Electronic Supplementary Material (ESI) for ChemComm.

A Systematic Approach to Diverse, Lead-Like Scaffolds from α,α-Disubstituted Amino Acids

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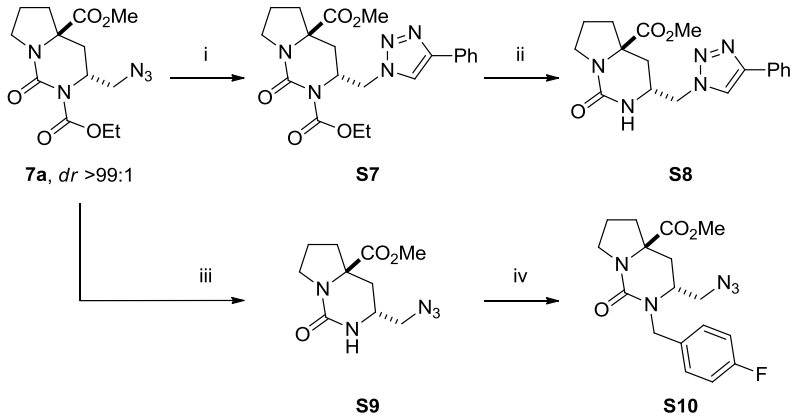
Supplementary Information

Contents:

1.0 Exemplar scaffold decoration

To confirm the validity of the library analysis, we demonstrated experimentally that *N*-deprotection and decoration reactions were viable (Scheme S1, **S7**, **S8**, **S9** and **S10**).



Scheme S1. Exemplar scaffold diversifications. Reagents and conditions: i) phenyl acetylene (2.0 eq.), $Cu(OAc)_2$ (20 mol%), sodium ascorbate (40 mol%), $^tBuOH/H_2O$ 1:1, 89%; ii) NaOH (2.2 eq.), MeOH, 80%; iii) NaOMe, MeOH, 76%; iv) 4-F-C_6H_4-CH_2Br (2.0 eq), NaH (1.1 eq), DMF, 1 h, 52%.

2.0 Computational Analysis

2.1 Virtual Library Enumeration

The virtual library was enumerated and manipulated using Accelrys Pipeline Pilot version 8.5 (Pipeline Pilot v8.5.0.200, Accelrys® Software Inc., 2011). The enumeration process is illustrated in Figure S1 and was based upon the 22 scaffolds detailed in the manuscript. To enumerate the virtual library, any protecting groups were removed and the manipulations shown in Scheme S2 were performed followed by the decoration reactions shown in Scheme S3, using the 80 capping groups shown in Figure S2. The underivatised scaffolds were retained in the final virtual library.

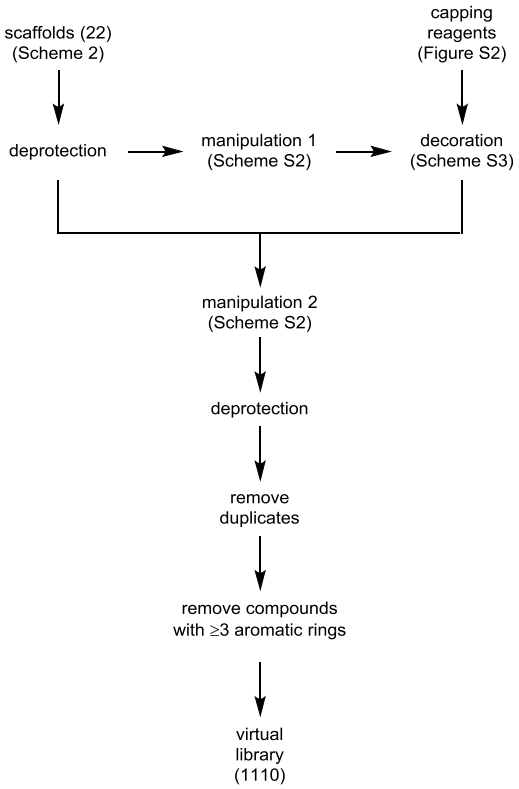
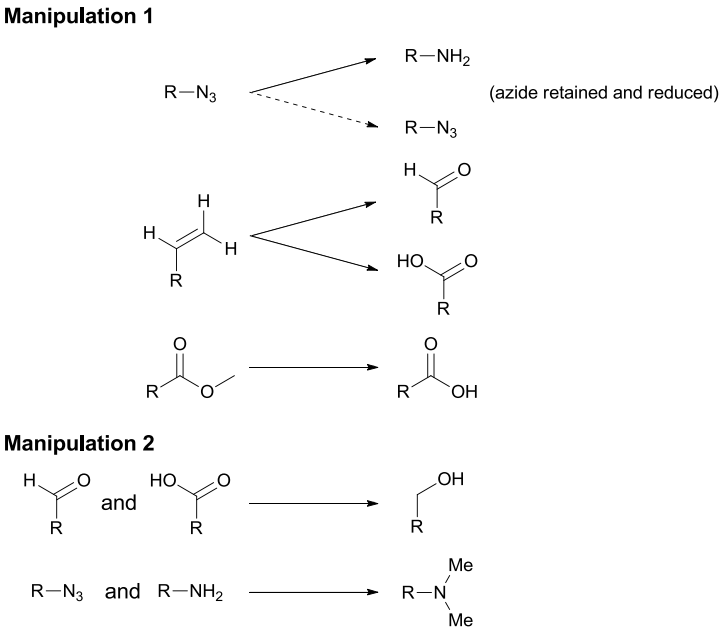
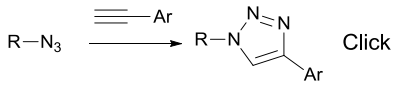


Figure S1. Overview of the process for the enumeration of the virtual library.

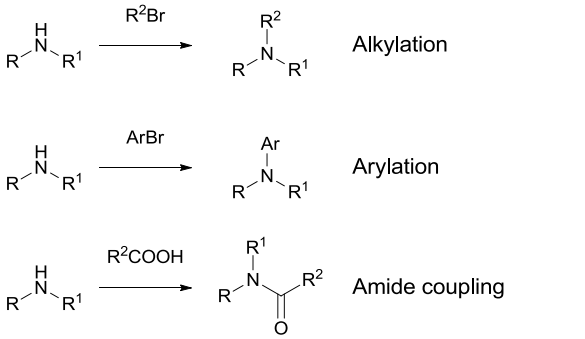


Scheme S2. Functional group manipulations of scaffolds (Manipulation 1) and final compounds (Manipulation 2).

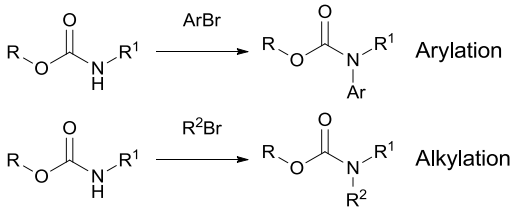
Azide Decoration



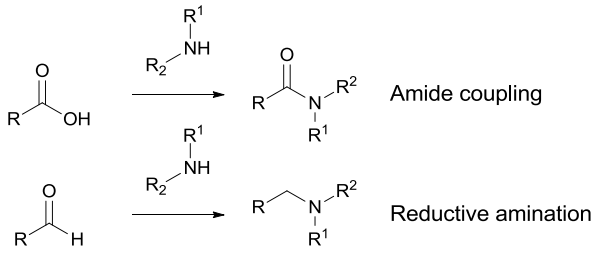
Amine Decoration (R^1 = H, alkyl)



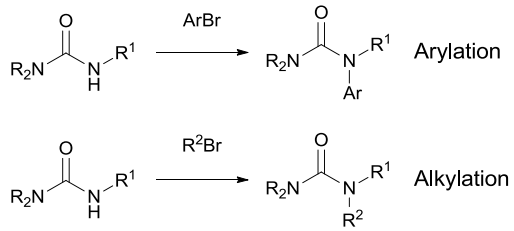
Carbamate Decoration



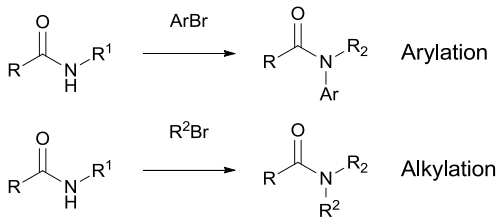
Acid/aldehyde Decoration (R^1 = H, alkyl, aryl)



Urea Decoration



Amide Decoration



Scheme S3. Decoration reactions exploited in the enumeration of the virtual library.

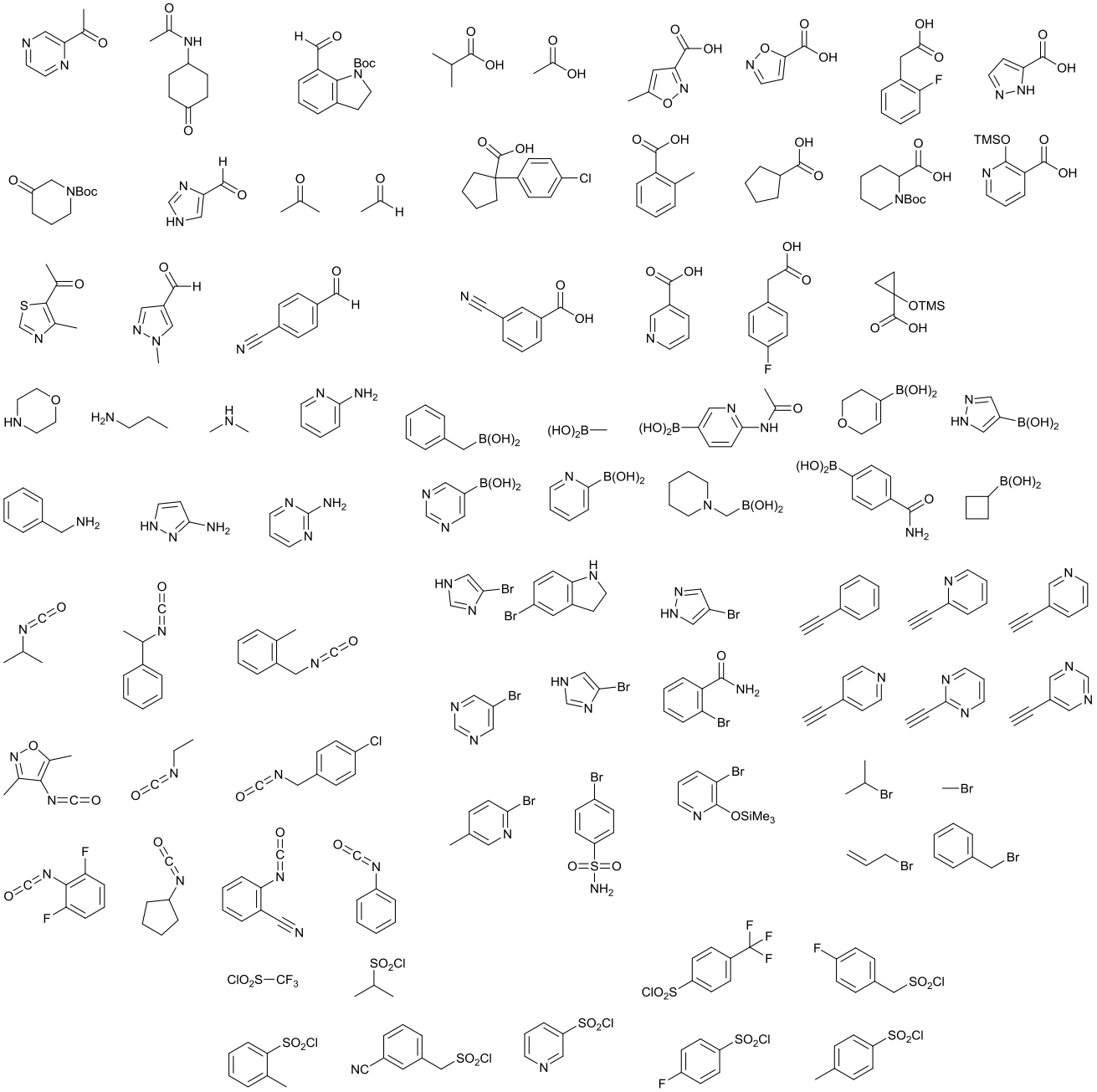


Figure S2. 80 capping reagents exploited in the enumeration of the virtual library.

3.0 Novelty Assessment

3.1 Search 1: Murcko fragments against a random 5% of the ZINC database (453698 compounds)

Substructure search (Figure S3):

1. Murcko fragments were generated then:
2. Exo-cylic alkenes both removed and reduced to methyl groups
3. Cyclic alkenes retained and reduced

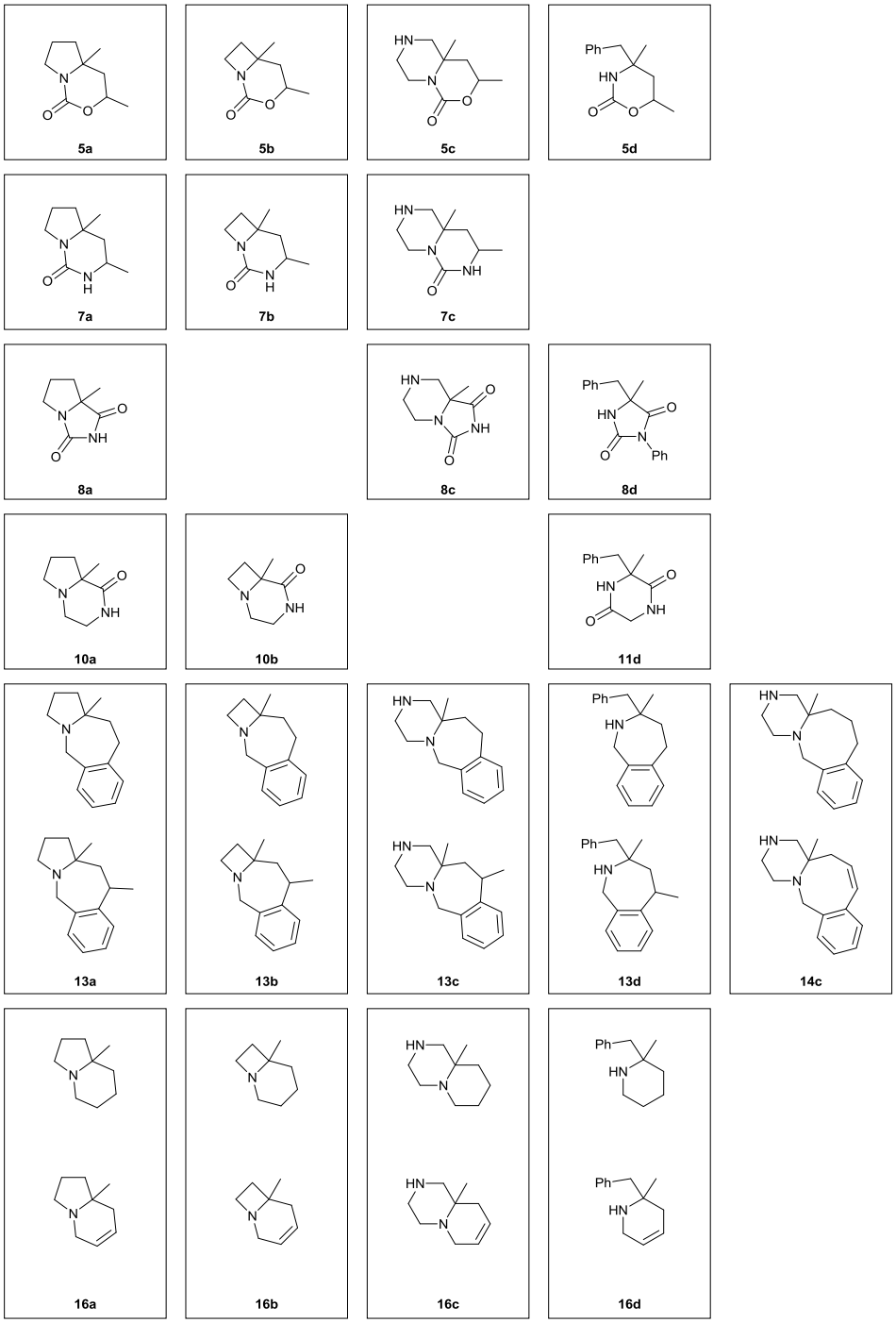


Figure S3. Murcko fragments used in the substructure search against a random 5% of the ZINC database.

4 substructure hits found (Table S1)

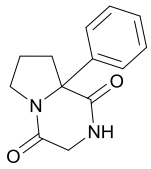
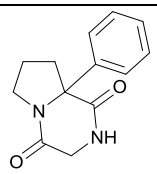
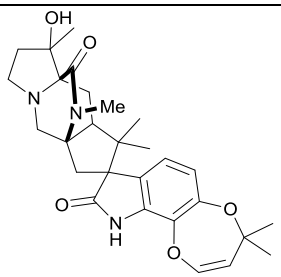
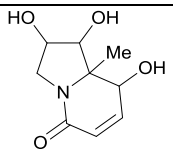
Entry	Murcko assembly	Original Smiles	ZINC identity	Corresponding scaffold
1		c1ccc(cc1)[C@@]23CCCN2C(=O)CNC3=O	ZINC04753275	**10a**
2		c1ccc(cc1)[C@]23CCCN2C(=O)CNC3=O	ZINC04753277	**10a**
3		C[C@]1(CC[NH+]2[C@]13C[C@H]4[C@](C2)(C[C@@]5(C4(C)C)c6ccc7c(c6NC5=O)OC=CC(O7)(C)C)N(C3=O)C)O	ZINC14637262	**10a/16a**
4		CC(=O)O[C@@H]1CN2C(=O)C=C[C@@H]([C@@]2([C@@H]1OC(=O)C)C)OC(=O)C	ZINC22067059	**16a**

Table S1. Substructure hits when the Murcko fragments (Figure S3) were searched for in a random 5% of the ZINC database.

3.2 Search 2: Scaffolds against the ZINC database (9039756 compounds)

Substructure search (Figure S4):

1. Esters converted to 'any carbonyl'
2. Azides converted to 'any N'
3. Exo-cylic alkenes both removed and reduced to methyl groups
4. Cyclic alkenes retained and reduced
5. Allyl groups converted to ‘any carbonyl’ and “dehomologated alkyl-H”

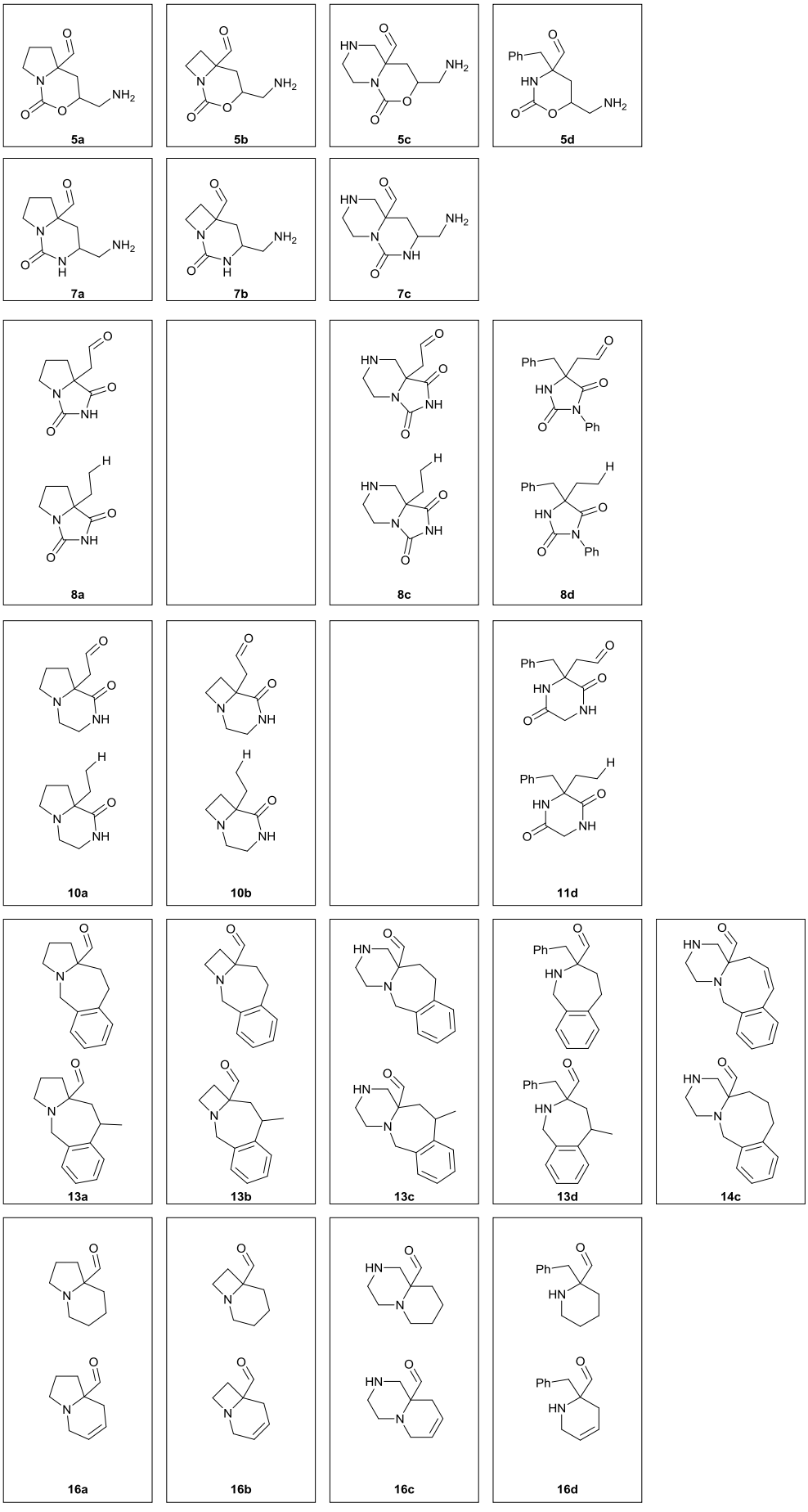
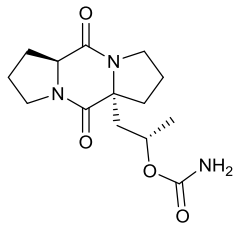
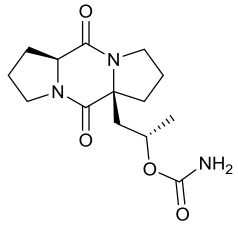
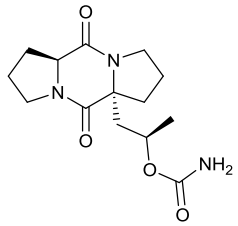
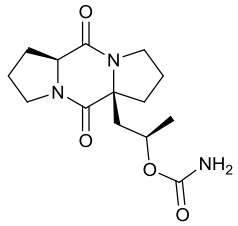
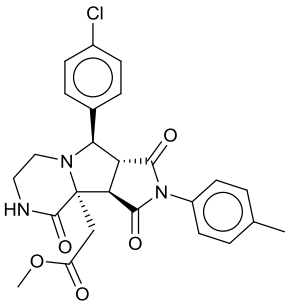
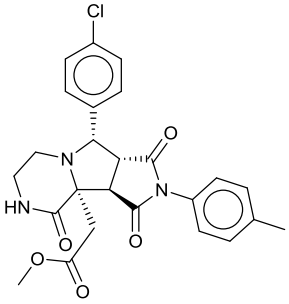
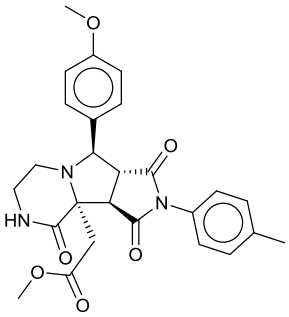
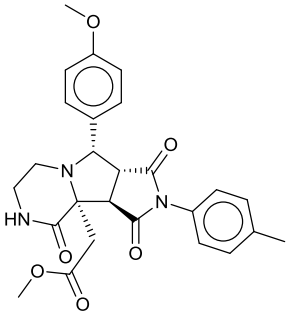
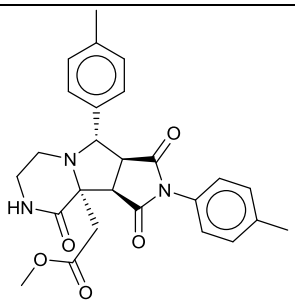
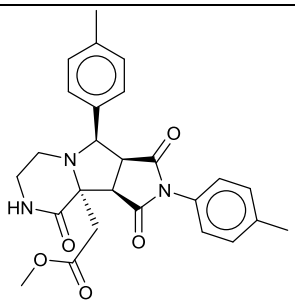
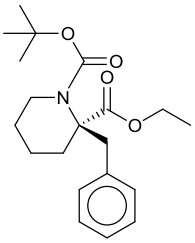
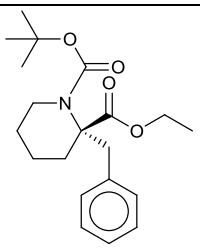
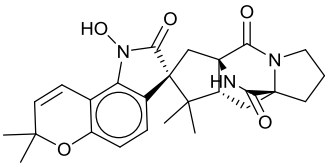
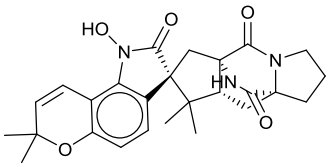
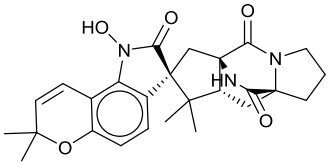
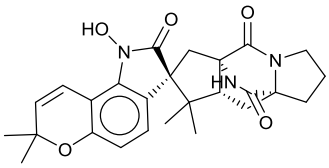
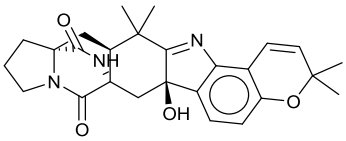
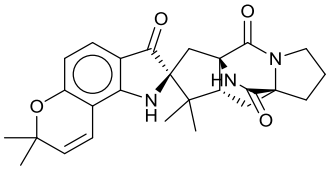
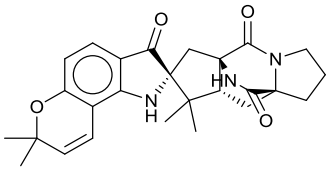
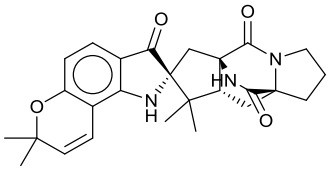


Figure S4. Scaffolds used in the substructure search against the ZINC database.

28 substructure hits found (Table S2)

Entry	Structure	SMILES	ZINC identity	Corresponding scaffold
1		C[C@@H](C[C@@]12CCCN1C(=O)[C@@H]3CCCN3C2=O)OC(=O)N	ZINC35457219	**10a**
2		C[C@@H](C[C@]12CCCN1C(=O)[C@@H]3CCCN3C2=O)OC(=O)N	ZINC35457226	**10a**
3		C[C@H](C[C@@]12CCCN1C(=O)[C@@H]3CCCN3C2=O)OC(=O)N	ZINC35457222	**10a**
4		C[C@H](C[C@]12CCCN1C(=O)[C@@H]3CCCN3C2=O)OC(=O)N	ZINC35457229	**10a**
5		Cc1ccc(cc1)N2C(=O)[C@H]3[C@@H](N4CCNC(=O)[C@@]4([C@@H]3C2=O)CC(=O)OC)c5ccc(cc5)Cl	ZINC85408785	**10a**
6		Cc1ccc(cc1)N2C(=O)[C@H]3[C@H](N4CCNC(=O)[C@@]4([C@@H]3C2=O)CC(=O)OC)c5ccc(cc5)Cl	ZINC85408790	**10a**

Entry	Structure	SMILES	ZINC identity	Corresponding scaffold
7		Cc1ccc(cc1)N2C(=O)[C@H]3[C@@H](N4CCNC(=O)[C@@]4([C@@H]3C2=O)CC(=O)OC)c5ccc(cc5)OC	ZINC85408758	**10a**
8		Cc1ccc(cc1)N2C(=O)[C@H]3[C@H](N4CCNC(=O)[C@@]4([C@@H]3C2=O)CC(=O)OC)c5ccc(cc5)OC	ZINC85408763	**10a**
9		Cc1ccc(cc1)[C@@H]2[C@@H]3[C@@H](C(=O)N(C3=O)c4ccc(cc4)C)[C@@]5(N2CCNC5=O)CC(=O)OC	ZINC19960843	**10a**
10		Cc1ccc(cc1)[C@H]2[C@@H]3[C@@H](C(=O)N(C3=O)c4ccc(cc4)C)[C@@]5(N2CCNC5=O)CC(=O)OC	ZINC36092083	**10a**
11		CCOC(=O)[C@@]1(CCCCN1C(=O)OC(C)(C)C)Cc2ccccc2	ZINC67794623	**16d**
12		CCOC(=O)[C@]1(CCCCN1C(=O)OC(C)(C)C)Cc2ccccc2	ZINC67794624	**16d**

Entry	Structure	SMILES	ZINC identity	Corresponding scaffold
13		CC1(C=Cc2c(ccc3c2N(C(=O)[C@@]34C[C@@]56[C@@H](C4(C)C)C[C@]7(CCCN7C5=O)C(=O)N6)O)O1)C	ZINC31169877	**10a/16a**
14		CC1(C=Cc2c(ccc3c2N(C(=O)[C@@]34C[C@]56[C@@H](C4(C)C)C[C@@]7(CCCN7C5=O)C(=O)N6)O)O1)C	ZINC35456356	**10a/16a**
15		CC1(C=Cc2c(ccc3c2N(C(=O)[C@]34C[C@@]56[C@@H](C4(C)C)C[C@]7(CCCN7C5=O)C(=O)N6)O)O1)C	ZINC31169880	**10a/16a**
16		CC1(C=Cc2c(ccc3c2N(C(=O)[C@]34C[C@]56[C@@H](C4(C)C)C[C@@]7(CCCN7C5=O)C(=O)N6)O)O1)C	ZINC35456361	**10a/16a**
17		CC1(C=Cc2c(ccc3c2N=C4[C@]3(C[C@]56[C@H](C4(C)C)C[C@@]7(CCCN7C5=O)C(=O)N6)O)O1)C	ZINC31162601	**10a/16a**
18		CC1(C=Cc2c(ccc3c2N[C@@]4(C3=O)C[C@@]56[C@@H](C4(C)C)C[C@]7(CCCN7C5=O)C(=O)N6)O1)C	ZINC31169883	**10a/16a**
19		CC1(C=Cc2c(ccc3c2N[C@@]4(C3=O)C[C@]56[C@@H](C4(C)C)C[C@@]7(CCCN7C5=O)C(=O)N6)O1)C	ZINC35271063	**10a/16a**
20		CC1(C=Cc2c(ccc3c2N[C@]4(C3=O)C[C@@]56[C@@H](C4(C)C)C[C@]7(CCCN7C5=O)C(=O)N6)O1)C	ZINC31169886	**10a/16a**

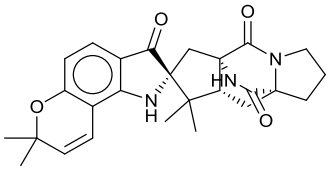
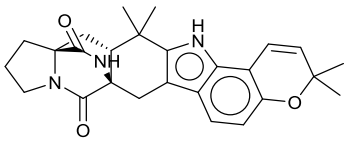
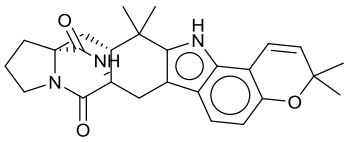
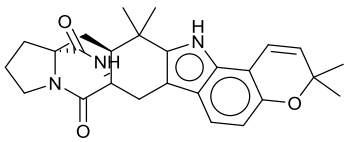
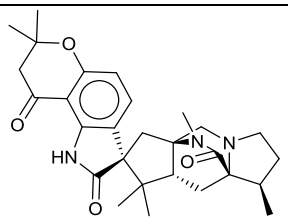
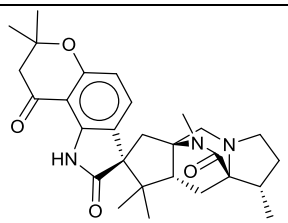
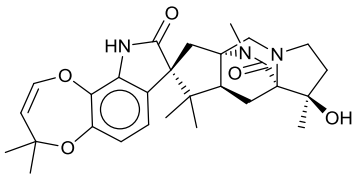
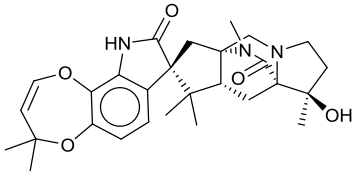
Entry	Structure	SMILES	ZINC identity	Corresponding scaffold
21		CC1(C=Cc2c(ccc3c2N[C@]4(C3=O)C[C@]56[C@@H](C4(C)C)C[C@@]7(CCCN7C5=O)C(=O)N6)O1)C	ZINC35271065	**10a/16a**
22		CC1(C=Cc2c(ccc3c2[nH]c4c3C[C@@]56[C@@H](C4(C)C)C[C@]7(CCCN7C5=O)C(=O)N6)O1)C	ZINC14856966	**10a/16a**
23		CC1(C=Cc2c(ccc3c2[nH]c4c3C[C@]56[C@@H](C4(C)C)C[C@@]7(CCCN7C5=O)C(=O)N6)O1)C	ZINC13373546	**10a/16a**
24		CC1(C=Cc2c(ccc3c2[nH]c4c3C[C@]56[C@H](C4(C)C)C[C@@]7(CCCN7C5=O)C(=O)N6)O1)C	ZINC13373547	**10a/16a**
25		C[C@@H]1CC[NH+]2[C@@]13C[C@H]4[C@@](C2)(C[C@]5(C4(C)C)c6ccc7c(c6NC5=O)C(=O)CC(O7)(C)C)N(C3=O)C	ZINC72320575	**10a/16a**
26		C[C@H]1CC[NH+]2[C@@]13C[C@H]4[C@@](C2)(C[C@]5(C4(C)C)c6ccc7c(c6NC5=O)C(=O)CC(O7)(C)C)N(C3=O)C	ZINC72320576	**10a/16a**
27		C[C@]1(CC[NH+]2[C@]13C[C@@H]4[C@](C2)(C[C@@]5(C4(C)C)c6ccc7c(c6NC5=O)OC=CC(O7)(C)C)N(C3=O)C)O	ZINC14637263	**10a/16a**
28		C[C@]1(CC[NH+]2[C@]13C[C@H]4[C@](C2)(C[C@@]5(C4(C)C)c6ccc7c(c6NC5=O)OC=CC(O7)(C)C)N(C3=O)C)O	ZINC14637262	**10a/16a**

Table S2. Substructure hits when the scaffolds (Figure S4) were searched for in the ZINC database.

4.0 Lead-likeness Assessment

AlogP and number of heavy atoms were calculated using the tools within Pipeline Pilot. The fraction of sp^3-hybridised carbon atoms (Fsp^3) was calculated using Dotmatics Vortex (Vortex v2013.12.25046). The data were visualized and analysed using Vortex.

The structural filtering was performed by interrogating two sets of SMARTS definitions with each of the final compounds using the substructure search tool within Pipeline Pilot. The first set contained 240 definitions (Table S3) as compiled by Shoichet, Simeonev *et al.* and used at the NIH Chemical Genomics Centre.[1] The second set contained 36 definitions (Table S4) and are examples from the 'GSKB' filter as described by Churcher *et al*.[2] In addition, the structural element of the high throughput screening filter embedded in Pipeline Pilot was also used, which comprises the filters for undesirable functionality outlined in Table S5.

Data from our lead-likeness assessment of both the ZINC database of compounds 'available now'[3] and our virtual library are provided in Tables S6, S7 and S8. The distribution of the molecular properties of the virtual library is shown in Figure S6. The distribution for each scaffold is shown in Figure S7.

Filter	SMARTS
2,3,4-trihydroxyphenyl	c([OH])c([OH])c([OH])
2,4,5-trihydroxyphenyl	c([OH])c([OH])cc([OH])
2halo_pyrazine_3EWG	[#7;R1]1[#6]([F,Cl,Br,I])[#6]([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])[#7][#6][#6]1
2halo_pyrazine_5EWG	[#7;R1]1[#6]([F,Cl,Br,I])[#6;!$(c-N)][#7][#6]([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])[#6;!$(c-N)]1
2halo_pyridazine_3EWG	[#7;R1]1[#6]([F,Cl,Br,I])[#6]([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])[#6][#6][#7]1
2halo_pyridazine_5EWG	[#7;R1]1[#6]([F,Cl,Br,I])[#6][#6][#6]([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])[#7]1
2halo_pyridine_3EWG	[#7;R1]1[#6;!$(c=O)]([F,Cl,Br,I])[#6]([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])[#6;!$(c-N)][#6][#6;!$(c-N)]1
2halo_pyridine_5EWG	[#7;R1]1[#6;!$(c=O)]([F,Cl,Br,I])[#6][#6;!$(c-N)][#6]([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])[#6;!$(c=O);!$(c-N)]1
2halo_pyrimidine_5EWG	[#7;R1]1[#6]([F,Cl,Br,I])[#7][#6][#6]([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])[#6]1
2-Halopyridine	[F,Cl,Br]-c1n[c,n][c,n][c,n][c,n]1
3halo_pyridazine_2EWG	[#7;R1]1[#6]([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])[#6]([F,Cl,Br,I])[#6][#6][#7]1
3halo_pyridazine_4EWG	[#7;R1]1[#6][#6]([F,Cl,Br,I])[#6]([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])[#6][#7]1

Filter	SMARTS
4_pyridone_3_5_EWG	[#7,#8,#16]1~[#6;H]~[#6]([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])~[#6](=O)~[#6]([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])~[#6;H]1
4halo_pyridine_3EWG	[#7;R1]1[#6;!$(c=O);!$(c-N)][#6]([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])[#6]([F,Cl,Br,I])[#6][#6;!$(c=O);!$(c-N)]1
4halo_pyrimidine_2_6EWG	[#7]1[#6]([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])[#7;R1][#6]([F,Cl,Br,I])[#6][#6]1([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])
4halo_pyrimidine_5EWG	[#7]1[#6][#7;R1][#6]([F,Cl,Br,I])[#6]([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])[#6]1
acetal	[#6]-O[CH1](-[#6])O[#6]
acid_halide	[S,C](=[O,S])[F,Br,Cl,I]
acrylate	[CH2]=[C;!$(C-N);!$(C-O)]C(=O)
activated_4mem_ring	[#6]1~[$(C(=O)),$(S(=O))]~[O,S,N]~[$(C(=O)),$(S(=O))]1
activated_acetylene	[$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O))]C#[C;!$(C-N);!$(C-n)]
activated_diazo	[N;!R]([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O))])=[N;!R]([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O))])
activated_S#O_3_ring	C1~[O,S]~[C,N,O,S]1[a,N,O,S]
activated_vinyl_ester	O=COC=[$(C(S(=O)(=O))),$(C(C(F)(F)(F))),$(C(C#N)),$(C(N(=O)(=O))),$(C([N+](=O)[O-])),$(C(C(=O)));!$(C(N))]
activated_vinyl_sulfonate	O(-S(=O)(=O))C=[$(C(S(=O)(=O))),$(C(C(F)(F)(F))),$(C(C#N)),$(C(N(=O)(=O))),$(C([N+](=O)[O-])),$(C(C(=O)));!$(C(N))]
acyclic_imide	[C,c][C;!R](=O)[N;!R][C;!R](=O)[C,c]
acyl_123_triazole	[#7;R1]1~[#7;R1]~[#7;R1](-C(=O))~[#6]~[#6]1
acyl_134_triazole	[#7]1~[#7]~[#6]~[#7](-C(=O)[!N])~[#6]1
acyl_activated_NO	O=C(-[!N])O[$([#7;+]),$(N(C=[O,S,N])(C=[O,S,N]))]
acyl_cyanide	C(=O)-C#N
acyl_imidazole	[C;!$(C-N)](=O)[#7]1[#6;H1,$([#6]([*;!R]))][#7][#6;H1,$([#6]([*;!R]))][#6;H1,$([#6]([*;!R]))]1
acyl_pyrazole	[C;!$(C-N)](=O)[#7]1[#7][#6;H1,$([#6]([*;!R]))][#6;H1,$([#6]([*;!R]))][#6;H1,$([#6]([*;!R]))]1
aldehyde	[C,c][C;H1](=O)
aliphatic_chain_6	[CD2;R0][CD2;R0][CD2;R0][CD2;R0][CD2;R0][CD2;R0]
alkynyl_michael_acceptor1	[#6]-C#CC(=O)-[#6,#7,#8]
alkynyl_michael_acceptor2	[CH1]#CC(=O)-[#6,#7,#8]
allene	*=C=*
alpha_dicarbonyl	C(=O)!@C(=O)
alpha_halo_amine	[F,Cl,Br,I,$(O(S(=O)(=O)))]-[CH,CH2;!$(CF2)]-[N,n]
alpha_halo_carbonyl	C(=O)([CH,CH2][Cl,Br,I,$(O(S(=O)(=O)))])
alpha_halo_EWG	[$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-])]-[CH,CH2]-[Cl,Br,I,$(O(S(=O)(=O)))]
alpha_halo_heteroatom	[N,n,O,S;!$(S(=O)(=O))]-[CH,CH2;!$(CF2)][F,Cl,Br,I,$(O(S(=O)(=O)))]
alpha_halo_heteroatom_tert	[N,n,O,S;!$(S(=O)(=O))]-C([Cl,Br,I,$(O(S(=O)(=O)))])(C)(C)
anhydride	[$(C(=O)),$(C(=S))]-[O,S]-[$(C(=O)),$(C(=S)),$(C(=[N;!R])),$(C(=N(-[C;X4])))]
aromatic_azide c	N=[N+]=[N-]
aryl_phosphonate	P(=O)-[O;!R]-a
aryl_thiocarbonyl	a-[S;X2;!R]-[C;!R](=O)
azide	[$(N#[N+]-[N-]),$([N-]=[N+]=N)]
aziridine_diazirine	[C,N]1~[C,N]~N~1
azo_amino	[N]=[N;!R]-[N]
azo_aryl	c[N;!R;!+]=[N;!R;!+]-c
azo_filter1	[N;!R]=[N;!R]-[N]=[*]

Filter	SMARTS
azo_filter2	[N;!$(N-S(=O)(=O));!$(N-C=O)]-[N;!r3;!$(N-S(=O)(=O));!$(N-C=O)]-[N;!$(N-S(=O)(=O));!$(N-C=O)]
azo_filter3	[N;!R]-[N;!R]-[N;!R]
azo_filter4	a-N=N-[N;H2]
azoalkanal	[N;R0]=[N;R0]CC=O
azocyanamide	[N;R0]=[N;R0]C#N
bad_boron	[B-,BH2,BH3,$(B(F)(F))]
bad_cations	[C+,F+,Cl+,Br+,I+,Se+]
b-carbonyl_quaternary_nitrogen	C(=O)CC[N+,n+]
benzhydrol	[OH1]-C(-c1ccccc1)-c2ccccc2
benzidine_like	c([N;!+])1ccc(c2ccc([N;!+])cc2)cc1
benzylic-quaternary_nitrogen	cC[N+]
beta_lactam	C1(=O)~[#6]~[#6]N1
beta_lactone	[#6,#15,#16]1(=O)~[#6]~[#6]~[#8,#16]1
betalactam_EWG	C1(=O)~[#6]~[#6]N1([$(S(=O)(=O)[C,c,O&D2]),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)[C,c,O&D2])])
bis_activated_aryl_ester	O=[C,S]Oc1aaa([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])aa([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])1
bis_keto_olefin	CC(=O)[$([C&H1]),$(C-F),$(C-Cl),$(C-Br),$(C-I)]=[$([C&H1]),$(C-F),$(C-Cl),$(C-Br),$(C-I)]C(=O)C
boron_wAr-Head	[C,c]~[#5]
branched_polycyclic_aromatic	a1(a2aa(a3aaaaa3)aa(a4aaaaa4)a2)aaaaa1
carbazide	O=*N=[N+]=[N-]
carbodiimide_isothiocyanate	N=C=[N,O,S]
carbonyl_halide	O=C[F,Cl,Br,I]
chloramidine	[Cl]C([C&R0])=N
crown_ether	[$([O,S,#7;R1;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][O,S,#7;R1;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][O,S,#7;R1;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18]),$([O,S,#7;R1;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][O,S,#7;R1;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][O,S,#7;R1;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18]),$([O,S,#7;R1;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][O,S,#7;R1;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][O,S,#7;R1;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18])]
cyanamide	N[CH2]C#N
cyanidin	[OH]c1cc([OH])cc2=[O+]C(=C([OH])Cc21)c3cc([OH])c([OH])cc3
cyano_phosphonate	P(O[A,a])(O[A,a])(=O)C#N
cyanohydrin	[C;X4](-[OH,NH1,NH2,SH])(-C#N)
cyanophosphonate	P(OCC)(OCC)(=O)C#N
cycloheximide	O=C1CCCC(N1)=O
cytochalasin	O=C1NCC2CCCCC21
di_tri_phosphate	P(=O)([OH])OP(=O)[OH]
diamino_sulfide	[N,n]~[S;!R;D2]~[N,n]
diazo_carbonyl	[$(N=N=C~C=O),$(N#N-C~C=O)]
diazonium	a[N+]#N
dicarbonyl_sulfonamide	[$(N(-C(=O))(-C(=O))(-S(=O))),$(n([#6](=O))([#6](=O))([#16](=O)))]

Filter	SMARTS
dihydroxybenzene	[OH1]c1ccc([OH1])cc1
disulfide	SS
disulfide_acyclic	[S;!R;X2]-[S;!R;X2]
disulfonyliminoquinone	S(=O)(=O)N=C1C=CC(=NS(=O)(=O))C=C1
double_trouble_wAr-Head	NC(C[S;D1])C([N;H1]([O;D1]))=O
epoxide_aziridine_thioepoxide	[CH2]1[O,S,N]C1
flavanoid	O=C2CC(a3aaaaa3)Oa1aaaaa12
four_nitriles	C#N.C#N.C#N.C#N
free_thiol	[SH]
halo_5heterocycle_bis_EWG	[#7,#8,#16]1[#6]([$(S(=O)(=O)),$([F,Cl]),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O))])[#6]([$(S(=O)(=O)),$([F,Cl]),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O))])[#7][#6]1([Cl,Br,I])
halo_acrylate	[$([C;H2]),$([C&H1;$(C-F)]),$([C&H1;$(C-Cl)]),$([C&H1;$(C-Br)]),$([C&H1;$(C-I)]),$(C(F)F),$(C(Cl)Cl),$(C(Br)Br),$(C(I)I),$(C(F)Cl),$(C(F)Br),$(C(F)I),$(C(Cl)Br),$(C(Br)I)](=[$([C&H1;$(C(-C(=O))))]),$(C(F)(C(=O))),$(C(Cl)(C(=O))),$(C(Br)(C(=O))),$(C(I)(C(=O))),$(C(C)(C(=O))),$(C(c)(C(=O)))])
halo_imino	C(=[#7])([Cl,Br,I,$(O(S(=O)(=O)))])
halo_olefin_bis_EWG	C([Cl,Br,I,$(O(S(=O)(=O)))])=C([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])
halo_phenolic_carbonyl	C(=O)Oc1c([Cl,F])[cH1,$(c[F,Cl])]c([F,Cl])[cH1,$(c[F,Cl])]c1([F,Cl])
halo_phenolic_sulfonyl	S(=O)Oc1c([Cl,F])[cH1,$(c[F,Cl])]c([F,Cl])[cH1,$(c[F,Cl])]c1([F,Cl])
halogen_heteroatom	[!C;!c;!H][F,Cl,Br,I]
hemiacetal	[#6]-O[CH1](-[#6])[OH1]
hetero_silyl	[Si]~[!#6]
heteroaryl_sulfonate	a-S(=O)(=O)-O-[$([a&!#6]),$(c[a&!#6]),$(cc[a&!#6]),$(ccc[a&!#6]),$(cccc[a&!#6]),$(ccccc[a&!#6])]
HOBT_ester	O=C(-[!N])O[$(nnn),$([#7]-[#7]=[#7])]
hydrazine2	[#7]!@-N!@=C
hydrazine	[N;X3;!$(N-S(=O)(=O));!$(N-C(F)(F)(F));!$(N-C#N);!$(N-C(=O));!$(N-C(=S));!$(N-C(=N))]-[N;X3;!$(N-S(=O)(=O));!$(N-C(F)(F)(F));!$(N-C#N);!$(N-C(=O));!$(N-C(=S));!$(N-C(=N))]
hydrazothiourea	[N;!R]=NC(=S)N
hydroxamate_wAr-Head	C([N;H1]([O;D1]))=O
hyperval_sulfur	[$([#16&D3]),$([#16&D4])]=,:[#6]
Imine1	[#6;R0]C([#6;R0])=[NH1]
Imine2	[#6;R0][CH1]=[NH1]
isonitrile	[N+]#[C-]
Lawesson_reagent_derivatives	P(=S)(S)S
linear_polycyclic_aromatic_I	[$(a12aaaaa1aa3a(aa(aaaa4)a4a3)a2),$(a12aaaaa1aa3a(aaa4a3aaaa4)a2),$(a12aaaaa1a(aa5)a3a(aaa4a3a5aaa4)a2)]
linear_polycyclic_aromatic_II	[$(a12aaaa4a1a3a(aaaa3aa4)aa2),$(a12aaaaa1a3a(aaa4a3aaaa4)aa2),$(a1(a(aaaa4)a4a3a2aaaa3)a2aaaa1)]
maleimide_etc	[$([C;H1]),$(C(-[F,Cl,Br,I]))]1=[$([C;H1]),$(C(-[F,Cl,Br,I]))]C(=O)[N,O,S]C(=O)1
meldrums_acid_etc	O=C1OC(C)(C)OC(C1)=O
metal	[$([Ru]),$([Mg]),$([Rh]),$([Se]),$([se]),$([Pd]),$([Sc]),$([Bi]),$([Sb]),$([Ag]),$([Ti]),$([Al]),$([Cd]),$([V]),$([In]),$([Cr]),$([Sn]),$([Mn]),$([La]),$([Fe]),$([Er]),$([Tm]),$([Yb]),$([Lu]),$([Hf]),$([Ta]),$([W]),$([Re]),$([Co]),$([Os]),$([Ni]),$([Ir]),$([Cu]),$([Zn]),$([Ga]),$([Ge]),$([As]),$([as]),$([Y]),$([Zr]),$([Nb]),$([Ce]),$([Pr]),$([Nd]),$([Sm]),$([Eu]),$([Gd]),$([Tb]),$([Dy]),$([Ho]),$([Pt]),$([Au]),$([Hg]),$([Tl]),$([Pb]),$([Ac]),$([Th]),$([Pa]),$([Mo]),$([U]),$([Tc]),$([Te]),$([Po]),$([At])]
michael_acceptor6	[#6,#7]-&!@[#6](=&!@[CH])-&!@C(=O)-&!@[C,N,O,S]

Filter	SMARTS
michael_acceptor5	N#CC(=C)C#N
michael_acceptor_misc	O=C1[O,N]C~[N,C]C1=[C,N]
michael_acceptor_misc2	*~\C=C1/CC2=CC=CC=C2N1
michael_acceptor_vinyl2	[CH2]=C-C(=O)-[#6,#7,#8]
misc_10_carbon_sb_chain	[C;!R]-[C;!R]-[C;!R]-[C;!R]-[C;!R]-[C;!R]-[C;!R]-[C;!R]-[C;!R]-[C;!R]
misc_2_free_phos	P([O;D1])=O.P([O;D1])=O
misc_2_N_quats	[N,n;H0;+;!$(N~O);!$(n~O)].[N,n;H0;+;!$(N~O);!$(n~O)]
misc_2_sulfonic_acid	[C,c]S(=O)(=O)[O;D1].[C,c]S(=O)(=O)[O;D1]
misc_3_COOH	C(=O)[O;D1].C(=O)[O;D1].C(=O)[O;D1]
misc_3_iodine	[#53].[#53].[#53]
misc_4_basic_N	[N;!$(N(=[N,O,S,C]));!$(N(S(=O)(=O)));!$(N(C(F)(F)(F)));!$(N(C#N));!$(N(C(=O)));!$(N(C(=S)));!$(N(C(=N)));!$(N(#C));!$(N-c)].[N;!$(N(=[N,O,S,C]));!$(N(S(=O)(=O)));!$(N(C(F)(F)(F)));!$(N(C#N));!$(N(C(=O)));!$(N(C(=S)));!$(N(C(=N)));!$(N(#C));!$(N-c)].[N;!$(N(=[N,O,S,C]));!$(N(S(=O)(=O)));!$(N(C(F)(F)(F)));!$(N(C#N));!$(N(C(=O)));!$(N(C(=S)));!$(N(C(=N)));!$(N(#C));!$(N-c)]
misc_4_nitro	[$([N+](=O)[O-]),$(N(=O)=O)].[$([N+](=O)[O-]),$(N(=O)=O)].[$([N+](=O)[O-]),$(N(=O)=O)].[$([N+](=O)[O-]),$(N(=O)=O)]
misc_5_phenolic_OH	a[O;D1].a[O;D1].a[O;D1].a[O;D1].a[O;D1]
misc_7_aliphatic_OH	C[O;D1].C[O;D1].C[O;D1].C[O;D1].C[O;D1].C[O;D1].C[O;D1]
misc_7_total_hal	[Cl,Br,I].[Cl,Br,I].[Cl,Br,I].[Cl,Br,I].[Cl,Br,I].[Cl,Br,I].[Cl,Br,I]
misc_8_CF2_or_CH2	[CH2,$(CF2);R0][CH2,$(CF2);R0][CH2,$(CF2);R0][CH2,$(CF2);R0][CH2,$(CF2);R0][CH2,$(CF2);R0][CH2,$(CF2);R0][CH2,$(CF2);R0]
monensin	O1CCCCC1C2CCCO2
monofluoroacetate	[C;H2](F)C(=O)[O,N,S]
nitrate	[#6]-O-[N+](=O)[O-]
nitro_aromatic	(a-[N+](=O)[O-].a-[N+](=O)[O-])
nitroalkane	C[N+](=O)[O-]
nitrone	[C;!R]=[N+][O;D1]
nitrosamine	N-[N;X2](=O)
nitroso	[N&D2](=O)
NO_phosphonate	P(=O)ON
ortho_hydroiminoquinone	c1c([N;D1])c([N;D1])c[cH1][cH1]1
ortho_hydroquinone	a1c([O,S;D1])c([O,S;D1])a[cH1][cH1]1
ortho_nitrophenyl_carbonyl	[#6]1(-O-[C;!R](=[O,N;!R]))[#6]([$(N(=O)(=O)),$([N+](=O)[O-])])[#6][#6][#6][#6]1
ortho_quinone	[CH1,$(C(-[Cl,Br,I]))]1=CC(=[O,N,S;!R])C(=[O,N,S])C=[CH1,$(C(-[Cl,Br,I]))]1
oxaziridine	C1~[O,S]~N1
oxime	[$(C=N[O;D1]);!$(C=[N+])][#6][#6]
oxonium	[o+,O+]
P_S_halide	[P,S][F,Cl,Br,I]
para_hydroiminoquinone	a1[cH1]c([N;D1])[cH1]ac([N;D1])1
para_hydroquinone	a1[cH1]c([O,S;D1])[cH1]ac([O,S;D1])1
para_nitrophenyl_ester	[#6]1(-O(-[C;!R](-[!N])(=[O,N;!R])))[#6][#6][#6]([$(N(=O)(=O)),$([N+](=O)[O-])])[#6][#6]1
para_quinone	[CH1,$(C(-[Cl,Br,I]))]1=[CH1,$(C(-[Cl,Br,I]))]C(=[O,N,S])[CH1,$(C(-[Cl,Br,I]))]=[CH1,$(C(-[Cl,Br,I]))]C1(=[O,N,S])
paraquat_like	[#6]1[#6][#6]([#6]2[#6][#6][#7;+][#6][#6]2)[#6][#6][#7;+]1

Filter	SMARTS
pentafluorophenylester	C(=O)Oc1c(F)c(F)c(F)c(F)c1(F)
perchloro_cp	C1(Cl)(Cl)C(Cl)C(Cl)=C(Cl)C1(Cl)
perhalo_dicarbonyl_phenyl	c1(C=O)c([Br,Cl,I])c([Br,Cl,I])c([Br,Cl,I])c([Br,Cl,I])c1(C=O)
perhalo_ketone	O=CC(-[F,Cl,Br,I])(-[F,Cl,Br,I])-[F,Cl,Br,I]
perhalo_phenyl	c1c([F,Br,Cl,I])c([F,Br,Cl,I])c([F,Br,Cl,I])c([F,Br,Cl,I])c1([F,Br,Cl,I])
peroxide	[#8]~[#8]
phenolate_bis_EWG	O=[C,S]Oc1aaa([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])aa([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])1
phos_serine_wAr-Head	NC(COP(O)(O)=O)C(O)=O
phos_threonine_wAr-Head	NC(C(C)OP(O)(O)=O)C(O)=O
phos_tyrosine_wAr-Head	NC(Cc1ccc(OP(O)(O)=O)cc1)C(O)=O
phosphite	[c,C]-[P;v3]
phosphonate_esters	COP(=O)(=O)[C,c]
phosphonium	[#15;+]~[!O]
phosphoramide	NP(=O)(N)N
phosphorane	C=P
phosphorous_nitrogen_bond	[#15]~[N,n]
phosphorus_phosphorus_bond	P~P
phosphorus_sulfur_bond	P~S
polyacidic4	[C,S,P](=O)[OH].[C,S,P](=O)[OH].[C,S,P](=O)[OH].[C,S,P](=O)[OH]
polyazoanthracene	c12:[c,n]:[c,n]:[c,n]:[c,n]:c1[c,n]c3:[c,n]:[c,n]:[c,n]:[c,n]:c3[c,n]2
polyazophenanthrene	c12:[c,n]:[c,n]:[c,n]:[c,n]:c1:[c,n]:[c,n]:c3:[c,n]:[c,n]:[c,n]:[c,n]:c23
polyene	C=[C;!R][C;!R]=[C;!R][C;!R]=[C;!R]
polyhalo_phenol_a	c1c([O;D1])c(-[Cl,Br,I])c(-[Cl,Br,I])cc1.c1c([O;D1])c(-[Cl,Br,I])c(-[Cl,Br,I])cc1
polyhalo_phenol_b	c1c([O;D1])c(-[Cl,Br,I])cc(-[Cl,Br,I])c1.c1c([O;D1])c(-[Cl,Br,I])cc(-[Cl,Br,I])c1
polyhalo_phenol_c	c1c([O;D1])ccc(-[Cl,Br,I])c(-[Cl,Br,I])1.c1c([O;D1])ccc(-[Cl,Br,I])c(-[Cl,Br,I])1
polyhalo_phenol_d	c(-[Cl,Br,I])1c([O;D1])c(-[Cl,Br,I])ccc1.c(-[Cl,Br,I])1c([O;D1])c(-[Cl,Br,I])ccc1
polyhalo_phenol_e	c1c([O;D1])ccc(-[Cl,Br,I])c(-[Cl,Br,I])1.c1c([O;D1])ccc(-[Cl,Br,I])c(-[Cl,Br,I])1
polysulfide	[S;D2]-[S;D2]-[S;D2]
porphyrin	[#6;r16,r17,r18]~[#6]1~[#6]~[#6]~[#6](~[#6])~[#7]1
primary_halide_sulfate	[CH2][Cl,Br,I,$(O(S(=O)(=O)[!$(N);!$([O&D1])]))]
propiolactone	C1(=O)OCC1
quat_N_acyl	[N,n;+]!@C(=O)
quat_N_N	[N,n;R;+]!@[N,n]
quaternary_C_Cl_I_P_S	[C+,Cl+,I+,P+,S+]
quaternary_nitroxy	C[N+](-[O-])(C)C
quinone_methide	[#6;!$([#6](-[N,O,S]))]1=[#6;!$([#6](-[N,O,S]))][#6](=[#6])[#6;!$([#6](-[N,O,S]))]=[#6;!$([#6](-[N,O,S]))][#6]1(=[O,N,S])
rhodanine	C(=C)1SC(=S)NC(=O)1
secondary_halide_sulfate	[CH;!$(C=C)][Cl,Br,I,$(O(S(=O)(=O)[!$(N);!$([O&D1])]))]
squalestatin	C12OCCC(O1)CC2
sulf_D2_nitrogen	[S;D2](-[N;!$(N(=C));!$(N(-S(=O)(=O)));!$(N(-C(=O)))])
sulf_D2_oxygen_D2	[S;D2][O;D2]
sulf_D3_nitrogen	[S;D3](-N)(-[c,C])(-[c,C])
sulfite_sulfate_ester	[C,c]OS(=O)O[C,c]
sulfonate	COS(=O)(=O)[C,c]

Filter	SMARTS
sulfonium	[S+;X3;$(S-C);!$(S-[O;D1])]
sulfonyl_anhydride	[$(C(=O)),$(S(=O)(=O))][O,S](S(=O)(=O))
sulfonyl_halide	S(=O)(=O)[F,Cl,Br,I]
sulfonyl_heteroatom	[!#6;!#1;!#11;!#19]O(S(=O)(=O)(-[C,c]))
sulphonyl_cyanide	S(=O)(=O)C#N
tertiary_halide_sulfate	[C;X4](-[Cl,Br,I,$(O(S(=O)(=O)[!$(N);!$([O&D1])]))])(-[c,C])(-[c,C])(-[c,C])
thio_hydroxamate	[S;D2]([$(N(=C)),$(N(-S(=O)(=O))),$(N(-C(=O)))])
thio_xanthate	[S;!R]-[C;!R](=[S;!R])(-[S;!R])
thioamide	[#6]C([#7H2])=S
thiocarbonate	SC(=O)[O,S]
thiocyanate	SC#N
thioester	[S;!R;H0]C(=[S,O;!R])([!O;!S;!N])
thioketone	CC(=S)C
thiol_wAr-Head	NC(C[S;D1])C(O)=O
thiopyrylium	c1[S,s;+]cccc1
thiosulfoxide	[C,c][S;X3](~O)-S
thiourea	C([#7H2])([#7H2])=S
tri_phosphoric_esters	([#6]OP(=O)(-*)O[#6].[#6]OP(=O)(-*)O[#6].[#6]OP(=O)(-*)O[#6])
triacyloxime	C(=O)N(C(=O))OC(=O)
triamide	[$(N(-C(=O))(-C(=O))(-C(=O))),$(n([#6](=O))([#6](=O))([#6](=O)))]
triaryl_phosphine_oxide	P(=O)(a)(a)(a)
trichloromethyl_ketone	[$(C(=O));!$(C-N);!$(C-O);!$(C-S)]C(Cl)(Cl)(Cl)
triflate	OS(=O)(=O)(C(F)(F)(F))
trifluoroacetate_ester	C(F)(F)(F)C(=O)O
trifluoroacetate_thioester	C(F)(F)(F)C(=O)S
trifluoromethyl_ketone	[$(C(=O));!$(C-N);!$(C-O);!$(C-S)]C(F)(F)(F)
trihalovinyl_heteroatom	C(-[Cl,Br,I])(-[Cl,Br,I])=C(-[Cl,Br,I])(-[N,O,S])
trinitro_aromatic	[$(a1aaa([$(N(=O)(=O)),$([N+](=O)[O-])])a([$(N(=O)(=O)),$([N+](=O)[O-])])a1([$(N(=O)(=O)),$([N+](=O)[O-])])),$(a1aa([$(N(=O)(=O)),$([N+](=O)[O-])])a([$(N(=O)(=O)),$([N+](=O)[O-])])aa1([$(N(=O)(=O)),$([N+](=O)[O-])])),$(a1a([$(N(=O)(=O)),$([N+](=O)[O-])])aa([$(N(=O)(=O)),$([N+](=O)[O-])])aa1([$(N(=O)(=O)),$([N+](=O)[O-])]))]
trinitromethane_derivative	C([$([N+](=O)[O-]),$(N(=O)=O)])([$([N+](=O)[O-]),$(N(=O)=O)])([$([N+](=O)[O-]),$(N(=O)=O)])
tris_activated_aryl_ester	[$(O=[C,S]Oc1a([$(S(=O)(=O)),F,$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])a([$(S(=O)(=O)),F,$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])a([$(S(=O)(=O)),F,$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])aa1),$(O=[C,S]Oc1a([$(S(=O)(=O)),F,$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])a([$(S(=O)(=O)),F,$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])aaa([$(S(=O)(=O)),F,$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])1),$(O=[C,S]Oc1a([$(S(=O)(=O)),F,$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])aa([$(S(=O)(=O)),F,$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])a([$(S(=O)(=O)),F,$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])a1),$(O=[C,S]Oc1a([$(S(=O)(=O)),F,$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])aa([$(S(=O)(=O)),F,$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])aa([$(S(=O)(=O)),F,$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])1)]
trisub_bis_act_olefin	[[CH;!R];!$(C-N)]=C([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O))])([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O))])
unacceptable_atoms1	[!#6;!#7;!#8;!#16;!#1;!#3;!#9;!#11;!#12;!#15;!#17;!#19;!#20;!#30;!#35]
unacceptable_atoms2	[!#6;!#7;!#8;!#16;!#1;!#3;!#9;!#11;!#12;!#15;!#17;!#19;!#20;!#30;!#35;!#53]

Filter	SMARTS
vinyl_carbonyl_EWG	[C;!R]([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])=[C;!R]([C;!R](=O))([!$([#8]);!$([#7])])
vinyl_sulfone	O=S([#6]=[#6])([#6]=[#6])=O
vinyloxazole	[N,C]=CC1=COC=N1
2,3,4-trihydroxyphenyl	c([OH])c([OH])c([OH])

Table S3. Undesirable functionality SMARTS definitions utilised by the NIH.[1]

Filter	SMARTS
thiocarbonyl	[c,C]=[S;X1]
termalkyne	[CH]#C
quinonepara	O=[#6]1[#6]~[#6][#6](=O)[#6]~[#6]1
nonpeptidic_macrocycle	[!R0!r3!r4!r5!r6!r7!r8!$([N;!H0,$(N1[CH2][CH2][CH2][CH1]1)][CH]C=O)!$([CH]([N;!H0,$(N1[CH2][CH2][CH2][CH1]1)])C=O)!$(C(=O)[CH][N;!H0,$(N1[CH2][CH2][CH2][CH1]1)])]
nitrogen_oxygen_bond	*-[n,N]-[O;H0;R0]
methyl_ester_x2	[$([CH3]OC=O)].[$([CH3]OC=O)]
imide	O=C([#6])NC(=O)[#6]
exocyclic_double_bond_toC	[R;#7,#8,#16,#6X3][R]=!@C
ethyl_ester_x2	[$([CH2](OC=O)[CH3])][CH3].[$([CH2](OC=O)[CH3])][CH3]
ester_deep_in_mol	*[#6]C(=O)[O;R0][#6;$(*(OC=O)**),$(*(OC=O)(*)*)]
enolether	C=!@C[OD2]
conjugated_C=C	C=[C;R0][C;R0]=C
benzyl_ester	[$([CH2](OC=O)c1[cH][cH][cH][cH][cH]1)]c1[cH][cH][cH][cH][cH]1
aromatic_tricyclic1	c1ccc3c(c1)[C;!$(C=O)]c2ccccc23
allyl_ester	[$([CH2](OC=O)[CH]=[CH2])][CH]=[CH2]
alkylNandNonC	N[CX4]!@N
alkCl	[C][Cl!$(ClC(Cl)(Cl))]
alkBr	CBr
acyclic_sulphur_michael_acceptor	[C!$(*[Nv3X3])]=!@[C!$(*[Nv3X3])][S!$(*[Nv3X3])]=O
acyclic_imine	[C!$(*(=N)[N,n])]=!@[Nv3!$(*O)]
acyclic_hydrazine	[Nv3X3!$(*(C=O)NC=O)]-!@[Nv3X3!$(*(C=O)NC=O)]
acetyl_x2	[CH3]C(=O)O.[CH3]C(=O)O
acetal	[OX2;$(OC[OX2])][C;!$(C1(O)CNCCO1);!$(C1(O)(CO)OC(CO)C(O)C1O);!$(C1(O)OC(CO)C(O)C(O)C1O)][OX2][!a]
OCO_protecting_group	[O;R0][C;X4][O;R0]
N-SO_group	N[S;!$(S(=O)(=O))]=O
C=N=O_gp	C=N=O
C(=O)CC(=O)_gp	[c,C]C(=O)[C!H0!R]C(=O)[C,c]
4_fused_ring_sys	[R2][R3][R2][R2][R2]
C#C	C#C.C#C
C#C-c_gp	cC#[C!H1]
3_mem_ring_with_het	[S,O,N;r3]
acylcarbamate	O=[S,C]NC(=O)O
anyNO	[Nv3,n]=O
phenol_x2	[OH][c;$(c1ccccc1)].[OH][c;$(c1ccccc1)]

formamide	[#7;!$(N[OH])][CH1]=O
benzyl_halide	[CX4](a)[F,Cl,Br,I;!$(FC(F)F)]

Table S4. Undesirable functionality SMARTS definitions that comprise the 'GSKB' filter.[2]

Filter	
Acyl halide	Disulfide
Aldehyde	Hydrazine (terminal)
Alkyl halide	Isocyanate
Anhydride	Isothiocyanate
Diazo	Peroxide
Dicarbonyl	Quaternary ammonium

Table S5. Undesirable functionality filters used in the 'HTS Filter' embedded in Pipeline Pilot.

Filter	ZINC Database (9046036)		Random 1% of ZINC Database (90911)		Virtual Library (1110)	
	Successive Filtering	Parallel Filtering	Successive Filtering	Parallel Filtering	Successive Filtering	Parallel Filtering
Fail 14 ≤ nHA ≤ 26	4395739	4395739 (48%)	43971	43971 (48%)	173	173 (16%)
Fail –1 ≤ AlogP ≤ 3	1768807	4478982 (49%)	17828	44746 (49%)	200	220 (20%)
Fail Structural	819652	2805505 (31%)	8180	28147 (31%)	3	5 (0.5%)
Pass All	2061838 (23%)	n/a	20932 (23%)	n/a	734 (66%)	n/a

Table S6. Lead-likeness assessment data. For comparison, data obtained from parallel filtering of all compounds using each filter in isolation is also shown.

Scaffold	Number of Final Compounds	Number of Lead-like Compounds	% Lead-like Compounds
5a	64	62	97
5b	64	55	86
5c	116	68	59
5d	71	37	52
7a	76	62	82
7b	75	46	61
7c	127	47	37
8a	26	24	92
8c	78	39	50
8d	10	4	40
10a	26	24	92
10b	26	18	69
11d	37	31	84
13a	15	14	93
13b	15	14	93
13c	67	40	60
13d	21	7	33
14c	60	33	55
16a	8	7	88
16b	8	6	75

Scaffold	Number of Final Compounds	Number of Lead-like Compounds	% Lead-like Compounds
16c	60	58	97
16d	60	38	63
Total	1110	734	66

Table S7. Number of final compounds derived from each scaffold, together with the number and percentage of compounds that are lead-like (i.e. pass all filters).

Scaffold or Library	Mean Fsp^3
ZINC (random 1%, 90911)	0.33
Virtual Library (1110)	0.57

Table S8. Mean Fsp^3 data for the random 1% of the ZINC database and the virtual library of 1110 decorated final compounds.

