Synthesis of 1,3,4-oxadiazole derivatives with antidepressant activity and their binding to the 5-HT_{1A} receptor

Forced swimming test (FST)

Male Kun-Ming mice (22 ± 2 g) were used in the FSTs. On the test day, mice were assigned to different groups (n = 8 for each group). The synthesized compounds and the standard drug fluoxetine were administered as intraperitoneal injections. Control animals received a 3% aqueous solution of Tween 80. After 30 min, the mice were dropped one at a time into a Plexiglas cylinder (height 25 cm, diameter 10 cm, containing water to a height of 10 cm at 23-25 ^{o}C) and observed for 6 min. After the first 2 min of vigorous struggling, the animals were immobile. A mouse was judged immobile if it floated in the water in an upright position and made only slight movements to prevent sinking. The total duration of immobility was recorded during the last 4 min of the 6-min test.

Tail suspension test (TST)

Male mice were individually suspended by the tail above the floor and affixed with adhesive tape placed approximately 1-2 cm from the tip of the tail. The total duration of immobility was recorded in the last 6 min of a total period of 7 min. Mice were determined to be immobile when they were completely motionless and hung passively.

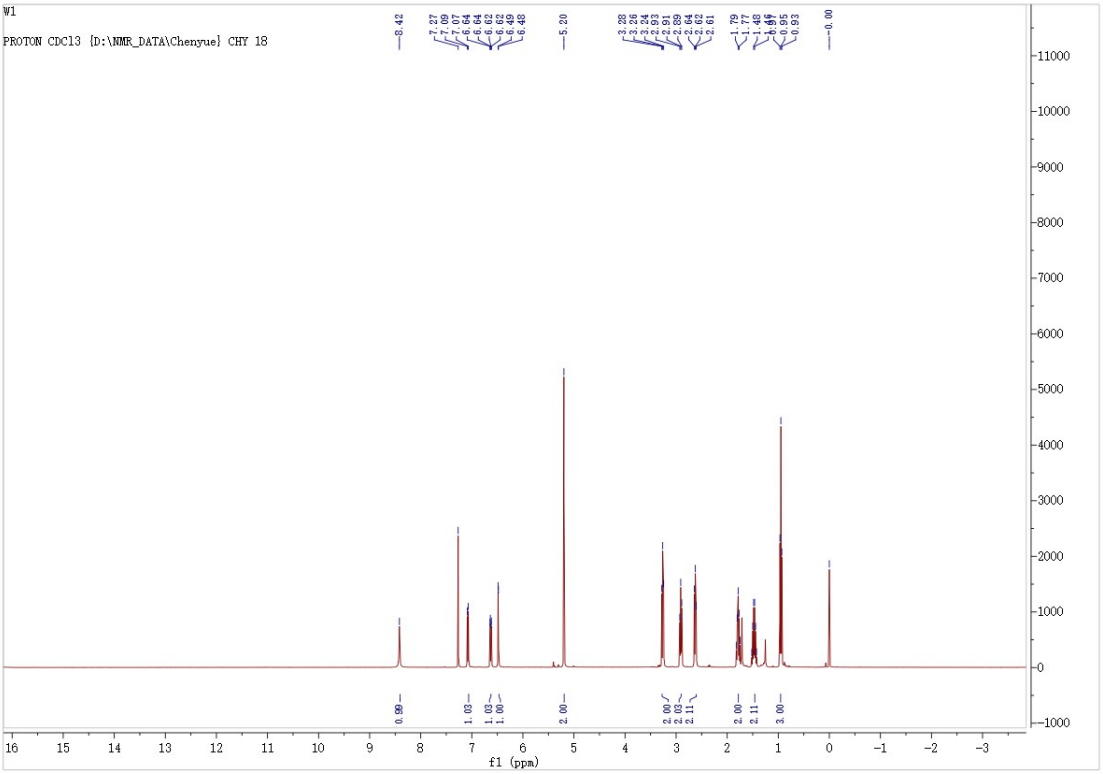
5-HT_{1A} binding assay

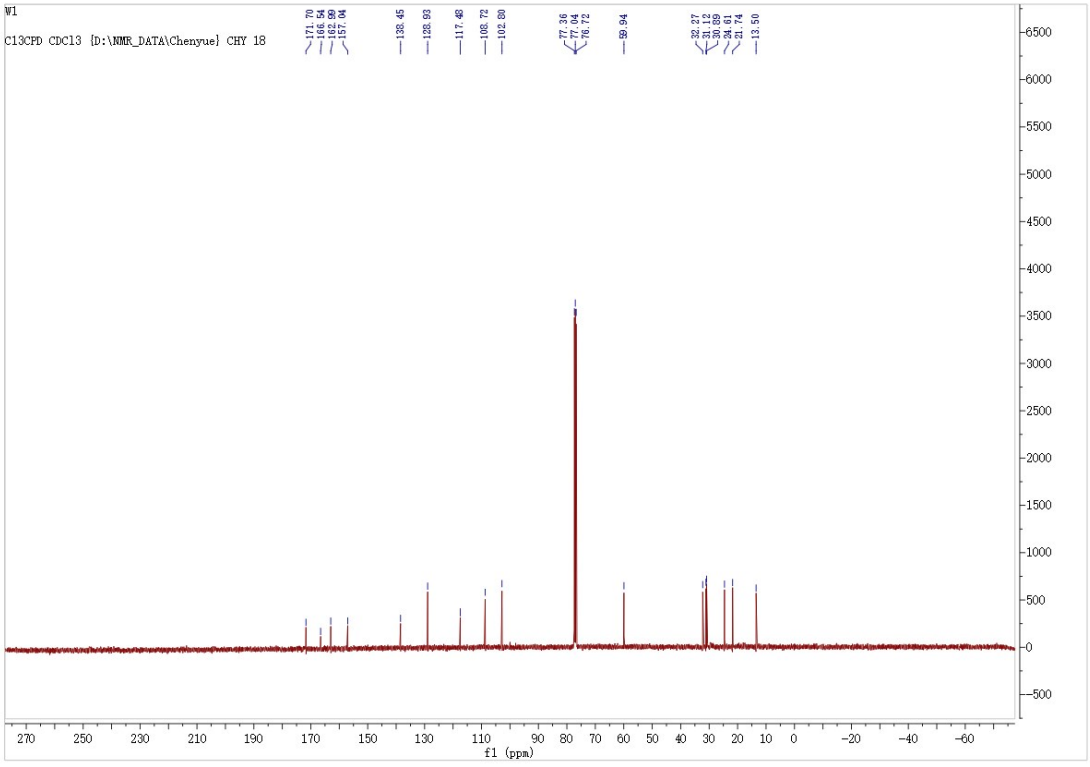
Cell membrane homogenates (10 μg protein) are incubated for 60 min at 22°C with 1 nM [^{3}H]8-OH-DPAT in the absence or presence of the test compound in a buffer containing 50 mM Tris-HCl (pH 7.4), 10 mM $MgSO_4$, 0.5 mM EDTA and 0.1% ascorbic acid. Nonspecific binding is determined in the presence of 10 μM 8-OH-DPAT. Following incubation, the samples are filtered rapidly under vacuum through glass fiber filters (GF/B, Packard) presoaked with 0.3% PEI and rinsed several times (200 ml) with ice-cold 50 mM Tris-HCl using a 96-sample cell harvester (Unifilter, Packard). The filter mates were dried at 37 ^{o}C in forced air fan incubator and then solid scintillator MeltiLex was melted on filter mates at 90 ^{o}C for 4 min. Radioactivity

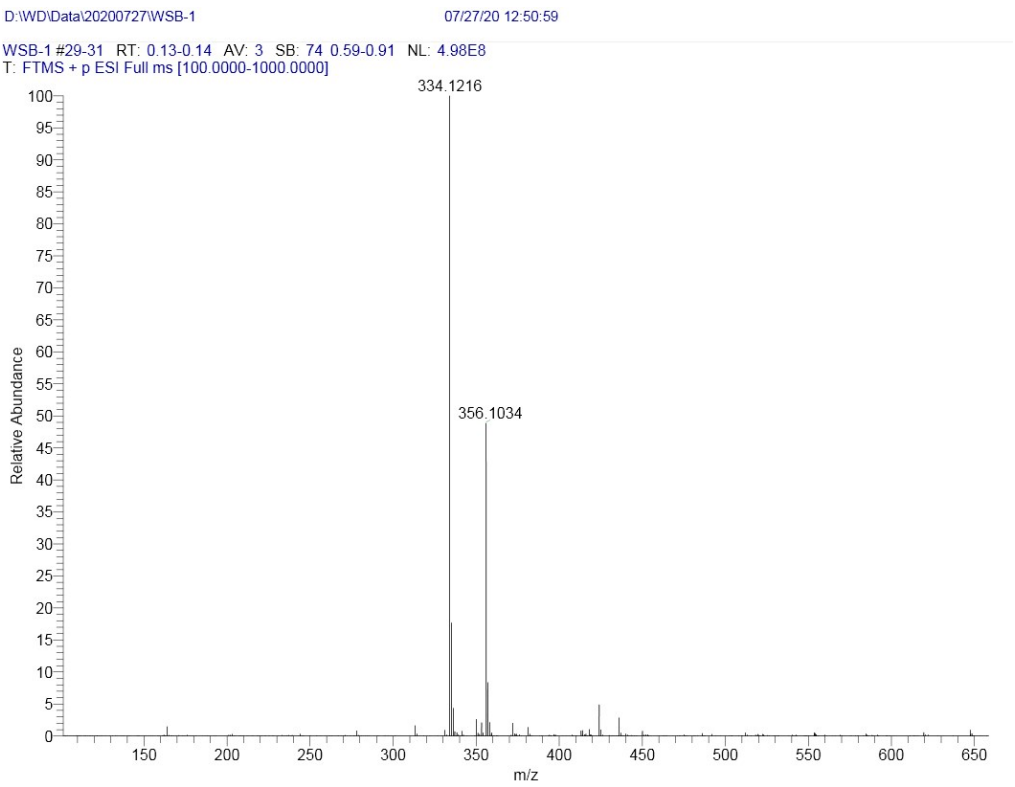
was counted in MicroBeta2 scintillation counter (PerkinElmer). Data were fitted to a one-site curve-fitting equation with Prism 5 (GraphPad Software) and Ki values were estimated from the Cheng-Prusoff equation.

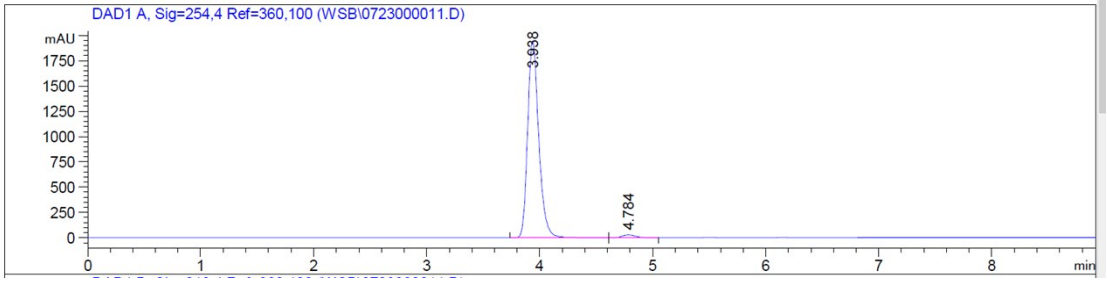
[1]HNMR, **[13]CNMR**, **HRMS** and **HPLC** Spectra of Products

7-((5-(Butylthio)-1,3,4-oxadiazol-2-yl)methoxy)-3,4-dihydroquinolin-2(1*H*)-one（5a）



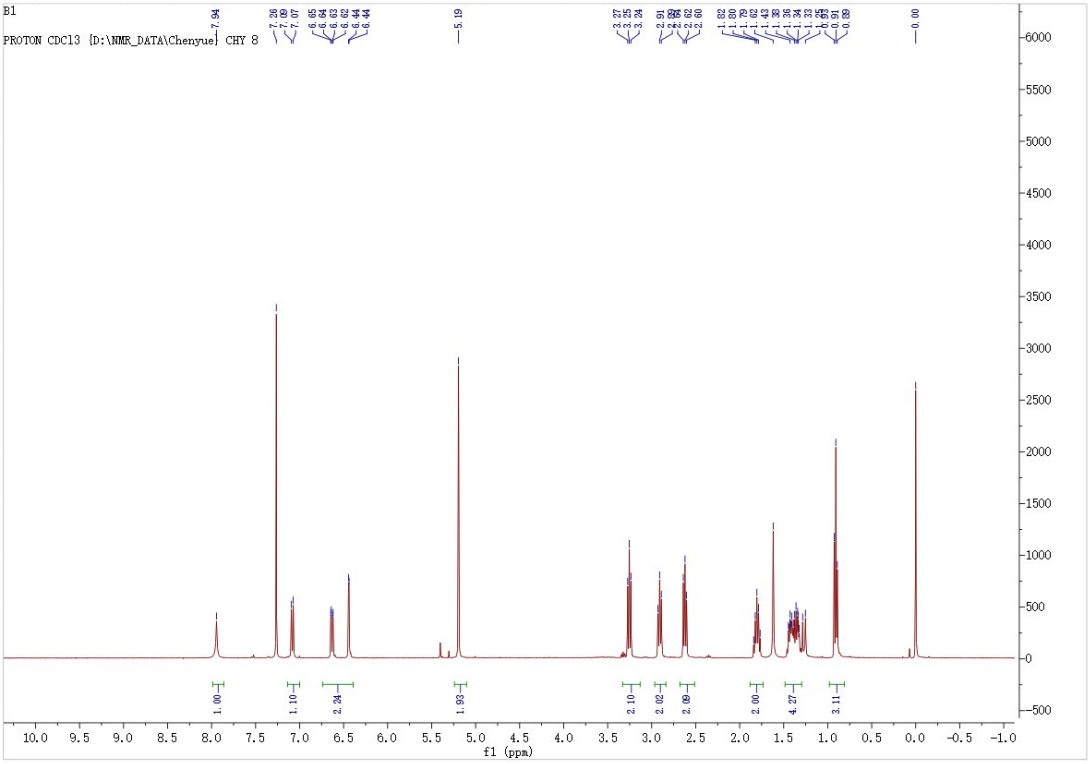


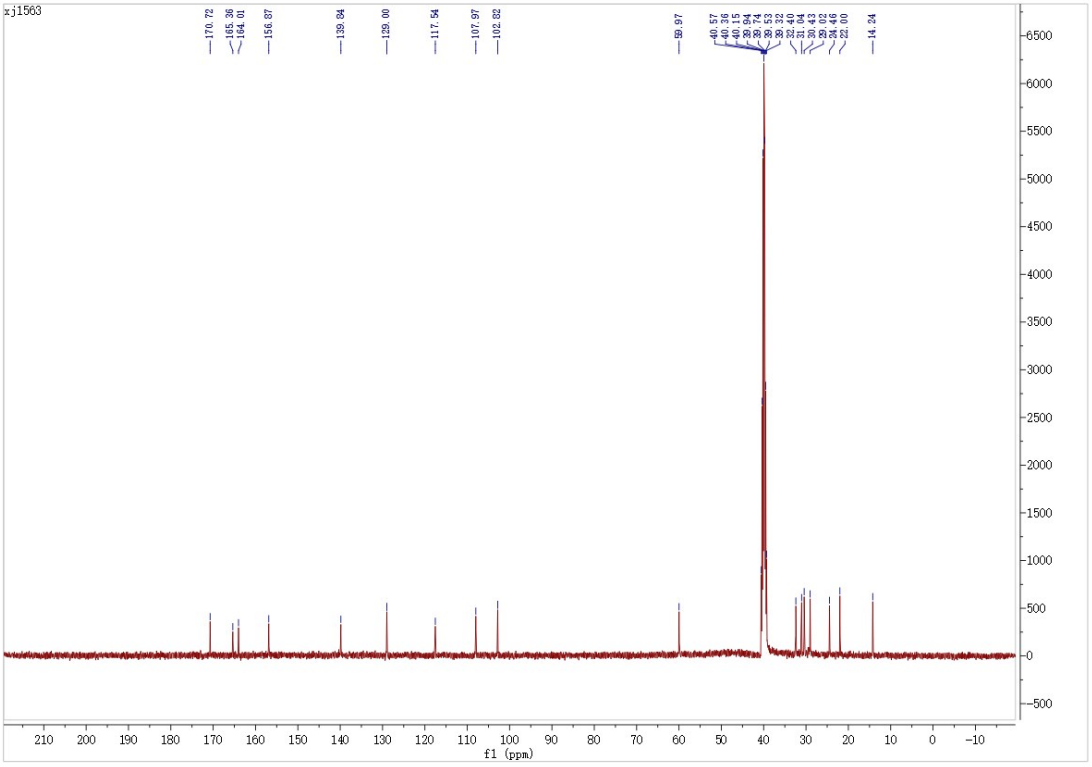


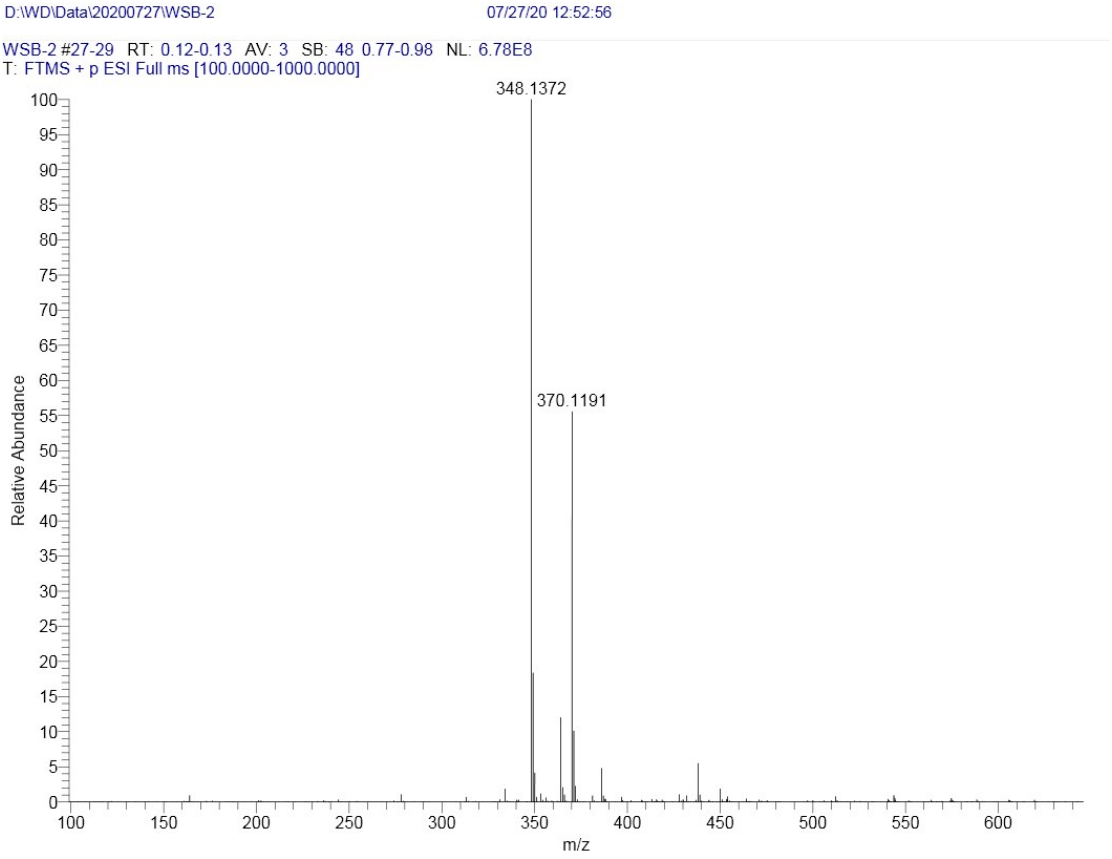


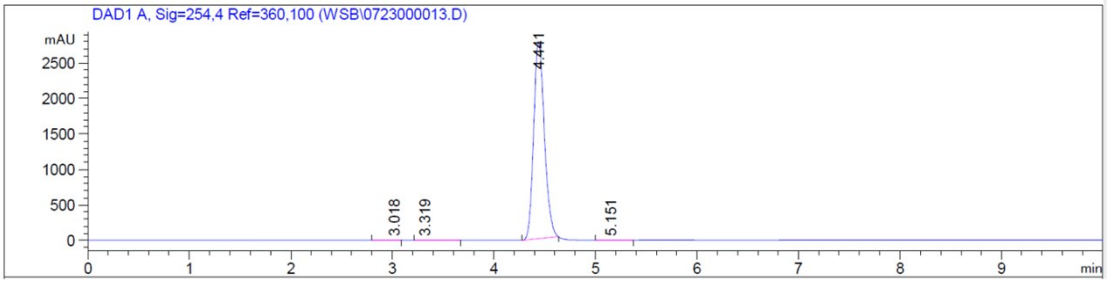
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	3.938	BV	0.1032	1.32400e4	1949.43030	98.2037
2	4.784	VV	0.1221	242.17978	30.02106	1.7963

7-((5-(Pentylthio)-1,3,4-oxadiazol-2-yl)methoxy)-3,4-dihydroquinolin-2(1*H*)-one（5b）



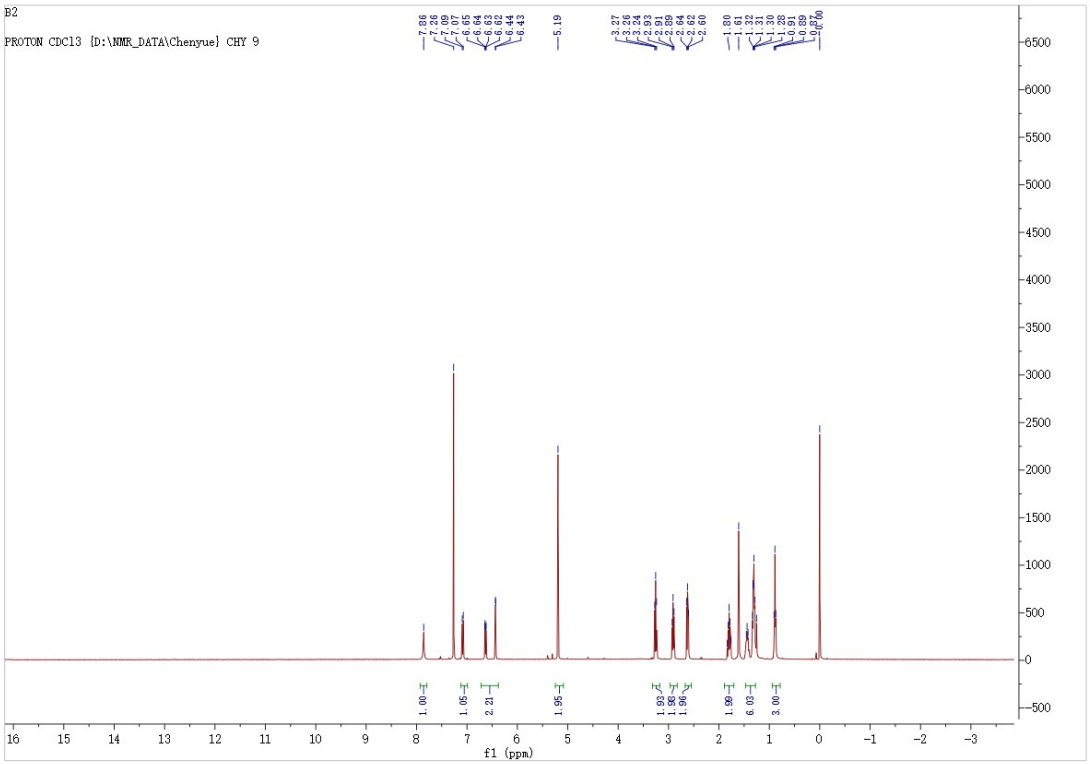


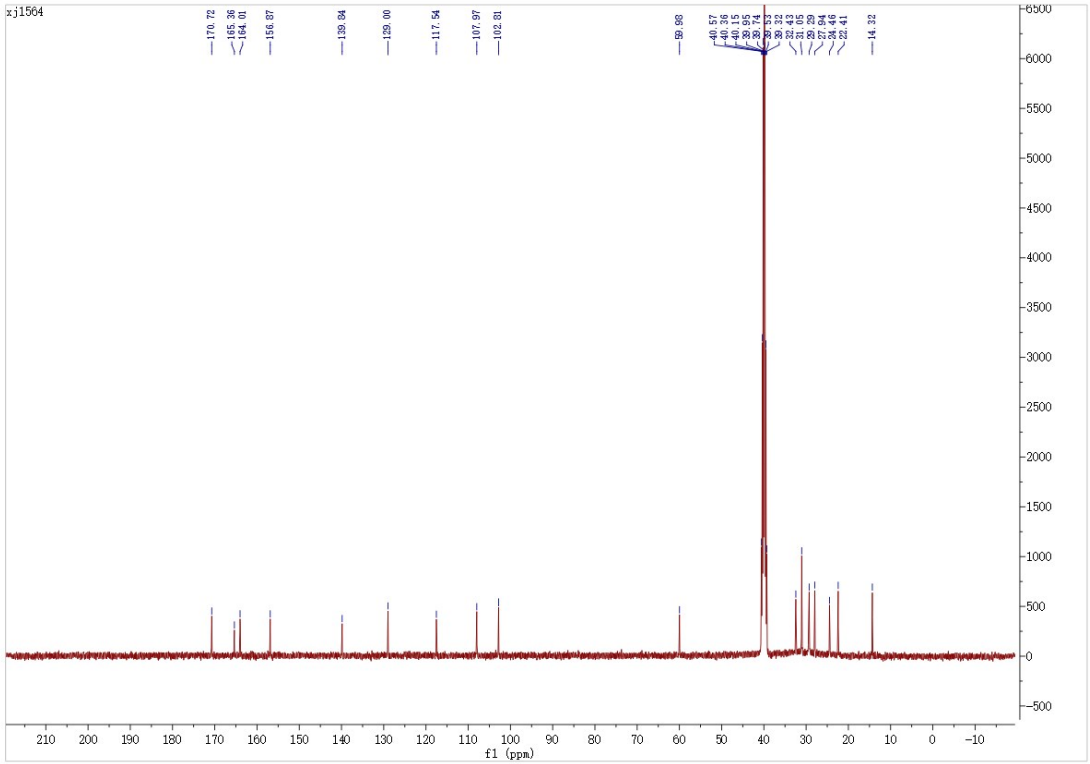




峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	3.018	BV	0.0795	6.35668	1.24644	0.0311
2	3.319	VB	0.1090	16.67444	2.23595	0.0816
3	4.441	BBA	0.1156	2.03934e4	2778.36377	99.7664
4	5.151	BH	0.1410	24.72833	2.60013	0.1210

