SUPPORTING INFORMATION

Computer-Aided Design and Synthesis of a New Class of PEX14 Inhibitors: Substituted 2,3,4,5-tetrahydrobenzo[f][1,4]oxazepines as Potential New Trypanocidal Agents

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General information

Reactions containing moisture sensitive compounds were conducted in flame-dried glass vessels under argon atmosphere. Dry solvents (THF, Et_2O) were purchased from Acros Organics. Common solvents for chromatography [Cyclohexane (Cy) and EtOAc] were distilled prior to use. IR spectra were recorded on a PerkinElmer Frontier™ FT-IR spectrometer (ATR); LC-MS spectra were recorded on a Dionex UltiMate 3000 HPLC system coupled with a Thermo Scientific ISQ EC-LC using following method: Column: Thermo Scientific Accucore RP-MS, 50x2.1 mm, particle size 2.6 µm; Gradient: water/MeCN containing 0.1% (v/v) formic acid each, 5% MeCN for 0.5 min, 5-95% MeCN over the course of 2 min, 95% MeCN for 4 min, flow rate 0.6 ml/min; UV detection at 254 nm; temperature 20 °C. HRMS measurements were performed on a Thermo Finnigan LTQ FT (HRMS-ESI). ^{1}H-, ^{13}C-, and ^{19}F-NMR: Bruker AV HD-300, Bruker AV HD-400, Bruker AV HD-500 recorded at 300K if not noted otherwise. Chemical shifts are reported in parts per million (ppm) relative to the residual solvent signals ($CHCl_3$) in ^{1}H-NMR-spectra or deuterium coupled solvent signals in ^{13}C-NMR-spectra. Multiplets which arise from accidental equality of coupling constants of magnetically non-equivalent protons are marked as virtual (virt.). Melting points were measured on a Kofler melting point apparatus (Reichert) and are uncorrected.

Virtual screening, structural database and SMILES structures

Docking calculations were performed on a standard workstation (Intel® Core™ i7-5960X, 8 cores/16 threads). Molecular dynamics simulations were performed on NVIDIA GTX 1070.

The database of compounds screened was manually curated by ETH Modlab and consisted in a merged version of the following supplier catalogs. Original libraries can be downloaded from respective vendors' websites.

Table S1. Composition of the ETH ModLab database of compounds.

Name	Vendor	Website	Version

Asinex Elite	Asinex	www.asinex.com	S1_2015
Asinex Fragments	Asinex	www.asinex.com	S1_2015
Asinex Gold	Asinex	www.asinex.com	S1_2015
Asinex Platinum	Asinex	www.asinex.com	S1_2015
ChemBridge Screening Compounds	ChemBridge	www.chembridge.com	June 2015
Enamine Advanced	Enamine	www.enamine.net	May 2015
Enamine Advanced HTS	Enamine	www.enamine.net	May 2015
Specs Natural products 1mg	Specs	www.specs.net	June 2015
Specs Sreening Compounds 10mg	Specs	www.specs.net	June 2015

In Table S2 are reported all the ChemBridge analogs identified by substructure match of the modified Murcko scaffold based on oxazepine core-hopping results.

In Table S3 is reported the naming conversion reference for the docked files names, compound names, SMILES strings, and the respective ChemBridge ID.

Table S2. ChemBridge analogs with IDs identified after substructure search of the modified Murcko scaffold of the original hit **7t**.

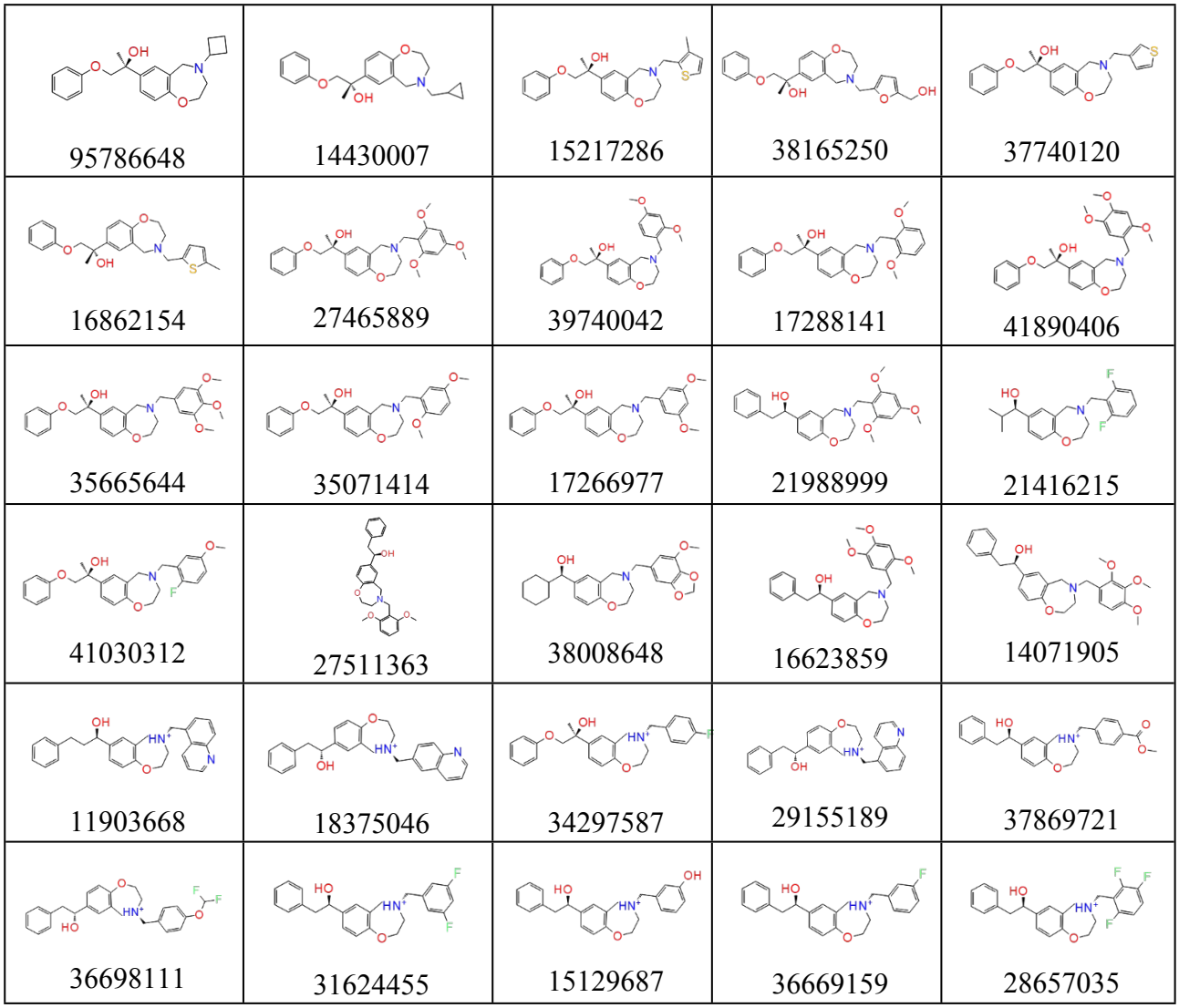
ID	SMILES	VINA	IV-MD	WMD	AVG	LE
66134836	c1cnccc1C[N@H+](CCO2)Cc(c23)cc(cc3)[C@H](O)C(c4ccccc4)c5ccccc5	-8.14	-8.39	-10.30	-8.94	0.13

60664466	CC(C)[C@@H](O)c(cc1)cc(c12)C[N@@H+](CCO2)Cc(cc3)cc(c34)cccn4	-8.20	-7.16	-9.47	-8.28	0.16
28367920	c1ccccc1C[C@@H](O)c(cc2)cc(c23)C[N@@H+](CCO3)Cc4c(F)ccc(c4)OC	-8.31	-7.96	-10.45	-8.91	0.15
45261515	Fc1cccc(F)c1C[N@H+](CCO2)Cc(c23)cc(cc3)[C@H](O)Cc4ccccc4	-9.05	-8.44	-10.86	-9.45	0.17
35491727	c1ccccc1C[C@@H](O)c(cc2)cc(c23)C[N@@H+](CCO3)Cc4c(OC)ccc(c4)OC	-7.64	-7.37	-7.86	-7.62	0.13
97395195	c1ccccc1C[C@@H](O)c(cc2)cc(c23)C[N@@H+](CCO3)Cc4cc(ccc4)OCCO	-8.33	-6.70	-8.94	-7.99	0.14
28727504	c1ccccc1C[C@@H](O)c(cc2)cc(c23)C[N@@H+](CCO3)Cc4cc(c(cc4)OC)OCC	-7.85	-7.46	-9.43	-8.25	0.12
42644399	c1ccccc1C[C@@H](O)c(cc2)cc(c23)C[N@@H+](CCO3)Cc4c(OC)cccc4	-8.26	-7.75	-9.97	-8.66	0.15
27888553	c1ccccc1C[C@@H](O)c(cc2)cc(c23)C[N@@H+](CCO3)Cc4c(OC)cc(cc4)OC	-8.35	-8.07	-9.98	-8.80	0.14
16130590	c1ccccc1C[C@@H](O)c(cc2)cc(c23)C[N@@H+](CCO3)Cc4ccc(cc4)OCCO	-8.24	-7.84	-9.61	-8.56	0.14
21578719	s1cccc1C[N@H+](CCO2)Cc(c23)cc(cc3)[C@H](O)Cc4ccccc4	-8.07	-7.88	-8.90	-8.28	0.16
43529482	o1cccc1C[N@H+](CCO2)Cc(c23)cc(cc3)[C@H](O)Cc4ccccc4	-7.83	-7.30	-9.29	-8.14	0.16
71845607	c1occc1C[N@H+](CCO2)Cc(c23)cc(cc3)[C@H](O)Cc4ccccc4	-7.75	-7.08	-9.65	-8.16	0.16
81347845	OCCOc1cccc(c1)C[N@H+](CCO2)Cc(c23)cc(cc3)C4(O)CCN(CC4)c5c(F)cccc5	-8.55	-8.37	-10.34	-9.09	0.13
36331411	COCc1ccc(o1)C[N@H+](CCO2)Cc(c23)cc(cc3)[C@H](O)Cc4ccccc4	-7.52	-6.66	-9.01	-7.73	0.14
54146122	c1ccccc1OC[C@](O)(C)c(cc2)cc(c23)C[N@@H+](CCO3)Cc4cc(OC)c(F)cc4	-8.32	-7.89	-9.32	-8.51	0.14
29086920	COc1cccc(c1)C[N@H+](CCO2)Cc(c23)cc(cc3)[C@@](O)(C)COc4ccccc4	-8.44	-7.68	-8.40	-8.17	0.14
10650809	Fc1cccc(c1)C[N@H+](CCO2)Cc(c23)cc(cc3)[C@@](O)(C)COc4ccccc4	-8.62	-7.68	-9.01	-8.44	0.15
36596859	COc1ccc(cc1)C[N@H+](CCO2)Cc(c23)cc(cc3)[C@@](O)(C)COc4ccccc4	-8.16	-8.10	-8.32	-8.19	0.14

17121656	COc1ccccc1C[N@H+](CCO2)Cc(c23)cc(cc3)[C@@](O)(C)COc4ccccc4	-8.29	-7.21	-8.67	-8.06	0.14
33150906	Cn1ncc(c1C)C[N@H+](CCO2)Cc(c23)cc(cc3)[C@@](O)(C)COc4ccccc4	-7.83	-6.99	-9.50	-8.11	0.13
35418243	c1ccccc1OC[C@](O)(C)c(cc2)cc(c23)C[N@@H+](CCO3)Cc4ccc(cc4)C(=O)OC	-8.54	-8.30	-8.66	-8.50	0.14
18661989	c1ccccc1C[C@@H](O)c(cc2)cc(c23)C[N@@H+](CCO3)Cc(cc4)cc(c45)OCO5	-9.29	-8.10	-10.82	-9.41	0.17
34402486	c1ccccc1C[C@@H](O)c(cc2)cc(c23)C[N@@H+](CCO3)Cc4cc(OC)c(OC)c(c4)OC	-7.80	-6.73	-8.96	-7.83	0.12
44810429	c1ccccc1C[C@@H](O)c(cc2)cc(c23)C[N@@H+](CCO3)Cc4cc(OC)c(cc4)OC	-8.18	-7.80	-9.84	-8.61	0.14
40557889	c1ccccc1OC[C@](O)(C)c(cc2)cc(c23)C[N@@H+](CCO3)Cc(ccc4)c(c45)cccn5	-8.72	-8.23	-11.28	-9.41	0.14
13688281	c1cccc(c12)c(c[nH]2)C[N@H+](CCO3)Cc(c34)cc(cc4)[C@H](O)Cc5ccccc5	-9.13	-9.04	-10.63	-9.60	0.16
19830955	c1ccccc1C[C@@H](O)c(cc2)cc(c23)C[N@@H+](CCO3)Cc(cc4)cc(c45)OCCO5	-9.17	-8.93	-10.39	-9.50	0.16
33744199	c1ccccc1C[C@@H](O)c(cc2)cc(c23)C[N@@H+](CCO3)Cc4c(F)cc(F)cc4	-8.76	-8.43	-10.58	-9.26	0.17
44918381	c1ccccc1C[C@@H](O)c(cc2)cc(c23)C[N@@H+](CCO3)Cc4c(F)ccc(F)c4	-8.48	-8.39	-10.46	-9.11	0.16
28657035	Fc1ccc(F)c(F)c1C[N@H+](CCO2)Cc(c23)cc(cc3)[C@H](O)Cc4ccccc4	-9.25	-8.53	-10.31	-9.36	0.18
36669159	c1ccccc1C[C@@H](O)c(cc2)cc(c23)C[N@@H+](CCO3)Cc4cc(F)ccc4	-8.66	-8.17	-11.14	-9.32	0.17
15129687	c1ccccc1C[C@@H](O)c(cc2)cc(c23)C[N@@H+](CCO3)Cc4cc(O)ccc4	-8.22	-7.88	-10.69	-8.93	0.16
31624455	c1ccccc1C[C@@H](O)c(cc2)cc(c23)C[N@@H+](CCO3)Cc4cc(F)cc(F)c4	-8.70	-8.15	-10.11	-8.98	0.17
36698111	c1ccccc1C[C@@H](O)c(cc2)cc(c23)C[N@@H+](CCO3)Cc4ccc(cc4)OC(F)F	-8.79	-8.29	-10.28	-9.12	0.16
37869721	c1ccccc1C[C@@H](O)c(cc2)cc(c23)C[N@@H+](CCO3)Cc4ccc(cc4)C(=O)OC	-8.80	-8.48	-10.55	-9.28	0.15
29155189	c1ccccc1C[C@@H](O)c(cc2)cc(c23)C[N@@H+](CCO3)Cc(ccc4)c(c45)cccn5	-8.45	-7.94	-9.85	-8.74	0.15

34297587	Fc1ccc(cc1)C[N@H+](CCO2)Cc(c23)cc(cc3)[C@@](O)(C)COc4ccccc4	-8.74	-7.78	-10.63	-9.05	0.16
18375046	c1ccccc1C[C@@H](O)c(cc2)cc(c23)C[N@@H+](CCO3)Cc(cc4)cc(c45)cccn5	-9.41	-9.37	-11.05	-9.94	0.17
11903668	c1ccccc1CC[C@@H](O)c(cc2)cc(c23)C[N@@H+](CCO3)Cc(ccc4)c(c45)cccn5	-8.72	-8.32	-10.34	-9.13	0.15
14071905	COc1ccc(c(OC)c1OC)CN(CCO2)Cc(c23)cc(cc3)[C@H](O)Cc4ccccc4	-7.71	-6.58	-9.19	-7.83	0.12
16623859	COc1cc(OC)c(cc1OC)CN(CCO2)Cc(c23)cc(cc3)[C@H](O)Cc4ccccc4	-7.81	-7.79	-9.75	-8.45	0.13
38008648	O1COc(c12)c(OC)cc(c2)CN(CCO3)Cc(c34)cc(cc4)[C@H](O)C5CCCCC5	-8.46	-7.58	-10.90	-8.98	0.14
27511363	COc1cccc(OC)c1CN(CCO2)Cc(c23)cc(cc3)[C@H](O)Cc4ccccc4	-8.08	-6.92	-8.80	-7.93	0.14
41030312	COc1cc(c(F)cc1)CN(CCO2)Cc(c23)cc(cc3)[C@@](O)(C)COc4ccccc4	-7.90	-7.09	-9.58	-8.19	0.14
21416215	Fc1cccc(F)c1CN(CCO2)Cc(c23)cc(cc3)[C@H](O)C(C)C	-7.04	-6.98	-8.67	-7.56	0.15
21988999	COc1cc(OC)cc(OC)c1CN(CCO2)Cc(c23)cc(cc3)[C@H](O)Cc4ccccc4	-7.98	-7.68	-9.01	-8.23	0.13
17266977	COc1cc(cc(c1)OC)CN(CCO2)Cc(c23)cc(cc3)[C@@](O)(C)COc4ccccc4	-7.88	-7.32	-8.91	-8.04	0.13
35071414	COc1cc(c(cc1)OC)CN(CCO2)Cc(c23)cc(cc3)[C@@](O)(C)COc4ccccc4	-7.14	-6.92	-8.74	-7.60	0.12
35665644	COc1c(OC)cc(cc1OC)CN(CCO2)Cc(c23)cc(cc3)[C@@](O)(C)COc4ccccc4	-7.97	-7.06	-8.95	-7.99	0.12
41890406	COc1cc(OC)c(cc1OC)CN(CCO2)Cc(c23)cc(cc3)[C@@](O)(C)COc4ccccc4	-7.37	-6.96	-9.58	-7.97	0.11
17288141	COc1cccc(OC)c1CN(CCO2)Cc(c23)cc(cc3)[C@@](O)(C)COc4ccccc4	-7.90	-4.61	-7.96	-6.82	0.13
39740042	COc1ccc(c(c1)OC)CN(CCO2)Cc(c23)cc(cc3)[C@@](O)(C)COc4ccccc4	-8.11	-7.48	-9.50	-8.36	0.13
27465889	COc1cc(OC)cc(OC)c1CN(CCO2)Cc(c23)cc(cc3)[C@@](O)(C)COc4ccccc4	-7.13	-6.96	-8.99	-7.70	0.11
16862154	Cc1ccc(s1)CN(CCO2)Cc(c23)cc(cc3)[C@@](O)(C)COc4ccccc4	-8.01	-7.23	-8.89	-8.04	0.14

37740120	c1sccc1CN(CCO2)Cc(c23)cc(cc3)[C@@](O)(C)COc4ccccc4	-7.51	-6.76	-7.82	-7.36	0.14
38165250	OCc1ccc(o1)CN(CCO2)Cc(c23)cc(cc3)[C@@](O)(C)COc4ccccc4	-7.68	-7.13	-8.74	-7.85	0.13
15217286	Cc1ccsc1CN(CCO2)Cc(c23)cc(cc3)[C@@](O)(C)COc4ccccc4	-5.94	-4.99	-7.49	-6.14	0.11
14430007	C1CC1CN(CCO2)Cc(c23)cc(cc3)[C@@](O)(C)COc4ccccc4	-7.09	-6.30	-7.98	-7.12	0.14
95786648	C1CCC1N(CCO2)Cc(c23)cc(cc3)[C@@](O)(C)COc4ccccc4	-7.31	-6.82	-8.44	-7.52	0.14



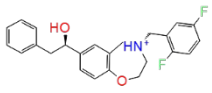
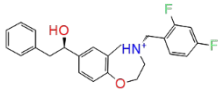
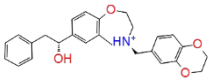
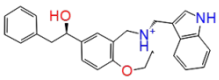
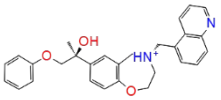
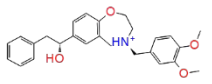
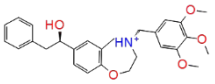
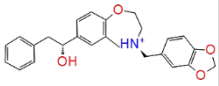
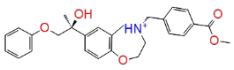
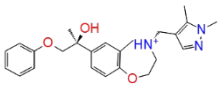
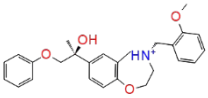
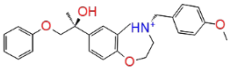
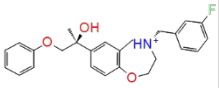
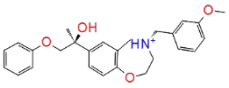
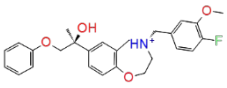
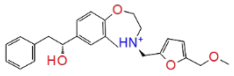
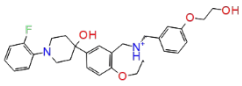
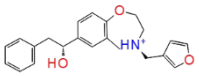
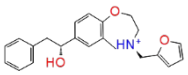
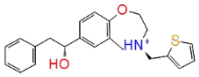
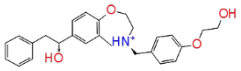
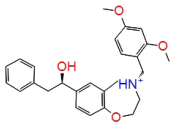
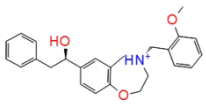
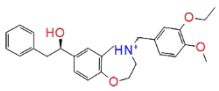
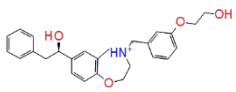
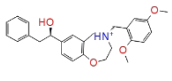
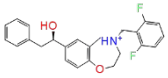
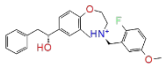
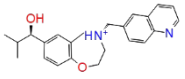
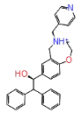
 44918381	 33744199	 19830955	 13688281	 40557889
 44810429	 34402486	 18661989	 35418243	 33150906
 17121656	 36596859	 10650809	 29086920	 54146122
 36331411	 81347845	 71845607	 43529482	 21578719
 16130590	 27888553	 42644399	 28727504	 97395195
 35491727	 45261515	 28367920	 60664466	 66134836

Table S3. QSAR Table compounds docking structures names conversion and ChemBridge IDs.

Compound	Docking	ChemBridge ID	SMILES
7a	CATS004	27888553	c1ccccc1C[C@@H](O)c(c2)ccc(c23)OCC[N@H+](C3)Cc4c(OC)cc(cc4)OC
7b	DOL196	-	Clc1cccc(c1)C[C@H](O)c(cc2)cc(c23)CN(CCO3)Cc4ccc(OC)cc4OC
7c	DOL189	-	Fc1ccc(cc1)C[C@H](O)c(cc2)cc(c23)CN(CCO3)Cc4ccc(OC)cc4OC
7d	CATS010	36698111	c1ccccc1C[C@@H](O)c(c2)ccc(c23)OCC[N@H+](C3)Cc(cc4)ccc4OC(F)F
7e	CATS001	28367920	c1ccccc1C[C@H](O)c(c2)ccc(c23)OCC[N@H+](C3)Cc4c(F)ccc(c4)OC

7f	DOL187	-	c1ccccc1C[C@H](O)c(cc2)cc(c23)CN(CCO3)Cc4ccc(OC)c(c45)cccc5
7g	CATS002	33150906	c1nn(C)c(C)c1C[N@@H+](C2)CCOc(c23)ccc(c3)[C@@](O)(C)COc4ccccc4
7h	CATS003	97395195	c1ccccc1C[C@@H](O)c(c2)ccc(c23)OCC[N@H+](C3)Cc4cc(ccc4)OCCO
7i	CATS005	16130590	c1ccccc1C[C@@H](O)c(c2)ccc(c23)OCC[N@H+](C3)Cc4ccc(cc4)OCCO
7j	CATS006	71845607	c1cocc1C[N@@H+](C2)CCOc(c23)ccc(c3)[C@H](O)Cc4ccccc4
7k	CATS007	36331411	COCc(cc1)oc1C[N@@H+](C2)CCOc(c23)ccc(c3)[C@H](O)Cc4ccccc4
7l	CATS008	54146122	c1ccccc1OC[C@](O)(C)c(c2)ccc(c23)OCC[N@H+](C3)Cc(c4)ccc(F)c4OC
7m	CATS009	36596859	c1cc(OC)ccc1C[N@@H+](C2)CCOc(c23)ccc(c3)[C@@](O)(C)COc4ccccc4
7n	CATS011	29155189	c1ccccc1C[C@@H](O)c(c2)ccc(c23)OCC[N@H+](C3)Cc4cccc(c45)nccc5
7o	CATS012	18661989	c1ccccc1C[C@@H](O)c(c2)ccc(c23)OCC[N@H+](C3)Cc(c4)ccc(c45)OCO5
7p	CATS013	28727504	c1ccccc1C[C@@H](O)c(c2)ccc(c23)OCC[N@H+](C3)Cc(c4)ccc(OC)c4OCC
7q	CATS014	13688281	c1cccc(c12)[nH]cc2C[N@@H+](C3)CCOc(c34)ccc(c4)[C@H](O)Cc5ccccc5
7r	CATS015	33744199	c1ccccc1C[C@@H](O)c(c2)ccc(c23)OCC[N@H+](C3)Cc4c(F)cc(F)cc4
7s	CATS016	15129687	c1ccccc1C[C@@H](O)c(c2)ccc(c23)OCC[N@H+](C3)Cc4cc(O)ccc4
7t	CATS017	67105500	O=C(N)c1nc(on1)C[N@@H+](C2)CCOc(c23)c(O)cc(c3)-c4csc(c45)cccc5
10	DOL195	-	c1ccccc1CNC(=O)c(cc2)cc(c23)CN(CCO3)Cc4ccc(OC)cc4OC
11	DOL192	-	c1ccccc1CC(=O)c(cc2)cc(c23)CN(CCO3)Cc4ccc(OC)cc4OC
12	MAB-NH2	-	COc1ccc(c(c12)cccc2)CN(C3)CCc(c34)n(CC[NH3+])nc4C(=O)NCc5cccc(c56)cccc6

Docking/MD screening protocol

The docking/MD macro reported in Table S5 was written using Yasara built-in scripting language Yanaconda and it can be run on any version of Yasara Structure above 15.

Table S4. Yasara Structure macro used for rescoring docking poses.

```
Clear
Console off

#### SET PATH AND VARIABLES HERE ####
path='path\to\main\docking'
#receptor
target='CATS'
#ligands
expname='redock'
 #sdf name
 cpdname=''

 Shell mkdir (path)\(expname)
 Shell mkdir (path)\(expname)\SDF
 Shell mkdir (path)\(expname)\SDF\MA
 Shell mkdir (path)\(expname)\SDF\IVMD
 Shell mkdir (path)\(expname)\SDF\WMD
 Shell mkdir (path)\(expname)\Poses
 Shell mkdir (path)\(expname)\Results

 prefix='0000'

 #set VINA runs
 runs=16

 #Tabulate scores
 MakeTab (target)_(expname)_results,Dimensions=2,Columns=6

 #Onerror continue

 #load receptor and simcell
 LoadSce (path)\(target)_(expname)_receptor.sce,Settings=No
 nameobj 1,Receptor
 namemol obj 1,R
 Joinmol R
 #Save a copy of the receptor
 saveYob 1,(path)\(target)_new.yob
 SavePDB
  1,(path)\(expname)\SDF\(target)_receptor.pdb,Format=PDB,transform=Yes
 #wait continuebutton

 #Load ligands as sdf file
 LoadSDF (path)\(target)_(expname)_ligands.sdf
 # Stickobj !1
 # HideObj !1 and !2 and !3
 #wait continuebutton
 TransferObj !1 and !2,1,Local=Keep

 totobj = countobj all
 ligands_num = totobj - 2
 nameres Unk,lig
 #Extract data
```

```
52.  RecordLog (path)\(expname)\Results\(expname)_results.log
53.  print ('')
54.  print ('-----------------------------------------------   Screening
   results for (expname) on protein (target)  ------------------------------
   ------------------------')
55.  print ('')
56.  print ('Docking results are in Kcal/mol. Total ligands screened:
   (ligands_num)')
57.  print ('Efficacy: * = <-7.5 Kcal/mol; ** = <-8.5 Kcal/mol; *** = <-9.5
   Kcal/mol' )
58.  print ('')
59.  print ('LigNo | Name          | Effic. | Initial affinity | VINA Docking
   | InVacuo MD Score | InWater MD Score | Avg Binding En. | Ligand
   Efficiency | Contacs  - Residues with distance <4A from current ligand')
60.  print ('------|--------------|--------|------------------|--------------
   |------------------|------------------|-----------------|----------------
   --|-----------------------------------------------------------')
61.  StopLog
62.
63.  showmessage 'Loaded (ligands_num) ligands'
64.  #wait continuebutton
65.
66.
67.  #mind the increment of 2 (receptor and simcell)
68.  for l=3 to totobj
69.    #keep track of ligand number
70.    Tabulate (0+(l-2))
71.    #used to transfer the ligand in the same coordinate of the simcell
72.    #wait continuebutton
73.    TransferObj (l),1,Local=Keep
74.    #clean current ligand (assuming that ions and other stuff are res
   number >1)
75.    rescheck = countres obj (l)
76.    if rescheck >1
77.      delres lig 2-(rescheck)
78.
79.    #wait continuebutton
80.    molname = namemol obj (l)
81.    # Use this with weird names
82.    #cpdname_win = '(000+(l-2)_Ligand(000+(l-2))'
83.    cpdname_ori = Compoundmol obj (l)
84.    cpdname = Compoundmol obj (l)
85.    cpd_num = 000+(l-2)
86.    cpdname_win = '(cpd_num)_(cpdname)'
87.
88.    #docking 1 score 1 - INITIAL AFFINITY
89.    #Remove all object
90.    RemoveObj !2 and !(l)
91.    clean
92.    StickObj (l)
93.    Nameobj (l),ScoringLS1
94.    ForceField AMBER14,SetPar=No
95.    AddObj 1
96.    Experiment Docking
97.      ResultFile (path)\(expname)\Poses\IA_(cpdname_win)_000
98.      ClusterRMSD 5.00
99.      Runs 1
```

```
    Method VINALS
    LigandObj (l)
    ReceptorObj 1
  Experiment On
  Wait ExpEnd

  score = bfactormol Obj (l)
  #first column
  Tabulate (0.00+(score))


  #Wait Continuebutton
  A() = listres aminoacid with distance <5 from Lig 1,format=RESNUM
    #print (A())
  For r in A()
    Showres (r)
    ShowSurfRes Res
   (r),Type=Molecular,Update=Dynamic,OutCol=AtomCol,OutAlpha=55,InCol=AtomCol
   ,InAlpha=85,Specular=Yes
  StickRes Lig
  ShowHBoObj (l),Extend=Yes
  HideAtom !CA Backbone
  HideAtom Element H with bond to Element C

  #wait continuebutton


  #Minimization of current ligand inflate and get a proper 3D structure
  #remove receptor first and use current simcell for minimization
  removeobj 1
  removeobj !2
  addobj (l)
  Nameobj (l),Relaxing
  Experiment Minimization
  Experiment On
  Wait ExpEnd

  #docking 2 score 2 - MINIMIZED AFFINITY no MD
  ForceField AMBER14,SetPar=No
  AddObj 1
  Nameobj (l),Docking
  Experiment Docking
    ResultFile (path)\(expname)\Poses\VINA_(cpdname_win)_000
    Runs (runs)
    ClusterRMSD 1000
    Method VINA
    LigandObj (l)
    ReceptorObj 1
  Experiment On
  Wait ExpEnd

  #Load the best complex
  LoadYOB (path)\(expname)\Poses\VINA_(cpdname_win)_000
  index = Countobj all
  Delobj (l)
  NumberObj (index),(l)
  Nameobj (l),Saving
```

```
155.   DelMol res aminoacid obj (l)
156.   FixRes Aminoacid
157.   Experiment Minimization
158.   Experiment On
159.   Wait ExpEnd
160.   #wait continuebutton
161.
162.   score_ma = bfactormol Obj (l)
163.   Tabulate (0.00+(score_ma))
164.   file_score_ma = (0.0+score_ma)*-1
165.   Compoundmol all obj (l),'(cpdname_win)_MA-BndNrg=(file_score_ma)'
166.   #wait continuebutton
167.   SDF_title = Compoundmol obj (l)
168.   Showmessage '(SDF_title)'
169.   SaveSDF (l),(path)\(expname)\SDF\MA\MA-
   (cpdname_win)_BndNrg=(file_score_ma).sdf,transform=Yes
170.   Compoundmol obj (l),(cpdname_win)
171.
172.   #Wait Continuebutton
173.   A() = listres aminoacid with distance <5 from Lig 1,format=RESNUM
174.     #print (A())
175.   For r in A()
176.     Showres (r)
177.     ShowSurfRes Res
   (r),Type=Molecular,Update=Dynamic,OutCol=AtomCol,OutAlpha=55,InCol=AtomCol
   ,InAlpha=85,Specular=Yes
178.   StickRes Lig
179.   ShowHBoObj (l),Extend=Yes
180.   HideAtom !CA Backbone
181.   HideAtom Element H with bond to Element C
182.
183.   #Relax the structure - Short MD IN VACUO
184.   ForceField NOVA,SetPar=No
185.   Nameobj (l),InVacuoMD
186.   #Fix Backbone to avoid distortions
187.
188.   #Anneal
189.   Nameobj (l),Annealing
190.   FreeAll
191.
192.   #FixAtom Backbone
193.   Sim On
194.   ShowHBoObj (l),Extend=Yes
195.   Wait 150
196.   #TempCtrl Anneal
197.   Sim Off
198.
199.   #Switch to AMBER14 for VINA Scoring
200.   ForceField AMBER14,SetPar=No
201.   #Score 2
202.   Nameobj (l),ScoringLS2
203.   Experiment Docking
204.     ResultFile (path)\(expname)\Poses\MD_(cpdname_win)_000
205.     ClusterRMSD 1000
206.     Runs 1
207.     Method VINALS
208.     LigandObj (l)
```

```
    ReceptorObj 1
  Experiment On
  Wait ExpEnd
  HideAtom Element H with bond to Element C

  score_md = bfactormol Obj (l)

  #Tab column 2
  Tabulate (0.00+score_md)
  file_score_md = (0.0+score_md)*-1
  Compoundmol obj (l),'(cpdname_win)_IVMD-BndNrg=(file_score_md)'
  SDF_title = Compoundmol obj (l)
  Showmessage '(SDF_title)'
  SaveSDF (l),(path)\(expname)\SDF\IVMD\IVMD-(cpdname_win)_IVMD-
BndNrg=(file_score_md).sdf,transform=Yes
  Compoundmol obj (l),(cpdname_win)

  #Wait continuebutton

  #FF is set, go for water
  #Neutralize and small solvent MD
  #removeobj (l)
  Nameobj (l),Solvating
  #Free Atoms
  FreeAll
  FillCellWater Density=0.997,Probe=1.4,BumpSum=1.0,DisMax=0
  namemol res hoh,W
  Showobj Water
  Showmol W
  Hideres Hoh with distance >3 from Lig 1
  #AddObj (l)
  Sim On
  Wait 250
  Sim off
  Nameobj (l),H2OMinim
  Experiment Minimization
  Experiment On
  Wait ExpEnd

  #score 3
  Showres Hoh with distance <3 from Lig 1
  Delres hoh with distance >3 from Lig 1
  JoinObj Water,1
  #wait continuebutton
  Nameobj (l),ScoringLS3
  Experiment Docking
    ResultFile (path)\(expname)\Poses\WMD_(cpdname_win)_000
    ClusterRMSD 5.00
    Runs 1
    Method VINALS
    LigandObj (l)
    ReceptorObj 1
  Experiment On
  Wait ExpEnd

  Nameobj (l),Saving
  #score 3
```

```
265.   score_hoh = bfactormol Obj (l)
266.   Tabulate (0.00+(score_hoh))
267.   file_score_hoh = (0.0+score_hoh)*-1
268.   Compoundmol obj (l),'(cpdname_win)_WMD-BndNrg=(file_score_hoh)'
269.   SaveSDF (l),(path)\(expname)\SDF\WMD\WMD-(cpdname_win)_WMD-
   BndNrg=(file_score_hoh).sdf,transform=Yes
270.   Compoundmol obj (l),(cpdname_win)
271.   #Tabulate ('contacts()')
272.
273.   HideAtom Element H with bond to Element C
274.   #wait continuebutton
275.   Delres hoh
276.   #wait continuebutton
277.
278.   #save compounds SMILES for purchasing
279.   TransferObj (l),Receptor,Local=Fix
280.
281.   #Average binding energy
282.   #with initial affinity (aligned to known ligand)
283.
   #listenergies()=(0.000+(score)),(0.000+(score_ma)),(0.000+(score_md)),(0.0
   00+(score_hoh))
284.   #without initial affinity (no alignment)
285.
   listenergies()=(0.000+(score_ma)),(0.000+(score_md)),(0.000+(score_hoh))
286.   avg = mean listenergies
287.   file_avg = (0.0+avg)*-1
288.   print (avg)
289.   #wait continuebutton
290.
291.   #Calculate Ligand Efficiency
292.   HeavyAtoms = CountAtom !H Obj (l)
293.   LigEff = 0.00+(score_ma)/(HeavyAtoms)
294.   Tabulate (0.00+(LigEff))
295.
296.   #efficiency
297.   eff=''
298.   if (score_ma)>9.5
299.     Shell mkdir (path)\(expname)\VeryHigh_aff
300.     Shell mkdir (path)\(expname)\VeryHigh_aff\SMILES
301.     Compoundmol obj (l),'(cpdname_win)_MA-BndNrg=(file_score_ma)'
302.     SaveSMILES
   (l),(path)\(expname)\VeryHigh_aff\SMILES\(cpdname_win)_MA-
   BndNrg=(file_score_ma).smi,transform=Yes
303.     SaveSDF (l),(path)\(expname)\VeryHigh_aff\(cpdname_win)_MA-
   BndNrg=(file_score_ma).sdf,transform=Yes
304.     eff = '***'
305.   elif (score_ma)>8.5
306.     Shell mkdir (path)\(expname)\High_aff
307.     Shell mkdir (path)\(expname)\High_aff\SMILES
308.     Compoundmol obj (l),'(cpdname_win)_MA-BndNrg=(file_score_ma)'
309.     SaveSMILES (l),(path)\(expname)\High_aff\SMILES\(cpdname_win)_MA-
   BndNrg=(file_score_ma).smi,transform=Yes
310.     SaveSDF (l),(path)\(expname)\High_aff\(cpdname_win)_MA-
   BndNrg=(file_score_ma).sdf,transform=Yes
311.     eff = '** '
312.   elif (score_ma)>7.5
```

```
313.     Shell mkdir (path)\(expname)\Good_aff
314.     Shell mkdir (path)\(expname)\Good_aff\SMILES
315.     Compoundmol obj (l),'(cpdname_win)_MA-BndNrg=(file_score_ma)'
316.     SaveSMILES (l),(path)\(expname)\Good_aff\SMILES\(cpdname_win)_MA-
   BndNrg=(file_score_ma).smi,transform=Yes
317.     SaveSDF (l),(path)\(expname)\Good_aff\(cpdname_win)_MA-
   BndNrg=(file_score_ma).sdf,transform=Yes
318.     eff = '*  '
319.
320.   else
321.     eff= '   '
322.     Shell mkdir (path)\(expname)\Others
323.     Shell mkdir (path)\(expname)\Others\SMILES
324.     Compoundmol obj (l),'(cpdname_win)_MA-BndNrg=(file_score_ma)'
325.     SaveSMILES (l),(path)\(expname)\Others\SMILES\(cpdname_win)_MA-
   BndNrg=(file_score_ma).smi,transform=Yes
326.     SaveSDF (l),(path)\(expname)\Others\(cpdname_win)_MA-
   BndNrg=(file_score_ma).sdf,transform=Yes
327.
328.   Compoundmol obj (l),'(cpdname_win)_AVG-BndNrg=(file_avg)'
329.   SaveSDF (l),(path)\(expname)\SDF\(cpdname_win)_AVG-
   BndNrg=(file_avg).sdf,transform=Yes
330.
331.   ######################## Nice log file module
   ##############################
332.   RecordLog (path)\(expname)\Results\(expname)_results.log,append=yes
333.   contacts() = listres aminoacid with distance <4 from Lig
   1,format=RESNAME RESNUM
334.   print ('(00000+(l-2)) | (cpdname)    | (eff)  | (0.000+((-
   1.000)*(score)))          | (0.000+((-1.000)*(score_ma)))       |
   (0.000+((-1.000)*(score_md)))          | (0.000+((-1.000)*(score_hoh)))
   | (0.000+(-1.000)*(avg))          |  (LigEff)          | (contacts())')
335.   # print ('Residues with distance <5 A from ligand are: (contacts())')
336.   # print ('_____________________________________________________')
337.   # print ('  ')
338.   # Print ('(score)')
339.   StopLog
340.
341.   Nameobj (l),Done
342.   #Print (totobj)
343.   #wait continuebutton
344.   #iterate
345.   if l == (totobj)
346.     SaveTab
   1,(path)\(expname)\Results\(target)_(expname)_results.txt,Format=text,Colu
   mns=6,Numformat=6.2f,Ligand |  IA  VINA  IV-MA   WMD-MA  LigEff |
   Kcal/mol - the higher the better
347.     SaveSCE (path)\(expname)\(target)_(expname)_docked.sce
348.     Stop
349.   else
350.   addobj (l+1)
351.   #fresh receptor structure
352.   LoadYOB (path)\(target)_new.yob
353.   nameobj (target)_new,new
354.   TransferObj new,1
355.   Delobj 1
356.   RenumberObj new,1
```

```
357.    Nameobj new,Receptor
358.    removeobj (1)
359.
360. #Print ('(score_md)')
361. #print ('(score_hoh)')
```

Synthesis of CATS-compounds

General procedure for conversion of Boc-protected amines to tertiary amines via reductive amination:[1]

Boc-protected amines are treated with HCl-solution (4M in 1,4-dioxan, 1 ml/100 mg amine) and stirred for 4 h. All volatile compounds are removed in vacuo and the residue is taken up in 1,2 DCE (5 ml/100 mg amine) and 1.00 eq. of NEt_3 is added. The mixture is stirred for 30 min at room temperature. Consecutively, 1.50 eq. of AcOH, 1.00 eq. of aldehyde and 1.50 eq. of $NaBH(OAc)_3$ are added. The reaction mixture is stirred for 12 h at room temperature followed by addition of CH_2Cl_2 (10 ml/ 100 mg amine) and saturated $NaHCO_3$-solution (5 ml / 100 g amine). The layers are separated and the aqueous layer is extracted with CH_2Cl_2 (3x, 10 ml/100 mg amine). The combined organic layers are washed with water and brine (10 ml/ 100 mg amine each) and dried over Na_2SO_4. After filtration, all volatile compounds are removed and the residue is purified by flash column chromatography on silica.

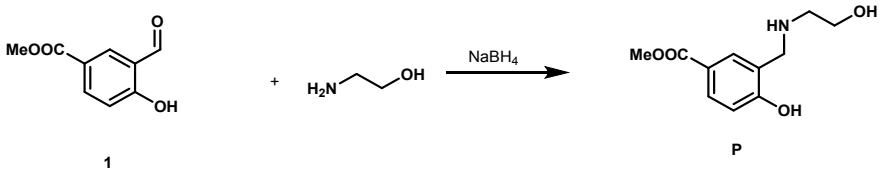
General procedure for MnO_2-mediated oxidations of benzylic alcohols to aldehydes:

Benzylic alcohol is dissolved in CH_2Cl_2 (c = 15 mM) and 30.0 eq. of MnO_2 (Merck KGaA, precipitated active, for synthesis) are added at room temperature. The resulting suspension is vigorously stirred until full conversion is achieved (TLC). The reaction mixture is filtered through a pad of *Celite*® and all volatile compounds are removed under reduced pressure. The crude aldehydes are pure enough for the following steps or can be further purified via flash column chromatography on silica.

General procedure for synthesis of Grignard reagents[2]:

Magnesium turnings were vigorously pestled and dried in high vacuum. 6.00 eq. of prepared Magnesium turnings are suspended in dry THF. A solution of 1.00 eq. of the corresponding halide in dry THF is added dropwise to the magnesium turnings until the suspension turns turbid. Addition is continued in a manner that the temperature doesn´t exceed 30 °C. After complete addition, the reaction mixture is stirred for 2 h at room temperature.

Methyl 4-hydroxy-3-(((2´-hydroxyethyl)amino)methyl)benzoate



A solution of 2.00 g aldehyde **1** (11.1 mmol, 1.00 eq) in 100 ml of a THF/MeOH mixture (9:1 v/v) is treated with 0.85 ml 2-hydroxyethylamine (865 mg, 14.2 mmol, 1.25 eq.) and stirred at room temperature for 1 h. After that, 378 mg of $NaBH_4$ (9.99 mmol, 0.90 eq.) are added in one portion and the reaction mixture is stirred for 45 min. All volatile compounds are removed under reduced pressure and the residue is portioned between 40 ml of water and 100 ml of EtOAc. The layers are separated and the aqueous layer is extracted with EtOAc (3x30 ml). The combined organic layers are dried over $MgSO_4$, the solid is filtered and the solvent removed in vacuo. The residue is washed with 10 ml cold CH_2Cl_2 and dried to yield 1.62 g (7.19 mmol, 65%) of the title compound as off-white solid pure enough for the next reaction. The compound can also be purified via reversed phase (C18-silica) column chromatography (Water/MeCN 9:1).

TLC: R_f = 0.11 (EtOAc/MeOH 4:1) [UV, $KMnO_4$].

M.p.: 154 °C

IR (ATR): = 3026 cm^{-1}, 2984, 2945, 2847, 2765, 2560, 1692, 1605, 1488, 1467.

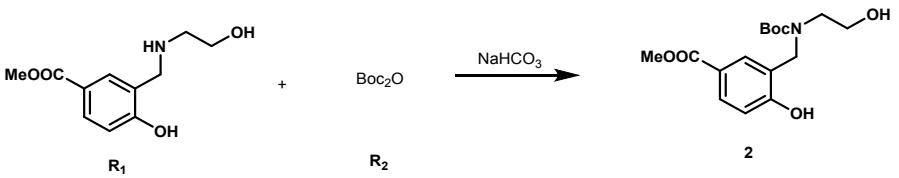
^{1}H-NMR: (500 MHz, DMSO-d6): δ [ppm] = 7.71 (d, ^{4}J = 2.1 Hz, 1H), 7.69 (dd, ^{3}J = 8.4 Hz, ^{4}J = 2.1 Hz, 1H), 6.74 (d, ^{3}J = 8.4 Hz, 1H), 3.88 (s, 2H), 3.77 (s, 3H), 3.50 (t, ^{3}J = 5.6 Hz, 2H), 2.60 (t, ^{3}J = 5.6 Hz, 2H).

