Design, Synthesis and Evaluation of β-Lactam Antigenic Peptide Hybrids; Unusual Opening of the β-Lactam Ring in Acidic Media

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Supporting Information

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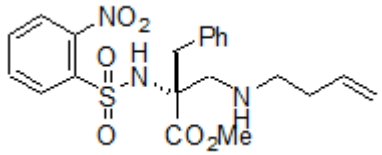
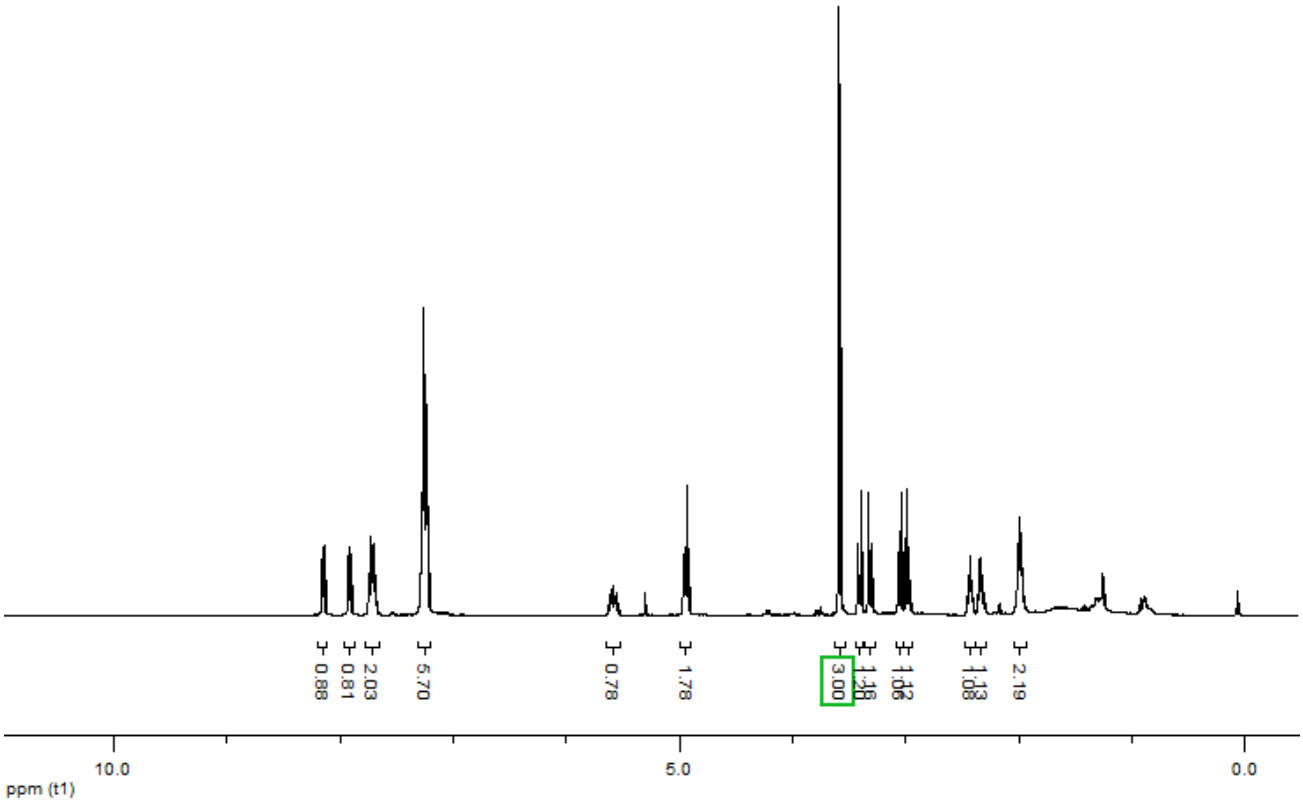
1. NMR Spectra

Methyl (*R*)-2-benzyl-3-(but-3-enylamino)-2-(2-nitrophenylsulfonamido)-propanoate





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5	7.766	3884.047	13849.240	129.840
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7	7.736	3869.055	13896.795	269.019
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9	7.714	3857.914	13932.134	271.785
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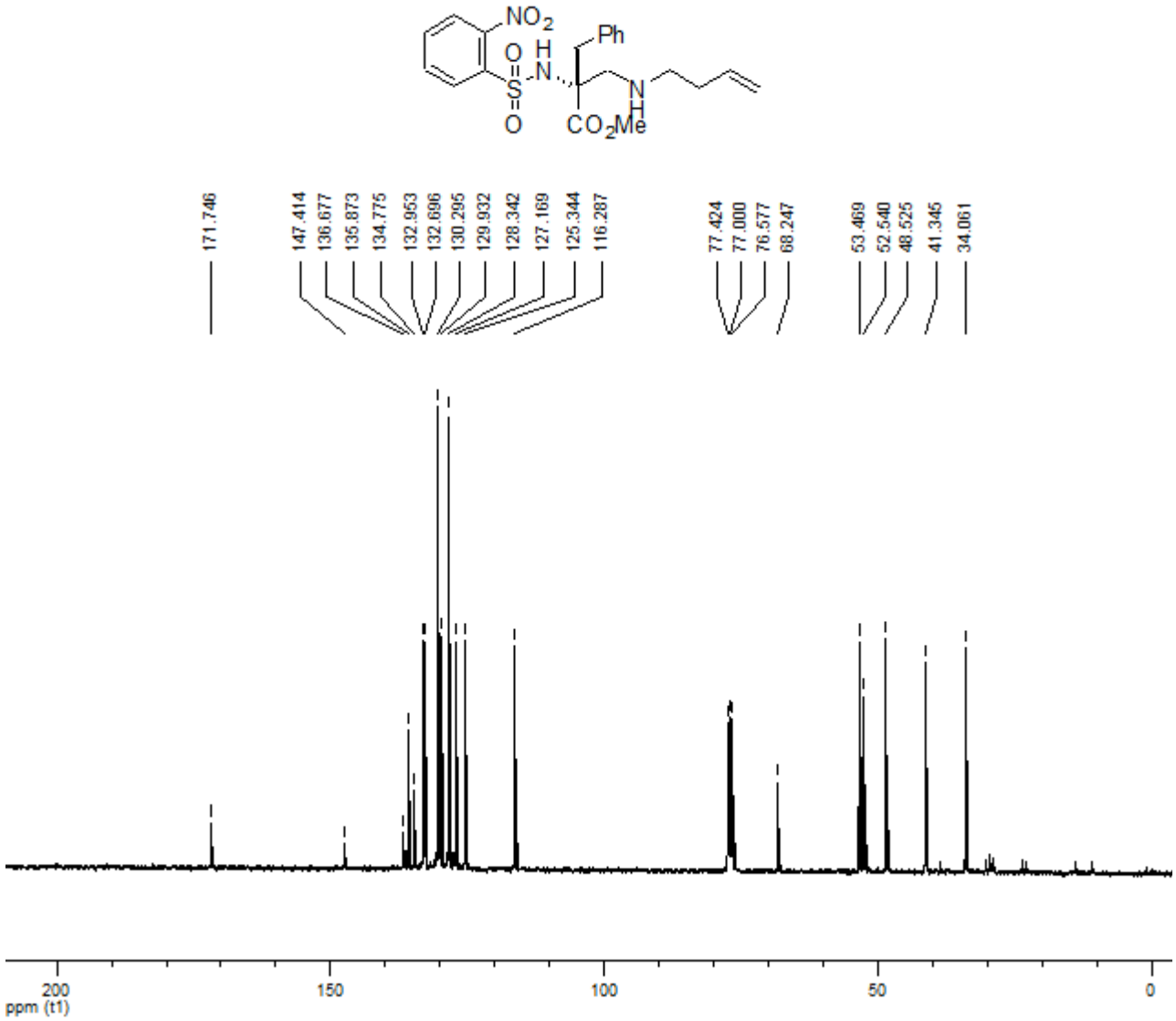
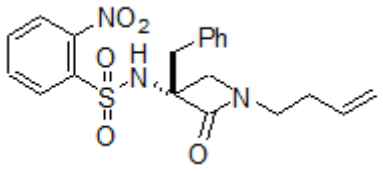
11	7.288	3645.150	14607.010	481.124

12	7.279	3640.180	14622.774	1164.308
13	7.260	3630.650	14653.000	902.062
14	7.245	3623.462	14675.803	380.240
15	5.646	2823.717	17212.548	38.392
16	5.632	2816.871	17234.261	78.274
17	5.624	2812.926	17246.777	48.271
18	5.612	2806.630	17266.748	101.807
19	5.599	2799.933	17287.990	109.387
20	5.592	2796.621	17298.494	61.789
21	5.585	2793.231	17309.248	54.371
22	5.578	2789.658	17320.580	88.292
23	5.564	2782.806	17342.314	43.800
24	5.318	2659.816	17732.433	83.929
25	4.981	2490.867	18268.328	234.439
26	4.966	2483.619	18291.318	257.797
27	4.946	2473.603	18323.087	491.520
28	3.607	1803.742	20447.849	2302.932
29	3.442	1721.243	20709.533	271.606
30	3.414	1707.428	20753.351	473.061
31	3.347	1673.692	20860.359	467.330
32	3.319	1659.857	20904.244	273.925
33	3.085	1542.685	21275.906	238.541
34	3.060	1530.133	21315.722	465.989
35	3.013	1506.636	21390.253	477.747
36	2.988	1494.090	21430.048	251.332
37	2.479	1239.570	22237.371	70.111
38	2.465	1232.746	22259.017	149.738
39	2.455	1227.667	22275.125	149.824
40	2.442	1221.251	22295.478	224.905
41	2.428	1214.460	22317.019	125.952
42	2.376	1188.033	22400.841	106.214
43	2.362	1181.231	22422.417	219.280
44	2.349	1174.628	22443.363	157.106
45	2.339	1169.715	22458.945	156.042
46	2.325	1162.898	22480.570	89.063
47	2.033	1016.714	22944.255	116.099
48	2.020	1010.189	22964.953	273.740
49	2.007	1003.731	22985.437	372.012
50	1.994	997.178	23006.222	272.130
51	1.981	990.506	23027.388	123.015

Methyl (*R*)-2-benzyl-3-(but-3-enylamino)-2-(2-nitrophenylsulfonamido)-propanoate





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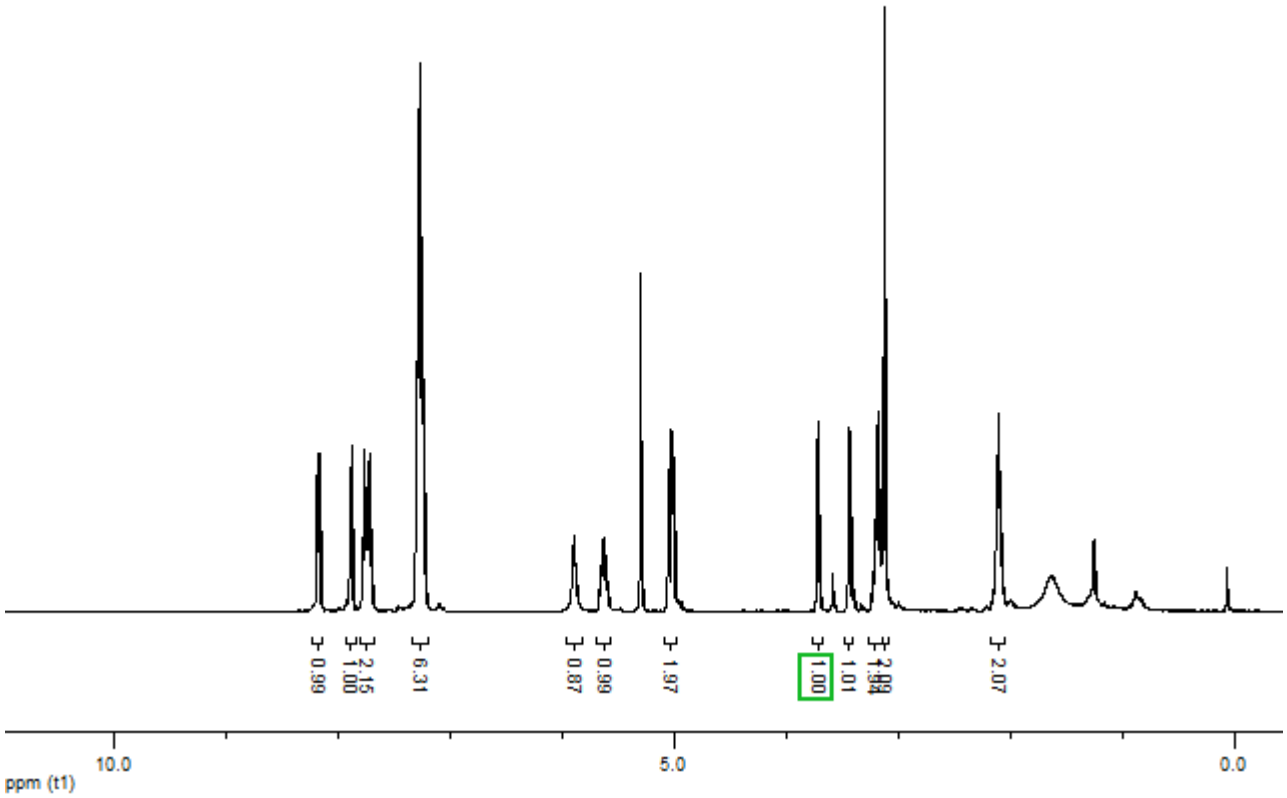

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5	7.775	3888.386	13799.630	127.224
6	7.760	3880.921	13823.306	280.852
7	7.745	3873.252	13847.633	214.662
8	7.731	3866.235	13869.891	236.468
9	7.715	3858.644	13893.970	272.878
10	7.701	3851.208	13917.554	109.419
11	7.287	3644.560	14573.031	432.836
12	7.274	3637.955	14593.982	867.712
13	7.260	3630.651	14617.150	946.135
14	7.242	3622.126	14644.190	644.915
15	7.230	3615.724	14664.497	401.498
16	5.890	2945.503	16790.400	132.062
17	5.667	2834.166	17143.554	39.521

18	5.653	2827.408	17164.990	79.393
19	5.633	2817.378	17196.804	125.247
20	5.620	2810.482	17218.679	126.910
21	5.607	2804.369	17238.068	75.788
22	5.600	2800.493	17250.363	98.825
23	5.586	2793.684	17271.960	49.415
24	5.297	2649.122	17730.501	586.604
25	5.049	2524.971	18124.302	244.564
26	5.021	2511.059	18168.431	314.436
27	5.003	2502.131	18196.750	267.348
28	3.721	1860.854	20230.845	298.290
29	3.710	1855.491	20247.855	328.861
30	3.442	1721.304	20673.488	319.778
31	3.431	1715.982	20690.369	312.710
32	3.209	1604.817	21042.978	159.009
33	3.194	1597.143	21067.320	322.994
34	3.178	1589.378	21091.949	344.712
35	3.164	1582.144	21114.896	181.811
36	3.150	1575.106	21137.220	106.819
37	3.124	1562.397	21177.533	1044.478
38	2.122	1060.964	22768.048	245.723
39	2.108	1054.205	22789.488	342.466
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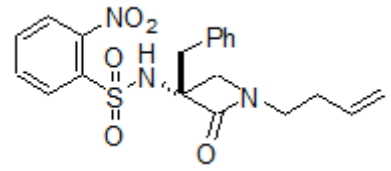
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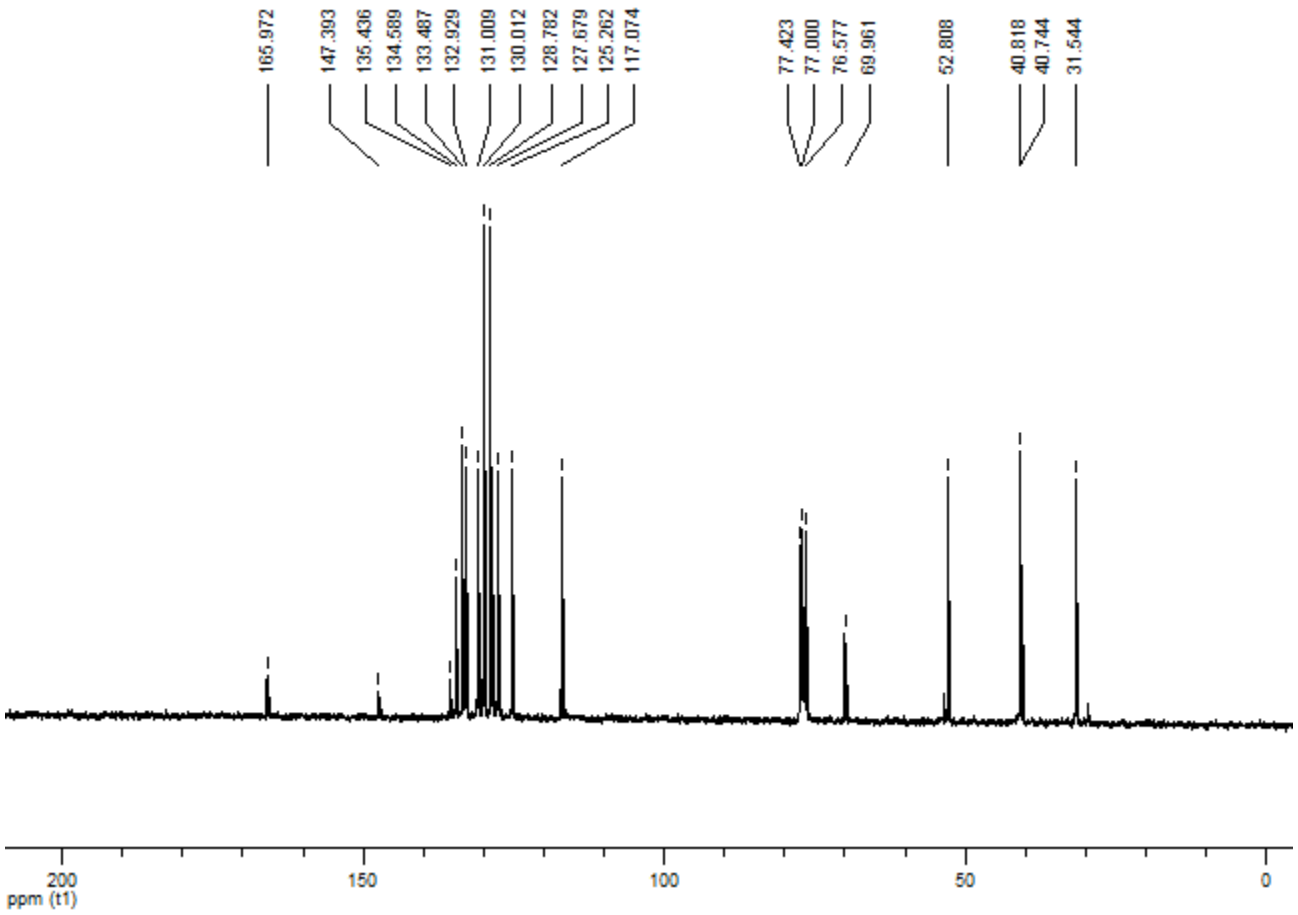
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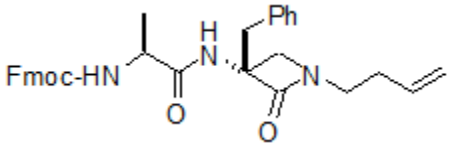
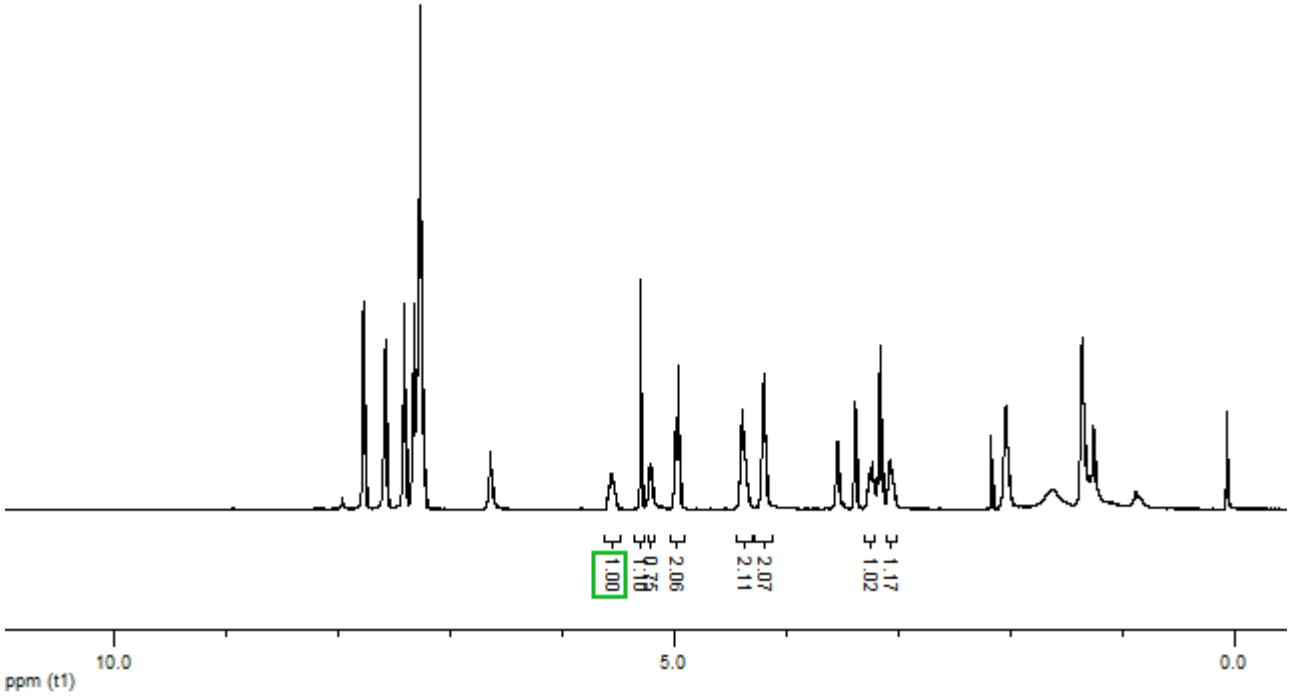
ppm (t1)

