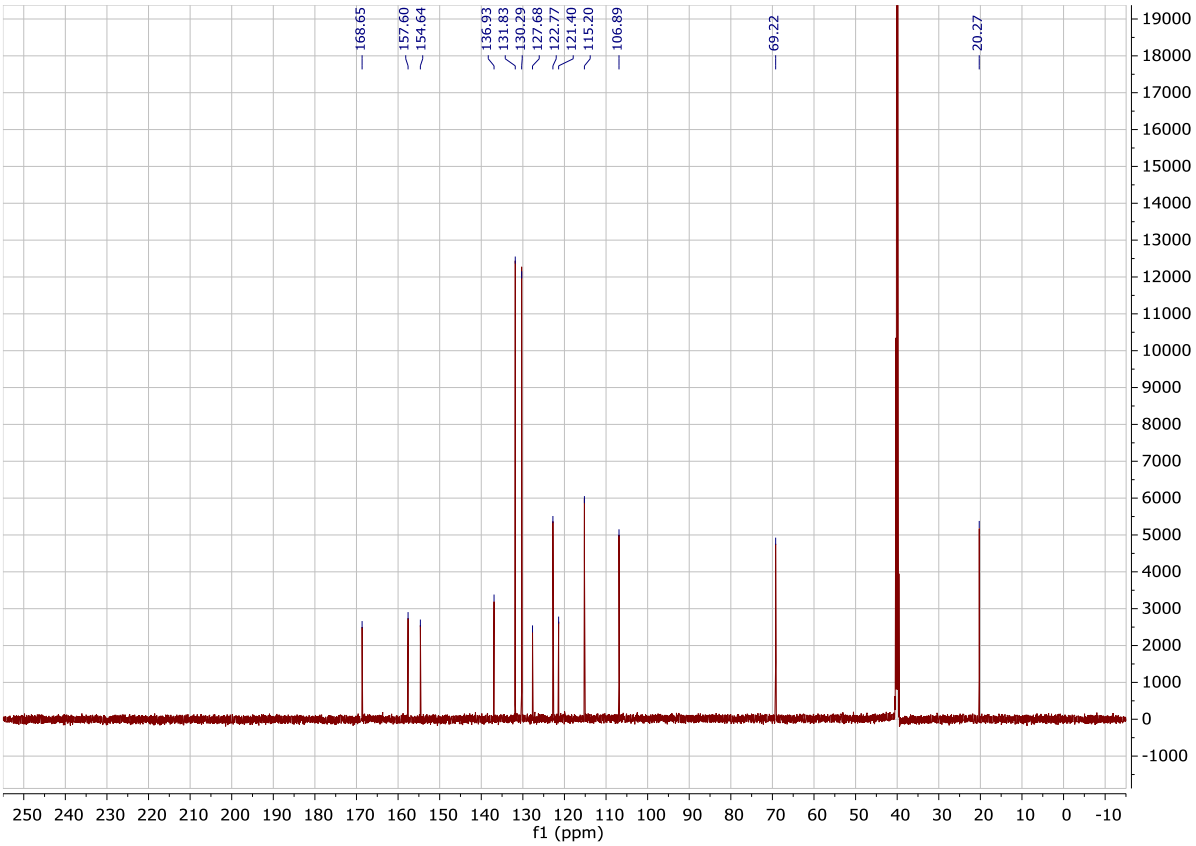
5-(Benzyloxy)-2-methylbenzo[*d*]thiazole **(5a)**



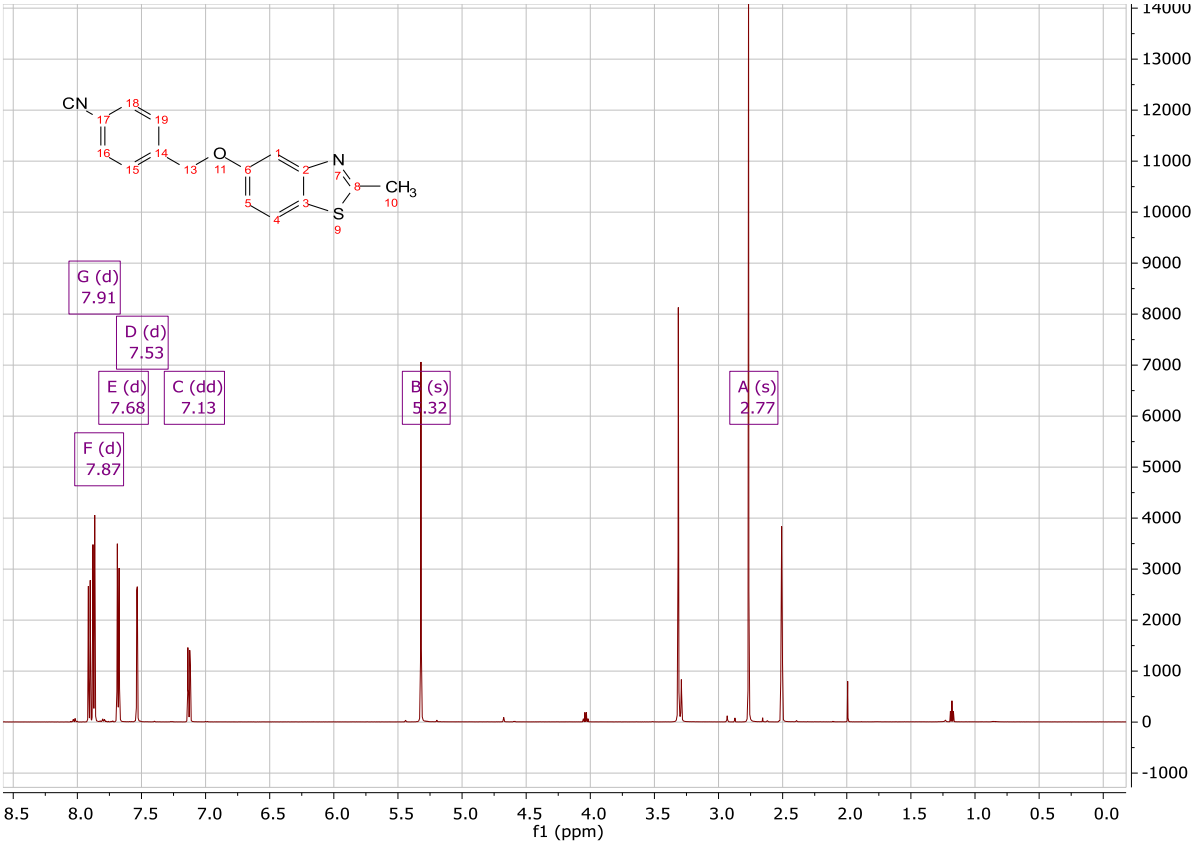


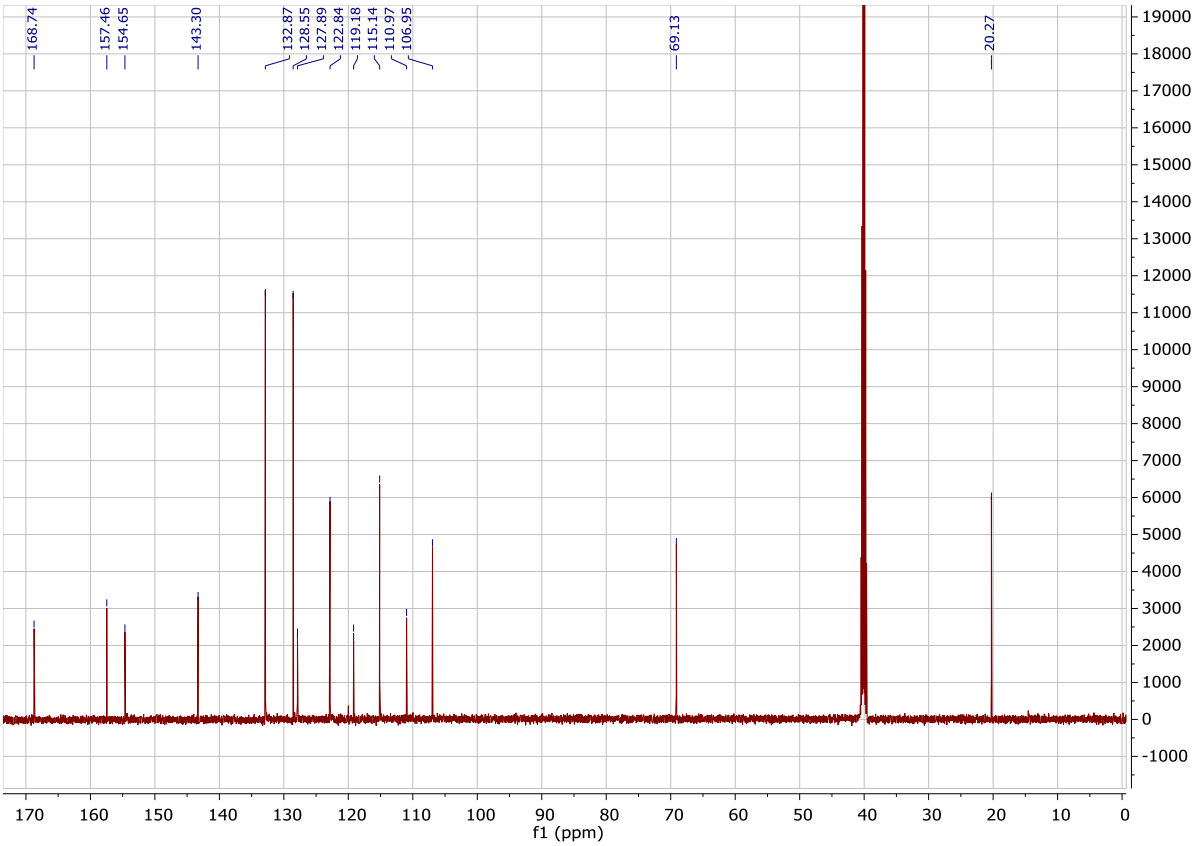
5-((4-Bromobenzyl)oxy)-2-methylbenzo[*d*]thiazole **(5b)**



