

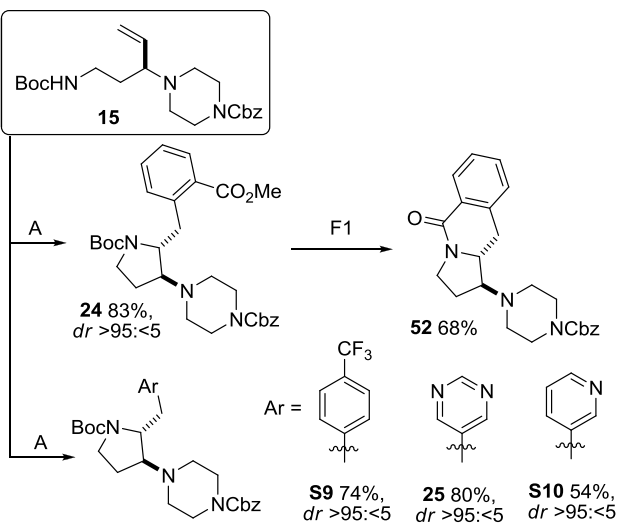
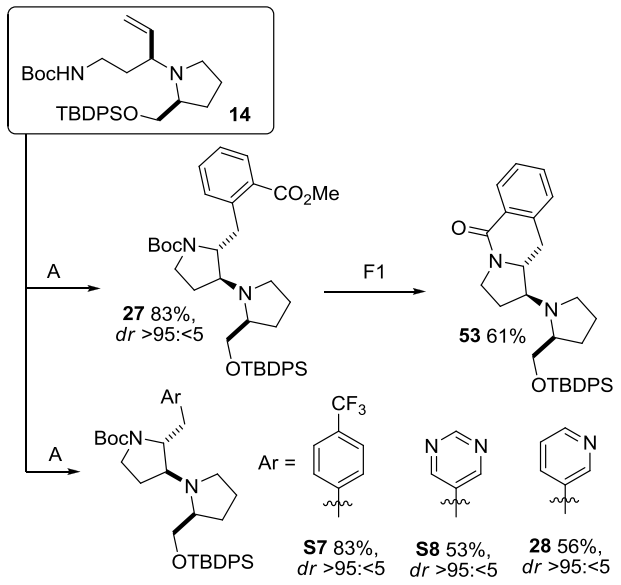
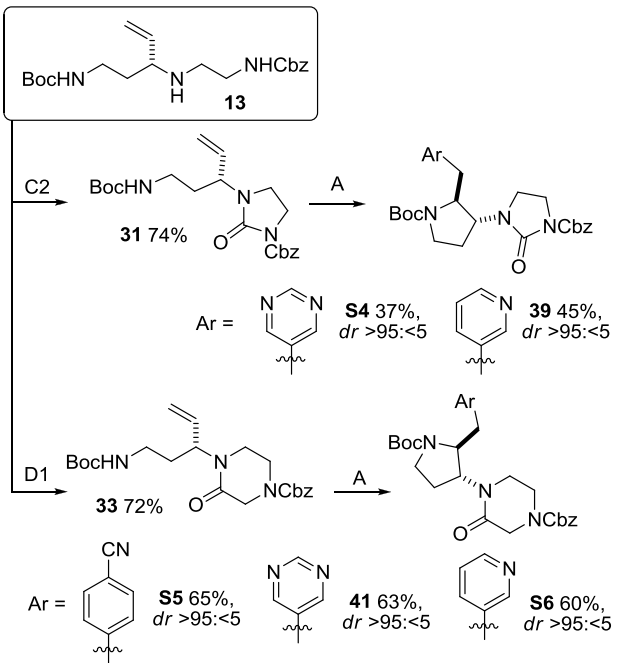
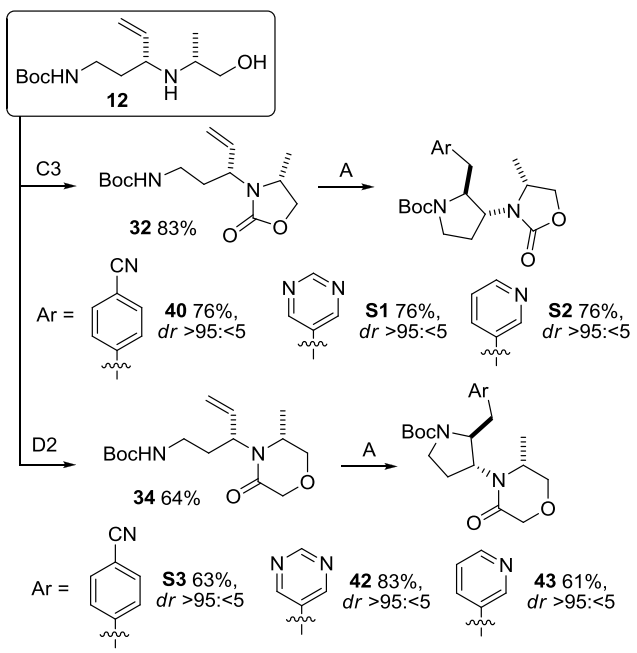
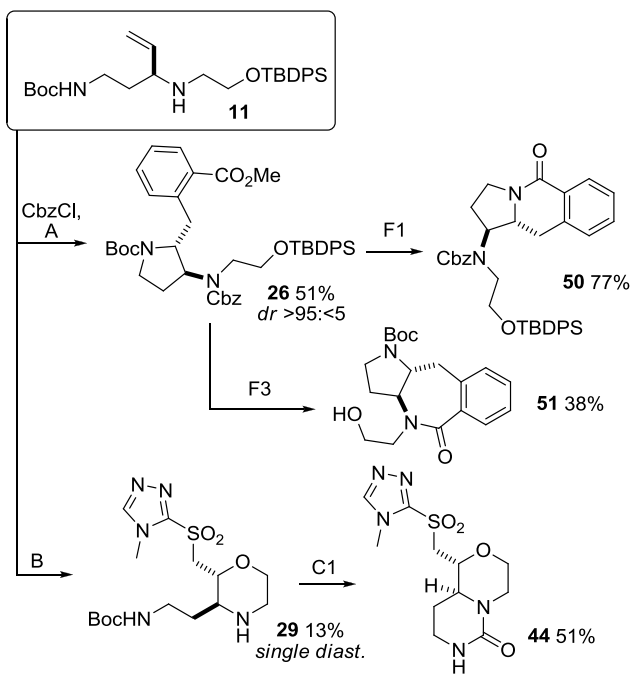
A Unified Lead-Oriented Synthesis of Over Fifty Molecular Scaffolds

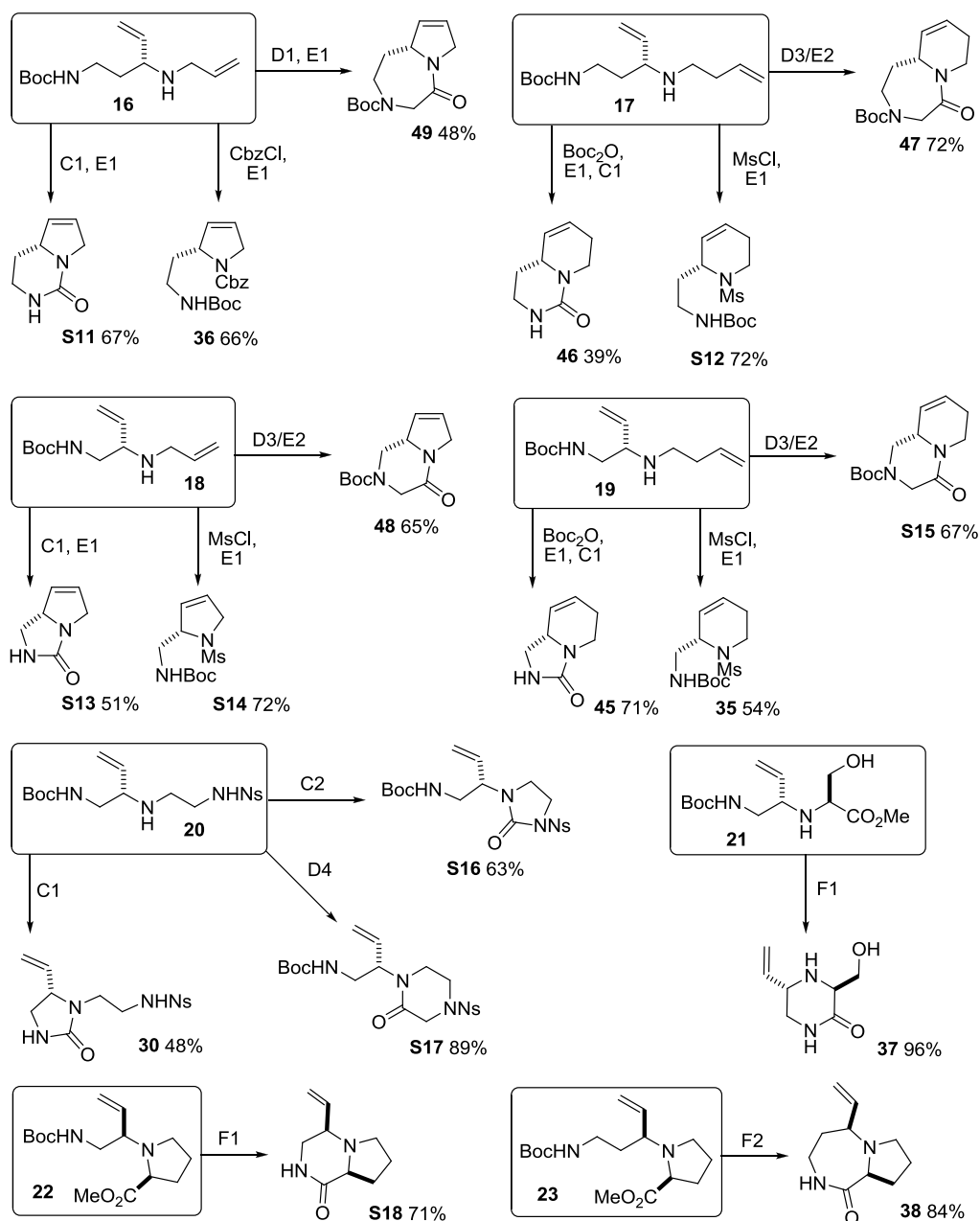
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Supporting Information

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Scheme S1. Synthesis of the 52 scaffolds arranged by cyclisation precursor. Cyclic cyclisation precursors are also considered to be distinct scaffolds (**14**, **15**, **22**, **23**).

Typical methods (see Experimental Section for full details including any deviation from typical methods):

A: Aryl bromide (1.2 eq.), 5 mol% Pd(OAc)₂, 10 mol% DPE-Phos, Cs₂CO₃ (2.5 eq.), 1,4-dioxane, 105 °C;

B: i) NsCl (1.2 eq.), NEt₃ (2.0 eq.), DMAP (0.1 eq.), rt, then TBAF (1.2 eq.), AcOH (1.2 eq.), THF, rt; ii) NIS (1.5 eq.), MeCN, 65 °C; iii) ArSH (1.5 eq.), DBU (2.5 eq.), MeCN, rt; iv) *m*CPBA (4.0 eq.), CH₂Cl₂, rt; v) PhSH (1.2 eq.), DBU (1.5 eq.), MeCN, rt;

C1: CH₂Cl₂/TFA, 0 °C → rt, 3 h then CDI (1.5 eq.), DBU (4.0 eq.), THF, 50 °C;

C2: CDI (4.5 eq.), DMF, 110 °C;

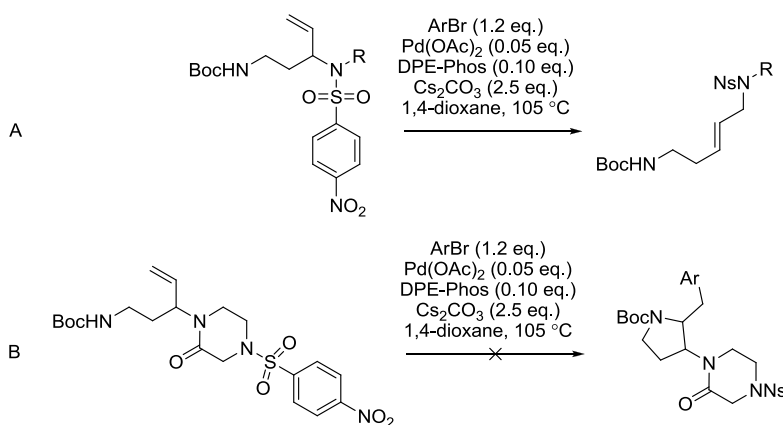
C3: CDI (1.5 eq.), DBU (2.5 eq.), THF, 50 °C;

D1: Chloroacetyl chloride (1.5 eq.), NEt₃ (5.0 eq.), CH₂Cl₂, 0 °C → rt, 6 h then NaH (2.0 eq.), NaI (1.0 eq.), THF, rt;
D2: i) TMSCl (1.1 eq.), NEt₃ (3.0 eq.), CH₂Cl₂, 0 °C → rt, 2 h then bromoacetyl bromide (1.5 eq.), 2 h then 20% AcOH (aq), rt;
 ii) 35% NaOH (aq) (5.0 eq.), Bu₄NSO₄ (0.5 eq.), CH₂Cl₂, 0 °C → rt;
D3/E2: i) Bromoacetyl bromide (1.1 eq.), DIPEA (1.2 eq.), CH₂Cl₂, 0 °C → rt; ii) 5 mol% Grubbs II, CH₂Cl₂, 45 °C; iii) NaH (2.0 eq.), THF, rt;
D4: Bromoacetyl bromide (1.0 eq.), NEt₃ (1.1 eq.), CHCl₃, -45 °C → rt, 1 h then NEt₃ (72.0 eq.), rt, 16 h.
E1: 5 mol% Grubbs II, CH₂Cl₂, 45 °C;
F1: CH₂Cl₂/TFA, 0 °C → rt, then K₂CO₃ (6.0 equiv), CH₂Cl₂, H₂O, rt;
F2: CH₂Cl₂/TFA, 0 °C → rt, then NaOtBu (1.0 eq.), THF, reflux;
F3: H₂, 10% Pd/C (0.1 eq.), ethylenediamine (1.0 eq.), MeOH, rt, then Cs₂CO₃ (10.0 eq.), DMF, 110 °C;

TBDPS = *tert*-butyldiphenylsilyl; Ns = 2- or 4-nitrobenzenesulfonyl (see Experimental Section for details); DMAP = 4-dimethylaminopyridine; TBAF = tetra-*n*-butylammonium fluoride; DBU = 1,8-diazabicycloundec-7-ene; *m*CPBA = *m*-chloroperoxybenzoic acid; DPE-Phos = bis-[2-(diphenylphosphino)phenyl]ether; TFA = trifluoroacetic acid; CDI = carbonyl diimidazole.

S2. Scope and Limitations

Method A: In other studies, we found that substrates bearing a remote *o*-nitrobenzenesulfonyl (Ns) protecting group did not undergo aminoarylation as expected. For example, an allylic *o*-nitrobenzenesulfonamide underwent rearrangement to the linear alkene (Scheme S2, example A). In other cases where the group was more remote, no reaction was observed (for example, see Scheme S2, example B). The carboxybenzyl (Cbz) protecting group was widely tolerated for this transformation, although lower yields were observed in the case of Cbz-protected ureas owing to instability under the reaction conditions.



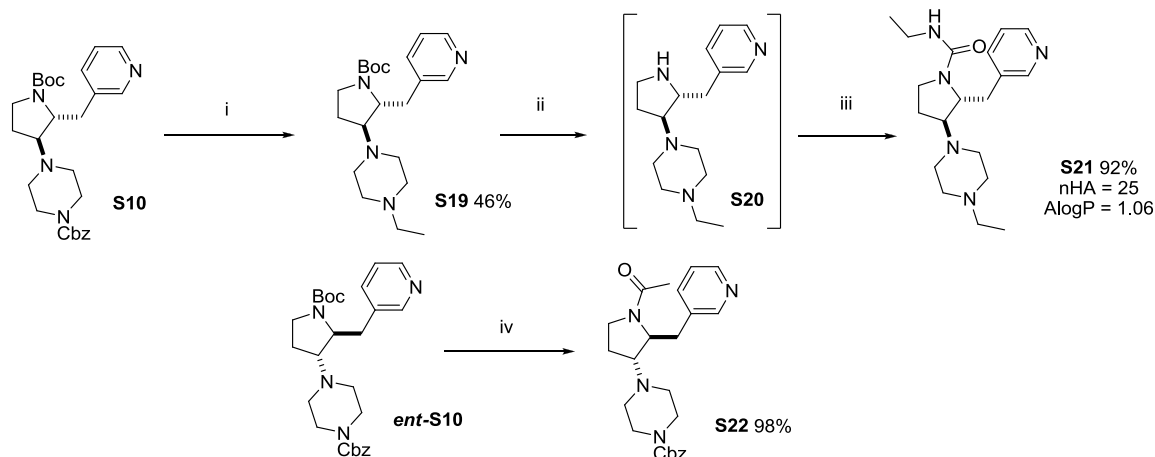
Scheme S2. Limitations of aminoarylation, Method A.

S3. Exemplar Scaffold Decoration

To confirm the validity of the library analysis, we demonstrated experimentally that *N*-deprotection and decoration reactions were viable. Furthermore we showed that scaffold decoration was possible to:

1. Prepare exemplar compounds from the virtual library with and without protecting groups in place (Scheme S3, **S23**, **S24** and **S26**).

2. Prepare lead-like compounds following two decorations where scaffold synthesis involved a reaction (aminoarylation) with a potentially variable reactant (Scheme S3, **S21**). Such scaffolds were actually only decorated once in the enumeration of the virtual library.



Scheme S3. Exemplar scaffold diversifications. Reagents and conditions - **i:** a) H_2 , ethylene diamine (1.0 eq), 10% Pd/C (20 mol%), MeOH, rt, 18 h; b) MeCHO (3.0 eq), AcOH (1.0 eq), $NaBH(OAc)_3$ (3.0 eq), MeOH/THF, rt, 3 h; **ii:** 1:3 TFA/ CH_2Cl_2 , rt, 18 h; **iii:** EtNCO (1.2 eq), NEt_3 (5.0 eq), CH_2Cl_2 , 0 °C → rt, 18 h; **iv:** a) 1:3 TFA/ CH_2Cl_2 , rt, 18 h; b) AcCl (1.5 eq), DIPEA (5.0 eq), CH_2Cl_2 , 0 °C → rt, 18 h.

S4. 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 52 scaffolds in Scheme S1, removal of protecting groups, the manipulations shown in Scheme S4, the decorating reactions shown in Scheme S5 and the 59 capping groups shown in Figure S2. Underivatized and mono-derivatized scaffolds were retained in the final virtual library. For scaffolds whose synthesis involved a variable reactant (e.g. aminoarylation) only a single decoration was performed.

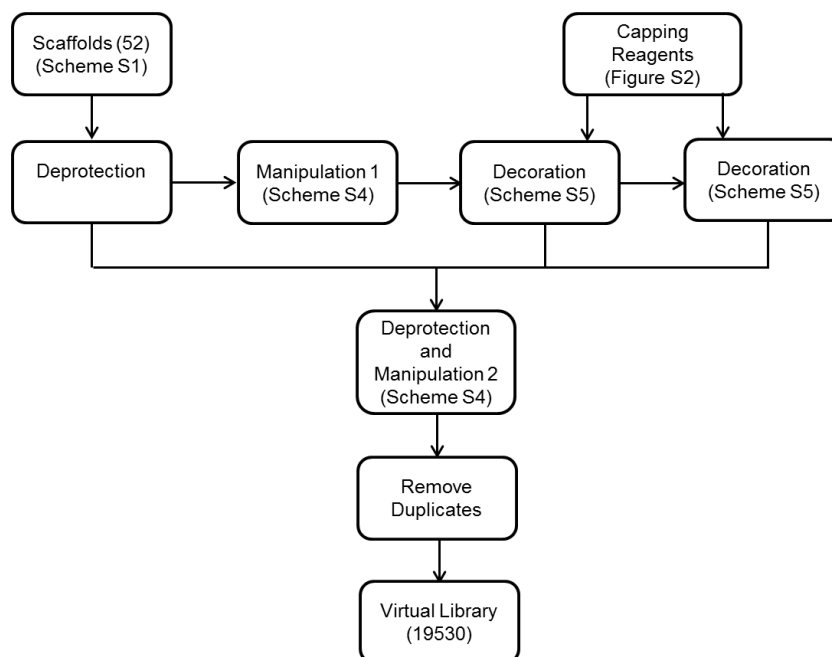
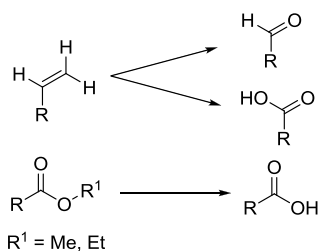
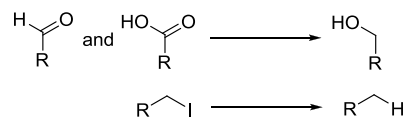
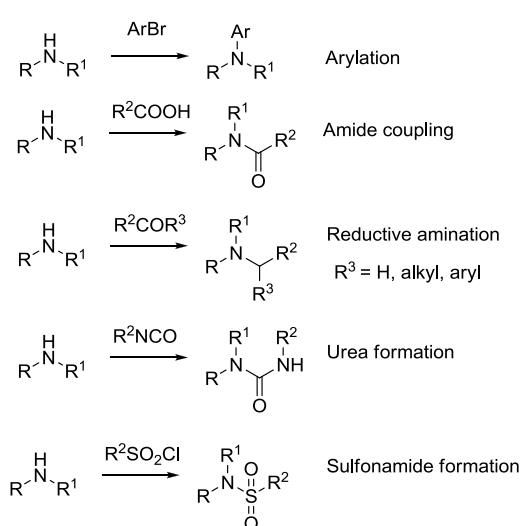
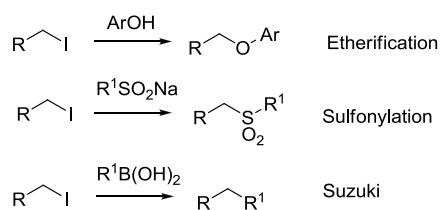
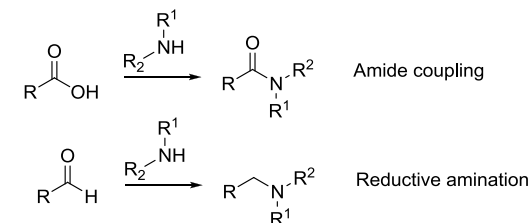
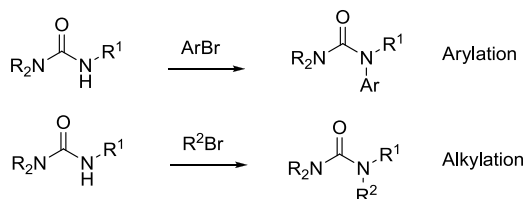
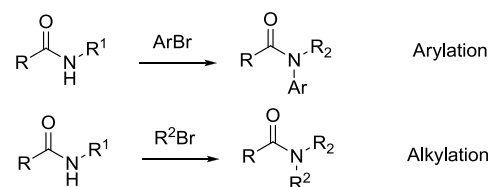
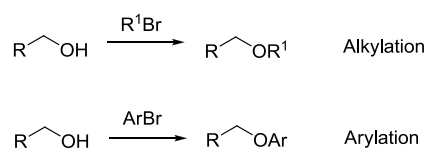


Figure S1. Overview of the process for the enumeration of the virtual library.

Manipulation 1**Manipulation 2****Scheme S4.** Functional group manipulations of scaffolds (Manipulation 1) and final compounds (Manipulation 2).**Amine Decoration ($R^1 = \text{H, alkyl}$)****Iodide Decoration****Acid/aldehyde Decoration ($R^1 = \text{H, alkyl, aryl}$)****Urea Decoration****Amide Decoration****Alcohol Decoration****Scheme S5.** Decoration reactions exploited in the enumeration of the virtual library.

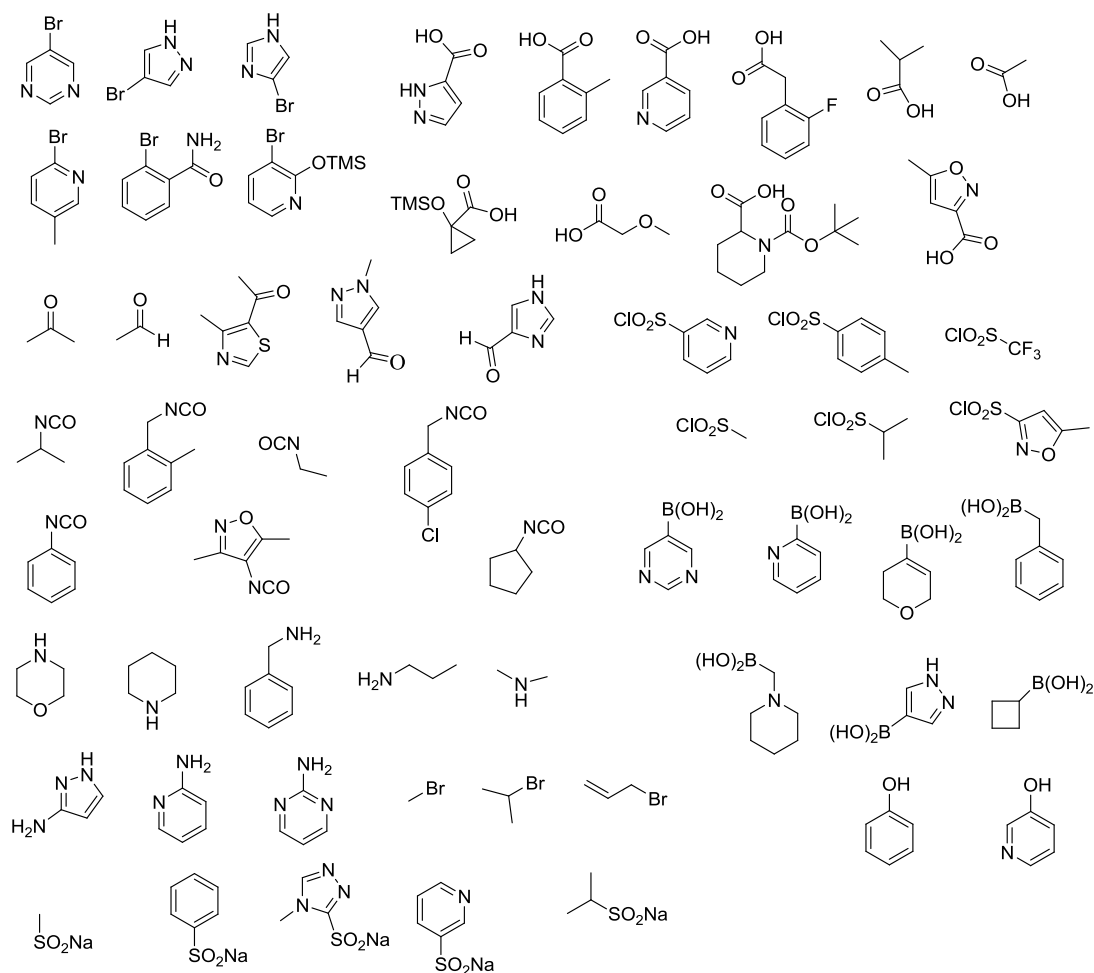


Figure S2. Capping reagents exploited in the enumeration of the virtual library.

S5. 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 (F_{sp^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 S1) as compiled by Shoichet, Simeonev *et al.* and used at the NIH Chemical Genomics Centre.^[1] The second set contained 36 definitions (Table S2) 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 that comprised the filters for undesirable functionality outlined in Table S3.

Data from our lead-likeness assessment of both the ZINC database of compounds ‘available now’^[3] and our virtual library (as summarised in Figure 1, main text) are provided in Tables S4, S5 and S6. The distribution of the molecular properties of the virtual library based upon each scaffold is shown in Figure S3.

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]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
4_pyridone_3_5_EWG	[#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
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]1[#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]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]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)]~[O,S,N]~[\$(C(=O)),\$(S(=O)=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]))][#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]))][#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]=[*]
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(-c1cccc1)-c2cccc2
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,\$]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_warhead	[C,c]~[#5]
branched_polycyclic_aromatic	a1(a2aa(a3aaaaa3)aa(a4aaaaa4)a2)aaaaa1
carbazine	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][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][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][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][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][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][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][O,S,#7;R1;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18]
cyanamide	N[CH2]C#N
cyanidin	[OH]c1ccc([OH])cc2=[O+]C=C([OH])Cc21c3cc([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)))]
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_warhead	NC(C[S;D1])C([N;H1])([O;D1])=O
epoxide_aziridine_thioepoxide	[CH2]1[O,S,N]C1
flavonoid	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(D)D),\$(C(F)Cl),\$(C(F)Br),\$(C(F)I),\$(C(Cl)Br),\$(C(Br)D)=[\$(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_warhead	C([N;H1])([O;D1])=O

phosphite	[c,C]-[P;v3]
phosphonate_esters	COP(=O)(=O)[C,c]
phosphonium	[#15;+~!O]
phosphoramidate	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]: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]: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]~[#6]~[#6]~[#6]~[#6]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;!\$(#6)(-[N,O,S])]#61(=[O,N,S])
rhodanine	C(=C)ISC(=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]
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_warhead	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]O)1a([\$(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]O)1a([\$(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]O)1a([\$(S(=O)(=O)),F,\$(C(F)(F)(F)),\$(C#N),\$(N(=O)(=O)),\$([N+](=O)[O-

	<chem>],\$(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)</chem>
trisub_bis_act_olefin	<chem>[[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)))</chem>
unacceptable_atoms1	<chem>[!#6;!#7;!#8;!#16;!#1;!#3;!#9;!#11;!#12;!#15;!#17;!#19;!#20;!#30;!#35]</chem>
unacceptable_atoms2	<chem>[!#6;!#7;!#8;!#16;!#1;!#3;!#9;!#11;!#12;!#15;!#17;!#19;!#20;!#30;!#35;!#53]</chem>
vinyl_carbonyl_EWG	<chem>[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)))</chem>
vinyl_sulfone	<chem>O=S([#6]=[#6])([#6]=[#6])=O</chem>
vinylloxazole	<chem>[N,C]=CC1=COC=N1</chem>
2,3,4-trihydroxyphenyl	<chem>c([OH])c([OH])c([OH])</chem>

Table S1. Undesirable functionality SMARTS definitions utilised by the NIH.^[1]

Filter	SMARTS
thiocarbonyl	<chem>[c,C]=[S;X1]</chem>
termalkyne	<chem>[CH]#C</chem>
quinonepara	<chem>O=[#6]1[#6]-[#6][#6](=O)[#6]-[#6]1</chem>
nonpeptidic_macrocycle	<chem>[!R0;r3;r4;!5;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))]</chem>
nitrogen_oxygen_bond	<chem>*-[n,N]-[O;H0;R0]</chem>
methyl_ester_x2	<chem>[\$([CH3]OC=O)].[\$([CH3]OC=O)]</chem>
imide	<chem>O=C([#6])NC(=O)[#6]</chem>
exocyclic_double_bond_toC	<chem>[R;!#7;!#8;!#16;!#6X3][R]=!@C</chem>
ethyl_ester_x2	<chem>[\$([CH2](OC=O)[CH3])[CH3].[\$([CH2](OC=O)[CH3])[CH3]</chem>
ester_deep_in_mol	<chem>*[#6]C(=O)[O;R0][#6;\$(*OC=O)*,\$(*OC=O)(**)]</chem>
enoether	<chem>C=!@C[OD2]</chem>
conjugated_C=C	<chem>C=[C;R0][C;R0]=C</chem>
benzyl_ester	<chem>[\$([CH2](OC=O)c1[cH][cH][cH][cH]1)]c1[cH][cH][cH][cH][cH]1</chem>
aromatic_tricyclic1	<chem>c1ccc3c(c1)[C;!\$(C=O)]c2ccccc23</chem>
allyl_ester	<chem>[\$([CH2](OC=O)[CH]=[CH2])][CH]=[CH2]</chem>
alkylNandNonC	<chem>N[CX4]!@N</chem>
alkCl	<chem>[C][C]!\$(Cl)(Cl)(Cl)</chem>
alkBr	<chem>CBr</chem>
acyclic_sulphur_michael_acceptor	<chem>[C]!\$(Nv3X3)=!@[C]!\$(Nv3X3)[S]!\$(Nv3X3)=O</chem>
acyclic_imine	<chem>[C]!\$(=N)[N,n]=!@[Nv3]!\$(O)</chem>
acyclic_hydrazine	<chem>[Nv3X3]!\$(C=O)NC=O]-!@[Nv3X3]!\$(C=O)NC=O]</chem>
acetyl_x2	<chem>[CH3]C(=O)O.[CH3]C(=O)O</chem>
acetal	<chem>[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]</chem>
OCO_protecting_group	<chem>[O;R0][C;X4][O;R0]</chem>
N-SO_group	<chem>N[S;!\$(S(=O)(=O))]=O</chem>
C=N=O_gp	<chem>C=N=O</chem>
C(=O)CC(=O)_gp	<chem>[c,C]C(=O)[C!H0!R]C(=O)[C,c]</chem>
4_fused_ring_sys	<chem>[R2][R3][R2][R2][R2]</chem>
C#C	<chem>C#C.C#C</chem>
C#C-c_gp	<chem>c#C[C!H1]</chem>
3_mem_ring_with_het	<chem>[S,O,N;r3]</chem>
acylcarbamate	<chem>O=[S,C]NC(=O)O</chem>
anyNO	<chem>[Nv3,n]=O</chem>
phenol_x2	<chem>[OH][c;\$c1ccccc1],[OH][c;\$c1ccccc1]</chem>
formamide	<chem>[#7;!\$(N[OH])][CH1]=O</chem>
benzyl_halide	<chem>[CX4](a)[F,Cl,Br,I;!\$(FC(F)F)]</chem>

Table S2. 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

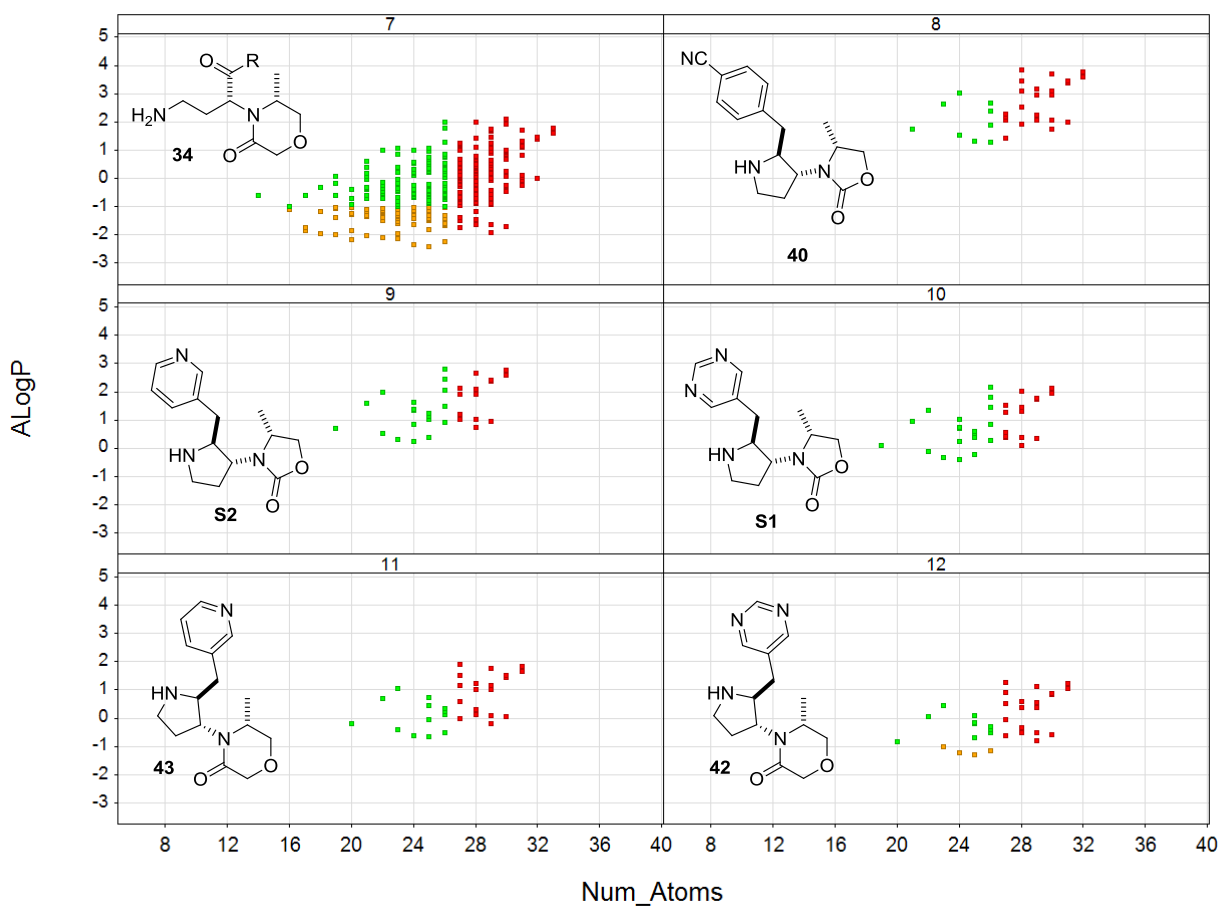
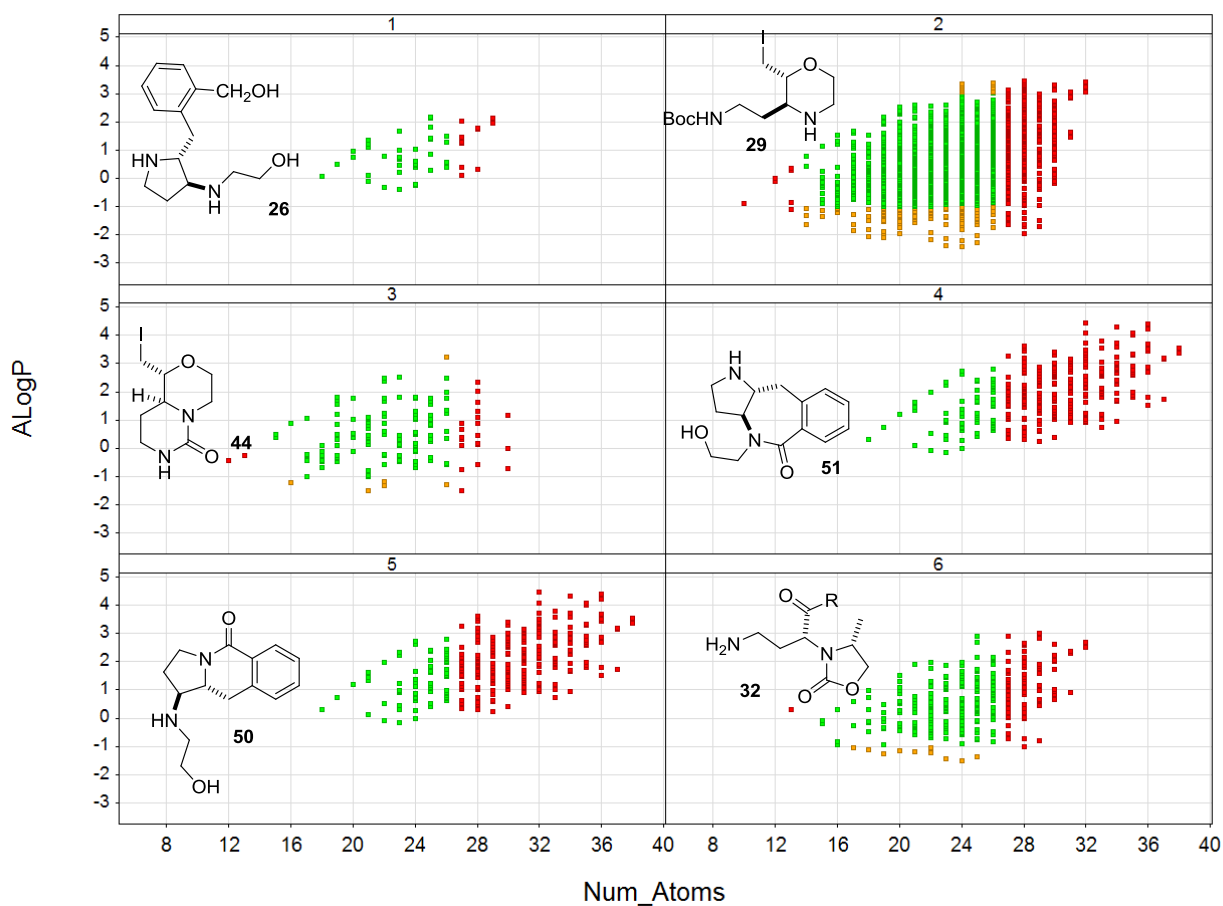
Table S3. Undesirable functionality filters used in the 'HTS Filter' embedded in Pipeline Pilot.

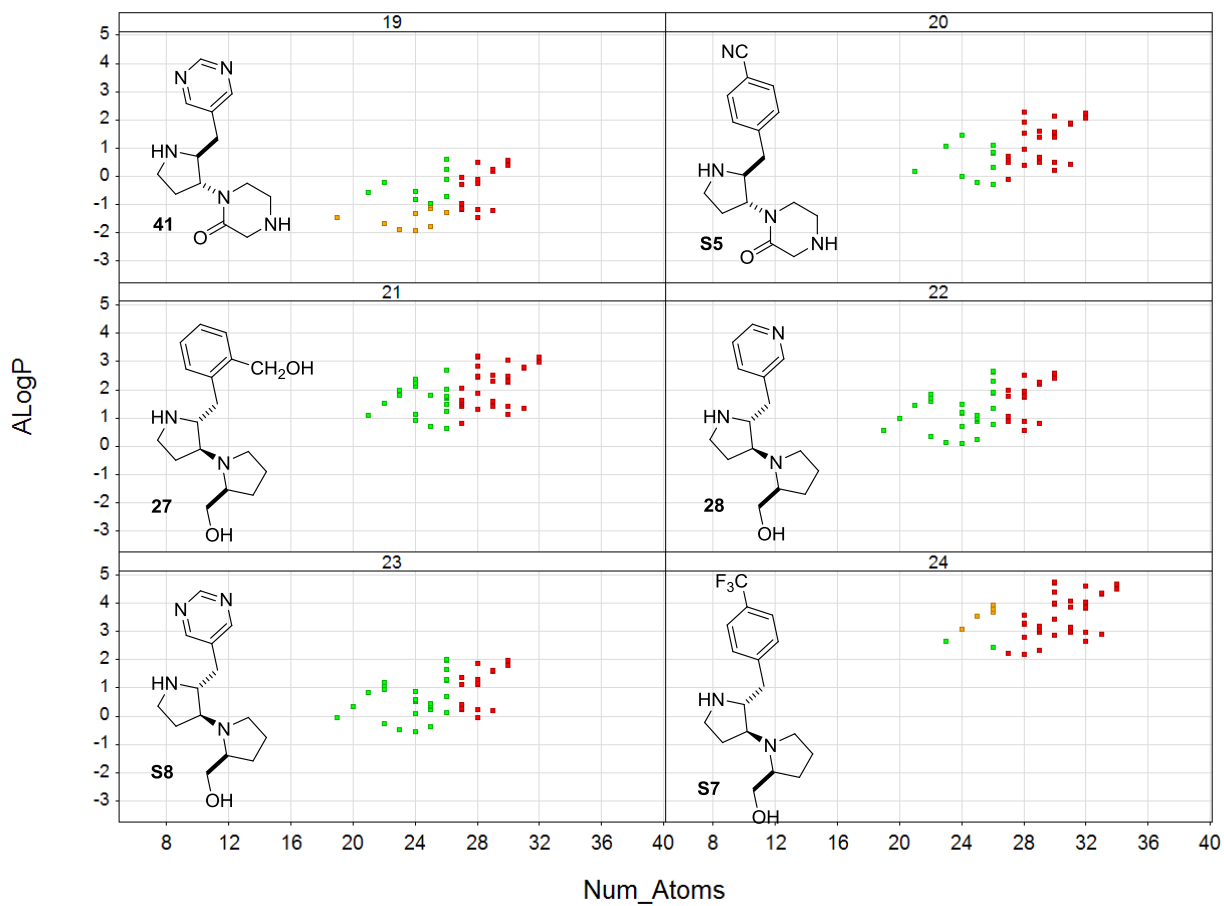
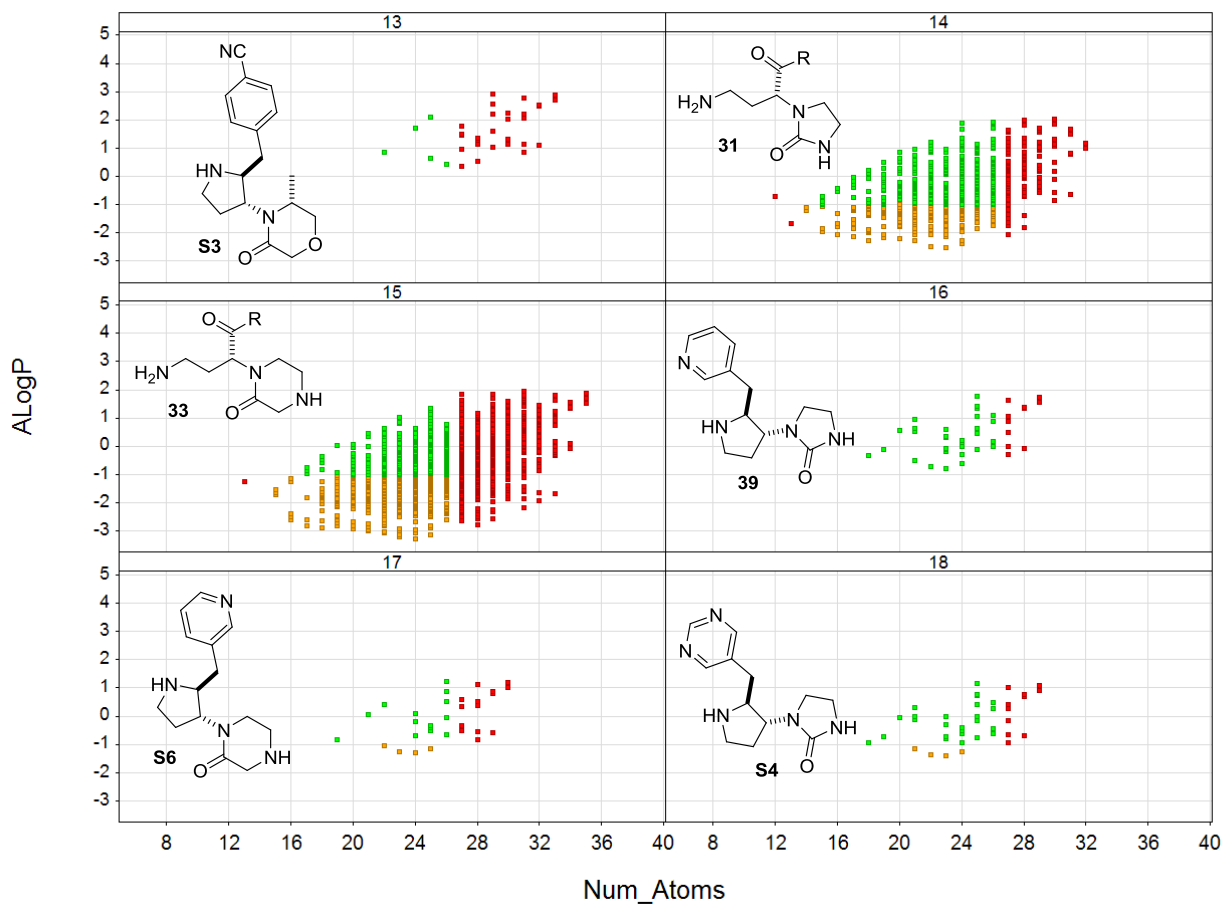
Filter	ZINC Database (9046036)		Random 1% of ZINC Database (90911)		Virtual Library (19530)	
	Successive Filtering	Parallel Filtering	Successive Filtering	Parallel Filtering	Successive Filtering	Parallel Filtering
Fail $14 \leq n_{HA} \leq 26$	4395739	4395739 (48%)	43971	43971 (48%)	5104	5104 (26%)
Fail $-1 \leq AlogP \leq 3$	1768807	4478982 (49%)	17828	44746 (49%)	2905	3643 (19%)
Fail Structural	819652	2805505 (31%)	8180	28147 (31%)	53	74 (0.4%)
Pass All	2061838 (23%)	n/a	20932 (23%)	n/a	11468 (59%)	n/a

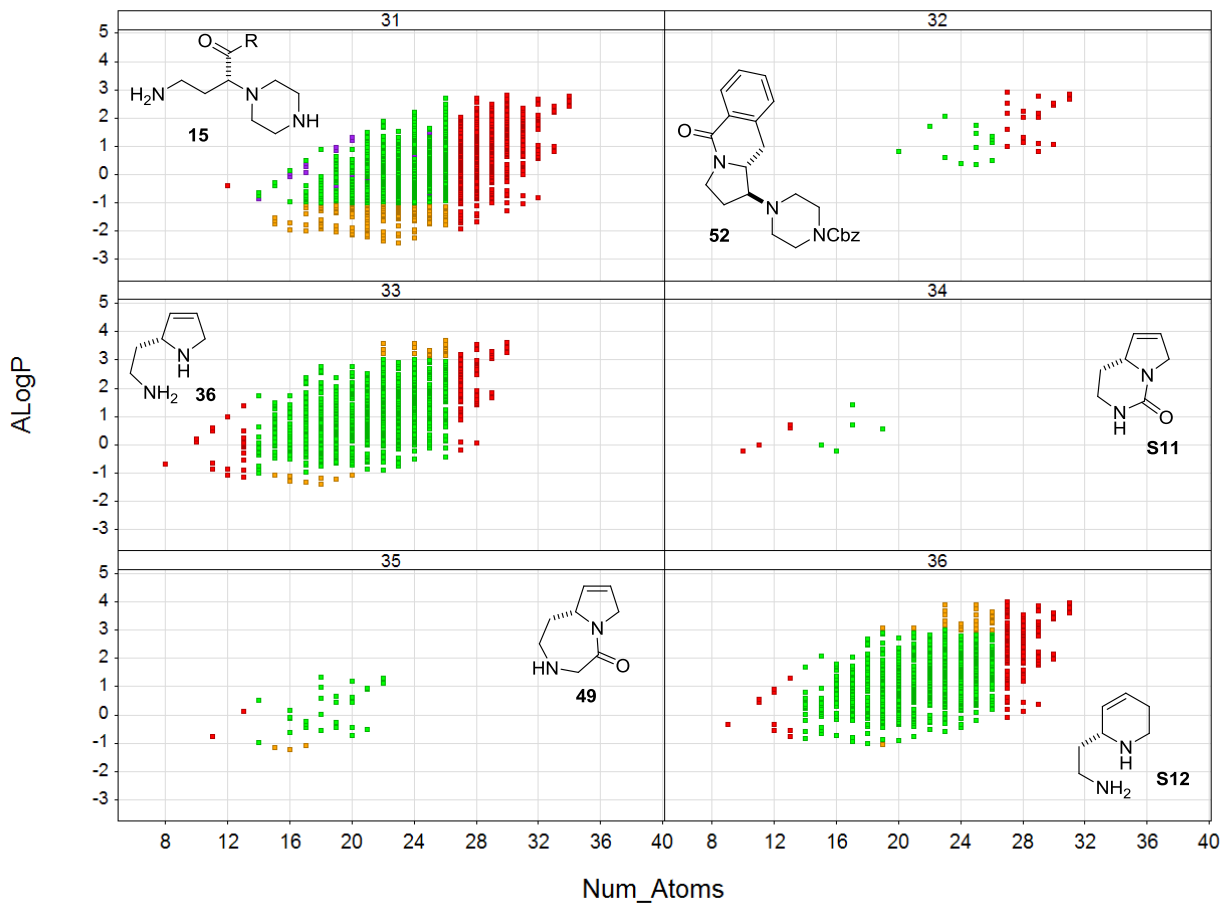
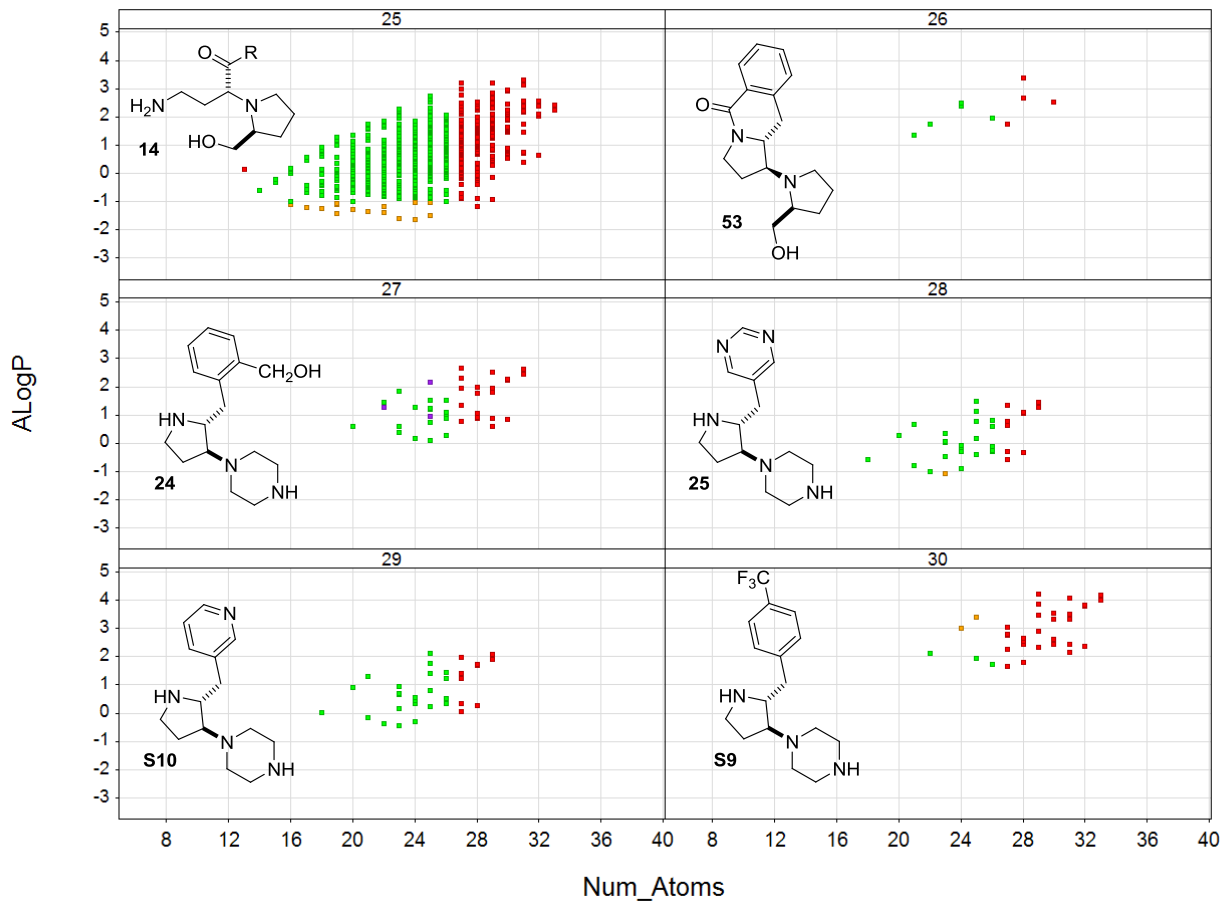
Table S4. Lead-likeness assessment data. The data shown in Figure 1, Panels A and B (main text) was obtained by successive filtering by the number of heavy atoms, lipophilicity and structural filters. For comparison, data obtained from parallel filtering of all compounds using each filter in isolation is also shown.

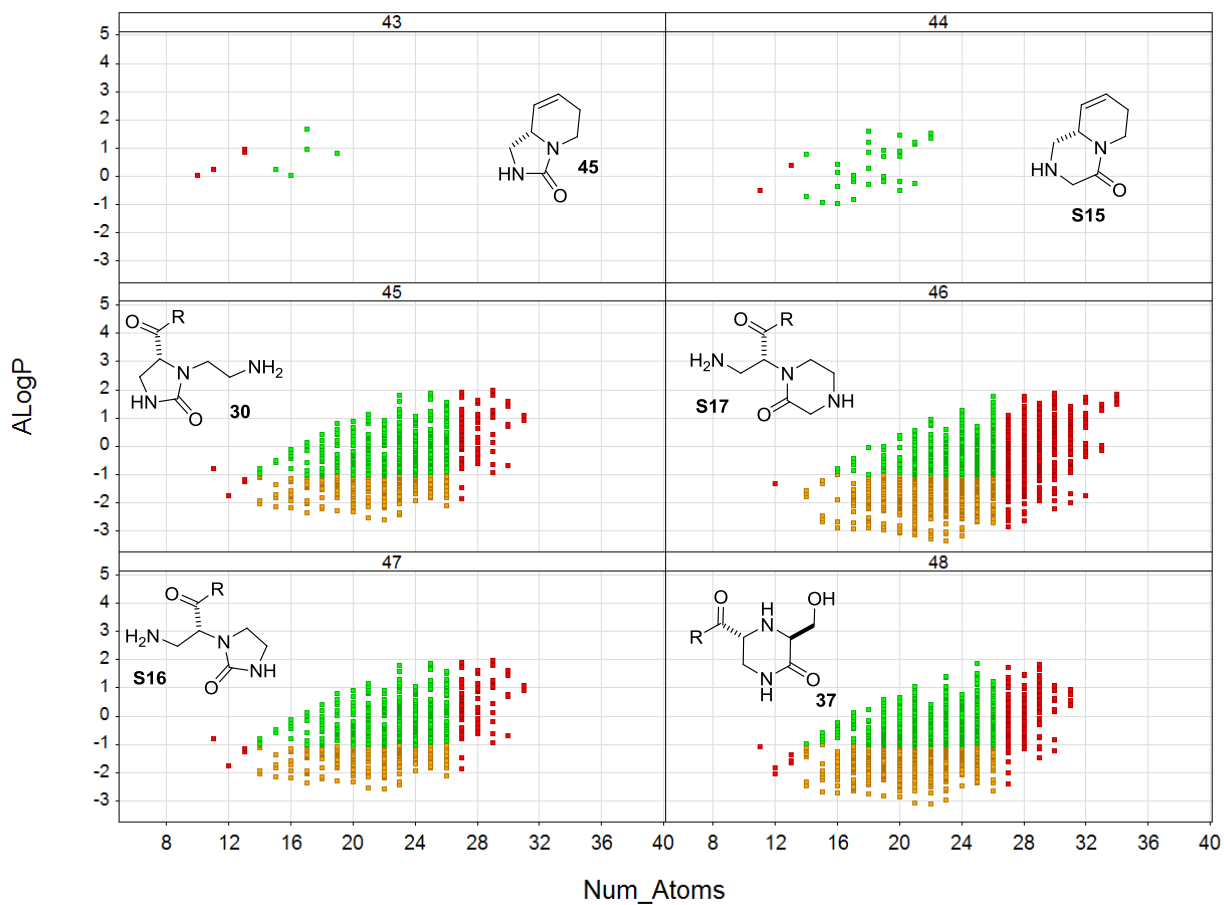
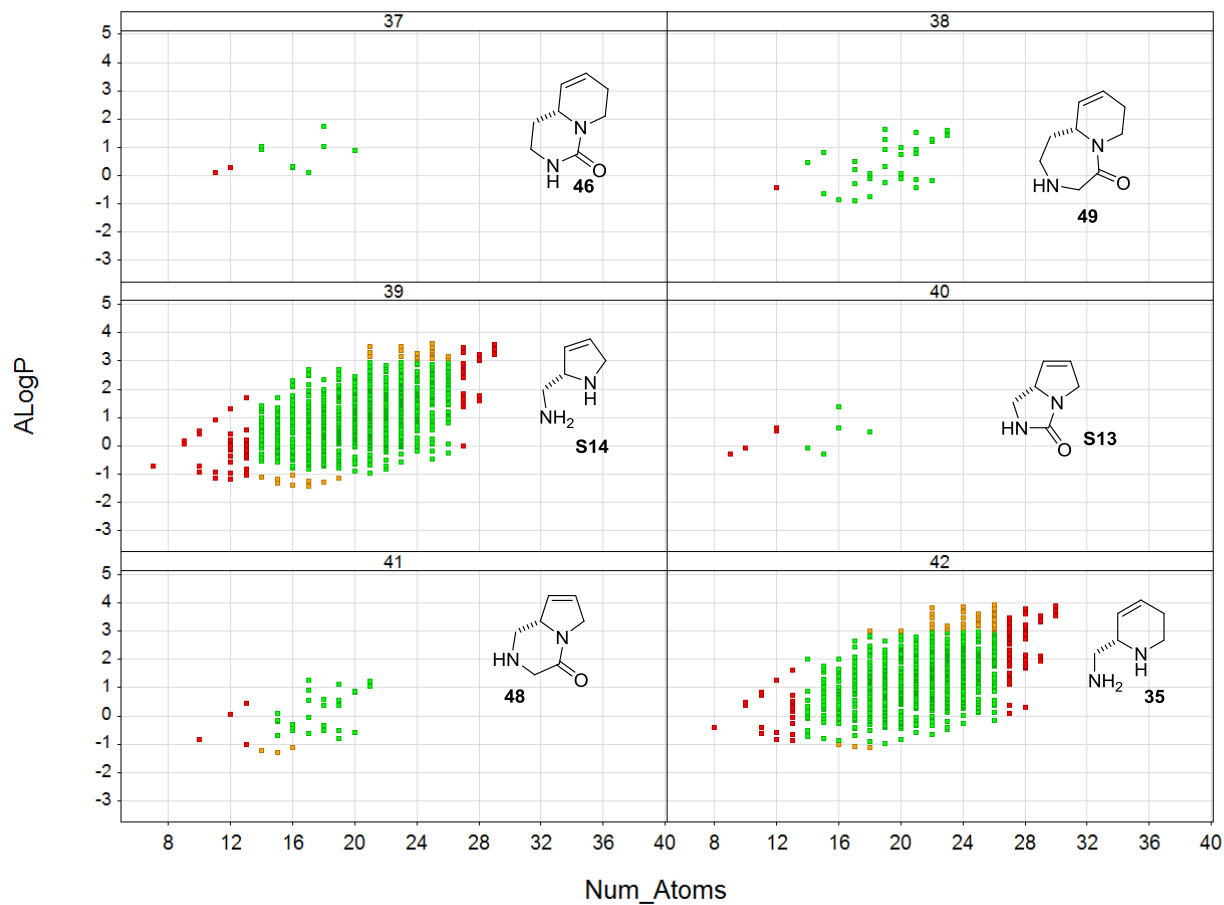
Scaffold	Number of Final Compounds	Number of Lead-like Compounds	% Lead-like Compounds
14	684	471	69
15	1692	817	48
22	336	224	67
23	642	493	77
24	75	31	41
25	67	45	67
26	90	68	76
27	51	20	39
28	43	27	63
29	2094	1547	74
30	684	396	58
31	684	372	54
32	306	214	70
33	1692	366	22
34	306	121	40
35	1156	992	86
36	1156	1004	87
37	1143	558	49
38	90	79	88
39	43	32	74
40	34	10	29
41	67	20	30
42	34	10	29
43	34	14	41
44	150	121	81
45	10	6	60
46	10	8	80
47	34	33	97
48	34	27	80
50	340	75	22
51	340	75	22
52	34	14	41
53	10	6	60
S1	34	19	56
S2	34	19	56
S3	34	5	15
S4	43	28	65
S5	67	19	28
S6	67	29	43
S7	43	2	5
S8	43	27	63
S9	67	5	7
S10	67	47	70
S11	10	6	60
S12	1156	941	81
S13	10	6	60
S14	1156	1034	89
S15	34	32	94
S16	684	396	58
S17	1692	447	26
S18	90	81	90

Table S5. 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).









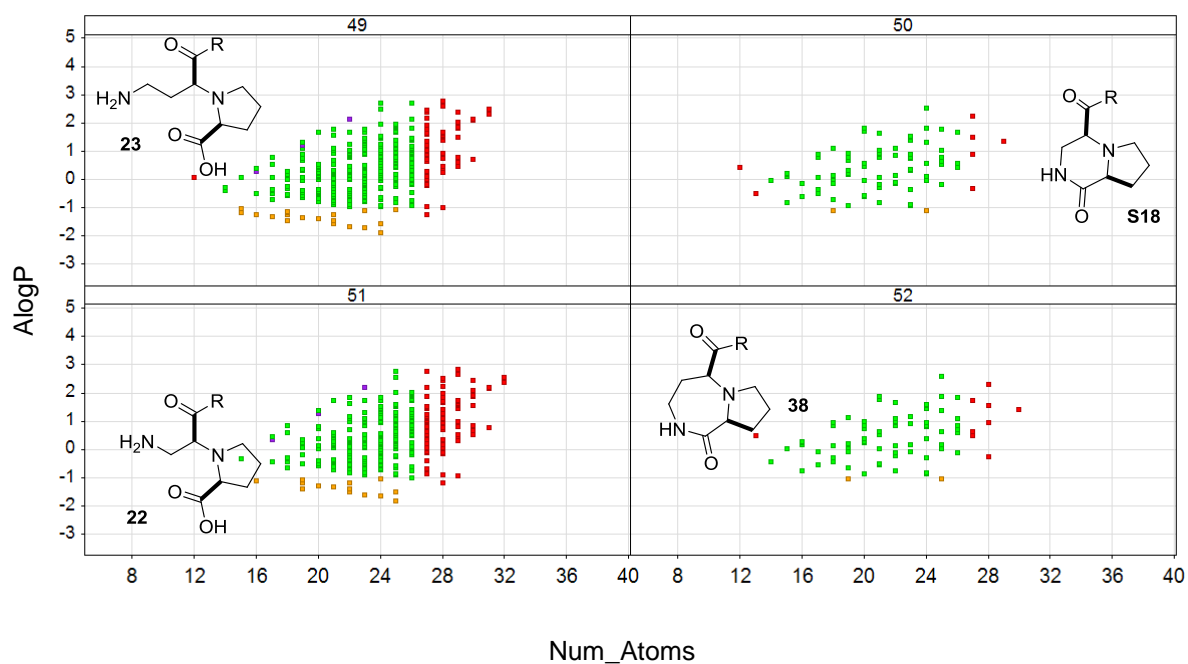


Figure S3. Distribution of number of heavy atoms (Num_Atoms) and AlogP for the virtual library based upon each scaffold. The scaffolds shown have undergone virtual deprotection and manipulation 1 in each case; R = H or OH (see Scheme S4 for manipulations after decoration). Compounds that survive successive filtering are shown in green. Compounds that fail successive filtering by number of heavy atoms (red), AlogP (orange) and structural features (purple) are shown as appropriate.

Scaffold or Library	Mean Fsp ³	Scaffold or Library	Mean Fsp ³
ZINC (random 1%, 90911)	0.33	45	0.46
Virtual Library (19530)	0.58	46	0.5
14	0.71	47	0.56
15	0.68	48	0.48
22	0.78	49	0.53
23	0.76	50	0.42
24	0.57	51	0.42
25	0.6	52	0.51
26	0.51	53	0.52
27	0.59	S1	0.54
28	0.59	S2	0.51
29	0.63	S3	0.49
30	0.58	S4	0.51
31	0.61	S5	0.46
32	0.68	S6	0.51
33	0.62	S7	0.58
34	0.7	S8	0.62
35	0.47	S9	0.56
36	0.47	S10	0.57
37	0.56	S11	0.46
38	0.69	S12	0.5
39	0.48	S13	0.4
40	0.46	S14	0.4
41	0.54	S15	0.53
42	0.57	S16	0.58
43	0.54	S17	0.6
44	0.58	S18	0.66

Table S6. Fsp³ data illustrated in Figure 1, Panel C (main text).

S6. Novelty Assessment

For the purposes of the novelty assessment scaffolds were virtually deprotected but did not undergo manipulation 1. In each case, a substructure search was performed against the ZINC database (9046036). Scaffolds that returned substructure hits in either database were searched for in the CAS registry. None of these scaffolds were known.

Scaffold	ZINC Substructure Hits	Scaffold	ZINC Substructure Hits
14	0	46	0
15	14	47	2
22	0	48	0
23	0	49	0
24	0	50	0
25	0	51	0
26	0	52	0
27	0	53	0
28	0	S1	0
29	0	S2	0
30	0	S3	0
31	0	S4	0
32	0	S5	0
33	0	S6	0
34	0	S7	0
35	2698	S8	0
36	10	S9	0
37	0	S10	0
38	0	S11	0
39	0	S12	1670
40	0	S13	0
41	0	S14	1364
42	0	S15	970
43	0	S16	0
44	0	S17	9
45	770	S18	0

Table S7. Novelty assessment data.

S7. Scaffold Diversity Assessment

The hierarchical framework analysis applied the ‘scaffold tree’ approach described by Schuffenhauer and co-workers.^[4] The results are summarized in Figure S4 and the frameworks illustrated in Scheme S5. 42 frameworks were represented at the graph-node-bond level, ultimately related to 13 parental frameworks.

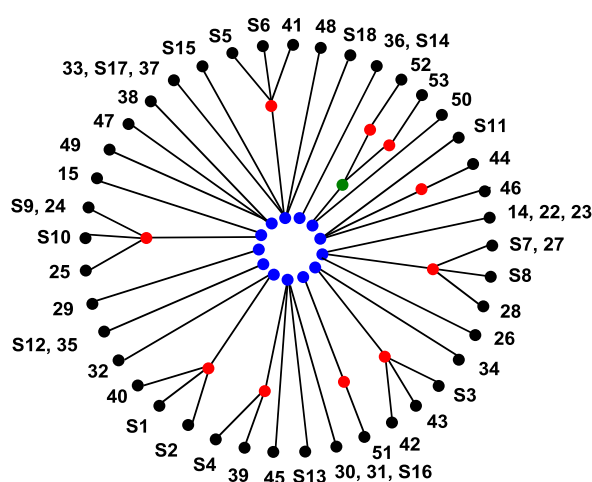


Figure S4. Hierarchical relationship between the 42 distinct molecular frameworks at the graph-node-bond level (black) and the 13 parental frameworks (blue). Daughter frameworks are shown in red and green. The scaffolds based on each graph-node-bond-level framework are indicated.

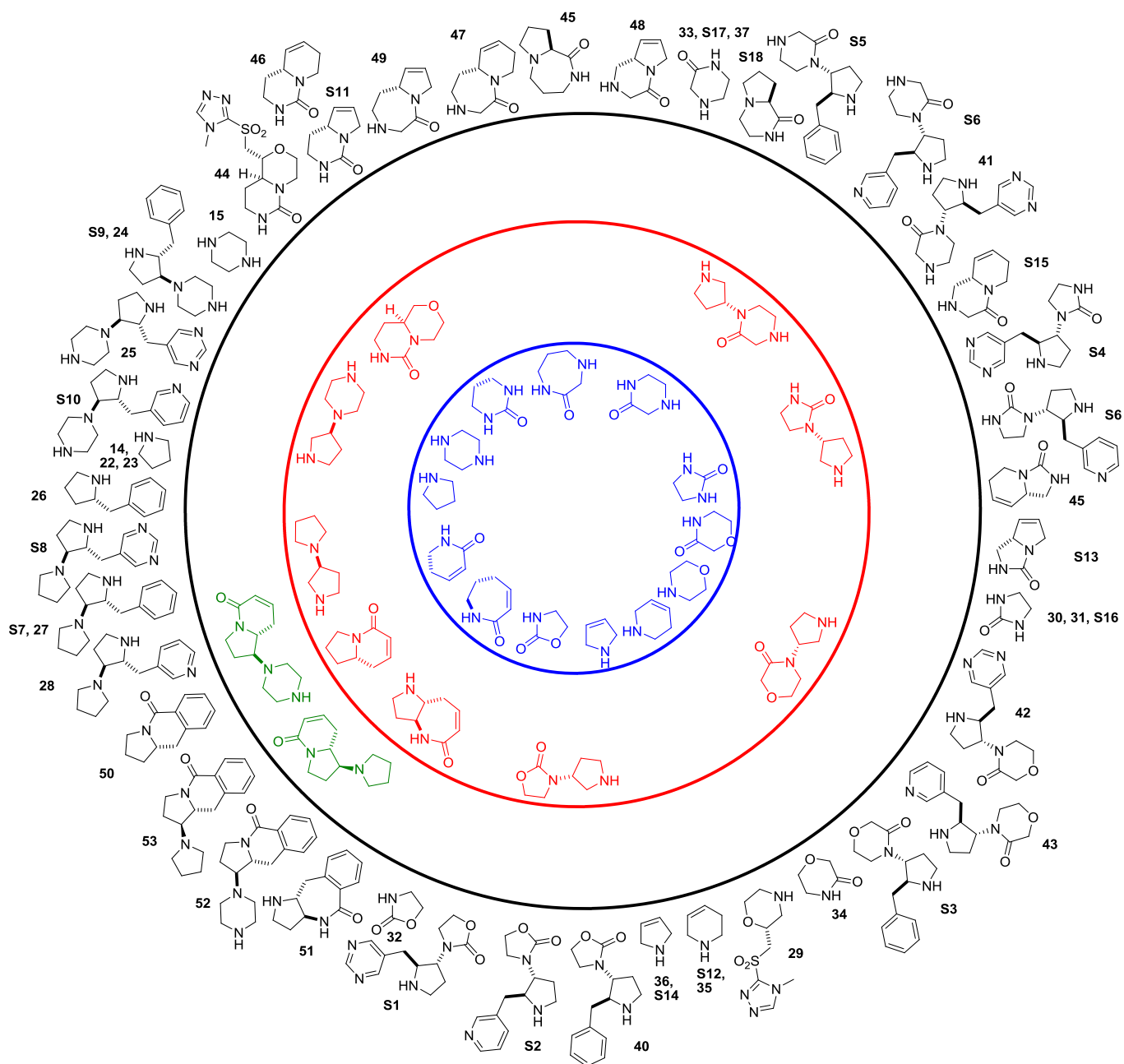


Figure S5. The 42 distinct molecular frameworks at the graph-node-bond level (black) and the 13 parental frameworks (blue). Daughter frameworks are shown in red and green. The scaffolds which represent each framework are indicated. See Figure S4 for the relationship between scaffolds at each level of hierarchy.

S8. Experimental

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. Solvents were removed *in vacuo* using a Büchi rotary evaporator and a Vacuubrand PC2001 Vario diaphragm pump. A Genevac HT-4X or EZ-2 Elite centrifugal evaporator was used for the removal of DMSO where stated. Tetrahydrofuran (THF), CH₂Cl₂, toluene and CH₃CN were dried and purified by means of a Pure Solv MD solvent purification system (Innovative Technology Inc.). Anhydrous *N,N*-dimethylformamide (DMF) and 1,4-dioxane was obtained in SureSeal bottles 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 or Alfa-Aesar and were used without purification unless stated.

Thin layer chromatography (TLC) was carried out on aluminium backed silica (Merck silica gel 60 F₂₅₄) plates supplied by Merck. Visualisation of the plates was achieved using an ultraviolet lamp ($\lambda_{\text{max}} = 254 \text{ nm}$), KMnO₄, anisaldehyde or ninhydrin. LCMS analysis was generally carried out on an Agilent 1200 series LC system comprising a Bruker HCT Ultra ion trap mass spectrometer. The solvent system used was CH₃CN/H₂O + 0.1% formic acid with a Phenomenex Luna C18 50 × 2 mm 5 micron column.

Flash chromatography was carried out using silica gel 60 (60-63 μm particles) supplied by Merck or using Biotage silica or ISOLUTE C₁₈ pre-packed cartridges on a Flashmaster II or CombiFlash Companion. Strong cation exchange solid phase extraction (SCX-SPE) was carried out using pre-packed Discovery DSC-SCX cartridges supplied by Supleco. Mass-directed HPLC purification was carried out using an Agilent 1260 Infinity HPLC system comprising an Agilent 6120 Quadrupole LC/MS and Agilent G1968D active splitter.

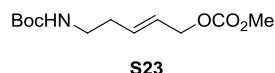
Optical rotation measurements were carried out at the sodium D-line (589 nm) on a Schmidt and Haensch H532 or an Optical Activity AA-1000 polarimeter instrument; concentrations are g/100 mL, temperatures given in °C, optical rotations are given in $10^{-1}\text{degcm}^2\text{g}^{-1}$ (units are omitted). Infrared spectra were recorded on a Perkin-Elmer One FT-IR spectrometer with absorption reported in wavenumbers (cm^{-1}). Chiral HPLC was carried out on either an Agilent 1100 or an Agilent Infinity 1290 series HPLC system. Racemic standards were obtained by preparing samples of both enantiomers and then combining in an approx. 1:1 ratio.

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 (¹³C) NMR spectral data were collected on a Bruker Advance 400, 500 or 600, 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.

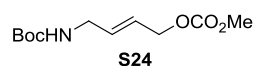
Preparation of Allylic Carbonates

2-(((3E)-5-[(Methoxycarbonyl)oxy]pent-3-en-1-yl)carbamoyl)oxy)-2-methylpropane S23



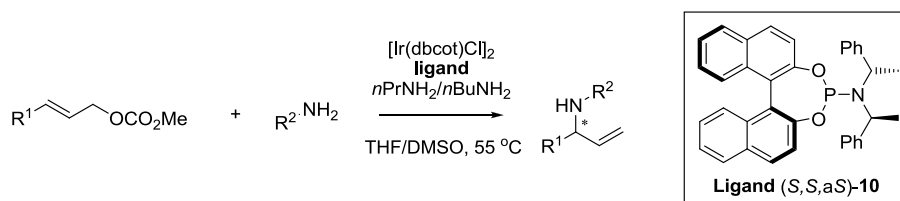
Pyridine (9.90 mL, 122 mmol) and methyl chloroformate (9.40 mL, 122 mmol) were added to a solution of (*E*)-tert-butyl(5-hydroxypent-3-en-1-yl)carbamate^[5] (22.3 g, 110 mmol) in CH₂Cl₂ (220 mL) at 0 °C (ice). The reaction mixture was allowed to warm to room temperature and stirred for 2 d before being quenched by the addition of saturated aqueous NH₄Cl (200 mL). The phases were separated and the aqueous phase extracted with CH₂Cl₂ (2 × 100 mL). The combined organic phase was washed with water (250 mL) and brine (250 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography, eluting with 7:3 petrol–EtOAc to furnish the title compound **S23** (20.18 g, 70%) as a colourless oil, *R*_f 0.17 (4:1 petrol–EtOAc); δ_H (500 MHz, CDCl₃) 5.75 (1 H, dt, *J* 15.1, 6.8, 3-H), 5.65 (1 H, dt, *J* 15.1, 6.2, 4-H), 4.57 (2 H, d, *J* 6.2, 5-H), 3.77 (3 H, s, OCH₃), 3.22-3.14 (2 H, m, 2-H), 2.24 (2 H, app. q, *J* 6.6, 1-H), 1.43 (9 H, s, OC(CH₃)₃); δ_C (75 MHz, CDCl₃) 155.7 (NHCO₂), 155.5 (OCO₂CH₃), 133.2 (4-C), 125.6 (3-C), 79.0 (OC(CH₃)₃), 68.1 (5-C), 54.6 (2-C), 39.4 (1-C), 28.3 (OC(CH₃)₃); ν_{max}/cm⁻¹ (neat) 3365, 2976, 1746, 1689, 1513, 1442, 1390, 1365, 1246, 1164; *m/z* (ESI) 282 (100%, MNa⁺); Found: MNa⁺, 282.1314. C₁₂H₂₁NO₅ requires *MNa*, 282.1312.

2-(((2E)-4-[(Methoxycarbonyl)oxy]but-2-en-1-yl)carbamoyl)oxy)-2-methylpropanecarbamate S24



The compound was prepared using a previously reported procedure.^[6]

Iridium-Catalysed Allylic Amination (Scheme 2, main text)



[Ir(dbcot)Cl]₂ was prepared according to the method of Crabtree *et al.*^[7] The ligands (*S,S,aS*)-**10** and (*R,R,aR*)-**10** were prepared according to the method of Mezzetti *et al.*^[8]

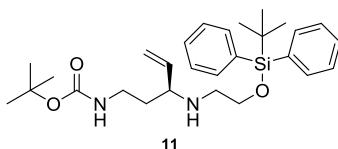
General Procedure 1

*n*BuNH₂ (0.04 eq) was added to a solution of [Ir(dbcot)Cl]₂ (0.02 eq) and chiral phosphoramidite (0.04 eq) in DMSO (~0.7 M). The mixture was heated at 55 °C until the reaction mixture changed in colour from orange to yellow. The allylic carbonate (1.0 eq) was then added, followed by the amine (1.3 eq) and K₃PO₄ (1.3 eq) if an amine salt was used. The reaction mixture was stirred at 55 °C for the time specified, cooled to room temperature and concentrated *in vacuo* by means of a GeneVac centrifugal evaporator to give a crude product which was purified by SCX solid phase extraction followed by flash column chromatography using the specified eluent.

General Procedure 2

n-PrNH₂ (0.04 eq) was added to a solution of [Ir(dbot)Cl]₂ (0.02 eq) and chiral phosphoramidite (0.04 eq) in THF (~0.5 M). The mixture was heated at 55 °C until the reaction mixture changed in colour from orange to yellow. The allylic carbonate (1.0 eq) was then added, followed by the amine (1.3 eq) and K₃PO₄ (1.3 eq) if an amine salt was used. The reaction mixture was stirred at 55 °C for the time specified, cooled to room temperature, concentrated *in vacuo* and purified by flash column chromatography using the specified eluent.

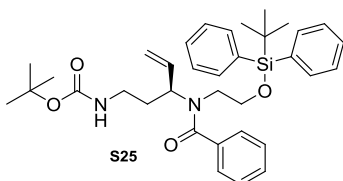
tert-Butyl *N*-[(3*S*)-3-({2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}amino)pent-4-en-1-yl]carbamate **11**



According to General Procedure 1, allylic carbonate **S23** (0.200 g, 0.770 mmol) was combined with (2-aminoethoxy(*tert*-butyl)diphenylsilane)^[9] (0.300 g, 1.00 mmol) and heated for 9 h. Purification by flash column chromatography, eluting with 97:2.7:0.3 CH₂Cl₂–EtOH–NH₄OH furnished the amine **11** (0.219 g, 59%, 84% *ee*) as a yellow oil, *R*_f 0.18 (97:2.7:0.3 DCM–EtOH–NH₄OH); [α]_D²⁴ +4 (*c.* 0.69, CHCl₃); δ_H (500 MHz, CDCl₃) 7.66 (4 H, m, Ar 2-H), 7.44–7.36 (6H, m, Ar H), 5.61 (1H, ddd, *J* 16.8, 10.0, 8.0, 4-H), 5.12 (1H, app. d, *J* 10.0, 5-H_A), 5.10 (1H, app. d, *J* 16.8, 5-H_B), 3.79–3.72 (2H, m, CH₂OSi), 3.23 (1H, app. dt, *J* 11.4, 6.1, 1-H_A), 3.14 (1H, app. dt, *J* 11.4, 5.4, 1-H_B), 3.05 (1H, ddd, *J* 8.0, 6.1, 5.4, 3-H), 2.78 (1H, ddd, *J* 11.5, 6.8, 4.5, NHCH_{2A}), 2.61 (1H, app. dt, *J* 11.5, 5.0, NHCH_{2B}), 1.64–1.60 (2H, m, 1-H), 1.43 (9H, s, OC(CH₃)₃), 1.05 (9H, s, SiC(CH₃)₃); δ_C (75 MHz, CDCl₃) 155.9 (NHCO₂), 140.4 (4-C), 135.5 (Ar 2-C), 133.5 (Ar 1-C), 129.6 (Ar 4-C), 127.6 (Ar 3-C), 116.2 (5-C), 79.9 (OC(CH₃)₃), 63.2 (CH₂OSi), 59.9 (3-C), 48.8 (NHCH₂), 37.9 (1-C), 35.2 (2-C), 28.4 (OC(CH₃)₃), 26.8 (SiC(CH₃)₃), 19.2 (SiC(CH₃)₃); ν_{max}/cm⁻¹ (neat) 3347, 2931, 1710, 1506, 1472, 1428, 1390, 1365, 1250; *m/z* (ESI) 483 (100%, MH⁺); Found: MH⁺, 483.3050. C₂₈H₄₂N₂O₃Si requires *MH*, 483.3037.

For the purposes of chiral HPLC analysis, the respective benzamide derivative **S25** was prepared.

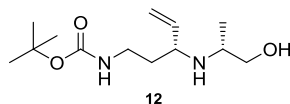
tert-Butyl *N*-[(3*S*)-3-(*N*-{2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}-1-phenylformamido)pent-4-en-1-yl]carbamate **S25**



NEt₃ (0.130 mL, 0.900 mmol) and benzoyl chloride (68.0 μL, 0.580 mmol) were added to a solution of amine **11** (0.218 g, 0.450 mmol) in CH₂Cl₂ (4.0 mL) at 0 °C (ice). The mixture was allowed to warm to room temperature and then stirred for 18 h before being diluted with CH₂Cl₂ (10 mL), saturated aqueous NH₄Cl (10 mL) added, the phases separated and the aqueous phase extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phase was dried (MgSO₄), filtered and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography, eluting with 3:1 petrol–EtOAc to furnish the amide **S25** (0.132 g, 50%, 84% *ee*) as a colourless viscous oil, *R*_f 0.35 (7:3 petrol–EtOAc); [α]_D²⁰ –21 (*c.* 1.06, CHCl₃); δ_H (500 MHz, MeOD, 333 K) 7.62 (5 H, m, Ar H) 7.44–7.31 (10 H, m, silyloxy Ar-H), 5.88 (1 H, app. br s, 4-H), 5.13 (2 H, m, H-5), 4.32 (1 H, app. br s, 3-H), 3.81 (2 H, app. br s, CH₂OSi), 3.51 (2 H, app. br s, 1-H), 2.95 (2 H, app. br s, NHCH₂), 1.80 (2 H, app. br s, 2-H), 1.40 (9H, s, OC(CH₃)₃), 1.04 (9H, s, SiC(CH₃)₃); δ_C (75 MHz, MeOD, 333 K) 174.8 (NCOPh), 158.2 (NHCO₂), 137.7 (Ar 1-C), 136.7 (4-C) 134.7 (SiAr 1-C), 130.9 (SiAr 4-C), 130.7 (Ar 4-C), 129.7 (SiAr 3-C), 128.9 (Ar 3-C), 128.8 (SiAr 2-C), 127.6 (Ar 2-C), 118.1 (5-C), 80.2 (OC(CH₃)₃), 63.0 (CH₂OSi), 62.9 (3-C), 38.8 (1-C), 33.4 (2-C), 28.9

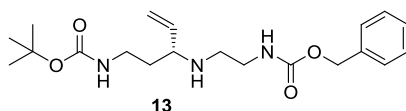
(OC(CH₃)₃), 27.5 (SiC(CH₃)₃), 20.0 (SiC(CH₃)₃), (NCH₂) signal not observed – under residual solvent signal; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3347, 2932, 1712, 1634, 1515, 1428, 1365, 1250, 1173, 1111; m/z (ESI) 587 (100%, MH⁺); Found: MH⁺, 587.3302. C₃₅H₄₆N₂O₄Si requires *MH*, 587.3299; HPLC: CHIRALPAK[®] OD-H, 5% IPA–hexane over 60 min, 0.3 mL/min; $t_1 = 32.27$ min (minor), $t_2 = 36.70$ min (major).

tert*-Butyl-*N*-[(3*R*)-3-[(2*S*)-1-hydroxypropan-2-yl]amino]pent-4-en-1-yl]carbamate **12*



According to General Procedure 1, allylic carbonate **S23** (2.00 g, 7.70 mmol) was combined with (*R*)-2-aminopropan-1-ol (0.780 mL, 10.0 mmol) and heated for 18 h. Purification by flash column chromatography, eluting with 92:7:1 CH₂Cl₂–EtOH–NH₄OH furnished the amine **12** (1.21 g, 61%, *dr* 93:7) as an amorphous colourless solid, R_f 0.19 (92:7:1 CH₂Cl₂–EtOH–NH₄OH); δ_{H} (500 MHz, CDCl₃) 5.62 (1 H, ddd, J 16.9, 10.3, 8.3, 4-H), 5.10 (1 H, d, J 10.3, H-5_A), 5.09 (1 H, d, J 16.9, H-5_B), 4.86 (1 H, br s, CO₂NH), 3.58 (1 H, dd, J 10.8, 3.6, CH_AOH), 3.32-3.28 (1 H, m, 1-H_A), 3.24 (1 H, dd, J 10.8, 4.9, CH_BOH), 3.17-3.10 (2 H, m, 1-H_B, 3-H), 2.85-2.79 (1 H, m, NHCHCH₃), 1.66-1.54 (2 H, m, 2-H), 1.44 (9 H, s, OC(CH₃)₃), 1.07 (3 H, d, J 6.6, CHCH₃); δ_{C} (75 MHz, CDCl₃) 156.1 (NHCO₂), 140.9 (4-C), 115.5 (5-C), 79.2 (OC(CH₃)₃), 64.3 (CH₂OH), 57.0 (3-C), 51.1 (NHCHCH₃), 37.4 (1-C), 36.1 (2-C), 28.3 (OC(CH₃)₃), 18.6 (CHCH₃); $\nu_{\max}/\text{cm}^{-1}$ (neat) 3374, 2984, 1684, 1528, 1276, 1261, 1172, 1048; m/z (ESI) 259 (100%, MH⁺); Found: MH⁺, 259.2018. C₁₃H₂₆N₂O₃ requires *MH*, 259.2016.

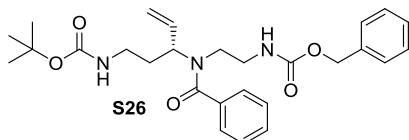
tert*-Butyl-*N*-[(3*R*)-3-[(2-[(benzyloxy)carbonyl]amino)ethyl]amino]pent-4-en-1-yl]carbamate **13*



According to General Procedure 1, allylic carbonate **S23** (0.450 g, 1.74 mmol) was combined with benzyl-2-aminoethylcarbamate^[10] (0.405 g, 2.09 mmol) and heated for 18 h. Purification by flash column chromatography, eluting with 92:7:1 CH₂Cl₂–EtOH–NH₄OH furnished the amine **13** (0.300 g, 46%, *ee* 84%) as a yellow oil, R_f 0.39 (92:7:1 CH₂Cl₂–EtOH–NH₄OH); $[\alpha]_{\text{D}}^{24} +0.4$ (c. 1.59, CHCl₃); δ_{H} (500 MHz, CDCl₃) 7.37-7.30 (5 H, m, Ar-H), 5.57 (1 H, ddd, J 16.6, 10.3, 8.1, 4-H), 5.38 (1 H, br s, BnCO₂NH), 5.13-5.08 (4 H, m, 5-H, CH₂Ph), 4.98 (1 H, br s, *t*BuCO₂NH), 3.28-3.26 (3 H, m, 1-H_A, BnCO₂NHCH₂), 3.13-3.09 (1 H, m, 3-H), 3.05 (1 H, app. dd, J 13.6, 6.6, 1-H_B), 2.81-2.76 (1 H, m, NHCH_A), 2.64-2.59 (1 H, m, NHCH_B), 1.64-1.54 (2 H, m, 2-H), 1.42 (9 H, s, OC(CH₃)₃); δ_{C} (75 MHz, CDCl₃) 156.5 (NHCO₂Bn), 155.9 (NHCO₂*t*Bu), 140.2 (4-C), 136.6 (Ar 1-C), 128.3 (Ar 3-C), 128.0 (Ar 4-C), 127.9 (Ar 2-C), 116.1 (5-C), 79.0 (OC(CH₃)₃), 66.4 (CH₂Ph), 59.2 (3-C), 46.2 (NHCH₂), 40.7 (BnCO₂NHCH₂), 37.6 (1-C), 35.5 (2-C), 28.3 (OC(CH₃)₃); $\nu_{\max}/\text{cm}^{-1}$ (neat) 3332, 2977, 1701, 1527, 1455, 1366, 1254, 1171; m/z (ESI) 259 (100%, MH⁺); Found: MH⁺, 378.2400. C₂₀H₃₁N₃O₄ requires *MH*, 378.2387.

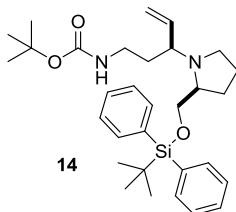
For the purposes of chiral HPLC analysis the respective benzamide derivative **S26** was prepared.

tert*-Butyl-*N*-[(3*R*)-3-[*N*-(2-[[*(benzyloxy)carbonyl*]amino}ethyl)-1-phenylformamido]pent-4-en-1-yl]carbamate **S26*



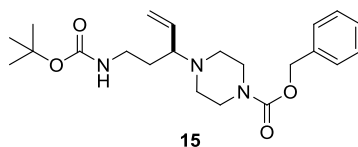
NEt₃ (0.730 mL, 1.30 mmol) and benzoyl chloride (46.0 μL, 0.390 mmol) were added to a solution of amine **13** (0.100 g, 0.260 mmol) in CH₂Cl₂ (2.6 mL) at 0 °C (ice). The mixture was allowed to warm to room temperature and then stirred for 18 h before being diluted with CH₂Cl₂ (10 mL), saturated aqueous NH₄Cl (10 mL) added, the phases separated and the aqueous phase extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phase was dried (MgSO₄), filtered and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography, eluting with 96:3.6:0.4 CH₂Cl₂ –EtOH–NH₄OH to furnish the amide **S26** (97.0 mg, 77%, 84% *ee*) as a pale yellow oil, *R*_f 0.28 (95:4.5:0.5 CH₂Cl₂ –EtOH–NH₄OH); [α]_D²⁰ +10.2 (*c.* 2.40, CHCl₃); δ_H (500 MHz, DMSO-*d*₆, 343 K) 7.43-7.30 (10 H, m, Ar-H), 5.91 (1 H, app. br s, H-4), 5.15 (1 H, app. d, *J* 10.5, 5-H_A), 5.07 (1 H, app. d, *J* 16.9, 5-H_B), 5.02 (2 H, s, CH₂Ph), 4.23 (1 H, app. br s, 3-H), 3.32-3.29 (2 H, m, BnCO₂NHCH₂), 3.21 (2 H, app. br s, 1-H), 2.86 (2 H, app. br s, NHCH₂), 1.83-1.78 (2 H, m, 1-H), 1.37 (9 H, s, OC(CH₃)₃); δ_C (75 MHz, DMSO-*d*₆, 343 K) 171.0 (NCOPh), 155.6 (NHCO₂*t*Bu), 154.9 (NHCO₂Bn), 136.8 (Ar 1-C), 136.7 (Ar 1-C), 136.5 (4-C), 128.6 (broad, Ar 4-C), 127.8 (app. d, Ar 3-C), 127.2 (app. d, Ar 2-C), 116.2 (5-C), 77.2 (OC(CH₃)₃), 64.9 (CH₂Ph), 31.3 (2-C), 27.8 (OC(CH₃)₃), (1-C), (3-C), (NHCH₂) and (BnCO₂NHCH₂) not observed - rotameric; ν_{max}/cm⁻¹ (neat) 3327, 2975, 1697, 1618, 1510, 1447, 1412, 1391, 1245; *m/z* (ESI) 587 (100%, MNa⁺); Found: MNa⁺, 504.2476. C₂₇H₃₅N₃O₅ requires *MNa*, 504.2468; HPLC: Daicel Chiralcel AS-H, 5% EtOH–hexane over 60 min, 0.5 mL/min; t₁ = 31.91 min (major), t₂ = 39.64 min (minor).

tert*-Butyl-*N*-[(3*S*)-3-[(2*S*)-2-[[*tert*-butyldiphenylsilyloxy]methyl]pyrrolidin-1-yl]pent-4-en-1-yl]carbamate **14*



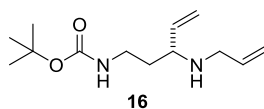
According to General Procedure 1, allylic carbonate **S23** (2.00 g, 7.7 mmol) was combined with (3.41 g, 10.0 mmol, 1.3 eq) *O*-TBDPS-*S*-prolinol^[11] and heated for 16 h. Purification by flash column chromatography, eluting with 20:79:1 EtOAc–petrol–NEt₃ furnished the amine **14** (2.1 g, 52%, *dr* >95:<5) as a yellow oil, *R*_f 0.2 (30:70 Et₂O–pentane); δ_H (500 MHz, CDCl₃) 7.67 (4H, d, *J* 6.5, silyloxy Ar H), 7.45-7.36 (6H, m, silyloxy Ar H), 5.74 (1 H, ddd, *J* 17.5, 10.2, 8.5, 4-H), 5.33 (1H, br s, NH), 5.14 (1H, dd, *J* 10.2, 1.4 Hz, 5-H_A), 4.96 (1H, d, *J* 17.5, 5-H_B), 3.59 (1H, dd, *J* 10.0, 4.8, CH_AOSi), 3.45 (1H, dd, *J* 10.0, 7.5, CH_BOSi), 3.24 (1H, dd, *J* 12.9, 6.1, 1-H_A), 3.17 (1H, dd, *J* 15.0, 7.7, 3-H), 3.06-2.98 (1H, m, 1-H_B), 2.90 (1H, br s, pyrrolidine 2-H), 2.84 (1H, br s, pyrrolidine 5-H_A), 2.54 (1H, dd, *J* 15.8, 8.2, pyrrolidine 5-H_B), 1.82-1.42 (6H, m, 2-H_{AB}, pyrrolidine 3-H_{AB} and 4-H_{AB}), 1.40 (9H, s, OC(CH₃)₃), 1.05 (9H, s, SiC(CH₃)₃); δ_C (125 MHz, CDCl₃) 156.1 (NHCO₂), 135.9 (4-C), 135.6 (Ar 2-C), 133.9 (Ar 1-C), 129.6 (Ar 4-C), 127.6 (Ar 3-C), 117.4 (5-C), 78.6 (OC(CH₃)₃), 67.3 (SiOCH₂), 61.9 (NCH), 61.0 (3-C), 46.8 (NCH₂), 39.2 (1-C), 33.3 (2-C), 28.4 (OC(CH₃)₃), 26.9 (SiC(CH₃)₃), 26.8 (CHCH₂), 23.5 (NCH₂CH₂), 19.2 (SiC(CH₃)₃); ν_{max}/cm⁻¹ (film) 3358, 3071, 3052, 2964, 2932, 2859, 2708, 2305, 1709, 1505, 1428, 1365, 1275, 1262, 1173, 1112; *m/z* (ESI) 523 (100%, MH⁺); Found: MH⁺, 523.3362. C₃₁H₄₇N₂O₃Si requires *MH*, 523.3350.

Benzyl-4-[(3S)-5-[[*tert*-butoxy]carbonyl]amino]pent-1-en-3-yl]piperazine-1-carboxylate **15**



According to General Procedure 1, allylic carbonate **S23** (2.00 g, 7.7 mmol) was combined with 1-*Z*-piperazine (2.2 g, 10.0 mmol) and heated for 16 h. Purification by flash column chromatography, eluting with 30:70 EtOAc–petrol furnished the amine **15** (2.1 g, 68%, *ee* 88%) as a pale yellow oil, R_f 0.19 (Et₂O–pentane); $[\alpha]_D^{20} +19.4$ (*c* 1.04, CHCl₃); δ_H (500 MHz; CDCl₃) 7.39–7.28 (5H, m, Cbz), 5.69 (1H, ddd, *J* 17.2, 9.8 and 9.4-H), 5.2 (1H, d, *J* 9.8, 5-H_A), 5.12 (2H, s, Cbz), 5.10 (1H, d, *J* 17.2, 5-H_B), 3.55–3.54 (4H, m, 2'-H), 3.32–3.22 (1H, m, 1-H_A), 3.16–3.08 (1H, m, 1-H_A), 2.94–2.88 (1H, m, 3-H), 2.56 (2H, br s, 3'-H_A), 2.39 (2H, br s, 3'-H_B), 1.85–1.77 (1H, m, 2-H_A), 1.63–1.58 (1H, m, 2-H_B), 1.44 (9H, s, OC(CH₃)₃); δ_C (125 MHz; C₆D₆/MeOD) 155.7 (NHCO₂), 154.9 (NHCO₂), 137.5 (4-C), 136.1 (Ar 1-C), 128.5 (Ar 2-C), 128.2 (Ar 3-C), 117.4 (5-C), 78.3 (OC(CH₃)₃), 67.1 (CH₂Ar), 66.3 (pip 3-C), 48.8 (MeOH), 44.3 (pip 2-C), 38.5 (3-C), 31.4 (1-C), 29.9 (2-C), 28.5 (OC(CH₃)₃); $\nu_{\max}/\text{cm}^{-1}$ (film) 3359, 2976, 1703, 1519, 1432, 1365, 1245; m/z (ES⁺) 404.3 (100%, MH⁺); found 404.2585, C₂₂H₃₃N₃O₄ requires *MH* 404.2544; HPLC: Chiralcel AD-H, 5% EtOH/hexane over 60 min, 1 ml/min; $t_1 = 31.8$ min (minor), $t_2 = 37.3$ min (major).

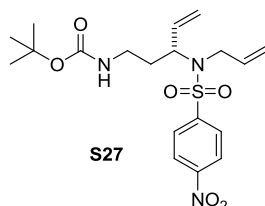
tert-butyl-*N*-[(3*R*)-3-[(prop-2-en-1-yl)amino]pent-4-en-1-yl]carbamate **16**



According to General Procedure 2, allylic carbonate **S23** (0.613 g, 2.50 mmol) was combined with allylamine (0.244 mL, 3.25 mmol) and heated for 20 h. Purification by flash column chromatography, eluting with 8:2→1:9 petrol–EtOAc furnished amine **16** (0.372 g, 62%, *ee* 87%) as a yellow oil, R_f 0.09 (1:1 cyclohexane–EtOAc); $[\alpha]_D^{22} -10$ (*c* 1.10, CHCl₃); δ_H (400 MHz, DMSO-*d*₆) 6.73 (1 H, br. s, BocNH), 5.81 (1 H, ddt, *J* 17.2, 10.2, 5.7 Hz, CH=CH₂), 5.60–5.48 (1 H, m, CH=CH₂), 5.11 (1 H, dq, *J* 17.3, 1.6 Hz, *trans* CH=CH₂), 5.05 (1 H, dq, *J* 13.4, 2.1 Hz, *cis* CH=CH₂), 5.00 (1 H, dd, *J* 10.3, 1.6 Hz, *cis* CH=CH₂), 3.14 (1 H, ddt, *J* 14.5, 5.4, 1.7 Hz, CHCH=CH₂), 3.03–2.87 (4 H, m, BocNHCH₂, CH₂CH=CH₂), 1.68 (1 H, br. s, NHCH₂CH=CH₂), 1.53 (1H, ddt, *J* 12.9, 8.0, 6.5 Hz, NHCH₂CH₂), 1.48–1.40 (1 H, m, NHCH₂CH₂), 1.37 (9 H, s, C(CH₃)₃); δ_C (100 MHz, DMSO-*d*₆) 155.4 (C=O), 141.3 (CH=CH₂), 137.8 (CH=CH₂), 115.1 (CH=CH₂), 114.8 (CH=CH₂), 77.3 (C(CH₃)₃), 58.1 (CHCH=CH₂), 48.9 (CH₂CH=CH₂), 37.1 (BocNHCH₂), 35.1 (BocNHCH₂CH₂), 28.2 (C(CH₃)₃); $\nu_{\max}/\text{cm}^{-1}$ (neat) 3333, 3076, 2977, 2930, 1692, 1643, 1515, 1454, 1391, 1365, 1273, 1249, 1169, 1041, 993, 916, 864, 778; m/z (ESI) 241 (100%, MH⁺); Found: MH⁺, 241.1907. C₁₃H₂₅O₂N₂ requires *MH*, 241.1911.

For the purposes of chiral HPLC analysis the respective sulfonamide derivative **S27** was prepared.

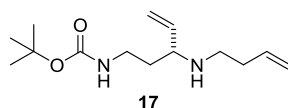
tert-Butyl-*N*-[(3*R*)-3-[*N*-(prop-2-en-1-yl)4-nitrobenzenesulfonamido]pent-4-en-1-yl]carbamate **S27**



NEt₃ (836 μ l, 6.00 mmol) and 4-nitrobenzene-1-sulfonyl chloride (665 mg, 3.00 mmol) were added to a solution of amine **16** (0.480 g, 2.00 mmol) in CHCl₃ (4.0 mL). The reaction mixture was stirred at room temperature for 3 d, diluted with MeOH (5

mL), concentrated *in vacuo* and then purified by flash chromatography, eluting with 1:3→4:0 MTBE–cyclohexane to furnish sulfonamide **S27** (0.362 g, 43 % yield, *ee* 87%) as a yellow oil, $[\alpha]_{\text{D}}^{22} = +148.4$, ($c = 3.20$, CHCl_3); δ_{H} (400 MHz, CDCl_3) 8.35 (2H, d, J 8.8, Ar 3-H), 8.02 (2H, d, J 8.8, Ar 2-H), 5.79 (1H, dddd, J 17.3, 9.9, 7.7, 5.3, CH_2CHCH_2), 5.49 (1H, ddd, J 17.3, 10.7, 6.1, 4-H), 4.99-5.25 (5H, m, CO_2NH , 5-H, and CH_2CHCH_2), 4.44-4.52 (1H, m, 3-H), 3.88 (1H, dd, J 16.0, 5.0, CH_ACH_2), 3.70 (1H, dd, J 16.0, 7.7, CH_BCH_2), 3.35 (1H, dd, J 13.5, 6.5, 1- H_A), 3.05 - 3.15 (1H, ddt, J 13.5, 8.7, 5.5, 1- H_B), 1.81 - 1.91 (1H, m, 2- H_A), 1.71-1.80 (1H, m, 2- H_B), 1.46 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_{C} (100 MHz, CDCl_3) 156.0 (C=O), 150.0 (Ar 4-C), 146.6 (Ar 1-C), 134.9 (4-C), 134.8 (CHCH_2), 128.4 (Ar 2-C), 124.3 (Ar 3-C), 115.1 (5-C), 114.8 (CHCH_2), 79.3 ($\text{OC}(\text{CH}_3)_3$), 58.1 (2-C), 47.2 (CH_2CHCH_2), 36.8 (1-C), 32.2 (2-C), 28.5 ($\text{C}(\text{CH}_3)_3$); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3422, 3104, 2977, 2934, 1702, 1528, 1347, 1268, 1248, 1160, 1088; m/z (ESI) 448 (100%, MNa^+); Found: MNa^+ , 448.1516. $\text{C}_{19}\text{H}_{27}\text{N}_3\text{O}_6\text{S}$ requires *MNa*, 448.1513. HPLC: CHIRALPAK® IA, 5% EtOH/heptane over 30 min, 1 ml/min; $t_1 = 24.1$ min (major), $t_2 = 26.7$ min (minor).