Fmoc-Ala-(β-lactam)-but-3-ene





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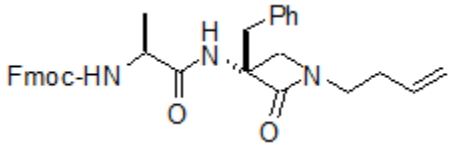
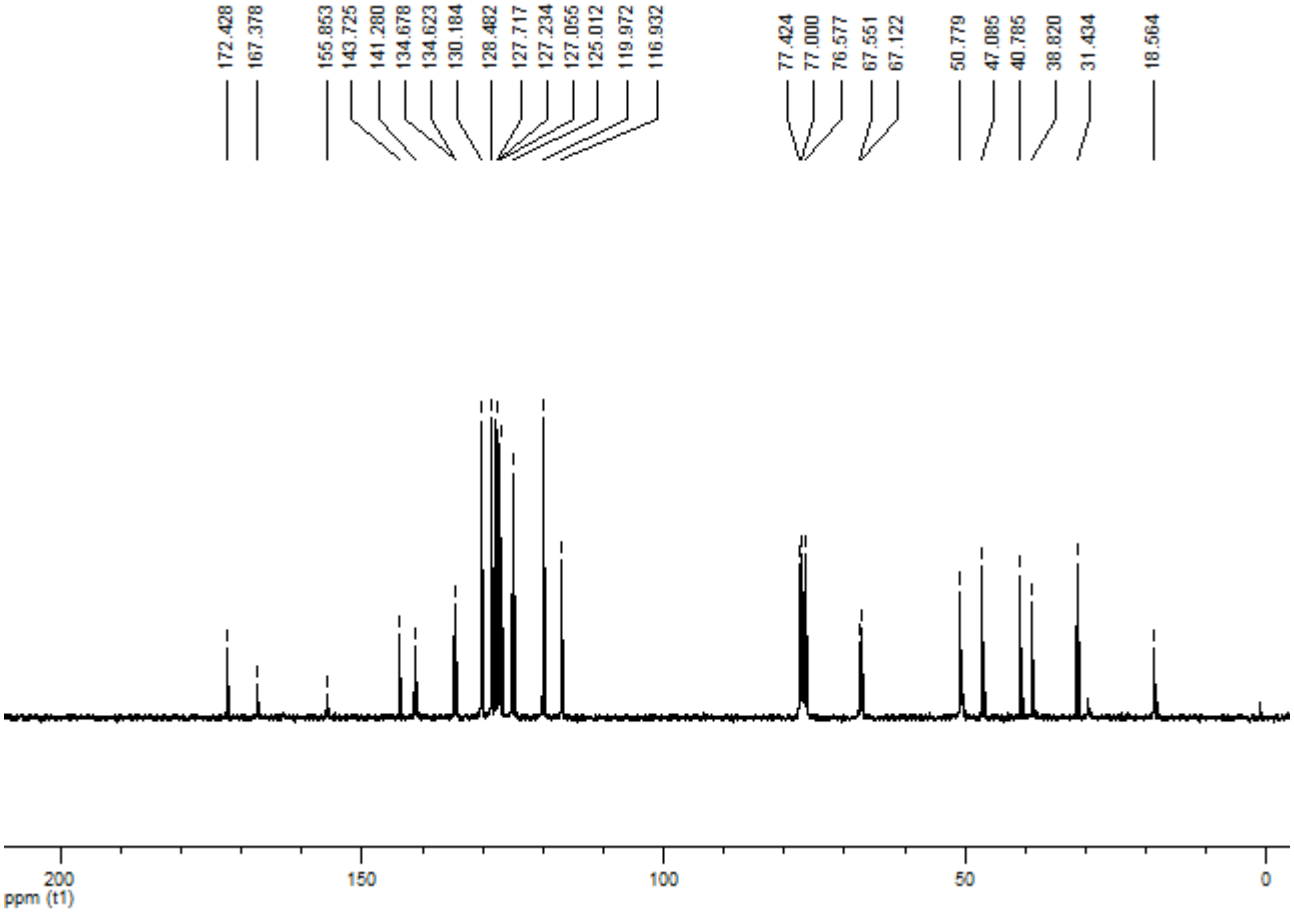
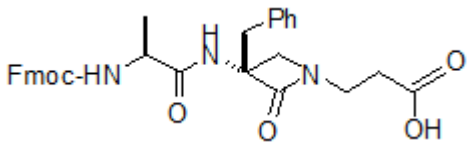
4	7.568	3784.865	14127.187	339.199
5	7.418	3709.875	14365.051	208.366
6	7.403	3702.612	14388.089	413.903
7	7.389	3695.228	14411.510	241.072
8	7.331	3666.560	14502.444	274.792
9	7.317	3659.241	14525.659	411.009
10	7.301	3651.607	14549.873	266.708
11	7.285	3643.370	14576.000	335.893
12	7.260	3630.651	14616.346	1007.126
13	7.234	3617.678	14657.496	165.726
14	6.635	3318.183	15607.475	115.609
15	5.592	2796.627	17261.822	23.590
16	5.579	2790.257	17282.027	48.436

17	5.560	2780.849	17311.869	71.682
18	5.547	2773.978	17333.664	73.686
19	5.527	2764.192	17364.703	57.518
20	5.514	2757.752	17385.130	28.982
21	5.209	2605.365	17868.492	92.118
22	5.205	2603.018	17875.939	92.724
23	4.990	2495.731	18216.246	158.155
24	4.977	2489.334	18236.537	183.498
25	4.957	2479.061	18269.121	290.069
26	4.417	2209.113	19125.382	56.528
27	4.398	2199.421	19156.123	170.467
28	4.383	2192.023	19179.589	202.532
29	4.366	2183.307	19207.238	105.553
30	4.211	2106.017	19452.396	181.099
31	4.198	2099.485	19473.117	271.428
32	4.185	2092.934	19493.896	151.646
33	3.538	1769.593	20519.515	136.952
34	3.389	1694.648	20757.236	215.731
35	3.378	1689.404	20773.869	198.921
36	3.260	1630.264	20961.458	72.664
37	3.246	1623.416	20983.179	86.722
38	3.233	1616.679	21004.548	96.310
39	3.220	1610.262	21024.902	58.534
40	3.199	1599.770	21058.181	63.410
41	3.170	1585.574	21103.210	274.133
42	3.157	1579.088	21123.785	328.649
43	3.130	1565.393	21167.226	76.667
44	3.087	1543.964	21235.195	56.856
45	3.074	1537.412	21255.978	100.328
46	3.061	1530.720	21277.205	94.421
47	3.047	1523.677	21299.546	82.150
48	3.034	1517.546	21318.992	50.372
49	2.040	1020.083	22896.917	207.070
50	1.354	677.105	23984.824	344.473

Fmoc-Ala-(β-lactam)-but-3-ene







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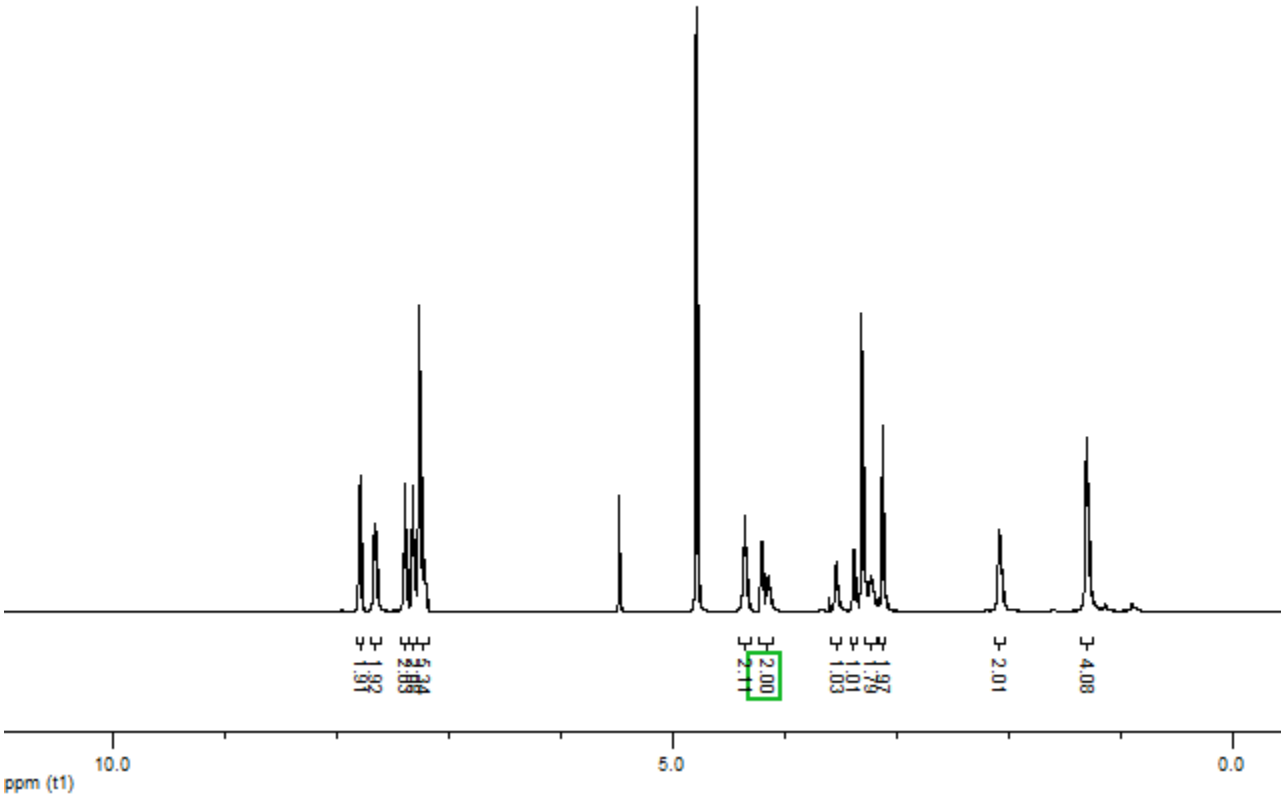

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4	7.648	3824.962	14014.072	125.088
5	7.401	3701.283	14406.375	83.136
6	7.386	3693.973	14429.561	180.479
7	7.371	3686.629	14452.858	115.150
8	7.325	3663.547	14526.071	116.863
9	7.311	3656.246	14549.230	179.270
10	7.296	3649.143	14571.761	84.673
11	7.263	3632.206	14625.483	433.231
12	7.257	3629.297	14634.711	407.761
13	7.218	3609.935	14696.126	76.907
14	5.476	2738.676	17459.710	164.332
15	4.787	2394.097	18552.695	854.575
16	4.364	2182.447	19224.037	91.764
17	4.352	2176.458	19243.033	134.618
18	4.213	2107.108	19463.005	57.262

19	4.200	2100.467	19484.072	98.982
20	4.187	2093.963	19504.703	47.603
21	4.150	2075.517	19563.212	47.867
22	4.137	2069.232	19583.148	51.951
23	3.534	1767.496	20540.236	72.246
24	3.385	1693.127	20776.130	87.982
25	3.376	1688.517	20790.753	87.195
26	3.310	1655.125	20896.671	421.564
27	3.280	1640.548	20942.908	66.577
28	3.231	1615.814	21021.363	51.014
29	3.219	1609.905	21040.107	45.016
30	3.155	1577.835	21141.832	19.991
31	3.123	1562.051	21191.896	263.428
32	3.095	1547.898	21236.789	26.778
33	2.079	1039.605	22849.064	115.662
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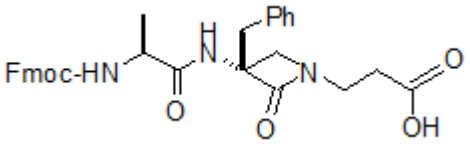
35	1.296	648.196	24090.591	246.113



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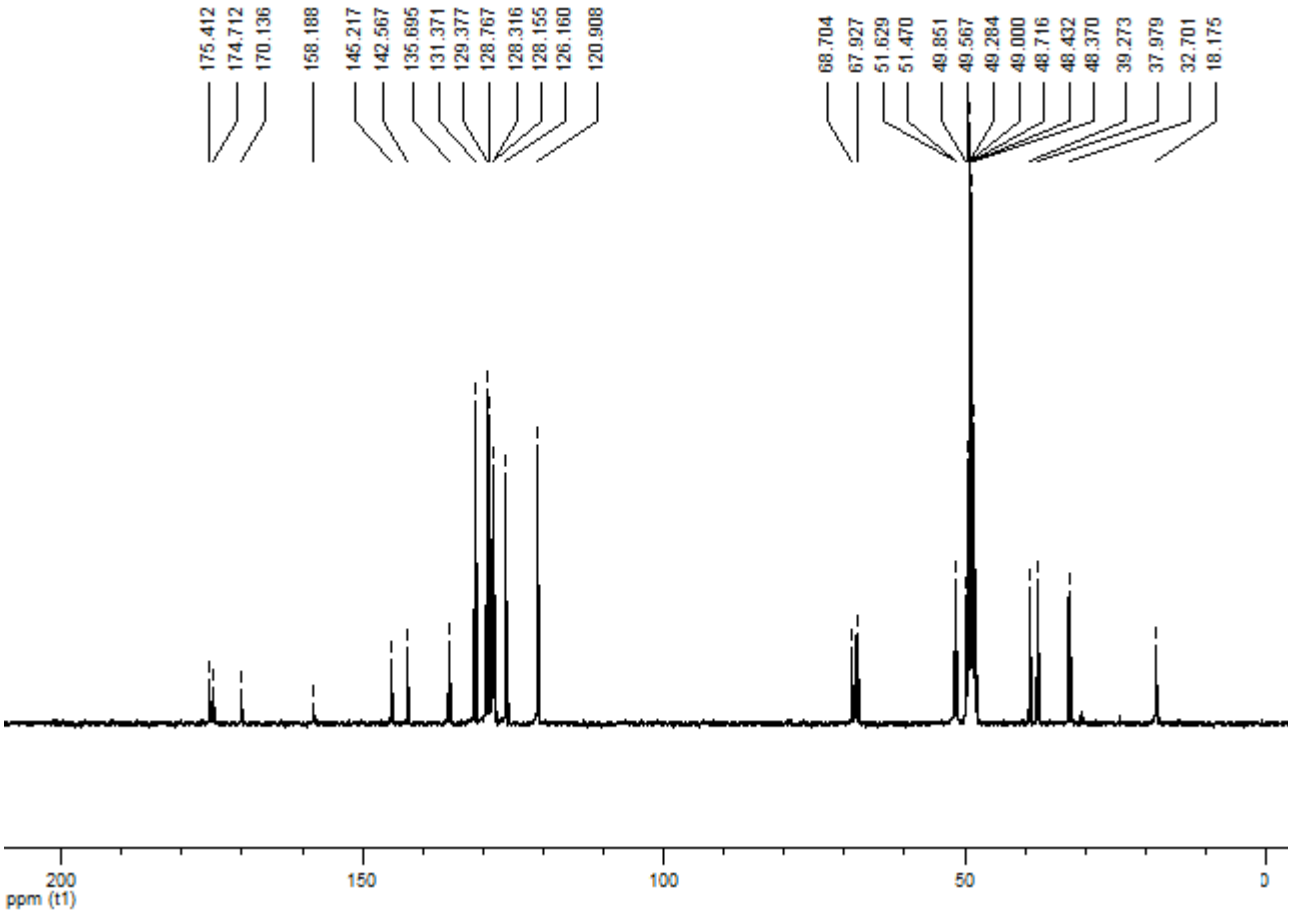
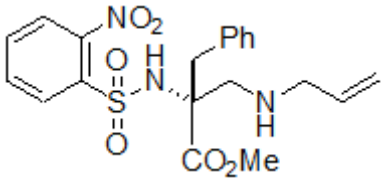
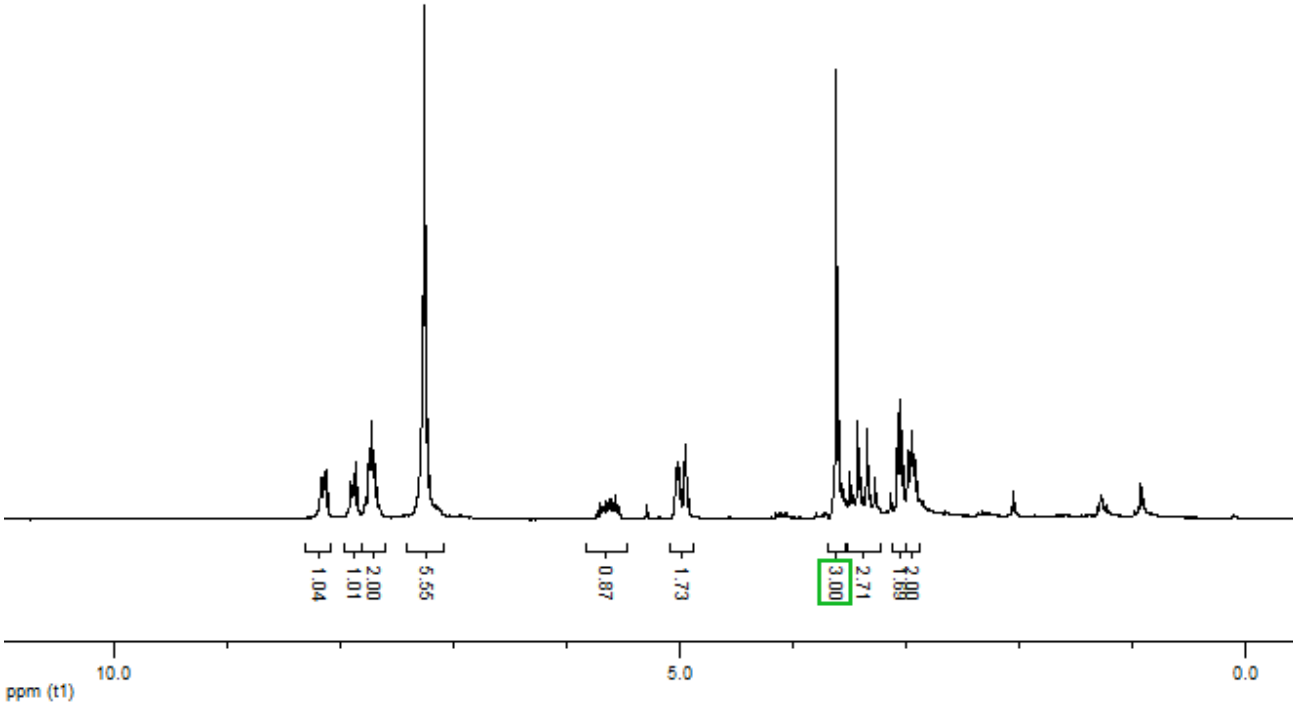


Methyl (*R*)-2-benzyl-3-(prop-2-enylamino)-2-(2-nitrophenylsulfonamido)-propanoate





Index	ppm	Hz	Point	Height
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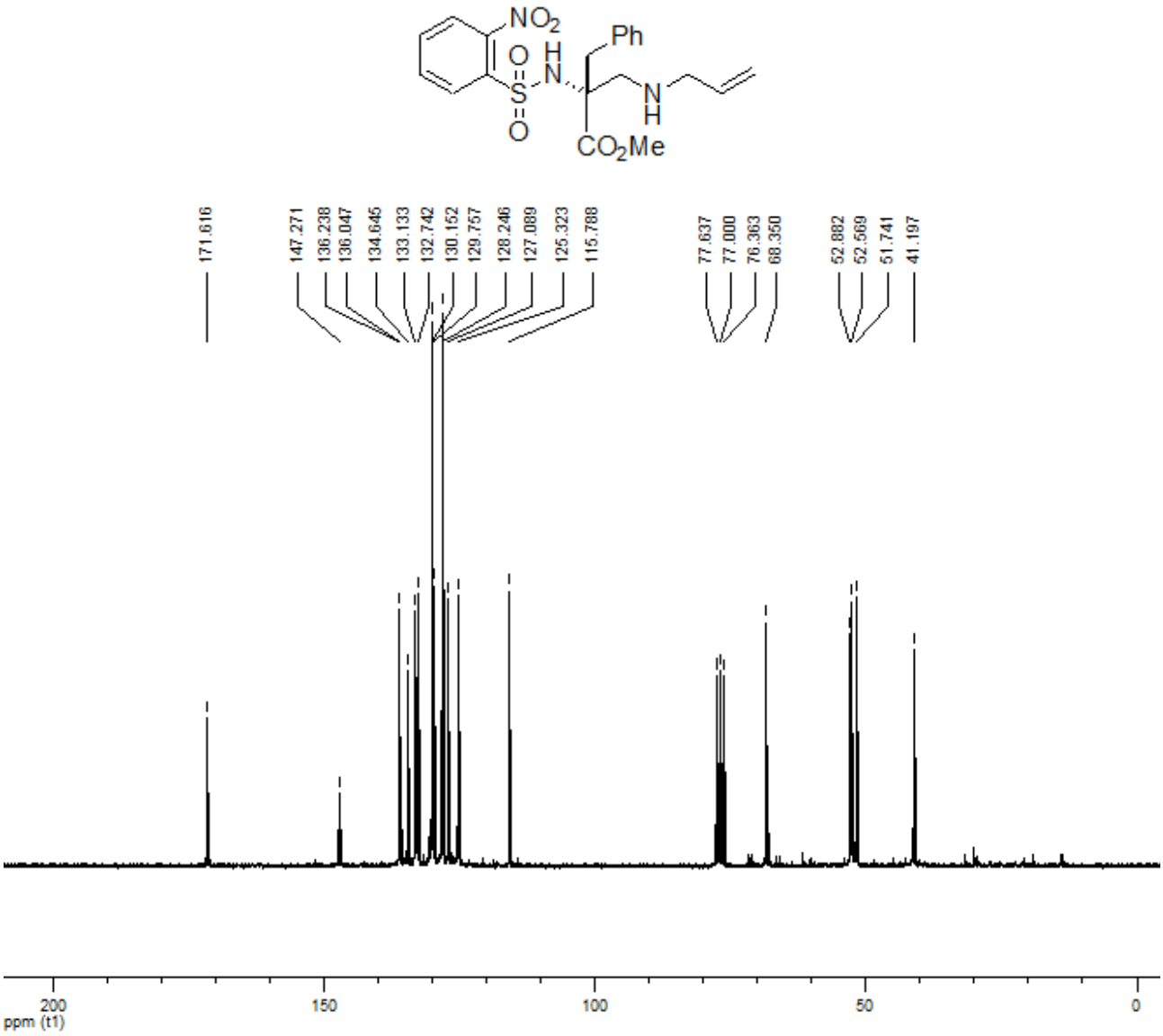
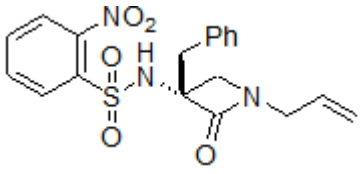
4	7.910	1581.501	2517.097	34.840
5	7.901	1579.685	2522.056	30.856
6	7.877	1574.880	2535.175	41.292
7	7.864	1572.348	2542.088	50.961
8	7.777	1554.877	2589.793	20.154
9	7.749	1549.368	2604.834	53.263
10	7.736	1546.689	2612.147	63.463
11	7.718	1543.225	2621.607	88.976
12	7.701	1539.756	2631.077	54.029
13	7.688	1537.125	2638.261	39.028
14	7.260	1451.460	2872.162	462.303
15	7.183	1436.158	2913.941	13.488