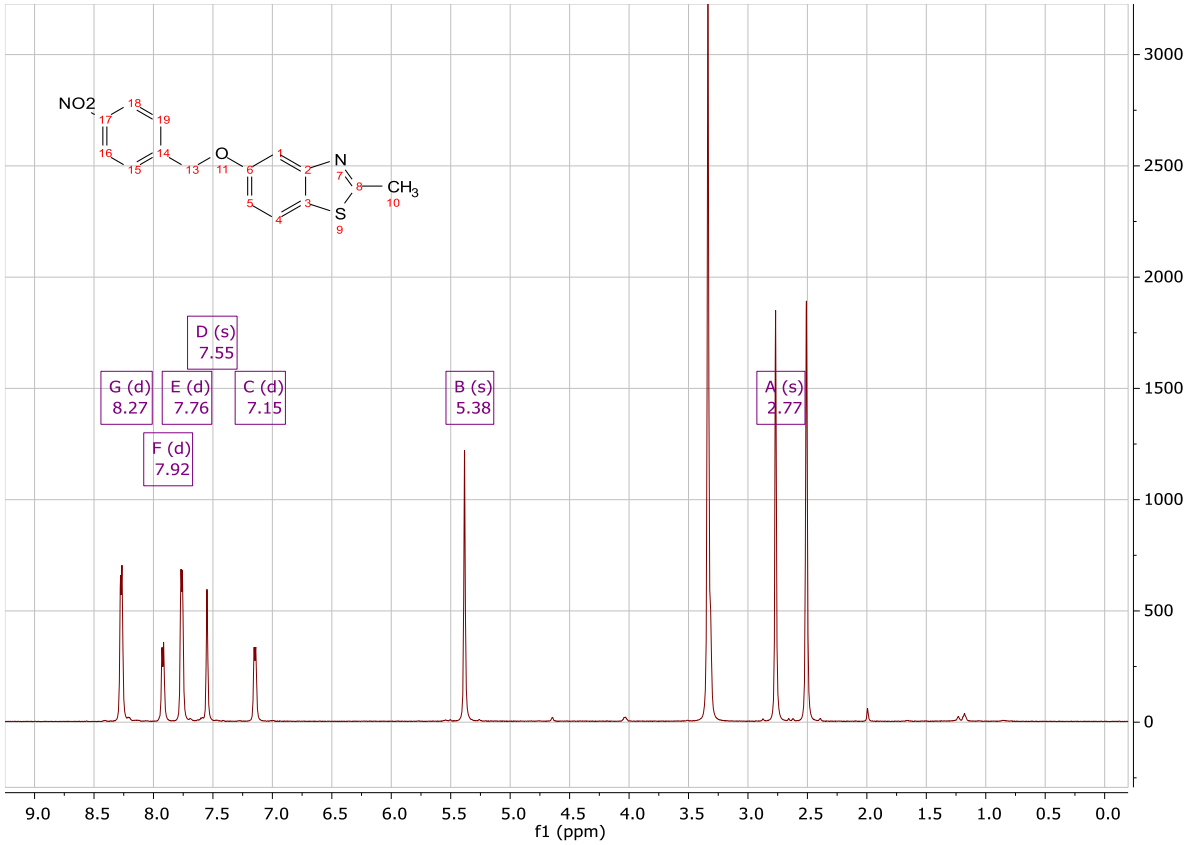


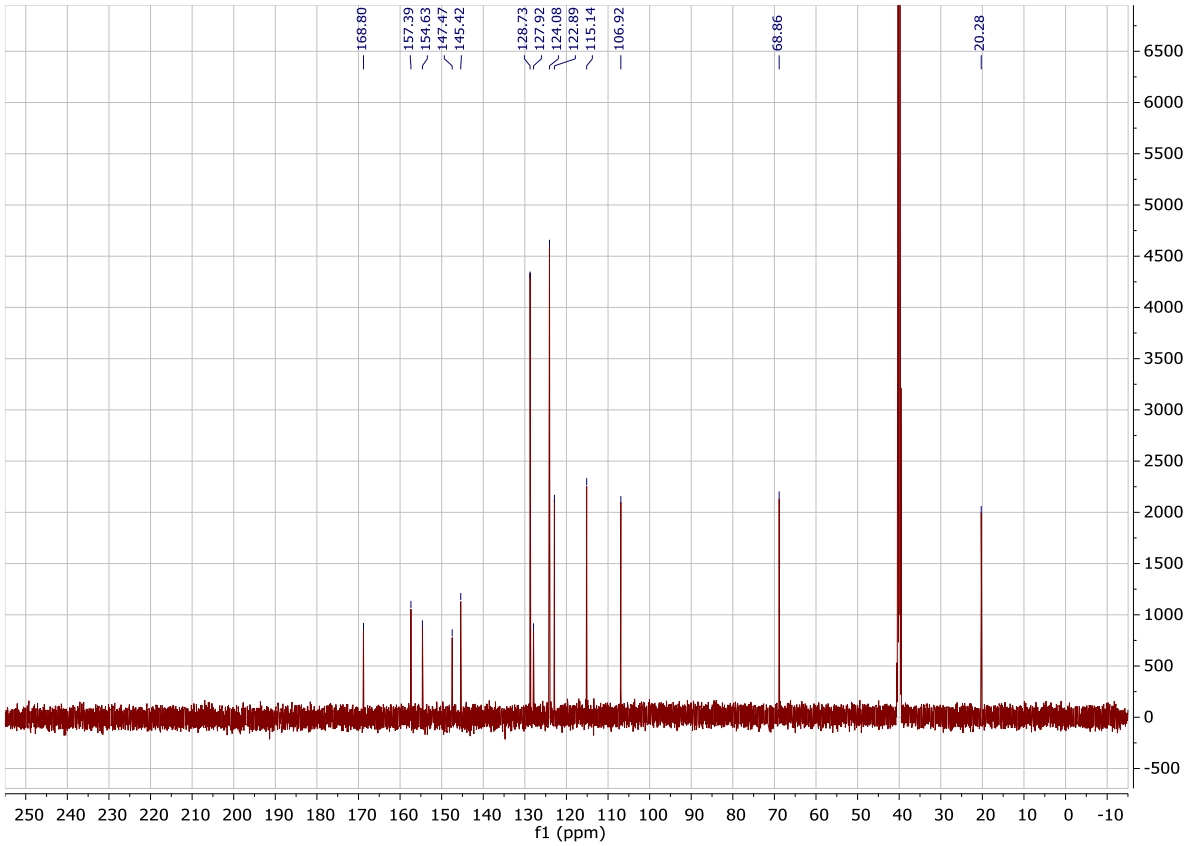
4-(((2-Methylbenzo[*d*]thiazol-5-yl)oxy)methyl)benzonitrile **(5c)**



