Supporting information

Effect of capping groups at the *N*-and *C*-termini on the conformational preference of α,β-peptoids.

Emiliana De Santis,[a] Thomas Hjelmgaard,[b,c] Cécile Caumes,[b,c] Sophie Faure,[b,c] Bruce D. Alexander,[d] Simon J. Holder,[e] Giuliano Siligardi,[f] Claude Taillefumier,[b,c*] Alison A. Edwards.[a*]

[a] *Medway School of Pharmacy, Universities of Kent and Greenwich at Medway, Central Avenue, Chatham Maritime, Kent, ME4 4TB, United Kingdom. Fax: +44 (0)1634 883927; Tel: +44 (0)1634 202947; a.a.edwards@kent.ac.uk*

[b] *Clermont Université, Université Blaise Pascal, Laboratoire SEESIB, BP 10448, F-63000 Clermont-Ferrand*

[c] *CNRS, UMR 6504, Laboratoire SEESIB, F-63177 AUBIERE cedex, France. Fax: +33 (0)4 73 40 77 17; Tel: +33 (0)4 73 40 54 27; E-mail: claude.taillefumier@univ-bpclermont.fr*

[d] *School of Science, University of Greenwich, Central Avenue, Chatham Maritime, Kent, ME4 4TB, United Kingdom*

[e] *Functional materials Group, School of Physical Sciences, University of Kent, Canterbury, CN2 7NZ, United Kingdom*

[f] *Diamond Light Source Ltd., Diamond House, Harwell Science and Innovation Campus, Didcot, Oxfordshire, OX11 0DE, United Kingdom*

Contents

CD studies

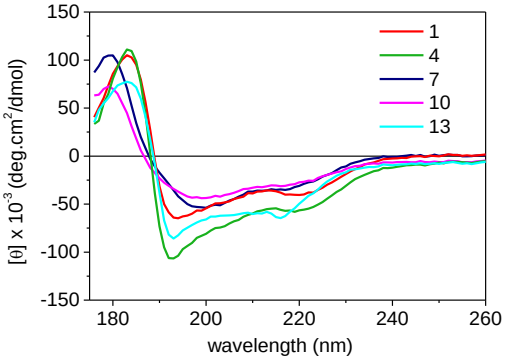


Fig. S1 Molar ellipticity spectra of dimers in MeCN by ECD. All spectra were recorded at 20 °C at known concentrations in the range 650 – 700 μM.

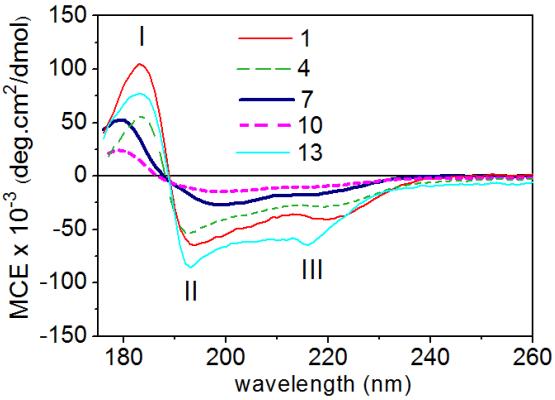


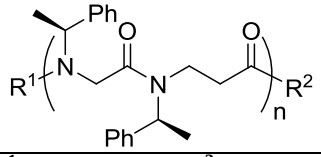
Fig. S2 ECD spectra of dimers in MeCN processed by the number of chromophores. MCE is mean chromophore ellipticity. All spectra were recorded at 20 °C at known concentrations in the range 650 – 700 μM.

Mean chromophore ellipticity (MCE) spectra were obtained by dividing the molar ellipticity spectra by the number of chromophores that should contribute to the far UV region *i.e.* not only the tertiary amide in the backbone. Therefore, this took into account the tertiary amide in the backbone, the carbamate in the protecting group (Boc) and the free amine when the *N*-terminus was unprotected. This was based on literature values identified for the molar extinction coefficient (ε) (reference S1) (Table S1). The ester, the acid and the terminal amide were not considered due to their contribution to the far UV region being negligible. When doing this calculation it was found that by considering these three chromophores, all the compounds would have been divided by the same number. For this reason it was decided to repeat the calculation without considering the amine chromophore which was the least intense of the three (Table S2). However, it is of note that the values of ε reported for the isolated chromophores are an approximation obtained from the value of the simplest molecule containing the functional group considered. In addition to this MCE data were not corrected for the relative contribution of the isolated chromophore *i.e.* all the contributing chromophores were assumed to have the same contribution (same ε value). Due to these approximations, processing by MCE is arbitrary.

Despite this, the processing is still adequate to show that additional chromophores would change the spectral intensity but not the spectral shape. This confirms that the difference observed in the MRE spectra (Figure 2) was due to the effect of protecting groups on the conformational preference and not simply to the presence of the additional chromophores.

Isolated chromophore	**Reference compound**	**Typical wavelength**	**ε (liter mol^{-1} cm^{-1})**
Tertiary amide	$CH_3CON(CH_3)_2$	218	1000
	$CH_3CON(CH_3)(Ph)$	224	7870
Primary amide	CH_3CONH_2	205	162
	$HCONH_2$	205	158
Ester	CH_3COOEt	209	72
Carbamate	$NO_2NHCOOC_2H_5$	215	7943
Carboxyl	CH_3COOH	208	32
Secondary amine	$(CH_3)_2NH$	191	3236

Table S1. Molar extinction coefficient (ε) of chromophores from literature.[1]



Series	**R^1**	**R^2**	**Processing**
a	H	O*t*Bu	[θ]/[(2n-1) + 0]
b	H	NH_2	[θ]/[(2n-1) + 0]
c	Boc	O*t*Bu	[θ]/[(2n-1) + 1]
d	Boc	NH_2	[θ]/[(2n-1) + 1]
e	TFA·H	OH	[θ]/[(2n-1) + 0]

Table S2 Processing strategy used to obtain MCE spectra. [θ] is molar ellipticity and (2n-1) is the number of peptoid linkages within the backbone.

Dimer	**λ_{max} peak I**	**λ_{max} peak II**	**λ_{max} peak III**
1	184 (+ve)	194 (-ve)	219 (-ve)
4	184 (+ve)	194 (-ve)	219 (-ve)
7	180 (+ve)	200 (-ve)	217 (-ve)
10	180 (+ve)	200 (-ve)	217 (-ve)
13	184 (+ve)	194 (-ve)	216 (-ve)

Table S3 Position of positive and negative maxima for α,β-peptoid dimers in MeCN. All spectra were recorded at 20 °C at known concentrations in the range 650 – 700 μM.

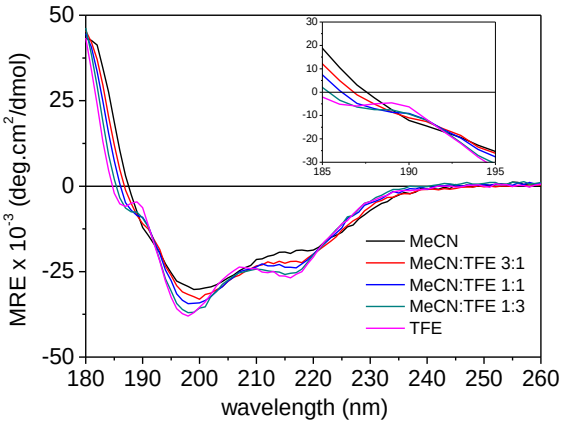
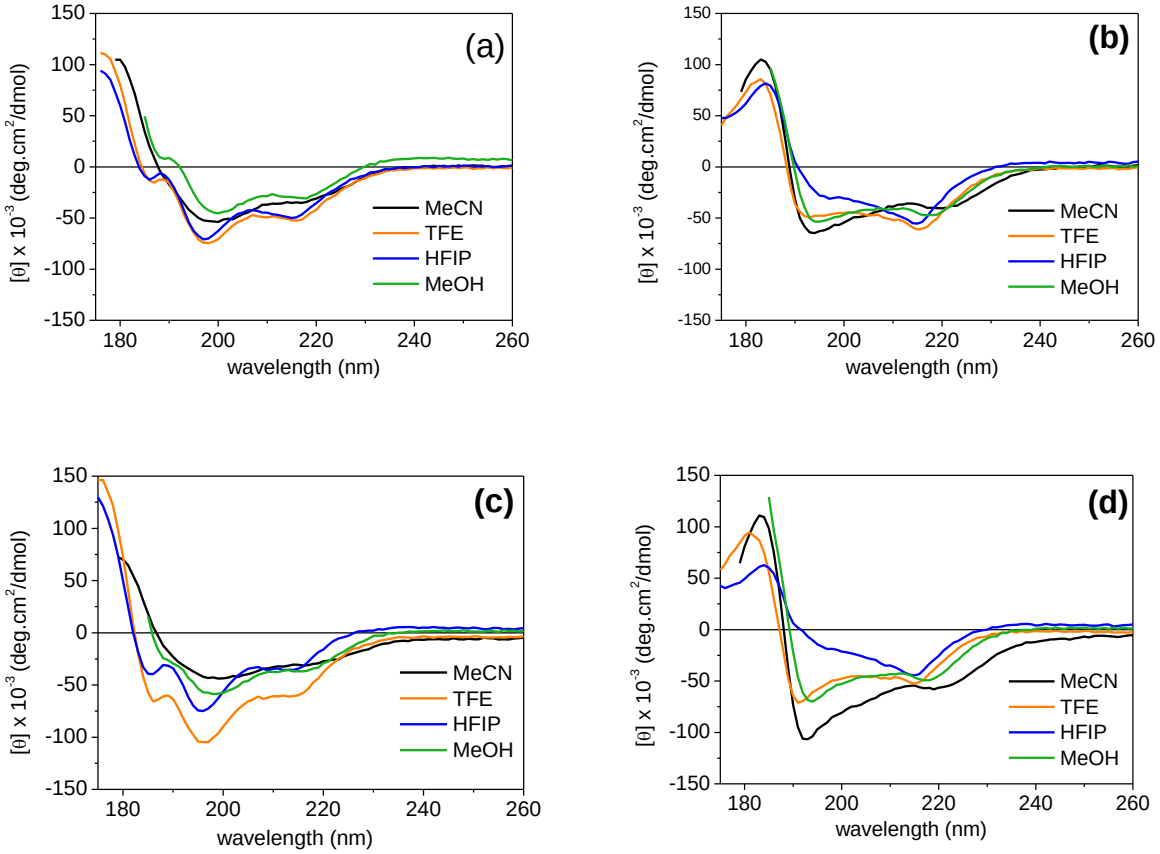


Fig. S3 MeCN/TFE solvent titration of **7** by ECD. All spectra were recorded at 20 °C at 699 μM or 700 μM.



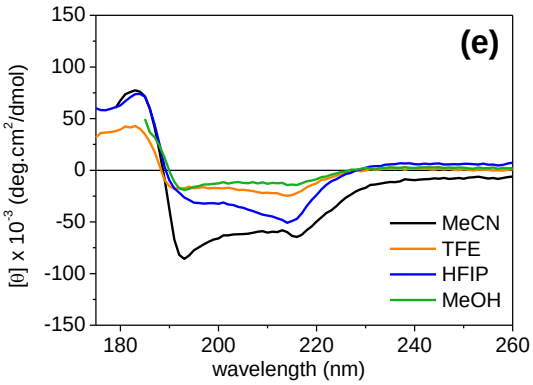


Fig. S4 ECD spectra of compounds (a) **7**, (b) **1**, (c) **10**, (d) **4** and (e) **13**. All spectra were recorded at 20 °C at known concentrations in the range 650 - 750 μM.

Functional group	α-value	β-value
3° Amide	0.00	0.69 - 0.78
Carbamate	0.00	0.6 - 0.65
2° Amine	0.08	0.6 - 0.7
Ester	0.00	0.47
1° Amide	0.54	0.66-0.69
Acid	0.55	0.45

Table S4 H-bonding ability of functional groups at the *N*- and *C*-termini.[2-7]

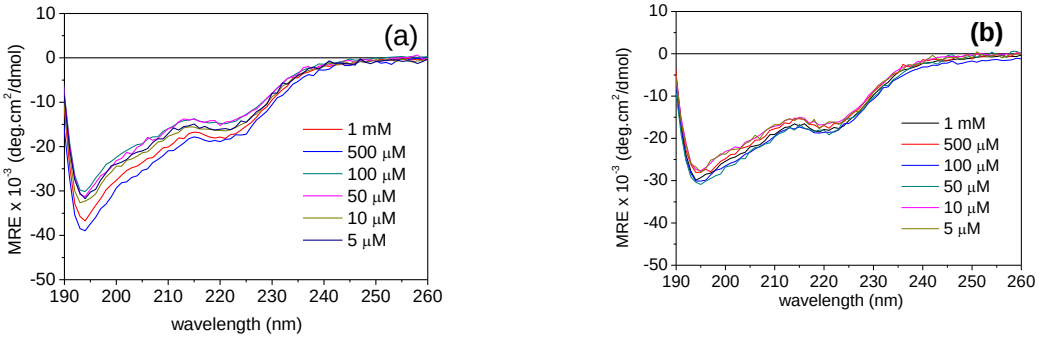


Fig. S5 Concentration studies of compounds (a) **4** and (b) **1** in MeCN by ECD. All spectra were recorded at 20 °C at the concentrations stated.

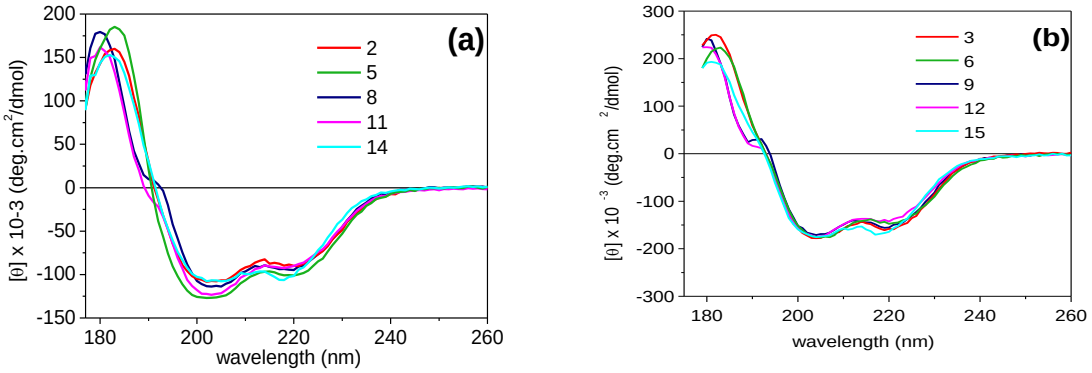


Fig. S6 Molar ellipticity spectra of (a) tetramers and (b) hexamers by ECD in MeCN. All spectra were recorded at 20 °C at known concentrations in the range 499 – 500 μM for tetramers and 249 - 300 μM for hexamers.