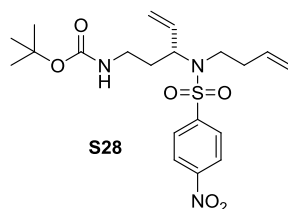
tert-Butyl-*N*-[(3*R*)-3-[(but-3-en-1-yl)amino]pent-4-en-1-yl]carbamate **17**



According to General Procedure 2, allylic carbonate **S23** (0.613 g, 2.50 mmol) was combined with but-3-en-1-amine (0.231 g, 3.25 mmol) and heated for 20 h. Purification by flash column chromatography, eluting with 8:2→1:9 petrol–EtOAc furnished amine **17** (0.375 g, 59%, *ee* 69%) as a yellow oil, R_f 0.09 (1:1 cyclohexane–EtOAc); $[\alpha]_{\text{D}}^{23} = -6.1$ ($c = 1.30$, CHCl_3); δ_{H} (400 MHz, CDCl_3) 5.79 (1 H, ddt, J 17.0, 10.2, 6.9 Hz, $\text{CH}=\text{CH}_2$), 5.67–5.51 (1 H, m, $\text{CH}=\text{CH}_2$), 5.15–5.06 (3 H, m, $\text{CH}=\text{CH}_2$), 5.04 (1 H, ddt, J 10.3, 2.3, 1.3 Hz, *cis* $\text{CH}=\text{CH}_2$), 3.24 (1 H, dq, J 13.3, 6.4 Hz, BocNHCH_2), 3.15 (1 H, dt, J 13.2, 6.4 Hz, BocNHCH_2), 3.06 (1 H, q, J 6.8 Hz, $\text{CHCH}=\text{CH}_2$), 2.70 (1 H, dt, J 11.4, 6.9 Hz, CHNHCH_2), 2.54 (1 H, dt, J 11.4, 6.7 Hz, CHNHCH_2), 2.23 (2 H, qt, J 7.0, 1.4 Hz, $\text{CH}_2\text{CH}=\text{CH}_2$), 1.62 (2 H, q, J 6.6 Hz, $\text{BocNHCH}_2\text{CH}_2$), 1.44 (9 H, s, $\text{C}(\text{CH}_3)_3$); δ_{C} (100 MHz, CDCl_3) 155.9 (C=O), 140.5 ($\text{CH}=\text{CH}_2$), 136.5 ($\text{CH}=\text{CH}_2$), 116.3 ($\text{CH}=\text{CH}_2$), 115.9 ($\text{CH}=\text{CH}_2$), 78.9 ($\text{C}(\text{CH}_3)_3$), 60.3 ($\text{CHCH}=\text{CH}_2$), 46.1 (NHCH_2CH_2), 38.2 (BocNHCH_2), 35.3 ($\text{CH}_2\text{CH}=\text{CH}_2$), 34.4 ($\text{BocNHCH}_2\text{CH}_2$), 28.4 ($\text{C}(\text{CH}_3)_3$); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3342, 3076, 2976, 2930, 1693, 1640, 1516, 1453, 1391, 1365, 1273, 1247, 1169, 1042; m/z (ESI) 277 (100%, MNa^+); Found: MNa^+ , 277.1886. $\text{C}_{14}\text{H}_{26}\text{N}_2\text{O}_2$ requires *MNa*, 277.1886.

For the purposes of chiral HPLC analysis the respective sulfonamide derivative **S28** was prepared.

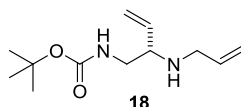
tert-Butyl-*N*-[(3*R*)-3-[*N*-(but-3-en-1-yl)-4-nitrobenzenesulfonamido]pent-4-en-1-yl]carbamate **S28**



NEt_3 (836 μl , 6.00 mmol) and 4-nitrobenzene-1-sulfonyl chloride (665 mg, 3.00 mmol) were added to a solution of amine **17** (0.508 g, 2.00 mmol) in CHCl_3 (4.0 mL). The reaction mixture was stirred at room temperature for 3 d, diluted with MeOH (5 mL), concentrated *in vacuo* and then purified by flash chromatography, eluting with 1:3→4:0 MTBE–cyclohexane to furnish sulfonamide **S28** (0.576 g, 66% yield, *ee* 69%) as a yellow oil, $[\alpha]_{\text{D}}^{22} = +166.7$, ($c = 3.30$, CHCl_3); δ_{H} (400 MHz, CDCl_3) 8.36 (2H, d, J 8.8, Ar 3-H), 8.04 (2H, d, J 8.8, Ar 2-H), 5.70 (1H, app. ddt, J 17.1, 10.3, 5.4, CH_2CHCH_2), 5.41 (1H, ddd, J 17.1, 10.8, 5.4, 4-H), 5.00-5.14 (5H, m, CO_2NH , 5-H, and CH_2CHCH_2), 4.43 (1H, dt, J 9.5, 5.4, 3-H), 3.39 (1H, dd, J 13.1, 6.5, 1- H_A), 3.23-3.02 (3H, m, 1- H_B , NCH_2CH_2), 2.55-2.44 (1 H, m, 2- H_A), 2.38-2.28 (1H, m, 2- H_B), 1.96-1.85 (1H, m, CH_ACHCH_2),

1.76-1.67 (1H, m, CH_BCHCH_2), 1.46 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_C (100 MHz, CDCl_3) 156.0 (C=O), 150.0 (Ar 4-C), 146.3 (Ar 1-C), 134.8 (4-C), 134.2 (CHCH_2), 128.4 (Ar 2-C), 124.4 (Ar 3-C), 118.9 (5-C), 117.5 (CHCH_2), 79.4 ($\text{OC}(\text{CH}_3)_3$), 57.9 (3-C), 44.4 (NCH_2), 36.9 (1-C), 35.6 (2-C), 32.4 (CH_2CHCH_2), 28.5 ($\text{C}(\text{CH}_3)_3$); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3419, 3104, 2977, 2934, 1703, 1528, 1452, 1347, 1308, 1269, 1427, 1160, 1087; m/z (ESI) 462 (100%, MNa^+); Found: MNa^+ , 462.1672. $\text{C}_{20}\text{H}_{29}\text{N}_3\text{O}_6\text{S}$ requires MNa , 462.1669. HPLC: CHIRALPAK[®] AD-H, 10% EtOH/heptane over 30 min, 1 ml/min; t_1 = 12.4 min (major), t_2 = 10.5 min (minor).

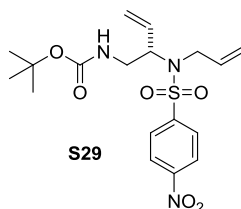
tert*-Butyl-*N*-[(2*S*)-2-[(prop-2-en-1-yl)amino]but-3-en-1-yl]carbamate **18*



According to General Procedure 2, allylic carbonate **S24** (0.648 g, 2.50 mmol) was combined with allylamine (0.244 mL, 3.25 mmol) and heated for 20 h. Purification by flash chromatography, eluting with 8:2→1:9 petrol–EtOAc) furnished amine **18** (0.350 g, 62%, *ee* 86%) as a yellow oil, R_f 0.09 (1:1 cyclohexane–EtOAc); $[\alpha]_D^{22}$ –10 (c 1.1, CHCl_3); δ_H (400 MHz, $\text{DMSO}-d_6$) 6.73 (1 H, br. s, BocNH), 5.81 (1 H, ddt, J 17.2, 10.2, 5.7 Hz, $\text{CH}=\text{CH}_2$), 5.60–5.48 (1 H, m, $\text{CH}=\text{CH}_2$), 5.11 (1 H, dq, J 17.3, 1.6 Hz, *trans* $\text{CH}=\text{CH}_2$), 5.05 (1 H, dq, J 13.4, 2.1 Hz, *cis* $\text{CH}=\text{CH}_2$), 5.00 (1 H, dd, J 10.3, 1.6 Hz, *cis* $\text{CH}=\text{CH}_2$), 3.14 (1 H, ddt, J 14.5, 5.4, 1.7 Hz, $\text{CHCH}=\text{CH}_2$), 3.03–2.87 (4 H, m, BocNHCH₂, CH₂CH=CH₂), 1.68 (1 H, br. s, NHCH₂CH=CH₂), 1.53 (1H, ddt, J 12.9, 8.0, 6.5 Hz, NHCH₂CH₂), 1.48–1.40 (1 H, m, NHCH₂CH₂), 1.37 (9 H, s, $\text{C}(\text{CH}_3)_3$); δ_C (100 MHz, $\text{DMSO}-d_6$) 155.4 (C=O), 141.3 ($\text{CH}=\text{CH}_2$), 137.8 ($\text{CH}=\text{CH}_2$), 115.1 ($\text{CH}=\text{CH}_2$), 114.8 ($\text{CH}=\text{CH}_2$), 77.3 ($\text{C}(\text{CH}_3)_3$), 58.1 ($\text{CHCH}=\text{CH}_2$), 48.9 ($\text{CH}_2\text{CH}=\text{CH}_2$), 37.1 (BocNHCH₂), 35.1 (BocNHCH₂CH₂), 28.2 ($\text{C}(\text{CH}_3)_3$); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3333, 3076, 2977, 2930, 1692, 1643, 1515, 1454, 1391, 1365, 1273, 1249, 1169, 1041, 993, 916, 864, 778; m/z (ESI) 241 (100%, MH^+); Found: MH^+ , 241.1907. $\text{C}_{13}\text{H}_{25}\text{O}_2\text{N}_2$ requires MH , 241.1911.

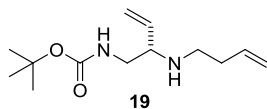
For the purposes of chiral HPLC analysis the respective sulfonamide derivative **S29** was prepared.

tert*-Butyl-*N*-[(2*S*)-2-[*N*-(prop-2-en-1-yl)4-nitrobenzenesulfonamido]but-3-en-1-yl]carbamate **S29*



NEt_3 (92.0 μL , 0.660 mmol) and 4-nitrobenzene-1-sulfonyl chloride (73.0 mg, 0.330 mmol) were added to a solution of amine **18** (50.0 mg, 0.220 mmol) in CHCl_3 (2.2 mL). The reaction mixture was stirred at room temperature for 4 h after which the reaction mixture was concentrated *in vacuo* and purified by flash chromatography, eluting with 0:1→1:3 MTBE–cyclohexane) to furnish sulfonamide **S29** (51.0 mg, 56 %, *ee* 86%) as a yellow oil, $[\alpha]_D^{19}$ = +35.3, (c = 2.55, CHCl_3); δ_H (400 MHz, CDCl_3) 8.34 (d, J = 8.8 Hz, 2H, H_{15}), 8.02 (d, J = 8.8 Hz, 2H, H_{14}), 5.77 (dddd, J = 17.2, 10.0, 7.3, 5.6 Hz, 1H, H_{11}), 5.57 (ddd, J = 17.2, 10.5, 6.3 Hz, 1H, H_7), 5.05 - 5.29 (m, 4H, H_8 and H_{12}), 4.80 (br. s., 1H, H_4), 4.51 (dd, J = 15.4, 6.6 Hz, 1H, H_6), 3.96 (dd, J = 16.2, 5.6 Hz, 1H, 5- CH_AH_B), 3.75 (dd, J = 16.0, 7.5 Hz, 1H, 5- CH_AH_B), 3.36 - 3.46 (m, 1H, 10- CH_AH_B), 3.23 - 3.34 (m, 1H, 10- CH_AH_B), 1.45 (s, 9H, H_1); δ_C (100 MHz, CDCl_3) 155.8 (C_3), 149.9 (C_{16}), 146.7 (C_{13}), 134.4 (C_7), 132.8 (C_{11}), 128.5 (C_{14}), 124.3 (C_{15}), 120.0 (C_8), 119.0 (C_{12}), 79.8 (C_2), 60.2 (C_6), 47.7 (C_{10}), 42.0 (C_5), 28.4 (C_1); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3410, 2978, 2933, 1703, 1606, 1528, 1347, 1308, 1250, 1158, 1088, 1009; m/z (ESI) 450 (100%, MK^+); Found: MK^+ , 450.1087. $\text{C}_{18}\text{H}_{25}\text{N}_3\text{O}_6\text{S}$ requires MK , 450.1096. HPLC: CHIRALPAK[®] IC, 20% EtOH/heptane over 30 min, 1 ml/min; t_1 = 14.6 min (major), t_2 = 16.3 min (minor).

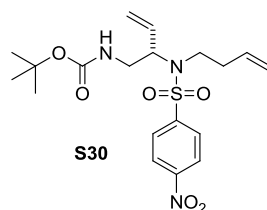
tert*-Butyl-*N*-[(2*S*)-2-[(but-3-en-1-yl)amino]but-3-en-1-yl]carbamate **19*



According to General Procedure 2, allylic carbonate **S24** (0.648 g, 2.50 mmol) was combined with but-3-en-1-amine (0.231 g, 3.25 mmol) and heated for 20 h. Purification by flash chromatography, eluting with 8:2→1:9 petrol–EtOAc) furnished amine **18** (0.324 g, 54%, *ee* 81%) as a yellow oil, R_f 0.12 (1:1 cyclohexane–EtOAc); $[\alpha]_D^{23}$ -2.7 (c 1.6, CHCl_3); δ_H (400 MHz, CDCl_3) 5.78 (1 H, ddt, $J=17.1, 10.2, 6.8$ Hz, $\text{CH}=\text{CH}_2$), 5.70–5.55 (1 H, m, $\text{CH}=\text{CH}_2$), 5.23–5.14 (2 H, m, $\text{CH}=\text{CH}_2$), 5.12–5.01 (2 H, m, $\text{CH}=\text{CH}_2$), 4.86 (1 H, br. s, BocNH), 3.23–3.02 (4 H, m, $\text{NHCHCH}=\text{CH}_2$, $\text{CH}_2\text{CH}=\text{CH}_2$), 2.71 (1 H, dt, J 11.4, 7.0 Hz, BocNHCH_2), 2.58 (1 H, dt, J 11.4, 6.6 Hz, BocNHCH_2), 2.23 (2 H, qd, J 7.0, 1.3 Hz, $\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$), 1.45 (9 H, $\text{C}(\text{CH}_3)_3$); δ_C (100 MHz, CDCl_3) 156.2 ($\text{C}=\text{O}$), 138.7 ($\text{CH}=\text{CH}_2$), 136.5 ($\text{CH}=\text{CH}_2$), 117.2 ($\text{CH}=\text{CH}_2$), 116.5 ($\text{CH}=\text{CH}_2$), 79.3 ($\text{C}(\text{CH}_3)_3$), 61.0 ($\text{CHCH}=\text{CH}_2$), 55.4 (NHCH_2CH_2), 46.2 (BocNHCH_2), 34.5 ($\text{CH}_2\text{CH}=\text{CH}_2$), 28.6 ($\text{C}(\text{CH}_3)_3$); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3341, 3077, 2977, 2929, 1695, 1641, 1501, 1455, 1391, 1365, 1270, 1249, 1167, 1043; m/z (ESI) 450 (100%, MH^+); Found: MH^+ , 241.1909. $\text{C}_{13}\text{H}_{24}\text{N}_2\text{O}_2$ requires *MH*, 241.1910.

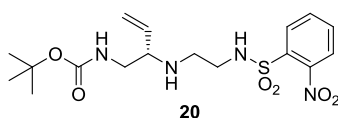
For the purposes of chiral HPLC analysis the respective sulfonamide derivative **S30** was prepared.

tert*-Butyl-*N*-[(2*S*)-2-[*N*-(but-3-en-1-yl)4-nitrobenzenesulfonamido]but-3-en-1-yl]carbamate **S30*



NEt_3 (87.0 μL , 0.620 mmol) and 4-nitrobenzene-1-sulfonyl chloride (69.0 mg, 0.310 mmol) were added to a solution of amine **19** (50.0 mg, 0.210 mmol) in CHCl_3 (2.2 mL). The reaction mixture was stirred at room temperature for 4 h after which the reaction mixture was concentrated *in vacuo* and purified by flash chromatography, eluting with 0:1→1:3 MTBE– cyclohexane) to furnish sulfonamide **S30** (82.0 mg, 93%, *ee* 88%) as a yellow oil, $[\alpha]_D^{19}$ $= +30.8$, (c = 4.10, CHCl_3); δ_H (400 MHz, CDCl_3) 8.35 (d, J = 8.8 Hz, 2H, H_{16}), 8.03 (d, J = 8.6 Hz, 2H, H_{15}), 5.70 (ddt, J = 17.2, 10.4, 6.8 Hz, 1H, H_{12}), 5.52 (ddd, J = 17.2, 10.6, 6.3 Hz, 1H, H_7), 5.04–5.21 (m, 4H, H_8 and H_{13}), 4.85 (br. s., 1H, H_4), 4.42 (dd, J = 15.2, 6.3 Hz, 1H, H_6), 3.41–3.51 (m, 1H, $5\text{-CH}_A\text{H}_B$), 3.22–3.31 (m, 2H, $5\text{-CH}_A\text{H}_B$ and $10\text{-CH}_A\text{H}_B$), 3.10 - 3.20 (m, 1H, $10\text{-CH}_A\text{H}_B$), 2.28 - 2.50 (m, 2H, H_{11}), 1.45 (s, 9H, H_1); δ_C (100 MHz, CDCl_3) 155.8 (C_3), 150.0 (C_{17}), 146.4 (C_{14}), 134.2 (C_{12}), 132.8 (C_7), 128.5 (C_{15}), 124.3 (C_{16}), 120.0 (C_8), 117.7 (C_{13}), 79.8 (C_3), 60.2 (C_6), 45.0 (C_{10}), 42.2 (C_5), 35.1 (C_{11}), 28.4 (C_1); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3412, 3105, 2978, 2933, 1706, 1528, 1347, 1309, 1249, 1157, 1088; m/z (ESI) 464 (100%, MK^+); Found: MK^+ , 464.1242. $\text{C}_{19}\text{H}_{27}\text{N}_3\text{O}_6\text{S}$ requires *MK*, 464.1252. HPLC: CHIRALPAK® AD, 10% EtOH/heptane over 30 min, 1 ml/min; t_1 = 11.4 min (major), t_2 = 13.8 min (minor).

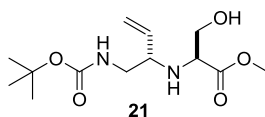
tert*-Butyl-*N*-[(2*S*)-2-[[2-(2-nitrobenzenesulfonamido)ethyl]amino]but-3-en-1-yl]carbamate **20*



According to General Procedure 1, allylic carbonate **S24** (245 mg, 1.00 mmol) was combined with *N*-(2-aminoethyl)-2-nitrobenzenesulfonamide hydrochloride^[12] (366 mg, 1.30 mmol) and K_3PO_4 (276 mg, 1.30 mmol) and heated for 20 h. The

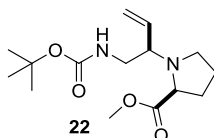
reaction mixture was not concentrated - direct purification by reverse phase chromatography (C₁₈) eluting with 5%-40% MeCN-H₂O-1% formic acid) furnished the amine **20** (254 mg, 61 %, 79% *ee*) as a yellow oil, $[\alpha]_D^{21} +0.80$ (c = 5.50, CDCl₃); δ_H (400 MHz, CDCl₃) 8.06-8.13 (1 H, m, Ar H-5), 7.80-7.86 (1 H, m, Ar H-6), 7.70-7.76 (2 H, m, Ar H-4, Ar H-3), 5.47 (1 H, ddd, *J* 17.5, 10.1, 7.3 Hz, 4-H), 5.05-5.12 (2-H, m, 5-H), 4.85 (1 H, br s, *t*BuCO₂NH), 3.07-3.15 (3 H, m, NHCH₂ and 1-H_A), 2.95-3.04 (2 H, m, 2-H and 1-H_B), 2.72-2.81 (1 H, m, CH_ANHSO₂), 2.60-2.68 (m, 1H, CH_BNHSO₂), 1.41 (9 H, s, OC(CH₃)₃); δ_C (100 MHz, CDCl₃) 156.0 (NHCO₂*t*Bu), 148.1 (Ar 2-C), 138.0 (Ar 5-C), 133.5 (Ar 4-C), 133.4 (Ar 1-C), 132.6 (Ar 6-C), 130.9 (4-C), 125.2 (Ar 3-C), 117.5 (5-C), 79.3 (OC(CH₃)₃), 60.7 (2-C), 45.3, 44.4, 43.5 (1-C, NHCH₂ or CH₂NHSO₂), 28.3 (OC(CH₃)₃); ν_{max}/cm^{-1} (neat): 3325, 3094, 2977, 2931, 1692, 1593, 1539, 1442, 1392, 1363, 1340, 1248, 1161, 1124; *m/z* (ESI) 415 (100%, MH⁺); Found: MH⁺, 415.1656. C₁₇H₂₆N₄O₆S requires *MH*, 415.1646). HPLC: CHIRALPAK[®] IA, 40% EtOH/heptane over 15 min, 1 ml/min; *t*₁ = 6.15 min (major), *t*₂ = 8.45 min (minor).

Methyl-(2*S*)-2-[[[(2*S*)-1-[[*tert*-butoxy]carbonyl]amino]but-3-en-2-yl]amino]-3-hydroxypropanoate **21**



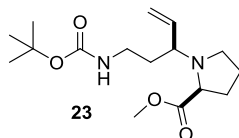
The compound was prepared from allylic carbonate **S24** using a previously reported procedure.^[6]

Methyl-(2*S*)-1-[(2*R*)-1-[[*tert*-butoxy]carbonyl]amino]but-3-en-2-yl]pyrrolidine-2-carboxylate **22**



According to General Procedure 1, allylic carbonate **S24** (0.122 g, 0.500 mmol) was combined with L-Pro-OMe•HCl (0.107 g, 0.650 mmol) and K₃PO₄ (0.138 g, 0.650 mmol) and heated for 24 h. Purification by flash chromatography, eluting with 1:1→2:8 cyclohexane-EtOAc) furnished amine **22** (0.103 g, 69%, *dr* 92:8) as a pale yellow oil, *R*_f 0.32 (2:8 cyclohexane-EtOAc); δ_H (400 MHz, CDCl₃) 5.76 (1H, ddd, *J* = 17.1, 10.4, 7.7 Hz, CH=CH₂), 5.31 (1H, br. s, BocNH), 5.22 (1H, dd, *J* = 10.4, 1.7 Hz, *cis*-CH=CH₂), 5.15 (1H, dd, *J* = 17.2, 1.7 Hz, *trans*-CH=CH₂), 3.69 (3H, s, CO₂CH₃), 3.48 (1H, dt, *J* = 9.1, 5.0 Hz, CHCO₂CH₃), 3.28–3.09 (3H, m, BocNHCH₂, CHCH=CH₂), 2.94 (1H, ddd, *J* = 8.8, 7.3, 3.7 Hz, CHNCH₂), 2.65 (1H, q, *J* = 7.9 Hz, CHNCH₂), 2.11–1.97 (1H, m, NCHCH₂CH₂), 1.95–1.68 (3H, m, CHNCH₂, CHNCH₂CH₂), 1.43 (9H, s, C(CH₃)₃); δ_C (100 MHz, CDCl₃) 175.3 (CO₂CH₃), 156.2 (CO₂*t*Bu), 134.1 (CH=CH₂), 119.2 (CH=CH₂), 79.0 (C(CH₃)₃), 62.9 (CHCO₂CH₃), 62.6 (CHCH=CH₂), 51.9 (CO₂CH₃), 46.8 (CHNCH₂), 43.0 (BocNHCH₂), 29.7 (NCHCH₂CH₂), 28.6 (C(CH₃)₃), 23.9 (NCHCH₂CH₂); ν_{max}/cm^{-1} (neat): 3392, 2976, 1705, 1499, 1390, 1365, 1246, 1166; *m/z* (ESI) 299 (100%, MH⁺); Found: MH⁺, 299.1967. C₁₅H₂₇N₂O₄ requires *MH*, 299.1971).

Methyl-(2*S*)-1-[(3*S*)-5-[[*tert*-butoxy]carbonyl]amino]pent-1-en-3-yl]pyrrolidine-2-carboxylate **23**



According to General Procedure 1, allylic carbonate **S23** (0.129 g, 0.500 mmol) was combined with L-Pro-OMe•HCl (0.107 g, 0.650 mmol) and K₃PO₄ (0.138 g, 0.650 mmol) and heated for 24 h. Purification by flash chromatography, eluting with 1:1→2:8 cyclohexane-EtOAc) furnished amine **22** (0.112 g, 72%, *dr* >95:<5) as a pale yellow oil, *R*_f 0.37 (2:8 cyclohexane-EtOAc); δ_H (400 MHz, CDCl₃) 5.74 (1H, ddd, *J* = 17.3, 10.2, 8.6 Hz, CH=CH₂), 5.66 (1H, br. s, BocNH), 5.18 (1H, dd, *J* =

10.3, 1.8 Hz, *cis*-CH=CH₂), 5.06 (1H, ddd, *J* = 17.2, 1.9, 0.8 Hz, *trans*-CH=CH₂), 3.71 (3H, s, CO₂CH₃), 3.44 (1H, dd, *J* = 9.0, 5.7 Hz, CHCO₂CH₃), 3.30–3.15 (3H, m, BocNHCH₂, CHCH=CH₂), 2.92 (1H, ddd, *J* = 8.7, 7.2, 3.6 Hz, CHNCH₂), 2.60 (1H, q, *J* = 8.1 Hz, CHNCH₂), 2.09–1.96 (1H, m, NCH₂CH₂CH₂), 1.93–1.56 (5H, m, BocNHCH₂CH₂, NCH₂CH₂CH₂, NCH₂CH₂CH₂), 1.42 (9H, s, C(CH₃)₃); δ_C (100 MHz, CDCl₃) 175.5 (CO₂CH₃), 156.4 (CO₂*t*Bu), 135.2 (CH=CH₂), 118.2 (CH=CH₂), 78.6 (C(CH₃)₃), 62.2 (CHCO₂CH₃), 60.8 (CHCH=CH₂), 51.9 (CO₂CH₃), 45.8 (CHNCH₂), 38.1 (BocNHCH₂), 33.0 (BocNHCH₂CH₂), 29.6 (NCH₂CH₂CH₂), 28.6 (C(CH₃)₃), 23.8 (NCH₂CH₂CH₂); ν_{max}/cm⁻¹ (neat): 3365, 2975, 1737, 1710, 1512, 1441, 1391, 1365, 1268, 1246, 116; *m/z* (ESI) 313 (100%, MH⁺); Found: MH⁺, 313.2115. C₁₆H₂₉N₂O₄ requires *MH*, 313.2127).

Scaffold Preparation (Schemes 3 and 4 (main text) and Scheme S1)

Experimental details for all scaffolds are organised in accordance with Scheme S1. Any deviation from the general procedures is specified.

General Procedure A

A solution of the respective alkene (1.0 eq) and aryl bromide (1.2 eq) in 1,4-dioxane (0.17 M) was added to a mixture of Pd(OAc)₂ (0.05 eq), DPE-Phos (0.10 eq) and CsCO₃ (2.5 eq) in a sealed tube under an atmosphere of nitrogen. The reaction mixture was heated to 105 °C until consumption of the alkene was observed by TLC and LCMS, and then diluted with EtOAc and filtered. The filtrate was washed with saturated aqueous NH₄Cl and the aqueous phase twice back extracted with EtOAc. The combined organic phase was dried (MgSO₄), filtered and concentrated *in vacuo* to give a crude product which was purified as specified.

Procedure B – See experimental details for preparation of **28**.

General Procedure C1

TFA was added to a solution of the respective carbamate (1.0 eq) in CH₂Cl₂ (0.1 M) at 0 °C (ice) such that the final ratio of TFA:CH₂Cl₂ was 1:3 unless otherwise stated. The mixture was stirred at room temperature until complete consumption of the carbamate was observed by TLC, and then concentrated *in vacuo*. The crude product was dissolved in THF (0.2 M) and to this was added CDI (1.5 eq) and DBU (4.0 eq). The mixture was heated at 50 °C for 18 h before concentration *in vacuo* to give a crude product which was purified as specified.

General Procedure C2

CDI (4.5 eq) was added to a solution of the amine (1.0 eq) in DMF (0.13 M) and the mixture was heated at 110 °C until complete conversion to the desired urea was observed. The reaction mixture was then concentrated *in vacuo* and purified by SCX solid phase extraction.

General Procedure C3

CDI (1.5 eq) and DBU (2.5 eq) were added to a solution of the aminoalcohol (1.0 eq) in THF (0.2 M) and the mixture stirred at 50 °C until complete conversion to the desired urea/carbamate was observed. The reaction mixture was then concentrated *in vacuo* and the material obtained purified by SCX solid phase extraction.

General Procedure D1

NEt₃ (5.0 eq) and chloroacetyl chloride or freshly procured bromoacetyl bromide (1.2 eq) were added to a solution of the respective amine (1.0 eq) in CH₂Cl₂ (0.1 M) at 0 °C (ice). The reaction mixture was stirred at room temperature until complete consumption of the amine was observed and then diluted with CH₂Cl₂ and saturated aqueous NH₄Cl. The phases were separated and the aqueous phase extracted with CH₂Cl₂ (2 ×). The combined organic phase was dried (MgSO₄), filtered and concentrated *in vacuo*. The crude material was dissolved in THF (0.07 M) and cooled to 0 °C (ice) before NaH (60% dispersion, 2.0 eq) and NaI (1.0 eq, when chloroacetyl chloride was used) were added. The mixture was stirred at room temperature for 18 h before the addition of sufficient water to quench the reaction mixture and then concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography using the eluent specified.

General Procedure D2

NEt₃ (2.0 eq) and TMSCl (1.5 eq) were added to a solution of the alcohol (1.0 eq) in CH₂Cl₂ (0.2 M) at room temperature. The reaction mixture was stirred until complete consumption of the alcohol was observed, before being cooled to 0 °C (ice) at which point further NEt₃ (2.0 eq) followed by newly procured bromoacetyl bromide (1.5 eq) were added. After 15 min the reaction mixture was warmed to room temperature and stirred until consumption of the intermediate amine was observed. 50% aqueous AcOH (10.0 eq) was then added to the reaction mixture which was stirred at room temperature for 18 h before being concentrated *in vacuo*. The crude material was dissolved in CH₂Cl₂ (0.6 M) and cooled to 0 °C (ice). To this was added *n*Bu₄NSO₄ (0.5 eq) followed by sufficient 35% aqueous NaOH such that the ratio of CH₂Cl₂–35% aq. NaOH was 1:1. After 3 h the reaction mixture was diluted with water and CH₂Cl₂, the phases separated and the aqueous phase extracted with CH₂Cl₂ (2 ×). The combined organic phase was dried (MgSO₄), filtered and concentrated *in vacuo* to give a crude product that was purified by flash column chromatography using the eluent specified.

General Procedure D3/E2

i) NEt₃ or DIPEA (1.2 eq) followed by bromoacetyl bromide or chloroacetyl chloride (1.1 eq) was added to a solution of the respective amine (1.0 eq) in CH₂Cl₂ (0.1 M) at 0 °C (ice). The reaction mixture was stirred at room temperature until complete consumption of the amine was observed and then diluted with CH₂Cl₂ and saturated aqueous NH₄Cl. The phases were separated and the aqueous phase extracted with CH₂Cl₂ (2 ×). The combined organic phase was dried (MgSO₄), filtered and concentrated *in vacuo* to give a crude product that was used immediately.

ii) The crude product was used according to General Procedure E1 and the reaction mixture was worked-up as specified to give a crude product that was used immediately.

iii) NaH (60% dispersion in oil, 2.0 eq) and NaI (1.0 eq, where chloroacetyl chloride was used only) were added to a solution of the crude product in THF (0.1 M) at room temperature. The reaction mixture was stirred at room temperature until complete conversion to product was observed, quenched by the addition of a minimum volume of water and concentrated *in vacuo* to give a crude product that was purified as specified.

General Procedure D4

NEt₃ (1.0 eq) and freshly procured bromoacetyl bromide (1.0 eq) were added to a solution of the respective amine (1.0 eq) in CH₂Cl₂ (0.05 M) at 0 °C (ice). The reaction mixture was stirred at room temperature until complete consumption of the amine was observed and then further NEt₃ (72 eq) was added. The reaction mixture was stirred at room temperature for 16 h then diluted with CH₂Cl₂ and saturated aqueous NH₄Cl. The phases were separated and the aqueous phase extracted with CH₂Cl₂ (2

×). The combined organic phase was dried (MgSO_4), filtered and concentrated *in vacuo*. The resulting crude product was purified as specified.

General Procedure E1

A solution of Grubbs Second Generation Catalyst (0.05 eq) in de-gassed CH_2Cl_2 (2.5 mM) was added dropwise over 15 min to a refluxing solution of the respective dialkene (1.0 eq) in de-gassed CH_2Cl_2 (0.03 M). The reaction mixture was then heated at reflux until complete consumption of the dialkene was observed, cooled to room temperature and then purified or used directly as specified.

General Procedure F1

TFA was added to a solution of the respective carbamate (1.0 eq) in CH_2Cl_2 (0.1 M) at 0 °C (ice) such that the final ratio of TFA: CH_2Cl_2 was 1:4. The mixture was stirred at room temperature until complete consumption of the carbamate was observed by TLC, and then concentrated *in vacuo*. The crude product was dissolved in 4:1 CH_2Cl_2 -water (0.05 M) and to this was added K_2CO_3 (6.0 eq). The reaction mixture was stirred vigorously at room temperature until consumption of the intermediate amine was observed by TLC, and then diluted with CH_2Cl_2 and water, the phases separated and the aqueous phase extracted with CH_2Cl_2 (3 ×). The combined organic phase was dried (MgSO_4), filtered and concentrated *in vacuo* to give a crude product that was purified by flash column chromatography using the eluent specified.

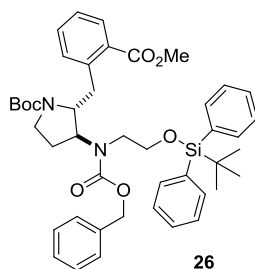
General Procedure F2

TFA was added to a solution of the respective carbamate (1.0 eq) in CH_2Cl_2 (0.1 M) at 0 °C (ice) such that the final ratio of TFA: CH_2Cl_2 was 1:1. The mixture was stirred at room temperature until complete consumption of the carbamate was observed by TLC, and then concentrated *in vacuo*. The crude product was then dissolved in THF (0.1 M) and Na_2CO_3 (2.0 eq) was added. The reaction mixture was heated at reflux for 30 min, then cooled to room temperature, filtered and concentrated *in vacuo*. The resulting crude product was purified as specified.

General Procedure F3

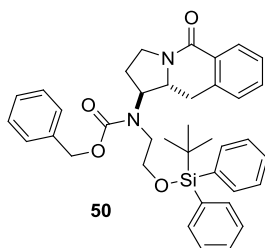
10% Pd/C (0.2 eq Pd) and ethylene diamine (1.0 eq) were added to a solution of the respective Cbz-carbamate (1.0 eq) in MeOH (0.05 M). The reaction vessel was evacuated and purged with H_2 and this process repeated 5 times. The mixture was then stirred under an atmosphere of H_2 for 18 h before being filtered and concentrated *in vacuo* to give a crude product that was passed through a plug of SiO_2 . The crude product was then dissolved in DMF (0.1 M) and to this was added Cs_2CO_3 (10.0 eq). The reaction mixture was heated at 110 °C for 8 h, filtered and concentrated *in vacuo* to give a crude product that was purified by flash column chromatography using the eluent specified.

tert*-Butyl-(2*R*,3*S*)-3-(9,9-dimethyl-3-oxo-1,8,8-triphenyl-2,7-dioxa-4-aza-8-siladecan-4-yl)-2-[[2-(methoxycarbonyl)phenyl]methyl]pyrrolidine-1-carboxylate **26*



NaHCO₃ (0.174 g, 2.07 mmol) followed by CbzCl (0.232 mL, 2.07 mmol) were added to a biphasic mixture of amine **11** (0.500 g, 1.03 mmol) in CHCl₃ (6.00 mL) and water (2.00 mL). The reaction mixture was stirred vigorously for 20 h and then diluted with CH₂Cl₂ (20 mL) and water (20 mL), the phases separated and the aqueous phase extracted with CH₂Cl₂ (2 × 20 mL). The combined organic phase was dried (MgSO₄), filtered and concentrated *in vacuo* to give a crude product that was purified by flash column chromatography, eluting with 85:15 petrol–EtOAc to furnish a dicarbamate (0.556 g) that was used immediately. Then, according to General Procedure A, the dicarbamate (0.300 g, 0.480 mmol) was combined with methyl-2-bromobenzoate (82.0 μL, 0.580 mmol), Pd(OAc)₂ (5.40 mg, 24.0 μmol), DPE-Phos (26.0 mg, 48.0 μmol) and Cs₂CO₃ (0.391 g, 1.20 mmol) and heated for 16 h. The crude product was purified by flash column chromatography, eluting with 85:15 petrol–EtOAc to furnish the pyrrolidine **26** (0.258 g, 51%, d.r. >95:5 *trans:cis*) as a colourless oil, *R*_f 0.30 (4:1 petrol–EtOAc); δ_H (500 MHz, DMSO, 353 K) 7.75 (1 H, d, *J* 7.6, Me-benzoate Ar 3-H), 7.58-7.56 (4 H, m, Si-Ar 2-H), 7.45-7.20 (14 H, m, Ar-H), 4.95 (2 H, app. s, OCH₂Ar), 4.24 (1 H, ddd, *J* 7.3, 4.9, 3.0, 3-H), 4.17 (1 H, app. dt, *J* 7.3, 7.0, 3.0, 2-H), 3.76 (3 H, s, CO₂CH₃), 3.66 (2 H, app. t, *J* 6.6, CH₂OSi), 3.63-3.58 (1 H, m, 5-H_A), 3.27-3.08 (5 H, m, 5-H_B, NCH₂, ArCH₂), 2.07-1.99 (1 H, m, 4-H_A), 1.91-1.85 (1 H, m, 4-H_B), 1.23 (9 H, s, OC(CH₃)₃), 0.98 (9 H, s, SiC(CH₃)₃); δ_C (125 MHz, DMSO, 353 K) 166.9 (CO₂CH₃), 154.4 (NHCO₂), 152.7 (NCO₂CH₂Ph), 138.6 (Me-benzoate Ar 1-C), 136.2 (Cbz Ar 1-C), 134.4 (SiAr 4-C), 132.7 (SiAr 1-C), 131.1 (Ar-C), 131.0 (Ar-C), 129.9 (Me-benzoate Ar 2-C), 129.4 (Ar-C), 129.2 (Ar-C), 127.7 (Ar-C), 127.2 (Ar-C), 127.1 (Ar-C), 126.8 (Ar-C), 125.7 (Ar-C), 78.6 and 77.8 (OC(CH₃)₃), 65.7 (OCH₂Ar), 61.8 (2-C), 61.7 (3-C), 61.6 (CH₂OSi), 51.1 (CO₂CH₃), 45.9 (NCH₂), 43.8 (5-C), 36.5 (ArCH₂), 27.9 (4-C), 27.4 (OC(CH₃)₃), 26.1 (SiC(CH₃)₃), 18.1 (SiC(CH₃)₃); ν_{max}/cm⁻¹ (neat) 2955, 1693, 1454, 1392, 1261, 1168, 1113; *m/z* (ESI) 773 (100%, MNa⁺); Found: MNa⁺, 773.3613. C₄₄H₅₄N₂O₇Si requires *MNa*, 773.3592.

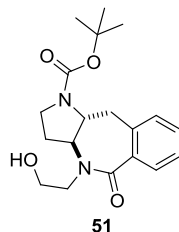
Benzyl-*N*-[(1*S*,10*aR*)-5-oxo-1*H*,2*H*,3*H*,5*H*,10*H*,10*aH*-pyrrolo[1,2-*b*]isoquinolin-1-yl]-*N*-{2-[[*tert*-butyldiphenylsilyl]oxy]ethyl}carbamate **50**



According to general procedure F1 ester **26** (0.200 g, 0.260 mmol) gave a crude product that was purified by flash column chromatography, eluting with 6:4 petrol–EtOAc to furnish the lactam **50** (0.124 g, 77%) as a colourless film, *R*_f 0.31 (1:1 petrol–EtOAc); δ_H (500 MHz, MeOD, 333 K) 7.90 (1 H, d, *J* 7.6, Me-benzoate Ar 2-H), 7.60-7.57 (4 H, m, SiAr 2-H), 7.42-7.26 (13 H, m, Ar-H), 7.06 (1 H, d, *J* 6.6, Me-benzoate Ar 5-H), 5.17-5.10 (2 H, m, OCH₂Ar), 4.38 (1 H, app. dd, *J* 18.5, 9.3, pyrrolo 3-H), 3.86-3.66 (4 H, m, CH₂OSi, pyrrolo 2-H, pyrrolo 5-H_A), 3.57-3.48 (2 H, m, pyrrolo 5-H_B, NCH_A), 3.39 (1 H, app.

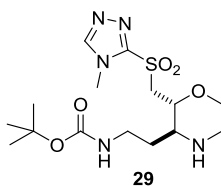
dt, J 13.5, 6.2, NCH_B), 2.88-2.85 (1 H, m, $ArCH_B$), 2.77-2.72 (1 H, m, $ArCH_A$), 2.06-2.04 (2 H, m, pyrrollo 4-H), 0.99 (9 H, s, $SiC(CH_3)_3$); δ_C (125 MHz, MeOD, 333 K) 165.6 ($ArCO$), 157.9 (NCO_2CH_2Ph), 138.8 (Me-benzoate Ar 1-C), 137.8 (Cbz Ar 1-C), 136.7 (SiAr 2-C), 136.6 (Ar-C), 134.6 (SiAr 1-C), 133.2 (Ar-C), 131.0 (Ar-C), 130.8 (Me-benzoate Ar 6-C), 129.6 (Ar-C), 129.3 (Ar-C), 128.9 (Ar-C), 128.8 (Ar-C), 128.7 (Ar-C), 128.2 (Me-benzoate Ar 2-C), 68.8 (OCH_2Ar), 63.8 (broad, pyrrollo 3-C and CH_2OSi), 58.5 (pyrrollo 2-C), 47.7 (NCH_2), 43.4 (pyrrollo 5-C), 34.2 ($ArCH_2$), 27.5 ($SiC(CH_3)_3$), 26.8 (pyrrollo 4-C), 20.0 ($SiC(CH_3)_3$); ν_{max}/cm^{-1} (neat) 2957, 1701, 1654, 1464, 1427, 1345, 1276, 1141, 1111; m/z (ESI) 619 (100%, MH^+); Found: MH^+ , 619.3009. $C_{38}H_{42}N_2O_4Si$ requires MH , 619.2987.

tert*-Butyl-(3*R*,7*S*)-8-(2-hydroxyethyl)-9-oxo-4,8-diazatricyclo[8.4.0.0^{3,7}]tetradeca-1(10),11,13-triene-4-carboxylate **51*



According to General Procedure F3, ester **26** (0.180 g, 0.24 mmol) gave a crude product that was purified by flash column chromatography, eluting with 95:4.5:0.5 DCM–EtOH– NH_3OH furnished the azepine **51** (0.032 g, 38%) as a colourless waxy solid, R_f 0.12 (95:4.5:0.5 DCM–EtOH– NH_3OH); δ_H (500 MHz, MeOD, 333 K) 7.68 (1 H, dd, J 7.6, 1.0, Ar 11-H), 7.41 (1 H, app. td, J 7.5, 1.4, Ar 12-H), 7.34 (1 H, app. td, J 7.6, 1.0, Ar 13-H), 7.15 (1 H, d, J 7.5, Ar 14-H), 4.02 (1 H, ddd, J 10.6, 8.5, 2.2, 3-H), 3.88-3.79 (2 H, m, 7-H and CH_AOH), 3.77-3.71 (2 H, m, CH_AOH and NCH_A), 3.68 (1 H, app. dd, J 11.0, 8.6, 5- H_A), 3.58 (1 H, ddd, J 13.6, 6.9, 5.5, NCH_B), 3.49 (1 H, app. d, J 16.7, 2- H_A), 3.27 (1 H, dd, J 16.7, 8.5, 2- H_B), 3.20 (1 H, app. dd, J 11.0, 5.8, 5- H_B), 2.23 (1 H, app. dtd, J 12.1, 11.1, 8.6, 6- H_A), 2.02 (1 H, app. dt, J 11.1, 5.8, 6- H_B), 1.52 (9 H, s, $OC(CH_3)_3$); δ_C (125 MHz, MeOD, 333 K) 172.6 (9-C), 157.1 (NCO_2), 138.1 (10-C), 136.7 (1-C), 132.3 (12-C), 131.0 (11-C), 130.9 (14-C), 128.1 (13-C), 81.6 ($OC(CH_3)_3$), 63.5 (3-C), 61.8 (7-C), 61.5 (CH_2OH), 47.2 (5-C), 46.1 (NCH_2), 36.9 (2-C), 28.9 ($OC(CH_3)_3$), 27.3 (6-C); ν_{max}/cm^{-1} (neat) 3423, 2974, 1692, 1622, 1396, 1340, 1126; m/z (ESI) 347 (100%, MH^+); Found: MH^+ , 347.1971. $C_{19}H_{27}N_2O_4$ requires MH , 347.1965.

tert*-Butyl-*N*-{2-[(2*R*,3*S*)-2-[(4-methyl-4*H*-1,2,4-triazol-3-yl)sulfonyl]methyl]morpholin-3-yl]ethyl}carbamate **29*



Procedure B:

i) NEt_3 (1.13 mL, 8.10 mmol), 4-nitrobenzenesulfonyl chloride (1.08 g, 4.86 mmol) and 4-dimethylaminopyridine (49.0 mg, 0.405 mmol) were added to a solution of amine **11** in CH_2Cl_2 (30.0 mL). The reaction mixture was heated to 40 °C for 16 h before being diluted with CH_2Cl_2 (30 mL), saturated aqueous NH_4Cl (30 mL) added, the phases separated, and the aqueous phase extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a crude product which was immediately dissolved in THF (30.0 mL) and AcOH (0.280 mL, 4.86 mmol) followed by TBAF (1 M in THF, 4.86 mL, 4.86 mmol) added at 0 °C (ice). The reaction mixture was allowed to warm to room temperature and then stirred for 2 h before being diluted with CH_2Cl_2 (30 mL), saturated aqueous NH_4Cl (30 mL) added, the phases separated, and the aqueous phase extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phase was dried ($MgSO_4$), filtered

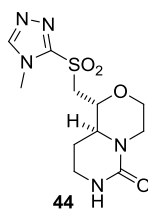
and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography, eluting with 96:3.6:0.4 DCM–EtOH–NH₄OH to furnish a primary alcohol (1.37 g, 78%) which was used immediately.

ii) NIS (1.07 g, 4.76 mmol) was added to a solution of the primary alcohol (1.36 g, 3.17 mmol) in CH₃CN (40.0 mL). The reaction mixture was heated to 65 °C for 2 h, cooled to room temperature and saturated aqueous Na₂S₂O₃ (40 mL) and CH₂Cl₂ (30 mL) added. The aqueous phase was extracted with CH₂Cl₂ (2 × 30 mL) and the combined organic phase dried (MgSO₄), filtered and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography, eluting with 7:3 petrol–EtOAc) to furnish a morpholine (1.12 g, 64%, 56:44 *dr* (trans:cis)) which was used immediately.

iii) DBU (0.650 mL, 4.38 mmol) and 4-methyl-4*H*-1,2,4-triazole-3-thiol (0.303 g, 2.63 mmol) were added to a solution of the morpholine (0.974 g, 1.75 mmol) in CH₃CN (19.0 mL). The reaction mixture was stirred at room temperature for 18 h before being concentrated *in vacuo* and purified by SCX solid phase extraction to furnish the product (0.777 g, 82%). The diastereomers were then separated by flash column chromatography, eluting with 96:3.6:0.4 DCM–EtOH–NH₄OH) to furnish *cis*- (0.266 g, 28%) and *trans*- (0.314, 33%) diastereomers.

iv) *m*CPBA (77% purity, 0.399 g, 2.30 mmol) was added to a solution of the *trans*-diastereomer (0.314 g, 0.570 mmol) in CH₂Cl₂ (3.50 mL). The reaction mixture was stirred at room temperature for 18 h before being diluted with CH₂Cl₂ (10 mL), washed with saturated aqueous Na₂S₂O₃ (10 mL) and saturated aqueous NaHCO₃ (10 mL). The organic phase was dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was dissolved in CH₃CN (5.00 mL) and thiophenol (70.0 μL, 0.680 mmol) followed by DBU (128 μL, 0.86 mmol) added. The mixture was stirred at room temperature for 18 h before being concentrated *in vacuo* to give a crude product which was purified by SCX solid phase extraction to furnish the morpholine **28** (0.176 g, 79%, 13% over the 4 steps) as a yellow waxy solid, *R*_f 0.44 (85:13.5:1.5 DCM–EtOH–NH₄OH); [α]_D²² +22 (*c.* 1.08, CHCl₃); δ_H (500 MHz, CDCl₃) 8.18 (1 H, s, Ar 3-H), 4.95 (1 H, br s, CO₂NH), 4.35 (1 H, app. dt, *J* 10.3, 2.4, 2-H), 4.11 (1 H, dd, *J* 15.1, 10.3, SO₂CH_A), 3.95 (3 H, s, NCH₃), 3.52 (1 H, dd, *J* 15.1, 2.4, SO₂CH_B), 3.61–3.57 (1 H, m, 6-H_A), 3.42–3.38 (1 H, m, 6-H_B), 2.99 (1 H, app. d, *J* 10.3, 3-H), 3.34–3.27 (1 H, m, CO₂NHCH_B), 3.18 (1 H, ddd, *J* 11.1, 9.8, 5.3, CO₂NHCH_A), 2.89 (1 H, ddd, *J* 12.3, 6.3, 3.3, 5-H_A), 2.73–2.70 (1 H, m, 5-H_B), 1.71 (1 H, app. ddd, *J* 18.8, 10.3, 5.0, CO₂NHCH₂CH_A), 1.43 (10 H, app. br s, CO₂NHCH₂CH_B and OC(CH₃)₃); δ_C (75 MHz, CDCl₃) 156.3 (NHCO₂), 151.7 (Ar 5-C), 146.6 (Ar 3-C), 79.4 (OC(CH₃)₃), 72.2 (2-C), 63.7 (6-C), 55.1 (SO₂CH₂), 53.0 (3-C), 41.9 (5-C), 36.8 (CO₂NHCH₂), 33.1 (NCH₃), 28.3 (OC(CH₃)₃ and CO₂NHCH₂CH₂); ν_{max}/cm⁻¹ (neat) 3377, 2976, 1692, 1515, 1453, 1366, 1335, 1285, 1250, 1177, 1137, 1101; *m/z* (ESI) 390 (100%, MH⁺); Found: MH⁺, 390.1805. C₁₅H₂₈N₅O₅S requires *MH*, 390.1806.

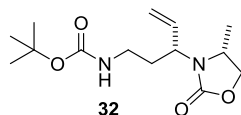
(1*R*,9*α**S*)-1-[[[4-Methyl-4*H*-1,2,4-triazol-3-yl)sulfonyl]methyl]-octahydropyrimido[4,3-*c*]morpholin-6-one **44**



According to General Procedure C1 morpholine **29** (0.156 g, 0.400 mmol) gave a crude product that was purified by SCX solid phase extraction followed by flash column chromatography, eluting with 95:5 CH₂Cl₂–saturated methanolic NH₃ to furnish urea **44** (0.065 g, 51%) as a colourless waxy solid, *R*_f 0.31 (95:5 CH₂Cl₂–saturated methanolic NH₃); [α]_D²⁸ +55 (*c.* 0.190, CH₃OH); δ_H (500 MHz, MeOD) 8.65 (1 H, s, Ar 3-H), 4.46 (1 H, ddd, *J* 11.2, 3.8, 2.7, 1-H), 4.36 (1 H, dd, *J* 15.0, 11.2, SO₂CH_A), 3.98 (3 H, s, NCH₃), 3.97–3.94 (1 H, m, 3-H_A), 3.74 (1 H, dd, *J* 15.0, 2.7, SO₂CH_B), 3.75–3.72 (1 H, m, H-9a), 3.40 (1 H, app. dt, *J* 12.1, 3.2, 3-H_B), 3.32–3.28 (1 H, under MeOD signal, 4-H_A), 3.22–3.19 (2 H, m, 8-H), 2.83 (1 H, ddd, *J* 13.2,

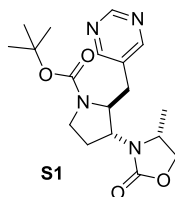
12.1, 4.1, 4-H_B), 1.98 (1 H, ddd, *J* 13.4, 9.1, 4.1, 9-H_A), 1.74 (1 H, ddd, *J* 13.4, 9.5, 5.6, 9-H_B); δ_C (125 MHz, MeOD) 159.3 (6-C), 153.5 (Ar 5-C), 149.1 (Ar 3-C), 71.1 (1-C), 60.6 (3-C), 56.8 (9a-C), 53.6 (SO₂CH₂), 43.3 (4-C), 38.8 (8-C), 34.0 (NCH₃), 25.1 (9-C); $\nu_{\max}/\text{cm}^{-1}$ (neat) 3317, 2935, 1642, 1499, 1331, 1288, 1171, 1136; *m/z* (ESI) 316 (100%, MH⁺); Found: MH⁺, 316.1070. C₁₁H₁₈N₅O₄S requires *MH*, 316.1074.

tert*-Butyl-*N*-[(3*R*)-3-[(4*R*)-4-methyl-2-oxo-1,3-oxazolidin-3-yl]pent-4-en-1-yl]carbamate **32*



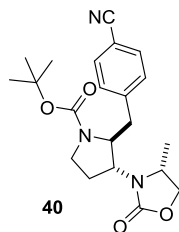
According to General Procedure C3, aminoalcohol **12** (1.00 g, 3.87 mmol) furnished cyclic carbamate **32** (0.909 g, 83%, >95:5 d.r.) as a colourless oil, *R_f* 0.4 (1:1 petrol–EtOAc); δ_H (500 MHz, CDCl₃) 5.94 (1 H, ddd, *J* 17.2, 10.4, 6.5, 4-H), 5.32-5.28 (2 H, m, 5-H), 5.23-5.16 (1 H, m, CO₂NH), 4.38 (1 H, app. t, *J* 8.4, oxazolidine 3-H_A), 4.31-4.27 (1 H, m, 3-H), 4.00-3.92 (1 H, m, oxazolidine 4-H), 3.85-3.82 (1 H, m, oxazolidine 3-H_B), 3.38 (1 H, br s, 1-H_A), 3.04 (1 H, app. dq, *J* 13.8, 7.0, 1-H_B), 1.87 (2 H, app. dd, *J* 13.5, 7.0, 2-H), 1.43 (9 H, s, OC(CH₃)₃), 1.27 (3 H, d, *J* 6.1, oxazolidine CH₃); δ_C (75 MHz, CDCl₃), 158.3 (oxazolidine 1-C), 155.9 (CO₂NH), 134.8 (4-C), 118.6 (5-C), 79.0 (OC(CH₃)₃), 69.1 (oxazolidine 3-C), 53.3 (3-C), 50.8 (oxazolidine 4-C), 36.8 (1-C), 33.0 (2-C), 28.3 (OC(CH₃)₃), 20.3 oxazolidine CH₃); $\nu_{\max}/\text{cm}^{-1}$ (neat) 3359, 2981, 1738, 1515, 1415, 1367, 1275, 1260, 1170; *m/z* (ESI) 307 (100%, MNa⁺); Found: MNa⁺, 307.1623. C₁₄H₂₄N₂O₄ requires *MNa*, 307.1628.

tert*-Butyl-(2*S*,3*R*)-3-[(4*R*)-4-methyl-2-oxo-1,3-oxazolidin-3-yl]-2-(pyrimidin-5-ylmethyl)pyrrolidine-1-carboxylate **S1*



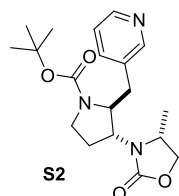
According to General Procedure A, cyclic carbamate **32** (0.150 g, 0.530 mmol) and 5-bromopyrimidine (0.100 g, 0.630 mmol) gave a crude product that was purified by flash column chromatography, eluting with 93:6:1 CH₂Cl₂–EtOH–NH₃OH to furnish pyrrolidine **S1** (0.192 g, 90% (based on 86% purity), >95:5 *dr*) as a colourless oil. A sample was further purified by mass-directed preparative HPLC (XBridge Prep C18 5 μ m OBD, 50-95% MeOH–water with 0.1% HCOOH) for the purposes of analysis, *R_f* 0.28 (93:6:1 CH₂Cl₂–EtOH–NH₃OH); δ_H (500 MHz, MeOD, 333 K) 9.02 (1 H, s, Ar 2-H), 8.68 (2 H, s, Ar 4-H), 4.39 (1 H, app. br s, pyrrolidine 2-H), 4.31 (1 H, dd, *J* 8.5, 7.8, oxazolidine 3-H_A), 3.97 (1 H, ddd, *J* 7.1, 6.0, 4.3, pyrrolidine 3-H), 3.94-3.88 (1 H, m, oxazolidine 4-H), 3.83 (1 H, dd, *J* 8.5, 5.3, oxazolidine 3-H_B), 3.73 (1 H, app. br s, pyrrolidine 5-H_A), 3.19-3.15 (1 H, m, pyrrolidine 5-H_B), 3.03 (1 H, dd, *J* 13.5, 7.3, ArCH_A), 2.97 (1 H, dd, *J* 13.5, 5.8, ArCH_B), 2.18 (1 H, app. br s, pyrrolidine 4-H_A), 2.06 (1 H, app. ddt, *J* 13.2, 8.0, 6.8, pyrrolidine 4-H_B), 1.41 (9 H, s, OC(CH₃)₃), 1.21 (3 H, d, *J* 6.1, oxazolidine CH₃); δ_C (125 MHz, MeOD, 333 K), 159.8 (oxazolidine 1-C), 159.0 (Ar 4-C), 157.6 (Ar 2-C), 156.1 (CO₂NH), 133.5 (Ar 5-C), 81.6 (OC(CH₃)₃), 70.9 (oxazolidine 3-C), 61.6 (broad, pyrrolidine 2-C), 59.3 (broad, pyrrolidine 3-C), 52.8 (oxazolidine 4-C), 46.2 (broad, pyrrolidine 5-C), 34.4 (broad, ArCH₂), 29.2 (broad, pyrrolidine 4-C), 28.2 (OC(CH₃)₃), 19.8 oxazolidine CH₃); $\nu_{\max}/\text{cm}^{-1}$ (neat) 2974, 1747, 1695, 1562, 1480, 1410, 1234, 1168, 1123, 1046; *m/z* (ESI) 307 (100%, MH⁺); Found: MH⁺, 363.2031. C₁₈H₂₆N₄O₄ requires *MH*, 363.2031.

tert*-Butyl-(2*S*,3*R*)-2-[(4-cyanophenyl)methyl]-3-[(4*R*)-4-methyl-2-oxo-1,3-oxazolidin-3-yl]pyrrolidine-1-carboxylate **40*



According to General Procedure A, cyclic carbamate **32** (0.133 g, 0.460 mmol) and 4-bromobenzonitrile (0.102 g, 0.560 mmol) gave a crude product that was purified by flash column chromatography, eluting with 96:3.6:0.4 CH₂Cl₂–EtOH–NH₃OH to furnish pyrrolidine **40** (0.142 g, 76% (based on 95% purity), >95:5 *dr*) as a colourless oil. A sample was further purified by mass-directed preparative HPLC (XBridge Prep C18 5μm OBD, 50-95% MeOH–water with 0.1% HCOOH) for the purposes of analysis, *R*_f 0.38 (95:4.5:0.5 CH₂Cl₂–EtOH–NH₃OH); δ_H (500 MHz, MeOD, 333 K) 7.64 (2 H, d, *J* 8.0, Ar 3-H), 7.44 (2 H, d, *J* 8.0, Ar 2-H), 4.37 (1 H, app. br s, pyrrolidine 2-H), 4.21–4.16 (1 H, m, oxazolidine 3-H_A), 4.00–3.95 (1 H, m, pyrrolidine 3-H), 3.81–3.75 (2 H, m, oxazolidine 4-H, oxazolidine 3-H_B), 3.72–3.67 (1 H, m, pyrrolidine 5-H_A), 3.19–3.13 (2 H, m, pyrrolidine 5-H_B, ArCH_A), 2.94 (1 H, dd, *J* 13.4, 7.9, ArCH_B), 2.11 (1 H, app. br s, pyrrolidine 4-H_A), 2.02–1.96 (1 H, m, pyrrolidine 4-H_B), 1.45 (9 H, s, OC(CH₃)₃), 1.12 (3 H, d, *J* 6.0, oxazolidine CH₃); δ_C (125 MHz, MeOD, 333 K), 156.1 (CO₂NH), 145.2 (Ar 1-C), 133.3 (Ar 3-C), 131.9 (Ar 2-C), 119.7 (C≡N), 111.6 (Ar 1-C), 81.5 (OC(CH₃)₃), 70.8 (oxazolidine 3-C), 61.8 (broad, pyrrolidine 2-C), 59.3 (broad, pyrrolidine 3-C), 52.9 (oxazolidine 4-C), 46.2 (broad, pyrrolidine 5-C), 40.0 (broad, ArCH₂), 29.6 (broad, pyrrolidine 4-C), 28.8 (OC(CH₃)₃), 19.7 (oxazolidine CH₃); ν_{max}/cm⁻¹ (neat) 2975, 2227, 1747, 1694, 1608, 1403, 1366, 1232, 1169, 1122, 1040; *m/z* (ESI) 408 (100%, MNa⁺); Found: MNa⁺, 408.1898. C₂₁H₂₇N₃O₄ requires MNa, 408.1894.

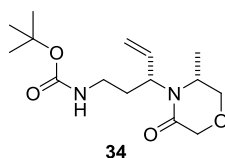
tert*-Butyl-(2*S*,3*R*)-3-[(4*R*)-4-methyl-2-oxo-1,3-oxazolidin-3-yl]-2-(pyridin-3-ylmethyl)pyrrolidine-1-carboxylate **S2*



According to General Procedure A, cyclic carbamate **32** (0.150 g, 0.530 mmol) and 3-bromopyridine (61.0 μL, 0.630 mmol) gave a crude product that was purified by flash column chromatography, eluting with 95:4.5:0.5 CH₂Cl₂–EtOH–NH₃OH to furnish pyrrolidine **S2** (0.140 g, 66% (based on 90% purity), >95:5 *d.r.*) as a colourless oil. A sample was further purified by mass-directed preparative HPLC (XBridge Prep C18 5μm OBD, 5-95% MeOH–water with 0.1% HCOOH) for the purposes of analysis, *R*_f 0.20 (95:4.5:0.5 CH₂Cl₂–EtOH–NH₃OH); δ_H (500 MHz, MeOD, 333 K) 8.47 (1 H, br s, Ar 2-H), 8.43 (1 H, br s, Ar 4-H), 7.75 (1 H, d, *J* 7.7, Ar 6-H), 7.38 (1 H, dd, *J* 7.6, 5.0, Ar 5-H), 4.38 (1 H, app. br s, pyrrolidine 2-H), 4.24 (1 H, dd, *J* 8.4, 7.6, oxazolidine 3-H_A), 3.97 (1 H, ddd, *J* 6.9, 6.3, 4.3, pyrrolidine 3-H), 3.87–3.81 (1 H, m, oxazolidine 4-H), 3.78 (1 H, dd, *J* 8.4, 5.5, oxazolidine 3-H_B), 3.73–3.68 (1 H, m, pyrrolidine 5-H_A), 3.17–3.12 (1 H, m, pyrrolidine 5-H_B), 3.06 (1 H, dd, *J* 13.5, 4.5, ArCH_A), 2.96 (1 H, dd, *J* 13.5, 7.6, ArCH_B), 2.16–2.09 (1 H, m, pyrrolidine 4-H_A), 2.01 (1 H, app. ddt, *J* 13.2, 8.1, 6.9, pyrrolidine 4-H_B), 1.44 (9 H, s, OC(CH₃)₃), 1.14 (3 H, d, *J* 6.1, oxazolidine CH₃); δ_C (125 MHz, MeOD, 333 K), 159.7 (oxazolidine 1-C), 156.1 (CO₂NH), 151.2 (Ar 2-C), 148.4 (Ar 6-C), 139.4 (Ar 4-C), 135.5 (Ar 3-C), 125.1 (Ar 5-C), 81.5 (OC(CH₃)₃), 70.8 (oxazolidine 3-C), 61.7 (broad, pyrrolidine 2-C), 59.2 (broad, pyrrolidine 3-C), 52.9 (oxazolidine 4-C), 46.2 (broad, pyrrolidine 5-C), 37.4 (broad, ArCH₂), 29.5 (broad, pyrrolidine 4-C), 28.8 (OC(CH₃)₃), 19.7 (oxazolidine CH₃);

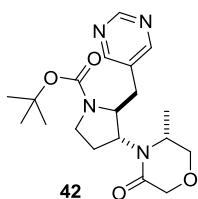
$\nu_{\max}/\text{cm}^{-1}$ (neat) 2975, 1746, 1693, 1479, 1402, 1366, 1231, 1170, 1124, 1044; m/z (ESI) 362 (100%, MH^+); Found: MH^+ , 362.2079. $\text{C}_{19}\text{H}_{27}\text{N}_3\text{O}_4$ requires MH , 362.2074.

tert*-Butyl-*N*-[(3*R*)-3-[(3*R*)-3-methyl-5-oxomorpholin-4-yl]pent-4-en-1-yl]carbamate **34*



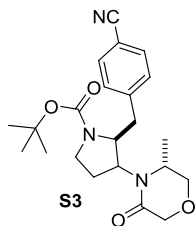
According to General Procedure D2, aminoalcohol **12** (0.500 g, 1.93 mmol) gave a crude product that was purified by flash column chromatography, eluting with 6:4 EtOAc–petrol to furnish the ketomorpholine **34** (0.368 g, 64%, >95:5 *dr*) as a colourless oil, R_f 0.18 (1:1 petrol–EtOAc); δ_{H} (500 MHz, CDCl_3) 5.98 (1 H, ddd, J 17.2, 10.4, 6.4, H-4), 5.28 (1 H, app. d, J 10.4, H-5_A), 5.27 (1 H, app. d, J 17.2, H-5_B), 5.14 (1 H, br s, CO_2NH), 4.59–4.57 (1 H, m, 3-H), 4.23 (1 H, dd, J 16.8, 9.3, morpholine 6-H_A), 4.14 (1 H, d, J 16.8, morpholine 6-H_B), 3.77–3.65 (2 H, m, morpholine 2-H), 3.52–3.50 (1 H, m, morpholine 3-H), 3.29 (1 H, app. dt, J 11.5, 5.2, 1-H_A), 3.01 (1 H, ddd, J 11.5, 8.1, 6.0, 1-H_B), 2.00 (1 H, app. ddt, J 11.6, 9.1, 5.2, 2-H_A), 1.96–1.88 (1 H, m, 1-H_B), 1.43 (9 H, s, $\text{OC}(\text{CH}_3)_3$), 1.32 (3 H, d, J 6.5, morpholine CH_3); δ_{C} (125 MHz, CDCl_3), 166.9 (morpholine 5-C), 155.8 (CO_2NH), 135.7 (4-C), 118.1 (5-C), 78.2 ($\text{OC}(\text{CH}_3)_3$), 69.4 (morpholine 2-C), 67.5 (morpholine 6-C), 56.4 (3-C), 50.4 (morpholine 3-C), 37.0 (1-C), 32.0 (2-C), 28.2 ($\text{OC}(\text{CH}_3)_3$), 18.8 (morpholine CH_3); $\nu_{\max}/\text{cm}^{-1}$ (neat) 3334, 2977, 1709, 1643, 1524, 1366, 1275, 1171; m/z (ESI) 299 (100%, MH^+); Found: MH^+ , 299.1973. $\text{C}_{15}\text{H}_{26}\text{N}_2\text{O}_4$ requires MH , 299.1965.

tert*-Butyl-(2*S*,3*R*)-3-[(3*R*)-3-methyl-5-oxomorpholin-4-yl]-2-(pyrimidin-5-ylmethyl)pyrrolidine-1-carboxylate **42*



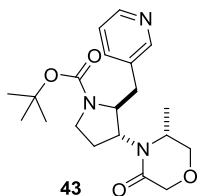
According to general procedure A ketomorpholine **34** (0.150 g, 0.500 mmol) and 5-bromopyrimidine (96.0 mg, 0.600 mmol) gave a crude product that was purified by flash column chromatography, eluting with 95:4.5:0.5 CH_2Cl_2 –EtOH– NH_3OH to furnish pyrrolidine **42** (0.180 g, 84% (based on 87% purity), >95:5 *dr*) as a colourless film. A sample was further purified by mass-directed preparative HPLC (XBridge Prep C18 5 μm OBD, 50–95% MeOH–water with 0.1% HCOOH) for the purposes of analysis, R_f 0.30 (93:6:1 CH_2Cl_2 –EtOH– NH_3OH); δ_{H} (500 MHz, MeOD, 333 K) 9.10 (1 H, s, Ar 2-H), 8.69 (2 H, s, Ar 4-H), 4.50 (1 H, br s, pyrrolidine 3-H), 4.19–4.15 (1 H, m, pyrrolidine 2-H), 4.15 (1 H, d, J 16.9, morpholine 6-H_A), 4.03 (1 H, d, J 16.9, morpholine 6-H_B), 3.78 (1 H, br s, pyrrolidine 5-H_A), 3.71 (1 H, dd, J 11.6, 1.7, morpholine 2-H_A), 3.63 (1 H, dd, J 11.6, 2.5, morpholine 2-H_B), 3.52–3.48 (1 H, m, morpholine 3-H), 3.14–3.00 (2 H, m, pyrrolidine 5-H_B and Ar CH_A), 2.94 (1 H, dd, J 13.9, 5.3, Ar CH_B), 2.10–2.08 (2 H, m, pyrrolidine 4-H), 1.41 (9 H, s, $\text{OC}(\text{CH}_3)_3$), 1.30 (3 H, d, J 6.4, morpholine CH_3); δ_{C} (125 MHz, MeOD, 333 K), 169.6 (morpholine 5-C), 159.1 (Ar 2-C), 157.6 (Ar 4-C), 156.1 (CO_2NH), 133.4 (Ar 1-C), 81.6 ($\text{OC}(\text{CH}_3)_3$), 70.5 (morpholine 2-C), 68.3 (morpholine 6-C), 62.0 (broad, pyrrolidine 2-C), 60.2 (broad, pyrrolidine 3-C), 51.3 (morpholine 3-C), 46.6 (pyrrolidine 5-C), 34.3 (broad, Ar CH_2), 28.7 ($\text{OC}(\text{CH}_3)_3$, and pyrrolidine 4-C), 19.7 (morpholine CH_3); $\nu_{\max}/\text{cm}^{-1}$ (neat) 2978, 1694, 1651, 1562, 1409, 1367, 1286, 1152, 1124, 1048; m/z (ESI) 377 (100%, MH^+); Found: MH^+ , 377.2190. $\text{C}_{19}\text{H}_{28}\text{N}_4\text{O}_4$ requires MH , 377.2183.

tert*-Butyl-(2*S*,3*R*)-2-[(4-cyanophenyl)methyl]-3-[(3*R*)-3-methyl-5-oxomorpholin-4-yl]pyrrolidine-1-carboxylate **S3*



According to General Procedure A, ketomorpholine **34** (0.153 g, 0.510 mmol) and 4-bromobenzonitrile (0.112 g, 0.620 mmol) gave a crude product that was purified by flash column chromatography, eluting with 96:3.6:0.4 CH₂Cl₂–EtOH–NH₃OH to furnish pyrrolidine **S3** (0.159 g, 63% (based on 80% purity), >95:5 *dr*) as a colourless waxy solid. A sample was further purified by mass-directed preparative HPLC (XBridge Prep C18 5µm OBD, 50-95% MeOH–water with 0.1% HCOOH) for the purposes of analysis, *R*_f 0.25 (96:3.6:0.4 CH₂Cl₂–EtOH–NH₃OH); δ_H (500 MHz, MeOD, 333 K) 7.64 (2 H, d, *J* 8.0, Ar 3-H), 7.45 (2 H, d, *J* 8.0, Ar 2-H), 4.45 (1 H, br s – under signal for residual water, pyrrolidine 3-H), 4.21-4.18 (1 H, m, pyrrolidine 2-H), 4.10 (1 H, d, *J* 16.9, morpholine 6-H_A), 3.95 (1 H, d, *J* 16.9, morpholine 6-H_B), 3.73 (1 H, app. br s, pyrrolidine 5-H_A), 3.64 (1 H, dd, *J* 11.6, 1.3, morpholine 2-H_A), 3.51 (1 H, dd, *J* 11.6, 1.9, morpholine 2-H_B), 3.43-3.39 (1 H, m, morpholine 3-H), 3.13-3.05 (2 H, m, pyrrolidine 5-H_B and ArCH_A), 3.00 (1 H, dd, *J* 13.4, 7.3, ArCH_B), 2.08-1.98 (2 H, m, pyrrolidine 4-H), 1.45 (9 H, s, OC(CH₃)₃), 1.20 (3 H, d, *J* 6.4, morpholine CH₃); δ_C (125 MHz, MeOD, 333 K), 169.4 (morpholine 5-C), 156.0 (CO₂NH), 145.2 (Ar 1-C), 133.2 (Ar 3-C), 132.0 (Ar 2-C), 119.8 (C≡N), 111.5 (Ar 4-C), 81.4 (OC(CH₃)₃), 70.4 (morpholine 2-C), 68.4 (morpholine 6-C), 62.5 (broad, pyrrolidine 2-C), 60.6 (broad, pyrrolidine 3-C), 51.6 (morpholine 3-C), 46.5 (pyrrolidine 5-C), 40.0 (broad, ArCH₂), 29.2 (broad, pyrrolidine 4-C), 28.8 (OC(CH₃)₃), 19.4 (morpholine CH₃); ν_{max}/cm⁻¹ (neat) 2974, 2226, 1696, 1652, 1396 (broad), 1151, 1124, 104; *m/z* (ESI) 422 (100%, MNa⁺); Found: MNa⁺, 422.2054. C₂₂H₂₉N₃O₄ requires MNa, 422.2231.

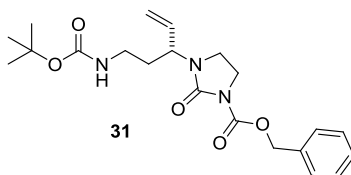
tert*-Butyl-(2*S*,3*R*)-3-[(3*R*)-3-methyl-5-oxomorpholin-4-yl]-2-(pyridin-3-ylmethyl)pyrrolidine-1-carboxylate **43*



According to General Procedure A, ketomorpholine **34** (0.159 g, 0.570 mmol) and 3-bromopyridine (66.0 µL, 0.680 mmol) gave a crude product that was purified by flash column chromatography, eluting with 95:4.5:0.5 CH₂Cl₂–EtOH–NH₃OH to furnish pyrrolidine **43** (0.150 g, 61% (based on 87% purity), >95:5 *dr*) as a colourless oil. A sample was further purified by mass-directed preparative HPLC (XBridge Prep C18 5µm OBD, 5-95% MeOH–water with 0.1% HCOOH) for the purposes of analysis, *R*_f 0.17 (95:4.5:0.5 CH₂Cl₂–EtOH–NH₃OH); δ_H (500 MHz, MeOD, 333 K) 8.45 (1 H, s, Ar 2-H), 8.41 (1 H, app. br s, Ar 6-H), 7.75 (1 H, d, *J* 7.4, Ar 6-H), 7.36 (1 H, dd, *J* 7.4, 4.9, Ar 5-H), 4.46 (1 H, br s – under signal for residual water, pyrrolidine 3-H), 4.21-4.17 (1 H, m, pyrrolidine 2-H), 4.11 (1 H, d, *J* 16.9, morpholine 6-H_A), 3.98 (1 H, d, *J* 16.9, morpholine 6-H_B), 3.74 (1 H, app. br s, pyrrolidine 5-H_A), 3.65 (1 H, dd, *J* 11.6, 1.6, morpholine 2-H_A), 3.54 (1 H, dd, *J* 11.6, 2.4, morpholine 2-H_B), 3.46-3.42 (1 H, m, morpholine 3-H), 3.05-3.01 (3 H, m, pyrrolidine 5-H_B and ArCH₂), 2.05-2.02 (2 H, m, pyrrolidine 4-H), 1.44 (9 H, s, OC(CH₃)₃), 1.23 (3 H, d, *J* 6.4, morpholine CH₃); δ_C (125 MHz, MeOD, 333 K), 169.5 (morpholine 5-C), 156.1 (CO₂NH), 151.3 (Ar 2-C), 148.3 (Ar 6-C), 139.5 (Ar 3-C), 135.6 (1-C), 125.1 (Ar 5-C), 81.5 (OC(CH₃)₃), 70.5 (morpholine 2-C), 68.4 (morpholine 6-C), 62.0 (broad, pyrrolidine 2-C), 60.5 (broad, pyrrolidine 3-C), 51.6 (morpholine 3-C), 46.6 (pyrrolidine 5-C), 37.0 (broad, ArCH₂), 28.8 (OC(CH₃)₃), 28.5 (pyrrolidine 4-C), 19.5 (morpholine

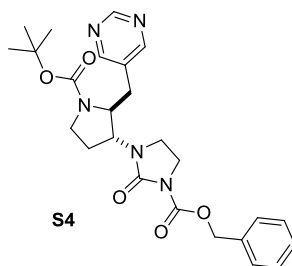
CH₃); $\nu_{\max}/\text{cm}^{-1}$ (neat) 2976, 1688, 1652, 1426, 1402, 1367, 1166, 1123; m/z (ESI) 376 (100%, MH⁺); Found: MH⁺, 376.2236. C₂₀H₂₉N₃O₄ requires *MH*, 376.2231.

Benzyl-3-[(3*R*)-5-[(*tert*-butoxy)carbonyl]amino]pent-1-en-3-yl]-2-oxoimidazolidine-1-carboxylate **31**

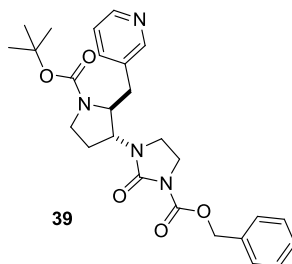


According to General Procedure C2 amine **13** (0.569 g, 1.51 mmol) furnished urea **31** (0.453 g, 74%) as a colourless oil, R_f 0.29 (1:1 petrol–EtOAc); $[\alpha]_D^{26} +65$ (c. 0.36, CHCl₃); δ_H (500 MHz, MeOD, 333 K) 7.42-7.28 (5 H, m, Ar-H), 5.83 (1 H, ddd, J 17.5, 10.3, 6.1, 2-H), 5.24-5.20 (4 H, m, 1-H, OCH₂Ar), 4.45-4.40 (1 H, m, 3-H), 3.87-3.83 (2 H, m, imidazolidine 4-H), 3.43-3.34 (2 H, m, imidazolidine 5-H), 3.11 (1 H, app. dt, J 13.3, 6.6, 5-H_A), 3.01 (1 H, app. dt, J 13.3, 7.3, 5-H_B), 1.85-1.80 (2 H, m, 4-H), 1.42 (OC(CH₃)₃); δ_C (125 MHz, MeOD, 333 K) 158.3 (CO₂NH), 155.8 (imidazolidine 2-C), 153.4 (ArCH₂OCO₂), 137.4 (Ar 1-C), 136.4 (2-C), 129.6 (Ar-C), 129.3 (Ar-C), 129.2 (Ar-C), 117.9 (1-C), 80.2 (OC(CH₃)₃), 68.8 (OCH₂Ar), 53.8 (3-C), 42.2 (imidazolidine 4-C), 38.5 (5-C), 38.3 (imidazolidine 5-C), 32.0 (4-H), 28.8 (OC(CH₃)₃); $\nu_{\max}/\text{cm}^{-1}$ (neat) 3362, 2975, 1774, 1701, 1509, 1389, 1250, 1165; m/z (ESI) 426 (100%, MNa⁺); Found: MNa⁺, 426.2004. C₂₁H₂₉N₃O₅ requires *MNa*, 426.2000.

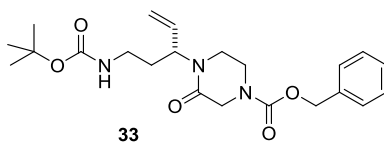
Benzyl-3-[(2*S*,3*R*)-1-[(*tert*-butoxy)carbonyl]-2-(pyrimidin-5-ylmethyl)pyrrolidin-3-yl]-2-oxoimidazolidine-1-carboxylate **S4**



According to General Procedure A, urea **31** (0.100 g, 0.248 mmol) and 5-bromopyrimidine (47.0 mg, 0.297 mmol) gave a crude product that was purified by flash column chromatography, eluting with 93.25:6:0.75 DCM–EtOH–NH₃OH to furnish pyrrolidine **S4** (0.046 g, 37% (based upon 81% purity), >95:5 *dr*) as a colourless film. A sample was further purified by mass-directed preparative HPLC (XBridge Prep C18 5 μ m OBD, 50-95% MeOH–water with 0.1% HCOOH) for the purposes of analysis, R_f 0.27 (93.25:6:0.75 DCM–EtOH–NH₃OH); δ_H (500 MHz, MeOD, 333 K) 8.99 (1 H, s, Ar 2-H), 8.69 (2 H, s, Ar 4-H), 7.41-7.30 (5 H, m, Ar-H), 5.23 (2 H, s, OCH₂Ar), 4.32 (1 H, app. td, J 6.0, 4.2, pyrrolidine 3-H), 4.09 (1 H, app. td, J 5.9, 4.4, pyrrolidine 2-H), 3.84-3.74 (2 H, m, imidazolidine 4-H), 3.66 (1 H, app. dt, J 10.9, 8.2, pyrrolidine 5-H_A), 3.42 (1 H, ddd, J 9.4, 8.6, 6.6, imidazolidine 5-H_A), 3.34 (1 H, app. dd, J 9.4, 6.2, imidazolidine 5-H_A), 3.22-3.15 (1 H, m, pyrrolidine 5-H_B), 3.05 (1 H, dd, J 13.6, 5.9, ArCH_A), 2.95 (1 H, dd, J 13.6, 5.9, ArCH_B), 2.11 (1 H, app. br s, pyrrolidine 4-H_A), 2.02 (1 H, ddd, J 13.6, 8.2, 6.2, pyrrolidine 4-H_B), 1.40 (OC(CH₃)₃); δ_C (125 MHz, MeOD, 333 K) 159.0 (Ar 4-C), 157.6 (Ar 2-C), 156.0 (*t*BuCO₂N), 155.6 (imidazolidine 2-C), 153.3 (ArCH₂OCO₂), 137.3 (Cbz Ar 1-C), 133.3 (Ar 5-C), 129.6 (Cbz Ar-C), 129.4 (Cbz Ar-C), 129.2 (Cbz Ar-C), 81.8 (OC(CH₃)₃), 68.8 (OCH₂Ar), 57.8 (broad, pyrrolidine 3-C), 55.9 (broad, pyrrolidine 2-C), 46.2 (pyrrolidine 5-C), 42.2 (imidazolidine 4-C), 39.3 (imidazolidine 5-C), 34.0 (broad, ArCH₂), 28.7 (OC(CH₃)₃), 27.6 (pyrrolidine 4-C); $\nu_{\max}/\text{cm}^{-1}$ (neat) 2974, 1775, 1684, 1362, 1259, 1212; m/z (ESI) 504 (100%, MNa⁺); Found: MNa⁺, 504.2223. C₂₅H₃₁N₅O₅ requires *MNa*, 504.2217.

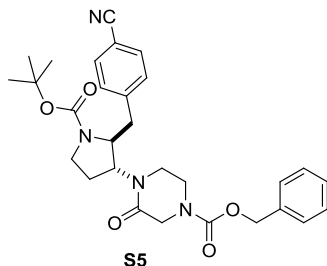
Benzyl-3-[(2*S*,3*R*)-1-[(*tert*-butoxy)carbonyl]-2-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-2-oxoimidazolidine-1-carboxylate **39**

According to General Procedure A, urea **31** (0.149 g, 0.370 mmol) and 3-bromopyridine (43.0 μ L, 0.440 mmol) gave a crude product that was purified by flash column chromatography, eluting with 95:4.5:0.5 DCM–EtOH–NH₃OH to furnish pyrrolidine **39** (0.085 g, 45% (based upon 96% purity), >95:5 *dr*) as a colourless film. A sample was further purified by mass-directed preparative HPLC (XBridge Prep C18 5 μ m OBD, 5–95% MeOH–water with 0.1% HCOOH) for the purposes of analysis, *R_f* 0.20 (93.25:6:0.75 DCM–EtOH–NH₃OH); δ_{H} (500 MHz, MeOD, 333 K) 8.45 (2 H, br s, Ar 2-H, Ar 6-H), 7.74 (1 H, d, *J* 7.4, Ar 4-H), 7.40–7.30 (6 H, Cbz Ar-H, Ar 5-H), 5.22 (2 H, s, OCH₂Ar), 4.34 (1 H, app. td, *J* 6.3, 4.4, pyrrolidine 3-H), 4.08 (1 H, app. dt, *J* 6.3, 4.9, pyrrolidine 2-H), 3.77 (1 H, app. td, *J* 10.0, 6.0, imidazolidine 4-H_A), 3.69 (1 H, app. td, *J* 10.0, 6.6, imidazolidine 4-H_B), 3.66–3.61 (1 H, m, pyrrolidine 5-H_A), 3.37 (1 H, ddd, *J* 9.7, 8.9, 6.7, imidazolidine 5-H_A), 3.29–3.25 (1 H, m, imidazolidine 5-H_B), 3.19–3.09 (1 H, m, pyrrolidine 5-H_B), 3.00 (1 H, app. br s, ArCH₂), 2.06–1.93 (2 H, m, 4-H), 1.43 (OC(CH₃)₃); δ_{C} (125 MHz, MeOD, 333 K) 155.9 (*t*BuCO₂N and imidazolidine 2-C), 153.3 (ArCH₂OCO₂), 151.0 (Ar 2-C), 148.1 (Ar 6-C), 139.5 (Ar 4-C), 137.3 (Cbz Ar 1-C), 129.7 (Ar 3-C), 129.6 (Cbz Ar-C), 129.3 (Cbz Ar-C), 129.2 (Cbz Ar-C), 125.2 (Ar 5-C), 81.6 (OC(CH₃)₃), 68.8 (OCH₂Ar), 61.9 (broad, pyrrolidine 3-C), 57.9 (broad, pyrrolidine 2-C), 46.2 (pyrrolidine 5-C), 42.1 (imidazolidine 4-C), 39.3 (imidazolidine 5-C), 34.0 (broad, ArCH₂), 28.8 (OC(CH₃)₃), 27.7 (pyrrolidine 4-C); ν_{max} /cm⁻¹ (neat) 2974, 1775, 1684, 1387, 1362, 1259, 1164, 1114; *m/z* (ESI) 503 (100%, MNa⁺); Found: MNa⁺, 503.2270. C₂₆H₃₂N₅O₅ requires *MNa*, 503.2265.

Benzyl-4-[(3*R*)-5-[[(*tert*-butoxy)carbonyl]amino]pent-1-en-3-yl]-3-oxopiperazine-1-carboxylate **33**

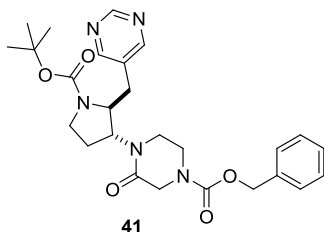
According to General Procedure D1, amine **13** (0.500 g, 1.32 mmol) gave a crude product that was purified by flash column chromatography, eluting with 96:3.6:0.4 CH₂Cl₂–EtOH–NH₃OH to furnish ketopiperazine **33** (0.399 g, 72%) as a yellow oil, *R_f* 0.20 (1:1 petrol–EtOAc); $[\alpha]_{\text{D}}^{24}$ +47 (*c.* 0.95, CHCl₃); δ_{H} (500 MHz, MeOD, 333 K) 7.37–7.28 (5 H, m, Ar H), 5.82 (1 H, ddd, *J* 17.2, 10.6, 5.7, 2-H), 5.24 (1 H, dd, *J* 10.6, 1.3, 1-H_A), 5.22 (1 H, dd, *J* 17.2, 1.3, 1-H_B), 5.16 (2 H, s, OCH₂Ar), 5.10–5.05 (1 H, m, 3-H), 4.17 (1 H, d, *J* 17.9, piperazine 2-H_A), 4.10 (1 H, d, *J* 17.9, piperazine 2-H_B), 3.75 (1 H, ddd, *J* 13.4, 5.9, 4.5, piperazine 5-H_A), 3.61 (1 H, ddd, *J* 13.4, 6.4, 4.8, piperazine 5-H_B), 3.34–3.28 (2 H, m (under residual solvent signal), piperazine 6-H), 3.08 (1 H, ddd, *J* 12.1, 7.4, 5.6, 5-H_A), 3.00–2.94 (1 H, m, 5-H_B), 1.86–1.76 (2 H, m, 4-H), 1.42 (9 H, s, OC(CH₃)₃); δ_{C} (125 MHz, MeOD, 333 K), 168.0 (piperazine 3-C), 158.3 (ArCH₂OCO₂), 156.3 (CO₂NH), 137.8 (Ar 1-C), 136.5 (2-C), 129.6 (Ar-C), 129.2 (Ar-C), 129.0 (Ar-C), 118.3 (1-C), 80.2 (OC(CH₃)₃), 68.8 (OCH₂Ar), 54.3 (3-C), 48.6 (piperazine 2-C), 42.4 (piperazine 6-C), 42.0 (piperazine 5-C), 38.4 (5-C), 31.4 (4-C), 28.9 (OC(CH₃)₃); ν_{max} /cm⁻¹ (neat) 3355, 2977, 1704, 1645, 1516, 1427, 1366, 1327, 1240, 1172, 1123; *m/z* (ESI) 440 (100%, MNa⁺); Found: MNa⁺, 440.2158. C₂₂H₃₁N₃O₅ requires *MNa*, 440.2156.

Benzyl-4-[(2*S*,3*R*)-1-[(*tert*-butoxy)carbonyl]-2-[(4-cyanophenyl)methyl]pyrrolidin-3-yl]-3-oxopiperazine-1-carboxylate **S5**



According to General Procedure A, ketopiperazine **33** (0.070 g, 0.167 mmol) and 4-bromobenzonitrile (36.0 mg, 0.200 mmol) gave pyrrolidine **S5** (0.113 g, 64% (based upon 50% purity), <95:5 *dr*) as a yellow oil. A sample was purified by mass-directed preparative HPLC (XBridge Prep C18 5 μ m OBD, 50-95% MeOH–water with 0.1% HCOOH) for the purposes of analysis, R_f 0.35 (95:4.5:0.5 CH₂Cl₂–EtOH–NH₃OH); δ_H (500 MHz, MeOD, 333 K) 7.60 (2 H, d, *J* 8.0, Ar 3-H), 7.42 (2 H, d, *J* 8.0, Ar 2-H), 7.37-7.30 (5 H, Cbz Ar-H), 5.17 (1 H, d, *J* 15.2, OCHAAr), 5.14 (1 H, d, *J* 15.2, OCHBAr), 4.91 (1 H, app. td, *J* 7.4, 5.0, pyrrolidine 3-H), 4.04 (1 H, app. dt, *J* 8.1, 5.0, pyrrolidine 2-H), 3.99 (1 H, d, *J* 18.0, piperazine 2-HA), 3.94 (1 H, d, *J* 18.0, piperazine 2-HB), 3.70-3.66 (1 H, m, pyrrolidine 5-HA), 3.53 (2 H, app. t, *J* 5.4, piperazine 5-H), 3.26 (1 H, app. dt, *J* 12.3, 5.3, pyrrolidine 5-HB), 3.20-3.09 (3 H, m, piperazine 6-H, ArCHA), 2.92 (1 H, dd, *J* 13.2, 7.9, ArCHB), 1.95-1.88 (2 H, m, pyrrolidine 4-H), 1.46 (9 H, s, OC(CH₃)₃); δ_C (125 MHz, MeOD, 333 K) 167.1 (piperazine 3-C), 156.1 (ArCH₂OCO₂ and CO₂NH), 144.9 (Ar 1-C), 137.8 (CbzAr 1-C), 133.2 (Ar 3-C), 131.8 (Ar 2-C), 129.6 (Cbz Ar-C), 129.3 (Cbz Ar-C), 129.0 (Cbz Ar-C), 119.8 (C \equiv N), 111.6 (Ar 4-C), 68.8 (OCH₂Ar), 52.5 (piperazine 2-C), 42.7 (piperazine 6-C), 42.3 (piperazine 5-C), 28.8 (OC(CH₃)₃), 27.6 (pyrrolidine 4-C). Signals not observed (rotameric): (OC(CH₃)₃), pyrrolidine 2-C, pyrrolidine 3-C, pyrrolidine 5-C, ArCH₂; $\nu_{\max}/\text{cm}^{-1}$ (neat) 2972, 2226, 1687, 1649, 1393, 1364, 1235, 1164, 1115; *m/z* (ESI) 541 (100%, MNa⁺); Found: MNa⁺, 541.2426. C₂₉H₃₄N₄O₅ requires MNa, 541.2602.

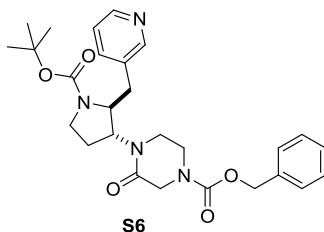
Benzyl-4-[(2*S*,3*R*)-1-[(*tert*-butoxy)carbonyl]-2-(pyrimidin-5-ylmethyl)pyrrolidin-3-yl]-3-oxopiperazine-1-carboxylate **41**



According to General Procedure A, ketopiperazine **33** (60.0 mg, 0.140 mmol) and 5-bromopyrimidine (27.0 mg, 0.170 mmol) gave a crude product that was purified by flash column chromatography, eluting with 95:4.5:0.5 CH₂Cl₂–EtOH–NH₃OH to furnish pyrrolidine **41** (57.0 mg, 63% (based upon 78% purity), >95:5 *dr*) as a colourless oil. A sample was further purified by mass-directed preparative HPLC (XBridge Prep C18 5 μ m OBD, 50-95% MeOH–water with 0.1% HCOOH) for the purposes of analysis, R_f 0.28 (95:4.5:0.5 CH₂Cl₂–EtOH–NH₃OH); δ_H (500 MHz, MeOD, 333 K) 8.97 (1 H, s, Ar 2-H), 8.67 (2 H, s, Ar 4-H), 7.37-7.30 (5 H, m, Cbz Ar-H), 5.15 (1 H, s, OCH₂Ar), 4.91 (1 H, app. td, *J* 7.3, 5.3, pyrrolidine 3-H), 4.09-4.00 (3 H, m, pyrrolidine 2-H and piperazine 2-H), 3.71 (1 H, app. br s, pyrrolidine 5-H_A), 3.65 (1 H, ddd, *J* 13.3, 6.5, 4.0, piperazine 5-H_A), 3.57 (1 H, ddd, *J* 13.3, 6.8, 4.0, piperazine 5-H_B), 3.35 (1 H, ddd, *J* 12.3, 6.8, 4.0, piperazine 6-H_A), 3.23 (1 H, ddd, *J* 12.3, 6.5, 4.0, piperazine 6-H_B), 3.14-3.09 (1 H, m, pyrrolidine 5-H_B), 3.05-2.98 (2 H, m, OCH₂Ar), 2.01-1.94 (2 H, m, pyrrolidine 4-H), 1.43 (9 H, s, OC(CH₃)₃); δ_C (125 MHz, MeOD, 333 K) 167.9 (piperazine 3-C), 159.0 (Ar 4-C), 157.7 (Ar 2-C), 156.2 (ArCH₂OCO₂), 156.0 (CO₂NH), 137.8 (Cbz Ar 1-C), 133.2 (Ar 5-C), 129.6 (Cbz Ar-C), 129.3 (Cbz Ar-C), 129.0 (Cbz Ar-C), 81.8 (OC(CH₃)₃), 68.8 (OCH₂Ar), 61.0 (broad, pyrrolidine 2-C), 58.6 (broad, pyrrolidine 3-C), 48.6 (piperazine 2-C), 46.2

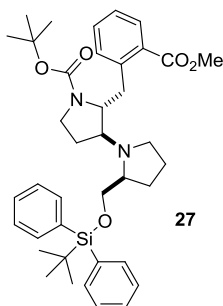
(broad, pyrrolidine 5-C), 42.6 (piperazine 6-C), 42.4 (piperazine 5-C), 33.9 (ArCH₂), 28.7 (OC(CH₃)₃), 27.3 (pyrrolidine 4-C); $\nu_{\max}/\text{cm}^{-1}$ (neat) 2973, 1687, 1649, 1560, 1393, 1364, 1234, 1164, 1118, 1049; m/z (ESI) 518 (100%, MNa⁺); Found: MNa⁺, 518.2375. C₂₆H₃₃N₅O₅ requires MNa, 518.2374.

Benzyl-4-[(2*S*,3*R*)-1-[(*tert*-butoxy)carbonyl]-2-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-3-oxopiperazine-1-carboxylate **S6**



According to General Procedure A, ketopiperazine **33** (0.174 g, 0.416 mmol) and 3-bromopyridine (48.0 μL , 0.500 mmol) gave a crude product that was purified by flash column chromatography, eluting with 95:4.5:0.5 CH₂Cl₂–EtOH–NH₃OH to furnish pyrrolidine **S6** (0.124 g, 60% (based upon 91% purity), >95:5 *dr*) as a colourless oil. A sample was further purified by mass-directed preparative HPLC (XBridge Prep C18 5 μm OBD, 50–95% MeOH–water with 0.1% HCOOH) for the purposes of analysis – a 3:1 mixture of diastereomers was obtained due to close-running impurities. Major diastereomer characterised, R_f 0.31 (95:4.5:0.5 CH₂Cl₂–EtOH–NH₃OH); δ_{H} (500 MHz, MeOD, 333 K) 8.44 (1 H, br s, Ar 2-H), 8.35 (1 H, br s, Ar 4-H), 7.71 (1 H, d, J 7.6, Ar 6-H), 7.37–7.34 (6 H, Cbz Ar-H, Ar 5-H), 5.14 (1 H, s, OCH₂Ar), 4.92 (1 H, app. td, J 7.4, 5.3, pyrrolidine 3-H), 4.05–3.94 (3 H, m, pyrrolidine 2-H and piperazine 2-H), 3.68 (1 H, app. br s, pyrrolidine 5-H_A), 3.58–3.50 (2 H, m, piperazine 5-H), 3.29–3.25 (1 H, m, piperazine 6-H_A), 3.16 (1 H, ddd, J 12.3, 6.5, 4.2, piperazine 6-H_B), 3.10–3.06 (2 H, m, pyrrolidine 5-H_B, OCH_AAr), 2.93 (1 H, dd, J 13.6, 7.5, OCH_BAr), 1.95–1.91 (2 H, m, pyrrolidine 4-H), 1.45 (9 H, s, OC(CH₃)₃); δ_{C} (125 MHz, MeOD, 333 K) 167.8 (piperazine 3-C), 156.1 (ArCH₂OCO₂), 155.9 (*t*BuCO₂N), 151.2 (Ar 2-C), 148.4 (Ar 6-C), 139.3 (Ar 4-C), 137.8 (Cbz Ar 1-C), 135.3 (Ar 3-C), 129.6 (Cbz Ar-C), 129.3 (Cbz Ar-C), 129.0 (Cbz Ar-C), 125.0 (Ar 5-C), 81.7 (OC(CH₃)₃), 68.8 (OCH₂Ar), 61.2 (broad, pyrrolidine 2-C), 58.8 (broad, pyrrolidine 3-C), 48.5 (piperazine 2-C), 46.1 (broad, pyrrolidine 5-C), 42.7 (piperazine 6-C), 42.4 (piperazine 5-C), 33.9 (ArCH₂), 28.8 (OC(CH₃)₃), 27.5 (pyrrolidine 4-C); $\nu_{\max}/\text{cm}^{-1}$ (neat) 2974, 1685, 1649, 1422, 1392, 1364, 1322, 1234, 1165, 1119, 1051; m/z (ESI) 495 (100%, MH⁺); Found: MH⁺, 495.2612. C₂₇H₃₄N₄O₅ requires MH, 495.2602.

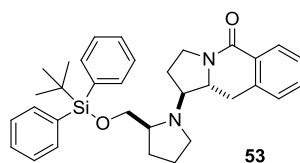
tert-Butyl-(2*R*,3*S*)-3-[(2'*S*)-2'-{[(*tert*-butyldiphenylsilyl)oxy]methyl}pyrrolidin-1'-yl]-2-[[2-(methoxycarbonyl)phenyl]methyl]pyrrolidine-1-carboxylate **27**



According to General Procedure A, amine **14** (0.200 g, 0.382 mmol) and methyl 2-bromobenzoate (108 mg, 0.5 mmol) gave a crude product that was purified by flash column chromatography, eluting with 30:70→50:50 Et₂O–pentane to furnish pyrrolidine **27** (0.208 g, 83%, >95:5 *dr*) as a yellow oil; R_f 0.15 (70:30, pentane–Et₂O); δ_{H} (500 MHz; DMSO; 353 K) 7.72 (1H, d, J 6.7, Ar 3-H), 7.61 (4H, d, J 6.4, silyloxy Ar H), 7.47–7.37 (7H, m, silyloxy Ar H and Ar 5-H), 7.29 (1H, t, J 7.2, Ar 4-

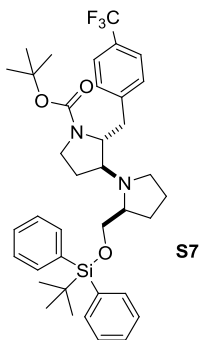
H), 7.21 (1H, d, J 7.4, Ar 6-H), 4.12 (1H, br s, 2-H), 3.79 (3H, s, OMe), 3.38 (2H, br s,), 3.27 (1H, br s, CH_AOSi), 3.14 (1H, ddd, J 10.6, 9.6 and 3.5, CH_BOSi), 3.08 (2H, br s, 5'-H_B and 5-H_A), 2.88 (1H, br s, CH_AAr), 2.81-2.77 (1H, m, CH_BAr), 2.72 (1H, br s, 5-H_A), 2.22 (1H, br s, 5-H_B), 2.05-1.95 (1H, m, 3'-H_A), 1.73-1.63 (3H, m, 4-H₂ and 3'-H_B), 1.56 (2H, br s, 3-H), 1.19 (9H, br s, OC(CH₃)₃), 1.00 (9H, s, SiC(CH₃)₃); δ_c (125 MHz; DMSO *d*₆; 353 K) 167.5 (CO₂Me), 153.3 (NHCO₂), 135.1 (TBDPS Ar 2-C), 133.6 (TBDPS Ar 1-C), 133.5 (Ar 2-C), 131.7 (Ar 1-C), 131.4 (Ar 6-C), 129.8 (Ar 5-C), 129.6, 129.5 (TBDPS 4-C), 127.7 (Ar 4-C), 126.1 (Ar 3-C), 77.9 (OC(CH₃)₃), 66.7 (SiOCH₂), 61.9 (NCH), 61.1 (CH₂Ar), 51.7 (OCH₃), 49.5 (5'-C), 44.6 (5-C), 27.9 (OC(CH₃)₃ and 4'-C), 27.7 (4-C), 26.7 (SiC(CH₃)₃), 23.3 (3'-C), 18.8 (SiC(CH₃)₃); $\nu_{\max}/\text{cm}^{-1}$ (film) 3426, 2963, 2519, 2235, 2071, 1720, 1674, 1404, 1366, 1275, 1261, 1115; m/z (ES⁺) 657.4 (100%, [M+H]⁺); found 657.3707, C₃₉H₅₂N₂O₅Si requires *MH* 657.3718.

(1S,10aR)-1-[(2S)-2-[[*tert*-Butyldiphenylsilyl]oxy]methyl]pyrrolidin-1-yl]-1H,2H,3H,5H,10H,10aH-pyrrolo[1,2-b]isoquinolin-5-one **53**



According to General Procedure F1, *N*-Boc-pyrrolidine **27** (70.0 mg, 0.110 mmol) gave a crude product that was purified by flash column chromatography, eluting with 7:3 EtOAc–petrol to furnish the lactam **53** (0.035 g, 61%) as a colourless film, R_f 0.15 (1:1 petrol–EtOAc); δ_H (500 MHz, CDCl₃) 8.03 (1 H, dd, J 7.4, 1.0, Ar 2-H), 7.63-7.58 (4 H, SiAr 3-H), 7.39-7.28 (6 H, SiAr-H), 7.21 (2 H, app. t, J 7.4, Ar 5-H, Ar 4-H), 7.05 (1 H, d, J 7.4, Ar 3-H), 3.68-3.63 (1 H, m, 7-H_A), 3.45 (1 H, ddd, J 12.0, 10.2, 8.1, 7-H_B), 3.40 (1 H, br s, SiOCH_A), 3.39 (1 H, br s, SiOCH_B), 3.25-3.14 (2 H, m, 1-H, 9-H), 3.02-3.00 (1 H, m, 2-H_A), 2.95-2.92 (2 H, m, pyrrolidine 2-H, pyrrolidine 5-H_A), 2.70 (1 H, app. dd, J 16.2, 11.6, pyrrolidine 5-H_B), 2.63 (1 H, app. dd, J 15.8, 8.3, 2-H_B), 1.95-1.89 (2 H, m, 8-H_A, pyrrolidine 3-H_A), 1.81-1.75 (3 H, m, pyrrolidine 3-H_B, pyrrolidine 4-H), 1.66-1.58 (1 H, 8-H_B), 1.03 (9 H, s, SiC(CH₃)₃); δ_c (75 MHz, CDCl₃) 163.4(ArCO), 137.2 (Ar 1-C), 135.6 (SiAr 2-C), 133.7 (SiAr 1-C), 131.5 (SiAr 2-C), 130.2 (Ar 6-C), 129.7 (SiAr 3-C), 127.6 (Ar 4-C), 127.3 (Ar 3-C), 127.2 (Ar 5-C), 127.0 (Ar 2-C), 68.4 (1-C), 67.5 (SiOCH₂), 60.6 (pyrrolidine 2-C), 58.2 (9-C), 52.5 (7-C), 42.3 (ArCH₂), 34.4 (pyrrolidine 5-C), 28.5 (8-C), 26.9 (SiC(CH₃)), 24.9 (pyrrolidine 3-C), 23.9 (pyrrolidine 4-C), 19.2 (SiC(CH₃)₃); $\nu_{\max}/\text{cm}^{-1}$ (neat) 2954, 1639, 1469, 1427, 1360, 1117, 1065; m/z (ESI) 525 (100%, MH⁺); Found: MH⁺, 525.2942. C₃₃H₄₀N₂O₂Si requires *MH*, 525.2932.