^{13}C-NMR: (101 MHz, DMSO-d6): δ [ppm] = 166.2, 163.3, 130.1, 129.9, 123.9, 118.9, 115.6, 59.6, 51.5, 50.2, 49.8.

LC-MS: tR = 0.94 min, m/z = 226 $[M+H]^{+}$.

HRMS (ESI): calculated for $C_{11}H_{16}NO_4$: 226.10793, found: 226.10734.

Methyl 3-(((tert-butoxycarbonyl)(2´-hydroxyethyl)amino)methyl)-4-hydroxybenzoate (2)



A suspension of 1.40 g Amine R1 (6.22 mmol, 1.00 eq) in 90 ml of a mixture of EtOAc/saturated aqueous $NaHCO_3$ solution (2:1 v/v) is treated with 2.08 g Boc_2O (9.51 mmol, 1.50 eq.) and stirred at room temperature for 16 h. The layers are separated and the aqueous layer is extracted with EtOAc (3x20 ml). The combined organic layers are dried over Na_2SO_4, the solid is filtered off and all volatile compounds are removed under reduced pressure. The residue is purified via flash column chromatography on silica (Cy/EtOAc 3:1 → 1:1) yielding 1.46 g (4.49 mmol, 72%) of the desired compound as a colourless liquid which solidifies upon standing.

TLC: R_f = 0.18 (Cy/EtOAc 1:1) [UV, $KMnO_4$].

M.p.: 133 °C

IR (ATR): = 3236 cm^{-1}, 2977, 2953, 1714, 1650, 1607, 1417, 1367, 1277, 1238.

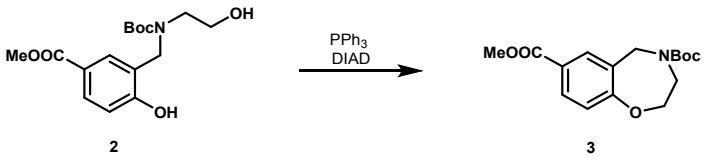
^{1}H-NMR: (400 MHz, $CDCl_3$): δ [ppm] = 10.01 (br. s, 1H), 7.90 (dd, ^{3}J = 8.5 Hz, ^{4}J = 2.2 Hz, 1H), 7.84 (d, ^{4}J = 2.2 Hz, 1H), 6.93 (d, ^{3}J = 8.5 Hz, 1H), 4.46 (s, 2H), 3.87 (s, 3H), 3.77 (t, ^{3}J = 5.6 Hz, 2H), 3.38 (t, ^{3}J = 5.6 Hz, 2H), 1.48 (s, 9H).

^{13}C-NMR: (101 MHz, $CDCl_3$): δ [ppm] = 167.0, 160.9, 158.4, 133.5, 132.1, 122.8, 121.3, 117.6, 82.6, 61.2, 52.0, 49.1, 48.6, 28.5.

LC-MS: tR = 3.29 min, m/z = 348 $[M+Na]^{+}$.

HRMS (ESI): calculated for $C_{16}H_{24}NO_6$= 326.16036, found: 326.15981.

4-(*tert*-butyl) 7-methyl 2,3-dihydrobenzo[f][1,4]oxazepine-4,7(5H)-dicarboxylate (3)



2 3

A solution of 1.15 g Triphenylphosphine (4.38 mmol, 1.50 eq) in 30 ml of dry THF is cooled to 0 °C and treated with 853 µl DIAD (876 mg, 4.34 mmol, 1.50 eq.). The mixture is stirred at 0 °C for 30 min followed by addition of a solution of 940 mg **2** (2.89 mmol, 1.00 eq.) dissolved in 70 ml of dry THF. The solution is allowed to warm to room temperature and is stirred for 3 h. All volatile compounds are removed under reduced pressure and the residue is purified via flash column chromatography on silica (Cy/EtOAc 95:5) yielding 804 mg (2.62 mmol, 91%) of the title compound as white solid.

TLC: R_f = 0.37 (Cy/EtOAc 3:1) [UV, $KMnO_4$].

M.p.: 84 °C

IR (ATR): = 2975 cm^{-1}, 2931, 1718, 1692, 1602, 1495, 1453, 1437, 1407, 1366.

^{1}H-NMR*: (400 MHz, $CDCl_3$, 323 K): δ [ppm] = 7.91 (br.s, 1H), 7.87 (dd, ^{3}J = 8.4 Hz, ^{4}J = 2.2 Hz, 1H), 7.02 (d, ^{3}J = 8.4 Hz, 1H), 4.47 (br.s, 2H), 4.11-4.09 (m, 2H), 3.88 (s, 3H), 3.81-3.79 (m, 2H), 1.40 (s, 9H).

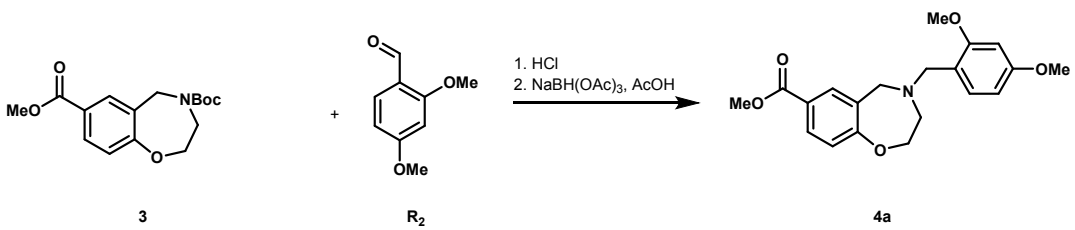
^{13}C-NMR*: (101 MHz, $CDCl_3$, 323 K): δ [ppm] = 166.6, 163.1, 154.9, 131.7, 130.7, 125.4, 121.4, 80.5, 72.7, 52.0, 50.2, 49.8, 28.5 (3xC).

*despite elevated temperatures were applied, line broadening could not be surpressed. One C-signal could not be detected.

LC−MS: tR = 3.74 min, m/z = 208 $[M-Boc+H]^{+}$.

HRMS (ESI): calculated for $C_{12}H_{14}NO_5$= 252.08720, found: 252.08667.

Methyl 4-(2′,4′-dimethoxybenzyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxylate (4a)



According to the general procedure 1, 700 mg of Boc-protected amine **3** (2.28 mmol, 1.00 eq.) are reacted with 378 mg of aldehyde **R2** (2.28 mmol, 1.00 eq.) to yield after purification (silica, Cy/EtOAc 85:15 → 75:25) 632 mg (1.77 mmol, 90%) of the title compound as colourless liquid.

TLC: R_f = 0.29 (Cy/EtOAc 1:1) [UV, $KMnO_4$].

IR (ATR): = 2949 cm^{-1}, 2835, 1715, 1609, 1587, 1505, 1454, 1436, 1419, 1286.

^{1}H-NMR: (400 MHz, $CDCl_3$): δ [ppm] = 7.88 (dd, ^3J = 8.3 Hz, ^4J = 2.2 Hz, 1H), 7.82 (d, ^4J= 2.2 Hz, 1H), 7.21 (d, ^3J = 7.8 Hz, 1H), 7.03 (d, ^3J = 8.3 Hz, 1H), 6.47* (dd, 1H), 6.46* (s, 1H), 4.16-4.14 (m, 2H), 3.90 (s, 2H), 3.89 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.61 (s, 2H), 3.10-3.08 (m, 2H).

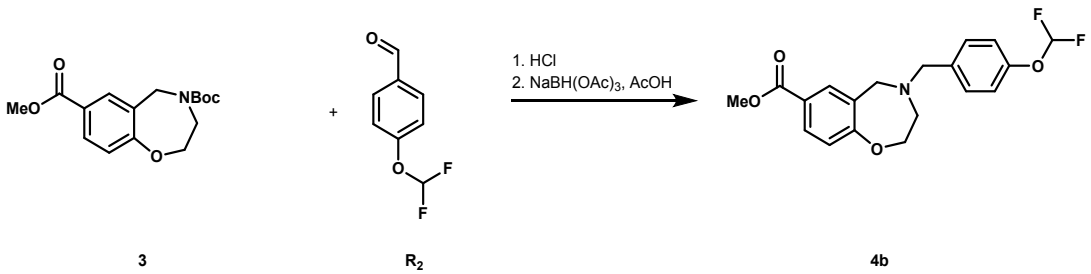
*signals overlap

^{13}C-NMR: (101 MHz, $CDCl_3$): δ [ppm] = 166.9, 164.1, 160.3, 158.9, 132.8, 132.0, 131.4, 130.4, 125.1, 120.9, 119.0, 104.3, 98.7, 70.8, 58.5, 57.2, 55.6, 55.5, 52.1, 52.0.

LC-MS: tR = 2.83 min, m/z = 358 $[M+H]^+$.

HRMS (ESI): calculated for $C_{20}H_{24}NO_5$ = 358,16545, found: 358.16482.

Methyl 4-(4´-(difluoromethoxy)benzyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxylate (4b)



3 R_2 4b

According to general procedure 1, 300 mg of Boc-protected amine **3** (976 µmol, 1.00 eq.) are reacted with 131 µl of aldehyde R2 (171 mg, 976 µmol, 1.00 eq.) to yield after purification (silica, Cy/EtOAc 90:10 → 75:25) 258 mg (710 µmol, 73%) of the title compound as white solid.

TLC: R_f = 0.45 (Cy/EtOAc 1:1) [UV, $KMnO_4$].

M.p.: 90 °C

IR (ATR): = 2951 cm^{-1}, 2823, 1715, 1608, 1508, 1498, 1437, 1290, 1253, 1220.

^{1}H-NMR: (400 MHz, $CDCl_3$): δ [ppm] = 7.88 (dd, ^3J = 8.3 Hz, ^4J = 2.2 Hz, 1H), 7.73 (d, ^4J = 2.2 Hz, 1H), 7.31 (d, ^3J = 8.6 Hz, 2H), 7.08 (d, ^3J = 8.6 Hz, 2H), 7.05 (d, ^3J = 8.3 Hz, 1H), 6.52 (t, $^2J_{H\text{-}F}$ = 74.1 Hz, 1H), 4.14-4.11 (m, 2H), 3.88 (s, 3H), 3.84 (s, 2H), 3.63 (s, 2H), 3.07-3.05 (m, 2H).

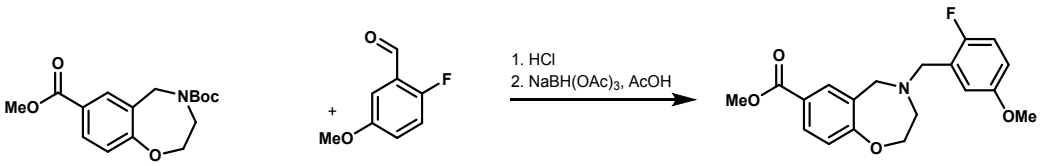
^{19}F-NMR (376 MHz, $CDCl_3$): δ [ppm] = −80.6 ($^2J_{H\text{-}F}$ = 74.1 Hz).

^{13}C-NMR: (101 MHz, $CDCl_3$): δ [ppm] = 166.8, 164.0, 150.6, 135.8, 132.5, 131.5, 130.6, 130.3 (2xC), 125.3, 121.1, 119.6 (2xC), 116.1, 70.7, 58.5, 58.3, 57.6, 52.2.

LC-MS: tR = 2.87 min, m/z = 364 $[M+H]^+$.

HRMS (ESI): calculated for $C_{19}H_{20}F_2NO_4$ = 364.13604, found: 364.13542.

Methyl 4-(2´-fluoro-5´-methoxybenzyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-



carboxylate (4c) 3 R_2 4c

According to general procedure 1, 272 mg of Boc-protected amine **3** (885 µmol, 1.00 eq.) are reacted with 112 µl of aldehyde R2 (139 mg, 885 µmol, 1.00 eq.) to yield after purification (SiO_2, Cy/EtOAc 85:15 → 75:25) 189 mg (547 µmol, 62%) of the title compound as colourless liquid.

TLC: R_f = 0.43 (Cy/EtOAc 1:1) [UV, $KMnO_4$].

IR (ATR): = 2997 cm^{-1}, 2950, 2836, 1715, 1607, 1494, 1435, 1366, 1252, 1193.

^{1}H-NMR: (400 MHz, $CDCl_3$): δ [ppm] = 7.89 (dd, 1H), 7.81 (d, 1H), 7.05 (d, 1H), 6.96* (*virt*.t, 1H), 6.93* (dd, 1H), 6.77 (dt, 1H), 4.16-4.14 (m, 2H), 3.90 (s, 2H), 3.89 (s, 3H), 3.77 (s, 3H), 3.69 (s, 2H), 3.11-3.08 (m, 2H).

*signals overlap

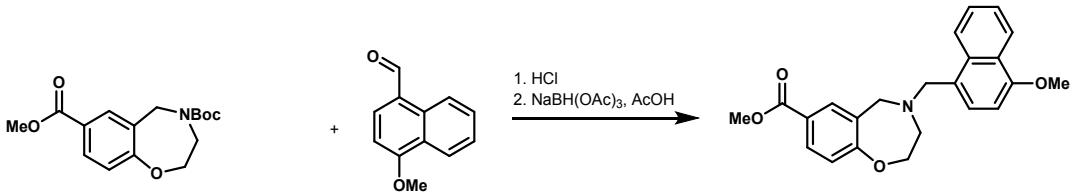
^{13}C-NMR: (101 MHz, $CDCl_3$): δ [ppm] = 166.8, 164.1, 155.8 (d), 155.8 (d), 132.6, 131.6, 130.6, 125.9 (d), 125.3, 121.1, 116.0 (d), 115.5 (d), 114.3 (d), 70.8, 58.7, 57.4, 55.9, 52.1, 51.9 (d).

^{19}F-NMR: (376 MHz, $CDCl_3$): δ [ppm] = −129.1.

LC-MS: tR = 2.83 min, m/z = 346 $[M+H]^+$.

HRMS (ESI): calculated for $C_{19}H_{21}FNO_4$ = 346.14546, found: 346.14496.

Methyl 4-((4´-methoxynaphthalen-1´-yl)methyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxylate (4d)



3 R_2 4d

According to the general procedure 1, 300 mg of Boc-protected amine **3** (976 µmol, 1.00 eq.) are reacted with 188 mg of aldehyde R2 (976 µmol, 1.00 eq.) to yield after purification (silica, Cy/EtOAc 95:05) 166 mg (440 µmol, 45%) of the title compound as colourless oil.

TLC: R_f = 0.56 (Cy/EtOAc 1:1) [UV, $KMnO_4$].

IR (ATR): = 2949 cm^{-1}, 2840, 1717, 1607, 1585, 1463, 1391, 1292, 1254, 1226.

^{1}H-NMR: (300 MHz, $CDCl_3$): δ [ppm] = 8.29 (dd, 1H), 8.19 (dd, 1H), 7.90 (d, 1H), 7.81 (d, 1H), 7.54-7.45 (m, 2H), 7.22 (d, 1H), 7.06 (d, 1H), 6.73 (d, 1H), 4.16-4.14 (m, 2H), 4.01 (s, 3H), 3.98 (s, 2H), 3.94 (s, 2H), 3.90 (s, 3H), 3.12-3.09 (m, 2H).

^{13}C-NMR: (75.0 MHz, $CDCl_3$): δ [ppm] = 166.9, 164.1, 155.6, 133.5, 132.9, 131.9, 130.5, 127.8, 126.6, 126.2, 125.9, 125.2, 125.2, 124.6, 122.5, 121.0, 102.9, 70.7, 58.4, 57.1, 57.0, 55.6, 52.1.

LC-MS: tR = 3.08 min, m/z = 378 $[M+H]^+$.

HRMS (ESI): calculated for $C_{23}H_{24}NO_4$ = 378.17053, found: 378.16998.

(4-(2´,4´-dimethoxybenzyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-7-yl)methanol (5a)

4a **R_2** **5a**

A solution of 500 mg Ester **4a** (1.34 mmol, 1.00 eq.) in 30 ml of dry THF is cooled to 0 °C. To this solution, 83.3 mg (2.21 mmol, 1.50 eq.) $LiAlH_4$ are added in one portion. The mixture is stirred at 0 °C for 90 min. The reaction is quenched by addition of 15 ml water. Extraction with CH_2Cl_2 (3x 25 ml) is followed by drying over Na_2SO_4. The solid is filtered and all volatile compounds are removed under reduced pressure. The residue is purified via flash column chromatography on silica (Cy/EtOAc 1:1 → 1:4) yielding 617 mg of the title compound (992 µmol, 74%) as colorless oil.

TLC: R_f = 0.08 (Cy/EtOAc 1:1) [UV, KMnO4].

IR (ATR): = 3375 cm^{-1}, 2936, 2835, 2896, 1612, 1587, 1504, 1462, 1291, 1208.

^{1}H-NMR: (400 MHz, $CDCl_3$): δ [ppm] = 7.22 (d, ^3J = 8.6 Hz, 1H), 7.17 (dd, ^3J = 8.1 Hz, ^4J = 2.4 Hz, 1H), 7.11 (d, ^4J =2.1 Hz, 1H), 6.99 (d, ^3J = 8.1 Hz, 1H), 6.47* (dd, 1H), 6.46* (s, 1H), 4.61 (s, 2H), 4.10-4.08 (m, 2H), 3.86 (s, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.60 (s, 2H), 3.07-3.05 (m, 2H).

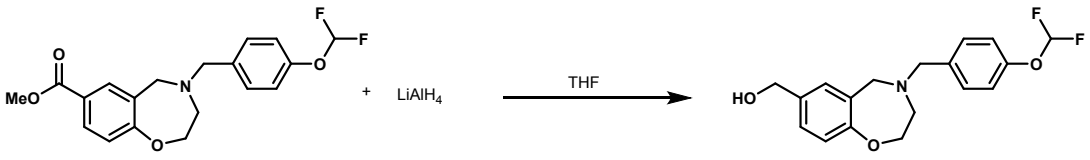
*signals overlap

^{13}C-NMR: (101 MHz, $CDCl_3$): δ [ppm] = 160.2, 159.8, 159.0, 135.9, 132.5, 131.4, 129.9, 127.4, 121.0, 119.2, 104.2, 98.7, 70.8, 65.1, 58.9, 57.6, 55.6, 55.5, 52.2.

LC-MS: tR = 3.56 min, m/z = 330 $[M+H]^+$.

HRMS (ESI): calculated for $C_{19}H_{24}NO_4$ = 330.17053, found: 330.16988.

(4-(4´-(difluoromethoxy)benzyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-7-yl)methanol (5b)



4b R_2 5b

A solution of 220 mg Ester **4b** (605 µmol, 1.00 eq.) in 15 ml of dry THF is cooled to 0 °C. To this solution, 36.3 mg (956 µmol, 1.50 eq.) $LiAlH_4$ are added in one portion. The mixture is stirred at 0 °C for 90 min. The reaction is quenched by addition of 15 ml water. Extraction with CH_2Cl_2 (3x 25 ml) is followed by drying over Na_2SO_4. The solid is filtered and all volatile compounds are removed under reduced pressure. The residue is purified via flash column chromatography on silica (Cy/EtOAc 7:3 → 1:1) yielding 135 mg (403 µmol, 67%) as colorless oil.

TLC: R_f = 0.13 (Cy/EtOAc 1:1) [UV, $KMnO_4$].

IR (ATR): = 3026 cm–1, 2984, 2847, 2765, 1692, 1605, 1488, 1444, 1428, 1311.

^{1}H-NMR: (400 MHz, $CDCl_3$): δ [ppm] = 7.32 (d, ^3J = 8.5 Hz, 2H), 7.19 (d, ^3J = 8.1 Hz, 1H), 7.08 (d, ^3J = 8.5 Hz, 2H), 7.01 (d, ^3J = 8.1 Hz, 2H), 6.51 (t, $^2J_{H-F}$ = 74.0 Hz, 1H), 4.61 (s, 2H), 4.08-4.06 (m, 2H), 3.79 (s, 2H), 3.63 (s, 2H), 3.06-3.04 (m, 2H).

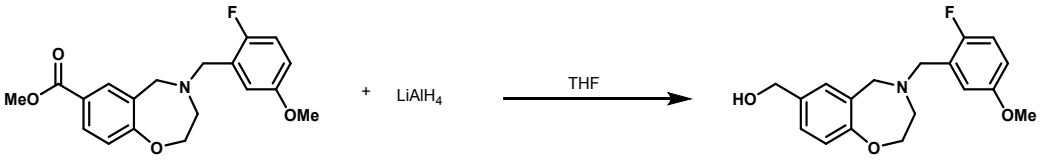
^{19}F-NMR (376 MHz, $CDCl_3$): δ [ppm] = −80.7.

^{13}C-NMR: (101 MHz, $CDCl_3$): δ [ppm] = 159.7, 150.5, 136.1, 136.0, 132.0, 130.4 (2xC), 129.7, 127.6, 121.1, 119.6 (2xC), 118.7, 116.1, 113.5, 70.6, 65.0, 58.5, 58.5, 58.1.

LC-MS: tR = 2.57 min, m/z = 336 $[M+H]^+$.

HRMS (ESI): calculated for $C_{18}H_{20}F_2NO_3$ = 336.14112, found: 336.14050.

(4-(2´-fluoro-5´-methoxybenzyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-7yl)methanol (5c)



A solution of 181 mg Ester **4c** (524 µmol, 1.00 eq.) in 15 ml of dry THF is cooled to 0 °C. To this solution, 31.4 mg (827 µmol, 1.50 eq.) $LiAlH_4$ are added in one portion. The mixture is stirred at 0 °C for 3h. The reaction is quenched by addition of 15 ml water. Extraction with CH_2Cl_2 (3x 25 ml) is followed by drying over Na_2SO_4. The solid is filtered and all volatile compounds are removed under reduced pressure. The residue is purified via flash column chromatography on silica (Cy/EtOAc 80:20 → 50:50) yielding 86.6 mg (273 µmol, 52%) as clear liquid.

TLC: R_f = 0.18 (Cy/EtOAc 1:1) [UV, CAM].

IR (ATR): = 3321 cm^{-1}, 2934, 1464, 1257, 1241, 1202, 1152, 1109, 1033, 870.

^{1}H-NMR: (400 MHz, $CDCl_3$): δ [ppm] = 7.19 (dd, 1H), 7.09 (d, 1H), 7.01 (d, 1H), 6.97-6.93 (m, 2H), 6.76 (dt, 1H), 4.61 (s, 2H), 4.10-4.08 (m, 2H), 3.86 (s, 2H), 3.77 (s, 3H), 3.67 (s, 2H), 3.10-3.08 (m, 2H).

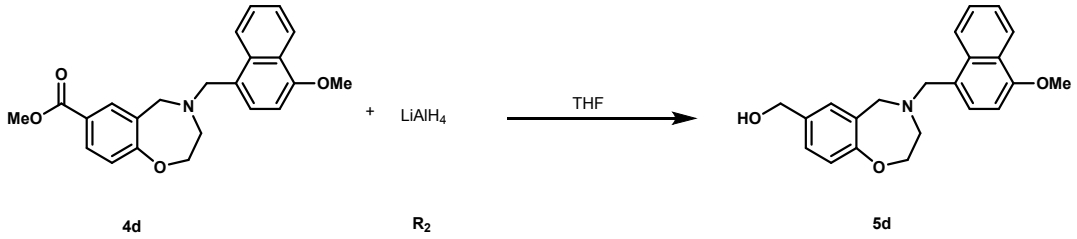
^{13}C-NMR: (101 MHz, $CDCl_3$): δ [ppm] = 159.7, 155.8 (d), 155.8(d), 136.1, 132.0, 129.8, 127.6, 126.1, 121.1, 116.0 (d), 115.8 (d), 114.1 (d), 70.6, 65.1, 58.8, 57.9, 55.9, 51.8 (d).

^{19}F-NMR (376 MHz, $CDCl_3$): δ [ppm] = −129.0.

LC-MS: tR = 2.49 min, m/z = 318 $[M+H]^+$.

HRMS (ESI): calculated for $C_{18}H_{21}FNO_3$ = 318.15005, found: 318.14990.

(4-((4´-methoxynaphthalen-1-yl)methyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-7-yl)methanol (5d)



4d R_2 5d

A solution of 150 mg Ester **4d** (397 µmol, 1.00 eq.) in 15 ml of dry THF is cooled to 0 °C. To this solution, 23.8 mg (627 µmol, 1.50 eq.) $LiAlH_4$ are added in one portion. The mixture is stirred at 0 °C for 3 h. The reaction is quenched by addition of 15 ml water. Extraction with CH_2Cl_2 (3x 25 ml) is followed by drying over Na_2SO_4. The solid is filtered and all volatile compounds are removed under reduced pressure. The residue is purified via flash column chromatography on silica (Cy/EtOAc 70:30 → 50:50) yielding 96.6 mg (276 µmol, 70%) colourless oil.

TLC: R_f = 0.30 (Cy/EtOAc 1:1) [UV, CAM].

IR (ATR): = 3371 cm–1, 2937, 1585, 1498, 1391, 1273, 1244, 1225, 1155, 1092.

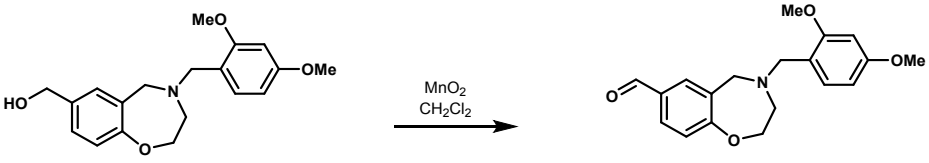
^{1}H-NMR: (300 MHz, $CDCl_3$): δ [ppm] = 8.31-8.28 (m, 1H), 8.21-8.18 (m, 1H), 7.54-7.45 (m, 2H), 7.24 (d, 1H), 7.19 (dd, 1H), 7.07 (d, 1H), 7.02 (d, 1H), 6.73 (d, 1H), 4.61 (s, 2H), 4.11-4.09 (m, 2H), 4.01 (s, 3H), 3.97 (d, 2H), 3.89 (s, 2H), 3.12-3.09 (m, 2H).

^{13}C-NMR: (75.0 MHz, $CDCl_3$): δ [ppm] = 159.8, 155.5, 135.9, 133.5, 132.3, 130.1, 127.7, 127.4, 126.6, 126.2, 125.2, 124.7, 122.5, 121.0, 102.9, 70.4, 65.1, 58.5, 57.7, 56.8, 55.6.

LC-MS: tR = 2.78 min, m/z = 350 $[M+H]^+$.

HRMS (ESI): calculated for $C_{22}H_{24}NO_3$ = 350.17562, found: 350.17496.

4-(2´,4´-dimethoxybenzyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carbaldehyde (6a)



5a 6a

According to the general procedure 2, 466 mg of alcohol **5a** (1.42 mmol, 1.00 eq.) are reacted with 3.69 g MnO_2 (42.2 mmol, 30.0 eq.) for 1 h to yield after purification (SiO_2, Cy/EtOAc 50:50) 463 mg (1.25 mmol, 89%) of the title compound as colourless oil.

TLC: R_f = 0.32 (Cy/EtOAc 1:1) [UV, CAM].

IR (ATR): = 2936 cm–1, 2834, 1691, 1601, 1588, 1505, 1456, 1419, 1288, 1235.

^{1}H-NMR: (300 MHz, $CDCl_3$): δ [ppm] = 9.91 (s, 1H), 7.72 (dd, 1H), 7.64 (d, 1H), 7.21 (d, 1H), 7.12 (d, 1H), 6.48* (dd, 1H), 6.47* (s, 1H), 4.20-4.17 (m, 2H), 3.91 (s, 2H), 3.82 (s, 3H), 3.78(s, 3H), 3.62 (s, 2H), 3.12-3.09 (m, 2H).

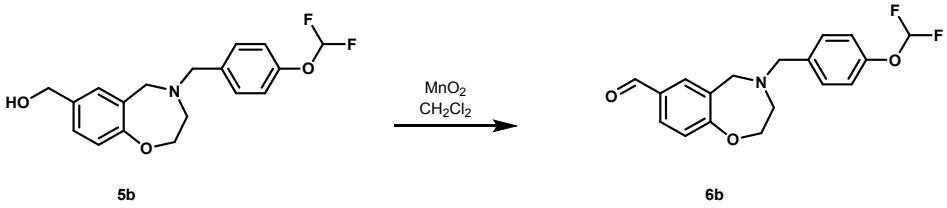
*signals overlap

^{13}C-NMR: (75.0 MHz, $CDCl_3$): δ [ppm] = 191.2, 165.5, 160.3, 158.9, 132.7, 132.6, 132.0, 131.4, 131.0, 121.7, 118.8, 104.3, 98.7, 71.1, 58.4, 57.3, 55.6, 55.5, 52.2.

LC-MS: tR = 2.65 min, m/z = 328 $[M+H]^+$.

HRMS (ESI): calculated for $C_{19}H_{22}NO_4$ = 328.15488, found: 328.15437.

4-(4´-(difluoromethoxy)benzyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carbaldehyde (6b)



5b 6b

According to the general procedure 2, 105 mg of alcohol **5b** (313 µmol, 1.00 eq.) are reacted with 816 mg MnO_2 (9.39 mmol, 30.0 eq.) for 1 h to yield after purification (SiO_2, Cy/EtOAc 90:10 → 70:30) 69.2 mg (208 µmol, 66%) of the title compound as colourless oil.

TLC: R_f = 0.45 (Cy/EtOAc 1:1) [UV, CAM].

IR (ATR): = 2931 cm–1, 2819, 1692, 1601, 1577, 1508, 1494, 1381, 1290, 1234.

^{1}H-NMR: (400 MHz, $CDCl_3$): δ [ppm] = 9.90 (s, 1H), 7.74 (dd, 1H), 7.56 (d, 1H), 7.31 (d, 2H), 7.14 (d, 1H), 7.09 (d, 2H), 6.52 (t, 1H), 4.18-4.15 (m, 2H), 3.85 (s, 2H), 3.65 (s, 2H), 3.09-3.07 (m, 2H).

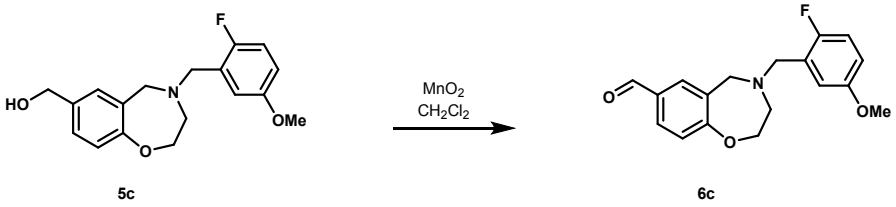
^{13}C-NMR: (101 MHz, $CDCl_3$): δ [ppm] = 191.1, 165.4, 150.6, 135.6, 132.4, 132.2, 132.1, 131.1, 130.3 (2xC), 121.8, 119.7 (2xC), 116.1 (t), 71.1, 58.8, 58.2, 57.7.

^{19}F-NMR: (376 MHz, $CDCl_3$): δ [ppm] = −80.7.

LC-MS: tR = 2.73 min, m/z = 334 $[M+H]^+$.

HRMS (ESI): calculated for $C_{18}H_{18}F_2NO_3$ = 334.12547, found: 334.12486.

4-(2´-fluoro-5´-methoxybenzyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carbaldehyde (6c)



5c 6c

According to the general procedure 2, 75.0 mg of alcohol **5c** (236 µmol, 1.00 eq.) are reacted with 616 mg MnO_2 (7.09 mmol, 30.0 eq.) for 1 h to yield after purification (SiO_2, Cy/EtOAc 80:20 → 60:40) 48.3 mg (153 µmol, 65%) of the title compound as colourless oil.

TLC: R_f = 0.41 (Cy/EtOAc 1:1) [UV, CAM].

IR (ATR): = 2940 cm^{-1}, 2834, 1693, 1601, 1577, 1496, 1428, 1237, 1200, 1154.

^{1}H-NMR: (300 MHz, $CDCl_3$): δ [ppm] = 9.91 (s, 1H), 7.74 (dd, 1H), 7.63 (d, 1H), 7.14 (d, 1H), 6.96* (t, 1H), 6.94* (dd, 1H), 6.77 (ddd, 1H), 4.20-4.17 (m, 2H), 3.91 (s, 2H), 3.77 (s, 3H), 3.70 (s, 2H), 3.12-3.10 (m, 2H).

*signals overlap

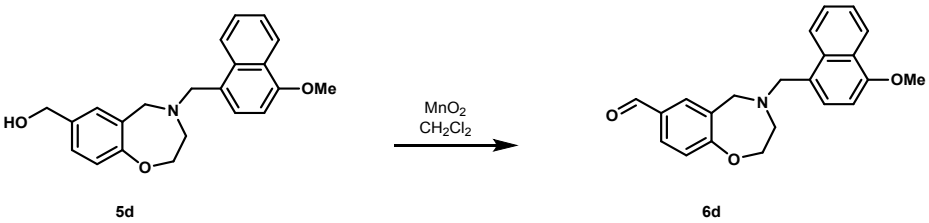
^{13}C-NMR: (75.0 MHz, $CDCl_3$): δ [ppm] = 191.1, 165.4, 155.9 (d), 155.9 (d), 132.5, 132.3, 132.1, 131.2, 125.8 (d), 121.8, 116.0 (d), 115.7 (d), 114.2 (d), 71.1, 58.5, 57.4, 55.9, 52.1 (d).

^{19}F-NMR: (376 MHz, $CDCl_3$): δ [ppm] = −129.1.

LC-MS: tR = 2.70 min, m/z = 316 $[M+H]^+$.

HRMS (ESI): calculated for $C_{18}H_{19}FNO_3$ = 316.13490, found: 316.13428.

4-((4´-methoxynaphthalen-1-yl)methyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carbaldehyde (6d)



5d 6d

According to the general procedure 2, 90.6 mg of alcohol **5d** (259 µmol, 1.00 eq.) are reacted with 676 mg MnO_2 (7.78 mmol, 30.0 eq.) for 1 h to yield after purification (SiO_2, Cy/EtOAc 85:15 → 70:30) 51.1 mg (150 µmol, 58%) of the title compound as colourless oil.

TLC: R_f = 0.55 (Cy/EtOAc 1:1) [UV, CAM].

IR (ATR): = 2937 cm^{-1}, 2827, 1693, 1600, 1585, 1512, 1493, 1463, 1442, 1426.

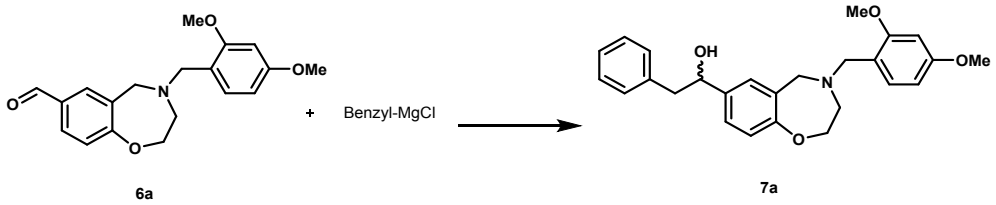
^{1}H-NMR: (300 MHz, $CDCl_3$): δ [ppm] = 9.91 (s, 1H), 8.32-8.28 (m, 1H), 8.21-8.17 (s, 1H), 7.74 (dd, 1H), 7.61 (d, 1H), 7.54-7.45 (m, 2H), 7.22 (d, 1H), 7.15 (d, 1H), 6.74 (d, 1H), 4.21-4.18 (m, 2H), 4.02 (s, 3H), 4.00 (s, 2H), 3.94 (s, 2H), 3.15-3.12 (s, 2H).

^{13}C-NMR: (75.0 MHz, $CDCl_3$): δ [ppm] = 191.2, 165.4, 155.6, 133.5, 132.8, 132.6, 132.1, 131.0, 127.8, 126.7, 126.2, 125.8, 125.3, 124.6, 122.5, 121.8, 102.9, 71.0, 58.1, 57.2, 57.2, 55.7.

LC-MS: tR = 2.97 min, m/z = 348 $[M+H]^+$.

HRMS (ESI): calculated for $C_{22}H_{22}NO_3$ = 348.15997, found: 348.15933.

1-(4´-(2´´,4´´-dimethoxybenzyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-7´-yl)-2-phenylethan-1-ol (7a)



6a 7a

To a solution of 170 mg of aldehyde **6a** (519 µmol, 1.00 eq.) in 10 ml of dry THF, 390 µl (779 µmol, 1.50 eq.) of benzyl magnesiumchloride solution (2M in THF) are added dropwise at room temperature. After 90 min, another 390 µl of benzyl magnesiumchloride solution are added and the mixture is stirred for one more hour. The reaction is quenched by addition of 2 ml sat. NH_4Cl solution

and 25 ml CH_2Cl_2. The resulting layers are separated and the aqueous layer is extracted with CH_2Cl_2 (2x10 ml). The combined organic layers are dried over Na_2SO_4, the solid filtered off and all volatile compounds are removed in vacuo. The residue is subjected to flash column chromatography (SiO_2, Cy/EtOAc 75:25 → 50:50) to yield 138 mg (329 µmol, 63%) of the title compound as white foam.

TLC: R_f = 0.08 (Cy/EtOAc 1:1) [UV, CAM].

IR (ATR): = 3385 cm^{-1}, 2936, 1611, 1587, 1499, 1454, 1438, 11419, 1290, 1264.

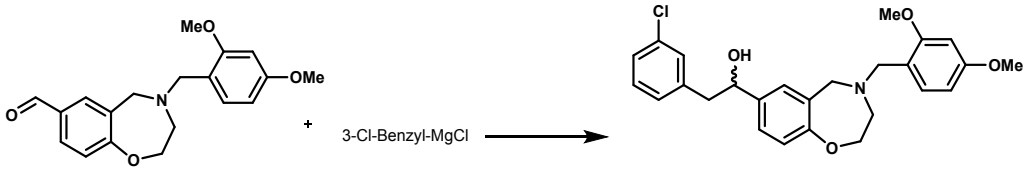
^{1}H-NMR: (400 MHz, $CDCl_3$): δ [ppm] = 7.32-7.28 (m, 2H), 7.25-7.22 (m, 1H), 7.21-7.16 (m, 4H), 7.11 (d, 1H), 6.99 (d, 1H), 6.48-6.45 (m, 2H), 4.84 (dd, 1H), 4.11-4.08 (m, 2H), 3.87 (s, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.59 (s, 2H), 3.08-3.06 (m, 2H), 3.03-2.94 (m, 2H).

^{13}C-NMR: (101 MHz, $CDCl_3$): δ [ppm] = 160.2, 159.7, 159.0, 138.8, 138.3, 132.3, 131.5, 129.6 (2xC), 128.6 (2xC), 128.6, 126.8, 126.1, 120.8, 119.2, 104.2, 98.7, 75.1, 70.6, 59.0, 57.5, 55.6, 55.5, 52.0, 46.2.

LC-MS: tR = 3.03 min, m/z = 420 $[M+H]^+$.

HRMS (ESI): calculated for $C_{26}H_{30}NO_4$ = 420.21748, found: 420.21688.

2-(3´´-chlorophenyl)-1-(4´-(2´´´,4´´´-dimethoxybenzyl)-2´,3´,4´,5´-tetrahydrobenzo[f][1´,4´]oxazepin-7´-yl)ethan-1-ol (7b)



6a 7b

To a solution of 45.0 mg of aldehyde **6a** (137 µmol, 1.00 eq.) in 10 ml of dry THF, 206 µmol, (1.50 eq.) of 3-Cl-Benzylmagnesiumchlorid* solution (in THF) are added dropwise at room temperature. After 90 min, another µmol of 3-Cl-benzyl magnesiumchloride solution are added and the mixture is stirred for one more hour. The reaction is quenched by addition of 2 ml sat. NH_4Cl solution and 15 ml CH_2Cl_2. The resulting layers are separated and the aqueous layer is extracted with CH_2Cl_2 (2x10 ml). The combined organic layers are dried over Na_2SO_4, the solid filtered off and all volatile compounds are removed in vacuo. The residue is subjected to flash column chromatography (SiO_2, Cy/EtOAc 80:20 → 50:50) to yield 25.2 mg (56.0 µmol, 40%) of the title compound as colourless oil.

*see general procedures for preparation of Grignard reagents

TLC: R_f = 0.09 (Cy/EtOAc 1:1) [UV, CAM].

IR (ATR): = 3477 cm^{-1}, 2935, 2863, 1612, 1586, 1504, 1464, 1438, 1291, 1238.

^{1}H-NMR: (400 MHz, $CDCl_3$): δ [ppm] = 7.21-7.13 (m, 5H), 7.07 (d, 1H), 7.06-7.03 (m, 1H), 6.99 (d, 1H), 6.47-6.45 (m, 2H), 4.82 (t, 1H), 4.10-4.08 (m, 2H), 3.86 (s, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.59 (s, 2H), 3.07-3.05 (m, 2H), 2.96 (d, 2H).

^{13}C-NMR: (101 MHz, $CDCl_3$): δ [ppm] = 160.3, 159.8, 159.0, 140.4, 138.6, 134.3, 132.3, 131.5, 129.7 (2xC), 128.6, 127.9, 126.9, 126.0, 120.9, 119.1, 104.2, 98.7, 74.9, 70.6, 58.9, 57.5, 55.6, 55.5, 52.1, 45.7.

LC-MS: tR = 3.03 min, m/z = 454 $[M+H]^+$.

HRMS (ESI): calculated for $C_{26}H_{29}ClNO_4$ = 454.17851, found: 454.17789.

1-(4´-(2´´,4´´-dimethoxybenzyl)-2´,3´,4´,5´-tetrahydrobenzo[f][1´,4´]oxazepin-7´-yl)-2-(4´´´-fluorophenyl)ethan-1-ol (7c)

To a solution of 50.0 mg of aldehyde **6a** (153 µmol, 1.00 eq.) in 10 ml of dry THF, 230 µmol, (1.50 eq.) of 4-F-benzyl magnesiumchloride* solution (in THF) are added dropwise at room temperature. After 90 min, another 230 µl of 4-F-benzyl magnesiumchloride solution are added and the mixture is stirred for one more hour. The reaction is quenched by addition of 2 ml sat. NH_4Cl solution and 15 ml CH_2Cl_2. The resulting layers are separated and the aqueous layer is extracted with CH_2Cl_2 (2x10 ml). The combined organic layers are dried over Na_2SO_4, the solid filtered off and all volatile compounds are removed in vacuo. The residue is subjected to flash column chromatography (SiO_2, Cy/EtOAc 80:20 → 50:50) to yield 41.0 mg (94.0 µmol, 61%) of the title compound as colourless oil.

*see general procedures for preparation of Grignard reagents

TLC: R_f = 0.08 (Cy/EtOAc 1:1) [UV, CAM].

IR (ATR): = 3423 cm^{-1}, 2935, 2835, 1612, 1588, 1508, 1464, 1439, 1291, 1265.

^{1}H-NMR: (400 MHz, $CDCl_3$): δ [ppm] = 7.20-7.18 (m, 1H), 7.15-7.11 (m, 3H), 7.07 (d, 1H), 6.99-6.95 (m, 3H), 6.48-6.45 (m, 2H), 4.80 (t, 1H), 4.10-4.08 (m, 2H), 3.86 (s, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.59 (s, 2H), 3.07-3.05 (m, 2H), 2.97 (d, 2H).

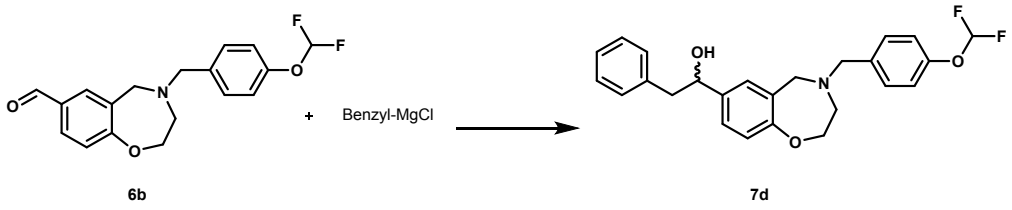
^{13}C-NMR: (101 MHz, $CDCl_3$): δ [ppm] = 161.9 (d), 160.2, 159.7, 159.0, 138.7, 133.9 (d), 132.2, 131.4, 131.1 (d, 2xC), 128.6, 126.1, 120.9, 119.2, 115.3 (d, 2xC), 104.2, 98.7, 75.1, 70.7, 59.0, 57.6, 55.6, 55.5, 52.1, 45.2.

^{19}F-NMR: (376 MHz, $CDCl_3$): δ [ppm] = −116.6.

LC-MS: tR = 3.01 min, m/z = 438 $[M+H]^+$.

HRMS (ESI): calculated for $C_{25}H_{26}F_2NO_3$ = 438.20806, found: 438.20748.

1-(4´-(4´´-(difluoromethoxy)benzyl)-2´,3´,4´,5´-tetrahydrobenzo[f][1´,4´]oxazepin-7´-yl)-2-phenylethan-1-ol (7d)



6b 7d

To a solution of 60.0 mg of aldehyde **7d** (180 µmol, 1.00 eq.) in 5 ml of dry THF, 135 µl (270 µmol, 1.50 eq.) of benzyl magnesiumchloride solution (2M in THF) are added dropwise at room temperature. After 90 min, another 135 µl of benzyl magnesiumchloride solution are added and the mixture is stirred for one more hour. The reaction is quenched by addition of 2 ml sat. NH_4Cl solution and 15 ml CH_2Cl_2. The resulting layers are separated and the aqueous layer is extracted with CH_2Cl_2 (2x7 ml). The combined organic layers are dried over Na_2SO_4, the solid filtered off and all volatile compounds are removed in vacuo. The residue is subjected to flash column chromatography (SiO_2,

Cy/EtOAc 75:25 → 50:50) to yield 29.6 mg (70.0 µmol, 39%) of the title compound as white foam or sticky oil.

TLC: R_f = 0.32 (Cy/EtOAc 1:1) [UV, CAM].

IR (ATR): = 3284 cm^{-1}, 2922, 1498, 1454, 1381, 1291, 1221, 1126, 1041, 840.

^{1}H-NMR: (400 MHz, $CDCl_3$): δ [ppm] = 7.33-7.27 (m, 4H), 7.25-7.18 (m, 4H), 7.07 (d, 2H), 7.01 (d, 1H), 6.99 (d, 1H), 6.52 (t, 1H), 4.83 (dd, 1H), 4.08-4.06 (m, 2H), 3.80 (s, 2H), 3.60 (s, 2H), 3.08-3.06 (m, 2H), 3.04-2.93 (m, 2H).