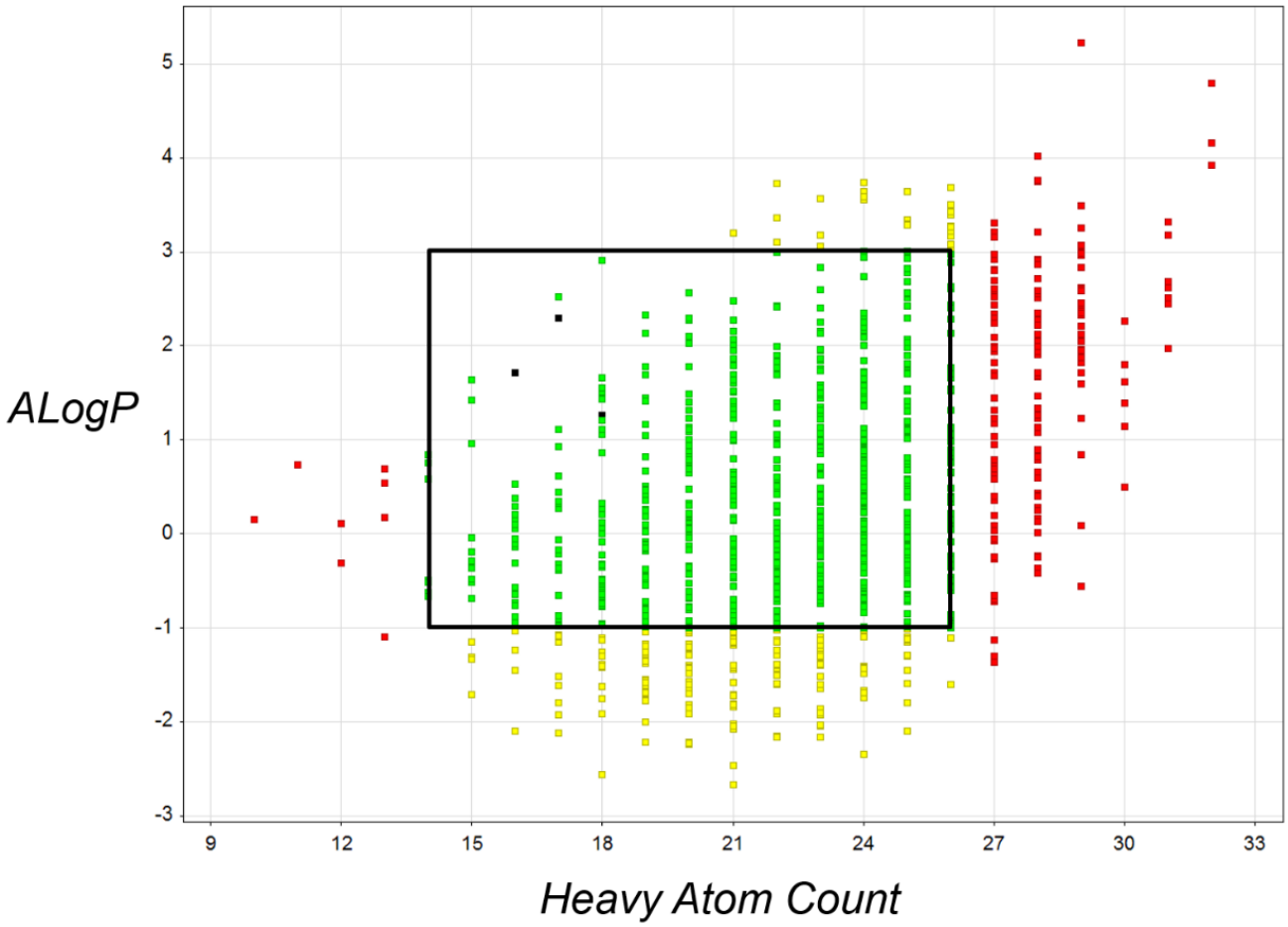
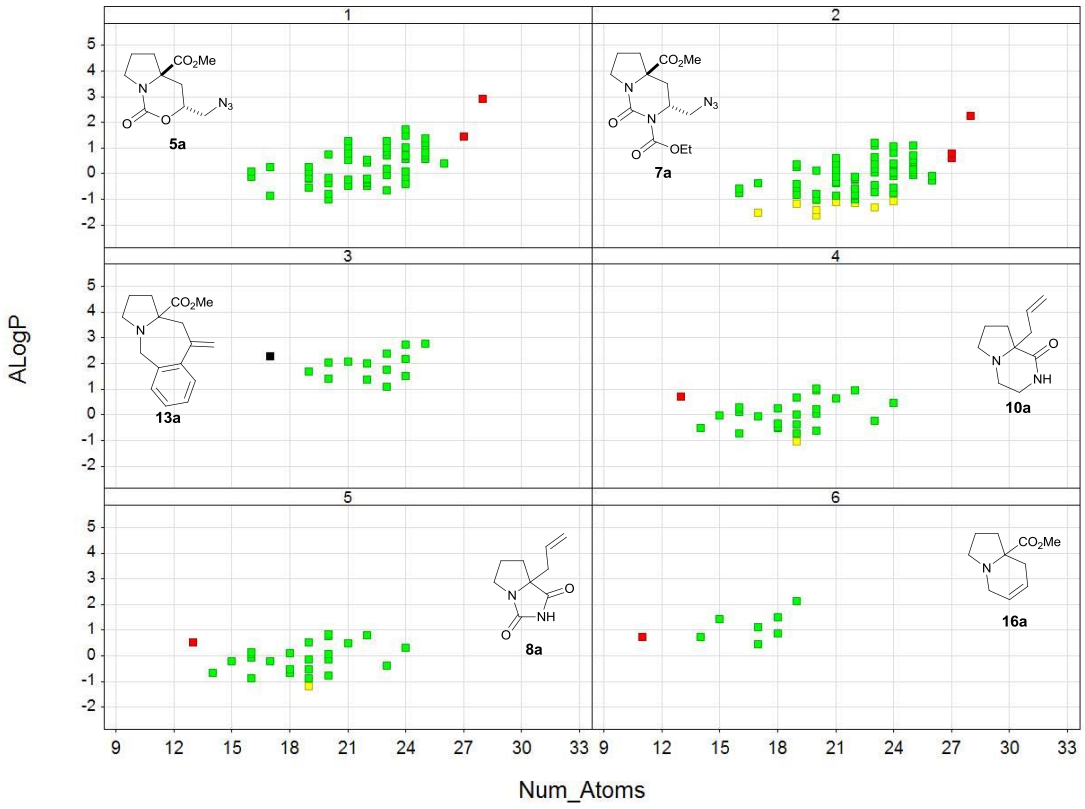
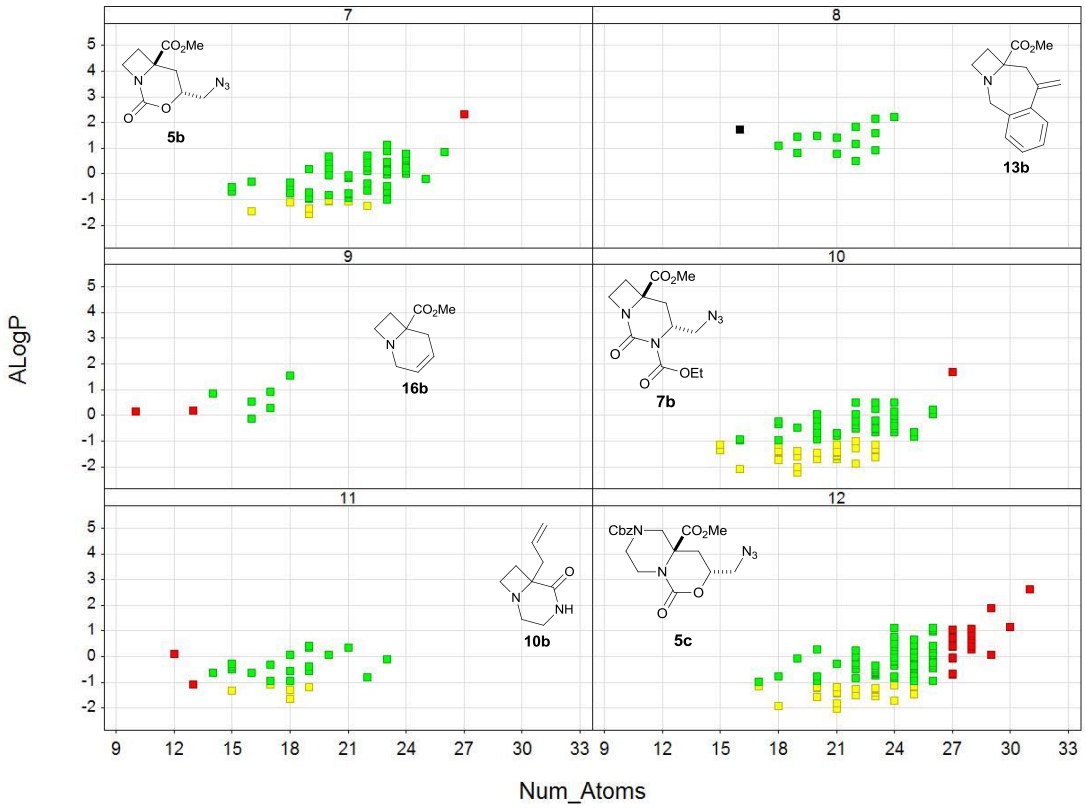


Figure S6. Distribution of the number of heavy atoms (Num_Atoms) and AlogP for the 1110 decorated final compounds derived from the 22 scaffolds using the virtual library enumeration process (Figure S1). Compounds that survive successive filtering are shown in green (734 compounds, 66%). Compounds that fail successive filtering by number of heavy atoms (red, 173 compounds, 16%), AlogP (yellow, 200 compounds, 18%) and structural liabilities (black, 3 compounds, 0.3%) are shown.


ALogP
Num_Atoms
1
2
3
4
5
6
5a
7a
13a
10a
8a
16a


ALogP
Num_Atoms
7
8
9
10
11
12
5b
13b
16b
7b
10b
5c

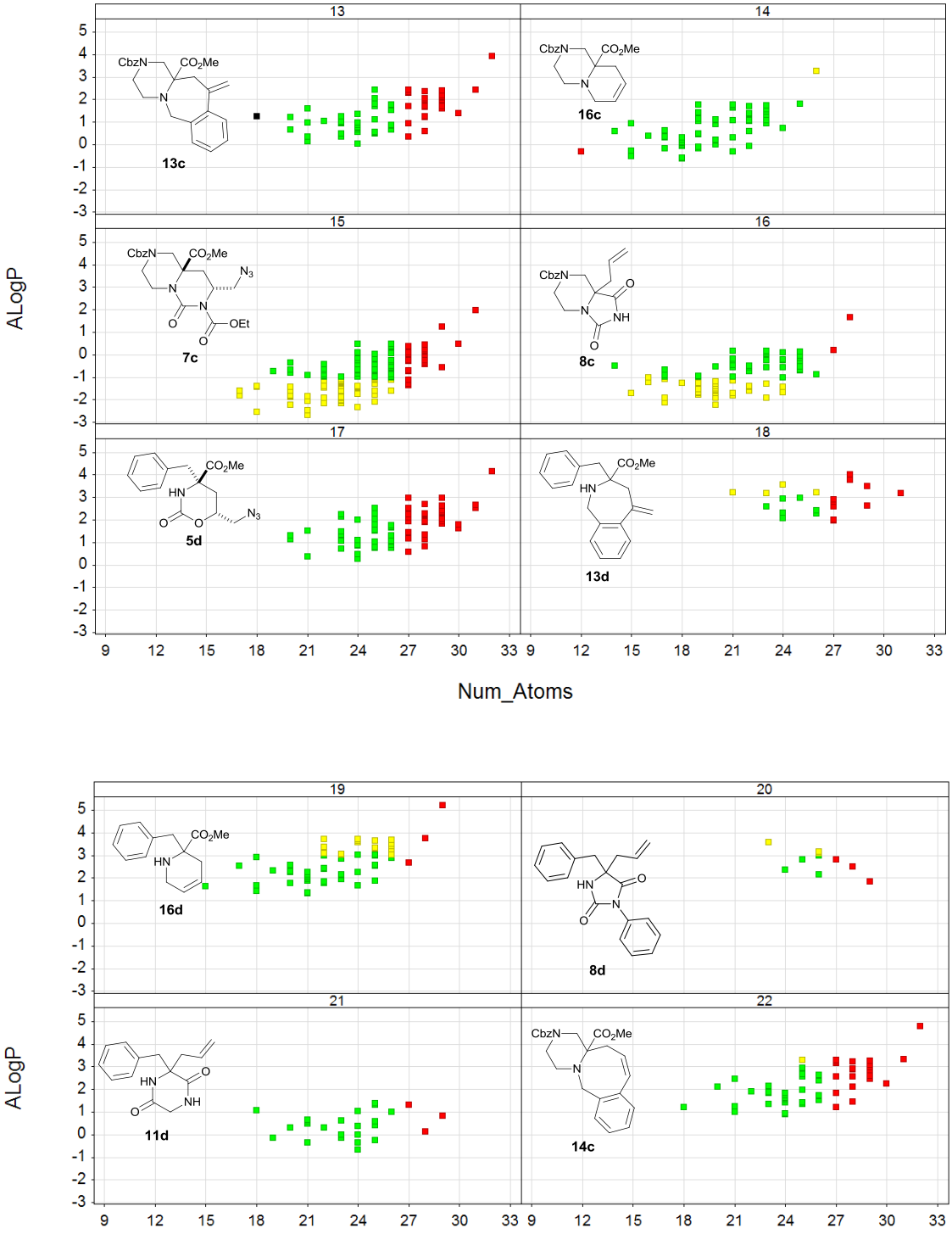


Figure S7. Distribution of number of heavy atoms (Num_Atoms) and AlogP for the virtual library based upon each scaffold. Compounds that survive successive filtering are shown in green. Compounds that fail successive filtering by number of heavy atoms (red), AlogP (yellow) and structural features (black) are shown as appropriate.

5.0 Shape Analysis – Principal Moments of Inertia

3D structures were generated from the 2D Pipeline Pilot output using OpenEye OMEGA (OMEGA 2.4.3, OpenEye Scientific Software, 2010) and the lowest energy conformer was selected.[4] The 3D structures were used to generate the three Principal Moments of Inertia (I_1, I_2 and I_3) using Accelrys Pipeline Pilot (Pipeline Pilot v8.5.0.200, Accelrys© Software Inc., 2011) which were then normalised by dividing the two lower values by the largest (I_1/I_3 and I_2/I_3). These Normalised PMI plots generate a triangular plot with the corners defined by a perfect sphere, a perfect disk and a perfect rod shape.[5] We thank George Burslem for carrying out the PMI analysis.

6.0 Scaffold Diversity Assessment

The hierarchical framework analysis applied the 'scaffold tree' approach described by Schuffenhauer and co-workers.[6] The results are summarized in Figure S8 and the frameworks illustrated in Figure S9. 22 frameworks were represented at the graph-node-bond level, ultimately related to 7 parental frameworks.

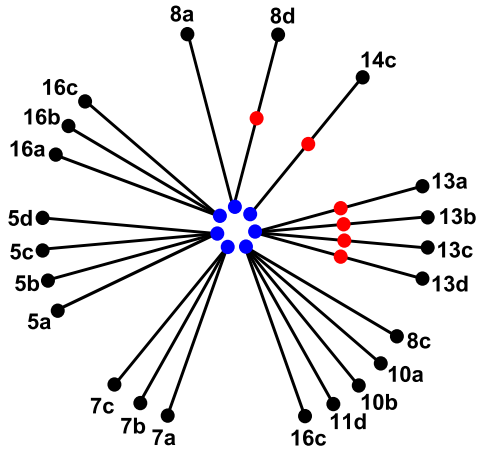


Figure S8. Hierarchical relationship between the 22 distinct molecular frameworks at the graph-node-bond level (black) and the 7 parental frameworks (blue). Daughter frameworks are shown in red.

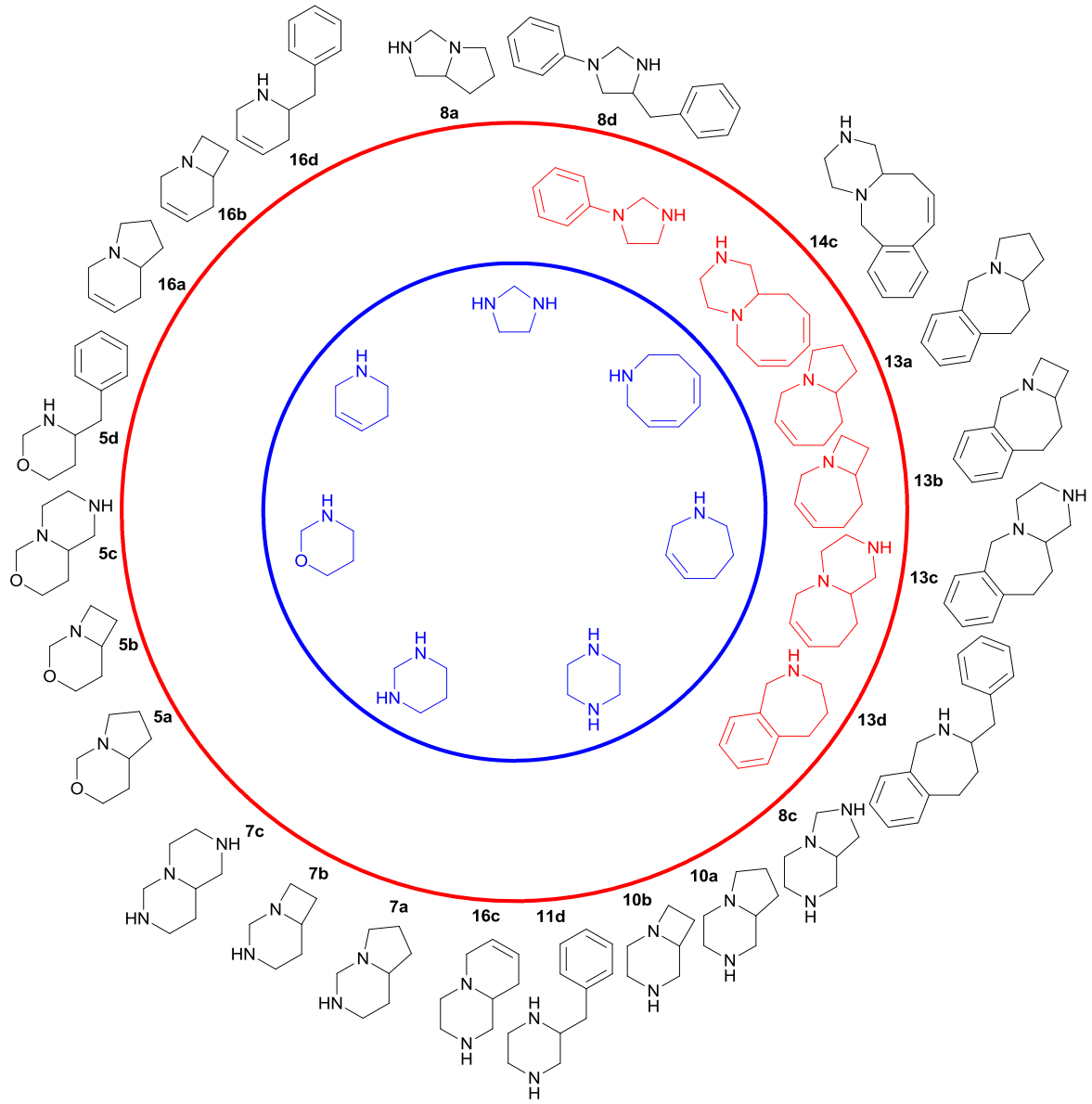


Figure S9. The 22 distinct molecular frameworks at the graph-node-bond level (black) and the 7 parental frameworks (blue). Daughter frameworks are shown in red. The scaffolds which represent each framework are indicated. See Figure S8 for the relationship between scaffolds at each level of hierarchy.

7.0 Experimental

7.1 General experimental

All non-aqueous reactions were performed under an atmosphere of nitrogen unless otherwise stated. Water-sensitive reactions were performed in oven-dried glassware, cooled under nitrogen before use. THF, CH_2Cl_2, PhMe and MeCN were dried and purified by means of a Pure Solv MD solvent purification system (Innovative Technology Inc.). Anhydrous DMF was obtained in a SureSeal bottle from Sigma-Aldrich. All other solvents used were of chromatography or analytical grade. Petrol refers to petroleum spirit (b.p. 40-60 °C). Commercially available starting materials were obtained from Sigma-Aldrich, Fluka, Acros, Alfa-Aesar or Fluorochem and were used without purification.

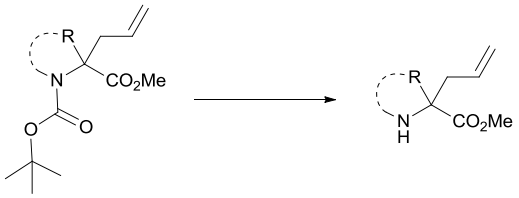
Thin layer chromatography (TLC) was carried out on aluminium backed silica plates (Merck silica gel 60 F254). Visualisation of the plates was achieved using an ultraviolet lamp (λ_{max} = 254 nm) and $KMnO_4$. Flash chromatography was carried out using silica gel 60 (60-63 μm particles) supplied by Merck. Columns with solvent gradients were carried out using a Biotage Flashmaster II on pre-packed Redisep normal-phase silica or cyanosilica cartridges (as specified). Strong cation exchange solid phase extraction (SCX-SPE) was carried out using pre-packed Discovery DSC-SCX cartridges supplied by Supleco, see General procedure **M**.

Optical rotation measurements were carried out at the sodium D-line (589 nm) on a Schmidt and Haensch H532; concentrations are in g/100 mL, temperatures are given in °C, optical rotations are given in deg $dm^{-1}cm^3\ g^{-1}$ (units are omitted). Infrared spectra were recorded on a Perkin-Elmer One FT-IR spectrometer with absorption reported in wavenumbers (cm^{-1}). High resolution mass spectra (HRMS) were recorded on a Bruker Daltonics micrOTOF or Bruker MaXis Impact spectrometer with electrospray ionisation (ESI) source. Where EI ionisation was required, a Waters/Micromass GCT Premier spectrometer was used.

Proton (^1H) and carbon (^{13}C) NMR spectral data were collected on a Bruker Advance 500 or Bruker DPX500 or DPX300 spectrometers. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to the residual solvent peak. Coupling constants (*J*) are quoted in Hertz (Hz) and splitting patterns reported in an abbreviated manner: app. (apparent), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Assignments were made with the aid of COSY, DEPT-135, HMQC, HMBC and NOESY experiments. Compounds are numbered with respect to their IUPAC names. Where necessary, coloured text is used to distinguish similar protons and carbons. Diastereomeric ratios were calculated by analysis of the ^1H NMR spectra and assigned through the interpretation of coupling constants, NOESY spectra, and through crystallographic studies.

7.2 General procedures

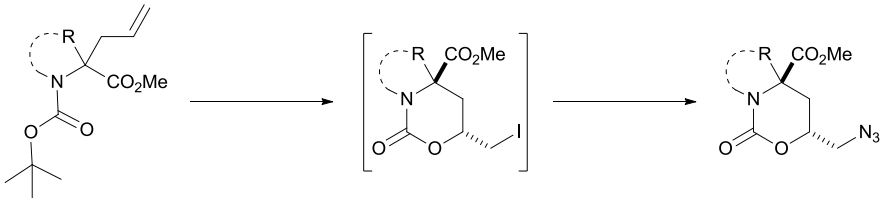
General procedure A: Boc-carbamate deprotection



1 **S2**

Boc-carbamate **1** (1.0 eq.) was diluted in 2:1 CH_2Cl_2–TFA (0.5 M) at 0 °C. The reaction mixture was stirred for 1 h at rt then concentrated *in vacuo*. The compounds **S2** were purified by SCX, according to General procedure **M**.

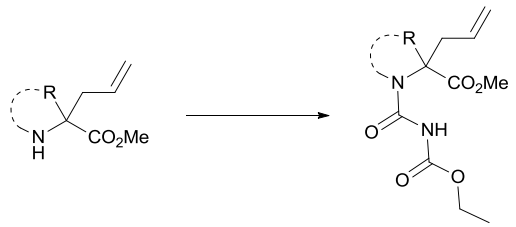
General procedure B: Cyclic carbamate synthesis



1 **5**

Following a procedure by Licini,[7] iodine (3.0 eq.) was added to Boc-carbamate **1** (1.0 eq.) in 1:1 THF–H_2O (0.04 M, 1 volume) and the reaction mixture was stirred for 2-3 h. Sat. aq. $Na_2S_2O_3$ was added until the reaction mixture turned colourless. The reaction mixture was extracted with CH_2Cl_2 (2 × 0.25 volume). The organics were washed with brine (0.5 volume) then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude iodide. The iodide was diluted in DMF (0.1 M, 1 volume) and NaN_3 (2.0 eq.) was added *(CAUTION: azides are potentially explosive and should be handled with care – this reaction should be performed behind a blast shield. NaN_3 is extremely toxic and should be weighed out using a non-metal spatula inside a fumehood)*. The reaction mixture was stirred for 15 h. H_2O was added at 0 °C. The reaction mixture was extracted with EtOAc (3 × 0.25 volume). The organics were washed with brine then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Compounds **5** were purified by flash chromatography.

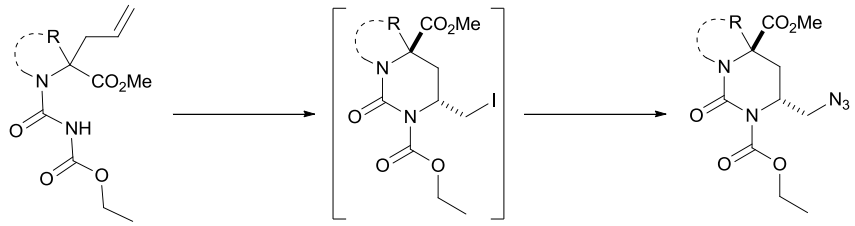
General procedure C: Carbamoyl urea synthesis



S2 **6**

Following a procedure by Taguchi,[8] ethyl isocyanatoformate (1.2 eq.) was added to a stirred solution of amino ester **S2** (1.0 eq.) in CH_2Cl_2 (0.1 M). The reaction mixture was stirred for 0.5 h then concentrated *in vacuo* to give the crude urea **6**.

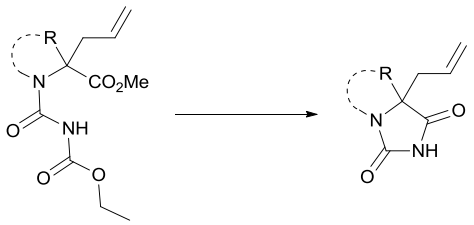
General procedure D: Cyclic urea synthesis



6 **7**

Following a procedure by Taguchi,[8] Li[Al(O^{t}Bu)$_4$] (0.7 M in THF, 1.0 eq., prepared following general procedure **N**) was added to the crude urea **6** in PhMe (0.1 M, 1 volume) at −5 °C. The reaction mixture was stirred for 0.5 h, then iodine (3.0 eq.) was added. The reaction mixture was stirred for 15 h at −5 °C, then quenched with ice-cold sat. aq. $Na_2S_2O_3$ until colourless. The reaction mixture was extracted with ice-cold EtOAc (3 × 0.5 volume). The organics were dried over Na_2SO_4 at 0 °C, filtered, then concentrated *in vacuo* to give the crude iodide. The residue was dissolved in DMF (0.2 M, 1 volume) and NaN_3 (2.0 eq.) was added *(CAUTION: azides are potentially explosive and should be handled with care – this reaction should be performed behind a blast shield. NaN_3 is extremely toxic and should be weighed out using a non-metal spatula inside a fumehood)*. The reaction mixture was stirred for 15 h at rt. H_2O (0.5 volume) was added at 0 °C. The reaction mixture was extracted with EtOAc (3 × 0.25 volume). The organics were washed with brine then dried, filtered, and concentrated *in vacuo*. Compounds **7** were purified by flash chromatography.

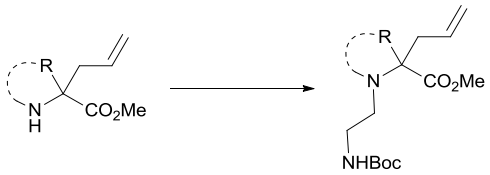
General procedure E: Hydantoin synthesis



6 **8**

NaOMe (25 wt% in MeOH, 1.0 eq.) was added to the crude urea **6** in 85:15 PhMe–MeOH (0.1 M). The reaction mixture was heated at 65 °C for 2 h, then concentrated *in vacuo*. Compounds **8** were purified by SCX eluting with MeOH.

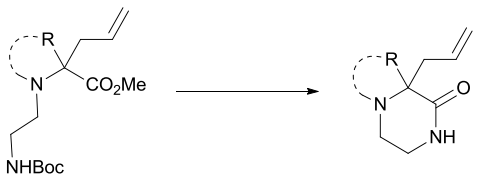
General procedure F: Reductive amination with *N*-Boc glycinal



S2 **9**

A suspension of amino ester **S2** (1.0 eq.), *N*-Boc glycinal (2.0 eq.) and 4 Å MS (50 mg for 2.5 mmol of amine) in CH_2Cl_2 (0.1 M, 1 volume) was stirred for 1 h. $NaBH(OAc)_3$ (2.0 eq.) was added in one portion and the reaction mixture was stirred for 15 h. The reaction mixture was filtered through Celite then concentrated *in vacuo*. The residue was dissolved in EtOAc (0.5 volume) and washed with brine (0.5 volume). The aqueous phase was extracted with EtOAc (2 × 0.25 volume). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Compounds **9** were carried on crude without further purification.

General procedure G: Lactamisation



9 **10**

The crude *N*-Boc glycinated amino ester **9** (1.0 eq.) was deprotected, following general procedure **A**. The residue was diluted in DMF (0.04 M) and Cs_2CO_3 (2.0 eq.) was added. The reaction mixture was heated at reflux for 1 h, then concentrated *in vacuo*. The compounds **10** were purified by flash chromatography or by SCX, according to General procedure **M**.

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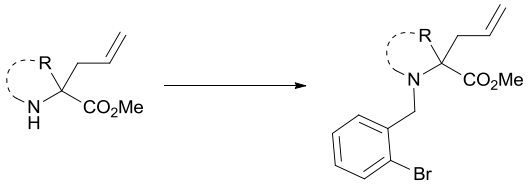
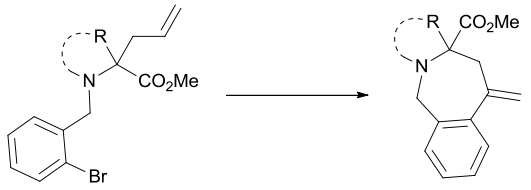
General procedure H: Reductive amination with 2-bromobenzaldehyde



S2 **12**

A suspension of amino ester **S2** (1.0 eq.), 2-bromobenzaldehyde (2.0 eq.) and 4 Å MS (50 mg for 2.5 mmol of amine) in CH_2Cl_2 (0.1 M) was stirred for 1 h. $NaBH(OAc)_3$ (2.0 eq.) was added in one portion and the reaction mixture was stirred for 15 h. The reaction mixture was filtered through Celite then concentrated *in vacuo*. The residue was dissolved in EtOAc (0.5 volume) and washed with brine (0.5 volume). The aqueous phase was extracted with EtOAc (2 × 0.25 volume). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Compounds **12** were purified by flash chromatography or by SCX, according to General procedure **M**.

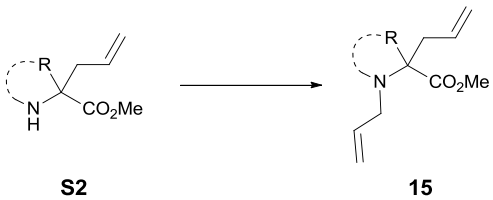
General procedure I: Intramolecular Heck reaction



12 **13**

Et_3N (2.5 eq.) was added to a stirred solution of amino ester **12** (1.0 eq.) and $Pd(PPh_3)_4$ (5 mol%) in MeCN (0.1 M). The mixture was heated at 125 °C under microwave irradiation for 1 h, then filtered through Celite and concentrated *in vacuo*. Compounds **13** were purified by flash chromatography.

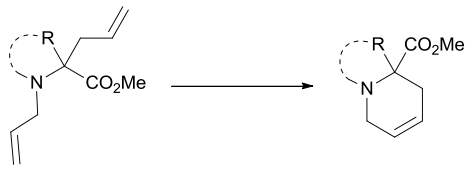
General procedure J: *N*-Allylation of amines



S2 **15**

Allyl bromide (3.0 eq.) and K_2CO_3 (1.1 eq.) were added to a stirred solution of amino ester **S2** (1.0 eq.) in DMF (0.2 M, 1 volume) and the reaction mixture was stirred for 15 h. The reaction mixture was diluted with H_2O (0.5 volume) and extracted with EtOAc (3 × 0.25 volume). The organics were washed with brine (0.5 volume) then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The compounds **15** were purified by SCX, according to General procedure **M**.

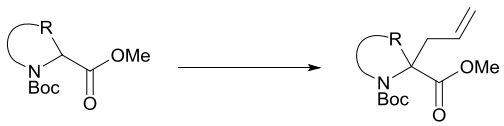
General procedure K: Ring-closing metathesis



15 **16**

Following a procedure by Gracias *et al.*,[9] *p*-TsOH (2.0 eq.) was added to a stirred solution of *N*-allyl amino ester **15** (1.0 eq.) in CH_2Cl_2 or PhMe as specified (0.03 M, 1 volume). The reaction mixture was heated at reflux for 0.5 h then cooled to rt. GII (2.5-7.5 mol%) was added, the mixture was heated at reflux and monitored by NMR until complete consumption of the starting material was observed. The reaction mixture was cooled to rt. Sat. aq. $NaHCO_3$ solution (0.25 volume) was added. The reaction mixture was extracted with CH_2Cl_2 (for reactions performed in CH_2Cl_2, 2 × 0.25 volume) or EtOAc (for reactions performed in PhMe, 2 × 0.25 volume). The organic phase was washed with brine, dried over Na_2SO_4, filtered, then concentrated *in vacuo*. Compounds **16** were purified by flash chromatography or by SCX, according to General procedure **M**.

General procedure L: Allylation of Boc-protected amino esters



S1 **1**

LiHMDS (1.0 M in THF, 1.1 eq.) was added dropwise to a stirred solution of Boc-protected amino ester **S1** (1.0 eq.) in THF (0.45 M, 1 volume) at −78 °C. The reaction mixture was stirred for 15 min, then allyl bromide (1.5 eq.) was added dropwise. The reaction mixture was stirred for 1 h, the dry-ice bath was removed and the reaction mixture was warmed to rt and stirred for 15 h. Sat. aq. NH_4Cl solution (0.1 volume) was added, then the reaction mixture was partitioned between EtOAc (1 volume) and brine (1 volume). The aqueous layer was extracted with EtOAc (2 × 1 volume). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Compounds **1** were purified by flash chromatography.

General procedure M: SCX purification

TfOH (0.5 M in MeOH, 10 mL / 5 g SPE-SCX) was dripped through the SPE-SCX cartridge prior to use. MeOH (20 mL) was then flushed through using pressurised air (bellows). The crude residue was loaded (3.5 mmol / 5 g SPE-SCX silica) in the minimum amount of MeOH. The cartridge was flushed with MeOH and the fractions were collected and monitored by TLC. The cartridge was then

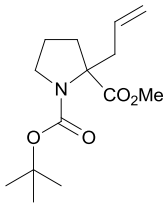
flushed with sat. NH_3/MeOH and the fractions were collected and monitored by TLC. Fractions containing product were combined and concentrated.

General procedure N: Preparation of a Li[Al(O^{t}Bu)$_4$] solution in THF

t-BuOH (4.0 eq.) was added dropwise to $LiAlH_4$ in THF (1.0 M solution) at 0 °C (*CAUTION: gas evolution*). The reaction mixture was stirred for 0.5 h warming to rt and was considered to constitute a 0.7 M solution of Li[Al(O^{t}Bu)$_4$].

7.3 Experimental data

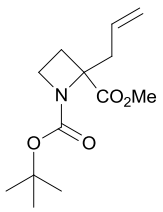
1-*tert*-Butyl 2-methyl 2-(prop-2-en-1-yl)pyrrolidine-1,2-dicarboxylate 1a



1a

General procedure **L** was followed using Boc-protected amino ester **S1a** (2.50 g, 10.9 mmol). Flash chromatography eluting with pentane–EtOAc (5:1) gave the title compound **1a** (2.4 g, 8.8 mmol, 81%) as a colourless oil. **R_f** 0.35 (4:1 petrol–EtOAc). **^{1}H NMR** (300 MHz, $CDCl_3$, 1:2 mixture of rotamers): δ 5.89-5.64 (1H, m, C*H*=CH_2), 5.22-5.05 (2H, m, CH=CH_2), 3.76-3.54 (4H, includes 1H, m, 5-H_A and at δ 3.72: 3H, s, CO_2CH_3), 3.50-3.28 (1H, m, 5-H_B), 3.11 (0.33H, dd, *J* 14.1, 6.5, C$H_A$$H_B$CH=$CH_2$), 2.92 (0.67H, dd, *J* 14.1, 6.5, C$H_A$$H_B$CH=$CH_2$), 2.61 (1H, dd, *J* 14.1, 8.1, C$H_A$$H_B$CH=$CH_2$), 2.20-1.96 (2H, m, 3-H), 1.96-1.72 (2H, m, 4-H), 1.46 (3H, s, C(CH_3)$_3$), 1.43 (6H, s, C(CH_3)$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$, mixture of two rotamers): δ 175.4 (major and minor, CO_2CH_3), 154.2 (minor, N(CO)O), 153.8 (major, N(CO)O), 134.0 (minor, CH=CH_2), 133.6 (major, CH=CH_2), 119.3 (major, CH=CH_2), 119.0 (minor, CH=CH_2), 79.8 (C_q(CH_3)$_3$, major and minor), 67.8 (minor, 2-C), 67.2 (major, 2-C), 52.5 (minor, CO_2CH_3), 52.4 (major, CO_2CH_3), 48.8 (minor, 5-C), 48.7 (major, 5-C), 39.9 (major, CH_2CH=CH_2), 38.6 (minor, CH_2CH=CH_2), 37.3 (major, 3-C, major), 36.0 (minor, 3-C), 28.7 (minor, C(CH_3)$_3$), 28.6 (major, C(CH_3)$_3$), 23.4 (minor, 4-C), 22.9 (major, 4-C). **IR** ν_{max}(film)/cm^{-1} 2977, 2878, 1742 (CO), 1698 (CO), 1392, 1253, 1162, 1022. **HRMS** (ESI): $C_{14}H_{23}NNaO_4$ [M+Na]$^+$; calculated 292.1525, found 292.1519. Spectra consistent with the literature values.[10,11]

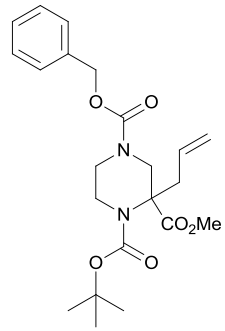
1-*tert*-Butyl 2-methyl 2-(prop-2-en-1-yl)azetidine-1,2-dicarboxylate 1b



1b

General procedure **L** was followed using 1-*tert*-butyl 2-methyl azetidine-1,2-dicarboxylate* (2.4 g, 11 mmol). The residue was washed through a pad of silica with EtOAc to give the *title compound* **1b** (2.26 g, 8.85 mmol, 80%) as a yellow oil. $\mathbf{R_f}$ 0.07 (91:9 pentane–EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$, 1:2 mixture of rotamers): δ 5.97-5.84 (1H, m, C*H*=CH_2), 5.23-5.16 (2H, m, CH=C*H*$_2$), 4.00-3.86 (1H, m, 4-H_A), 3.77 (3H, s, CO_2CH_3), 3.69 (1H, m, 4-H_B), 2.96-2.86 (0.33H, m, C*H*$_A$H$_B$CH=CH_2), 2.76 (0.67H, m, dd, *J* 14.2, 6.0, C*H*$_A$H$_B$CH=CH_2), 2.60 (1H, dd, *J* 14.2, 8.1, CH$_A$*H*$_B$CH=CH_2), 2.29-2.21 (1H, m, 3-H_A), 2.19-2.11 (1H, m, 3-H_B), 1.40 (9H, s, C(CH_3)$_3$). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.1 (*C*O_2CH_3), 155.1 (N(CO)O), 132.6 (*C*H=CH_2), 119.6 (CH=*C*H$_2$), 80.0 (*C*$_q$(CH_3)$_3$), 70.3 (2-C), 52.4 (CO_2*C*H_3), 44.9 (4-C), 38.8 (C_q*C*H_2CH=CH_2), 28.4 (C(*C*H_3)$_3$), 24.3 (3-C). **IR** ν_{max}(film)/cm^{-1} 2977, 2895, 1739 (CO), 1713 (CO), 1392, 1257, 1157, 1112. **HRMS** (ESI): $C_{13}H_{22}NO_4$ [M+H]$^+$; calculated 256.1543, found 256.1541.

4-Benzyl 1-*tert*-butyl 2-methyl 2-(prop-2-en-1-yl)piperazine-1,2,4-tricarboxylate 1c

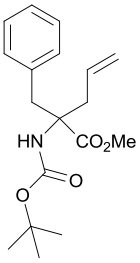


1c

General procedure **L** was followed using Boc-protected amino ester **S1c** (3.5 g, 9.2 mmol). The residue was washed through a pad of silica with EtOAc to give the *title compound* **1c** (3.7 g, 8.8 mmol, 96%) was isolated as a yellow oil. **^{1}H NMR** (500 MHz, *d*^{6}-DMSO, 340 K): δ 7.41-7.28 (5H, m, Cbz Ar-H), 5.85-5.71 (1H, m, C*H*=CH_2), 5.17-5.02 (4H, m, CH=C*H*$_2$ and OC*H*$_2$Ph), 4.01-3.93 (1H, m, NC*H*$_A$H$_B$CH$_2$N), 3.82-3.77 (1H, m, 3-H_A), 3.66-3.58 (1H, m, 3-H_B), 3.56-3.47 (1H, m, NC*H*$_A$H$_B$CH$_2$N), 3.43-3.36 (4H, m, includes NCH$_A$*H*$_B$CH$_2$N and at δ 3.52: 3H, s, CO_2CH_3), 3.35-3.26 (1H, m, NCH$_A$*H*$_B$CH$_2$N), 2.92 (1H, d, *J* 14.5, C*H*$_A$H$_B$CH=CH_2), 2.53-2.44 (1H, m, CH$_A$*H*$_B$CH=CH_2), 1.37 (9H, s, C(CH_3)$_3$). **^{13}C NMR** (125 MHz, *d*^{6}-DMSO, 340 K, one carbamate CO peak not observed): δ 172.0 (*C*O_2CH_3), 153.1 (N(CO)O), 136.5 (Ar-C_q), 132.1 (*C*H=CH_2), 128.0 (Ar-C), 127.5 (Ar-C), 127.2 (Ar-C), 118.9 (CH=*C*H$_2$), 80.0 (*C*$_q$(CH_3)$_3$), 66.0 (CH_2Ph), 63.1 (2-C), 51.6 (CO_2*C*H_3), 45.3 (3-C), 43.2 (NCH_2CH_2N), 38.3 (NCH_2CH_2N or *C*H_2CH=CH_2), 37.6 (NCH_2CH_2N or *C*H_2CH=CH_2), 27.6 (C(*C*H_3)$_3$). **IR** ν_{max}(film)/cm^{-1} 2976, 1746 (CO), 1704 (CO), 1417, 1394, 1366, 1270, 1219. **HRMS** (ESI): $C_{22}H_{31}N_2O_6$ [M+H]$^+$; calculated 419.2177, found 419.2181.

* Purchased from Fluorochem.

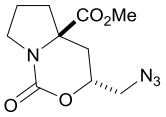
Methyl 2-benzyl-2-[(*tert*-butoxycarbonyl)amino]pent-4-enoate 1d



1d

To a stirred solution of amino ester **S2d** (322 mg, 1.47 mmol, 1.00 eq.) in THF (10 mL) was added Boc_2O (321 mg, 1.47 mmol, 1.00 eq.) and the reaction mixture was heated at reflux for 15 h. The reaction mixture was concentrated *in vacuo*, diluted with EtOAc (50 mL), washed with H_2O (50 mL) then brine (50 mL). The organic phase was dried over $MgSO_4$, filtered, then concentrated *in vacuo* to give the title compound **1d** (470 mg, 1.47 mmol, 99%) as a yellow oil. $\mathbf{R_f}$ 0.35 (4:1 pentane–EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.27-7.19 (3H, m, Ar-H), 7.07-7.04 (2H, m, Ar-H), 5.70-5.59 (1H, m, C*H*=CH_2), 5.33 (1H, br. s, NH), 5.14-5.06 (2H, m, CH=C*H*$_2$), 3.75 (3H, s, CO_2CH_3), 3.61 (1H, d, *J* 13.6, C*H*$_A$H$_B$Ph), 3.21 (1H, dd, *J* 13.7, 7.1, C*H*$_A$H$_B$CH=CH_2), 3.12 (1H, d, *J* 13.6, CH$_A$*H*$_B$Ph), 2.59 (1H, dd, *J* 13.7, 7.4, CH$_A$*H*$_B$CH=CH_2), 1.47 (9H, s, C(CH_3)$_3$). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.2 (*C*O_2CH_3), 154.2 (NH(*C*O)O), 136.6 (Ar-C_q), 132.6 (*C*H=CH_2), 130.0 (Ar-C), 128.3 (Ar-C), 127.0 (Ar-C), 119.1 (CH=*C*H_2), 79.4 (*C*$_q$(CH_3)$_3$), 65.1 (C_q), 52.6 (CO_2*C*H_3), 40.9 (*C*H_2Ph), 40.1 (*C*H_2CH=CH_2), 28.6 (C(*C*H_3)$_3$). **IR** ν_{max}(film)/cm^{-1} 3430, 2978, 1739 (CO), 1714 (CO), 1495, 1447, 1348, 1232. **HRMS** (ESI): $C_{18}H_{25}NNaO_4$ $[M+Na]^+$; calculated 342.1681, found 342.1676. Spectra consistent with the literature values.[12]

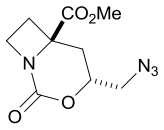
Methyl (*3R*,4aR)-3-(azidomethyl)-1-oxo-hexahydro-1H-pyrrolo[1,2-c][1,3]oxazine-4a-carboxylate 5a**



5a, *dr* 95:5

General procedure **B** was followed using Boc-carbamate **1a** (200 mg, 0.740 mmol). Flash chromatography eluting with 0-100% EtOAc in pentane gave the *title compound* **5a** (99 mg, 0.39 mmol, 53%, 95:5 mixture of diastereomers) as a yellow oil. $\mathbf{R_f}$ 0.05 (1:1 petrol–EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.30-4.21 (1H, m, 3-H), 3.79 (3H, s, CO_2CH_3), 3.77-3.71 (1H, m, 7-H$_A$), 3.67-3.61 (1H, m, 7-H$_B$), 3.57 (1H, dd, *J* 13.0, 4.6, C*H*$_A$H$_B$N$_3$), 3.46 (1H, dd, *J* 13.0, 4.5, HCH$_A$*H*$_B$N$_3$), 2.63 (1H, dd, *J* 13.5, 2.6, 4-H$_A$), 2.55-2.43 (1H, m, 5-H$_A$), 2.07-1.96 (1H, m, 6-H$_A$), 1.90-1.79 (2H, m, 5-H$_B$ and 6-H$_B$), 1.74 (1H, dd, *J* 13.5, 12.3, 4-H$_B$). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.5 (*C*O_2CH_3), 151.5 (1-C), 74.1 (3-C), 67.1 (4a-C), 54.1 (CH_2N_3), 53.6 (CO_2*C*H_3), 47.4 (7-C), 38.5 (5-C), 33.9 (4-C), 21.7 (6-C). **IR** ν_{max}(film)/cm^{-1} 2955, 2898, 2106 (N_3), 1738 (CO), 1416, 1302, 1210, 1171. **HRMS** (ESI): $C_{10}H_{15}N_4O_4$ $[M+H]^+$; calculated 255.1093, found 255.1088. **X-Ray Crystallography**: CCDC 1008922 contains the supplementary crystallographic data for this compound. Crystals were grown by slow diffusion of Et_2O into the sample dissolved in the minimum amount of $CHCl_3$.

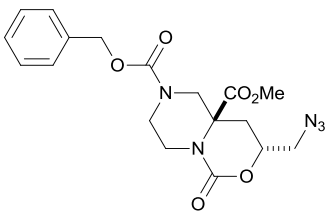
Methyl (*4R,*6R**)-4-(azidomethyl)-2-oxo-3-oxa-1-azabicyclo[4.2.0]octane-6-carboxylate 5b**



5b, *dr* >99:1

Following a procedure by Licini,[7] NIS (160 mg, 0.710 mmol, 1.20 eq.) was added to a stirred solution of Boc-carbamate **1b** (150 mg, 0.560 mmol, 1.00 eq.) in $CHCl_3$ (6.0 mL). The reaction mixture was stirred for 4 days and monitored by TLC until complete. The reaction mixture was concentrated *in vacuo*, extracted with EtOAc (25 mL) and washed with sat. aq. $Na_2S_2O_3$ until colourless. The aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organics were dried over Na_2SO_4, filtered, then concentrated *in vacuo* to give the crude iodide. The iodide was dissolved in DMF (6.0 mL). NaN_3 (114 mg, 1.76 mmol, 3.0 eq.) was added and the reaction mixture was stirred for 48 h. H_2O (25 mL) was added at 0 °C. The reaction mixture was extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried over Na_2SO_4, filtered, then concentrated *in vacuo*. Flash chromatography eluting with 0-100% EtOAc in pentane gave co-elution of the title compound with succinimide. Trituration of the residue with Et_2O gave the *title compound* **5b** (53 mg, 0.22 mmol, 37%) as a colourless solid. **R_f** 0.09 (4:1 pentane–EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.44-4.37 (1H, m, 4-H), 4.33-4.25 (1H, m, 8-H_A), 4.15 (1H, td, *J* 9.6, 4.8, 8-H_B), 3.87 (3H, s, CO_2CH_3), 3.56 (1H, dd, *J* 13.1, 4.5, C*H*$_A$H$_B$N$_3$), 3.45 (1H, dd, *J* 13.1, 4.5, CH$_A$*H*$_B$N$_3$), 2.72-2.58 (2H, m, 7-H), 2.48 (1H, dd, *J* 13.5, 2.2, 5-H_A), 2.02 (1H, dd, *J* 13.5, 11.9, 5-H_B). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.3 (*C*O_2CH$_3$), 154.0 (2-C), 75.9 (4-C), 69.3 (6-C), 53.9 (CH_2N_3), 53.4 (CO_2*C*H$_3$), 50.3 (8-C), 33.3 (7-C), 31.6 (5-C). **IR** ν_{max}(film)/cm^{-1} 2959, 2107 (N_3), 1713 (CO), 1392, 1293, 1208, 1155, 762. **HRMS** (ESI): $C_9H_{13}N_4O_4$ $[M+H]^+$; calculated 241.0931, found 241.0930.

2-Benzyl 9a-methyl (*8R,*9aS**)-8-(azidomethyl)-6-oxo-octahydropiperazino[1,2-c][1,3]oxazine-2,9a-dicarboxylate 5c**

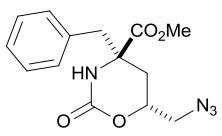


5c, dr 93:7

General procedure **B** was followed using Boc-carbamate **1c** (314 mg, 0.750 mmol). Flash chromatography eluting with 0-100% EtOAc in pentane gave the *title compound* **5c** (195 mg, 0.480 mmol, 64%, 93:7 mixture of diastereomers) as a brown oil. **R_f** 0.04 (4:1 petrol–EtOAc). **^{1}H NMR** (500 MHz, *d*^{6}-DMSO, 319 K): δ 7.42-7.29 (5H, m, Cbz Ar-H), 5.12 (1H, d, *J* 12.7, C*H*$_A$H$_B$Ph), 5.08 (1H, d, *J* 12.7, CH$_A$*H*$_B$Ph), 4.55 (1H, dd, *J* 13.4, 1.7, 1-H_A), 4.34-4.28 (1H, m, 8-H), 4.13-4.07 (1H, m, NC*H*$_A$H$_B$CH$_2$N), 4.03-3.97 (1H, m, NC*H*$_A$H$_B$CH$_2$N), 3.66 (3H, s, CO_2CH_3), 3.61 (1H, dd, *J* 13.5, 3.2, C*H*$_A$H$_B$N$_3$), 3.44 (1H, dd, *J* 13.5, 5.3, CH$_A$*H*$_B$N$_3$), 3.01 (1H, d, *J* 13.4, 1-H_B), 2.98-2.86 (2H, m, NCH$_A$*H*$_B$CH$_2$N and NCH$_A$*H*$_B$CH$_2$N), 2.26 (1H, dd, *J* 14.0, 2.6, 9-H_A), 2.02 (1H, dd, *J* 14.0, 12.4, 9-H_B). **^{13}C NMR** (125 MHz, *d*^{6}-DMSO, 319 K): δ 170.8 (*C*O_2CH$_3$), 153.7 (N(CO)O), 151.0 (N(CO)O), 136.4 (Ar-C_q), 128.2 (Ar-C), 127.7 (Ar-C), 127.3

(Ar-C), 71.8 (8-C), 66.4 (*C*H_2Ph), 61.6 (9a-C), 53.0 (CO_2*C*H_3), 52.8 (CH_2N_3), 49.9 (1-C), 42.4 (N*C*$H_2$$CH_2$N), 41.0 (N*C*$H_2$$CH_2$N), 30.8 (9-C). **IR** ν_{max}(film)/cm^{-1} 2953, 2107 (N_3), 1741 (CO), 1701 (CO), 1432, 1421, 1280, 1230. **HRMS** (ESI): $C_{18}H_{22}N_5O_6$ [M+H]$^+$; calculated 404.1565, found 404.1580.

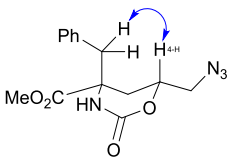
Methyl (*4R,*6R**)-6-(azidomethyl)-4-benzyl-2-oxo-1,3-oxazinane-4-carboxylate 5d**



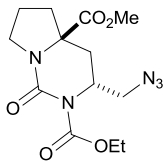
5d, *dr* 87:13

General procedure **B** was followed using Boc-carbamate **1d** (100 mg, 0.310 mmol). The residue was washed through a pad of silica with EtOAc–MeOH (9:1) to give the *title compound* **5d** (84 mg, 0.28 mmol, 88%, 87:13 mixture of diastereomers) as a yellow oil. **R$_f$** 0.08 (3:2 petrol–EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$, *dr* 87:13, diastereomers were assigned by NOESY, major diastereomer peaks assigned): δ 7.37-7.30 (3H, m, Ar-H), 7.13-7.07 (2H, m, Ar-H), 5.42 (1H, br. s, NH), 4.29-4.22 (1H, m, 6-H), 3.73 (3H, s, CO_2CH_3), 3.55 (1H, dd, *J* 13.2, 4.4, C*H*$_A$H$_B$N$_3$), 3.45 (1H, dd, *J* 13.2, 4.7, CH$_A$*H*$_B$N$_3$), 3.31 (1H, d, *J* 13.4, C*H*$_A$H$_B$Ph), 2.90 (1H, d, *J* 13.4, CH$_A$*H*$_B$Ph), 2.51 (1H, app. dt, *J* 13.9, 2.0, 5-H$_A$), 1.94 (1H, dd, *J* 13.9, 12.2, 5-H$_B$). Minor diastereomer characteristic peaks: 5.55 (1H, br. s, NH), 4.43-4.37 (1H, m, 6-H), 3.74 (3H, s, CO_2CH_3), 3.58-3.47 (2H, m, C*H*$_2$N$_3$), 3.14 (1H, d, *J* 13.3, C*H*$_A$H$_B$Ph), 3.04 (1H, d, *J* 13.3, CH$_A$*H*$_B$Ph), 2.30 (1H, ddd, *J* 14.3, 2.5, 1.3, 5-H$_A$), 2.14 (1H, dd, *J* 14.3, 11.6, 5-H$_B$). **^{13}C NMR** (125 MHz, $CDCl_3$, peaks of major diastereomer assigned): δ 172.6 (*C*O_2CH_3), 151.9 (2-C), 133.0 (Ar-C$_q$), 129.9 (Ar-C), 129.3 (Ar-C), 128.3 (Ar-C), 73.6 (6-C), 61.9 (4-C), 53.7 (*C*H_2N_3), 53.2 (CO_2*C*H_3), 46.2 (*C*H_2Ph), 33.0 (5-C). **IR** ν_{max}(film)/cm^{-1} 3247, 2927, 2105 (N_3), 1713 (CO), 1435, 1403, 1284, 1214. **HRMS** (ESI): $C_{14}H_{16}N_4NaO_4$ [M+Na]$^+$; calculated 327.1064, found 327.1076. The relative configuration of the minor diastereomer was determined by interpretation of the NOESY correlations.

5d, minor diastereomer
NOESY correlations:



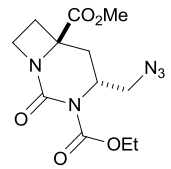
2-Ethyl 4a-methyl (*3R,*4aR**)-3-(azidomethyl)-1-oxo-octahydropyrrolo[1,2-c]pyrimidine-2,4a-dicarboxylate 7a**



7a, *dr* >99:1

General procedures **C** and **D** were followed using amino ester **S2a** (1.1 g, 6.7 mmol). Flash chromatography on cyanosilica eluting with a gradient of 0-100% EtOAc in pentane gave the *title compound* **7a** (1.17 g, 3.60 mmol, 54%) as a colourless oil. $\mathbf{R_f}$ 0.11 (1:1 pentane–EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.34-4.20 (3H, m, C*H*$_2$CH$_3$ and 3-H), 3.75-3.67 (5H, includes 2H, m, 7-H and at δ 3.72: 3H, s, CO_2CH_3), 3.65 (1H, dd, *J* 12.3, 5.6, C*H*$_A$H$_B$N$_3$), 3.50 (1H, dd, *J* 12.3, 2.9, CH$_A$*H*$_B$N$_3$), 2.89 (1H, dd, *J* 13.2, 8.5, 4-H$_A$), 2.37-2.30 (1H, m, 5-H$_A$), 2.06-1.92 (3H, m, 5-H$_B$ and 6-H), 1.83 (1H, dd, *J* 13.2, 9.7, 4-H$_B$), 1.31 (3H, t, *J* 7.1, CH$_2$C*H*$_3$). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.1 (*C*O$_2$CH$_3$), 154.3 (CO), 150.4 (CO), 65.8 (4a-C), 63.1 (O*C*H$_2$CH$_3$), 54.5 (*C*H$_2$N$_3$), 53.1 (CO$_2$*C*H$_3$), 52.5 (3-C), 46.7 (7-C), 38.1 (5-C), 37.6 (4-C), 22.8 (6-C), 14.5 (OCH$_2$*C*H$_3$). **IR** ν_{max}(film)/cm^{-1} 3597, 3507, 2981, 2106 (N$_3$), 1708 (CO), 1420, 1296, 1018. **HRMS** (ESI): $C_{13}H_{20}N_5O_5$ $[M+H]^+$; calculated 326.1459, found 326.1462.

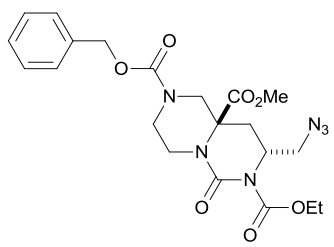
3-Ethyl 6-methyl (*4R,*6R**)-4-(azidomethyl)-2-oxo-1,3-diazabicyclo[4.2.0]octane-3,6-dicarboxylate 7b**



7b, *dr* 97:3

General procedures **C** and **D** were followed using amino ester **S2b** (150 mg, 0.970 mmol, 1.00 eq.). Flash chromatography eluting with a gradient of 0-100% EtOAc in pentane gave the *title compound* **7b** (98 mg, 0.31 mmol, 32%, 97:3 mixture of diastereomers) as a pale yellow oil. $\mathbf{R_f}$ 0.17 (1:1 pentane–EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.32-4.19 (3H, m, C*H*$_2$CH$_3$ and 4-H), 4.16 (1H, td, *J* 9.4, 6.8, 8-H$_A$), 4.05 (1H, td, *J* 9.4, 5.7, 8-H$_B$), 3.82-3.76 (4H, m, includes 1H, m, C*H*$_A$H$_B$N$_3$ and at δ 3.80: 3H, s, CO_2CH_3), 3.53 (1H, dd, *J* 12.4, 2.5, CH$_A$*H*$_B$N$_3$), 2.75-2.68 (1H, m, 7-H$_A$), 2.63 (1H, dd, *J* 13.6, 6.5, 5-H$_A$), 2.42-2.34 (1H, m, 7-H$_B$), 2.25 (1H, dd, *J* 13.6, 11.7, 5-H$_B$), 1.31 (3H, t, *J* 7.1, CH$_2$C*H*$_3$). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 171.4 (*C*O$_2$CH$_3$), 153.8 (CO), 153.3 (CO), 68.5 (6-C), 63.2 (O*C*H$_2$CH$_3$), 55.1 (4-C), 54.0 (*C*H$_2$N$_3$), 53.2 (CO$_2$*C*H$_3$), 47.2 (8-C), 35.9 (5-C), 28.8 (7-C), 14.4 (OCH$_2$*C*H$_3$). **IR** ν_{max}(film)/cm^{-1} 2978, 2108 (N$_3$), 1712 (CO), 1390, 1372, 1289, 1245, 1033. **HRMS** (ESI): $C_{12}H_{18}N_5O_5$ $[M+H]^+$; calculated 312.1303, found 312.1307.

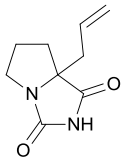
2-Benzyl 7-ethyl 9a-methyl (*8R,*9aS**)-8-(azidomethyl)-6-oxo-octahydro-1H-pyrimido[1,6-a]piperazine-2,7,9a-tricarboxylate 7c**



7c, *dr* >99:1

General procedures **C** and **D** were followed using amino ester **S2c** (150 mg, 0.470 mmol, 1.00 eq.). Flash chromatography eluting with a gradient of 0-100% EtOAc in pentane gave the *title compound* **7c** (98 mg, 0.21 mmol, 44%) as a pale yellow oil. $\mathbf{R_f}$ 0.15 (1:1 pentane–EtOAc). **^{1}H NMR** (500 MHz, *d*^{6}-DMSO, 348 K): δ 7.40-7.30 (5H, m, Cbz Ar-H), 5.11 (2H, s, C*H*$_2$Ph), 4.33-4.26 (1H, m, 8-H), 4.22 (1H, d, *J* 13.8, 1-H$_A$), 4.17 (2H, q, *J* 7.1, C*H*$_2$CH$_3$), 3.91-3.79 (2H, m, NC*H*$_A$H$_B$CH$_2$N and NC*H*$_A$H$_B$CH$_2$N), 3.62-3.57 (4H, m, includes 1H, m, C*H*$_A$H$_B$N$_3$ and at δ 3.59: 3H, s, CO$_2$CH$_3$), 3.49 (1H, dd, *J* 12.7, 5.5, CH$_A$*H*$_B$N$_3$), 3.35 (1H, d, *J* 13.8, 1-H$_B$), 3.35 (1H, d, *J* 13.9, NCH$_A$*H*$_B$CH$_2$N) 3.33-3.25 (1H, m, NCH$_A$*H*$_B$CH$_2$N), 2.57 (1H, dd, *J* 14.1, 8.5, 9-H$_A$), 1.96 (1H, dd, *J* 14.1, 6.7, 9-H$_B$), 1.22 (3H, t, *J* 7.1, CH$_2$C*H*$_3$). **^{13}C NMR** (125 MHz, *d*^{6}-DMSO, 348 K): δ 171.1 (*C*O$_2$CH$_3$), 154.0 (CO), 153.0 (CO), 151.1 (CO), 136.3 (Ar-C$_q$), 128.0 (Ar-C), 127.5 (Ar-C), 127.1 (Ar-C), 66.2 (*C*H$_2$Ph), 61.9 (O*C*H$_2$CH$_3$), 60.9 (9a-C), 53.0 (*C*H$_2$N$_3$), 52.4 (CO$_2$*C*H$_3$), 50.1 (8-C), 48.0 (1-C), 42.4 (NCH$_2$CH$_2$N), 38.6 (NCH$_2$CH$_2$N), 33.5 (9-C), 13.6 (OCH$_2$*C*H$_3$). **IR** ν_{max}(film)/cm^{-1} 2106 (N$_3$), 1740 (CO), 1705 (CO), 1416, 1290, 1226, 1145, 769. **HRMS** (ESI): C$_{21}$H$_{27}$N$_6$O$_7$ [M+H]$^+$; calculated 475.1936, found 475.1950.

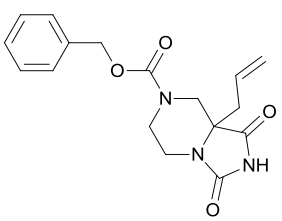
7a-(Prop-2-en-1-yl)-hexahydro-1H-pyrrolo[1,2-c]imidazolidine-1,3-dione 8a



8a

General procedures **C** and **E** were followed using amino ester **S2a** (200 mg, 1.18 mmol). Purification by SCX, eluting with MeOH, gave the *title compound* **8a** (200 mg, 1.11 mmol, 94%) as a colourless oil. **^{1}H NMR** (500 MHz, CDCl$_3$): δ 8.14 (1H, br. s, NH), 5.81-5.71 (1H, m, C*H*=CH$_2$), 5.22-5.15 (2H, m, CH=C*H*$_2$), 3.83-3.75 (1H, m, 5-H$_A$), 3.21-3.14 (1H, m, 5-H$_B$), 2.58 (1H, dd, *J* 14.0, 7.7, C*H*$_A$H$_B$CH=CH$_2$), 2.41 (1H, dd, *J* 14.0, 6.8, CH$_A$*H*$_B$CH=CH$_2$), 2.17-2.03 (2H, m, 6-H), 2.02-1.89 (2H, m, 7-H). **^{13}C NMR** (125 MHz, CDCl$_3$): δ 176.3 (1-C), 159.5 (3-C), 131.0 (*C*H=CH$_2$), 120.6 (CH=*C*H$_2$), 73.8 (7a-C), 44.9 (5-C), 39.6 (*C*H$_2$CH=CH$_2$), 32.2 (7-C), 26.3 (6-C). **IR** ν_{max}(film)/cm^{-1} 3210, 3074, 2978, 1771 (CO), 1715 (CO), 1391, 1332, 1208. **HRMS** (EI): C$_9$H$_{12}$N$_2$O$_2$ [M]$^+$; calculated 180.0899, found 180.0897.

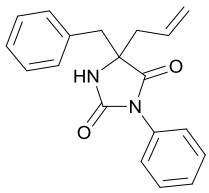
Benzyl 1,3-dioxo-8a-(prop-2-en-1-yl)-octahydroimidazolidino[1,5-a]piperazine-7-carboxylate 8c



8c

General procedures **C** and **E** were followed using amino ester **S2c** (141 mg, 0.440 mmol). Purification by SCX, eluting with MeOH, gave the *title compound* **8c** (139 mg, 0.420 mmol, 96%). **^{1}H NMR** (500 MHz, *d*^{6}-DMSO, 319 K): δ 10.98 (1H, s, NH), 7.42-7.28 (5H, m, Cbz Ar-H), 5.57-5.44 (1H, m, C*H*=CH$_2$), 5.18-5.03 (4H, m, CH=C*H*$_2$ and C*H*$_2$Ph), 4.02-3.91 (1H, m, NC*H*$_A$H$_B$CH$_2$N), 3.93 (1H, d, *J* 13.1, 8-H$_A$), 3.83 (1H, dd, *J* 13.2, 3.0, NC*H*$_A$H$_B$CH$_2$N), 3.19-3.01 (1H, m, 8-H$_B$), 2.98-2.92 (2H, m, NCH$_A$*H*$_B$CH$_2$N and NCH$_A$*H*$_B$CH$_2$N), 2.56 (1H, dd, *J* 14.3, 7.3, C*H*$_A$H$_B$CH=CH$_2$), 2.34 (1H, dd, *J* 14.3, 6.9, CH$_A$*H*$_B$CH=CH$_2$). **^{13}C NMR** (125 MHz, *d*^{6}-DMSO, 319 K, one C$_q$ peak not observed): δ 174.1 (1-C), 154.4 (CO), 136.4 (Ar-C$_q$), 130.4 (*C*H=CH$_2$), 128.2 (Ar-C), 127.8 (Ar-C), 127.5 (Ar-C), 119.7 (CH=*C*H$_2$), 66.7 (*C*H$_2$Ph), 62.8 (8a-C), 47.5 (8-C), 42.8 (NCH$_2$CH$_2$N), 35.8 (NCH$_2$CH$_2$N), 34.0 (*C*H$_2$CH=CH$_2$). **IR** ν$_{max}$(film)/cm^{-1} 3199, 1772 (CO), 1708 (CO), 1455, 1428, 1353, 1267, 1244. **HRMS** (ESI): C$_{17}$H$_{20}$N$_3$O$_4$ [M+H]$^+$; calculated 330.1448, found 330.1449.

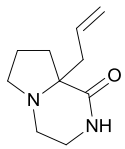
5-Benzyl-3-phenyl-5-(prop-2-en-1-yl)imidazolidine-2,4-dione 8d



8d

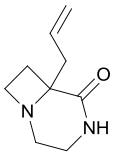
To a solution of urea **S3d** (47 mg, 0.14 mmol, 1.0 eq.) in PhMe (1.5 mL) was added NaO*t*Bu (14 mg, 0.14 mmol, 1.0 eq.) and the reaction mixture was heated at 100 °C for 15 h. The reaction mixture was cooled to rt then concentrated *in vacuo*. Flash chromatography eluting with 0-100% EtOAc in pentane gave the *title compound* **8d** (36 mg, 0.12 mmol, 85%) as a colourless oil. **^{1}H NMR** (500 MHz, CDCl$_3$): δ 7.41-7.36 (2H, m, Ar-H), 7.35-7.29 (4H, m, Ar-H), 7.24-7.18 (2H, m, Ar-H), 6.99-6.94 (2H, m, Ar-H), 6.30 (1H, s, NH), 5.94-5.84 (1H, m, C*H*=CH$_2$), 5.31-5.21 (2H, m, CH=C*H*$_2$), 3.21 (1H, d, *J* 13.6, C*H*$_A$H$_B$Ph), 2.96 (1H, d, *J* 13.6, CH$_A$*H*$_B$Ph), 2.75 (1H, dd, *J* 13.9, 7.7, C*H*$_A$H$_B$CH=CH$_2$), 2.56 (1H, dd, *J* 13.9, 7.1, CH$_A$*H*$_B$CH=CH$_2$). **^{13}C NMR** (125 MHz, CDCl$_3$): δ 174.2 (4-C), 155.9 (2-C), 134.1 (Ar-C$_q$), 131.4 (Ar-C$_q$), 130.4 (2 × C; *C*H=CH$_2$ and Ar-C); 129.2 (Ar-C), 128.7 (Ar-C), 128.5 (Ar-C), 127.7 (Ar-C), 126.5 (Ar-C), 121.4 (CH=*C*H$_2$), 66.0 (5-C), 42.9 (*C*H$_2$Ph), 41.1 (*C*H$_2$CH=CH$_2$). **IR** ν$_{max}$(film)/cm^{-1} 3290, 1778, 1715 (CO), 1502, 1414, 1123, 919, 703. **HRMS** (ESI): C$_{19}$H$_{19}$N$_2$O$_2$ [M+H]$^+$; calculated 307.1441, found 307.142

8a-(Prop-2-en-1-yl)-octahydropyrrolo[1,2-a]piperazin-1-one 10a


10a

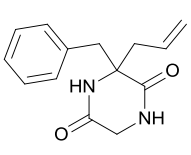
General procedures **F** and **G** were followed using amino ester **1a** (400 mg, 2.36 mmol). The residue was purified by SCX, eluting first with MeOH then sat. NH_3/MeOH, to give the *title compound* **10a** (270 mg, 1.50 mmol, 62%) as a brown oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.95-5.84 (1H, m, C*H*=CH_2), 5.76 (1H, br. s, NH), 5.16-5.07 (2H, m, CH=C*H*$_2$), 3.72-3.62 (1H, m, 3-H_A), 3.32-3.18 (2H, m, 3-H_B and 4-H_A), 3.09-3.02 (1H, m, 6-H_A), 2.96-2.82 (2H, m, 4-H_B and 6-H_B), 2.62 (1H, dd, *J* 13.9, 6.6, C*H*$_A$H$_B$CH=CH_2), 2.43 (1H, dd, *J* 13.9, 7.9, CH$_A$*H*$_B$CH=CH_2), 2.20-2.12 (1H, m, 8-H_A), 2.01-1.93 (1H, m, 8-H_B), 1.83-1.69 (2H, m, 7-H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 176.3 (1-C), 134.4 (*C*H=CH_2), 117.8 (CH=*C*H$_2$), 68.4 (8a-C), 51.9 (6-C), 43.4 (4-C), 42.6 (*C*H$_2$CH=CH_2), 38.5 (3-C), 34.9 (8-C), 22.8 (7-C). **IR** ν_{max}(film)/cm^{-1} 3218, 3074, 2944, 1655 (CO), 1487, 1447, 915, 753. **HRMS** (ESI): $C_{10}H_{17}N_2O$ $[M+H]^+$; calculated 181.1341, found 181.1335.

6-(Prop-2-en-1-yl)-1,4-diazabicyclo[4.2.0]octan-5-one 10b


10b

General procedures **F** and **G** were followed using the TFA salt of the amino ester **S2b** (404 mg, 1.50 mmol). Flash chromatography on eluting with a gradient of 0-100% EtOAc in pentane containing 1% Et_3N gave the *title compound* **10b** (54 mg, 0.32 mmol, 22%) as a pale yellow oil. **R_f** 0.19 (1:1 petrol–EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.97 (1H, br. s, NH), 5.83-5.72 (1H, m, C*H*=CH_2), 5.29-5.19 (2H, m, CH=C*H*$_2$), 4.39-4.32 (1H, m, 8-H_A), 4.28-4.20 (1H, m, 8-H_B), 3.47-3.34 (2H, m, 3-H), 2.94-2.86 (1H, m, 2-H_A), 2.77-2.70 (1H, m, 2-H_B), 2.52 (1H, dd, *J* 14.0, 7.2, C*H*$_A$H$_B$CH=CH_2), 2.38 (1H, dd, *J* 14.0, 7.5, CH$_A$*H*$_B$CH=CH_2), 2.29-2.19 (2H, m, 7-H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 178.4 (5-C), 131.1 (*C*H=CH_2), 121.0 (CH=*C*H$_2$), 65.0 (8-C), 61.8 (6-C), 41.6 (2-C), 40.1 (2 × C; 3-C and *C*H$_2$CH=CH_2), 32.1 (7-C). **IR** ν_{max}(film)/cm^{-1} 3325 (NH), 2982, 1763 (CO), 1719, 1560, 1183, 1024, 927. **HRMS** (EI): $C_9H_{14}N_2O$ $[M]^+$; calculated 166.1106, found 166.1133.

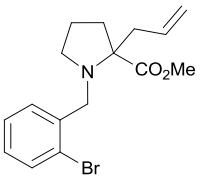
3-Benzyl-3-(prop-2-en-1-yl)piperazine-2,5-dione 11d


11d

General procedure **G** was followed using amide **S4d** (50 mg, 0.13 mmol, 1.0 eq.). Flash chromatography eluting with a gradient of 0-10% MeOH in CH_2Cl_2 gave the *title compound* **11d** (30 mg, 0.12 mmol, 93%) as a colourless solid. **R_f** 0.33 (5:95 CH_2Cl_2–MeOH).**^{1}H NMR** (500 MHz, CD_3OD, 2 × NH not observed): δ 7.34-7.30 (3H, m, Ar-H), 7.27-7.22 (2H, m, Ar-H), 5.85-5.75 (1H, m, C*H*=CH_2), 5.28-5.18 (2H, m, CH=C*H*$_2$), 3.46 (1H, d, *J* 17.9, 6-H_A), 3.27 (1H, d, *J* 13.3, C*H*$_A$H$_B$Ph), 2.95 (1H, dd, *J* 13.8, 6.6, C*H*$_A$H$_B$CH=CH_2), 2.80 (1H, d, *J* 13.3, CH$_A$*H*$_B$Ph), 2.62 (1H, d, *J* 17.9, 6-H_B), 2.43 (1H, dd, *J* 13.8, 7.8, CH$_A$*H*$_B$CH=CH_2).

^{13}C NMR (125 MHz, CD_3OD): δ 170.8 (CO), 168.8 (CO), 136.5 (*C*H=CH_2), 133.1 (Ar-C_q), 131.8 (Ar-C), 129.4 (Ar-C), 128.4 (Ar-C), 120.4 (CH=*C*H_2), 65.4 (3-C), 47.4 (6-C), 44.9 (*C*H_2Ph), 44.6 (*C*H_2CH=CH_2). **IR** ν_{max}(film)/cm^{-1} 3192, 3071, 2917, 2332, 1673 (CO), 1451, 1316, 1108. **HRMS** (ESI): $C_{14}H_{16}N_2NaO_2$ $[M+Na]^+$; calculated 267.1104, found 267.1092.