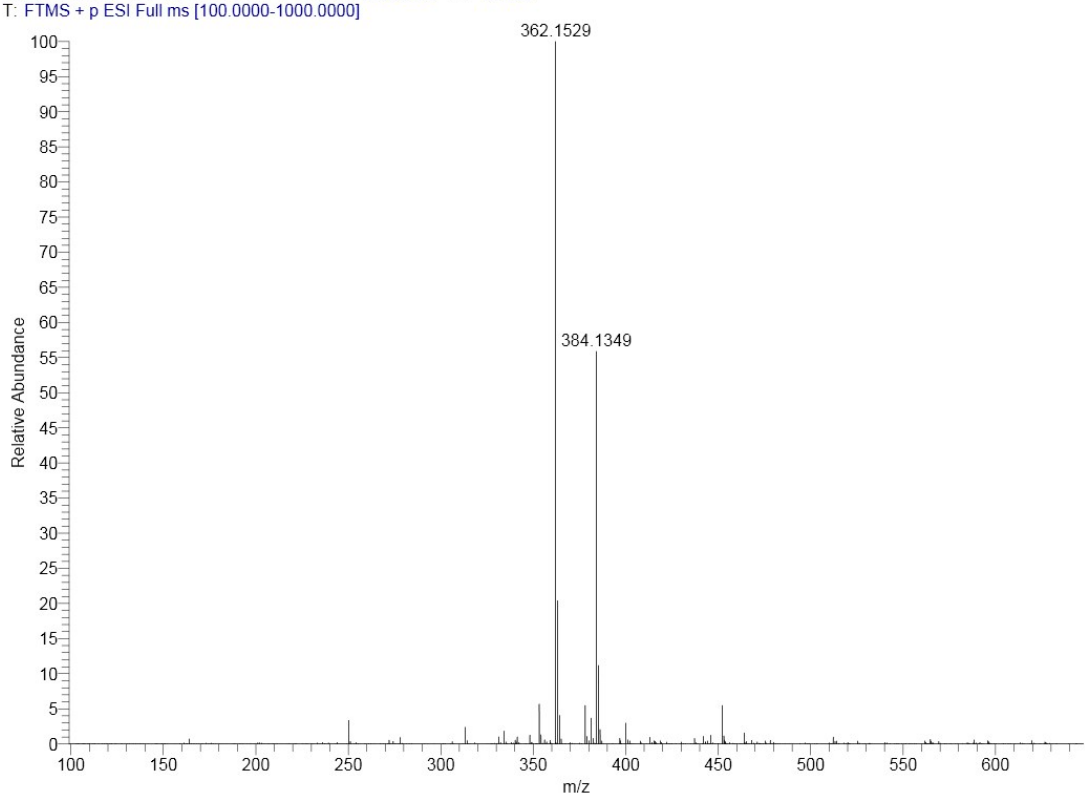
7-((5-(Hexylthio)-1,3,4-oxadiazol-2-yl)methoxy)-3,4-dihydroquinolin-2(1H)-one (5c)

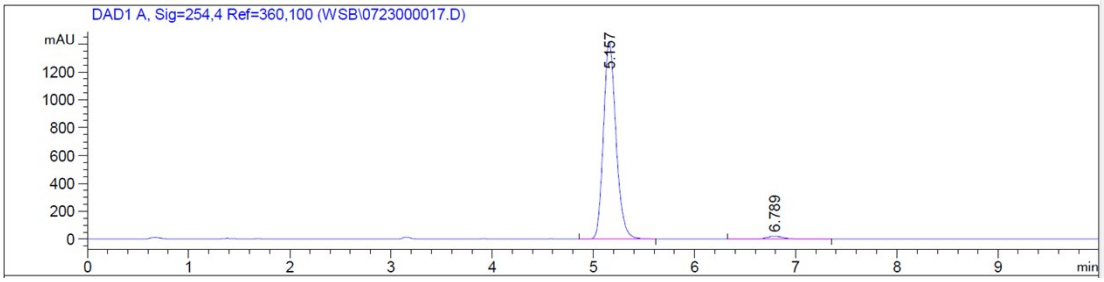




D:\WD\Data\20200727\WSB-3 07/27/20 12:54:54

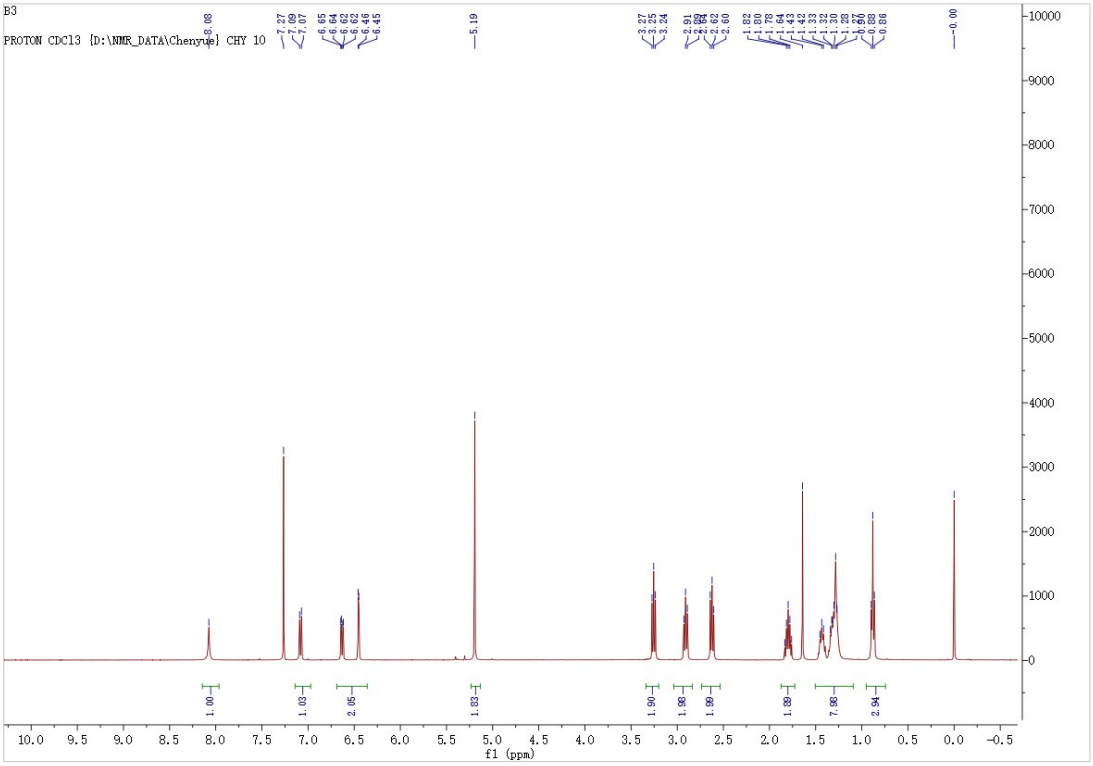
WSB-3 #26-29 RT: 0.12-0.13 AV: 4 SB: 37 0.53-0.69 NL: 4.40E8
T: FTMS + p ESI Full ms [100.0000-1000.0000]

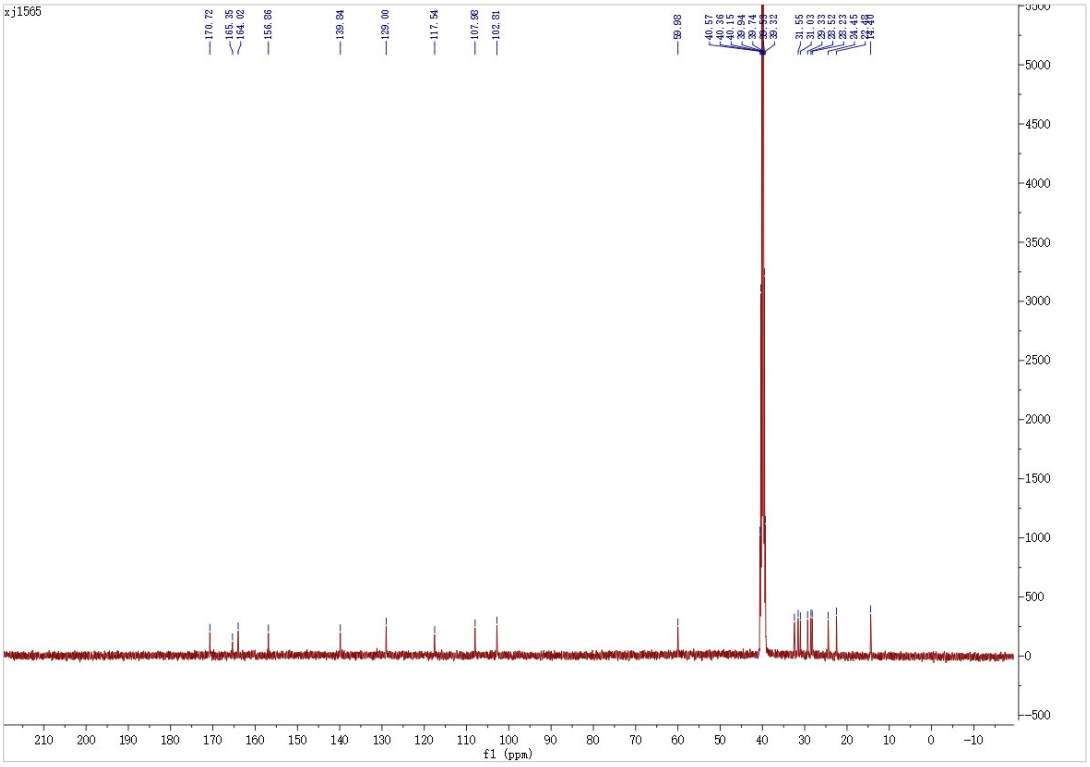


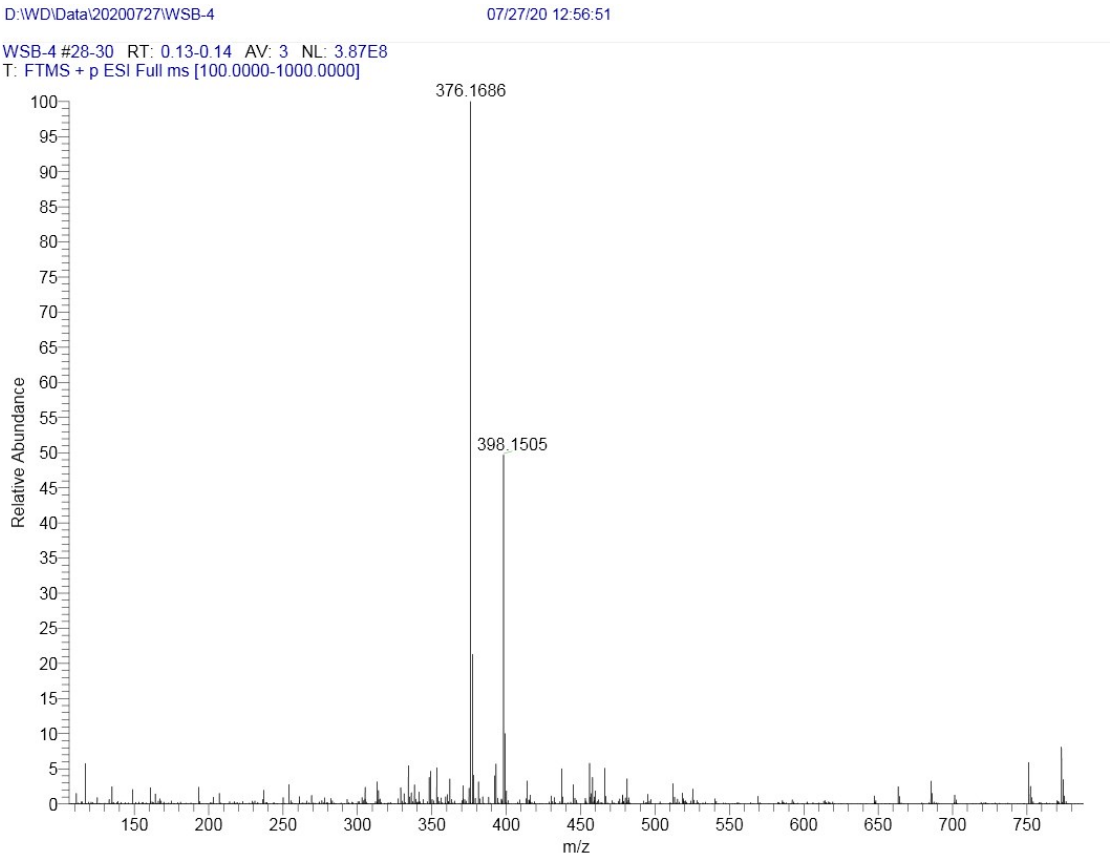


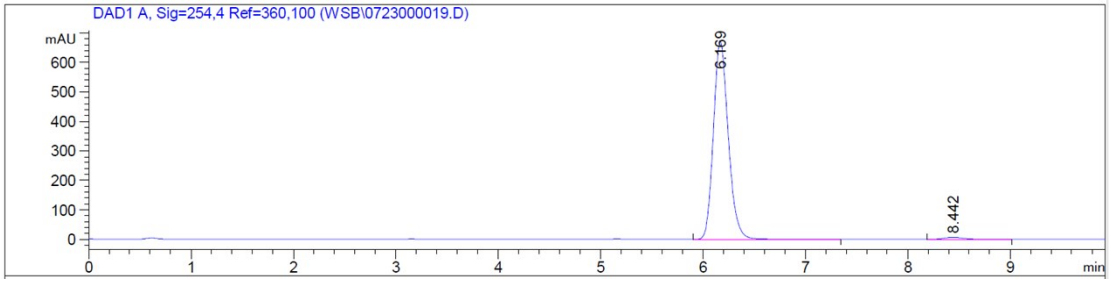
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	5.157	HHA	0.1325	1.22567e4	1422.35437	98.1127
2	6.789	HB	0.1717	235.76608	21.20602	1.8873

7-((5-(Heptylthio)-1,3,4-oxadiazol-2-yl)methoxy)-3,4-dihydroquinolin-2(1*H*)-one (5d)



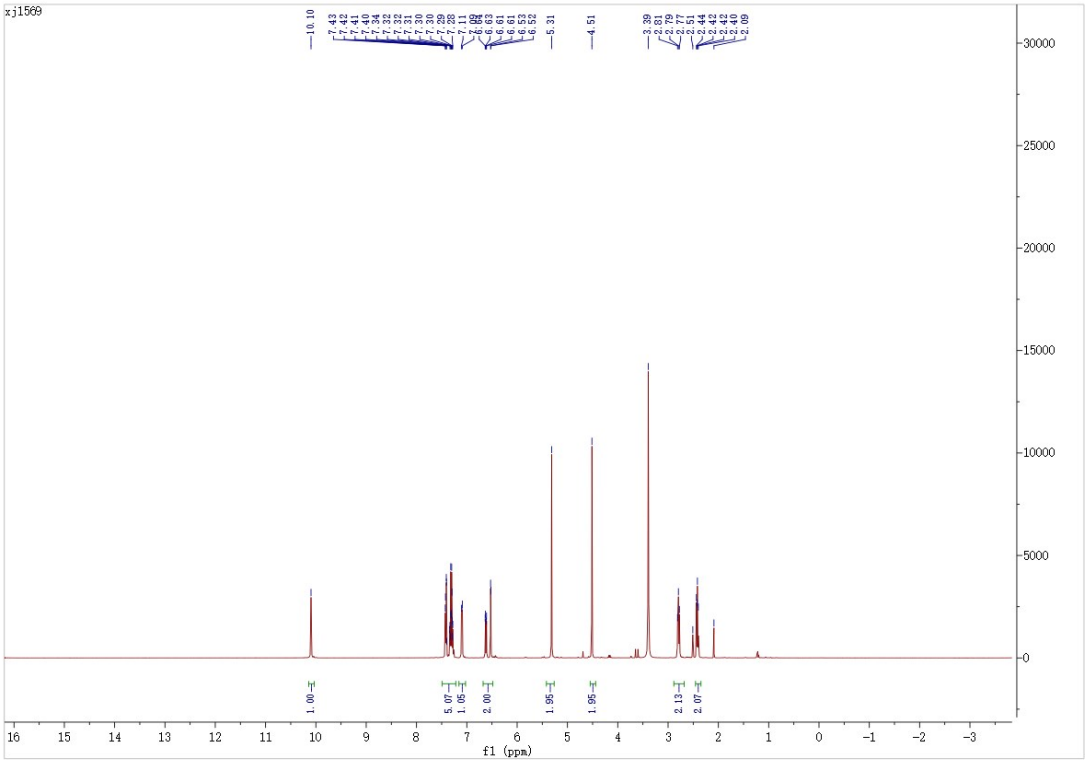


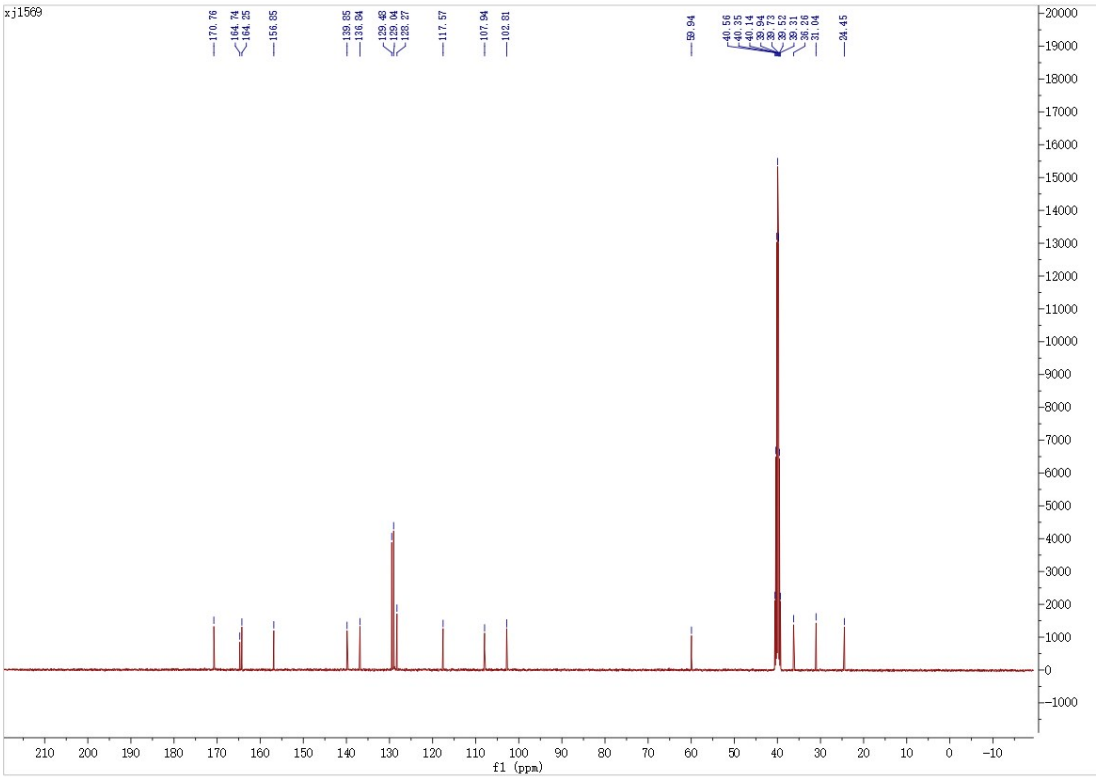


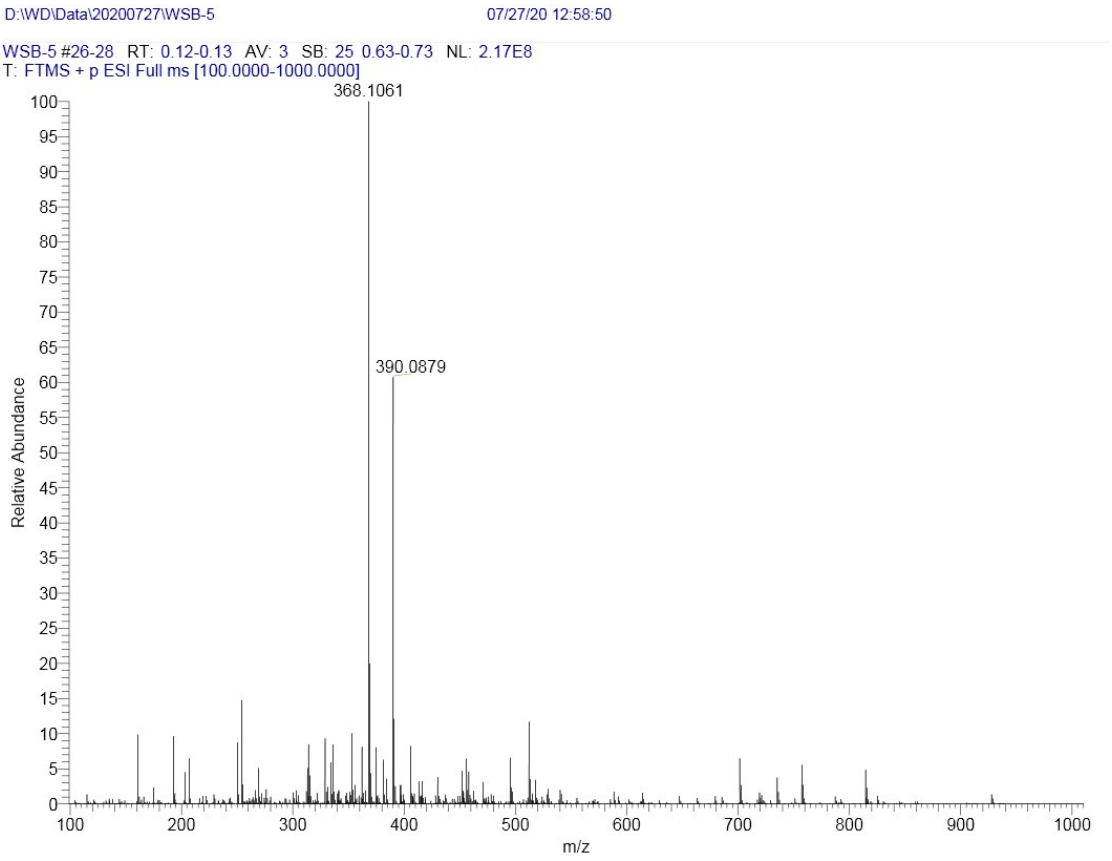


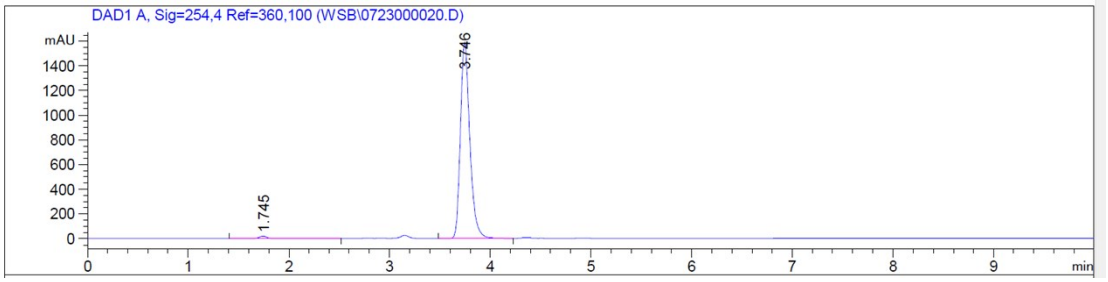
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	6.169	BB	0.1550	6770.88232	674.97656	98.6861
2	8.442	HB	0.2053	90.14445	6.77200	1.3139

7-((5-(Benzylthio)-1,3,4-oxadiazol-2-yl)methoxy)-3,4-dihydroquinolin-2(1*H*)-one (5e)