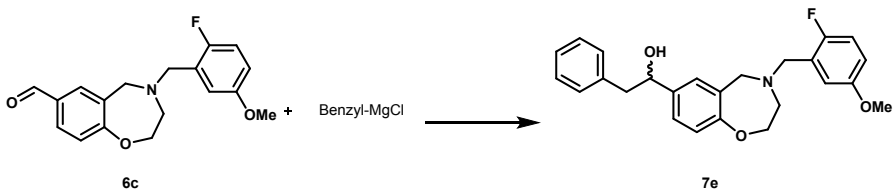
^{13}C-NMR: (101 MHz, $CDCl_3$): δ [ppm] = 159.6, 150.5 (t), 139.0, 138.1, 136.0, 131.7, 130.4 (2xC), 129.6 (2xC), 128.7 (2xC), 128.5, 126.8, 126.3, 120.9, 119.6 (2xC), 116.1 (t), 75.0, 70.3, 58.4, 58.1, 58.0, 46.3.

^{19}F-NMR: (376 MHz, $CDCl_3$): δ [ppm] = −80.6.

LC-MS: tR = 2.98 min, m/z = 426 $[M+H]^+$.

HRMS (ESI): calculated for $C_{25}H_{26}F_2NO_3$ = 426.18808, found: 426.18759.

1-(4´-(2´´-fluoro-5´´-methoxybenzyl)-2´,3´,4´,5´-tetrahydrobenzo[f][1´,4´]oxazepin-7´-yl)-2-phenylethan-1-ol (7e)



6c 7e

To a solution of 45.0 mg of aldehyde **6c** (143 µmol, 1.00 eq.) in 5 ml of dry THF, 107 µl (214 µmol, 1.50 eq.) of benzyl magnesiumchloride solution (2M in THF) are added dropwise at room temperature. After 90 min, another 107 µl of benzyl magnesiumchloride solution are added and the mixture is stirred for one more hour. The reaction is quenched by addition of 2 ml sat. NH_4Cl solution and 15 ml CH_2Cl_2. The resulting layers are separated and the aqueous layer is extracted with CH_2Cl_2 (2x7 ml). The combined organic layers are dried over Na_2SO_4, the solid filtered off and all volatile compounds are removed in vacuo. The residue is subjected to flash column chromatography (SiO_2, Cy/EtOAc 75:25 → 50:50) to yield 31.7 mg (78.0 µmol, 55%) of the title compound as colourless oil.

TLC: R_f = 0.32 (Cy/EtOAc 1:1) [UV, CAM].

IR (ATR): = 3411 cm^{-1}, 3061, 3027, 2918, 1603, 1494, 1453, 1427, 1275, 1029.

^{1}H-NMR: (400 MHz, $CDCl_3$): δ [ppm] = 7.31-7.27 (m, 2H), 7.23 (d, 2H), 7.20-7.16 (m, 3H), 7.08 (br.s, 1H), 7.00-6.93 (m, 3H), 6.76 (dt, 1H), 4.83 (t, 1H), 4.10-4.08 (m, 2H), 3.86 (s, 2H), 3.78 (s, 3H), 3.65 (s, 2H), 3.10-3.08 (m, 2H), 3.00-2.93 (m, 2H).

^{13}C-NMR: (101 MHz, $CDCl_3$): δ [ppm] = 159.5, 155.8 (d), 155.8 (d), 139.1, 138.3, 131.8, 129.6 (2xC), 128.6 (2xC), 128.5, 126.7, 126.3, 126.2 (d), 120.8, 115.9* (d), 115.8* (d), 114.0 (d), 75.0, 70.4, 58.8, 57.8, 55.9, 51.5 (d), 46.2.

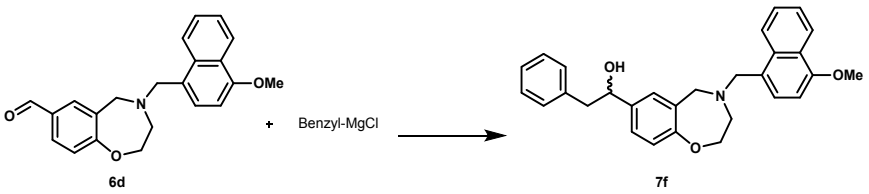
*signals overlap

^{19}F-NMR: (376 MHz, $CDCl_3$): δ [ppm] = −129.0.

LC-MS: tR = 2.97 min, m/z = 408 $[M+H]^+$.

HRMS (ESI): calculated for $C_{25}H_{27}FNO_3$ = 408.19750, found: 408.19694.

1-(4´-((4´´-methoxynaphthalen-1´´-yl)methyl)-2´,3´,4´,5´-tetrahydrobenzo[f][1´,4´]oxazepin-7´-yl)-2-phenylethan-1-ol (7f)



6d 7f

To a solution of 50.9 mg of aldehyde **6d** (147 µmol, 1.00 eq.) in 5 ml of dry THF, 110 µl (214 µmol, 1.50 eq.) of benzyl magnesiumchloride solution (2M in THF) are added dropwise at room temperature. After 90 min, another 110 µl of benzyl magnesiumchloride solution are added and the mixture is stirred for one more hour. The reaction is quenched by addition of 2 ml sat. NH_4Cl solution and 15 ml CH_2Cl_2. The resulting layers are separated and the aqueous layer is extracted with CH_2Cl_2 (2x7 ml). The combined organic layers are dried over Na_2SO_4, the solid filtered off and all volatile compounds are removed in vacuo. The residue is subjected to flash column chromatography (SiO_2, Cy/EtOAc 90:10 → 75:25) to yield 53.1 mg (121 µmol, 83%) of the title compound as white foam or sticky oil.

TLC: R_f = 0.48 (Cy/EtOAc 1:1) [UV, CAM].

M.p.: 68 °C

IR (ATR): = 3443 cm^{-1}, 3027, 2935, 2863, 1585, 1497, 1462, 1391, 1297, 1273.

^{1}H-NMR: (400 MHz, $CDCl_3$): δ [ppm] = 8.30 (dd, 1H), 8.21 (d, 1H), 7.52-7.48 (m, 2H), 7.33-7.28 (m, 2H), 7.25-7.18 (m, 5H), 7.05 (d, 1H), 7.02 (d, 1H), 6.71 (d, 1H), 4.85 (dd, 1H), 4.12-4.10 (m, 2H), 4.01 (s, 3H), 3.95 (s, 2H), 3.90 (s, 2H), 3.13-3.11 (m, 2H), 3.06-2.95 (m, 2H).

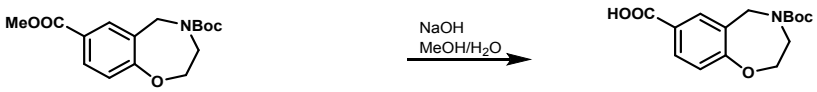
^{13}C-NMR*: (101 MHz, $CDCl_3$): δ [ppm] = 159.6, 155.5, 138.8, 138.2, 133.6, 132.1, 129.7 (2xC), 128.8, 128.7 (2xC), 127.8, 126.8, 126.6, 126.2, 126.1, 125.2, 124.7, 122.5, 120.9, 102.9, 75.1, 70.2, 58.4, 57.6, 56.5, 55.6, 46.2.

*one signal could not be detected

LC-MS: tR = 3.13 min, m/z = 440 $[M+H]^+$.

HRMS (ESI): calculated for $C_{29}H_{30}NO_3$ = 420.22257, found: 440.22199.

4-(*tert*-butoxycarbonyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxylic acid (8)



3 8

A solution of 350 mg Ester **3** (1.14 mmol ,1,00 eq.) in 10 ml MeOH/water mixture (4:1 v/v) is treated with 182 mg NaOH (4.56 mmol, 4.00 eq.) and stirred at room temperature for 12 h. Methanol is removed under reduced pressure and 30 ml CH_2Cl_2 and 15 ml citric acid solution (1M in water) are added. The layers are separated and the aqueous phase is extracted with CH_2Cl_2 (3 x 15 ml). The combined organic layers are dried over Na_2SO_4 and the solid is filtered off. All volatile compounds are removed under reduced pressure to yield 318 mg (1.08 mmol, 95%) of the title compound as white solid.

TLC: R_f = 0.66 (EtOAc) [UV, $KMnO_4$].

IR (ATR): = 2976 cm^{-1}, 2931, 1685, 1609, 1409, 1366, 1297, 1233, 1160, 1133.

^{1}H-NMR*: (400 MHz, $CDCl_3$, 323 K): δ [ppm] = 9.69 (br.s, 1H), 7.99-7.95 (m, 2H), 7.09-7.06 (m, 1H), 4.51 (br.s, 2H), 4.15-4.13 (m, 2H), 3.84-3.82 (m, 2H), 1.42 (br.s, 9H).

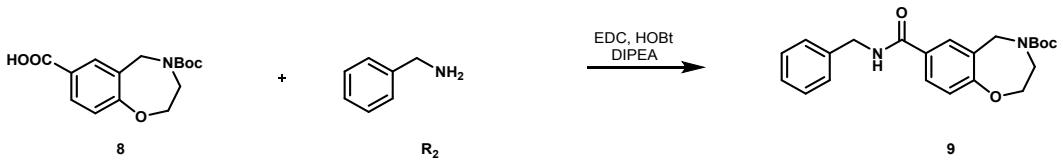
^{13}C-NMR*: (101 MHz, $CDCl_3$, 323 K): δ [ppm] = 170.9, 164.2, 155.1, 132.3, 131.6, 131.4, 124.6, 121.6, 80.7, 72.7, 50.2, 49.9, 28.5 (3xC).

**despite elevated temperatures were applied, line broadening could not be surpressed.

LC−MS: tR = 3.36 min, m/z = 292 $[M-H]^-$.

HRMS (ESI): calculated for $C_{15}H_{18}NO_5$ = 292.11850, found: 292.11909.

***tert*-butyl 7-(benzylcarbamoyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate (9)**



To a solution of 283 mg **8** (811 µmol, 1.00 eq.) in 15 ml CH_2Cl_2 are consecutively added 0.56 ml Dipea (419 mg, 3,25 mmol, 4.00 eq.), 90.4 µl benzylamine (88.7 mg, 811 µmol, 1.00 eq.), 132 mg HOBt (974 µmol, 1.20 eq.) and 187 mg EDC·HCl (974 µmol, 1.20 eq.). The reaction mixture is stirred for 15h at room temperature followed by the addition of 10 ml CH_2Cl_2 and 5 ml citric acid (1M in water). The layers are separated and the organic layer is washed with water and sat. $NaHCO_3$ solution (5 ml each). The organic layer is dried over Na_2SO_4 and the solid is filtered off. All volatile compounds are removed in vacuo and the residue is subjected to flash column chromatography (SiO_2, Cy/EtOAc 75:25 → 65:35) to yield 257 mg (672 µmol, 83%) of the title compound as white solid.

TLC: R_f = 0.33 (Cy/EtOAc 1:1) [UV, $KMnO_4$].

IR (ATR): = 3327 cm^{-1}, 2975, 2927, 1692, 1638, 1606, 1541, 1491, 1453, 1298.

^{1}H-NMR*: (400 MHz, $CDCl_3$, 323 K): δ [ppm] = 7.61 (br.s, 2H), 7.27 (s, 2H), 7.24-7.19 (m, 2H), 6.95 (dd, ^{3}J = 8.3 Hz, ^{4}J = 1.8 Hz, 1H), 6.34 (br.s, 1H), 4.55 (d, ^{3}J = 5.7 Hz, 2H), 4.40 (s, 2H), 4.01 (t, ^{3}J = 4.1 Hz, 2H), 3.72 (t, ^{3}J = 4.1 Hz, 2H), 1.33 (s, 9H).

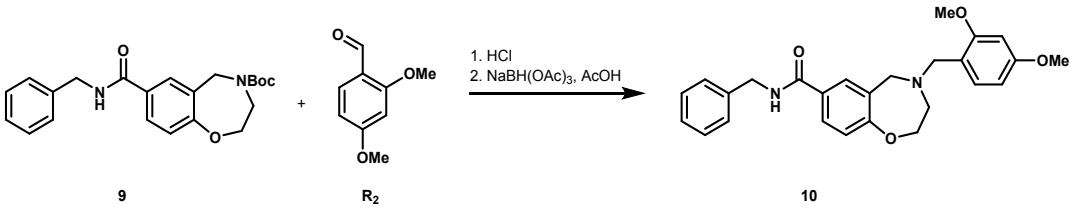
^{13}C-NMR*: (101 MHz, $CDCl_3$, 323 K): δ [ppm] = 166.7, 162.3, 154.9, 138.5, 129.7, 129.4, 128.9 (2xC), 128.0 (2xC), 127.7, 121.5, 80.5, 72.8, 50.2, 49.9, 44.3, 28.5 (3xC).

*despite elevated temperatures were applied, line broadening could not be surpressed. Two C-signals could not be detected.

LC-MS: tR = 3.65 min, m/z = 383 $[M+H]^{+}$.

HRMS (ESI): calculated for $C_{22}H_{27}N_2O_4$ = 383.19708, found: 383.19660.

_N_-benzyl-4-(2´,4´-dimethoxybenzyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxamide (10)



9 R_2 10

According to the general procedure 1, 230 mg of Boc-protected amine **9** (601 µmol, 1.00 eq.) are reacted with 99.3 mg of aldehyde **R2** (601 µmol, 1.00 eq.) to yield after purification (SiO_2, Cy/EtOAc 75:25 → 50:50) 88.9 mg (206 µmol, 34%) of the title compound as light yellow, sticky oil.

TLC: R_f = 0.08 (Cy/EtOAc 1:1) [UV, $KMnO_4$].

IR (ATR): = 3317 cm–1, 2932, 2835, 1637, 1609, 1587, 1505, 1493, 1454, 1259.

^{1}H-NMR: (400 MHz, $CDCl_3$): δ [ppm] = 7.62-7.58 (m, 2H), 7.36-7.35 (m, 4H), 7.33-7.28 (m, 1H), 7.20 (d, 1H), 7.03 (d, 1H), 6.46* (dd, 1H), 6.45* (s, 1H), 6.33 (t, 1H), 4.63 (d, 2H), 4.14-4.12 (m, 2H), 3.88 (s, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 3.60 (s, 2H), 3.09-3.07 (m, 2H).

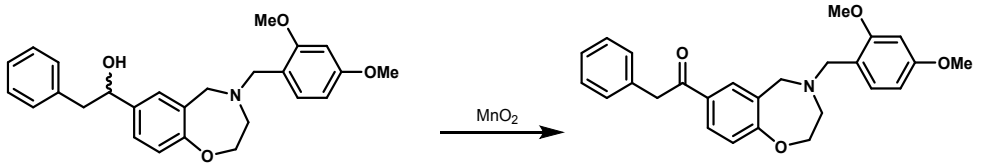
*signals overlap

^{13}C-NMR: (101 MHz, $CDCl_3$): δ [ppm] = 167.0, 163.0, 160.3, 158.9, 138.4, 132.4, 131.4, 129.3, 128.9 (2xC), 128.1 (2xC), 127.8, 127.4, 121.0, 118.9, 104.3, 98.7, 70.8, 58.6, 57.3, 55.6, 55.5, 52.0, 44.3.

LC-MS: tR = 2.99 min, m/z = 433 $[M+H]^+$.

HRMS (ESI): calculated for $C_{26}H_{29}N_2O_4$ = 433.21273, found: 433.21208.

1-(4´-(2´´,4´´-dimethoxybenzyl)-2´,3´,4´,5´-tetrahydrobenzo[f][1´,4´]oxazepin-7´-yl)-2-phenylethan-1-one (11)



7a 11

According to general procedure 2, 36.3 mg of **7a** (87.0 µmol, 1.00 eq.) are reacted with 301 mg of MnO_2 (3.46 mmol, 40.0 eq.) to yield after purification (silica, Cy/EtOAc 70:30) 17.2 mg (41.0 µmol, 48%) of the title compound as yellowish oil.

TLC: R_f = 0.27 (Cy/EtOAc 1:1) [UV, CAM].

IR (ATR): = 2927 cm^{-1}, 2823, 1676, 1601, 1505, 1454, 1293, 1238, 1208, 1156.

^{1}H-NMR: (400 MHz, $CDCl_3$): δ [ppm] = 7.87 (dd, 1H), 7.81 (d, 1H), 7.34-7.31 (m, 2H), 7.27-7.23* (m, 3H), 7.20 (d, 1H), 7.04 (d, 1H), 6.47$^{\#}$ (dd, 1H), 6.46$^{\#}$ (s, 1H), 4.23 (s, 2H), 4.17-4.15 (m, 2H), 3.89 (s, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.62 (s, 2H), 3.10-3.08 (m, 2H).

*signal overlaps with $CHCl_3$-signal

$^{\#}$signals overlap

^{13}C-NMR: (101 MHz, $CDCl_3$): δ [ppm] = 196.6, 164.3, 160.4, 159.0, 134.9, 132.0, 132.0, 131.5, 129.8, 129.6 (2xC), 128.8 (2xC), 127.0, 121.1, 104.3, 98.7, 70.9, 58.4, 57.2, 55.6, 55.5, 52.2, 45.4.

LC-MS: tR = 3,14 min, m/z = 418 $[M+H]^+$.

HRMS (ESI): calculated for $C_{26}H_{28}NO_4$ = 418.20183, found: 418.20124.

AlphaScreen™ binding assays

Newly developed compounds were evaluated for their ability to inhibit PEX5-PEX14 using an optimized protocol for AlphaScreen competition-based assay[1]. N-terminal his-tagged PEX14 at the final concentration of 3nM was mixed with 10nM biotinylated PEX5-derived peptide (ALSENWAQEFLA) in a PBS buffer supplemented with 5 mg/mL of BSA and 0.01 % (v/v) Tween-20. 5 µg/mL of streptavitin donor beads and 5 µg/mL of nickel chelate acceptor beads (PerkinElmer) were added to the mixture. Serial dilutions of inhibitors were prepared in DMSO (12 points) and mixed with the above mixture and incubate for 1h in the dark. Doing so the concentration of DMSO was kept constant to 5% (which was shown to have no effect on the assay readout) and the only variable was the ligand concentration. Data were analyzed using Origin Pro 9.0. Experimental points were interpolate using Hill sigmoidal fitting fixing the asymptotes at the maximal assay signal (no inhibitor added) and 0, respectively and Half maximal effective concentration (EC50) was calculated for each compound. Dose/response curves are reported in Figure S1.

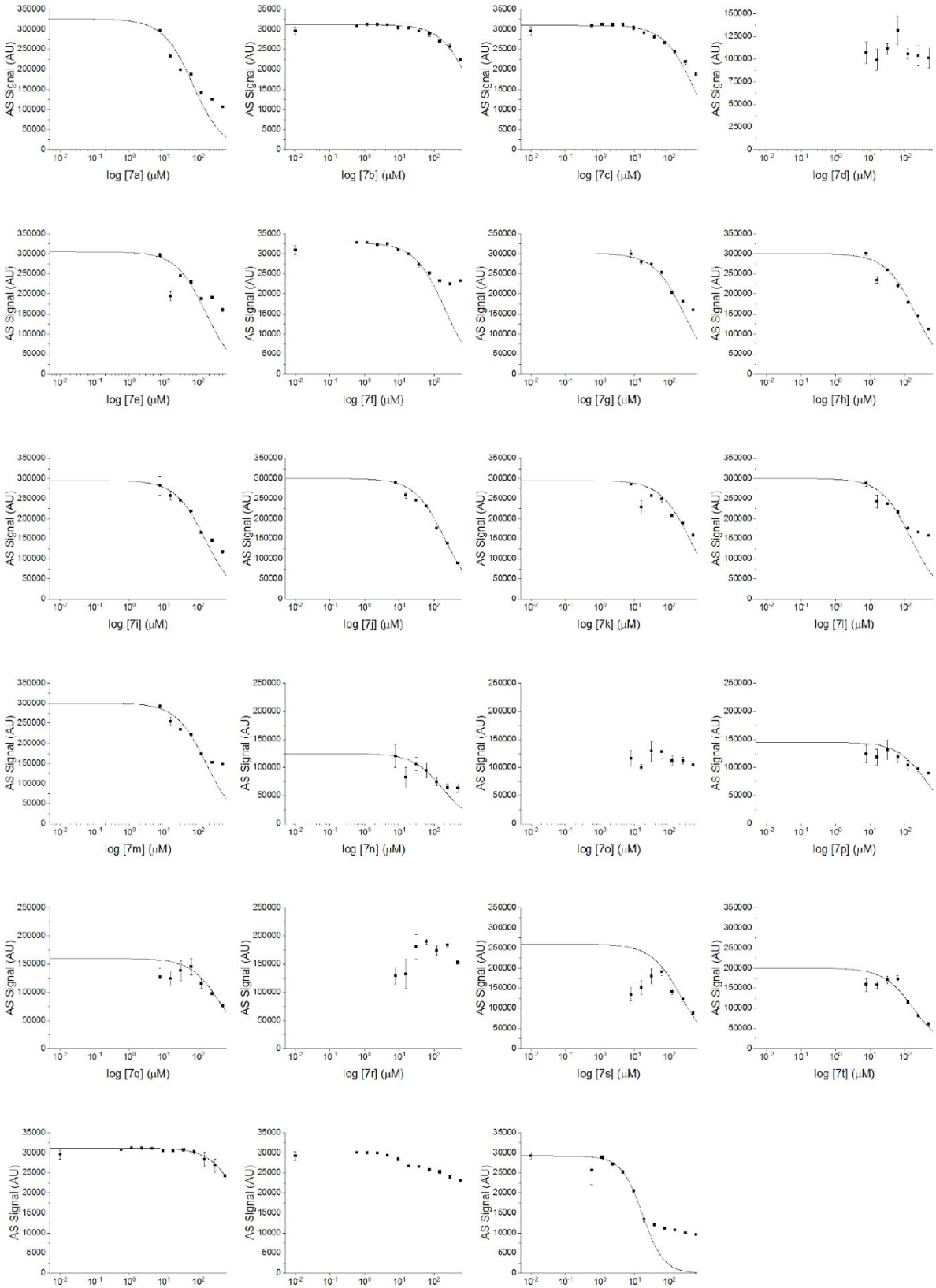


Figure S1. Dose/response curves for tested compounds

Trypanocidal assay and immunofluorescence microscopy

Trypanocidal activity against bloodstream form *T. b. brucei* (mammalian stage) was performed as described before.[1]

Logarithmically growing *T. b. brucei* parasites were treated with DMSO alone as negative control or with 5 μM of compound **7a** or **7e** for 24 hours. Parasites were fixed with formaldehyde and immunofluorescence microscopic analysis was performed essentially as described before[1] except that the primary antibodies against glycosomal GAPDH were used at 1:1500 dilution and images were analysed using Zen 2.3 Blue edition software (Carl Zeiss).

ADME properties evaluation

ADME studies were conducted by Bienta (Enamine).

hERG binding evaluation

Preliminary assessment of **h**uman ***E****ther-a-go-go*-**R**elated **G**ene (hERG) predictor binding for 3 tested compounds using fluorescence polarization assay. hERG Predictor Assay provides valuable information about the possible binding of test compounds to the potassium channel and potential QT prolongation on Echocardiogram. All experiments were performed using PredictorTM hERG Fluorescence Polarization Assay in accordance with the manufacturer's protocol (Protocol PV5365, http://tools.invitrogen.com/content/ sfs/manuals/Predictor_hERG_FP_Assay_man.pdf).

Fluorescence Polarization (FP) readout technology is based on the observation that when a small fluorescent molecule (the tracer) is excited by the polarized light, the emitted light is largely depolarized because of the rapid rotation of the molecule in the solution during its fluorescence lifetime. The hERG reaction is performed by incubating the tracer and membranes with hERG channel for 2-4 hours in the solution. The fluorescence polarization is maximal when nothing interferes with the reaction of the tracer and hERG membranes (minimal tracer rotation). But when a tested compound competes with the tracer for the hERG channel, the polarization of emitted light lowers due to the ability of free unbound tracer to rotate rapidly in the solution. The reference compound (E-4031, provided by the manufacturer) was used to validate assay performance. The calibration curve of the E-4031 was used to compare the IC50 of E-4031 in the performed assay with the manufacturer's provided data. "Sigmoidal dose-response (variable slope)" function of GraphPad Prism software was used for the calibration curve building and calculation of IC50 for E-4031

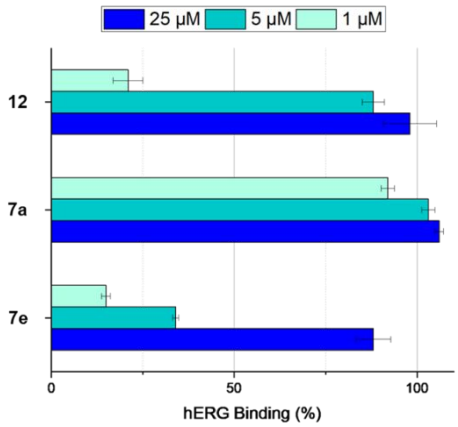
assessment. IC50 value for E-4031 was found to be approximately 70 nM in accordance with the published data.

All test points for the compounds were performed in quadruplicates. Three dilutions of the tested compounds were assessed – 1 µM, 5 µM and 25 µM.

The set of positive and negative controls (Assay blank – no tracer added, Assay Negative - 30 µM of E-4031 that represents 100 % tracer displacement and gives minimum assay polarization value) was performed with 4 repeats.

Table S5. Reported hERG binding values for Compound 7a, 7e, and 12.

Compound ID	Concentration	Binding values, %				Mean	SE
12	25 µM	76.3	105.4	105.4	106.0	**98**	7.3
	5 µM	95.7	90.2	81.9	85.3	**88**	3.0
	1 µM	25.2	30.1	14.2	13.5	**21**	4.1
7a	25 µM	108.1	106.7	105.4	102.6	**106**	1.2
	5 µM	104.7	107.4	99.8	100.5	**103**	1.8
	1 µM	97.1	92.2	88.8	90.2	**92**	1.8
7e	25 µM	102.2	80.7	85.5	83.9	**88**	4.8
	5 µM	36.2	33.6	34.1	32.5	**34**	0.8
	1 µM	17.3	13.6	17.8	13.1	**15**	1.2
E403 -C	30µM	99.1	101.7	100.7	98.6	**100**	0.7
+C	30µM	1.6	-1.0	2.6	-3.1	**0**	1.3



Determination of Distribution Coefficient (LogD, pH 7.4)

Incubations were carried out in Eppendorf-type polypropylene microtubes in duplicates. 5 µL aliquot of compound DMSO stock (10 mM) was dissolved in the previously mutually saturated mixture containing 500 µL of PBS and 500 µL of octanol, followed by mixing in a rotator for 1 hour at 30 rpm. Phase separation was assured by centrifugation for 2 min at 6000 rpm. Octanol phase was diluted 100-fold with 40% acetonitrile, and aqueous phase was diluted 10-fold with 5% acetonitrile. If a signal is not sufficient or excessive, we analyze the aqueous phase without dilution or 100-fold dilution respectively. The samples (both phases) were analyzed using HPLC system coupled with tandem mass spectrometer. Mebendazole was used as a reference compound (predicted logD, pH7.4 is 2.83 as calculated using ACD Labs logD Suite and experimental logD, pH 7.4 range is 2.8-3.0 as found in our previous studies).

Calculations of the partition ratios were carried out using the equation below.

$$D = \frac{100 * S_O}{S_P}$$

S_O - peak area of the analyte in octanol phase;

S_P - peak area of the analyte in PBS buffer.

Table S6. Reported hERG binding values for Compound **12**, **7a** and **7e**.

Compound ID	Incubation	S_P	S_O	D	LogD, pH 7.4	
Mebendazole	1	1.72E+05	2.42E+06	1.41E+03	3.15	**3.18**
	2	1.77E+05	2.62E+06	1.48E+03	3.17	
	3	1.68E+05	2.85E+06	1.70E+03	3.23	
12	1	9.33E+03	3.66E+05	3.92E+03	3.59	**3.62**

	2	8.50E+03	3.82E+05	4.49E+03	3.65	
	3	9.19E+03	3.80E+05	4.13E+03	3.62	
7a	1	7.51E+04	2.46E+06	3.28E+03	3.52	**3.57**
	2	7.18E+04	2.62E+06	3.65E+03	3.56	
	3	6.74E+04	2.89E+06	4.29E+03	3.63	
7e	1	8.46E+03	1.47E+06	1.74E+04	4.24	**4.21**
	2	8.91E+03	1.41E+06	1.58E+04	4.20	
	3	9.46E+03	1.50E+06	1.59E+04	4.20	

Analysis of Mouse Plasma Protein Binding

Determination of binding capabilities of 12, 7a, 7e and reference compound (Verapamil) to mouse plasma proteins using HPLC-MS/MS was performed by spiking test compounds at concentration of 1 μM into mouse plasma and dialyzing against buffer until equilibrium is achieved. Concentrations of the compound in both plasma and buffer were determined to calculate the percentage of plasma protein bound compound.

The assay was performed in a multiple-use 96-well dialysis unit (HTD96b dialyzer). Each individual well unit consisted of 2 chambers separated by a vertically aligned dialysis membrane of

predetermined pore size (MWCO 12-14 kDa). 120 µl of non-diluted plasma spiked with thecompound (1 µM, final DMSO concentration 1%) was added to one chamber and the same volume of PBS buffer pH 7.4 to the other chamber. HTD96b dialyzer was covered with adhesive sealing film and incubated at 37 °C, shaking at 100 rpm for 5 hours.

For samples preparation an aliquot of the content of each chamber had been mixed with the same volume of the blank opposite matrix. In order to define non-specific loss of the compound during this assay, standard solution was created by mixing an aliquot of spiked plasma with blank buffer without dialysis. Samples were diluted 10-fold with 100% acetonitrile with subsequent plasma proteins sedimentation by centrifuging at 6000 rpm for 5 minutes. Supernatants were analyzed using HPLC system coupled with tandem mass spectrometer.

The percentage of plasma protein bound compound and recovery were calculated using following equations:

$$Binding(\%) = \left(1 - \frac{A_{peak(in\ buffer)}}{A_{peak(in\ plasma)}}\right) \cdot 100$$

$$Recovery(\%) = \left(\frac{A_{peak(in\ buffer)} + A_{peak(in\ plasma)}}{A_{peak(standard)}}\right) \cdot 100$$

Table S7. Plasma binding protein for compounds.

Compound ID	Concentration, µM	Incubation #	Compound peak area		% of bound compound	% of bound compound, mean	Peak area of compound in standard solution, mean	Recovery, %
			Buffer	Plasma				
Verapamil	1.0	# 1	1.34E+03	1.03E+04	87.0	**87.3***	1.27E+04	91.7
		# 2	1.25E+03	1.01E+04	87.6			89.4
12	1.0	# 1	8.76E+01	4.50E+04	99.8	**99.5**	5.70E+04	79.0
		# 2	3.17E+02	4.36E+04	99.3			77.0
7e	1.0	# 1	1.65E+04	2.75E+05	94.0	**93.7**	3.14E+05	92.8
		# 2	1.69E+04	2.59E+05	93.5			87.9
7a	1.0	# 1	1.91E+04	4.61E+05	95.9	**95.5**	4.98E+05	96.3
		# 2	2.28E+04	4.75E+05	95.2			99.9

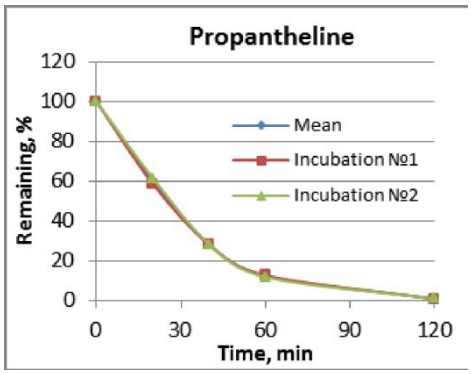
*Verapamil plasma protein binding data are consistent with previously obtained.

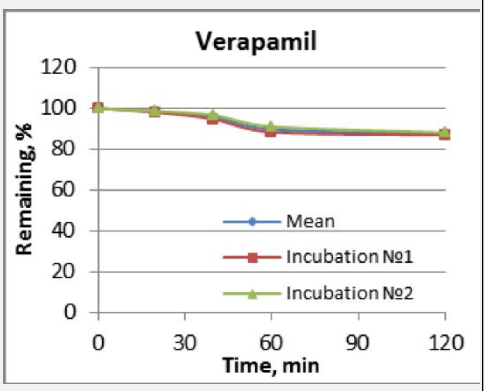
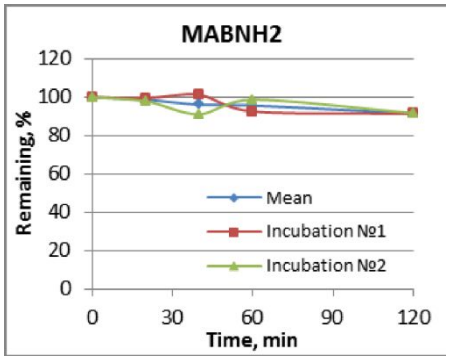
Stability in Mouse Plasma

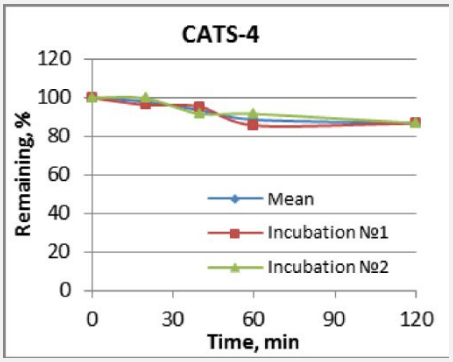
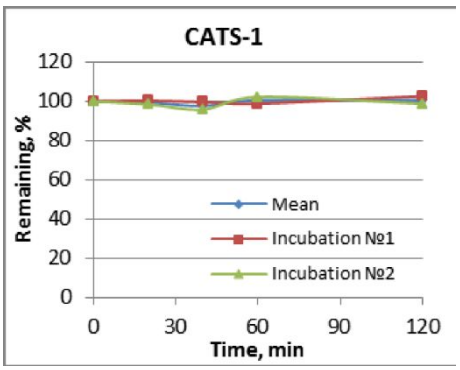
Determination of mouse plasma stability of 12, 7a, 7e, and two reference compounds (Verapamil and Propantheline) at five time points over 120 minutes using HPLC-MS/MS. Plasma stability is defined as the percentage of parent compound remaining in the plasma over the time.

Incubations were carried out in 5 aliquots of 70 µL each (one for each time point), in duplicates. Test compounds (1 µM, final DMSO concentration 1%) were incubated at 37 °C with shaking at 100 rpm. Five time points over 120 minutes have been analyzed. The reactions were stopped by adding 420 µL of acetonitrile-water mixture (90:10) with the subsequent plasma proteins sedimentation by centrifugation at 5500 rpm for 5 minutes. Supernatants were analyzed by the HPLC system coupled with tandem mass spectrometer. The percentage of the test compounds remaining after incubation in plasma and their half-lives (T1/2) were calculated. Results are reported in Table S8.

Table S8. Mouse plasma stability results for tested compounds.

Compound ID	Time, min	Analyte Peak Area		Mean Analyte Peak Area	% Remain. Mean	T1/2, min	Plot
		Inc. 1	Inc. 2				
Propantheline	0	5.64E+05	5.45E+05	5.54E+05	**100**	17.7	
	20	3.31E+05	3.36E+05	3.34E+05	**60**		
	40	1.59E+05	1.55E+05	1.57E+05	**28**		
	60	7.24E+04	6.53E+04	6.88E+04	**12**		

	120	5.45E+03	5.63E+03	5.54E+03	**1**		
Verpamil	0	3.60E+04	3.58E+04	3.59E+04	**100**	>240 (580.6)	
	20	3.53E+04	3.53E+04	3.53E+04	**98**		
	40	3.41E+04	3.46E+04	3.44E+04	**96**		
	60	3.18E+04	3.26E+04	3.22E+04	**90**		
	120	3.13E+04	3.15E+04	3.14E+04	**87**		
12	0	6.35E+04	6.40E+04	6.38E+04	**100**	>240 (942.8)	
	20	6.32E+04	6.27E+04	6.30E+04	**99**		
	40	6.43E+04	5.83E+04	6.13E+04	**96**		
	60	5.88E+04	6.32E+04	6.10E+04	**96**		
	120	5.80E+04	5.87E+04	5.84E+04	**92**		
7a	0	5.45E+05	5.37E+05	5.41E+05	**100**	>240 (557.5)	
	20	5.25E+05	5.35E+05	5.30E+05	**98**		

	40	5.20E+05	4.92E+05	5.06E+05	**94**		
	60	4.67E+05	4.92E+05	4.80E+05	**89**		
	120	4.73E+05	4.66E+05	4.70E+05	**87**		
7e	0	2.63E+05	2.64E+05	2.64E+05	**100**	>240 (6144.2)	
	20	2.64E+05	2.60E+05	2.62E+05	**99**		
	40	2.62E+05	2.53E+05	2.58E+05	**98**		
	60	2.60E+05	2.70E+05	2.65E+05	**101**		
	120	2.70E+05	2.61E+05	2.66E+05	**101**		

Stability in Mouse Liver Microsomes

Determination of metabolic stability compounds 12, 7a, 7e, and two reference compounds (Imipramine and Propranolol) in mouse liver microsomes at five time points over 40 minutes using HPLC-MS. Metabolic stability is defined as the percentage of parent compound lost over time in the presence of a metabolically active test system.

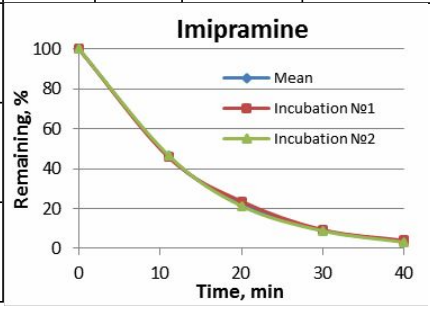
Mouse hepatic microsomes were isolated from pooled (50), perfused livers of Balb/c male mice according to the standard protocol (Hill, J.R. in *Current Protocols in Pharmacology* 7.8.1-7.8.11, Wiley Interscience, 2003). The batch of microsomes was tested for quality control using Imipramine, Propranolol and Verapamil as reference compounds.

Microsomal incubations were carried out in 96-well plates in 5 aliquots of 40 µL each (one for each time point). Liver microsomal incubation medium contained PBS (100 mM, pH 7.4), MgCl2 (3.3 mM), NADPH (3 mM), glucose-6-phosphate (5.3 mM), glucose-6-phosphate dehydrogenase (0.67 units/ml) with 0.42 mg of liver microsomal protein per ml. Control incubations were performed replacing the NADPH-cofactor system with PBS. Test compound (2 µM, final solvent concentration 1.6 %) was incubated with microsomes at 37 °C, shaking at 100 rpm. Incubations were performed in duplicates. Five time points over 40 minutes had been analyzed. The reactions were stopped by adding 12 volumes of 90% acetonitrile-water to incubation aliquots, followed by protein sedimentation by centrifuging at 5500 rpm for 3 minutes. Incubations were performed in duplicates. Supernatants were analyzed using the HPLC system coupled with tandem mass spectrometer. The elimination constant (k_{el}), half-life ($t_{1/2}$) and intrinsic clearance (Cl_{int}) were determined in plot of ln(AUC) versus time, using linear regression analysis:[1]

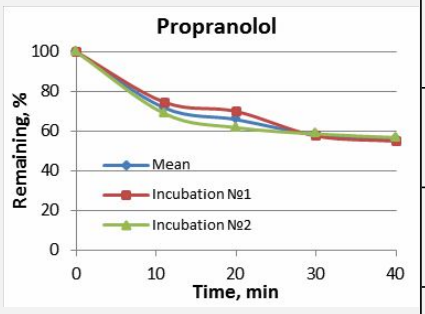
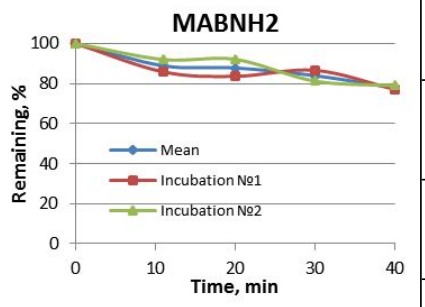
$$k_{el} = -slope$$

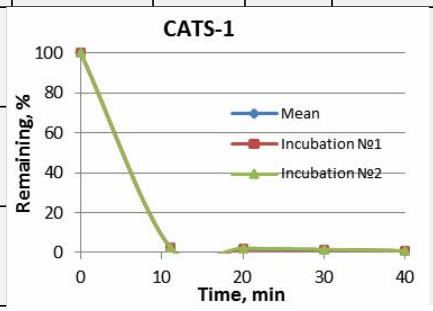
$$t_{\frac{1}{2}} = \frac{0.693}{k}$$

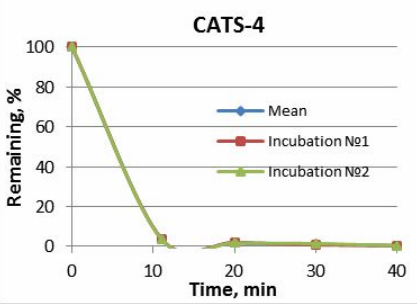
$$Cl_{int} = \frac{0.693}{k} \times \frac{\mu L_{incubation}}{mg_{microsomes}}$$

Compound ID		Analyte Peak Area		Analyte Peak Area, Mean of 2	% Remaining, Mean of 2	R	k_{el}, min^{-1}	$t_{1/2}$, min	Cl_{int}, µl/min/mg	% Remaining without cofactor, Mean of 2
		Inc. 1	Inc. 2							
Imipramine	0	4.21E+05	4.64E+05	4.42E+05	**100**	0.998	0.084	8.30	201.30	100.00
	11	1.93E+05	2.17E+05	2.05E+05	**46**					
	20	9.96E+04	9.89E+04	9.92E+04	**22**					
	30	3.94E+04	4.09E+04	4.02E+04	**9**					

[1] In order to indicate the quality of the linear regression analysis, the R (correlation coefficient) values are provided. In some cases, the last time point is excluded from the calculations to ensure acceptable logarithmic linearity of decay.

	40	1.71E+04	1.48E+04	1.60E+04	**4**					99.59
Propranolol	0	5.34E+04	5.35E+04	5.34E+04	**100**	0.944	0.014	49.68	33.62	100.00
	11	3.99E+04	3.69E+04	3.84E+04	**72**					
	20	3.74E+04	3.31E+04	3.52E+04	**66**					
	30	3.08E+04	3.14E+04	3.11E+04	**58**					
	40	2.94E+04	3.04E+04	2.99E+04	**56**					89.05
12	0	1.03E+05	1.01E+05	1.02E+05	**100**	0.971	0.006	121.60	13.74	100.00
	11	8.84E+04	9.29E+04	9.06E+04	**89**					
	20	8.61E+04	9.30E+04	8.96E+04	**88**					
	30	8.92E+04	8.20E+04	8.56E+04	**84**					
	40	7.93E+04	7.97E+04	7.93E+04	**78**					92.24

7e	0	3.36E+04	2.96E+04	3.16E+04	**100**	0.848	0.102	<5	245.12	100.00
	11	9.22E+02	7.78E+02	8.50E+02						
	20	5.68E+02	6.53E+02	6.10E+02						
	30	4.86E+02	4.83E+02	4.84E+02						

	40	2.98E+02	2.82E+02	2.90E+02	**1**					99.06
7a	0	2.20E+05	2.02E+05	2.11E+05	**100**	0.927	0.122	<5	294.15	100.00
	11	8.46E+03	7.41E+03	7.94E+03	**4**					
	20	4.53E+03	3.69E+03	4.11E+03	**2**					
	30	1.86E+03	2.99E+03	2.42E+03	**1**					
	40	1.01E+03	8.95E+02	9.52E+02	**0**					94.99

NMR assignment

TcPEX14 N-terminal domain backbone assignment was carried out using ^{1}H,^{15}N 2D correlation experiments, 3D HNCA, HNCACB and CBCACONH experiments, recorded on a uniformly ^{15}N,^{13}C-labelled sample in NMR phosphate buffer. The sample concentration was 600µM and the solvent 90% water, supplemented with 10% D_2O. Experiments were carried out on a Bruker Avance III 800 MHz spectrometer (^{1}H frequency 800 MHz) equipped with a 5 mm TCI cryoprobe. Data processing was carried out with NMRpipe[3] and visualised with nmrDraw and analysis and assignment was carried out with CCPN Analysis[4].

NMR assay and CSP analysis

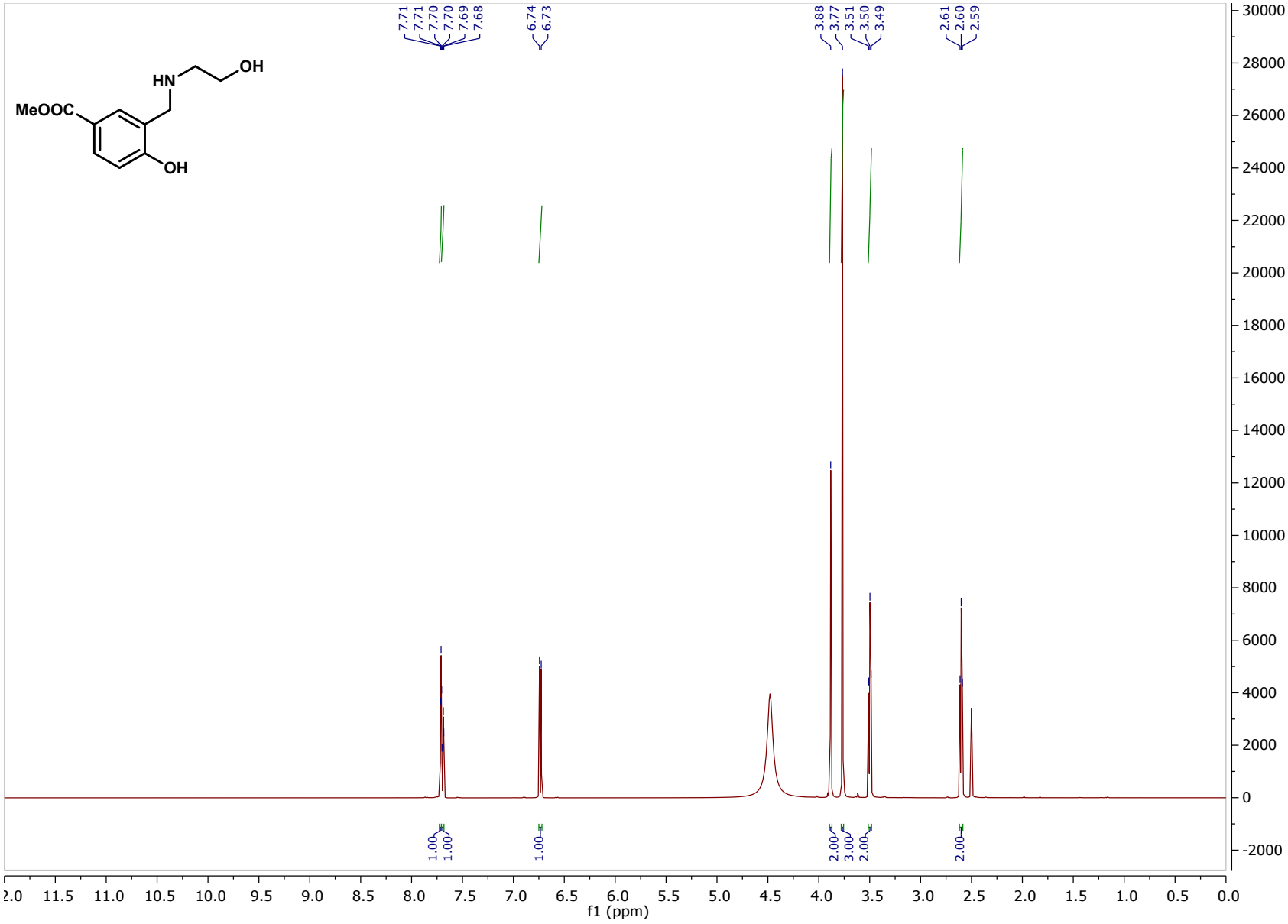
Compounds were tested using ^{1}H, ^{15}N 2D correlation spectra on a Bruker Avance III 600MHz spectrometer (^{1}H frequency 600 MHz) with a QCI cryoprobe). Samples were made up with 200µM uniformly ^{15}N-labelled TcPEX14 protein in phosphate NMR buffer (pH 6.5, 20mM NaCl, 5mM Na_2PO_4) in water, supplemented with 10% D_2O. Compounds, dissolved in d_6-DMSO were added to the test samples at 3:1 and the equivalent volume of d_6-DMSO to the reference sample.