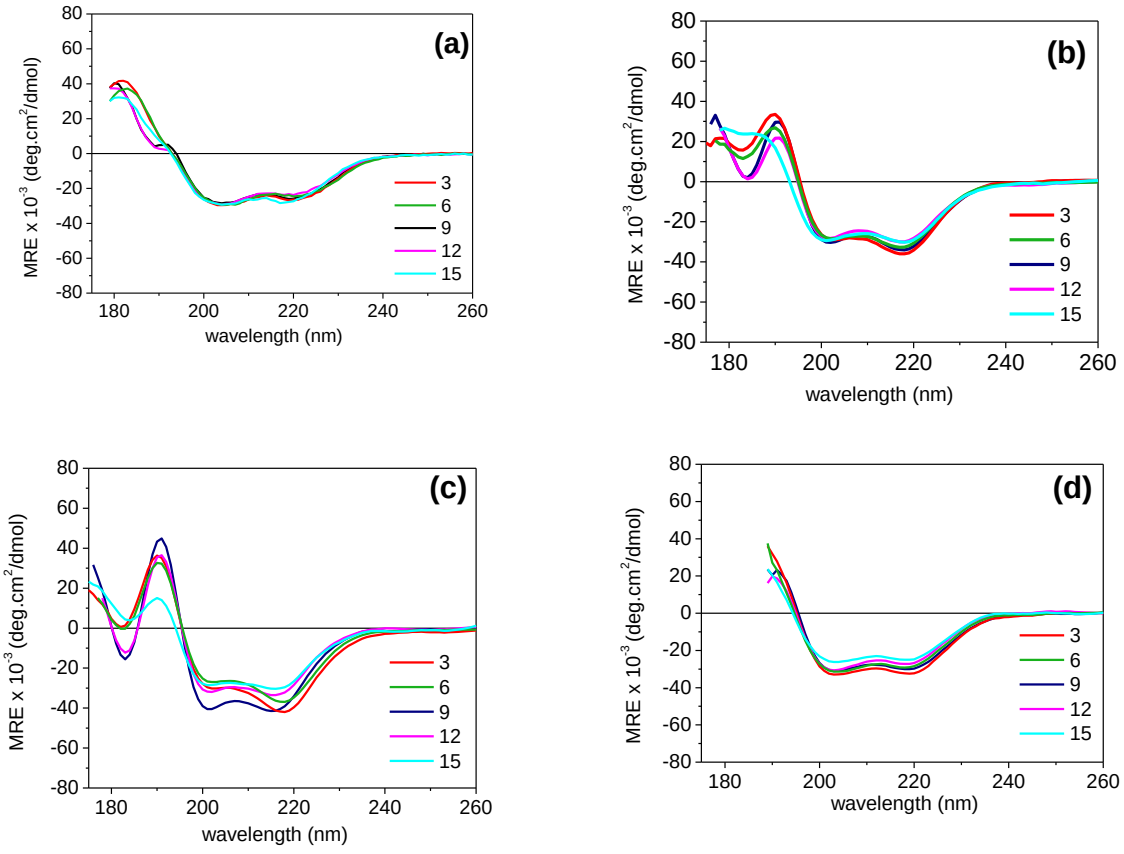


Fig. S7 ECD spectra of hexamers in (a) MeCN, (b) TFE, (c) HFIP and (d) MeOH. All spectra were recorded at 20 °C at known concentrations in the range 326 – 430 μM.

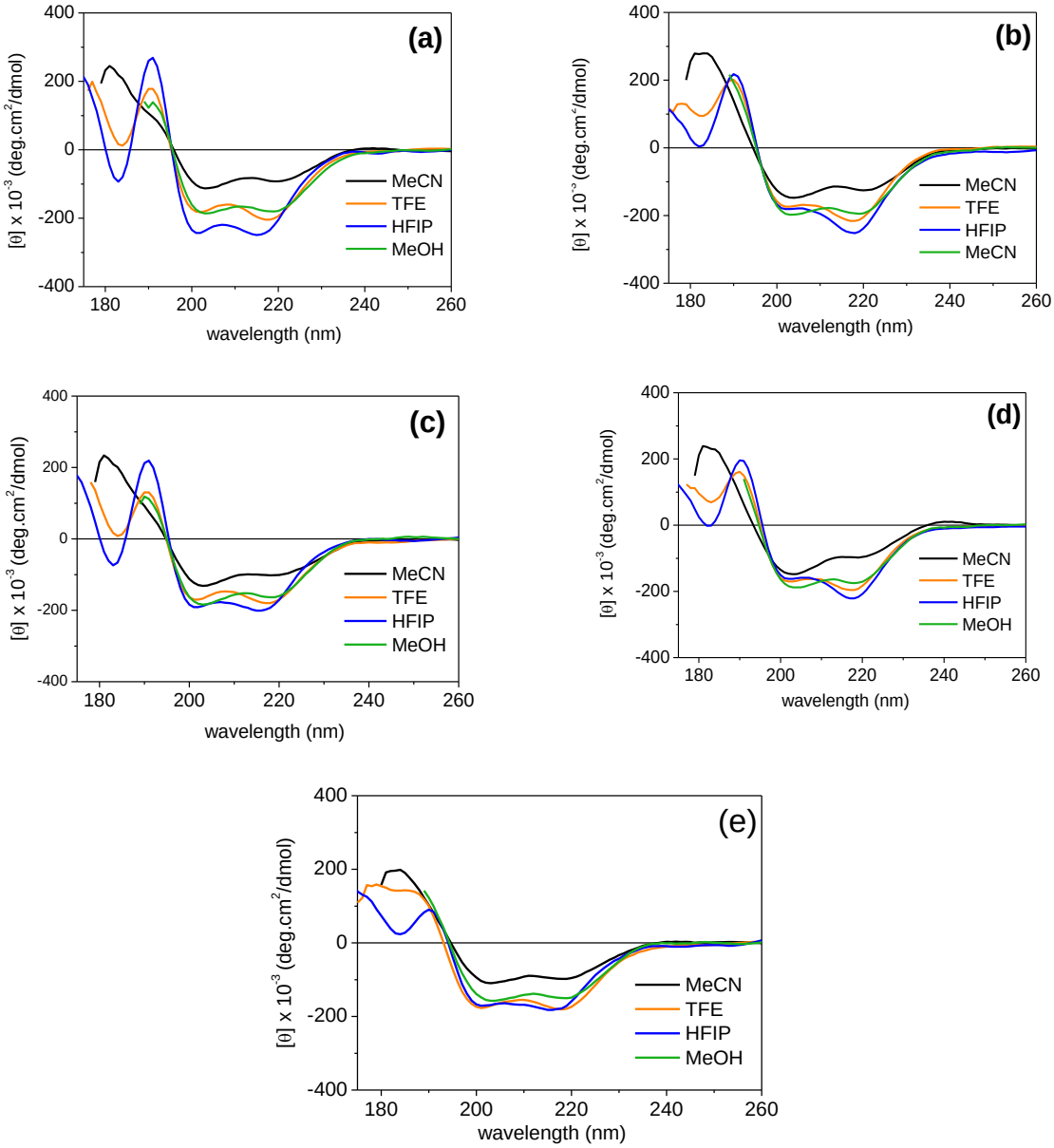


Fig. S8 ECD spectra of hexamers of compounds (a) **9**, (b) **3**, (c) **12**, (d) **6** and (e) **15** in different solvents. All spectra were recorded at 20 °C at known concentrations in the range 326 – 430 μM.

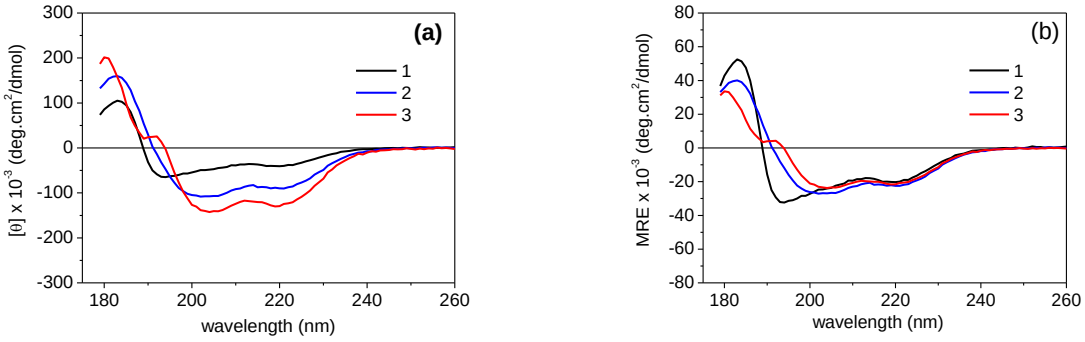


Fig. S9 ECD spectra of dimers of **a series** in MeCN. (a) Molar ellipticity spectra and (b) MRE spectra. All spectra were recorded at 20 °C at known concentrations in the range 299 - 700 μM.

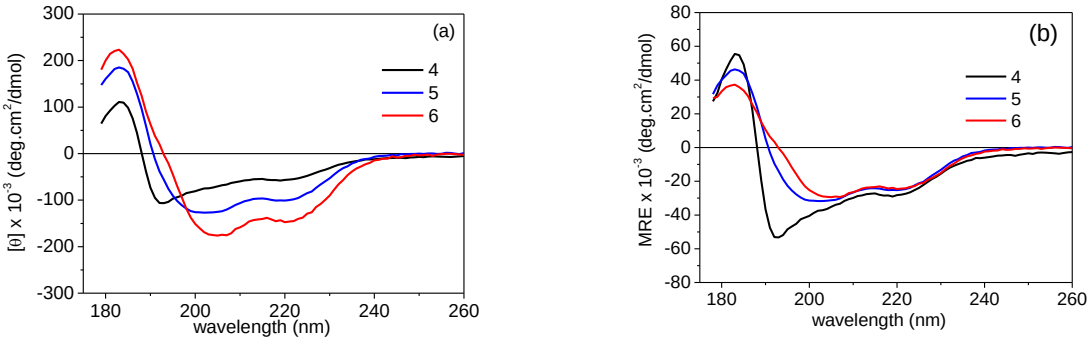


Fig. S10 ECD spectra of dimers of **b series** in MeCN. (a) Molar ellipticity spectra and (b) MRE spectra. All spectra were recorded at 20 °C at known concentrations in the range 299 – 700 μM.

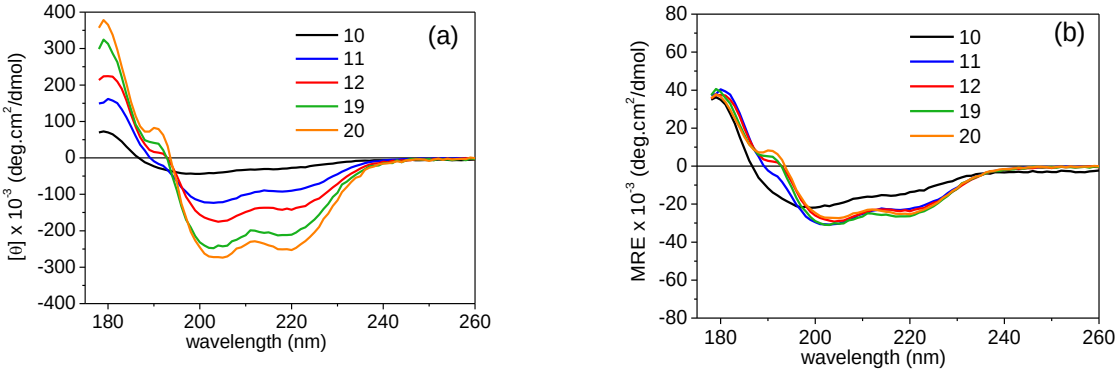


Fig. S11 ECD spectra of dimers of **d series** in MeCN. (a) Molar ellipticity spectra and (b) MRE spectra. All spectra were recorded at 20 °C at known concentrations in the range 200 - 700 μM.

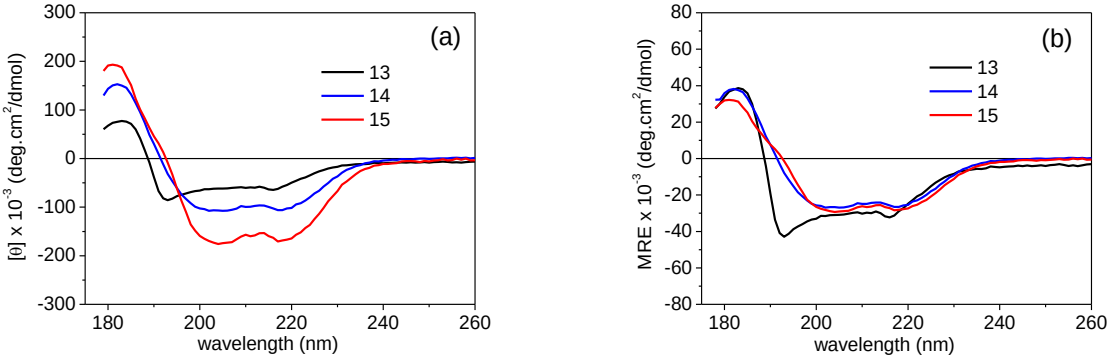


Fig. S12 ECD spectra of dimers of **e series** in MeCN. (a) Molar ellipticity spectra and (b) MRE spectra. All spectra were recorded at 20 °C at known concentrations in the range 299 – 700 μM.

Series	peptoid	MeCN	TFE	HFIP	MeOH
a	**1**	700 µM	779 µM	718 µM	705 µM
	2	500 µM	-	-	-
	3	299 µM 441 µM*	402 µM*	384 µM*	381 µM*
b	**4**	700 µM	699 µM	750 µM	743 µM
	5	500 µM	-	-	-
	6	299 µM 365 µM*	399 µM*	371 µM*	366 µM*
c	**7**	652 µM 2.3 mM*	700 µM	700 µM	734 µM
		MeCN/TFE 1:0 699 µM MeCN/TFE 3:1 699 µM MeCN/TFE 1:1 699 µM MeCN/TFE 1:3 699 µM MeCN/TFE 0:1 700 µM			
	8	499 µM 666 µM*	-	-	-
	9	249 µM 385 µM* 385 µM*	365 µM*	326 µM*	392 µM*
	17	188 µM*	-	-	-
	18	150 µM*	-	-	-
d	**10**	700 µM	710 µM	727 µM	710 µM
		MeCN/TFE 1:0 700 µM MeCN/TFE 3:1 700 µM MeCN/TFE 1:1 700 µM MeCN/TFE 1:3 700 µM MeCN/TFE 0:1 698 µM		-	-
	11	500 µM	-	-	-
	12	300 µM 430 µM*	415 µM*	405 µM*	429 µM*
	19	200 µM	-	-	-
	20	200 µM	-	-	-
e	**13**	700 µM	703 µM	700 µM	724 µM
	14	499 µM	-	-	-
	15	299 µM 352 µM*	370 µM*	399 µM*	382 µM*

***** Data recorded by SRCD

Table S5 Actual concentrations used for CD analyses. All data have been recorded on a Chirascan CD instrument (unless stated otherwise) by using a 0.01 cm path length cell.

