A Unified Lead-Oriented Synthesis of Over Fifty Molecular Scaffolds

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Supporting Information

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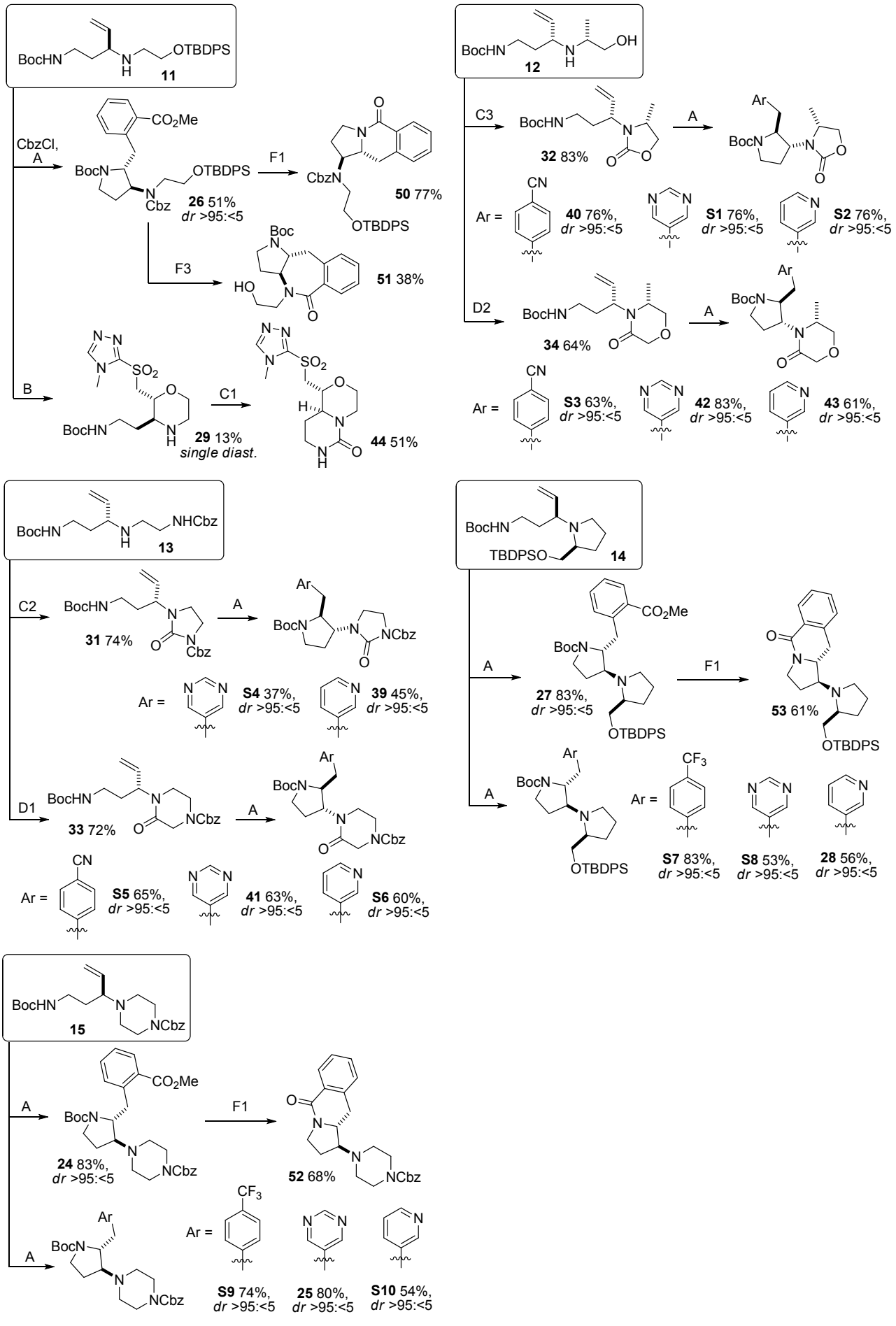
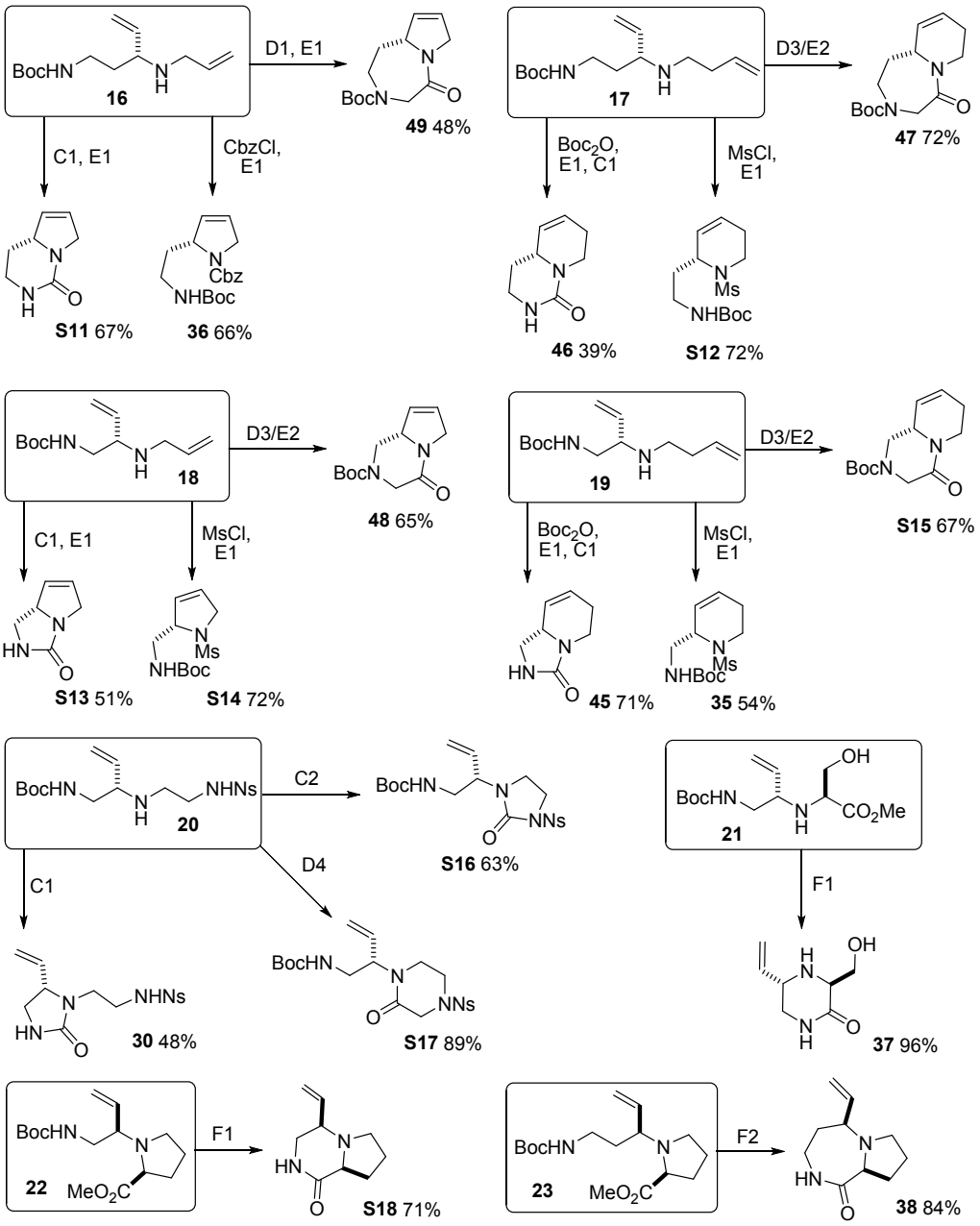

11
CbzCl, A
F1
26 51% dr >95:<5
50 77%
F3
51 38%
B
C1
29 13% single diast.
44 51%
12
C3
32 83%
A
40 76% dr >95:<5
S1 76% dr >95:<5
S2 76% dr >95:<5
D2
34 64%
S3 63% dr >95:<5
42 83% dr >95:<5
43 61% dr >95:<5
13
C2
31 74%
S4 37% dr >95:<5
39 45% dr >95:<5
D1
33 72%
S5 65% dr >95:<5
41 63% dr >95:<5
S6 60% dr >95:<5
14
27 83% dr >95:<5
53 61%
S7 83% dr >95:<5
S8 53% dr >95:<5
28 56% dr >95:<5
15
24 83% dr >95:<5
52 68%
S9 74% dr >95:<5
25 80% dr >95:<5
S10 54% dr >95:<5



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, Cs_2CO_3 (2.5 eq.), 1,4-dioxane, 105 °C;

B: i) NsCl (1.2 eq.), NEt_3 (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.), CH_2Cl_2, rt; v) PhSH (1.2 eq.), DBU (1.5 eq.), MeCN, rt;

C1: CH_2Cl_2/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.), NEt_3 (5.0 eq.), CH_2Cl_2, 0 °C → rt, 6 h then NaH (2.0 eq.), NaI (1.0 eq.), THF, rt;

D2: i) TMSCl (1.1 eq.), NEt_3 (3.0 eq.), CH_2Cl_2, 0 °C → rt, 2 h then bromoacetyl bromide (1.5 eq.), 2 h then20% AcOH (aq), rt; ii) 35% NaOH (aq) (5.0 eq.), Bu_4NSO_4 (0.5 eq.), CH_2Cl_2, 0 °C → rt;

D3/E2: i) Bromoacetyl bromide (1.1 eq.), DIPEA (1.2 eq.), CH_2Cl_2, 0°C → rt; ii) 5 mol% Grubbs II, CH_2Cl_2, 45 °C; iii) NaH (2.0 eq.), THF, rt;

D4: Bromoacetyl bromide (1.0 eq.), NEt_3 (1.1 eq.), $CHCl_3$, –45 °C → rt, 1 h then NEt_3 (72.0 eq.), rt, 16 h.

E1: 5 mol% Grubbs II, CH_2Cl_2, 45 °C;

F1: CH_2Cl_2/TFA, 0 °C → rt, then K_2CO_3 (6.0 equiv), CH_2Cl_2, H_2O, rt;

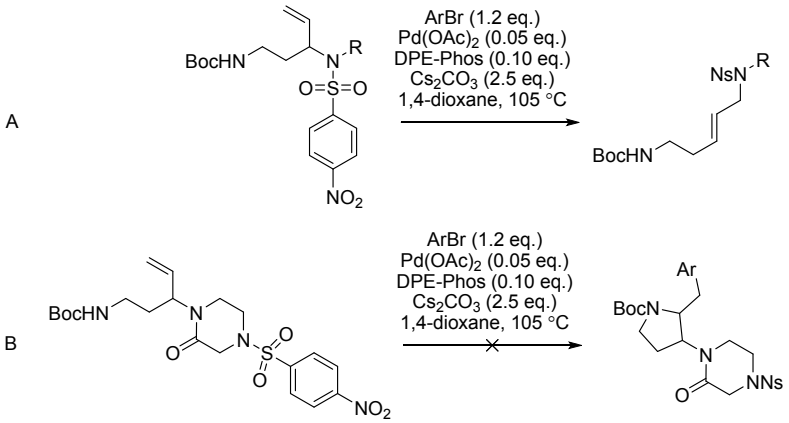
F2: CH_2Cl_2/TFA, 0 °C → rt, then NaO*t*Bu (1.0 eq.), THF, reflux;

F3: H_2, 10% Pd/C (0.1 eq.), ethylenediamine (1.0 eq.), MeOH, rt, then Cs_2CO_3 (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.



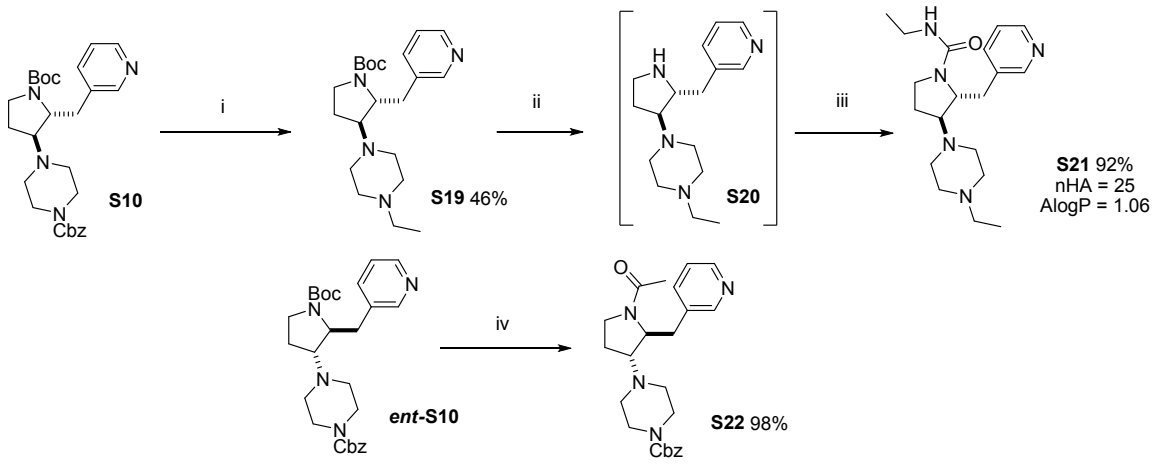
Scheme S2. *Limitations of aminoarylation, Method A.*

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. Underivatised and mono-derivatised 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.

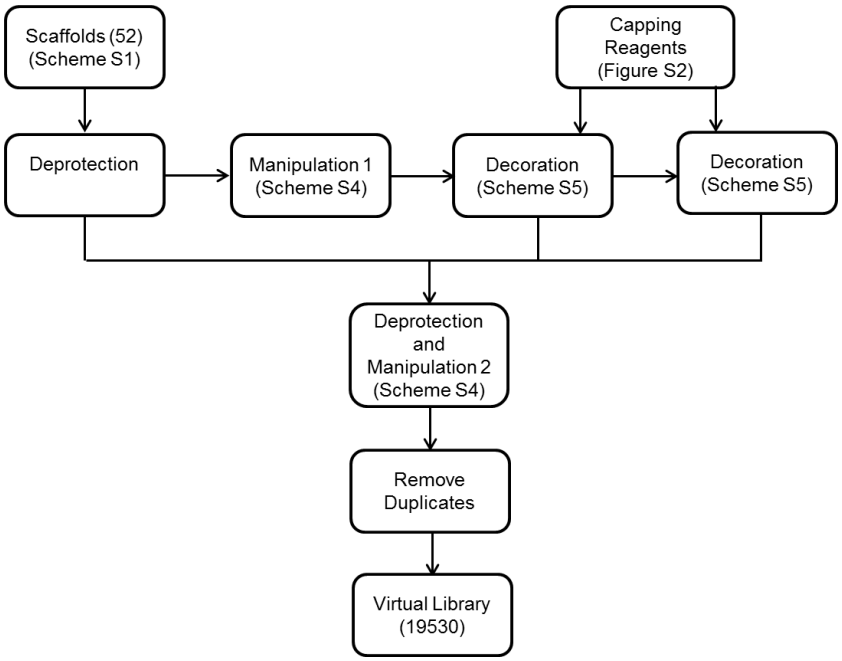
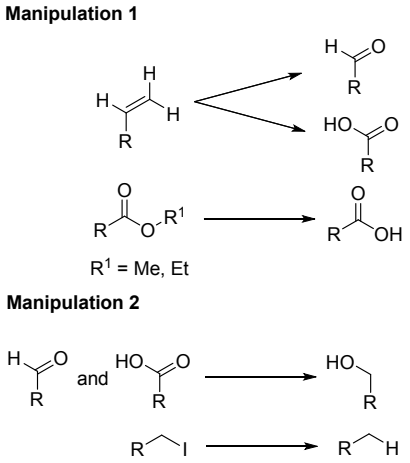
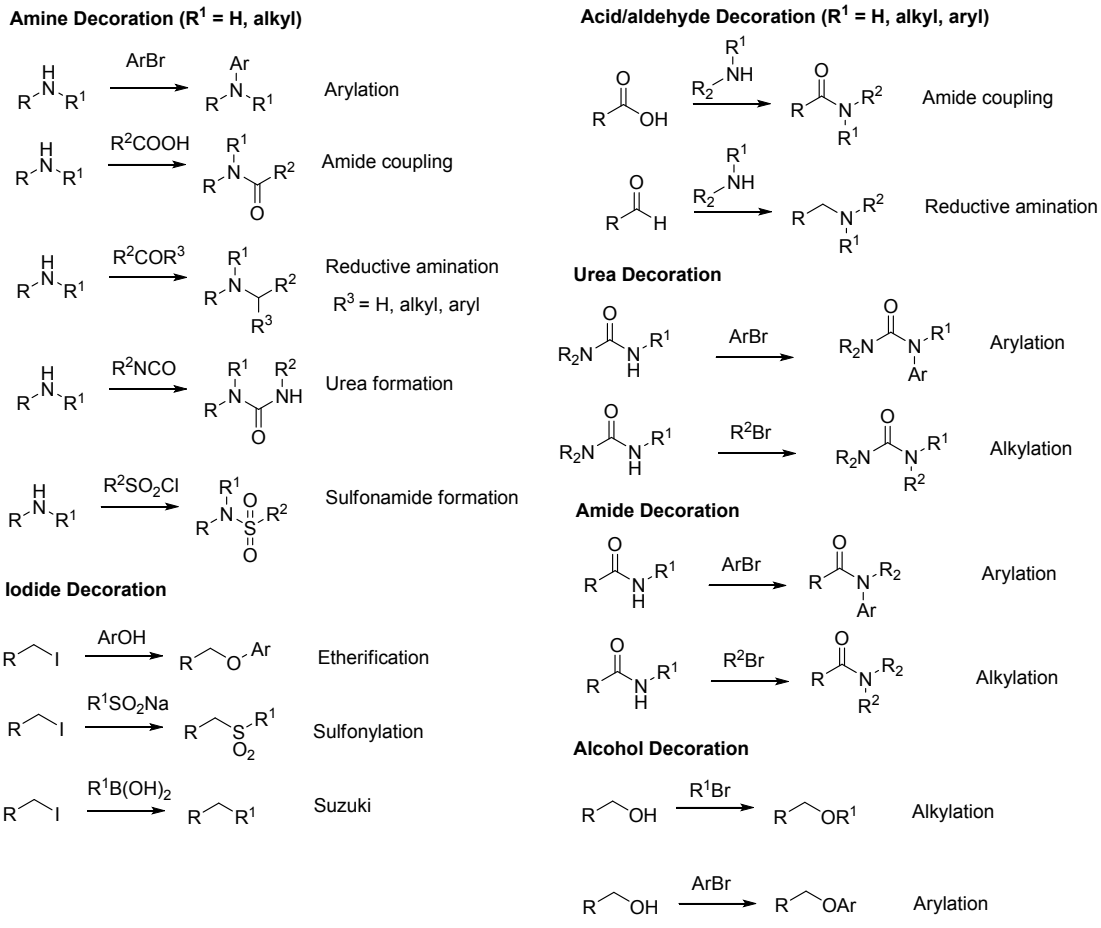


Figure S1. *Overview of the process for the enumeration of the virtual library.*



Scheme S4. *Functional group manipulations of scaffolds (Manipulation 1) and final compounds (Manipulation 2).*



Scheme S5. *Decoration reactions exploited in the enumeration of the virtual library.*

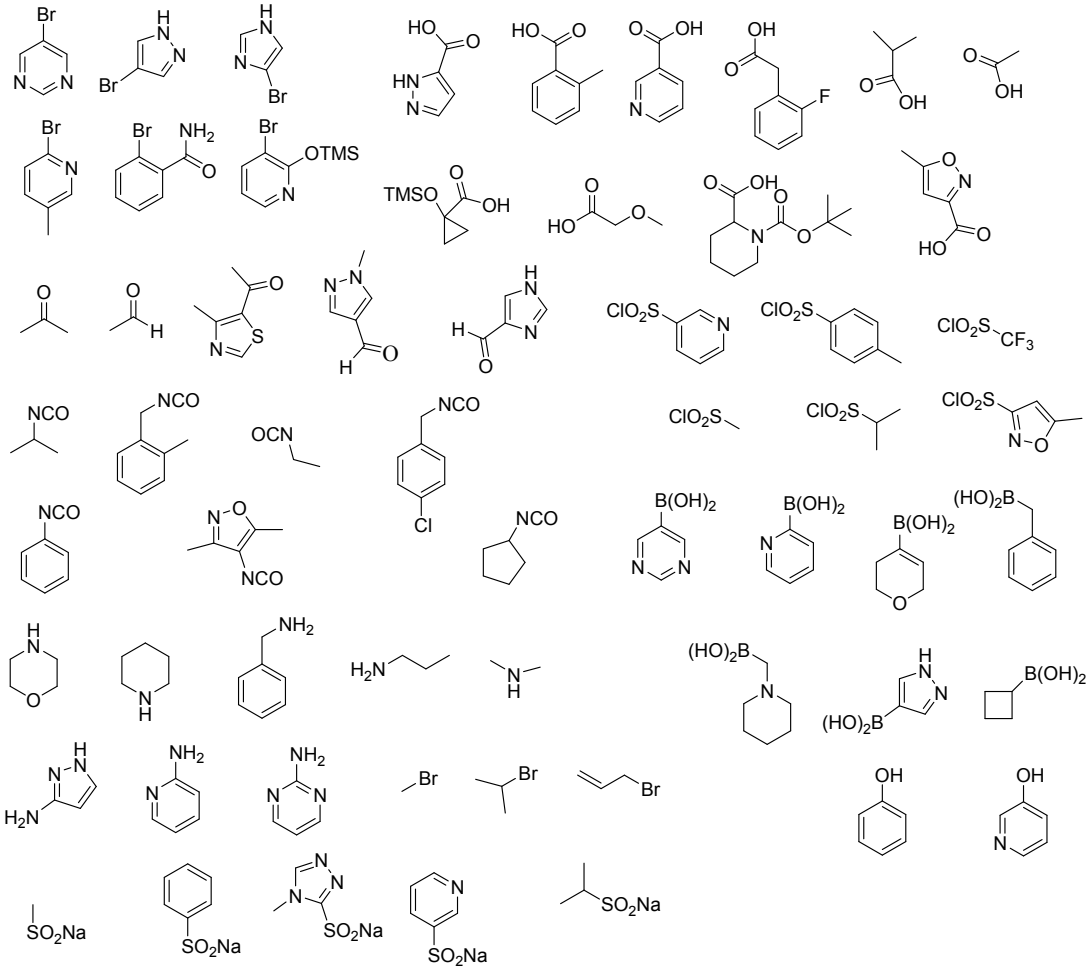


Figure S2. *Capping reagents exploited in the enumeration of the virtual library.*

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 (Fsp^3) was calculated using Dotmatics Vortex (Vortex v2013.12.25046). The data were visualized and analysed using Vortex.

The structural filtering was performed by interrogating two sets of SMARTS definitions with each of the final compounds using the substructure search tool within Pipeline Pilot. The first set contained 240 definitions (Table 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-]),$(C=O)])[#6]1
2-Halopyridine	[F,Cl,Br]-c1n[c,n][c,n][c,n][c,n]1
3halo_pyridazine_2EWG	[#7;R1]1[#6]([$(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-]),$(C=O)])[#6][#7]1
4_pyridone_3_5_EWG	[#7,#8,#16]1~[#6;H]~[#6]([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])~[#6](=O)~[#6]([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])~[#6;H]1
4halo_pyridine_3EWG	[#7;R1]1[#6;!$(c=O);!$(c-N)][#6]([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])[#6]([F,Cl,Br,I])[#6][#6;!$(c=O);!$(c-N)]1
4halo_pyrimidine_2_6EWG	[#7]1[#6]([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])[#7;R1][#6]([F,Cl,Br,I])[#6][#6]1([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])
4halo_pyrimidine_5EWG	[#7]1[#6][#7;R1][#6]([F,Cl,Br,I])[#6]([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])[#6]1
acetal	[#6]-O[CH1](-[#6])O[#6]
acid_halide	[S,C](=[O,S])[F,Br,Cl,I]
acrylate	[CH2]=[C;!$(C-N);!$(C-O)]C(=O)
activated_4mem_ring	[#6]1~[$(C(=O)),$(S(=O))]~[O,S,N]~[$(C(=O)),$(S(=O))]1
activated_acetylene	[$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O))]C#[C;!$(C-N);!$(C-n)]
activated_diazo	[N;!R]([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O))])=[N;!R]([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O))])
activated_S#O_3_ring	C1~[O,S]~[C,N,O,S]1[a,N,O,S]
activated_vinyl_ester	O=COC=[$(C(S(=O)(=O))),$(C(C(F)(F)(F))),$(C(C#N)),$(C(N(=O)(=O))),$(C([N+](=O)[O-])),$(C(C(=O)));!$(C(N))]
activated_vinyl_sulfonate	O(-S(=O)(=O))C=[$(C(S(=O)(=O))),$(C(C(F)(F)(F))),$(C(C#N)),$(C(N(=O)(=O))),$(C([N+](=O)[O-])),$(C(C(=O)));!$(C(N))]
acyclic_imide	[C,c][C;!R](=O)[N;!R][C;!R](=O)[C,c]
acyl_123_triazole	[#7;R1]1~[#7;R1]~[#7;R1](-C(=O)~[#6]~[#6]1
acyl_134_triazole	[#7]1~[#7]~[#6]~[#7](-C(=O)[!N])~[#6]1
acyl_activated_NO	O=C(-[!N])O[$([#7;+]),$(N(C=[O,S,N])(C=[O,S,N]))]
acyl_cyanide	C(=O)-C#N
acyl_imidazole	[C;!$(C-N)](=O)[#7]1[#6;H1,$([#6]([*;!R]))][#7][#6;H1,$([#6]([*;!R]))][#6;H1,$([#6]([*;!R]))]1
acyl_pyrazole	[C;!$(C-N)](=O)[#7]1[#7][#6;H1,$([#6]([*;!R]))][#6;H1,$([#6]([*;!R]))][#6;H1,$([#6]([*;!R]))]1
aldehyde	[C,c][C;H1](=O)
aliphatic_chain_6	[CD2;R0][CD2;R0][CD2;R0][CD2;R0][CD2;R0][CD2;R0]
alkynyl_michael_acceptor1	[#6]-C#CC(=O)-[#6,#7,#8]
alkynyl_michael_acceptor2	[CH1]#CC(=O)-[#6,#7,#8]
allene	*=C=*
alpha_dicarbonyl	C(=O)!@C(=O)
alpha_halo_amine	[F,Cl,Br,I,$(O(S(=O)(=O)))]-[CH,CH2;!$(CF2)]-[N,n]
alpha_halo_carbonyl	C(=O)([CH,CH2][Cl,Br,I,$(O(S(=O)(=O)))])
alpha_halo_EWG	[$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-])]-[CH,CH2]-[Cl,Br,I,$(O(S(=O)(=O)))]
alpha_halo_heteroatom	[N,n,O,S;!$(S(=O)(=O))]-[CH,CH2;!$(CF2)][F,Cl,Br,I,$(O(S(=O)(=O)))]
alpha_halo_heteroatom_tert	[N,n,O,S;!$(S(=O)(=O))]-C([Cl,Br,I,$(O(S(=O)(=O)))])(C)(C)
anhydride	[$(C(=O)),$(C(=S))]-[O,S]-[$(C(=O)),$(C(=S)),$(C(=[N;!R])),$(C(=N(-[C;X4])))]
aromatic_azide c	N=[N+]=[N-]
aryl_phosphonate	P(=O)-[O;!R]-a
aryl_thiocarbonyl	a-[S;X2;!R]-[C;!R](=O)
azide	[$(N#[N+]-[N-]),$([N-]=[N+]=N)]
aziridine_diazirine	[C,N]1~[C,N]~N~1
azo_amino	[N]=[N;!R]-[N]
azo_aryl	c[N;!R;!+]=[N;!R;!+]-c
azo_filter1	[N;!R]=[N;!R]-[N]=[*]
azo_filter2	[N;!$(N-S(=O)(=O));!$(N-C=O)]-[N;!r3;!$(N-S(=O)(=O));!$(N-C=O)]-[N;!$(N-S(=O)(=O));!$(N-C=O)]
azo_filter3	[N;!R]-[N;!R]-[N;!R]
azo_filter4	a-N=N-[N;H2]

azoalkanal	[N;R0]=[N;R0]CC=O
azocyanamide	[N;R0]=[N;R0]C#N
bad_boron	[B-,BH2,BH3,$(B(F)(F))]
bad_cations	[C+,F+,Cl+,Br+,I+,Se+]
b-carbonyl_quaternary_nitrogen	C(=O)CC[N+,n+]
benzhydrol	[OH1]-C(-c1ccccc1)-c2ccccc2
benzidine_like	c([N;!+])1ccc(c2ccc([N;!+])cc2)cc1
benzylic-quaternary_nitrogen	cC[N+]
beta_lactam	C1(=O)~[#6]~[#6]N1
beta_lactone	[#6,#15,#16]1(=O)~[#6]~[#6]~[#8,#16]1
betalactam_EWG	C1(=O)~[#6]~[#6]N1([$(S(=O)(=O)[C,c,O&D2]),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)[C,c,O&D2])])
bis_activated_aryl_ester	O=[C,S]Oc1aaa([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])aa([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])1
bis_keto_olefin	CC(=O)[$([C&H1]),$(C-F),$(C-Cl),$(C-Br),$(C-I)]=[$([C&H1]),$(C-F),$(C-Cl),$(C-Br),$(C-I)]C(=O)C
boron_warhead	[C,c]~[#5]
branched_polycyclic_aromatic	a1(a2aa(a3aaaaa3)aa(a4aaaaa4)a2)aaaaa1
carbazide	O=*N=[N+]=[N-]
carbodiimide_isothiocyanate	N=C=[N,O,S]
carbonyl_halide	O=C[F,Cl,Br,I]
chloramidine	[Cl]C([C&R0])=N
crown_ether	[$([O,S,#7;R1;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][O,S,#7;R1;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][O,S,#7;R1;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18]),$([O,S,#7;R1;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][O,S,#7;R1;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][O,S,#7;R1;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18]),$([O,S,#7;R1;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][O,S,#7;R1;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][CH,CH2;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18][O,S,#7;R1;r9,r10,r11,r12,r13,r14,r15,r16,r17,r18])]
cyanamide	N[CH2]C#N
cyanidin	[OH]c1cc([OH])cc2=[O+]C(=C([OH])Cc21)c3cc([OH])c([OH])cc3
cyano_phosphonate	P(O[A,a])(O[A,a])(=O)C#N
cyanohydrin	[C;X4](-[OH,NH1,NH2,SH])(-C#N)
cyanophosphonate	P(OCC)(OCC)(=O)C#N
cycloheximide	O=C1CCCC(N1)=O
cytochalasin	O=C1NCC2CCCCC21
di_tri_phosphate	P(=O)([OH])OP(=O)[OH]
diamino_sulfide	[N,n]~[S;!R;D2]~[N,n]
diazo_carbonyl	[$(N=N=C~C=O),$(N#N-C~C=O)]
diazonium	a[N+]#N
dicarbonyl_sulfonamide	[$(N(-C(=O))(-C(=O))(-S(=O))),$(n([#6](=O))([#6](=O))([#16](=O)))]
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
flavanoid	O=C2CC(a3aaaaa3)Oa1aaaaa12
four_nitriles	C#N.C#N.C#N.C#N
free_thiol	[SH]
halo_5heterocycle_bis_EWG	[#7,#8,#16]1[#6]([$(S(=O)(=O)),$([F,Cl]),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O))])[#6]([$(S(=O)(=O)),$([F,Cl]),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O))])[#7][#6]1([Cl,Br,I])
halo_acrylate	[$([C;H2]),$([C&H1;$(C-F)]),$([C&H1;$(C-Cl)]),$([C&H1;$(C-Br)]),$([C&H1;$(C-I)]),$(C(F)F),$(C(Cl)Cl),$(C(Br)Br),$(C(I)I),$(C(F)Cl),$(C(F)Br),$(C(F)I),$(C(Cl)Br),$(C(Br)I)](=[$([C&H1;$(C(-C(=O))))]),$(C(F)(C(=O))),$(C(Cl)(C(=O))),$(C(Br)(C(=O))),$(C(I)(C(=O))),$(C(C)(C(=O))),$(C(c)(C(=O)))])
halo_imino	C(=[#7])([Cl,Br,I,$(O(S(=O)(=O))))])
halo_olefin_bis_EWG	C([Cl,Br,I,$(O(S(=O)(=O))))])=C([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])
halo_phenolic_carbonyl	C(=O)Oc1c([Cl,F])[cH1,$(c[F,Cl])]c([F,Cl])[cH1,$(c[F,Cl])]c1([F,Cl])
halo_phenolic_sulfonyl	S(=O)Oc1c([Cl,F])[cH1,$(c[F,Cl])]c([F,Cl])[cH1,$(c[F,Cl])]c1([F,Cl])
halogen_heteroatom	[!C;!c;!H][F,Cl,Br,I]
hemiacetal	[#6]-O[CH1](-[#6])[OH1]
hetero_silyl	[Si]~[!#6]
heteroaryl_sulfonate	a-S(=O)(=O)-O-[$([a&!#6]),$(c[a&!#6]),$(cc[a&!#6]),$(ccc[a&!#6]),$(cccc[a&!#6]),$(ccccc[a&!#6])]
HOBT_ester	O=C(-[!N])O[$(nnn),$([#7]-[#7]=[#7])]
hydrazine2	[#7]!@-N!@=C
hydrazine	[N;X3;!$(N-S(=O)(=O));!$(N-C(F)(F)(F));!$(N-C#N);!$(N-C(=O));!$(N-C(=S));!$(N-C(=N))]-[N;X3;!$(N-S(=O)(=O));!$(N-C(F)(F)(F));!$(N-C#N);!$(N-C(=O));!$(N-C(=S));!$(N-C(=N))]
hydrazothiourea	[N;!R]=NC(=S)N
hydroxamate_warhead	C([N;H1]([O;D1]))=O

hyperval_sulfur	[$([#16&D3]),$([#16&D4])]=,:[#6]
Imine1	[#6;R0]C([#6;R0])=[NH1]
Imine2	[#6;R0][CH1]=[NH1]
isonitrile	[N+]#[C-]
Lawesson_reagent_derivatives	P(=S)(S)S
linear_polycyclic_aromatic_I	[$(a12aaaaa1aa3a(aa(aaaa4)a4a3)a2),$(a12aaaaa1aa3a(aaa4a3aaaa4)a2),$(a12aaaaa1a(aa5)a3a(aaa4a3a5aaa4)a2)]
linear_polycyclic_aromatic_II	[$(a12aaaa4a1a3a(aaaa3aa4)aa2),$(a12aaaaa1a3a(aaa4a3aaaa4)aa2),$(a1(a(aaaa4)a4a3a2aaaa3)a2aaaa1)]
maleimide_etc	[$([C;H1]),$(C(-[F,Cl,Br,I]))]1=[$([C;H1]),$(C(-[F,Cl,Br,I]))]C(=O)[N,O,S]C(=O)1
meldrums_acid_etc	O=C1OC(C)(C)OC(C1)=O
metal	[$([Ru]),$([Mg]),$([Rh]),$([Se]),$([se]),$([Pd]),$([Sc]),$([Bi]),$([Sb]),$([Ag]),$([Ti]),$([Al]),$([Cd]),$([V]),$([In]),$([Cr]),$([Sn]),$([Mn]),$([La]),$([Fe]),$([Er]),$([Tm]),$([Yb]),$([Lu]),$([Hf]),$([Ta]),$([W]),$([Re]),$([Co]),$([Os]),$([Ni]),$([Ir]),$([Cu]),$([Zn]),$([Ga]),$([Ge]),$([As]),$([as]),$([Y]),$([Zr]),$([Nb]),$([Ce]),$([Pr]),$([Nd]),$([Sm]),$([Eu]),$([Gd]),$([Tb]),$([Dy]),$([Ho]),$([Pt]),$([Au]),$([Hg]),$([Tl]),$([Pb]),$([Ac]),$([Th]),$([Pa]),$([Mo]),$([U]),$([Tc]),$([Te]),$([Po]),$([At])]
michael_acceptor6	[#6,#7]-&!@[#6](=&!@[CH])-&!@C(=O)-&!@[C,N,O,S]
michael_acceptor5	N#CC(=C)C#N
michael_acceptor_misc	O=C1[O,N]C~[N,C]C1=[C,N]
michael_acceptor_misc2	*~\C=C1/CC2=CC=CC=C2N1
michael_acceptor_vinyl2	[CH2]=C-C(=O)-[#6,#7,#8]
misc_10_carbon_sb_chain	[C;!R]-[C;!R]-[C;!R]-[C;!R]-[C;!R]-[C;!R]-[C;!R]-[C;!R]-[C;!R]-[C;!R]
misc_2_free_phos	P([O;D1])=O.P([O;D1])=O
misc_2_N_quats	[N,n;H0;+;!$(N~O);!$(n~O)].[N,n;H0;+;!$(N~O);!$(n~O)]
misc_2_sulfonic_acid	[C,c]S(=O)(=O)[O;D1].[C,c]S(=O)(=O)[O;D1]
misc_3_COOH	C(=O)[O;D1].C(=O)[O;D1].C(=O)[O;D1]
misc_3_iodine	[#53].[#53].[#53]
misc_4_basic_N	[N;!$(N(=[N,O,S,C]));!$(N(S(=O)(=O)));!$(N(C(F)(F)(F)));!$(N(C#N));!$(N(C(=O)));!$(N(C(=S)));!$(N(C(=N)));!$(N(#C));!$(N-c)].[N;!$(N(=[N,O,S,C]));!$(N(S(=O)(=O)));!$(N(C(F)(F)(F)));!$(N(C#N));!$(N(C(=O)));!$(N(C(=S)));!$(N(C(=N)));!$(N(#C));!$(N-c)].[N;!$(N(=[N,O,S,C]));!$(N(S(=O)(=O)));!$(N(C(F)(F)(F)));!$(N(C#N));!$(N(C(=O)));!$(N(C(=S)));!$(N(C(=N)));!$(N(#C));!$(N-c)].[N;!$(N(=[N,O,S,C]));!$(N(S(=O)(=O)));!$(N(C(F)(F)(F)));!$(N(C#N));!$(N(C(=O)));!$(N(C(=S)));!$(N(C(=N)));!$(N(#C));!$(N-c)]
misc_4_nitro	[$([N+](=O)[O-]),$(N(=O)=O)].[$([N+](=O)[O-]),$(N(=O)=O)].[$([N+](=O)[O-]),$(N(=O)=O)].[$([N+](=O)[O-]),$(N(=O)=O)]
misc_5_phenolic_OH	a[O;D1].a[O;D1].a[O;D1].a[O;D1].a[O;D1]
misc_7_aliphatic_OH	C[O;D1].C[O;D1].C[O;D1].C[O;D1].C[O;D1].C[O;D1].C[O;D1]
misc_7_total_hal	[Cl,Br,I].[Cl,Br,I].[Cl,Br,I].[Cl,Br,I].[Cl,Br,I].[Cl,Br,I].[Cl,Br,I]
misc_8_CF2_or_CH2	[CH2,$(CF2);R0][CH2,$(CF2);R0][CH2,$(CF2);R0][CH2,$(CF2);R0][CH2,$(CF2);R0][CH2,$(CF2);R0][CH2,$(CF2);R0][CH2,$(CF2);R0]
monensin	O1CCCCC1C2CCCO2
monofluoroacetate	[C;H2](F)C(=O)[O,N,S]
nitrate	[#6]-O-[N+](=O)[O-]
nitro_aromatic	(a-[N+](=O)[O-].a-[N+](=O)[O-])
nitroalkane	C[N+](=O)[O-]
nitrone	[C;!R]=[N+][O;D1]
nitrosamine	N-[N;X2](=O)
nitroso	[N&D2](=O)
NO_phosphonate	P(=O)ON
ortho_hydroiminoquinone	c1c([N;D1])c([N;D1])c[cH1][cH1]1
ortho_hydroquinone	a1c([O,S;D1])c([O,S;D1])a[cH1][cH1]1
ortho_nitrophenyl_carbonyl	[#6]1(-O-[C;!R](=[O,N;!R]))[#6]([$(N(=O)(=O)),$([N+](=O)[O-])])[#6][#6][#6][#6]1
ortho_quinone	[CH1,$(C(-[Cl,Br,I]))]1=CC(=[O,N,S;!R])C(=[O,N,S])C=[CH1,$(C(-[Cl,Br,I]))]1
oxaziridine	C1~[O,S]~N1
oxime	[$(C=N[O;D1]);!$(C=[N+])][#6][#6]
oxonium	[o+,O+]
P_S_halide	[P,S][F,Cl,Br,I]
para_hydroiminoquinone	a1[cH1]c([N;D1])[cH1]ac([N;D1])1
para_hydroquinone	a1[cH1]c([O,S;D1])[cH1]ac([O,S;D1])1
para_nitrophenyl_ester	[#6]1(-O(-[C;!R](-[!N])(=[O,N;!R])))[#6][#6][#6]([$(N(=O)(=O)),$([N+](=O)[O-])])[#6][#6]1
para_quinone	[CH1,$(C(-[Cl,Br,I]))]1=[CH1,$(C(-[Cl,Br,I]))]C(=[O,N,S])[CH1,$(C(-[Cl,Br,I]))]=[CH1,$(C(-[Cl,Br,I]))]C1(=[O,N,S])
paraquat_like	[#6]1[#6][#6]([#6]2[#6][#6][#7;+][#6][#6]2)[#6][#6][#7;+]1
pentafluorophenylester	C(=O)Oc1c(F)c(F)c(F)c(F)c1(F)
perchloro_cp	C1(Cl)(Cl)C(Cl)C(Cl)=C(Cl)C1(Cl)
perhalo_dicarbonyl_phenyl	c1(C=O)c([Br,Cl,I])c([Br,Cl,I])c([Br,Cl,I])c([Br,Cl,I])c1(C=O)
perhalo_ketone	O=CC(-[F,Cl,Br,I])(-[F,Cl,Br,I])-[F,Cl,Br,I]
perhalo_phenyl	c1c([F,Br,Cl,I])c([F,Br,Cl,I])c([F,Br,Cl,I])c([F,Br,Cl,I])c1([F,Br,Cl,I])
peroxide	[#8]~[#8]
phenolate_bis_EWG	O=[C,S]Oc1aaa([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])aa([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])1
phos_serine_warhead	NC(COP(O)(O)=O)C(O)=O
phos_threonine_warhead	NC(C(C)OP(O)(O)=O)C(O)=O
phos_tyrosine_warhead	NC(Cc1ccc(OP(O)(O)=O)cc1)C(O)=O

phosphite	[c,C]-[P;v3]
phosphonate_esters	COP(=O)(=O)[C,c]
phosphonium	[#15;+]~[!O]
phosphoramide	NP(=O)(N)N
phosphorane	C=P
phosphorous_nitrogen_bond	[#15]~[N,n]
phosphorus_phosphorus_bond	P~P
phosphorus_sulfur_bond	P~S
polyacidic4	[C,S,P](=O)[OH].[C,S,P](=O)[OH].[C,S,P](=O)[OH].[C,S,P](=O)[OH]
polyazoanthracene	c12:[c,n]:[c,n]:[c,n]:[c,n]:c1[c,n]c3:[c,n]:[c,n]:[c,n]:[c,n]:c3[c,n]2
polyazophenanthrene	c12:[c,n]:[c,n]:[c,n]:[c,n]:c1:[c,n]:[c,n]:c3:[c,n]:[c,n]:[c,n]:[c,n]:c23
polyene	C=[C;!R][C;!R]=[C;!R][C;!R]=[C;!R]
polyhalo_phenol_a	c1c([O;D1])c(-[Cl,Br,I])c(-[Cl,Br,I])cc1.c1c([O;D1])c(-[Cl,Br,I])c(-[Cl,Br,I])cc1
polyhalo_phenol_b	c1c([O;D1])c(-[Cl,Br,I])cc(-[Cl,Br,I])c1.c1c([O;D1])c(-[Cl,Br,I])cc(-[Cl,Br,I])c1
polyhalo_phenol_c	c1c([O;D1])ccc(-[Cl,Br,I])c(-[Cl,Br,I])1.c1c([O;D1])ccc(-[Cl,Br,I])c(-[Cl,Br,I])1
polyhalo_phenol_d	c(-[Cl,Br,I])1c([O;D1])c(-[Cl,Br,I])ccc1.c(-[Cl,Br,I])1c([O;D1])c(-[Cl,Br,I])ccc1
polyhalo_phenol_e	c1c([O;D1])ccc(-[Cl,Br,I])c(-[Cl,Br,I])1.c1c([O;D1])ccc(-[Cl,Br,I])c(-[Cl,Br,I])1
polysulfide	[S;D2]-[S;D2]-[S;D2]
porphyrin	[#6;r16,r17,r18]~[#6]1~[#6]~[#6]~[#6](~[#6])~[#7]1
primary_halide_sulfate	[CH2][Cl,Br,I,$(O(S(=O)(=O)[!$(N);!$([O&D1])]))]
propiolactone	C1(=O)OCC1
quat_N_acyl	[N,n;+]!@C(=O)
quat_N_N	[N,n;R;+]!@[N,n]
quaternary_C_Cl_I_P_S	[C+,Cl+,I+,P+,S+]
quaternary_nitroxy	C[N+](-[O-])(C)C
quinone_methide	[#6;!$([#6](-[N,O,S]))]1=[#6;!$([#6](-[N,O,S]))][#6](=[#6])[#6;!$([#6](-[N,O,S]))]=[#6;!$([#6](-[N,O,S]))][#6]1(=[O,N,S])
rhodanine	C(=C)1SC(=S)NC(=O)1
secondary_halide_sulfate	[CH;!$(C=C)][Cl,Br,I,$(O(S(=O)(=O)[!$(N);!$([O&D1])]))]
squalestatin	C12OCCC(O1)CC2
sulf_D2_nitrogen	[S;D2](-[N;!$(N(=C));!$(N(-S(=O)(=O)));!$(N(-C(=O)))])
sulf_D2_oxygen_D2	[S;D2][O;D2]
sulf_D3_nitrogen	[S;D3](-N)(-[c,C])(-[c,C])
sulfite_sulfate_ester	[C,c]OS(=O)O[C,c]
sulfonate	COS(=O)(=O)[C,c]
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]Oc1a([$(S(=O)(=O)),F,$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])a([$(S(=O)(=O)),F,$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])a([$(S(=O)(=O)),F,$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])aa1),$(O=[C,S]Oc1a([$(S(=O)(=O)),F,$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])a([$(S(=O)(=O)),F,$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])aaa([$(S(=O)(=O)),F,$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])1),$(O=[C,S]Oc1a([$(S(=O)(=O)),F,$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-

	]),$(C(=O)O),$(C(=O)N)])aa([$(S(=O)(=O)),F,$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])a([$(S(=O)(=O)),F,$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])a1),$(O=[C,S]Oc1a([$(S(=O)(=O)),F,$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])aa([$(S(=O)(=O)),F,$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])aa([$(S(=O)(=O)),F,$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O)O),$(C(=O)N)])1)]
trisub_bis_act_olefin	[[CH;!R];!$(C-N)]=C([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O))])([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C(=O))])
unacceptable_atoms1	[!#6;!#7;!#8;!#16;!#1;!#3;!#9;!#11;!#12;!#15;!#17;!#19;!#20;!#30;!#35]
unacceptable_atoms2	[!#6;!#7;!#8;!#16;!#1;!#3;!#9;!#11;!#12;!#15;!#17;!#19;!#20;!#30;!#35;!#53]
vinyl_carbonyl_EWG	[C;!R]([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])([$(S(=O)(=O)),$(C(F)(F)(F)),$(C#N),$(N(=O)(=O)),$([N+](=O)[O-]),$(C=O)])=[C;!R]([C;!R](=O))([!$([#8]);!$([#7])])
vinyl_sulfone	O=S([#6]=[#6])([#6]=[#6])=O
vinyloxazole	[N,C]=CC1=COC=N1
2,3,4-trihydroxyphenyl	c([OH])c([OH])c([OH])

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

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

Table 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

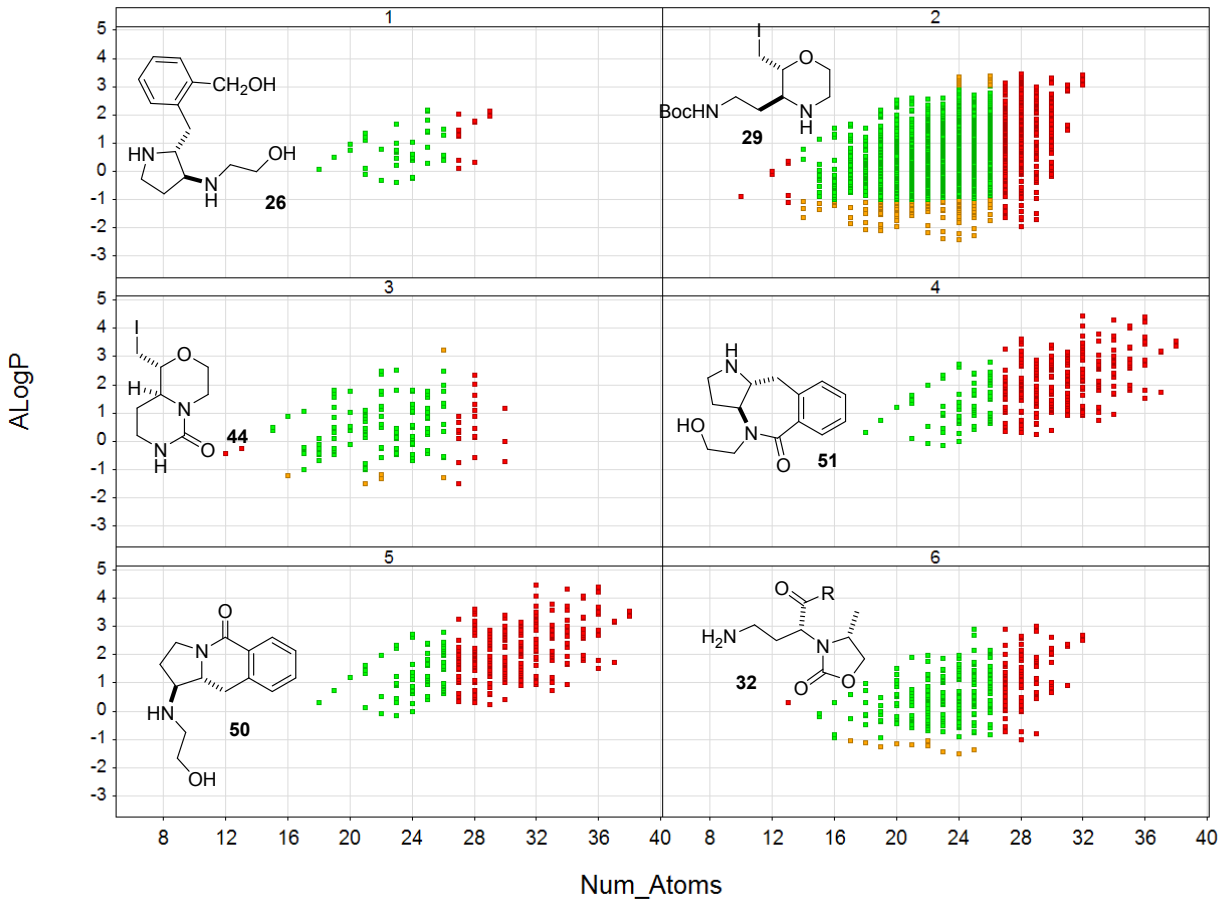
Table S3. *Undesirable functionality filters used in the 'HTS Filter' embedded in Pipeline Pilot.*

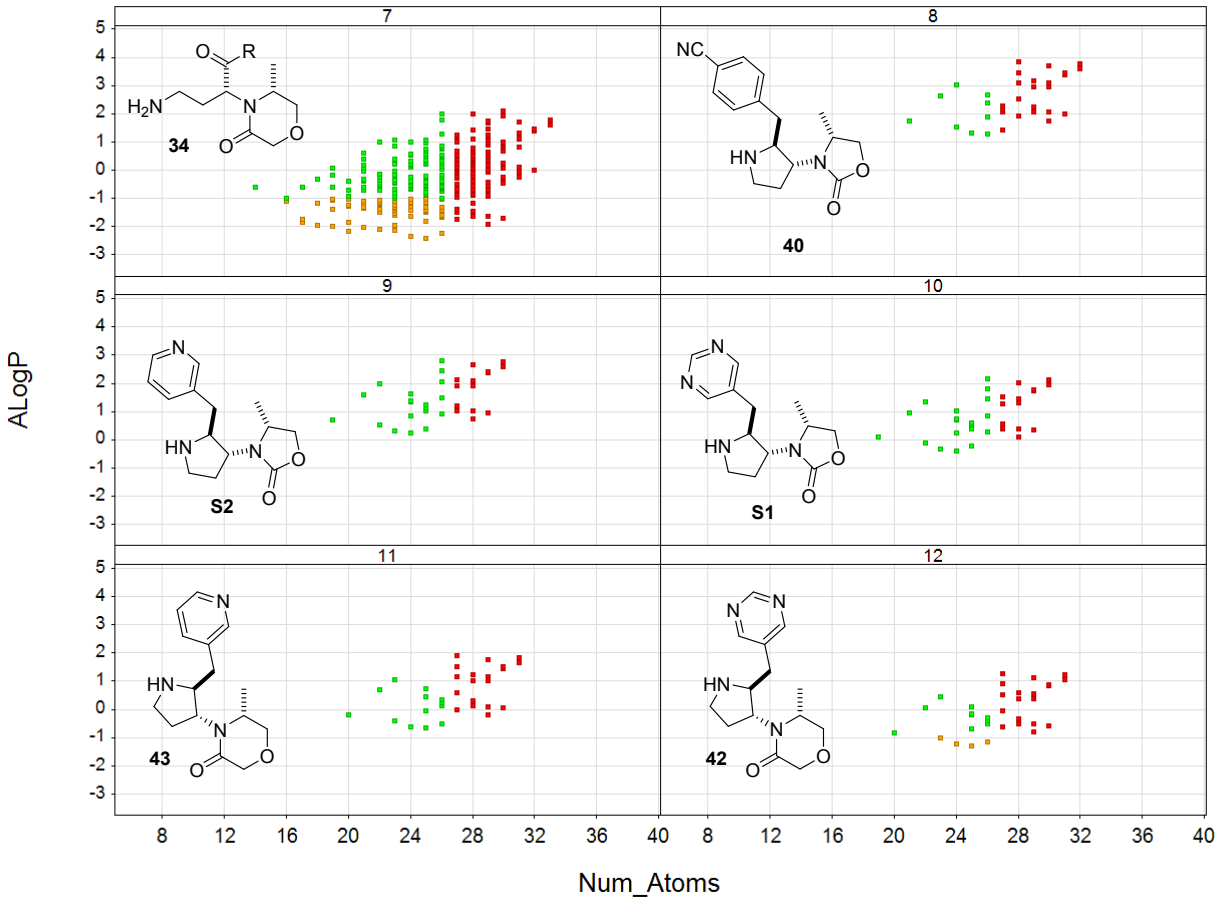
Filter	ZINC Database (9046036)		Random 1% of ZINC Database (90911)		Virtual Library (19530)	
	Successive Filtering	**Parallel Filtering**	**Successive Filtering**	**Parallel Filtering**	**Successive Filtering**	**Parallel Filtering**
Fail $14 \leq nHA \leq 26$	4395739	4395739 (48%)	43971	43971 (48%)	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

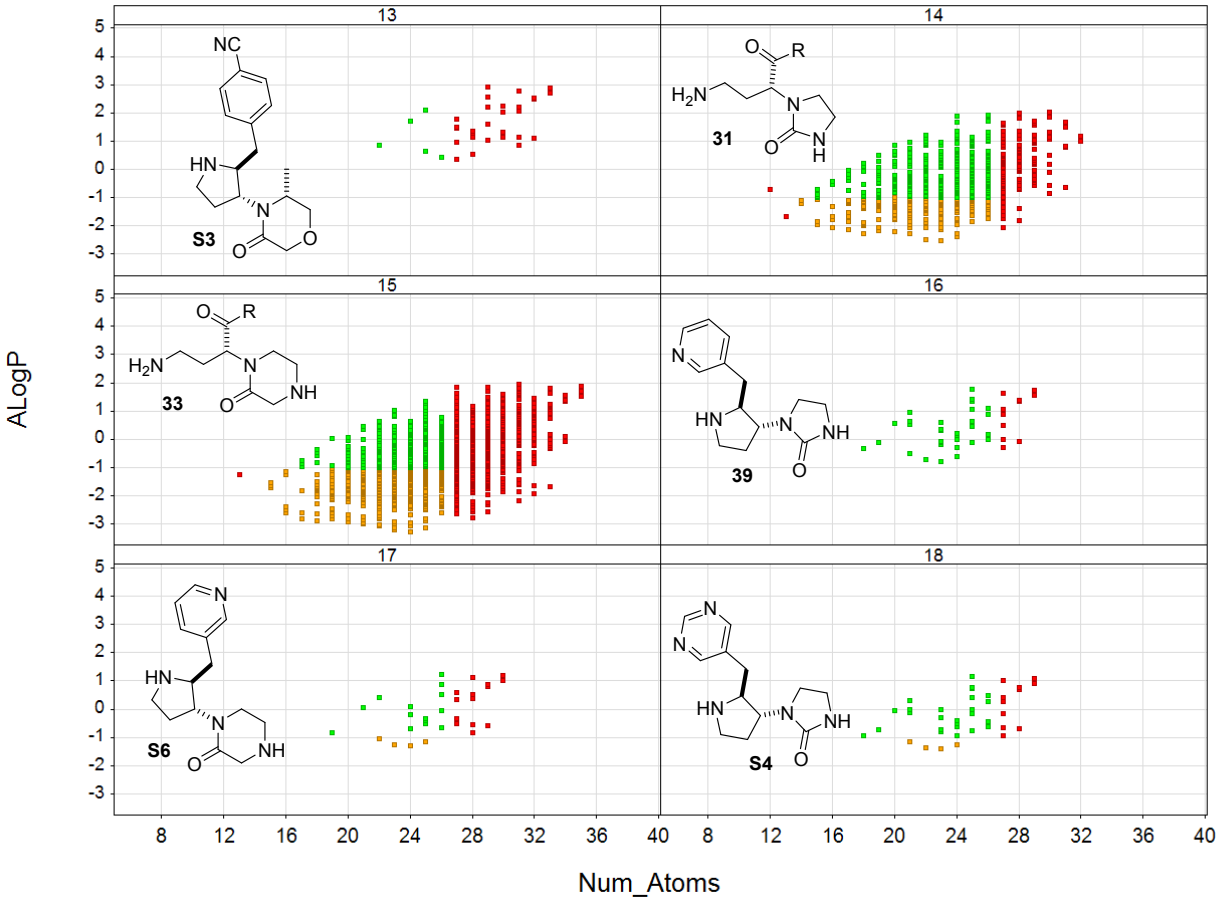
Table S4. *Lead-likeness assessment data. The data shown in Figure 1, Panels A and B (main text) was obtained by successive filtering by the number of heavy atoms, lipophilicity and structural filters. For comparison, data obtained from parallel filtering of all compounds using each filter in isolation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


1
2
3
4
5
6
ALogP
Num_Atoms
26
29
44
51
50
32


7
8
9
10
11
12
ALogP
Num_Atoms
34
40
S2
S1
43
42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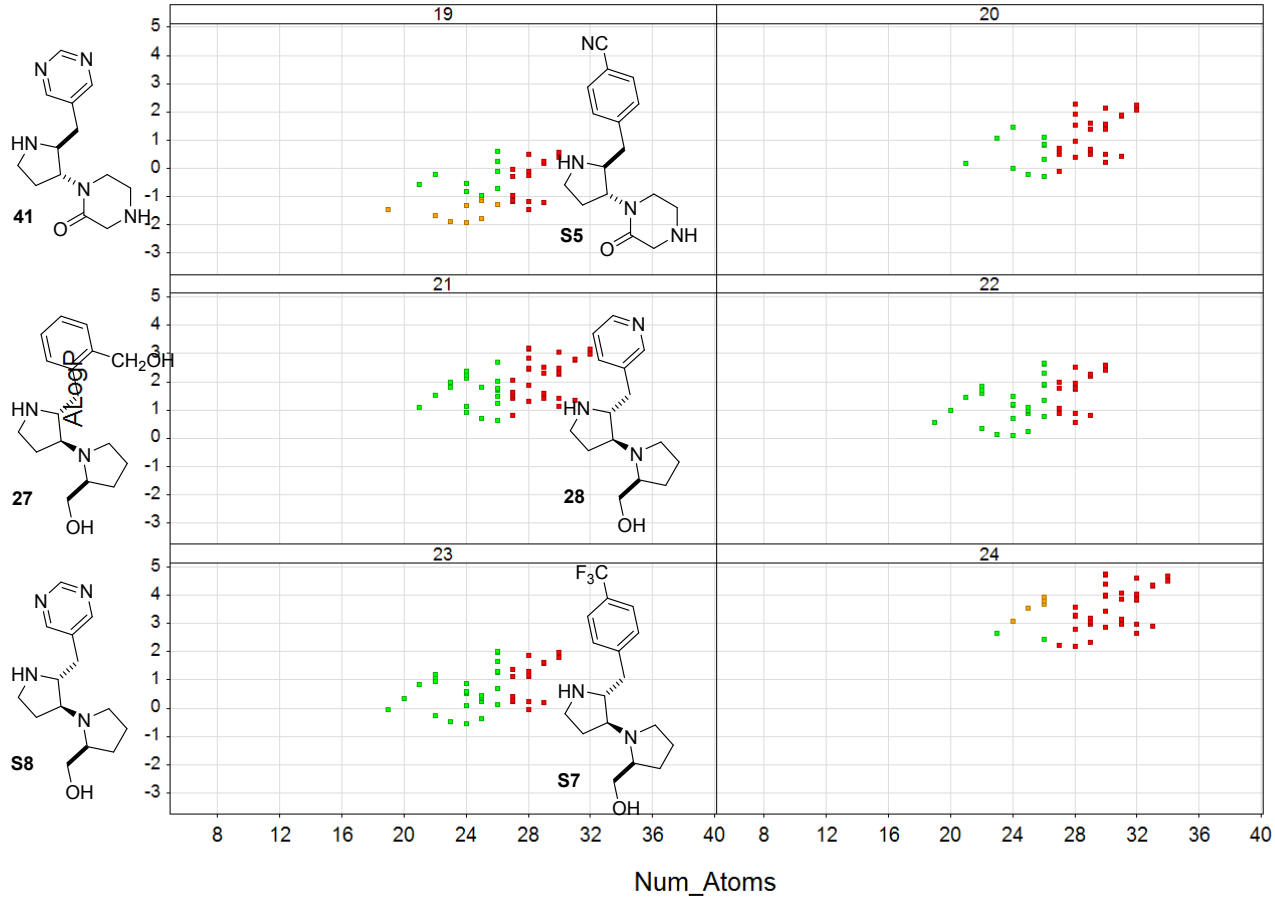
14
15
16
17
18
S3
31
33
39
S6
S4
ALogP
Num_Atoms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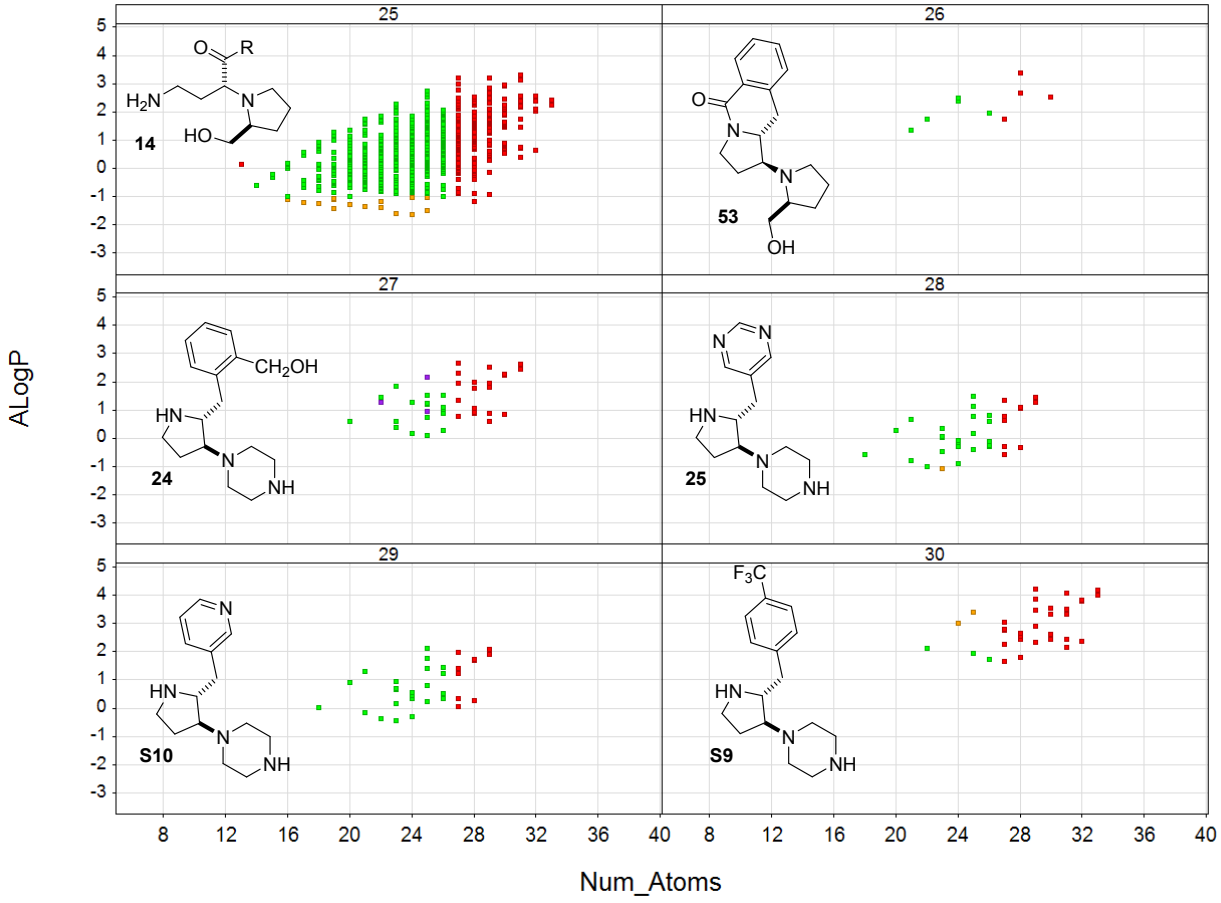
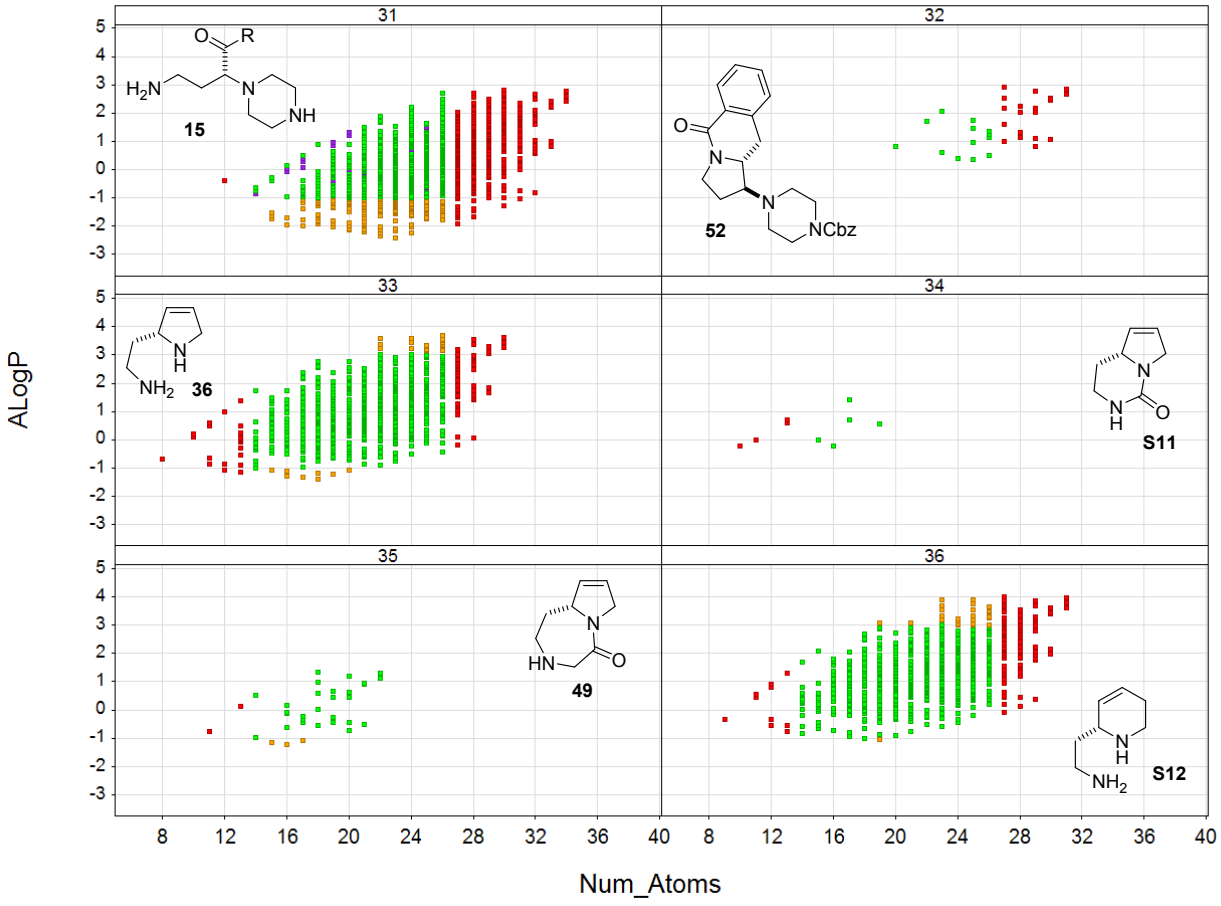
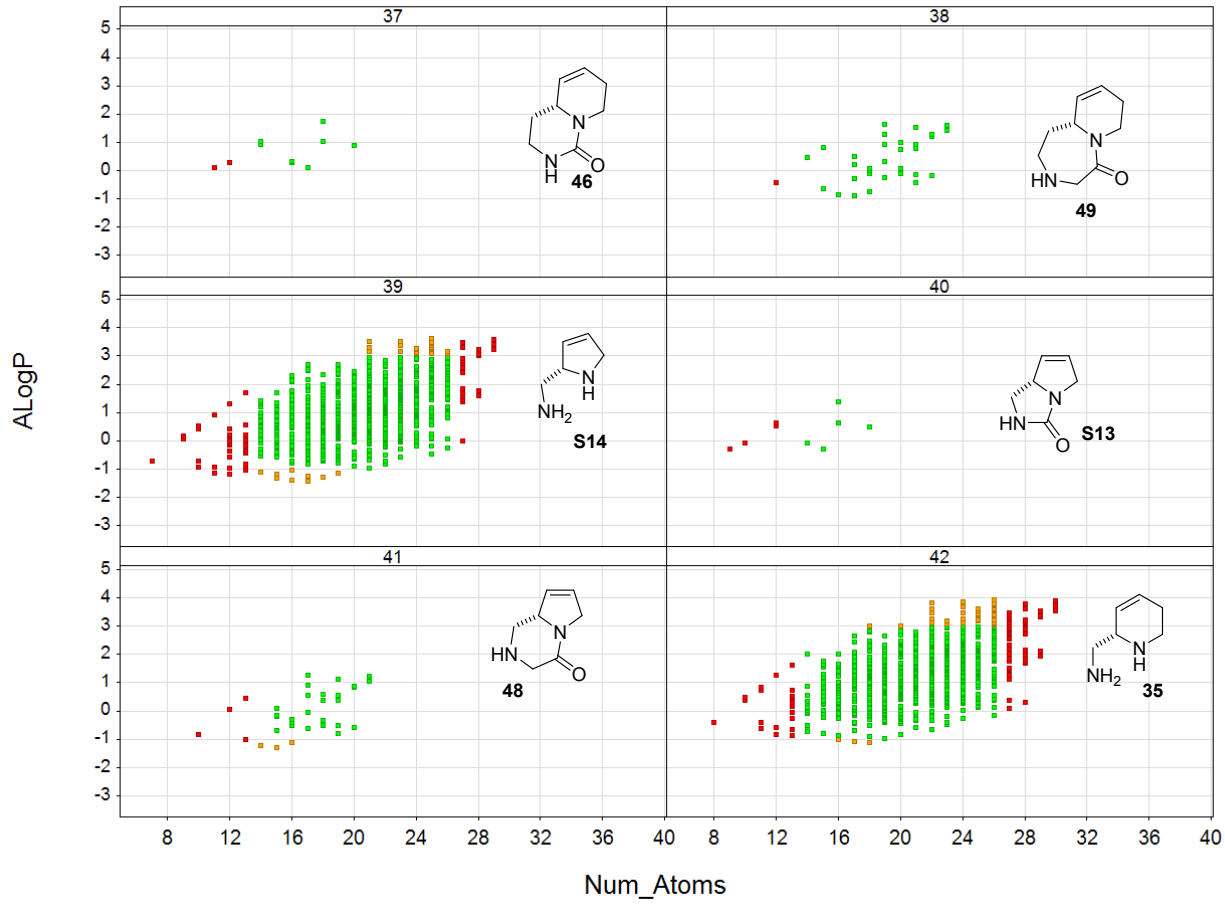
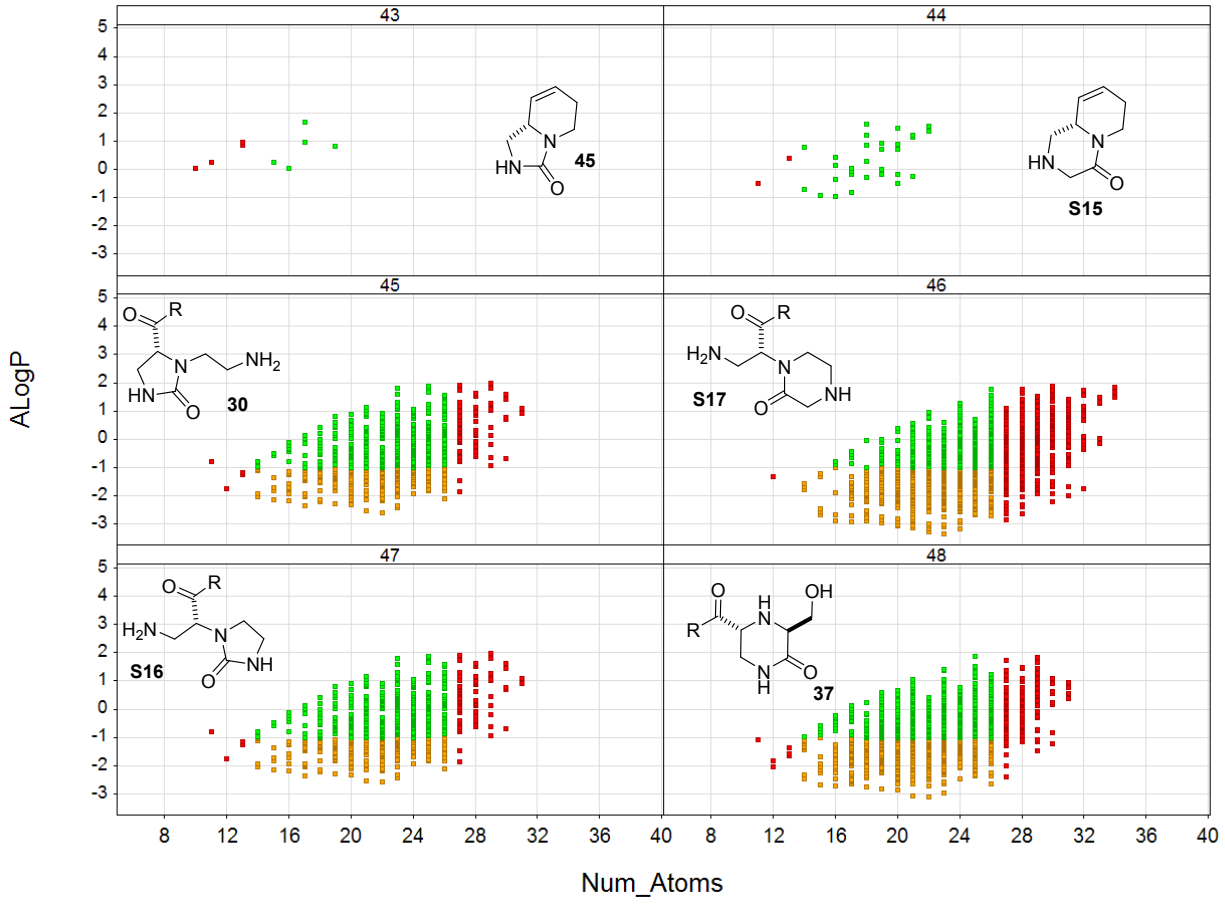
20
21
22
23
24
41
S5
27
28
S8
S7
ALogP
Num_Atoms


25
26
27
28
29
30
14
53
24
25
S10
S9
ALogP
Num_Atoms


31
32
33
34
35
36
15
52
36
S11
49
S12
ALogP
Num_Atoms


37
38
39
40
41
42
46
49
S14
S13
48
35
ALogP
Num_Atoms


43
44
45
46
47
48
45
S15
30
S17
S16
37
ALogP
Num_Atoms

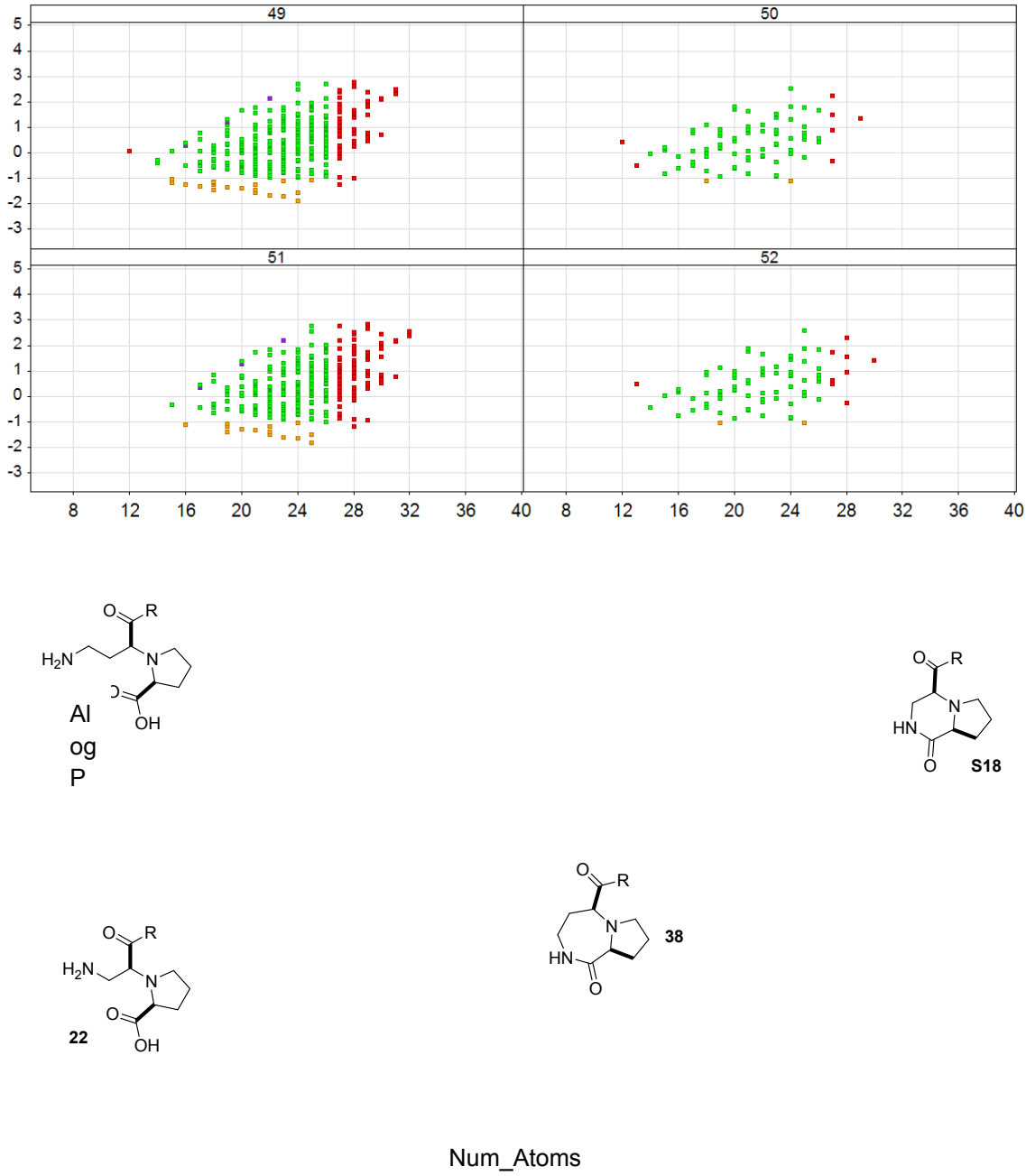


Figure S3. *Distribution of number of heavy atoms (Num_Atoms) and AlogP for the virtual library based upon each scaffold. The scaffolds shown have undergone virtual deprotection and manipulation 1 in each case; R = H or OH (see Scheme S4 for manipulations after decoration). Compounds that survive successive 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. *Fsp^3 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.

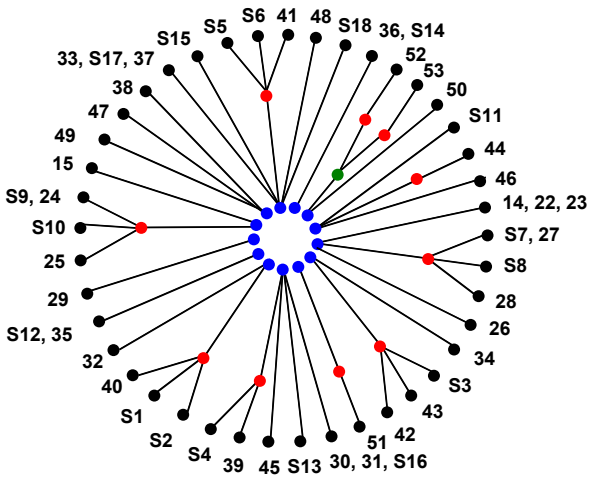


Figure S4. *Hierarchical relationship between the 42 distinct molecular frameworks at the graph-node-bond level (black) and the 13 parental frameworks (blue). Daughter frameworks are shown in red and green. The scaffolds based on each graph-node-bond-level framework are indicated.*

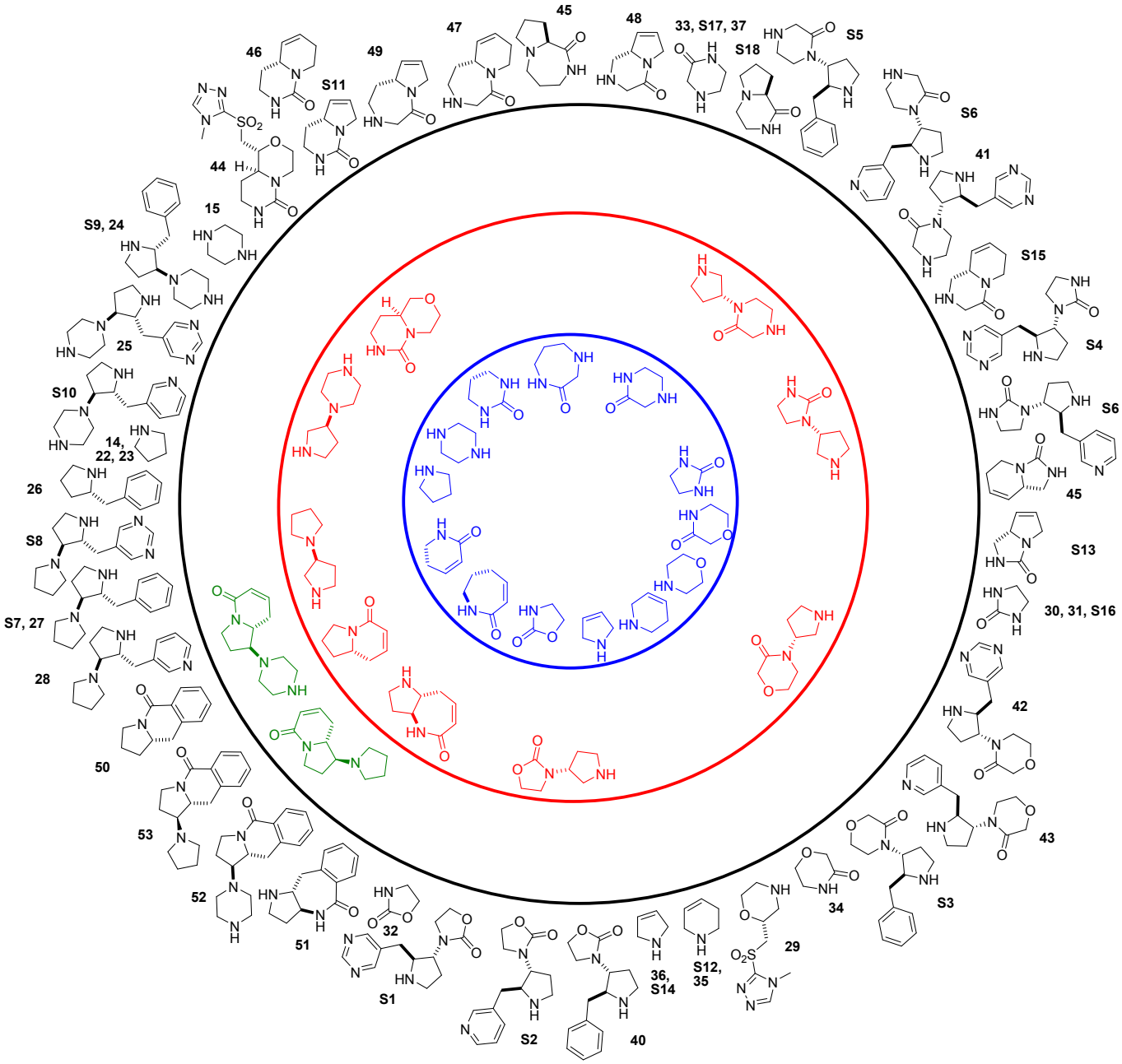


Figure S5. *The 42 distinct molecular frameworks at the graph-node-bond level (black) and the 13 parental frameworks (blue). Daughter frameworks are shown in red and green. The scaffolds which represent each framework are indicated. See Figure S4 for the relationship between scaffolds at each level of 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), CH_2Cl_2, toluene and CH_3CN 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 F_{254}) plates supplied by Merck. Visualisation of the plates was achieved using an ultraviolet lamp (λ_{max} = 254 nm), $KMnO_4$, 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 CH_3CN/H_2O + 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 C_{18} 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.

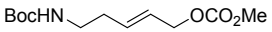
Optical rotation measurements were carried out at the sodium D-line (589 nm) on a Schmidt and Haensch H532 or an Optical Activity AA-1000 polarimeter instrument; concentrations are g/100 mL, temperatures given in °C, optical rotations are given in $10^{-1}degcm^2g^{-1}$ (units are omitted). Infrared 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 (^{13}C) 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

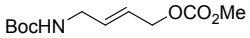
2-({[(3*E*)-5-[(Methoxycarbonyl)oxy]pent-3-en-1-yl]carbamoyl}oxy)-2-methylpropane S23



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 CH_2Cl_2 (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 NH_4Cl (200 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phase was washed with water (250 mL) and brine (250 mL), dried ($MgSO_4$), 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, $CDCl_3$) 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, OCH_3), 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(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 155.7 (NH*C*O$_2$), 155.5 (O*C*O$_2$CH$_3$), 133.2 (4-C), 125.6 (3-C), 79.0 (O*C*(CH$_3$)$_3$), 68.1 (5-C), 54.6 (2-C), 39.4 (1-C), 28.3 (OC(*C*H$_3$)$_3$); υ_{max}/cm^{-1} (neat) 3365, 2976, 1746, 1689, 1513, 1442, 1390, 1365, 1246, 1164; *m/z* (ESI) 282 (100%, MNa$^+$); Found: MNa$^+$, 282.1314. $C_{12}H_{21}NO_5$ requires *MNa*, 282.1312.

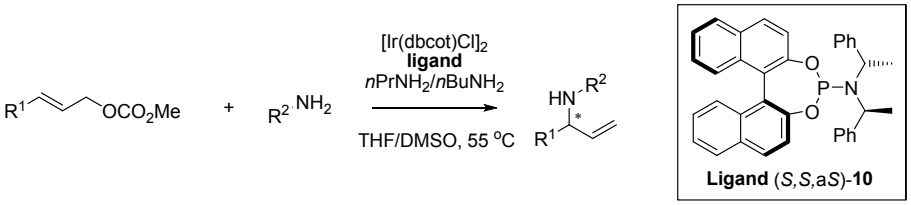
2-({[(2*E*)-4-[(Methoxycarbonyl)oxy]but-2-en-1-yl]carbamoyl}oxy)-2-methylpropanecarbamate S24



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,*a*S*)-**10** and (*R,R,*a*R*)-**10** were prepared according to the method of Mezzetti *et al*.[8]

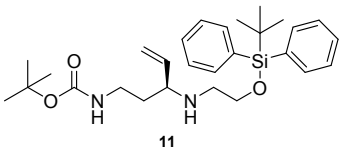
General Procedure 1

n$BuNH_2$ (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 K_3PO_4 (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-$PrNH_2$ (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 K_3PO_4 (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**

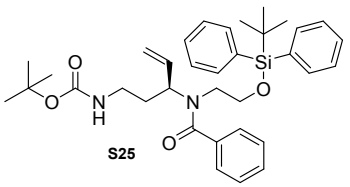


11

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 CH_2Cl_2 –EtOH–NH_4OH 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–NH_4OH); $[\alpha]_D^{24}$ +4 (*c.* 0.69, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 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, CH_2OSi), 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(CH_3)$_3$), 1.05 (9H, s, SiC(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 155.9 (NH*C*O_2), 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 (O*C*(CH$_3$)$_3$), 63.2 (*C*H_2OSi), 59.9 (3-C), 48.8 (NH*C*H_2), 37.9 (1-C), 35.2 (2-C), 28.4 (OC(*C*H$_3$)$_3$), 26.8 (SiC(*C*H$_3$)$_3$), 19.2 (Si*C*(CH$_3$)$_3$); υ_{max}/cm^{-1} (neat) 3347, 2931, 1710, 1506, 1472, 1428, 1390, 1365, 1250; *m/z* (ESI) 483 (100%, MH^+); Found: MH^+, 483.3050. $C_{28}H_{42}N_2O_3Si$ 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**

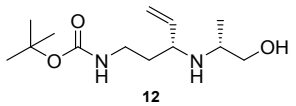


S25

NEt_3 (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 CH_2Cl_2 (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 CH_2Cl_2 (10 mL), saturated aqueous NH_4Cl (10 mL) added, the phases separated and the aqueous phase extracted with CH_2Cl_2 (3 × 10 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 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); $[\alpha]_D^{20}$ –21 (*c.* 1.06, $CHCl_3$); 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, CH_2OSi), 3.51 (2 H, app. br s, 1-H), 2.95 (2 H, app. br s, NHCH_2), 1.80 (2 H, app. br s, 2-H), 1.40 (9H, s, OC(CH_3)$_3$), 1.04 (9H, s, SiC(CH_3)$_3$); δ_C (75 MHz, MeOD, 333 K) 174.8 (N*C*OPh), 158.2 (NH*C*O_2), 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 (O*C*(CH$_3$)$_3$), 63.0 (*C*H_2OSi), 62.9 (3-C), 38.8 (1-C), 33.4 (2-C), 28.9

(OC(CH_3)$_3$), 27.5 (SiC(CH_3)$_3$), 20.0 (SiC(CH$_3$)$_3$), (NCH_2) signal not observed – under residual solvent signal; υ_{max}/cm^{-1} (neat) 3347, 2932, 1712, 1634, 1515, 1428, 1365, 1250, 1173, 1111; *m/z* (ESI) 587 (100%, MH$^+$); Found: MH$^+$, 587.3302. $C_{35}H_{46}N_2O_4Si$ 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).