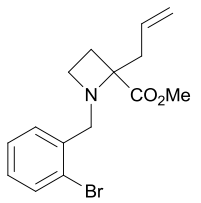
Methyl 1-[(2-bromophenyl)methyl]-2-(prop-2-en-1-yl)pyrrolidine-2-carboxylate 12a



12a

General procedure **H** was followed using amino ester **S2a** (250 mg, 1.48 mmol). The residue was purified by SCX cartridge, eluting first with MeOH then sat. NH_3/MeOH, to give the *title compound* (392 mg, 1.16 mmol, 78%) as a colourless oil. **R_f** 0.26 (4:1 pentane–EtOAc). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.52 (1H, dd, *J* 7.9, 1.1, Ar-H), 7.47 (1H, dd, *J* 7.6, 1.1, Ar-H), 7.31-7.23 (1H, m, Ar-H), 7.09 (1H, td, *J* 7.6, 1.6, Ar-H), 5.96-5.78 (1H, C*H*=CH_2), 5.14-5.06 (2H, CH=CH_2), 3.98 (1H, d, *J* 15.0, C$H_A$$H_B$Ar), 3.76 (3H, s, CO_2CH_3), 3.67 (1H, d, *J* 15.0, CH_AH_BAr), 2.97 (1H, td, *J* 8.5, 3.5, 5-H_A), 2.77-2.58 (2H, m, 5-H_B and *CH*$_A$$H_B$CH=$CH_2$), 2.46 (1H, dd, *J* 14.1, 6.6, *C*$H_A$$H_B$CH=$CH_2$), 2.24-2.16 (1H, m, 3-$H_A$), 1.95-1.82 (2H, m, 3-$H_B$ and 4-H_A), 1.81-1.72 (1H, m, 4-H_B). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 174.9 (*C*O_2CH_3), 139.1 (Ar-C_q), 134.4 (*C*H=CH_2), 132.7 (Ar-C), 130.2 (Ar-C), 128.2 (Ar-C), 127.3 (Ar-C), 124.0 (Ar-C_q-Br), 118.1 (CH=*C*H_2), 70.7 (2-C), 53.2 (*C*H_2Ar), 51.9 (5-C), 51.4 (CO_2*C*H_3), 39.7 (*C*H_2CH=CH_2), 34.0 (3-C), 22.0 (4-C). **IR** ν_{max}(film)/cm^{-1} 2949, 1727 (CO), 1439, 1219, 1193, 1171, 1025, 916. **HRMS** (ESI): $C_{16}H_{21}{}^{79}BrNO_2$ $[M+H]^+$; calculated 338.0756, found 338.0750.

Methyl 1-[(2-bromophenyl)methyl]-2-(prop-2-en-1-yl)azetidine-2-carboxylate 12b

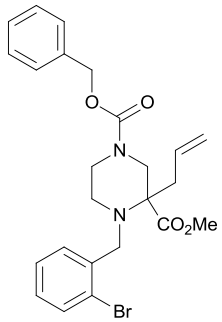


12b

Method 1: General procedure **H** was followed using amino ester **S2b** (175 mg, 1.13 mmol). The residue was purified by SCX cartridge, eluting first with MeOH then sat. NH_3/MeOH, to give the *title compound* **12b** (246 mg, 0.759 mmol, 67%) as a colourless oil. **Method 2:** To a stirred solution of the TFA salt of the amino ester **S2b** (404 mg, 1.50 mmol, 1.00 eq.) in DMF (7.5 mL) was added 2-bromobenzyl bromide (0.01 M in THF, 0.45 mL, 0.45 mmol, 3.00 eq.) and K_2CO_3 (456 mg, 3.30 mmol, 2.20 eq.) and the reaction mixture was heated at 60 °C for 15 h. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (2 × 20 mL). The combined organics were washed with brine (20 mL) then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by SCX cartridge, eluting first with MeOH then sat. NH_3/MeOH, gave the *title compound* **12b** (358 mg, 1.10 mmol, 74%) as a colourless oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.51 (1H, dd, *J* 8.0, 1.2, Ar-H), 7.43 (1H, dd, *J* 7.7, 1.2, Ar-H), 7.28-7.24 (1H, m, Ar-H), 7.08 (1H, td, *J* 7.7, 1.7, Ar-H), 5.84-5.74 (1H, m, C*H*=CH_2), 5.17-5.07 (2H, m, CH=CH_2), 3.86-3.76 (5H, m includes 2H, dd, *J* 14.3, CH_2Ar and at δ 3.77: 3H, s, CO_2CH_3),

3.31-3.25 (1H, m, 4-H_A), 3.25-3.19 (1H, m, 4-H_B), 2.71 (1H, dd, *J* 13.7, 7.3, C*H*$_A$H$_B$CH=CH$_2$), 2.65 (1H, dd, *J* 13.7, 6.9, CH$_A$*H*$_B$CH=CH$_2$), 2.58-2.51 (1H, m, 3-H_A), 2.15-2.07 (1H, m, 3-H_B). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.7 (*C*O$_2$CH$_3$), 138.0 (Ar-C$_q$), 132.9 (Ar-C or *C*H=CH$_2$), 132.8 (Ar-C or *C*H=CH$_2$), 130.3 (Ar-C), 128.4 (Ar-C), 127.4 (Ar-C), 124.2 (Ar-C$_q$-Br), 118.6 (CH=*C*H$_2$), 72.0 (2-C), 55.6 (*C*H$_2$Ar), 51.7 (CO$_2$*C*H$_3$), 50.3 (4-C), 38.9 (*C*H$_2$CH=CH$_2$), 25.9 (3-C). **IR** ν_{max}(film)/cm^{-1} 2950, 2843, 1728 (CO), 1440, 1214, 1146, 1025, 751. **HRMS** (ESI): C$_{15}$H$_{19}$^{79}BrNO$_2$ [M+H]$^+$; calculated 324.0594, found 324.0598.

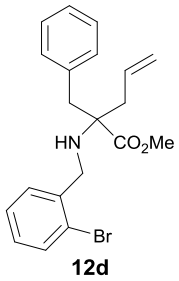
1-Benzyl 3-methyl 4-[(2-bromophenyl)methyl]-3-(prop-2-en-1-yl)piperazine-1,3-dicarboxylate 12c



12c

To a stirred solution amino ester **S2c** (225 mg, 0.71 mmol, 1.00 eq.) in DMF (3.6 mL) was added 2-bromobenzyl bromide (10.4 M in THF, 200 μL, 2.13 mmol, 3.00 eq.) and K_2CO_3 (108 mg, 0.780 mmol, 1.10 eq.). The reaction mixture was heated at 60 °C for 24 h, then diluted with H_2O (20 mL) and extracted with EtOAc (2 × 20 mL). The combined organics were washed with brine (20 mL) then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by SCX cartridge, eluting first with MeOH then sat. NH_3/MeOH, gave the *title compound* **12c** (288 mg, 0.591 mmol, 83%) as an orange oil. **^{1}H NMR** (500 MHz, *d*^{6}-DMSO, 319 K): δ 7.61 (1H, d, *J* 7.0, Ar-H), 7.57 (1H, dd, *J* 7.9, 0.9, Ar-H), 7.42-7.29 (6H, m, Ar-H), 7.19 (1H, td, *J* 7.9, 1.5, Ar-H), 5.82-5.71 (1H, m, C*H*=CH$_2$), 5.14-5.01 (4H, m, CH=C*H*$_2$ and OC*H*$_2$Ph), 4.27 (1H, d, *J* 13.4, 2-H_A), 4.12 (1H, d, *J* 16.6, NC*H*$_A$H$_B$Ar), 3.84 (1H, d, *J* 12.9, NC*H*$_A$H$_B$CH$_2$N), 3.79 (1H, d, *J* 16.6, NCH$_A$*H*$_B$Ar), 3.59 (3H, s, CO$_2$CH$_3$), 3.09 (1H, d, *J* 13.4, 2-H_B), 3.05-2.95 (1H, m, NCH$_A$*H*$_B$CH$_2$N), 2.71 (1H, td, *J* 11.8, 3.5, NC*H*$_A$H$_B$CH$_2$N), 2.65-2.53 (2H, m, C*H*$_2$CH=CH$_2$), 2.53-2.46 (1H, m, NCH$_A$*H*$_B$CH$_2$N). **^{13}C NMR** (125 MHz, *d*^{6}-DMSO, 319 K): δ 172.5 (*C*O$_2$CH$_3$), 154.0 (N(CO)O), 138.1 (Ar-C$_q$), 136.8 (Ar-C$_q$), 132.3 (Ar-C or *C*H=CH$_2$), 132.2 (Ar-C or *C*H=CH$_2$), 129.2 (Ar-C), 128.3 (Ar-C), 128.2 (Ar-C), 127.6 (Ar-C), 127.5 (Ar-C), 127.2 (Ar-C), 122.9 (Ar-C$_q$-Br), 118.7 (CH=*C*H$_2$), 66.0 (O*C*H$_2$Ph), 64.5 (3-C), 53.3 (N*C*H$_2$Ar), 51.2 (CO$_2$*C*H$_3$), 49.6 (2-C), 46.6 (NCH$_2$CH$_2$N), 43.2 (NCH$_2$CH$_2$N), 38.0 (*C*H$_2$CH=CH$_2$). **IR** ν_{max}(film)/cm^{-1} 2950, 1732 (CO), 1704, 1456, 1435, 1284, 1228, 1212. **HRMS** (ESI): C$_{24}$H$_{28}$^{79}BrN$_2$O$_4$ [M+H]$^+$; calculated 487.1227, found 487.1233.

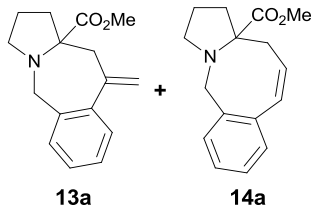
Methyl 2-benzyl-2-[(2-bromobenzyl)amino]pent-4-enoate 12d



12d

General procedure **H** was followed using amino ester **S2d** (268 mg, 1.22 mmol) with two changes; the reaction was performed in THF at 45 °C. After heating for 3 days, additional $NaBH(OAc)_3$ (518 mg, 2.44 mmol, 2.0 eq.) was added and the reaction mixture was stirred for 3 h. Flash chromatography eluting with a gradient of 0-20% EtOAc in hexane gave the *title compound* **12d** (327 mg, 0.842 mmol, 69%) as a colourless oil. $\mathbf{R_f}$ 0.68 (4:1 petrol–EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.53 (1H, dd, *J* 8.0, 1.2, Ar-H), 7.47 (1H, d, *J* 7.5, Ar-H), 7.26 (4H, m, Ar-H), 7.16 (2H, d, *J* 6.9, Ar-H), 7.11 (1H, td, *J* 7.7, 1.6, Ar-H), 6.00-5.88 (1H, m, C*H*=CH_2), 5.23-5.13 (2H, m, CH=C*H*$_2$), 3.89-3.79 (2H, m, NHC*H*$_2$Ar), 3.67 (3H, s, CO_2CH_3), 3.09 (1H, d, *J* 13.7, C*H*$_A$H$_B$Ph), 3.01 (1H, d, *J* 13.7, CH$_A$*H*$_B$Ph), 2.65 (1H, dd, *J* 14.8, 6.1, C*H*$_A$H$_B$CH=CH_2), 2.52 (1H, dd, *J* 14.8, 7.6, CH$_A$*H*$_B$CH=CH_2). **^{13}C NMR** (125 MHz, $CDCl_3$, one Ar-C peak not observed): δ 175.3 (*C*O_2CH_3), 139.5 (Ar-C_q), 136.4 (Ar-C_q), 133.3 (Ar-C), 132.8 (*C*H=CH_2), 130.3 (Ar-C), 128.7 (Ar-C), 128.3 (Ar-C), 127.7 (Ar-C), 127.0 (Ar-C), 124.0 (Ar-C_q-Br), 118.8 (CH=*C*H_2), 66.2 (C_q), 51.8 (CO_2*C*H_3), 47.3 (NH*C*H_2Ar), 42.3 (*C*H_2Ph), 38.1 (*C*H_2CH=CH_2). **IR** ν_{max}(film)/cm^{-1} 2949, 1732 (CO), 1465, 1439, 1213, 1197, 1206, 750. **HRMS** (ESI): $C_{20}H_{23}{}^{79}BrNO_2$ $[M+H]^+$; calculated 388.0907, found 388.0913.

Methyl 9-methylidene-3-azatricyclo[8.4.0.0^{3,7}]tetradeca-1(10),11,13-triene-7-carboxylate 13a and methyl (9*Z*)-3-azatricyclo[9.4.0.0^{3,7}]pentadeca-1(11),9,12,14-tetraene-7-carboxylate 14a



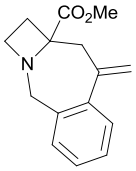
13a **14a**

92:8 mixture **13a**:**14a**

General procedure **I** was followed using amino ester **12a** (105 mg, 0.310 mmol, 1.0 eq.). Flash chromatography eluting with pentane–EtOAc (4:1) gave the *title compound* (43 mg, 0.17 mmol, 54%, 92:8 mixture of **13a**:**14b**) as a yellow oil. $\mathbf{R_f}$ 0.21 (4:1 petrol–EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$, peaks for **13a**): δ 7.37-7.30 (1H, m, Ar-H), 7.25-7.18 (2H, m, Ar-H), 7.17-7.11 (1H, m, Ar-H), 5.33 (1H, d, *J* 1.6, C=C*H*$_A$H$_B$), 5.12 (1H, s, C=CH$_A$*H*$_B$), 4.54 (1H, d, *J* 16.0, 2-H$_A$), 3.89 (1H, d, *J* 16.0, 2-H$_B$), 3.73 (3H, s, CO_2CH_3), 3.13 (1H, d, *J* 13.6, 8-H$_A$), 3.05 (1H, td, *J* 8.4, 2.4, 4-H$_A$), 2.76 (1H, app. q, *J* 8.4, 4-H$_B$), 2.58 (1H, d, *J* 13.6, 8-H$_B$), 2.26-2.16 (1H, m, 6-H$_A$), 2.10-2.00 (1H, m, 6-H$_B$), 1.95-1.83 (1H, m, 5-H$_A$), 1.81-1.69 (1H, m, 5-H$_B$). Characteristic peaks for **14a**: 6.79 (1H, d, *J* 10.6, 10-H), 5.94-5.87 (1H, m, 9-H), 4.09 (1H, d, *J* 14.8, 2-H$_A$), 4.02 (1H, d, *J* 14.8, 2-H$_B$), 3.77 (3H, s, CO_2CH_3), 2.74-2.67 (1H, m), 2.46 (1H, dd, *J* 13.4, 7.5, 8-H$_A$), 2.37-2.30 (1H, m). **^{13}C NMR** (125 MHz, $CDCl_3$, peaks for **13a** assigned): δ 175.7 (*C*O_2CH_3), 145.5 (9-C), 141.3 (Ar-C_q), 136.8 (Ar-C_q), 129.3 (Ar-C), 127.5 (Ar-C), 127.4 (Ar-C), 127.2 (Ar-C), 116.9 (C=*C*H_2), 69.9 (7-C), 52.9 (2-C), 52.0 (CO_2*C*H_3), 50.7 (4-C), 41.8 (8-C), 36.1 (6-C), 22.3 (5-C). **IR** ν_{max}(film)/cm^{-1}

2949, 2902, 1727 (CO), 1433, 1256, 1209, 1157, 1111. **HRMS** (EI): $C_{16}H_{19}N_2O$ $[M]^+$; calculated 257.1409, found 257.1416.

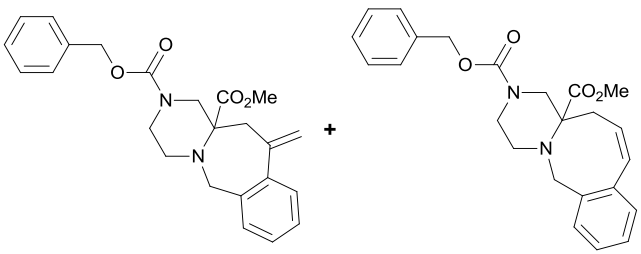
Methyl 8-methylidene-3-azatricyclo[7.4.0.0^{3,6}]trideca-1(9),10,12-triene-6-carboxylate 13b



13b

General procedure **I** was followed using amino ester **12b** (163 mg, 0.500 mmol). After heating at 125 °C under microwave irradiation for 2 h, additional $Pd(PPh_3)_4$ (29 mg, 25 μmol, 5.0 mol%) was added and the reaction mixture heated for a further 2 h. Flash chromatography eluting with a gradient of 0-100% EtOAc in pentane (containing 1% Et_3N) gave the *title compound* **13b** (35 mg, 0.14 mmol, 29%) as a yellow oil. **R_f** 0.07 (4:1 petrol–EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.49-7.43 (1H, m, Ar-H), 7.30-7.18 (2H, m, Ar-H), 7.15-7.10 (1H, m, Ar-H), 5.50 (1H, s, C=CH_AH$_B$), 5.23 (1H, d, *J* 1.0, C=CH$_A$$H_B$), 4.22 (1H, d, *J* 15.2, 2-H$_A$), 3.89 (1H, d, *J* 15.2, 2-H$_B$), 3.60 (3H, s, CO_2CH_3), 3.35-3.28 (1H, m, 4-H$_A$), 3.25-3.15 (2H, m, 4-H$_B$ and 7-H$_A$), 3.06 (1H, d, *J* 15.1, 7-H$_B$), 2.65-2.55 (1H, m, 5-H$_A$), 2.29-2.26 (1H, m, 5-H$_B$). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 175.5 (*C*O_2CH_3), 144.7 (8-C), 139.8 (Ar-C_q), 135.8 (Ar-C_q), 129.8 (Ar-C), 128.2 (Ar-C), 127.8 (Ar-C), 127.6 (Ar-C), 117.2 (C=*C*H_2), 69.2 (6-C), 54.9 (2-C), 52.2 (CO_2*C*H_3), 46.6 (4-C), 39.6 (7-C), 26.7 (5-C). **IR** ν_{max}(film)/cm^{-1} 2921, 1736 (CO), 1484, 1435, 1257, 1235, 1104, 775. **HRMS** (ESI): $C_{15}H_{18}NO_2$ $[M+H]^+$; calculated 244.1332, found 244.1335.

13-Benzyl 11-methyl 9-methylidene-1,13-diazatricyclo[9.4.0.0^{3,8}]pentadeca-3(8),4,6-triene-11,13-dicarboxylate 13c and 14-benzyl 12-methyl (9*Z*)-1,14-diazatricyclo[10.4.0.0^{3,8}]hexadeca-3(8),4,6,9-tetraene-12,14-dicarboxylate 14c



13c **14c**

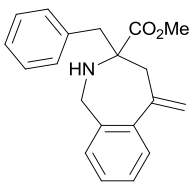
General procedure **I** was followed using amino ester **12c** (280 mg, 0.570 mmol, 1.00 eq.). Flash chromatography eluting with a gradient of 0-100% EtOAc in pentane gave the separable *title compounds* **13c** (74 mg, 0.18 mmol, 32%) and **14c** (72 mg, 0.18 mmol, 31%) as pale yellow oils.[*]

13-Benzyl 11-methyl 9-methylidene-1,13-diazatricyclo[9.4.0.0^{3,8}]pentadeca-3(8),4,6-triene-11,13-dicarboxylate 13c: **R_f** 0.11 (4:1 petrol–EtOAc). **^{1}H NMR** (500 MHz, *d*^{6}-DMSO, 319 K): δ 7.42-7.29 (6H, m, Ar-H), 7.21-7.14 (2H, m, Ar-H), 7.13-7.08 (1H, m, Ar-H), 5.40 (1H, s, C=CH_AH$_B$), 5.12 (1H, s, C=CH$_A$$H_B$), 5.12-5.03 (2H, m, OC$H_2$Ph), 4.49 (1H, d, *J* 17.0, 2-H$_A$), 4.22 (1H, d, *J* 12.8, 12-H$_A$), 3.79 (1H, d, *J* 12.8, NCH_AH$_B$CH$_2$N), 3.64 (1H, d, *J* 17.0, 2-H$_B$), 3.58 (3H, s, CO_2CH_3),

[*] Analysis of the crude product by 500 MHz NMR spectroscopy showed 100% conversion to a 42:58 mixture of **13c**:**14c**.

3.28-3.18 (1H, m, NC$H_A$$H_B$$CH_2$N), 3.15 (1H, d, *J* 12.8, 12-H_B), 2.90 (1H, br. s, NC$H_A$$H_B$$CH_2$N), 2.78 (1H, d, *J* 13.8, 10-H_A), 2.69 (1H, d, *J* 11.4, NC$H_A$$H_B$$CH_2$N), 2.63 (1H, d, *J* 13.8, 10-H_B). **^{13}C NMR** (125 MHz, *d*^{6}-DMSO, 319 K): δ 172.7 (*C*$O_2$$CH_3$), 154.2 (N(CO)O), 143.9 (9-C), 139.4 (Ar-C_q), 139.1 (Ar-C_q), 136.7 (Ar-C_q), 128.2 (Ar-C), 127.6 (Ar-C), 127.5 (Ar-C), 127.3 (Ar-C), 127.0 (Ar-C), 126.8 (Ar-C), 126.2 (Ar-C), 115.9 (C=*C*H_2), 66.1 (O*C*H_2Ph), 64.8 (11-C), 56.6 (2-C), 51.2 (CO_2*C*H_3), 49.0 (12-C), 48.8 (NC$H_2$$CH_2$N), 43.4 (N*C*$H_2$$CH_2$N), 41.2 (10-C). **IR** ν_{max}(film)/cm^{-1} 2946, 1732 (CO), 1702, 1461, 1432, 1277, 1223, 1128. **HRMS** (ESI): $C_{24}H_{27}N_2O_4$ [M+H]$^+$; calculated 407.1965, found 407.1975. **14-Benzyl 12-methyl (9*Z*)-1,14-diazatricyclo[10.4.0.0^{3,8}]hexadeca-3(8),4,6,9-tetraene-12,14-dicarboxylate 14c**: **R_f** 0.21 (4:1 petrol–EtOAc). **^{1}H NMR** (500 MHz, *d*^{6}-DMSO, 319 K): δ 7.45 (1H, d, *J* 7.0, Ar-H), 7.40-7.30 (5H, m, Ar-H), 7.29-7.22 (2H, m, Ar-H), 7.16 (1H, d, *J* 7.1, Ar-H), 6.78 (1H, d, *J* 10.7, 9-H), 5.78 (1H, app. q, *J* 9.1, 10-H), 5.13-5.00 (2H, m, O*C*H_2Ph), 4.23 (1H, d, *J* 13.0, 13-H_A), 3.93-3.81 (2H, m, NC$H_A$$H_B$$CH_2$N and 2-$H_A$), 3.65-3.51 (4H, m, includes 1H, m, 2-H_B and at δ 3.57: 3H, s, $CO_2$$CH_3$), 3.42 (1H, td, *J* 11.5, 3.3, NC$H_A$$H_B$$CH_2$N), 3.06-2.90 (2H, m, NC$H_A$$H_B$$CH_2$N and NC$H_A$$H_B$$CH_2$N), 2.73 (1H, d, *J* 13.0, 13-H_B), 2.40 (1H, dd, *J* 13.2, 7.6, 11-H_A), 1.66 (1H, dd, *J* 13.2, 9.3, 11-H_B). **^{13}C NMR** (125 MHz, *d*^{6}-DMSO, 319 K): δ 171.6 (*C*$O_2$$CH_3$), 153.8 (N(CO)O), 138.7 (Ar-C_q), 136.6 (Ar-C_q), 135.3 (Ar-C_q), 132.5 (9-C), 130.9 (Ar-C), 128.2 (2 × Ar-C), 127.6 (Ar-C), 127.2 (3 peaks, 3 × C; 10-C and 2 × Ar-C), 126.5 (Ar-C), 66.1 (O*C*H_2Ph), 60.4 (12-C), 55.8 (2-C), 52.4 (13-C), 51.1 (N*C*$H_2$$CH_2$N and CO_2*C*H_3), 44.0 (N*C*$H_2$$CH_2$N), 35.3 (11-C). **IR** ν_{max}(film)/cm^{-1} 3010, 2948, 1733 (CO), 1701, 1456, 1432, 1284, 1232. **HRMS** (ESI): $C_{24}H_{27}N_2O_4$ [M+H]$^+$; calculated 407.1965, found 407.1980.

Methyl 3-benzyl-5-methylidene-2,3,4,5-tetrahydro-1H-2-benzazepine-3-carboxylate 13d

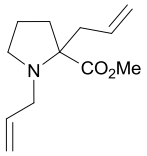


13d

Et_3N (90 μL, 0.65 mmol, 2.5 eq.) was added to a stirred solution of amino ester **12d** (100 mg, 0.260 mmol, 1.00 eq.), $Pd(OAc)_2$ (3.0 mg, 13 μmol, 5.0 mol%) and PPh_3 (7.0 mg, 27 μmol, 10 mol%) in MeCN (4 mL). The reaction mixture was heated at 125 °C under microwave irradiation for 1 h. Additional $Pd(OAc)_2$ (3.0 mg, 13 μmol, 5.0 mol%) and PPh_3 (7.0 mg, 27 μmol, 10 mol%) was added and the reaction mixture heated for 1 h. The reaction mixture was filtered through Celite then concentrated *in vacuo*. Flash chromatography eluting with 80:20:1 pentane–EtOAc–Et_3N gave the *title compound* **13d** (72 mg, 0.23 mmol, 90%) as a colourless oil. **R_f** 0.29 (4:1 petrol–EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.38-7.29 (1H, m, Ar-H), 7.24-7.14 (4H, m, Ar-H), 7.13-7.04 (4H, m, Ar-H), 7.00-6.95 (1H, m, NH), 5.37 (1H, s, C=C$H_A$$H_B$), 5.06 (1H, s, C=C$H_A$$H_B$), 3.97-3.87 (2H, m, 1-H), 3.59 (3H, s, $CO_2$$CH_3$), 3.02-2.97 (3H, m, 4-H and C$H_A$$H_B$Ph), 2.72 (1H, d, *J* 13.5, C$H_A$$H_B$Ph). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 175.4 (*C*$O_2$$CH_3$), 144.8 (5-C), 140.3 (Ar-C_q), 139.8 (Ar-C_q), 136.3 (Ar-C_q), 130.1 (Ar-C),

128.4 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 127.5 (Ar-C), 127.1 (Ar-C), 126.9 (Ar-C), 116.0 (C=*C*H_2), 67.5 (3-C), 51.9 (CO_2*C*H_3), 48.8 (1-C), 44.3 (4-C or *C*H_2Ph), 43.8 (4-C or *C*H_2Ph). **IR** ν_{max}(film)/cm^{-1} 2949, 1733 (CO), 1454, 1435, 1196, 909, 735, 701. **HRMS** (ESI): $C_{20}H_{22}NO_2$ $[M+H]^+$; calculated 308.1645, found 308.1635.

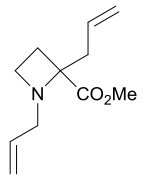
Methyl 1,2-bis(prop-2-en-1-yl)pyrrolidine-2-carboxylate 15a



15a

General procedure **J** was followed using amino ester **S2a** (1.0 g, 5.9 mmol). Purification by SCX cartridge, eluting first with MeOH then sat. NH_3/MeOH, gave the *title compound* **15a** (1.0 g, 4.8 mmol, 81%) as an orange oil. $\mathbf{R_f}$ 0.27 (1:1 pentane–EtOAc). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.92–5.67 (2H, m, C_qCH_2CH=CH_2 and NCH_2CH=CH_2), 5.22-4.96 (4H, m, C_qCH_2CH=CH_2 and NCH_2CH=CH_2), 3.67 (3H, s, CO_2CH_3), 3.38 (1H, dd, *J* 13.7, 5.0, NCH_AH_BCH=CH_2), 3.15-2.97 (1H, m, 5-H_A), 2.84 (1H, dd, *J* 13.7, 7.5, NCH_AH_BCH=CH_2), 2.69-2.48 (2H, m, 5-H_B and $C_qCH_AH_BCH$=CH_2), 2.31 (1H, dd, *J* 14.0, 6.8, $C_qCH_AH_BCH$=CH_2), 2.19-1.99 (1H, m, 3-H_A), 1.92-1.65 (3H, m, 3-H_B and 4-H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 174.6 (CO_2CH_3), 136.9 (NCH_2CH=CH_2 or C_qCH_2CH=CH_2), 134.3 (NCH_2CH=CH_2 or C_qCH_2CH=CH_2), 118.0 (NCH_2CH=CH_2 or C_qCH_2CH=CH_2), 116.2 (NCH_2CH=CH_2 or C_qCH_2CH=CH_2), 70.2 (2-C), 52.5 (NCH_2CH=CH_2), 51.8 (5-C), 51.2 (CO_2CH_3), 39.4 (C_qCH_2CH=CH_2), 33.9 (3-C), 21.6 (4-C). **IR** ν_{max}(film)/cm^{-1} 3077, 2978, 2951, 2814, 1738 (CO), 1642, 1445, 1434. **HRMS** (ESI): $C_{12}H_{20}NO_2$ $[M+H]^+$; calculated 210.1494, found 210.1489.

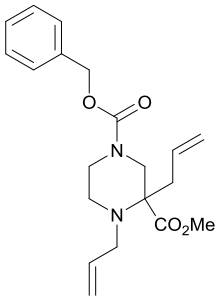
Methyl 1,2-bis(prop-2-en-1-yl)azetidine-2-carboxylate 15b



15b

General procedure **J** was followed using the TFA salt of the amino ester **S2b** (404 mg, 1.50 mmol, 1.0 eq.) and K_2CO_3 (2.2 eq.). Purification by SCX cartridge, eluting first with MeOH then sat. NH_3/MeOH, gave the *title compound* **15b** (183 mg, 0.937 mmol, 62%) as an orange oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.81-5.65 (2H, m, NCH_2CH=CH_2 and C_qCH_2CH=CH_2), 5.19-5.02 (4H, m, NCH_2CH=CH_2 and C_qCH_2CH=CH_2), 3.74 (3H, s, CO_2CH_3), 3.25-3.18 (1H, m, 4-H_A), 3.18-3.12 (3H, m, 4-H_B and NCH_2CH=CH_2), 2.66 (1H, dd, *J* 13.6, 7.3, $C_qCH_AH_BCH$=CH_2), 2.55 (1H, m, $C_qCH_AH_BCH$=CH_2), 2.52-2.47 (1H, m, 3-H_A), 2.08-2.00 (1H, m, 3-H_B). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.7 (CO_2CH_3), 134.9 (NCH_2CH=CH_2 or C_qCH_2CH=CH_2), 132.8 (NCH_2CH=CH_2 or C_qCH_2CH=CH_2), 118.5 (NCH_2CH=CH_2 or C_qCH_2CH=CH_2), 117.1 (NCH_2CH=CH_2 or C_qCH_2CH=CH_2), 71.5 (2-C), 54.9 (NCH_2CH=CH_2), 51.6 (CO_2CH_3), 49.4 (4-C), 38.7 (C_qCH_2CH=CH_2), 25.8 (3-C). **IR** ν_{max}(film)/cm^{-1} 2952, 2848, 1728 (CO), 1640 (CO), 1435, 1259, 1200, 1146. **HRMS** (ESI): $C_{11}H_{18}NO_2$ $[M+H]^+$; calculated 196.1338, found 196.1328.

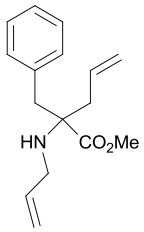
1-Benzyl 3-methyl 3,4-bis(prop-2-en-1-yl)piperazine-1,3-dicarboxylate 15c



15c

General procedure **J** was followed using amino ester **S2c** (230 mg, 0.720 mmol). Purification by SCX cartridge, eluting first with MeOH then sat. NH_3/MeOH, gave the *title compound* **15c** (212 mg, 0.591 mmol, 82%) as an orange oil. **^{1}H NMR** (500 MHz, *d*^{6}-DMSO, 319 K): δ 7.42-7.27 (5H, m, Cbz Ar-H), 5.86-5.66 (2H, m, NCH_2CH=CH_2 and C_qCH_2CH=CH_2), 5.22-5.01 (6H, m, CH_2Ph, NCH_2CH=CH_2 and C_qCH_2CH=CH_2), 4.15 (1H, dd, *J* 13.3, 1.5, 2-H_A), 3.85 (1H, d, *J* 13.0, $NCH_AH_BCH_2N$), 3.62-3.56 (1H, m, NCH_AH_BCH=CH_2), 3.54 (3H, s, CO_2CH_3), 3.00-2.85 (3H, m, 2-H_B, NCH_AH_BCH=CH_2 and $NCH_AH_BCH_2N$), 2.72-2.54 (3H, m, NCH_2CH_2N, and $C_qCH_AH_BCH$=CH_2), 2.50 (1H, m, $C_qCH_AH_BCH$=CH_2). **^{13}C NMR** (125 MHz, *d*^{6}-DMSO, 319 K): δ 172.5 (CO_2CH_3), 154.0 (N(CO)O), 136.8 (Ar-C_q), 136.5 (NCH_2CH=CH_2 or C_qCH_2CH=CH_2), 132.6 (NCH_2CH=CH_2 or C_qCH_2CH=CH_2), 128.2 (Ar-C), 127.6 (Ar-C), 127.2 (Ar-C), 118.1 (NCH_2CH=CH_2 or C_qCH_2CH=CH_2), 116.0 (NCH_2CH=CH_2 or C_qCH_2CH=CH_2), 66.0 (CH_2Ph), 63.9 (3-C), 52.4 (NCH_2CH=CH_2), 51.0 (CO_2CH_3), 49.2 (2-C), 45.6 (NCH_2CH_2N), 43.2 (NCH_2CH_2N), 37.8 (C_qCH_2CH=CH_2). **IR** ν_{max}(film)/cm^{-1} 2950, 1734 (CO), 1706 (CO), 1458, 1431, 1283, 1225, 1124. **HRMS** (ESI): $C_{20}H_{27}N_2O_4$ $[M+H]^+$; calculated 359.1965, found 359.1975.

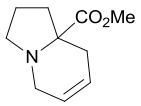
Methyl 2-benzyl-2-[(prop-2-en-1-yl)amino]pent-4-enoate 15d



15d

General procedure **J** was followed using amino ester **S2d** (400 mg, 1.82 mmol) and allyl bromide (0.8 mL, 9 mmol, 5 eq.). The reaction mixture was stirred for 2 days at rt. Purification by SCX cartridge, eluting first with MeOH then sat. NH_3/MeOH, gave the *title compound* **15d** (297 mg, 1.15 mmol, 63%) as a pale yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$, NH not observed): δ 7.18-7.07 (3H, m, Ar-H), 6.99 (2H, m, Ar-H), 5.87-5.67 (2H, m, $NHCH_2CH$=CH_2 and C_qCH_2CH=CH_2), 5.16-5.02 (4H, m, $NHCH_2CH$=CH_2 and C_qCH_2CH=CH_2), 3.52 (3H, s, CO_2CH_3), 3.12 (1H, dd, *J* 13.0, 5.8, $NHCH_AH_BCH$=CH_2), 3.05 (1H, dd, *J* 13.0, 6.1, $NHCH_AH_BCH$=CH_2), 2.88 (1H, d, *J* 13.6, CH_AH_BPh), 2.81 (1H, d, *J* 13.6, CH_AH_BPh), 2.41 (1H, dd, *J* 14.8, 6.5, $C_qCH_AH_BCH$=CH_2), 2.31 (1H, dd, *J* 14.8, 7.8, $C_qCH_AH_BCH$=CH_2). **^{13}C NMR** (125 MHz, $CDCl_3$, Ar-C_q not observed): δ 175.3 (CO_2CH_3), 136.4 (NCH_2CH=CH_2 or C_qCH_2CH=CH_2), 133.0 (NCH_2CH=CH_2 or C_qCH_2CH=CH_2), 130.0 (Ar-C), 128.2 (Ar-C), 126.8 (Ar-C), 118.7 (NCH_2CH=CH_2 or C_qCH_2CH=CH_2), 116.0 (NCH_2CH=CH_2 or C_qCH_2CH=CH_2), 66.0 (C_q), 51.7 (CO_2CH_3), 46.0 ($NHCH_2CH$=CH_2), 41.8 (CH_2Ph), 38.1 (C_qCH_2CH=CH_2). **IR** ν_{max}(film)/cm^{-1} 2949 (NH), 1731 (CO), 1495, 1454, 1119, 917, 701, 614. **HRMS** (ESI): $C_{16}H_{22}NO_2$ $[M+H]^+$; calculated 260.1645, found 260.1647.

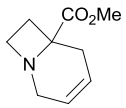
Methyl 1,2,3,5,8,8a-hexahydroindolizine-8a-carboxylate 16a



16a

Method A: General procedure **K** was followed using amino ester **15a** (266 mg, 1.27 mmol) with GII (27 mg, 32 μmol, 2.5 mol%) in PhMe. The residue was washed through a pad of silica with EtOAc–MeOH (9:1) to give the *title compound* **16a** (191 mg, 1.05 mmol, 83%) as a red-brown oil. **Method B:** General procedure **K** was followed using amino ester **15a** (1.89 g, 9.03 mmol) with two changes; the addition of *p*-TsOH was omitted and HGII (245 mg, 0.290 mmol, 3.20 mol%) was used as the catalyst. The residue was washed through a pad of silica with EtOAc–MeOH (9:1) to give the *title compound* (1.12 g, 6.18 mmol, 69% [100% conversion based on crude ^{1}H NMR study]) as a red-brown oil. $\mathbf{R_f}$ 0.28 (1:1 pentane–EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.74-5.67 (2H, m, 6-H and 7-H), 3.67 (3H, s, CO_2CH_3), 3.55-3.48 (1H, m, 5-H_A), 3.40-3.33 (1H, m, 5-H_B), 3.18-2.98 (2H, m, 3-H), 2.86-2.71 (1H, m, 8-H_A), 2.23-2.08 (2H, m, 1-H_A and 8-H_B), 1.98-1.70 (3H, m, 1-H_B and 2-H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 175.6 (CO_2CH_3), 125.9 (6-C or 7-C), 123.9 (6-C or 7-C), 65.5 (8a-C), 51.5 (CO_2CH_3), 50.9 (3-C), 47.4 (5-C), 36.8 (1-C), 33.8 (8-C), 20.6 (2-C). **IR** ν_{max}(film)/cm^{-1} 3033, 2949, 2853, 1935 (C=C), 1731 (CO), 1447, 1192, 1175. **HRMS** (ESI): $C_{10}H_{16}NO_2$ $[M+H]^+$; calculated 182.1181, found 182.1176.

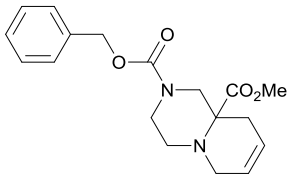
Methyl 1-azabicyclo[4.2.0]oct-3-ene-6-carboxylate 16b



16b

General procedure **K** was followed using amino ester **15b** (100 mg, 0.510 mmol) with GII (33 mg, 38 μmol, 7.5 mol%) in PhMe. Flash chromatography eluting with a gradient of 0-10% MeOH in CH_2Cl_2, gave the *title compound* (49 mg, 0.29 mmol, 57%) as a red-brown oil. $\mathbf{R_f}$ 0.35 (10:1 CH_2Cl_2–MeOH). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.05-5.98 (1H, m, 3-H), 5.94-5.88 (1H, m, 4-H), 3.73 (3H, s, CO_2CH_3), 3.48-3.37 (2H, m, 2-H_A and 8-H_A), 3.18-3.11 (1H, m, 8-H_B), 2.95-2.88 (1H, m, 2-H_B), 2.69-2.60 (1H, m, 7-H_A), 2.43-2.39 (2H, m, 5-H), 2.03-1.96 (1H, m, 7-H_B). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 175.8 (CO_2CH_3), 127.0 (4-C), 124.1 (3-C), 64.2 (6-C), 52.3 (CO_2CH_3), 49.0 (8-C), 47.4 (2-C), 30.5 (7-C), 28.5 (5-C). **IR** ν_{max}(film)/cm^{-1} 2952, 2928, 1734 (CO), 1437, 1267, 1225, 1202, 1156. **HRMS** (ESI): $C_9H_{14}NO_2$ $[M+H]^+$; calculated 168.1019, found 168.1022.

2-Benzyl 9a-methyl 1H,2H,3H,4H,6H,9H,9aH-pyrido[1,2-a]piperazine-2,9a-dicarboxylate 16c

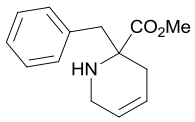


16c

General procedure **K** was followed using amino ester **15c** (211 mg, 0.590 mmol) with GII (13 mg, 15 μmol, 2.5 mol%) in PhMe. Flash chromatography eluting with a gradient of 0-100% EtOAc in pentane (containing 1% Et_3N) gave the *title compound* **16c** (176 mg, 0.533 mmol, 90%) as a pale yellow oil. $\mathbf{R_f}$ 0.15 (3:2 petrol–EtOAc). **^{1}H NMR** (500 MHz,

d^6-DMSO, 319 K): δ 7.42-7.26 (5H, m, Cbz Ar-H), 5.69-5.58 (2H, m, 7-H and 8-H), 5.12-4.99 (2H, m, C*H*$_2$Ph), 4.25 (1H, dd, *J* 13.1, 2.1, 1-H$_A$), 3.98-3.90 (1H, m, NC*H*$_A$H$_B$CH$_2$N), 3.47 (3H, s, CO$_2$CH$_3$), 3.38-3.30 (1H, m, 6-H$_A$), 3.19-3.13 (1H, m, 6-H$_B$), 3.10-2.99 (2H, m, NC*H*$_A$H$_B$CH$_2$N and NCH$_A$*H*$_B$CH$_2$N), 2.86 (1H, d, *J* 13.1, 1-H$_B$), 2.65-2.55 (1H, m, NCH$_A$*H*$_B$CH$_2$N), 2.44-2.33 (1H, m, 9-H$_A$), 2.11-2.02 (1H, m, 9-H$_B$). **^{13}C NMR** (125 MHz, *d*^{6}-DMSO, 319 K): δ 172.3 (*C*O$_2$CH$_3$), 153.8 (N(CO)O), 136.7 (Ar-*C*$_q$), 128.2 (Ar-C), 127.6 (Ar-C), 127.2 (Ar-C), 125.1 (7-C or 8-C), 121.2 (7-C or 8-C), 66.1 (*C*H$_2$Ph), 59.8 (9a-C), 51.6 (1-C), 50.9 (CO$_2$*C*H$_3$), 49.8 (6-C), 47.6 (NCH$_2$CH$_2$N), 43.4 (NCH$_2$CH$_2$N), 32.2 (9-C). **IR** ν$_{max}$(film)/cm^{-1} 3034, 2949, 1732 (CO), 1704 (CO), 1463, 1434, 1286, 1228. **HRMS** (ESI): C$_{18}$H$_{23}$N$_2$O$_4$ [M+H]$^+$; calculated 331.1652, found 331.1652.

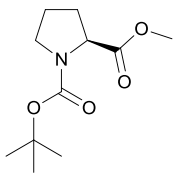
Methyl 2-benzyl-1,2,3,6-tetrahydropyridine-2-carboxylate 16d



16d

General procedure **K** was followed using amino ester **15d** (38 mg, 0.15 mmol) with GII (7.0 mg, 7.5 μmol, 5.0 mol%) in CH$_2$Cl$_2$. Flash chromatography eluting with pentane–EtOAc (4:1) gave the *title compound* **16d** (24 mg, 0.10 mmol, 69%) as an orange oil. **R$_f$** 0.06 (4:1 petrol–EtOAc). **^{1}H NMR** (500 MHz, CDCl$_3$): δ 7.31-7.22 (3H, m, Ar-H), 7.12-7.08 (2H, m, Ar-H), 5.74-5.69 (1H, m, 4-H), 5.69-5.64 (1H, m, 5-H), 3.62 (3H, s, CO$_2$CH$_3$), 3.54-3.48 (1H, m, 6-H$_A$), 3.43-3.36 (1H, m, 6-H$_B$), 3.04 (1H, d, *J* 13.2, C*H*$_A$H$_B$Ph), 2.91 (1H, d, *J* 13.2, CH$_A$*H*$_B$Ph), 2.68-2.61 (1H, m, 3-H$_A$), 2.31-2.24 (1H, m, 3-H$_B$). **^{13}C NMR** (125 MHz, CDCl$_3$): δ 175.3 (*C*O$_2$CH$_3$), 135.7 (Ar-C$_q$), 130.0 (Ar-C), 128.5 (Ar-C), 127.2 (Ar-C), 125.3 (5-C), 123.3 (4-C), 61.7 (2-C), 51.8 (CO$_2$*C*H$_3$), 46.5 (*C*H$_2$Ph), 42.7 (6-C), 33.3 (3-C). **IR** ν$_{max}$(film)/cm^{-1} 3030 (NH), 2949, 1730, (CO), 1454, 1435, 1200, 1110, 1084, 1041. **HRMS** (ESI): C$_{14}$H$_{18}$NO$_2$ [M+H]$^+$; calculated 232.1332, found 232.1342.

1-*tert*-Butyl 2-methyl (*2S*)-pyrrolidine-1,2-dicarboxylate S1a

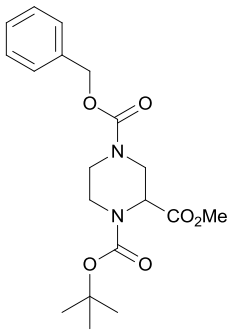


S1a

Boc$_2$O (5.20 g, 23.9 mmol, 1.03 eq.) and Et$_3$N (9.7 mL, 70 mmol, 2.9 eq.) were added to a stirred solution of L-proline methyl ester hydrochloride (3.84 g, 23.2 mmol, 1.00 eq.) in CH$_2$Cl$_2$ (230 mL). The reaction mixture was stirred for 1 h, then concentrated *in vacuo*. The residue was triturated with Et$_2$O (3 × 50 mL) and filtered to remove the insoluble Et$_3$N•HCl. The resulting solution was dry-loaded onto silica. Flash chromatography eluting with pentane–EtOAc (4:1) gave the title compound **S1a** (5.30 g, 23.1 mmol, 99%) as a colourless oil. **R$_f$** 0.19 (4:1 petrol–EtOAc). **[α]$^{27}_D$** −61.4 (c. 0.83, MeOH) {lit.[13] -61.7 (c. 1.15, MeOH)}. **^{1}H NMR** (300 MHz, CDCl$_3$, 2:3 mixture of rotamers): δ 4.34 (0.4H, dd, *J* 8.5, 3.1, 2-H), 4.23 (0.6H, dd, *J* 8.5, 4.1, 2-H), 3.73 (3H, s, CO$_2$CH$_3$), 3.62-3.33 (2H, m, 5-H), 2.33-2.09 (1H, m, 3-H$_A$), 2.05-1.77 (3H, m, 3-H$_B$ and 4-H), 1.47 (3.6H, s, C(CH$_3$)$_3$), 1.42 (5.4H, s, C(CH$_3$)$_3$). **^{13}C NMR**

(75 MHz, $CDCl_3$, mixture of rotamers): δ 173.8 (major, CO_2CH_3), 173.5 (minor, CO_2CH_3), 154.5 (minor, N(CO)O), 153.8 (major, N(CO)O), 79.9 (major and minor, $C_q(CH_3)_3$), 59.2 (major, 2-C), 58.8 (minor, 2-C), 52.1 (minor, CO_2CH_3), 52.0 (major, CO_2CH_3), 46.6 (minor, 5-C), 46.4 (major, 5-C), 30.9 (major, 3-C), 30.0 (minor, 3-C), 28.5 (minor, $C_q(CH_3)_3$), 28.3 (major, $C_q(CH_3)_3$), 24.4 (minor, 4-C), 23.7 (major, 4-C). **IR** ν_{max}(film)/cm^{-1} 2977, 2882, 1747 (CO), 1694 (CO), 1393, 1201, 1121, 1088. **HRMS** (ESI): $C_{11}H_{19}NNaO_4$ $[M+Na]^+$; calculated 252.1212, found 252.1206. Spectra consistent with the literature values.[10]

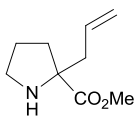
4-Benzyl 1-*tert*-butyl 2-methyl piperazine-1,2,4-tricarboxylate S1c



S1c

Benzyl chloroformate (3.5 mL, 24 mmol, 1.3 eq.) was added dropwise to a stirred solution of 1-*tert*-butyl 2-methyl piperazine-1,2-dicarboxylate* (4.59 g, 18.8 mmol, 1.00 eq.) and Et_3N (3.4 mL, 24 mmol, 1.3 eq.) in CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was warmed to rt and stirred for 15 h, then partitioned between H_2O (50 mL) and CH_2Cl_2 (50 mL). The organics were dried over $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography eluting with pentane–EtOAc (4:1) gave the *title compound* **S1c** (5.52 g, 14.6 mmol, 85%) as a straw-coloured oil. $\mathbf{R_f}$ 0.11 (4:1 petrol–EtOAc). **^{1}H NMR** (500 MHz, *d*^{6}-DMSO, 343 K): δ 7.40-7.29 (5H, m, Cbz Ar-H), 5.11 (1H, d, *J* 12.7, CH_AH_BPh), 5.07 (1H, d, *J* 12.7, CH_AH_BPh), 4.61 (1H, br. s, 2-H), 4.34 (1H, d, *J* 13.8, 3-H_A), 3.92-3.85 (1H, m, $NCH_AH_BCH_2N$), 3.74 (1H, dt, *J* 13.0, 3.4, $NCH_AH_BCH_2N$), 3.60 (3H, s, CO_2CH_3), 3.27 (1H, dd, *J* 13.8, 4.5, 3-H_B), 3.16-3.07 (1H, m, $NCH_AH_BCH_2N$), 3.04-2.03 (1H, m, $NCH_AH_BCH_2N$), 1.40 (9H, s, $C(CH_3)_3$). **^{13}C NMR** (125 MHz, *d*^{6}-DMSO, 373 K): δ 169.9 (CO_2CH_3), 154.0 (N(CO)O), 153.9 (N(CO)O), 136.3 (Ar-C_q), 127.8 (Ar-C), 127.2 (Ar-C), 126.8 (Ar-C), 79.5 ($C_q(CH_3)_3$), 66.0 (CH_2Ph), 53.7 (2-C), 51.3 (CO_2CH_3), 43.5 (3-C and NCH_2CH_2N), 42.3 (NCH_2CH_2N), 27.4 ($C(CH_3)_3$). **IR** ν_{max}(film)/cm^{-1} 2976, 1744 (CO), 1694, 1457, 1431, 1224, 1168, 1106. **HRMS** (ESI): $C_{19}H_{27}N_2O_6$ $[M+H]^+$; calculated 379.1864, found 379.1866.

Methyl 2-(prop-2-en-1-yl)pyrrolidine-2-carboxylate S2a



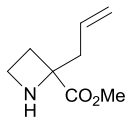
S2a

General procedure **A** was followed using Boc-protected amino ester **1a** (6.7 g, 25 mmol). Purification by SCX cartridge, eluting first with MeOH then sat. NH_3/MeOH, gave the *title compound* **S2a** (3.10 g, 18.3 mmol, 74%) as an orange oil. **^{1}H NMR** (500 MHz, $CDCl_3$, NH not observed): δ 5.78-5.69 (1H, m, $CH=CH_2$), 5.15-5.07 (2H, m, $CH=CH_2$), 3.74 (3H, s, CO_2CH_3), 3.14-3.02 (2H, m, 5-H), 2.61 (1H, ddt, *J* 13.7, 7.3, 1.1, $CH_AH_BCH=CH_2$), 2.45 (1H, ddt, *J* 13.7, 7.2,

* Purchased from Fluorochem.

1.0, $CH_AH_BCH=CH_2$), 2.27-2.18 (1H, m, 3-H_A), 1.91-1.79 (2H, m, 3-H_B and 4-H_A), 1.79-1.68 (1H, m, 4-H_B). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 176.3 (CO_2CH_3), 133.3 ($CH=CH_2$), 119.0 ($CH=CH_2$), 70.0 (2-C), 52.6 (CO_2CH_3), 46.5 (5-C), 43.3 ($CH_2CH=CH_2$), 35.2 (3-C), 24.7 (4-C). **IR** ν_{max}(film)/cm^{-1} 3352 (NH), 2953, 1732 (CO), 1435, 1217, 1200, 997, 918. **HRMS** (ESI): $C_9H_{16}NO_2$ $[M+H]^+$; calculated 170.1181, found 170.1176.

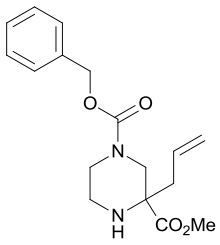
Methyl 2-(prop-2-en-1-yl)azetidine-2-carboxylate S2b



S2b

General procedure **A** was followed using Boc-protected amino ester **1b** (1.93 g, 7.53 mmol). Purification by SCX cartridge, eluting first with MeOH then sat. NH_3/MeOH, gave the *title compound* **S2b** (771 mg, 4.97 mmol, 66%) as an orange oil. **^{1}H NMR** (500 MHz, $CDCl_3$, NH not observed): δ 5.80-5.68 (1H, m, $CH=CH_2$), 5.14-5.07 (2H, m, $CH=CH_2$), 3.78 (3H, s, CO_2CH_3), 3.51 (1H, app. q, *J* 7.9, 4-H_A), 3.37-3.31 (1H, m, 4-H_B), 2.63-2.51 (2H, m, $CH_2CH=CH_2$), 2.49-2.39 (2H, m, 3-H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 176.6 (CO_2CH_3), 132.2 ($CH=CH_2$), 118.5 ($CH=CH_2$), 67.4 (2-C), 52.3 (CO_2CH_3), 43.8 ($CH_2CH=CH_2$), 41.5 (4-C), 30.0 (3-C). **IR** ν_{max}(film)/cm^{-1} 3329, 2954, 2879, 1732 (CO), 1436, 1266, 1216, 1140. **HRMS** (EI): $C_8H_{13}NO_2$ $[M]^+$; calculated 155.0945, found 155.0946.

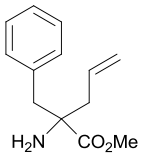
1-Benzyl 3-methyl 3-(prop-2-en-1-yl)piperazine-1,3-dicarboxylate S2c



S2c

General procedure **A** was followed using Boc-protected amino ester **1c** (3.37 g, 8.05 mmol). Purification by SCX cartridge, eluting first with MeOH then sat. NH_3/MeOH, gave the *title compound* **S2c** (2.19 g, 6.88 mmol, 85%) as a colourless oil. **R_f** 0.18 (3:2 pentane–EtOAc). **^{1}H NMR** (500 MHz, d^6-DMSO, 340 K): δ 7.41-7.28 (5H, m, Cbz Ar-H), 5.74-5.64 (1H, m, $CH=CH_2$), 5.13-5.03 (4H, m, CH_2Ph and $CH=CH_2$), 4.19 (1H, d, *J* 12.8, 3-H_A), 3.70 (1H, d, *J* 12.5, $NCH_AH_BCH_2N$), 3.58 (3H, s, CO_2CH_3), 3.00-2.92 (1H, m, $NCH_AH_BCH_2N$), 2.90 (1H, d, *J* 12.8, 3-H_B), 2.80-2.74 (1H, m, $NCH_AH_BCH_2N$), 2.73-2.66 (1H, m, $NCH_AH_BCH_2N$), 2.65 (1H, br. s, NH), 2.32 (1H, dd, *J* 13.8, 7.2, $CH_AH_BCH=CH_2$), 2.25 (1H, dd, *J* 13.8, 7.5, $CH_AH_BCH=CH_2$). **^{13}C NMR** (125 MHz, d^6-DMSO, 340 K): δ 173.2 (CO_2CH_3), 154.1 (N(CO)O), 136.7 (Ar-C_q), 131.7 ($CH=CH_2$), 128.0 (Ar-C), 127.4 (Ar-C), 127.0 (Ar-C), 118.4 ($CH=CH_2$), 65.9 (CH_2Ph), 61.1 (2-C), 51.1 (CO_2CH_3), 49.0 (3-C), 43.2 (NCH_2CH_2), 41.0 ($CH_2CH=CH_2$ or NCH_2CH_2N), 40.8 ($CH_2CH=CH_2$ or NCH_2CH_2N). **IR** ν_{max}(film)/cm^{-1} 3564, 3339, 2951, 1731 (CO), 1704 (CO), 1434, 1358, 1229, 1122, 761. **HRMS** (ESI): $C_{17}H_{23}N_2O_4$ $[MH^+]$; calculated 319.1652, found 319.1658.

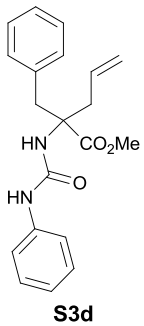
Methyl 2-amino-2-benzylpent-4-enoate S2d



S2d

Benzaldehyde (1.2 mL, 12 mmol, 1.0 eq.) was added to a stirred suspension of L-phenylalanine methyl ester hydrochloride (2.5 g, 12 mmol, 1.0 eq.), Et_3N (1.6 mL, 12 mmol, 1.0 eq.) and 4 Å MS (500 mg) in THF (60 mL). The reaction mixture was stirred for 15 h, then filtered to remove the insoluble Et_3N•HCl and concentrated *in vacuo* to give the crude imine as a pale yellow oil. The residue was diluted in THF (60 mL) and LiHMDS (1.0 M in THF, 17.4 mL, 17.4 mmol, 1.50 eq.) was added dropwise at −78 °C. The reaction mixture was stirred for 15 min then allyl bromide (1.50 mL, 17.4 mmol, 1.50 eq.) was added dropwise. After 1 h the dry-ice bath was removed, the reaction mixture was warmed to rt and stirred for 15 h. Aqueous citric acid (15 wt%, 100 mL) was added and the reaction mixture was stirred for 1 h, then partitioned with Et_2O (100 mL). The aqueous layer was neutralised with solid $NaHCO_3$, then extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. The *title compound* **S2d** (2.26 g, 10.3 mmol, 89%) was isolated as a yellow oil after flushing through a pad of silica with EtOAc–MeOH (9:1). $\mathbf{R_f}$ 0.14 (4:1 pentane–EtOAc). **^{1}H NMR** (300 MHz, $CDCl_3$, NH_2 not observed): δ 7.24-7.10 (3H, m, Ar-H), 7.10-7.02 (2H, m, Ar-H), 5.70-5.54 (1H, m, C*H*=CH_2), 5.15-5.05 (2H, m, CH=C*H*$_2$), 3.62 (3H, s, CO_2CH_3), 3.11 (1H, d, *J* 13.2, C*H*$_A$H$_B$Ph), 2.71 (1H, d, *J* 13.2, CH$_A$*H*$_B$Ph), 2.65 (1H, ddt, *J* 13.4, 6.4, 1.2, C*H*$_A$H$_B$CH=CH_2), 2.24 (1H, dd, *J* 13.4, 8.5, CH$_A$*H*$_B$CH=CH_2). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.6 (*C*O_2CH_3), 136.2 (Ar-C_q), 132.6 (*C*H=CH_2), 129.9 (Ar-C), 128.5 (Ar-C), 127.1 (Ar-C), 119.9 (CH=*C*H$_2$), 62.0 (*C*$_q$), 52.1 (CO_2*C*H$_3$), 45.9 (*C*H$_2$Ph), 44.6 (*C*H$_2$CH=CH_2). **IR** ν_{max}(film)/cm^{-1} 3378, 2951, 1738 (CO), 1603, 1441, 1218, 1030, 922. **HRMS** $C_{13}H_{18}NO_2$ $[M+H]^+$; calculated 220.1332, found 220.1340. Spectra consistent with the literature values.[14]

Methyl 2-benzyl-2-[(phenylcarbamoyl)amino]pent-4-enoate S3d

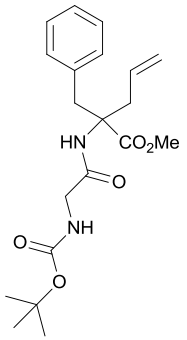


S3d

Phenyl isocyanate (180 μL, 1.61 mmol, 1.05 eq.) was added to a stirred solution of amino ester **S2d** (337 mg, 1.54 mmol, 1.0 eq.) in PhMe (20 mL). Flash chromatography eluting with pentane–EtOAc (4:1) gave the *title compound* **S3d** (271 mg, 0.80 mmol, 52%) as a colourless solid. $\mathbf{R_f}$ 0.46 (4:1 pentane−EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.32-7.18 (7H, m, Ar-H), 7.13-7.04 (3H, m, Ar-H), 6.23 (1H, br. s., NH), 5.75-5.61 (1H, m, C*H*=CH_2), 5.5 (1H, br. s., NH), 5.17-5.03 (2H, m, CH=C*H*$_2$), 3.84-3.75 (4H, m, includes 1H, m, C*H*$_A$H$_B$Ph and at δ 3.78: 3H, s, CO_2CH_3), 3.42 (1H, dd, *J* 13.9, 7.1, C*H*$_A$H$_B$CH=CH_2), 3.18 (1H, d, *J* 13.5, CH$_A$*H*$_B$Ph), 2.65 (1H, dd, *J* 13.9, 7.6, CH$_A$*H*$_B$CH=CH_2). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.8 (*C*O_2CH_3), 154.3 (CO), 138.6 (Ar-C_q), 136.6 (Ar-C_q), 132.7 (*C*H=CH_2), 130.0 (Ar-C), 129.4 (Ar-C), 128.4 (Ar-C), 127.0 (Ar-C), 124.0 (Ar-C), 121.1 (Ar-C), 119.1

(CH=*C*H_2), 65.8 (C_q), 52.7 (CO_2*C*H_3), 41.1 (*C*H_2Ph), 40.3 (*C*H_2CH=CH_2). **IR** ν_{max}(film)/cm^{-1} 3355, 3030, 1742 (CO), 1651 (CO), 1599, 1549, 1497, 1441. **HRMS** (ESI): $C_{20}H_{22}N_2NaO_3$ $[M+Na]^+$; calculated 361.1523, found 361.1525.

Methyl 2-benzyl-2-(2-{[(*tert*-butoxy)carbonyl]amino}acetamido)pent-4-enoate S4d

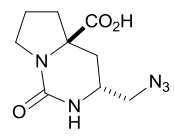


S4d

Amino ester **S2d** (535 mg, 2.44 mmol, 1.0 eq.) was added to a stirred solution of *N*-Boc-glycine (855 mg, 4.88 mmol, 2.0 eq.), EDCI (936 mg, 4.88 mmol, 2.0 eq.) and Et_3N (0.85 mL, 6.10 mmol, 2.50 eq.) in CH_2Cl_2 (20 mL). The reaction mixture was stirred for 15 h. Additional *N*-Boc-glycine (855 mg, 4.88 mmol, 2.00 eq.) and EDCI (936 mg, 4.88 mmol, 2.00 eq.) were added and the reaction mixture was stirred for 3 h, then concentrated *in vacuo*. The residue was diluted with EtOAc (50 mL) and washed with H_2O (50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, then concentrated *in vacuo*. Flash chromatography eluting with pentane–EtOAc–Et_3N (80:20:1) gave the *title compound* **S4d** (790 mg, 2.09 mmol, 86%) as a colourless oil. **R*f*** 0.22 (4:1 petrol–EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.28-7.20 (3H, m, Ar-H), 7.01 (2H, dd, *J* 7.9, 1.4, Ar-H), 6.66 (1H, br. s, NH), 5.65-5.55 (1H, m, C*H*=CH_2), 5.13-5.06 (2H, m, CH=C*H*$_2$), 5.03 (1H, br. s, NH), 3.78 (3H, s, CO_2CH_3), 3.76-3.72 (3H, m, includes 2H, m, C*H*$_2$NHBoc and at δ 3.74: 1H, d, *J* 13.6, C*H*$_A$H$_B$Ph), 3.38 (1H, dd, *J* 13.9, 7.1, C*H*$_A$H$_B$CH=CH_2), 3.14 (1H, d, *J* 13.6, CH$_A$*H*$_B$Ph), 2.64 (1H, dd, *J* 13.9, 7.7, CH$_A$*H*$_B$CH=CH_2), 1.44 (9H, s, C(CH_3)$_3$). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.9 (*C*O_2CH_3), 168.8 (NH(*C*O)CH_2), 155.9 (NH(*C*O)O), 136.1 (Ar-C_q), 132.1 (*C*H=CH_2), 129.7 (Ar-C), 128.4 (Ar-C), 127.1 (Ar-C), 119.3 (CH=*C*H_2), 80.1 (*C*$_q$(CH_3)$_3$), 66.0 (C_q), 52.7 (CO_2*C*H_3), 44.9 (*C*H_2NHBoc), 40.5 (*C*H_2CH=CH_2), 39.6 (*C*H_2Ph), 28.3 (C(*C*H_3)$_3$). **IR** ν_{max}(film)/cm^{-1} 3385, 2978, 1740 (CO), 1716 (CO), 1679, 1514, 1448, 1367. **HRMS** (ESI): $C_{20}H_{28}N_2NaO_5$ $[M+Na]^+$; calculated 399.1890, found 399.1895.

7.4 Synthesis of scaffold derivatives

(*3R,*4aR**)-3-(Azidomethyl)-1-oxo-octahydropyrrolo[1,2-c]pyrimidine-4a-carboxylic acid S5a**

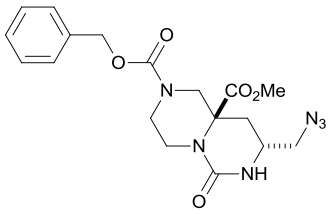


S5a

NaOH (14 mg, 0.35 mmol, 2.2 eq.) was added to a solution of urea **7a** (50 mg, 0.15 mmol, 1.0 eq.) in MeOH (0.3 mL) and the reaction mixture was stirred for 2 h by which point a colourless precipitate had formed. The reaction mixture was diluted with MeOH (10 mL), then Amberlite IR-120 (hydrogen form, 94 mg) was added at 0 °C. The reaction mixture was stirred for 0.5 h, then filtered through Celite and concentrated *in vacuo*. The resulting residue was triturated with $CHCl_3$ to give the *title compound* **S5a** (37 mg, 0.15 mmol, 99%) as a colourless solid. **^{1}H NMR** (500 MHz, *d*^{6}-DMSO, 343 K, CO_2H not observed): δ 6.13 (1H,

s, NH), 3.52-3.41 (2H, m, C*H*$_A$H$_B$N$_3$, 7-H$_A$), 3.40-3.29 (3H, m, CH$_A$*H*$_B$N$_3$, 3-H, 7-H$_B$), 2.46-2.40 (1H, m, 4-H$_A$), 2.34-2.28 (1H, m, 5-H$_A$), 1.89-1.76 (2H, m, 5-H$_B$ and 6-H$_A$), 1.75-1.63 (1H, m, 6-H$_B$), 1.46 (1H, app. t, *J* 12.2, 4-H$_B$). **^{13}C NMR** (125 MHz, *d*^{6}-DMSO): δ 175.1 (*C*O$_2$H), 153.8 (1-C), 65.6 (4a-C), 53.5 (CH$_2$N$_3$), 48.5 (3-C), 44.9 (7-C), 37.4 (5-C), 33.6 (4-C), 21.1 (6-C). **IR** ν_{max}(film)/cm^{-1} 3265, 2105 (N$_3$), 1685 (CO), 1530, 1453, 1308, 1233, 1078. **HRMS** (ESI): C$_9$H$_{14}$N$_5$O$_3$ [M+H]$^+$; calculated 240.1091, found 240.1091. **X-Ray Crystallography**: CCDC 1008923 contains the supplementary crystallographic data for this compound. Crystals were grown by slow diffusion of Et$_2$O into the sample dissolved in the minimum amount of CHCl$_3$.

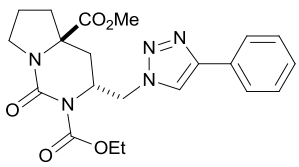
2-Benzyl 9a-methyl (*8R**,*9aS**)-8-(azidomethyl)-6-oxo-octahydro-1H-pyrimido[1,6 a]piperazine-2,9a-dicarboxylate S6c



S6c

NaOMe (25 wt% in MeOH, 18 μL, 80 μmol, 1.0 eq.) was added to a stirred solution of urea **7c** (37 mg, 80 μmol, 1.0 eq.) in MeOH (0.8 mL). The reaction mixture was stirred at rt for 0.5 h, then concentrated *in vacuo*. The residue was redissolved in MeOH (10 mL) and Amberlite IR-120 (hydrogen form, 50 mg) was added. After stirring for 1 h the reaction mixture was filtered and concentrated to give the *title compound* **S6c** (28 mg, 70 μmol, 88%) as a pale yellow oil. . **R$_f$** 0.16 (4:1 pentane−EtOAc). **^{1}H NMR** (500 MHz, *d*^{6}-DMSO, 319 K): δ 7.42-7.28 (5H, m, Cbz Ar-H), 6.68 (1H, s, NH), 5.11 (1H, d, *J* 12.7, C*H*$_A$H$_B$Ph), 5.06 (1H, d, *J* 12.7, CH$_A$*H*$_B$Ph), 4.50 (1H, d, *J* 13.2, 1-H$_A$), 4.04 (1H, d, *J* 12.1, NC*H*$_A$H$_B$CH$_2$N), 3.96 (1H, d, *J* 13.1, NC*H*$_A$H$_B$CH$_2$N), 3.60 (3H, s, CO$_2$CH$_3$), 3.53-3.45 (1H, m, C*H*$_A$H$_B$N$_3$), 3.33-3.24 (2H, m, 8-H and CH$_A$*H*$_B$N$_3$), 3.01-2.84 (2H, m, 1-H$_B$ and NCH$_A$*H*$_B$CH$_2$N), 2.83-2.73 (1H, m, NCH$_A$*H*$_B$CH$_2$N), 2.14 (1H, d, *J* 12.7, 9-H$_A$), 1.78 (1H, app. t, *J* 12.7, 9-H$_B$). **^{13}C NMR** (125 MHz, *d*^{6}-DMSO, 319 K): δ 171.5 (*C*O$_2$CH$_3$), 154.9 (CO), 153.8 (CO), 136.5 (Ar-C$_q$), 128.2 (Ar-C), 127.7 (Ar-C), 127.3 (Ar-C), 66.3 (*C*H$_2$Ph), 61.3 (9a-C), 53.2 (CH$_2$N$_3$), 52.5 (CO$_2$*C*H$_3$), 50.2 (1-C), 46.6 (8-C), 42.8 (NCH$_2$CH$_2$N), 39.3 (NCH$_2$CH$_2$N), 32.2 (9-C). **IR** ν_{max}(film)/cm^{-1} 2107 (N$_3$), 1738 (CO), 1704 (CO), 1664 (CO), 1432, 1284, 1234, 1122. **HRMS** (ESI): C$_{18}$H$_{23}$N$_6$O$_5$ [M+H]$^+$; calculated 403.1724, found 403.1728. **X-Ray Crystallography**: CCDC 1008924 contains the supplementary crystallographic data for this compound. Crystals were grown by slow diffusion of Et$_2$O into the sample dissolved in the minimum amount of CHCl$_3$.

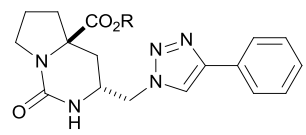
2-Ethyl 4a-methyl (*3R,*4aR**)-1-oxo-3-[(4-phenyl-1H-1,2,3-triazol-1-yl)methyl]-octahydropyrrolo[1,2-c]pyrimidine-2,4a-dicarboxylate S7**



S7

Phenyl acetylene (70 μL, 0.62 mmol, 2.0 eq) was added to a stirred solution of azide **7a** (100 mg, 0.31 mmol, 1.0 eq.), $Cu(OAc)_2$ (11 mg, 60 μmol, 20 mol%) and sodium ascorbate (24 mg, 0.12 mmol, 40 mol%) in degassed* ^{t}BuOH–H_2O (1:1, 2.0 mL). After 15 h the reaction mixture was extracted with EtOAc (25 mL) and washed with brine (25 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography on cyanosilica eluting with a gradient of 0-100% EtOAc in pentane, gave the *title compound* **S7** (117 mg, 0.27 mmol, 88%) as colourless oil. **R_f** 0.29 (EtOAc). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.88 (1H, s, triazole 5-H), 7.83 (2H, d, *J* 7.1, Ar-H), 7.41 (2H, t, *J* 7.6, Ar-H), 7.35-7.30 (1H, m, Ar-H), 4.69 (2H, app. d, *J* 4.4, C*H*$_2$Ar), 4.59-4.51 (1H, m, 3-H), 4.39-4.20 (2H, m, C*H*$_2$CH$_3$), 3.70 (3H, s, CO_2CH_3), 3.58-3.51 (1H, m, 7-H_A), 3.43-3.37 (1H, m, 7-H_B), 2.86 (1H, dd, *J* 13.6, 8.7, 4-H_A), 2.28-2.21 (1H, m, 5-H_A), 1.96-1.72 (4H, m, 4-H_B; 5-H_B and 6-H), 1.33 (3H, t, *J* 7.1, CH_2CH_3). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.8 (*C*O_2CH_3), 154.5 (CO), 150.0 (CO), 148.5 (triazole 4-C), 130.5 (Ar-C_q), 129.0 (Ar-C), 128.4 (Ar-C), 126.1 (Ar-C), 121.2 (triazole 5-C), 65.6 (4a-C), 63.4 (*C*H_2CH$_3$), 53.2 (*C*H_2Ar), 53.2 (3-C), 53.1 (CO_2CH_3), 46.7 (7-C), 37.8 (5-C) 36.7 (4-C), 22.7 (6-C), 14.5 (CH_2CH_3). **IR** ν_{max}(film)/cm^{-1} 2981, 1703 (CO), 1419, 1288, 1230, 1171, 835, 767. **HRMS** (ESI): $C_{21}H_{26}N_5O_5$ $[M+H]^+$; calculated 428.1928, found 428.1930.

(*3R,*4aR**)-1-oxo-3-[(4-phenyl-1H-1,2,3-triazol-1-yl)methyl]-octahydropyrrolo[1,2-c]pyrimidine-4a-carboxylic acid S8**



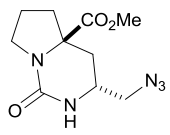
S8, R= 83:17 Me:H

NaOH (6.0 mg, 0.14 mmol, 2.0 eq.) was added to a stirred solution of urea **S7** (30 mg, 70 μmol, 1.0 eq.) in MeOH (0.3 mL). The reaction mixture was stirred for 2 h, by which point a colourless solid had preciptiated from the solution. The reaction mixture was diluted with MeOH (15 mL). Amberlite IR-120 (hydrogen form, 100 mg) was added and the mixture was stirred for 0.5 h, then filtered and concentrated. The residue was triturated with $CHCl_3$ to give the *title compound* **S8** (20 mg, 83:17 mixture of ester:acid, 56 μmol, 80%) as colourless solid. **^{1}H NMR** (500 MHz, *d*^{6}-DMSO, 318 K, ester peaks assigned): δ 8.52 (1H, s, triazole 5-H), 7.85-7.81 (2H, m, Ar-H), 7.46 (2H, t, *J* 7.7, Ar-H), 7.34 (1H, t, *J* 7.4, Ar-H), 6.49 (1H, s, NH), 4.56 (1H, dd, *J* 14.0, 4.5, C*H*$_A$H$_B$Ar), 4.44 (1H, dd, *J* 14.0, 6.3, NCH$_A$*H*$_B$Ar), 3.66 (3H, s, CO_2CH_3), 3.64-3.56 (1H, m, 3-H), 3.43-3.34 (1H, m, 7-H_A), 3.33-3.26 (1H,

* Degassed by bubbling N_2 through the solvent.

m, 7-H_B), 2.40-2.33 (1H, m, 4-H_A), 2.30-2.23 (1H, m, 5-H_A), 1.85-1.75 (2H, m, 5-H_B and 6-H_A), 1.68-1.57 (1H, m, 6-H_B), 1.40 (1H, t, *J* 12.4, 4-H_B). Carboxylic acid characteristic peaks: δ 8.53 (1H, s, triazole 5-H), 6.40 (1H, s, NH). **^{13}C NMR** (125 MHz, *d*^{6}-DMSO, 318 K, ester peaks assigned): δ 173.6 (*C*$O_2$$CH_3$), 153.3 (1-C), 146.3 (triazole 4-C), 130.5 (Ar-C_q), 128.7 (Ar-C), 127.7 (Ar-C), 125.0 (Ar-C), 122.1 (triazole 5-C), 65.8 (4a-C), 52.5 (*C*H_2Ar and CO_2*C*H_3), 48.5 (3-C), 44.9 (7-C), 37.3 (5-C), 33.8 (4-C), 20.8 (6-C). **IR** ν_{max}(film)/cm^{-1} 1737 (CO), 1649 (CO), 1488, 1473, 1221, 1170, 712, 693. **HRMS** (ESI): $C_{18}H_{22}N_5O_3$ $[M+H]^+$; calculated 356.1717, found 356.1723.