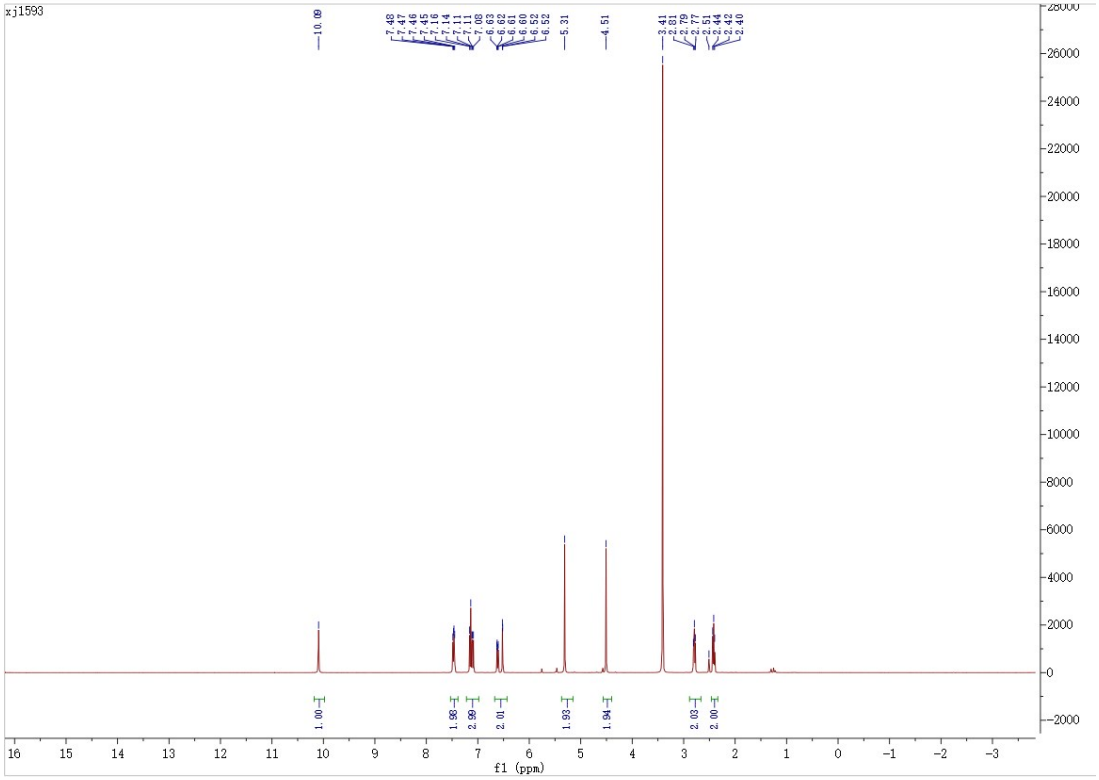


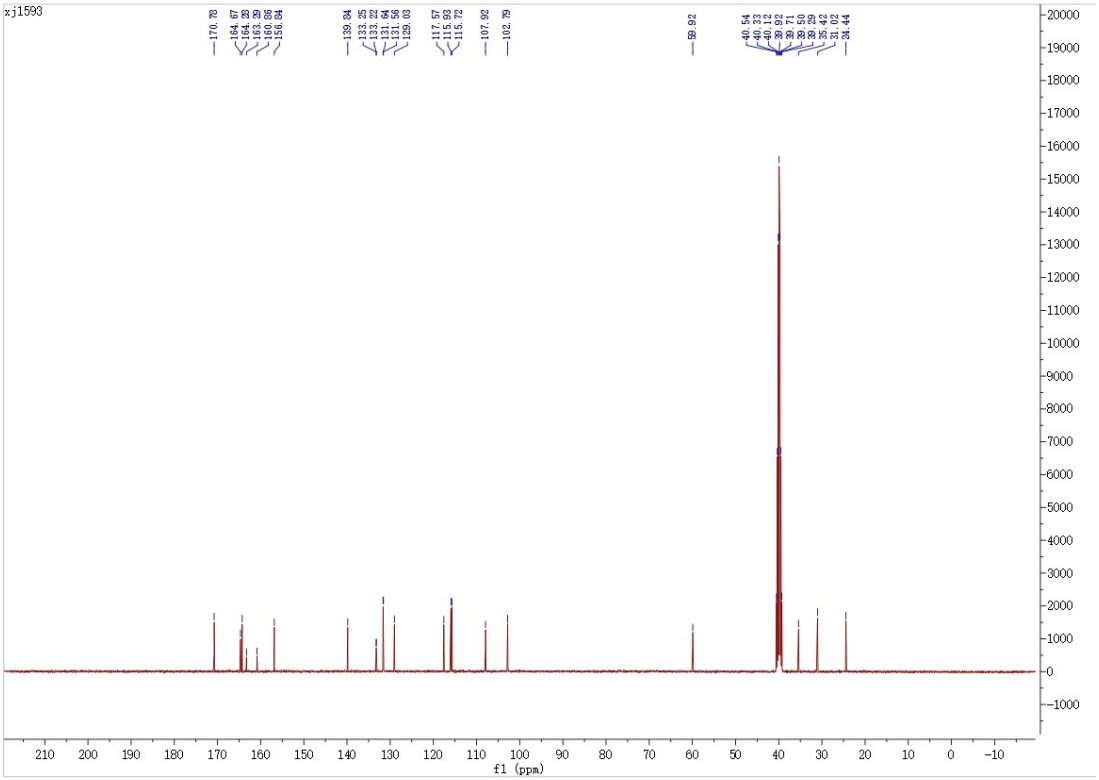


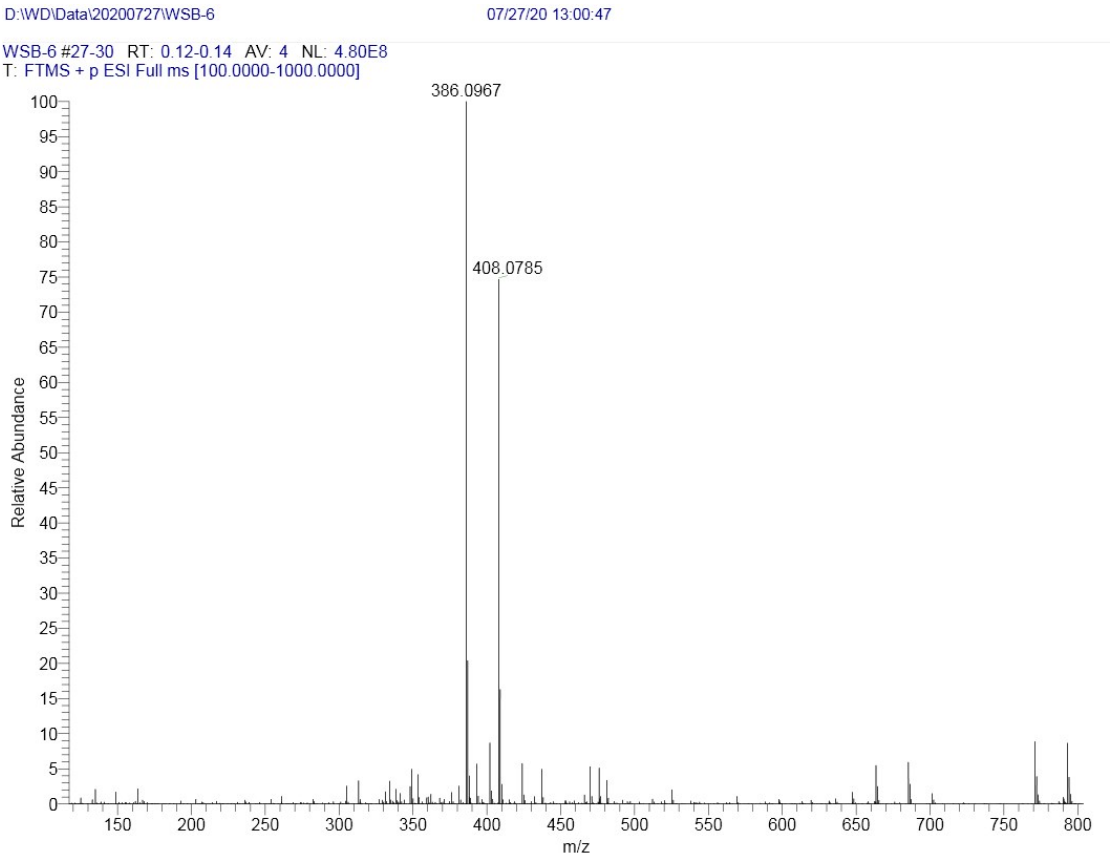


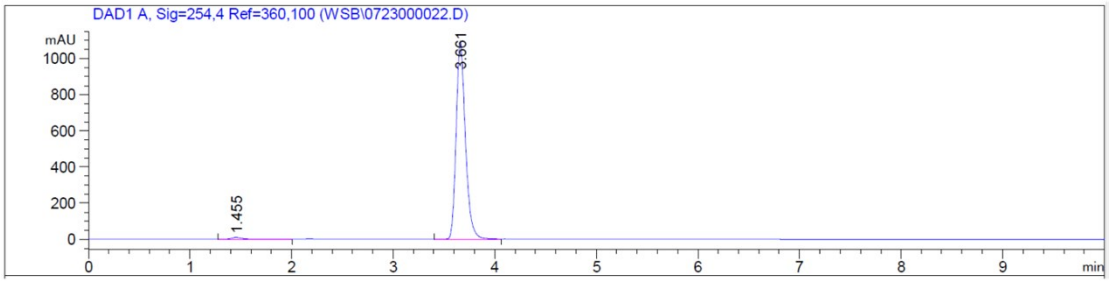
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	1.745	BB	0.0835	112.76347	20.73288	1.0790
2	3.746	BB	0.0998	1.03376e4	1592.00708	98.9210

7-((5-((4-Fluorobenzyl)thio)-1,3,4-oxadiazol-2-yl)methoxy)-3,4-dihydroquinolin-2(1*H*)-one (5f)



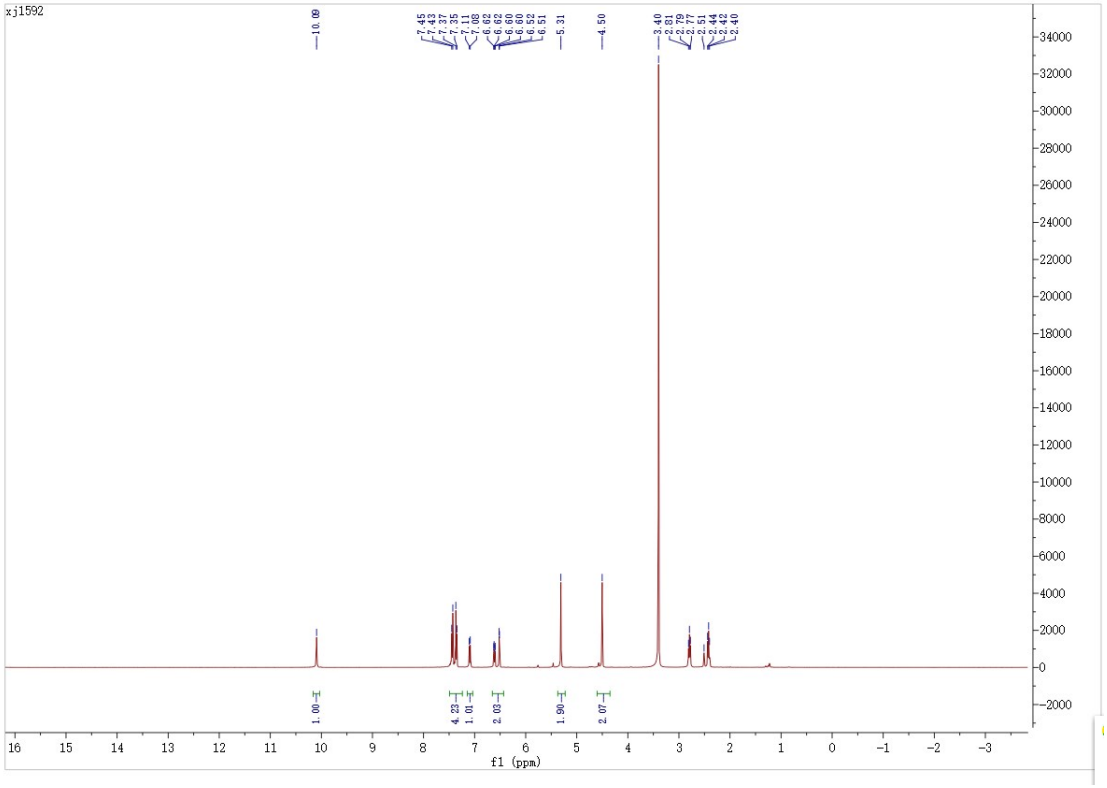


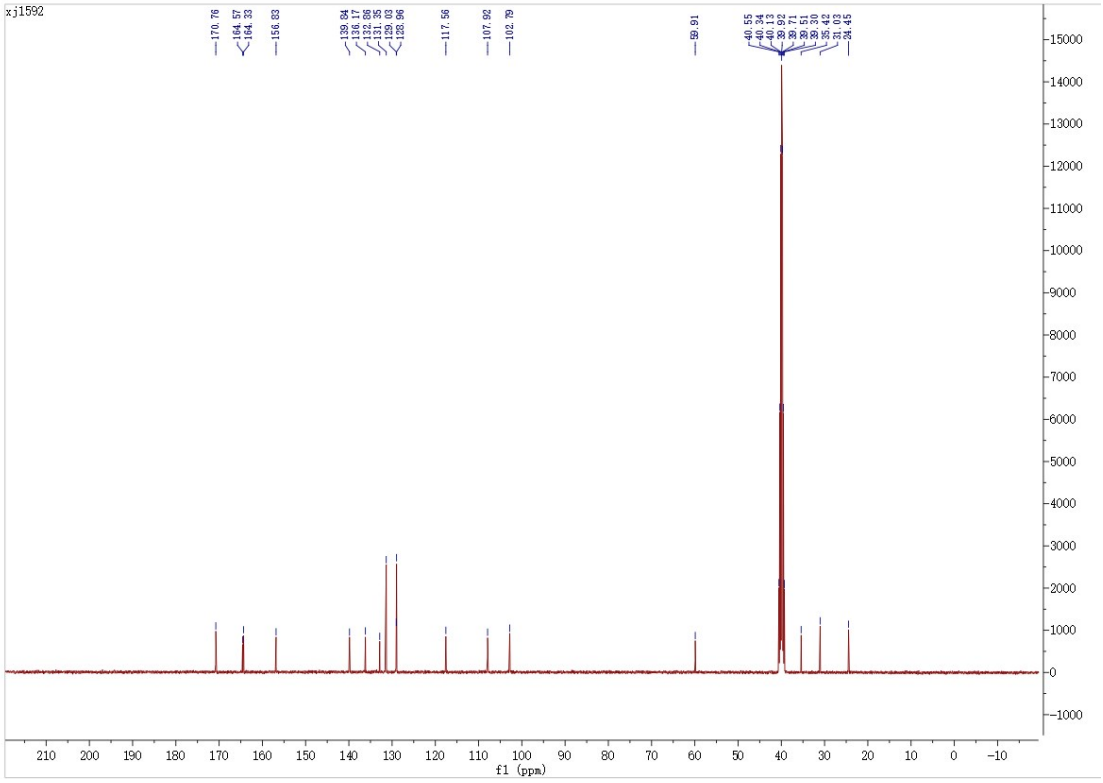




峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	1.455	BB	0.1173	77.38702	9.88971	1.1020
2	3.661	BV	0.0960	6944.82080	1095.42737	98.8980

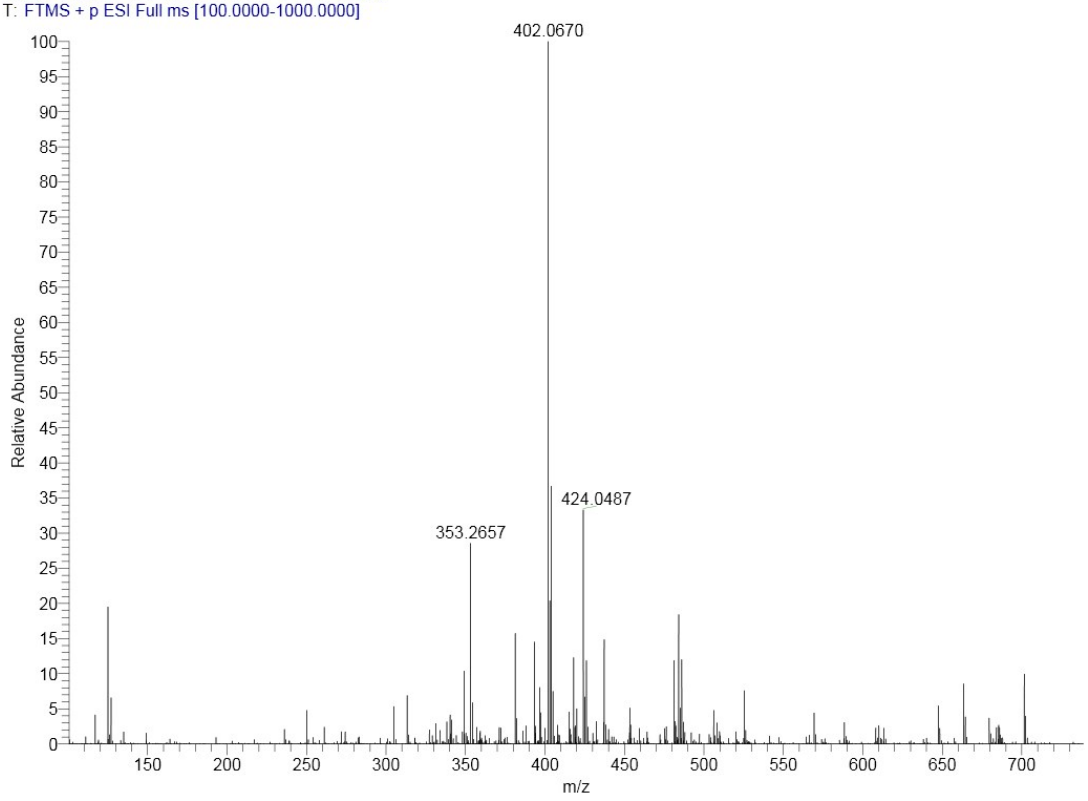
7-((5-((4-Chlorobenzyl)thio)-1,3,4-oxadiazol-2-yl)methoxy)-3,4-dihydroquinolin-2(1*H*)-one (5g)

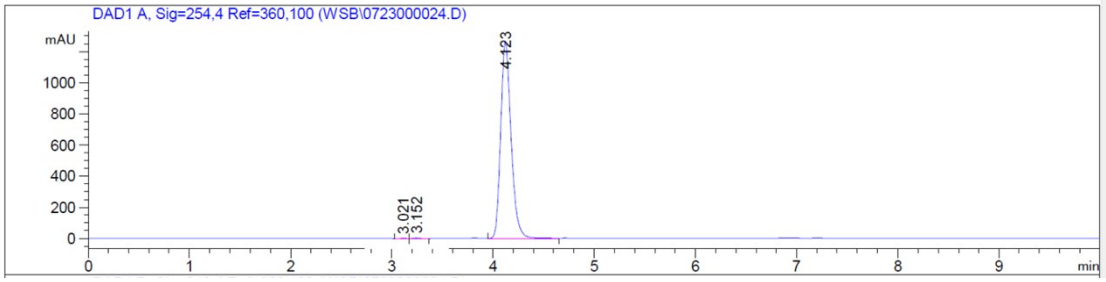




D:\WD\Data\20200727\WSB-7 07/27/20 13:02:43

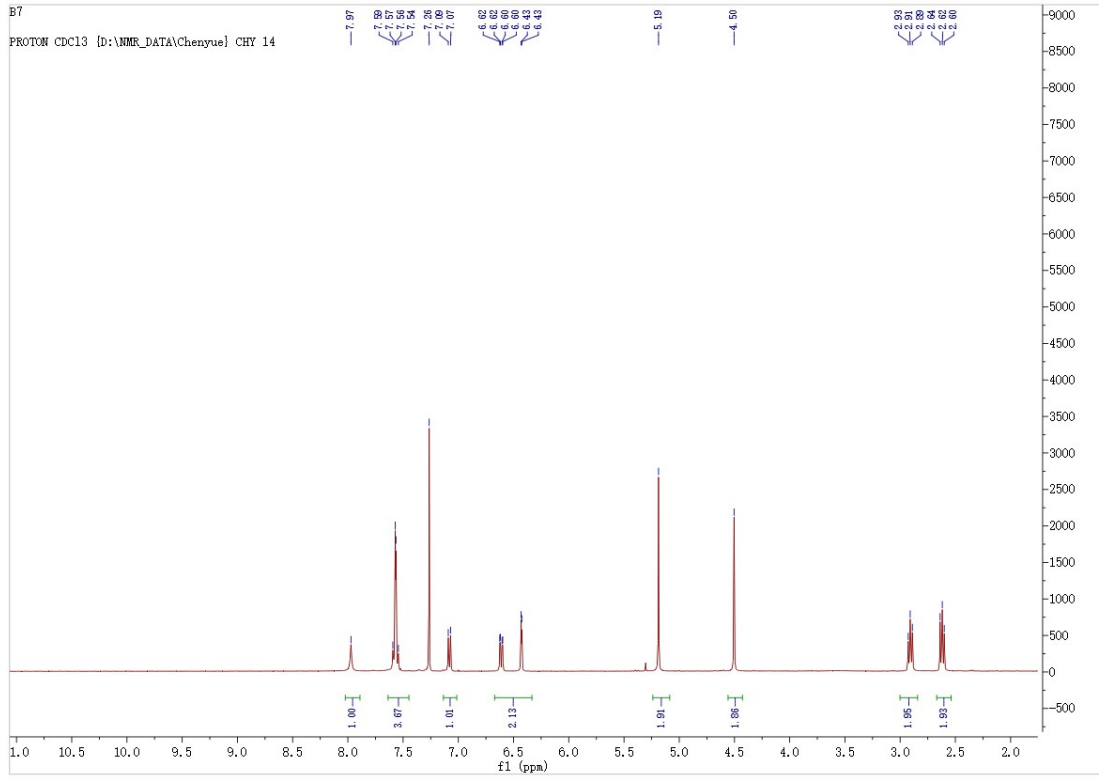
WSB-7 #20-22 RT: 0.10-0.10 AV: 3 NL: 4.29E8
T: FTMS + p ESI Full ms [100.0000-1000.0000]

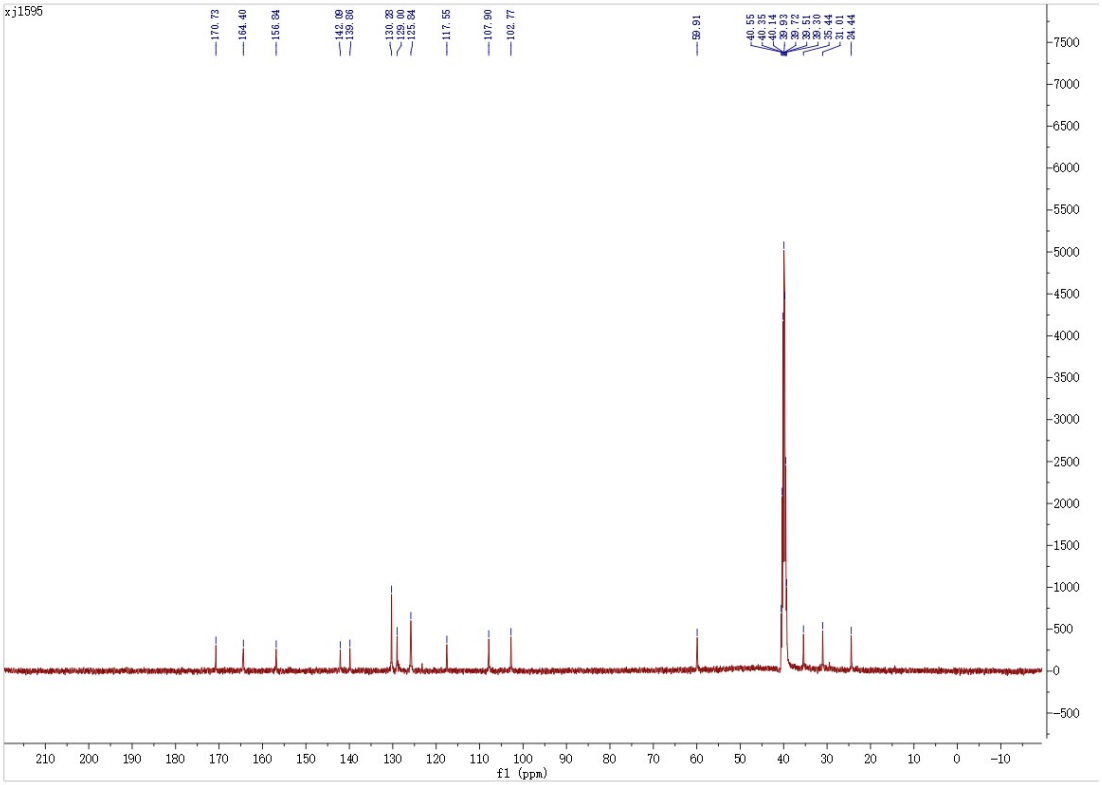




峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	3.021	BV	0.0709	9.98661	2.12349	0.1373
2	3.152	VV	0.0821	19.55841	3.55893	0.2689
3	4.123	BV	0.1091	7242.91016	1017.42377	99.5937

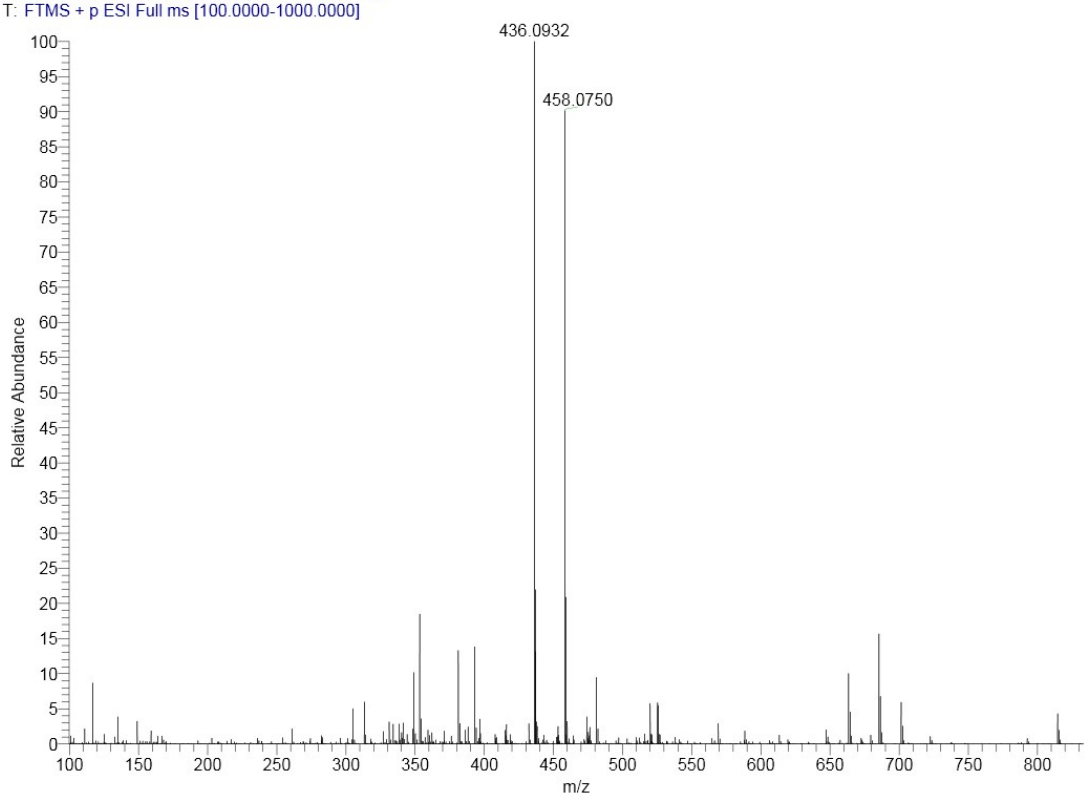
7-((5-((4-Trifluoromethylbenzyl)thio)-1,3,4-oxadiazol-2-yl)methoxy)-3,4-dihydroquinolin-2(1*H*)-one (5h)

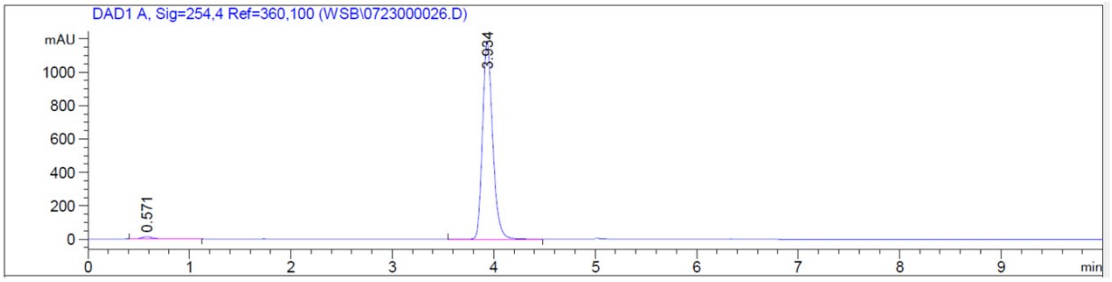




D:\WD\Data\20200727\WSB-8 07/27/20 13:04:42

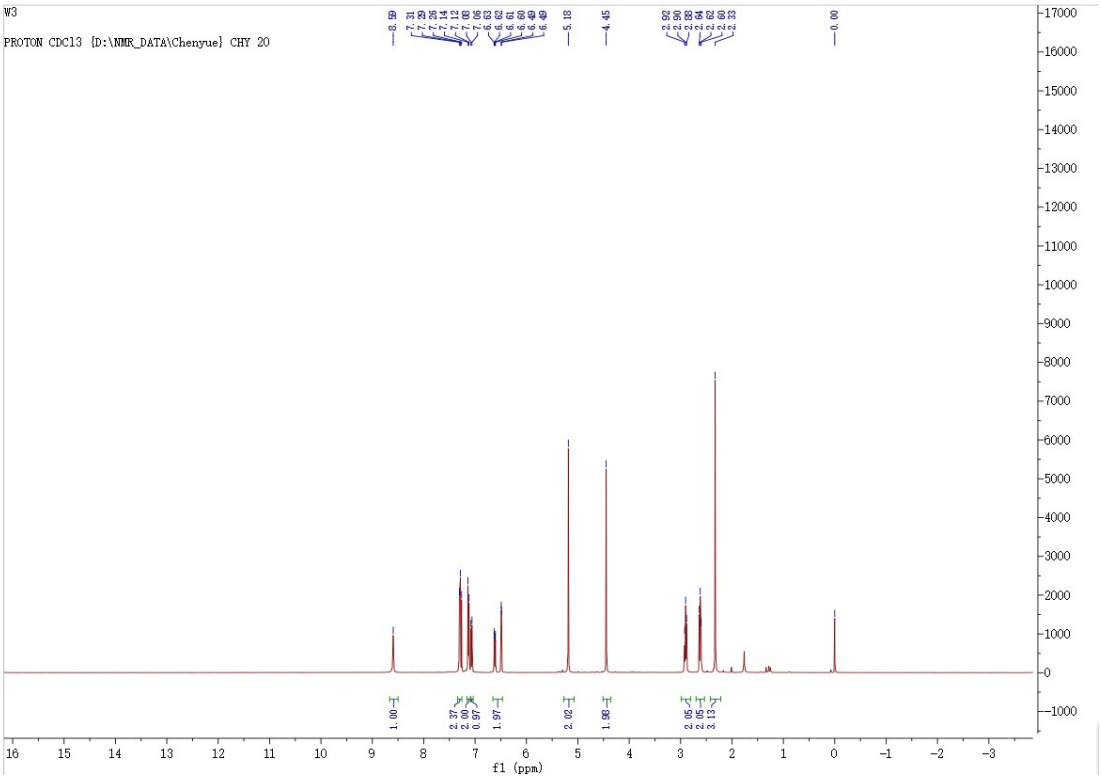
WSB-8 #25-28 RT: 0.11-0.13 AV: 4 NL: 2.77E8
T: FTMS + p ESI Full ms [100.0000-1000.0000]