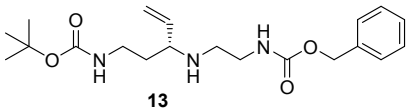
***tert*-Butyl-*N*-[(3*R*)-3-{[(2*S*)-1-hydroxypropan-2-yl]amino}pent-4-en-1-yl]carbamate 12**



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 CH_2Cl_2 –EtOH–NH_4OH furnished the amine **12** (1.21 g, 61%, *dr* 93:7) as an amorphous colourless solid, R_f 0.19 (92:7:1 CH_2Cl_2 –EtOH–NH_4OH); δ_H (500 MHz, $CDCl_3$) 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, CO_2NH), 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, NHCHCH$_3$), 1.66-1.54 (2 H, m, 2-H), 1.44 (9 H, s, OC(CH_3)$_3$), 1.07 (3 H, d, *J* 6.6, CHCH_3); δ_C (75 MHz, $CDCl_3$) 156.1 (NHCO_2), 140.9 (4-C), 115.5 (5-C), 79.2 (OC(CH$_3$)$_3$), 64.3 (CH_2OH), 57.0 (3-C), 51.1 (NHCHCH$_3$), 37.4 (1-C), 36.1 (2-C), 28.3 (OC(CH_3)$_3$), 18.6 (CHCH_3); υ_{max}/cm^{-1} (neat) 3374, 2984, 1684, 1528, 1276, 1261, 1172, 1048; *m/z* (ESI) 259 (100%, MH$^+$); Found: MH$^+$, 259.2018. $C_{13}H_{26}N_2O_3$ requires *MH*, 259.2016.

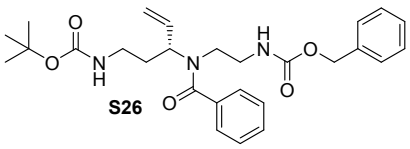
***tert*-Butyl-*N*-[(3*R*)-3-[(2-{[(benzyloxy)carbonyl]amino}ethyl)amino]pent-4-en-1-yl]carbamate 13**



13

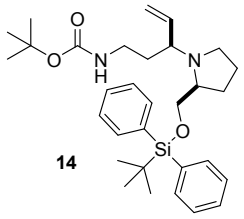
According to General Procedure 1, allylic carbonate **S23** (0.450 g, 1.74 mmol) was combined with benzyl-2-aminoethylcarbamate[10] (0.405 g, 2.09 mmol) and heated for 18 h. Purification by flash column chromatography, eluting with 92:7:1 CH_2Cl_2 –EtOH–NH_4OH furnished the amine **13** (0.300 g, 46%, *ee* 84%) as a yellow oil, R_f 0.39 (92:7:1 CH_2Cl_2 –EtOH–NH_4OH); $[\alpha]_D^{24}$ +0.4 (*c.* 1.59, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 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, BnCO_2NH), 5.13-5.08 (4 H, m, 5-H, CH_2Ph), 4.98 (1 H, br s, *t*BuCO_2NH), 3.28-3.26 (3 H, m, 1-H$_A$, BnCO_2NHCH_2), 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(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 156.5 (NHCO_2Bn), 155.9 (NHCO_2*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(CH$_3$)$_3$), 66.4 (CH_2Ph), 59.2 (3-C), 46.2 (NHCH_2), 40.7 (BnCO_2NHCH_2), 37.6 (1-C), 35.5 (2-C), 28.3 (OC(CH_3)$_3$); υ_{max}/cm^{-1} (neat) 3332, 2977, 1701, 1527, 1455, 1366, 1254, 1171; *m/z* (ESI) 259 (100%, MH$^+$); Found: MH$^+$, 378.2400. $C_{20}H_{31}N_3O_4$ 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**



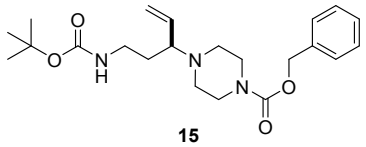
NEt_3 (0.730 mL, 1.30 mmol) and benzoyl chloride (46.0 μL, 0.390 mmol) were added to a solution of amine **13** (0.100 g, 0.260 mmol) in CH_2Cl_2 (2.6 mL) at 0 °C (ice). The mixture was allowed to warm to room temperature and then stirred for 18 h before being diluted with CH_2Cl_2 (10 mL), saturated aqueous NH_4Cl (10 mL) added, the phases separated and the aqueous phase extracted with CH_2Cl_2 (3 × 10 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 CH_2Cl_2 –EtOH–NH_4OH 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 CH_2Cl_2 –EtOH–NH_4OH); $[\alpha]_D^{20}$ +10.2 (*c*. 2.40, $CHCl_3$); 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, CH_2Ph), 4.23 (1 H, app. br s, 3-H), 3.32-3.29 (2 H, m, $BnCO_2NHCH_2$), 3.21 (2 H, app. br s, 1-H), 2.86 (2 H, app. br s, NHCH_2), 1.83-1.78 (2 H, m, 1-H), 1.37 (9 H, s, OC(CH_3)$_3$); δ_C (75 MHz, DMSO-d_6, 343 K) 171.0 (N*C*OPh), 155.6 (NH*C*O_2*t*Bu), 154.9 (NH*C*O_2Bn), 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 (O*C*(CH$_3$)$_3$), 64.9 (*C*H_2Ph), 31.3 (2-C), 27.8 (OC(*C*H$_3$)$_3$), (1-C), (3-C), (NH*C*H_2) and ($BnCO_2NHCH_2$) not observed - rotameric; υ_{max}/cm^{-1} (neat) 3327, 2975, 1697, 1618, 1510, 1447, 1412, 1391, 1245; *m/z* (ESI) 587 (100%, MNa^+); Found: MNa^+, 504.2476. $C_{27}H_{35}N_3O_5$ requires *MNa*, 504.2468; HPLC: Daicel Chiralcel AS-H, 5% EtOH–hexane over 60 min, 0.5 mL/min; t_1 = 31.91 min (major), t_2 = 39.64 min (minor).

***tert*-Butyl-*N*-[(3*S*)-3-[(2*S*)-2-{[(*tert*-butyldiphenylsilyl)oxy]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-NEt_3 furnished the amine **14** (2.1 g, 52%, *dr* >95:<5) as a yellow oil, R_f 0.2 (30:70 Et_2O-pentane); δ_H (500 MHz, $CDCl_3$) 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(CH_3)$_3$), 1.05 (9H, s, SiC(CH_3)$_3$); δ_C (125 MHz, $CDCl_3$) 156.1 (NH*C*O_2), 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 (O*C*(CH$_3$)$_3$), 67.3 (SiO*C*H_2), 61.9 (N*C*H), 61.0 (3-C), 46.8 (N*C*H_2), 39.2 (1-C), 33.3 (2-C), 28.4 (OC(*C*H$_3$)$_3$, 26.9 (SiC(*C*H$_3$)$_3$), 26.8 (CH*C*H_2), 23.5 (NCH$_2$*C*H_2), 19.2 (Si*C*(CH$_3$)$_3$); 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. $C_{31}H_{47}N_2O_3Si$ requires *MH*, 523.3350.

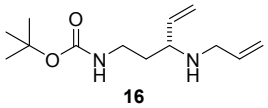
Benzyl-4-[(3*S*)-5-{[(*tert*-butoxy)carbonyl]amino}pent-1-en-3-yl]piperazine-1-carboxylate 15



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 (Et_2O-pentane); $[\alpha]_D^{20}$ +19.4 (*c* 1.04, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 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(CH_3)$_3$); δ_C (125 MHz; C_6D_6/MeOD) 155.7 (NH*C*O$_2$), 154.9 (NH*C*O$_2$), 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 (O*C*(CH$_3$)$_3$), 67.1 (*C*H$_2$Ar), 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 (O*C*(CH$_3$)$_3$); ν_{max}/cm^{-1} (film) 3359, 2976, 1703, 1519, 1432, 1365, 1245; *m/z* (ES$^+$) 404.3 (100%, MH$^+$); found 404.2585, $C_{22}H_{33}N_3O_4$ 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**

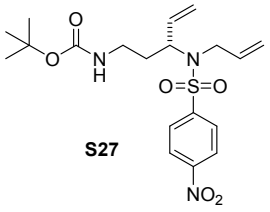


16

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, $CHCl_3$); δ_H (400 MHz, DMSO-d_6) 6.73 (1 H, br. s, BocN*H*), 5.81 (1 H, ddt, *J* 17.2, 10.2, 5.7 Hz, C*H*=CH$_2$), 5.60–5.48 (1 H, m, C*H*=CH$_2$), 5.11 (1 H, dq, *J* 17.3, 1.6 Hz, *trans* CH=C*H*$_2$), 5.05 (1 H, dq, *J* 13.4, 2.1 Hz, *cis* CH=C*H*$_2$), 5.00 (1 H, dd, *J* 10.3, 1.6 Hz, *cis* CH=C*H*$_2$), 3.14 (1 H, ddt, *J* 14.5, 5.4, 1.7 Hz, C*H*CH=CH$_2$), 3.03–2.87 (4 H, m, BocNHC*H*$_2$, C*H*$_2$CH=CH$_2$), 1.68 (1 H, br. s, N*H*CH$_2$CH=CH$_2$), 1.53 (1H, ddt, *J* 12.9, 8.0, 6.5 Hz, NHCH$_2$C*H*$_2$), 1.48–1.40 (1 H, m, NHCH$_2$C*H*$_2$), 1.37 (9 H, s, C(C*H*$_3$)$_3$); δ_C (100 MHz, DMSO-d_6) 155.4 (*C*=O), 141.3 (*C*H=CH$_2$), 137.8 (*C*H=CH$_2$), 115.1 (CH=*C*H$_2$), 114.8 (CH=*C*H$_2$), 77.3 (*C*(CH$_3$)$_3$), 58.1 (*C*HCH=CH$_2$), 48.9 (*C*H$_2$CH=CH$_2$), 37.1 (BocNH*C*H$_2$), 35.1 (BocNHCH$_2$*C*H$_2$), 28.2 (C(*C*H$_3$)$_3$); υ_{max}/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. $C_{13}H_{25}O_2N_{25}$ 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**

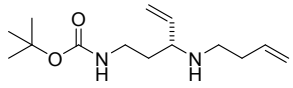


S27

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 **16** (0.480 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 **S27** (0.362 g, 43 % yield, *ee* 87%) as a yellow oil, $[\alpha]_D^{22}$ = +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, $C(CH_3)_3$); 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 ($OC(CH_3)_3$), 58.1 (2-C), 47.2 (CH_2CHCH_2), 36.8 (1-C), 32.2 (2-C), 28.5 ($C(CH_3)_3$); υ_{max}/cm^{-1} (neat) 3422, 3104, 2977, 2934, 1702, 1528, 1347, 1268, 1248, 1160, 1088; *m/z* (ESI) 448 (100%, MNa^+); Found: MNa^+, 448.1516. $C_{19}H_{27}N_3O_6S$ 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).

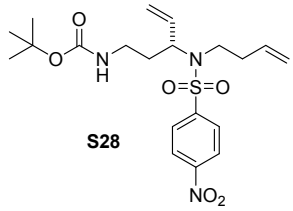
***tert*-Butyl-*N*-[(3*R*)-3-[(but-3-en-1-yl)amino]pent-4-en-1-yl]carbamate 17**



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); $[\alpha]_D^{23}$ –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, C*H*=CH_2), 5.67–5.51 (1 H, m, C*H*=CH_2), 5.15–5.06 (3 H, m, CH=CH_2), 5.04 (1 H, ddt, *J* 10.3, 2.3, 1.3 Hz, *cis* C*H*=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, C*H*CH=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, CH_2CH=CH_2), 1.62 (2 H, q, *J* 6.6 Hz, BocNHCH$_2$CH_2), 1.44 (9 H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 155.9 (*C*=O), 140.5 (*C*H=CH_2), 136.5 (*C*H=CH_2), 116.3 (CH=*C*H_2), 115.9 (CH=*C*H_2), 78.9 (*C*$(CH_3)_3$), 60.3 (*C*HCH=CH_2), 46.1 (NH*C*H_2CH_2), 38.2 (BocNH*C*H_2), 35.3 (*C*H_2CH=CH_2), 34.4 (BocNHCH$_2$*C*H_2), 28.4 ($C(CH_3)_3$); υ_{max}/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. $C_{14}H_{26}N_2O_2$ 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**

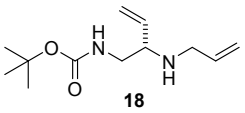


S28

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, $[\alpha]_D^{22}$ = +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, C(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 (*C*HCH$_2$), 128.4 (Ar 2-C), 124.4 (Ar 3-C), 118.9 (5-C), 117.5 (CH*C*H$_2$), 79.4 (O*C*(CH$_3$)$_3$), 57.9 (3-C), 44.4 (N*C*H$_2$), 36.9 (1-C), 35.6 (2-C), 32.4 (*C*H$_2$CHCH$_2$), 28.5 (C(*C*H$_3$)$_3$); υ_{max}/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. $C_{20}H_{29}N_3O_6S$ 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**

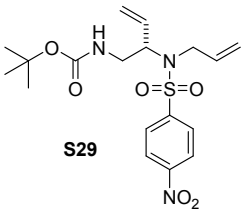


18

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, *DMSO-d*$_6$) 6.73 (1 H, br. s, BocN*H*), 5.81 (1 H, ddt, *J* 17.2, 10.2, 5.7 Hz, C*H*=CH$_2$), 5.60–5.48 (1 H, m, C*H*=CH$_2$), 5.11 (1 H, dq, *J* 17.3, 1.6 Hz, *trans* CH=C*H*$_2$), 5.05 (1 H, dq, *J* 13.4, 2.1 Hz, *cis* CH=C*H*$_2$), 5.00 (1 H, dd, *J* 10.3, 1.6 Hz, *cis* CH=C*H*$_2$), 3.14 (1 H, ddt, *J* 14.5, 5.4, 1.7 Hz, C*H*CH=CH$_2$), 3.03–2.87 (4 H, m, BocNHC*H*$_2$, C*H*$_2$CH=CH$_2$), 1.68 (1 H, br. s, N*H*CH$_2$CH=CH$_2$), 1.53 (1H, ddt, *J* 12.9, 8.0, 6.5 Hz, NHCH$_2$C*H*$_2$), 1.48–1.40 (1 H, m, NHCH$_2$C*H*$_2$), 1.37 (9 H, s, C(C*H*$_3$)$_3$); δ_C (100 MHz, *DMSO-d*$_6$) 155.4 (*C*=O), 141.3 (*C*H=CH$_2$), 137.8 (*C*H=CH$_2$), 115.1 (CH=*C*H$_2$), 114.8 (CH=*C*H$_2$), 77.3 (*C*(CH$_3$)$_3$), 58.1 (*C*HCH=CH$_2$), 48.9 (*C*H$_2$CH=CH$_2$), 37.1 (BocNH*C*H$_2$), 35.1 (BocNHCH$_2$*C*H$_2$), 28.2 (C(*C*H$_3$)$_3$); υ_{max}/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. $C_{13}H_{25}O_2N_2$ requires *MH*, 241.1911.

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

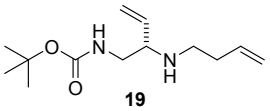
***tert*-Butyl-*N*-[(2*S*)-2-[*N*-(prop-2-en-1-yl)4-nitrobenzenesulfonamido]but-3-en-1-yl]carbamate S29**



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$_A$*H*$_B$), 3.75 (dd, *J* = 16.0, 7.5 Hz, 1H, 5-C*H*$_A$H$_B$), 3.36 - 3.46 (m, 1H, 10-C*H*$_A$H$_B$), 3.23 - 3.34 (m, 1H, 10-CH$_A$*H*$_B$), 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); υ_{max}/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. $C_{18}H_{25}N_3O_6S$ 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**

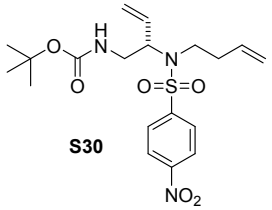


19

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, C*H*=CH_2), 5.70–5.55 (1 H, m, C*H*=CH_2), 5.23–5.14 (2 H, m, CH=CH_2), 5.12–5.01 (2 H, m, CH=CH_2), 4.86 (1 H, br. s, BocN*H*), 3.23–3.02 (4 H, m, N*HCH*CH=CH_2, CH_2CH=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, CH_2CH$_2$CH=CH_2), 1.45 (9 H, C(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 156.2 (*C*=O), 138.7 (*C*H=CH_2), 136.5 (*C*H=CH_2), 117.2 (CH=*C*H_2), 116.5 (CH=*C*H_2), 79.3 (*C*(CH$_3$)$_3$), 61.0 (*C*HCH=CH_2), 55.4 (NH*C*H$_2$CH$_2$), 46.2 (BocNH*C*H$_2$), 34.5 (*C*H$_2$CH=CH_2), 28.6 (C(*C*H$_3$)$_3$); υ_{max}/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. $C_{13}H_{24}N_2O_2$ requires *MH*, 241.1910.

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

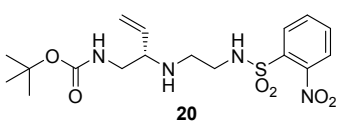
***tert*-Butyl-*N*-[(2*S*)-2-[*N*-(but-3-en-1-yl)4-nitrobenzenesulfonamido]but-3-en-1-yl]carbamate S30**



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-CH_AH$_B$), 3.22-3.31 (m, 2H, 5-CH$_A$*H$_B$* and 10-CH_AH$_B$), 3.10 - 3.20 (m, 1H, 10-CH$_A$*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); υ_{max}/cm^{-1} (neat) 3412, 3105, 2978, 2933, 1706, 1528, 1347, 1309, 1249, 1157, 1088; *m/z* (ESI) 464 (100%, MK$^+$); Found: MK$^+$, 464.1242. $C_{19}H_{27}N_3O_6S$ 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**

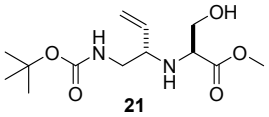


20

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 chromatohraphy (C_{18}) eluting with 5%-40% MeCN–H_2O–1% formic acid) furnished the amine **20** (254 mg, 61 %, 79% *ee*) as a yellow oil, $[\alpha]_D^{21}$ +0.80 (c = 5.50, $CDCl_3$); δ_H (400 MHz, $CDCl_3$) 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*BuCO$_2$N*H*), 3.07-3.15 (3 H, m, NHCH_2 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_ANHSO$_2$), 2.60-2.68 (m, 1H, CH_BNHSO$_2$), 1.41 (9 H, s, OC(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 156.0 (NH*C*O$_2$*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(*C*H$_3$)$_3$), 60.7 (2-C), 45.3, 44.4, 43.5 (1-C, NH*C*H$_2$ or *C*H$_2$NHSO$_2$), 28.3 (OC(*C*H$_3$)$_3$); υ_{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. $C_{17}H_{26}N_4O_6S$ 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).

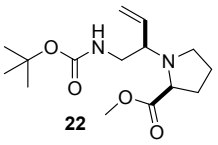
Methyl-(2*S*)-2-{[(2*S*)-1-{[(*tert*-butoxy)carbonyl]amino}but-3-en-2-yl]amino}-3-hydroxypropanoate 21



21

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

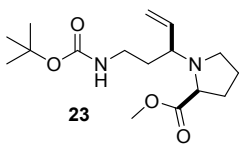
Methyl-(2*S*)-1-[(2*R*)-1-{[(*tert*-butoxy)carbonyl]amino}but-3-en-2-yl]pyrrolidine-2-carboxylate 22



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 K_3PO_4 (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, $CDCl_3$) 5.76 (1H, ddd, *J* = 17.1, 10.4, 7.7 Hz, C*H*=CH$_2$), 5.31 (1H, br. s, BocN*H*), 5.22 (1H, dd, *J* = 10.4, 1.7 Hz, *cis*-CH=C*H*$_2$), 5.15 (1H, dd, *J* = 17.2, 1.7 Hz, *trans*-CH=C*H*$_2$), 3.69 (3H, s, CO$_2$C*H*$_3$), 3.48 (1H, dt, *J* = 9.1, 5.0 Hz, C*H*CO$_2$CH$_3$), 3.28–3.09 (3H, m, BocNHC*H*$_2$, C*H*CH=CH$_2$), 2.94 (1H, ddd, *J* = 8.8, 7.3, 3.7 Hz, CHNC*H*$_2$), 2.65 (1H, q, *J* = 7.9 Hz, CHNC*H*$_2$), 2.11–1.97 (1H, m, NCHC*H*$_2$CH$_2$), 1.95–1.68 (3H, m, CHNC*H*$_2$, CHNCH$_2$C*H*$_2$), 1.43 (9H, s, C(C*H*$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 175.3 (*C*O$_2$CH$_3$), 156.2 (*C*O$_2$*t*Bu), 134.1 (*C*H=CH$_2$), 119.2 (CH=*C*H$_2$), 79.0 (*C*(CH$_3$)$_3$), 62.9 (*C*HCO$_2$CH$_3$), 62.6 (*C*HCH=CH$_2$), 51.9 (CO$_2$*C*H$_3$), 46.8 (CHN*C*H$_2$), 43.0 (BocNH*C*H$_2$), 29.7 (NCH*C*H$_2$CH$_2$), 28.6 (C(*C*H$_3$)$_3$), 23.9 (NCHCH$_2$*C*H$_2$); υ_{max}/cm^{-1} (neat): 3392, 2976, 1705, 1499, 1390, 1365, 1246, 1166; *m/z* (ESI) 299 (100%, MH$^+$); Found: MH$^+$, 299.1967. $C_{15}H_{27}N_2O_4$ requires *MH*, 299.1971).

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



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 K_3PO_4 (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, $CDCl_3$) 5.74 (1H, ddd, *J* = 17.3, 10.2, 8.6 Hz, C*H*=CH$_2$), 5.66 (1H, br. s, BocN*H*), 5.18 (1H, dd, *J* =

10.3, 1.8 Hz, *cis*-CH=CH_2), 5.06 (1H, ddd, *J* = 17.2, 1.9, 0.8 Hz, *trans*-CH=CH_2), 3.71 (3H, s, CO_2CH_3), 3.44 (1H, dd, *J* = 9.0, 5.7 Hz, C$H$$CO_2CH_3$), 3.30–3.15 (3H, m, BocNHCH_2, CHCH=CH_2), 2.92 (1H, ddd, *J* = 8.7, 7.2, 3.6 Hz, CHNCH_2), 2.60 (1H, q, *J* = 8.1 Hz, CHNCH_2), 2.09–1.96 (1H, m, $NCH_2CH_2CH_2$), 1.93–1.56 (5H, m, $BocNHCH_2CH_2$, $NCH_2CH_2CH_2$, $NCH_2CH_2CH_2$), 1.42 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 175.5 (CO_2CH_3), 156.4 (CO_2tBu), 135.2 (CH=CH_2), 118.2 (CH=CH_2), 78.6 ($C(CH_3)_3$), 62.2 ($CHCO_2CH_3$), 60.8 ($CHCH=CH_2$), 51.9 (CO_2CH_3), 45.8 ($CHNCH_2$), 38.1 ($BocNHCH_2$), 33.0 ($BocNHCH_2CH_2$), 29.6 ($NCH_2CH_2CH_2$), 28.6 ($C(CH_3)_3$), 23.8 ($NCH_2CH_2CH_2$); υ_{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. $C_{16}H_{29}N_2O_4$ 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 $CsCO_3$ (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 NH_4Cl and the aqueous phase twice back extracted with EtOAc. The combined organic phase was dried ($MgSO_4$), 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 CH_2Cl_2 (0.1 M) at 0 °C (ice) such that the final ratio of TFA:CH_2Cl_2 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

NEt_3 (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 CH_2Cl_2 (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 CH_2Cl_2 and saturated aqueous NH_4Cl. The phases were separated and the aqueous phase extracted with CH_2Cl_2 (2 ×). The combined organic phase was dried ($MgSO_4$), 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

NEt_3 (2.0 eq) and TMSCl (1.5 eq) were added to a solution of the alcohol (1.0 eq) in CH_2Cl_2 (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 NEt_3 (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 CH_2Cl_2 (0.6 M) and cooled to 0 °C (ice). To this was added $n$$Bu_4NSO_4$ (0.5 eq) followed by sufficient 35% aqueous NaOH such that the ratio of CH_2CL_2–35% aq. NaOH was 1:1. After 3 h the reaction mixture was diluted with water and CH_2Cl_2, the phases separated and the aqueous phase extracted with CH_2Cl_2 (2 ×). 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 D3/E2

i) NEt_3 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 CH_2Cl_2 (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 CH_2Cl_2 and saturated aqueous NH_4Cl. The phases were separated and the aqueous phase extracted with CH_2Cl_2 (2 ×). The combined organic phase was dried ($MgSO_4$), 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

NEt_3 (1.0 eq) and freshly procured bromoacetyl bromide (1.0 eq) were added to a solution of the respective amine (1.0 eq) in CH_2Cl_2 (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 NEt_3 (72 eq) was added. The reaction mixture was stirred at room temperature for 16 h then diluted with CH_2Cl_2 and saturated aqueous NH_4Cl. The phases were separated and the aqueous phase extracted with CH_2Cl_2 (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.

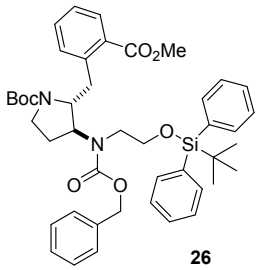
General Procedure F2

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.

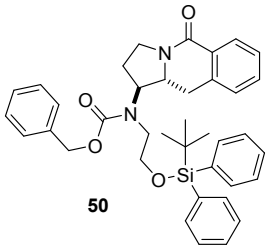
***tert*-Butyl-(2*R*,3*S*)-3-(9,9-dimethyl-3-oxo-1,8,8-triphenyl-2,7-dioxa-4-aza-8-siladecan-4-yl)-2-{[2-(methoxycarbonyl)phenyl]methyl}pyrrolidine-1-carboxylate 26**



26

$NaHCO_3$ (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 $CHCl_3$ (6.00 mL) and water (2.00 mL). The reaction mixture was stirred vigorously for 20 h and then diluted with CH_2Cl_2 (20 mL) and water (20 mL), the phases separated and the aqueous phase extracted with CH_2Cl_2 (2 × 20 mL). 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, 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 Cs_2CO_3 (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, OCH_2Ar), 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, CO_2CH_3), 3.66 (2 H, app. t, *J* 6.6, CH_2OSi), 3.63-3.58 (1 H, m, 5-H_A), 3.27-3.08 (5 H, m, 5-H_B, NCH_2, ArCH_2), 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(CH_3)$_3$), 0.98 (9 H, s, SiC(CH_3)$_3$); δ_C (125 MHz, DMSO, 353 K) 166.9 (CO_2CH_3), 154.4 (NHCO_2), 152.7 (NCO_2CH_2Ph), 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(CH$_3$)$_3$), 65.7 (OCH_2Ar), 61.8 (2-C), 61.7 (3-C), 61.6 (CH_2OSi), 51.1 (CO_2CH_3), 45.9 (NCH_2), 43.8 (5-C), 36.5 (ArCH_2), 27.9 (4-C), 27.4 (OC(CH_3)$_3$), 26.1 (SiC(CH_3)$_3$), 18.1 (SiC(CH$_3$)$_3$); υ_{max}/cm^{-1} (neat) 2955, 1693, 1454, 1392, 1261, 1168, 1113; *m/z* (ESI) 773 (100%, MNa$^+$); Found: MNa$^+$, 773.3613. $C_{44}H_{54}N_2O_7Si$ requires *MNa*, 773.3592.

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

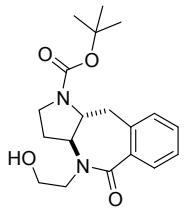


50

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, OCH_2Ar), 4.38 (1 H, app. dd, *J* 18.5, 9.3, pyrollo 3-H), 3.86-3.66 (4 H, m, CH_2OSi, pyrrolo 2-H, pyrollo 5-H_A), 3.57-3.48 (2 H, m, pyrollo 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, pyrollo 4-H), 0.99 (9 H, s, SiC(CH_3)$_3$); δ_C (125 MHz, MeOD, 333 K) 165.6 (Ar*C*O), 157.9 (N*C*O$_2$CH$_2$Ph), 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 (O*C*H$_2$Ar), 63.8 (broad, pyrollo 3-C and *C*H$_2$OSi), 58.5 (pyrollo 2-C), 47.7 (N*C*H$_2$), 43.4 (pyrollo 5-C), 34.2 (Ar*C*H$_2$), 27.5 (SiC(*C*H$_3$)$_3$), 26.8 (pyrollo 4-C), 20.0 (Si*C*(CH$_3$)$_3$);υ_{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.

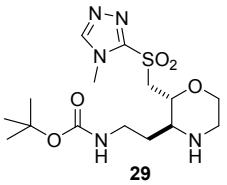
***tert*-Butyl-(3*R*,7*S*)-8-(2-hydroxyethyl)-9-oxo-4,8-diazatricyclo[8.4.0.0^{3,7}]tetradeca-1(10),11,13-triene-4-carboxylate 51**



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$_3$OH 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$_3$OH); 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 (N*C*O$_2$), 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 (O*C*(CH$_3$)$_3$), 63.5 (3-C), 61.8 (7-C), 61.5 (*C*H$_2$OH), 47.2 (5-C), 46.1 (N*C*H$_2$), 36.9 (2-C), 28.9 (OC(*C*H$_3$)$_3$), 27.3 (6-C); υ_{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**



29

Procedure B:

i) NEt$_3$ (1.13 mL, 8.10 mmol), 4-nitrobenzensulfonyl 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

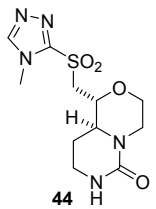
and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography, eluting with 96:3.6:0.4 DCM–EtOH–NH_4OH to furnish a primary alcohol (1.37 g, 78%) which was used immediately.

ii) NIS (1.07 g, 4.76 mmol) was added to a solution of the primary alcohol (1.36 g, 3.17 mmol) in CH_3CN (40.0 mL). The reaction mixture was heated to 65 °C for 2 h, cooled to room temperature and saturated aqueous $Na_2S_2O_3$ (40 mL) and CH_2Cl_2 (30 mL) added. The aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL) and the combined organic phase dried ($MgSO_4$), 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 CH_3CN (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– NH_4OH) 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 CH_2Cl_2 (3.50 mL). The reaction mixture was stirred at room temperature for 18 h before being diluted with CH_2Cl_2 (10 mL), washed with saturated aqueous $Na_2S_2O_3$ (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was dissolved in CH_3CN (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–NH_4OH); $[\alpha]_D^{22}$ +22 (*c.* 1.08, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 8.18 (1 H, s, Ar 3-H), 4.95 (1 H, br s, CO_2NH), 4.35 (1 H, app. dt, *J* 10.3, 2.4, 2-H), 4.11 (1 H, dd, *J* 15.1, 10.3, SO_2CH_A), 3.95 (3 H, s, NCH_3), 3.52 (1 H, dd, *J* 15.1, 2.4, SO_2CH_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, CO_2NHCH_B), 3.18 (1 H, ddd, *J* 11.1, 9.8, 5.3, CO_2NHCH_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, $CO_2NHCH_2CH_A$), 1.43 (10 H, app. br s, $CO_2NHCH_2CH_B$ and $OC(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 156.3 ($NHCO_2$), 151.7 (Ar 5-C), 146.6 (Ar 3-C), 79.4 ($OC(CH_3)_3$), 72.2 (2-C), 63.7 (6-C), 55.1 (SO_2CH_2), 53.0 (3-C), 41.9 (5-C), 36.8 (CO_2NHCH_2), 33.1 (NCH_3), 28.3 ($OC(CH_3)_3$ and $CO_2NHCH_2CH_2$); υ_{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. $C_{15}H_{28}N_5O_5S$ requires *MH*, 390.1806.

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

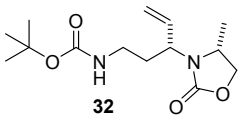


44

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 CH_2Cl_2–saturated methanolic NH_3 to furnish urea **44** (0.065 g, 51%) as a colourless waxy solid, R_f 0.31 (95:5 CH_2Cl_2–saturated methanolic NH_3); $[\alpha]_D^{28}$ +55 (*c.* 0.190, CH_3OH); 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, SO_2CH_A), 3.98 (3 H, s, NCH_3), 3.97-3.94 (1 H, m, 3-H_A), 3.74 (1 H, dd, *J* 15.0, 2.7, SO_2CH_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 (SO_2CH_2), 43.3 (4-C), 38.8 (8-C), 34.0 (NCH_3), 25.1 (9-C); υ_{max}/cm^{-1} (neat) 3317, 2935, 1642, 1499, 1331, 1288, 1171. 1136; *m/z* (ESI) 316 (100%, MH^+); Found: MH^+, 316.1070. $C_{11}H_{18}N_5O_4S$ requires *MH*, 316.1074.

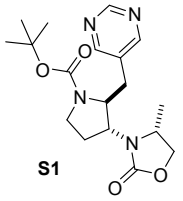
***tert*-Butyl-*N*-[(3*R*)-3-[(4*R*)-4-methyl-2-oxo-1,3-oxazolidin-3-yl]pent-4-en-1-yl]carbamate 32**



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, $CDCl_3$) 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, CO_2NH), 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, $OC(CH_3)_3$), 1.27 (3 H, d, *J* 6.1, oxazolidine CH_3); δ_C (75 MHz, $CDCl_3$), 158.3 (oxazolidine 1-C), 155.9 (CO_2NH), 134.8 (4-C), 118.6 (5-C), 79.0 ($OC(CH_3)_3$), 69.1 (oxazolidine 3-C), 53.3 (3-C), 50.8 (oxazolidine 4-C), 36.8 (1-C), 33.0 (2-C), 28.3 ($OC(CH_3)_3$), 20.3 oxazolidine CH_3); υ_{max}/cm^{-1} (neat) 3359, 2981, 1738, 1515, 1415, 1367, 1275, 1260, 1170; *m/z* (ESI) 307 (100%, MNa^+); Found: MNa^+, 307.1623. $C_{14}H_{24}N_2O_4$ requires *MNa*, 307.1628.

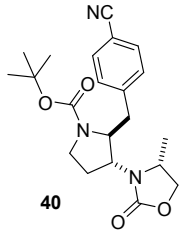
***tert*-Butyl-(2*S*,3*R*)-3-[(4*R*)-4-methyl-2-oxo-1,3-oxazolidin-3-yl]-2-(pyrimidin-5-ylmethyl)pyrrolidine-1-carboxylate S1**



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 CH_2Cl_2–EtOH–NH_3OH 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 5µm OBD, 50-95% MeOH–water with 0.1% HCOOH) for the purposes of analysis, R_f 0.28 (93:6:1 CH_2Cl_2–EtOH–NH_3OH); 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, $OC(CH_3)_3$), 1.21 (3 H, d, *J* 6.1, oxazolidine CH_3); δ_C (125 MHz, MeOD, 333 K), 159.8 (oxazolidine 1-C), 159.0 (Ar 4-C), 157.6 (Ar 2-C), 156.1 (CO_2NH), 133.5 (Ar 5-C), 81.6 ($OC(CH_3)_3$), 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, ArCH_2), 29.2 (broad, pyrrolidine 4-C), 28.2 ($OC(CH_3)_3$), 19.8 oxazolidine CH_3); υ_{max}/cm^{-1} (neat) 2974, 1747, 1695, 1562, 1480, 1410, 1234, 1168, 1123, 1046; *m/z* (ESI) 307 (100%, MH^+); Found: MH^+, 363.2031. $C_{18}H_{26}N_4O_4$ requires *MH*, 363.2031.

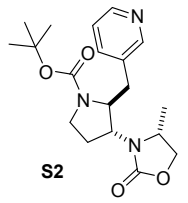
***tert*-Butyl-(2*S*,3*R*)-2-[(4-cyanophenyl)methyl]-3-[(4*R*)-4-methyl-2-oxo-1,3-oxazolidin-3-yl]pyrrolidine-1-carboxylate 40**



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 CH_2Cl_2–EtOH–NH_3OH 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 CH_2Cl_2–EtOH–NH_3OH); 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-HB), 3.72-3.67 (1 H, m, pyrrolidine 5-HA), 3.19-3.13 (2 H, m, pyrrolidine 5-HB, ArCHA), 2.94 (1 H, dd, J 13.4, 7.9, ArCHB), 2.11 (1 H, app. br s, pyrrolidine 4-HA), 2.02-1.96 (1 H, m, pyrrolidine 4-HB), 1.45 (9 H, s, OC(CH3)3), 1.12 (3 H, d, J 6.0, oxazolidine CH3); δC (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); υmax/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**

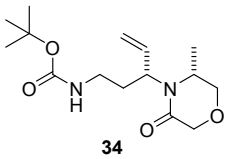


S2

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 CH_2Cl_2–EtOH–NH_3OH 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 CH_2Cl_2–EtOH–NH_3OH); 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(CH_3)$_3$), 1.14 (3 H, d, *J* 6.1, oxazolidine CH_3); δ_C (125 MHz, MeOD, 333 K), 159.7 (oxazolidine 1-C), 156.1 (*C*O_2NH), 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 (O*C*(CH_3)$_3$), 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, Ar*C*H_2), 29.5 (broad, pyrrolidine 4-C), 28.8 (OC(*C*H_3)$_3$), 19.7 (oxazolidine *C*H_3);

υ_{max}/cm^{-1} (neat) 2975, 1746, 1693, 1479, 1402, 1366, 1231, 1170, 1124, 1044; *m/z* (ESI) 362 (100%, MH$^+$); Found: MH$^+$, 362.2079. $C_{19}H_{27}N_3O_4$ requires *MH*, 362.2074.

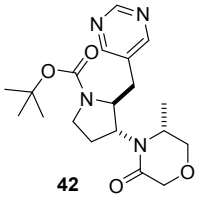
tert-Butyl-_N_-[(3_R_)-3-[(3_R_)-3-methyl-5-oxomorpholin-4-yl]pent-4-en-1-yl]carbamate 34



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, OC(C*H*$_3$)$_3$), 1.32 (3 H, d, *J* 6.5, morpholine C*H*$_3$); δ_C (125 MHz, $CDCl_3$), 166.9 (morpholine 5-C), 155.8 (*C*O$_2$NH), 135.7 (4-C), 118.1 (5-C), 78.2 (O*C*(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 (OC(*C*H$_3$)$_3$), 18.8 (morpholine *C*H$_3$); υ_{max}/cm^{-1} (neat) 3334, 2977, 1709, 1643, 1524, 1366, 1275, 1171; *m/z* (ESI) 299 (100%, MH$^+$); Found: MH$^+$, 299.1973. $C_{15}H_{26}N_2O_4$ requires *MH*, 299.1965.

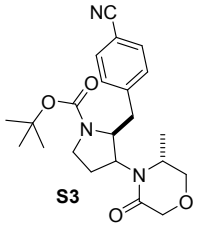
tert-Butyl-(2_S_,3_R_)-3-[(3_R_)-3-methyl-5-oxomorpholin-4-yl]-2-(pyrimidin-5-ylmethyl)pyrrolidine-1-carboxylate 42



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 5µm 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 ArC*H*$_A$), 2.94 (1 H, dd, *J* 13.9, 5.3, ArC*H*$_B$), 2.10-2.08 (2 H, m, pyrrolidine 4-H), 1.41 (9 H, s, OC(C*H*$_3$)$_3$), 1.30 (3 H, d, *J* 6.4, morpholine C*H*$_3$); δ_C (125 MHz, MeOD, 333 K), 169.6 (morpholine 5-C), 159.1 (Ar 2-C), 157.6 (Ar 4-C), 156.1 (*C*O$_2$NH), 133.4 (Ar 1-C), 81.6 (O*C*(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, ArC*H*$_2$), 28.7 (OC(*C*H$_3$)$_3$, and pyrrolidine 4-C), 19.7 (morpholine *C*H$_3$); υ_{max}/cm^{-1} (neat) 2978, 1694, 1651, 1562, 1409, 1367, 1286, 1152, 1124, 1048; *m/z* (ESI) 377 (100%, MH$^+$); Found: MH$^+$, 377.2190. $C_{19}H_{28}N_4O_4$ requires *MH*, 377.2183.

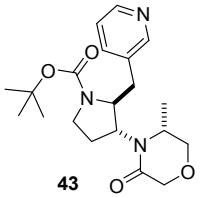
***tert*-Butyl-(2*S*,3*R*)-2-[(4-cyanophenyl)methyl]-3-[(3*R*)-3-methyl-5-oxomorpholin-4-yl]pyrrolidine-1-carboxylate S3**



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 CH_2Cl_2–EtOH–NH_3OH 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 CH_2Cl_2–EtOH–NH_3OH); 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-HA), 3.64 (1 H, dd, J 11.6, 1.3, morpholine 2-HA), 3.51 (1 H, dd, J 11.6, 1.9, morpholine 2-HB), 3.43-3.39 (1 H, m, morpholine 3-H), 3.13-3.05 (2 H, m, pyrrolidine 5-HB and ArCHA), 3.00 (1 H, dd, J 13.4, 7.3, ArCHB), 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); δC (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); υmax/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**

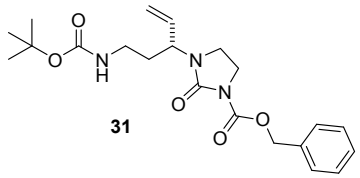


43

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 CH_2Cl_2–EtOH–NH_3OH 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 CH_2Cl_2–EtOH–NH_3OH); 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 ArCH_2), 2.05-2.02 (2 H, m, pyrrolidine 4-H), 1.44 (9 H, s, OC(CH_3)$_3$), 1.23 (3 H, d, *J* 6.4, morpholine CH_3); δ_C (125 MHz, MeOD, 333 K), 169.5 (morpholine 5-C), 156.1 (CO_2NH), 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(CH_3)$_3$), 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, ArCH_2), 28.8 (OC(CH_3)$_3$), 28.5 (pyrrolidine 4-C), 19.5 (morpholine

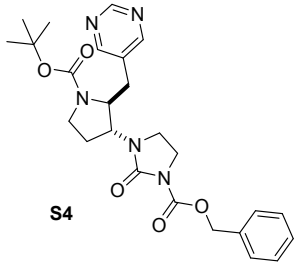
*C*H$_3$); υ_{max}/cm^{-1} (neat) 2976, 1688, 1652, 1426, 1402, 1367, 1166, 1123; *m/z* (ESI) 376 (100%, MH$^+$); Found: MH$^+$, 376.2236. $C_{20}H_{29}N_3O_4$ requires *MH*, 376.2231.

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



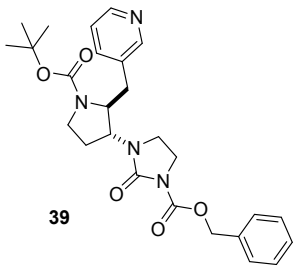
According to General Procedure C2 amine **13** (0.569 g, 1.51 mmol) furnished urea **31** (0.453 g, 74%) as a colourless oil, R_f 0.29 (1:1 petrol–EtOAc); $[\alpha]_D^{26}$ +65 (*c.* 0.36, $CHCl_3$); δ_H (500 MHz, MeOD, 333 K) 7.42-7.28 (5 H, m, Ar-H), 5.83 (1 H, ddd, *J* 17.5, 10.3, 6.1, 2-H), 5.24-5.20 (4 H, m, 1-H, OC*H*$_2$Ar), 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(C*H*$_3$)$_3$); δ_C (125 MHz, MeOD, 333 K) 158.3 (*C*O$_2$NH), 155.8 (imidazolidine 2-C), 153.4 (ArCH$_2$O*C*O$_2$), 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 (O*C*(CH$_3$)$_3$), 68.8 (O*C*H$_2$Ar), 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(*C*H$_3$)$_3$); υ_{max}/cm^{-1} (neat) 3362, 2975, 1774, 1701, 1509, 1389, 1250, 1165; *m/z* (ESI) 426 (100%, MNa$^+$); Found: MNa$^+$, 426.2004. $C_{21}H_{29}N_3O_5$ 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–NH_3OH 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 5µm 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–NH_3OH); 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, OC*H*$_2$Ar), 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, ArC*H*$_A$), 2.95 (1 H, dd, *J* 13.6, 5.9, ArC*H*$_B$), 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(C*H*$_3$)$_3$); δ_C (125 MHz, MeOD, 333 K) 159.0 (Ar 4-C), 157.6 (Ar 2-C), 156.0 (*t*Bu*C*O$_2$N), 155.6 (imidazolidine 2-C), 153.3 (ArCH$_2$O*C*O$_2$), 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 (O*C*(CH$_3$)$_3$), 68.8 (O*C*H$_2$Ar), 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, Ar*C*H$_2$), 28.7 (OC(*C*H$_3$)$_3$), 27.6 (pyrrolidine 4-C); υ_{max}/cm^{-1} (neat) 2974, 1775, 1684, 1362, 1259, 1212; *m/z* (ESI) 504 (100%, MNa$^+$); Found: MNa$^+$, 504.2223. $C_{25}H_{31}N_5O_5$ requires *MNa*, 504.2217.

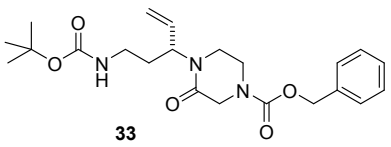
Benzyl-3-[(2*S*,3*R*)-1-[(*tert*-butoxy)carbonyl]-2-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-2-oxoimidazolidine-1-carboxylate 39



39

According to General Procedure A, urea **31** (0.149 g, 0.370 mmol) and 3-bromopyridine (43.0 μL, 0.440 mmol) gave a crude product that was purified by flash column chromatography, eluting with 95:4.5:0.5 DCM–EtOH–NH_3OH 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 5μm 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–NH_3OH); 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, OCH_2Ar), 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, ArCH_2), 2.06-1.93 (2 H, m, 4-H), 1.43 (OC(CH_3)$_3$); δ_C (125 MHz, MeOD, 333 K) 155.9 (*t*Bu*C*O_2N and imidazolidine 2-C), 153.3 (ArCH_2O*C*O_2), 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 (O*C*(CH$_3$)$_3$), 68.8 (O*C*H_2Ar), 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, Ar*C*H_2), 28.8 (OC(*C*H$_3$)$_3$), 27.7 (pyrrolidine 4-C); υ_{max}/cm^{-1} (neat) 2974, 1775, 1684, 1387, 1362, 1259, 1164, 1114; *m/z* (ESI) 503 (100%, MNa^+); Found: MNa^+, 503.2270. $C_{26}H_{32}N_5O_5$ requires *MNa*, 503.2265.

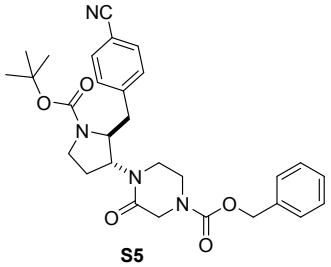
Benzyl-4-[(3*R*)-5-{[(*tert*-butoxy)carbonyl]amino}pent-1-en-3-yl]-3-oxopiperazine-1-carboxylate 33



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 CH_2Cl_2–EtOH–NH_3OH to furnish ketopiperazine **33** (0.399 g, 72%) as a yellow oil, R_f 0.20 (1:1 petrol–EtOAc); $[\alpha]_D^{24}$ +47 (*c.* 0.95, $CHCl_3$); 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, OCH_2Ar), 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(CH_3)$_3$); δ_C (125 MHz, MeOD, 333 K), 168.0 (piperazine 3-C), 158.3 (ArCH_2O*C*O_2), 156.3 (*C*O_2NH), 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 (O*C*(CH$_3$)$_3$), 68.8 (O*C*H_2Ar), 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(*C*H$_3$)$_3$); υ_{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. $C_{22}H_{31}N_3O_5$ requires *MNa*, 440.2156.

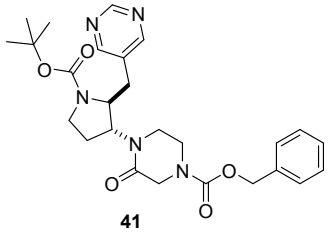
Benzyl-4-[(2*S*,3*R*)-1-[(*tert*-butoxy)carbonyl]-2-[(4-cyanophenyl)methyl]pyrrolidin-3-yl]-3-oxopiperazine-1-carboxylate S5



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 5µm OBD, 50-95% MeOH–water with 0.1% HCOOH) for the purposes of analysis, R_f 0.35 (95:4.5:0.5 CH_2Cl_2–EtOH–NH_3OH); 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); δC (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≡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; υmax/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

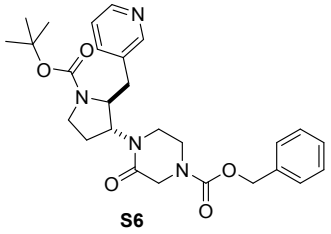


41

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 CH_2Cl_2–EtOH–NH_3OH 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 5µm OBD, 50-95% MeOH–water with 0.1% HCOOH) for the purposes of analysis, R_f 0.28 (95:4.5:0.5 CH_2Cl_2–EtOH–NH_3OH); 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, O*C*H_2Ar), 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, OCH_2Ar), 2.01-1.94 (2 H, m, pyrrolidine 4-H), 1.43 (9 H, s, OC(CH_3)$_3$); δ_C (125 MHz, MeOD, 333 K) 167.9 (piperazine 3-C), 159.0 (Ar 4-C), 157.7 (Ar 2-C), 156.2 (ArCH_2O*C*O_2), 156.0 (*C*O_2NH), 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 (O*C*(CH$_3$)$_3$), 68.8 (O*C*H_2Ar), 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 (Ar*C*H$_2$), 28.7 (OC(*C*H$_3$)$_3$), 27.3 (pyrrolidine 4-C); υ_{max}/cm^{-1} (neat) 2973, 1687, 1649, 1560, 1393, 1364, 1234, 1164, 1118, 1049; *m/z* (ESI) 518 (100%, MNa$^+$); Found: MNa$^+$, 518.2375. $C_{26}H_{33}N_5O_5$ requires *MNa*, 518.2374.

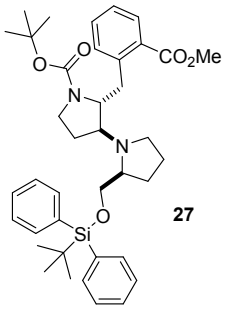
Benzyl-4-[(2*S*,3*R*)-1-[(*tert*-butoxy)carbonyl]-2-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-3-oxopiperazine-1-carboxylate S6



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 CH_2Cl_2–EtOH–NH_3OH 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 5μm 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 CH_2Cl_2–EtOH–NH_3OH); 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, O*C*H$_2$Ar), 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$_B$, OC*H*$_A$Ar), 2.93 (1 H, dd, *J* 13.6, 7.5, OC*H*$_B$Ar), 1.95-1.91 (2 H, m, pyrrolidine 4-H), 1.45 (9 H, s, OC(C*H*$_3$)$_3$); δ_C (125 MHz, MeOD, 333 K) 167.8 (piperazine 3-C), 156.1 (ArCH$_2$O*C*O$_2$), 155.9 (*t*Bu*C*O$_2$N), 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 (O*C*(CH$_3$)$_3$), 68.8 (O*C*H$_2$Ar), 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 (Ar*C*H$_2$), 28.8 (OC(*C*H$_3$)$_3$), 27.5 (pyrrolidine 4-C); υ_{max}/cm^{-1} (neat) 2974, 1685, 1649, 1422, 1392, 1364, 1322, 1234, 1165, 1119, 1051; *m/z* (ESI) 495 (100%, MH$^+$); Found: MH$^+$, 495.2612. $C_{27}H_{34}N_4O_5$ 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**

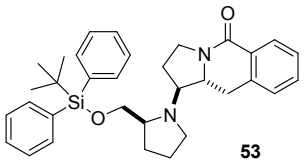


27

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 Et_2O–pentane to furnish pyrrolidine **27** (0.208 g, 83%, >95:5 *dr*) as a yellow oil; R_f 0.15 (70:30, pentane—Et_2O); 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-H_2 and 3′-H_B), 1.56 (2H, br s, 3-H), 1.19 (9H, br s, OC(CH_3)$_3$), 1.00 (9H, s, SiC(CH_3)$_3$); δ_C (125 MHz; DMSO *d*6; 353 K) 167.5 (*C*O_2Me), 153.3 (NH*C*O_2), 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 (O*C*(CH_3)$_3$), 66.7 (SiOCH_2), 61.9 (N*C*H), 61.1 (*C*H_2Ar), 51.7 (OCH_3), 49.5 (5′-C), 44.6 (5-C), 27.9 (OC(*C*H_3)$_3$ and 4′-C), 27.7 (4-C), 26.7 (SiC(*C*H_3)$_3$), 23.3 (3′-C), 18.8 (Si*C*(CH_3)$_3$); ν_{max}/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, $C_{39}H_{52}N_2O_5Si$ requires *MH* 657.3718.

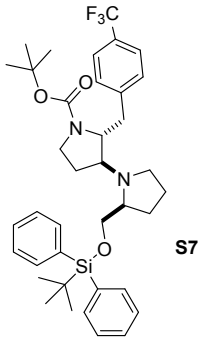
(1*S*,10a*R*)-1-[(2*S*)-2-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}pyrrolidin-1-yl]-1*H*,2*H*,3*H*,5*H*,10*H*,10a*H*-pyrrolo[1,2-b]isoquinolin-5-one 53



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, $CDCl_3$) 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(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 163.4(Ar*C*O), 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 (SiOCH_2), 60.6 (pyrrolidine 2-C), 58.2 (9-C), 52.5 (7-C), 42.3 (ArCH_2), 34.4 (pyrrolidine 5-C), 28.5 (8-C), 26.9 (SiC(*C*H_3), 24.9 (pyrrolidine 3-C), 23.9 (pyrrolidine 4-C), 19.2 (Si*C*(CH_3)$_3$); υ_{max}/cm^{-1} (neat) 2954, 1639, 1469, 1427, 1360, 1117, 1065; *m/z* (ESI) 525 (100%, MH$^+$); Found: MH$^+$, 525.2942. $C_{33}H_{40}N_2O_2Si$ requires *MH*, 525.2932.

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

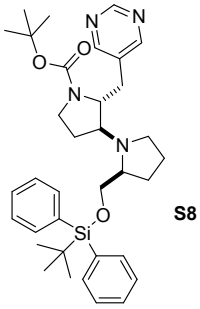


S7

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(CH_3)$_3$), 0.98 (9H, s, SiC(CH_3)$_3$); δ_C (125 MHz; DMSO; 343 K) 153.3 (NH*C*O$_2$), 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 (O*C*(CH$_3$)$_3$), 66.5 (SiO*C*H$_2$), 61.6 (N*C*H), 61.2 (*C*H$_2$Ar), 59.6 (1′-C), 49.9 (5-C), 49.1 (5-C), 28.1 (4-C), 27.5 (SiC(*C*H$_3$)$_3$ and 4′-C), 23.2 (3′-C), 18.8 (Si*C*(CH$_3$)$_3$); 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, $C_{38}H_{49}F_3N_2O_3Si$ requires *MH* 667.3537.

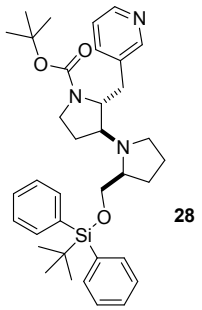
***tert*-Butyl-(2*R*,3*S*)-3-[(2*S*)-2-{[(*tert*-butyldiphenylsilyl)oxy]methyl}pyrrolidin-1-yl]-2-(pyrimidin-5-ylmethyl)pyrrolidine-1-carboxylate S8**



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 H_2), 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-H_2), 1.61-1.55 (2H, m, 3′ or 4-H_2), 1.29 (9H, s, OC(CH_3)$_3$), 1.01 (9H, s, SiC(CH_3)$_3$); δ_C (125 MHz; DMSO; 353 K) 157.2 (pyr 2-C), 156.4 (NH*C*O$_2$), 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 (O*C*(CH$_3$)$_3$), 66.9 (*C*H$_2$OSi), 61.6 (2-C), 60.7 (2′-C), 50.3 (5-C), 44.6 (5′-C), 33.8 (*C*H$_2$Ar), 28.0 (OC(*C*H$_3$)$_3$), 27.7 (3-C), 27.5 (3′-C), 26.8 (4-C), 24.1 (SiC(*C*H$_3$)$_3$), 18.7 (Si*C*(CH$_3$)$_3$; 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, $C_{35}H_{48}N_4O_3Si$ requires *MH* 601.3568.

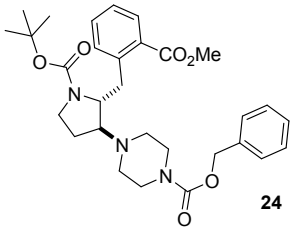
***tert*-Butyl-(2*R*,3*S*)-3-[(2*S*)-2-{[(*tert*-butyldiphenylsilyl)oxy]methyl}pyrrolidin-1-yl]-2-(pyridin-3-ylmethyl)pyrrolidine-1-carboxylate 28**



28

According to General Procedure A, amine **14** (0.150 g, 0.287 mmol) and 3-bromopyridine (33.0 μL, 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, SiOCH_2), 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(CH_3)$_3$), 1.04 (9 H, s, SiC(CH_3)$_3$); δ_C (125 MHz, MeOD, 333 K) 156.0 (*t*Bu*C*O_2N), 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 (O*C*(CH$_3$)$_3$), 68.3 (SiO*C*H$_2$), 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 pyrroldine 5-C), 38.2 (broad, Ar*C*H$_2$), 29.2 (pyrrolidine 3-C), 28.9 (OC(*C*H$_3$)$_3$), 27.6 (SiC(*C*H$_3$), 24.5 (pyrrolidine 4-C), 20.1 (Si*C*(CH$_3$)$_3$), signal for *N*-Boc pyrrolidine 4-C not observed; υ_{max}/cm^{-1} (neat) 2960, 1688, 1455, 1390, 1363, 1104, 1027; *m/z* (ESI) 600 (100%, MH$^+$); Found: MH$^+$, 600.3631. $C_{36}H_{50}N_3O_3Si$ requires *MH*, 600.3616.

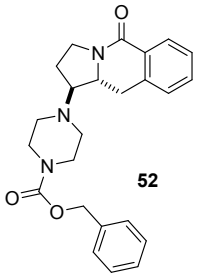
Benzyl-4-[(2*R*,3*S*)-1-[(tert-butoxy)carbonyl]-2-{[2-(methoxycarbonyl)phenyl]methyl}pyrrolidin-3-yl]piperazine-1′-carboxylate 24



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 $CHCl_3$–MeOH to furnish pyrrolidine **24** (0.310 g, 84%, >95:5 *dr*) as a yellow oil; R_f 0.3 (30:70, Et_2O—pentane); δ_H (500 MHz; C_6D_6; 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(CH_3)$_3$); δ_C (75 MHz; C_6D_6) 154.9 (NH*C*O_2), 153.9 (NH*C*O_2), 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 (O*C*(CH$_3$)$_3$), 66.9 (2-C), 53.0 (OCH$_3$), 51.3 (pip 3-C), 49.4 (pip 2-C), 44.2 (5-C), 29.8 (Ar*C*H$_2$), 28.3 (OC(*C*H$_3$)$_3$), 25.8 (4-C); ν_{max}/cm^{-1} (film) 2973, 1694, 1433, 1393, 1244; *m/z* (ES$^+$) 538.3 (100%, MH$^+$; found 538.2920, $C_{30}H_{39}N_3O_6$ requires *MH* 538.2912.

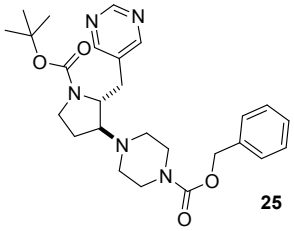
Benzyl-4-[(1*S*,10a*R*)-5-oxo-1*H*,2*H*,3*H*,5*H*,10*H*,10a*H*-pyrrolo[1,2-b]isoquinolin-1-yl]piperazine-1-carboxylate 52



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 CH_2Cl_2—MeOH (95:5) to furnish lactam **52** (51 mg, 68%) as a foam. R_f 0.55 (95:5, CH_2Cl_2—MeOH); δ_H (500 MHz; $CDCl_3$) 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; $CDCl_3$) 163.6 (9-C), 155.2 (NH*C*O_2), 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 (*C*H_2Ar), 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, $C_{24}H_{27}N_3O_3$ requires *MH* 406.2125.

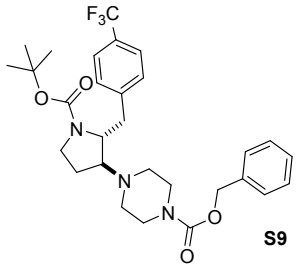
Benzyl-4-[(2*R*,3*S*)-1-[(*tert*-butoxy)carbonyl]-2-(pyrimidin-5-ylmethyl)pyrrolidin-3-yl]piperazine-1-carboxylate 25



25

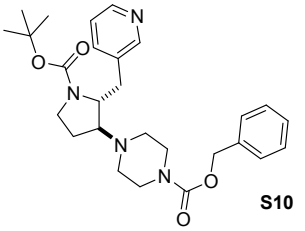
According to General Procedure A, amine **15** (0.908 g, 2.25 mmol) and 5-bromopyrimidine (467 mg, 2.93 mmol) gave a crude product that was purified by flash column chromatography, eluting with 95:5 CH_2Cl–MeOH to furnish pyrrolidine **25** (0.870 g, 80%, >95:5 *dr*) as a yellow oil; R_f 0.1 (50:50, Et_2O—pentane); δ_H (500 MHz; C_6D_6; 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(CH_3)$_3$), 1.27-1.21 (1H, m, 4-H_A), 1.08 (1H, br s, 4-H_B); δ_C (125 MHz; C_6D_6) 158.9 (pyr 2-C), 157.6 (NH*C*O_2), 157.5 (NH*C*O_2), 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 (O*C*(CH_3)$_3$), 67.1 (Ar*C*H_2O), 49.3 (3-C), 45.5 (pip 3-C), 44.1 (pip 2-C), 43.6 (5-C), 29.8 (Ar*C*H_2), 28.3 (OC(*C*H_3)$_3$), 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, $C_{26}H_{35}N_5O_4$ requires *MH* 482.2762.

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



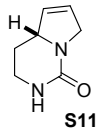
According to General Procedure A, amine **15** (0.287 g, 0.71 mmol) and 4-bromobenzenetrifluoride (209 mg, 0.93 mmol) gave a crude product that was purified by flash column chromatography, eluting with 95:5 $CHCl_3$–MeOH to furnish pyrrolidine **S9** (0.287 g, 74%, >95:5 *dr*) as a yellow oil; R_f 0.44 (95:5, $CHCl_3$—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, ap 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(CH_3)$_3$); δ_C (125 MHz; DMSO-*d*6; 353 K) 154.4 (NH*C*O_2), 153.2 (NH*C*O_2), 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 (O*C*(CH$_3$)$_3$), 66.1 O*C*H$_2$Ar, 59.8 (3′-C), 54.7 (pip 2-C), 48.8 (2′-C), 44.8 (pip 3-C), 43.8 (Ar*C*H$_2$), 28.1 (O*C*(CH$_3$)$_3$), 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, $C_{29}H_{36}F_3N_3O_4$ requires *MH* 548.2731.

Benzyl-4-[(2*R*,3*S*)-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, OCH_2Ar), 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(CH_3)$_3$); δ_C (125 MHz, MeOD, 333 K) 156.9 (*t*Bu*C*O_2N), 156.0 (ArCH$_2$O*C*O_2), 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 (O*C*(CH$_3$)$_3$), 68.4 (O*C*H$_2$Ar), 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, *C*H$_2$Ar), 28.8 (OC(*C*H$_3$)$_3$), 26.1 (pyrrolidine 4-C); υ_{max}/cm^{-1} (neat) 2971, 1685, 1423, 1390, 1240, 1168, 1113, 1012; *m/z* (ESI) 481 (100%, MH$^+$); Found: MH$^+$, 481.2816. $C_{27}H_{36}N_4O_4$ requires *MH*, 481.2809.

(4a*R*)-1*H*,2*H*,3*H*,4*H*,4a*H*,7*H*-pyrrolo[1,2-c]pyrimidin-1-one S11

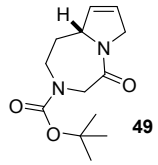


S11

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 CH_2Cl_2 (5 mL) and aqueous NaOH (1 M) (until aqeous phase was at pH 12). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3×3 mL). The combined organic phase was dried ($MgSO_4$) 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 CH_2Cl_2–MeOH) to furnish urea **S11** (24 mg, 67 %) as a brown oil; R_f 0.51 (9:1 CH_2Cl_2–MeOH); $[\alpha]_D^{21}$ –80 (*c* 0.80, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 5.88 (1 H, d, *J* 6.3 Hz, C*H*=CH), 5.78 (1 H, d, *J* 6.6 Hz, CH=C*H*), 5.20 (1 H, br. s, N*H*), 4.49 (1 H, dd, *J* 15.3, 5.31 Hz, NCH_2), 4.43–4.29 (1 H, m, NC*H*), 4.10 (1 H, ddd, *J* 15.3, 4.0, 2.0 Hz, NCH_2), 3.33 (2 H, d, *J* 8.3 Hz, NHCH_2), 2.09 (1 H, dd, *J* 12.3, 3.2 Hz, NHCH$_2$CH_2), 1.49 (1 H, qd, *J* 11.9, 7.8 Hz, NHCH$_2$CH_2); δ_C (100 MHz, $CDCl_3$) 155.7 (*C*=O), 129.1 (*C*H=CH), 127.1 (CH=*C*H), 62.5 (N*C*H), 53.7 (N*C*H$_2$), 40.2 (NH*C*H$_2$), 27.3 (NHCH$_2$*C*H$_2$); υ_{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. $C_7H_{10}ON_2$ requires *MH*, 138.0793.

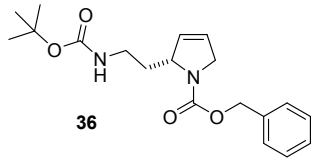
***tert*-Butyl-(9a*R*)-5-oxo-1*H*,2*H*,3*H*,4*H*,5*H*,7*H*,9a*H*-pyrrolo[1,2-d][1,4]diazepine-3-carboxylate 49**



49

According to General Procedure D1 where NEt_3 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 CH_2Cl_2–Et_2O to give dihydro-pyrrole **49** (0.021 g, 48%) as a yellow oil, R_f 0.19 (4:1 CH_2Cl_2–Et_2O); $[\alpha]_D^{26}$ –16 (*c.* 0.22, $CHCl_3$); 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(CH_3)$_3$); δ_C (125 MHz, MeOD, 333 K) 171.9 (diazepine 2-C), 156.6 (*t*Bu*C*O$_2$NH), 131.2 (pyrrole 4-C), 125.6 (pyrrole 3-C), 82.1 (O*C*(CH$_3$)$_3$), 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(*C*H$_3$)$_3$); υ_{max}/cm^{-1} (neat) 2977, 1755, 1682, 1394, 1365, 1240, 1155; *m/z* (ESI) 275 (100%, MNa^+); Found: MNa^+, 275.1367. $C_{13}H_{20}N_2O_3$ requires *MNa*, 275.1366.

Benzyl-(2*R*)-2-(2-{[(*tert*-butoxy)carbonyl]amino}ethyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate S36

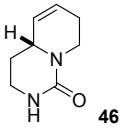


36

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, OC*H*$_2$Ar), 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, $OC(CH_3)_3$); δ_C (125 MHz, MeOD, 333 K) 158.3 (CO_2OCH_2Ar), 156.6 (*t*BuCO_2NH), 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 ($OC(CH_3)_3$), 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 ($OC(CH_3)_3$); υ_{max}/cm^{-1} (neat) 3355, 2976, 1713, 1682, 1514, 1416, 1327, 1251, 1172, 1107; *m/z* (ESI) 369 (100%, MNa^+); Found: MNa^+, 369.1782. $C_{19}H_{26}N_2O_4$ requires *MNa*, 369.1785.

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



46

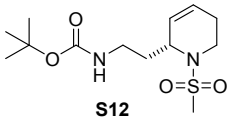
i) $NaHCO_3$ (88.0 mg, 1.05 mmol) followed by Boc_2O (0.229 g, 1.05 mmol) was added to a solution of amine **17** (0.222 g, 0.870 mmol) in THF (4.00 mL) and water (4.00 mL). The reaction mixture was stirred at room temperature for 2 h before being diluted with EtOAc (10.0 mL) and water (10.0 mL), the 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, N*H*), 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 (N*C*ONH), 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 ($NHCH_2CH_2$); υ_{max}/cm^{-1} (neat) 3206, 2916, 1650, 1499, 1439, 1367, 1287, 1139; *m/z* (ESI) 275 (100%, MH^+); Found: MH^+, 153.1021. $C_8H_{12}N_2O$ requires *MH*, 153.1022.

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

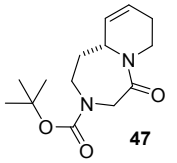


S12

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 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 (2 mL) and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 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 8:2→6:4 petrol–EtOAc) to furnish tetrahydropyridine **S12** (33.0 mg, 72%) as a yellow oil, R_f 0.28 (1:1 cylohexane–EtOAc); $[\alpha]_D^{21}$ –25 (*c* 1.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 5.88 (1 H, ddq, *J* 10.5, 5.2, 2.8 Hz, C*H*=CH), 5.72 (1 H, ddt, *J* 10.3, 4.0, 1.9 Hz, CH=C*H*), 5.25 (1 H, br. s, N*H*), 4.11 (1 H, d, *J* 10.3 Hz, NC*H*), 3.89 (1 H, ddd, *J* 14.9, 6.3, 0.7 Hz, NCH_2), 3.50–3.30 (1 H, m, NHCH_2), 3.20–3.00 (2 H, m, NCH_2, NHCH_2), 2.86 (3 H, s, SCH_3), 2.30 (1 H, dddq, *J* 18.6, 11.6, 6.8, 2.5 Hz, NCH_2CH_2), 1.99 (1 H, dt, *J* 18.2, 4.5 Hz, NCH_2CH_2), 1.80 (1 H, ddt, *J* 14.7, 9.6, 4.5 Hz, $NHCH_2CH_2$), 1.60 (1 H, ddt, *J* 14.6, 10.8, 4.1 Hz, $NHCH_2CH_2$), 1.44 (9 H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 156.2 (*C*=O), 128.6 (*C*H=CH), 125.3 (CH=*C*H), 79.1 (*C*$(CH_3)_3$), 51.0 (N*C*H), 39.7 (S*C*H_3), 38.1 (N*C*H_2), 36.6 (NH*C*H_2), 33.9 ($NHCH_2CH_2$), 28.6 ($C(CH_3)_3$), 23.2 (NCH_2CH_2); υ_{max}/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. $C_{13}H_{24}O_4N_2S$ requires *MNa*, 327.1349.

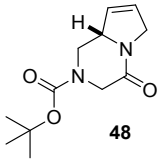
***tert*-Butyl-(10a*R*)-5-oxo-1*H*,2*H*,3*H*,4*H*,5*H*,7*H*,8*H*,10a*H*-pyrido[1,2-d][1,4]diazepine-3-carboxylate 47**



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, $CHCl_3$); δ_H (400 MHz, DMSO-d_6, 120 °C) 5.93 (1 H, ddd, *J* 10.3, 6.8, 4.0 Hz, CHC*H*=CH), 5.69–5.60 (1 H, ddt, *J* 10.2, 3.6, 1.9 Hz, CHCH=C*H*), 4.28–4.16 (1 H, m, NCH_2CO, NC*H*), 4.02 (1 H, d, *J* 15.6 Hz, NCH_2CO), 3.85 (1 H, dt, *J* 12.8, 5.0 Hz, NCH_2CH_2CH=CH), 3.49 (2 H, t, *J* 5.9 Hz, BocNCH_2CH_2), 3.14 (1 H, ddd, *J* 13.1, 7.3, 5.3 Hz, NCH_2CH_2CH=CH), 2.17–1.96 (2 H, m, NCH_2CH_2CH=CH), 1.97–1.82 (1 H, m, $BocNCH_2CH_2$), 1.77–1.60 (1 H, m, $BocNCH_2CH_2$), 1.42 (9 H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 168.6 (CH_2CON), 154.6 (O*C*ON), 127.4 (*C*H=CH), 126.5 (CH=*C*H), 80.6 (*C*$(CH_3)_3$), 53.0 (N*C*H_2CO), 52.7 (br., N*C*H), 43.6 (BocN*C*H_2CH_2), 37.0 (N*C*H_2CH_2CH=CH), 32.8 ($BocNCH_2CH_2$), 28.5 ($C(CH_3)_3$), 24.5 (NCH_2CH_2CH=CH); υ_{max}/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. $C_{14}H_{22}O_3N_2$ requires *MNa*, 289.1523.

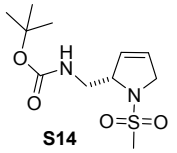
***tert*-Butyl-(8a*S*)-4-oxo-1*H*,2*H*,3*H*,4*H*,6*H*,8a*H*-pyrrolo[1,2-a]piperazine-2-carboxylate 48**



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, OC(CH_3)$_3$); δ_C (125 MHz, MeOD, 333 K) 167.2 (4-C), 155.7 (N*C*O_2), 128.8 (8-C), 127.7 (7-C), 82.3 (O*C*(CH_3)$_3$), 64.2 (8a-C), 53.7 (3-C), 48.1 (6-C), 46.7 (1-C), 28.7 (C(*C*H_3)$_3$); υ_{max}/cm^{-1} (neat) 2975, 1692, 1658, 1393, 1365, 1323, 1237, 1161, 1124; *m/z* (ESI) 239 (100%, MH^+); Found: MH^+, 239.1387. $C_{12}H_{18}N_2O_3$ requires *MH*, 239.1390.

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

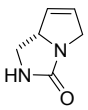


S14

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 × 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 cylohexane–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, C*H*=CH), 5.74 (1 H, dq, *J* 6.3, 2.3 Hz, CH=C*H*), 5.02 (1 H, br. s, N*H*), 4.52 (1 H, dt, *J* 5.8, 2.0 Hz, MsNC*H*), 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, C(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 156.3 (*C*=O), 128.2 (*C*H=CH), 126.5 (CH=*C*H), 79.4 (*C*(CH_3)$_3$), 67.7 (MsN*C*H), 56.0 (MsN*C*H_2), 44.7 (BocNH*C*H_2), 34.5 (S*C*H_3), 28.4 (C(*C*H_3)$_3$); υ_{max}/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. $C_{11}H_{20}O_4N_2S$requires *MNa*, 299.1036.

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



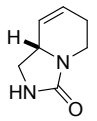
S13

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 aqeous phase was at pH 12). The layers were separated and the aqueous phase was

extracted with CH_2Cl_2 (3×3 mL). The combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. For the urea formation, 1.2 eq CDI and 2.0 eq DBU were used to give gave 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); $[\alpha]_D^{21}$ –82 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 6.24 (1 H, br. s, N*H*), 5.93 (1 H, dq, *J* 6.0, 2.0 Hz, C*H*=CH), 5.81 (1 H, ddt, *J* 5.9, 3.8, 1.7 Hz, CH=C*H*), 4.59 (1 H, ddq, *J* 8.0, 5.8, 3.6 Hz, NC*H*), 4.32 (1 H, dq, *J* 15.5, 2.3 Hz, NCH_2), 3.70 (1 H, t, *J* 9.2 Hz, NHCH_2), 3.63 (1 H, ddt, *J* 15.6, 4.5, 1.8 Hz, NCH_2), 3.39 (1 H, dd, *J* 8.9, 4.1 Hz, NHCH_2); δ_C (100 MHz, $CDCl_3$) 167.3 (*C*=O), 130.1 (*C*H=CH), 129.8 (CH=*C*H), 64.7 (N*C*H), 54.1 (N*C*H_2), 44.2 (NH*C*H_2); υ_{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. $C_6H_8ON_2$ 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



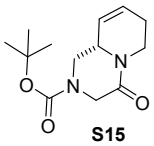
45

i) $NaHCO_3$ (21.0 mg, 0.250 mmol) followed by Boc_2O (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 ($MgSO_4$), 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 9:1 CH_2Cl_2–Et_2O 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 CH_2Cl_2–EtOH–NH_3OH; $[\alpha]_D^{28}$ +55 (*c.* 0.29, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 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, N*H*), 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, $CDCl_3$) 162.1 (N*C*ONH), 127.5 (3-C), 127.4 (4-C), 52.9 (2-C), 44.5 (NH*C*H_2), 37.4 (6-C), 23.5 (5-C); υ_{max}/cm^{-1} (neat) 3252, 2921, 1686, 1659, 1424, 1259, 1087; *m/z* (ESI) 139 (100%, MH^+); Found: MH^+, 139.0862. $C_7H_{10}N_2O$ 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**

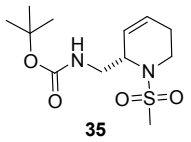


S15

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); $[\alpha]_D^{21}$ +67 (*c* 1.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 5.99 (1 H, ddt, *J* 9.6, 5.4, 1.6 Hz, CHCH=C*H*), 5.49 (1 H, ddt, *J* 10.1, 2.8, 1.4 Hz, CHC*H*=CH), 4.76 (1 H, ddt, *J* 13.1, 5.8, 1.3 Hz, NCH_2CH$_2$CH=CH), 4.45 (1 H, d, *J* 18.2 Hz, NCH_2CO), 4.37–4.11 (2 H, m, BocNCH_2C*H*), 3.78 (1 H, d, *J* 18.2 Hz, NCH_2CO), 2.75–2.70 (1H, m, BocNCH_2CH), 2.67 (1 H, td, *J* 12.2, 4.0 Hz, NCH_2CH$_2$CH=CH), 2.37–2.22 (1 H, m, NCH$_2$CH_2CH=CH), 2.15–2.04 (1 H, m, NCH$_2$CH_2CH=CH), 1.47 (9 H, s, C(CH_3)$_3$); δ_C

(100 MHz, $CDCl_3$) δ 165.1 (CH_2CON), 153.9 ($OCON$), 128.3 (CH=CH), 124.4 (CH=CH), 81.0 ($C(CH_3)_3$), 53.5 (NCH_2CO), 48.1 (NCH), 45.5 (BocNCH_2CH), 37.6 (NCH_2CH_2CH=CH), 28.5 ($C(CH_3)_3$), 25.0 (NCH_2CH_2CH=CH); υ_{max}/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. $C_{13}H_{20}O_3N_2$ requires *MNa*, 275.1366.

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

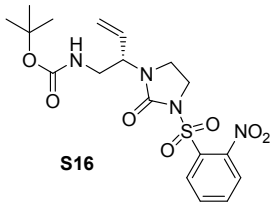


35

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 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 × 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 8:2→4:6 petrol–EtOAc) to furnish tetrahydro-pyridine **35** (27.0 mg, 54%) as a yellow oil, R_f 0.25 (1:1 cylohexane–EtOAc); $[\alpha]_D^{21}$ –81 (*c* 0.91, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 5.98 (1 H, ddt, *J* 9.8, 4.5, 2.1 Hz, C*H*=CH), 5.71 (1 H, dddd, *J* 10.4, 4.1, 2.6, 1.4 Hz, CH=C*H*), 5.00 (1 H, br. s, N*H*), 4.20 (1 H, dt, *J* 9.9, 3.3 Hz, NC*H*), 3.88 (1 H, dd, *J* 14.7, 6.2 Hz, NHCH_2), 3.35 (1 H, ddd, *J* 14.2, 6.8, 3.8 Hz, NCH_2), 3.25–3.08 (2 H, m, NHCH_2, NCH_2), 2.85 (3 H, s, SCH_3), 2.30 (1 H, dddd, *J* 18.3, 11.8, 6.2, 2.9 Hz, NCH_2CH_2), 2.02 (1 H, dt, *J* 18.0, 4.7 Hz, NCH_2CH_2), 1.43 (9 H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 156.2 (*C*=O), 127.5 (*C*H=CH), 125.3 (CH=*C*H), 79.6 ($C(CH_3)_3$), 53.5 (NCH), 43.0 (NCH_2), 39.9 (SCH_3), 38.3 ($NHCH_2$), 28.5 ($C(CH_3)_3$), 23.6 ($NCHCH_2$ υ_{max}/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. $C_{12}H_{22}O_4N_2S$ requires *MNa*, 313.1192.

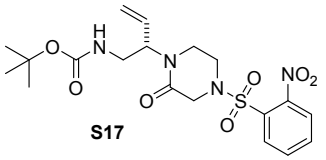
***tert*-Butyl-*N*-[(2*S*)-2-[3-(2-nitrobenzenesulfonyl)-2-oxoimidazolidin-1-yl]but-3-en-1-yl]carbamate S16**



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, $CDCl_3$) 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, CO_2NH), 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, $OC(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 155.9 (*t*BuCO_2N), 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 ($OC(CH_3)_3$), 55.1 (2-C), 42.1 (1-C), 40.6 (imidazolidine 5-C), 38.8 (imidazolidine 4-C), 28.2 (($OC(CH_3)_3$); υ_{max}/cm^{-1} (neat) 2979, 1713, 1591, 1541, 1482, 1427, 1268, 1168, 1128; *m/z* (ESI) 441 (100%, MH^+); Found: MH^+, 441.1456. $C_{18}H_{24}N_4O_7S$ requires *MH*, 441.1438.

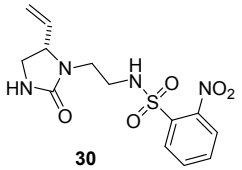
***tert*-Butyl-*N*-[(2*S*)-2-[4-(2-nitrobenzenesulfonyl)-2-oxopiperazin-1-yl]but-3-en-1-yl]carbamate S17**



S17

According to Procedure D4, amine **20** (0.390 g, 0.940 mmol) gave a crude product that was filtered through a plug of SiO_2, eluting with MTBE to furnish ketopiperazine **S17** (0.441 g, 89%) as a yellow oil, $[\alpha]_D^{20}$ +18.18 (c = 2.20, $CDCl_3$); δ_H (400 MHz, $CDCl_3$) 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, N*H*), 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(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 164.2 (piperazine 2-C), 156.0 (NH*C*O_2), 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 ((O*C*(CH_3)$_3$), 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(*C*H_3)$_3$); υ_{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. $C_{19}H_{26}N_4NaO_7S$ requires *MNa*, 477.1414.

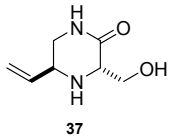
***N*-{2-[(5*S*)-5-Ethenyl-2-oxoimidazolidin-1-yl]ethyl}-2-nitrobenzene-1-sulfonamide 30**



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 SiO_2, 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-N*H*), 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-N*H*), 5.68-5.80 (1 H, m, ethenyl C*H*CH_2), 5.21-5.34 (2 H, m, ethenyl CHCH_2), 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, NCH_2), 2.91 - 3.08 (4 H, m, NCH_2, NCH_2CH_2 and imidazolidinone 4-H_B); δ_C (100 MHz, DMSO-d_6) 161.4 (imidazolidinone 2-C), 147.7 (Ar 2-C), 136.9 (ethenyl *C*HCH_2), 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 CH*C*H_2), 59.0 (imidazolidinone 5-C), 43.6 (imidazolidinone 4-C), 40.9 (N*C*H_2), 40.8 (N*C*H_2); υ_{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. $C_{13}H_{17}N_4O_5S$ requires *MH*, 341.0920.

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

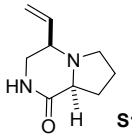


37

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, CH_{2A}OH), 3.82-

3.79 (1H, m, 5-H), 3.78 (1H, dd, *J* 11.0, 3.8, CH_{2B}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 (*C*H_2OH), 49.6 (6-C), 46.0 (5-C); υ_{max}/cm^{-1} (neat) 3317, 2984, 1682, 1497, 1430, 1352, 1206; *m/z* (ESI) 157 (100%, MH$^+$); Found: MH$^+$, 157.0979. $C_7H_{12}N_2O_2$ requires *MH*, 157.0972.

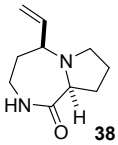
(4*R*,8a*S*)-4-ethenyl-octahydropyrrolo[1,2-a]piperazin-1-one S18



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); $[\alpha]_D^{20}$ −47 (*c* 0.5, MeOH); δ_H (600 MHz, $CDCl_3$) 6.78 (1H, br. s, N*H*), 5.77 (1H, ddd, *J* = 17.5, 10.4, 7.3 Hz, C*H*=CH_2), 5.28 (1H, dt, *J* = 17.2, 1.1 Hz, *trans*-CH=CH_2), 5.20 (1H, dd, *J* = 10.4, 1.3 Hz, *cis*-CH=CH_2), 3.39–3.31 (1H, m, CONHCH_2), 3.29–3.20 (2H, m, CONHCH_2, C*H*CH=CH_2), 3.01 (1H, t, *J* = 8.3 Hz, C*H*CONH), 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 (*C*=O), 136.4 (*C*H=CH_2), 118.7 (CH=*C*H_2), 64.4 (N*C*HCONH), 61.0 (*C*HCH=CH_2), 49.6 (CHN*C*H_2), 45.7 (CONH*C*H_2), 26.0 (*C*H_2CHCONH), 21.4 (NCH_2CH_2); υ_{max}/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. $C_9H_{15}N_2O$ requires *MH*, 167.118.

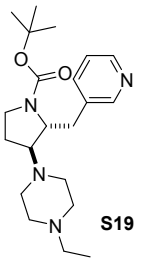
(5*S*,9a*S*)-5-ethenyl-octahydro-1*H*-pyrrolo[1,2-a][1,4]diazepin-1-one 38



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 an white solid, m.p. 101–102 °C; R_f 0.47 (8:2 CH_2Cl_2–MeOH); $[\alpha]_D^{21}$ +13 (*c* 0.8, MeOH); δ_H (500 MHz, $CDCl_3$) 6.04 (1H, br. s, N*H*), 5.84 (1H, ddd, *J* = 17.2, 10.1, 8.7 Hz, C*H*=CH_2), 5.17 (1H, dd, *J* = 17.1, 1.3 Hz, *trans*-CH=CH_2), 5.02 (1H, dd, *J* = 10.2, 1.6 Hz, *cis*-CH=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, C*H*CONH), 3.19–3.10 (1H, m, CHNCH_2), 2.99 (1H, td, *J* = 8.4, 4.8 Hz, C*H*CH=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, CH_2CH_2CHCONH, CH_2CHCH=CH_2); δ_C (100MHz, $CDCl_3$) δ 176.1 (*C*=O), 141.4 (*C*H=CH_2), 115.1 (CH=*C*H_2), 71.1 (*C*HCH=CH_2), 63.6 (*C*HCONH), 56.5 (CHN*C*H_2), 40.2 (CONH*C*H_2), 37.7 (*C*H_2CHCH=CH_2), 28.4 (*C*H_2CHCONH), 23.6 (*C*H_2CH_2CHCONH); υ_{max}/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. $C_{10}H_{17}N_2O$ requires *MH*, 181.1341.

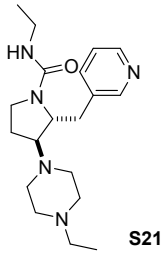
***tert*-Butyl-(2*R*,3*S*)-3-(4-ethylpiperazin-1-yl)-2-(pyridin-3-ylmethyl)pyrrolidine-1-carboxylate S19**



S19

10% Pd/C (0.244 g, 20 mol% Pd) and ethylene diamine (77.0 μL, 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 H_2, 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 μL, 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 $NaHCO_3$ 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–NH_4OH to furnish amine **S19** (0.200 g, 46%) as a colourless oil, R_f 0.16 (95:4.5:0.5 DCM–EtOH–NH_4OH); 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 CH_2), 1.98 (2 H, app. br s, pyrrolidine 4-H), 1.42 (9 H, s, $OC(CH_3)_3$), 1.05 (3 H, t, *J* 7.3, ethyl CH_3); δ_C (125 MHz, MeOD, 333 K) 155.9 (*t*BuCO_2N), 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 ($OC(CH_3)_3$), 76.9 (pyrrolidine 3-C), 61.6 (pyrrolidine 2-C), 54.2 (ethyl CH_2), 53.7 (piperazine 3-C and 5-C), 53.2 (piperazine 2-C and 6-C), 50.3 (pyrrolidine 5-C), 34.3 (CH_2Ar), 28.8 ($OC(CH_3)_3$), 26.3 (pyrrolidine 4-C), 11.7 (ethyl CH_3); υ_{max}/cm^{-1} (neat) 2970, 2812, 1686, 1390, 1363, 1162, 1111, 1027; *m/z* (ESI) 375 (100%, MH^+); Found: MH^+, 375.2765. $C_{21}H_{35}N_4O_2$ requires *MH*, 375.2754.

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

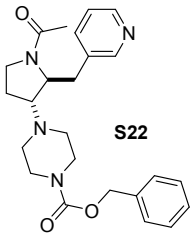


S21

TFA (1.00 mL) was added to a solution of pyrrolidine **S19** (0.100 g, 0.270 mmol) in CH_2Cl_2 (3.0 mL). The reaction mixture was stirred at room temperature for 16 h and concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 (3.0 mL) and cooled to 0 °C (ice). To this was added NEt_3 (0.190 mL, 1.35 mmol) and ethyl isocyanate (23.0 μL, 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 CH_2Cl_2–saturated methanolic NH_3 to furnish urea **S21** as a colourless oil, R_f 0.15 (CH_2Cl_2–saturated methanolic NH_3); δ_H (500 MHz, $CDCl_3$) 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, NCON*H*), 4.20-4.18 (1 H, m, 4.10, pyrrolidine 2-H), 3.33 (2 H, q, *J* 8.6, ethyl CH_2), 3.30-3.25 (2 H, m, urea CH_2), 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, piprazine 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 CH_3), 1.15 (3 H, t, *J* 7.2, ethyl CH_3); δ_C (75 MHz, $CDCl_3$) 156.3 (N*C*O_2N), 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 *C*H_2), 35.4 (ethyl *C*H_2 and ArCH_2), 24.1 (pyrrolidine 4-C), 15.5 (urea *C*H_2), 9.3 (ethyl *C*H_3); υ_{max}/cm^{-1} (neat) 3336, 2973, 1673, 1623, 1532, 1449, 1373, 1197, 1125; *m/z* (ESI) 346 (100%, MH^+); Found: MH^+, 346.2604. $C_{19}H_{31}N_5O$ 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 CH_2Cl_2 (6.0 mL). The reaction mixture was stirred at room temperature for 16 h and concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 (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–NH_4OH 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–NH_4OH); 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, OCH_2Ar), 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 NCOCH_3); δ_C (125 MHz, MeOD, 333 K) 171.6 (N*C*OCH_3), 156.8 (ArCH_2O*C*O_2), 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 (O*C*H_2Ar), 61.3 (pyrrolidine 2-C), 50.6 (piperazine 3-C), 47.9 (pyrrolidine 5-C), 45.0 (piperazine 2-C), 36.5 (*C*H_2Ar), 26.5 (pyrrolidine 4-C), 22.4 (NCO*C*H_3); υ_{max}/cm^{-1} (neat) 2948, 1695, 1629, 1422, 1358, 1243, 1119, 1079; *m/z* (ESI) 423 (100%, MH^+); Found: MH^+, 423.2399. $C_{24}H_{31}N_4O_3$ requires *MH*, 423.2391.