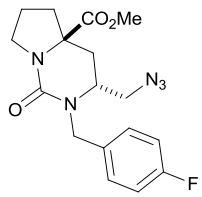
Methyl (*3R*,4aR)-3-(azidomethyl)-1-oxo-octahydropyrrolo[1,2-c]pyrimidine-4a-carboxylate S9**



S9

NaOMe (25 wt% in MeOH, 82 μL, 37 μmol, 1.0 eq.) was added to a stirred solution of urea **7a** (120 mg, 0.370 mmol, 1.00 eq.) in MeOH (3.0 mL). The reaction mixture was stirred at rt for 1.5 h, then concentrated *in vacuo*. The residue was redissolved in MeOH (10 mL) and Amberlite IR-120 (hydrogen form, 240 mg) was added. After stirring for 0.5 h the reaction mixture was filtered and concentrated to give the *title compound* (72 mg, 0.28 mmol, 76%) as a white solid which was carried on crude to the next step. **^{1}H NMR** (300 MHz, $CDCl_3$, characteristic peaks): δ 5.47 (1H, s, NH), 3.74 (3H, s, CO_2CH_3), 3.67-3.53 (2H, m), 3.49 (1H, dd, *J* 11.5, 4.2), 3.44-3.34 (1H, m), 3.25 (1H, dd, *J* 11.5, 7.1), 2.57 (1H, dd, *J* 12.8, 2.4), 2.48-2.32 (1H, m), 2.01-1.69 (3H, m), 1.47-1.34 (1H, m).

Methyl (*3R*,4aR)-3-(azidomethyl)-2-[(4-fluorophenyl)methyl]-1-oxo-octahydropyrrolo[1,2-c]pyrimidine-4a-carboxylate S10**



S10

To a stirred solution of urea **S9** (72 mg, 0.28 mmol, 1.0 eq.) in DMF (2.0 mL) was added NaH (60% dispersion in oil, 13 mg, 0.31 mmol, 1.1 eq.). The reaction mixture was stirred for 10 min then 4-fluorobenzyl bromide (70 μL, 0.56 mmol, 2.0 eq.) was added. The reaction mixture was stirred for 1 h then H_2O (0.1 mL) was added. The reaction mixture was diluted with Et_2O (10 mL) and washed with brine (10 mL). The aqueous layer was extracted with Et_2O (10 mL), then the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* Flash chromatography on cyanosilica eluting with a gradient of 0-100% EtOAc in pentane, gave the *title compound* **S10** (53 mg, 0.15 mmol, 52%) as colourless oil. **R_f** 0.26 (EtOAc–petrol). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.21 (2H, app. dd, *J* 8.4, 5.5, Ar 2-H), 6.99 (2H, app. t, *J* 8.7, Ar 3-H), 5.32 (1H, d, *J* 15.9, C*H*$_A$$H_B$Ar), 3.99 (1H, d, *J* 15.9, CH_A*H*$_B$Ar), 3.74-3.63 (5H, m includes 2H, m, 7-H and at δ 3.66: 3H, s, CO_2CH_3), 3.48 (1H, dd, *J* 12.9, 5.2, C*H*$_A$$H_B$$N_3$), 3.31 (1H, dd, *J* 12.9, 2.8, CH_A*H*$_B$$N_3$), 3.23-3.17 (1H, m, 3-H), 2.60 (1H, dd, *J* 13.0, 5.0,

4-H_A), 2.42-2.36 (1H, m, 5-H_A), 1.98-1.75 (4H, m, 4-H_B; 5-H_B and 6-H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 174.3 (*C*O_2Me), 162.1 (d, *J* 245.6, Ar 4-C), 155.3 (1-C), 133.5 (Ar 1-C), 129.4 (d, *J* 7.8, Ar 2-C), 115.5 (d, *J* 21.3, Ar 3-C), 65.0 (4a-C), 52.8 (CO_2*C*H_3), 52.4 (*C*H_2N_3), 51.2 (3-C), 46.5 (7-C or *C*H_2Ar), 46.3 (7-C or *C*H_2Ar), 38.6 (5-C), 35.8 (4-C), 21.7 (6-C). **IR** ν_{max}(film)/cm^{-1} 2953, 2101 (N_3), 1733 (CO), 1635, 1509, 1450, 1350,1218. **HRMS** (ESI): $C_{17}H_{21}FN_5O_3$ $[M+H]^+$; calculated 362.1623, found 362.1630.

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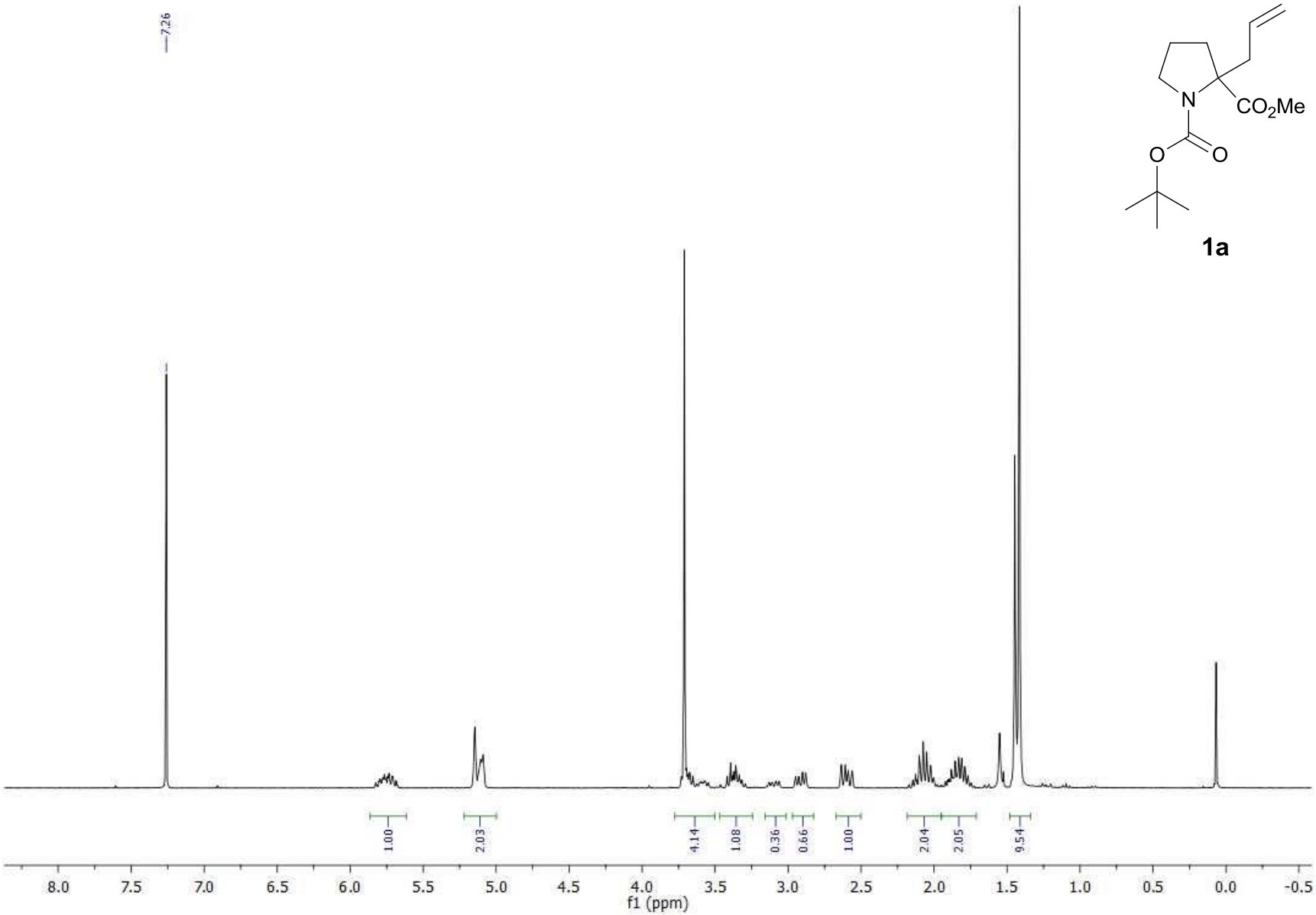
9.0 NMR Spectra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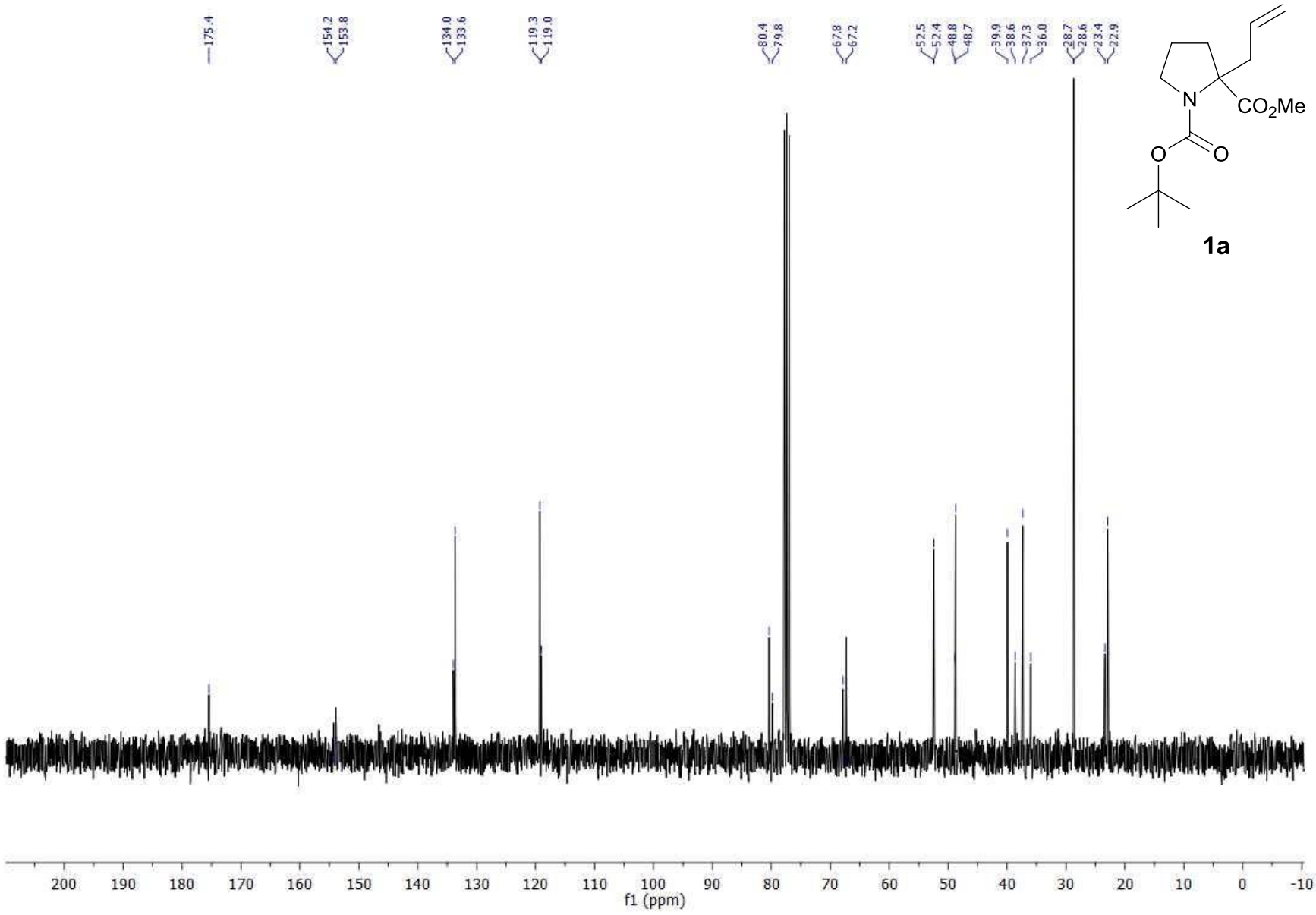
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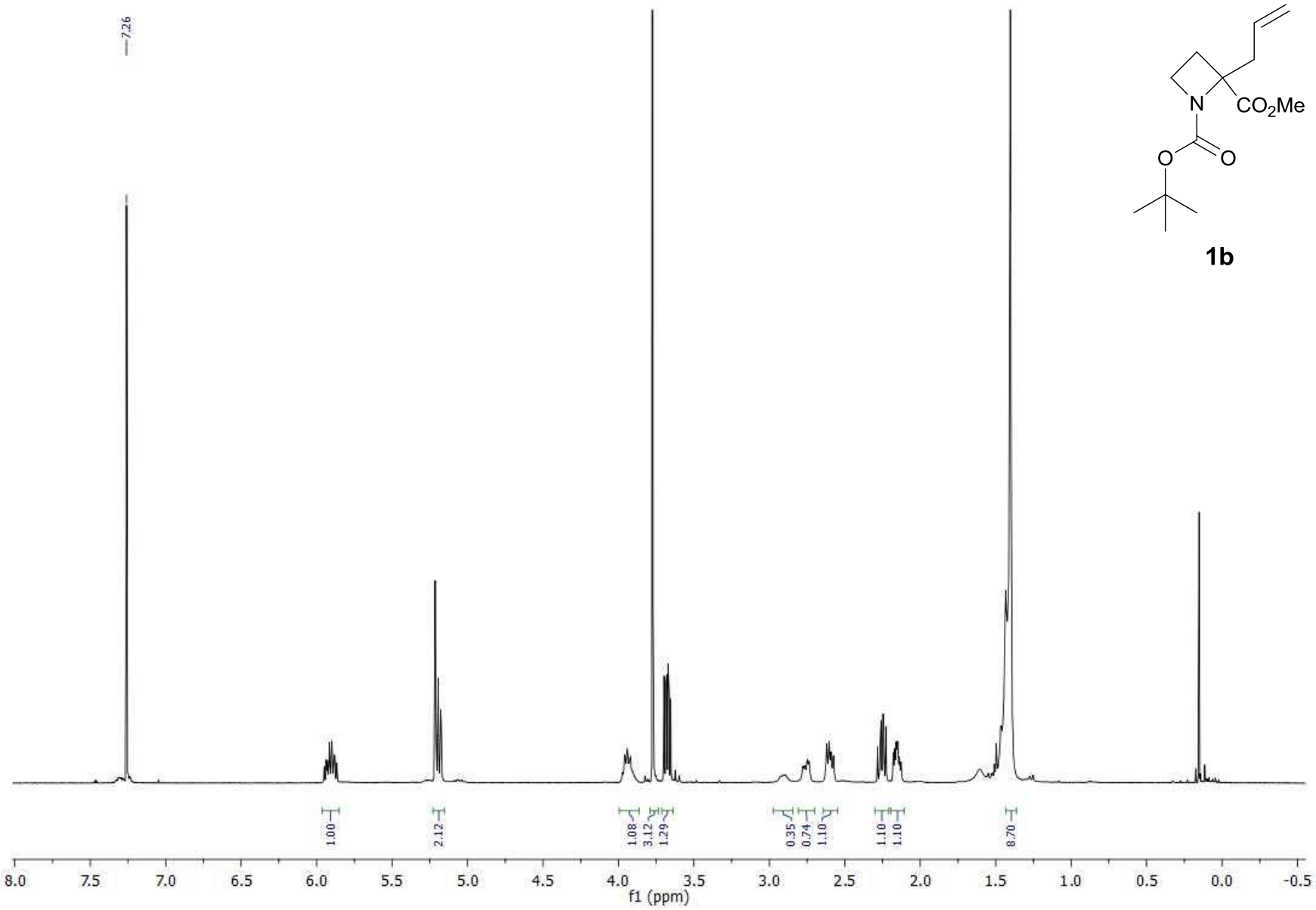
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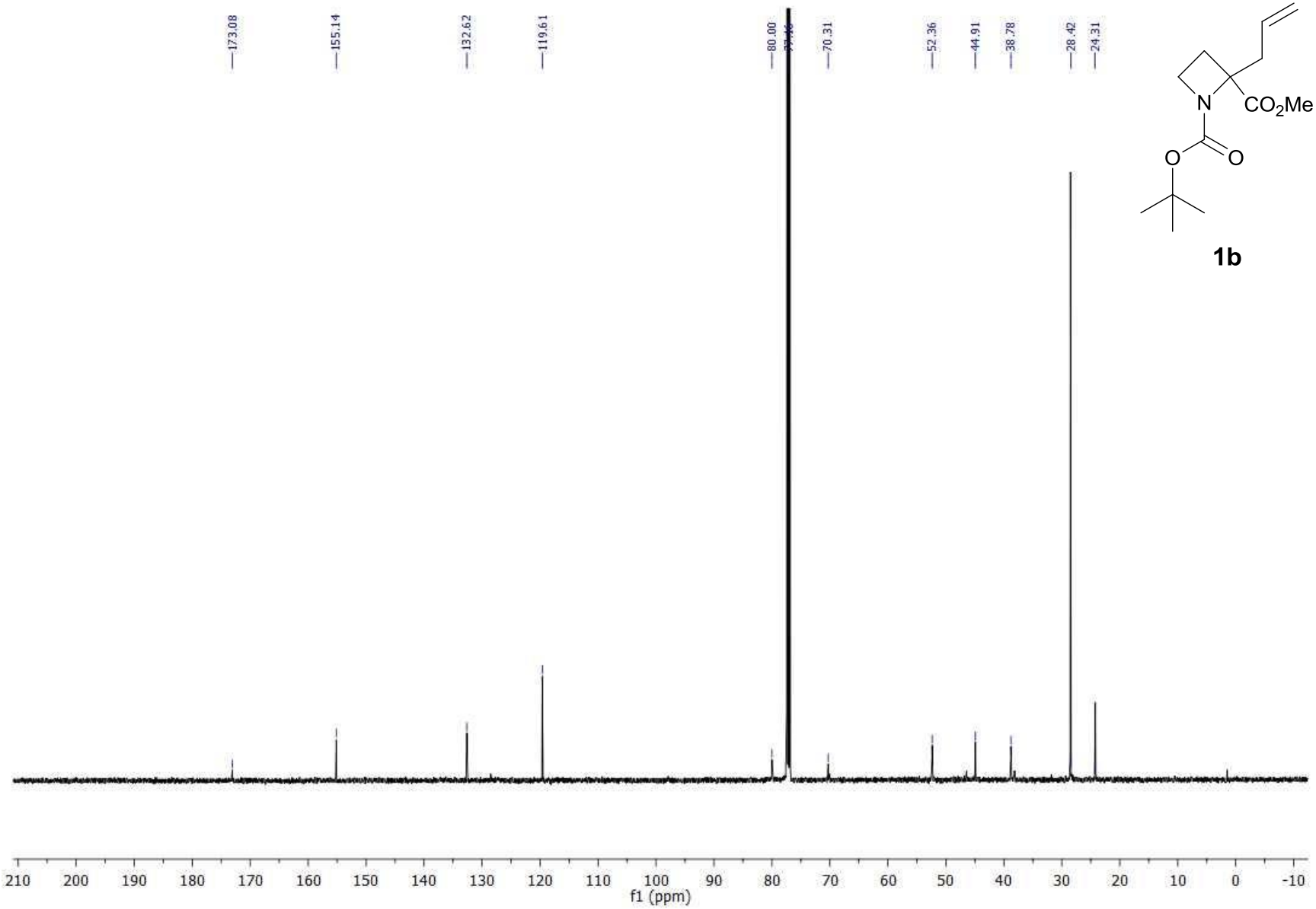
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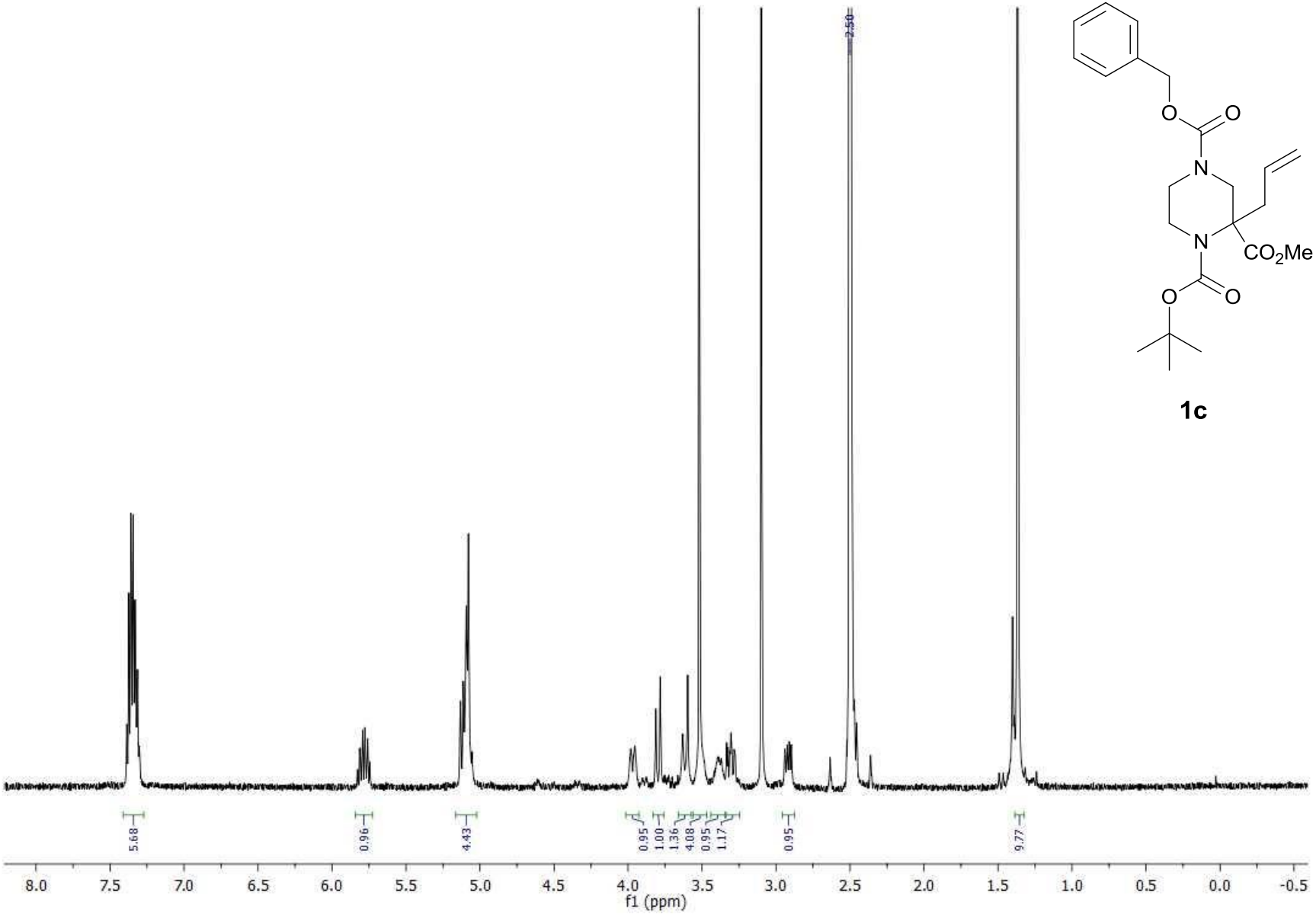
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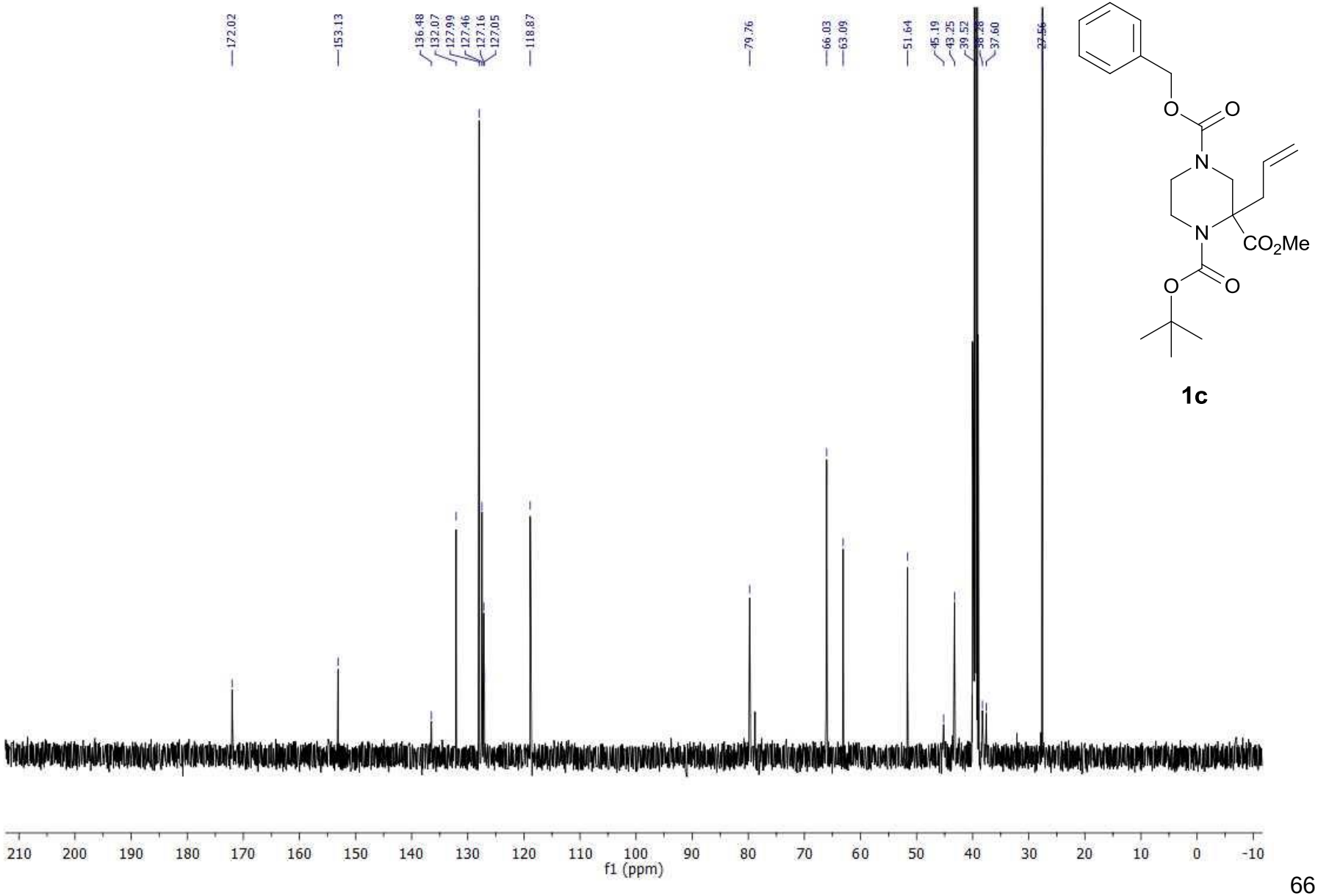
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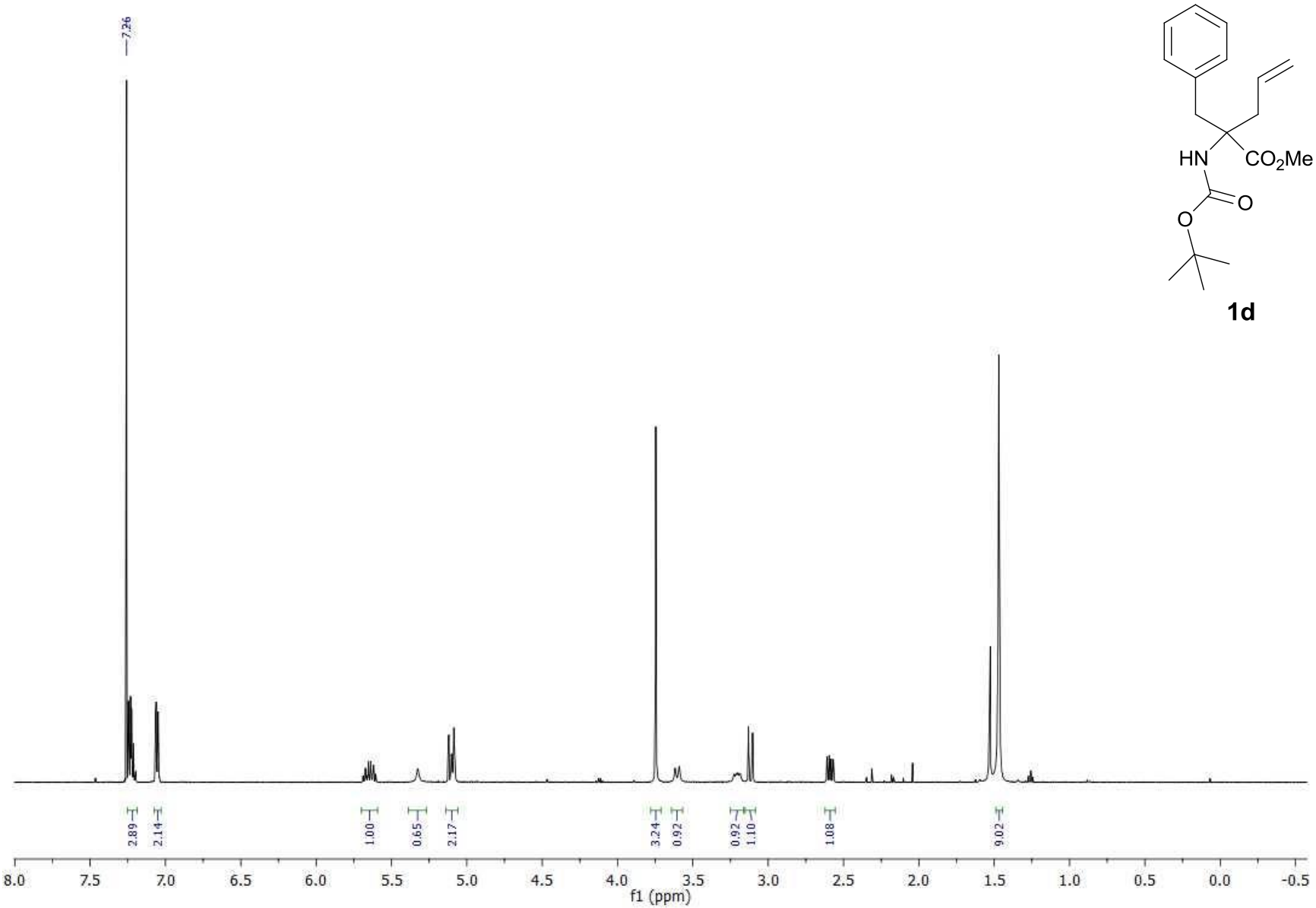
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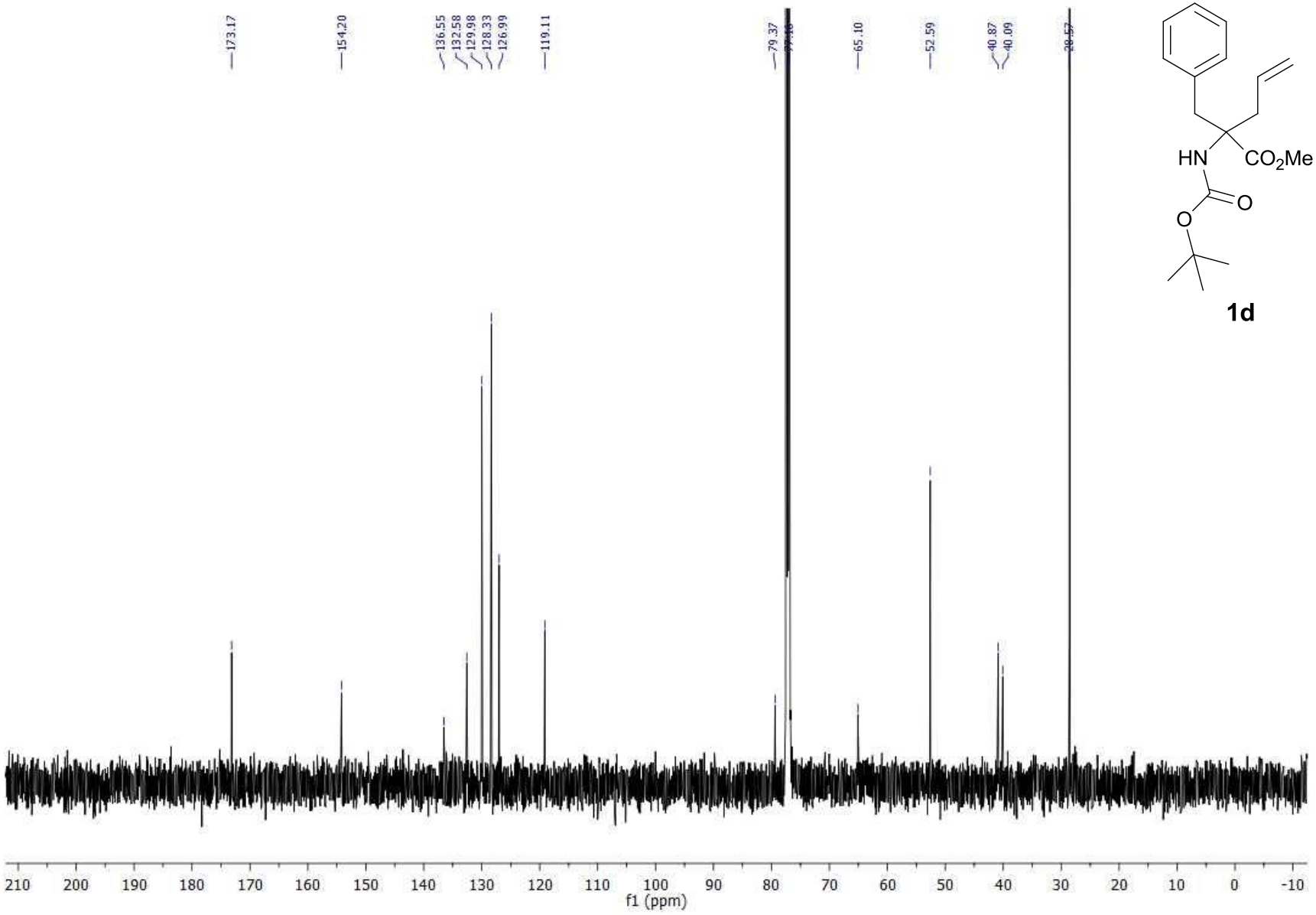
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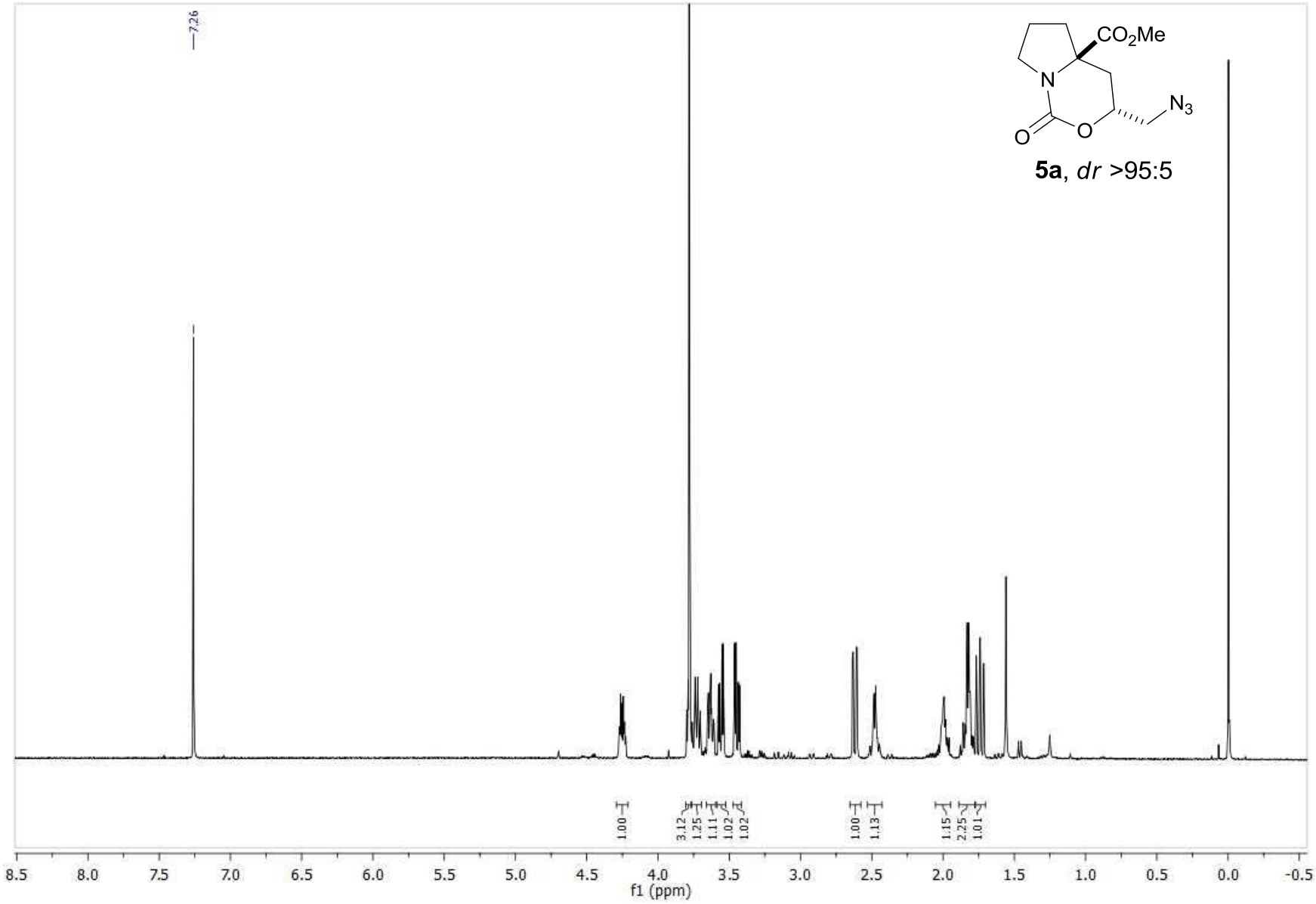
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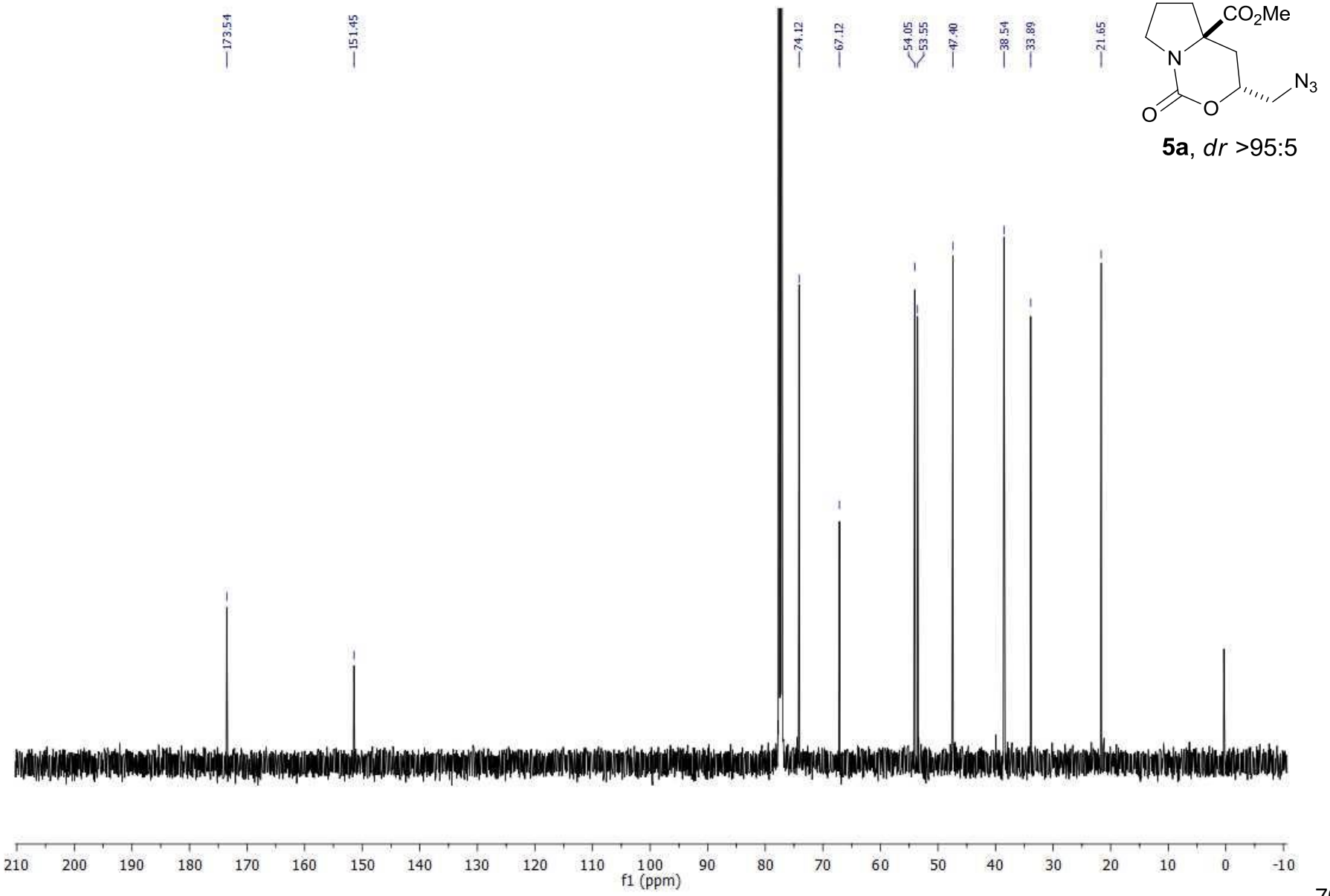
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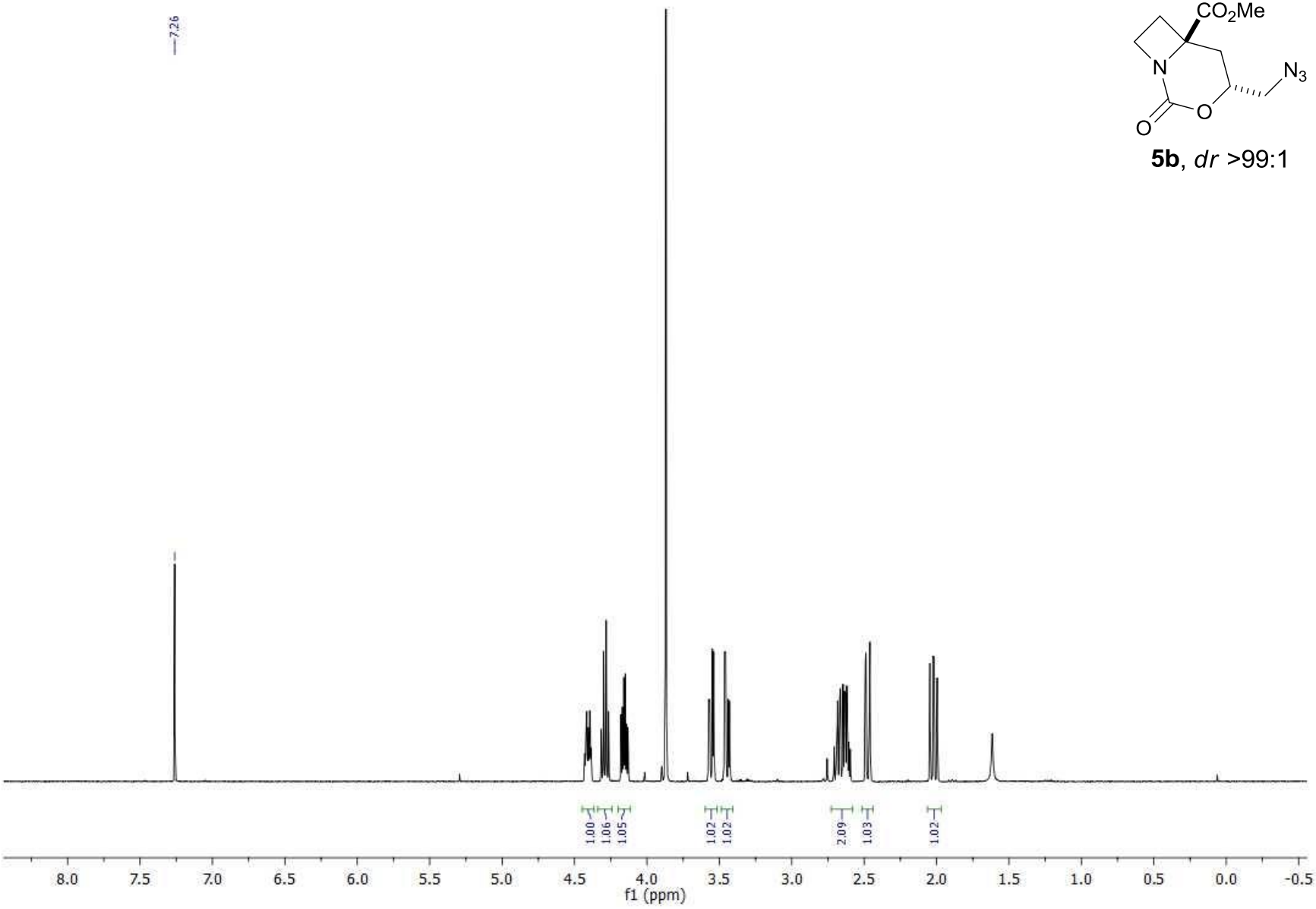
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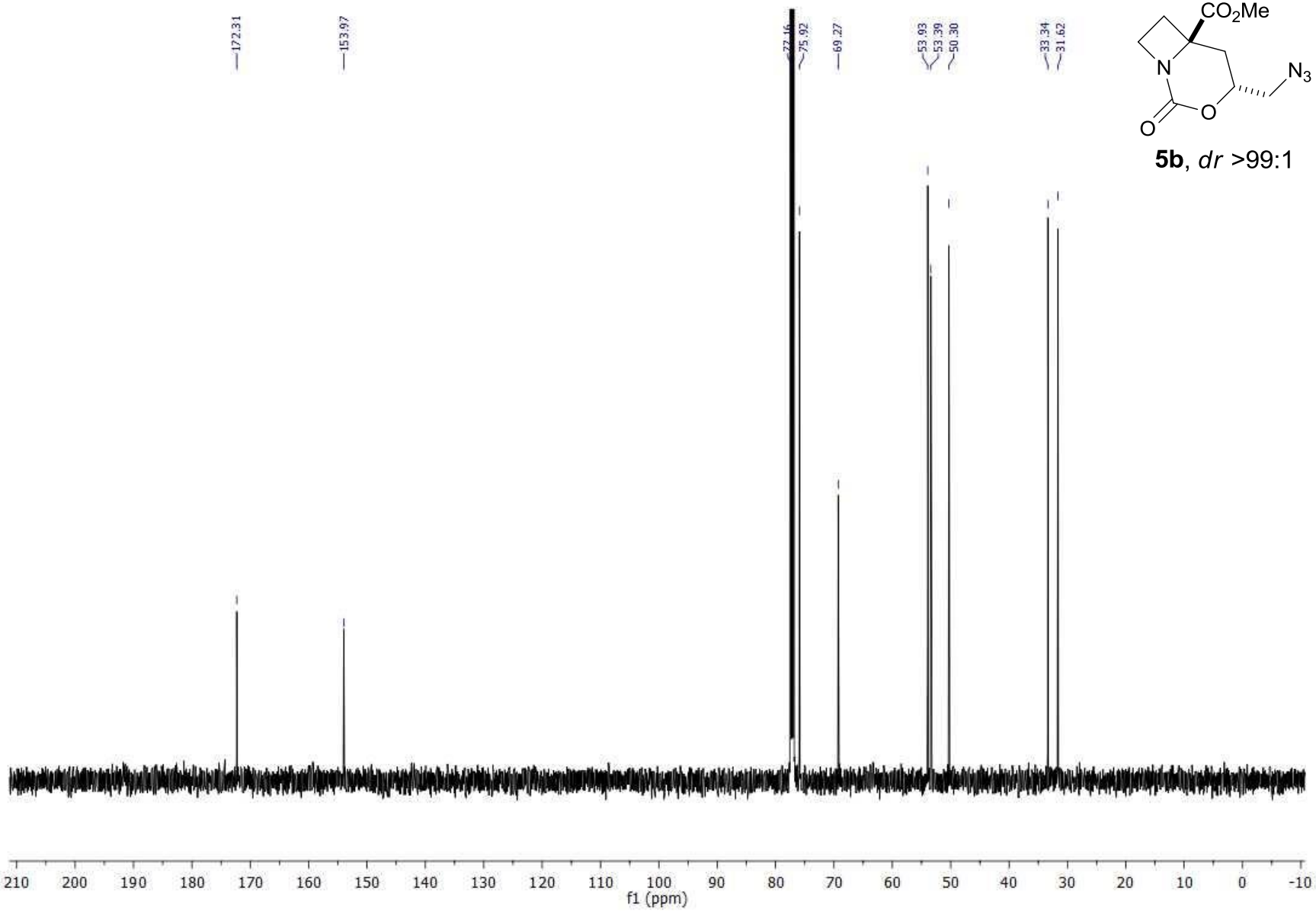
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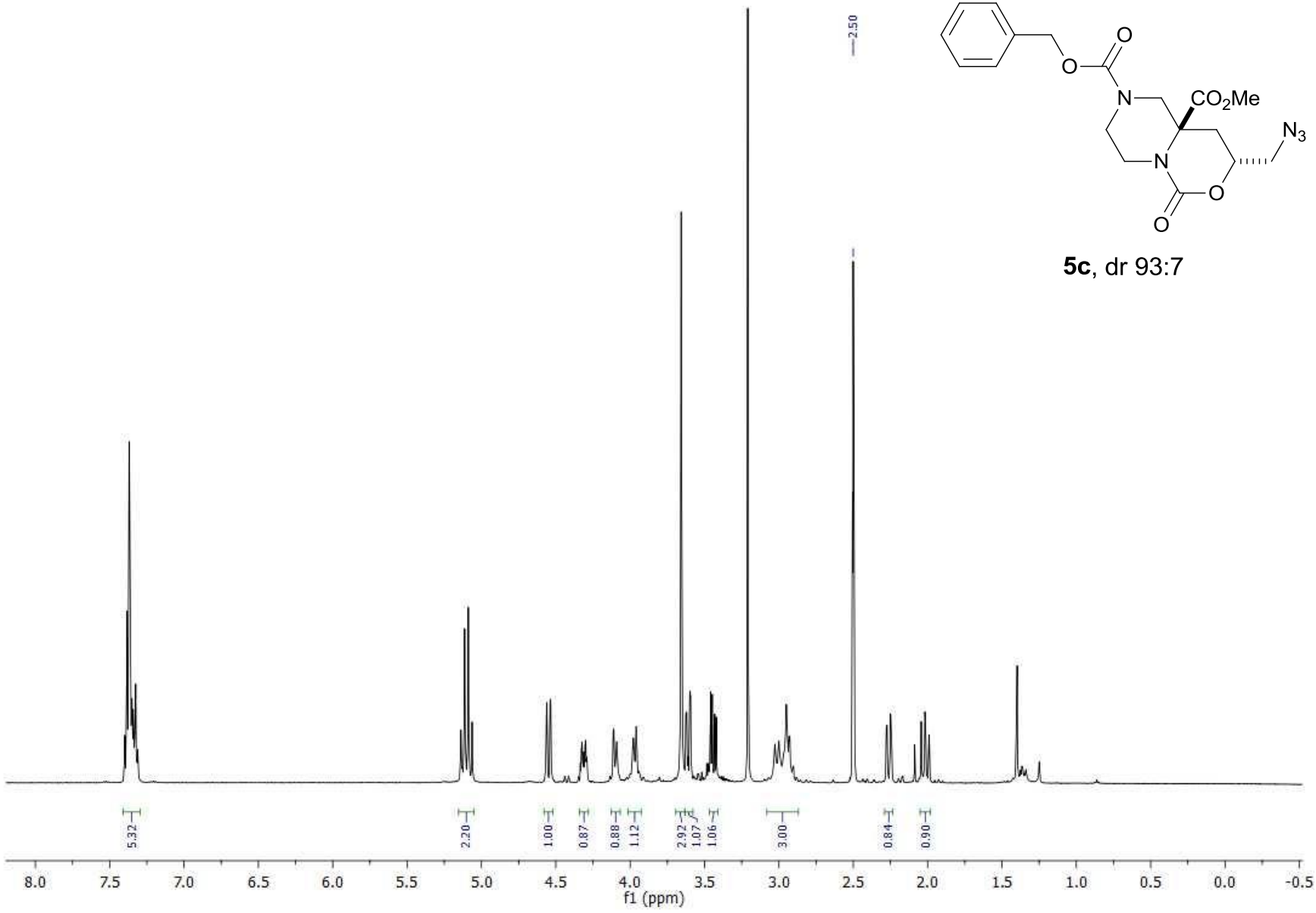
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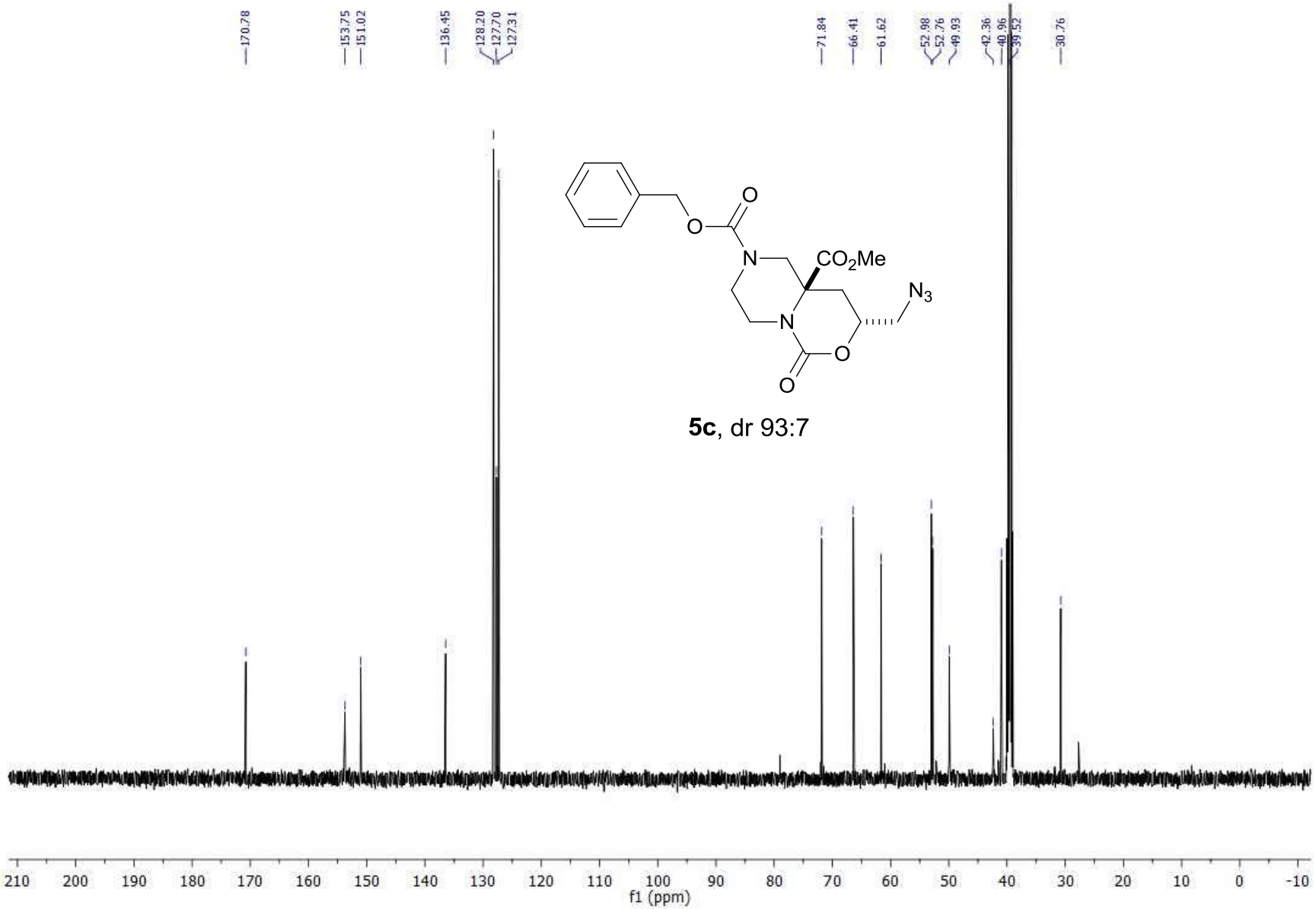
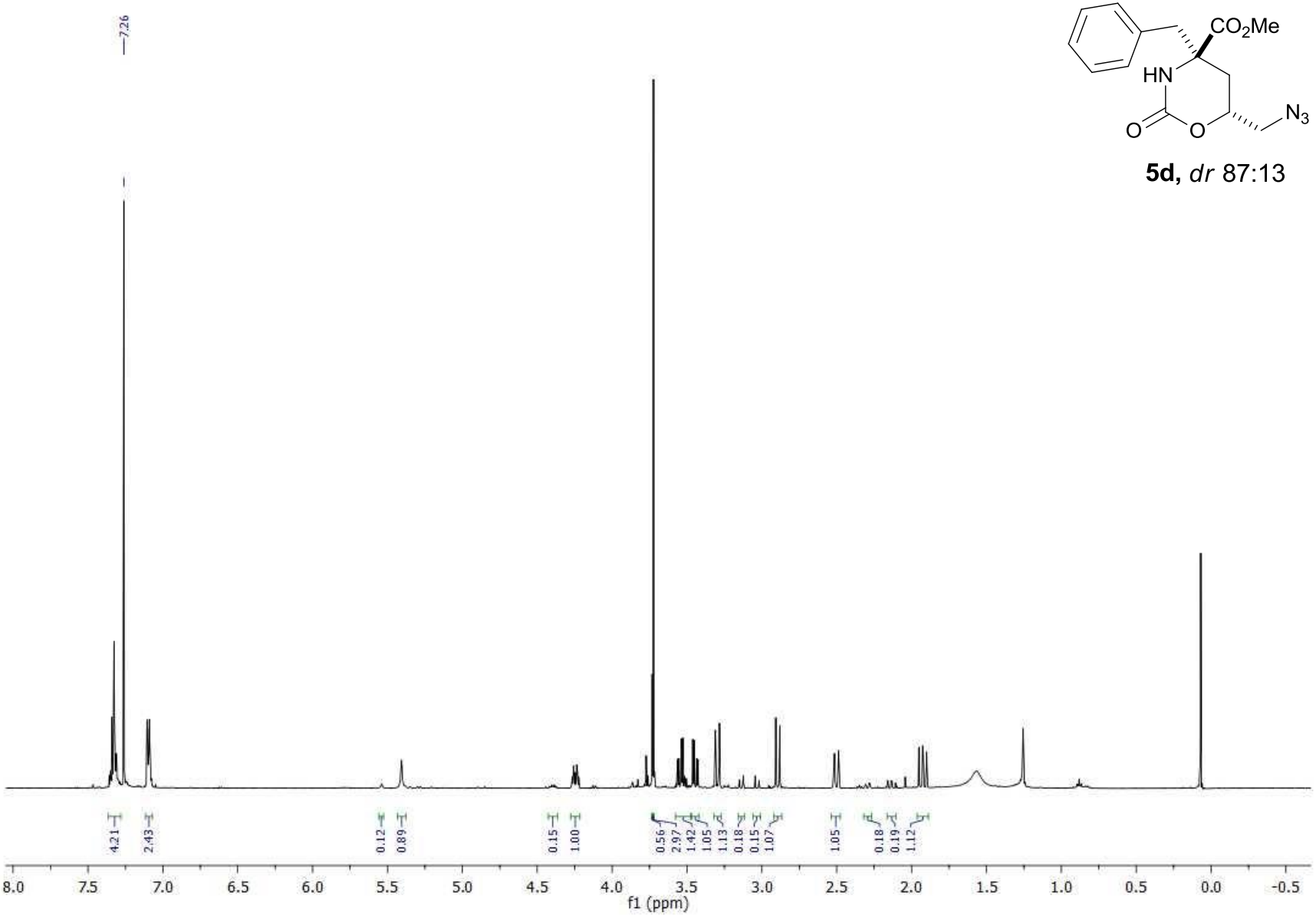
O

5c, dr 93:7

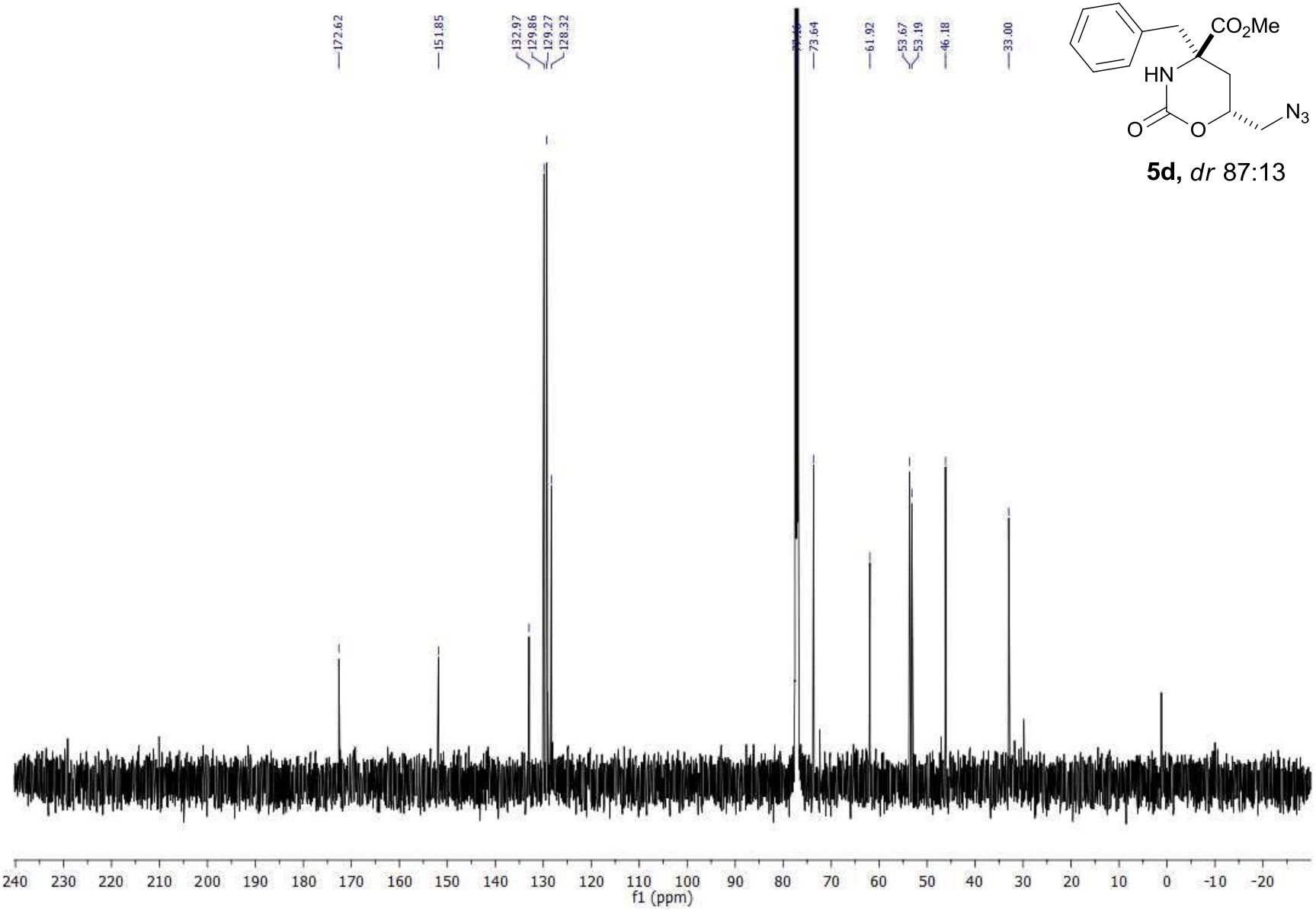

170.78
153.75
151.02
136.45
128.20
127.70
127.31
71.84
66.41
61.62
52.98
52.76
49.93
42.36
40.96
39.52
30.76
O
O
N
CO2Me
N3
N
O
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

5c, dr 93:7


7.26
4.21
2.43
0.12
0.89
0.15
1.00
0.56
2.97
1.42
1.05
1.13
0.18
0.15
1.07
1.05
0.18
0.19
1.12
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
-0.5
f1 (ppm)

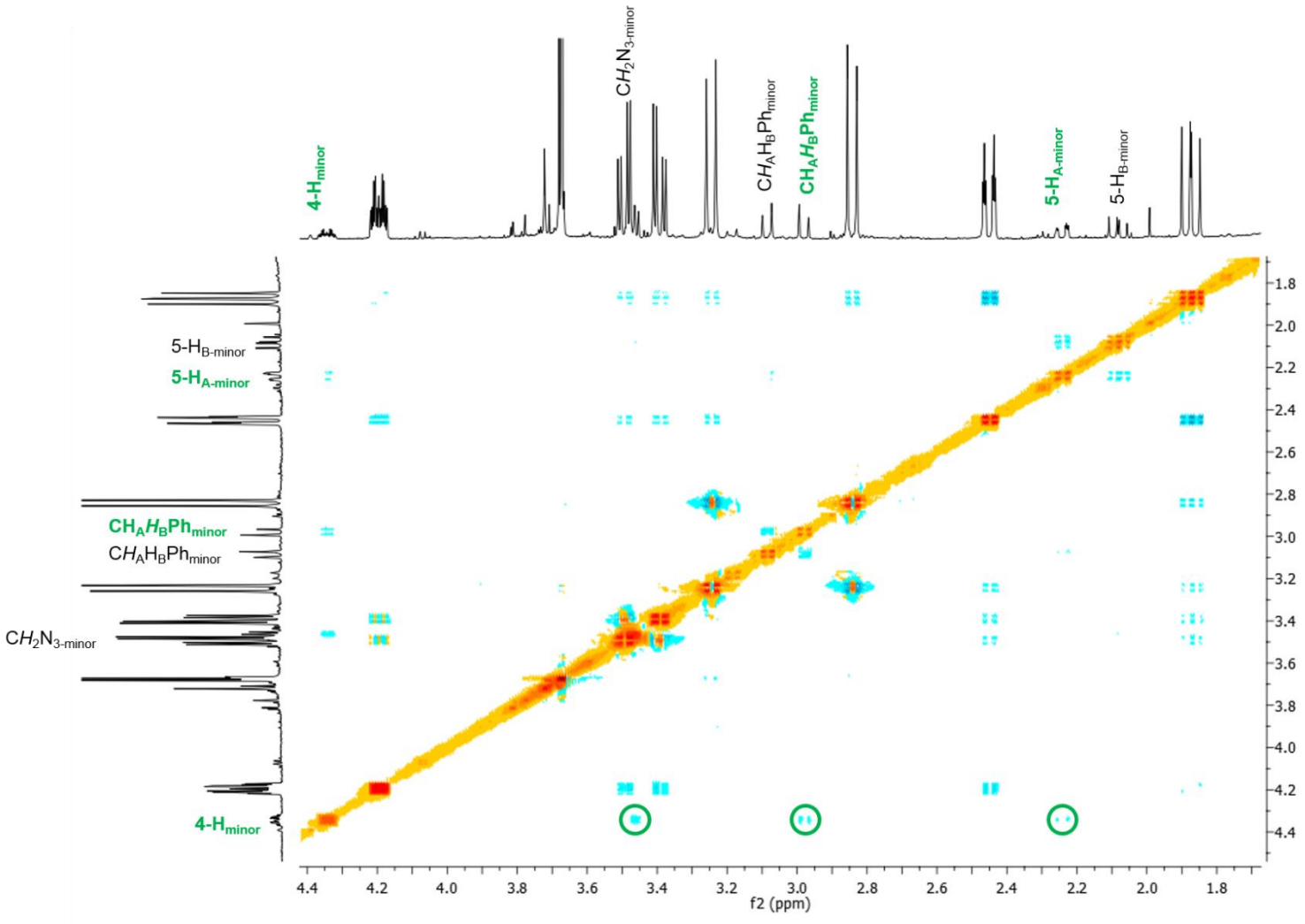
CO2Me
HN
O
O
N3

5d, *dr* 87:13

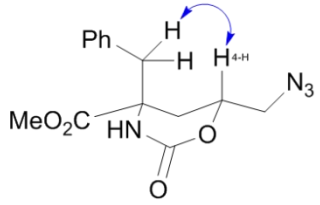

172.62
151.85
132.97
129.86
129.27
128.32
77.46
73.64
61.92
53.67
53.19
46.18
33.00
CO2Me
HN
O
O
N3
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

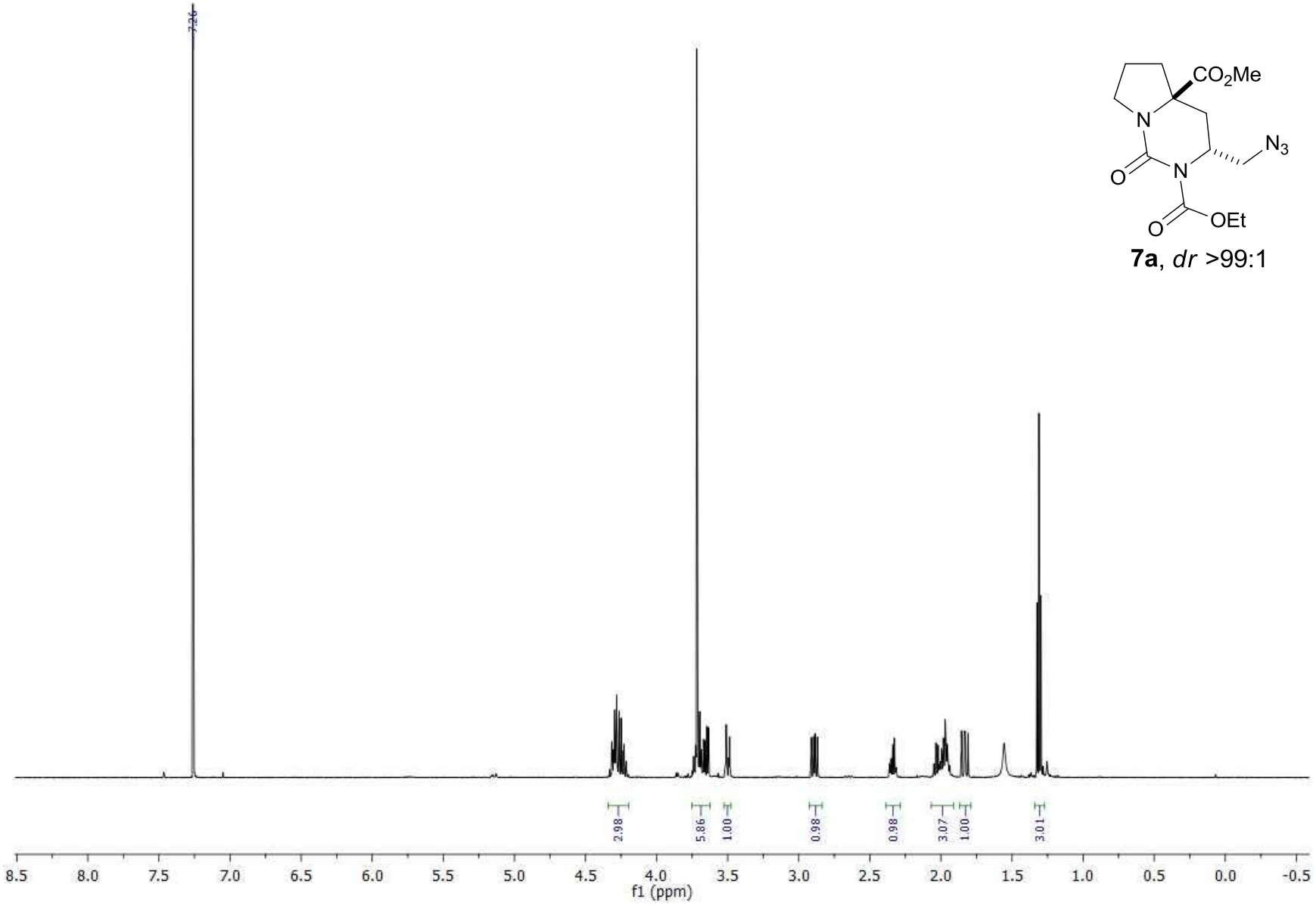
5d, *dr* 87:13

key nOe enhancement for **5d$_{minor}$**



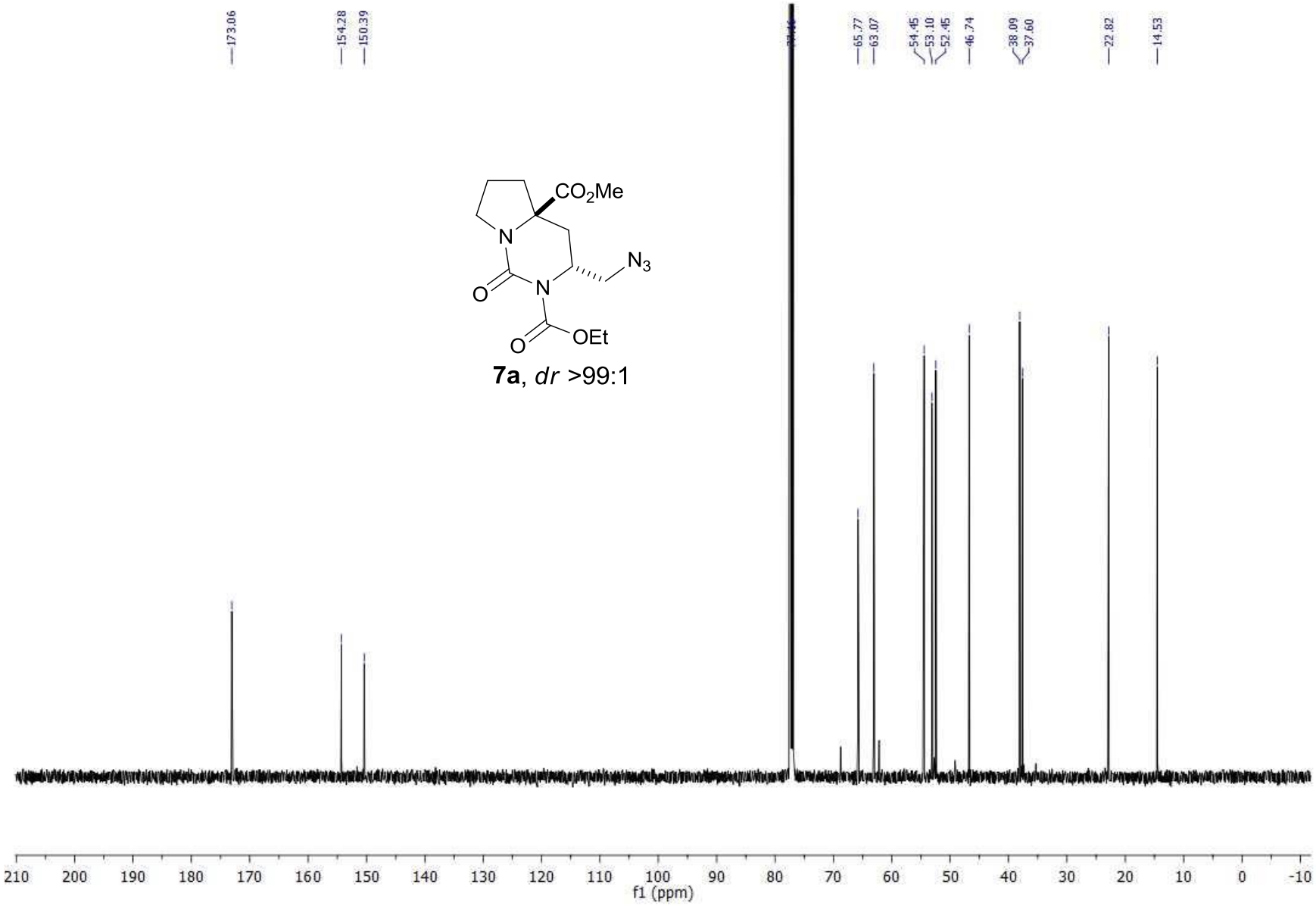
5d, minor diastereomer
NOESY correlations:

