

Elaboration of the Effective Multi-Target Therapeutic Platform for the Treatment of Alzheimer's Disease Based on Novel Monoterpene-Derived Hydroxamic Acids

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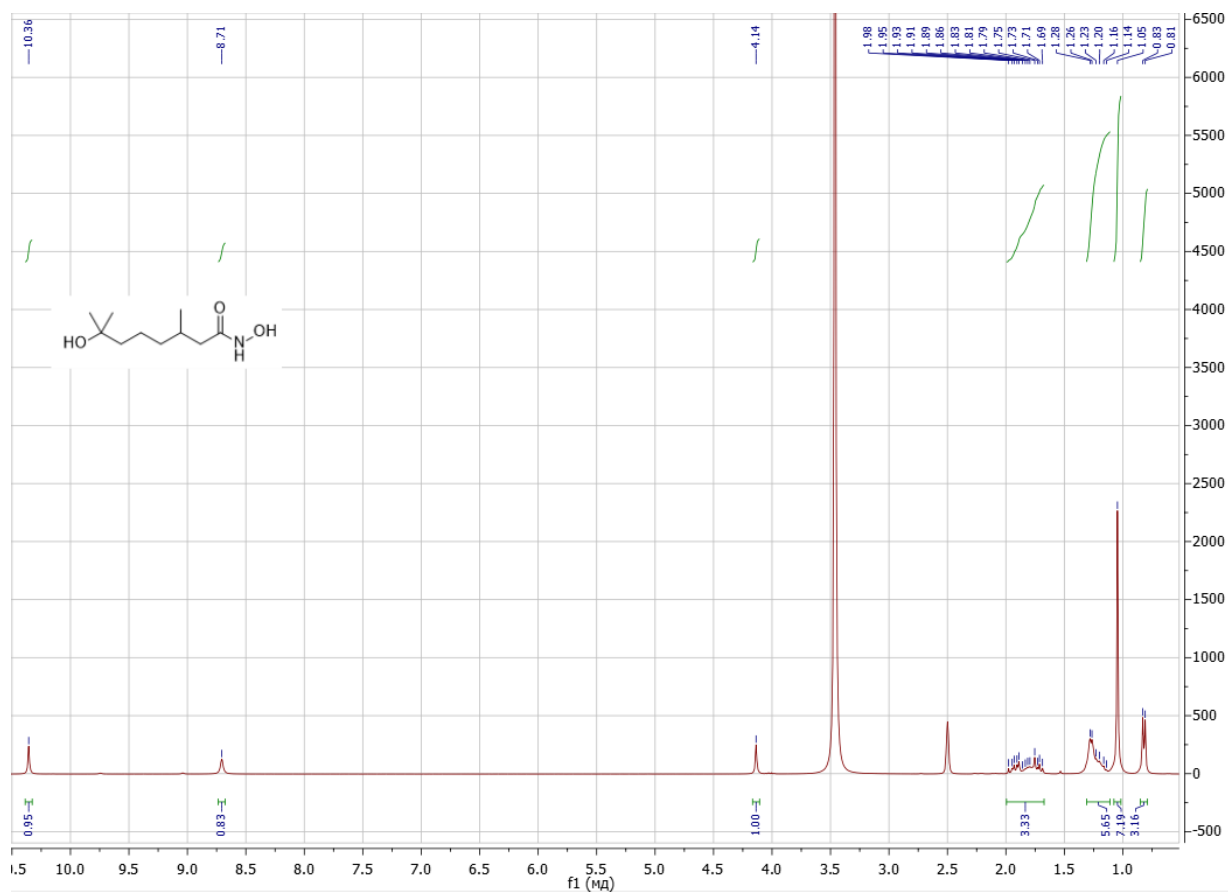
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² Department of Medicinal Chemistry, N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch, Russian Academy of Sciences, Lavrentiev Ave., 9, Novosibirsk 630090, Russia

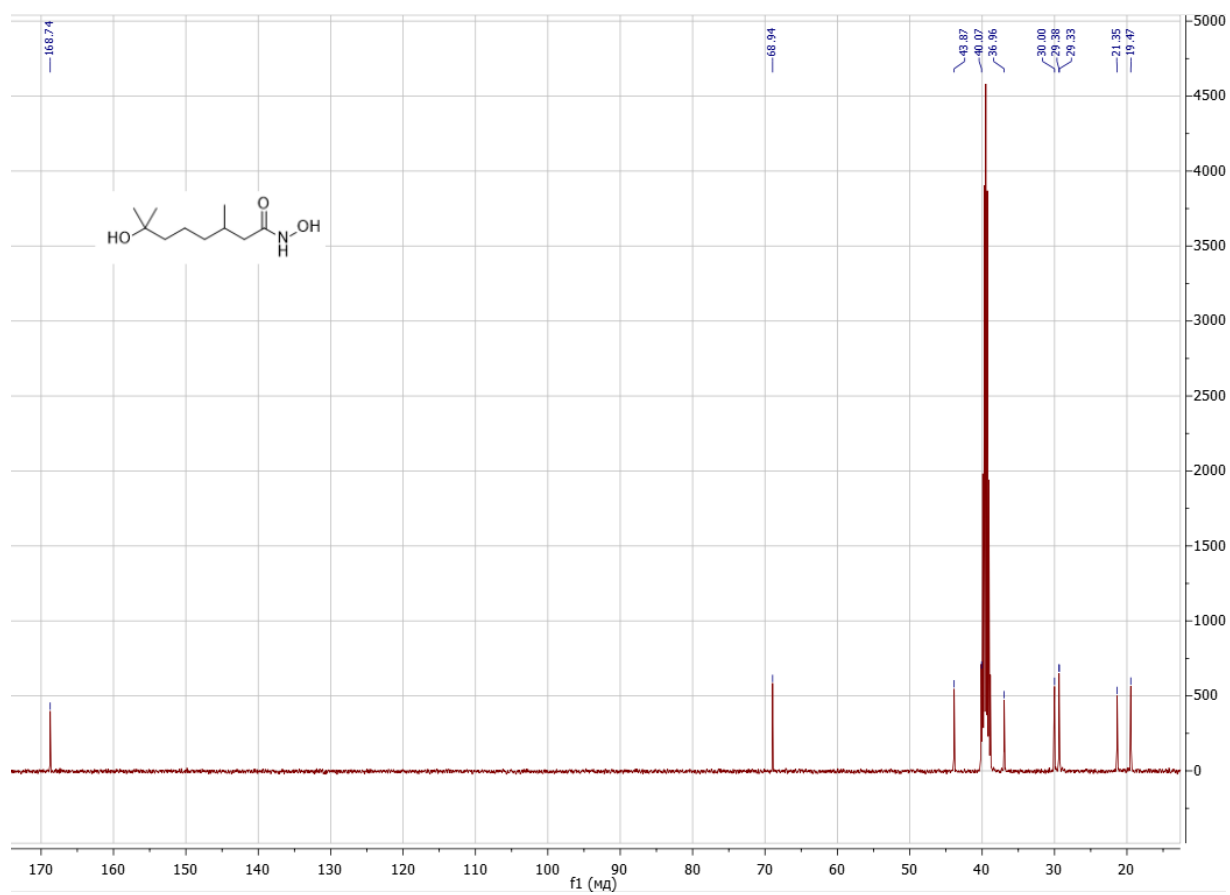
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^1H NMR spectrum of compound 5



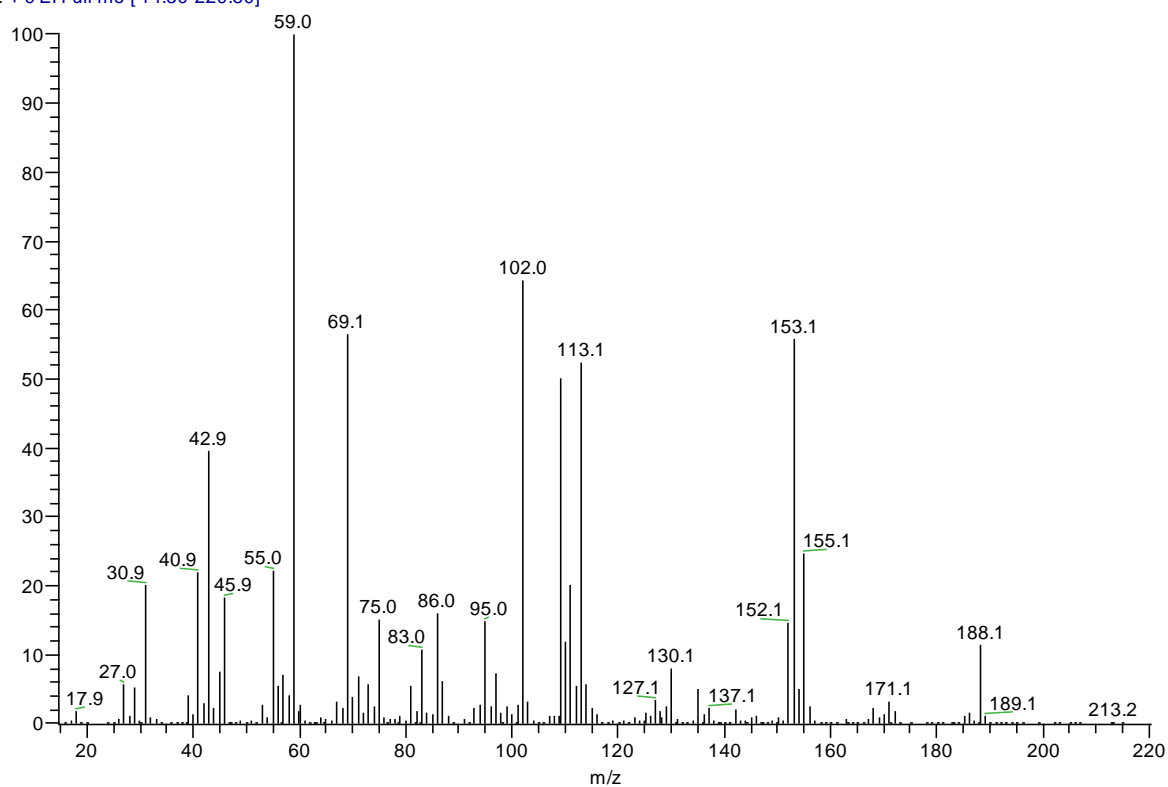
^{13}C NMR spectrum of compound 5



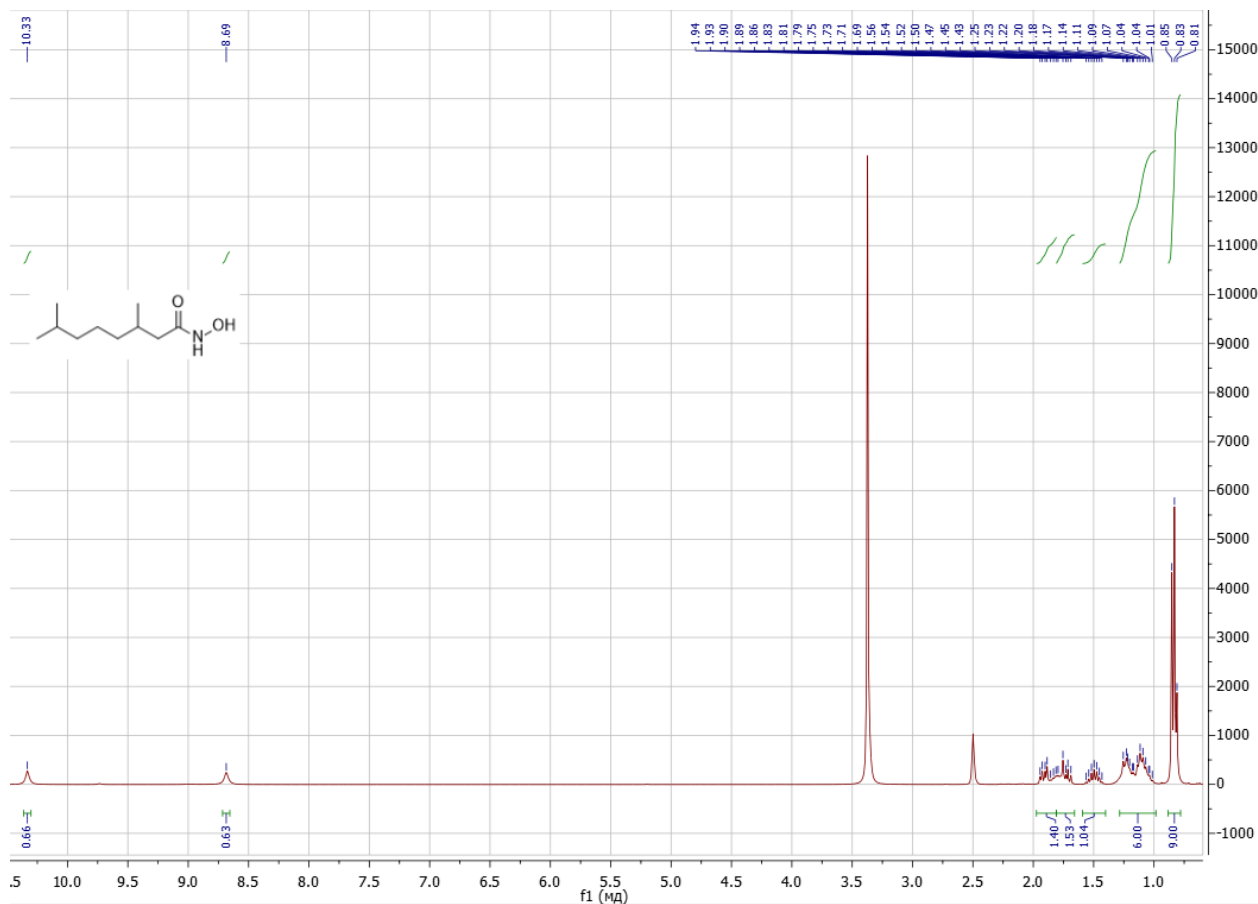
Mass-spectrum of compound 5

MS-315 #13 RT: 0.82 AV: 1 NL: 8.79E7

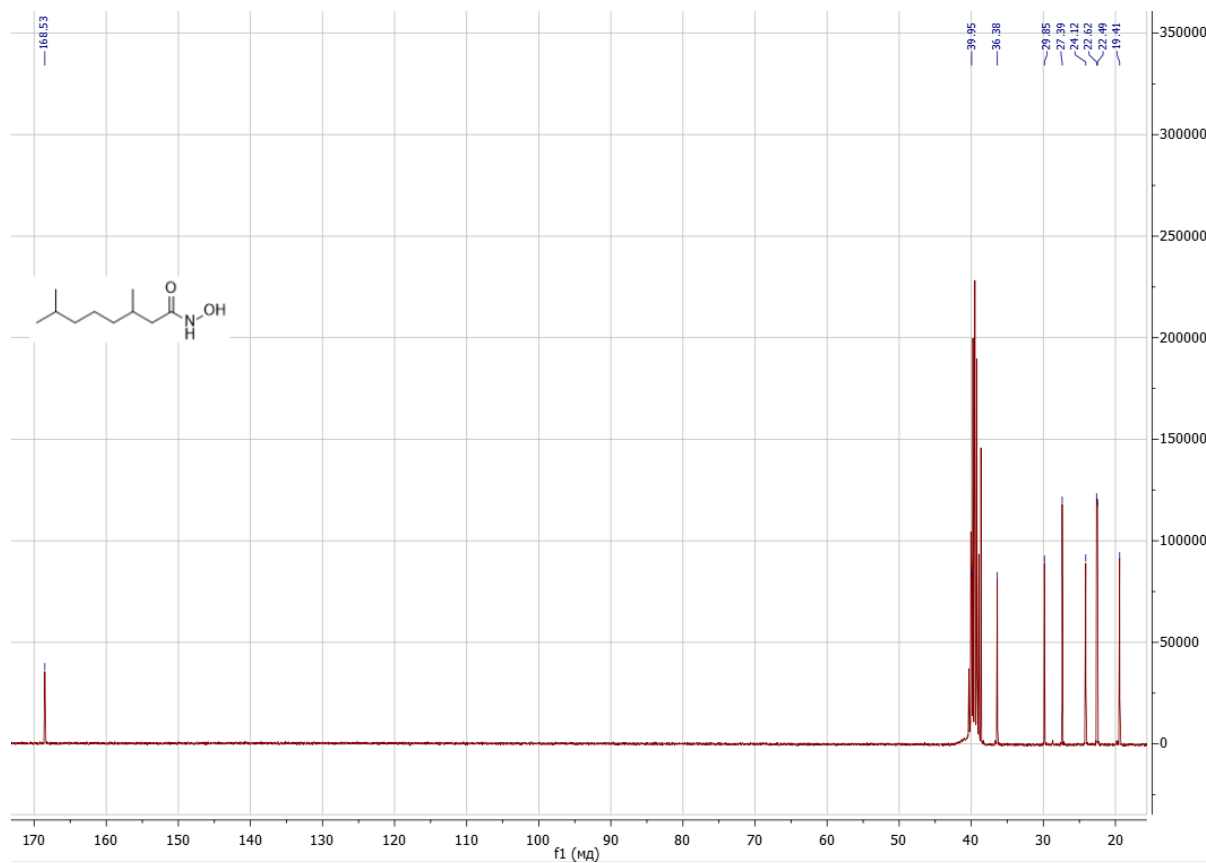
T: + c EI Full ms [14.50-220.50]