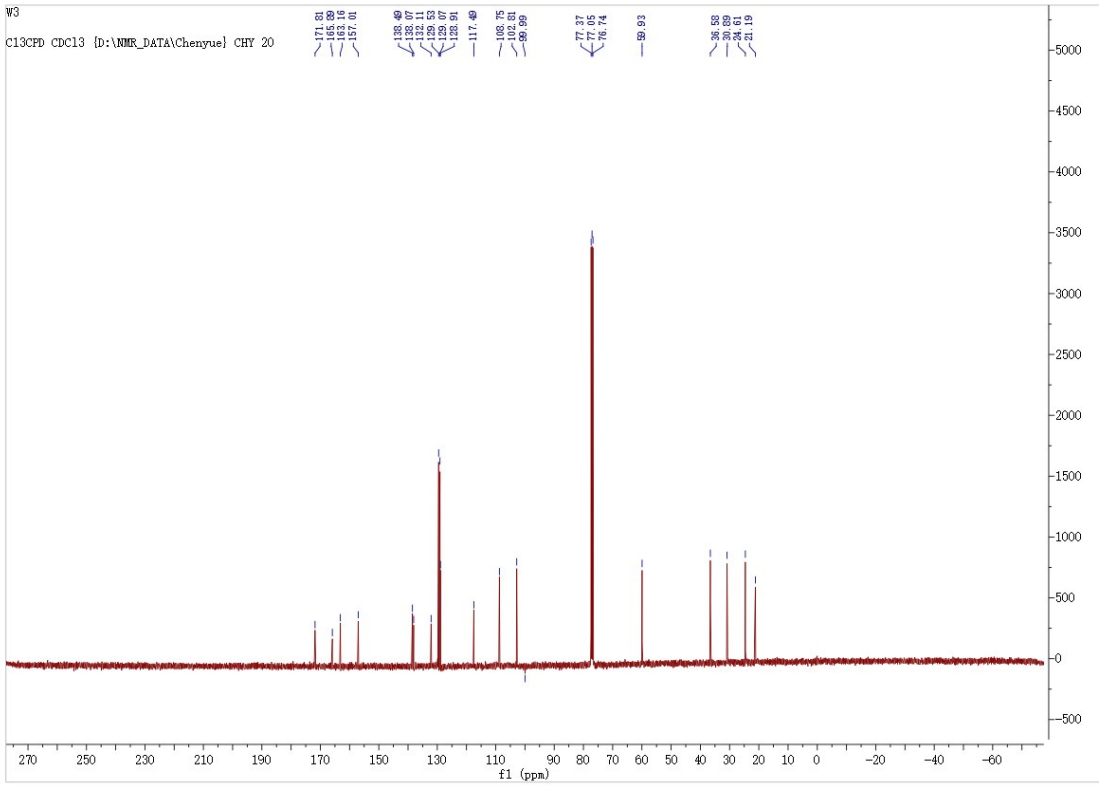


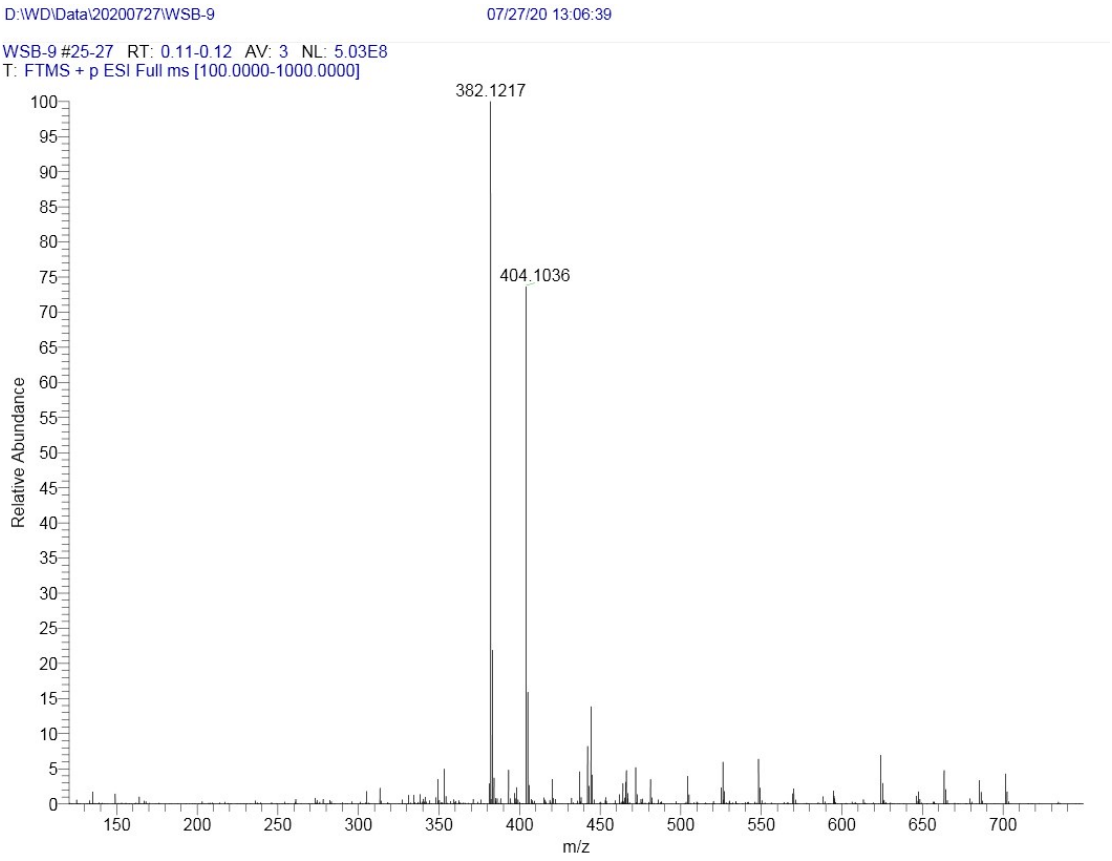


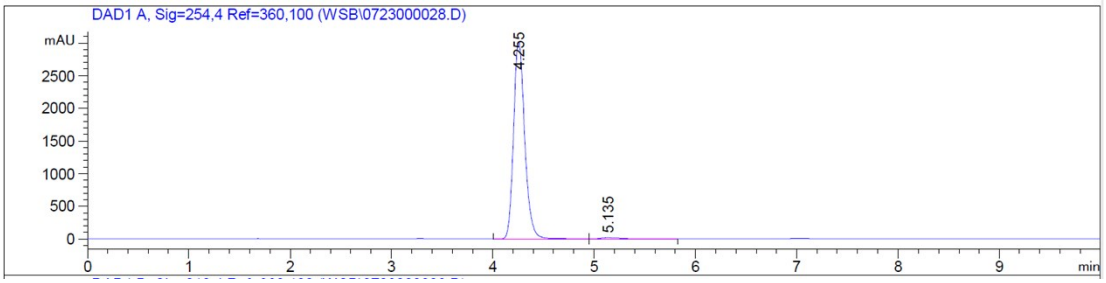
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	0.571	BB	0.1175	75.38078	9.82867	1.1011
2	3.934	BV	0.1071	6770.36963	974.33191	98.8989

7-((5-((4-Methylbenzyl)thio)-1,3,4-oxadiazol-2-yl)methoxy)-3,4-dihydroquinolin-2(1*H*)-one (5i)



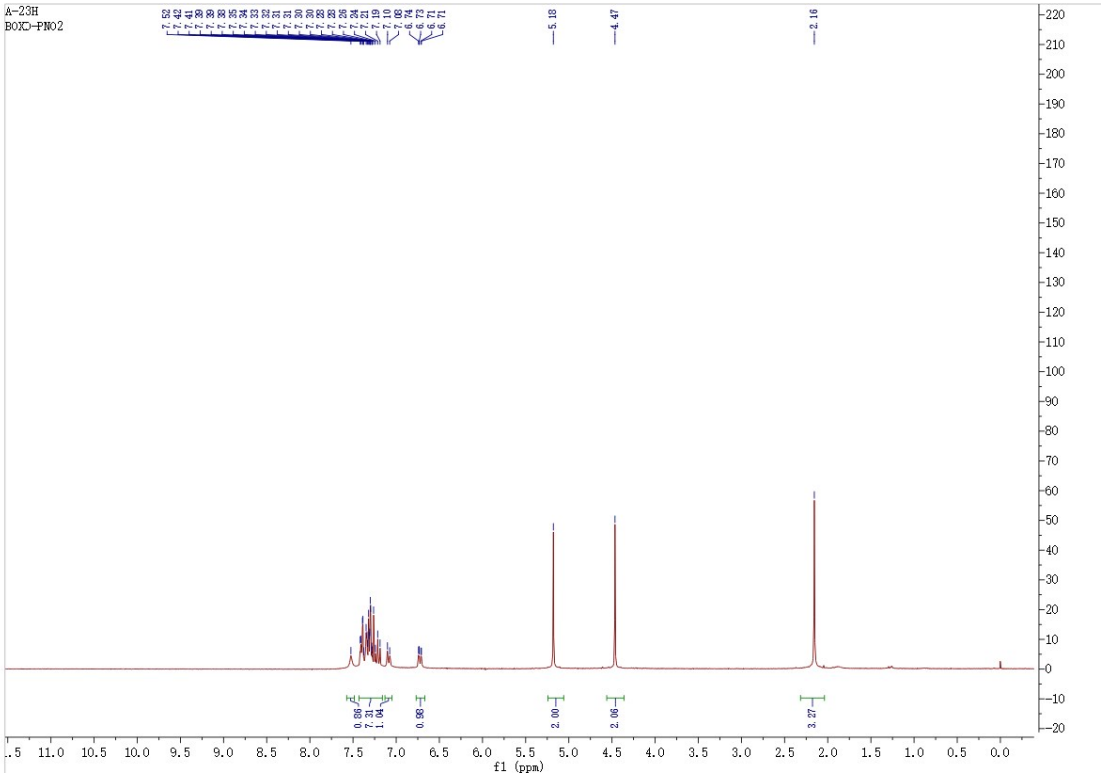


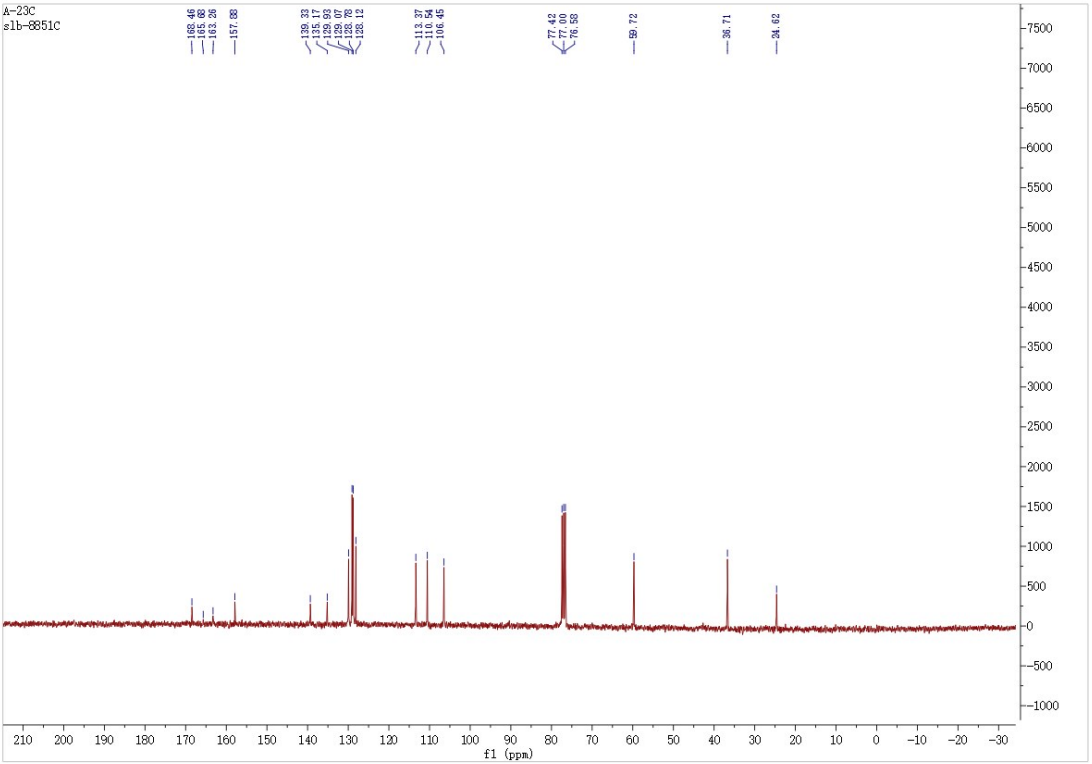




峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	4.255	VV	0.1174	2.31617e4	3023.70532	98.9102
2	5.135	VB	0.1820	255.19794	19.58198	1.0898

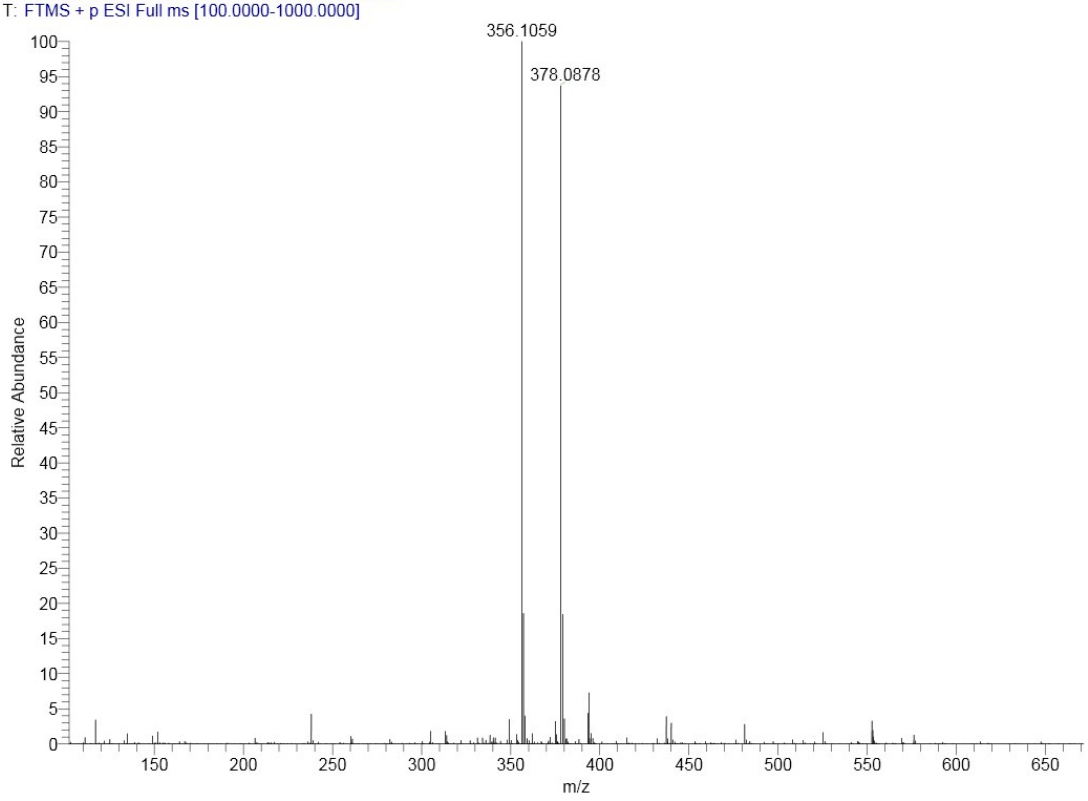
***N*-(3-((5-(Benzylthio)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)acetamide (10a)**

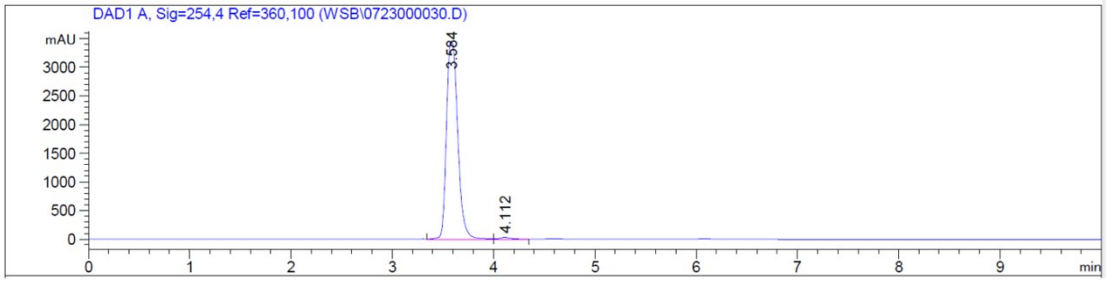




D:\WD\Data\20200727\WSB-10 07/27/20 13:08:35

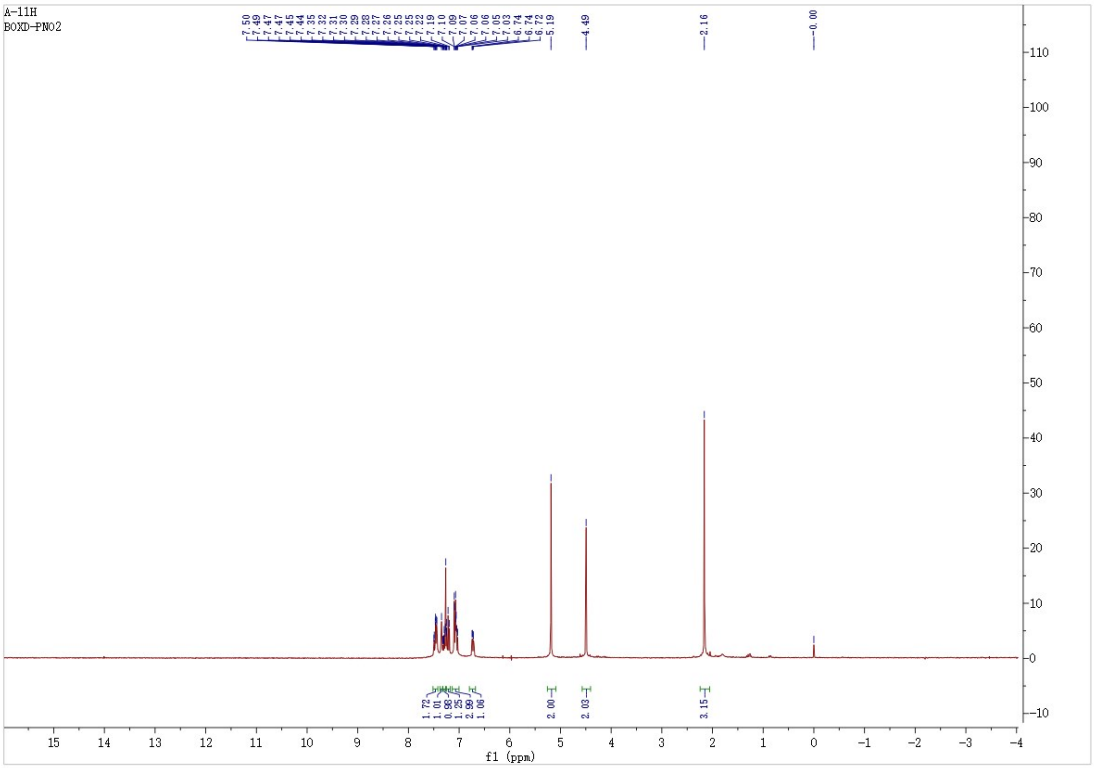
WSB-10 #28-31 RT: 0.13-0.14 AV: 4 NL: 6.83E8
T: FTMS + p ESI Full ms [100.0000-1000.0000]

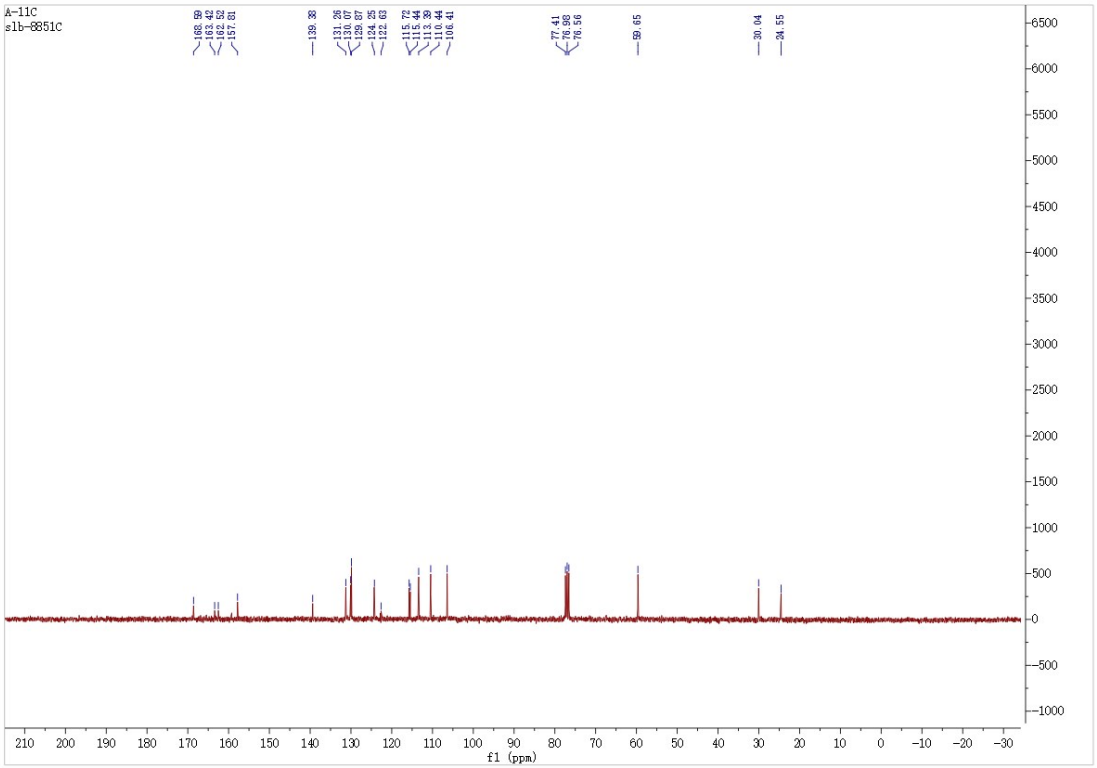


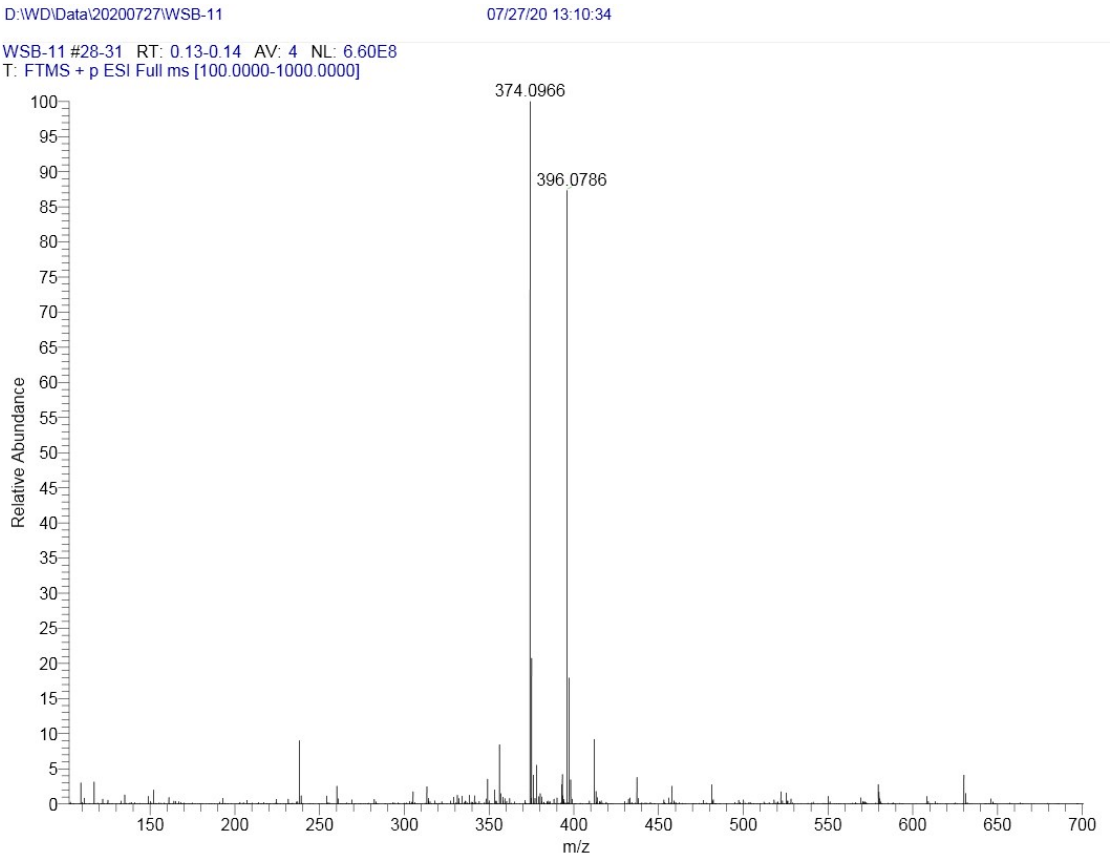


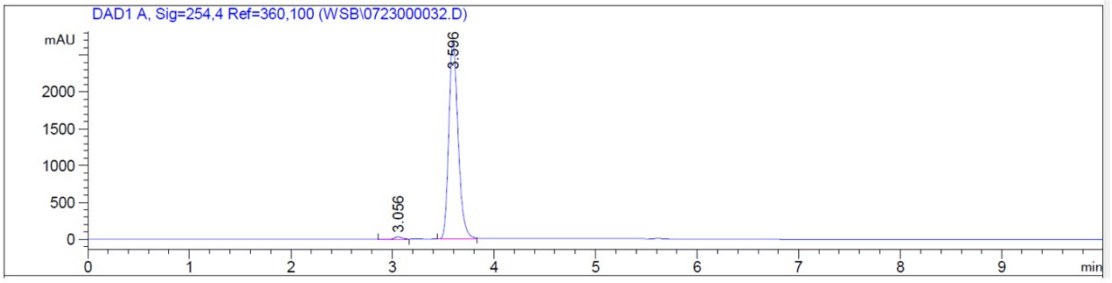
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	3.584	VV	0.1219	2.66512e4	3457.18848	99.1414
2	4.112	VB	0.1155	230.80208	30.08572	0.8586