IR studies and molecular modelling

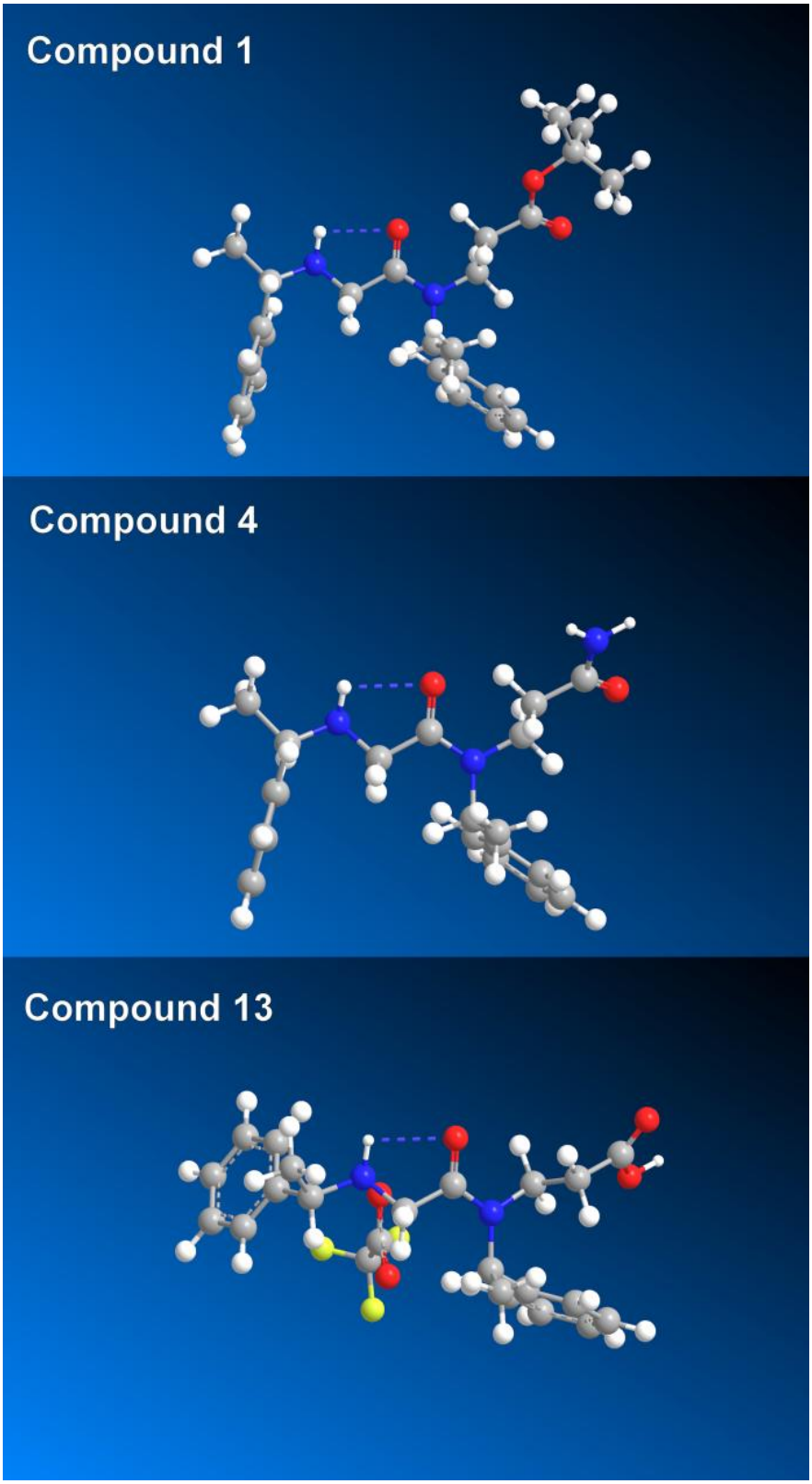


Fig. S13 Molecular modelling (PM6) for α,β-peptoid dimers 1, 4 and 13.

Compound	λ (cm^{-1})	Assignment
1	3420	NH (amine) unassociated
	3314	NH (amine) H-bonded
	1714	C=O (ester)C=O (3º amide) H-bonded
	1636	
4	3516	N-H (asym, 1º amide) unassociated
	~3485	N-H (sym, 1º amide) H-bonded
	3402	N-H (asym, 1º amide) unassociated
	3321	NH (amine) H-bonded and
		N-H (asym, 1ºamide) H-bonded
	1681	C=O (carbamate)
	1636	C=O (3º amide) H-bonded
	1600	δNH_2 H-bonded H-bonded
	1592	δ NH_2 H-bonded unassociated
7	1721	C=O (ester)
	1688	C=O (carbamate)C=O (3º amide) unassociated
	1660	
10	3526	N-H (asym, 1º amide) unassociated
	3485	N-H (sym, 1ºamide) H-bonded
	3409	N-H (asym, 1º amide) unassociated
	3344	N-H (asym, 1ºamide) H-bonded
	1687	C=O (carbamate)
	1656	C=O (3º amide)
	1601(sh)	δ NH_2 H-bonded H-bonded
	1592	δ NH_2 H-bonded unassociated

Table S6. Assignment of IR bands for α,β-peptoid dimers **1**, **4**, **7** and **10** in $CHCl_3$.

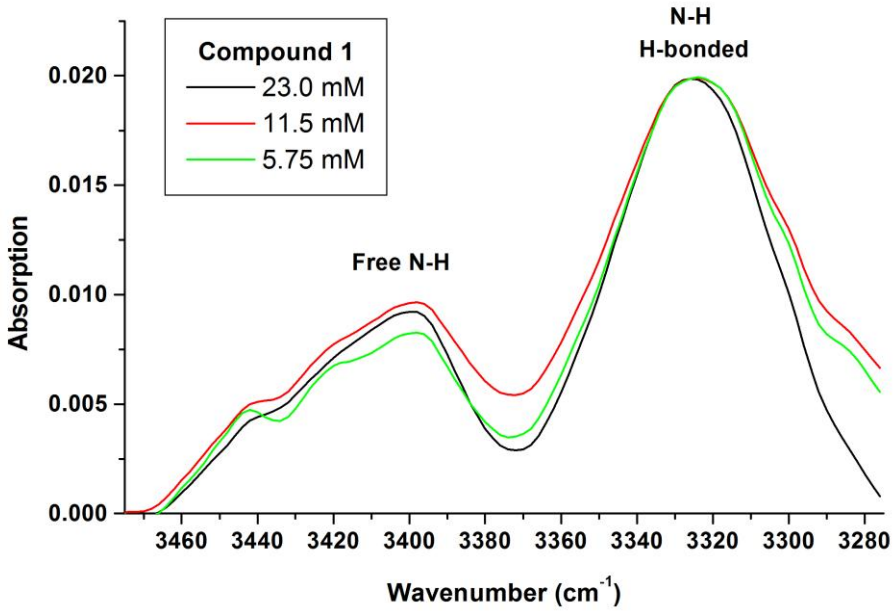


Fig. S14 N-H bonding spectral region and for α,β-peptoid **1** in $CHCl_3$. All spectra were recorded at room temperature at known concentrations in the range 1.43 – 23 mM but data are only shown for the concentration range 5.75 – 23.0 mM.

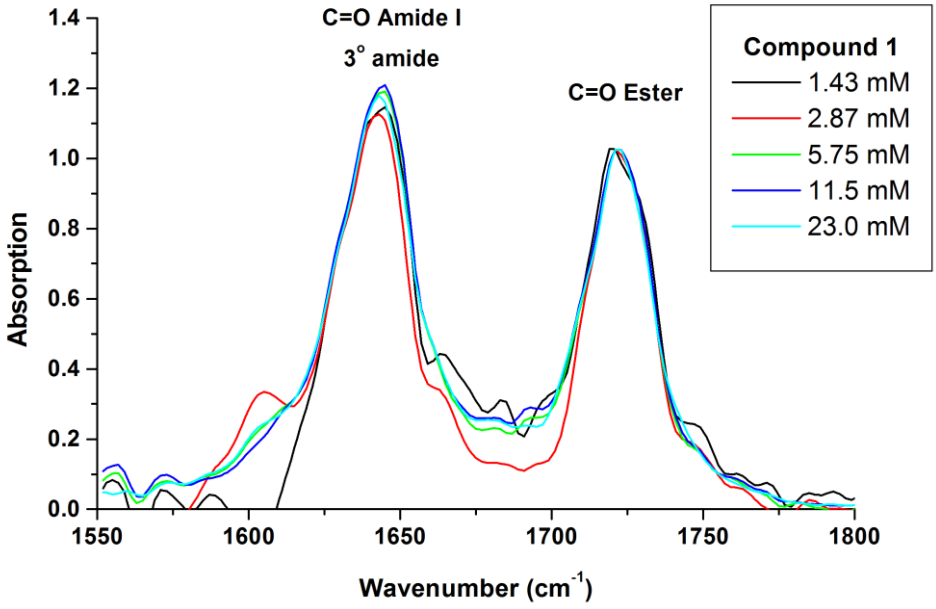


Fig. S15 C=O bonding spectral region and for α,β-peptoid **1** in $CHCl_3$. All spectra were recorded at room temperature at known concentrations in the range 1.43 – 23 mM.

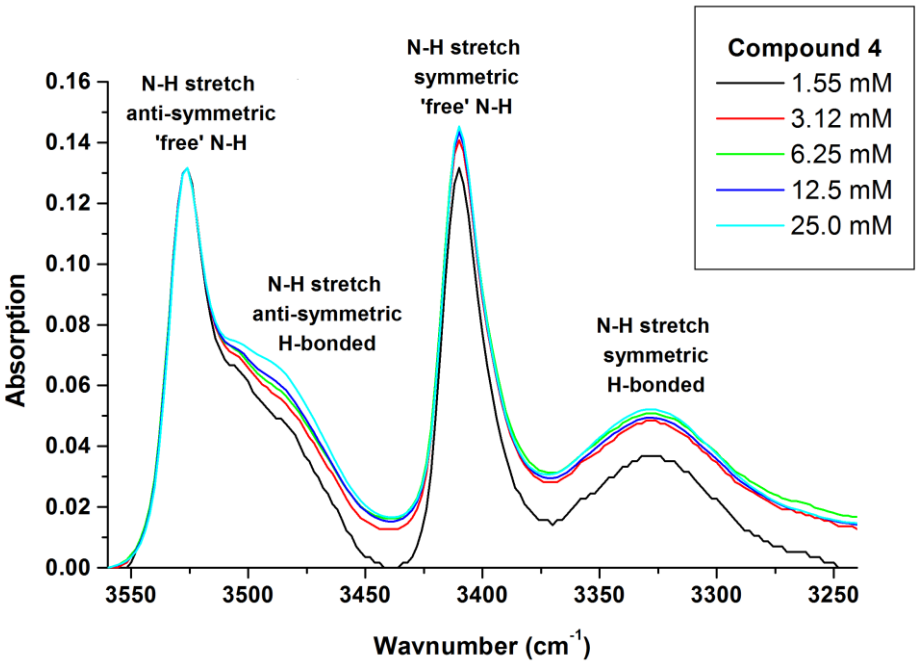


Fig. S16 N-H bonding spectral region and for α,β-peptoid **4** in $CHCl_3$. All spectra were recorded at room temperature at known concentrations in the range 1.55 – 25.0 mM.

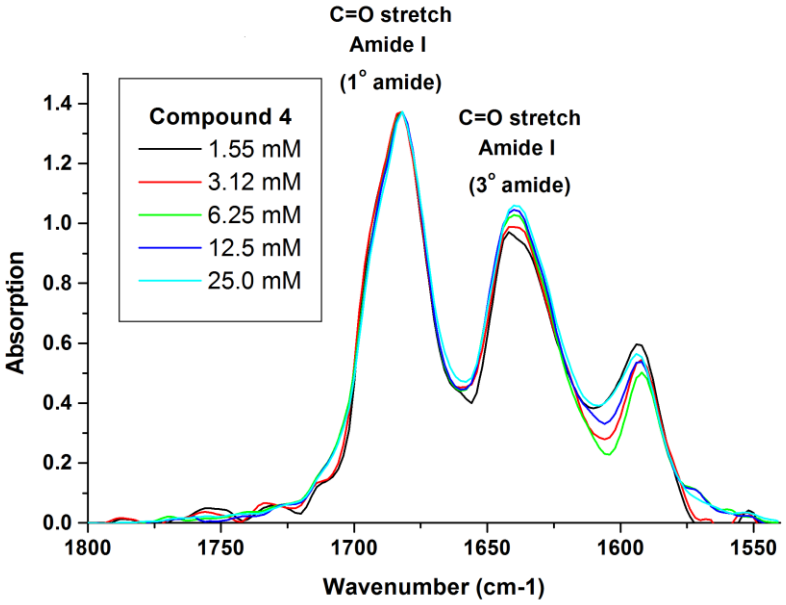


Fig. S17 C=O bonding spectral region and for α,β-peptoid **4** in $CHCl_3$. All spectra were recorded at room temperature at known concentrations in the range 1.55 – 25.0 mM.

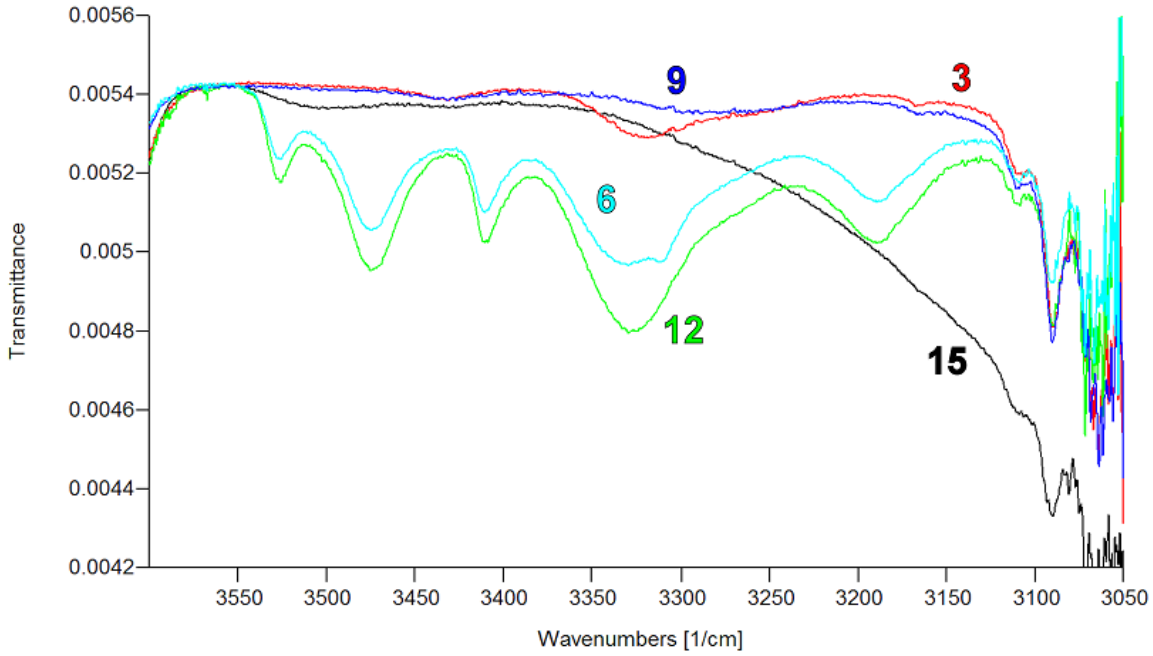


Fig. S18. N-H bonding spectral region and for α,β-peptoid hexamers **3**, **6**, **9**, **12** and **15** in $CHCl_3$. All spectra were recorded at room temperature at known concentrations in the range 2 – 6 mM.

Series	Peptoid	Concentration (mM)
a	**1**	23.7
	3	5.6
b	**4**	25.1
	6	5.8
c	**7**	10.0
	9	5.6
d	**10**	21.3
	12	5.1
e	**13**	21.0
	15	5.1

Table S7. Actual concentration used for IR of α,β-peptoid dimers and hexamers in $CHCl_3$. All spectra have been recorded by using a KBr cell of 0.1 cm pathlength.