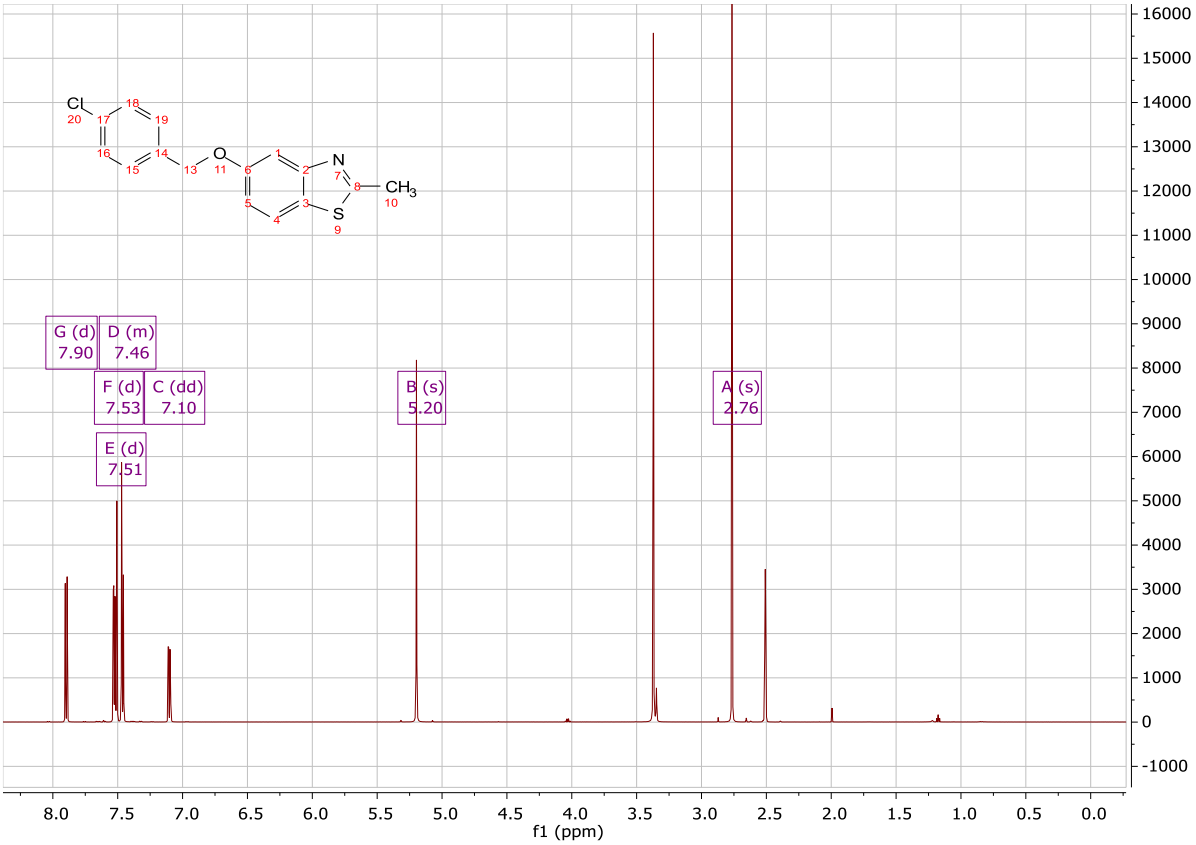


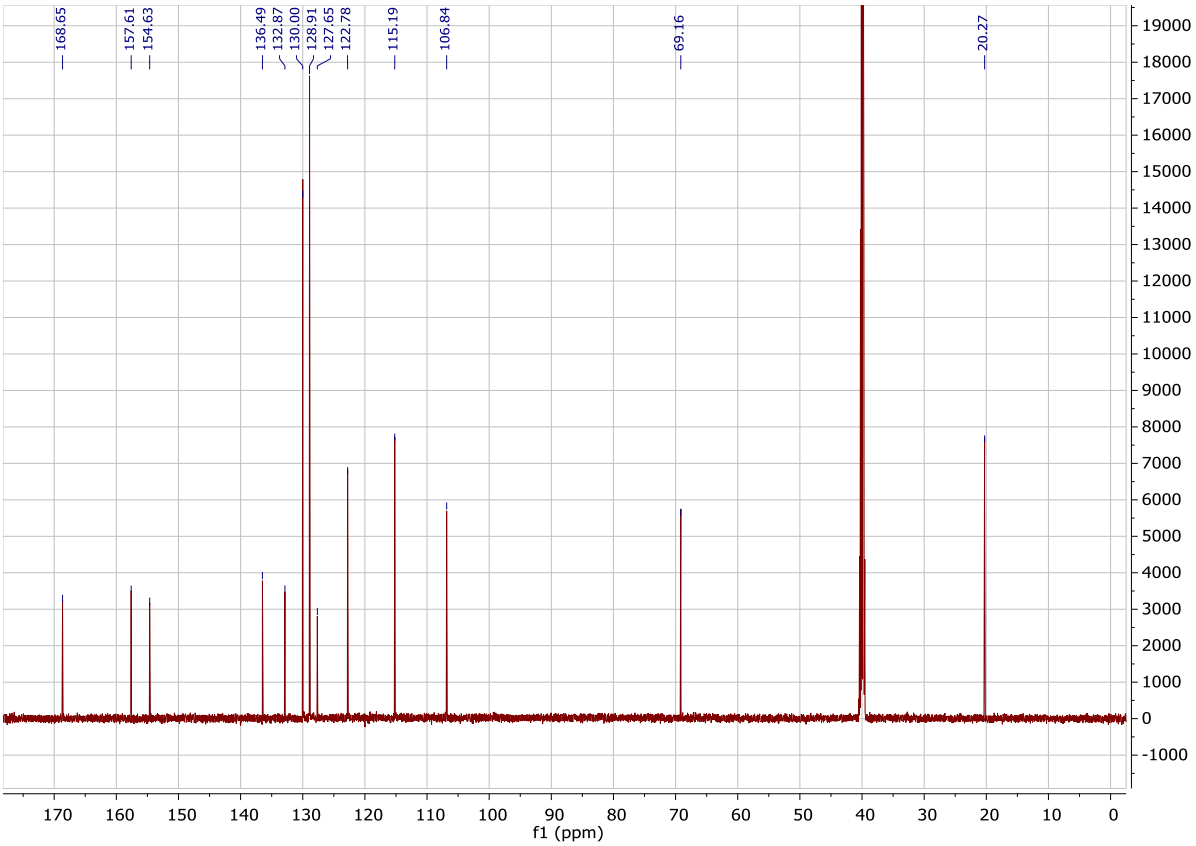
2-Methyl-5-((4-nitrobenzyl)oxy)benzo[*d*]thiazole **(5d)**



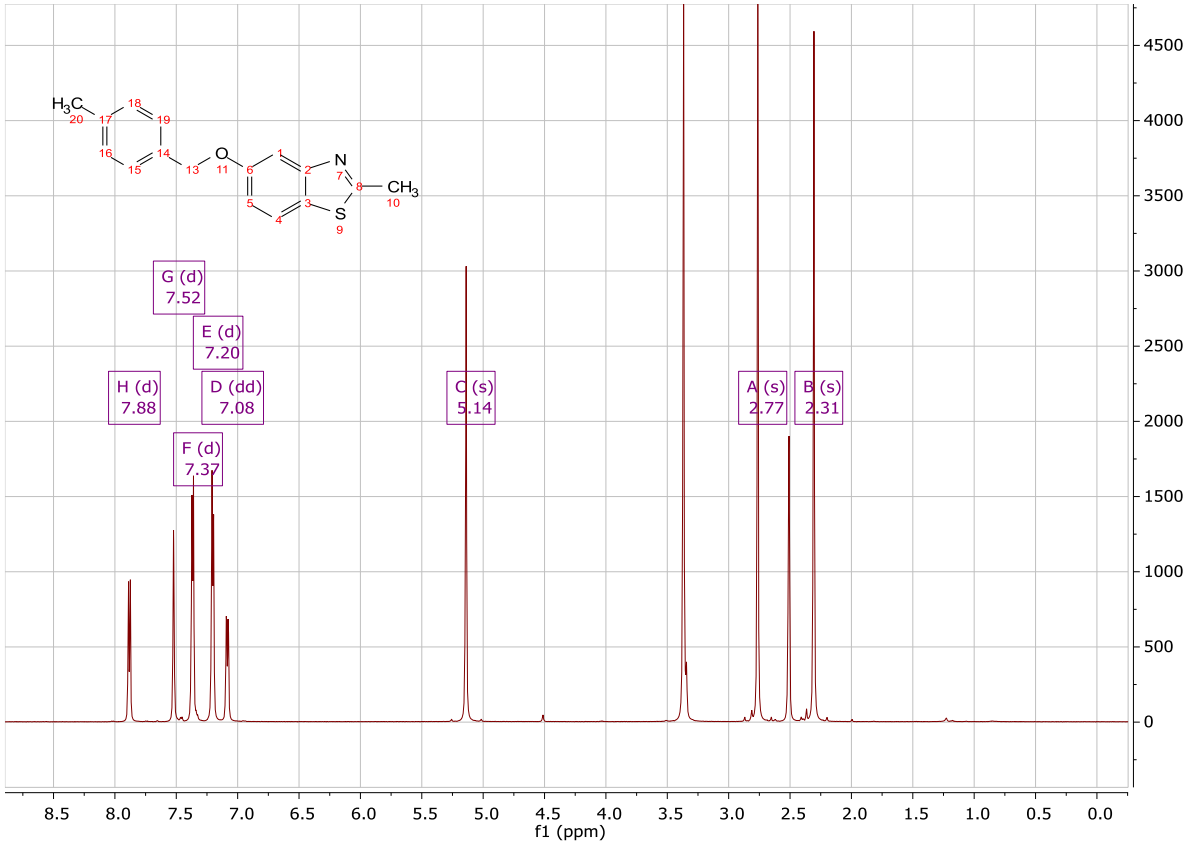


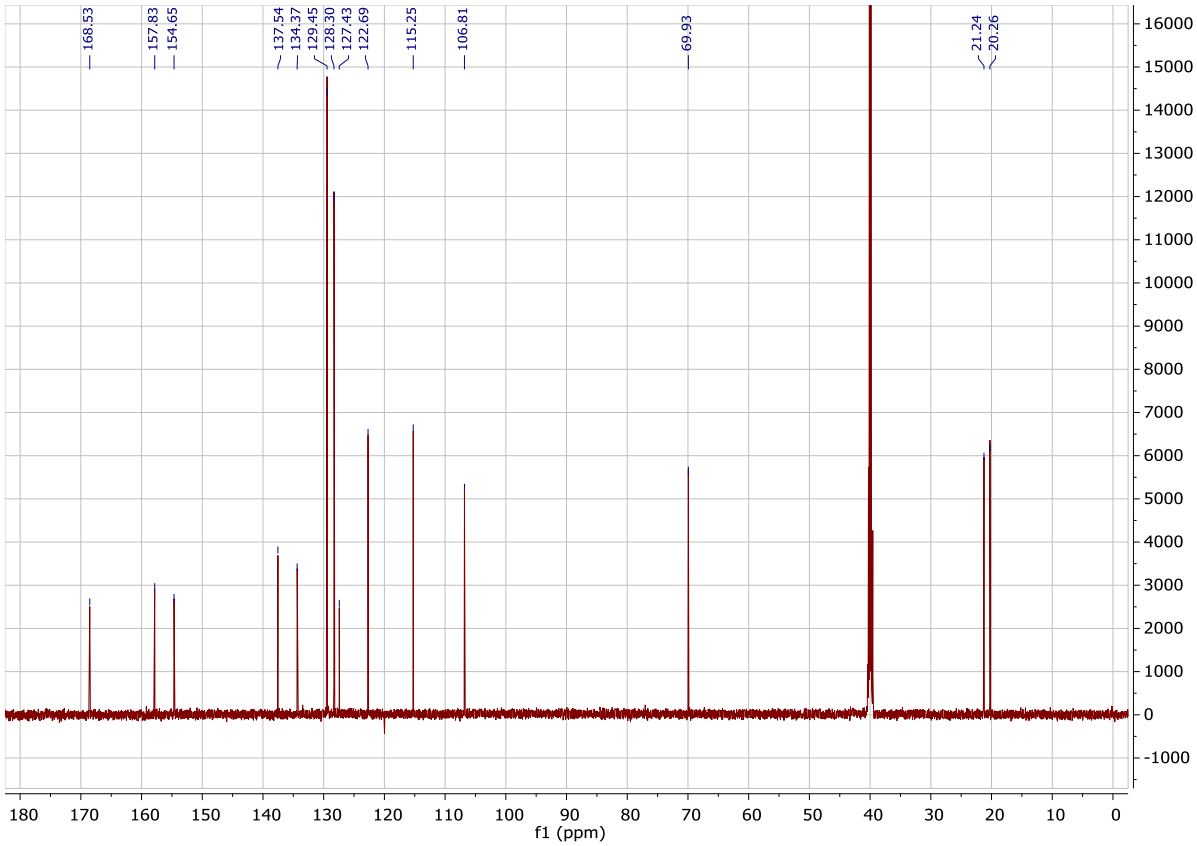
5-((4-Chlorobenzyl)oxy)-2-methylbenzo[*d*]thiazole **(5e)**