***N*-(3-((5-((2-Fluorobenzyl)thio)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)acetamide (10b)**



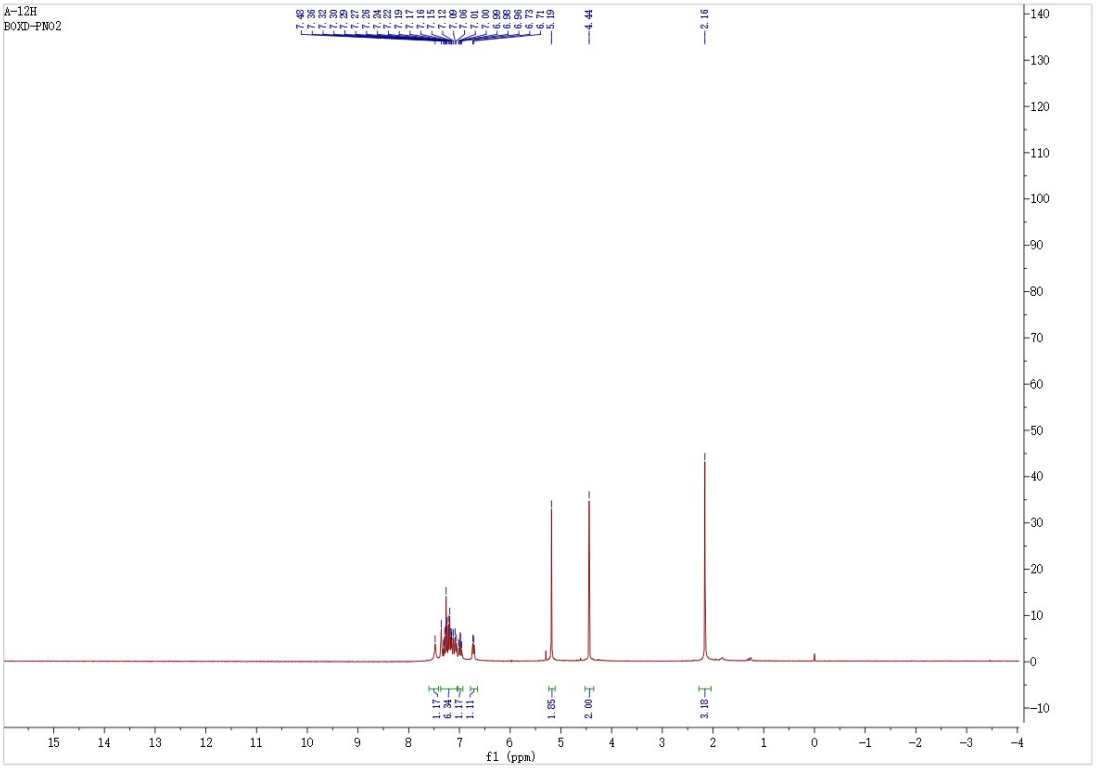


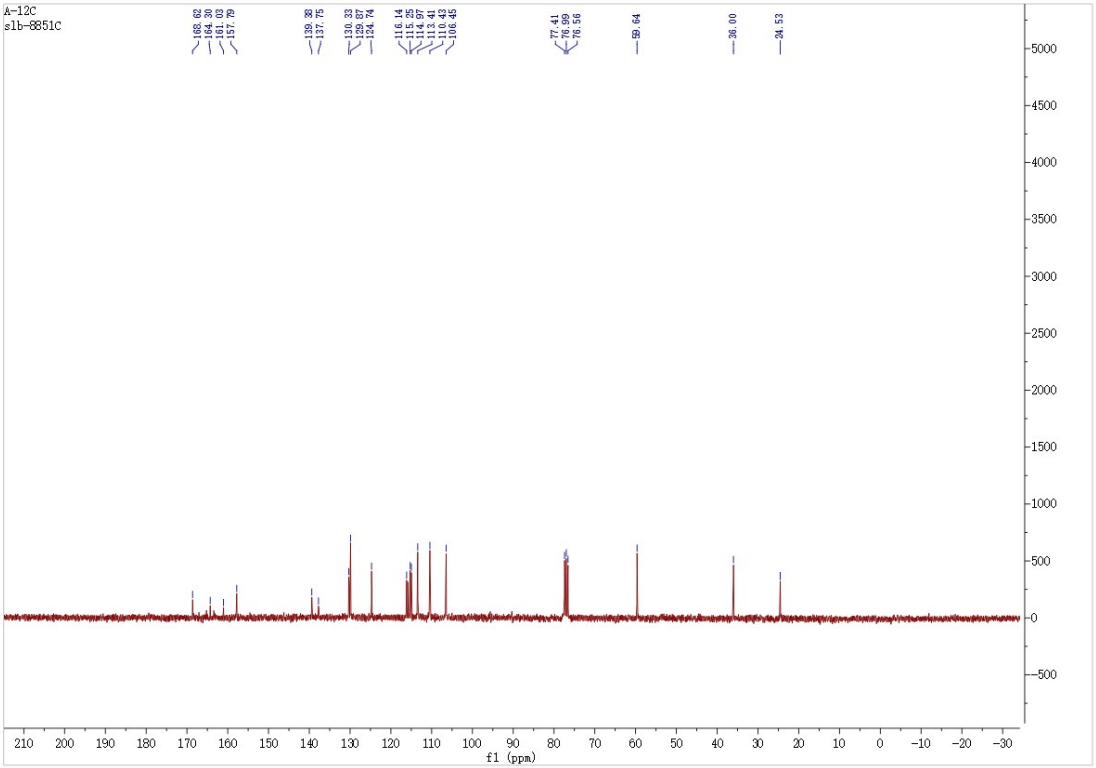


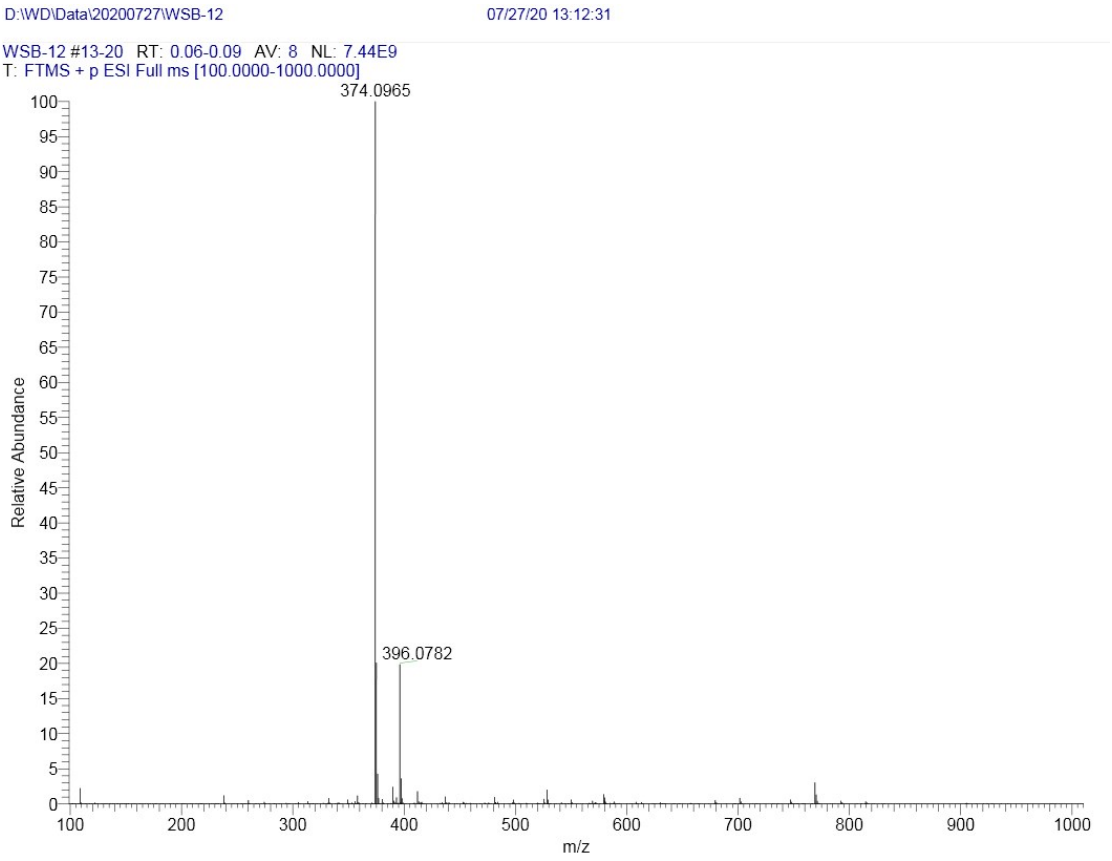


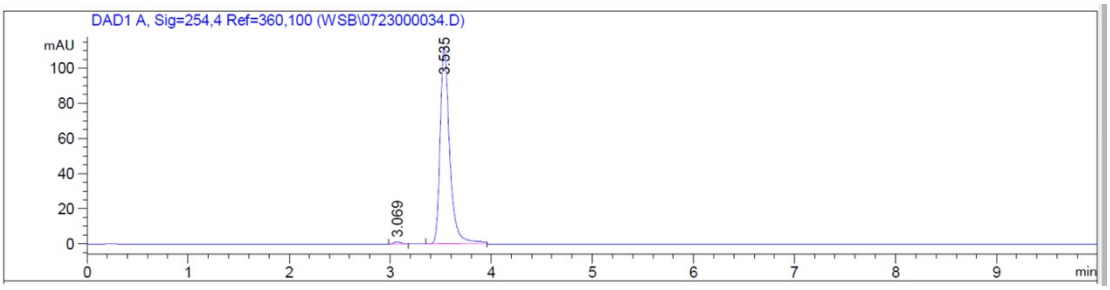
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	3.056	BV	0.0767	156.56313	31.10605	0.9053
2	3.596	BV	0.0984	1.71371e4	2688.71094	99.0947

***N*-(3-((5-((3-Fluorobenzyl)thio)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)acetamide (10c)**



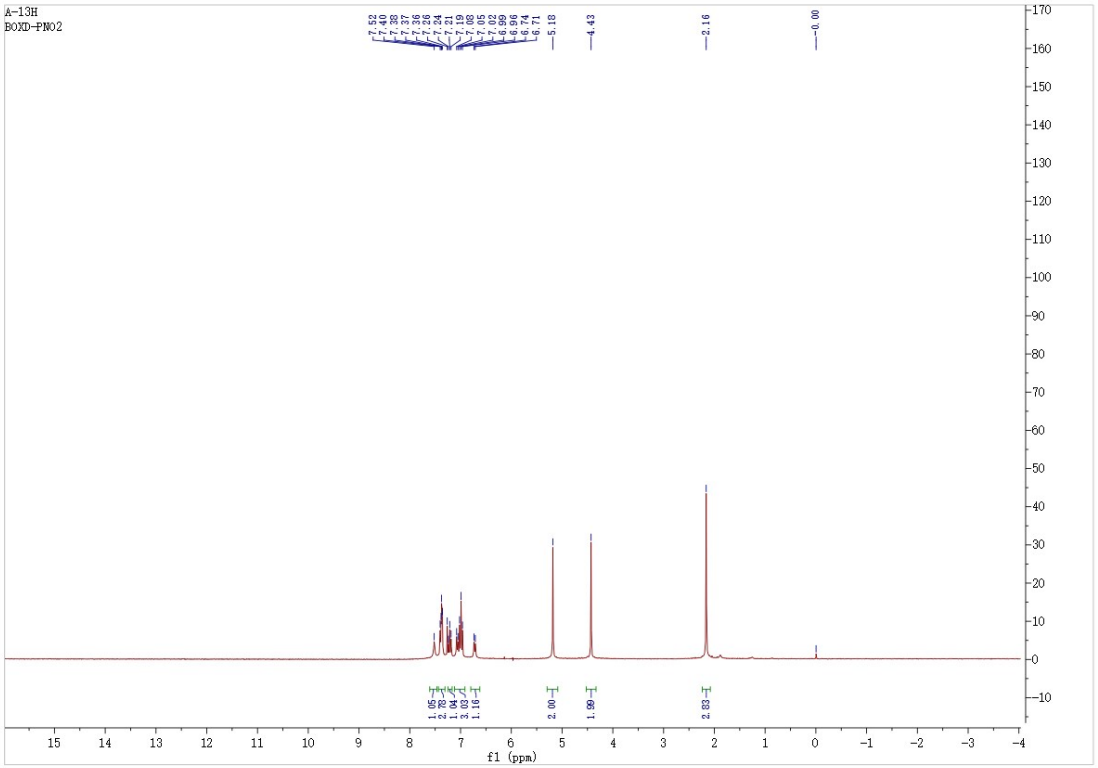


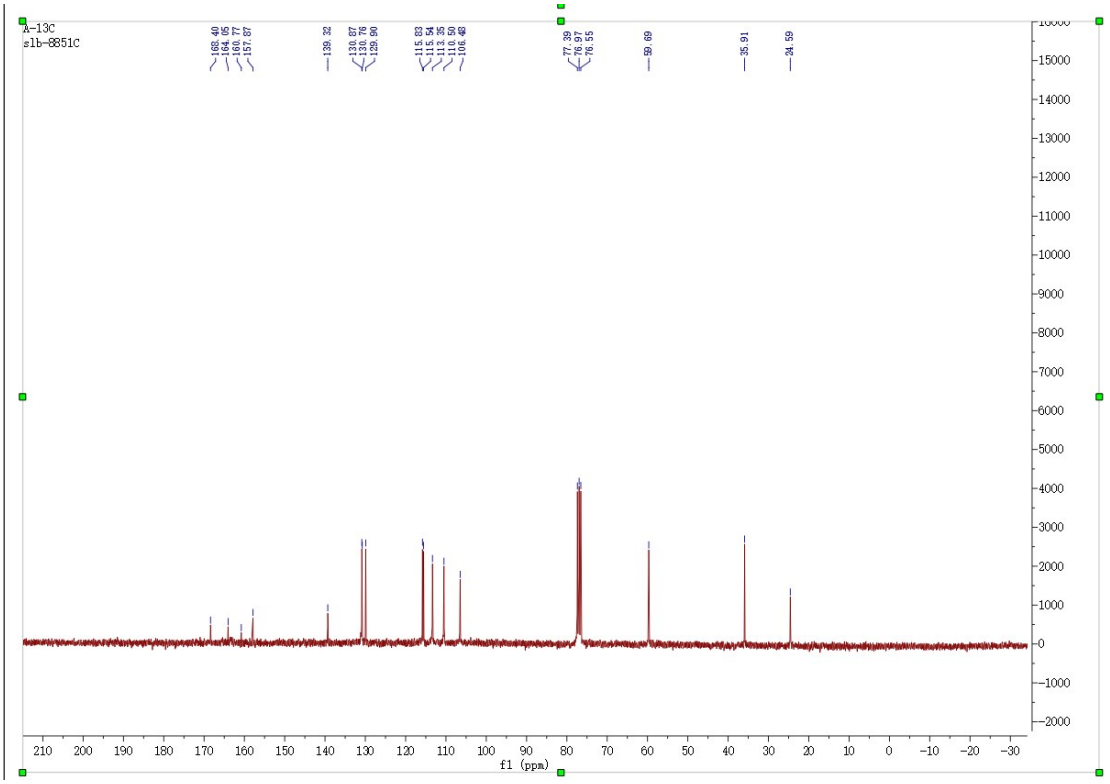


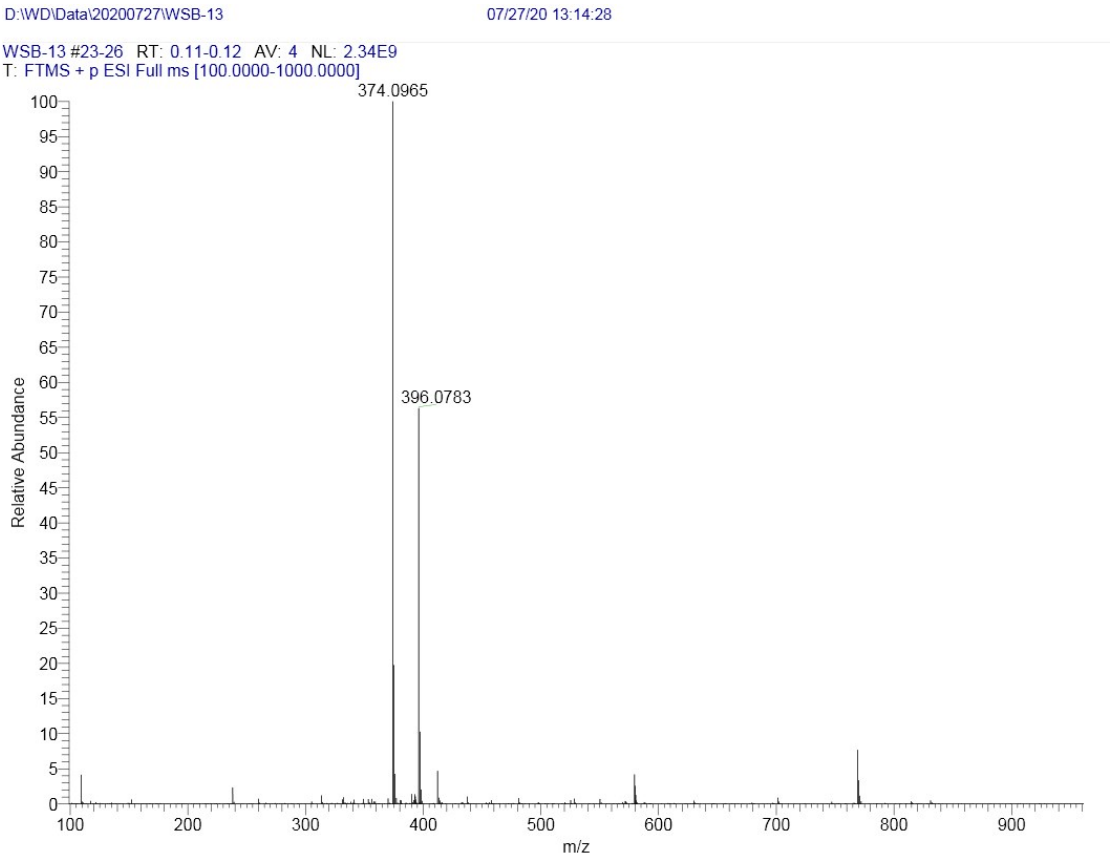


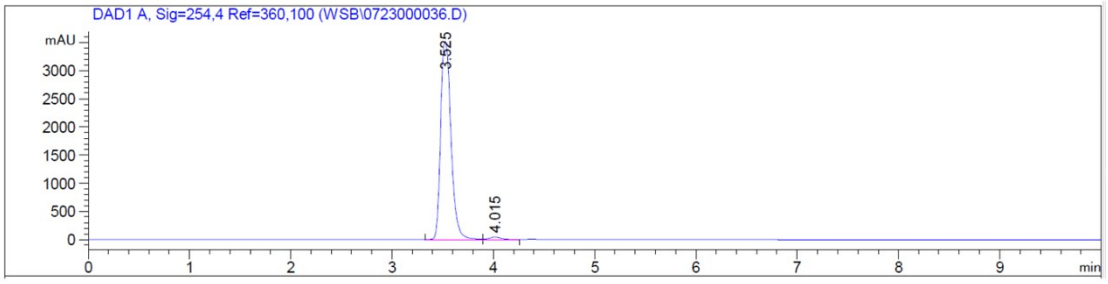
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	3.069	BB	0.0731	5.51989	1.16946	0.7487
2	3.535	BV	0.0981	731.73938	112.12041	99.2513

***N*-(3-((5-((4-Fluorobenzyl)thio)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)acetamide (10d)**



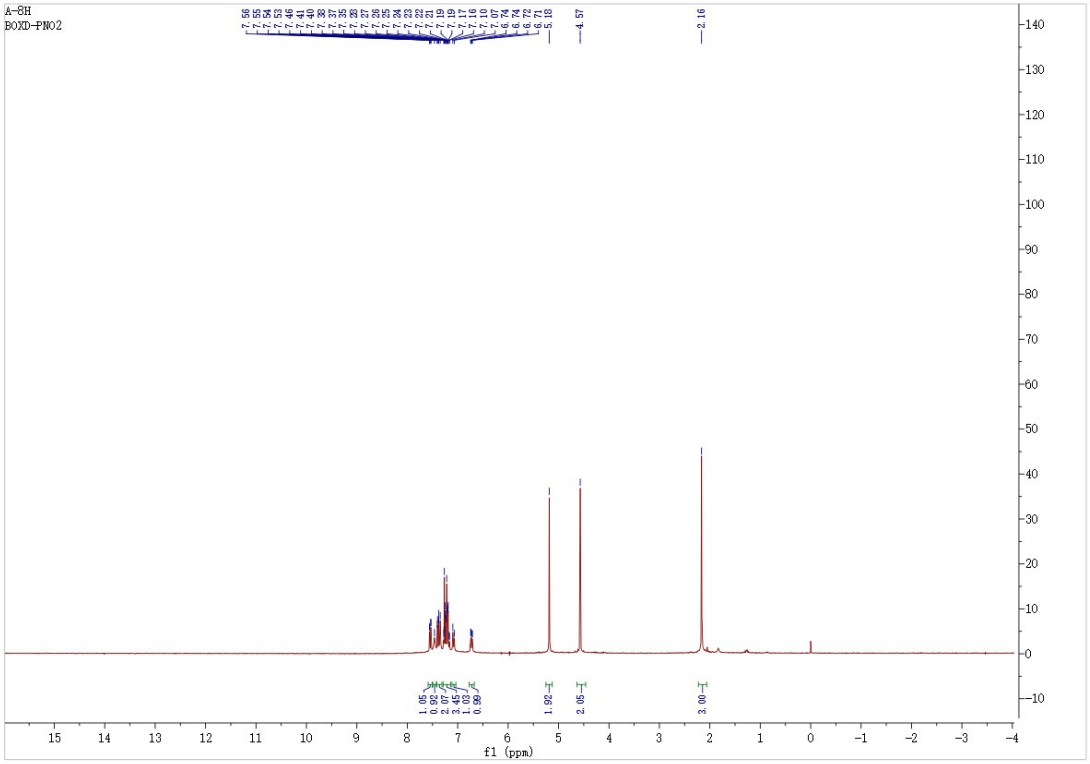


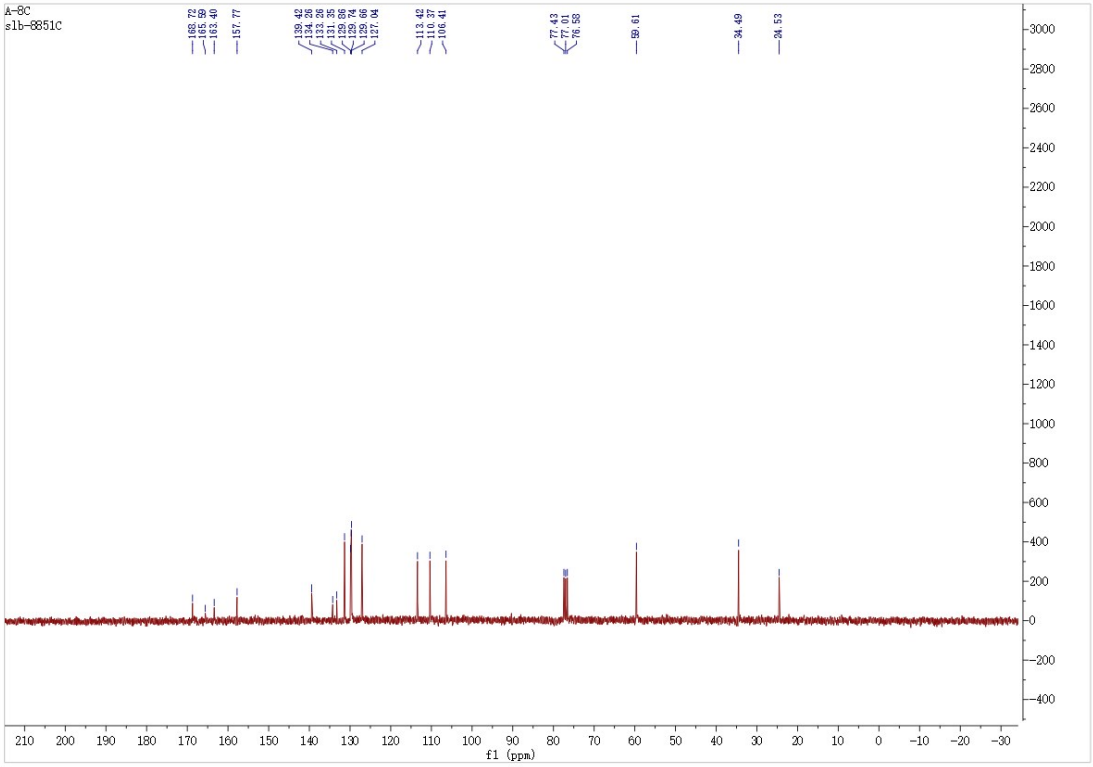




峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	3.525	VV	0.1130	2.50620e4	3522.91797	98.7015
2	4.015	VB	0.1172	329.71811	42.18111	1.2985