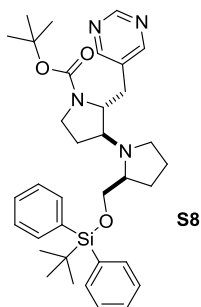
tert*-Butyl-(2R,3S)-3-[(2S)-2-[[*tert*-butyldiphenylsilyl]oxy]methyl]pyrrolidin-1-yl]-2-[[4-(trifluoromethyl)phenyl]methyl]pyrrolidine-1-carboxylate **S7*



According to General Procedure A, amine **14** (0.200 g, 0.382 mmol) and 4-bromobenzenetrifluoride (112.5 mg, 0.5 mmol) gave a crude product that was purified by flash column chromatography, eluting with 20:80 EtOAc–Petrol to furnish pyrrolidine **S7** (0.210 g, 83%, >95:5 *dr*) as a yellow oil; R_f 0.24 (20:80, EtOAc–petrol); δ_H (500 MHz; DMSO-*d*₆; 343 K)

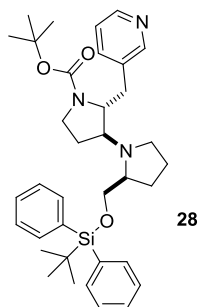
7.61-7.58 (4H, m, silyloxy Ar H), 7.56 (2H, d, *J* 8, Ar 3-H), 7.47-7.38 (6H, m, silyloxy Ar H), 7.33 (2H, d, *J* 8, Ar 2-H), 3.91 (1H, ap t, *J* 6.7, 2'-H), 3.35-3.28 (2H, m, 5'-H_A and CH_AOSi), 3.21 (1H, dd, *J* 9.8 and 7.3, CH_BOSi), 3.10-3.04 (2H, m, 5'-H_B and 5-H_A), 2.86-2.77 (2H, m, benzylic H_A and 5-H_B), 2.69 (1H, dd, *J* 13.1 and 8.3, benzylic H_B), 2.64-2.58 (1H, m, 2-H), 2.17 (1H, ap dt, *J* 8.6 and 8, 3'-H), 1.89 (1H, br s, 4'-H_A), 1.70-1.62 (3H, m, 4'-H_B, 3 or 4-H), 1.57-1.51 (2-H, m, 3 and 4-H), 1.33 (9H, s, OC(CH₃)₃), 0.98 (9H, s, SiC(CH₃)₃); δ_C (125 MHz; DMSO; 343 K) 153.3 (NHCO₂), 143.5 (Ar 4-C), 135.1, 135.0, 133.4, 129.9, 129.7, 129.6, 127.7, 124.9, 124.5 (q, *J* 280), 78.3 (OC(CH₃)₃), 66.5 (SiOCH₂), 61.6 (NCH), 61.2 (CH₂Ar), 59.6 (1'-C), 49.9 (5-C), 49.1 (5-C), 28.1 (4-C), 27.5 (SiC(CH₃)₃ and 4'-C), 23.2 (3'-C), 18.8 (SiC(CH₃)₃); ν_{max}/cm⁻¹ (film) 2967, 2859, 2305, 1892, 1758, 1687, 1618, 1399, 1326, 1262, 1166, 1111, 1067; *m/z* (ES⁺) 667.4 (100%, [M+H]⁺); found 667.3568, C₃₈H₄₉F₃N₂O₃Si requires *MH* 667.3537.

tert*-Butyl-(2*R*,3*S*)-3-[(2*S*)-2-[[*tert*-butyldiphenylsilyloxy]methyl]pyrrolidin-1-yl]-2-(pyrimidin-5-ylmethyl)pyrrolidine-1-carboxylate **S8*



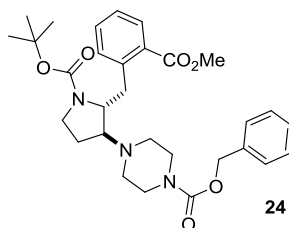
According to General Procedure A, amine **14** (0.200 g, 0.382 mmol) and 5-bromopyrimidine (79.5 mg, 0.5 mmol) gave a crude product that was purified by flash column chromatography, eluting with 20:80 EtOAc–Petrol to furnish pyrrolidine **S8** (0.121 g, 53%, >95:5 *dr*) as a yellow oil; *R_f* 0.11 (20:80, EtOAc—petrol); δ_H (500 MHz; DMSO-*d*₆; 353 k) 8.98 (1H, s, Ar 1-H), 8.54 (2H, s, Ar 4 and 6-H), 7.64-7.59 (4H, m, silyloxy Ar H), 7.47-7.38 (6H, m, silyloxy Ar H), 3.92 (1H, ap t, *J* 6.2, 2-H), 3.43 (1H, dd, *J* 10.1 and 4.6, CH_AOSi), 3.35 (1H, dt, *J* 9.6 and 8.8, 5-H_A), 3.31 (1H, dd, *J* 10.1 and 7.2, CH_BOSi), 3.11-3.01 (2H, m, 3-H, 5-H_B), 2.83 (1H, ddd, *J* 11.9, 6.2 and 3.2, 5'-H_A), 2.80-2.74 (1H, m, 2'-H), 2.70 (2H, d, *J* 6.1, benzylic H₂), 2.29-2.23 (1H, m, 5'-H_B), 1.95-1.86 (1H, m, 4-H_A), 1.74-1.63 (3H, m, 4-H_B, 3' or 4-H₂), 1.61-1.55 (2H, m, 3' or 4-H₂), 1.29 (9H, s, OC(CH₃)₃), 1.01 (9H, s, SiC(CH₃)₃); δ_C (125 MHz; DMSO; 353 K) 157.2 (pyr 2-C), 156.4 (NHCO₂), 153.3 (4- and 6-C), 135.1 (Ar 2-C), 134.5 (Ar 1-C), 133.5 (pyr 1-C), 133.4 (Ar 3-C), 132.1 (Ar 4-C), 129.6 (Ar 4-C), 127.7 (Ar 3-C), 78.5 (OC(CH₃)₃), 66.9 (CH₂OSi), 61.6 (2-C), 60.7 (2'-C), 50.3 (5-C), 44.6 (5'-C), 33.8 (CH₂Ar), 28.0 (OC(CH₃)₃), 27.7 (3-C), 27.5 (3'-C), 26.8 (4-C), 24.1 (SiC(CH₃)₃), 18.7 (SiC(CH₃)₃); ν_{max}/cm⁻¹ (film) 2965, 2932, 2064, 1688, 1561, 1473, 1410, 1366, 1275, 1262, 1169, 1113; *m/z* (ES⁺) 601.4 (100%, MH⁺); found 601.3592, C₃₅H₄₈N₄O₃Si requires *MH* 601.3568.

tert*-Butyl-(2*R*,3*S*)-3-[(2*S*)-2-[(*tert*-butyldiphenylsilyloxy)methyl]pyrrolidin-1-yl]-2-(pyridin-3-ylmethyl)pyrrolidine-1-carboxylate **28*

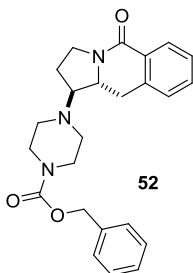


According to General Procedure A, amine **14** (0.150 g, 0.287 mmol) and 3-bromopyridine (33.0 μ L, 0.340 mmol) gave a crude product that was purified by flash column chromatography, eluting with 1:1 cyclohexane–EtOAc to furnish pyrrolidine **28** (96.0 mg, 56%, >95:5 *dr*) as a yellow oil, R_f 0.21 (1:1 cyclohexane–EtOAc); δ_H (500 MHz, MeOD, 333 K) 8.35–8.32 (2 H, m, Ar 2-H, Ar 6-H), 7.66–7.64 (4 H, silyloxy Ar 3-H), 7.57 (1 H, app. br s, Ar 4-H), 7.44–7.37 (6 H, m, silyloxy Ar), 7.27 (1 H, app. dd, J 7.2, 5.3, Ar 5-H), 4.00 (1 H, app. t, J 5.8, *N*-Boc pyrrolidine 2-H), 3.41–3.30 (3 H, m, pyrrolidine 2-H, SiOCH₂), 3.14–3.10 (2 H, m, pyrrolidine 5-H), 2.89–2.85 (1 H, m, *N*-Boc pyrrolidine 5-H_A), 2.81 (1 H, br s, ArCH_A), 2.72–2.67 (2 H, m, *N*-Boc pyrrolidine 3-H, ArCH_B), 2.22 (1 H, app. dd, J 16.3, 8.0, *N*-Boc pyrrolidine 5-H_B), 1.92–1.87 (1 H, m, pyrrolidine 3-H_A), 1.79–1.69 (3 H, m, pyrrolidine 3-H_B, pyrrolidine 4-H), 1.65–1.59 (2 H, *N*-Boc pyrrolidine 4-H), 1.39 (9 H, s, OC(CH₃)₃), 1.04 (9 H, s, SiC(CH₃)₃); δ_C (125 MHz, MeOD, 333 K) 156.0 (*t*BuCO₂N), 151.1 (Ar 2-C), 148.2 (Ar 6-C), 139.1 (Ar 4-C), 136.8 (SiAr 4-C), 135.2 (Ar 3-C), 135.0 (SiAr 1-C), 130.9 (SiAr 2-C), 128.8 (SiAr 3-C), 125.0 (Ar 5-C), 81.1 (OC(CH₃)₃), 68.3 (SiOCH₂), 66.5 (broad, pyrrolidine 2-C), 63.7 (broad, *N*-Boc pyrrolidine 3-C), 62.9 (broad, *N*-Boc pyrrolidine 2-C), 52.1 (pyrrolidine 5-C), 46.5 (broad, *N*-Boc pyrrolidine 5-C), 38.2 (broad, ArCH₂), 29.2 (pyrrolidine 3-C), 28.9 (OC(CH₃)₃), 27.6 (SiC(CH₃)₃), 24.5 (pyrrolidine 4-C), 20.1 (SiC(CH₃)₃), signal for *N*-Boc pyrrolidine 4-C not observed; $\nu_{\max}/\text{cm}^{-1}$ (neat) 2960, 1688, 1455, 1390, 1363, 1104, 1027; m/z (ESI) 600 (100%, MH⁺); Found: MH⁺, 600.3631. C₃₆H₅₀N₃O₃Si requires *MH*, 600.3616.

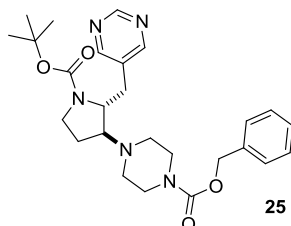
Benzyl-4-[(2*R*,3*S*)-1-[(*tert*-butoxy)carbonyl]-2-[[2-(methoxycarbonyl)phenyl]methyl]pyrrolidin-3-yl]piperazine-1'-carboxylate **24**



According to General Procedure A, amine **15** (0.281 g, 0.69 mmol) and methyl 2-bromobenzoate (195 mg, 0.91 mmol) gave a crude product that was purified by flash column chromatography, eluting with 95:5 CHCl₃–MeOH to furnish pyrrolidine **24** (0.310 g, 84%, >95:5 *dr*) as a yellow oil; R_f 0.3 (30:70, Et₂O—pentane); δ_H (500 MHz; C₆D₆; 333 K) 7.79 (1H, d, J 7.8, Ar 3-H), 7.25–6.89 (7H, m, Cbz and Ar 4 and 6-H), 6.93 (1H, ap t, J 8, Ar 5-H), 5.07 (2H, s, Cbz), 4.29 (1H, br s, 2-H), 3.52 (3H, s, OMe), 3.55–3.06 (8H, br m, 2'-H, 5-H_{AB} and benzylic H_{AB}), 2.75 (1H, br s, 3-H), 2.16–1.95 (4H, m, 3'-H), 1.67 (1H, br s, 4-H_A), 1.52 (1H, br s, 4-H_B), 1.34 (9H, s, OC(CH₃)₃); δ_C (75 MHz; C₆D₆) 154.9 (NHCO₂), 153.9 (NHCO₂), 137.6 (1-C), 132.2 (2-C), 131.5 (Ar 1-C), 130.5 (Ar 3-C), 128.5 (Ar 4-C), 128.1 (Ar 5-C), 126.0 (Ar 6-C), 78.5 (OC(CH₃)₃), 66.9 (2-C), 53.0 (OCH₃), 51.3 (pip 3-C), 49.4 (pip 2-C), 44.2 (5-C), 29.8 (ArCH₂), 28.3 (OC(CH₃)₃), 25.8 (4-C); $\nu_{\max}/\text{cm}^{-1}$ (film) 2973, 1694, 1433, 1393, 1244; m/z (ES⁺) 538.3 (100%, MH⁺; found 538.2920, C₃₀H₃₉N₃O₆ requires *MH* 538.2912.

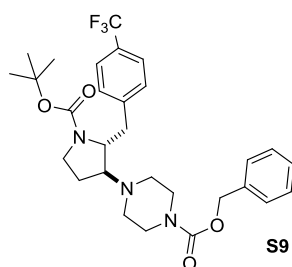
Benzyl-4-[(1*S*,10*aR*)-5-oxo-1*H*,2*H*,3*H*,5*H*,10*H*,10*aH*-pyrrolo[1,2-*b*]isoquinolin-1-yl]piperazine-1-carboxylate **52**

According to General Procedure F1, methyl ester **24** (100 mg, 0.186 mmol) gave a crude product that was purified by flash column chromatography, eluting with CH₂Cl₂—MeOH (95:5) to furnish lactam **52** (51 mg, 68%) as a foam. *R*_f 0.55 (95:5, CH₂Cl₂—MeOH); δ_H (500 MHz; CDCl₃) 8.03 (1H, dd, *J* 7.6 and 1, 7-H), 7.41 (1H, td, *J* 7.5 and 1.3, 9-H) 7.36-7.30 (1H, m, 8-H and Cbz), 7.19 (1H, d, *J* 7.5, 10-H), 5.14 (2H, s, Cbz) 3.82-3.76 (2H, m, 3-H_A and 1-H), 3.63 (1H, ddd, *J* 12.4, 9.5 and 8, 3-H_B), 3.58-3.50 (4H, m, 1'-H), 3.13 (1H, dd, *J* 15.3 and 3.9, 12-H_A), 3.05 (1H, ddd, *J* 10, 8.9 and 6.9, 13-H), 2.87 (1H, dd, *J* 14.5 and 14, 12-H_B), 2.61 (4H, br s, 2'-H), 2.10 (1H, ddd, *J* 12.5, 7.6, 7.6 and 2.6, 2-H_A), 1.9 (1H, dq, *J* 12.5 and 9.7, 2-H_B); δ_C (125 MHz; CDCl₃) 163.6 (9-C), 155.2 (NHCO₂), 137.1 (Ar 1-C), 136.7 (3-C), 131.7 (5-C), 130.2, 128.5, 128.1, 127.9, 127.6, 127.24, 127.22, 71.5 (CH₂Ar), 67.2 (13-C), 57.2 (1-C), 50.2 (pip 3-C), 44.1 (11-C), 42.7 (pip 2-C), 34.9 (2-C), 23.5 (12-C); ν_{max}/cm⁻¹ (film) 2950, 2888, 1698, 1650, 1465, 1432, 1243; *m/z* (ES⁺) 406.2 (100%, MH⁺); found 406.2131, C₂₄H₂₇N₃O₃ requires *MH* 406.2125.

Benzyl-4-[(2*R*,3*S*)-1-[(*tert*-butoxy)carbonyl]-2-(pyrimidin-5-ylmethyl)pyrrolidin-3-yl]piperazine-1-carboxylate **25**

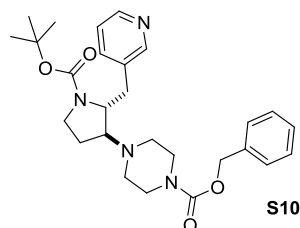
According to General Procedure A, amine **15** (0.908 g, 2.25 mmol) and 5-bromopyrimidine (467 mg, 2.93 mmol) gave a crude product that was purified by flash column chromatography, eluting with 95:5 CH₂Cl—MeOH to furnish pyrrolidine **25** (0.870 g, 80%, >95:5 *dr*) as a yellow oil; *R*_f 0.1 (50:50, Et₂O—pentane); δ_H (500 MHz; C₆D₆; 333K; *very broad*) 9.61 (1H, s, py), 8.41 (2H, s, py), 7.27-7.21 (2H, m, Cbz), 7.15-7.09 (2H, m, Cbz), 7.08-7.03 (1H, m, Cbz), 5.10 (2H, s, Cbz), 3.80 (1H, br s, 2-H), 3.51-3.01 (6H, m, 1'-H, and 5-H_{AB}), 2.74 (1H, br s, benzylic H_A), 2.57 (1H, br s, benzylic H_B), 2.33 (1H, dd, *J* 10.7 and 5.9, 3-H), 1.91-1.80 (4H, m, 3'-H), 1.39 (9H, s, OC(CH₃)₃), 1.27-1.21 (1H, m, 4-H_A), 1.08 (1H, br s, 4-H_B); δ_C (125 MHz; C₆D₆) 158.9 (pyr 2-C), 157.6 (NHCO₂), 157.5 (NHCO₂), 154.9 (pyr 4 or 6-C), 154.4 (pyr 4 or 6-C), 137.5 (Ar 1-C), 131.7 (pyr 5-C), 128.5, 128.2, 128.2, 128.1, 127.9, 127.7, 79.3 (OC(CH₃)₃), 67.1 (ArCH₂O), 49.3 (3-C), 45.5 (pip 3-C), 44.1 (pip 2-C), 43.6 (5-C), 29.8 (ArCH₂), 28.3 (OC(CH₃)₃), 24.1 (4'-C); ν_{max}/cm⁻¹ (film) 2977, 2280, 1693, 1409, 1275, 1245; *m/z* (ES⁺) 482.3 (100%, MH⁺); found 482.2775, C₂₆H₃₅N₅O₄ requires *MH* 482.2762.

Benzyl-4-[(2R,3S)-1-[(*tert*-butoxy)carbonyl]-2-{[4-(trifluoromethyl)phenyl]methyl}pyrrolidin-3-yl]piperazine-1-carboxylate S9



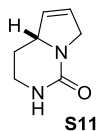
According to General Procedure A, amine **15** (0.287 g, 0.71 mmol) and 4-bromobenzotrifluoride (209 mg, 0.93 mmol) gave a crude product that was purified by flash column chromatography, eluting with 95:5 CHCl₃–MeOH to furnish pyrrolidine **S9** (0.287 g, 74%, >95:5 *dr*) as a yellow oil; *R*_f 0.44 (95:5, CHCl₃–MeOH); δ_H (500 MHz; DMSO-*d*₆; 353 K) 7.61 (2H, d, *J* 8.2, Ar 3-H), 7.41 (2H, d, *J* 8.2, Ar 2-H), 7.37-7.27 (5H, m, Cbz), 5.06 (2H, s, Cbz), 3.97 (1H, ddd, *J* 7.5, 5.4 and 2.2, 2-H), 3.43 (1H, dd, 5-H_A), 3.30 (4H, app t, *J* 5, 2'-H), 3.09 (1H, ddd, *J* 14.1, 7.4 and 7.4), 2.92 (1H, dd, *J* 13.7 and 4.8, benzylic H_A), 2.91-2.89 (1H, m, 3-H), 2.83 (1H, dd, *J* 13.7 and 7.6, benzylic H_B), 2.30-2.20 (4, m, 3'-H), 1.91-1.82 (2H, m, 4-H_{AB}), 1.38 (9H, s, OC(CH₃)₃); δ_C (125 MHz; DMSO-*d*₆; 353 K) 154.4 (NHCO₂), 153.2 (NHCO₂), 143.5 (Ar 1-C), 137.0 (Ar 1-C), 130.1, 128.3, 127.7, 127.4, 124.8 (q, *J* 3.8), 78.5 (OC(CH₃)₃), 66.1 OCH₂Ar, 59.8 (3'-C), 54.7 (pip 2-C), 48.8 (2'-C), 44.8 (pip 3-C), 43.8 (ArCH₂), 28.1 (OC(CH₃)₃), 24.8 (4'-C); ν_{max}/cm⁻¹ (film) 2976, 1694, 1393, 1275, 1260; *m/z* (ES⁺) 548.3 (100%, [M+H]⁺); found 548.2737, C₂₉H₃₆F₃N₃O₄ requires *MH* 548.2731.

Benzyl-4-[(2R,3S)-1-[(*tert*-butoxy)carbonyl]-2-(pyridin-3-ylmethyl)pyrrolidin-3-yl]piperazine-1-carboxylate S10



According to General Procedure A, amine **15** (1.02 g, 2.53 mmol) and 3-bromopyridine (0.290 mL, 3.04 mmol) gave a crude product that was purified by flash column chromatography, eluting with 9:1 EtOAc–MeOH to furnish pyrrolidine **S10** (0.764 g, 63%, >95:5 *dr*) as a yellow oil, *R*_f 0.20 (9:1 EtOAc–MeOH); δ_H (500 MHz, MeOD, 333 K) 8.40-8.38 (2 H, m, Ar 2-H, Ar 6-H), 7.68 (1 H, d, *J* 6.9, Ar 4-H), 7.36-7.27 (6 H, m, Ar 5-H, Cbz Ar-H), 5.09 (2 H, s, OCH₂Ar), 4.06 (1 H, ddd, *J* 7.5, 5.4, 2.3, pyrrolidine 2-H), 3.54-3.53 (1 H, m, pyrrolidine 5-H_A), 3.07 (4 H, app. t, *J* 5.1, piperazine 2-H and 6-H), 3.19-3.15 (1 H, m, pyrrolidine 5-H_B), 2.96 (2 H, app. br s, pyrrolidine 3-H, CH_AAr), 2.84 (1 H, dd, *J* 13.4, 7.7, CH_BAr), 2.38-2.29 (4 H, m, piperazine 3-H and 5-H), 1.95 (2 H, app. br s, pyrrolidine 4-H), 1.41 (9 H, s, OC(CH₃)₃); δ_C (125 MHz, MeOD, 333 K) 156.9 (*t*BuCO₂N), 156.0 (ArCH₂OCO₂), 151.2 (Ar 2-C), 148.3 (Ar 6-C), 139.3 (Ar 4-C), 138.2 (Cbz Ar 1-C), 136.2 (Ar 3-C), 129.5 (Cbz Ar-C), 129.1 (Cbz Ar-C), 128.9 (Cbz Ar-C), 125.0 (Ar 5-C), 81.3 (OC(CH₃)₃), 68.4 (OCH₂Ar), 61.5 (broad, pyrrolidine 2-C and 3-C), 50.5 (piperazine 3-C and 5-C), 46.4 (broad, pyrrolidine 5-C), 45.1 (piperazine 2-C and 6-C), 38.0 (broad, CH₂Ar), 28.8 (OC(CH₃)₃), 26.1 (pyrrolidine 4-C); ν_{max}/cm⁻¹ (neat) 2971, 1685, 1423, 1390, 1240, 1168, 1113, 1012; *m/z* (ESI) 481 (100%, MH⁺); Found: MH⁺, 481.2816. C₂₇H₃₆N₄O₄ requires *MH*, 481.2809.

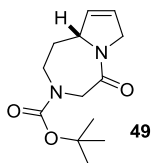
(4aR)-1H,2H,3H,4H,4aH,7H-pyrrolo[1,2-c]pyrimidin-1-one S11



i) General Procedure C1 was followed using amine **16** (48.0 mg, 0.200 mmol) with the following deviations: For the deprotection, a 1:1 ratio of TFA/DCM was used. Upon reaction completion, the reaction mixture was diluted with CH₂Cl₂ (5 mL) and aqueous NaOH (1 M) (until aqueous phase was at pH 12). The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (3×3 mL). The combined organic phase was dried (MgSO₄) and concentrated *in vacuo*. For the urea formation, 1.2 eq CDI and 2.0 eq DBU were used to give a crude product that was used immediately.

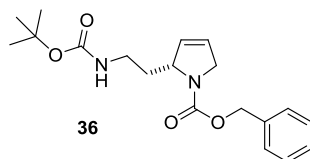
ii) According to General Procedure E1 a crude product was obtained that was purified by flash column chromatography, eluting with 100:0→95:5 CH₂Cl₂–MeOH) to furnish urea **S11** (24 mg, 67 %) as a brown oil; *R*_f 0.51 (9:1 CH₂Cl₂–MeOH); [α]_D²¹ –80 (*c* 0.80, CHCl₃); δ_H (400 MHz, CDCl₃) 5.88 (1 H, d, *J* 6.3 Hz, CH=CH), 5.78 (1 H, d, *J* 6.6 Hz, CH=CH), 5.20 (1 H, br. s, NH), 4.49 (1 H, dd, *J* 15.3, 5.31 Hz, NCH₂), 4.43–4.29 (1 H, m, NCH), 4.10 (1 H, ddd, *J* 15.3, 4.0, 2.0 Hz, NCH₂), 3.33 (2 H, d, *J* 8.3 Hz, NHCH₂), 2.09 (1 H, dd, *J* 12.3, 3.2 Hz, NHCH₂CH₂), 1.49 (1 H, qd, *J* 11.9, 7.8 Hz, NHCH₂CH₂); δ_C (100 MHz, CDCl₃) 155.7 (C=O), 129.1 (CH=CH), 127.1 (CH=CH), 62.5 (NCH), 53.7 (NCH₂), 40.2 (NHCH₂), 27.3 (NHCH₂CH₂); ν_{max}/cm⁻¹ (neat) 3299, 3079, 2933, 1635, 1502, 1467, 1417, 1346, 1291, 1222, 1179, 1116, 1068; *m/z* (EI) 138 (100%, M⁺); Found: M⁺, 138.0787. C₇H₁₀ON₂ requires *MH*, 138.0793.

tert*-Butyl-(9aR)-5-oxo-1H,2H,3H,4H,5H,7H,9aH-pyrrolo[1,2-d][1,4]diazepine-3-carboxylate **49*



According to General Procedure D1 where NEt₃ and chloroacetyl chloride was used, amine **16** (42.0 mg, 0.170 mmol) gave a crude product that was purified by flash column chromatography, eluting with 55:45 *n*-hexane–petrol to furnish a ketodiazepine that was used immediately according to General Procedure E1. The reaction was complete after 6 h, cooled to room temperature loaded directly onto a silica column, eluting with 4:1 CH₂Cl₂–Et₂O to give dihydro-pyrrole **49** (0.021 g, 48%) as a yellow oil, *R*_f 0.19 (4:1 CH₂Cl₂–Et₂O); [α]_D²⁶ –16 (*c* 0.22, CHCl₃); δ_H (500 MHz, MeOD, 333 K) 5.87 (1 H, app. dq, *J* 6.5, 2.0, pyrrole 3-H), 5.74 (1 H, ddd, *J* 6.5, 4.2, 2.1, pyrrole 4-H), 4.72 (1 H, app. dqd, *J* 8.4, 4.2, 2.0, pyrrole 2-H), 4.26 (1 H, ddd, *J* 16.6, 4.5, 2.1, pyrrole 5-H_A), 4.24 (1 H, d, *J* 15.9, diazepine 3-H_A), 4.15 (1 H, app. ddt, *J* 16.6, 4.2, 2.0, pyrrole 5-H_B), 4.03 (1 H, br s, diazepine 5-H_A), 3.98 (1 H, d, *J* 15.9, diazepine 3-H_B), 3.28 (1 H, br s, diazepine 5-H_B), 2.01 (1 H, app. d, *J* 14.0, diazepine 6-H_A), 1.61 (1 H, app. dtd, *J* 14.0, 11.2, 4.2, diazepine 6-H_B), 1.45 (9 H, s, OC(CH₃)₃); δ_C (125 MHz, MeOD, 333 K) 171.9 (diazepine 2-C), 156.6 (*t*BuCO₂NH), 131.2 (pyrrole 4-C), 125.6 (pyrrole 3-C), 82.1 (OC(CH₃)₃), 65.9 (pyrrole 2-C), 54.9 (diazepine 3-C), 53.8 (pyrrole 5-C), 40.7 (diazepine 5-C), 35.2 (diazepine 6-C), 28.7 ((OC(CH₃)₃); ν_{max}/cm⁻¹ (neat) 2977, 1755, 1682, 1394, 1365, 1240, 1155; *m/z* (ESI) 275 (100%, MNa⁺); Found: MNa⁺, 275.1367. C₁₃H₂₀N₂O₃ requires *MNa*, 275.1366.

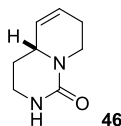
Benzyl-(2R)-2-([(tert-butoxy)carbonyl]amino)ethyl)-2,5-dihydro-1H-pyrrole-1-carboxylate **36**



i) NaHCO_3 (0.174 g, 2.08 mmol) and CbzCl (0.230 mL, 2.08 mmol) was added to a solution of amine **16** (0.250 g, 1.04 mmol) in CHCl_3 (6.00 mL) and water (2.00 mL) at 0 °C (ice). The reaction mixture was then stirred at room temperature for 18 h, diluted with CH_2Cl_2 (20.0 mL) and washed with saturated aqueous NH_4Cl (20.0 mL), saturated aqueous NaHCO_3 (20.0 mL) and water (20.0 mL). The organic phase was dried (MgSO_4), filtered and concentrated *in vacuo* to give a crude product that was purified by flash column chromatography, eluting with 4:1 petrol–EtOAc to furnish a dicarbonate that was used immediately.

ii) According to General Procedure E1 the reaction was complete after 20 h. The mixture was cooled to room temperature and loaded directly onto a silica column, eluting with 95:5 CH_2Cl_2 – Et_2O to give dihydro-pyrrole **36** (0.240 g, 66%) as a yellow oil, R_f 0.45 (9:1 CH_2Cl_2 – Et_2O); $[\alpha]_D^{24}$ –48 (c. 0.74, CHCl_3); δ_H (500 MHz, MeOD, 333 K) 7.38–7.27 (5 H, m, Ar-H), 5.84 (2 H, app. br s, 3-H, 4-H), 5.15 (2 H, app. br s, OCH_2Ar), 4.63 (1 H, ddd, J 10.8, 5.3, 2.0, 2-H), 4.25 (1 H, dd, J 15.0, 1.7, 5- H_A), 4.09 (1 H, d (broad), J 15.0, 5- H_B), 3.17–3.02 (2 H, m, CO_2NHCH_2), 1.93–1.87 (2 H, m, NHCH_2CH_2), 1.42 (9 H, s, $\text{OC}(\text{CH}_3)_3$); δ_C (125 MHz, MeOD, 333 K) 158.3 ($\text{CO}_2\text{OCH}_2\text{Ar}$), 156.6 ($t\text{BuCO}_2\text{NH}$), 138.2 (Ar 1-C), 130.8 (C-4), 129.6 (Ar 3-C), 129.0 (Ar 4-C), 128.9 (C-3), 126.3 (Ar 2-C), 80.1 ($\text{OC}(\text{CH}_3)_3$), 68.1 (OCH_2Ar), 64.2 (broad, 2-C), 54.6 (broad, 5-C), 37.7 (broad, CO_2NHCH_2), 35.5 and 34.8 (2 × rotameric signals, NHCH_2CH_2), 28.9 ($\text{OC}(\text{CH}_3)_3$); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3355, 2976, 1713, 1682, 1514, 1416, 1327, 1251, 1172, 1107; m/z (ESI) 369 (100%, MNa^+); Found: MNa^+ , 369.1782. $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_4$ requires MNa , 369.1785.

(4aR)-1H,2H,3H,4H,4aH,7H,8H-pyrido[1,2-c]pyrimidin-1-one **46**



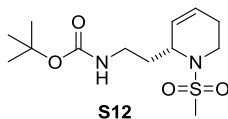
i) NaHCO_3 (88.0 mg, 1.05 mmol) followed by Boc_2O (0.229 g, 1.05 mmol) was added to a solution of amine **17** (0.222 g, 0.870 mmol) in THF (4.00 mL) and water (4.00 mL). The reaction mixture was stirred at room temperature for 2 h before being diluted with EtOAc (10.0 mL) and water (10.0 mL), the phases separated and the aqueous phase extracted with EtOAc (3 × 10.0 mL). The combined organic phase was dried (MgSO_4), filtered and concentrated *in vacuo* to give a crude product that was used immediately.

ii) According to General Procedure E1 the reaction was complete after 4 h. The mixture was cooled to room temperature and loaded directly onto a silica column, eluting with 98:2 CH_2Cl_2 – Et_2O to give a product that was used immediately.

iii) According to General Procedure C1, urea **46** (52.0 mg, 39%) was obtained as a pale yellow waxy solid, R_f 0.53 (85:13.5:0.5 CH_2Cl_2 – EtOH – NH_3OH); $[\alpha]_D^{20}$ +100 (c. 0.39, CHCl_3); δ_H (500 MHz, CDCl_3) 5.87 (1 H, dd, J 9.5, 6.6, pyrido 3-H), 5.54 (1 H, app. d (broad), J 9.5, pyrido 4-H), 5.17 (1 H, br s, NH), 4.53 (1 H, app. dd, J 12.5, 5.8, pyrido 6- H_A), 3.95 (1 H, app. dd, J 12.0, 2.0, pyrido 2-H), 3.33–3.25 (2 H, m, NHCH_2), 2.69 (1 H, app. td, J 12.5, 3.7, pyrido 6- H_B), 2.28–2.22 (1 H, m, pyrido 5- H_A), 2.00–1.97 (2 H, m, pyrido 5- H_B , NHCH_2CH_A), 1.68 (1 H, ddd, J 19.0, 12.0, 5.3, NHCH_2CH_A); δ_C (125 MHz, CDCl_3) 155.9 (NCONH), 127.8 (pyrido 3-C), 126.4 (pyrido 4-C), 52.4 (pyrido 2-C), 38.8 (pyrido 6-C), 38.3 (NHCH_2), 29.2 (pyrido 5-C),

25.0 (NHCH₂CH₂); $\nu_{\max}/\text{cm}^{-1}$ (neat) 3206, 2916, 1650, 1499, 1439, 1367, 1287, 1139; m/z (ESI) 275 (100%, MH⁺); Found: MH⁺, 153.1021. C₈H₁₂N₂O requires *MH*, 153.1022.

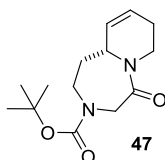
tert*-Butyl-*N*-{2-[(2*R*)-1-methanesulfonyl-1,2,5,6-tetrahydropyridin-2-yl]ethyl}carbamate **S12*



i) DIPEA (31.0 μL , 0.180 mmol) and methanesulfonyl chloride (13.0 μL , 0.160 mmol) were added to a solution of amine **17** (38.0 mg, 0.15 mmol) in CH₂Cl₂ (2 mL) at 0 °C (ice). The resulting mixture was stirred for 10 min at that temperature and at room temperature for 1 h. After this time the reaction mixture was diluted with CH₂Cl₂ (3 mL) and saturated aqueous NH₄Cl (2 mL) and the layers separated. The aqueous phase was extracted with CH₂Cl₂ (3 \times 2 mL). The combined organic phase was dried (MgSO₄), filtered and concentrated *in vacuo* to give a crude product that was used immediately.

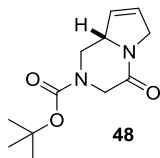
ii) According to General Procedure E1, a crude product was obtained that was purified by flash column chromatography, eluting with 8:2→6:4 petrol–EtOAc) to furnish tetrahydropyridine **S12** (33.0 mg, 72%) as a yellow oil, R_f 0.28 (1:1 cyclohexane–EtOAc); $[\alpha]_D^{21}$ –25 (*c* 1.2, CHCl₃); δ_H (400 MHz, CDCl₃) 5.88 (1 H, ddq, *J* 10.5, 5.2, 2.8 Hz, CH=CH), 5.72 (1 H, ddt, *J* 10.3, 4.0, 1.9 Hz, CH=CH), 5.25 (1 H, br. s, NH), 4.11 (1 H, d, *J* 10.3 Hz, NCH), 3.89 (1 H, ddd, *J* 14.9, 6.3, 0.7 Hz, NCH₂), 3.50–3.30 (1 H, m, NHCH₂), 3.20–3.00 (2 H, m, NCH₂, NHCH₂), 2.86 (3 H, s, SCH₃), 2.30 (1 H, dddq, *J* 18.6, 11.6, 6.8, 2.5 Hz, NCH₂CH₂), 1.99 (1 H, dt, *J* 18.2, 4.5 Hz, NCH₂CH₂), 1.80 (1 H, ddt, *J* 14.7, 9.6, 4.5 Hz, NHCH₂CH₂), 1.60 (1 H, ddt, *J* 14.6, 10.8, 4.1 Hz, NHCH₂CH₂), 1.44 (9 H, s, C(CH₃)₃); δ_C (100 MHz, CDCl₃) 156.2 (C=O), 128.6 (CH=CH), 125.3 (CH=CH), 79.1 (C(CH₃)₃), 51.0 (NCH), 39.7 (SCH₃), 38.1 (NCH₂), 36.6 (NHCH₂), 33.9 (NHCH₂CH₂), 28.6 (C(CH₃)₃), 23.2 (NCH₂CH₂); $\nu_{\max}/\text{cm}^{-1}$ 3397, 2976, 2932, 1701, 1508, 1454, 1391, 1366, 1321, 1251, 1211, 1149, 1097, 1075, 1041, m/z (ESI) 327 (100%, MNa⁺); Found: MNa⁺, 327.1358. C₁₃H₂₄O₄N₂S requires *MNa*, 327.1349.

tert*-Butyl-(10*aR*)-5-oxo-1*H*,2*H*,3*H*,4*H*,5*H*,7*H*,8*H*,10*aH*-pyrido[1,2-*d*][1,4]diazepine-3-carboxylate **47*



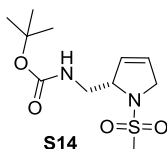
General Procedure D3/E2 was followed where DIPEA was used and following RCM the reaction mixture was simply concentrated *in vacuo*. Amine **17** (51.0 mg, 0.200 mmol) gave a crude product that was purified by flash column chromatography, eluting with 7:3→3:7 petrol–EtOAc to furnish diazepine **47** (38.0 mg, 72%) as a colourless oil, R_f 0.18 (1:1 cyclohexane–EtOAc); $[\alpha]_D^{21}$ –24 (*c* 1.3, CHCl₃); δ_H (400 MHz, DMSO-*d*₆, 120 °C) 5.93 (1 H, ddd, *J* 10.3, 6.8, 4.0 Hz, CHCH=CH), 5.69–5.60 (1 H, ddt, *J* 10.2, 3.6, 1.9 Hz, CHCH=CH), 4.28–4.16 (1 H, m, NCH₂CO, NCH), 4.02 (1 H, d, *J* 15.6 Hz, NCH₂CO), 3.85 (1 H, dt, *J* 12.8, 5.0 Hz, NCH₂CH₂CH=CH), 3.49 (2 H, t, *J* 5.9 Hz, BocNCH₂CH₂), 3.14 (1 H, ddd, *J* 13.1, 7.3, 5.3 Hz, NCH₂CH₂CH=CH), 2.17–1.96 (2 H, m, NCH₂CH₂CH=CH), 1.97–1.82 (1 H, m, BocNCH₂CH₂), 1.77–1.60 (1 H, m, BocNCH₂CH₂), 1.42 (9 H, s, C(CH₃)₃); δ_C (100 MHz, CDCl₃) 168.6 (CH₂CON), 154.6 (OCON), 127.4 (CH=CH), 126.5 (CH=CH), 80.6 (C(CH₃)₃), 53.0 (NCH₂CO), 52.7 (br., NCH), 43.6 (BocNCH₂CH₂), 37.0 (NCH₂CH₂CH=CH), 32.8 (BocNCH₂CH₂), 28.5 (C(CH₃)₃), 24.5 (NCH₂CH₂CH=CH); $\nu_{\max}/\text{cm}^{-1}$ (neat) 3407, 2975, 2930, 1690, 1641, 1404, 1365, 1334, 1234, 1158, 1118, 1076; m/z (ESI) 289 (100%, MNa⁺); Found: MNa⁺, 289.1517. C₁₄H₂₂O₃N₂ requires *MNa*, 289.1523.

tert*-Butyl-(8a*S*)-4-oxo-1*H*,2*H*,3*H*,4*H*,6*H*,8a*H*-pyrrolo[1,2-*a*]piperazine-2-carboxylate **48*



General Procedure D3/E2 was followed where NEt_3 was used and following RCM the reaction mixture was loaded directly onto a silica column, eluting with 4:1 CH_2Cl_2 – Et_2O to give a crude product that was used immediately. Amine **18** (0.100 g, 0.440 mmol) gave a crude product that was purified by flash column chromatography, eluting with 96:3.6:0.4 CH_2Cl_2 – EtOH – NH_3OH to furnish ketopiperazine **48** (0.068 g, 65%) as a yellow waxy solid, R_f 0.17 (96:3.6:0.4 CH_2Cl_2 – EtOH – NH_3OH); $[\alpha]_D^{20} +55$ (*c.* 0.59, CHCl_3); δ_H (500 MHz, MeOD, 333 K) 6.05 (1 H, app. dq, J 6.4, 2.0, 8-H), 5.88–5.86 (1 H, m, 7-H), 4.55–4.49 (2 H, m, 8a-H, 6- H_A), 4.33 (1 H, dd, J 13.0, 2.4, 1- H_A), 4.22 (1 H, d, J 17.8, 3- H_A), 4.06 (1 H, app. d, J 13.8, 6- H_B), 3.83 (1 H, d, J 17.8, 3- H_B), 2.73 (1 H, dd, J 13.0, 8.4, 1- H_B), 1.49 (9 H, s, $\text{OC}(\text{CH}_3)_3$); δ_C (125 MHz, MeOD, 333 K) 167.2 (4-C), 155.7 (NCO_2), 128.8 (8-C), 127.7 (7-C), 82.3 ($\text{OC}(\text{CH}_3)_3$), 64.2 (8a-C), 53.7 (3-C), 48.1 (6-C), 46.7 (1-C), 28.7 ($\text{C}(\text{CH}_3)_3$); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2975, 1692, 1658, 1393, 1365, 1323, 1237, 1161, 1124; m/z (ESI) 239 (100%, MH^+); Found: MH^+ , 239.1387. $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_3$ requires MH , 239.1390.

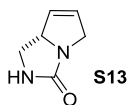
tert*-Butyl-*N*-{[(2*S*)-1-methanesulfonyl-2,5-dihydro-1*H*-pyrrol-2-yl]methyl}carbamate **S14*



i) DIPEA (31.0 μL , 0.180 mmol) and methanesulfonyl chloride (13.0 μL , 0.160 mmol) were added to a solution of amine **17** (34.0 mg, 0.15 mmol) in CH_2Cl_2 (2 mL) at 0 °C (ice). The resulting mixture was stirred for 10 min at that temperature and at room temperature for 1 h. After this time the reaction mixture was diluted with CH_2Cl_2 (3 mL) and saturated aqueous NH_4Cl (aq. sat., 2 mL) and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (3 \times 2 mL). The combined organic phase was dried (MgSO_4), filtered and concentrated *in vacuo* to give a crude product that was used immediately.

ii) According to General Procedure E1, a crude product was obtained that was purified by flash column chromatography, eluting with 7:3→1:1 petrol– EtOAc to furnish dihydro-pyrrole **S14** (36.0 mg, 72%) as a yellow oil, R_f 0.16 (1:1 cyclohexane– EtOAc); $[\alpha]_D^{21} -139$ (*c.* 1.1, CHCl_3); δ_H (400 MHz, CDCl_3) 5.86 (1 H, dq, J 6.1, 2.1 Hz, $\text{CH}=\text{CH}$), 5.74 (1 H, dq, J 6.3, 2.3 Hz, $\text{CH}=\text{CH}$), 5.02 (1 H, br. s, NH), 4.52 (1 H, dt, J 5.8, 2.0 Hz, MsNCH), 4.16 (2 H, dt, J 4.0, 2.1 Hz, MsNCH_2), 3.49–3.27 (2 H, m, BocNHCH_2), 2.80 (3 H, s, SCH_3), 1.42 (9 H, s, $\text{C}(\text{CH}_3)_3$); δ_C (100 MHz, CDCl_3) 156.3 ($\text{C}=\text{O}$), 128.2 ($\text{CH}=\text{CH}$), 126.5 ($\text{CH}=\text{CH}$), 79.4 ($\text{C}(\text{CH}_3)_3$), 67.7 (MsNCH), 56.0 (MsNCH_2), 44.7 (BocNHCH_2), 34.5 (SCH_3), 28.4 ($\text{C}(\text{CH}_3)_3$); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3385, 2978, 2932, 1696, 1516, 1453, 1393, 1365, 1328, 1250, 1150, 1079, 1053; m/z (ESI) 299 (100%, MNa^+); Found: MNa^+ , 299.1047. $\text{C}_{11}\text{H}_{20}\text{O}_4\text{N}_2\text{S}$ requires MNa , 299.1036.

(7a*S*)-1*H*,2*H*,3*H*,5*H*,7a*H*-pyrrolo[1,2-*c*]imidazolidin-3-one **S13**

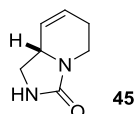


i) General Procedure C1 was followed using amine **18** (126 mg, 0.557 mmol) with the following deviations: For the deprotection, a 1:1 ratio of TFA/DCM was used. Upon reaction completion, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and aqueous NaOH (1 M) (until aqueous phase was at pH 12). The layers were separated and the aqueous phase was

extracted with CH₂Cl₂ (3×3 mL). The combined organic phase was dried (MgSO₄) and concentrated *in vacuo*. For the urea formation, 1.2 eq CDI and 2.0 eq DBU were used to give a crude product that was used immediately.

ii) According to General Procedure E1, a crude product was obtained that was purified by flash column chromatography, eluting with 10:0→9:1 EtOAc–MeOH to furnish the title compound **S13** (32.0 mg, 51%) as a white solid (m.p. 123–124 °C); *R_f* 0.10 (EtOAc); [α]_D²¹ –82 (*c* 1.0, CHCl₃); δ _H (400 MHz, CDCl₃) 6.24 (1 H, br. s, NH), 5.93 (1 H, dq, *J* 6.0, 2.0 Hz, CH=CH), 5.81 (1 H, ddt, *J* 5.9, 3.8, 1.7 Hz, CH=CH), 4.59 (1 H, ddq, *J* 8.0, 5.8, 3.6 Hz, NCH), 4.32 (1 H, dq, *J* 15.5, 2.3 Hz, NCH₂), 3.70 (1 H, t, *J* 9.2 Hz, NHCH₂), 3.63 (1 H, ddt, *J* 15.6, 4.5, 1.8 Hz, NCH₂), 3.39 (1 H, dd, *J* 8.9, 4.1 Hz, NHCH₂); δ _C (100 MHz, CDCl₃) 167.3 (C=O), 130.1 (CH=CH), 129.8 (CH=CH), 64.7 (NCH), 54.1 (NCH₂), 44.2 (NHCH₂); ν _{max}/cm⁻¹ (neat) 3270, 2867, 1682, 1605, 1487, 1459, 1429, 1385, 1325, 1285, 1261, 1217, 1133, 1110, 1086, 1049, 1019; *m/z* (EI) 124 (100%, M⁺); Found: M⁺, 124.0634. C₆H₈ON₂ requires *M*, 124.0637).

(8a*S*)-1*H*,2*H*,3*H*,5*H*,6*H*,8a*H*-imidazolidino[1,5-*a*]pyridin-3-one **45**

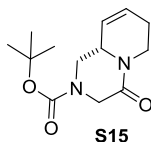


i) NaHCO₃ (21.0 mg, 0.250 mmol) followed by Boc₂O (54.0 mg, 0.250 mmol) was added to a solution of amine **19** (50.0 mg, 0.210 mmol) in THF (1.00 mL) and water (1.00 mL). The reaction mixture was stirred at room temperature for 2 h before being diluted with EtOAc (5.0 mL) and water (5.0 mL), the phases separated and the aqueous phase extracted with EtOAc (3 × 5.0 mL). The combined organic phase was dried (MgSO₄), filtered and concentrated *in vacuo* to give a crude product that was used immediately.

ii) According to General Procedure E1 the reaction was complete after 4 h. The mixture was cooled to room temperature and loaded directly onto a silica column, eluting with 9:1 CH₂Cl₂–Et₂O to give a product that was used immediately.

iii) According to General Procedure C1, urea **45** (17.0 mg, 61%) was obtained as a waxy colourless solid, *R_f* 0.66 (85:13.5:0.5 CH₂Cl₂–EtOH–NH₃OH); [α]_D²⁸ +55 (*c* 0.29, CHCl₃); δ _H (500 MHz, CDCl₃) 5.88 (1 H, dd, *J* 9.0, 6.3, 3-H), 5.60 (1 H, app. d, *J* 10.2, 4-H), 5.14 (1 H, br s, NH), 4.27 (1 H, app. br s, H-2), 3.91 (1 H, dd, *J* 13.4, 6.7, H-6_A), 3.59 (1 H, app. t, *J* 8.8, NHCH_A), 3.10 (1 H, dd, *J* 8.1, 5.5, NHCH_B), 2.94 (1 H, ddd, *J* 13.4, 11.4, 4.5, H-6_B), 2.35–2.29 (1 H, m, 5-H_A), 1.92 (1 H, app. d, *J* 17.5, 5-H_B); δ _C (125 MHz, CDCl₃) 162.1 (NCONH), 127.5 (3-C), 127.4 (4-C), 52.9 (2-C), 44.5 (NHCH₂), 37.4 (6-C), 23.5 (5-C); ν _{max}/cm⁻¹ (neat) 3252, 2921, 1686, 1659, 1424, 1259, 1087; *m/z* (ESI) 139 (100%, MH⁺); Found: MH⁺, 139.0862. C₇H₁₀N₂O requires *MH*, 139.0866.

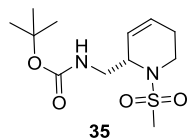
tert-Butyl-(9a*S*)-4-oxo-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*,9a*H*-pyrido[1,2-*a*]piperazine-2-carboxylate **S15**



General Procedure D3/E2 was followed where DIPEA was used and following RCM the reaction mixture was concentrated *in vacuo*. Amine **19** (44.0 mg, 0.180 mmol) gave a crude product that was purified by flash column chromatography, eluting with 7:3→3:7 petrol–EtOAc to furnish ketopiperazine **S15** (24.0 mg, 67%) as a colourless oil, *R_f* 0.19 (1:1 cyclohexane–EtOAc); [α]_D²¹ +67 (*c* 1.2, CHCl₃); δ _H (400 MHz, CDCl₃) 5.99 (1 H, ddt, *J* 9.6, 5.4, 1.6 Hz, CHCH=CH), 5.49 (1 H, ddt, *J* 10.1, 2.8, 1.4 Hz, CHCH=CH), 4.76 (1 H, ddt, *J* 13.1, 5.8, 1.3 Hz, NCH₂CH₂CH=CH), 4.45 (1 H, d, *J* 18.2 Hz, NCH₂CO), 4.37–4.11 (2 H, m, BocNCH₂CH), 3.78 (1 H, d, *J* 18.2 Hz, NCH₂CO), 2.75–2.70 (1H, m, BocNCH₂CH), 2.67 (1 H, td, *J* 12.2, 4.0 Hz, NCH₂CH₂CH=CH), 2.37–2.22 (1 H, m, NCH₂CH₂CH=CH), 2.15–2.04 (1 H, m, NCH₂CH₂CH=CH), 1.47 (9 H, s, C(CH₃)₃); δ _C

(100 MHz, CDCl₃) δ 165.1 (CH₂CON), 153.9 (OCON), 128.3 (CH=CH), 124.4 (CH=CH), 81.0 (C(CH₃)₃), 53.5 (NCH₂CO), 48.1 (NCH), 45.5 (BocNCH₂CH), 37.6 (NCH₂CH₂CH=CH), 28.5 (C(CH₃)₃), 25.0 (NCH₂CH₂CH=CH); $\nu_{\max}/\text{cm}^{-1}$ (neat) 3383, 2977, 2929, 1694, 1650, 1452, 1416, 1391, 1366, 1328, 1288, 1240, 1161, 1128, 1076, 1042, 1014; m/z (ESI) 275 (100%, MNa⁺); Found: MNa⁺, 275.1359. C₁₃H₂₀O₃N₂ requires MNa, 275.1366.

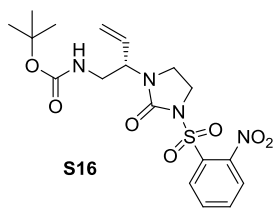
tert*-Butyl-*N*-{[(2*S*)-1-methanesulfonyl-1,2,5,6-tetrahydropyridin-2-yl]methyl}carbamate **35*



i) DIPEA (31.0 μL , 0.180 mmol) and methanesulfonyl chloride (13.0 μL , 0.160 mmol) were added to a solution of amine **17** (36.0 mg, 0.15 mmol) in CH₂Cl₂ (2 mL) at 0 °C (ice). The resulting mixture was stirred for 10 min at that temperature and at room temperature for 1 h. After this time the reaction mixture was diluted with CH₂Cl₂ (3 mL) and saturated aqueous NH₄Cl (aq. sat., 2 mL) and the layers separated. The aqueous phase was extracted with CH₂Cl₂ (3 \times 2 mL). The combined organic phase was dried (MgSO₄), filtered and concentrated *in vacuo* to give a crude product that was used immediately.

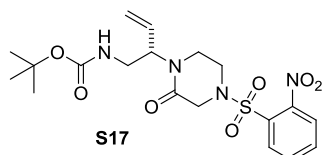
ii) According to General Procedure E1, a crude product was obtained that was purified by flash column chromatography, eluting with 8:2 \rightarrow 4:6 petrol–EtOAc) to furnish tetrahydro-pyridine **35** (27.0 mg, 54%) as a yellow oil, R_f 0.25 (1:1 cyclohexane–EtOAc); $[\alpha]_D^{21}$ –81 (*c* 0.91, CHCl₃); δ_H (400 MHz, CDCl₃) 5.98 (1 H, ddt, J 9.8, 4.5, 2.1 Hz, CH=CH), 5.71 (1 H, dddd, J 10.4, 4.1, 2.6, 1.4 Hz, CH=CH), 5.00 (1 H, br. s, NH), 4.20 (1 H, dt, J 9.9, 3.3 Hz, NCH), 3.88 (1 H, dd, J 14.7, 6.2 Hz, NHCH₂), 3.35 (1 H, ddd, J 14.2, 6.8, 3.8 Hz, NCH₂), 3.25–3.08 (2 H, m, NHCH₂, NCH₂), 2.85 (3 H, s, SCH₃), 2.30 (1 H, dddd, J 18.3, 11.8, 6.2, 2.9 Hz, NCH₂CH₂), 2.02 (1 H, dt, J 18.0, 4.7 Hz, NCH₂CH₂), 1.43 (9 H, s, C(CH₃)₃); δ_C (100 MHz, CDCl₃) 156.2 (C=O), 127.5 (CH=CH), 125.3 (CH=CH), 79.6 (C(CH₃)₃), 53.5 (NCH), 43.0 (NCH₂), 39.9 (SCH₃), 38.3 (NHCH₂), 28.5 (C(CH₃)₃), 23.6 (NCHCH₂); $\nu_{\max}/\text{cm}^{-1}$ (neat) 3392, 2977, 2931, 1699, 1513, 1453, 1391, 1366, 1322, 1276, 1251, 1208, 1147, 1094, 1058; m/z (ESI) 313 (100%, MNa⁺); Found: MNa⁺, 313.1187. C₁₂H₂₂O₄N₂S requires MNa, 313.1192.

tert*-Butyl-*N*-[(2*S*)-2-[3-(2-nitrobenzenesulfonyl)-2-oxoimidazolidin-1-yl]but-3-en-1-yl]carbamate **S16*



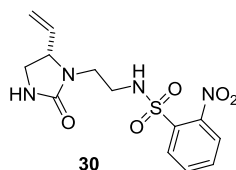
According to General Procedure C2, amine **20** (0.142 g, 0.340 mmol) furnished urea **S16** (0.095 g, 63%) as a yellow oil, δ_H (500 MHz, CDCl₃) 8.45–8.43 (1 H, Ar 3-H), 7.77–7.74 (2 H, m Ar 5-H, 6-H), 7.72–7.70 (1 H, m, Ar 4-H), 5.70 (1 H, dd, J 17.3, 10.6, 6.2, 3-H), 5.30 (1 H, app. d, J 10.6, 4-H_A), 5.23 (1 H, dd, J 17.3, 1.4, 4-H_B), 4.63 (1 H, br s, CO₂NH), 4.36–4.32 (1 H, m, 2-H), 4.11–4.01 (2 H, m, imidazolidine 4-H_A, 5-H_A), 3.63 (1 H, dd, J 14.8, 8.8, imidazolidine 5-H_B), 3.56–3.50 (1 H, m, 1-H_A), 3.45 (1 H, app. dd, J 16.4, 8.8, imidazolidine 4-H_B), 3.23–3.18 (1 H, m, 1-H_B), 1.39 (9 H, s, OC(CH₃)₃); δ_C (125 MHz, CDCl₃) 155.9 (*t*BuCO₂N), 153.6 (imidazolidine 2-C), 147.9 (Ar 2-C), 134.5 (Ar 5-C), 133.9 (Ar 4-C), 132.0 (Ar 1-C), 132.0 (Ar 3-C), 131.9 (3-C), 124.0 (Ar 6-C), 119.5 (4-C), 79.8 (OC(CH₃)₃), 55.1 (2-C), 42.1 (1-C), 40.6 (imidazolidine 5-C), 38.8 (imidazolidine 4-C), 28.2 ((OC(CH₃)₃); $\nu_{\max}/\text{cm}^{-1}$ (neat) 2979, 1713, 1591, 1541, 1482, 1427, 1268, 1168, 1128; m/z (ESI) 441 (100%, MH⁺); Found: MH⁺, 441.1456. C₁₈H₂₄N₄O₇S requires MH, 441.1438.

tert-Butyl-N-[(2S)-2-[4-(2-nitrobenzenesulfonyl)-2-oxopiperazin-1-yl]but-3-en-1-yl]carbamate **S17**



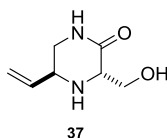
According to Procedure D4, amine **20** (0.390 g, 0.940 mmol) gave a crude product that was filtered through a plug of SiO₂, eluting with MTBE to furnish ketopiperazine **S17** (0.441 g, 89%) as a yellow oil, $[\alpha]_D^{20} +18.18$ ($c = 2.20$, CDCl₃); δ_H (400 MHz, CDCl₃) 8.01 (1 H, dd, J 7.7, 1.6, 1H, Ar 3-H), 7.69 - 7.79 (2 H, m, Ar 4-H, Ar 5-H), 7.65 (1 H, dd, J 7.5, 1.8, Ar 6-H), 5.72 (1 H, ddd, J 17.2, 10.8, 5.9, 3-H), 5.20-5.33 (2 H, m, 4-H), 5.09 - 5.17 (1 H, m, 2-H), 4.76 - 4.83 (1 H, m, NH), 4.04 (1 H, d, J 17.0, piperazine 3-H_A), 3.87 (1 H, d, J 17.0, piperazine 3-H_B), 3.67 (1 H, dt, J 12.8, 4.4, piperazine 5-H_A), 3.46 - 3.60 (2 H, m, 1-H_A and piperazine 5-H_A), 3.33 - 3.41 (2 H, m, piperazine 6-H), 3.21 (1 H, dt, J 14.2, 4.3, 1-H_B), 1.35 (9 H, s, OC(CH₃)₃); δ_C (100 MHz, CDCl₃) 164.2 (piperazine 2-C), 156.0 (NHCO₂), 148.3 (Ar 2-C), 134.3 (Ar 5-C), 132.3 (3-C), 131.8 (Ar 4-C), 131.3 (Ar 3-C), 130.5 (Ar 1-C), 124.4 (Ar 6-C), 119.7 (4-C), 79.5 ((OC(CH₃)₃), 55.1 (2-C), 48.3 (piperazine 3-C), 43.2 (piperazine 5-C), 42.0 (piperazine 6-C), 40.1 (1-C), 28.3 (OC(CH₃)₃); ν_{max}/cm^{-1} (neat) 3320, 2977, 2927, 1704, 1648, 1544, 1484, 1451, 1305, 1296, 1250, 1168, 1130, 1004; m/z (ESI) 477 (100%, MNa⁺); Found: MNa⁺, 477.1417. C₁₉H₂₆N₄NaO₇S requires MNa, 477.1414.

N-{2-[(5S)-5-Ethenyl-2-oxoimidazolidin-1-yl]ethyl}-2-nitrobenzene-1-sulfonamide **30**



According to General Procedure C1, amine **20** (0.250 g, 0.600 mmol) gave a crude product that was filtered through a plug of SiO₂, eluting with MTBE to furnish urea **30** (0.0980 g, 48%) as a yellow waxy solid, $[\alpha]_D^{19} +76$ ($c = 0.20$, EtOH); δ_H (400 MHz, DMSO) 8.20 (1 H, br. s., Ns-NH), 8.01-8.07 (2 H, m, Ar 3-H and Ar 6-H), 7.89-7.96 (2 H, m, Ar 4-H and Ar 5-H), 6.49 (1 H, s, imidazolidinone-NH), 5.68-5.80 (1 H, m, ethenyl CHCH₂), 5.21-5.34 (2 H, m, ethenyl CHCH₂), 4.11 (1 H, app. q, J 8.3, imidazolidinone 5-H), 3.35-3.44 (1 H, m, imidazolidinone-4-H_A), 3.15-3.26 (1 H, m, NCH₂), 2.91 - 3.08 (4 H, m, NCH₂, NCH₂CH₂ and imidazolidinone 4-H_B); δ_C (100 MHz, DMSO-d₆) 161.4 (imidazolidinone 2-C), 147.7 (Ar 2-C), 136.9 (ethenyl CHCH₂), 134.0 (Ar 5-C), 132.7 (Ar 1-C), 132.6 (Ar 4-C), 129.4 (Ar 6-C), 124.4 (Ar 3-C), 119.1 (ethenyl CHCH₂), 59.0 (imidazolidinone 5-C), 43.6 (imidazolidinone 4-C), 40.9 (NCH₂), 40.8 (NCH₂); ν_{max}/cm^{-1} (neat) 3301, 3234, 2924, 1690, 1538, 1491, 1426, 1356, 1340, 1262, 1163, 1060; m/z (ESI) 341 (100%, MH⁺); Found: MH⁺, 341.0905. C₁₃H₁₇N₄O₅S requires MH, 341.0920.

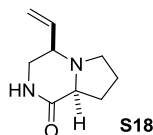
(3S,5S)-5-Ethenyl-3-(hydroxymethyl)piperazin-2-one **37**



According to General Procedure F1, amine **21** (58.0 mg, 0.200 mmol) gave a crude product which was purified by flash column chromatography, eluting with 4:1 EtOAc–MeOH to furnish the ketopiperazine **37** (30.0 mg, 96%) as a colourless oil, R_f 0.21 (4:1 DCM–MeOH); $[\alpha]_D^{24} -18$ ($c = 0.02$, DMSO); δ_H (500 MHz, MeOD) 5.88 (1H, ddd, J 17.4, 10.6, 5.8, ethenyl 1-H), 5.37 (1H, dd, J 17.4, 2.0, ethenyl 2-H_A), 5.26 (1H, dd, J 10.6, 2.0, ethenyl 2-H_B), 3.91 (1H, dd, J 11.0, 7.1, CH₂A-OH), 3.82-

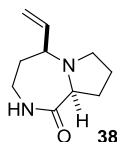
3.79 (1H, m, 5-H), 3.78 (1H, dd, J 11.0, 3.8, $\text{CH}_2\text{B(OH)}$), 3.51 (1H, dd, J 7.1, 3.8, 3-H), 3.36 (1H, dd, J 12.2, 4.0, 6- H_A), 3.21 (1H, dd, J 12.2, 8.0, 6- H_B); δ_C (75 MHz, DMSO) 169.2 (2-C), 137.9 (ethenyl 2-C), 116.0 (ethenyl 1-C), 61.6 (3-C), 58.1 (CH_2OH), 49.6 (6-C), 46.0 (5-C); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3317, 2984, 1682, 1497, 1430, 1352, 1206; m/z (ESI) 157 (100%, MH^+); Found: MH^+ , 157.0979. $\text{C}_7\text{H}_{12}\text{N}_2\text{O}_2$ requires MH , 157.0972.

(4*R*,8*aS*)-4-ethenyl-octahydropyrrolo[1,2-*a*]piperazin-1-one **S18**



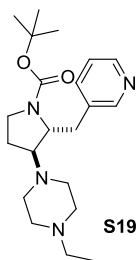
According to General Procedure F1 where a 1:1 TFA/DCM ratio was used for deprotection, amine **22** (92.0 mg, 0.310 mmol) gave a crude product that was purified by flash column chromatography, eluting with 10:0→9:1 CH_2Cl_2 -MeOH to furnish lactam **S18** (51.0 mg, 68%) as an orange solid; m.p. 91–92 °C; R_f 0.61 (8:2 CH_2Cl_2 -MeOH); $[\alpha]_\text{D}^{20}$ -47 (c 0.5, MeOH); δ_H (600 MHz, CDCl_3) 6.78 (1H, br. s, NH), 5.77 (1H, ddd, J = 17.5, 10.4, 7.3 Hz, $\text{CH}=\text{CH}_2$), 5.28 (1H, dt, J = 17.2, 1.1 Hz, $\text{trans-CH}=\text{CH}_2$), 5.20 (1H, dd, J = 10.4, 1.3 Hz, $\text{cis-CH}=\text{CH}_2$), 3.39–3.31 (1H, m, CONHCH_2), 3.29–3.20 (2H, m, CONHCH_2 , $\text{CHCH}=\text{CH}_2$), 3.01 (1H, t, J = 8.3 Hz, CHCONH), 2.96 (1H, td, J = 8.5, 4.2 Hz, CHNCH_2), 2.29 (1H, q, J = 8.4 Hz, CHNCH_2), 2.16 (1H, dddd, J = 12.8, 9.9, 8.1, 4.4 Hz, CH_2CHCONH), 1.92 (1H, dddd, J = 12.8, 11.0, 8.8, 7.3 Hz, CH_2CHCONH), 1.85–1.70 (2H, m, NCH_2CH_2); δ_C (150 MHz, CDCl_3) 172.7 ($\text{C}=\text{O}$), 136.4 ($\text{CH}=\text{CH}_2$), 118.7 ($\text{CH}=\text{CH}_2$), 64.4 (NCHCONH), 61.0 ($\text{CHCH}=\text{CH}_2$), 49.6 (CHNCH_2), 45.7 (CONHCH_2), 26.0 (CH_2CHCONH), 21.4 (NCH_2CH_2); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3229, 2972, 2877, 1660, 1489, 1422, 1359, 1270, 1199, 1177, 1131, 1083; m/z (ESI) 167 (100%, MH^+); Found: MH^+ , 167.1181. $\text{C}_9\text{H}_{15}\text{N}_2\text{O}$ requires MH , 167.118.

(5*S*,9*aS*)-5-ethenyl-octahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-1-one **38**



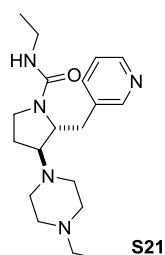
According to General Procedure F2, amine **23** (65.0 mg, 0.210 mmol) gave a crude product that was purified by flash column chromatography, eluting with 100:0→95:5 CH_2Cl_2 -MeOH to furnish lactam **38** (29.0 mg, 77%) as a white solid, m.p. 101–102 °C; R_f 0.47 (8:2 CH_2Cl_2 -MeOH); $[\alpha]_\text{D}^{21}$ +13 (c 0.8, MeOH); δ_H (500 MHz, CDCl_3) 6.04 (1H, br. s, NH), 5.84 (1H, ddd, J = 17.2, 10.1, 8.7 Hz, $\text{CH}=\text{CH}_2$), 5.17 (1H, dd, J = 17.1, 1.3 Hz, $\text{trans-CH}=\text{CH}_2$), 5.02 (1H, dd, J = 10.2, 1.6 Hz, $\text{cis-CH}=\text{CH}_2$), 3.41 (1H, dddd, J = 14.9, 9.8, 4.9, 2.9 Hz, CONHCH_2), 3.34–3.21 (2H, m, CONHCH_2 , CHCONH), 3.19–3.10 (1H, m, CHNCH_2), 2.99 (1H, td, J = 8.4, 4.8 Hz, $\text{CHCH}=\text{CH}_2$), 2.62 (1H, dddd, J = 12.3, 8.0, 4.0, 2.1 Hz, CH_2CHCONH), 2.26 (1H, ddd, J = 10.6, 9.3, 6.3 Hz, CHNCH_2), 1.95–1.63 (5H, m, $\text{CH}_2\text{CH}_2\text{CHCONH}$, $\text{CH}_2\text{CHCH}=\text{CH}_2$); δ_C (100MHz, CDCl_3) δ 176.1 ($\text{C}=\text{O}$), 141.4 ($\text{CH}=\text{CH}_2$), 115.1 ($\text{CH}=\text{CH}_2$), 71.1 ($\text{CHCH}=\text{CH}_2$), 63.6 (CHCONH), 56.5 (CHNCH_2), 40.2 (CONHCH_2), 37.7 ($\text{CH}_2\text{CHCH}=\text{CH}_2$), 28.4 (CH_2CHCONH), 23.6 ($\text{CH}_2\text{CH}_2\text{CHCONH}$); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3283, 3080, 2925, 2784, 1671, 1627, 1475, 1421, 1367, 1314, 1285, 1197, 1146, 1121, 1047; m/z (ESI) 181 (100%, MH^+); Found: MH^+ , 181.1344. $\text{C}_{10}\text{H}_{17}\text{N}_2\text{O}$ requires MH , 181.1341.

tert*-Butyl-(2*R*,3*S*)-3-(4-ethylpiperazin-1-yl)-2-(pyridin-3-ylmethyl)pyrrolidine-1-carboxylate **S19*



10% Pd/C (0.244 g, 20 mol% Pd) and ethylene diamine (77.0 μ L, 1.15 mmol) were added to a solution of pyrrolidine **S10** (0.551 g, 1.15 mmol) in MeOH (15.0 mL). The reaction vessel was placed under an atmosphere of H₂, stirred at room temperature for 18 h then filtered through celite (MeOH) and the filtrate concentrated *in vacuo*. The crude product (0.374 g) was dissolved in MeOH (3.7 mL) and to this was added acetaldehyde (5 M solution in THF, 0.690 mL, 3.45 mmol) and AcOH (66.0 μ L, 1.15 mmol). After 1 h NaBH(OAc)₃ (0.732 g, 3.45 mmol) was added and the reaction mixture stirred at room temperature for a further 2 h before being quenched by the addition of saturated aqueous NaHCO₃ and concentrated *in vacuo*. The crude material was taken in MeOH (5.0 mL), filtered and filtrate purified by SCX solid phase extraction followed by flash column chromatography, eluting with 95:4.5:0.5 DCM–EtOH–NH₄OH to furnish amine **S19** (0.200 g, 46%) as a colourless oil, *R*_f 0.16 (95:4.5:0.5 DCM–EtOH–NH₄OH); δ_{H} (500 MHz, MeOD, 333 K) 8.40–8.39 (2 H, m, Ar 2-H, Ar 6-H), 7.69 (1 H, d, *J* 67.5, Ar 4-H), 7.35 (1 H, dd, *J* 7.5, 4.9, Ar 5-H), 4.10 (1 H, dd, *J* 7.5, 5.3, 2.2, pyrrolidine 2-H), 3.54 (1 H, app. br s, pyrrolidine 3-H), 3.18 (1 H, app. br s, pyrrolidine 5-H_A), 2.93 (2 H, app. br s, pyrrolidine 5-H_B, ArCH_A), 2.86–2.82 (1 H, m, ArCH_B), 2.45–2.39 (8 H, m, piperazine 2-H and 3-H), 2.38 (2 H, q, *J* 7.3, ethyl CH₂), 1.98 (2 H, app. br s, pyrrolidine 4-H), 1.42 (9 H, s, OC(CH₃)₃), 1.05 (3 H, t, *J* 7.3, ethyl CH₃); δ_{C} (125 MHz, MeOD, 333 K) 155.9 (*t*BuCO₂N), 151.2 (Ar 2-C), 148.2 (Ar 6-C), 139.3 (Ar 4-C), 136.2 (Ar 3-C), 125.0 (Ar 5-C), 81.3 (OC(CH₃)₃), 76.9 (pyrrolidine 3-C), 61.6 (pyrrolidine 2-C), 54.2 (ethyl CH₂), 53.7 (piperazine 3-C and 5-C), 53.2 (piperazine 2-C and 6-C), 50.3 (pyrrolidine 5-C), 34.3 (CH₂Ar), 28.8 (OC(CH₃)₃), 26.3 (pyrrolidine 4-C), 11.7 (ethyl CH₃); ν_{max} /cm⁻¹ (neat) 2970, 2812, 1686, 1390, 1363, 1162, 1111, 1027; *m/z* (ESI) 375 (100%, MH⁺); Found: MH⁺, 375.2765. C₂₁H₃₅N₄O₂ requires *MH*, 375.2754.

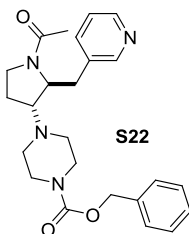
(2*R*,3*S*)-*N*-ethyl-3-(4-ethylpiperazin-1-yl)-2-(pyridin-3-ylmethyl)pyrrolidine-1-carboxamide **S21**



TFA (1.00 mL) was added to a solution of pyrrolidine **S19** (0.100 g, 0.270 mmol) in CH₂Cl₂ (3.0 mL). The reaction mixture was stirred at room temperature for 16 h and concentrated *in vacuo*. The crude product was dissolved in CH₂Cl₂ (3.0 mL) and cooled to 0 °C (ice). To this was added NEt₃ (0.190 mL, 1.35 mmol) and ethyl isocyanate (23.0 μ L, 0.290 mmol). The reaction was allowed to warm to room temperature with stirring over 18 h and then concentrated *in vacuo* to give a crude product that was purified by flash column chromatography, eluting with 95:5 CH₂Cl₂–saturated methanolic NH₃ to furnish urea **S21** as a colourless oil, *R*_f 0.15 (CH₂Cl₂–saturated methanolic NH₃); δ_{H} (500 MHz, CDCl₃) 8.47 (1 H, d, *J* 5.0, Ar 6-H), 8.43 (1 H, s, Ar 2-H), 7.56 (1 H, d, *J* 7.7, Ar 4-H), 7.22 (1 H, dd, *J* 7.7, 5.0, Ar 5-H), 4.31 (1 H, t, *J* 5.2, NCONH), 4.20–4.18 (1 H, m, 4.10, pyrrolidine 2-H), 3.33 (2 H, q, *J* 8.6, ethyl CH₂), 3.30–3.25 (2 H, m, urea CH₂), 3.17 (1 H, app. dt, *J* 9.1, 4.3, pyrrolidine 5-H_A),

3.07 (1 H, dd, J 13.6, 3.5, ArCH_A), 2.94 (3 H, app. br s, pyrrolidine 3-H, piperazine 2-H), 2.76 (1 H, dd, J 13.6, 8.4, ArCH_B), 2.69 (3 H, app. br s, pyrrolidine 5-H_B, piperazine 3-H), 2.04 (1 H, app. ddd, J 12.1, 7.2, 3.4, pyrrolidine 4-H_A), 1.80-1.73 (1 H, m, pyrrolidine 4-H_A), 1.32 (3 H, app. t, J 7.3, urea CH₃), 1.15 (3 H, t, J 7.2, ethyl CH₃); δ_{C} (75 MHz, CDCl₃) 156.3 (NCO₂N), 150.3 (Ar 2-C), 147.8 (Ar 6-C), 136.9 (Ar 4-C), 133.7 (Ar 3-C), 123.3 (Ar 5-C), 66.9 (pyrrolidine 3-C), 61.3 (pyrrolidine 2-C), 51.8 (piperazine 3-C and 5-C), 51.4 (piperazine 2-C and 6-C), 45.0 (pyrrolidine 5-C), 36.6 (urea CH₂), 35.4 (ethyl CH₂ and ArCH₂), 24.1 (pyrrolidine 4-C), 15.5 (urea CH₂), 9.3 (ethyl CH₃); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3336, 2973, 1673, 1623, 1532, 1449, 1373, 1197, 1125; m/z (ESI) 346 (100%, MH⁺); Found: MH⁺, 346.2604. C₁₉H₃₁N₅O requires MH , 346.2601.

Benzyl-4-[(2*S*,3*R*)-1-acetyl-2-(pyridin-3-ylmethyl)pyrrolidin-3-yl]piperazine-1-carboxylate **S22**

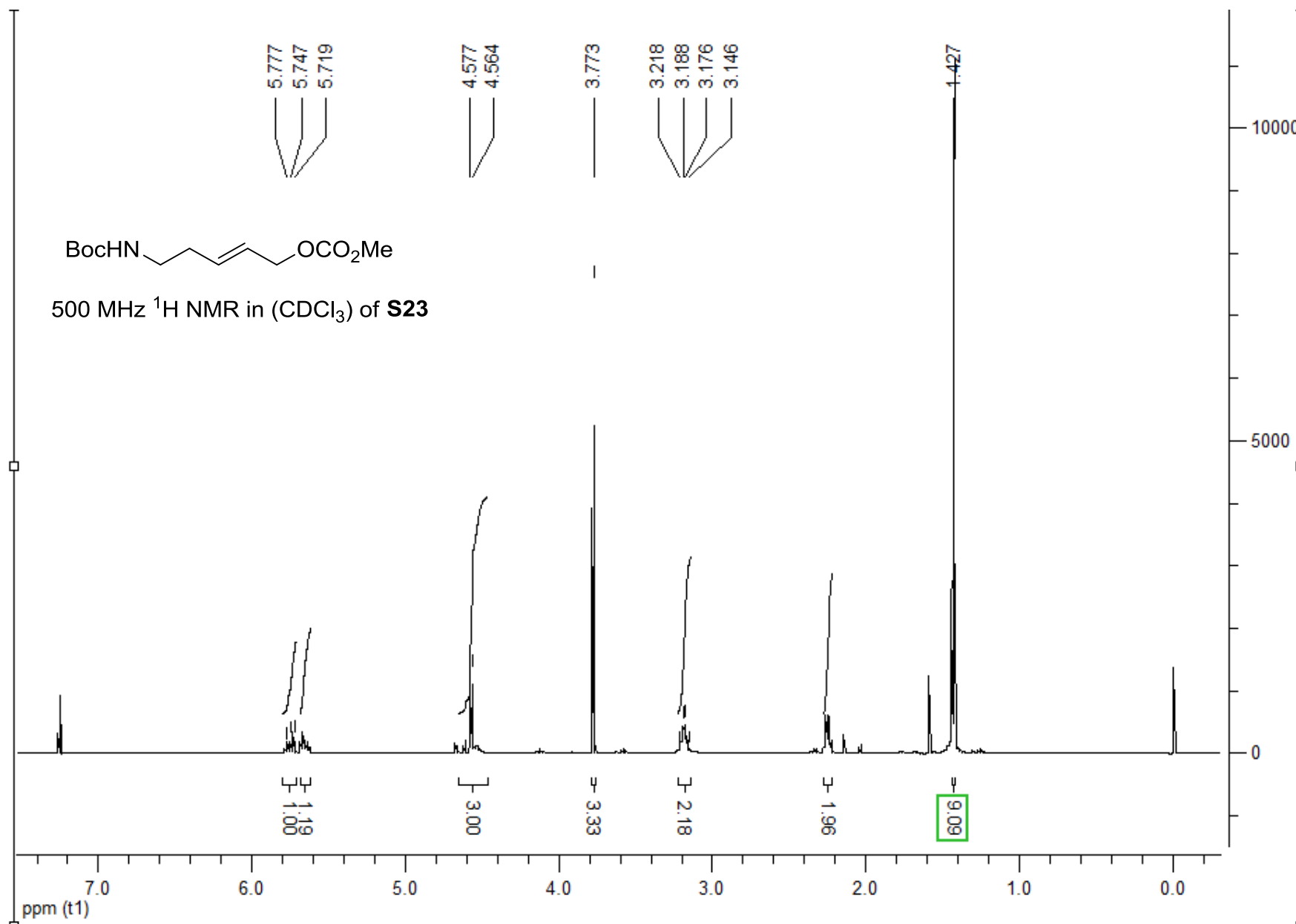


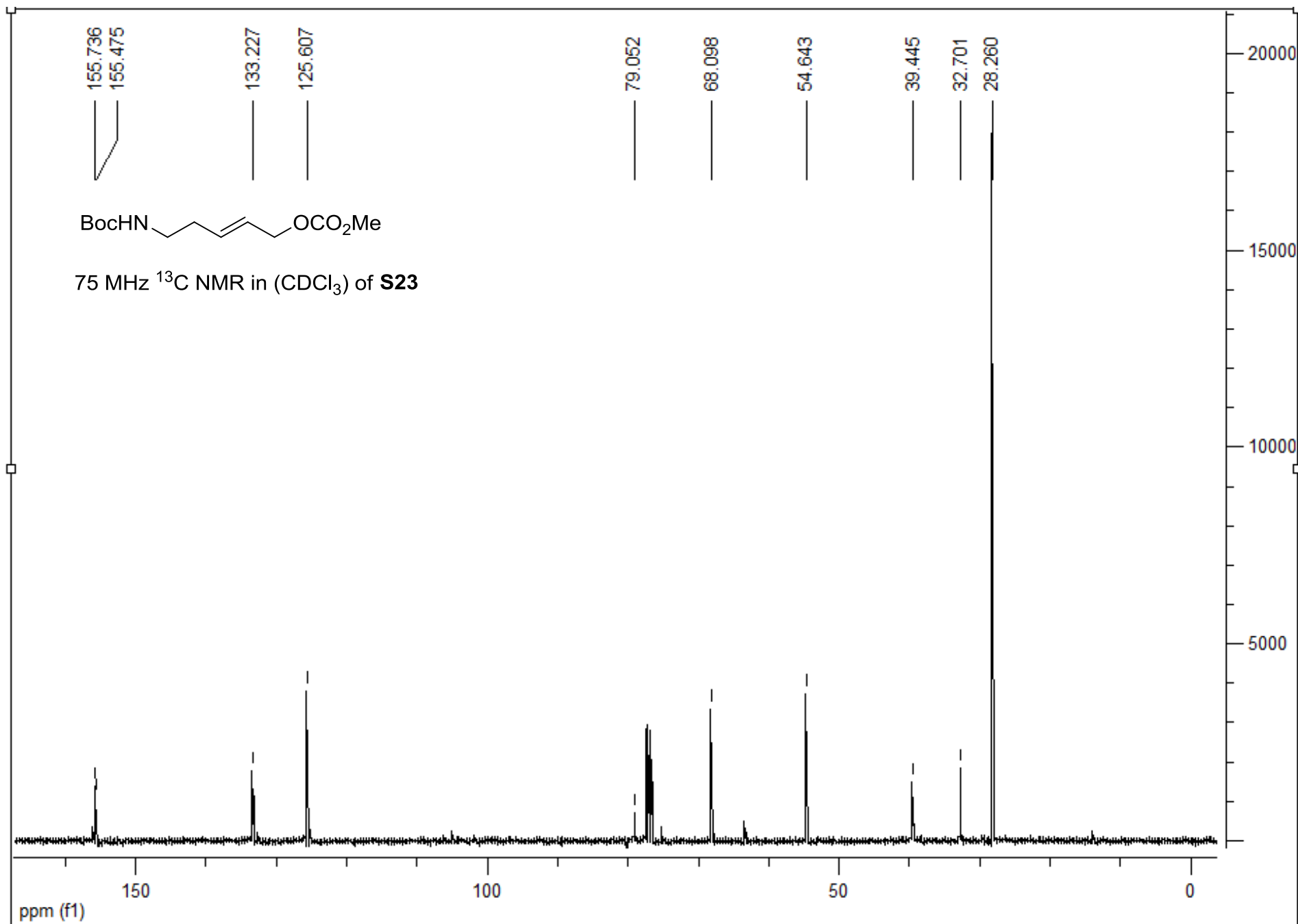
TFA (2.0 mL) was added to a solution of **ent-S10** (0.391 g, 0.810 mmol) in CH₂Cl₂ (6.0 mL). The reaction mixture was stirred at room temperature for 16 h and concentrated *in vacuo*. The crude product was dissolved in CH₂Cl₂ (0.8 mL) and cooled to 0 °C (ice). To this was added DIPEA (0.508 g, 4.00 mmol) and acyl chloride (94.0 mg, 1.20 mmol). The reaction was allowed to warm to room temperature with stirring over 18 h and then concentrated *in vacuo* to give a crude product that was purified by flash column chromatography, eluting with 96:3.6:0.4 DCM–EtOH–NH₄OH to furnish pyrrolidine **S22** (0.312 g, 93%, 4:1 mixture of rotameric species, major species characterised) as a colourless oil, R_f 0.0.2 (96:3.6:0.4 DCM–EtOH–NH₄OH); δ_{H} (500 MHz, MeOD, 333 K) 8.42 (1 H, d, J 1.8, Ar 2-H), 8.40 (1 H, dd, J 4.9, 1.8, Ar 6-H), 7.74 (1 H, app. dt, J 7.8, 1.8, Ar 4-H), 7.36-7.28 (6 H, m, Ar 5-H, Cbz Ar-H), 5.08 (2 H, s, OCH₂Ar), 4.32 (1 H, ddd, J 8.5, 5.0, 2.6, pyrrolidine 2-H), 3.61 (1 H, app. dt, J 10.6, 7.9, pyrrolidine 5-H_A), 3.42-3.37 (5 H, m, piperazine 2-H and pyrrolidine 5-H_B), 3.07 (1 H, dd, J 13.6, 5.0, ArCH_A), 2.93 (2 H, ddd, J 6.5, 3.9, 2.6, pyrrolidine 3-H), 2.80 (1 H, dd, J 13.6, 8.5, ArCH_B), 2.34-2.25 (4 H, m, piperazine 3-H), 2.07-2.01 (5 H, m, pyrrolidine 4-H and NCOCH₃); δ_{C} (125 MHz, MeOD, 333 K) 171.6 (NCOCH₃), 156.8 (ArCH₂OCO₂), 151.0 (Ar 2-C), 148.3 (Ar 6-C), 139.3 (Ar 4-C), 138.2 (Cbz Ar 1-C), 136.1 (Ar 3-C), 129.5 (Cbz Ar-C), 129.1 (Cbz Ar-C), 128.9 (Cbz Ar-C), 125.1 (Ar 5-C), 68.9 (pyrrolidine 3-C), 68.4 (OCH₂Ar), 61.3 (pyrrolidine 2-C), 50.6 (piperazine 3-C), 47.9 (pyrrolidine 5-C), 45.0 (piperazine 2-C), 36.5 (CH₂Ar), 26.5 (pyrrolidine 4-C), 22.4 (NCOCH₃); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2948, 1695, 1629, 1422, 1358, 1243, 1119, 1079; m/z (ESI) 423 (100%, MH⁺); Found: MH⁺, 423.2399. C₂₄H₃₁N₄O₃ requires MH , 423.2391.

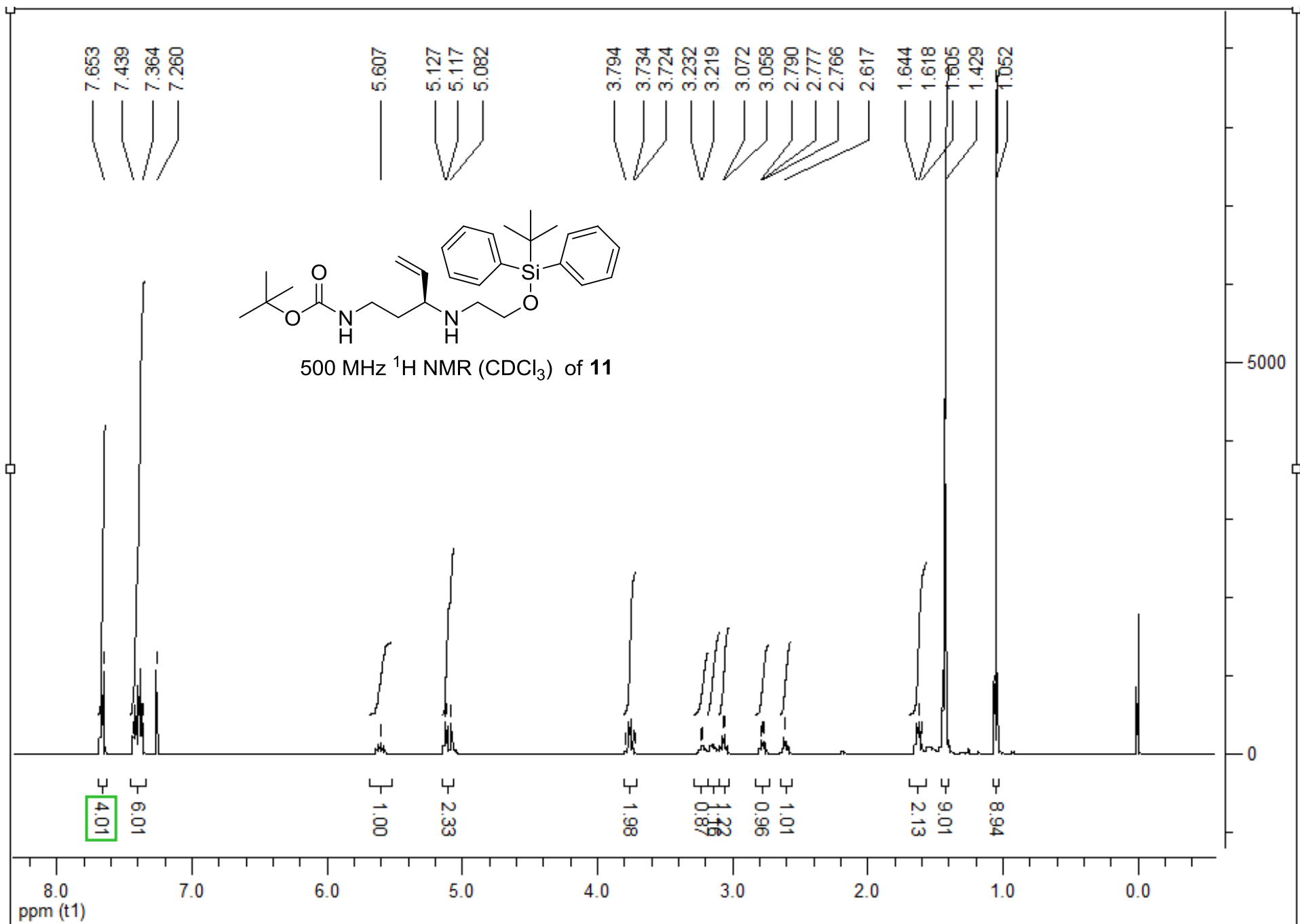
S9. References

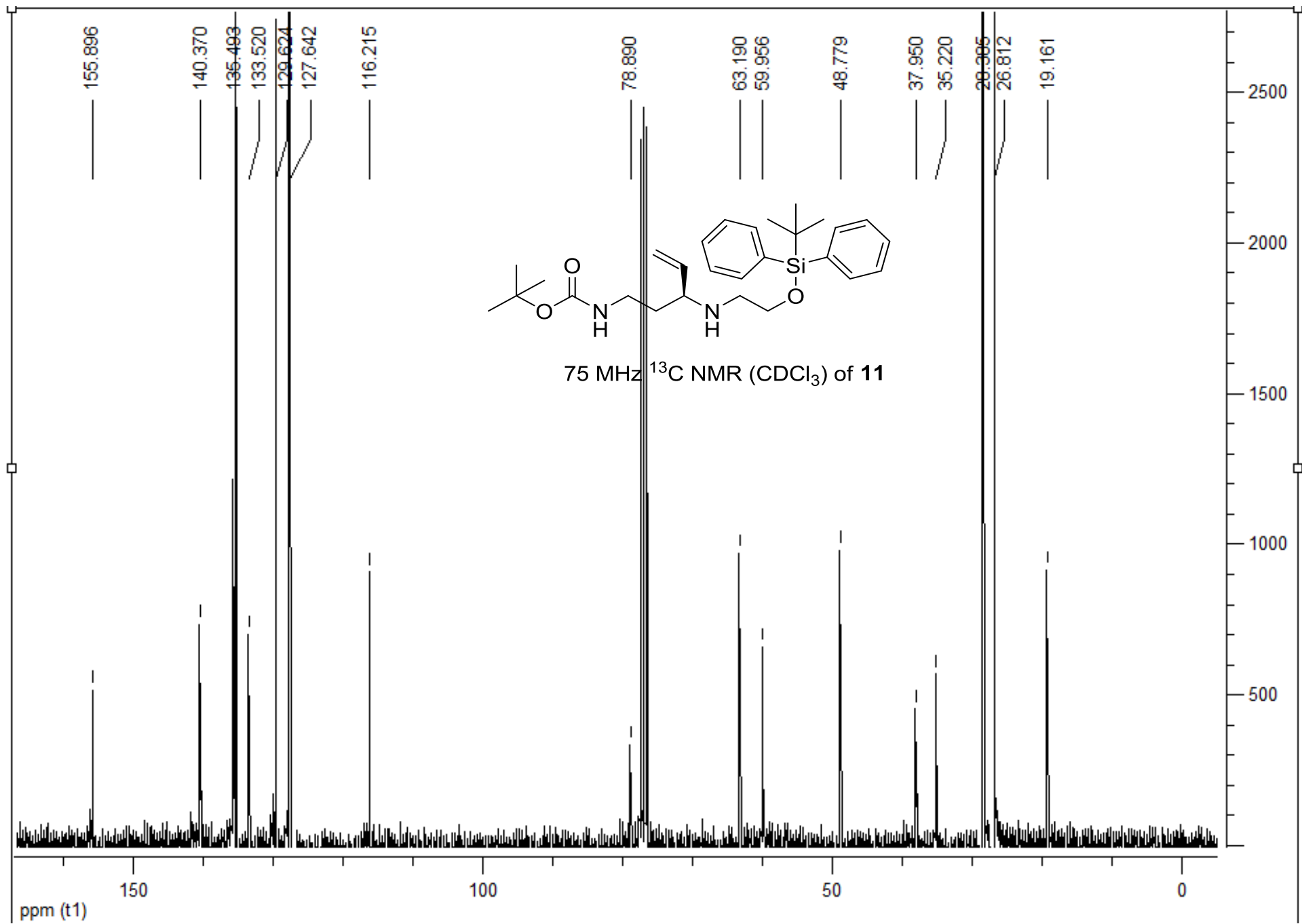
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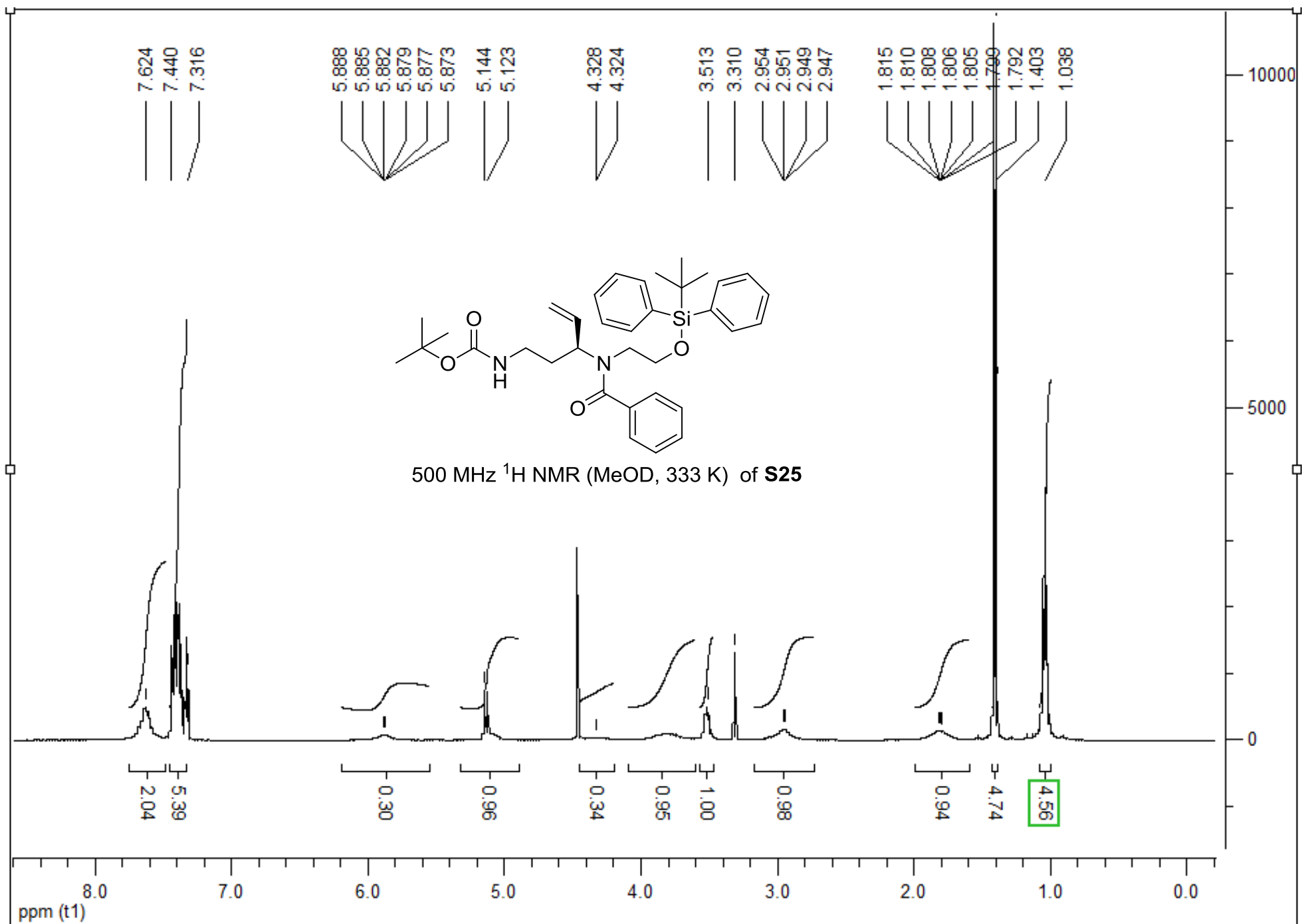
S10. NMR Spectra and HPLC Traces

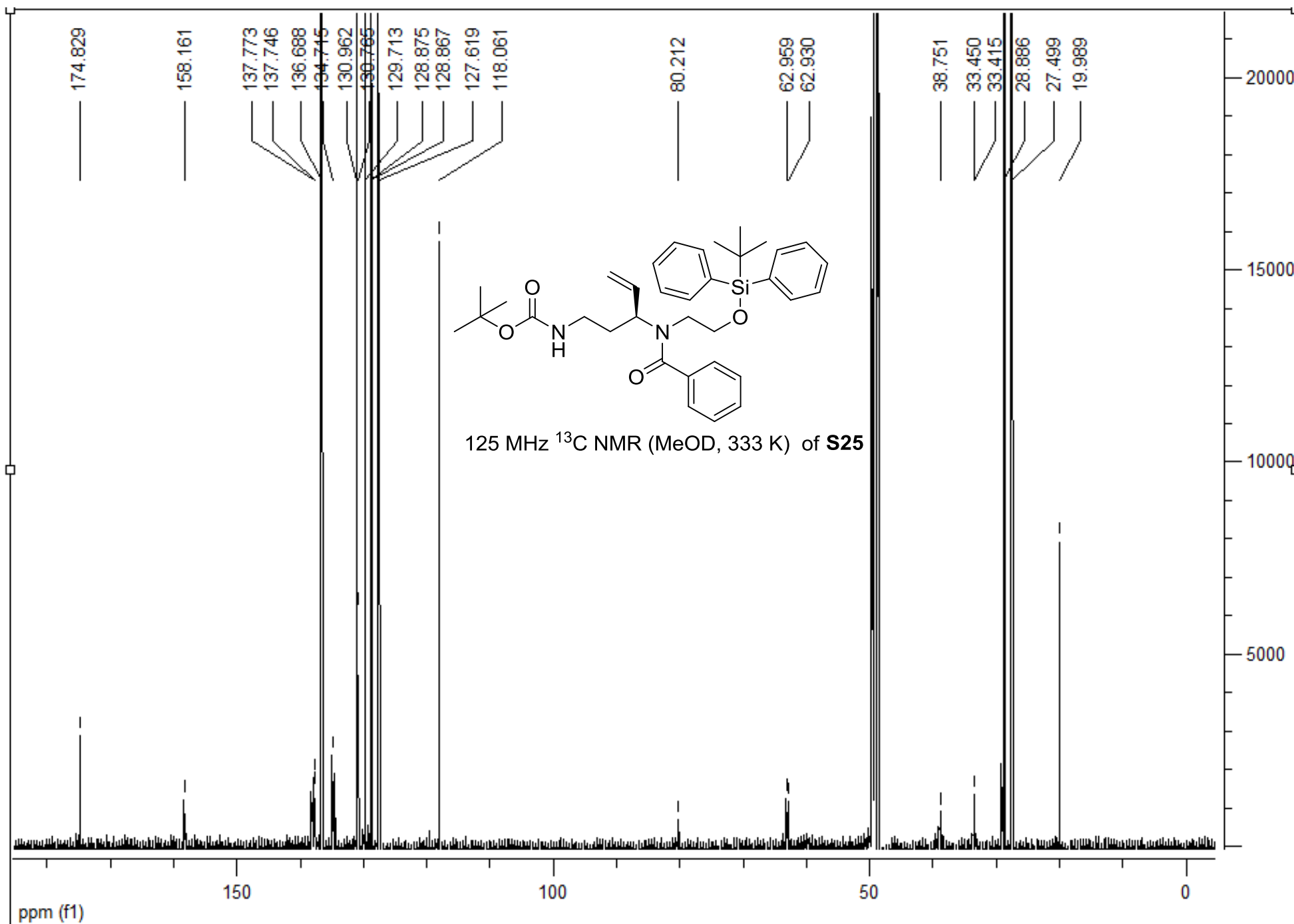






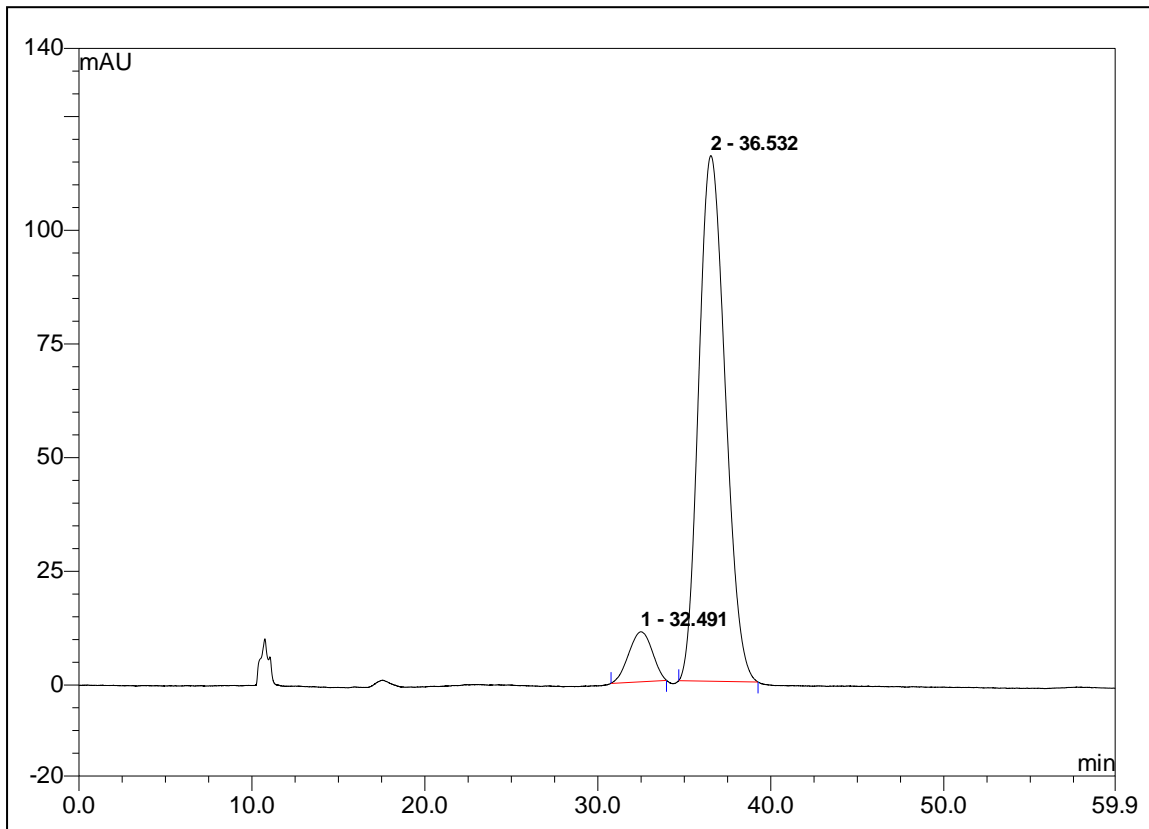






S25

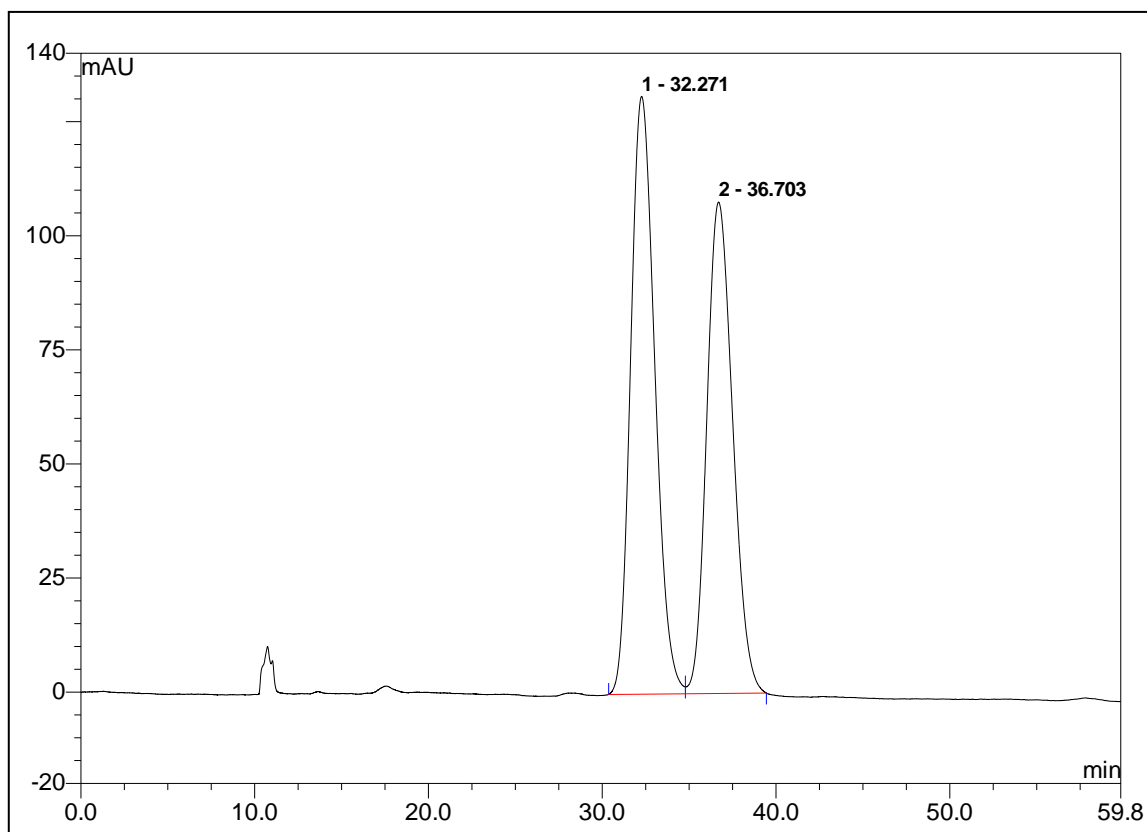
Sample Name:	RD256	Injection Volume:	10.0
Vial Number:	P1:F5	Channel:	DAD_Signal_A
Sample Type:	unknown	Wavelength:	n.a.
Control	NP PreMix 100%B 60min 0,3ml min pos3	Bandwidth:	n.a.
Program:	OD-H	Dilution Factor:	1.0000
Quantif. Method:	MH1	Sample Weight:	1.0000
Recording Time:	10/10/2013 12:08	Sample Amount:	1.0000
Run Time (min):	59.91		