For chemical shift perturbation (CSP) analysis with compound **7a**, amide assignments were transferred to the reference and test spectra using CCPN Analysis. CSP values were calculated for each amide using:

$$CSP = \sqrt{\delta_{NH}^2 + \left(\frac{\delta_N}{5}\right)^2}$$

CSP values were then assigned B-factors, binned into 11 bins and plotted using Pymol[5]. White demonstrates minimal shift, red demonstrates the highest shifts, with a gradient of pinks and reds between. Grey shows where assignments were not possible to transfer and orange where peaks disappeared upon binding to **7a**, indicating a strong effect not possible to plot using the shift gradient.

Compounds quality control - NMR Spectra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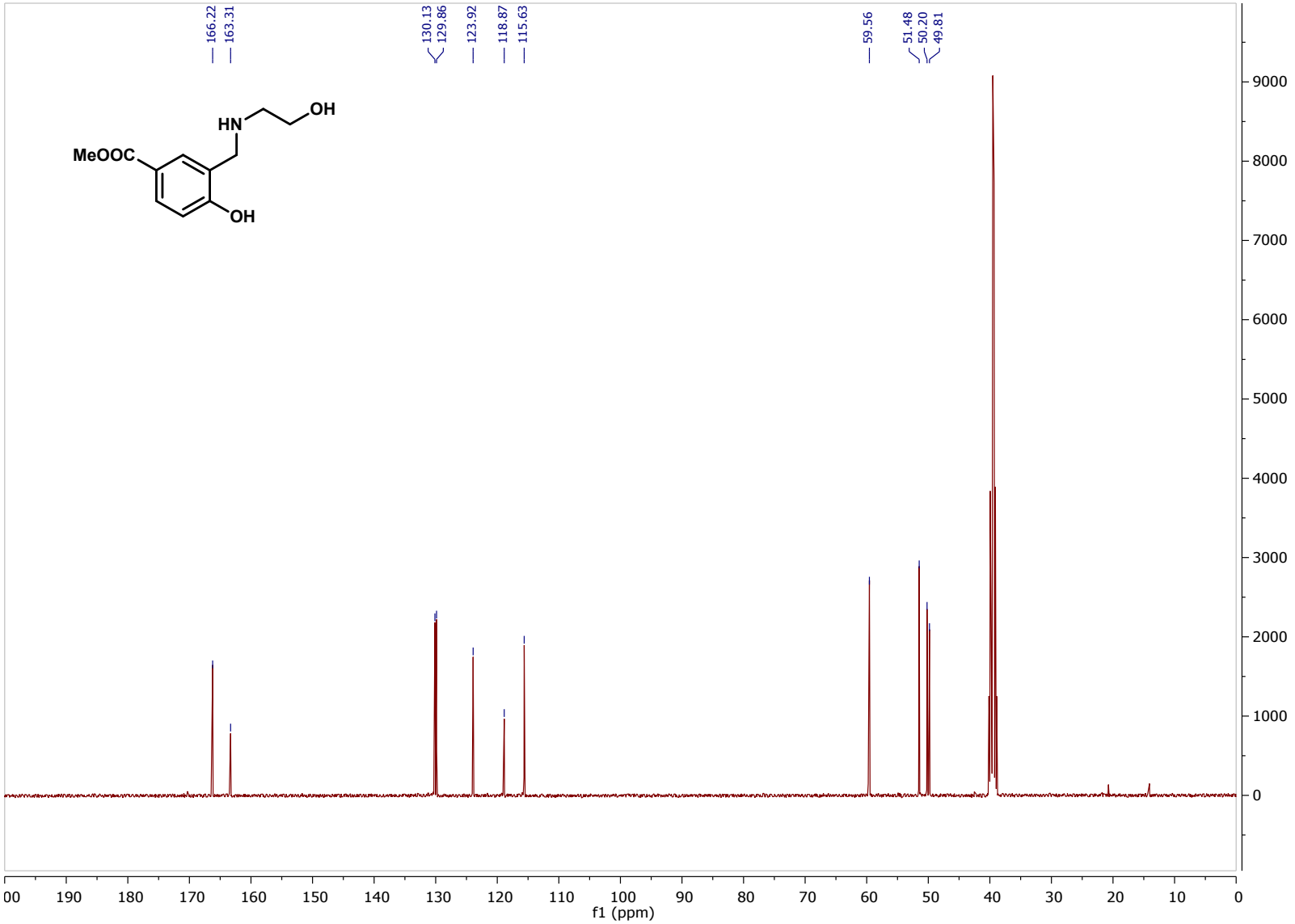
2.00
3.00
2.00
2.00
f1 (ppm)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123.92
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OH
MeOOC
OH
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
00
190
180
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40
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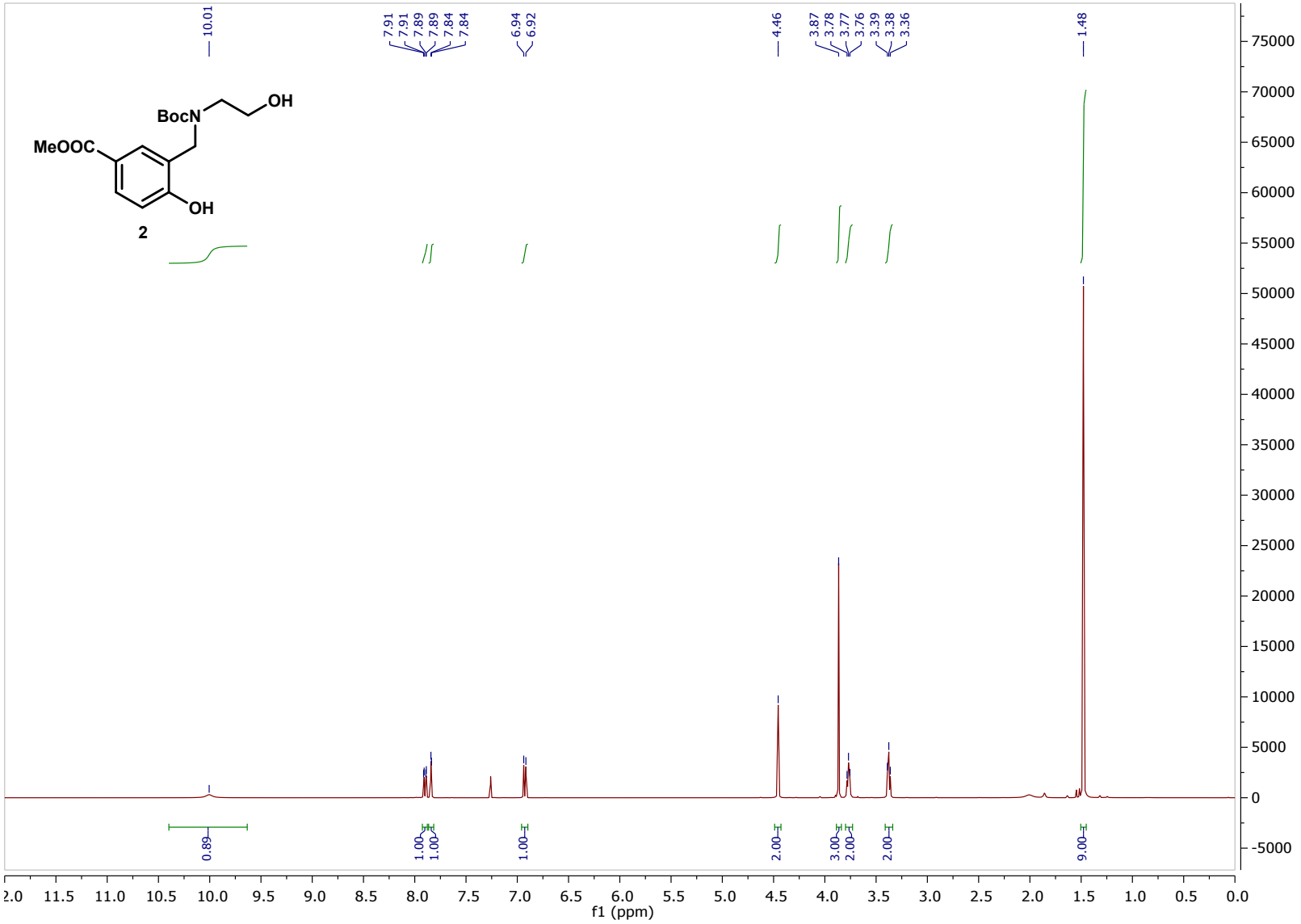
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3.76
3.39
3.38
3.36
1.48
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1.00
1.00
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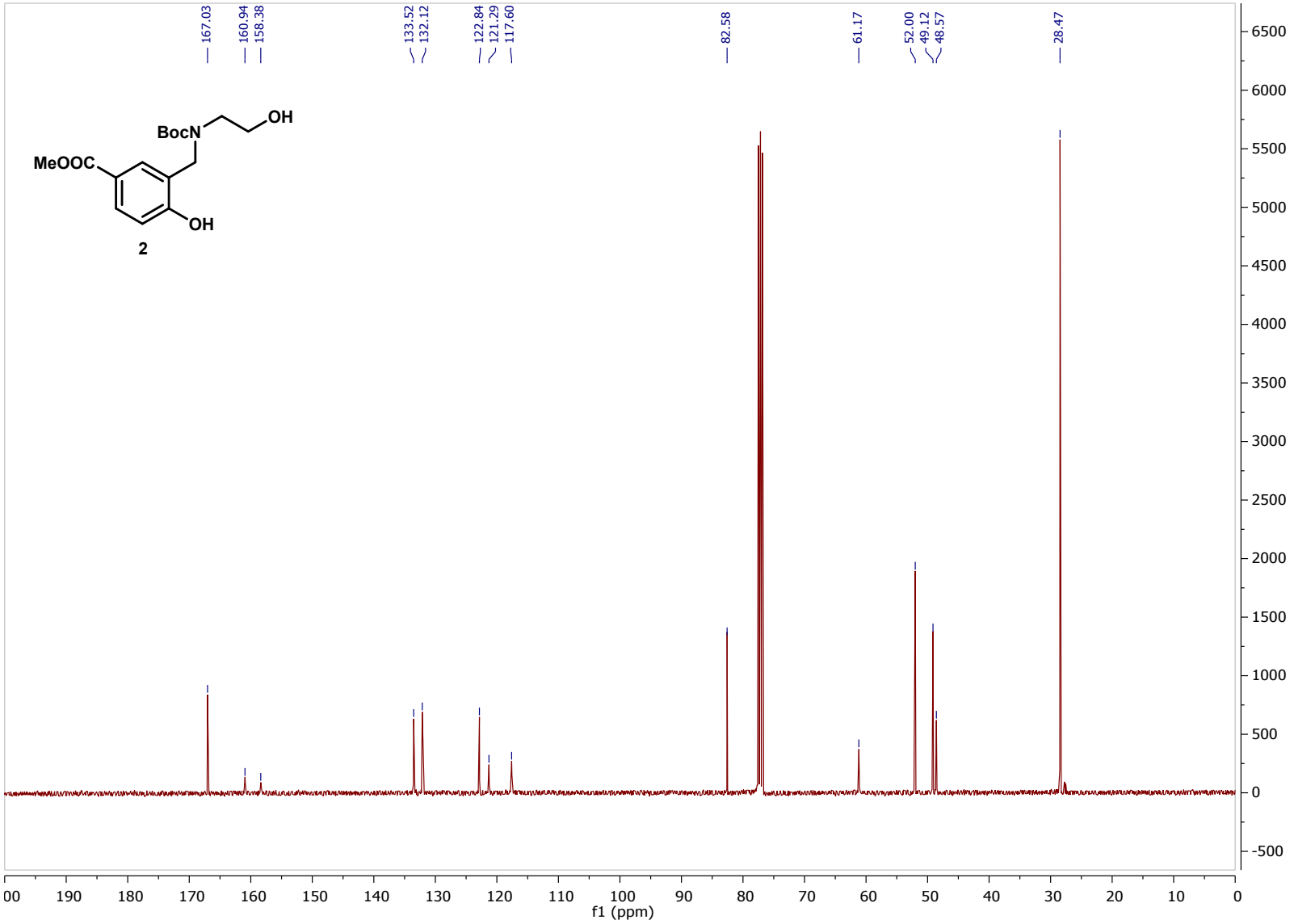
2.00
2.00
9.00
f1 (ppm)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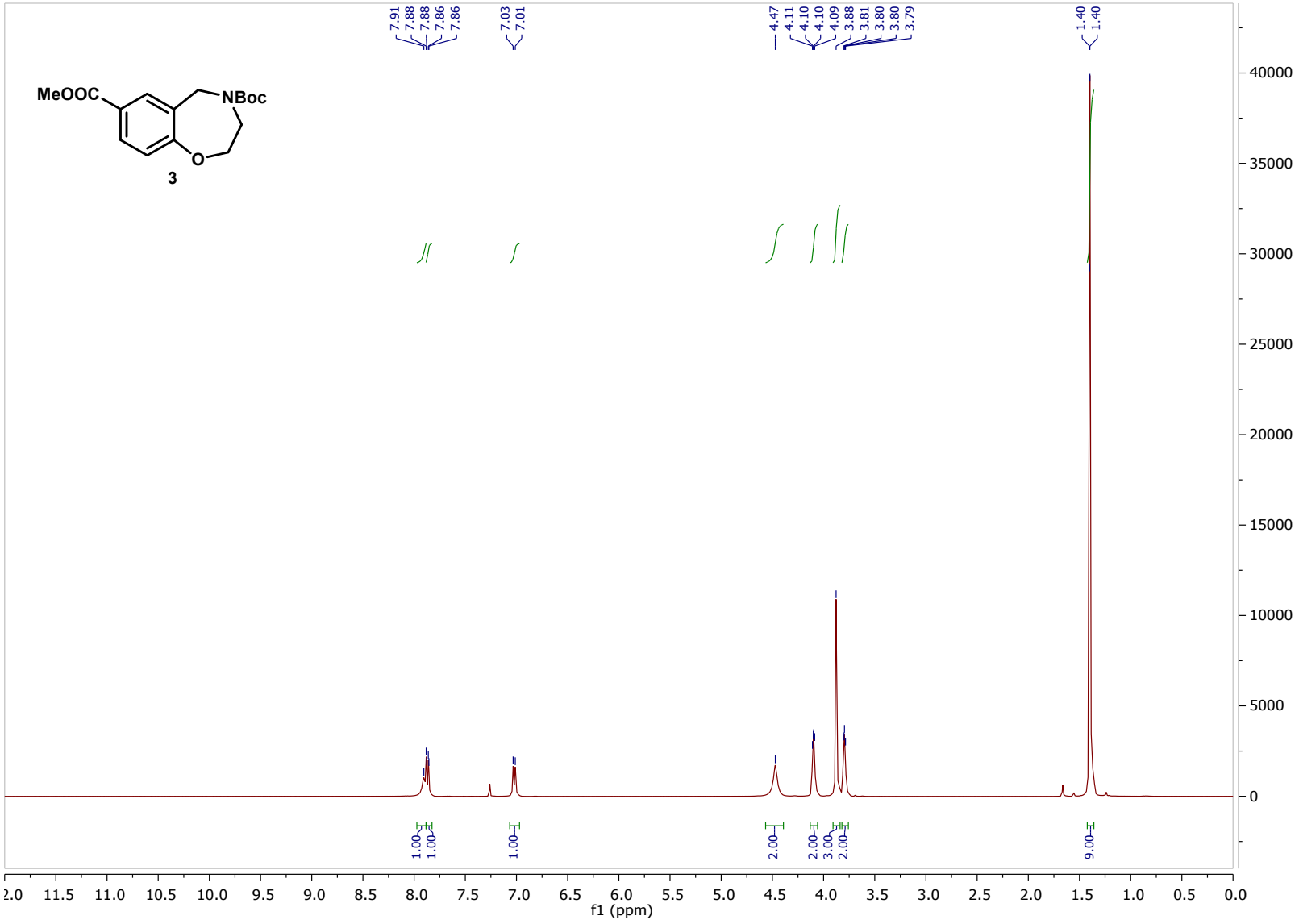
BocN
OH
MeOOC
OH
2
f1 (ppm)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7.01
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4.10
4.09
3.88
3.81
3.80
3.80
3.79
1.40
1.40
1.00
1.00
1.00
2.00
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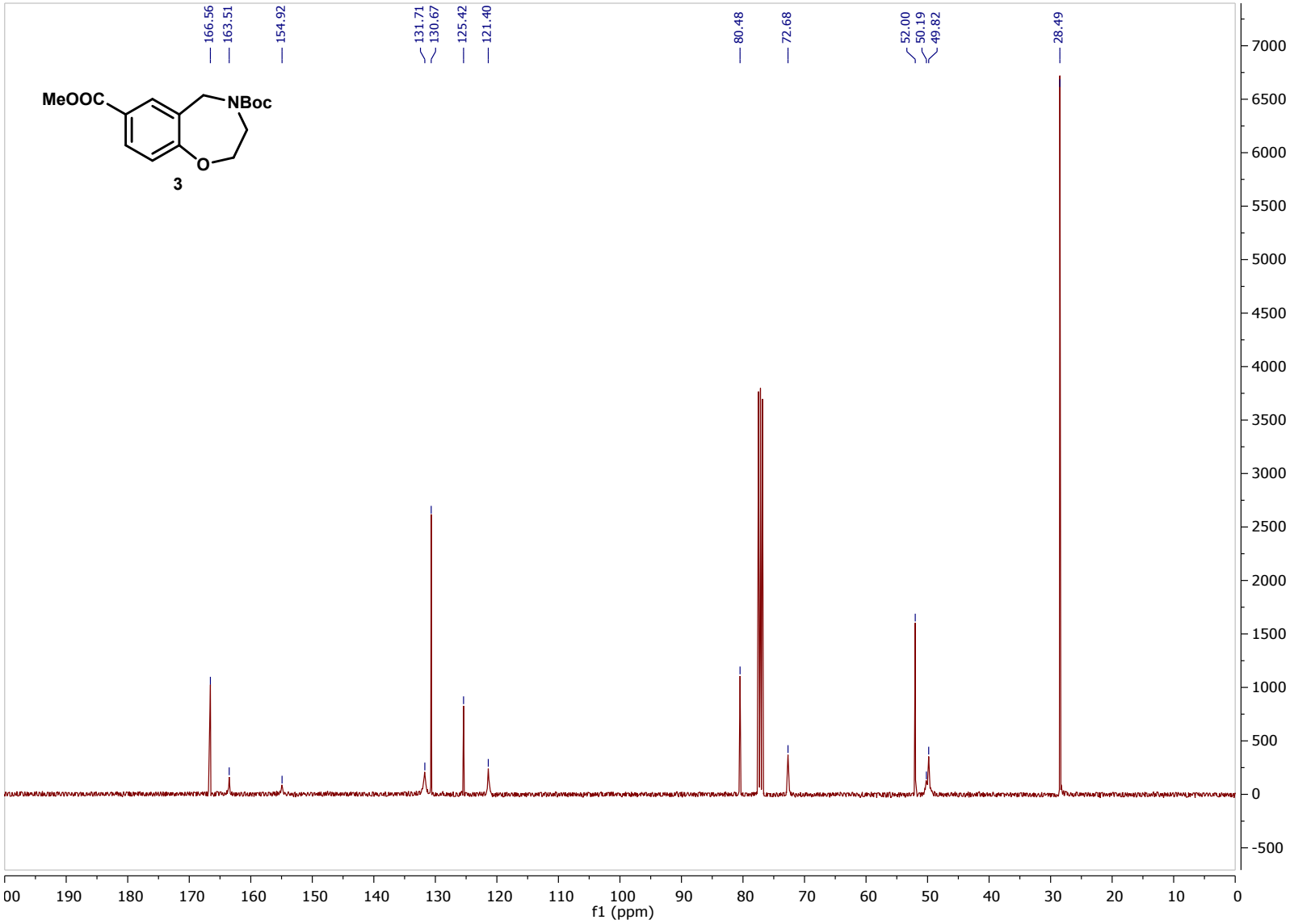
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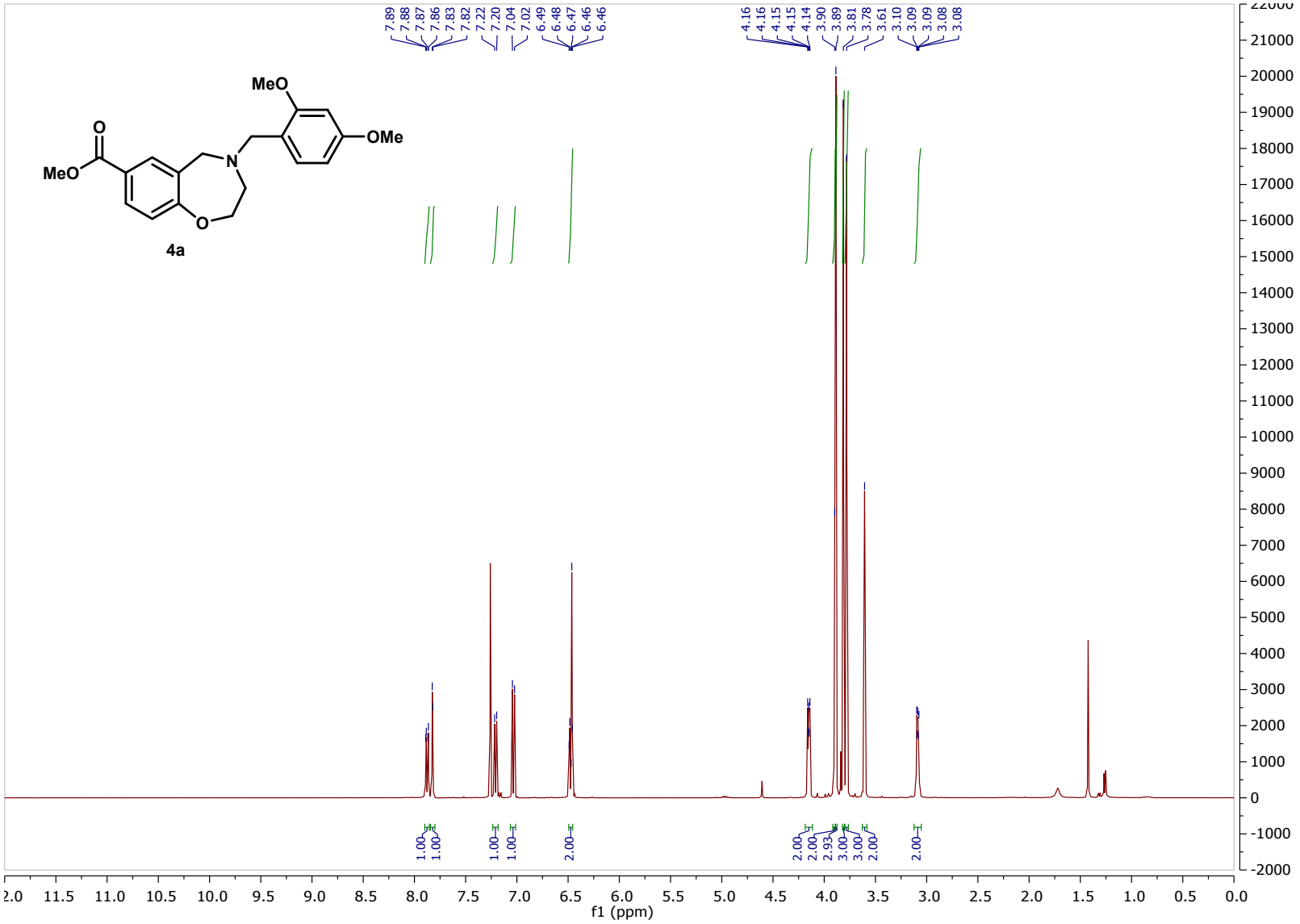
NBoc
O
3
f1 (ppm)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7.04
7.02
6.49
6.48
6.47
6.46
6.46
4.16
4.16
4.15
4.15
4.14
3.90
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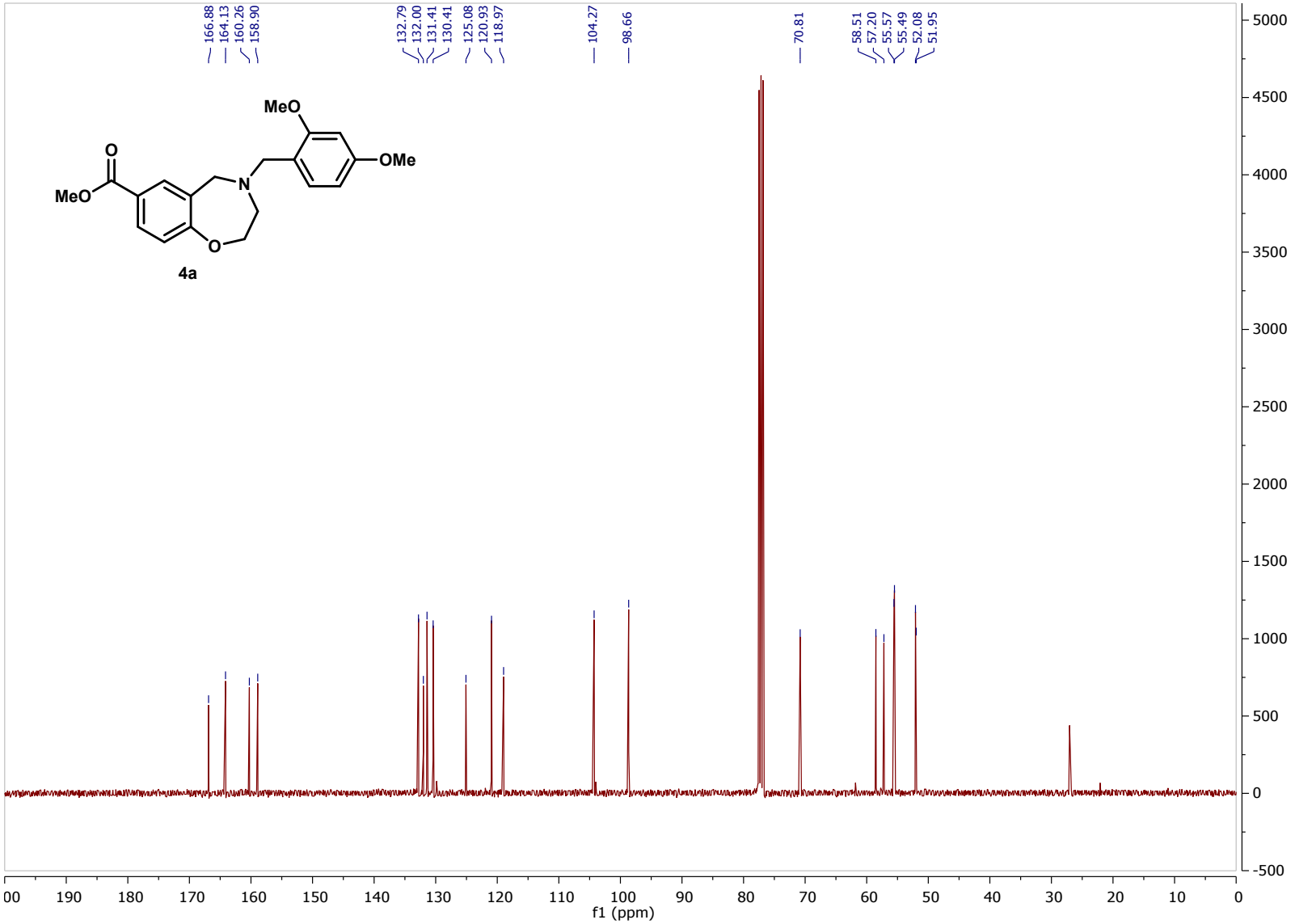
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98.66
70.81
58.51
57.20
55.57
55.49
52.08
51.95
MeO
OMe
MeO
O
N
O
4a
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
00
190
180
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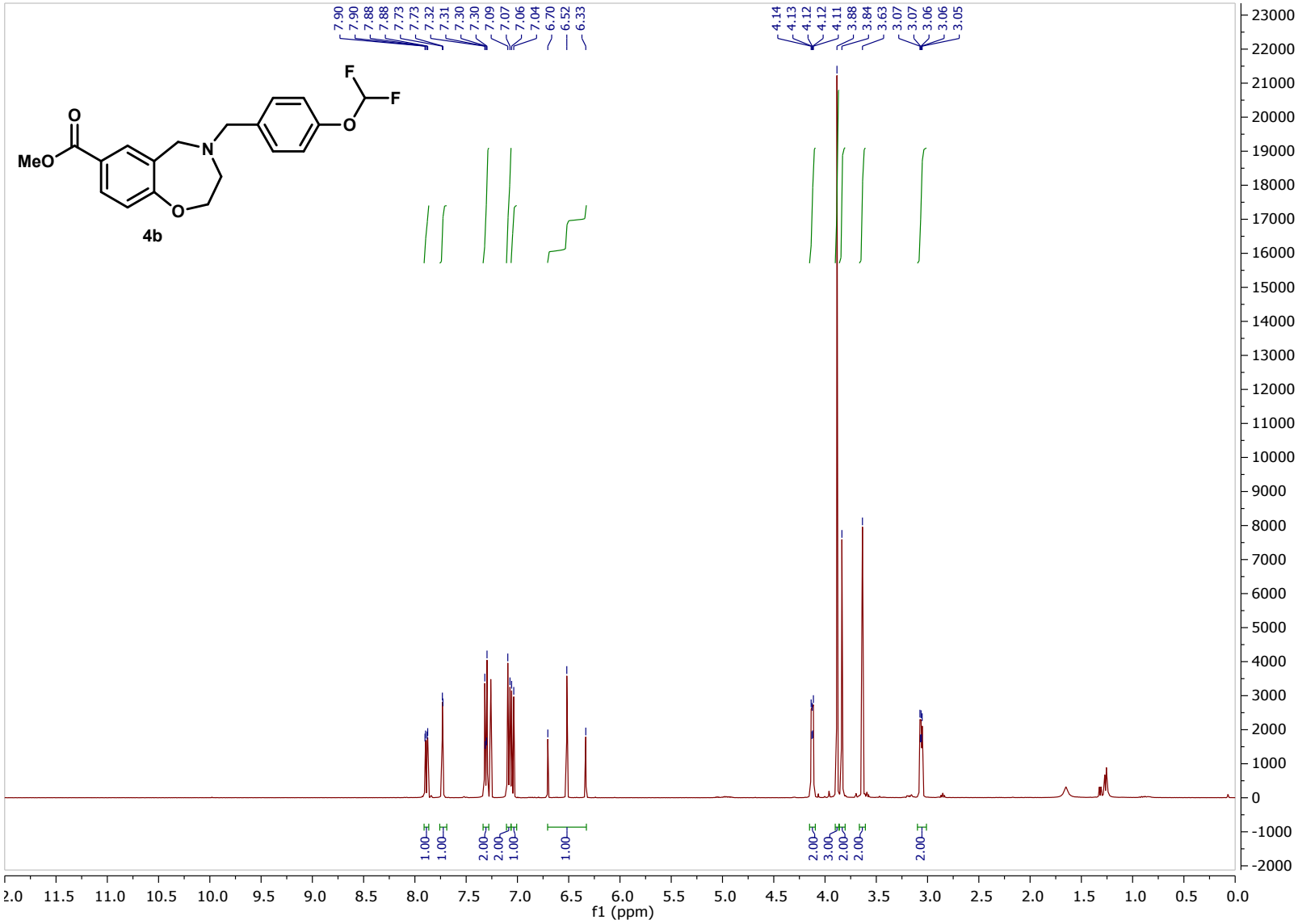
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4.11
3.88
3.84
3.63
3.07
3.07
3.06
3.06
3.05
MeO
O
N
O
F
F
O
4b
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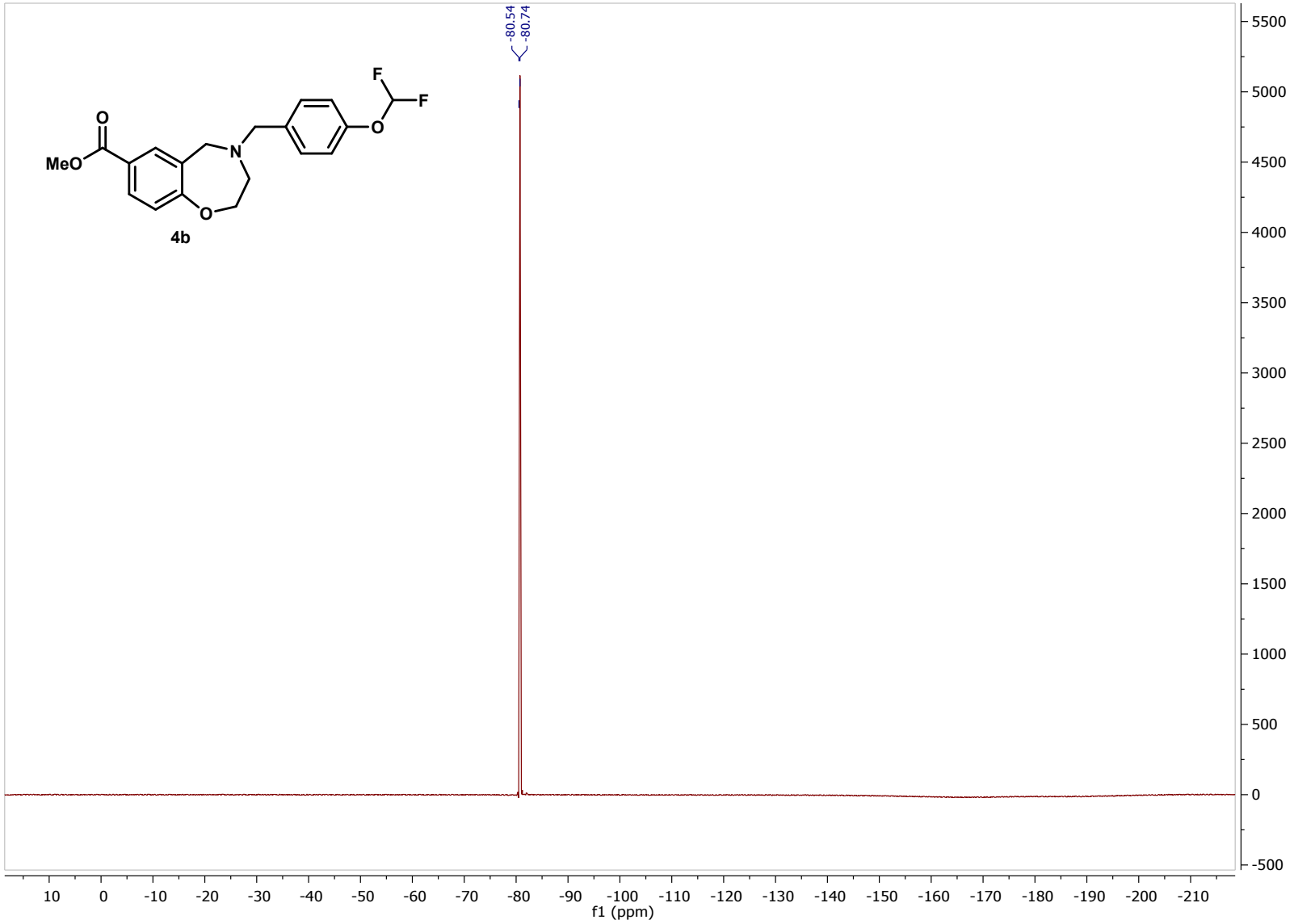
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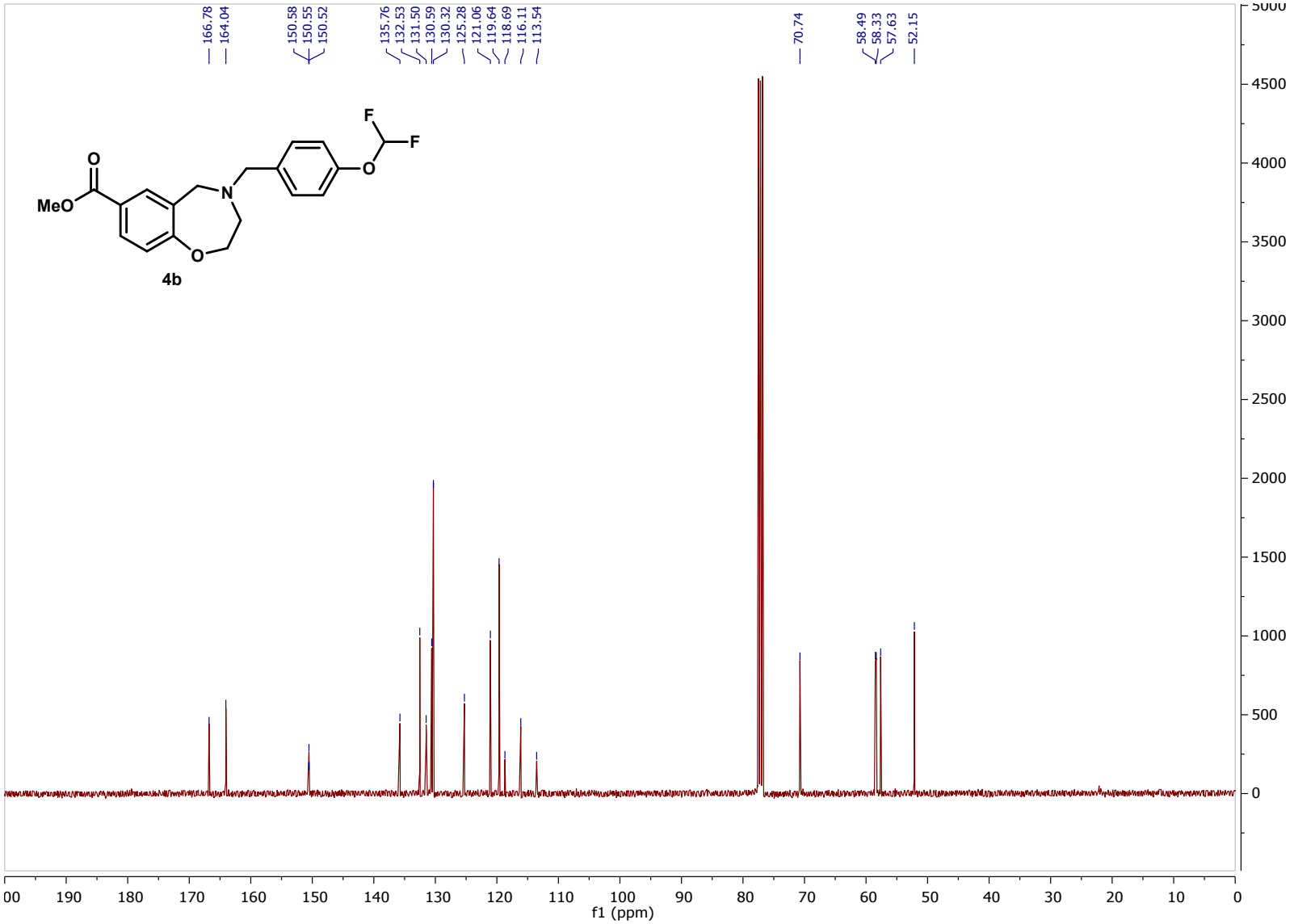
f1 (ppm)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116.11
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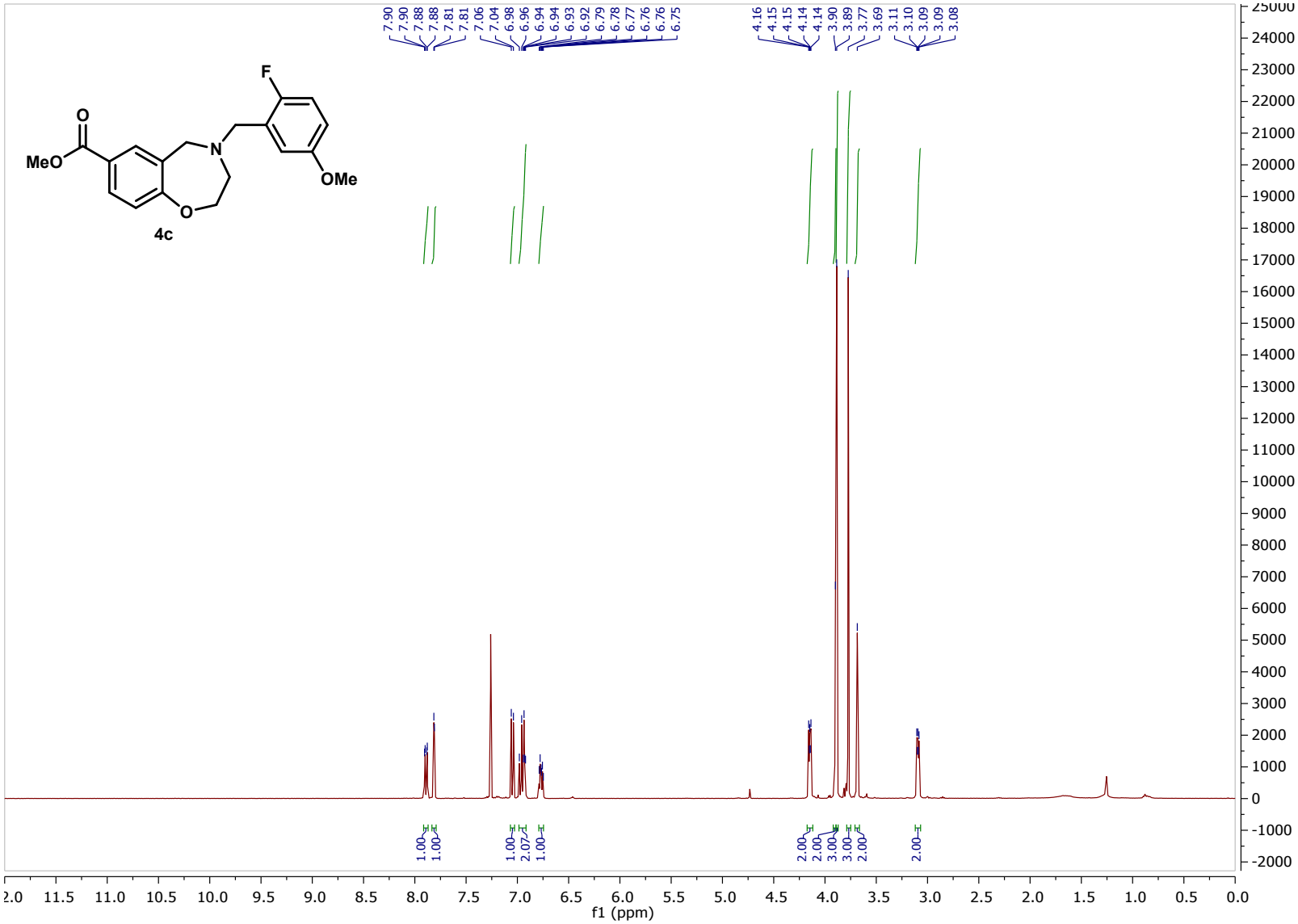
f1 (ppm)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7.88
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7.81
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7.04
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6.94
6.94
6.93
6.92
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6.78
6.77
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6.76
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4.14
4.14
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3.77
3.69
3.11
3.10
3.09
3.09
3.08
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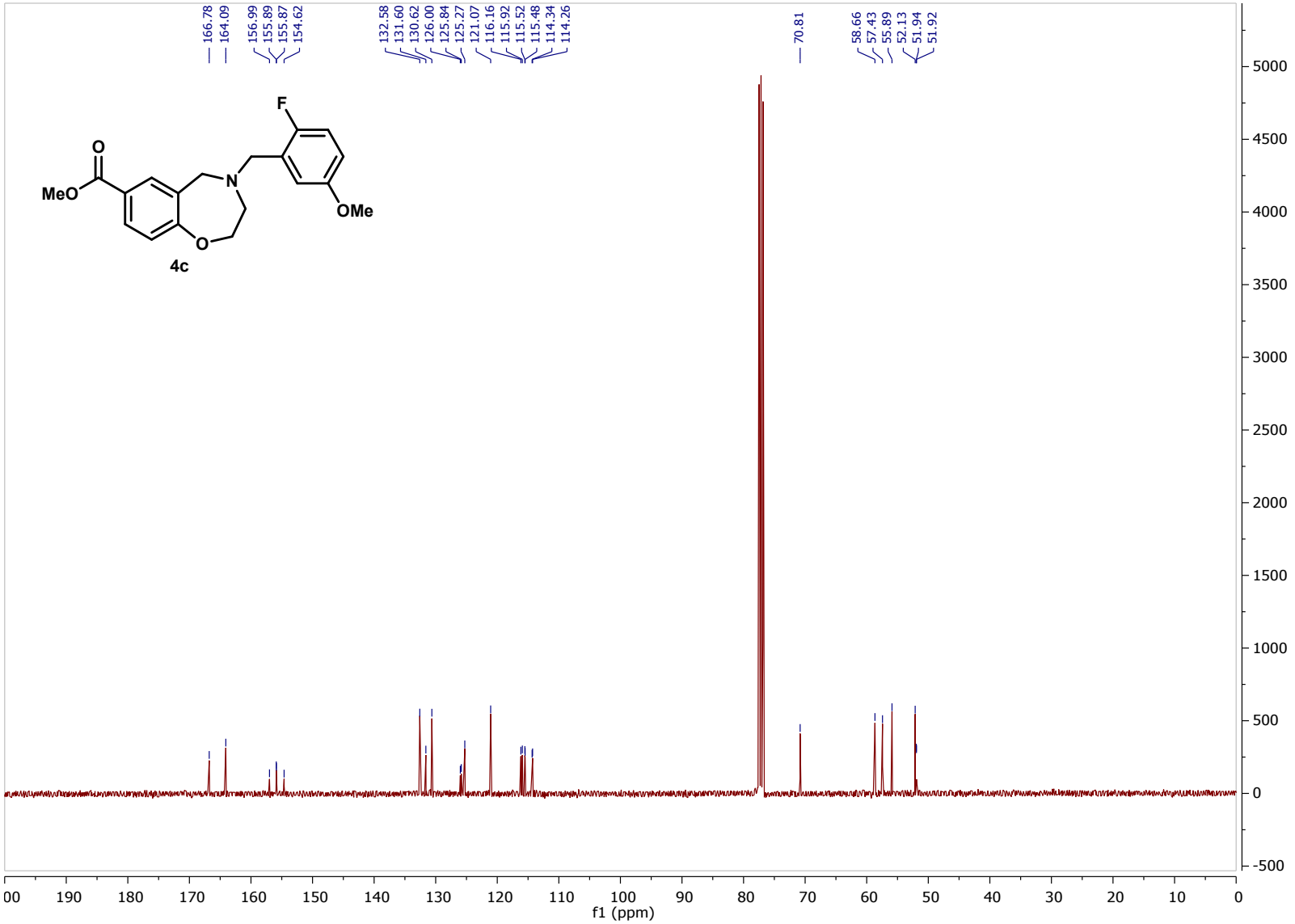
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125.27
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115.92
115.52
115.48
114.34
114.26
70.81
58.66
57.43
55.89
52.13
51.94
51.92
F
O
MeO
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OMe
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4c
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2000
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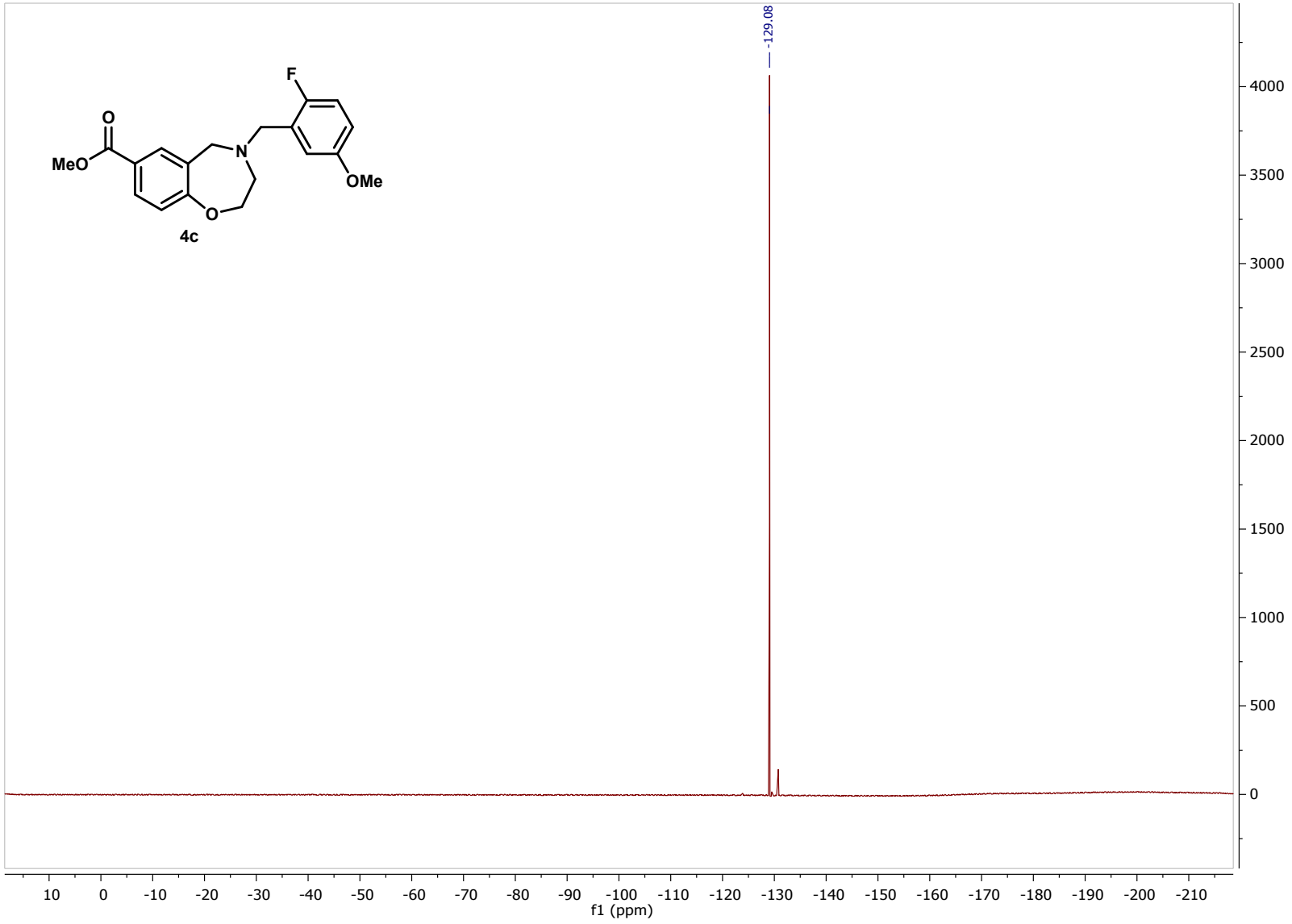
f1 (ppm)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1500
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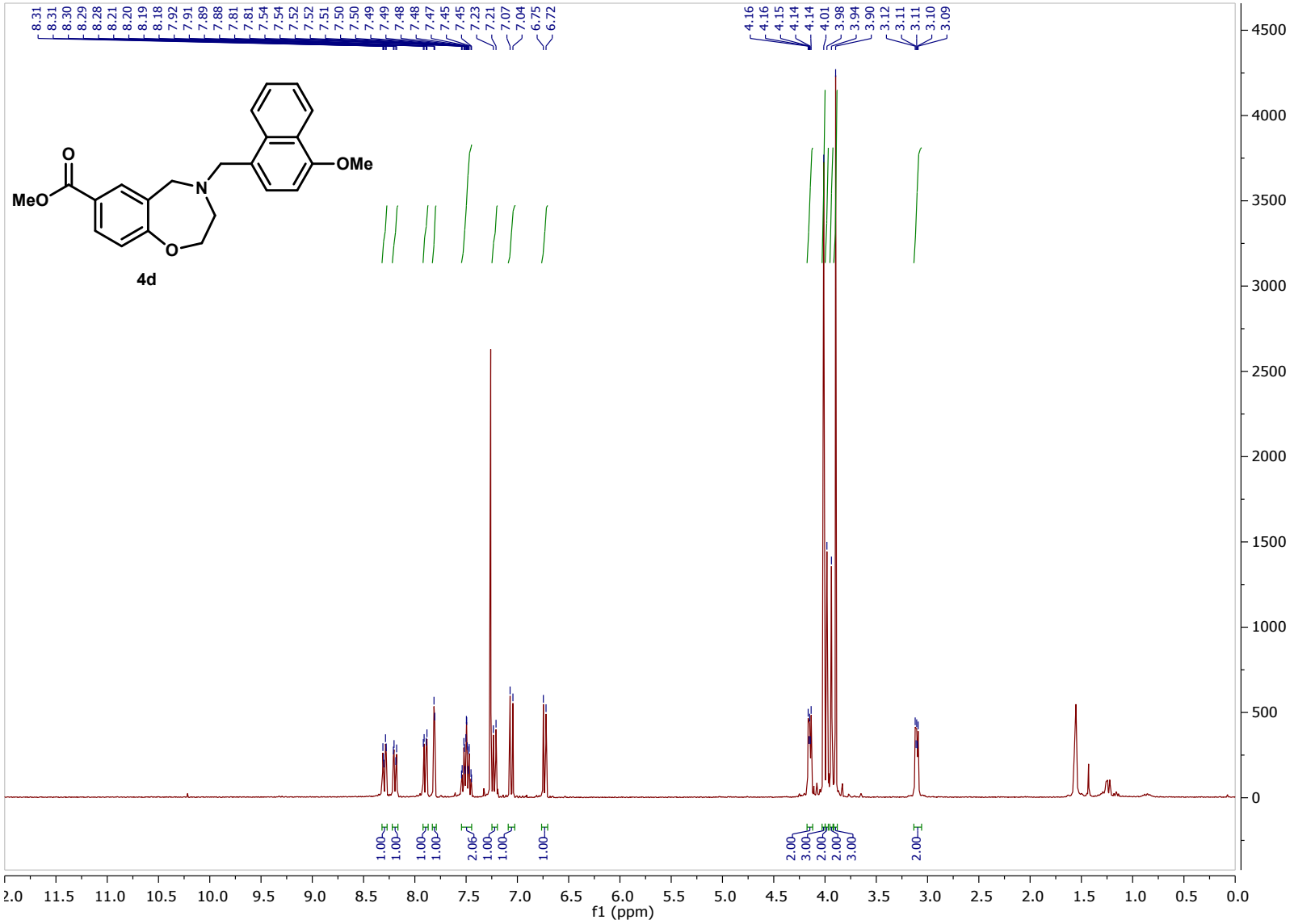
f1 (ppm)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7.52
7.52
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7.50
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7.48
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7.23
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4.15
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4.14
4.01
3.98
3.94
3.90
3.12
3.11
3.11
3.10
3.09
O
MeO
N
O
OMe
4d
4500
4000
3500
3000
2500
2000
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1000
500
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1.00
1.00
1.00
1.00
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1.00
1.00
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2.00
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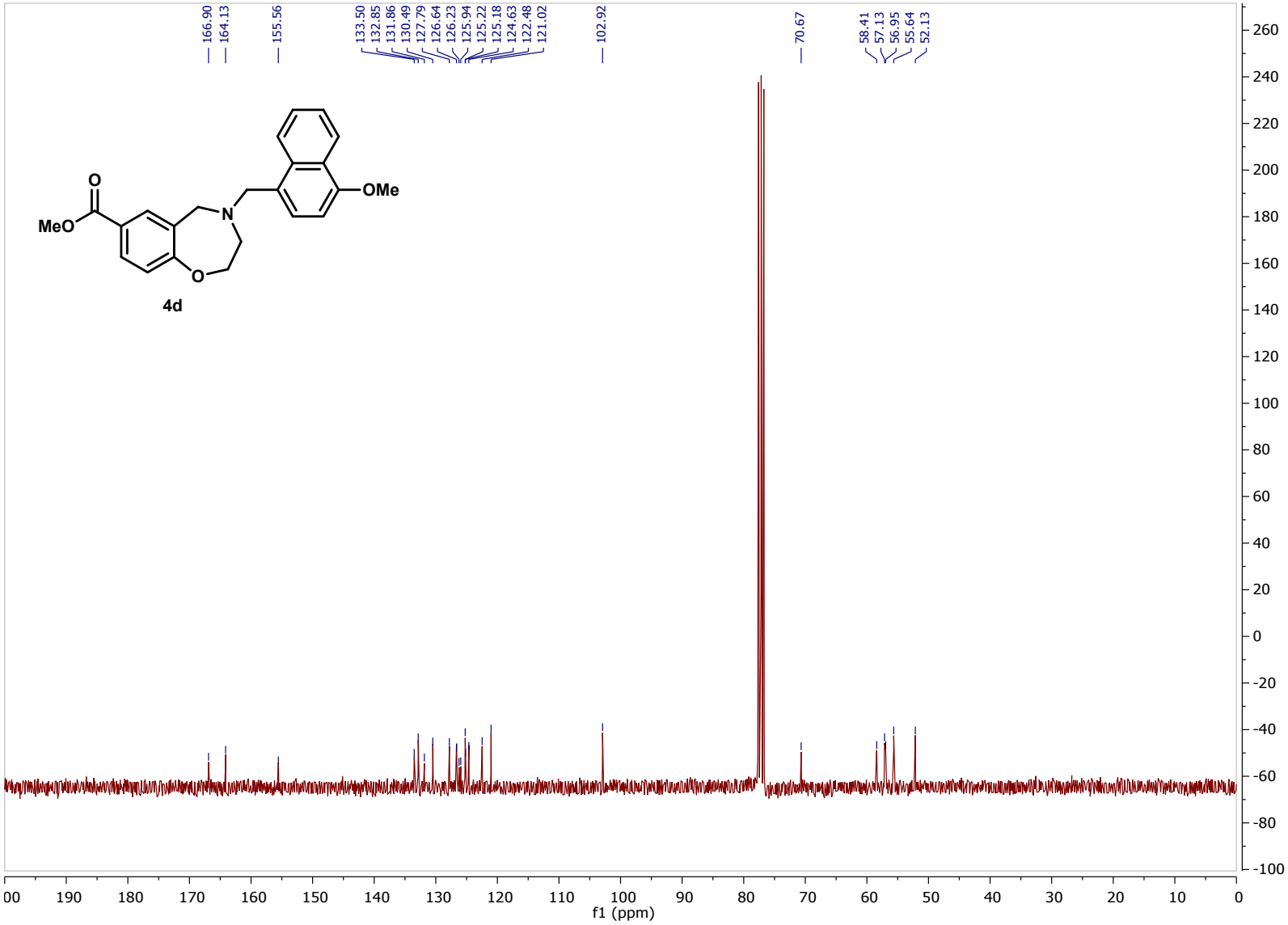
f1 (ppm)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126.23
125.94
125.22
125.18
124.63
122.48
121.02
102.92
70.67
58.41
57.13
56.95
55.64
52.13
O
MeO
N
OMe
O
4d
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
00
190
180
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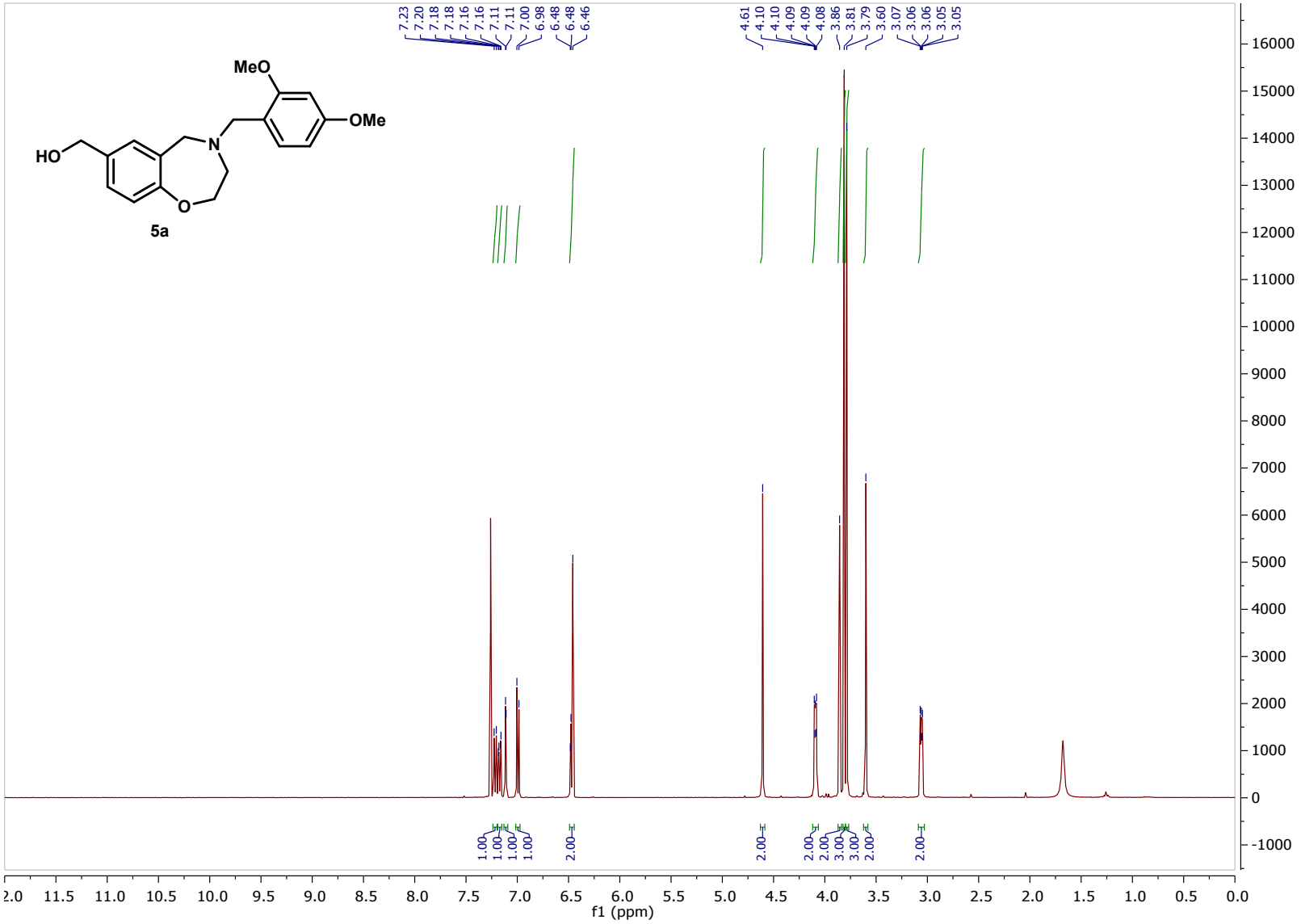
f1 (ppm)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OMe
HO
N
O
5a
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7.18
7.18
7.16
7.16
7.11
7.11
7.00
6.98
6.48
6.48
6.46
4.61
4.10
4.10
4.09
4.09
4.08
3.86
3.81
3.79
3.60
3.07
3.06
3.06
3.05
3.05
1.00
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1.00
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2.00
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3.00
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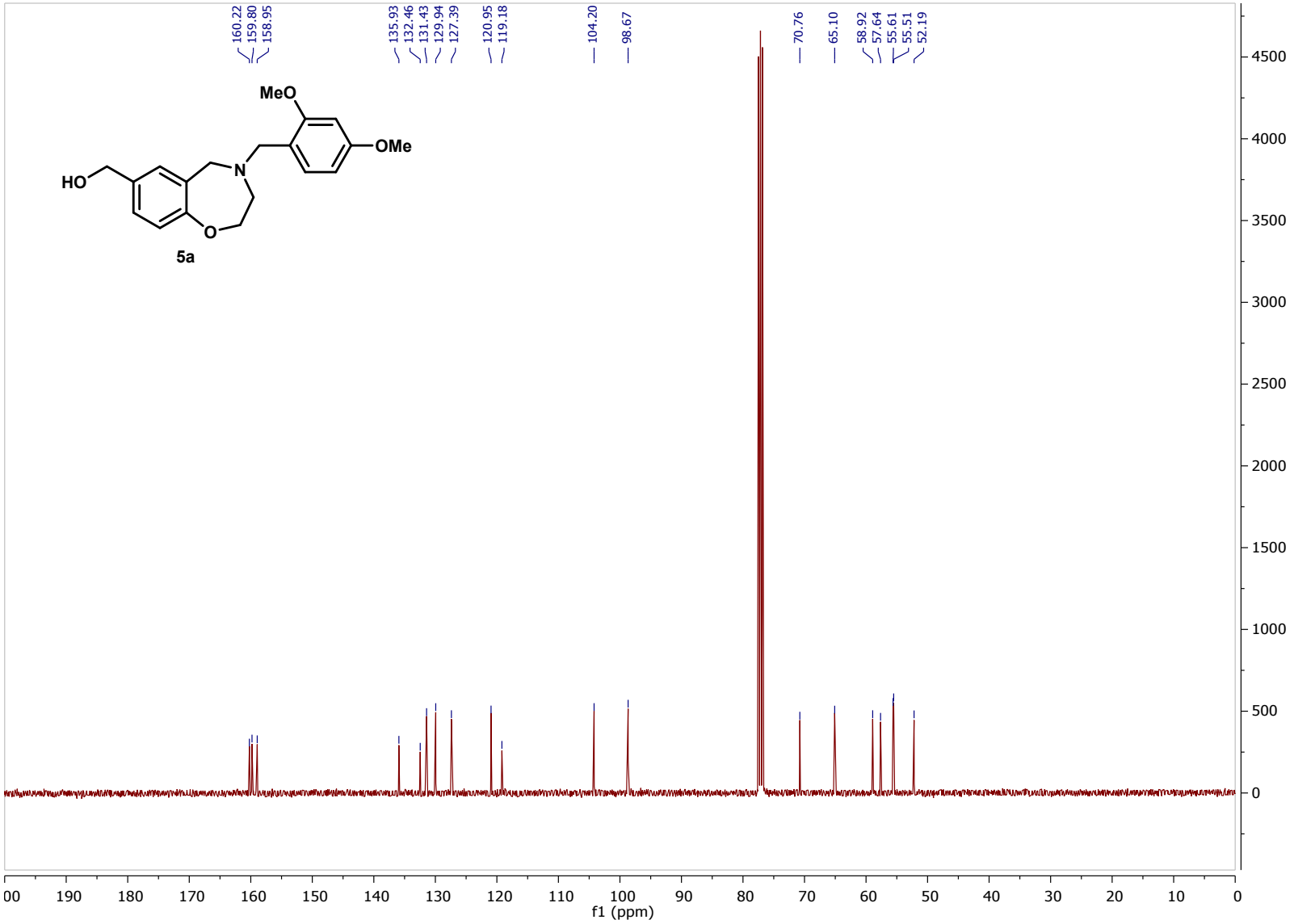
2.00
f1 (ppm)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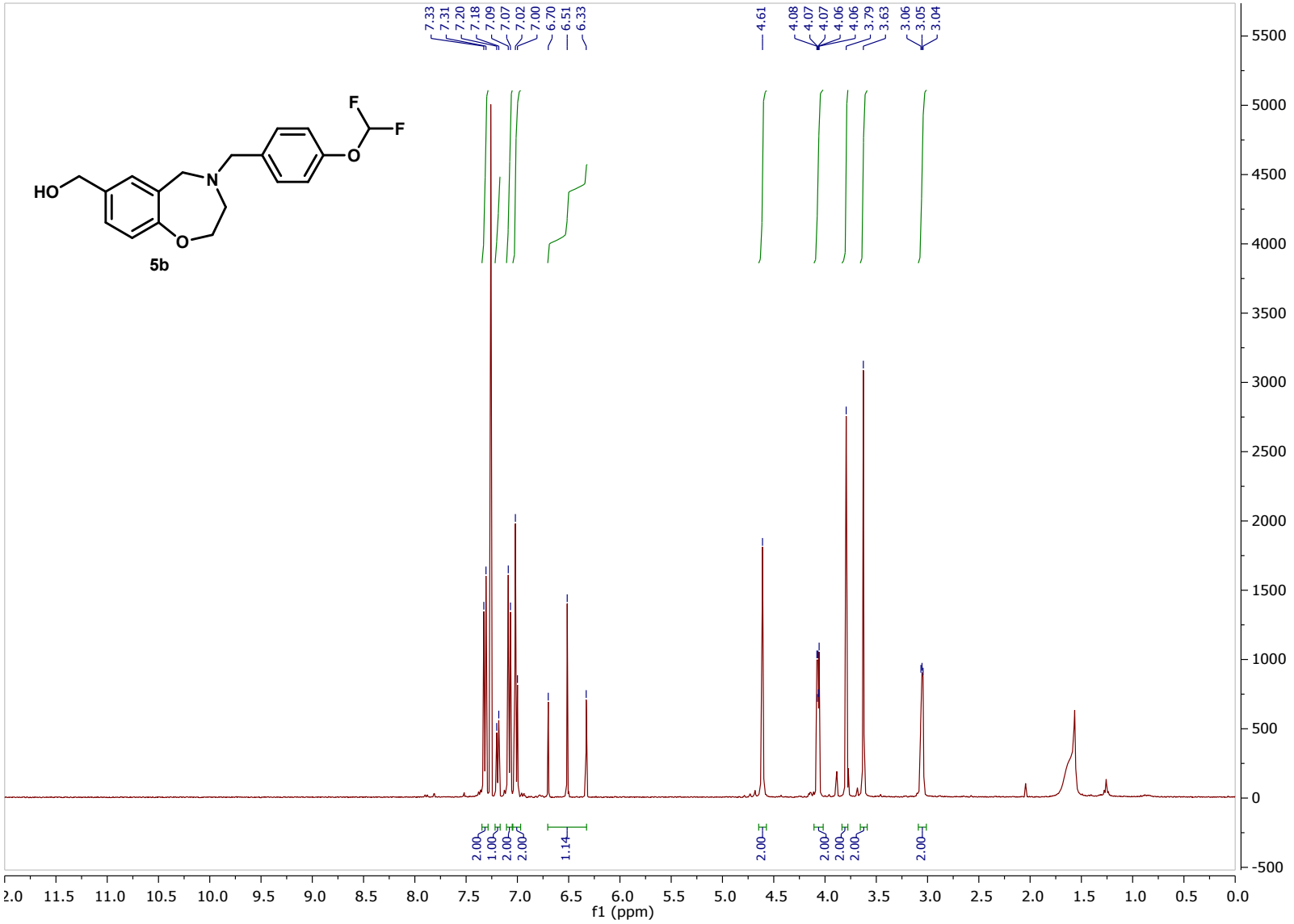
129.94
127.39
120.95
119.18
104.20
98.67
70.76
65.10
58.92
57.64
55.61
55.51
52.19
MeO
OMe
HO
N
O
5a
4500
4000
3500
3000
2500
2000
1500
1000
500
0
f1 (ppm)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7.20
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7.09
7.07
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6.51
6.33
4.61
4.08
4.07
4.07
4.06
4.06
3.79
3.63
3.06
3.05
3.04
F
F
O
N
HO
O
5b
2.00
1.00
2.00
2.00
1.14
2.00
2.00
2.00
2.00
2.00
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
2.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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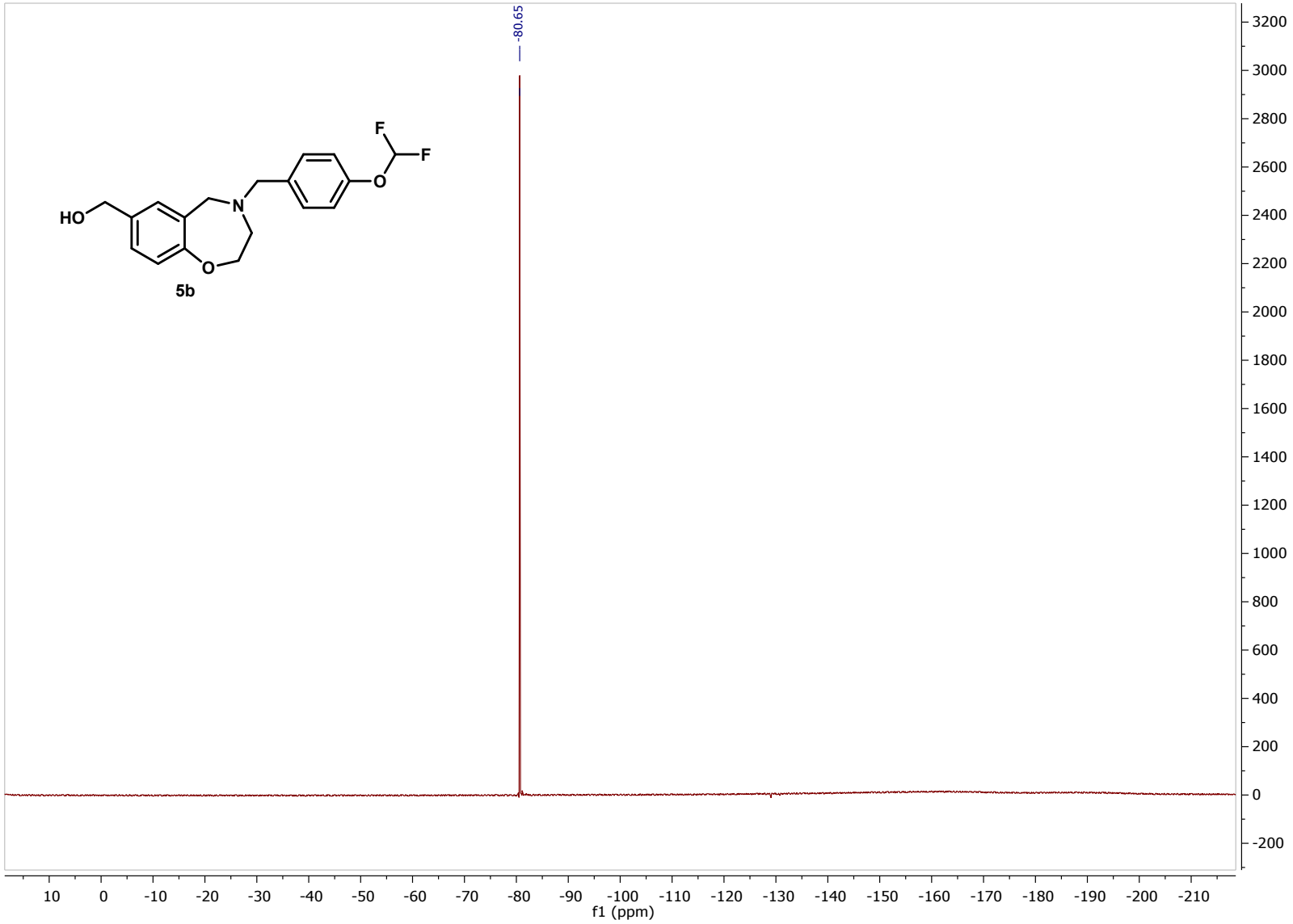
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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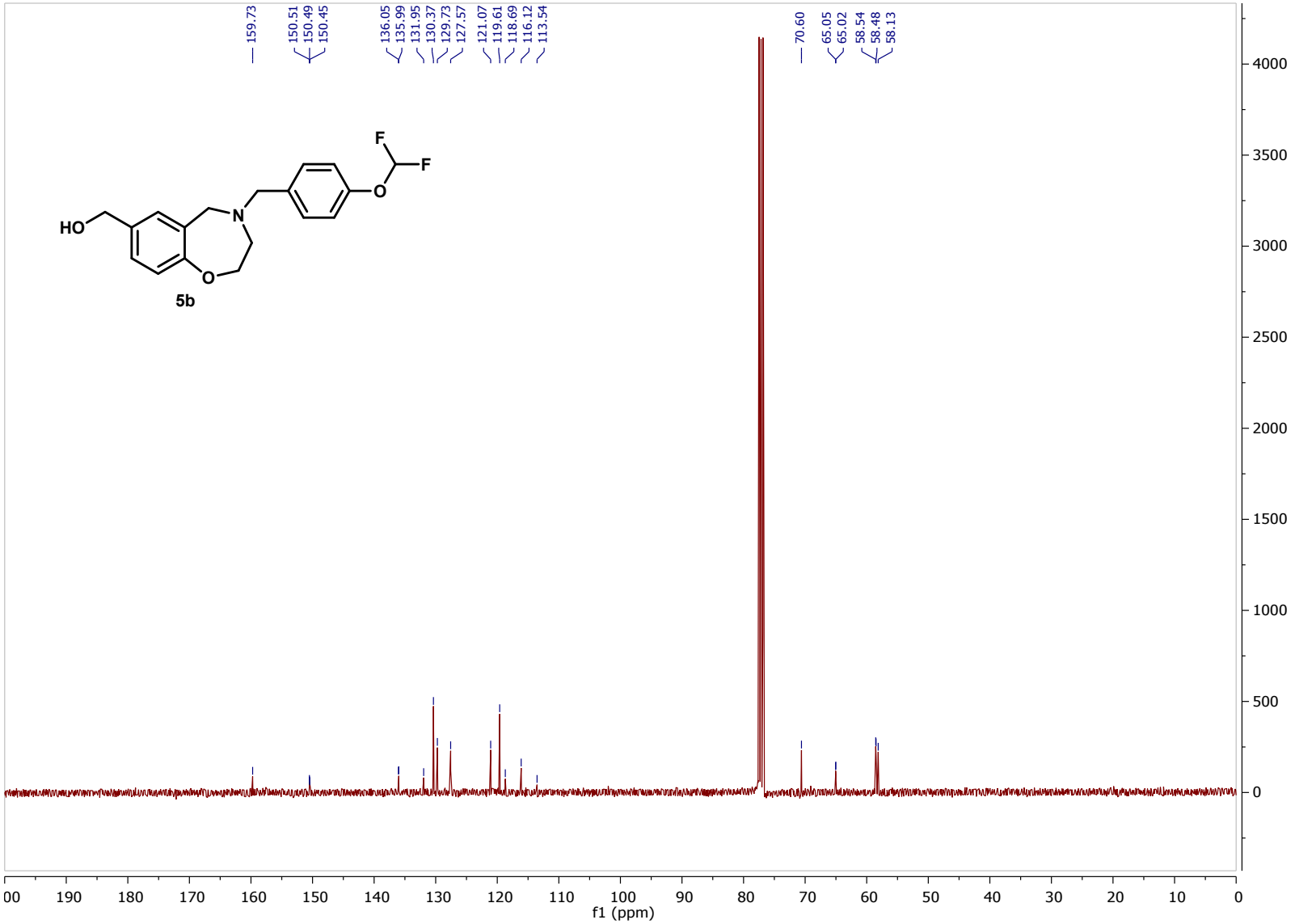
F
F
O
N
HO
O
5b
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)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135.99
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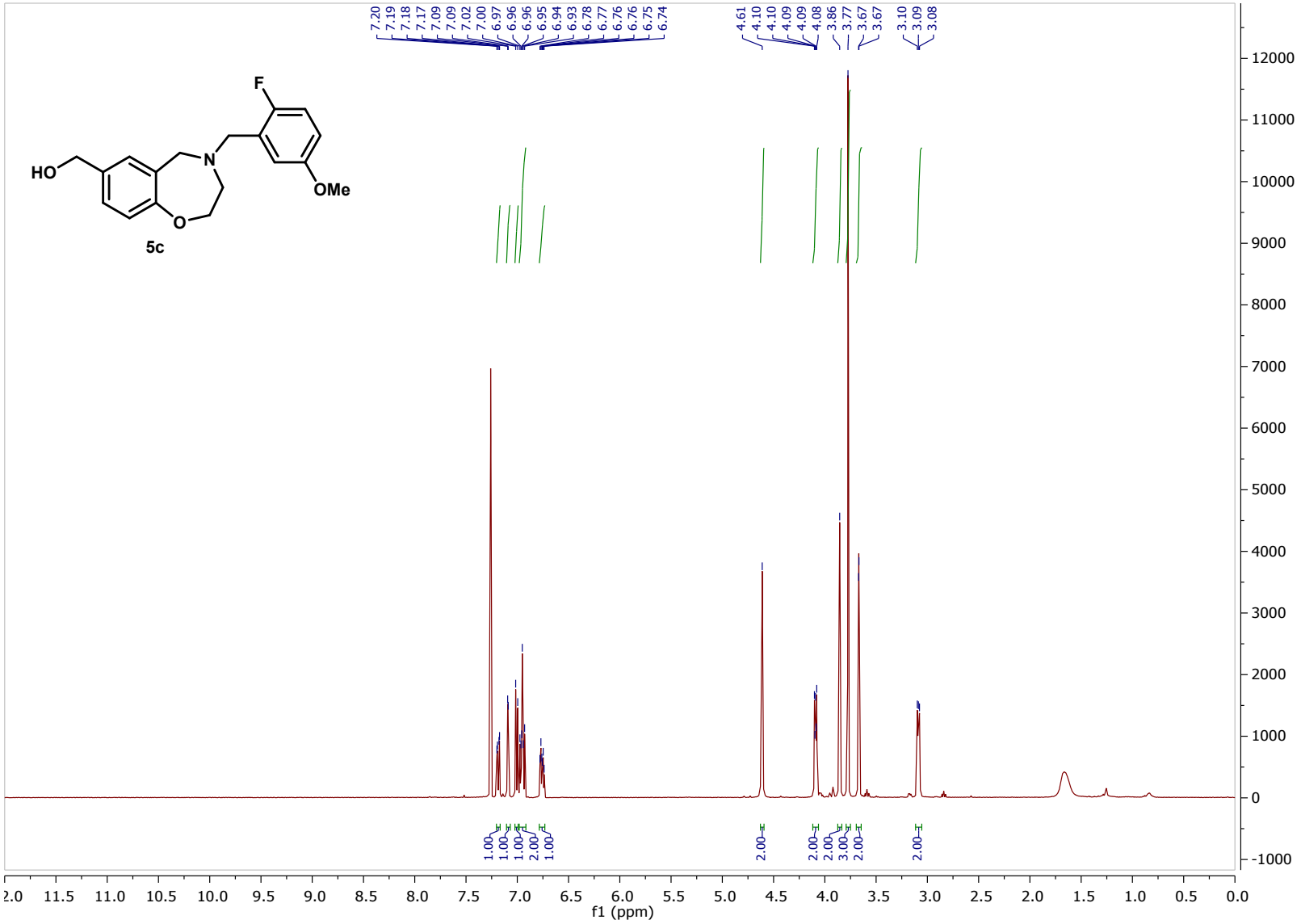
127.57
121.07
119.61
118.69
116.12
113.54
70.60
65.05
65.02
58.54
58.48
58.13
HO
N
O
F
F
O
5b
4000
3500
3000
2500
2000
1500
1000
500
0
f1 (ppm)