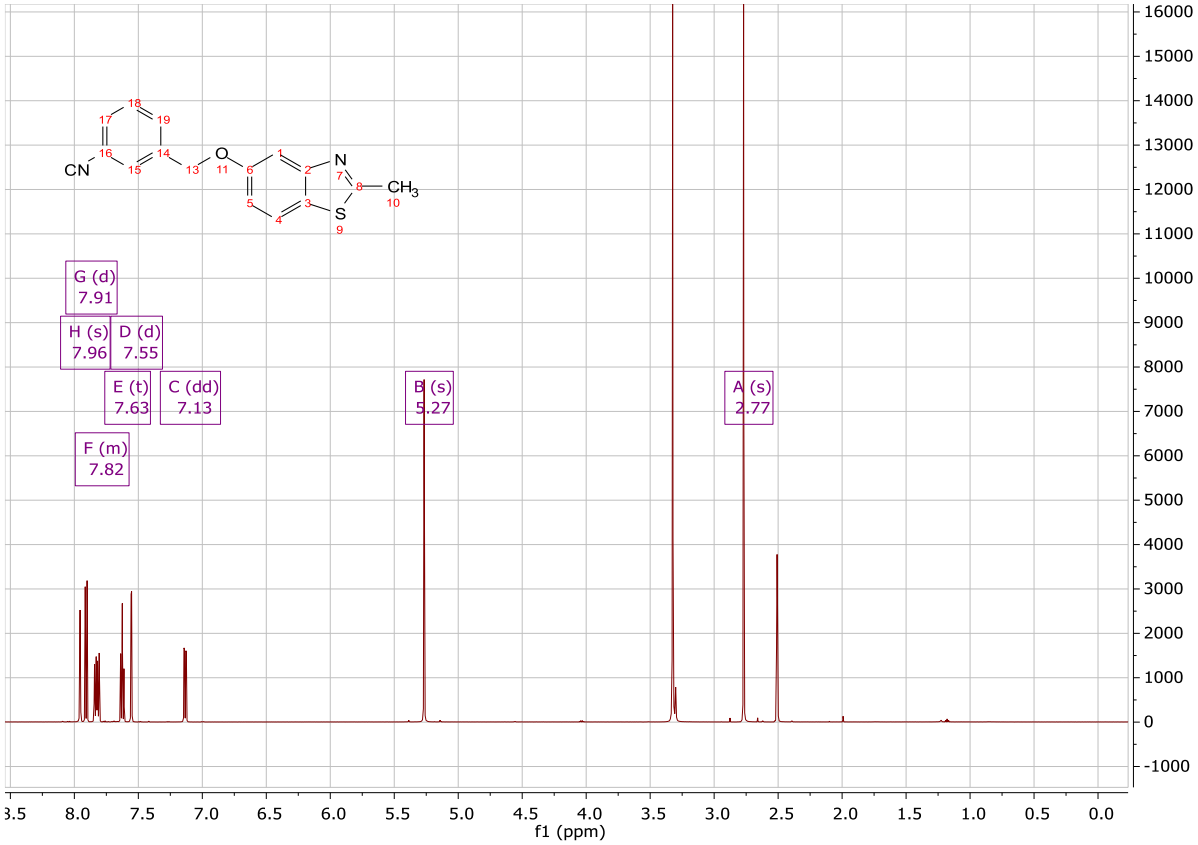


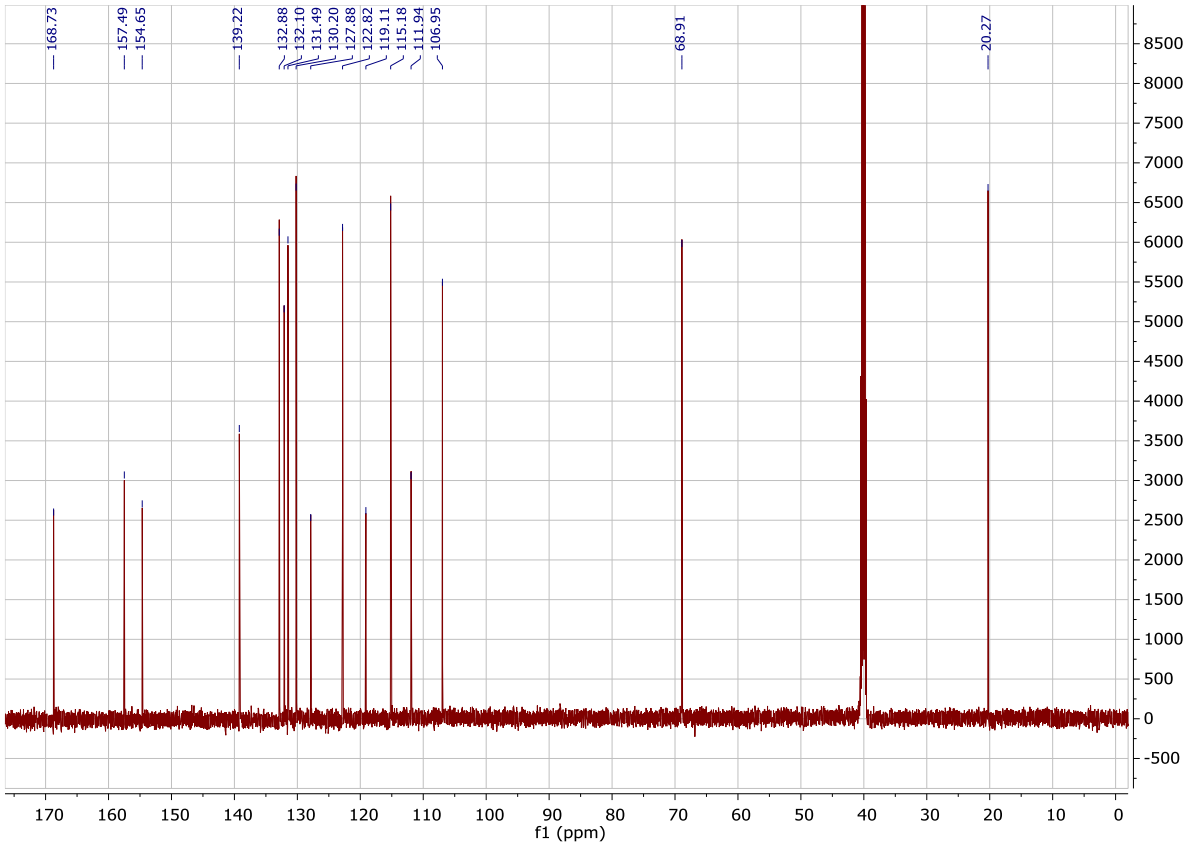
2-Methyl-5-((4-methylbenzyl)oxy)benzo[*d*]thiazole **(5f)**





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



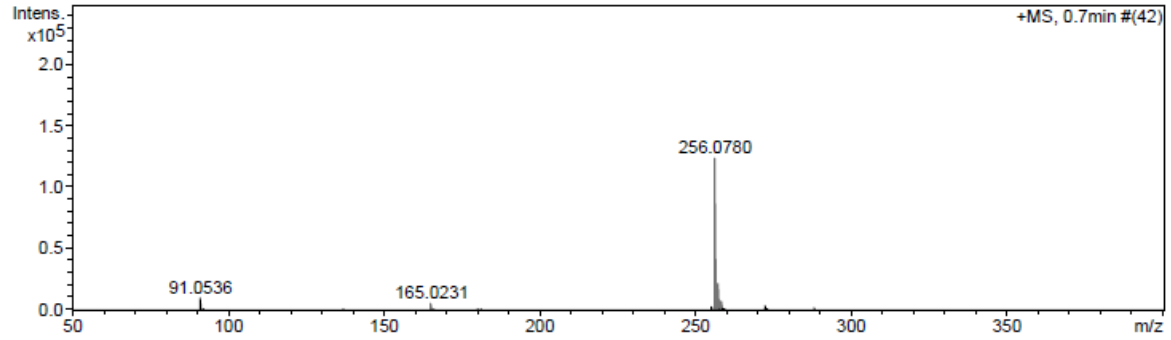


Mass spectra

6-(Benzyloxy)-2-methylbenzo[*d*]thiazole **(4a)**

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

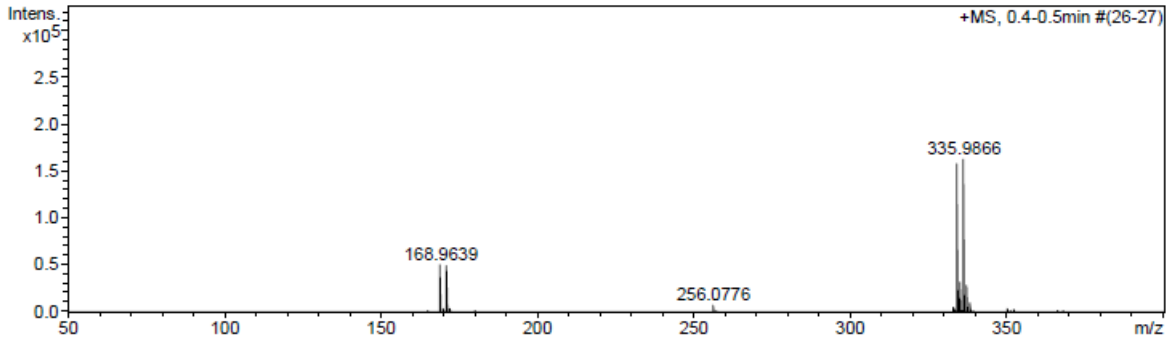


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e¯ Conf	N-Rule
256.0780	1	C 15 H 14 N O S	100.00	256.0791	1.0	4.0	1.3	9.5	even	ok

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

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

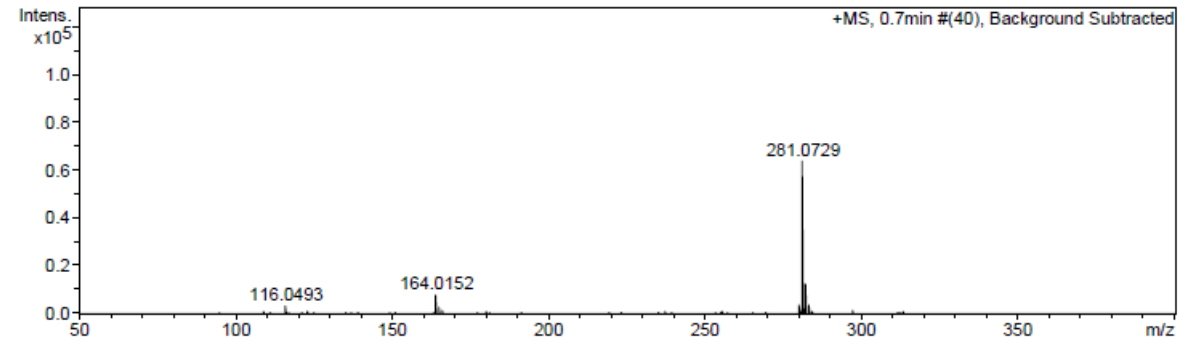


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e¯ Conf	N-Rule
168.9639	1	C 7 H 6 Br	100.00	168.9647	0.8	4.8	8.2	4.5	even	ok
	2	C 4 H 10 Br S	3.69	168.9681	4.2	24.7	26.2	-0.5	even	ok
	3	C 3 H 8 Br N S	0.00	168.9555	-8.4	-49.7	29.0	0.0	odd	ok
333.9885	1	C 15 H 13 Br N O S	100.00	333.9896	1.1	3.2	12.9	9.5	even	ok