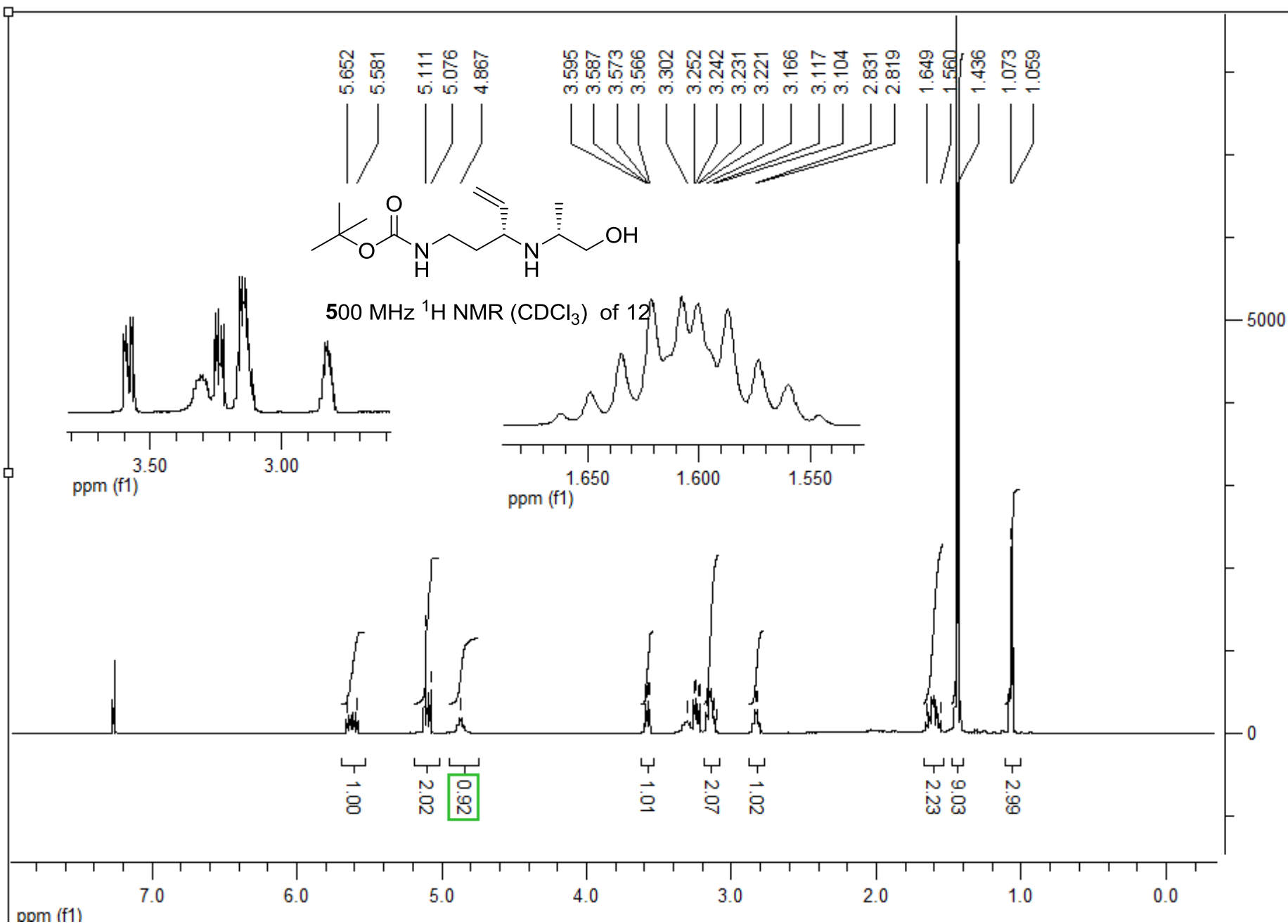
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	32.49	n.a.	11.000	17.324	7.78	n.a.	BMB
2	36.53	n.a.	115.572	205.417	92.22	n.a.	BMB
Total:			126.572	222.740	100.00	0.000	

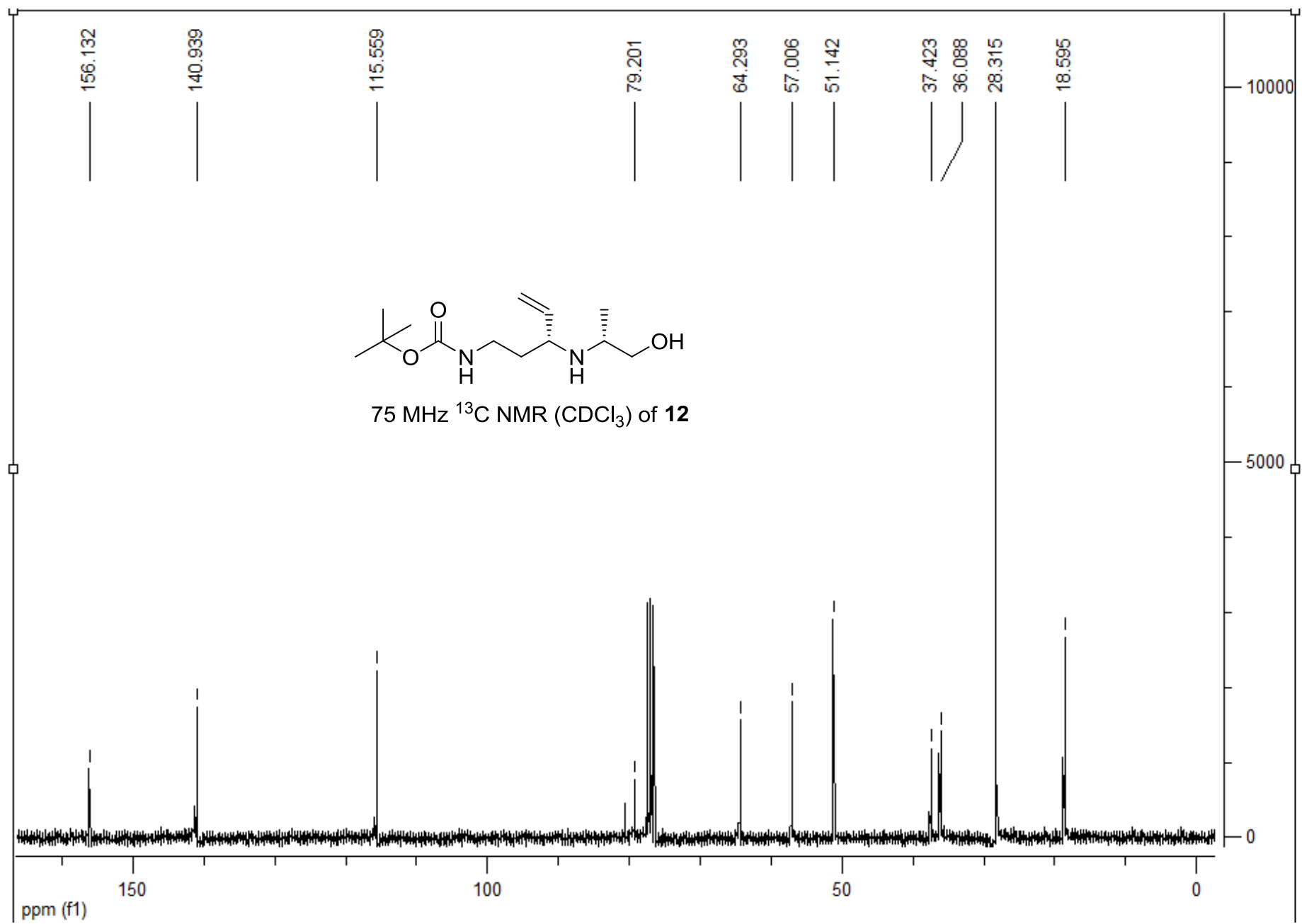
S25 mix 5%IPA95%Hexane

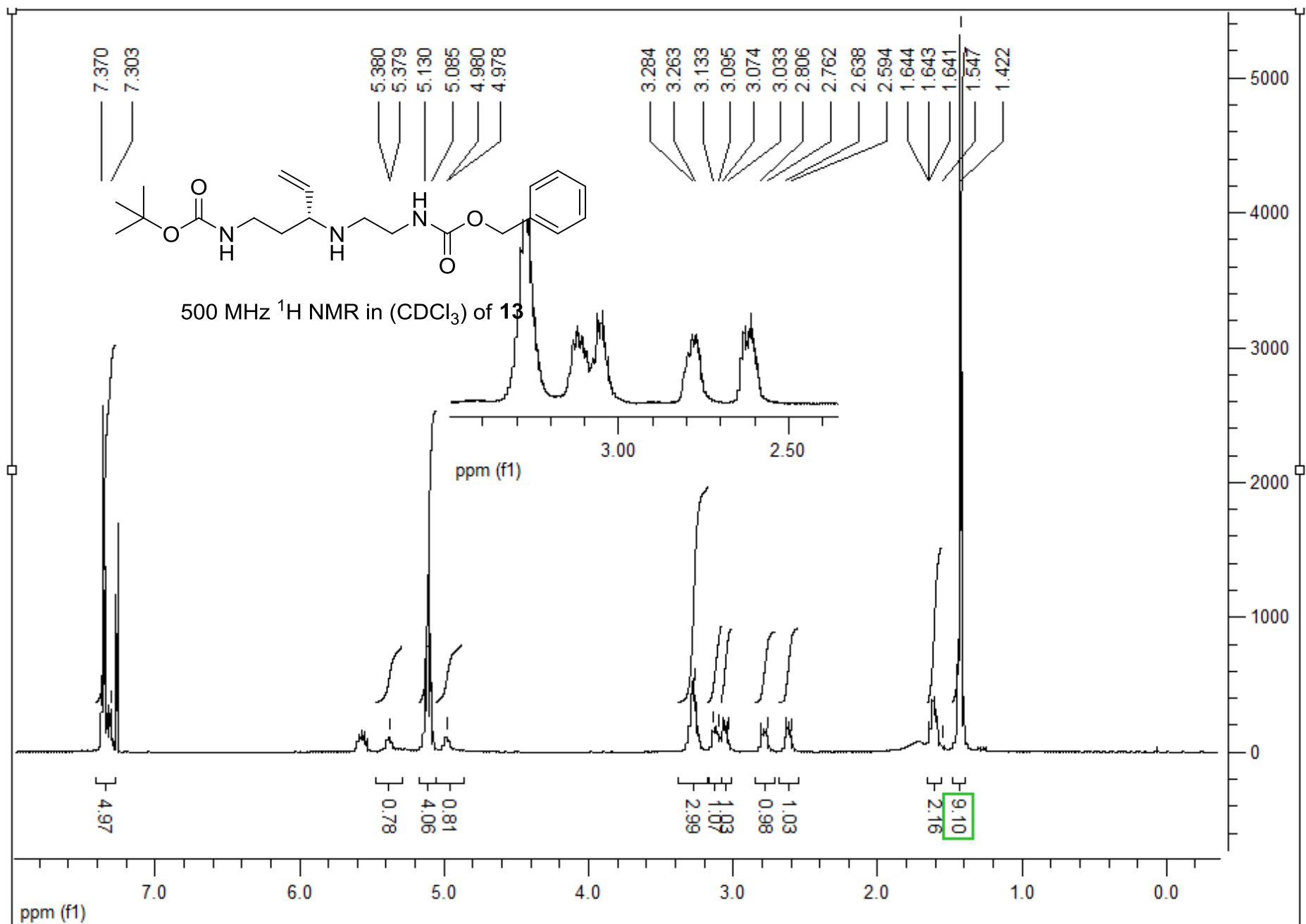
Sample Name: RD256/270 mix 5%IPA95%Hexane	Injection Volume: 10.0
Vial Number: P1:F4	Channel: DAD_Signal_A
Sample Type: unknown	Wavelength: n.a.
Control Program: NP PreMix 100%B 60min 0,3ml min pos3 OD-H	Bandwidth: n.a.
Quantif. Method: MH1	Dilution Factor: 1.0000
Recording Time: 10/10/2013 10:41	Sample Weight: 1.0000
Run Time (min): 59.84	Sample Amount: 1.0000

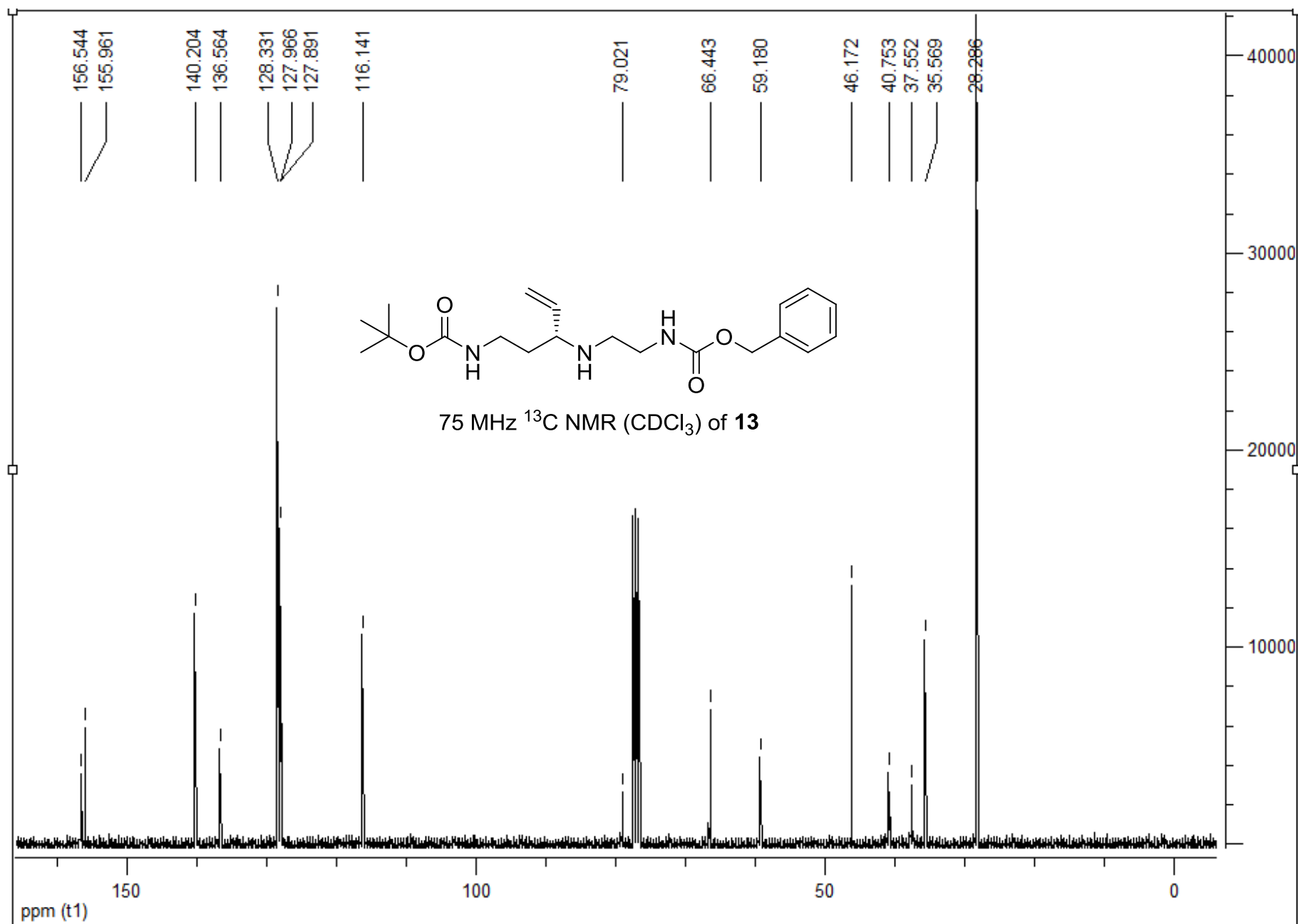


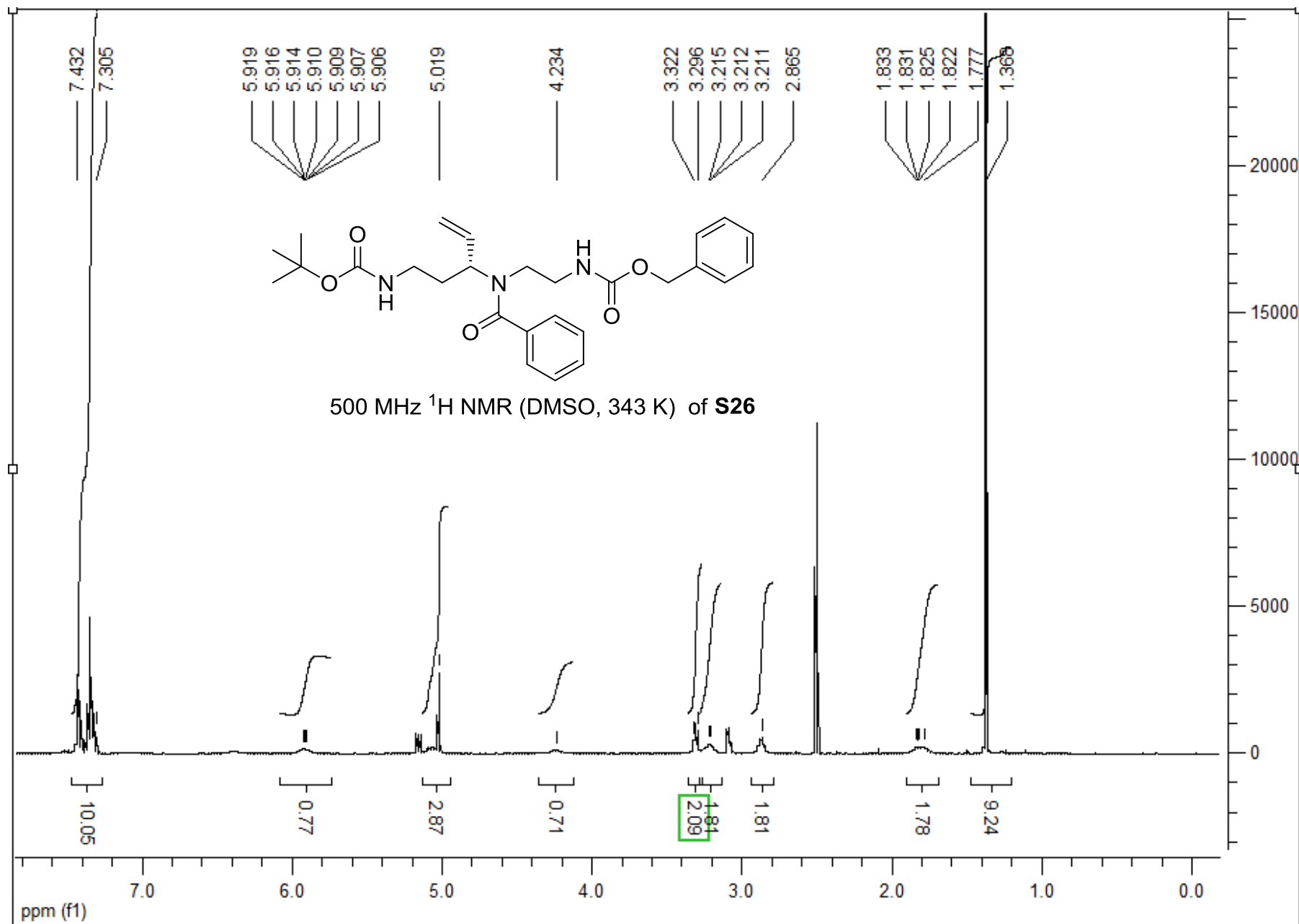
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	32.27	n.a.	130.988	211.581	53.20	n.a.	BM
2	36.70	n.a.	107.671	186.125	46.80	n.a.	MB
Total:			238.659	397.705	100.00	0.000	

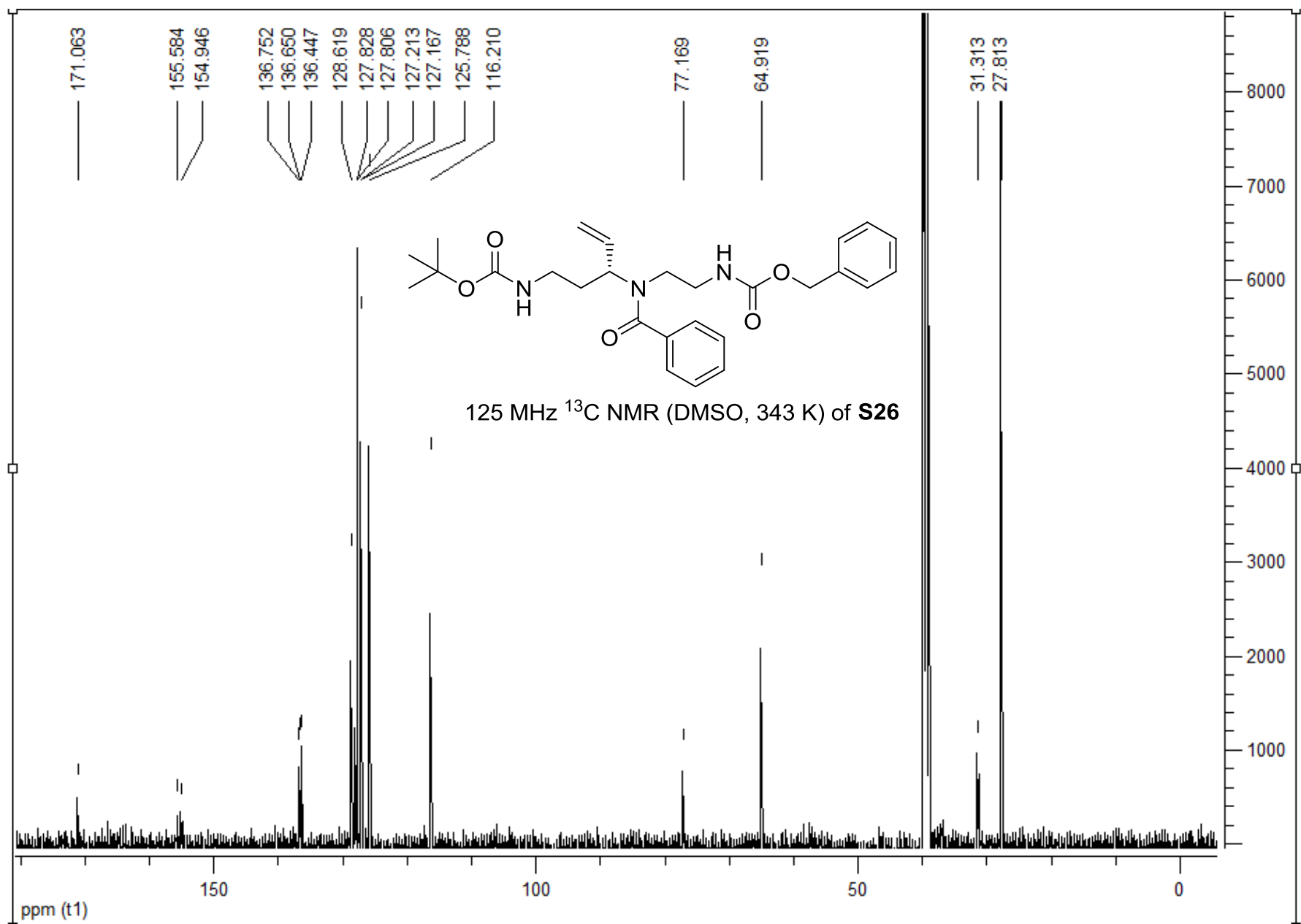




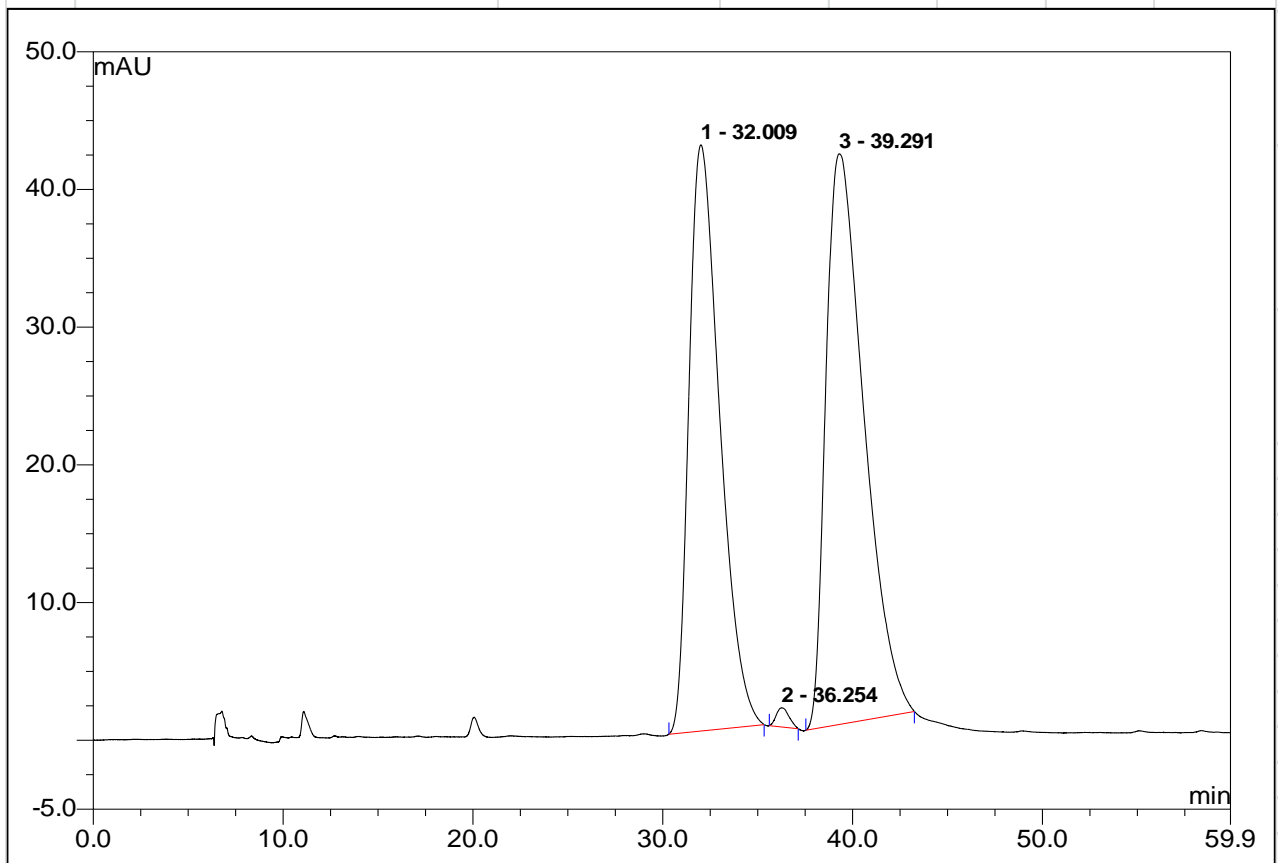






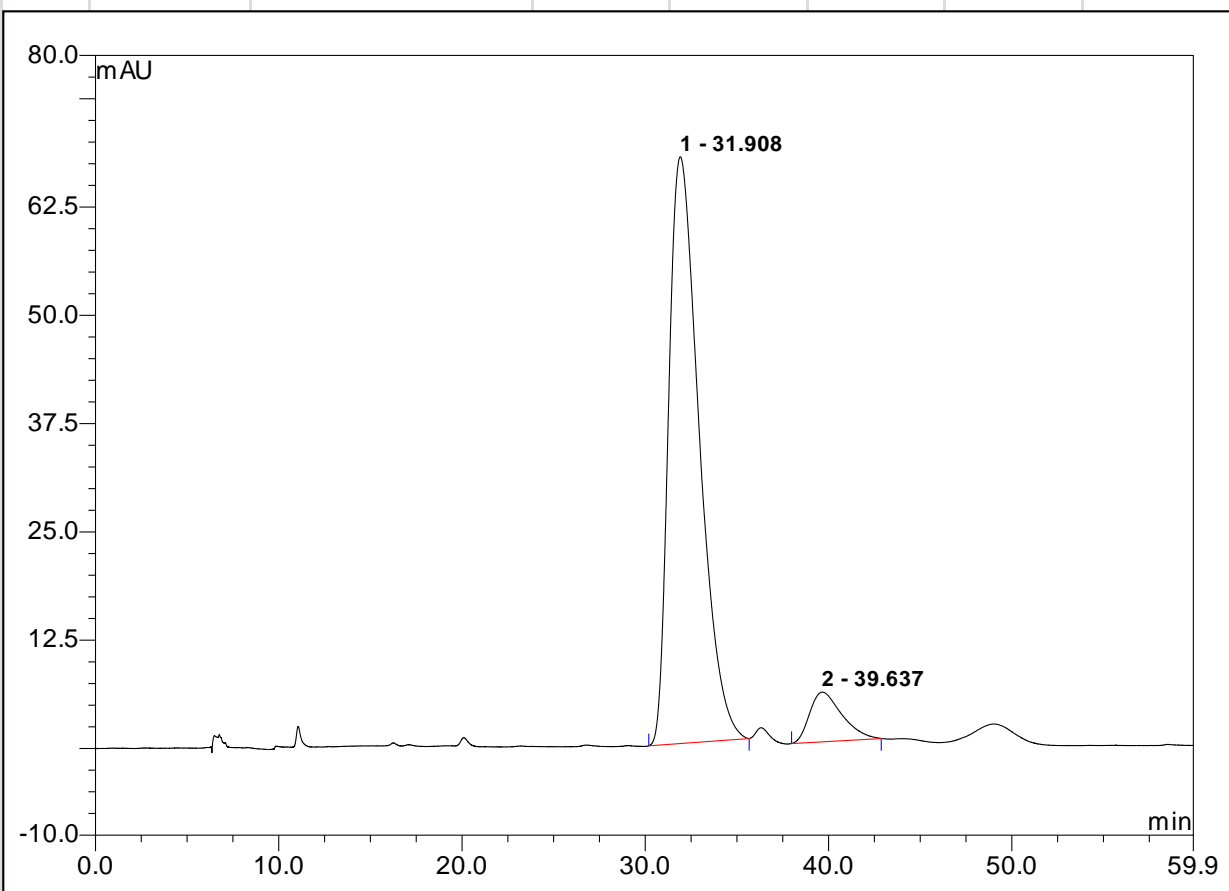


27	RD394/395 5%EtOH95%Hexane	S26			
Mobile phase - 5%EtOH / 95%Hexane					
Sampl	Flow Rate - 0.5ml/min	RD394/395 5%EtOH95%Hexane	Injection Volume:	10.0	
Vial N°	Column - Daicel Chiralcel AS-H 250mm x 4	P1:F5	Channel:	DAD_Signa	
Sample Type:	unknown		Wavelength:	n.a.	
Control Program:	NP PreMix 100%B 60min 0,5ml min pos1		Bandwidth:	n.a.	
Quantif. Method:	MH1		Dilution Factor:	1.0000	
Recording Time:	14/04/2014 12:02		Sample Weight:	1.0000	
Run Time (min):	59.90		Sample Amount:	1.0000	

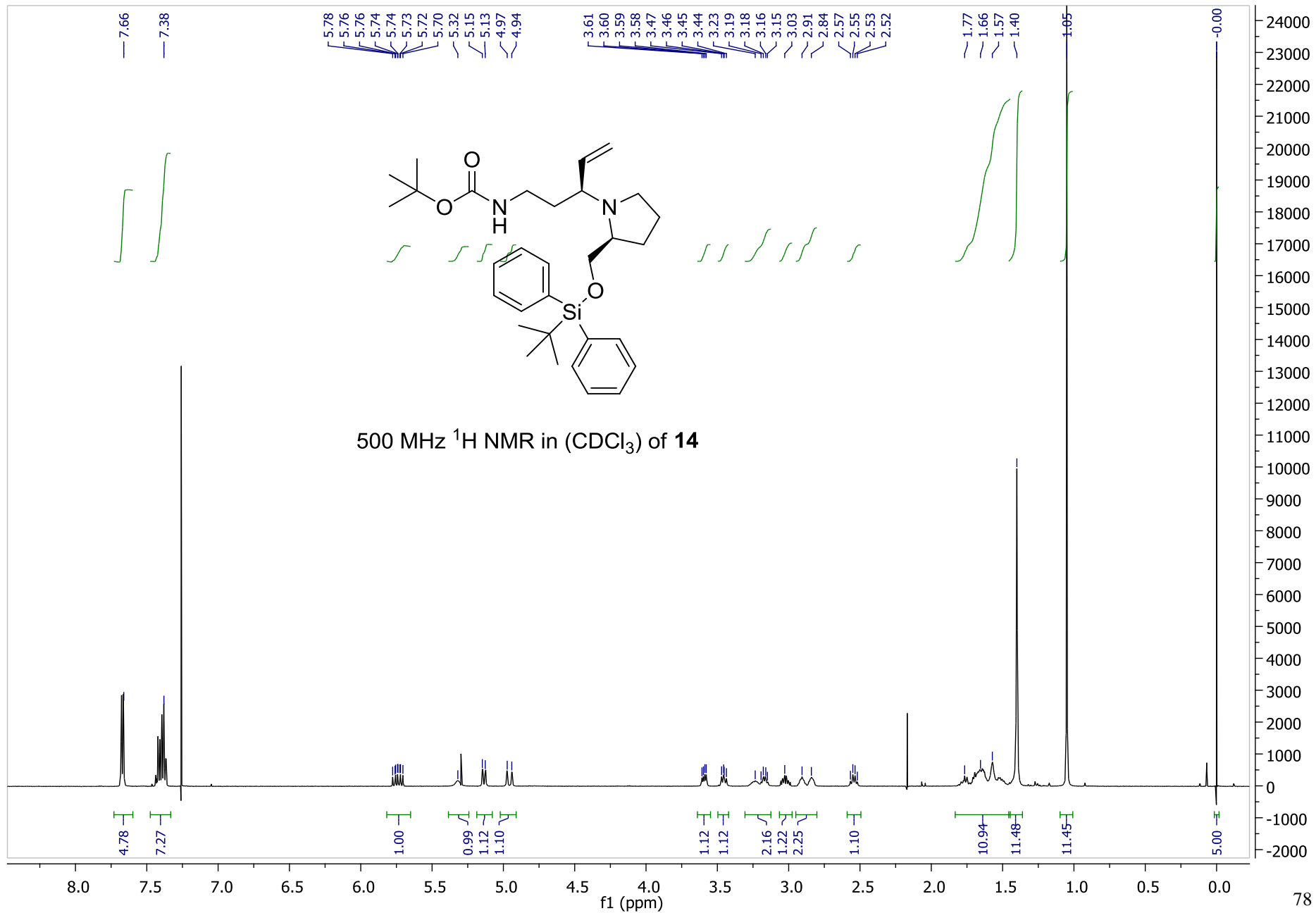


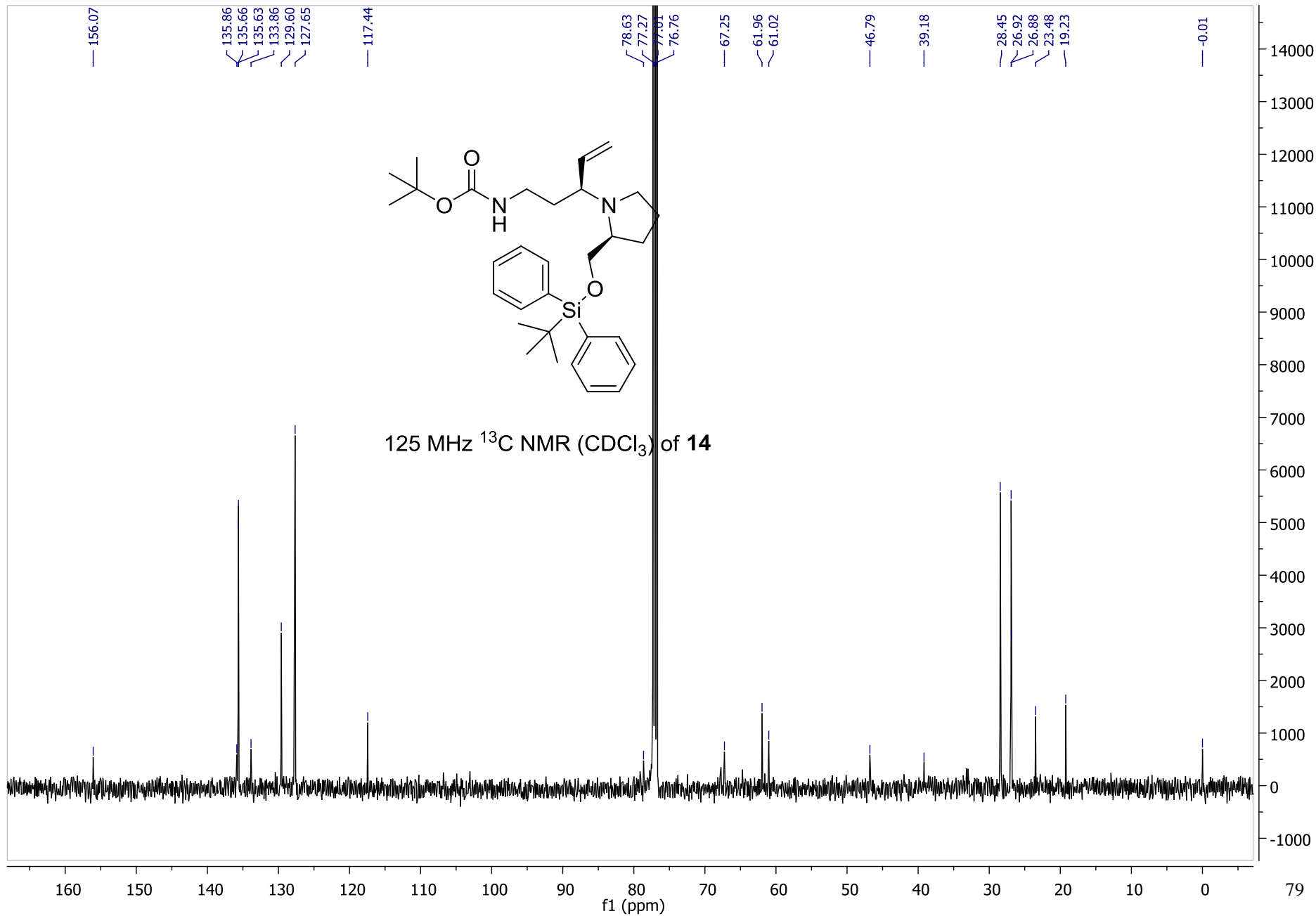
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	32.01	n.a.	42.576	80.107	45.14	n.a.	BMB
2	36.25	n.a.	1.401	1.090	0.61	n.a.	BMB
3	39.29	n.a.	41.449	96.259	54.24	n.a.	BMB
Total:			85.427	177.455	100.00	0.000	

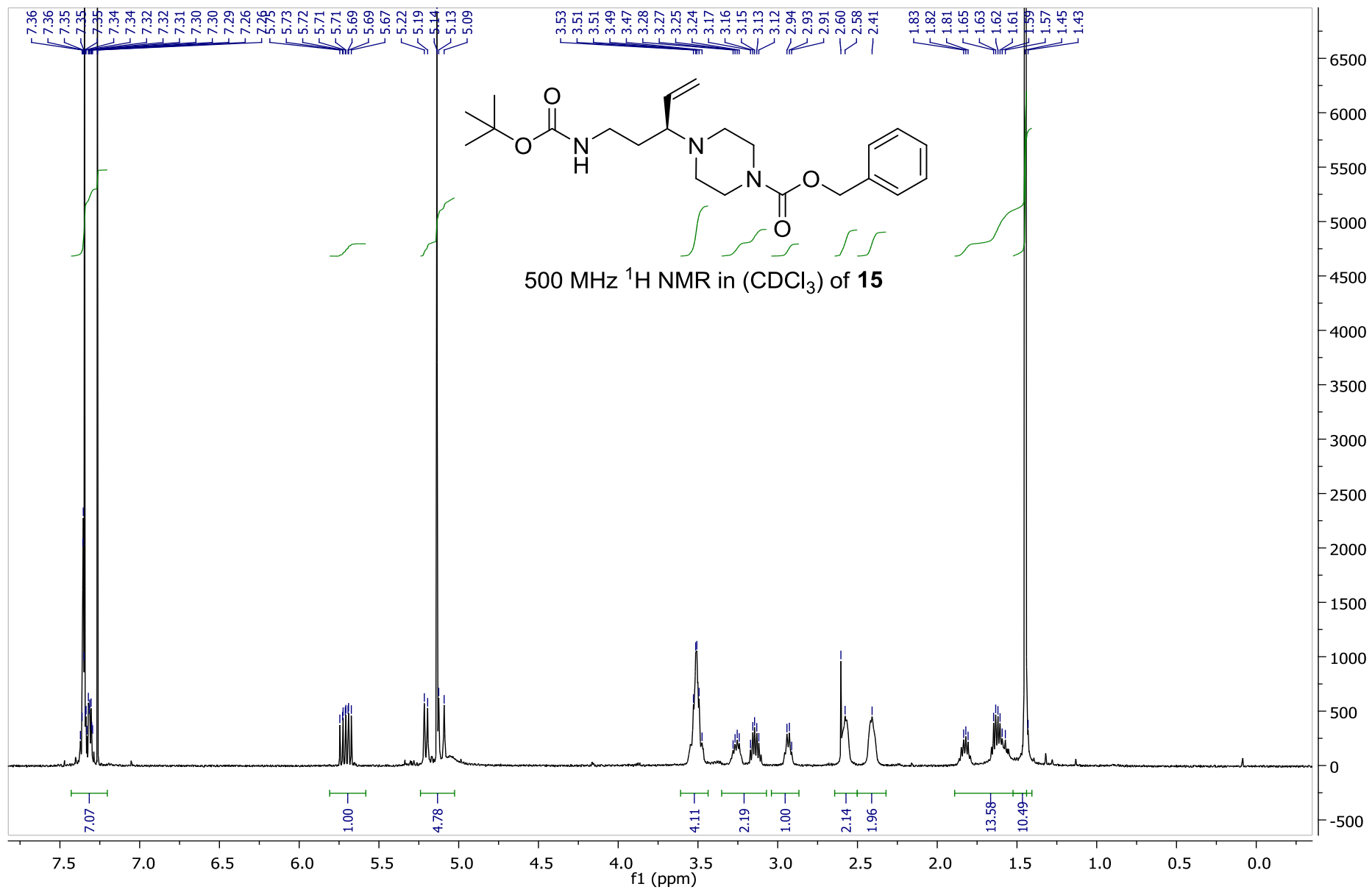
28	RD394 B1 5%EtOH95%Hexane	S26	
<i>Sample Name:</i>	RD394 B1 5%EtOH95%Hexane	<i>Injection Volume:</i>	10.0
<i>Vial Number:</i>	P1:F6	<i>Channel:</i>	DAD_Signa
<i>Sample Type:</i>	unknown	<i>Wavelength:</i>	n.a.
<i>Control Program:</i>	NP PreMix 100%B 60min 0,5ml min pos1	<i>Bandwidth:</i>	n.a.
<i>Quantif. Method:</i>	MH1	<i>Dilution Factor:</i>	1.0000
<i>Recording Time:</i>	14/04/2014 13:03	<i>Sample Weight:</i>	1.0000
<i>Run Time (min):</i>	59.90	<i>Sample Amount:</i>	1.0000

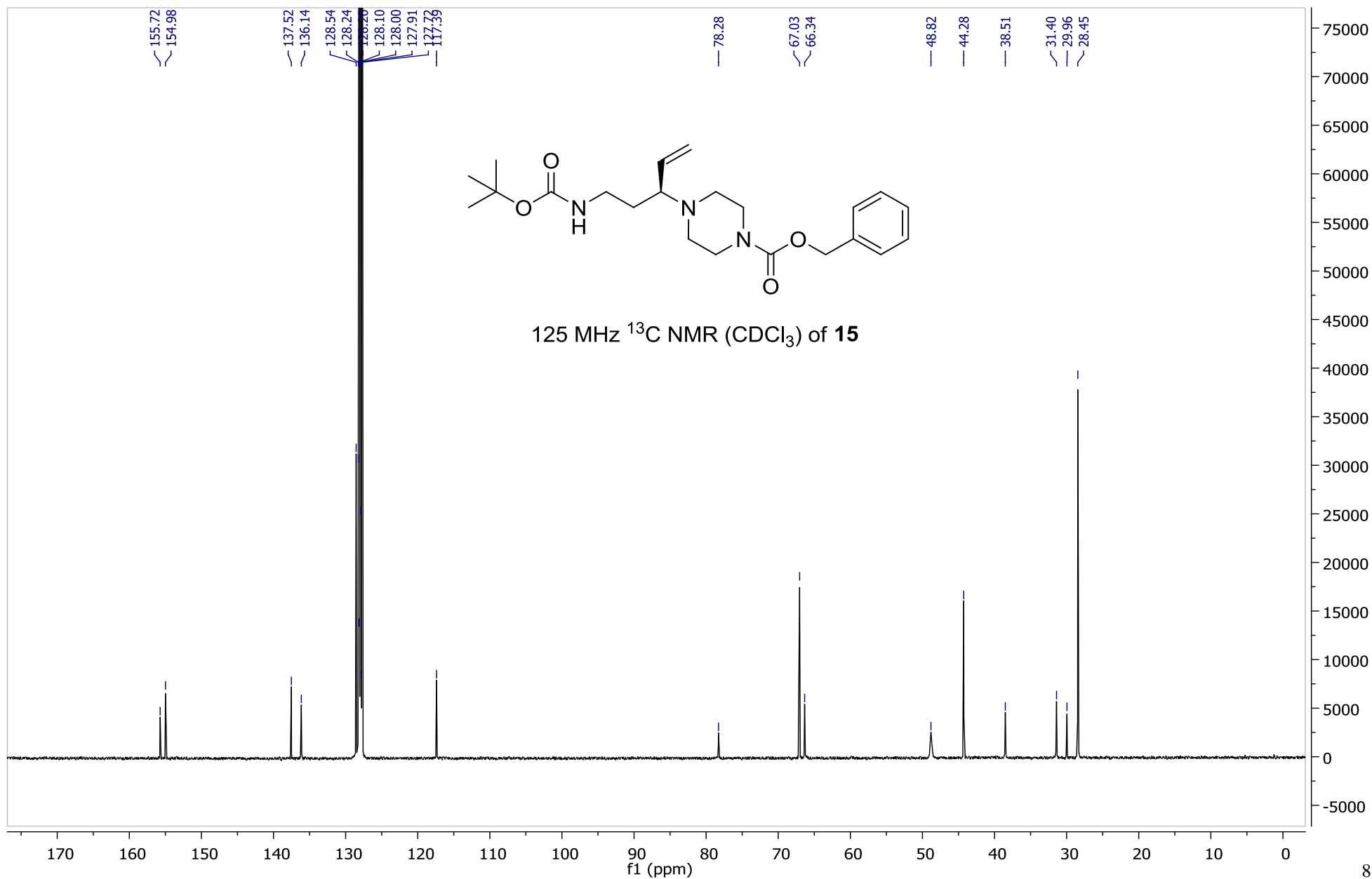


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	31.91	n.a.	67.736	130.474	91.77	n.a.	BMB*
2	39.64	n.a.	5.741	11.705	8.23	n.a.	BMB
Total:			73.477	142.179	100.00	0.000	





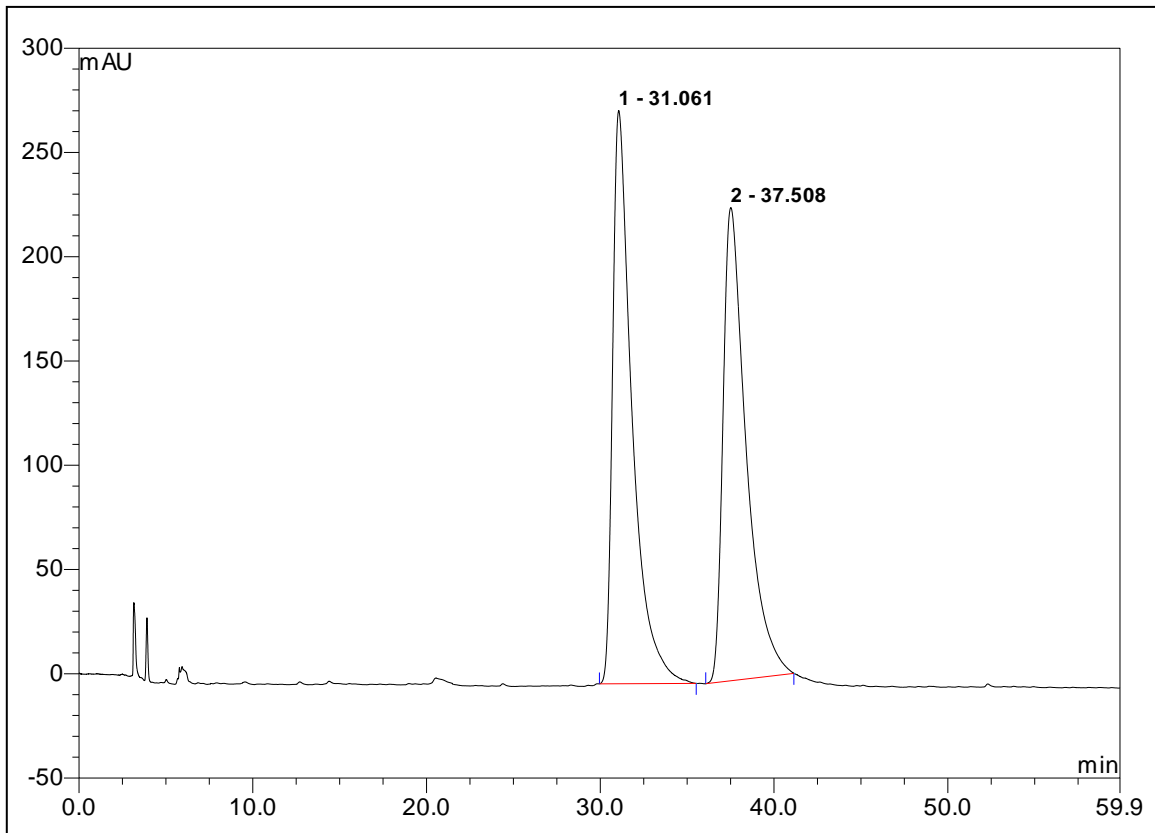




RD370/396 5%EtOH95%Hexane

15

<i>Sample Name:</i>	RD370/396 5%EtOH95%Hexane	<i>Injection Volume:</i>	10.0
<i>Vial Number:</i>	P1:F1	<i>Channel</i>	DAD_Signal_
<i>Sample Type:</i>	unknown	:	B
<i>Control Program:</i>	NP 100%B 60min 1,0ml min pos2 AD- H	<i>Wavelength:</i>	n.a.
<i>Quantif. Method:</i>	MH1	<i>Bandwidth:</i>	n.a.
<i>Recording Time:</i>	17/03/2014 12:40	<i>Dilution Factor:</i>	1.0000
<i>Run Time (min):</i>	59.91	<i>Sample Weight:</i>	1.0000
		<i>Sample Amount:</i>	1.0000

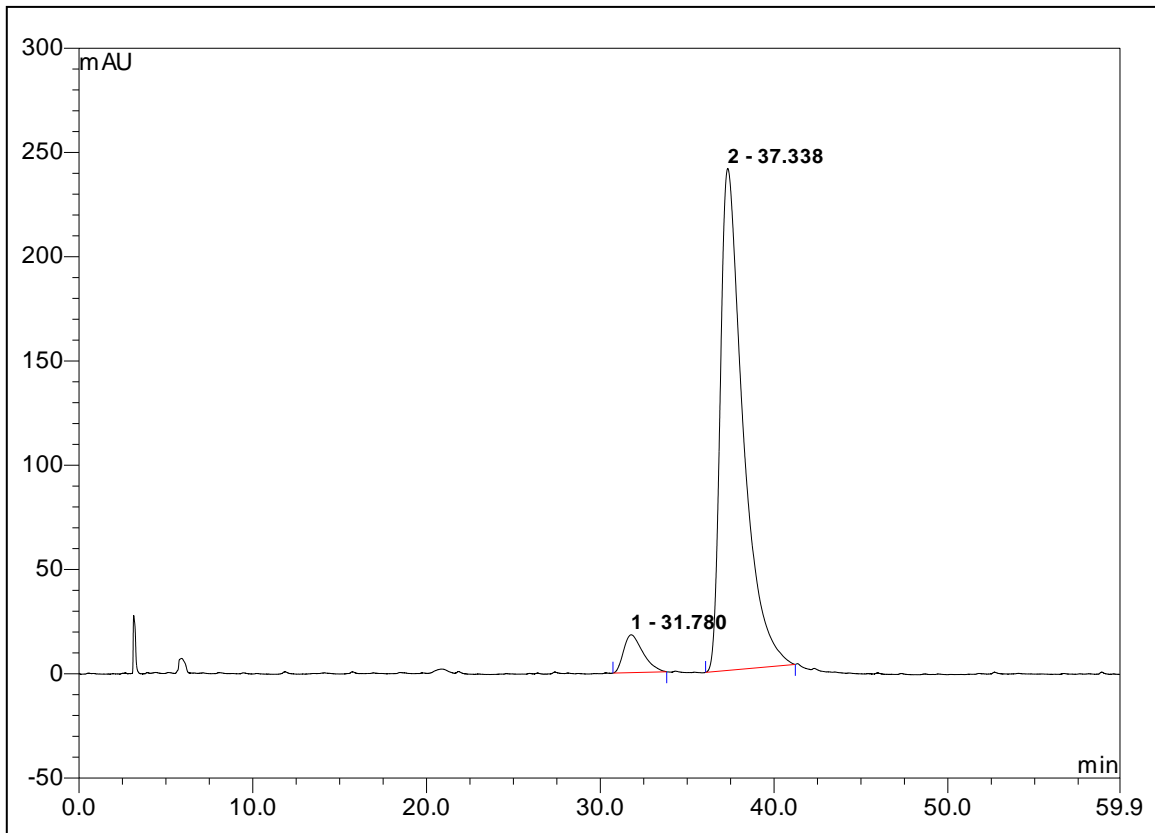


No.	Ret. Time min	Peak Name	Height mAU	Area mAU*min	Rel. Area %	Amount	Type
1	31.06	n.a.	274.76	357.454	50.47	n.a.	BMB
2	37.51	n.a.	226.95	350.863	49.53	n.a.	BMB
Total:			501.71	708.318	100.00	0.000	

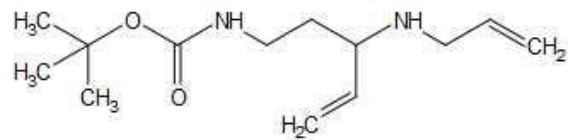
RD396 B1 5%EtOH95%Hexane

15

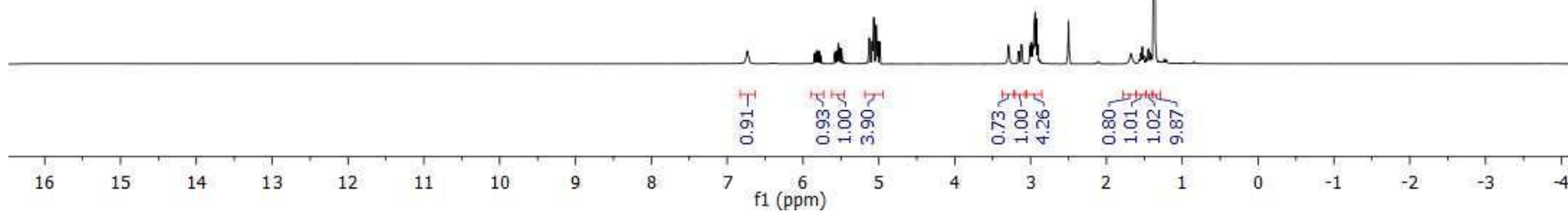
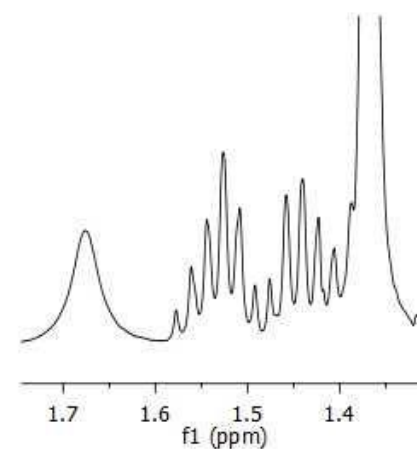
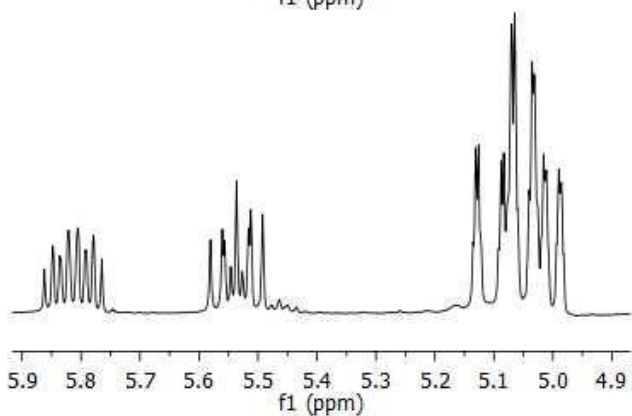
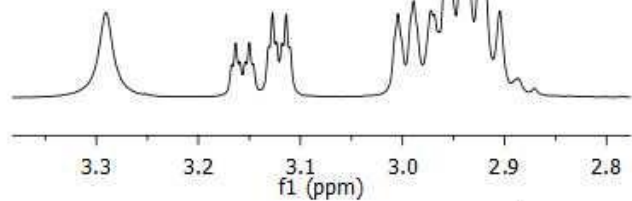
<i>Sample Name:</i>	RD396 B1 5%EtOH95%Hexane	<i>Injection Volume:</i>	10.0
<i>Vial Number:</i>	P1:F4	<i>Channel</i>	DAD_Signal_
<i>Sample Type:</i>	unknown	:	B
<i>Control Program:</i>	NP 100%B 60min 1,0ml min pos2 AD- H	<i>Wavelength:</i>	n.a.
<i>Quantif. Method:</i>	MH1	<i>Bandwidth:</i>	n.a.
<i>Recording Time:</i>	17/03/2014 14:42	<i>Dilution Factor:</i>	1.0000
<i>Run Time (min):</i>	59.90	<i>Sample Weight:</i>	1.0000
		<i>Sample Amount:</i>	1.0000

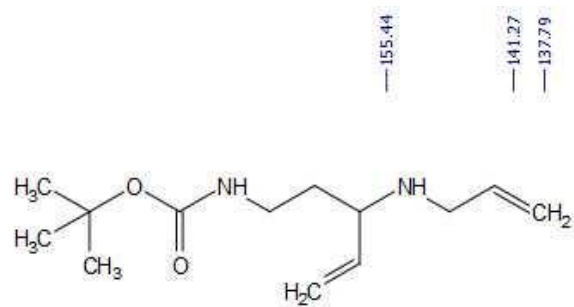


No.	Ret. Time min	Peak Name	Height mAU	Area mAU*min	Rel. Area %	Amount	Type
1	31.78	n.a.	18.171 240.76	23.359	6.01	n.a.	BMB
2	37.34	n.a.	7	365.221	93.99	n.a.	BMB
Total:			258.93 8	388.580	100.00	0.000	

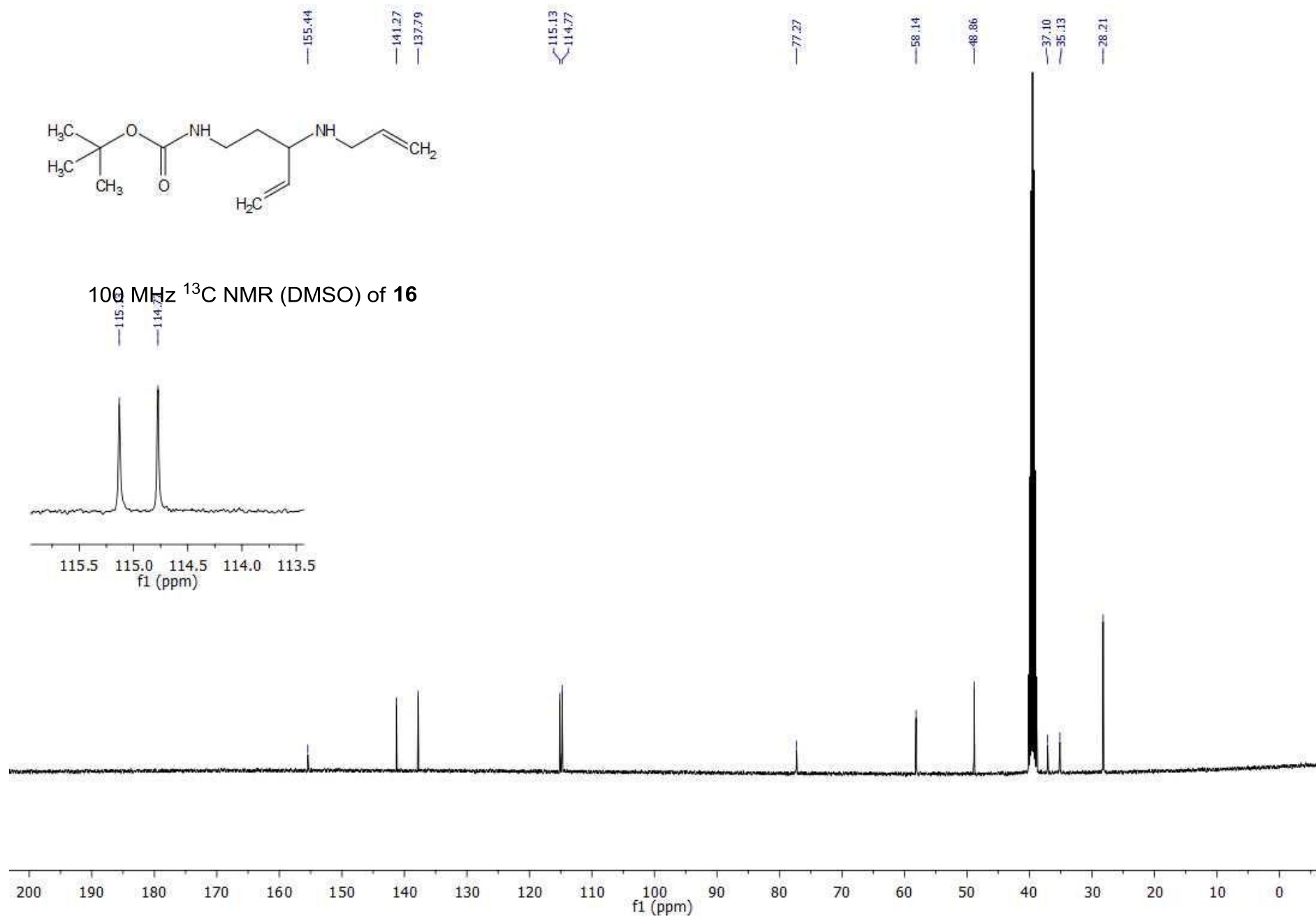


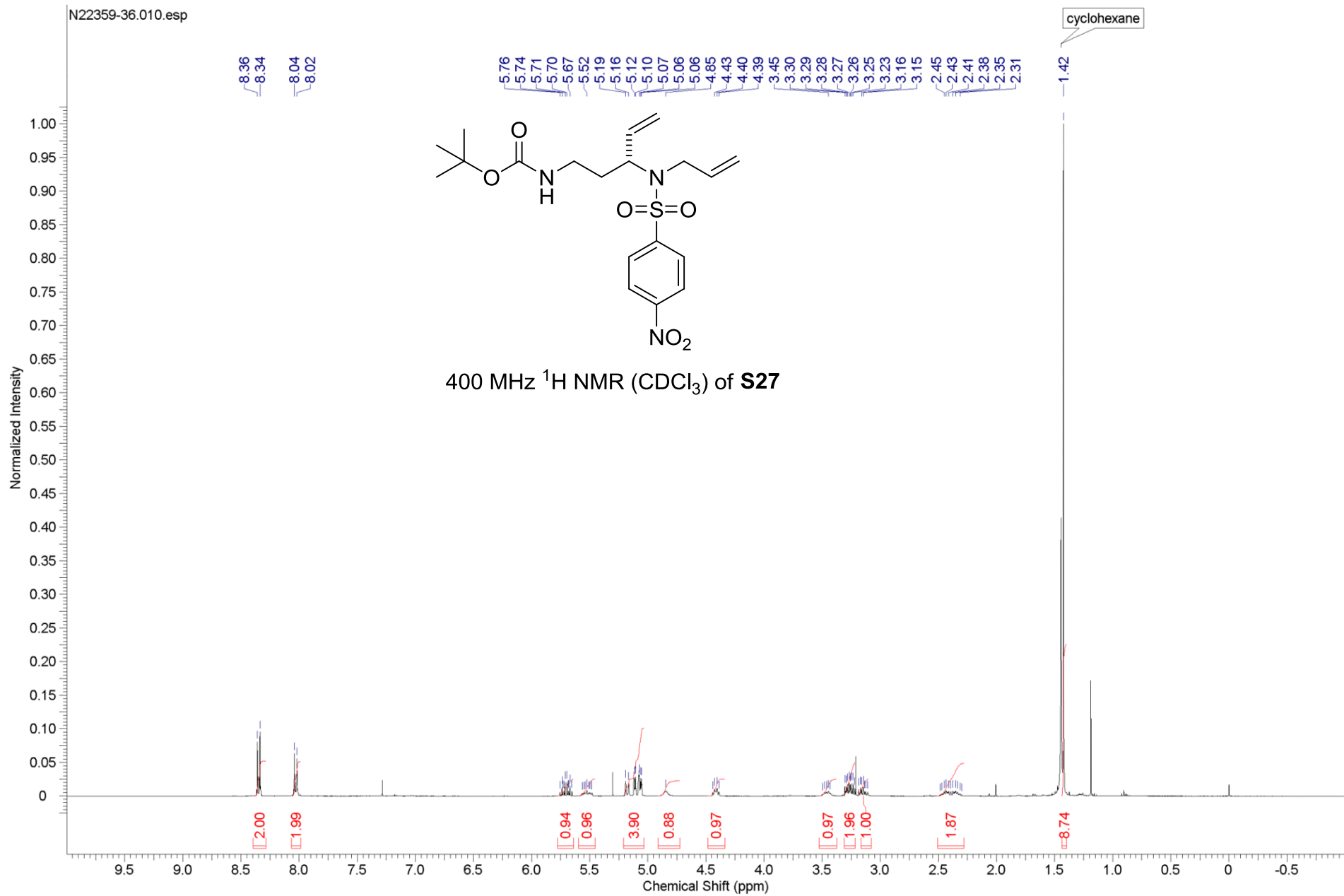
400 MHz ^1H NMR (DMSO) of **16**



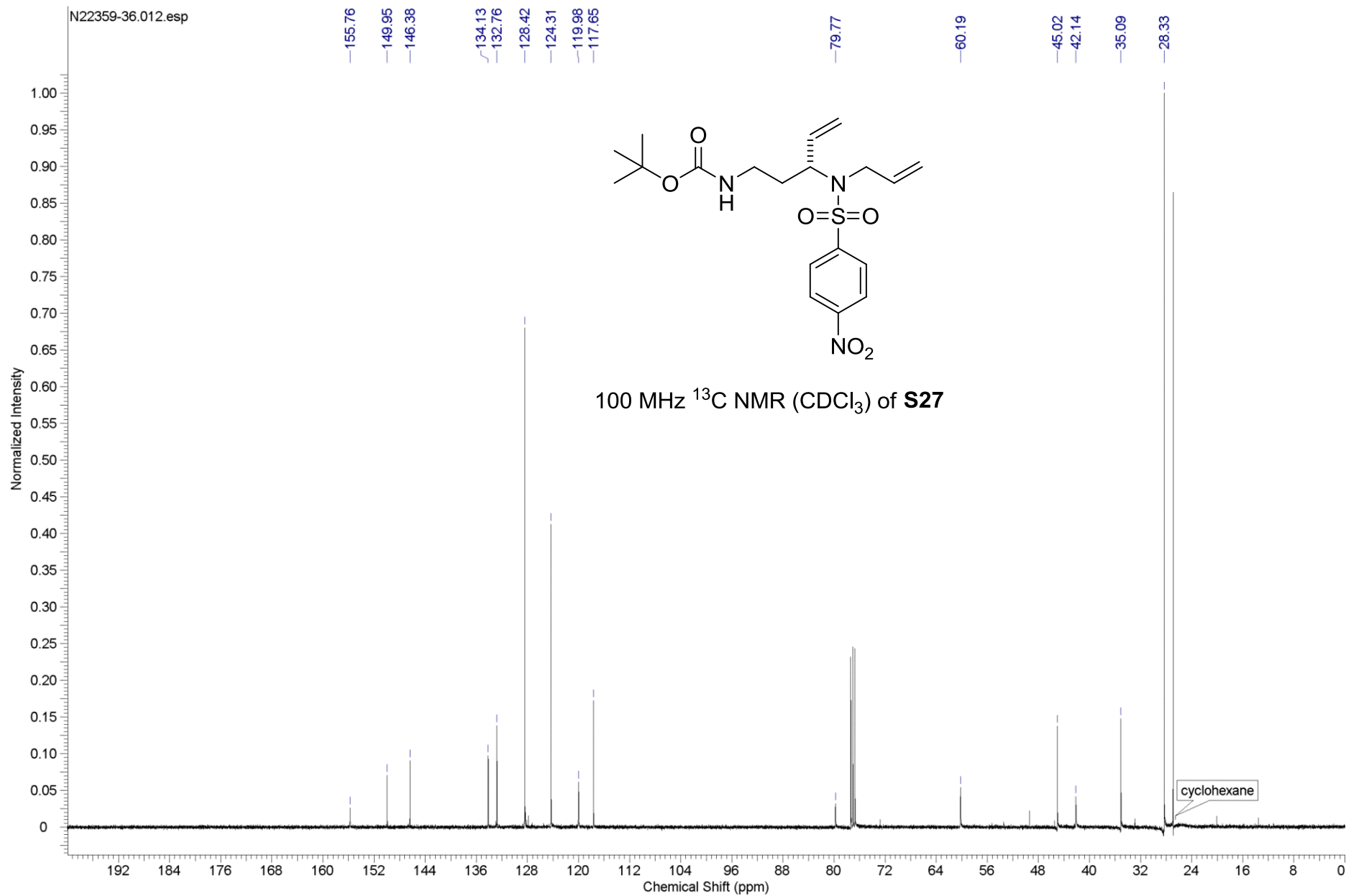


100 MHz ^{13}C NMR (DMSO) of 16



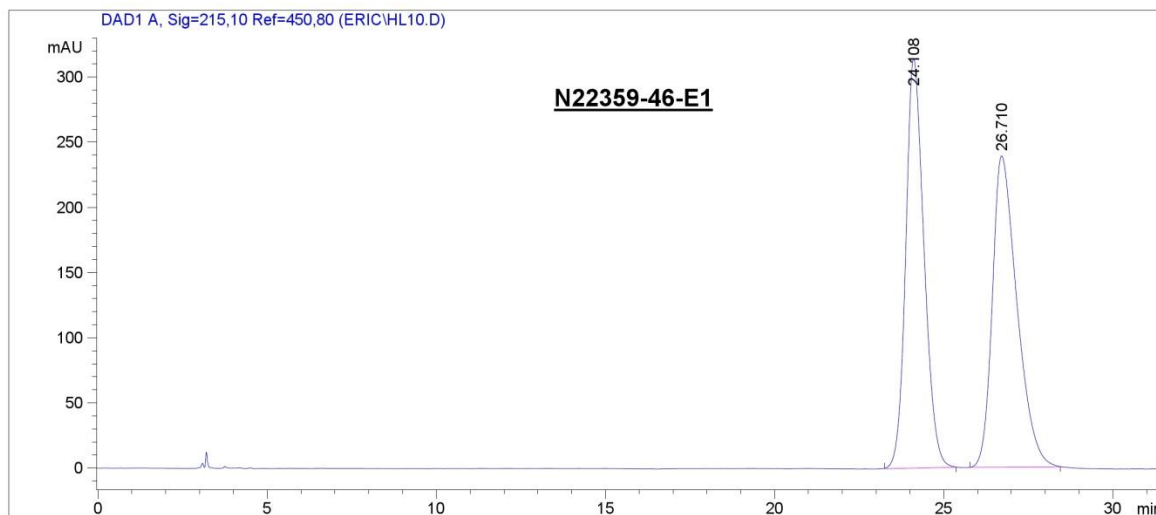
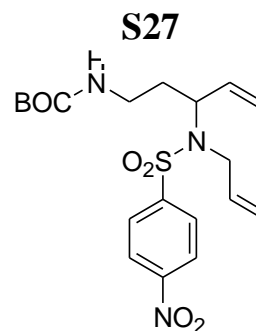


N22359-36.012.esp



Data File K:\HPCHEM\1\DATA\ERIC\HL10.D
Sample Name: N22359-46-E1

=====
Acq. Operator : ERIC HORTENSE
Acq. Instrument : LALANDRY
Injection Date : 15/02/2012 12:12:29
Location : Vial 1
Inj Volume : 5 µl
Method : C:\CHEM32\1\METHODS\ERIC1.M
Last changed : 15/02/2012 12:33:37 by ERIC HORTENSE
(modified after loading)
Sample Info : 25cm Chiralpak IA, col.no. IA00CE-MC024, 5%ETOH/C7, 1ml/min
, wavelength 215nm, RT
=====



=====
Area Percent Report
=====

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=215,10 Ref=450,80

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.108	BB	0.5741	1.18060e4	314.42432	49.3881
2	26.710	BB	0.7586	1.20986e4	238.99828	50.6119

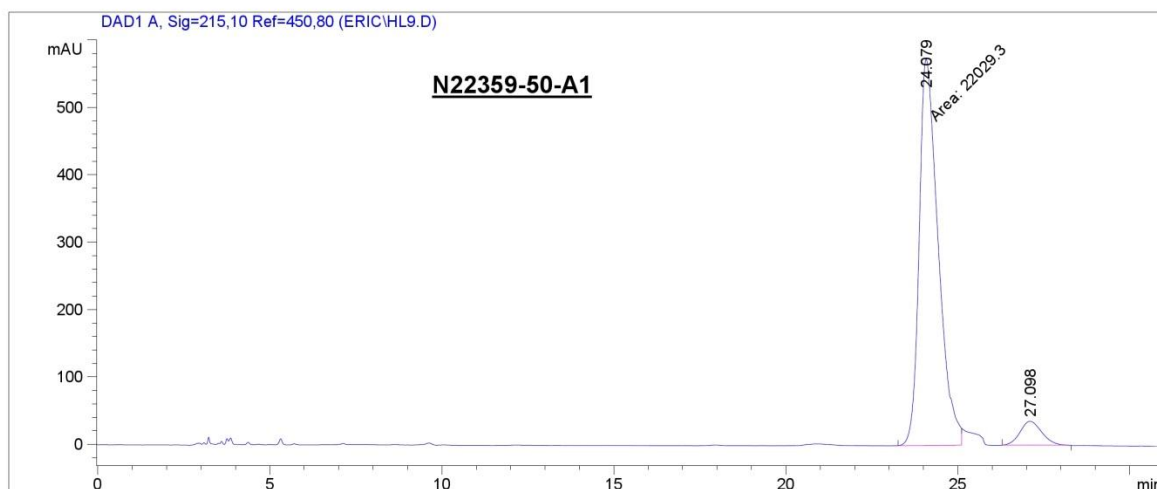
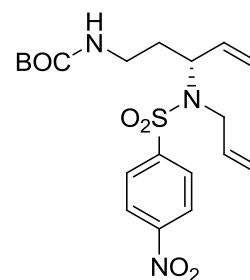
Totals : 2.39046e4 553.42259

=====
*** End of Report ***
=====

S27

Data File K:\HPCHEM\1\DATA\ERIC\HL9.D
Sample Name: N22359-50-A1

=====
Acq. Operator : ERIC HORTENSE
Acq. Instrument : LALANDRY Location : Vial 1
Injection Date : 15/02/2012 11:38:32 Inj Volume : 5 µl
Acq. Method : C:\CHEM32\1\METHODS\ERIC1.M
Last changed : 15/02/2012 11:37:38 by ERIC HORTENSE
(modified after loading)
Analysis Method : C:\CHEM32\1\METHODS\ERIC1.M
Last changed : 15/02/2012 12:33:37 by ERIC HORTENSE
(modified after loading)
Sample Info : 25cm Chiralpak IA, col.no. IA00CE-MC024, 5%ETOH/C7, 1ml/min
, wavelength 215nm, RT
=====



=====
Area Percent Report
=====

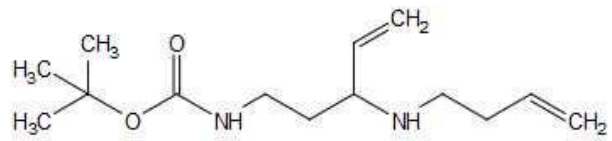
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=215,10 Ref=450,80

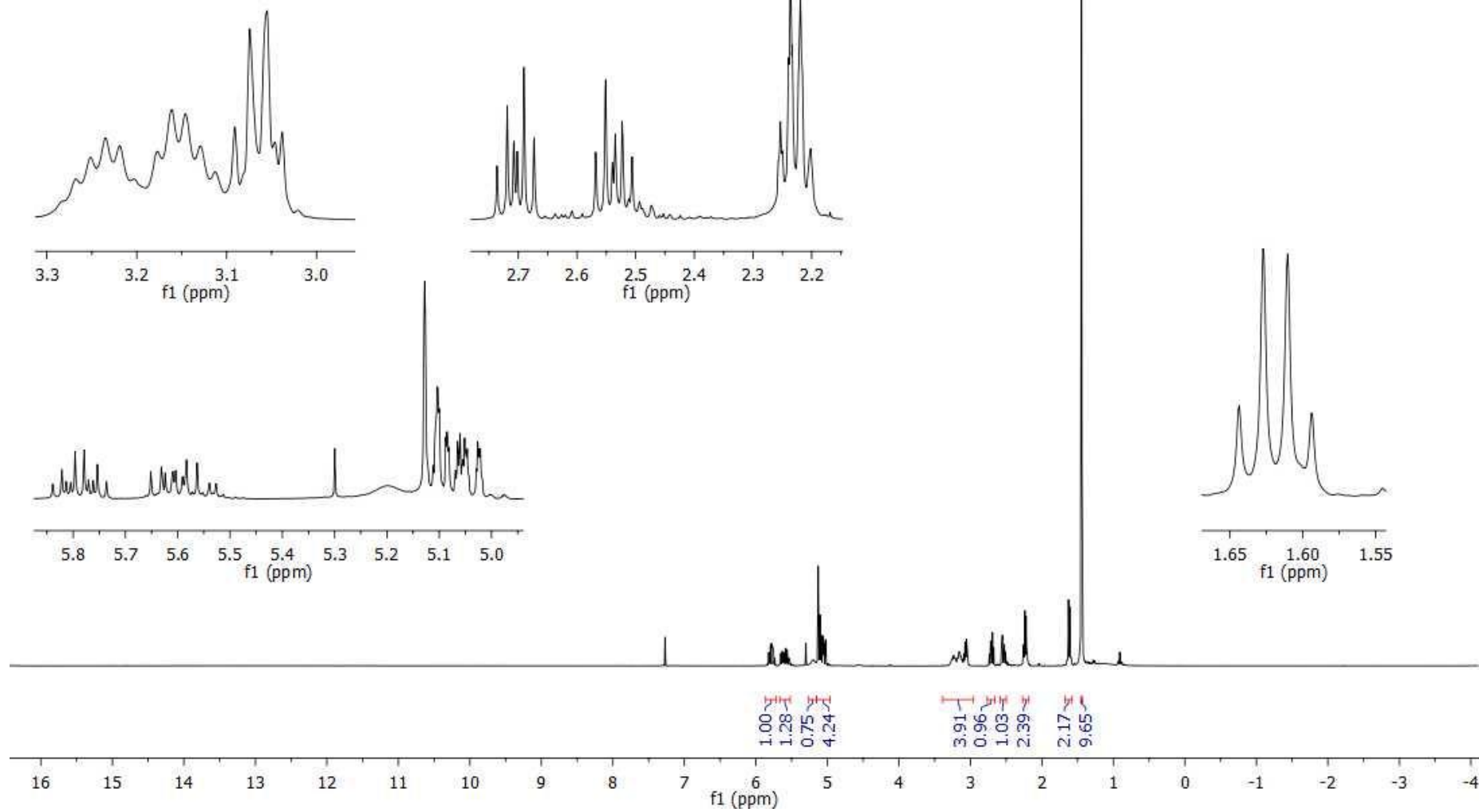
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.079	MF	0.6401	2.20293e4	573.58832	93.2988
2	27.098	BB	0.6757	1582.24622	35.65968	6.7012

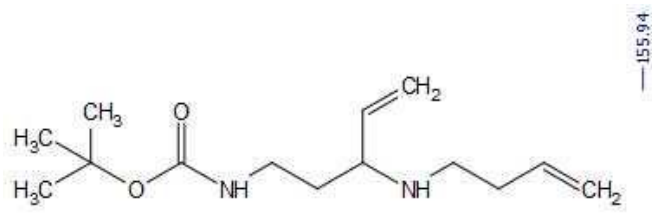
Totals : 2.36115e4 609.24800

=====
*** End of Report ***

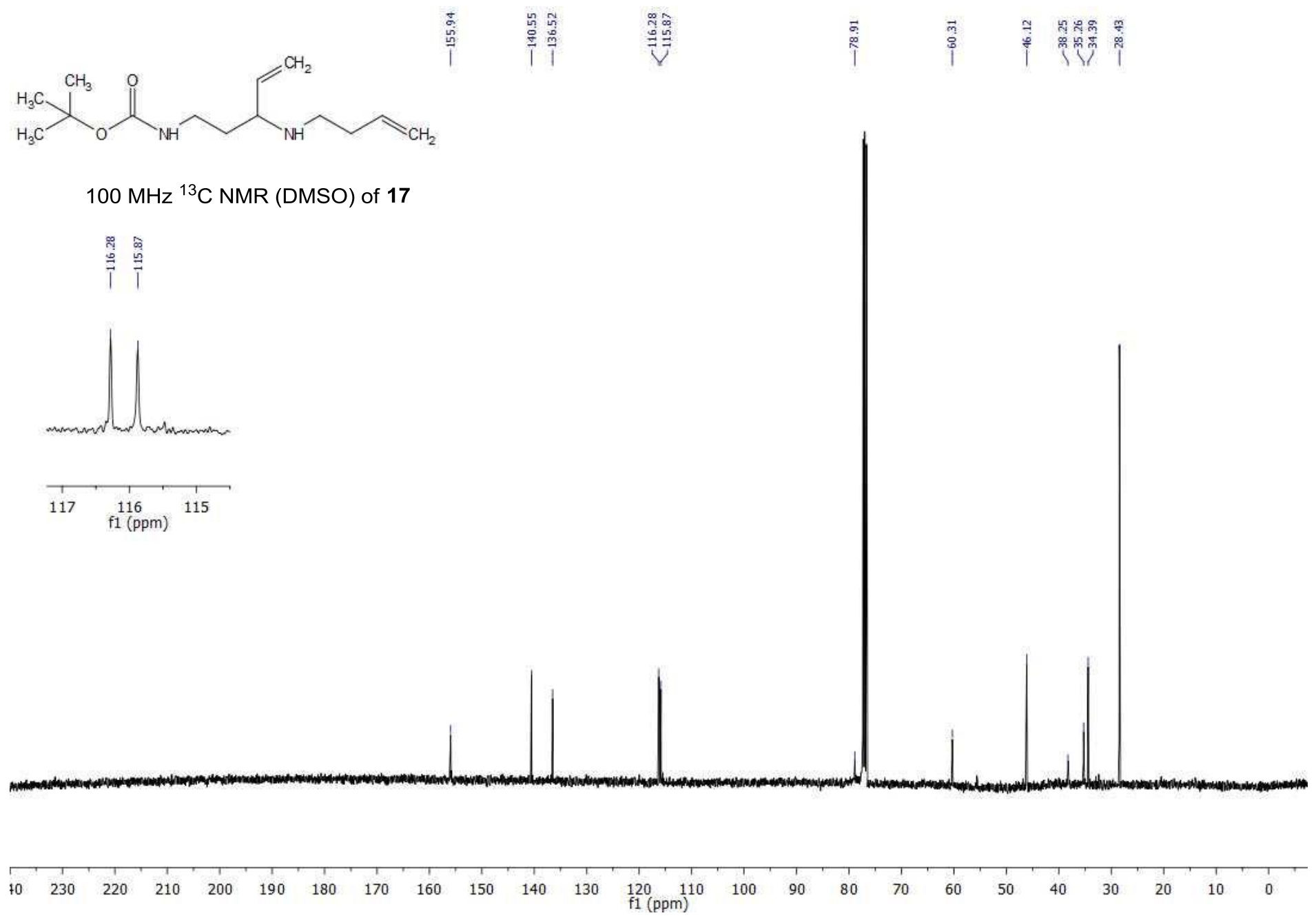


400 MHz ^1H NMR (DMSO) of 17





100 MHz ¹³C NMR (DMSO) of 17

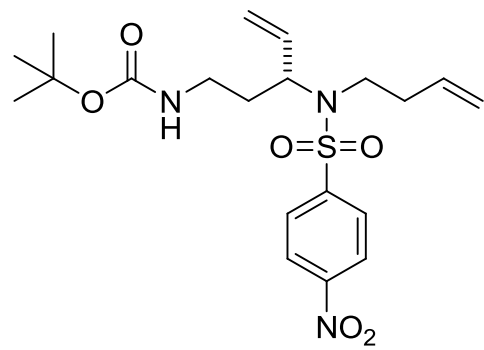


N22359-47.010.esp

cyclohexane

8.35
8.32
8.03
8.01

5.73
5.71
5.68
5.67
5.64
5.41
5.38
5.10
5.07
5.05
5.04
5.02
5.01
4.43
4.41
4.39
4.38
3.34
3.17
3.14
3.13
3.11
3.09
3.08
3.07
3.05
3.03
2.34
1.89
1.87
1.72
1.71
1.70
1.69
1.68
1.66
1.65
1.43



400 MHz ¹H NMR (CDCl₃) of **S28**

Normalized Intensity

0.30
0.25
0.20
0.15
0.10
0.05
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 -0.5

Chemical Shift (ppm)

2.21

2.21

1.00

1.09

5.35

1.14

1.11

3.07

1.03

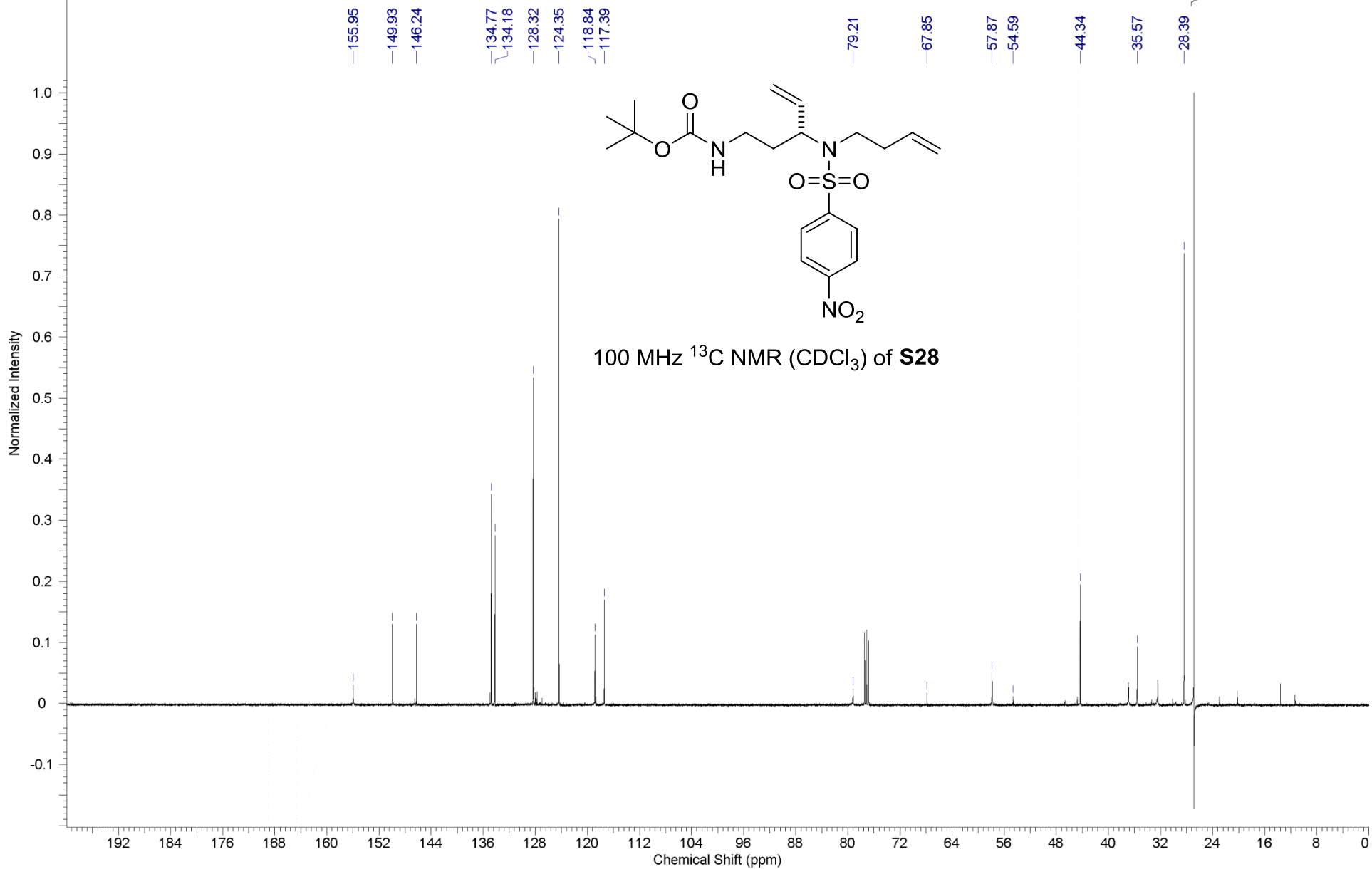
1.06

1.09

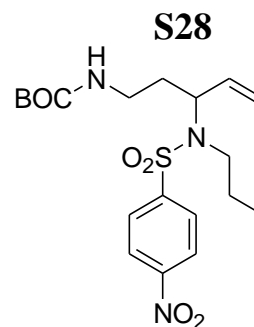
1.10

0.37

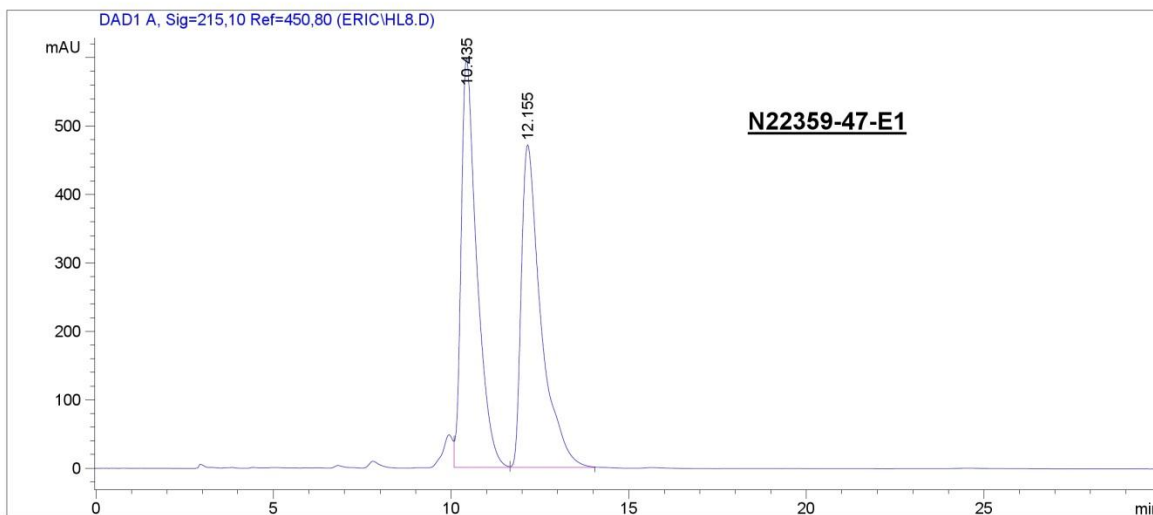
N22359-47.012.esp



Data File K:\HPCHEM\1\DATA\ERIC\HL8.D
Sample Name: N22359-47-E1



=====
Acq. Operator : ERIC HORTENSE
Acq. Instrument : LALANDRY
Injection Date : 15/02/2012 10:17:48
Location : Vial 1
Inj Volume : 5 µl
Method : C:\CHEM32\1\METHODS\ERIC1.M
Last changed : 15/02/2012 09:16:10 by ERIC HORTENSE
(modified after loading)
Sample Info : 25cm Chiralpak AD-H, col.no.ADHOCE-BH013, 10%ETOH/C7, 1ml/
min, wavelength 215nm, RT



=====
Area Percent Report
=====

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=215,10 Ref=450,80

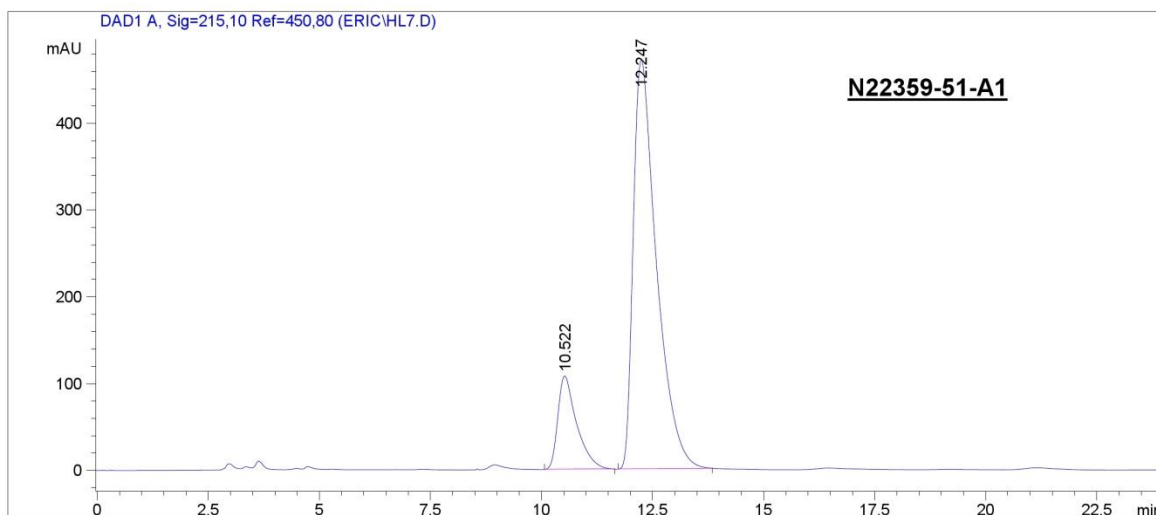
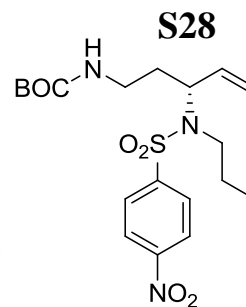
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.435	VV	0.4488	1.83904e4	598.03406	50.3302
2	12.155	VB	0.5632	1.81491e4	471.33688	49.6698

Totals : 3.65395e4 1069.37094

=====
*** End of Report ***

Data File K:\HPCHEM\1\DATA\ERIC\HL7.D
Sample Name: N22359-51-A1

=====
Acq. Operator : ERIC HORTENSE
Acq. Instrument : LALANDRY
Injection Date : 15/02/2012 09:51:36
Location : Vial 1
Inj Volume : 5 µl
Method : C:\CHEM32\1\METHODS\ERIC1.M
Last changed : 15/02/2012 09:16:10 by ERIC HORTENSE
(modified after loading)
Sample Info : 25cm Chiralpak AD-H, col.no.ADHOCE-BH013, 10%ETOH/C7, 1ml/
min, wavelength 215nm, RT



=====
Area Percent Report
=====

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=215,10 Ref=450,80

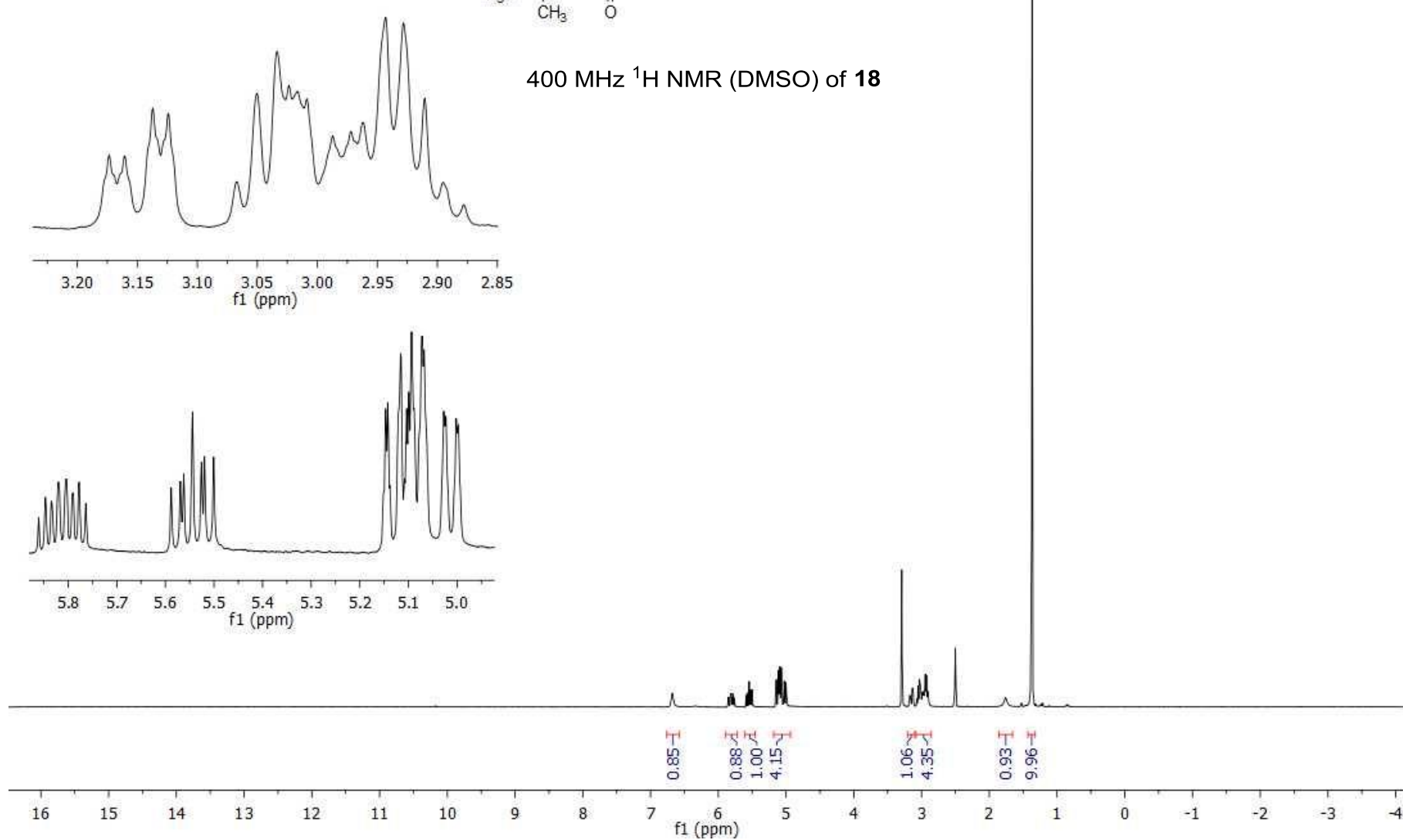
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.522	BB	0.4321	3174.91309	107.65047	15.5844
2	12.247	BB	0.5432	1.71974e4	471.84235	84.4156

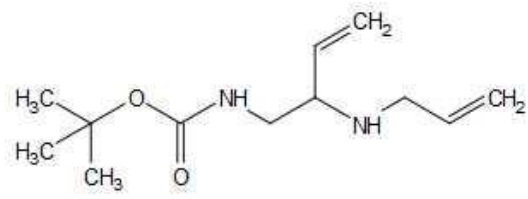
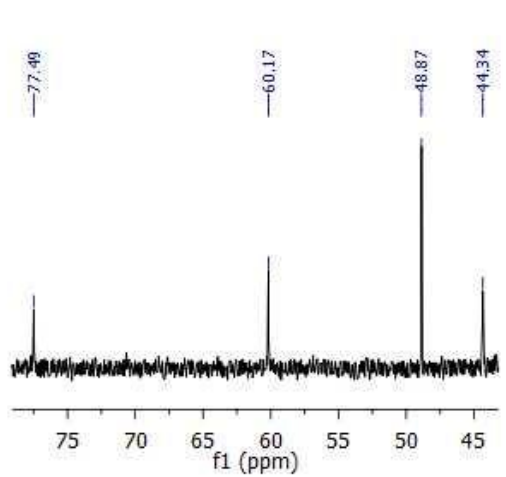
Totals : 2.03723e4 579.49282

=====
*** End of Report ***

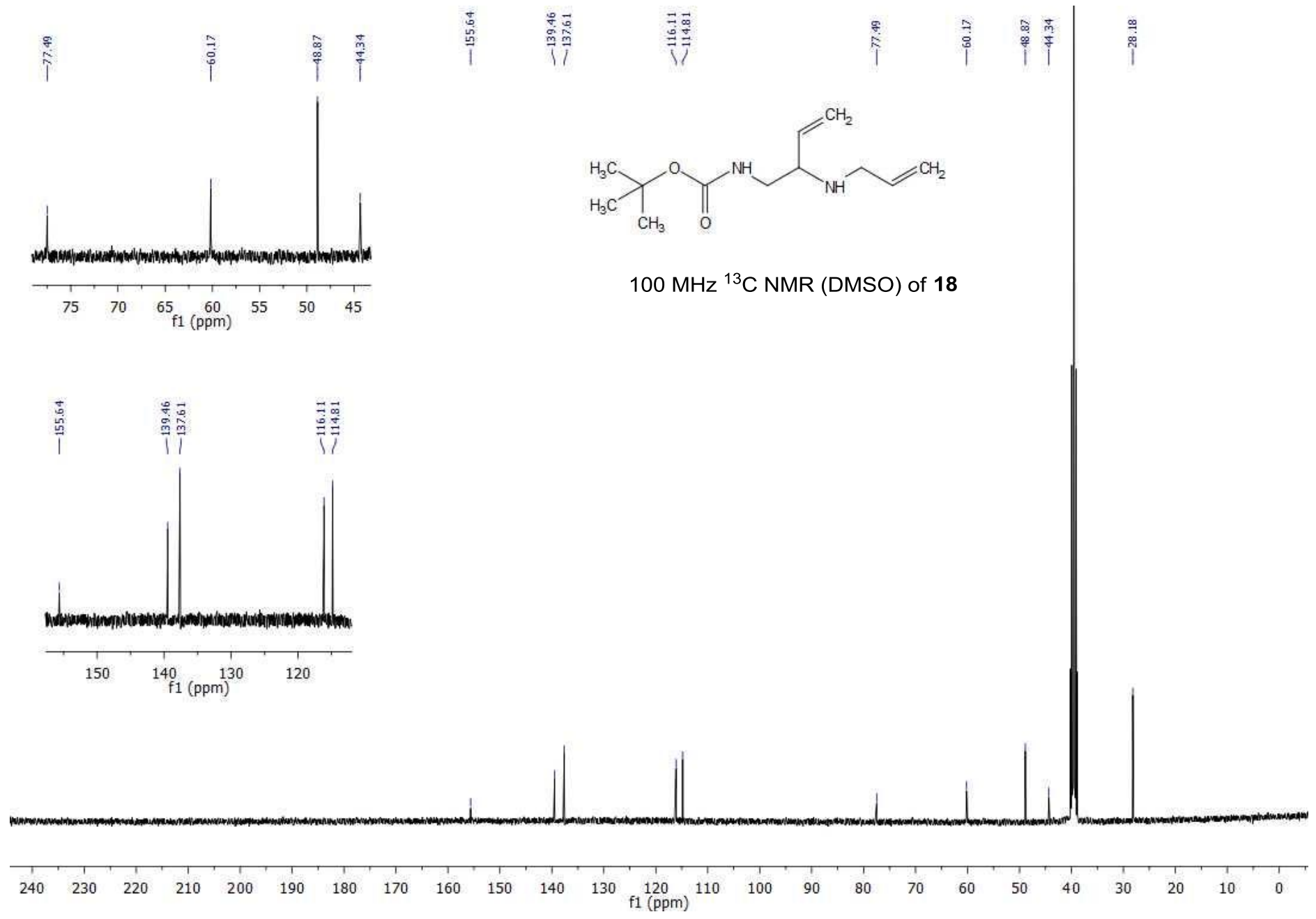
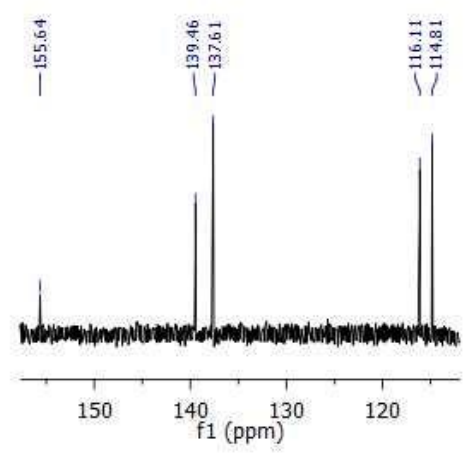