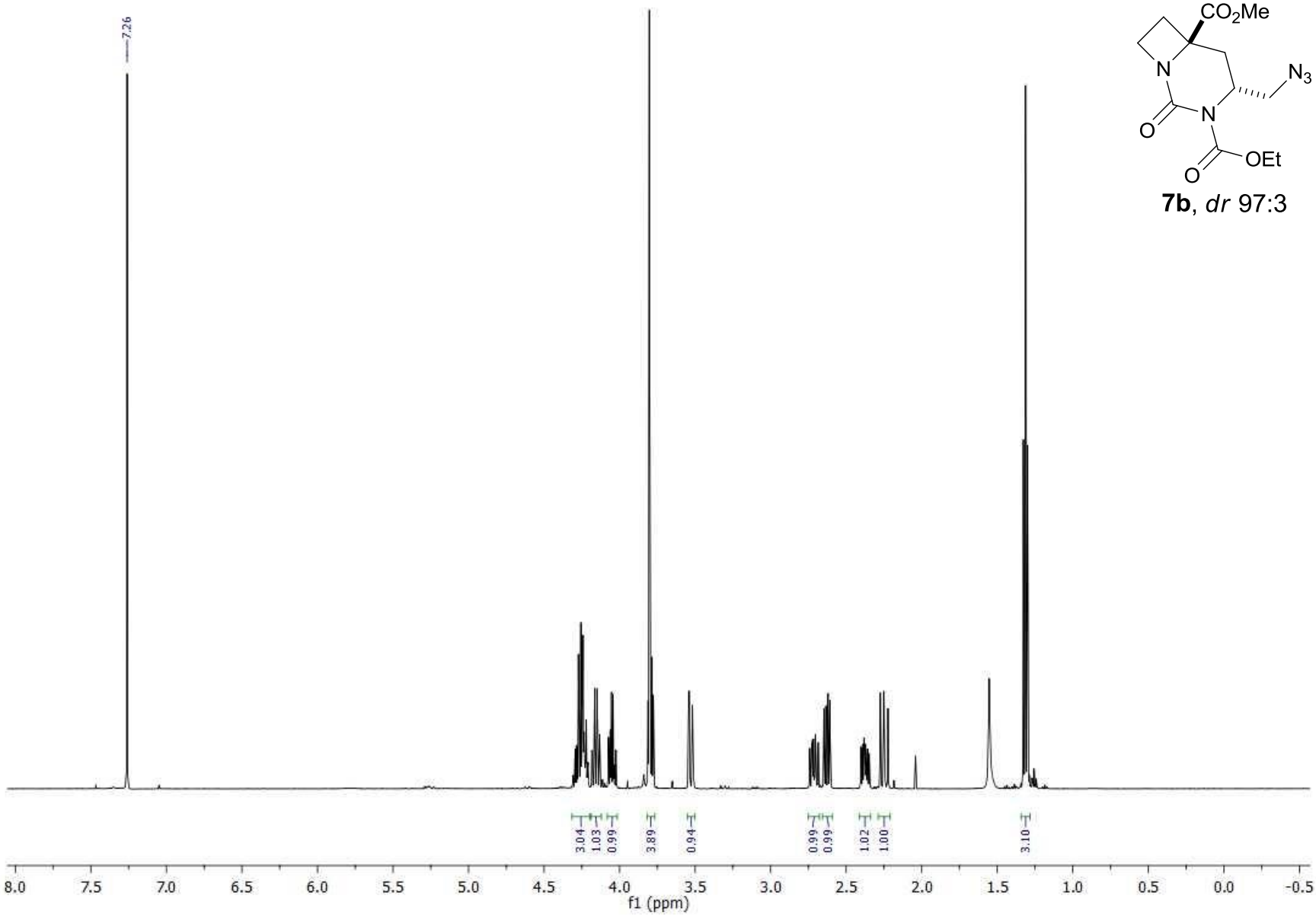



7.26
2.98
5.86
1.00
0.98
0.98
3.07
1.00
3.01
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

CO2Me
N
N3
O
N
O
OEt

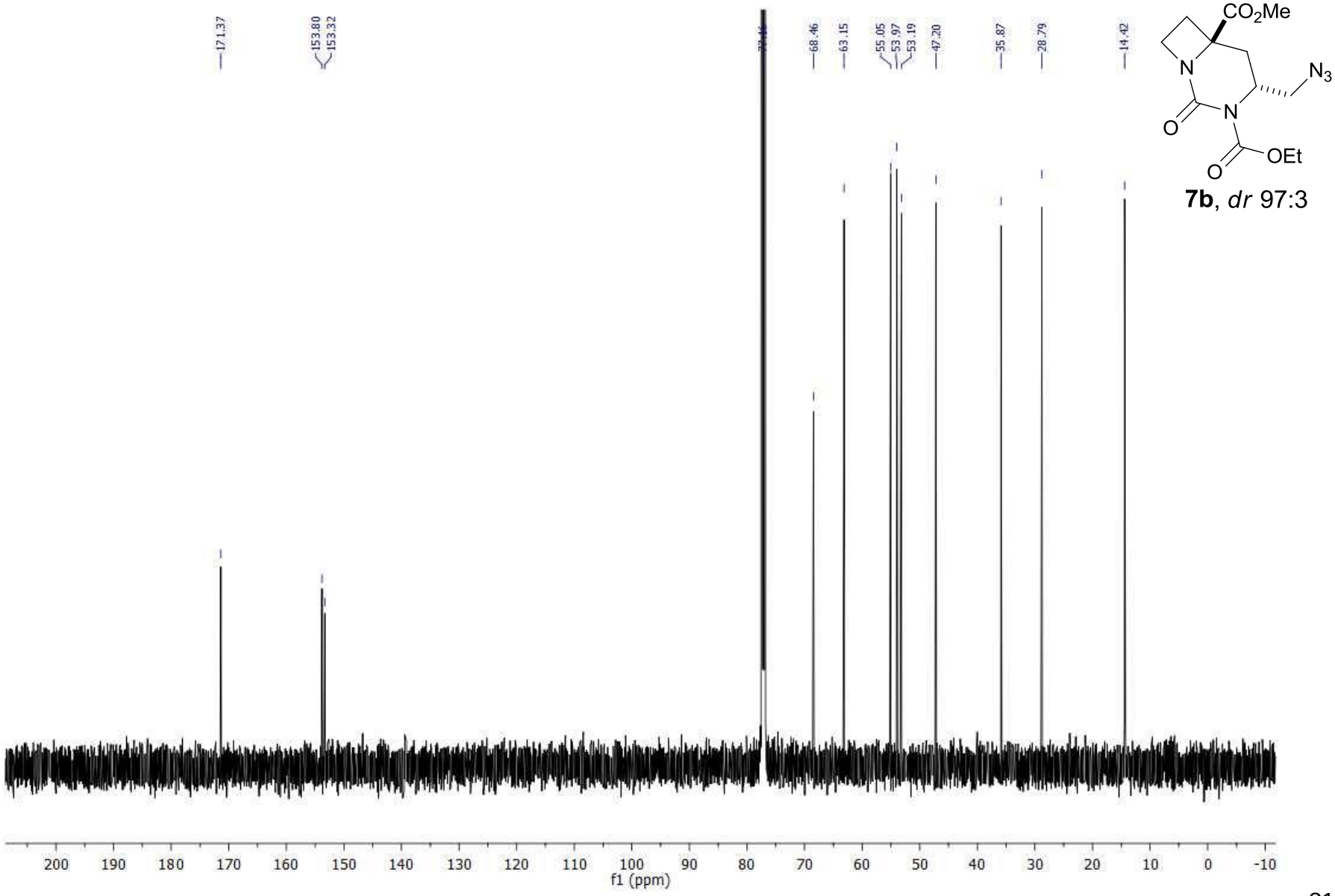
7a, *dr* >99:1

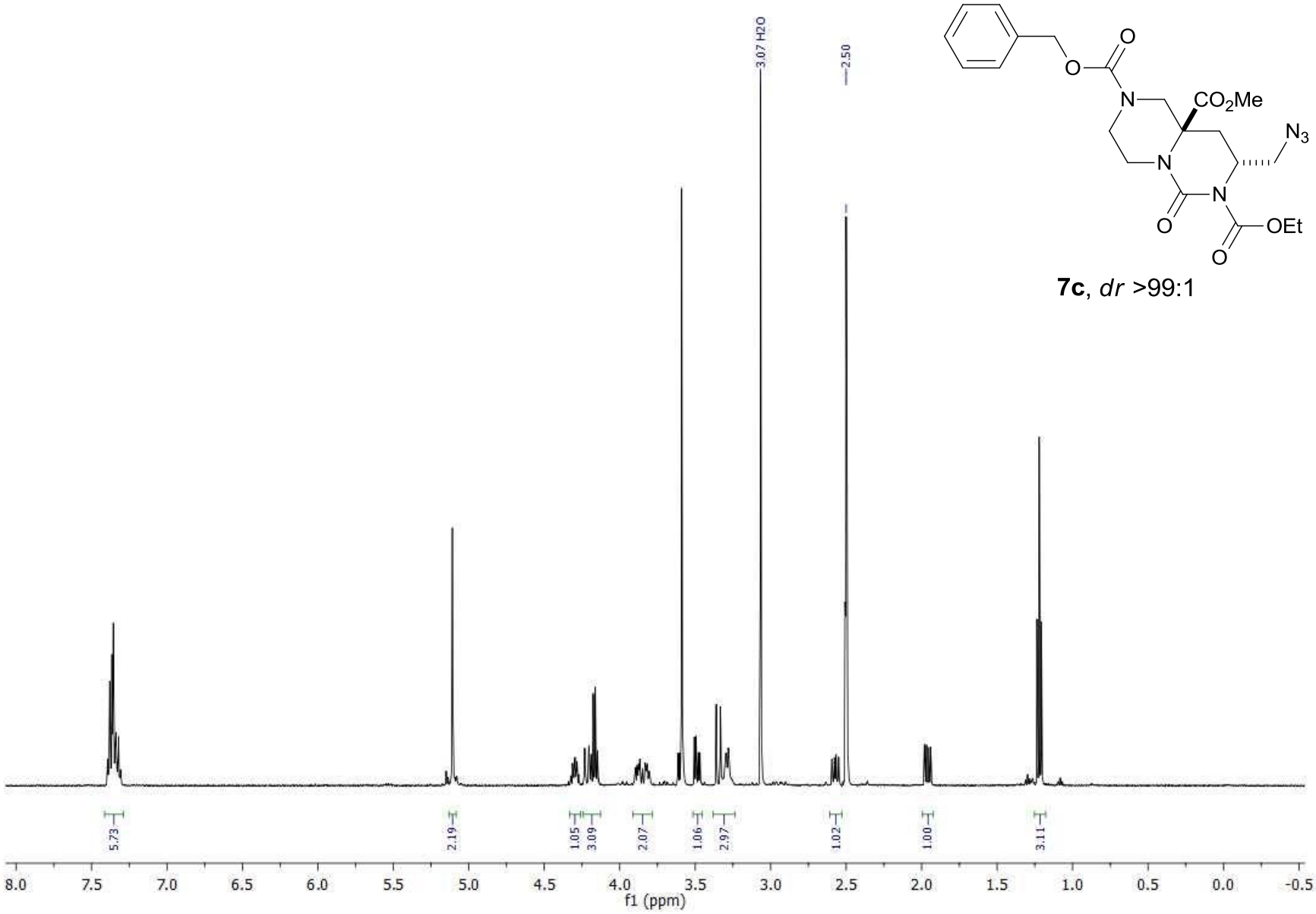

173.06
154.28
150.39
65.77
63.07
54.45
53.10
52.45
46.74
38.09
37.60
22.82
14.53
CO2Me
N
N3
O
N
O
OEt
7a, dr >99:1
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.26
3.04
1.03
0.99
3.89
0.94
0.99
0.99
1.02
1.00
3.10
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
-0.5
f1 (ppm)

CO2Me
N
N3
O
N
O
OEt

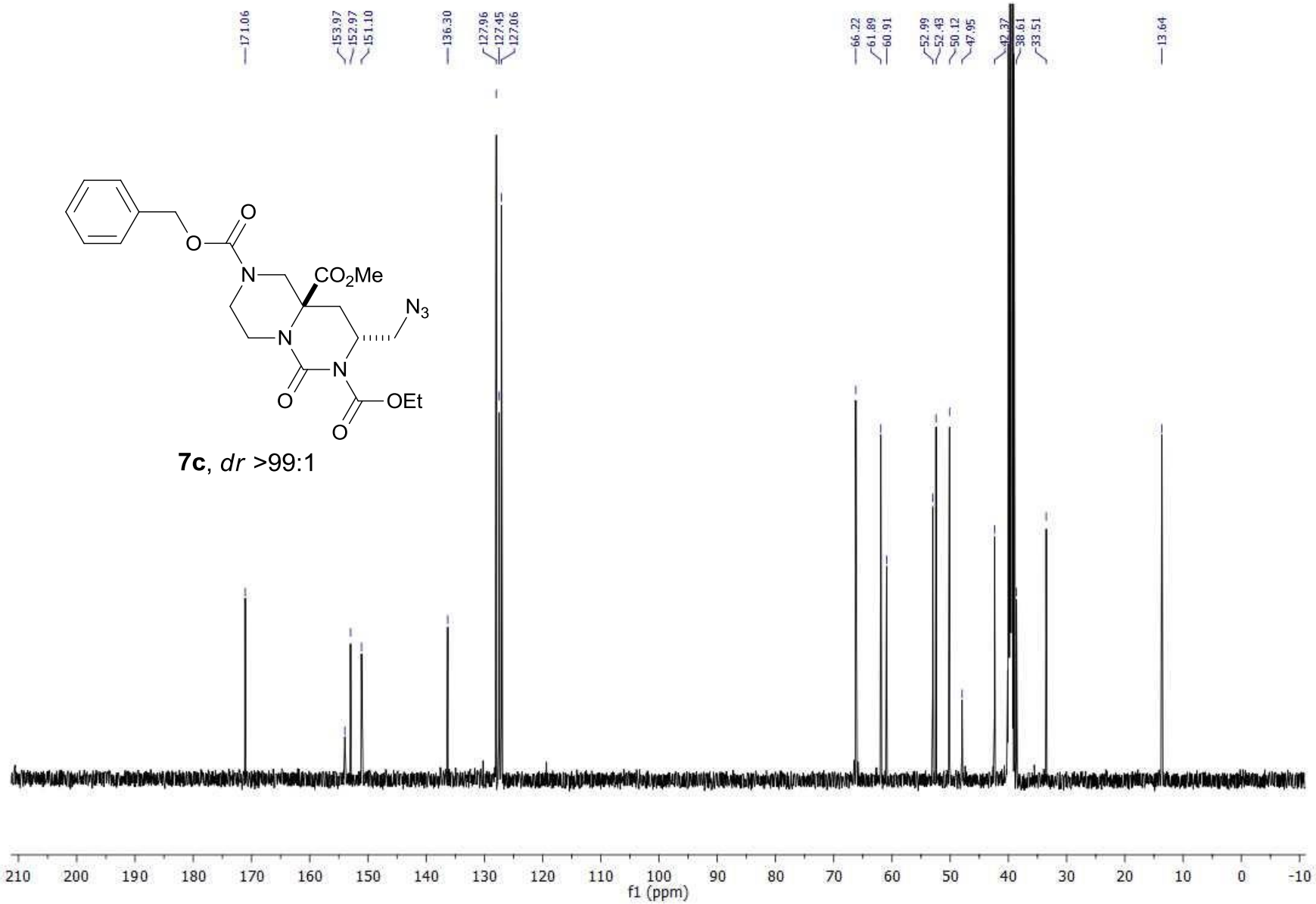
7b, *dr* 97:3


171.37
153.80
153.32
77.46
68.46
63.15
55.05
53.97
53.19
47.20
35.87
28.79
14.42
CO2Me
N
N3
O
N
O
OEt
O
7b, dr 97:3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

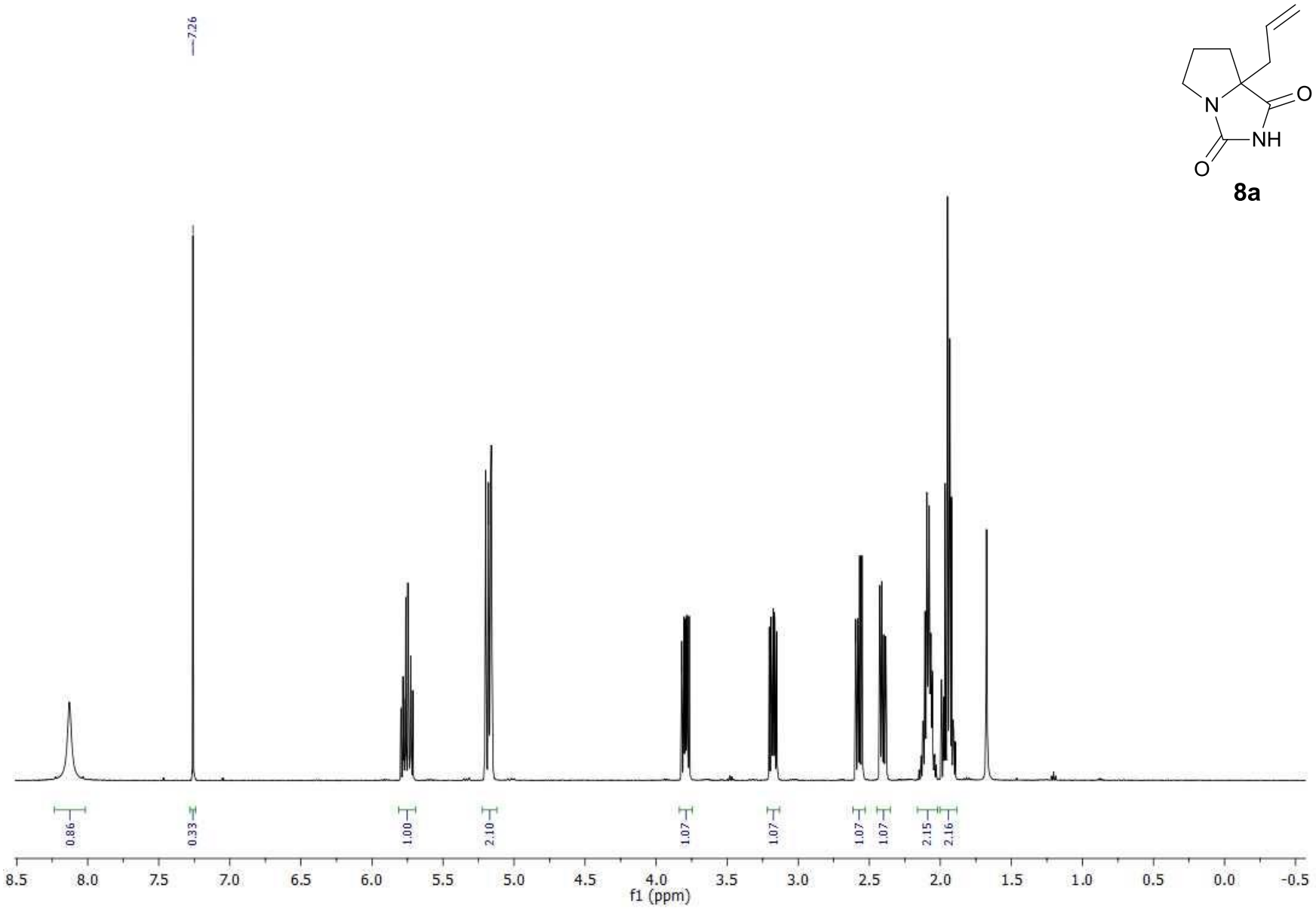

3.07 H2O
2.50
5.73
2.19
1.05
3.09
2.07
1.06
2.97
1.02
1.00
3.11
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

O
O
N
CO2Me
N3
N
N
O
O
OEt

7c, *dr* >99:1

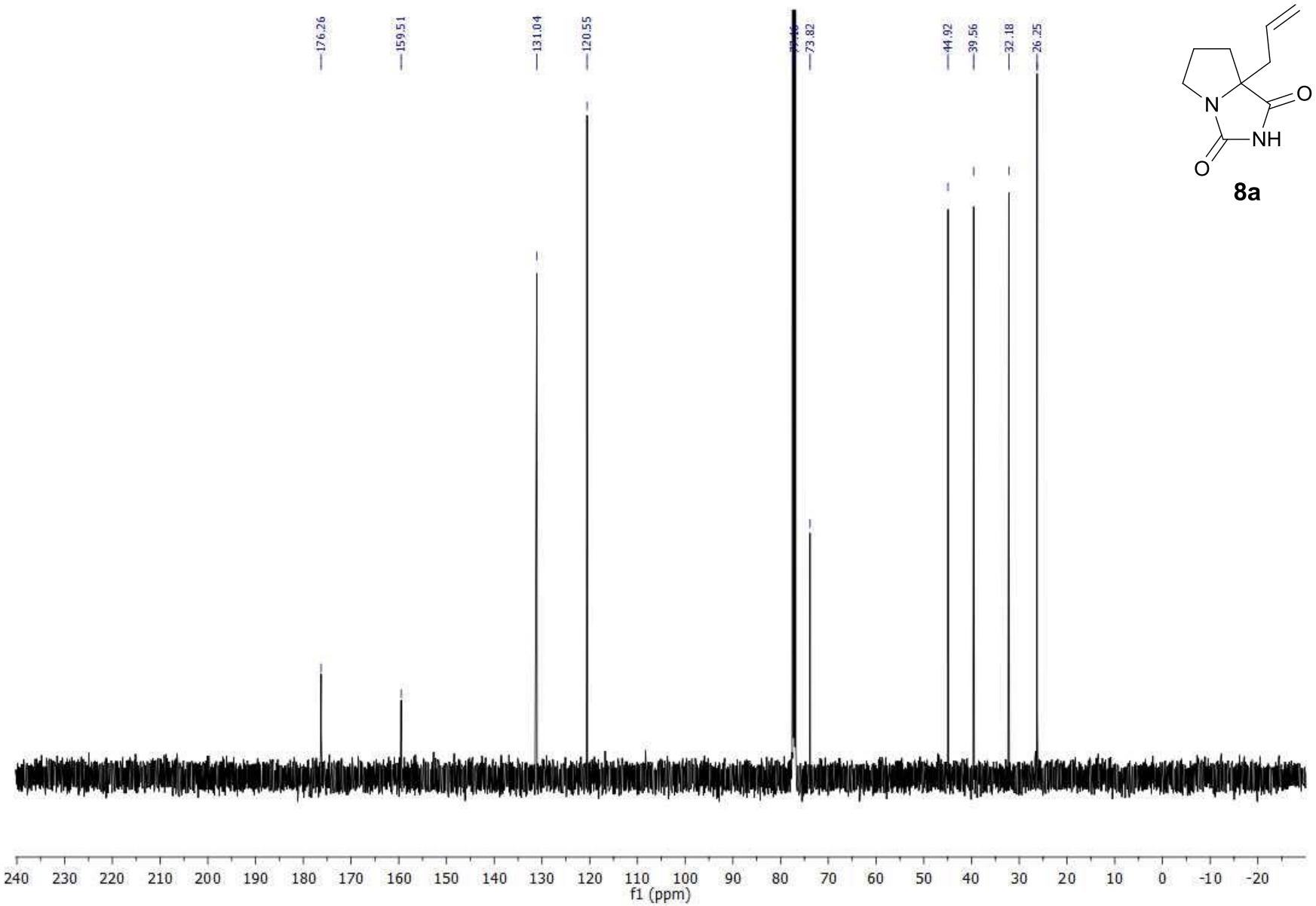

171.06
153.97
152.97
151.10
136.30
127.96
127.45
127.06
66.22
61.89
60.91
52.99
52.43
50.12
47.95
42.37
38.61
33.51
13.64
O
O
N
CO2Me
N3
N
N
O
O
OEt
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

7c, *dr* >99:1

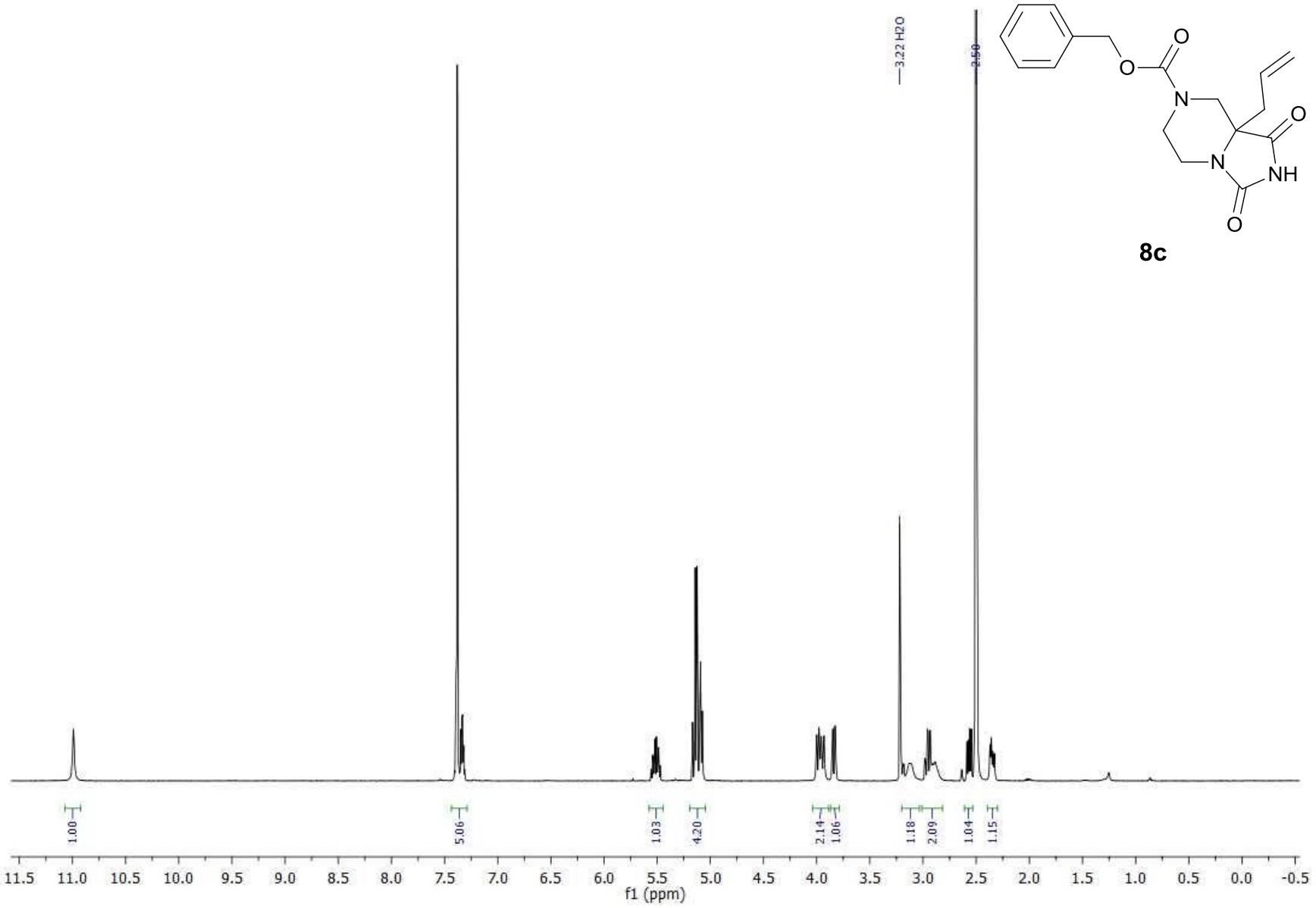

7.26
0.86
0.33
1.00
2.10
1.07
1.07
1.07
1.07
2.15
2.16
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

N
O
NH
O

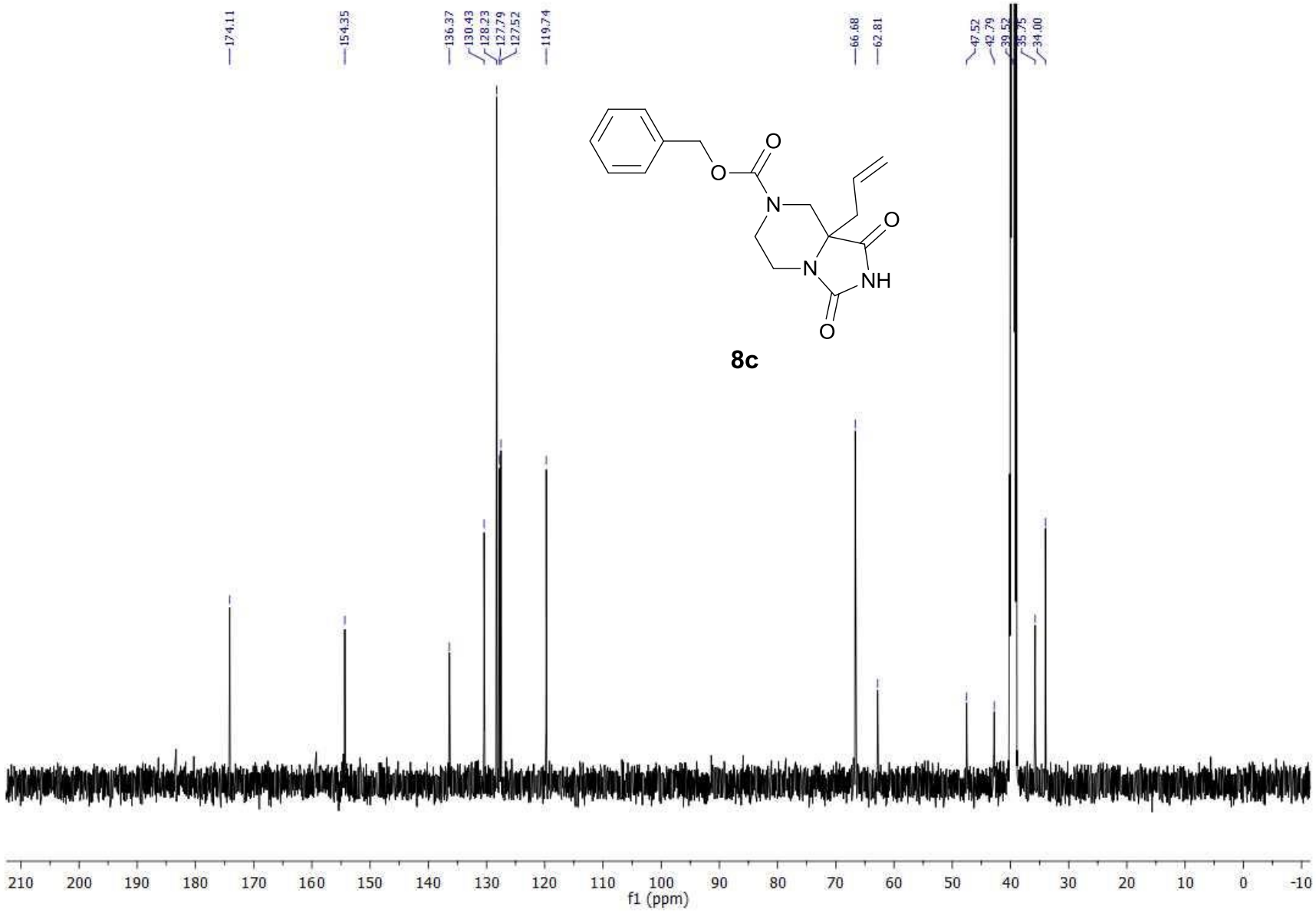
8a

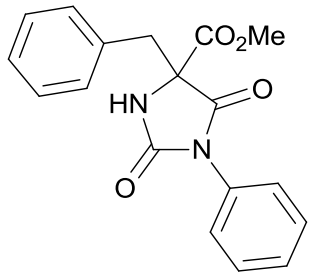

176.26
159.51
131.04
120.55
77.46
73.82
44.92
39.56
32.18
26.25
N
O
NH
O
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

8a


3.22 H2O
2.50
O
O
N
O
N
NH
O
1.00
5.06
1.03
4.20
2.14
1.06
1.18
2.09
1.04
1.15
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 -0.5
f1 (ppm)

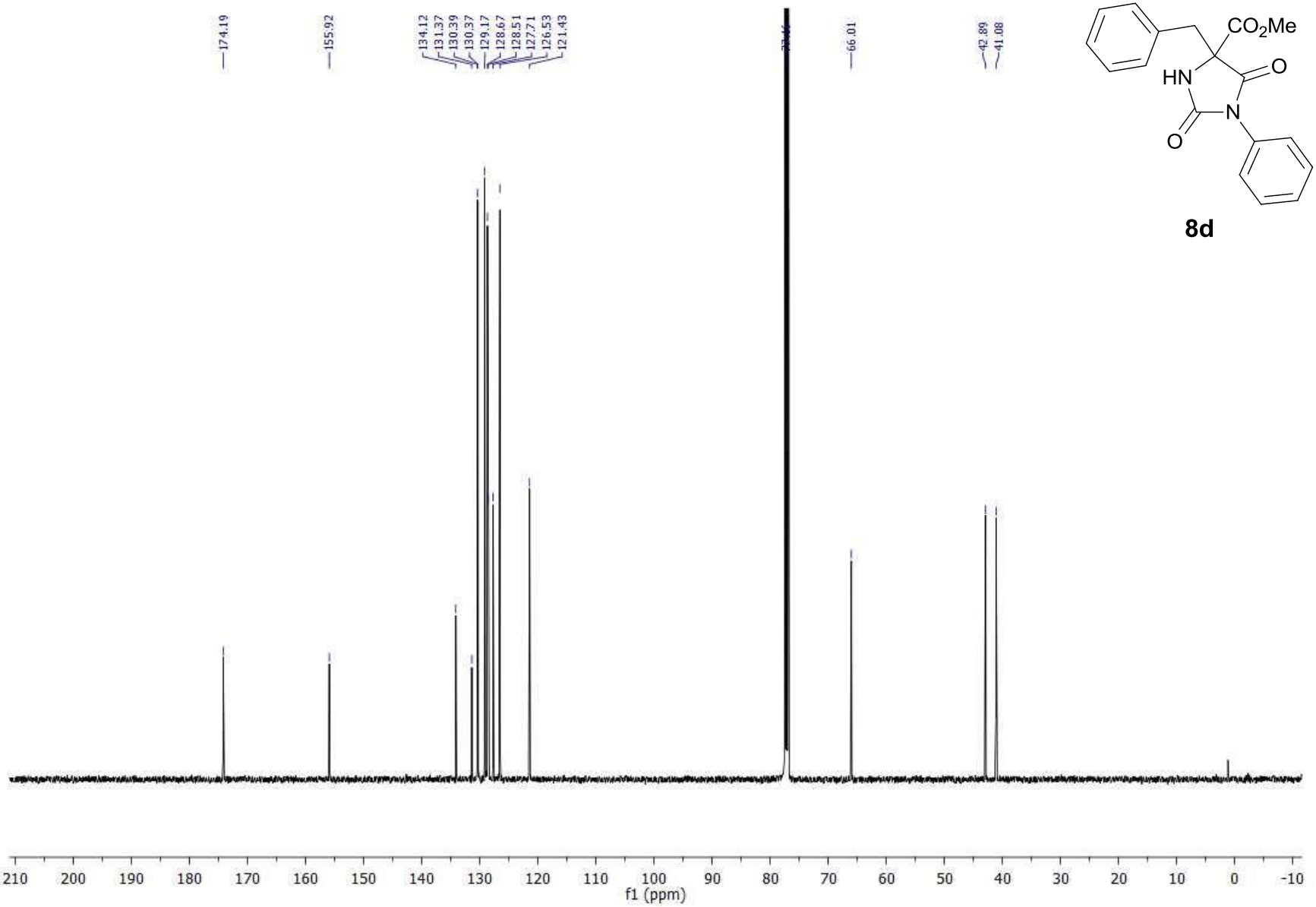
8c


174.11
154.35
136.37
130.43
128.23
127.79
127.52
119.74
66.68
62.81
47.52
42.79
39.52
35.75
34.00
O
O
N
O
N
NH
O
8c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

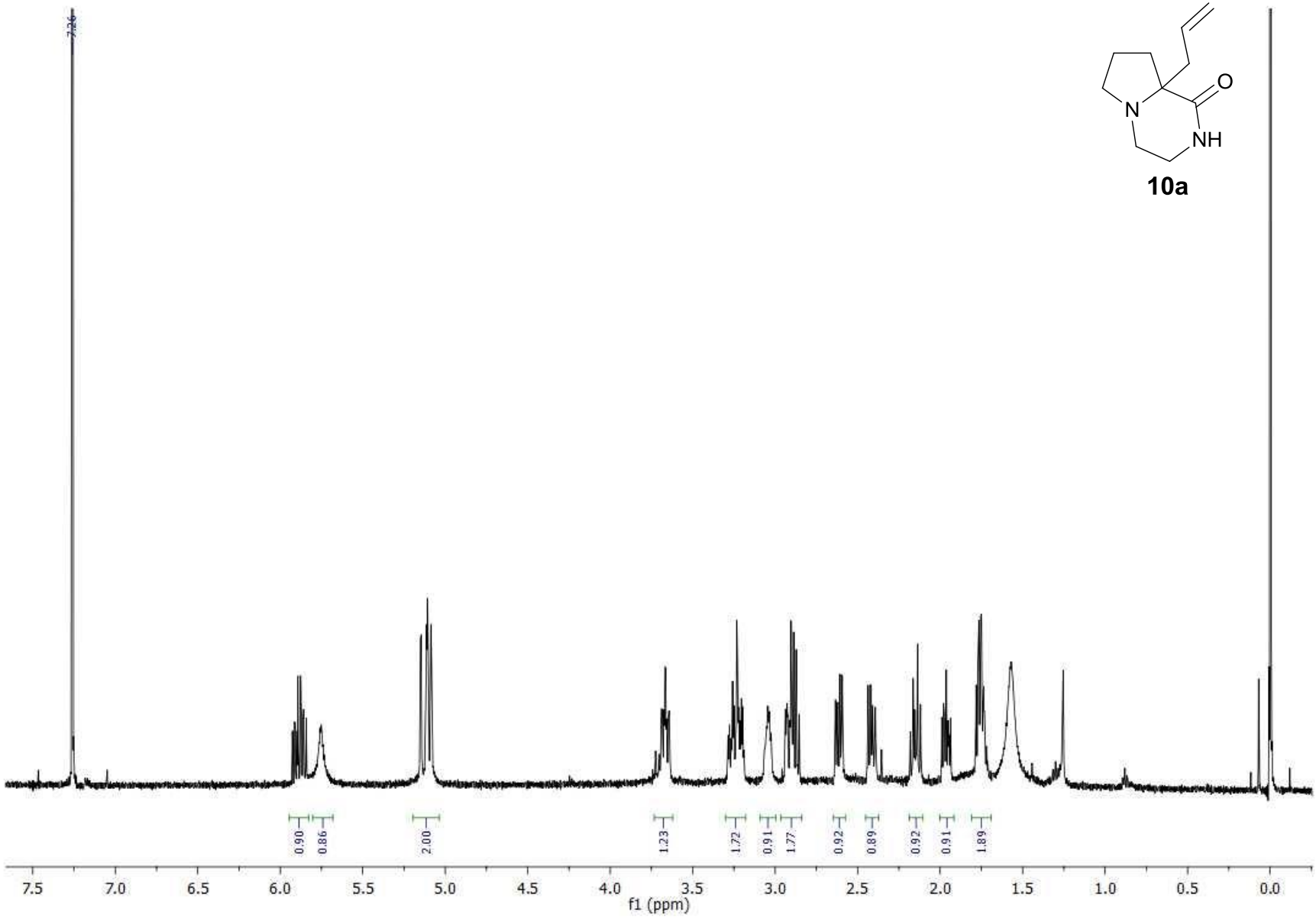

CO2Me
HN
O
N
O

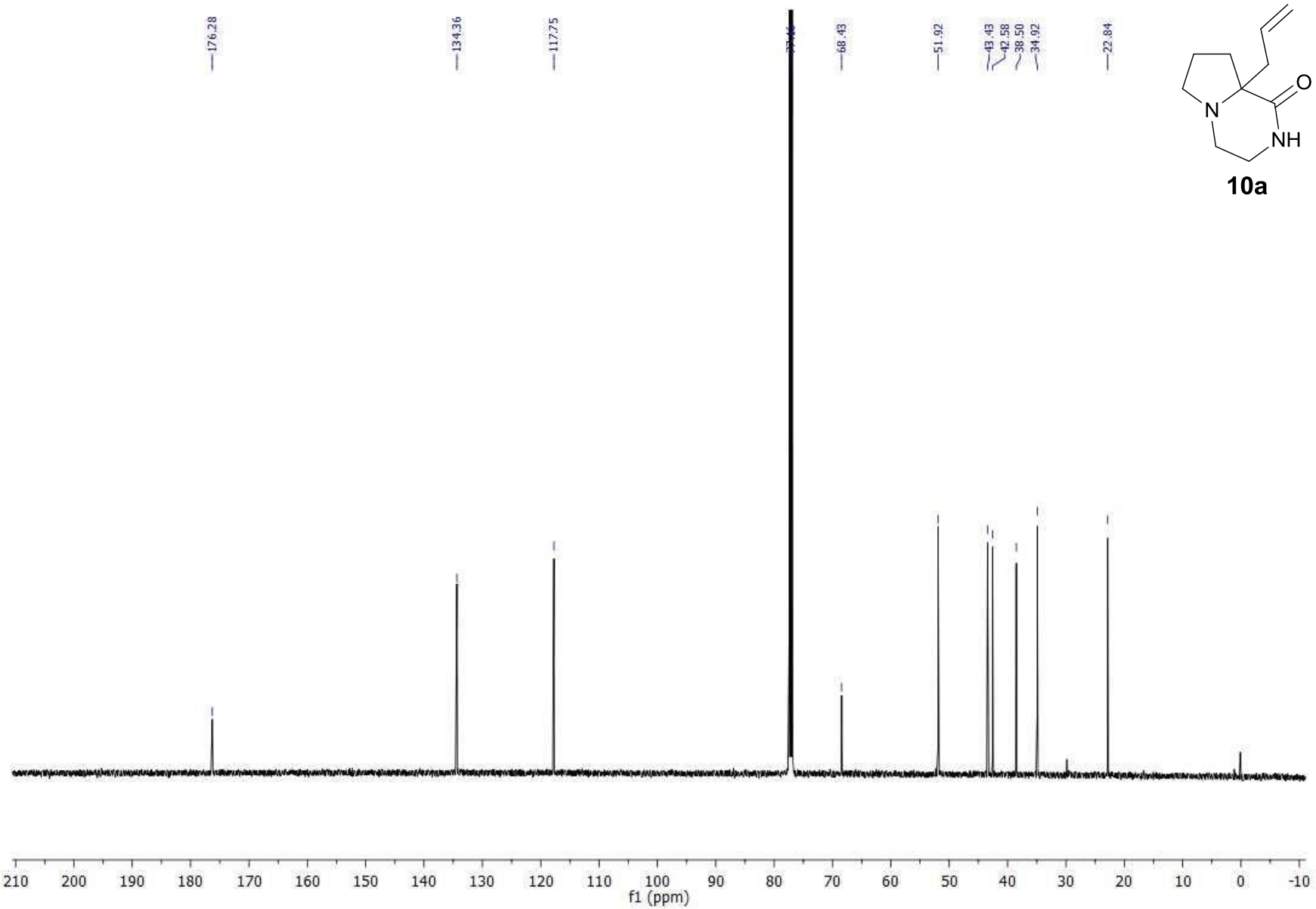
8d

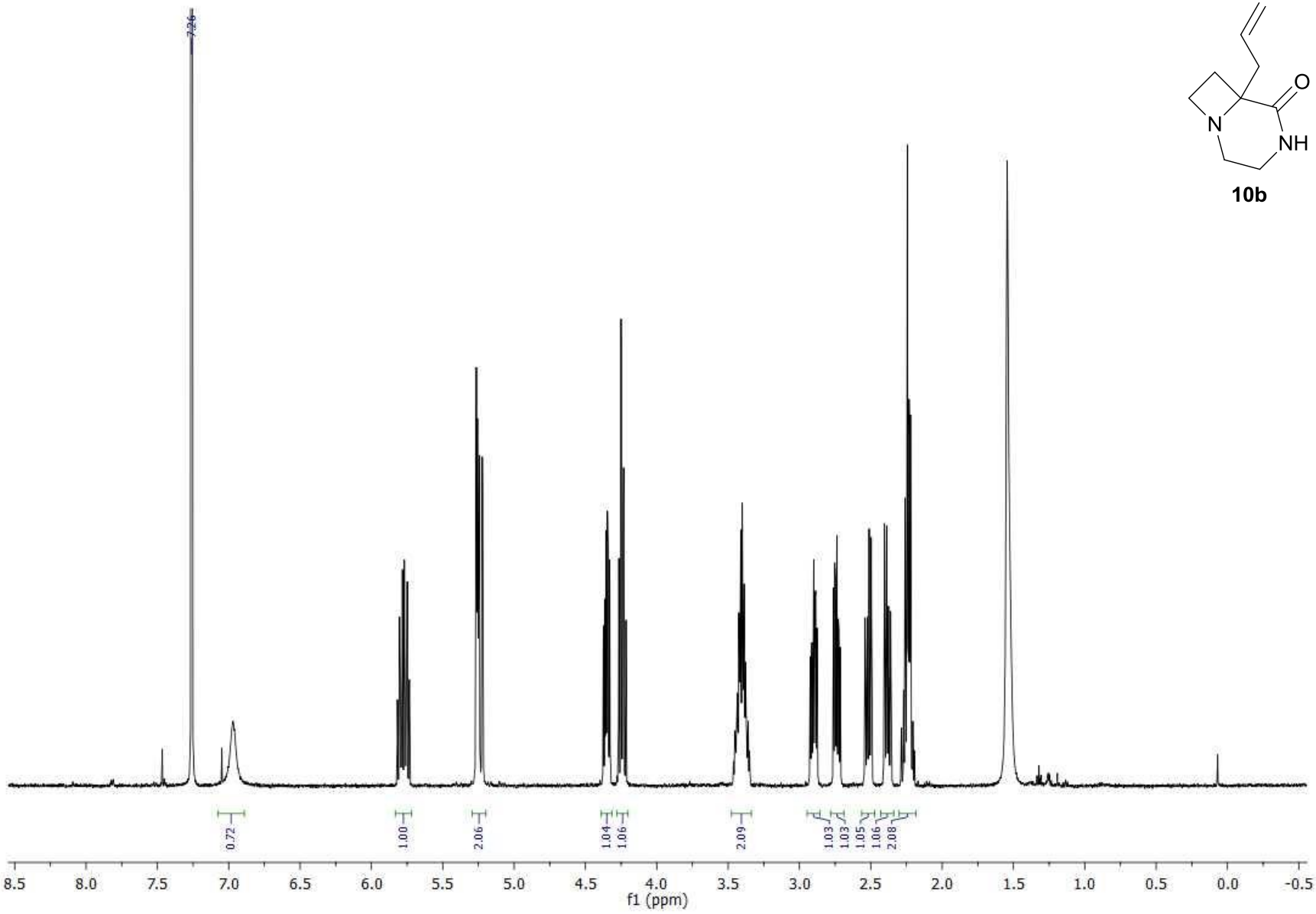
6.06
2.05
1.98
0.94
1.00
2.02
1.02
1.02
1.02
1.02
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


174.19
155.92
134.12
131.37
130.39
130.37
129.17
128.67
128.51
127.71
126.53
121.43
66.01
42.89
41.08
CO2Me
HN
O
N
O
f1 (ppm)

8d

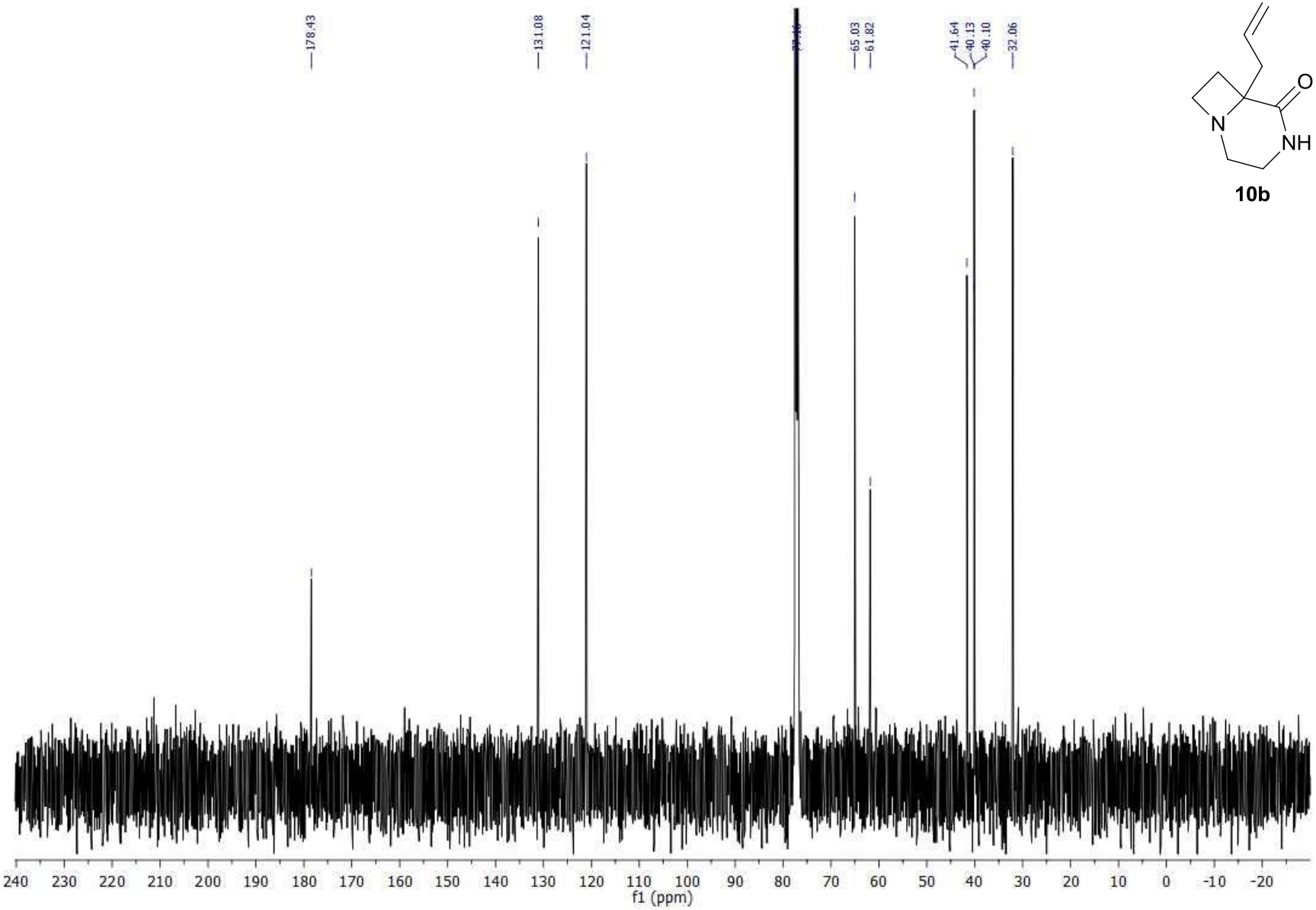

7.26
O
N
NH
10a
0.90
0.86
2.00
1.23
1.72
0.91
1.77
0.92
0.89
0.92
0.91
1.89
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

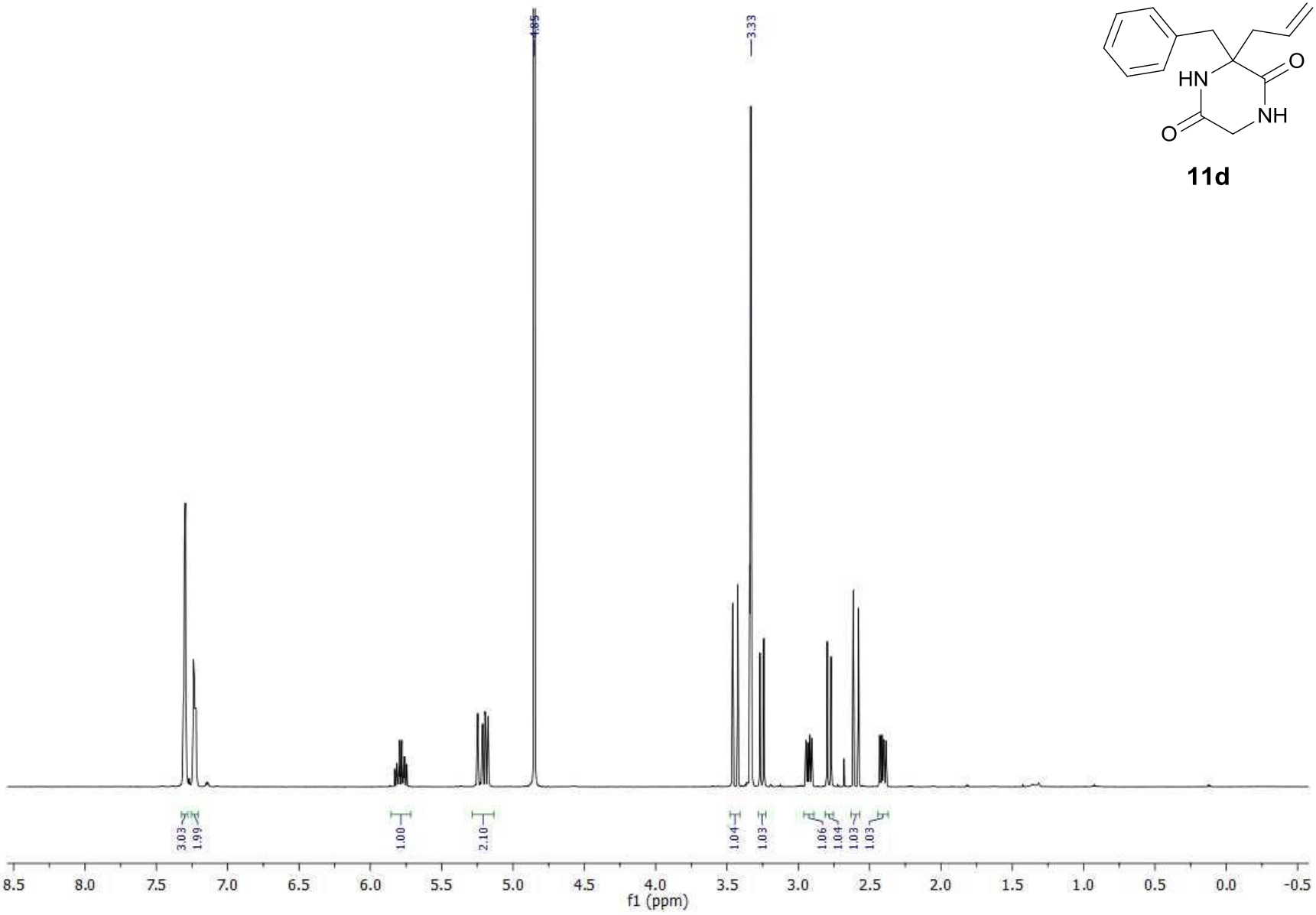

176.28
134.36
117.75
68.43
51.92
43.43
42.58
38.50
34.92
22.84
O
N
NH
10a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.26
0.72
1.00
2.06
1.04
1.06
2.09
1.03
1.03
1.05
1.06
2.08
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
-0.5
f1 (ppm)

O
N
NH

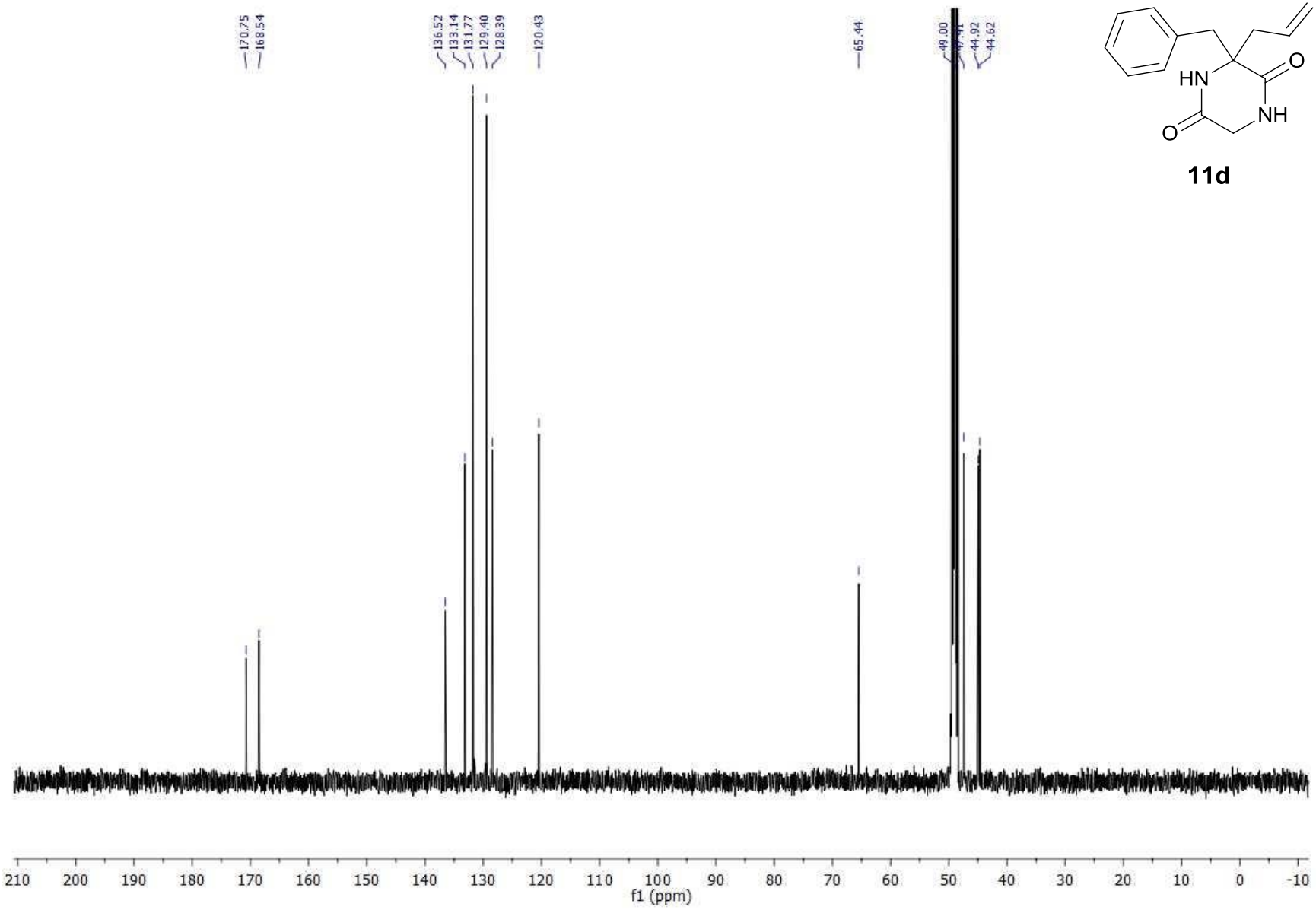
10b

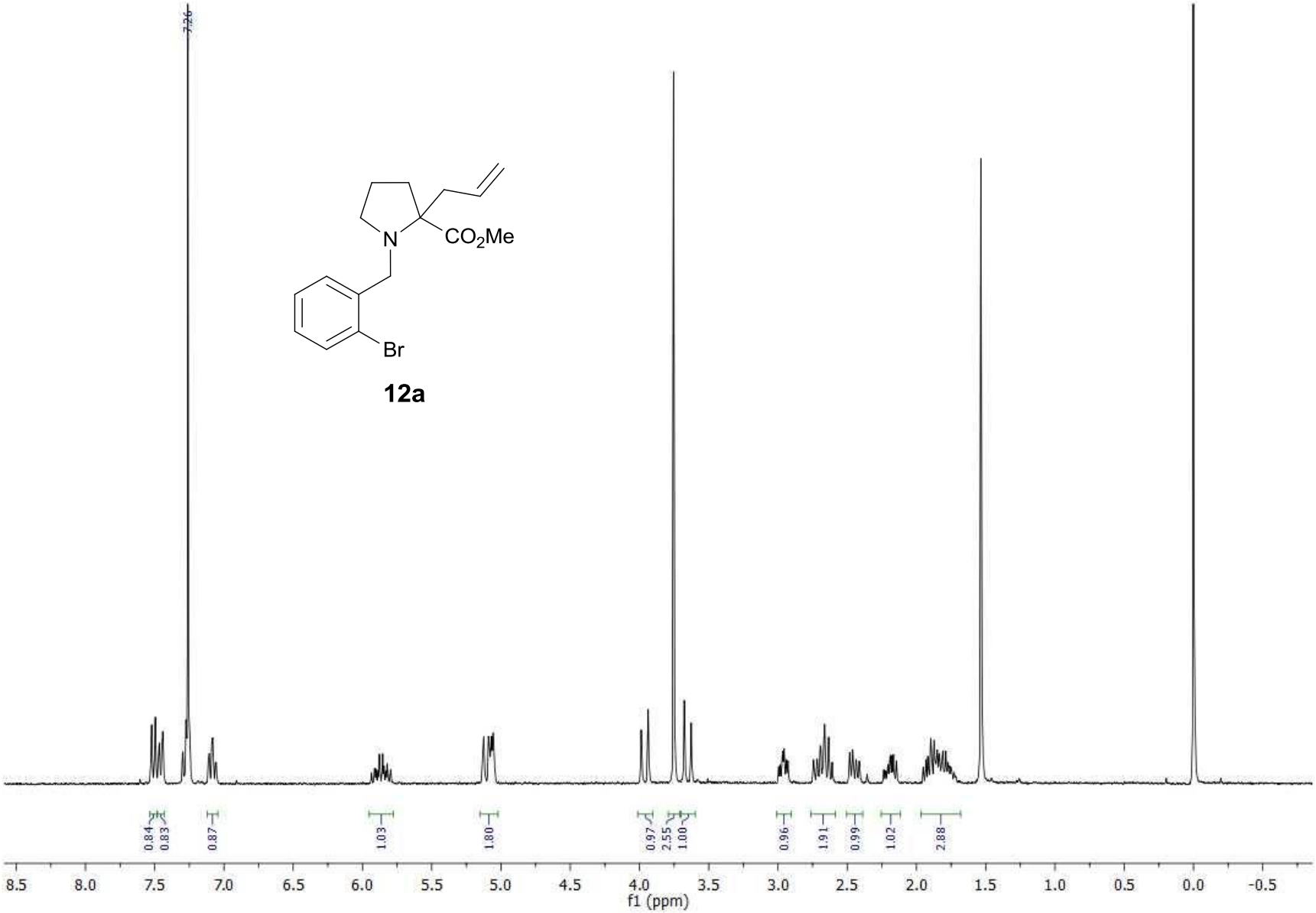

178.43
131.08
121.04
77.16
65.03
61.82
41.64
40.13
40.10
32.06
O
N
NH
10b
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


4.85
3.33
3.03
1.99
1.00
2.10
1.04
1.03
1.06
1.04
1.03
1.03
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
-0.5
f1 (ppm)

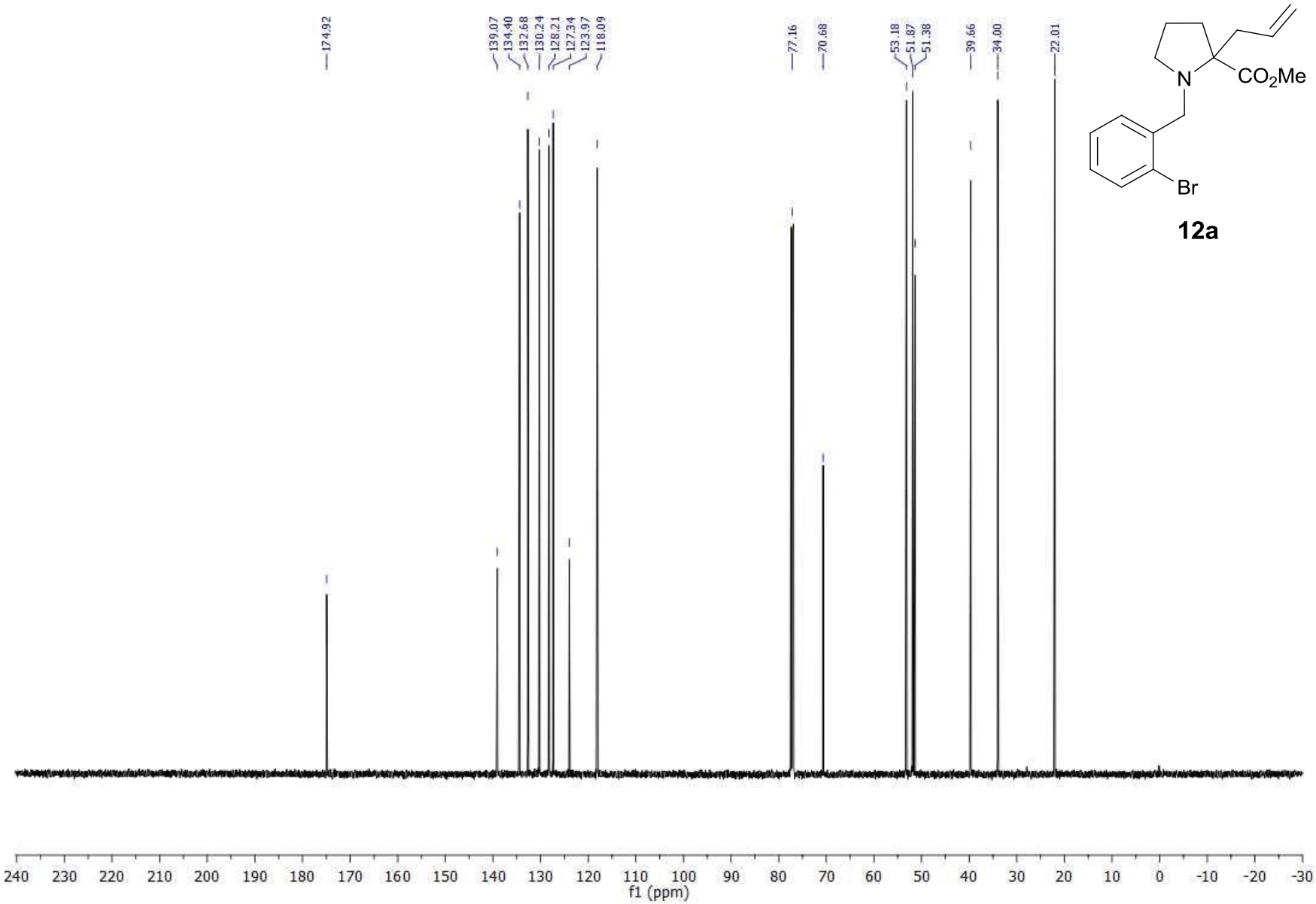
HN
O
NH
O

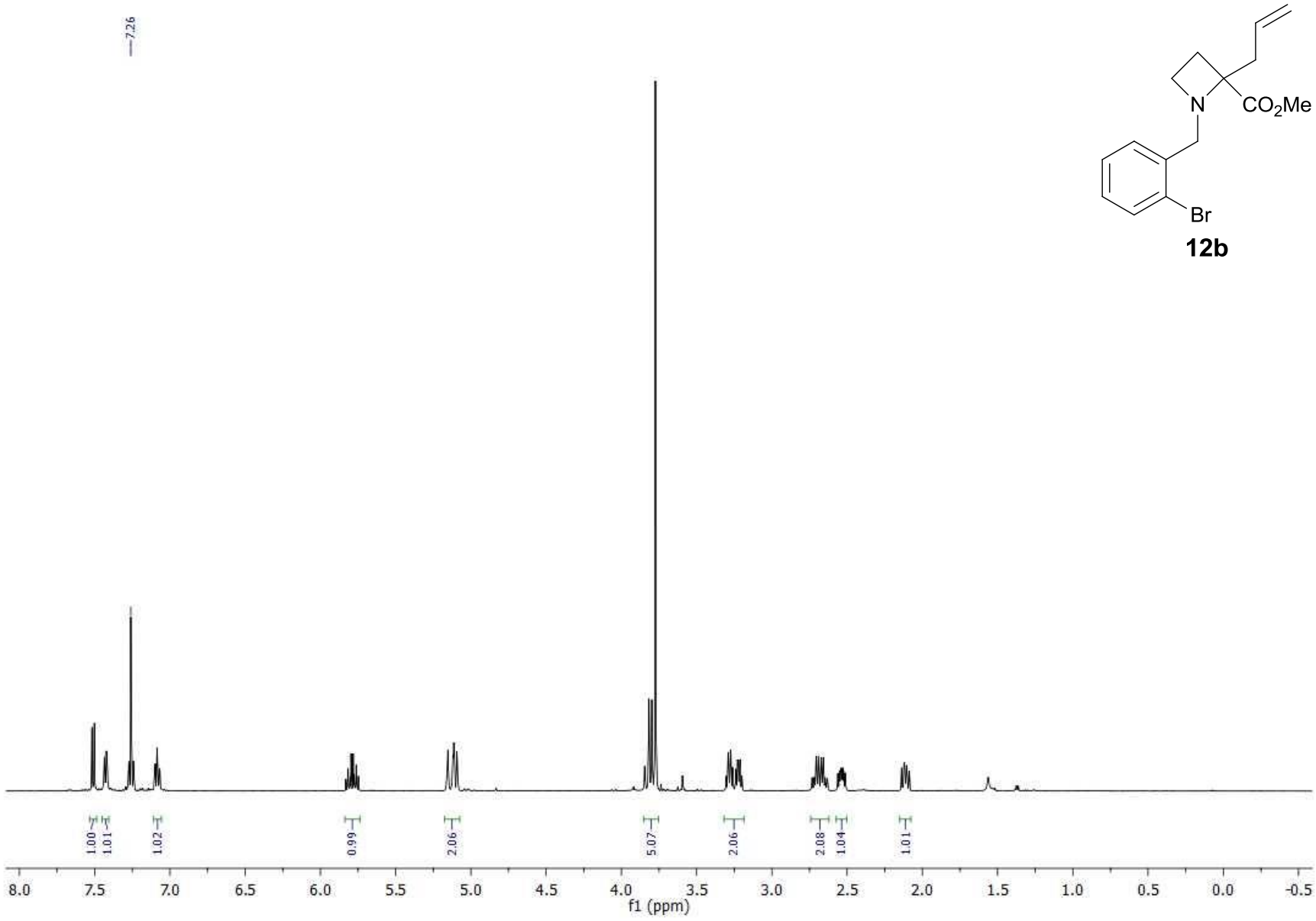
11d


170.75
168.54
136.52
133.14
131.77
129.40
128.39
120.43
65.44
49.00
44.92
44.62
HN
NH
O
O
11d
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.26
N
CO2Me
Br
0.84
0.83
0.87
1.03
1.80
0.97
2.55
1.00
0.96
1.91
0.99
1.02
2.88
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
-0.5
f1 (ppm)