Chemical structure of compounds 1a, 2a, 4a, 5a.

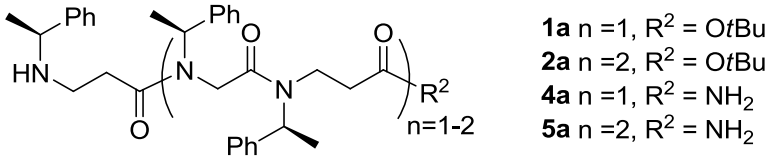


Fig. S19 Chemical structure of intermediates 1a, 2a, 4a and 5a.

NMR studies

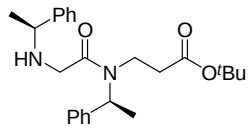
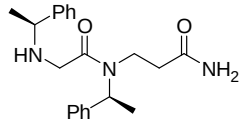
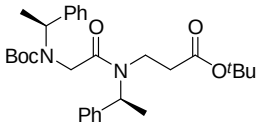
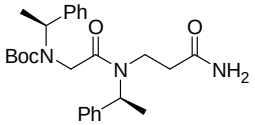
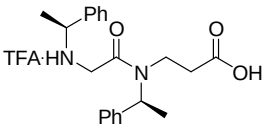
Structure	Peptoid	*cis*/*trans* ratio in $CDCl_3$	*cis*/*trans* ratio in CD_3CN
	**1**	0.61 (38:62) (^{1}H)	0.64 (39:61) (^{1}H)
	**4**	0.43 (30:70) (^{1}H) 0.39 (28:72) (HSQC)	0.89 (47:53) (^{1}H)
	**7**	inconclusive/overlapping signals	inconclusive/overlapping signals
	**10**	inconclusive/overlapping signals	inconclusive/overlapping signals
	**13**	0.69 (41:59) (^{1}H)	0.85 (46:54) (^{1}H)

Table S8. *Cis/trans* ratio for α,β-peptoid dimers in $CDCl_3$ and CD_3CN at 298 K by NMR.

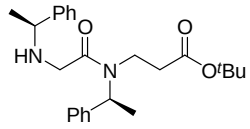
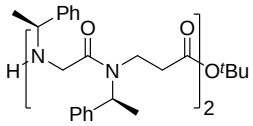
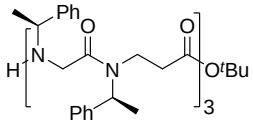
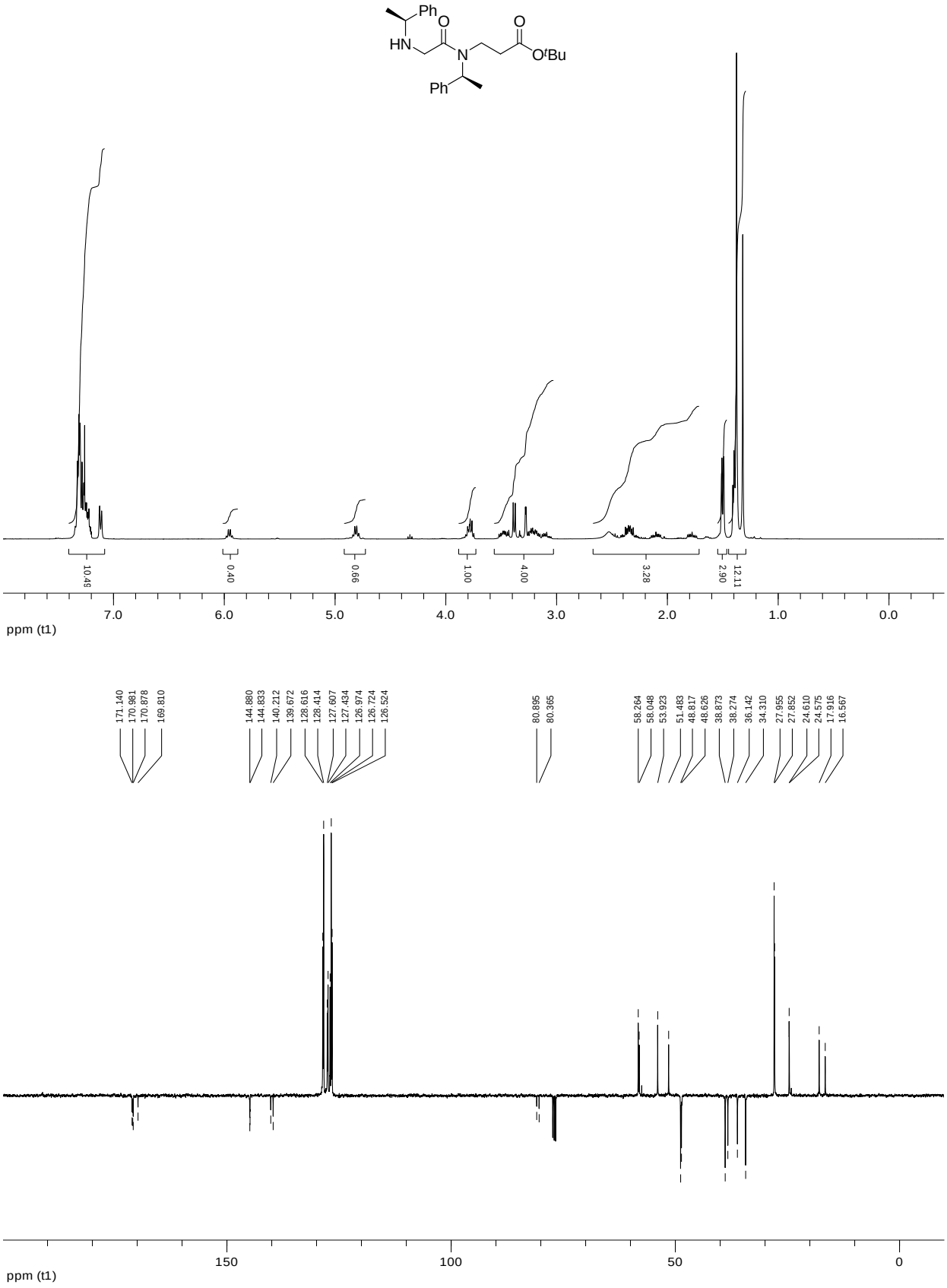
Structure	Peptoid	$K_{cis/trans}$ (*cis/trans* ratio)		
		298K	**318K**	**338K**
	**1**	0.65 (39:61)	0.63 (38:62)	-
	**2**	0.92 (48:52)	0.94 (49:51)	0.93 (48:52)
	**3**	1.08 (52:48)	1.08 (52:48)	1.10 (53:47)

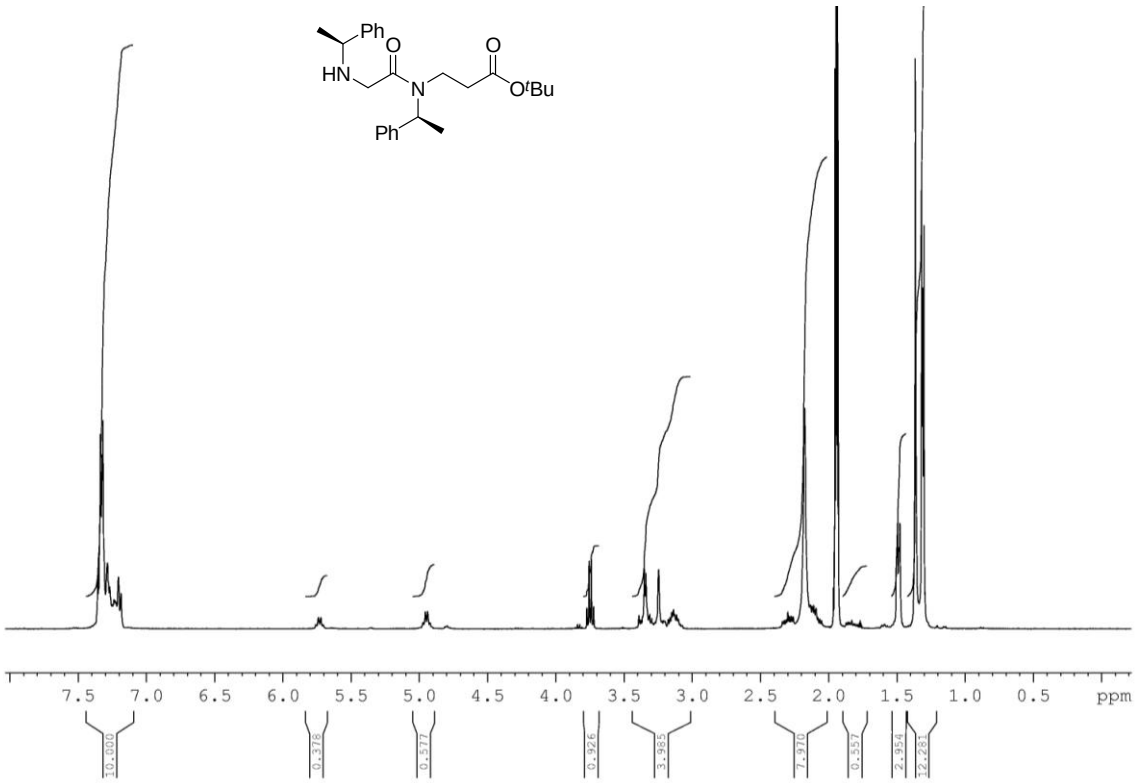
Table S9. $K_{cis/trans}$ for α,β-peptoid **1**, **2** and **3** in CD_3CN calculated by ^1H NMR.

^{1}H (400 MHz) and ^{13}C (100.9 MHz) NMR spectra of compounds 1-20, 1a, 2a, 4a and 5a.

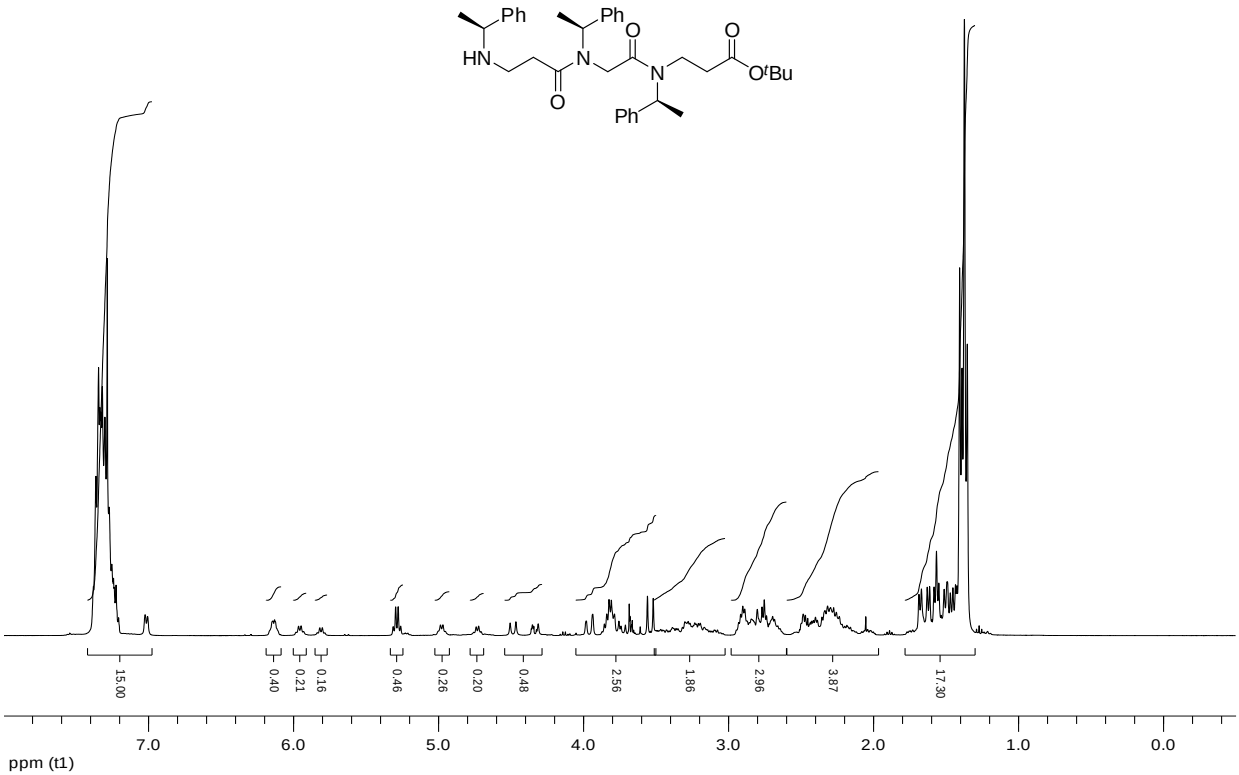
^{1}H and ^{13}C NMR spectra of compound **1** ($CDCl_3$)

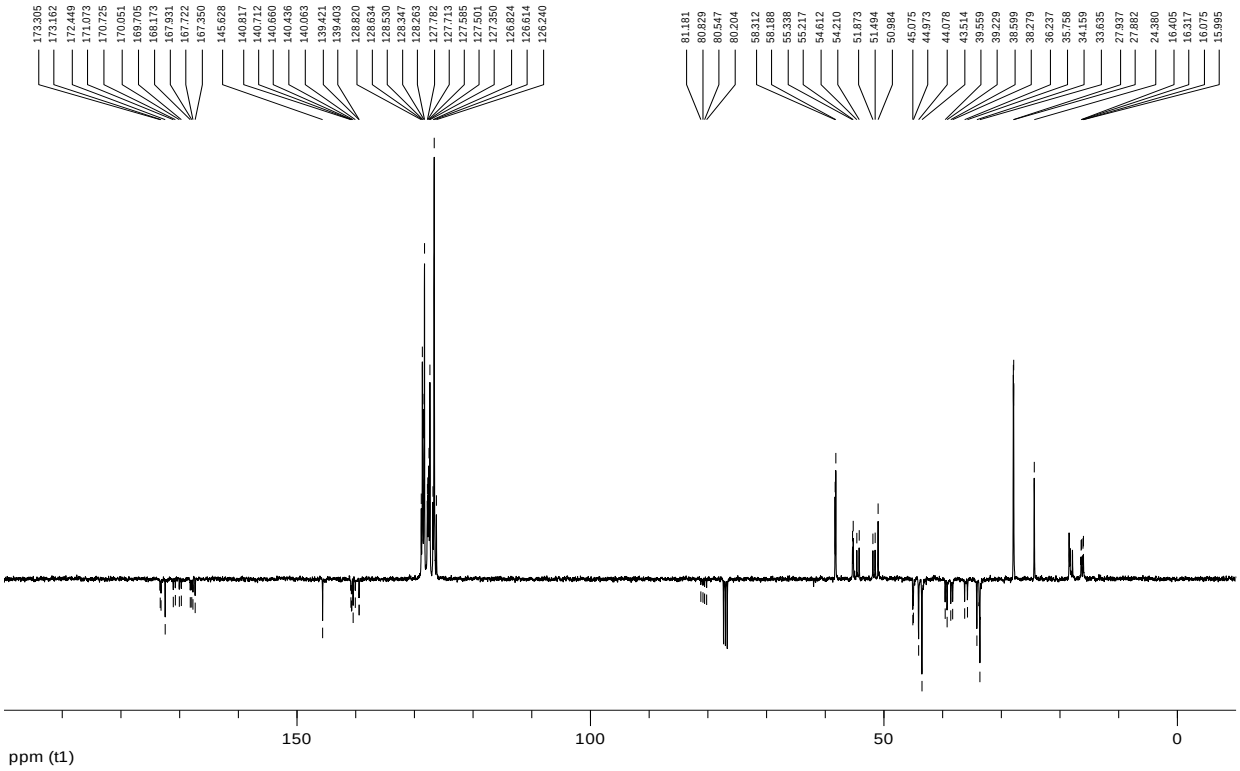


^{1}H NMR spectrum of compound **1** (CD_3CN)