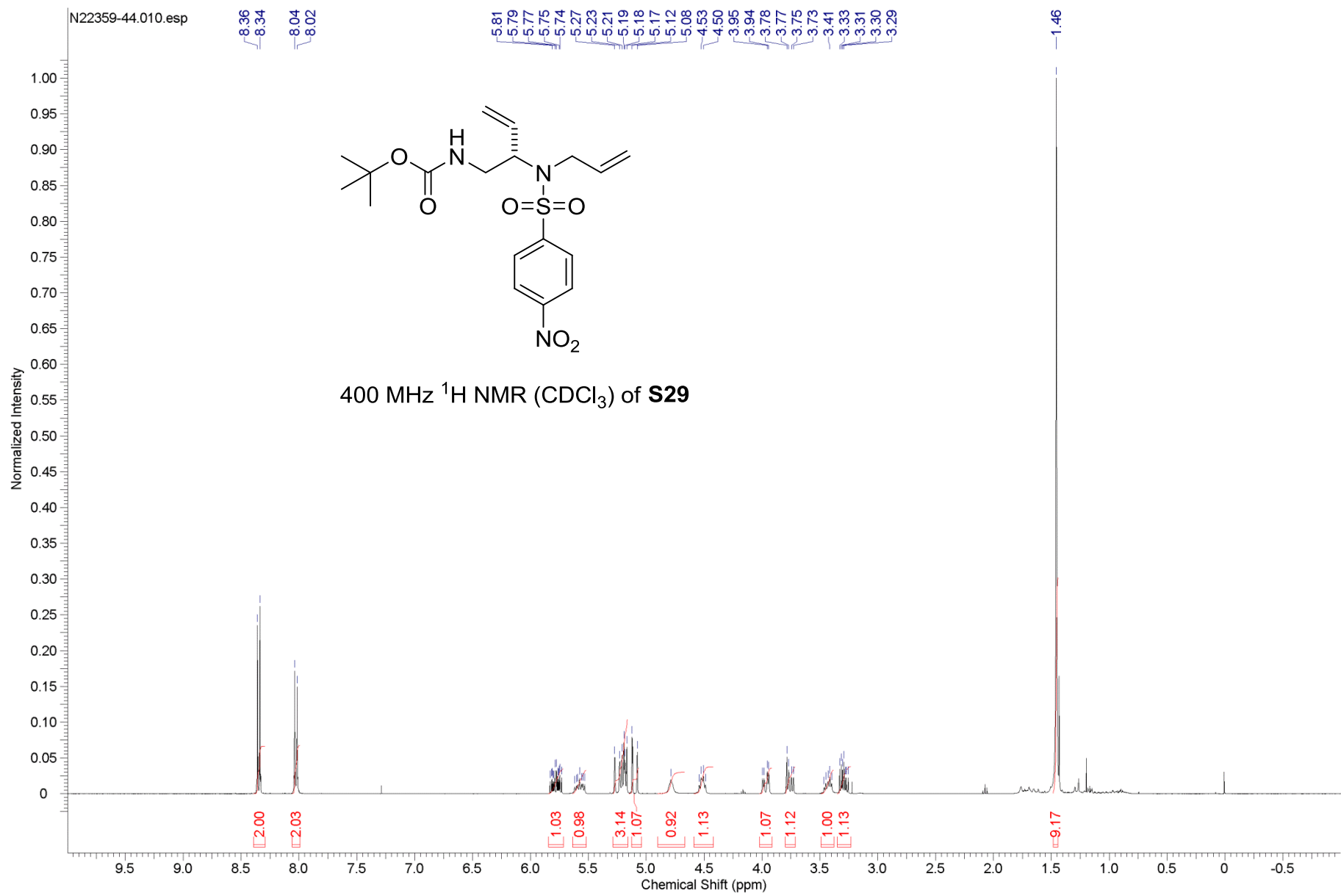
400 MHz ^1H NMR (DMSO) of **18**



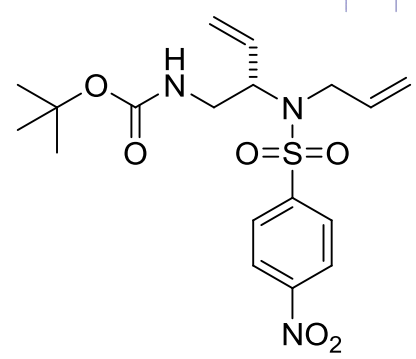


100 MHz ¹³C NMR (DMSO) of 18

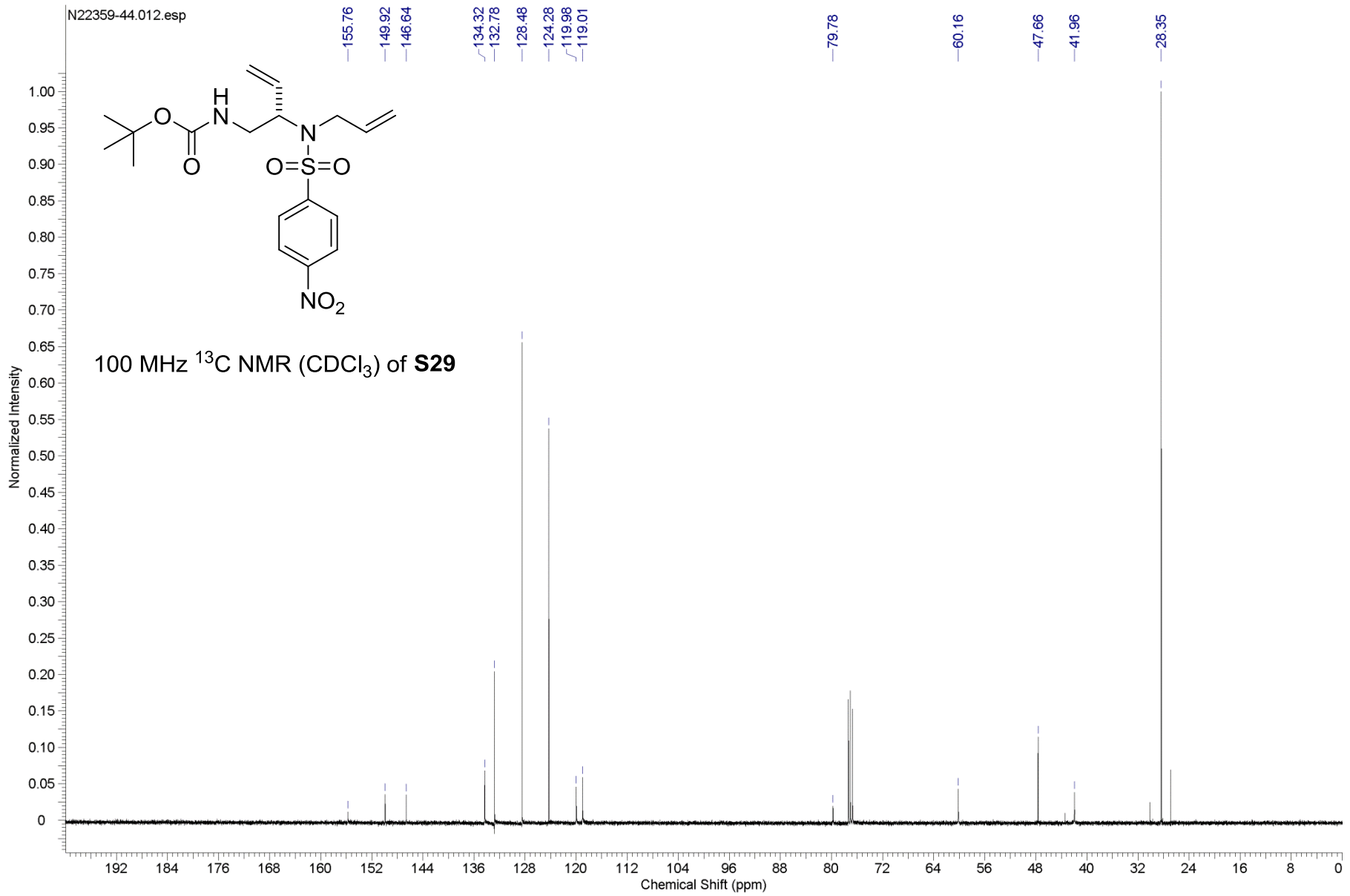




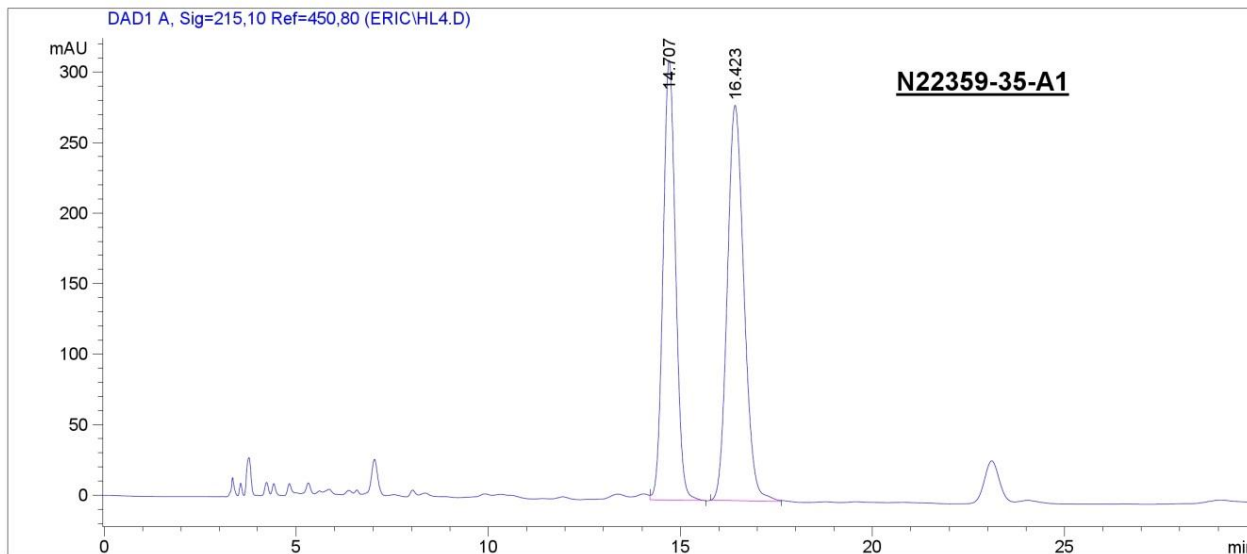
N22359-44.012.esp



100 MHz ¹³C NMR (CDCl₃) of S29



=====
Acq. Operator : ERIC HORTENSE
Acq. Instrument : LALANDRY Location : Vial 1
Injection Date : 06/02/2012 10:24:42 Inj Volume : 5 µl
Method : C:\CHEM32\1\METHODS\ERIC1.M
Last changed : 06/02/2012 10:28:52 by ERIC HORTENSE
(modified after loading)
Sample Info : 25cm Chiralpak IC, col.no. ICOOCE-MF060, 10%ETOH/C7, 1ml/min, wavelength 215nm, RT
=====



=====
Area Percent Report
=====

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=215,10 Ref=450,80

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.707	VB	0.3526	7076.60742	312.05734	45.4899
2	16.423	BB	0.4685	8479.84082	280.66971	54.5101

Totals : 1.55564e4 592.72705

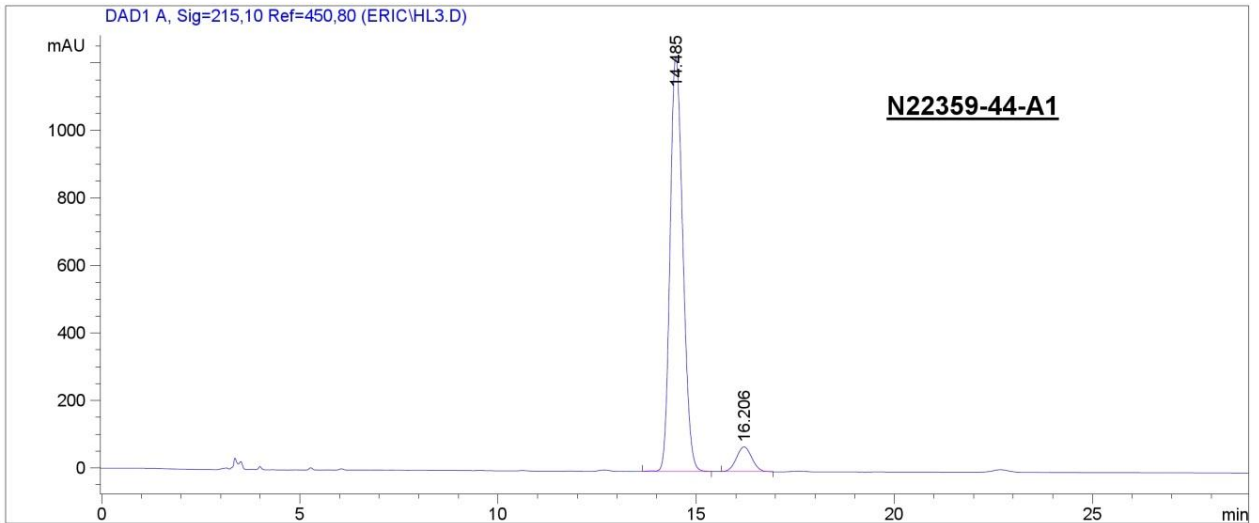
=====
*** End of Report ***
=====

Data File K:\HPCHEM\1\DATA\ERIC\HL3.D
Sample Name: N22359-44-A1

S29

=====
Acq. Operator : ERIC HORTENSE
Acq. Instrument : LALANDRY Location : Vial 1
Injection Date : 06/02/2012 09:54:05 Inj Volume : 5 µl

Acq. Method : C:\CHEM32\1\METHODS\ERIC1.M
Last changed : 06/02/2012 09:28:55 by ERIC HORTENSE
(modified after loading)
Analysis Method : C:\CHEM32\1\METHODS\ERIC1.M
Last changed : 06/02/2012 10:28:52 by ERIC HORTENSE
(modified after loading)
Sample Info : 25cm Chiralpak IC, col.no.ICOOCE-MF060, 10%ETOH/C7, 1ml/min,
wavelength 215nm, RT
=====



=====
Area Percent Report
=====

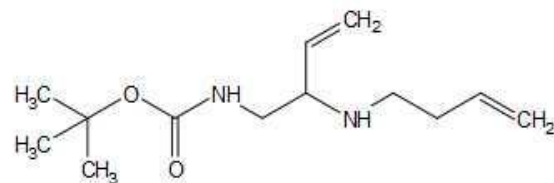
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=215,10 Ref=450,80

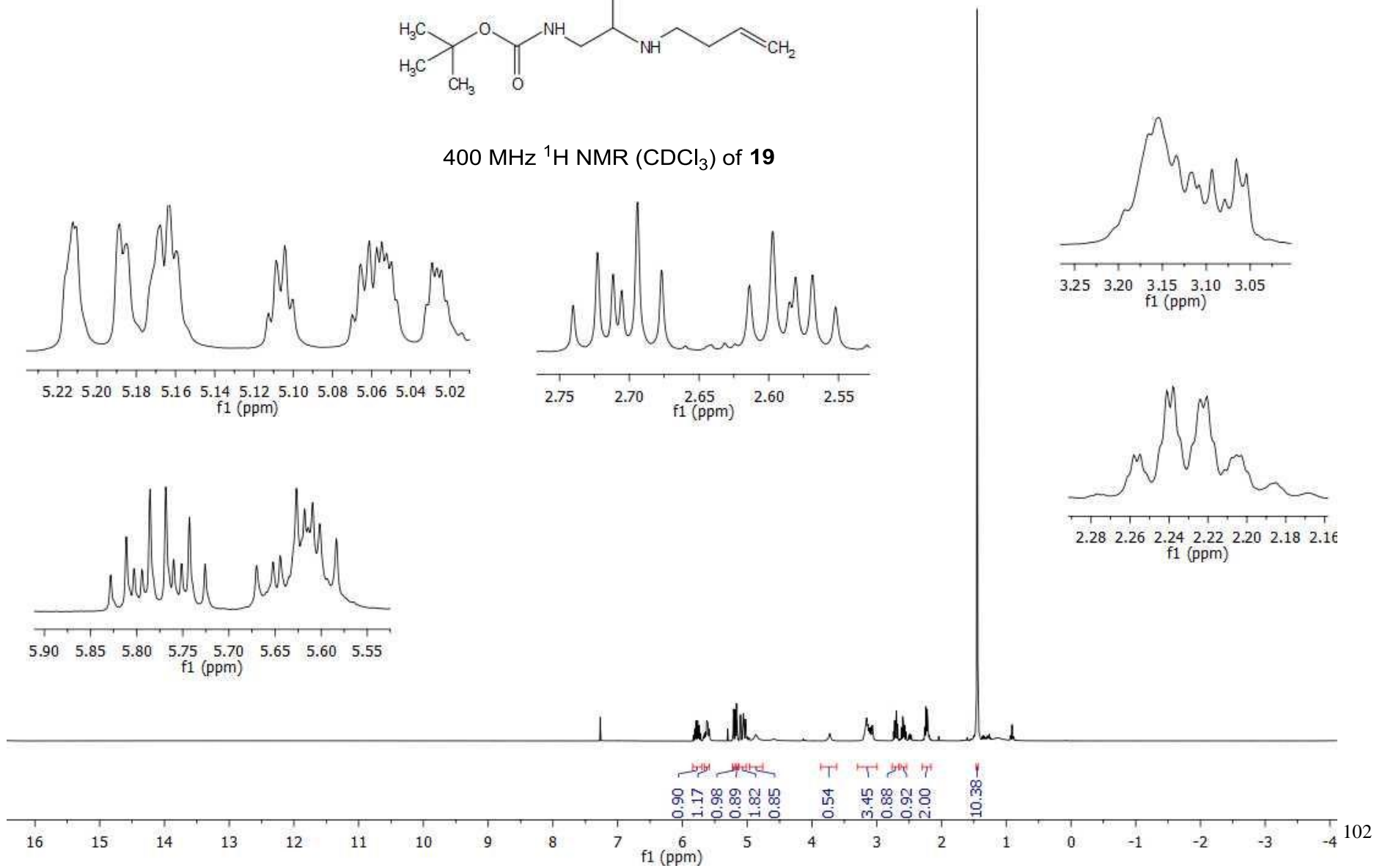
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.485	BB	0.3511	2.75342e4	1230.44348	93.2491
2	16.206	BB	0.4260	1993.38611	73.59498	6.7509

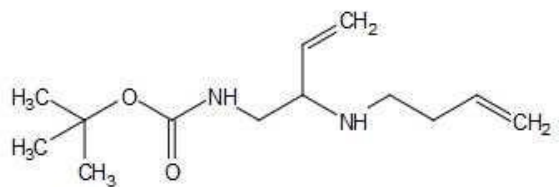
Totals : 2.95276e4 1304.03846

=====
*** End of Report ***
=====

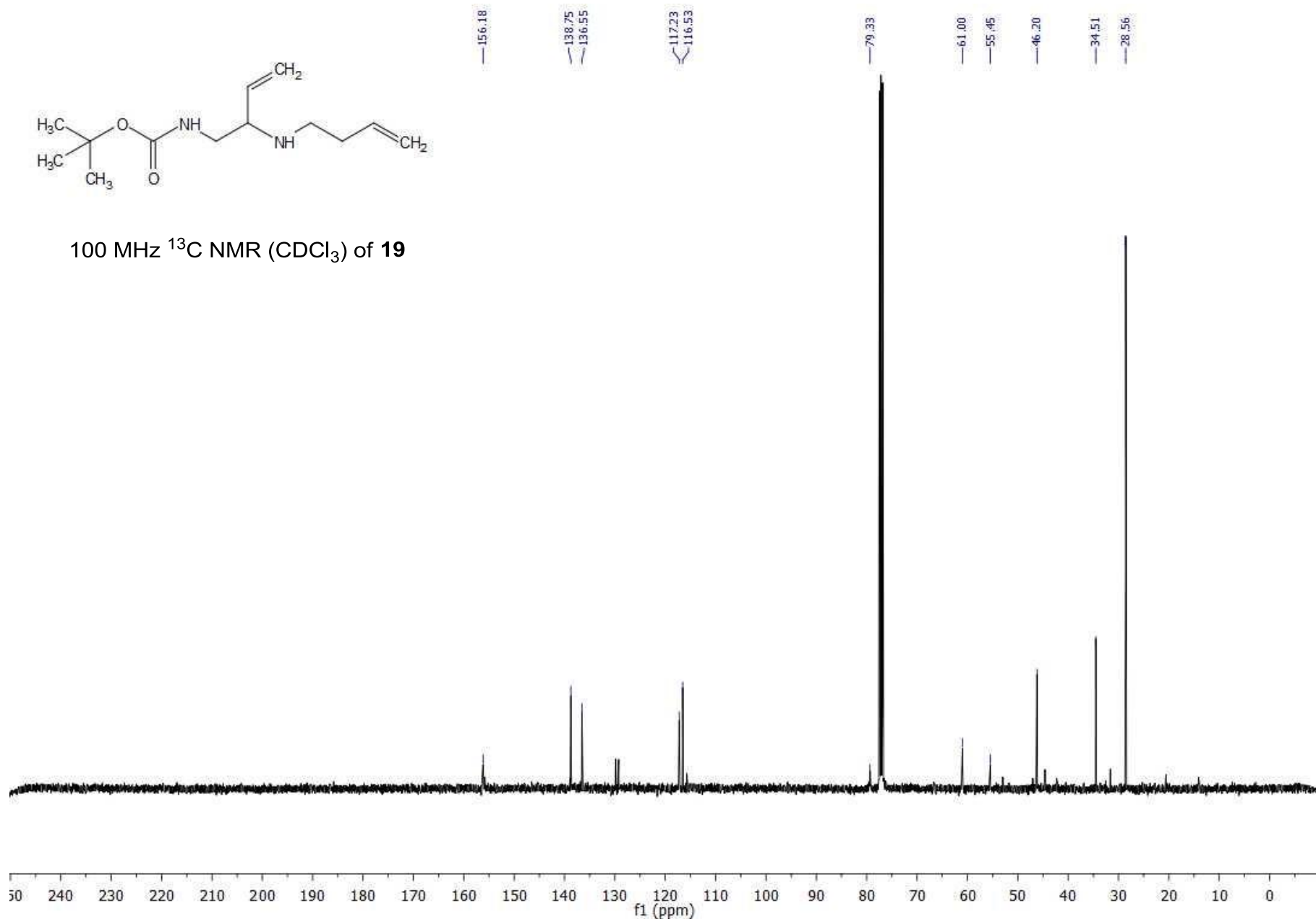


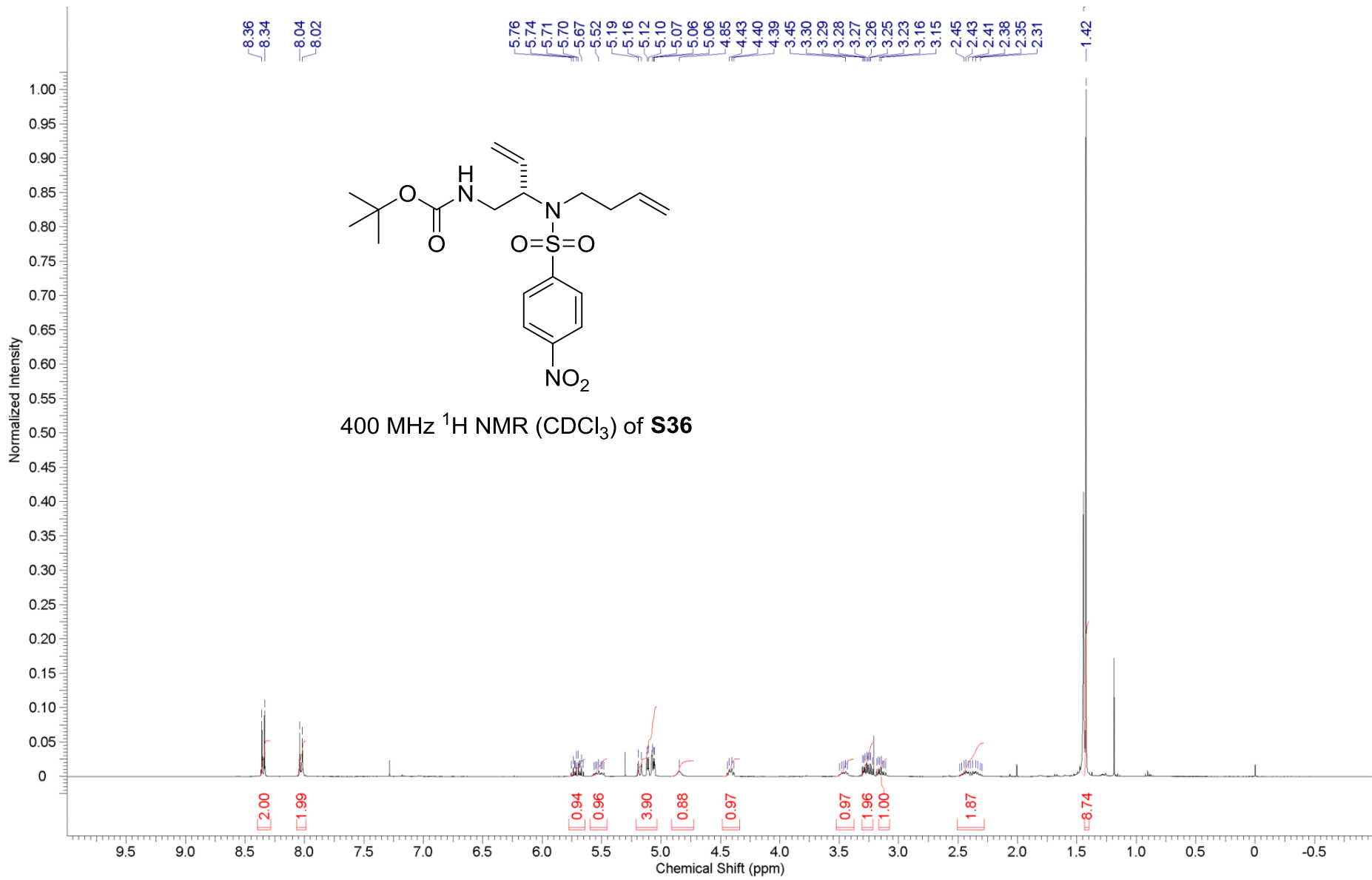
400 MHz ^1H NMR (CDCl_3) of **19**

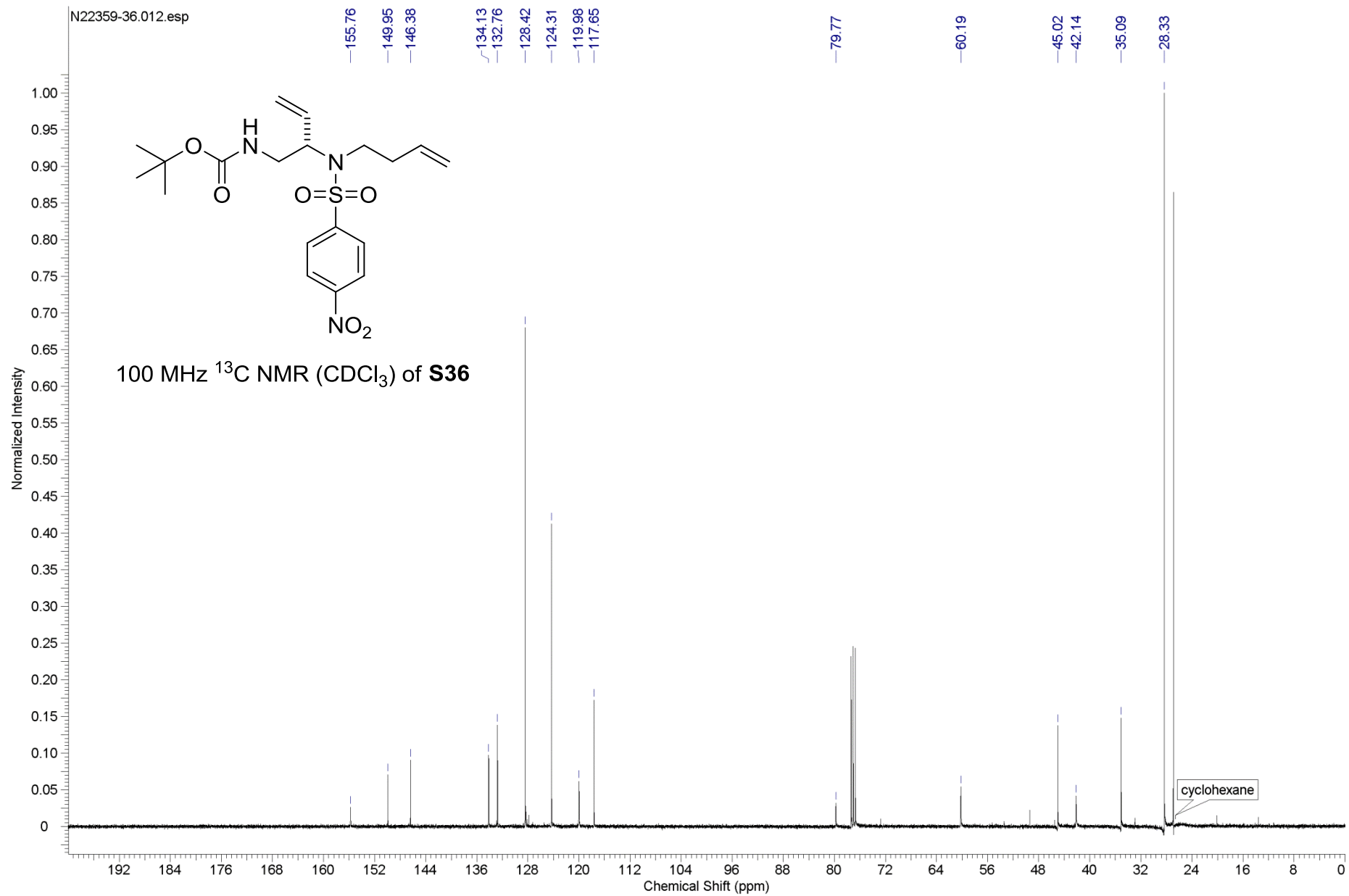




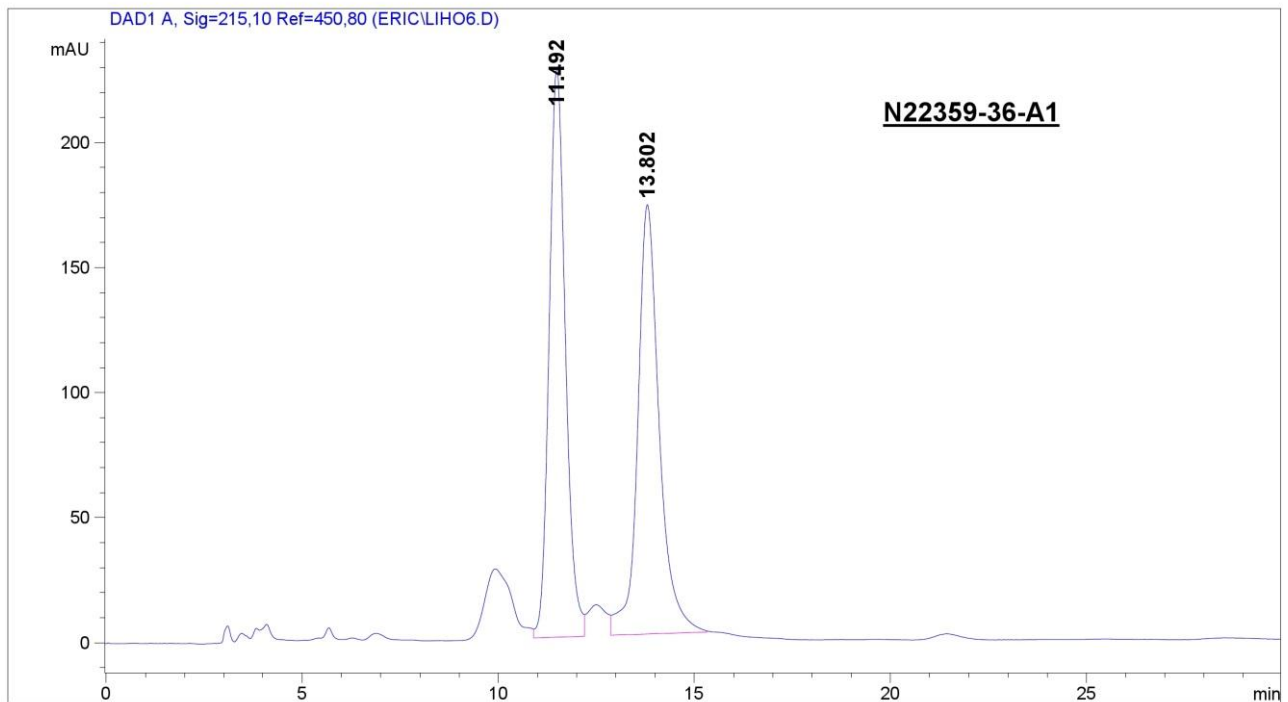
100 MHz ^{13}C NMR (CDCl_3) of **19**







=====
Acq. Operator : ERIC HORTENSE
Acq. Instrument : HOYTEN Location : Vial 1
Injection Date : 06/02/2012 10:11:39 Inj Volume : 5 µl
Acq. Method : K:\HOYTEN\HOYTENS METHODS\CHIMETH1.M
Last changed : 06/02/2012 09:22:23 by ERIC HORTENSE
(modified after loading)
Analysis Method : K:\HOYTEN\HOYTENS METHODS\CHIMETH1.M
Last changed : 06/02/2012 10:57:22 by ERIC HORTENSE
(modified after loading)
Method Info : Chiral Method 1. Isocratic Analysis at 1.000 ml/min.
Sample Info : 25cm Chiralpak AD
, col.no.ADOOCE-A1074, 10%ETOH/C7, 1ml/min, wavelength 215n
m, RT



=====
Area Percent Report
=====

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=215,10 Ref=450,80

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.492	VV	0.4413	6545.63965	227.72227	49.8532
2	13.802	VB	0.5711	6584.19092	171.80617	50.1468

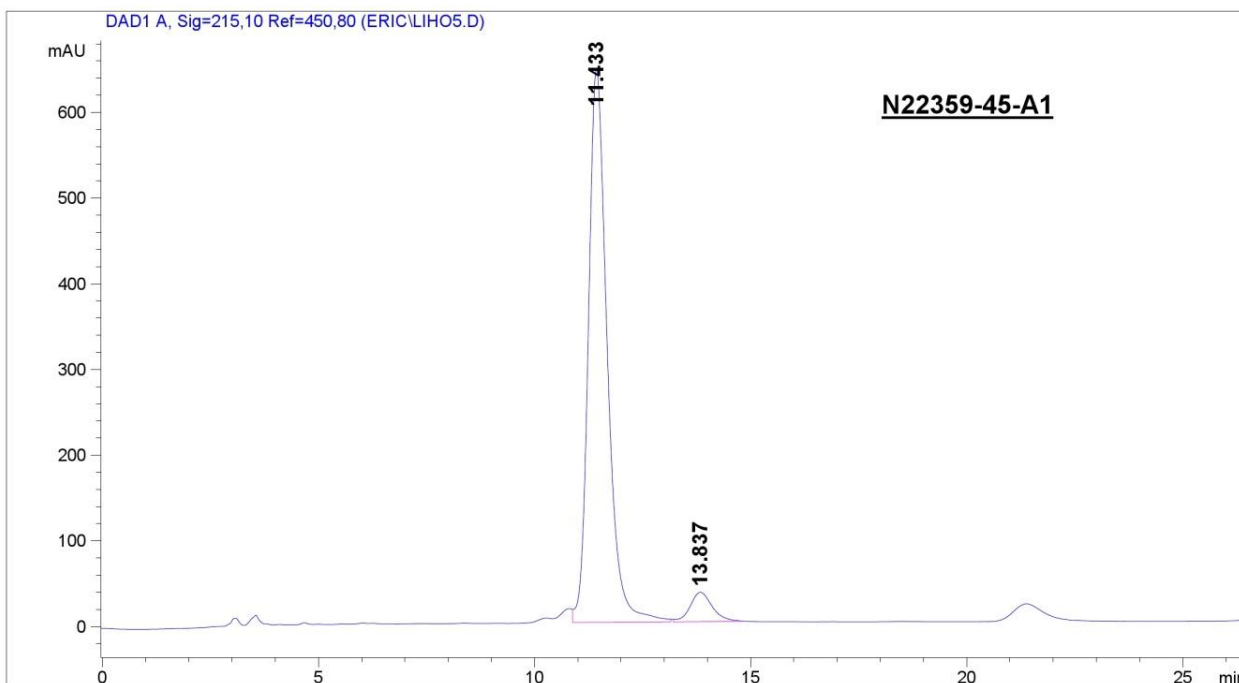
Totals : 1.31298e4 399.52844

=====
*** End of Report ***

Data File K:\HOYTEN\HPCHEM\1\DATA\ERIC\LIHO5.D
Sample Name: N22359-45-A1

S36

=====
Acq. Operator : ERIC HORTENSE
Acq. Instrument : HOYTEN Location : Vial 1
Injection Date : 06/02/2012 09:43:32 Inj Volume : 5 µl
Acq. Method : K:\HOYTEN\HOYTENS METHODS\CHIMETH1.M
Last changed : 06/02/2012 09:22:23 by ERIC HORTENSE
(modified after loading)
Analysis Method : K:\HOYTEN\HOYTENS METHODS\CHIMETH1.M
Last changed : 06/02/2012 10:57:22 by ERIC HORTENSE
(modified after loading)
Method Info : Chiral Method 1. Isocratic Analysis at 1.000 ml/min.
Sample Info : 25cm Chiralpak AD
, col.no.ADOOCE-A1074, 10%ETOH/C7, 1ml/min, wavelength 215nm, RT



=====
Area Percent Report
=====

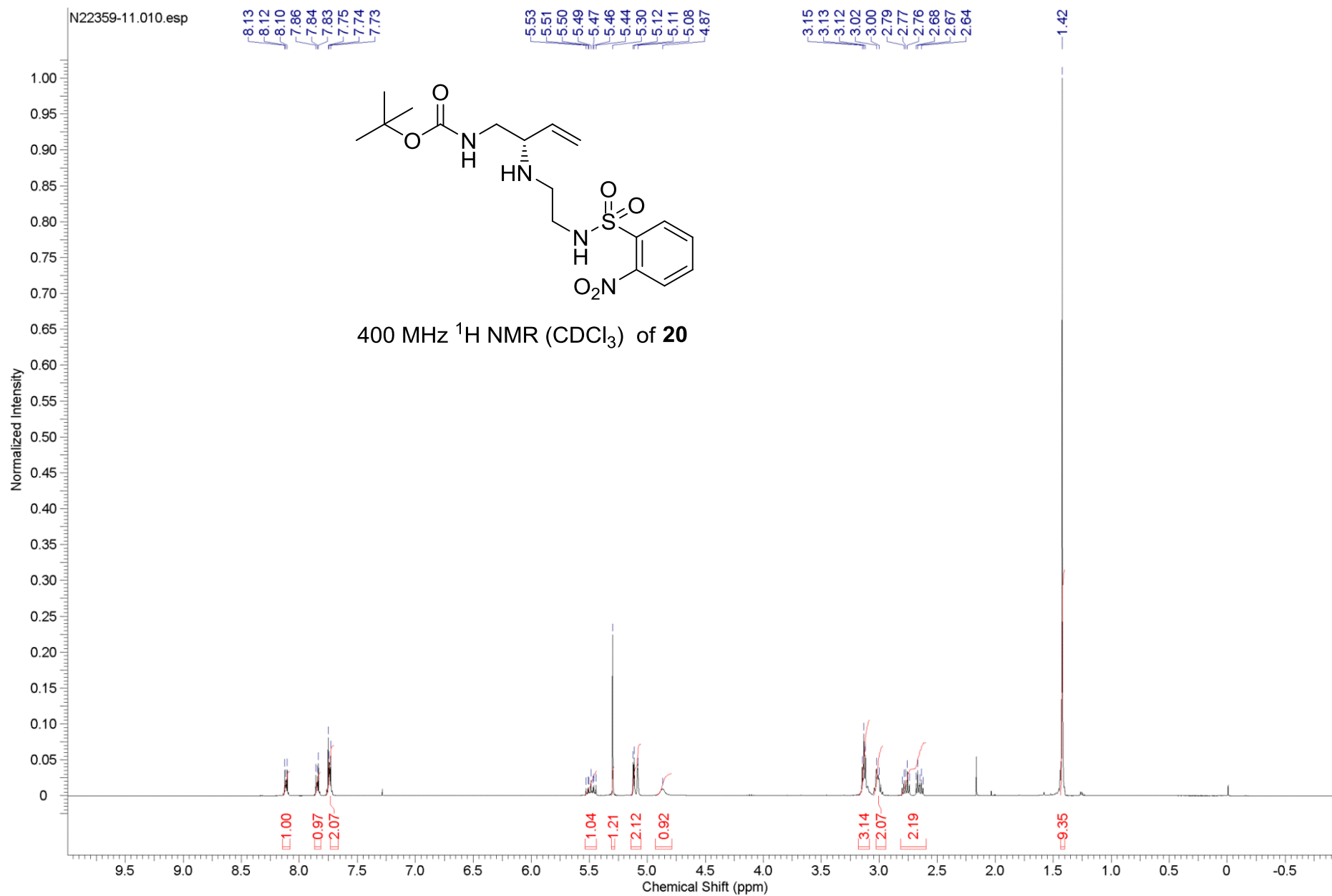
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=215,10 Ref=450,80

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.433	VB	0.4568	1.95434e4	646.32959	94.0047
2	13.837	BB	0.5502	1246.40088	34.43793	5.9953

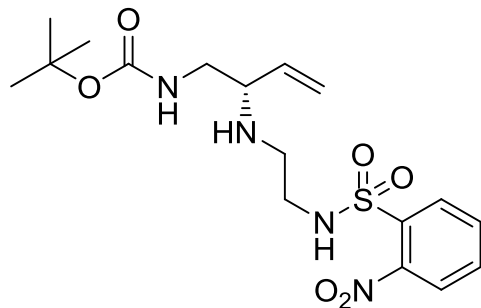
Totals : 2.07898e4 680.76752

=====
*** End of Report ***

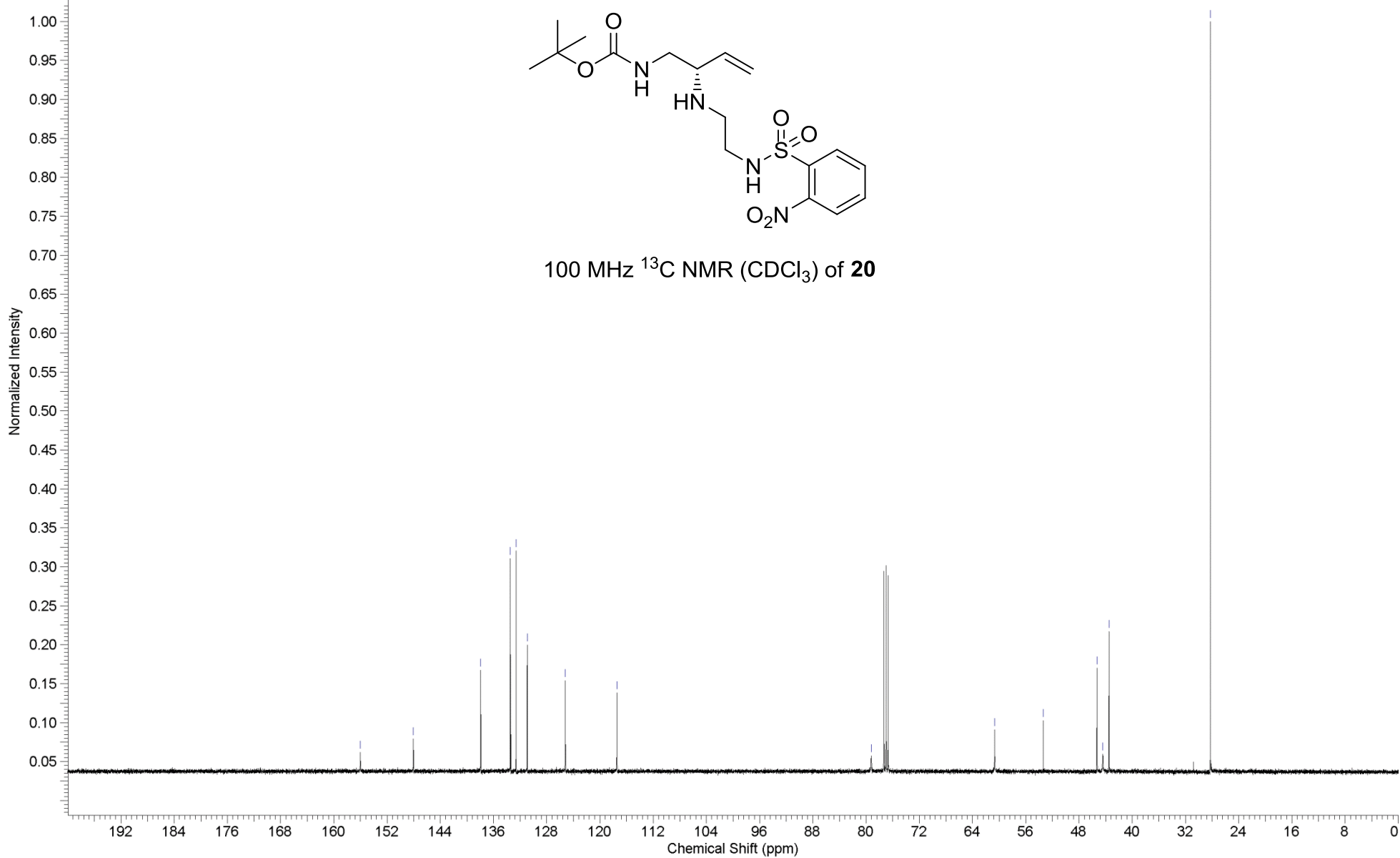


N22359-11.012.esp

156.00 148.04 137.93 133.48 132.60 130.92 125.20 117.45 79.23 60.68 53.38 45.31 44.42 43.49 28.27



100 MHz ¹³C NMR (CDCl₃) of **20**

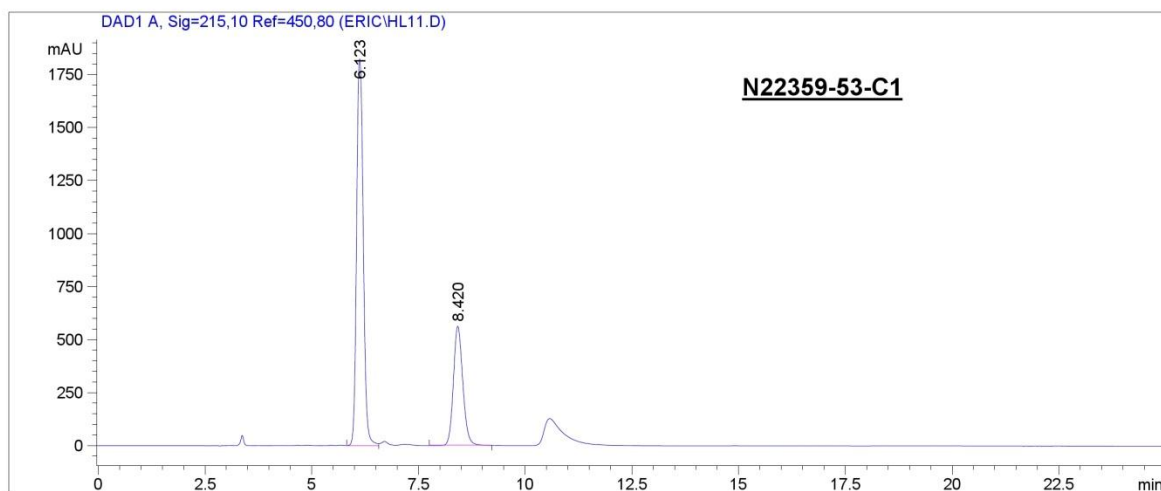


Data File K:\HPCHEM\1\DATA\ERIC\HL11.D
 Sample Name: N22359-53-C1

```

=====
Acq. Operator   : ERIC HORTENSE
Acq. Instrument : LALANDRY
Injection Date  : 28/02/2012 15:26:40
Location       : Vial 1
Inj Volume     : 5 µl

Acq. Method    : C:\CHEM32\1\METHODS\ERIC1.M
Last changed   : 28/02/2012 15:24:53 by ERIC HORTENSE
                (modified after loading)
Analysis Method: C:\CHEM32\1\METHODS\ERIC1.M
Last changed   : 15/03/2012 14:10:41 by ERIC HORTENSE
                (modified after loading)
Sample Info    : 25cm Chiralpak IA, col.no. IAOOCE-MC024, 40%ETOH/C7, 1ml/min,
                wavelength 215nm, RT
=====
  
```



```

=====
                          Area Percent Report
=====
  
```

```

Sorted By      :      Signal
Multiplier     :      1.0000
Dilution      :      1.0000
Use Multiplier & Dilution Factor with ISTDs
  
```

Signal 1: DAD1 A, Sig=215,10 Ref=450,80

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.123	VV	0.1727	1.98121e4	1824.43323	69.6540
2	8.420	VB	0.2349	8631.47852	562.92065	30.3460

```
Totals :                      2.84435e4  2387.35388
```

```

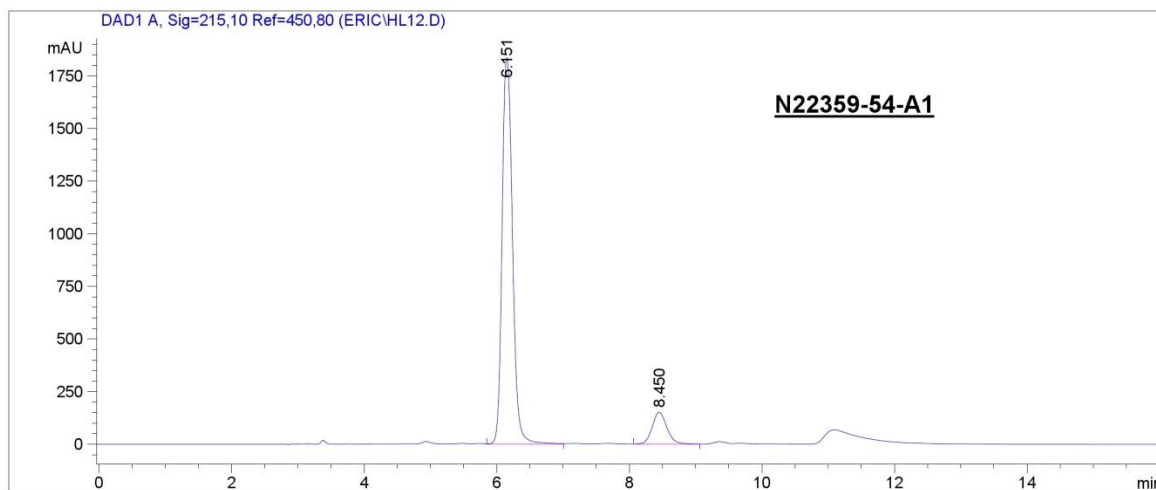
=====
*** End of Report ***
  
```

Data File K:\HPCHEM\1\DATA\ERIC\HL12.D
 Sample Name: N22359-54-A1

```

=====
Acq. Operator   : ERIC HORTENSE
Acq. Instrument : LALANDRY
Injection Date  : 28/02/2012 15:57:26
Location       : Vial 1
Inj Volume     : 5 µl

Acq. Method    : C:\CHEM32\1\METHODS\ERIC1.M
Last changed   : 28/02/2012 15:24:53 by ERIC HORTENSE
                (modified after loading)
Analysis Method: C:\CHEM32\1\METHODS\ERIC1.M
Last changed   : 15/03/2012 14:10:41 by ERIC HORTENSE
                (modified after loading)
Sample Info    : 25cm Chiralpak IA, col.no. IA00CE-MC024, 40% ETOH/C7, 1ml/min,
                wavelength 215nm, RT
=====
  
```



=====
 Area Percent Report
 =====

```

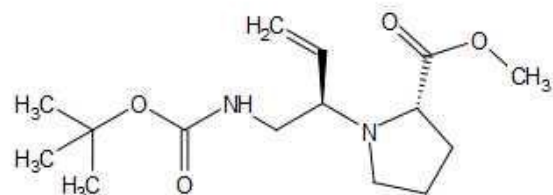
Sorted By      : Signal
Multiplier     : 1.0000
Dilution       : 1.0000
Use Multiplier & Dilution Factor with ISTDs
  
```

Signal 1: DAD1 A, Sig=215,10 Ref=450,80

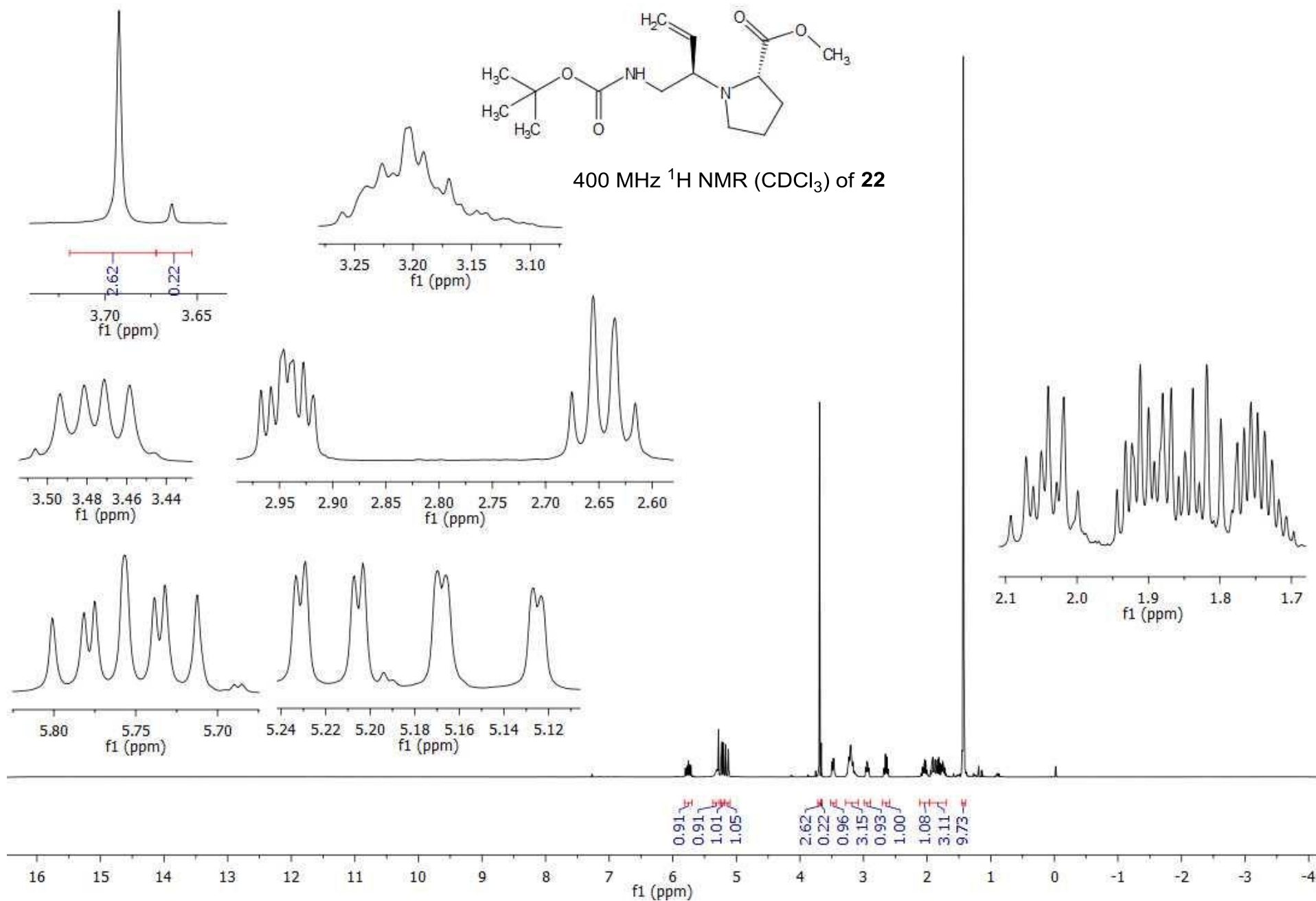
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2	8.450	VB	0.2373	2320.85327	150.97911	10.3792

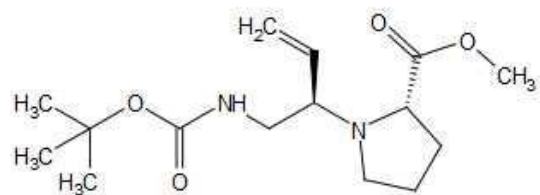
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 *** End of Report ***

