Electronic Supplementary Information (ESI)

Efficient Synthesis, Dual Anti-tubercular and Antioxidant Activity of Triazole-Acetophenone Derivatives: Enhanced Efficacy via Esterification and Quantum Mechanical Validation of CYP121 Binding

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Optimization Tables.

Table S1. Optimization for the synthesis of **3a** in binary solvent system.

Entry	Solvent ratio in water (1:1)	Temperature (°C)	Yield (%)	Reaction time (h)
1	t-butanol: Water	40-50	68	22
2	Ethanol: Water	70-80.	45	24
3	Acetonitrile: Water	60-70.	75	16
4	Toluene: Water	70-80.	73	24
5	Acetone: Water	40-50.	83	15

Table S2. Optimization for the synthesis of **3a** in single solvent system.

Entry	Solvent	Temperature (°C)	Yield (%)	Reaction time (h)
1	t-butanol	40-50	65	20
2	Ethanol	70-80	70	24
3	Acetonitrile	60-70	90	06
4	Toluene	70-80.	60	24
5	Acetone	40-50	60	10

Table S3. Optimization for synthesis of **4a** in single solvent system.

Entry	Solvent	Temperature (°C)	Yield (%)	Reaction time (h)
1	t-butanol	40-50	30	24
2	Ethanol	70-80	90	22
3	Acetonitrile	60-70	30	24
4	Methanol	50-60.	60	24
5	Acetone	40-50	60	24

Table S4 Synthesis of triazole-based acetophenone derivatives (**3a-3f**) and (**4a-4f**) in single solvent system.

Compound	Solvent	Temperature (°C)	Time (h)	Yield (%)
3a	acetonitrile	70	6	89
3b	acetonitrile	75	8	92
3c	acetonitrile	75	6	88
3d	acetonitrile	70	8	90
3e	acetonitrile	75	8	90
3f	acetonitrile	70	8	90
4a	ethanol	80	22	90
4b	ethanol	80	24	89
4c	ethanol	80	24	93
4d	ethanol	80	22	85
4e	ethanol	80	22	85
4f	ethanol	80	22	85

Table S5 Antioxidant activity and Cytotoxicity (RBC) of synthesized compounds. Results are presented as the mean ± standard deviation (SD) of three independent experiments (n=3).

Compound code	OH Scavenging (% ± SD)	DPPH Scavenging (% ± SD)	ABTS Scavenging (% ± SD)	RBC Cytotoxicity (% ± SD)
3a	61.4 ± 0.20	67.28 ± 0.39	42.11±0.22	0.35 ± 0.03
3b	59.46 ± 0.03	61.45 ± 1.07	72.97±1.71	0.13 ± 0.046
3c	68.71 ± 0.01	71.58 ± 0.90	74.64±0.96	1.28 ± 0.093
3d	41.21 ± 0.15	65.54 ± 0.70	71.58±0.90	0.36 ± 0.011
3e	71.37 ± 0.77	74.40 ± 1.75	66.15±0.84	0.87 ± 0.032
3f	65.40 ± 0.40	66.68 ± 0.85	74.33±1.16	0.57 ± 0.026
4a	65.39 ± 0.34	68.58 ± 2.20	67.04±0.67	1.05 ± 0.044
4b	76.23 ± 0.13	73.51 ± 1.12	66.68±0.93	0.45 ± 0.017
4c	69.11 ± 0.06	73.27 ± 3.05	75.98±0.93	1.03 ± 0.104
4d	76.18 ± 0.10	72.71 ± 2.15	68.11±0.51	0.84 ± 0.001
4e	70.96 ± 0.63	74.20 ± 0.93	76.08±0.20	0.54 ± 0.018
4f	65.23 ± 0.07	66.45 ± 0.81	71.15±0.26	1.05 ± 0.075
Ascorbic acid	81.75 ± 0.60	81.37 ± 0.40	81.03±0.50	-
Triton X 100	-	-	-	7.02 ± 0.463

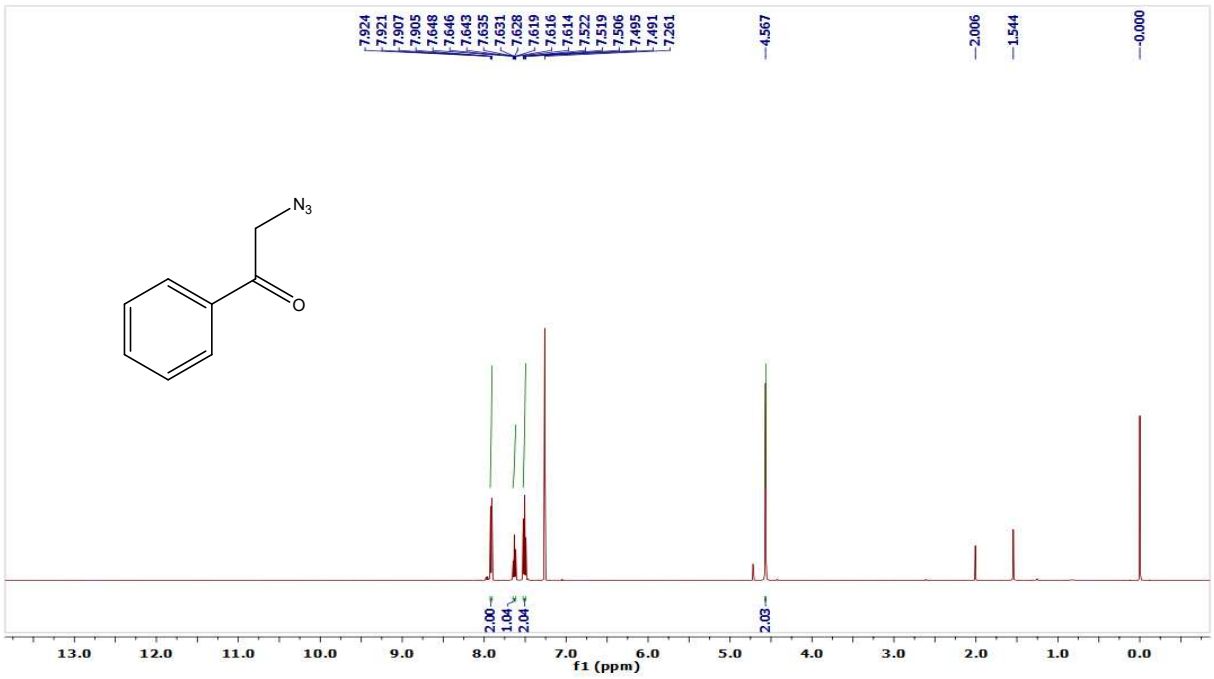
Entry	% Cytotoxicity	SD
3a	0.35	0.03
3b	0.13	0.046
3c	1.28	0.093
3d	0.36	0.011
3e	0.87	0.032
3f	0.57	0.026
4a	1.05	0.044
4b	0.45	0.017
4c	1.03	0.104
4d	0.84	0.001
4e	0.54	0.018
4f	1.05	0.075
Triton X 100	7.02	0.463

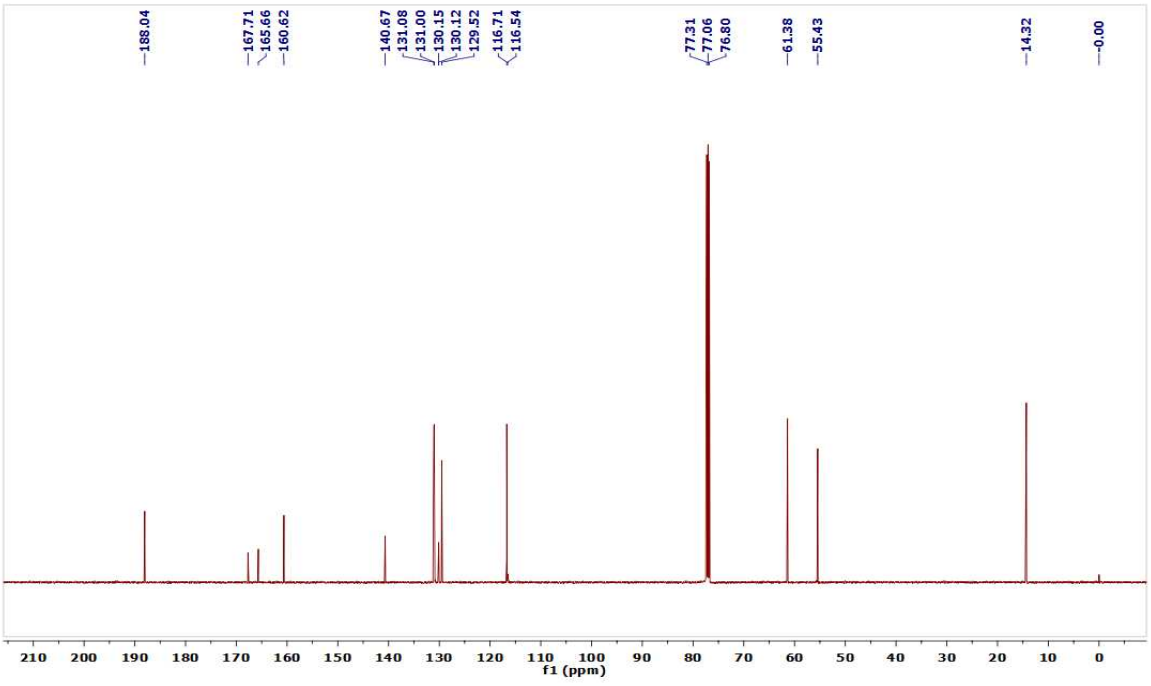
NMR, Mass and FT-IR Spectra for

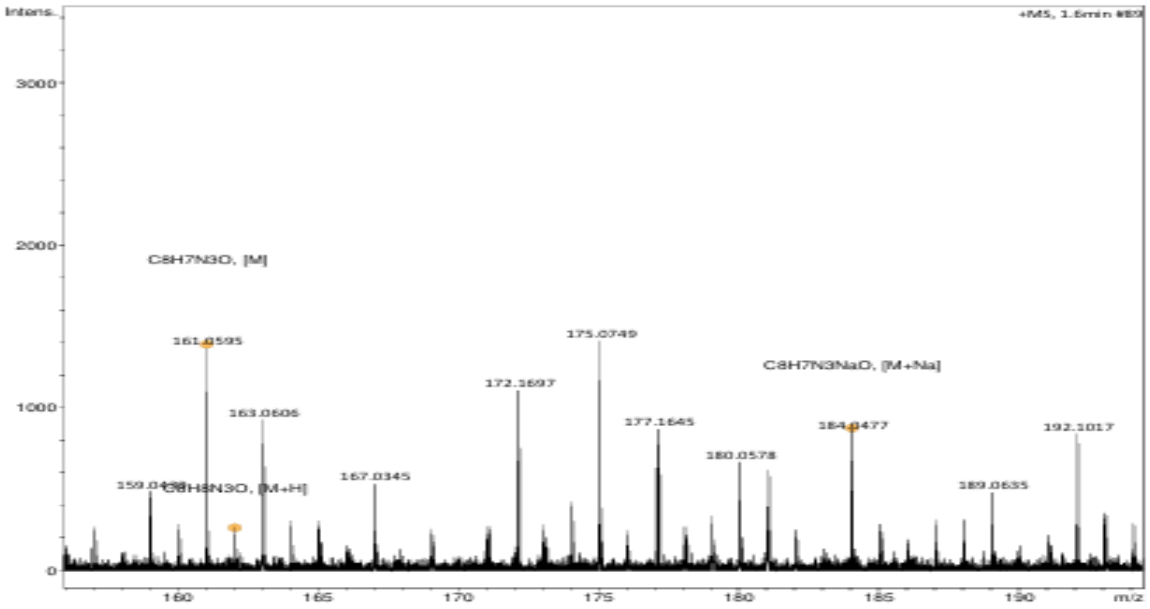
Representative Compounds 2a-2d,

3a-3f and 4a-4f

(2a) (2-azido-1-phenylethanone)



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0
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163.0606
159.0438
C8H8N3O, [M+H]
167.0345
172.1697
175.0749
177.1645
180.0578
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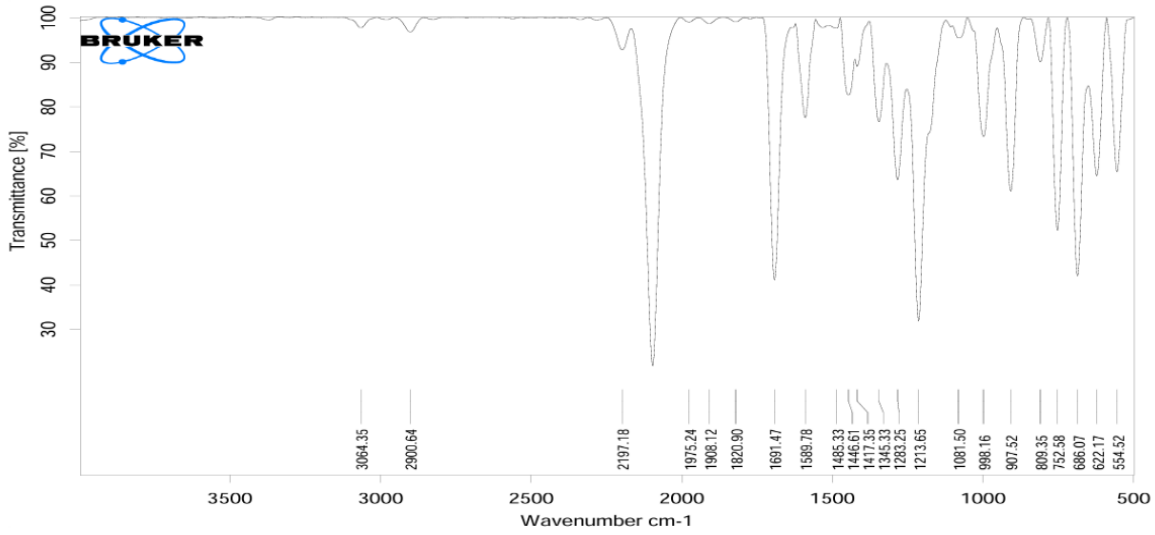
184.0477
189.0635
192.1017
160
165
170
175
180
185
190
m/z


BRUKER
Transmittance [%]
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80
70
60
50
40
30
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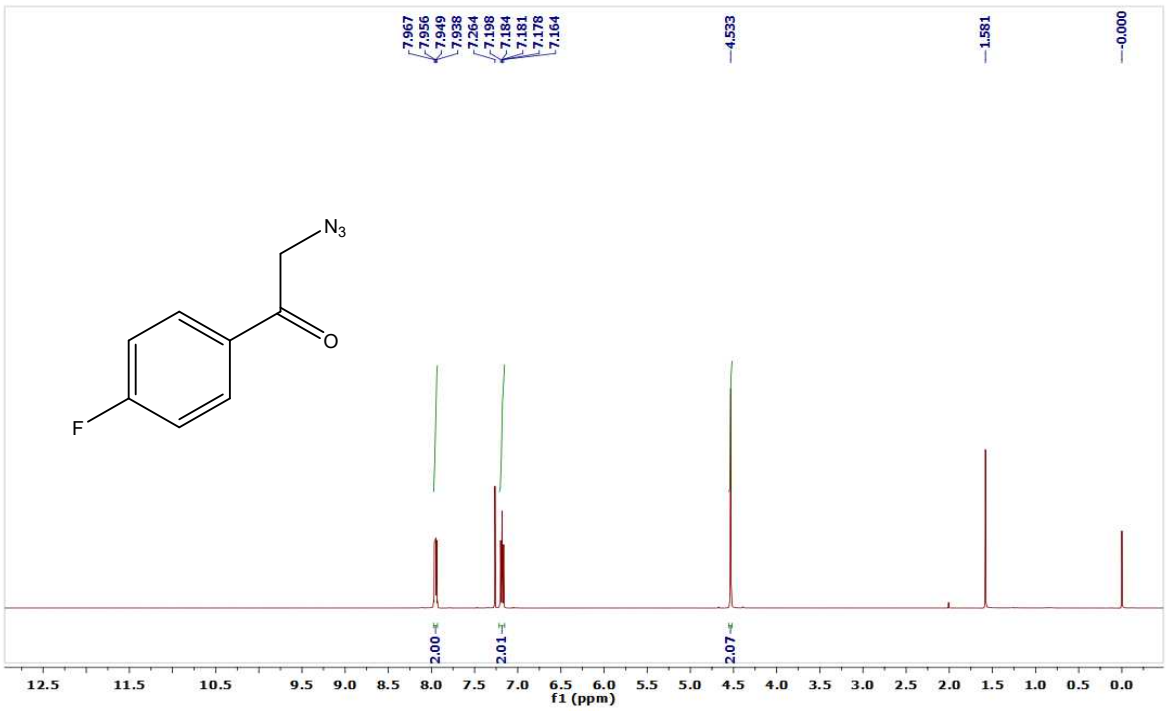
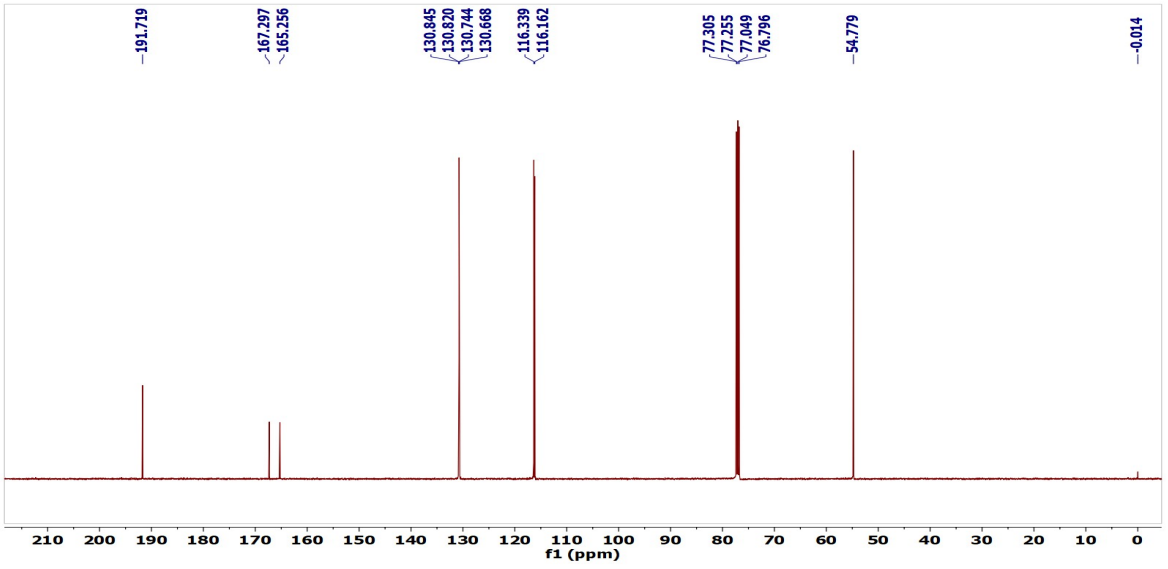
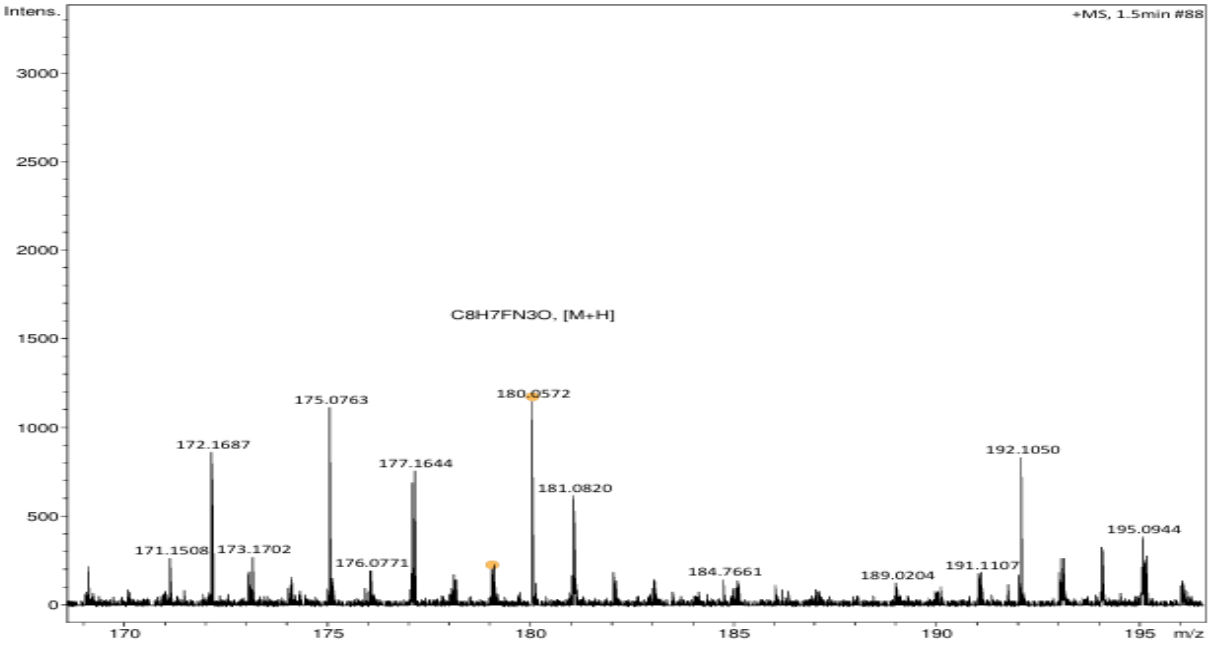
2900.64
2197.18
1975.24
1908.12
1820.90
1691.47
1589.78
1485.33
1446.61
1417.35
1345.33
1283.25
1213.65
1081.50
998.16
907.52
809.35
752.58
686.07
622.17
554.52
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1