F
HO
N
OMe
O
5c
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7.19
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7.09
7.02
7.00
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6.95
6.94
6.93
6.78
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6.76
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4.10
4.09
4.09
4.08
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3.10
3.09
3.08
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10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
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11.0
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10.0
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9.0
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7.0
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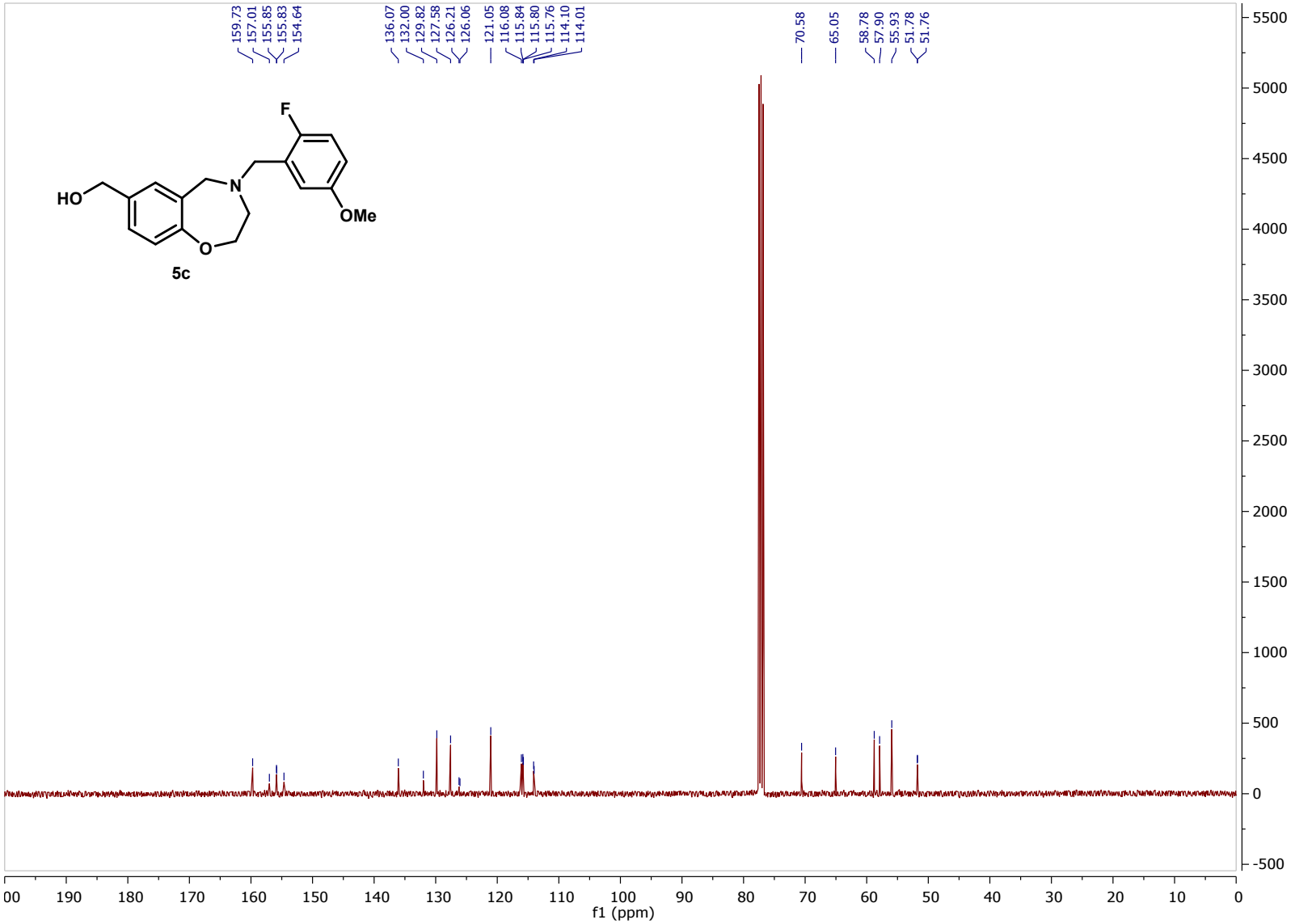
f1 (ppm)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126.21
126.06
121.05
116.08
115.84
115.80
115.76
114.10
114.01
70.58
65.05
58.78
57.90
55.93
51.78
51.76
F
HO
N
OMe
O
5c
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
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190
180
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130
120
110
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90
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50
40
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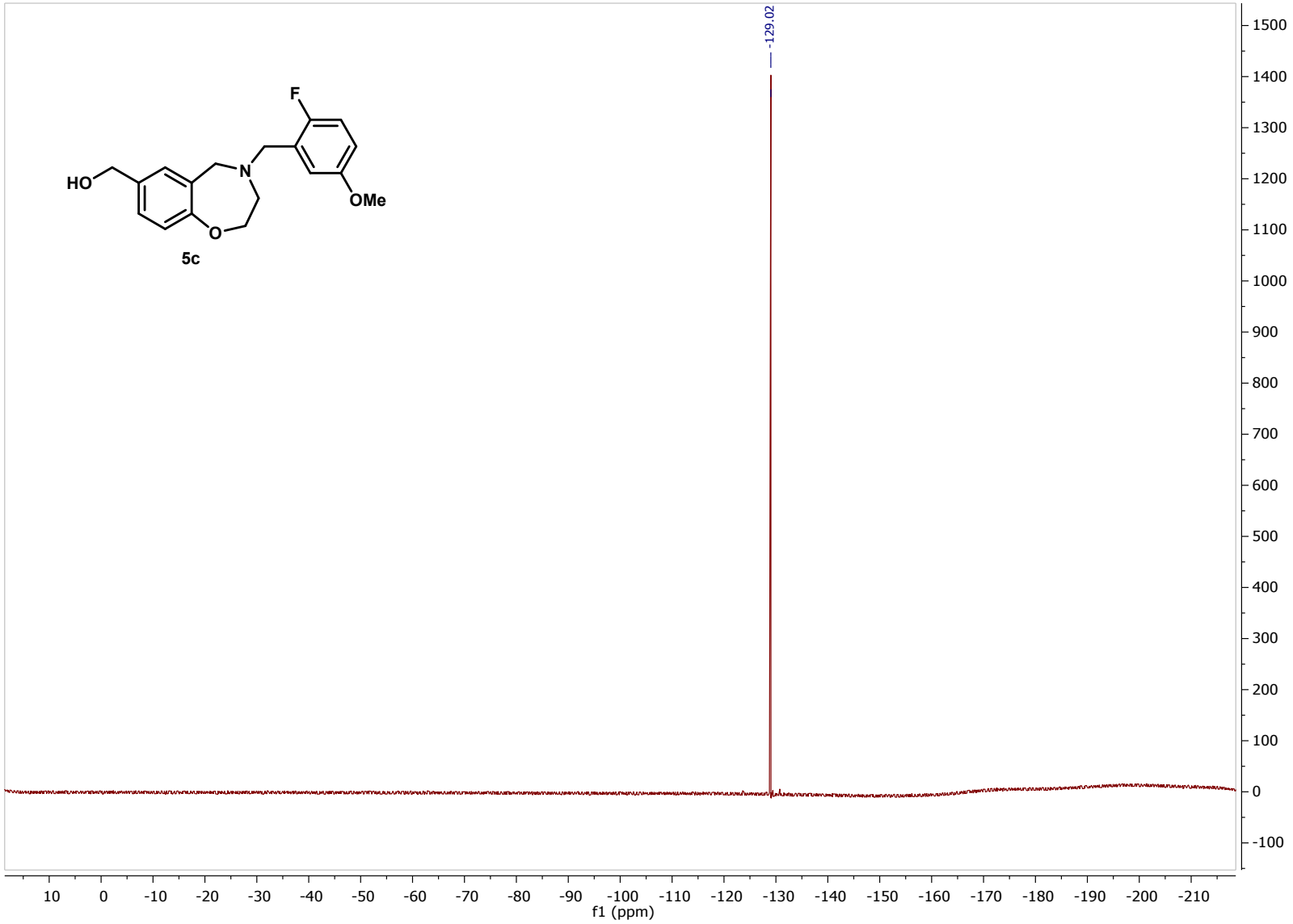
f1 (ppm)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F
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O
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1200
1100
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900
800
700
600
500
400
300
200
100
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-100
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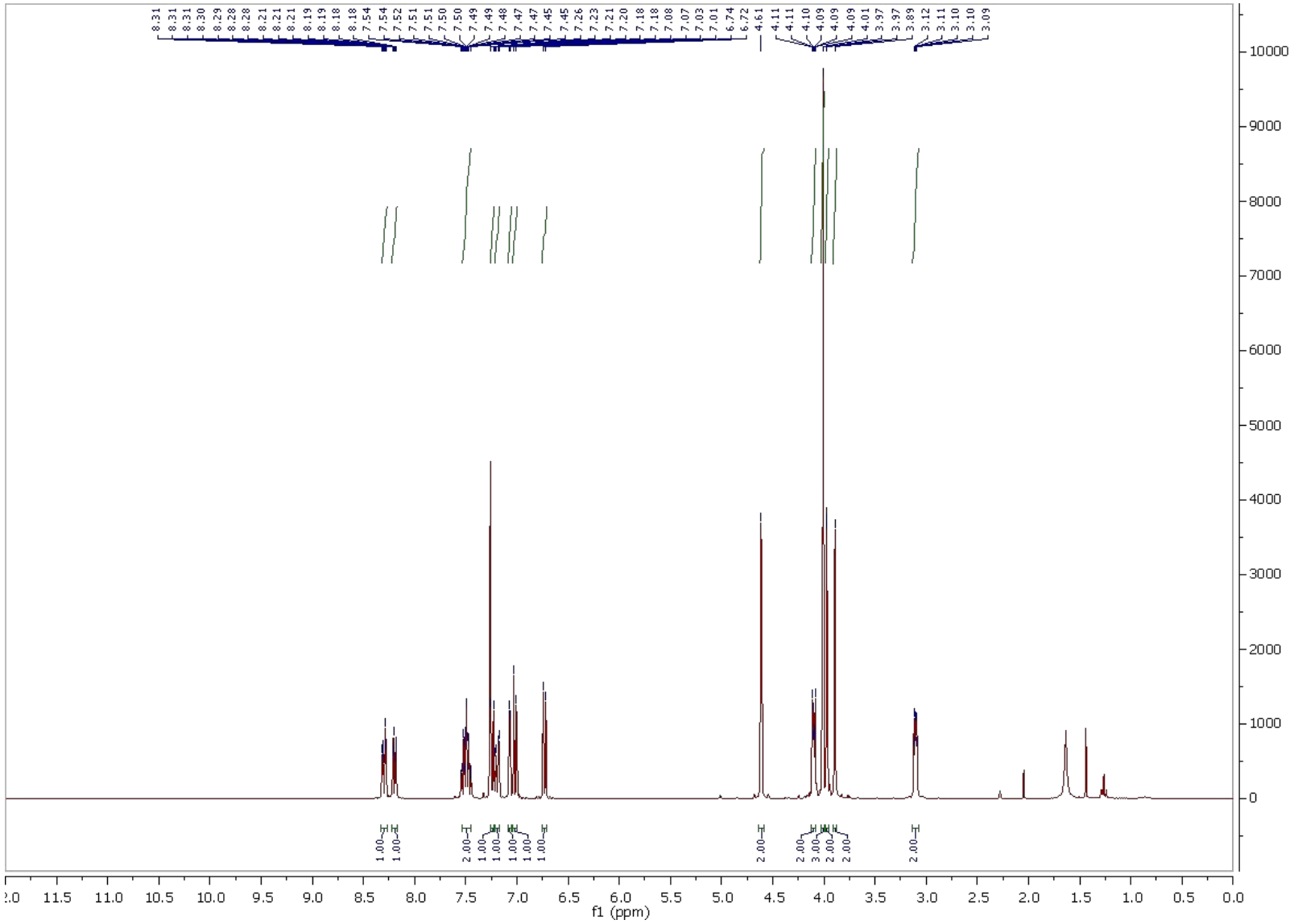
f1 (ppm)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7.50
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7.47
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7.45
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7.23
7.21
7.20
7.18
7.18
7.08
7.07
7.03
7.01
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6.72
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4.11
4.10
4.09
4.09
4.09
4.01
3.97
3.97
3.89
3.12
3.11
3.10
3.09
10000
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8000
7000
6000
5000
4000
3000
2000
1000
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1.00
2.00
1.00
1.00
1.00
1.00
1.00
2.00
2.00
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2.00
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3.0
2.5
2.0
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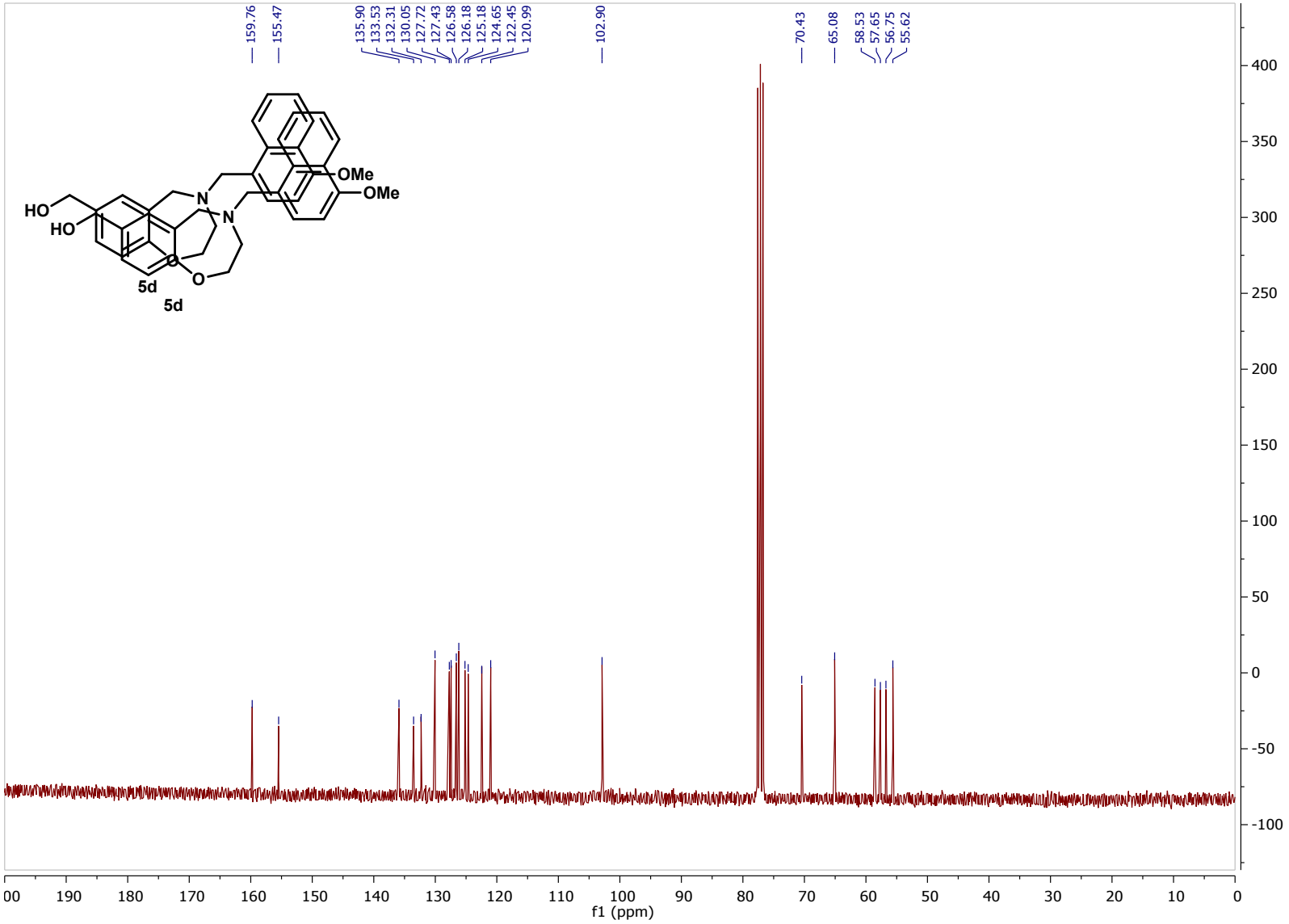
0.0
f1 (ppm)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126.18
125.18
124.65
122.45
120.99
102.90
70.43
65.08
58.53
57.65
56.75
55.62
HO
HO
N
N
OMe
OMe
O
O
5d
5d
400
350
300
250
200
150
100
50
0
-50
-100
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
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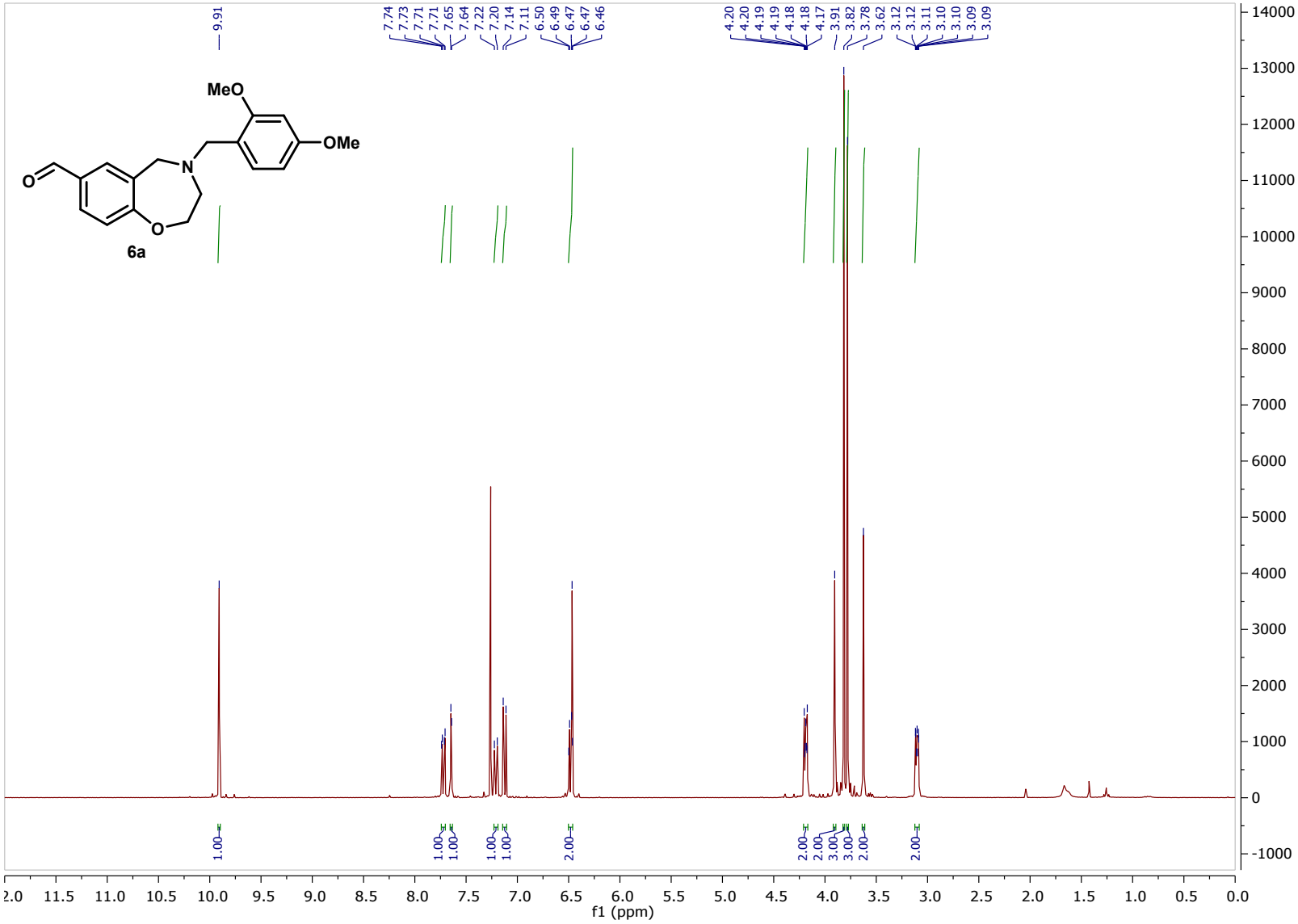
f1 (ppm)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7.14
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6.50
6.49
6.47
6.47
6.46
4.20
4.20
4.19
4.19
4.18
4.18
4.17
3.91
3.82
3.78
3.62
3.12
3.12
3.11
3.10
3.10
3.09
3.09
MeO
OMe
O
N
O
6a
1.00
1.00
1.00
1.00
2.00
2.00
2.00
3.00
3.00
2.00
2.00
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13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
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11.0
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10.0
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8.5
8.0
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7.0
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6.0
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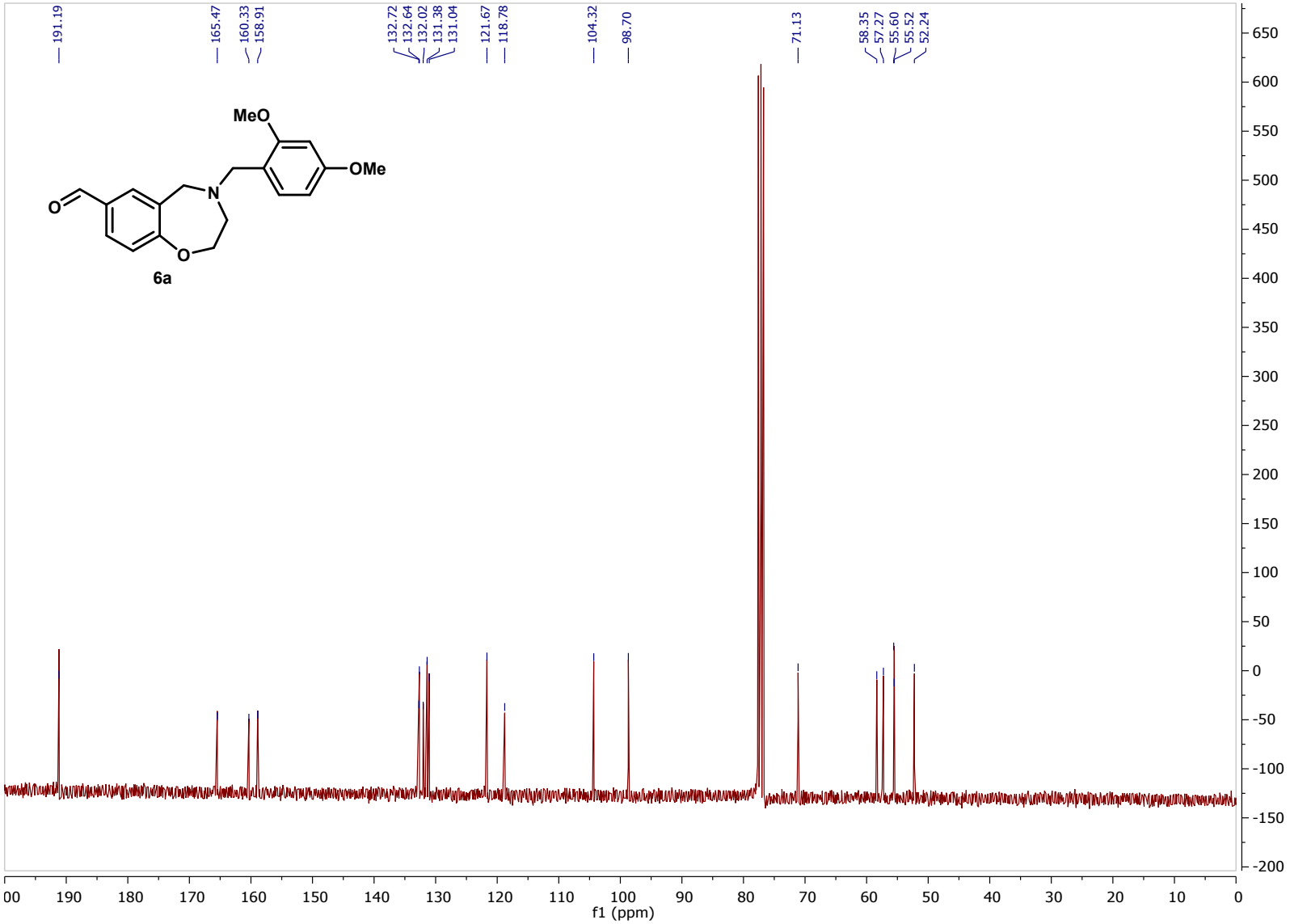
f1 (ppm)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131.04
121.67
118.78
104.32
98.70
71.13
58.35
57.27
55.60
55.52
52.24
MeO
OMe
O
N
O
6a
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
-100
-150
-200
00
190
180
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150
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130
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110
100
90
80
70
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50
40
30
20
10
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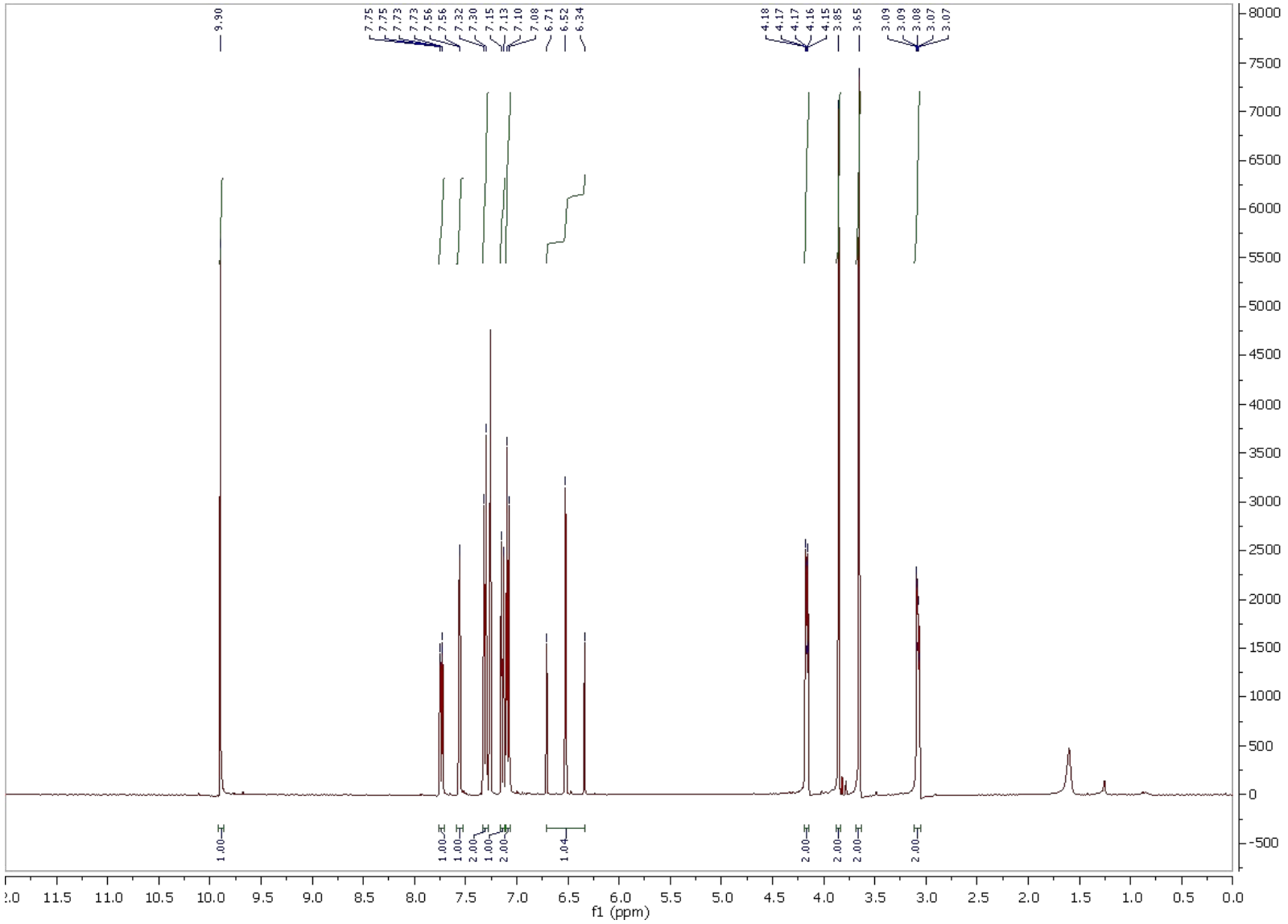
f1 (ppm)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7.15
7.13
7.10
7.08
6.71
6.52
6.34
4.18
4.17
4.17
4.16
4.15
3.85
3.65
3.09
3.09
3.08
3.07
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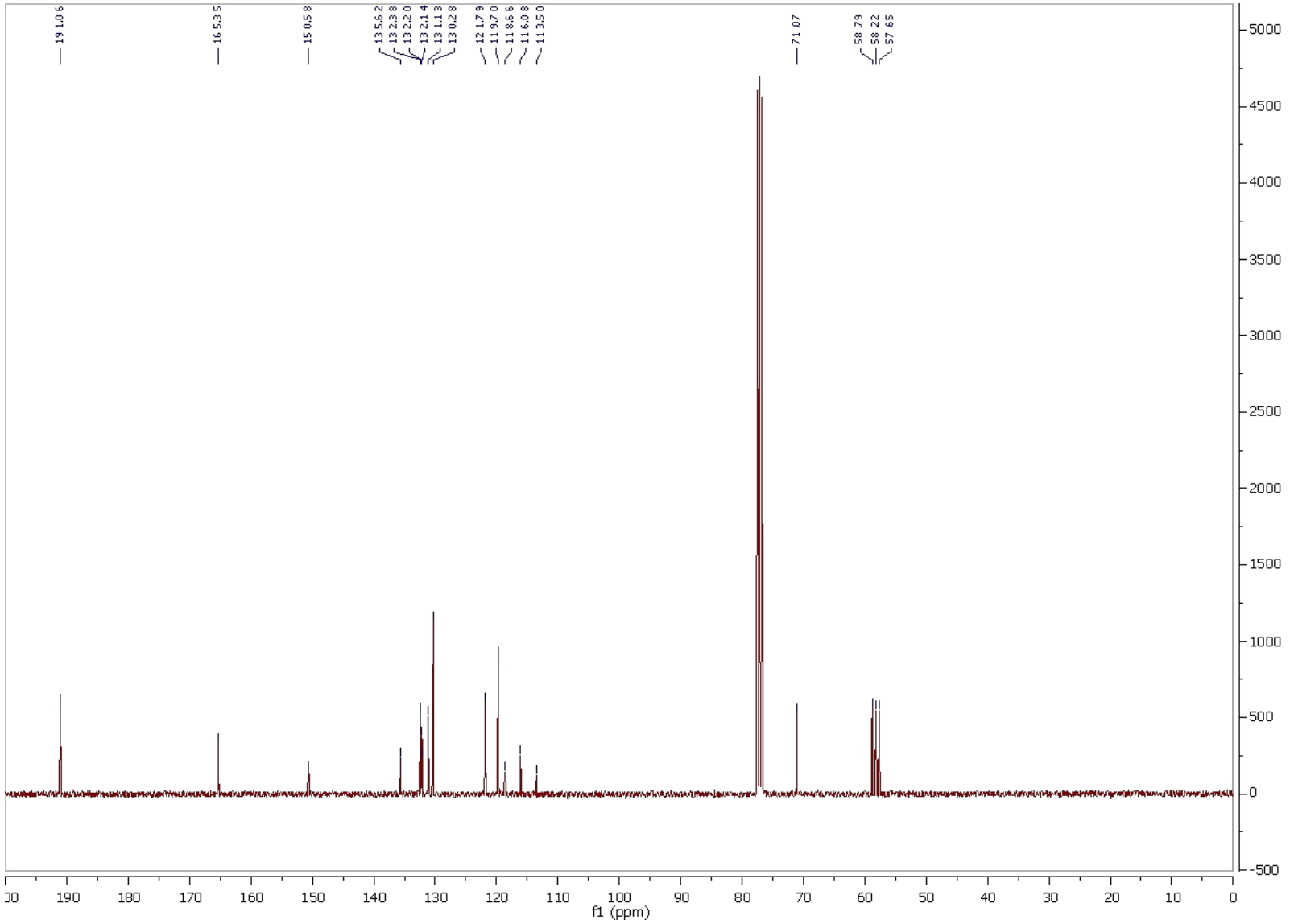
2.00
f1 (ppm)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121.79
119.70
118.66
116.08
113.50
71.07
58.79
58.22
57.65
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
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130
120
110
100
90
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70
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30
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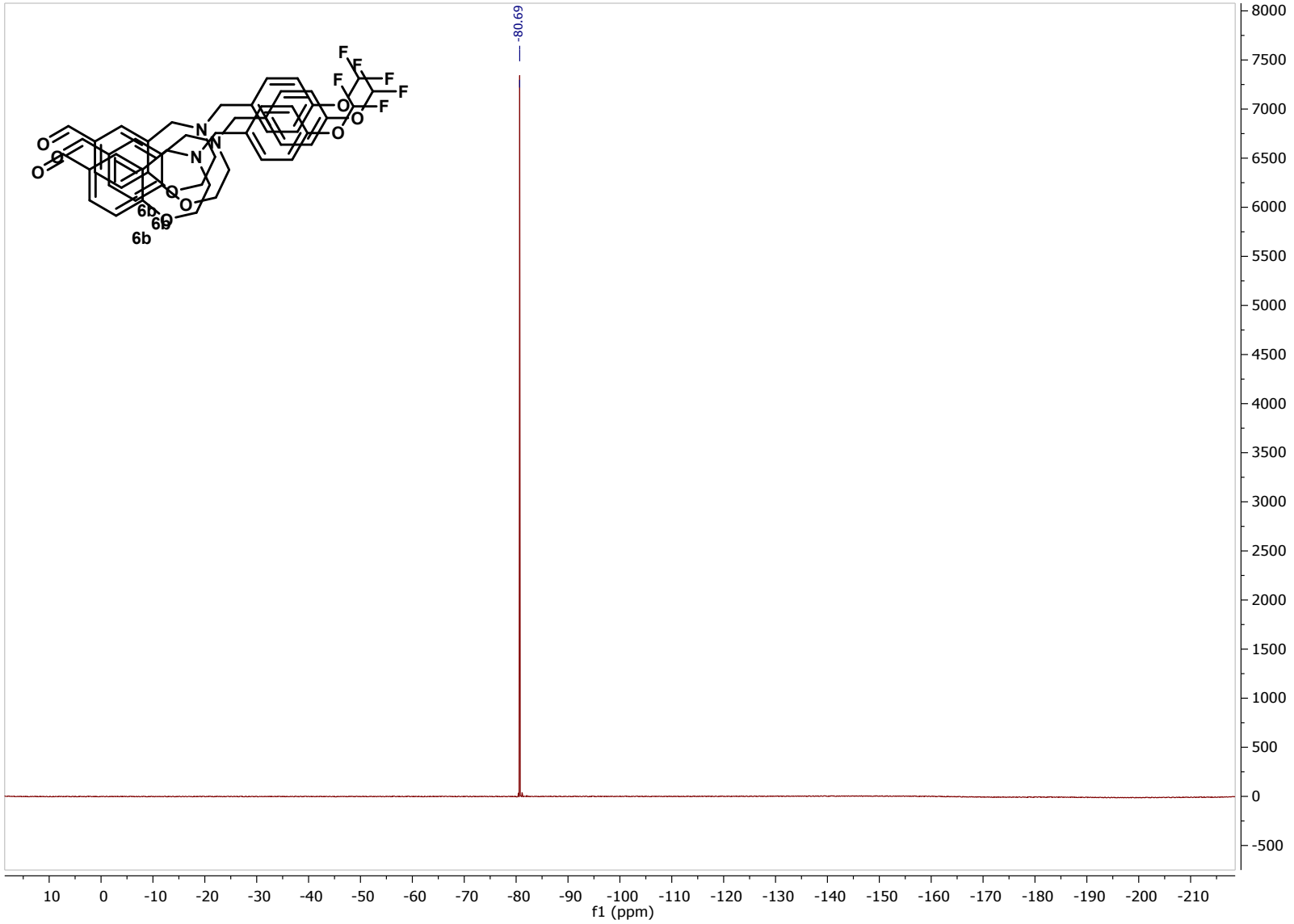
10
0
f1 (ppm)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F
F
F
F
F
F
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O
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N
N
N
O
O
O
O
6b
6b
6b
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
10
0
-10
-20
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-60
-70
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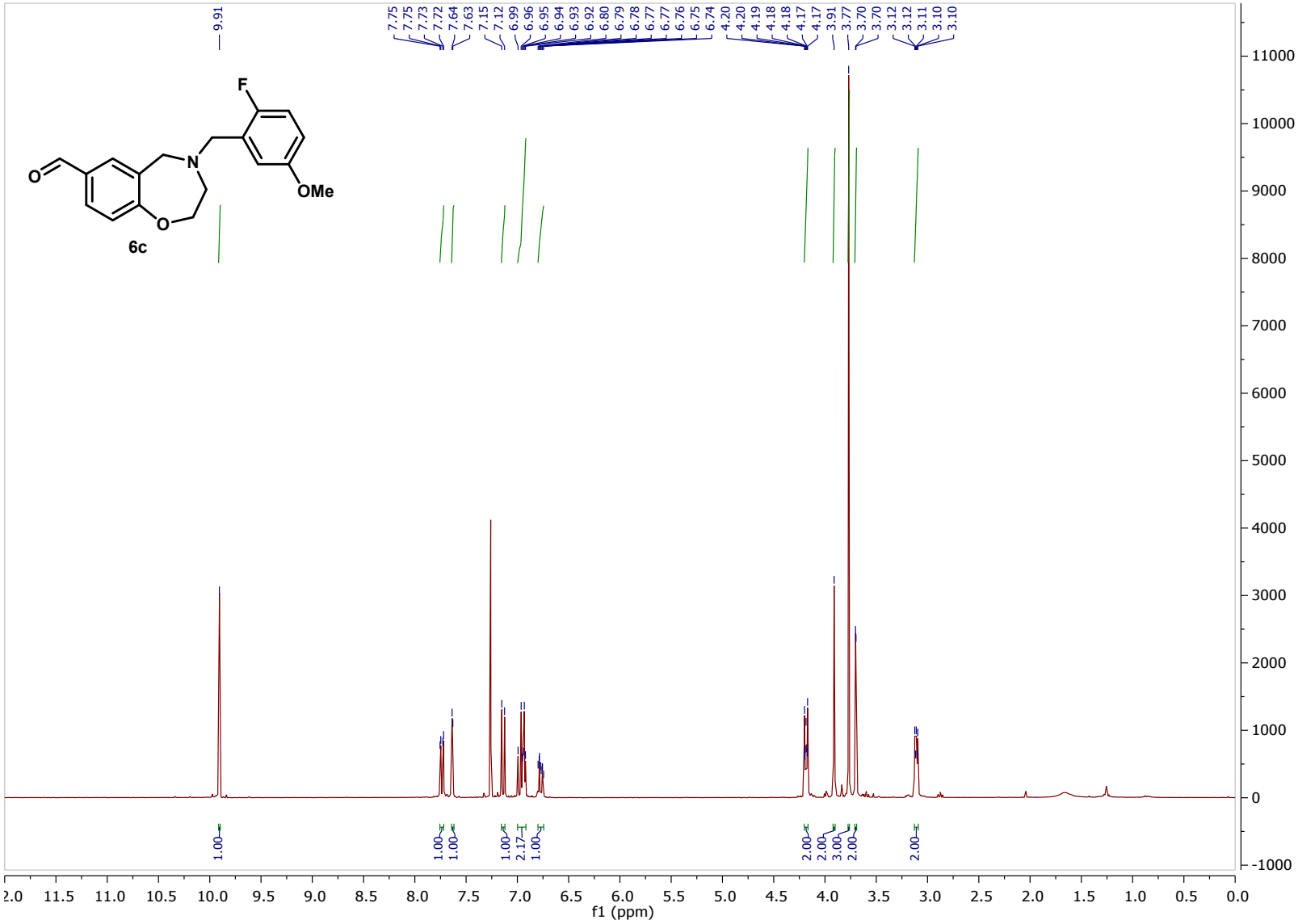
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)