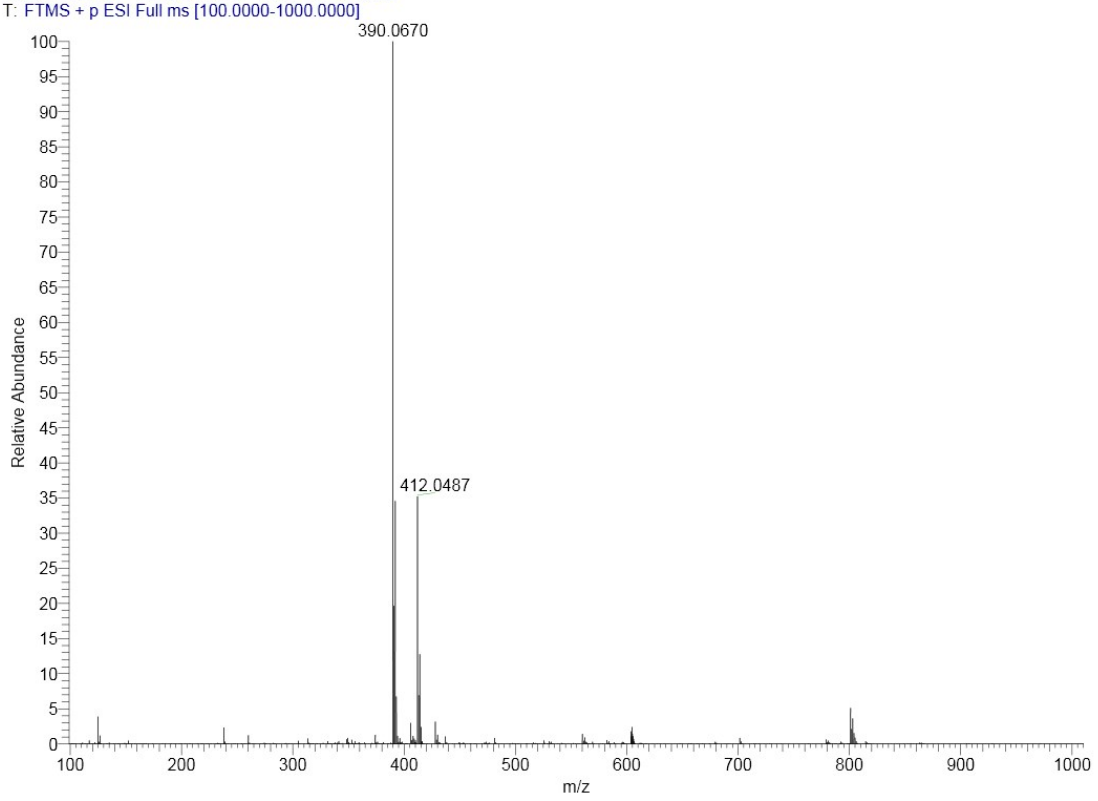
***N*-(3-((5-((2-Chlorobenzyl)thio)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)acetamide (10e)**

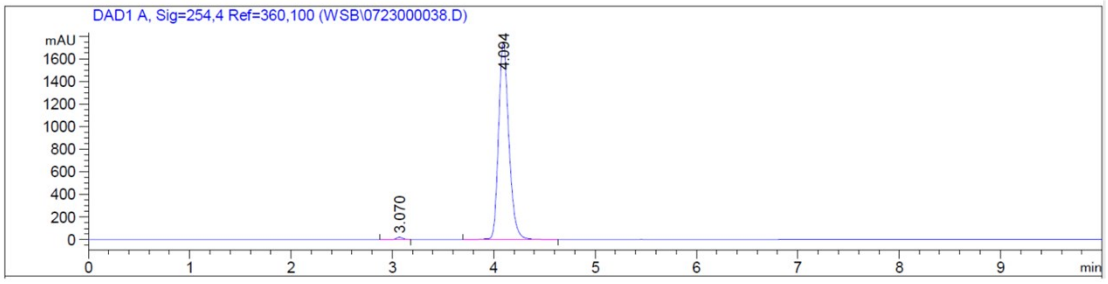




D:\WD\Data\20200727\WSB-14 07/27/20 13:16:24

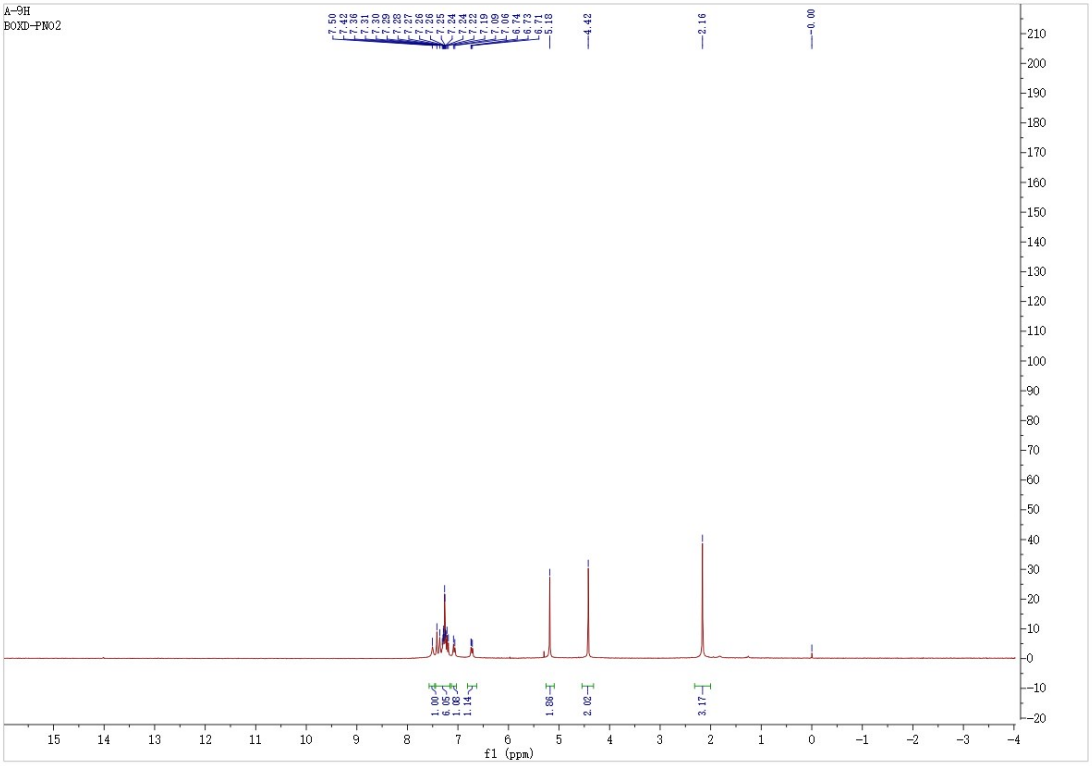
WSB-14 #24-27 RT: 0.11-0.12 AV: 4 NL: 2.46E9
T: FTMS + p ESI Full ms [100.0000-1000.0000]

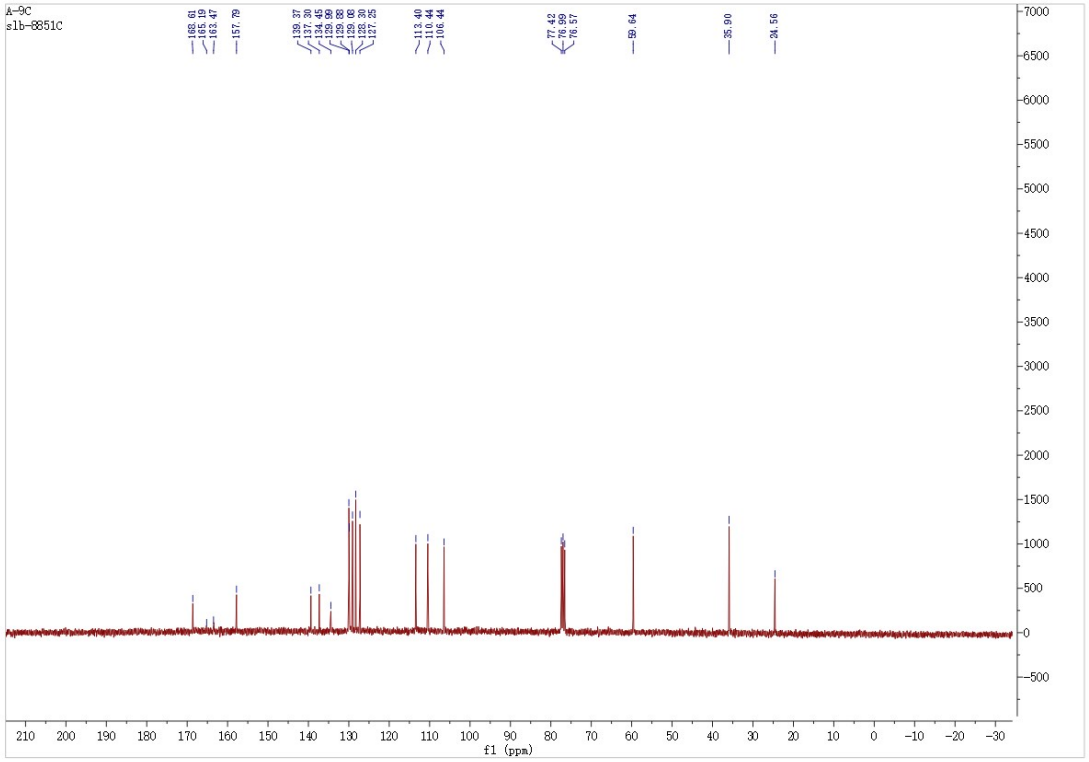




峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	3.070	BV	0.0807	103.27309	19.86325	0.8286
2	4.094	BBA	0.1086	1.23605e4	1746.55688	99.1714

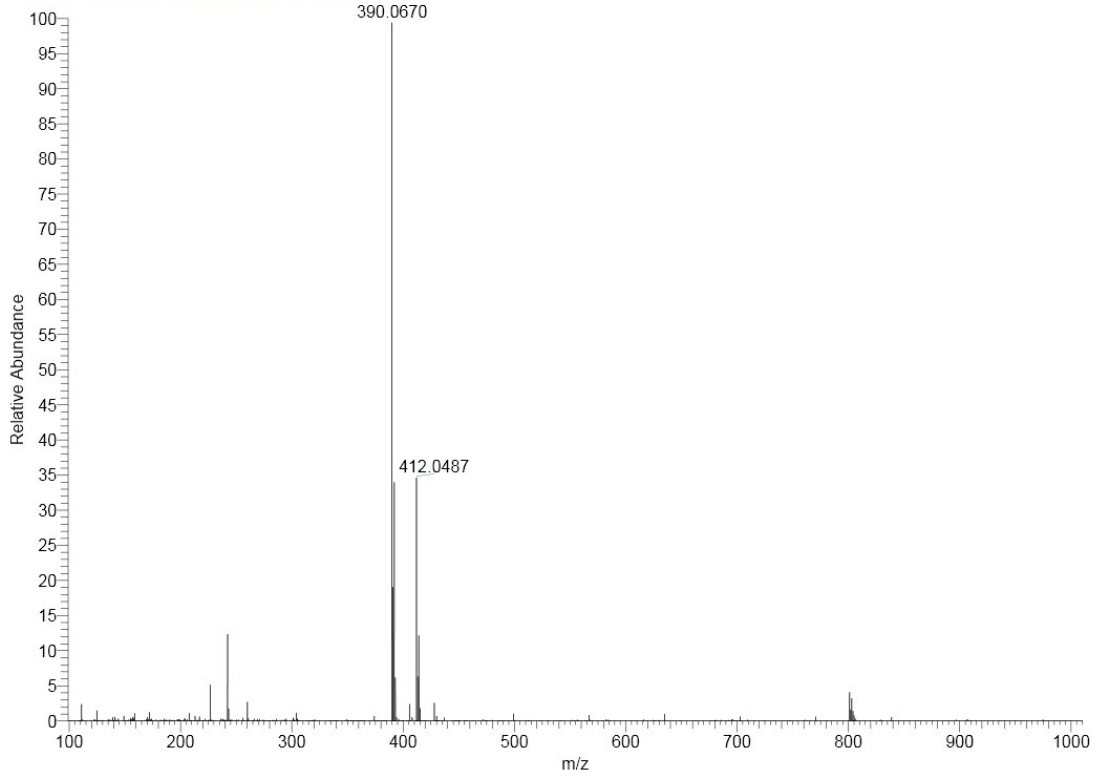
***N*-(3-((5-((3-Chlorobenzyl)thio)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)acetamide (10f)**

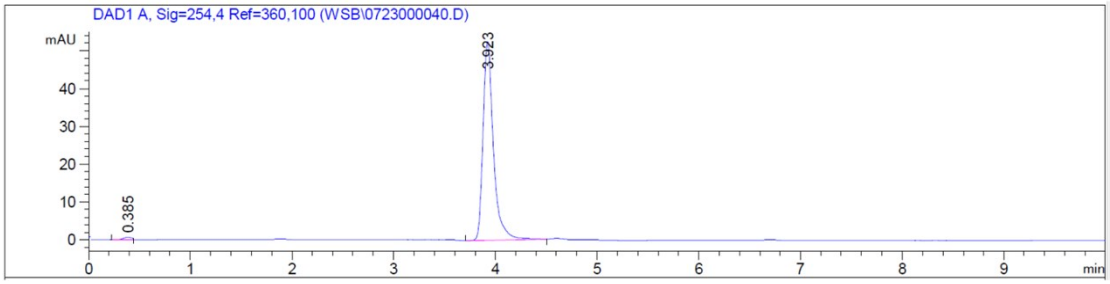




D:\WD\Data\20200727\WSB-15_200727141410 07/27/20 14:15:08

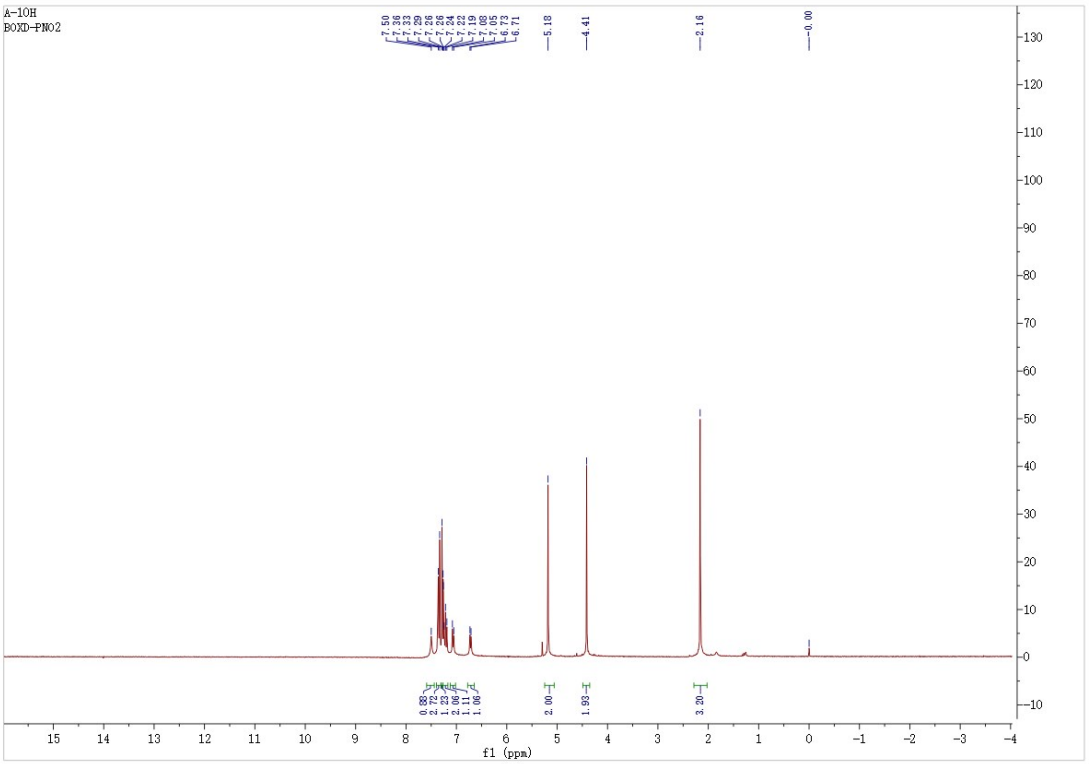
WSB-15_200727141410 #40 RT: 0.18 AV: 1 SB: 52 0.59-0.81 NL: 3.55E8
T: FTMS + p ESI Full ms [100.0000-1000.0000]

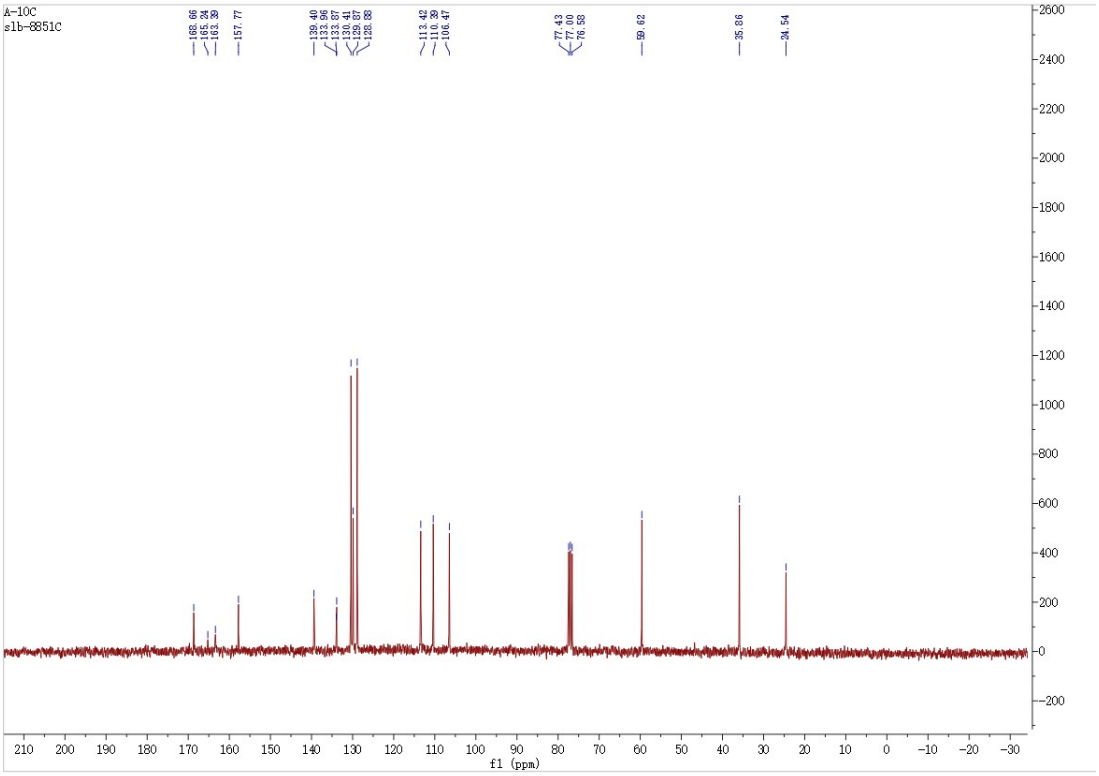




峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	0.385	BV	0.0864	4.01159	7.04689e-1	1.0647
2	3.923	BB	0.1066	372.76541	52.65183	98.9353

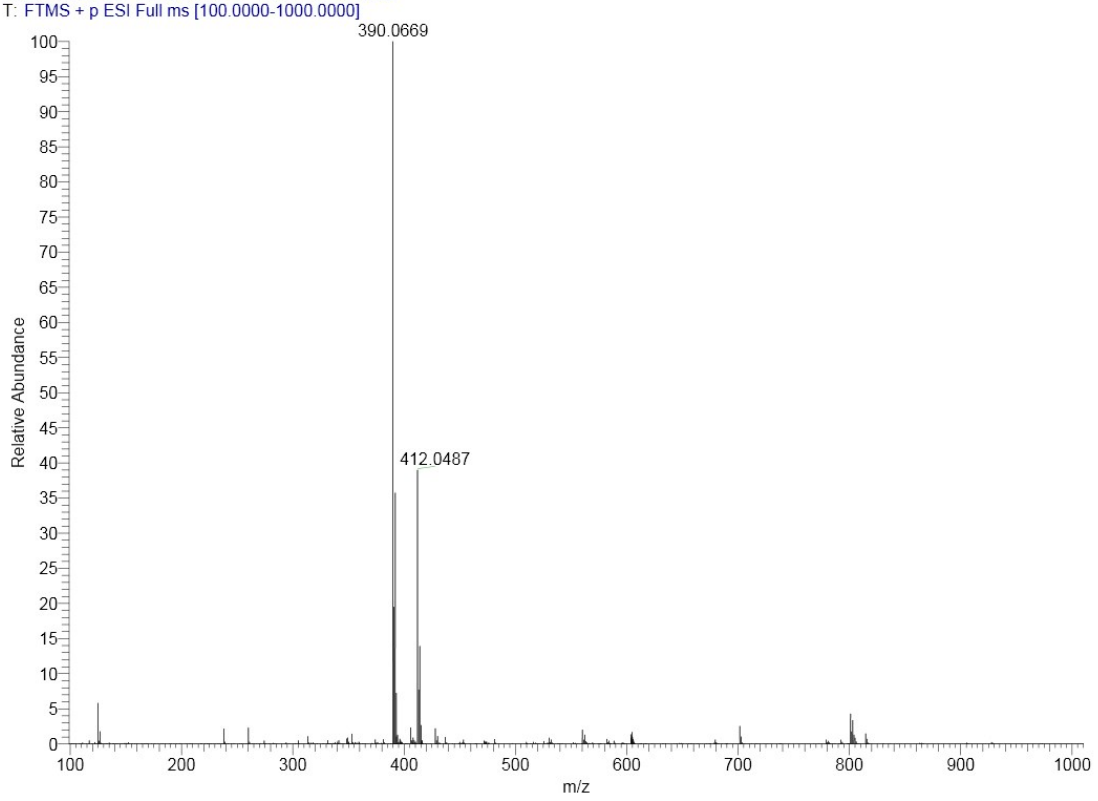
***N*-(3-((5-((4-Chlorobenzyl)thio)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)acetamide (10g)**

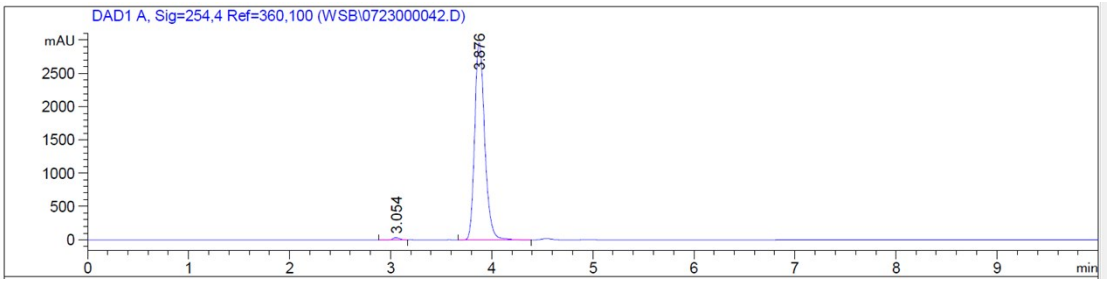




D:\WD\Data\20200727\WSB-16 07/27/20 13:20:20

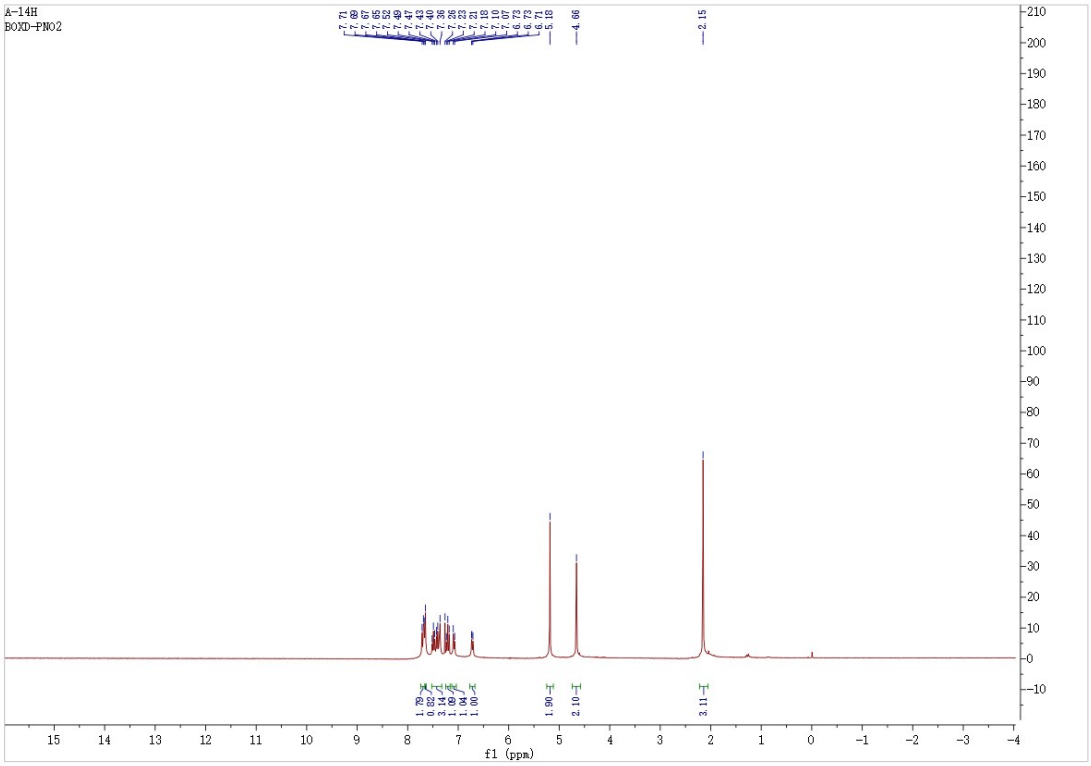
WSB-16 #21-23 RT: 0.10-0.11 AV: 3 NL: 2.48E9
T: FTMS + p ESI Full ms [100.0000-1000.0000]

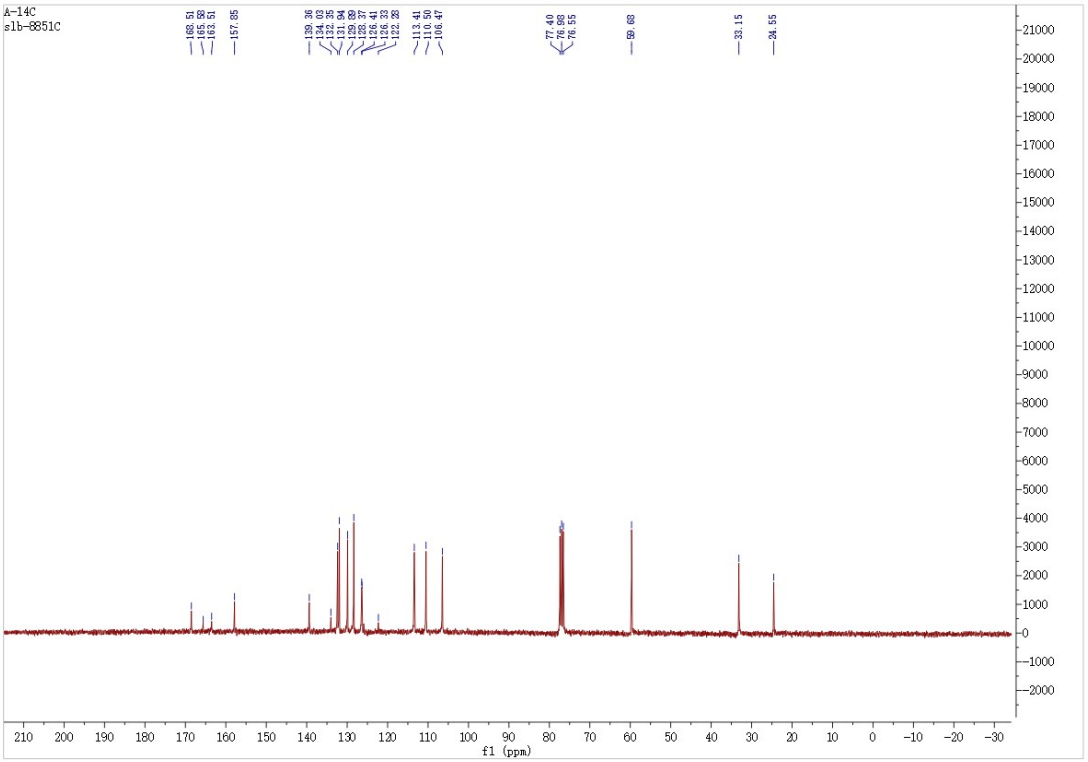




峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	3.054	VV	0.0775	194.85475	38.18985	0.9403
2	3.876	VB	0.1085	2.05280e4	2974.74121	99.0597