S9. References

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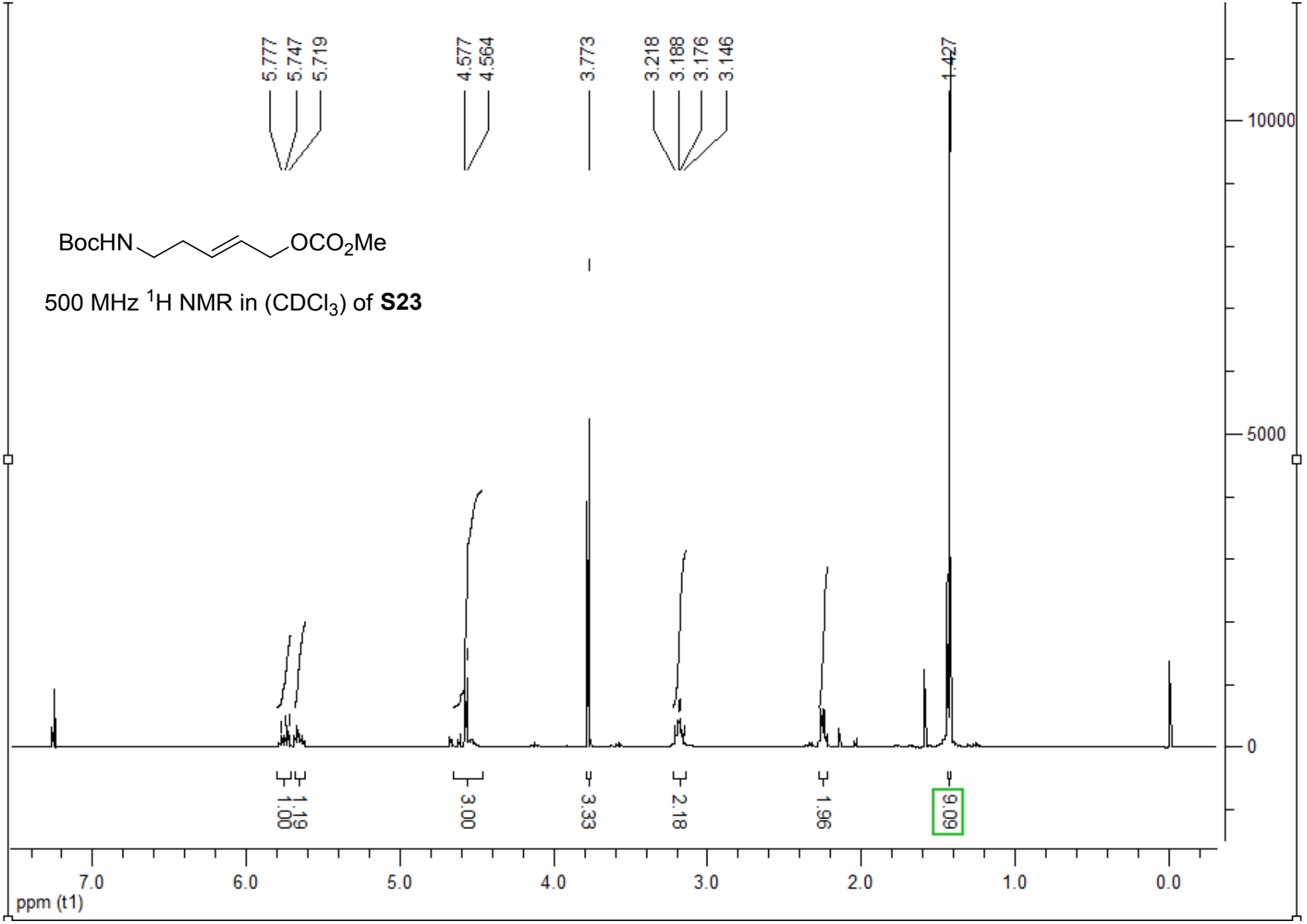
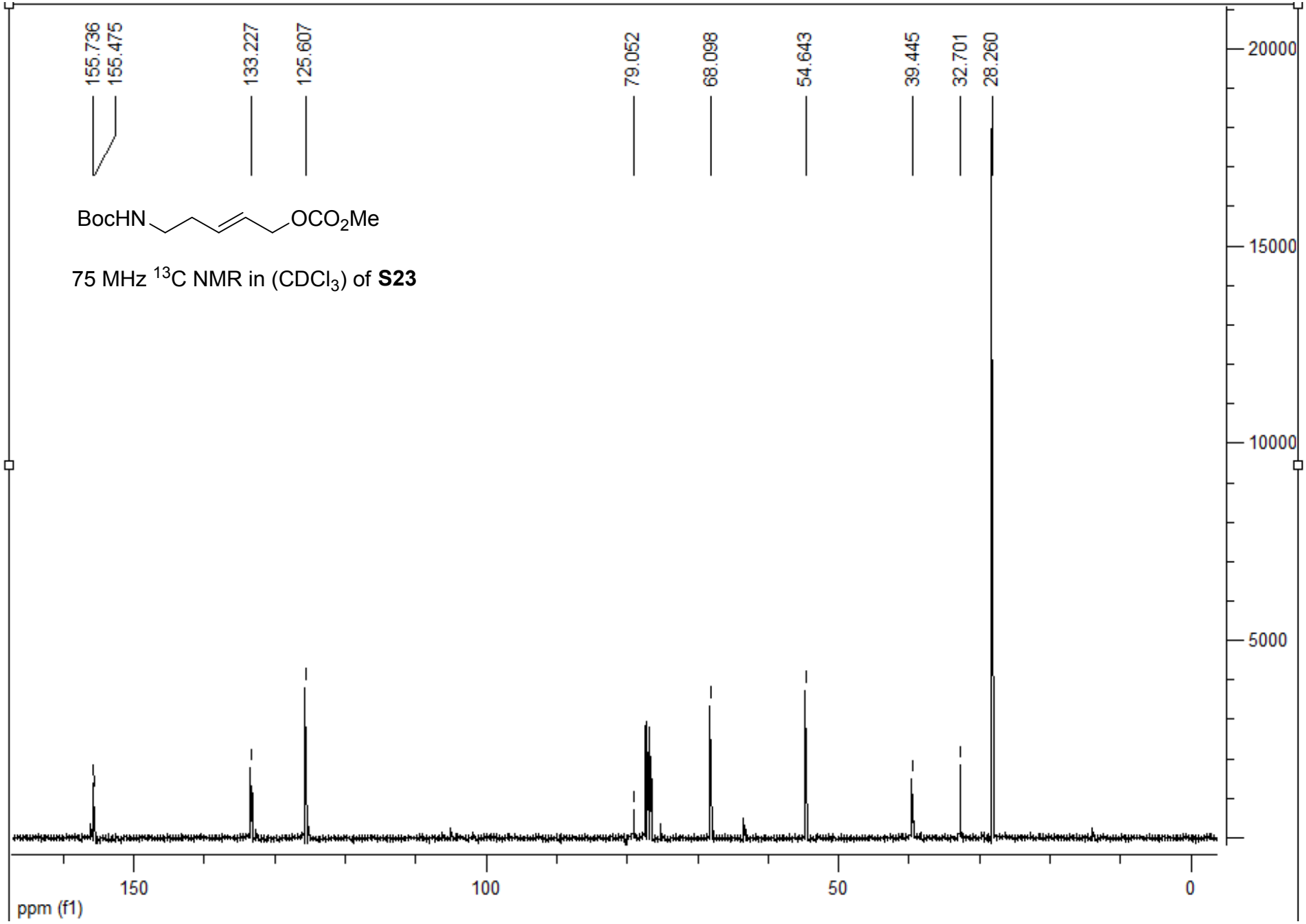
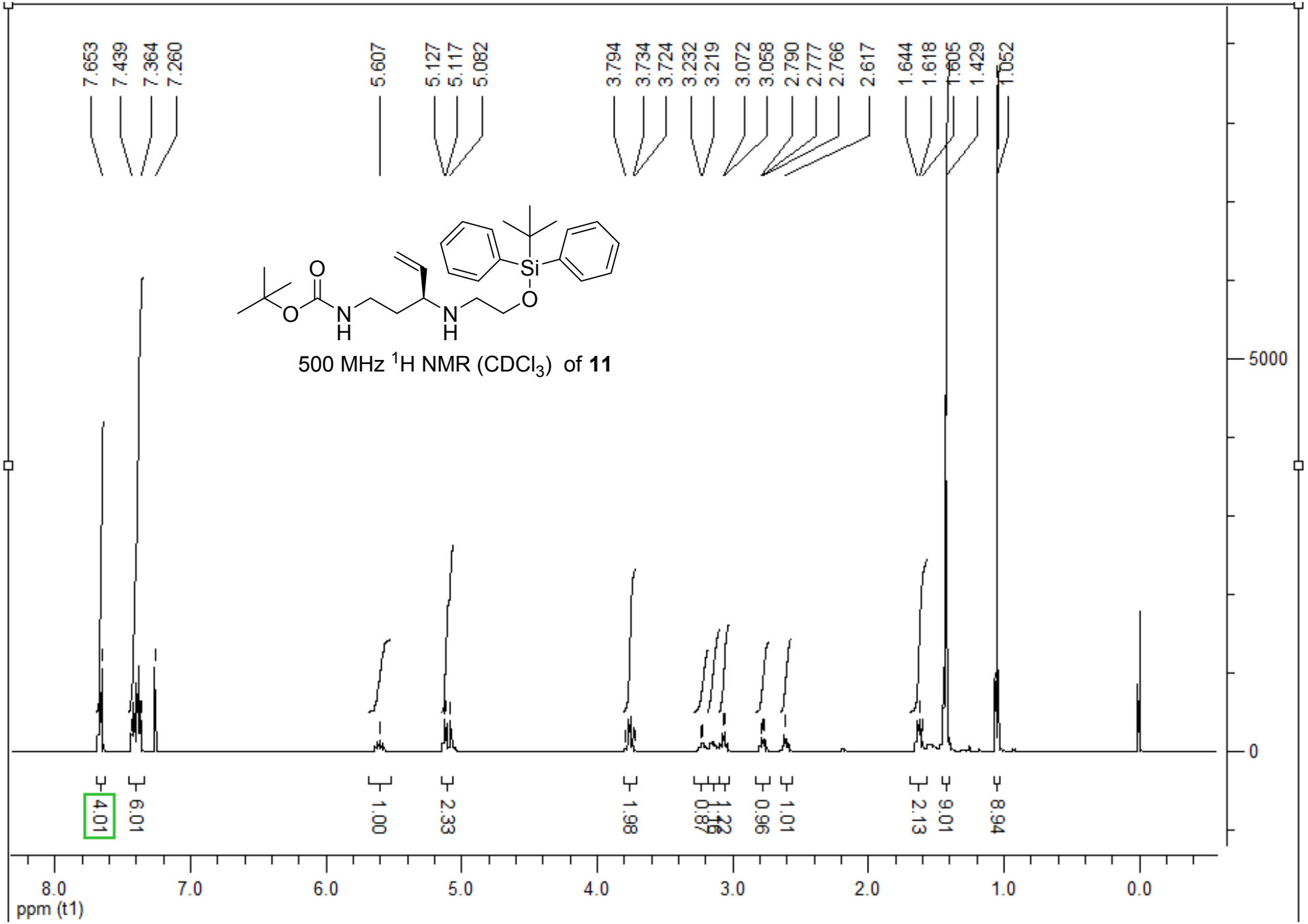
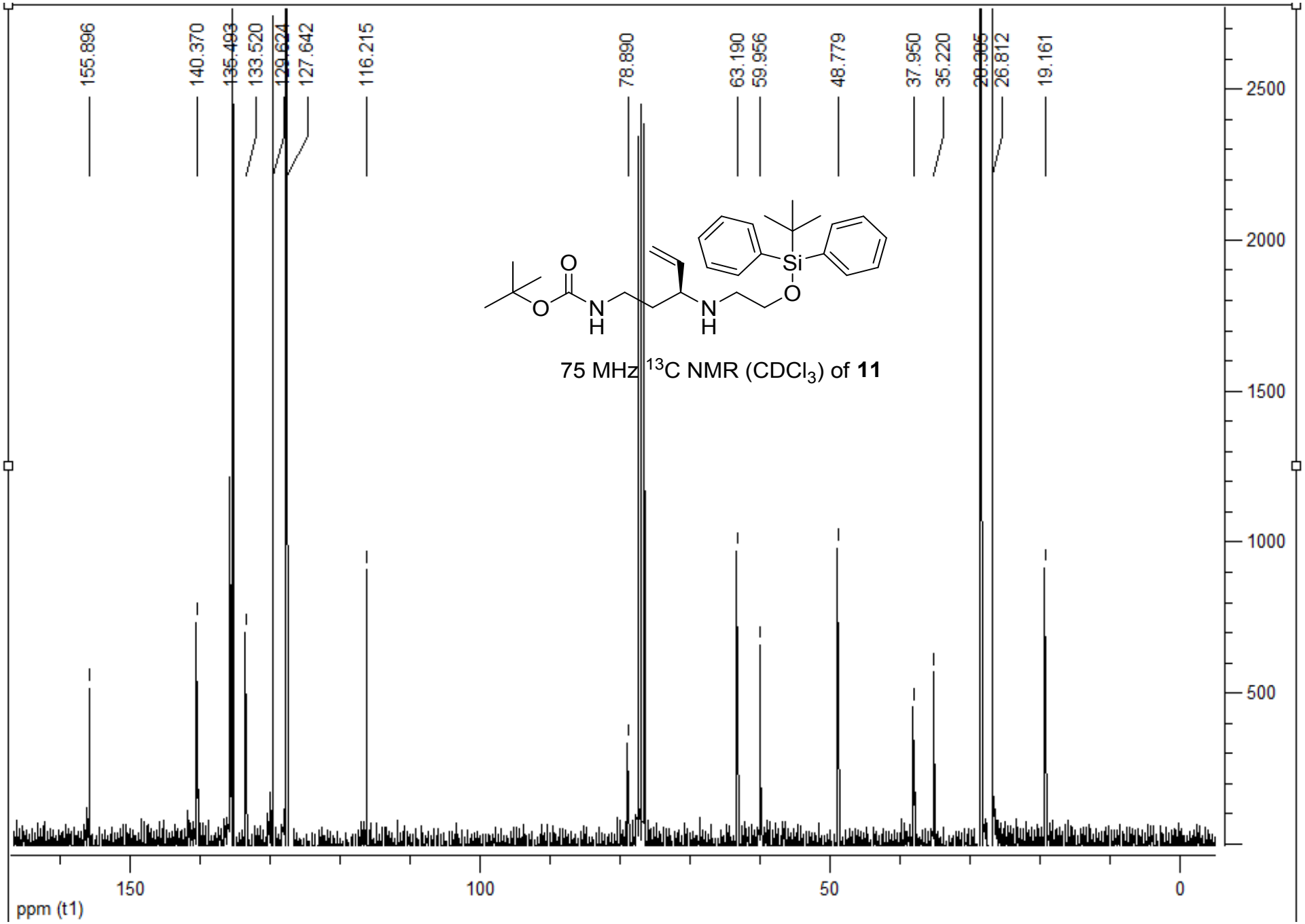
S10. NMR Spectra and HPLC Traces


5.777
5.747
5.719
4.577
4.564
3.773
3.218
3.188
3.176
3.146
1.427
BocHN
OCO2Me
500 MHz 1H NMR in (CDCl3) of S23
10000
5000
0
1.00
1.19
3.00
3.33
2.18
1.96
9.09
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

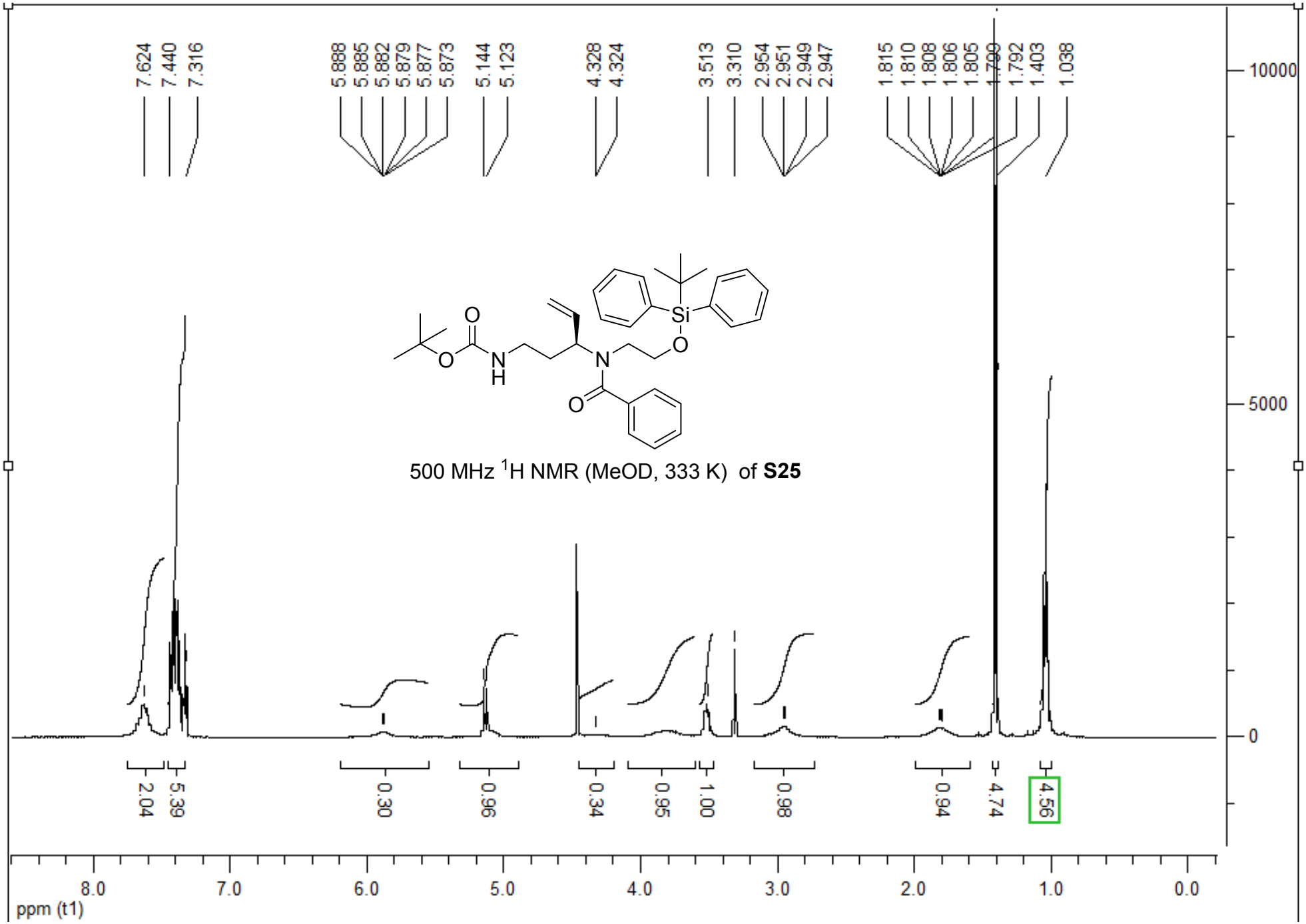

155.736
155.475
133.227
125.607
79.052
68.098
54.643
39.445
32.701
28.260
BocHN
OCO2Me
75 MHz 13C NMR in (CDCl3) of S23
20000
15000
10000
5000
150
100
50
0
ppm (f1)



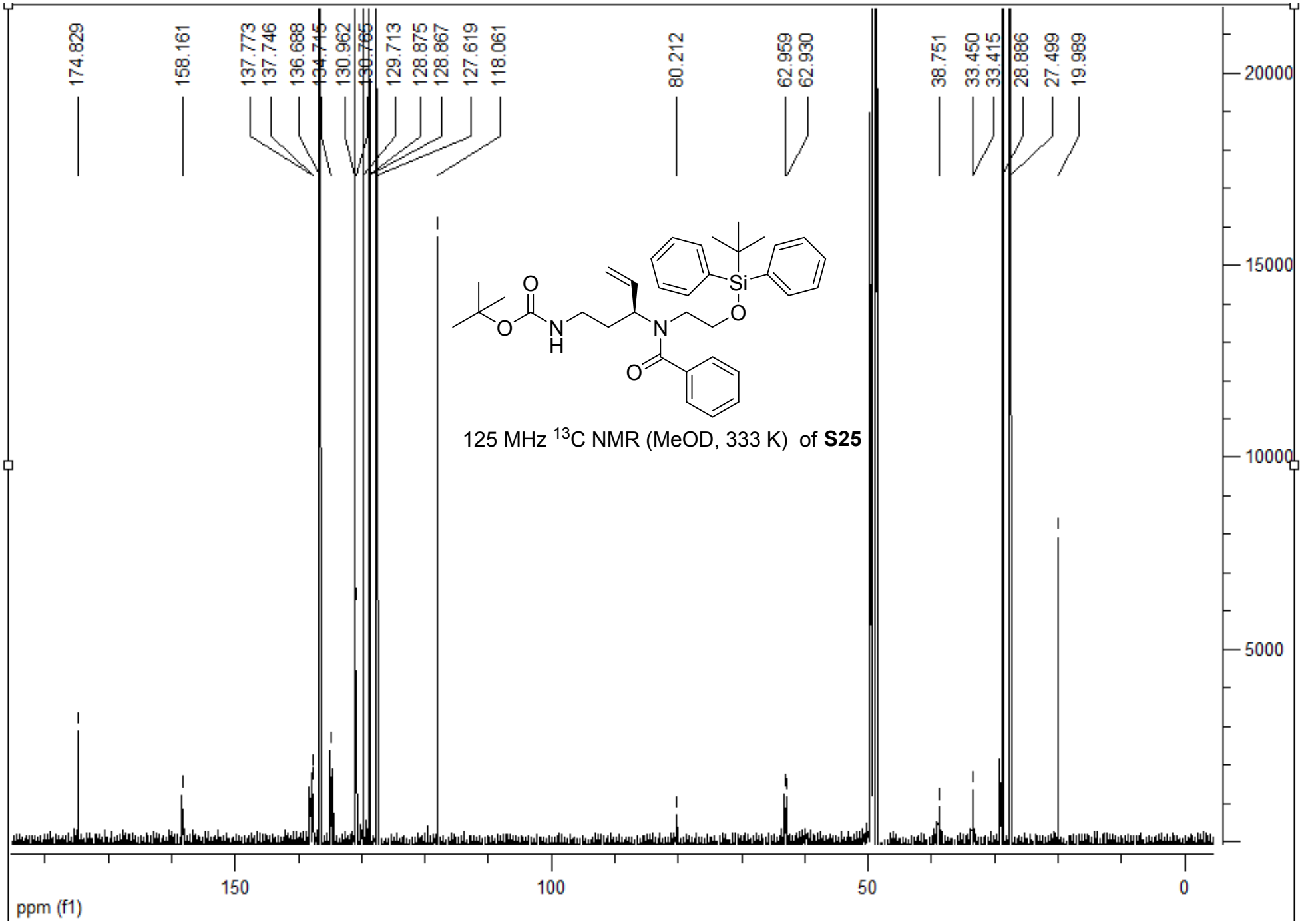
500 MHz ^{1}H NMR ($CDCl_3$) of **11**



75 MHz ^{13}C NMR ($CDCl_3$) of **11**



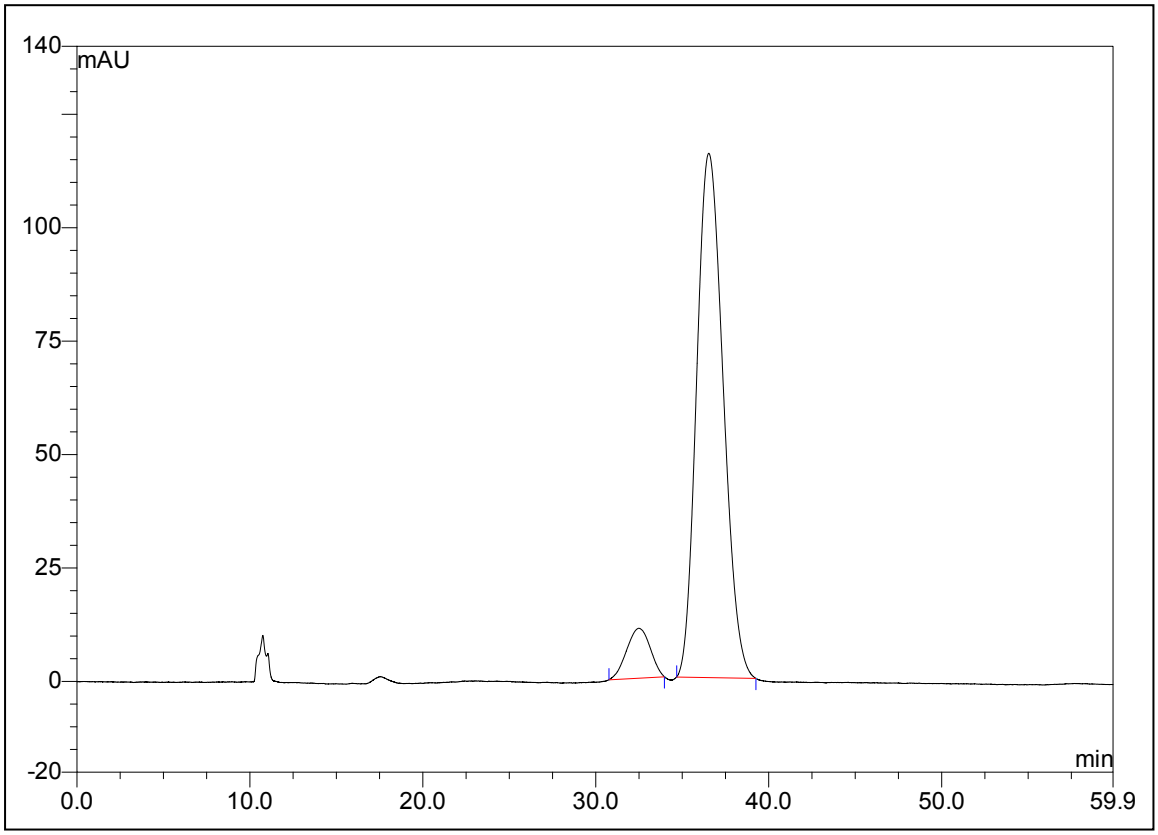
500 MHz ^{1}H NMR (MeOD, 333 K) of **S25**



125 MHz ^{13}C NMR (MeOD, 333 K) of **S25**

S25

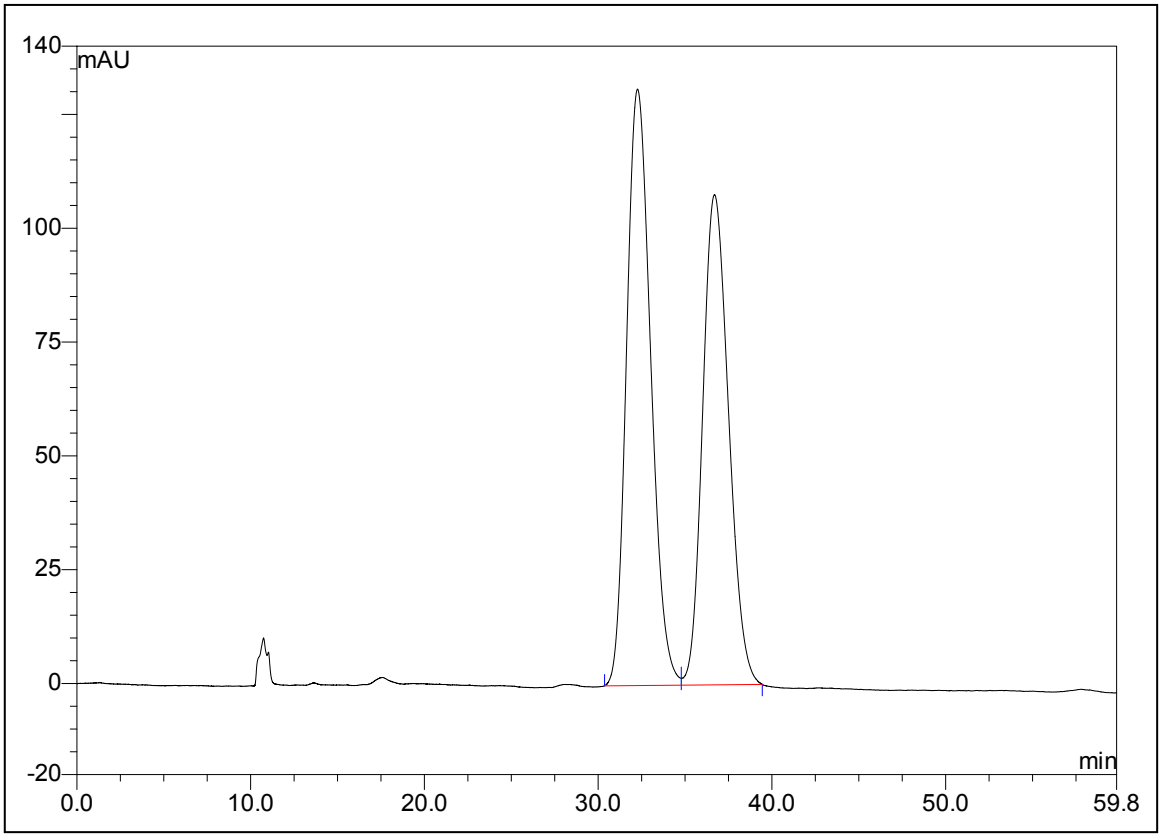
Sample Name:	**RD256**	*Injection Volume:*	**10.0**
Vial Number:	**P1:F5**	*Channel:*	**DAD_Signal_A**
Sample Type:	**unknown**	*Wavelength:*	**n.a.**
Control Program:	**NP PreMix 100%B 60min 0,3ml min pos3 OD-H**	*Bandwidth:*	**n.a.**
Quantif. Method:	**MH1**	*Dilution Factor:*	**1.0000**
Recording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



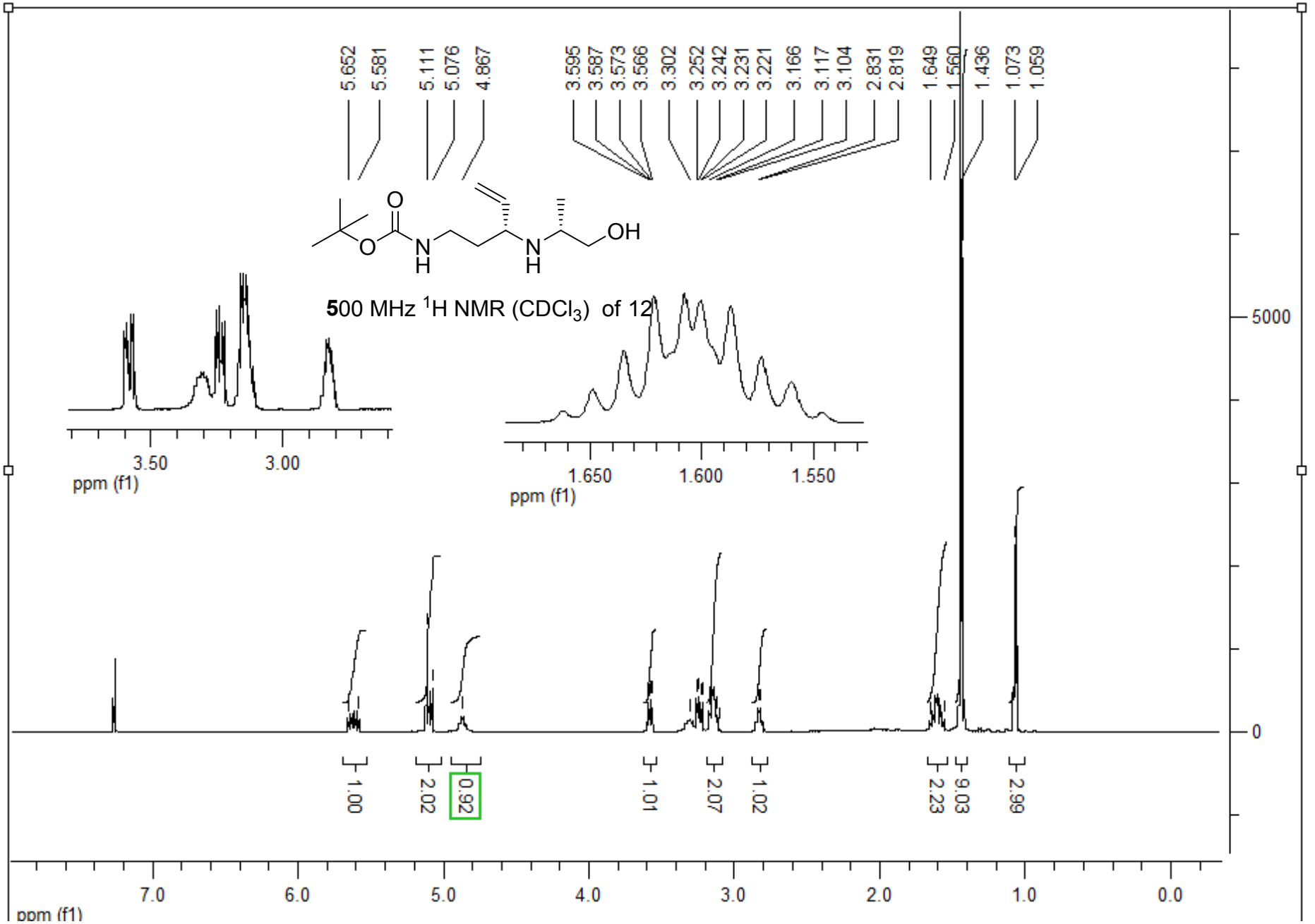
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	32.49	n.a.	11.000	17.324	7.78	n.a.	BMB
2	36.53	n.a.	115.572	205.417	92.22	n.a.	BMB
Total:			126.572	222.740	100.00	0.000	

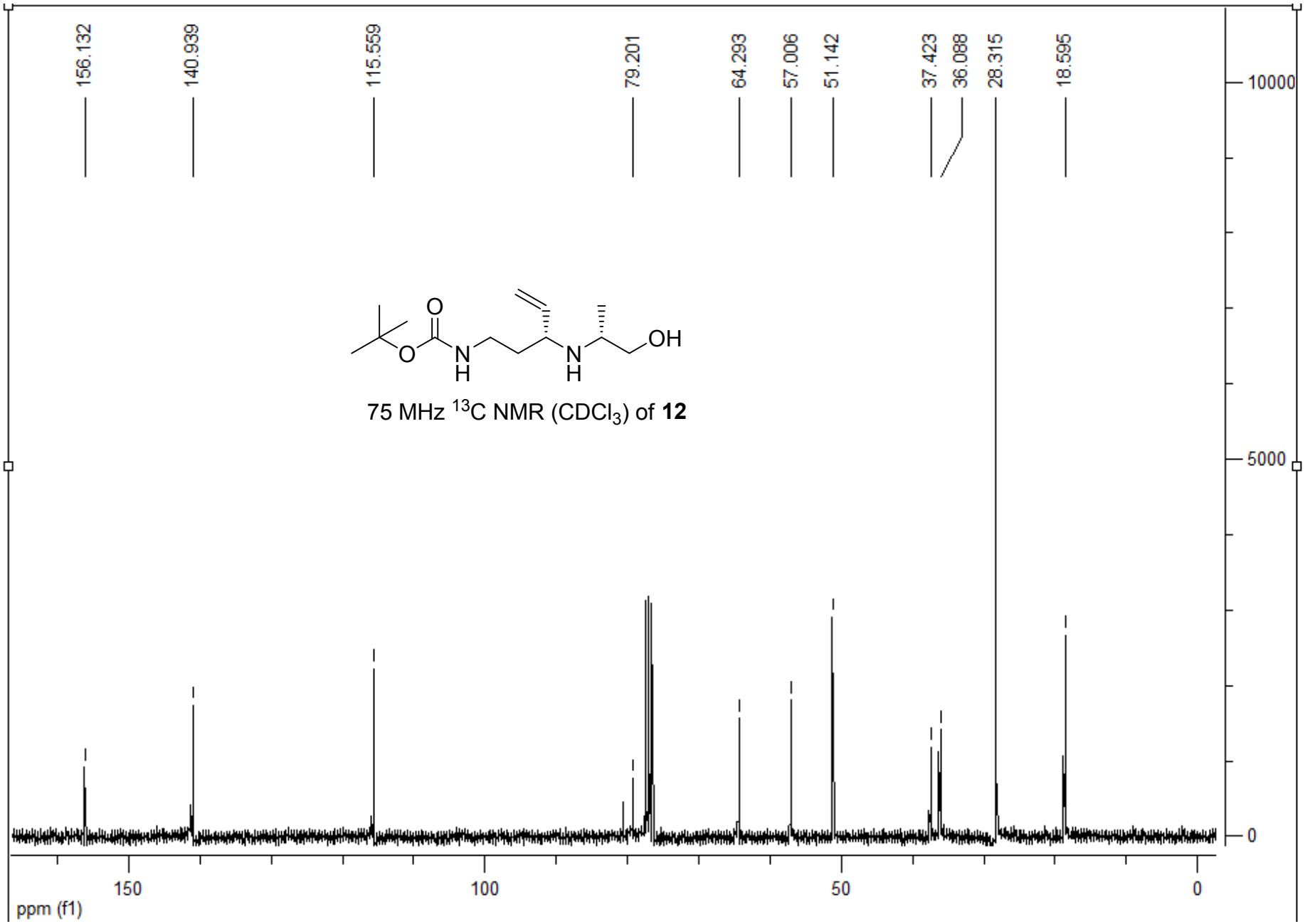
S25 mix 5%IPA95%Hexane

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**

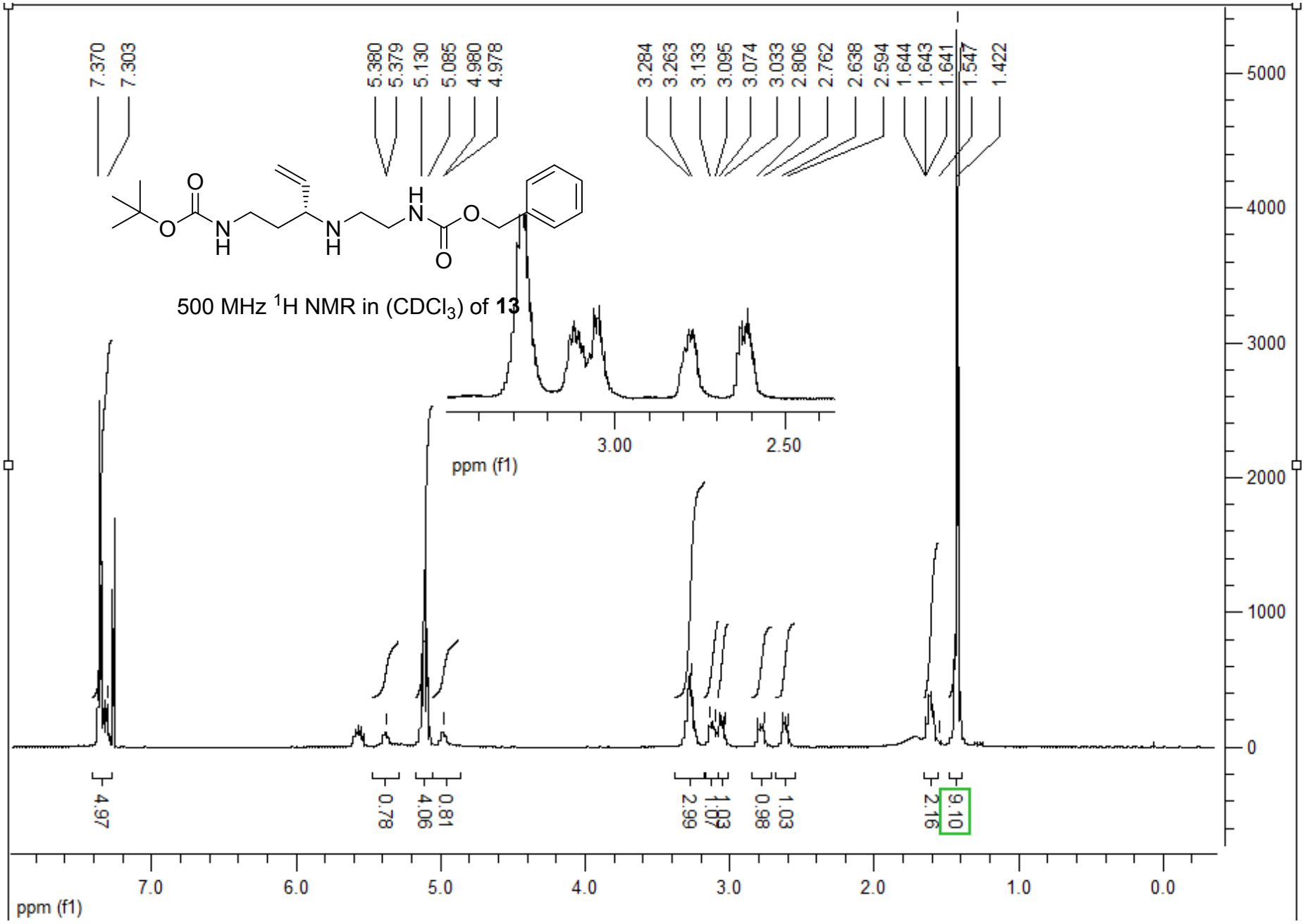


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	32.27	n.a.	130.988	211.581	53.20	n.a.	BM
2	36.70	n.a.	107.671	186.125	46.80	n.a.	MB
Total:			238.659	397.705	100.00	0.000	


5.652
5.581
5.111
5.076
4.867
3.595
3.587
3.573
3.566
3.302
3.252
3.242
3.231
3.221
3.166
3.117
3.104
2.831
2.819
1.649
1.560
1.436
1.073
1.059
O
O
N
H
N
H
OH
500 MHz ^{1}H NMR ($CDCl_3$) of 12
3.50
3.00
ppm (f1)
1.650
1.600
1.550
ppm (f1)
5000
0
1.00
2.02
0.92
1.01
2.07
1.02
2.23
9.03
2.99
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)



75 MHz ^{13}C NMR ($CDCl_3$) of **12**


7.370
7.303
5.380
5.379
5.130
5.085
4.980
4.978
3.284
3.263
3.133
3.095
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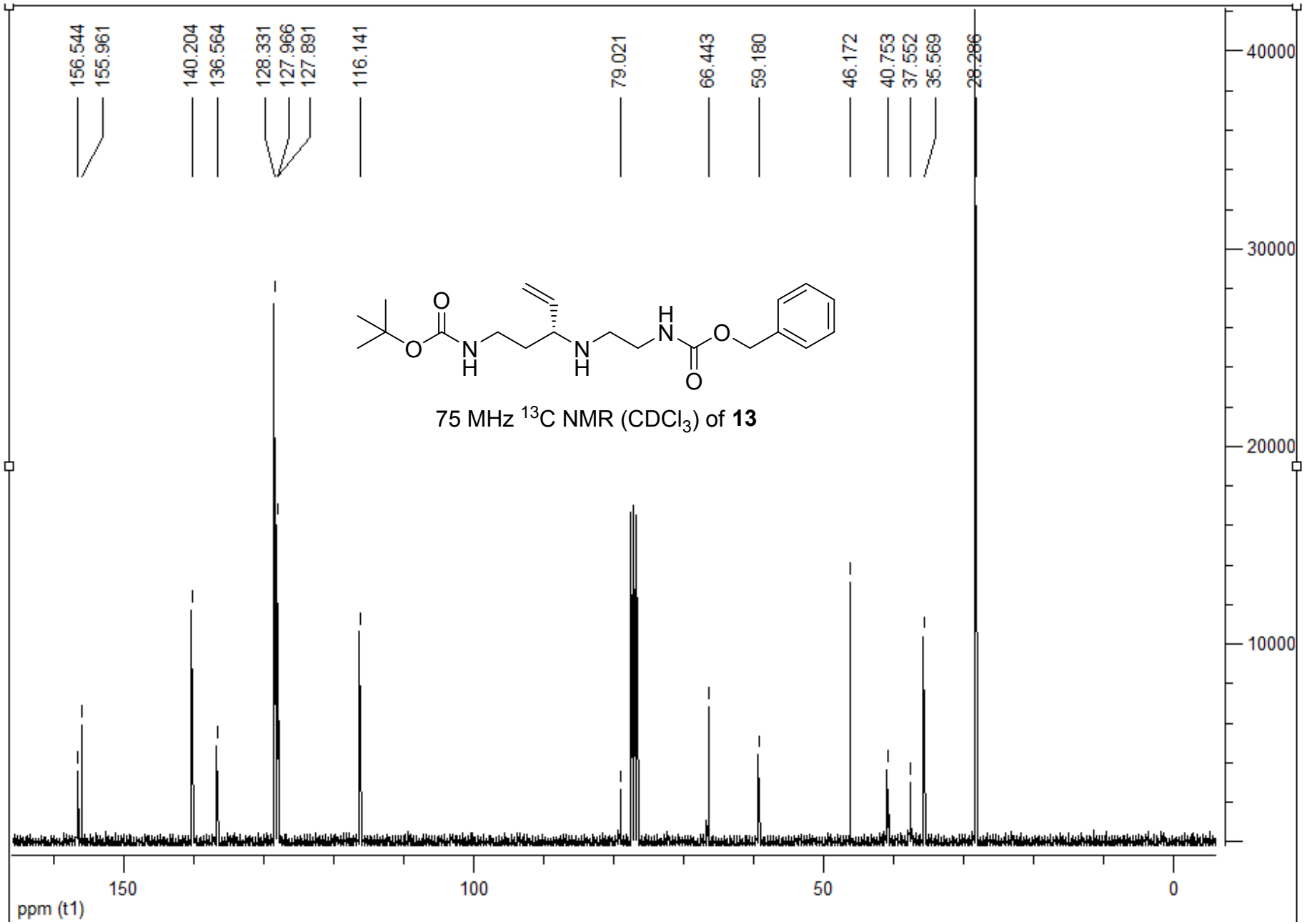
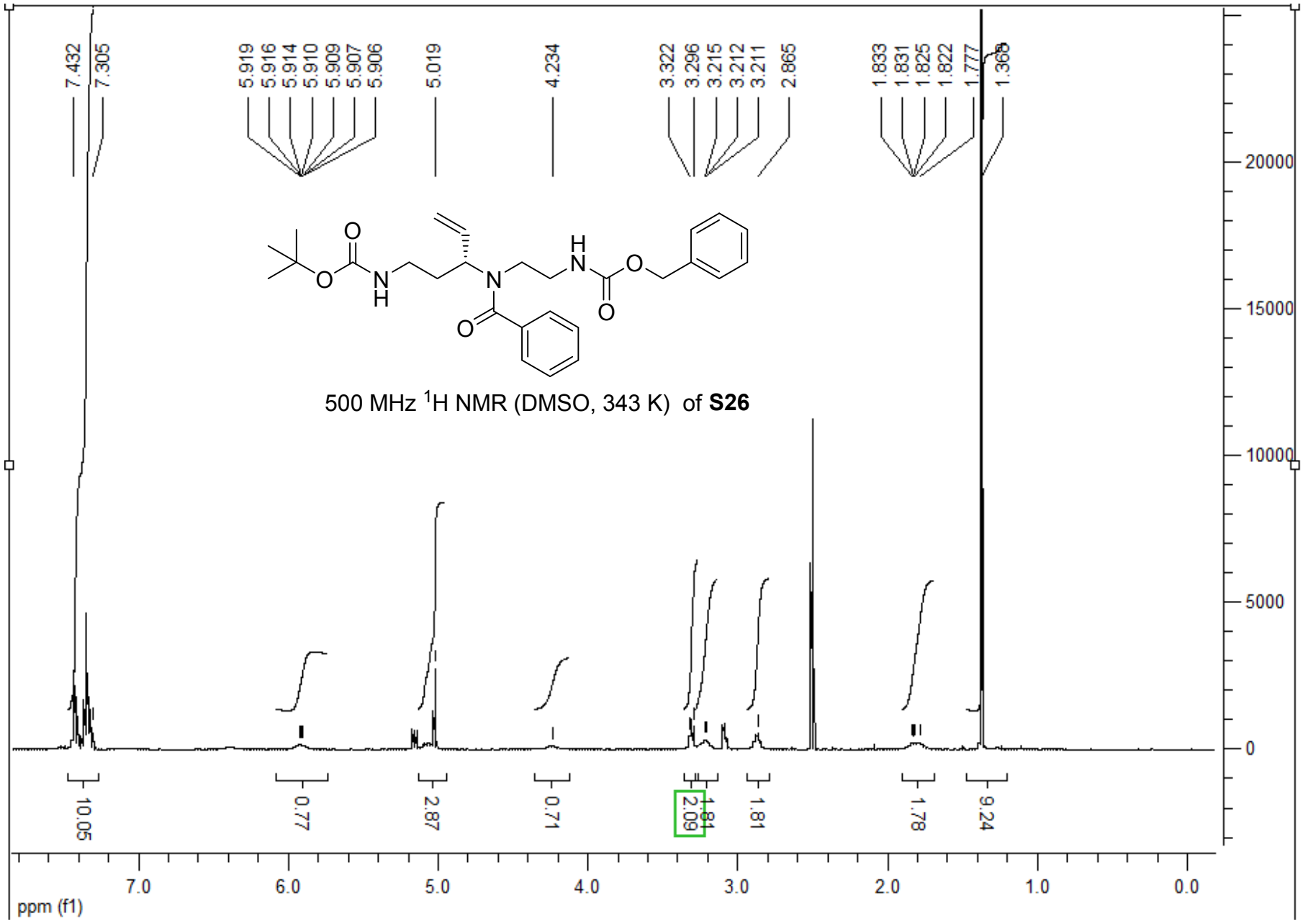
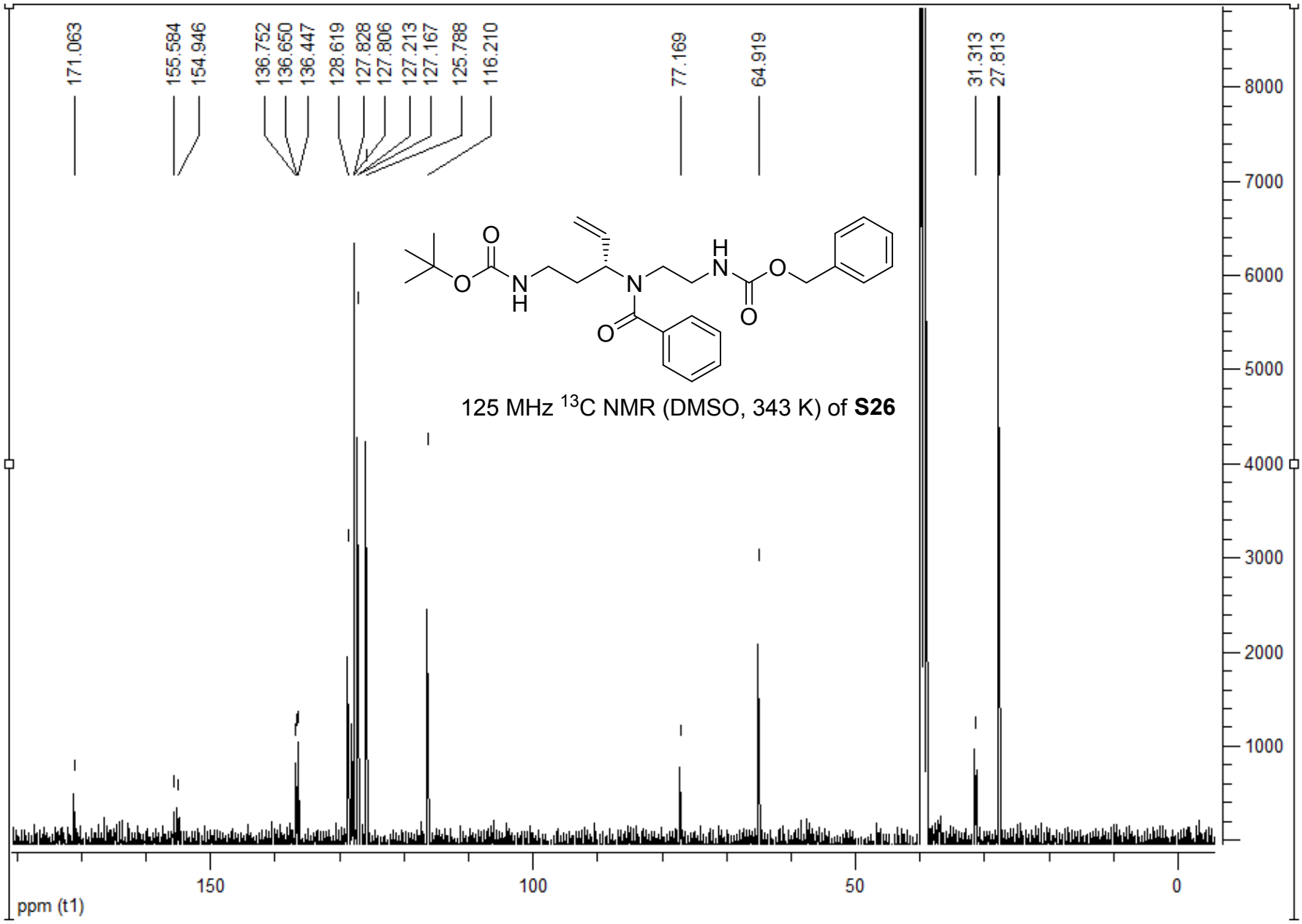
3.033
2.806
2.762
2.638
2.594
1.644
1.643
1.641
1.547
1.422
500 MHz ^{1}H NMR in ($CDCl_3$) of **13**
ppm (f1)
ppm (f1)



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

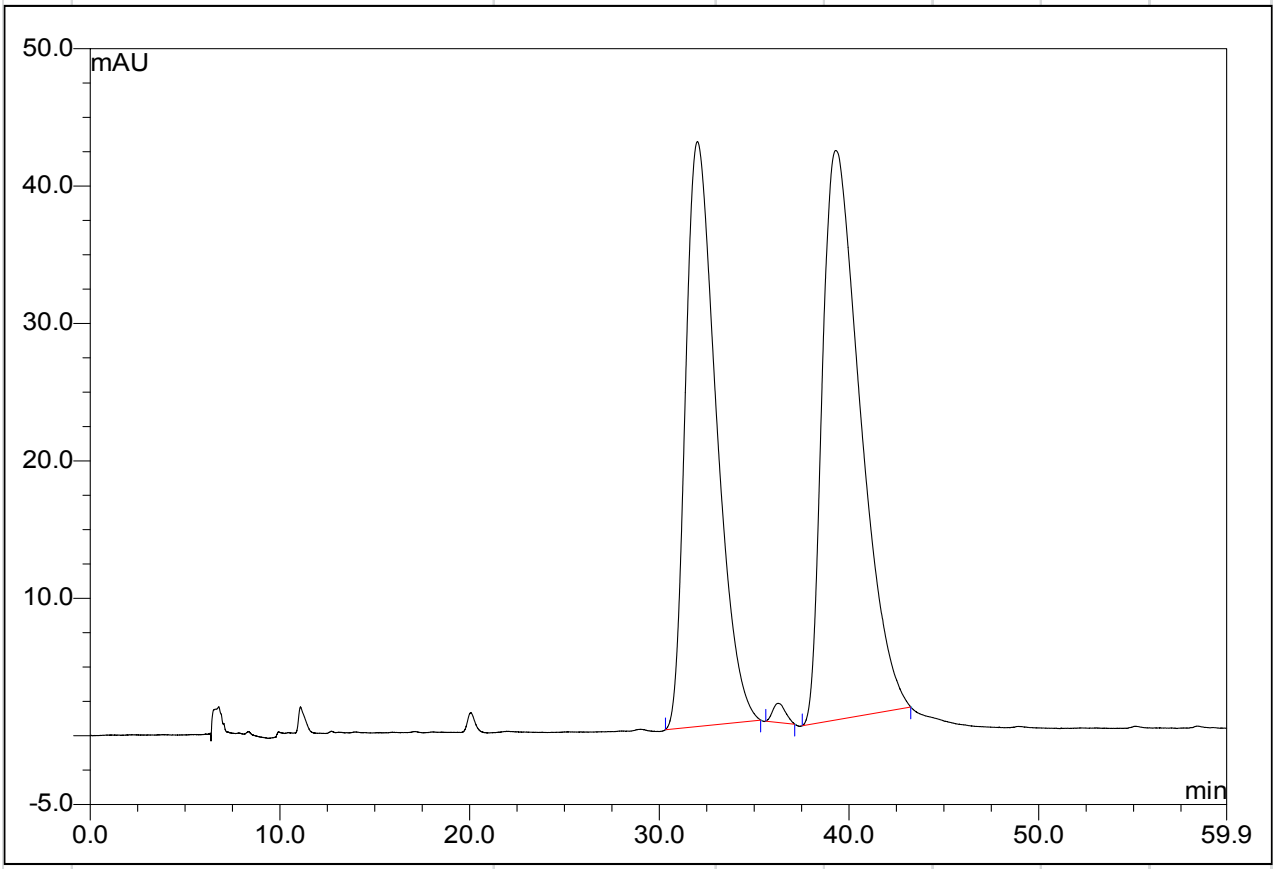


500 MHz ^{1}H NMR (DMSO, 343 K) of **S26**



125 MHz ^{13}C NMR (DMSO, 343 K) of **S26**

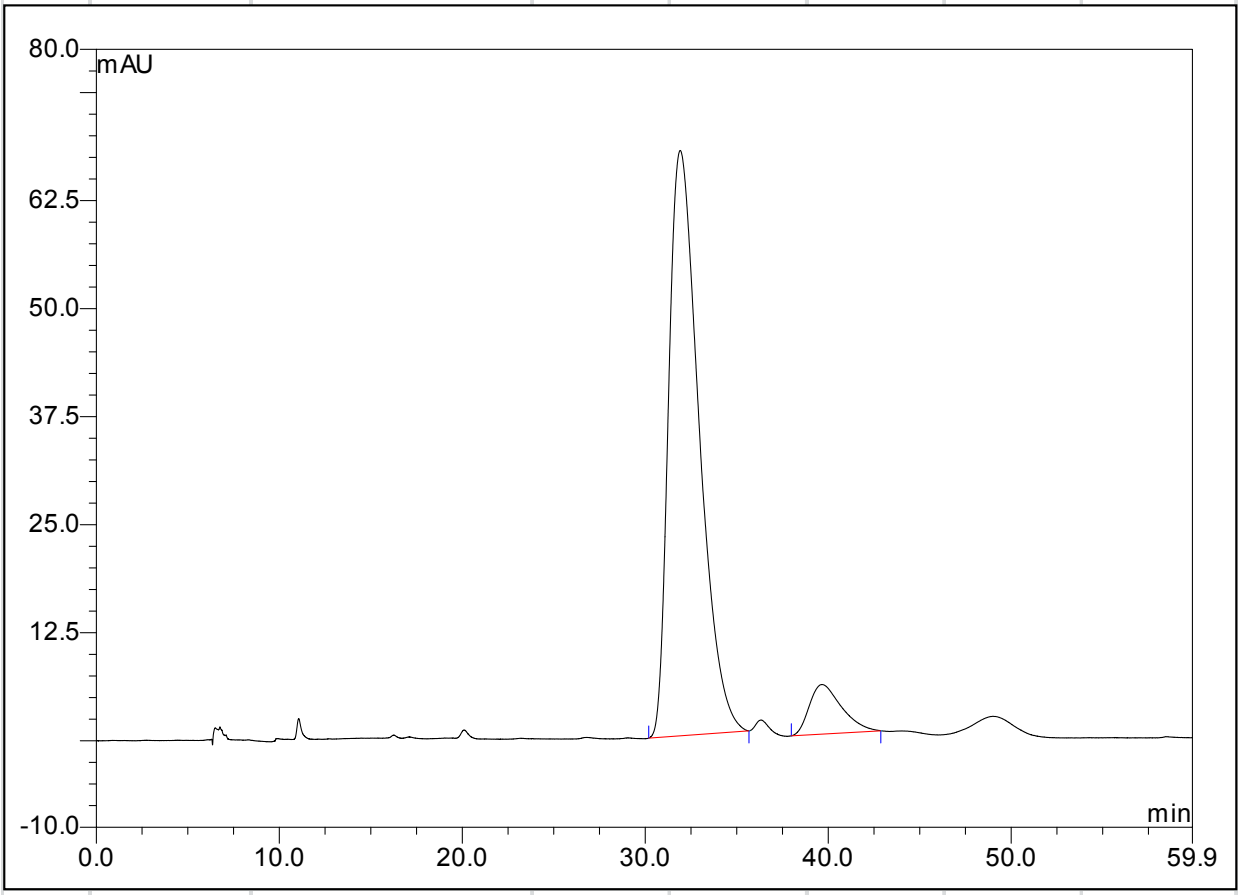
27	RD394/395 5%EtOH95%Hexane	S26		
	Mobile phase - 5%EtOH / 95%Hexane			
Sampl	Flow Rate - 0.5ml/min	**RD394/395 5%EtOH95%Hexane**	*Injection Volume:*	**10.0**
Vial N	Column - Daicel Chiralcel AS-H 250mm x 4	**P1:F5**	*Channel:*	**DAD_Signa**
Sample Type:		**unknown**	*Wavelength:*	**n.a.**
Control Program:		**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**



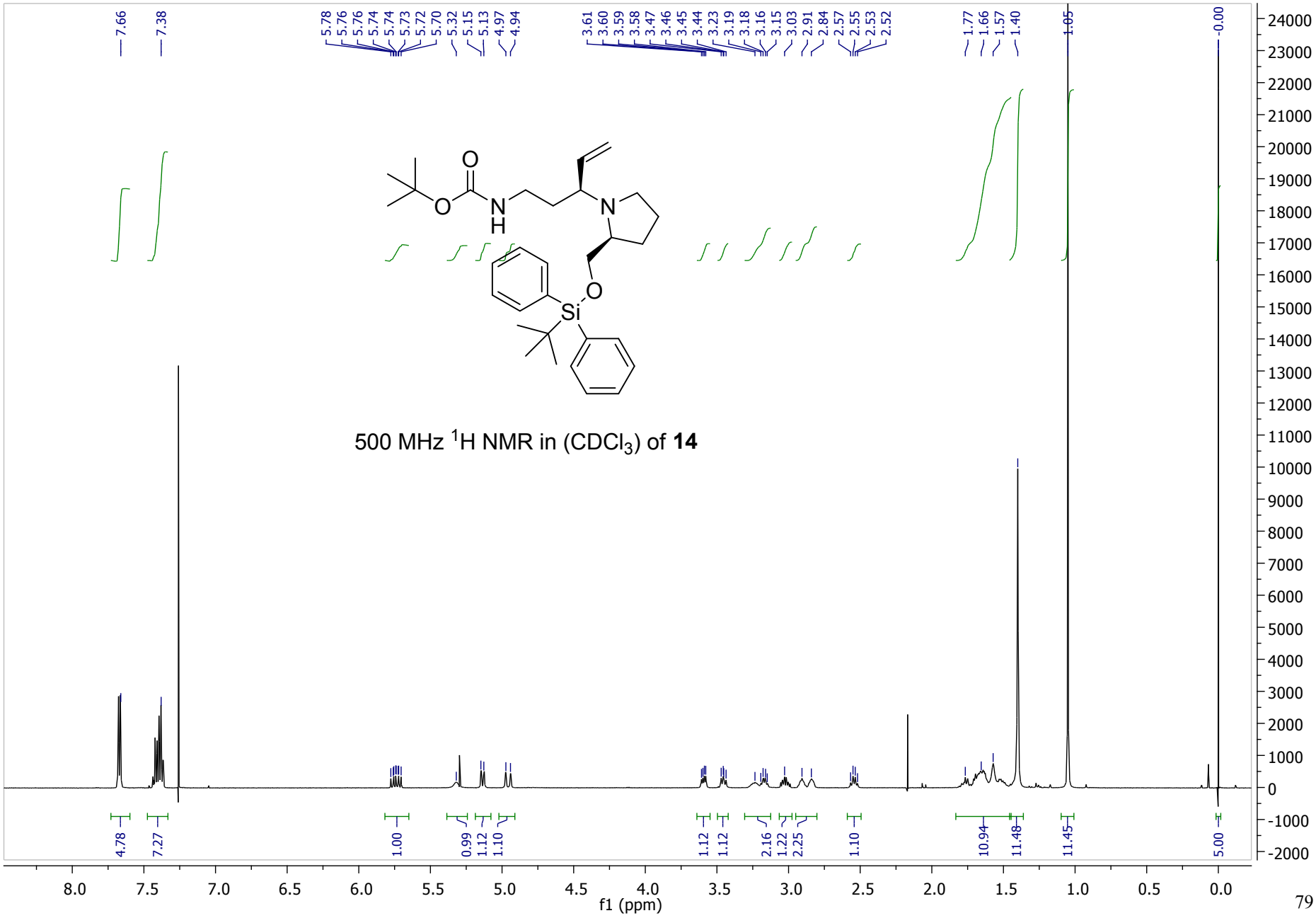
No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	32.01	n.a.	42.576	80.107	45.14	n.a.	BMB
2	36.25	n.a.	1.401	1.090	0.61	n.a.	BMB
3	39.29	n.a.	41.449	96.259	54.24	n.a.	BMB
Total:			85.427	177.455	100.00	0.000	

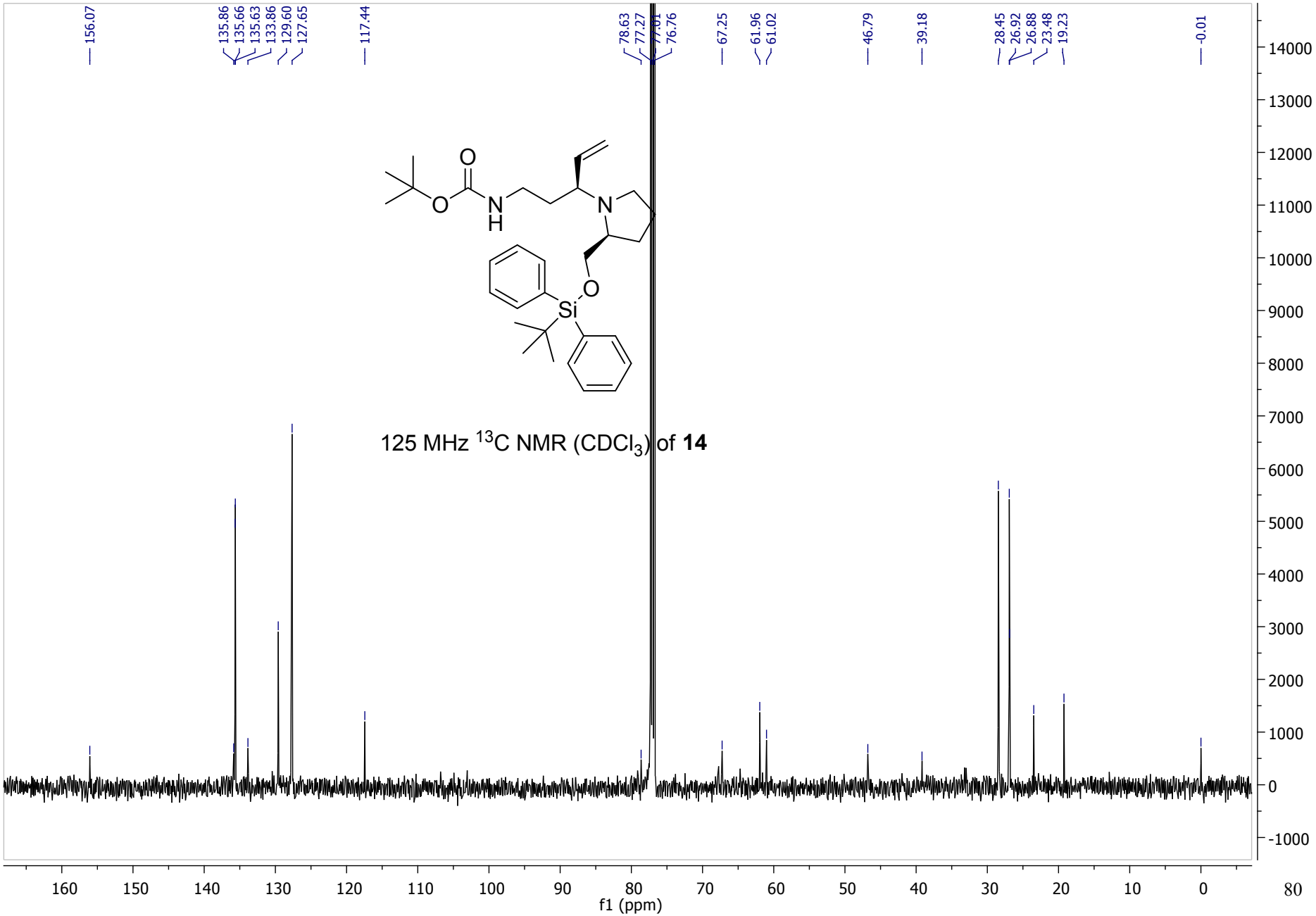
28	RD394 B1 5%EtOH95%Hexane	S26	

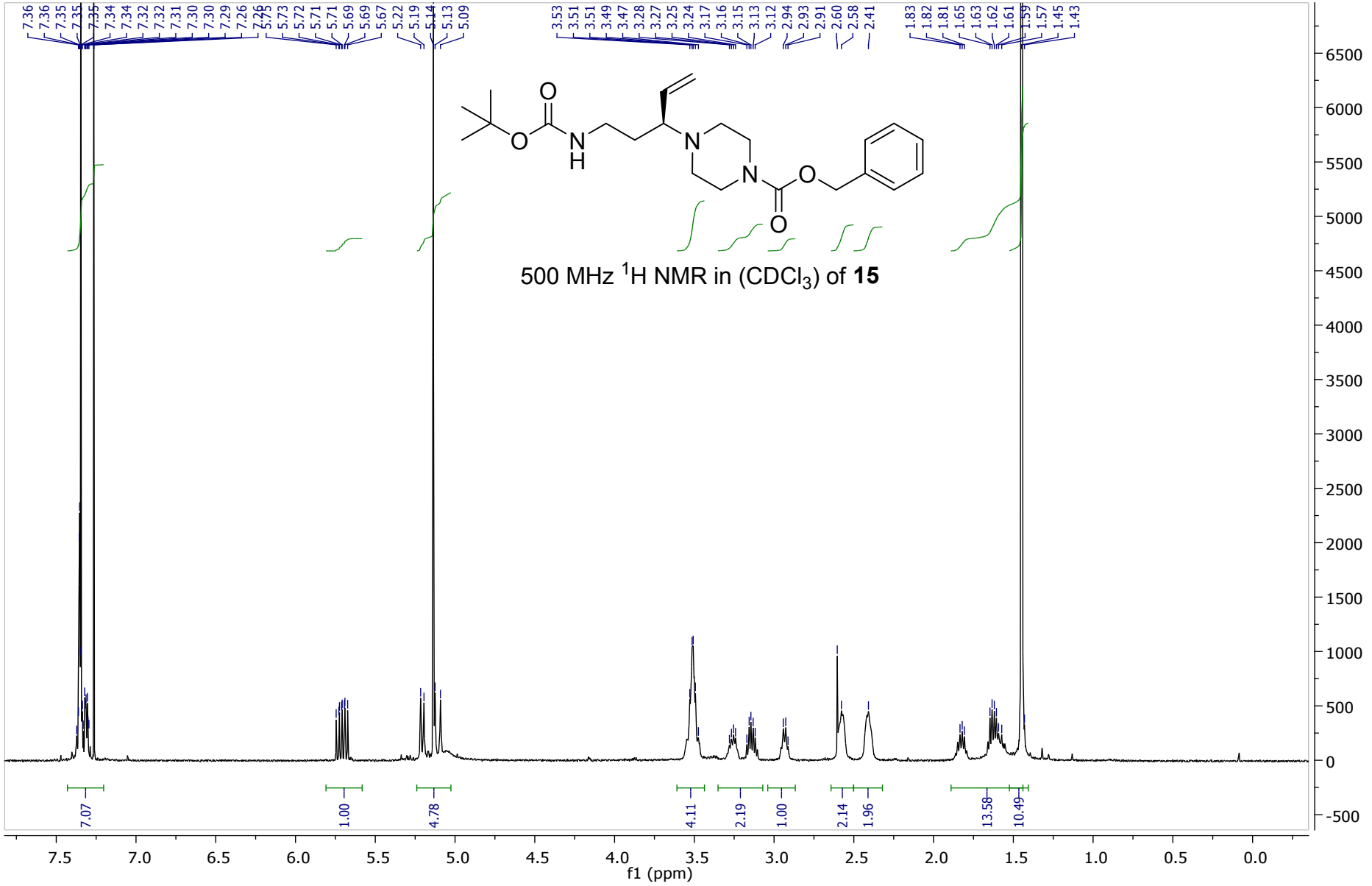
Sample Name:	**RD394 B1 5%EtOH95%Hexane**	*Injection Volume:*	**10.0**
Vial Number:	**P1:F6**	*Channel:*	**DAD_Signa**
Sample Type:	**unknown**	*Wavelength:*	**n.a.**
Control Program:	**NP PreMix 100%B 60min 0,5ml min pos1**	*Bandwidth:*	**n.a.**
Quantif. Method:	**MH1**	*Dilution Factor:*	**1.0000**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

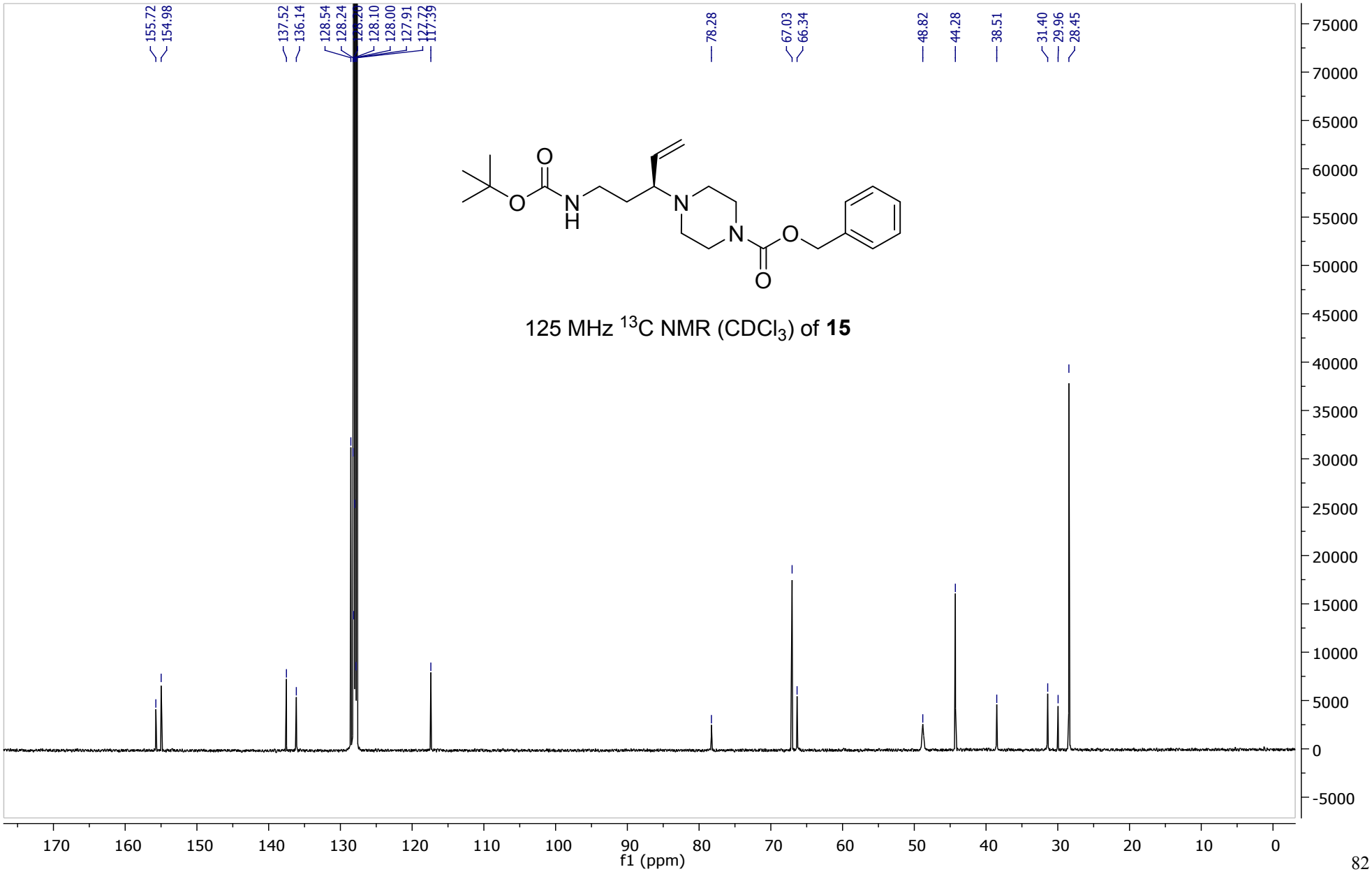


No.	Ret.Time	Peak Name	Height	Area	Rel.Area	Amount	Type
	min		mAU	mAU*min	%		
1	31.91	n.a.	67.736	130.474	91.77	n.a.	BMB*
2	39.64	n.a.	5.741	11.705	8.23	n.a.	BMB
Total:			73.477	142.179	100.00	0.000	


7.66
7.38
5.78
5.76
5.76
5.74
5.74
5.73
5.72
5.70
5.32
5.15
5.13
4.97
4.94
3.61
3.60
3.59
3.58
3.47
3.46
3.45
3.44
3.23
3.19
3.18
3.16
3.15
3.03
2.91
2.84
2.57
2.55
2.53
2.52
1.77
1.66
1.57
1.40
1.05
-0.00
O
O
N
H
N
O
Si
500 MHz ^{1}H NMR in ($CDCl_3$) of **14**
4.78
7.27
1.00
0.99
1.12
1.10
1.12
1.12
2.16
1.22
2.25
1.10
10.94
11.48
11.45
5.00
f1 (ppm)


156.07
135.86
135.66
135.63
133.86
129.60
127.65
117.44
78.63
77.27
77.01
76.76
67.25
61.96
61.02
46.79
39.18
28.45
26.92
26.88
23.48
19.23
-0.01
O
O
N
H
N
O
Si
125 MHz ^{13}C NMR ($CDCl_3$) of **14**
f1 (ppm)

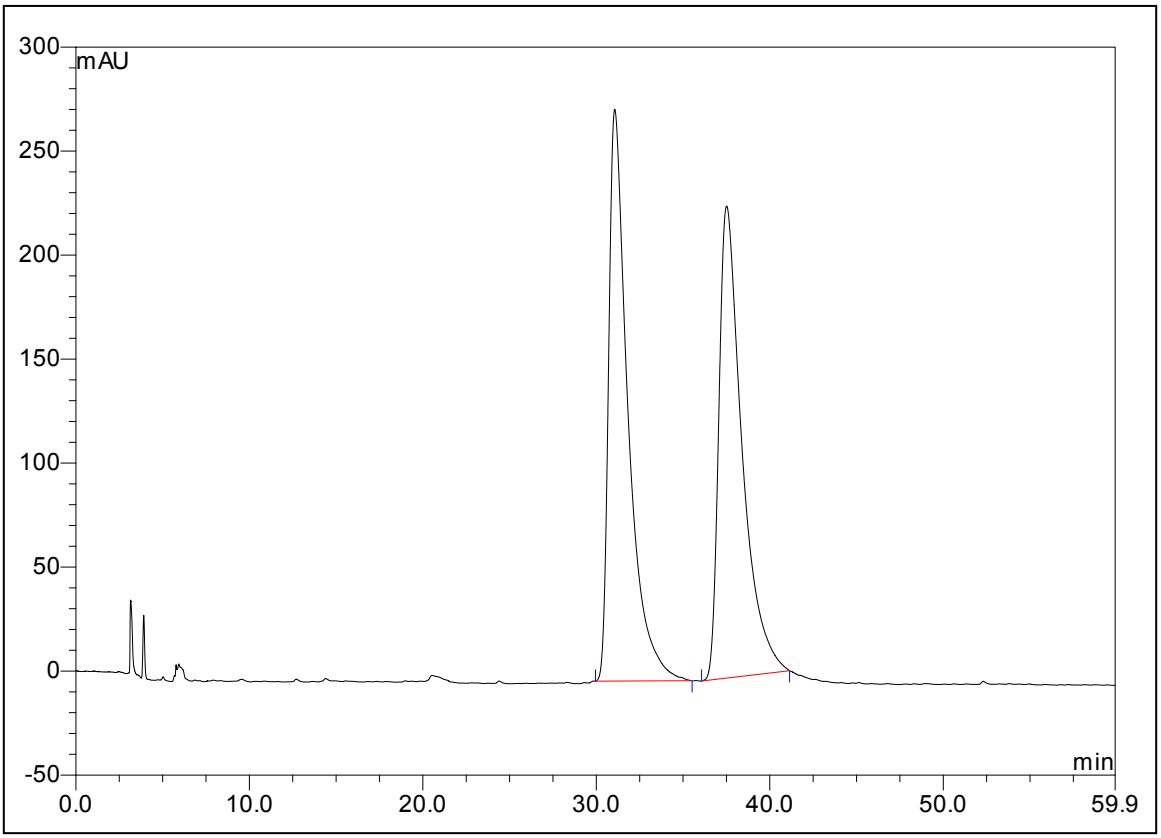

7.36 7.36 7.35 7.35 7.35 7.34 7.34 7.32 7.31 7.30 7.30 7.29 7.26 5.73 5.72 5.71 5.71 5.69 5.69 5.67 5.22 5.19 5.14 5.13 5.09
3.53 3.51 3.51 3.49 3.47 3.28 3.27 3.25 3.24 3.17 3.16 3.15 3.13 3.12 2.94 2.93 2.91 2.60 2.58 2.41
1.83 1.82 1.81 1.65 1.63 1.62 1.61 1.59 1.57 1.45 1.43
O
O
N
H
N
N
O
O
500 MHz ^{1}H NMR in ($CDCl_3$) of **15**
7.07
1.00
4.78
4.11
2.19
1.00
2.14
1.96
13.58
10.49
f1 (ppm)



125 MHz ^{13}C NMR ($CDCl_3$) of **15**

RD370/396 5%EtOH95%Hexane 15

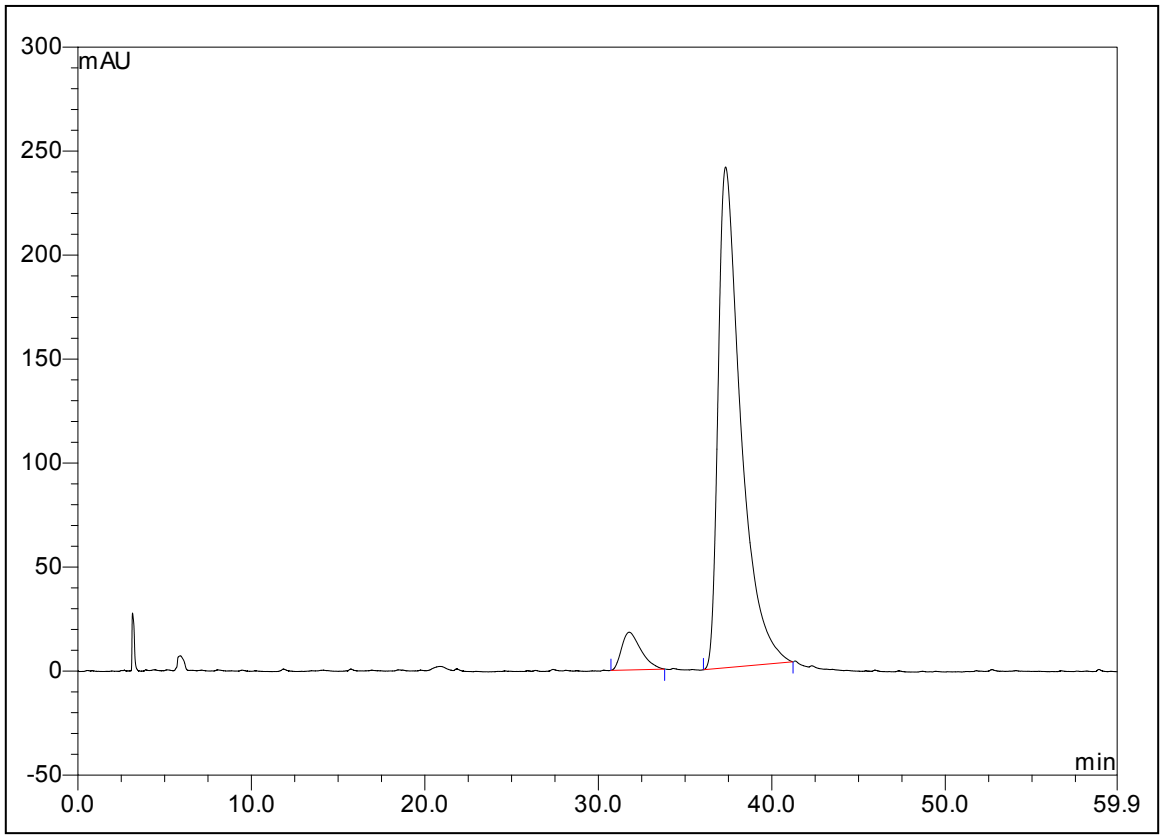
Sample Name:	**RD370/396 5%EtOH95%Hexane**	*Injection Volume:*	**10.0**
Vial Number:	**P1:F1**	*Channel :*	**DAD_Signal_B**
Sample Type:	**unknown**	*Wavelength:*	**n.a.**
Control Program:	**NP 100%B 60min 1,0ml min pos2 AD-H**	*Bandwidth:*	**n.a.**
Quantif. Method:	**MH1**	*Dilution Factor:*	**1.0000**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



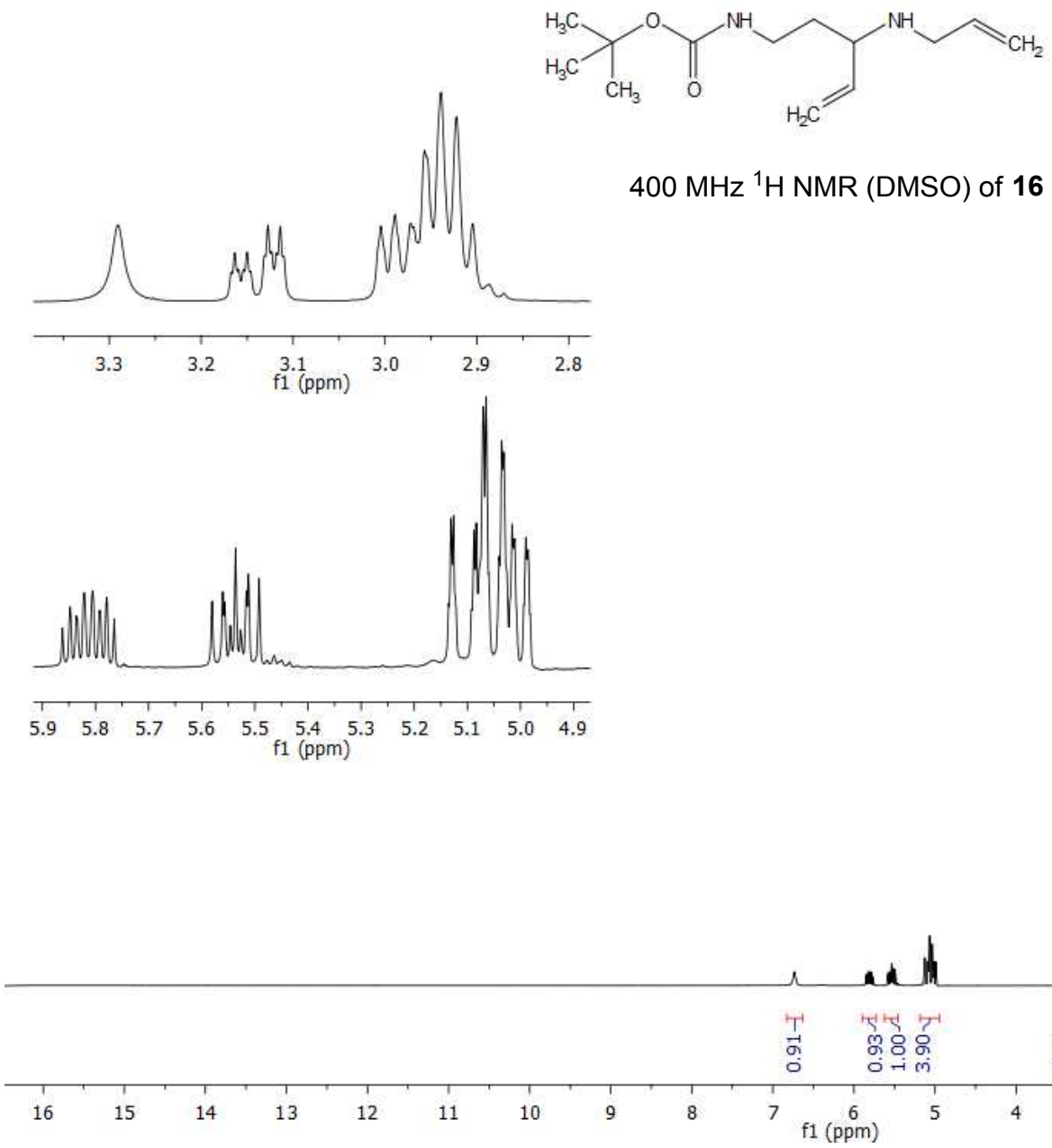
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	31.06	n.a.	274.764	357.454	50.47	n.a.	BMB
2	37.51	n.a.	226.952	350.863	49.53	n.a.	BMB
Total:			501.716	708.318	100.00	0.000	

RD396 B1 5%EtOH95%Hexane 15

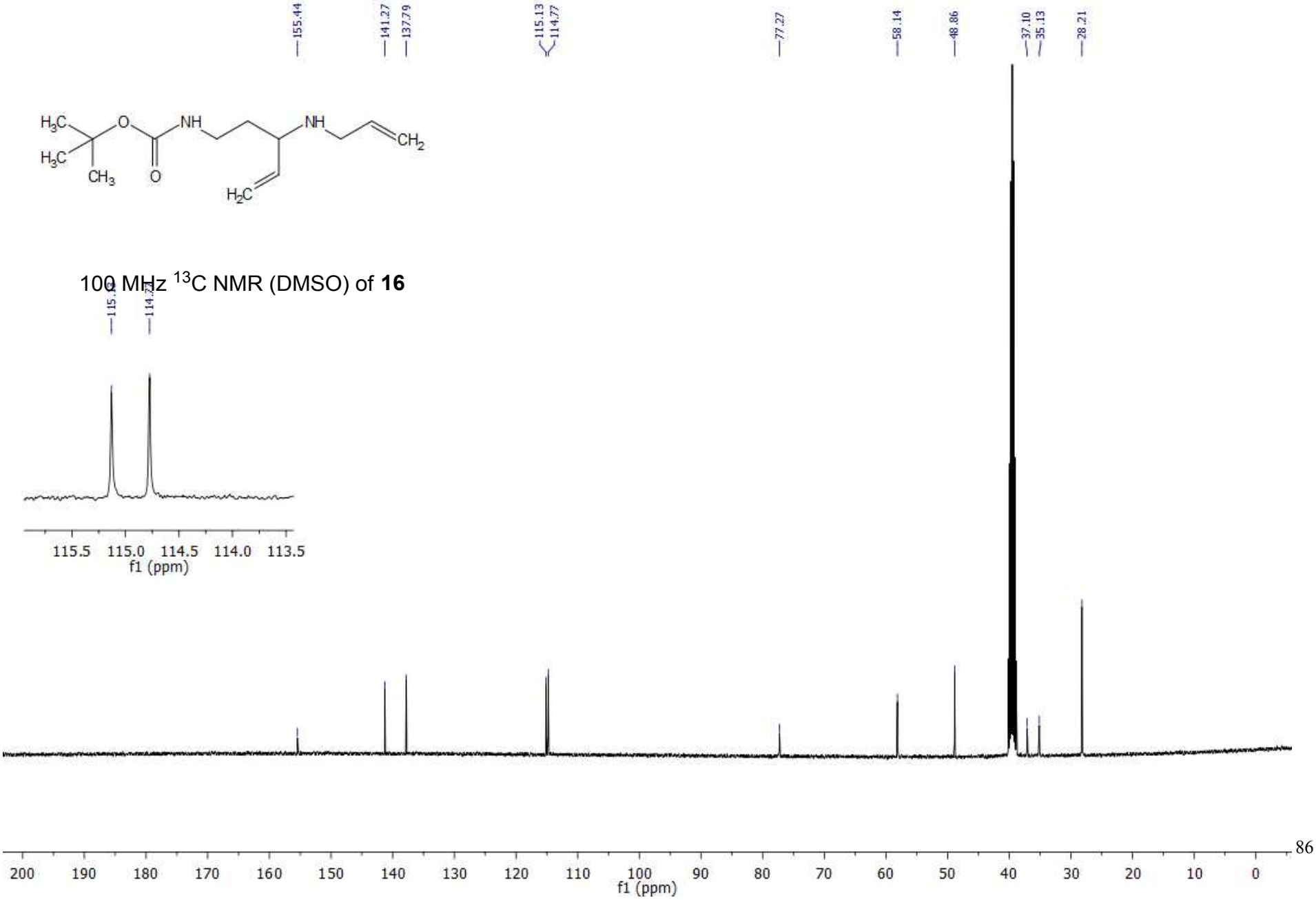
Sample Name:	**RD396 B1 5%EtOH95%Hexane**	*Injection Volume:*	**10.0**
Vial Number:	**P1:F4**	*Channel :*	**DAD_Signal_B**
Sample Type:	**unknown**	*Wavelength:*	**n.a.**
Control Program:	**NP 100%B 60min 1,0ml min pos2 AD-H**	*Bandwidth:*	**n.a.**
Quantif. Method:	**MH1**	*Dilution Factor:*	**1.0000**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