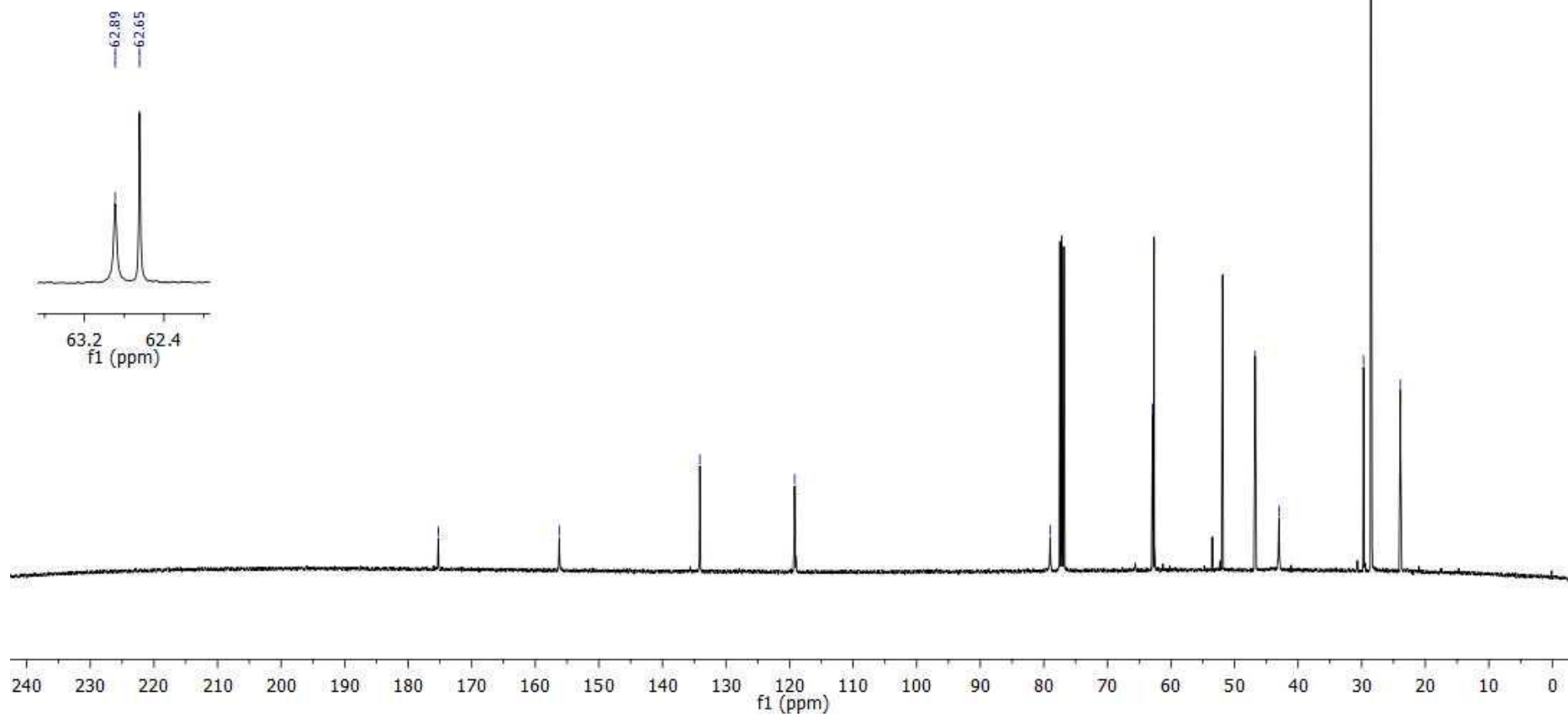


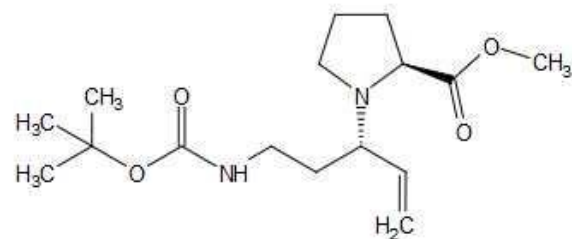
400 MHz ^1H NMR (CDCl_3) of **22**



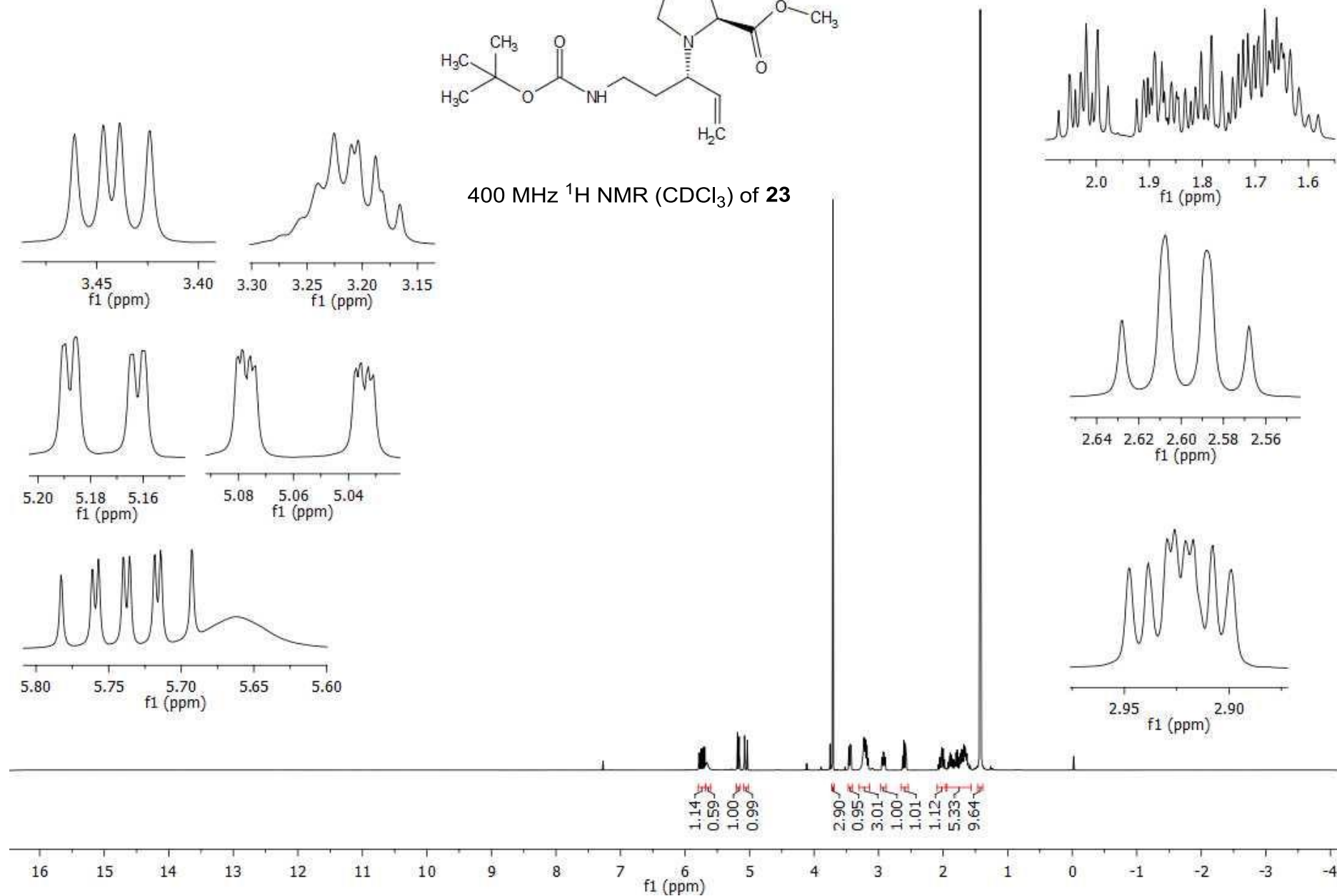


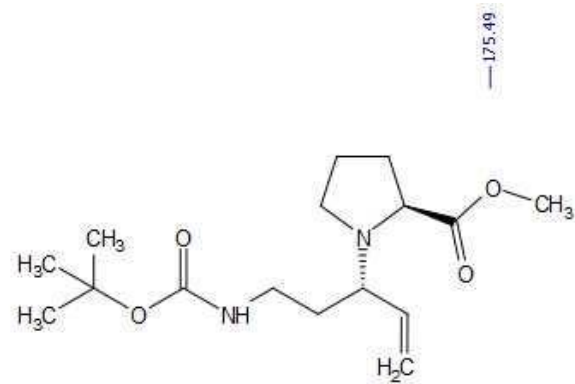
100 MHz ^{13}C NMR (CDCl_3) of **22**



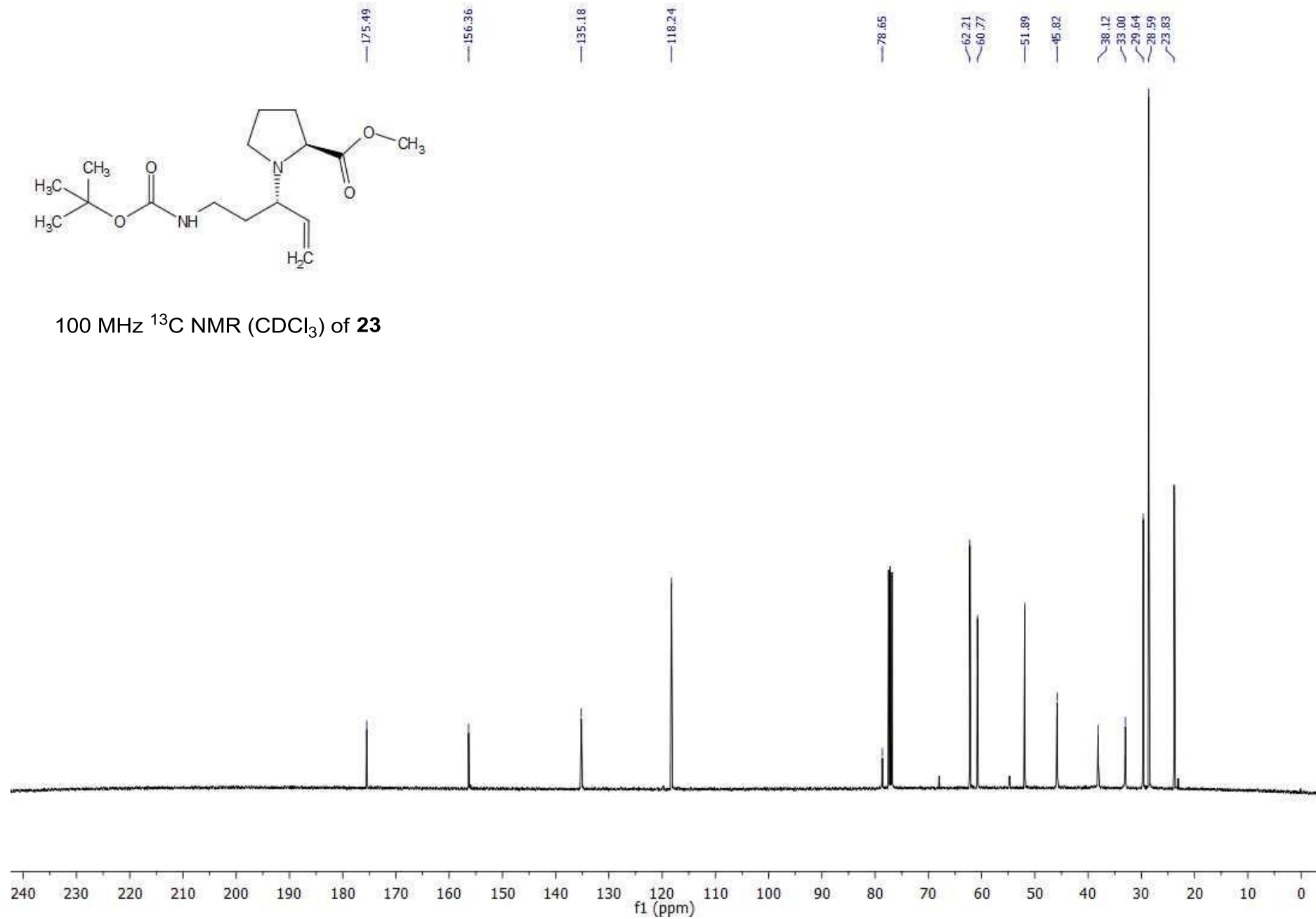


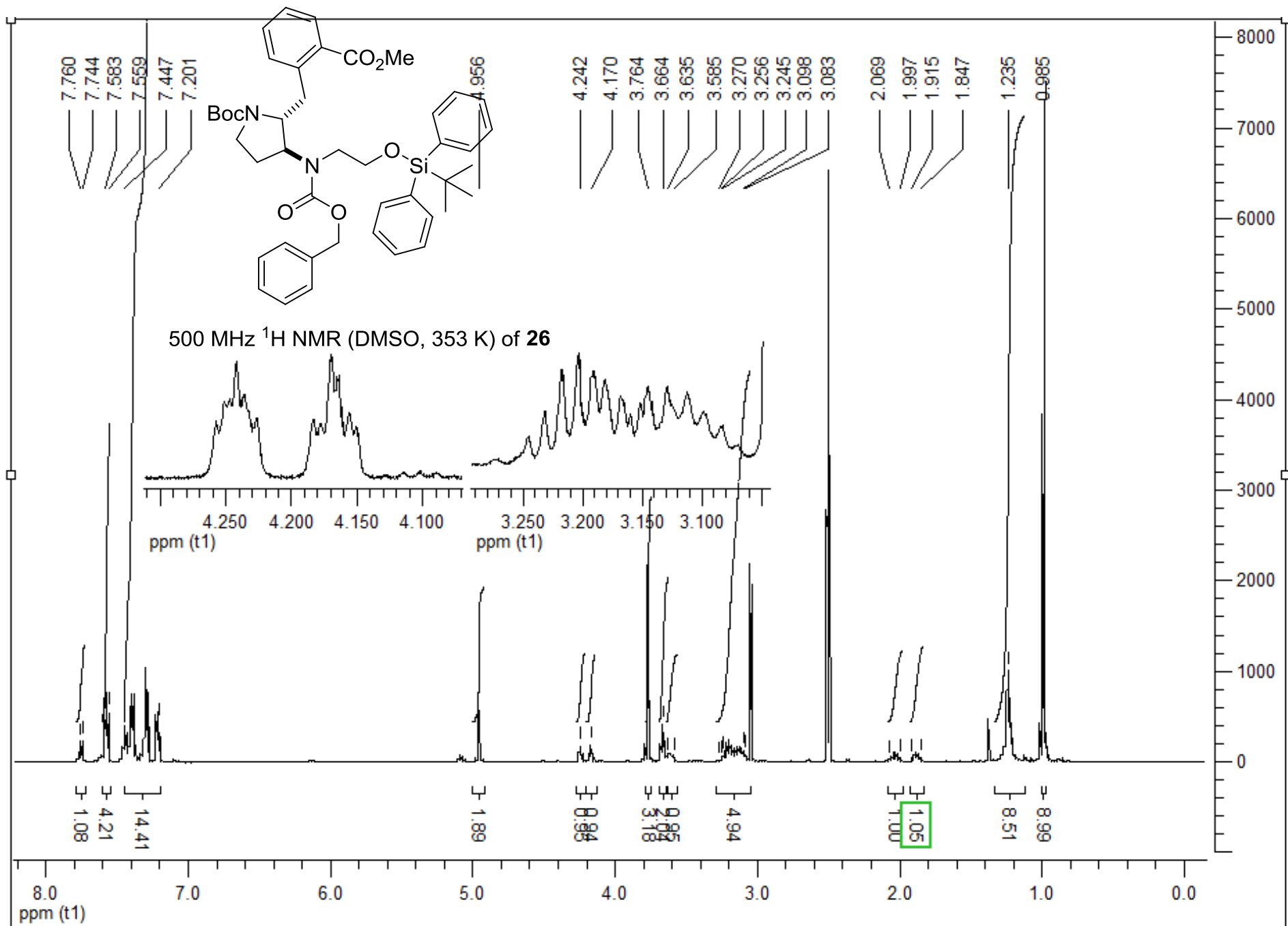
400 MHz ^1H NMR (CDCl_3) of **23**

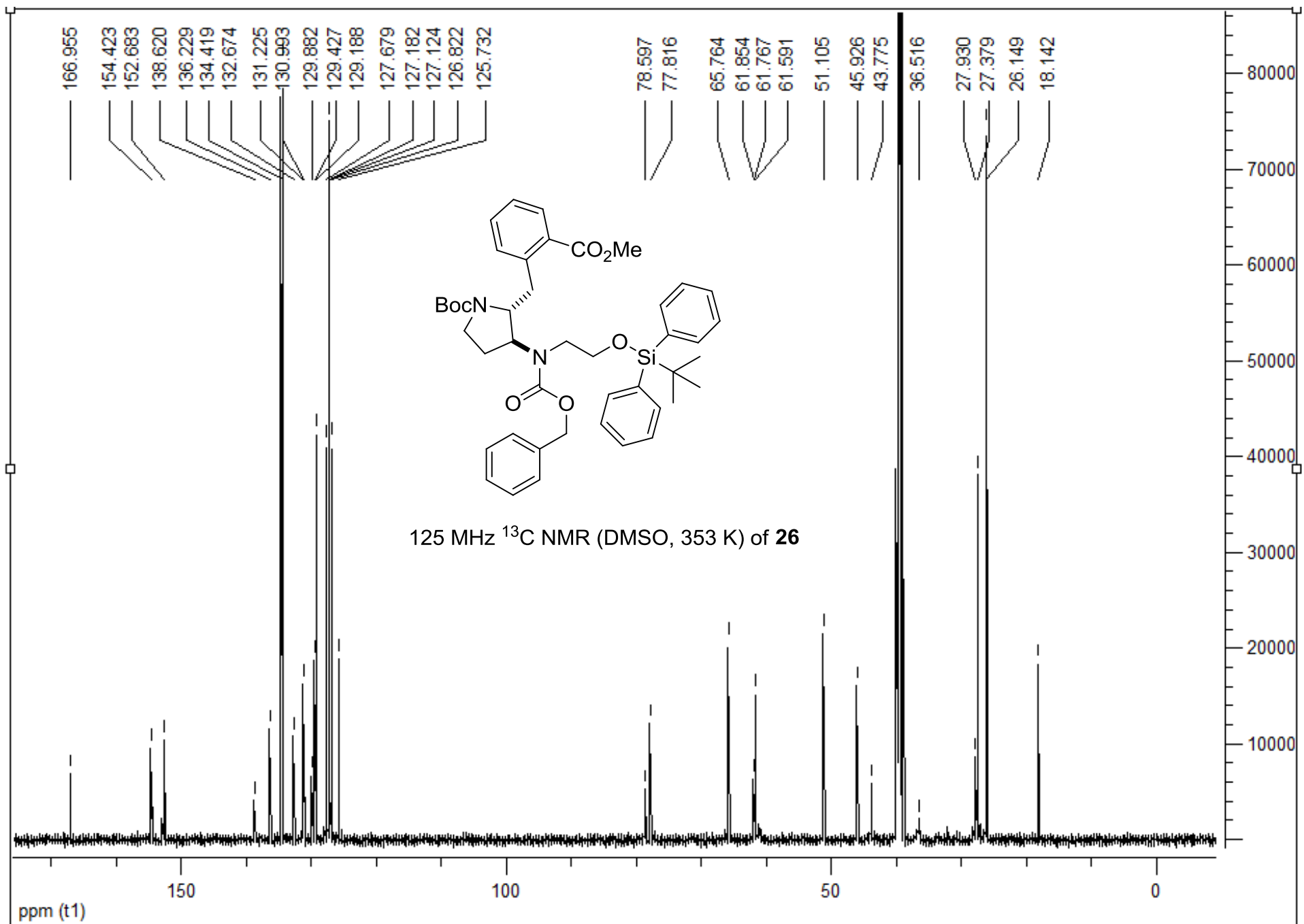


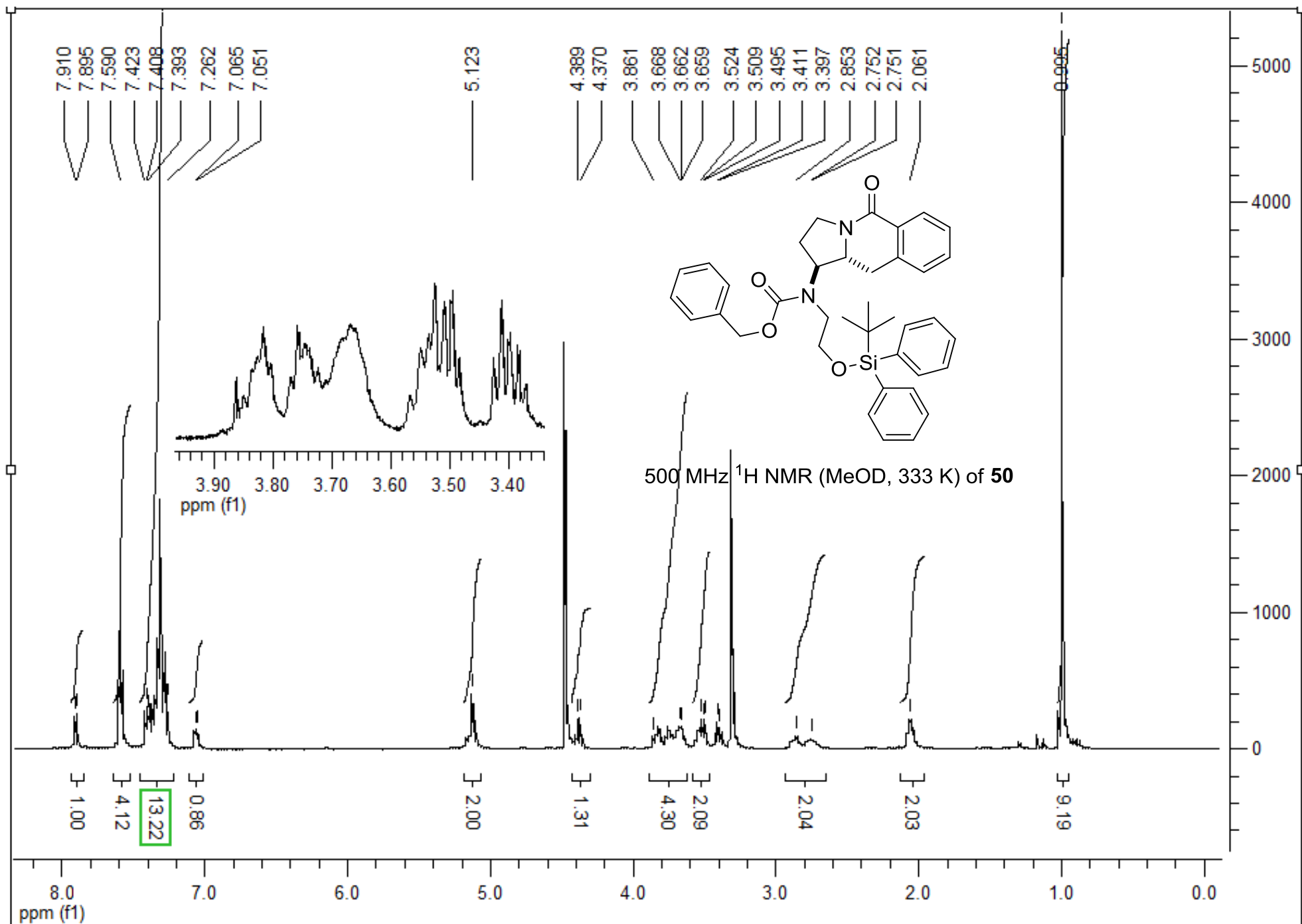


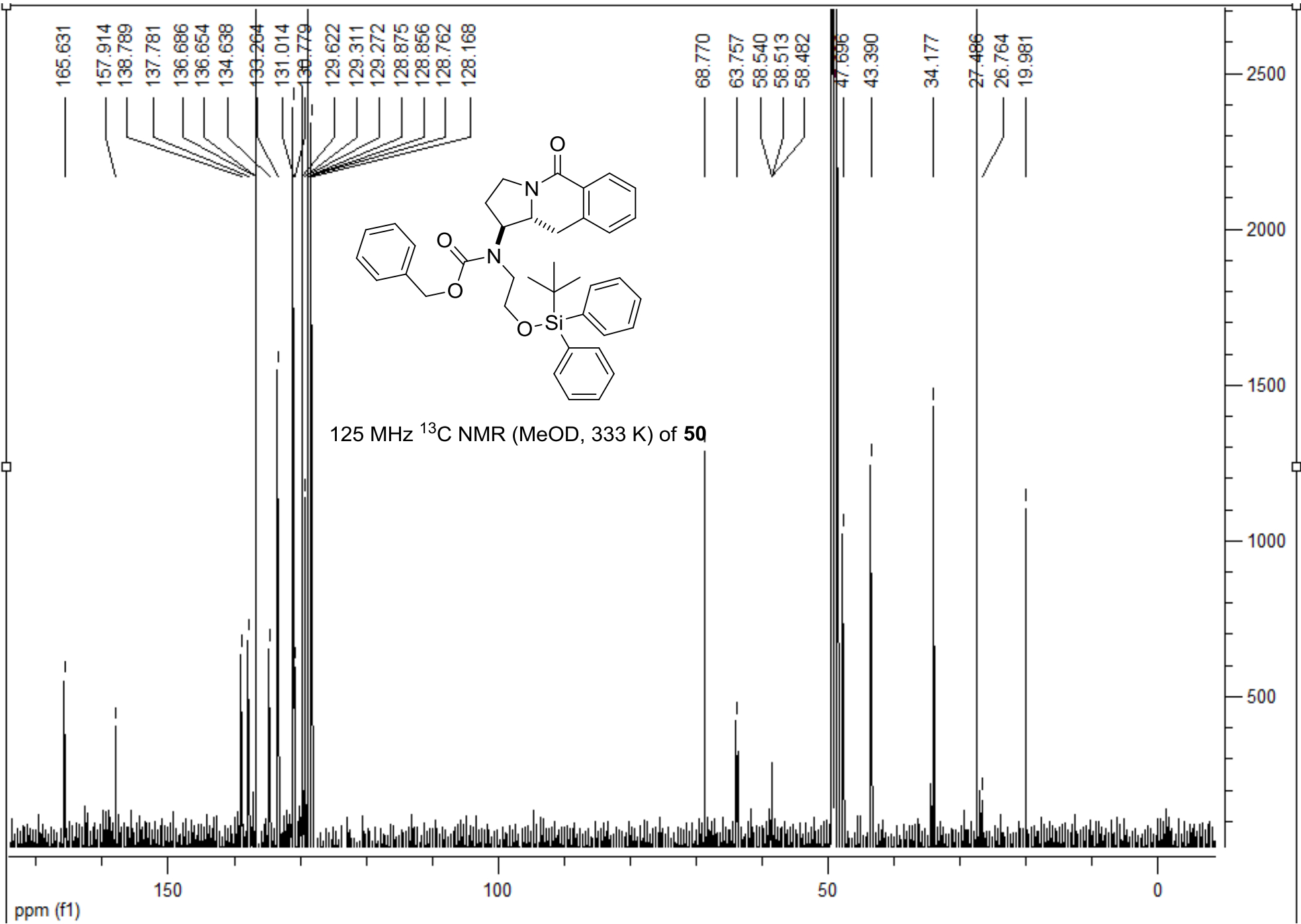
100 MHz ^{13}C NMR (CDCl_3) of **23**

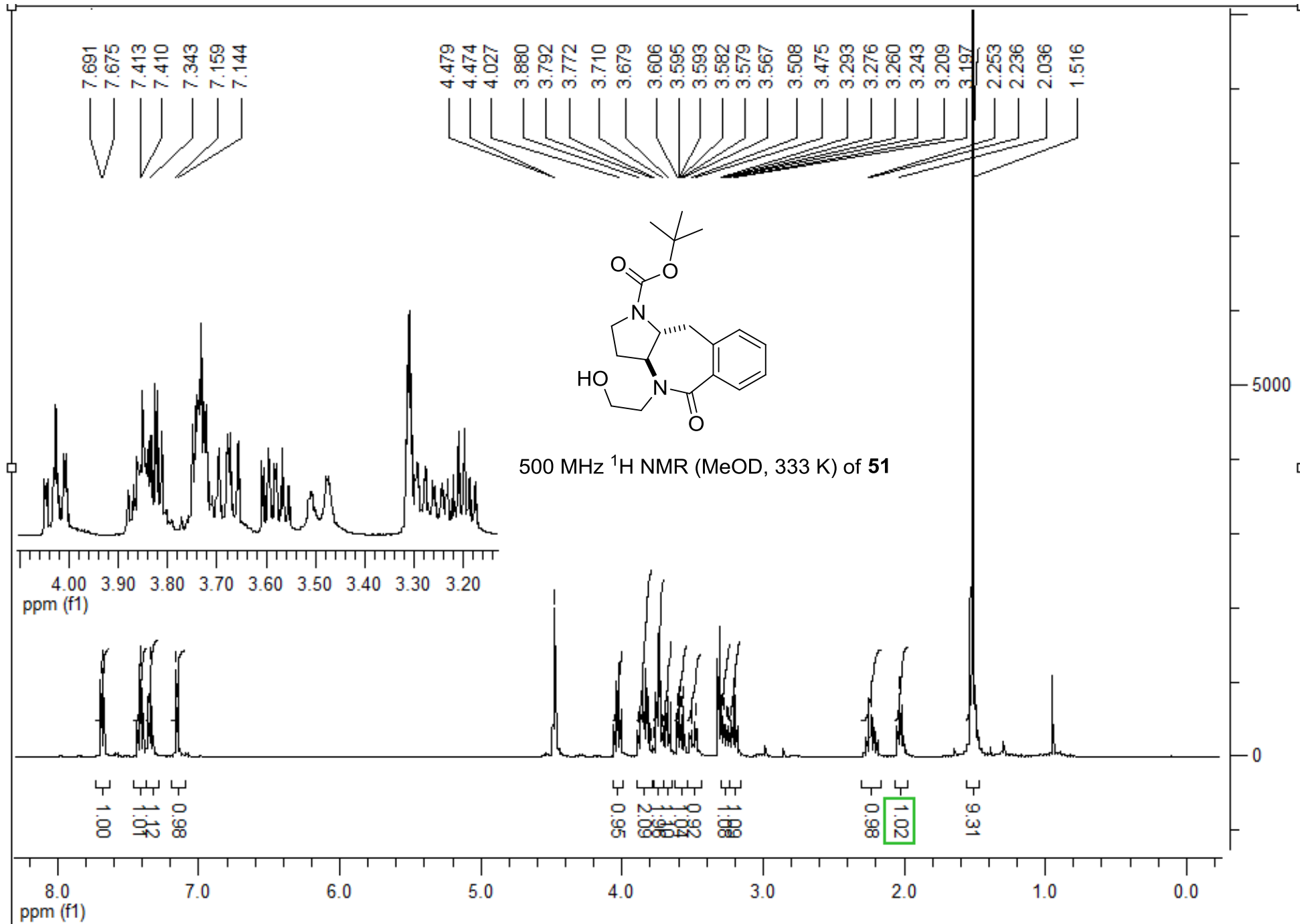


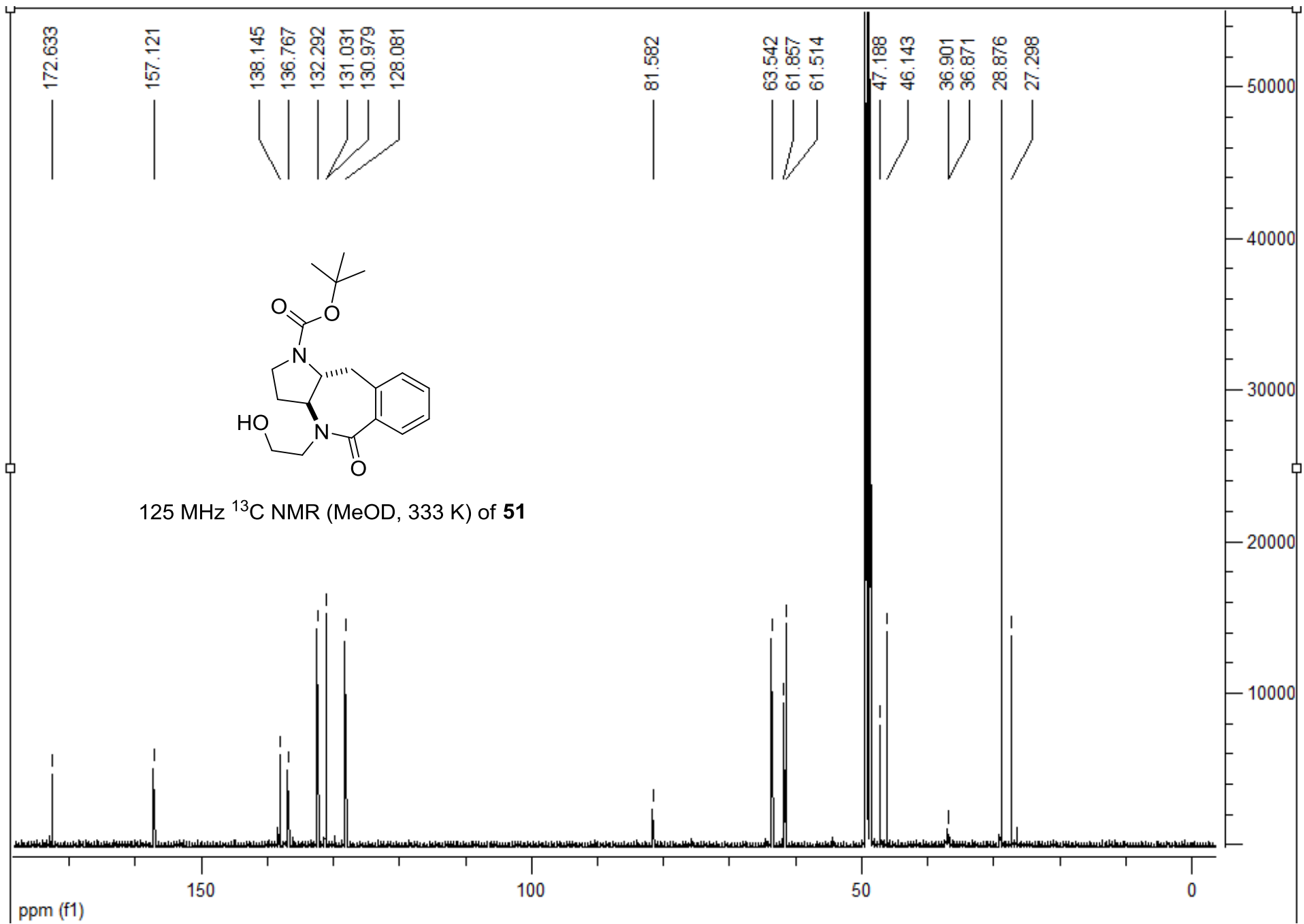


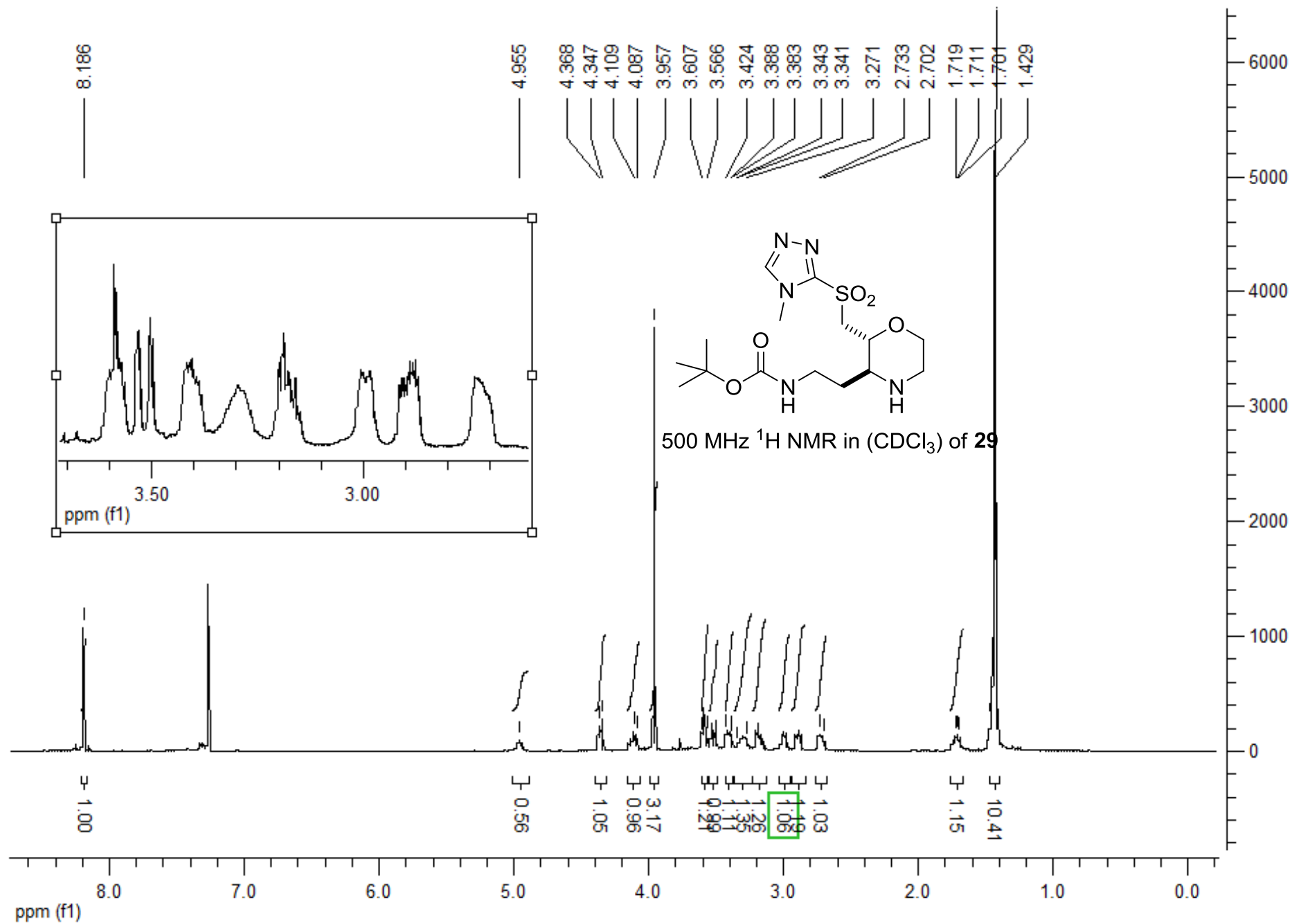


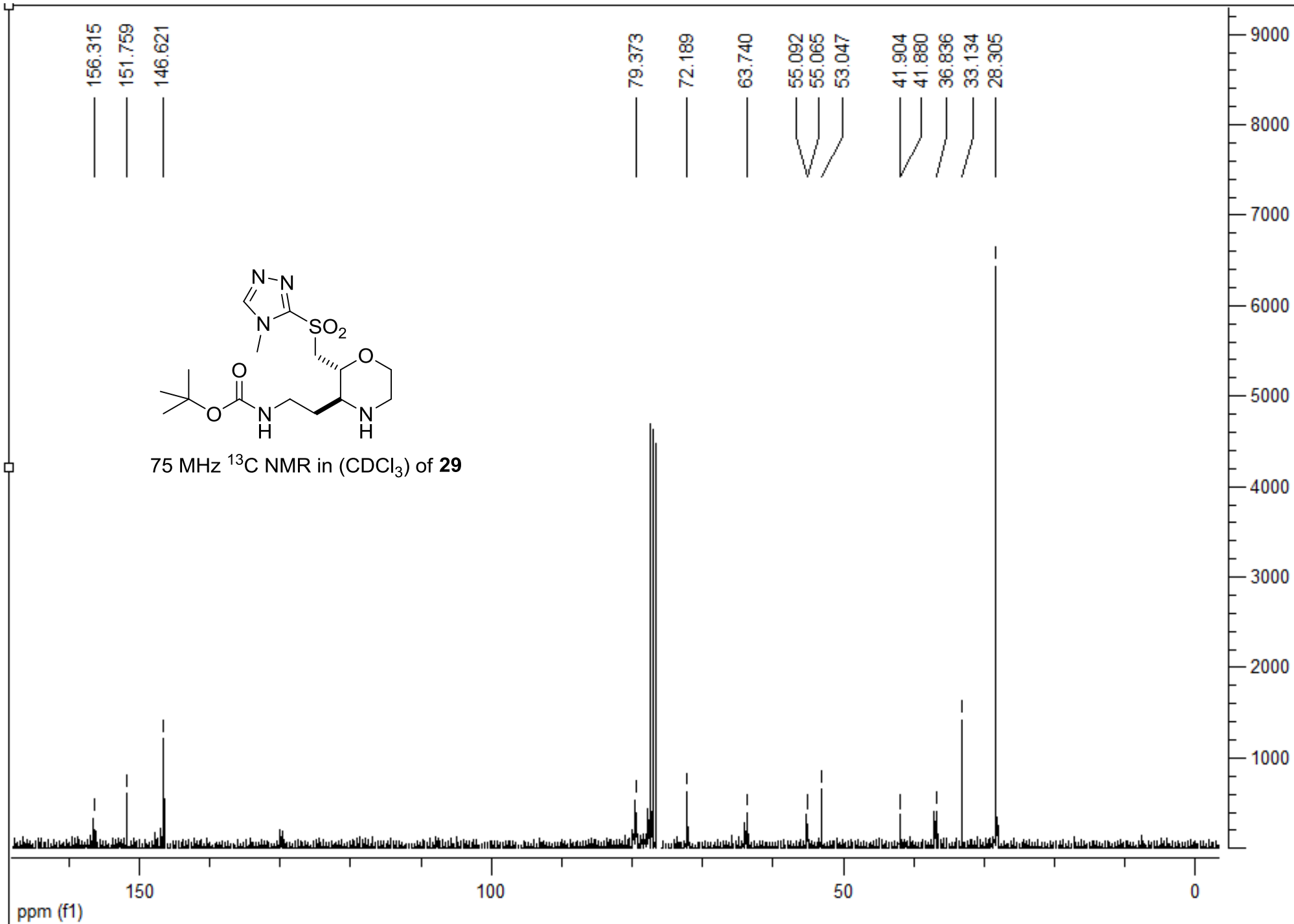


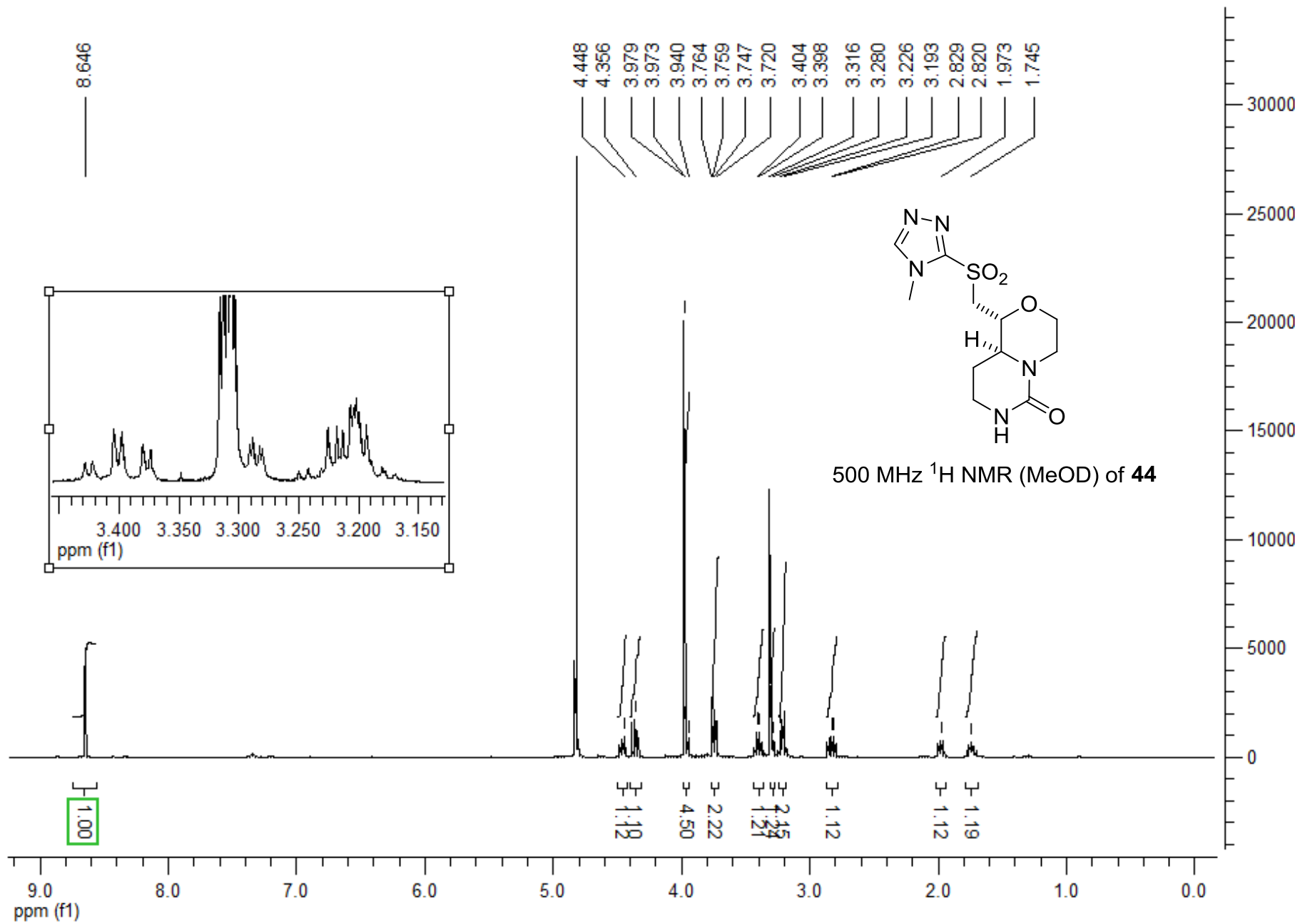


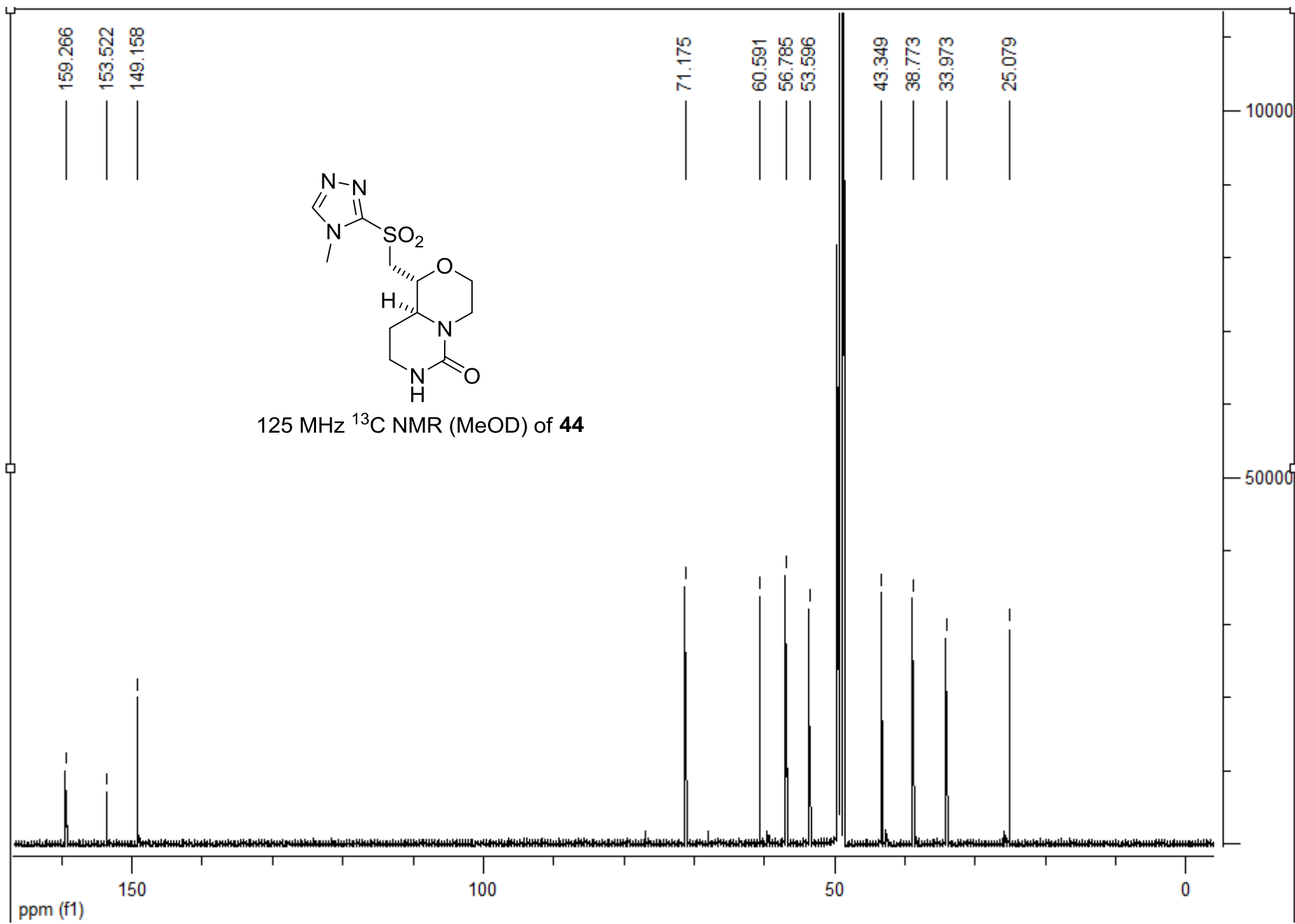


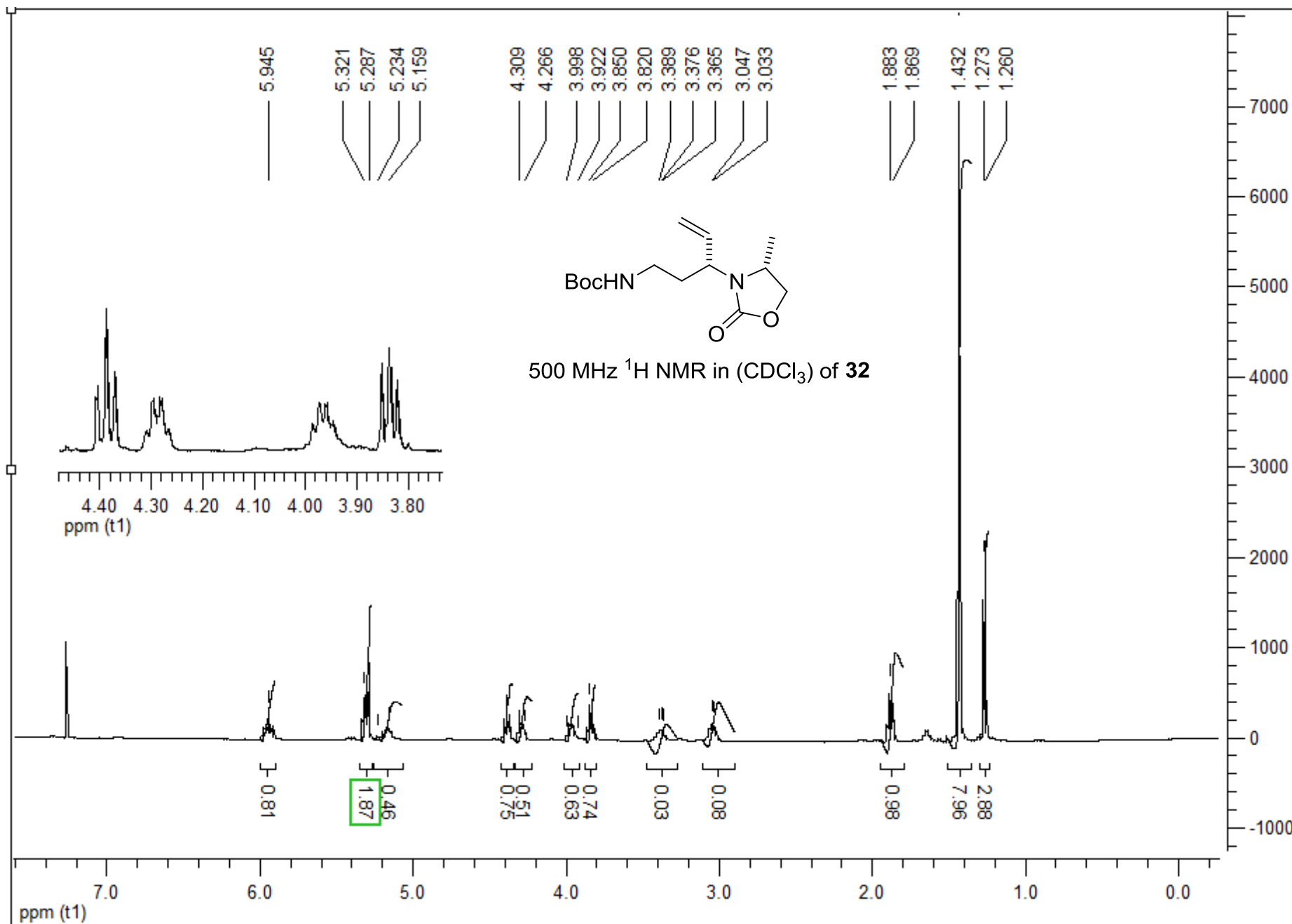


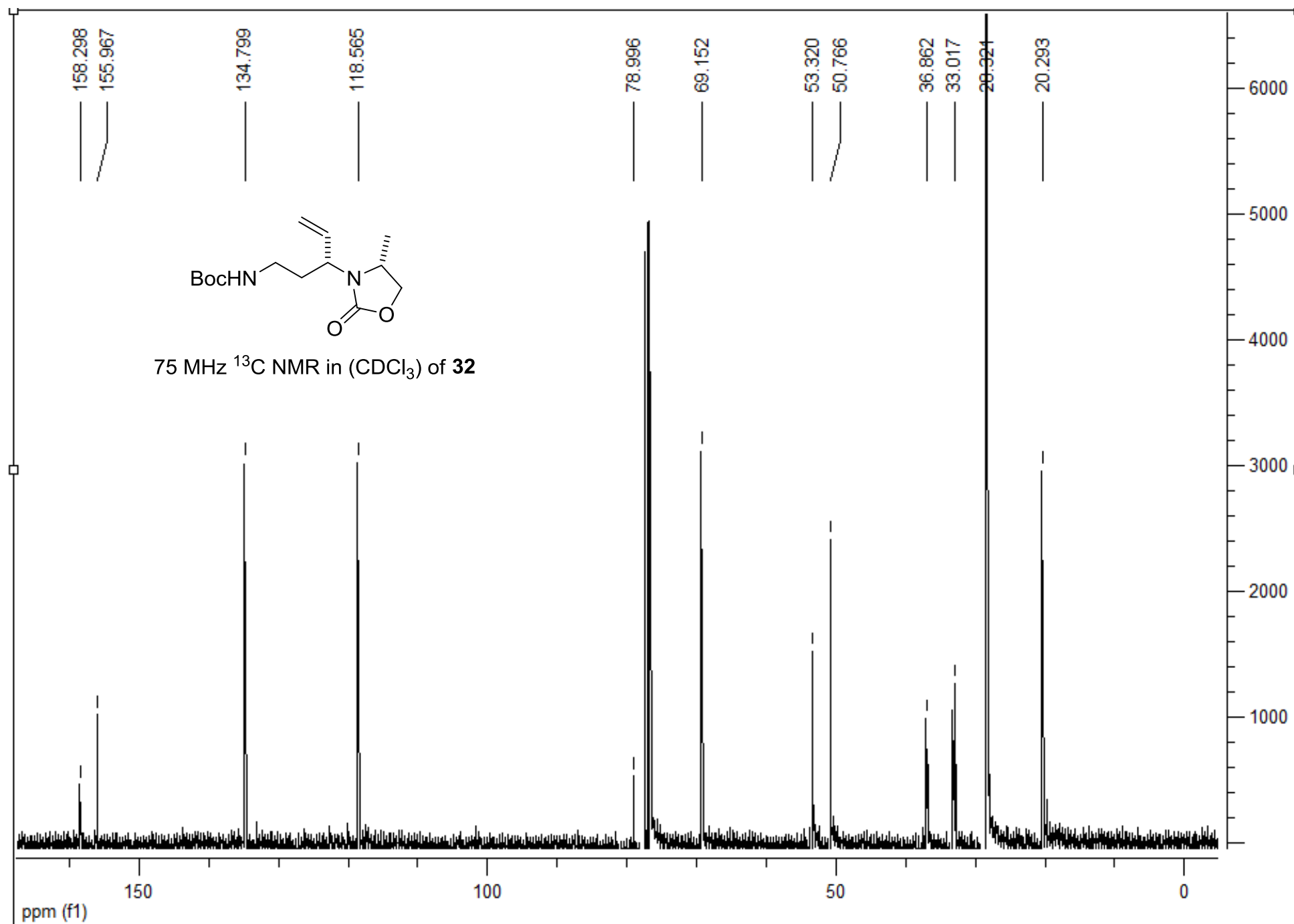


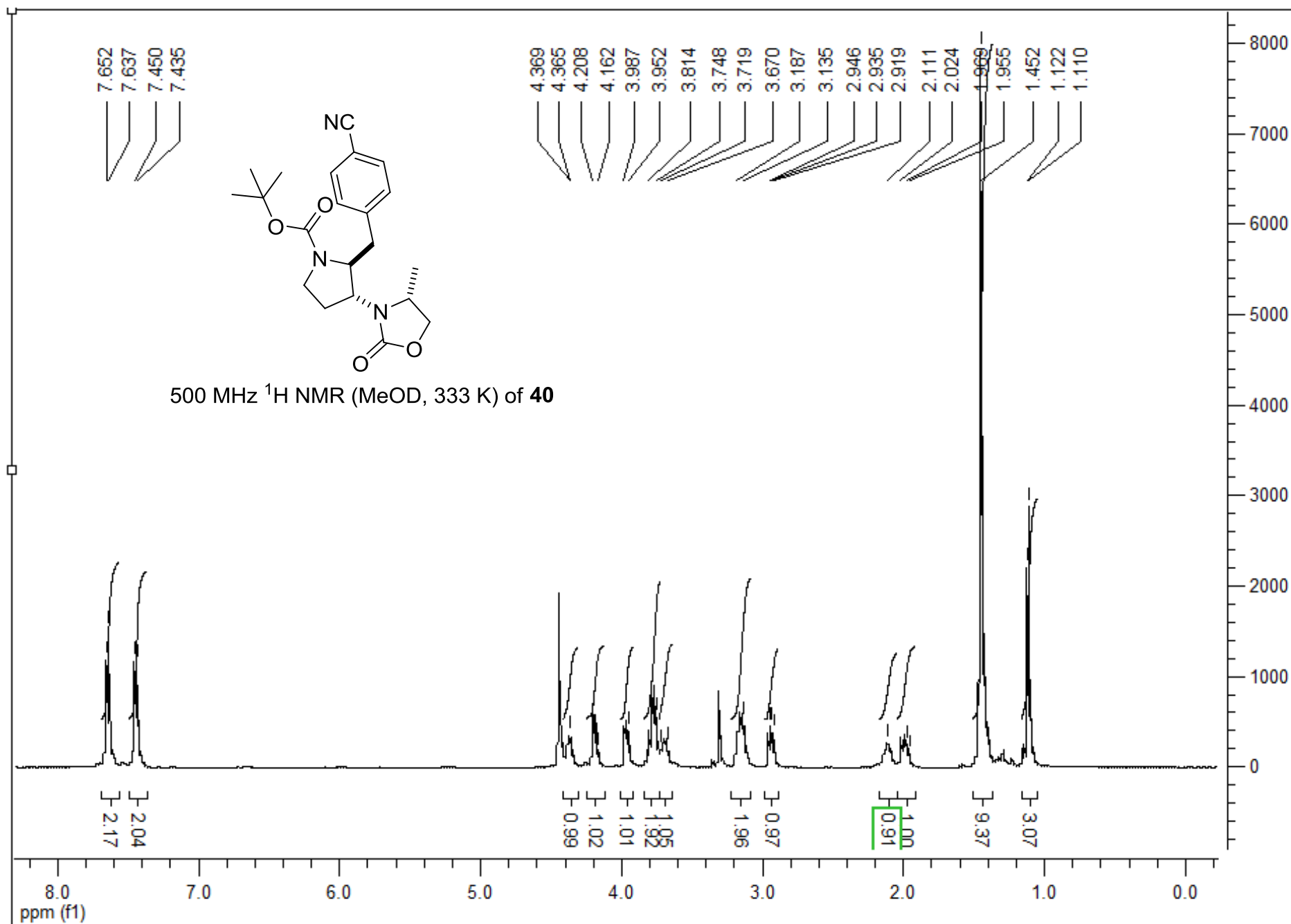


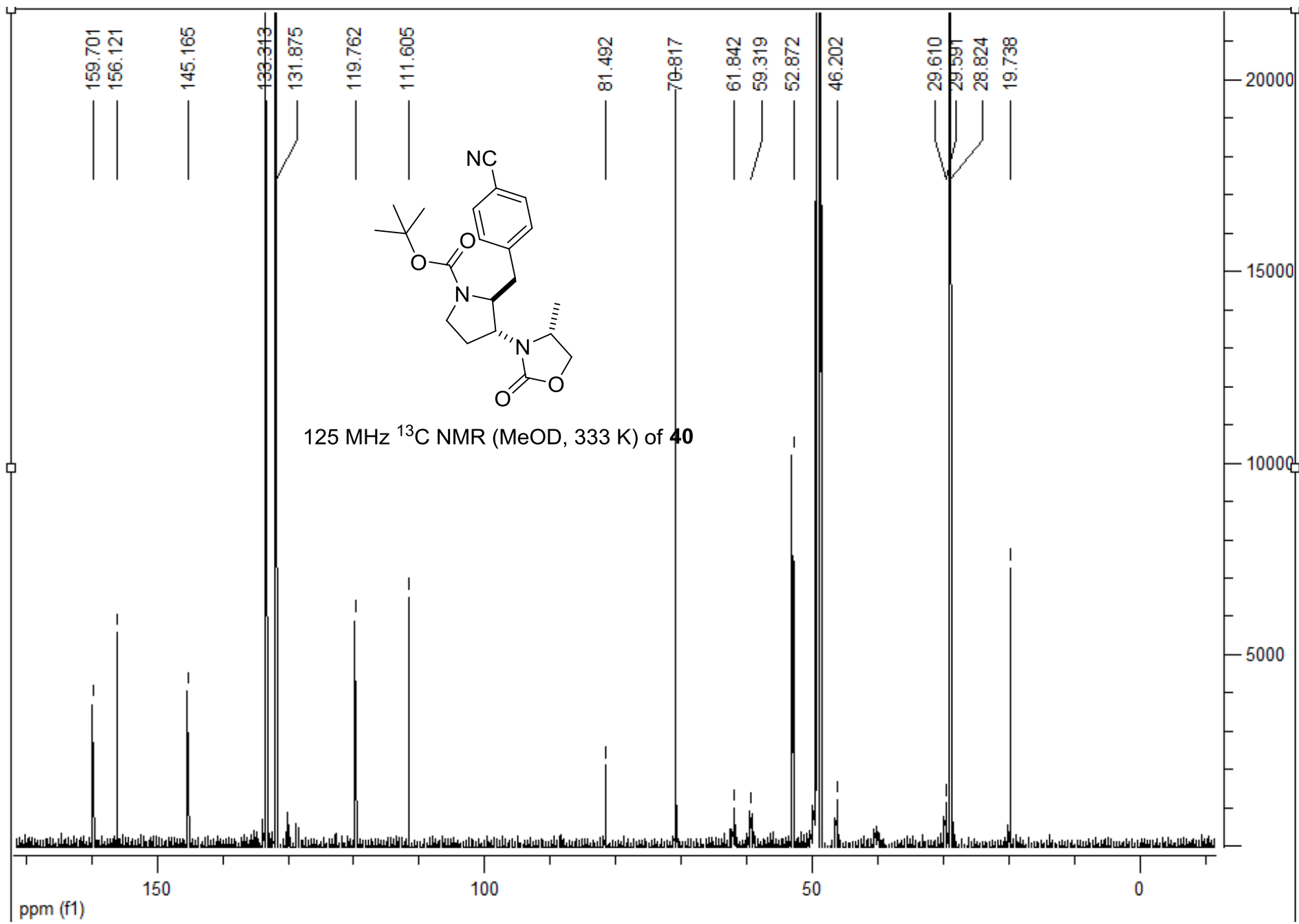


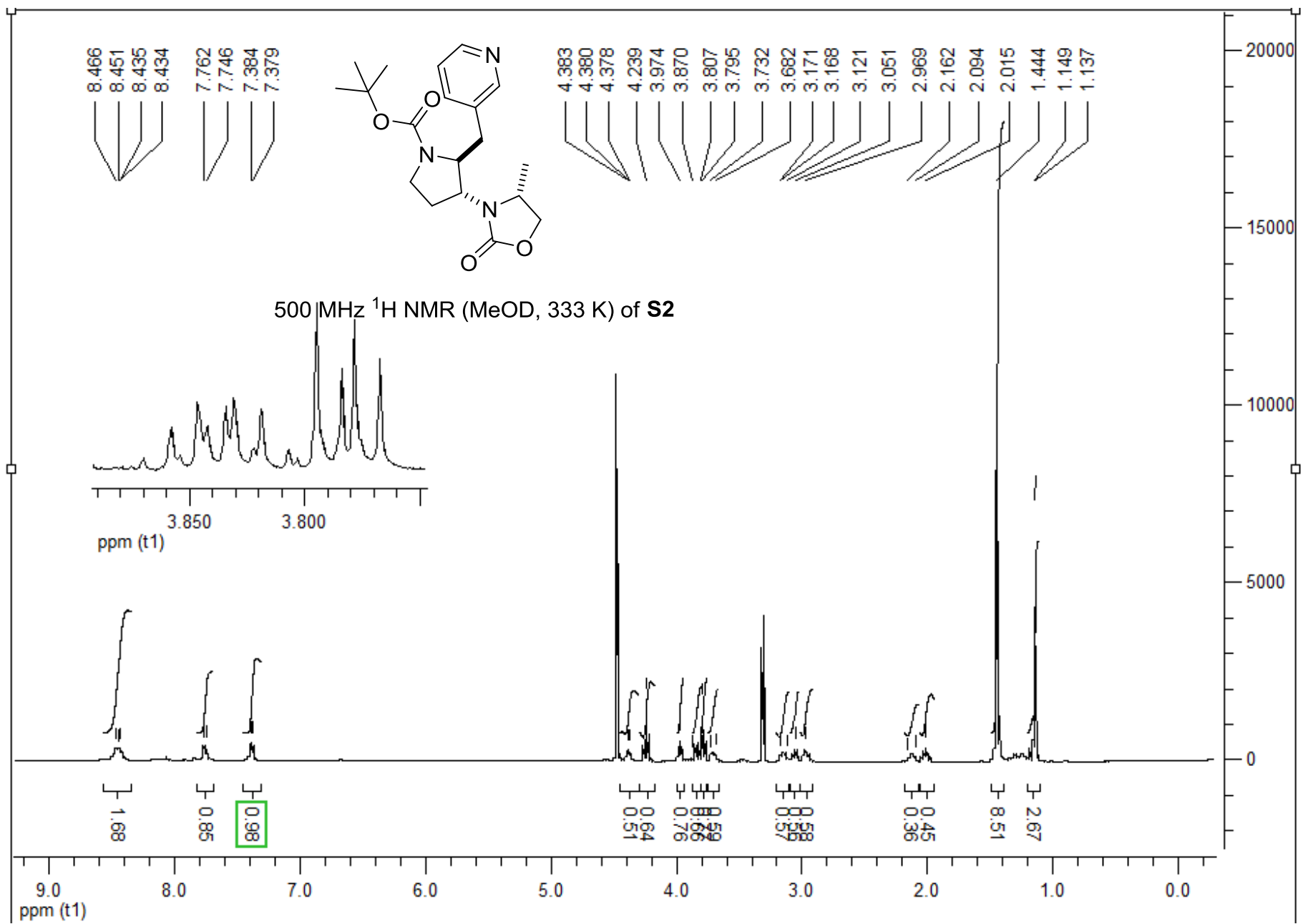


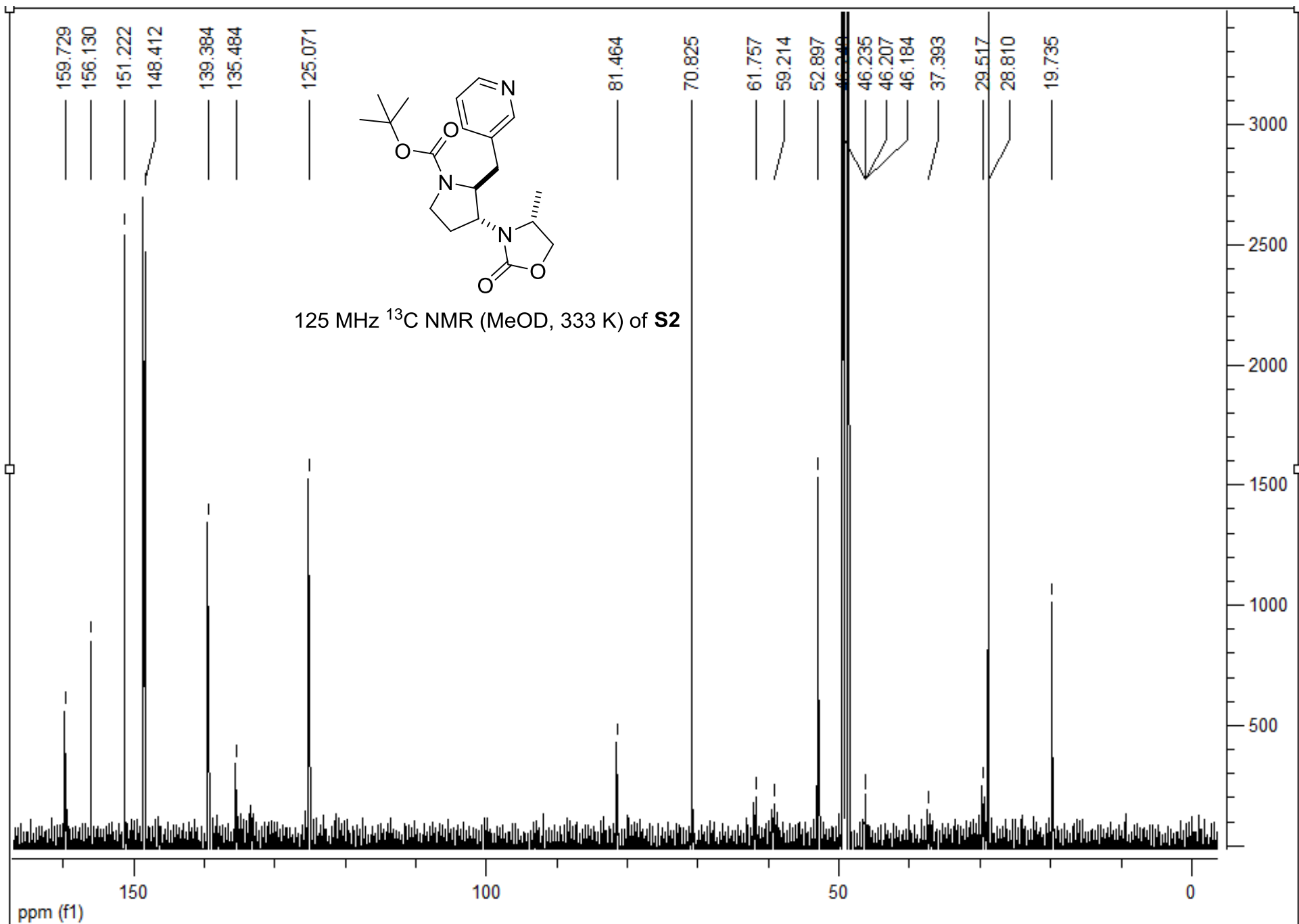


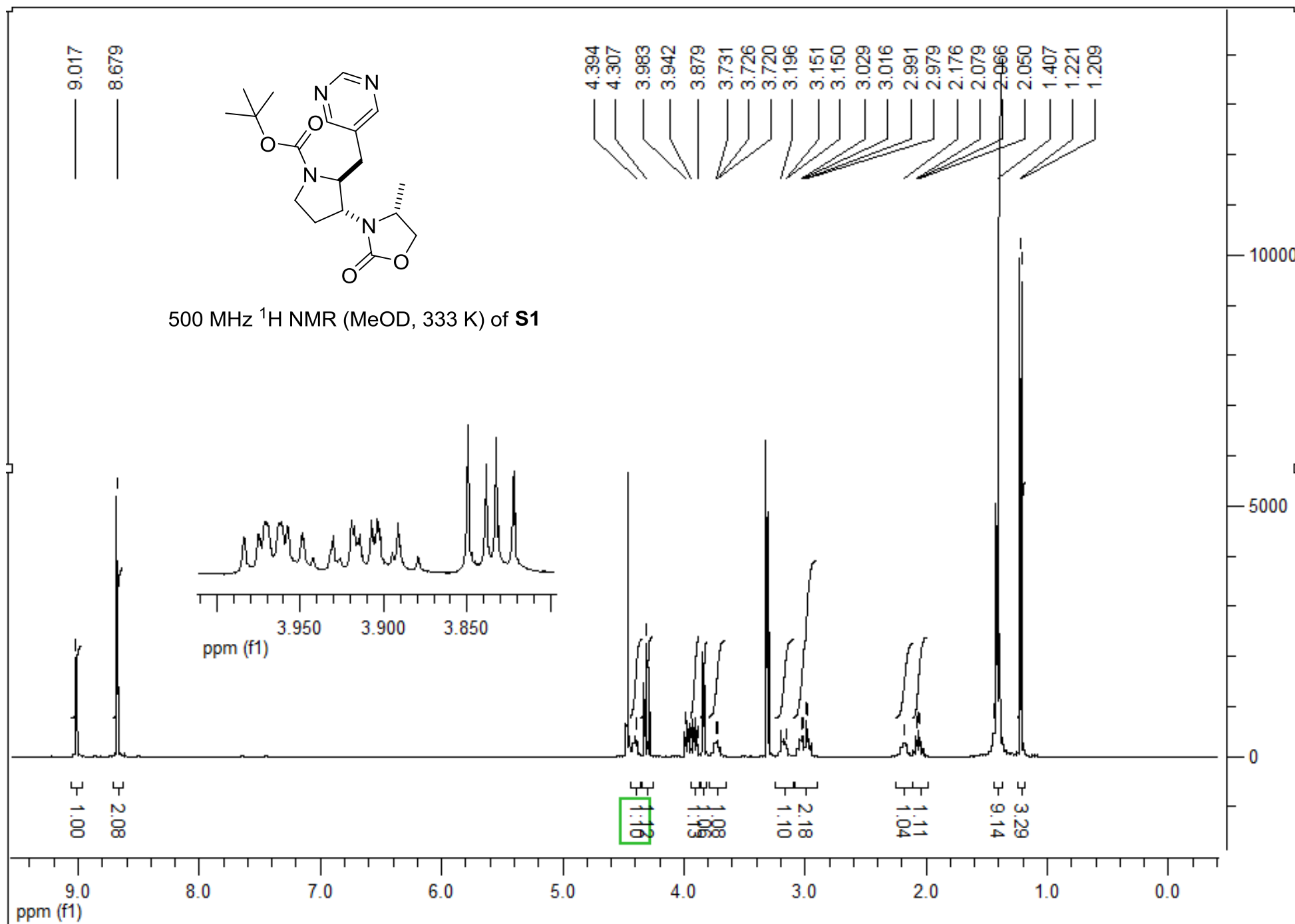


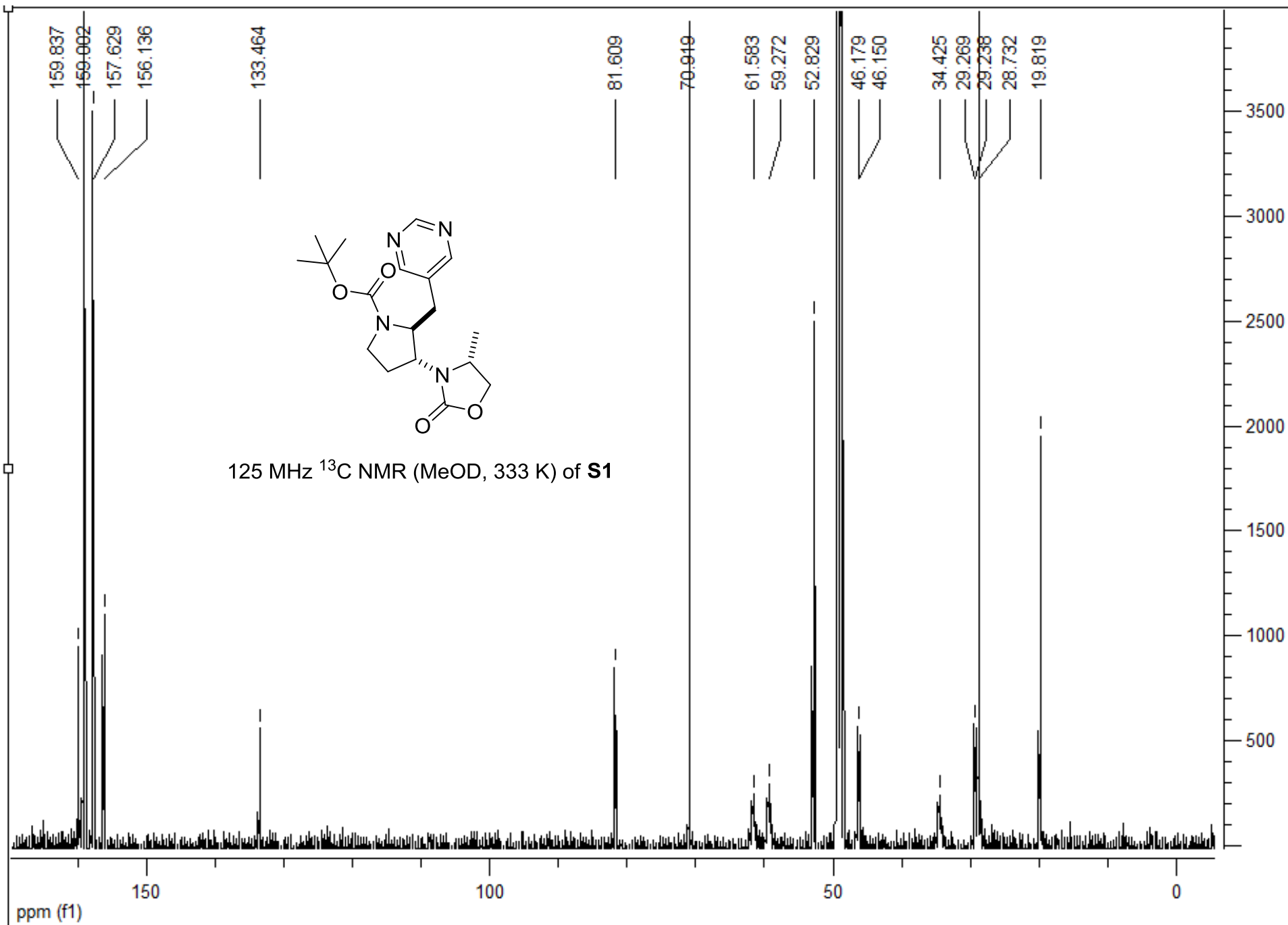


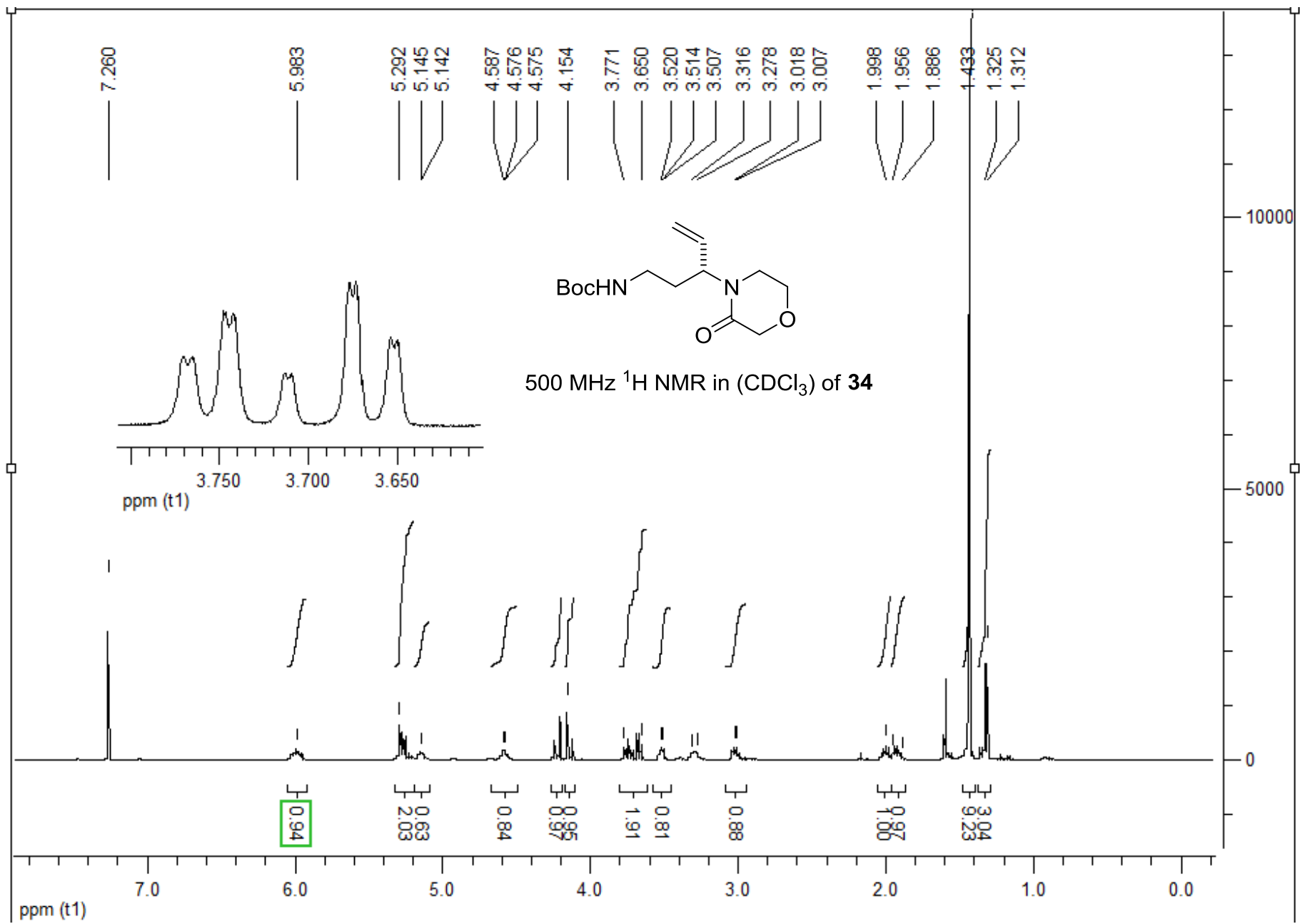


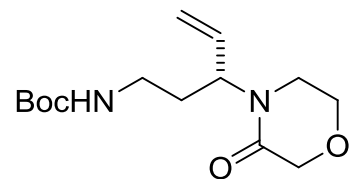




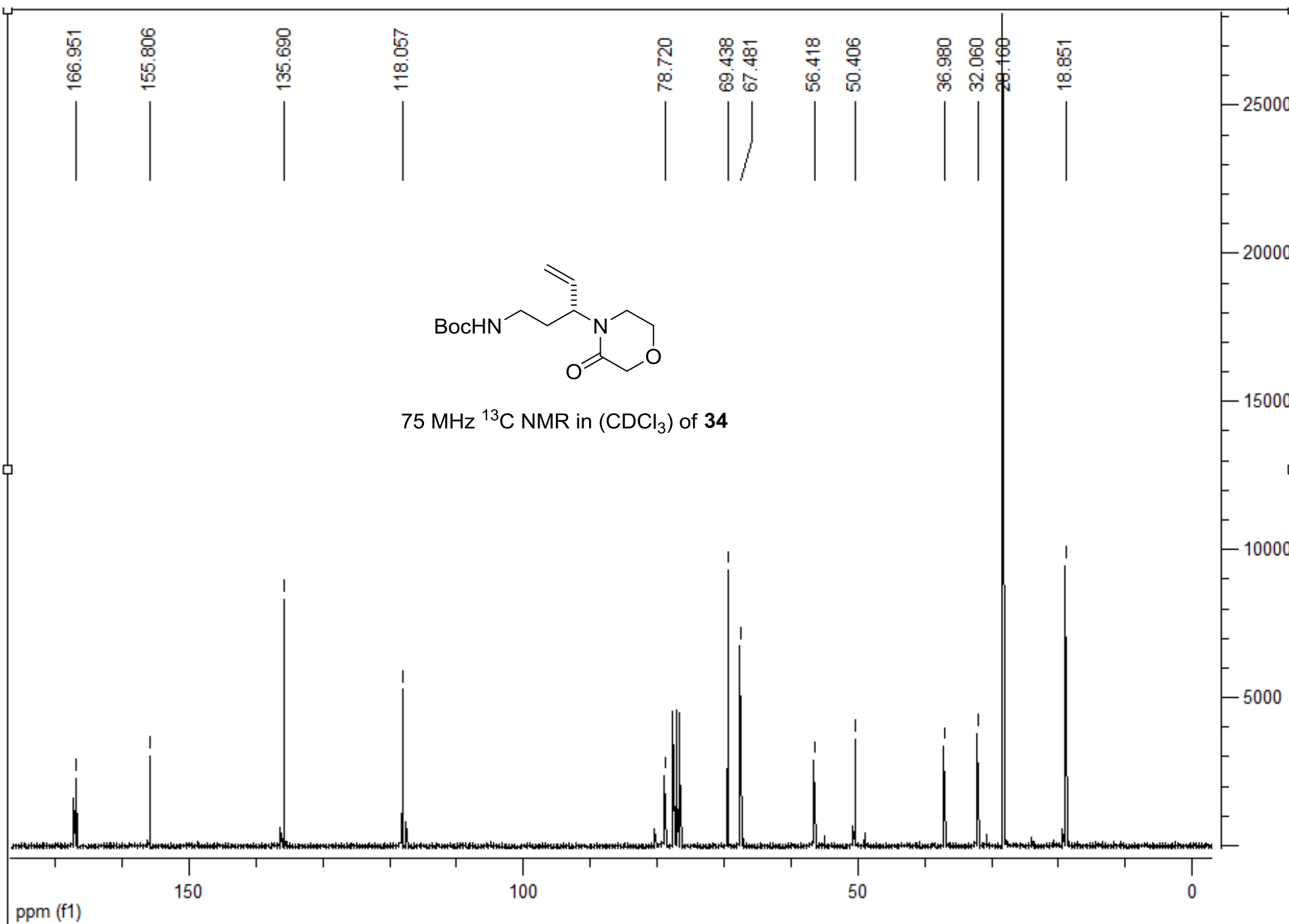


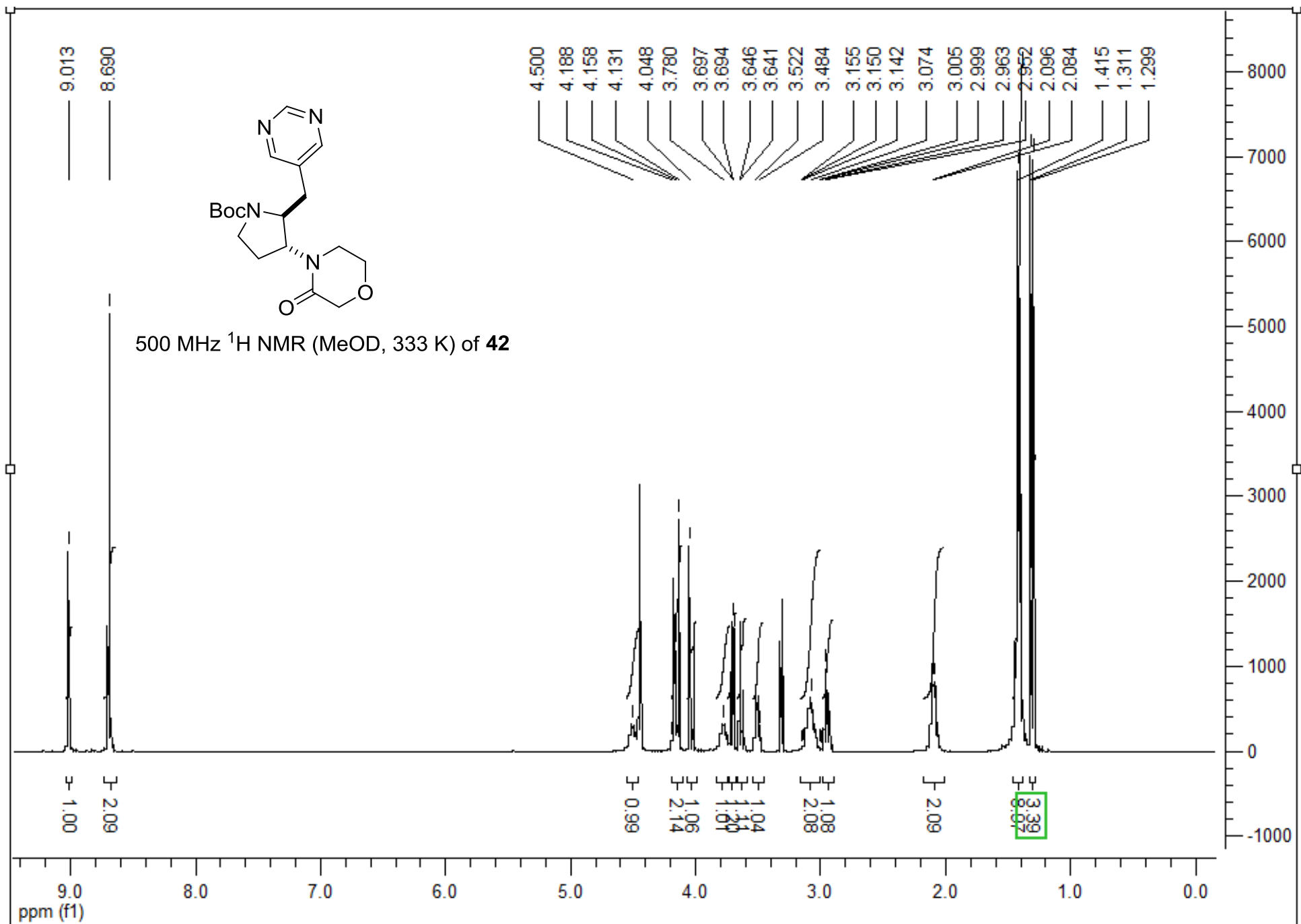


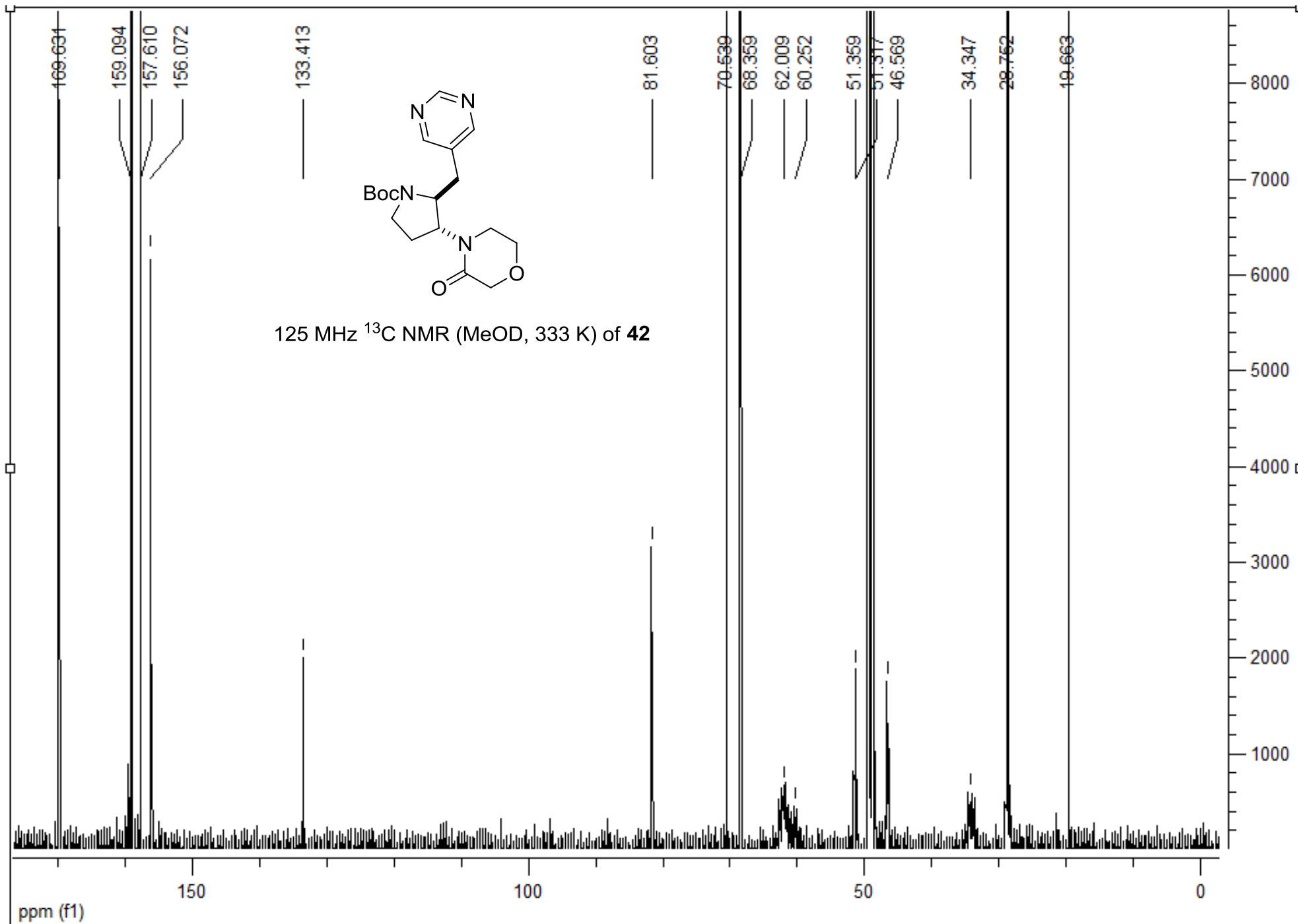


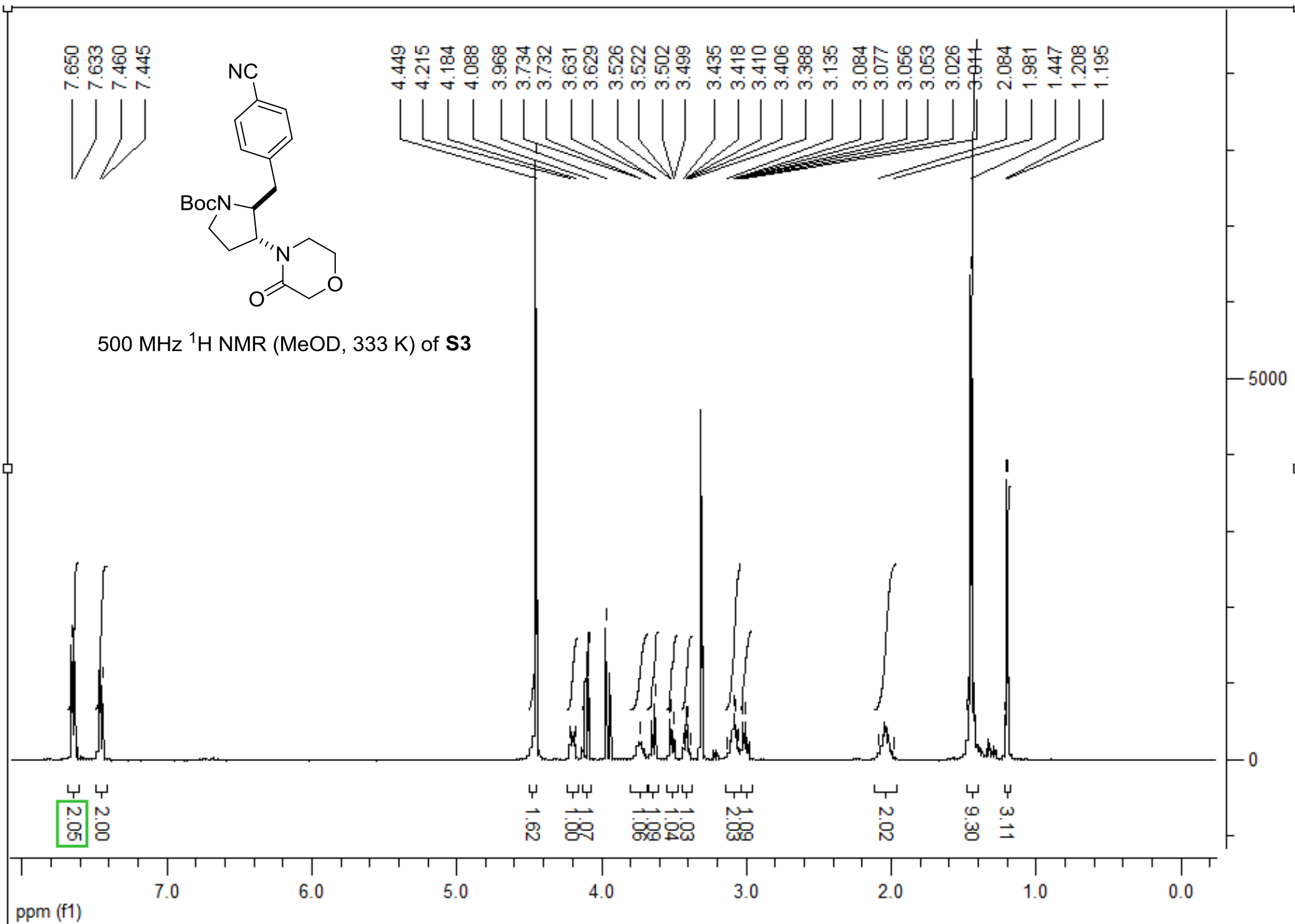


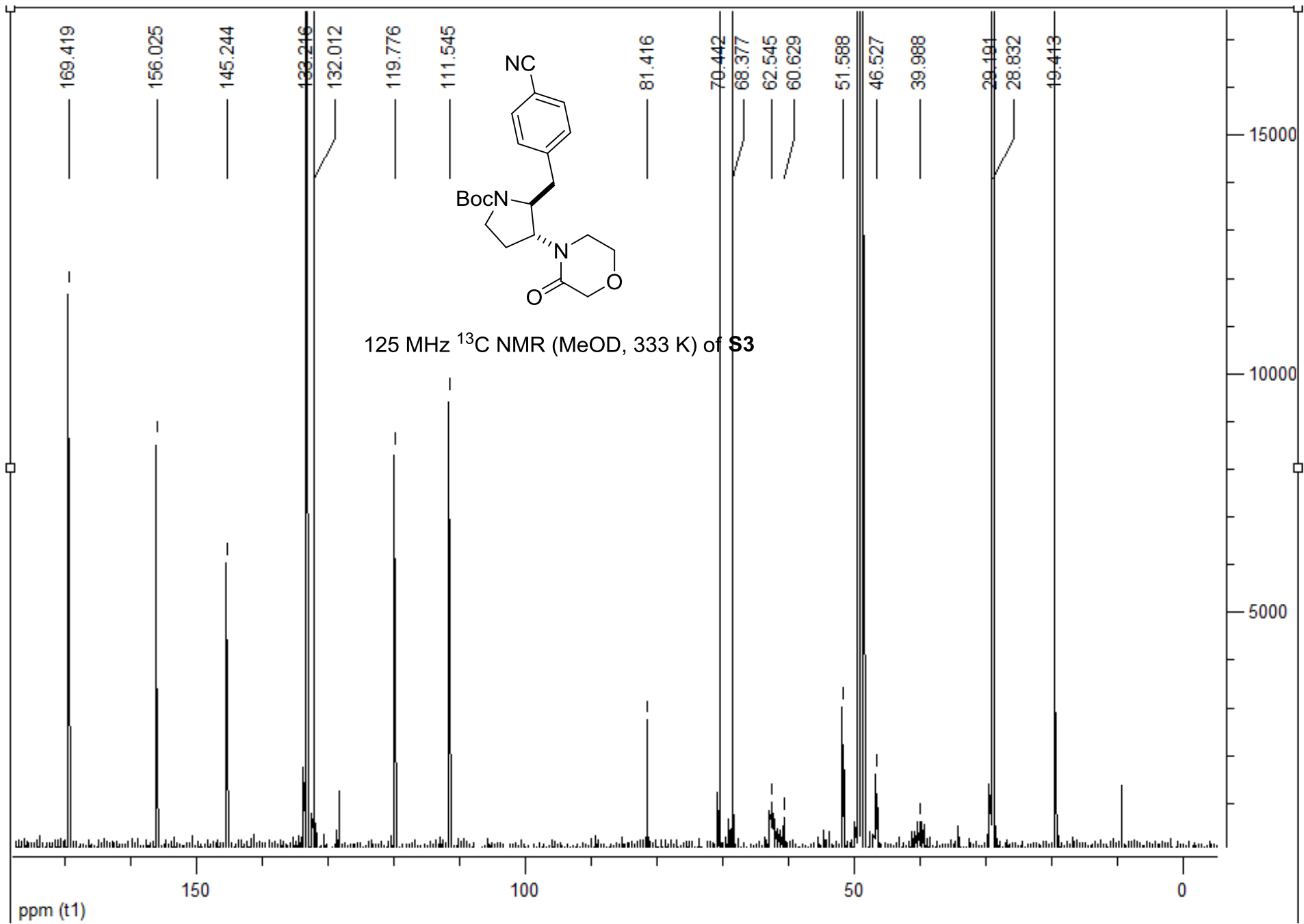
75 MHz ^{13}C NMR in (CDCl_3) of **34**

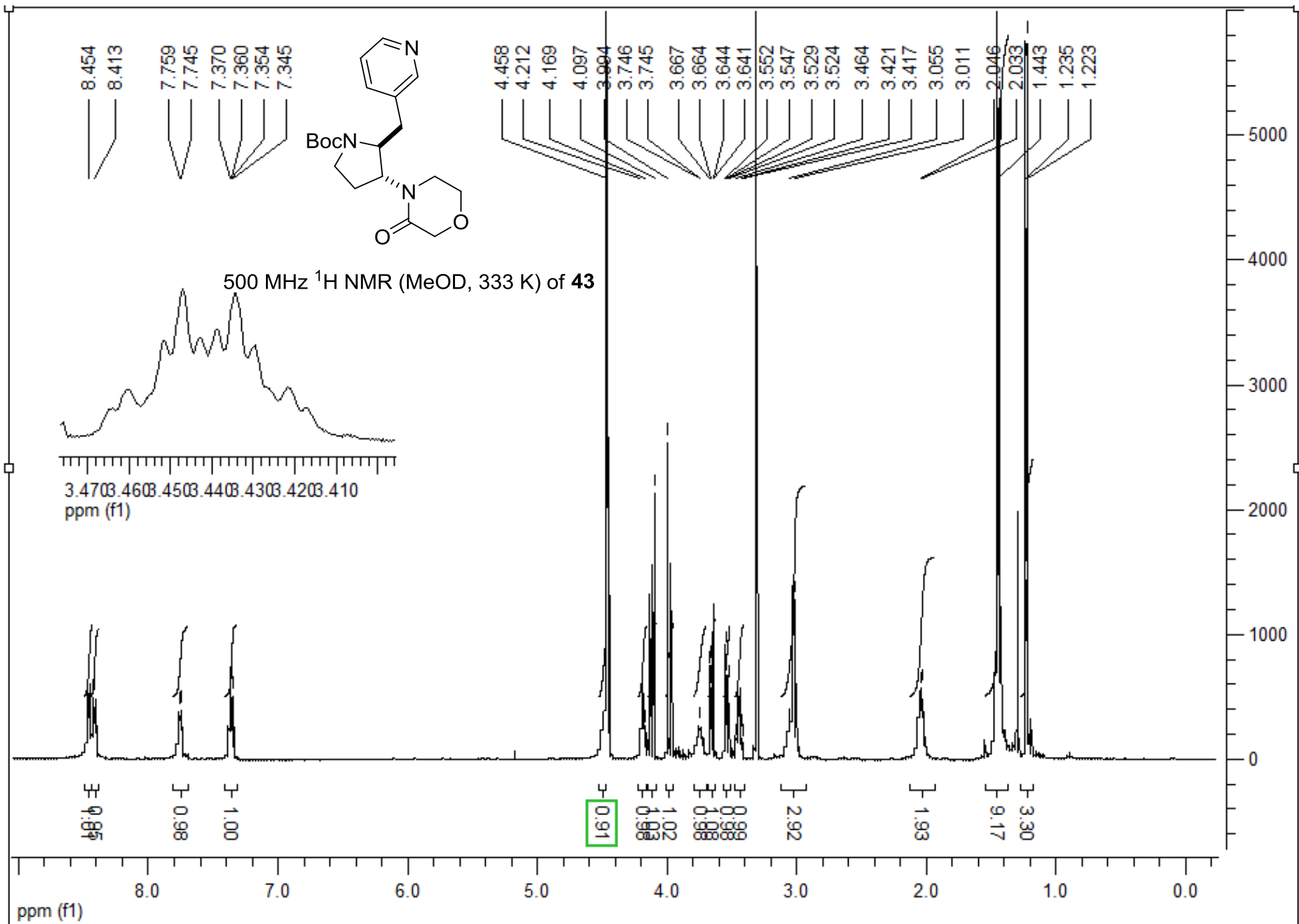


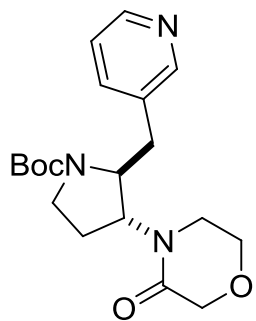




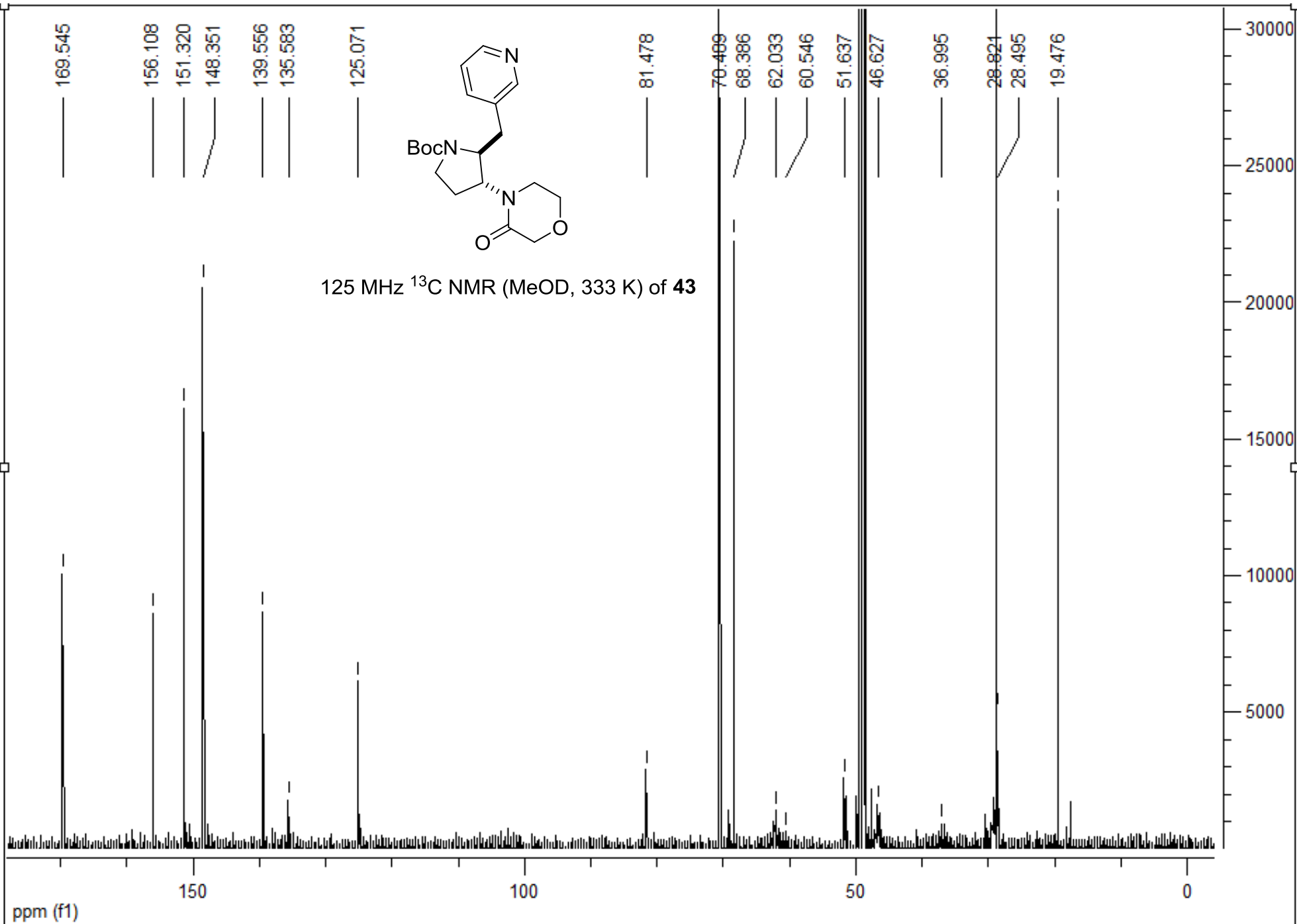


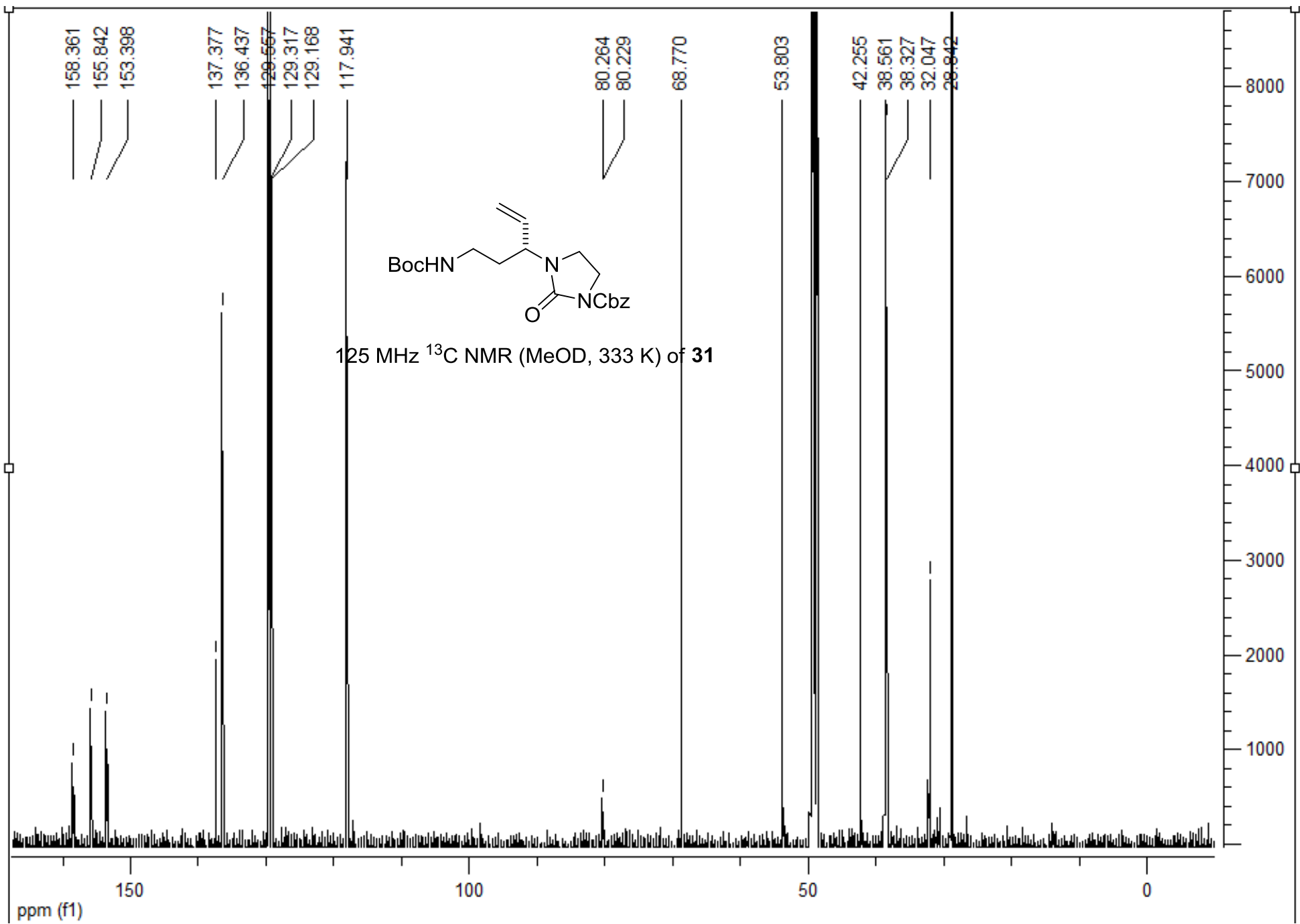


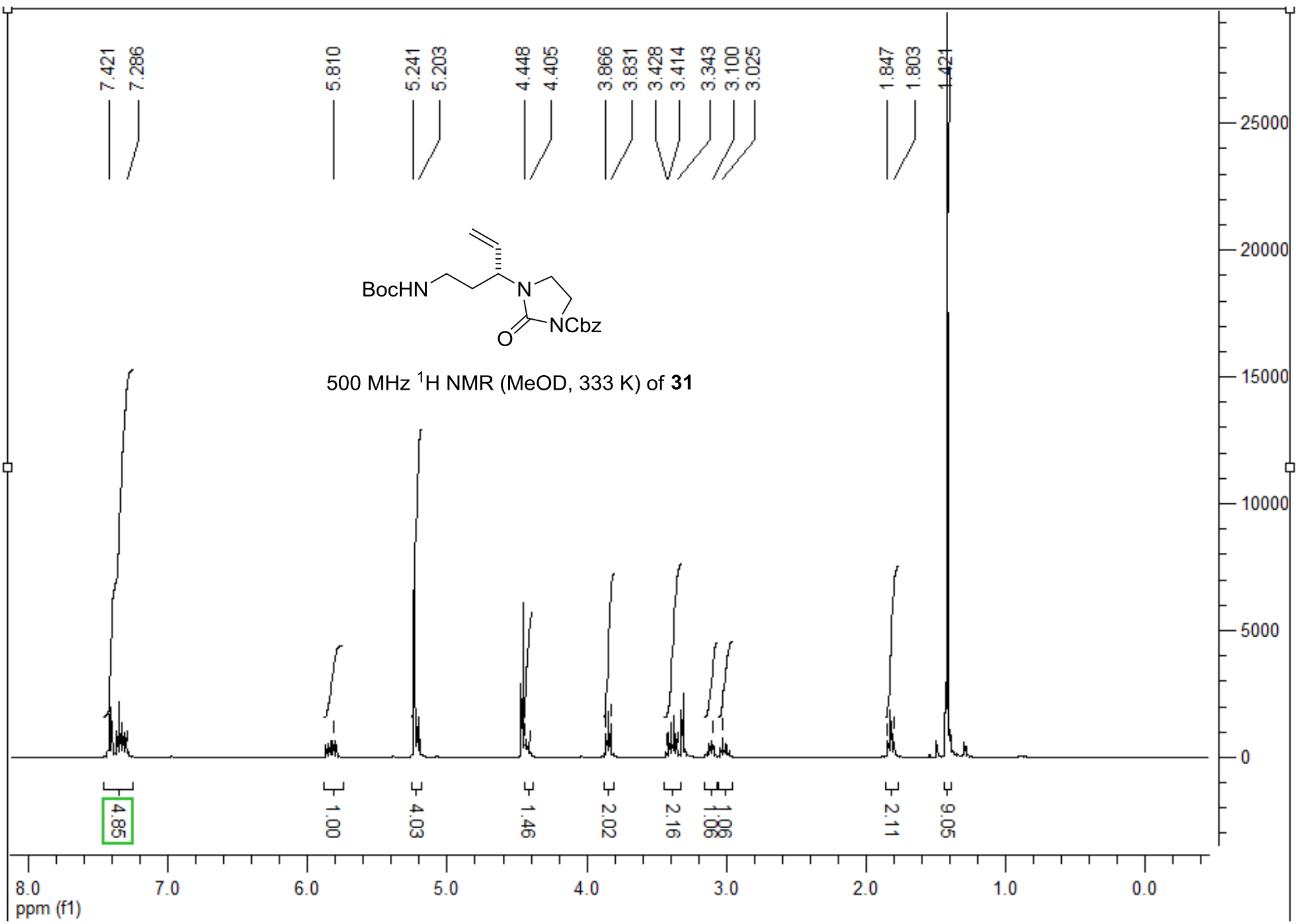


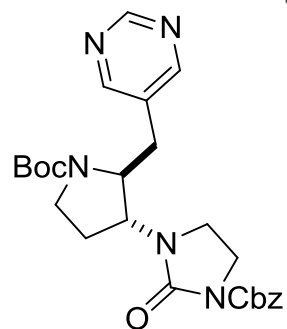


125 MHz ^{13}C NMR (MeOD, 333 K) of **43**

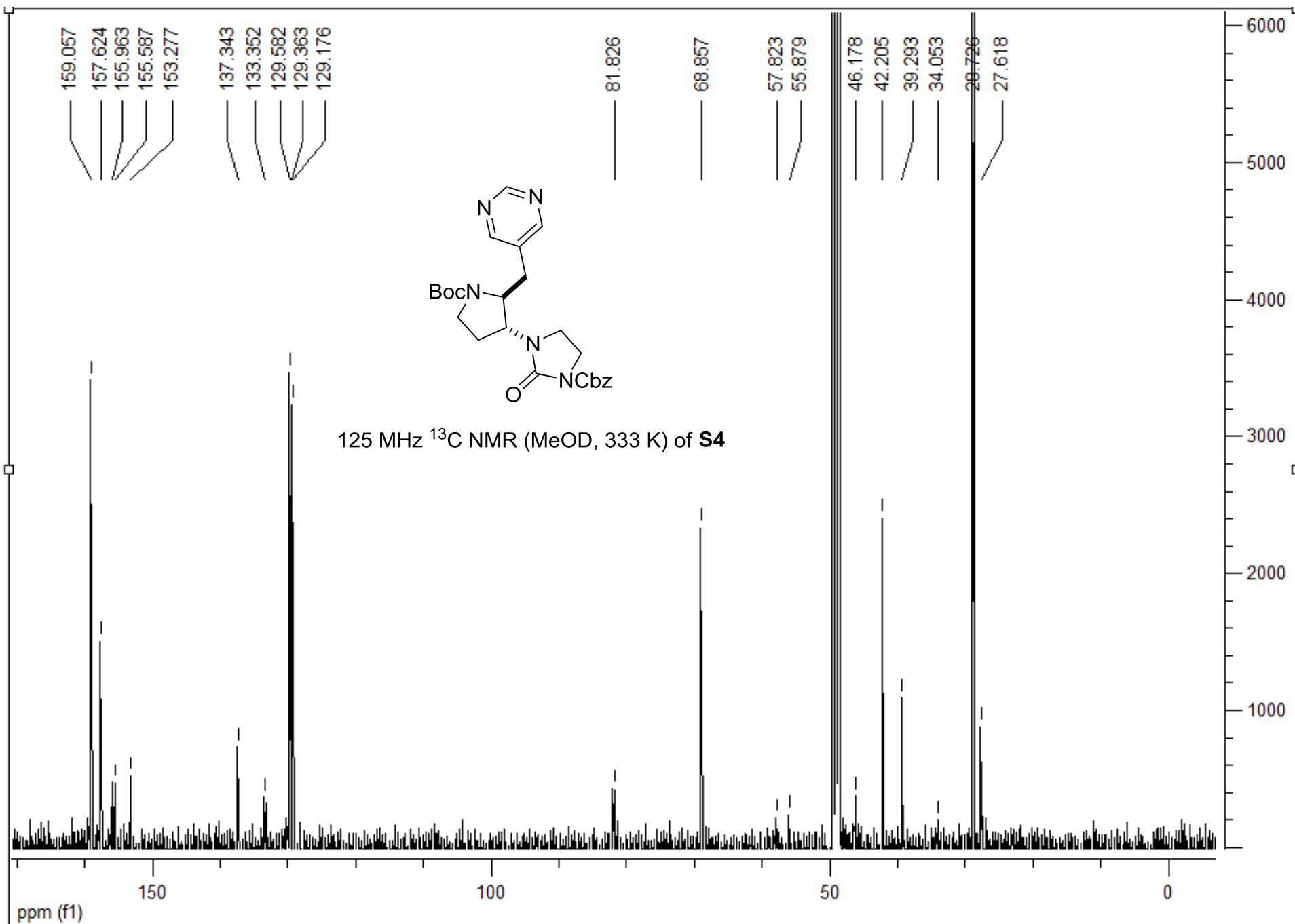


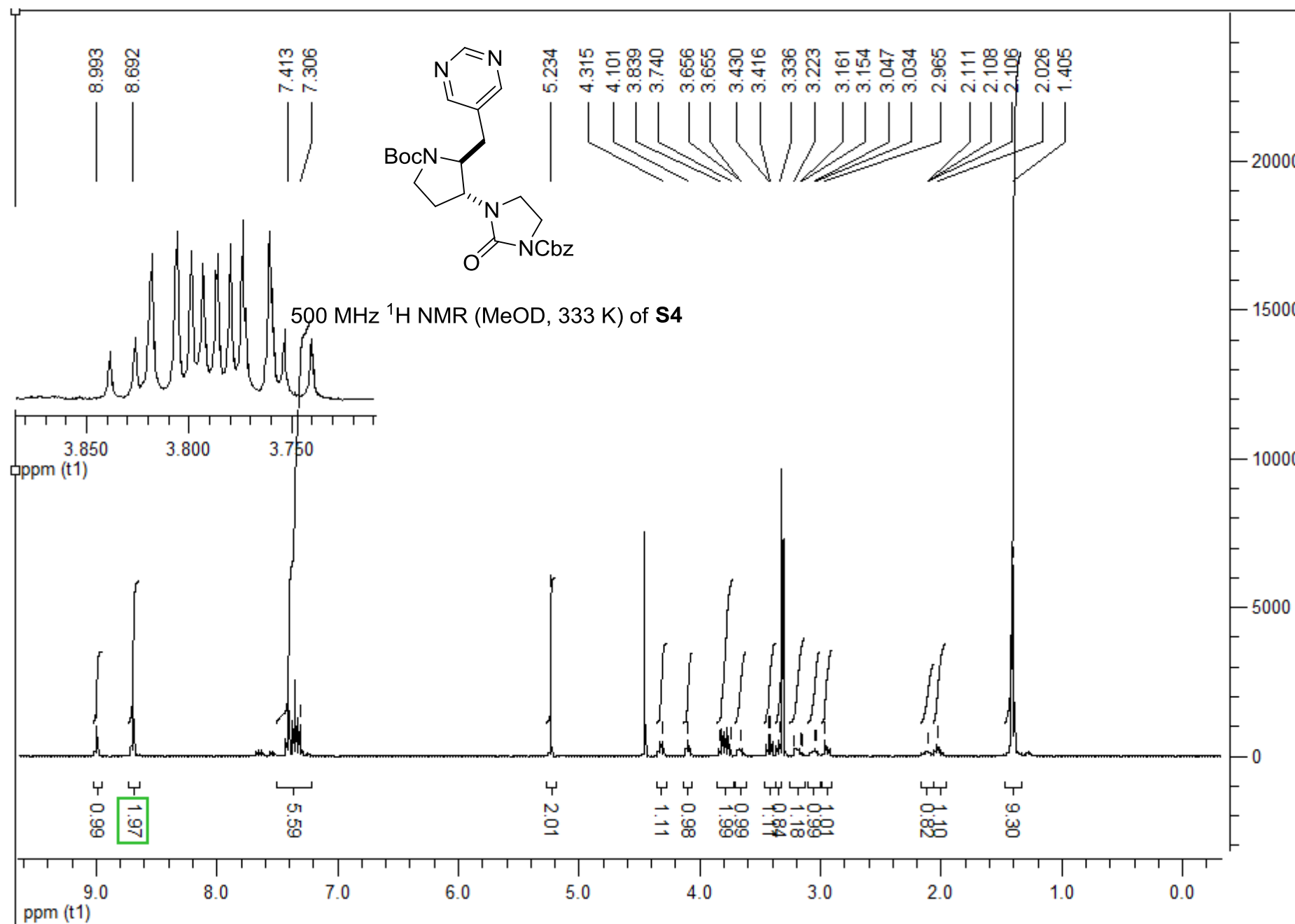


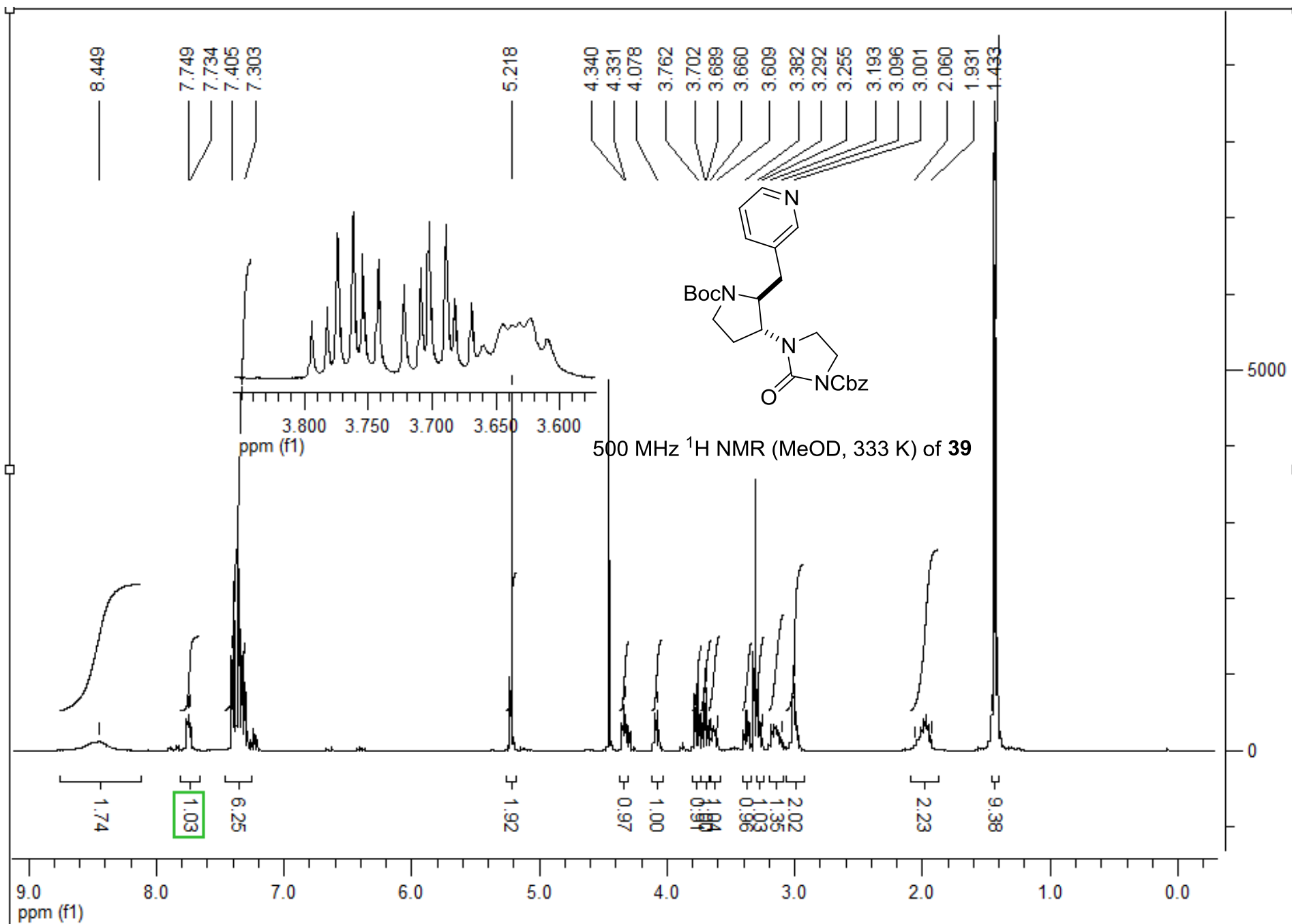


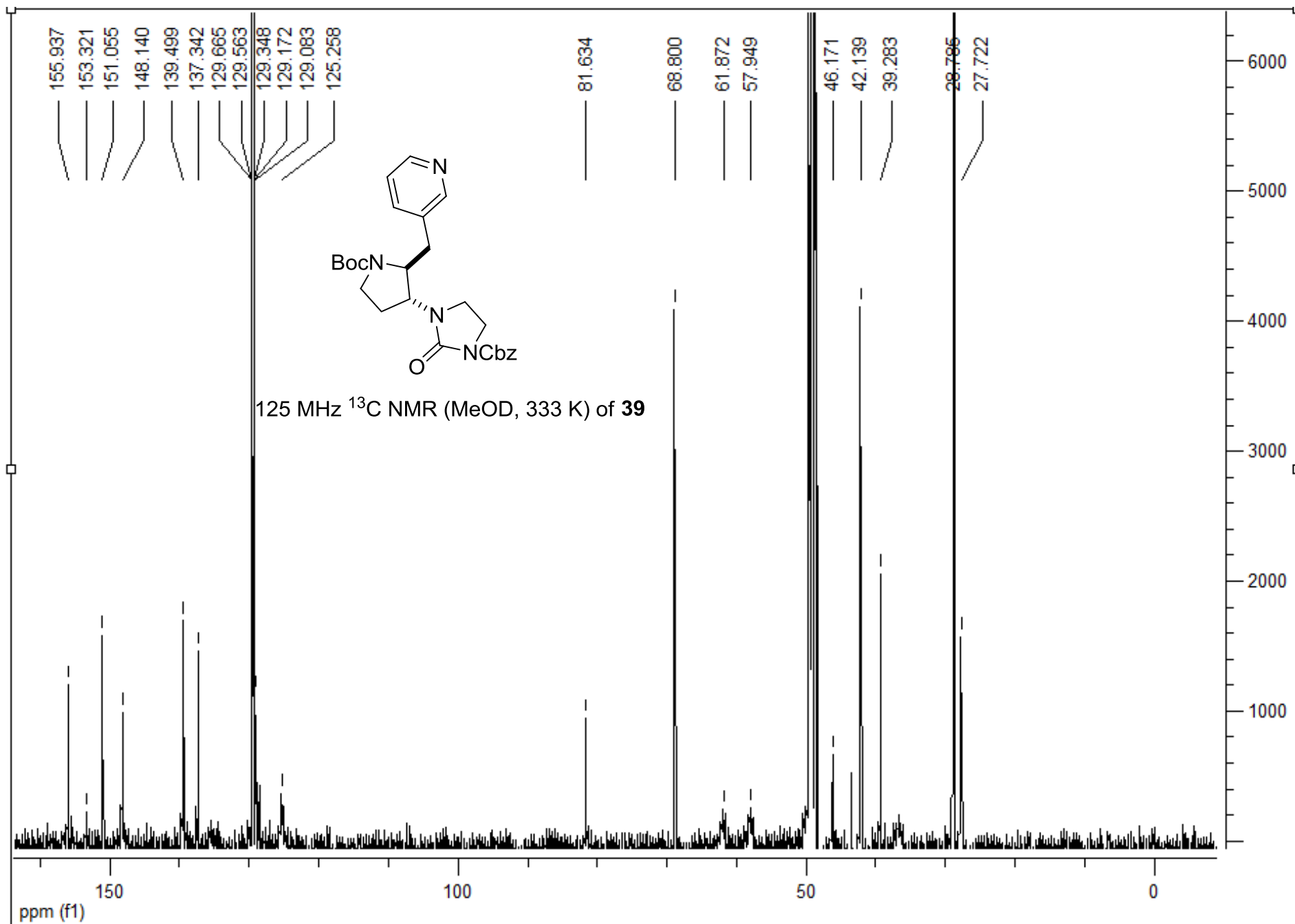


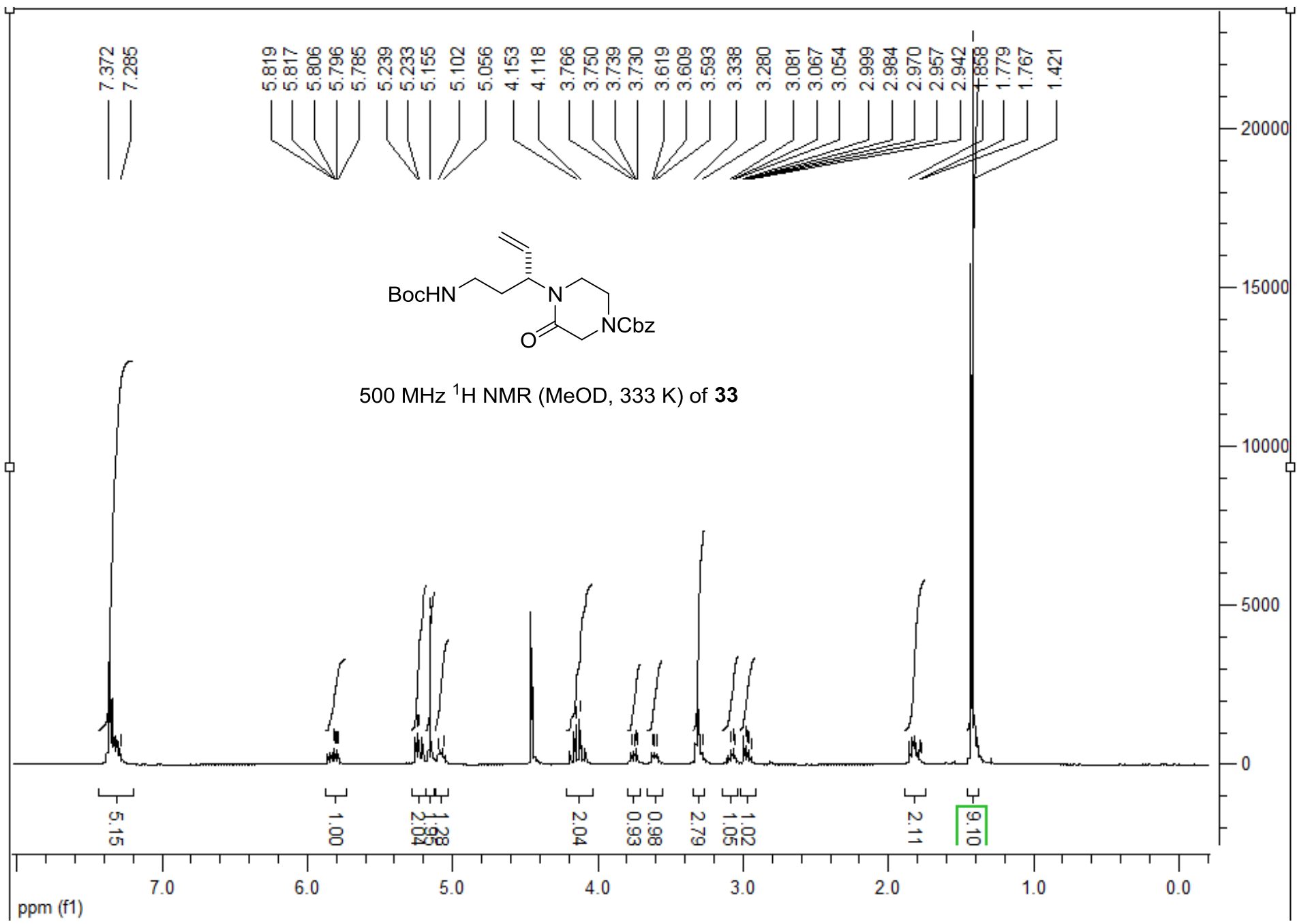
125 MHz ^{13}C NMR (MeOD, 333 K) of **S4**