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

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

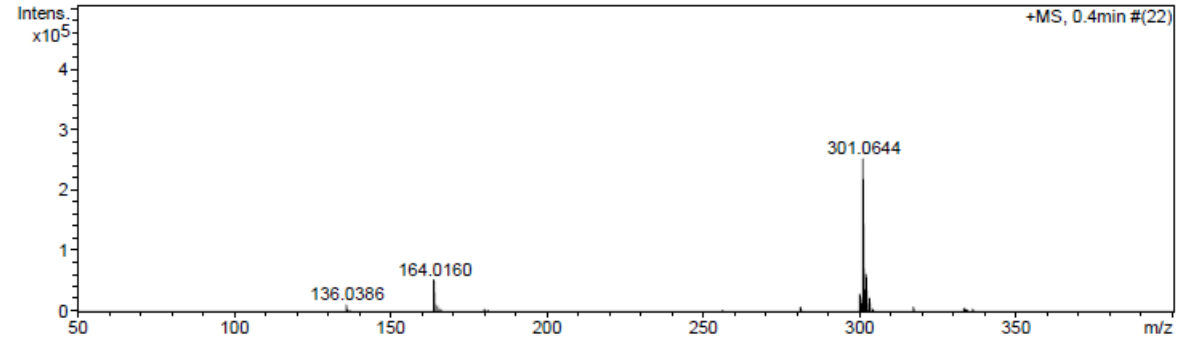


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e¯ Conf	N-Rule
164.0152	1	C 8 H 6 N O S	100.00	164.0165	1.3	7.7	144.6	6.5	even	ok
	2	C 11 H 2 N O	13.68	164.0131	-2.1	-12.8	165.3	11.5	even	ok
281.0729	1	C 16 H 13 N 2 O S	100.00	281.0743	1.4	4.9	2.3	11.5	even	ok

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

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

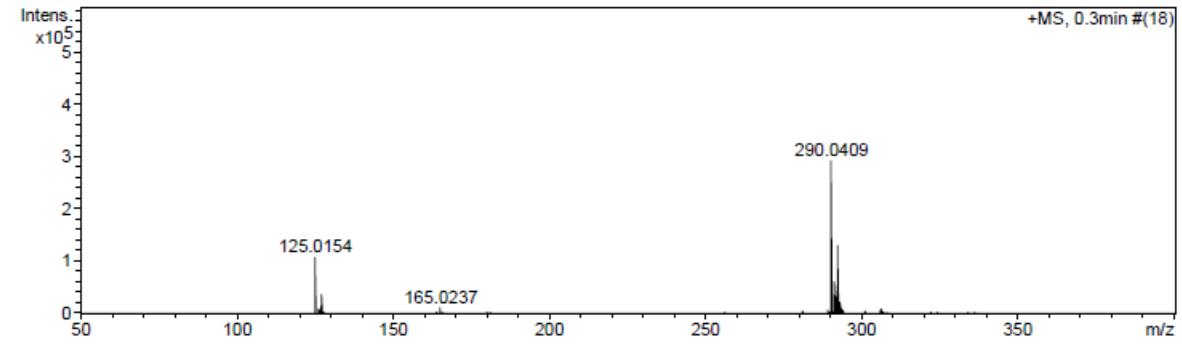


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e¯ Conf	N-Rule
164.0160	1	C 8 H 6 N O S	100.00	164.0165	0.5	2.9	50.7	6.5	even	ok
	2	C 11 H 2 N O	16.49	164.0131	-2.9	-17.6	53.9	11.5	even	ok
301.0644	1	C 15 H 13 N 2 O 3 S	100.00	301.0641	-0.3	-0.8	34.6	10.5	even	ok

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

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

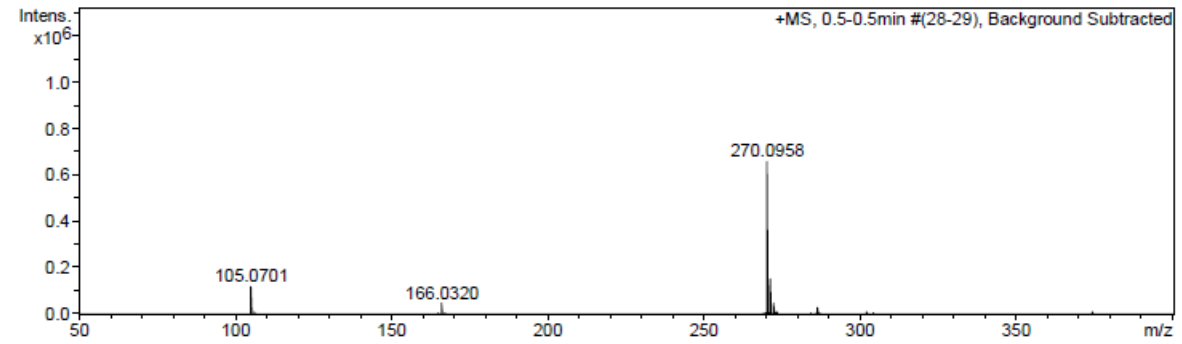


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e¯ Conf	N-Rule
125.0154	1	C 7 H 6 Cl	100.00	125.0153	-0.1	-1.1	8.1	4.5	even	ok
	2	C 4 H 10 Cl S	8.84	125.0186	3.2	25.9	19.7	-0.5	even	ok
290.0409	1	C 15 H 13 Cl N O S	100.00	290.0401	-0.8	-2.9	35.4	9.5	even	ok

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

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

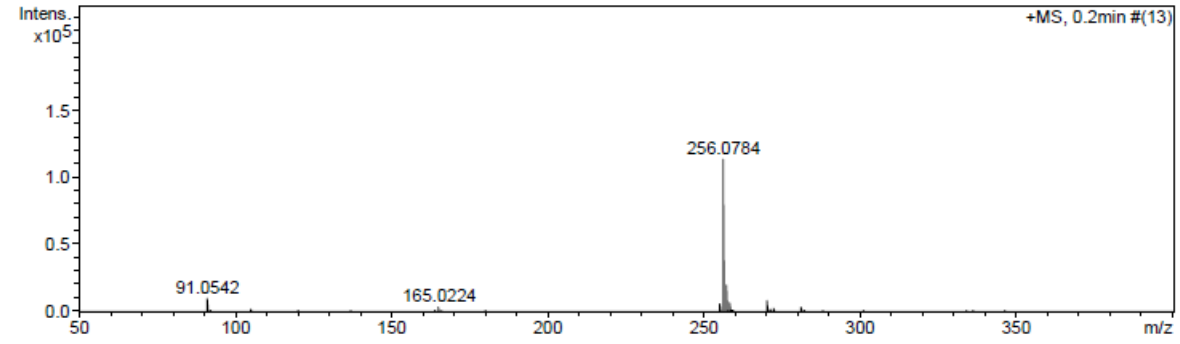


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e¯ Conf	N-Rule
105.0701	1	C 8 H 9	100.00	105.0699	-0.2	-2.0	4.9	4.5	even	ok
	2	C 5 H 13 S	6.94	105.0732	3.2	30.1	32.5	-0.5	even	ok
270.0958	1	C 16 H 16 N O S	100.00	270.0947	-1.1	-4.1	23.7	9.5	even	ok

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

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

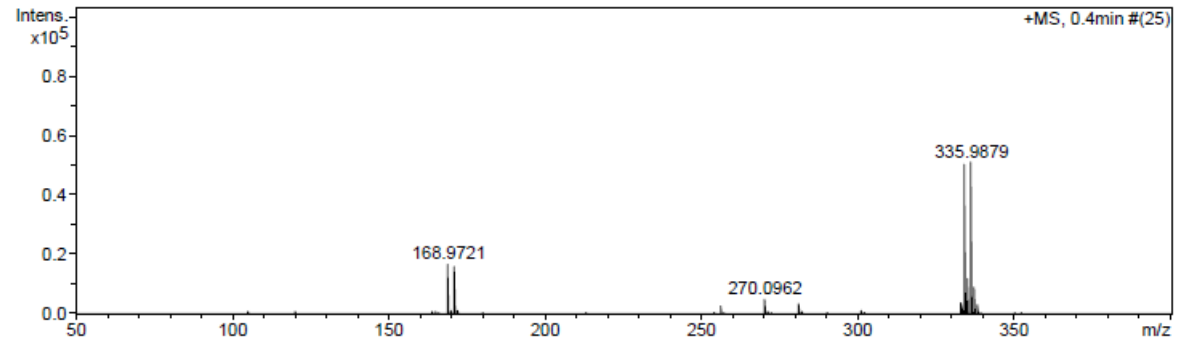


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e¯ Conf	N-Rule
256.0784	1	C 15 H 14 N O S	100.00	256.0791	0.7	2.7	1.4	9.5	even	ok

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

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

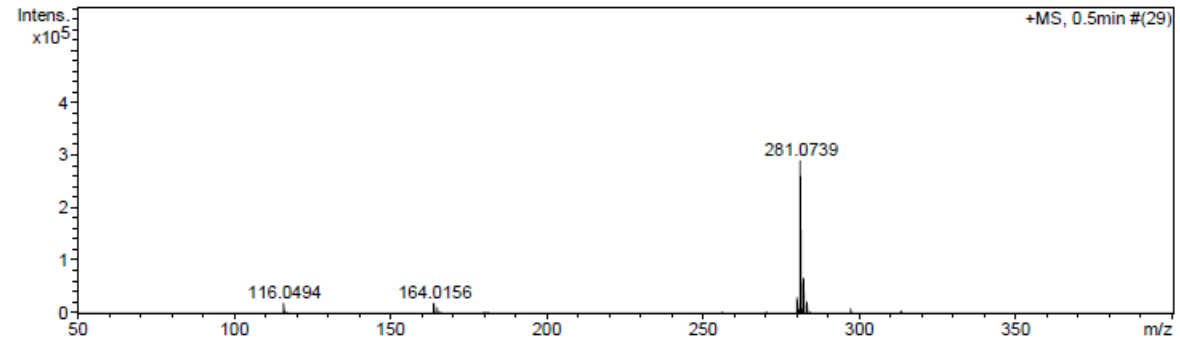


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e¯ Conf	N-Rule
168.9721	1	C 3 H 8 Br N O 2	100.00	168.9733	1.2	7.2	26.3	0.0	odd	ok
	2	C 4 H 10 Br S	7.22	168.9681	-4.0	-23.5	34.1	-0.5	even	ok
	3	C 10 H O S	0.00	168.9743	2.2	12.9	450.1	10.5	even	ok
333.9899	1	C 15 H 13 Br N O S	100.00	333.9896	-0.3	-0.9	26.6	9.5	even	ok