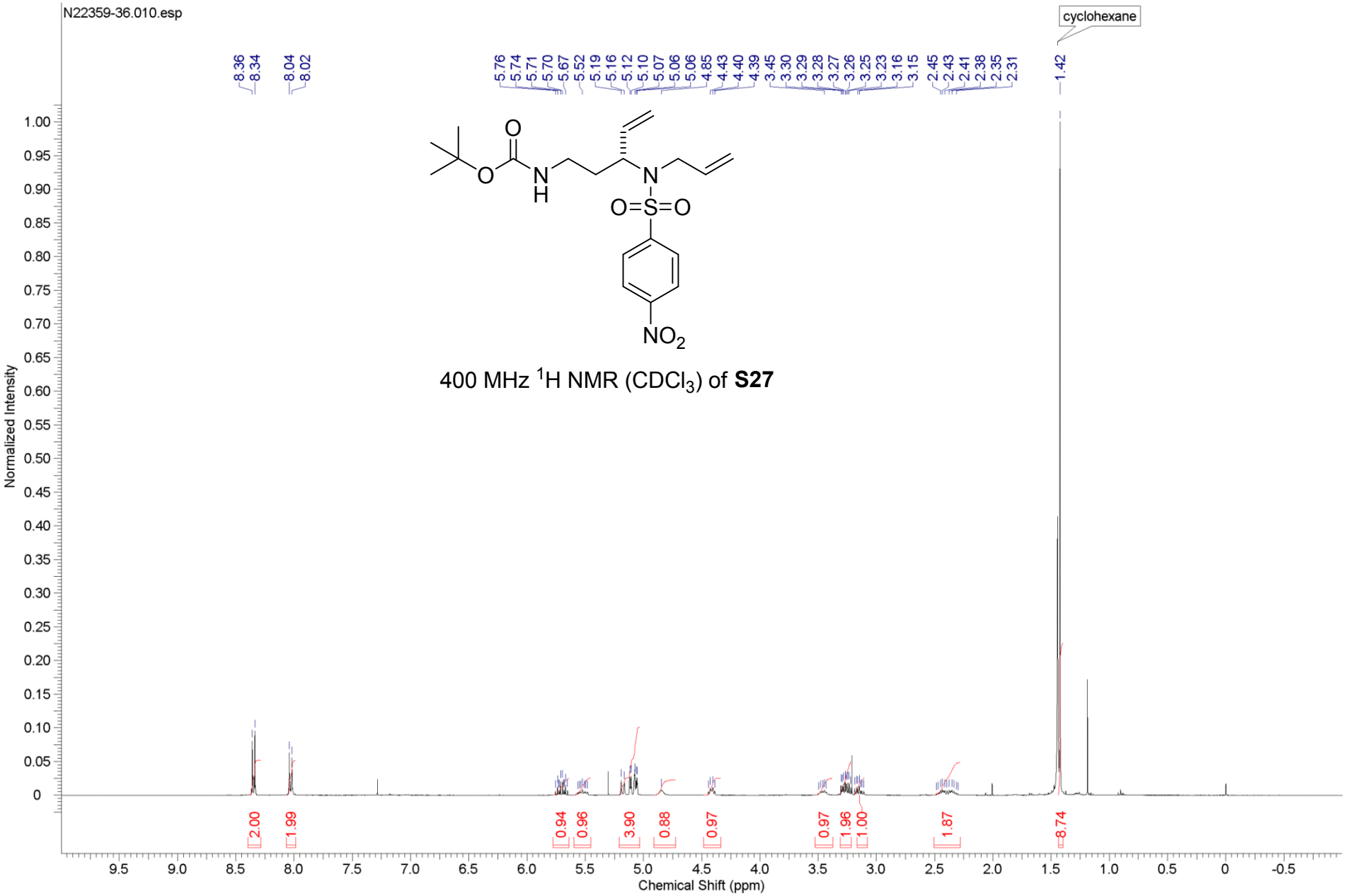
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	31.78	n.a.	18.171	23.359	6.01	n.a.	BMB
2	37.34	n.a.	240.767	365.221	93.99	n.a.	BMB
Total:			258.938	388.580	100.00	0.000	



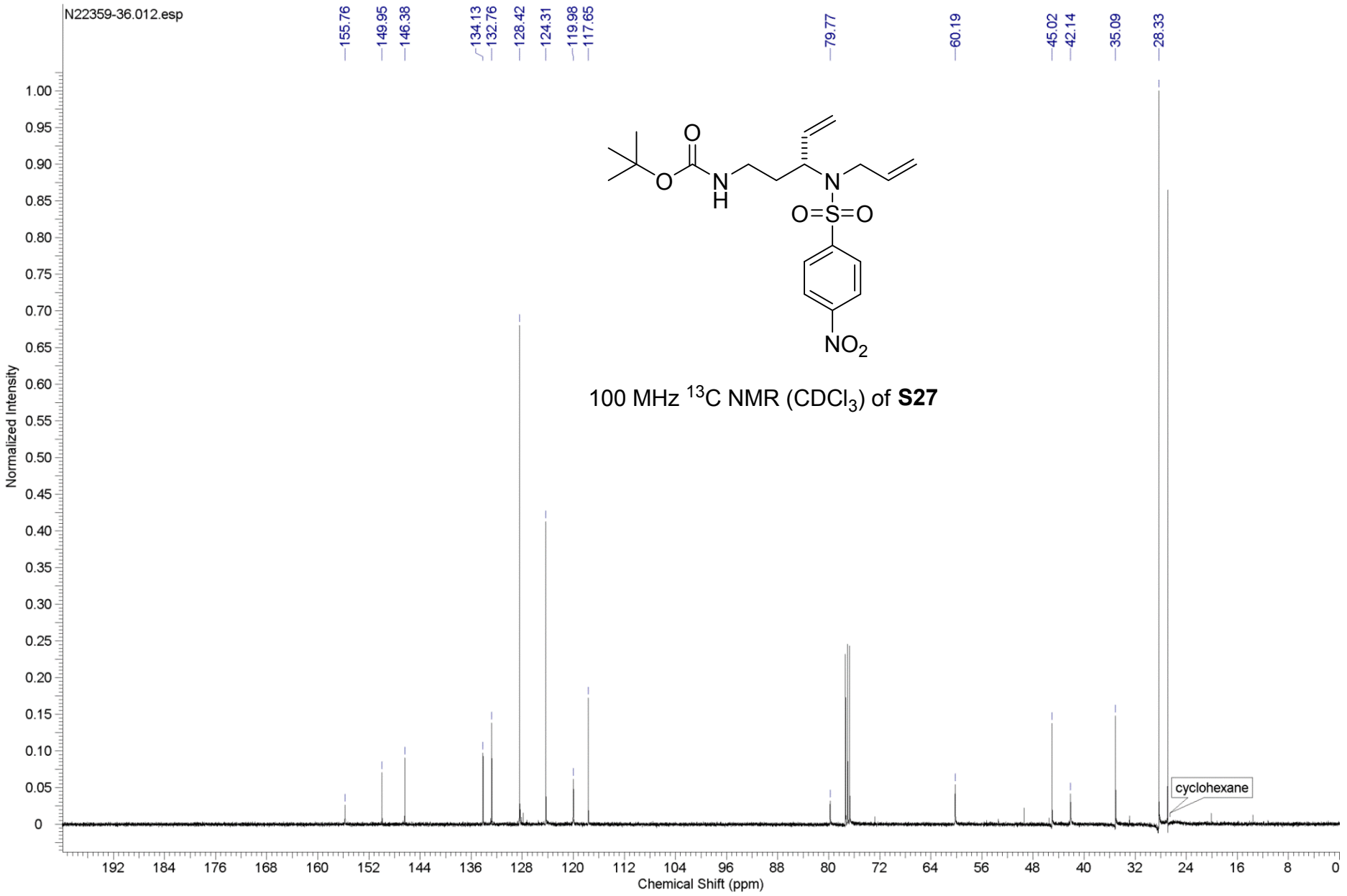
400 MHz ^{1}H NMR (DMSO) of **16**



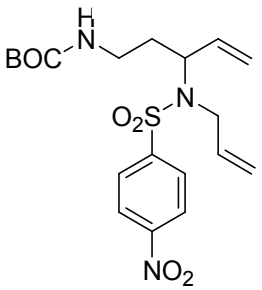
100 MHz ^{13}C NMR (DMSO) of **16**



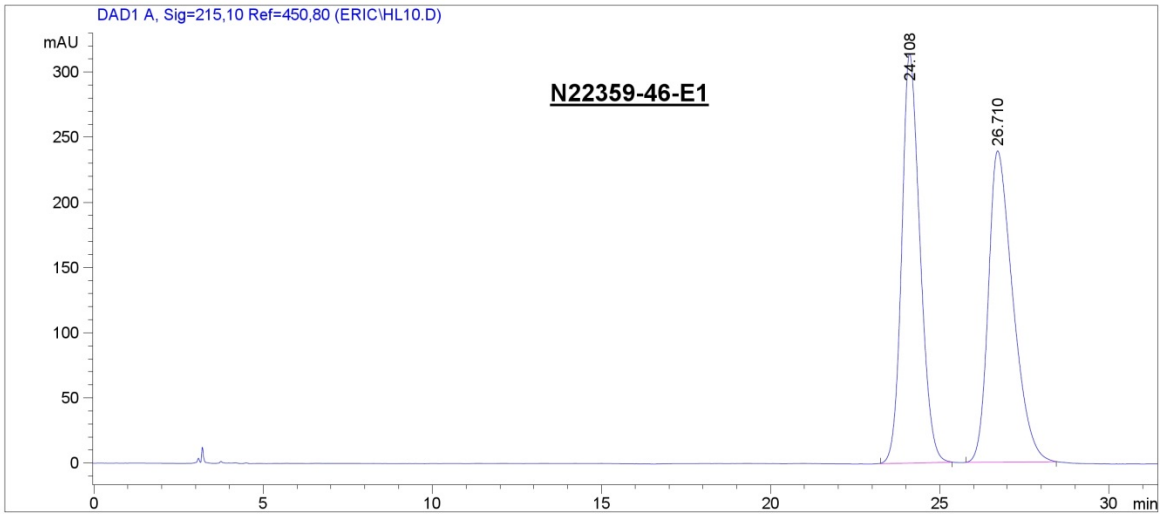
400 MHz ^{1}H NMR ($CDCl_3$) of **S27**



100 MHz ^{13}C NMR ($CDCl_3$) of **S27**




```
Data File K:\HPCHEM\1\DATA\ERIC\HL10.D
Sample Name: N22359-46-E1
    ======================================================================
    Acq. Operator   : ERIC HORTENSE
    Acq. Instrument : LALANDRY                        Location : Vial 1
    Injection Date  : 15/02/2012 12:12:29
                                                    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.IAOOCE-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 Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       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 ***
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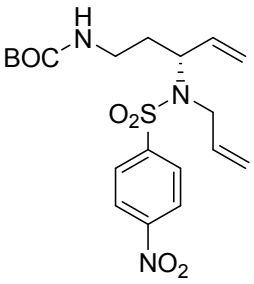
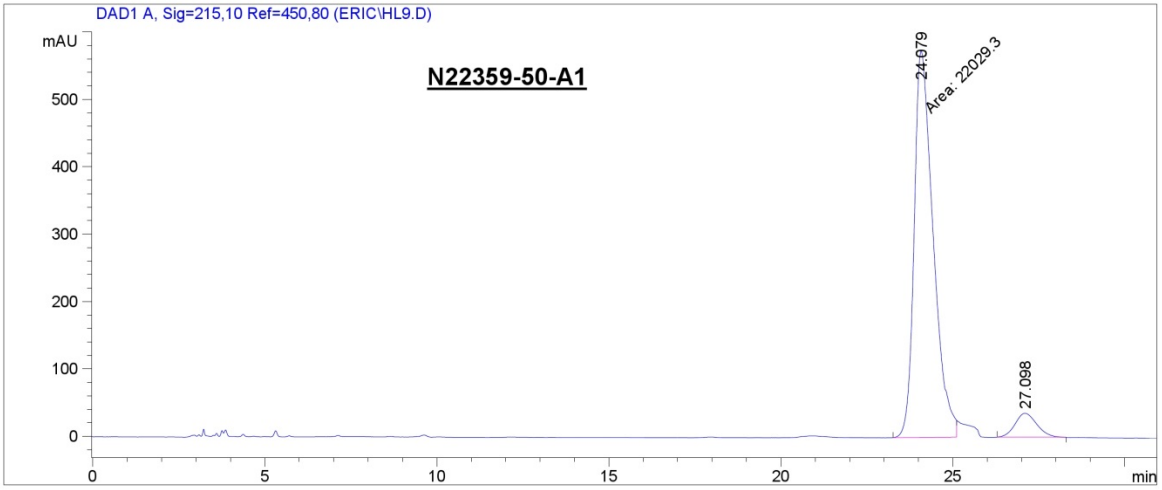



```
Data File K:\HPCHEM\1\DATA\ERIC\HL9.D
Sample Name: N22359-50-A1
    ======================================================================
    Acq. Operator   : ERIC HORTENSE
    Acq. Instrument : LALANDRY                        Location : Vial 1
    Injection Date  : 15/02/2012 11:38:32
                                                     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.IAOOCE-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 Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       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 ***
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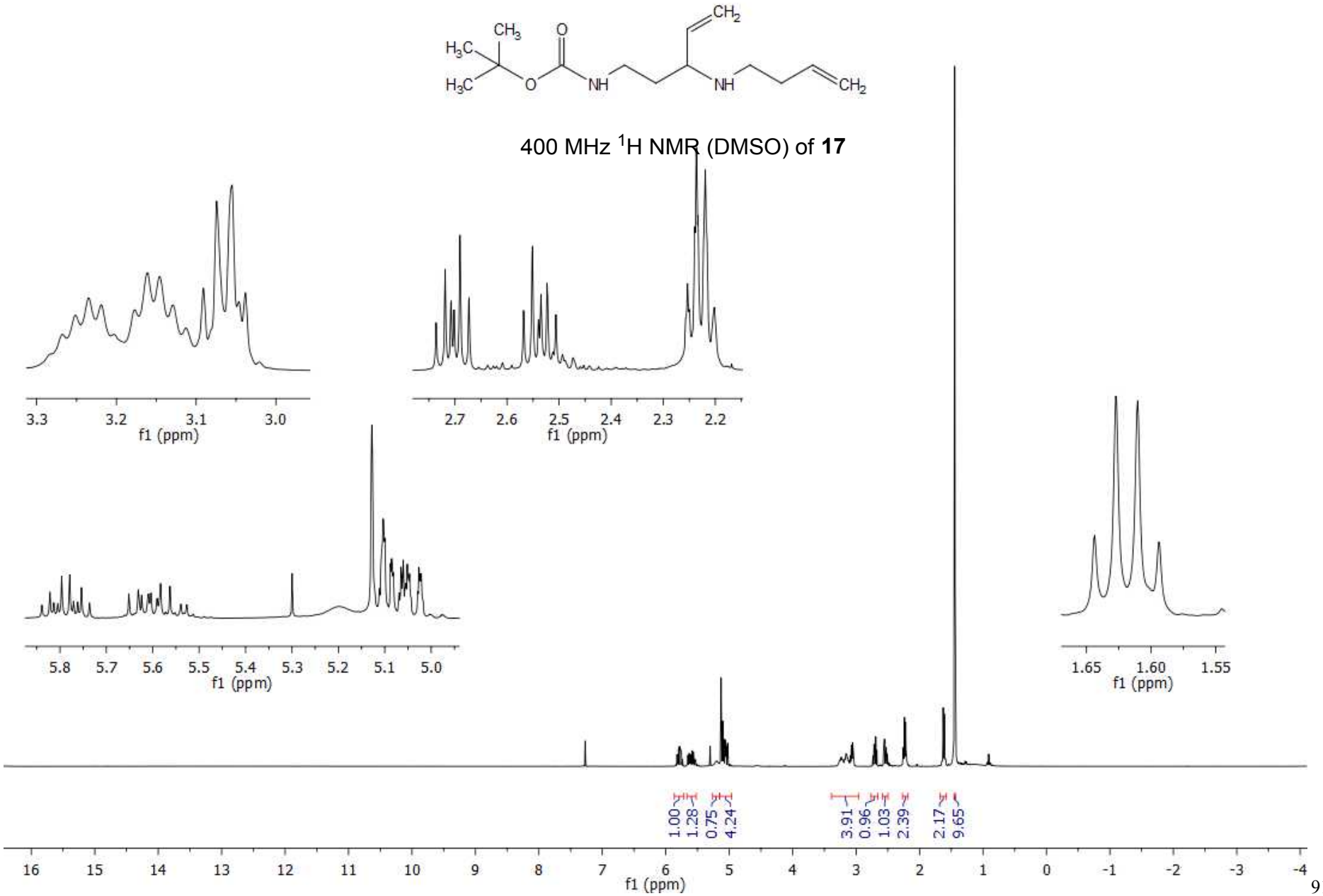
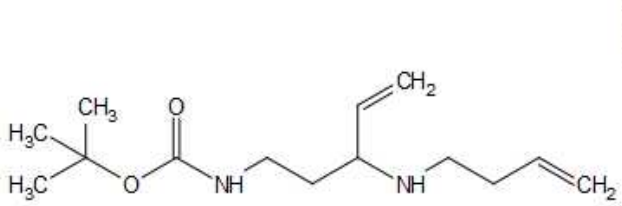
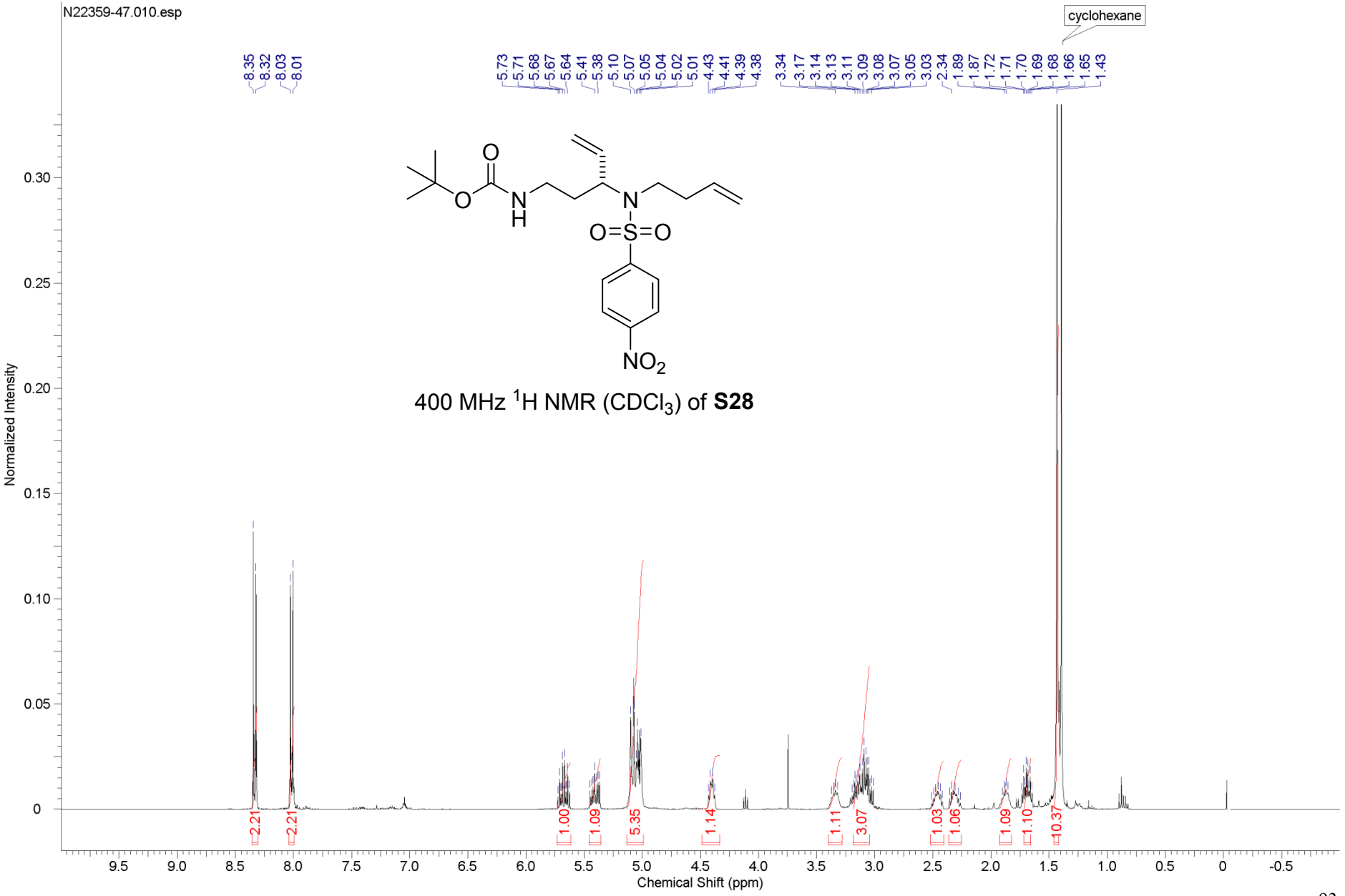


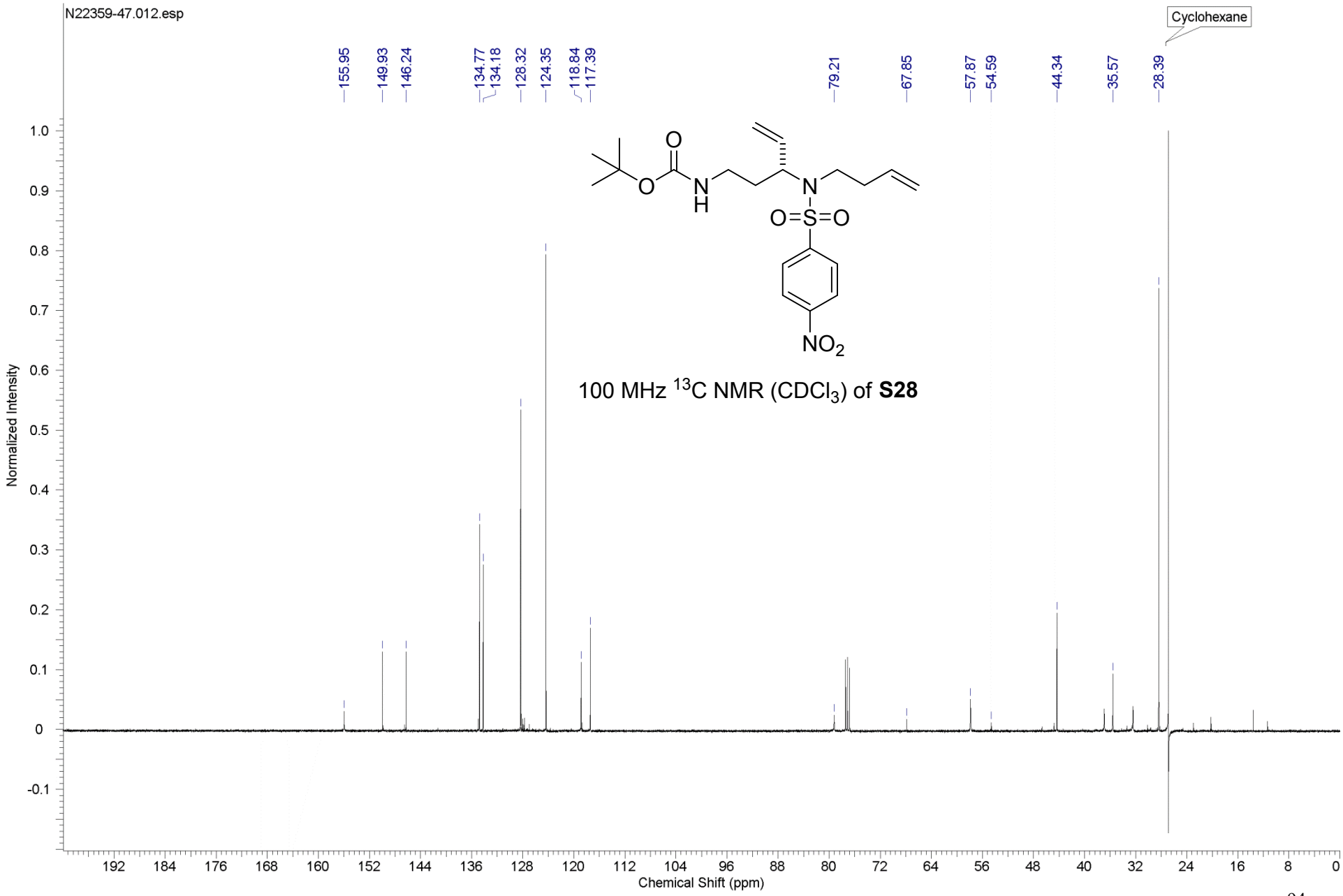
400 MHz ^{1}H NMR (DMSO) of **17**



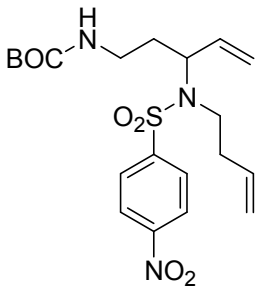
100 MHz ^{13}C NMR (DMSO) of **17**



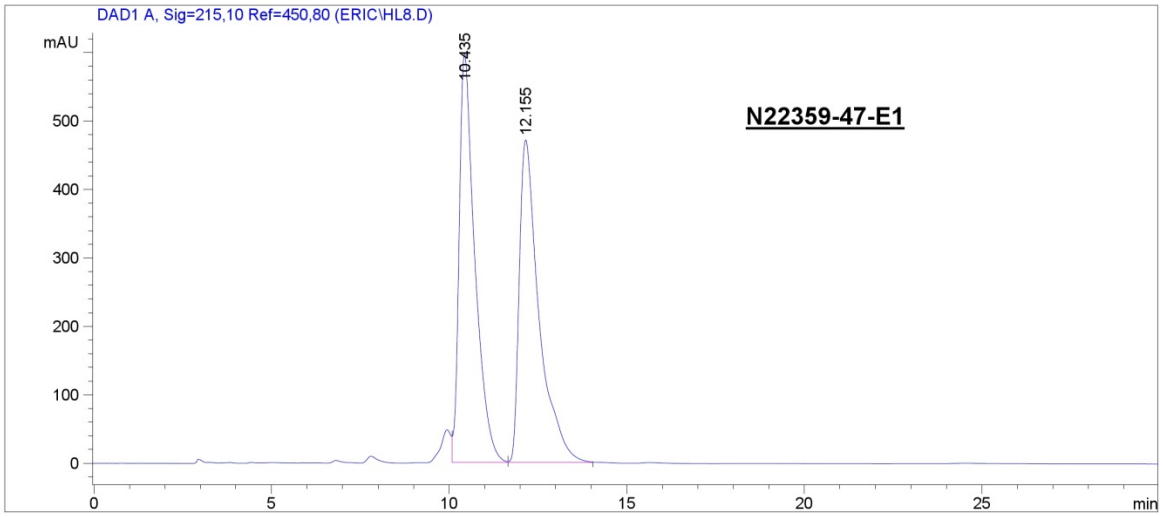
400 MHz ^{1}H NMR ($CDCl_3$) of **S28**



100 MHz ^{13}C NMR ($CDCl_3$) of **S28**




```
Data File K:\HPCHEM\1\DATA\ERIC\HL8.D
Sample Name: N22359-47-E1
    ======================================================================
    Acq. Operator   : ERIC HORTENSE
    Acq. Instrument : LALANDRY                        Location : Vial 1
    Injection Date  : 15/02/2012 10:17:48
                                                     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 Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       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 ***
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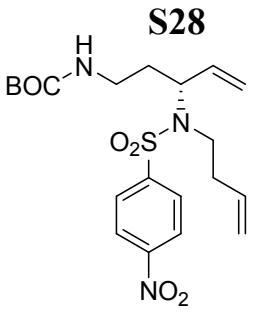
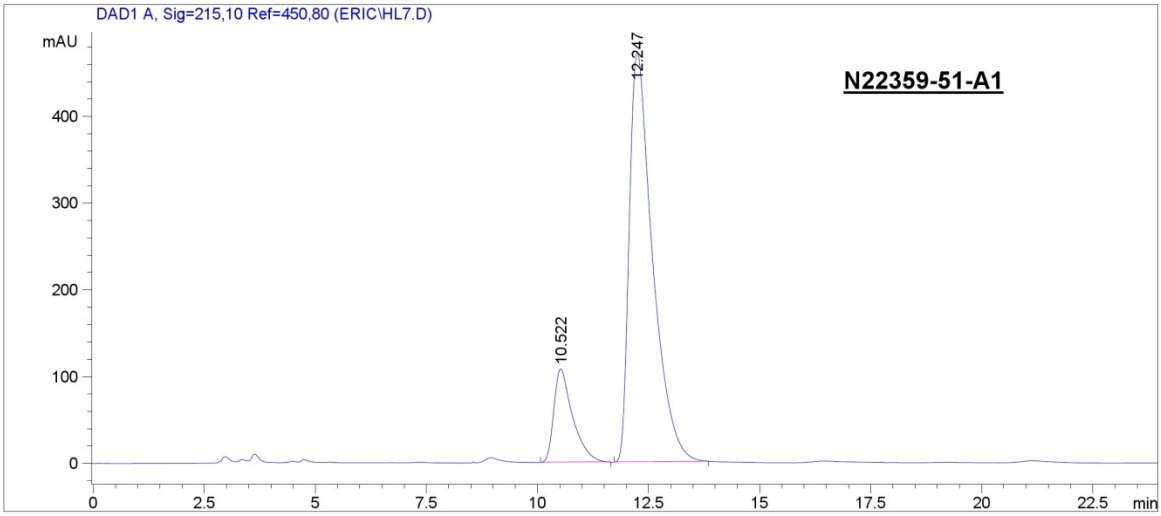



```
Data File K:\HPCHEM\1\DATA\ERIC\HL7.D
Sample Name: N22359-51-A1
    ======================================================================
    Acq. Operator   : ERIC HORTENSE
    Acq. Instrument : LALANDRY                        Location : Vial 1
    Injection Date  : 15/02/2012 09:51:36
                                                    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 Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       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 ***
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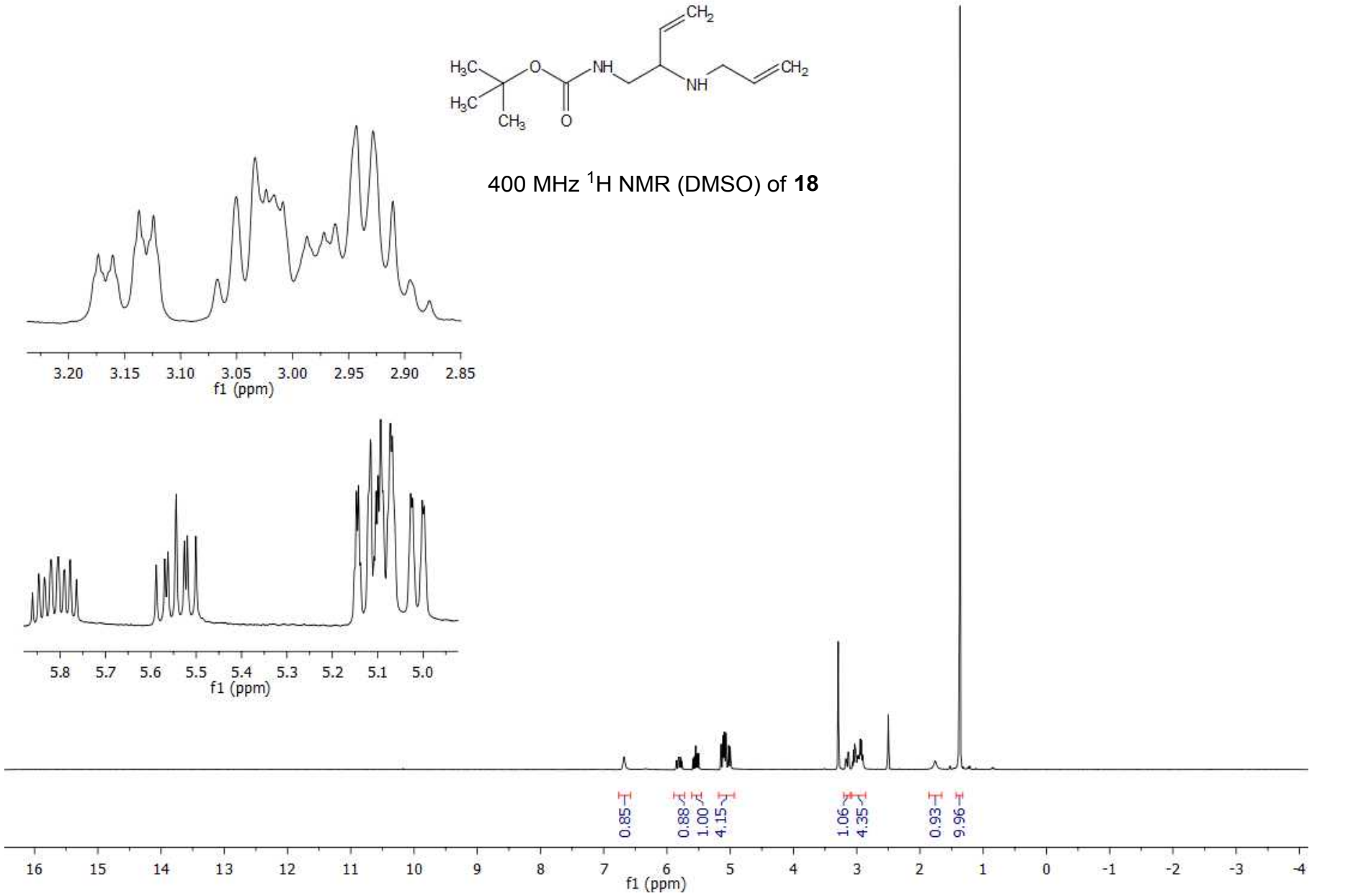
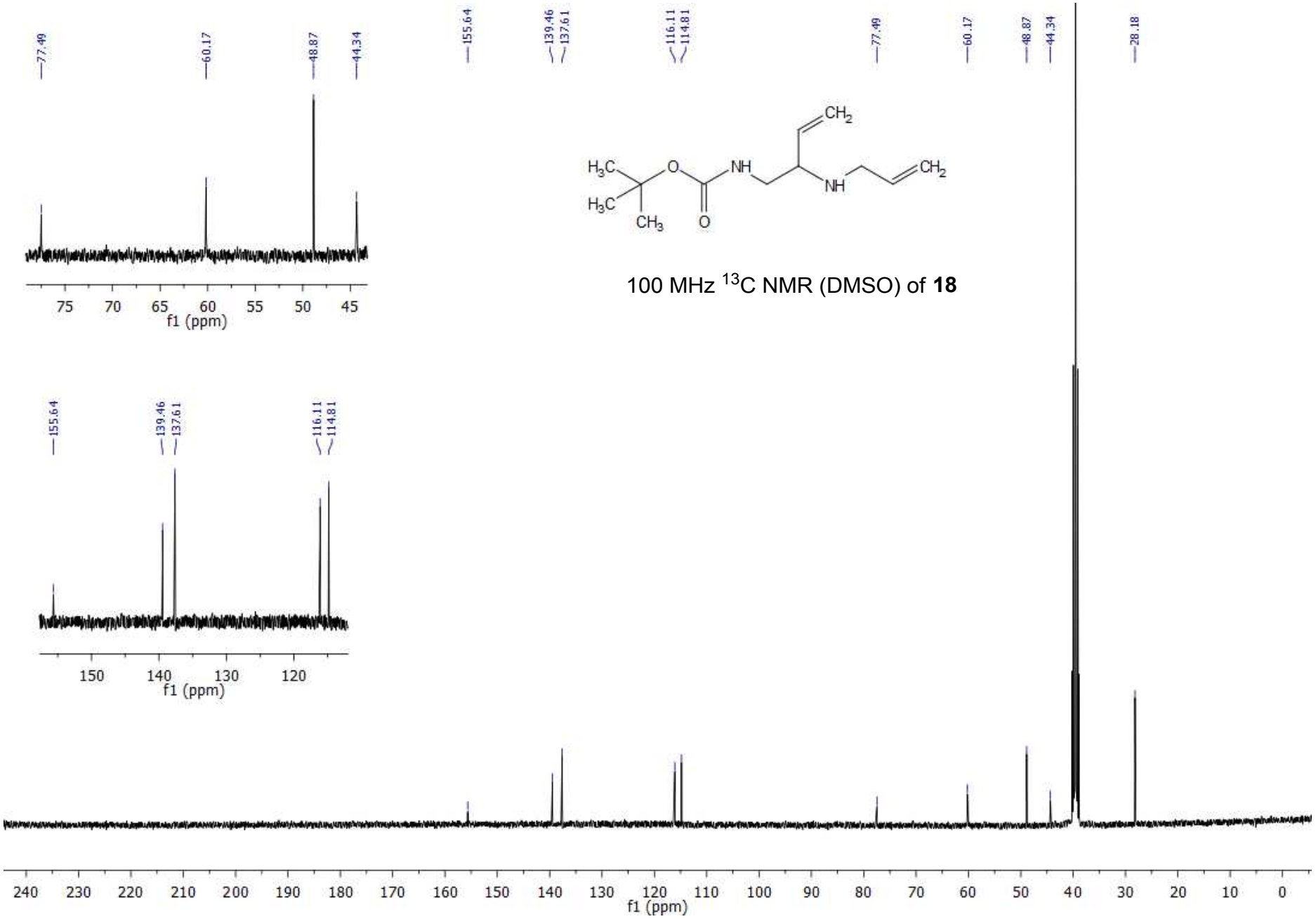
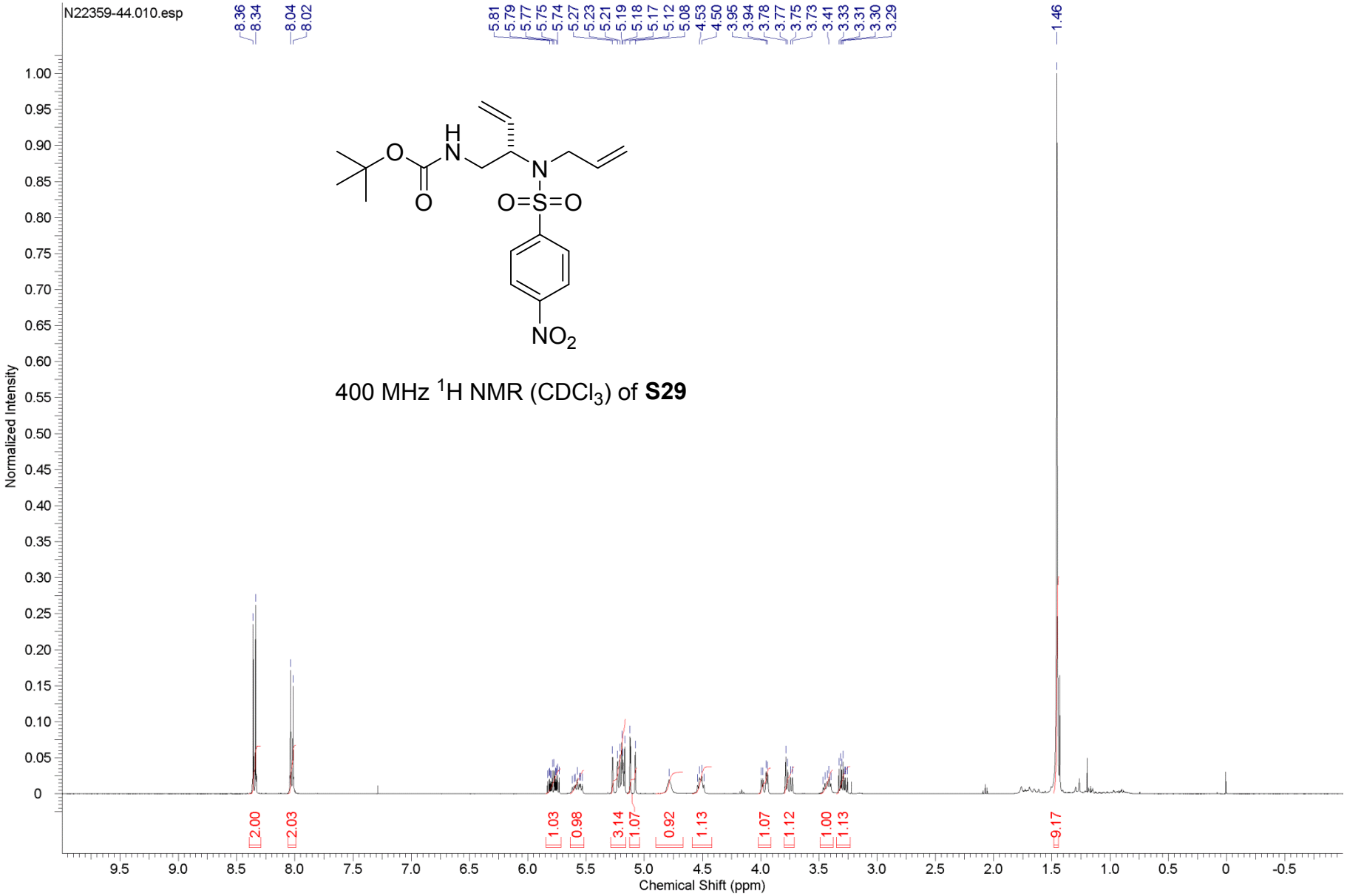


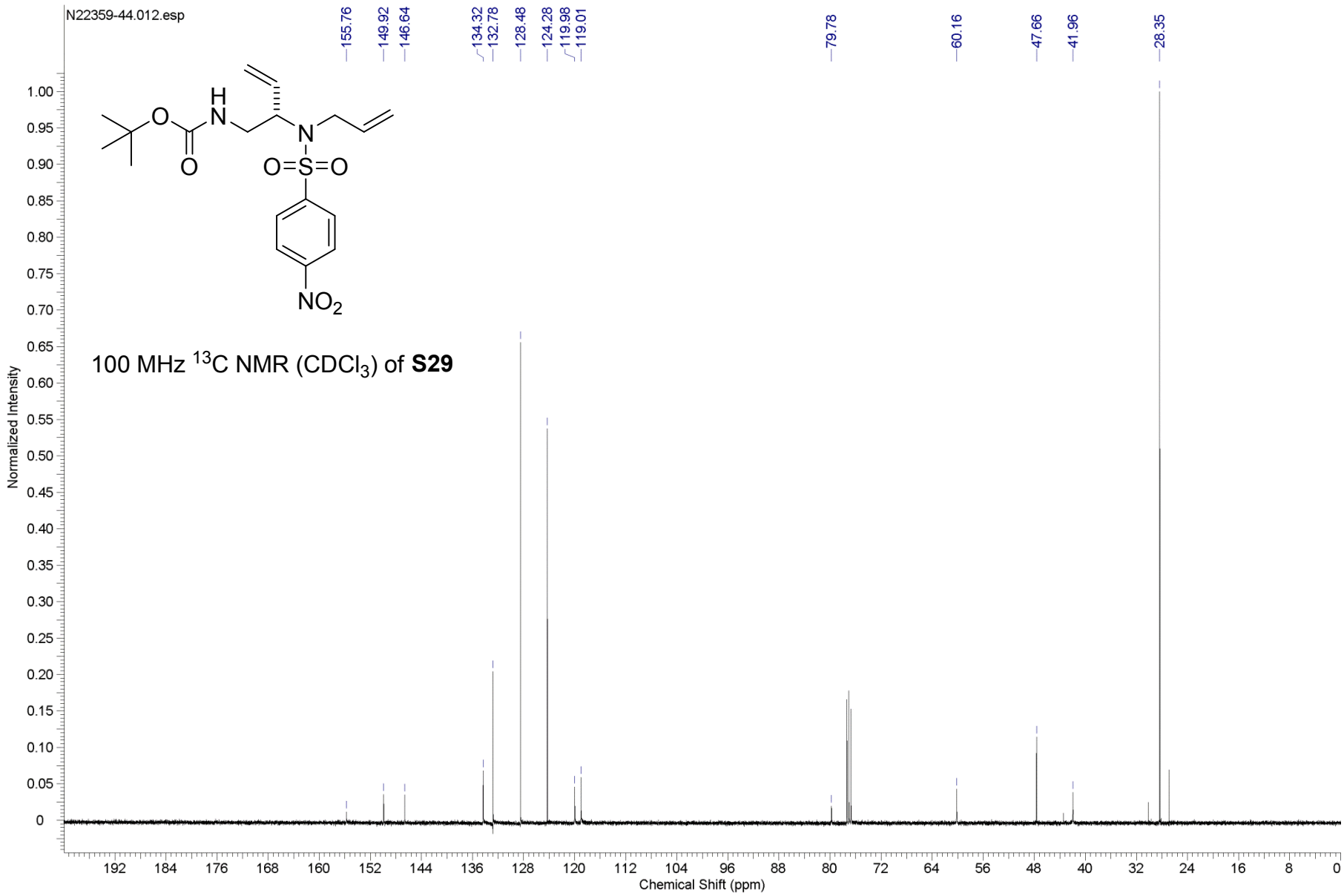
400 MHz ^{1}H NMR (DMSO) of **18**



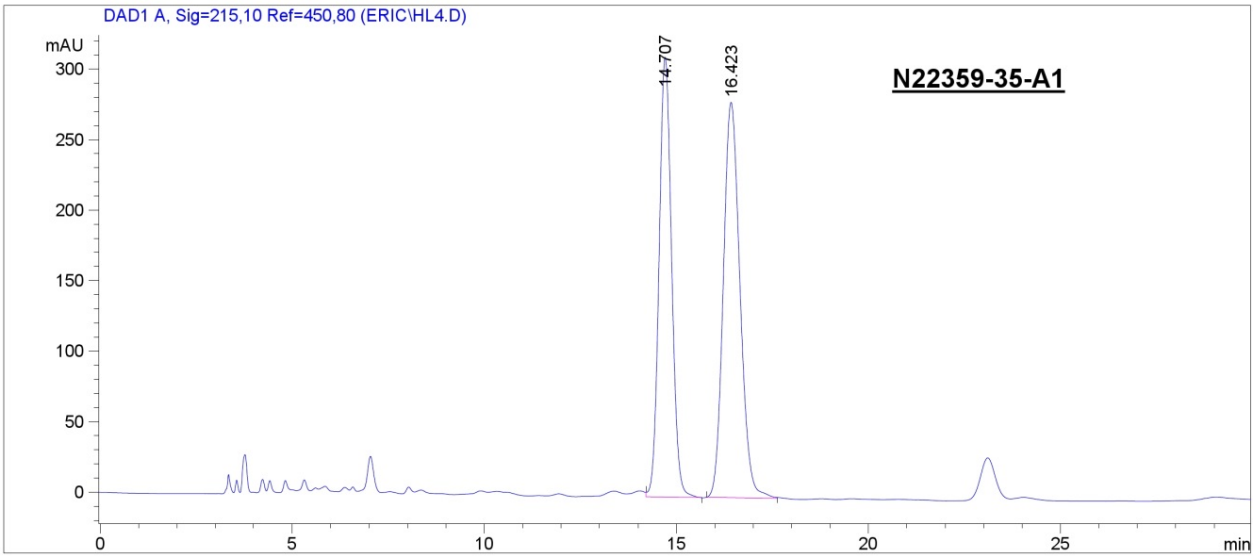
100 MHz ^{13}C NMR (DMSO) of **18**



400 MHz ^{1}H NMR ($CDCl_3$) of **S29**


N22359-44.012.esp
155.76
149.92
146.64
134.32
132.78
128.48
124.28
119.98
119.01
79.78
60.16
47.66
41.96
28.35
100 MHz ^{13}C NMR ($CDCl_3$) of **S29**
Normalized Intensity
Chemical Shift (ppm)

```
Data File K:\HPCHEM\1\DATA\ERIC\HL4.D
Sample Name: N22359-35-A1
    ======================================================================
    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/mi
                      n,wavelength 215nm,RT


    ======================================================================
```

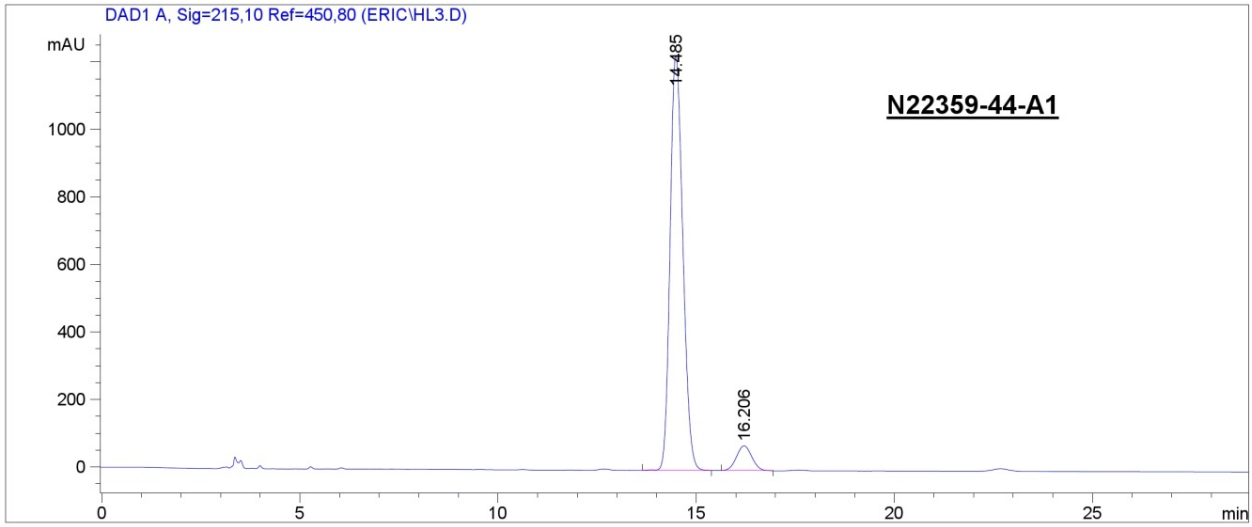



```
    ======================================================================
                              Area Percent Report
    ======================================================================

    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 Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|---------|---------|--------|
       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 ***
```

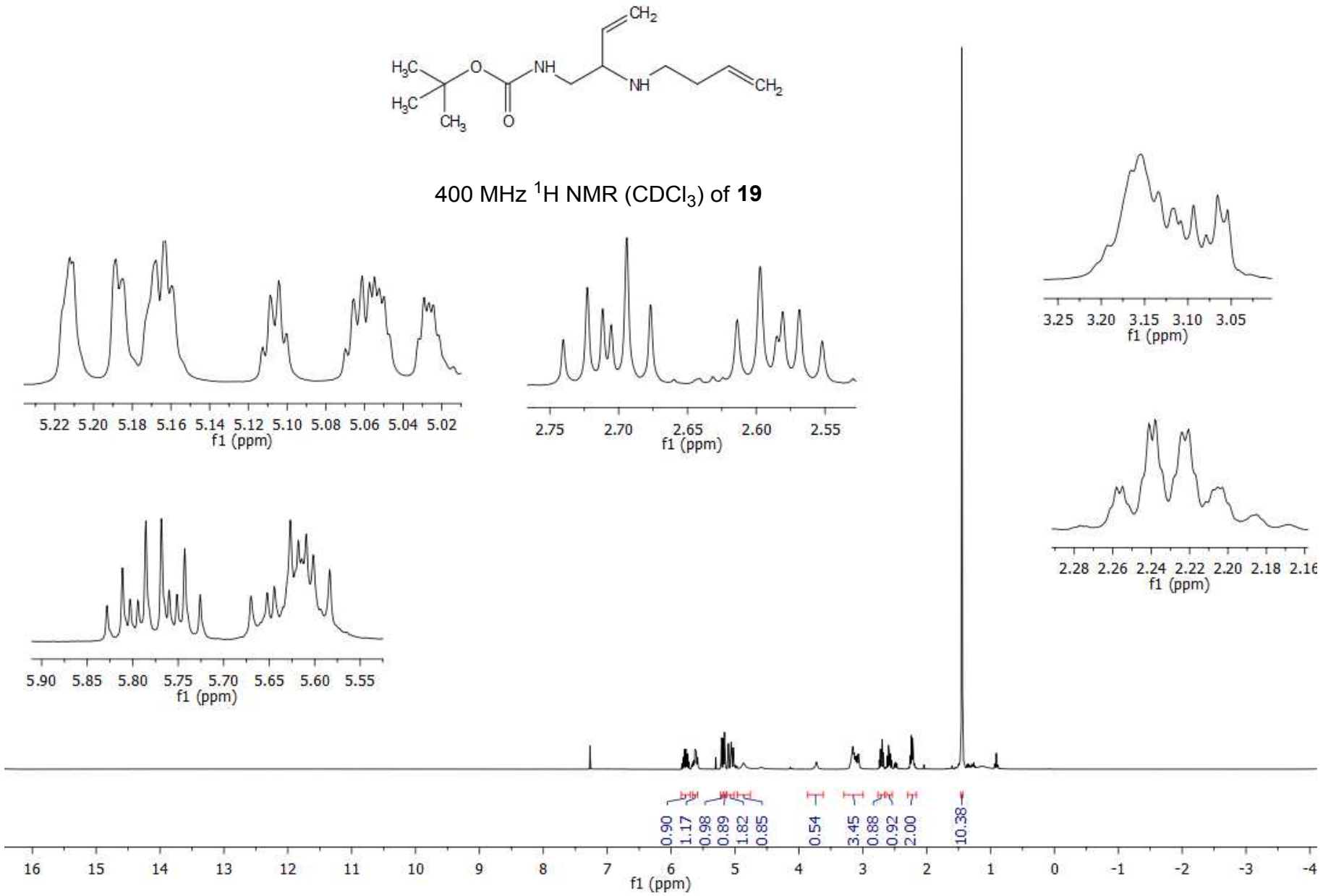
S29

```
Data File K:\HPCHEM\1\DATA\ERIC\HL3.D
Sample Name: N22359-44-A1
    ======================================================================
    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/mi
                      n,wavelength 215nm,RT
```

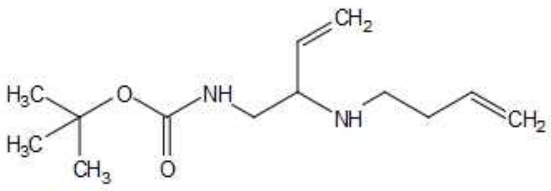
```
    ======================================================================
```



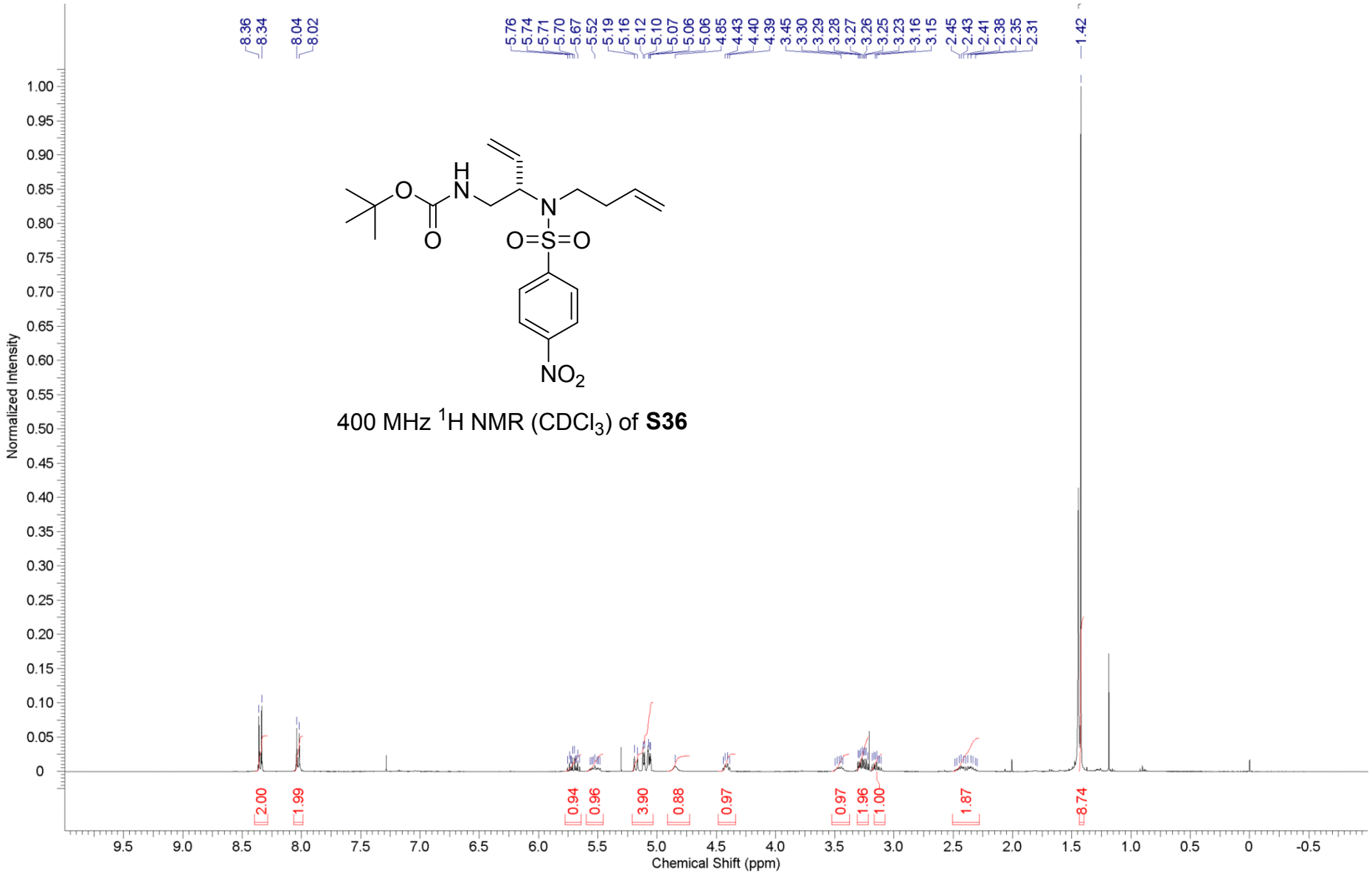

```
    ======================================================================
                            Area Percent Report
    ======================================================================

    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 Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       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 ***
```



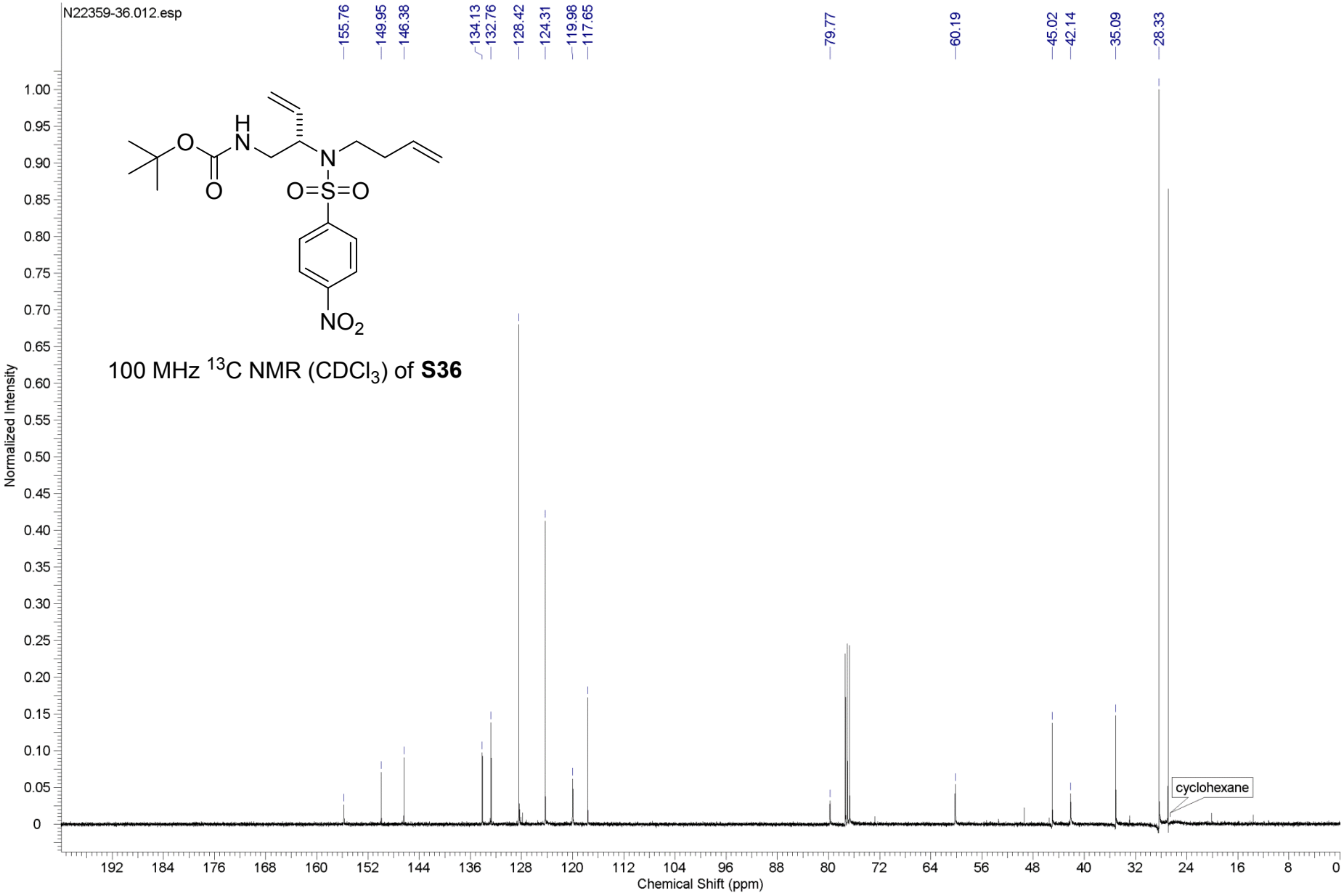
400 MHz ^{1}H NMR ($CDCl_3$) of **19**



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



400 MHz ^{1}H NMR ($CDCl_3$) of **S36**

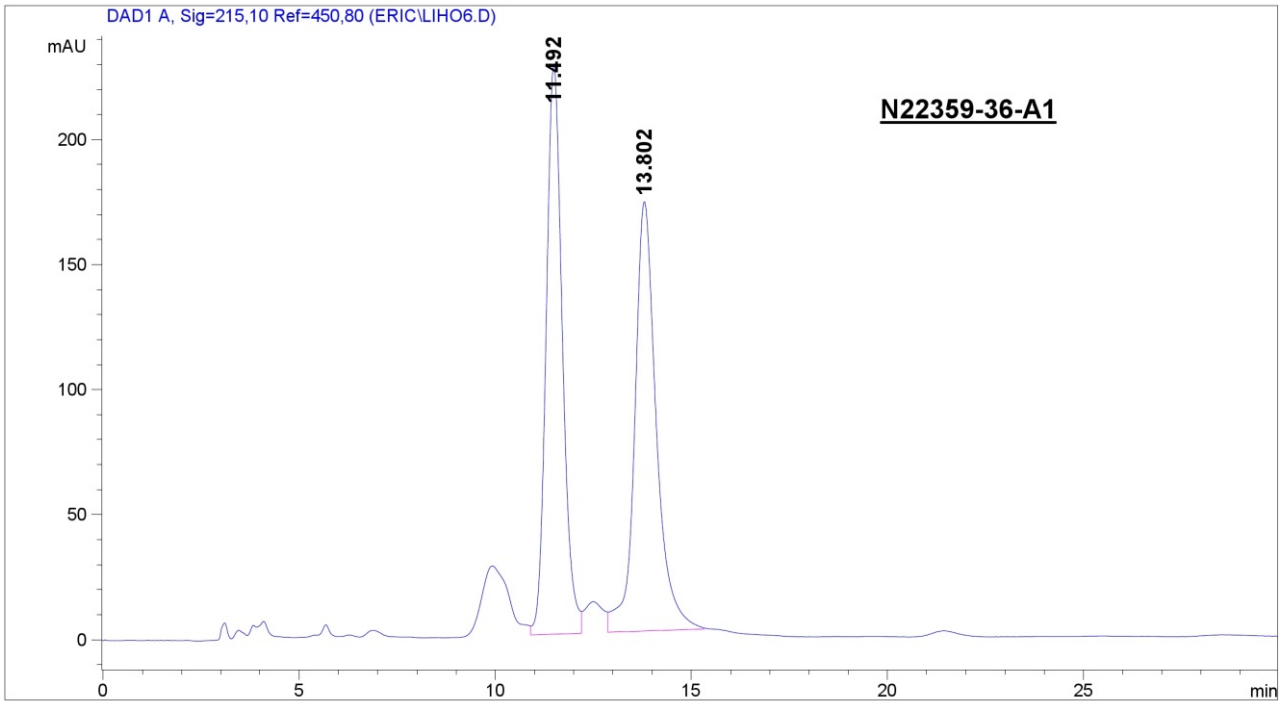


100 MHz ^{13}C NMR ($CDCl_3$) of **S36**

Data File K:\HOYTEN\HPCHEM\1\DATA\ERIC\LIHO6.D
Sample Name: N22359-36-A1

S36

```
==========================================================================
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
```

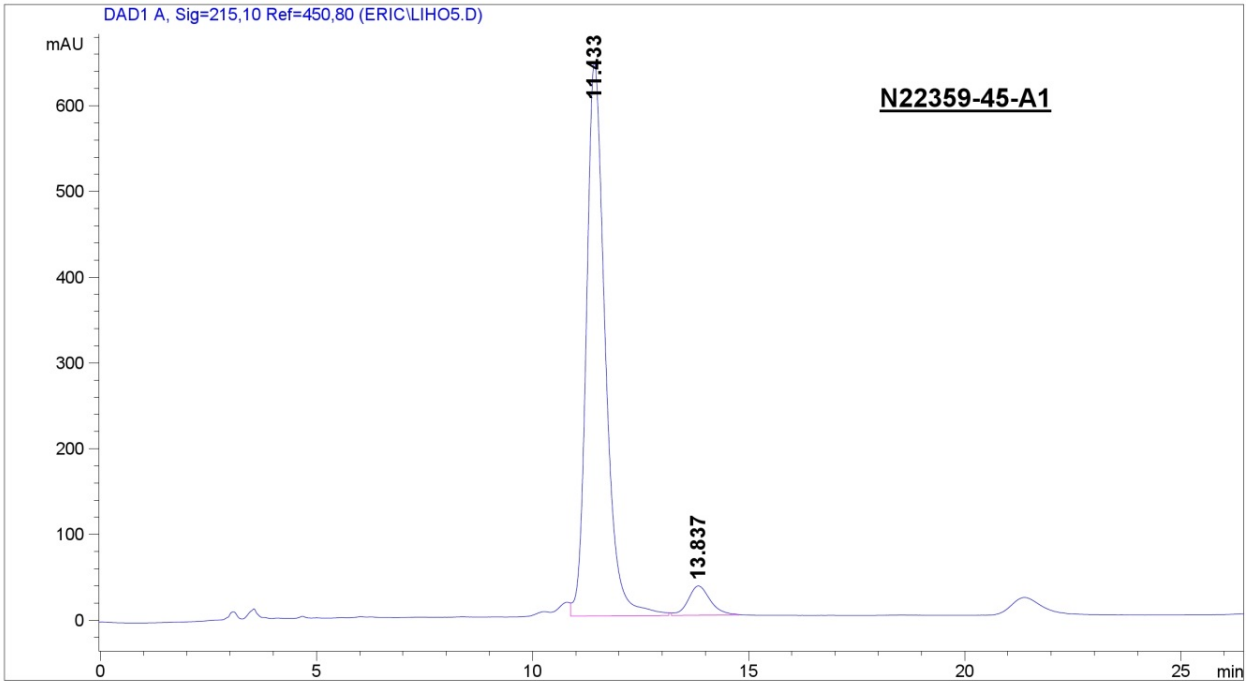



```
==========================================================================
                          Area Percent Report
==========================================================================

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 Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   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 ***
```

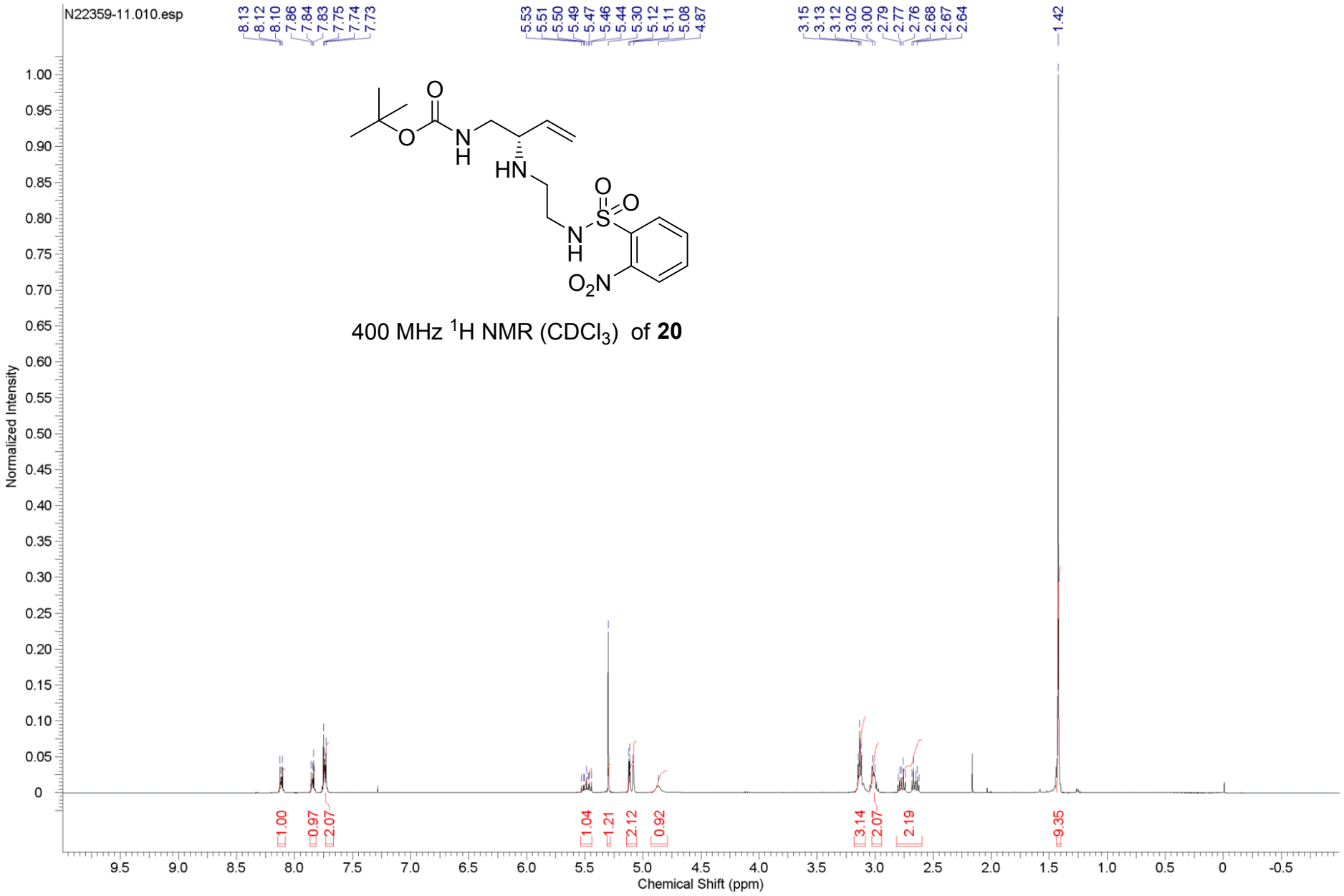
Data File K:\HOYTEN\HPCHEM\1\DATA\ERIC\LIHO5.D
Sample Name: N22359-45-A1

S36

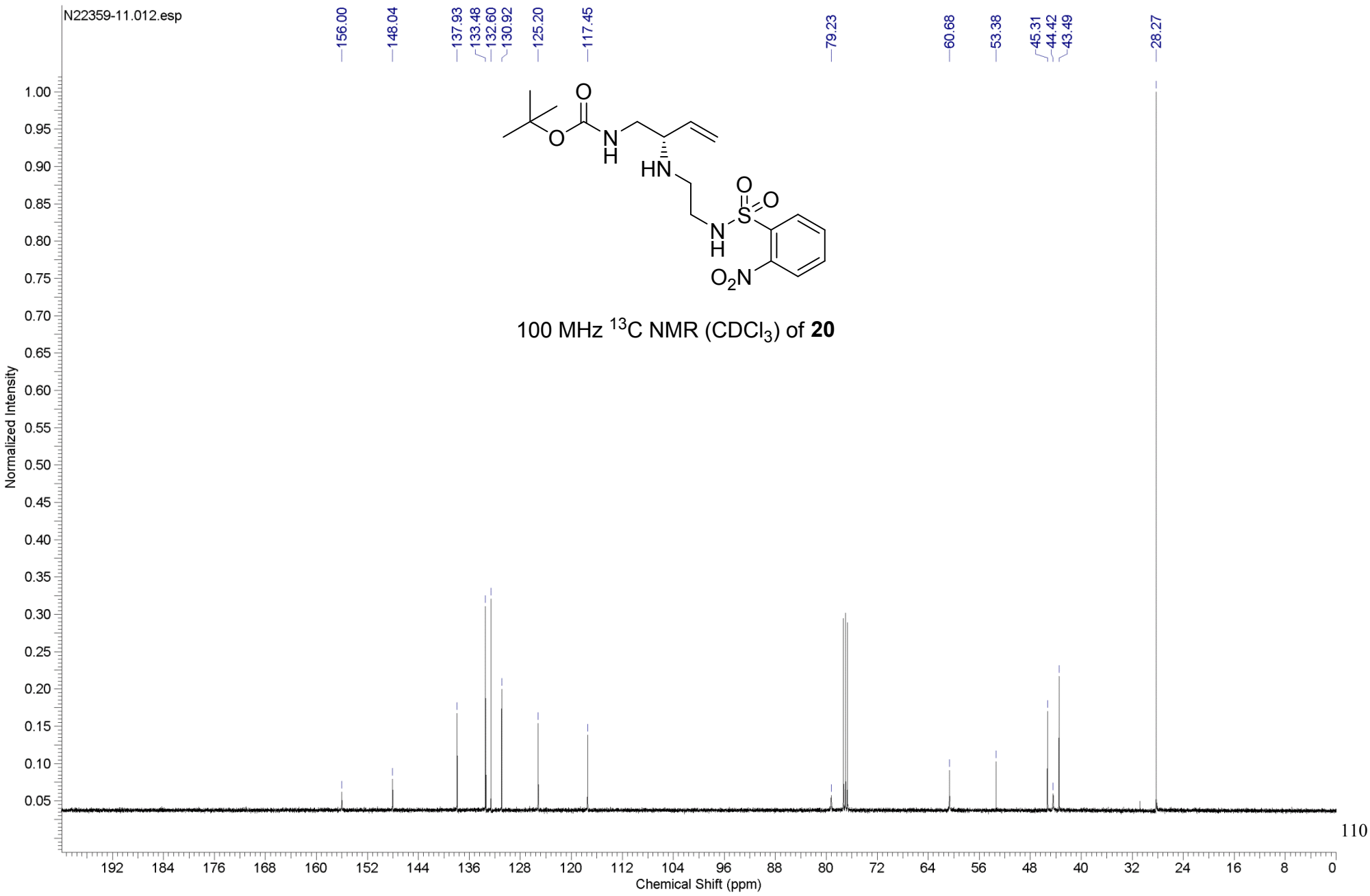
```
    ======================================================================
    Acq. Operator   : ERIC HORTENSE
    Acq. Instrument : HOYTEN                        Location : Vial 1
    Injection Date  : 06/02/2012 09:43:32
                                                   Inj Volume : 5 µl
    Acq. 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 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 Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       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 ***
```



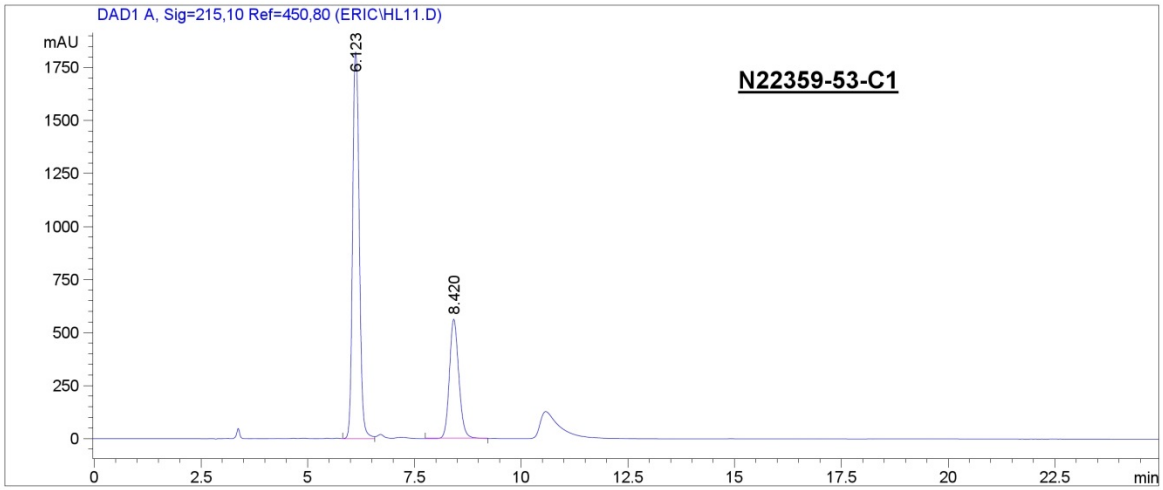
400 MHz ^{1}H NMR ($CDCl_3$) of **20**



100 MHz ^{13}C NMR ($CDCl_3$) of **20**

20

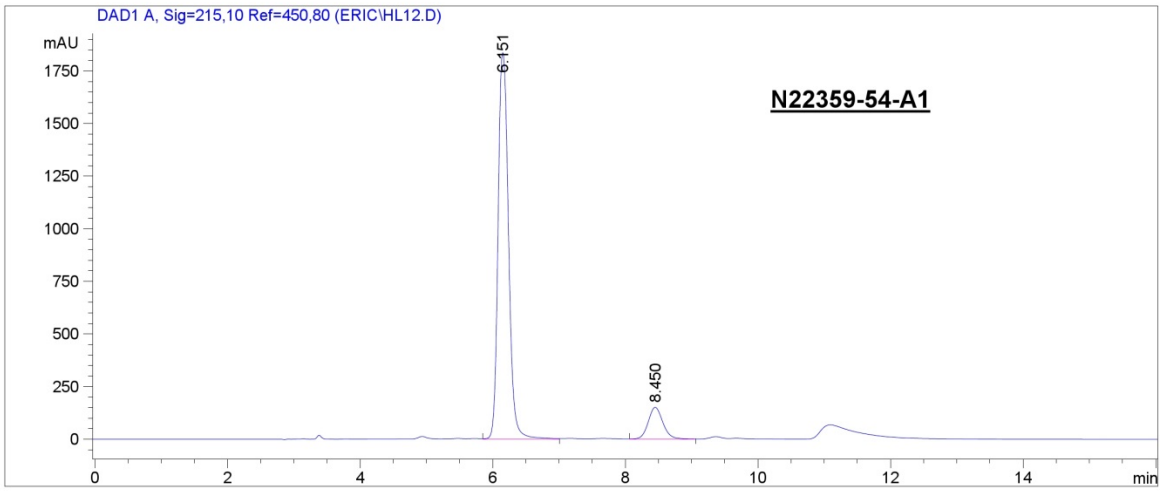
```
Data File K:\HPCHEM\1\DATA\ERIC\HL11.D
Sample Name: N22359-53-C1
    ======================================================================
    Acq. Operator   : ERIC HORTENSE
    Acq. Instrument : LALANDRY                      Location : Vial 1
    Injection Date  : 28/02/2012 15:26:40
                                                   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/mi
                      n,wavelength 215nm,RT


    ======================================================================
```



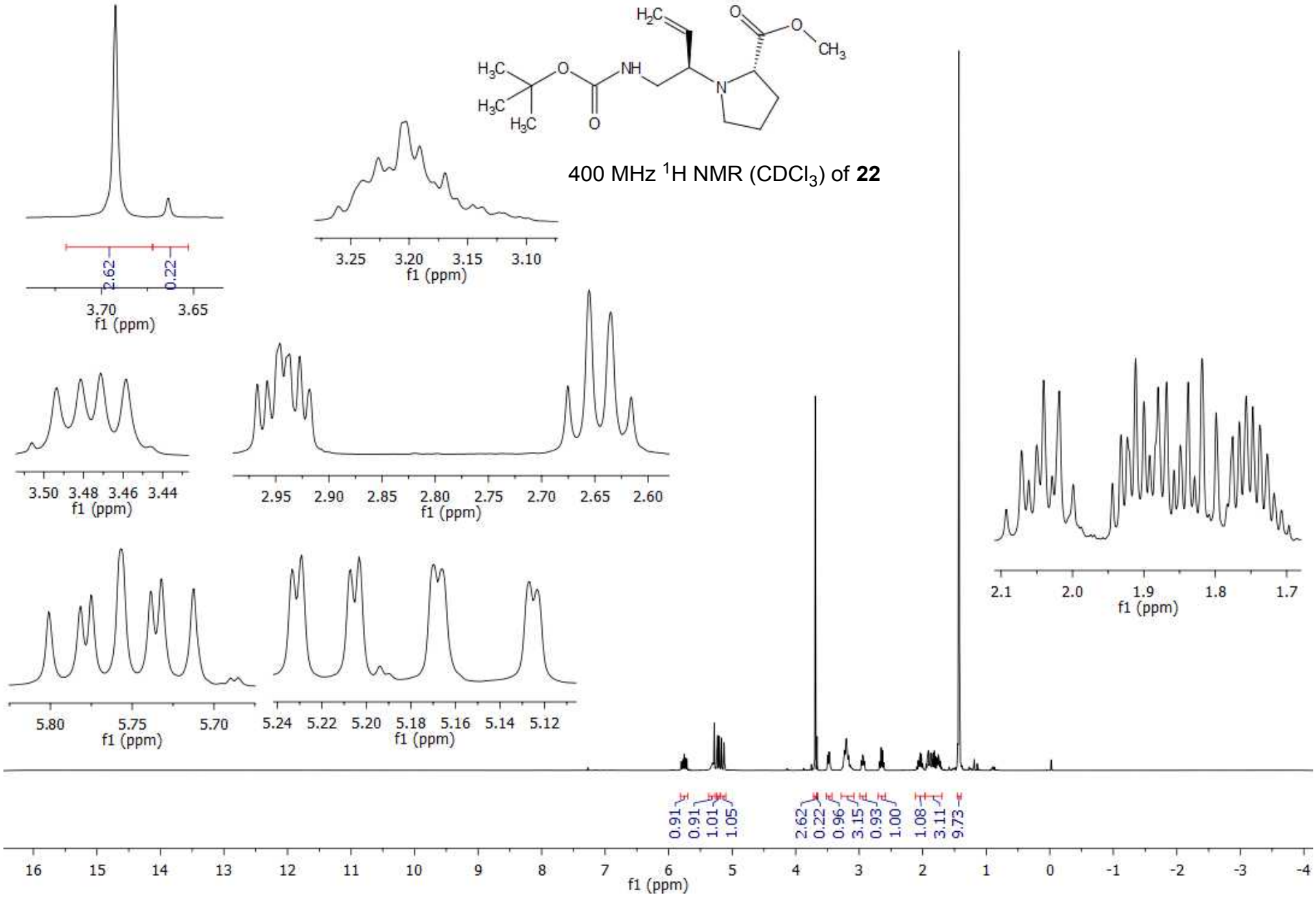

```
    ======================================================================
                              Area Percent Report
    ======================================================================

    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 Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       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 ***
```

20

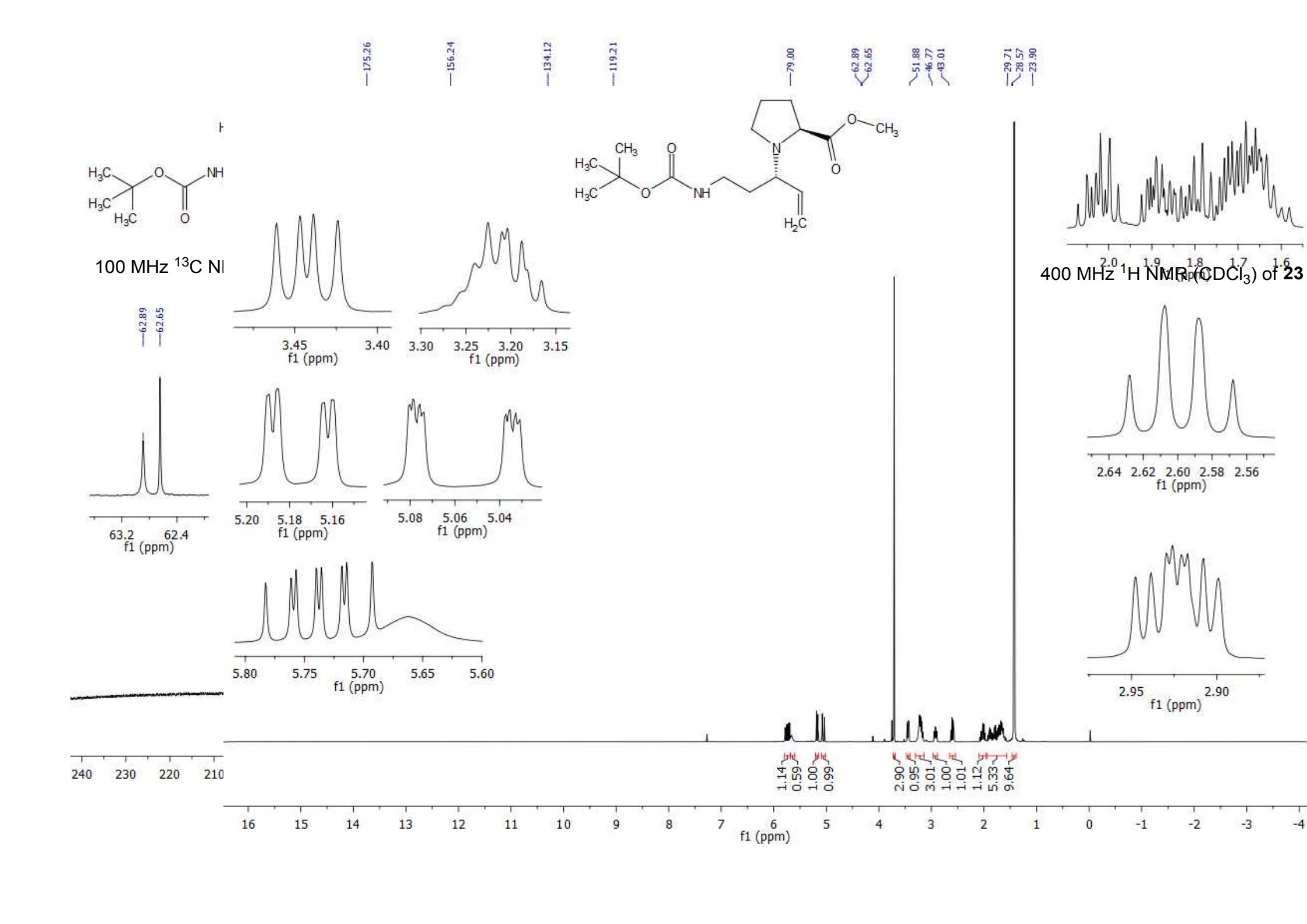
```
Data File K:\HPCHEM\1\DATA\ERIC\HL12.D
Sample Name: N22359-54-A1
    ======================================================================
    Acq. Operator   : ERIC HORTENSE
    Acq. Instrument : LALANDRY                        Location : Vial 1
    Injection Date  : 28/02/2012 15:57:26
                                                    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/mi
                      n,wavelength 215nm,RT


    ======================================================================
```