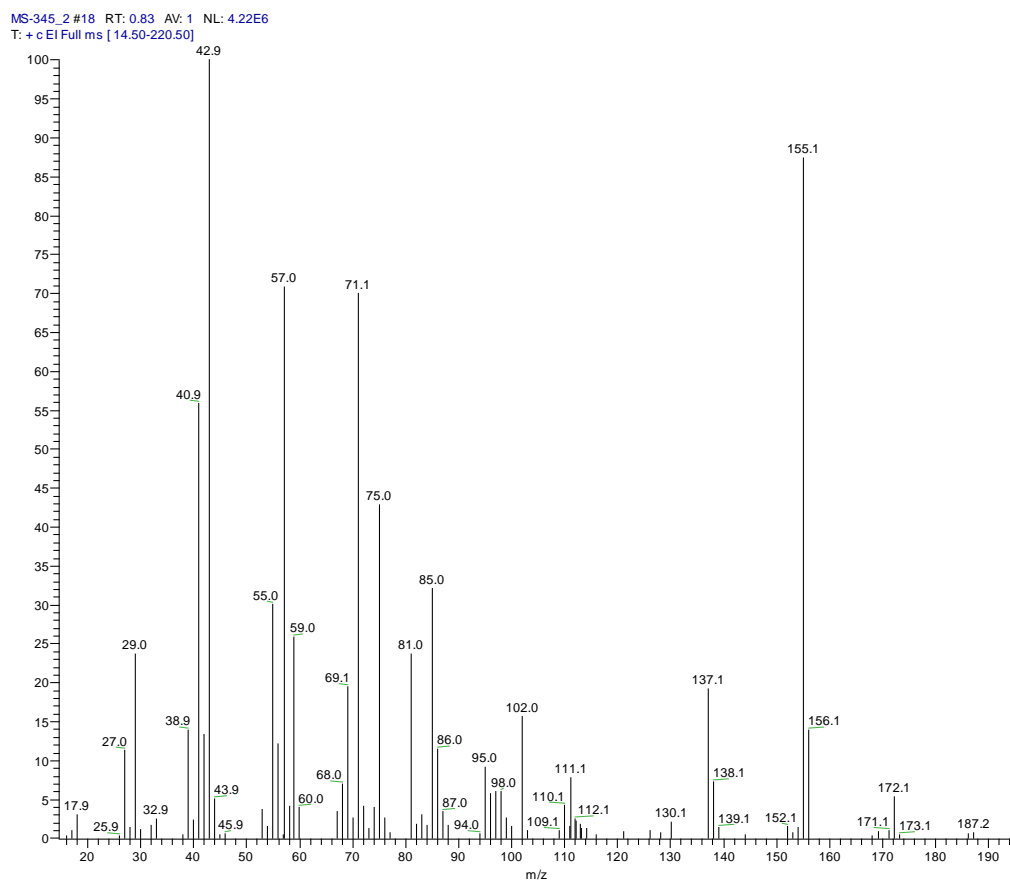
¹H NMR spectrum of compound 8



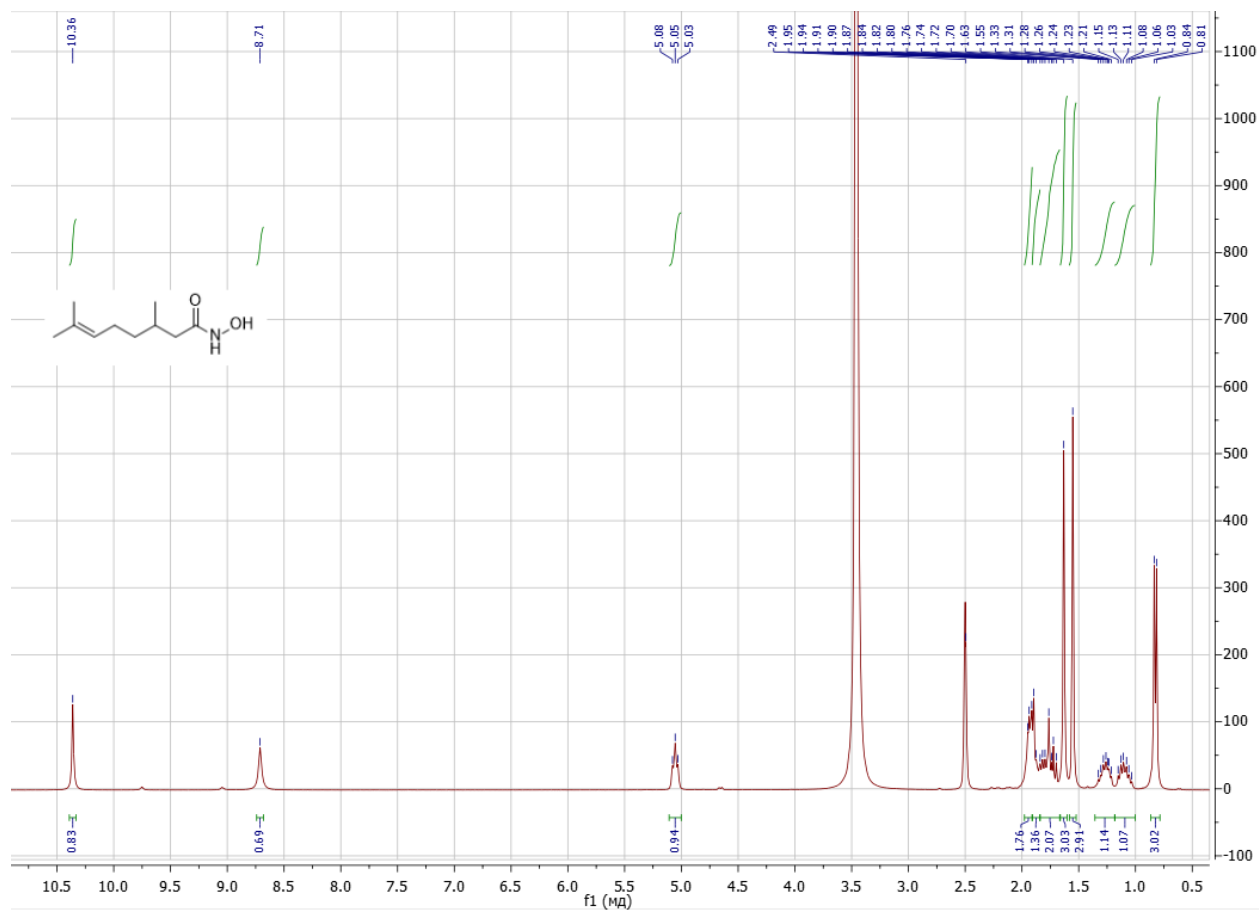
¹³C NMR spectrum of compound **8**



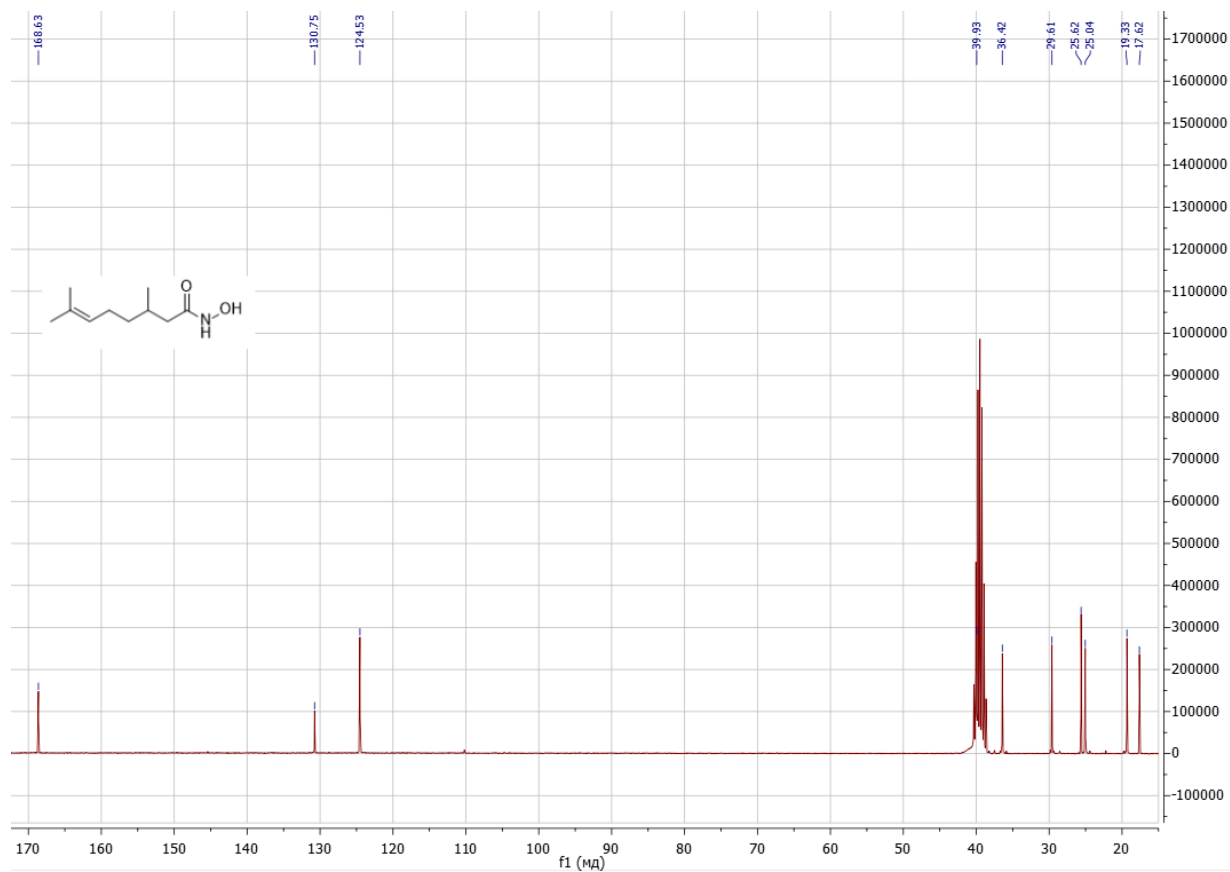
Mass-spectrum of compound **8**



¹H NMR spectrum of compound **10**

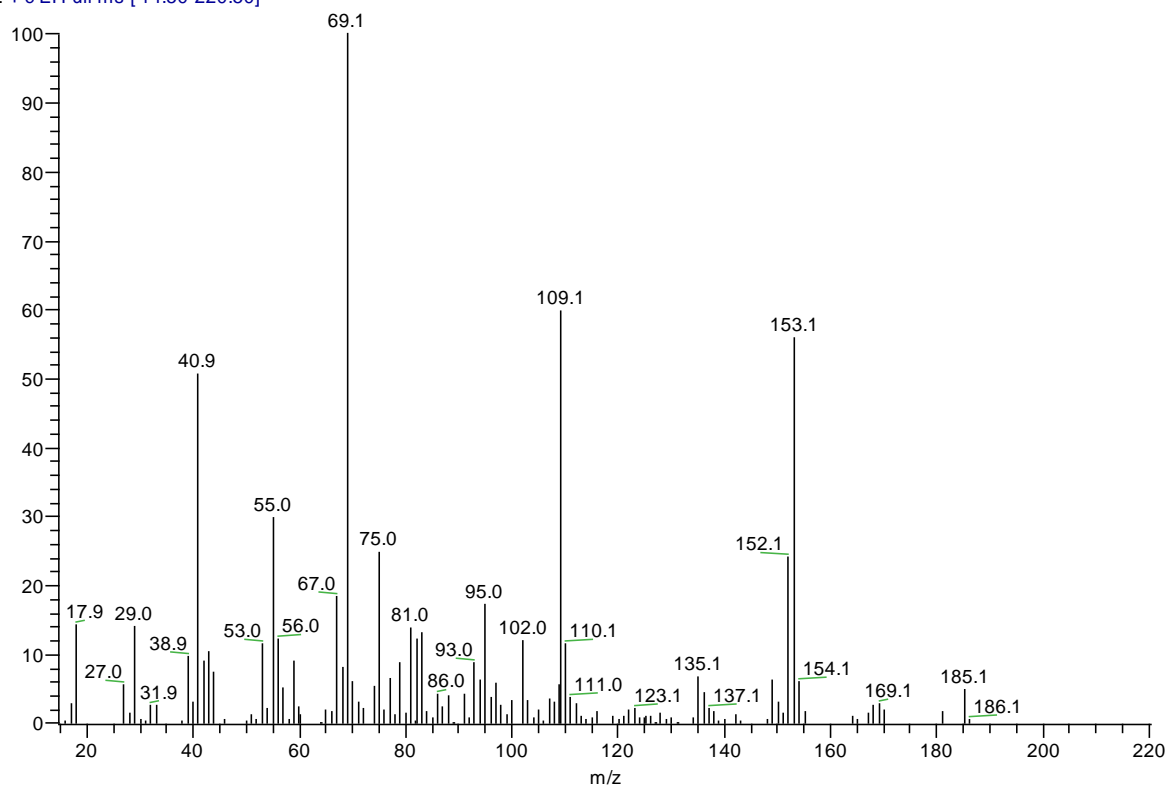


¹³C NMR spectrum of compound **10**

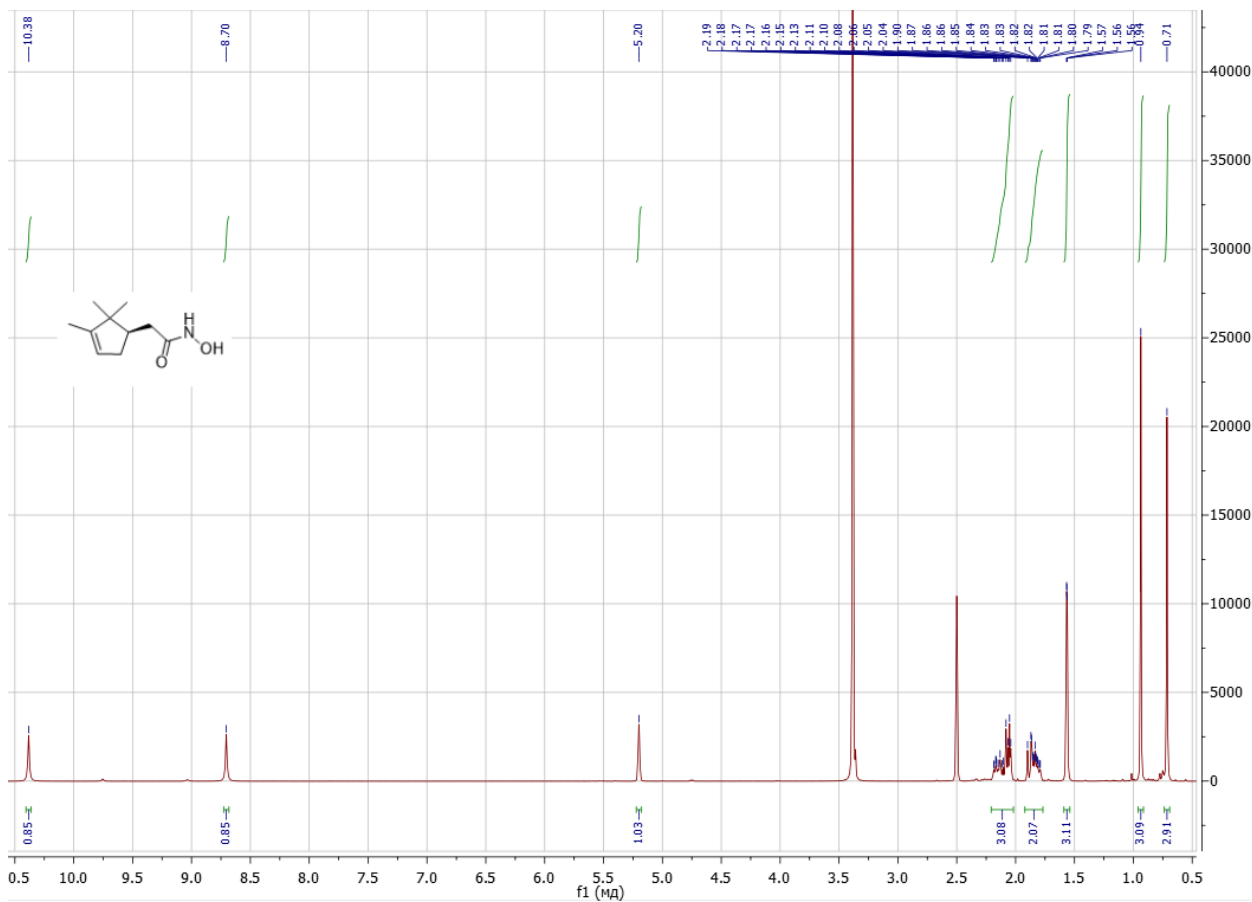


Mass-spectrum of compound **10**

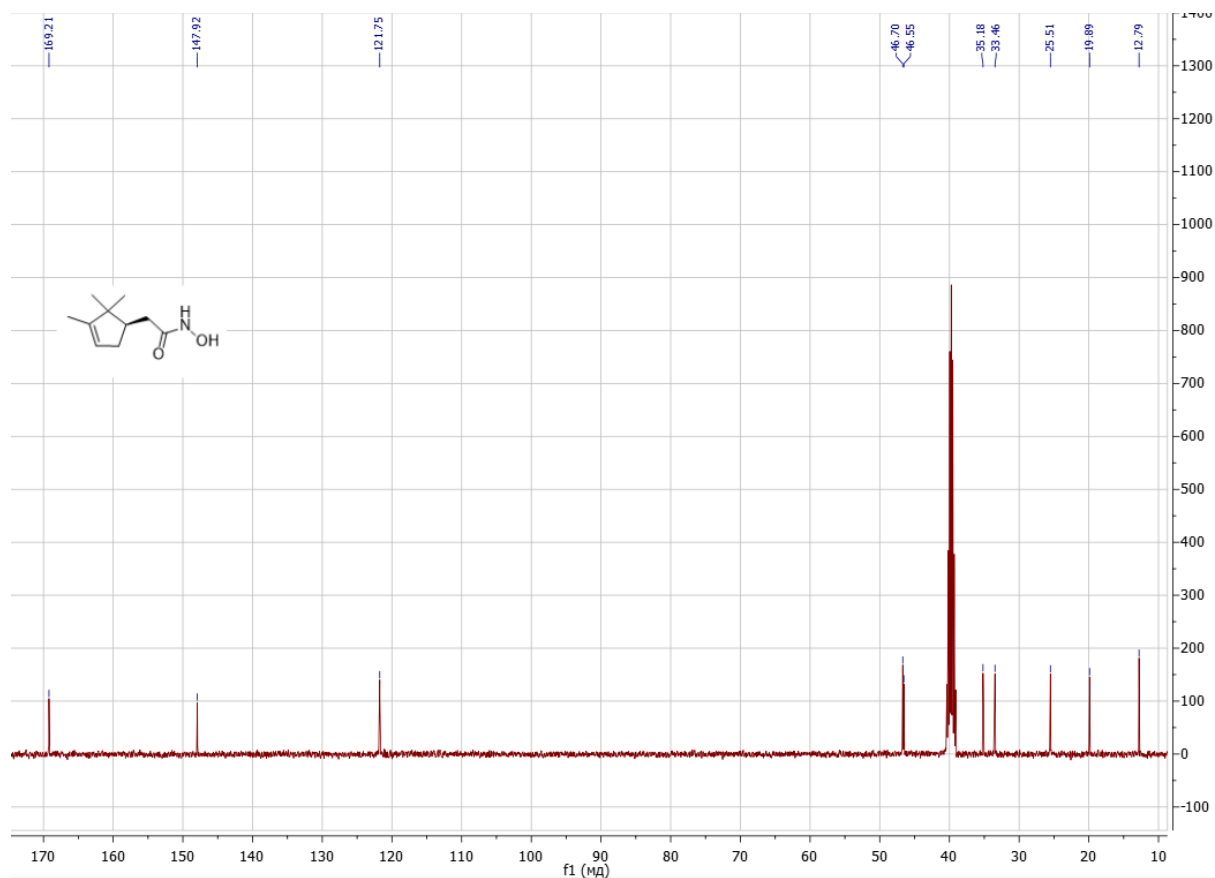
MS-329_200507184822 #13 RT: 0.76 AV: 1 NL: 5.00E6
T: + c EI Full ms [14.50-220.50]



¹H NMR spectrum of compound (+)-**13**

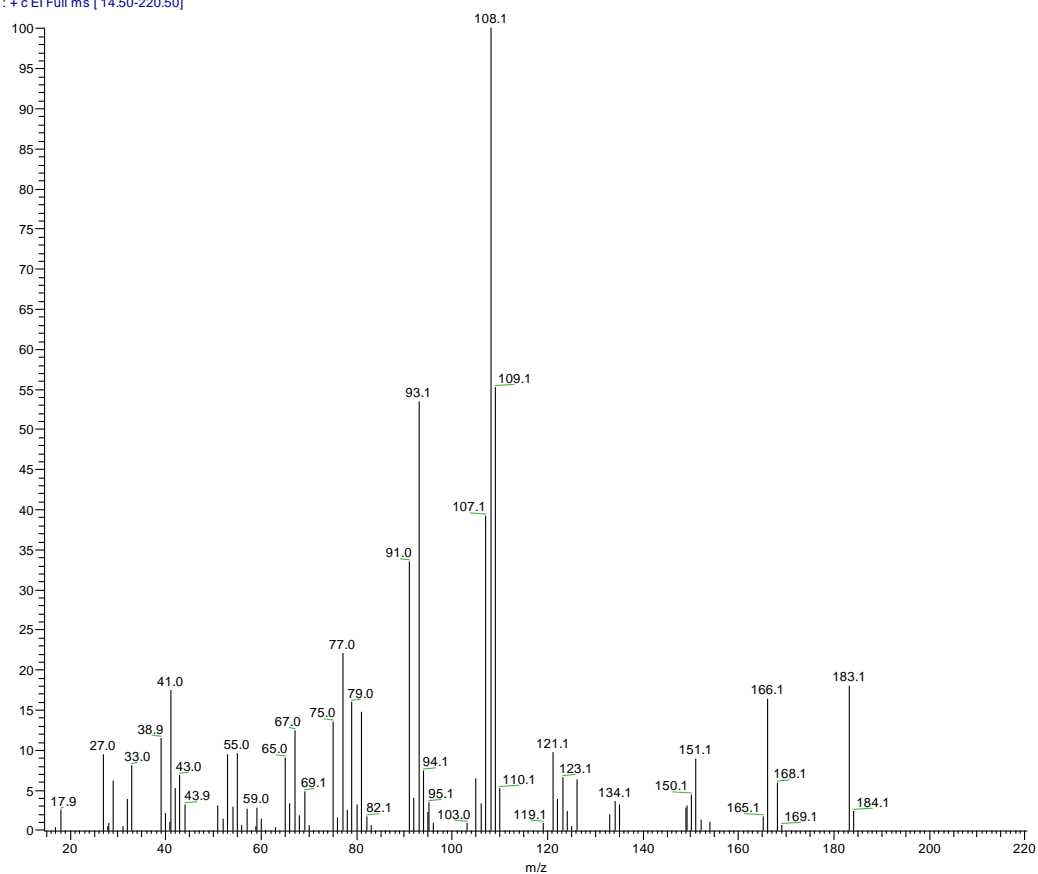


^{13}C NMR spectrum of compound (+)-13

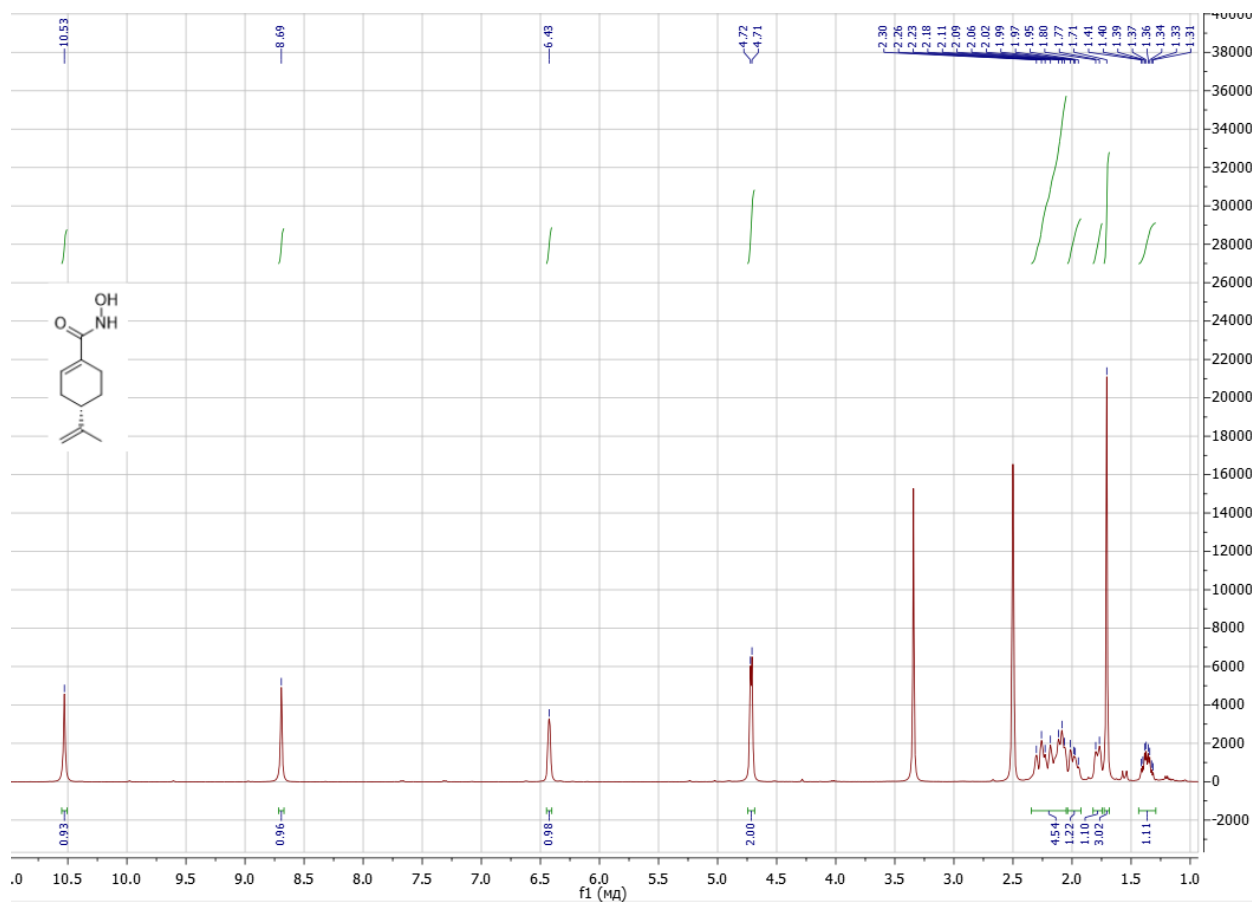


Mass-spectrum of compound (+)-13

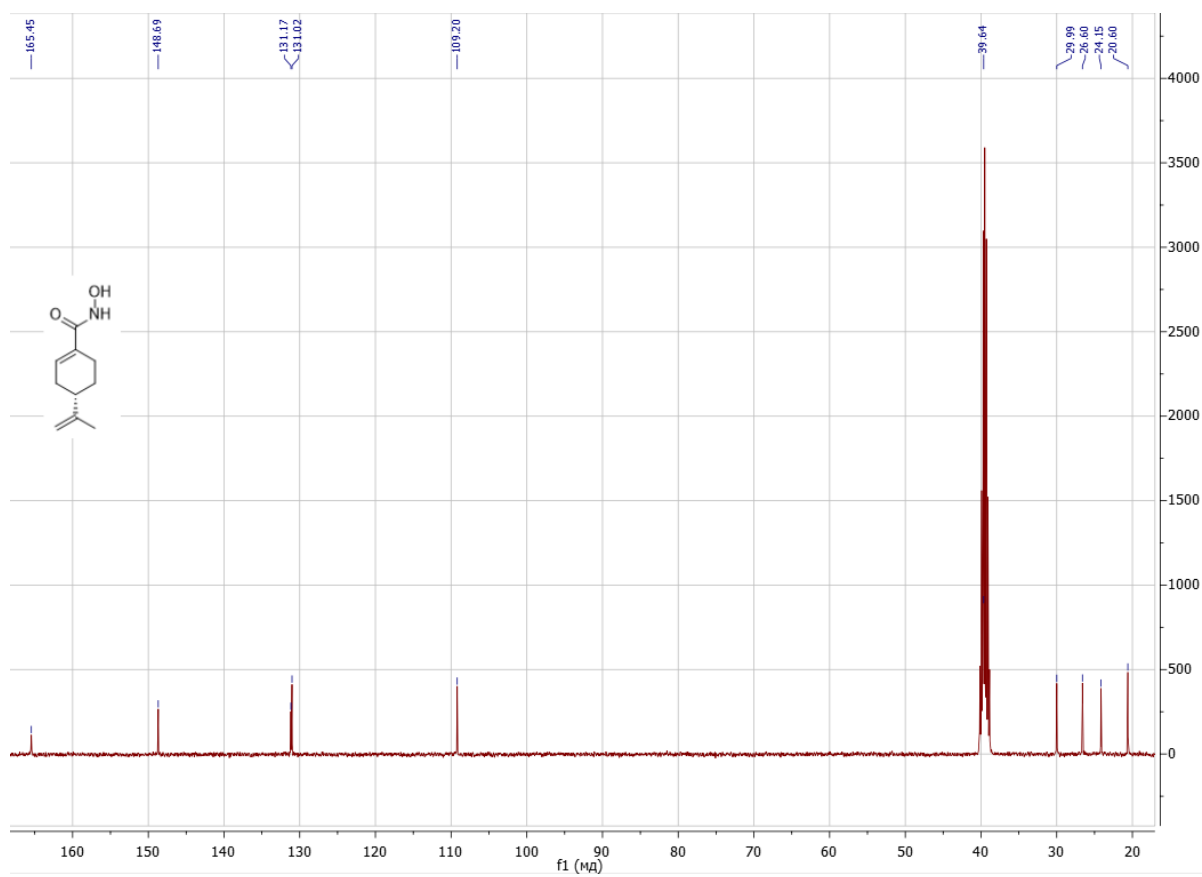
Ms-369 #10 RT: 0.57 AV: 1 NL: 2.01E6
T: + c EI Full ms [14.50-220.50]