16	7.162	1432.011	2925.264	13.198
17	7.144	1428.371	2935.203	10.530
18	5.729	1145.381	3707.877	7.008
19	5.700	1139.612	3723.629	13.970
20	5.671	1133.856	3739.345	10.756
21	5.651	1129.839	3750.314	16.826
22	5.642	1127.948	3755.476	14.179
23	5.622	1124.018	3766.206	14.521
24	5.613	1122.113	3771.408	18.921
25	5.592	1118.061	3782.472	15.444
26	5.563	1112.294	3798.218	21.578
27	5.535	1106.502	3814.033	10.864
28	5.029	1005.476	4089.874	46.945
29	5.010	1001.664	4100.282	50.897
30	4.951	989.905	4132.387	67.259
31	3.617	723.130	4860.790	404.518
32	3.495	698.617	4927.718	43.674
33	3.426	684.793	4965.463	87.892
34	3.344	668.458	5010.065	81.660
35	3.275	654.620	5047.848	37.599
36	3.074	614.469	5157.475	95.585
37	3.046	608.827	5172.880	107.246
38	2.982	596.008	5207.881	62.307
39	2.951	589.822	5224.772	80.189
40	2.922	584.013	5240.634	52.510

Methyl (*R*)-2-benzyl-3-(prop-2-enylamino)-2-(2-nitrophenylsulfonamido)-propanoate





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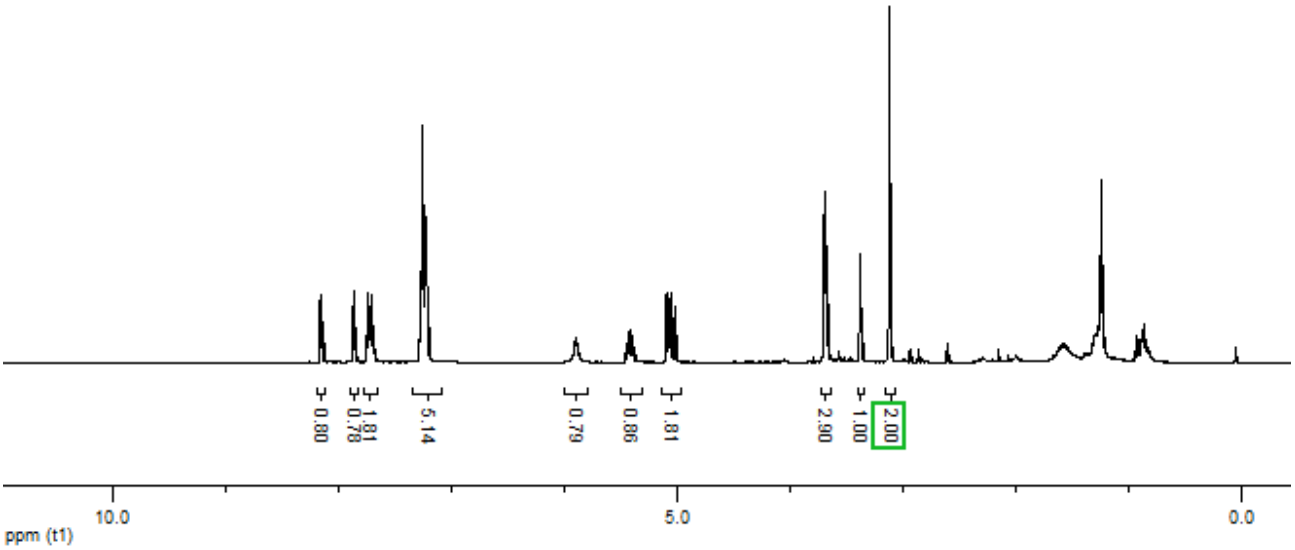

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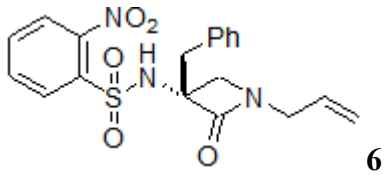
4	7.859	3930.362	6246.853	2721.669
5	7.758	3879.885	6350.064	1022.911
6	7.743	3872.534	6365.095	2636.011
7	7.729	3865.161	6380.171	2042.965
8	7.717	3859.232	6392.293	2172.274
9	7.701	3851.511	6408.080	2598.587
10	7.687	3844.091	6423.252	1105.632
11	7.273	3637.300	6846.083	3479.055
12	7.260	3630.476	6860.037	9048.246
13	7.243	3622.377	6876.596	4702.671
14	7.233	3616.979	6887.634	5975.769
15	7.217	3609.450	6903.028	3587.106
16	5.896	2948.667	8254.147	937.911
17	5.447	2723.979	8713.571	720.205

18	5.426	2713.562	8734.872	1185.174
19	5.413	2707.167	8747.948	1224.730
20	5.404	2702.513	8757.464	714.393
21	5.393	2696.746	8769.255	1034.680
22	5.094	2547.302	9074.827	2687.699
23	5.074	2537.191	9095.501	2473.431
24	5.057	2528.912	9112.430	2663.644
25	5.023	2511.770	9147.480	2123.637
26	3.699	1849.845	10500.934	5662.709
27	3.686	1843.396	10514.120	6531.231
28	3.671	1835.777	10529.700	4422.518
29	3.383	1691.815	10824.061	4182.829
30	3.372	1686.168	10835.607	4056.753
31	3.120	1560.308	11092.957	13552.251
32	1.252	625.892	13003.580	4084.553
33	1.240	619.886	13015.860	6971.591



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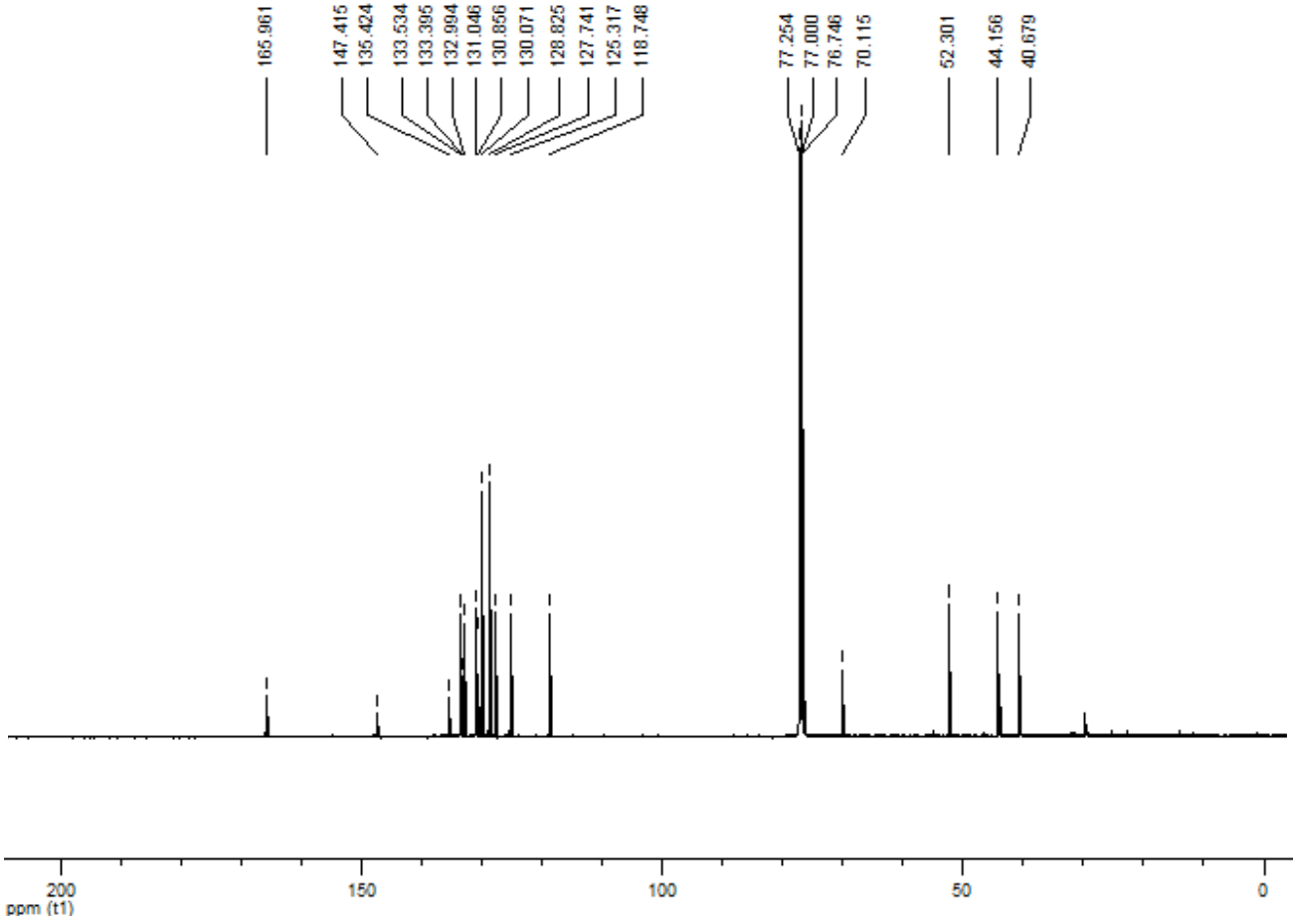
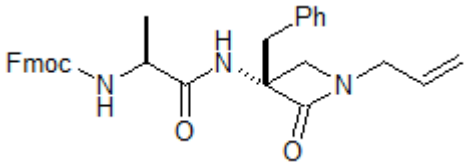
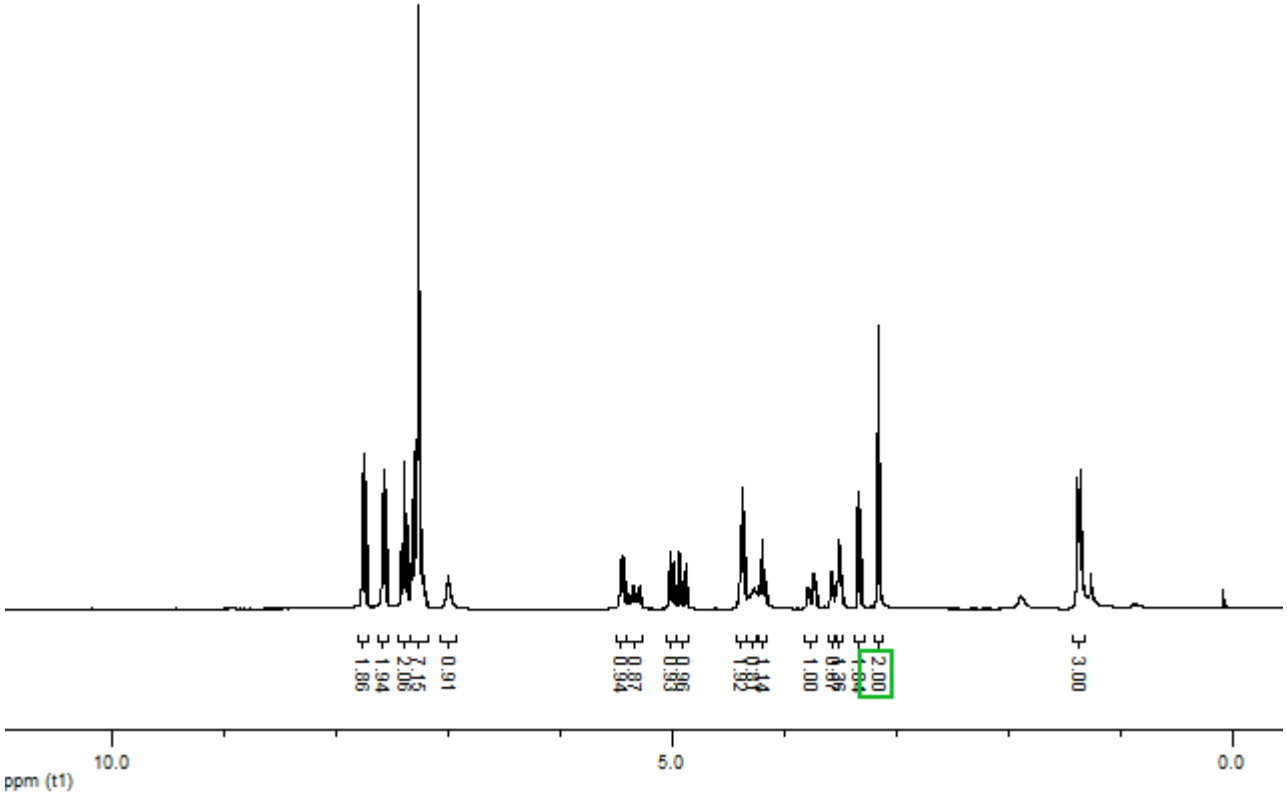


Fmoc-Ala-(β-lactam)-prop-2-ene





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1	7.762	2329.736	12816.349	553.560
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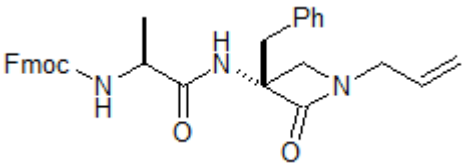
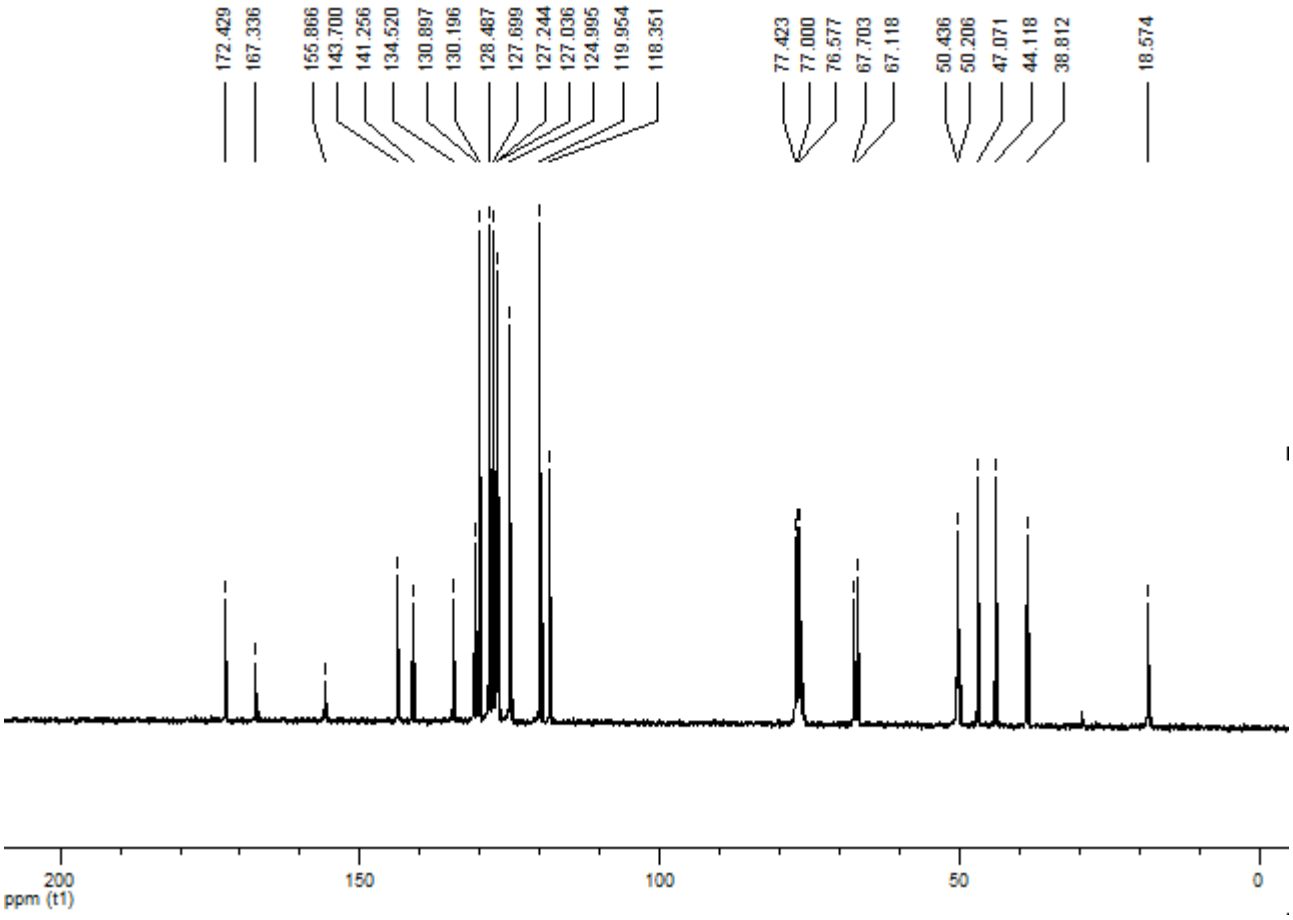
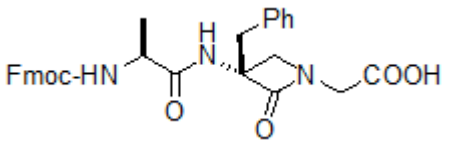
3	7.582	2275.958	13208.259	475.230
4	7.558	2268.561	13262.162	571.103
5	7.410	2224.340	13584.432	264.839
6	7.386	2217.114	13637.088	599.809
7	7.362	2209.816	13690.272	387.436
8	7.320	2197.064	13783.207	450.043
9	7.316	2196.140	13789.939	450.234
10	7.295	2189.625	13837.419	646.124
11	7.292	2188.734	13843.913	633.242
12	7.277	2184.282	13876.359	433.224
13	7.269	2181.962	13893.265	708.775
14	7.260	2179.037	13914.578	2472.574
15	7.246	2175.125	13943.088	486.593

16	7.240	2173.290	13956.459	344.088
17	7.231	2170.535	13976.539	175.745
18	7.222	2167.825	13996.287	130.330
19	7.218	2166.474	14006.132	147.843
20	6.993	2099.101	14497.123	134.089
21	5.458	1638.148	17856.369	205.146
22	5.432	1630.426	17912.642	215.273
23	5.350	1605.839	18091.822	95.029
24	5.329	1599.688	18136.646	96.932
25	5.294	1589.178	18213.236	90.358
26	5.279	1584.593	18246.652	98.425
27	5.018	1506.310	18817.148	228.581
28	5.015	1505.323	18824.343	237.906
29	4.984	1496.152	18891.177	196.060
30	4.981	1495.135	18898.583	197.538
31	4.933	1480.763	19003.324	234.498
32	4.929	1479.482	19012.658	228.870
33	4.876	1463.723	19127.505	181.399
34	4.872	1462.435	19136.888	182.717
35	4.389	1317.312	20194.490	343.798
36	4.383	1315.725	20206.056	277.512
37	4.364	1309.858	20248.812	494.734
38	4.266	1280.493	20462.810	84.038
39	4.212	1264.210	20581.480	202.147
40	4.188	1257.238	20632.287	286.961
41	4.165	1250.274	20683.035	122.090
42	3.792	1138.085	21500.626	86.557
43	3.773	1132.550	21540.966	88.260
44	3.740	1122.493	21614.257	143.095
45	3.721	1116.947	21654.669	142.553
46	3.584	1075.742	21954.958	152.311
47	3.563	1069.464	22000.707	153.647
48	3.532	1060.082	22069.080	115.737
49	3.513	1054.366	22110.736	282.129
50	3.494	1048.890	22150.646	256.934
51	3.342	1003.221	22483.462	478.756
52	3.323	997.406	22525.839	403.024
53	3.162	949.109	22877.810	1163.138
54	1.382	414.851	26771.267	535.640
55	1.359	407.929	26821.712	570.764