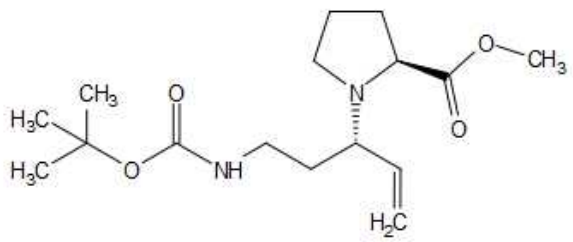



```
    ======================================================================
                            Area Percent Report
    ======================================================================

    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 Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1   6.151 VB    0.1733 2.00398e4  1836.55444  89.6208
       2   8.450 VB    0.2373 2320.85327  150.97911  10.3792

    Totals :                  2.23606e4  1987.53355

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

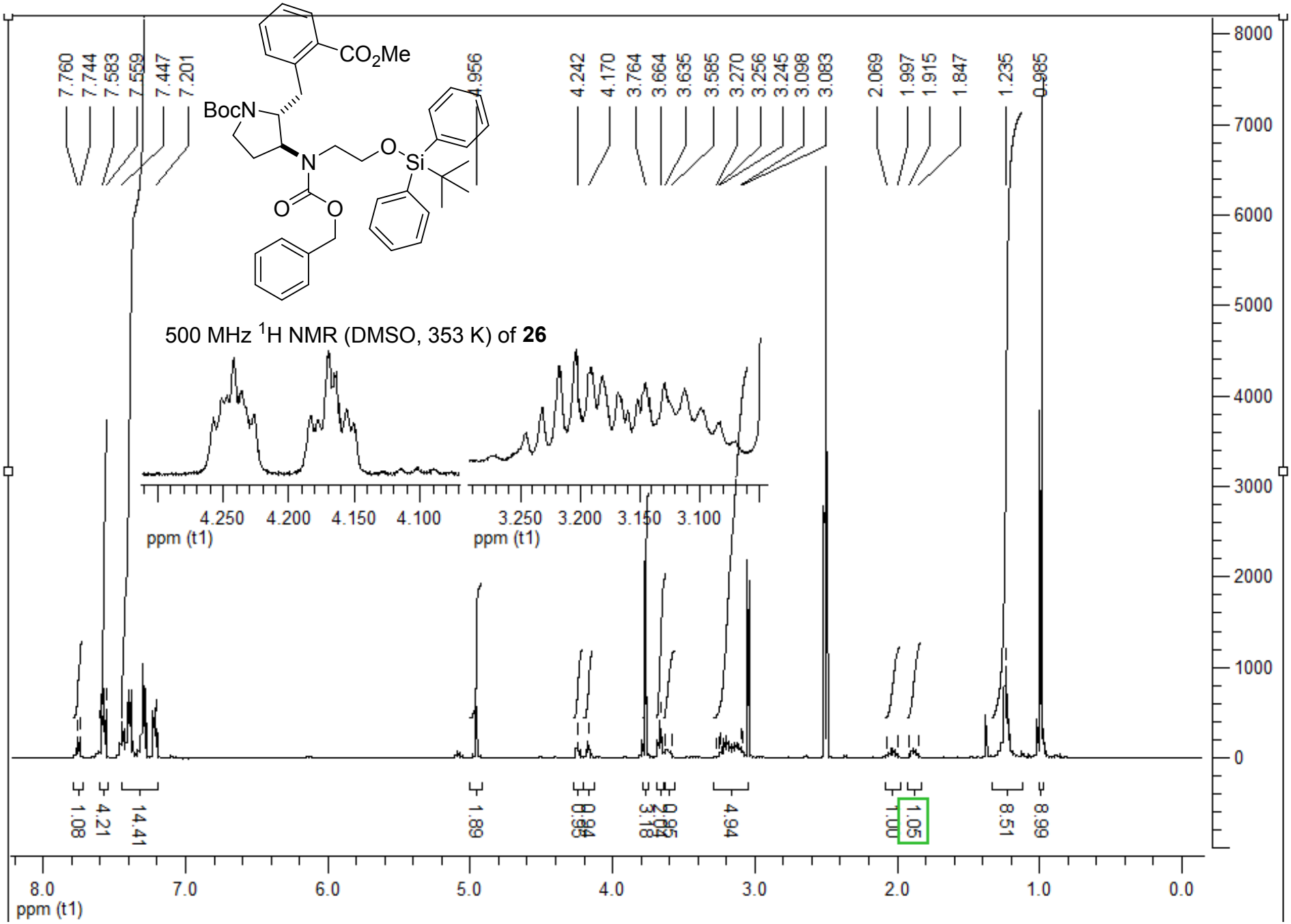


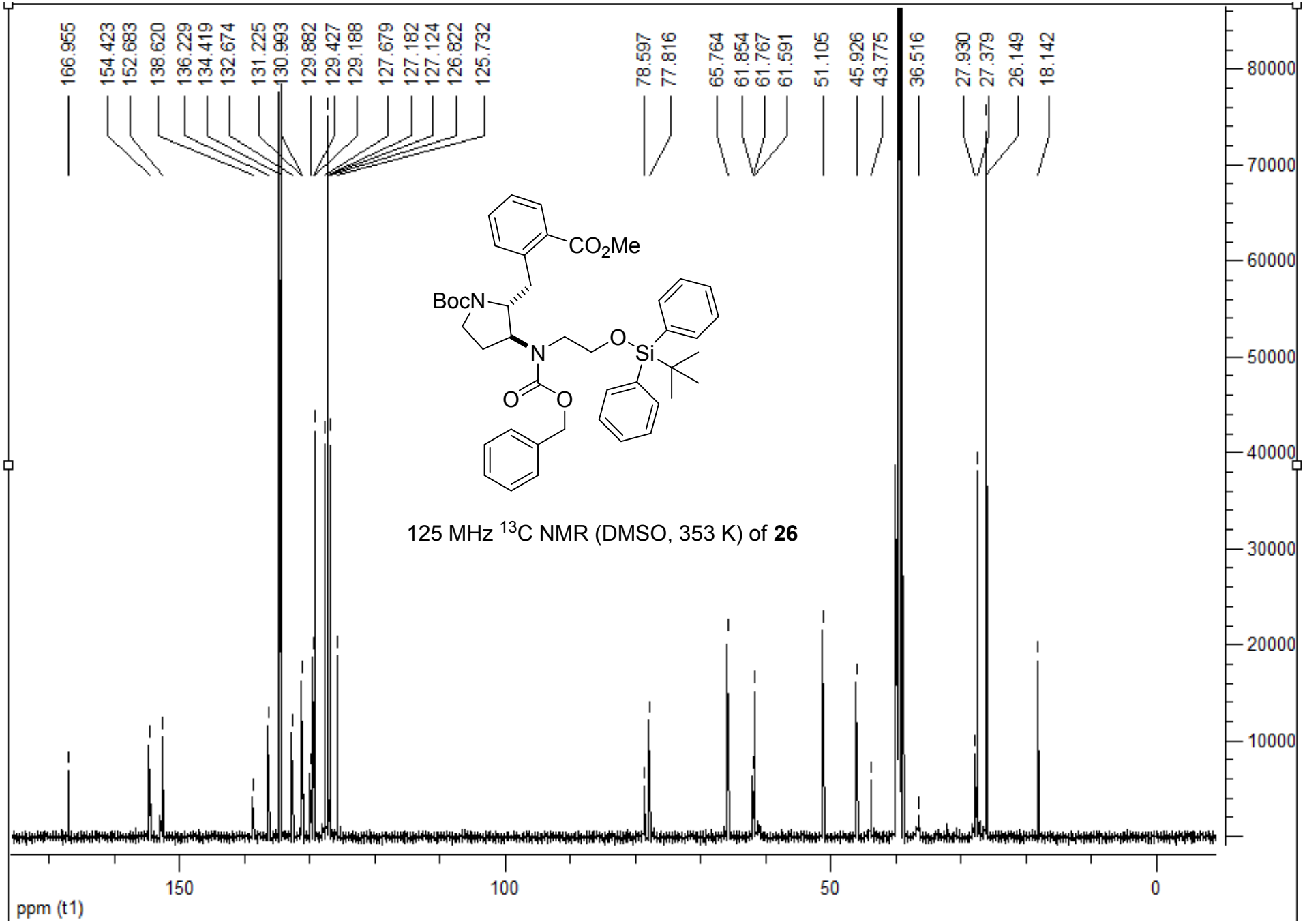
400 MHz ^{1}H NMR ($CDCl_3$) of **22**


175.26
156.24
134.12
119.21
79.00
62.89
62.65
51.88
46.77
43.01
29.71
28.57
23.90
100 MHz ^{13}C NI
400 MHz ^{1}H NMR (CDCl$_3$) of **23**
f1 (ppm)

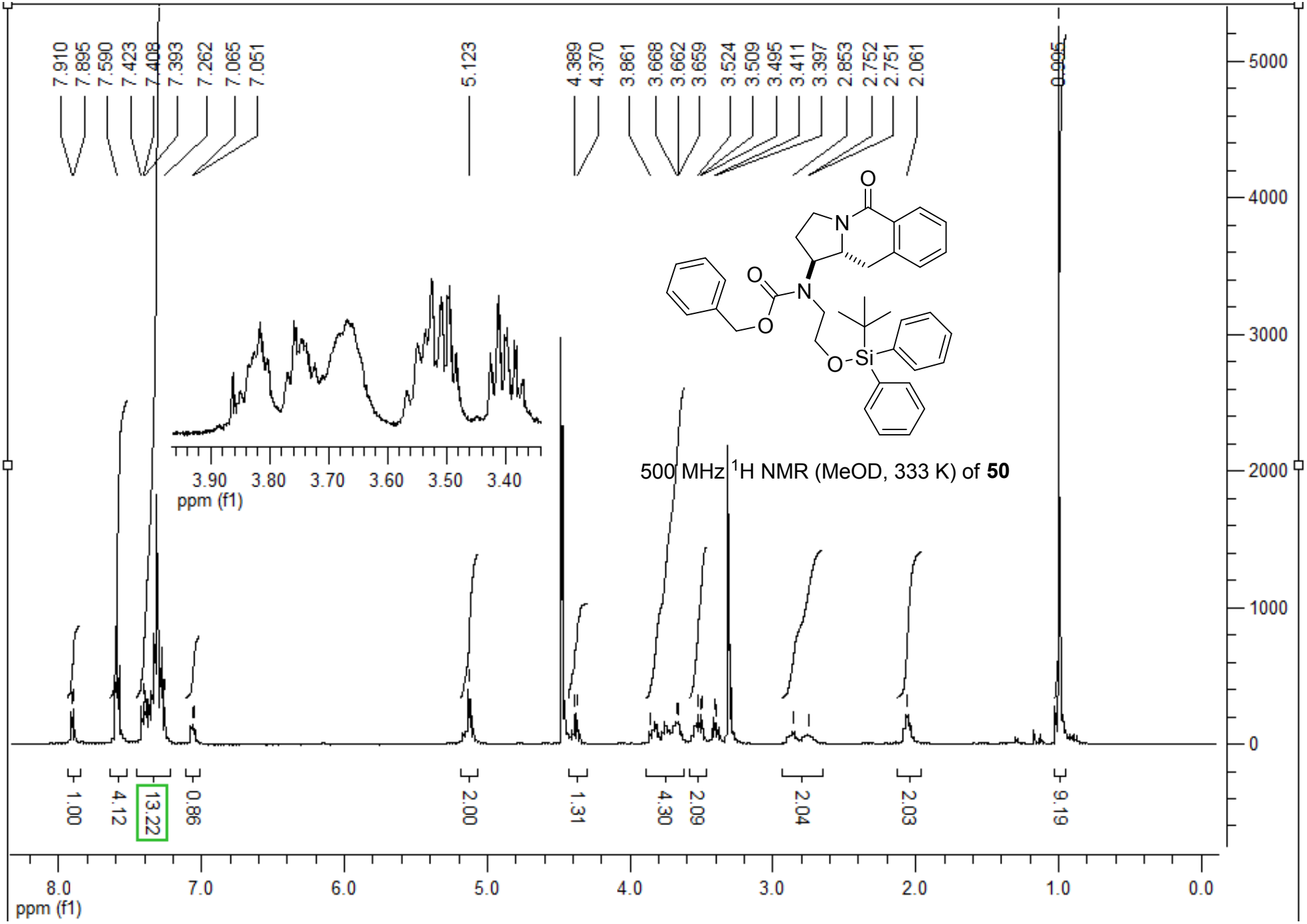


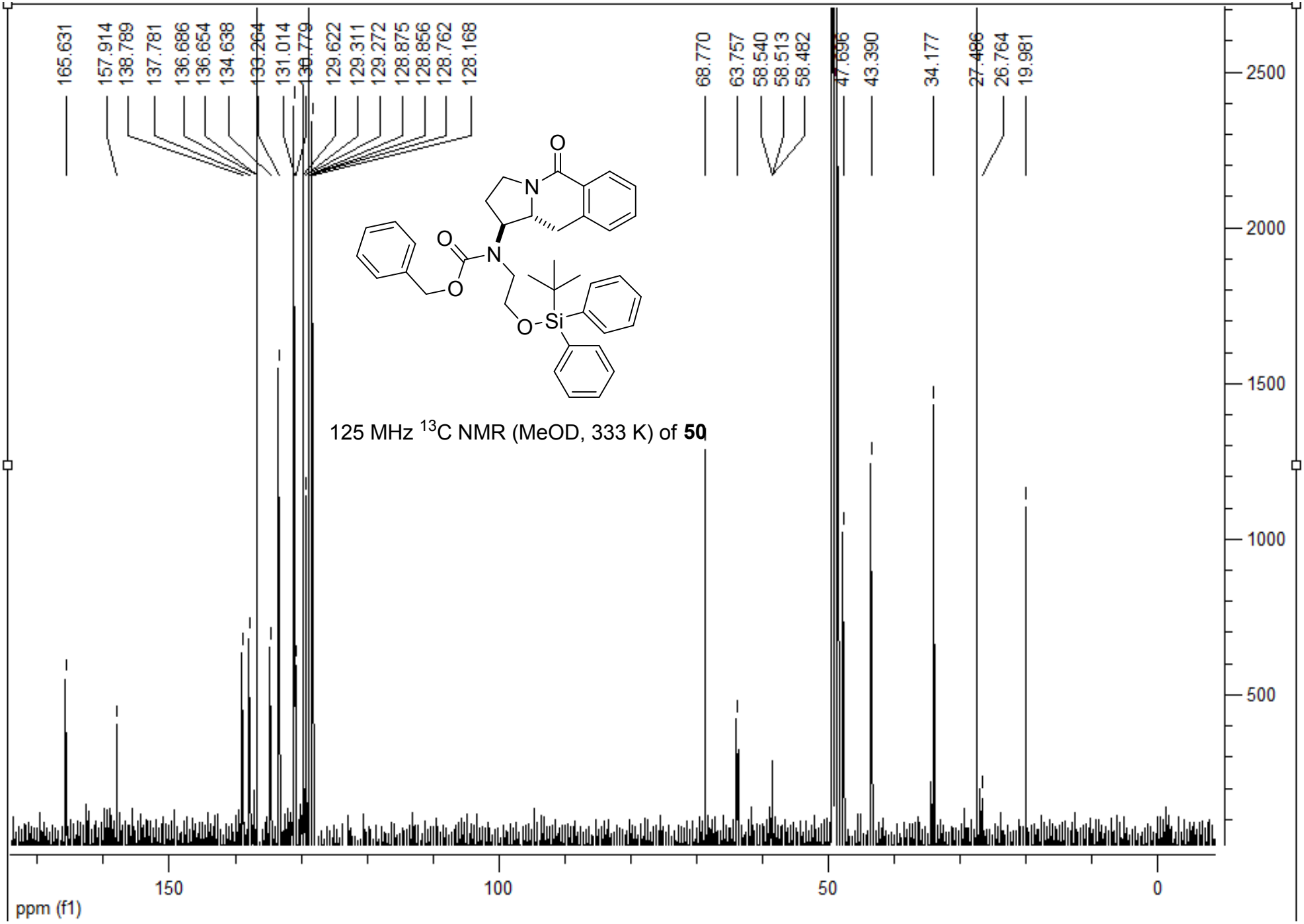
100 MHz ^{13}C NMR ($CDCl_3$) of **23**


7.760
7.744
7.583
7.559
7.447
7.201
4.956
4.242
4.170
3.764
3.664
3.635
3.585
3.270
3.256
3.245
3.098
3.083
2.069
1.997
1.915
1.847
1.235
0.985
BocN
N
O
Si
O
O
CO2Me
500 MHz 1H NMR (DMSO, 353 K) of 26
4.250 4.200 4.150 4.100
ppm (t1)
3.250 3.200 3.150 3.100
ppm (t1)
1.08
4.21
14.41
1.89
0.98
0.94
3.18
0.95
4.94
1.00
1.05
8.51
8.99
8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
ppm (t1)
8000
7000
6000
5000
4000
3000
2000
1000
0

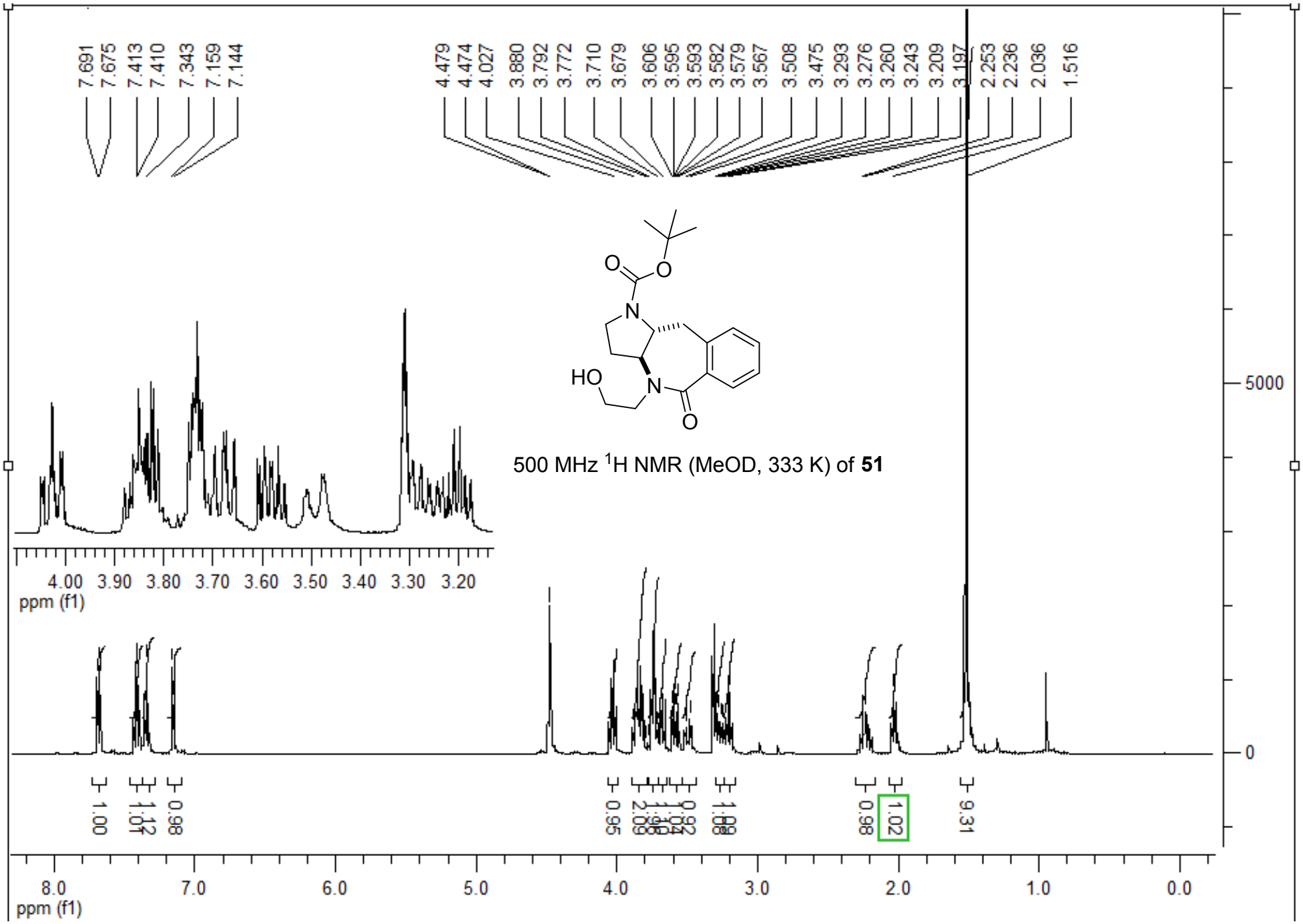


125 MHz ^{13}C NMR (DMSO, 353 K) of **26**

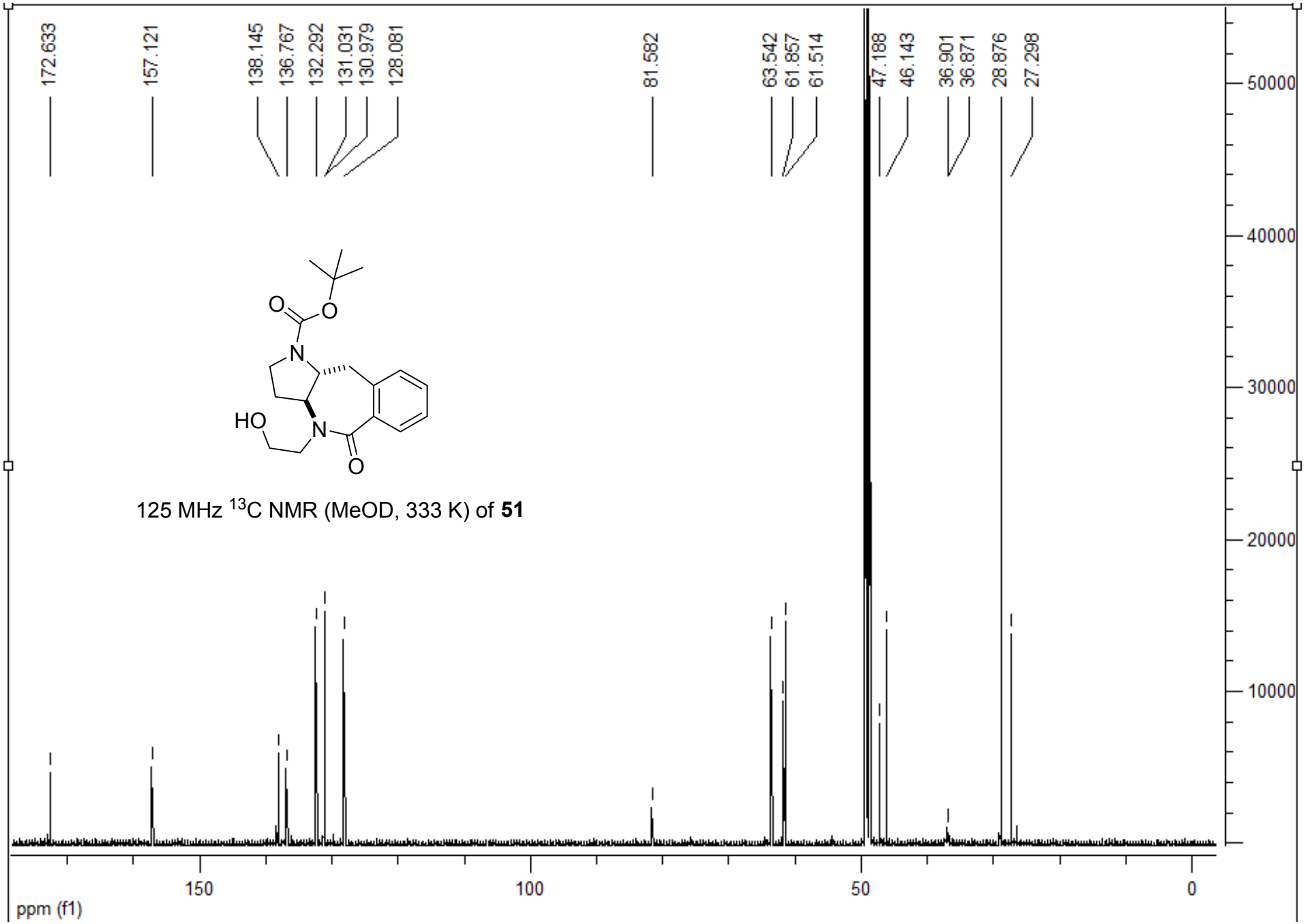

7.910
7.895
7.590
7.423
7.408
7.393
7.262
7.065
7.051
5.123
4.389
4.370
3.861
3.668
3.662
3.659
3.524
3.509
3.495
3.411
3.397
2.853
2.752
2.751
2.061
0.005
3.90 3.80 3.70 3.60 3.50 3.40
ppm (f1)
500 MHz ^{1}H NMR (MeOD, 333 K) of **50**
1.00
4.12
13.22
0.86
2.00
1.31
4.30
2.09
2.04
2.03
9.19
8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
ppm (f1)
5000
4000
3000
2000
1000
0



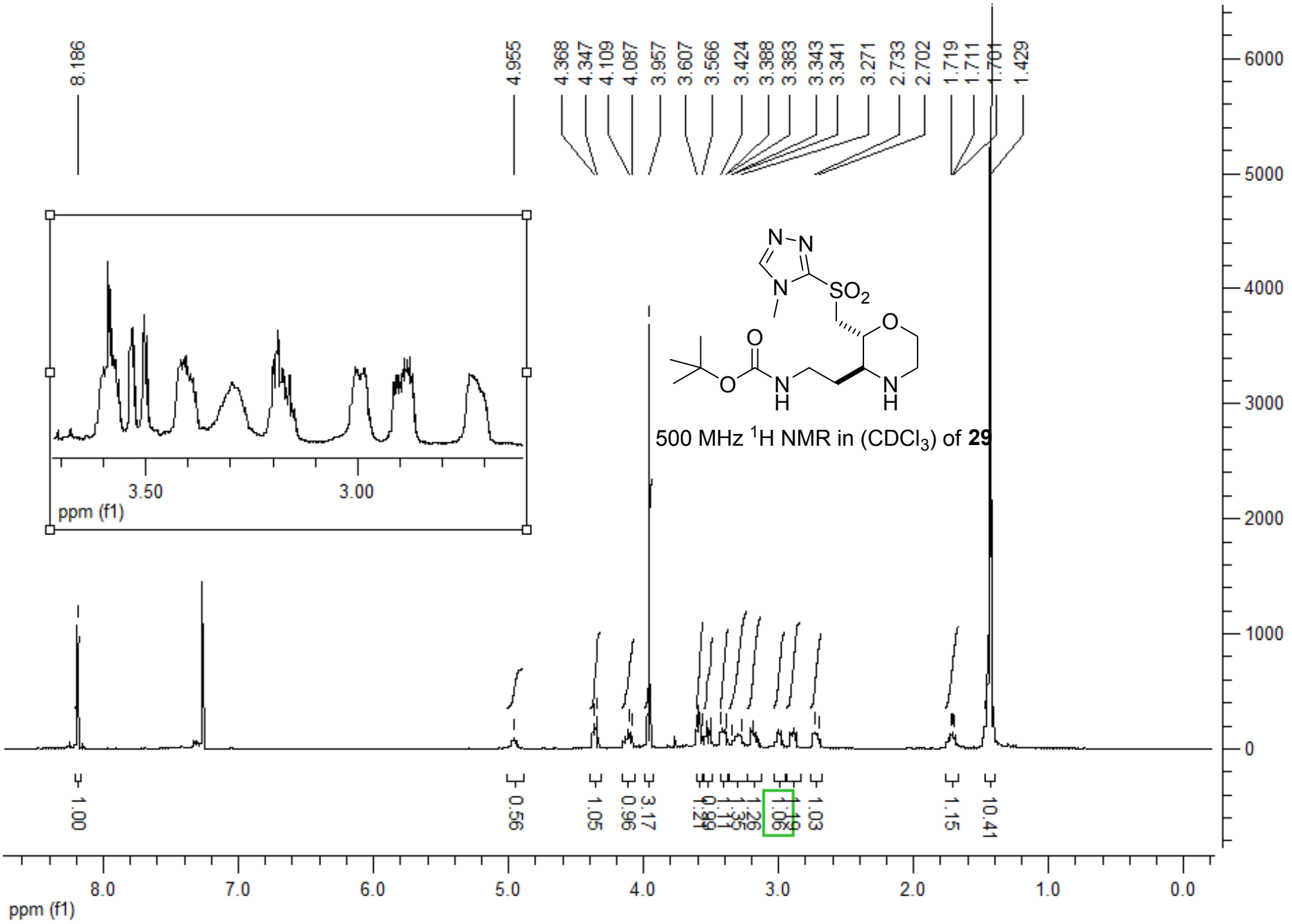
125 MHz ^{13}C NMR (MeOD, 333 K) of **50**

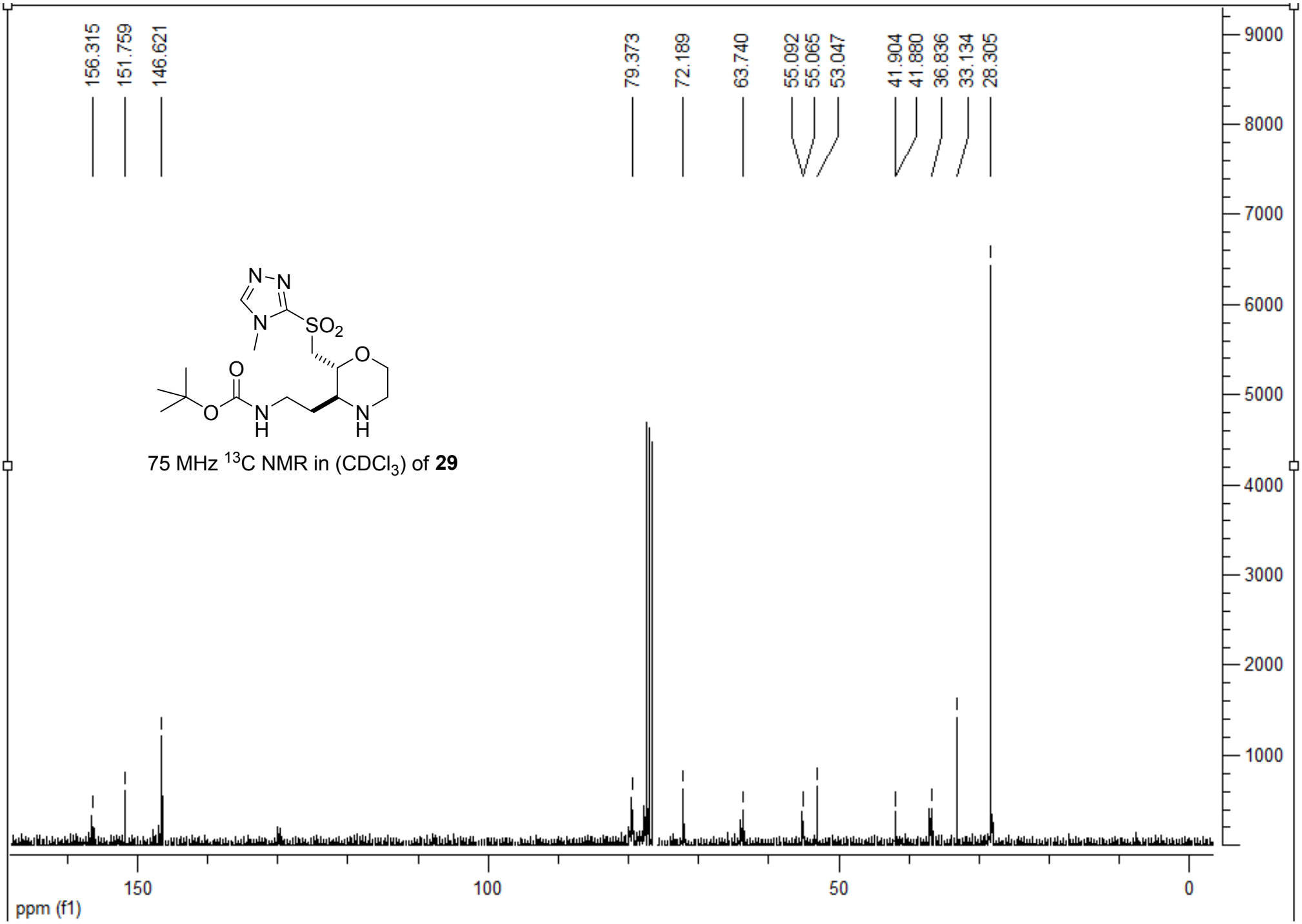


500 MHz ^{1}H NMR (MeOD, 333 K) of **51**

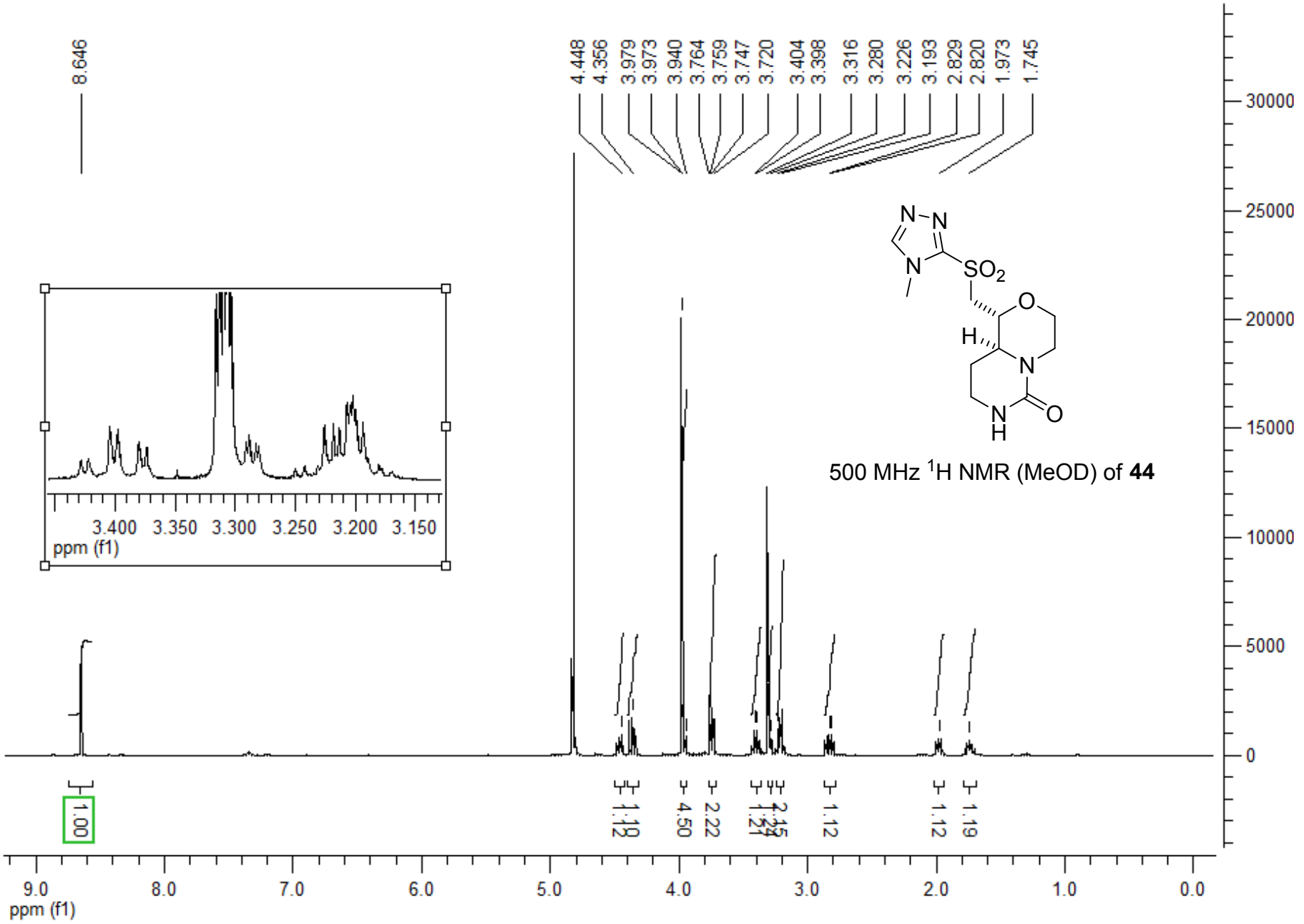


125 MHz ^{13}C NMR (MeOD, 333 K) of **51**

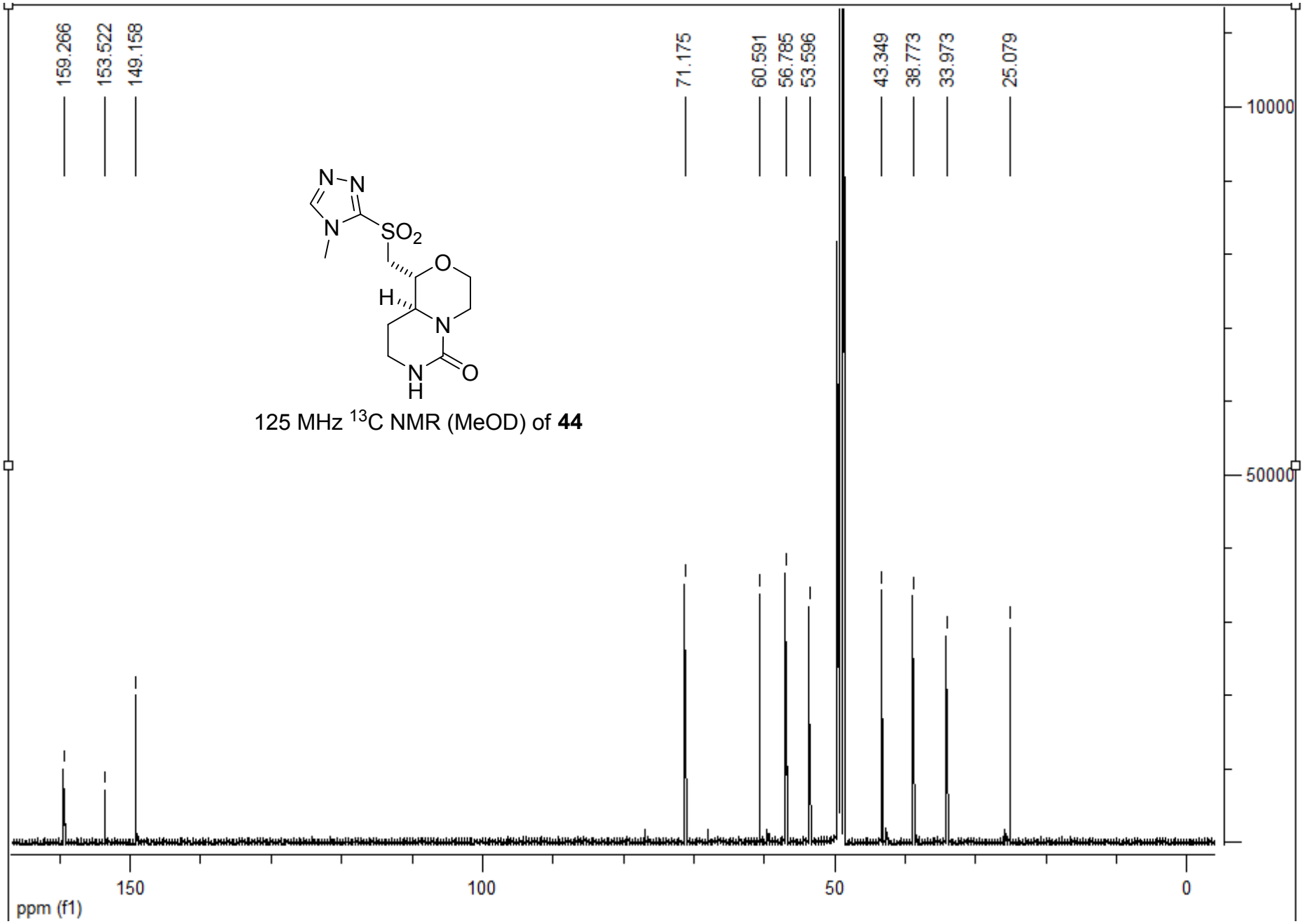

8.186
4.955
4.368
4.347
4.109
4.087
3.957
3.607
3.566
3.424
3.388
3.383
3.343
3.341
3.271
2.733
2.702
1.719
1.711
1.701
1.429
3.50
3.00
ppm (f1)
500 MHz ^{1}H NMR in ($CDCl_3$) of **29**
1.00
0.56
1.05
0.96
3.17
1.03
1.15
10.41
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)



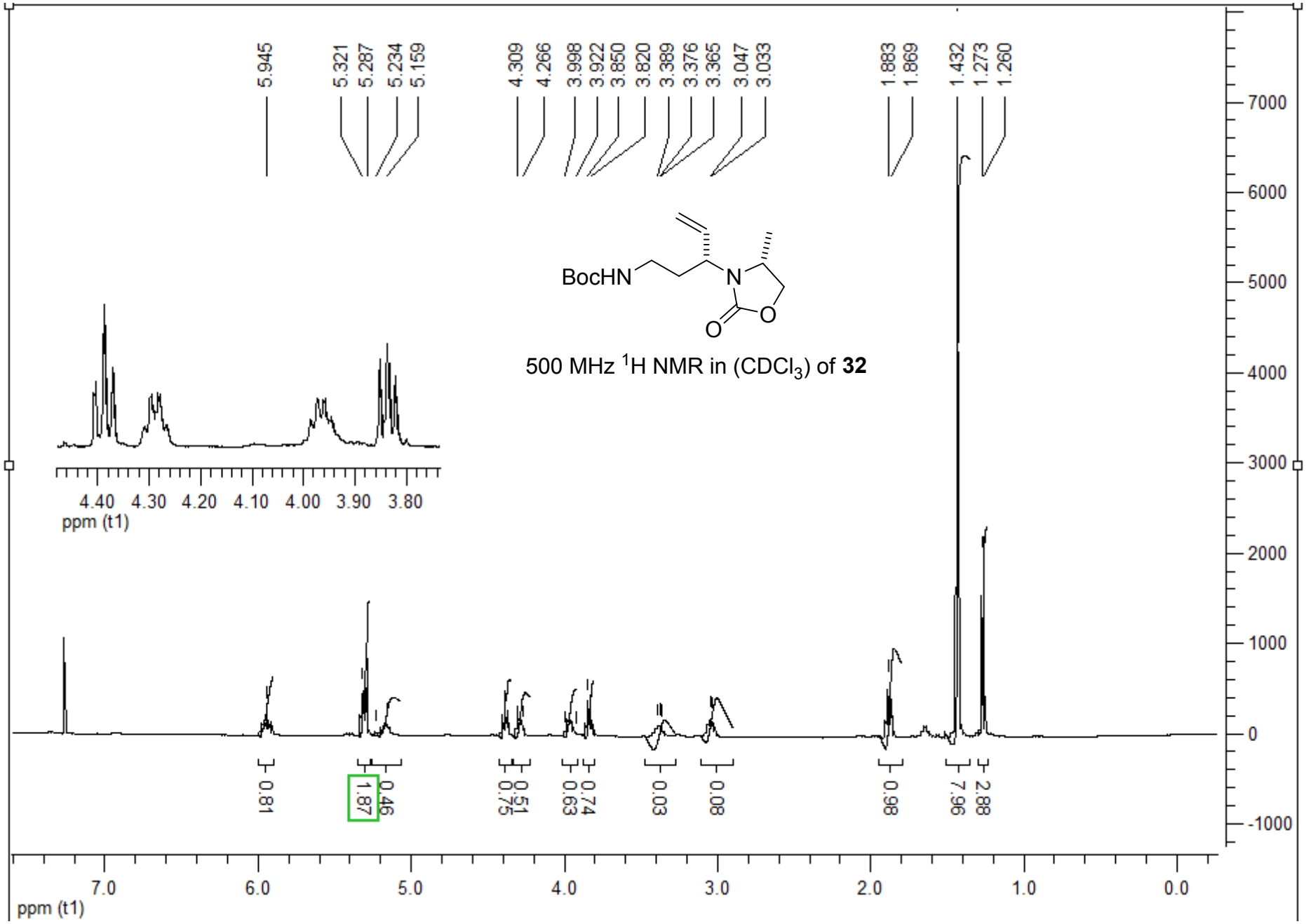
75 MHz ^{13}C NMR in ($CDCl_3$) of **29**



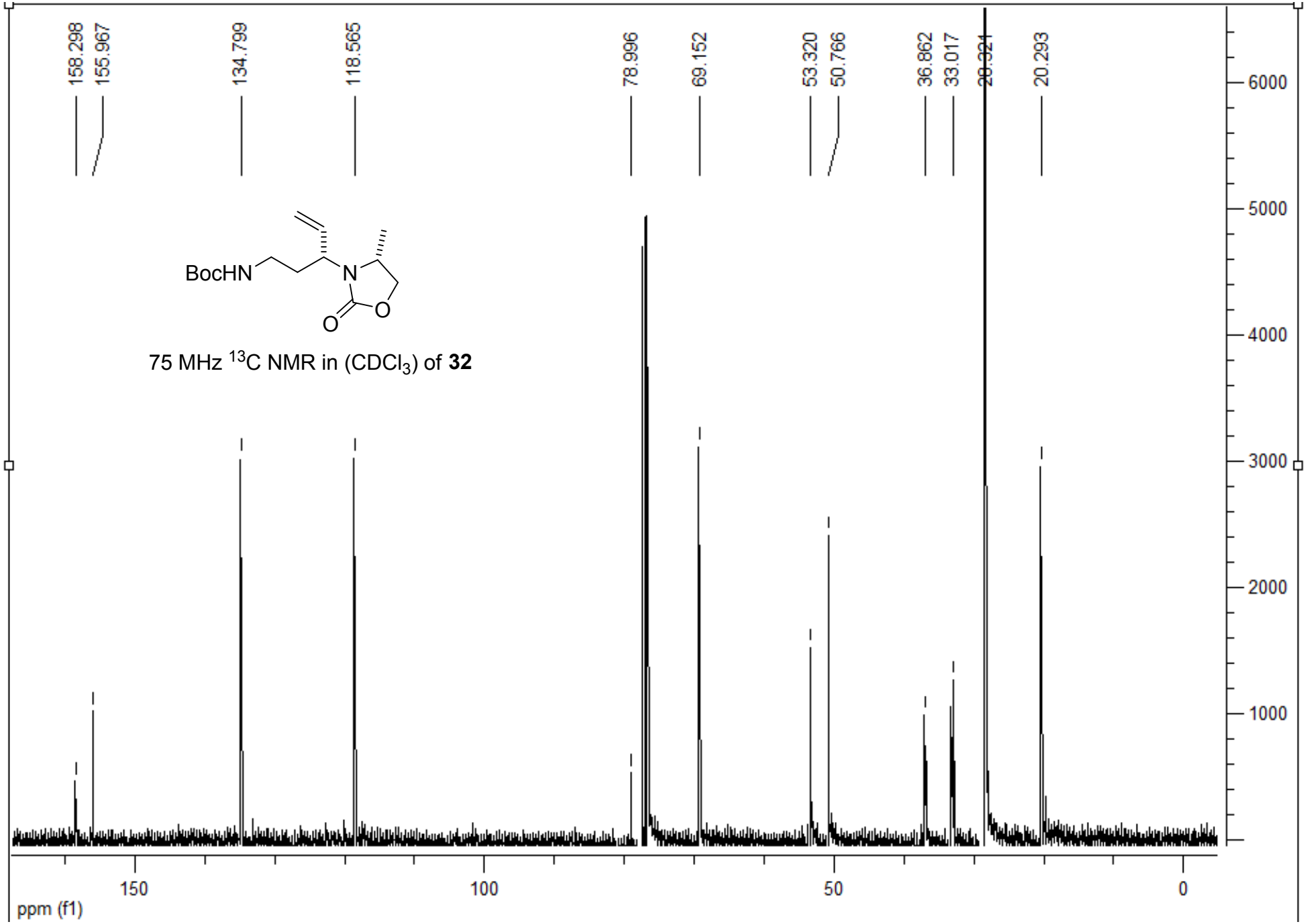
500 MHz ^{1}H NMR (MeOD) of **44**



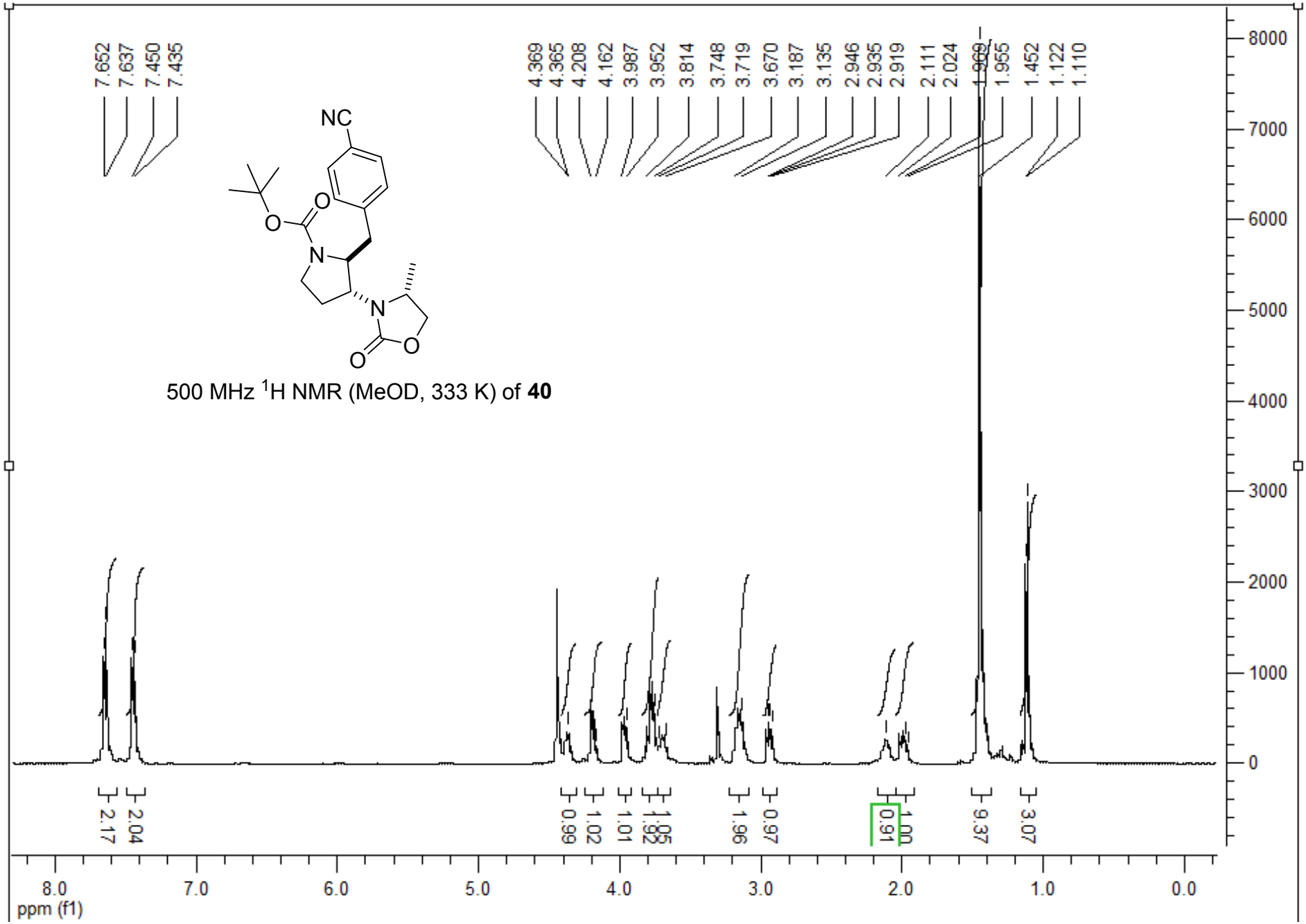
125 MHz ^{13}C NMR (MeOD) of **44**



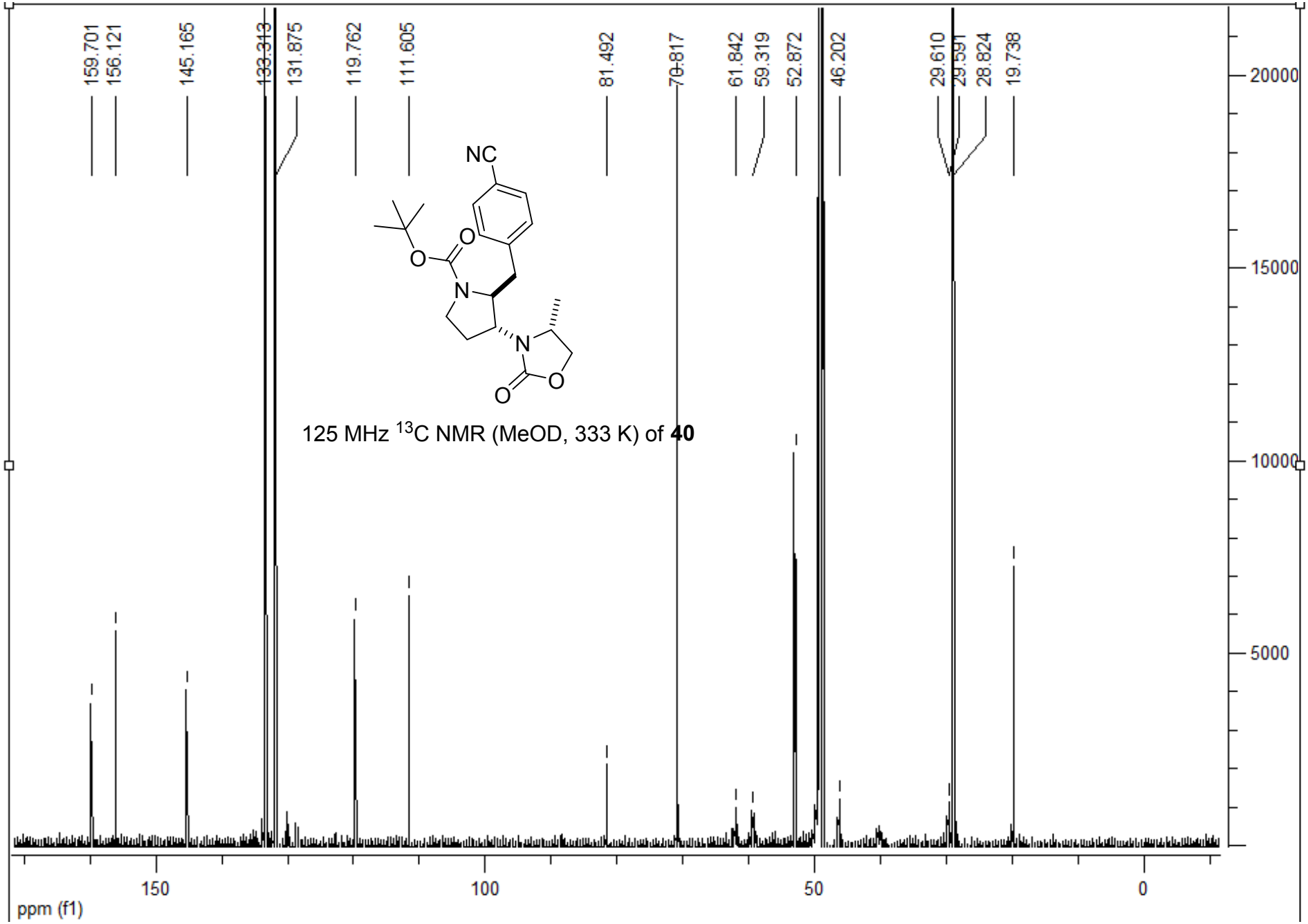
500 MHz ^{1}H NMR in ($CDCl_3$) of **32**



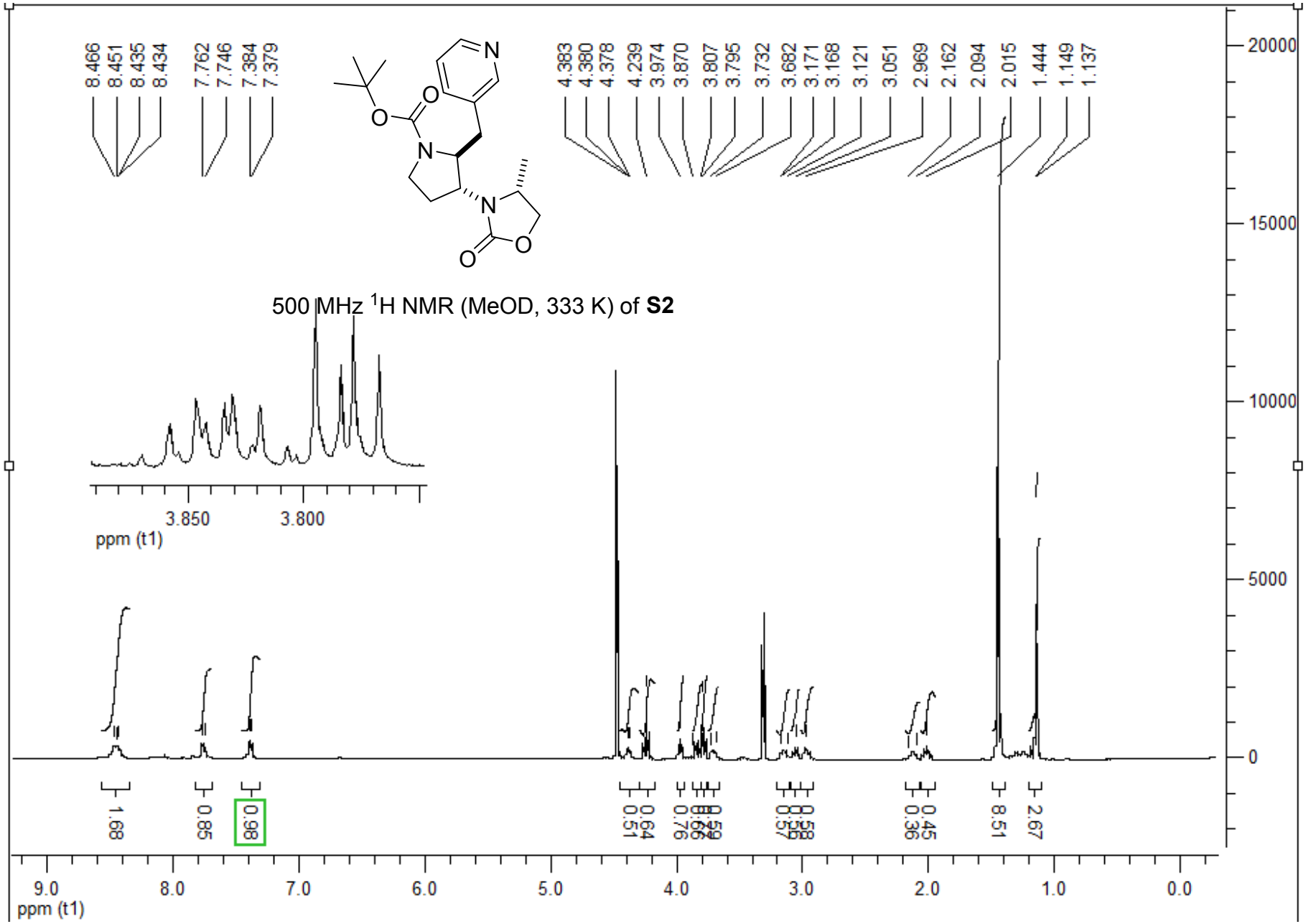
75 MHz ^{13}C NMR in ($CDCl_3$) of **32**



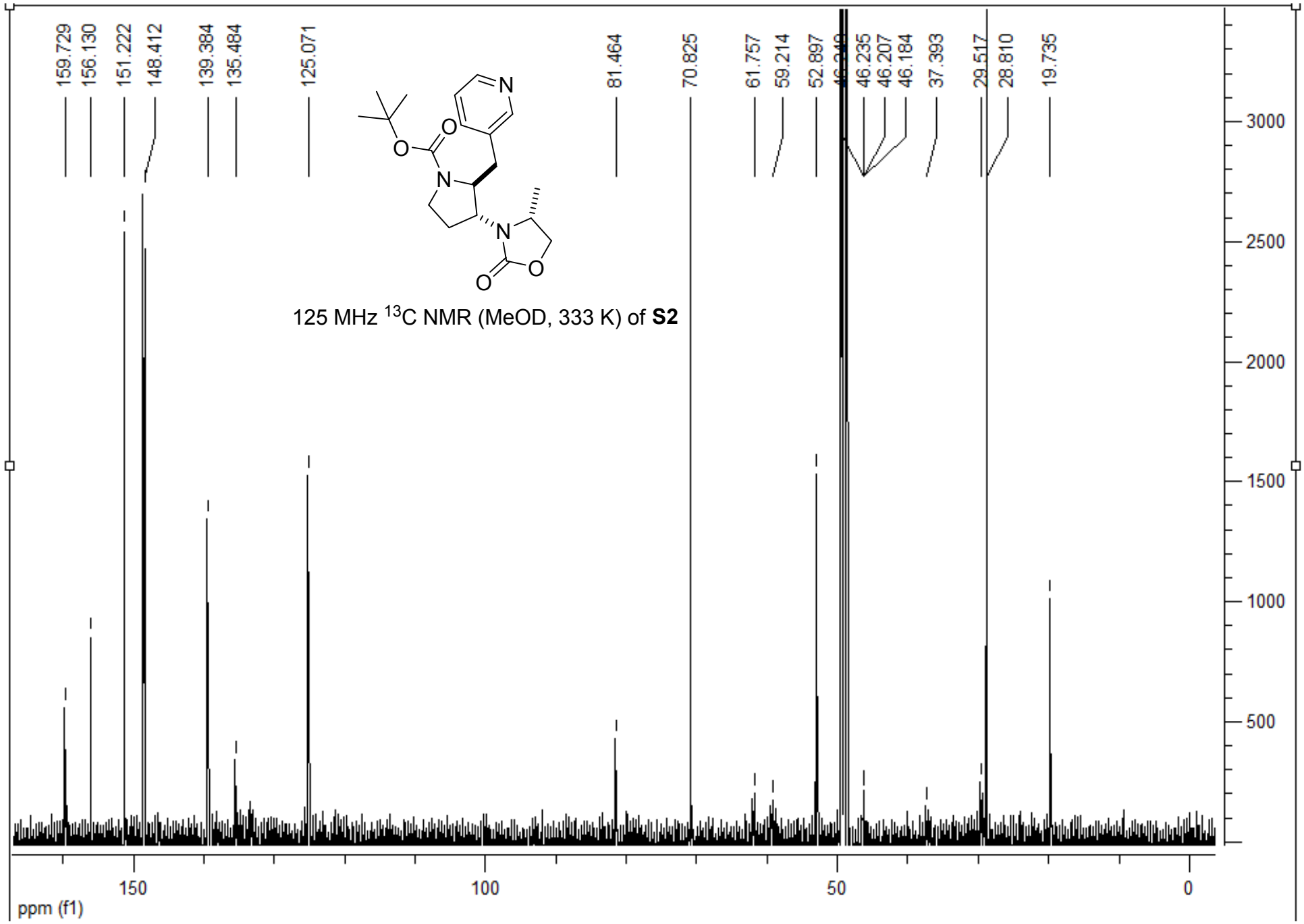
500 MHz ^{1}H NMR (MeOD, 333 K) of **40**



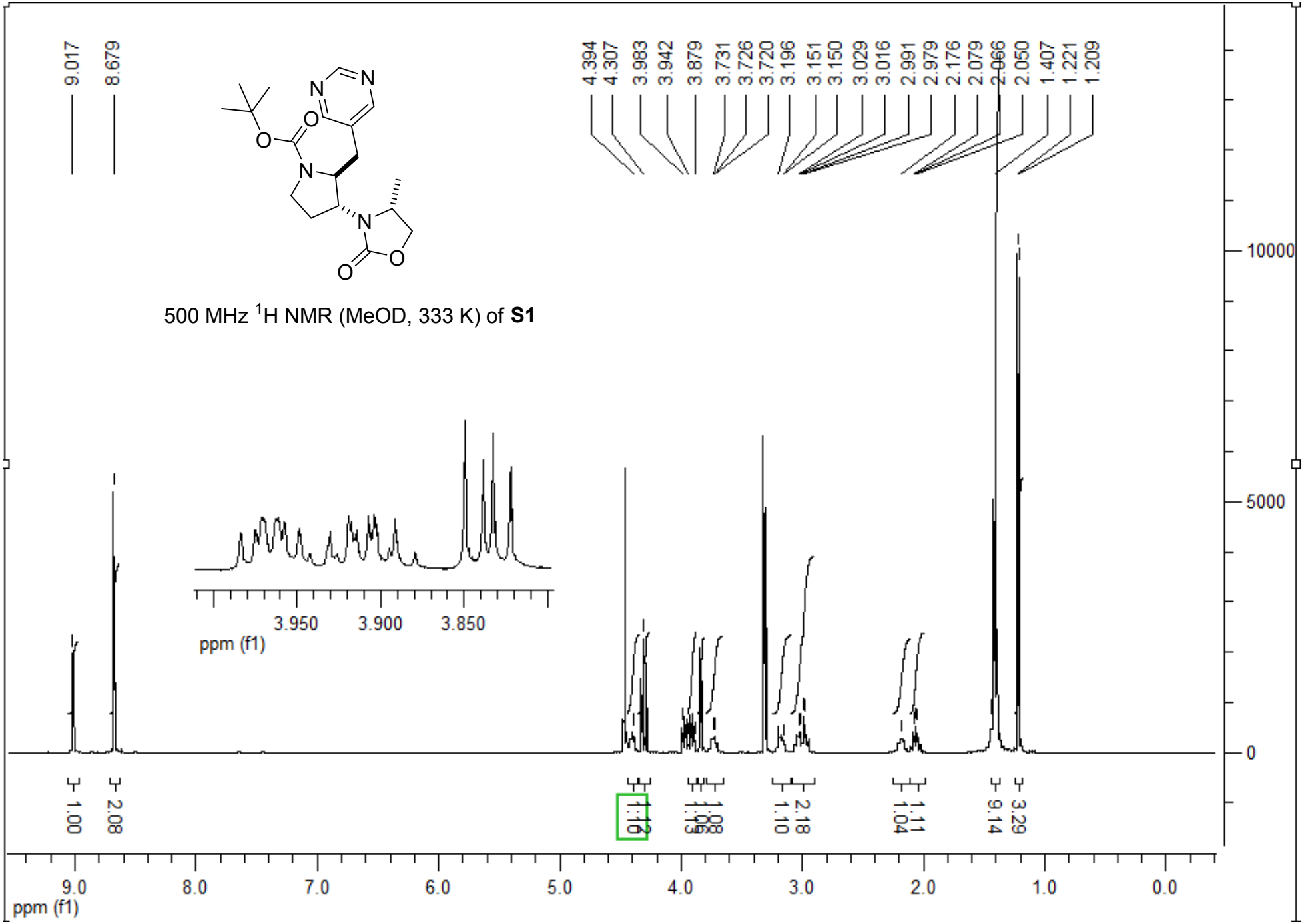
125 MHz ^{13}C NMR (MeOD, 333 K) of **40**



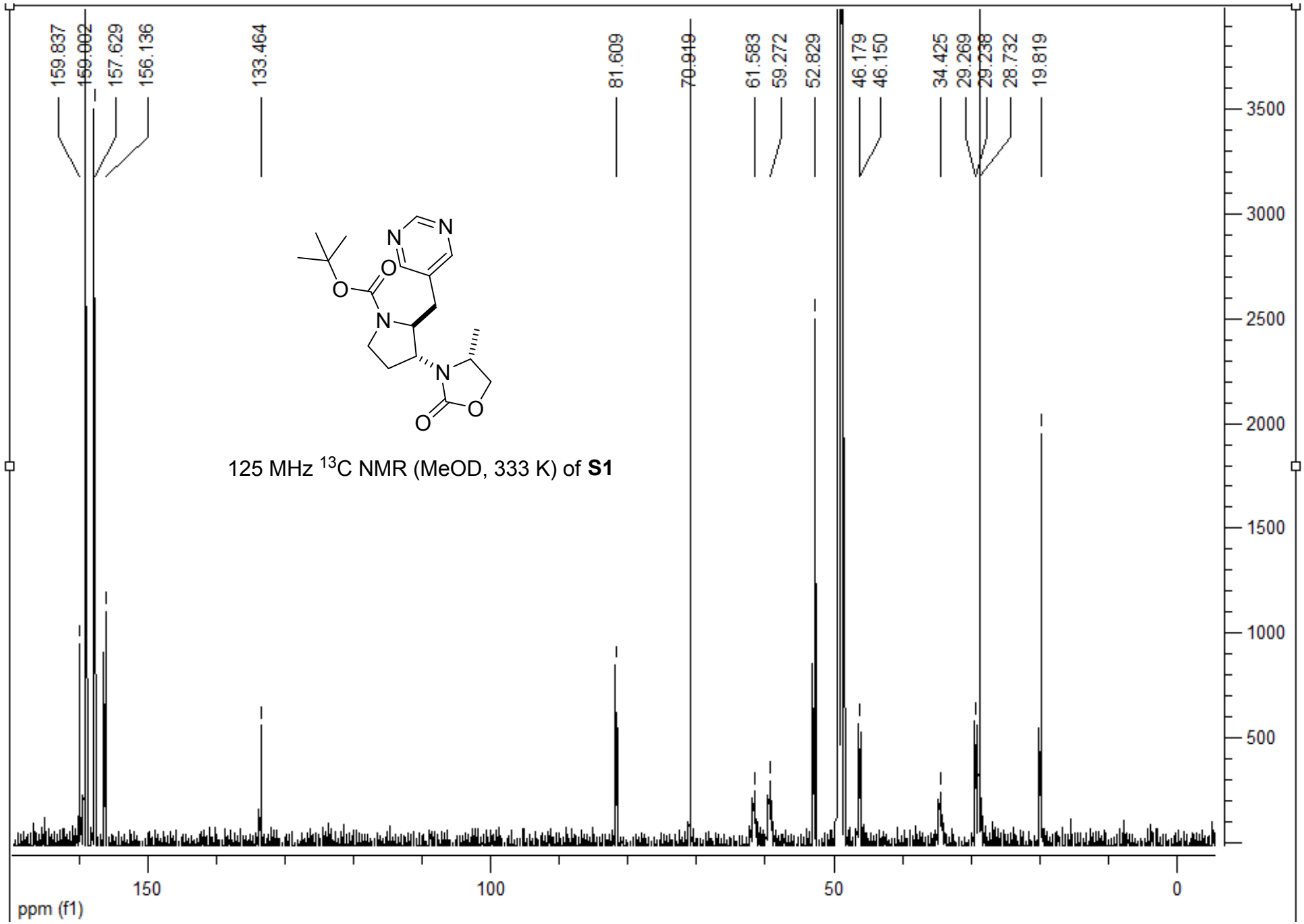
500 MHz ^{1}H NMR (MeOD, 333 K) of **S2**



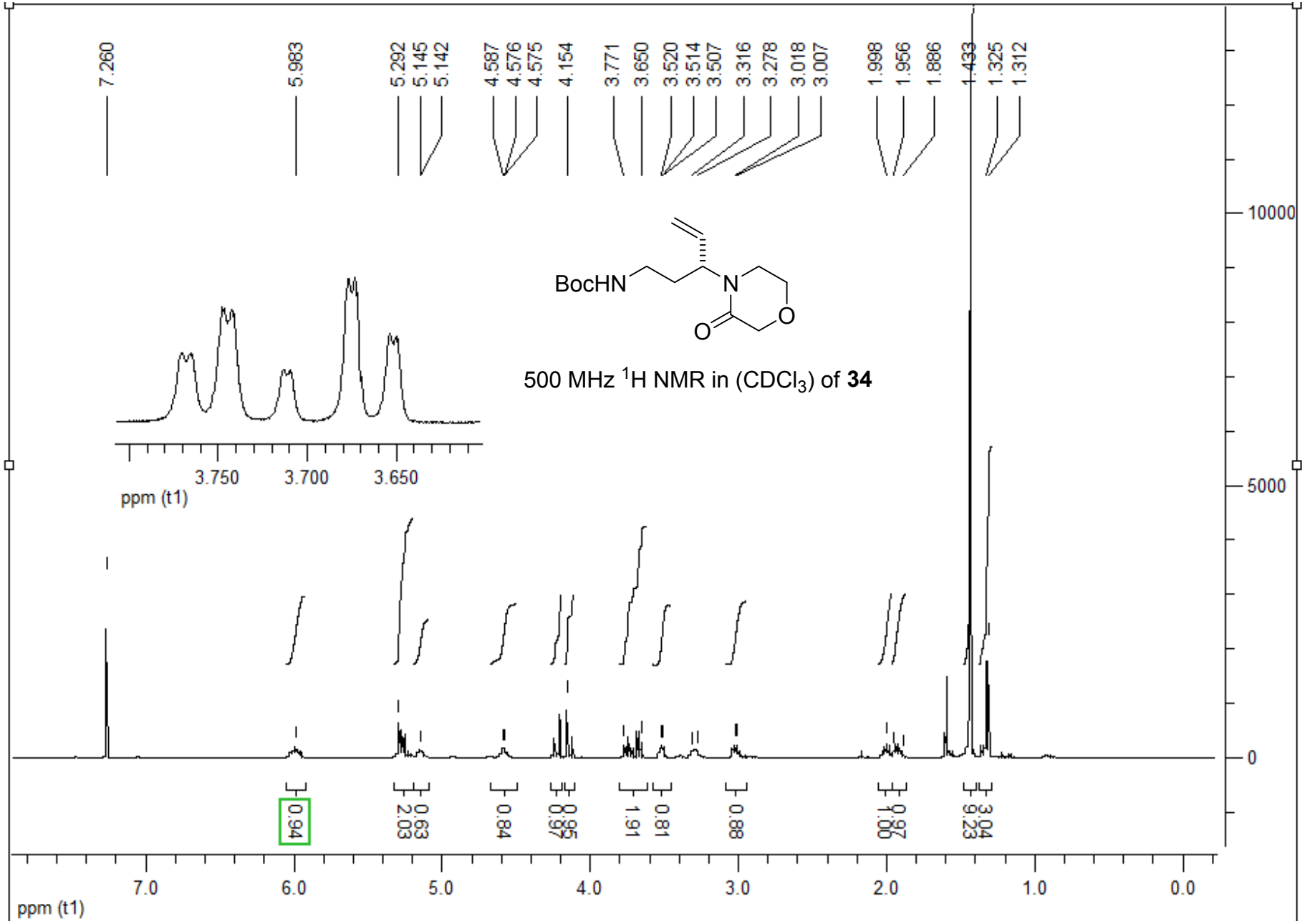
125 MHz ^{13}C NMR (MeOD, 333 K) of **S2**



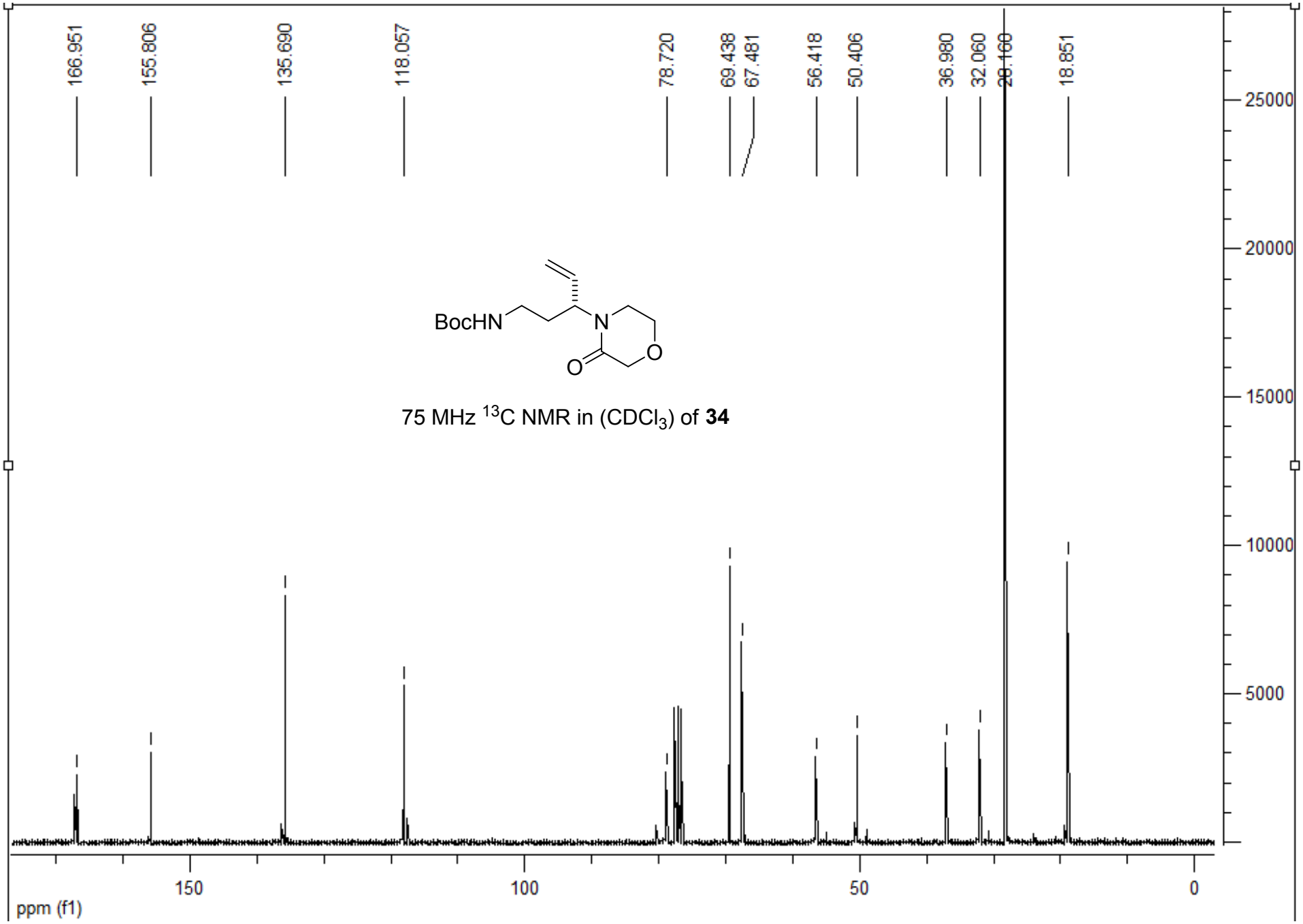
500 MHz ^{1}H NMR (MeOD, 333 K) of **S1**



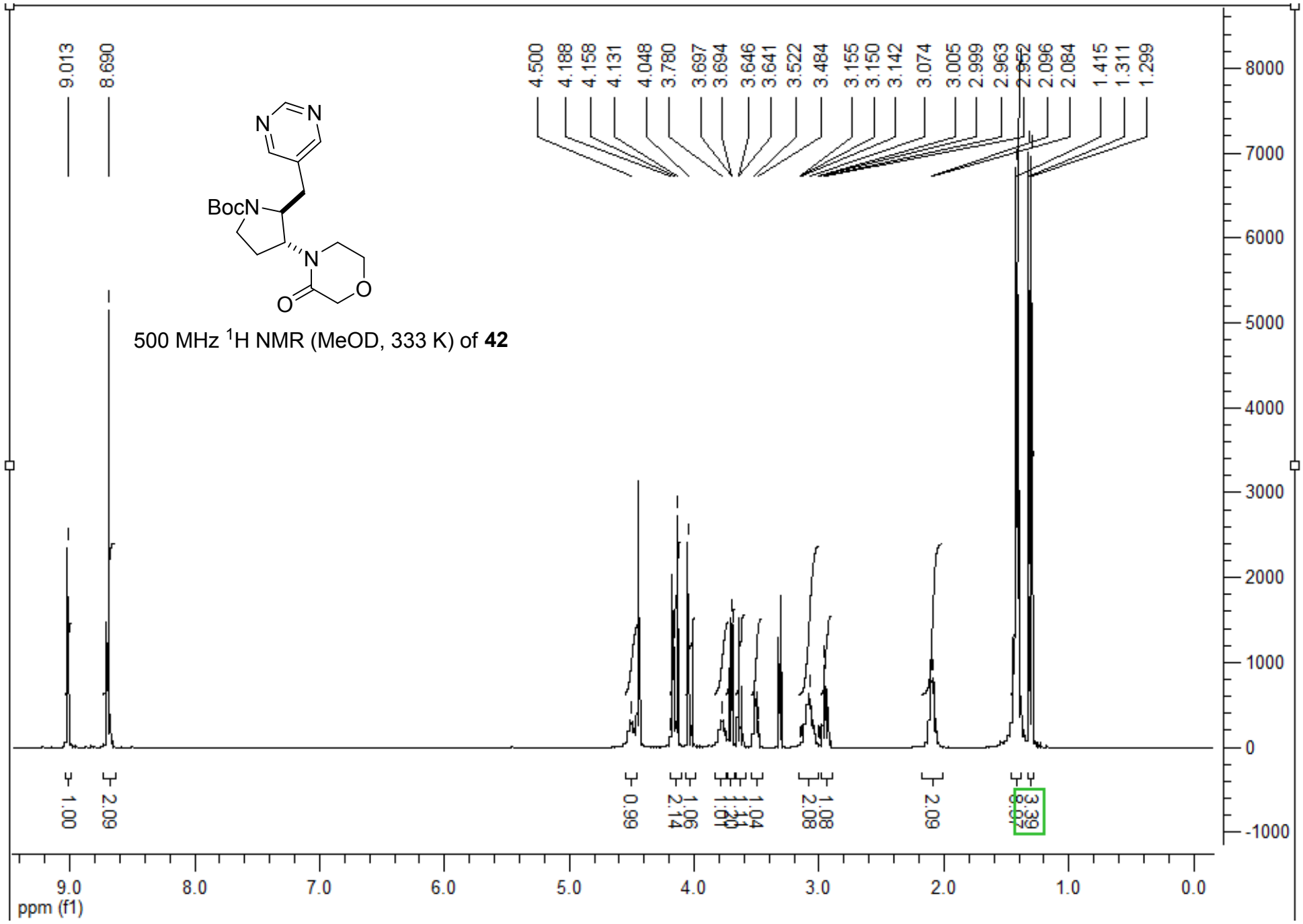
125 MHz ^{13}C NMR (MeOD, 333 K) of **S1**



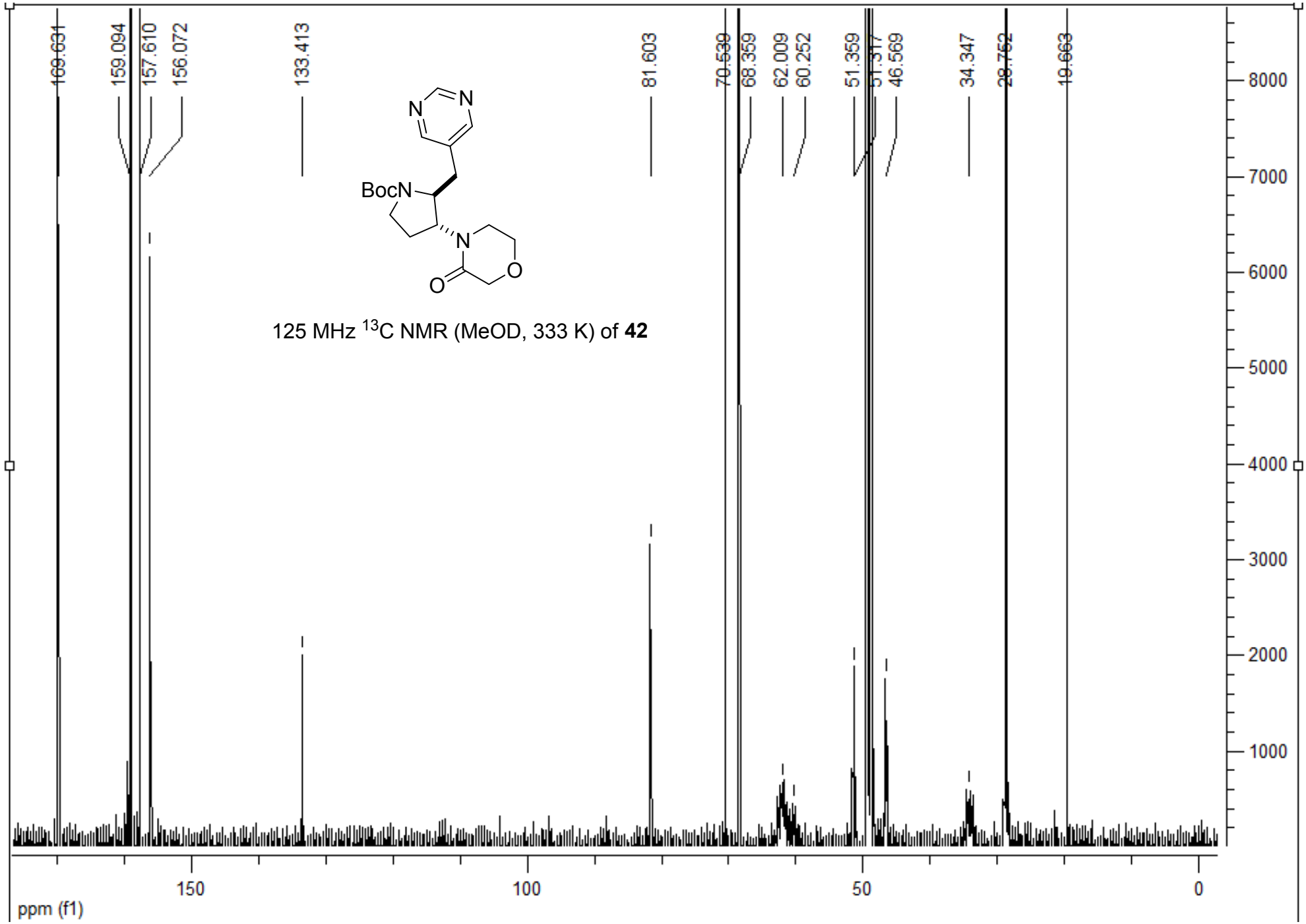
500 MHz ^{1}H NMR in ($CDCl_3$) of **34**



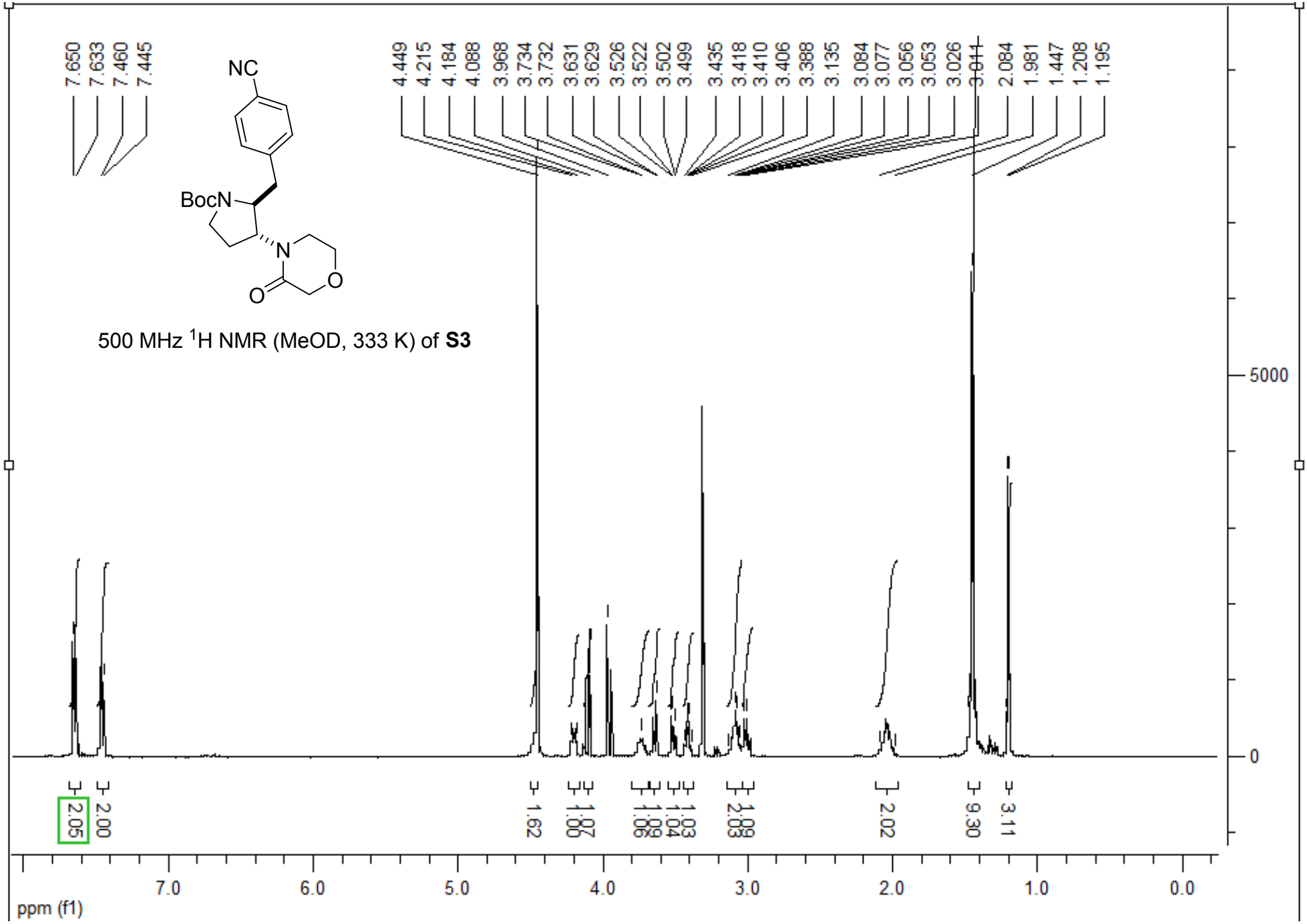
75 MHz ^{13}C NMR in ($CDCl_3$) of **34**

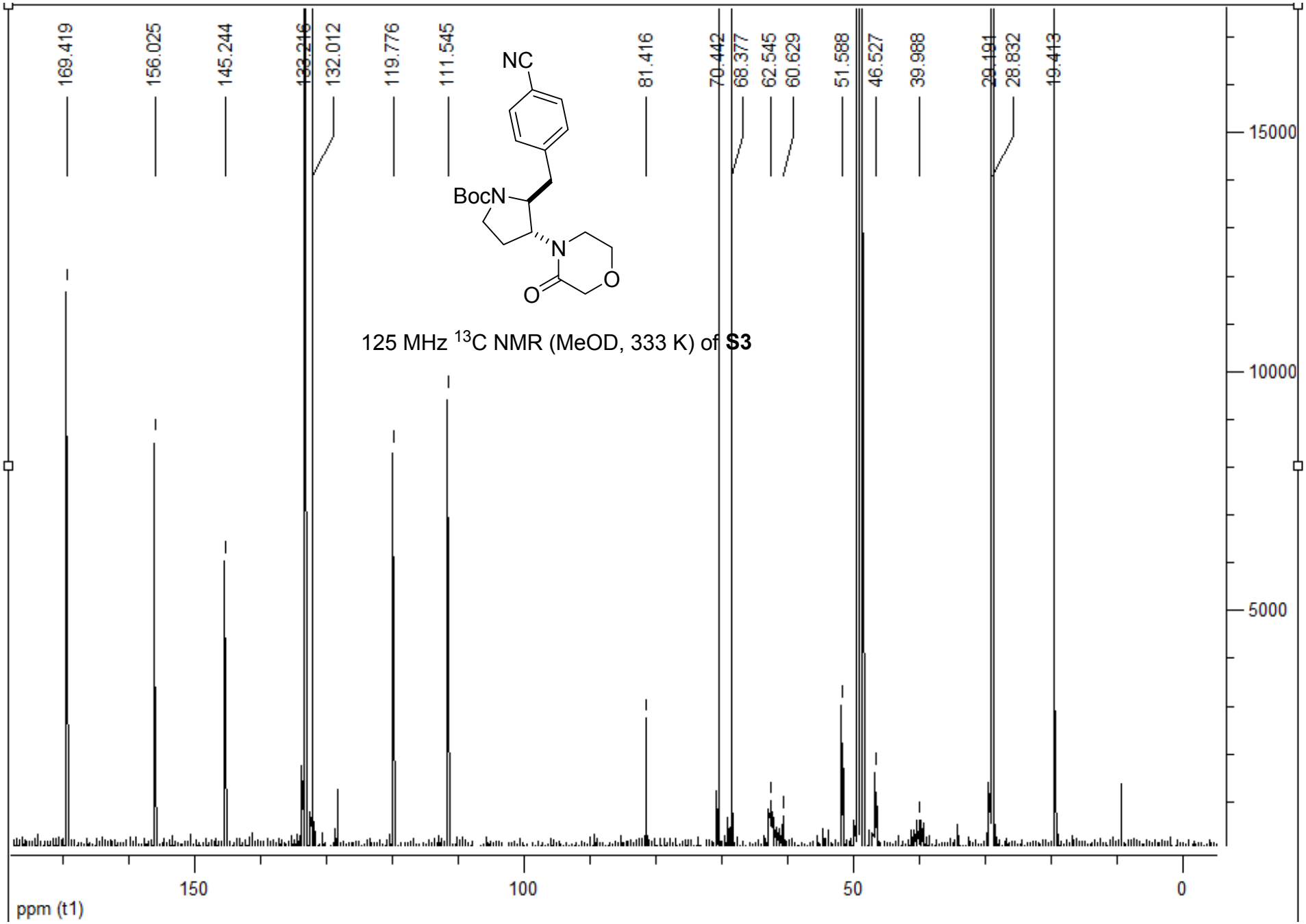


500 MHz ^{1}H NMR (MeOD, 333 K) of **42**

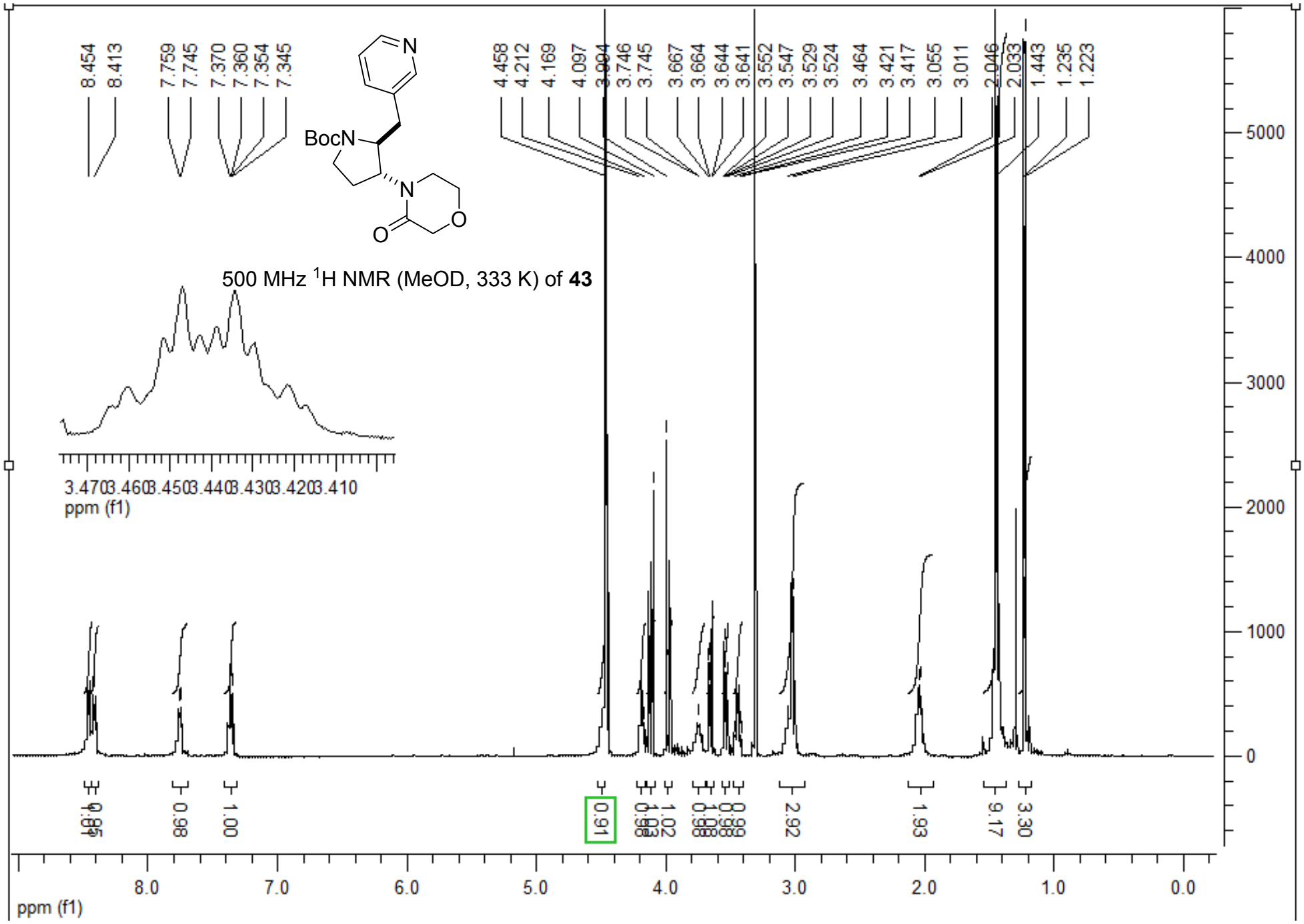


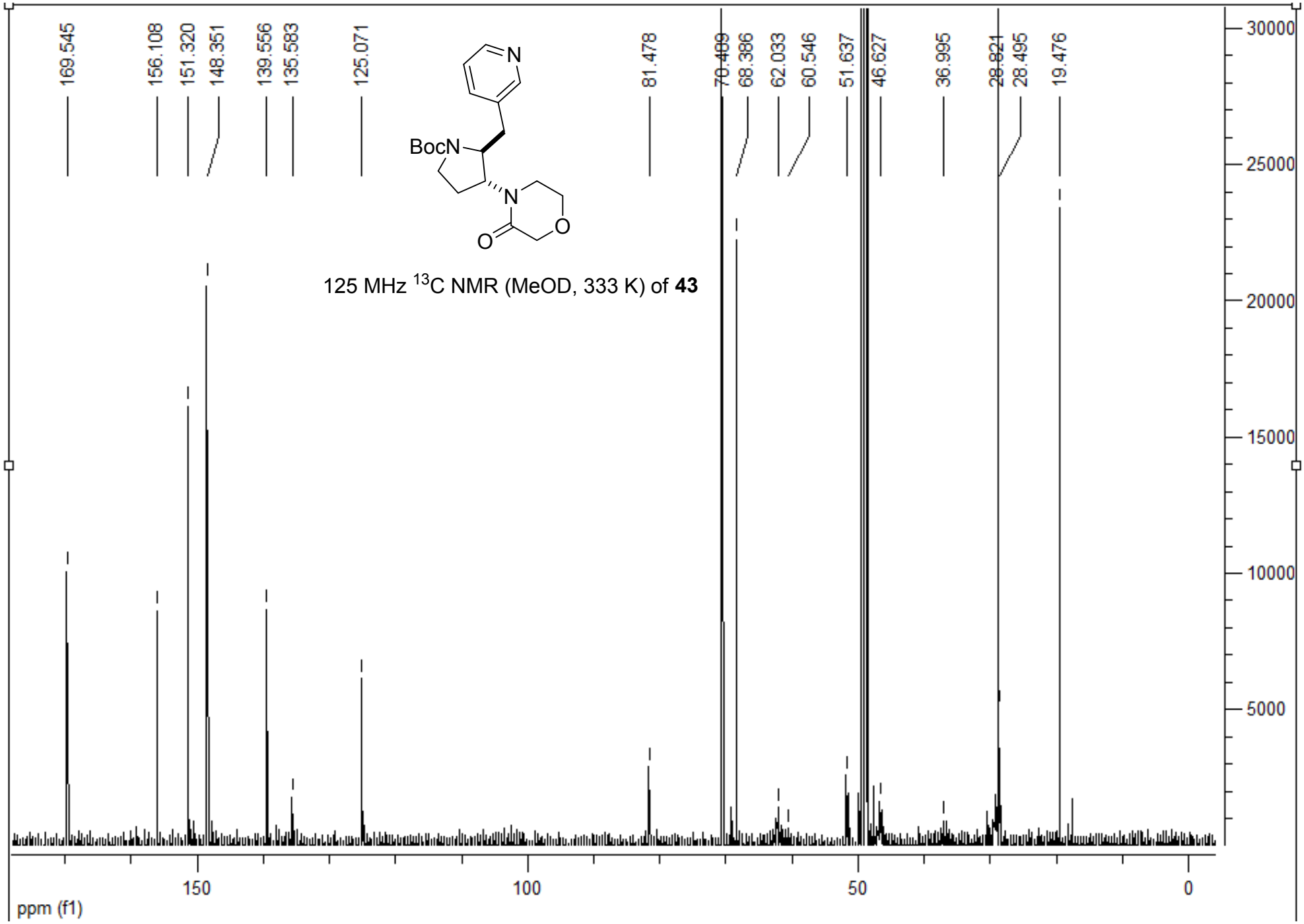
125 MHz ^{13}C NMR (MeOD, 333 K) of **42**


7.650
7.633
7.460
7.445
4.449
4.215
4.184
4.088
3.968
3.734
3.732
3.631
3.629
3.526
3.522
3.502
3.499
3.435
3.418
3.410
3.406
3.388
3.135
3.084
3.077
3.056
3.053
3.026
3.011
2.084
1.981
1.447
1.208
1.195
NC
BocN
N
O
O
500 MHz ^{1}H NMR (MeOD, 333 K) of **S3**
5000
0
2.05
2.00
1.92
1.00
1.07
1.08
1.04
1.03
2.03
1.89
2.02
9.30
3.11
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

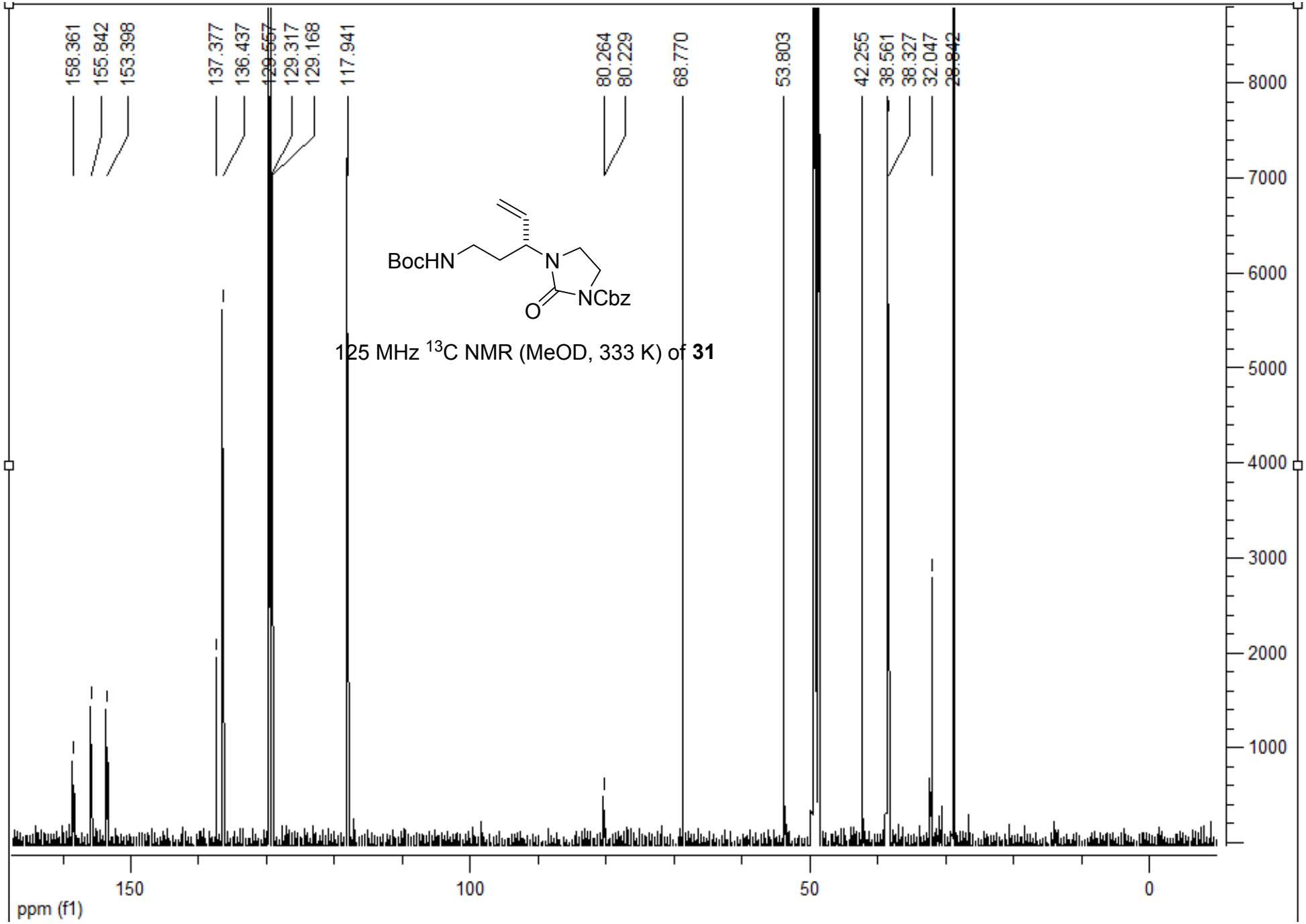


125 MHz ^{13}C NMR (MeOD, 333 K) of **S3**

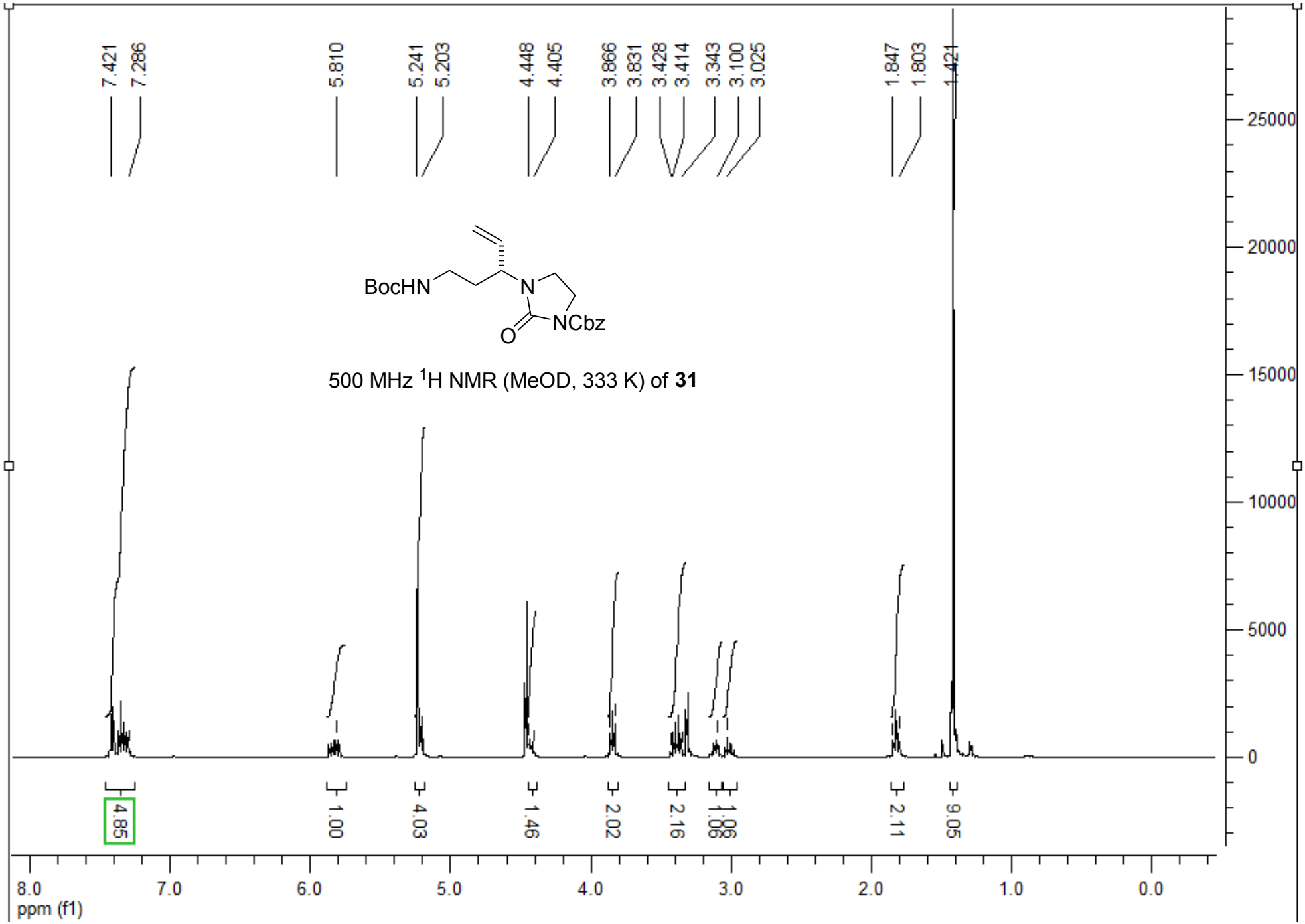

8.454
8.413
7.759
7.745
7.370
7.360
7.354
7.345
4.458
4.212