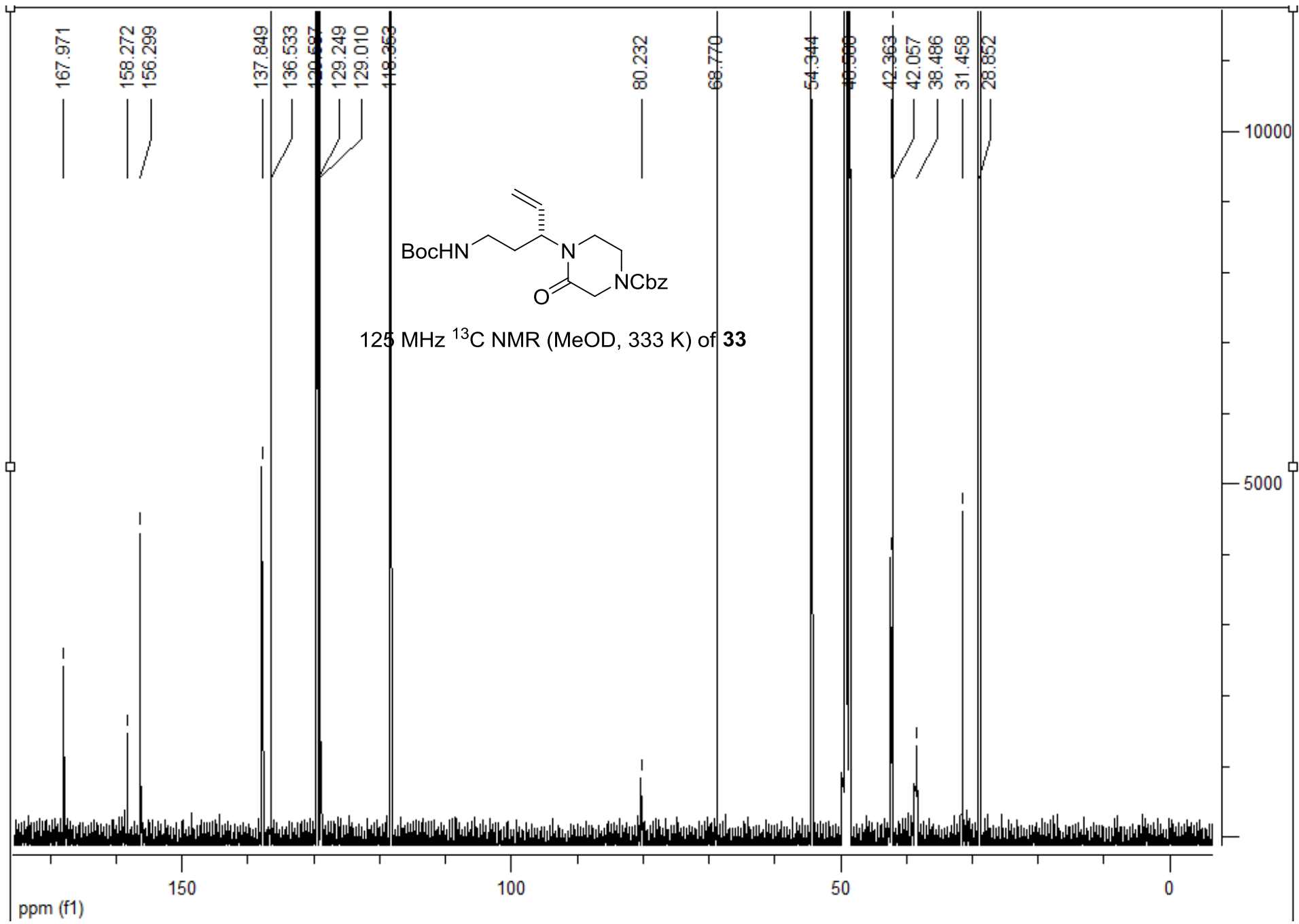


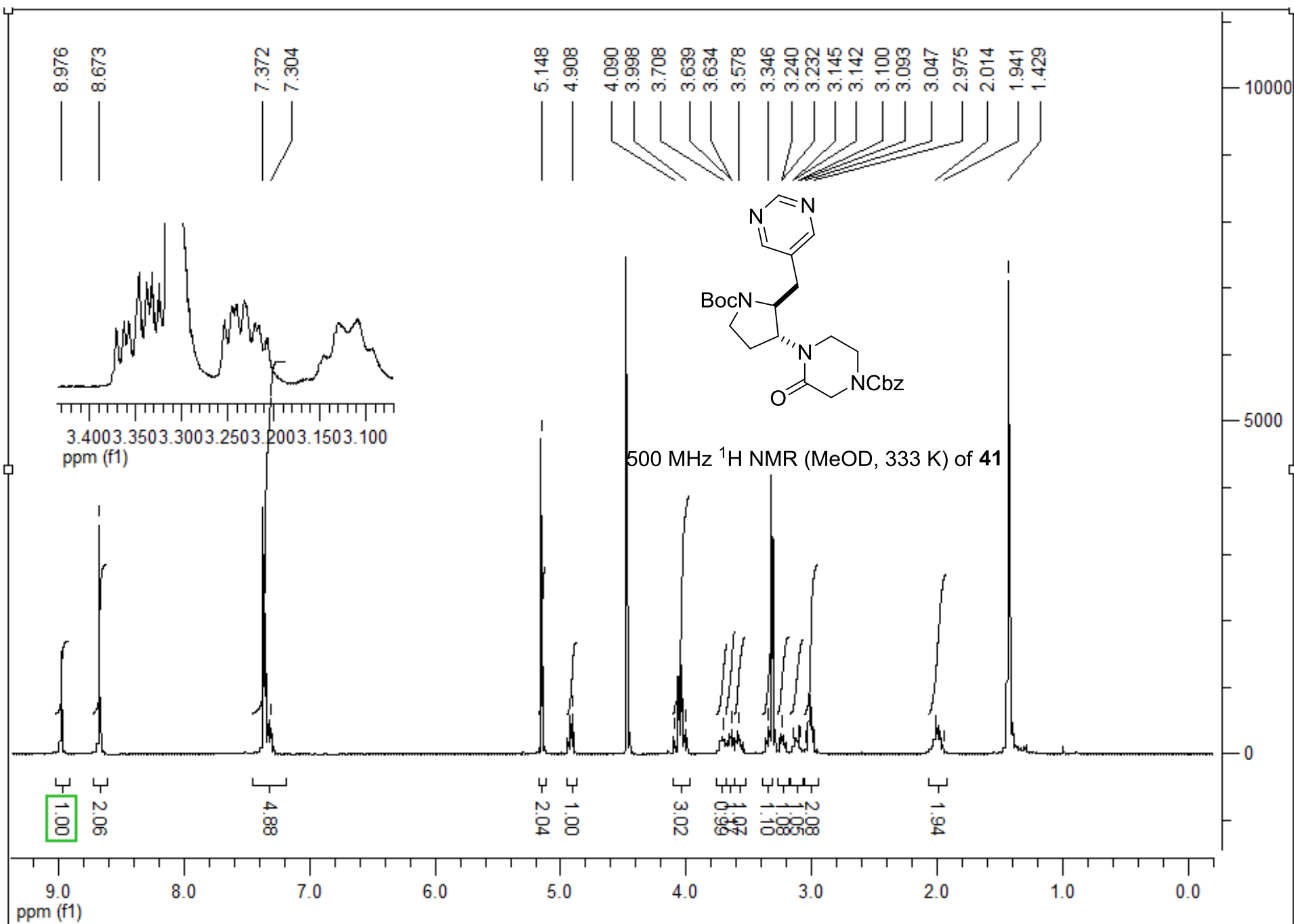


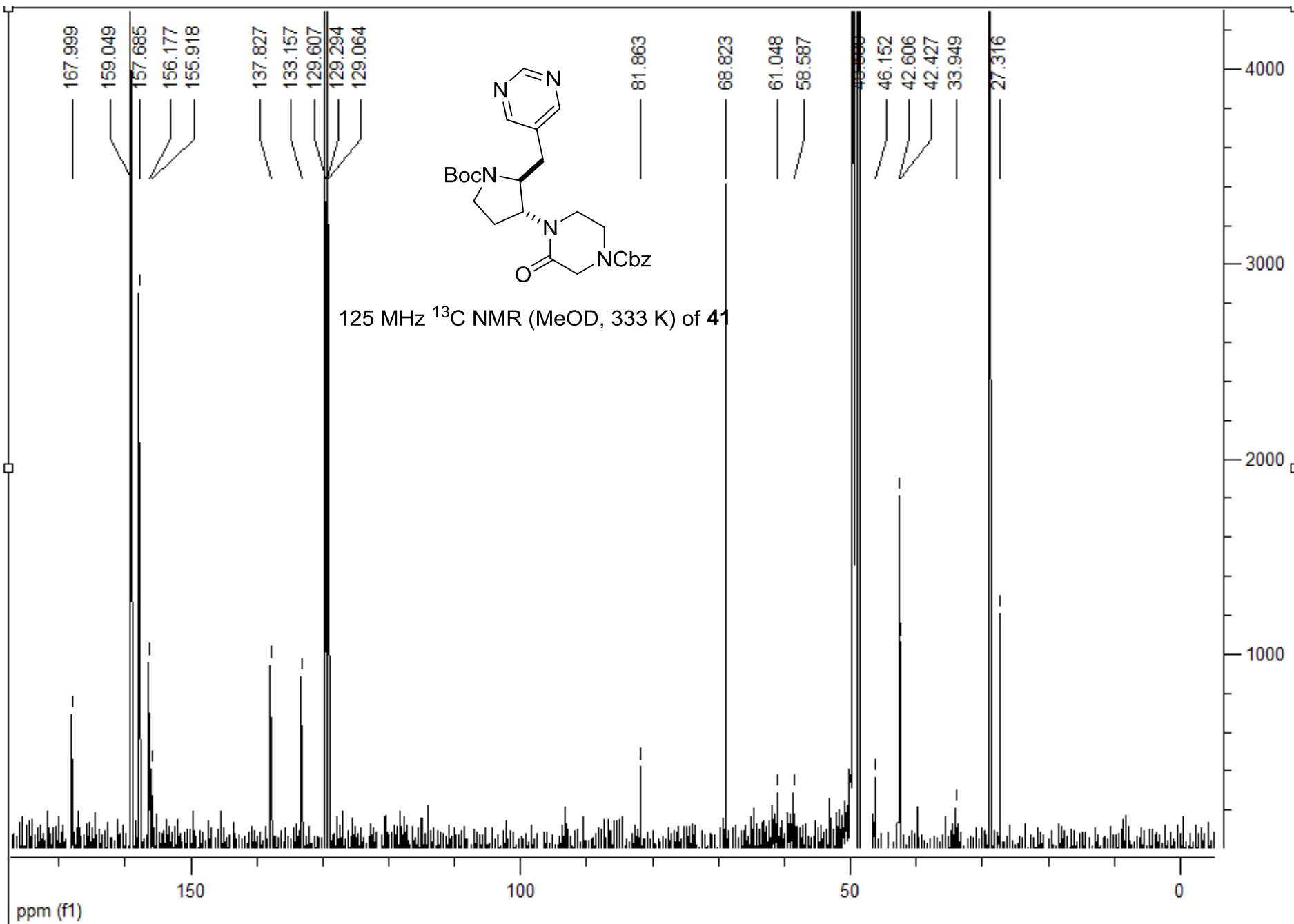


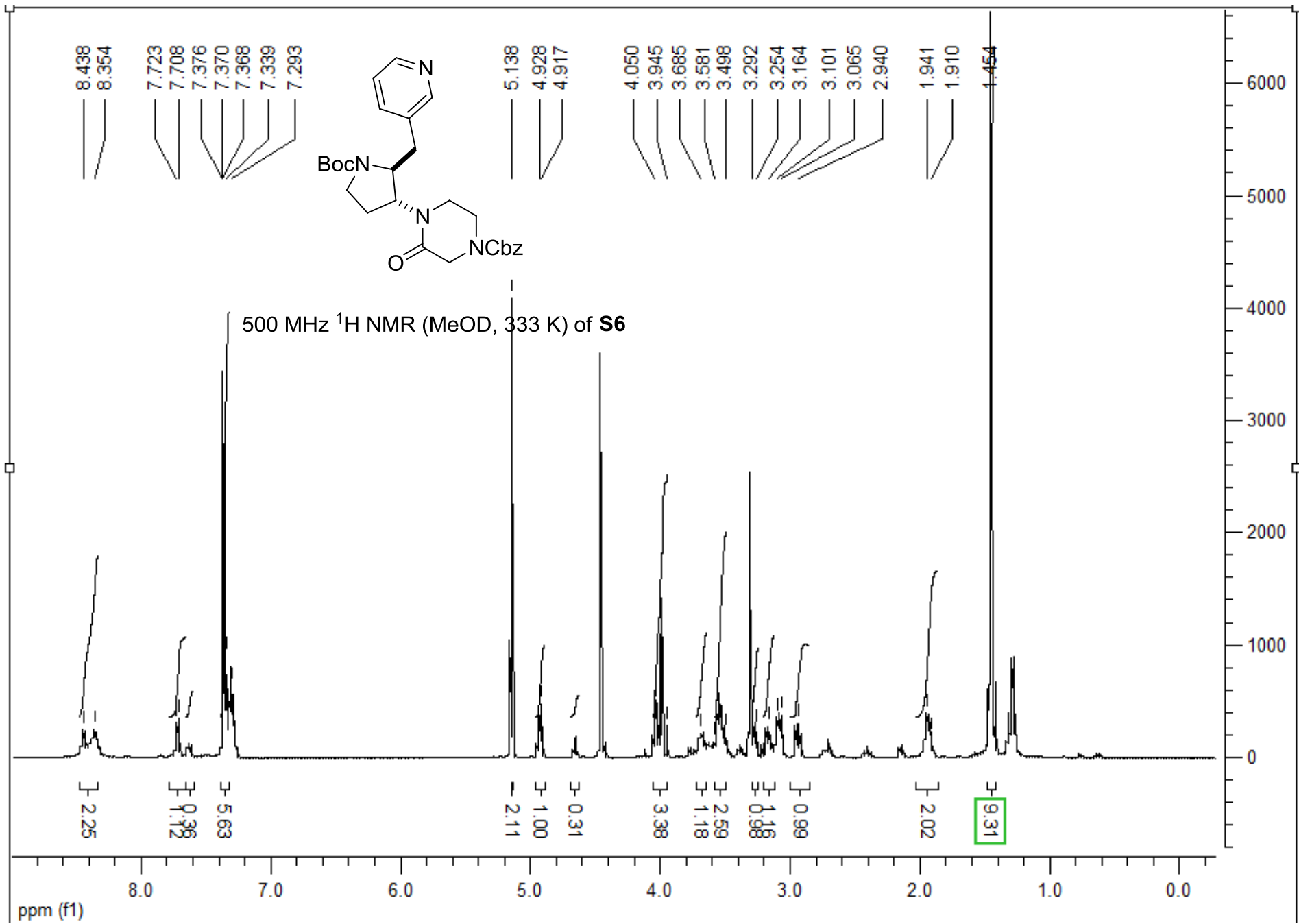


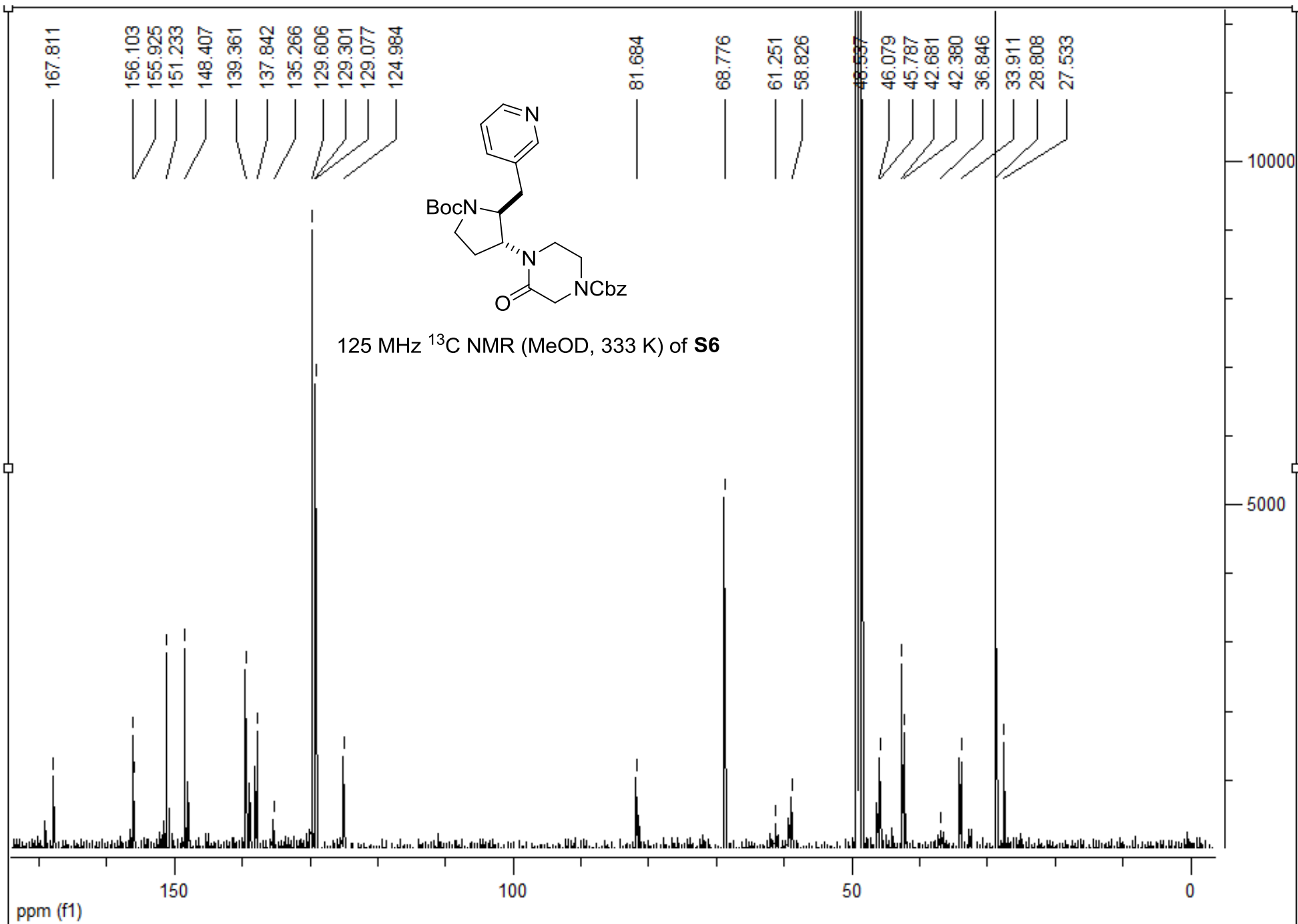


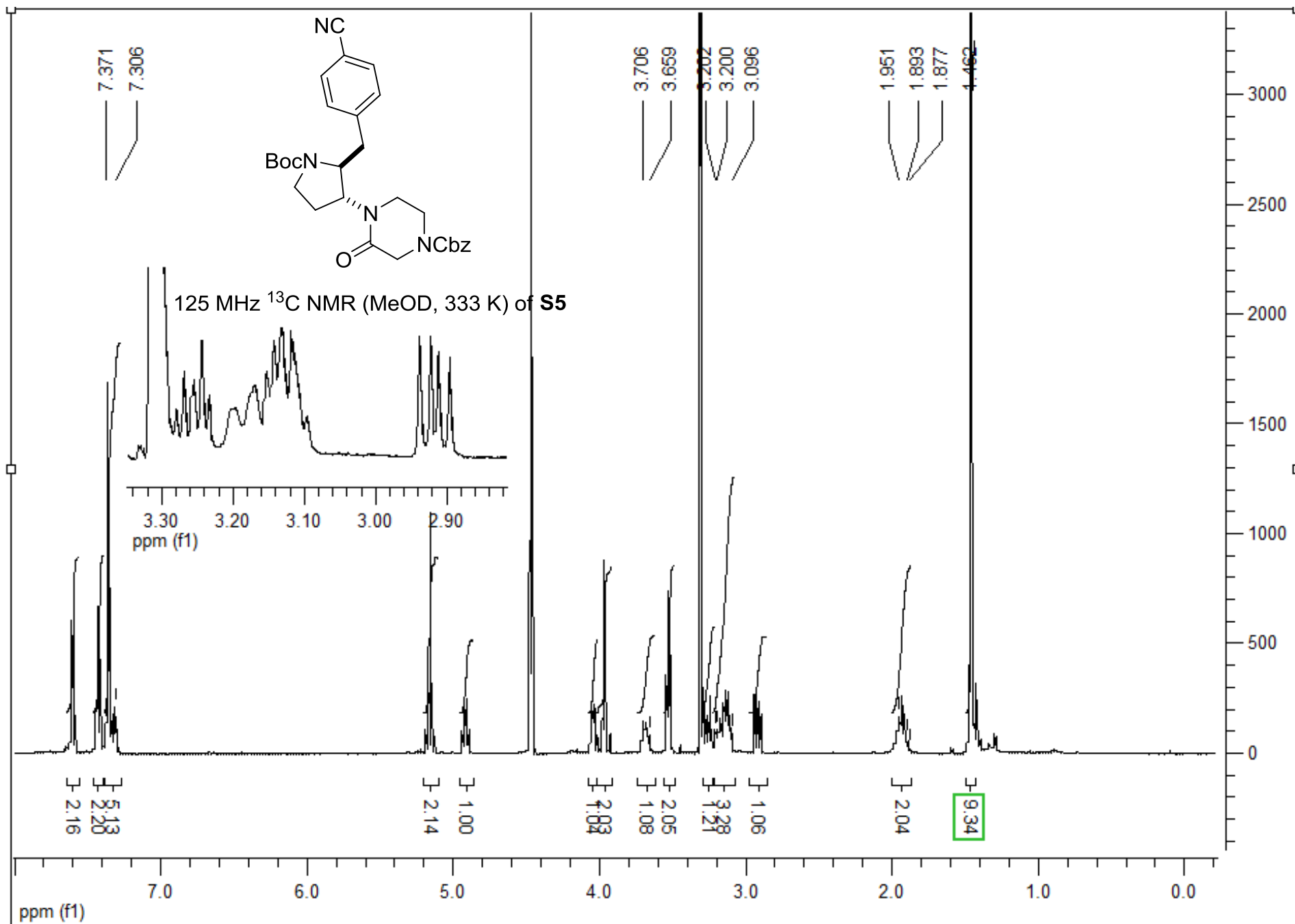


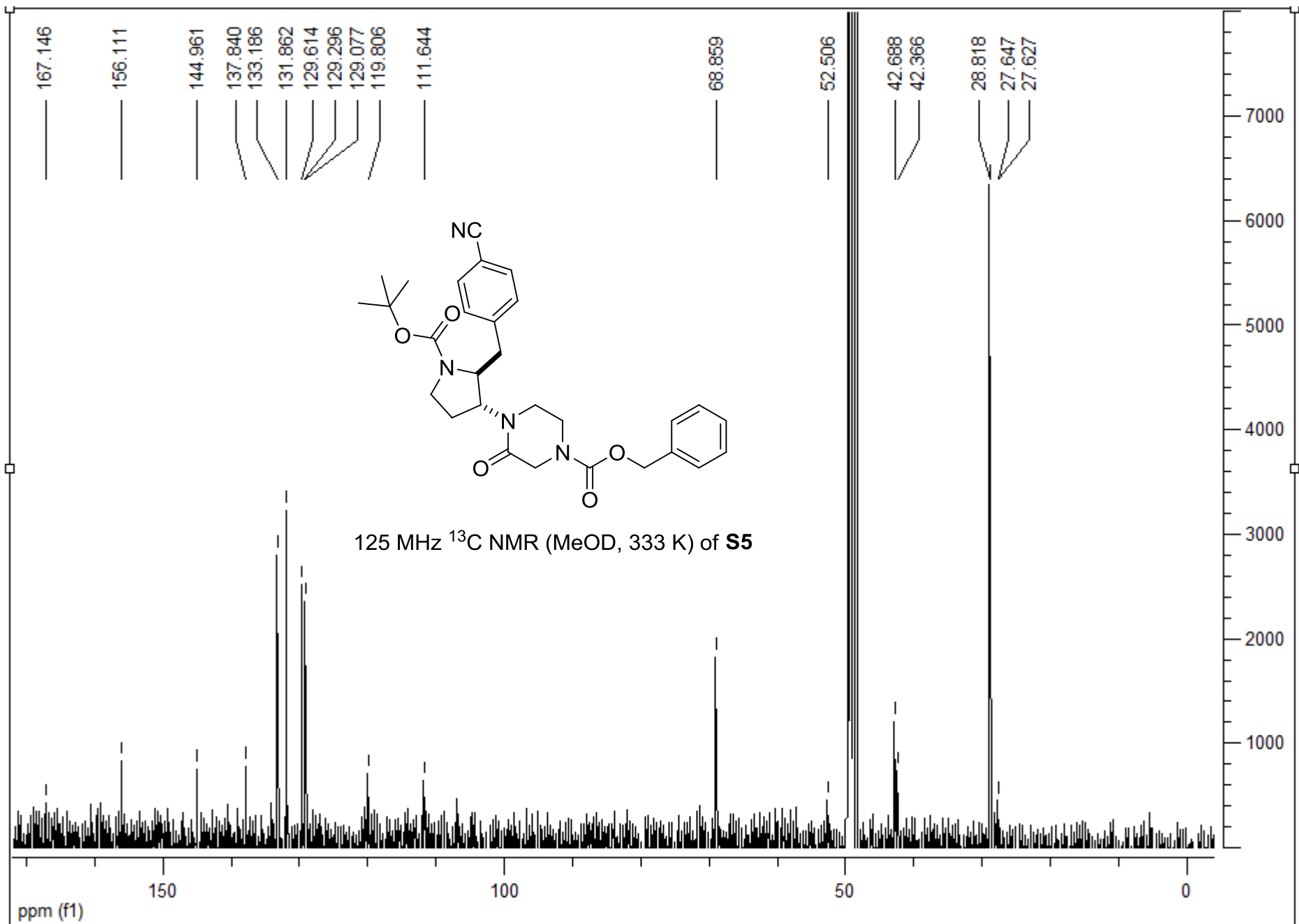


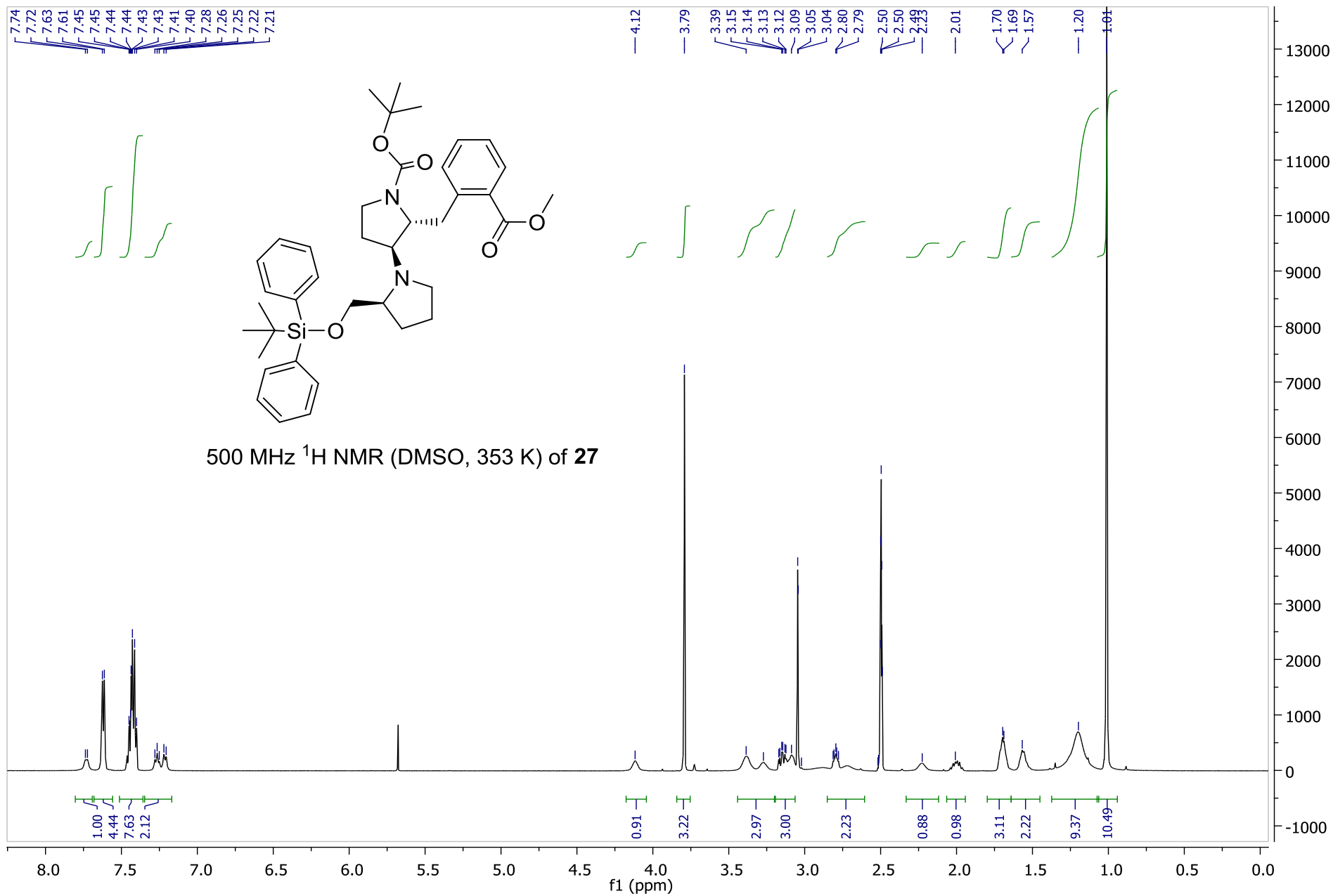


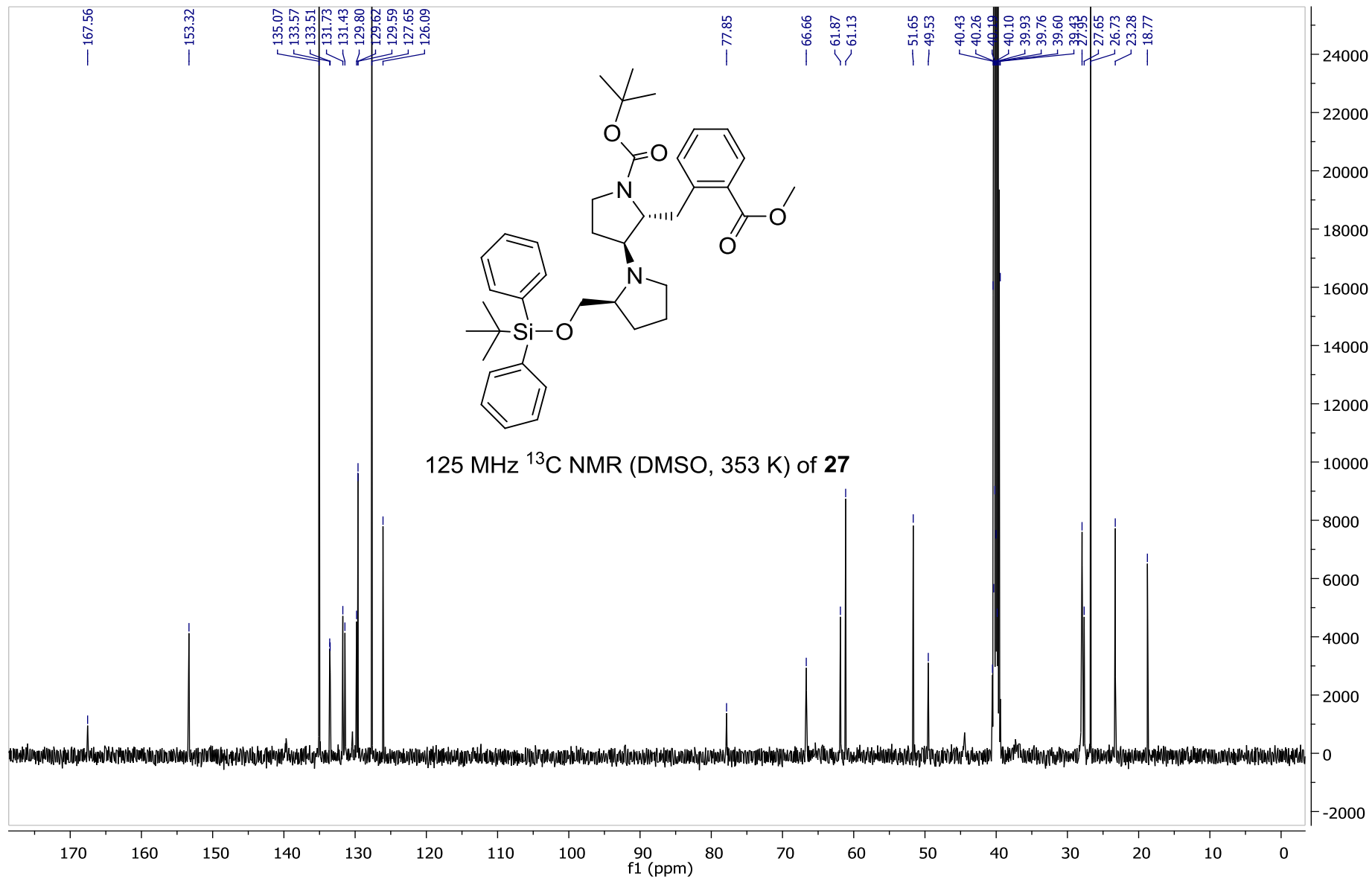


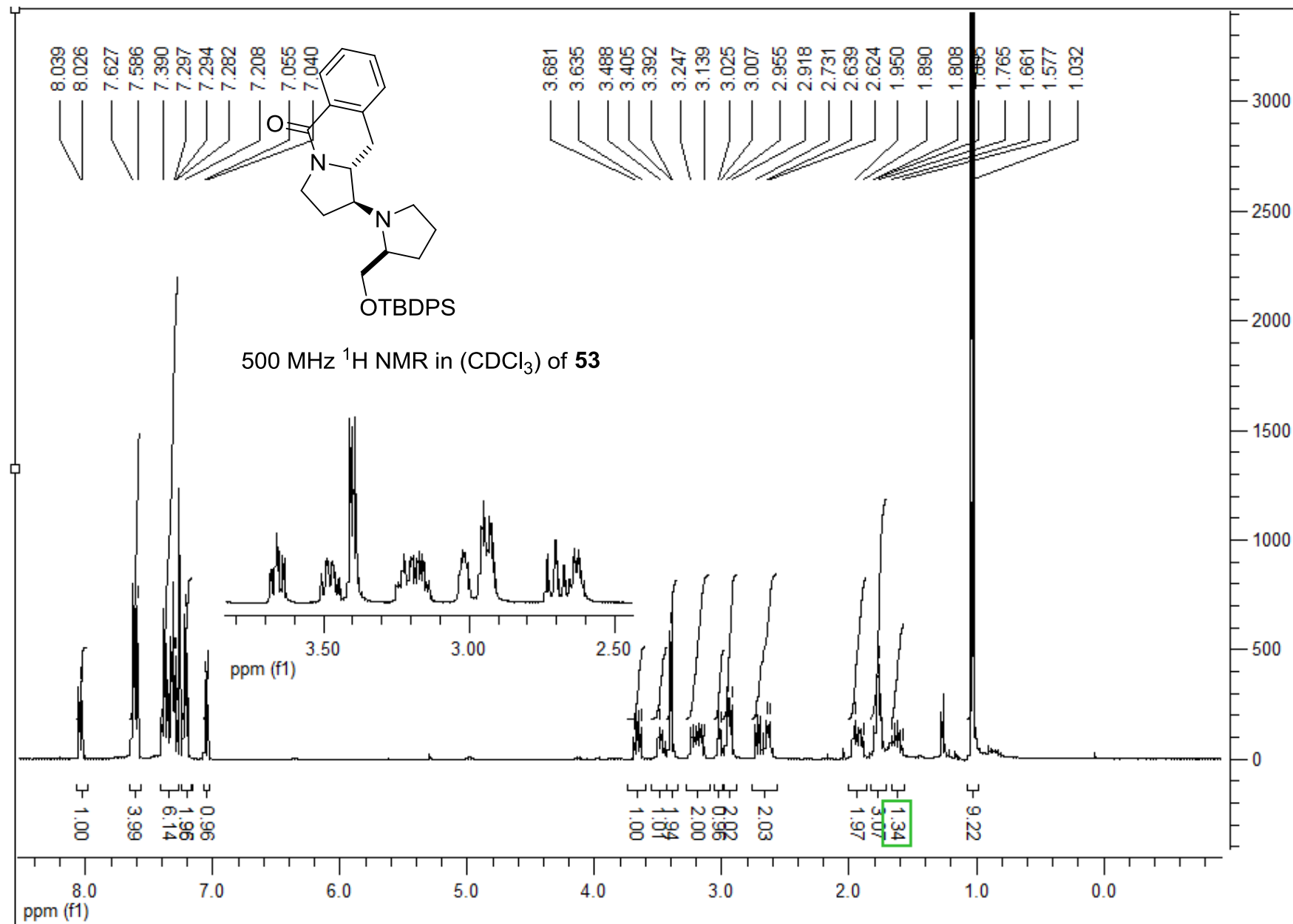


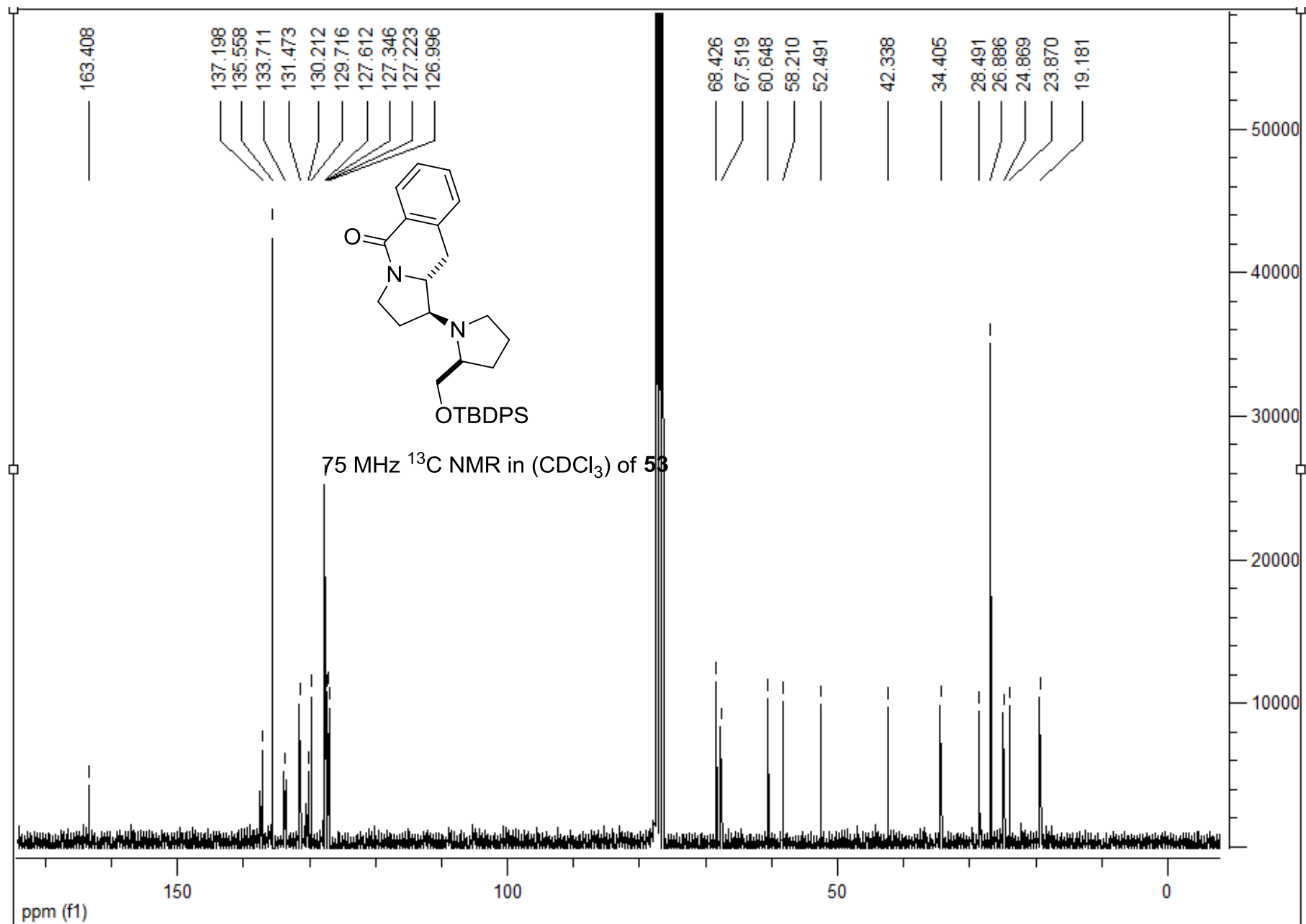


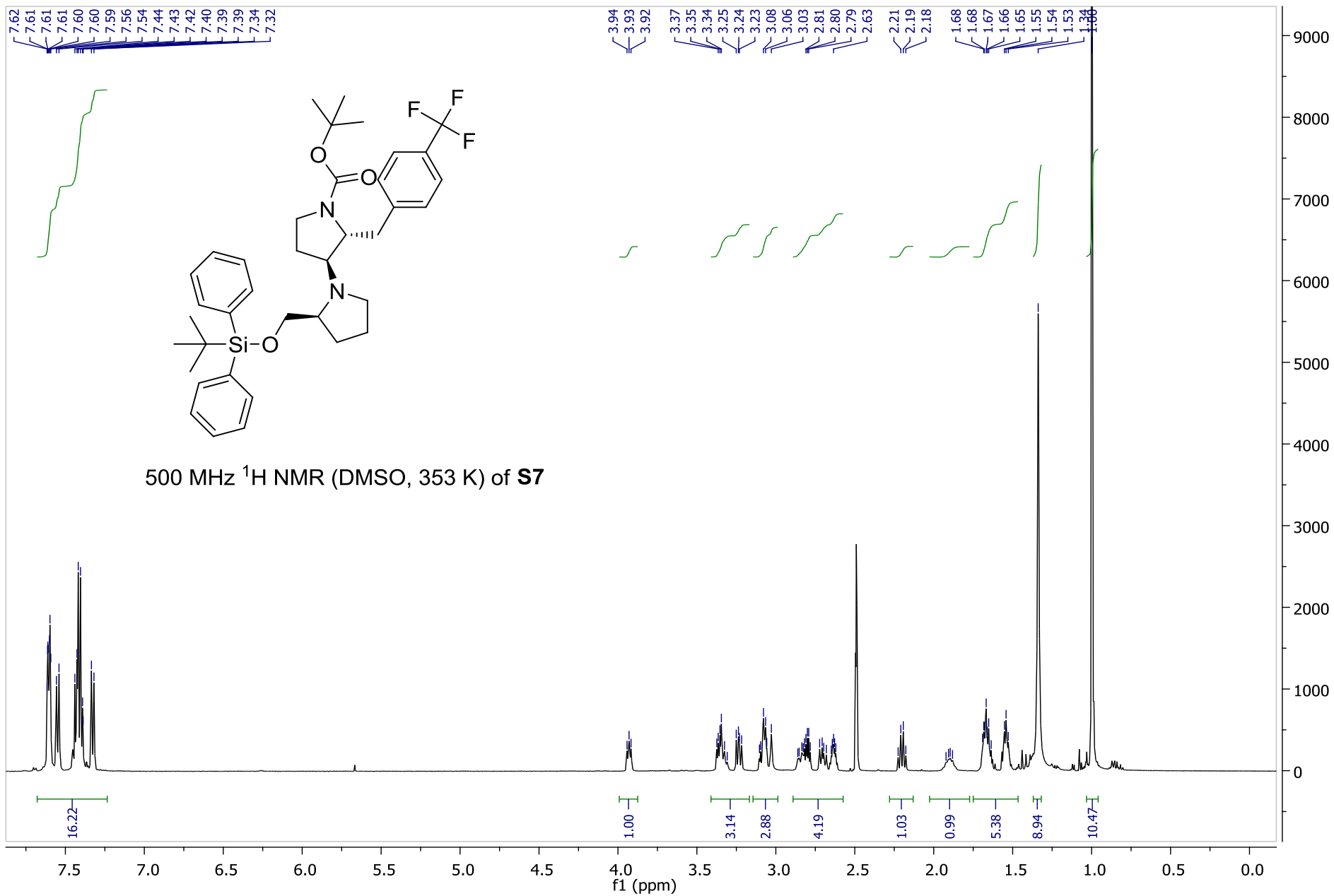


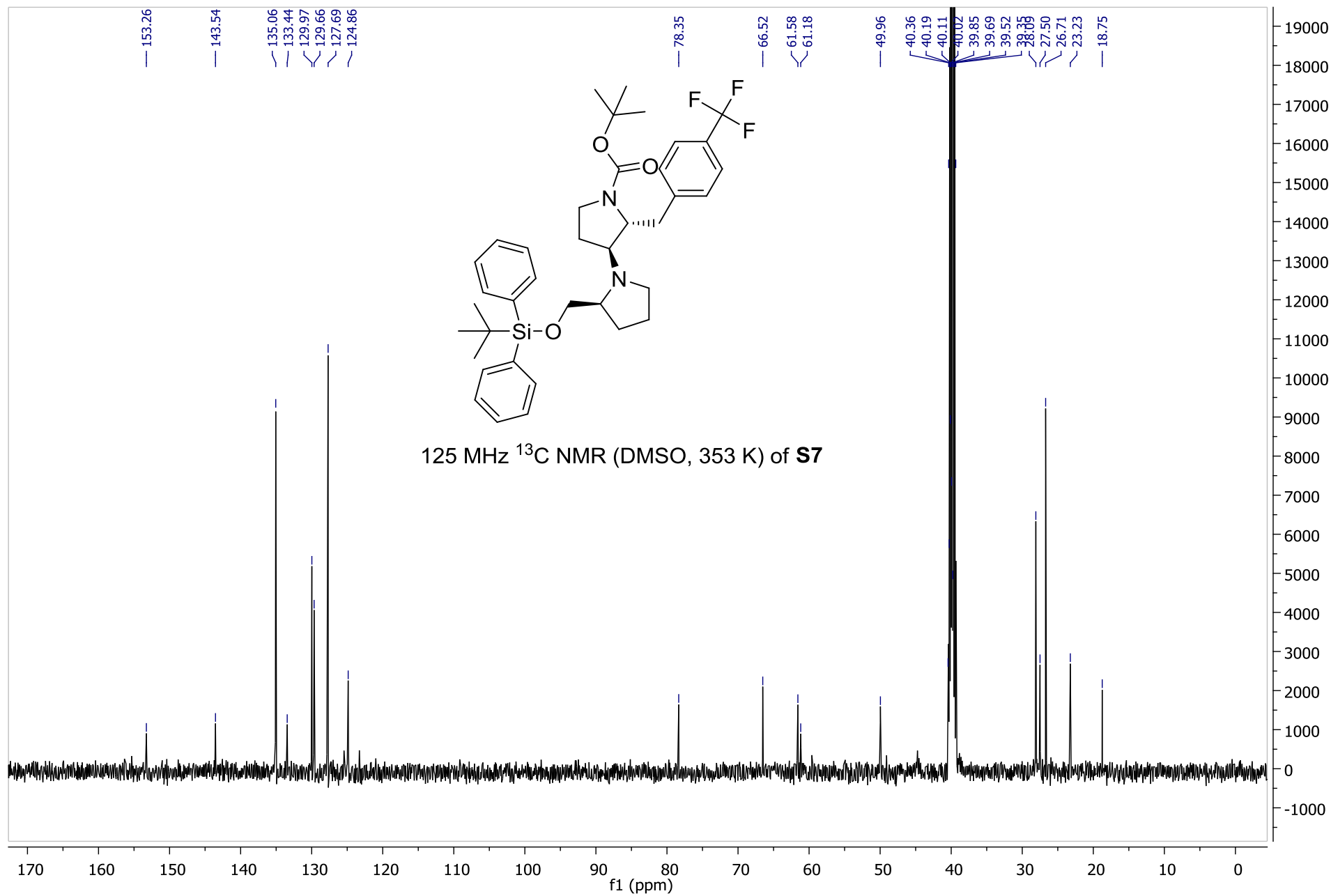


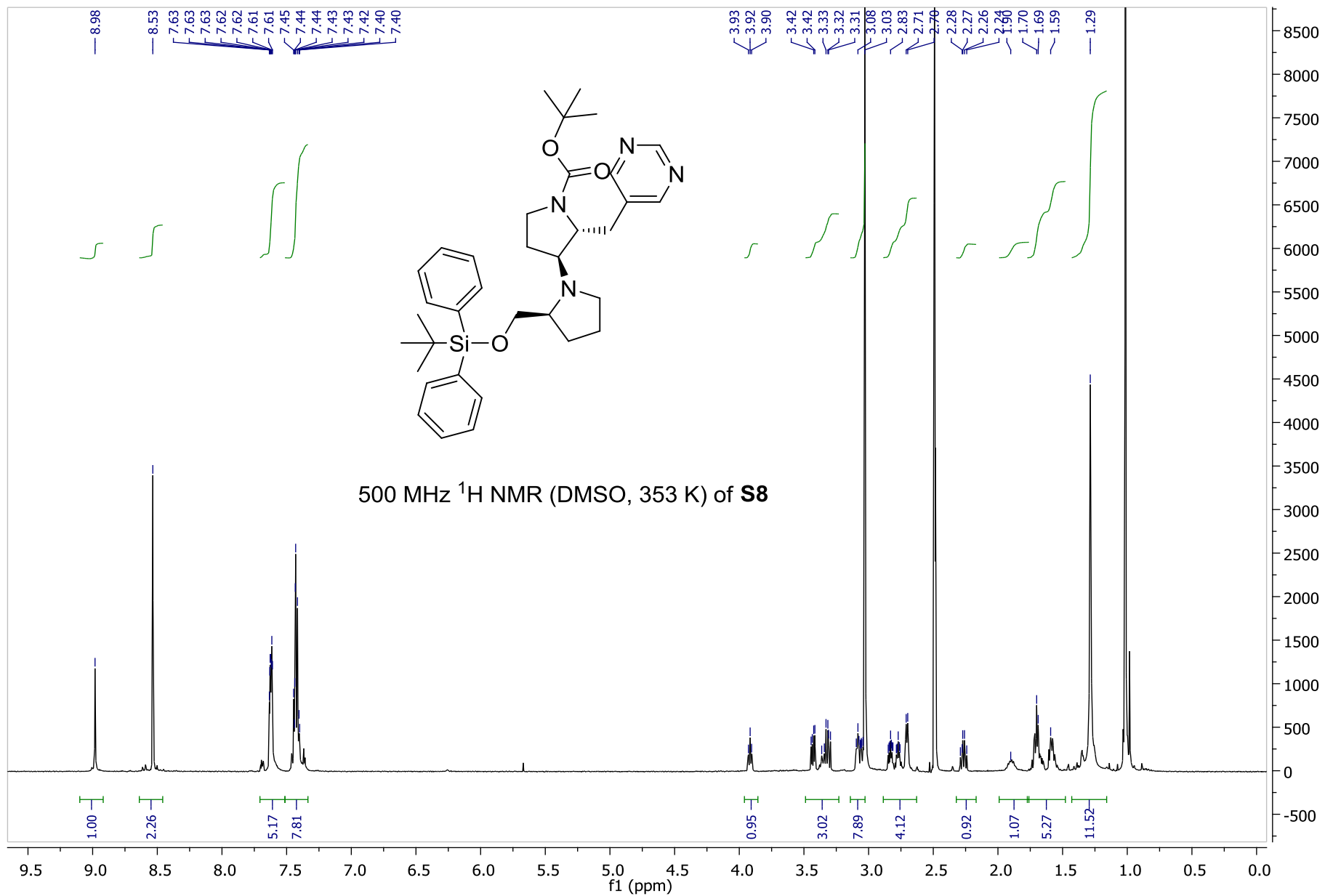


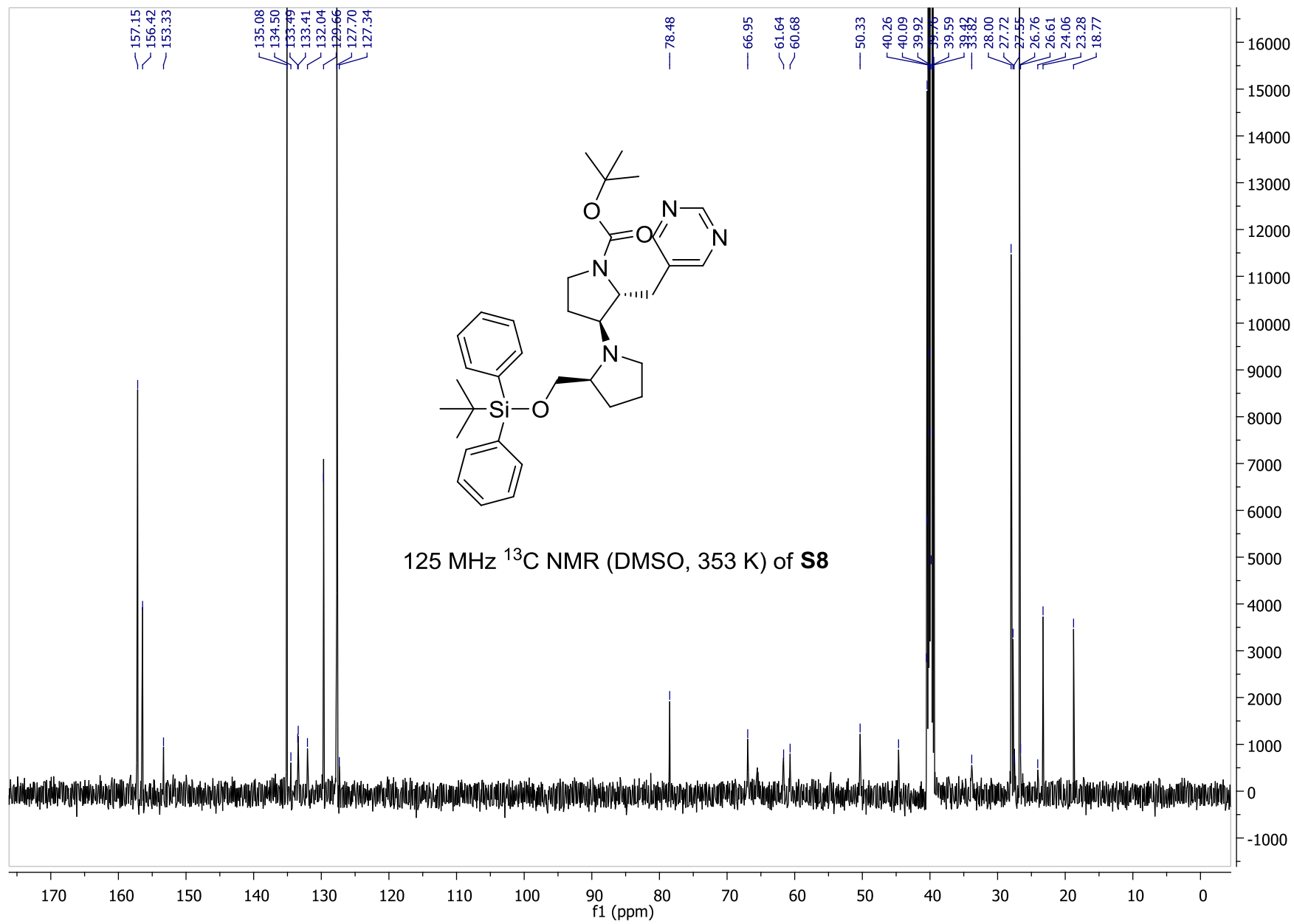


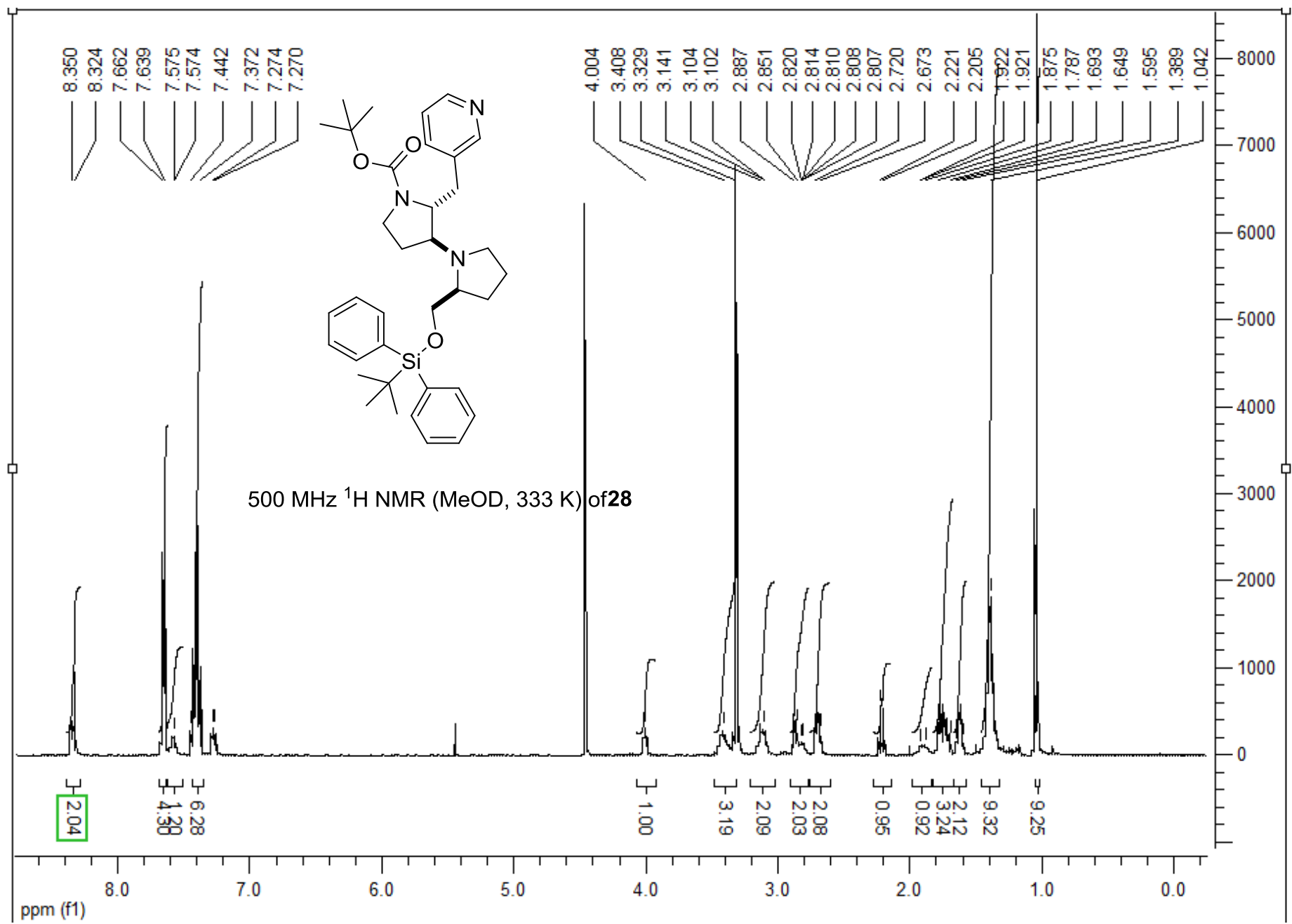


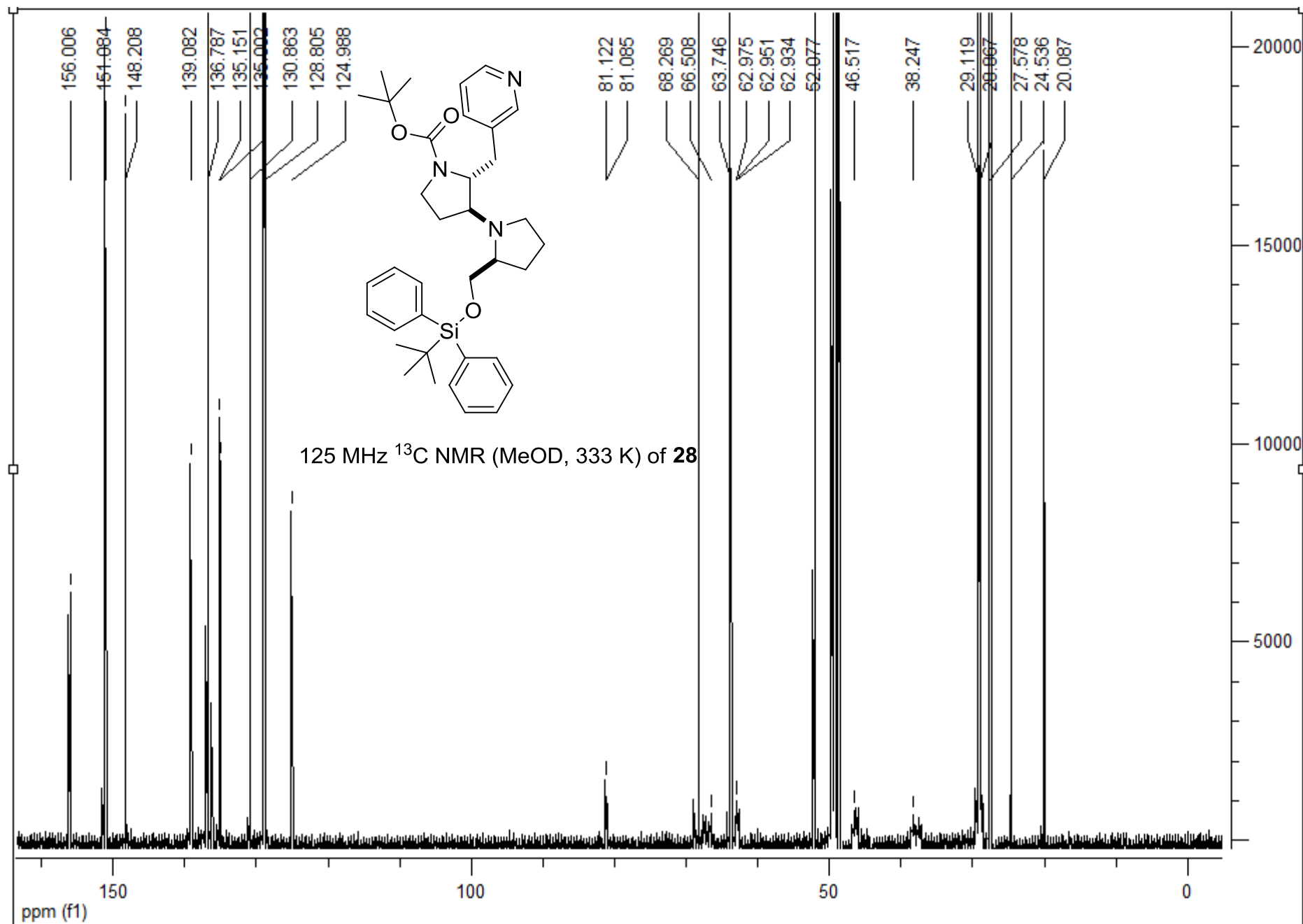


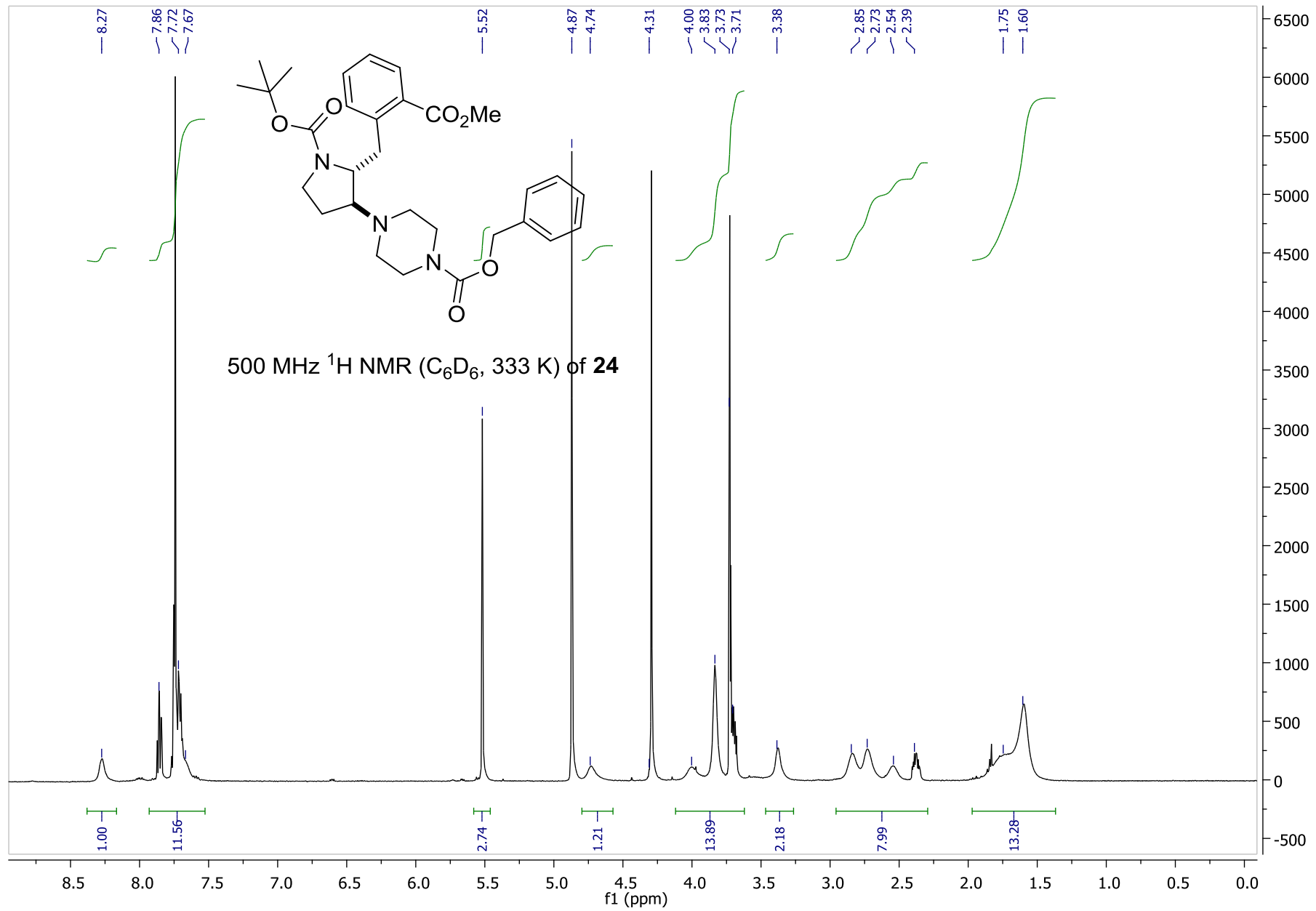


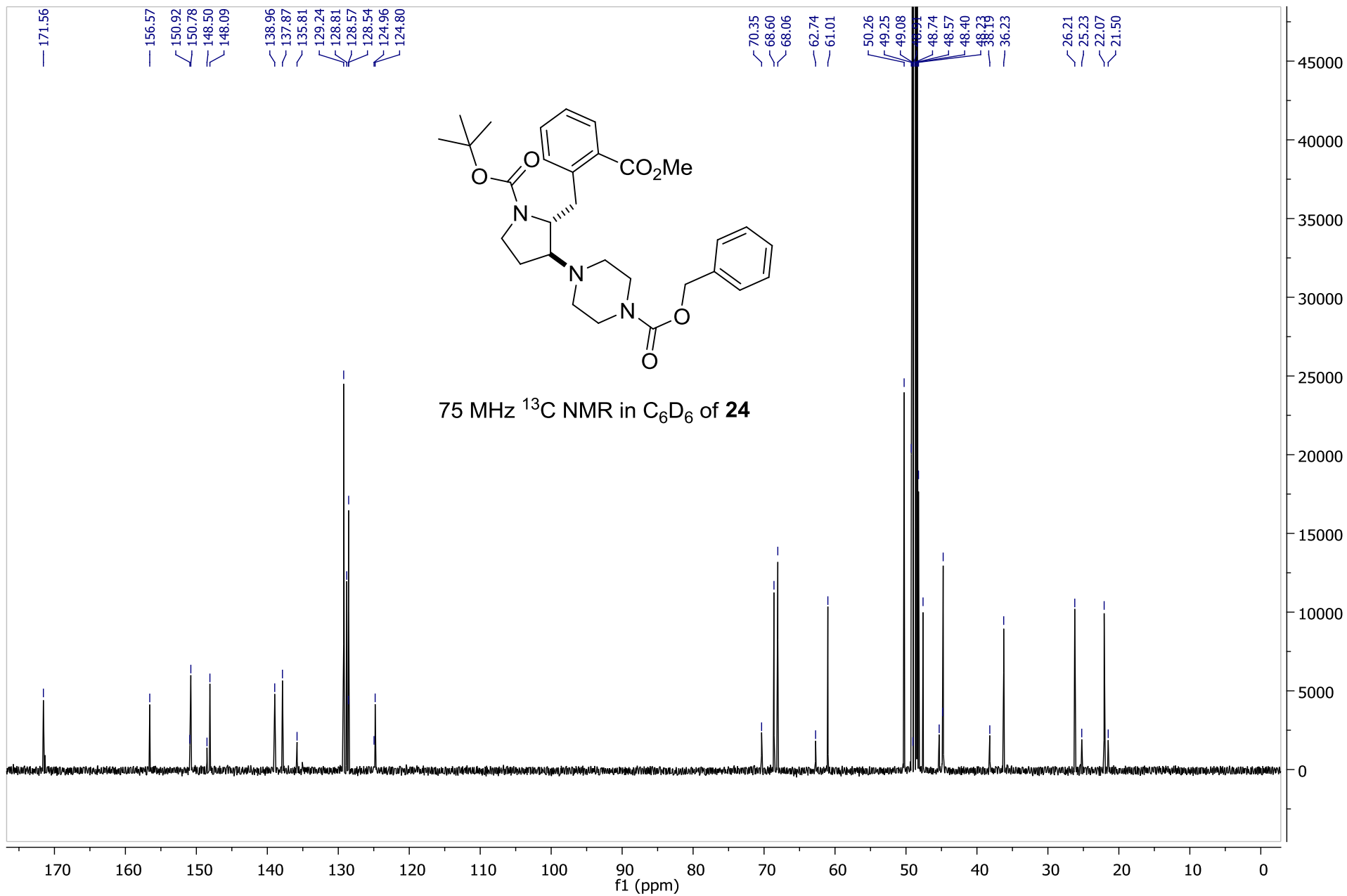


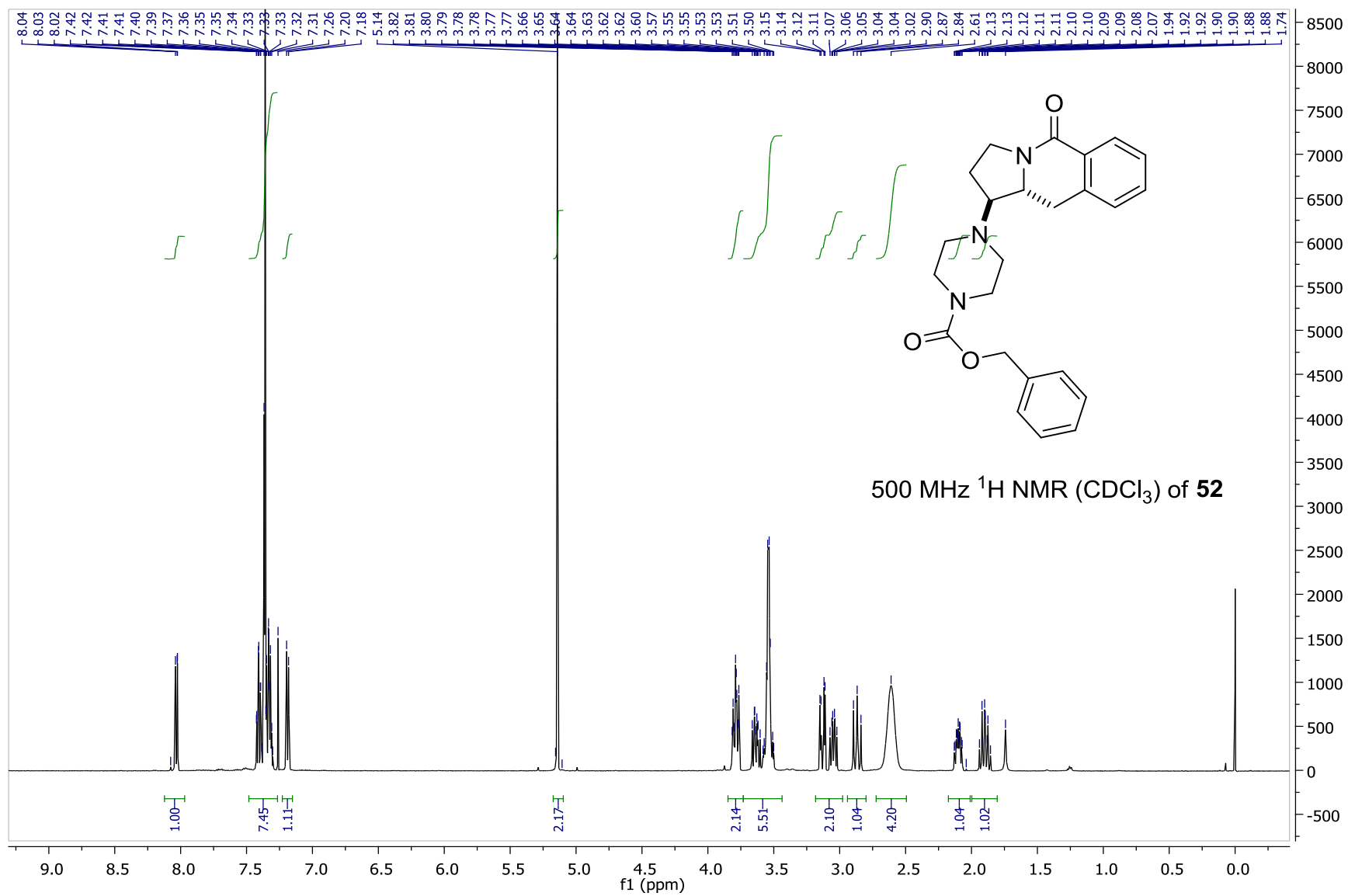


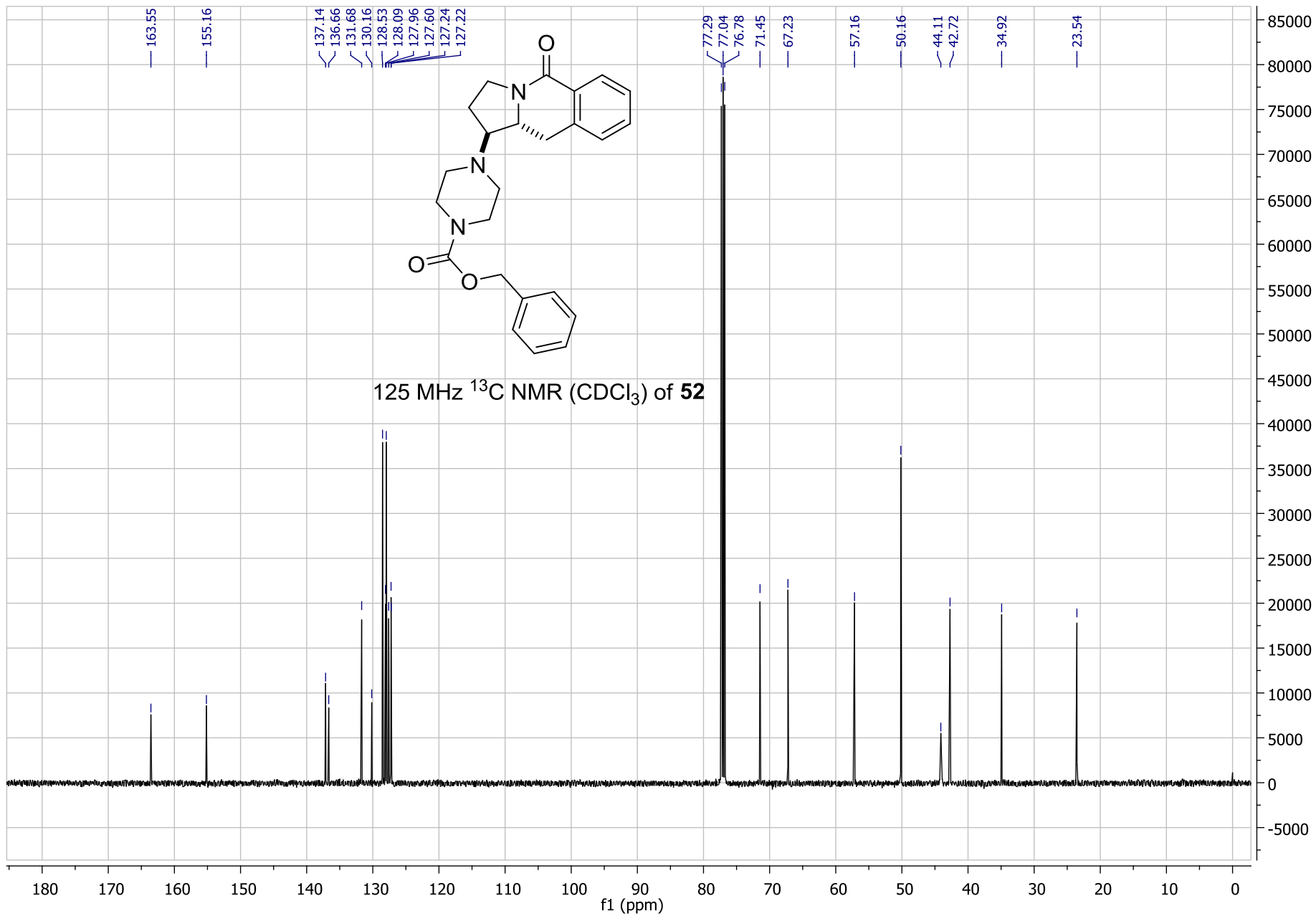


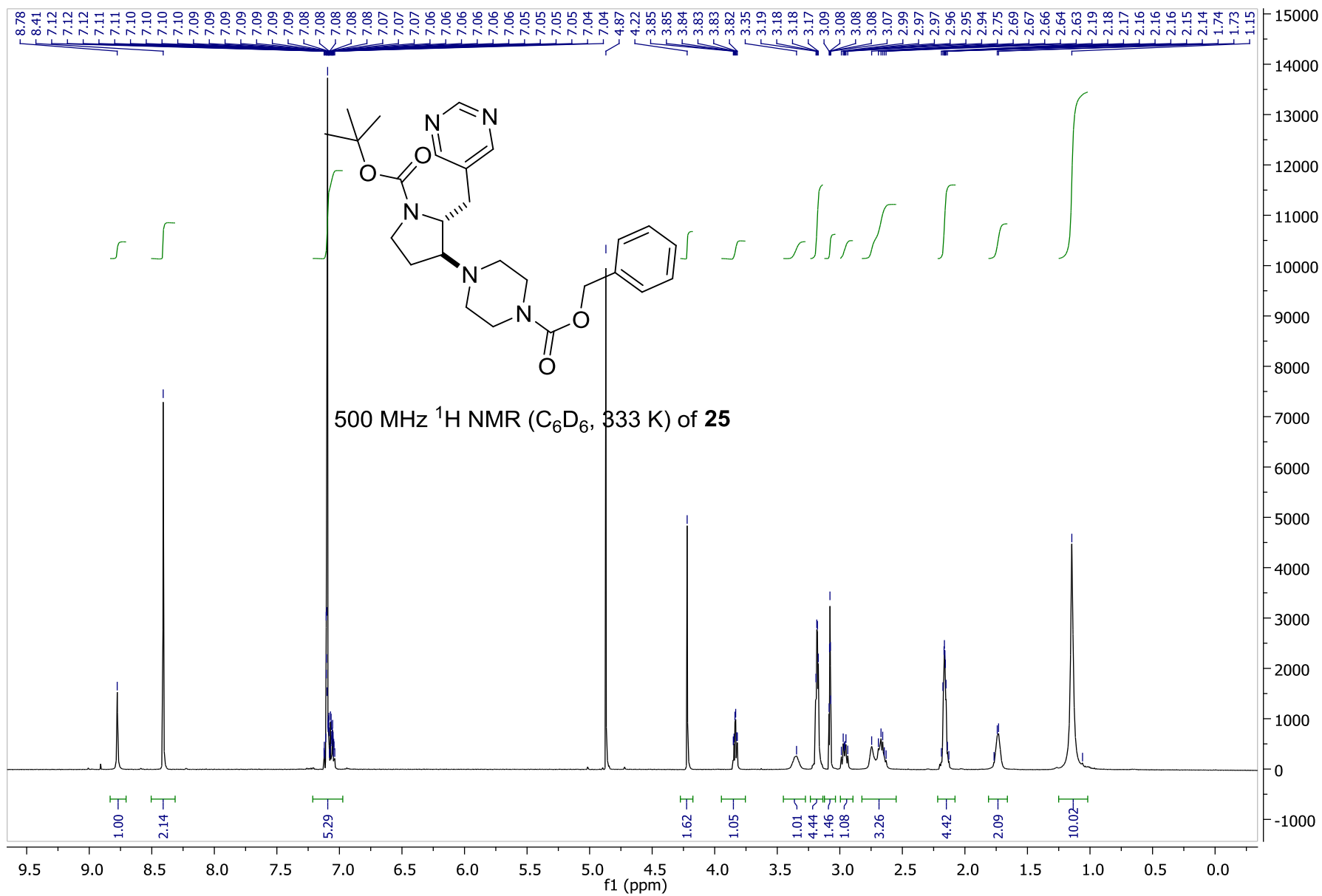


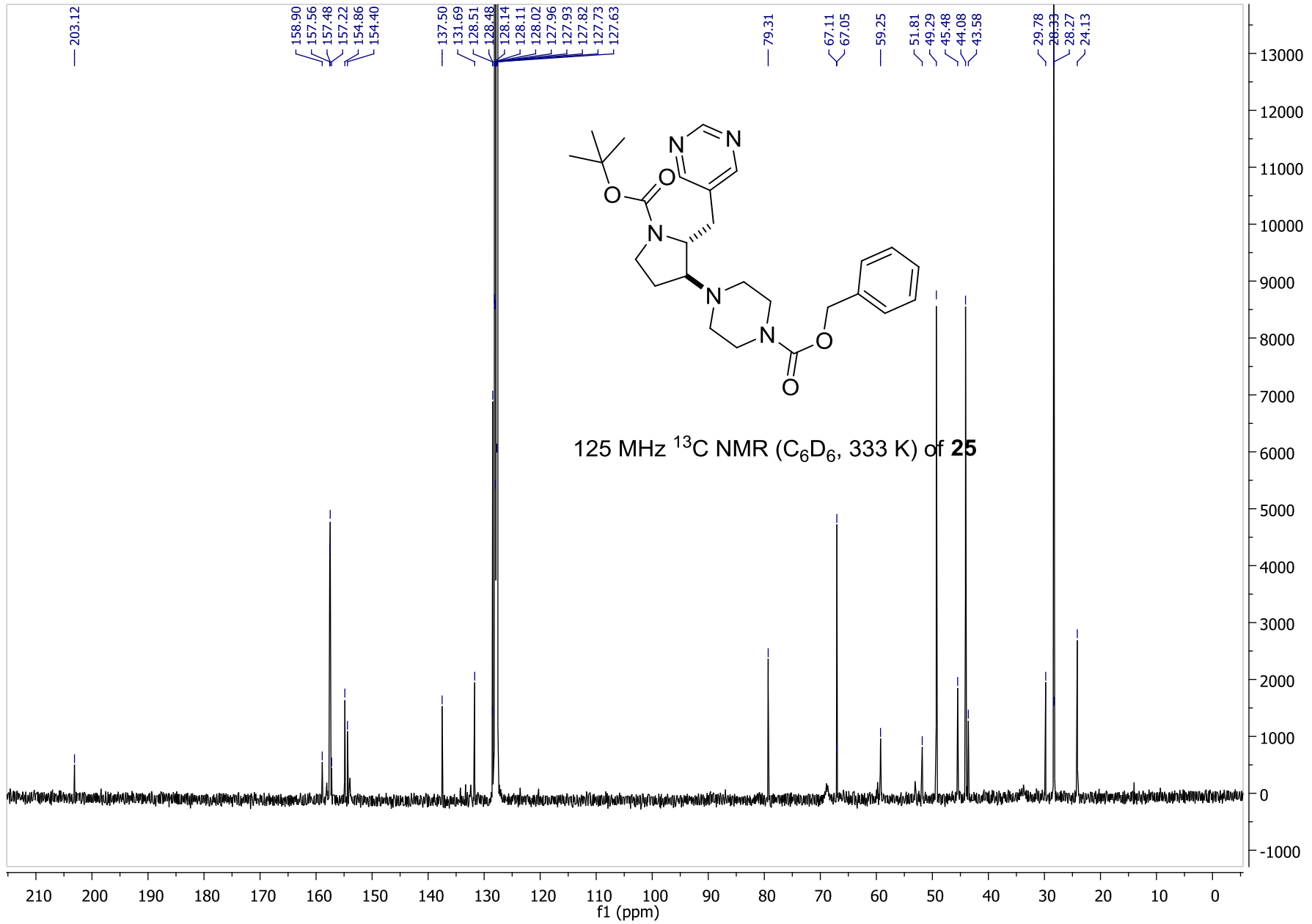


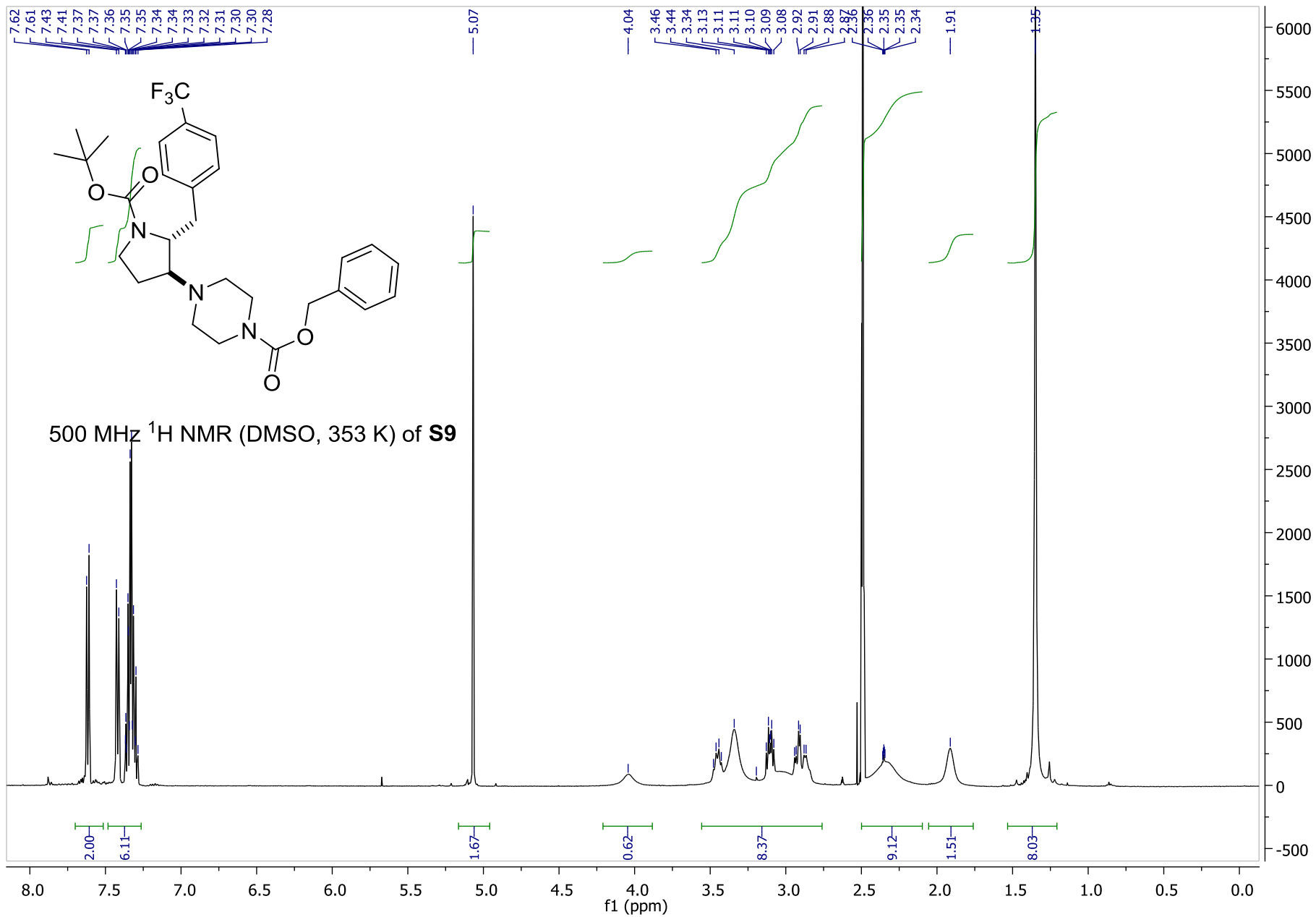


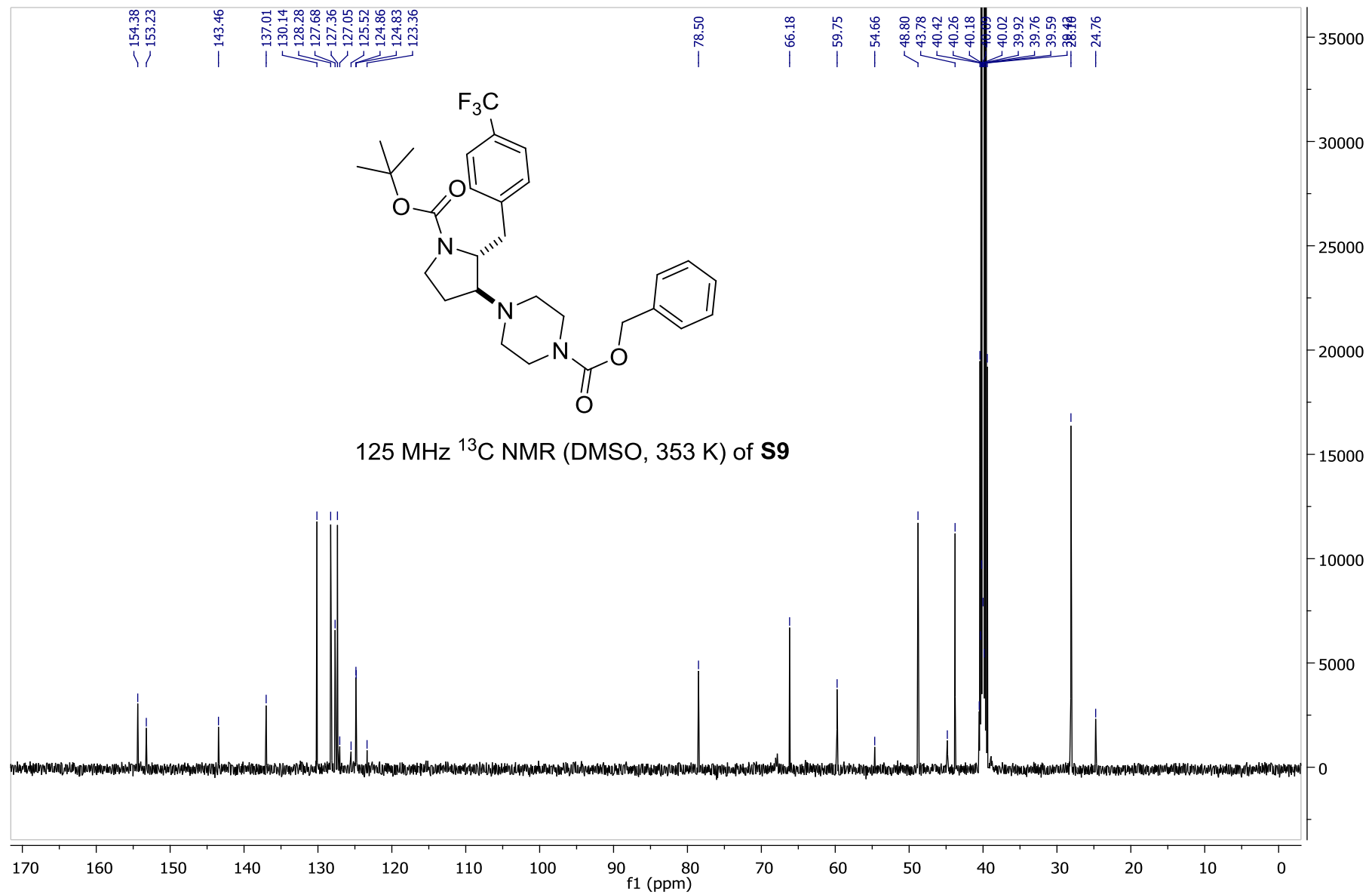


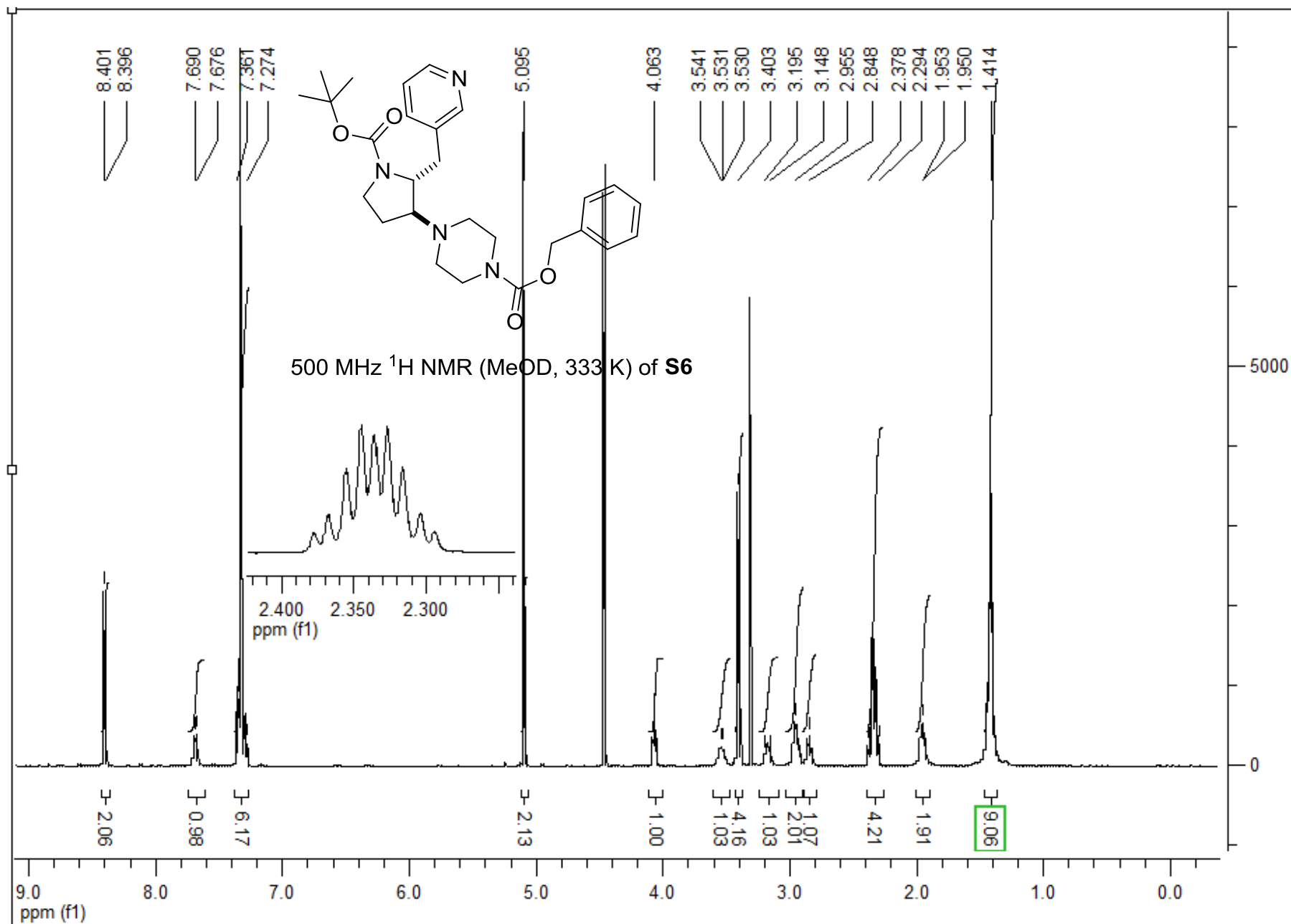


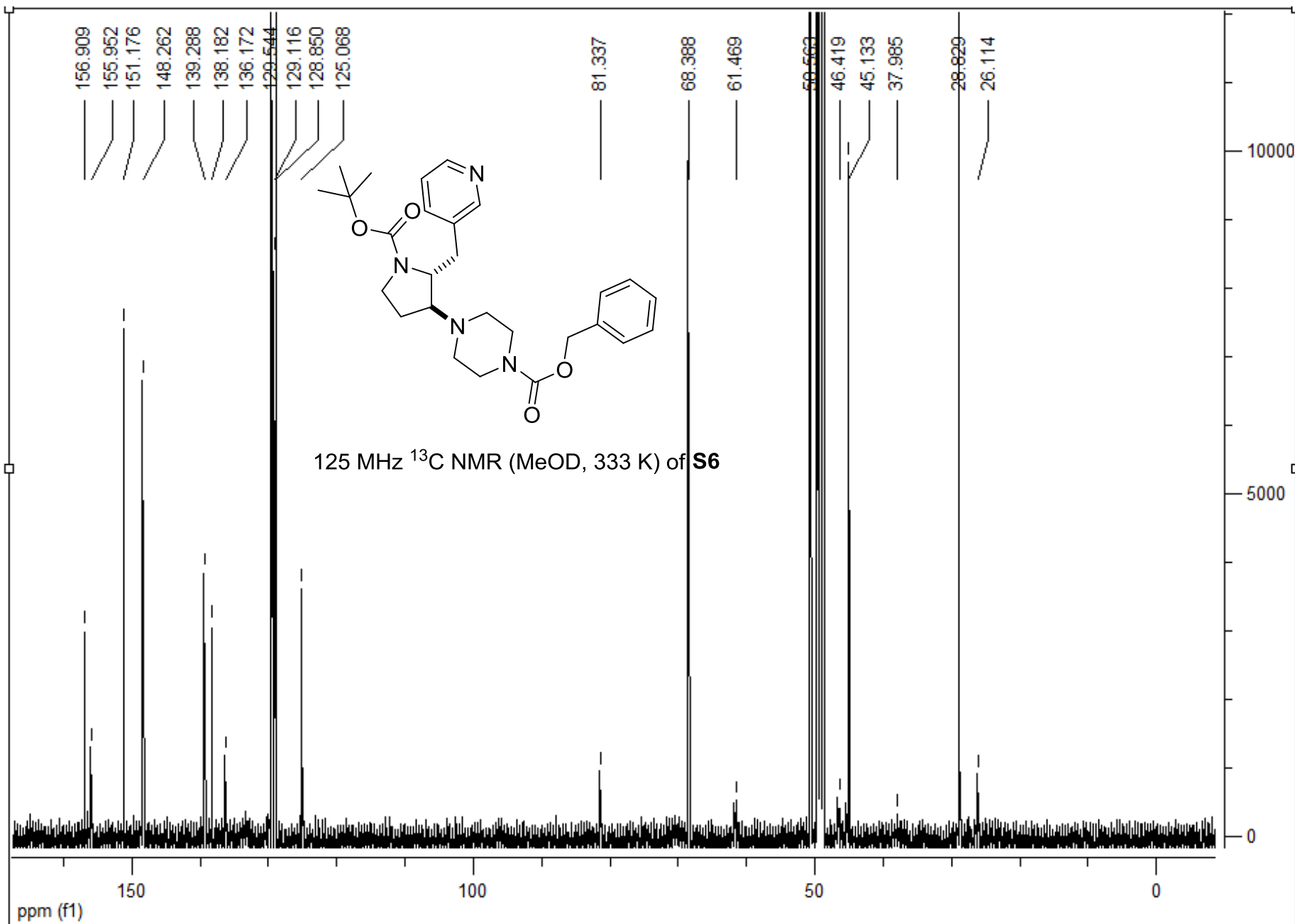


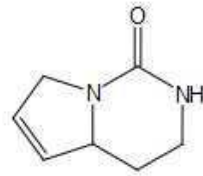




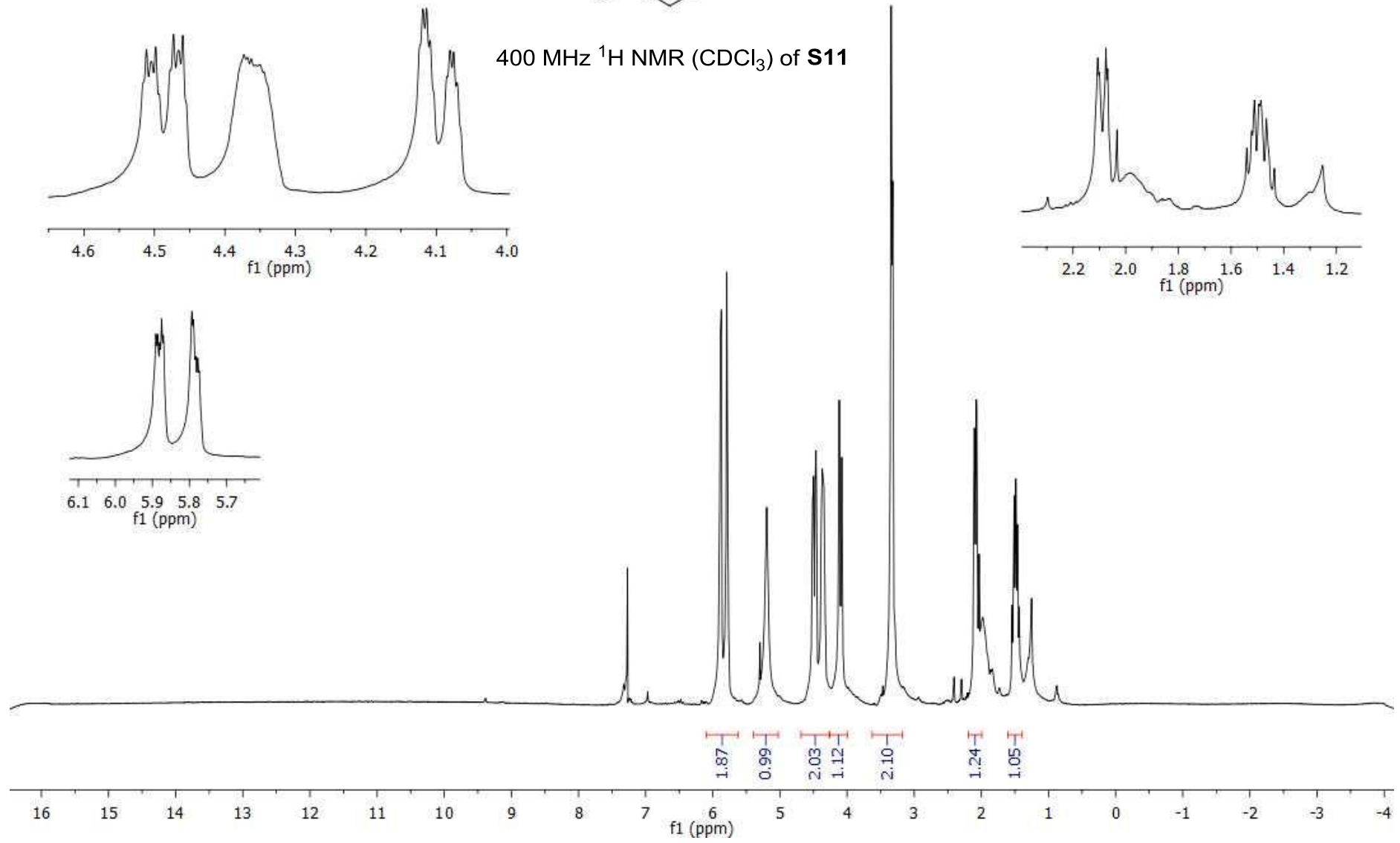


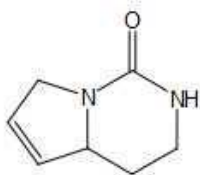




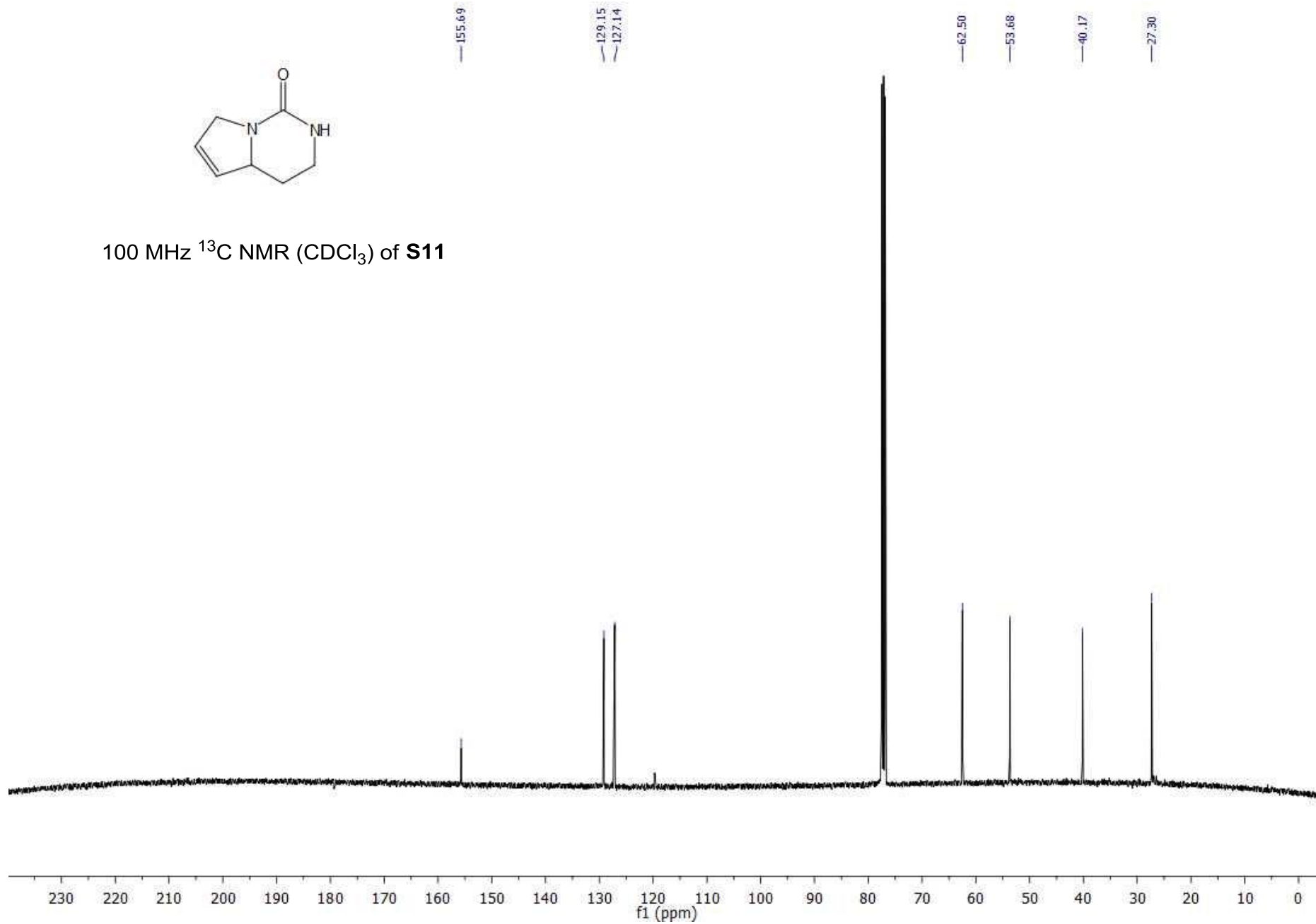


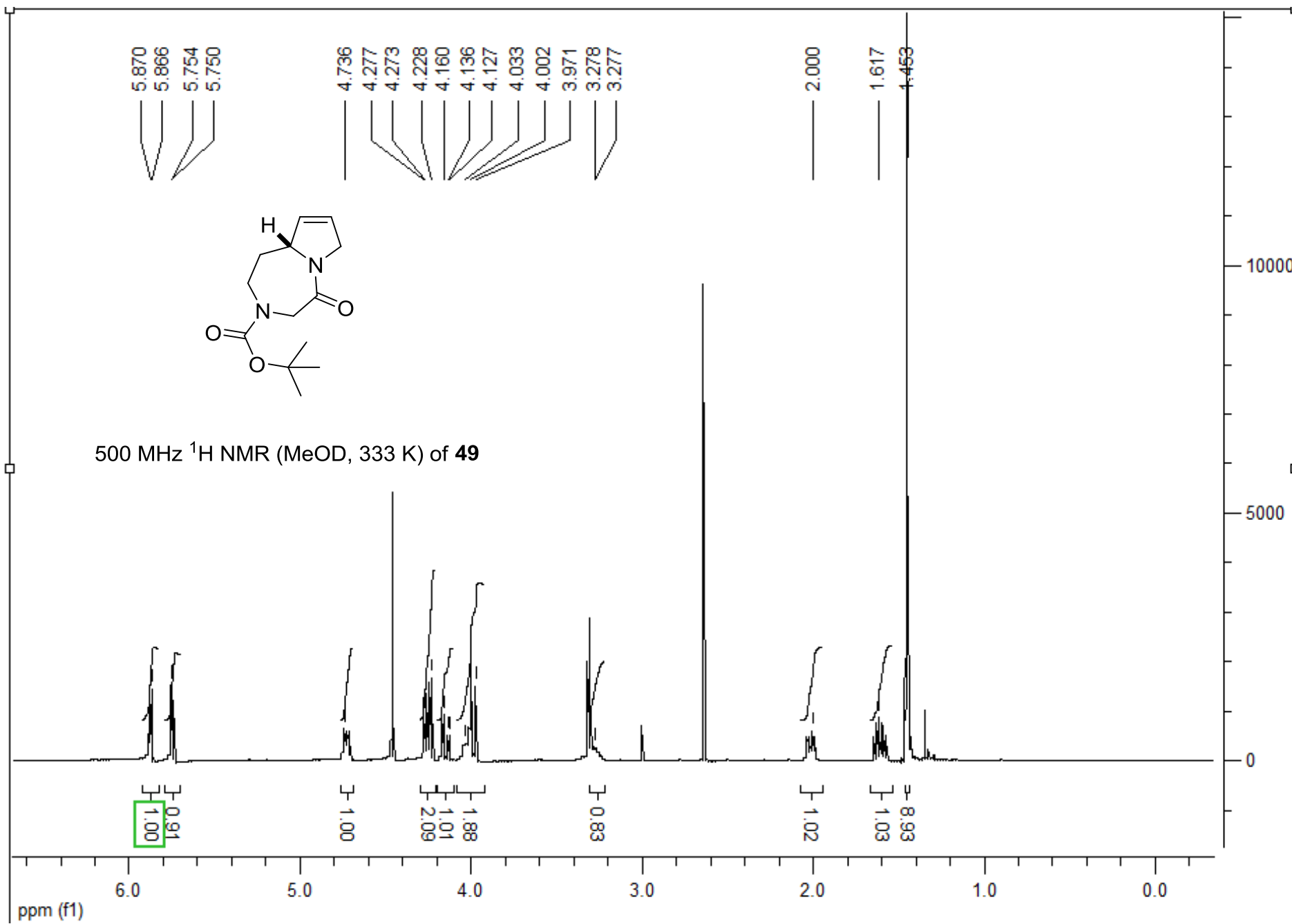
400 MHz ^1H NMR (CDCl_3) of **S11**

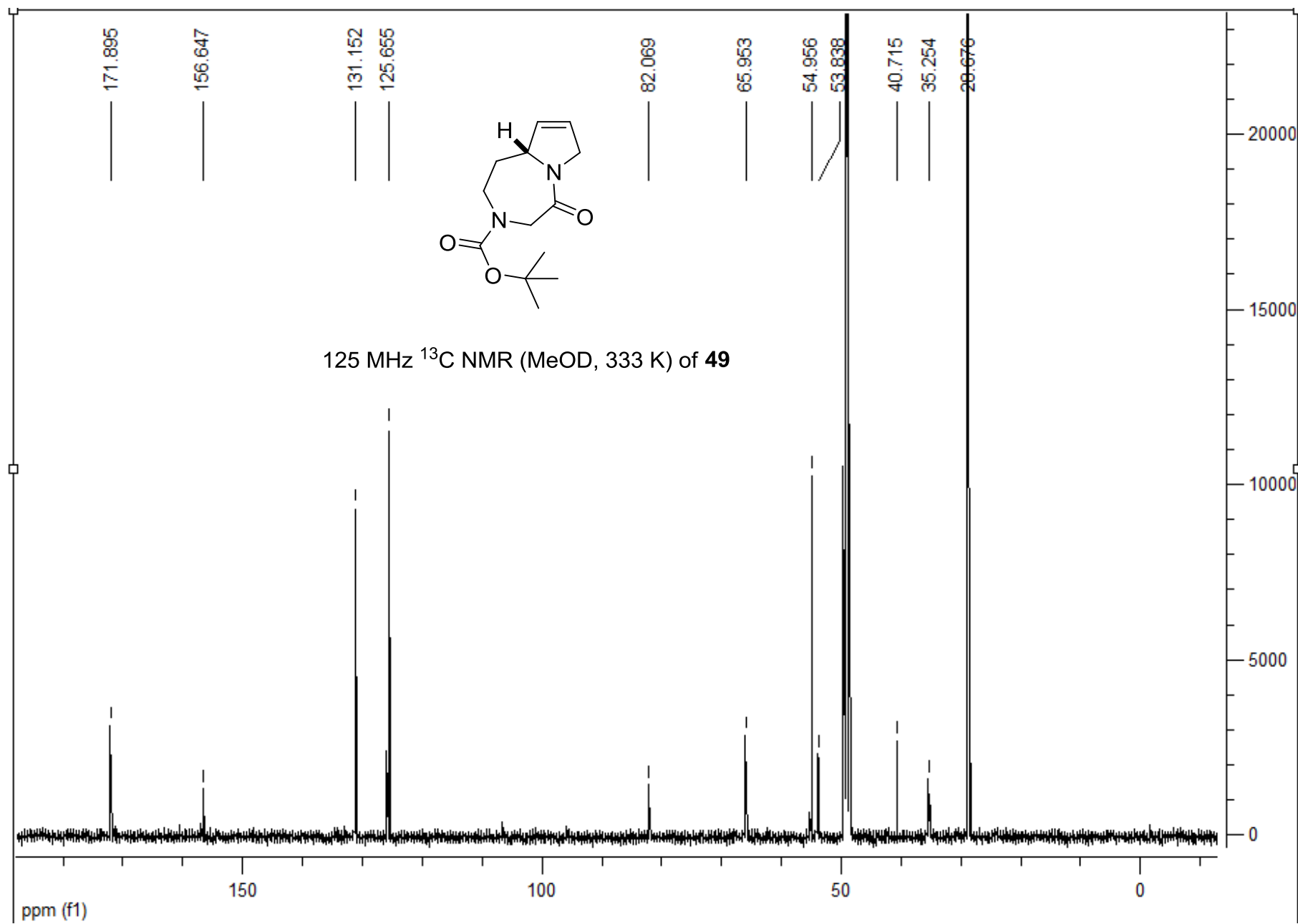


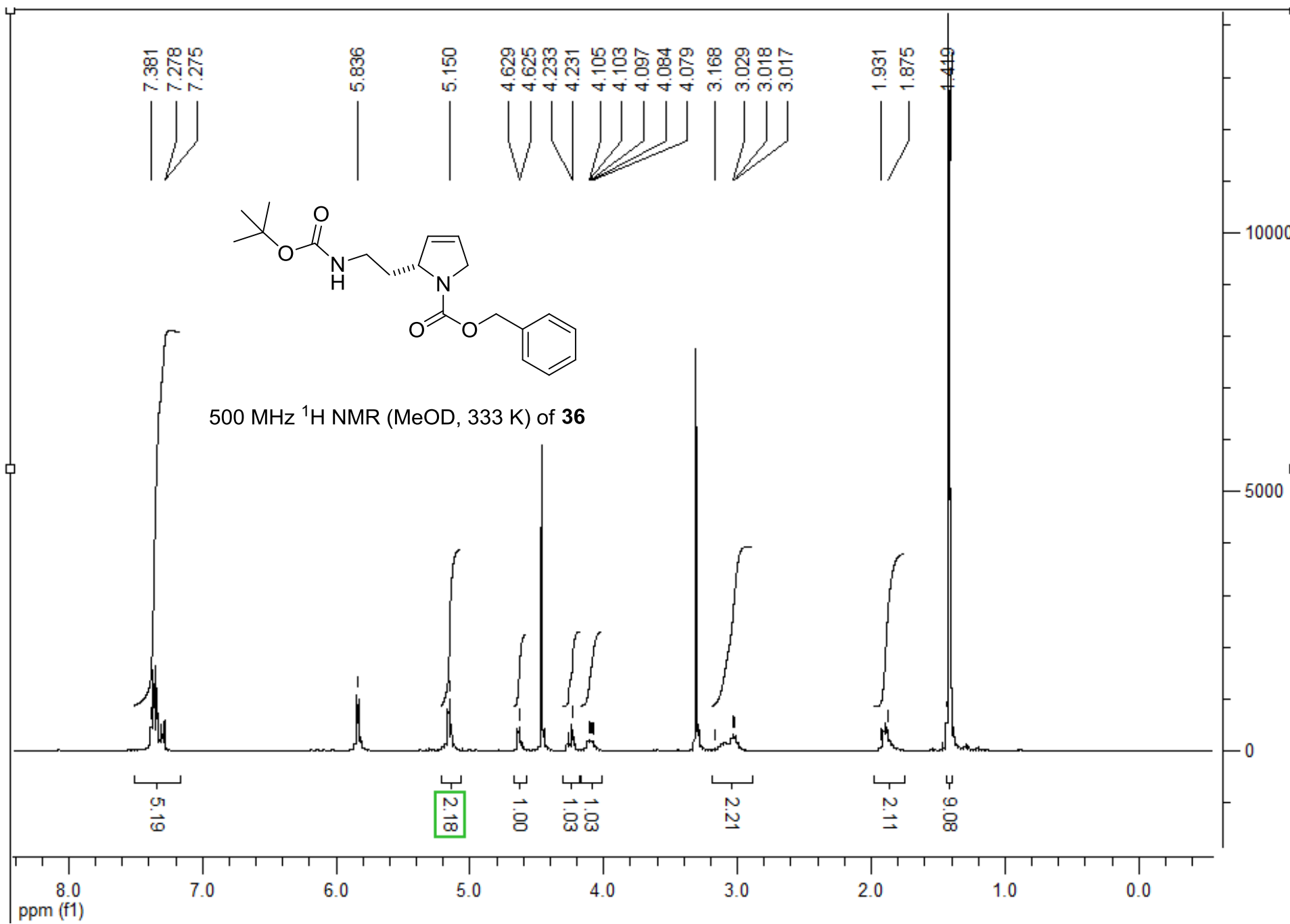


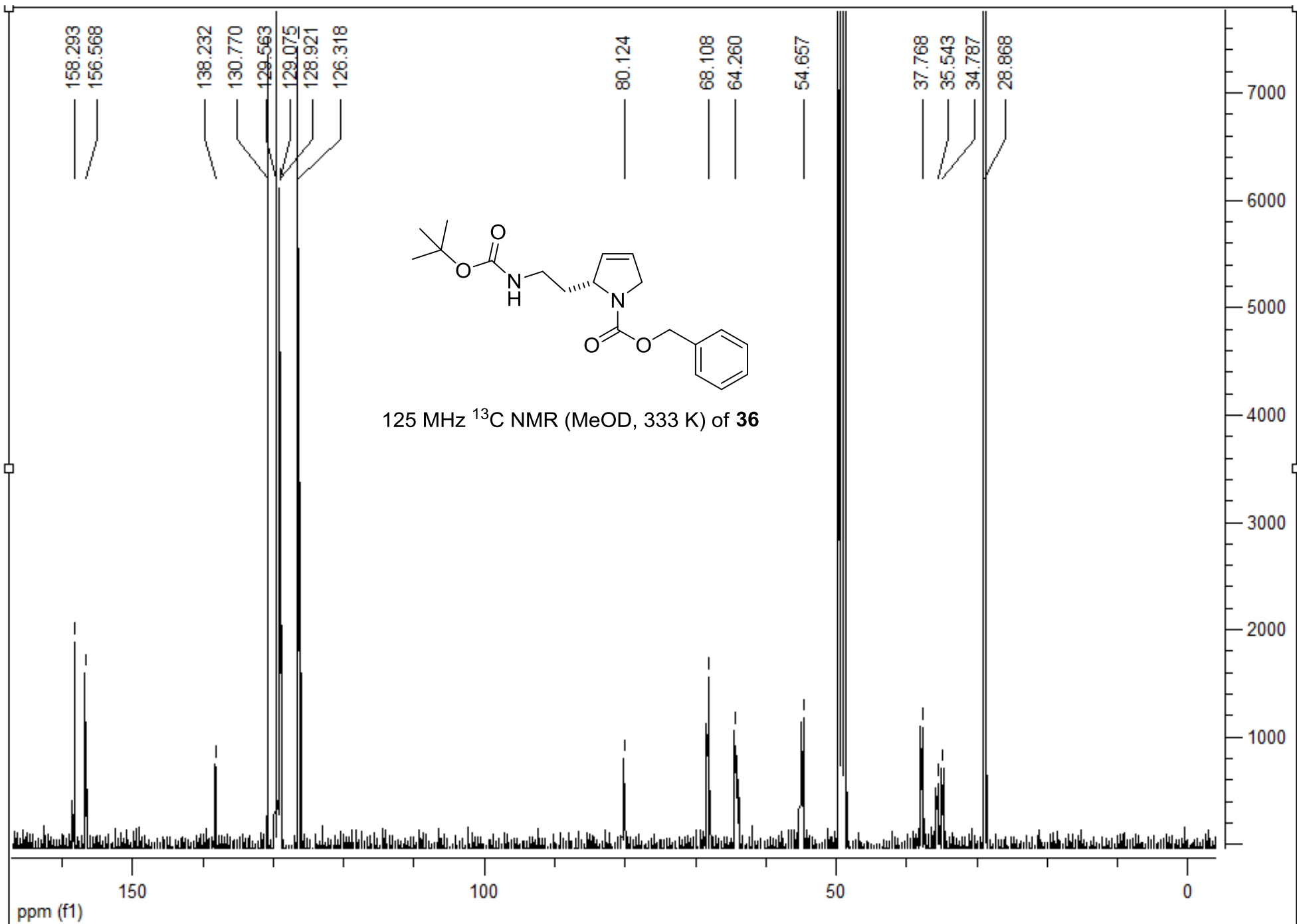
100 MHz ^{13}C NMR (CDCl_3) of **S11**

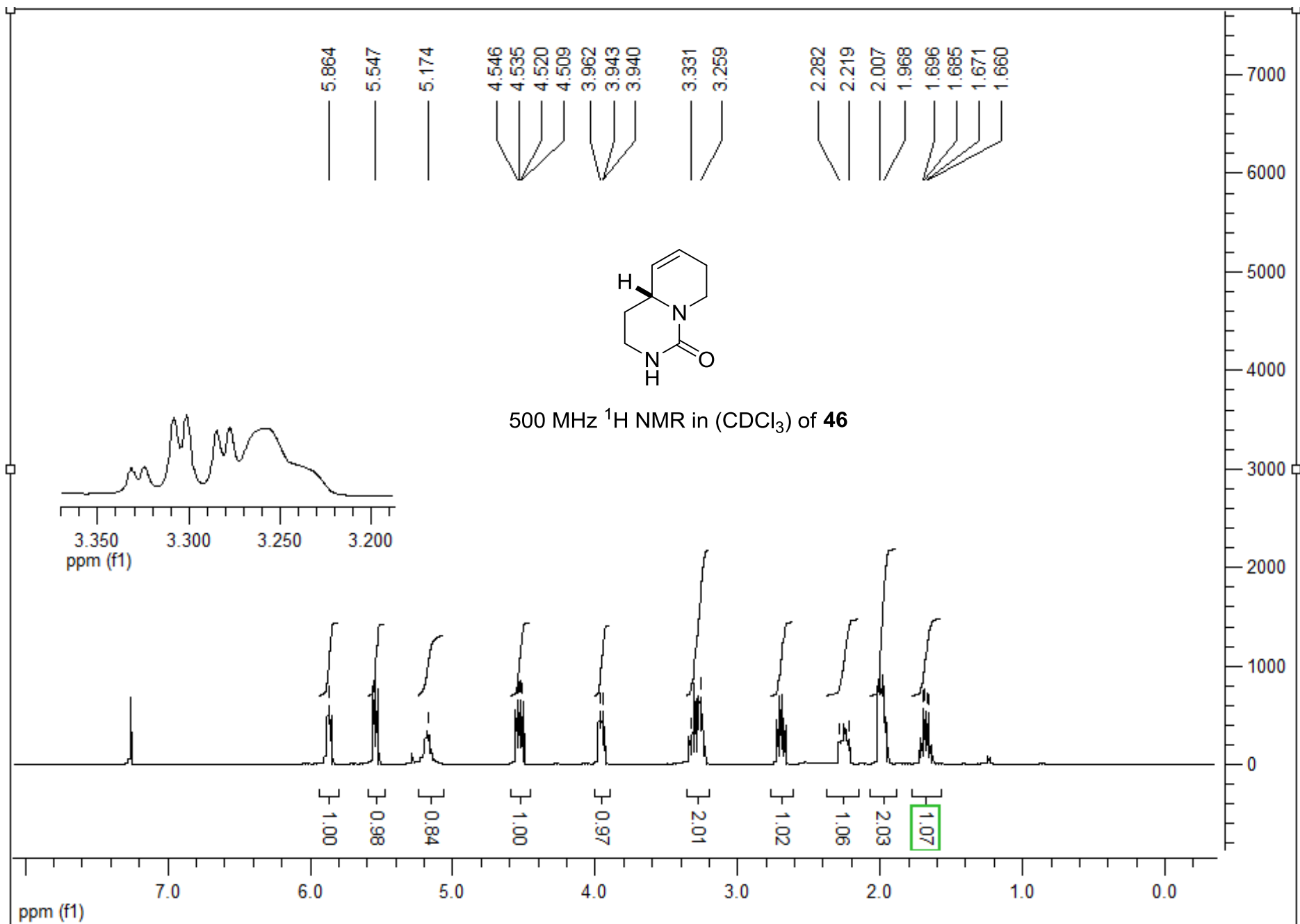


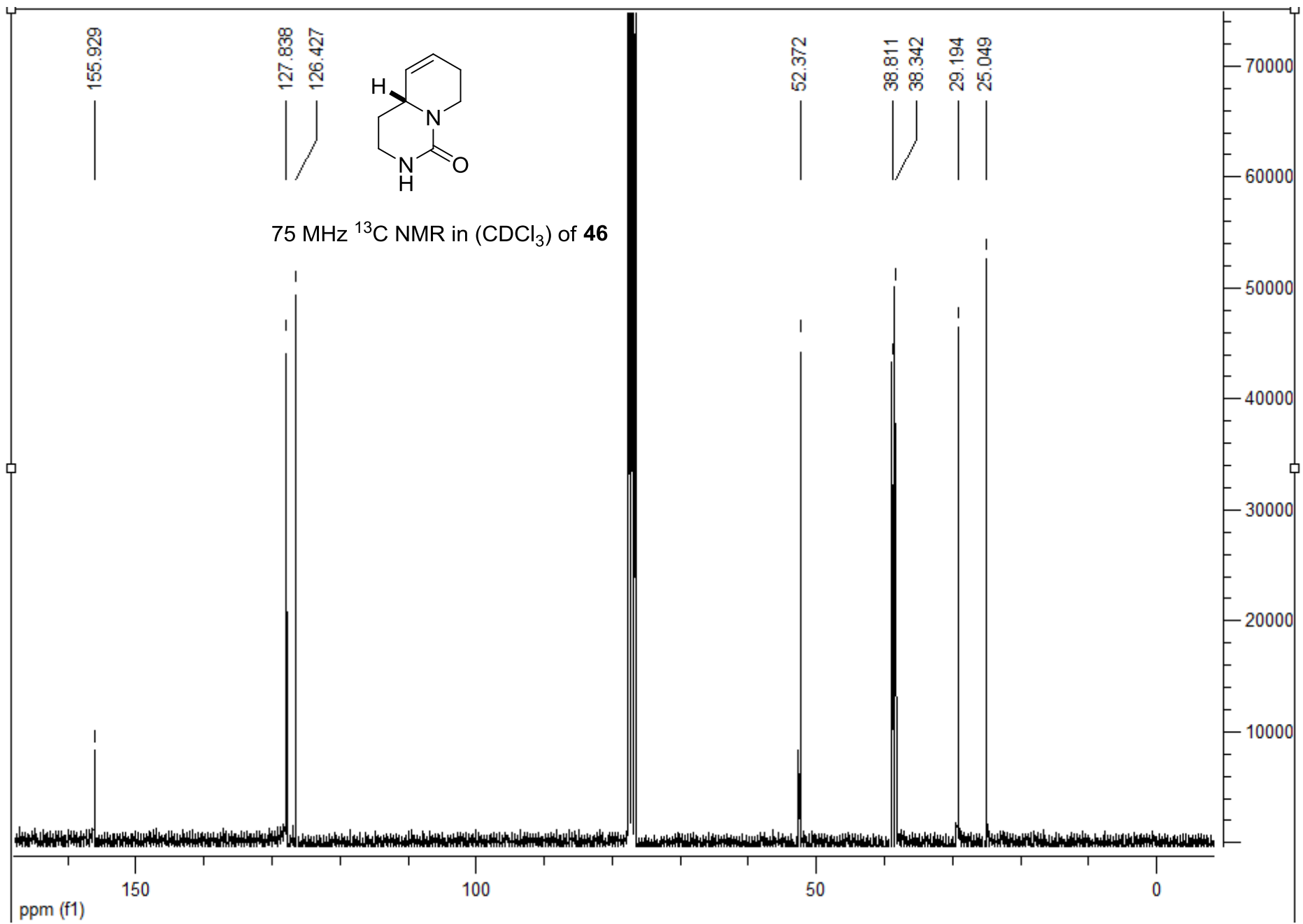


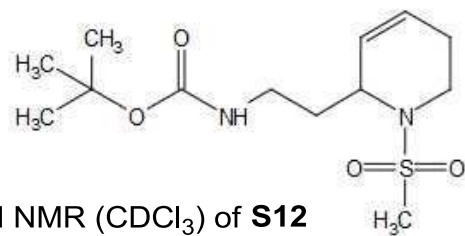




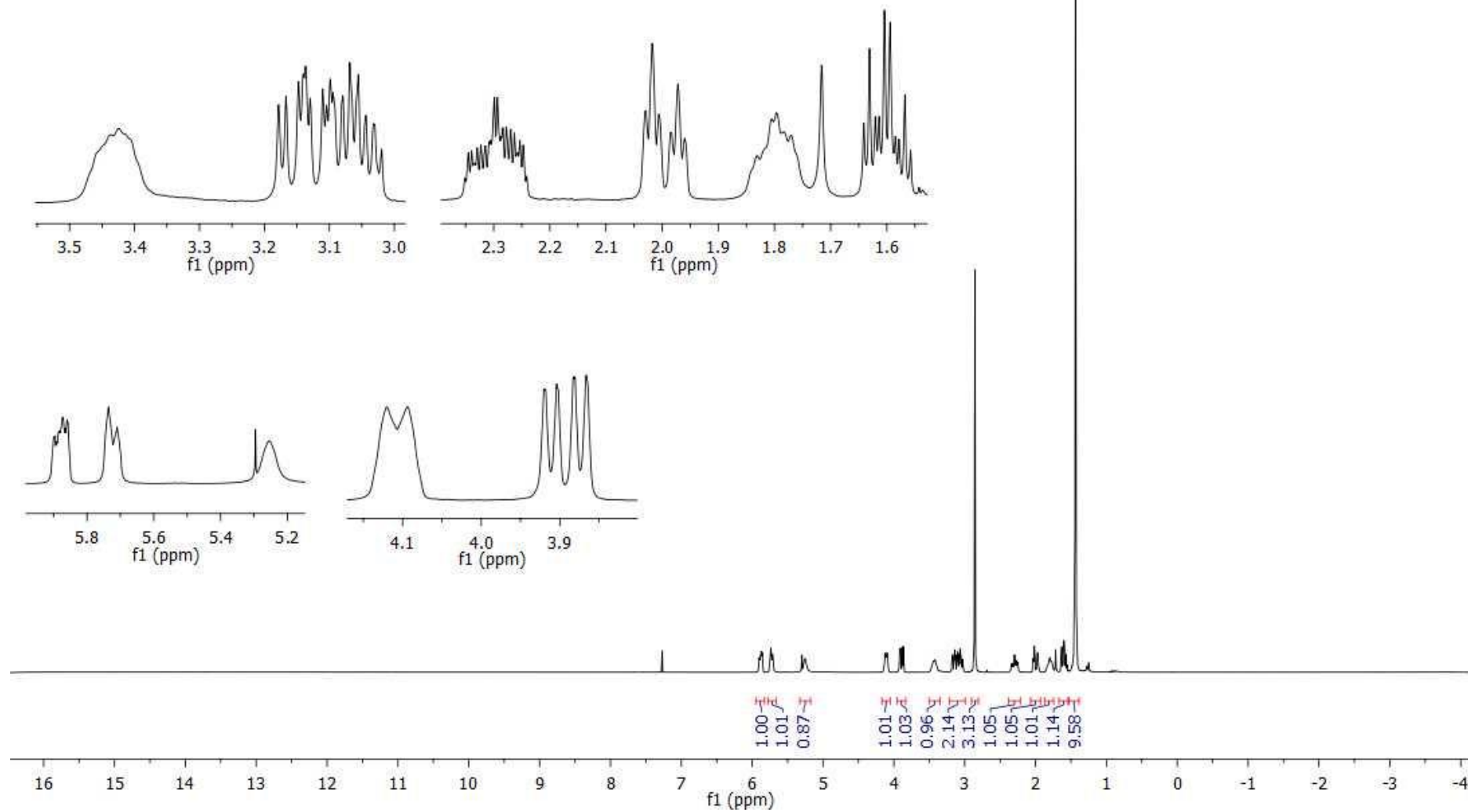


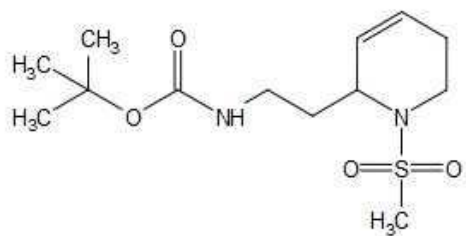




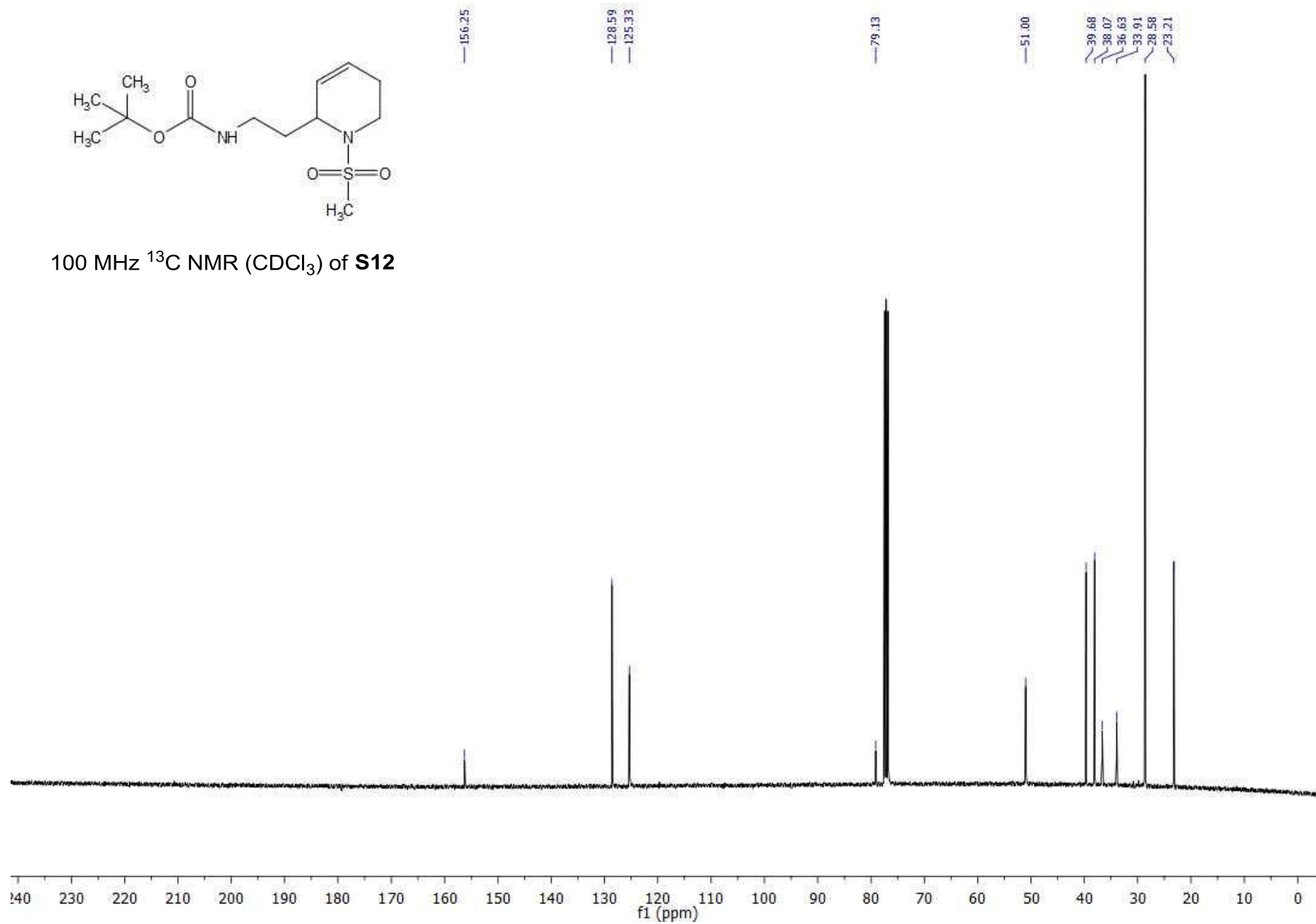


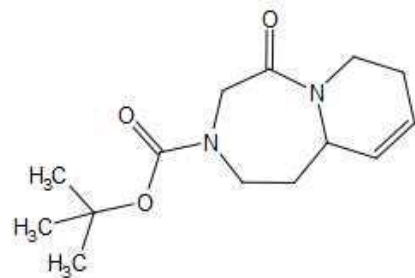
400 MHz ^1H NMR (CDCl_3) of **S12**



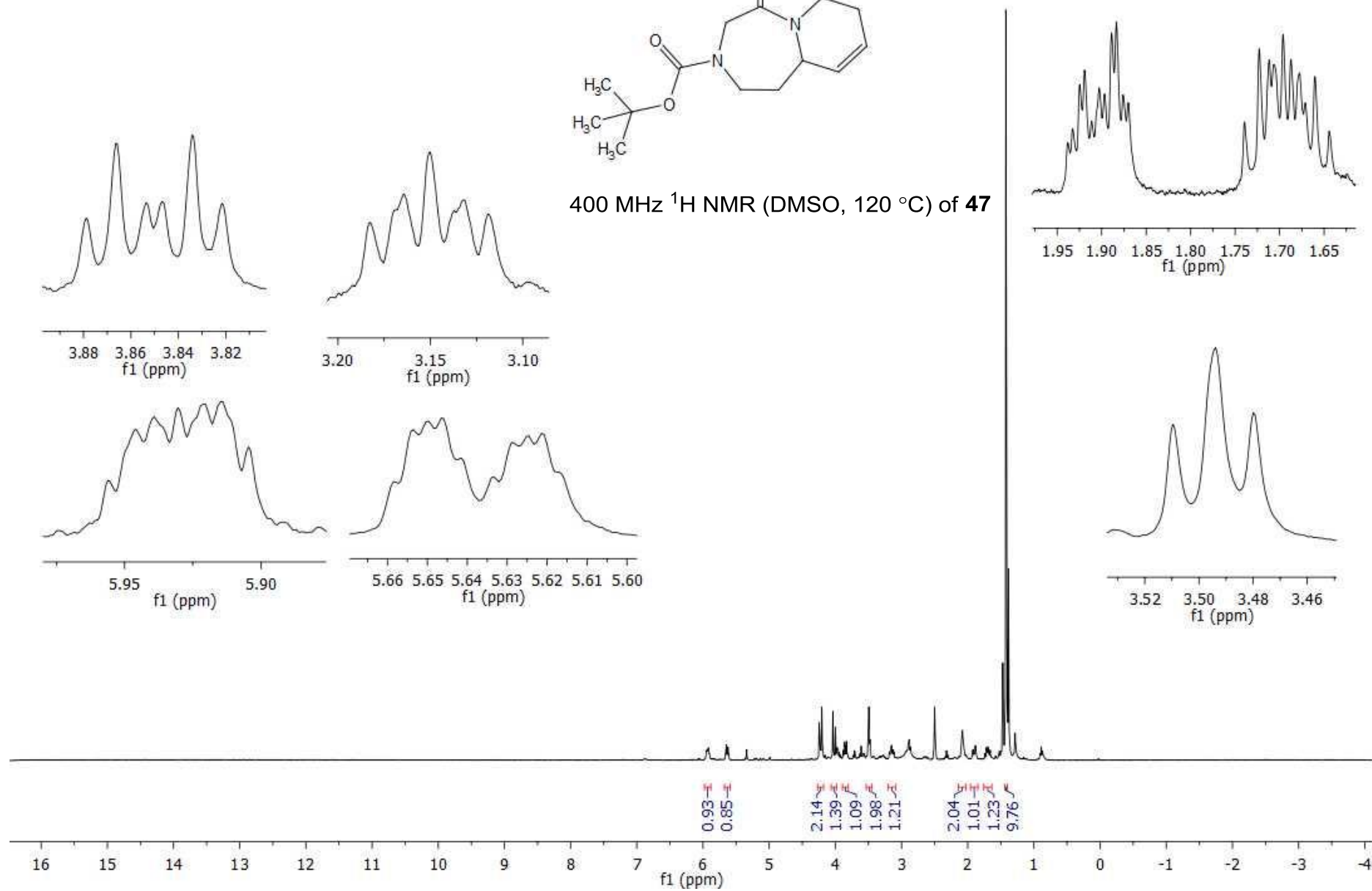


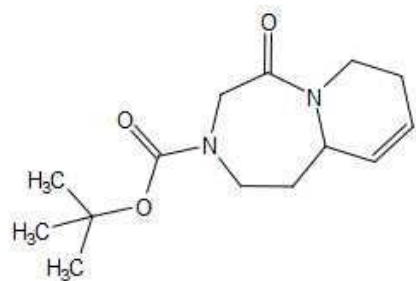
100 MHz ^{13}C NMR (CDCl_3) of **S12**



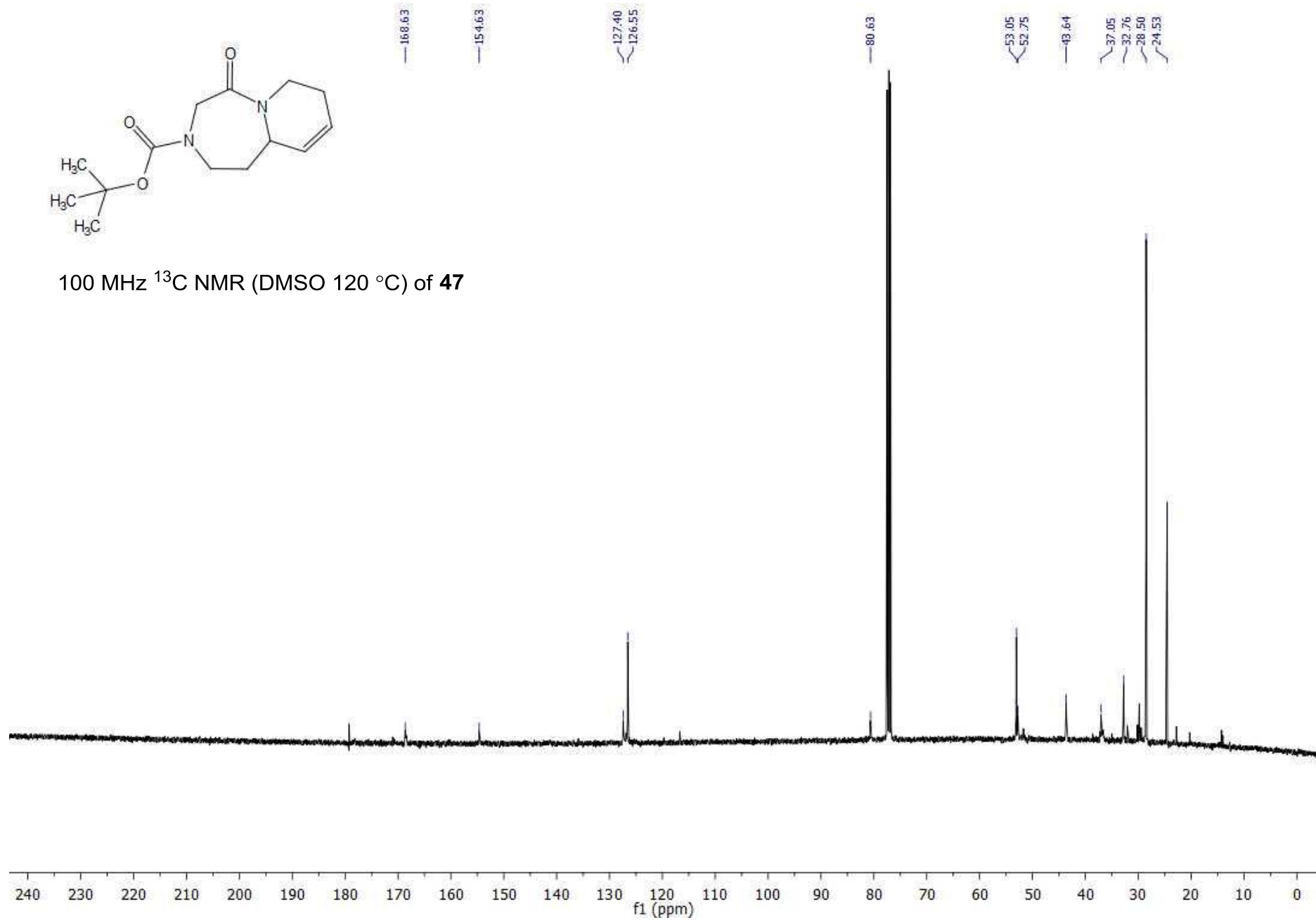


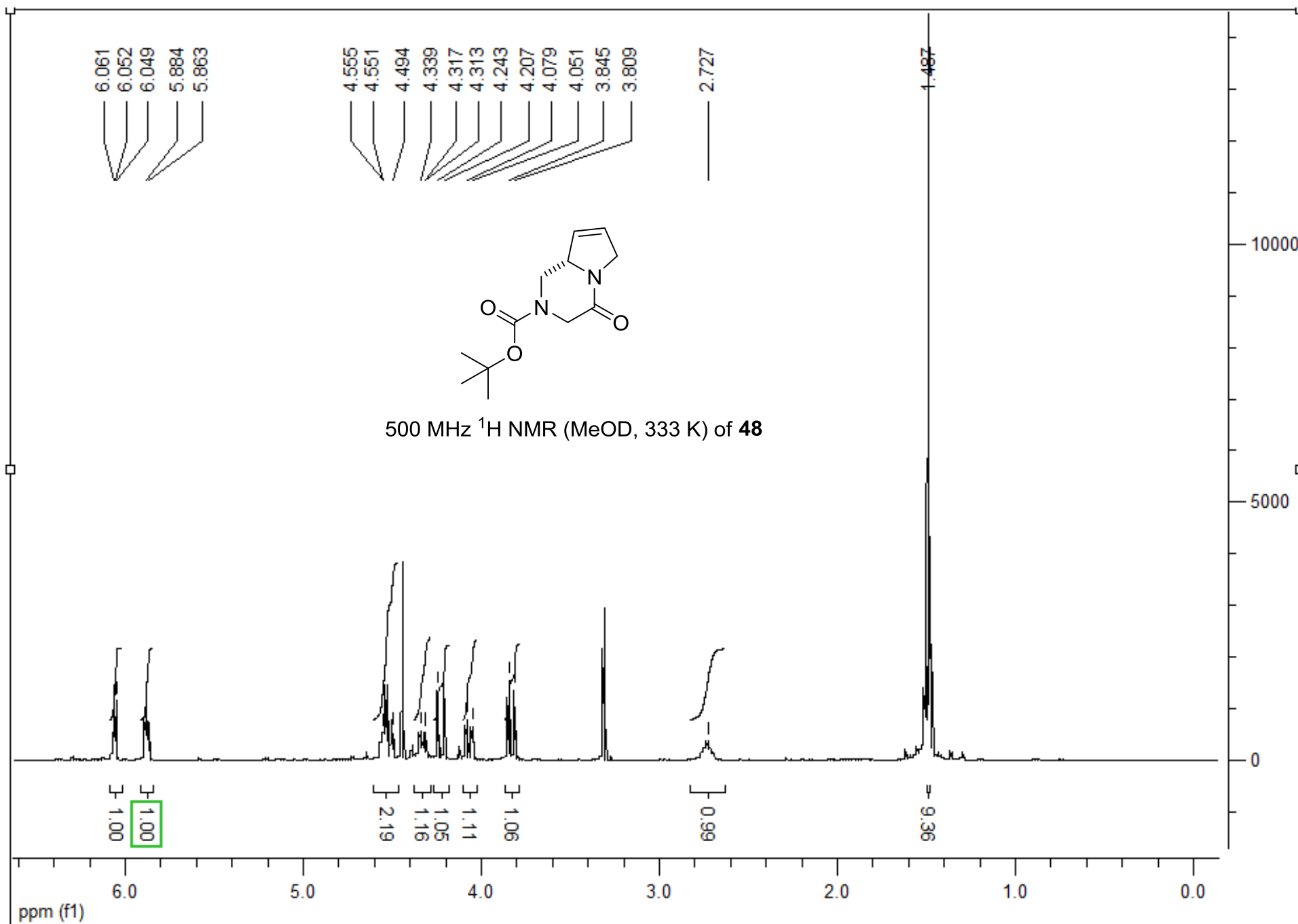
400 MHz ^1H NMR (DMSO, 120 $^\circ\text{C}$) of **47**

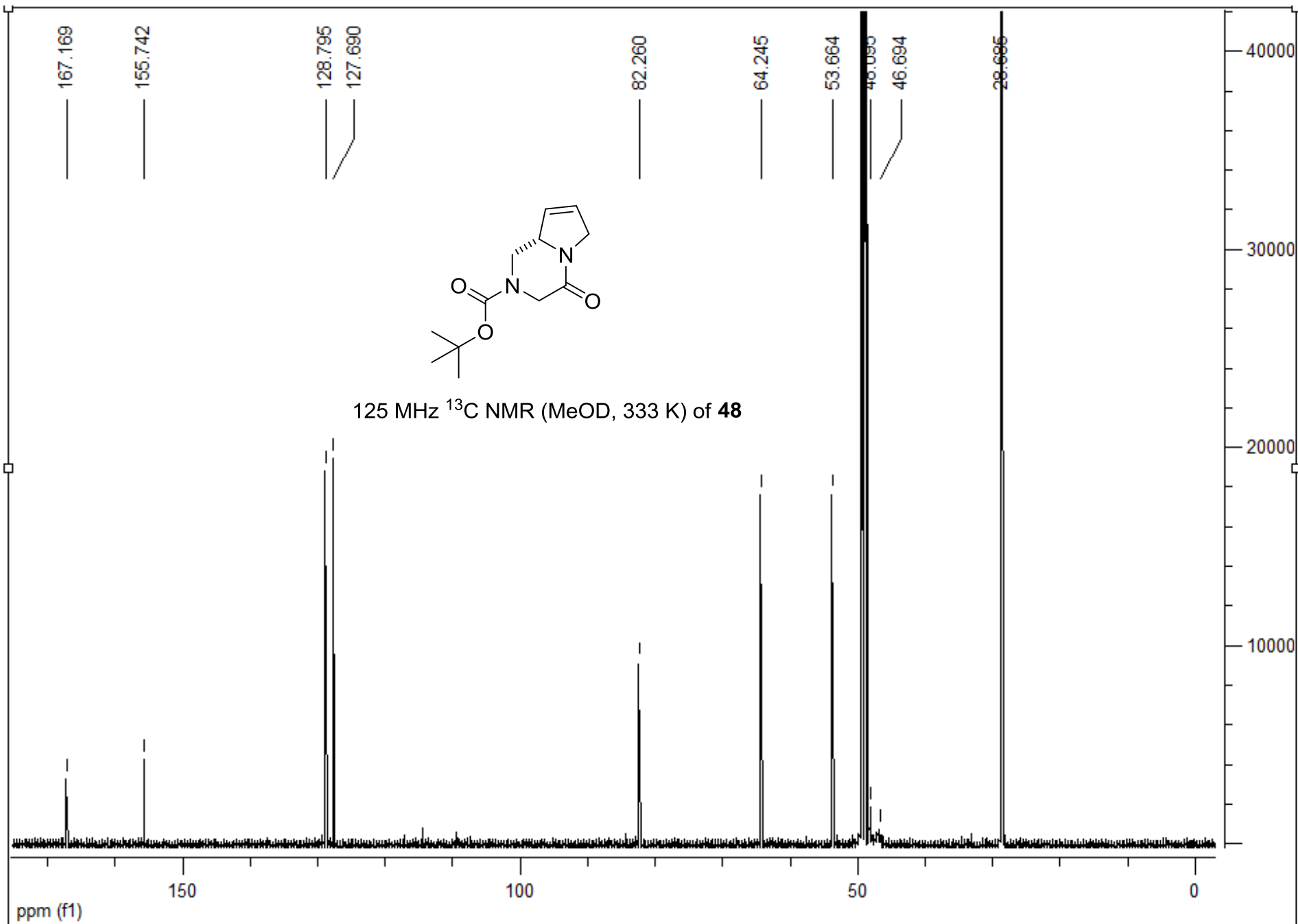




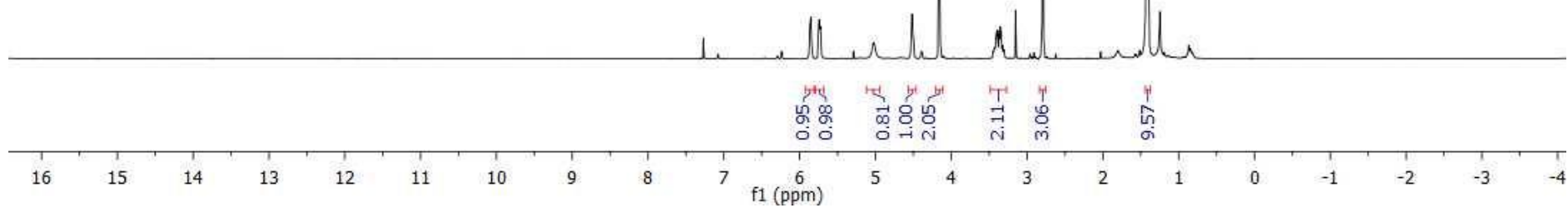
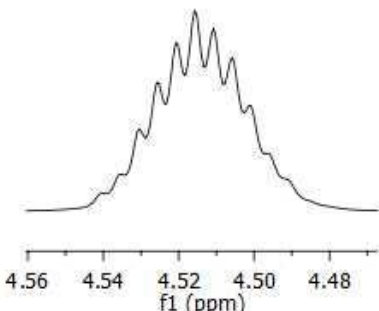
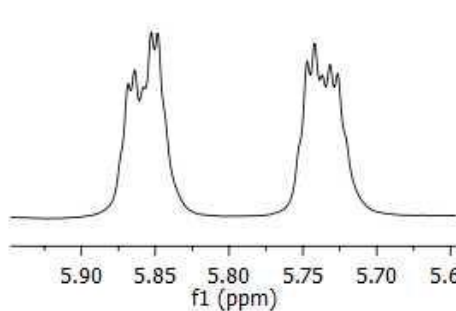
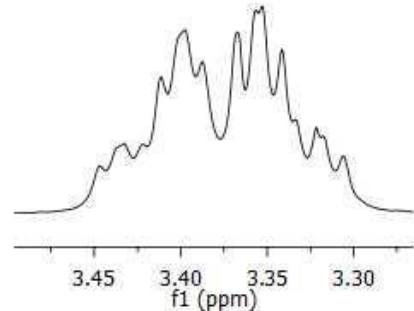
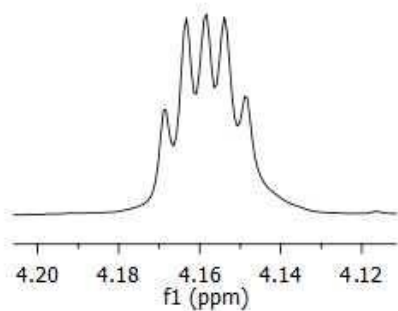
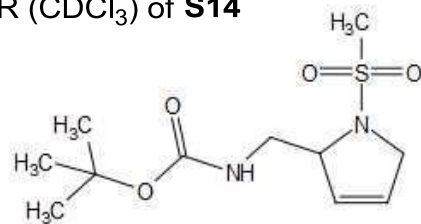