Fmoc-Ala-(β-lactam)-prop-2-ene







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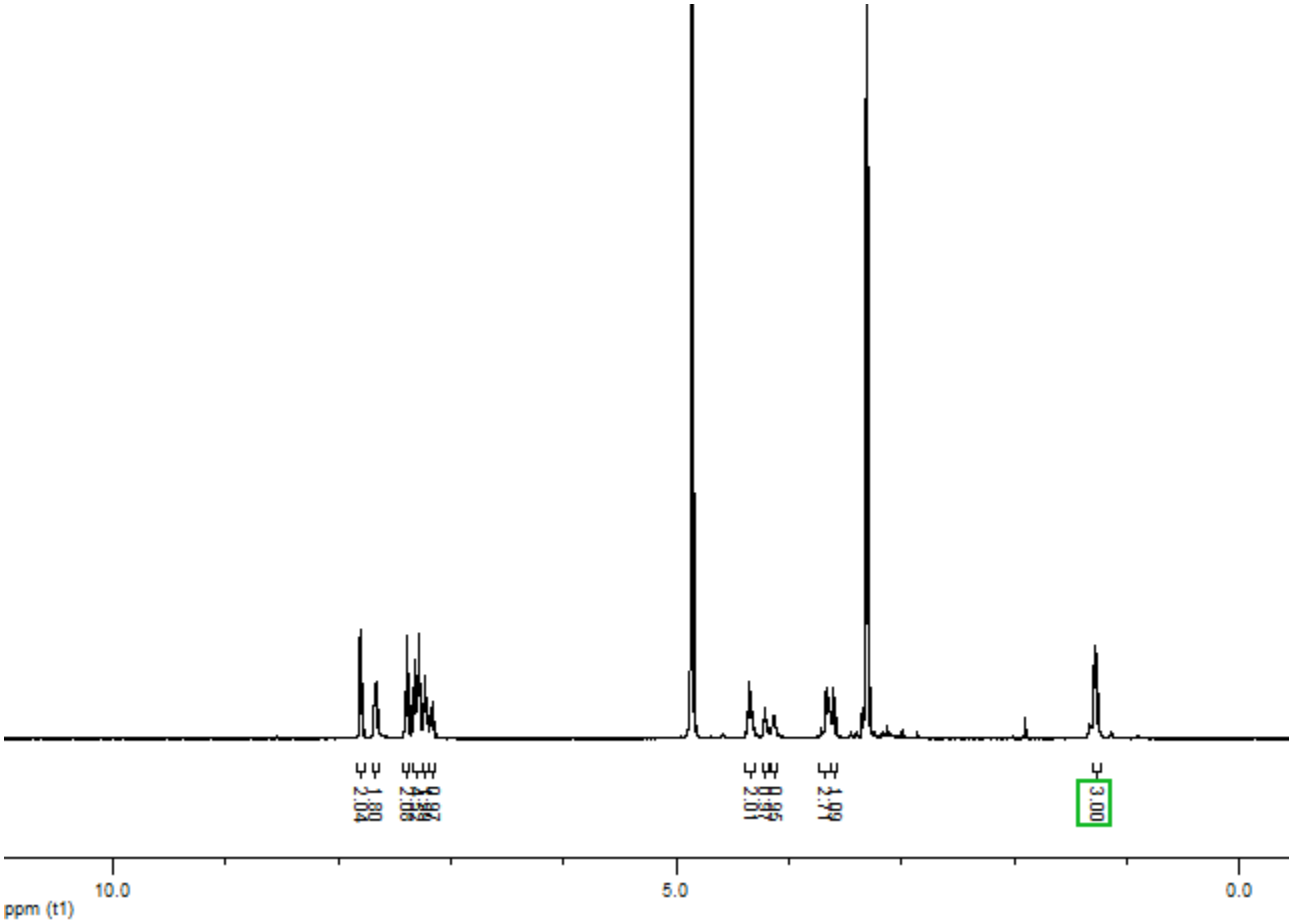

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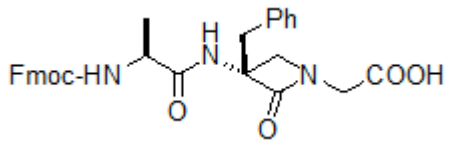
1	7.808	3905.054	13758.222	9622092.000
2	7.793	3897.534	13782.077	10471863.000
3	7.676	3838.868	13968.161	4779566.500
4	7.661	3831.666	13991.005	5486792.500
5	7.408	3704.696	14393.746	4392375.500
6	7.393	3697.276	14417.284	9759057.000
7	7.378	3689.861	14440.803	6106424.500
8	7.332	3666.735	14514.159	4919337.500
9	7.317	3659.270	14537.835	7522964.500
10	7.293	3647.416	14575.437	6053924.500
11	7.278	3639.904	14599.263	9956379.000
12	7.238	3620.096	14662.092	3402053.000
13	7.224	3612.783	14685.291	6033164.500
14	7.209	3605.365	14708.821	3677921.500
15	7.178	3589.809	14758.162	2995811.250
16	7.163	3582.601	14781.026	3527218.750
17	7.149	3575.402	14803.859	1272021.250

18	4.863	2432.147	18430.201	358414528.000
19	4.380	2190.699	19196.058	723896.000
20	4.359	2180.137	19229.560	2701275.000
21	4.345	2172.824	19252.757	5413615.500
22	4.331	2166.096	19274.099	3909275.250
23	4.311	2155.797	19306.767	1304346.625
24	4.219	2109.838	19452.544	1843557.500
25	4.206	2103.536	19472.535	2906714.750
26	4.194	2097.694	19491.064	1637610.875
27	4.155	2077.872	19553.939	1017011.062
28	4.141	2071.126	19575.337	2222854.500
29	4.127	2064.017	19597.888	2206344.500
30	4.113	2056.943	19620.324	1062795.500
31	3.707	1854.124	20263.654	1083132.250
32	3.673	1837.013	20317.929	4495484.000
33	3.657	1828.664	20344.414	4802042.500
34	3.638	1819.583	20373.216	3899300.000
35	3.623	1811.983	20397.324	1806264.875
36	3.606	1803.158	20425.316	4859326.500
37	3.595	1797.865	20442.105	3825506.000
38	3.310	1655.115	20894.902	108144192.000
39	1.287	643.427	24103.916	8917099.000
40	1.272	636.317	24126.470	8287496.000



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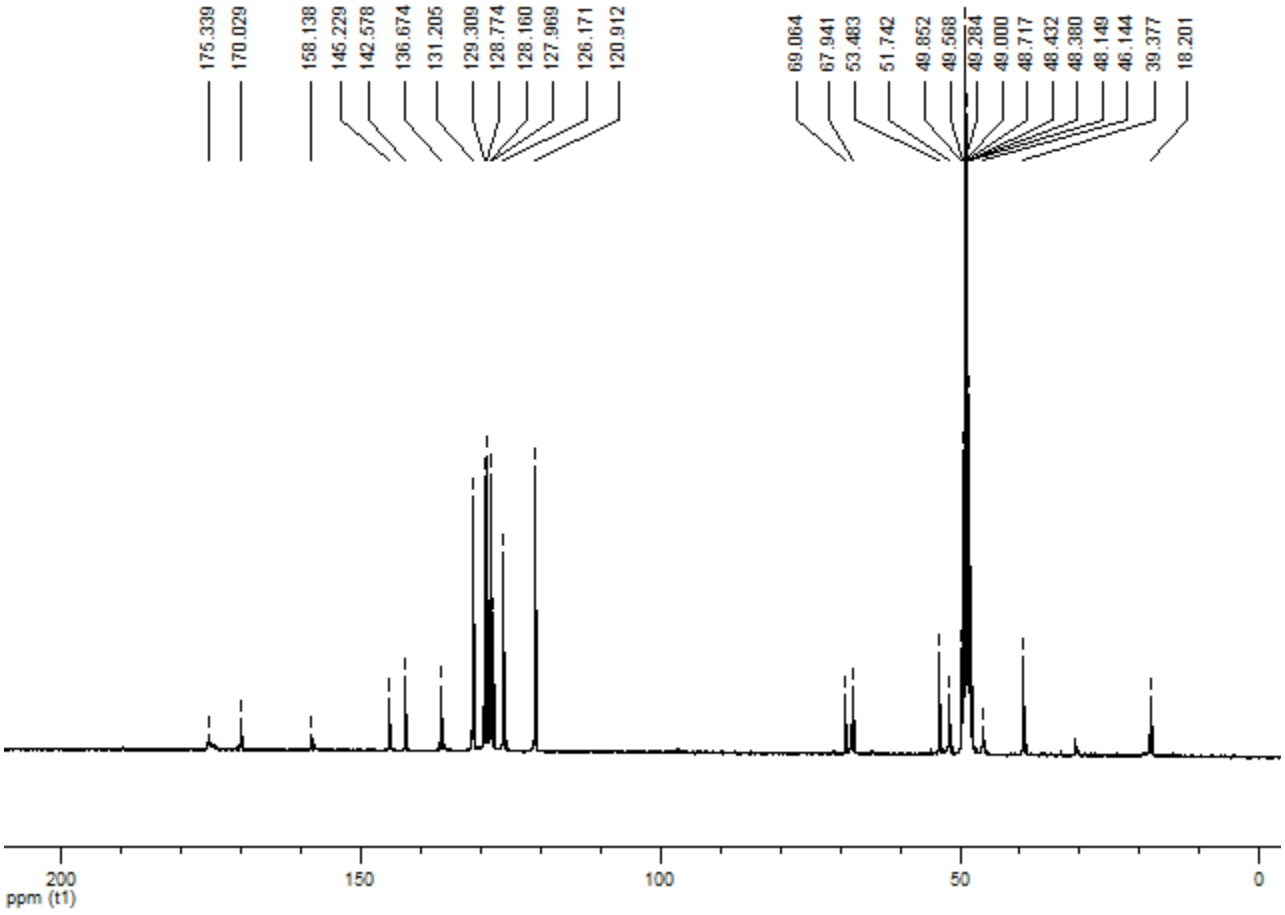

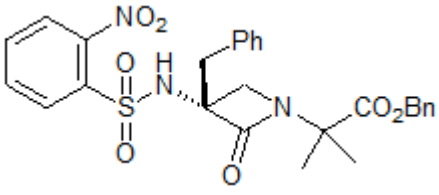

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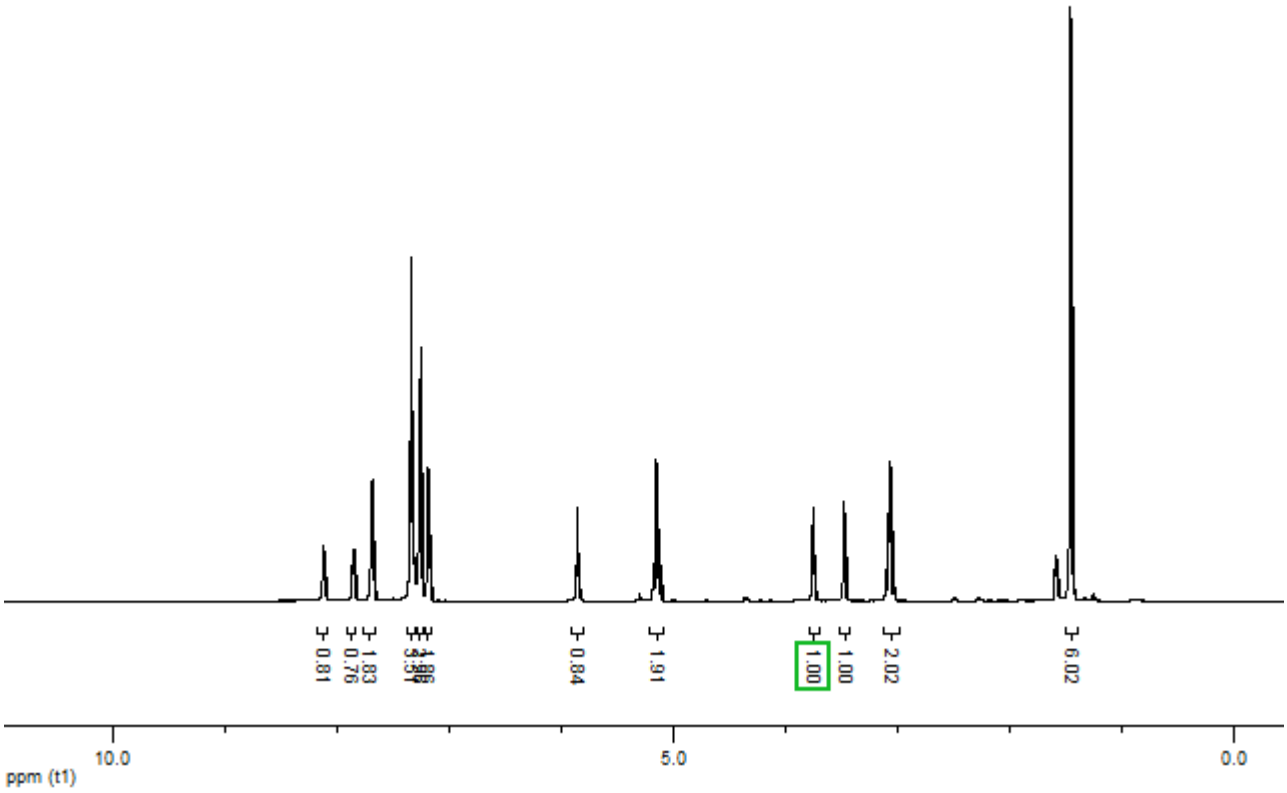
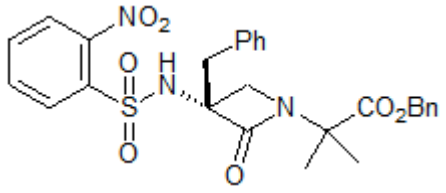


Index	ppm	Hz	Point	Height
Index	ppm	Hz	Point	Height
1	8.123	4062.393	13249.663	200.516
2	8.115	4058.743	13261.239	222.894
3	7.851	3926.247	13681.510	206.934
4	7.843	3922.649	13692.923	199.479
5	7.692	3846.844	13933.373	454.377
6	7.689	3845.451	13937.789	465.227
7	7.683	3842.432	13947.367	482.180
8	7.676	3838.895	13958.586	396.417
9	7.335	3668.247	14499.871	1375.920
10	7.260	3630.651	14619.125	882.981
11	7.252	3626.724	14631.579	1011.948
12	7.187	3594.152	14734.896	533.422
13	5.855	2928.071	16847.667	370.698
14	5.179	2589.958	17920.142	138.626
15	5.154	2577.716	17958.974	556.927
16	5.138	2569.661	17984.523	555.455

17	5.114	2557.399	18023.417	150.694
18	3.755	1877.938	20178.628	350.004
19	3.745	1872.894	20194.626	381.109
20	3.480	1740.526	20614.492	377.413
21	3.470	1735.397	20630.761	368.155
22	3.103	1551.841	21212.990	105.084
23	3.075	1537.794	21257.544	534.246
24	3.060	1530.403	21280.988	561.376
25	3.032	1516.361	21325.531	142.002
26	1.458	728.889	23823.345	2222.842
27	1.452	726.201	23831.873	2442.098



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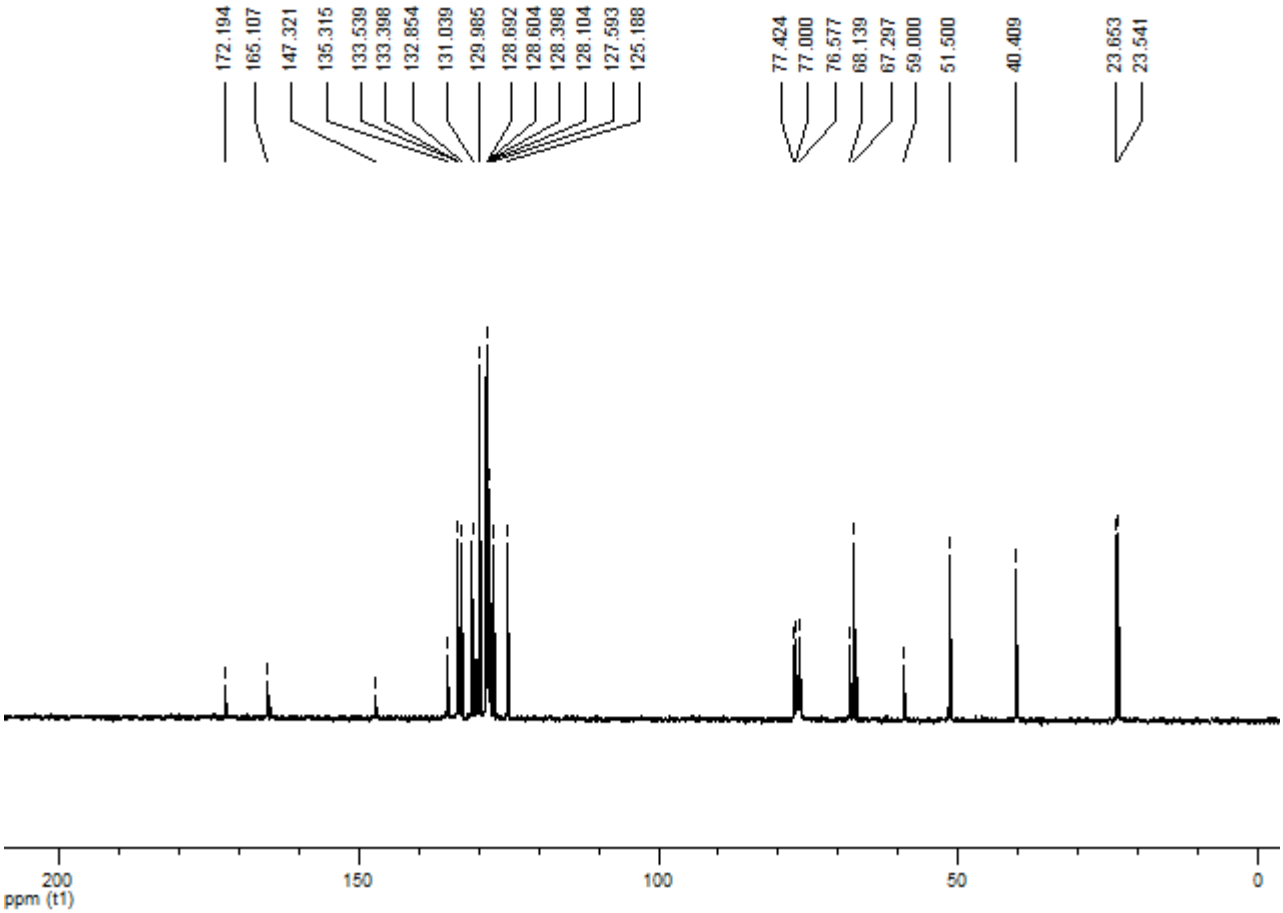
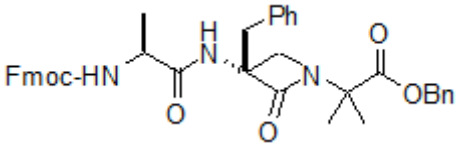
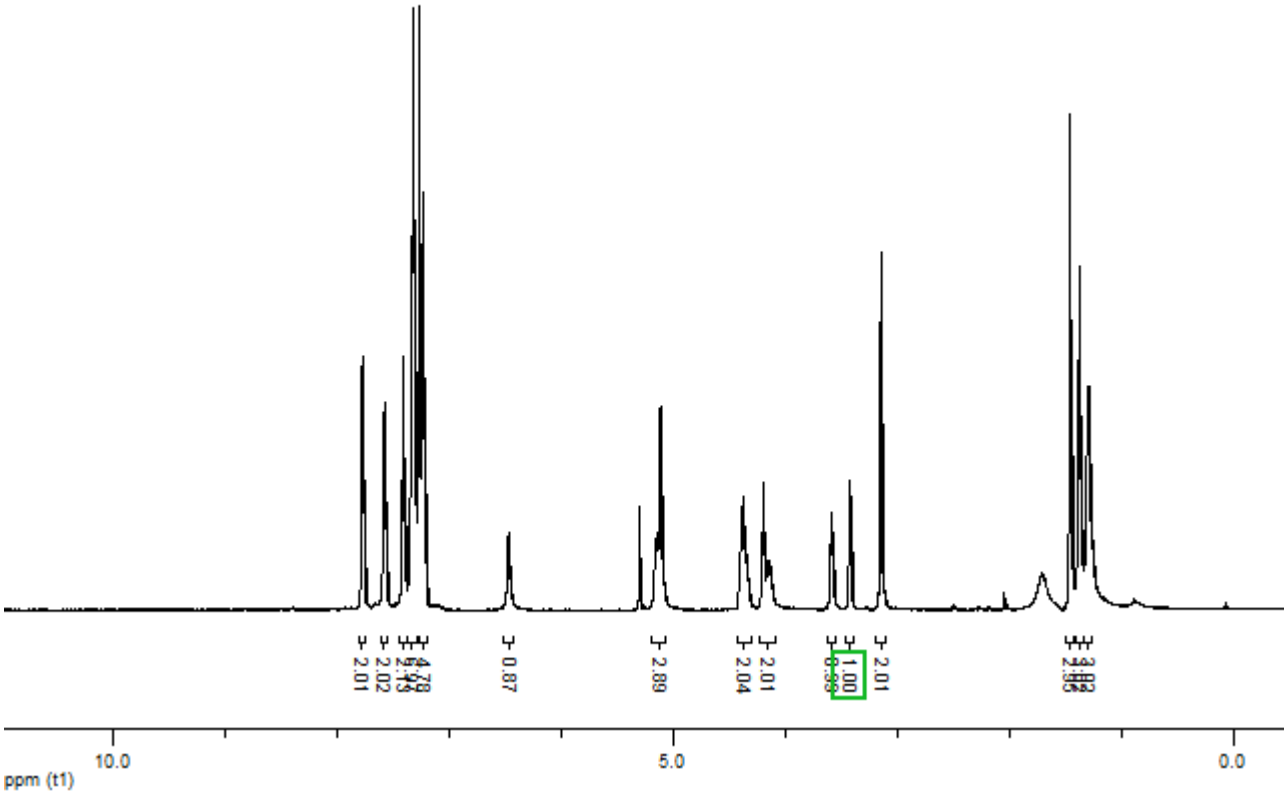