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

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

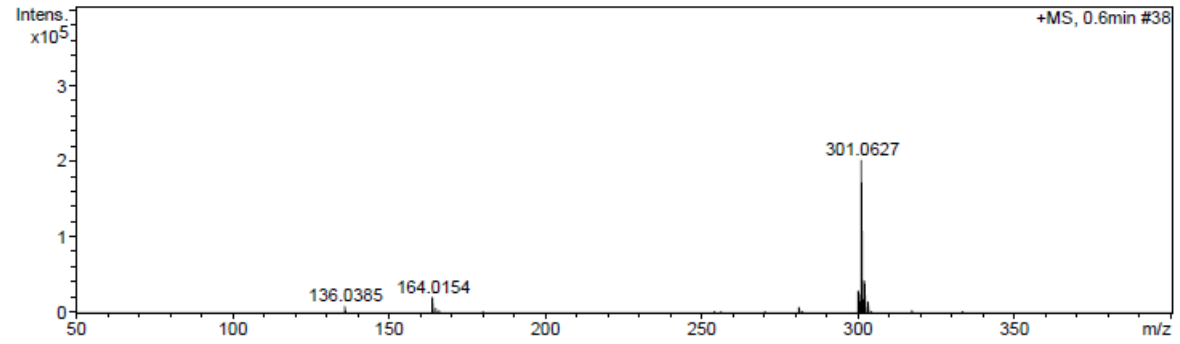


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e¯ Conf	N-Rule
281.0739	1	C 16 H 13 N 2 O S	100.00	281.0743	0.4	1.3	23.7	11.5	even	ok

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

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

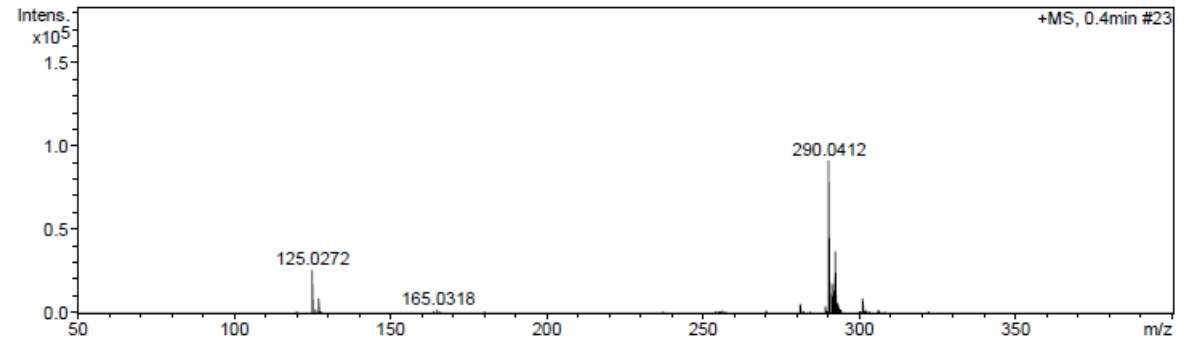


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e¯ Conf	N-Rule
301.0627	1	C 15 H 13 N 2 O 3 S	100.00	301.0641	1.4	4.8	15.0	10.5	even	ok

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

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

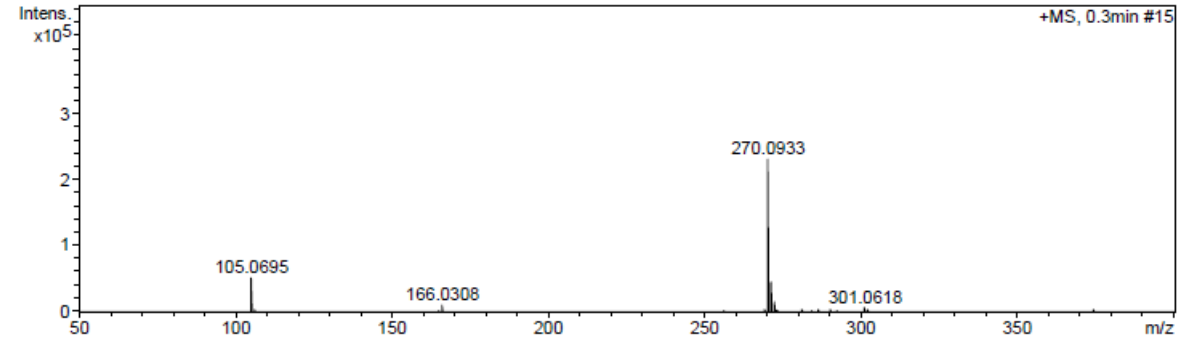


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e¯ Conf	N-Rule
125.0272	1	C 3 H 8 Cl N O 2	100.00	125.0238	-3.4	-27.3	22.8	0.0	odd	ok
	2	C 3 H 9 O 3 S	1.27	125.0267	-0.5	-4.2	165.8	-0.5	even	ok
	3	C 6 H 7 N S	0.40	125.0294	2.1	17.2	167.6	4.0	odd	ok
	4	C 6 H 5 O 3	0.01	125.0233	-3.9	-31.2	190.7	4.5	even	ok
	5	C 9 H 3 N	0.12	125.0260	-1.2	-9.8	191.9	9.0	odd	ok
290.0412	1	C 15 H 13 Cl N O S	100.00	290.0401	-1.1	-3.8	13.9	9.5	even	ok

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

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

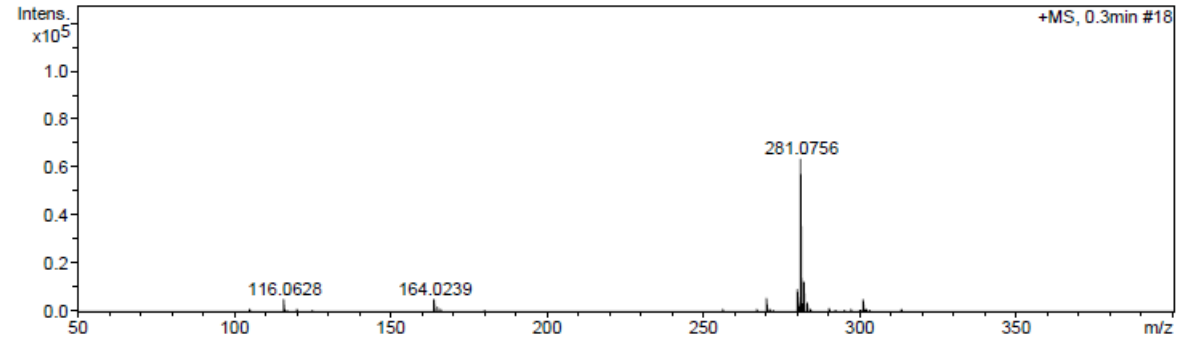


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e¯ Conf	N-Rule
105.0695	1	C 8 H 9	100.00	105.0699	0.4	3.5	0.1	4.5	even	ok
	2	C 3 H 9 N 2 O 2	4.67	105.0659	-3.7	-34.8	27.0	0.5	even	ok
	3	C 5 H 13 S	3.98	105.0732	3.7	35.6	29.8	-0.5	even	ok
270.0933	1	C 16 H 16 N O S	100.00	270.0947	1.5	5.4	7.1	9.5	even	ok

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

Acquisition Parameter

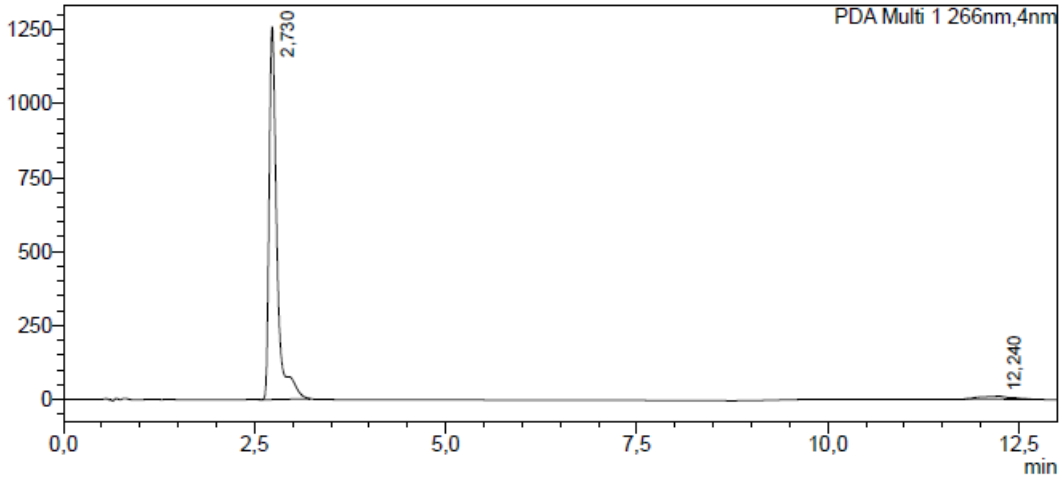
Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	0.8 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1600 m/z	Set Collision Cell RF	150.0 Vpp	Set Divert Valve	Waste



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e¯ Conf	N-Rule
281.0756	1	C 16 H 13 N 2 O S	100.00	281.0743	-1.3	-4.6	5.2	11.5	even	ok

HPLC traces for purity estimation

6-(Benzyloxy)-2-methylbenzo[*d*]thiazole **(4a)**

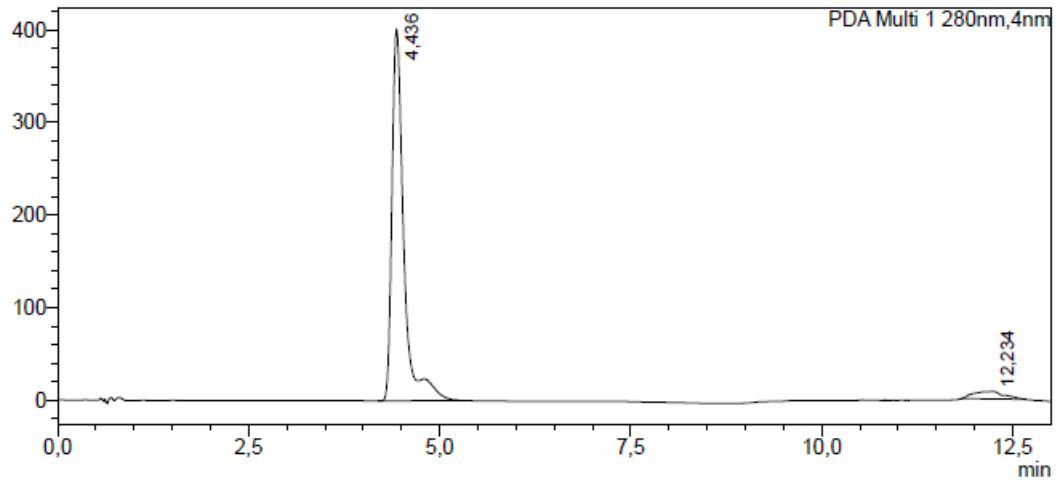


<Peak Table>

PDA Ch1 266nm

Peak#	Ret. Time	Area	Area%
1	2,730	8912380	96,935
2	12,240	281767	3,065
Total		9194146	100,000