¹H NMR spectrum of compound **16**

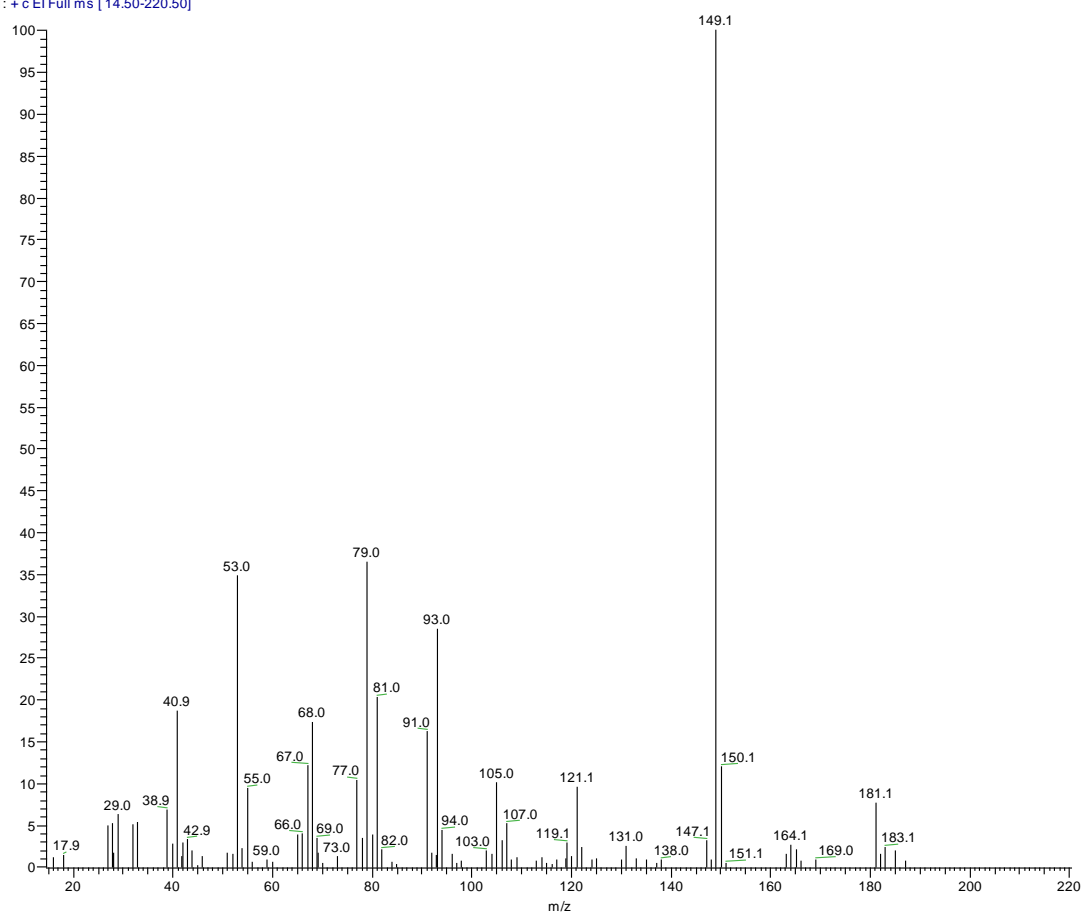


¹³C NMR spectrum of compound **16**

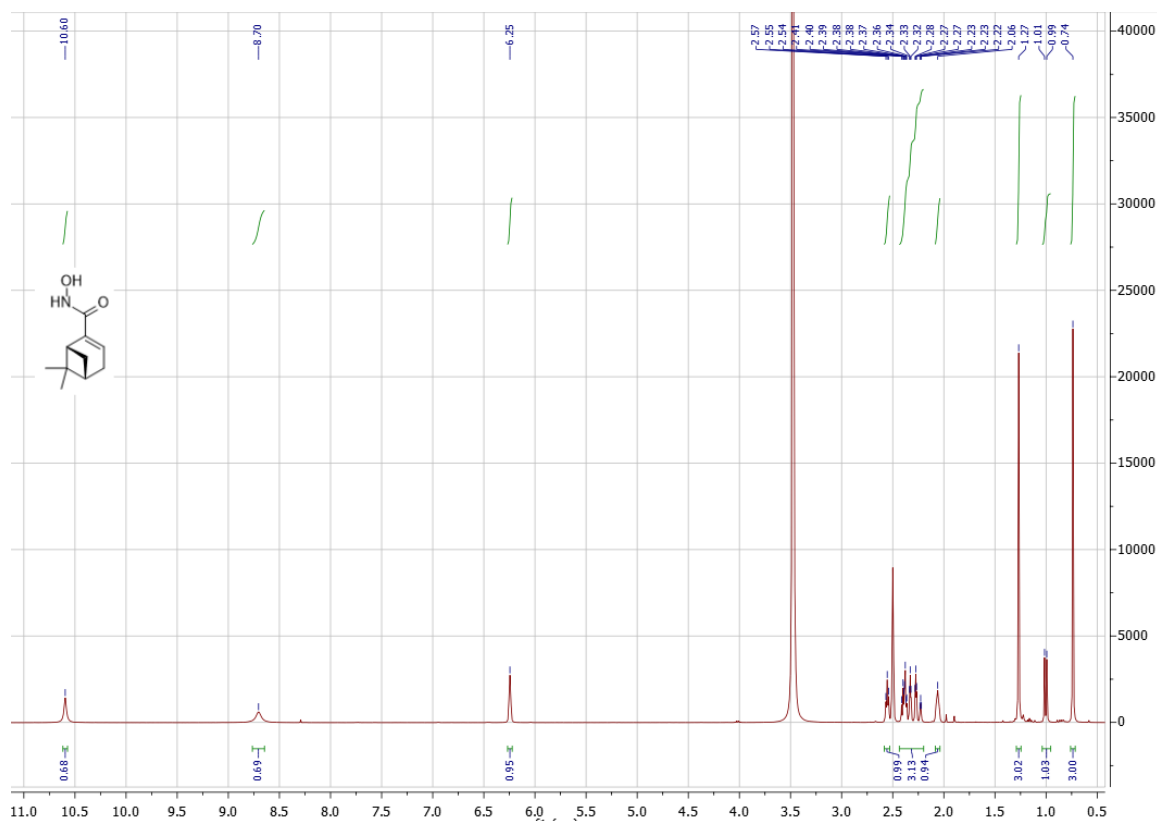


Mass-spectrum of compound **16**

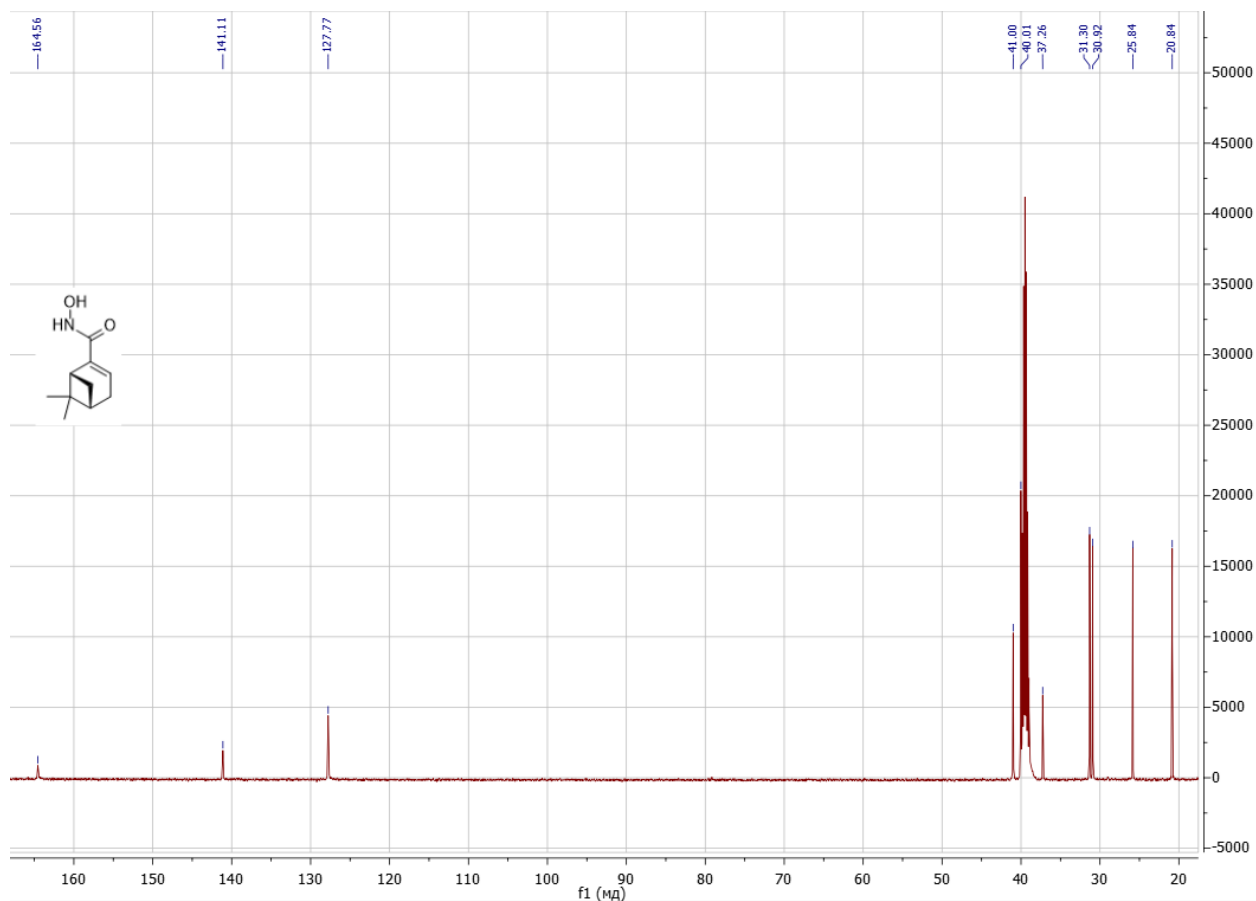
MS-333_pm #2 RT: 0.07 AV: 1 NL: 2.87E6
T: + c EI Full ms [14.50-220.50]



^1H NMR spectrum of compound (-)-**19**

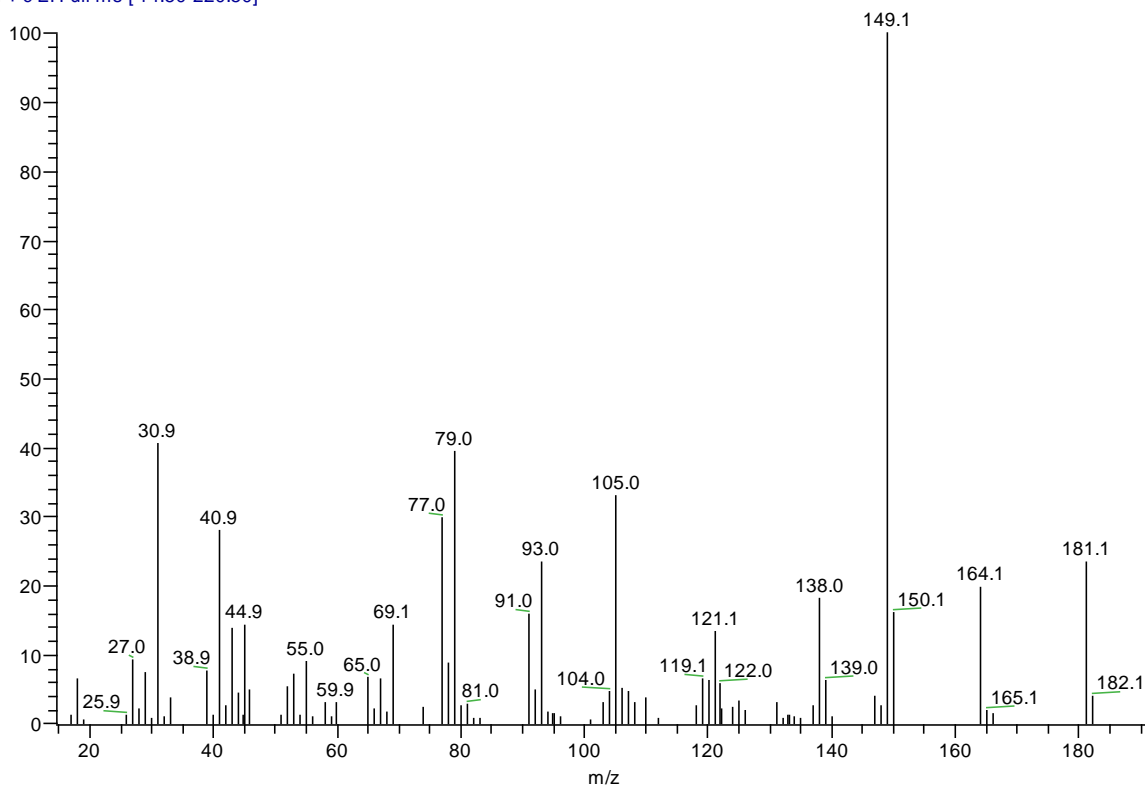


¹³C NMR spectrum of compound (-)-**19**

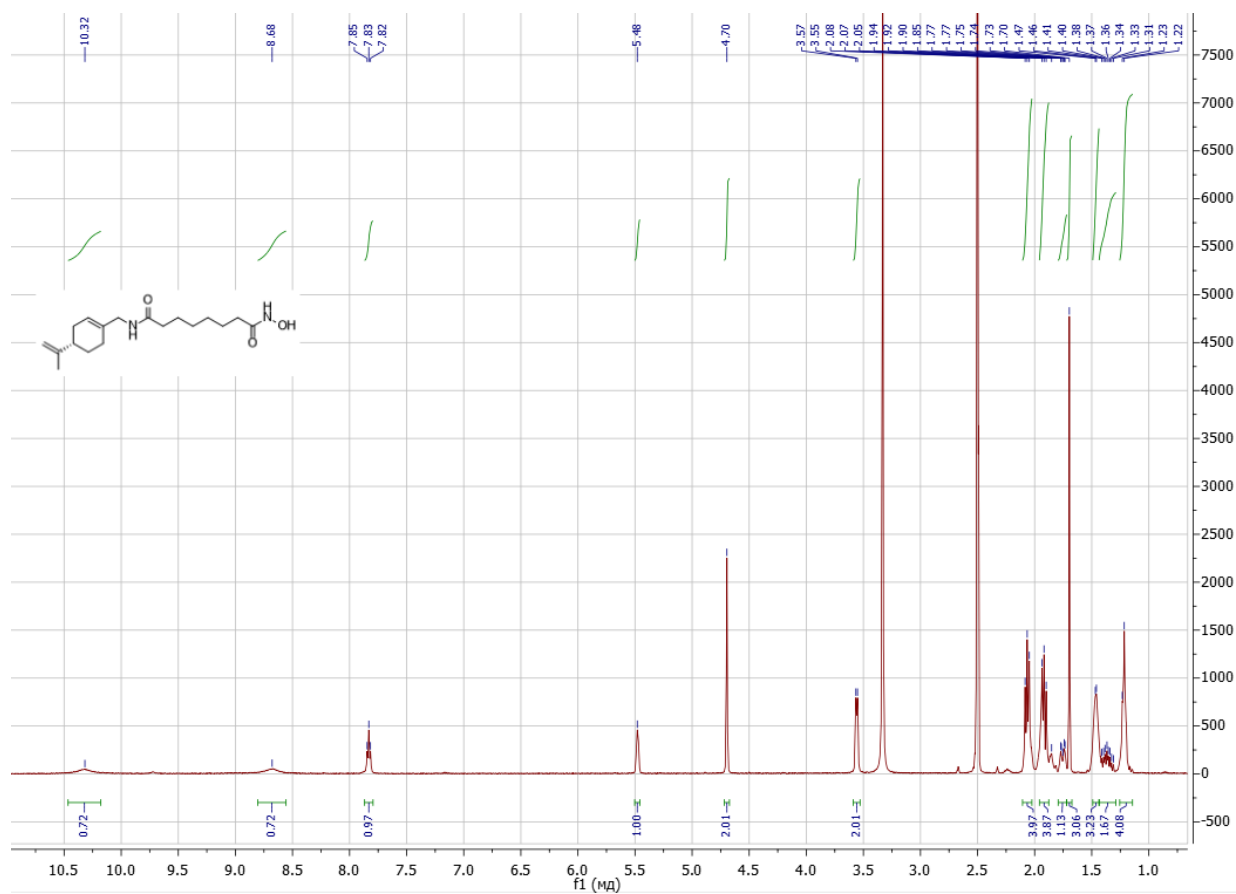


Mass-spectrum of compound (-)-**19**

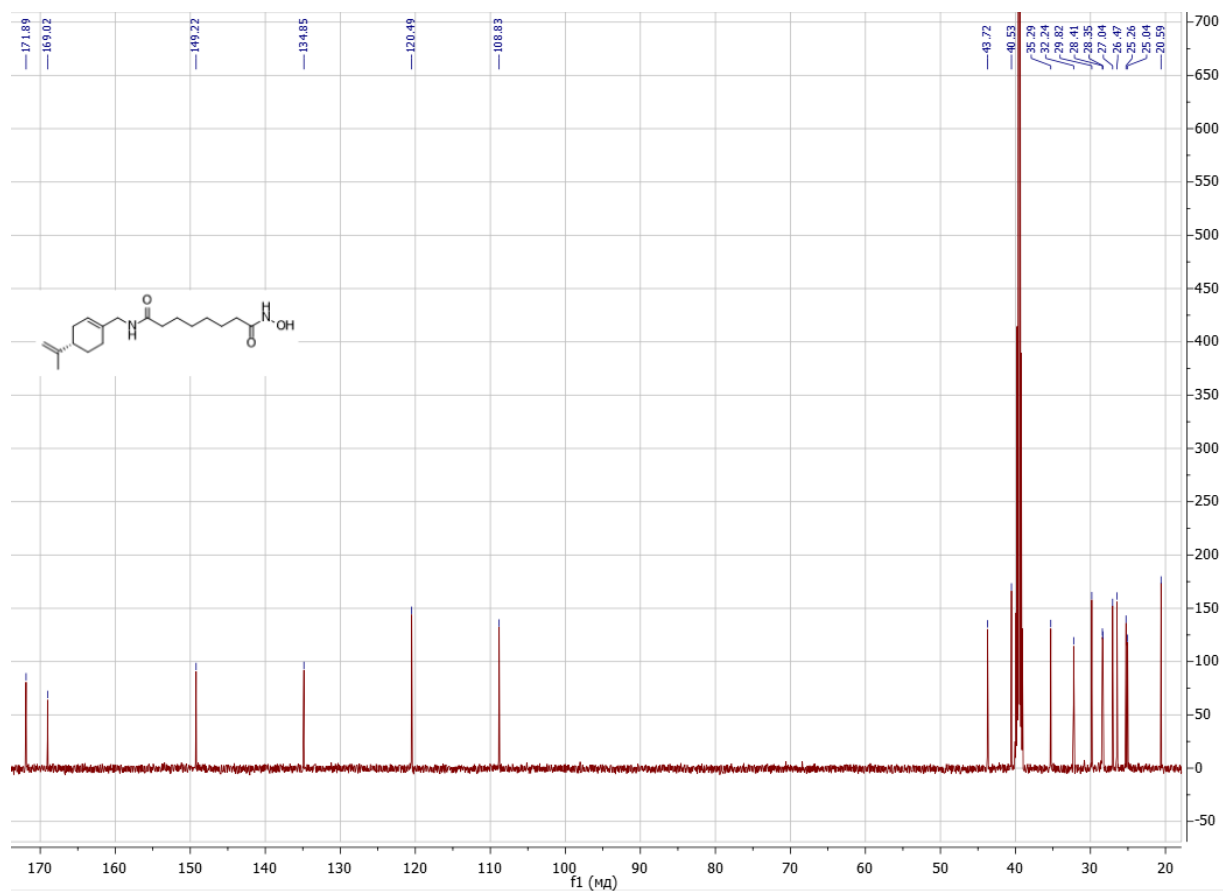
MS-316 #3 RT: 0.13 AV: 1 NL: 1.66E6
T: + c EI Full ms [14.50-220.50]