(2b) (2-azido-1-(4-fluorophenyl) ethan-1-one)



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C8H7FN3O, [M+H]
175.0763
180.0572
172.1687
177.1644
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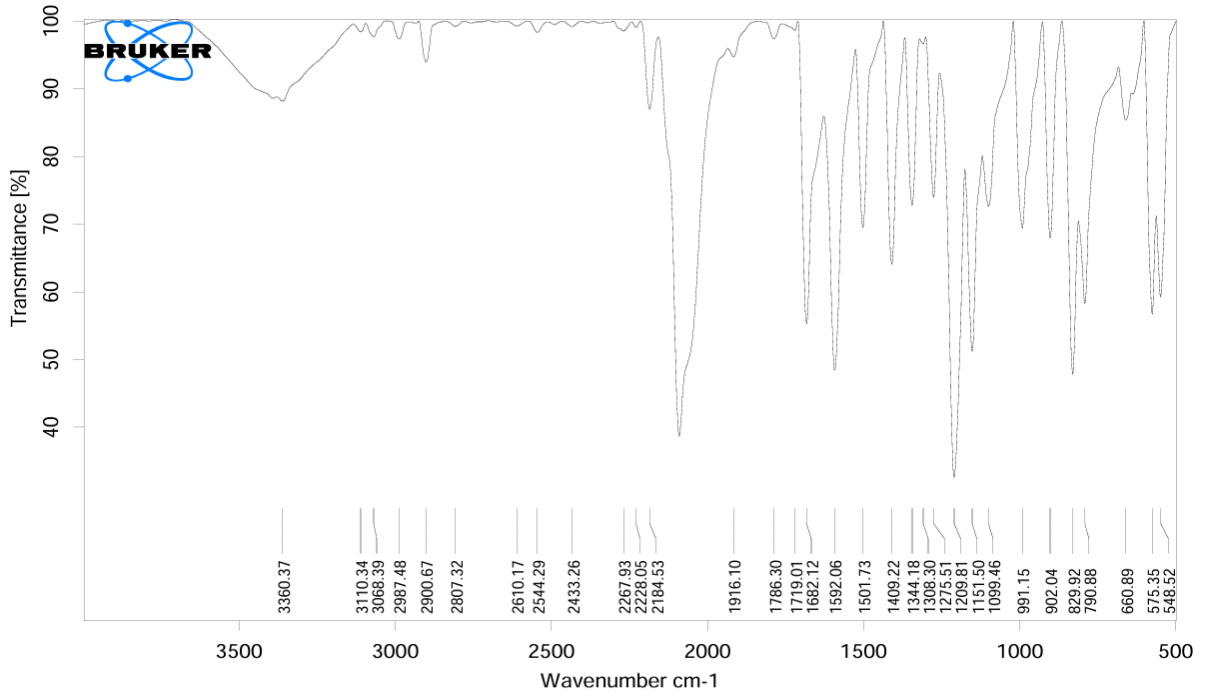
173.1702
176.0771
184.7661
189.0204
191.1107
m/z


BRUKER
Transmittance [%]
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3068.39
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2433.26
2267.93
2228.05
2184.53
1916.10
1786.30
1719.01
1682.12
1592.06
1501.73
1409.22
1344.18
1308.30
1275.51
1209.81
1151.50
1099.46
991.15
902.04
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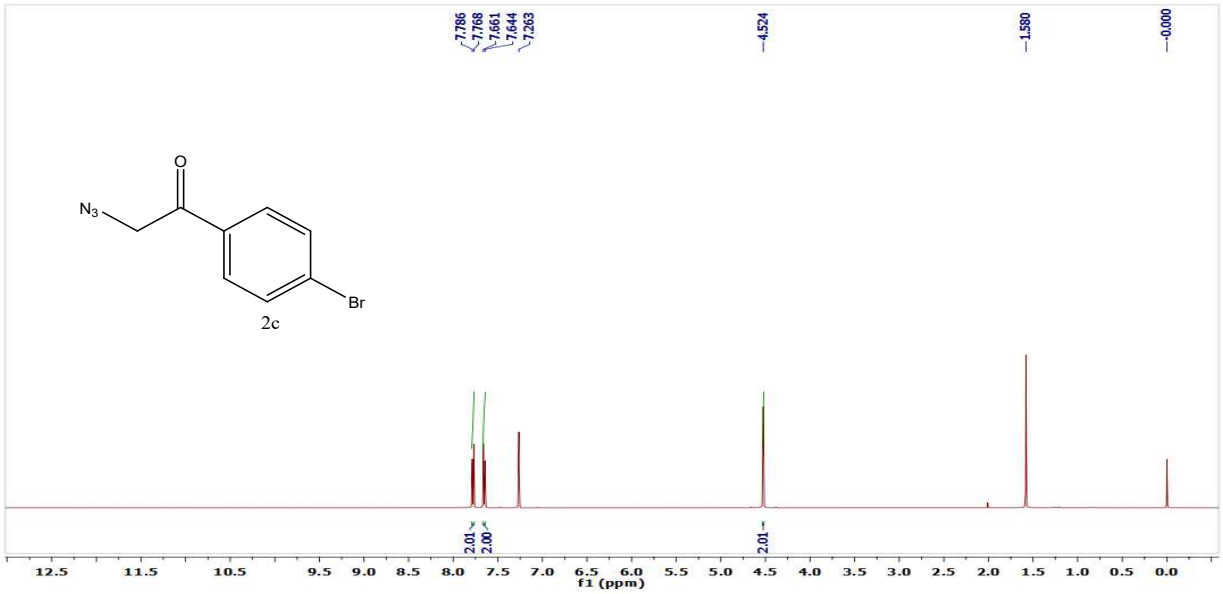
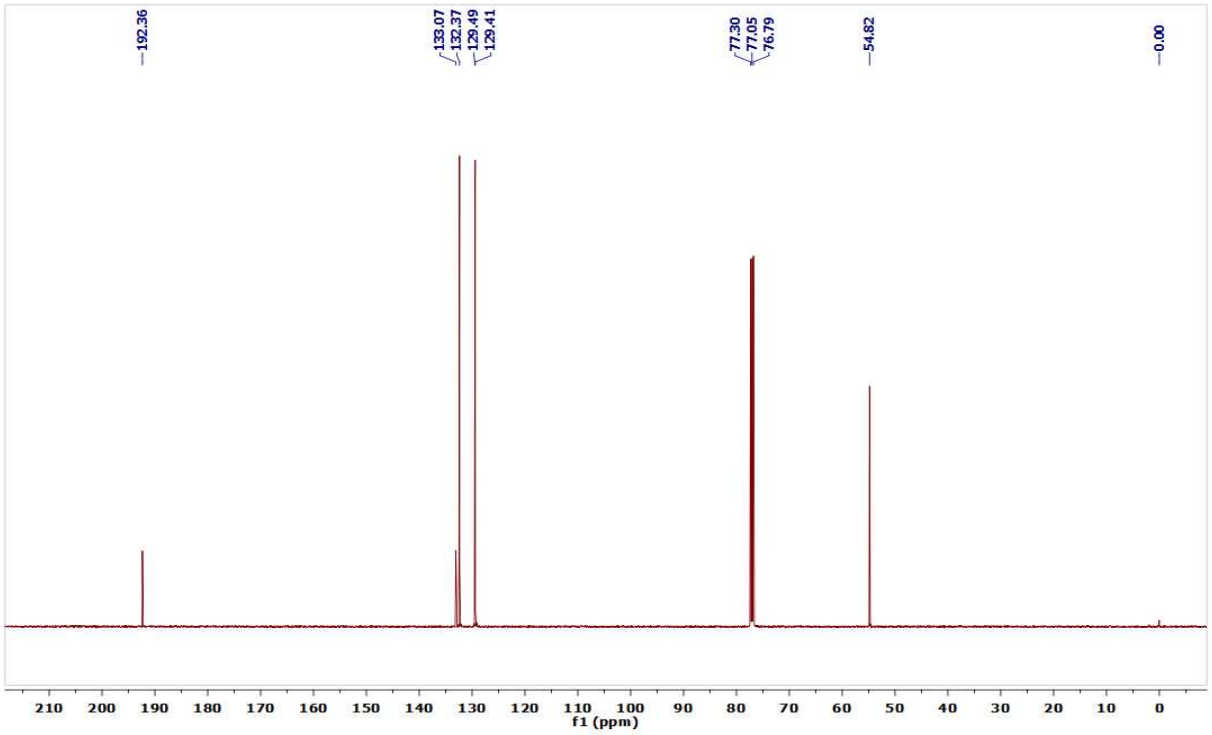
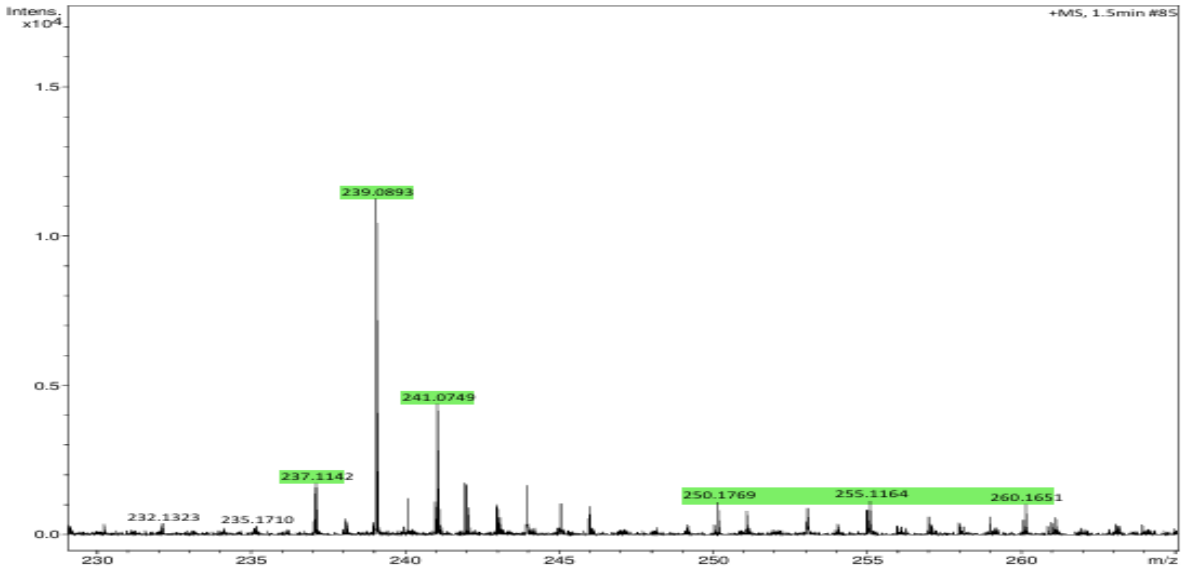
660.89
575.35
548.52
Wavenumber cm-1

(2c) 2-azido-1-(4-bromophenyl) ethan-1-one



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1.0
0.5
0.0
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241.0749
237.1142
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235.1710
250.1769
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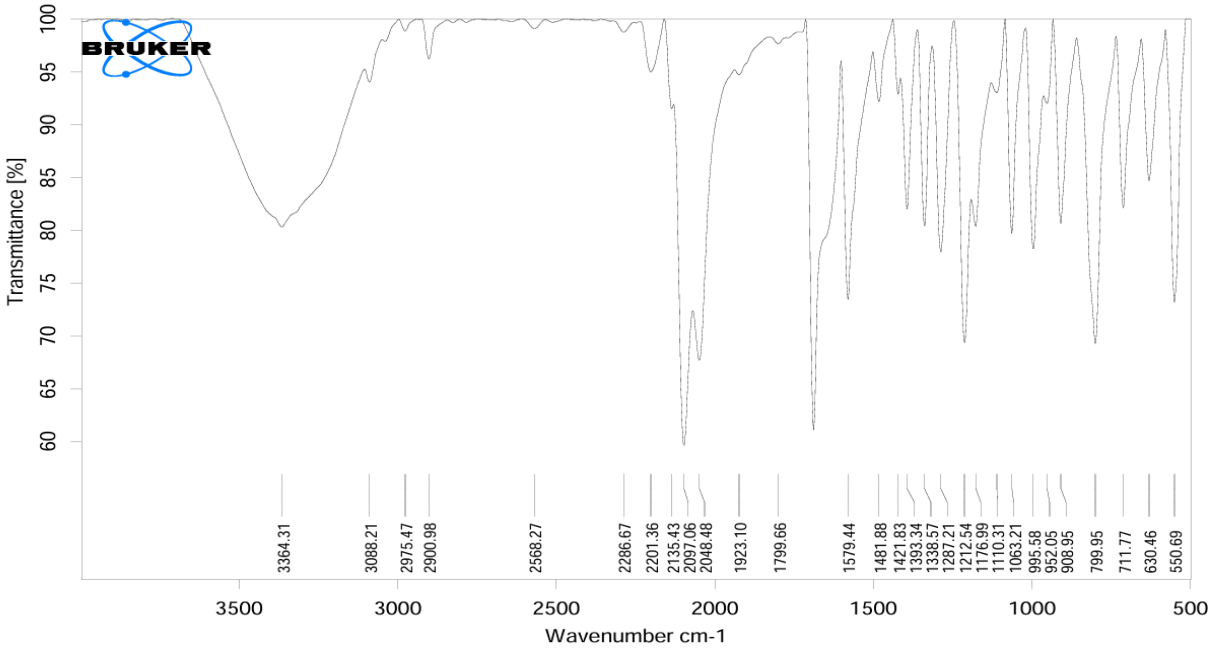
230
235
240
245
250
255
260
m/z


BRUKER
Transmittance [%]
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80
75
70
65
60
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2900.98
2568.27
2286.67
2201.36
2135.43
2097.06
2048.48
1923.10
1799.66
1579.44
1481.88
1421.83
1393.34
1338.57
1287.21
1212.54
1176.99
1110.31
1063.21
995.58
952.05
908.95
799.95
711.77
630.46
550.69
3500
3000
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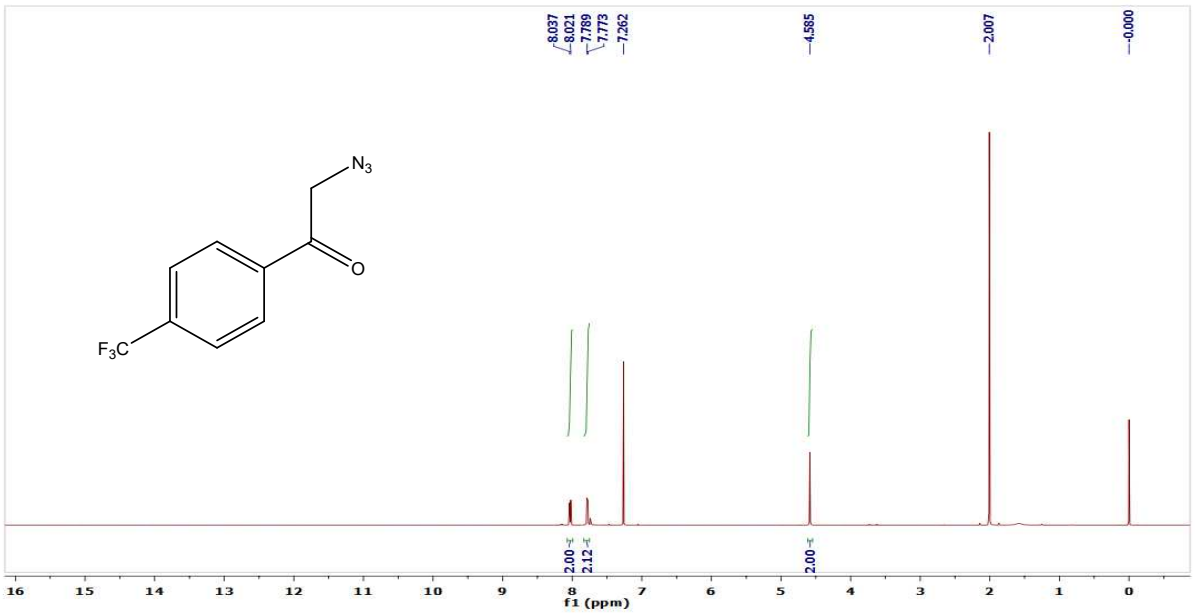
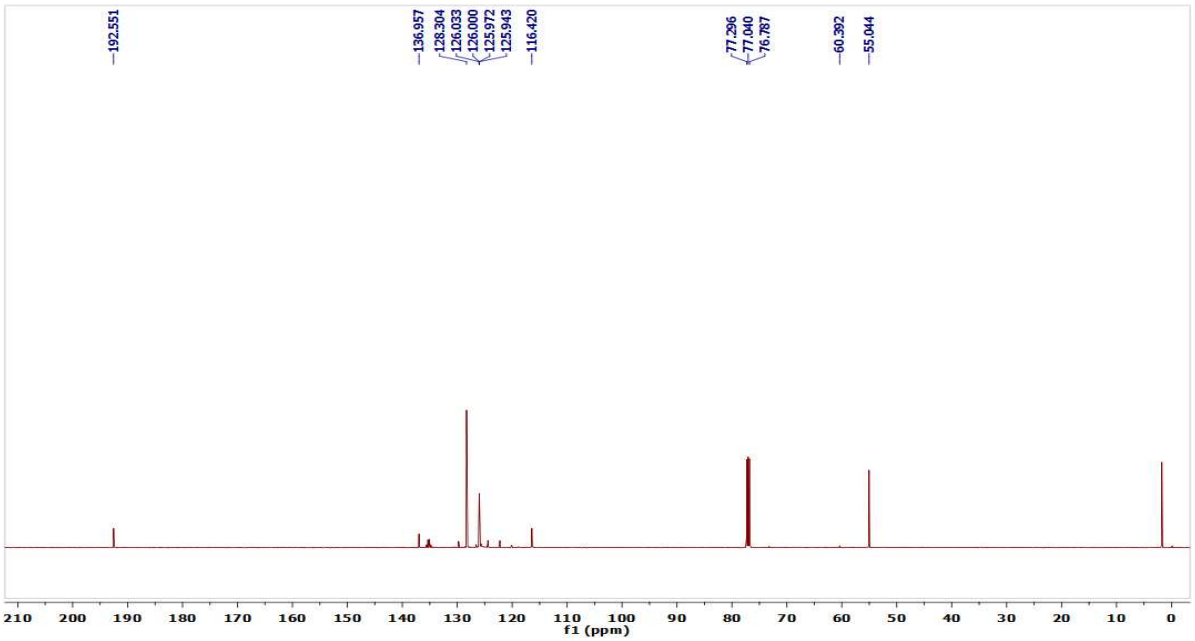
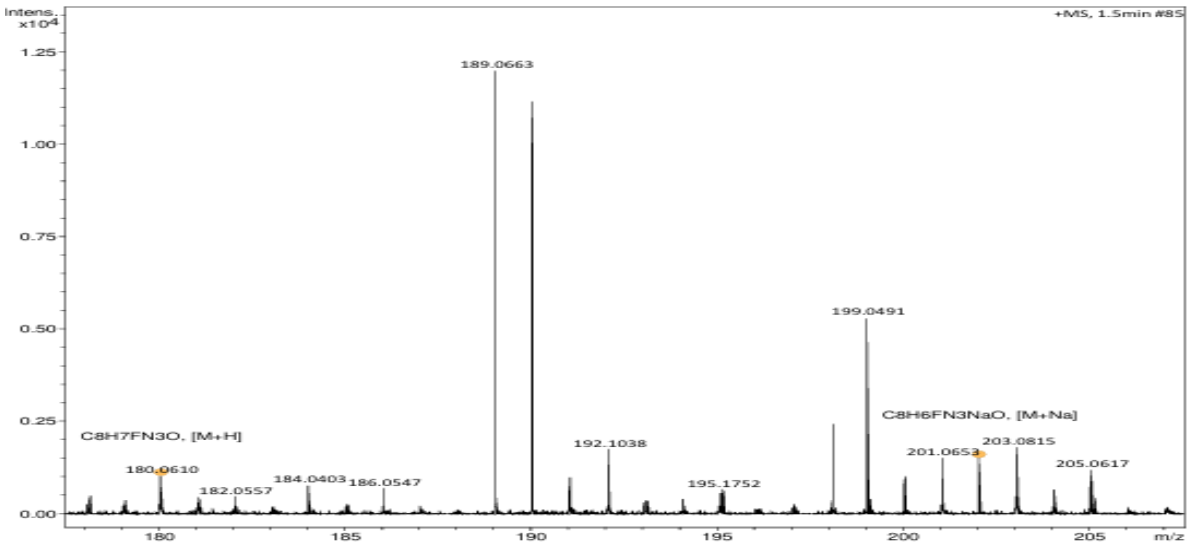
2000
1500
1000
500
Wavenumber cm-1

(2d) (2-azido-1-(4-(trifluoromethyl) phenyl) ethan-1-one)