9.91
7.75
7.75
7.73
7.72
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7.63
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7.12
6.99
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6.95
6.94
6.93
6.92
6.80
6.79
6.78
6.77
6.77
6.76
6.75
6.74
4.20
4.20
4.19
4.18
4.18
4.17
4.17
3.91
3.77
3.70
3.70
3.12
3.12
3.11
3.10
3.10
F
O
N
OMe
O
6c
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
1.00
1.00
1.00
1.00
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1.00
2.00
2.00
3.00
2.00
2.00
2.0
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8.0
7.5
7.0
6.5
6.0
5.5
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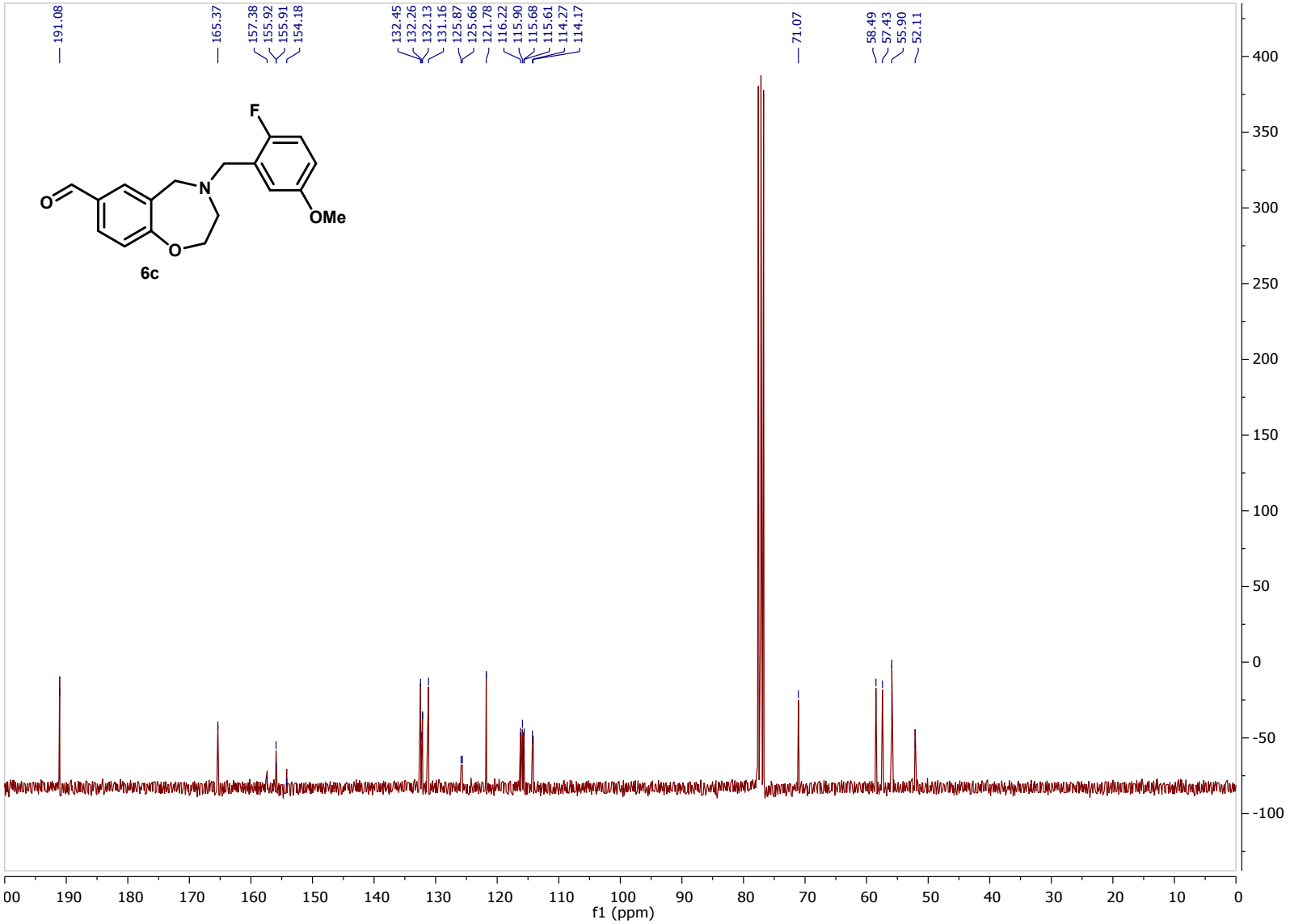
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154.18
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132.26
132.13
131.16
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125.66
121.78
116.22
115.90
115.68
115.61
114.27
114.17
71.07
58.49
57.43
55.90
52.11
F
O
N
OMe
O
6c
400
350
300
250
200
150
100
50
0
-50
-100
00
190
180
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150
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120
110
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90
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50
40
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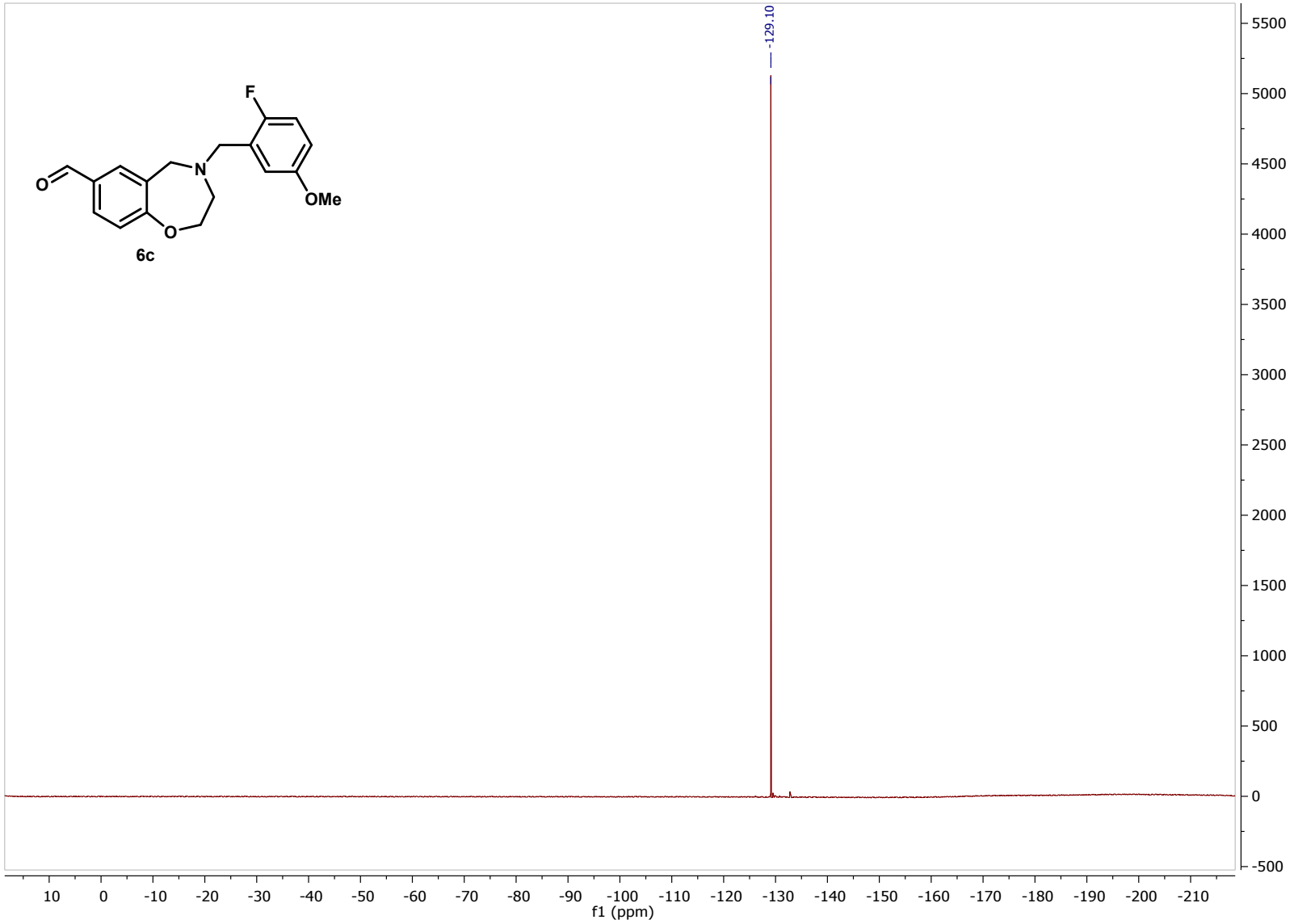
f1 (ppm)