^1H NMR spectrum of compound **30**

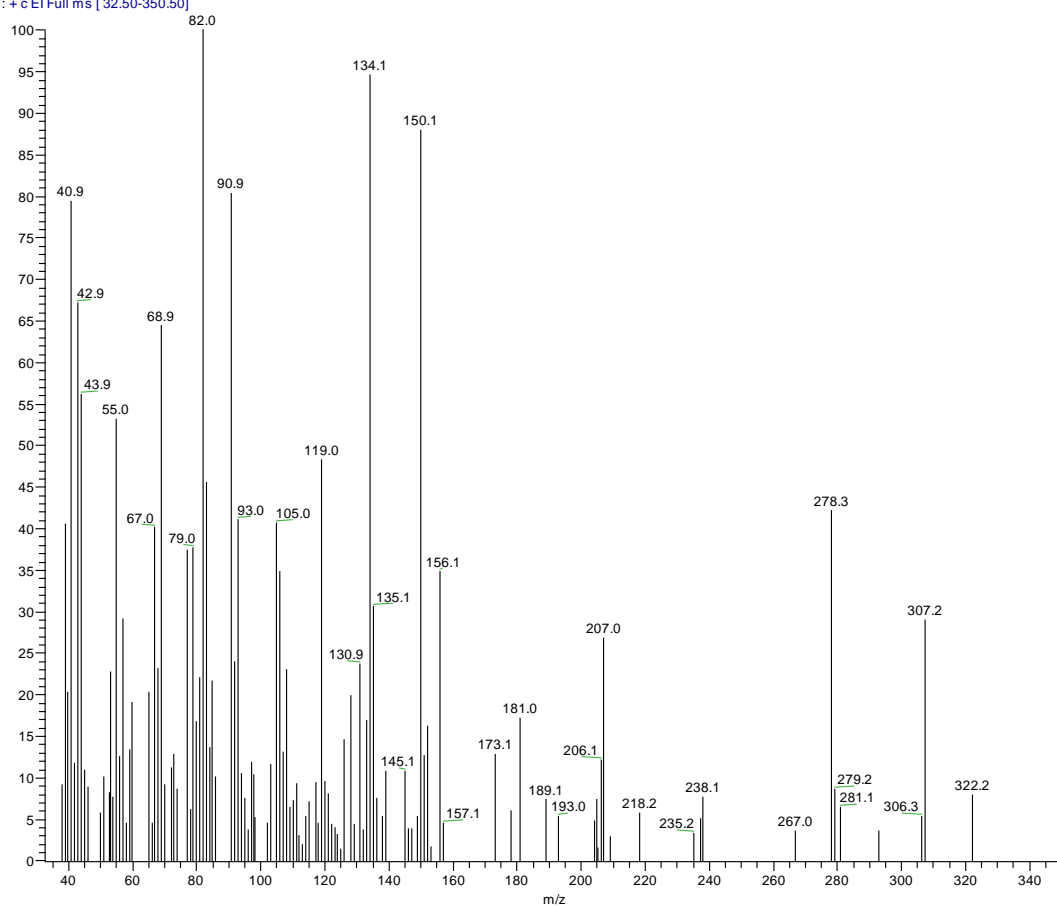


^{13}C NMR spectrum of compound **30**

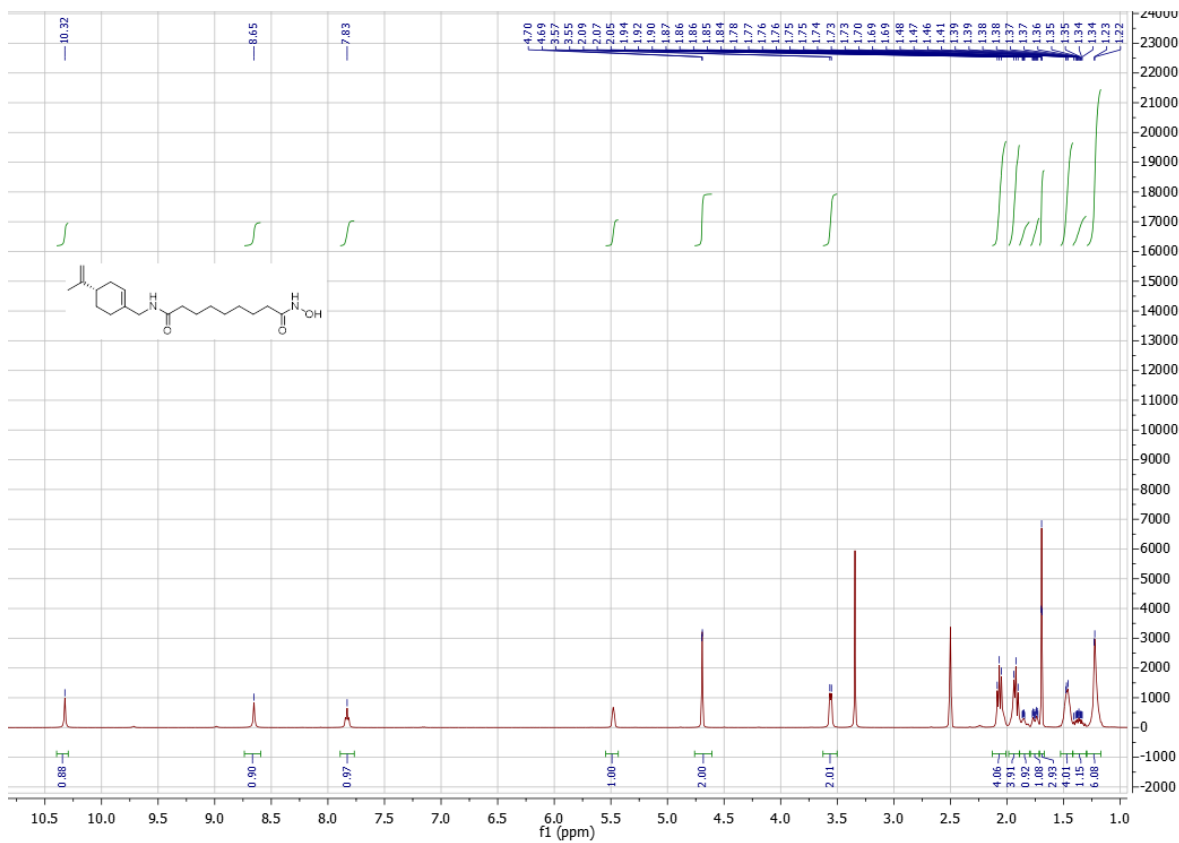


Mass-spectrum of compound **30**

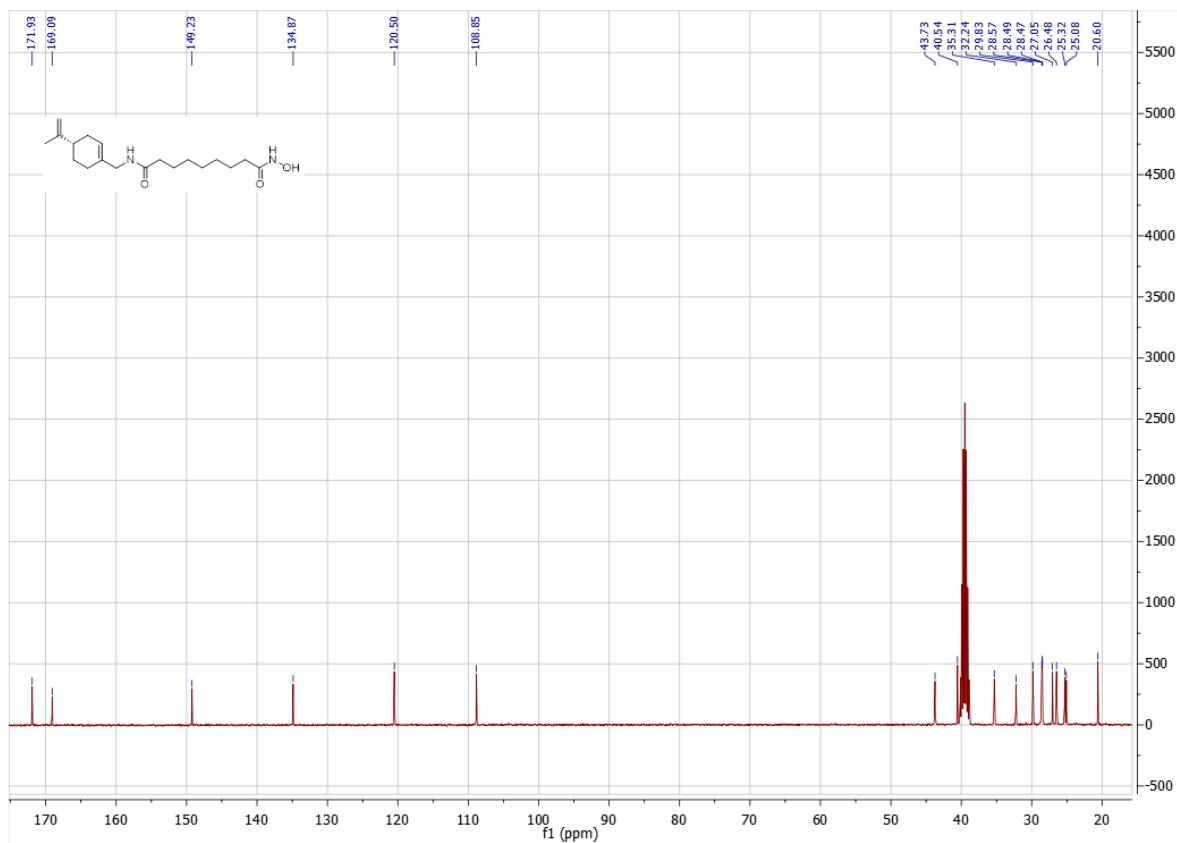
ms-469 #38 RT: 2.48 AV: 1 NL: 4.79E4
T: + c EI Full ms [32.50-350.50]



^1H NMR spectrum of compound **31**

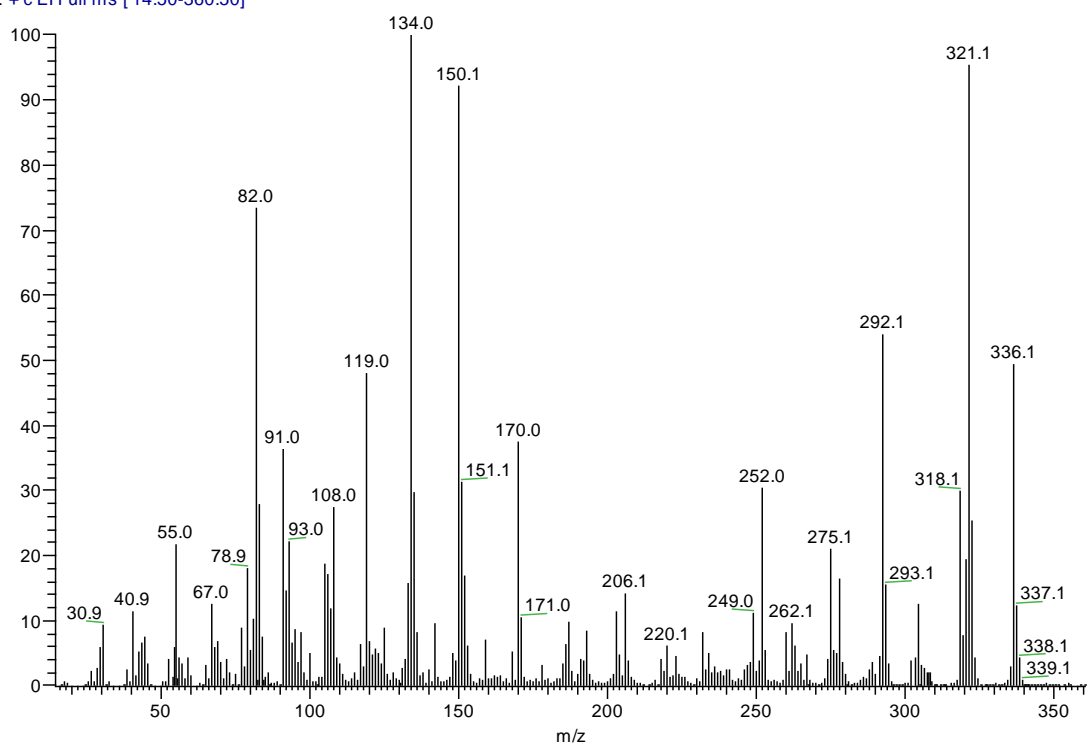


^{13}C NMR spectrum of compound **31**

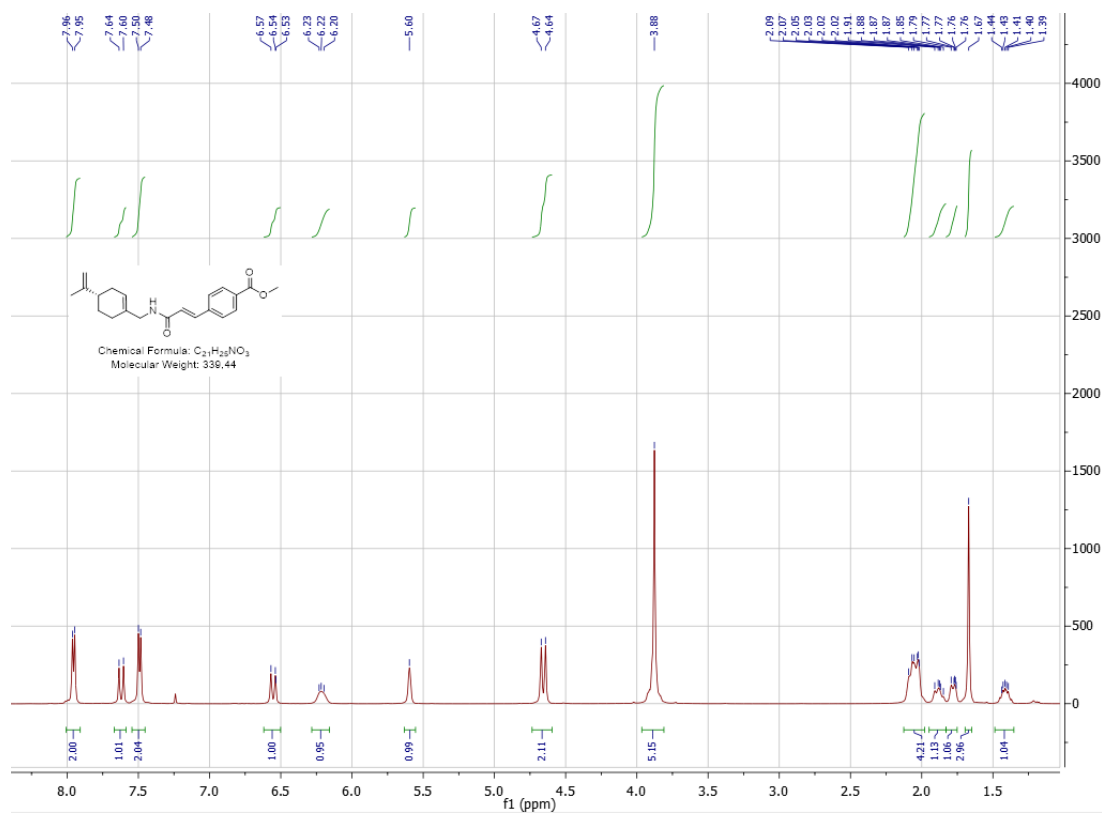


Mass-spectrum of compound **31**

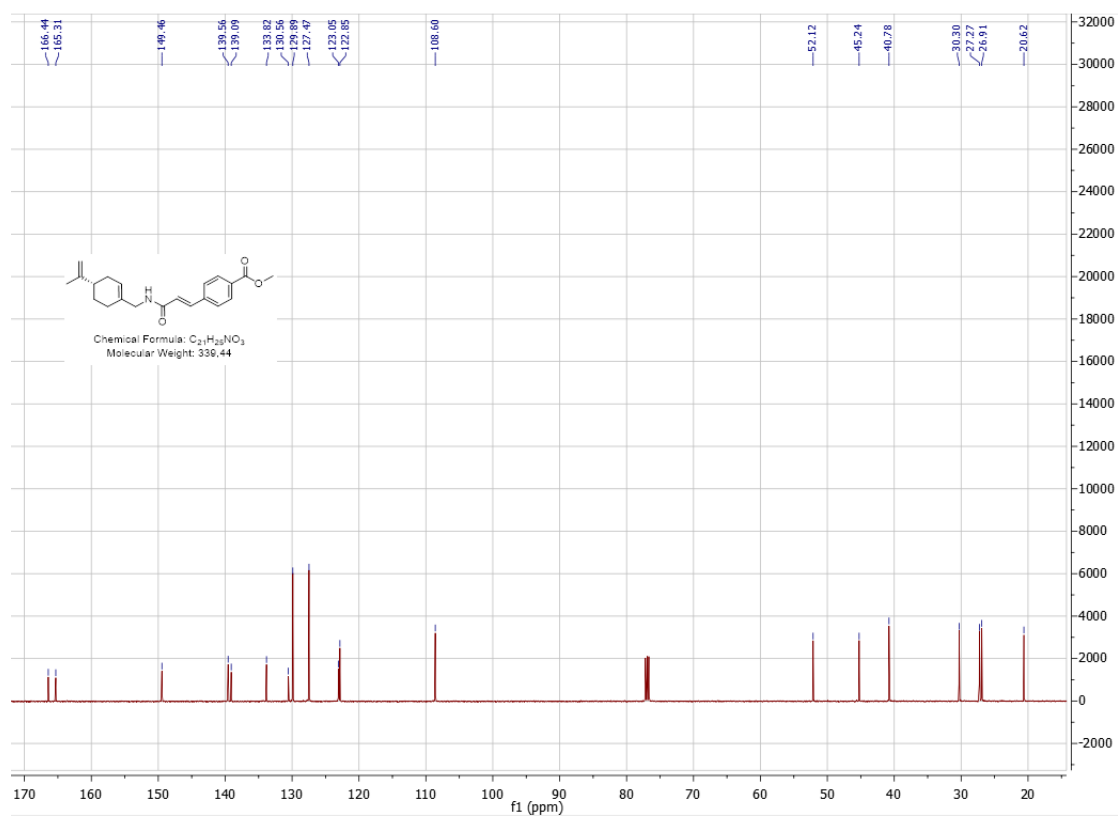
maa-497 #9 RT: 0.59 AV: 1 NL: 1.96E6
T: + c EI Full ms [14.50-360.50]