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0.00
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199.0491
C8H6FN3NaO, [M+Na]
C8H7FN3O, [M+H]
192.1038
203.0815
201.0653
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184.0403
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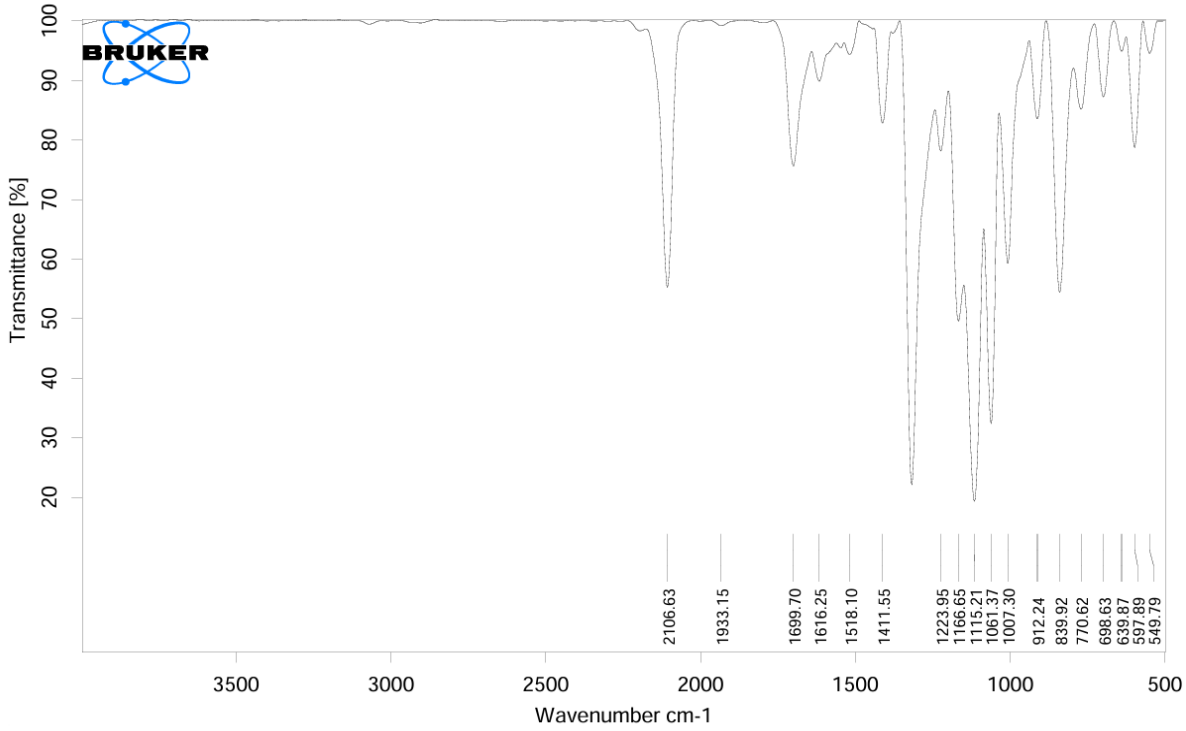
186.0547
195.1752
180
185
190
195
200
205
m/z


BRUKER
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80
70
60
50
40
30
20
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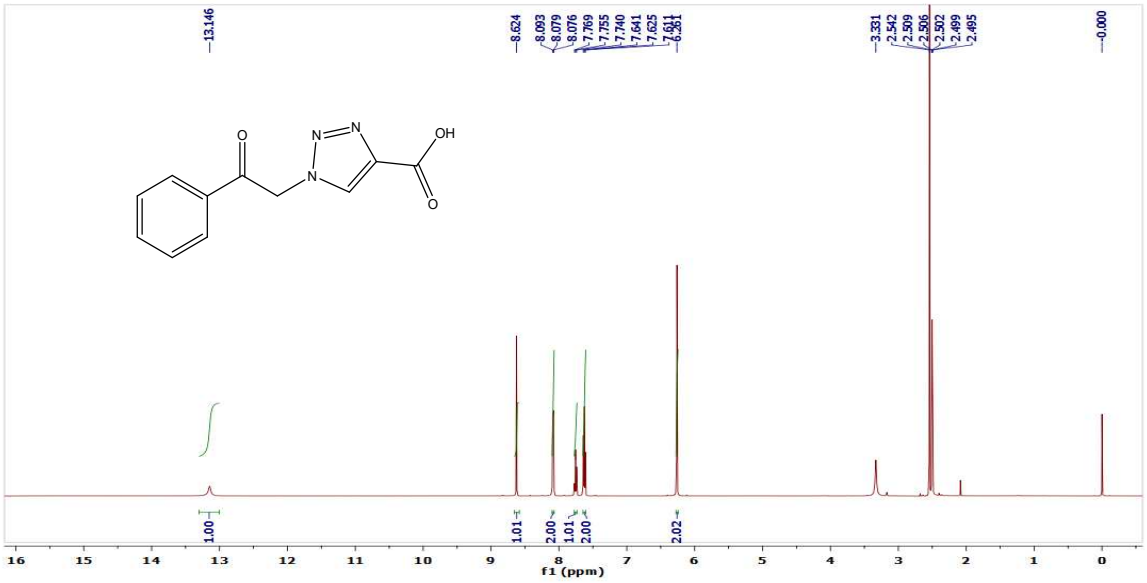
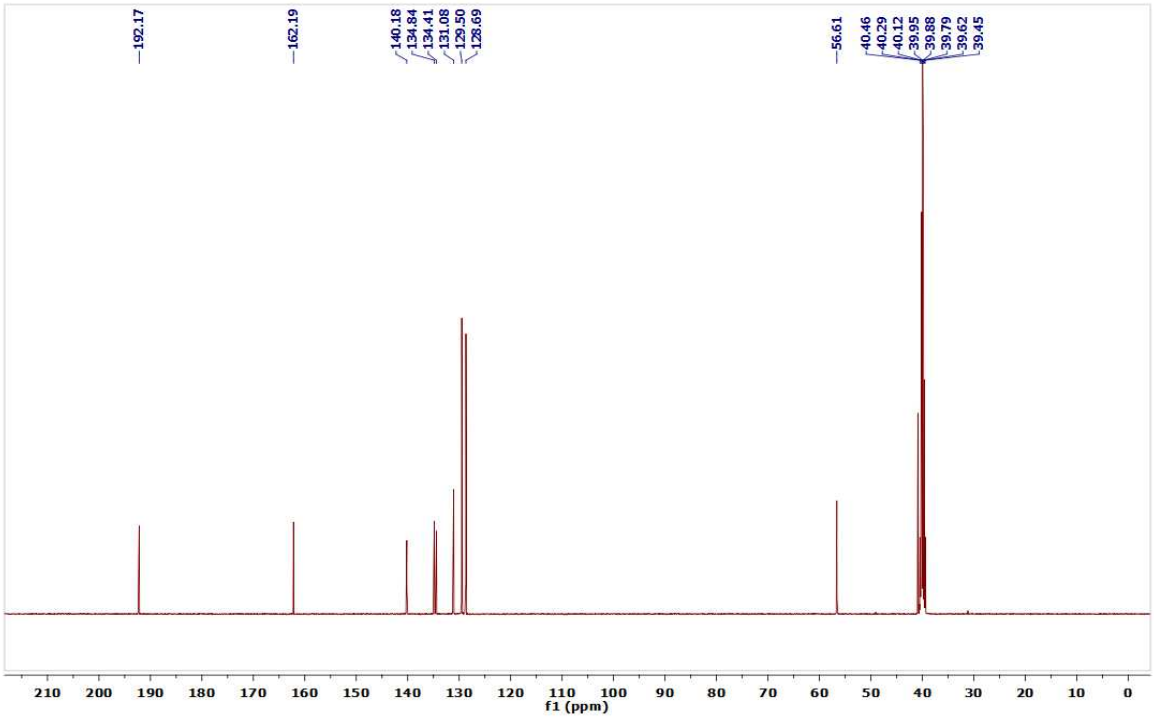
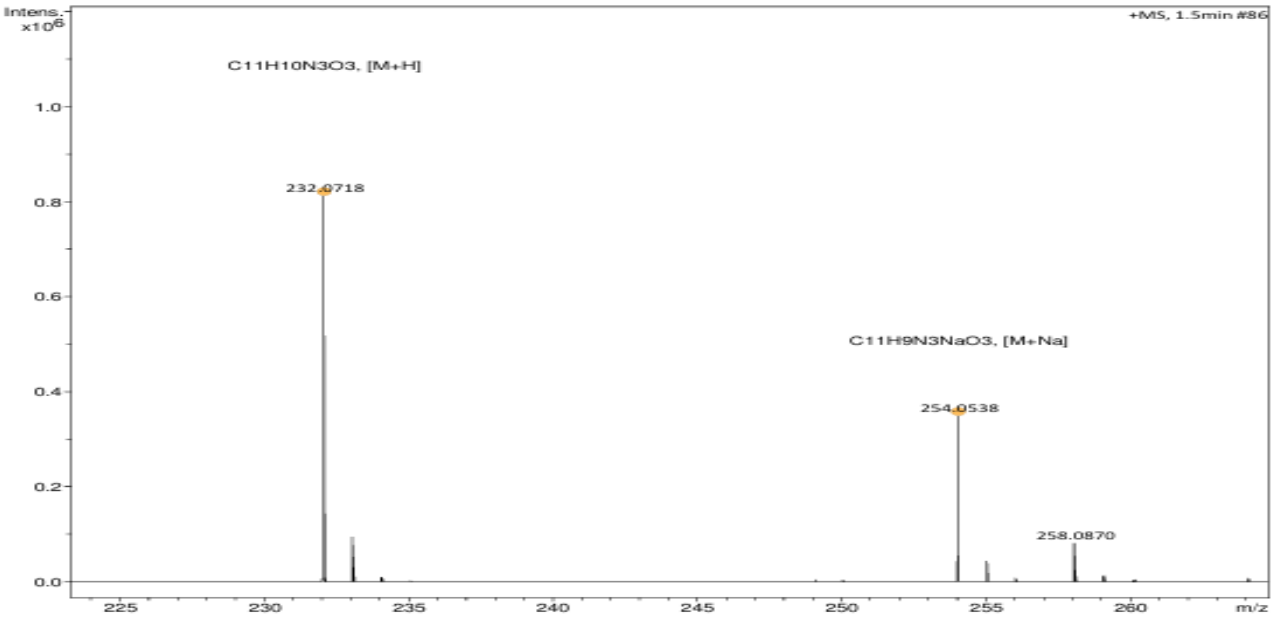
1699.70
1616.25
1518.10
1411.55
1223.95
1166.65
1115.21
1061.37
1007.30
912.24
839.92
770.62
698.63
639.87
597.89
549.79
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1

(3a) (2-oxo-2-phenylethyl)-1 *H*-1,2,3-triazole-4-carboxylic acid



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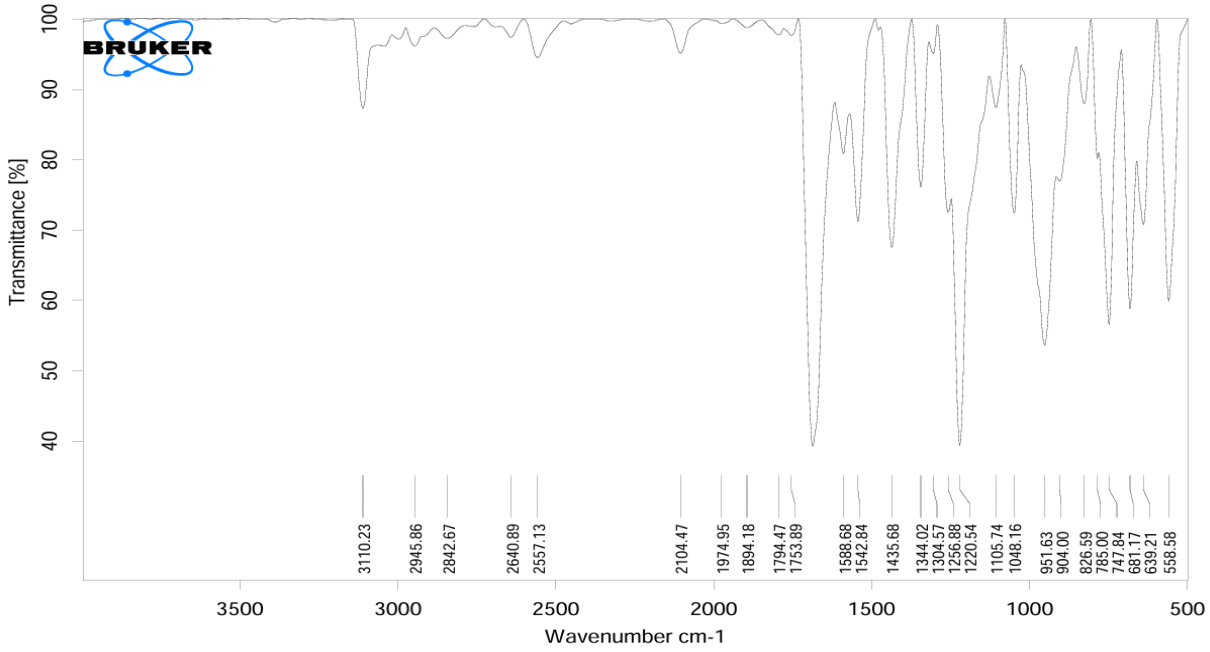
C11H9N3NaO3, [M+Na]
254.0538
258.0870
m/z


BRUKER
Transmittance [%]
Wavenumber cm-1
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2842.67
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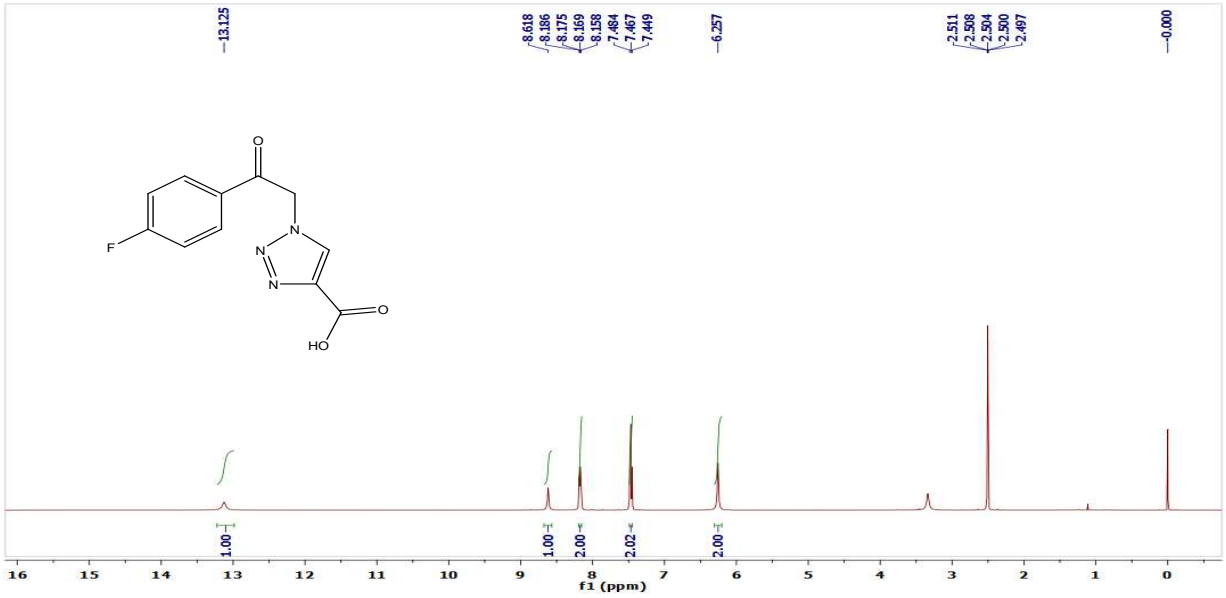
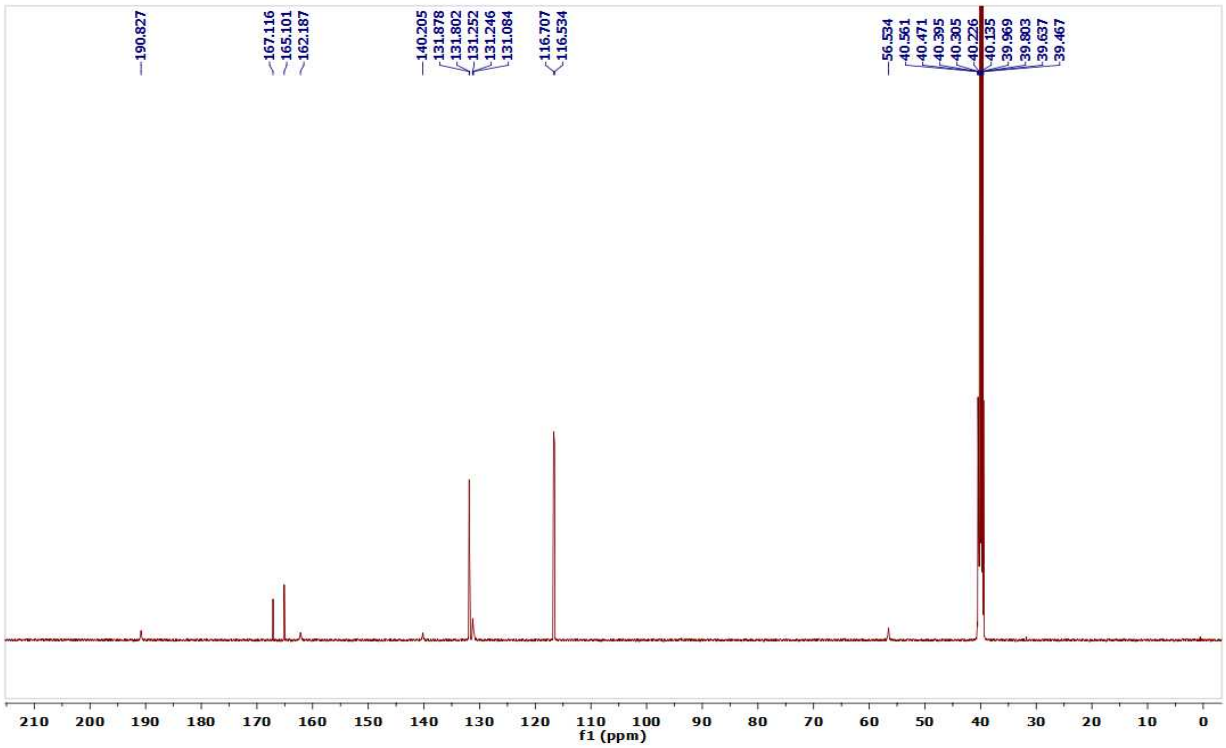
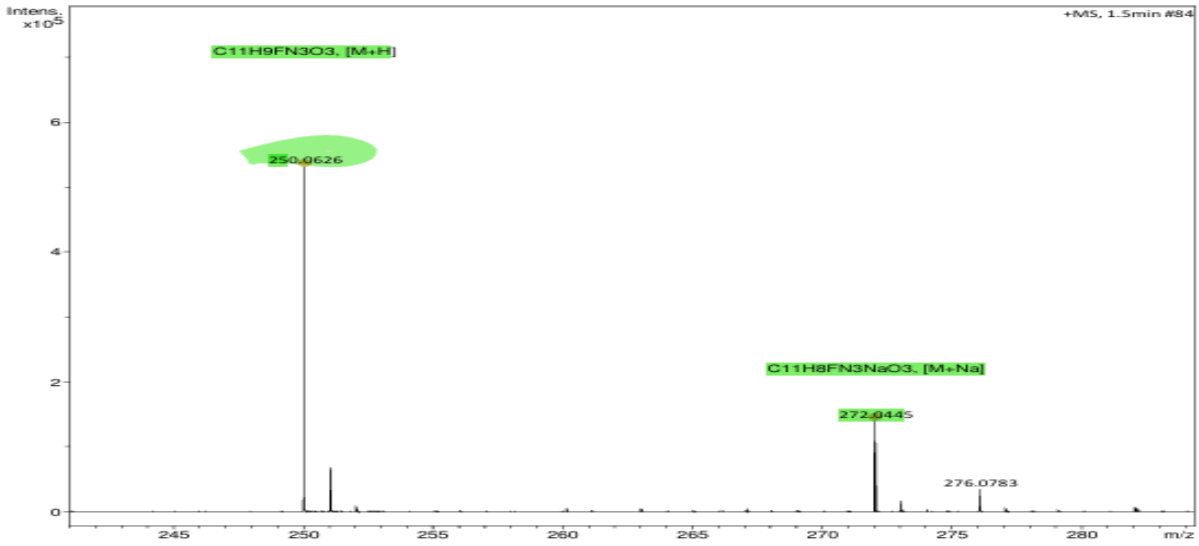
2557.13
2104.47
1974.95
1894.18
1794.47
1753.89
1588.68
1542.84
1435.68
1344.02
1304.57
1256.88
1220.54
1105.74
1048.16
951.63
904.00
826.59
785.00
747.84
681.17
639.21
558.58