4.169
4.097
3.994
3.746
3.745
3.667
3.664
3.644
3.641
3.552
3.547
3.529
3.524
3.464
3.421
3.417
3.055
3.011
2.046
2.033
1.443
1.235
1.223
BocN
N
N
O
O
500 MHz ^{1}H NMR (MeOD, 333 K) of **43**
3.470
3.460
3.450
3.440
3.430
3.420
3.410
ppm (f1)
0.91
0.98
1.00
0.91
0.98
1.02
0.98
0.98
0.98
2.92
1.93
9.17
3.30
5000
4000
3000
2000
1000
0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)



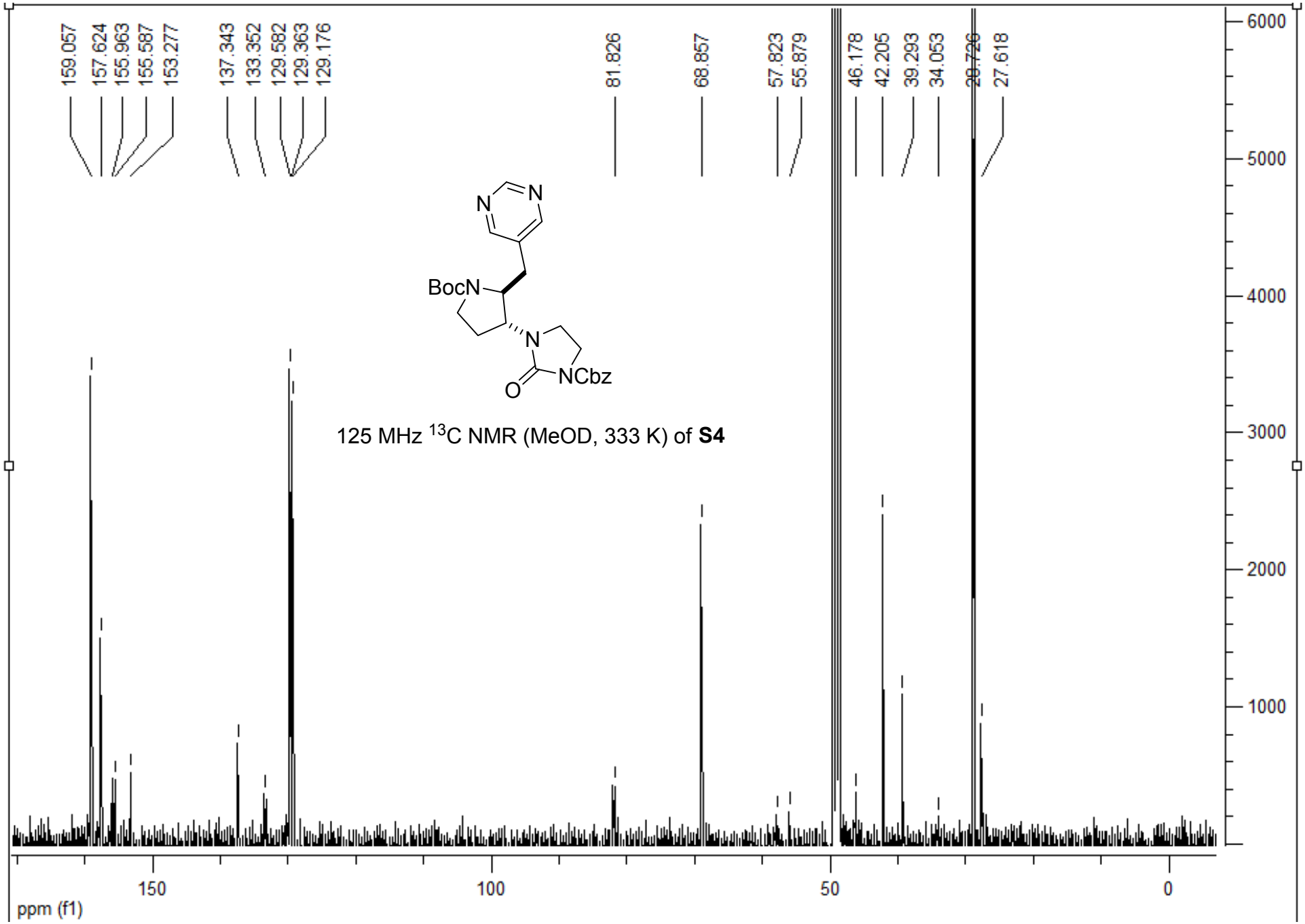
125 MHz ^{13}C NMR (MeOD, 333 K) of **43**



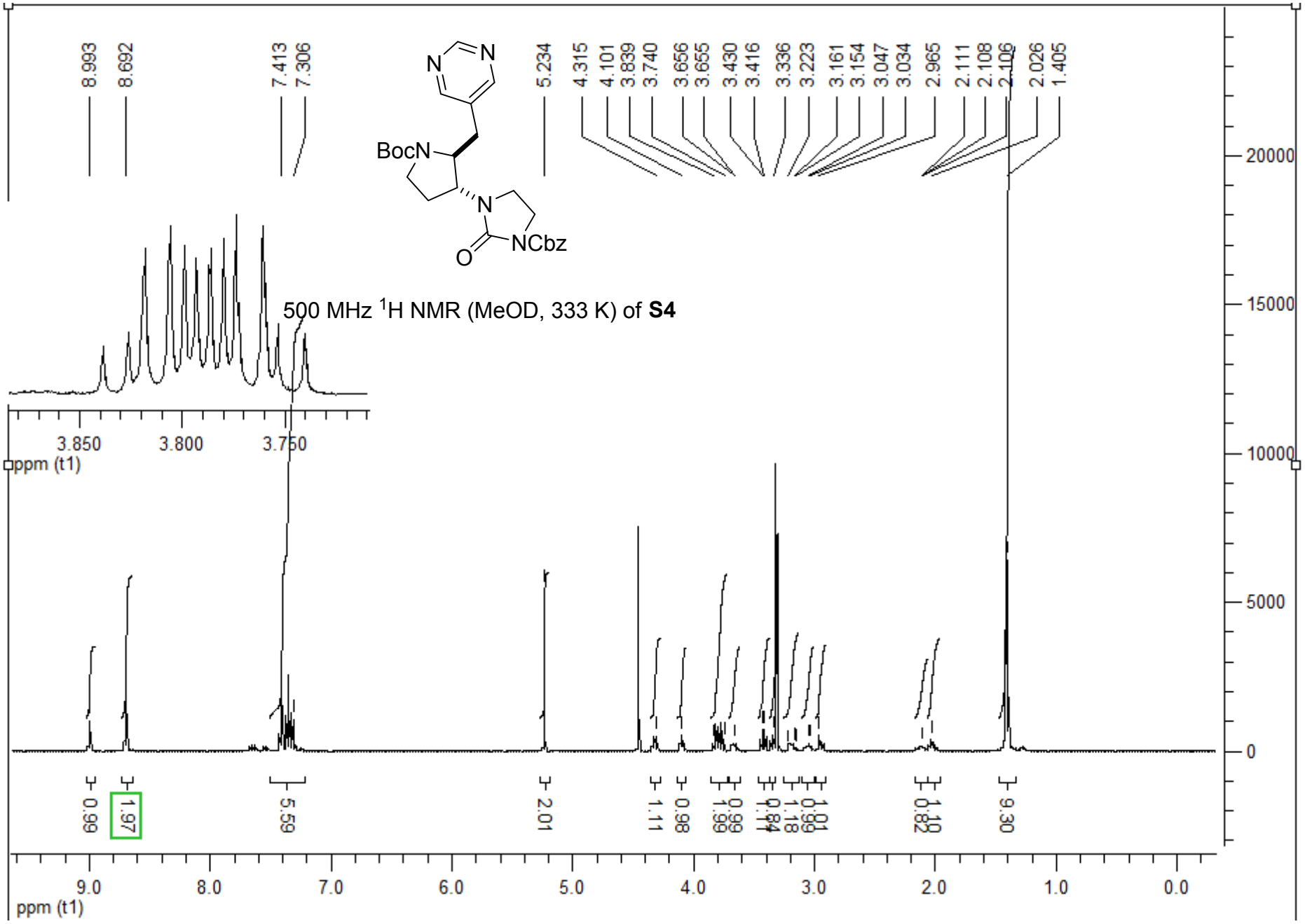
125 MHz ^{13}C NMR (MeOD, 333 K) of **31**



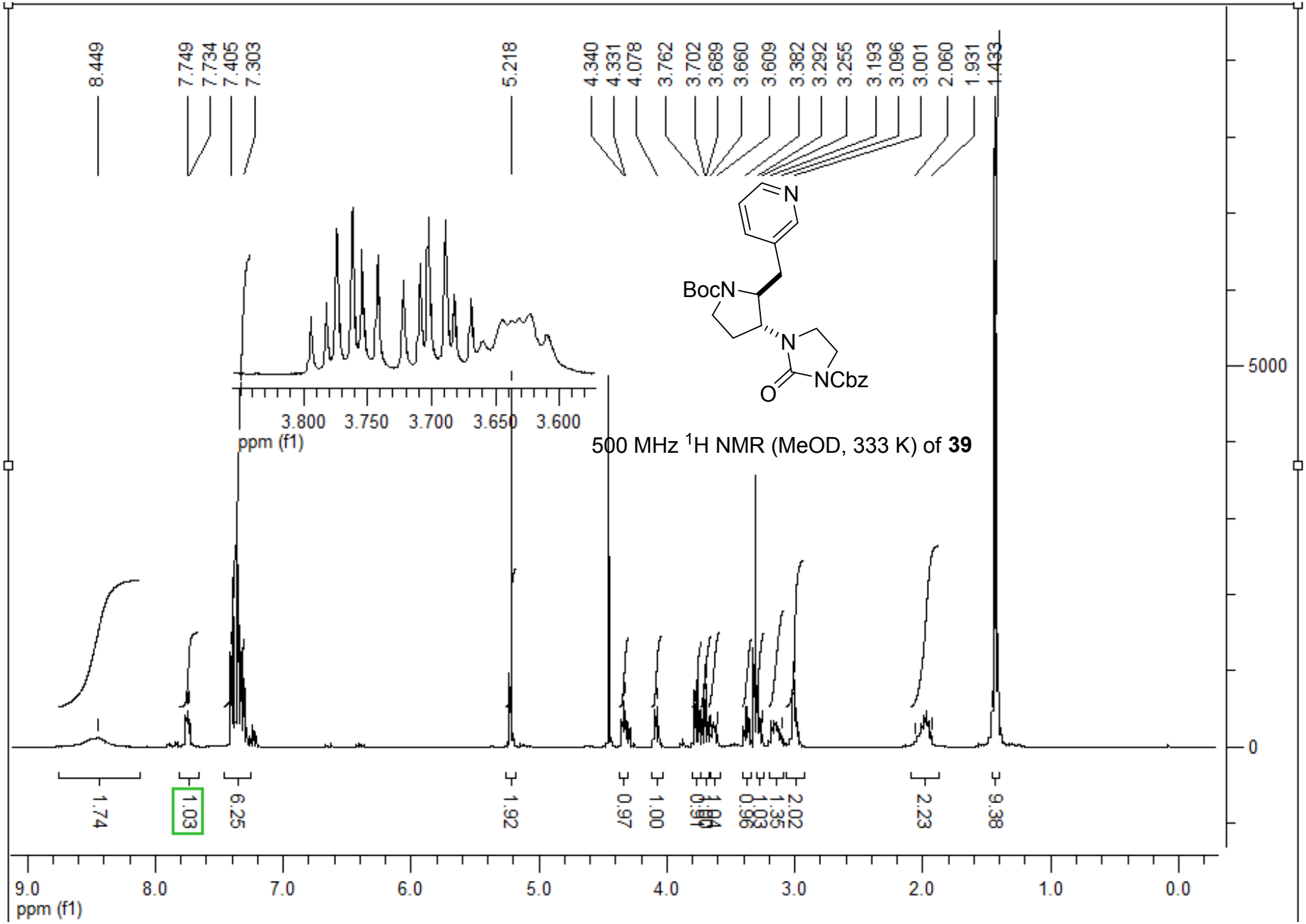
500 MHz ^{1}H NMR (MeOD, 333 K) of **31**



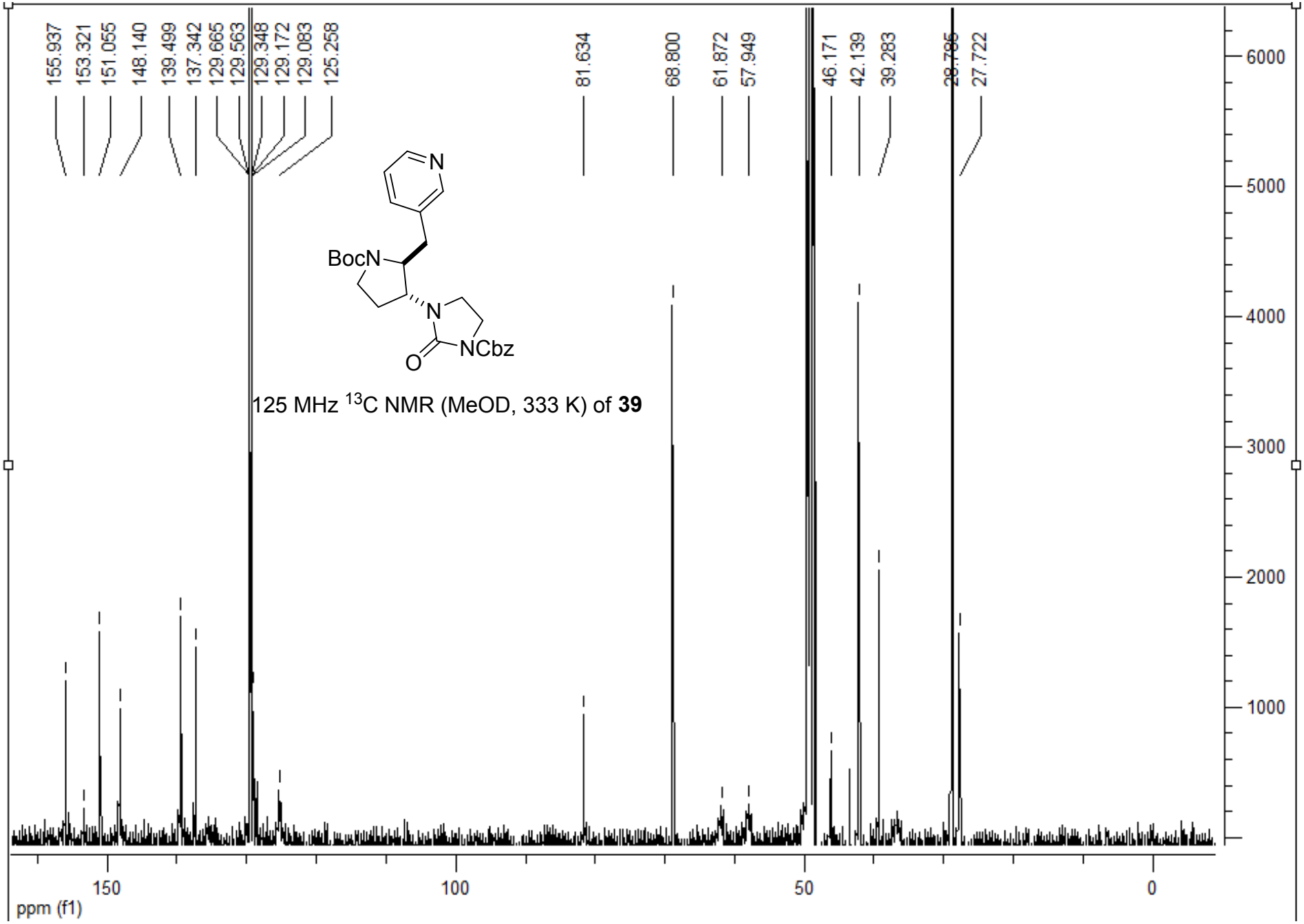
125 MHz ^{13}C NMR (MeOD, 333 K) of **S4**



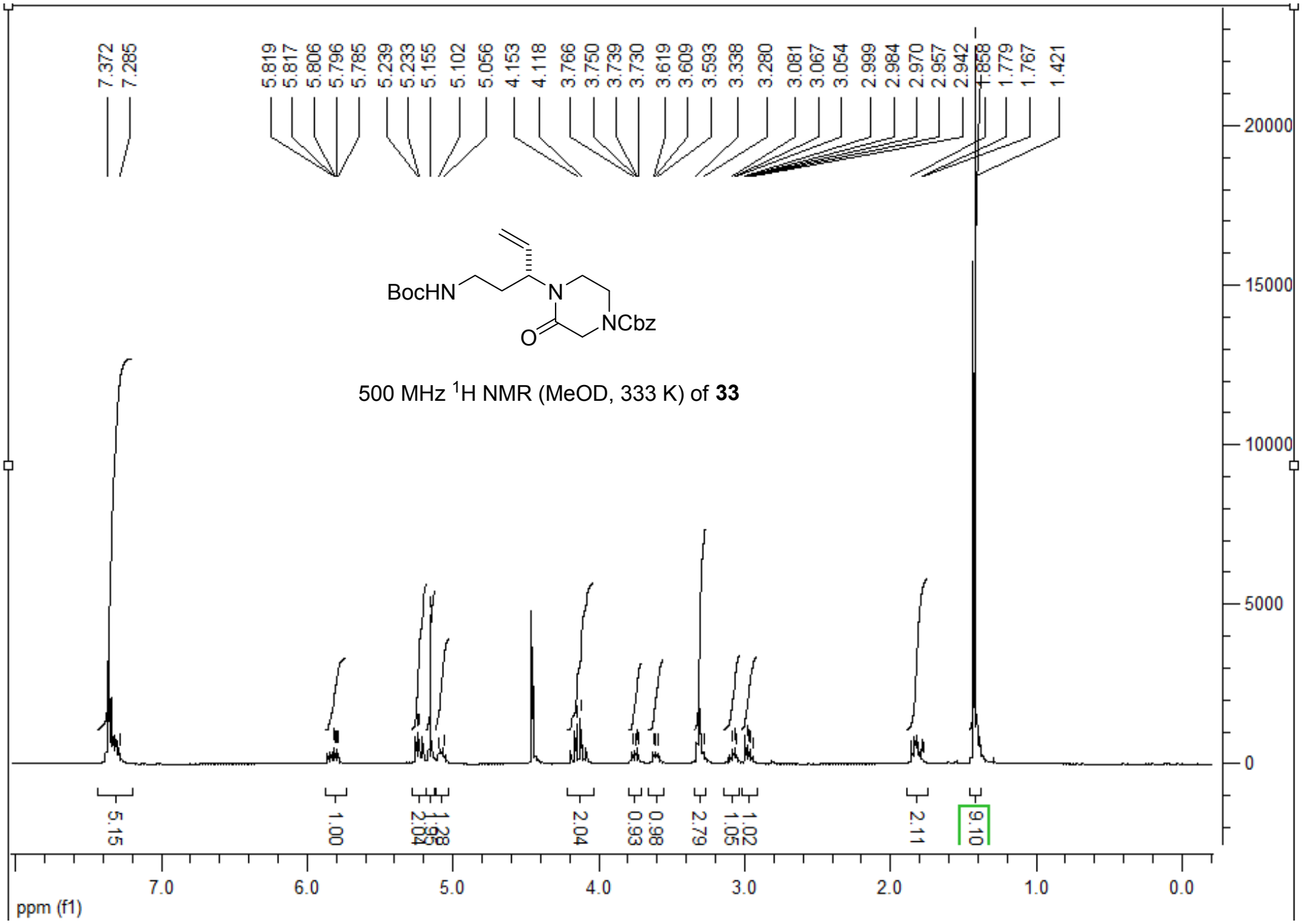
500 MHz ^{1}H NMR (MeOD, 333 K) of **S4**



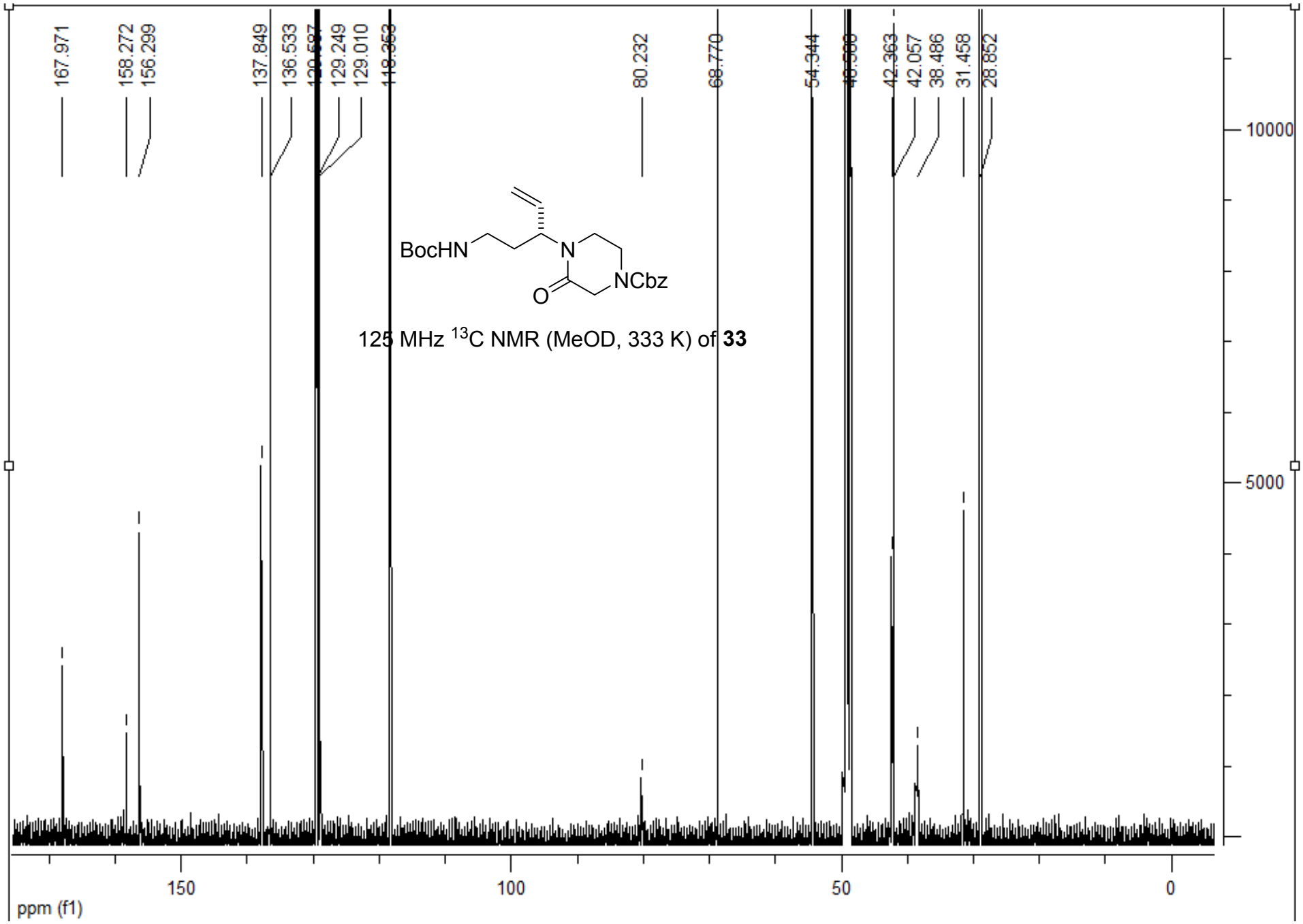
500 MHz ^{1}H NMR (MeOD, 333 K) of **39**



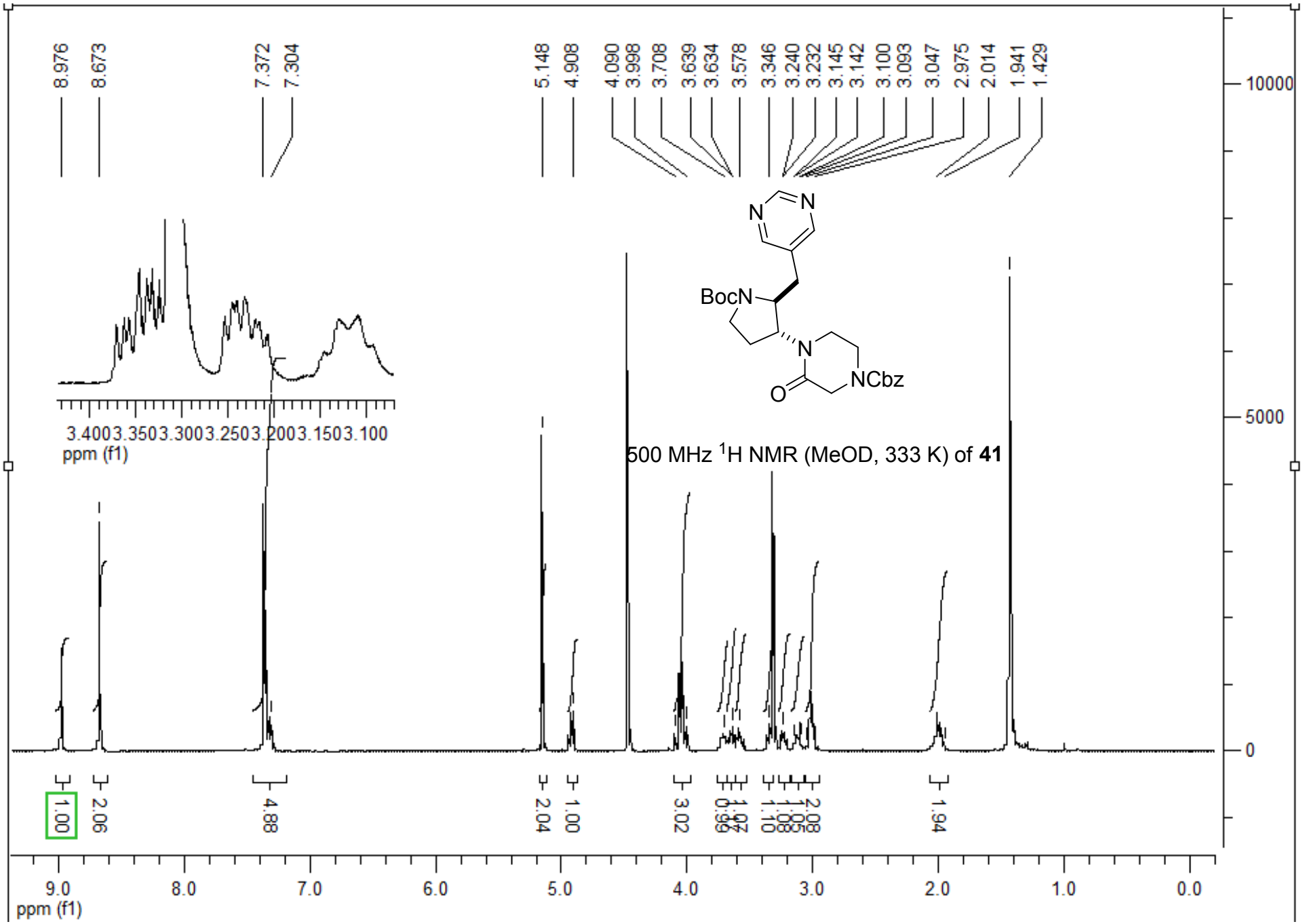
125 MHz ^{13}C NMR (MeOD, 333 K) of **39**

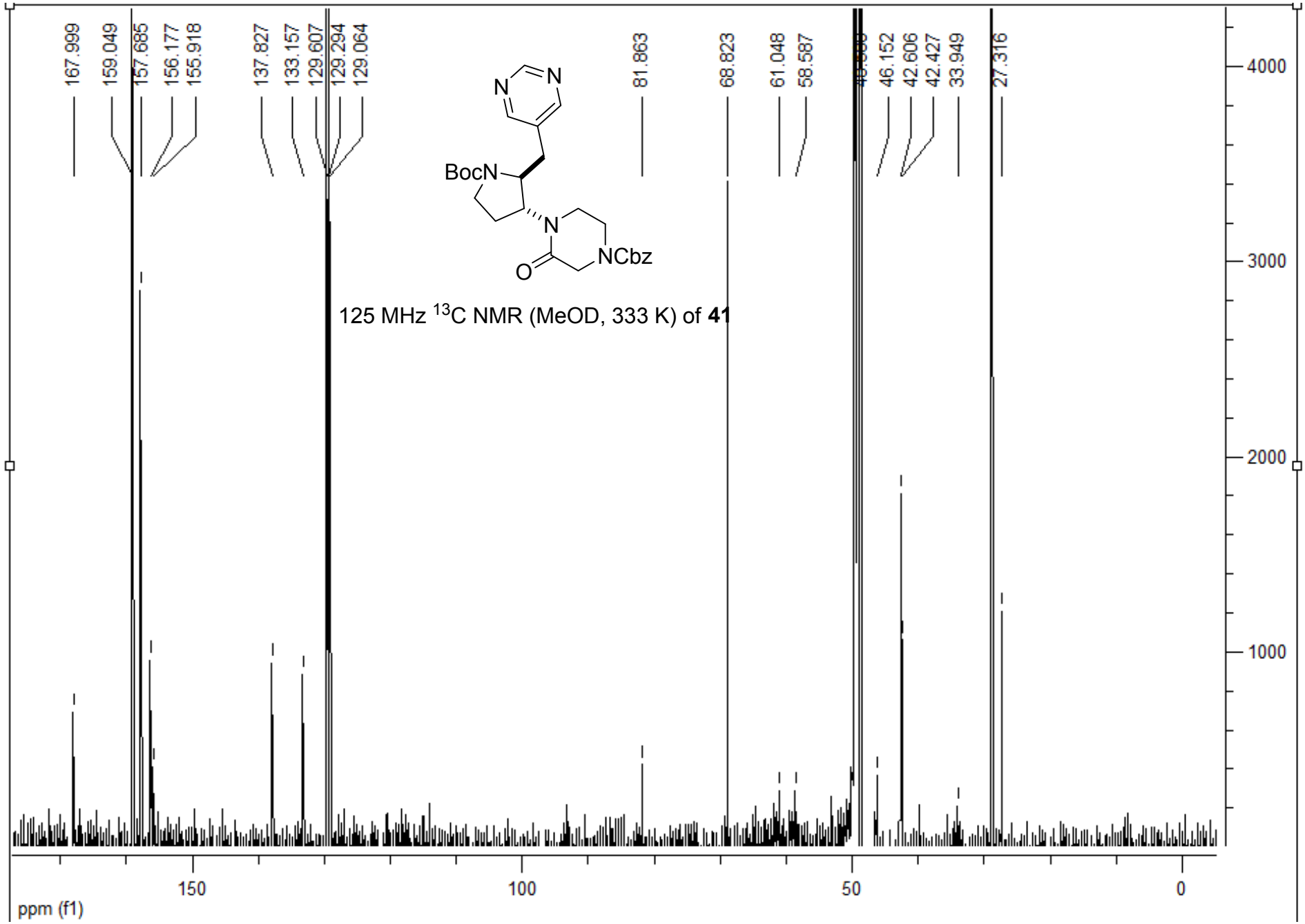


500 MHz ^{1}H NMR (MeOD, 333 K) of **33**

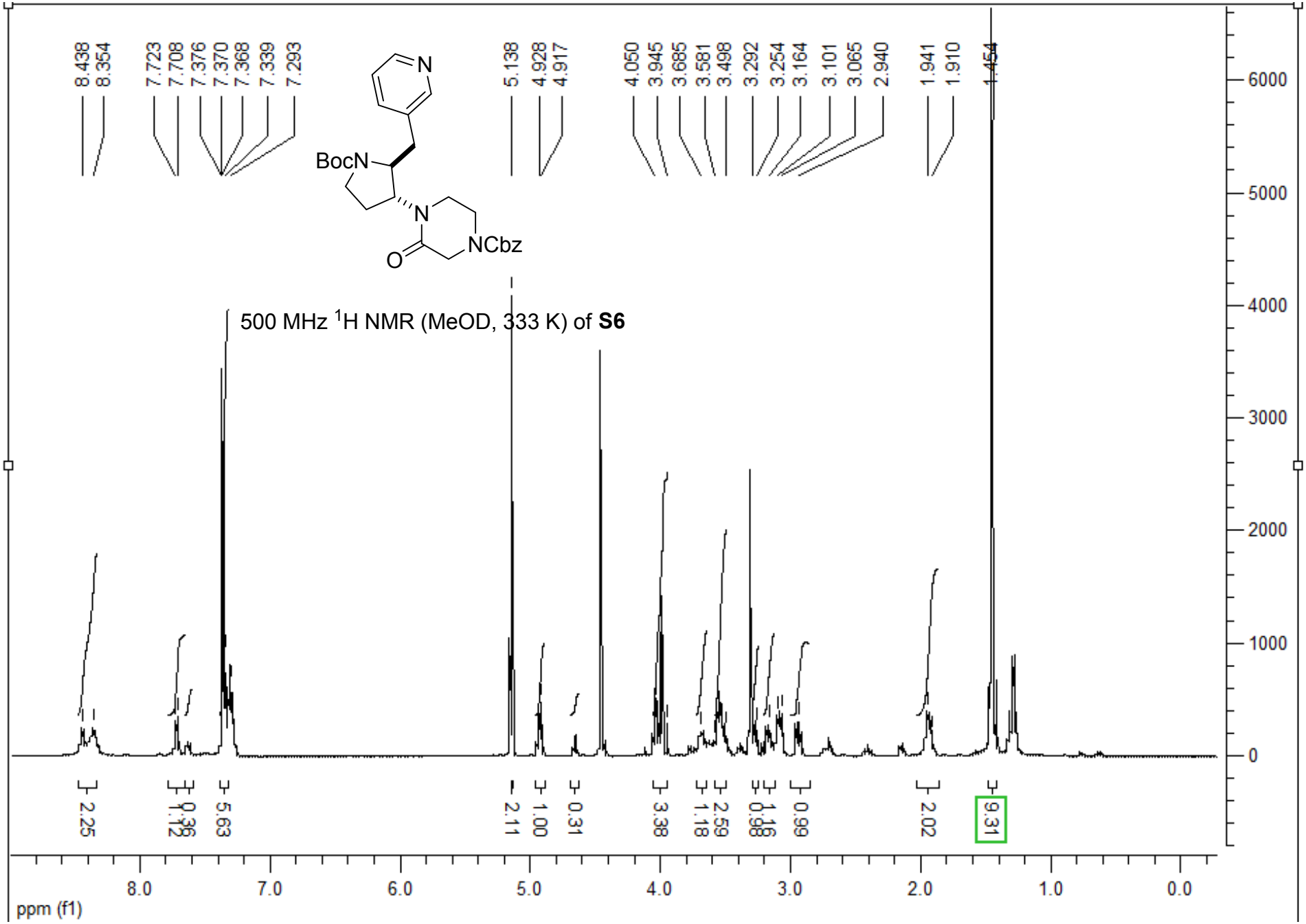


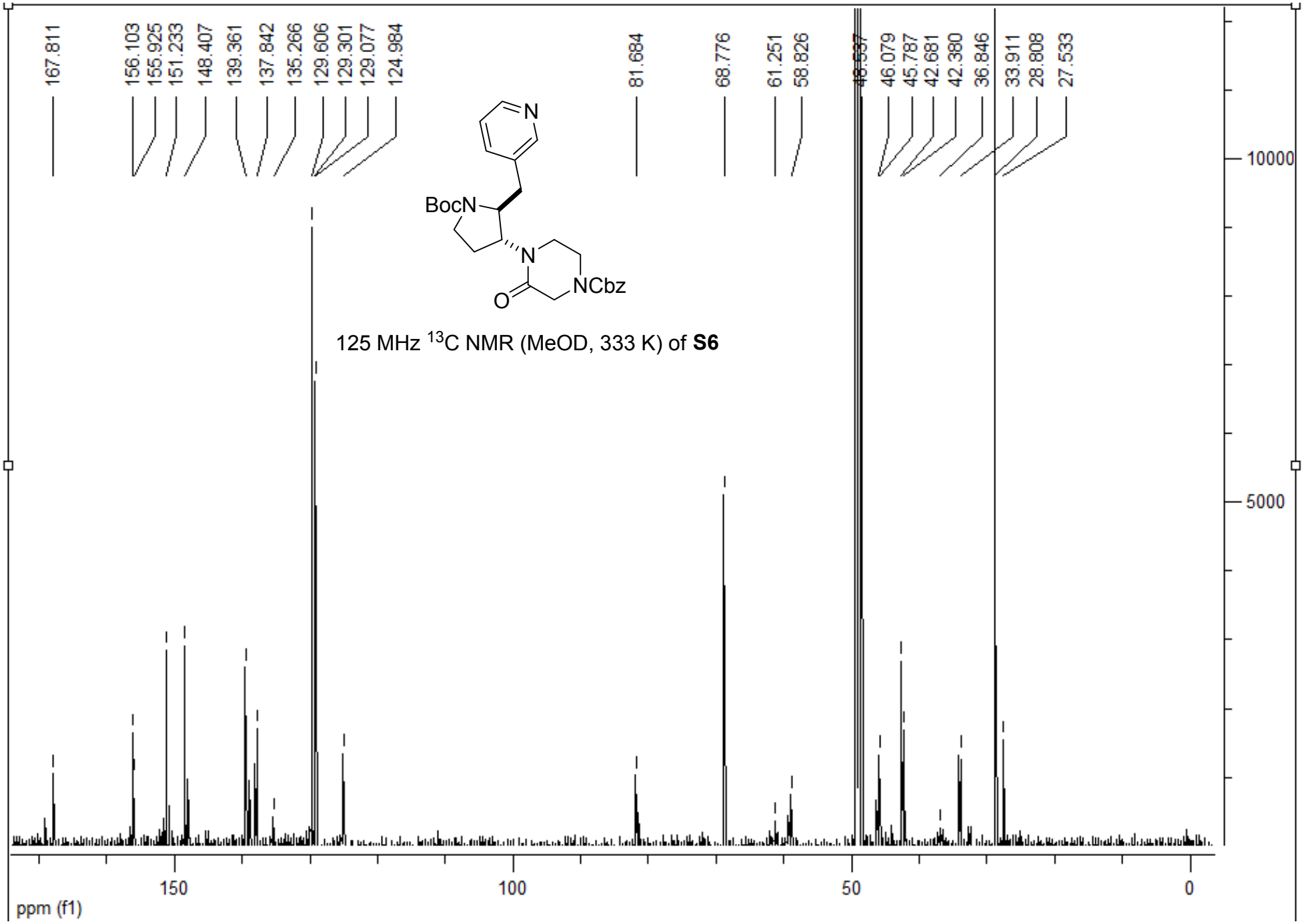
125 MHz ^{13}C NMR (MeOD, 333 K) of **33**


8.976
8.673
7.372
7.304
5.148
4.908
4.090
3.998
3.708
3.639
3.634
3.578
3.346
3.240
3.232
3.145
3.142
3.100
3.093
3.047
2.975
2.014
1.941
1.429
BocN
N
N
O
NCbz
500 MHz ^{1}H NMR (MeOD, 333 K) of **41**
3.400 3.350 3.300 3.250 3.200 3.150 3.100
ppm (f1)
1.00
2.06
4.88
2.04
1.00
3.02
0.99
1.40
1.10
1.08
1.05
2.08
1.94
10000
5000
0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

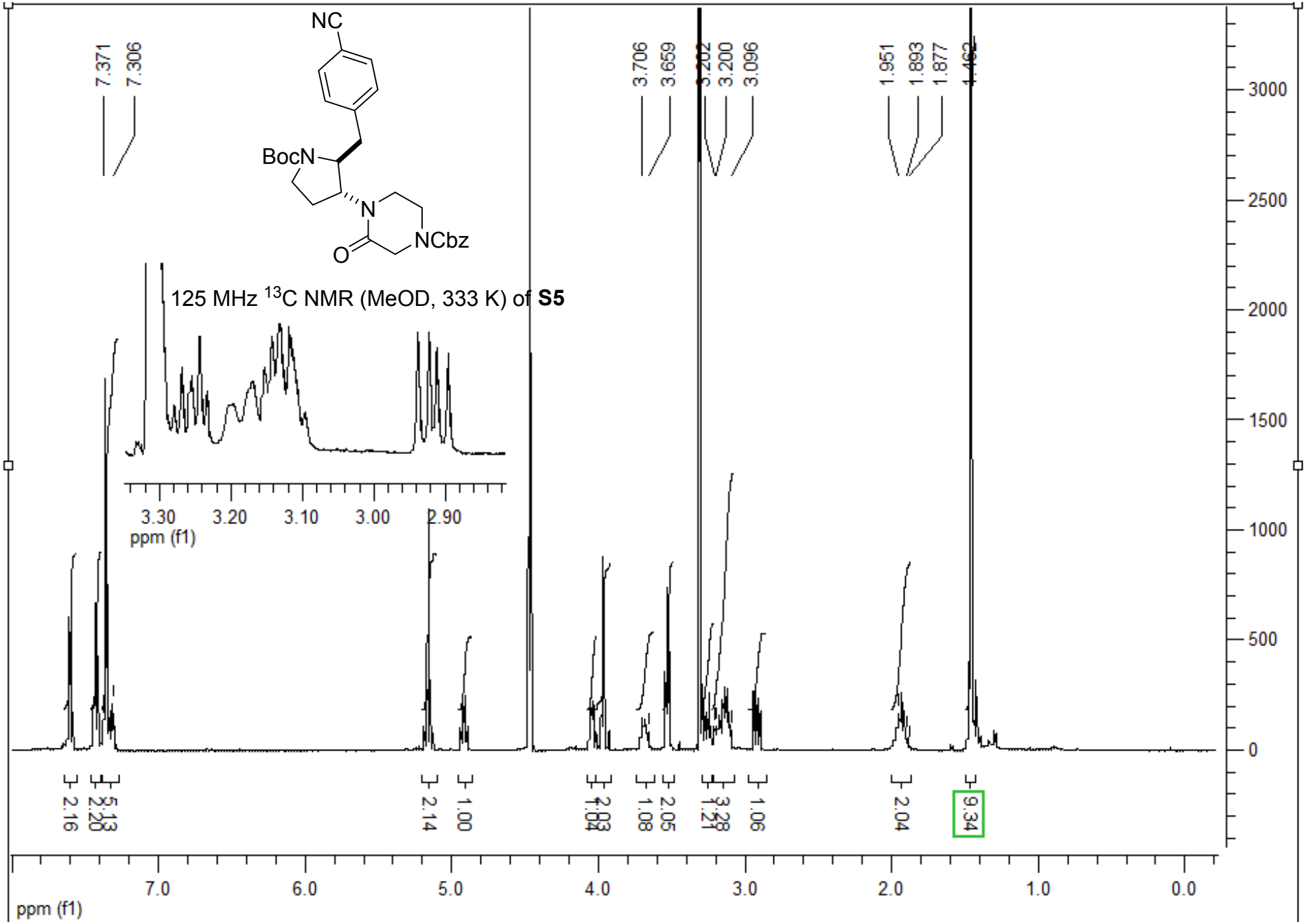


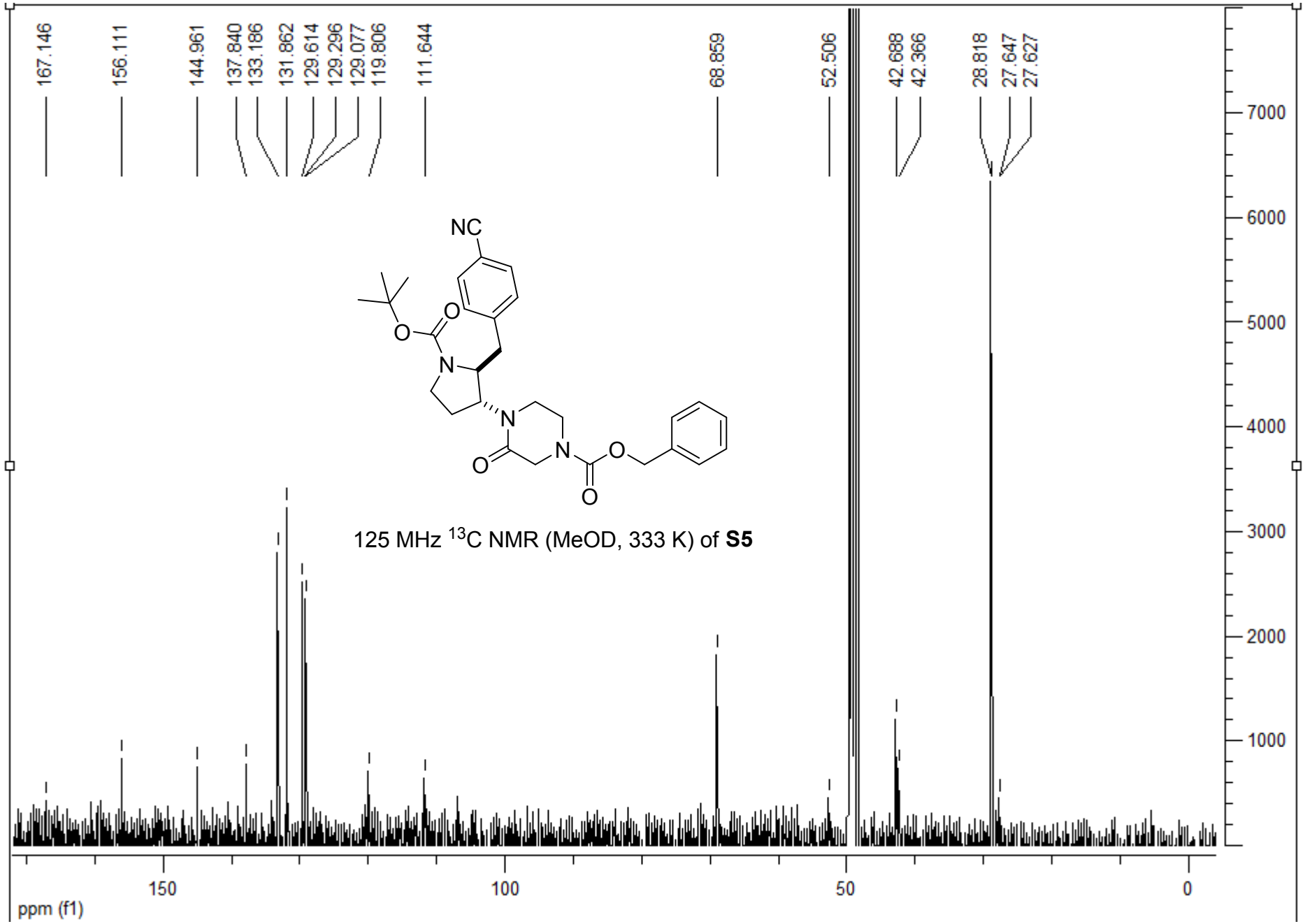
125 MHz ^{13}C NMR (MeOD, 333 K) of **41**


8.438
8.354
7.723
7.708
7.376
7.370
7.368
7.339
7.293
5.138
4.928
4.917
4.050
3.945
3.685
3.581
3.498
3.292
3.254
3.164
3.101
3.065
2.940
1.941
1.910
1.454
BocN
N
N
NCbz
O
500 MHz ^{1}H NMR (MeOD, 333 K) of **S6**
2.25
1.12
0.36
5.63
2.11
1.00
0.31
3.38
1.18
2.59
0.86
1.18
0.99
2.02
9.31
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)
6000
5000
4000
3000
2000
1000
0

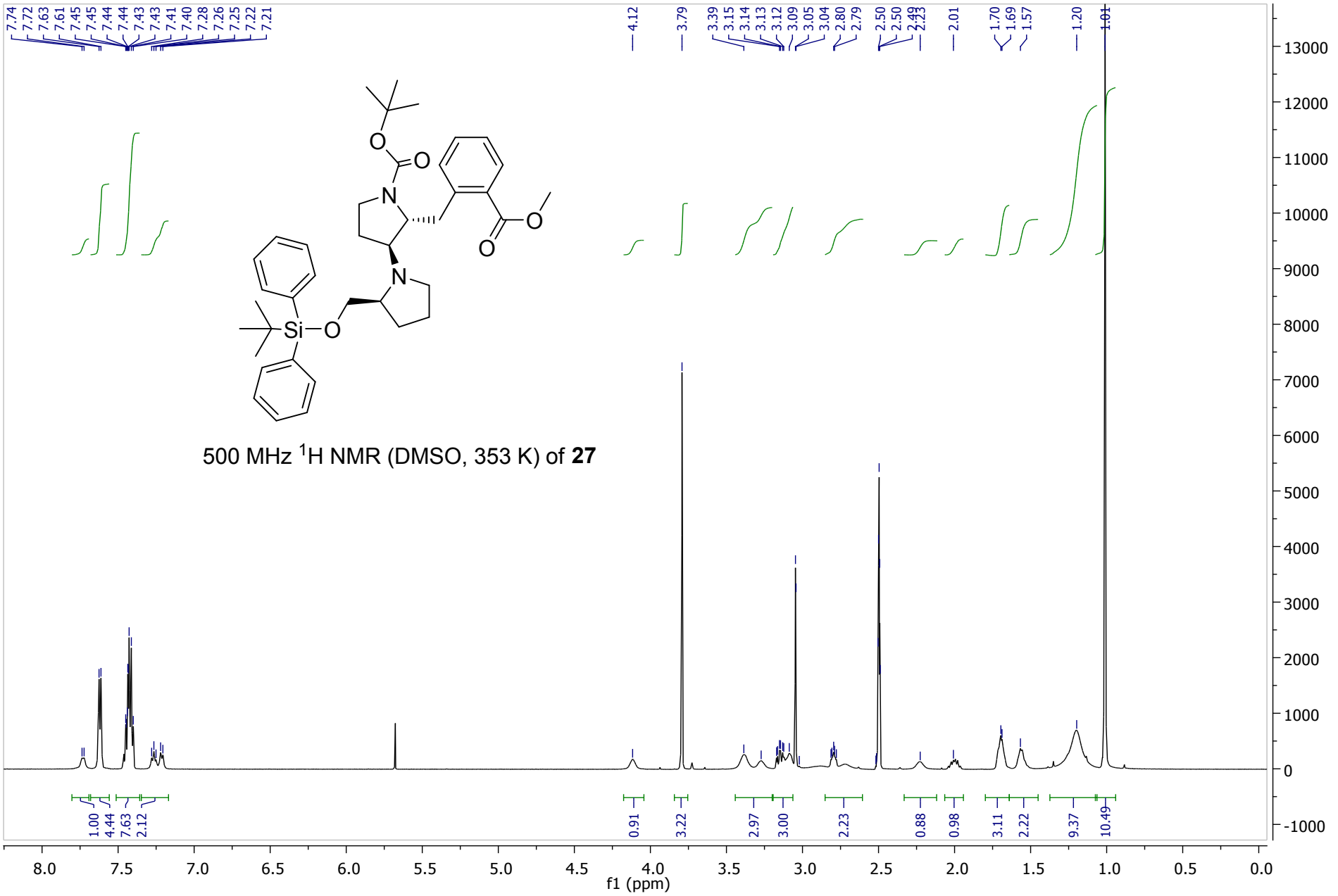


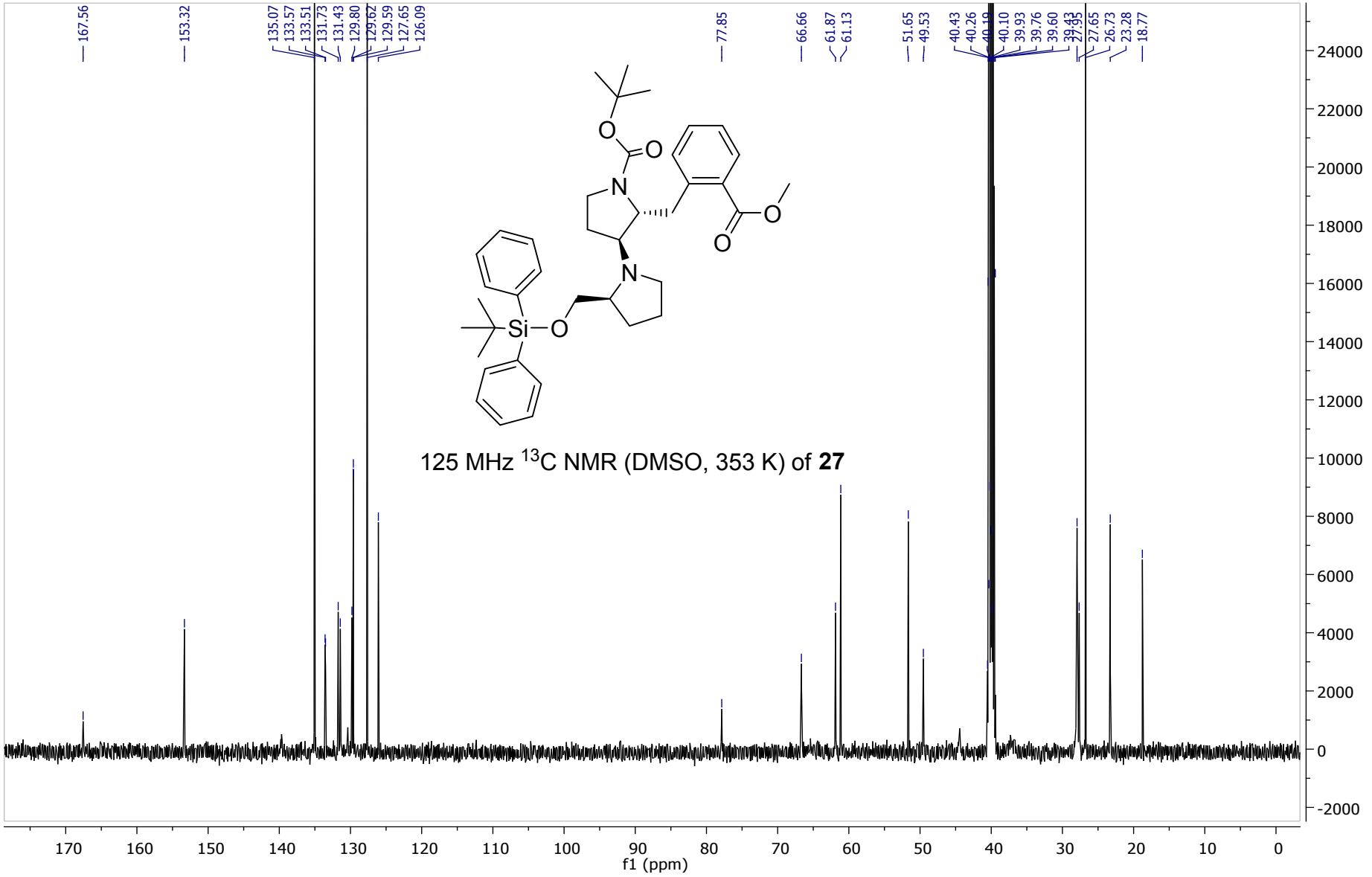
125 MHz ^{13}C NMR (MeOD, 333 K) of **S6**

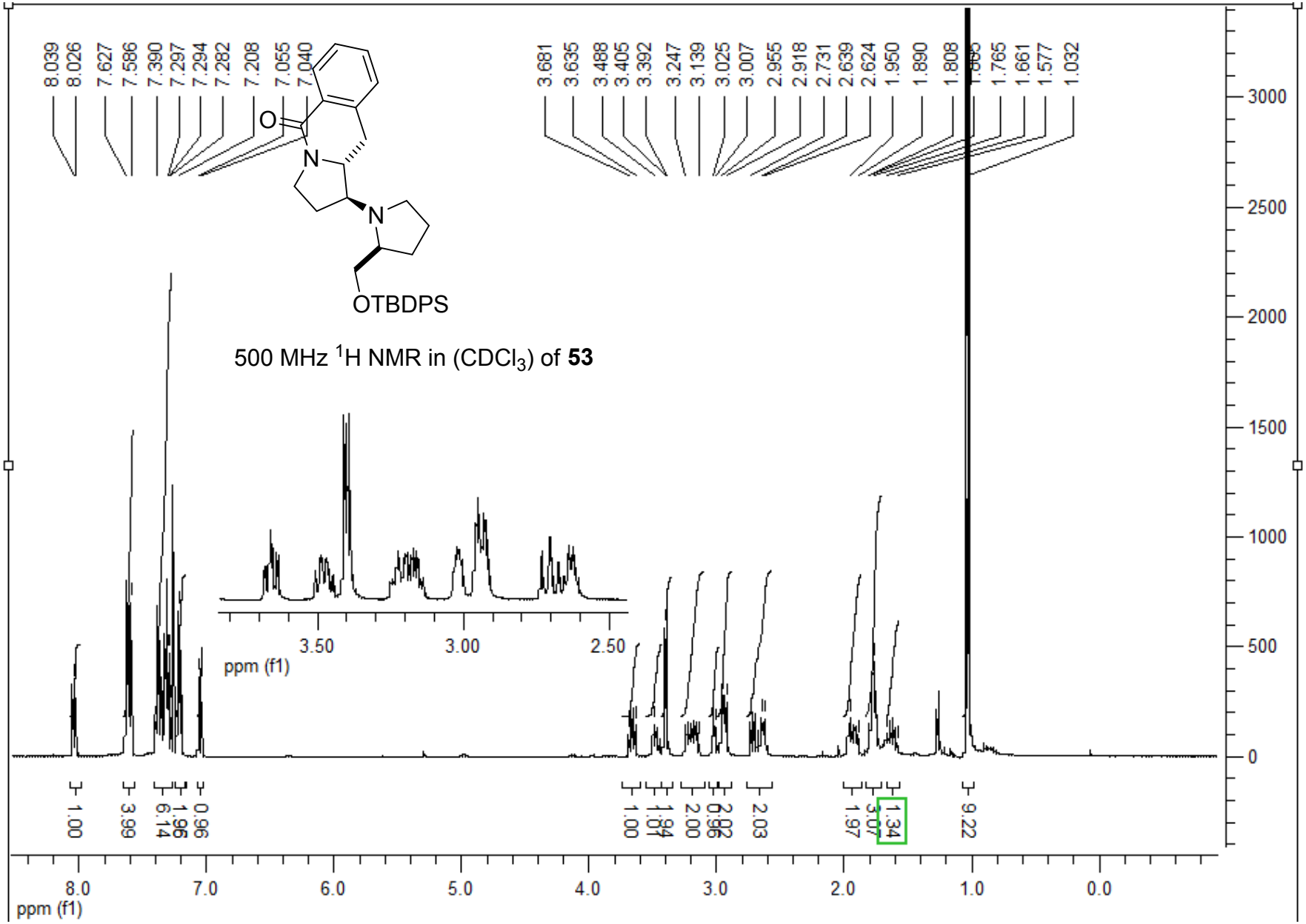

NC
BocN
N
O
NCbz
125 MHz ^{13}C NMR (MeOD, 333 K) of **S5**
7.371
7.306
3.706
3.659
3.202
3.200
3.096
1.951
1.893
1.877
1.462
2.16
2.20
5.13
2.14
1.00
2.03
1.08
2.05
3.28
1.21
1.06
2.04
9.34
ppm (f1)

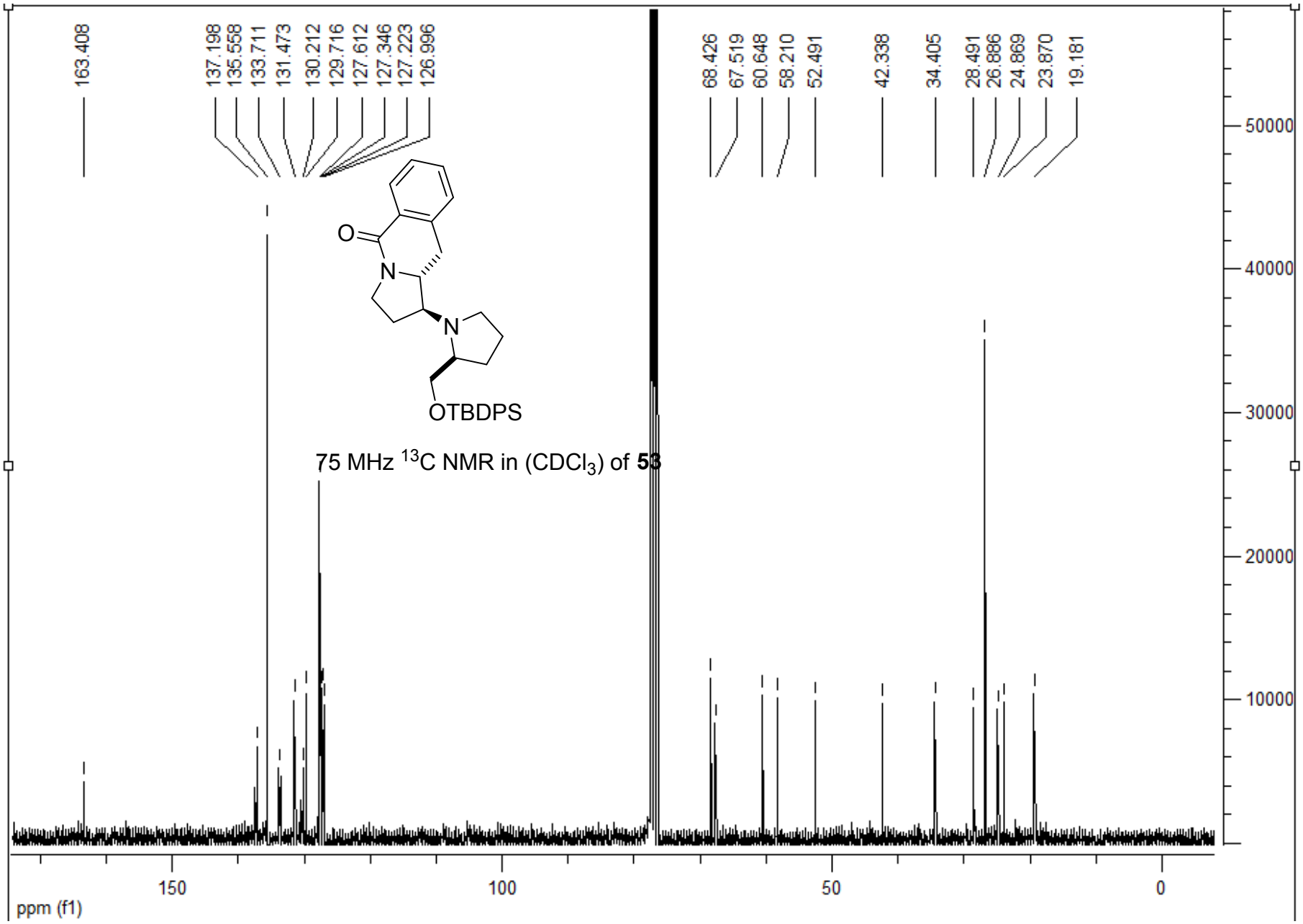


125 MHz ^{13}C NMR (MeOD, 333 K) of **S5**

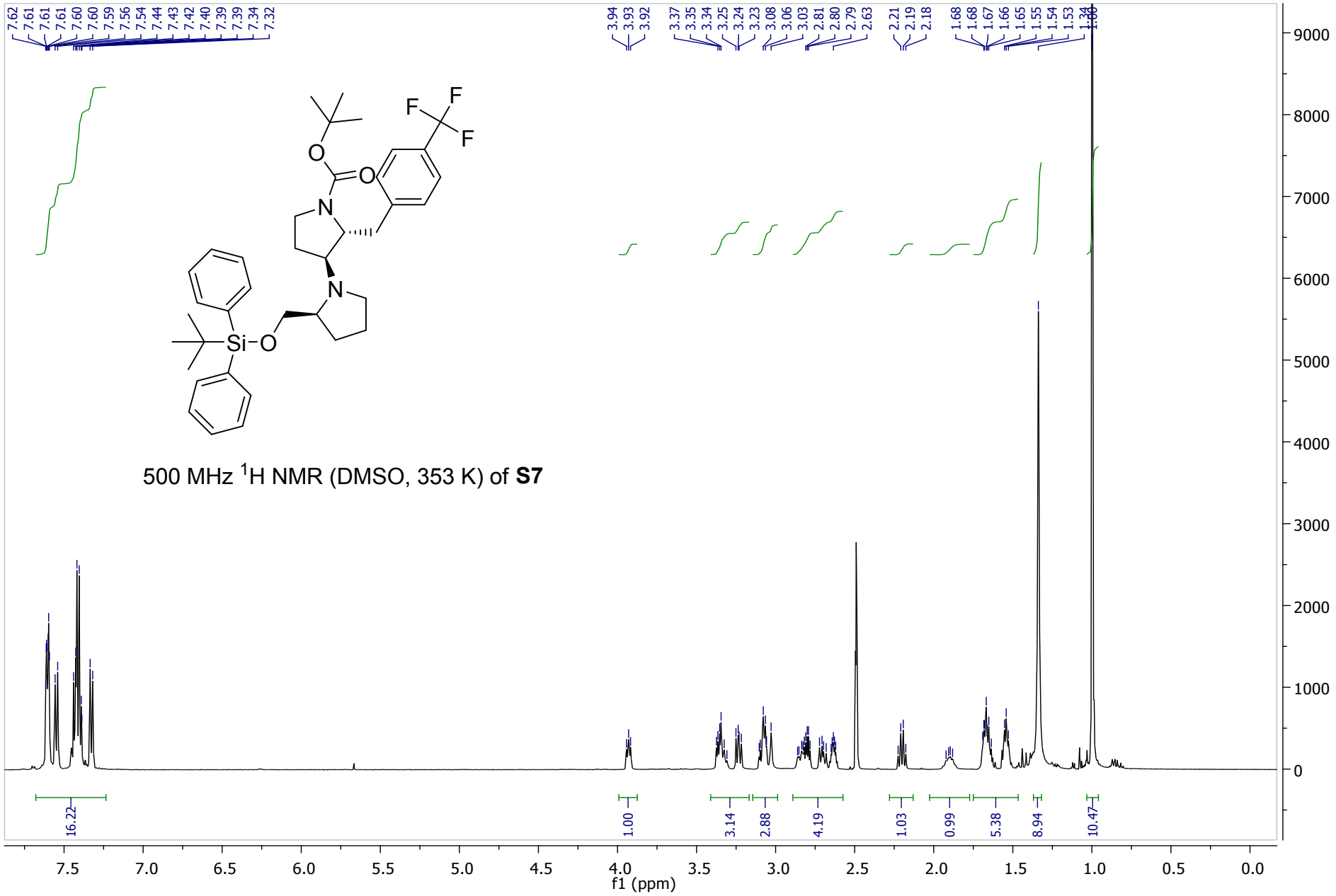

7.74
7.72
7.63
7.61
7.45
7.45
7.44
7.44
7.43
7.43
7.41
7.40
7.28
7.26
7.25
7.22
7.21
4.12
3.79
3.39
3.15
3.14
3.13
3.12
3.09
3.05
3.04
2.80
2.79
2.50
2.50
2.49
2.23
2.01
1.70
1.69
1.57
1.20
1.01
O
O
N
O
O
N
Si
O
500 MHz ^{1}H NMR (DMSO, 353 K) of **27**
1.00
4.44
7.63
2.12
0.91
3.22
2.97
3.00
2.23
0.88
0.98
3.11
2.22
9.37
10.49
f1 (ppm)


167.56
153.32
135.07
133.57
133.51
131.73
131.43
129.80
129.62
129.59
127.65
126.09
77.85
66.66
61.87
61.13
51.65
49.53
40.43
40.26
40.19
40.10
39.93
39.76
39.60
27.65
26.73
23.28
18.77
O
O
N
O
O
N
Si
O
125 MHz ^{13}C NMR (DMSO, 353 K) of **27**
f1 (ppm)

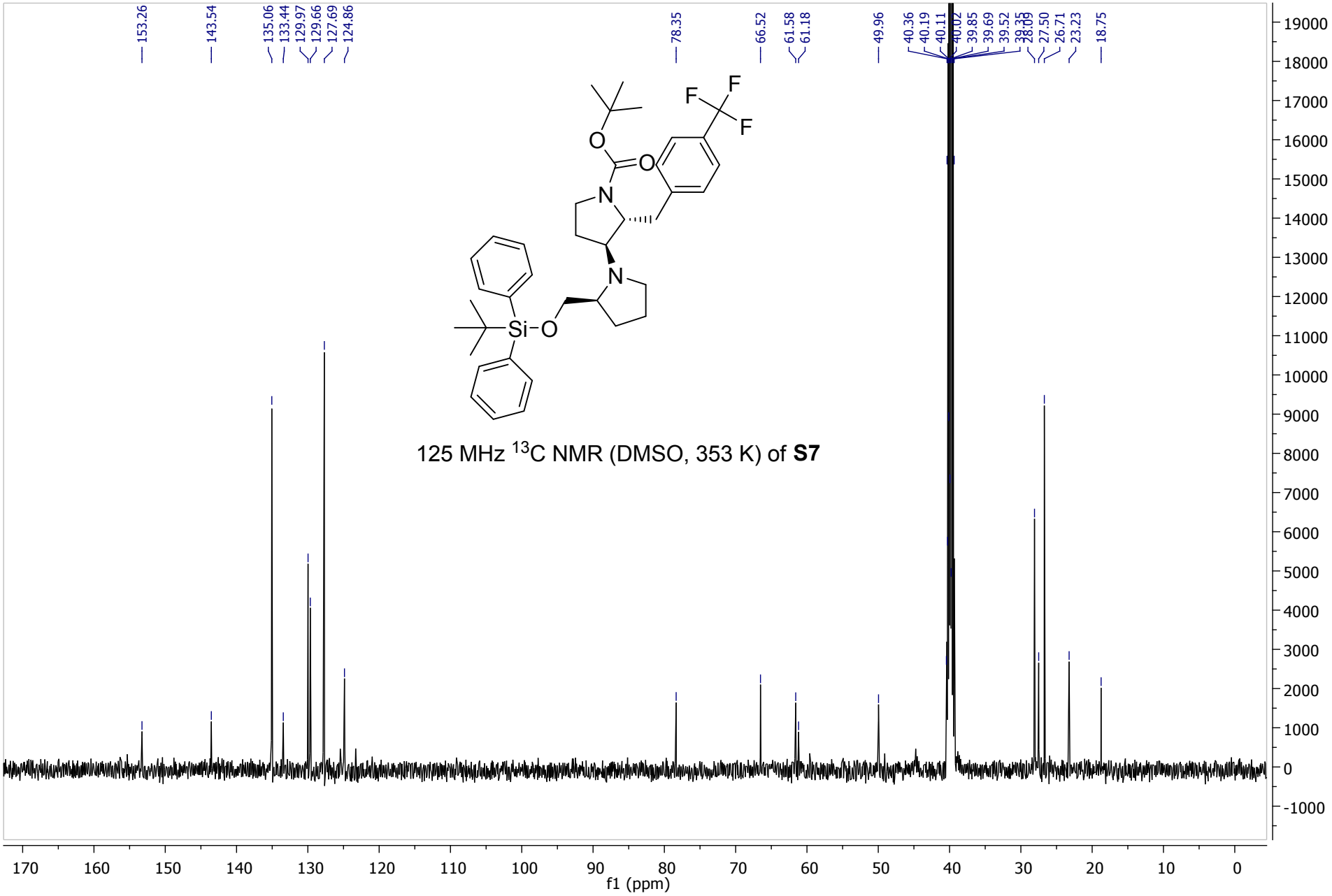

8.039
8.026
7.627
7.586
7.390
7.297
7.294
7.282
7.208
7.055
7.040
3.681
3.635
3.488
3.405
3.392
3.247
3.139
3.025
3.007
2.955
2.918
2.731
2.639
2.624
1.950
1.890
1.808
1.765
1.661
1.577
1.032
O
N
N
OTBDPS
500 MHz ^{1}H NMR in ($CDCl_3$) of **53**
3.50
3.00
2.50
ppm (f1)
3000
2500
2000
1500
1000
500
0
1.00
3.69
6.14
1.96
0.96
1.00
1.84
2.00
2.03
1.97
3.07
1.34
9.22
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

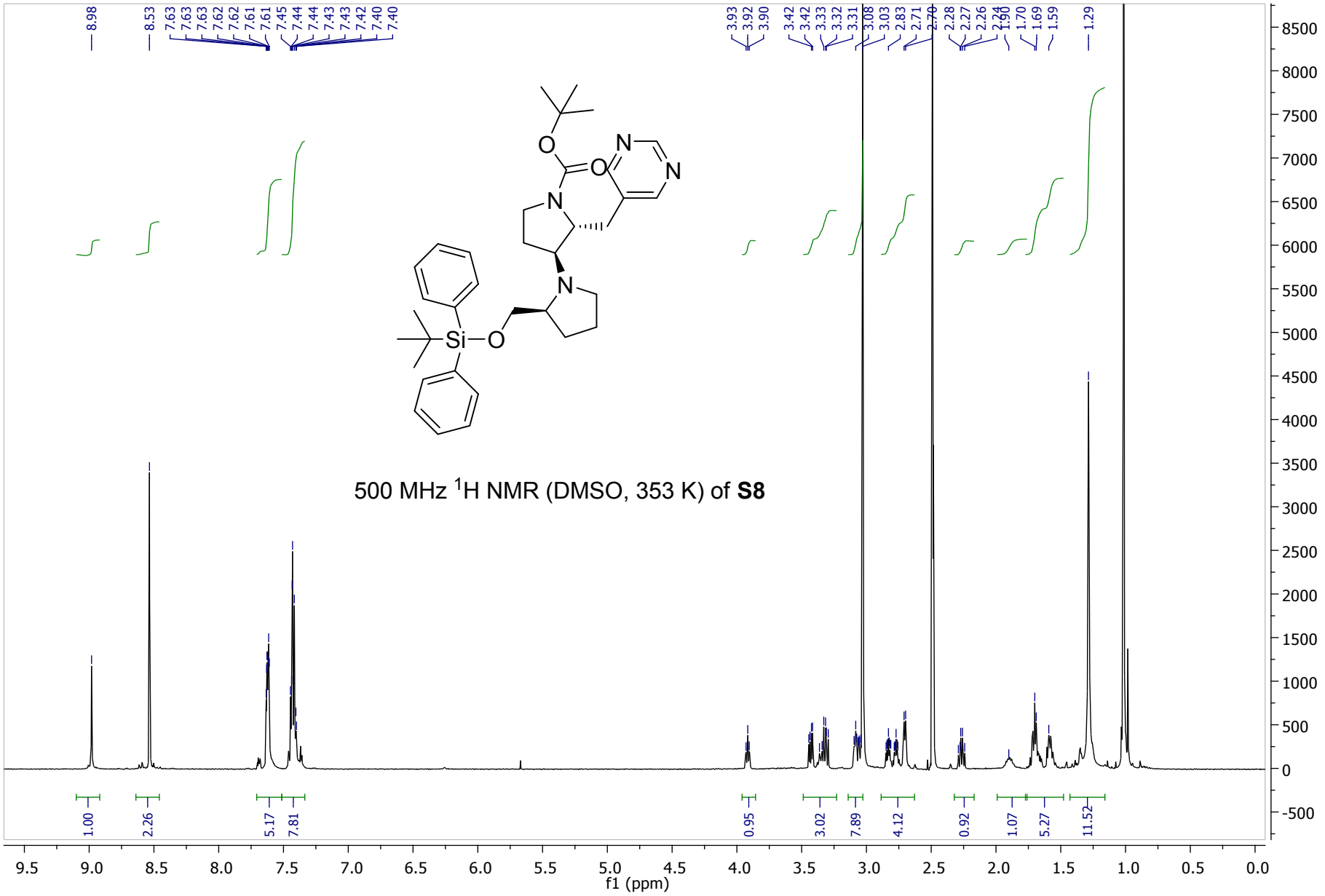


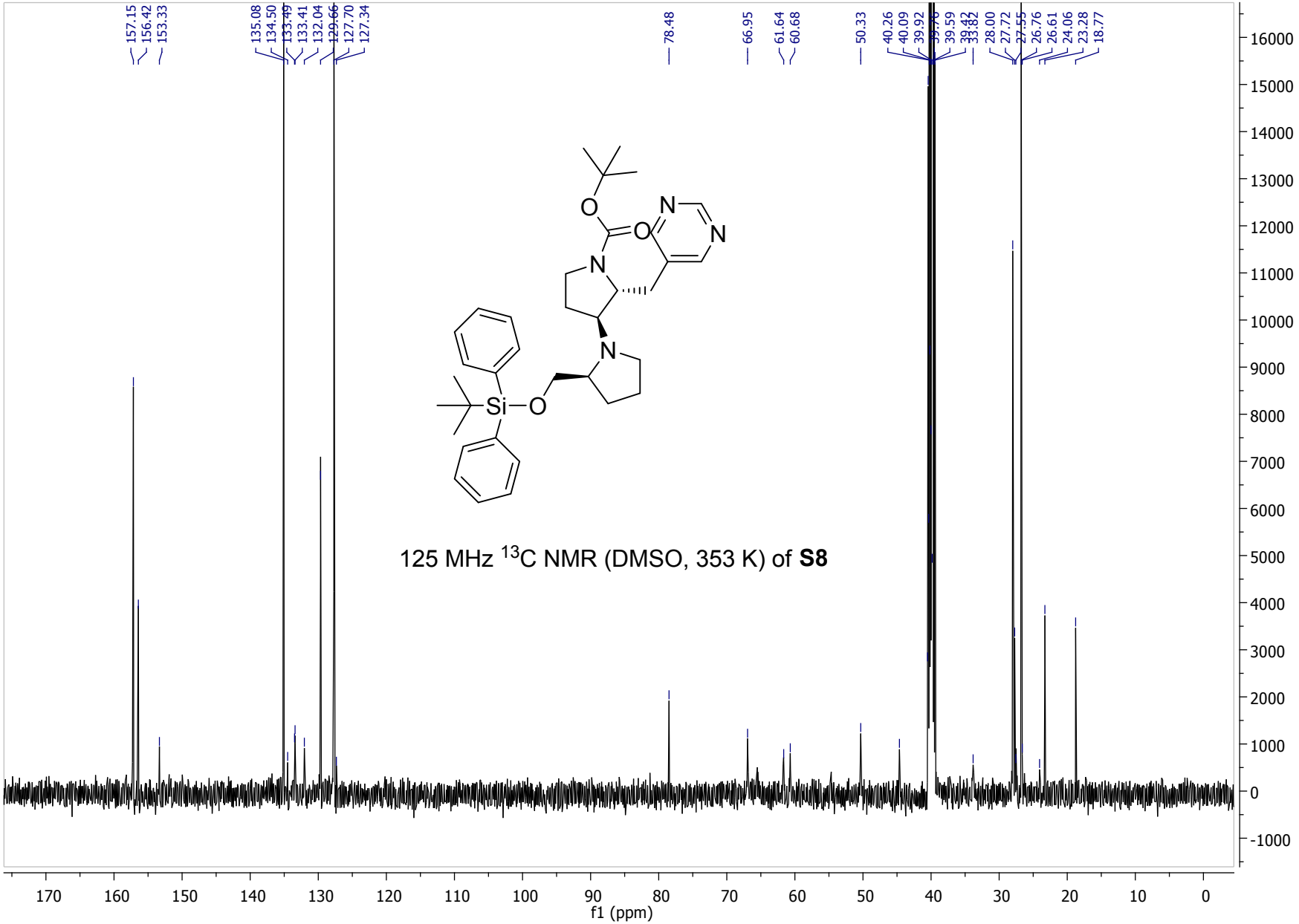
75 MHz ^{13}C NMR in ($CDCl_3$) of **53**

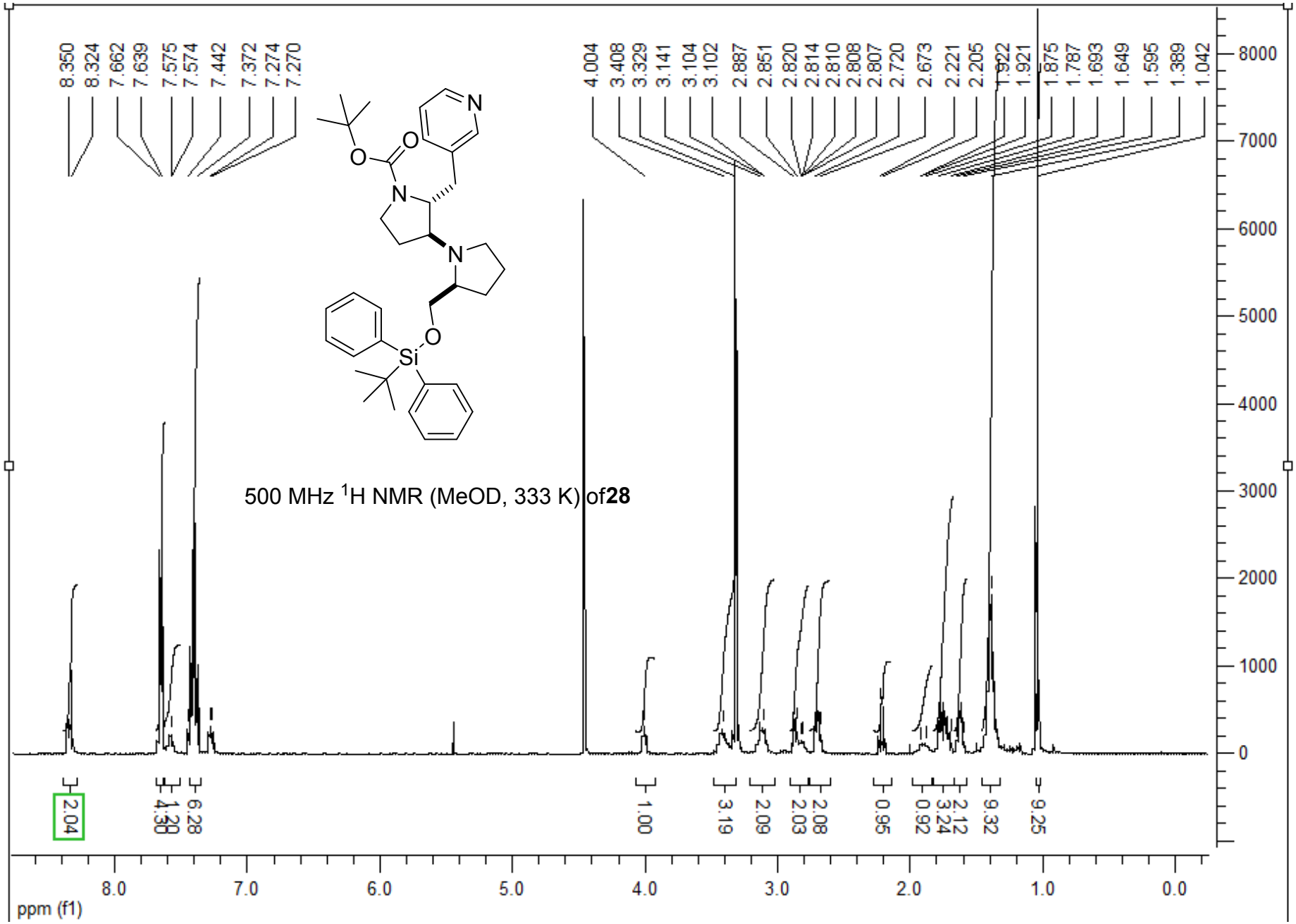


500 MHz ^{1}H NMR (DMSO, 353 K) of **S7**

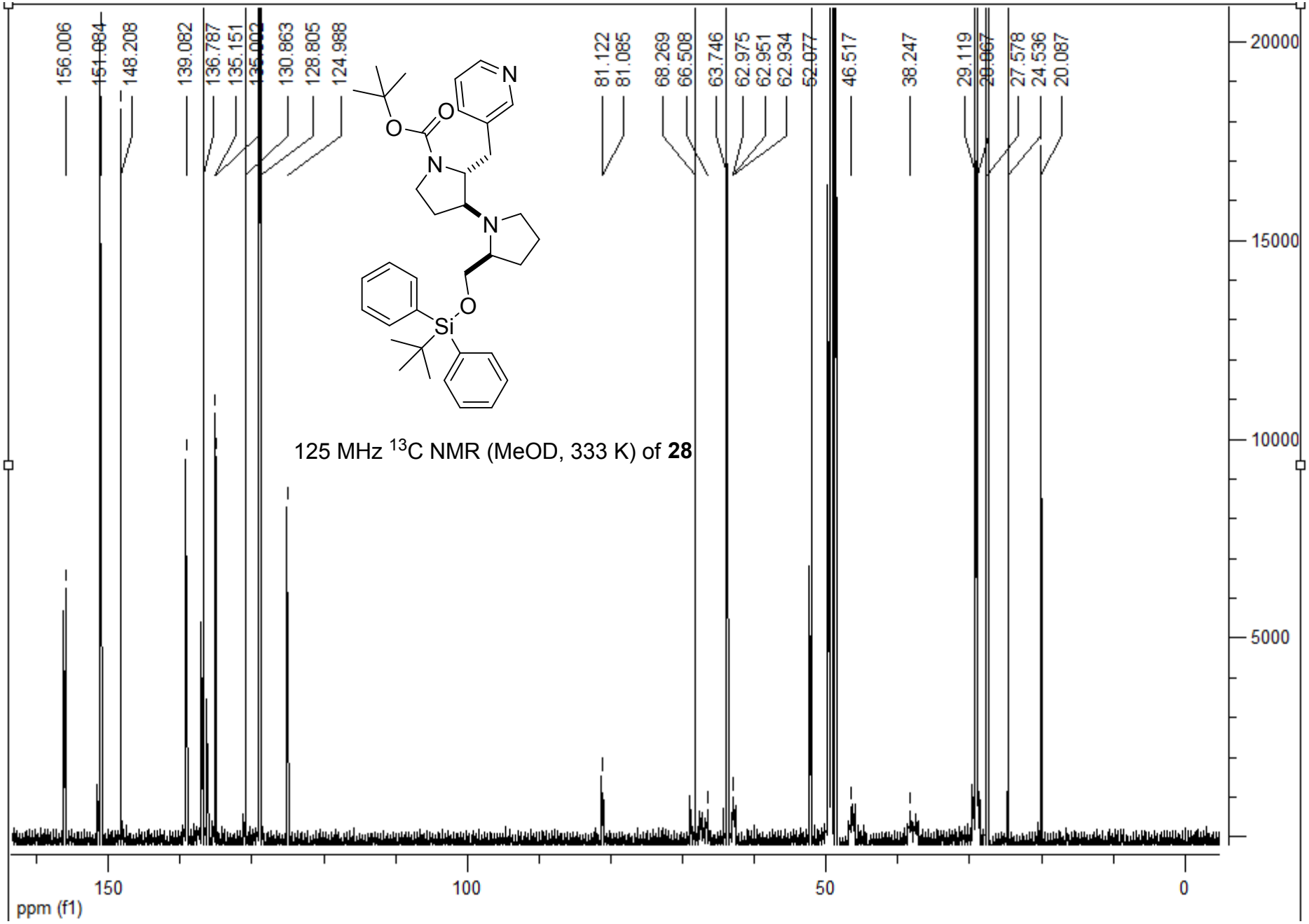

153.26
143.54
135.06
133.44
129.97
129.66
127.69
124.86
78.35
66.52
61.58
61.18
49.96
40.36
40.19
40.11
40.02
39.85
39.69
39.52
28.09
27.50
26.71
23.23
18.75
F
F
F
O
O
N
N
Si
O
125 MHz ^{13}C NMR (DMSO, 353 K) of **S7**
f1 (ppm)


8.98
8.53
7.63
7.63
7.63
7.62
7.62
7.61
7.61
7.45
7.44
7.44
7.43
7.43
7.42
7.40
7.40
3.93
3.92
3.90
3.42
3.42
3.33
3.32
3.31
3.08
3.03
2.83
2.71
2.70
2.28
2.27
2.26
2.24
1.90
1.70
1.69
1.59
1.29
O
O
N
N
N
N
Si
O
500 MHz ^{1}H NMR (DMSO, 353 K) of **S8**
1.00
2.26
5.17