Fmoc-Ala-(β-lactam)-Aib-OBn

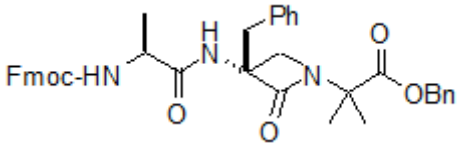


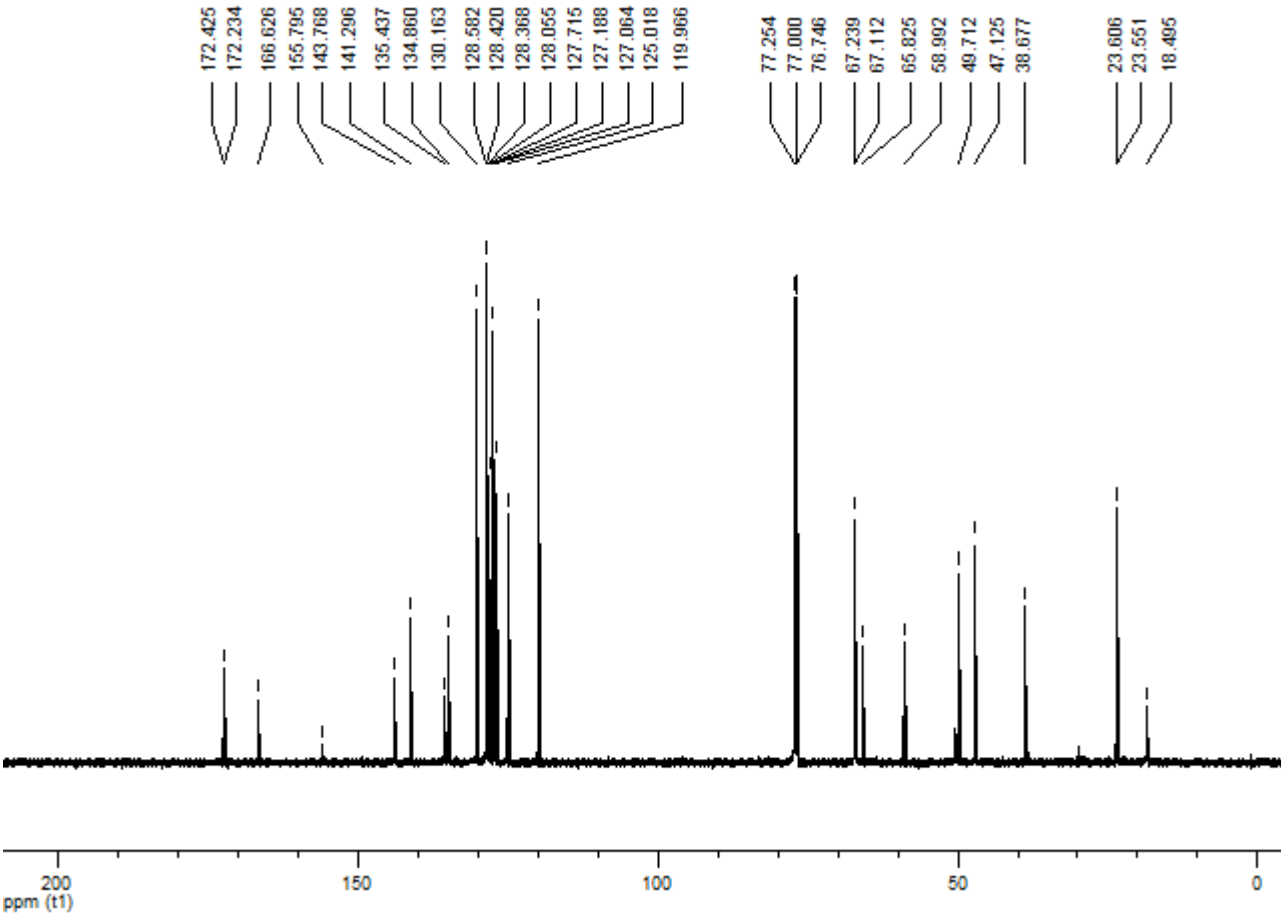


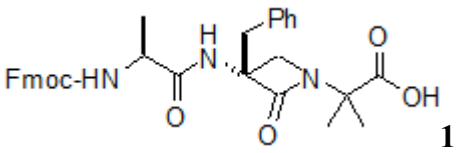
Index	ppm	Hz	Point	Height
1	7.773	3887.675	13804.249	388.082
2	7.759	3880.248	13827.807	403.619
3	7.631	3816.245	14030.821	9.502
4	7.579	3790.345	14112.973	312.103
5	7.565	3783.227	14135.549	330.519
6	7.417	3709.384	14369.778	204.364
7	7.402	3702.125	14392.802	403.406
8	7.388	3694.744	14416.214	241.464
9	7.330	3666.088	14507.110	592.275
10	7.316	3658.834	14530.119	955.344
11	7.260	3630.650	14619.515	960.726
12	7.246	3623.647	14641.728	410.755
13	7.227	3614.152	14671.848	662.538
14	7.215	3608.302	14690.402	362.871
15	6.465	3233.392	15879.596	122.825
16	5.142	2571.487	17979.121	121.617

17	5.111	2555.876	18028.636	322.013
18	5.086	2543.494	18067.914	63.539
19	4.409	2205.042	19141.462	63.916
20	4.389	2194.797	19173.958	164.156
21	4.374	2187.574	19196.869	180.406
22	4.363	2182.051	19214.390	98.555
23	4.349	2174.923	19237.000	104.143
24	4.207	2104.119	19461.585	122.838
25	4.194	2097.395	19482.914	201.093
26	4.180	2090.541	19504.652	106.371
27	4.144	2072.503	19561.869	79.621
28	4.137	2068.741	19573.800	74.236
29	3.588	1794.257	20444.449	148.141
30	3.582	1791.167	20454.251	153.822
31	3.427	1713.726	20699.888	205.462
32	3.417	1708.642	20716.015	181.569
33	3.174	1587.335	21100.792	27.777
34	3.146	1573.200	21145.628	568.936
35	3.116	1558.471	21192.347	35.467
36	1.458	728.939	23823.578	787.558
37	1.377	688.435	23952.054	545.155
38	1.293	646.687	24084.474	354.395
39	1.260	629.999	24137.408	127.910

Fmoc-Ala-(β-lactam)-Aib-OBn







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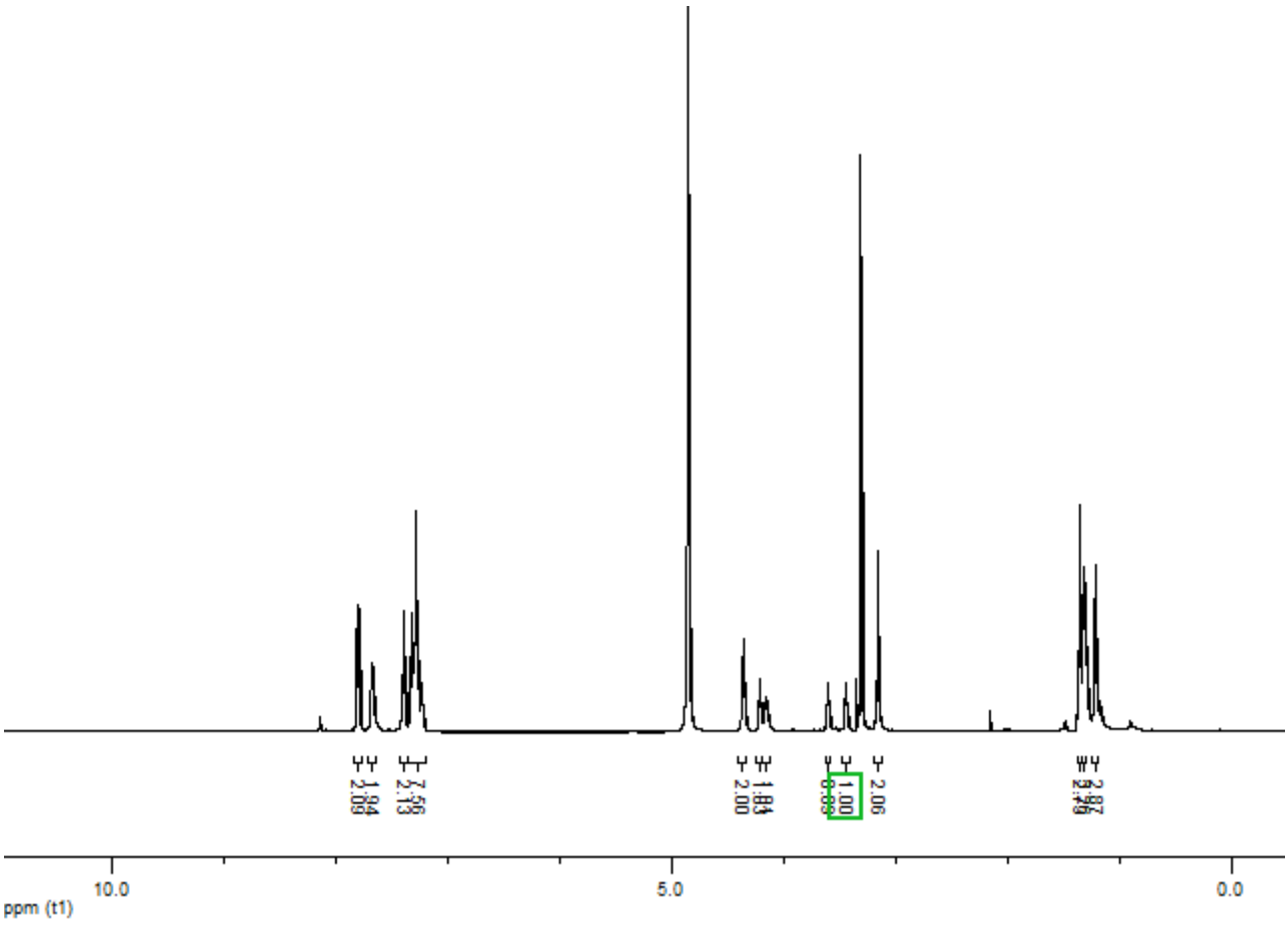
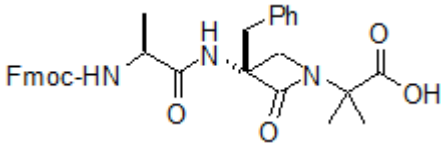
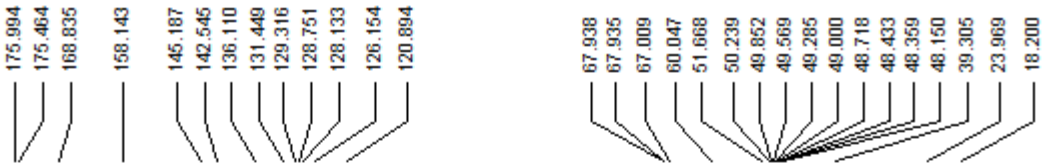


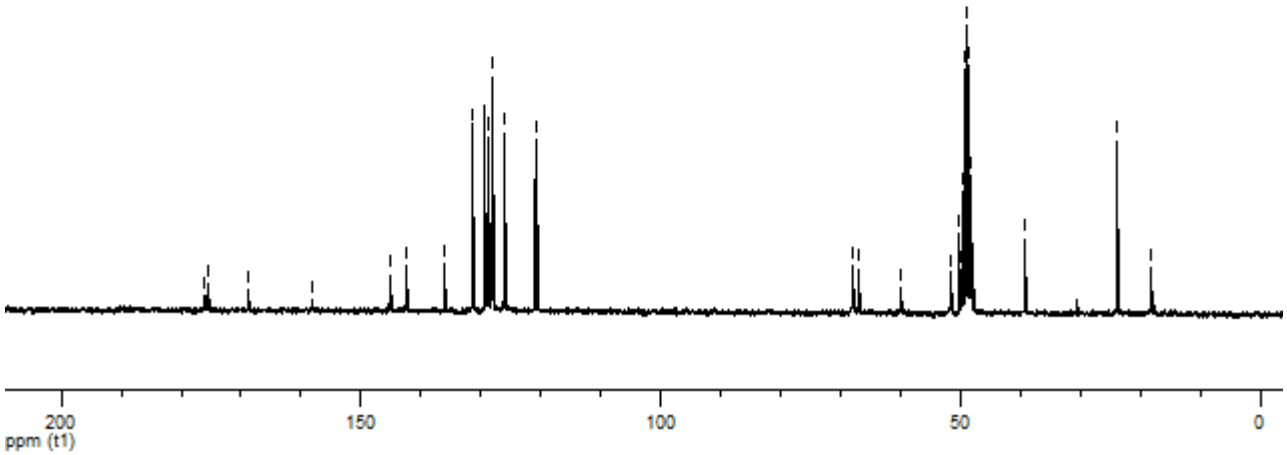
Index	ppm	Hz	Point	Height
1	7.804	3902.732	13765.785	285.489
2	7.789	3895.240	13789.549	306.511
3	7.666	3833.928	13984.026	166.145
4	7.658	3829.709	13997.409	153.372
5	7.403	3702.647	14400.443	136.859
6	7.389	3695.263	14423.866	291.158
7	7.374	3687.843	14447.402	182.468
8	7.329	3665.442	14518.455	179.260
9	7.315	3658.212	14541.389	285.996
10	7.298	3649.983	14567.492	213.362
11	7.280	3641.085	14595.715	532.341
12	7.266	3634.057	14618.006	297.095
13	7.251	3626.526	14641.893	128.226
14	7.233	3617.260	14671.286	115.501
15	7.220	3610.717	14692.039	115.629
16	4.851	2426.281	18449.001	2519.179
17	4.363	2181.948	19224.013	182.303

18	4.351	2175.771	19243.607	226.076
19	4.224	2112.699	19443.666	75.407
20	4.211	2106.077	19464.671	128.664
21	4.198	2099.605	19485.199	66.417
22	4.162	2081.441	19542.814	81.094
23	4.148	2074.463	19564.949	85.024
24	3.607	1803.972	20422.931	95.554
25	3.597	1799.021	20438.636	116.482
26	3.447	1723.907	20676.892	118.653
27	3.437	1718.864	20692.890	115.967
28	3.310	1655.125	20895.066	1391.493
29	3.159	1579.764	21134.107	436.050
30	1.356	677.954	23994.595	544.490
31	1.324	662.143	24044.746	376.444
32	1.310	655.136	24066.972	395.076
33	1.216	607.924	24216.726	401.435



11 (run in CD_3OD)



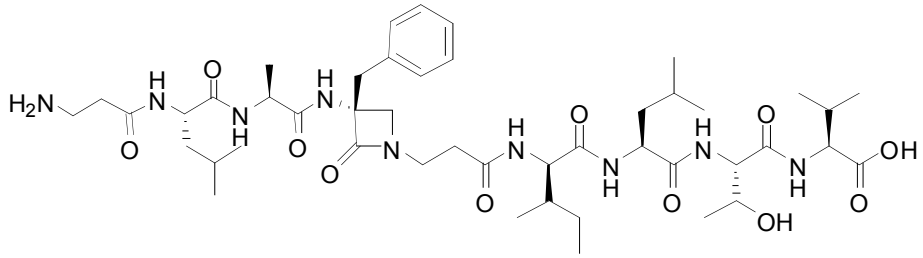


2. Characterization of β-lactam-peptide hybrids (opened and closed versions)

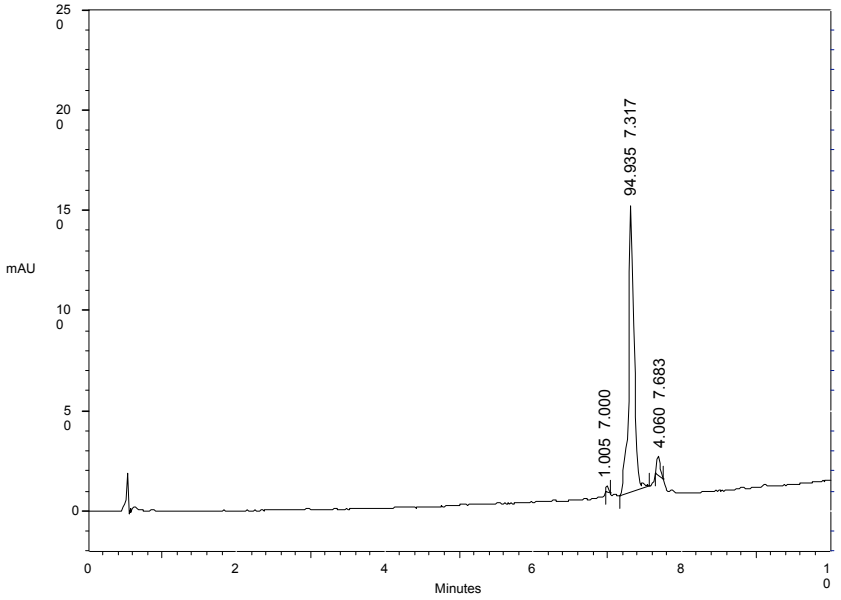
Table S1. Purity of ELA analogues MS characterization

Cpd	yield[a]	t_R, min[b]	Purity (%)[d]	m/z	Exact Mass[e]	Molecular Formula
1	3	7.32	95	930.6	929.58	$C_{46}H_{75}N_9O_{11}$
2	3	6.60	100	915.3	915.54	$C_{45}H_{73}N_9O_{11}$
3	10	9.07	99	944.6	943.57	$C_{47}H_{77}N_9O_{11}$
12	31	3.83[c]	100	948.7	947.57	$C_{46}H_{77}N_9O_{12}$
13	8	3.93[c]	80	934.6	933.55	$C_{45}H_{75}N_9O_{12}$
14	32	7.55	100	962.7	961.58	$C_{47}H_{79}N_9O_{12}$

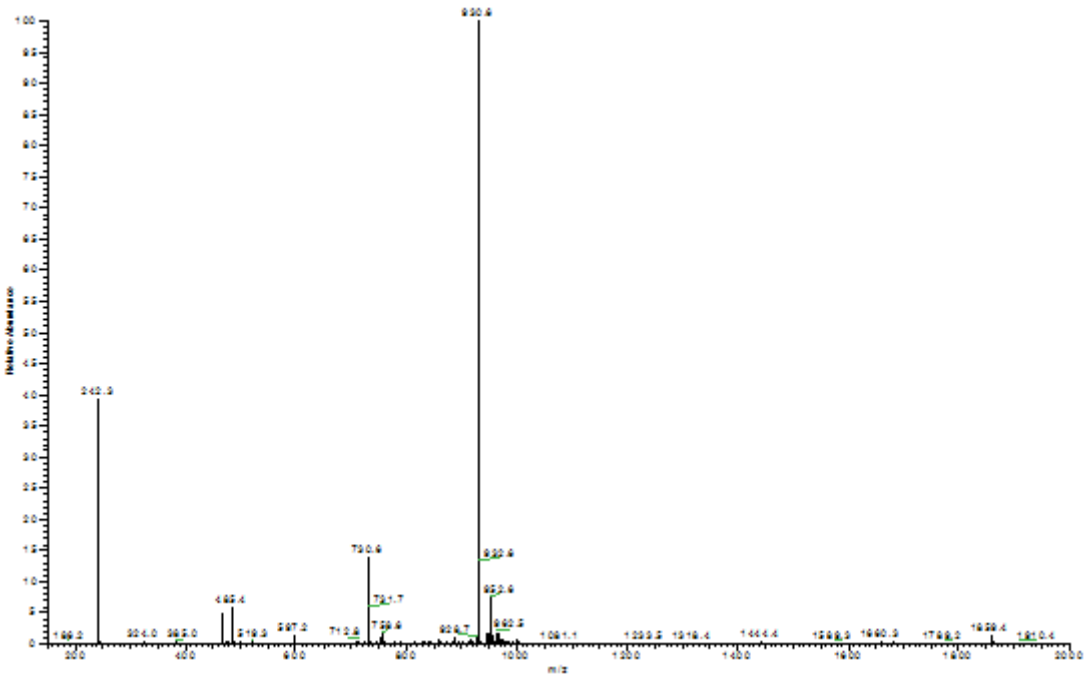
[a]Yield obtained after semi-preparative purification on Varian Mircrosorb C18 column. [b]Retention time on Chromolith performance RP-18e column, 0.46 × 10 cm, flow 3mL.min^{-1}. Solvent systems: A= 0.1% TFA in H_2O; B= 0.1% TFA in CH_3CN. Standard HPLC conditions 100% A to 50% in 10 min. [c]HPLC conditions: in 5 min instead of 10, flow 5ml. min^{-1}. The purity percentage was determined by HPLC analysis after purification. [e]Mass spectrometry analyses were performed on a Thermo- LCQ duo system.