¹H NMR spectrum of compound **34a**

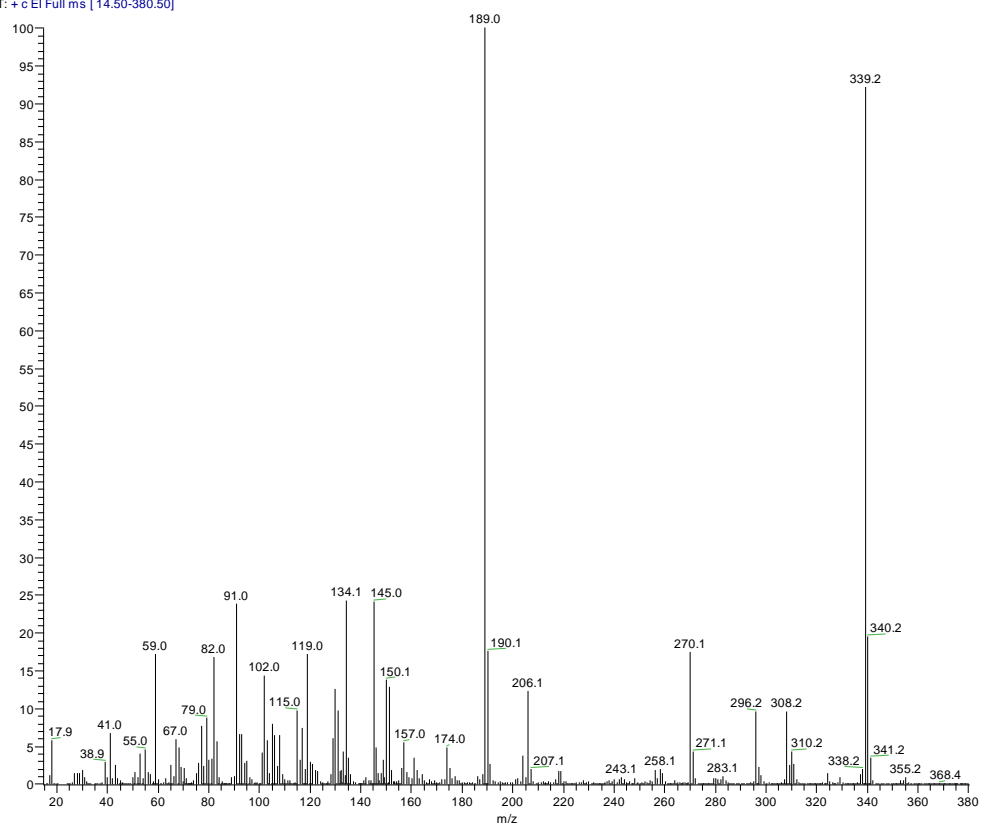


¹³C NMR spectrum of compound **34a**

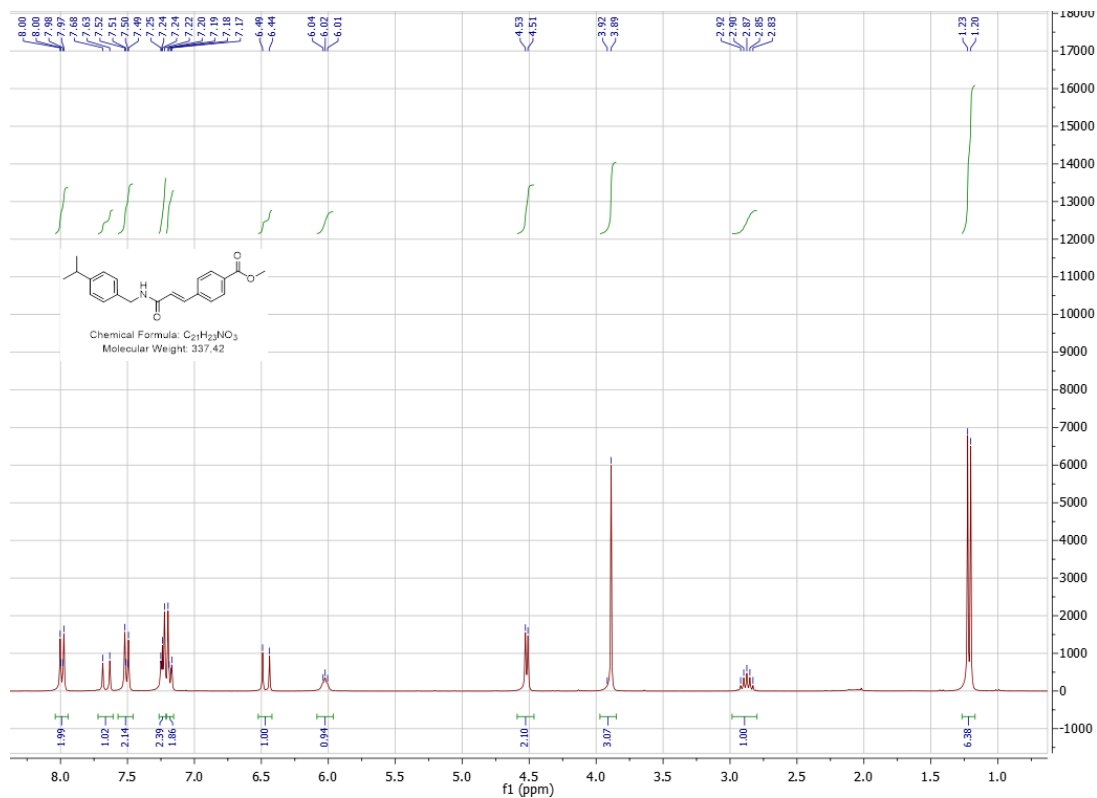


Mass-spectrum of compound **34a**

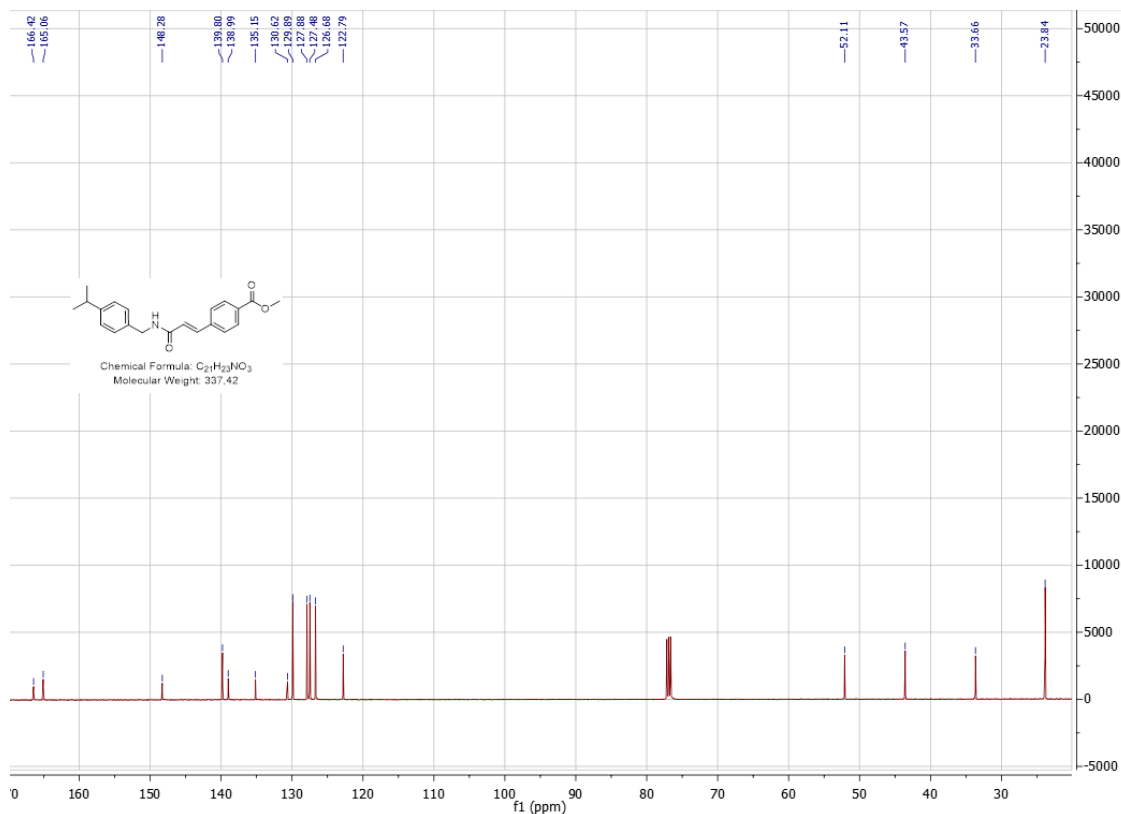
maa-493_210420153254 #4 RT: 0.23 AV: 1 NL: 4.49E7
T: + c EI Full ms [14.50-380.50]



¹H NMR spectrum of compound **34b**

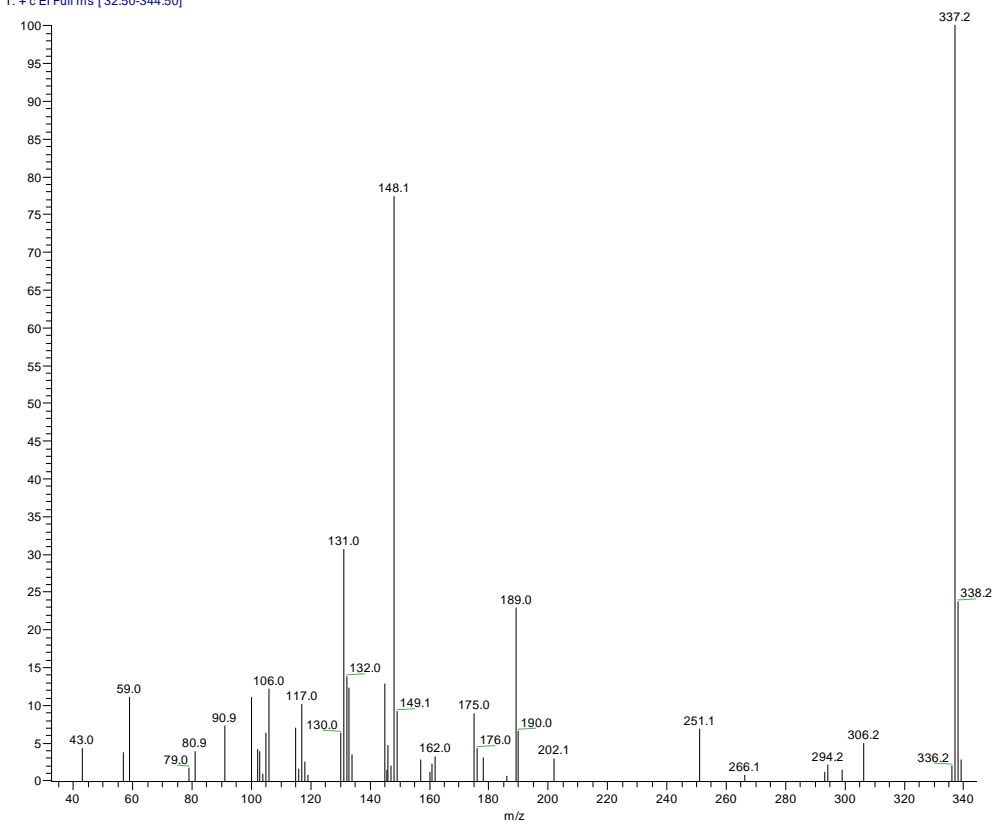


^{13}C NMR spectrum of compound **34b**

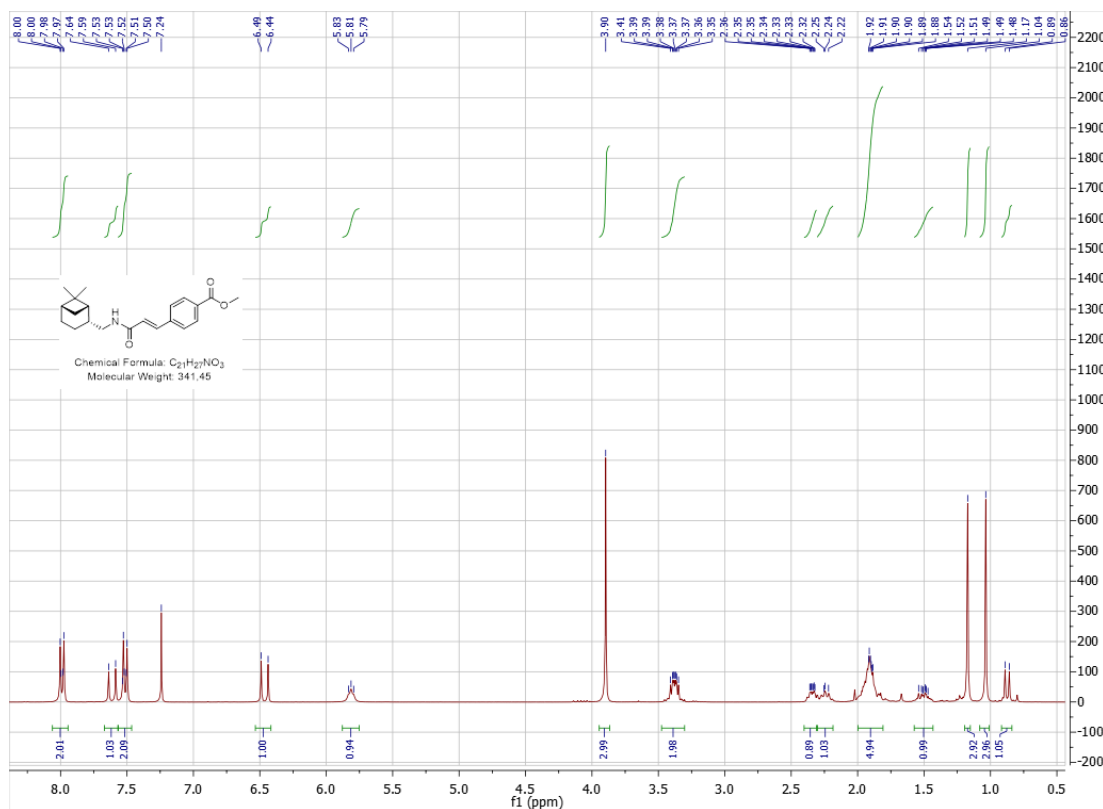


Mass-spectrum of compound **34b**

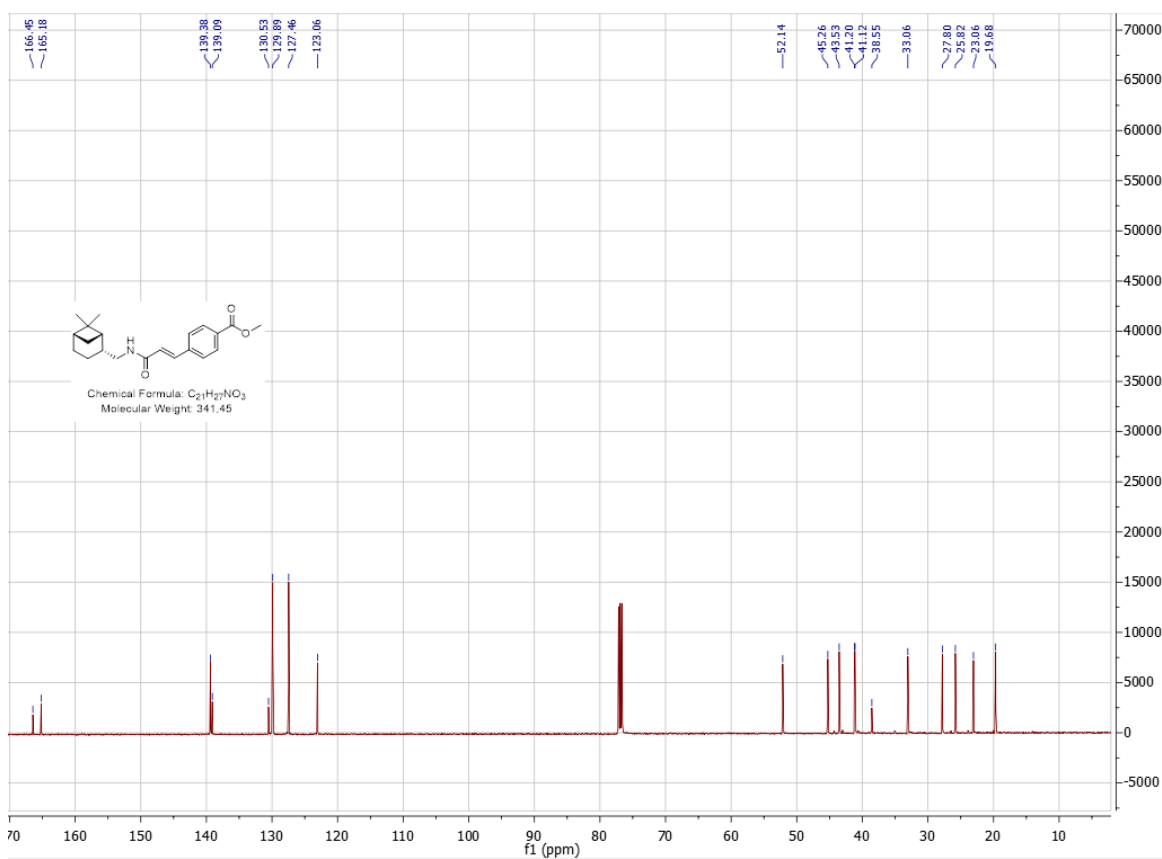
maa-596_220722155927 #2 RT: 0.06 AV: 1 NL: 1.17E5
T: + c EI Full ms [32.50-344.50]



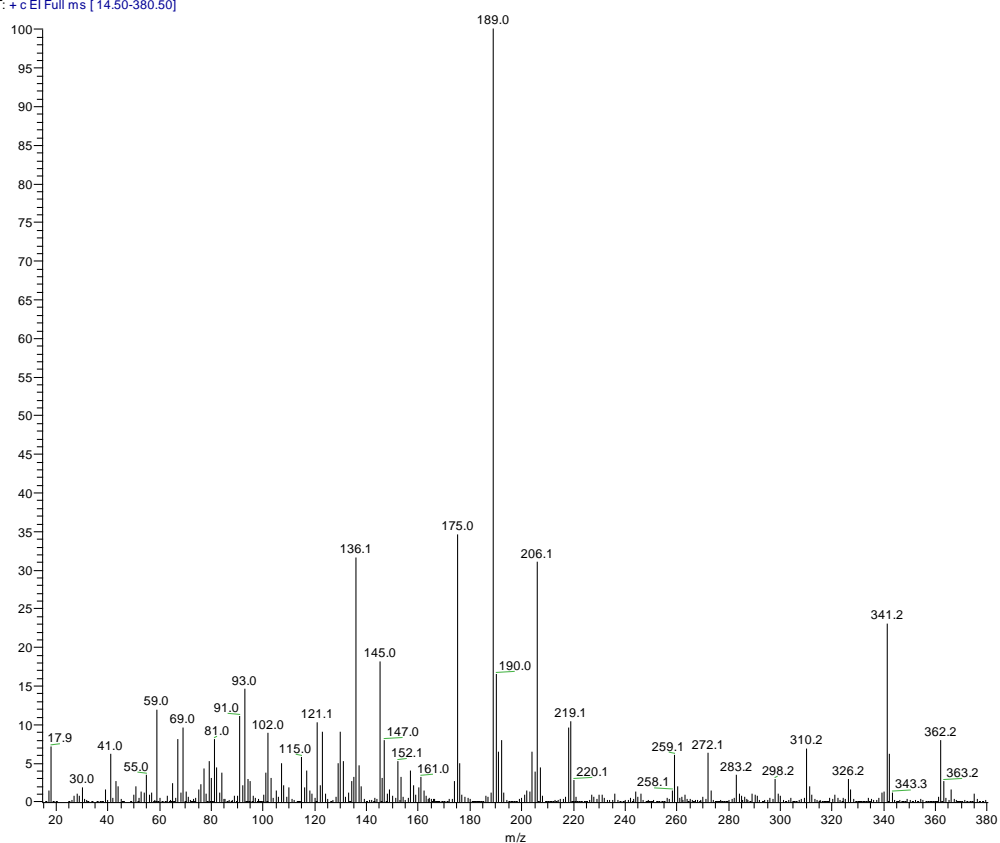
¹H NMR spectrum of compound **34c**



¹³C NMR spectrum of compound **34c**



maa-583 #24 RT: 1.69 AV: 1 NL: 9.60E6
T: + c EI Full ms [14.50-380.50]



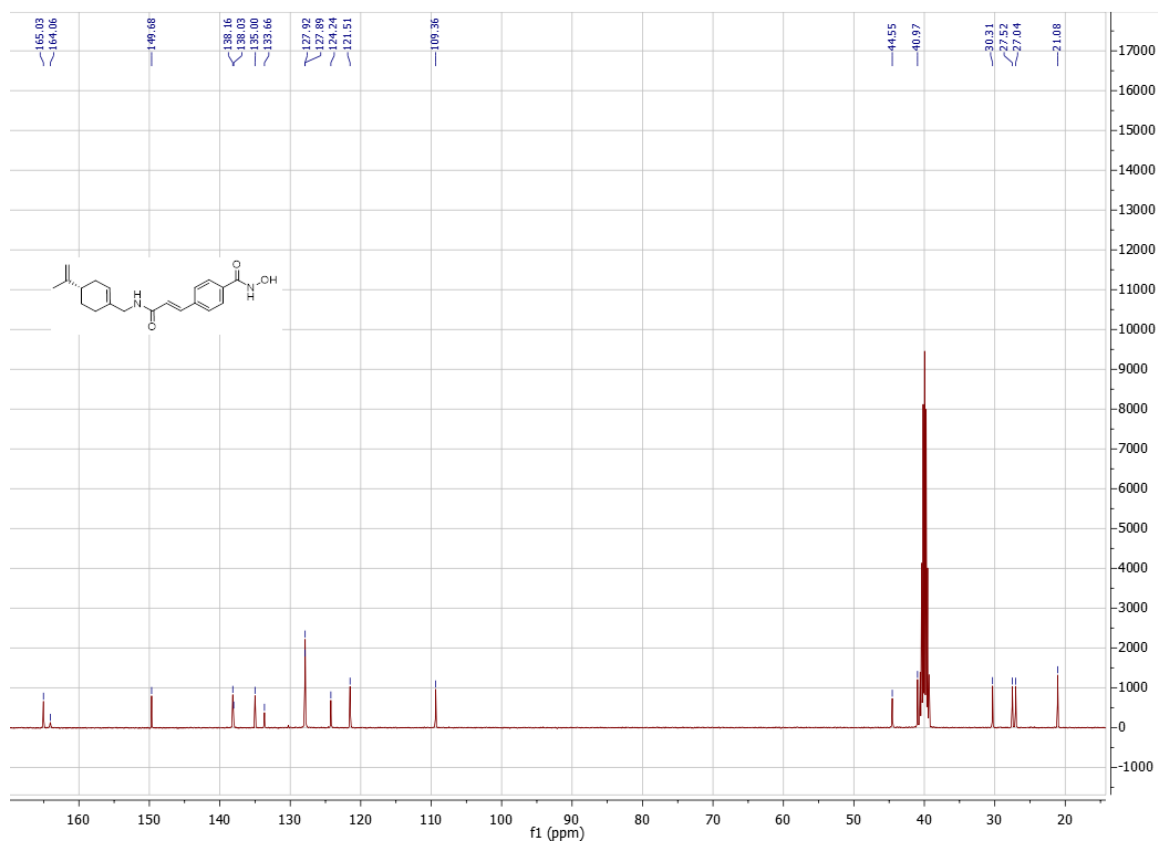
CC1=CC=C(C=C1)C(=O)NCC2=CC=CC=C2C(=O)N

11.28
9.11
8.26
8.25
8.23
7.79
7.75
7.63
7.61
7.48
7.44
6.78
6.74
5.55
5.54
4.70
4.68
3.72
3.22
2.50
2.50
2.50
2.07
2.06
2.00
1.96
1.91
1.85
1.87
1.80
1.79
1.78
1.78
1.76
1.75
1.75
1.74
1.69
1.61
1.40
1.37
1.36
1.35

0.83
0.82
0.94
1.94
2.02
1.90
0.97
0.98
2.03
1.98
4.05
1.00
2.94
1.00

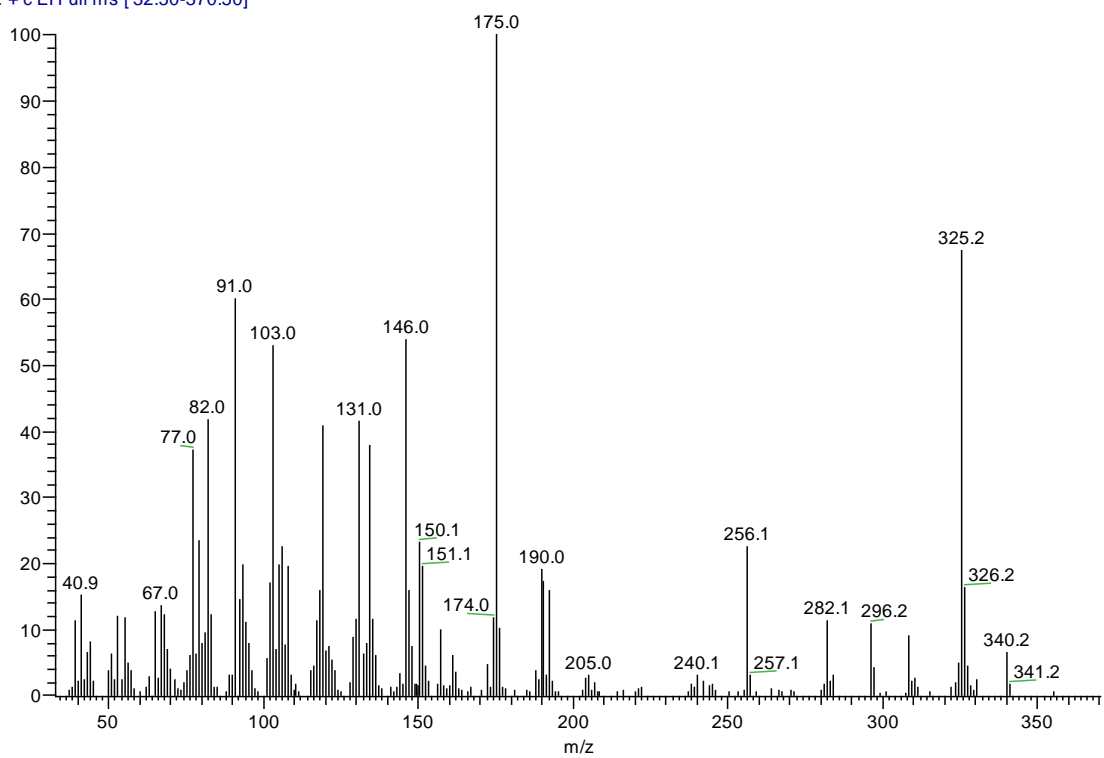
f1 (ppm)