7.81
0.95
3.02
7.89
4.12
0.92
1.07
5.27
11.52
f1 (ppm)

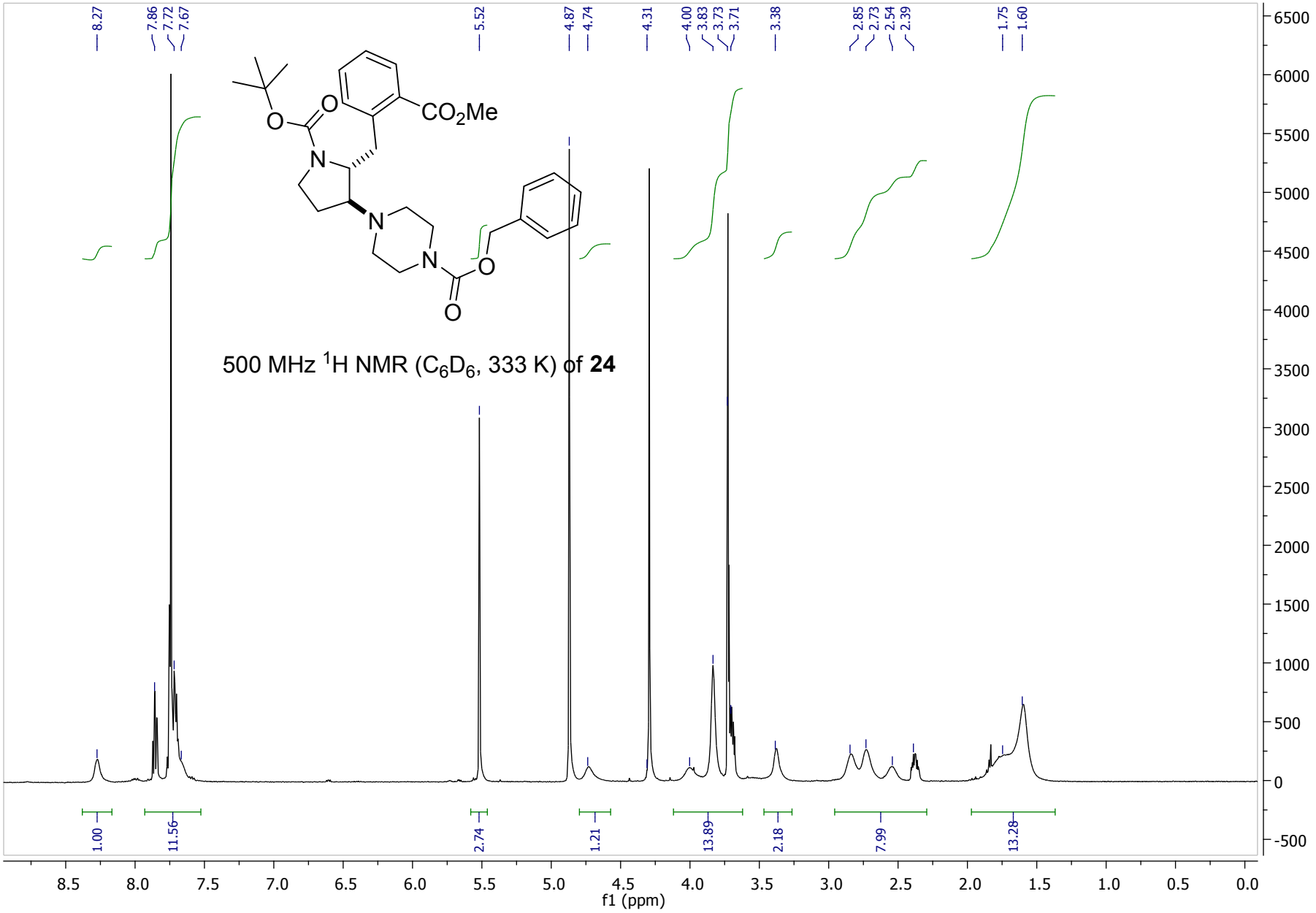

157.15
156.42
153.33
135.08
134.50
133.49
133.41
132.04
129.66
127.70
127.34
78.48
66.95
61.64
60.68
50.33
40.26
40.09
39.92
39.59
39.42
28.00
27.72
27.55
26.76
26.61
24.06
23.28
18.77
O
O
N
N
N
N
Si
O
125 MHz ^{13}C NMR (DMSO, 353 K) of **S8**
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

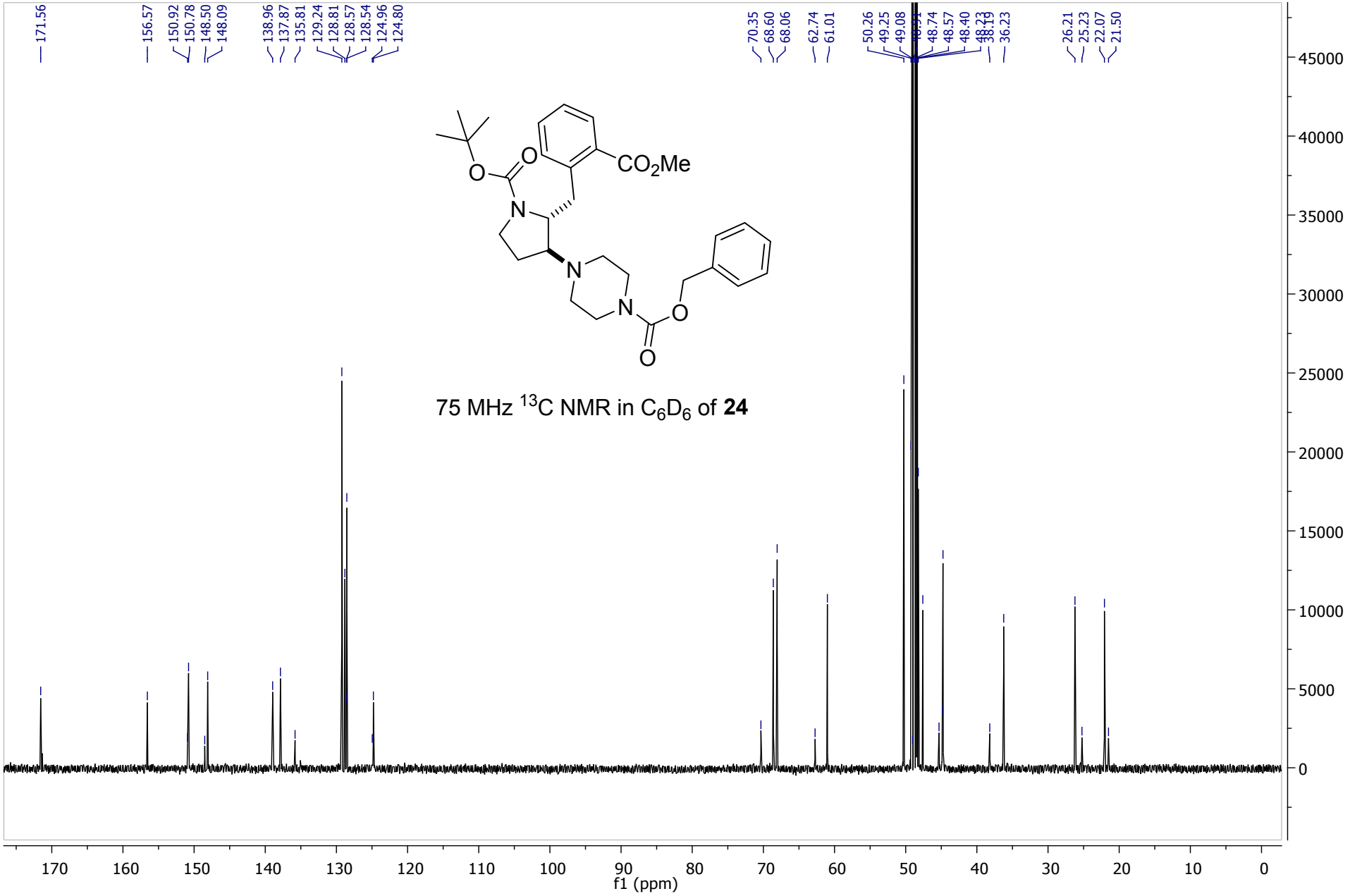


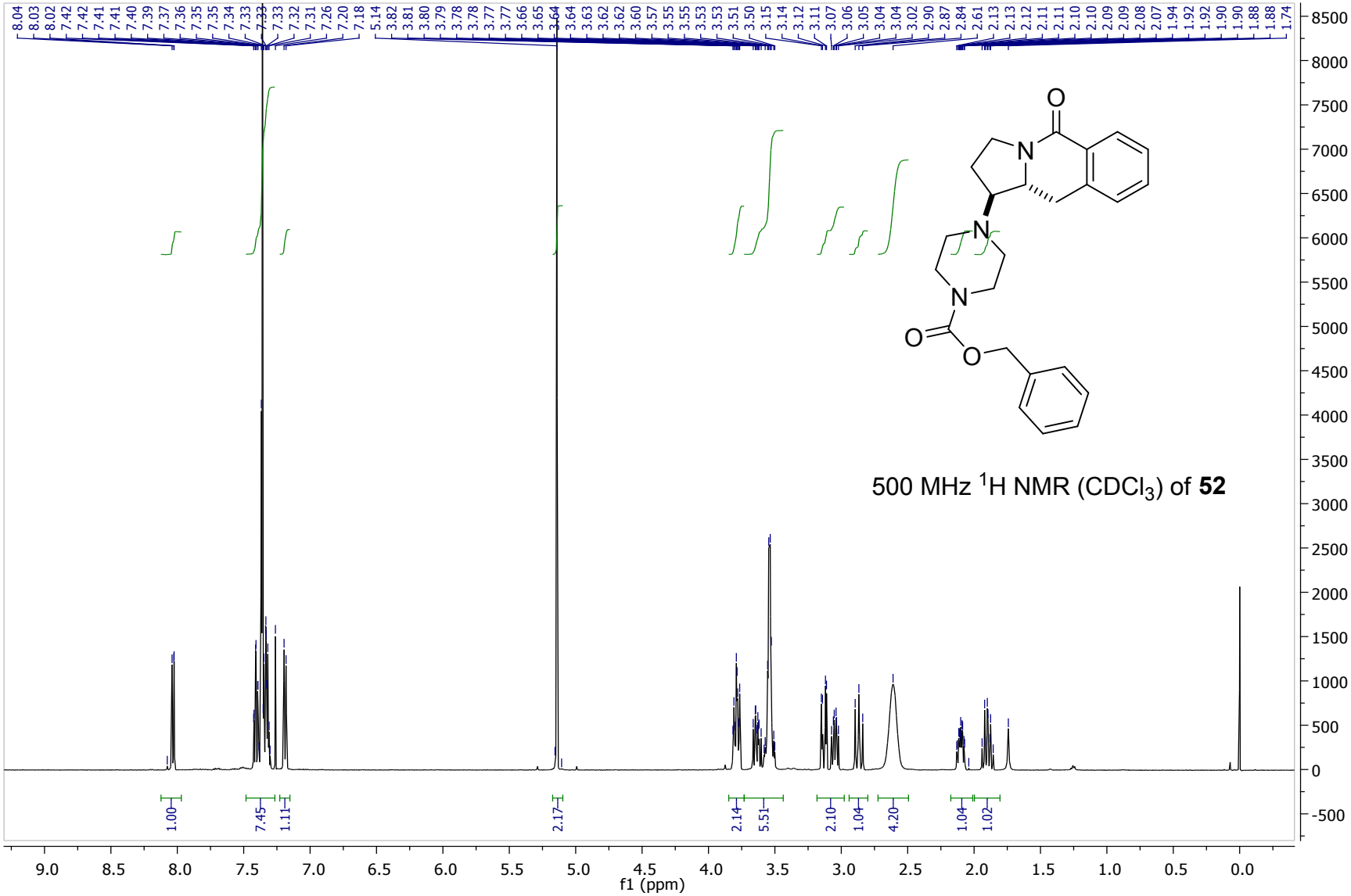
500 MHz ^{1}H NMR (MeOD, 333 K) of **28**

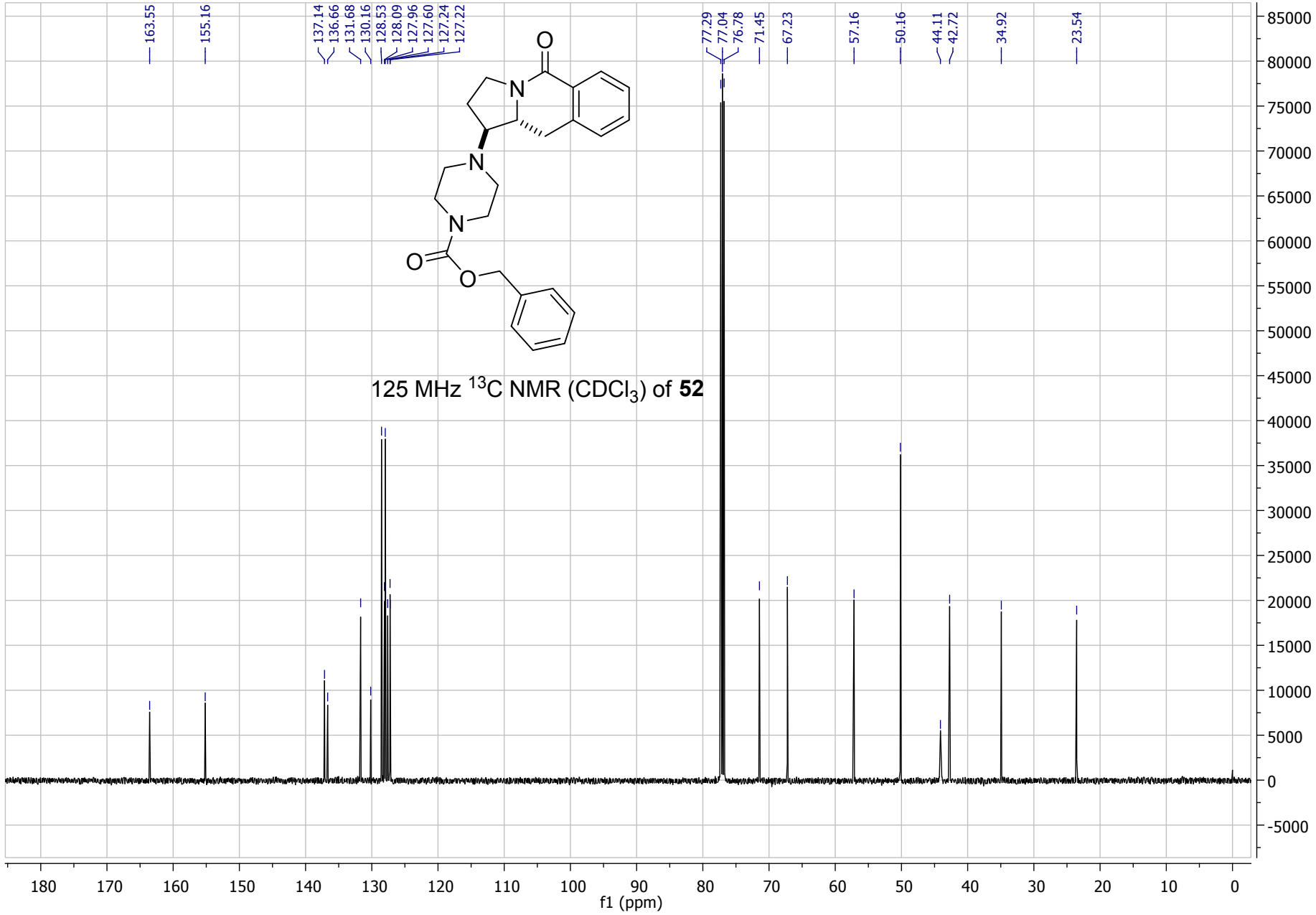


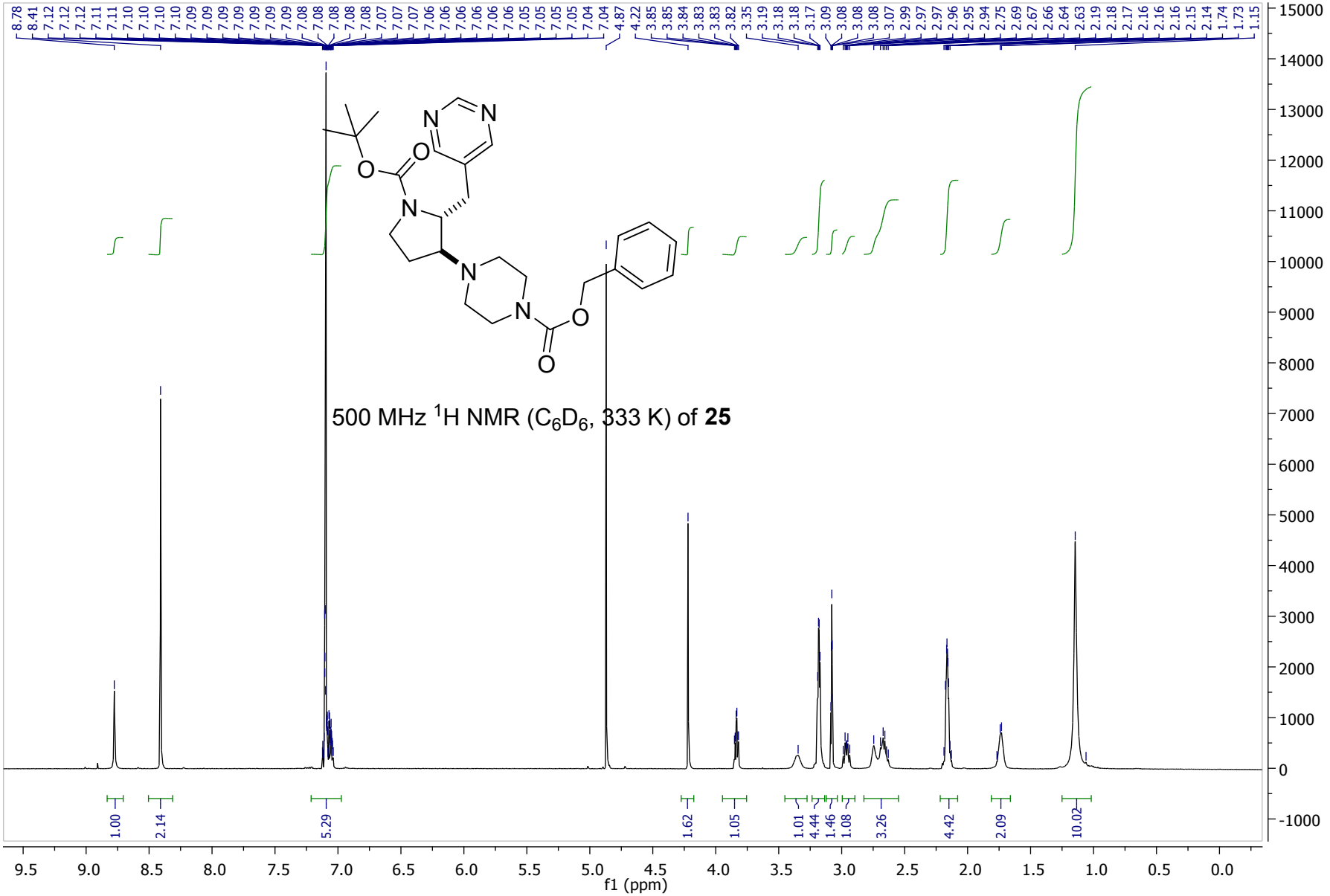
125 MHz ^{13}C NMR (MeOD, 333 K) of **28**

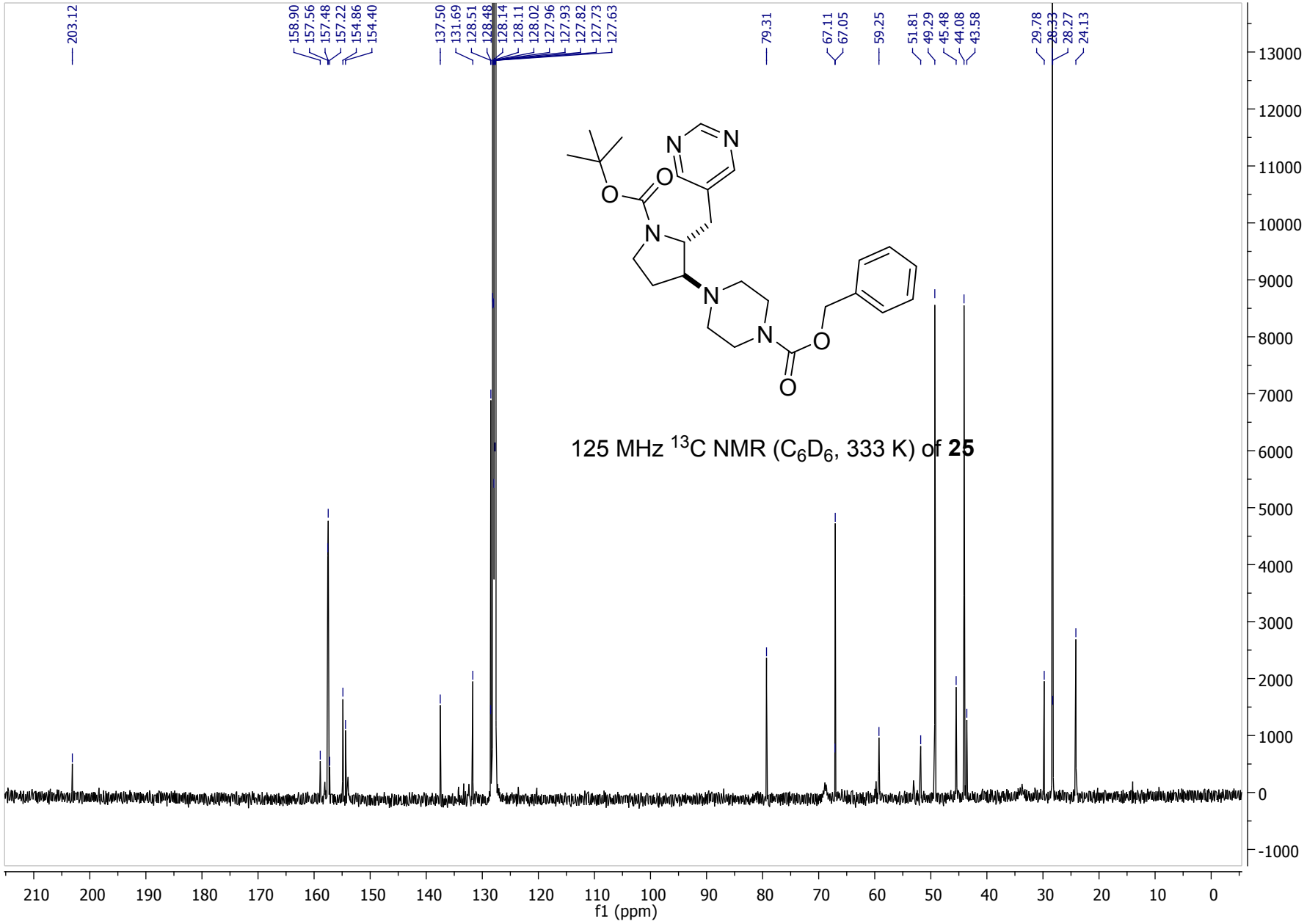

8.27
7.86
7.72
7.67
5.52
4.87
4.74
4.31
4.00
3.83
3.73
3.71
3.38
2.85
2.73
2.54
2.39
1.75
1.60
CO2Me
O
O
N
N
N
O
O
500 MHz 1H NMR (C6D6, 333 K) of 24
1.00
11.56
2.74
1.21
13.89
2.18
7.99
13.28
f1 (ppm)

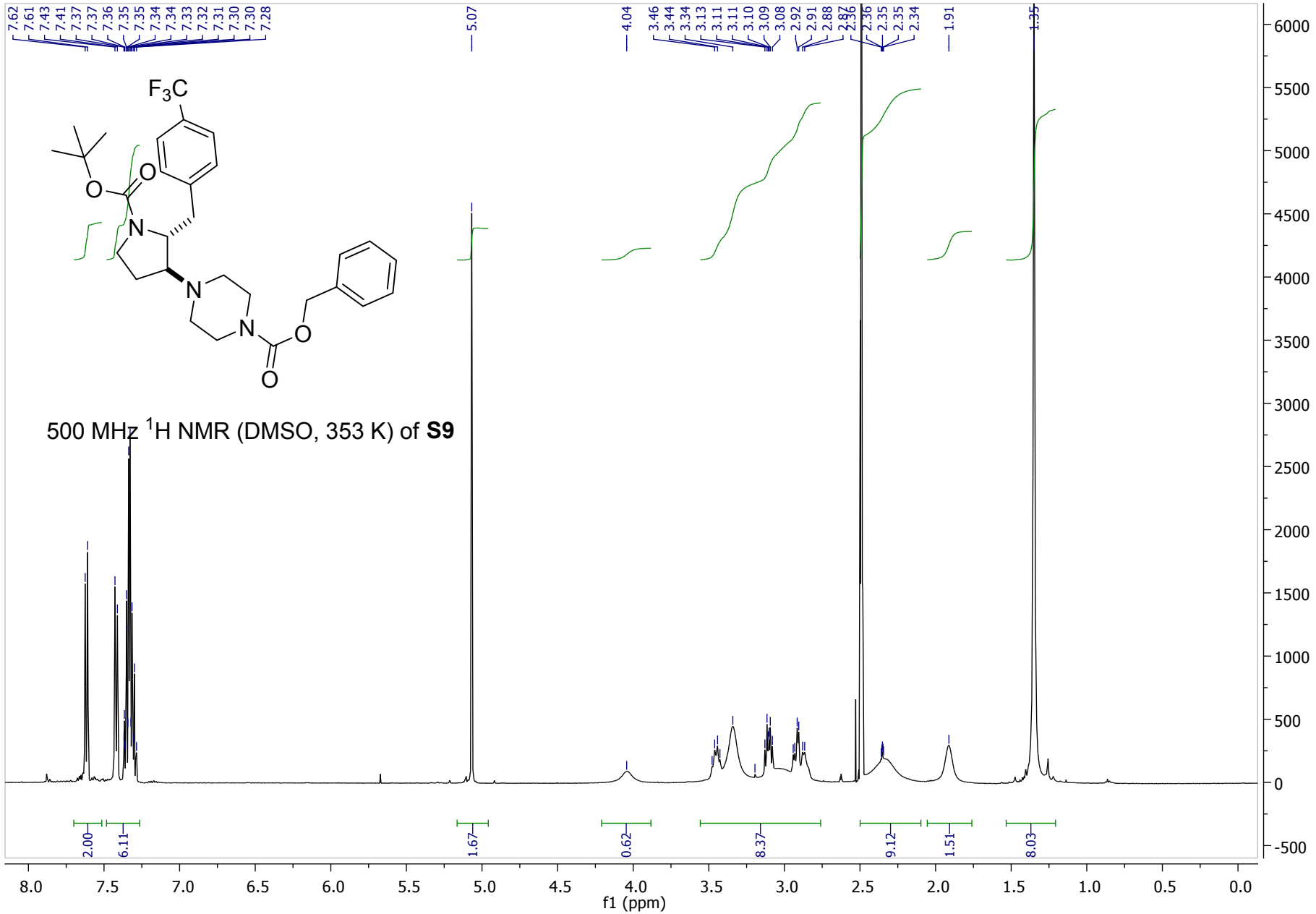

171.56
156.57
150.92
150.78
148.50
148.09
138.96
137.87
135.81
129.24
128.81
128.57
128.54
124.96
124.80
70.35
68.60
68.06
62.74
61.01
50.26
49.25
49.08
48.74
48.57
48.40
36.23
26.21
25.23
22.07
21.50
CO2Me
O
O
N
N
N
O
O
75 MHz 13C NMR in C6D6 of 24
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

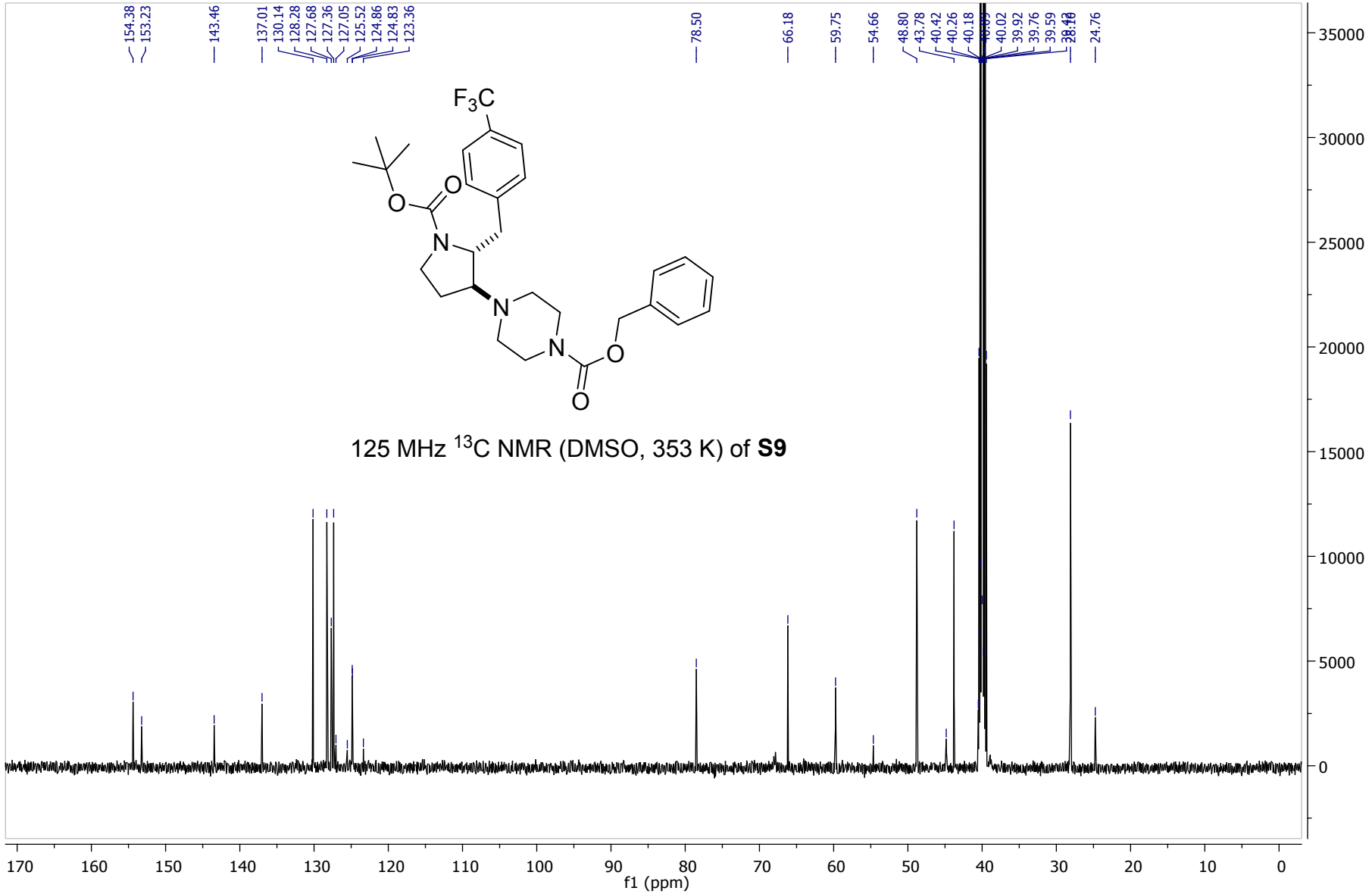

500 MHz ^{1}H NMR ($CDCl_3$) of **52**
f1 (ppm)


163.55
155.16
137.14
136.66
131.68
130.16
128.53
128.09
127.96
127.60
127.24
127.22
77.29
77.04
76.78
71.45
67.23
57.16
50.16
44.11
42.72
34.92
23.54
O
N
N
N
O
O
125 MHz ^{13}C NMR ($CDCl_3$) of **52**
f1 (ppm)

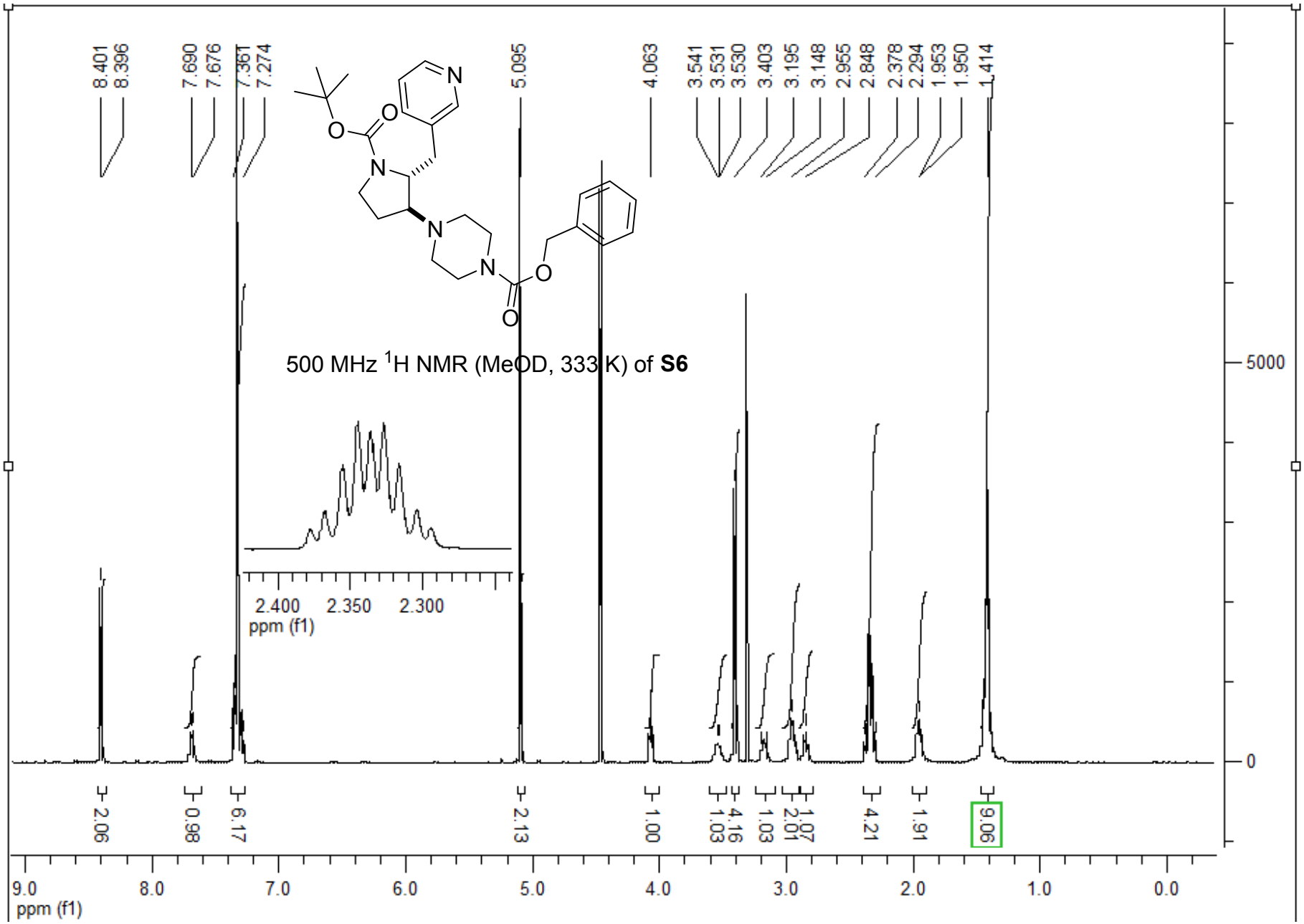

500 MHz ^{1}H NMR (C_6D_6, 333 K) of **25**
f1 (ppm)

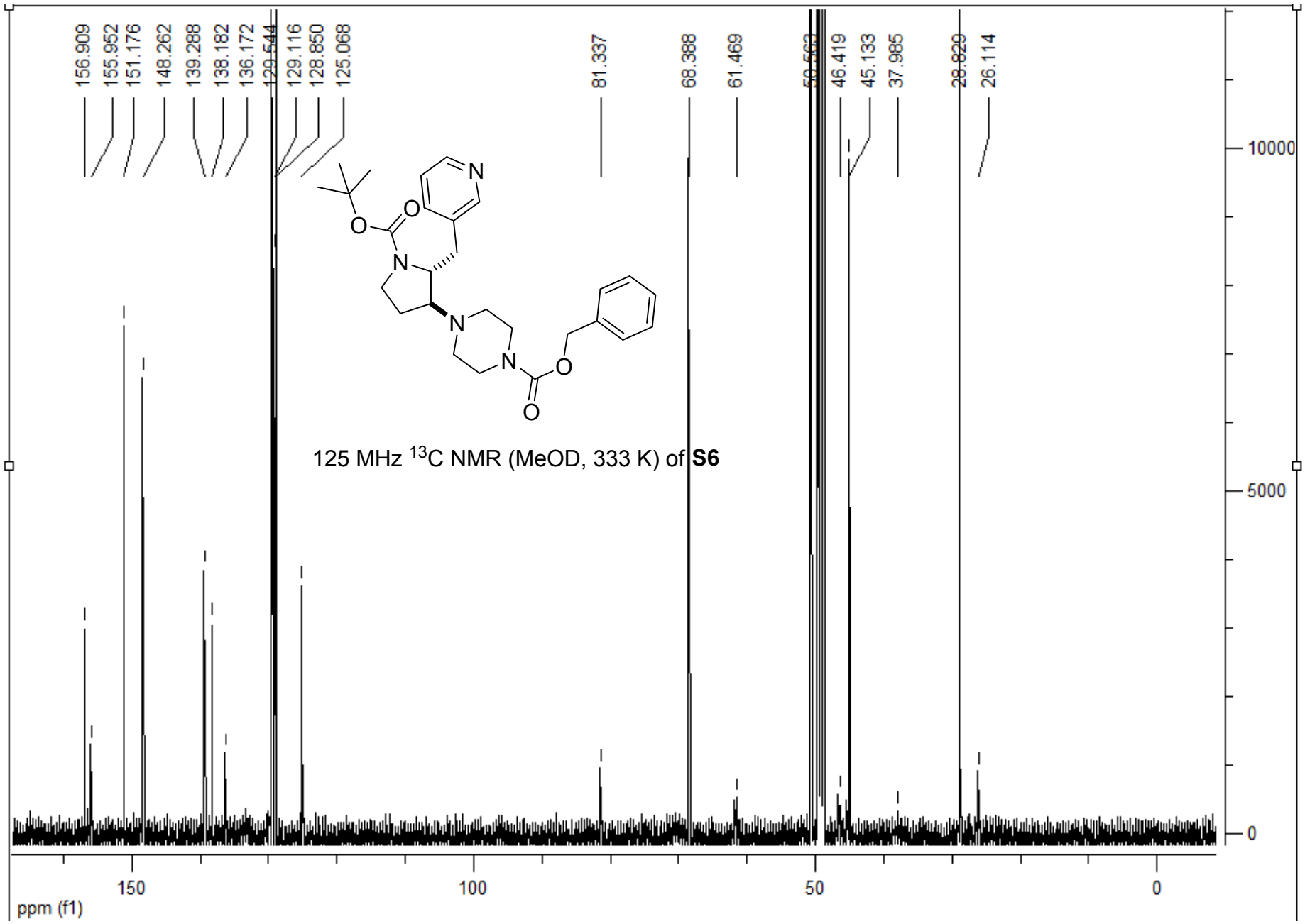

203.12
158.90
157.56
157.48
157.22
154.86
154.40
137.50
131.69
128.51
128.48
128.14
128.11
128.02
127.96
127.93
127.82
127.73
127.63
79.31
67.11
67.05
59.25
51.81
49.29
45.48
44.08
43.58
29.78
28.33
28.27
24.13
125 MHz ^{13}C NMR (C_6D_6, 333 K) of **25**
f1 (ppm)


7.62
7.61
7.43
7.41
7.37
7.37
7.36
7.35
7.35
7.34
7.34
7.33
7.32
7.31
7.30
7.30
7.28
5.07
4.04
3.46
3.44
3.34
3.13
3.11
3.10
3.09
3.08
2.92
2.91
2.88
2.87
2.36
2.36
2.35
2.35
2.34
1.91
1.35
F3C
O
O
N
N
N
O
O
500 MHz 1H NMR (DMSO, 353 K) of S9
2.00
6.11
1.67
0.62
8.37
9.12
1.51
8.03
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500

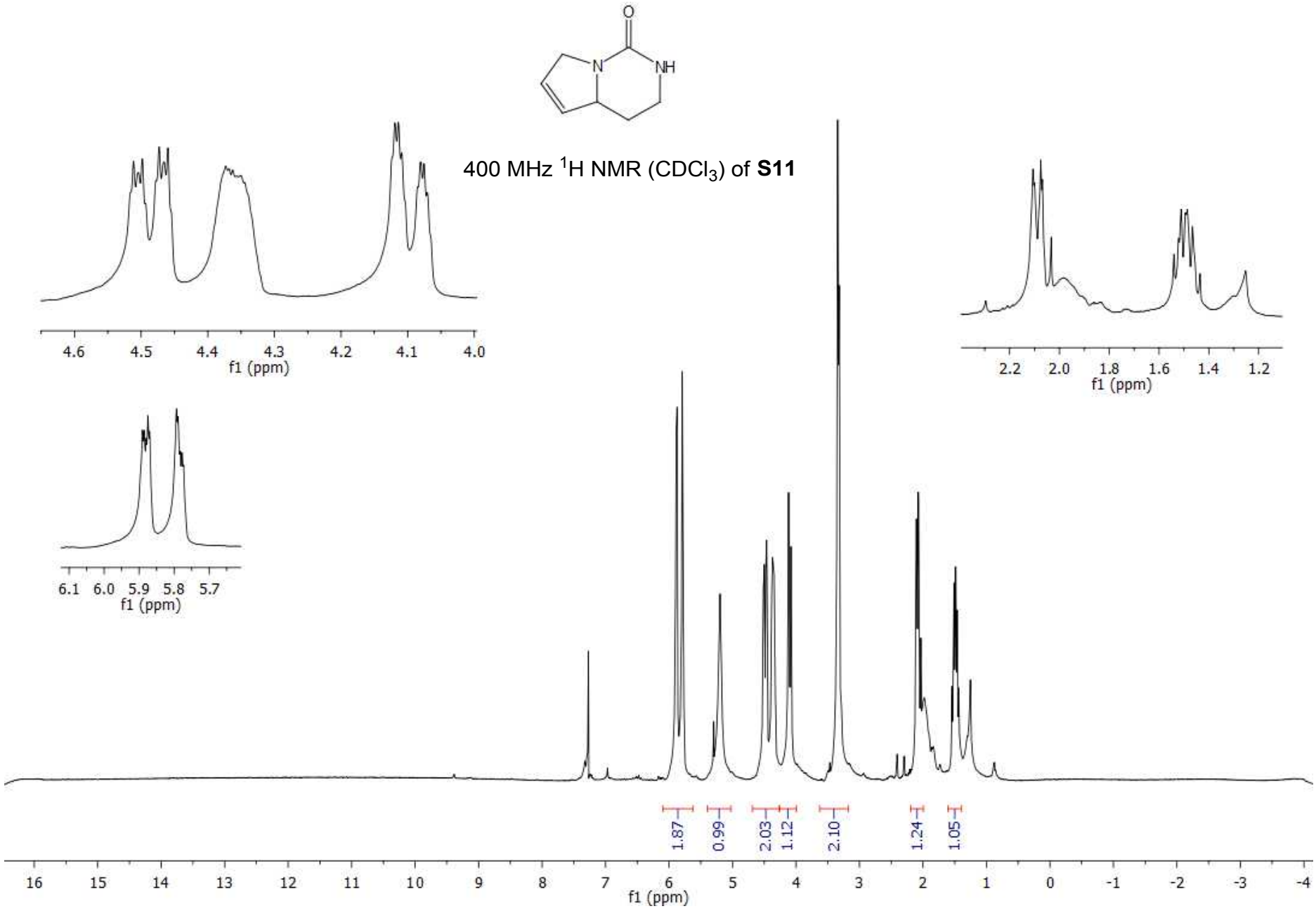


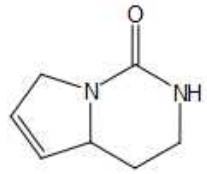
125 MHz ^{13}C NMR (DMSO, 353 K) of **S9**


8.401
8.396
7.690
7.676
7.361
7.274
5.095
4.063
3.541
3.531
3.530
3.403
3.195
3.148
2.955
2.848
2.378
2.294
1.953
1.950
1.414
500 MHz ^{1}H NMR (MeOD, 333 K) of **S6**
2.400
2.350
2.300
ppm (f1)
5000
0
2.06
0.98
6.17
2.13
1.00
1.03
4.16
1.03
2.01
1.07
4.21
1.91
9.06
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

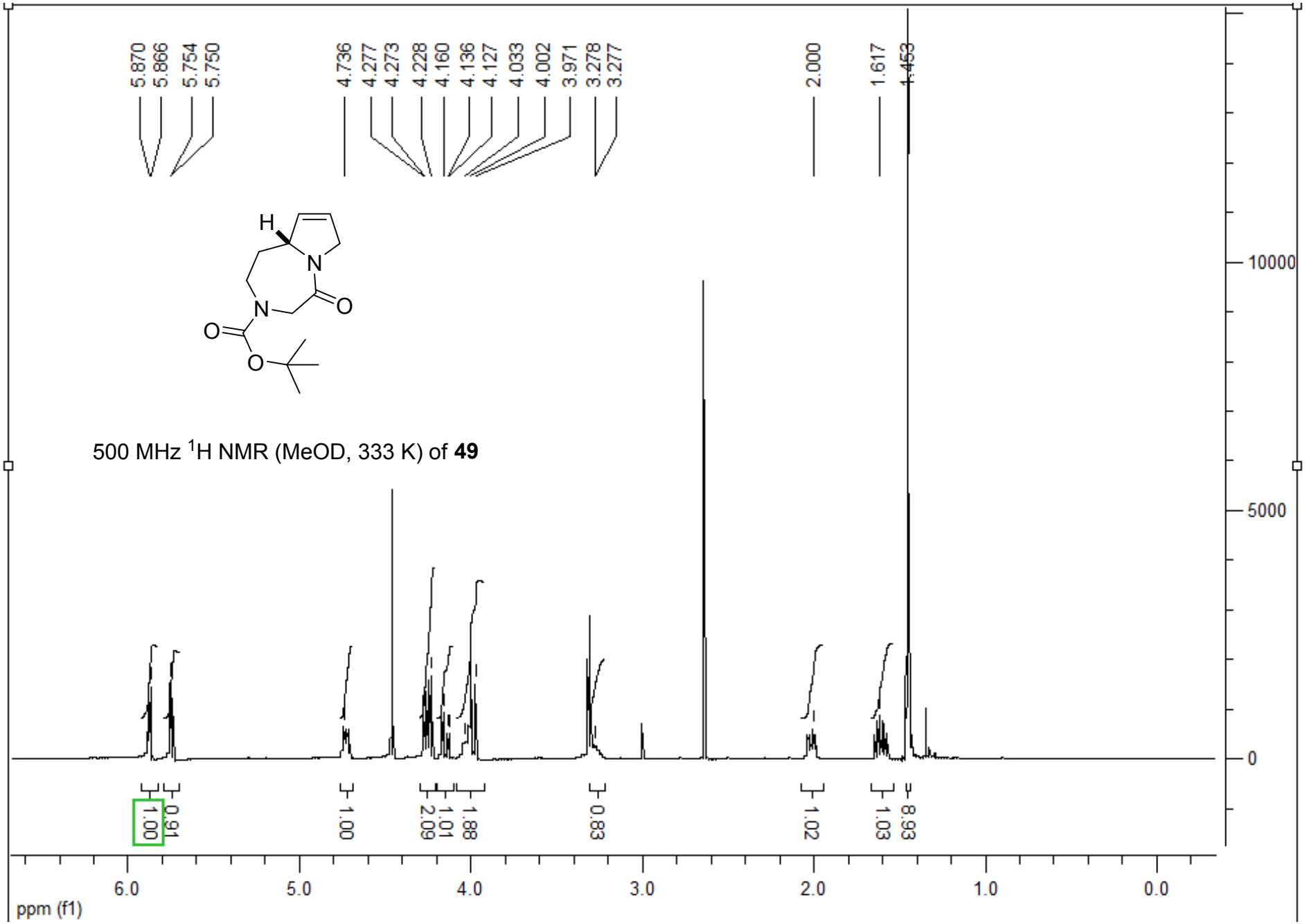


125 MHz ^{13}C NMR (MeOD, 333 K) of **S6**

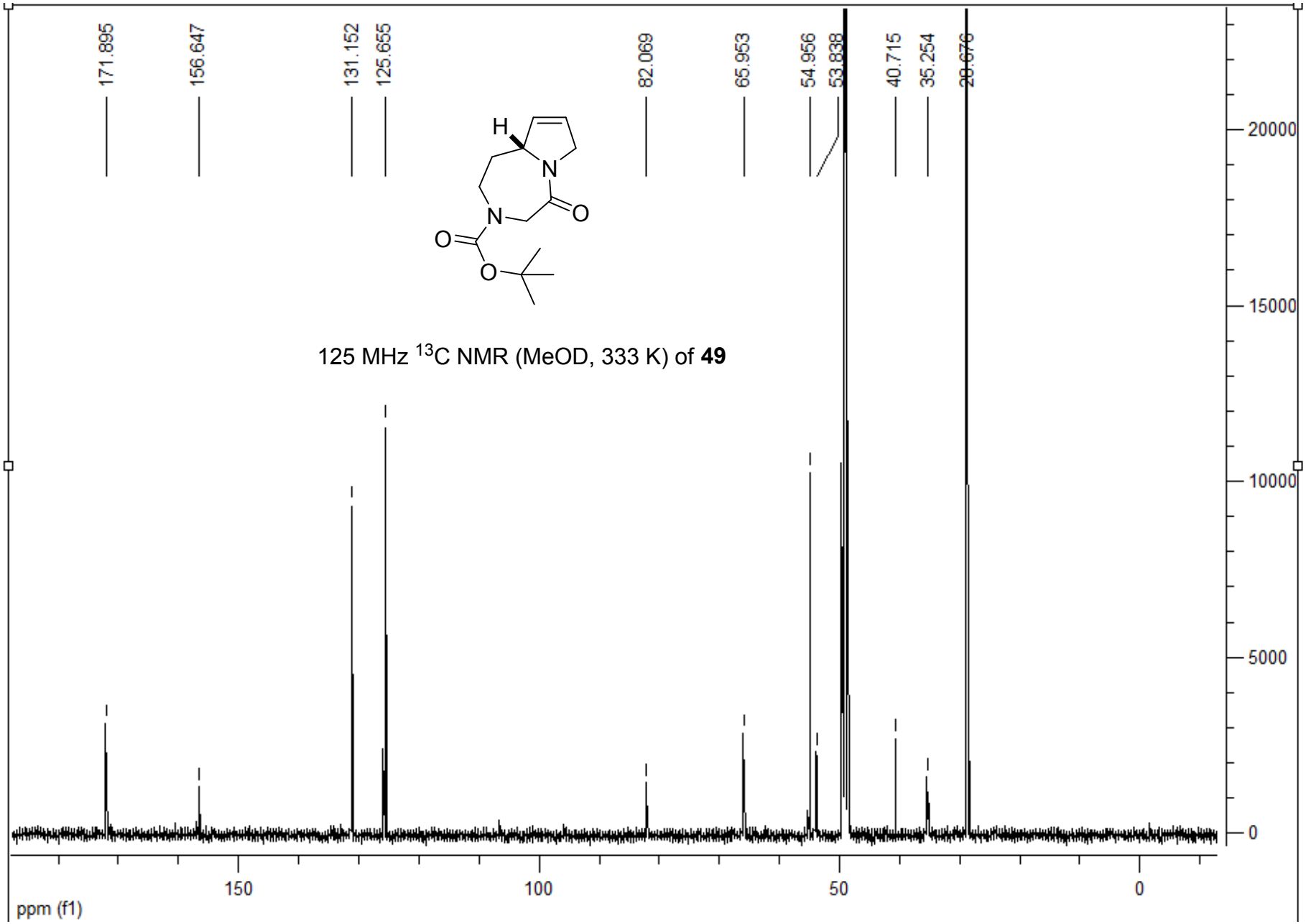

O
N
NH
400 MHz ^{1}H NMR ($CDCl_3$) of **S11**
4.6 4.5 4.4 4.3 4.2 4.1 4.0
f1 (ppm)
2.2 2.0 1.8 1.6 1.4 1.2
f1 (ppm)
6.1 6.0 5.9 5.8 5.7
f1 (ppm)
1.87
0.99
2.03
1.12
2.10
1.24
1.05
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4
f1 (ppm)



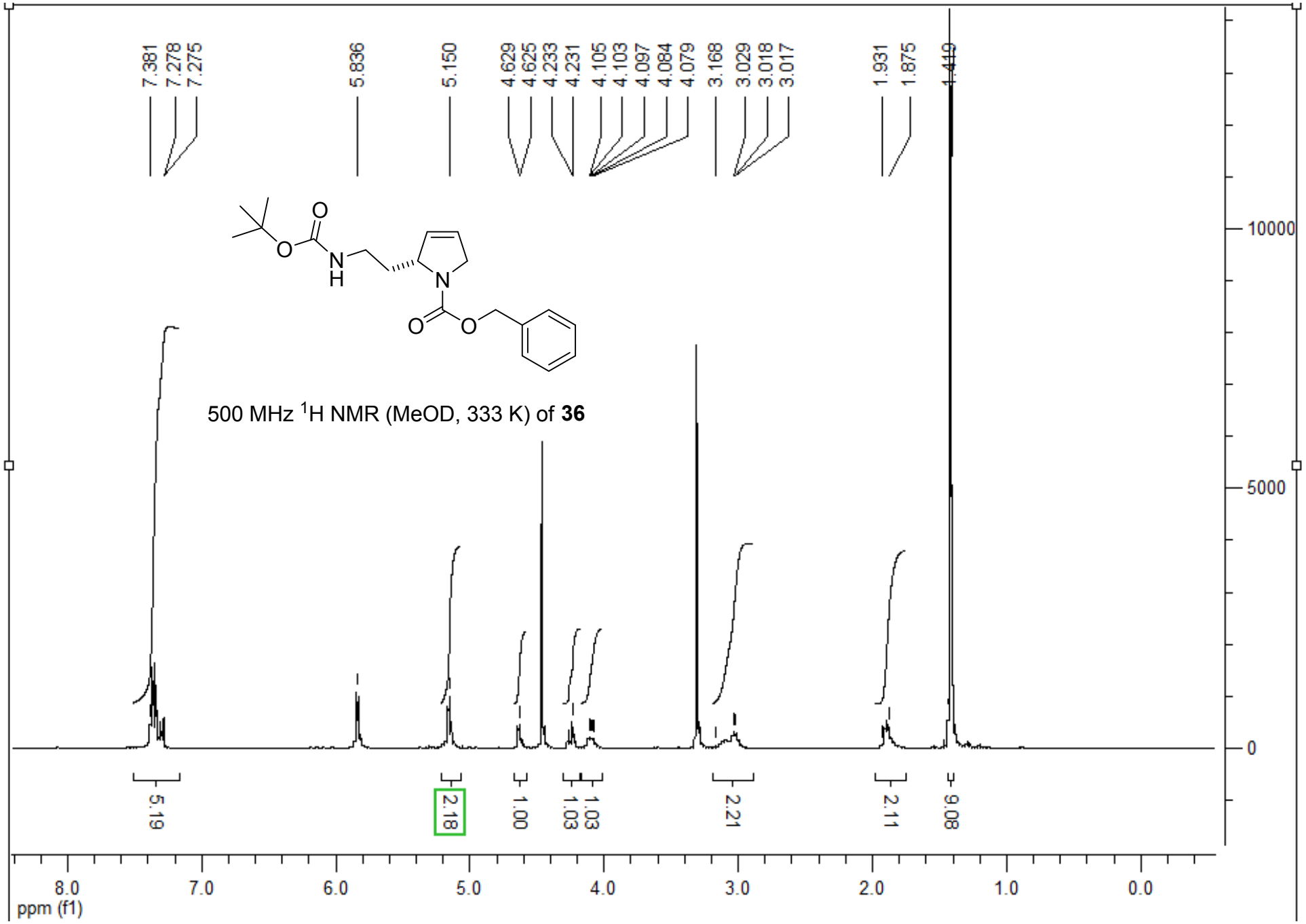
100 MHz ^{13}C NMR ($CDCl_3$) of **S11**



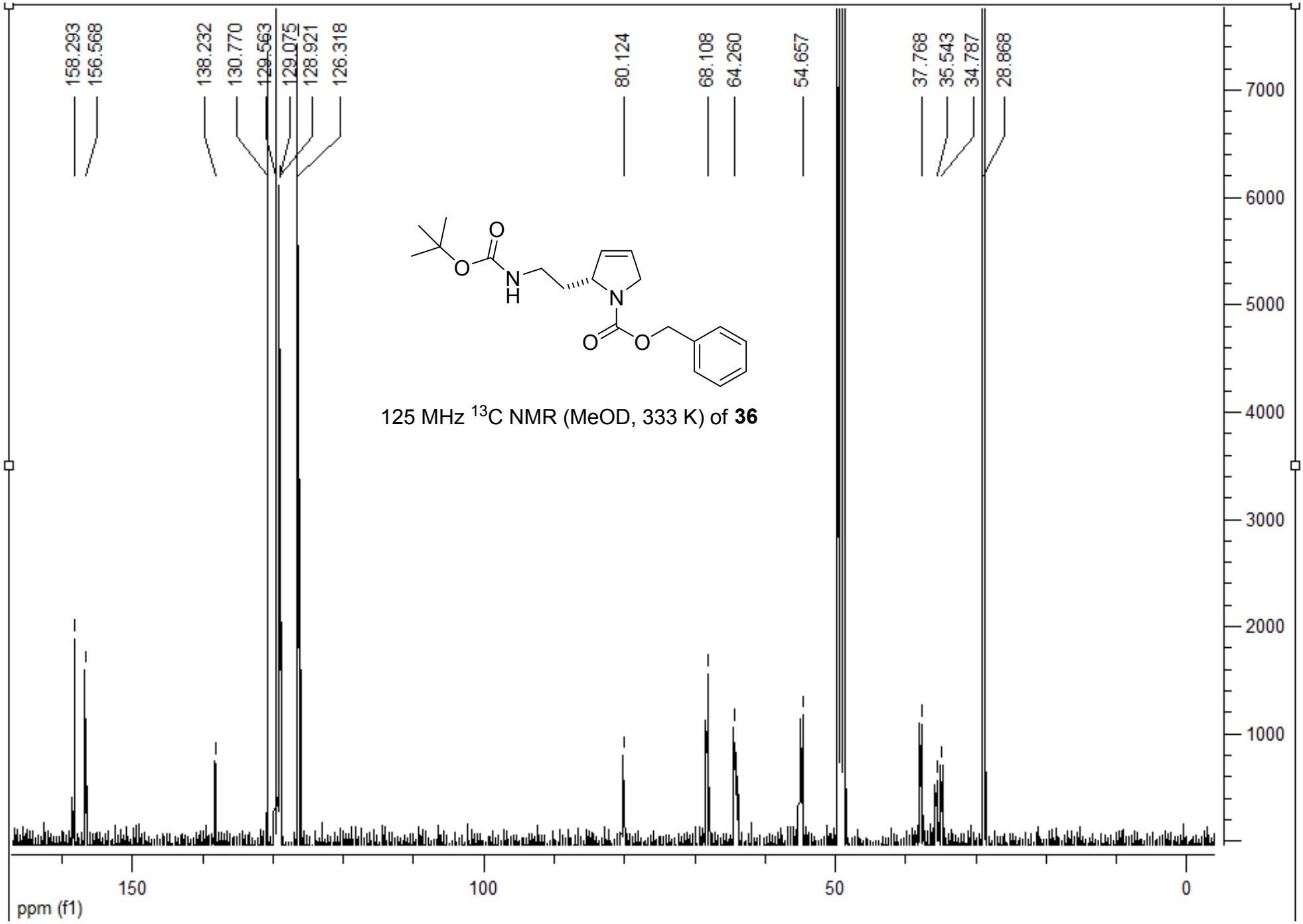
500 MHz ^{1}H NMR (MeOD, 333 K) of **49**



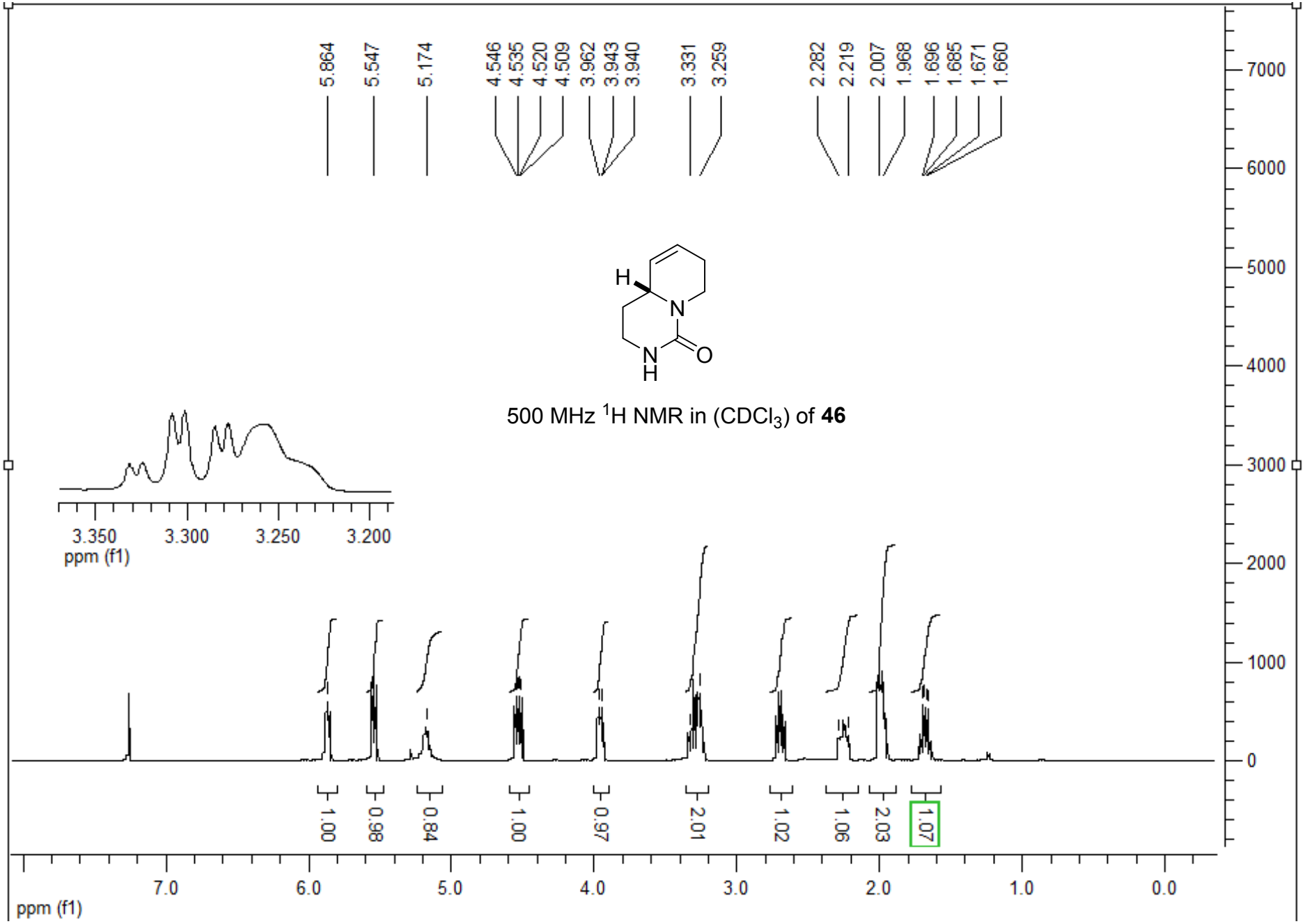
125 MHz ^{13}C NMR (MeOD, 333 K) of **49**



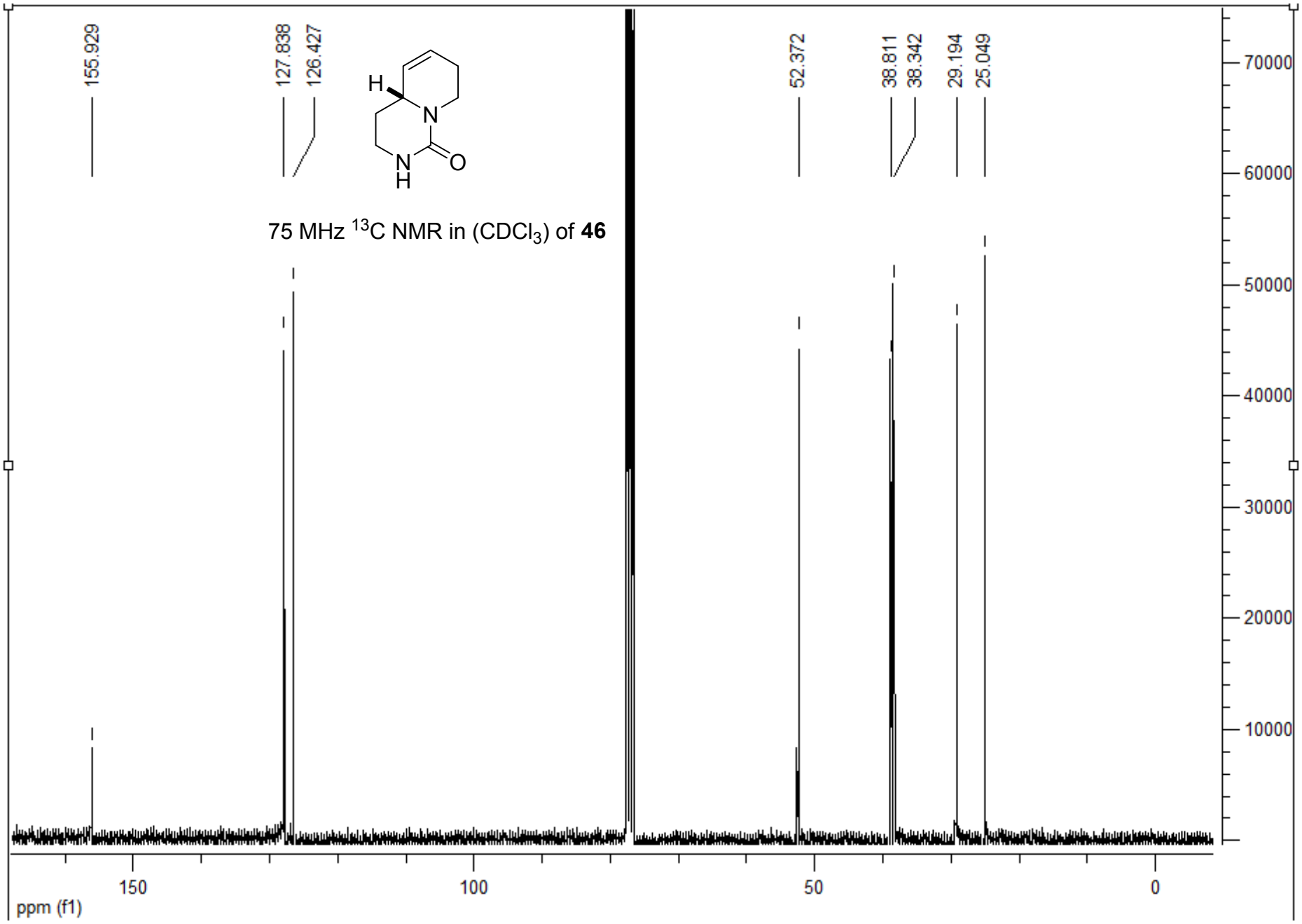
500 MHz ^{1}H NMR (MeOD, 333 K) of **36**

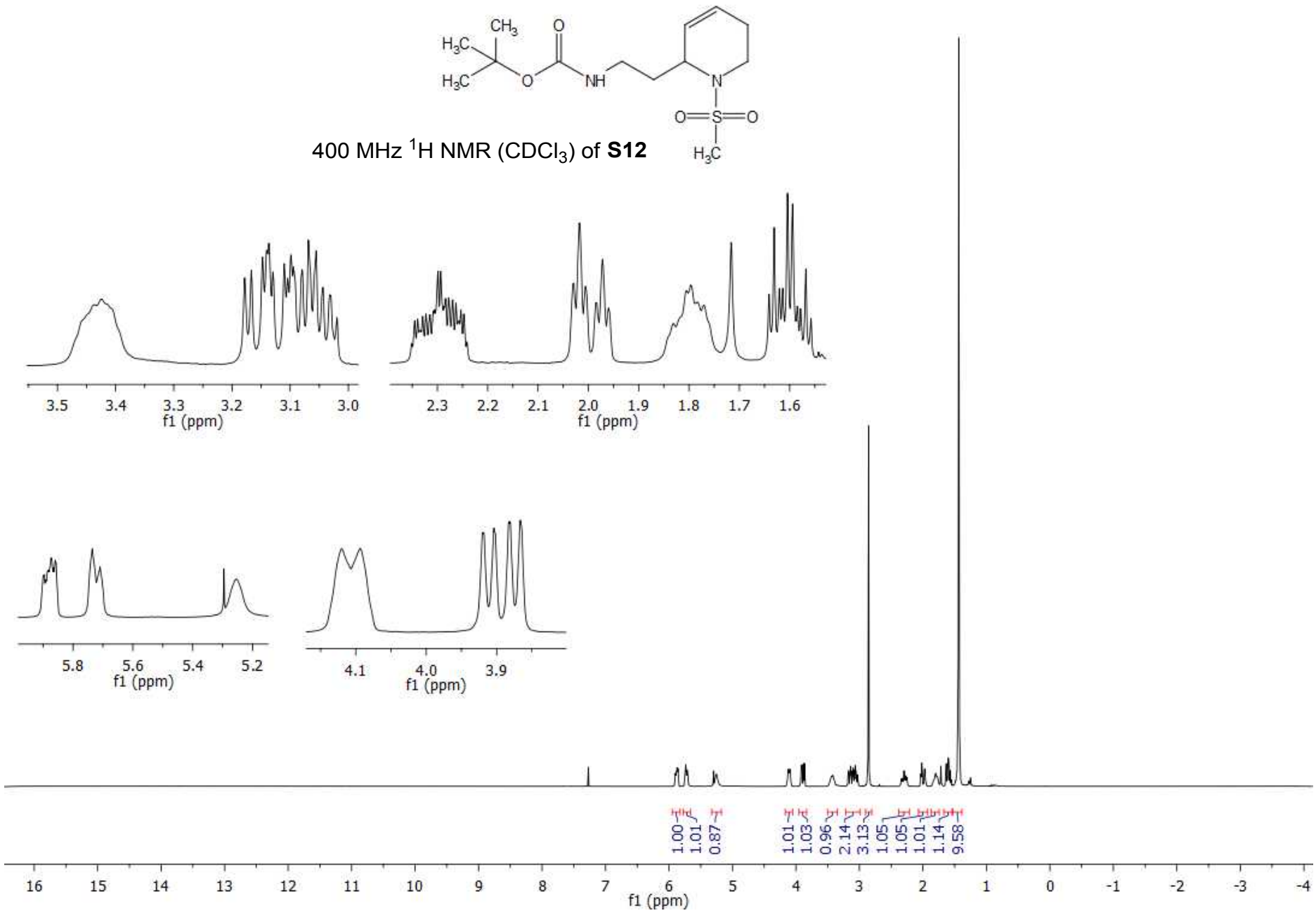


125 MHz ^{13}C NMR (MeOD, 333 K) of **36**

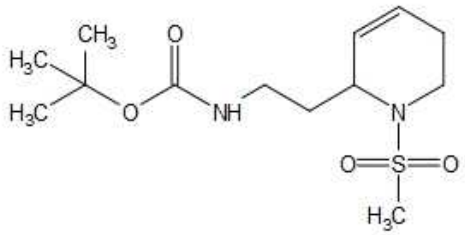


500 MHz ^{1}H NMR in ($CDCl_3$) of **46**

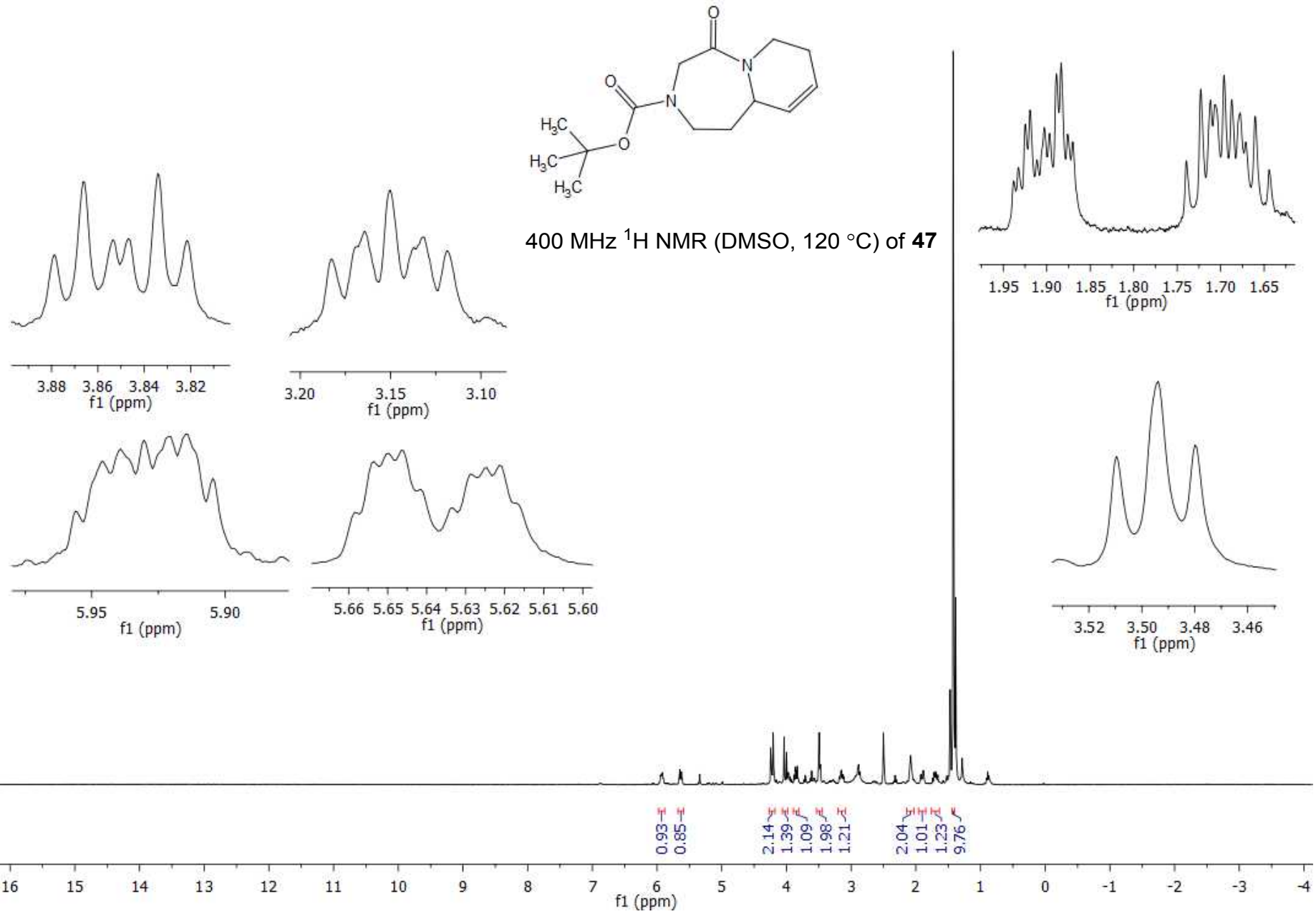

155.929
127.838
126.427
52.372
38.811
38.342
29.194
25.049
H
N
N
H
O
75 MHz ^{13}C NMR in ($CDCl_3$) of **46**
70000
60000
50000
40000
30000
20000
10000
150
100
50
0
ppm (f1)



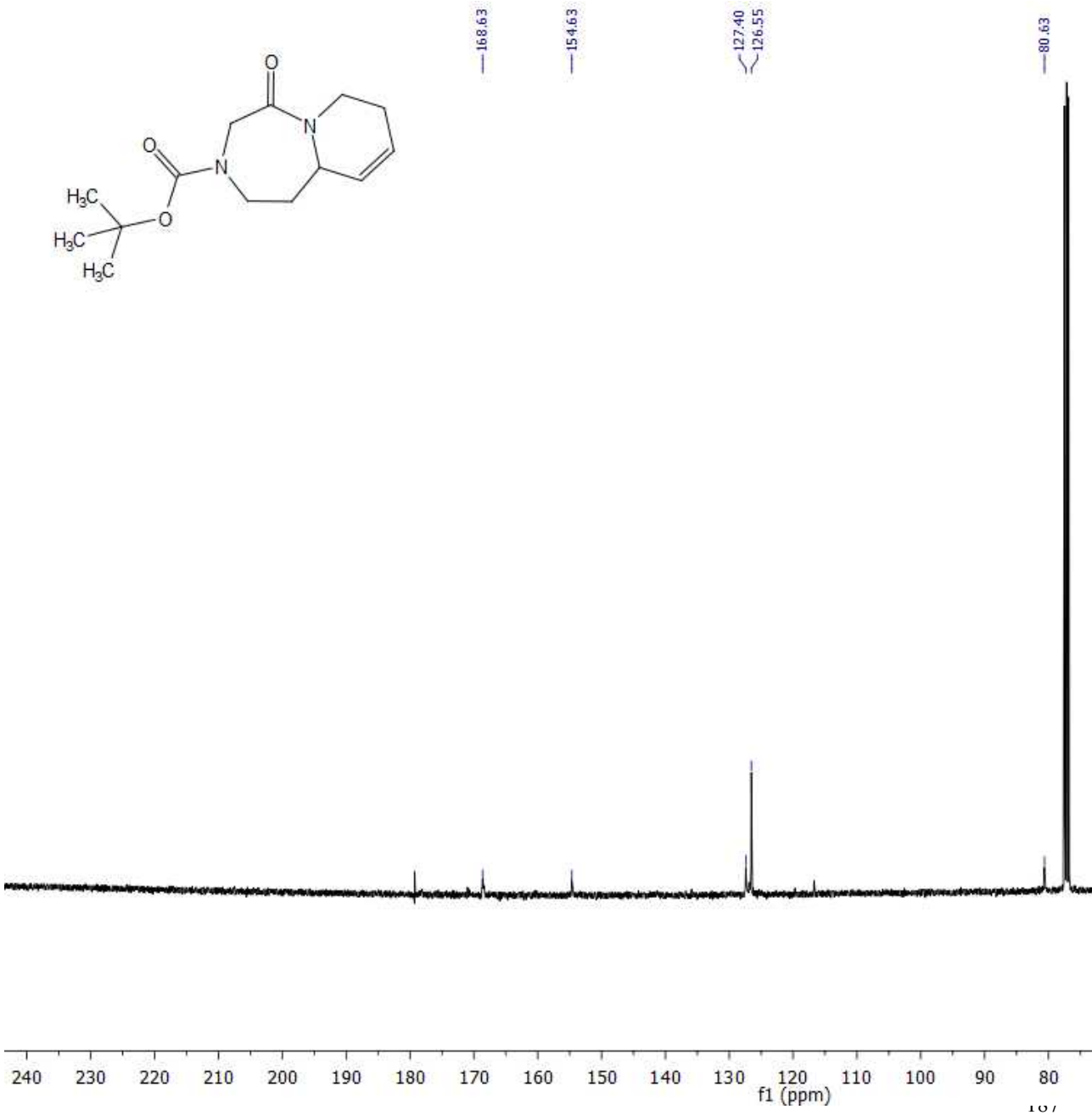
400 MHz ^{1}H NMR ($CDCl_3$) of **S12**

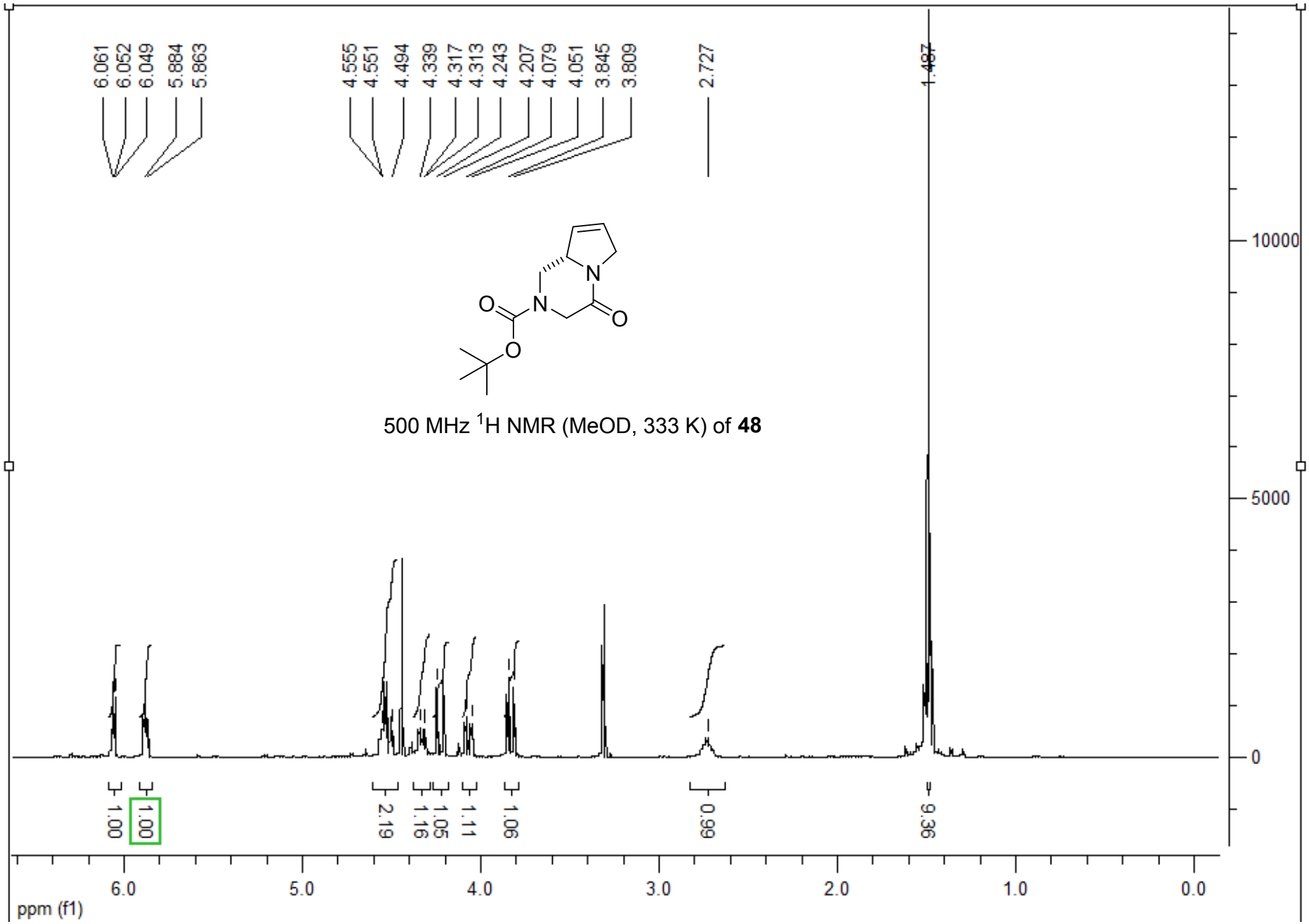


100 MHz ^{13}C NMR ($CDCl_3$) of **S12**

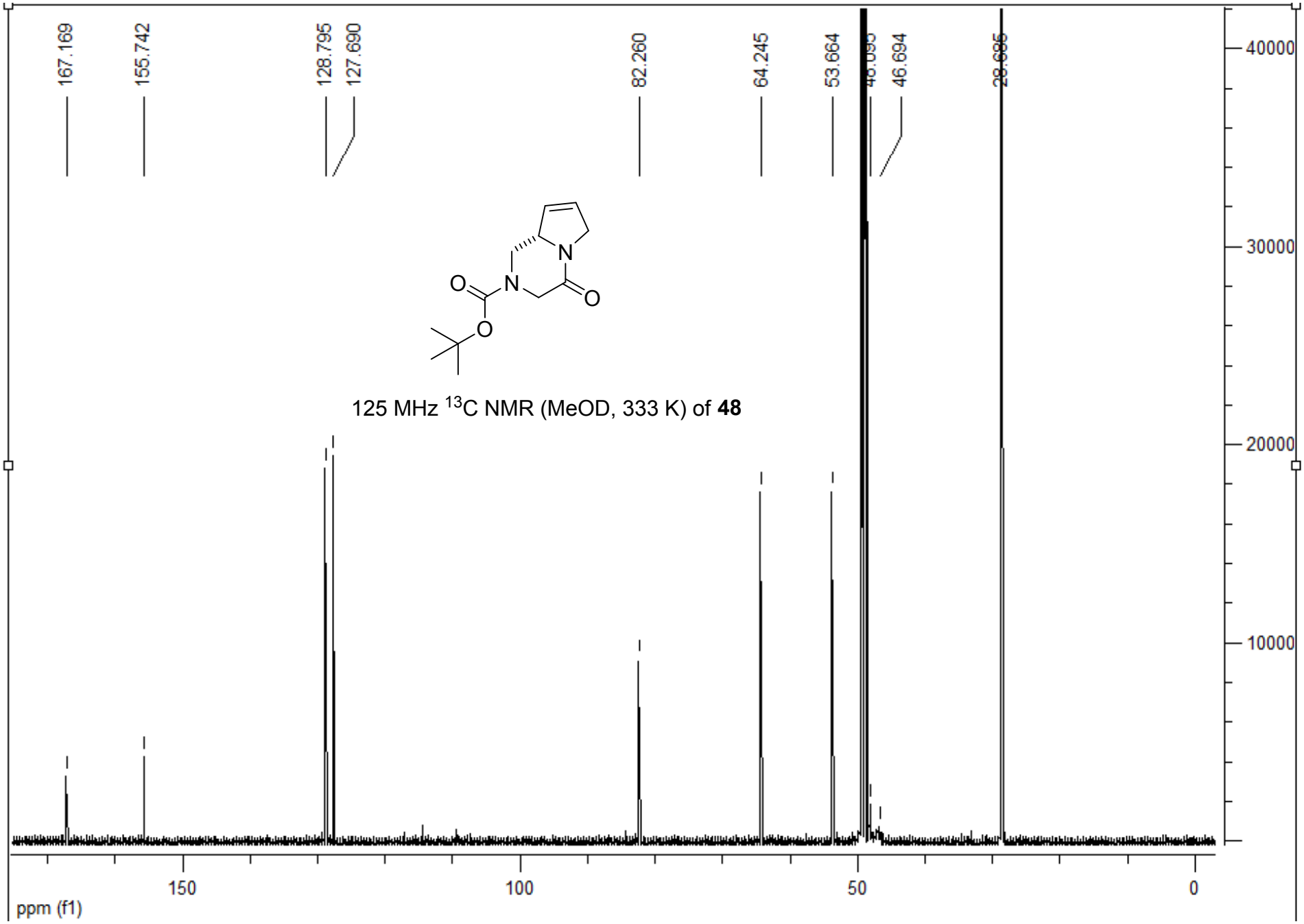

O
N
O
N
O
H3C
H3C
H3C
400 MHz 1H NMR (DMSO, 120 °C) of 47
3.88 3.86 3.84 3.82
f1 (ppm)
3.20 3.15 3.10
f1 (ppm)
1.95 1.90 1.85 1.80 1.75 1.70 1.65
f1 (ppm)
5.95 5.90
f1 (ppm)
5.66 5.65 5.64 5.63 5.62 5.61 5.60
f1 (ppm)
3.52 3.50 3.48 3.46
f1 (ppm)
0.93
0.85
2.14
1.39
1.09
1.98
1.21
2.04
1.01
1.23
9.76
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4