(3b) 1-(2-(4-flurophenylethyl)2-oxoethyl)-1 *H*-1,2,3-triazole-4-carboxylic acid



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x10^5
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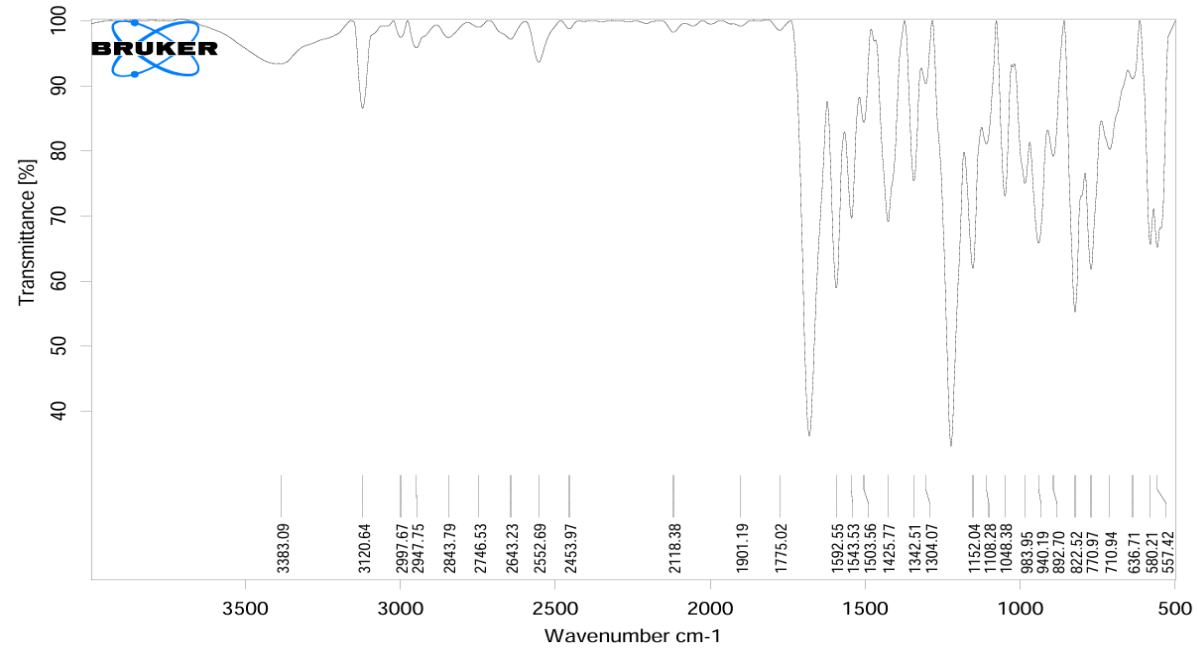
C11H8FN3NaO3, [M+Na]
272.0445
276.0783
m/z


BRUKER
Transmittance [%]
Wavenumber cm-1
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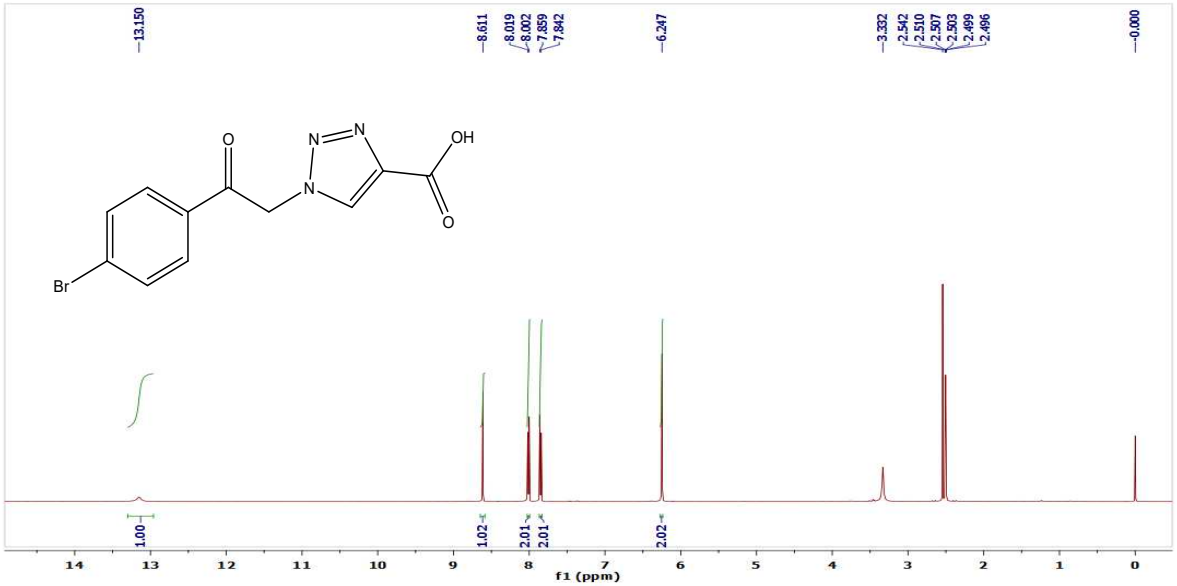
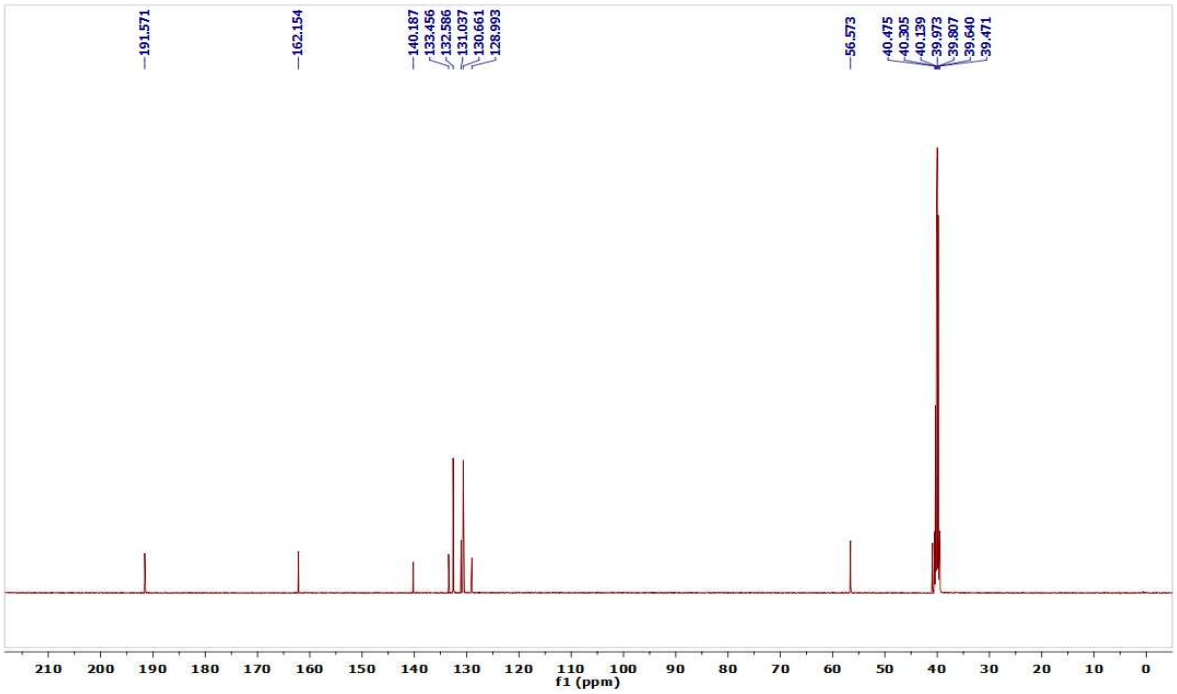
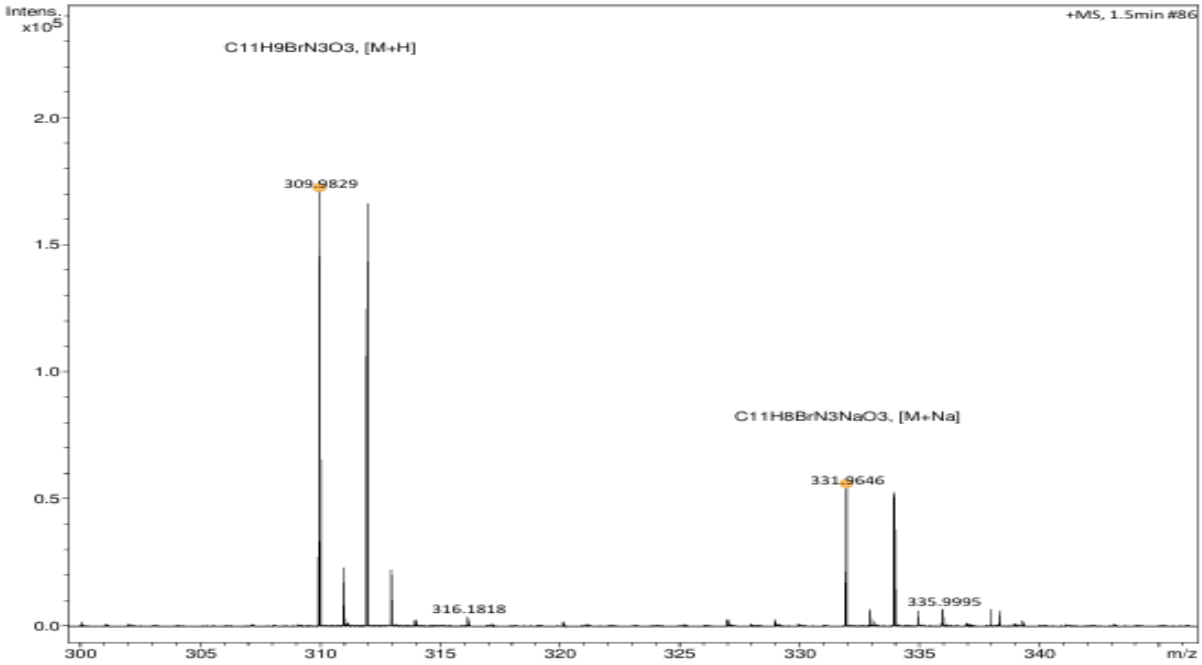
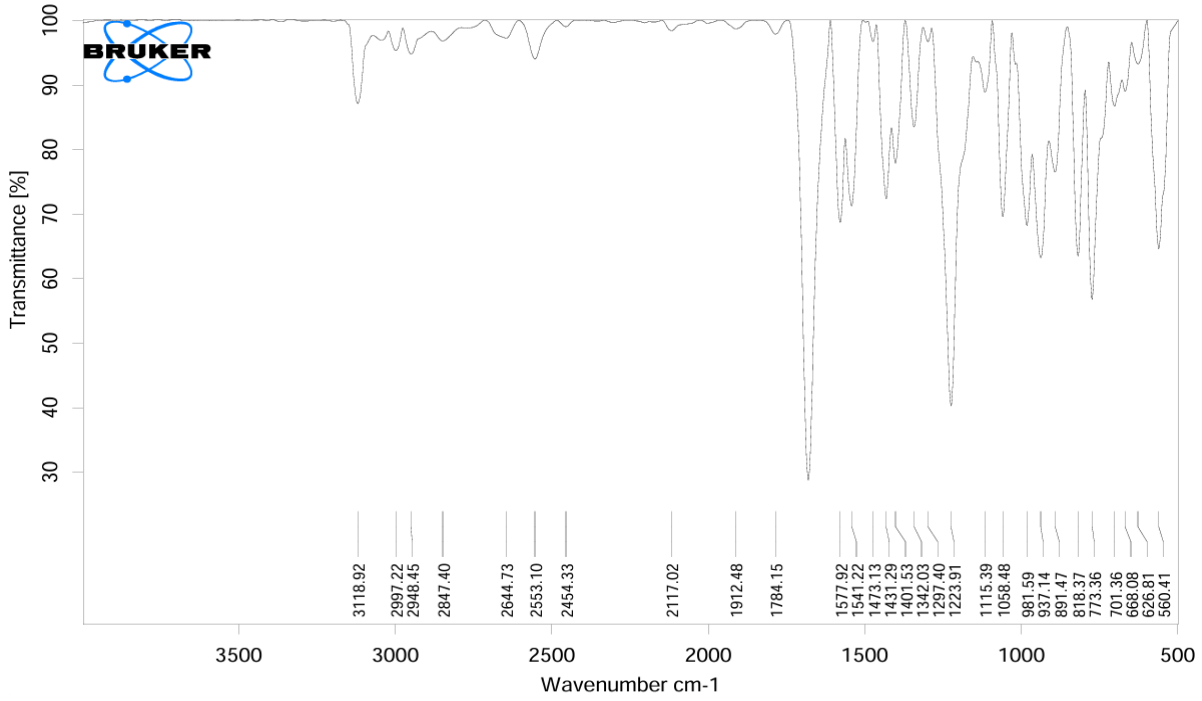
3120.64
2997.67
2947.75
2843.79
2746.53
2643.23
2552.69
2453.97
2118.38
1901.19
1775.02
1592.55
1543.53
1503.36
1425.77
1342.51
1304.07
1152.04
1108.28
1048.38
983.95
940.19
892.70
822.52
770.97
710.94
636.71
580.21
557.42

(3c) 1-(2-(4-bromophenylethyl)2-oxoethyl)-1 *H*-1,2,3-triazole-4-carboxylic acid

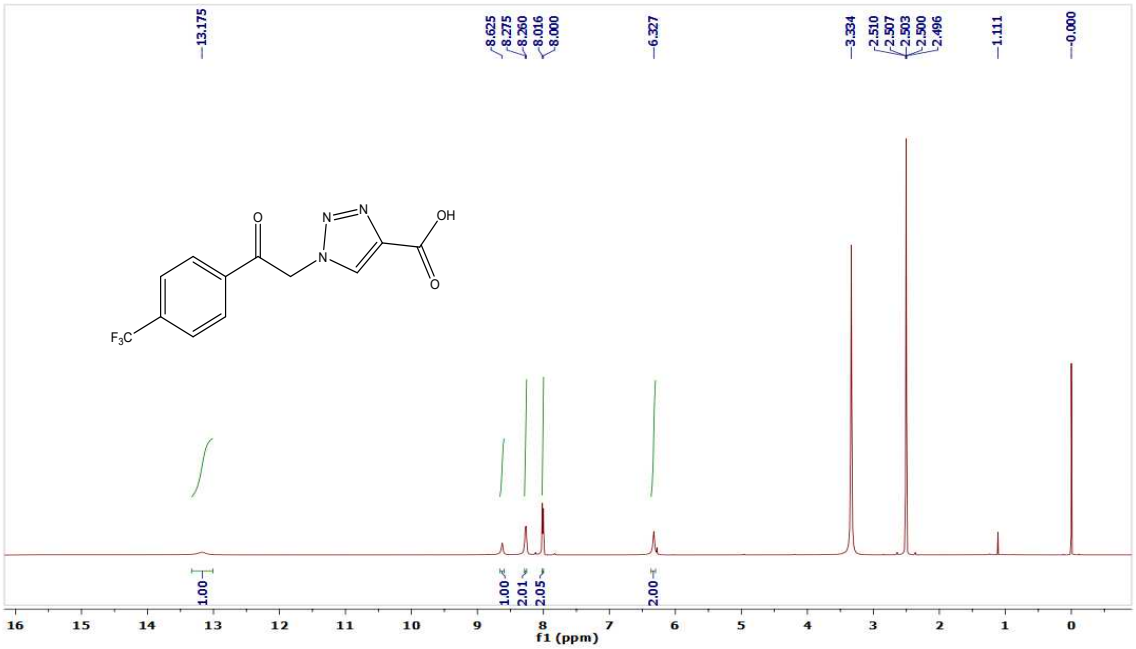


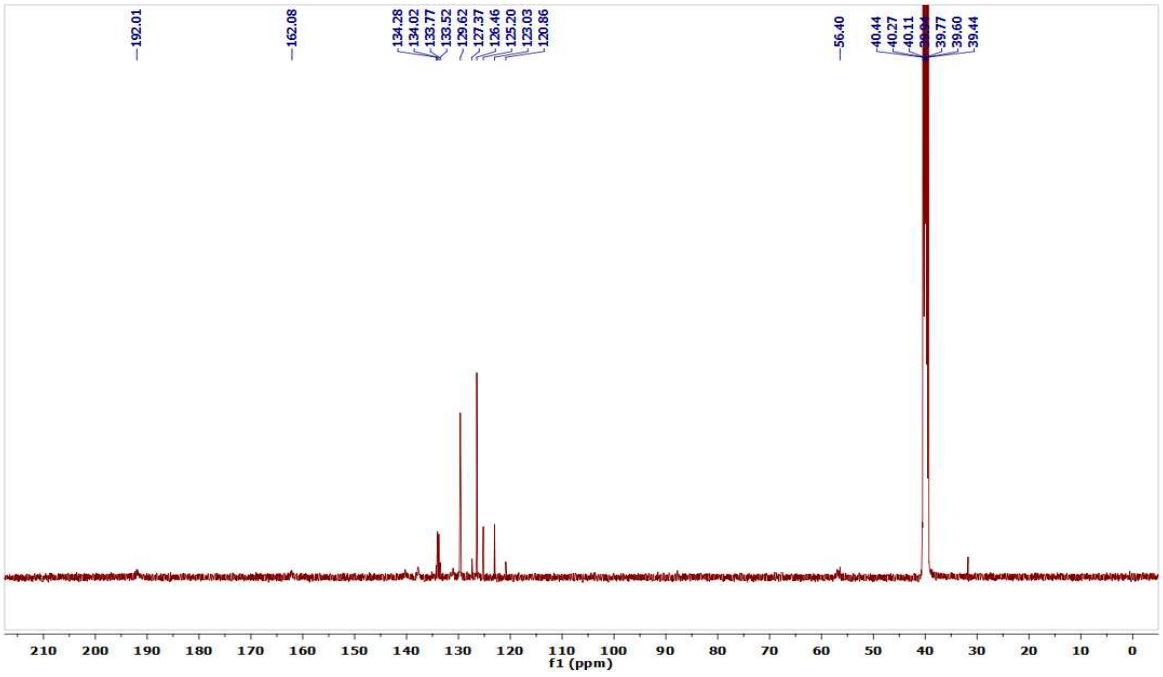


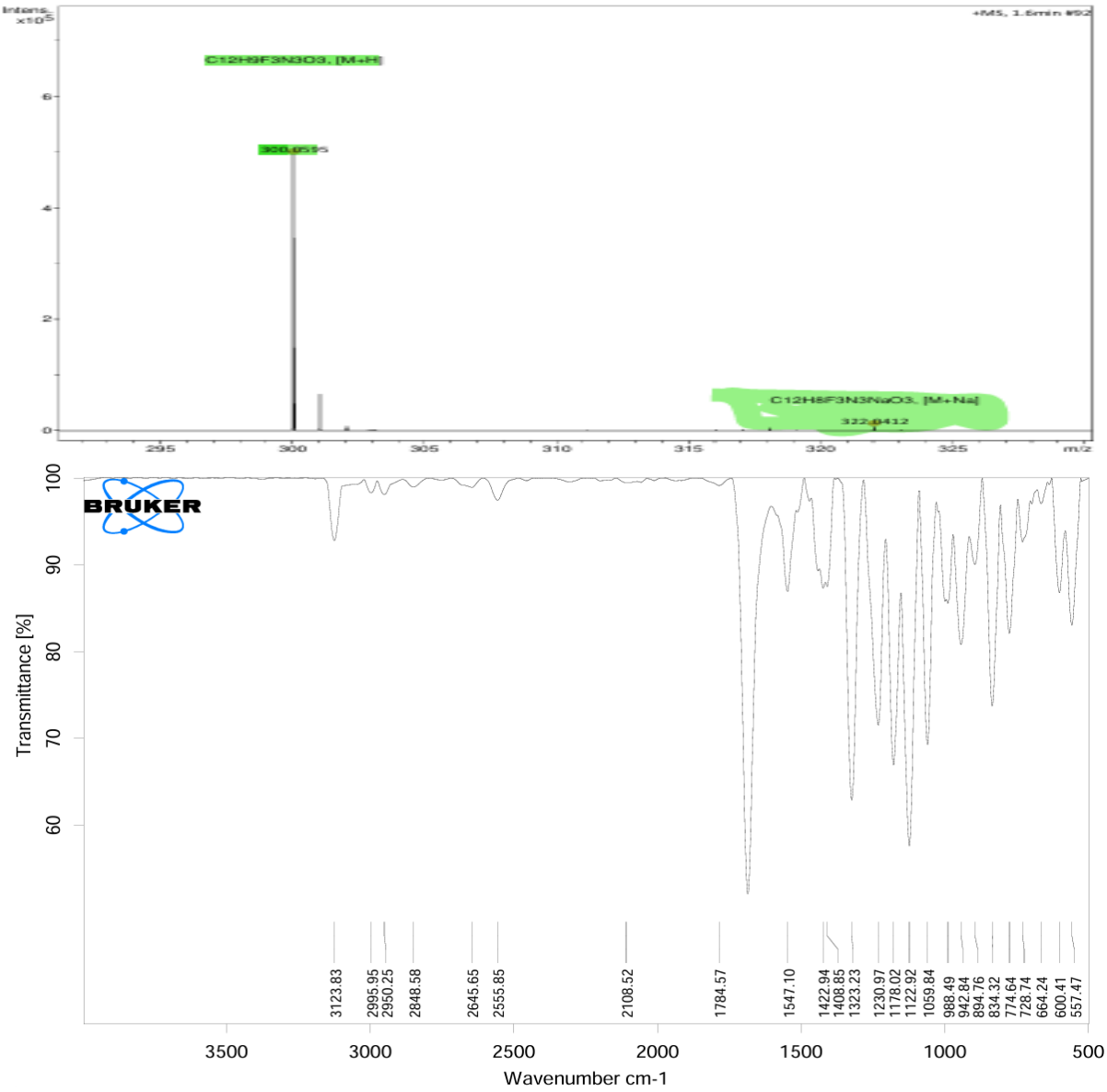

Intens.
x10^5
+MS, 1.5min #86
C11H9BrN3O3, [M+H]
309.9829
316.1818
C11H8BrN3NaO3, [M+Na]
331.9646
335.9995
m/z


BRUKER
Transmittance [%]
3118.92
2997.22
2948.45
2847.40
2644.73
2553.10
2454.33
2117.02
1912.48
1784.15
1577.92
1541.22
1473.13
1431.29
1401.53
1342.03
1297.40
1223.91
1115.39
1058.48
981.59
937.14
891.47
818.37
773.36
701.36
668.08
626.81
560.41
Wavenumber cm-1