F
O
N
OMe
O
6c
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4000
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3000
2500
2000
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1000
500
0
-500
10
0
-10
-20
-30
-40
-50
-60
-70
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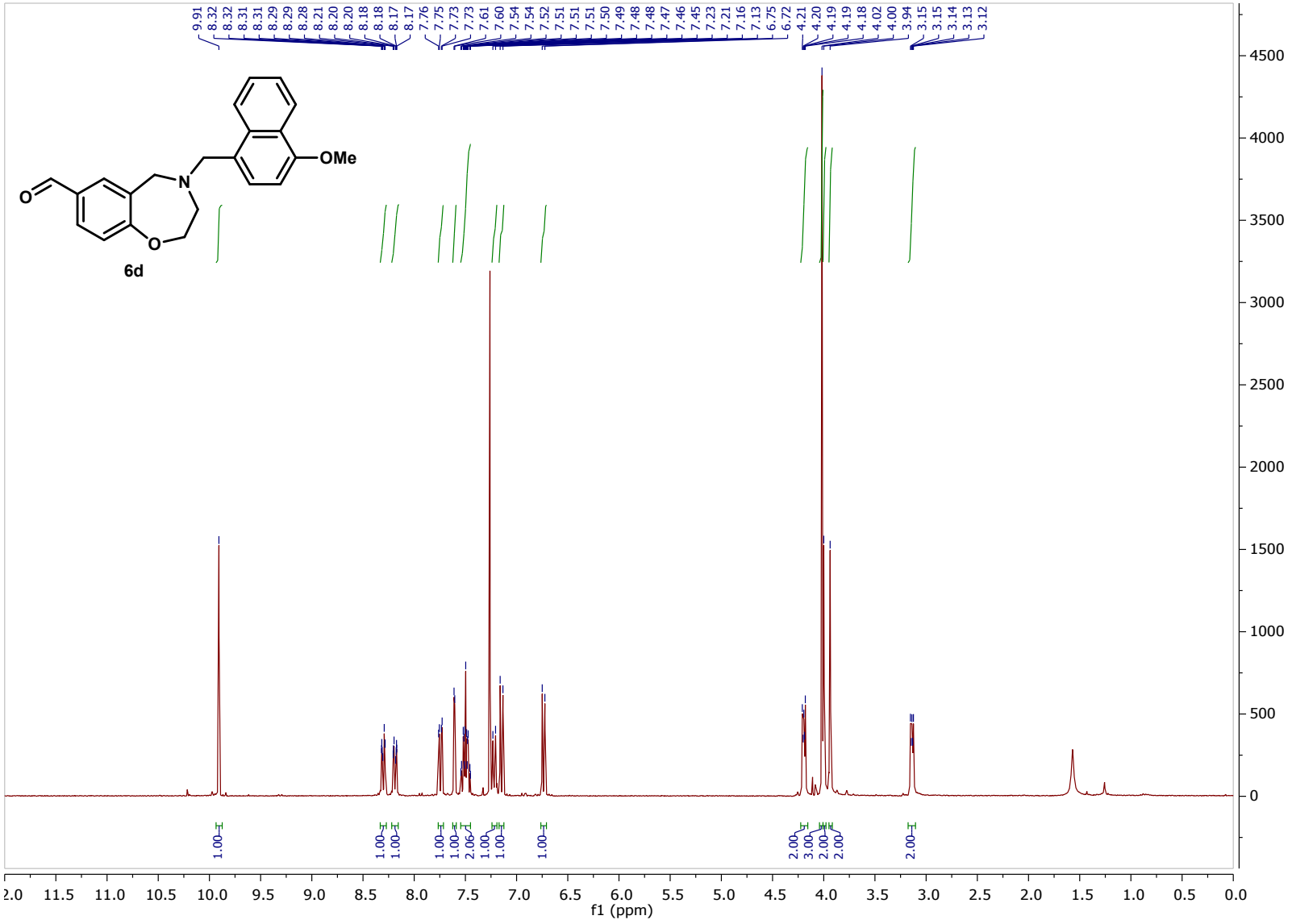
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)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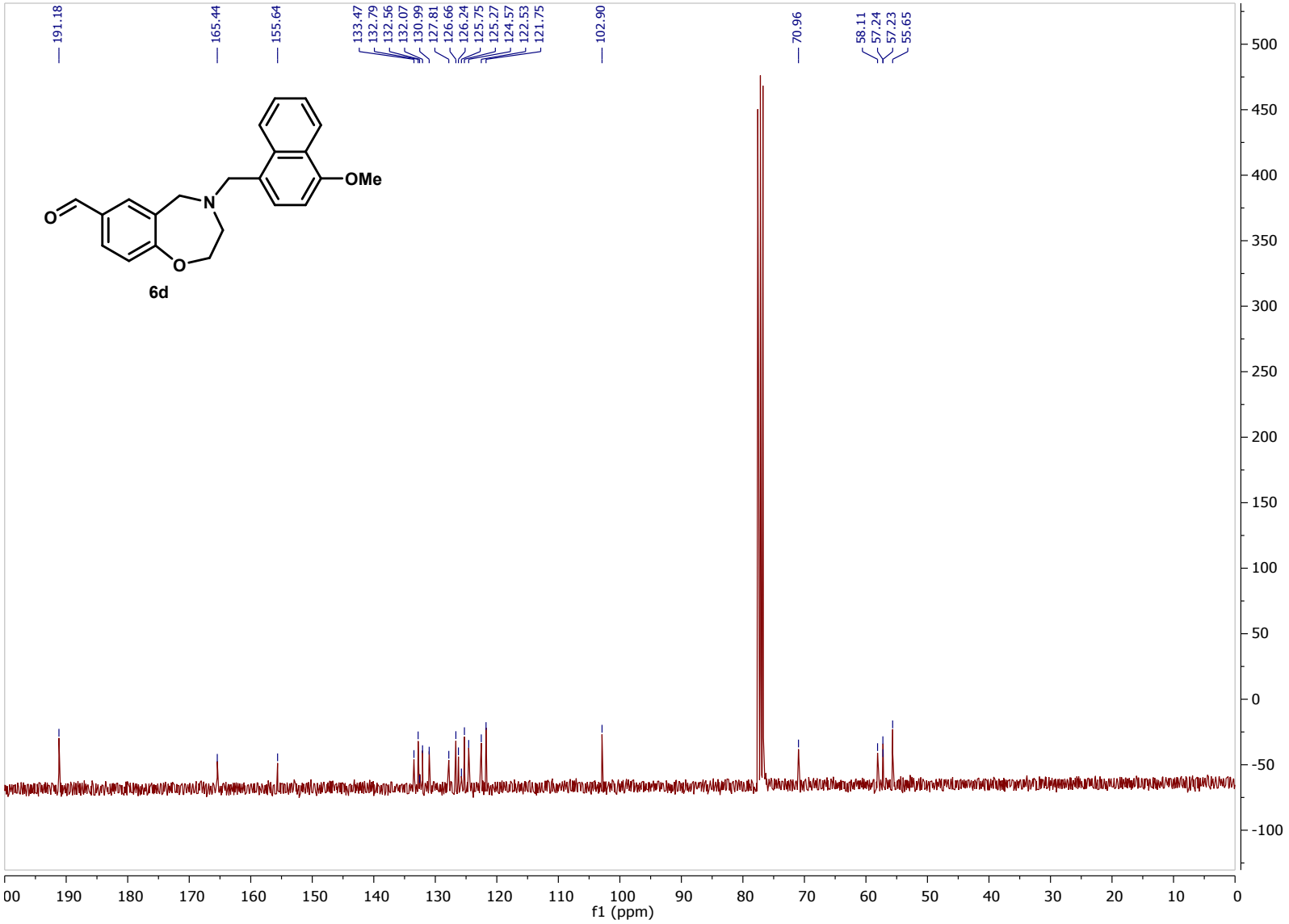
8.18
8.17
8.17
7.76
7.75
7.73
7.73
7.61
7.60
7.54
7.54
7.52
7.51
7.51
7.51
7.50
7.49
7.48
7.48
7.47
7.46
7.45
7.23
7.21
7.16
7.13
6.75
6.72
4.21
4.20
4.19
4.19
4.18
4.02
4.00
3.94
3.15
3.15
3.14
3.13
3.12
OMe
N
O
O
6d
4500
4000
3500
3000
2500
2000
1500
1000
500
0
1.00
1.00
1.00
1.00
1.00
2.06
1.00
1.00
1.00
2.00
3.00
2.00
2.00
2.00
2.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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132.79
132.56
132.07
130.99
127.81
126.66
126.24
125.75
125.27
124.57
122.53
121.75
102.90
70.96
58.11
57.24
57.23
55.65
OMe
O
N
O
6d
500
450
400
350
300
250
200
150
100
50
0
-50
-100
00
190
180
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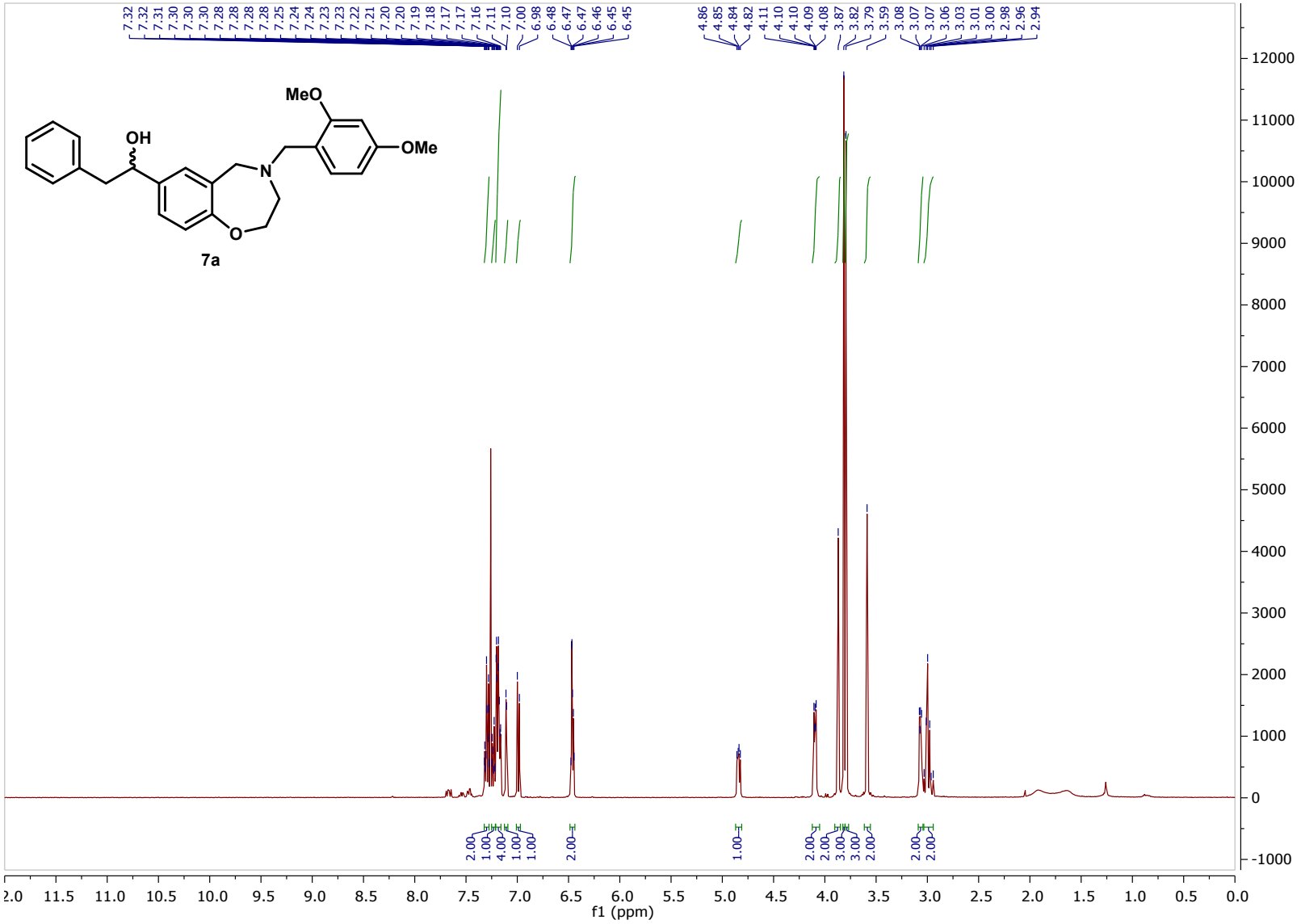
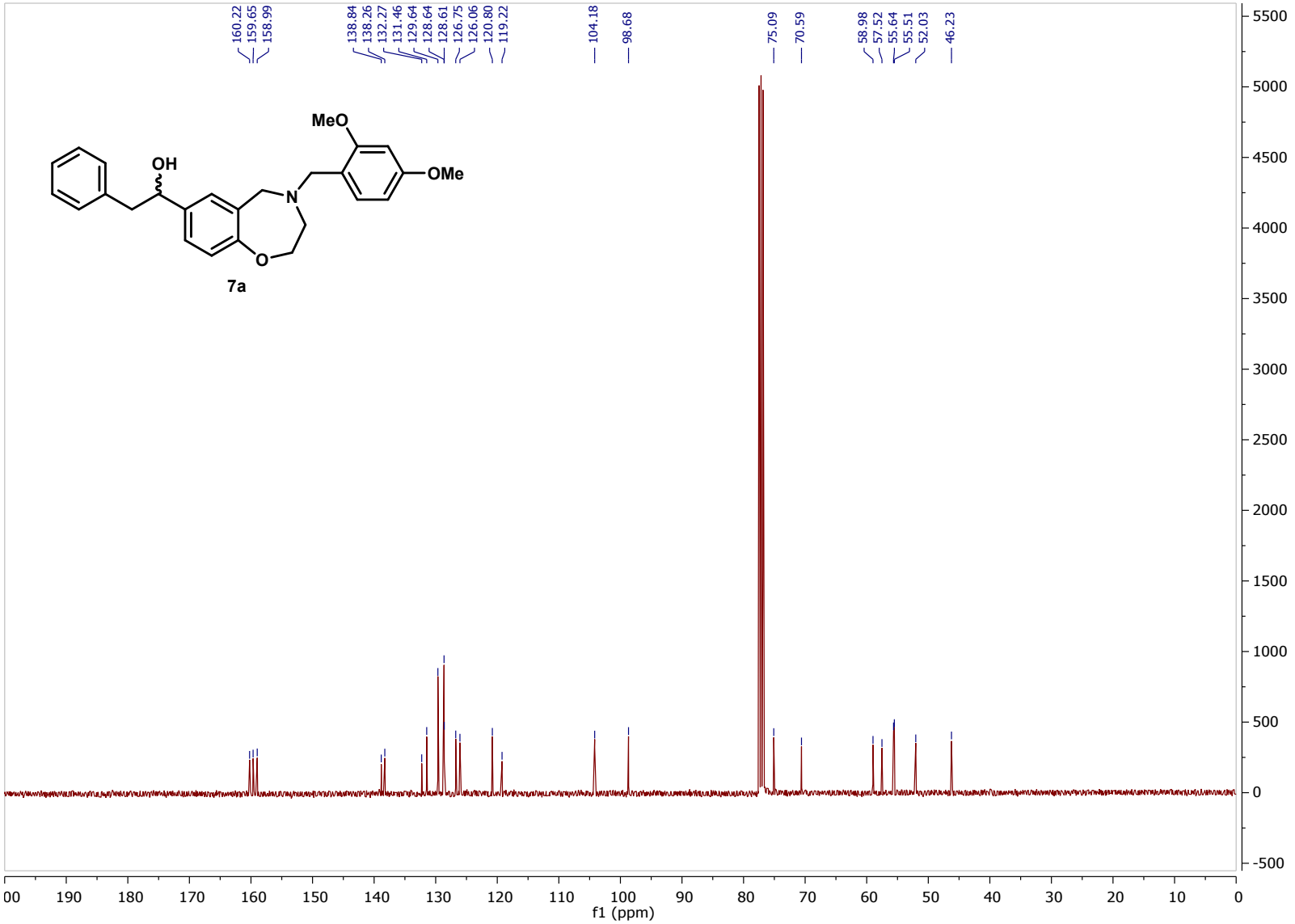
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


MeO
OH
OMe
N
O
7a
f1 (ppm)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132.27
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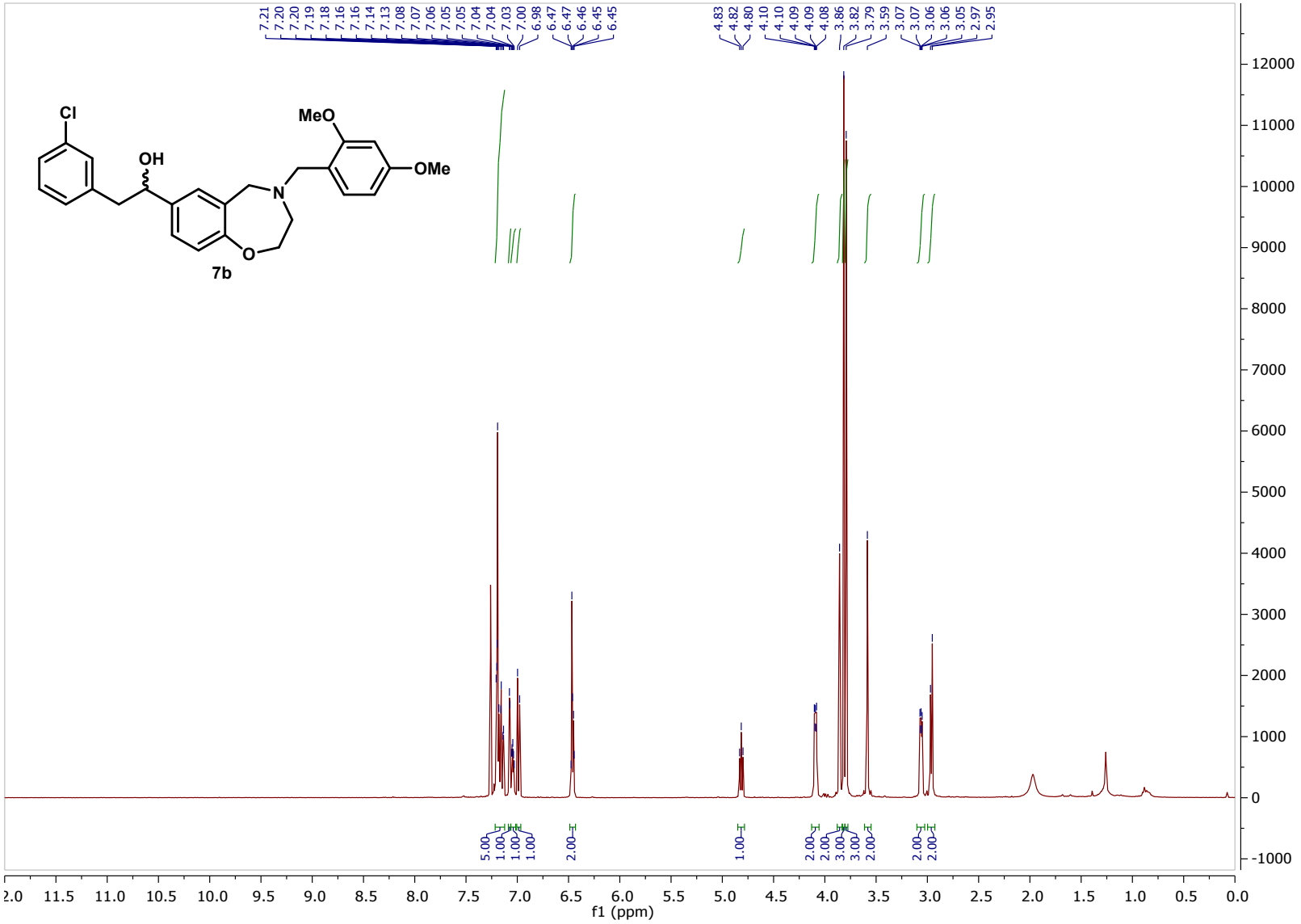
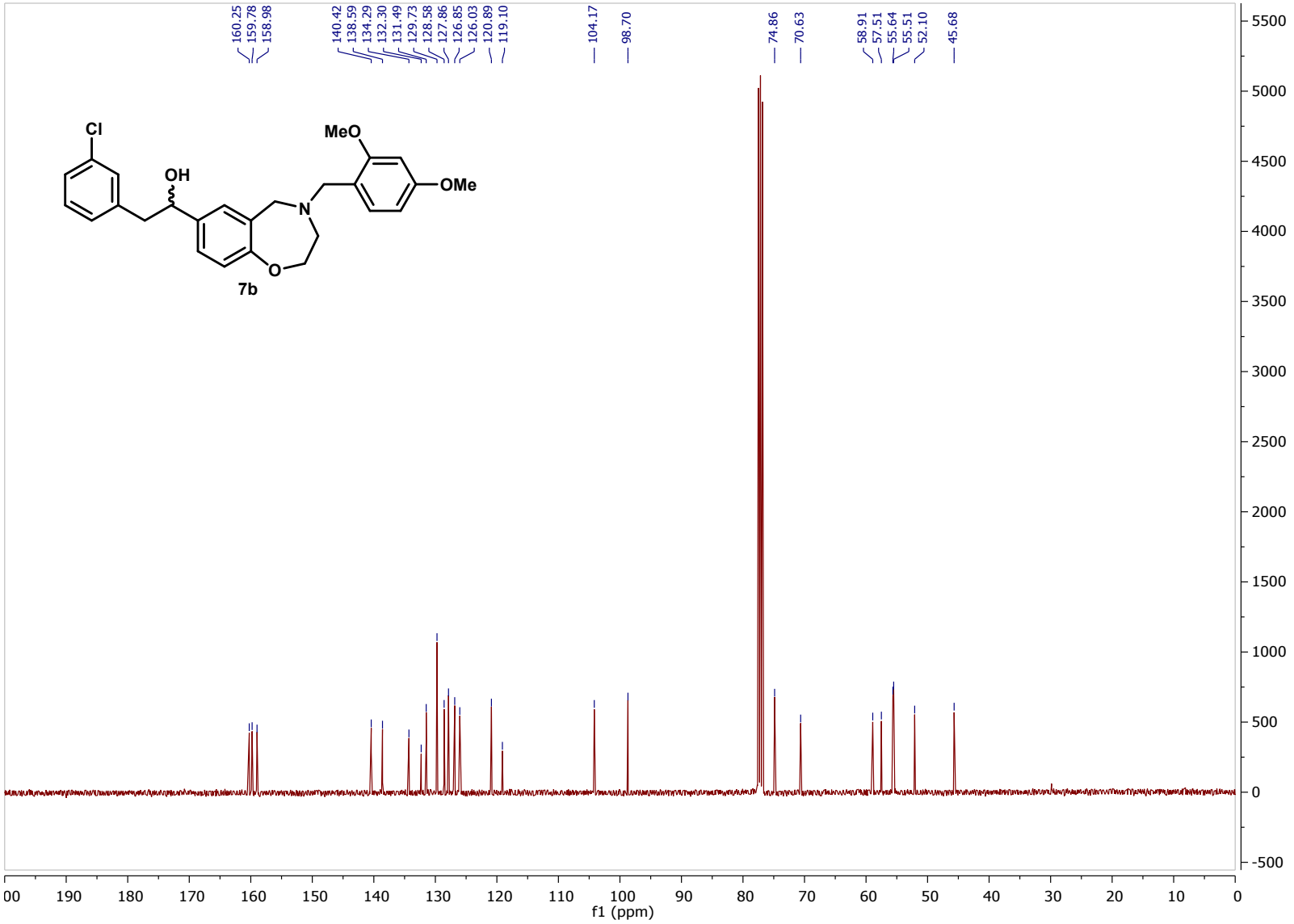
129.64
128.64
128.61
126.75
126.06
120.80
119.22
104.18
98.68
75.09
70.59
58.98
57.52
55.64
55.51
52.03
46.23
MeO
OH
OMe
N
O
7a
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Cl
OH
MeO
OMe
N
O
7b
7.21 7.20 7.20 7.19 7.18 7.16 7.16 7.14 7.13 7.08 7.07 7.06 7.05 7.05 7.04 7.04 7.03 7.00 6.98 6.47 6.46 6.45 6.45
4.83 4.82 4.80 4.10 4.10 4.09 4.09 4.08 3.86 3.82 3.79 3.59 3.07 3.07 3.06 3.06 3.05 2.97 2.95
5.00 1.00 1.00 1.00 2.00 1.00 2.00 2.00 3.00 3.00 2.00 2.00 2.00
f1 (ppm)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134.29
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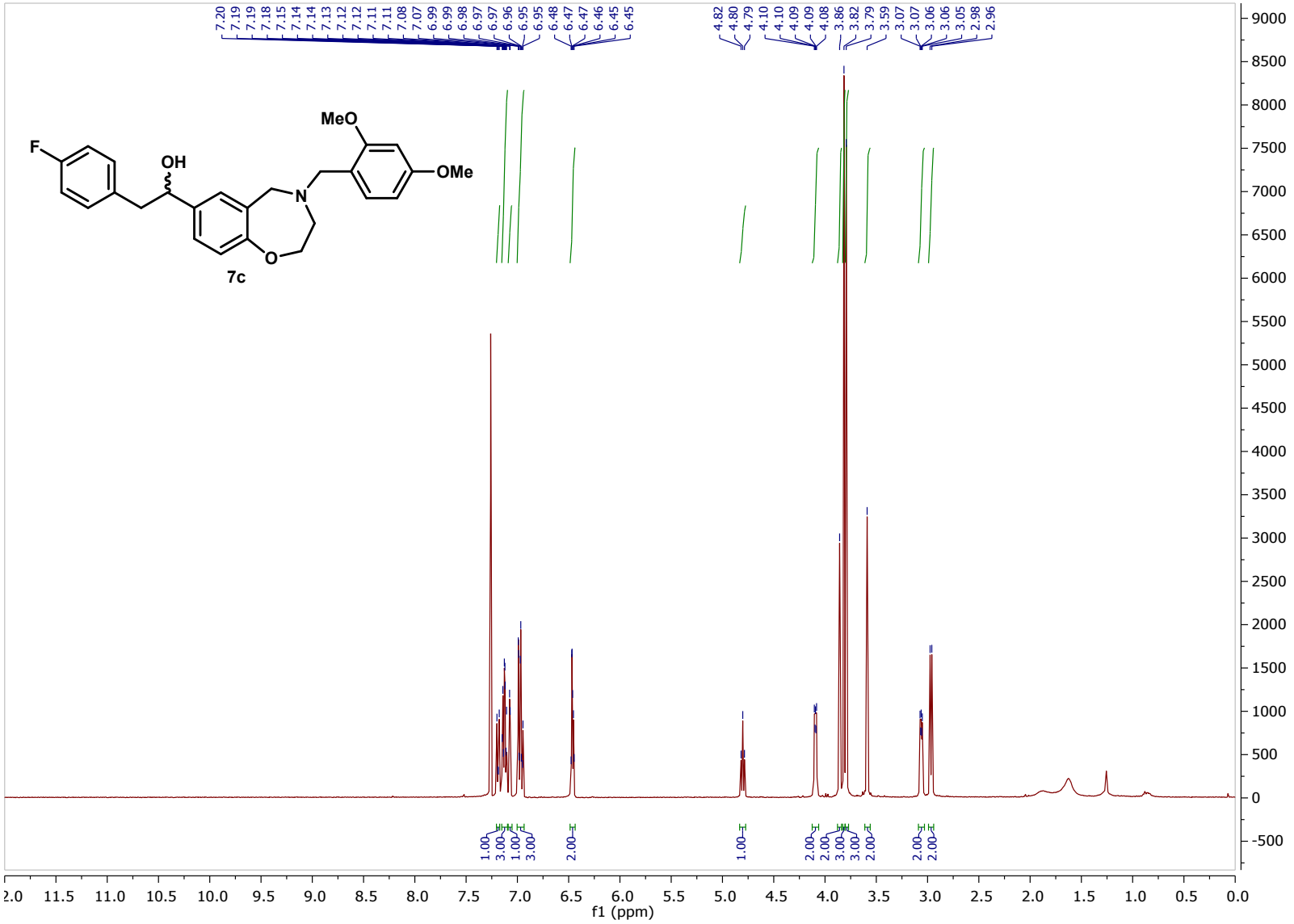
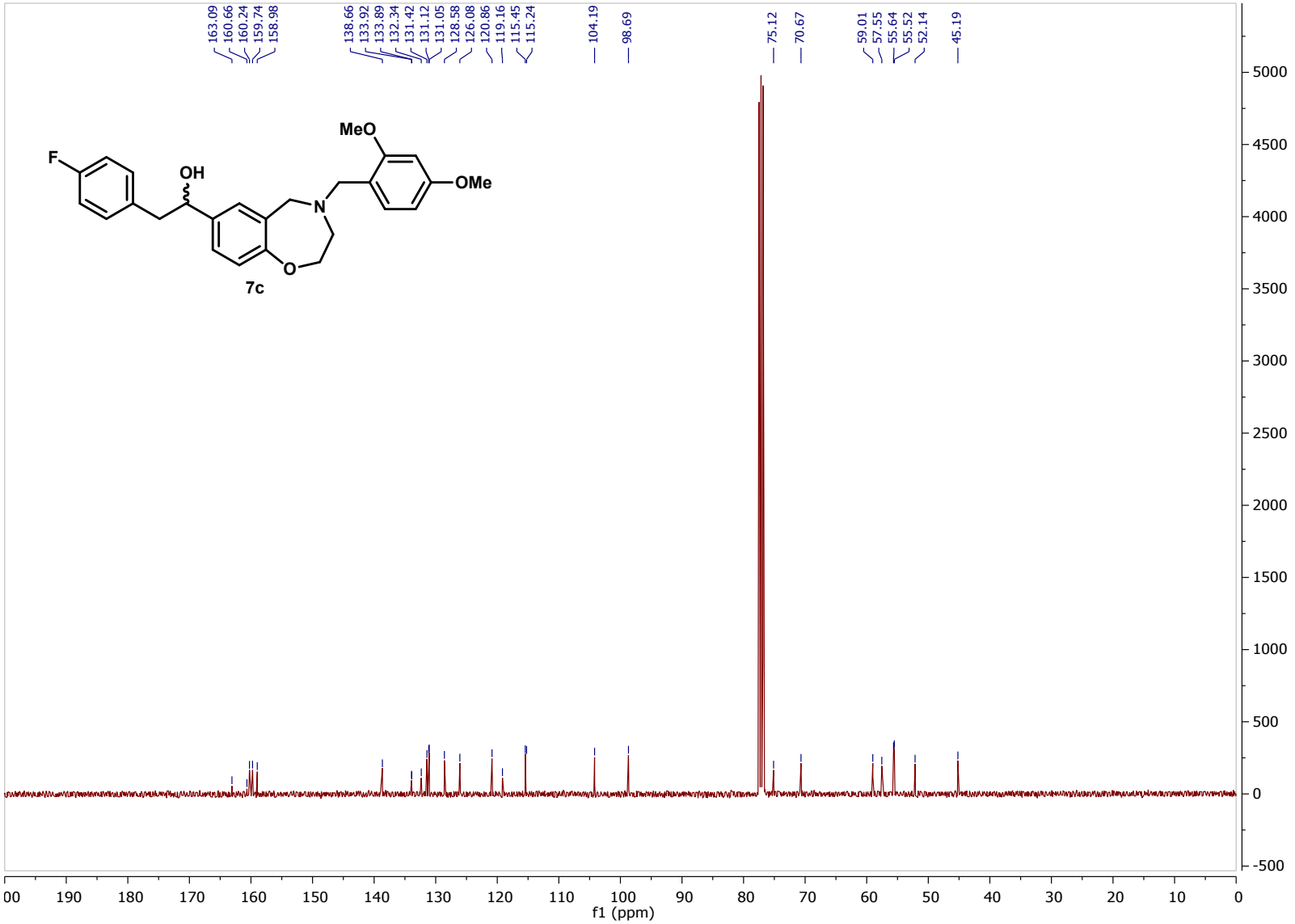
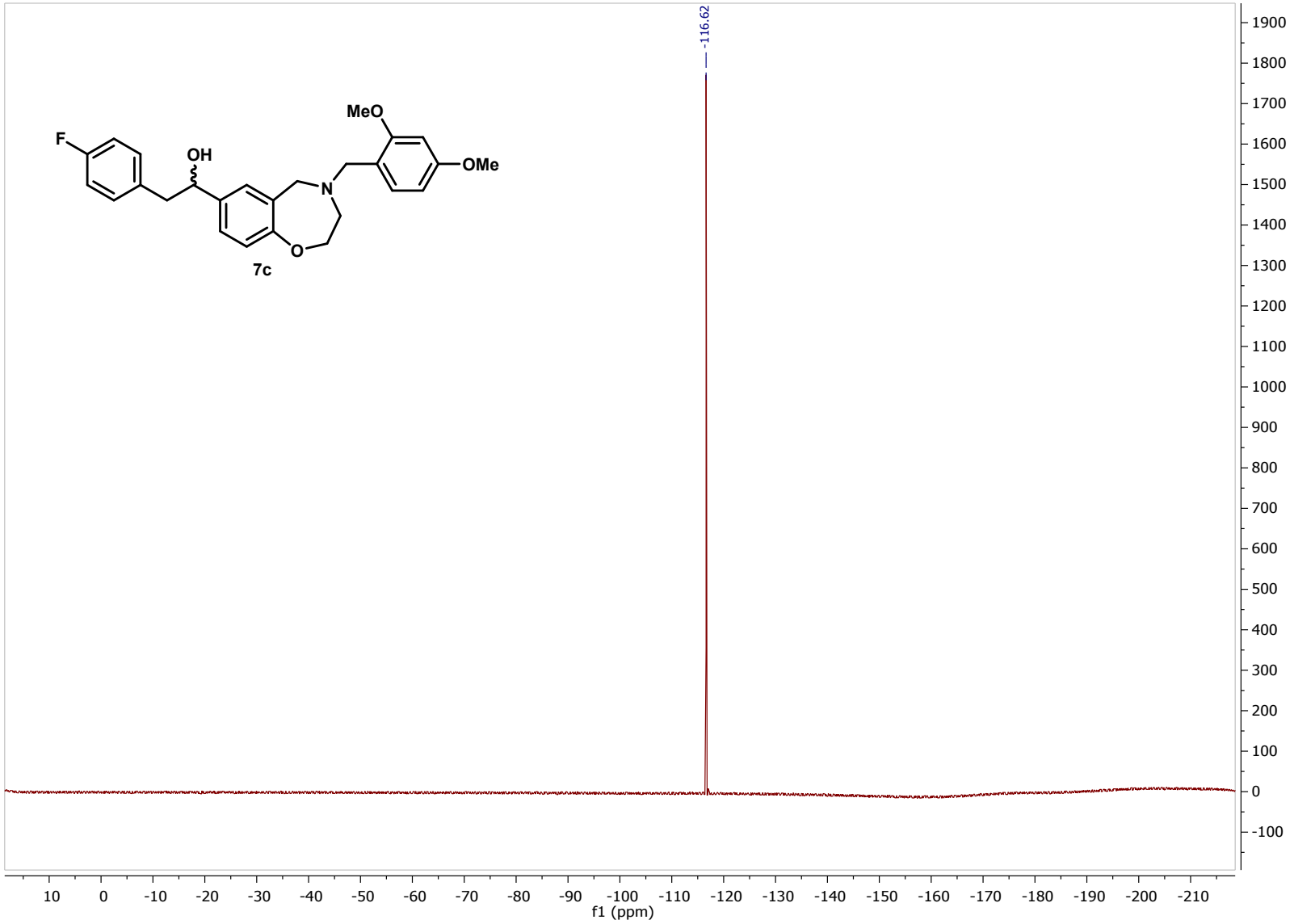
131.49
129.73
128.58
127.86
126.85
126.03
120.89
119.10
104.17
98.70
74.86
70.63
58.91
57.51
55.64
55.51
52.10
45.68
Cl
OH
MeO
OMe
N
O
7b
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


F
OH
MeO
OMe
N
O
7c
f1 (ppm)


163.09
160.66
160.24
159.74
158.98
138.66
133.92
133.89
132.34
131.42
131.12
131.05
128.58
126.08
120.86
119.16
115.45
115.24
104.19
98.69
75.12
70.67
59.01
57.55
55.64
55.52
52.14
45.19
F
OH
MeO
OMe
N
O
7c
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


F
OH
MeO
OMe
N
O
7c
-116.62
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
10
0
-10
-20
-30
-40
-50
-60
-70
-80
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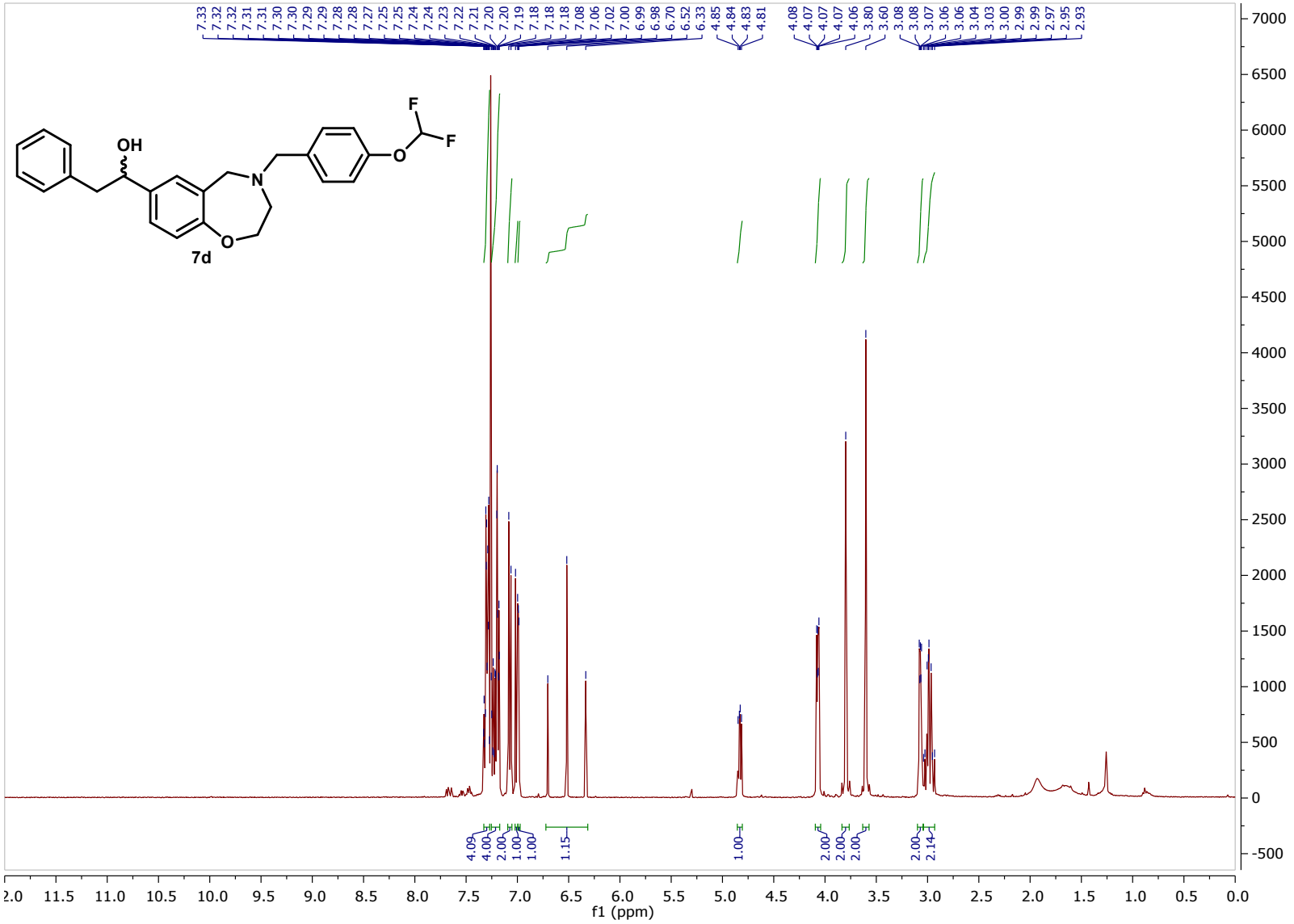
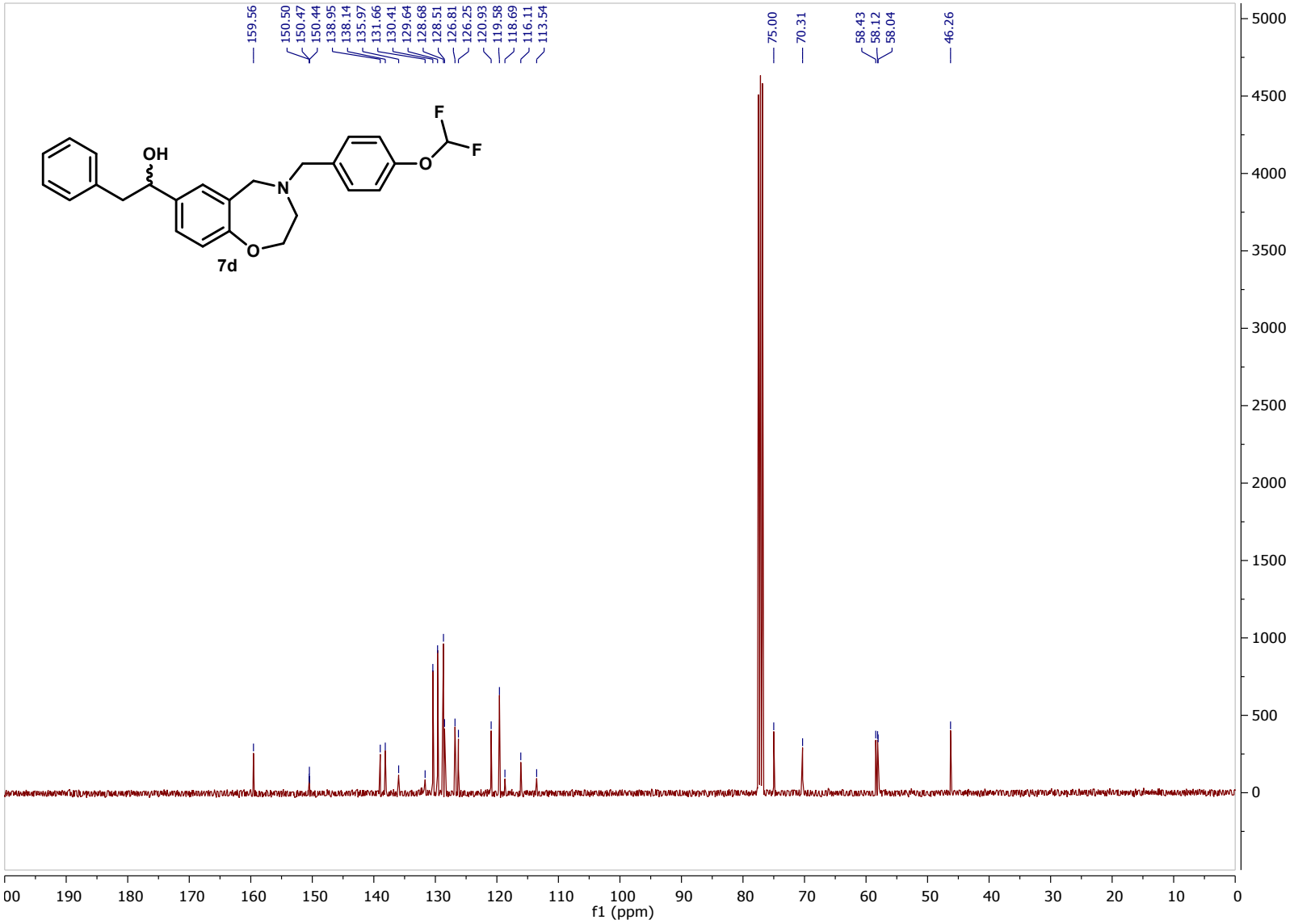
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)


OH
F
F
O
N
O
7d
f1 (ppm)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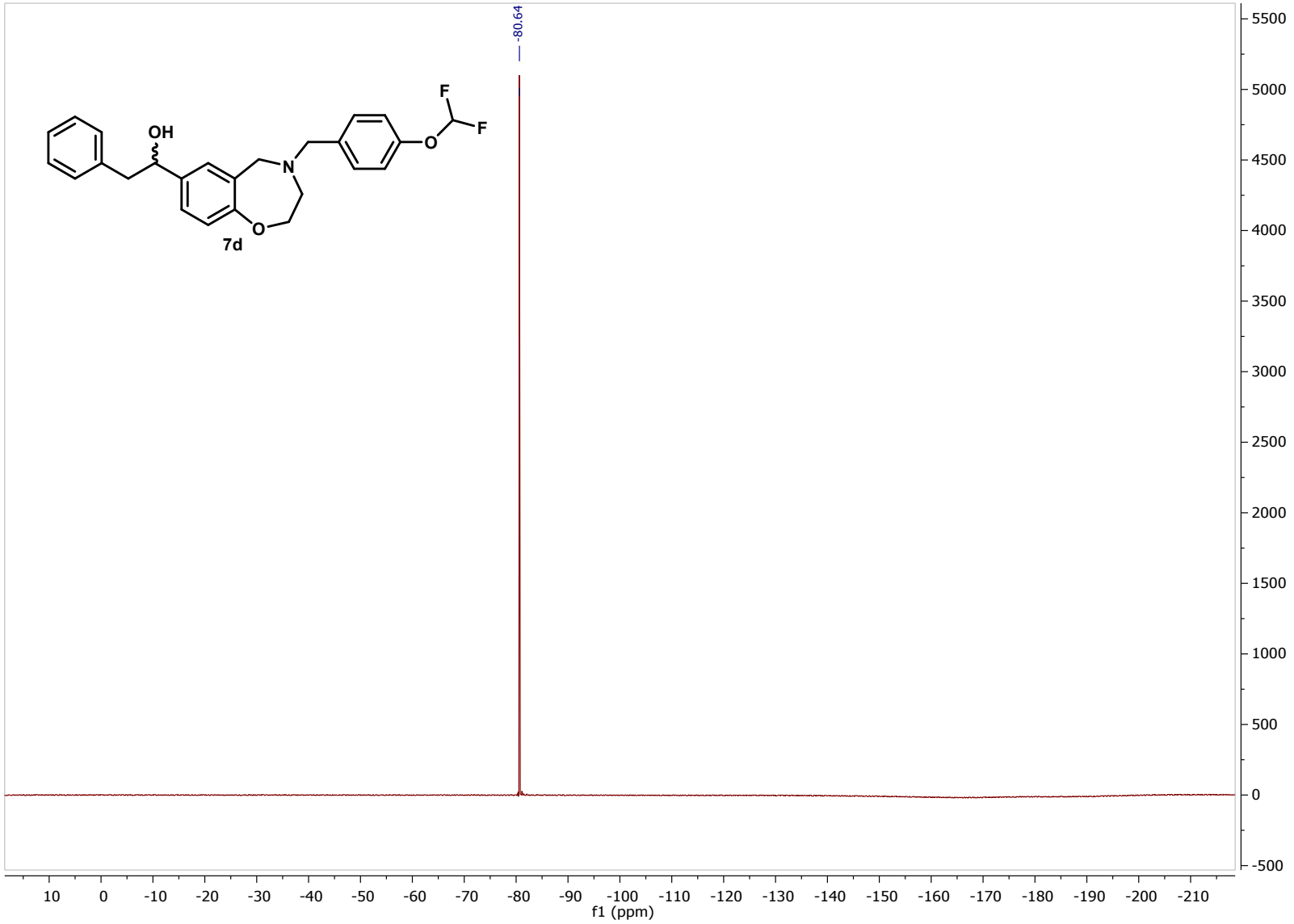
131.66
130.41
129.64
128.68
128.51
126.81
126.25
120.93
119.58
118.69
116.11
113.54
75.00
70.31
58.43
58.12
58.04
46.26
OH
N
O
F
F
O
7d
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
f1 (ppm)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OH
F
F
O
N
O
7d
5500
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4500
4000
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3000
2500
2000
1500
1000
500
0
-500
10
0
-10
-20
-30
-40
-50
-60
-70
-80
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-100
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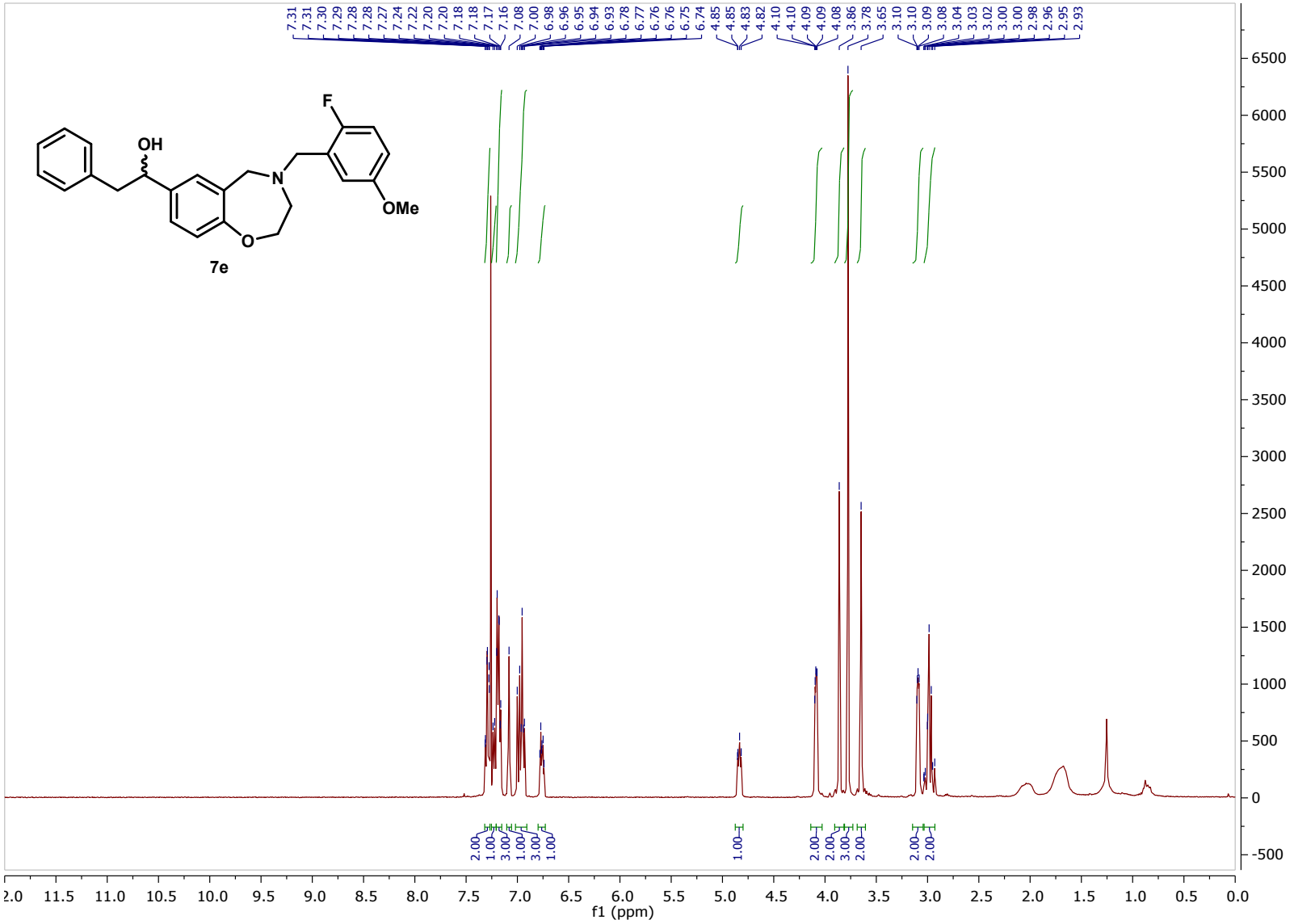
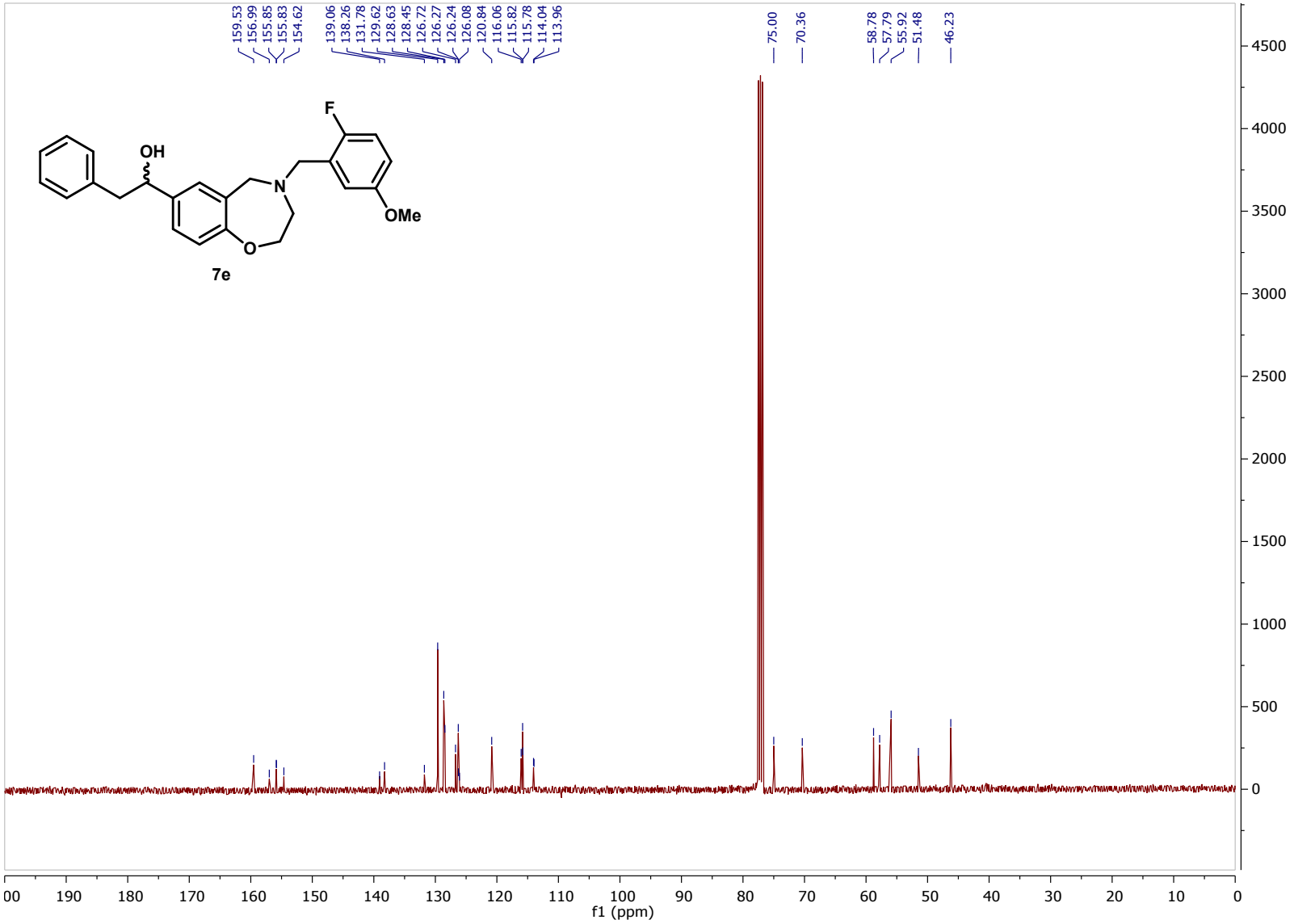
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)