^{13}C NMR spectrum of compound **35a**

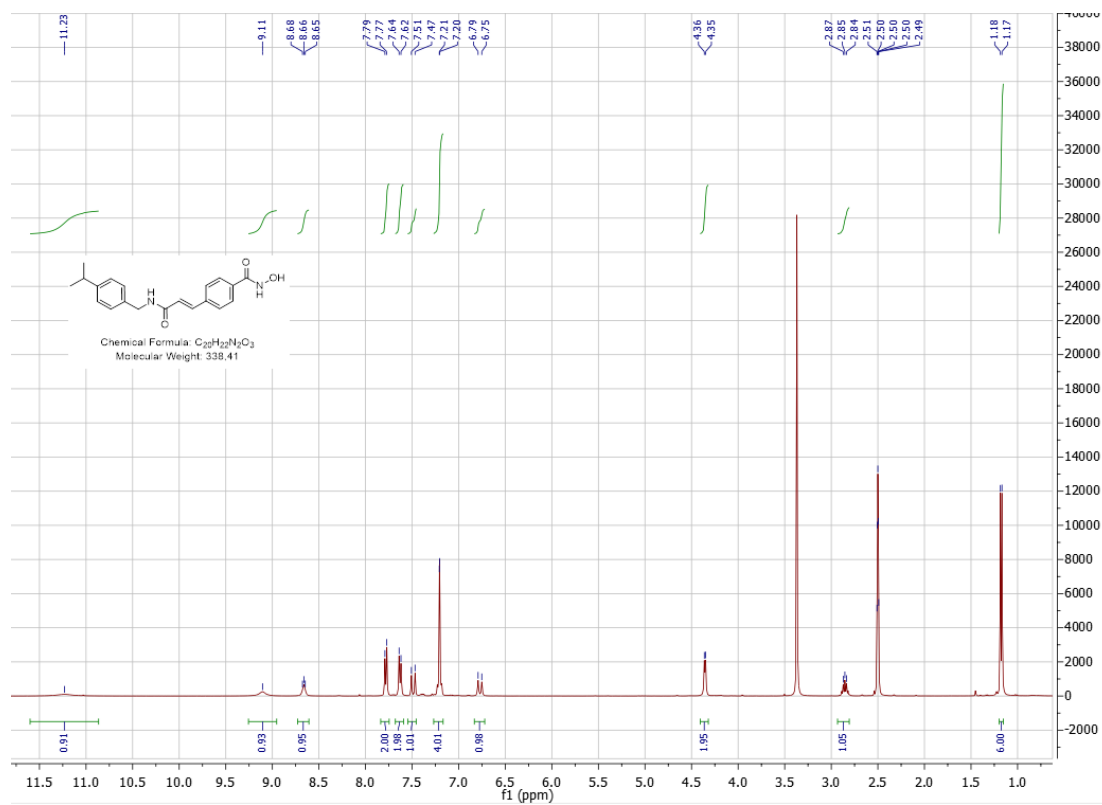


Mass-spectrum of compound **35a**

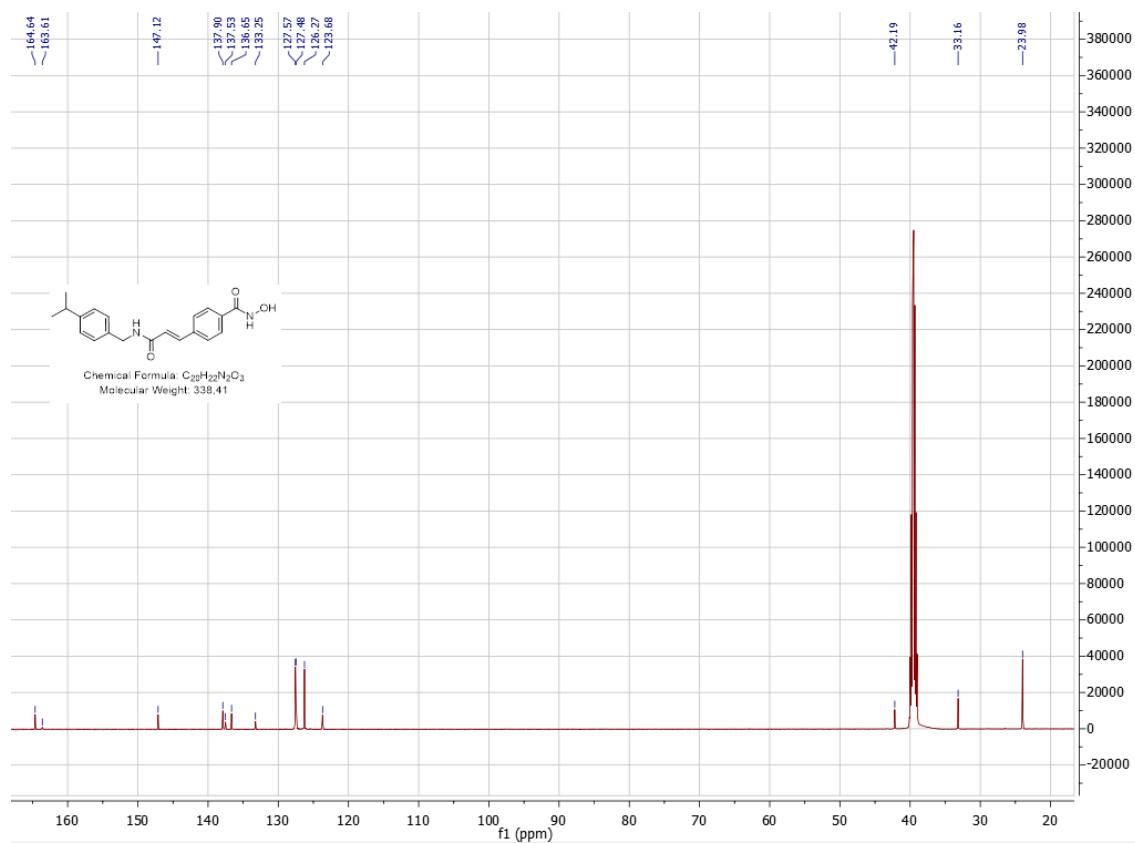
maa-496_210420161232 #9 RT: 0.53 AV: 1 NL: 3.82E5
T: + c EI Full ms [32.50-370.50]