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

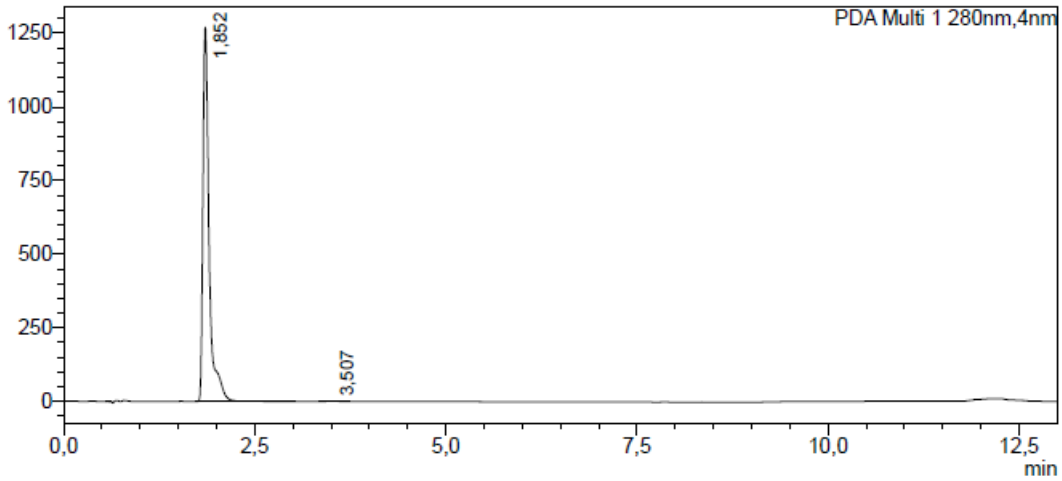


<Peak Table>

PDA Ch1 280nm

Peak#	Ret. Time	Area	Area%
1	4,436	4325237	94,984
2	12,234	228390	5,016
Total		4553627	100,000

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

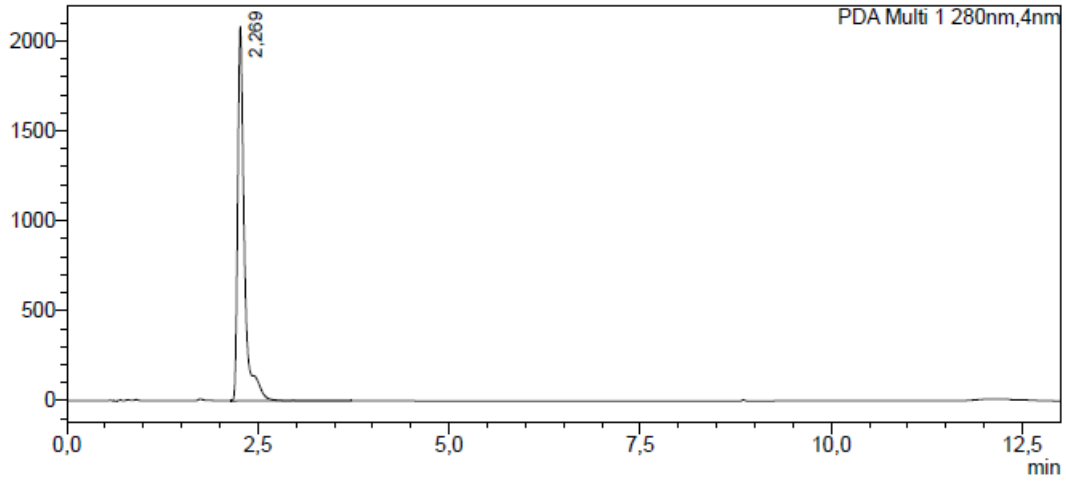


<Peak Table>

PDA Ch1 280nm

Peak#	Ret. Time	Area	Area%
1	1,852	7231209	99,774
2	3,507	16356	0,226
Total		7247565	100,000

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

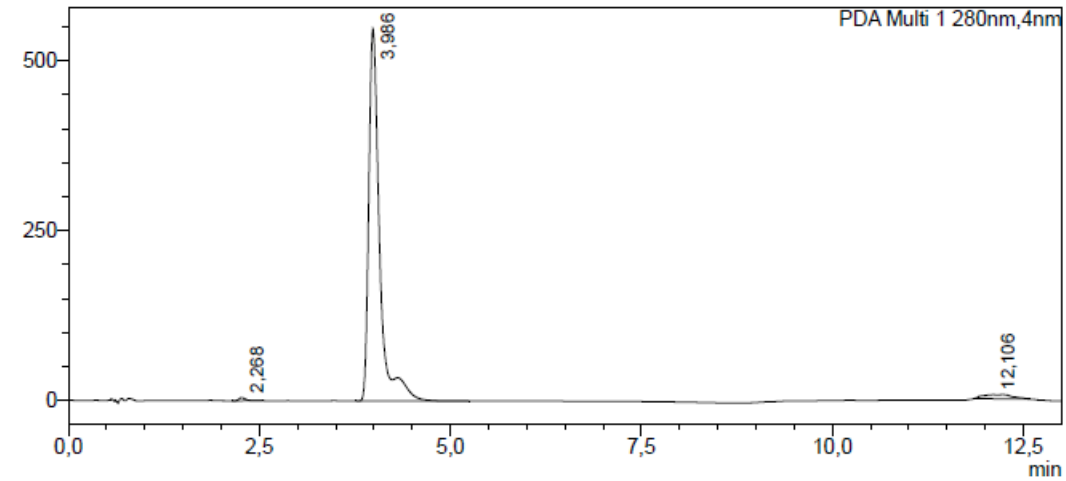


<Peak Table>

PDA Ch1 280nm

Peak#	Ret. Time	Area	Area%
1	2,269	12775360	100,000
Total		12775360	100,000

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

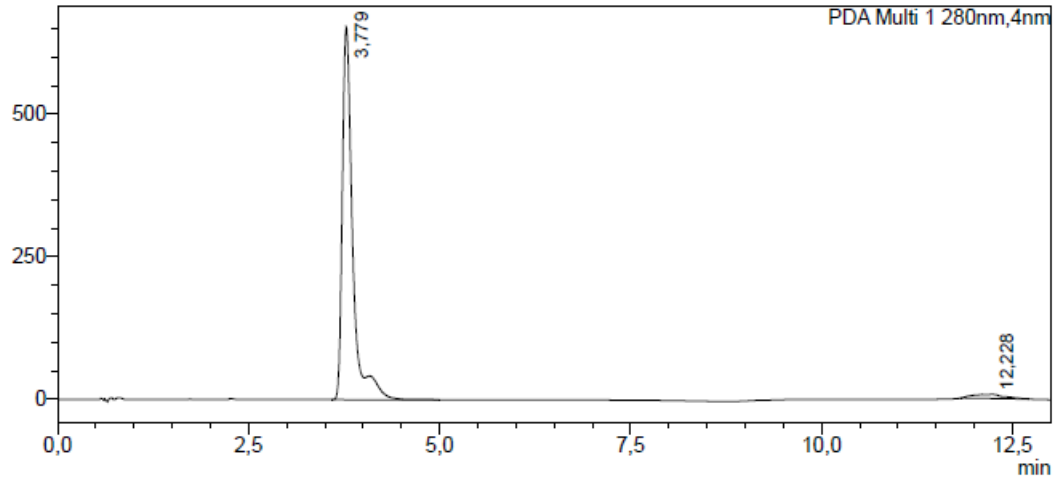


<Peak Table>

PDA Ch1 280nm

Peak#	Ret. Time	Area	Area%
1	2,268	26864	0,486
2	3,986	5331365	96,479
3	12,106	167693	3,035
Total		5525922	100,000

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

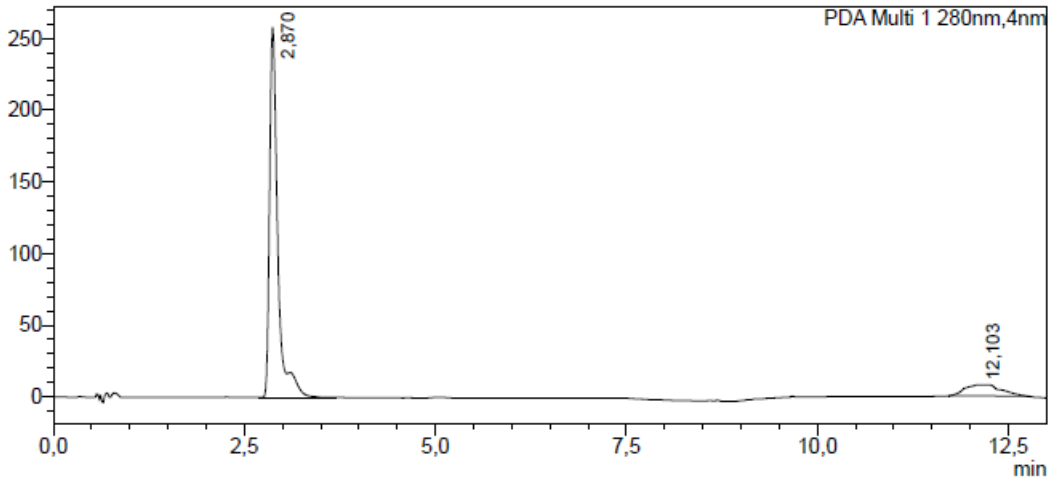


<Peak Table>

PDA Ch1 280nm

Peak#	Ret. Time	Area	Area%
1	3,779	6080959	96,696
2	12,228	207757	3,304
Total		6288716	100,000