7.31 7.31 7.30 7.29 7.28 7.28 7.27 7.24 7.22 7.20 7.20 7.18 7.18 7.17 7.16 7.08 7.00 6.98 6.96 6.95 6.94 6.93 6.78 6.77 6.76 6.76 6.75 6.74 4.85 4.85 4.83 4.82 4.10 4.10 4.09 4.09 4.08 3.86 3.78 3.65 3.10 3.10 3.09 3.08 3.04 3.03 3.02 3.00 3.00 2.98 2.96 2.95 2.93
F
OH
N
OMe
O
7e
6500 6000 5500 5000 4500 4000 3500 3000 2500 2000 1500 1000 500 0 -500
2.00 1.00 3.00 1.00 3.00 1.00 1.00 2.00 2.00 3.00 2.00 2.00 2.00
2.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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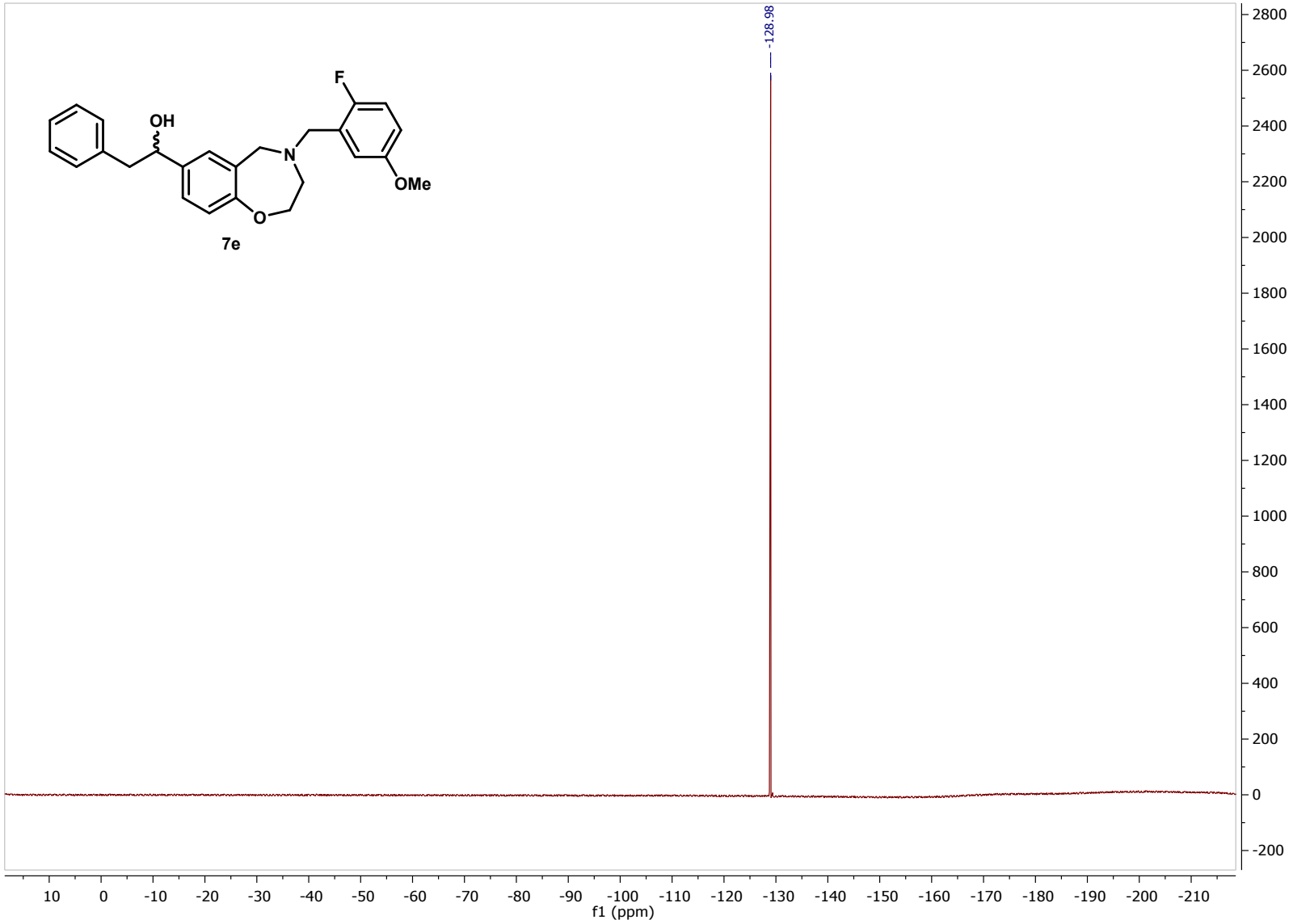
155.83
154.62
139.06
138.26
131.78
129.62
128.63
128.45
126.72
126.27
126.24
126.08
120.84
116.06
115.82
115.78
114.04
113.96
75.00
70.36
58.78
57.79
55.92
51.48
46.23
F
OH
N
OMe
O
7e
4500
4000
3500
3000
2500
2000
1500
1000
500
0
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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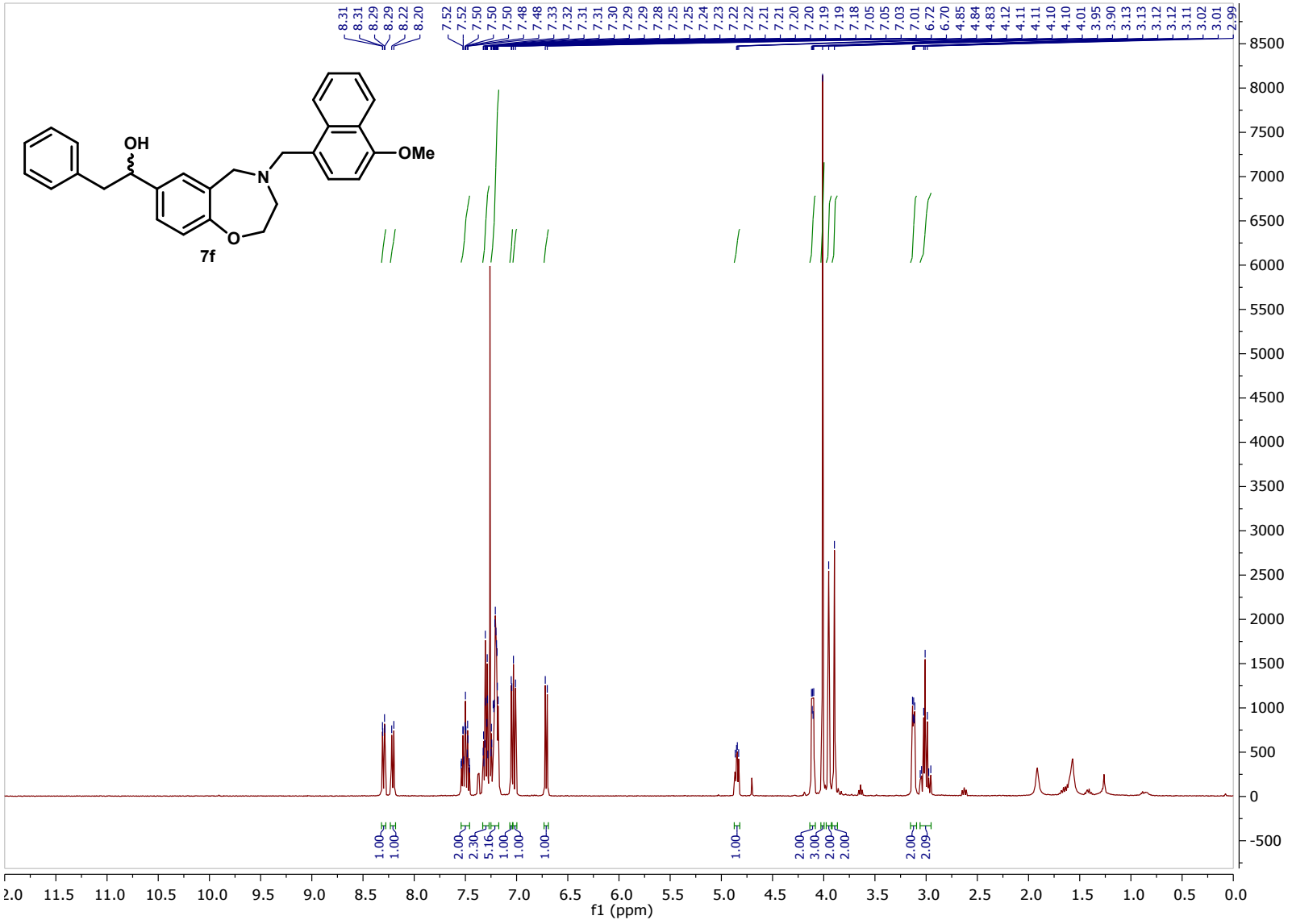
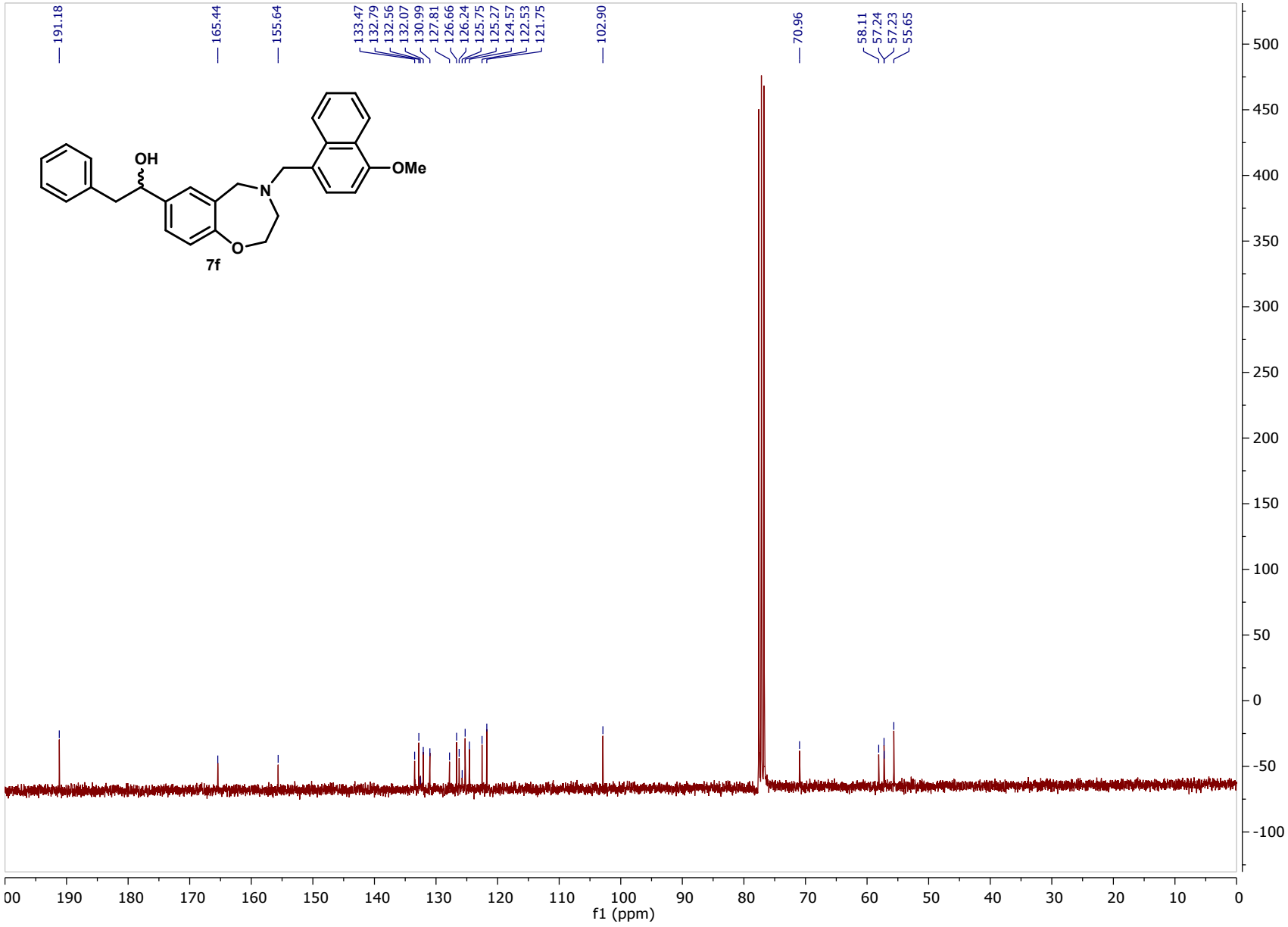
F
OH
N
OMe
O
7e
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)


OH
OMe
N
O
7f
f1 (ppm)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155.64
133.47
132.79
132.56
132.07
130.99
127.81
126.66
126.24
125.75
125.27
124.57
122.53
121.75
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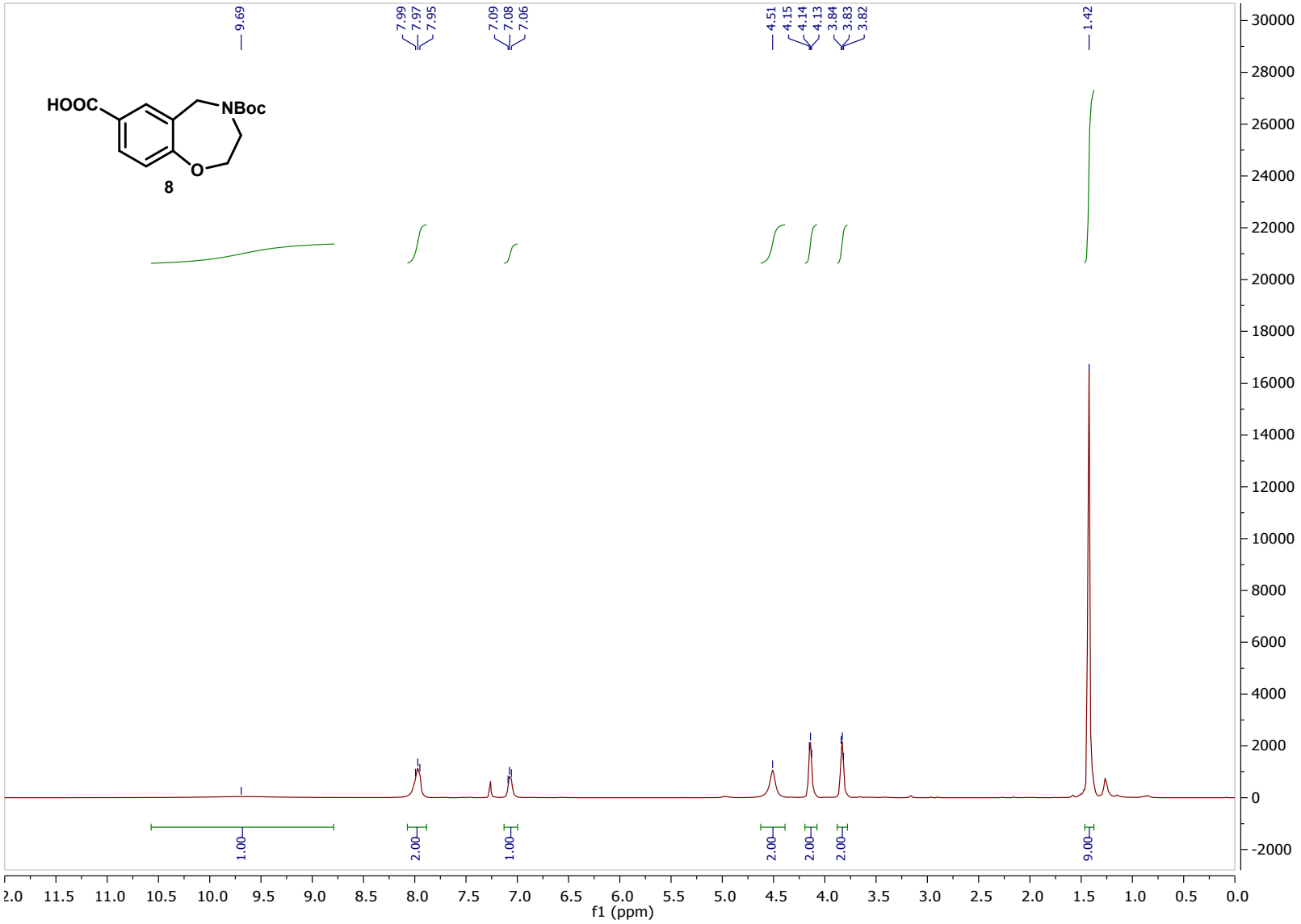
70.96
58.11
57.24
57.23
55.65
OH
N
OMe
O
7f
f1 (ppm)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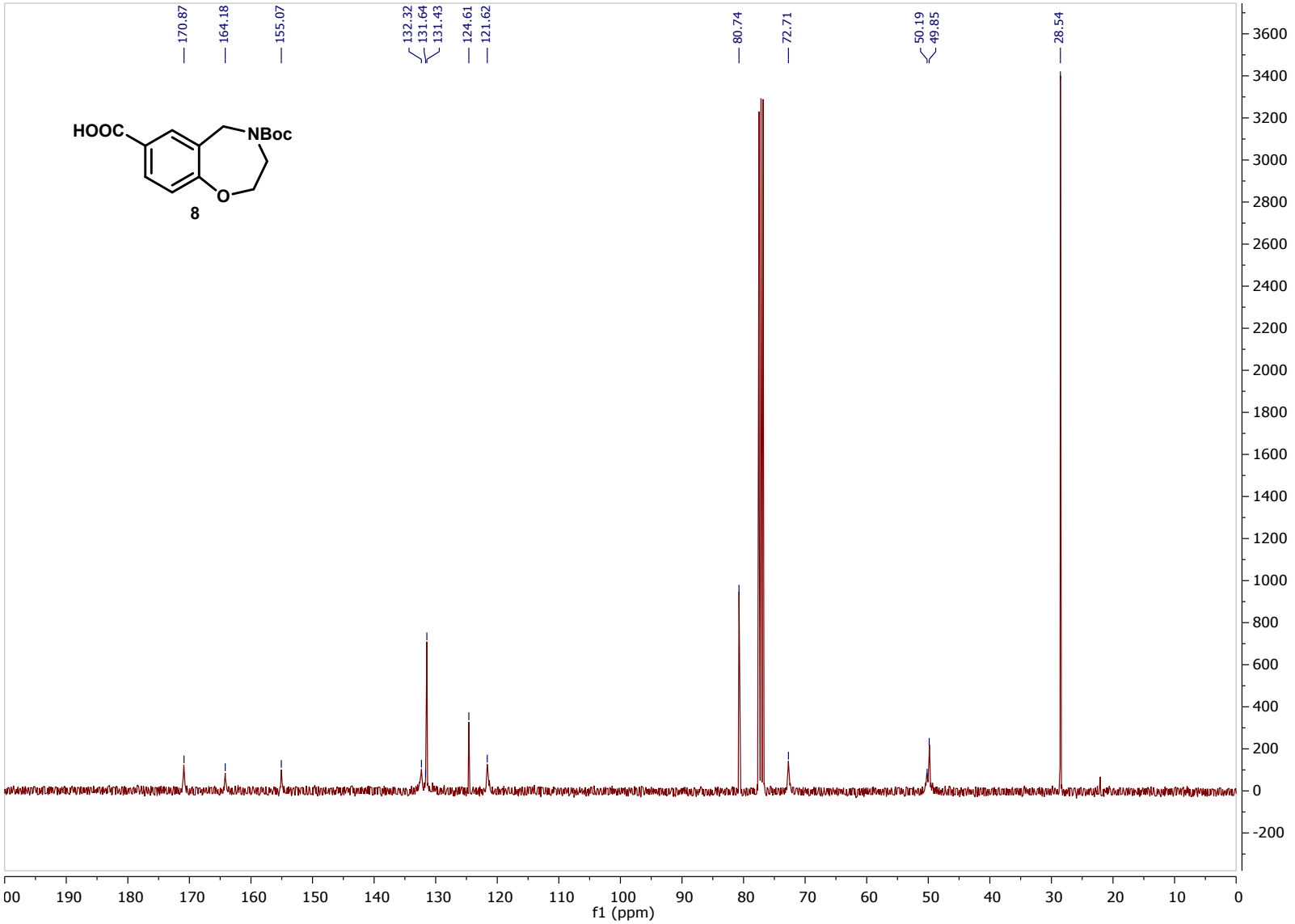
7.95
7.09
7.08
7.06
4.51
4.15
4.14
4.13
3.84
3.83
3.82
1.42
HOOC
NBoc
O
8
1.00
2.00
1.00
2.00
2.00
2.00
9.00
f1 (ppm)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132.32
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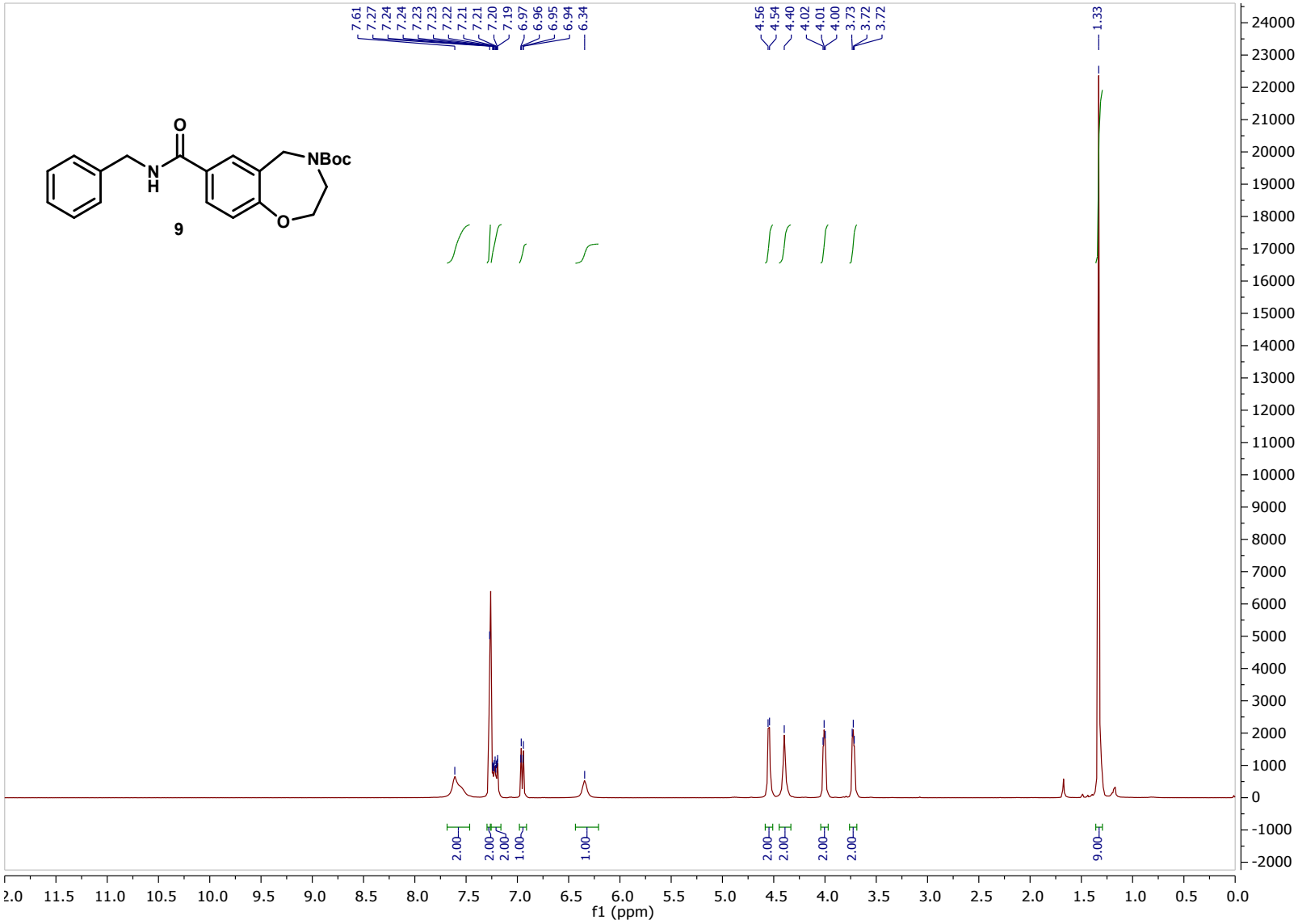
131.43
124.61
121.62
80.74
72.71
50.19
49.85
28.54
HOOC
NBoc
O
8
f1 (ppm)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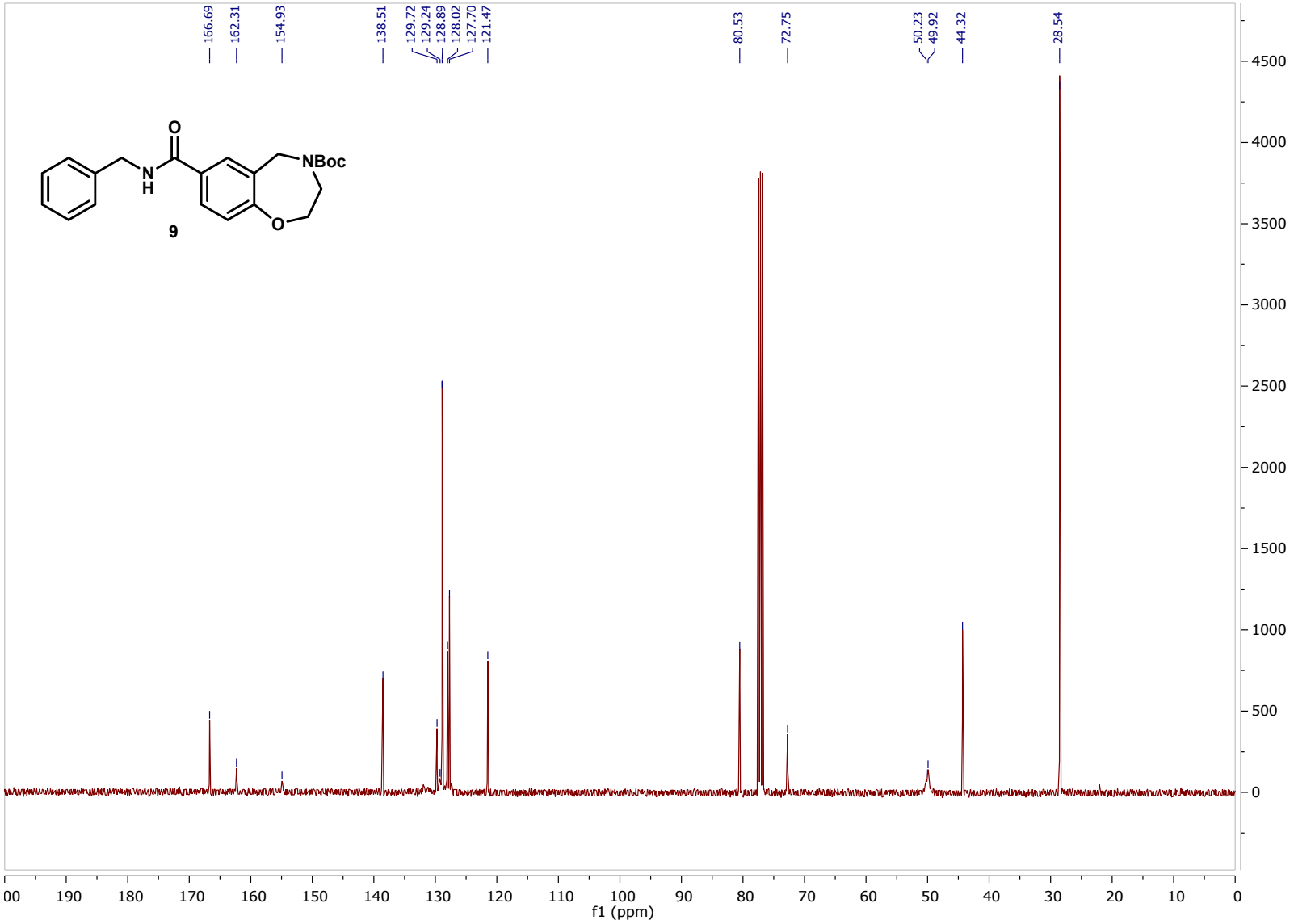
7.27
7.24
7.24
7.23
7.23
7.22
7.21
7.21
7.20
7.19
6.97
6.96
6.95
6.94
6.34
4.56
4.54
4.40
4.02
4.01
4.00
3.73
3.72
3.72
1.33
O
N
H
O
NBoc
9
2.00
2.00
2.00
1.00
1.00
2.00
2.00
2.00
2.00
9.00
f1 (ppm)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138.51
129.72
129.24
128.89
128.02
127.70
121.47
80.53
72.75
50.23
49.92
44.32
28.54
O
N
H
NBoc
O
9
4500
4000
3500
3000
2500
2000
1500
1000
500
0
00
190
180
170
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150
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130
120
110
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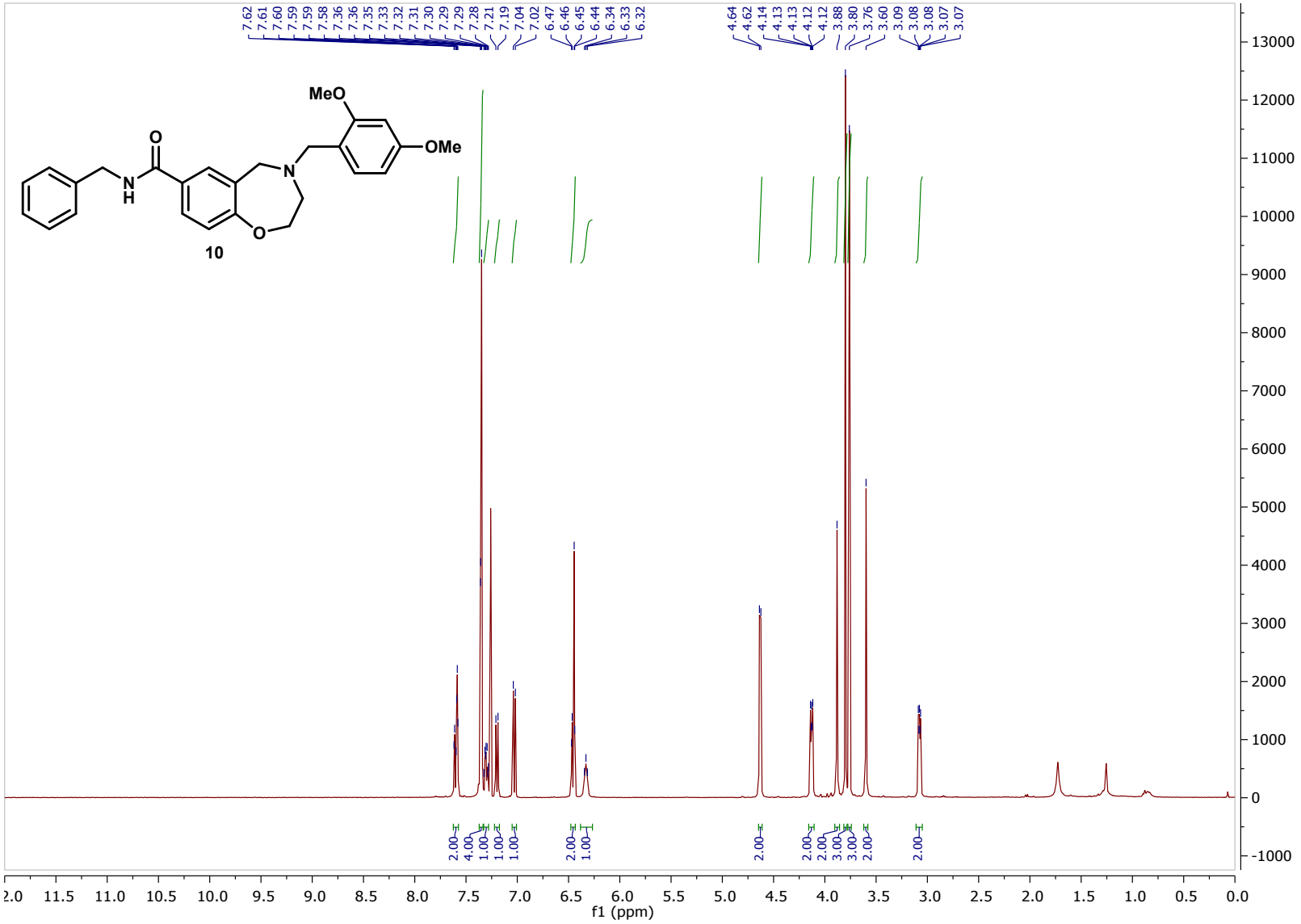
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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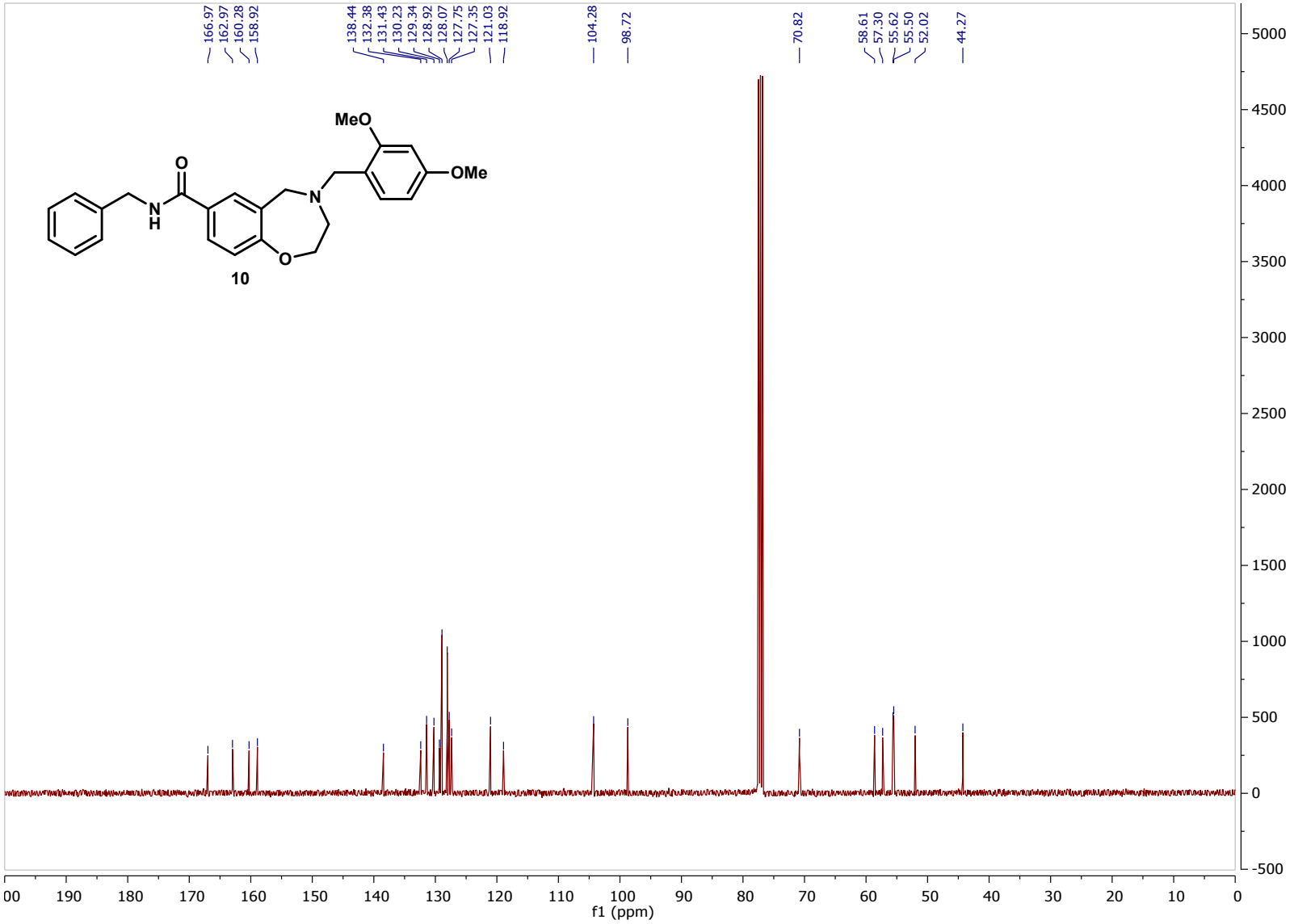
OMe
O
N
H
N
O
10
f1 (ppm)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129.34
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128.07
127.75
127.35
121.03
118.92
104.28
98.72
70.82
58.61
57.30
55.62
55.50
52.02
44.27
MeO
OMe
O
N
H
N
O
10
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
00
190
180
170
160
150
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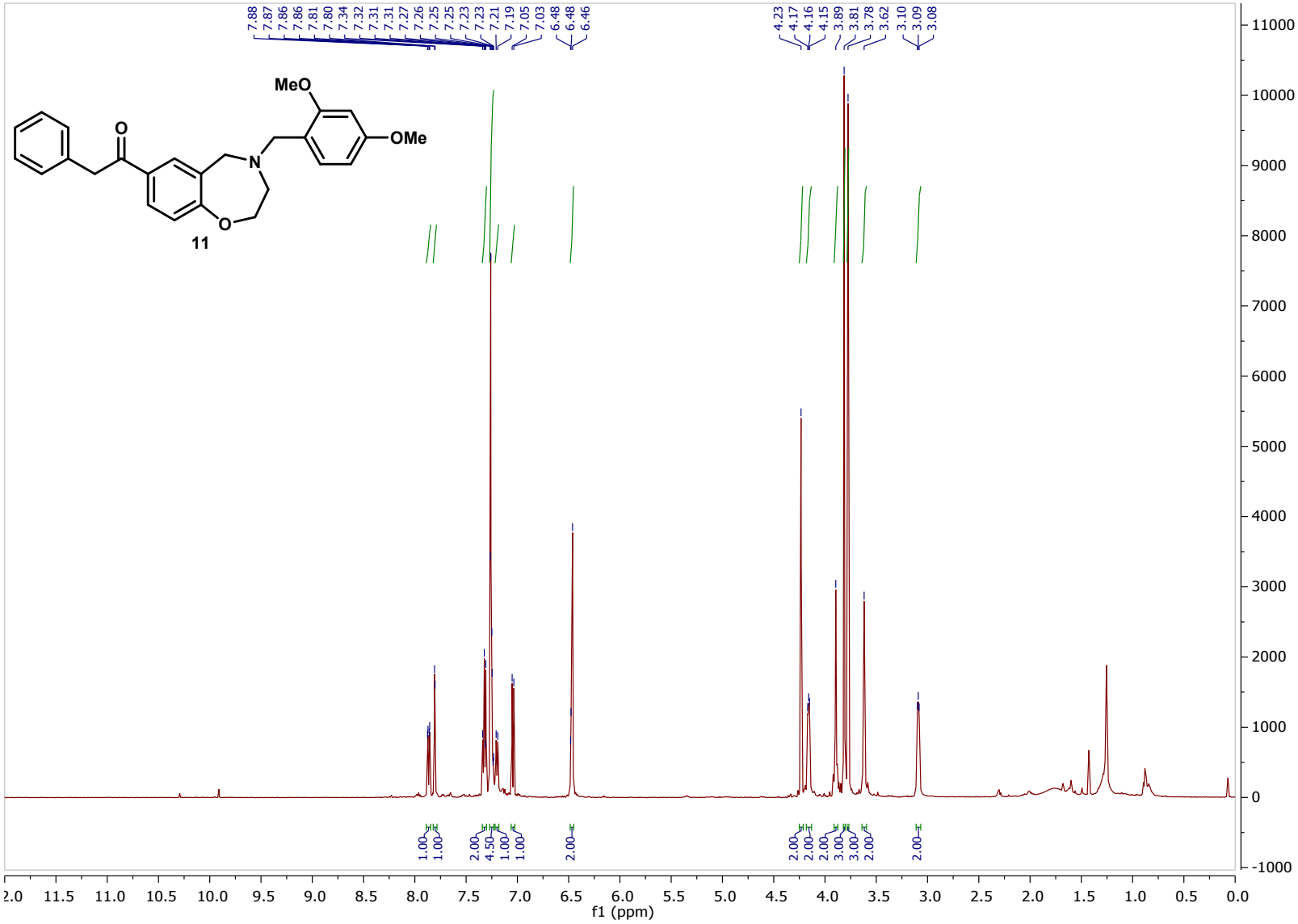
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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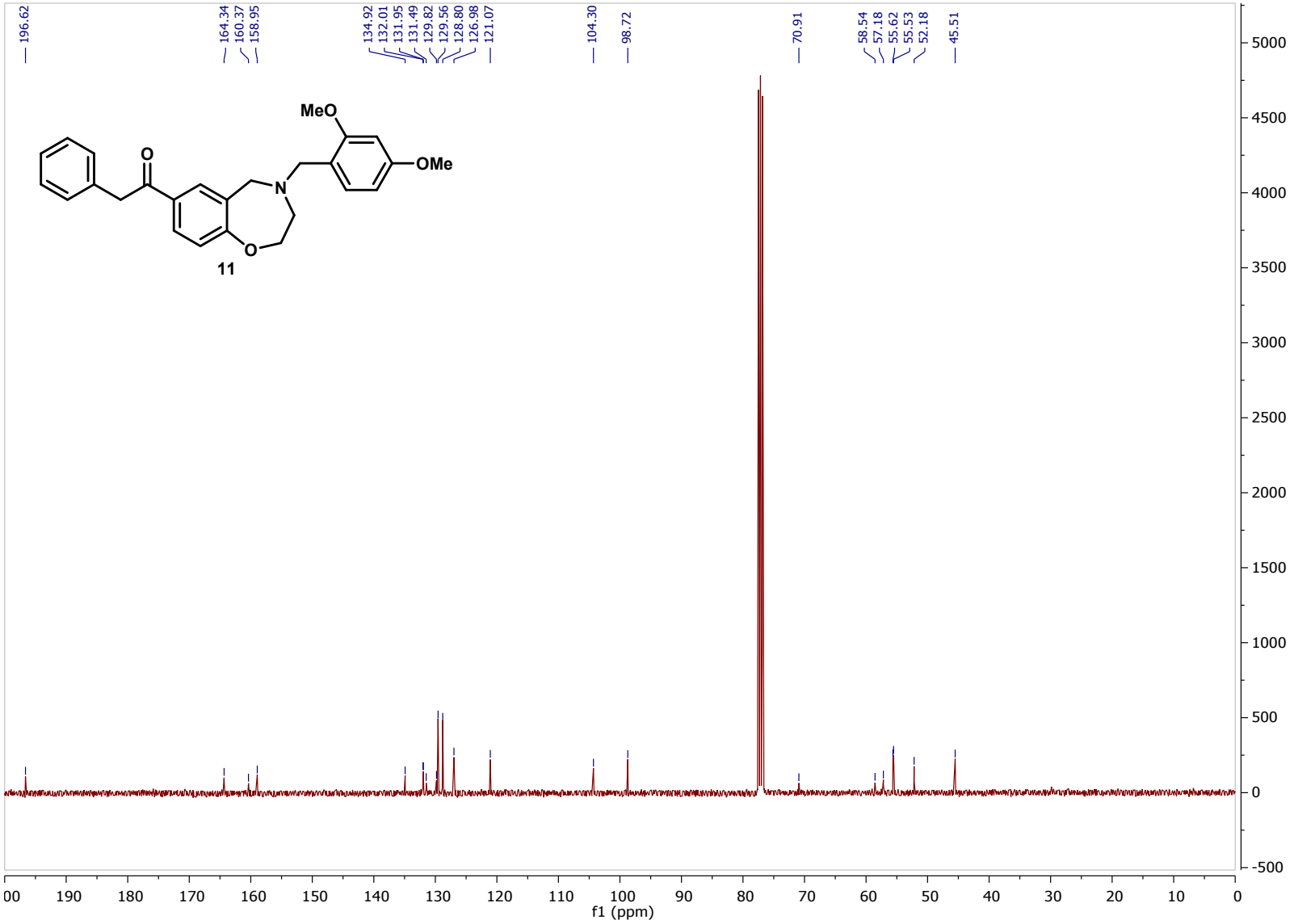
7.80
7.34
7.32
7.31
7.31
7.27
7.26
7.25
7.25
7.23
7.23
7.21
7.19
7.05
7.03
6.48
6.48
6.46
4.23
4.17
4.16
4.15
3.89
3.81
3.78
3.62
3.10
3.09
3.08
MeO
OMe
O
N
O
11
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
1.00
1.00
2.00
4.50
1.00
1.00
2.00
2.00
2.00
2.00
3.00
3.00
2.00
2.00
2.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


196.62
164.34
160.37
158.95
134.92
132.01
131.95
131.49
129.82
129.56
128.80
126.98
121.07
104.30
98.72
70.91
58.54
57.18
55.62
55.53
52.18
45.51
MeO
OMe
O
N
O
11
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

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