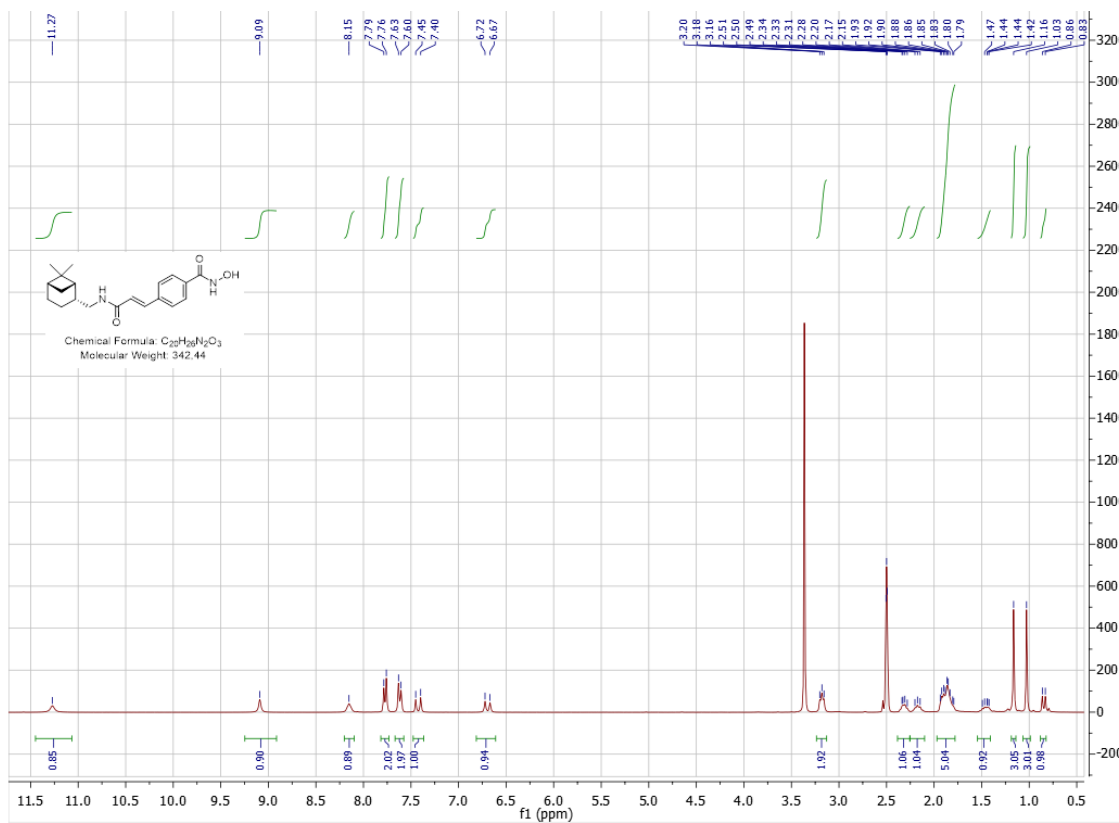
¹H NMR spectrum of compound **35b**



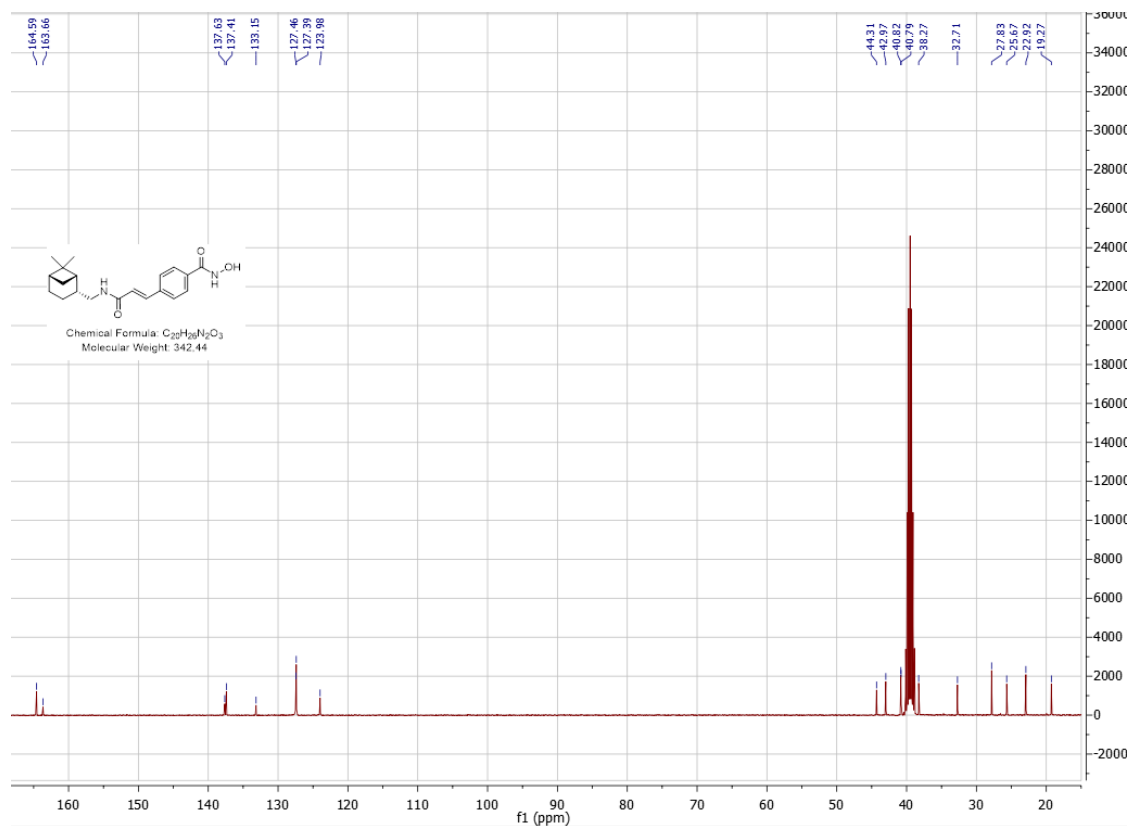
¹³C NMR spectrum of compound **35b**



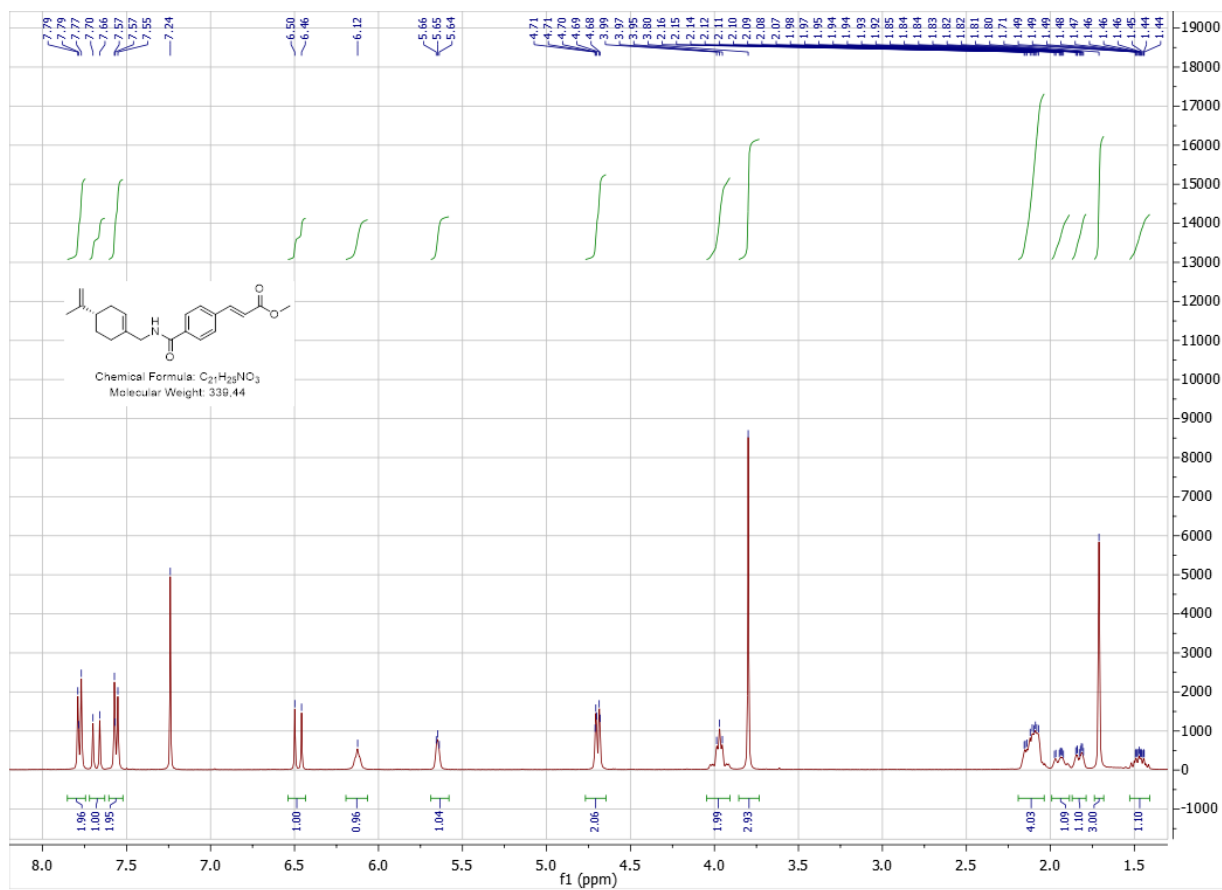
¹H NMR spectrum of compound **35c**



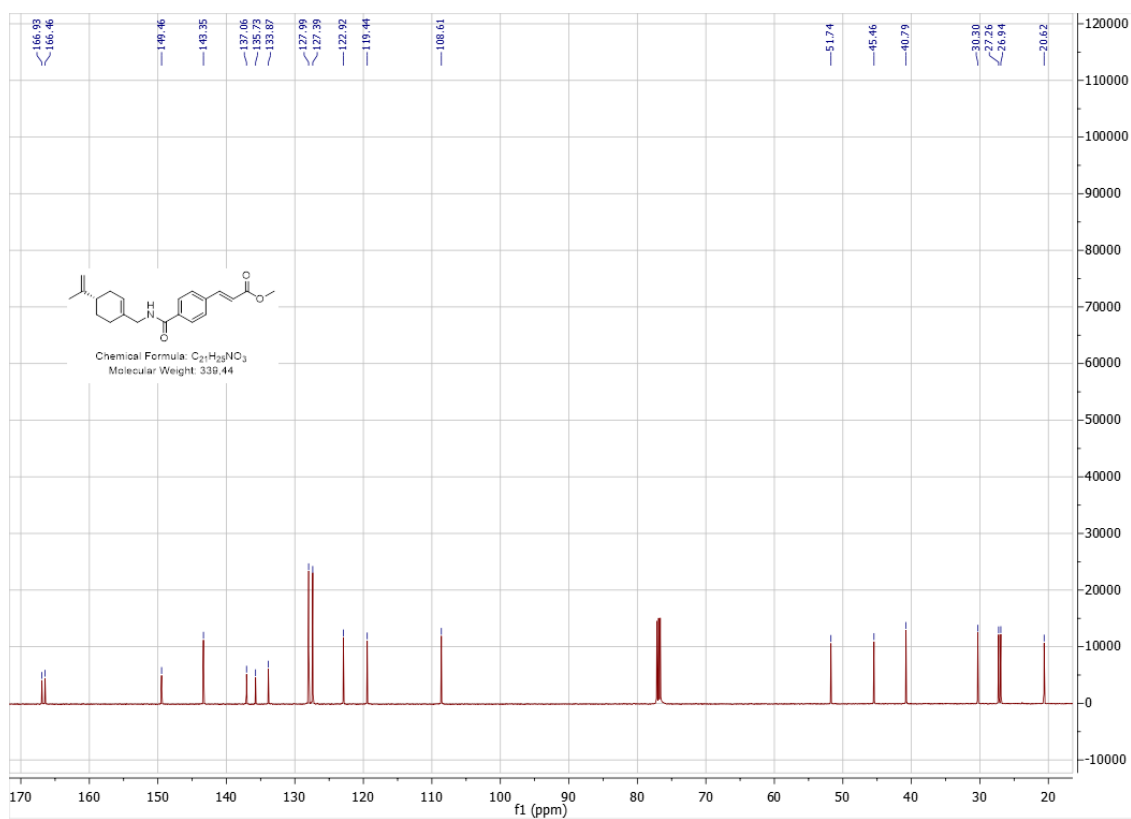
¹³C NMR spectrum of compound **35c**



¹H NMR spectrum of compound **37a**

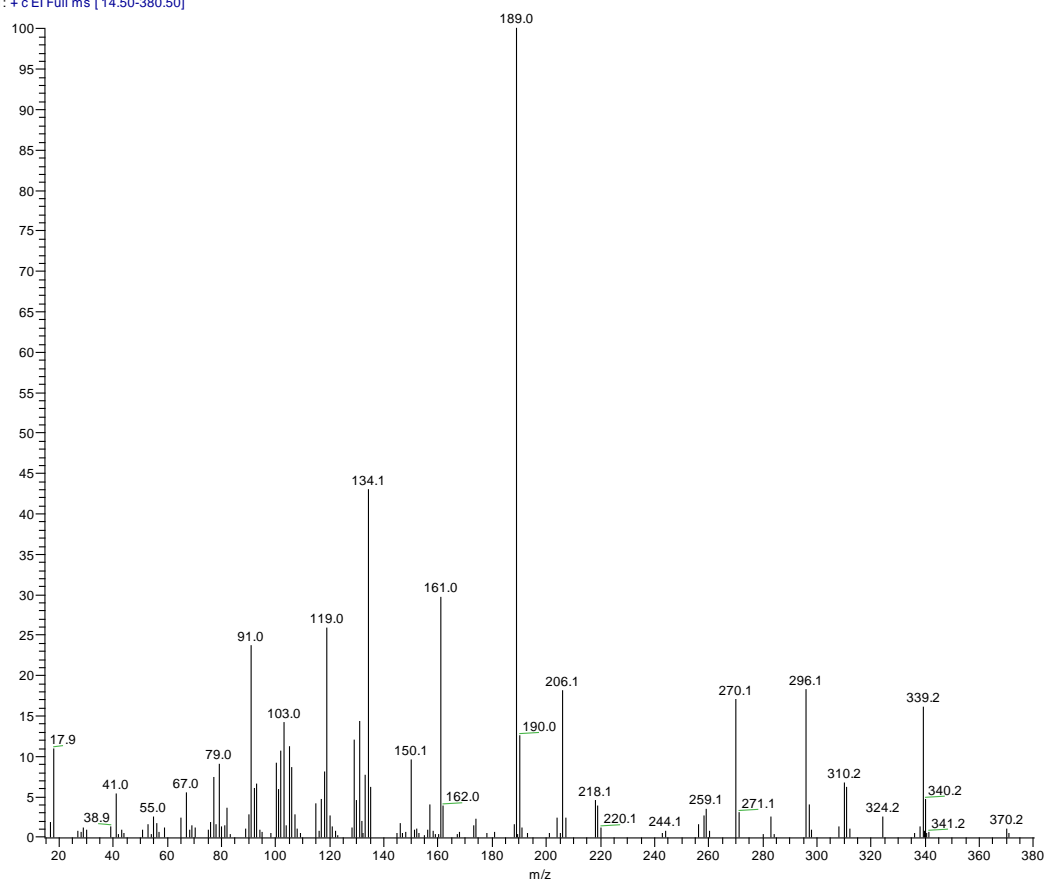


¹³C NMR spectrum of compound **37a**

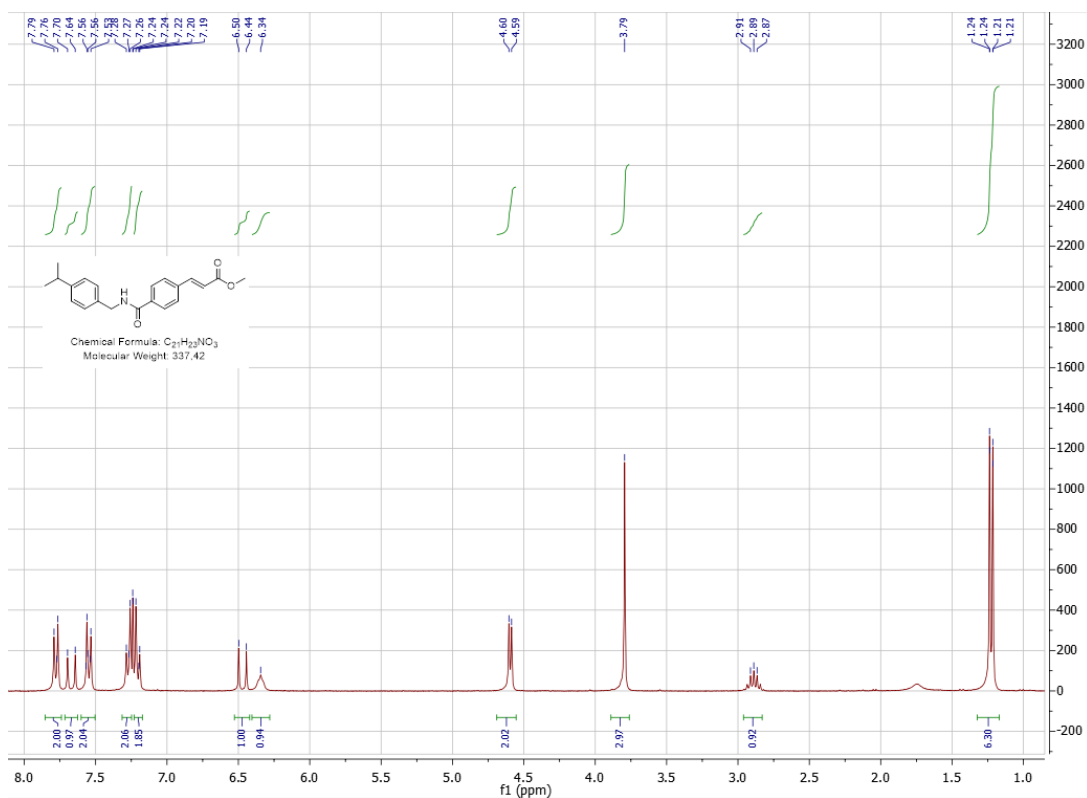


Mass-spectrum of compound **37a**

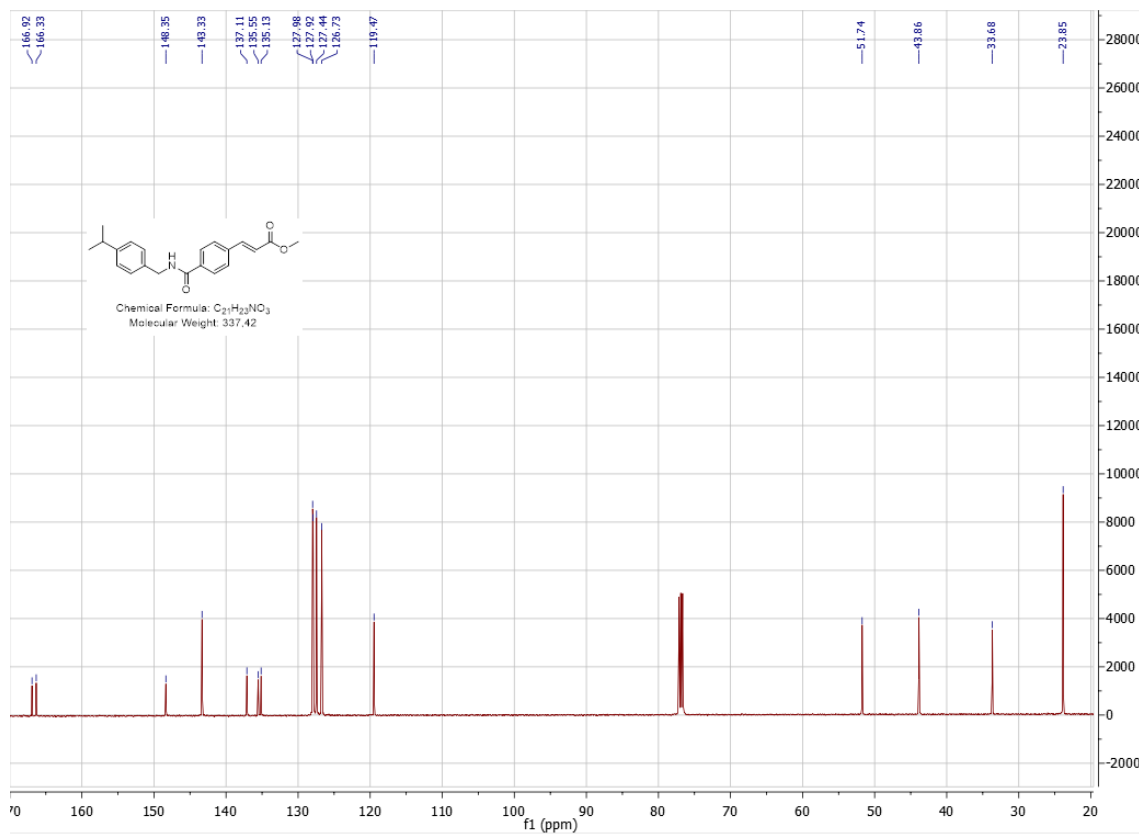
maa-604 #1 RT: 0.00 AV: 1 NL: 9.02E5
T: + c EI Full ms [14.50-380.50]



^1H NMR spectrum of compound **37b**

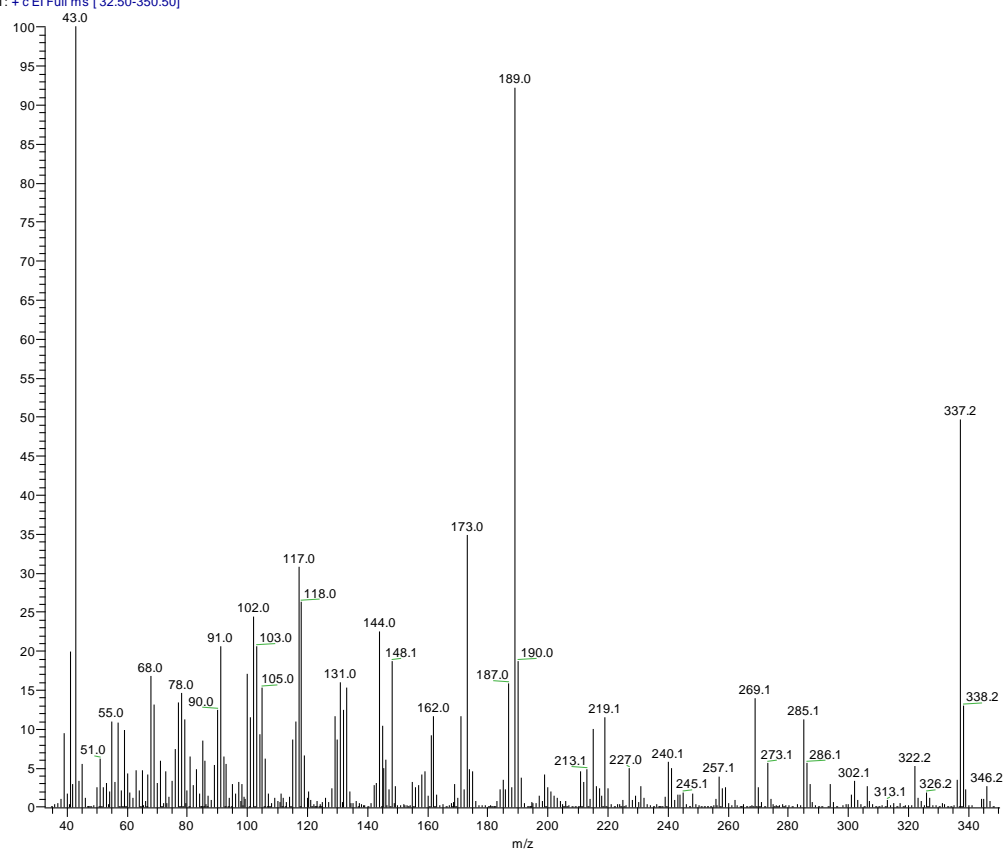


^{13}C NMR spectrum of compound **37b**

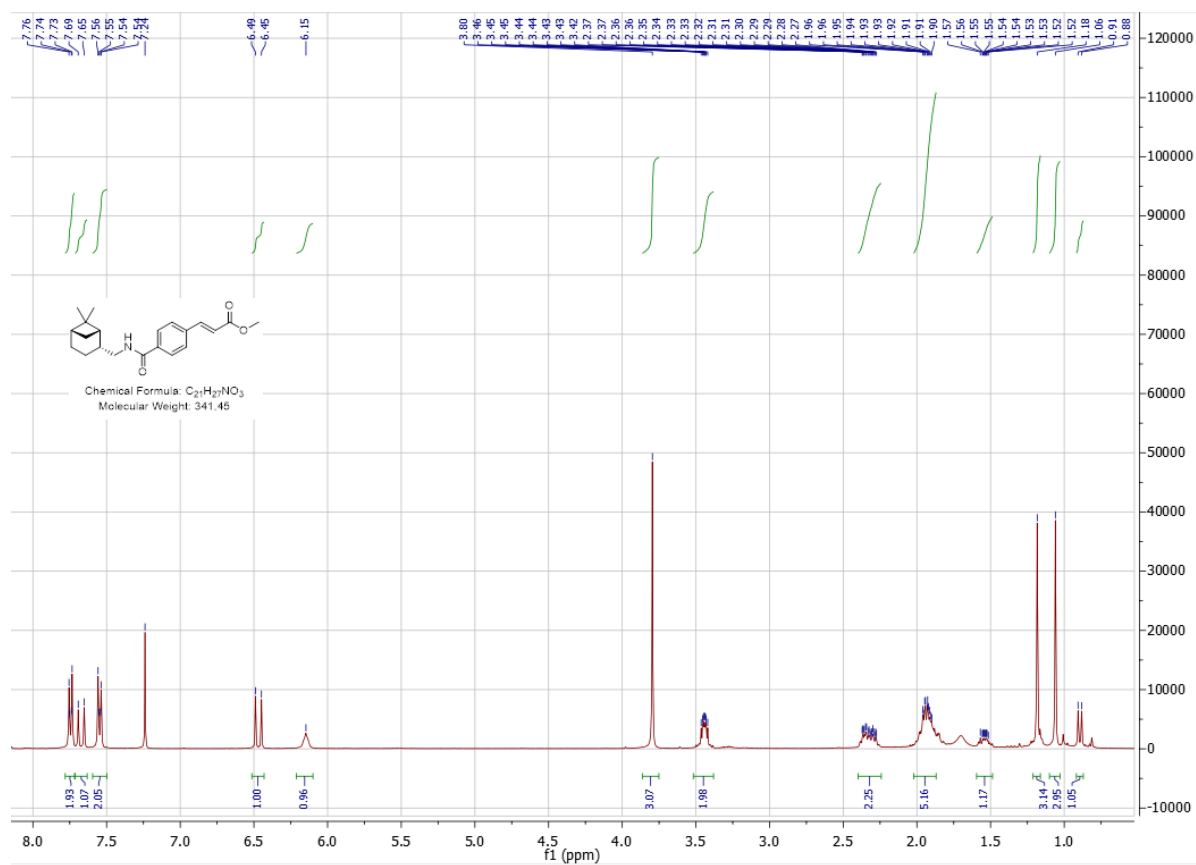


Mass-spectrum of compound **37b**

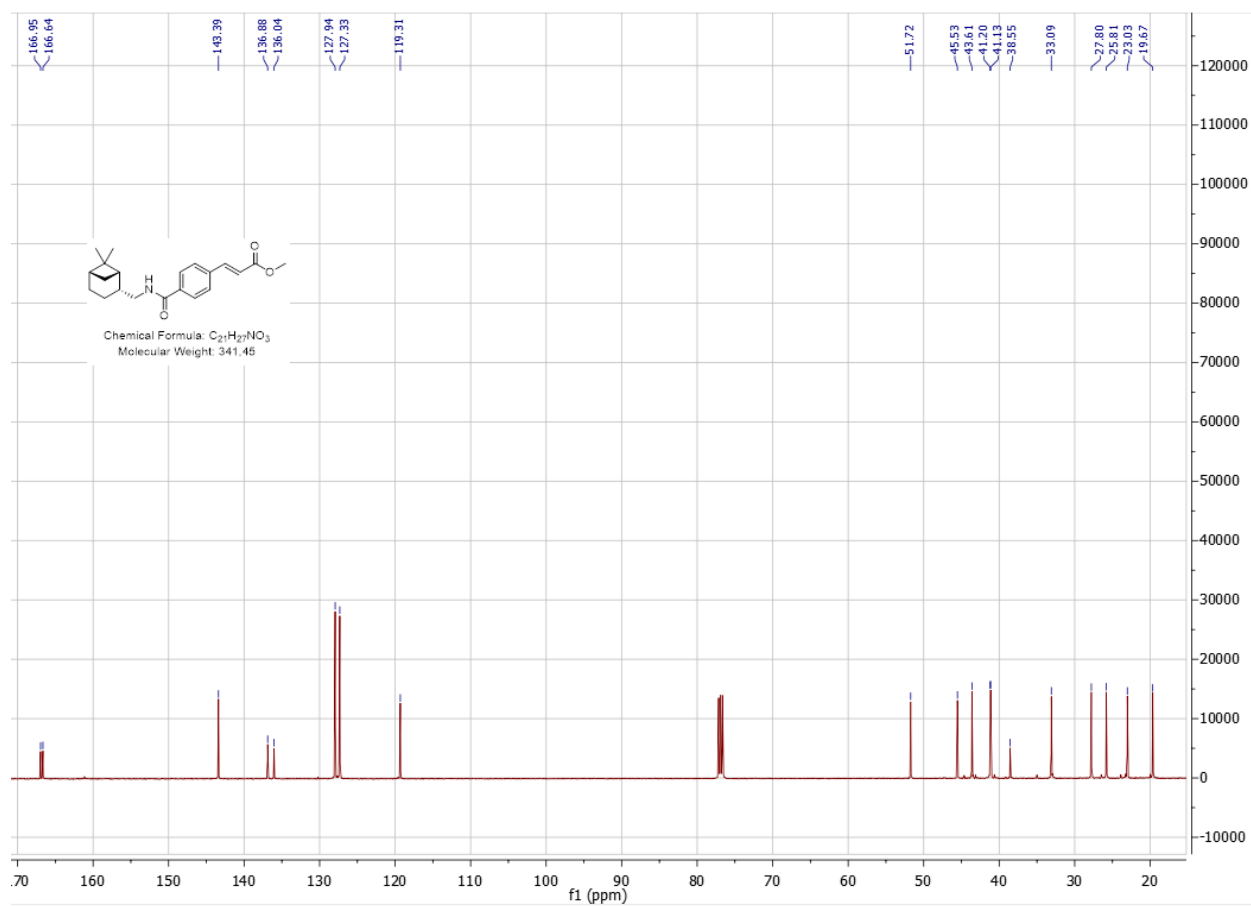
maa-597 #13 RT: 0.70 AV: 1 NL: 5.35E6
T: + c EI Full ms [32.50-350.50]



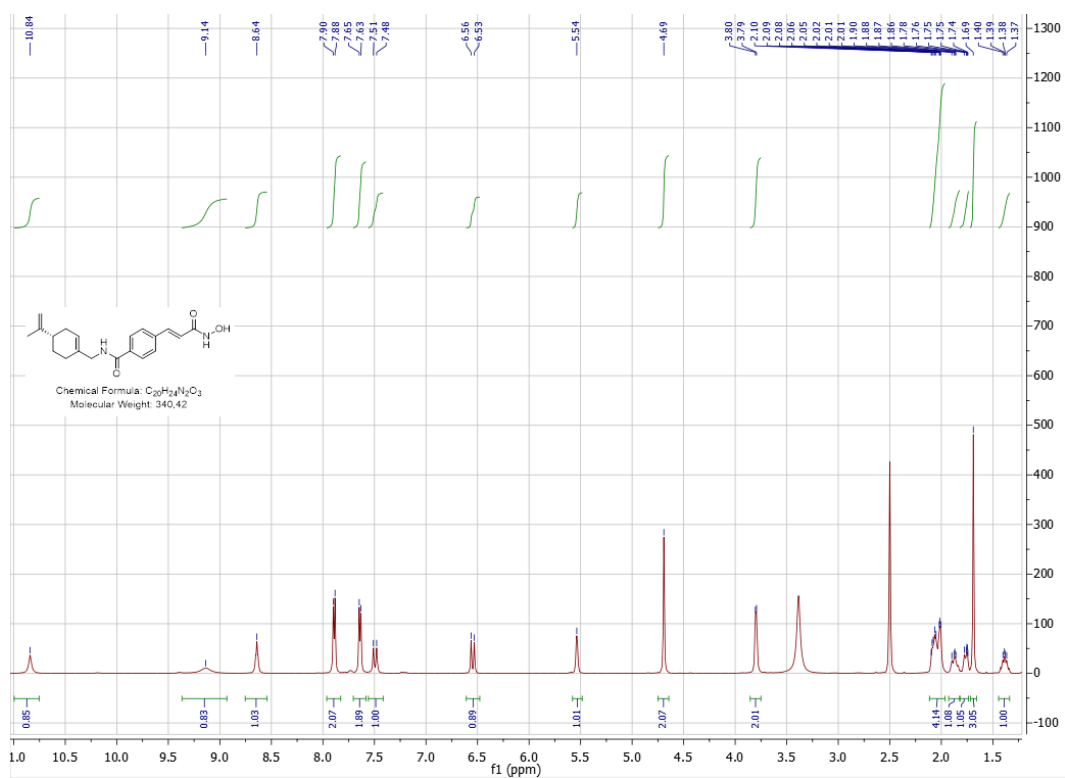
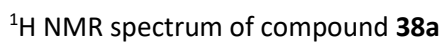
¹H NMR spectrum of compound **37c**



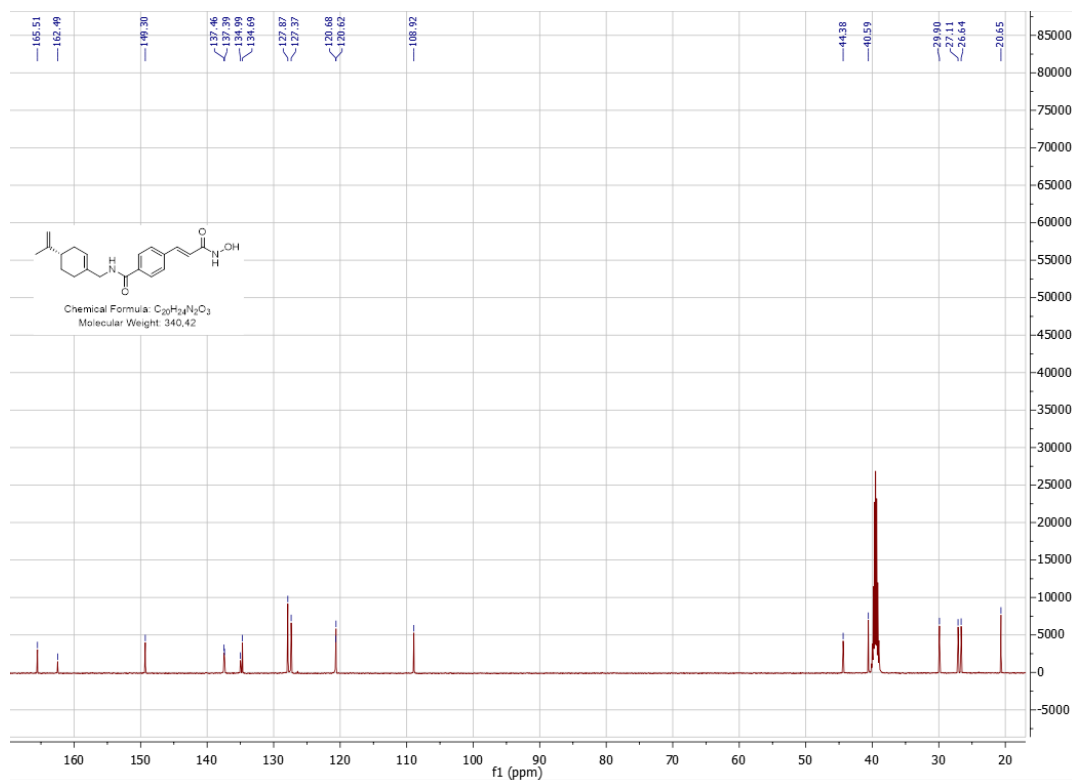
¹³C NMR spectrum of compound **37c**



maa-586 #9 RT: 0.51 AV: 1 NL: 3.70E6
T: + c EI Full ms [32.50-380.50]