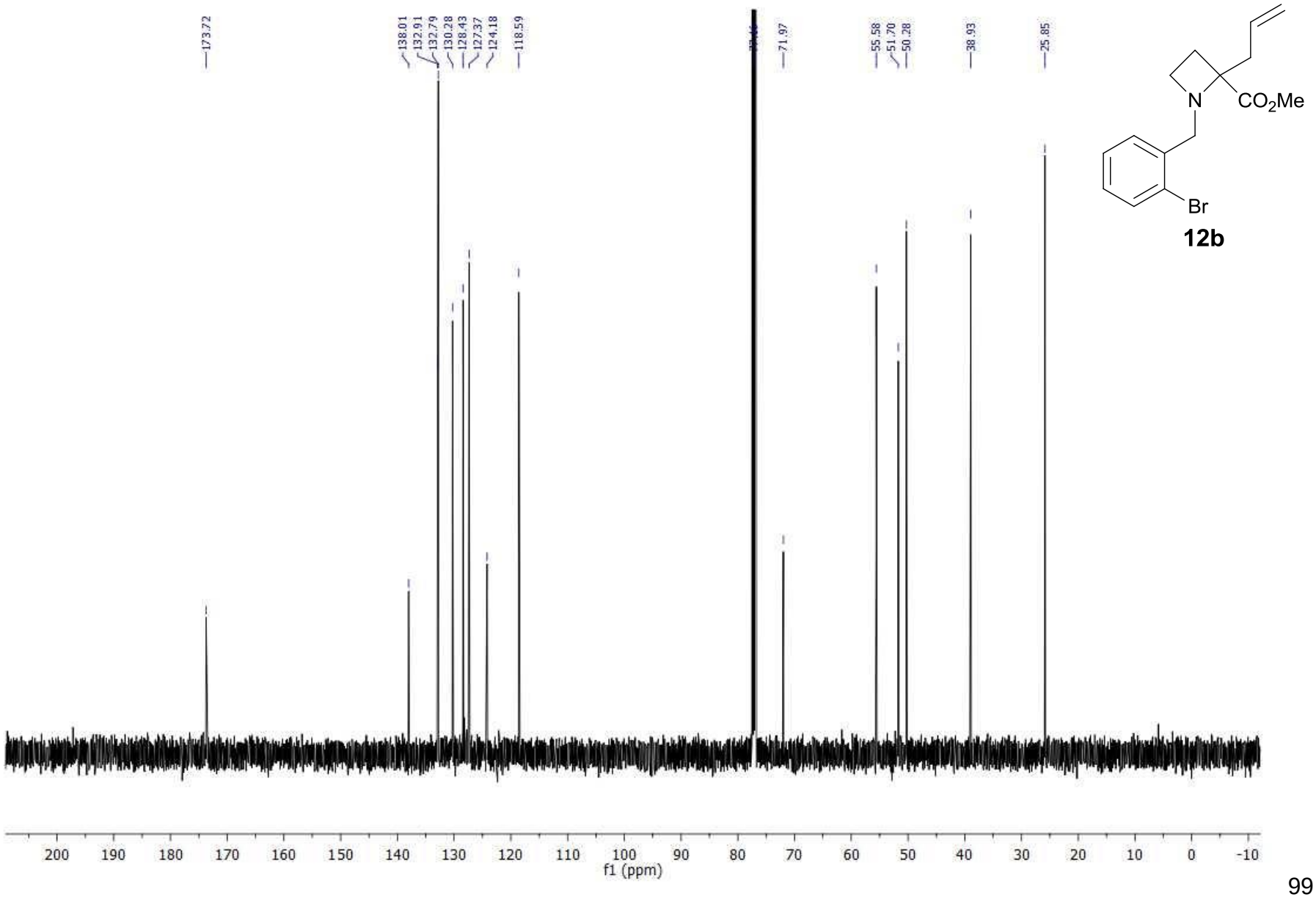
12a


174.92
139.07
134.40
132.68
130.24
128.21
127.34
123.97
118.09
77.16
70.68
53.18
51.87
51.38
39.66
34.00
22.01
N
CO2Me
Br
12a
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
f1 (ppm)


7.26
1.00
1.01
1.02
0.99
2.06
5.07
2.06
2.08
1.04
1.01
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
-0.5
f1 (ppm)

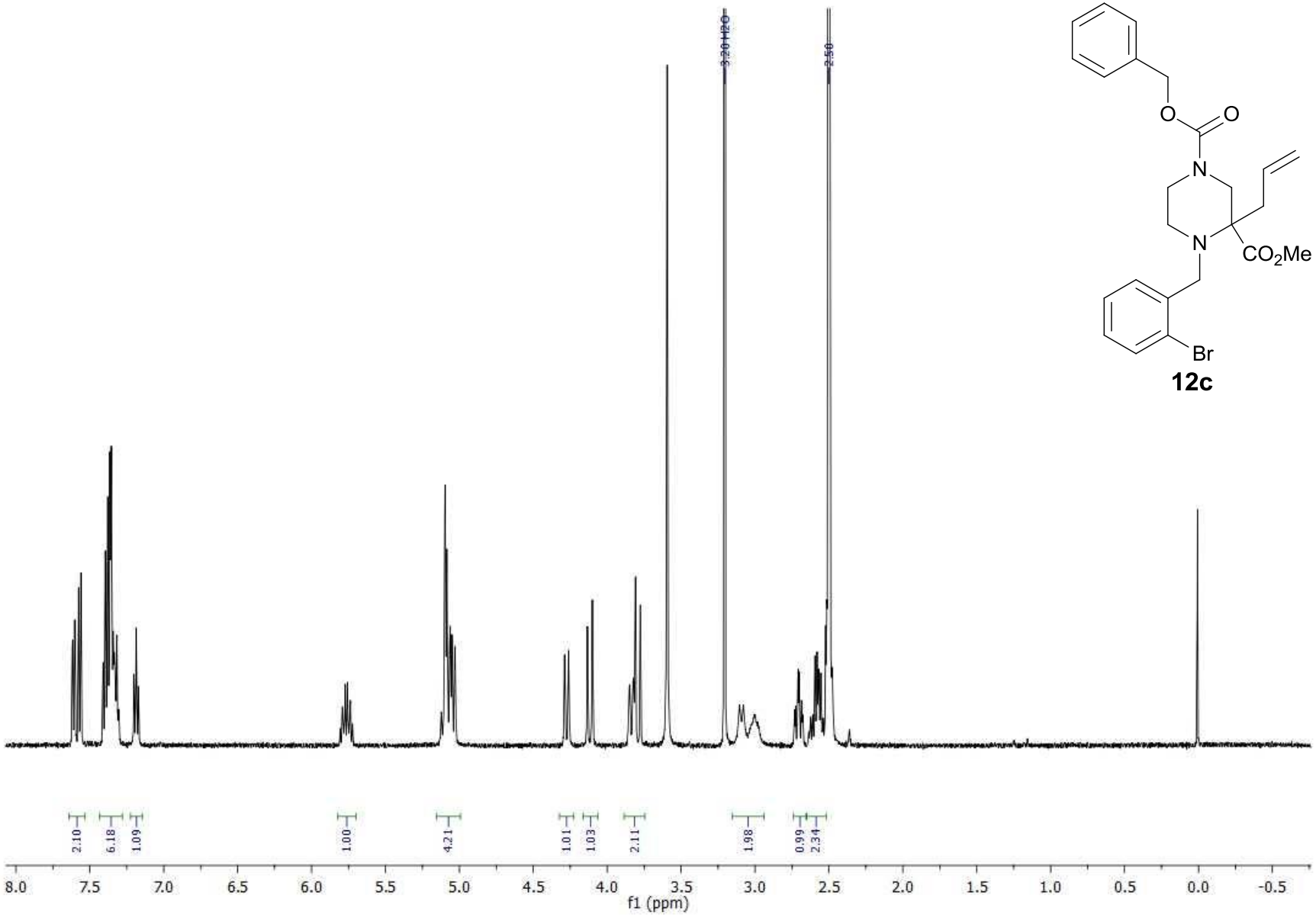
N
CO2Me
Br

12b

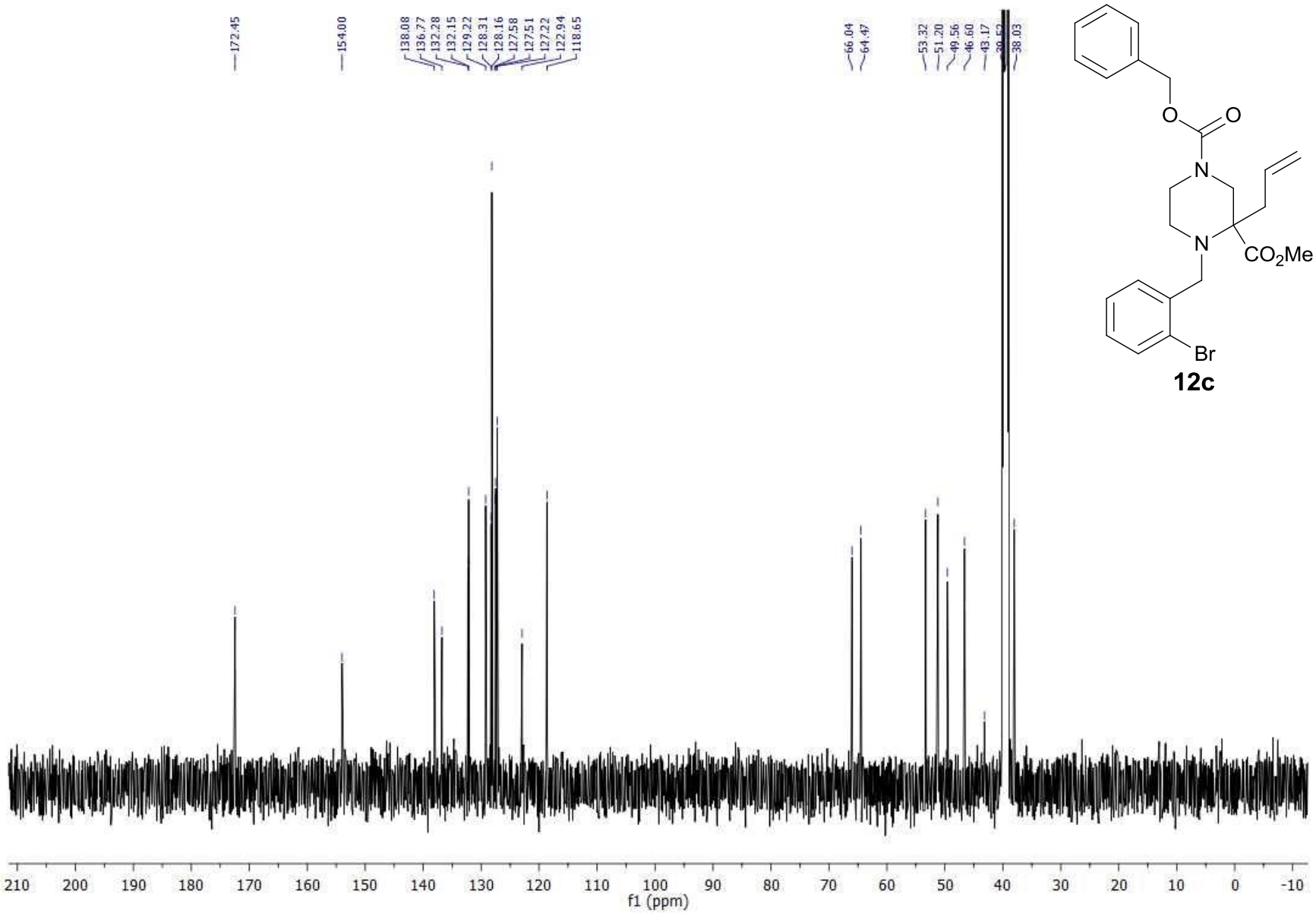

173.72
138.01
132.91
132.79
130.28
128.43
127.37
124.18
118.59
77.46
71.97
55.58
51.70
50.28
38.93
25.85
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

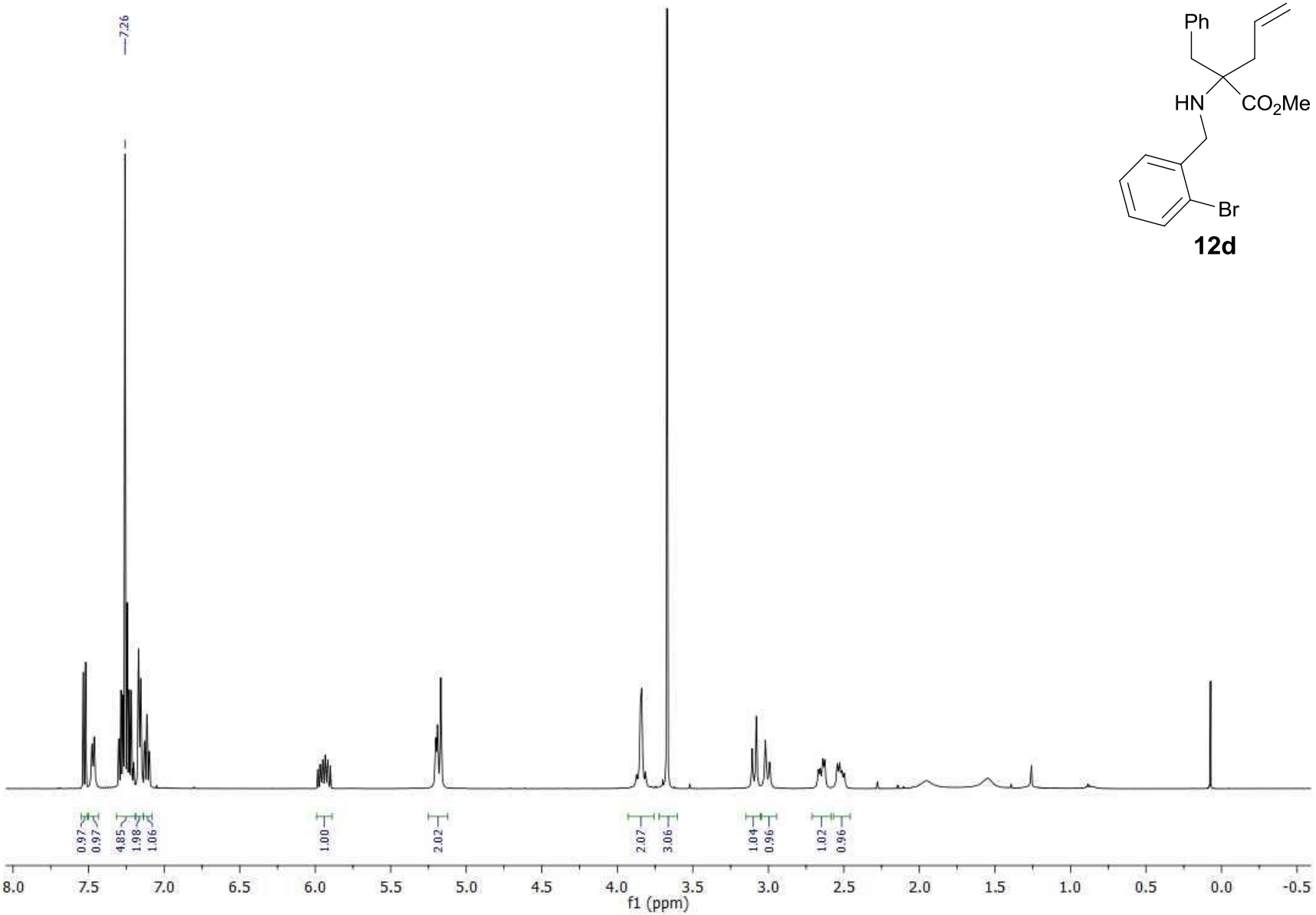
N
CO2Me
Br

12b


3.30 H2O
2.50
2.10
6.18
1.09
1.00
4.21
1.01
1.03
2.11
1.98
0.99
2.34
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
-0.5
f1 (ppm)
O
O
N
N
CO2Me
Br

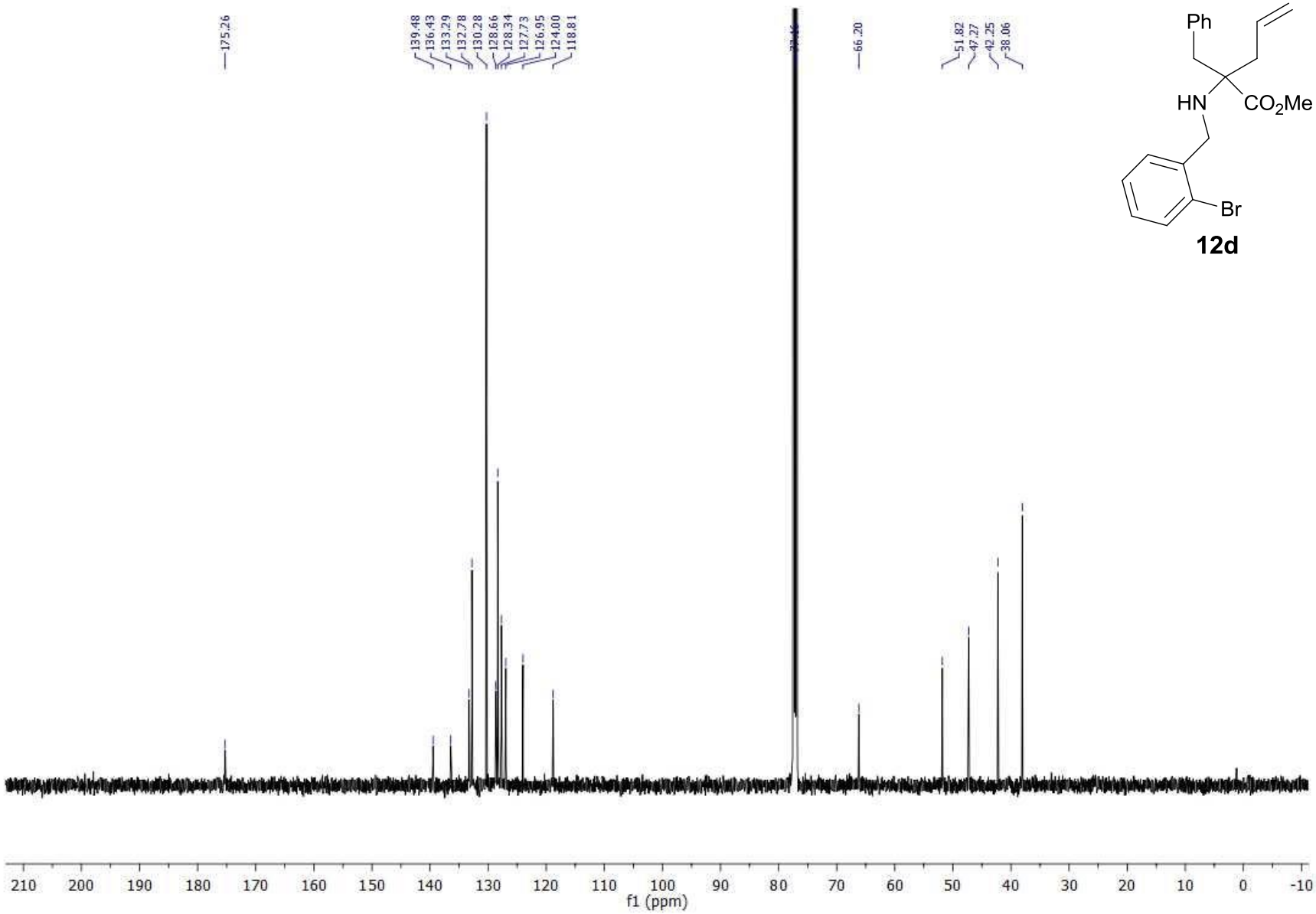
12c

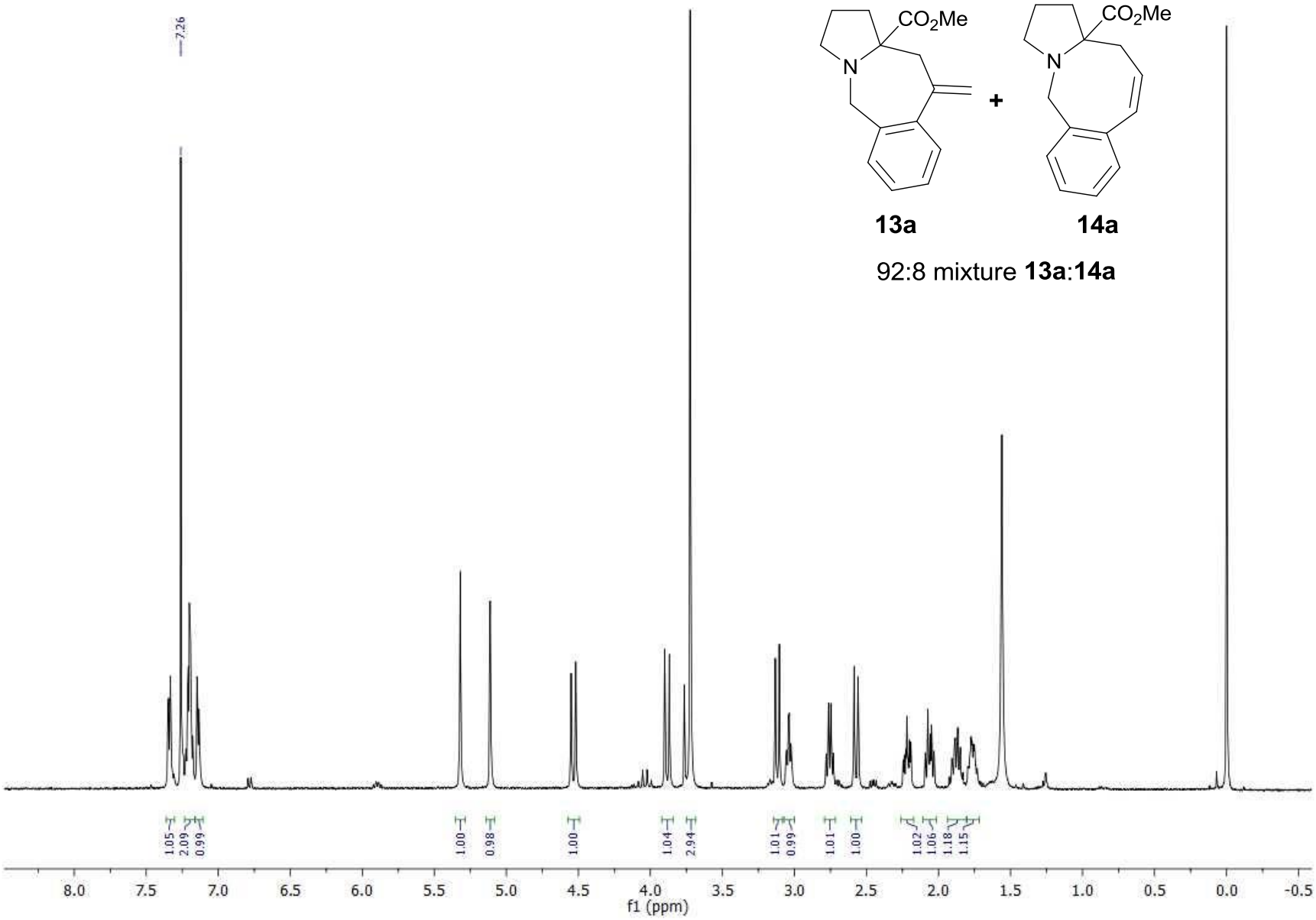

172.45
154.00
138.08
136.77
132.28
132.15
129.22
128.31
128.16
127.58
127.51
127.22
122.94
118.65
66.04
64.47
53.32
51.20
49.56
46.60
43.17
38.03
O
O
N
N
CO2Me
Br
12c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

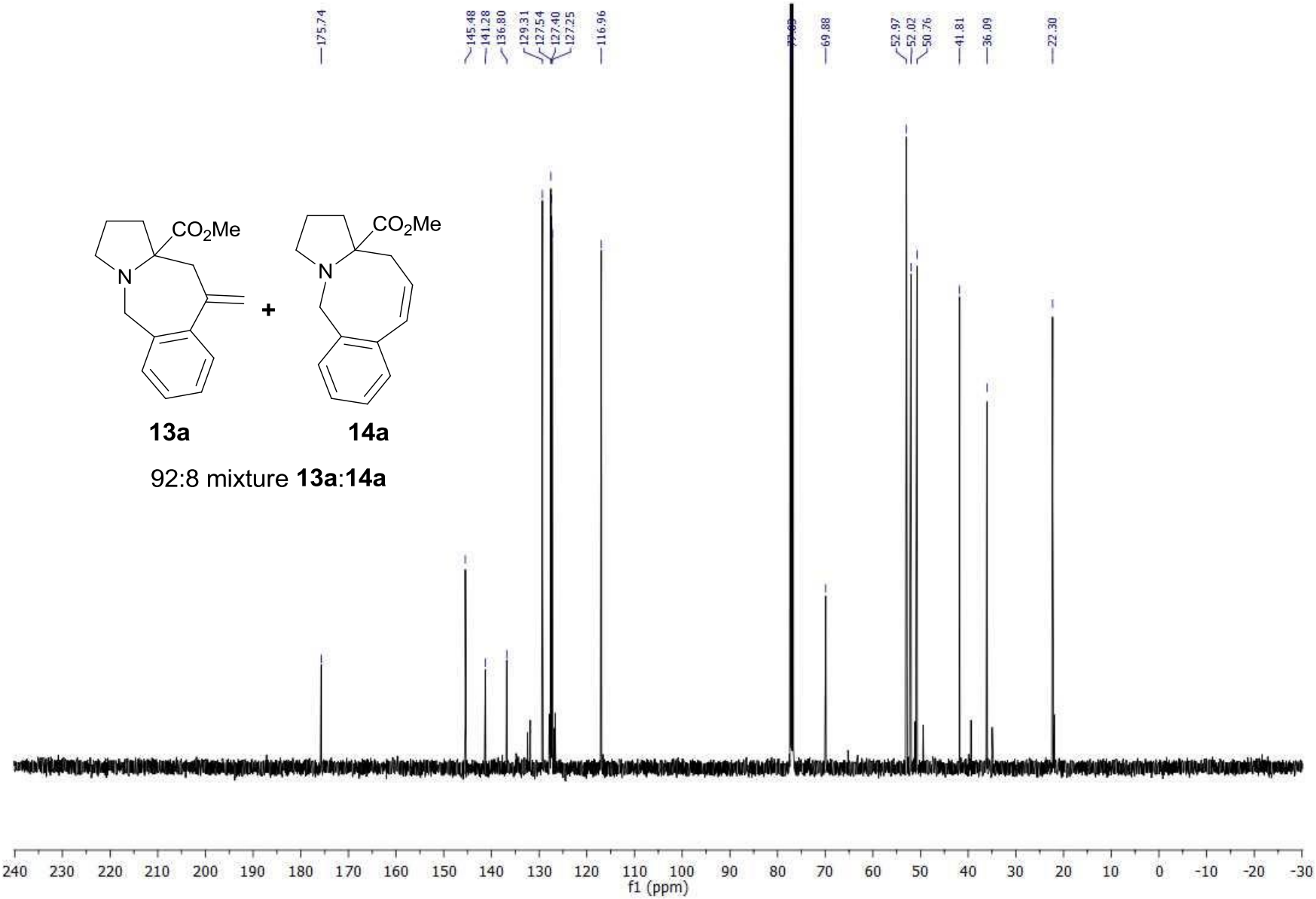

7.26
0.97
0.97
4.85
1.98
1.06
1.00
2.02
2.07
3.06
1.04
0.96
1.02
0.96
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

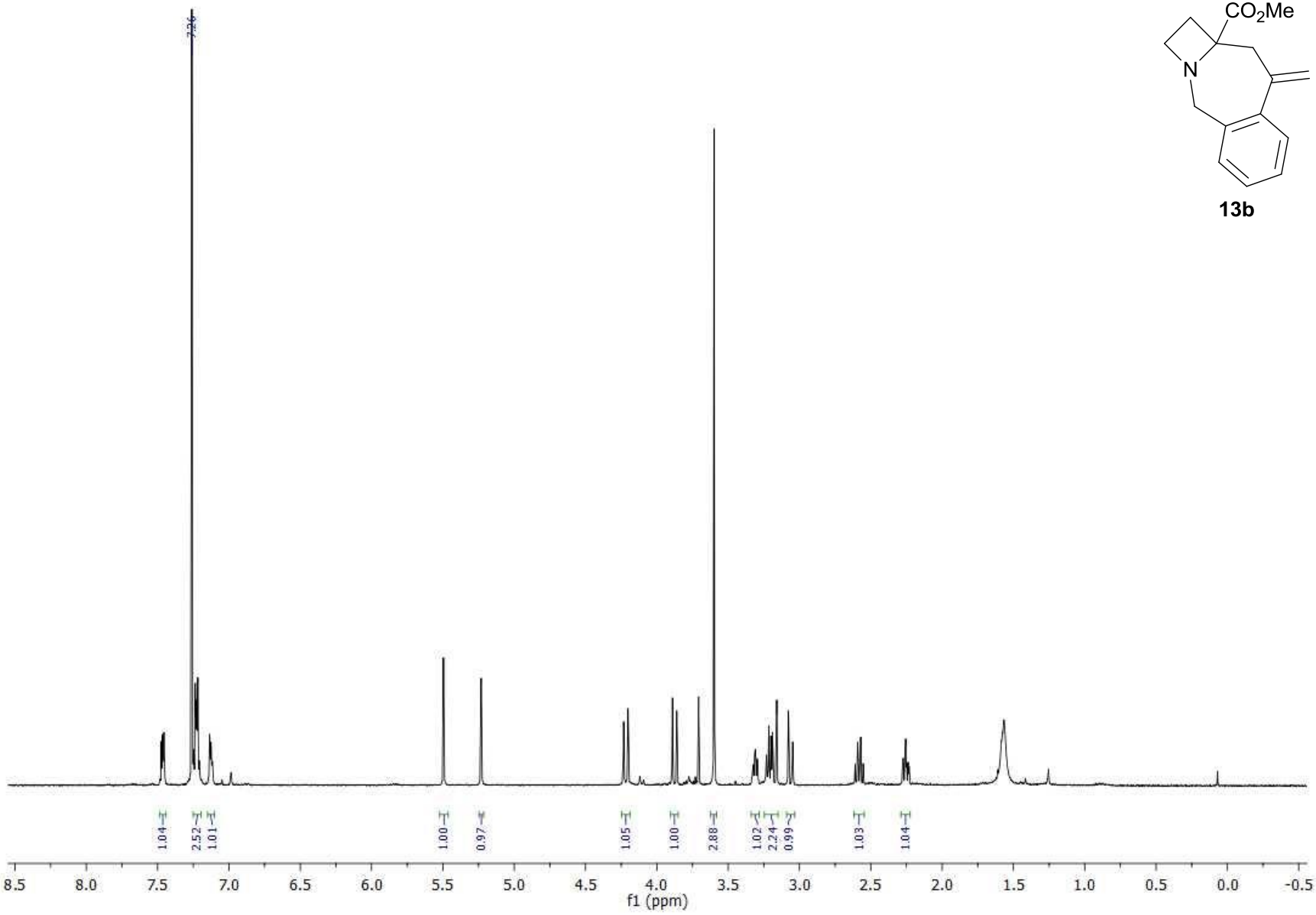
Ph
HN
CO2Me
Br

12d


175.26
139.48
136.43
133.29
132.78
130.28
128.66
128.34
127.73
126.95
124.00
118.81
77.46
66.20
51.82
47.27
42.25
38.06
Ph
HN
CO2Me
Br
12d
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

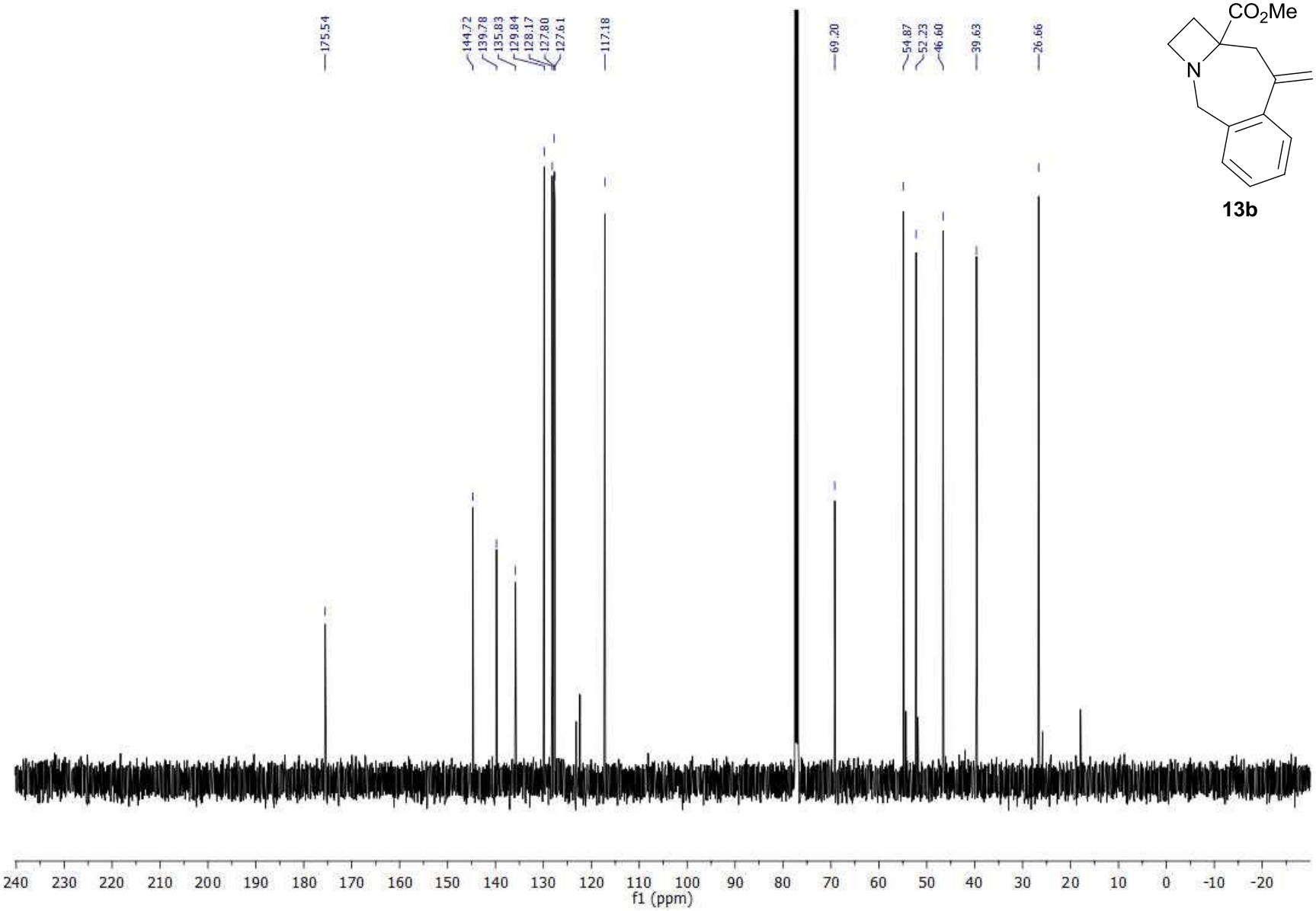

7.26
CO2Me
N
+
CO2Me
N
13a
14a
92:8 mixture 13a:14a
1.05
2.09
0.99
1.00
0.98
1.00
1.04
2.94
1.01
0.99
1.01
1.00
1.02
1.06
1.18
1.15
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

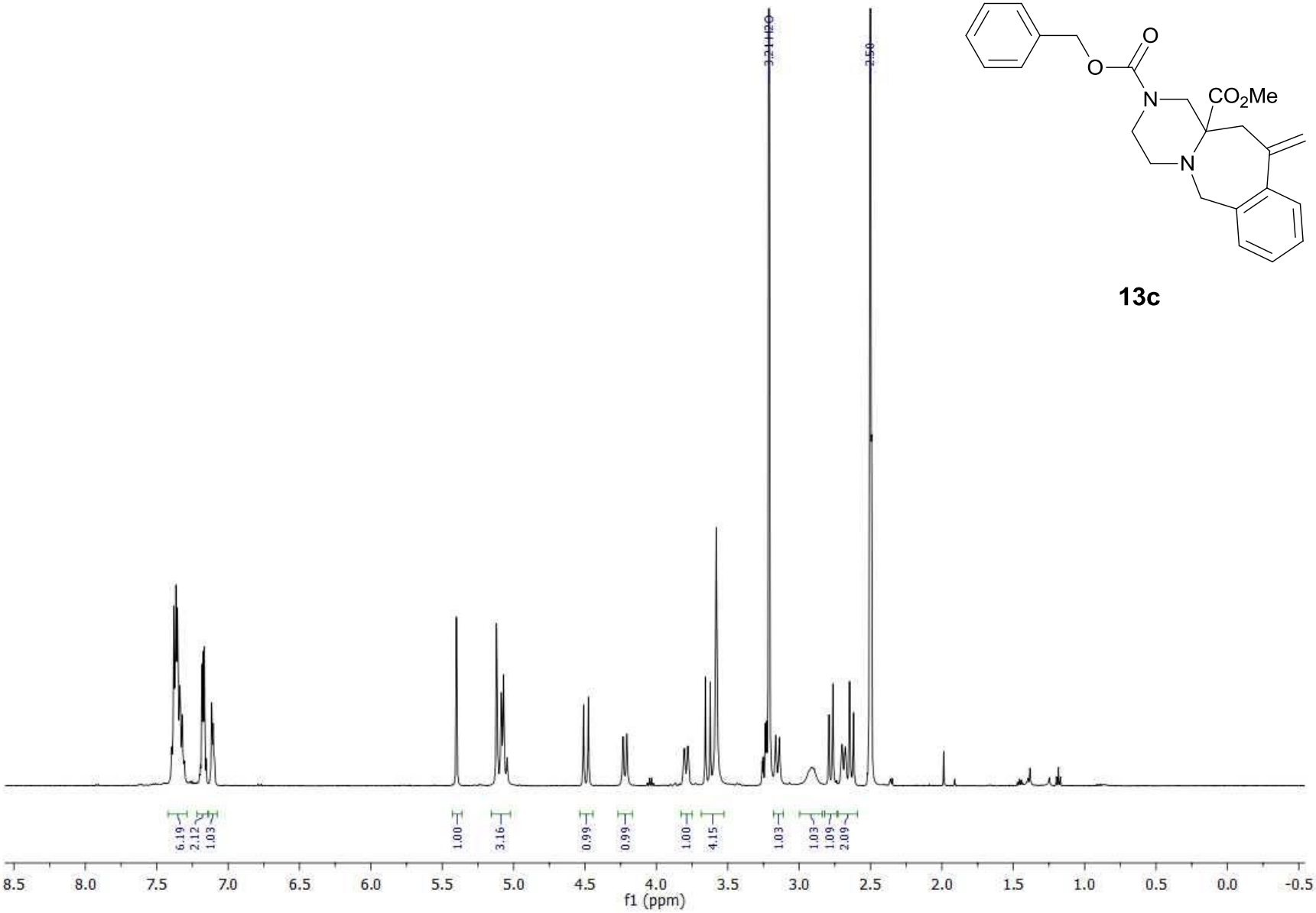

175.74
145.48
141.28
136.80
129.31
127.54
127.40
127.25
116.96
77.03
69.88
52.97
52.02
50.76
41.81
36.09
22.30
CO2Me
N
+
CO2Me
N
13a
14a
92:8 mixture 13a:14a
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
f1 (ppm)


7.26
1.04
2.52
1.01
1.00
0.97
1.05
1.00
2.88
1.02
2.24
0.99
1.03
1.04
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
-0.5
f1 (ppm)

CO2Me
N

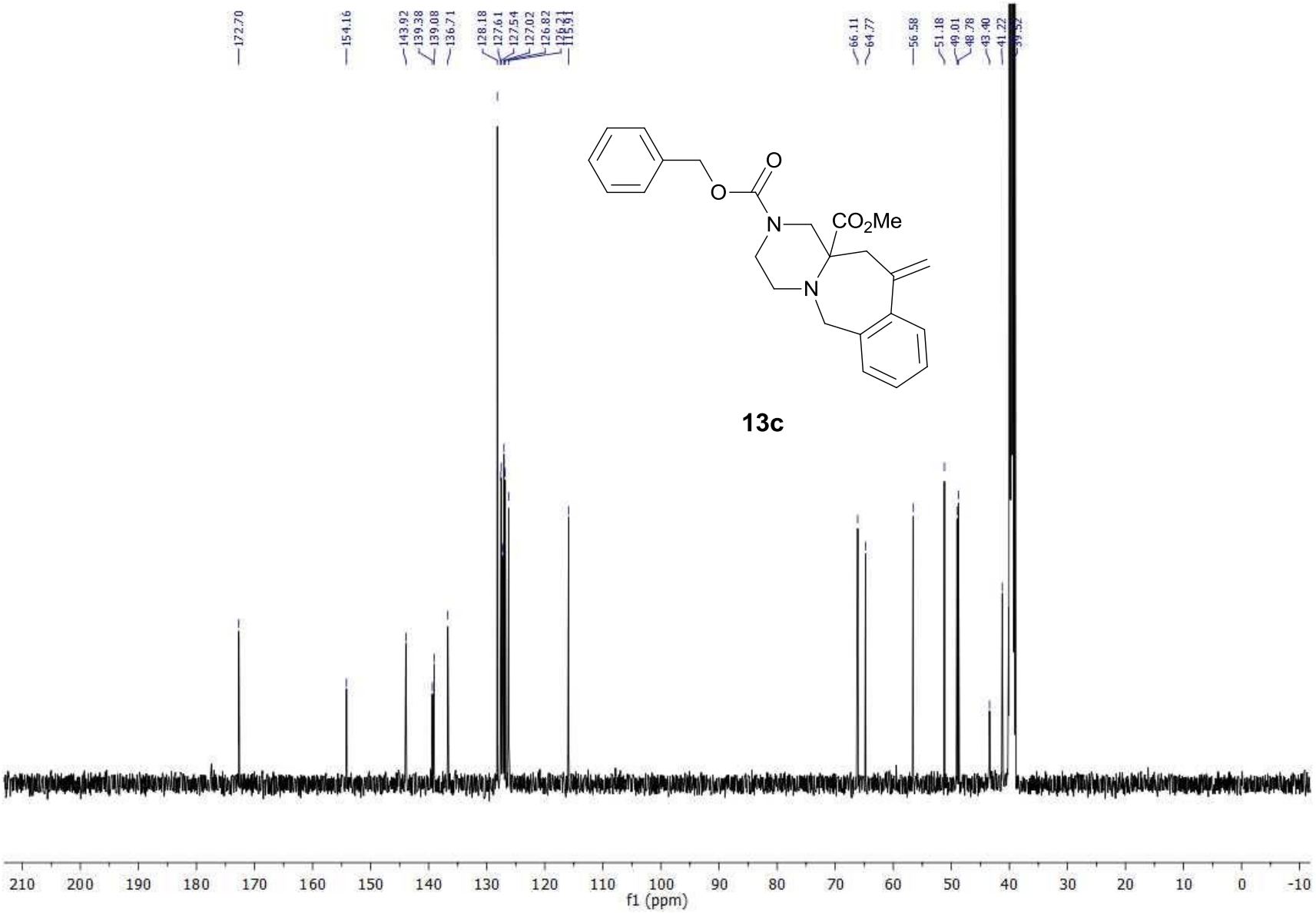
13b

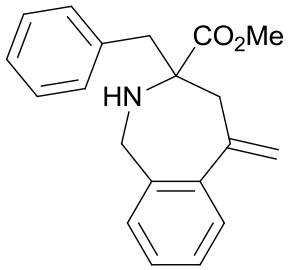

175.54
144.72
139.78
135.83
129.84
128.17
127.80
127.61
117.18
69.20
54.87
52.23
46.60
39.63
26.66
CO2Me
N
13b
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


3.21
2.50
6.19
2.12
1.03
1.00
3.16
0.99
0.99
1.00
4.15
1.03
1.03
1.09
2.09
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
-0.5
f1 (ppm)

O
O
N
CO2Me
N

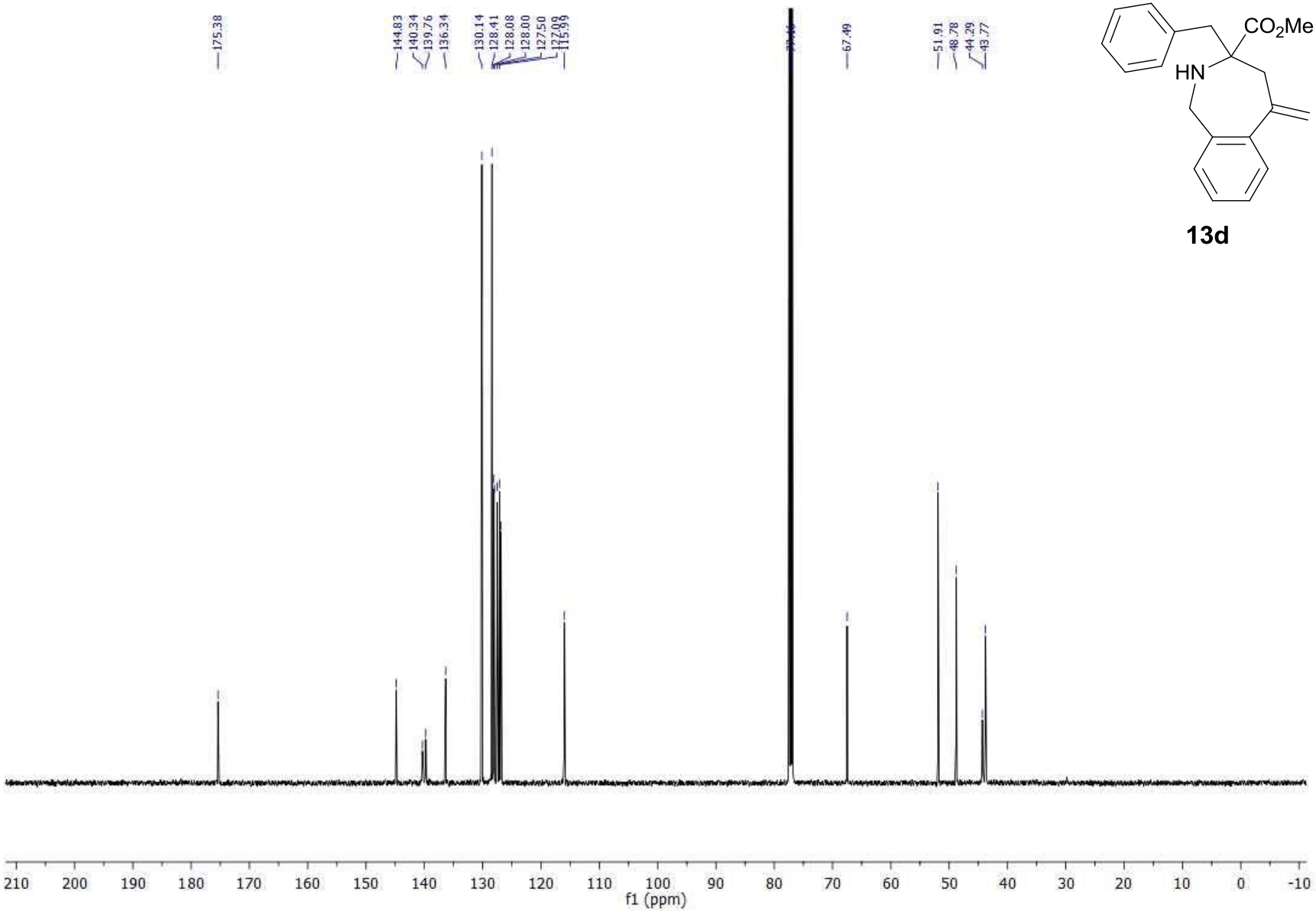
13c

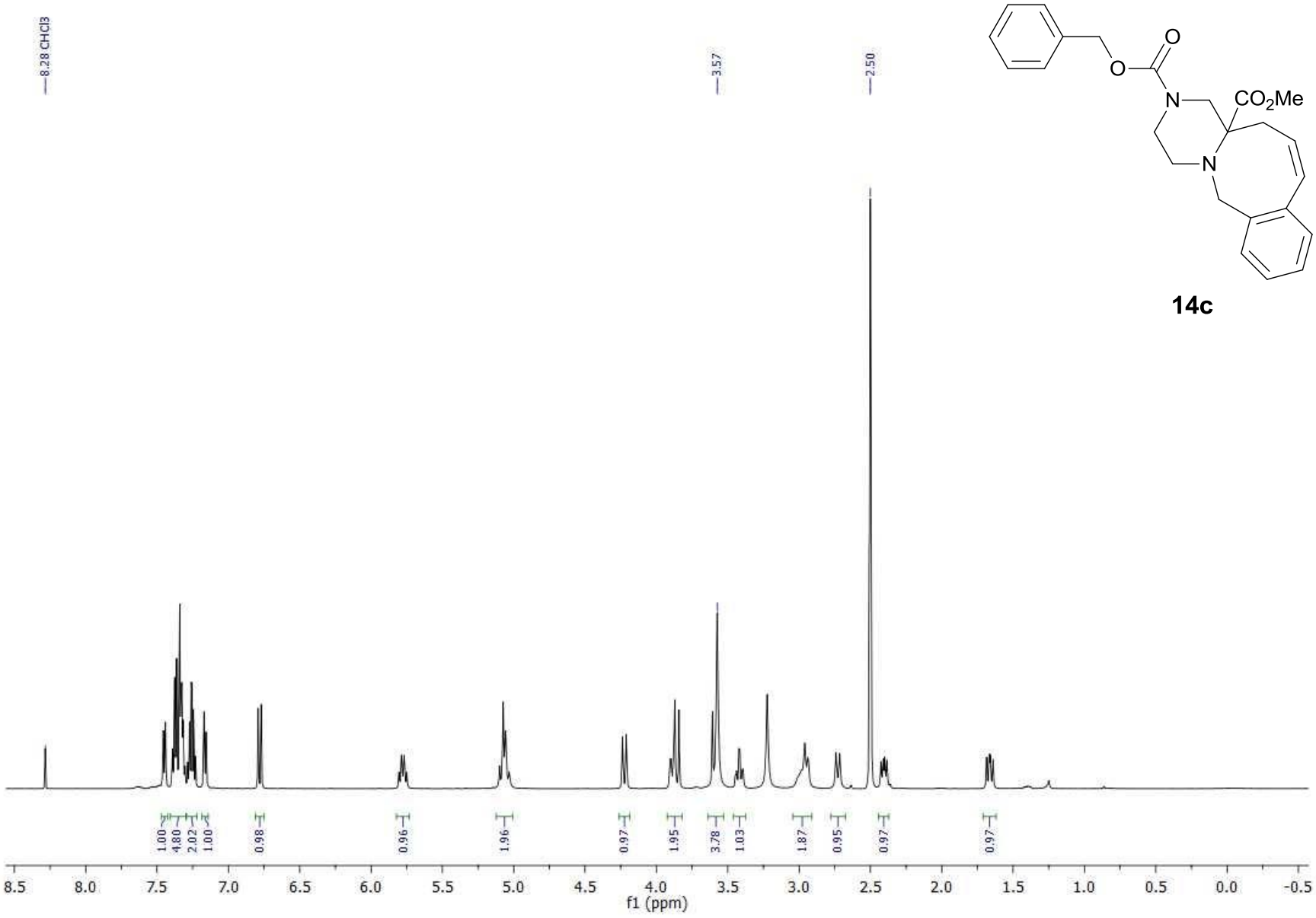

172.70
154.16
143.92
139.38
139.08
136.71
128.18
127.61
127.54
127.02
126.82
66.11
64.77
56.58
51.18
49.01
48.78
43.40
41.22
39.52
O
O
N
CO2Me
N
13c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


CO2Me
HN

13d

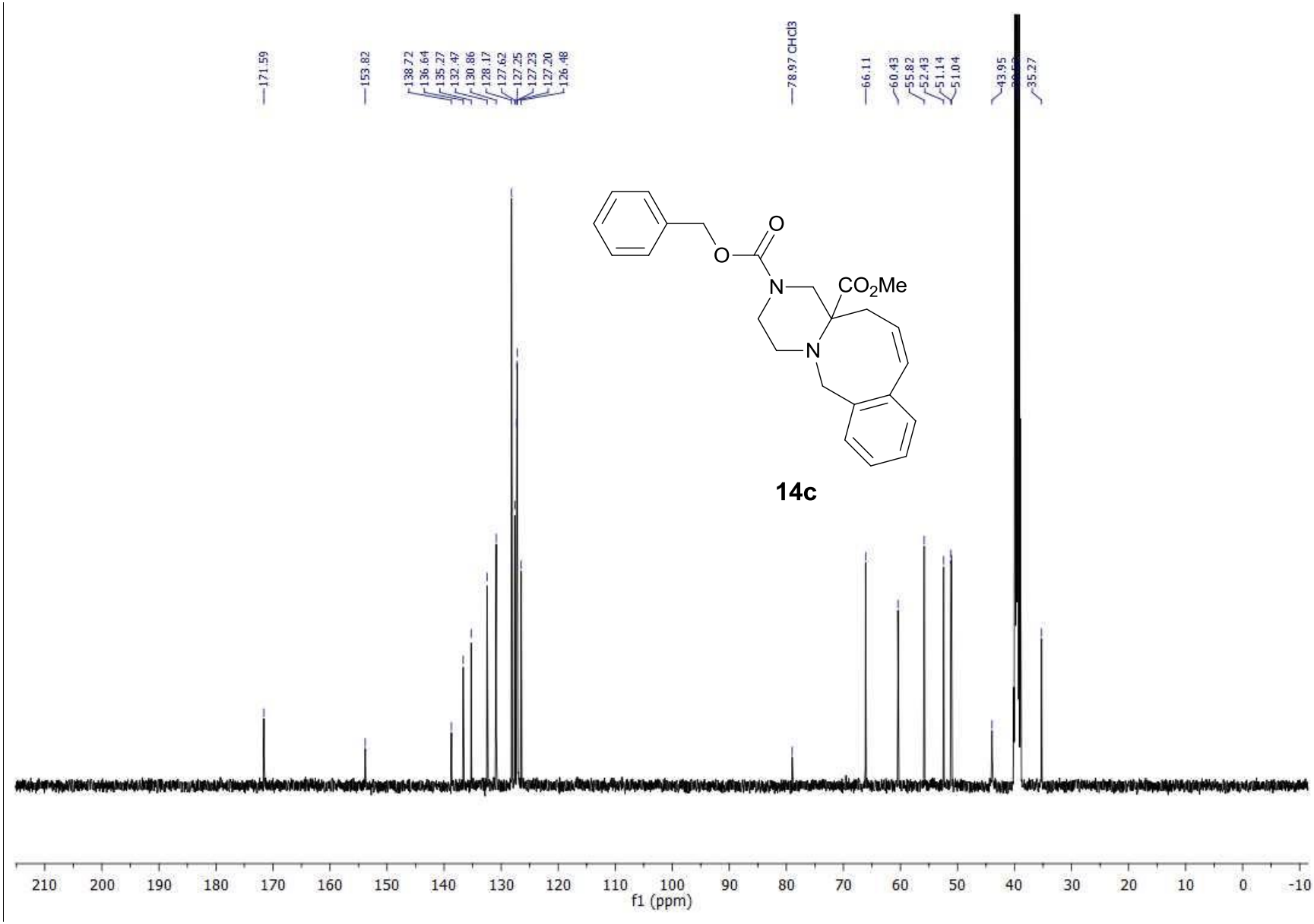
1.07
7.78
1.03
1.00
1.04
2.08
3.09
3.03
1.03
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

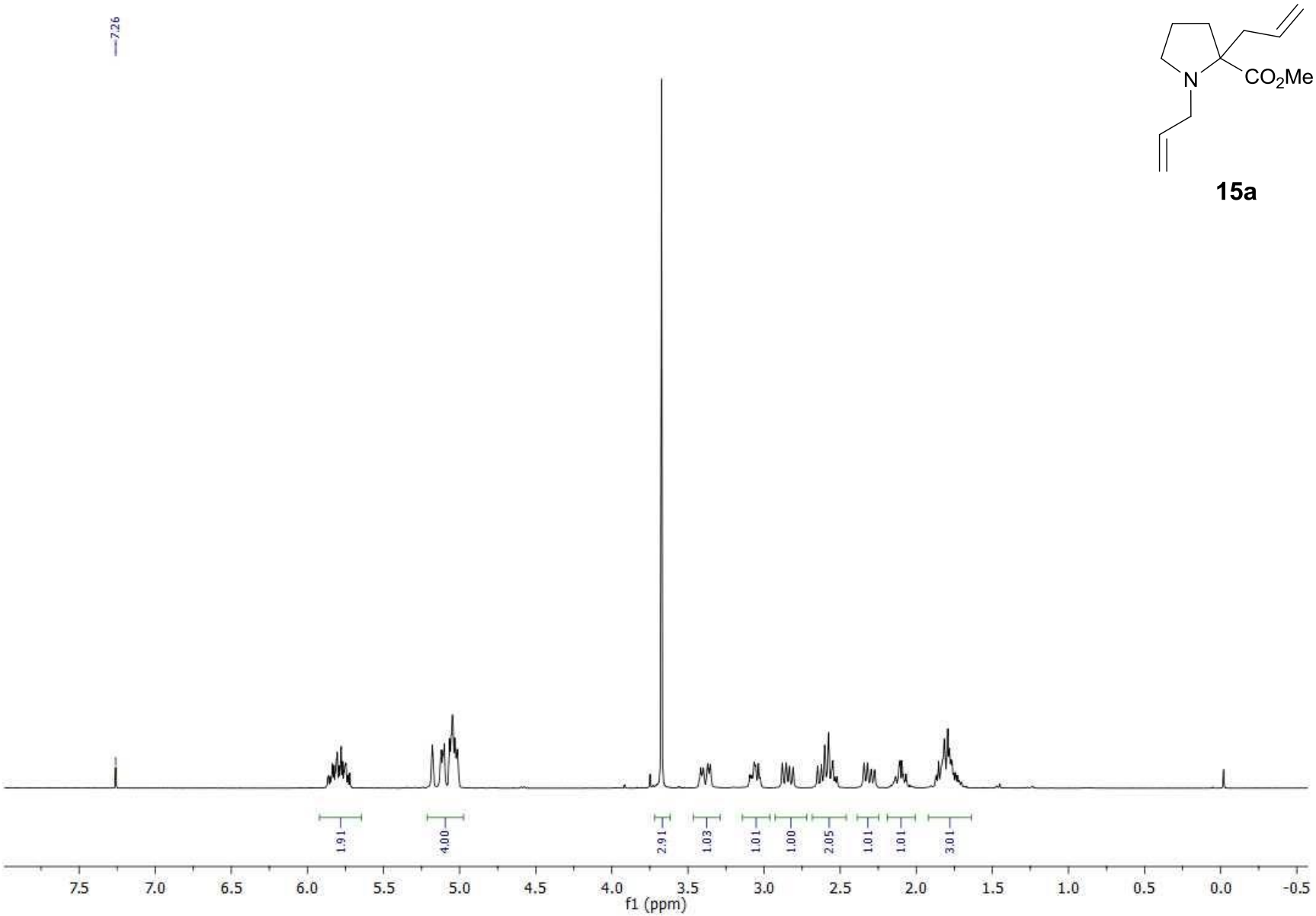

175.38
144.83
140.34
139.76
136.34
130.14
128.41
128.08
128.00
127.50
67.49
51.91
48.78
44.29
43.77
CO2Me
HN
13d
f1 (ppm)


8.28 CHCl3
3.57
2.50
1.00
4.80
2.02
1.00
0.98
0.96
1.96
0.97
1.95
3.78
1.03
1.87
0.95
0.97
0.97
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
-0.5
f1 (ppm)

O
O
N
CO2Me
N

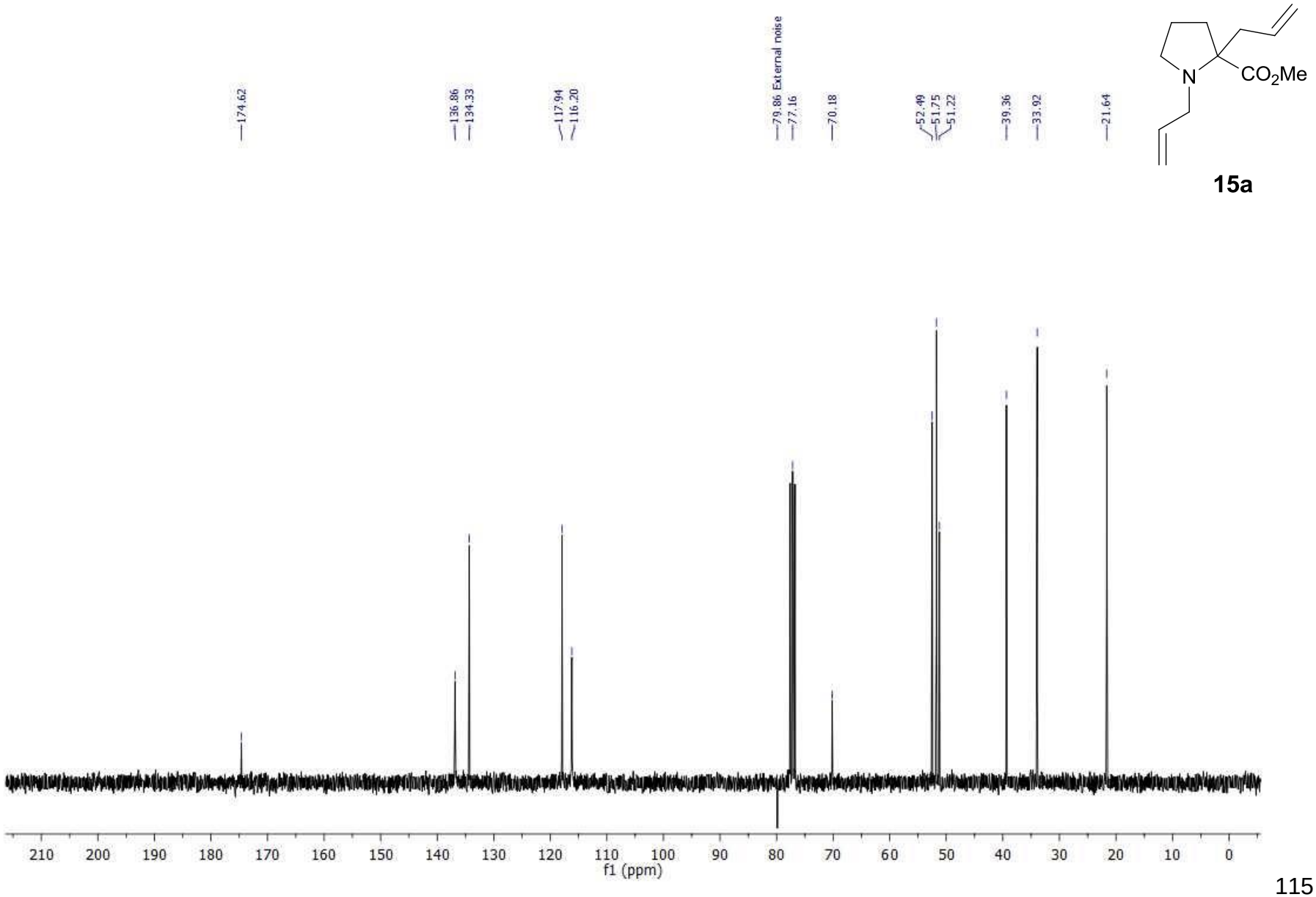
14c

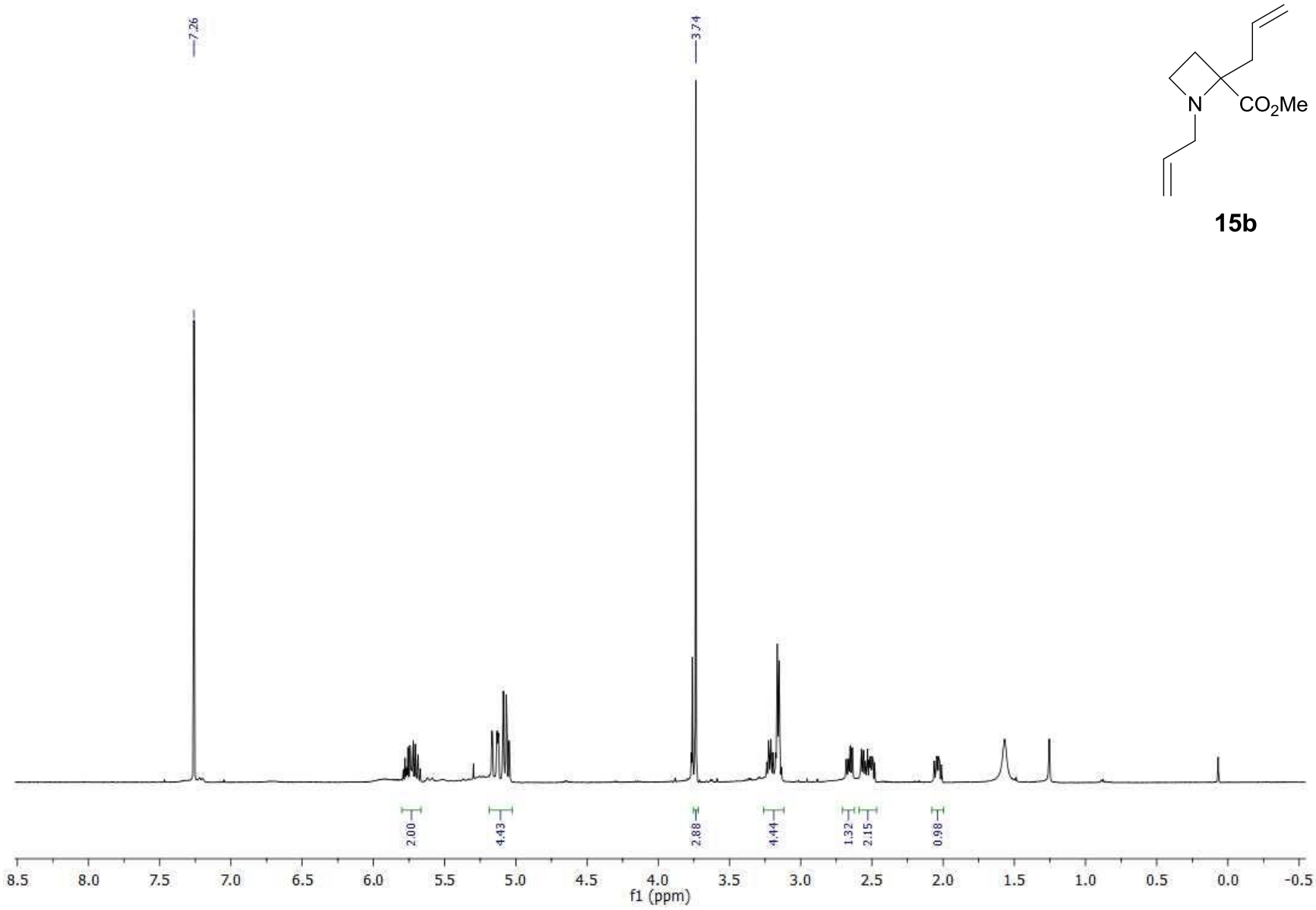

171.59
153.82
138.72
136.64
135.27
132.47
130.86
128.17
127.62
127.25
127.23
127.20
126.48
78.97 CHCl3
66.11
60.43
55.82
52.43
51.14
51.04
43.95
35.27
O
O
N
CO2Me
N
14c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.26
1.91
4.00
2.91
1.03
1.01
1.00
2.05
1.01
1.01
3.01
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
-0.5
f1 (ppm)

N
CO2Me

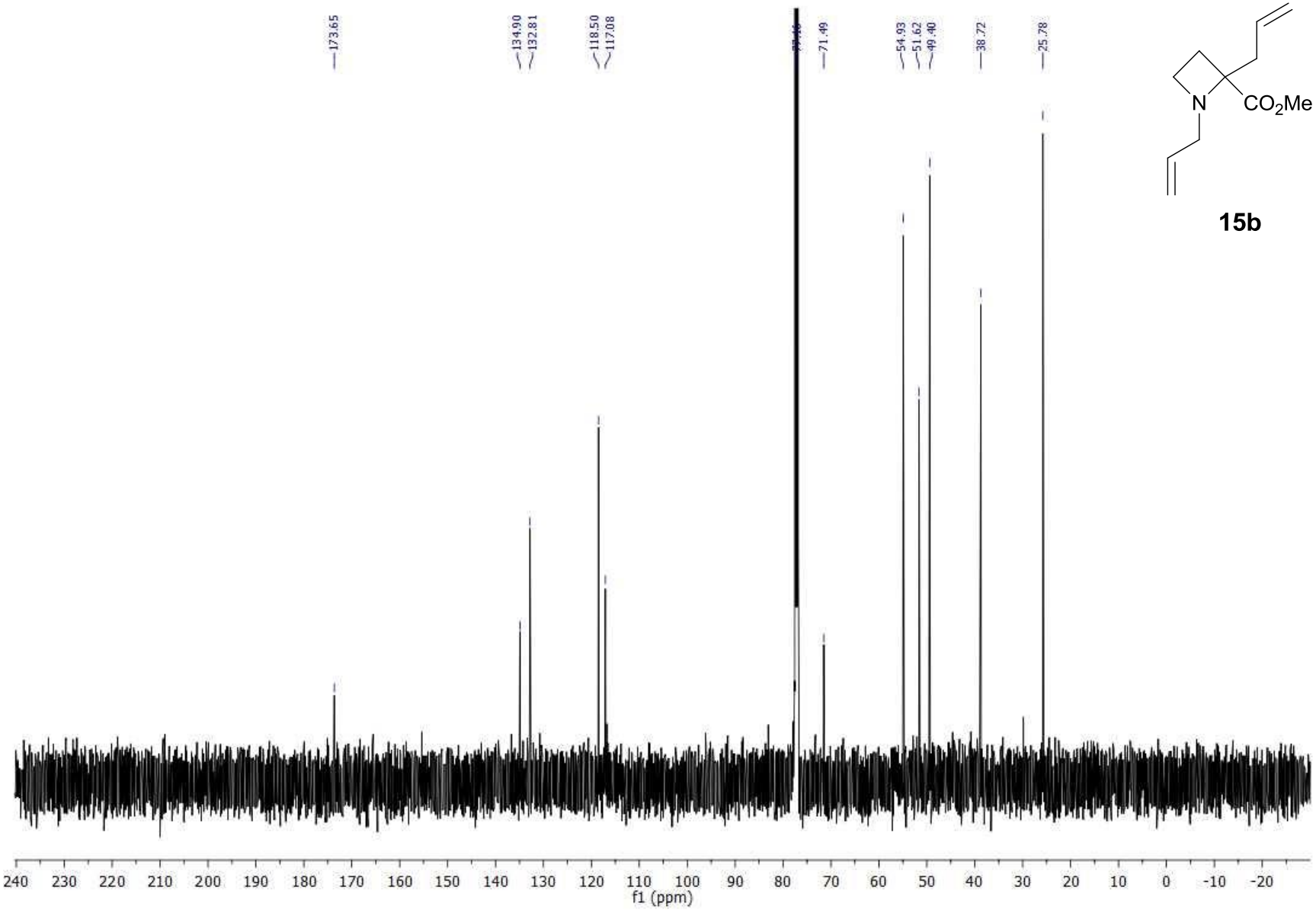
15a


174.62
136.86
134.33
117.94
116.20
79.86 External noise
77.16
70.18
52.49
51.75
51.22
39.36
33.92
21.64
N
CO2Me
15a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.26
3.74
2.00
4.43
2.88
4.44
1.32
2.15
0.98
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
-0.5
f1 (ppm)