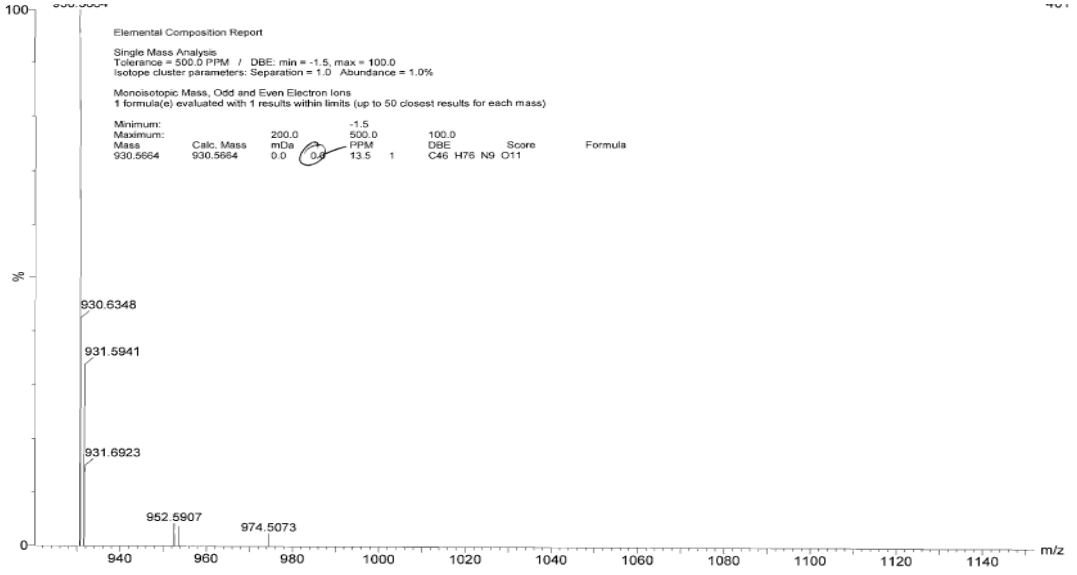
1: colorless foamy solid (1.2 mg, 3 %)



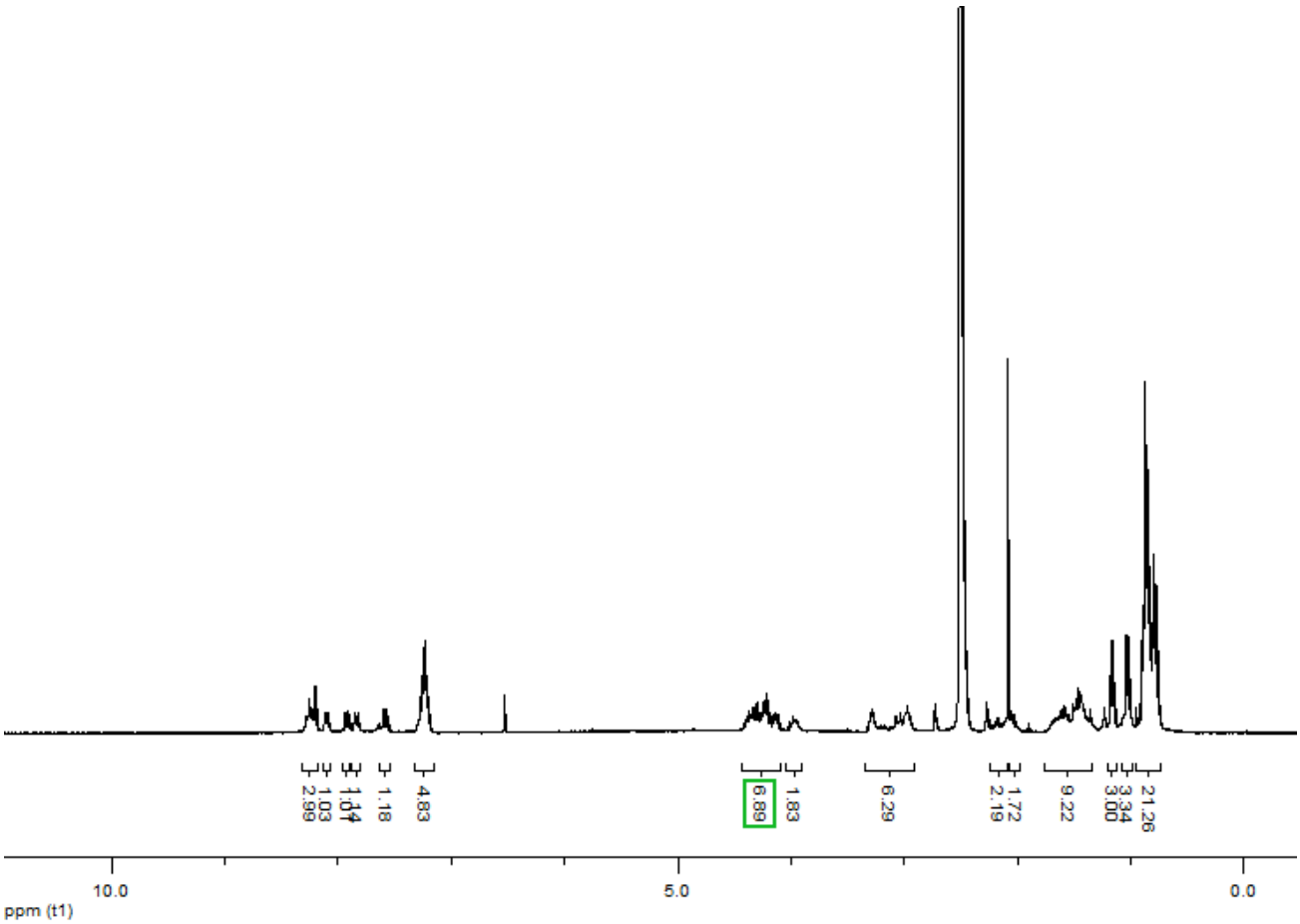
HPLC chromatogram of **1**



Low Resolution Mass Spectrum (ESI) of **1**



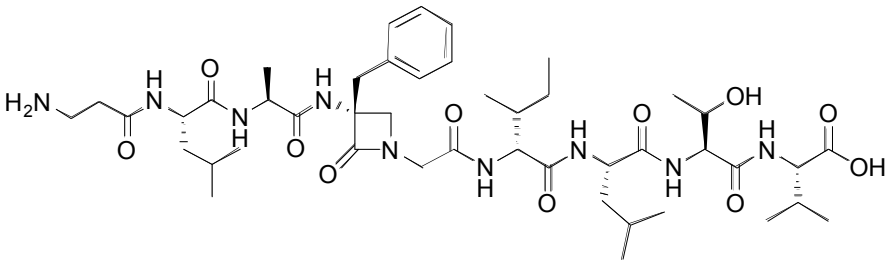
High Resolution Mass Spectrum (ESI) calcd. for $C_{46}H_{76}N_9O_{11}$ $[M+H]^+$ 930.5664, found 930.5664.



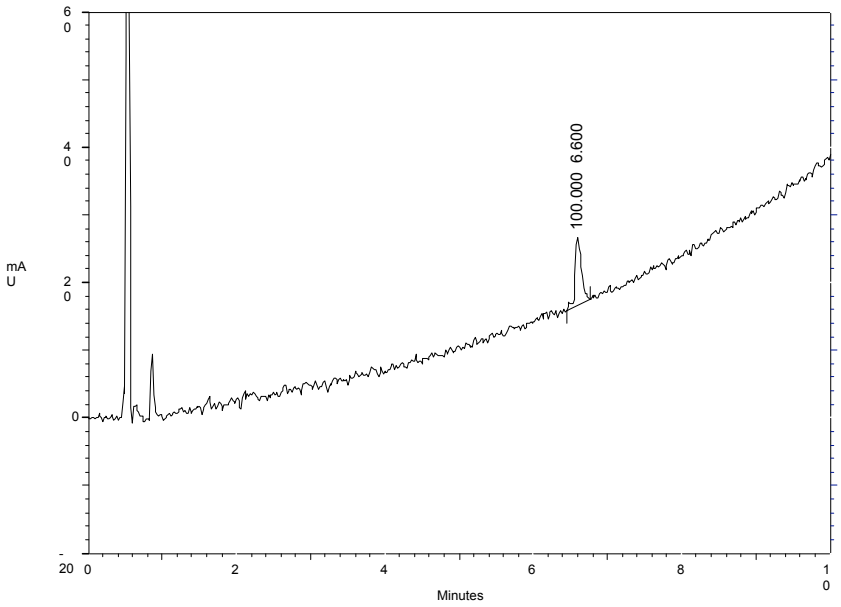
^{1}H NMR spectrum of **1** (run in DMSO-*d6* on a 300MHz spectrometer)

Table S2. ^{1}H NMR chemical shifts of **1** assigned from its TOCSY and ^{1}H NMR (spectra run in DMSO-*d6* on a 300 MHz spectrometer)

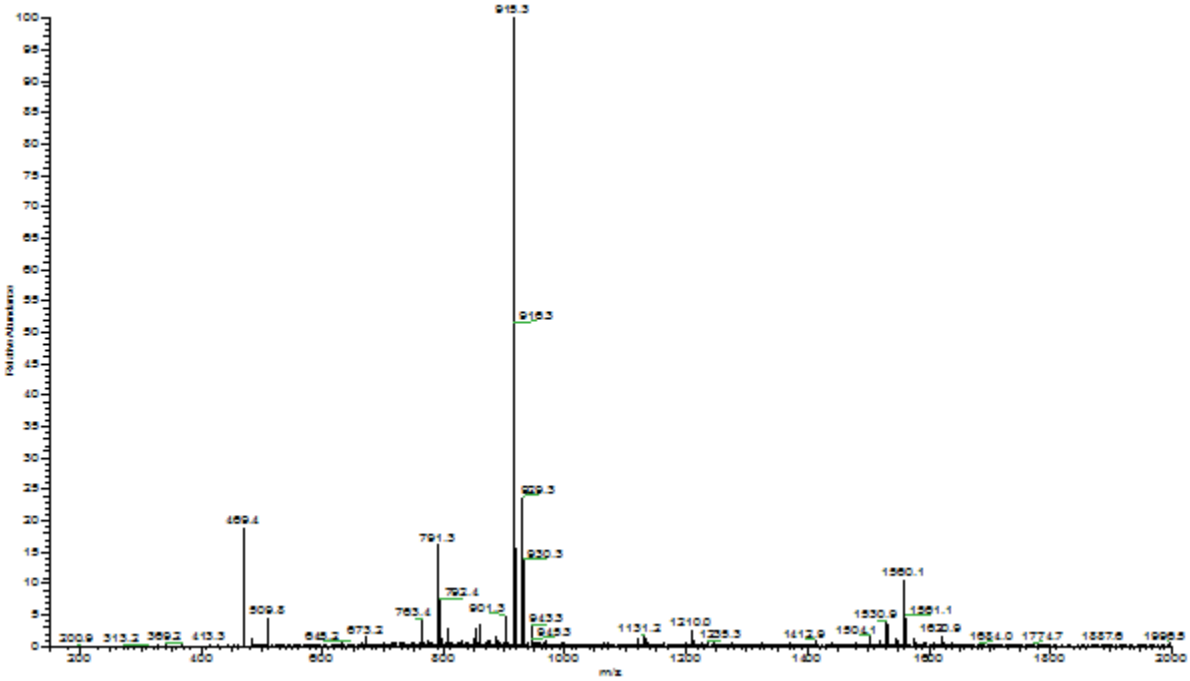
	NH δ (ppm)	Hα δ (ppm)	Hβ δ (ppm)	Hγ δ (ppm)	Hδ δ (ppm)	Hε/ others δ (ppm)
β-Ala1	-			-	-	-
Leu2	8.21-8.28	4.35	1.55	1.45	0.85	-
Ala3	8.11	4.28	1.17	-	-	-
β-lactam	8.21-8.28	-	-	-	-	$H_{aromatic}$: 7.20-7.30
(D)Ile6	7.93	4.22	1.70	1.65	0.85	0.79
Leu7	8.21-8.28	4.35	1.55	1.45	0.85	-
Thr8	7.82	4.24	3.98	1.04	-	-
Val9	7.57	4.35	2.03	0.86	-	-



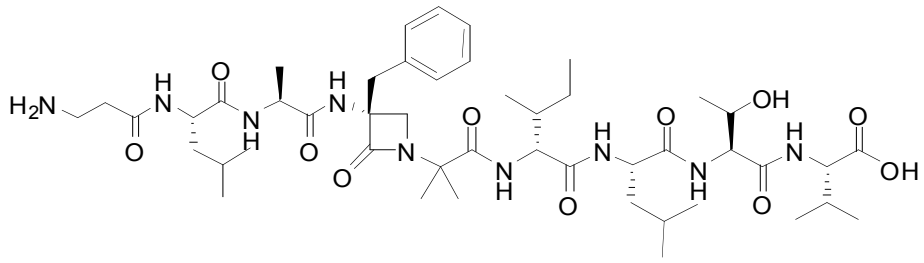
2: Colorless foamy solid (1.6 mg, 3 %)



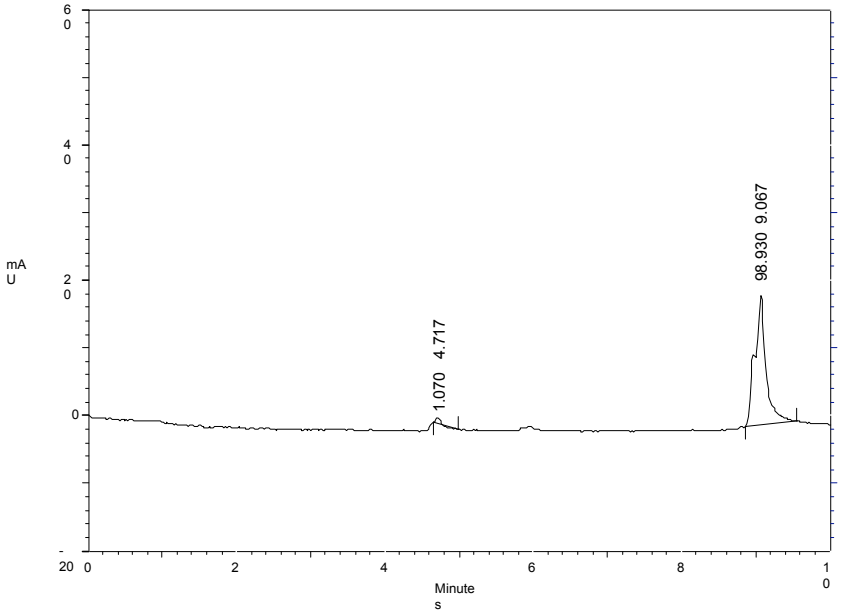
HPLC chromatogram of **2**



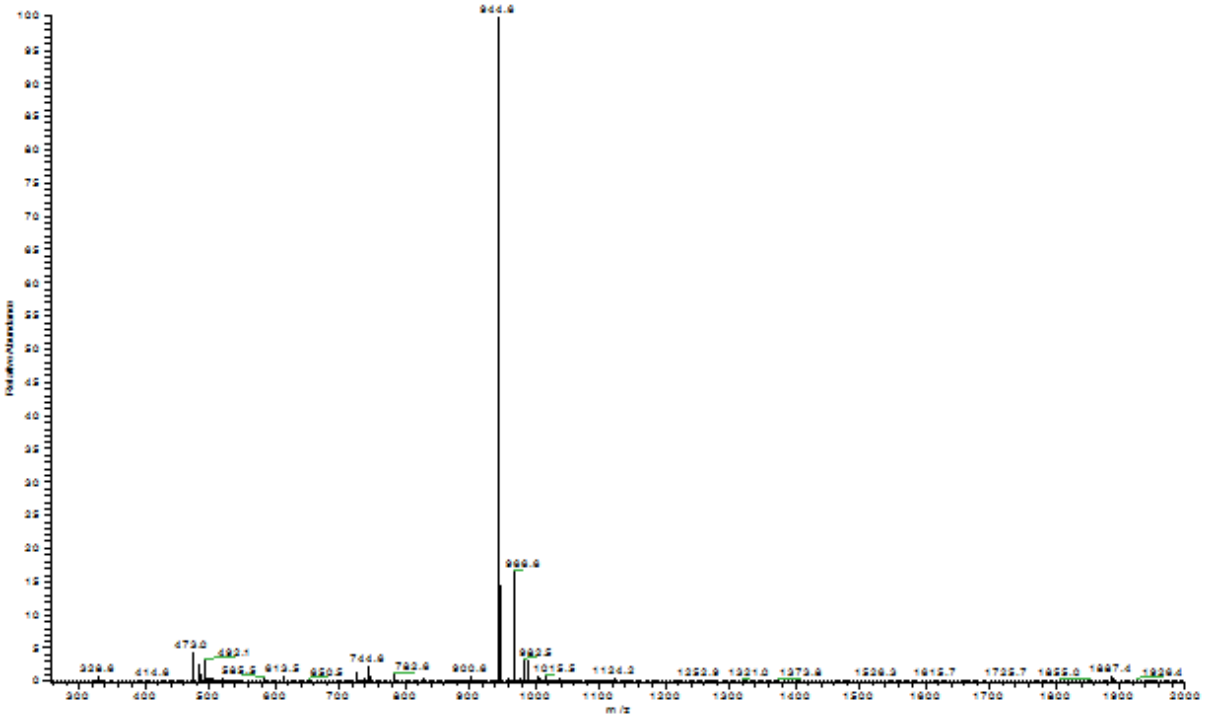
Low Resolution Mass Spectrum (ESI) of **2**



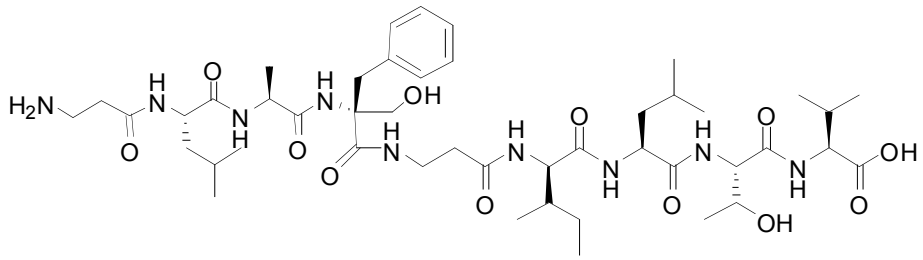
3: Colorless foamy solid (4.7 mg, 10 %)



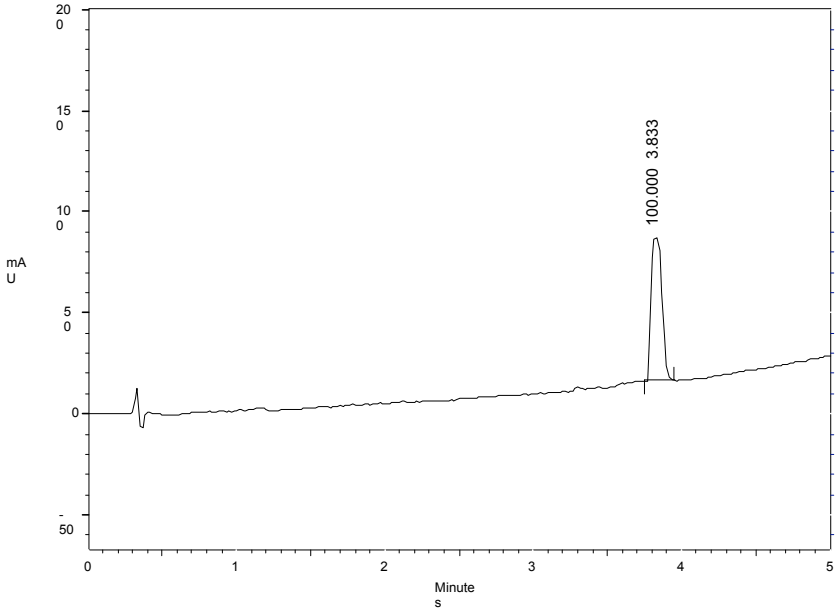
HPLC chromatogram of **3**



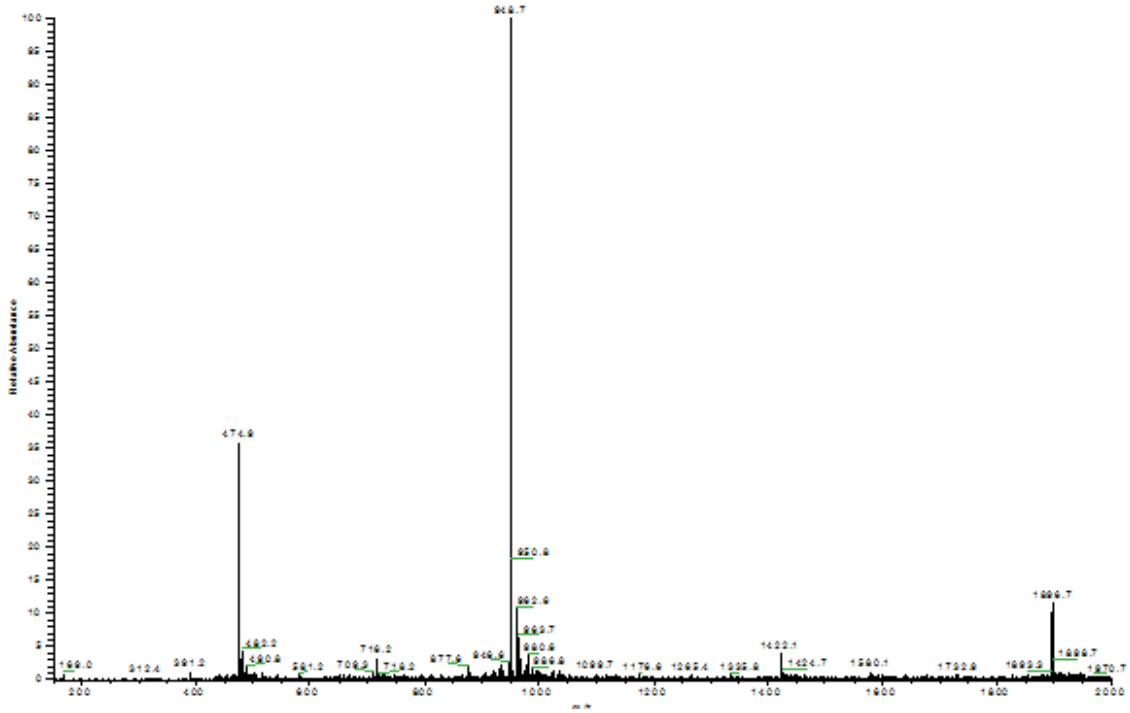
Low Resolution Mass Spectrum (ESI) of **3**