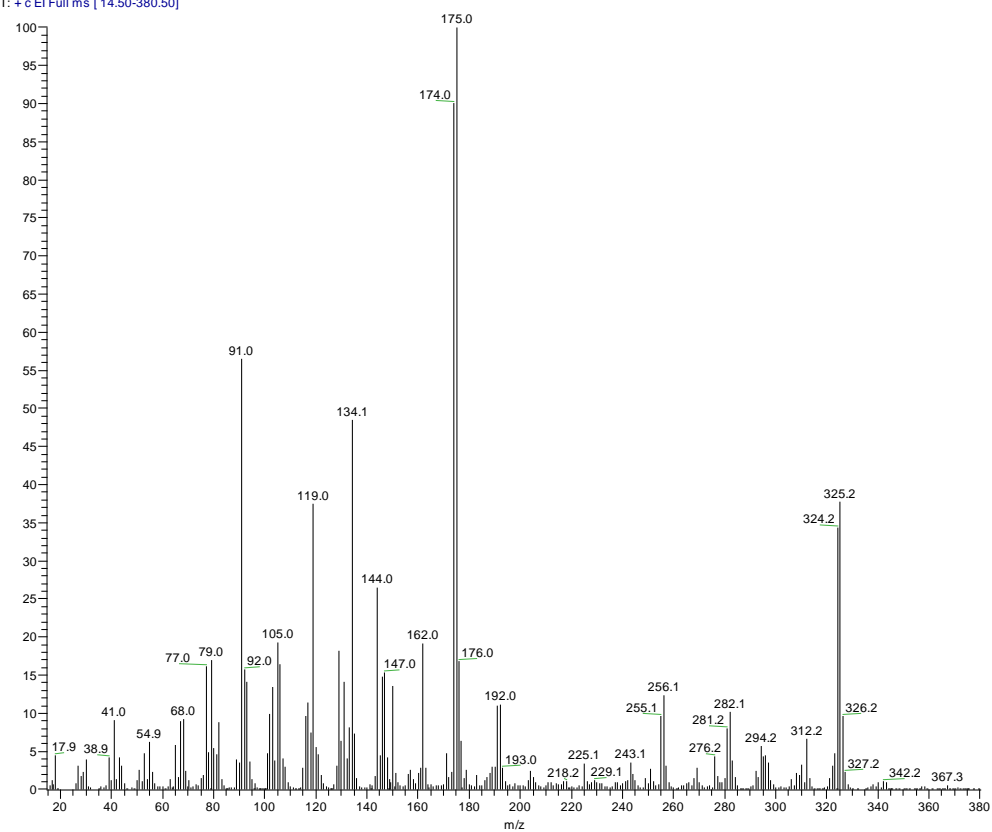


^{13}C NMR spectrum of compound **38a**

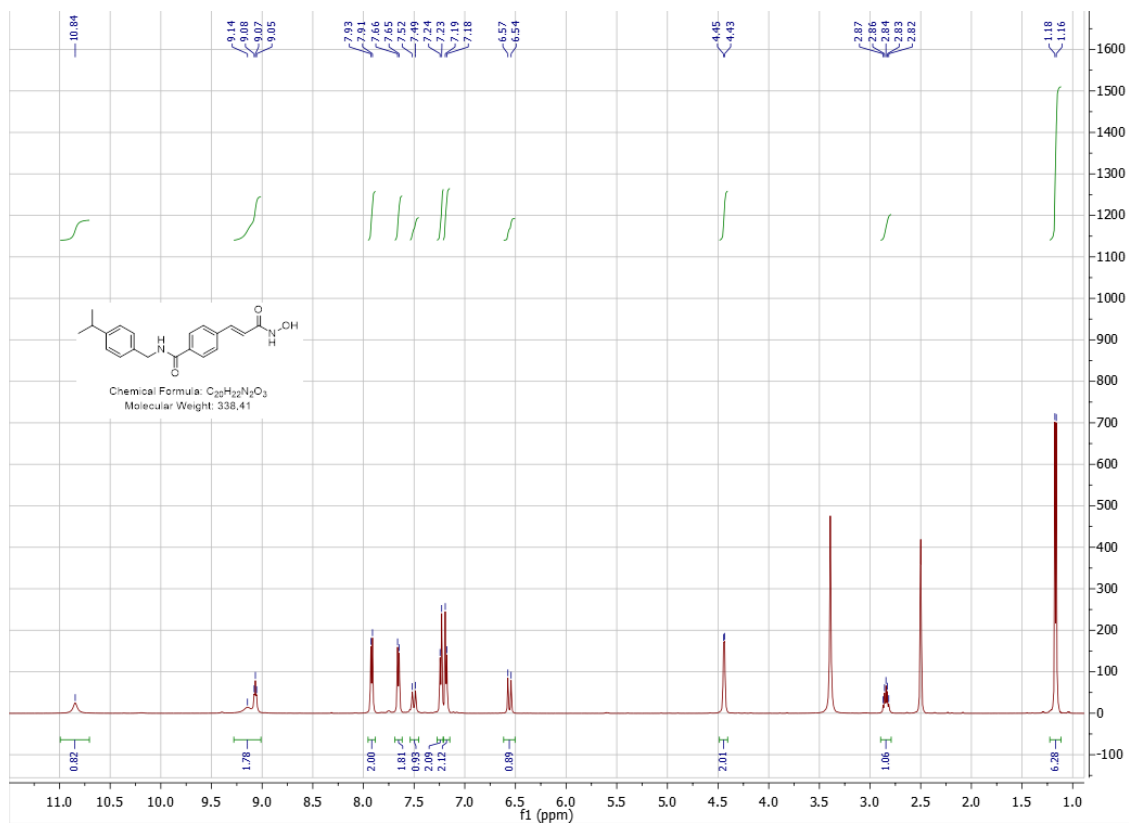


Mass-spectrum of compound **38a**

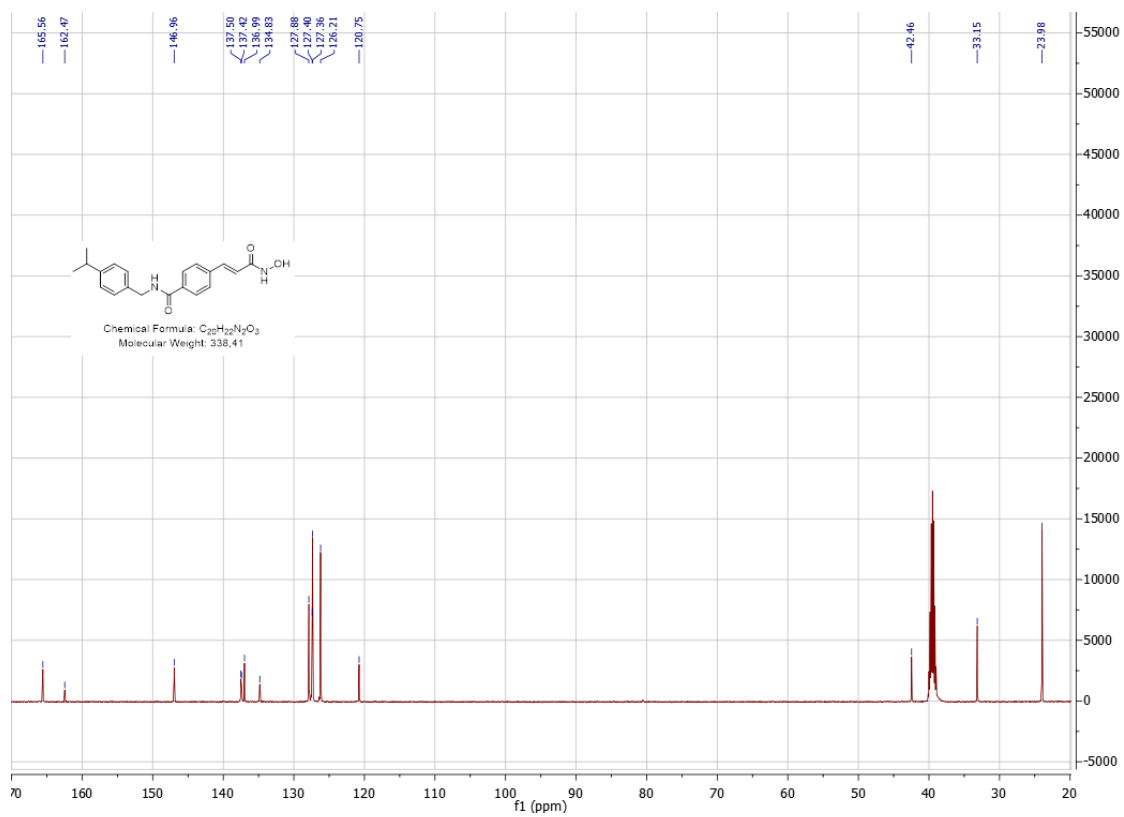
maa-605 #37 RT: 2.69 AV: 1 NL: 3.95E6
T: + c EI Full ms [14.50-380.50]



¹H NMR spectrum of compound **38b**

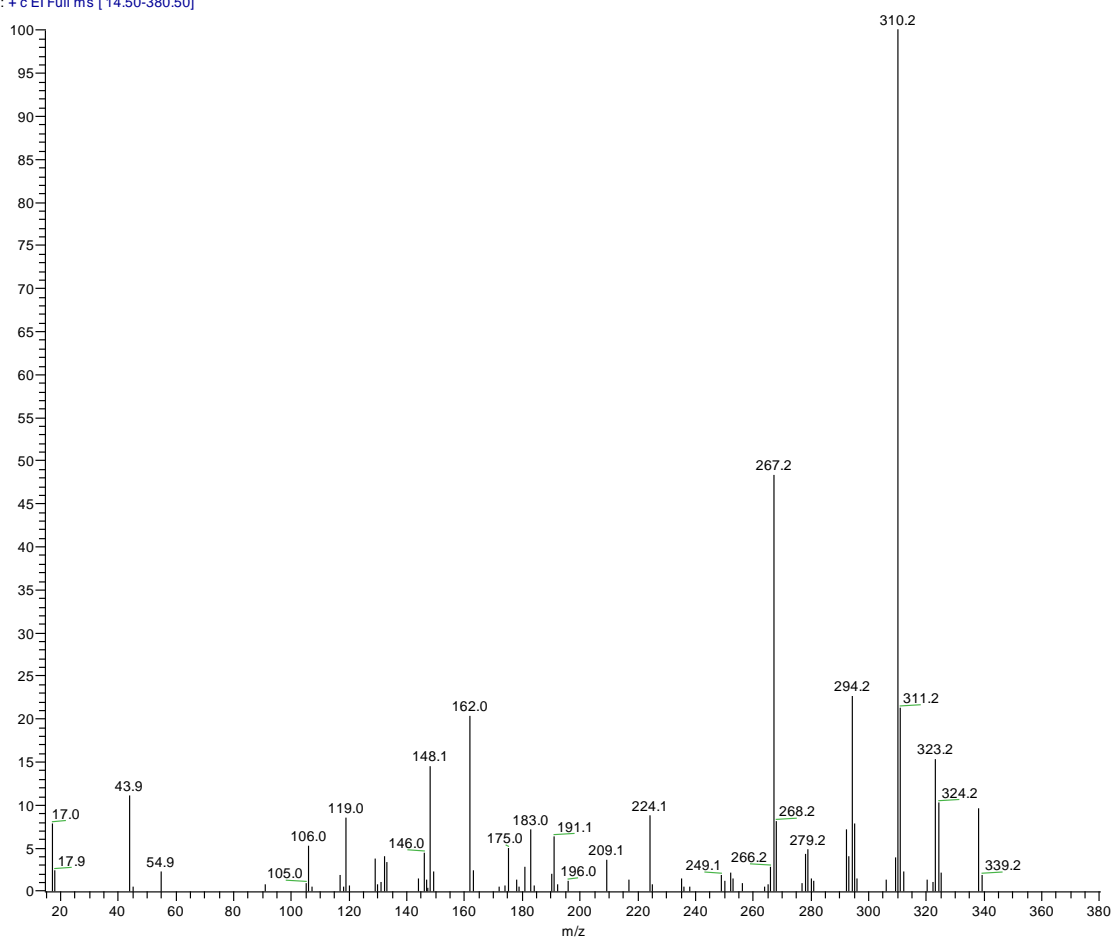


¹³C NMR spectrum of compound **38b**

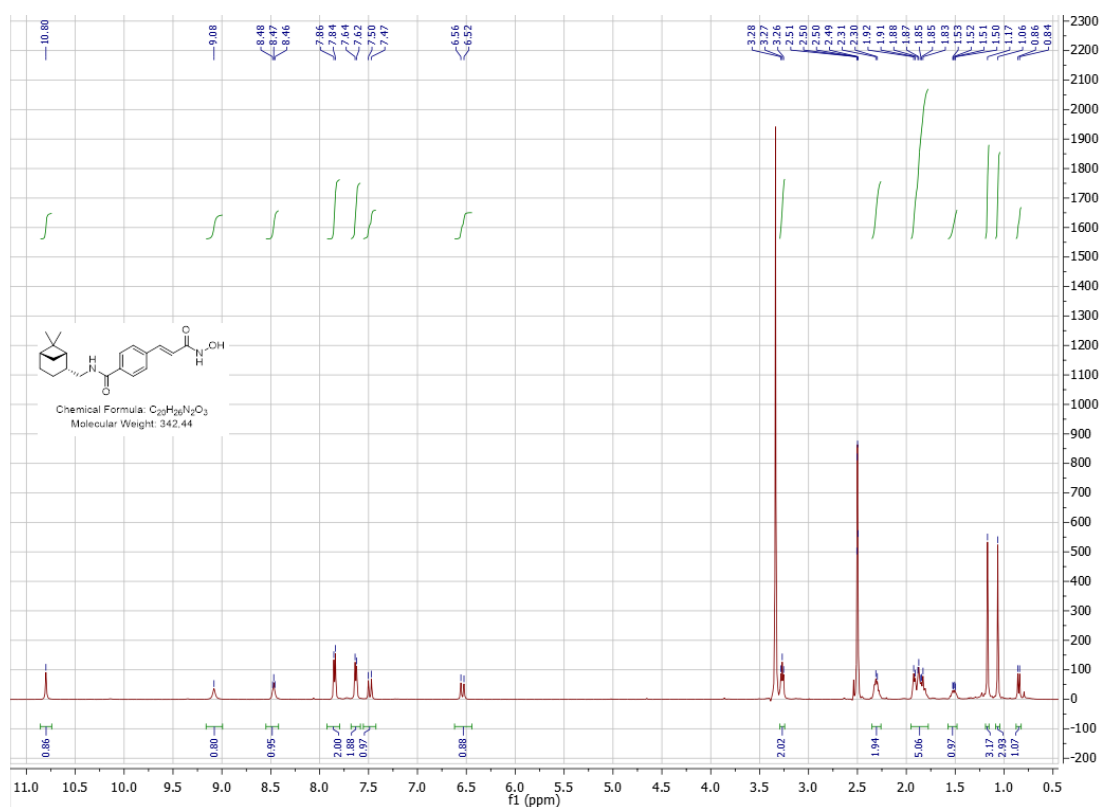


Mass-spectrum of compound **38b**

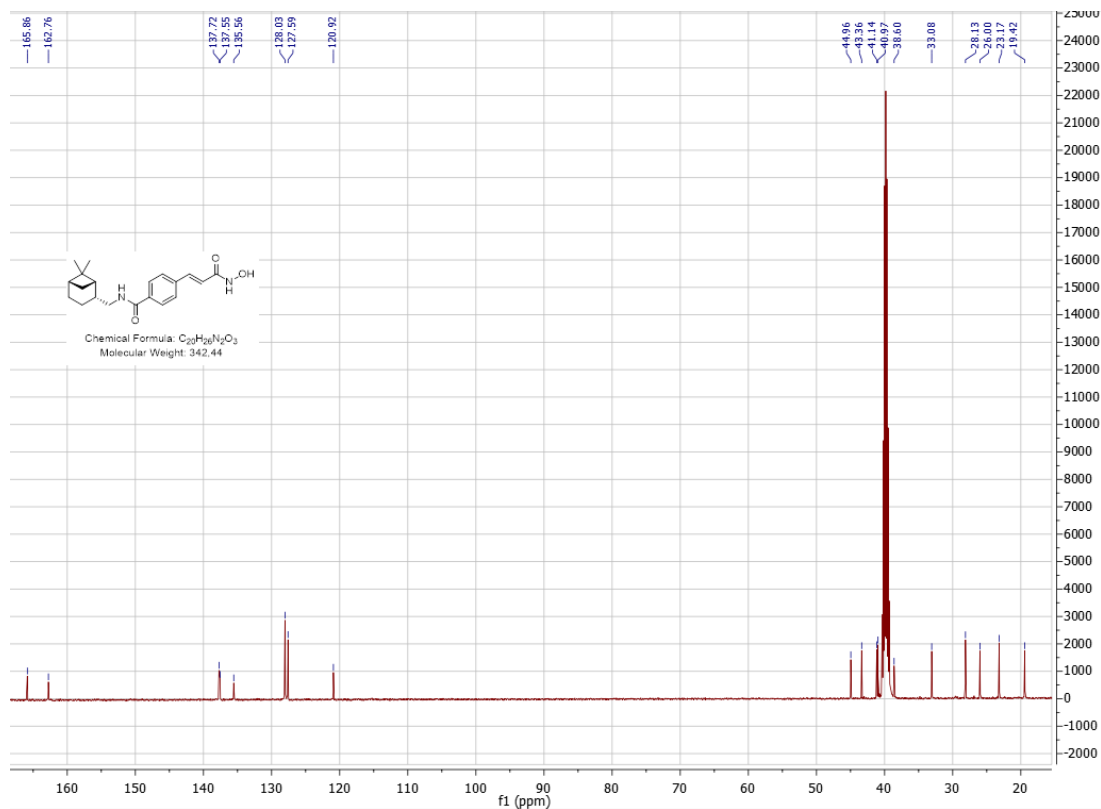
maa-601 #3 RT: 0.15 AV: 1 NL: 2.12E5
T: + c EI Full ms [14.50-380.50]



¹H NMR spectrum of compound **38c**



^{13}C NMR spectrum of compound **38c**



Mass-spectrum of compound **38c**

maa-588a #8 RT: 0.52 AV: 1 NL: 6.33E6
T: + c EI Full ms [14.50-370.50]

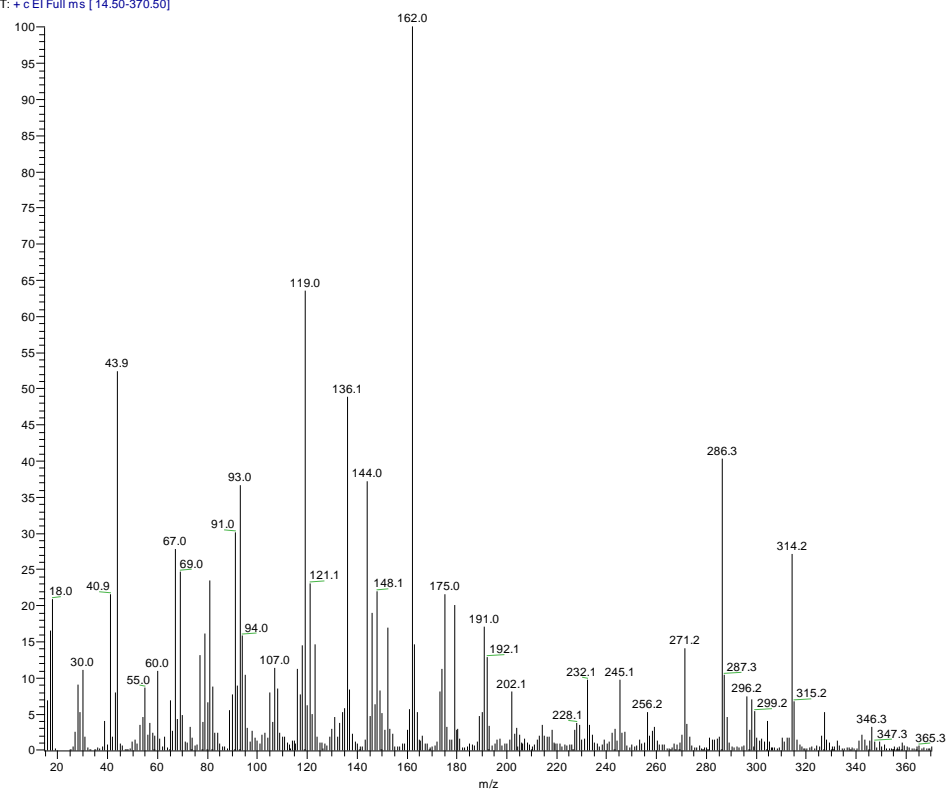


Table S1. Molecular docking of hydroxamic acids against HDAC6 (PDB ID: 5EDU) Hydrogen bonds are shown in the “H-bonds” column. Other interaction between peptide and ligand are shown in the “Other int-s”.

Compound	H-bonds	Other interactions	Docking Score	IC ₅₀ , μ M
Trichostatin A	HIS610	π - π stacking: HIE500	-8.798	
31	SER568 HIS610 TYR782	---	-9.547	0.66
30	SER568 GLY619 TYR782	---	-8.662	0.61
35a	HIE500 SER568 TYR782	π - π stacking: PHE620 HIE651	-8.120	3.87
38b	SER568	π - π stacking: PHE680	-7.125	4.81
38a	GLY619	π - π stacking: PHE680	-6.886	7.74
35b	HIE500 SER568 TYR782	π - π stacking: HIE500 PHE680	-6.689	8.23
35c	SER568 GLY619	π - π stacking: PHE620 HIE651 PHE680	-6.445	6.90
38c	TYR782	---	-6.210	8.03

Table S2. Results of docking procedures of molecules to the β -amyloid peptide (PDB ID: 1IYT). “C-term” corresponds to the C-terminus of the peptide (amino acids from 3 to 12, “N-term” corresponds to the fold in the vicinity of the N-terminus (amino acids from 22 to 30). Preferred position indicates the binding pocket with lower ΔG MM-GBSA. ΔG MM-GBSA is measured in kcal/mol. Hydrogen bonds are shown in the “H-bonds” columns. Other interaction between the β -amyloid and ligands are shown in the “Other int-s” columns.

Compound	Preferred position	ΔG bind _{pref.} pos (MM-GBSA)	H-bonds (C-term)	Other int-s (C-term)	H-bonds (N-term)	Other int-s (N-term)	ΔG C-term (MM-GBSA)	ΔG N-term (MM-GBSA)	Statistical distribution C-term:N-term (T = 298 K)
35b	C-term	-45.66	HIE6 GLU11	π - π stacking: TYR10 PHE4	ALA21 GLU22 SER26 LYS28	--	-45.66	-42.01	480:1
38a	C-term	-44.7	GLU3 ASP7 GLU 11	π - π stacking: TYR10	ALA21 GLU22 SER26	--	-44.7	-42.13	77:1

35c	N-term	-43.57	GLU3 ASP7 GLU 11	π - π stacking: TYR10	GLU22 GLY25 SER26	--	-38.89	-43.57	1:2700
38b	N-term	-41.05	GLU 11	π - π stacking: TYR10	ALA21 GLU22 LYS28	--	-37.84	-41.05	1:230
38c	C-term	-40.19	ASP7 GLU11	π - π stacking: TYR10	GLU22 LYS28	--	-40.19	-32.74	290000:1
35a	C-term	-38.14	GLU11 GIE14	π - π stacking: TYR10	ALA21 GLU22 LYS28	--	-38.14	-36.54	15:1