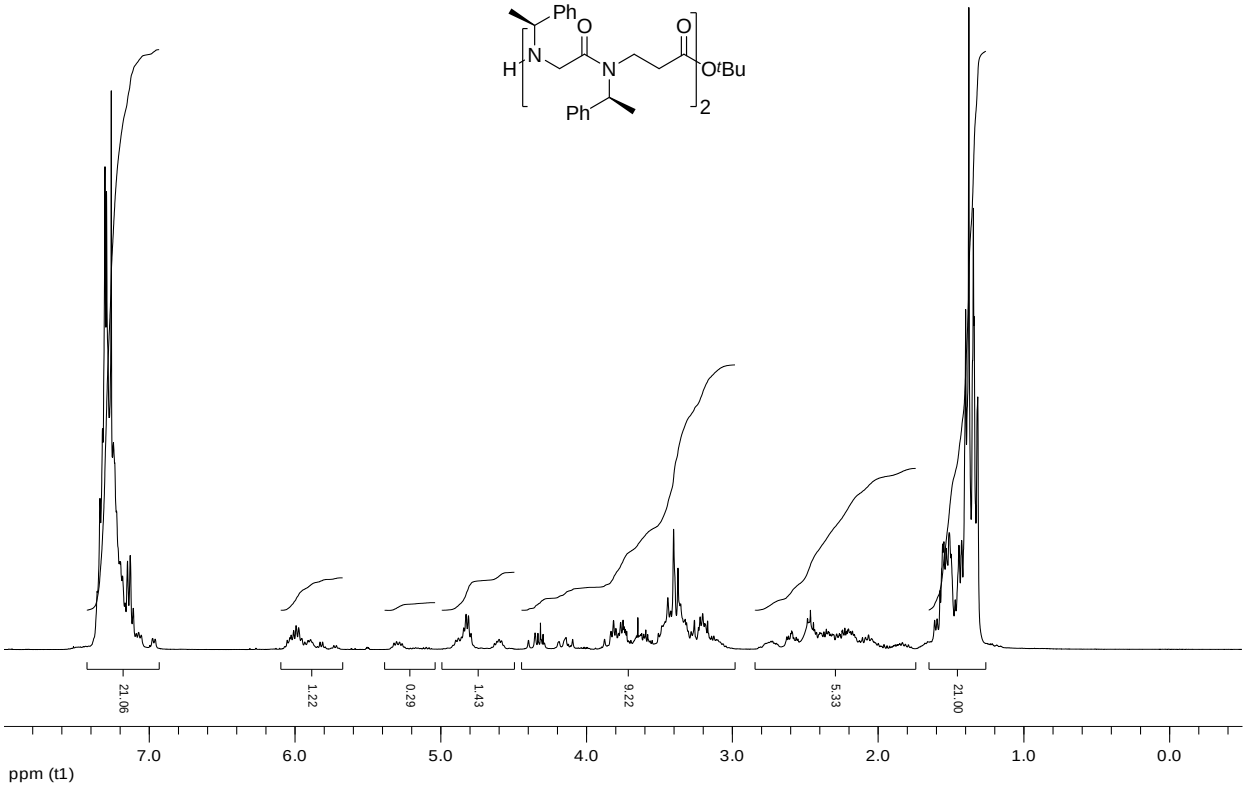


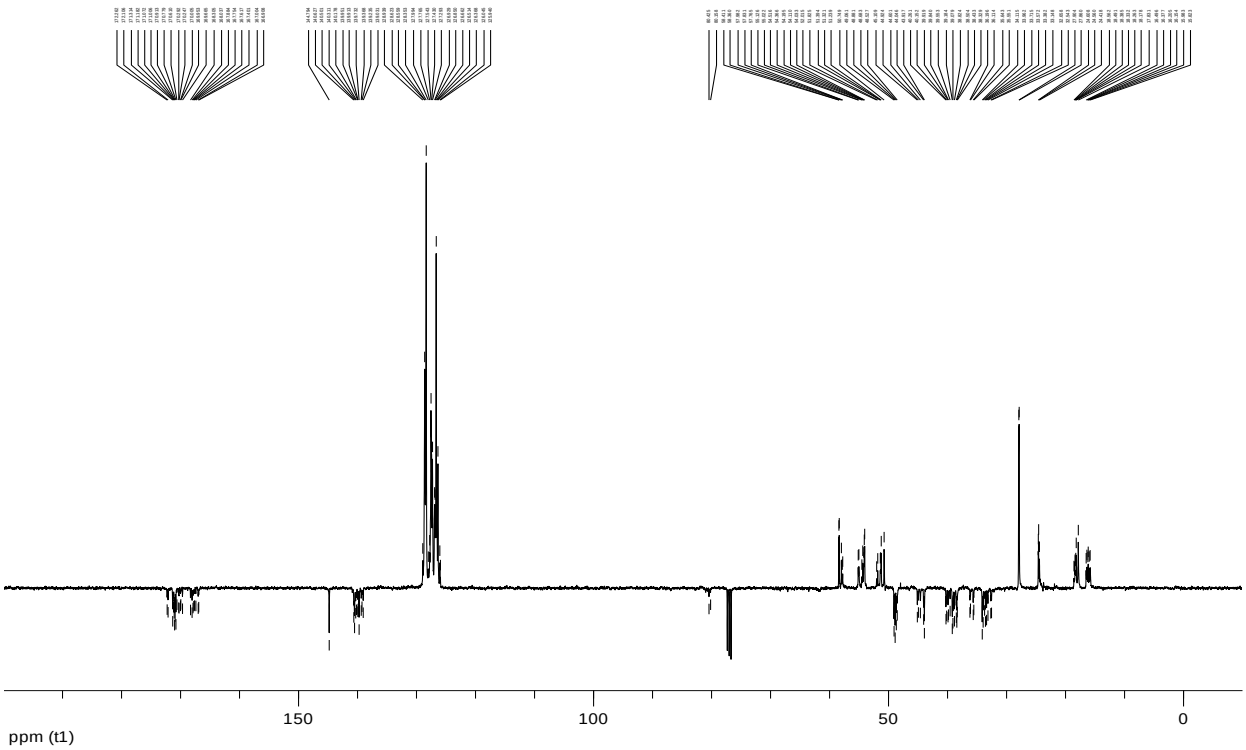
^{1}H and ^{13}C NMR spectra of compound **1a** ($CDCl_3$)



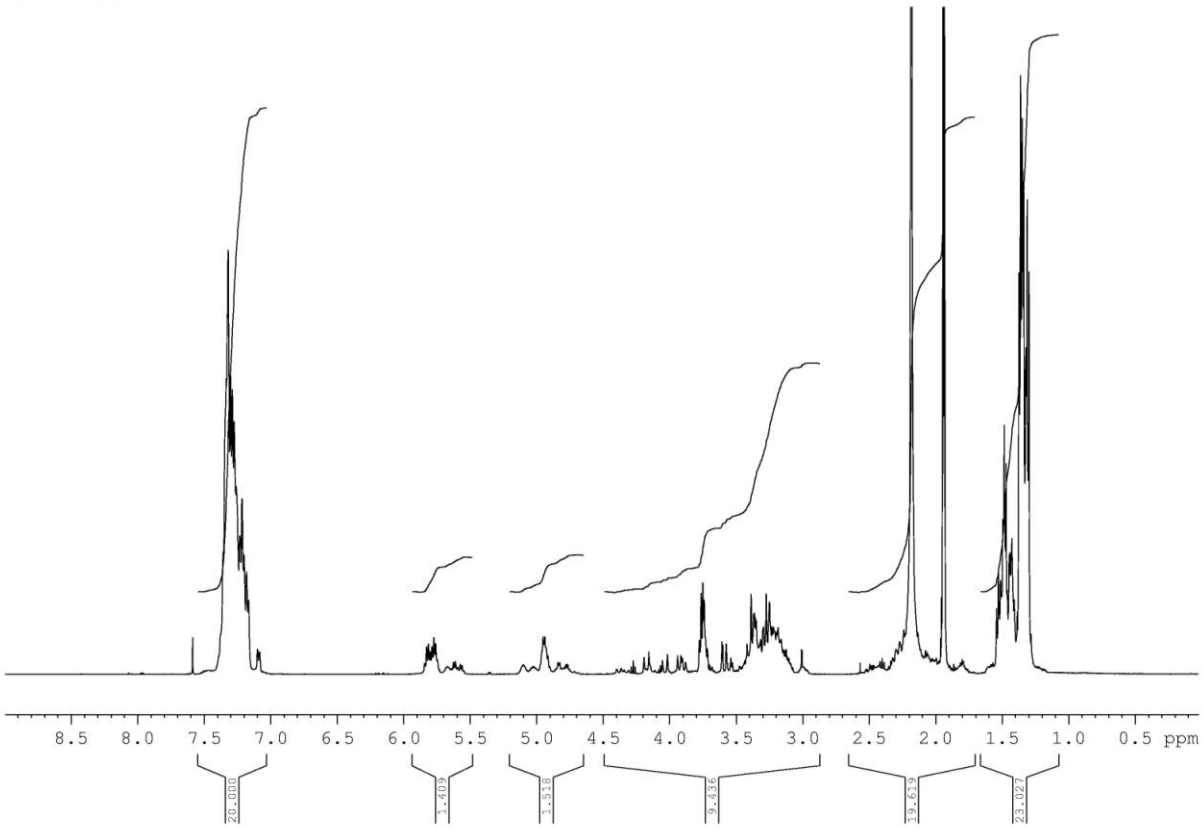


^{1}H and ^{13}C NMR spectra of compound **2** ($CDCl_3$)

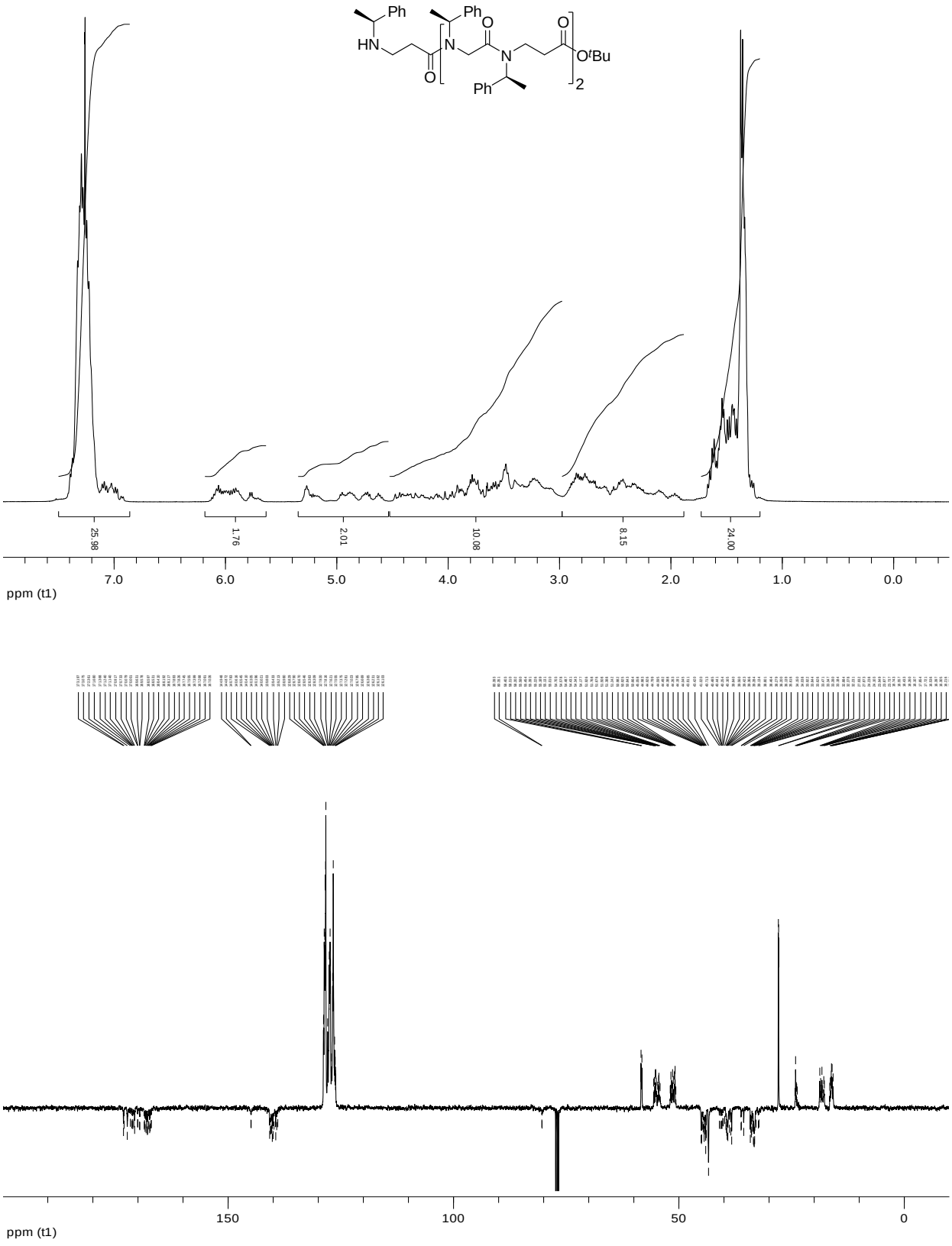




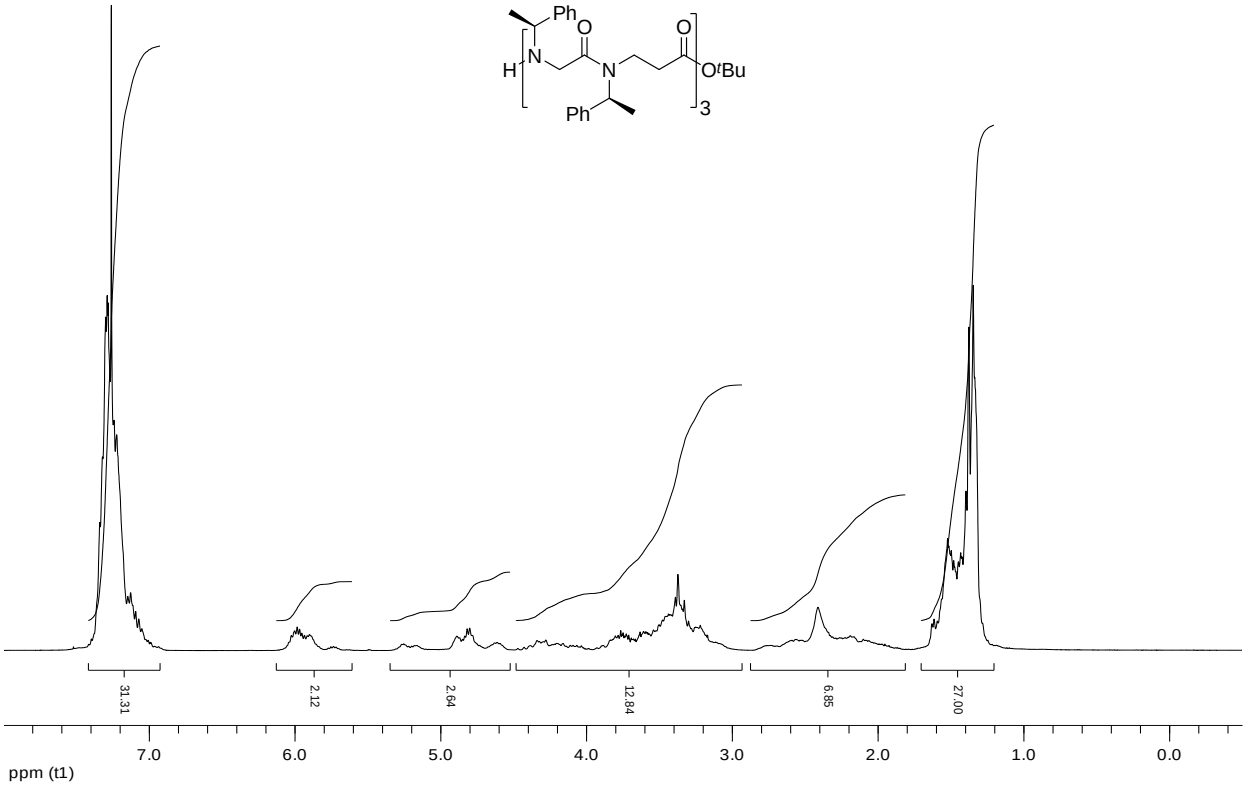
^{1}H NMR spectrum of compound **2** (CD_3CN)