f1 (ppm)

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



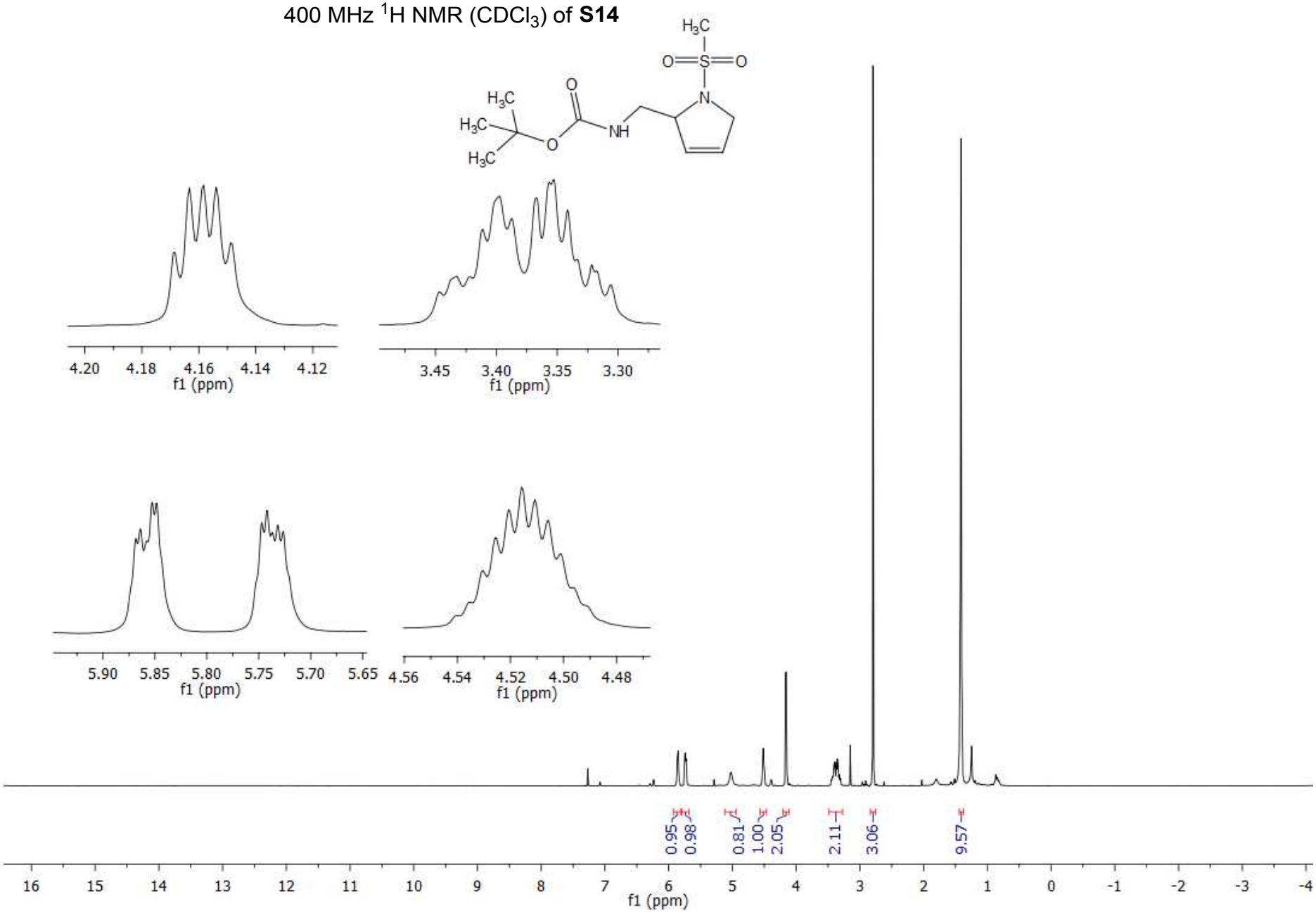


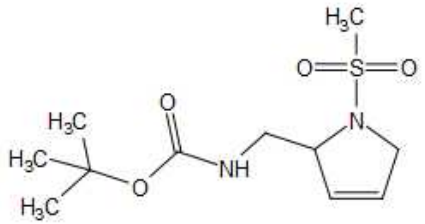
500 MHz ^{1}H NMR (MeOD, 333 K) of **48**



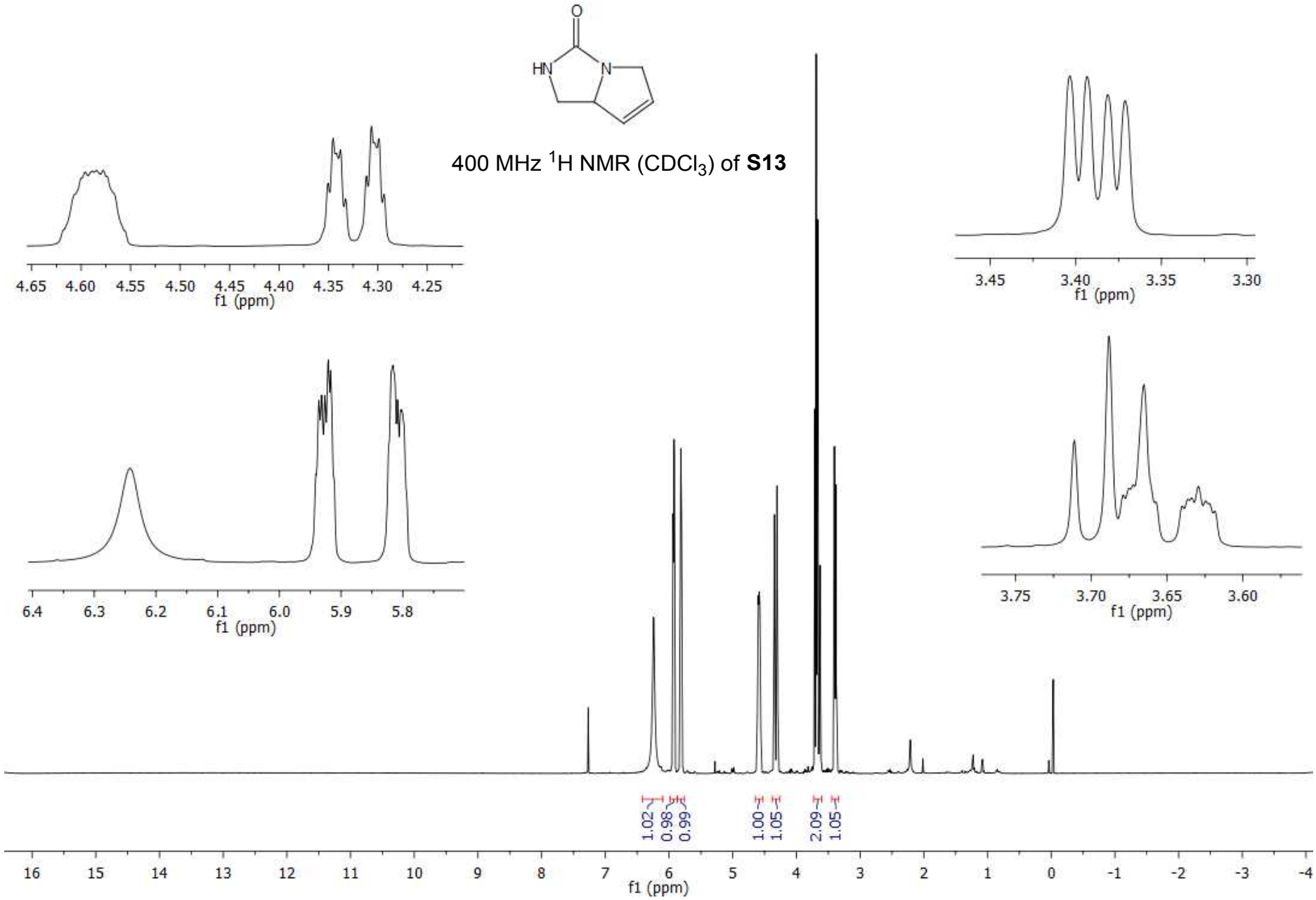
125 MHz ^{13}C NMR (MeOD, 333 K) of **48**

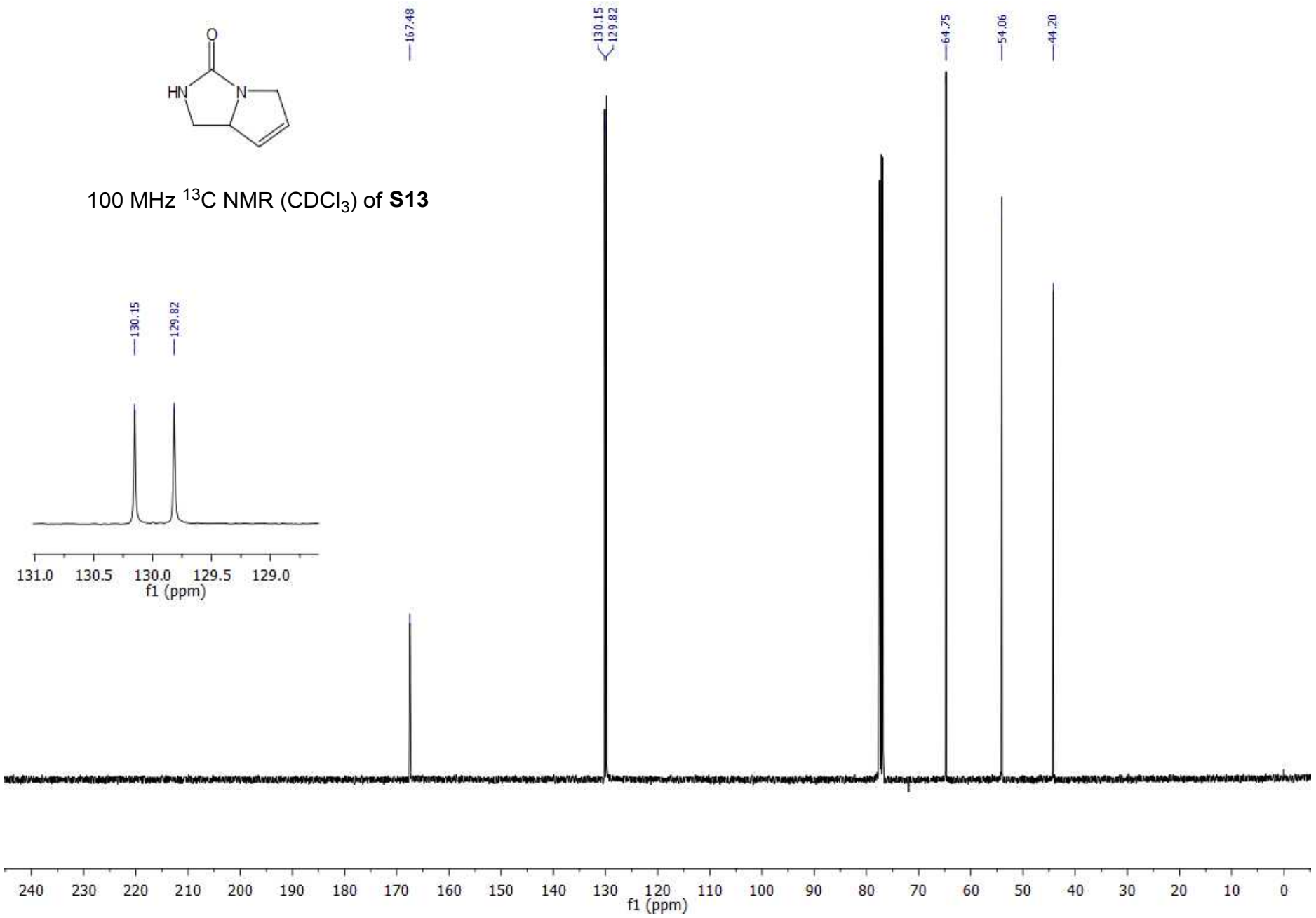
400 MHz ^{1}H NMR ($CDCl_3$) of **S14**



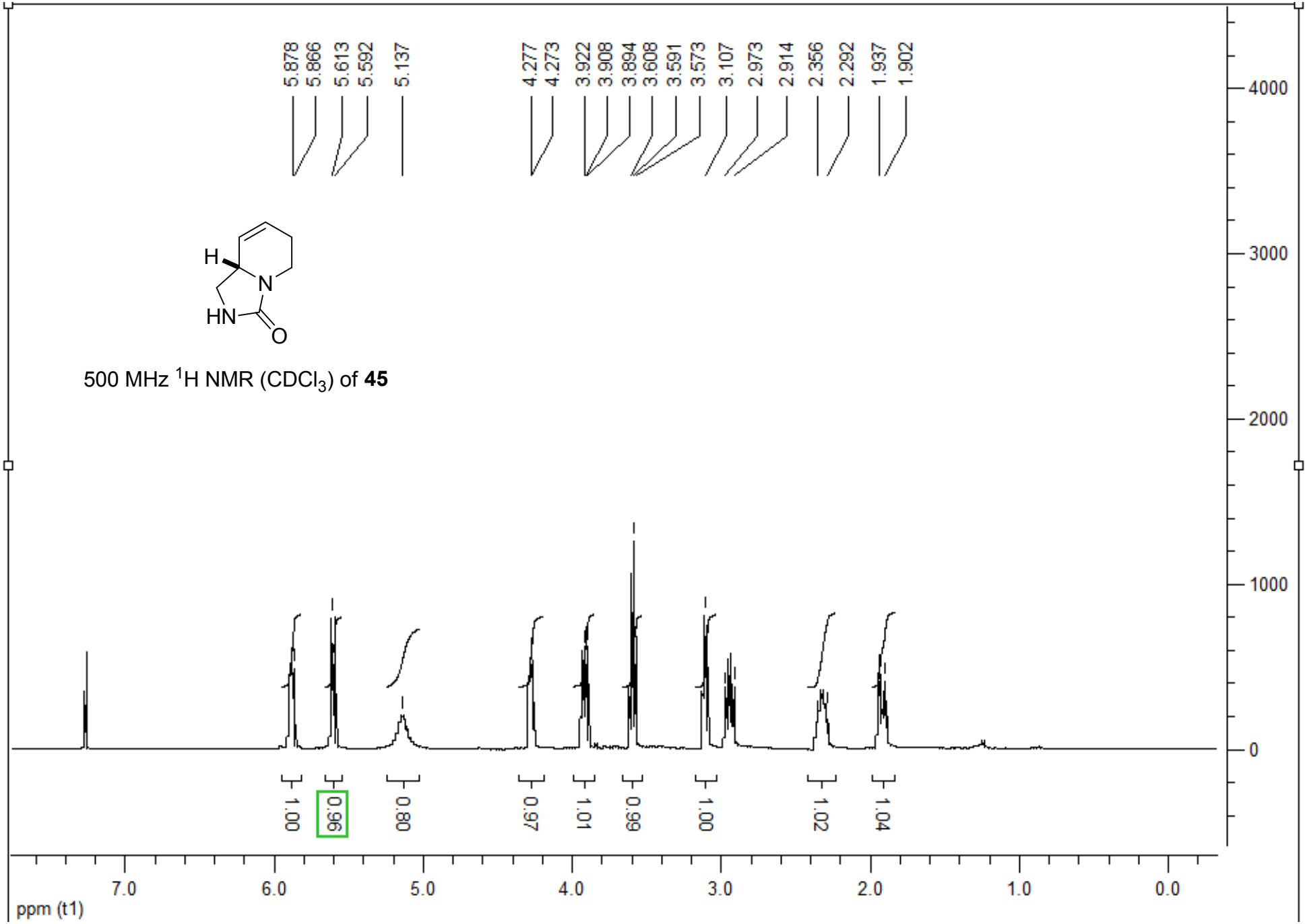


100 MHz ^{13}C NMR ($CDCl_3$) of **S14**

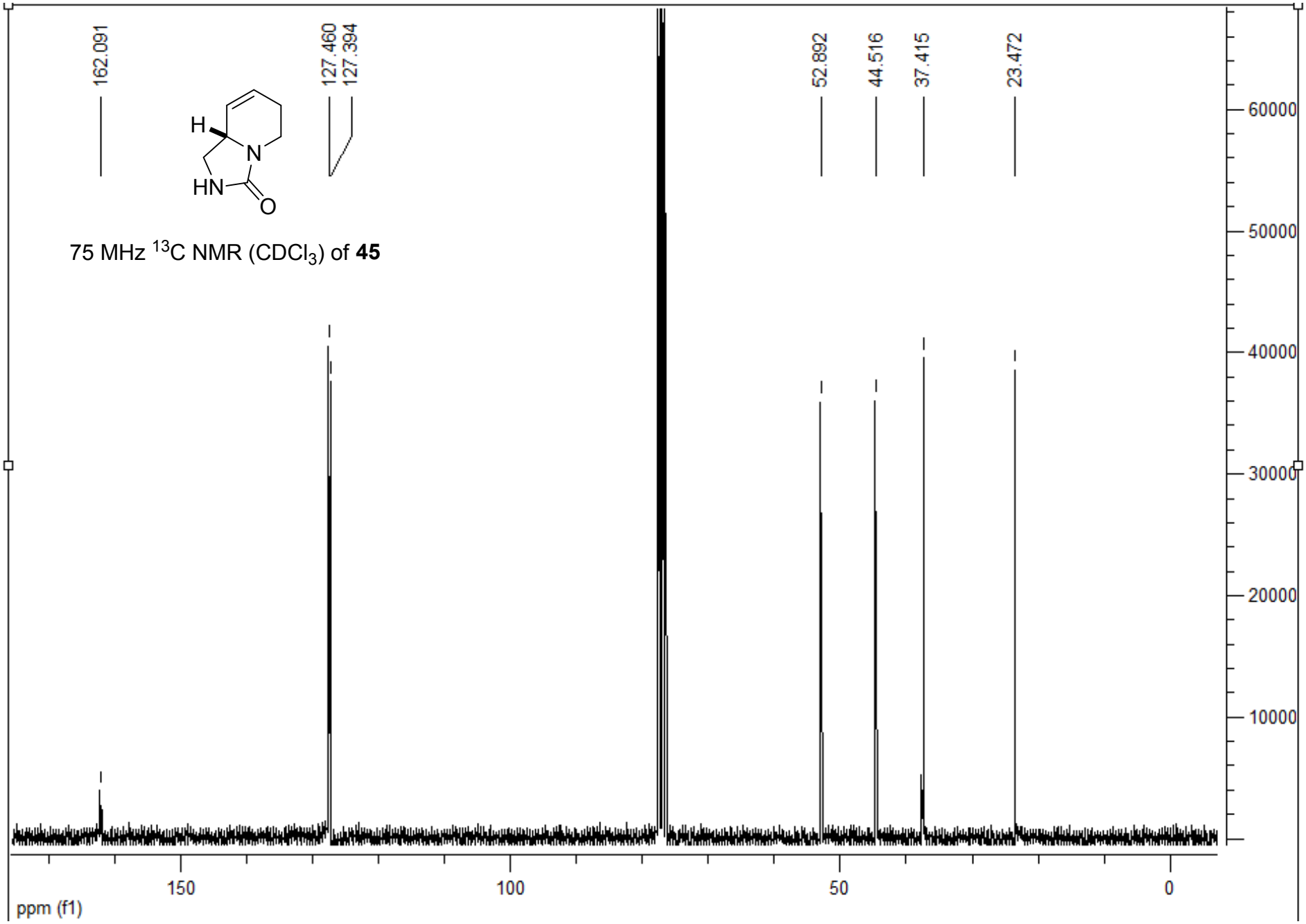

O
HN
N
400 MHz ^{1}H NMR ($CDCl_3$) of **S13**
4.65 4.60 4.55 4.50 4.45 4.40 4.35 4.30 4.25
f1 (ppm)
3.45 3.40 3.35 3.30
f1 (ppm)
6.4 6.3 6.2 6.1 6.0 5.9 5.8
f1 (ppm)
3.75 3.70 3.65 3.60
f1 (ppm)
1.02 0.98 0.99 1.00 1.05 2.09 1.05
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4
f1 (ppm)



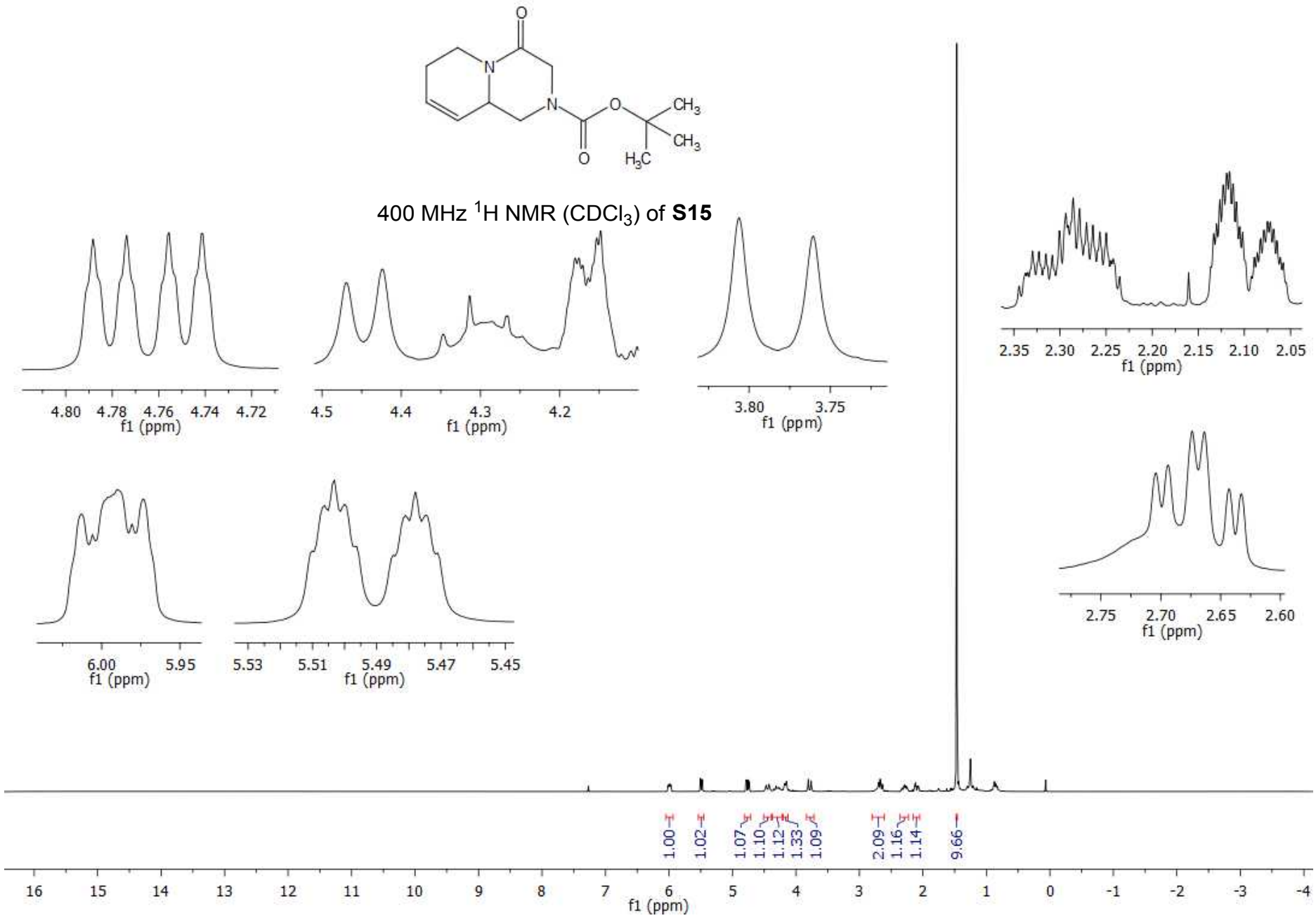
100 MHz ^{13}C NMR ($CDCl_3$) of **S13**

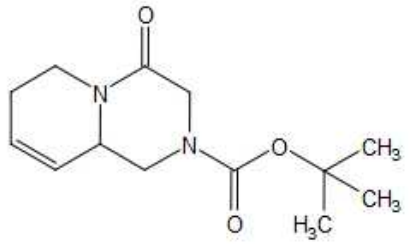


500 MHz ^{1}H NMR ($CDCl_3$) of **45**



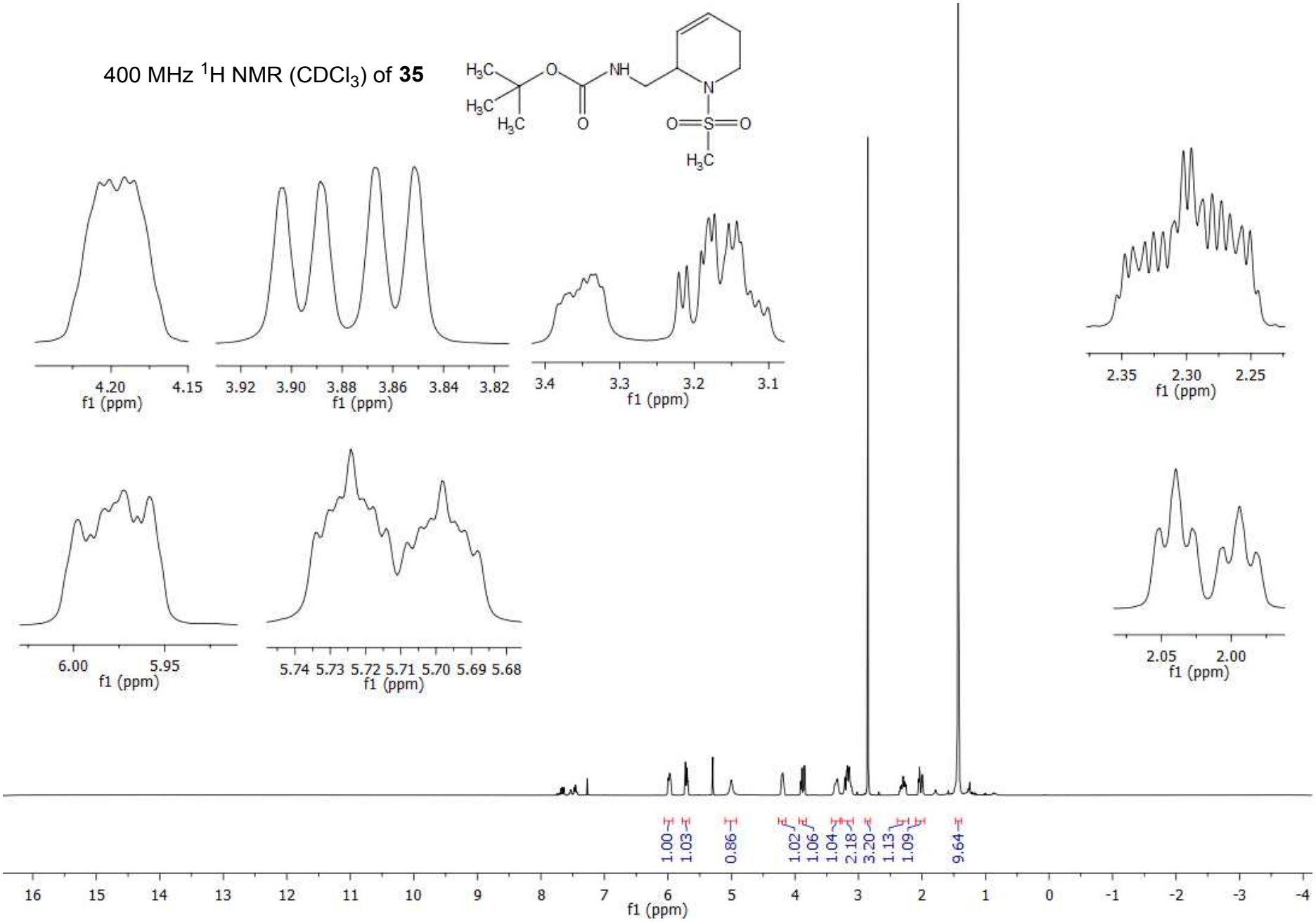
75 MHz ^{13}C NMR ($CDCl_3$) of **45**

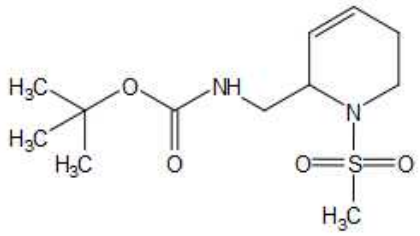

O
N
N
O
O
CH3
CH3
H3C
400 MHz 1H NMR (CDCl3) of S15
4.80 4.78 4.76 4.74 4.72
f1 (ppm)
4.5 4.4 4.3 4.2
f1 (ppm)
3.80 3.75
f1 (ppm)
2.35 2.30 2.25 2.20 2.15 2.10 2.05
f1 (ppm)
2.75 2.70 2.65 2.60
f1 (ppm)
6.00 5.95
f1 (ppm)
5.53 5.51 5.49 5.47 5.45
f1 (ppm)
1.00 1.02 1.07 1.10 1.12 1.33 1.09 2.09 1.16 1.14 9.66
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4
f1 (ppm)



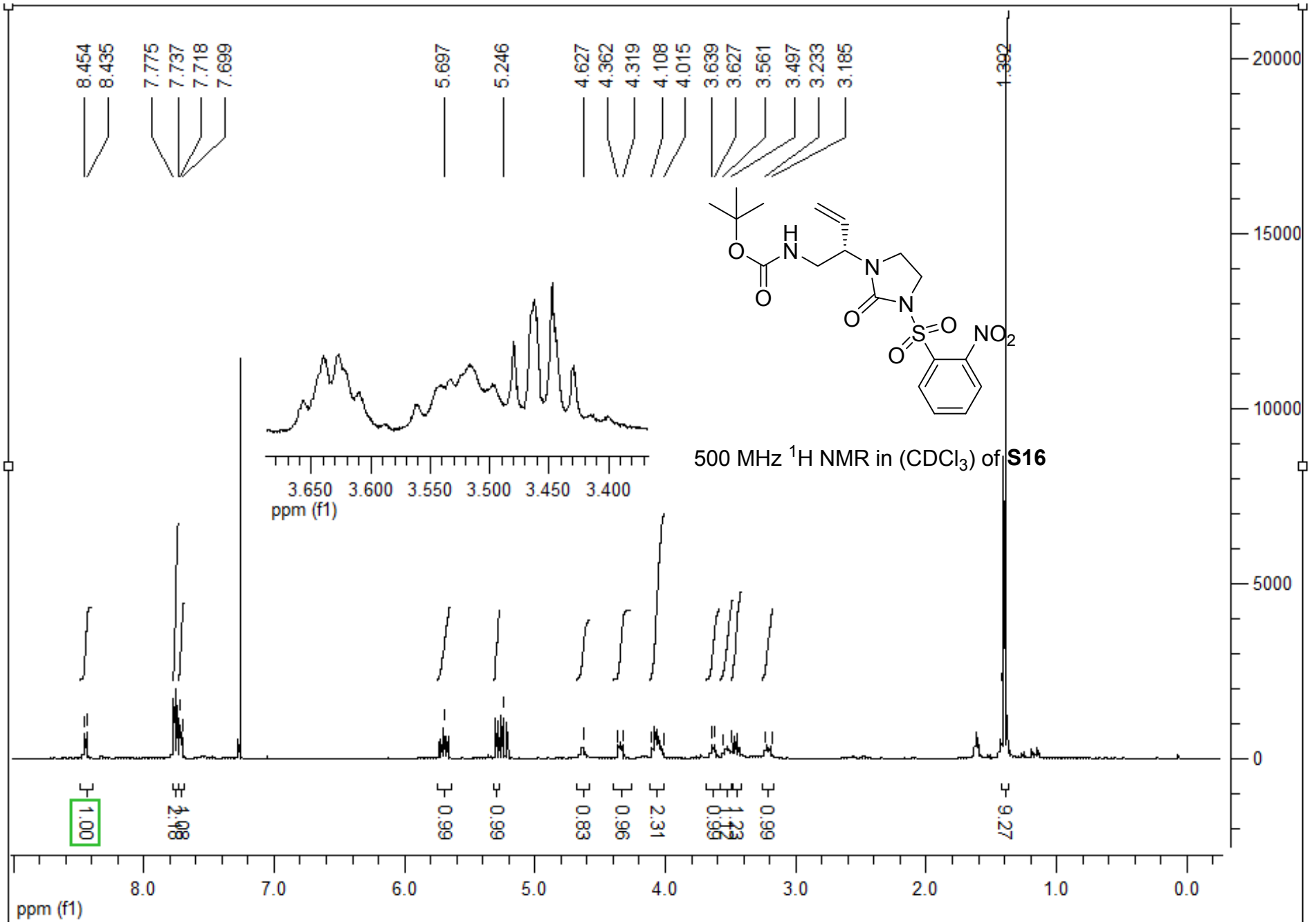
100 MHz ^{13}C NMR ($CDCl_3$) of **S15**

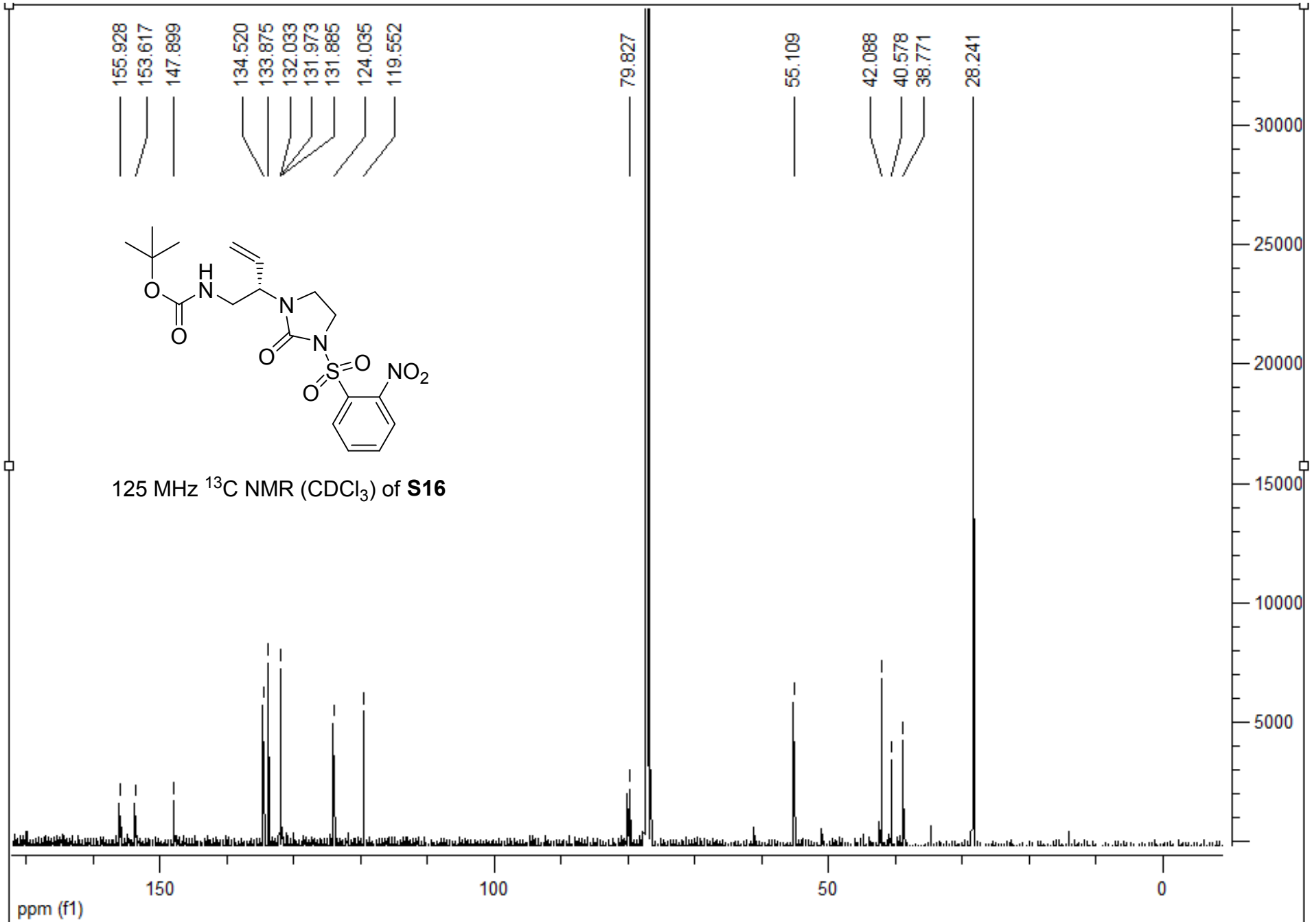
400 MHz ^{1}H NMR ($CDCl_3$) of **35**



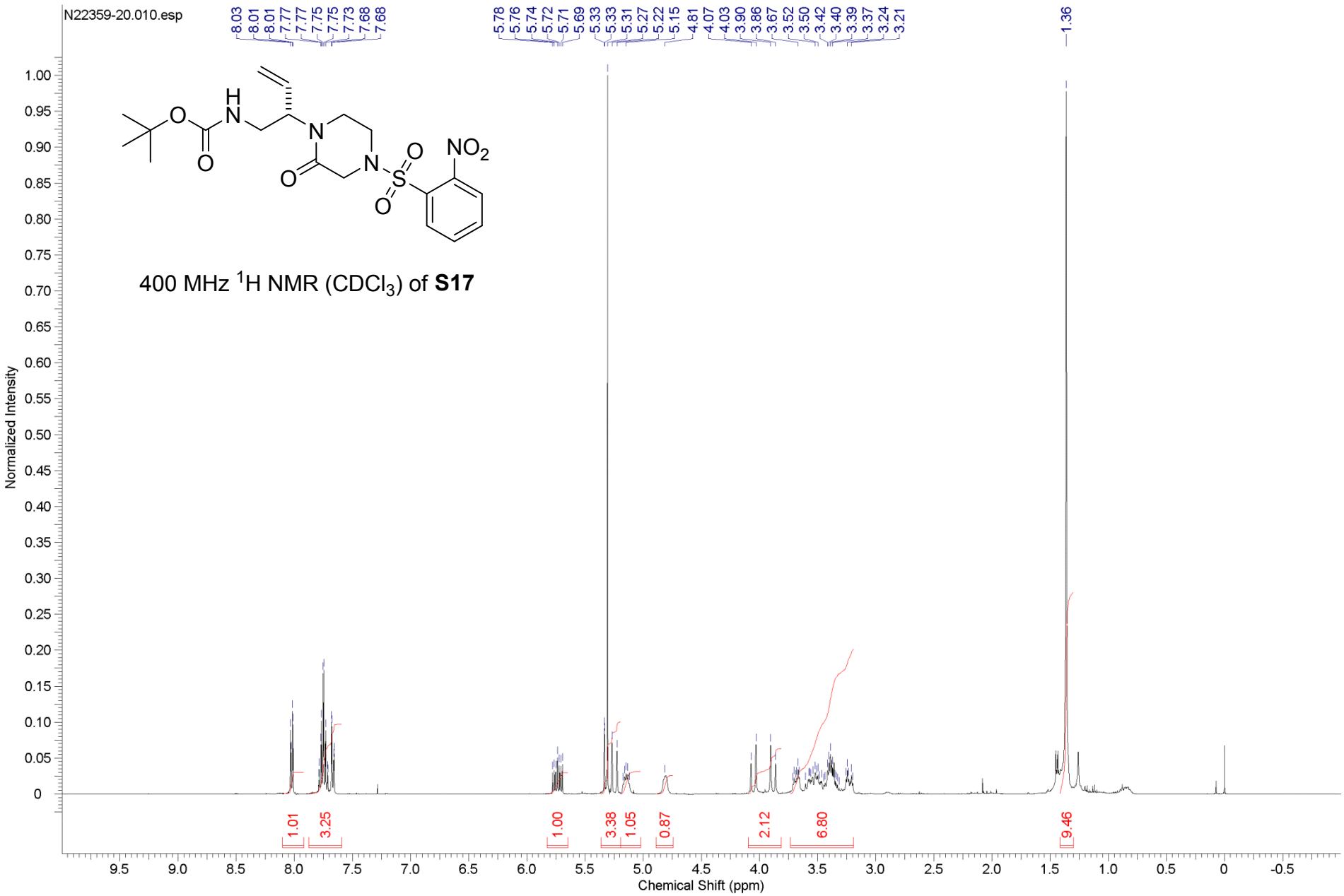


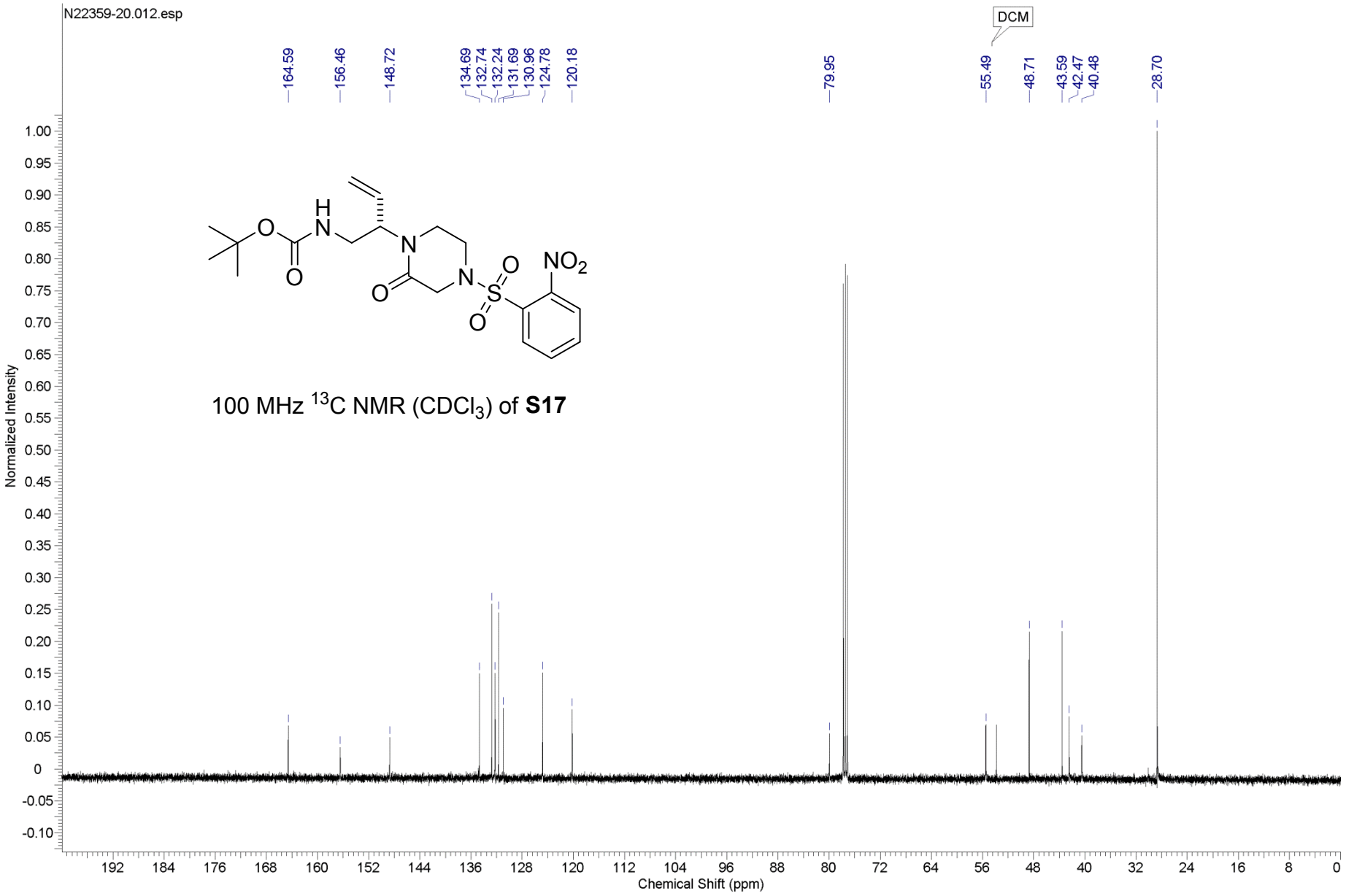
100 MHz ^{13}C NMR ($CDCl_3$) of **35**


8.454
8.435
7.775
7.737
7.718
7.699
5.697
5.246
4.627
4.362
4.319
4.108
4.015
3.639
3.627
3.561
3.497
3.233
3.185
1.392
20000
15000
10000
5000
0
3.650 3.600 3.550 3.500 3.450 3.400
ppm (f1)
500 MHz ^{1}H NMR in ($CDCl_3$) of **S16**
1.00
2.08
0.99
0.99
0.83
0.96
2.31
0.99
1.22
0.99
9.27
8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
ppm (f1)

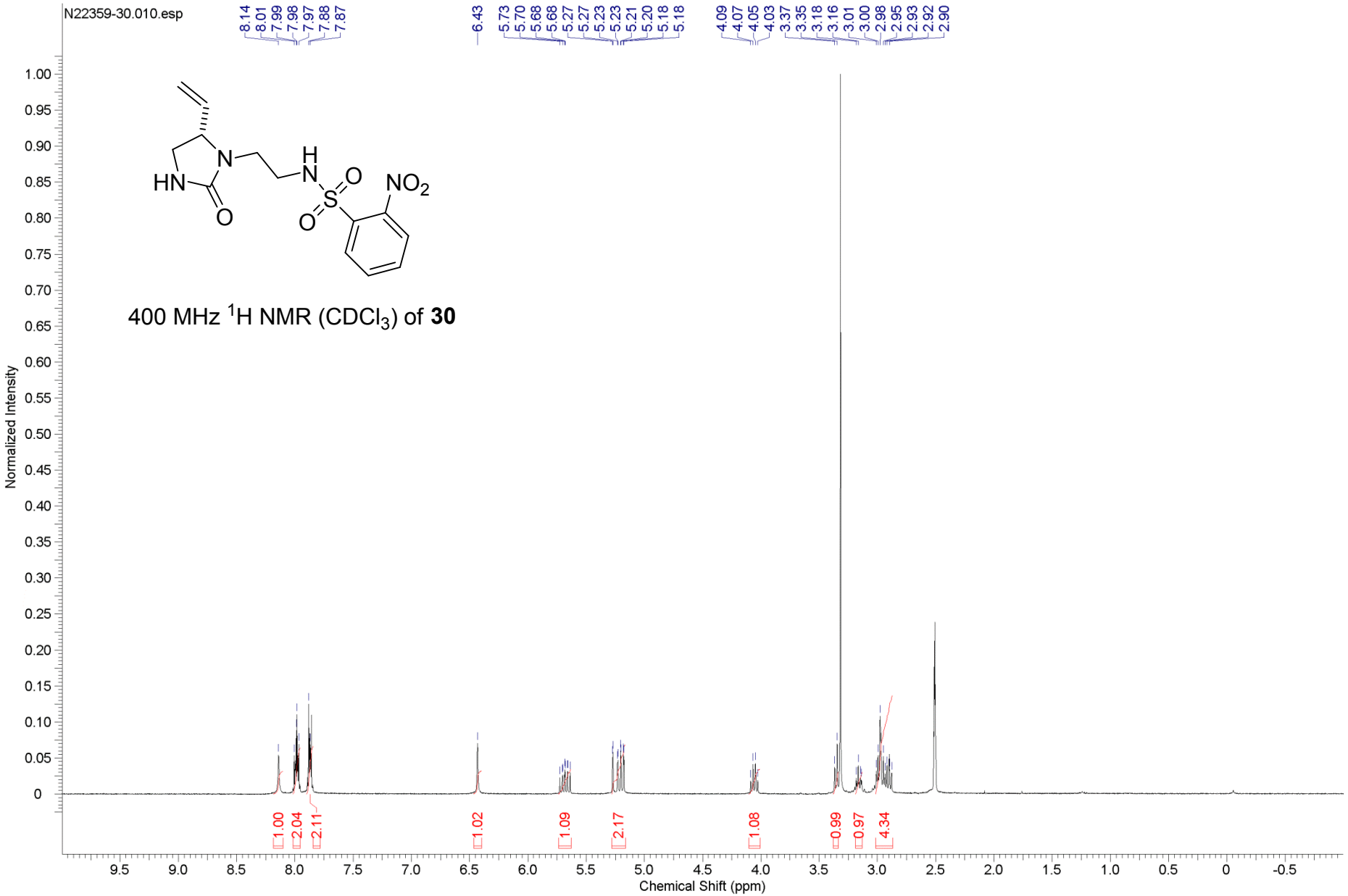


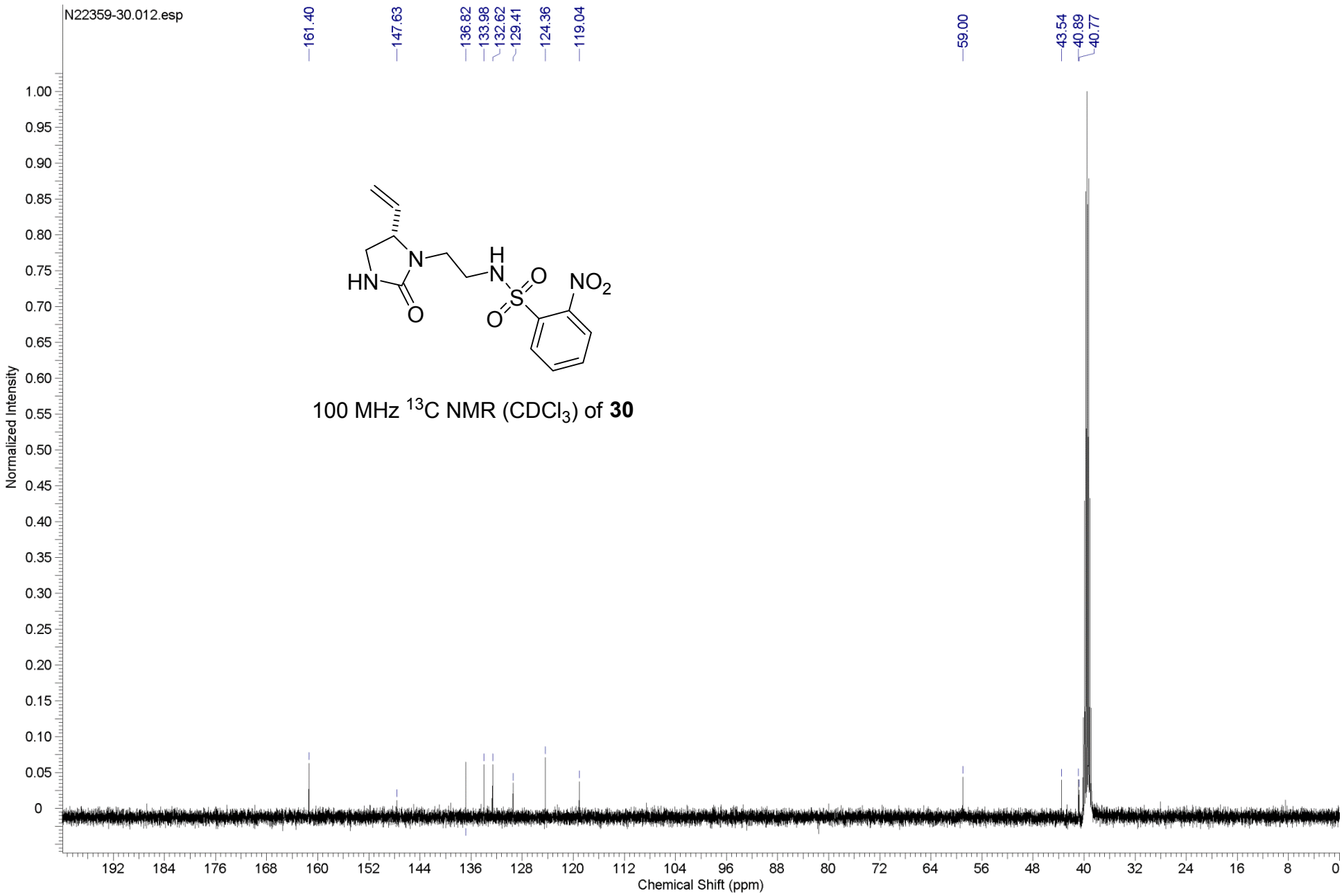
125 MHz ^{13}C NMR ($CDCl_3$) of **S16**


N22359-20.010.esp
8.03 8.01 8.01 7.77 7.77 7.75 7.75 7.73 7.68 7.68
5.78 5.76 5.74 5.72 5.71 5.69 5.33 5.33 5.31 5.27 5.22 5.15 4.81 4.07 4.03 3.90 3.86 3.67 3.52 3.50 3.42 3.40 3.39 3.37 3.24 3.21
1.36
O
H
N
O
N
O
N
S
O
O
NO2
400 MHz 1H NMR (CDCl3) of S17
Normalized Intensity
Chemical Shift (ppm)
1.01 3.25 1.00 3.38 1.05 0.87 2.12 6.80 9.46

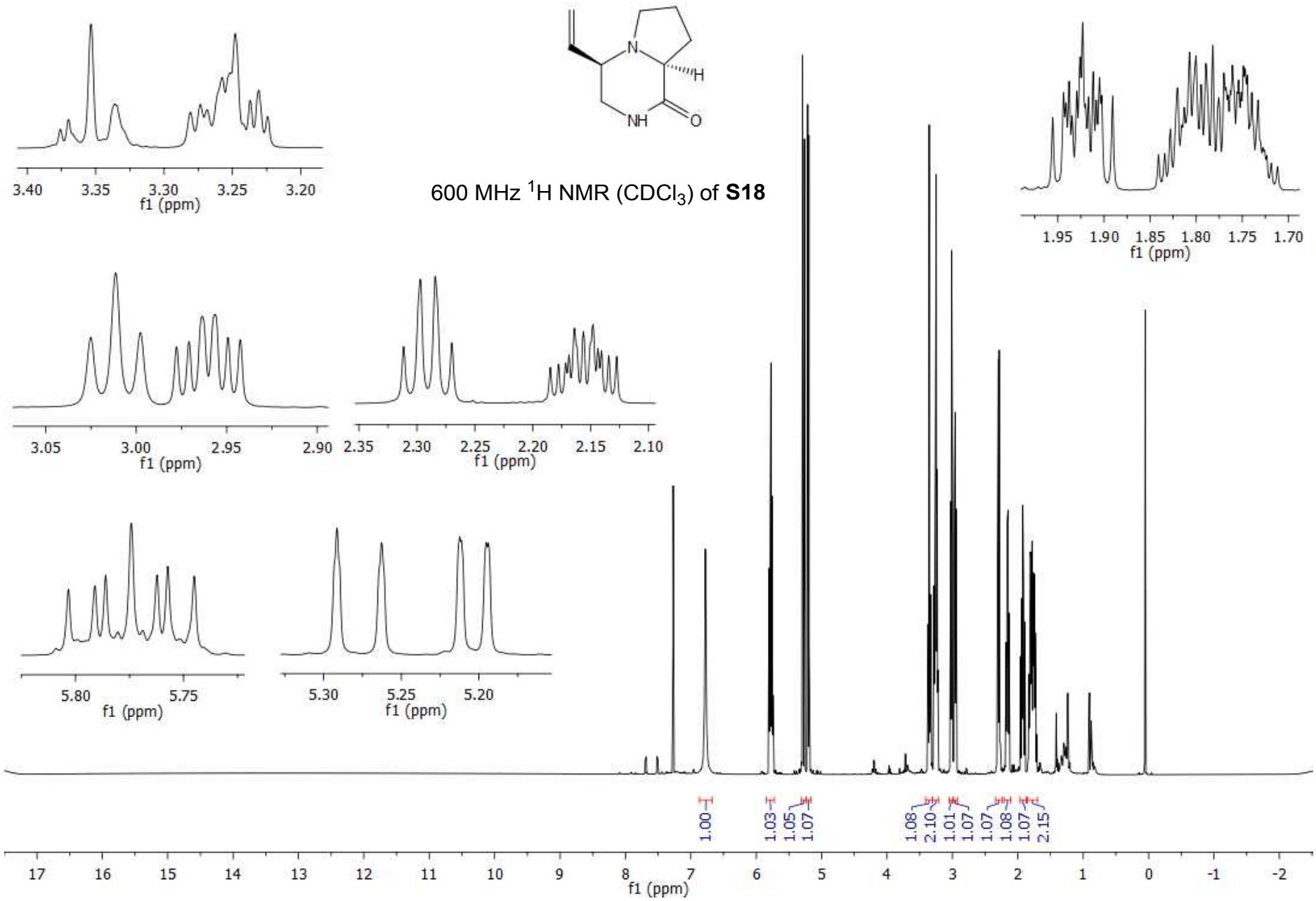


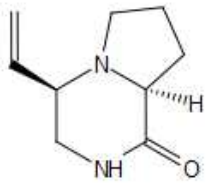
100 MHz ^{13}C NMR ($CDCl_3$) of **S17**


N22359-30.010.esp
8.14
8.01
7.99
7.98
7.97
7.88
7.87
6.43
5.73
5.70
5.68
5.68
5.27
5.27
5.23
5.23
5.21
5.20
5.18
5.18
4.09
4.07
4.05
4.03
3.37
3.35
3.18
3.16
3.01
3.00
2.98
2.95
2.93
2.92
2.90
HN
N
H
N
O
O
S
O
O
NO2
400 MHz 1H NMR (CDCl3) of 30
Normalized Intensity
Chemical Shift (ppm)
1.00
2.04
2.11
1.02
1.09
2.17
1.08
0.99
0.97
4.34



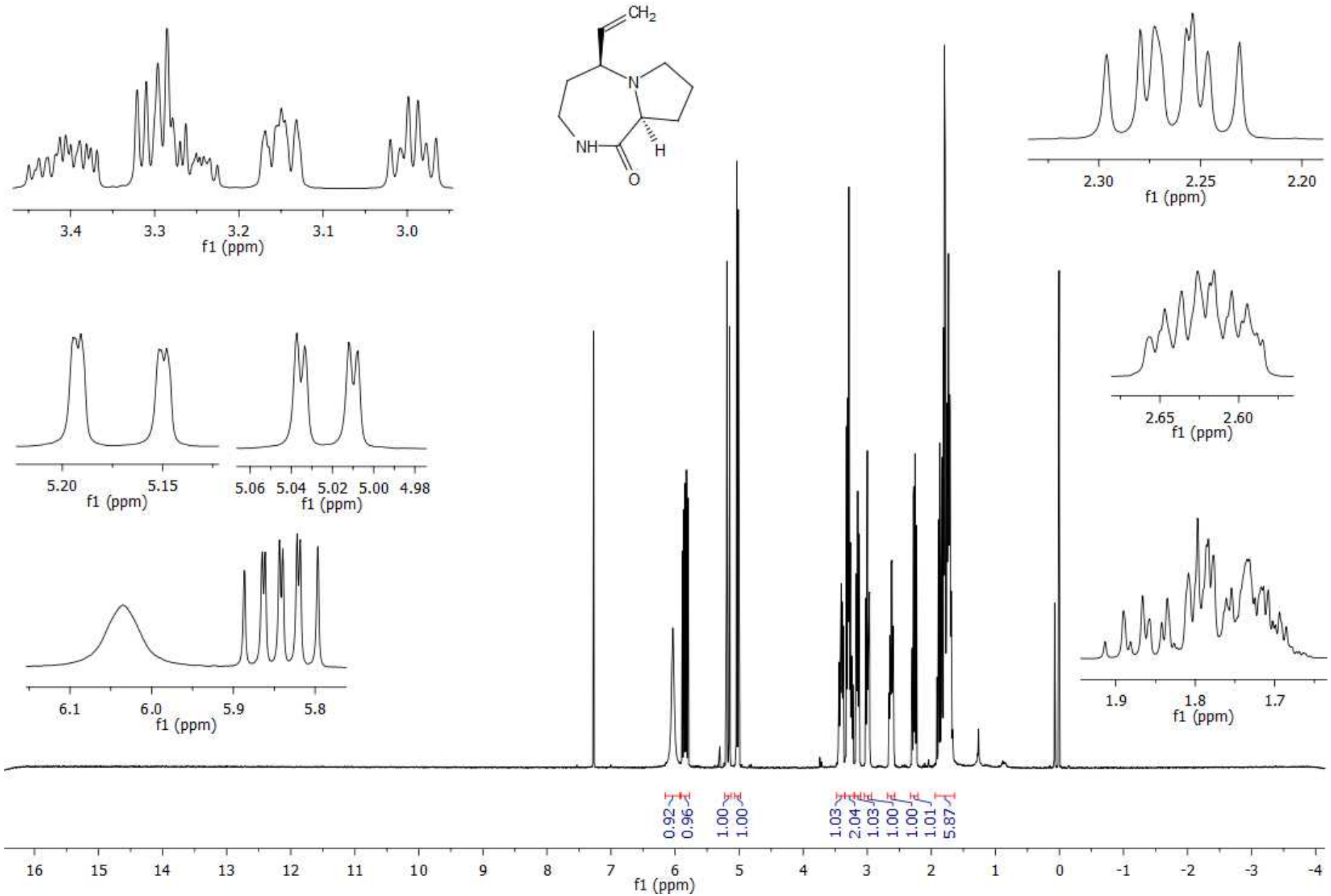
100 MHz ^{13}C NMR ($CDCl_3$) of **30**

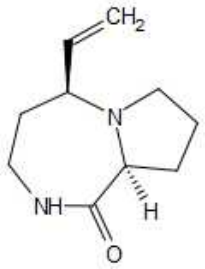

N
H
NH
O
600 MHz ^{1}H NMR ($CDCl_3$) of **S18**
f1 (ppm)
1.00
1.03
1.05
1.07
1.08
2.10
1.01
1.07
1.07
1.08
1.07
2.15



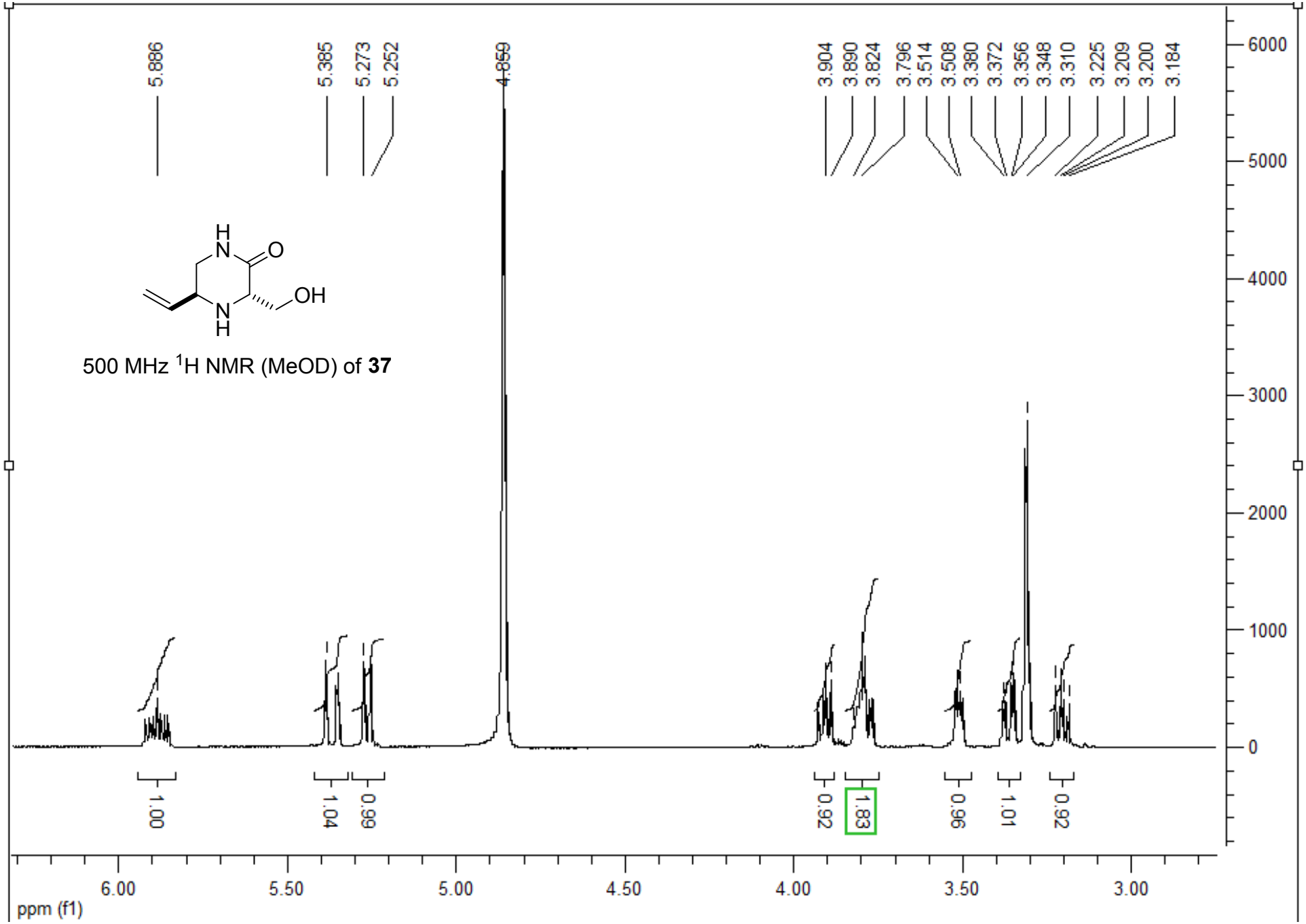
150 MHz ^{13}C NMR ($CDCl_3$) of **S18**

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

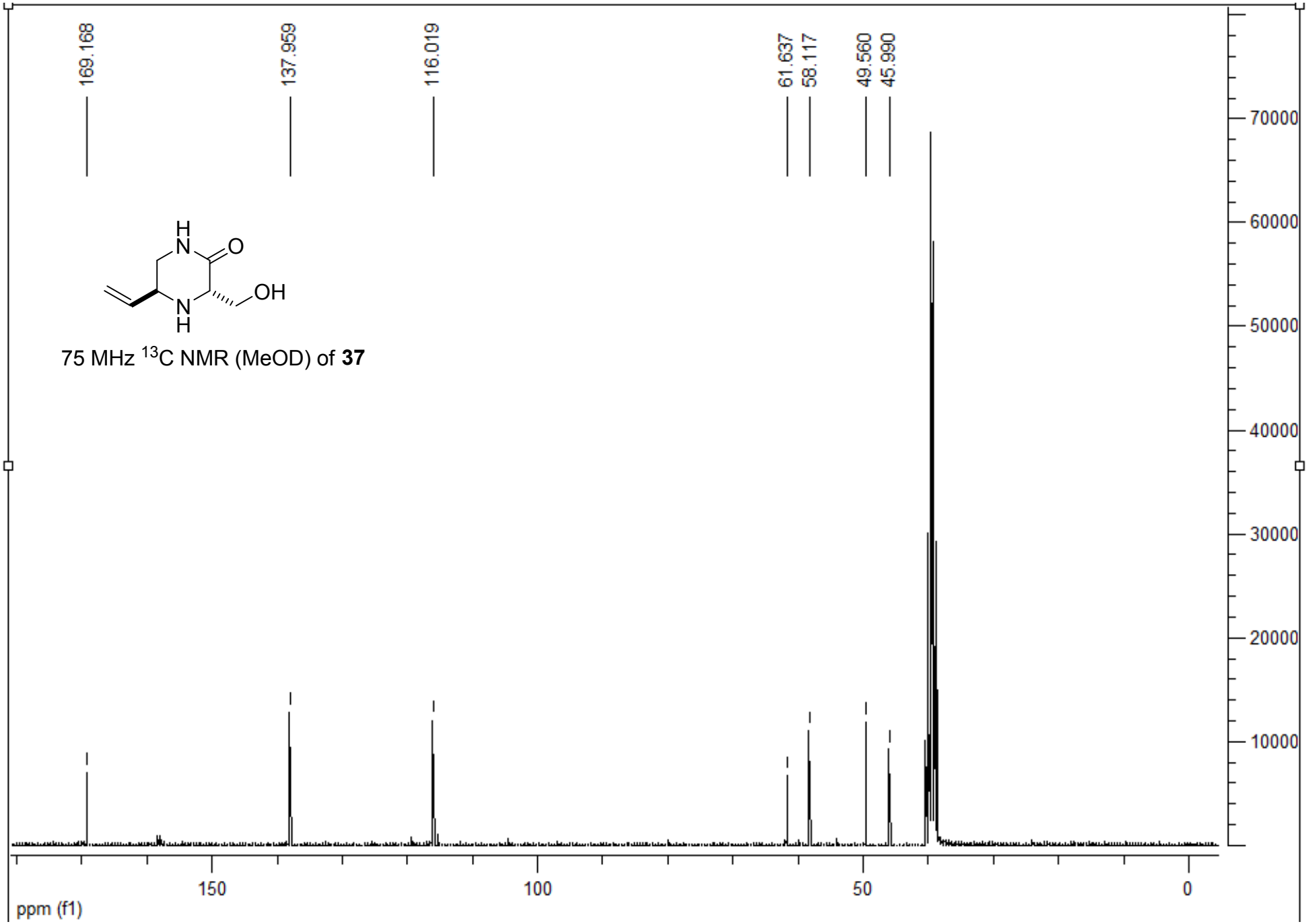




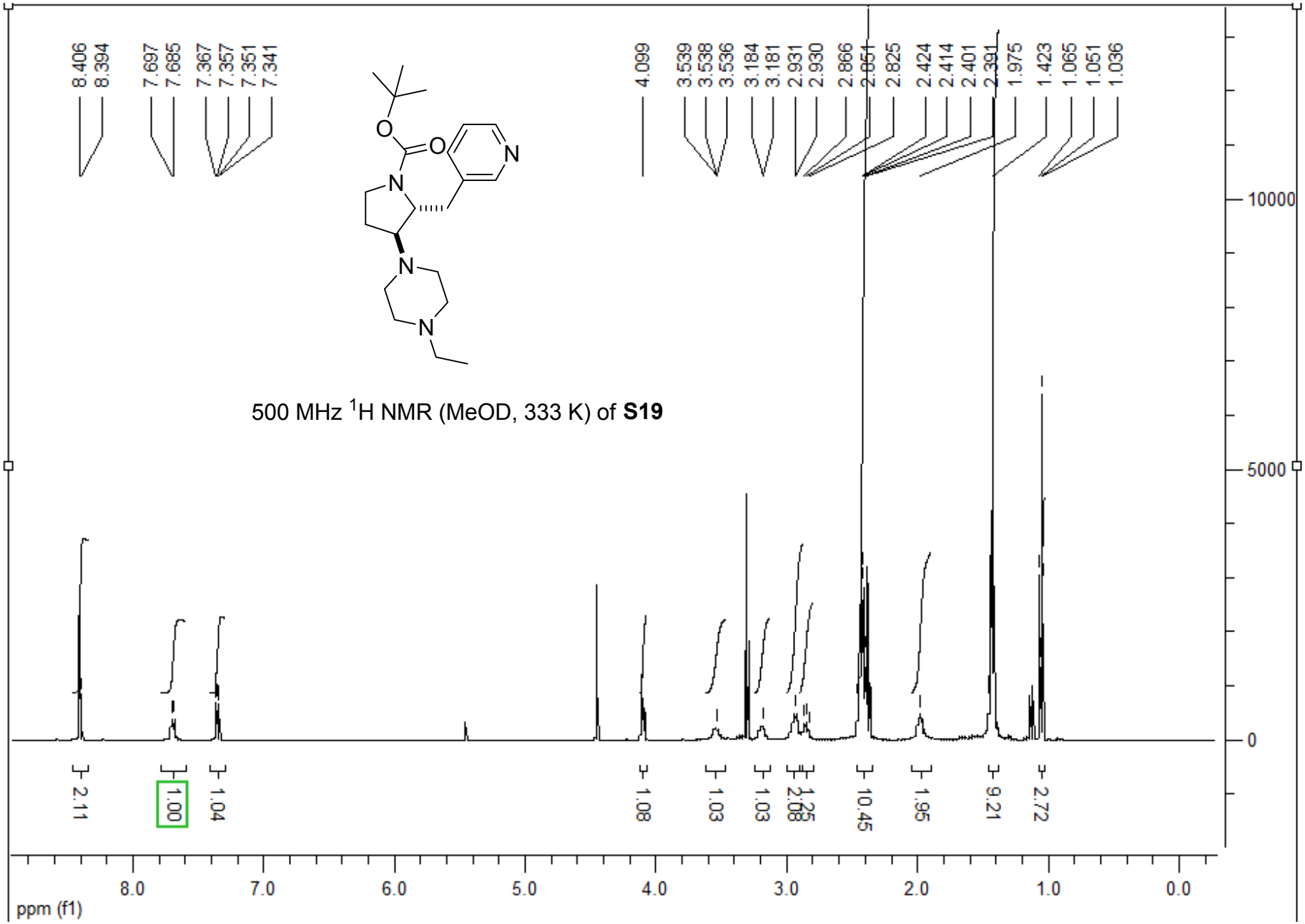
100 MHz ^{13}C NMR ($CDCl_3$) of **38**



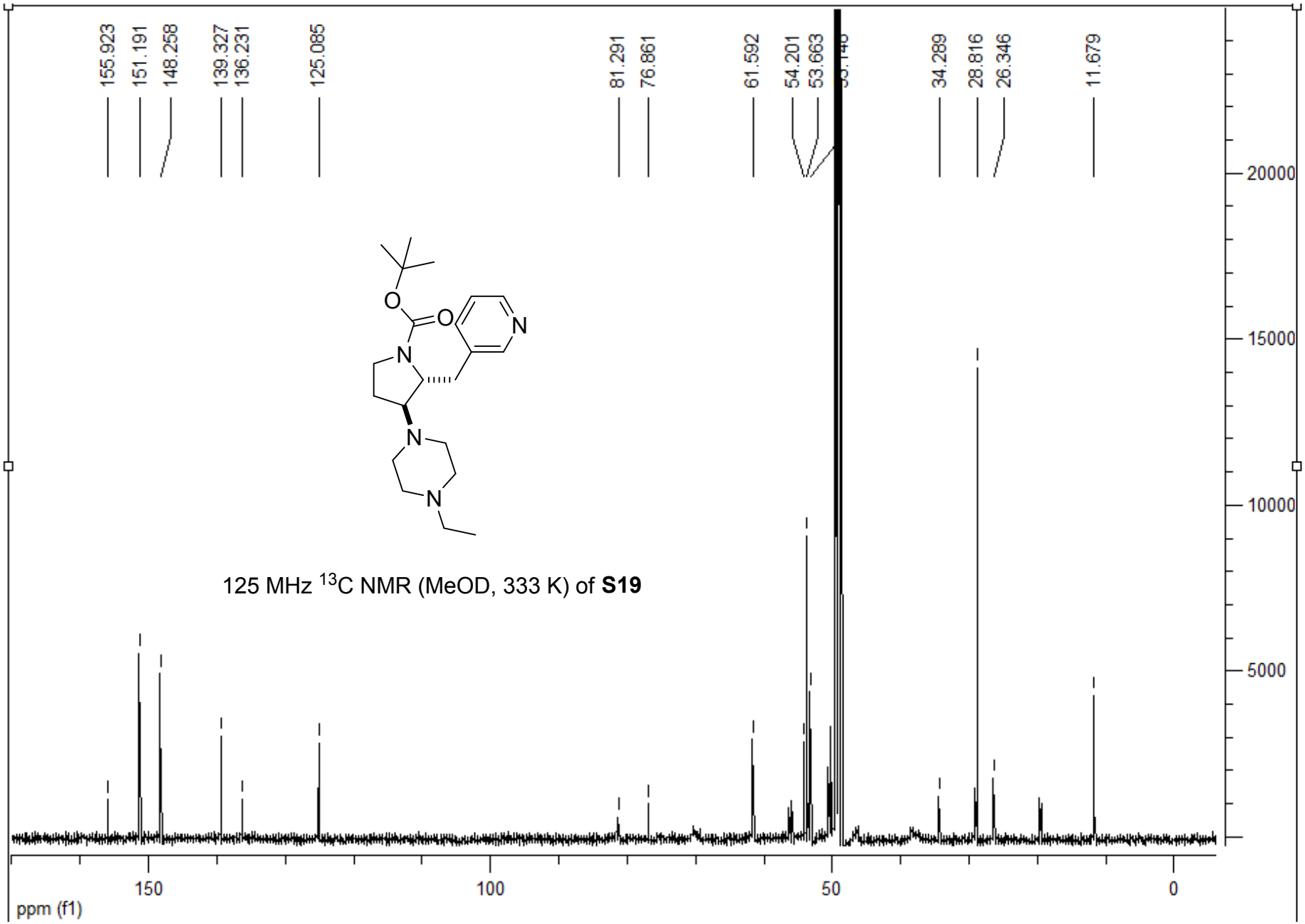
500 MHz ^{1}H NMR (MeOD) of **37**



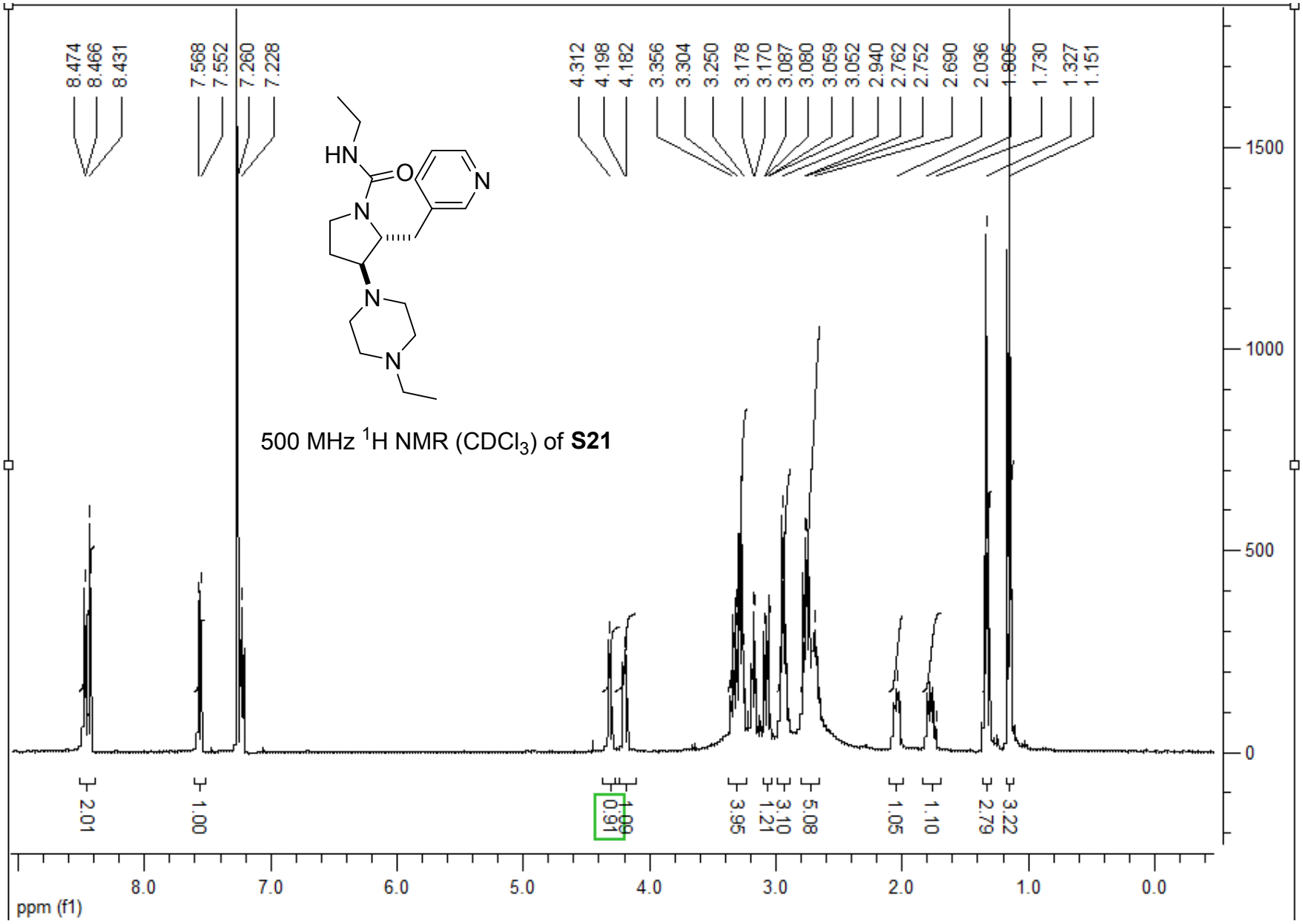
75 MHz ^{13}C NMR (MeOD) of **37**

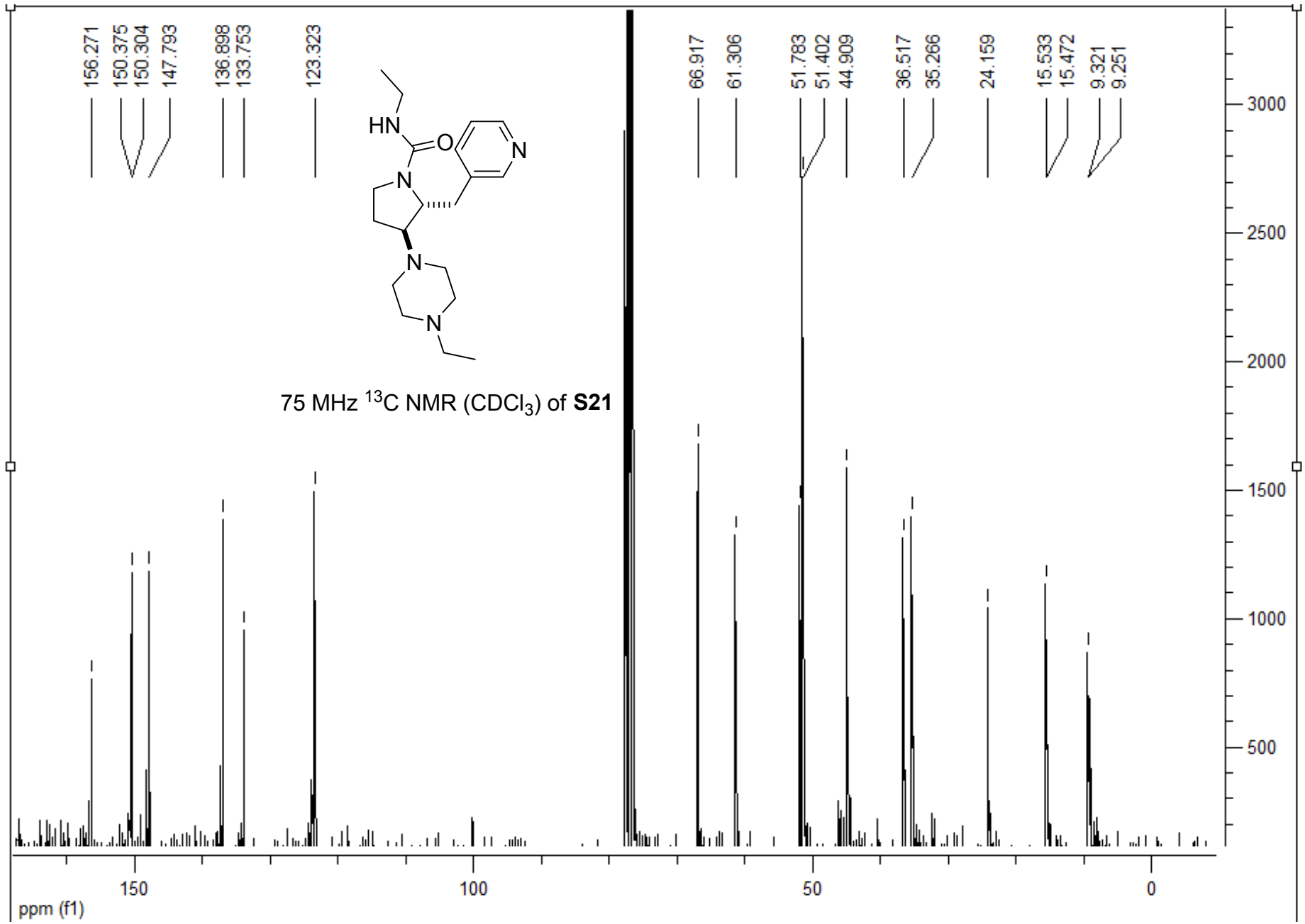


500 MHz ^{1}H NMR (MeOD, 333 K) of **S19**

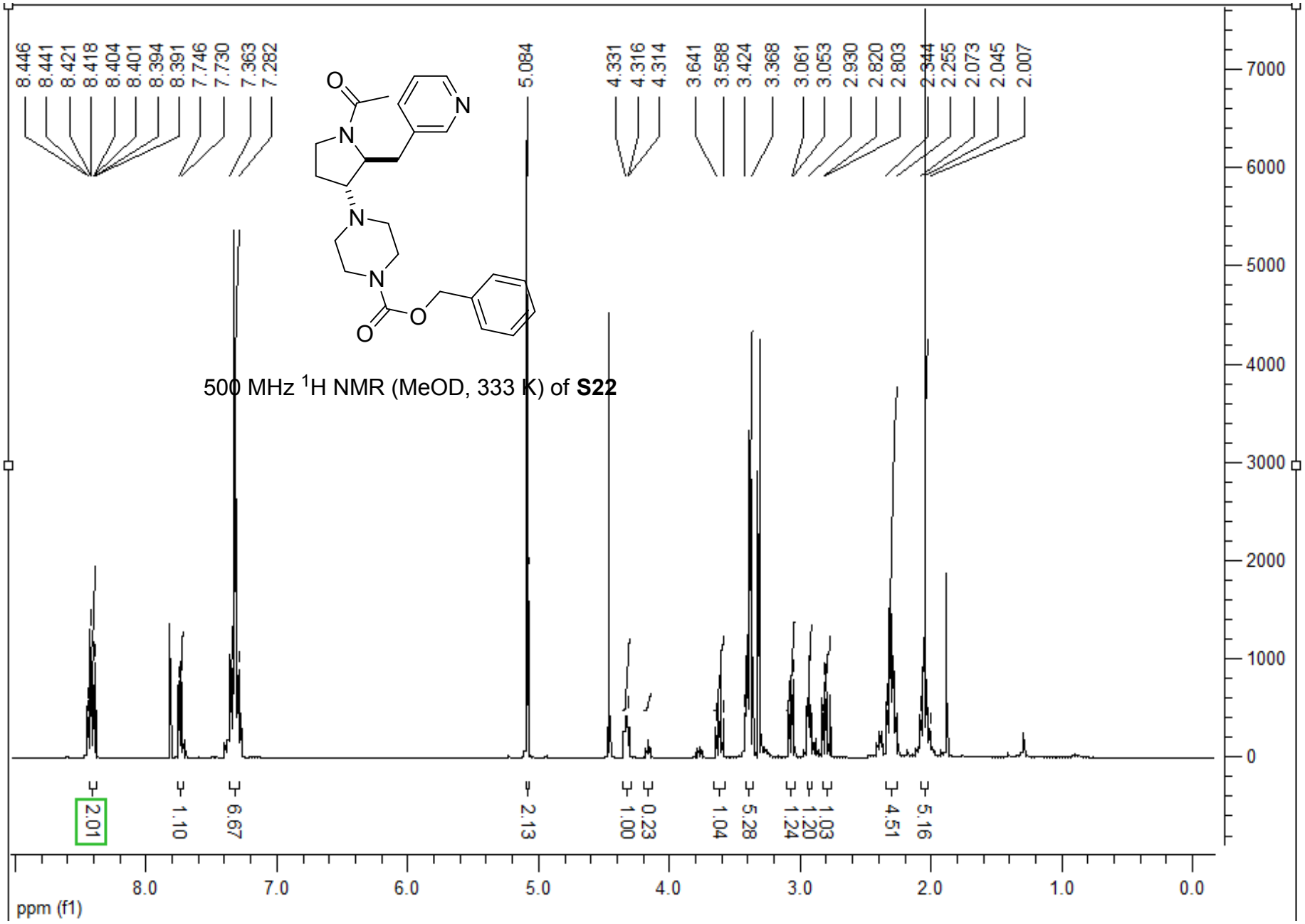


125 MHz ^{13}C NMR (MeOD, 333 K) of **S19**

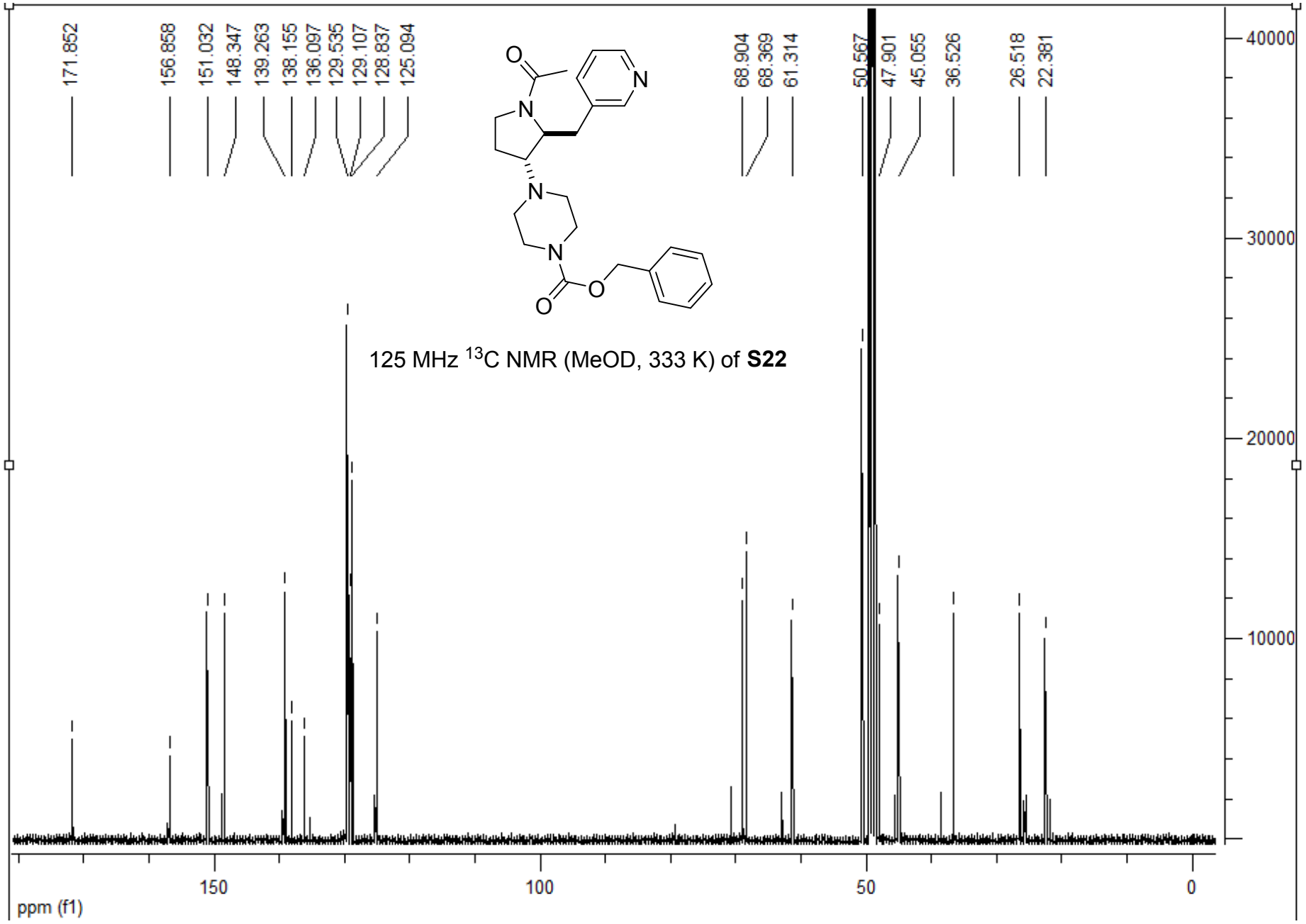

8.474
8.466
8.431
7.568
7.552
7.260
7.228
4.312
4.198
4.182
3.356
3.304
3.250
3.178
3.170
3.087
3.080
3.059
3.052
2.940
2.762
2.752
2.690
2.036
1.805
1.730
1.327
1.151
HN
O
N
N
N
N
500 MHz ^{1}H NMR ($CDCl_3$) of **S21**
2.01
1.00
0.91
1.09
3.95
1.21
3.10
5.08
1.05
1.10
2.79
3.22
1500
1000
500
0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)



75 MHz ^{13}C NMR ($CDCl_3$) of **S21**



500 MHz ^{1}H NMR (MeOD, 333 K) of **S22**



125 MHz ^{13}C NMR (MeOD, 333 K) of **S22**