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

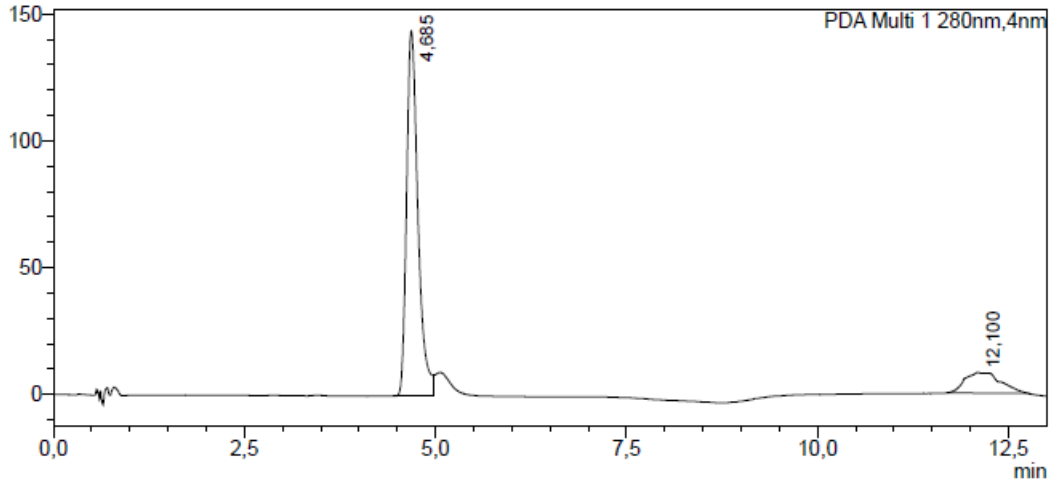


<Peak Table>

PDA Ch1 280nm

Peak#	Ret. Time	Area	Area%
1	2,870	1911312	88,264
2	12,103	254129	11,736
Total		2165441	100,000

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

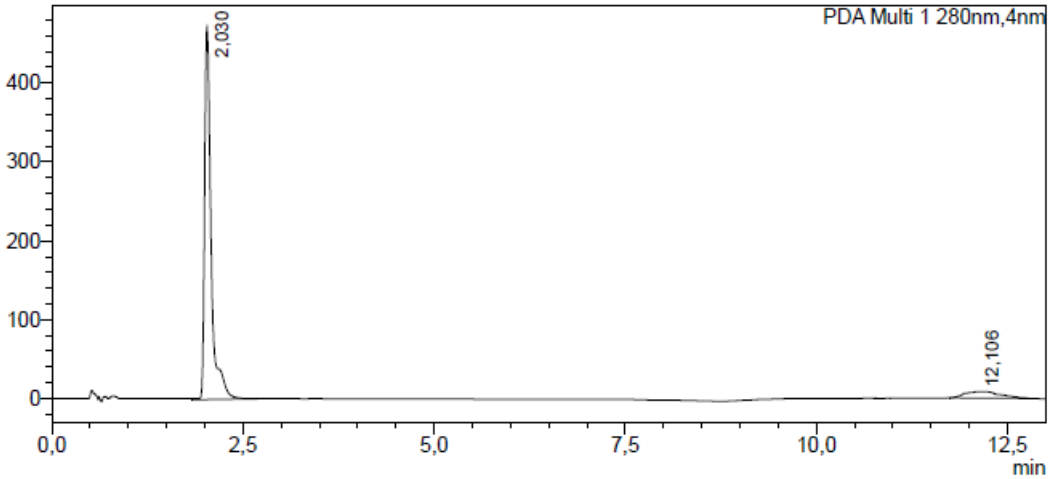


<Peak Table>

PDA Ch1 280nm

Peak#	Ret. Time	Area	Area%
1	4,685	1488810	84,879
2	12,100	265229	15,121
Total		1754040	100,000

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

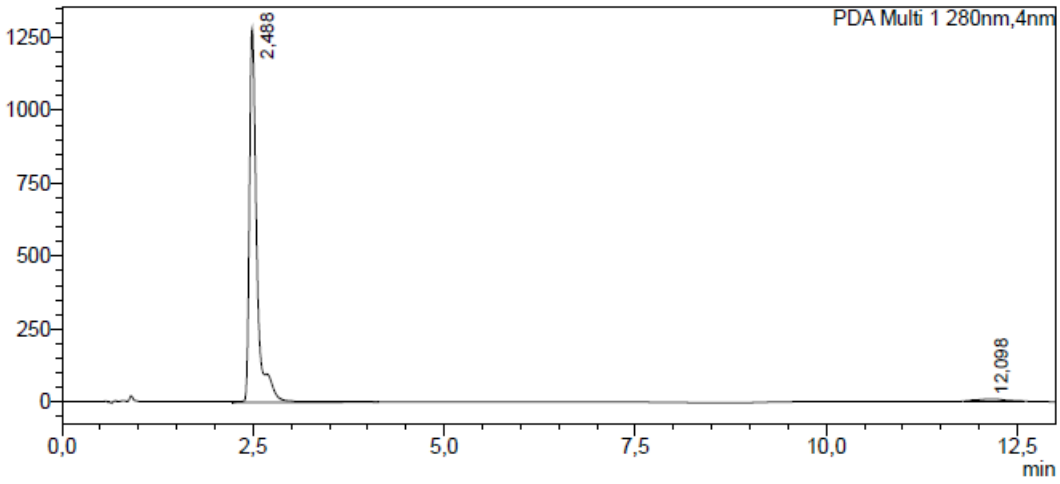


<Peak Table>

PDA Ch1 280nm

Peak#	Ret. Time	Area	Area%
1	2,030	2811768	91,565
2	12,106	259011	8,435
Total		3070779	100,000

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

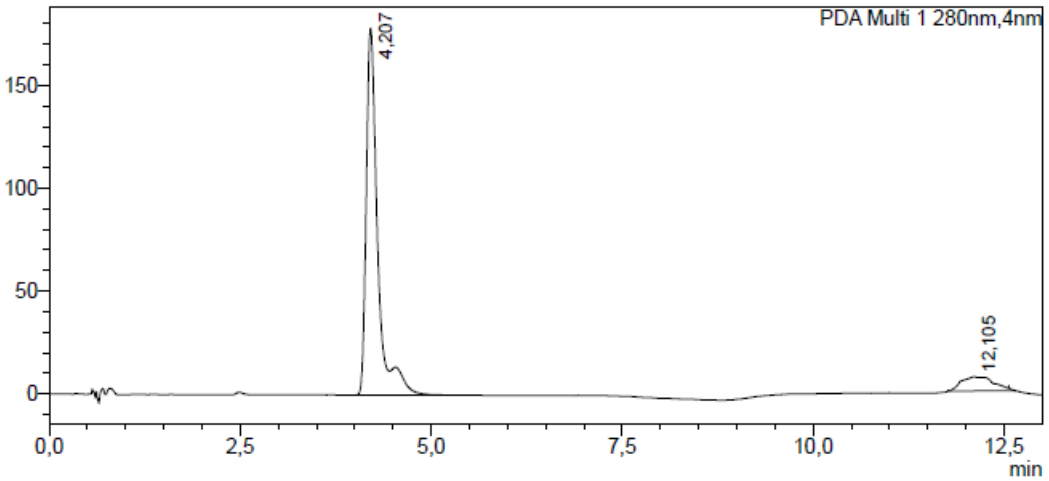


<Peak Table>

PDA Ch1 280nm

Peak#	Ret. Time	Area	Area%
1	2,488	8661199	98,052
2	12,098	172084	1,948
Total		8833283	100,000

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

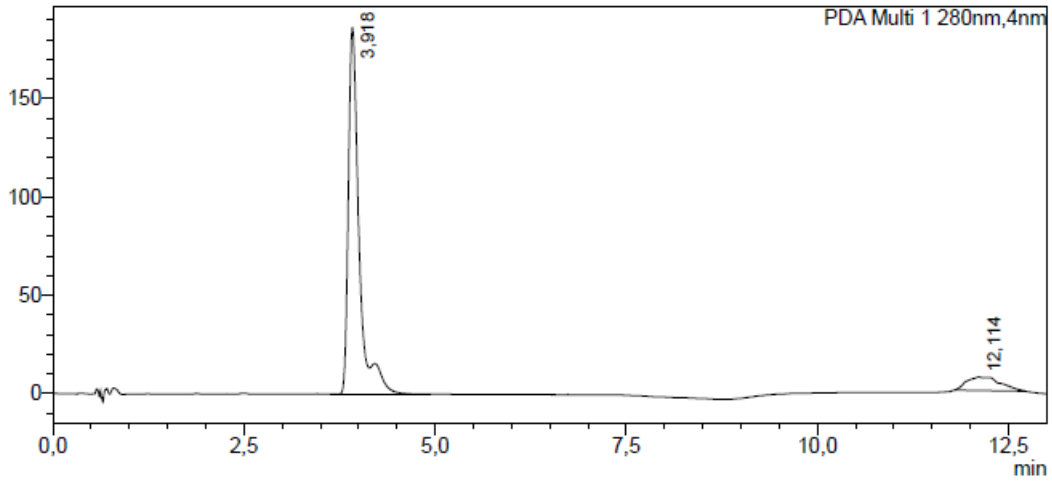


<Peak Table>

PDA Ch1 280nm

Peak#	Ret. Time	Area	Area%
1	4,207	1815008	89,887
2	12,105	204194	10,113
Total		2019202	100,000

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

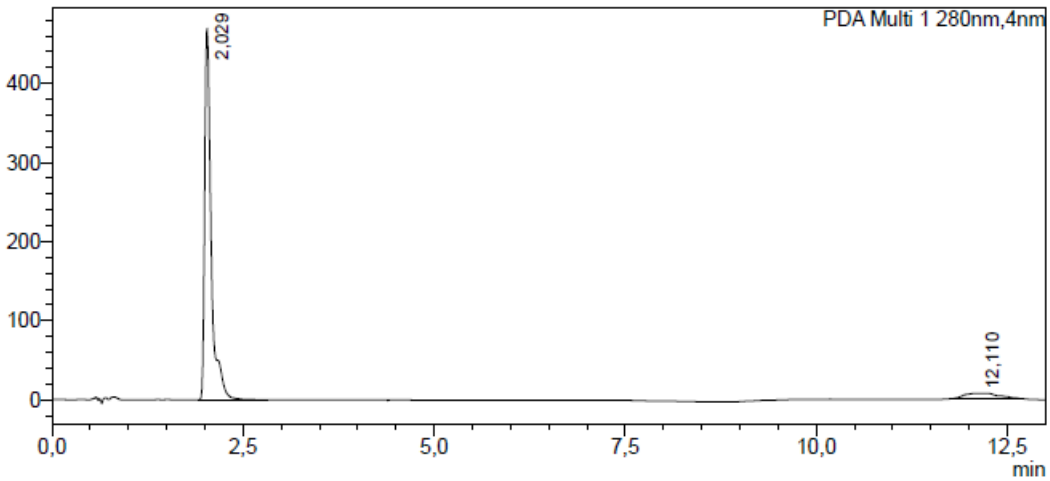


<Peak Table>

PDA Ch1 280nm

Peak#	Ret. Time	Area	Area%
1	3,918	1793478	89,636
2	12,114	207367	10,364
Total		2000845	100,000

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



<Peak Table>

PDA Ch1 280nm

Peak#	Ret. Time	Area	Area%
1	2,029	2798787	93,270
2	12,110	201951	6,730
Total		3000738	100,000