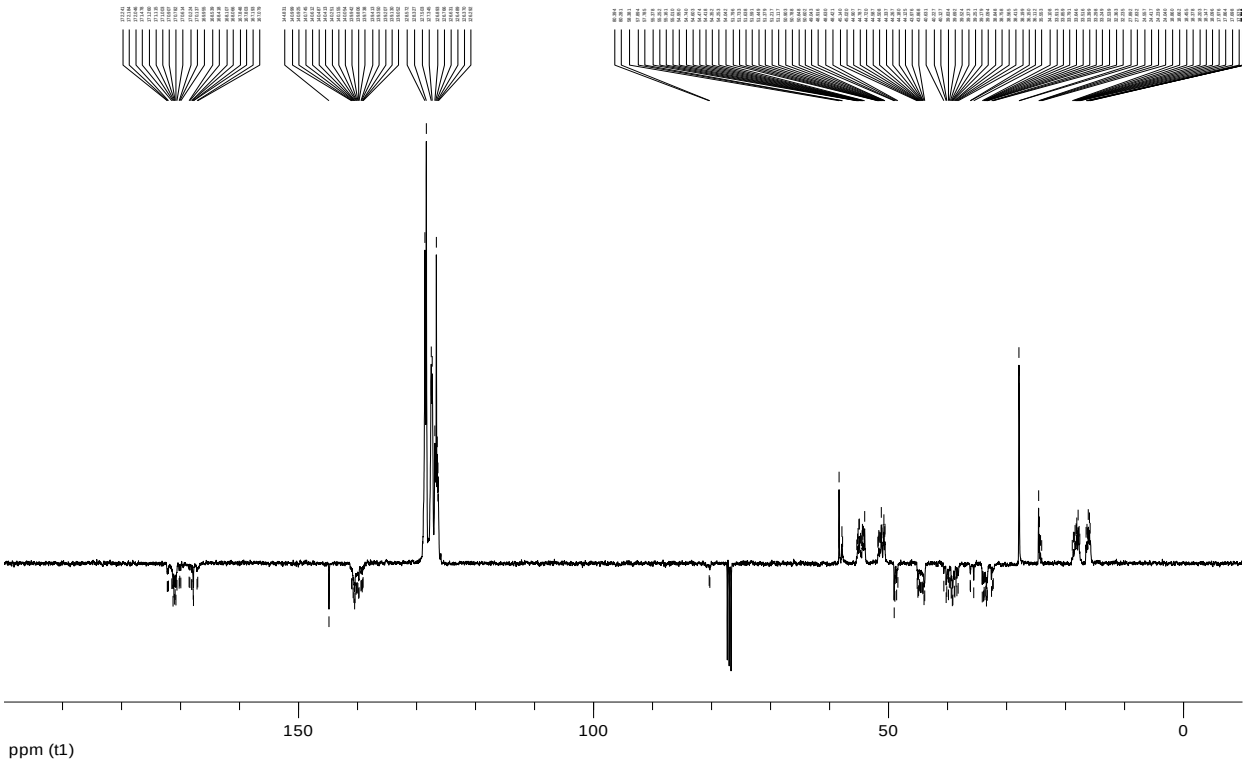


^{1}H and ^{13}C NMR spectra of compound **2a** ($CDCl_3$)

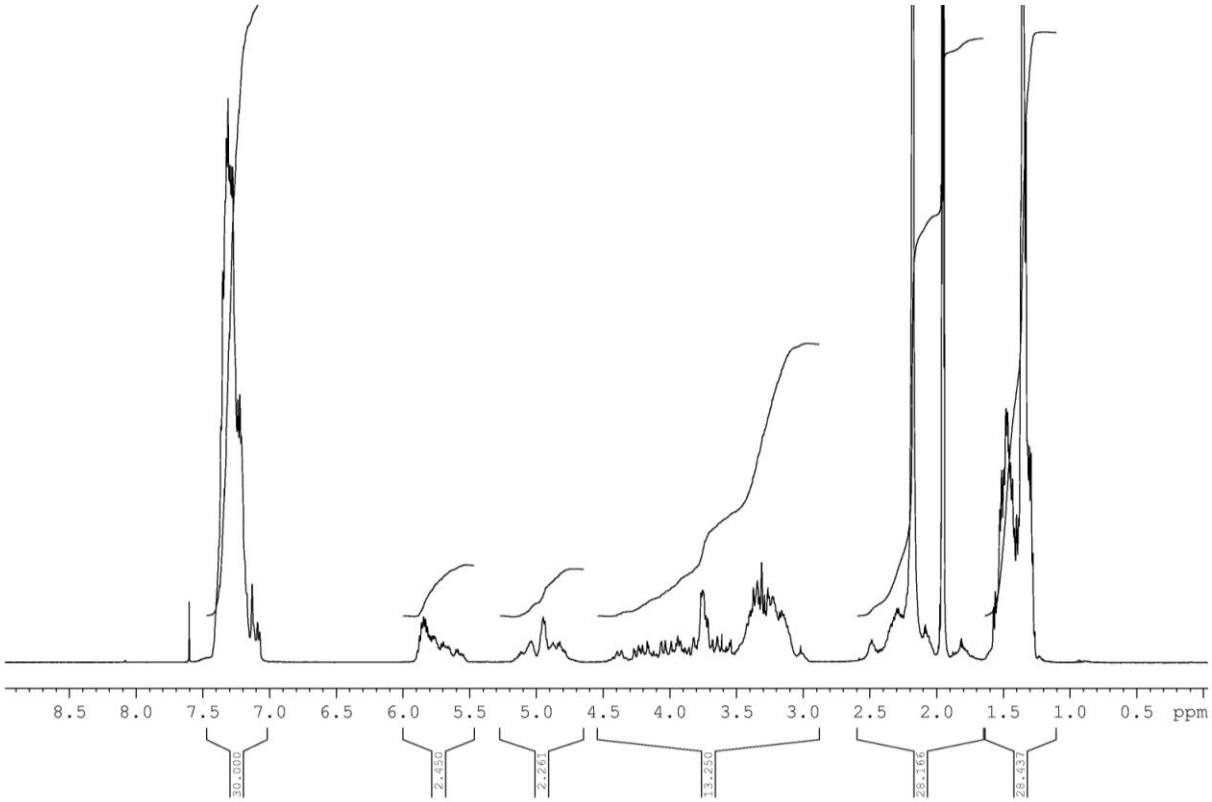


^{1}H and ^{13}C NMR spectra of compound **3** ($CDCl_3$)

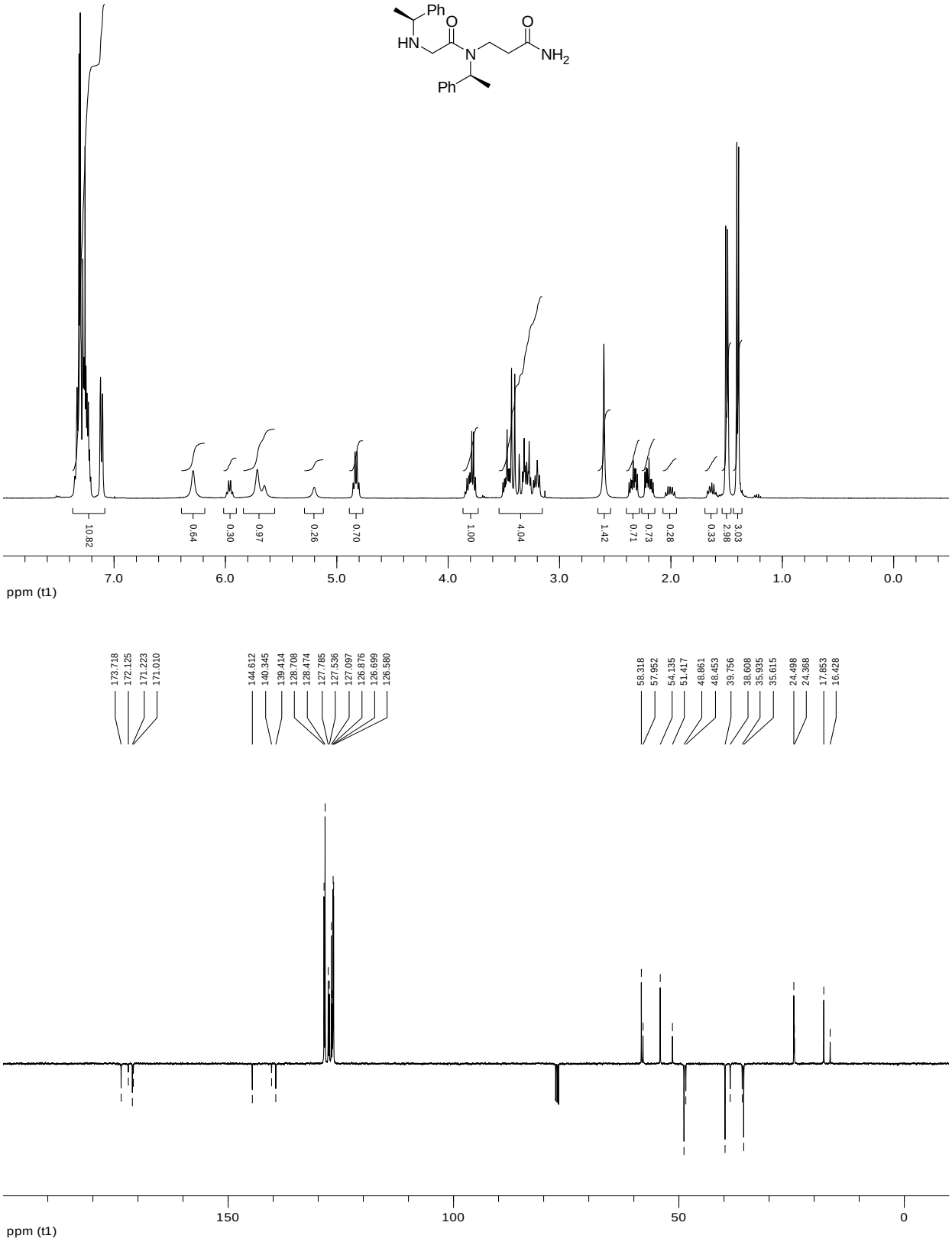




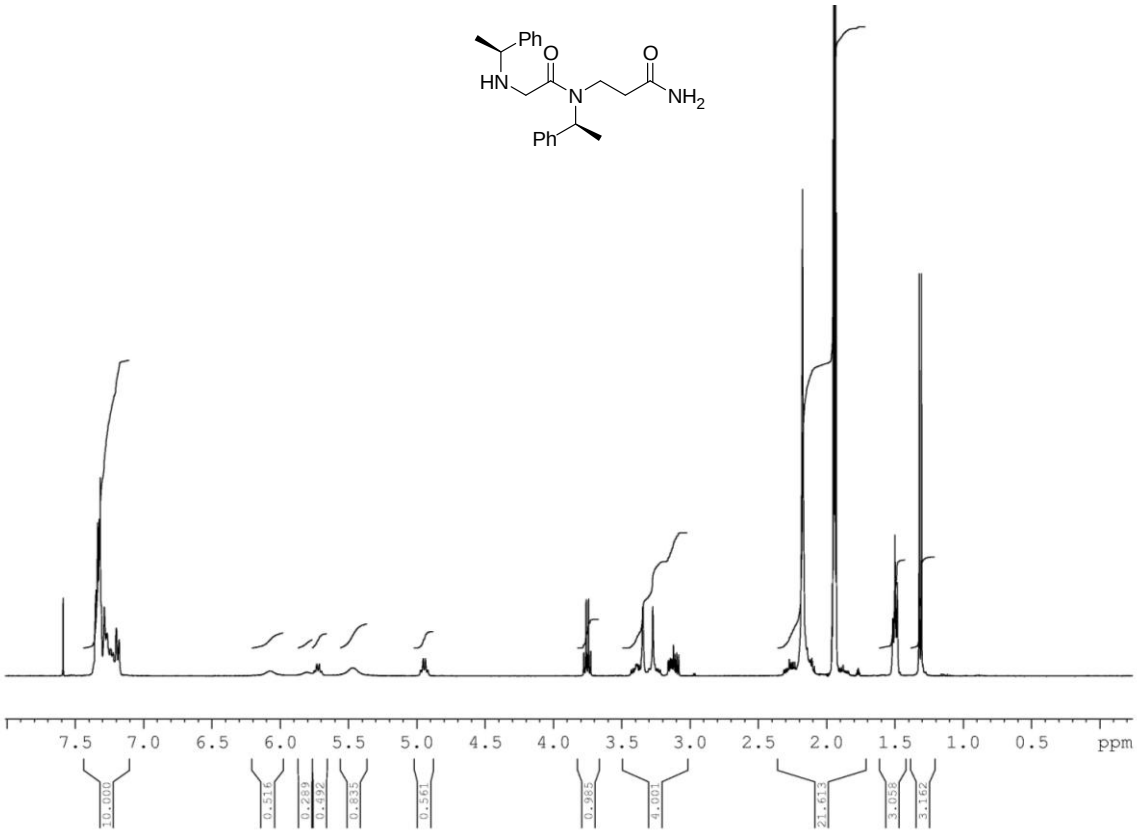
^{1}H NMR spectrum of compound **3** (CD_3CN)