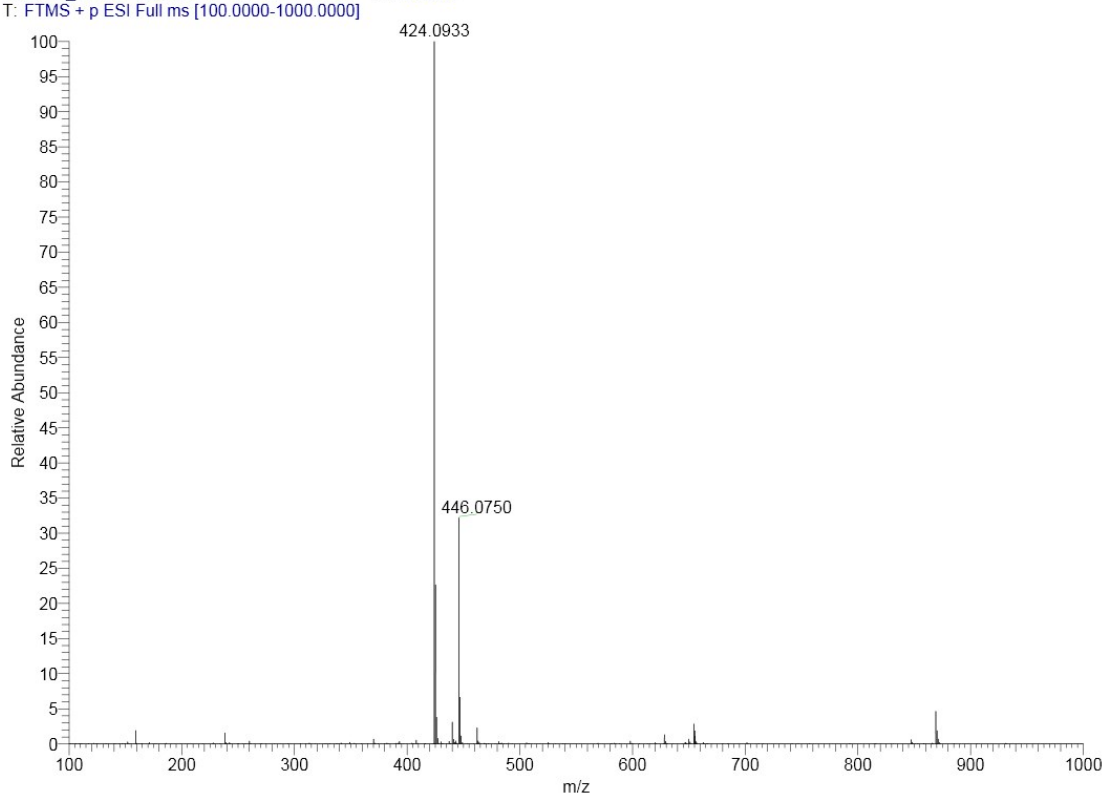
***N*-(3-((5-((2-Trifluoromethylbenzyl)thio)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)acetamide (10h)**

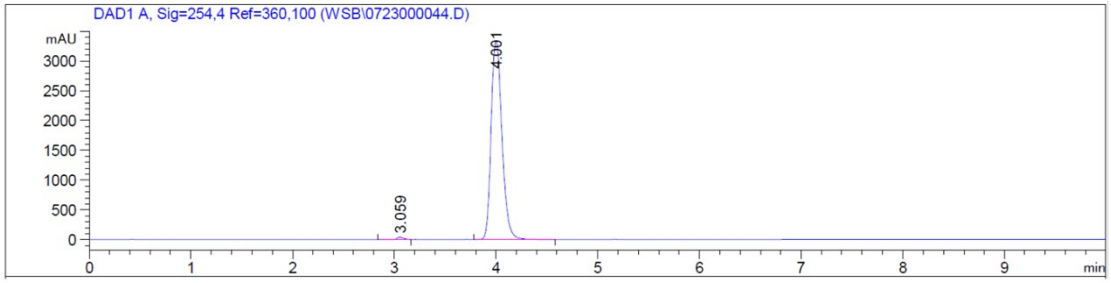




D:\WD\Data\20200727\WSB-17_200727142028 07/27/20 14:20:28

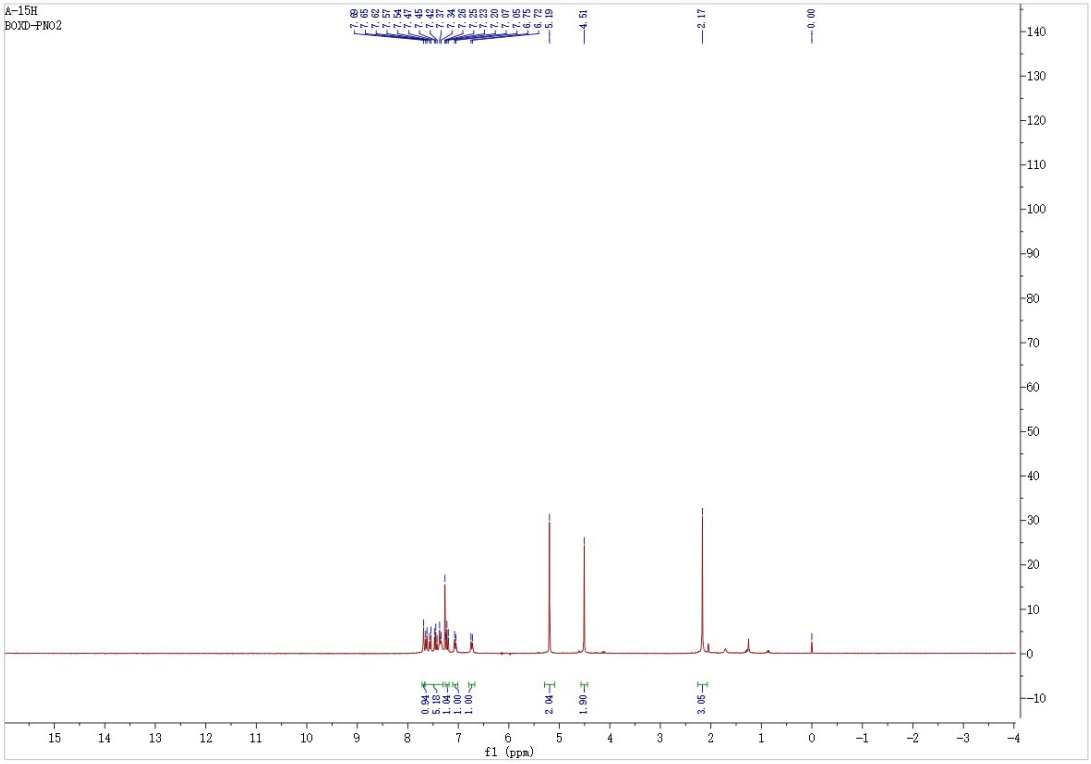
WSB-17_200727142028 #26 RT: 0.12 AV: 1 NL: 5.99E9
T: FTMS + p ESI Full ms [100.0000-1000.0000]

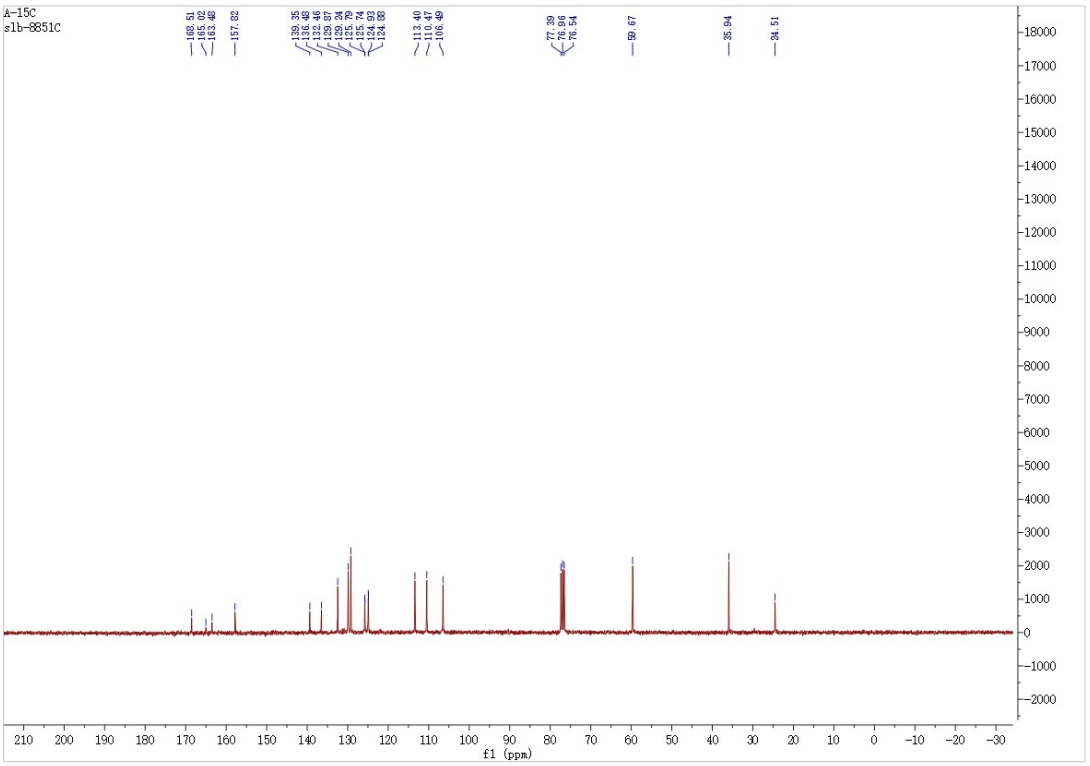


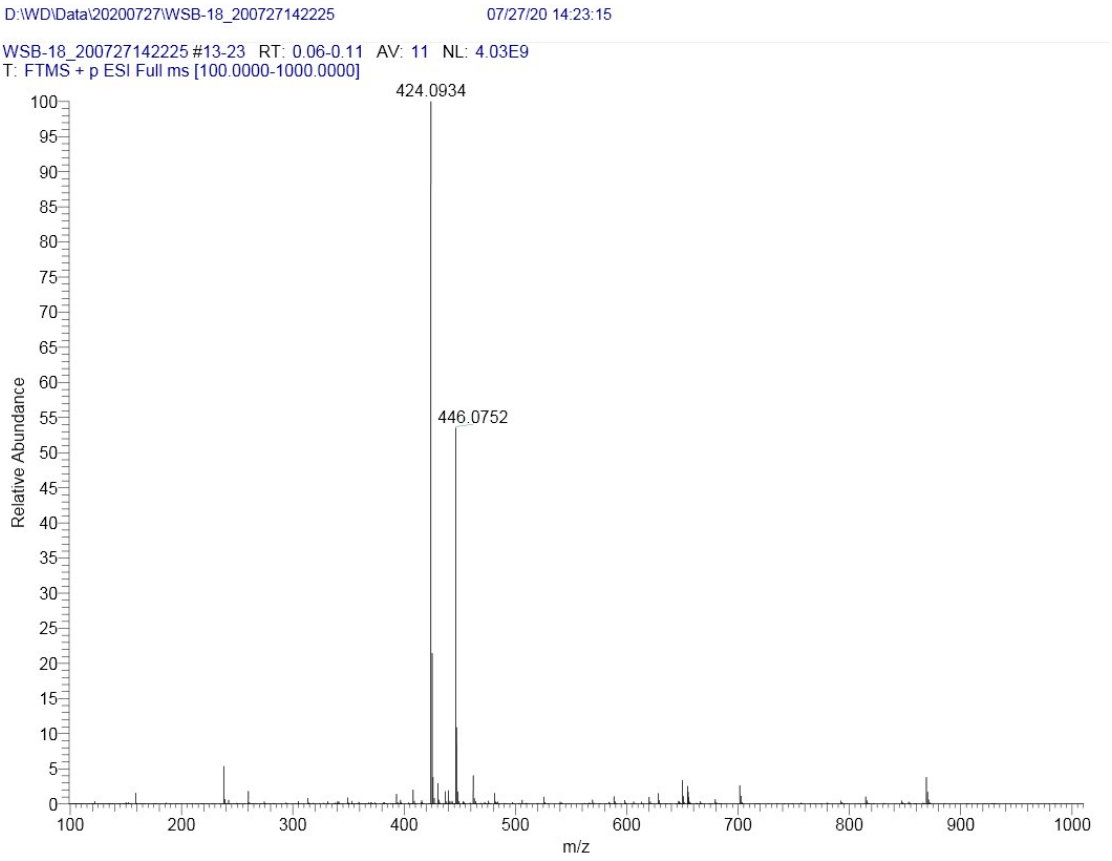


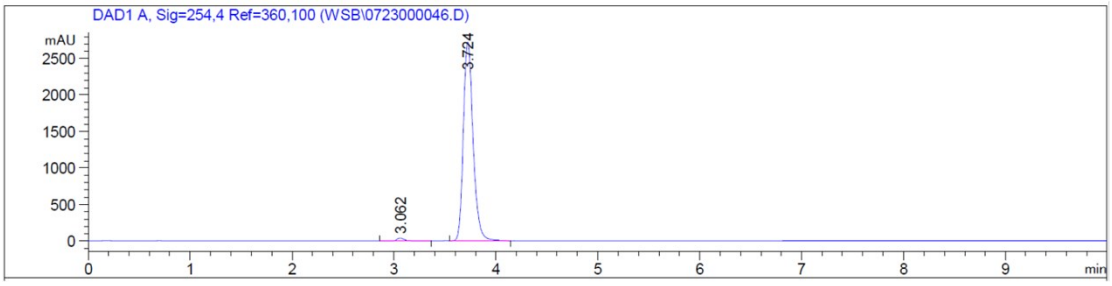
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	3.059	BV	0.0798	202.91615	39.60815	0.8124
2	4.001	VB	0.1166	2.47742e4	3337.57422	99.1876

***N*-(3-((5-((3-Trifluoromethylbenzyl)thio)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)acetamide (10i)**



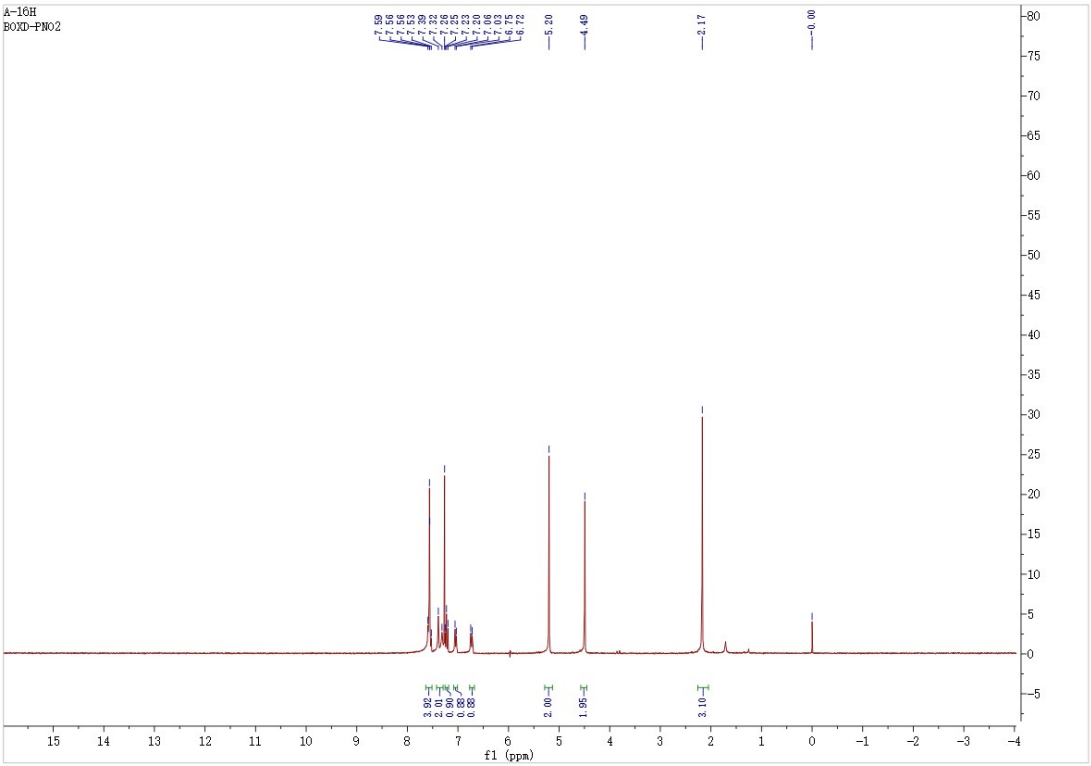


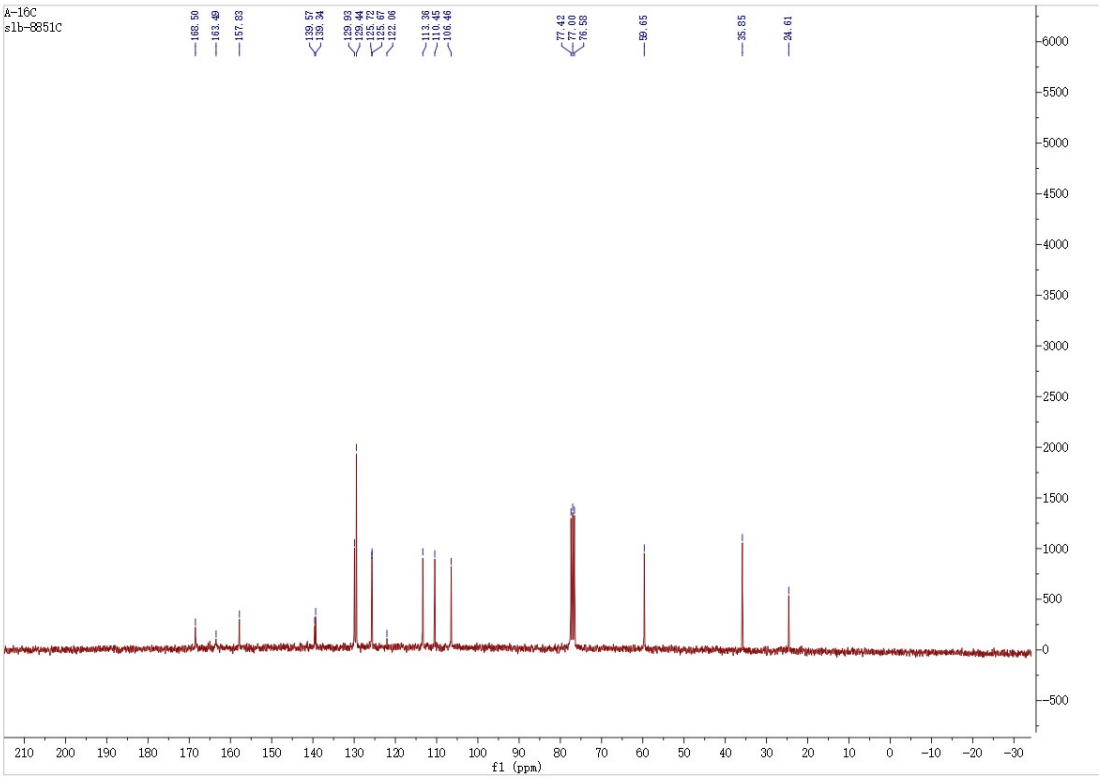


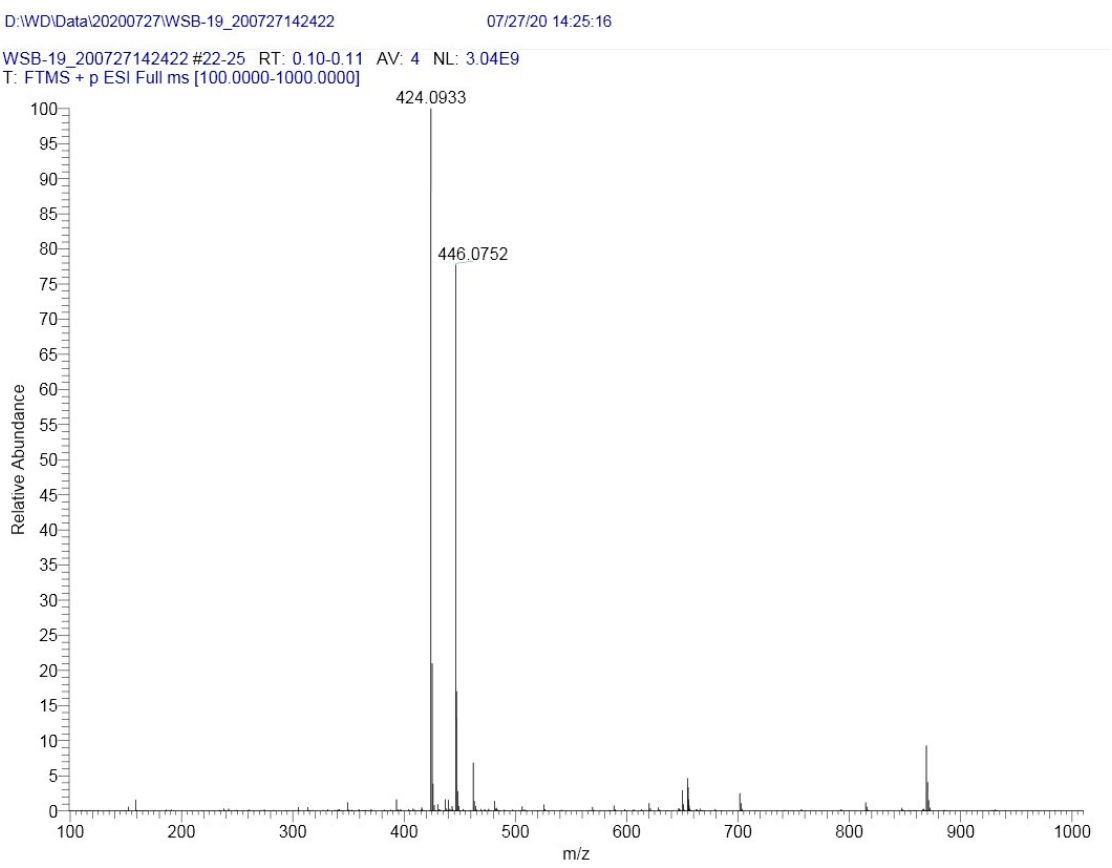


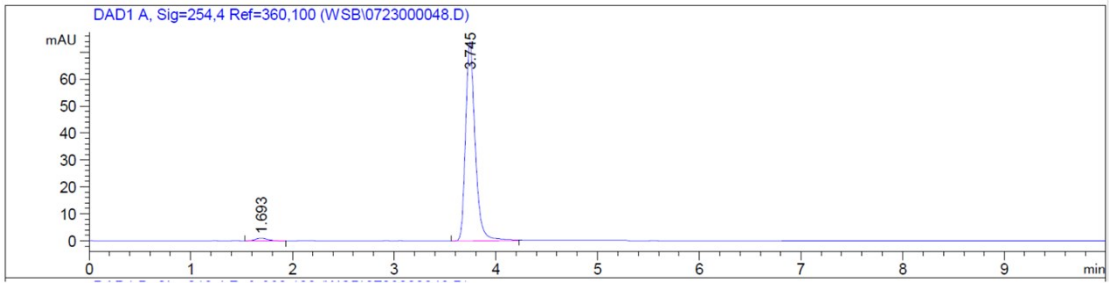
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	3.062	BB	0.0858	218.00792	38.65459	1.1855
2	3.724	VV	0.1017	1.81711e4	2728.22437	98.8145