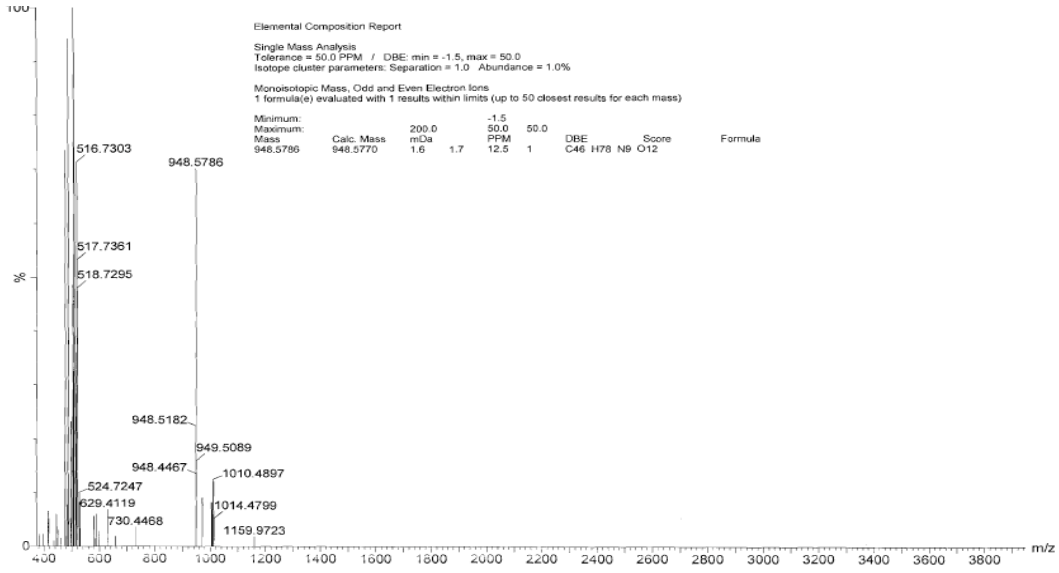
12: Colorless foamy solid (16 mg, 31 %)



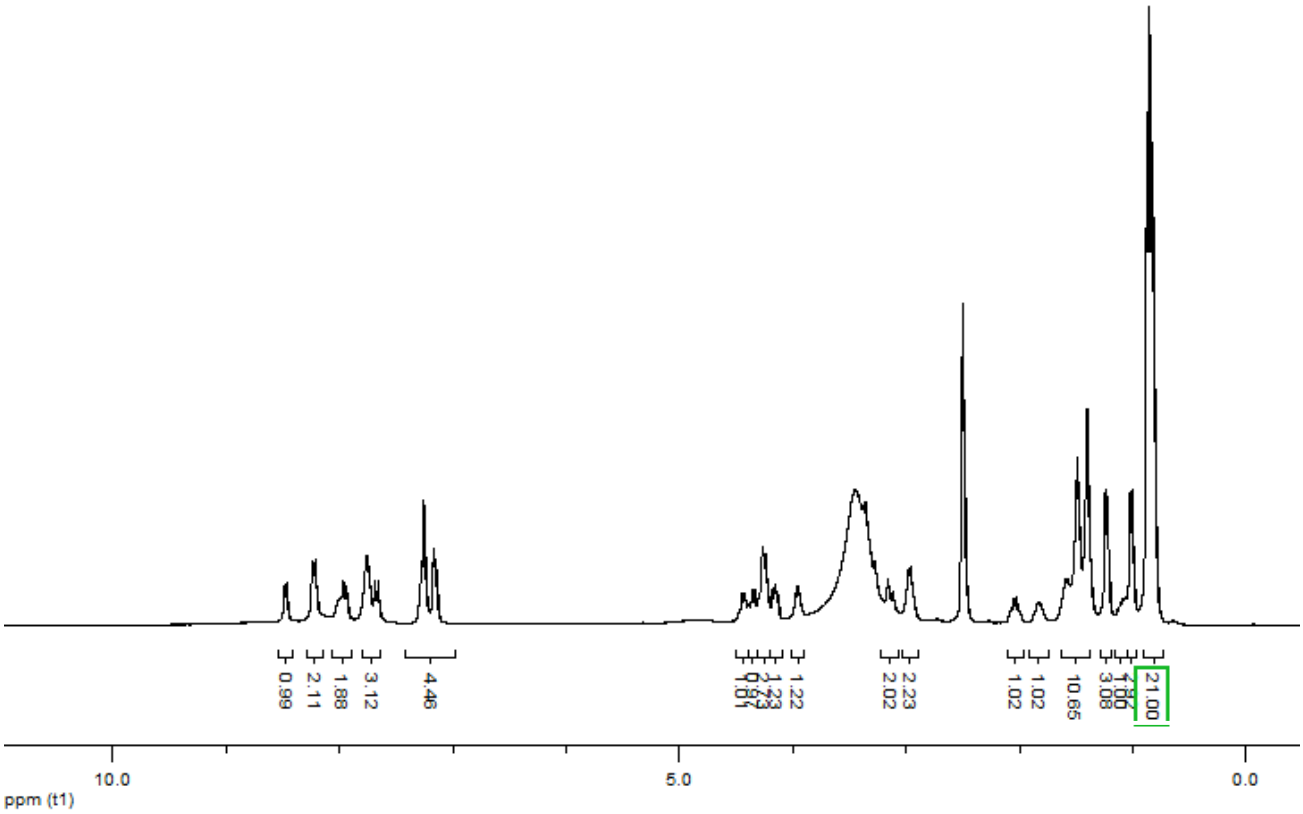
HPLC chromatogram of **12**



Low Resolution Mass Spectrum (ESI) of **12**



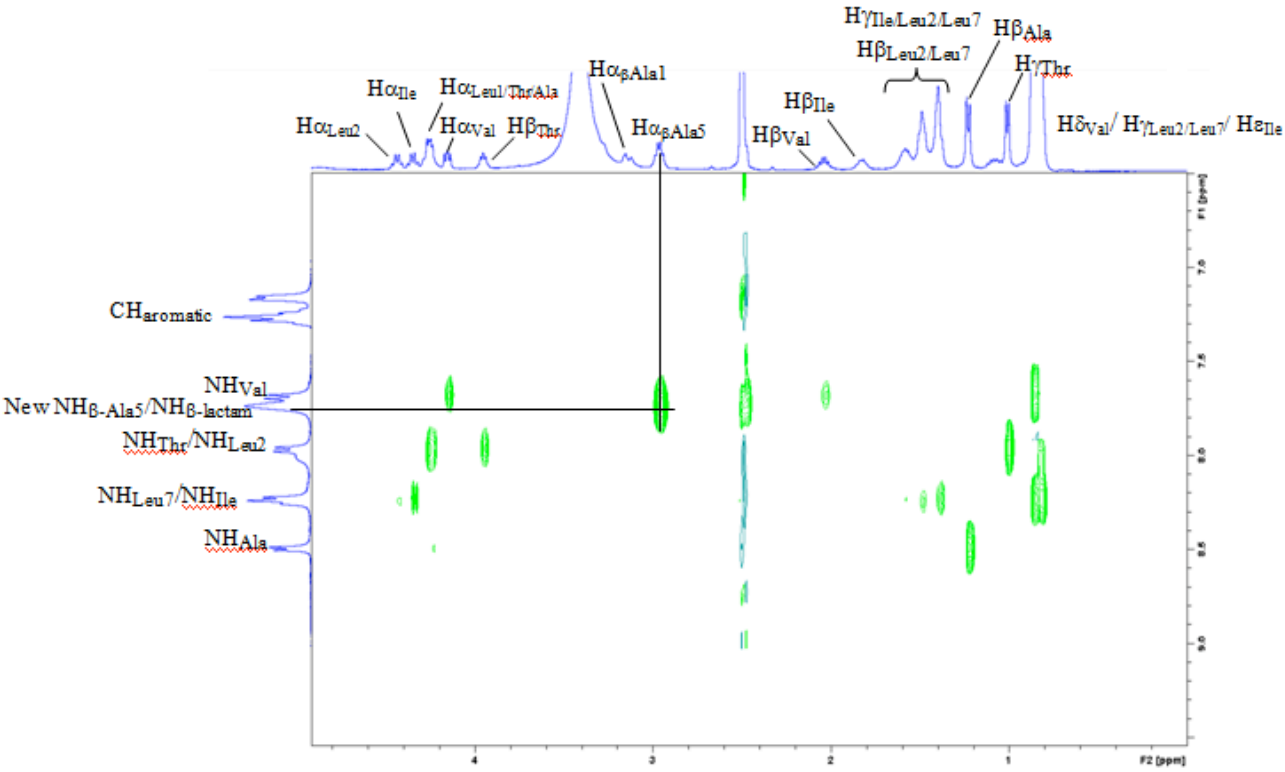
High Resolution Mass Spectrum (ESI) of **12**: calcd. for $C_{46}H_{78}N_9O_{12}$ $[M+H]^+$ 948.5770, found 948.5786.



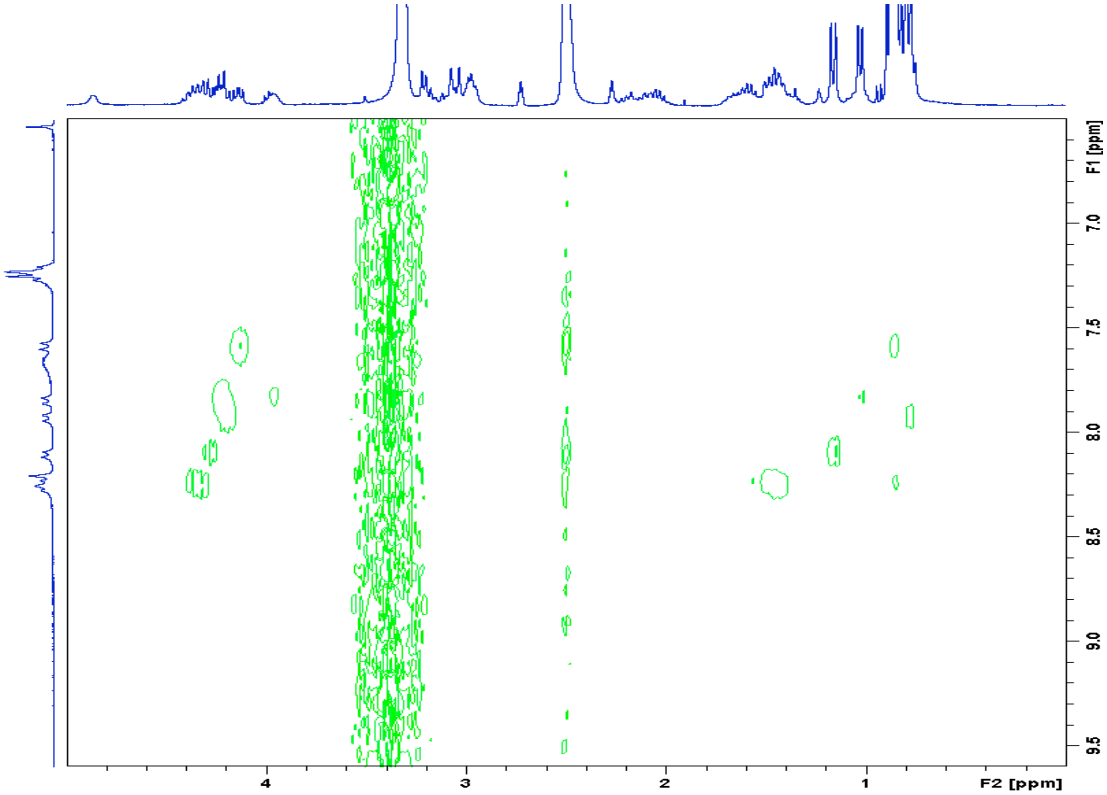
^{1}H NMR spectrum of **12** (run in DMSO-*d6* on a 400 MHz spectrometer)

Table S3. ^{1}H NMR chemical shifts of **12** assigned from its TOCSY and ^{1}H NMR (spectra run in DMSO-*d6* on a 400 MHz spectrometer)

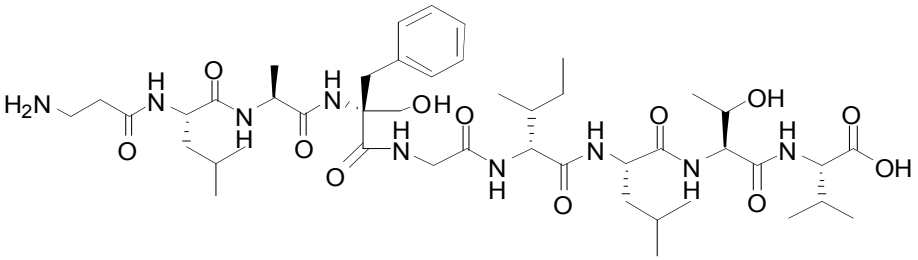
	NH δ (ppm)	Hα δ (ppm)	Hβ δ (ppm)	Hγ δ (ppm)	Hδ δ (ppm)	Hε/ others δ (ppm)
β-Ala1	-	3.14		-	-	-
Leu2	8.01	4.26	1.49	1.40	0.85	-
Ala3	8.48	4.26	1.23	-	-	-
α-D-benzyl Ser		-	-	-	-	$H_{aromatic}$: 7.16-7.27
β-Ala5	7.76	2.50	2.97			
D-Ile6	8.23	4.36	1.83	1.40	1.08	0.85
Leu7	8.23	4.43	1.49	1.40	0.85	-
Thr8	7.96	4.26	3.96	1.01	-	-
Val9	7.68	4.16	2.04	0.85	-	-



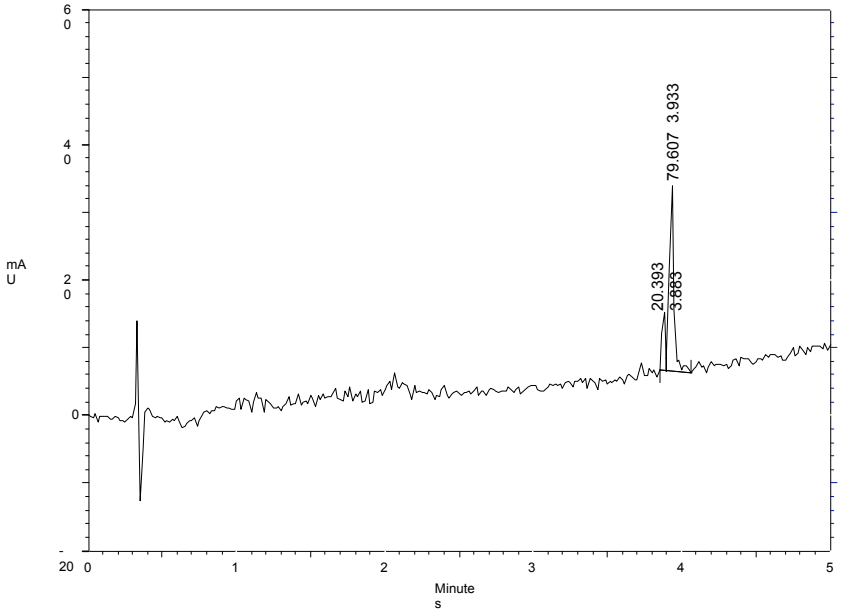
Section of the TOCSY NMR data map of **12** (run in DMSO-*d6* on a 400 MHz spectrometer) Enlargement of side chains/ amidic NH correlation region (0.0-5.0/6.5-9.6 ppm)



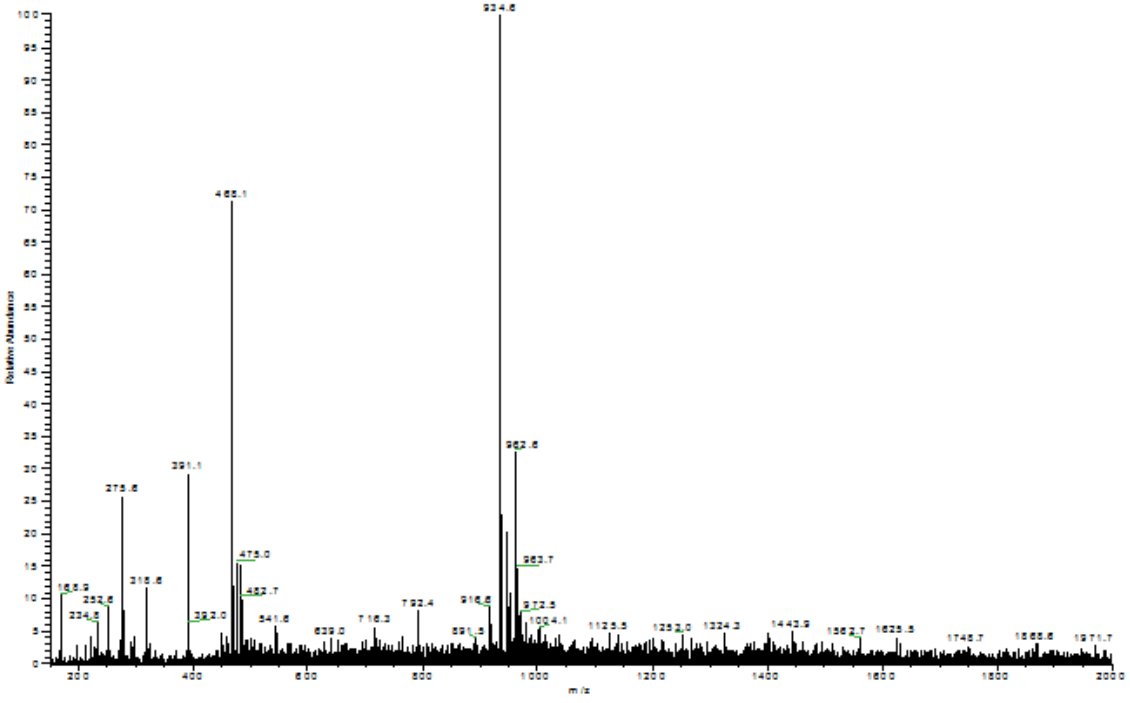
Section of the TOCSY NMR data map of **1** (run in DMSO-*d6* on a 400 MHz spectrometer) Enlargement of the same region than before (0.0-5.0/6.5-9.6 ppm)



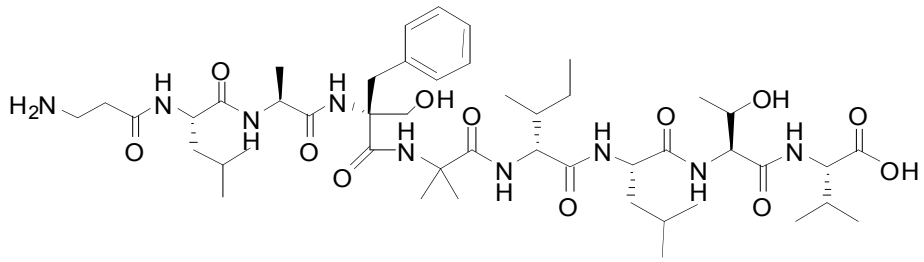
13: Colorless foamy solid (3.8 mg, 8 %)



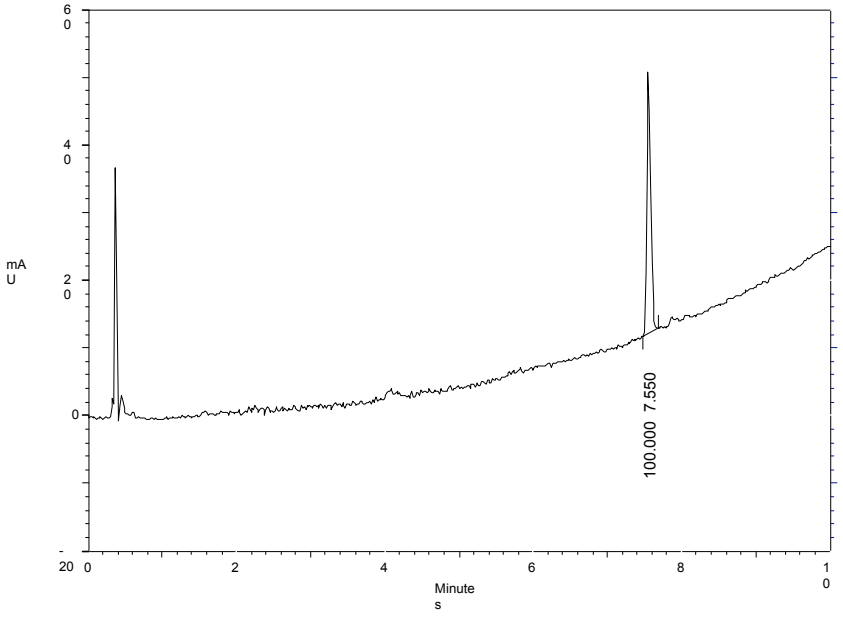
HPLC chromatogram of **13**



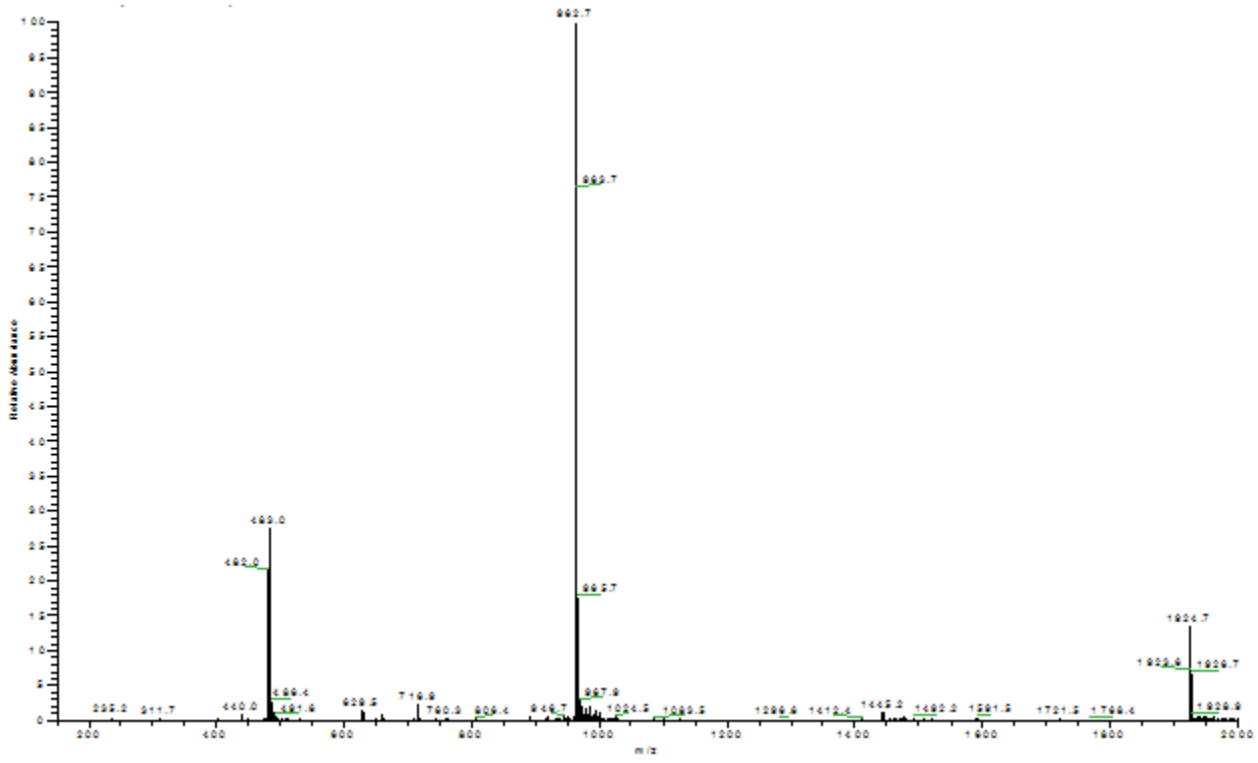
Low Resolution Mass Spectrum (ESI) of **13**