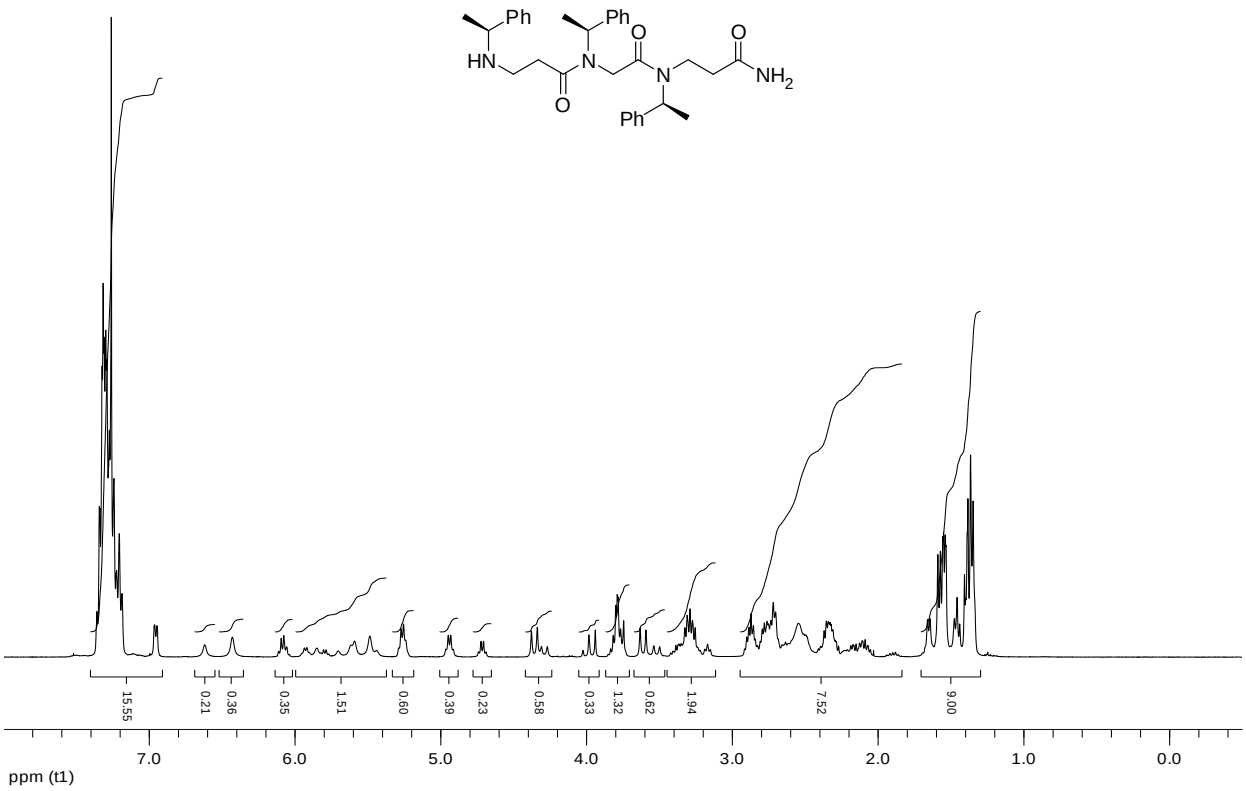
^{1}H and ^{13}C NMR spectra of compound **4** ($CDCl_3$)

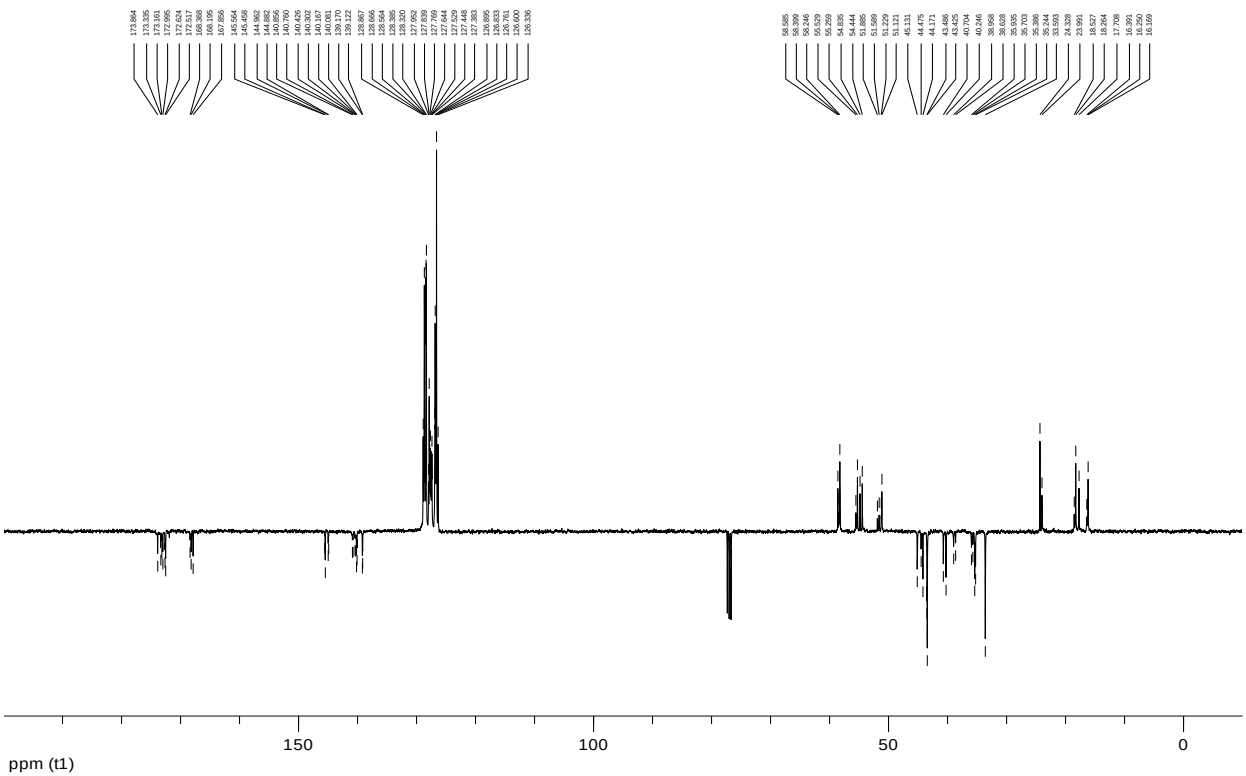


^{1}H NMR spectrum of compound **4** (CD_3CN)

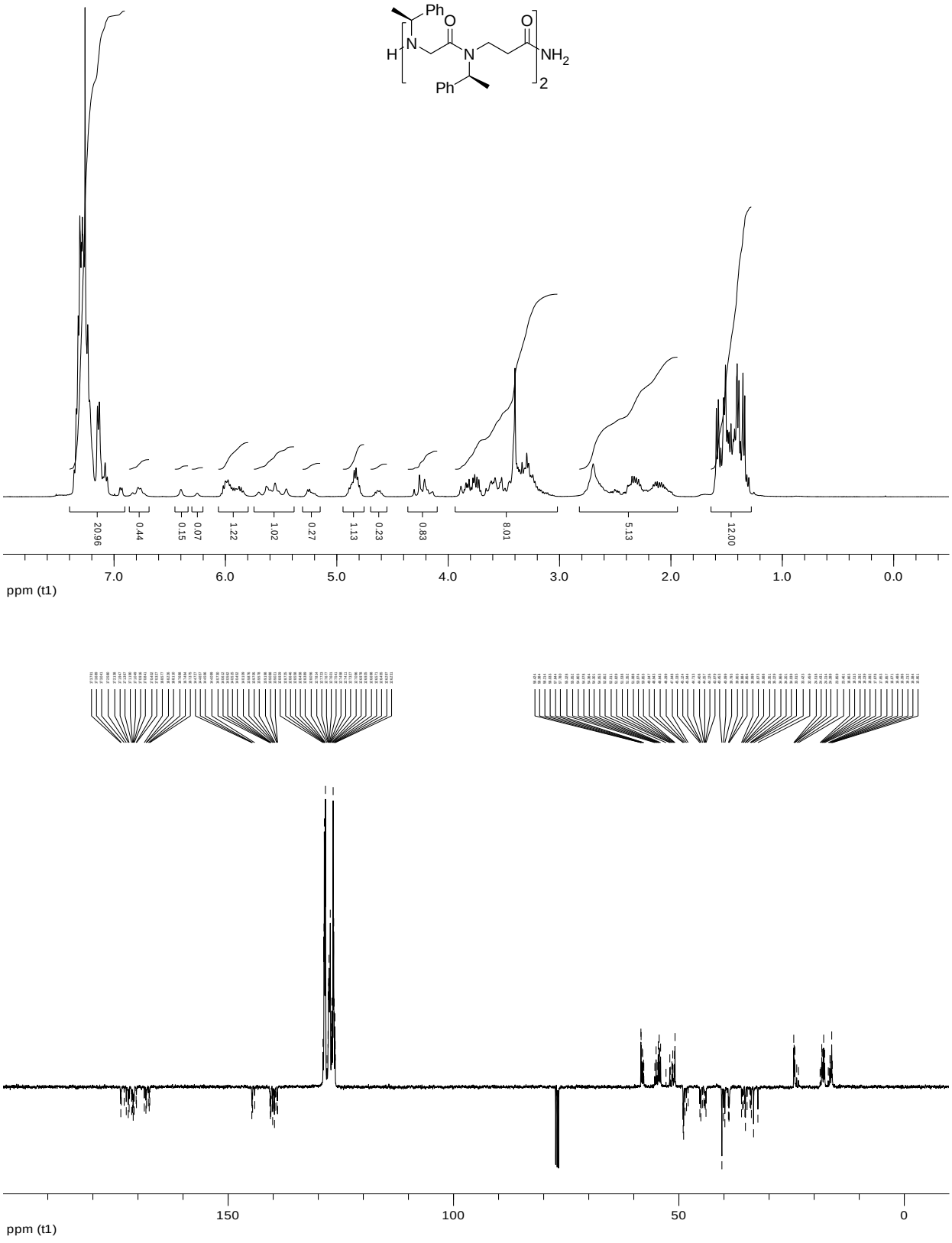


^{1}H and ^{13}C NMR spectra of compound **4a** ($CDCl_3$)

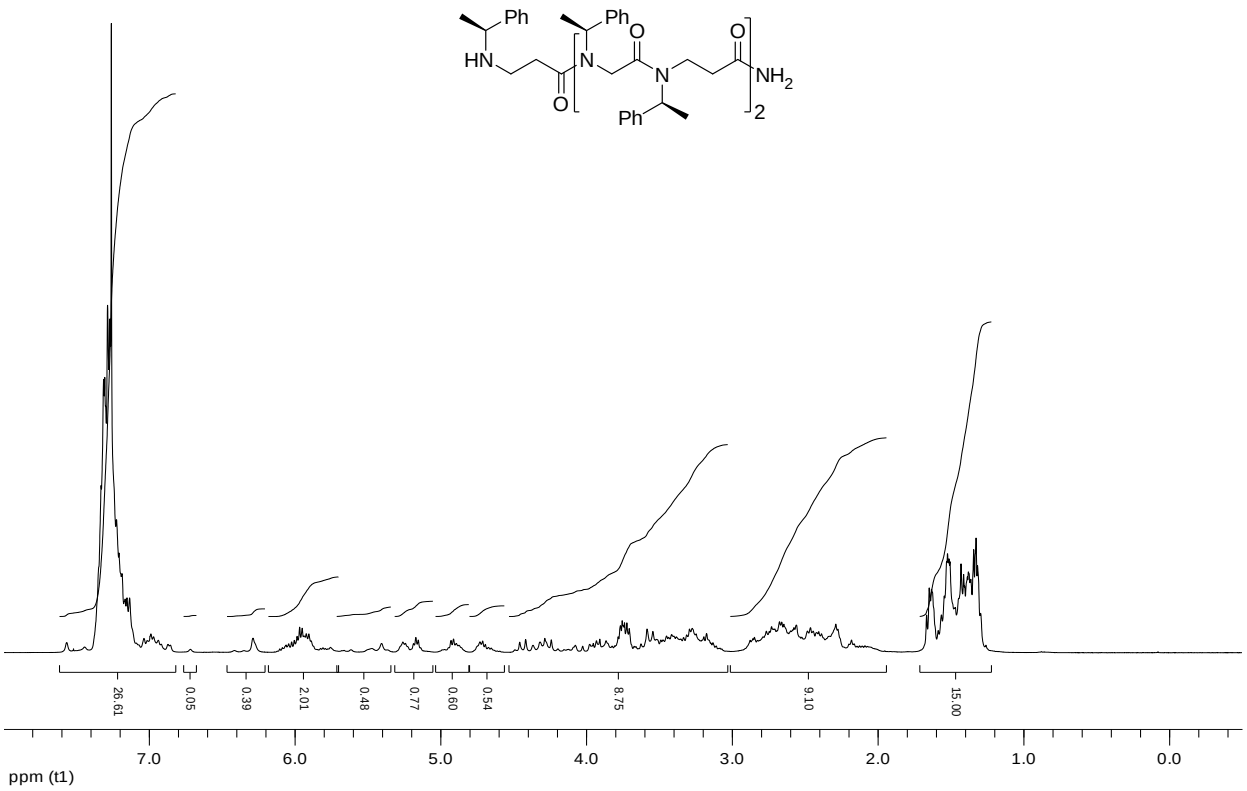


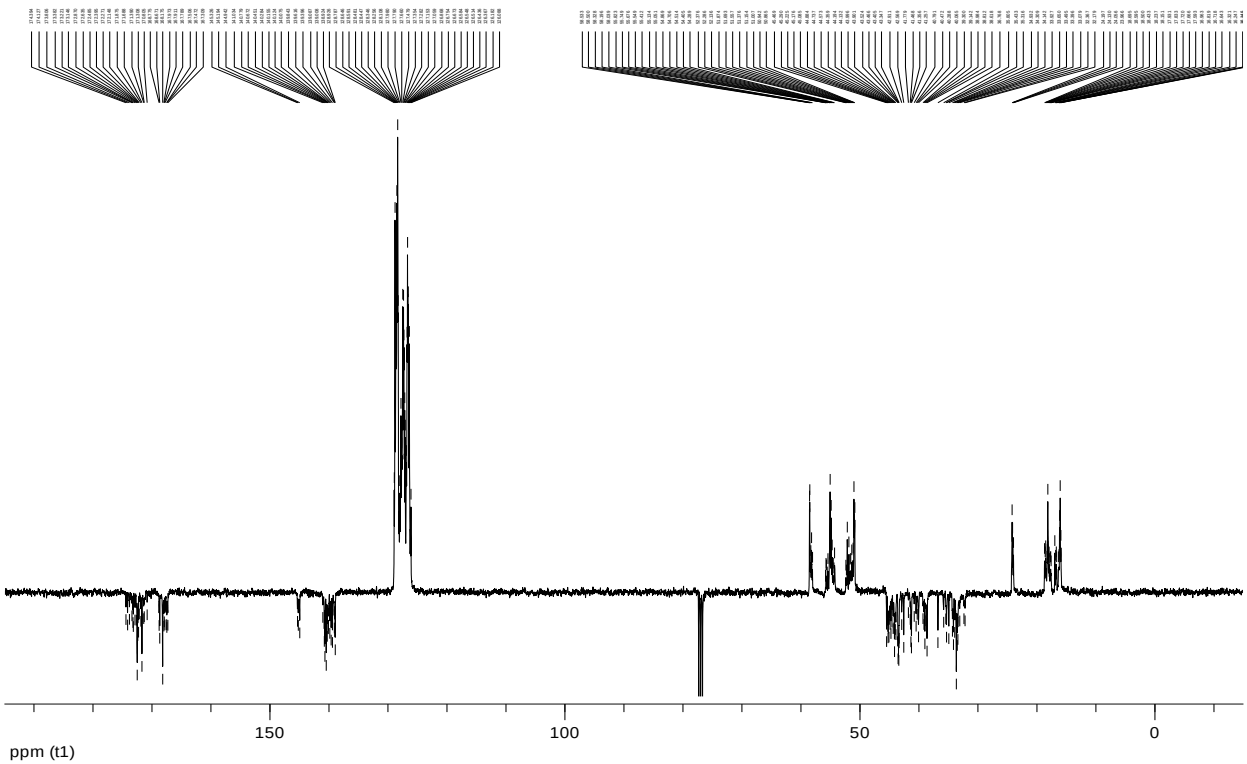


^{1}H and ^{13}C NMR spectra of compound **5** ($CDCl_3$)