***N*-(3-((5-((4-Trifluoromethylbenzyl)thio)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)acetamide (10j)**



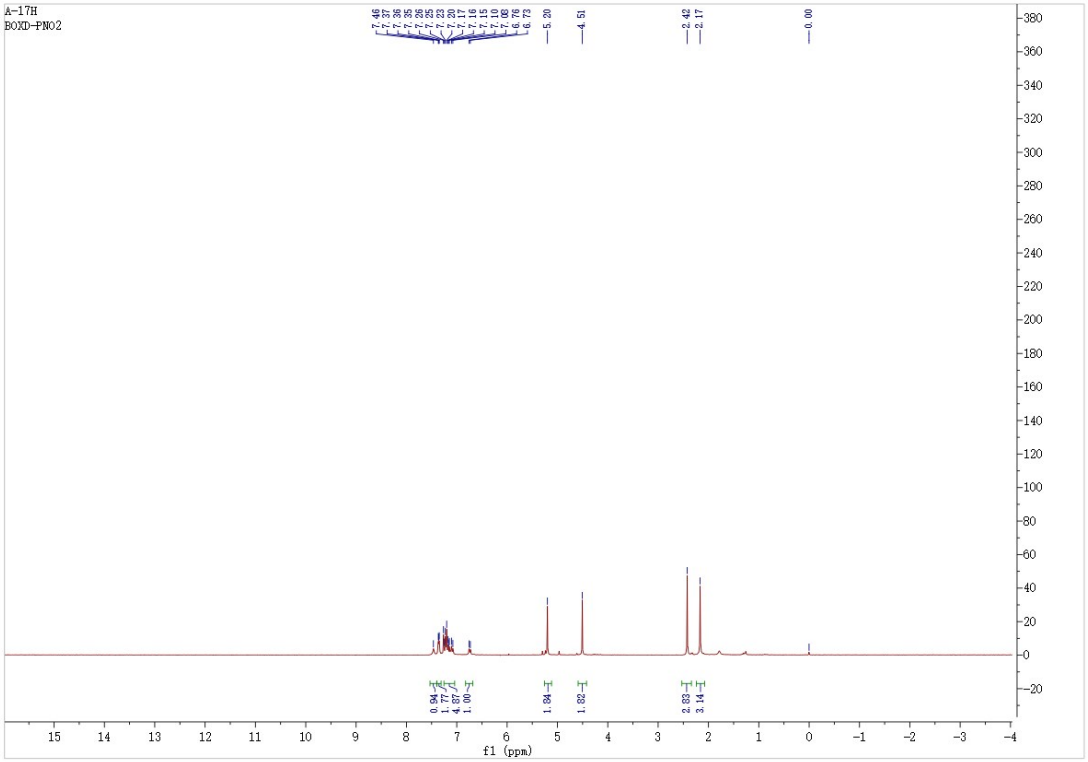


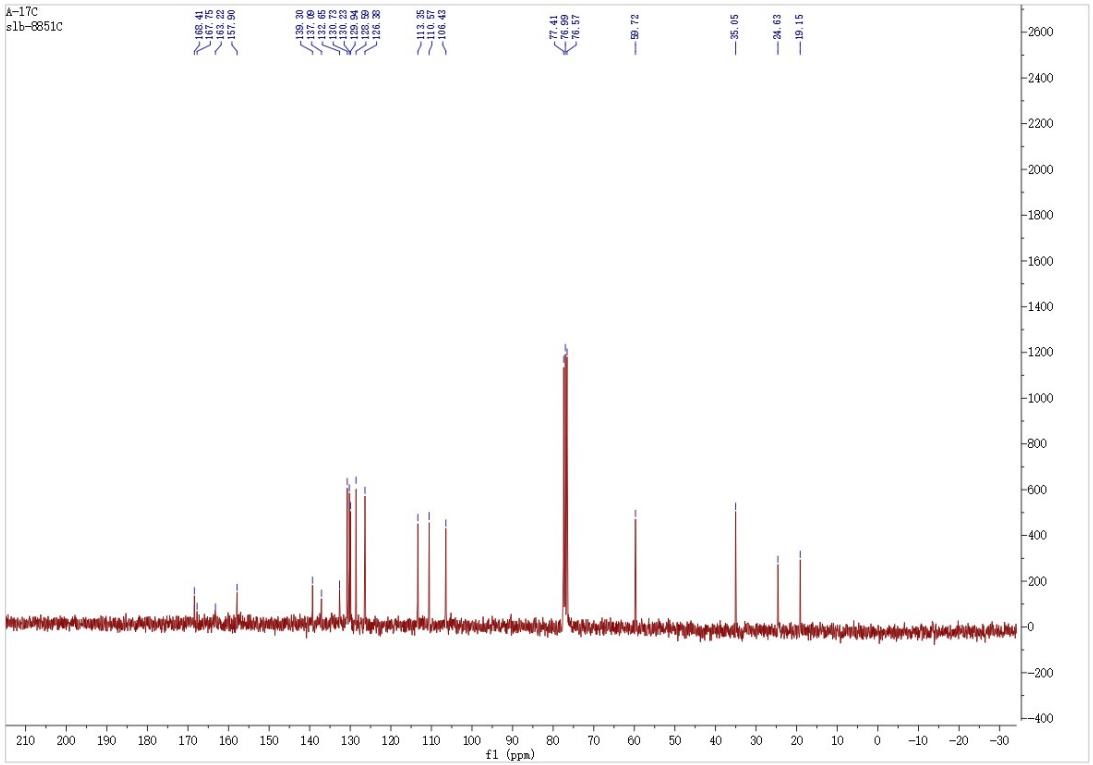




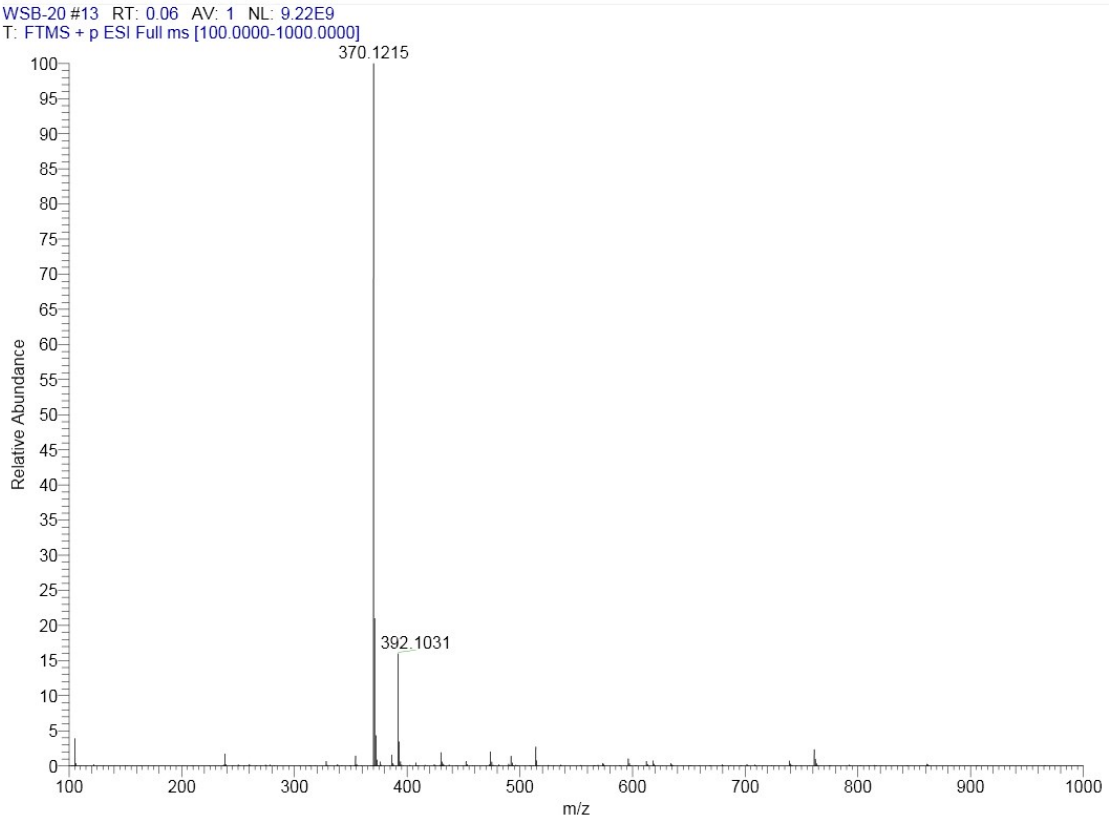
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	1.693	BB	0.1274	8.11832	9.92953e-1	1.6542
2	3.745	BV	0.1002	482.64783	73.85669	98.3458

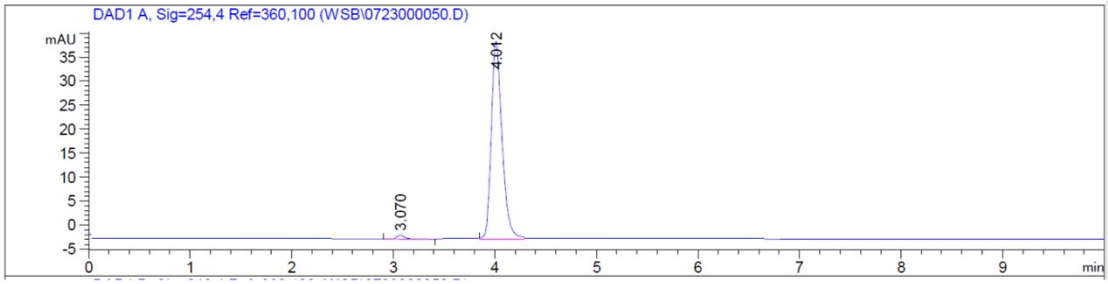
***N*-(3-((5-((2-Methylbenzyl)thio)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)acetamide (10k)**





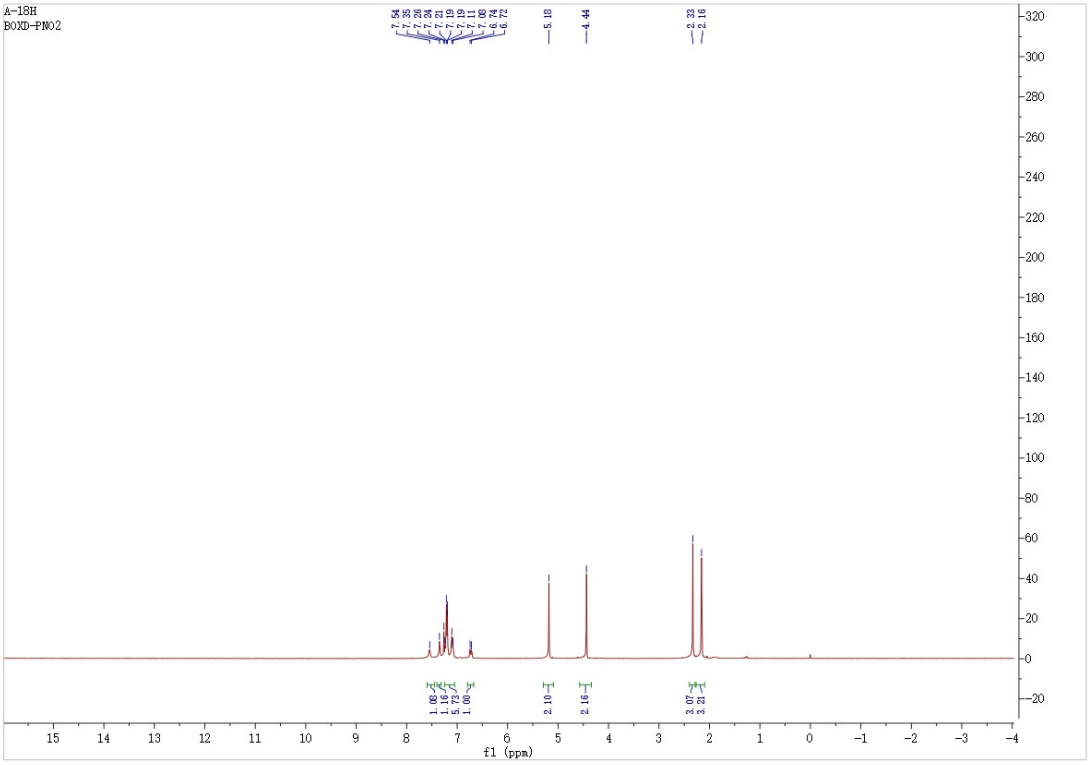
D:\WD\Data\20200727\WSB-20 07/27/20 13:28:08

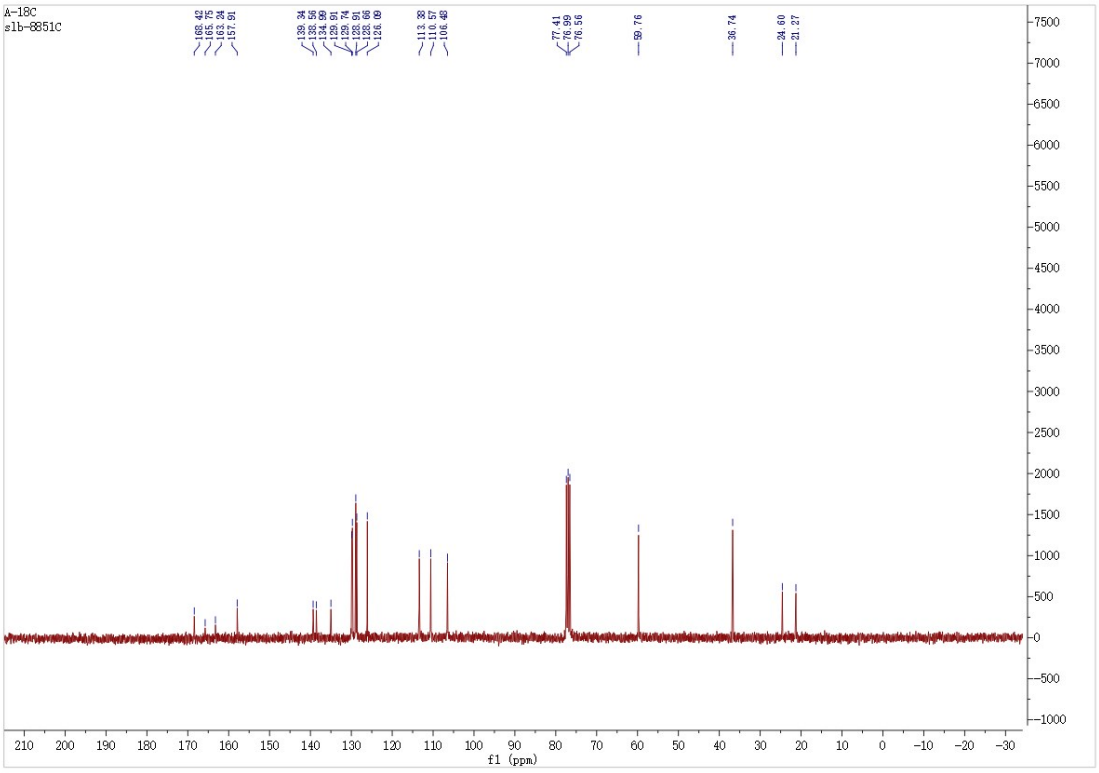




峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	3.070	BB	0.0836	4.67671	8.57661e-1	1.5225
2	4.012	VV	0.1118	302.48834	41.15192	98.4775

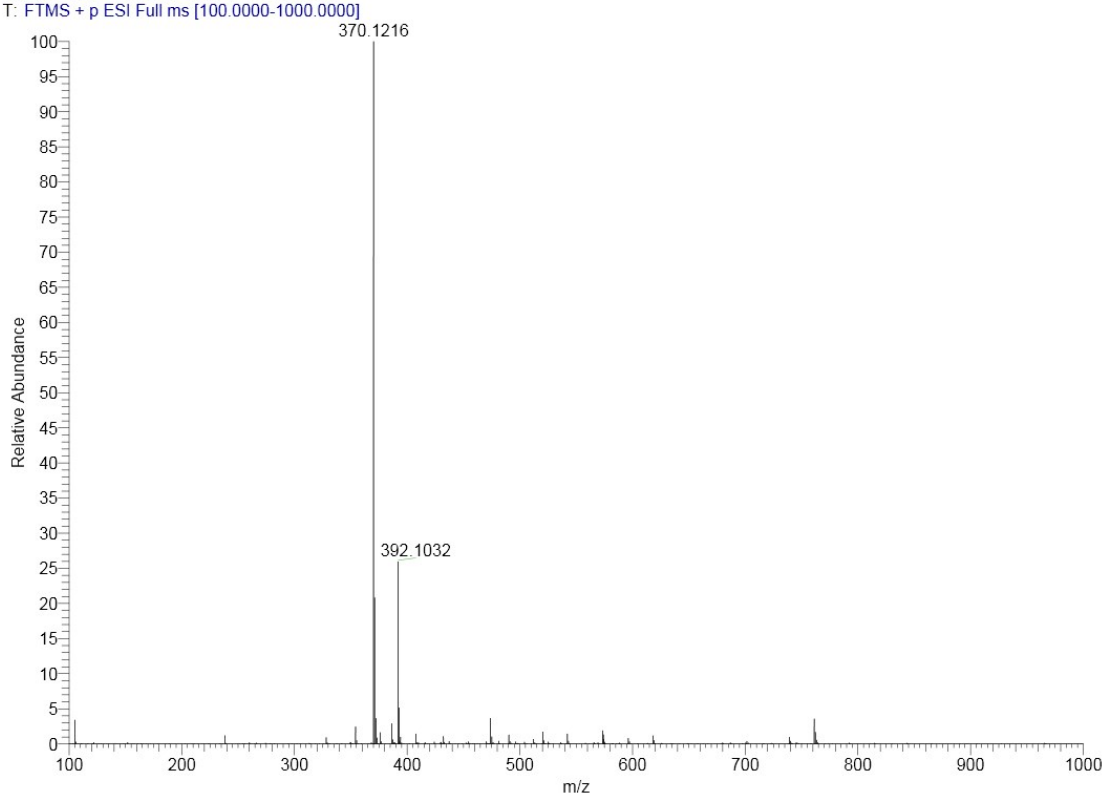
***N*-(3-((5-((3-Methylbenzyl)thio)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)acetamide (10l)**

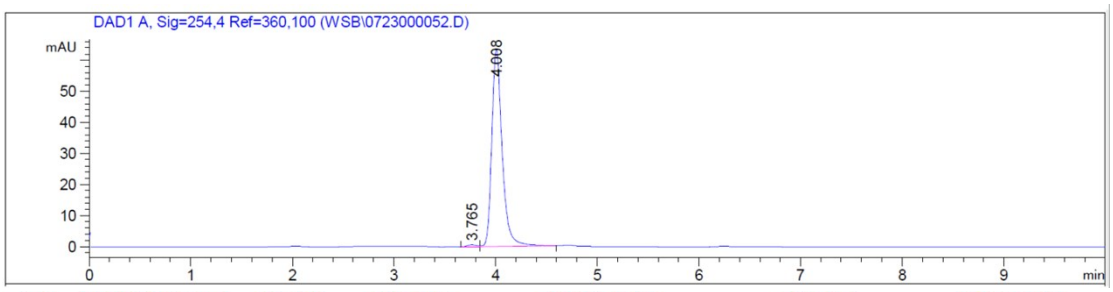




D:\WD\Data\20200727\WSB-21 07/27/20 13:30:05

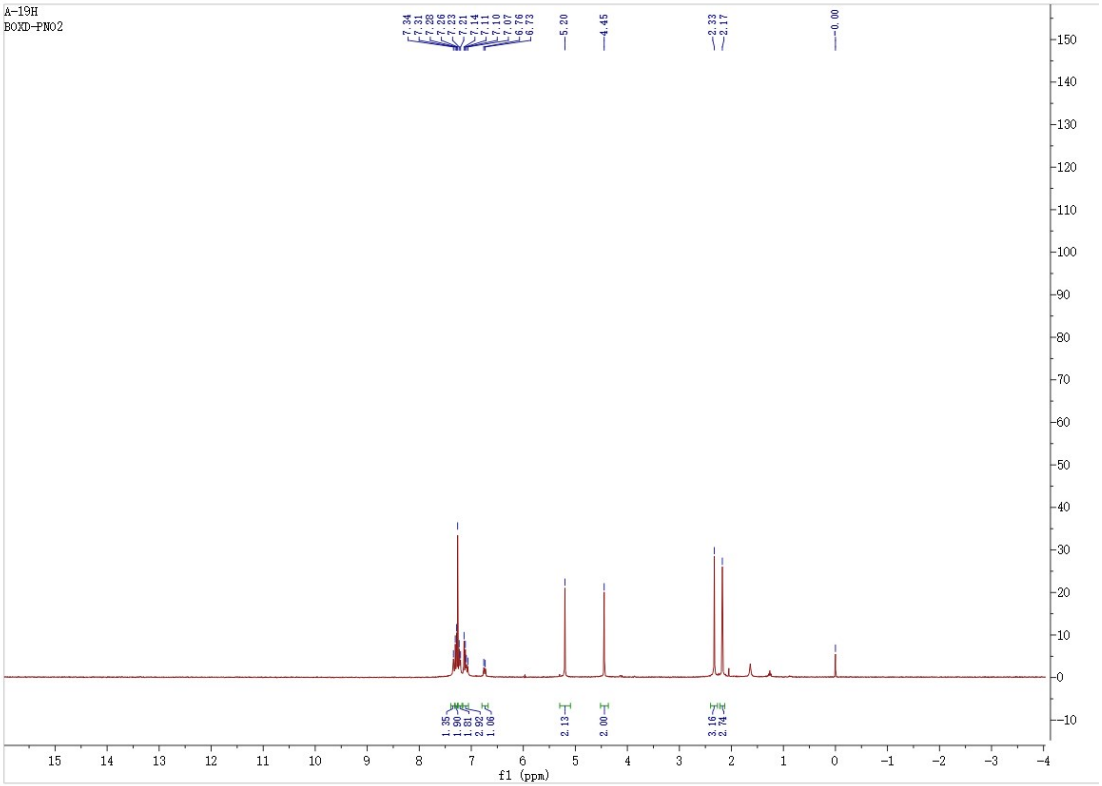
WSB-21 #21 RT: 0.10 AV: 1 NL: 7.49E9
T: FTMS + p ESI Full ms [100.0000-1000.0000]

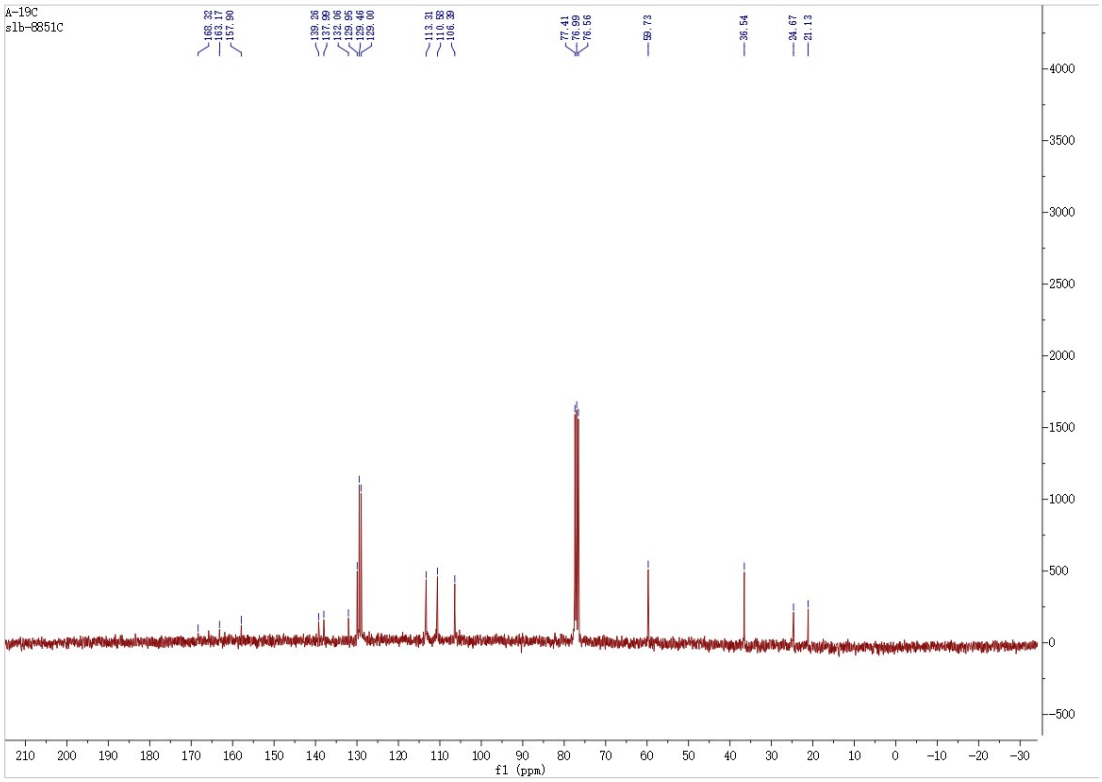




峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	3.765	BV	0.1028	3.94234	5.98952e-1	0.8634
2	4.008	VBA	0.1090	452.64636	63.59904	99.1366

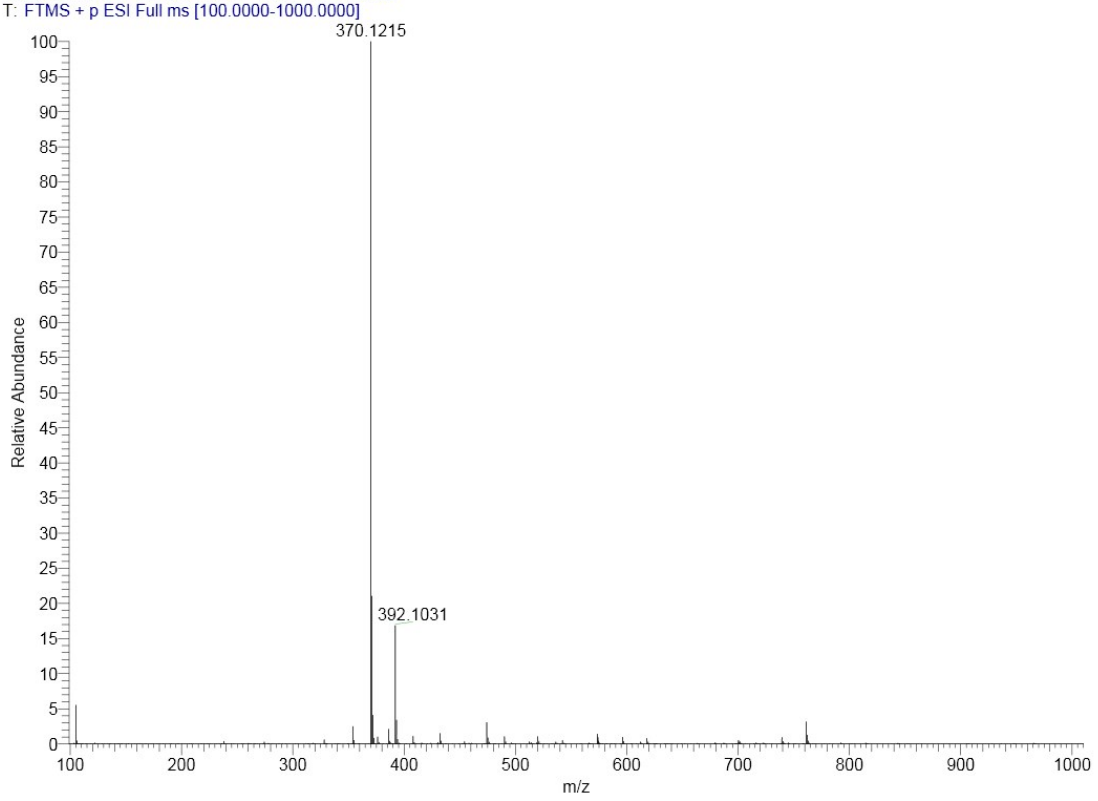
***N*-(3-((5-((4-Methylbenzyl)thio)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)acetamide (10m)**

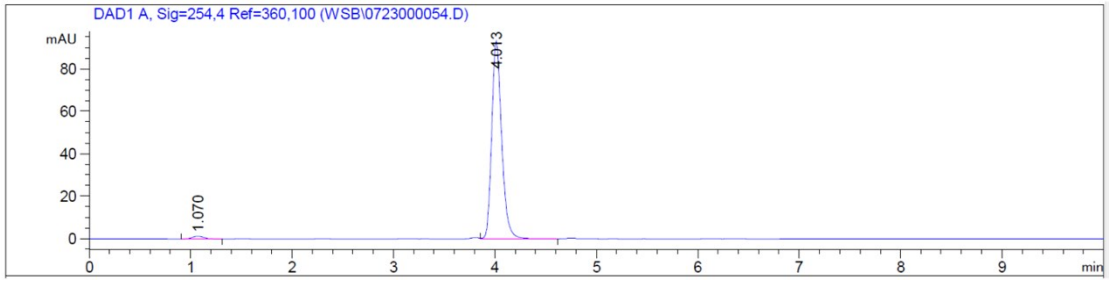




D:\WD\Data\20200727\WSB-22 07/27/20 13:32:02

WSB-22 #18-21 RT: 0.08-0.10 AV: 4 NL: 8.55E9
T: FTMS + p ESI Full ms [100.0000-1000.0000]





峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	1.070	VV	0.1309	11.31917	1.33590	1.7495
2	4.013	VBA	0.1054	635.67169	93.41692	98.2505