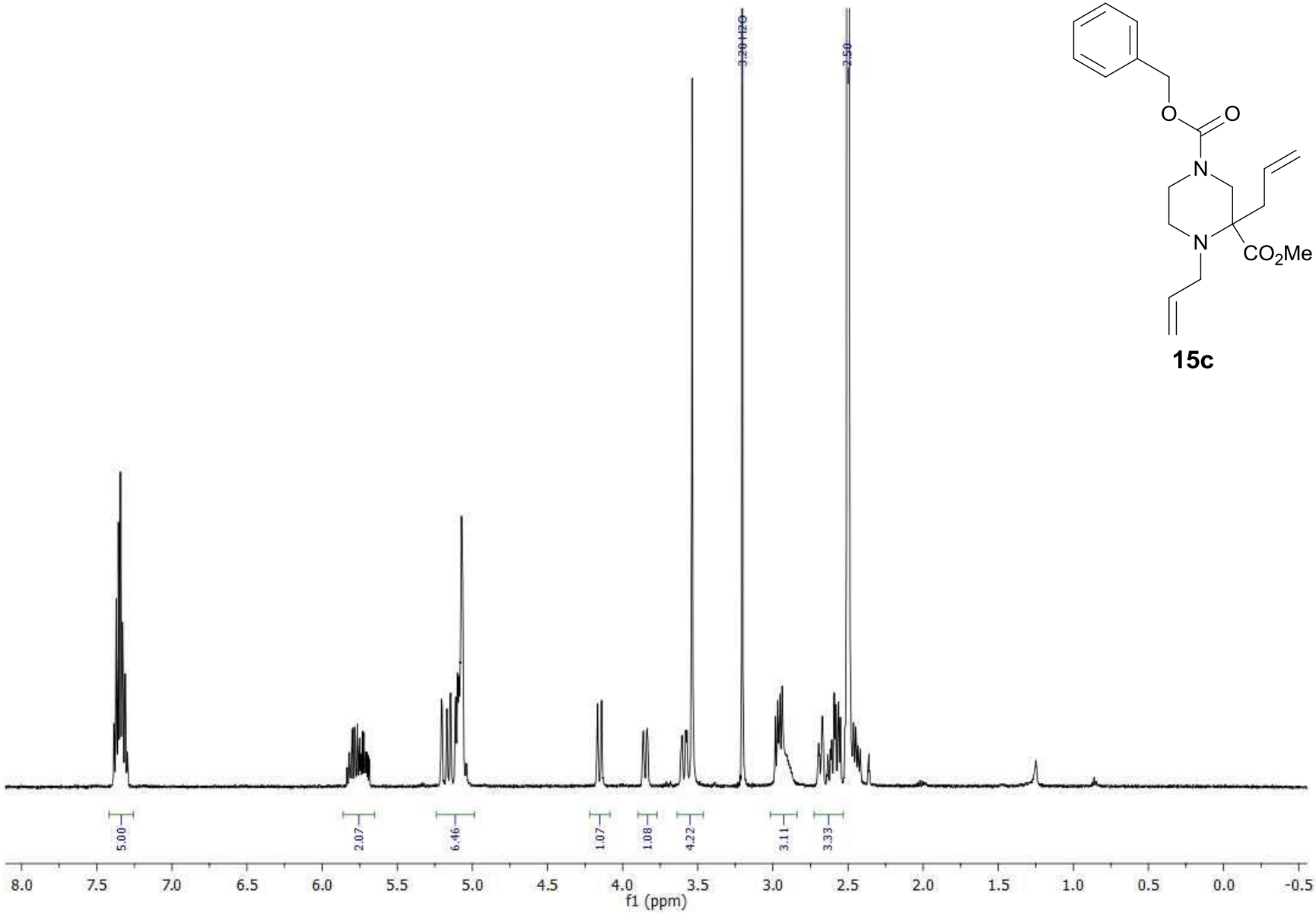
N
CO2Me

15b

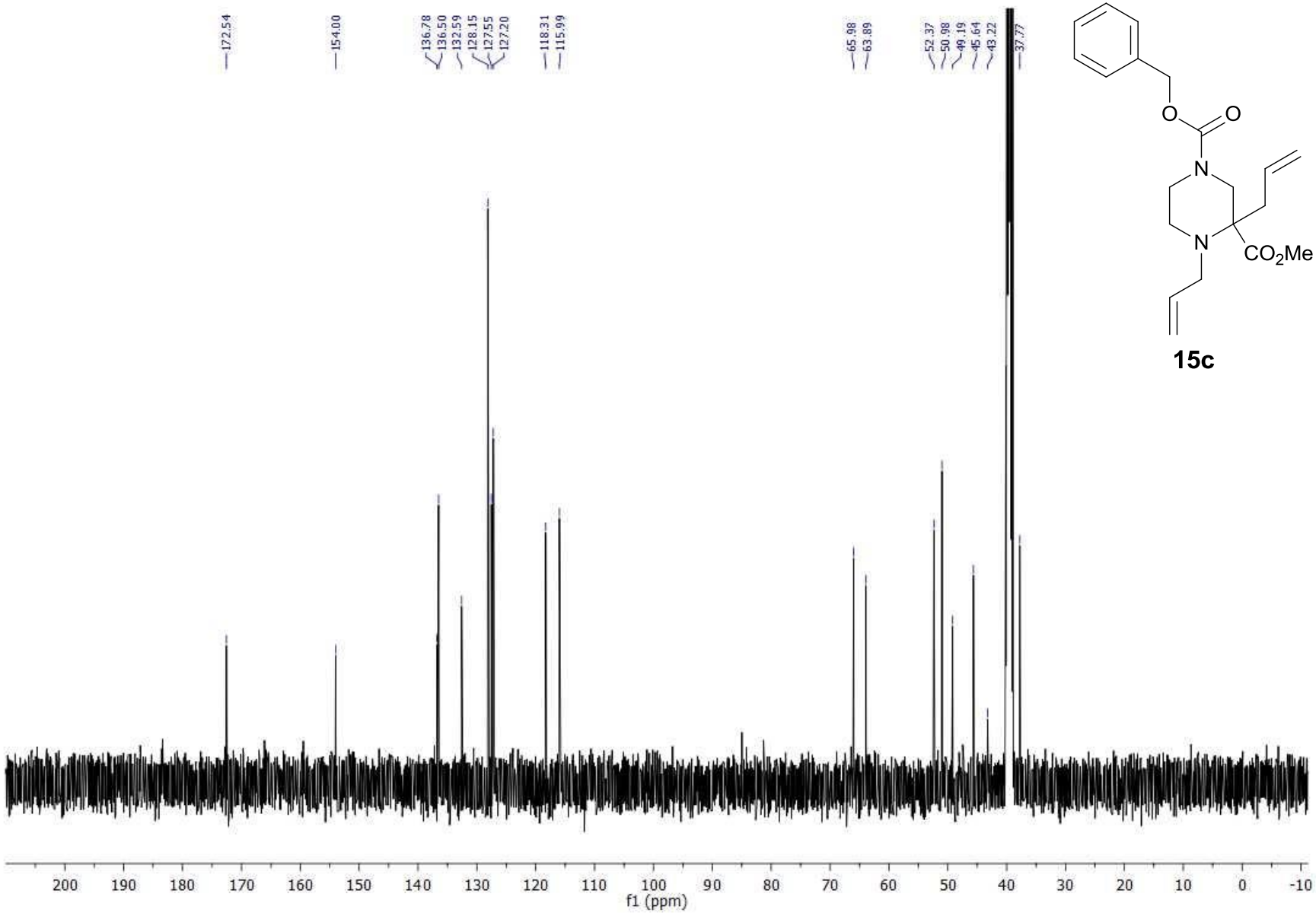

173.65
134.90
132.81
118.50
117.08
77.46
71.49
54.93
51.62
49.40
38.72
25.78
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

N
CO2Me

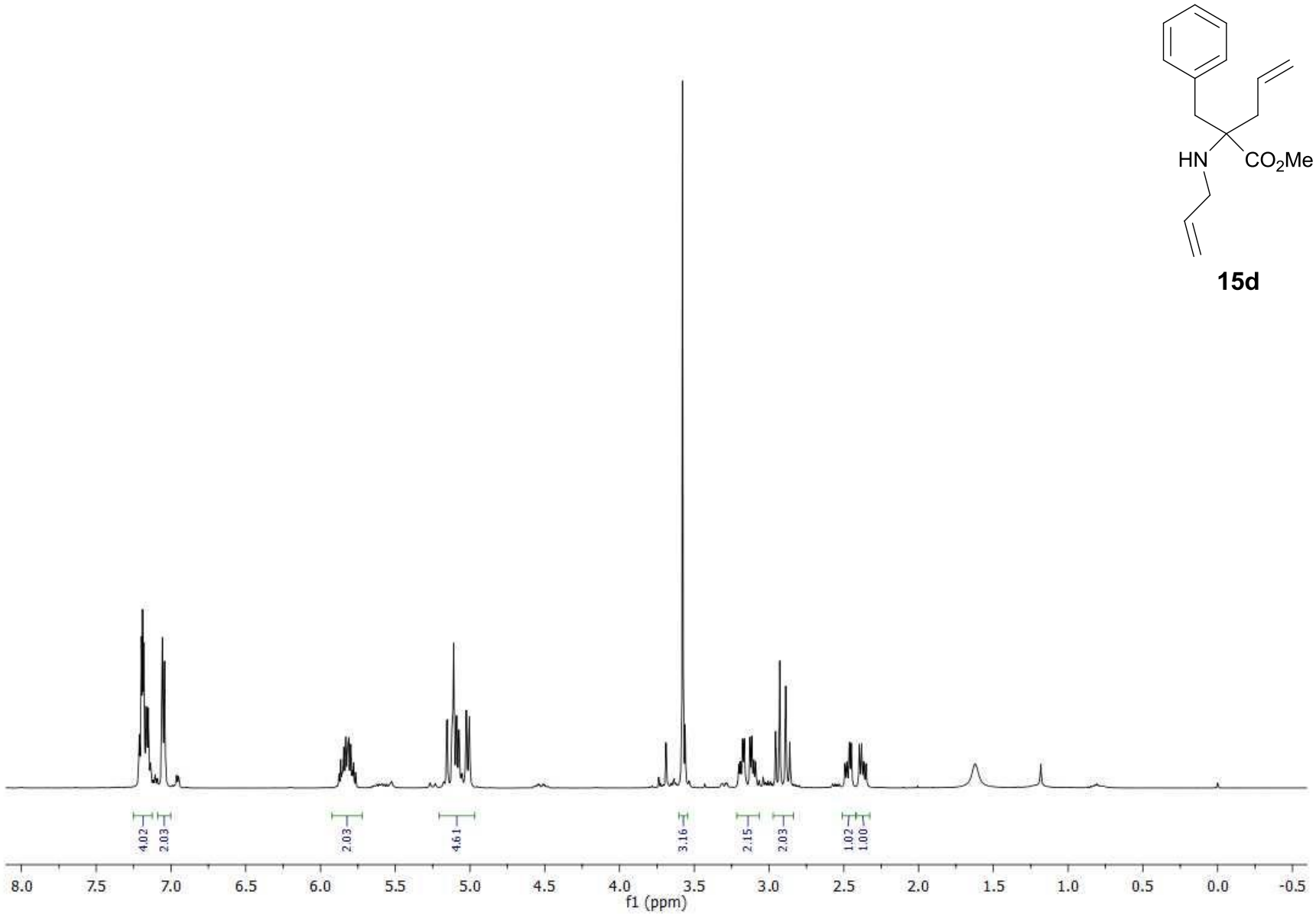
15b

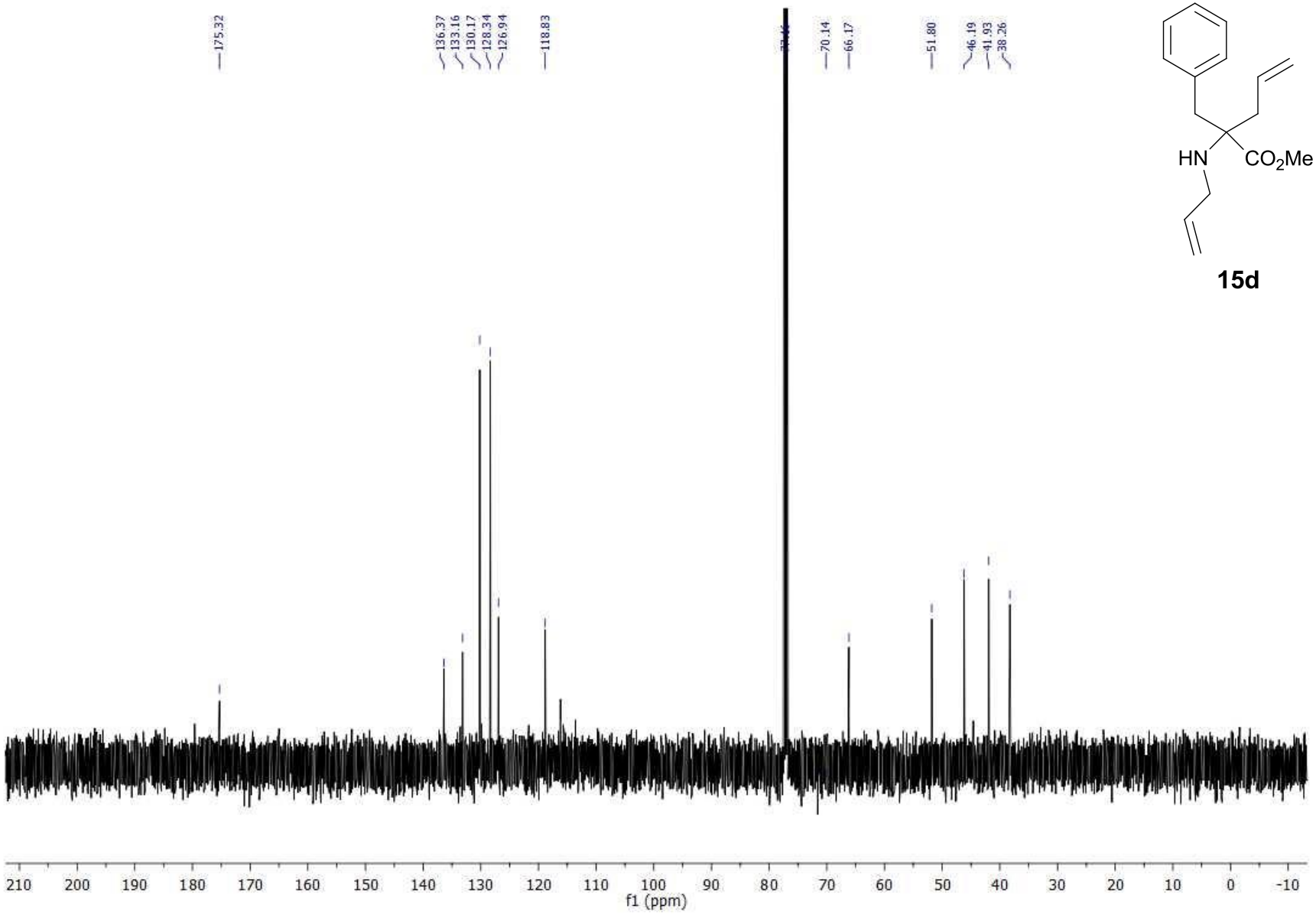

3.30 H2O
2.50
5.00
2.07
6.46
1.07
1.08
4.22
3.11
3.33
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)
O
O
N
N
CO2Me

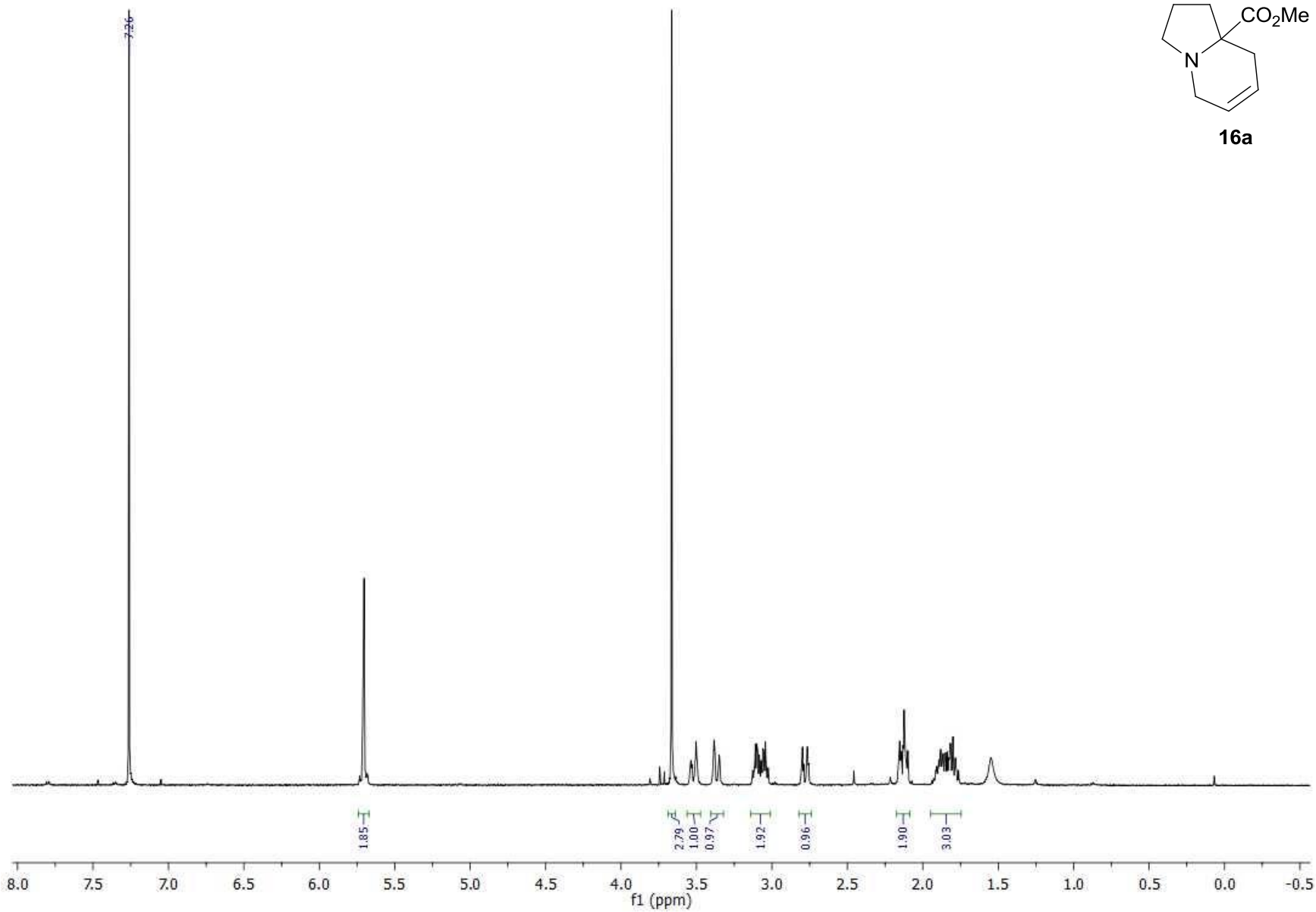
15c


172.54
154.00
136.78
136.50
132.59
128.15
127.55
127.20
118.31
115.99
65.98
63.89
52.37
50.98
49.19
45.64
43.22
37.77
O
O
N
N
CO2Me
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

15c

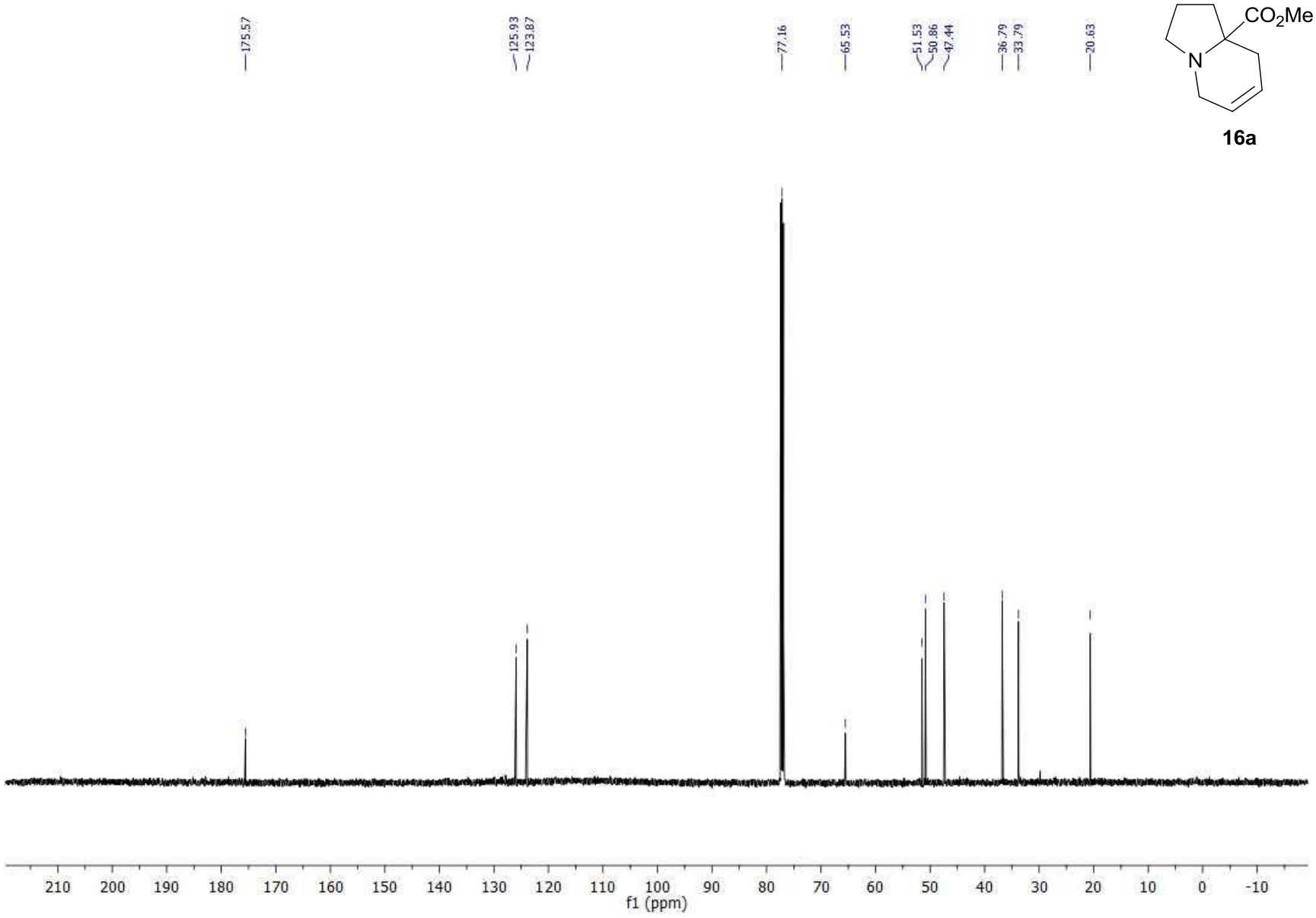

HN
CO2Me
15d
4.02
2.03
2.03
4.61
3.16
2.15
2.03
1.02
1.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

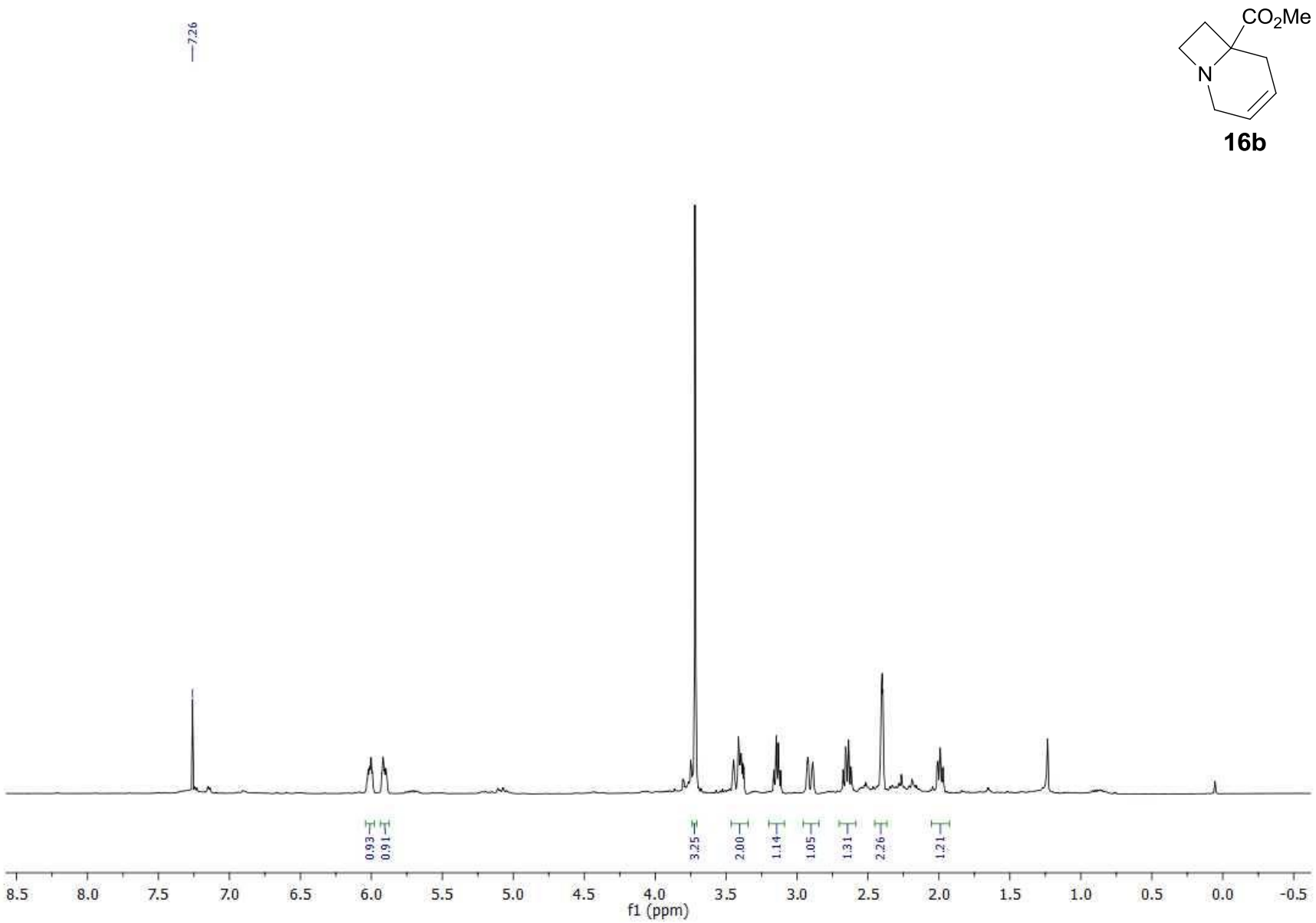

175.32
136.37
133.16
130.17
128.34
126.94
118.83
77.46
70.14
66.17
51.80
46.19
41.93
38.26
HN
CO2Me
15d
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

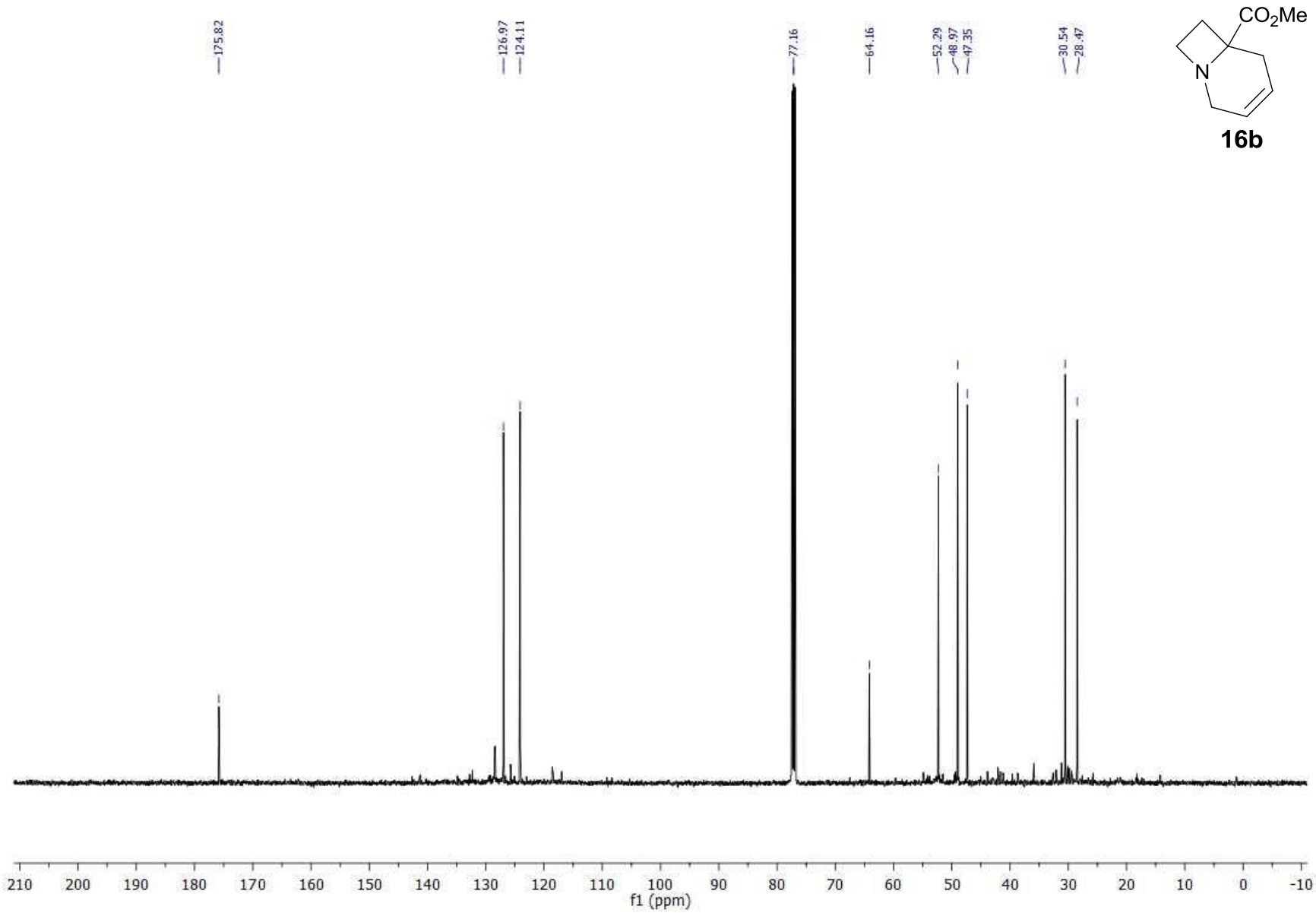

7.26
1.85
2.79
1.00
0.97
1.92
0.96
1.90
3.03
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

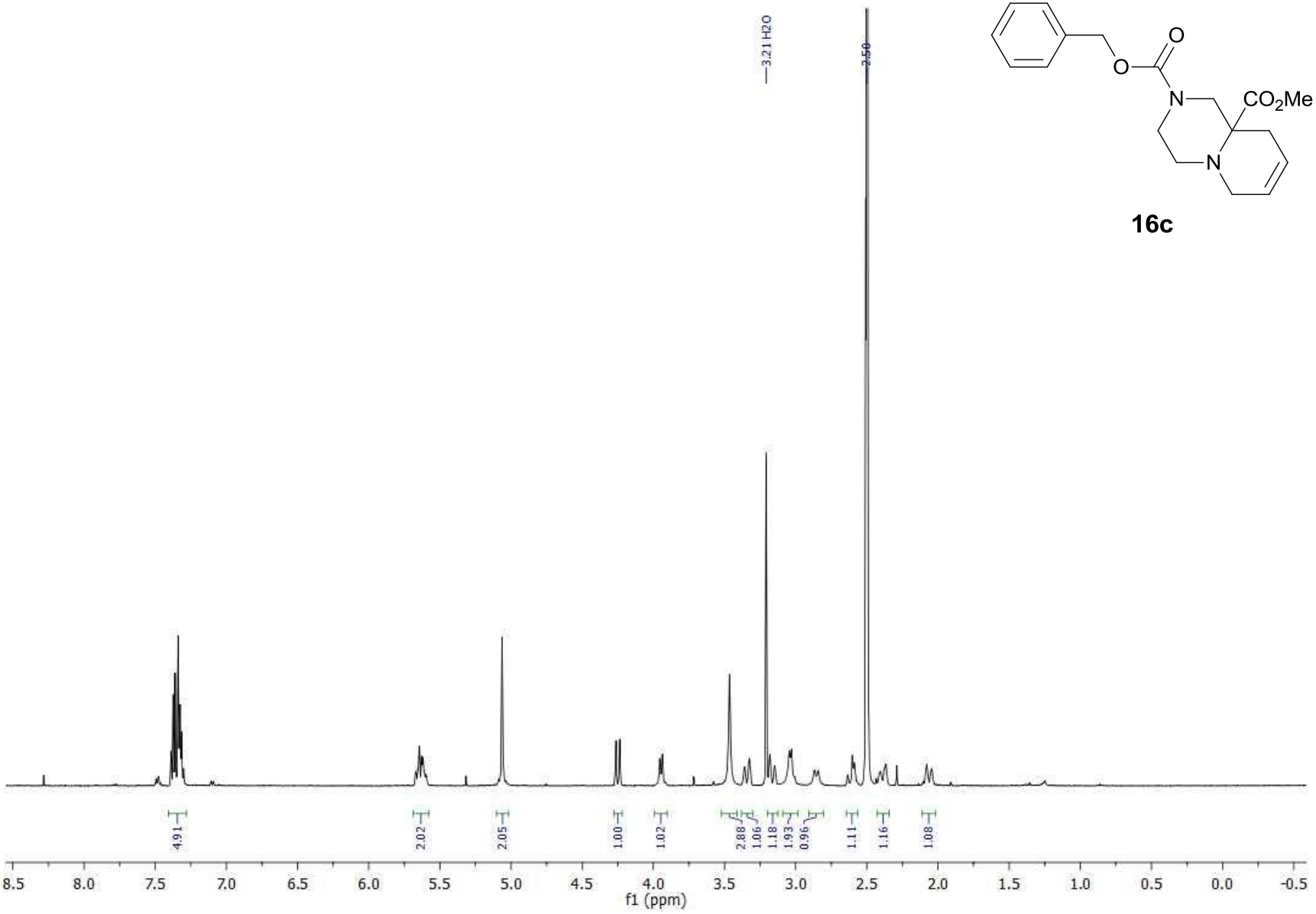
CO2Me
N

16a


175.57
125.93
123.87
77.16
65.53
51.53
50.86
47.44
36.79
33.79
20.63
CO2Me
N
16a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

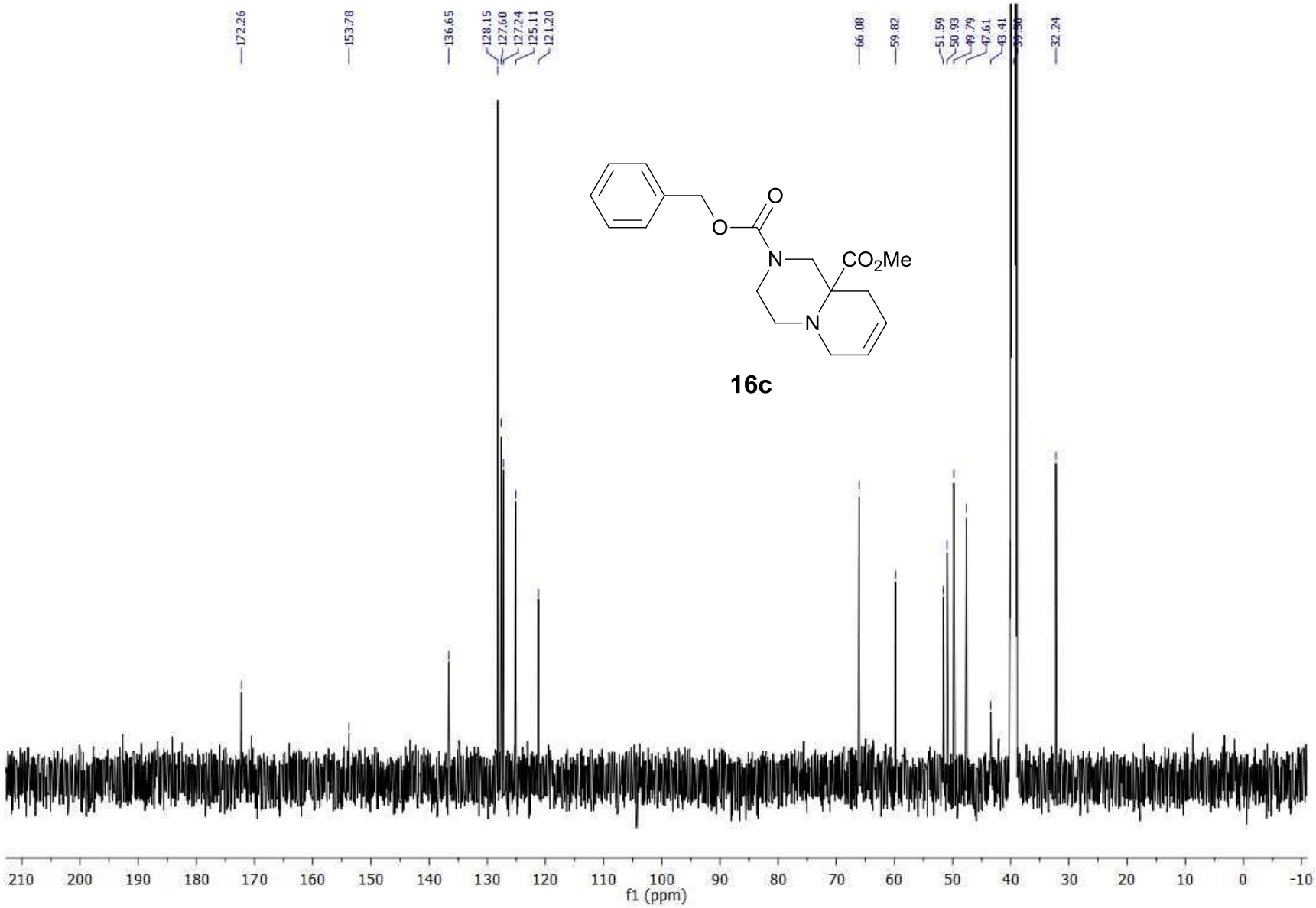

7.26
CO2Me
N
16b
0.93
0.91
3.25
2.00
1.14
1.05
1.31
2.26
1.21
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

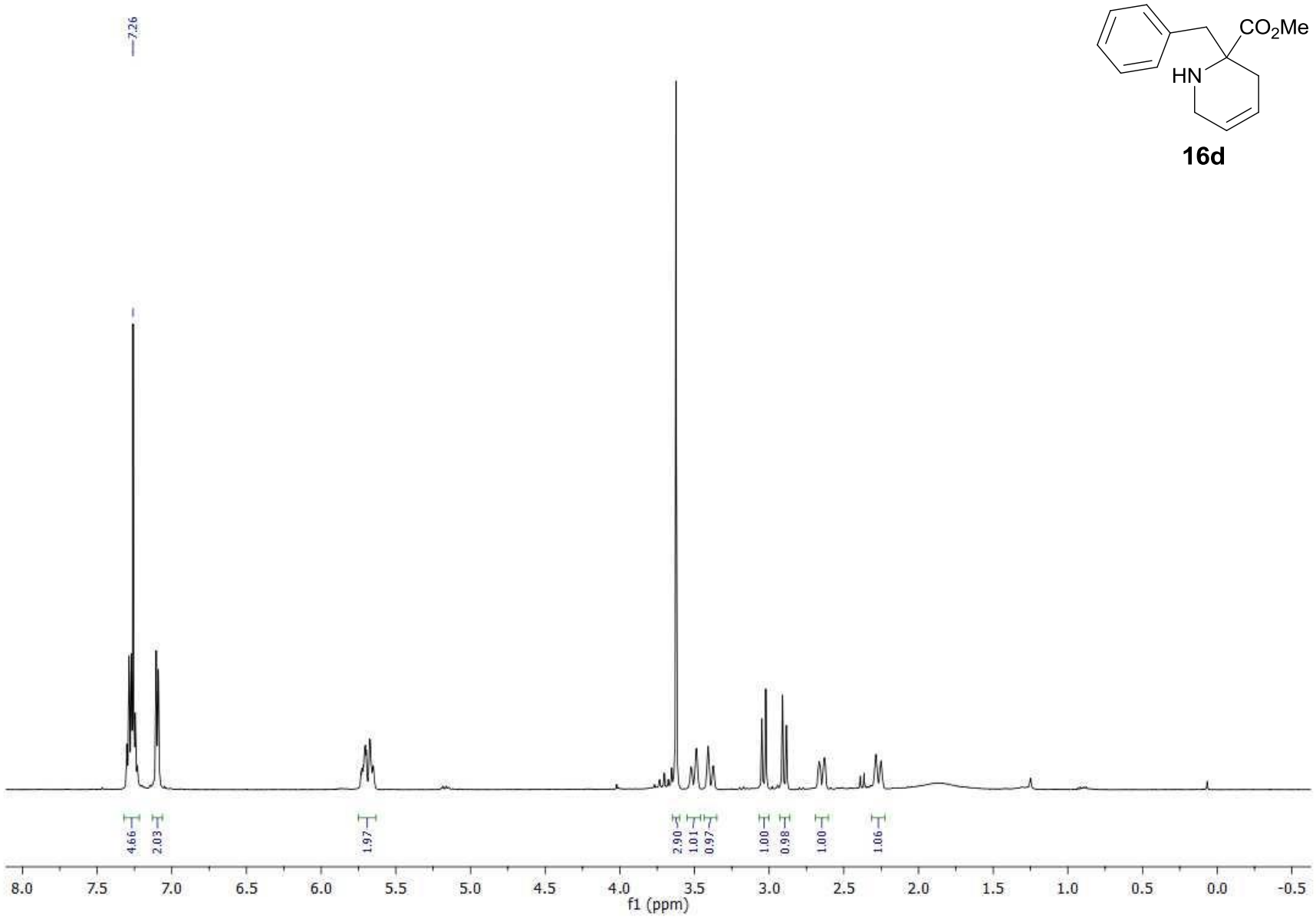

175.82
126.97
124.11
77.16
64.16
52.29
48.97
47.35
30.54
28.47
CO2Me
N
16b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


3.21 H2O
2.50
4.91
2.02
2.05
1.00
1.02
2.88
1.06
1.18
1.93
0.96
1.11
1.16
1.08
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
-0.5
f1 (ppm)

O
O
N
CO2Me
N

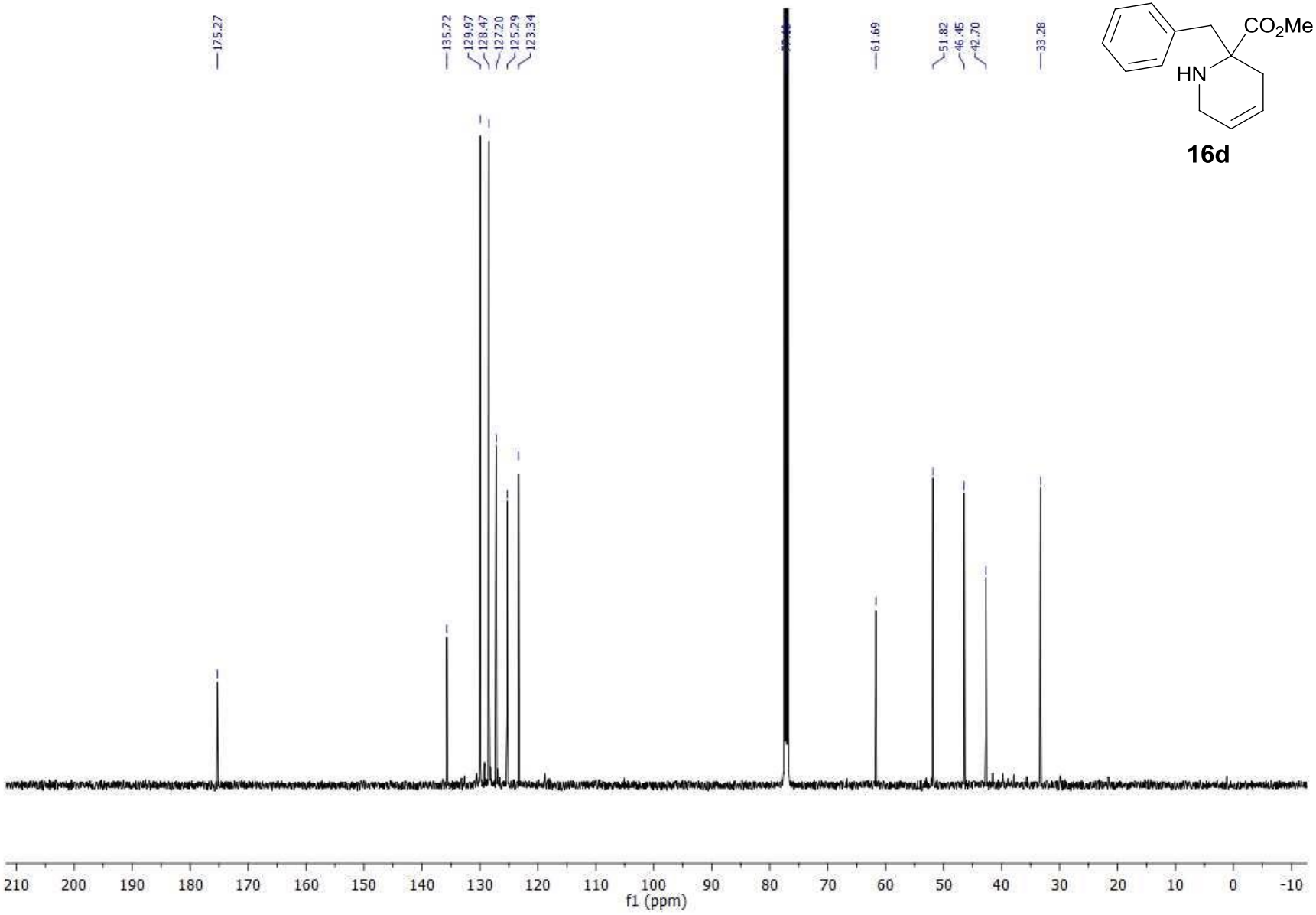
16c

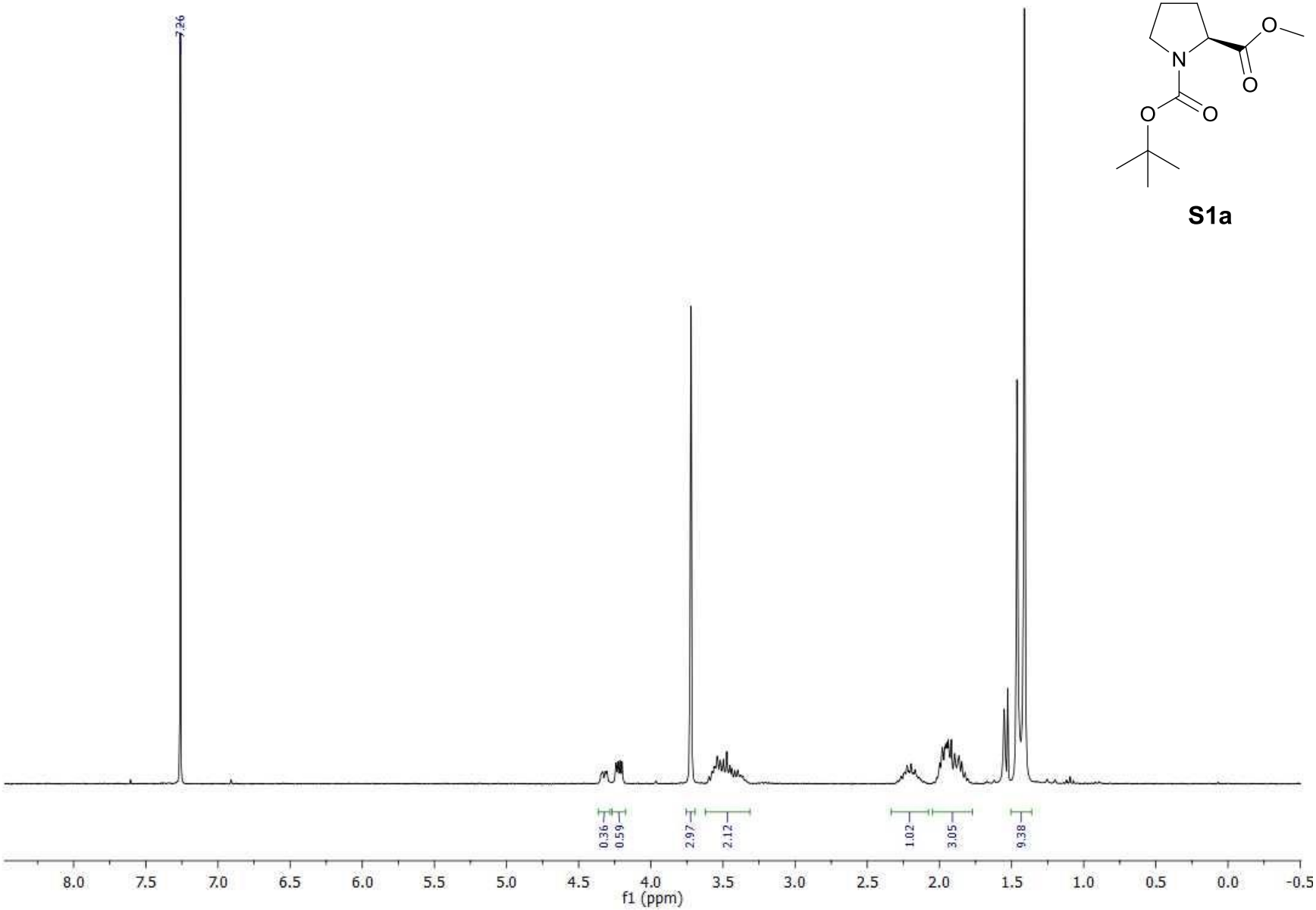

172.26
153.78
136.65
128.15
127.60
127.24
125.11
121.20
66.08
59.82
51.59
50.93
49.79
47.61
43.41
32.24
O
O
N
CO2Me
N
16c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.26
4.66
2.03
1.97
2.90
1.01
0.97
1.00
0.98
1.00
1.06
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
-0.5
f1 (ppm)

CO2Me
HN

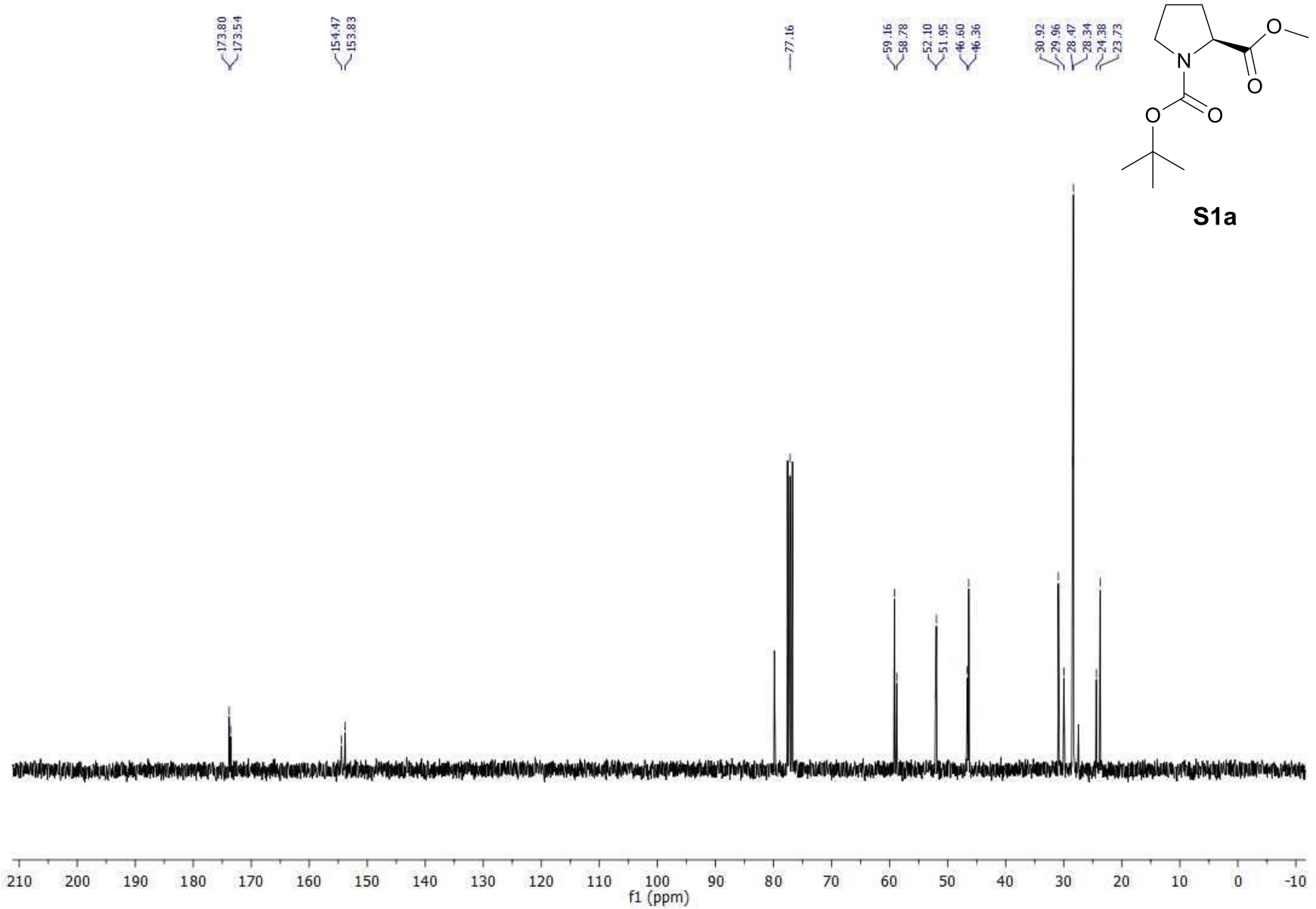
16d

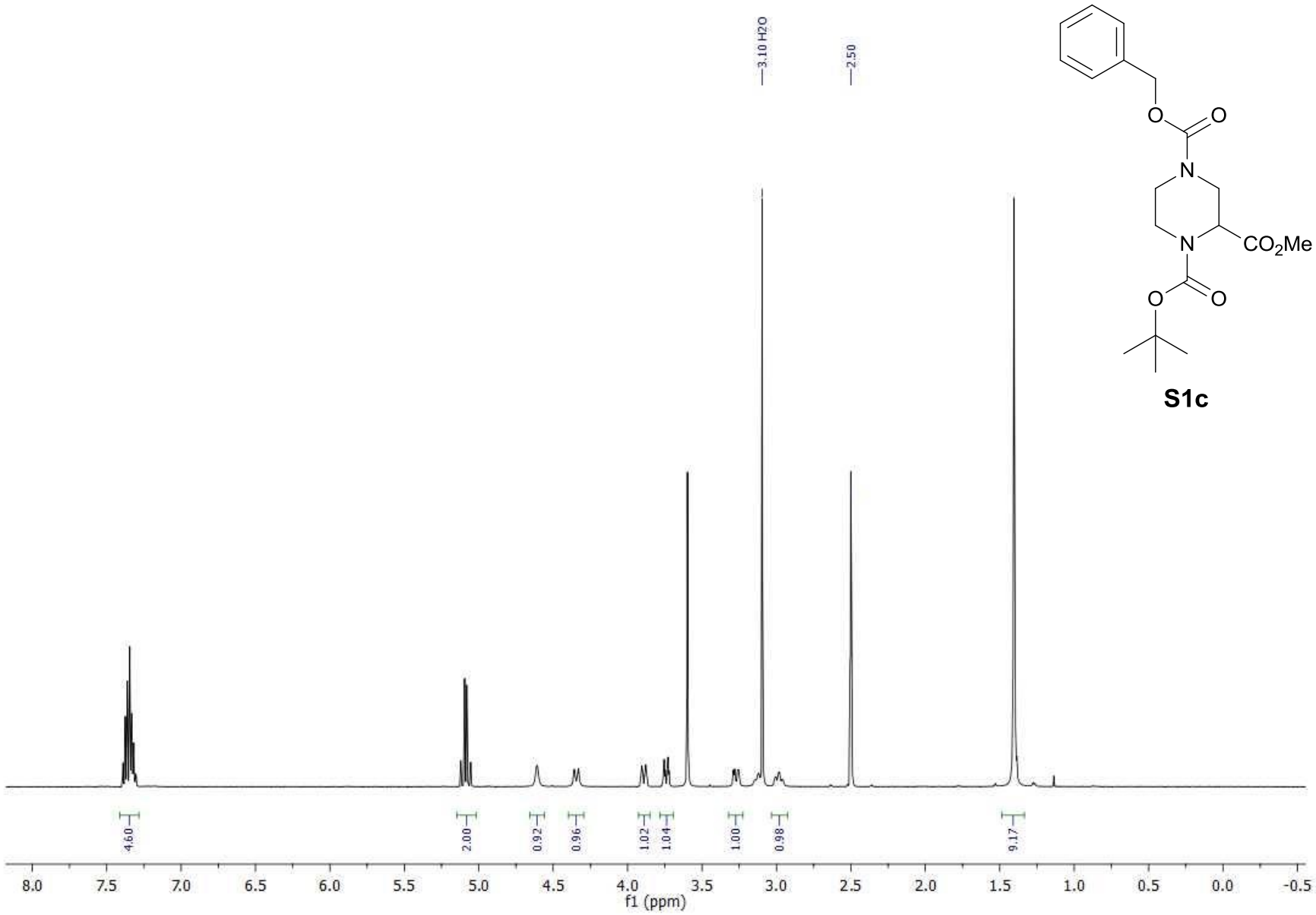

175.27
135.72
129.97
128.47
127.20
125.29
123.34
61.69
51.82
46.45
42.70
33.28
CO2Me
HN
16d
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.26
0.36
0.59
2.97
2.12
1.02
3.05
9.38
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
-0.5
f1 (ppm)

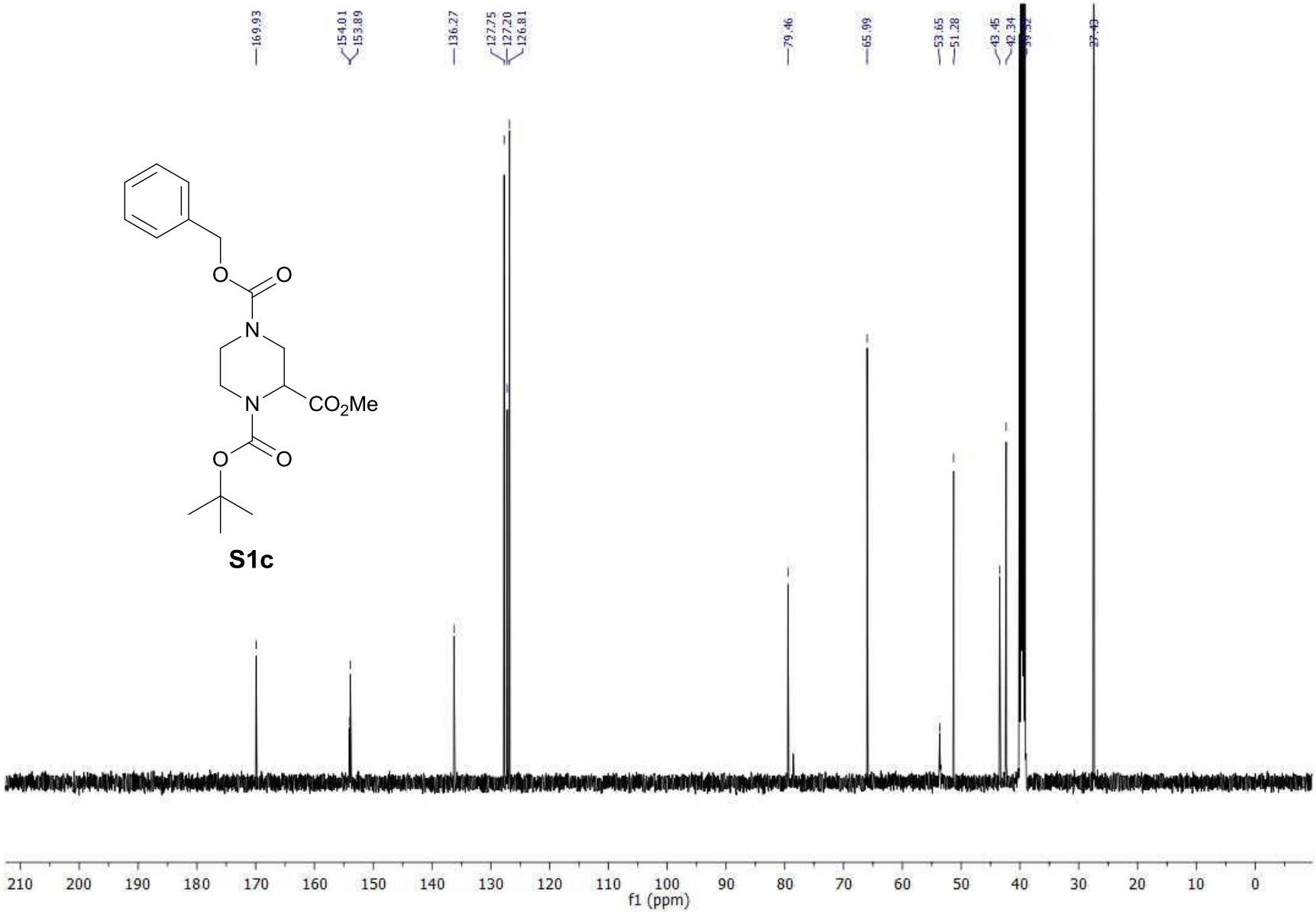
N
O
O
O
O
O

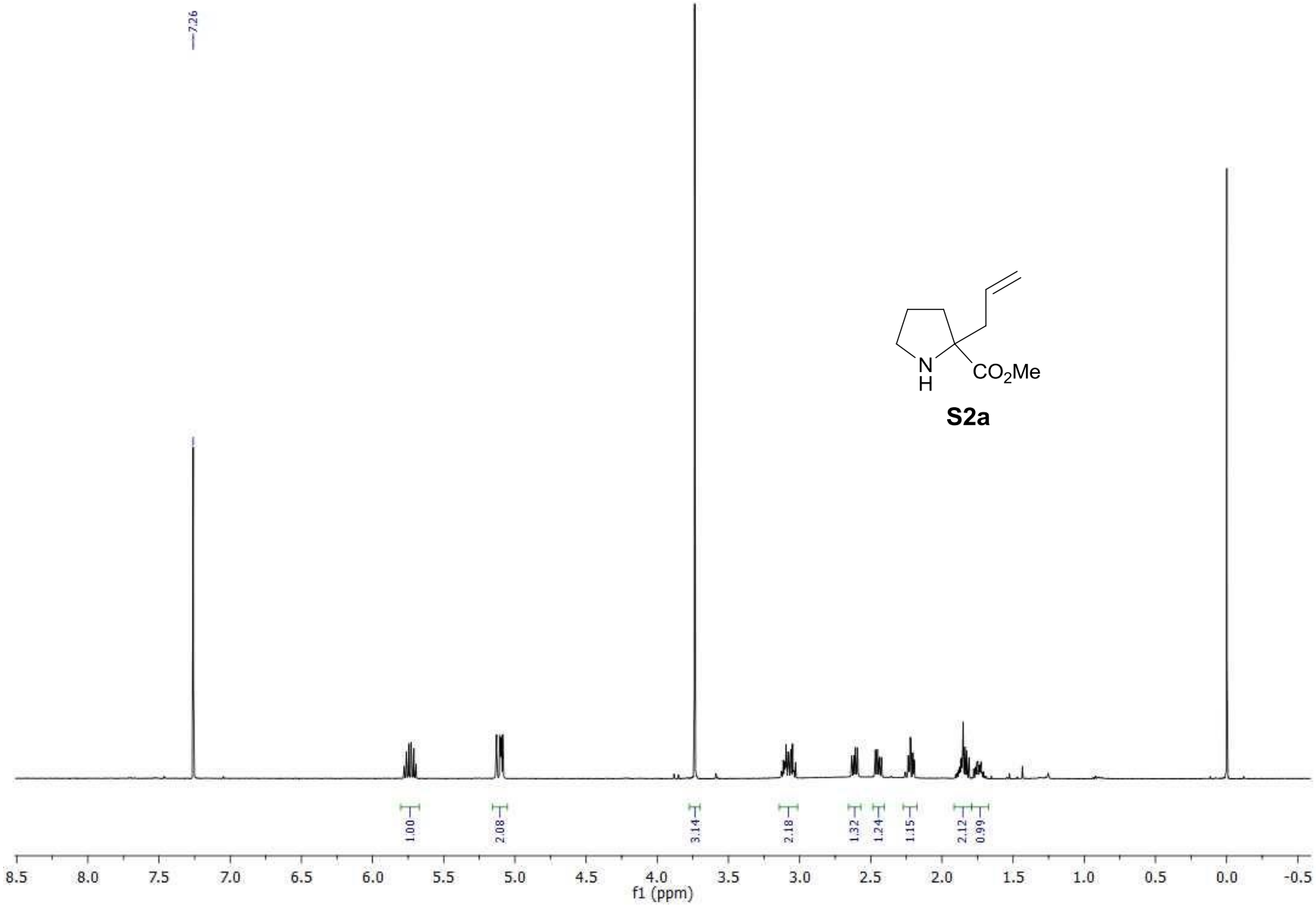
S1a


173.80
173.54
154.47
153.83
77.16
59.16
58.78
52.10
51.95
46.60
46.36
30.92
29.96
28.47
28.34
24.38
23.73
N
O
O
O
O
S1a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

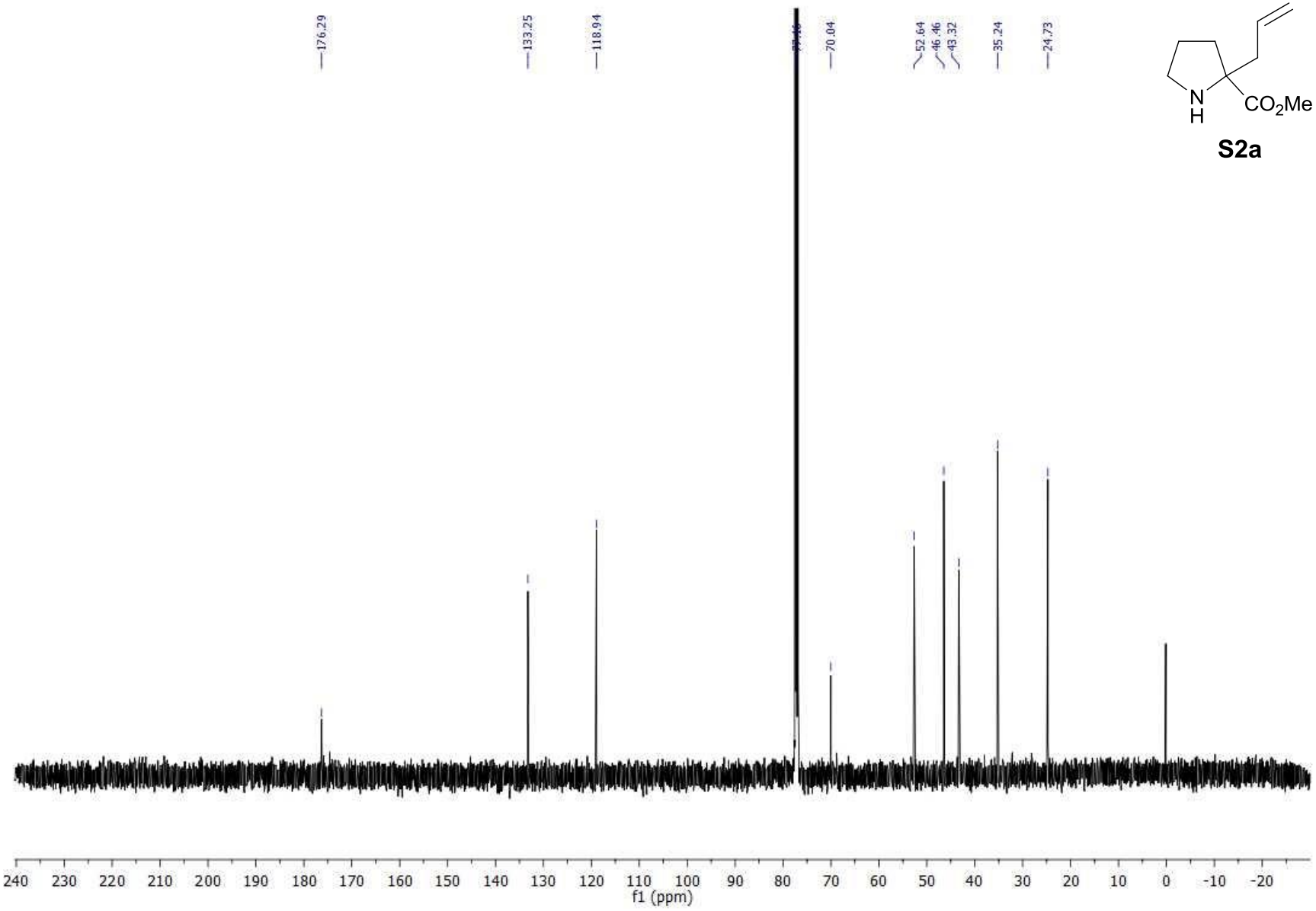

3.10 H2O
2.50
4.60
2.00
0.92
0.96
1.02
1.04
1.00
0.98
9.17
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)
O
O
N
N
O
O
CO2Me

S1c

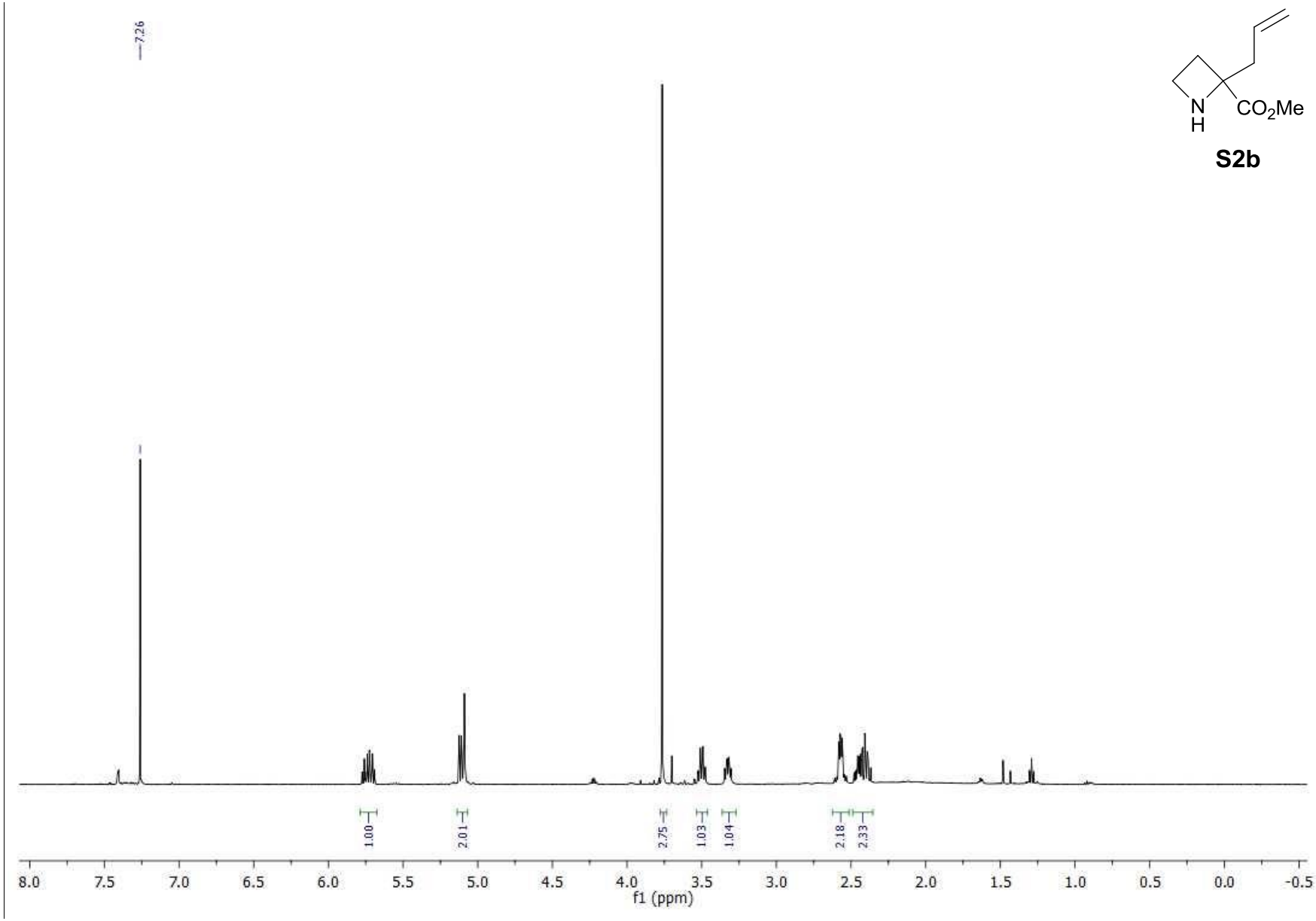

169.93
154.01
153.89
136.27
127.75
127.20
126.81
79.46
65.99
53.65
51.28
43.45
42.34
39.52
27.43
O
O
N
N
CO2Me
O
O
S1c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.26
1.00
2.08
3.14
2.18
1.32
1.24
1.15
2.12
0.99
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
-0.5
f1 (ppm)
N
H
CO2Me

S2a

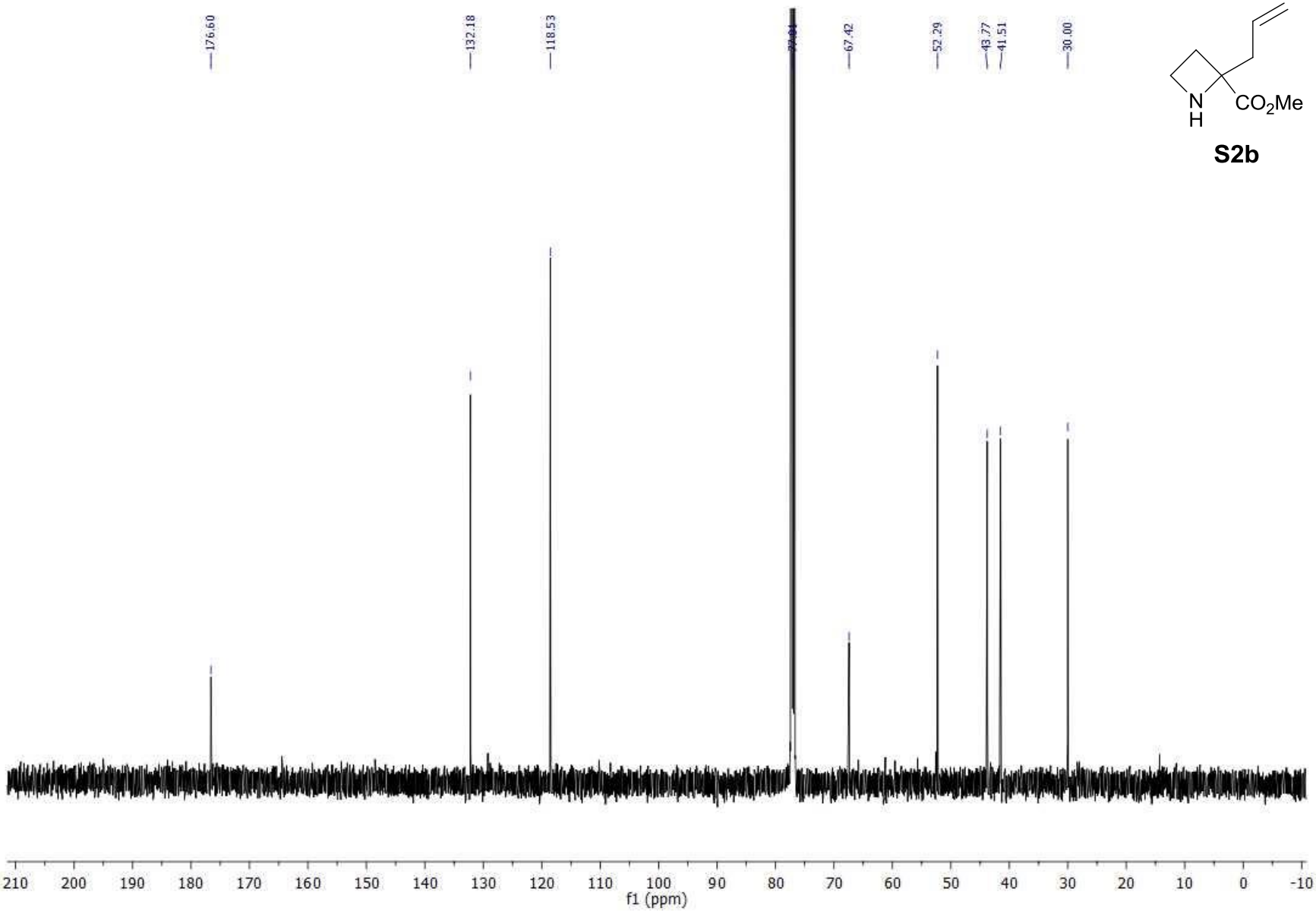

176.29
133.25
118.94
77.16
70.04
52.64
46.46
43.32
35.24
24.73
N
H
CO2Me
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