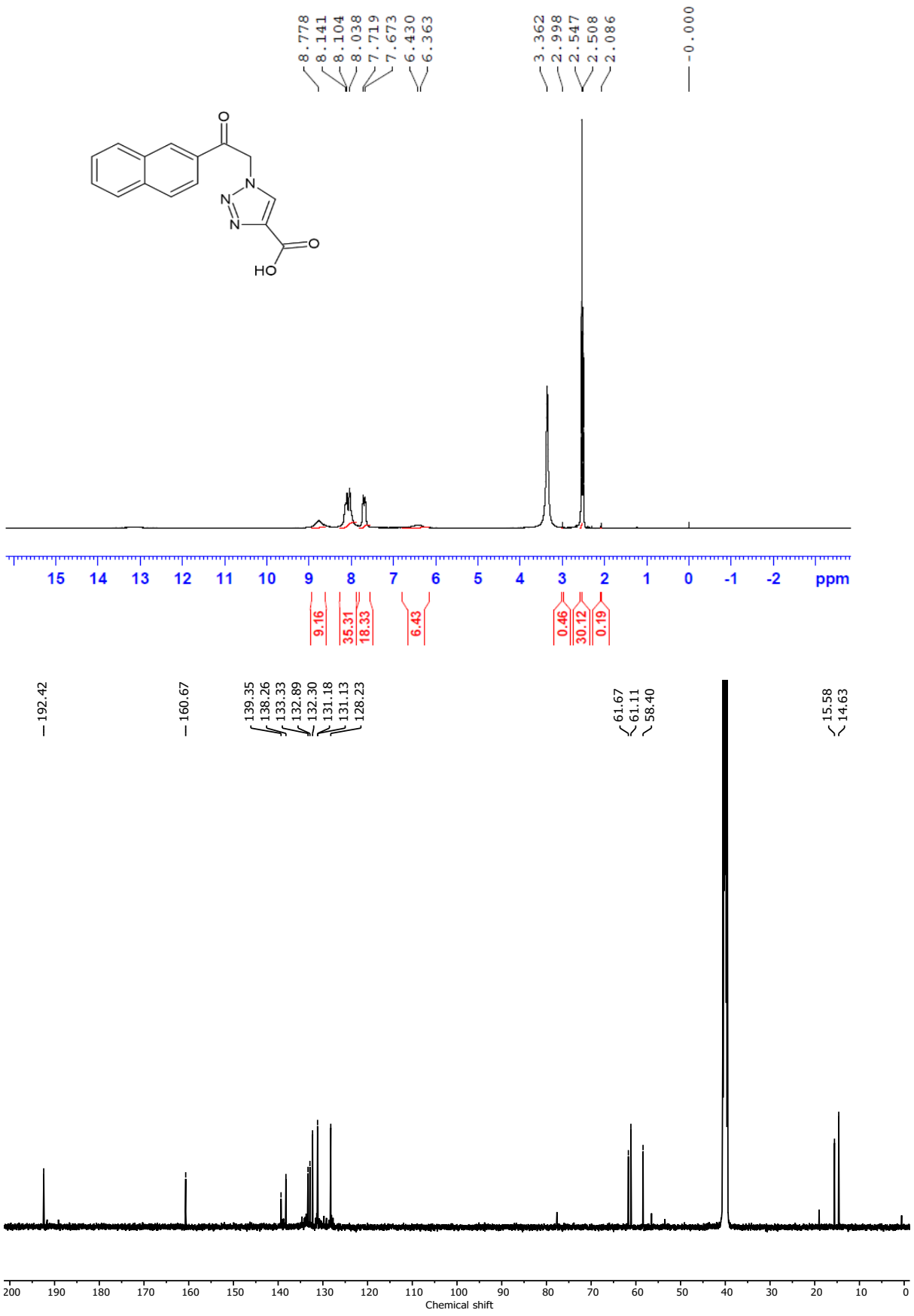
(3d) 1-(2-oxo-2-(4-trifluoromethyl) phenyl) ethyl)-1 *H*-1,2,3-triazole-4-carboxylic acid

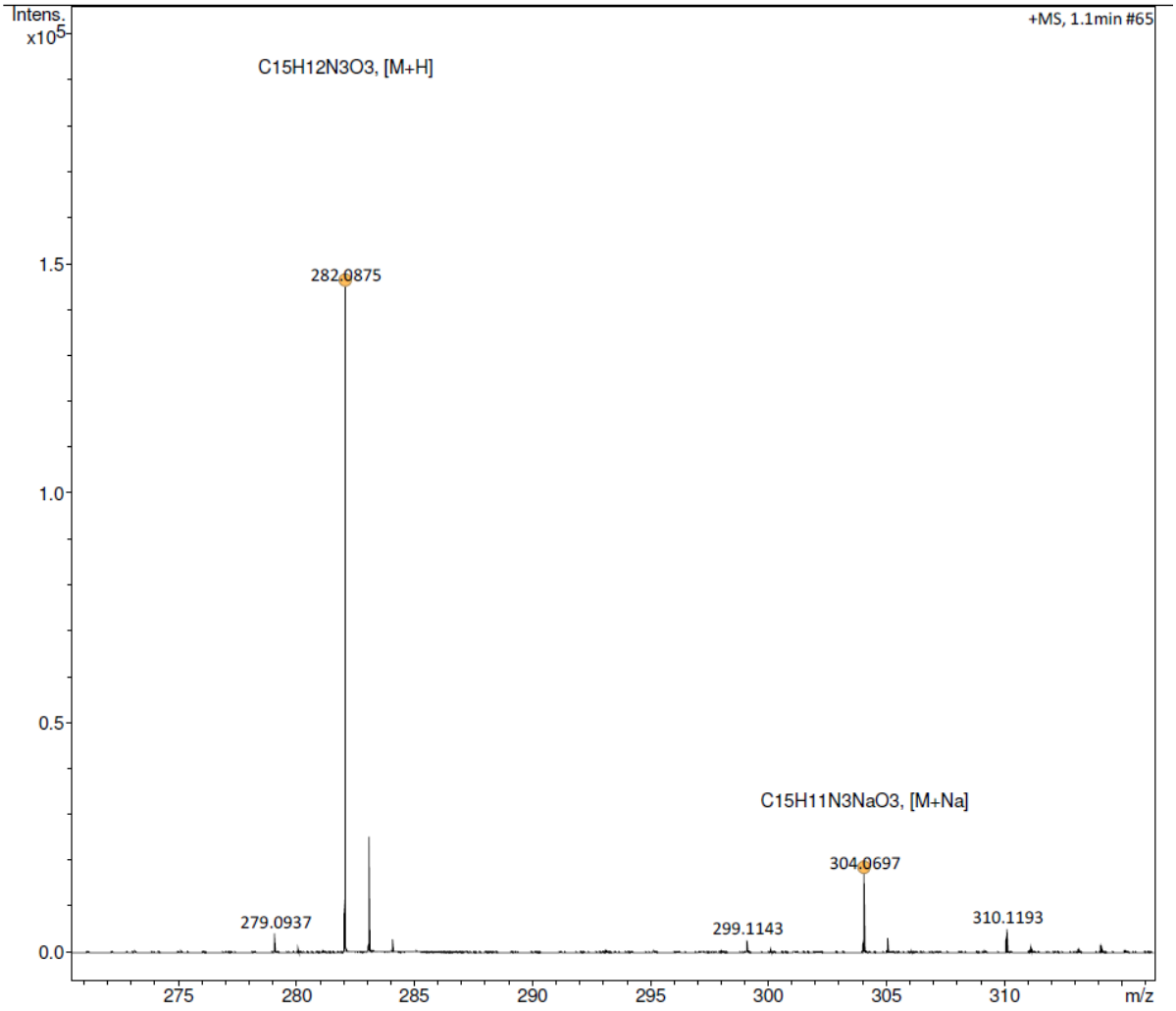


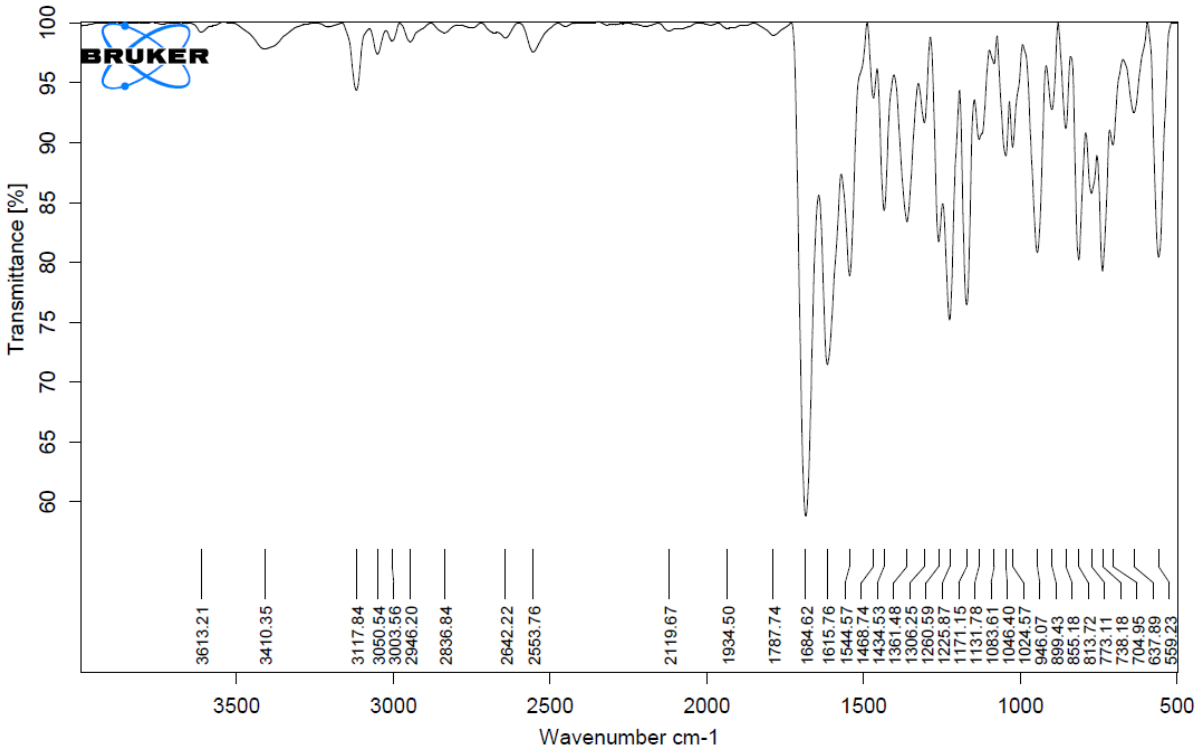



Intens.
x10^5
+MS, 1.6min #92
C12H8F3N3O3, [M+H]
300.0515
C12H8F3N3NaO3, [M+Na]
322.0412
295
300
305
310
315
320
325
m/z
BRUKER
Transmittance [%]
100
90
80
70
60
3123.83
2995.95
2950.25
2848.58
2645.65
2555.85
2108.52
1784.57
1547.10
1422.94
1408.85
1323.23
1230.97
1178.02
1122.92
1059.84
988.49
942.84
894.76
834.32
774.64
728.74
664.24
600.41
557.47
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1

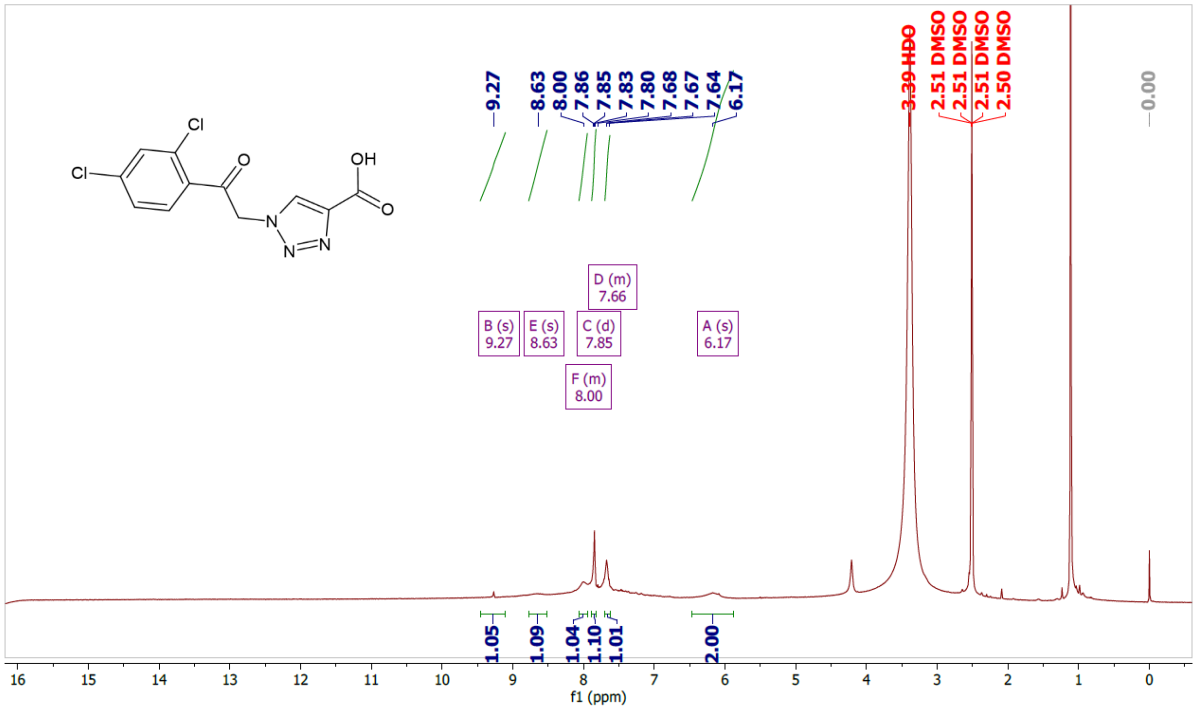
(3e) 1-(2-(naphthalen-2-yl)-2-oxoethyl)-1*H*-1,2,3-triazole-4-carboxylic acid

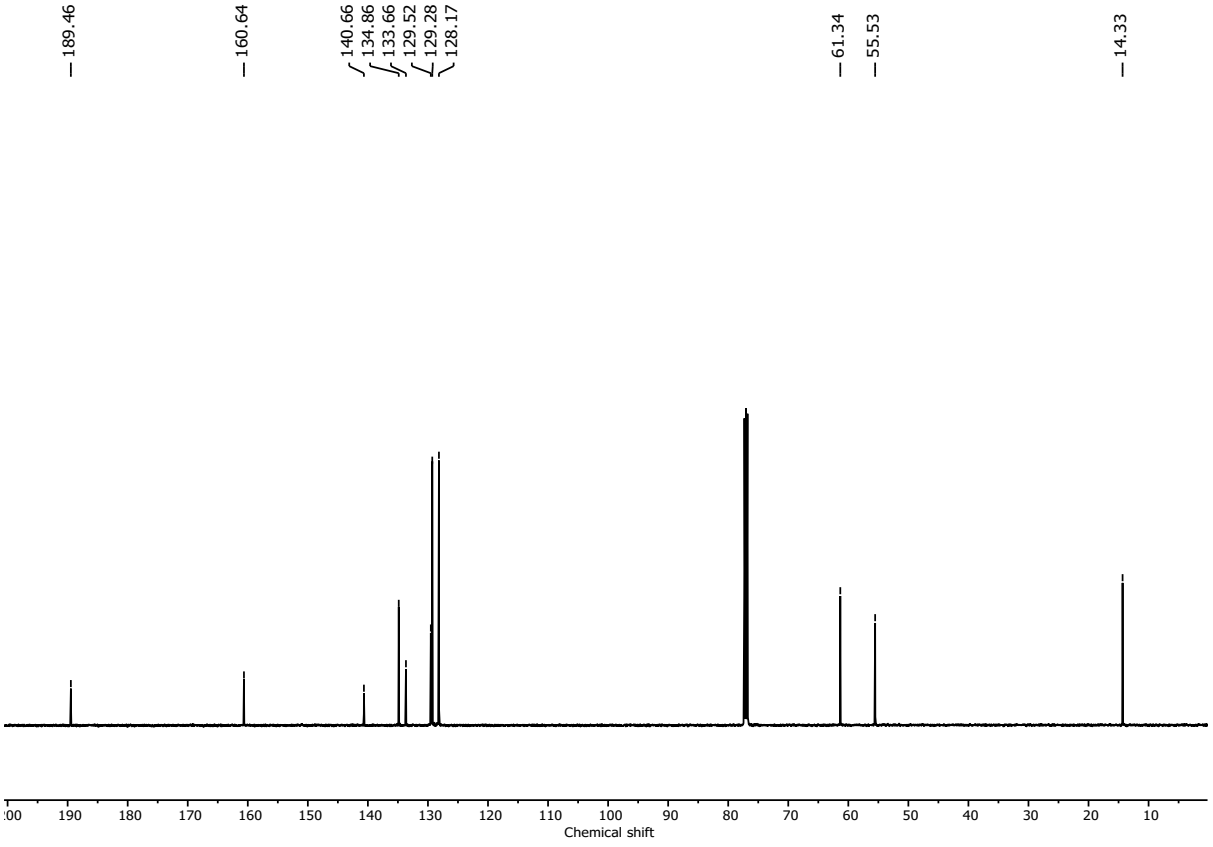


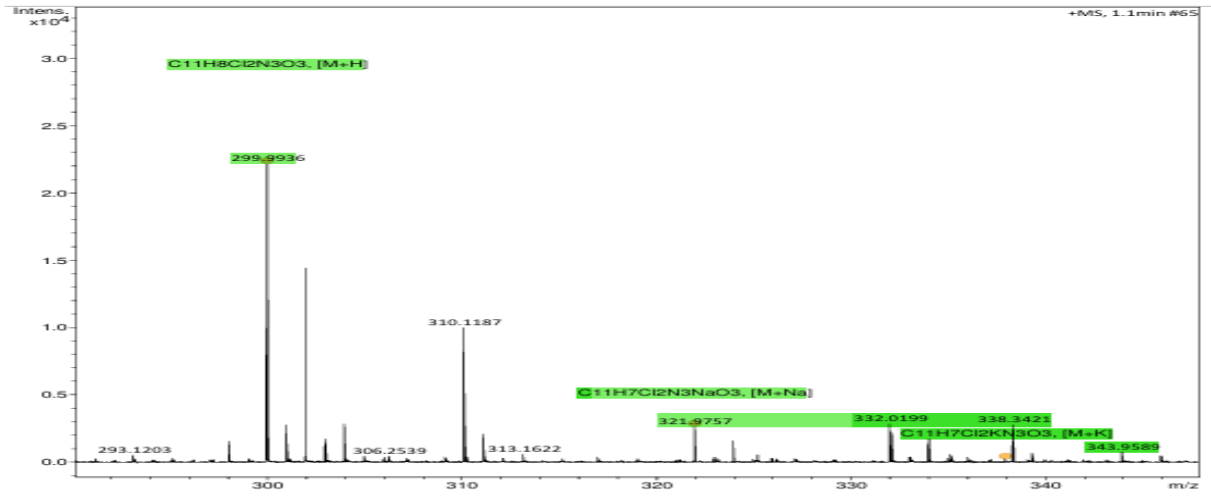

Intens.
x10^5
+MS, 1.1min #65
C15H12N3O3, [M+H]
282.0875
C15H11N3NaO3, [M+Na]
304.0697
279.0937
299.1143
310.1193
m/z

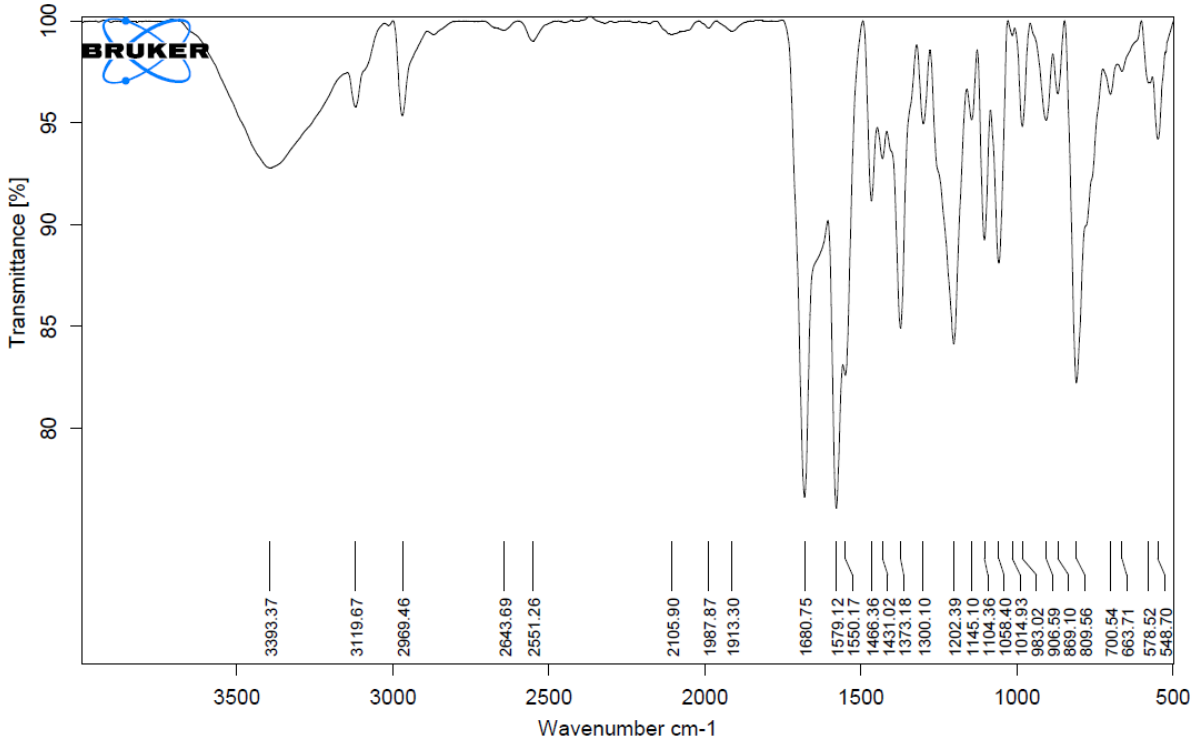

BRUKER
Transmittance [%]
Wavenumber cm-1
3613.21
3410.35
3117.84
3050.54
3003.56
2946.20
2836.84
2642.22
2553.76
2119.67
1934.50
1787.74
1684.62
1615.76
1544.57
1468.74
1434.53
1361.48
1306.25
1260.59
1225.87
1171.15
1131.78
1083.61
1046.40
1024.57
946.07
899.43
855.18
813.72
773.11
738.18
704.95
637.89
559.23