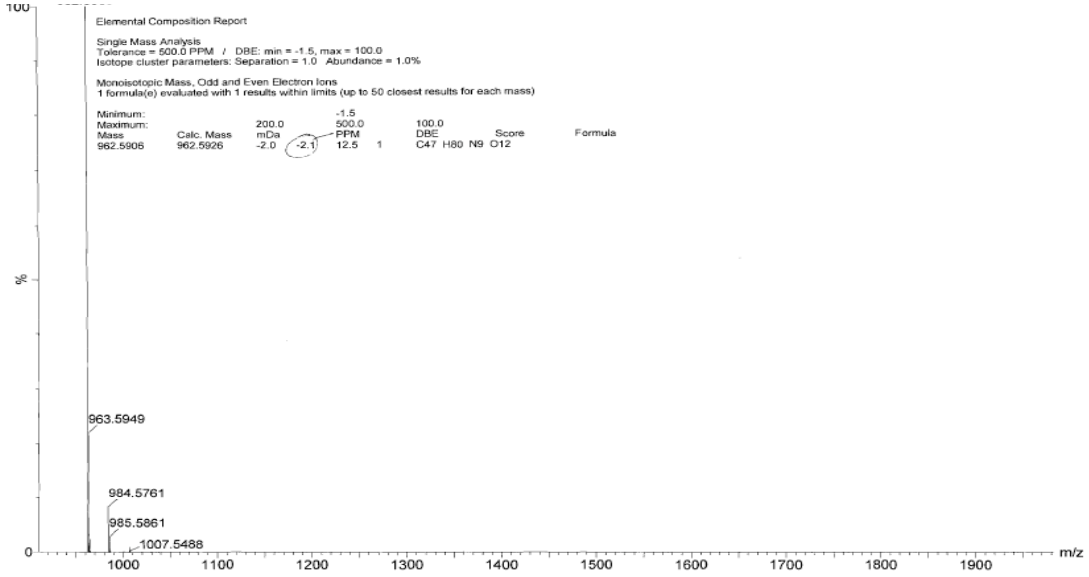
14: Colorless foamy solid (17 mg, 32 %)



HPLC Profil of **14**

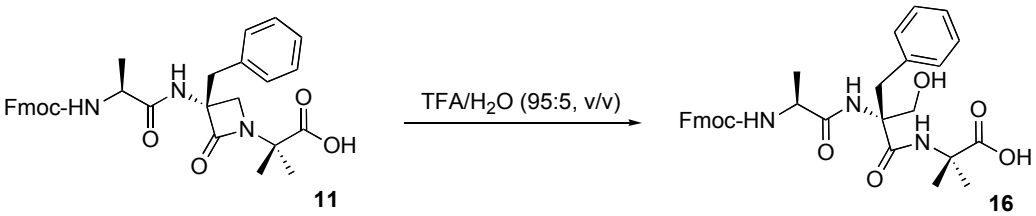


Low Resolution Mass Spectrum (ESI) of **14**

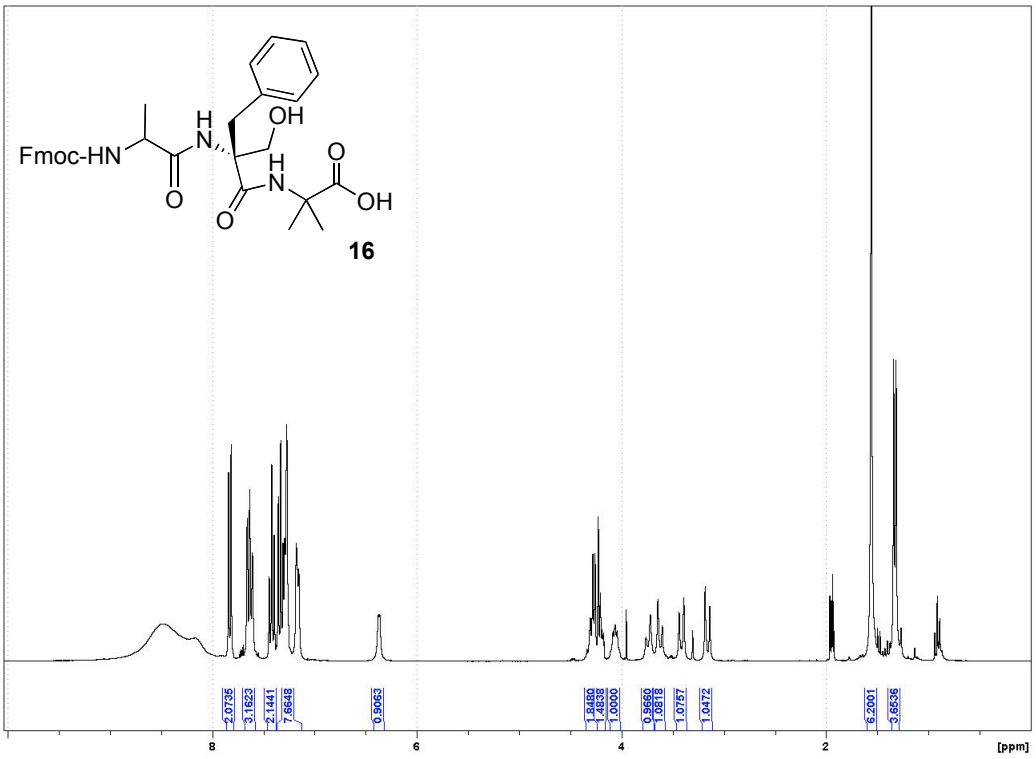


High Resolution Mass Spectrum (ESI) of **14**: calcd. for $C_{47}H_{80}N_9O_{12}$ $[M+H]^+$ 962.5926, found 962.5906.

3. Solution study of the opening of β-lactam ring in acidic media

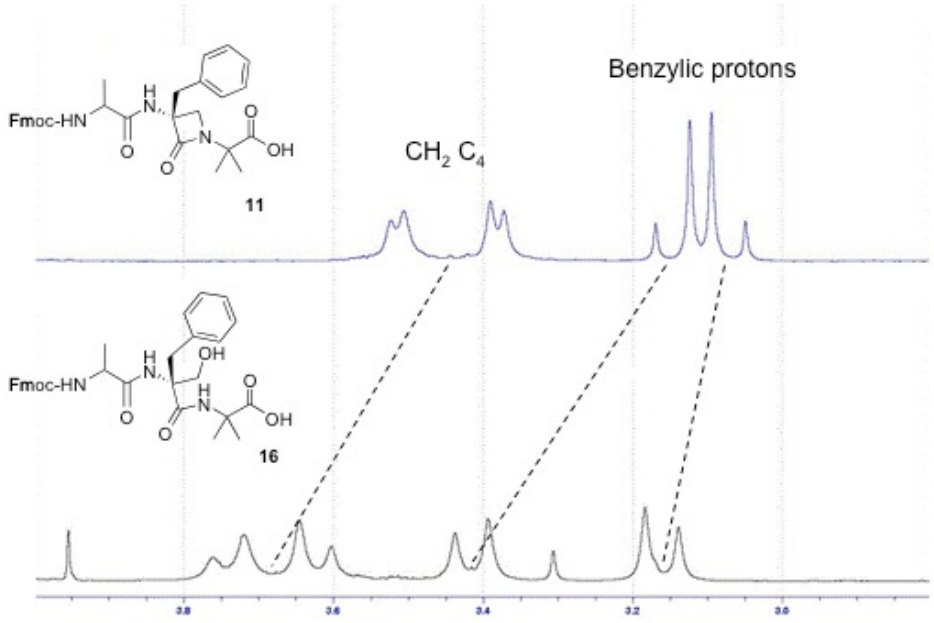


The *N*-Fmoc-Ala-(β-lactam)-Aib-OH (**11**) (15 mg, 0.03 mmol) was dissolved in 1 mL of a TFA-water solution mixture (95:5, v/v). The reaction mixture was let without stirring for 1 h 30 min. The solvent was then evaporated under reduced pressure to give quantitatively the corresponding *N*-Fmoc-Ala-D-α-benzylserine-Aib-OH (**16**) as a white solid. δ_H (300 MHz; CD_3CN) 1.33 (3H, d, *J* 7.1, Ala C*H*$_3$), 1.56 (6H, s, Aib C*H*$_3$), 3.16 (1H, d, *J* 14.1, C*H*$_2$Ph), 3.42 (1H, d, *J* 13.8, C*H*$_2$Ph), 3.62 (1H, d, *J* 12.5 C*H*$_2$OH), 3.74 (1H, d, J 12.6, C*H*$_2$OH) 4.12 (1H, m, Ala C*H*), 4.17-4.31 (3H, m, Fmoc C*H*$_2$ + Fmoc C*H*), 6.37 (1H, m, Fmoc N*H*), 7.16-7.18 (2H, m, Ph), 7.27-7.36 (8H, m, Fmoc + Ph), 7.42 (2H, t, *J* 7.3, Fmoc), 7.61-7.66 (3H, m, Fmoc + NH), 7.83 (2H, d, *J* 7.4, Fmoc); δ_C(125 MHz; CD_3OD) 175.83, 172.0, 170.9, 157.7, 143.8, 143.7, 141.2, 128.3, 126.9, 124.9, 119.6, 67.8, 67.1, 62.9, 62.1, 53.5, 51.1, 39.7, 20.7, 20.6, 15.6; *m/z* (ESI) 1146.9 (MH^+, 100%), 1168.9 (MNa^+, 45%).

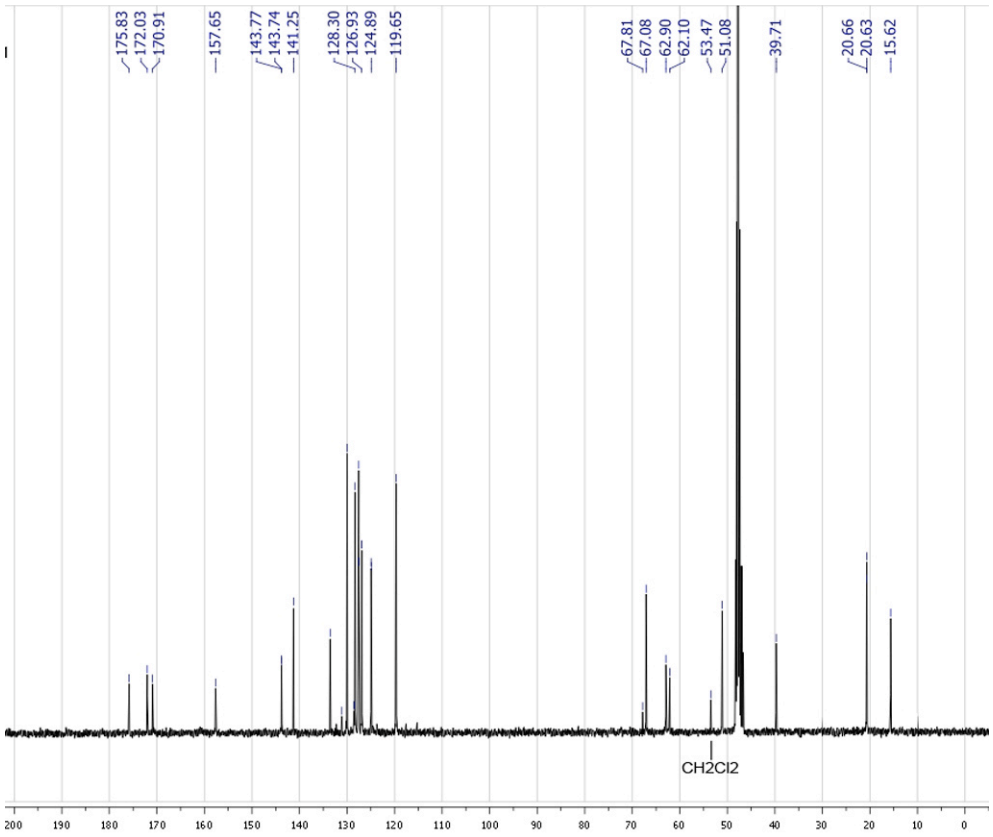


^{1}H NMR of compound **16** in CD_3CN after aqueous TFA treatment of **11**

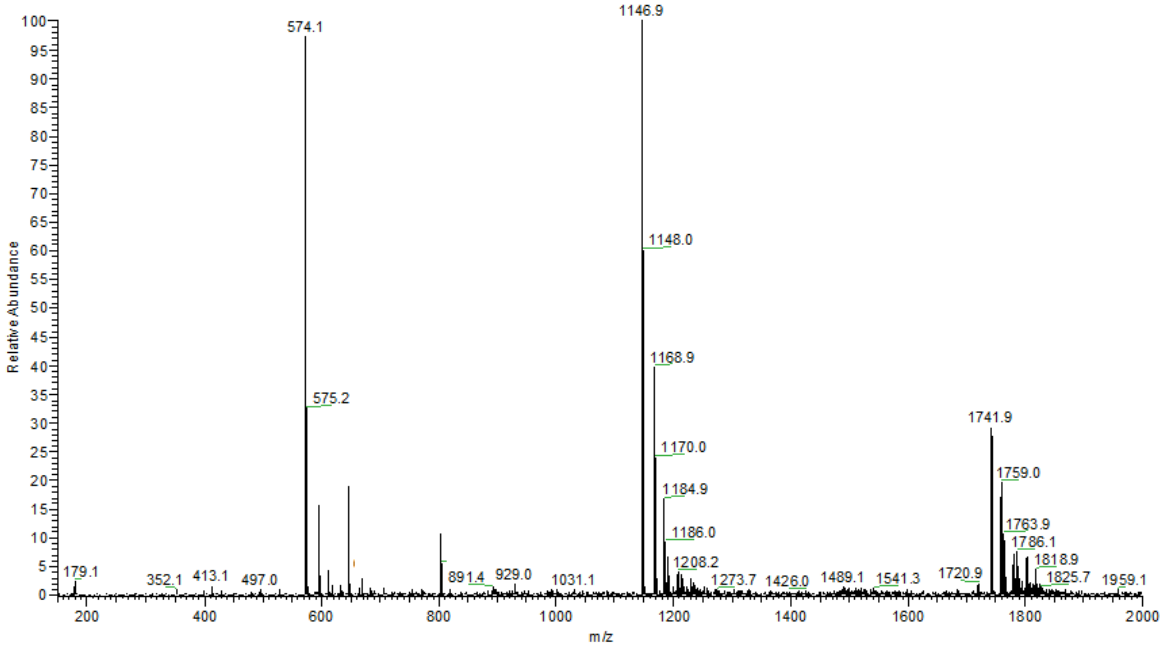
Index	ppm	Hz	Point	Height
1	7.840	2352.935	13697.960	116620456
2	7.815	2345.505	13737.305	134004152
3	7.658	2298.206	13987.766	88458392
4	7.633	2290.821	14026.873	106139280
5	7.607	2283.044	14068.056	67050008
6	7.442	2233.665	14329.534	52417540
7	7.418	2226.357	14368.228	121498704
8	7.394	2219.059	14406.876	78167688
9	7.358	2208.182	14464.472	94383528
10	7.354	2207.011	14470.671	102157544
11	7.333	2200.732	14503.923	133189816
12	7.329	2199.599	14509.920	136548304
13	7.308	2193.295	14543.304	72876264
14	7.304	2192.185	14549.182	73063400
15	7.292	2188.484	14568.779	75909536
16	7.271	2182.181	14602.156	146423600
17	7.180	2154.776	14747.273	73034512
18	7.172	2152.440	14759.642	67337216
19	7.155	2147.325	14786.727	57225980
20	6.376	1913.592	16024.418	28585218
21	6.364	1909.934	16043.790	29048632
22	4.304	1291.721	19317.416	26730782
23	4.280	1284.546	19355.410	66173884
24	4.259	1278.107	19389.507	66519360
25	4.227	1268.600	19439.849	89600872
26	4.205	1262.072	19474.416	42284108
27	4.082	1225.043	19670.498	18404480
28	4.064	1219.660	19699.000	22563916
29	4.061	1218.653	19704.333	22472320
30	4.042	1213.164	19733.400	18710868
31	3.760	1128.418	20182.158	15117772
32	3.718	1115.889	20248.503	29018020
33	3.644	1093.582	20366.623	38238156
34	3.601	1080.748	20434.583	21934072
35	3.436	1031.196	20696.976	30238702
36	3.392	1017.868	20767.554	39213912
37	3.182	954.956	21100.691	46256792
38	3.137	941.527	21171.804	33855920
39	1.940	582.063	23075.275	54030684
40	1.559	467.816	23680.248	446885728
41	1.340	402.112	24028.171	186968976
42	1.316	395.000	24065.833	186538032



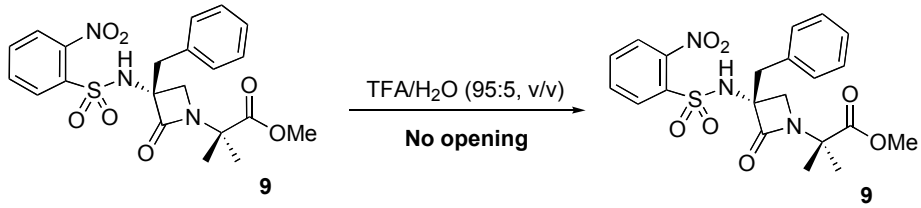
Section of the ^{1}H NMR of **11** before and after treatment with TFA-H_2O (95:5) in CD_3CN

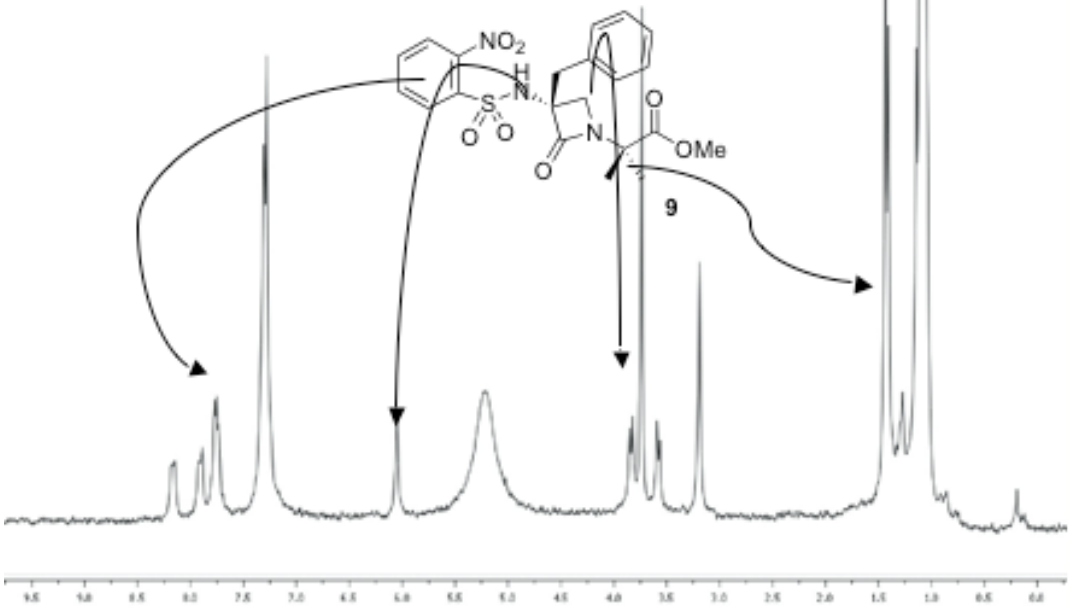


^{13}C NMR of compound **16** in CD_3OD



Low resolution ESI mass spectrum of compound **16**





^{1}H NMR in CD_3OD of compound **9** after aqueous TFA treatment; no opening reaction occurred.