100 MHz ^{13}C NMR (DMSO 120 °C) of **47**

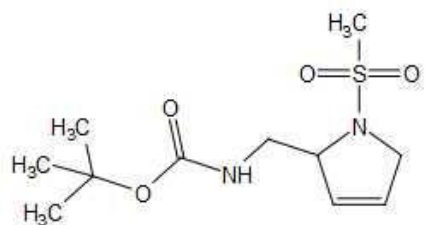




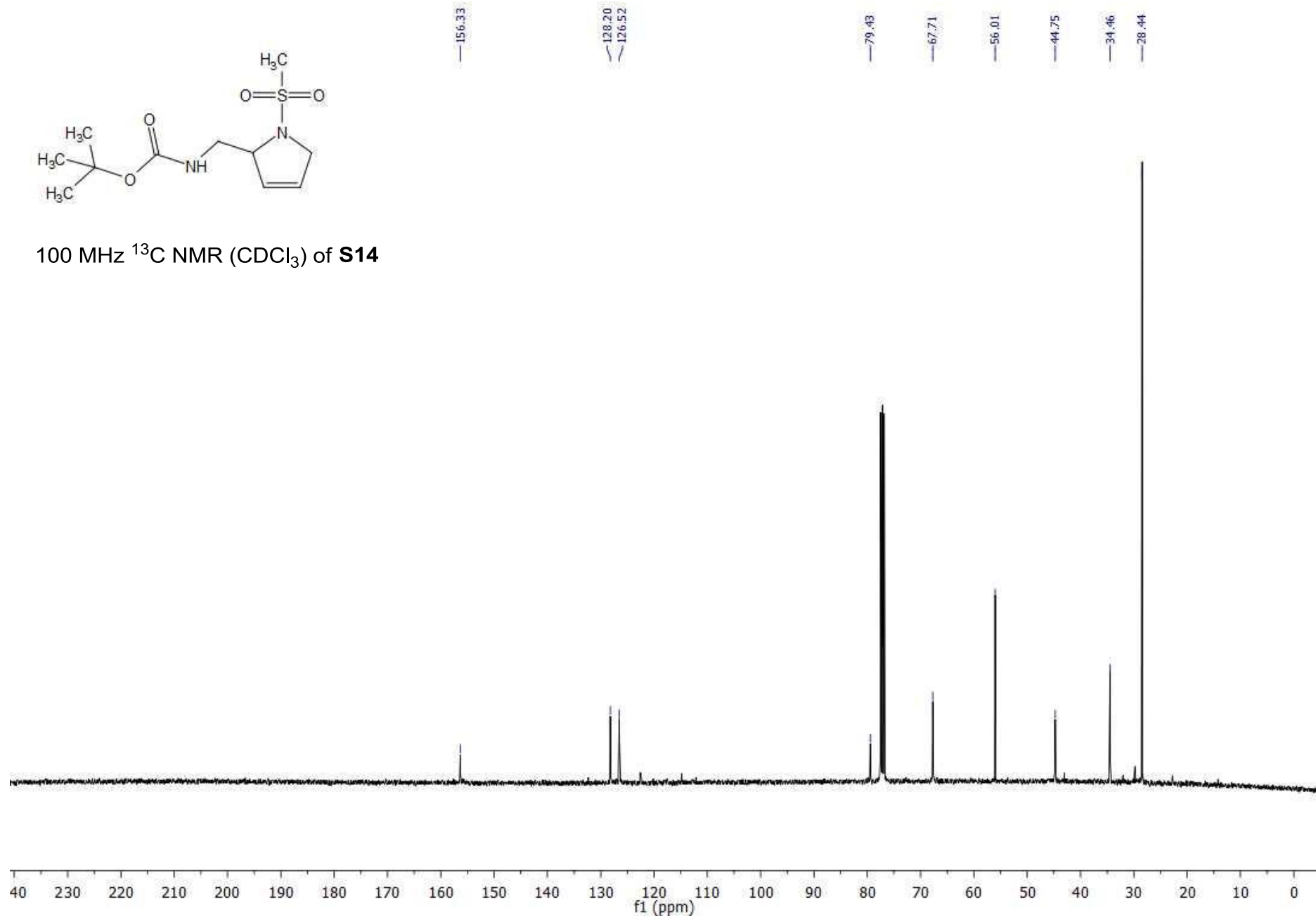


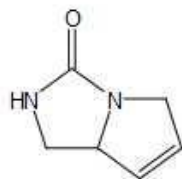
400 MHz ^1H NMR (CDCl_3) of **S14**



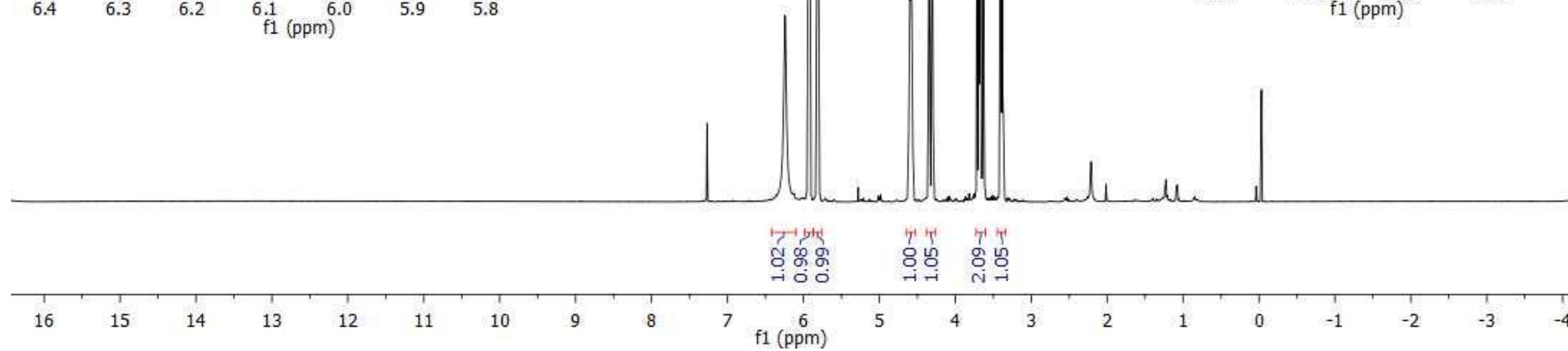
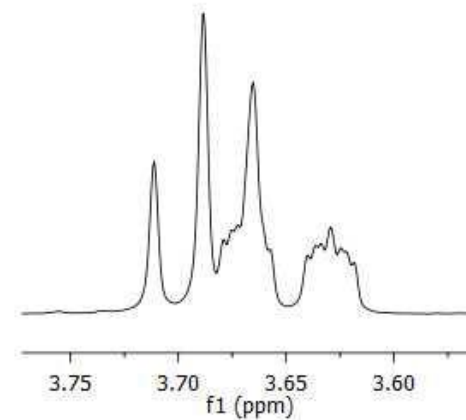
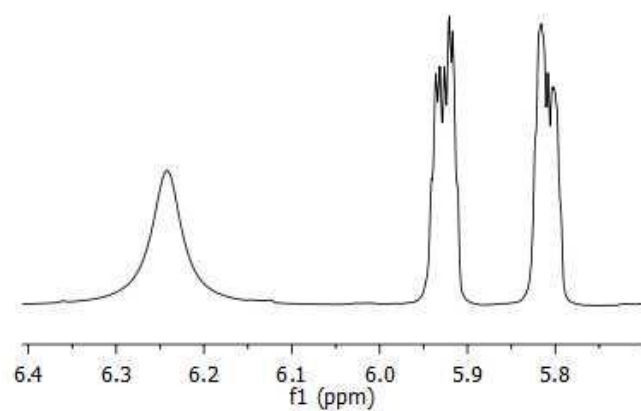
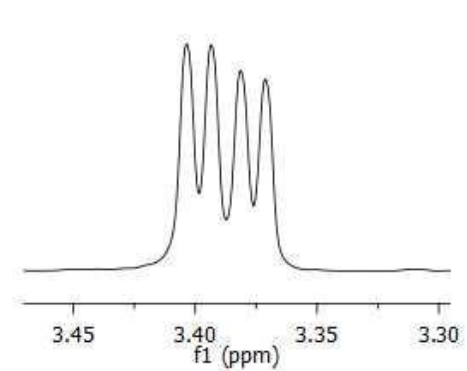
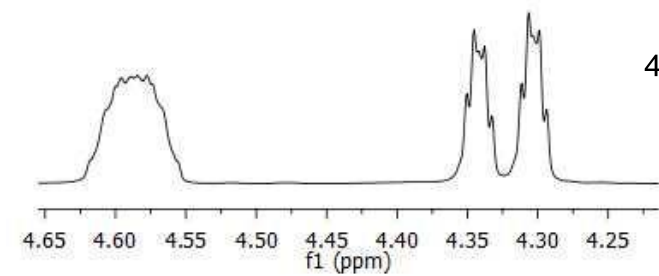


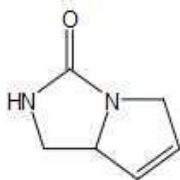
100 MHz ^{13}C NMR (CDCl_3) of **S14**



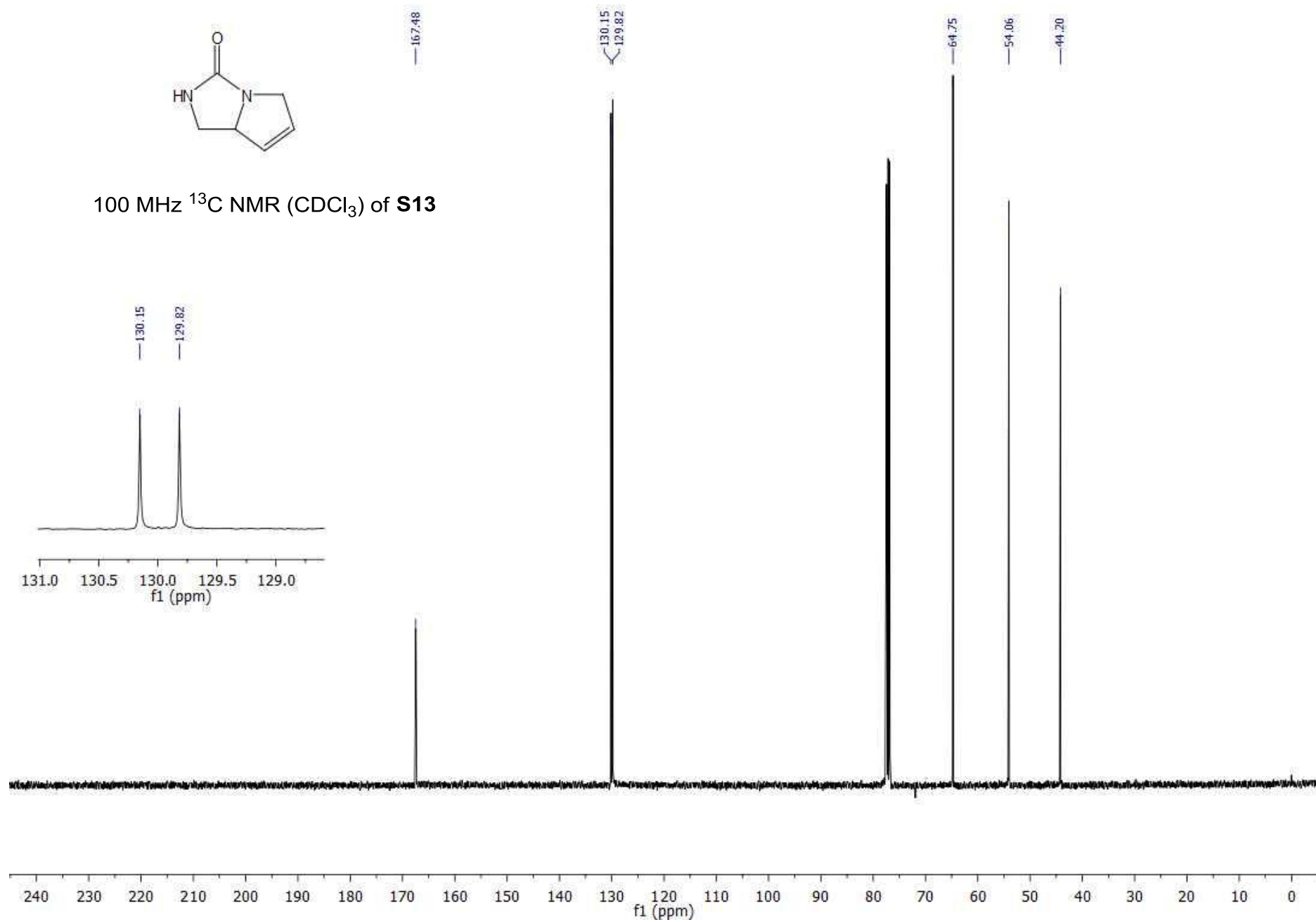


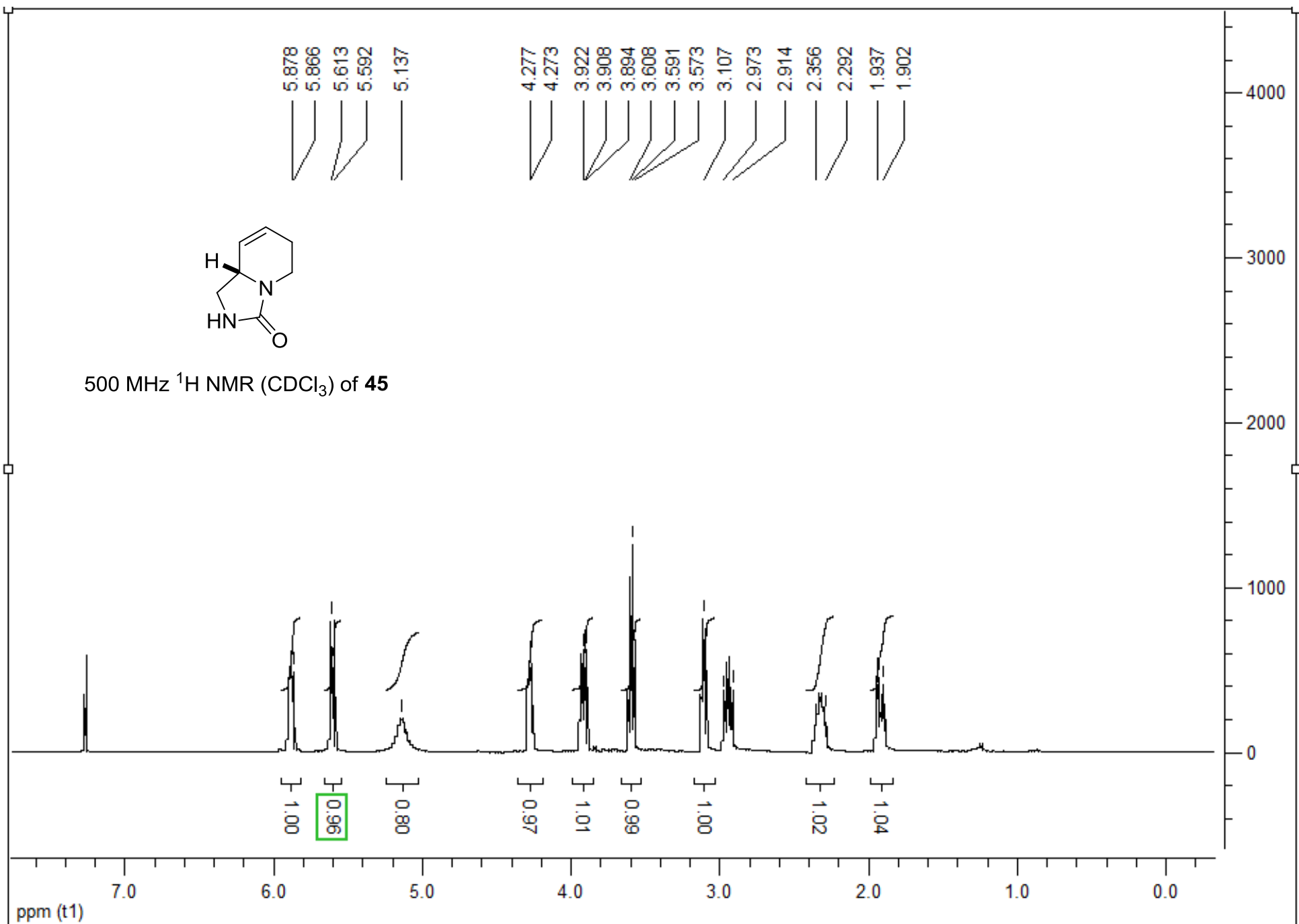
400 MHz ^1H NMR (CDCl_3) of **S13**

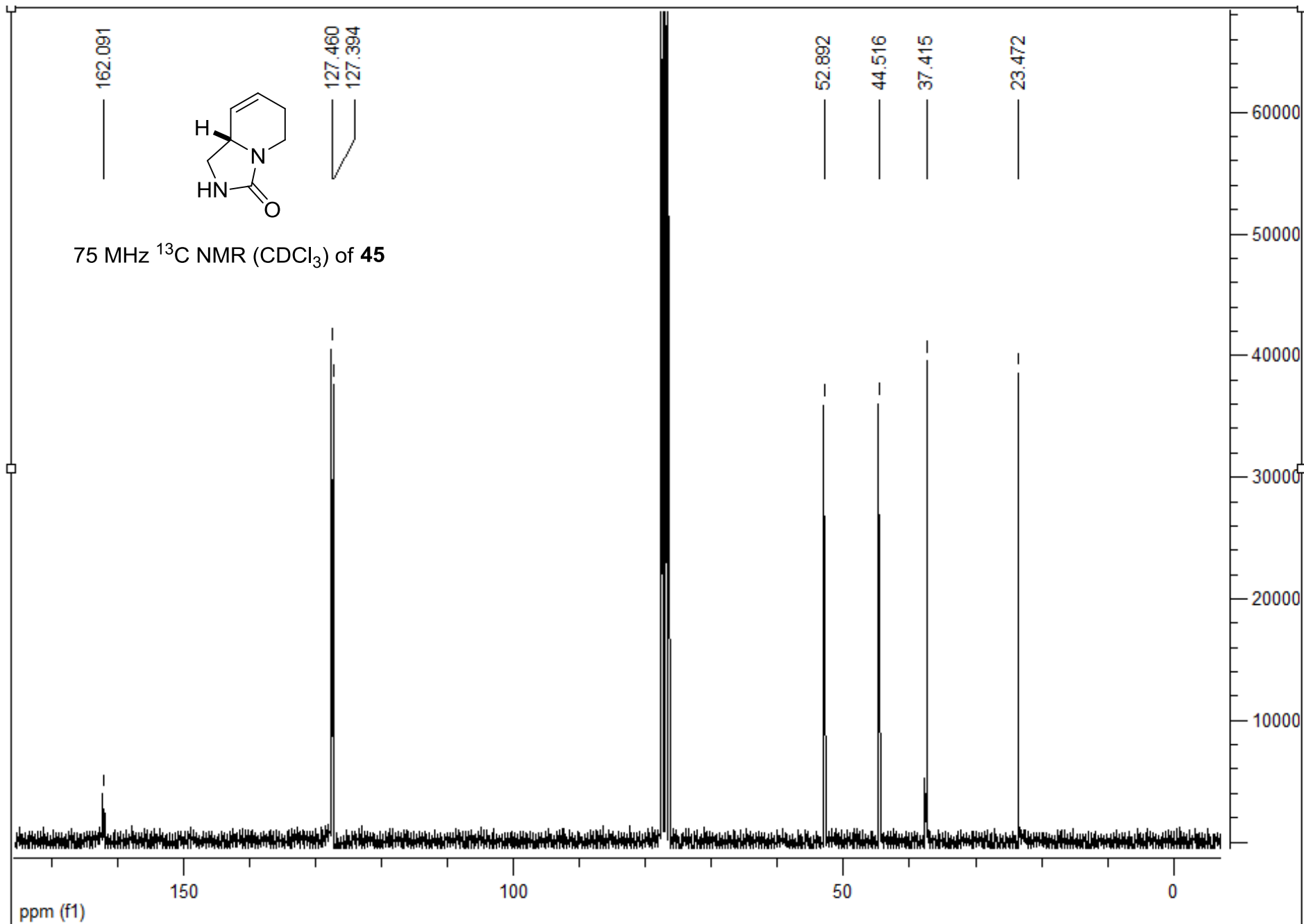


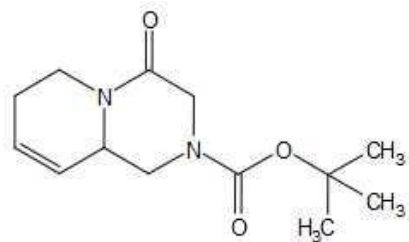


100 MHz ^{13}C NMR (CDCl_3) of **S13**

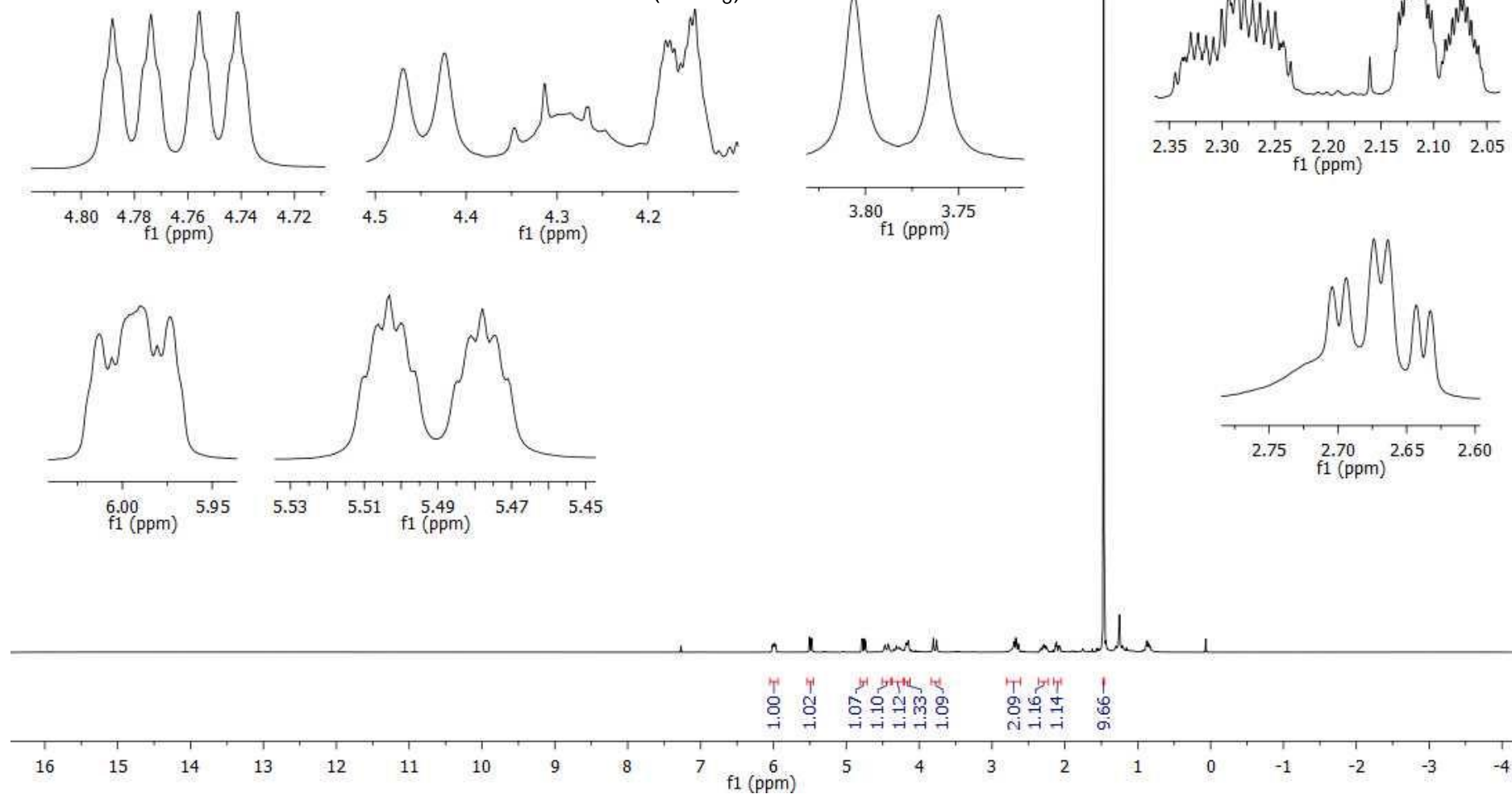


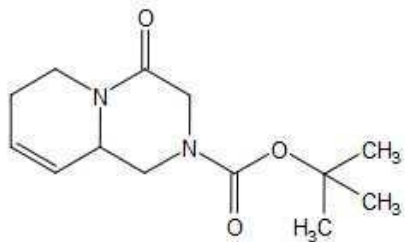




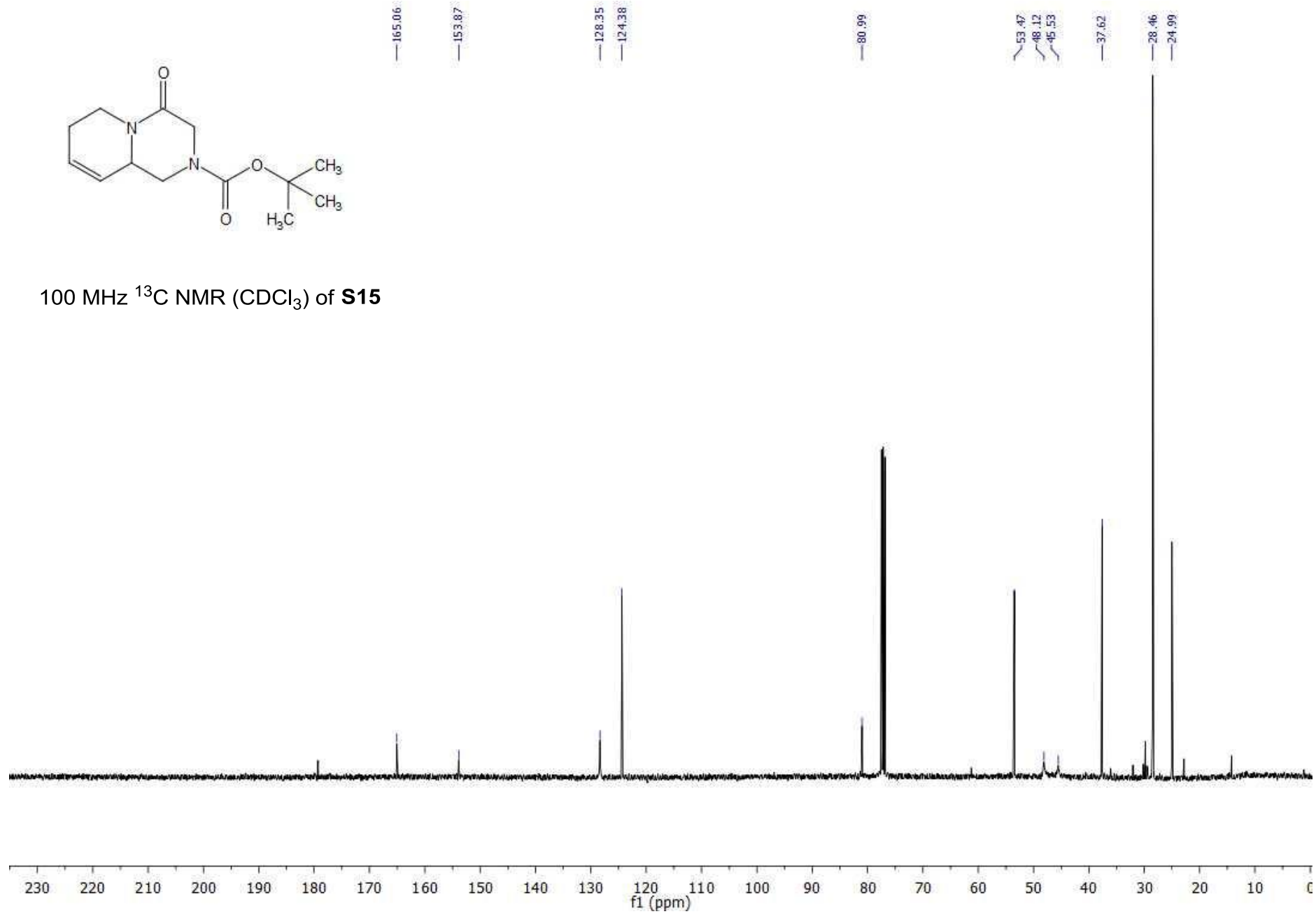


400 MHz ^1H NMR (CDCl_3) of **S15**

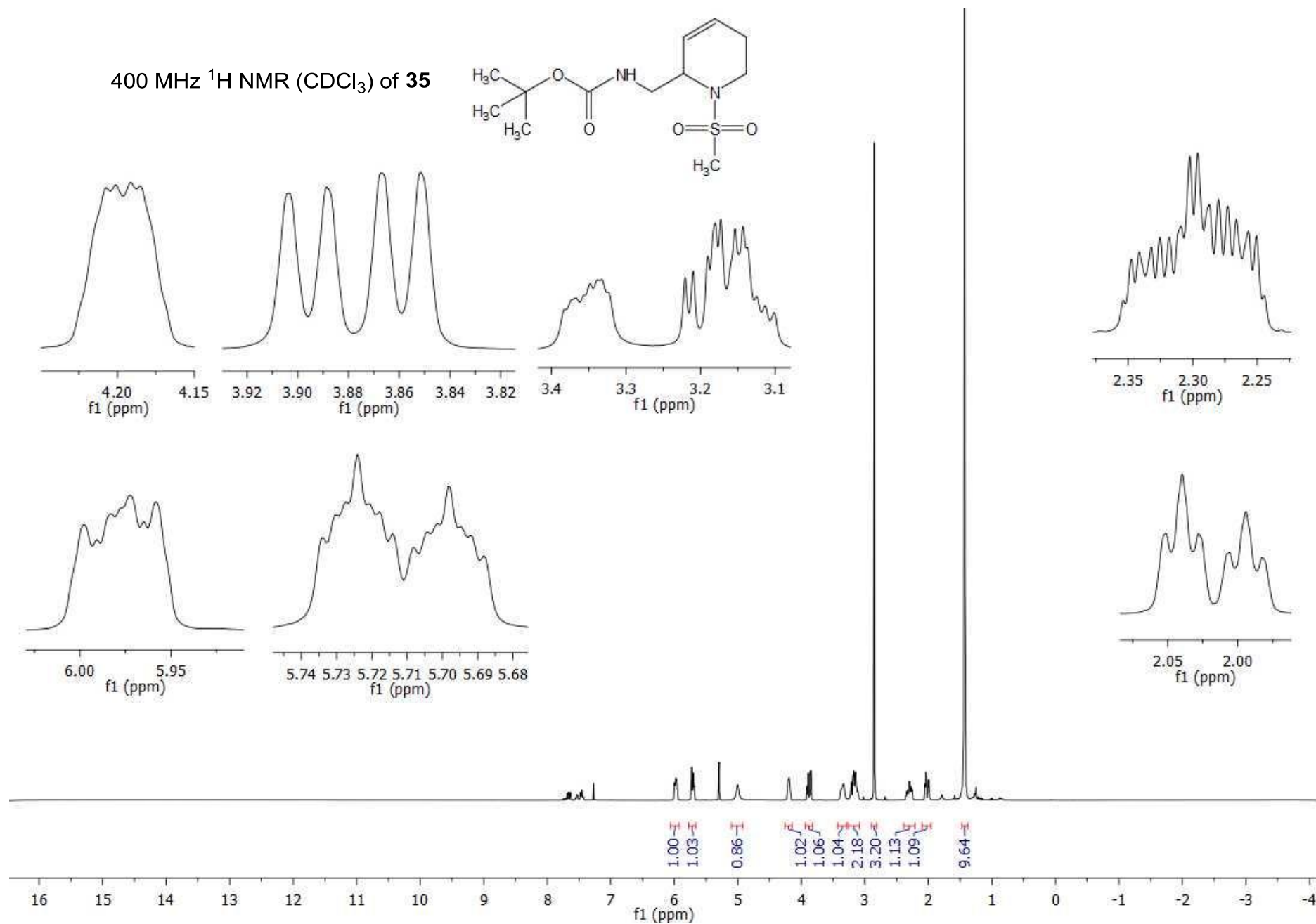
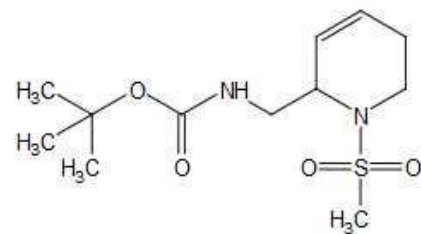


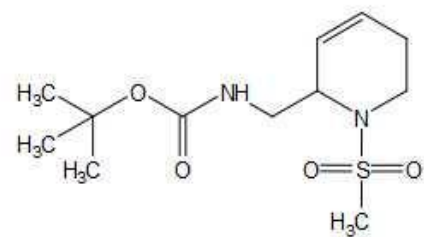


100 MHz ^{13}C NMR (CDCl_3) of **S15**

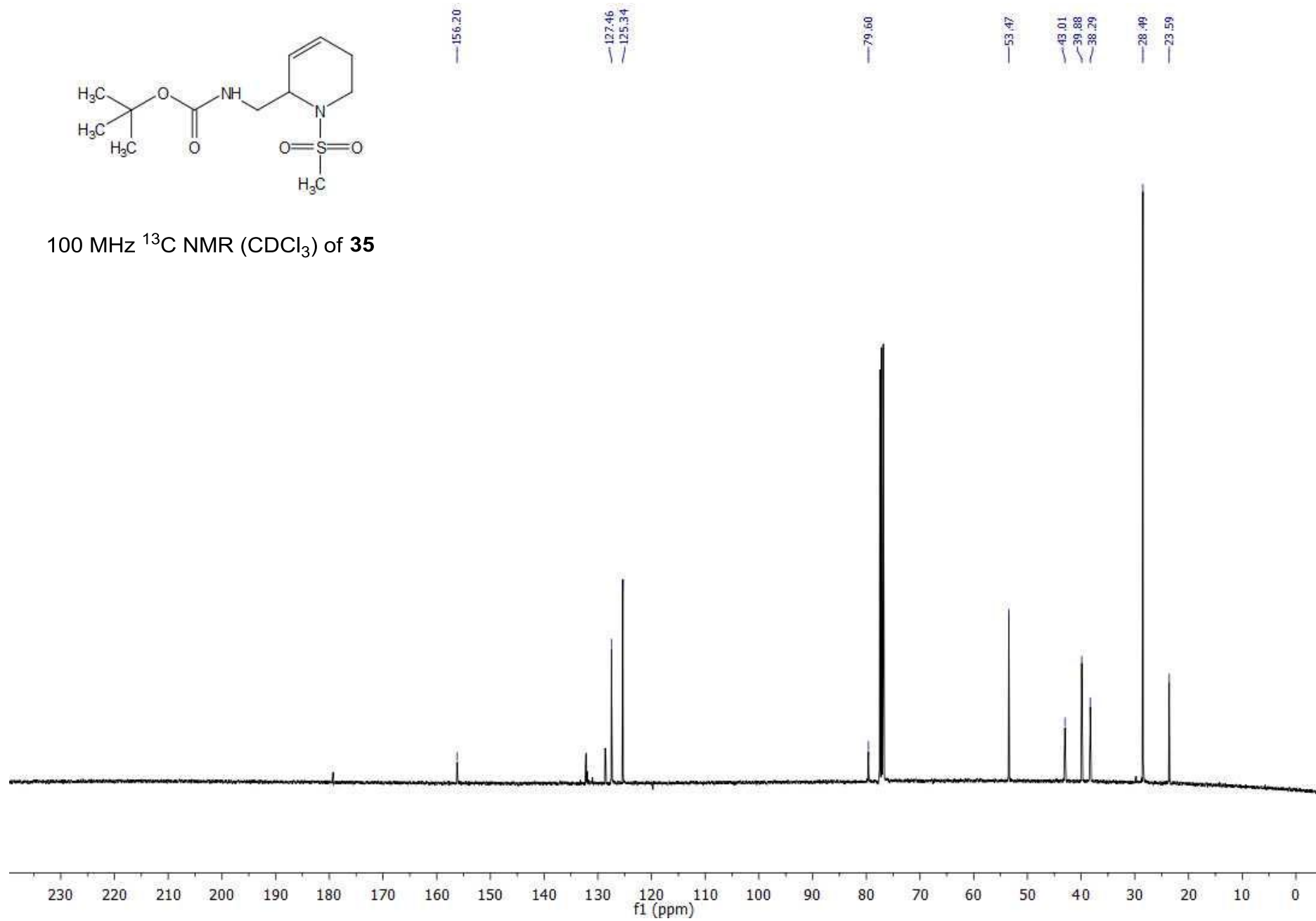


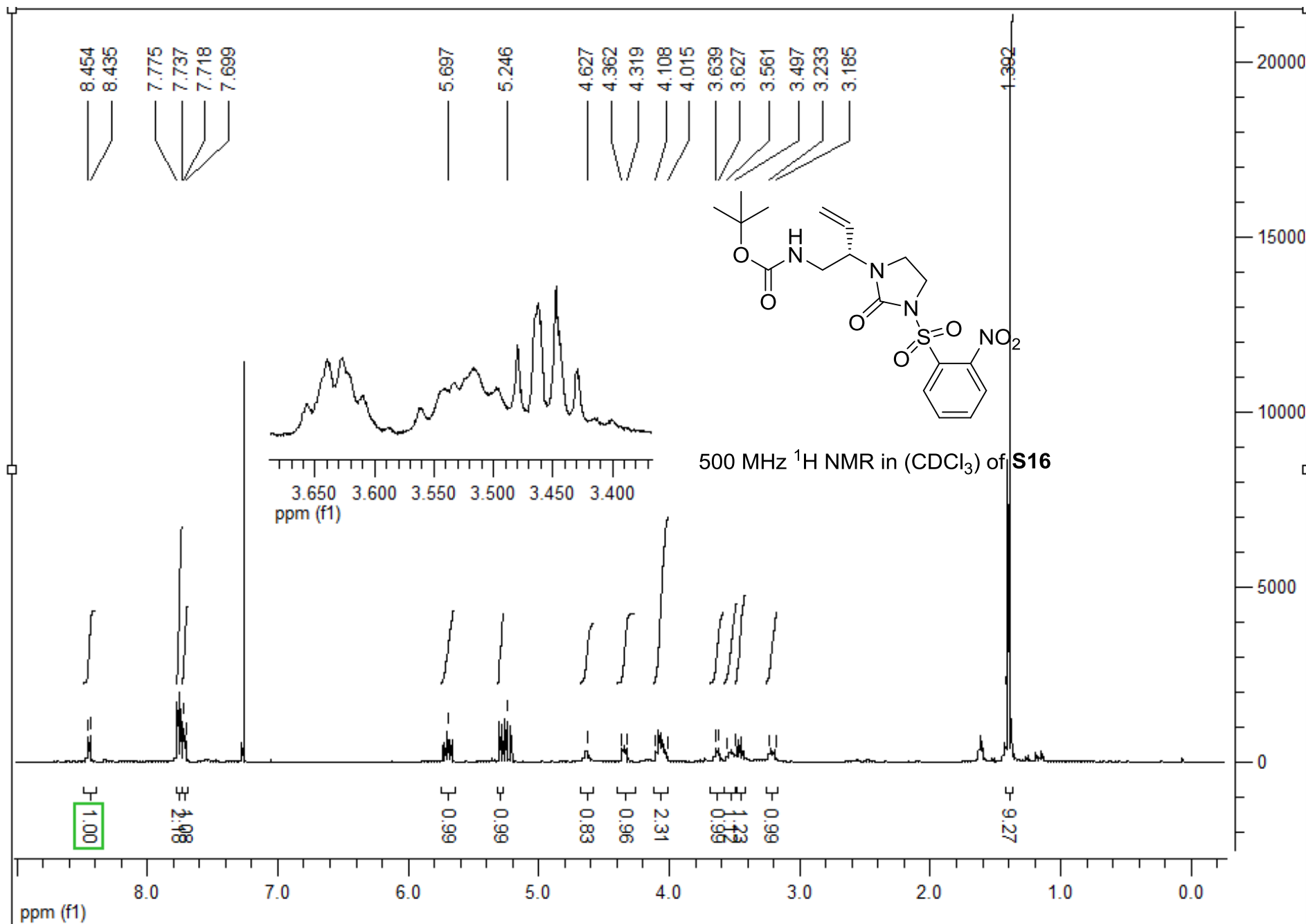
400 MHz ^1H NMR (CDCl_3) of **35**

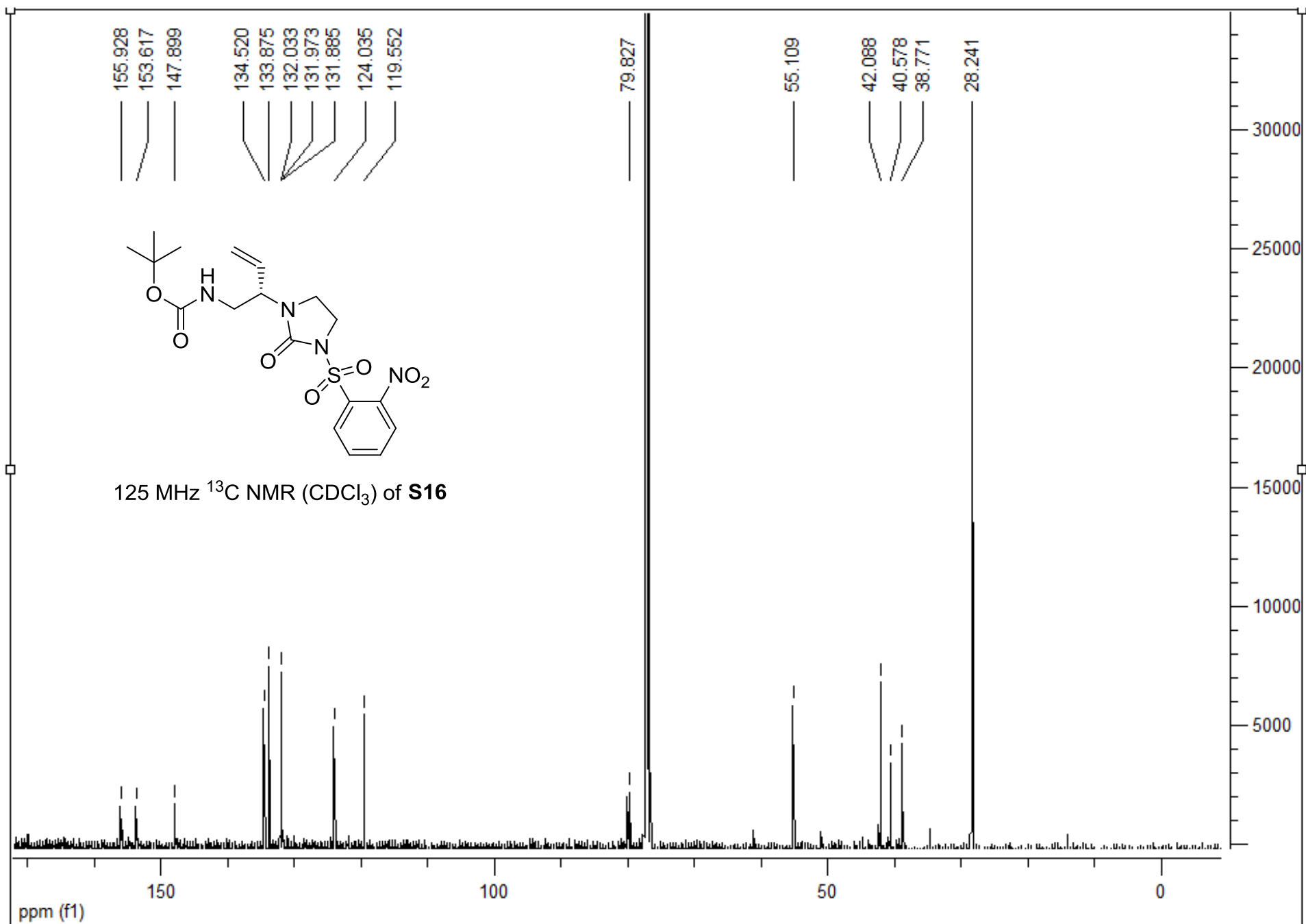


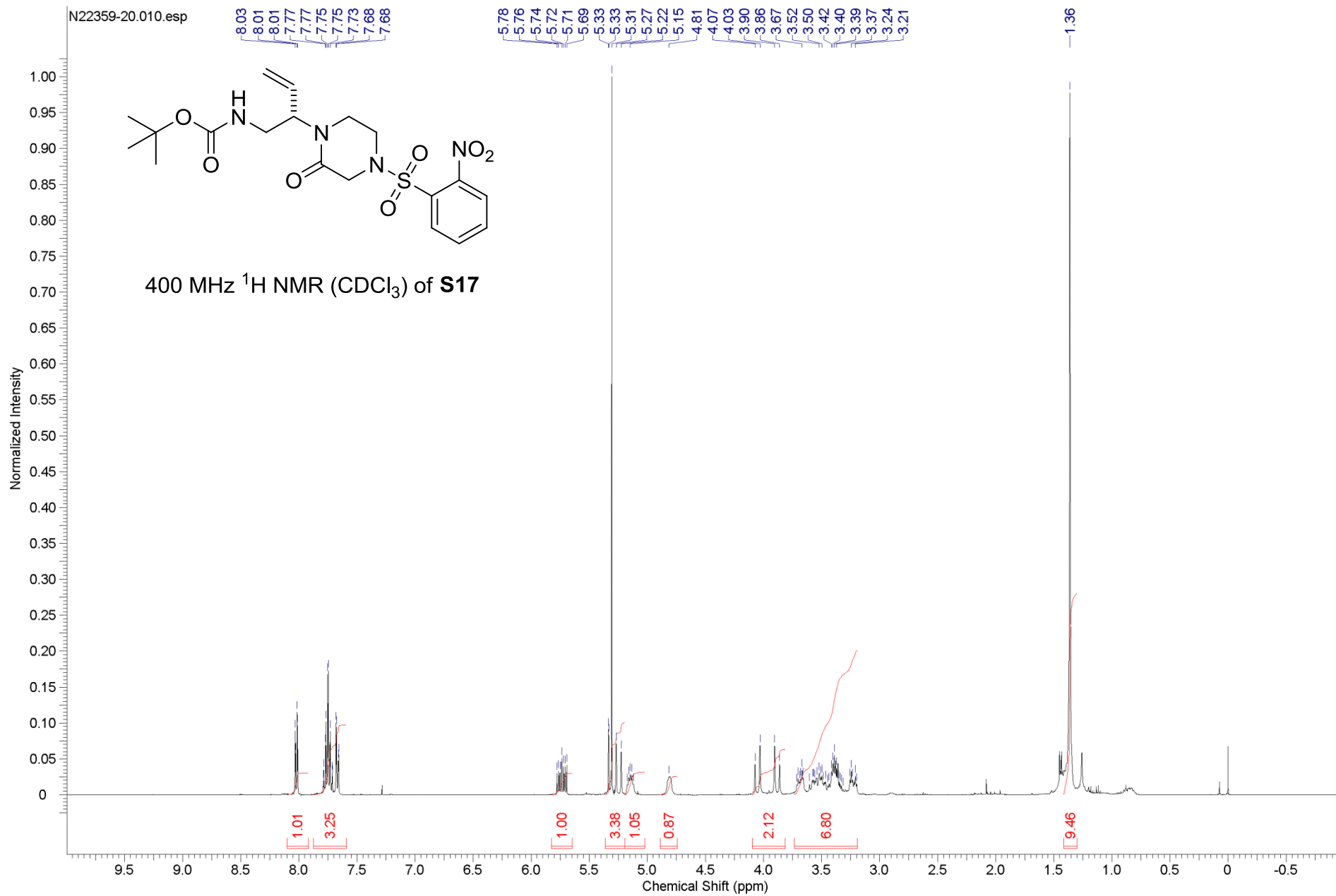


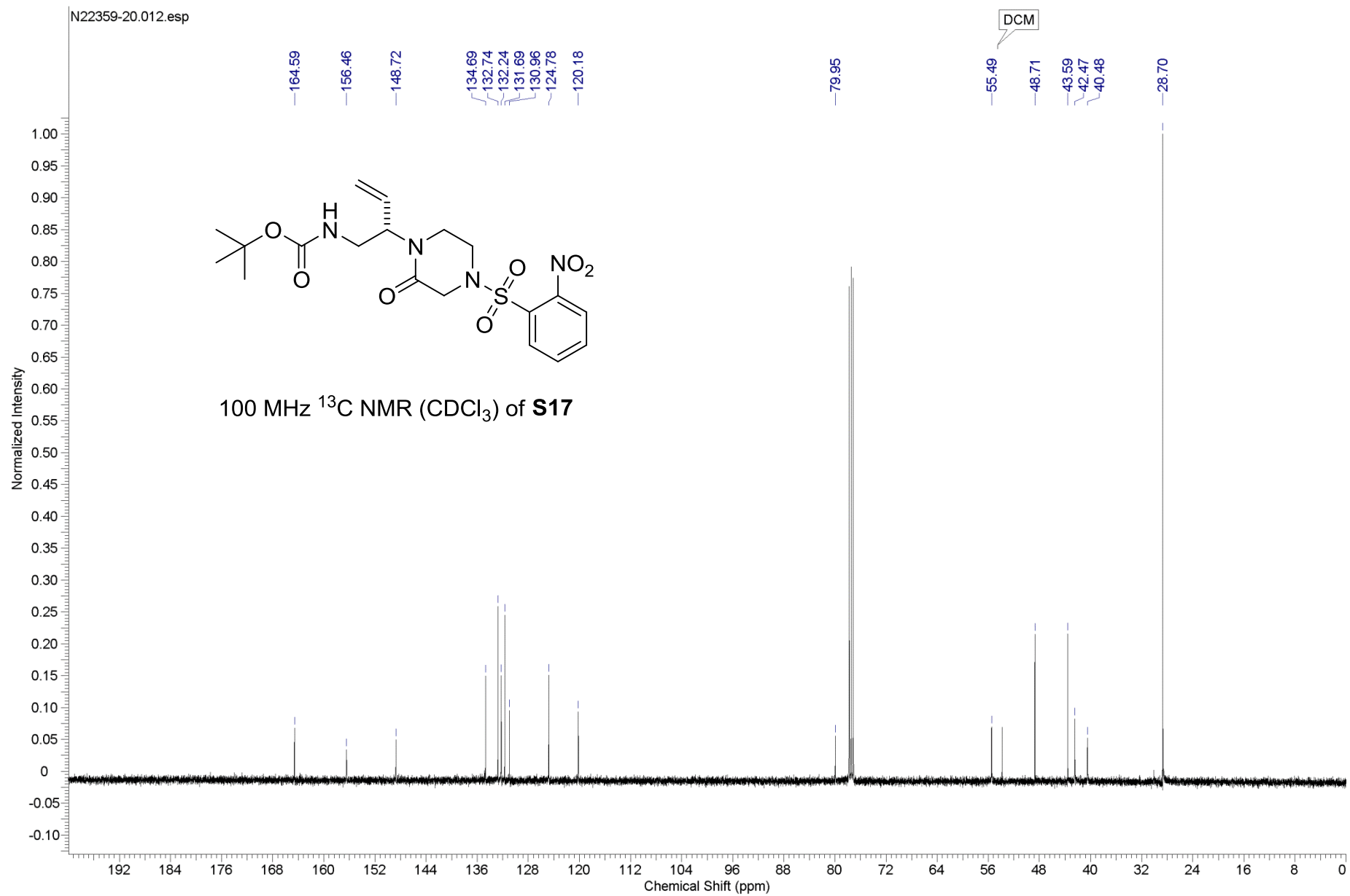
100 MHz ¹³C NMR (CDCl₃) of **35**

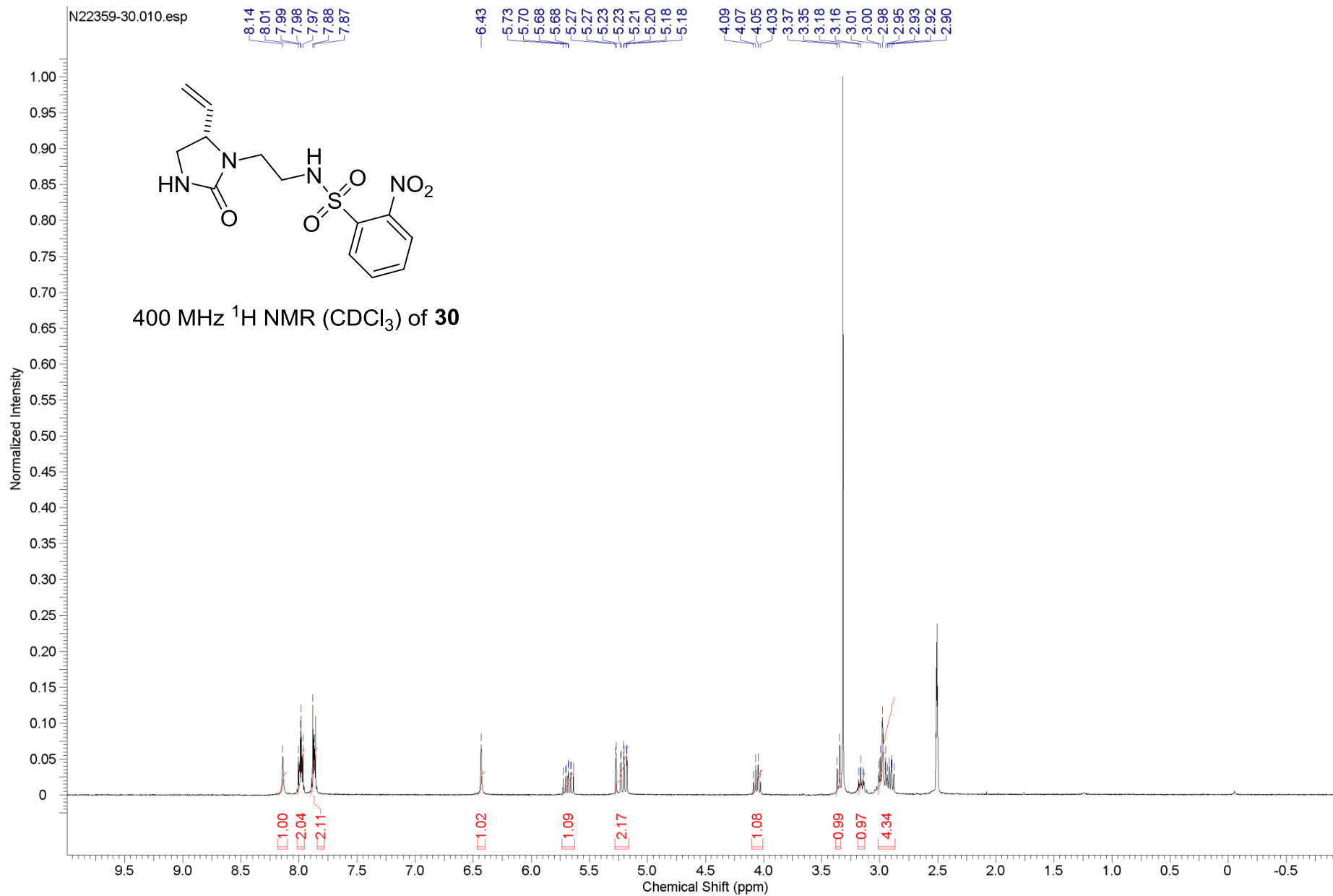






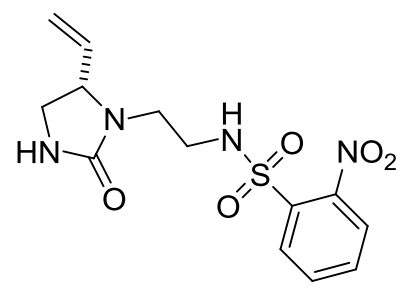




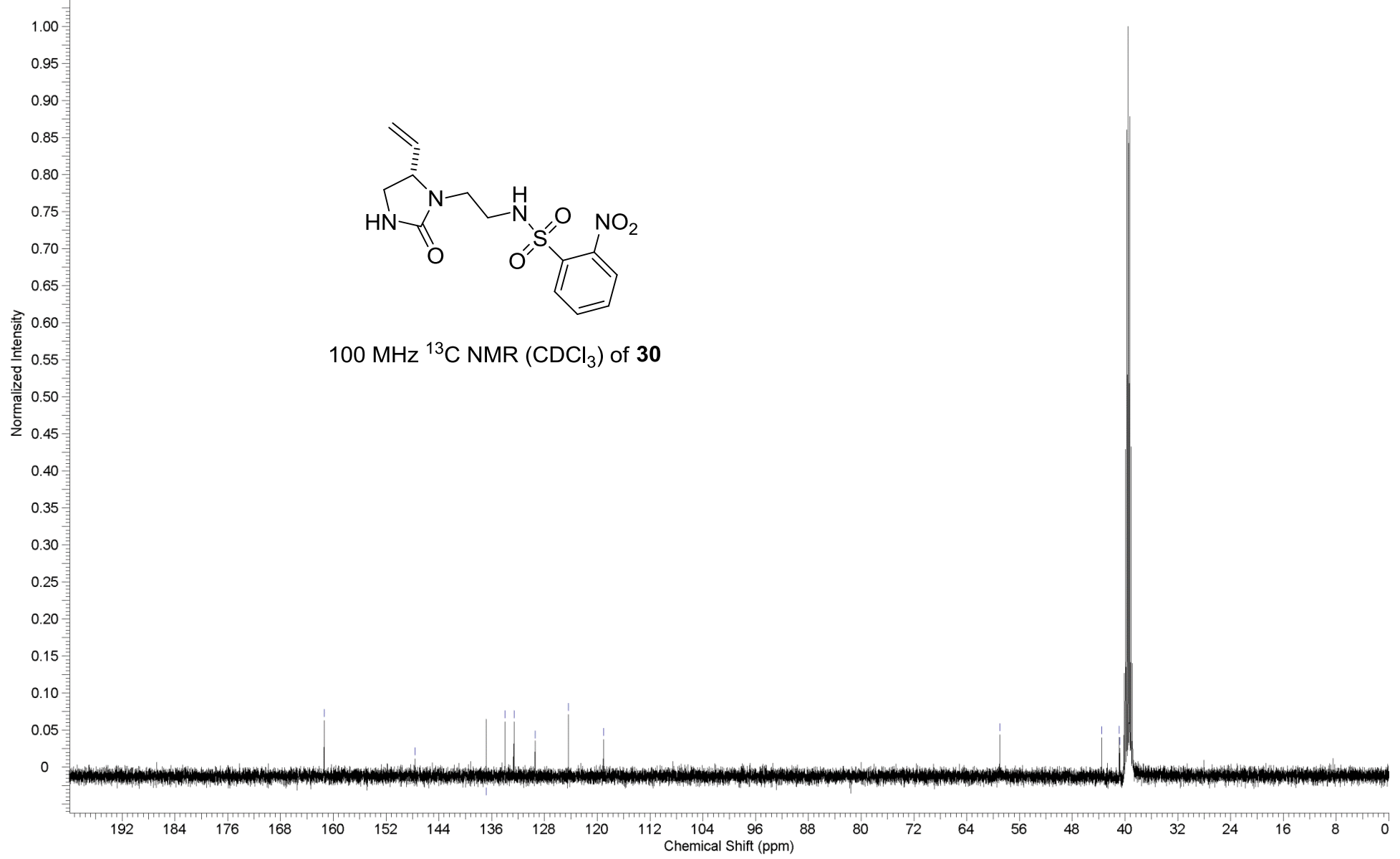


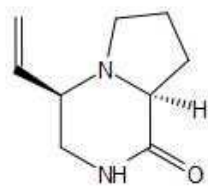
N22359-30.012.esp

- 161.40
- 147.63
- 136.82
- 133.98
- 132.62
- 129.41
- 124.36
- 119.04
- 59.00
- 43.54
- 40.89
- 40.77

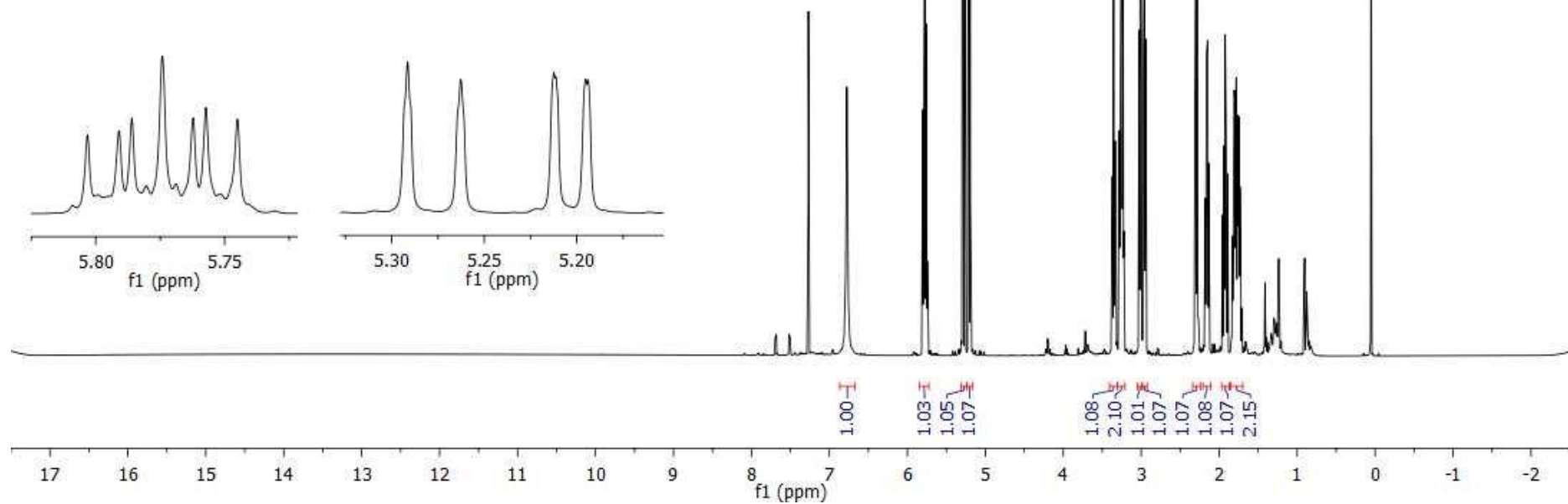
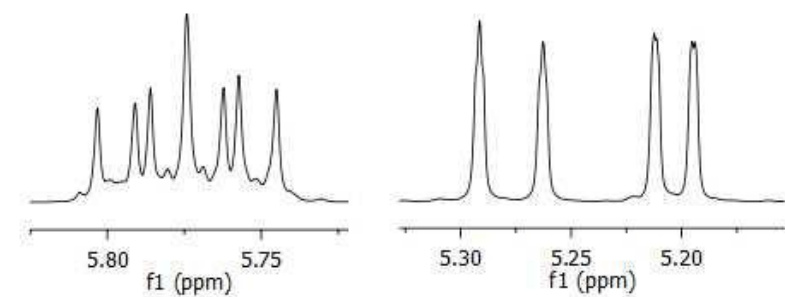
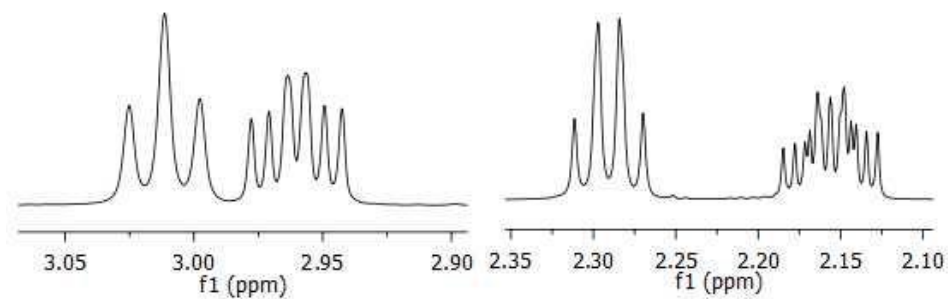
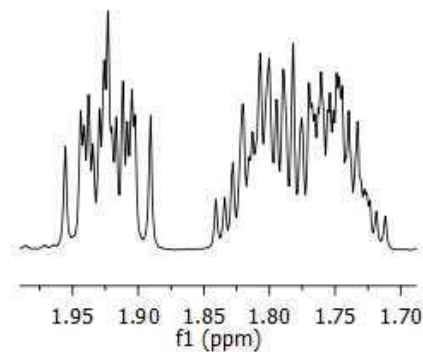
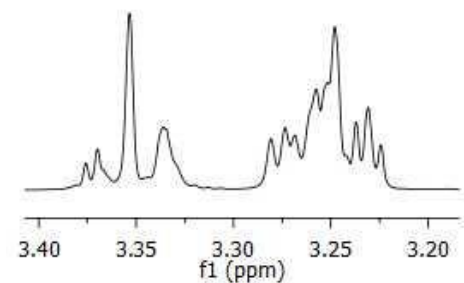


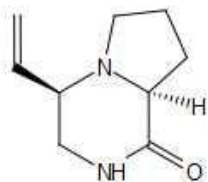
100 MHz ¹³C NMR (CDCl₃) of **30**



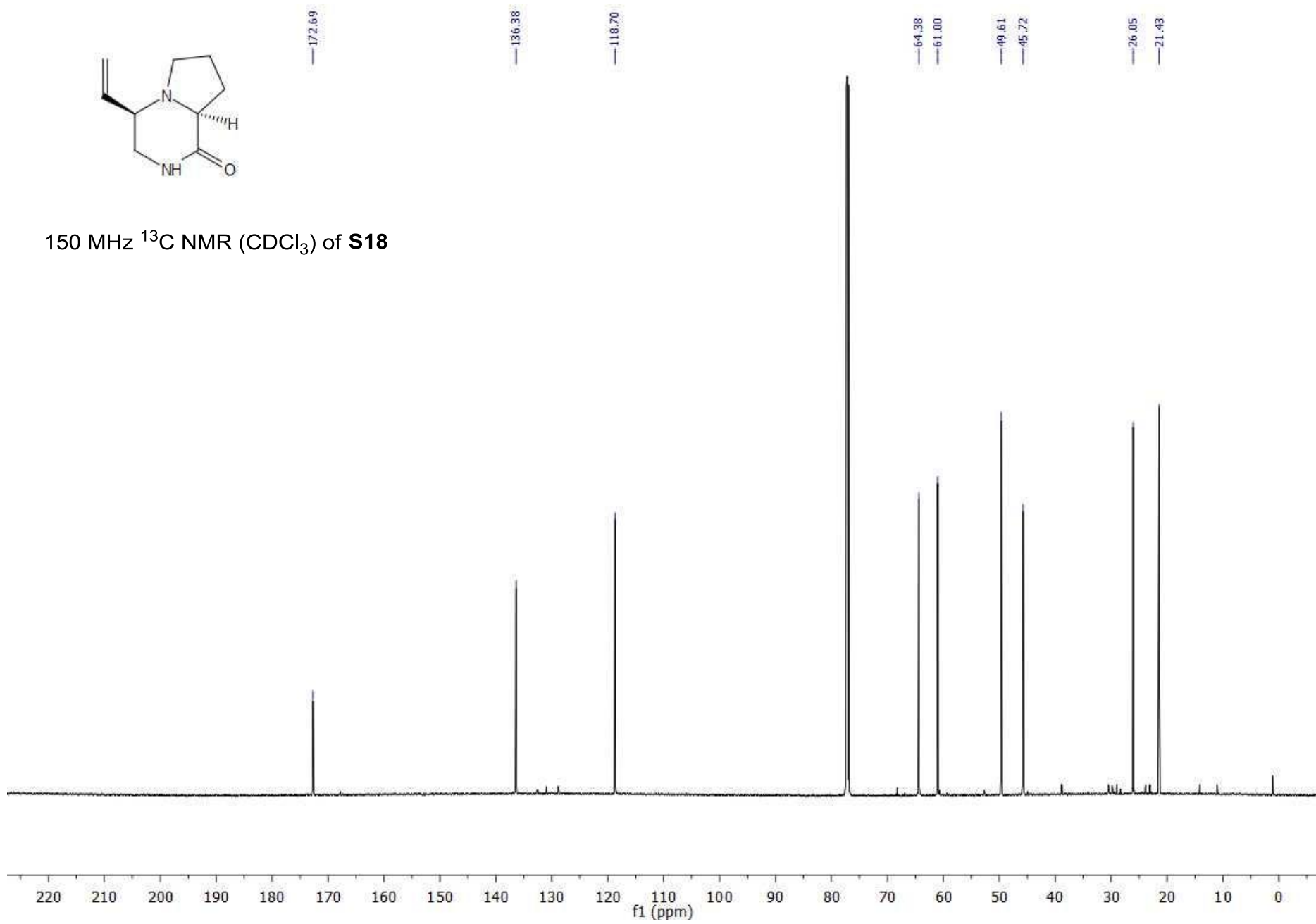


600 MHz ^1H NMR (CDCl_3) of **S18**

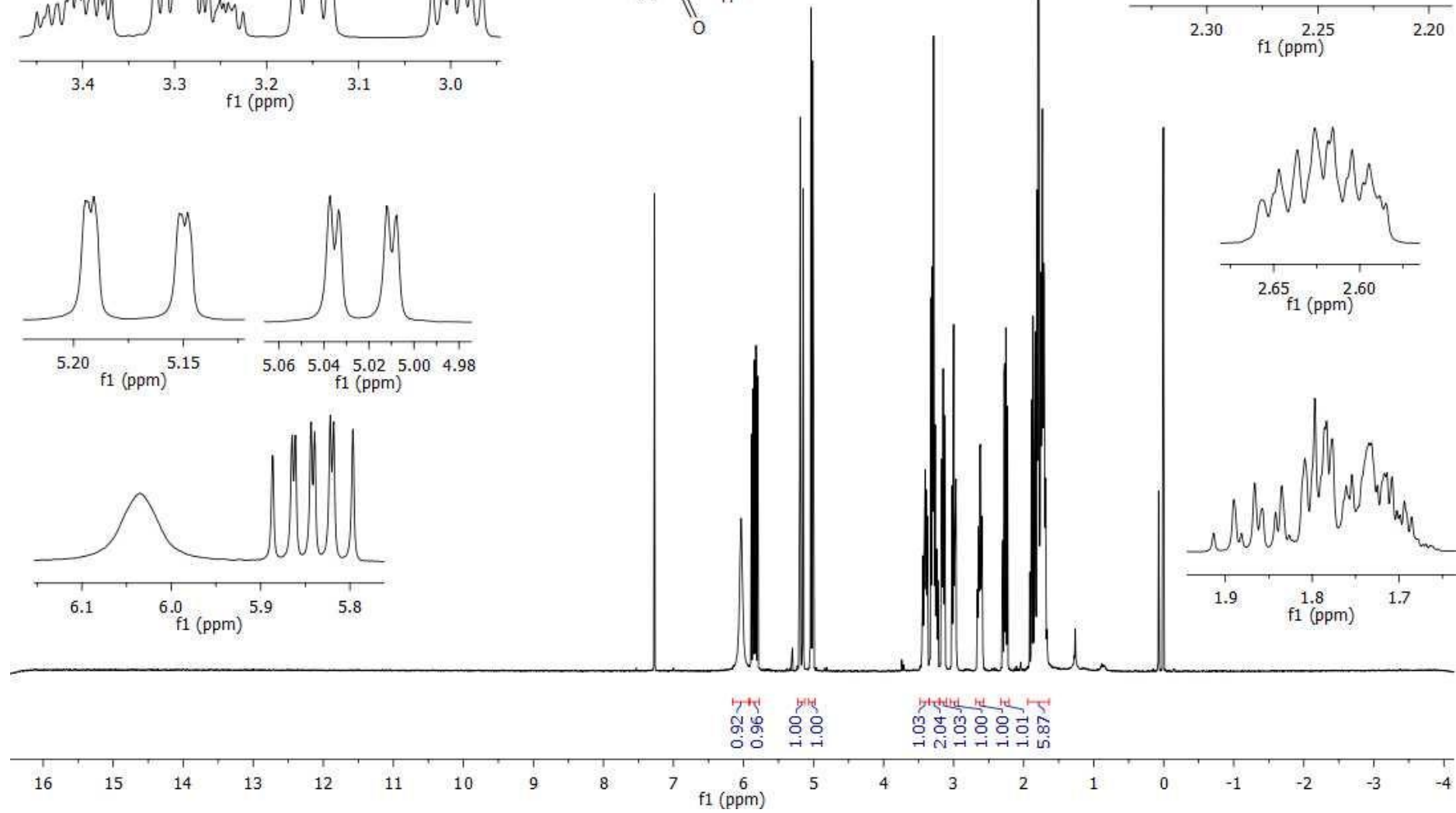
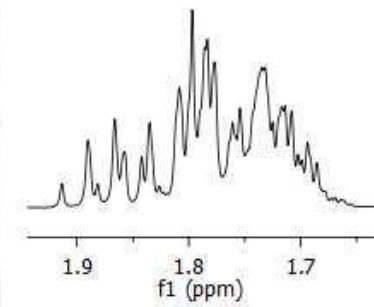
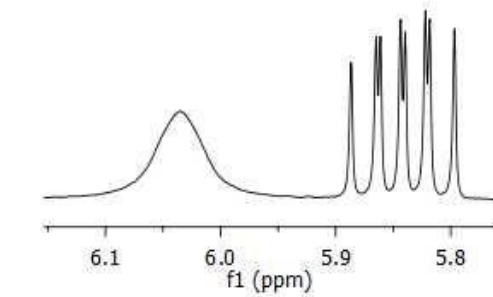
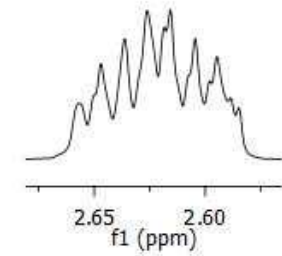
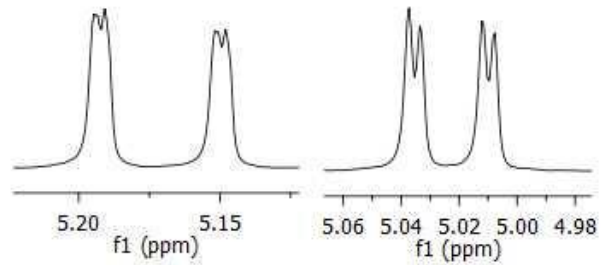
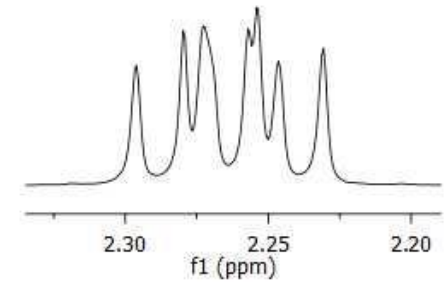
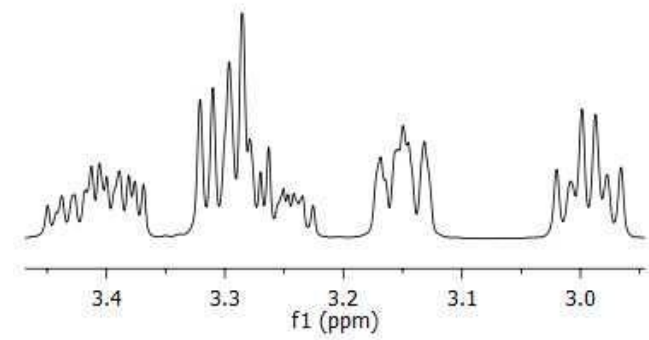
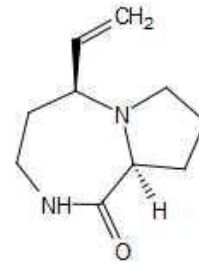


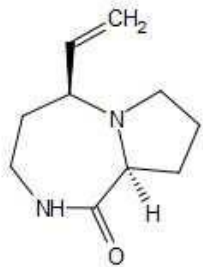


150 MHz ^{13}C NMR (CDCl_3) of **S18**



500 MHz ^1H NMR (CDCl_3) of **38**





100 MHz ^{13}C NMR (CDCl_3) of **38**