(3f) 1-(2-(2,4-dichlorophenyl)-2-oxo-ethyl)-1 *H*-1,2,3-triazole-4-carboxylic acid

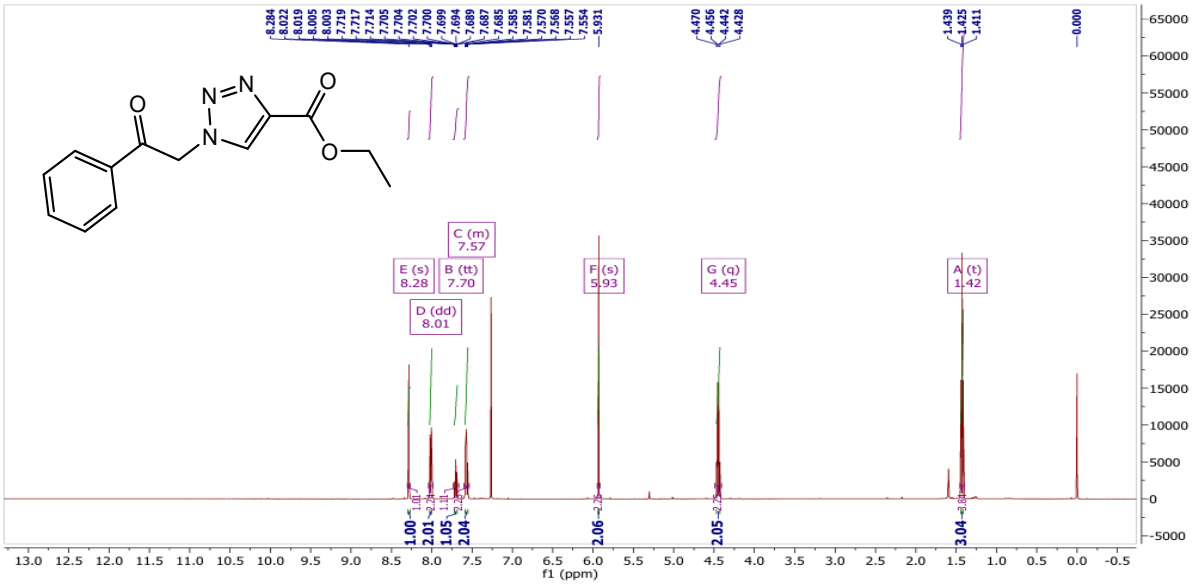


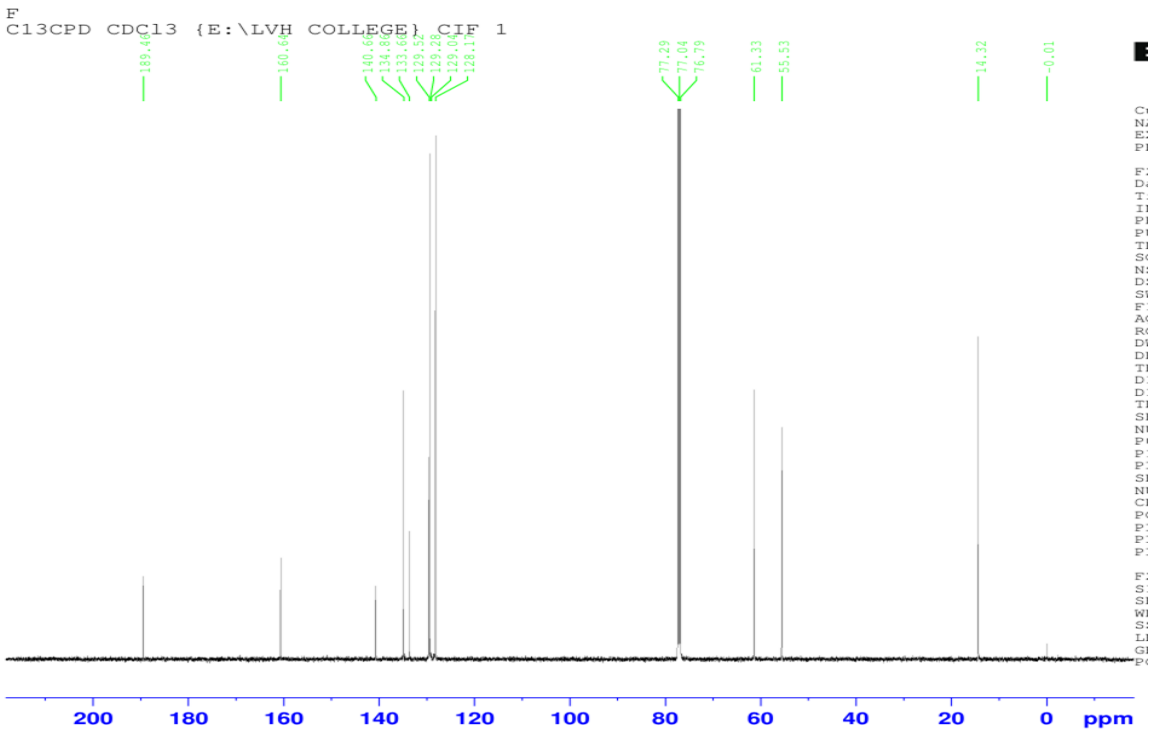


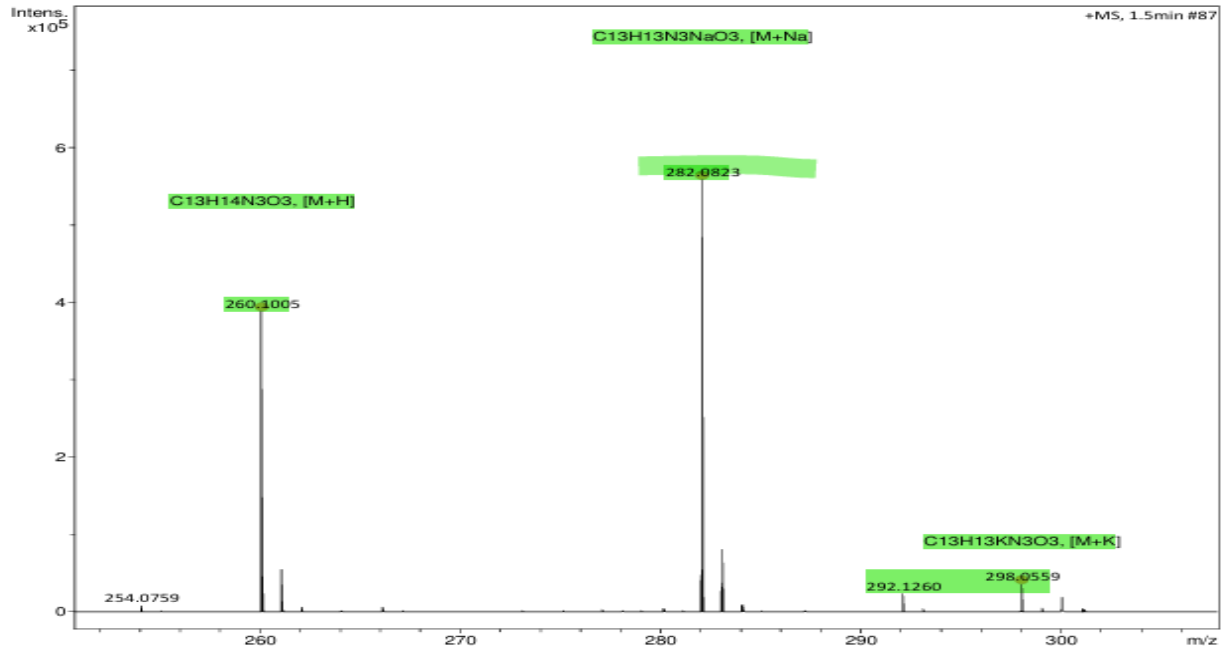

Intens.
x10^4
+MS, 1.1min #65
C11H8Cl2N3O3, [M+H]
299.9936
310.1187
C11H7Cl2N3NaO3, [M+Na]
321.9757
332.0199
338.3421
C11H7Cl2KN3O3, [M+K]
343.9589
293.1203
306.2539
313.1622
m/z

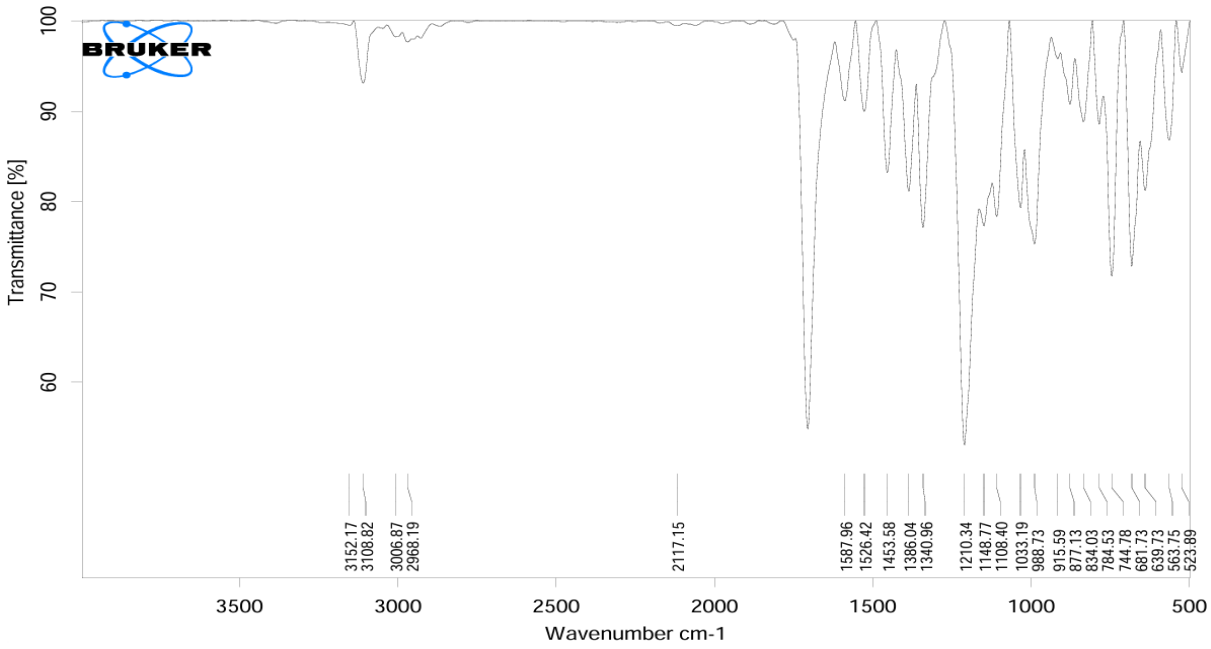

BRUKER
Transmittance [%]
Wavenumber cm-1
3393.37
3119.67
2969.46
2643.69
2551.26
2105.90
1987.87
1913.30
1680.75
1579.12
1550.17
1466.36
1431.02
1373.18
1300.10
1202.39
1145.10
1104.36
1058.40
1014.93
983.02
906.59
869.10
809.56
700.54
663.71
578.52
548.70

(4a) Ethyl 1-(2-oxo-2-phenylethyl)-1 *H*-1,2,3-triazole-4-carboxylate

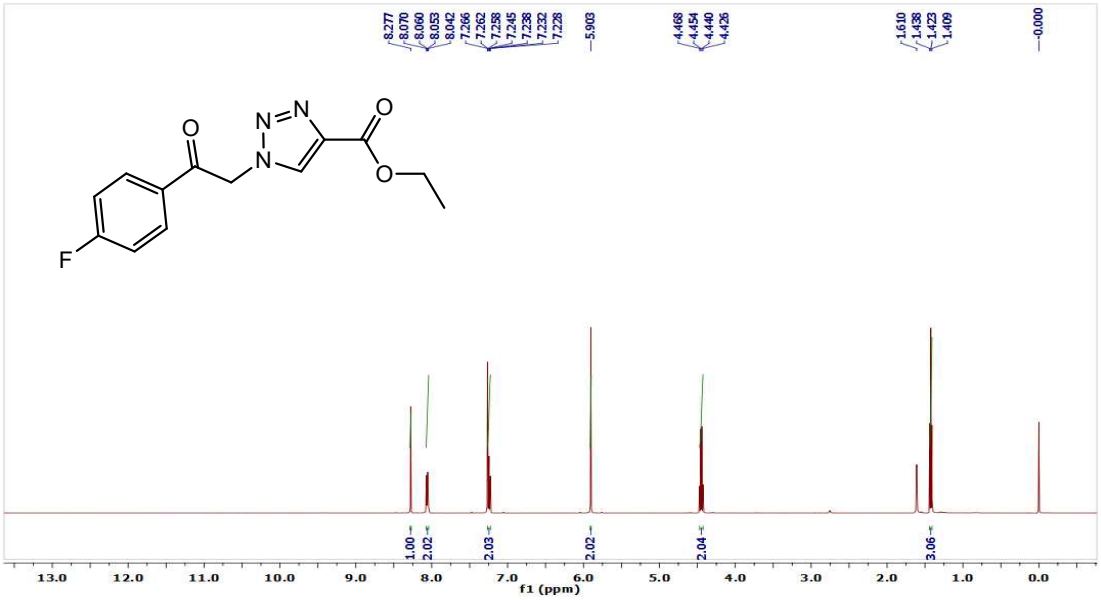


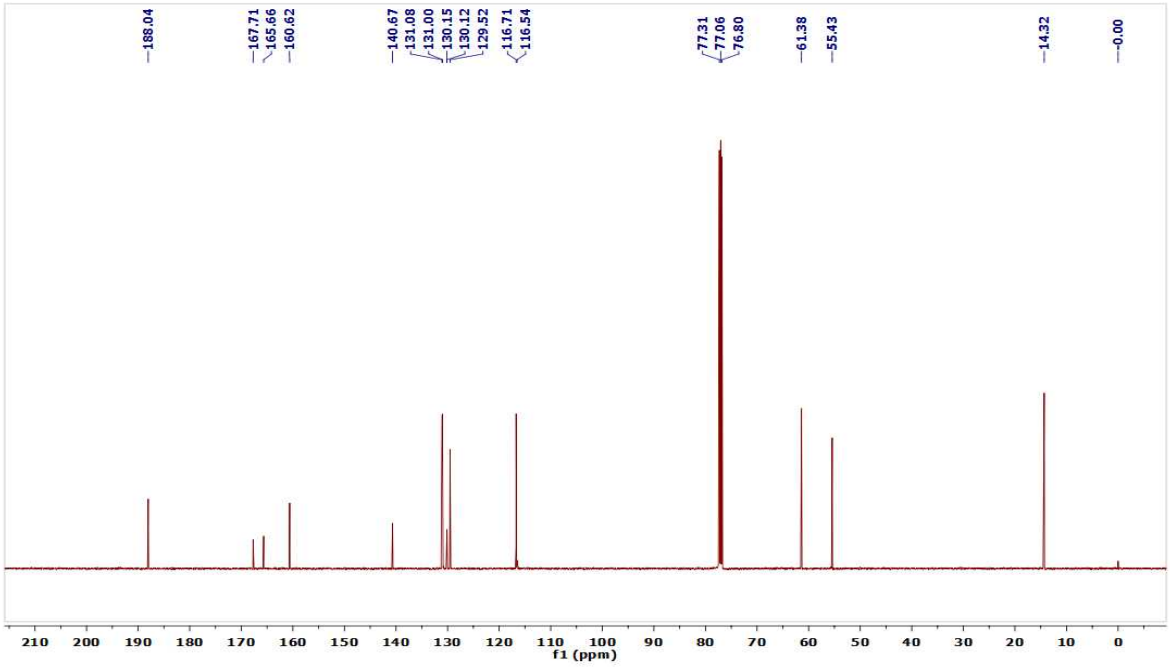


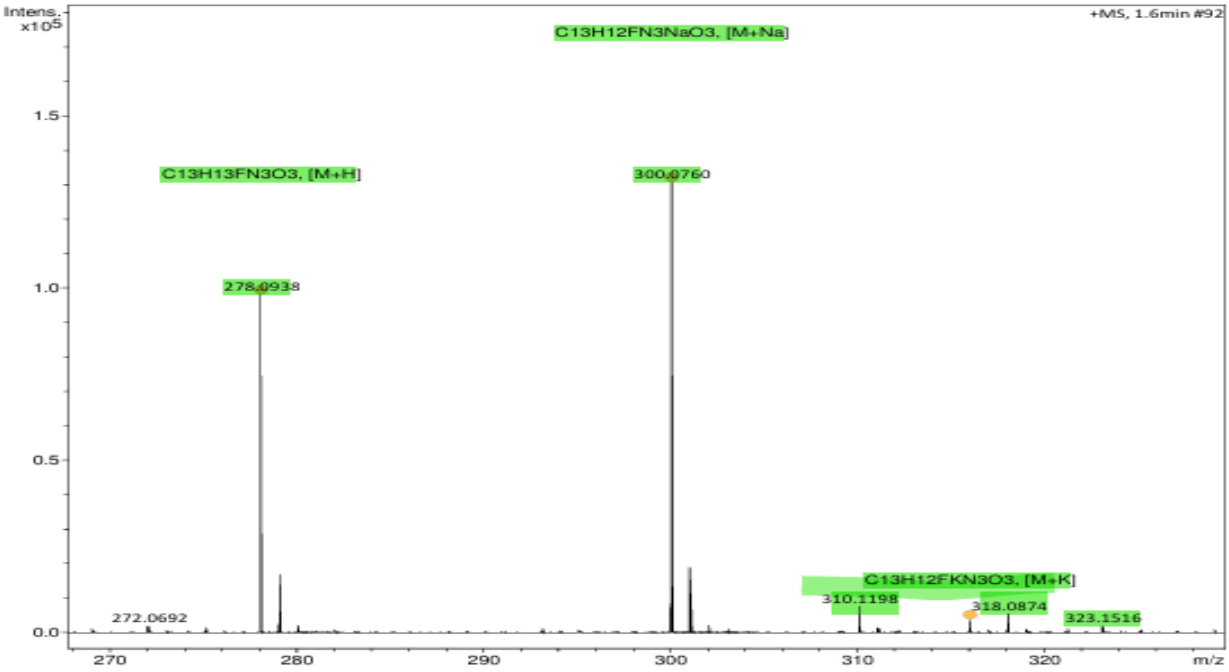

Intens.
x10^5
+MS, 1.5min #87
C13H13N3NaO3, [M+Na]
282.0823
C13H14N3O3, [M+H]
260.1005
C13H13KN3O3, [M+K]
254.0759
292.1260
298.0559
m/z

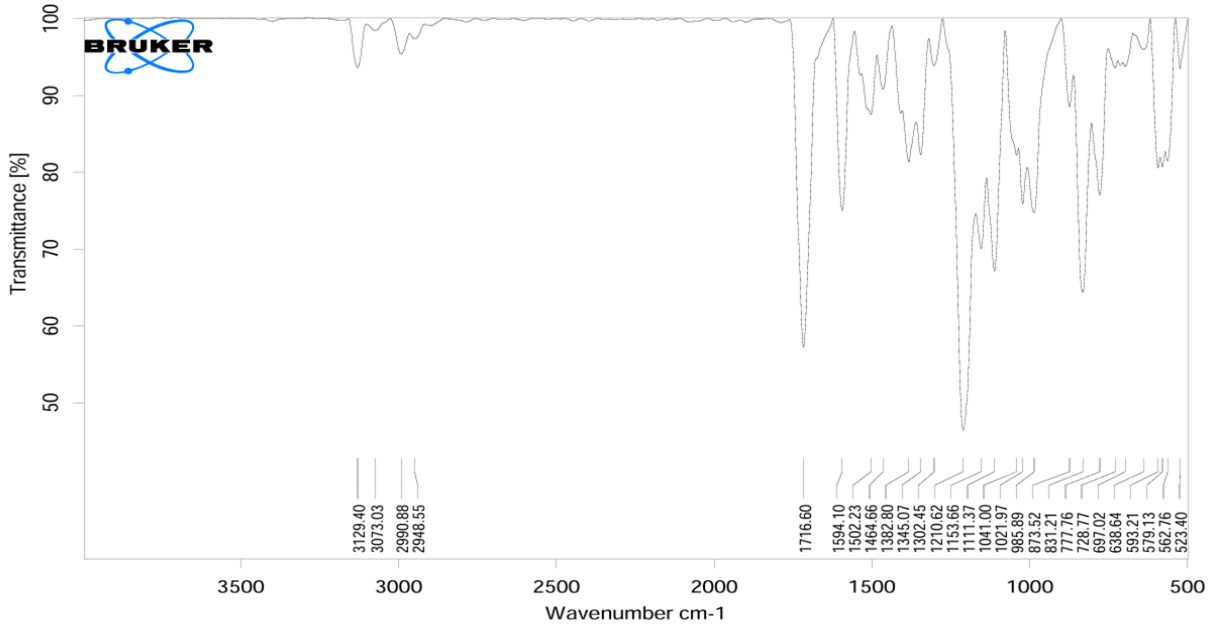

BRUKER
Transmittance [%]
Wavenumber cm-1
3152.17
3108.82
3006.87
2968.19
2117.15
1587.96
1526.42
1453.58
1386.04
1340.96
1210.34
1148.77
1108.40
1033.19
988.73
915.59
877.13
834.03
784.53
744.78
681.73
639.73
563.75
523.89