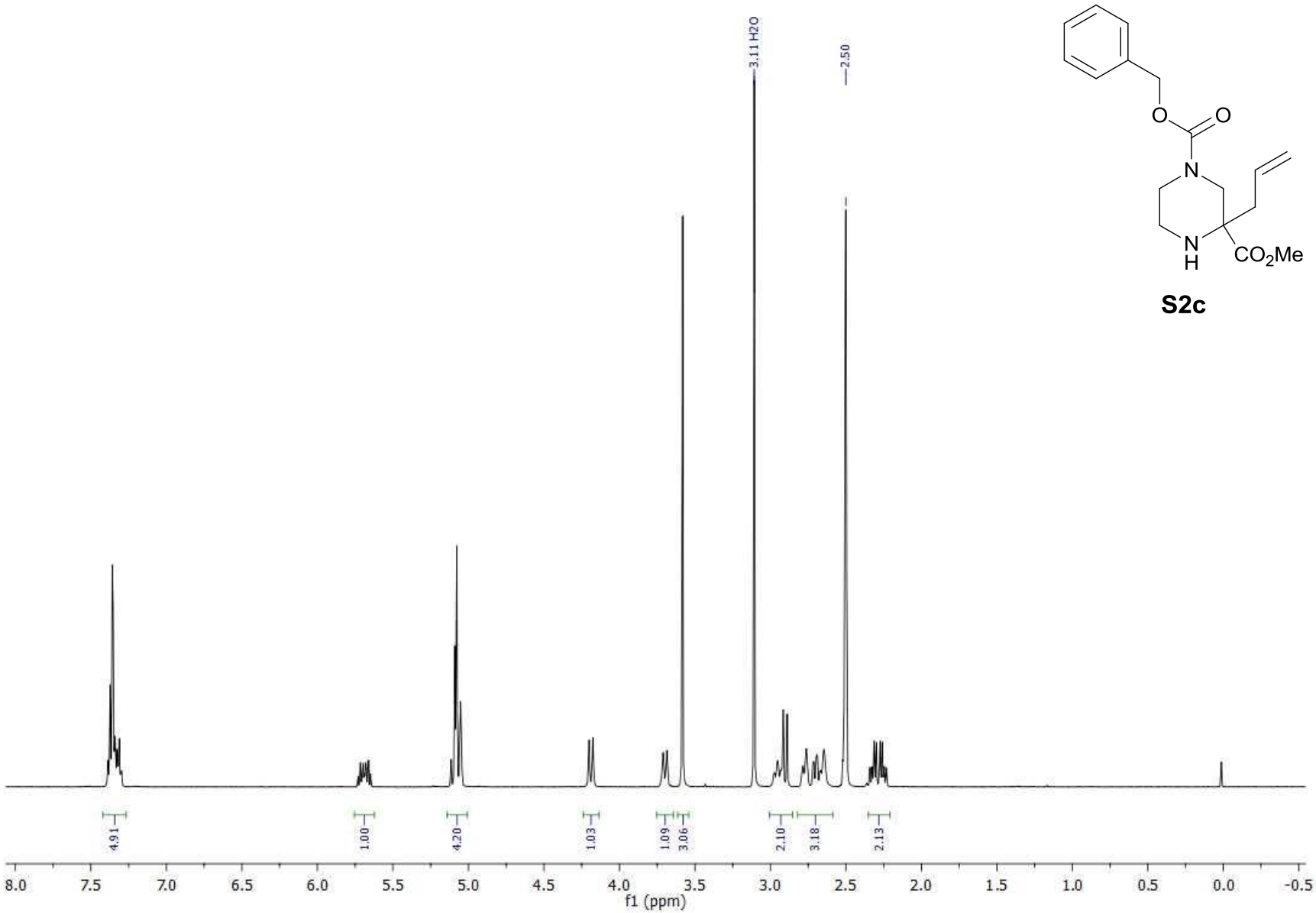
S2a


7.26
1.00
2.01
2.75
1.03
1.04
2.18
2.33
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
-0.5
f1 (ppm)

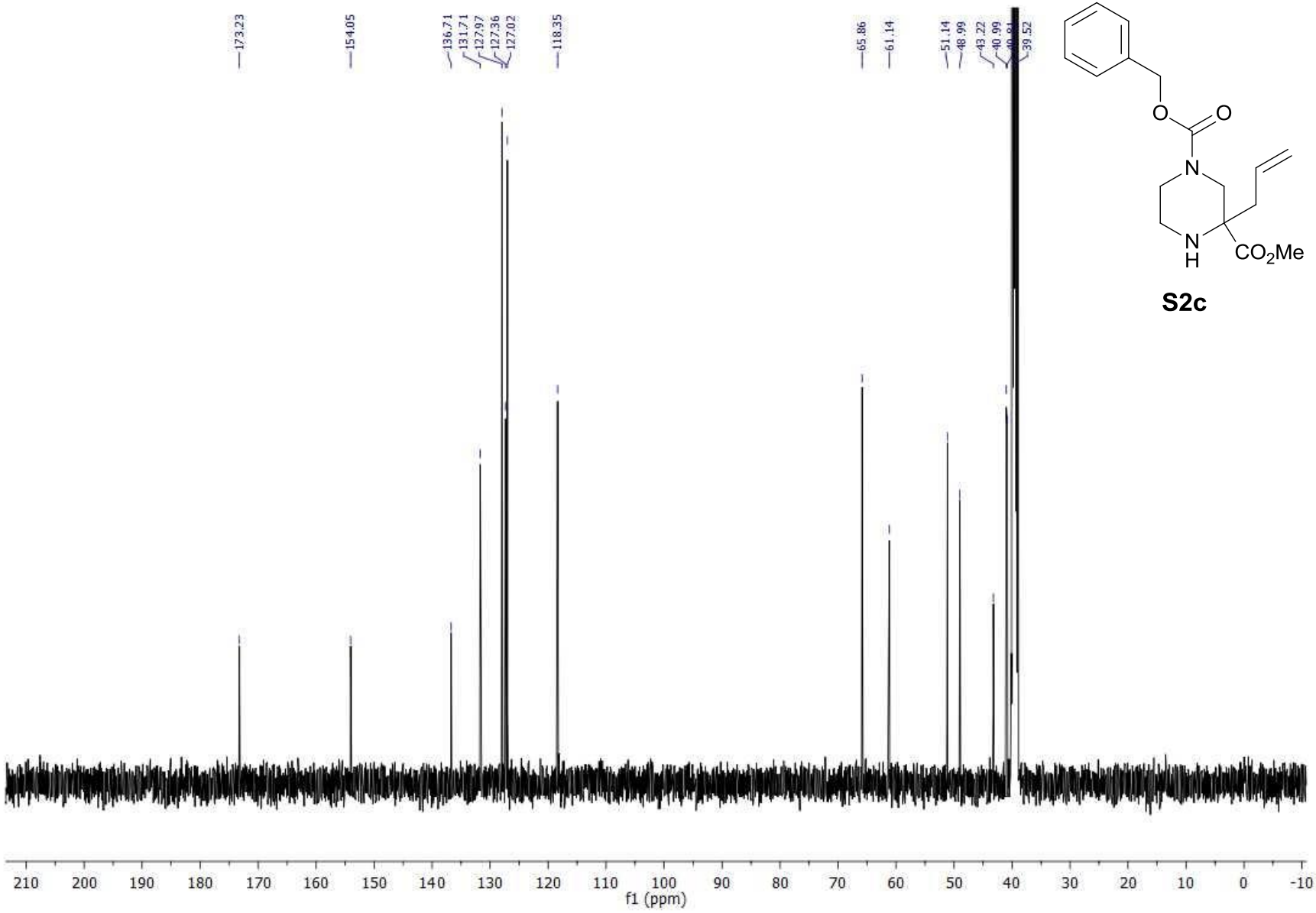
N
H
CO2Me

S2b

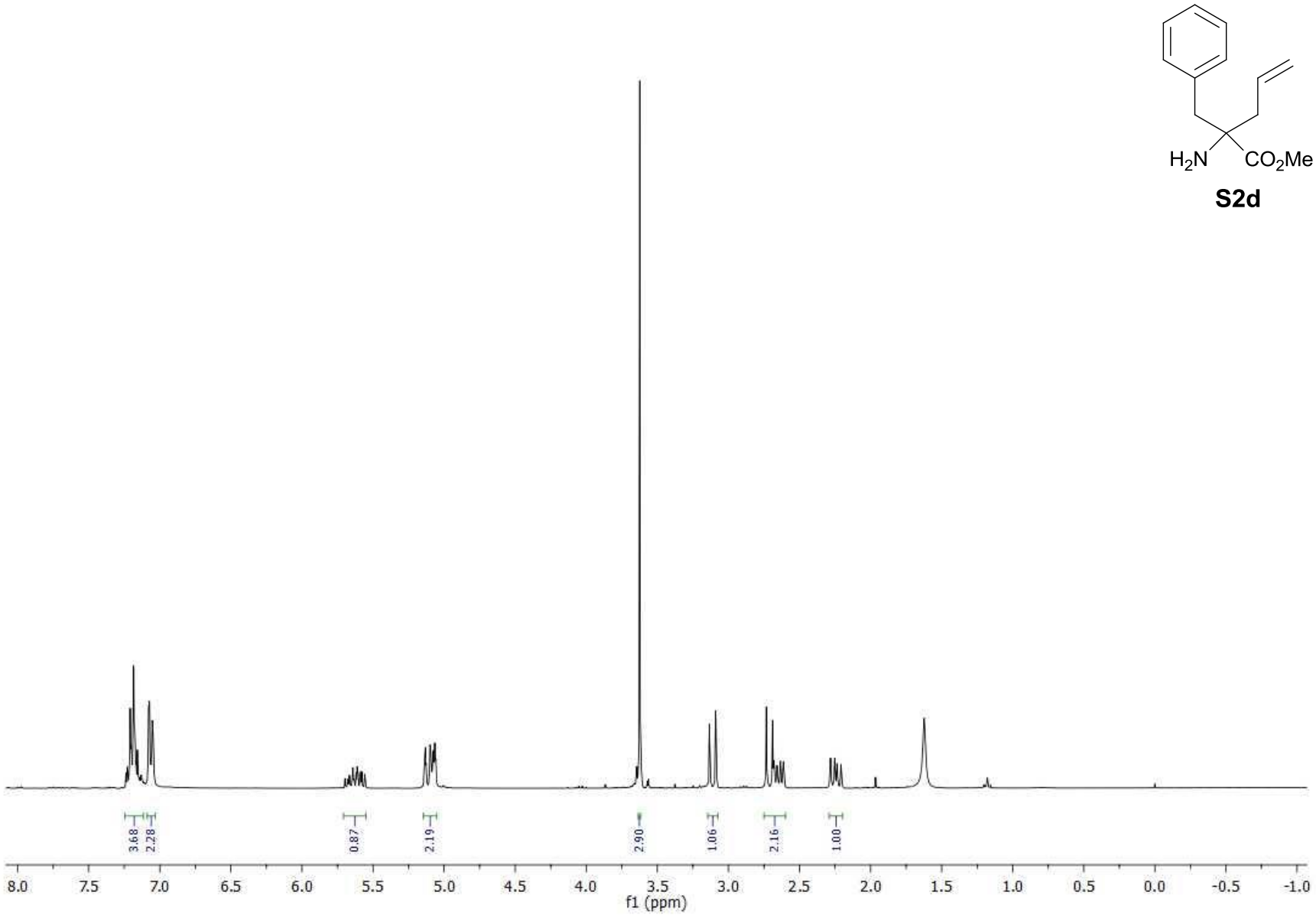

176.60
132.18
118.53
77.01
67.42
52.29
43.77
41.51
30.00
N
H
CO2Me
S2b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


3.11 H2O
2.50
4.91
1.00
4.20
1.03
1.09
3.06
2.10
3.18
2.13
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
-0.5
f1 (ppm)
O
O
N
N
H
CO2Me

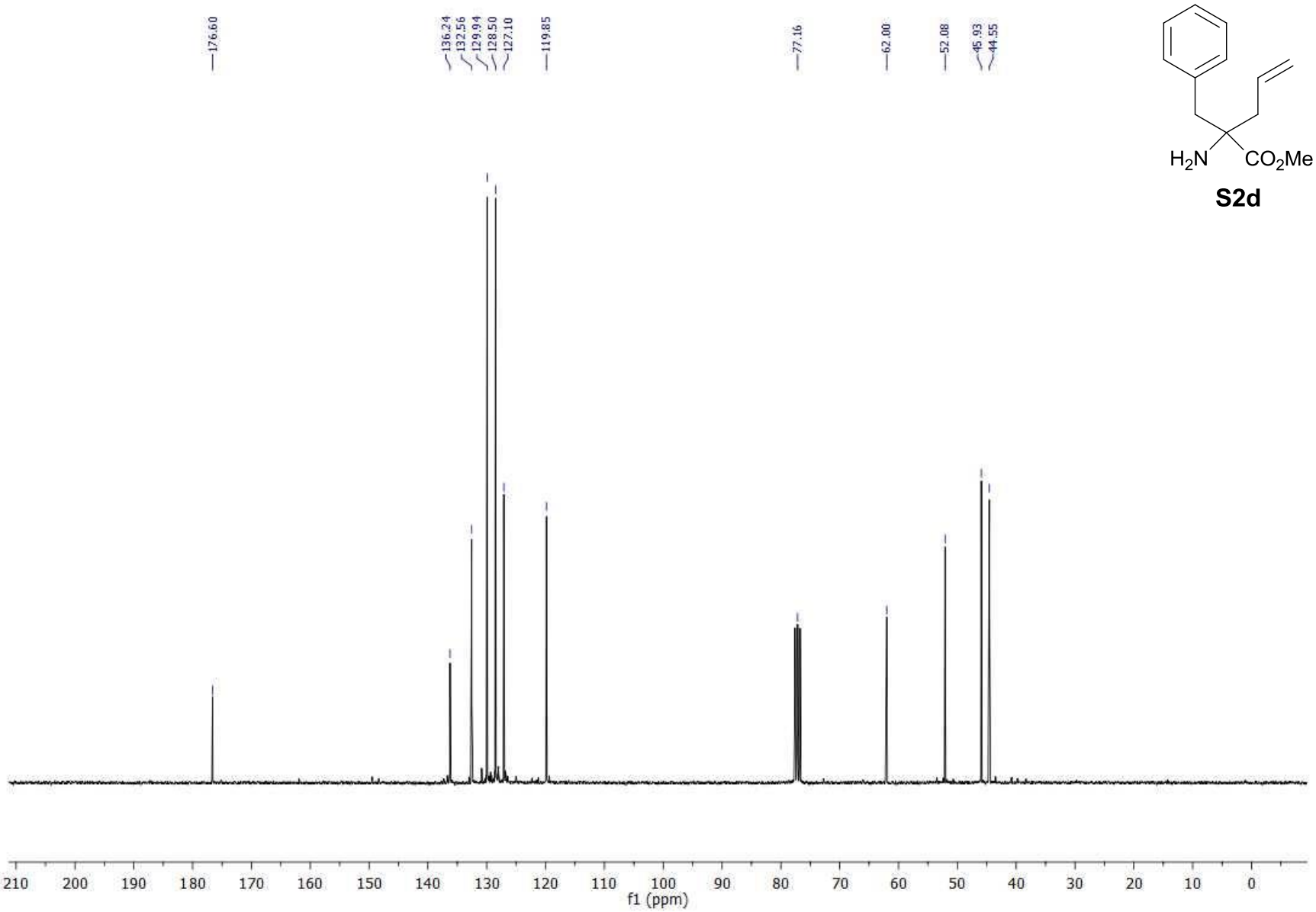
S2c

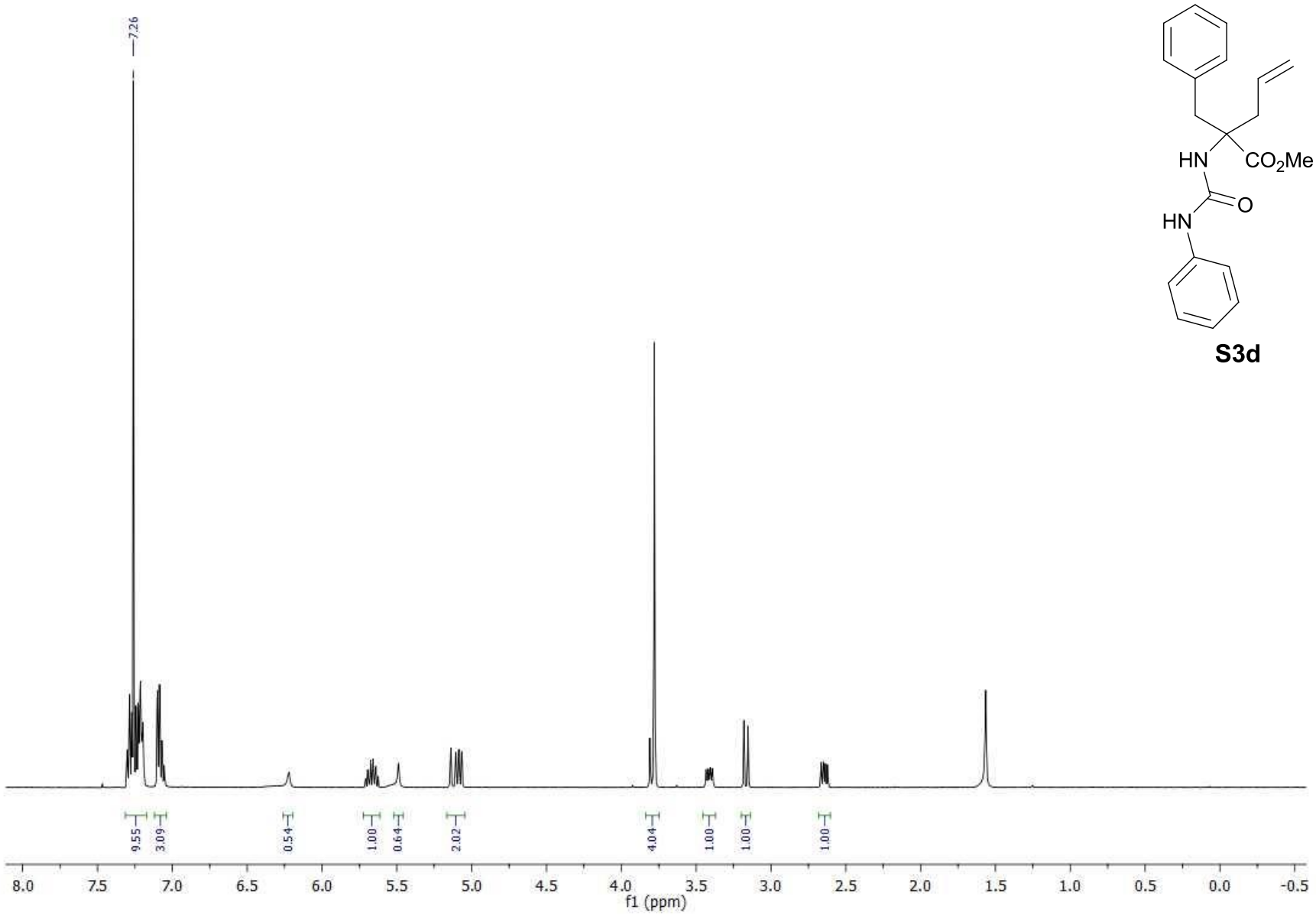

173.23
154.05
136.71
131.71
127.97
127.36
127.02
118.35
65.86
61.14
51.14
48.99
43.22
40.99
39.52
O
O
N
N
H
CO2Me
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

S2c


H2N
CO2Me
3.68
2.28
0.87
2.19
2.90
1.06
2.16
1.00
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
-0.5
-1.0
f1 (ppm)

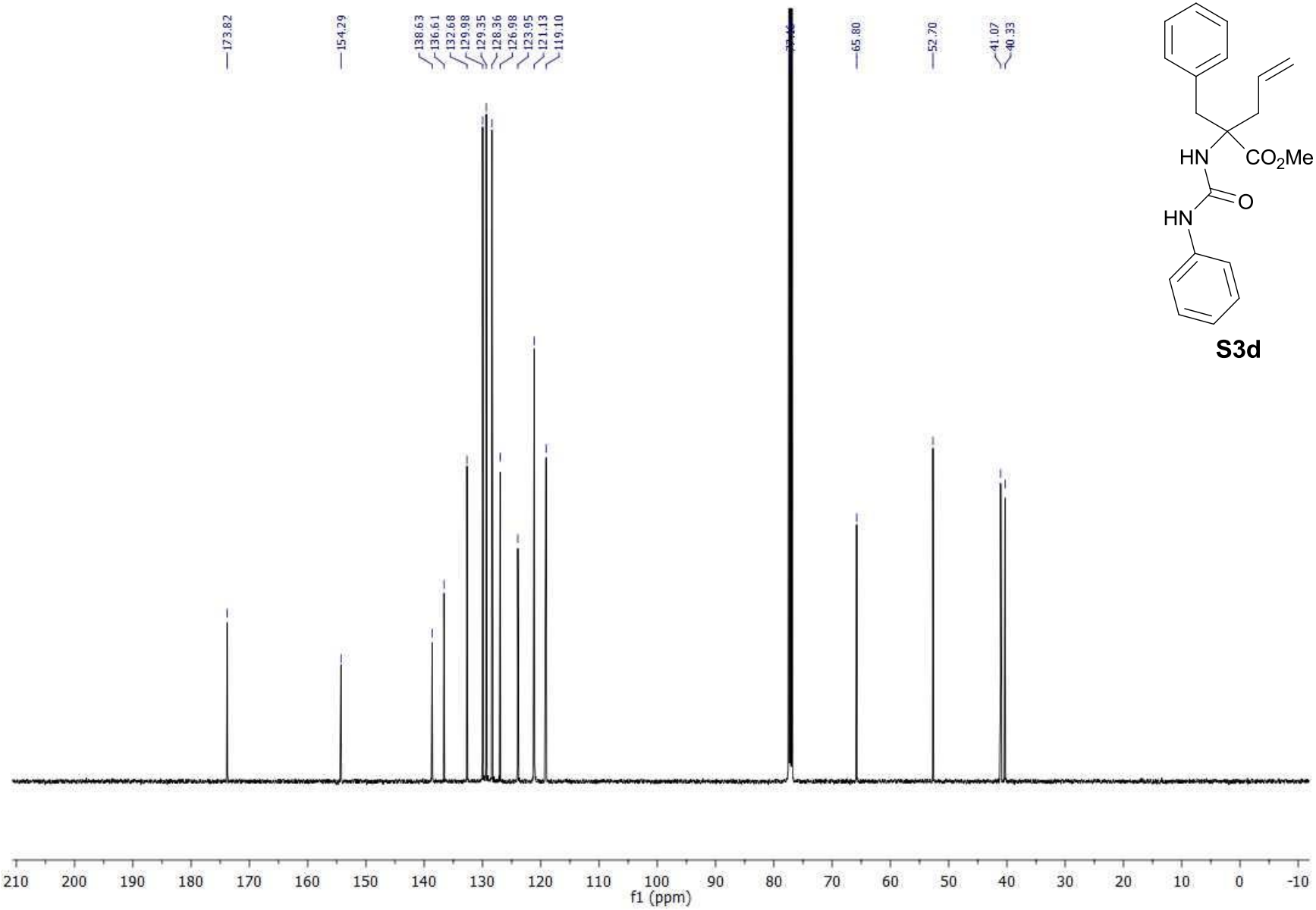
S2d


176.60
136.24
132.56
129.94
128.50
127.10
119.85
77.16
62.00
52.08
45.93
44.55
H2N
CO2Me
S2d
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

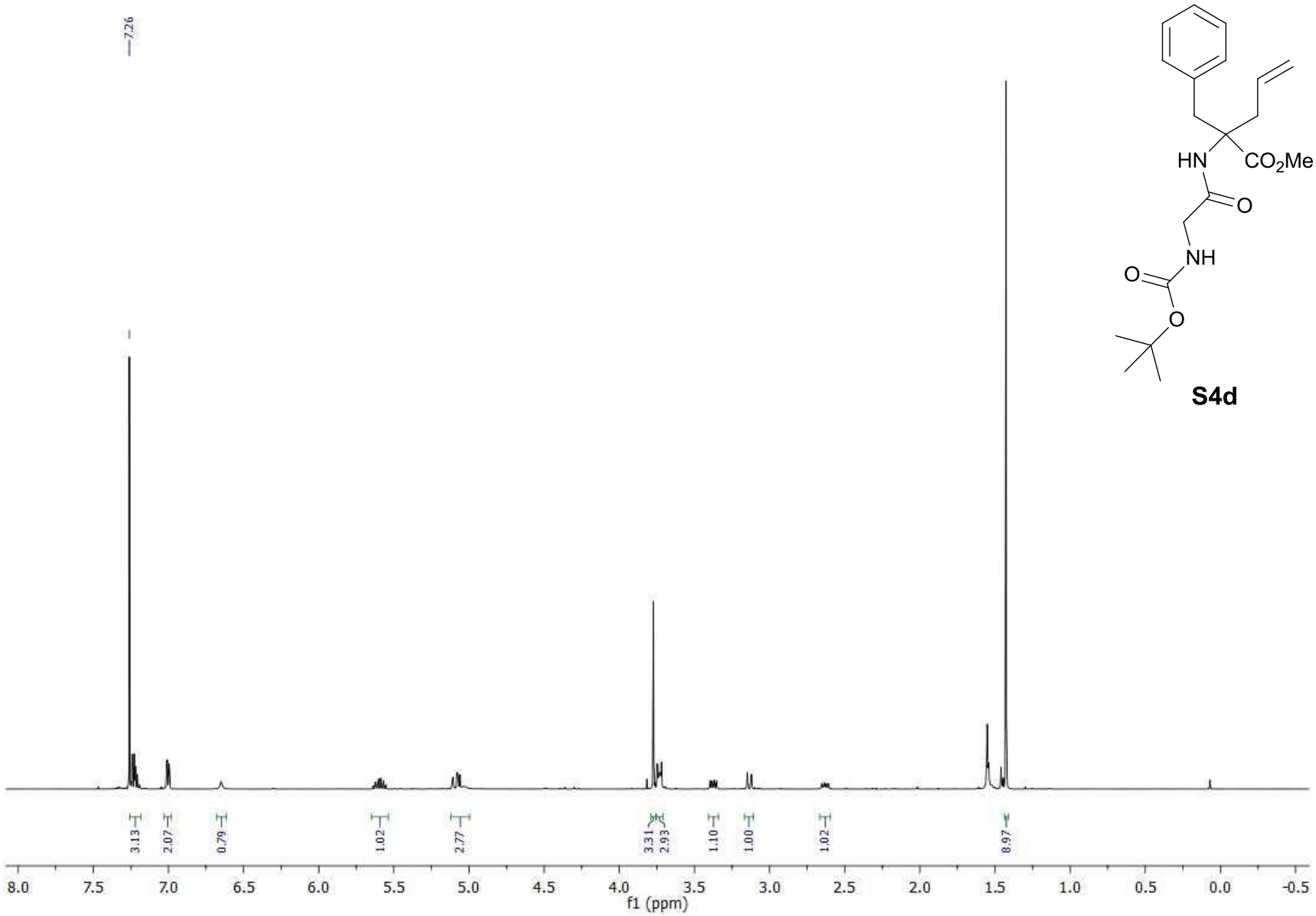

7.26
9.55
3.09
0.54
1.00
0.64
2.02
4.04
1.00
1.00
1.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

HN
CO2Me
O
HN

S3d

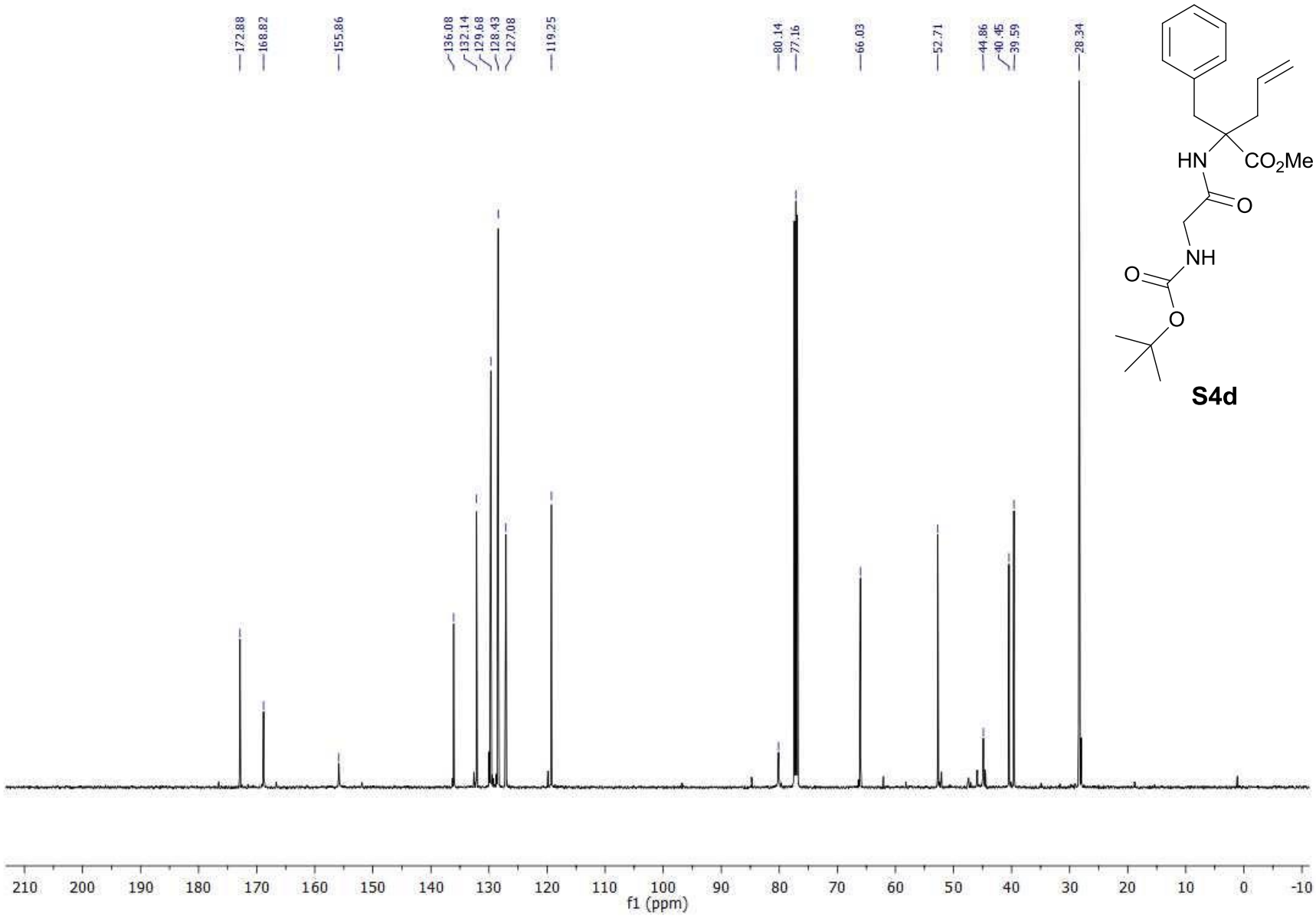

173.82
154.29
138.63
136.61
132.68
129.98
129.35
128.36
126.98
123.95
121.13
119.10
77.16
65.80
52.70
41.07
40.33
HN
CO2Me
O
HN
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

S3d

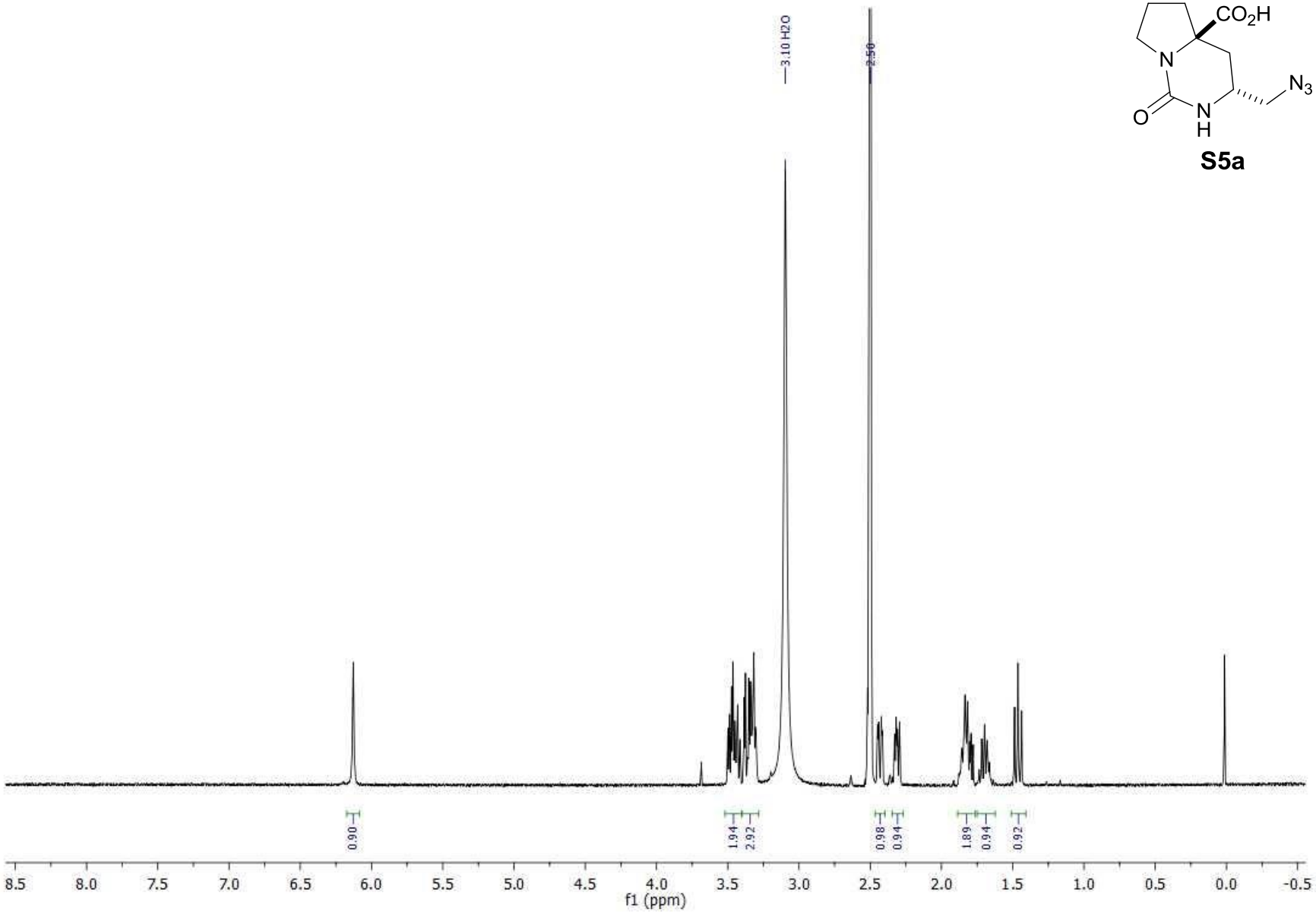

7.26
3.13
2.07
0.79
1.02
2.77
3.31
2.93
1.10
1.00
1.02
8.97
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

HN
CO2Me
O
NH
O
O

S4d

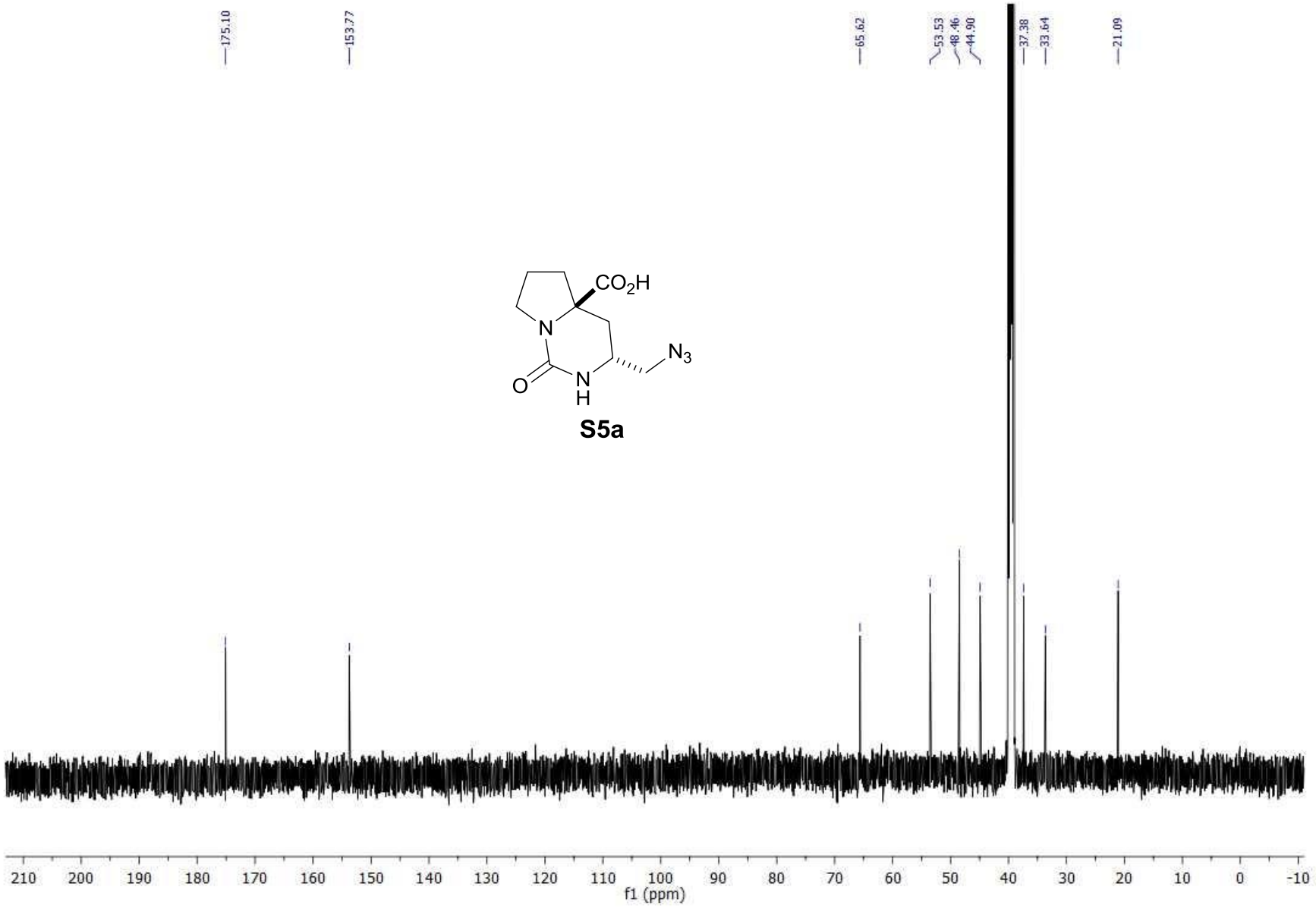

172.88
168.82
155.86
136.08
132.14
129.68
128.43
127.08
119.25
80.14
77.16
66.03
52.71
44.86
40.45
39.59
28.34
HN
CO2Me
O
NH
O
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

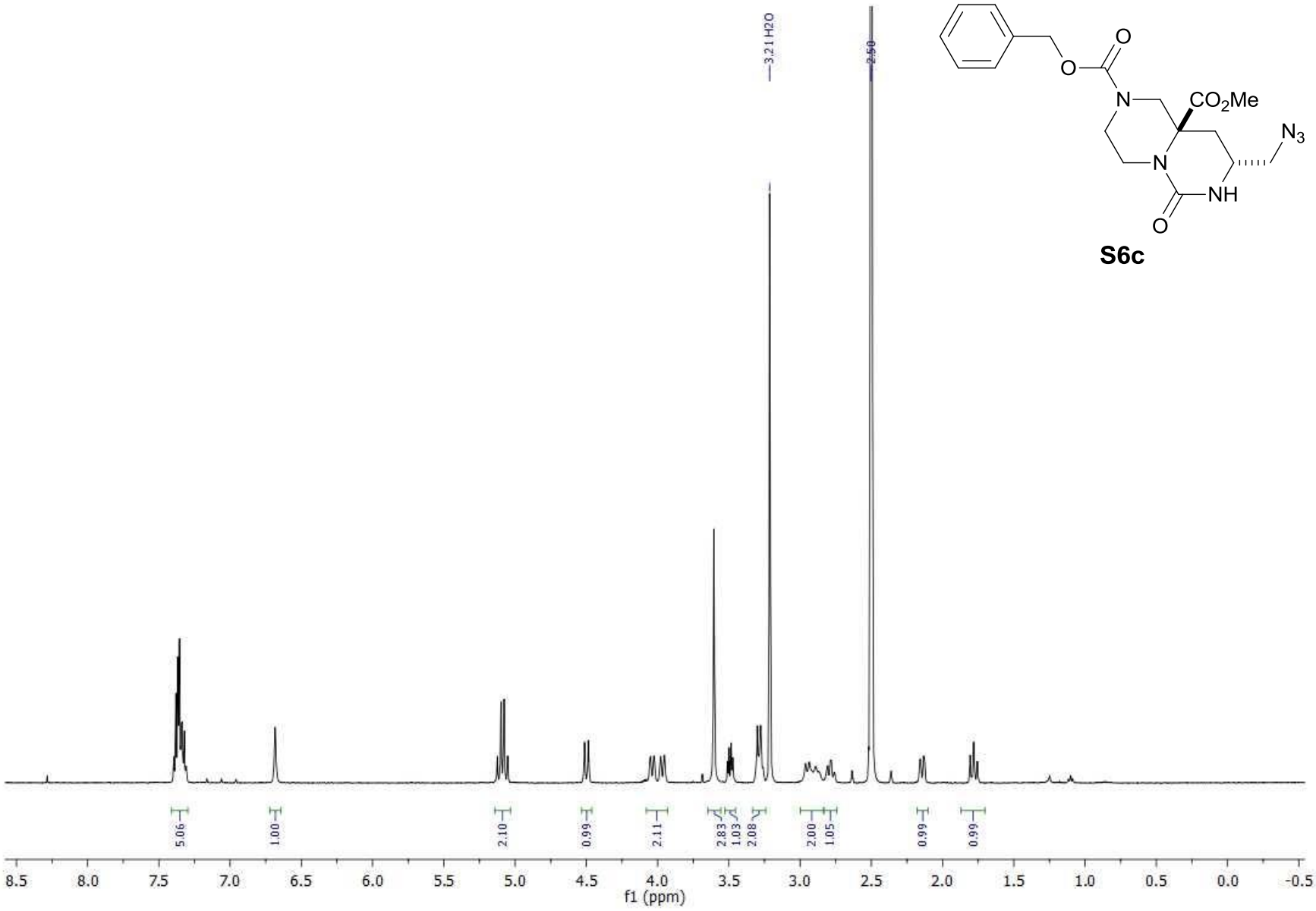
S4d


3.10 H2O
2.50
0.90
1.94
2.92
0.98
0.94
1.89
0.94
0.92
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
-0.5
f1 (ppm)

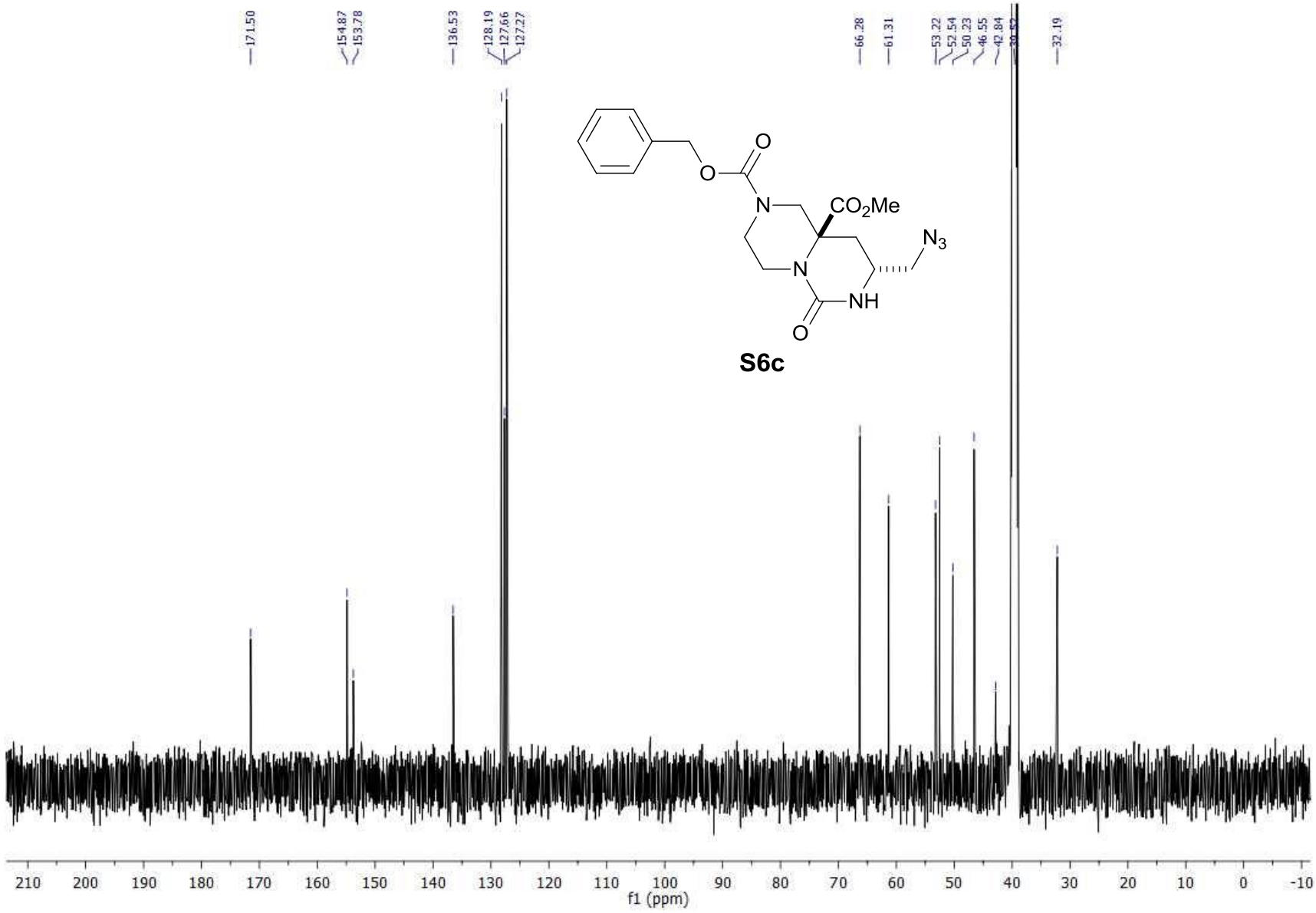
CO2H
N
N3
O
N
H

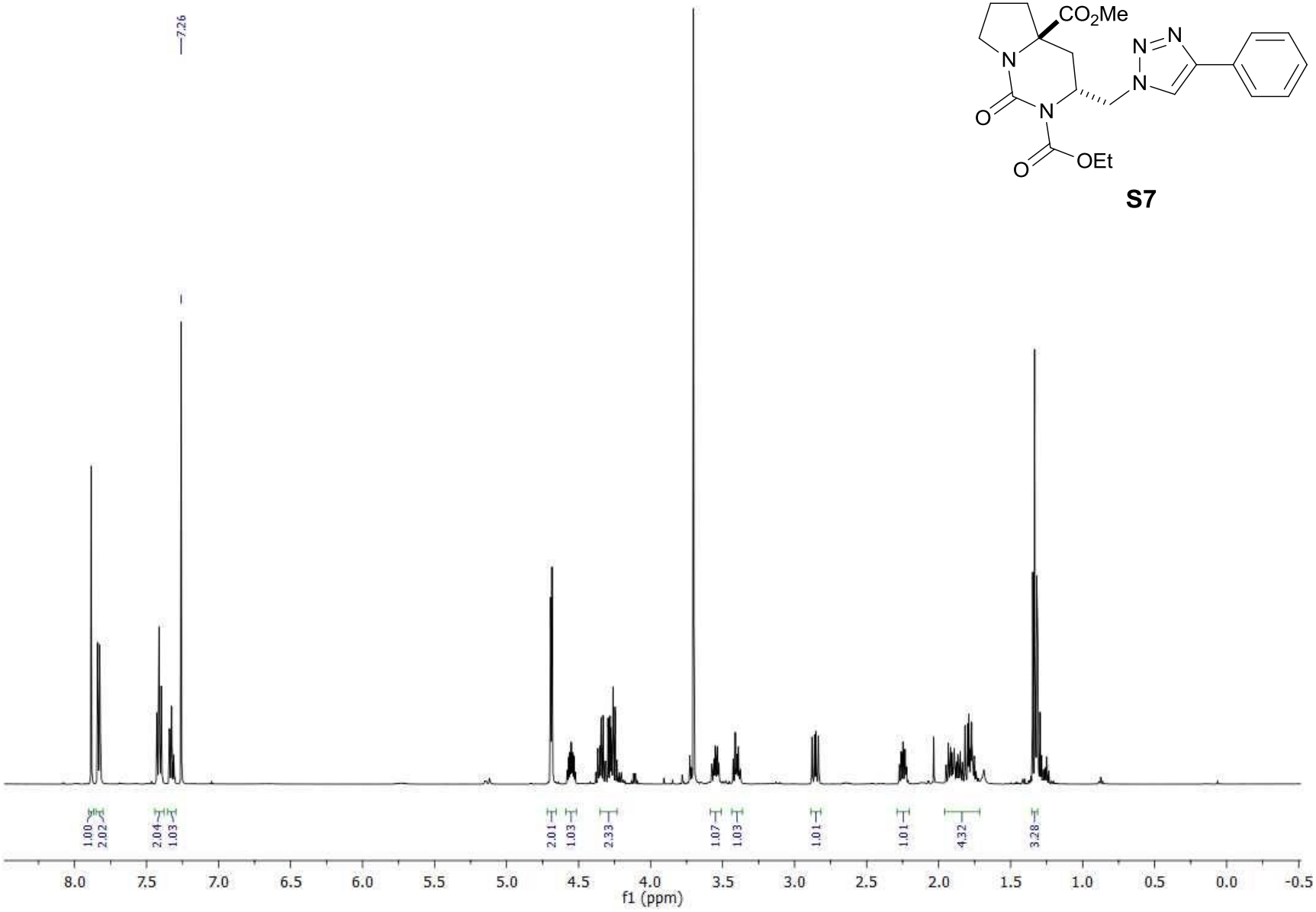
S5a


175.10
153.77
65.62
53.53
48.46
44.90
37.38
33.64
21.09
CO2H
N
N3
O
N
H
S5a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


3.21 H2O
2.50
5.06
1.00
2.10
0.99
2.11
2.83
1.03
2.08
2.00
1.05
0.99
0.99
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
-0.5
f1 (ppm)
O
O
N
CO2Me
N3
N
NH
O

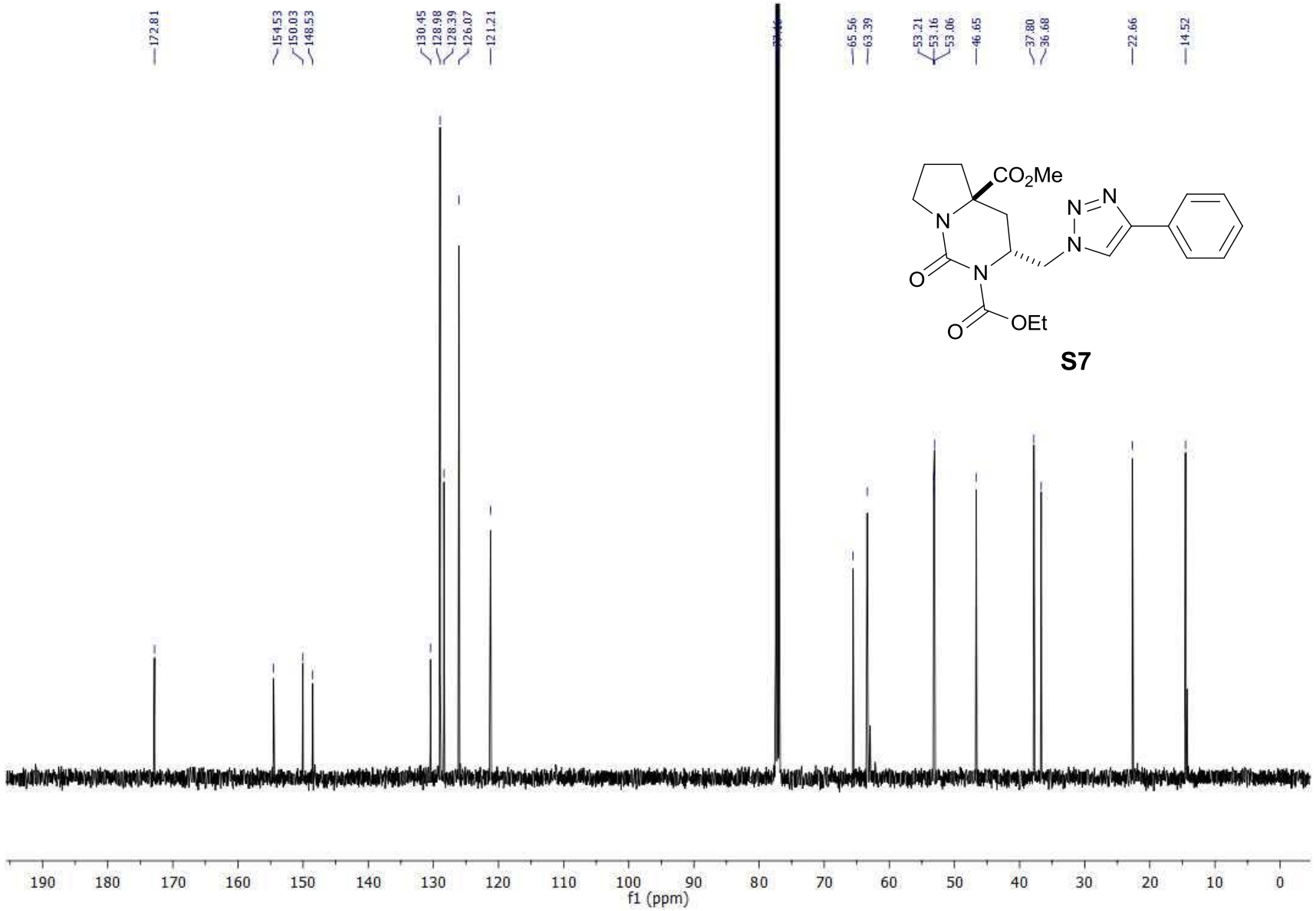
S6c


171.50
154.87
153.78
136.53
128.19
127.66
127.27
66.28
61.31
53.22
52.54
50.23
46.55
42.84
32.19
O
O
N
CO2Me
N3
N
NH
O
S6c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

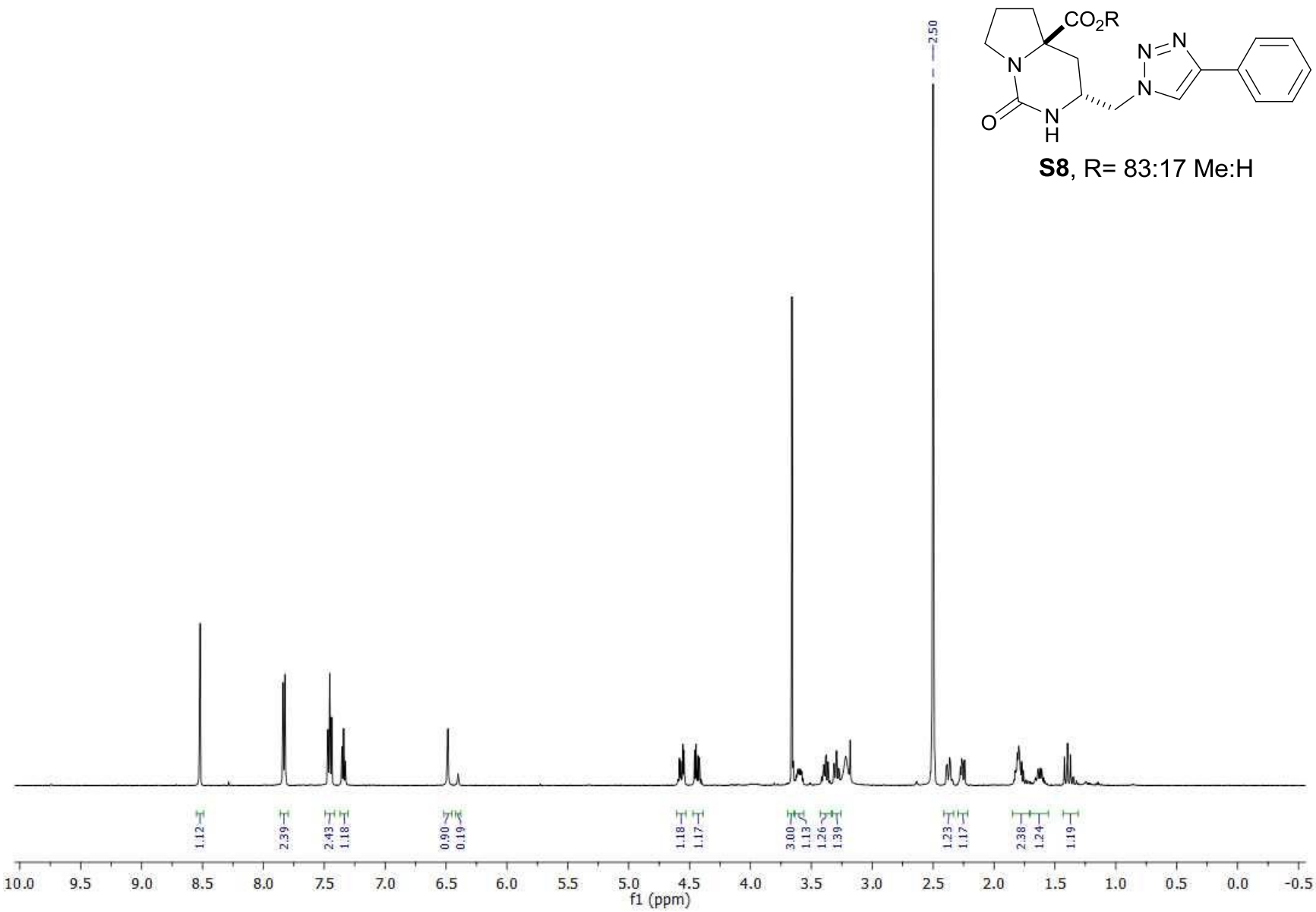

7.26
1.00
2.02
2.04
1.03
2.01
1.03
2.33
1.07
1.03
1.01
1.01
4.32
3.28
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

CO2Me
N
N
N
N
O
N
O
OEt

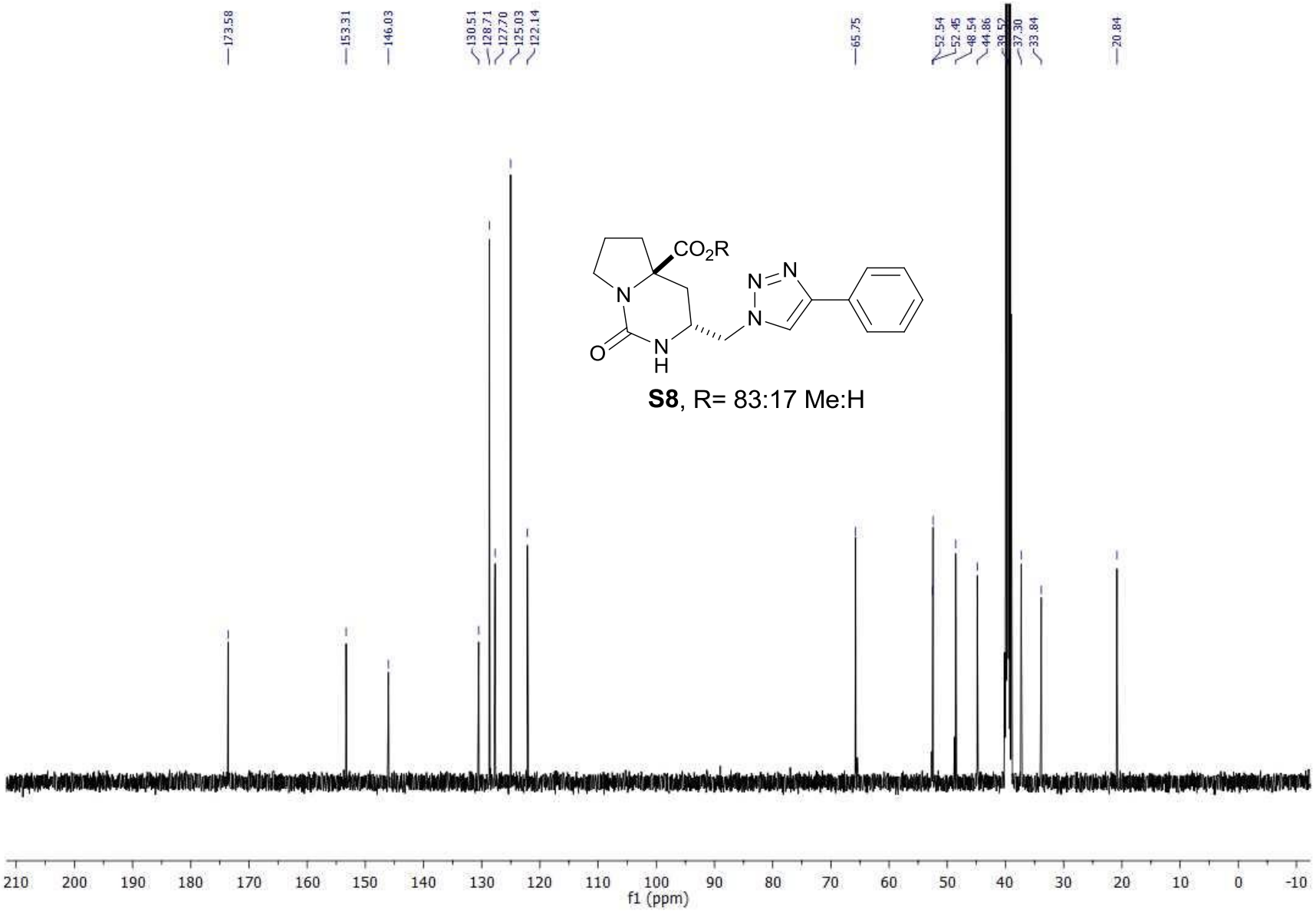
S7


172.81
154.53
150.03
148.53
130.45
128.98
128.39
126.07
121.21
65.56
63.39
53.21
53.16
53.06
46.65
37.80
36.68
22.66
14.52
CO2Me
N
N
N
N
O
N
O
OEt
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

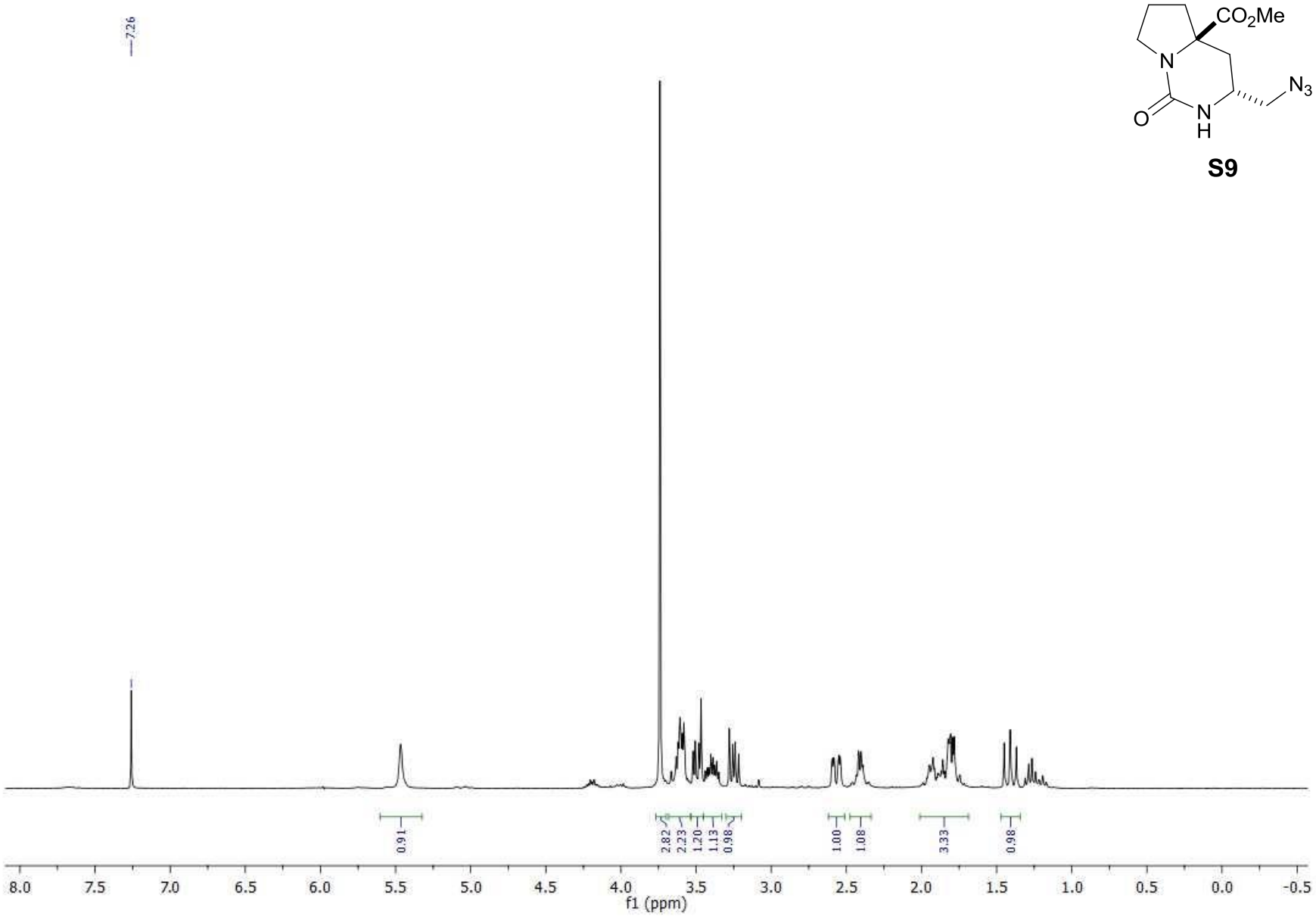
S7


CO2R
N
N
N
N
O
N
H
2.50
1.12
2.39
2.43
1.18
0.90
0.19
1.18
1.17
3.00
1.13
1.26
1.39
1.23
1.17
2.38
1.24
1.19
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
-0.5
f1 (ppm)

S8, R= 83:17 Me:H

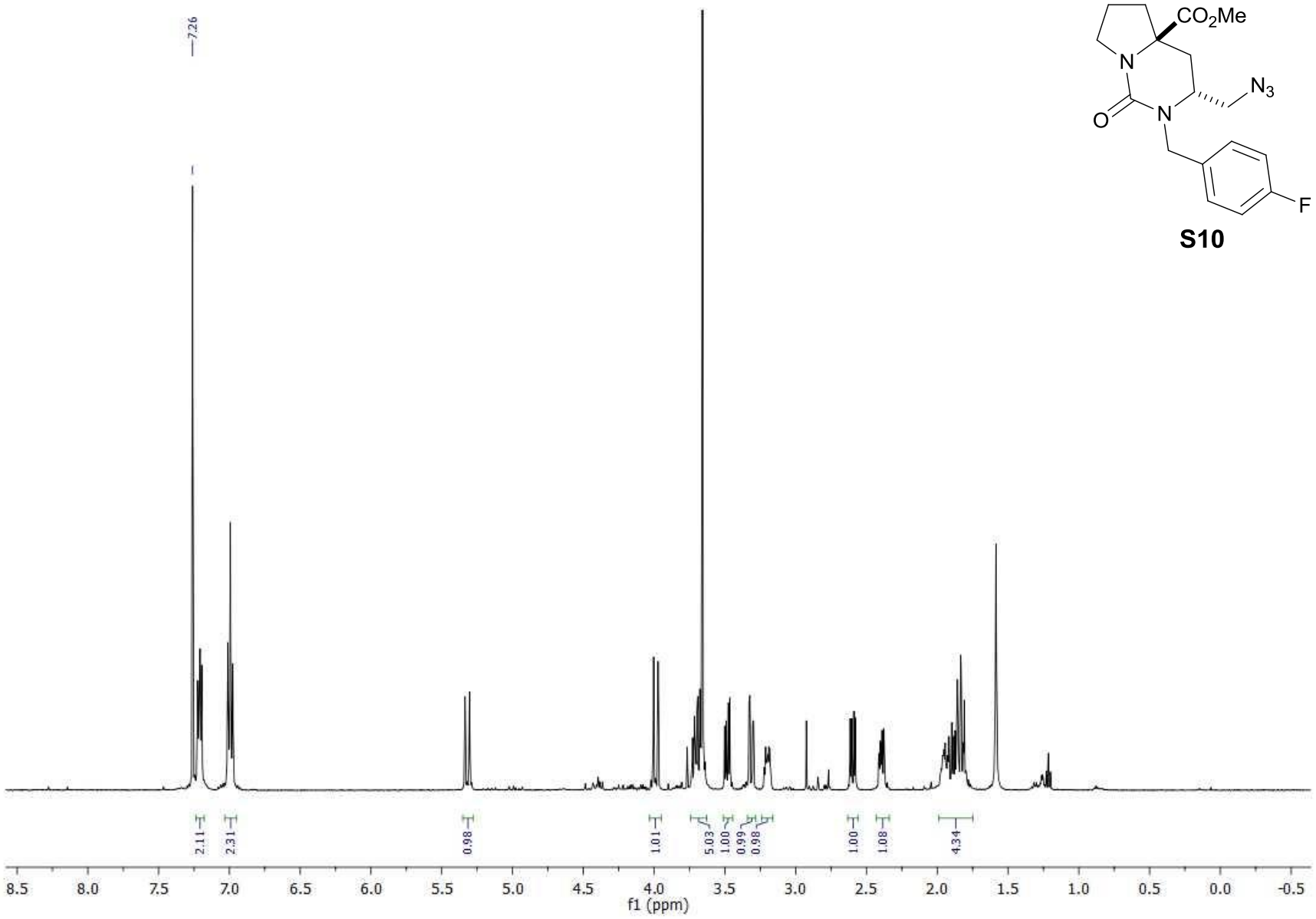

173.58
153.31
146.03
130.51
128.71
127.70
125.03
122.14
65.75
52.54
52.45
48.54
44.86
39.52
37.30
33.84
20.84
CO2R
N
N
N
N
O
H
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

S8, R= 83:17 Me:H


7.26
0.91
2.82
2.23
1.20
1.13
0.98
1.00
1.08
3.33
0.98
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
-0.5
f1 (ppm)

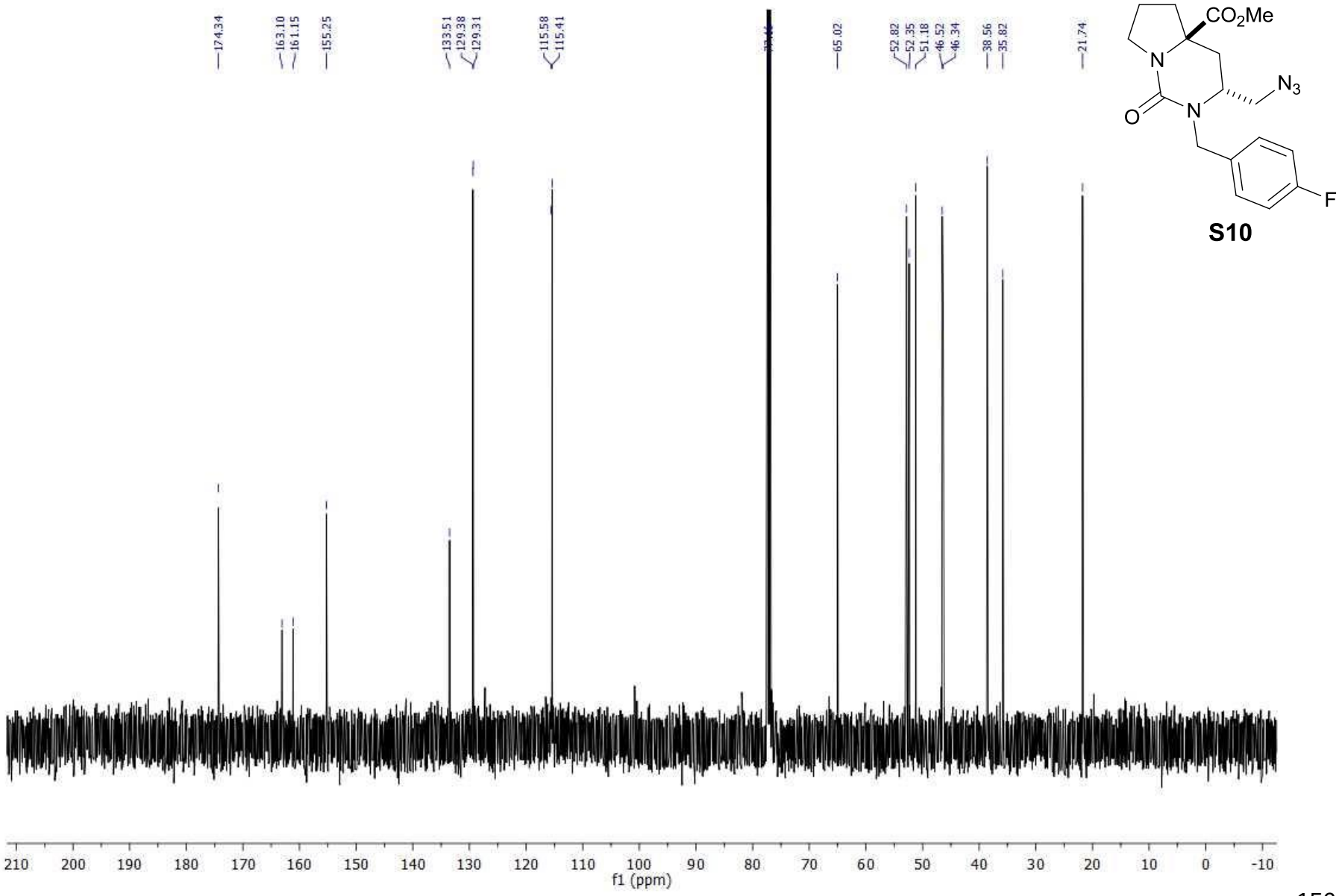
CO2Me
N
N3
O
N
H

S9


7.26
2.11
2.31
0.98
1.01
5.03
1.00
0.99
0.98
1.00
1.08
4.34
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
-0.5
f1 (ppm)

CO2Me
N
N3
O
N
F

S10


174.34
163.10
161.15
155.25
133.51
129.38
129.31
115.58
115.41
65.02
52.82
52.35
51.18
46.52
46.34
38.56
35.82
21.74
CO2Me
N
N3
O
N
F
S10
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)