(4b) Ethyl 1-(2-(4-fluorophenyl)-2-oxoethyl)-1 *H*-1,2,3-triazole-4-carboxylate

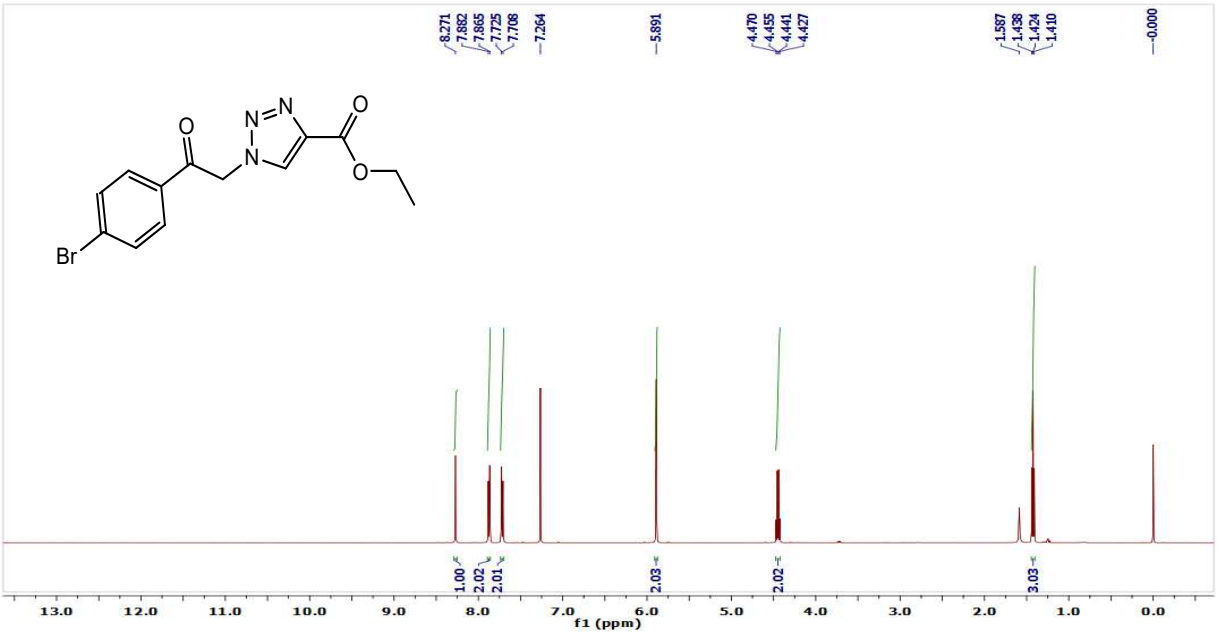


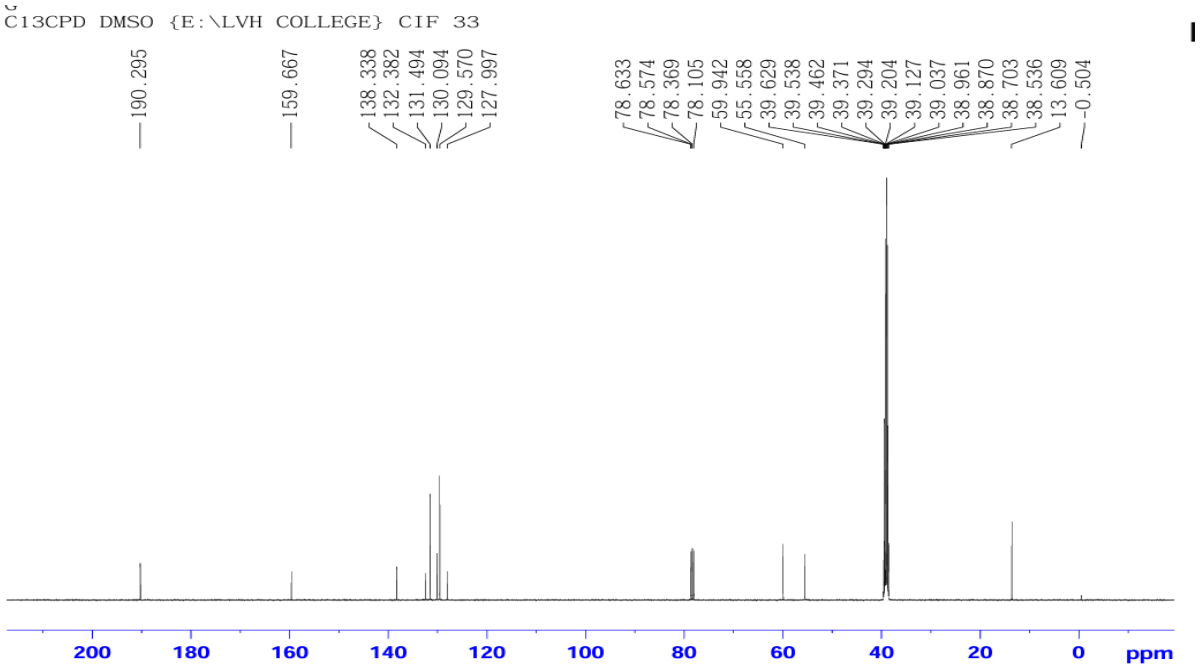


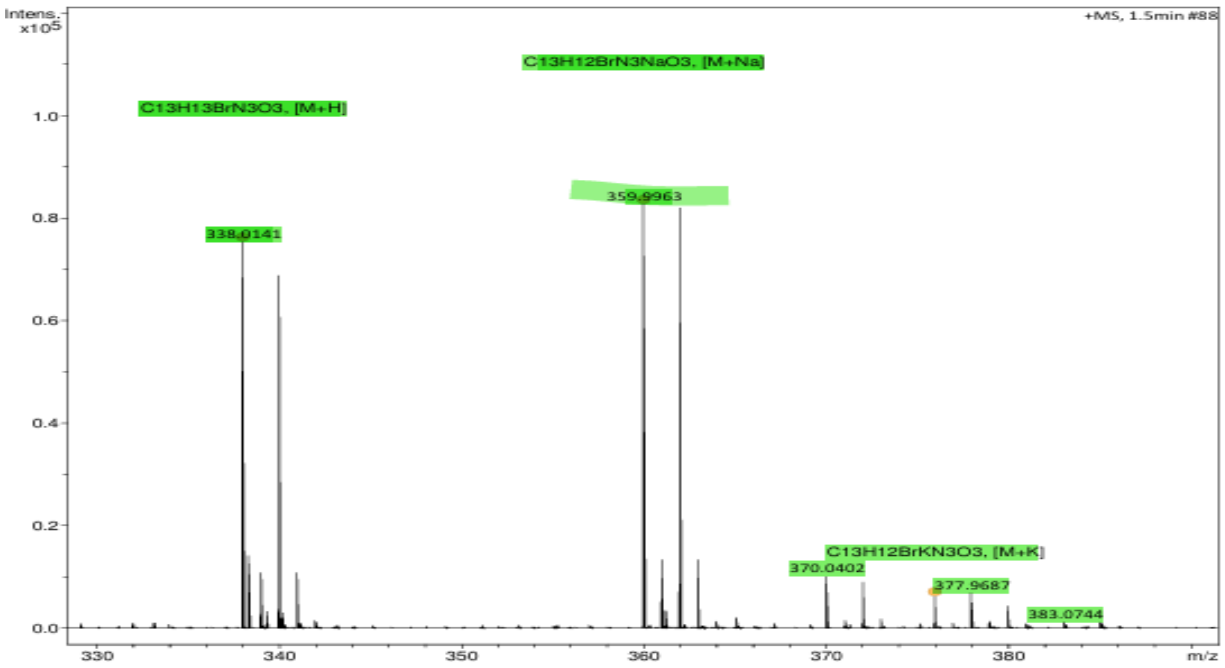

Intens.
x10^5
+MS, 1.6min #92
C13H12FN3NaO3, [M+Na]
C13H13FN3O3, [M+H]
300.0760
278.0938
C13H12FKN3O3, [M+K]
310.1198
318.0874
323.1516
272.0692
1.5
1.0
0.5
0.0
270
280
290
300
310
320
m/z

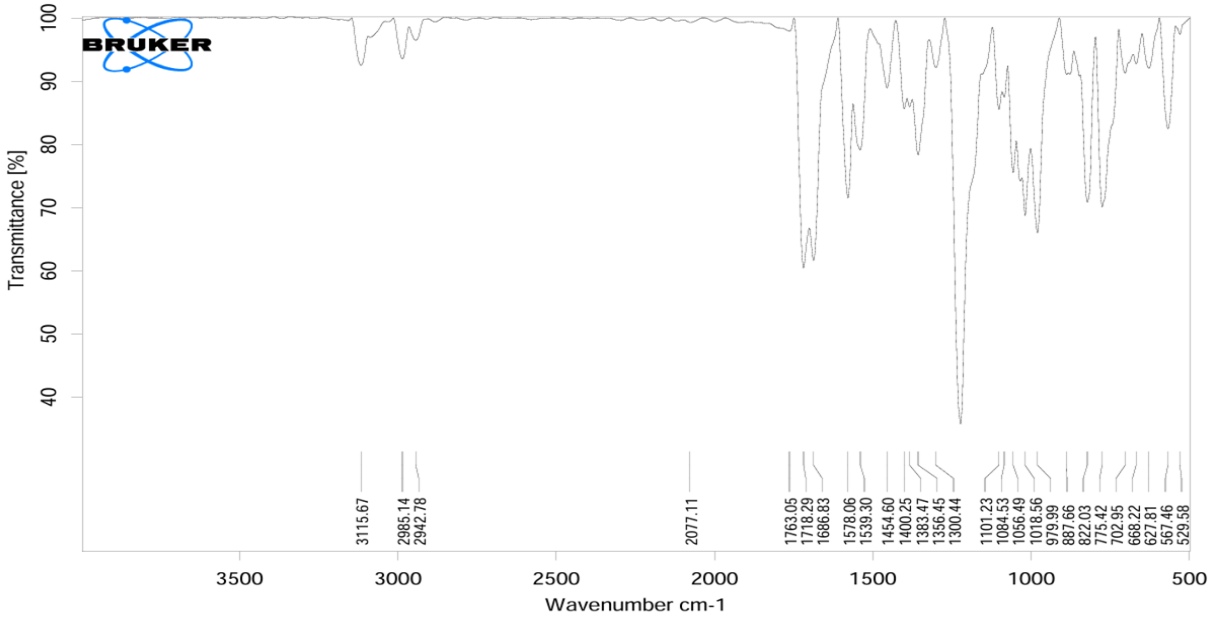

BRUKER
Transmittance [%]
100
90
80
70
60
50
3129.40
3073.03
2990.88
2948.55
1716.60
1594.10
1502.23
1464.66
1382.80
1345.07
1302.45
1210.62
1153.66
1111.37
1041.00
1021.97
985.89
873.52
831.21
777.76
728.77
697.02
638.64
593.21
579.13
562.76
523.40
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1

(4c) Ethyl 1-(2-(4-bromophenyl)-2-oxoethyl)-1*H*-1,2,3-triazole-4-carboxylate

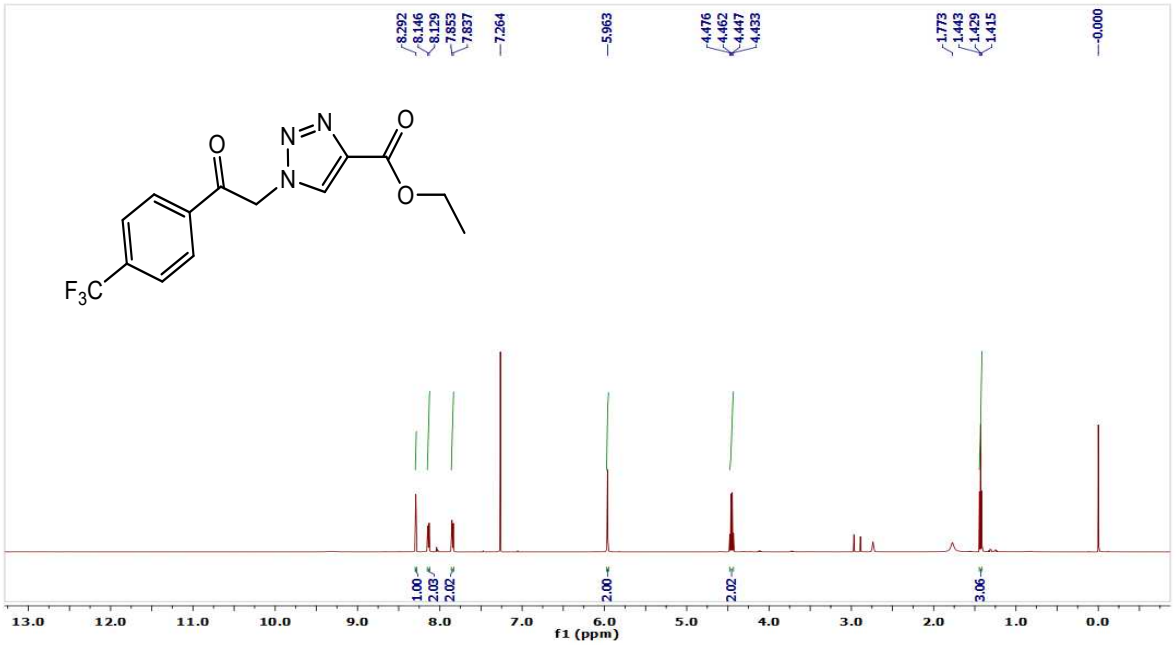


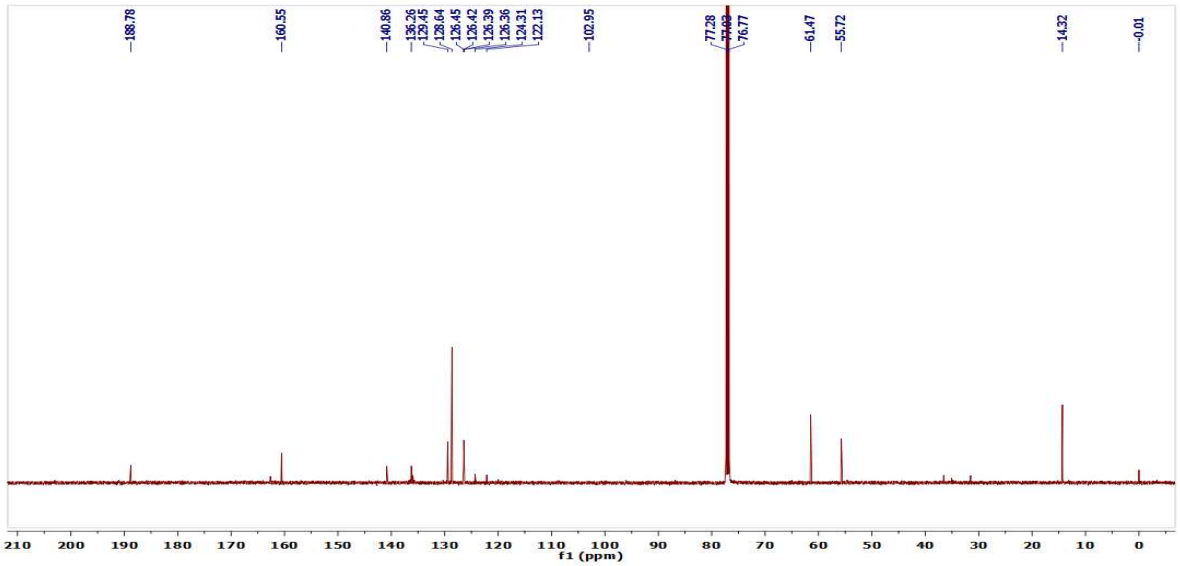


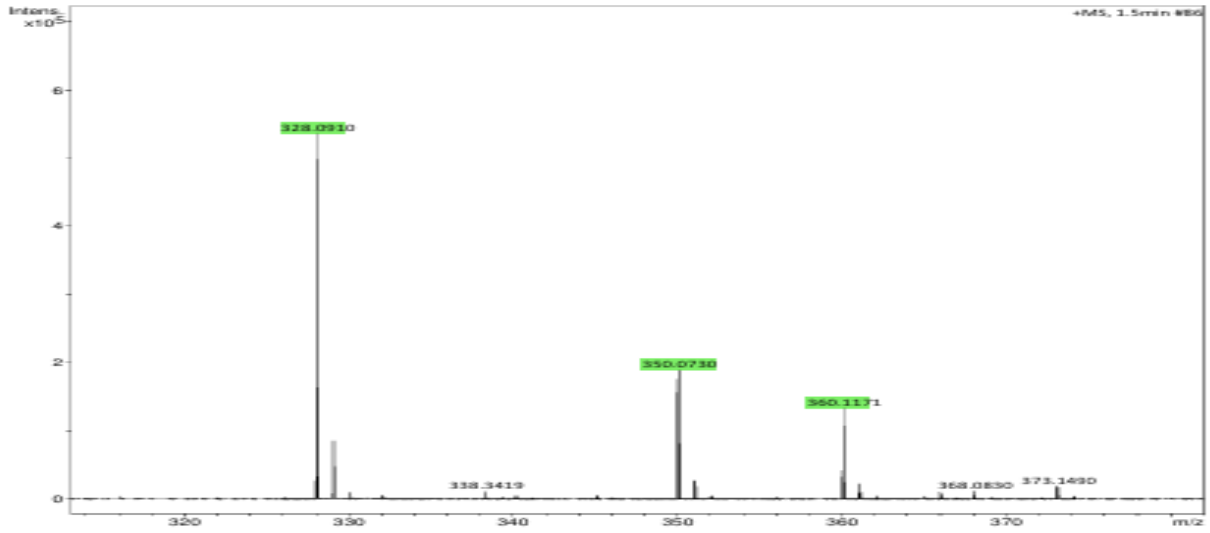

Intens.
x10^5
+MS, 1.5min #88
C13H12BrN3NaO3, [M+Na]
C13H13BrN3O3, [M+H]
359.9963
338.0141
C13H12BrKN3O3, [M+K]
370.0402
377.9687
383.0744
1.0
0.8
0.6
0.4
0.2
0.0
330
340
350
360
370
380
m/z

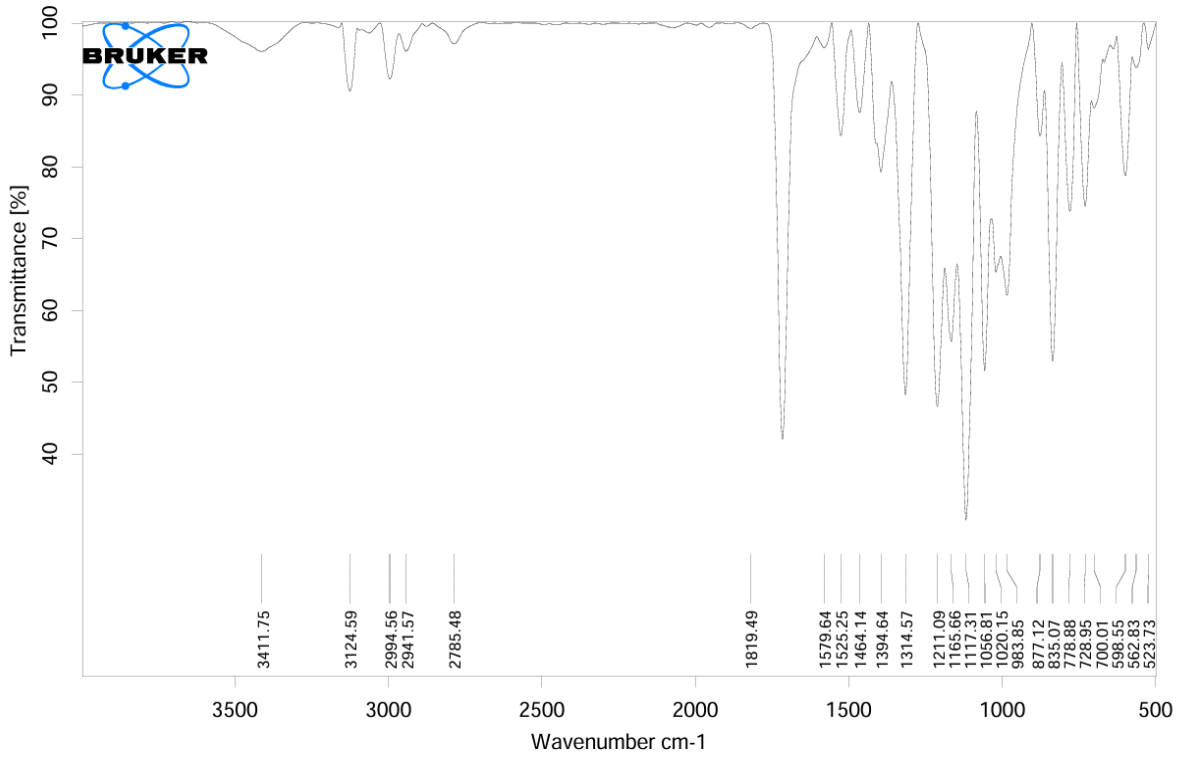

BRUKER
Transmittance [%]
100
90
80
70
60
50
40
3115.67
2985.14
2942.78
2077.11
1763.05
1718.29
1686.83
1578.06
1539.30
1454.60
1400.25
1383.47
1356.45
1300.44
1101.23
1084.53
1056.49
1018.56
979.99
887.66
822.03
775.42
702.95
668.22
627.81
567.46
529.58
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1

(4d) Ethyl 1-(2-(4-trifluoromethylphenyl)-2-oxoethyl)-1*H*-1,2,3-triazole-4-carboxylate



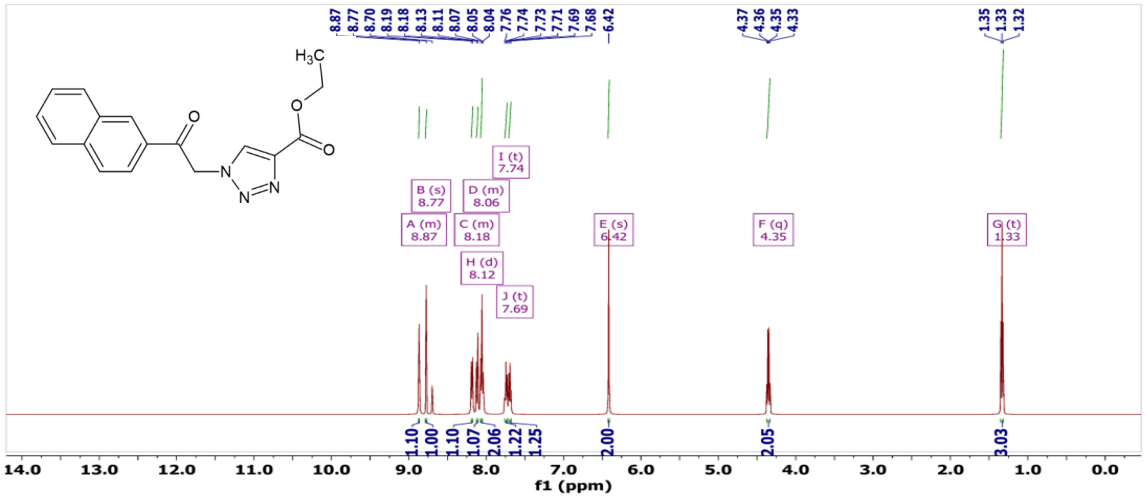


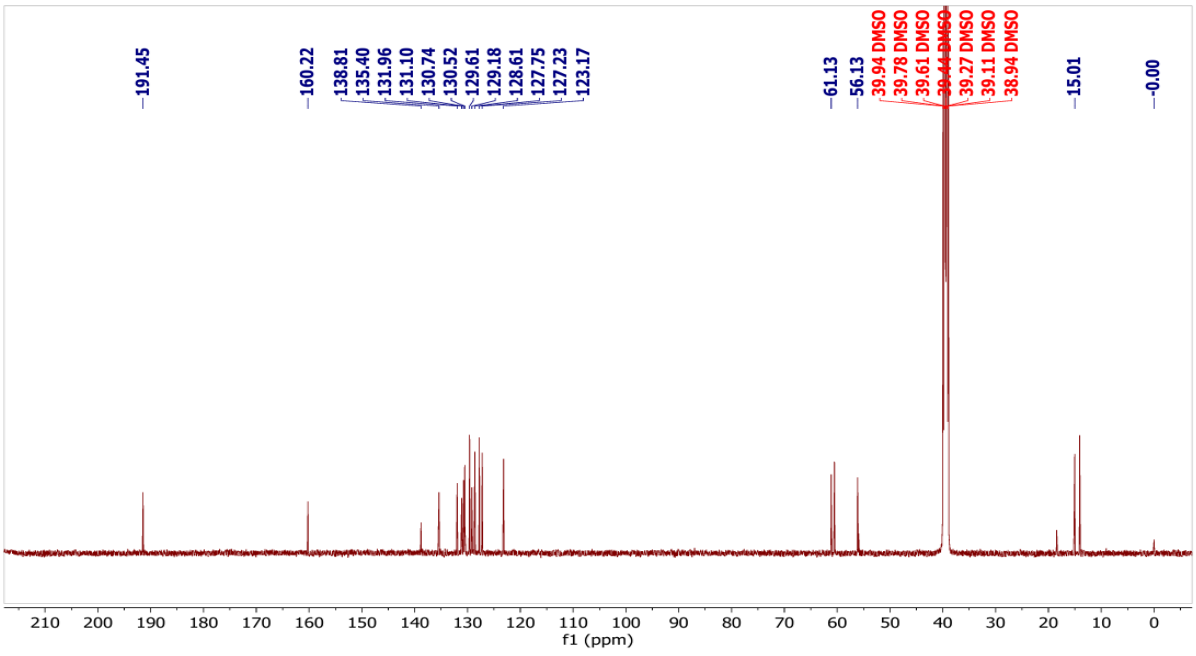

Intens.
x10^5
+MS, 1.5min #86
328.0910
350.0730
360.1171
338.3419
368.0830
373.1490
320
330
340
350
360
370
m/z

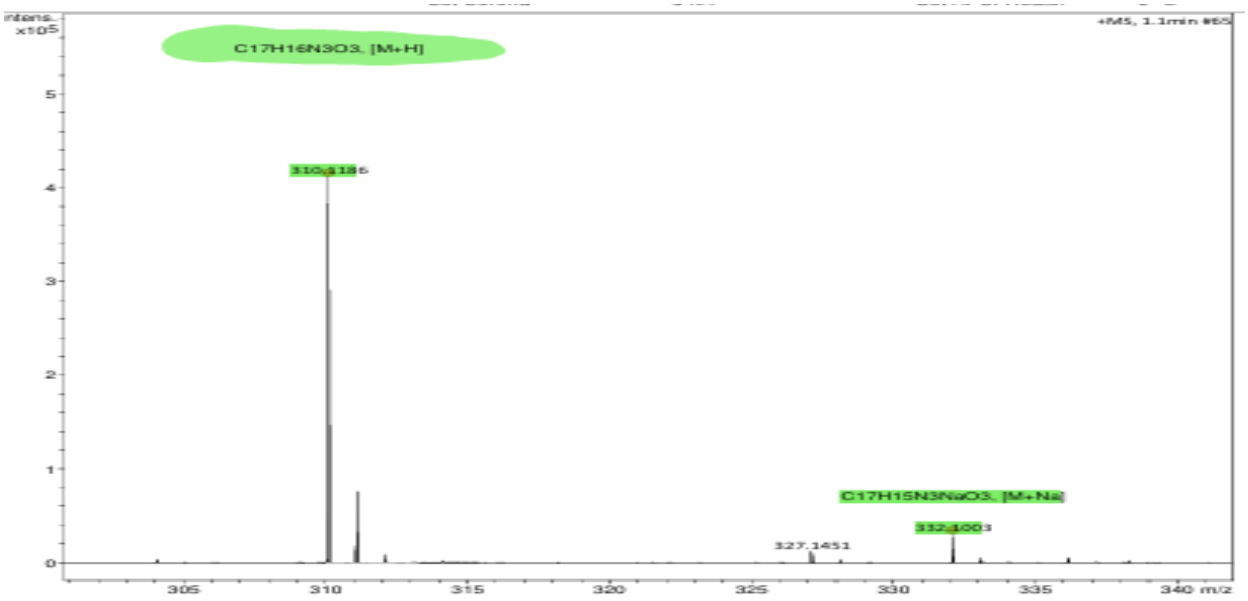

BRUKER
Transmittance [%]
100
90
80
70
60
50
40
3411.75
3124.59
2994.56
2941.57
2785.48
1819.49
1579.64
1525.25
1464.14
1394.64
1314.57
1211.09
1165.66
1117.31
1056.81
1020.15
983.85
877.12
835.07
778.88
728.95
700.01
598.55
562.83
523.73
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1

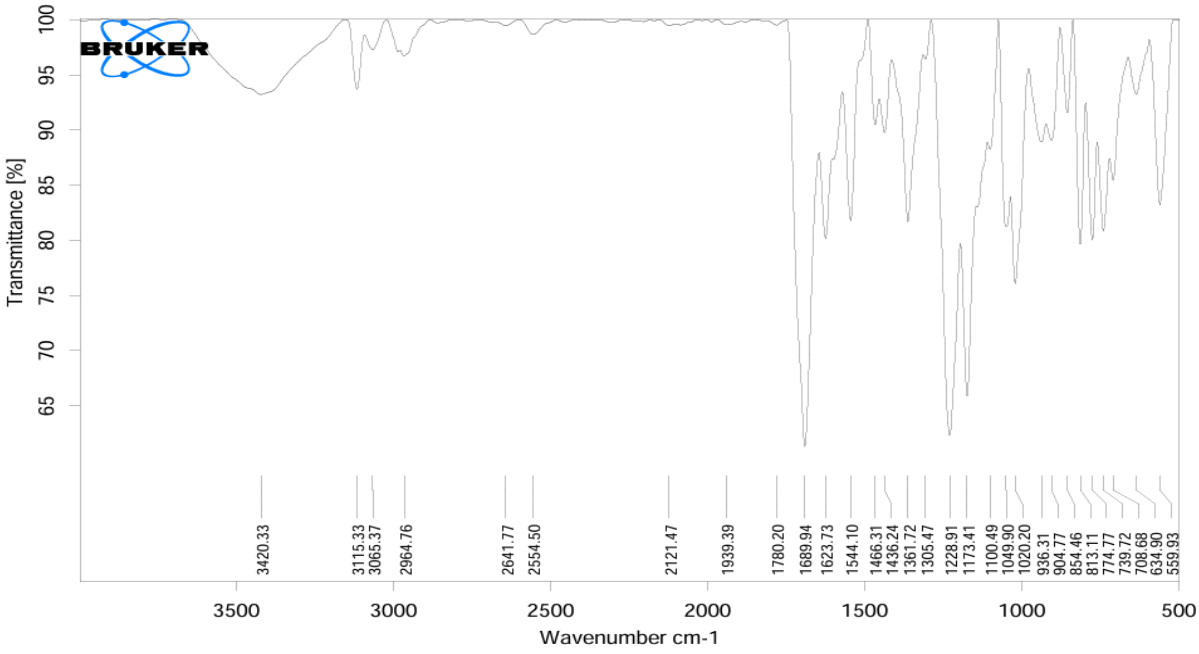
(4e) Ethyl 1-(2-(naphthalen-2-yl)-2-oxoethyl)-1*H*-1,2,3-triazole-4-carboxylate

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.87 – 8.86 (m, 1H), 8.77 (s, 1H), 8.19 – 8.17 (m, 1H), 8.12 (d, J = 8.7 Hz, 1H), 8.07 – 8.05 (m, 2H), 7.74 (t, J = 7.5 Hz, 1H), 7.69 (t, J = 7.5 Hz, 1H), 6.42 (s, 2H), 4.35 (q, J = 7.0 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H).

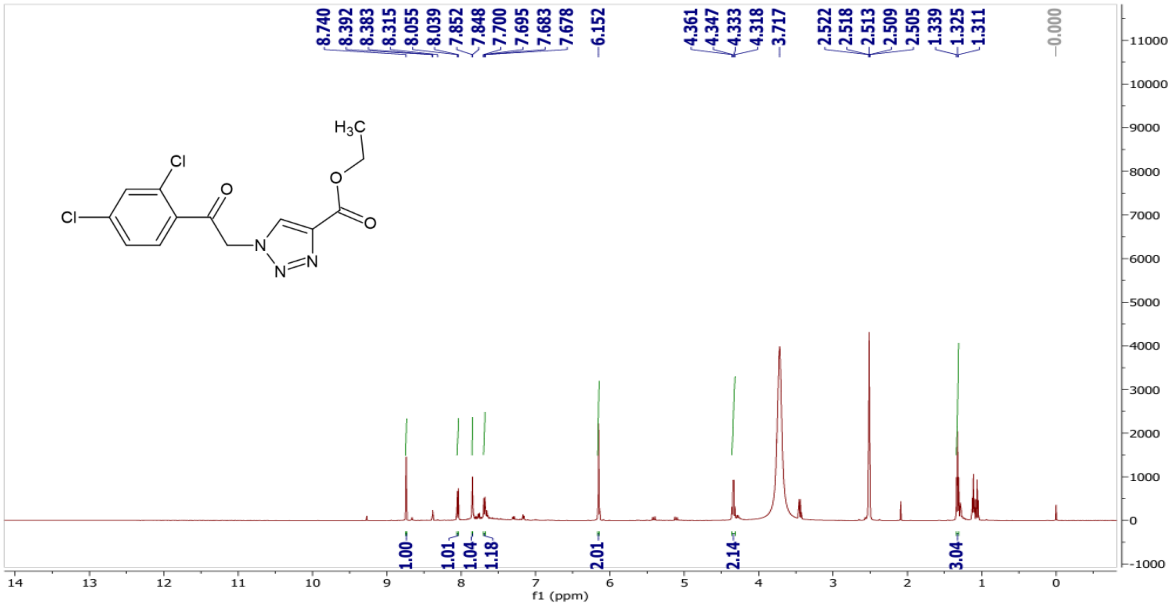


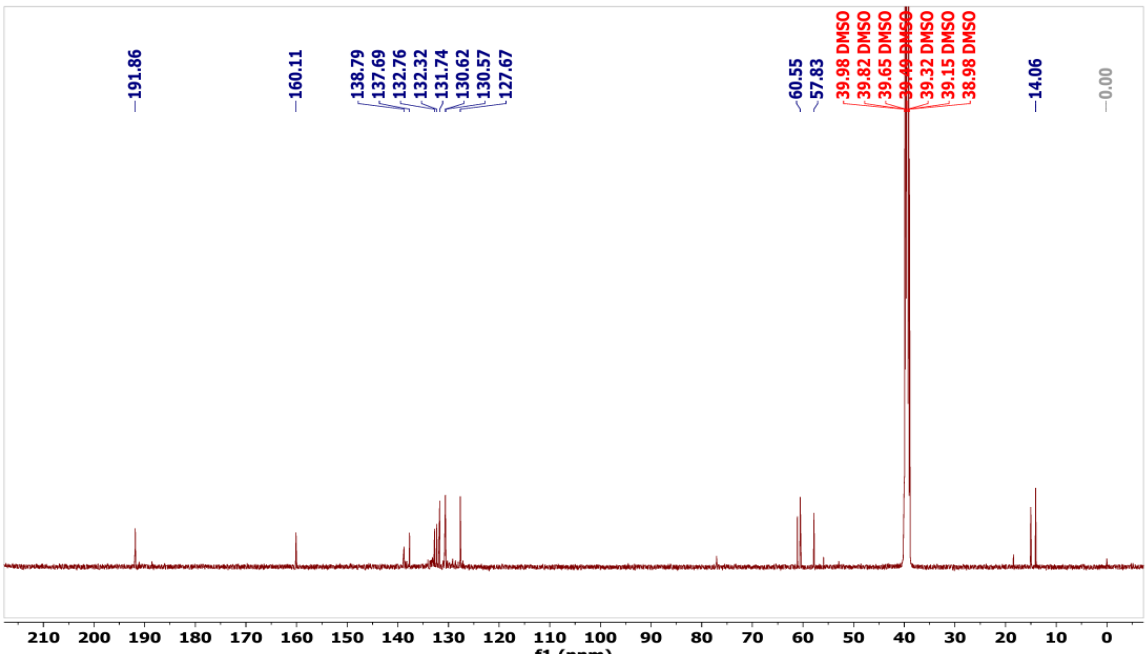


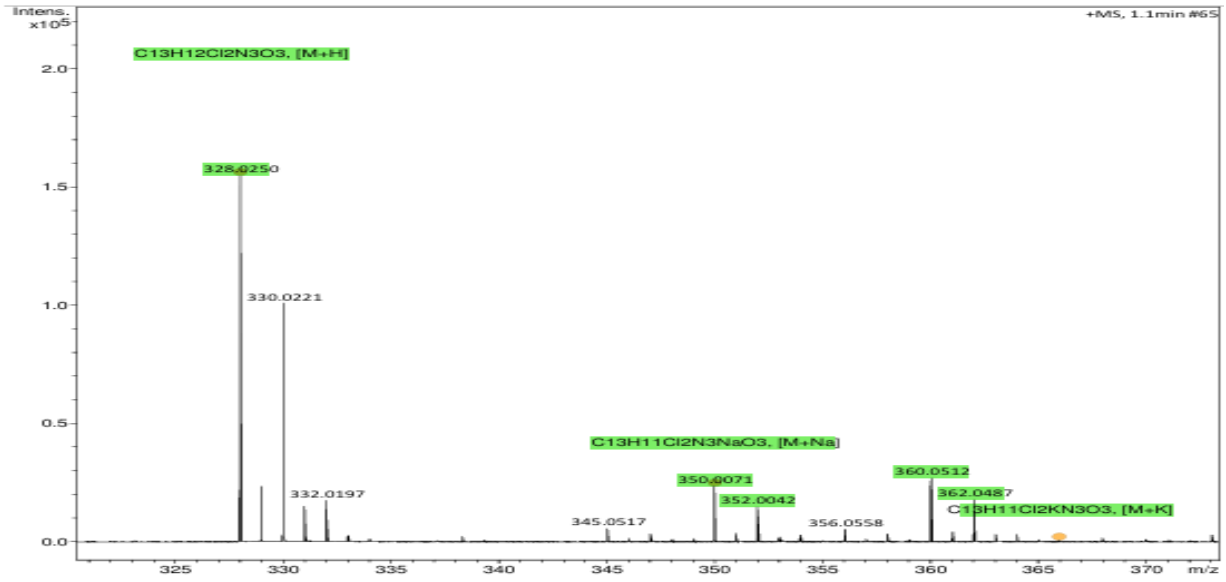

C17H16N3O3. [M+H]
310.1186
C17H15N3NaO3. [M+Na]
332.1003
327.1451
+MS, 1.1min #65
x10^5
305
310
315
320
325
330
335
340 m/z

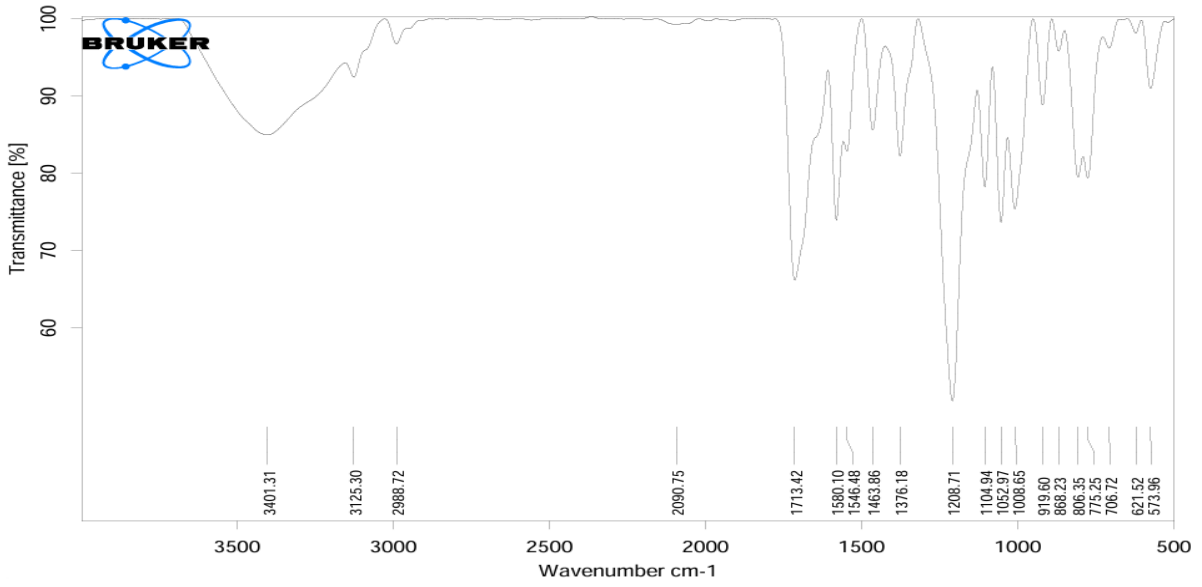

BRUKER
Transmittance [%]
100
95
90
85
80
75
70
65
3420.33
3115.33
3065.37
2964.76
2641.77
2554.50
2121.47
1939.39
1780.20
1689.94
1623.73
1544.10
1466.31
1436.24
1361.72
1305.47
1228.91
1173.41
1100.49
1049.90
1020.20
936.31
904.77
854.46
813.11
774.77
739.72
708.68
634.90
559.93
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1

(4f) Ethyl 1-(2-(2, 4-dichlorophenyl)-2-oxoethyl)-1*H*-1,2,3-triazole-4- carboxylate






Intens.
x10^5
+MS, 1.1min #65
C13H12Cl2N3O3, [M+H]
328.0250
330.0221
332.0197
C13H11Cl2N3NaO3, [M+Na]
350.0071
352.0042
345.0517
356.0558
360.0512
362.0487
C13H11Cl2KN3O3, [M+K]
m/z


BRUKER
Transmittance [%]
Wavenumber cm-1
3401.31
3125.30
2988.72
2090.75
1713.42
1580.10
1546.48
1463.86
1376.18
1208.71
1104.94
1052.97
1008.65
919.60
868.23
806.35
775.25
706.72
621.52
573.96