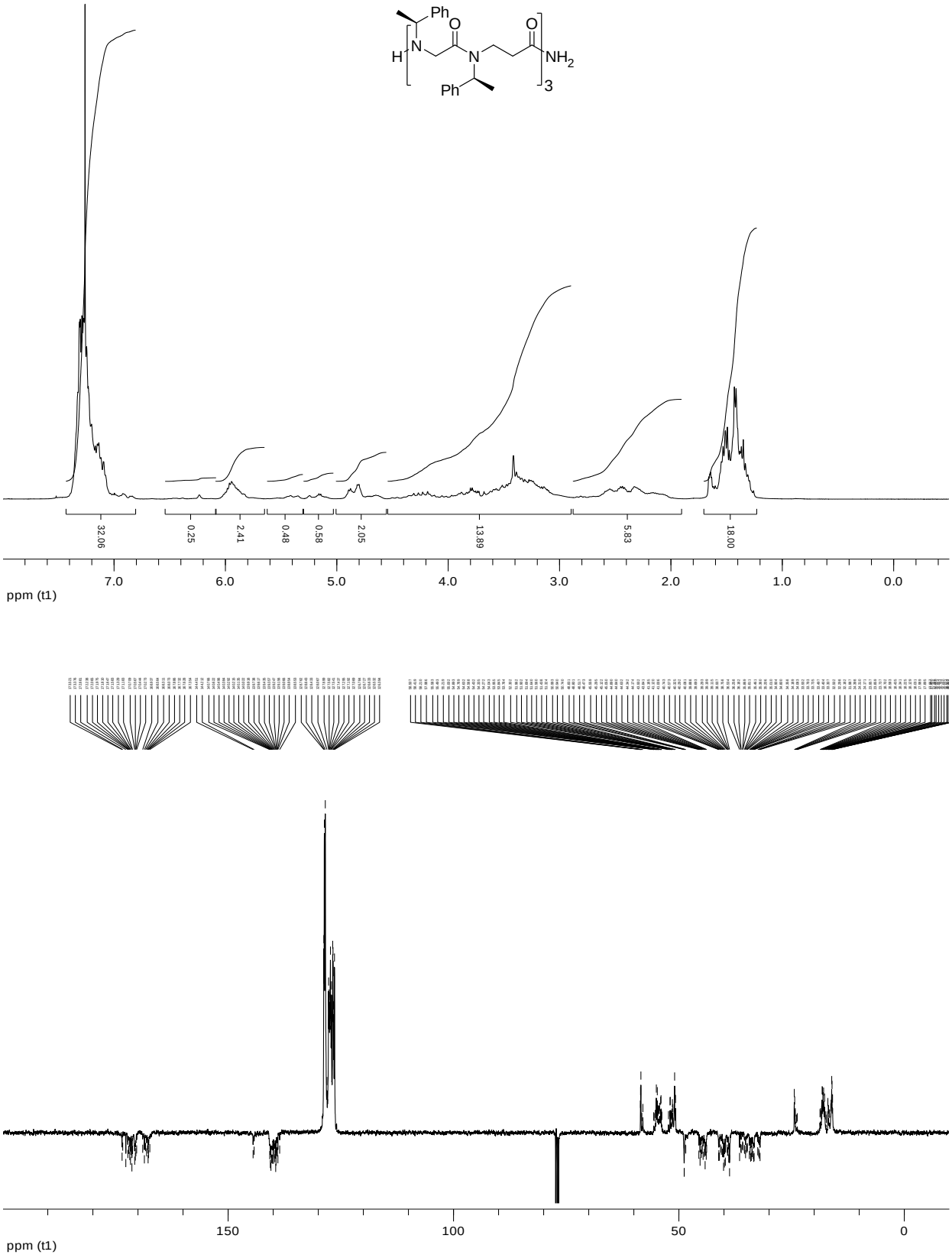


^{1}H and ^{13}C NMR spectra of compound **5a** ($CDCl_3$)

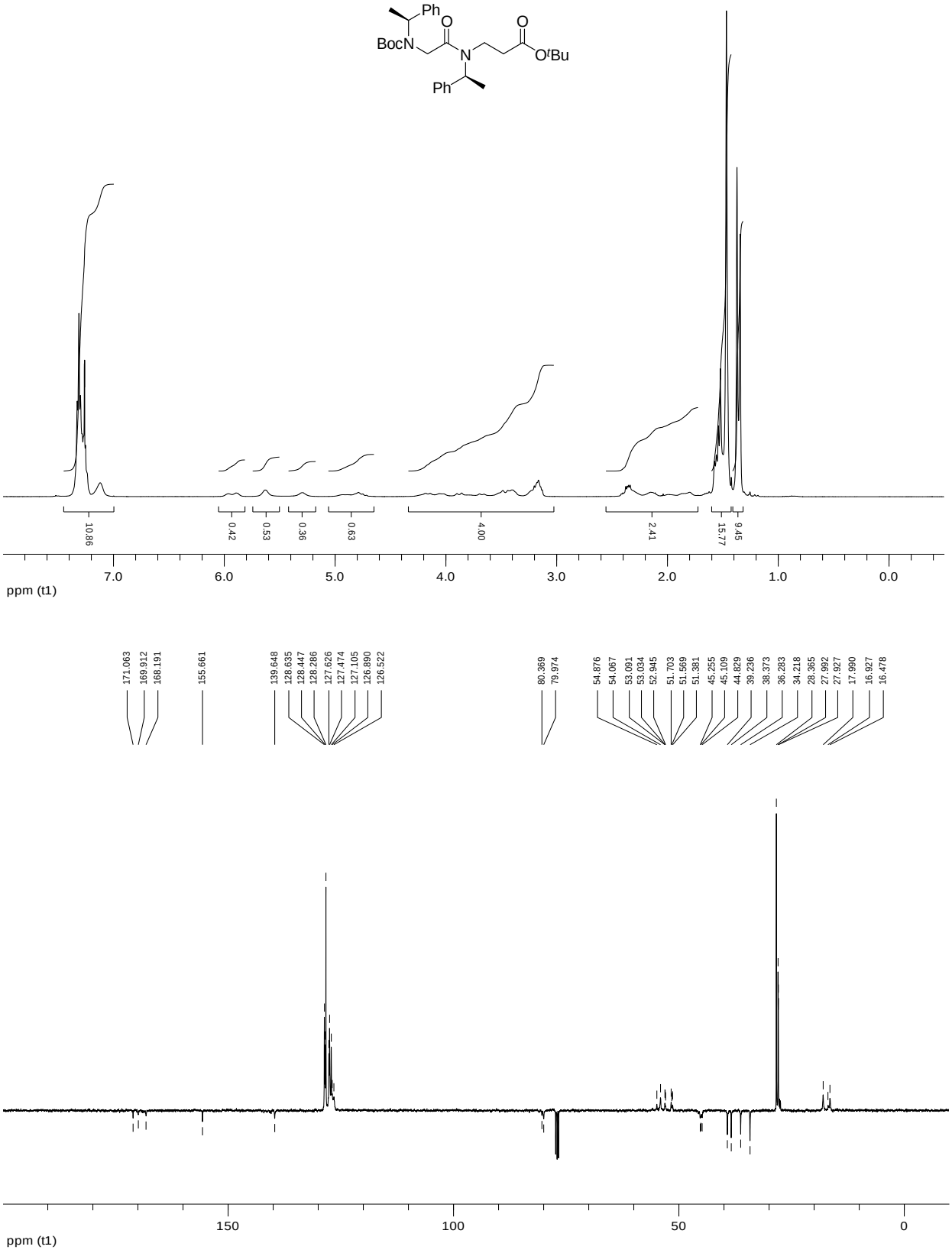




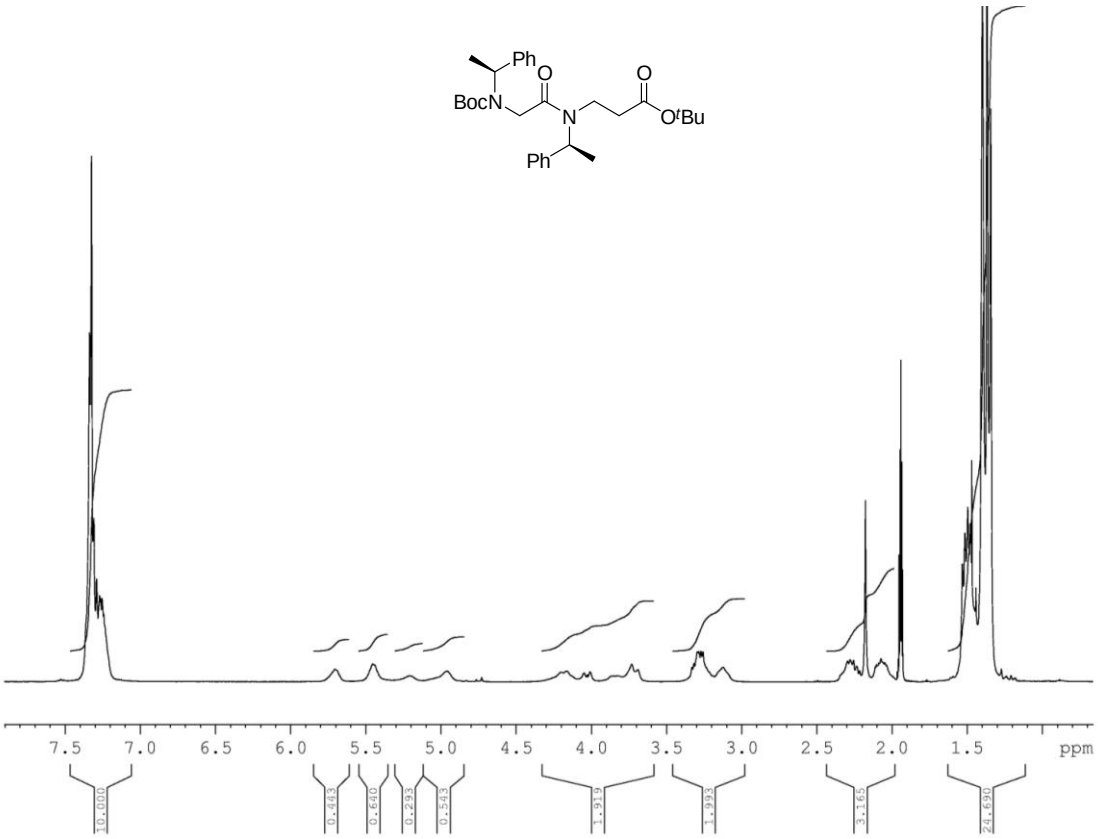
^{1}H and ^{13}C NMR spectra of compound **6** ($CDCl_3$)



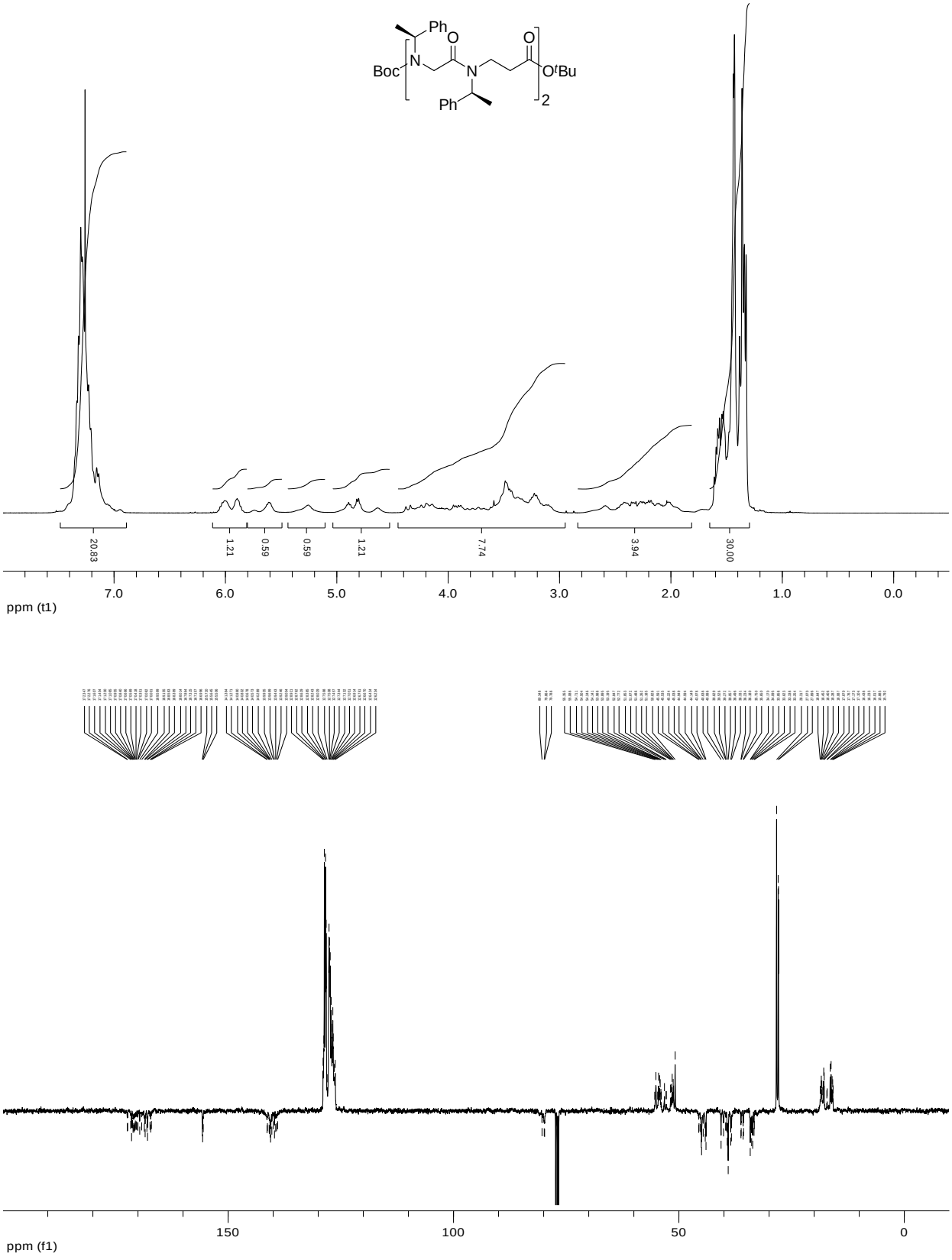
^{1}H and ^{13}C NMR spectra of compound **7** ($CDCl_3$)



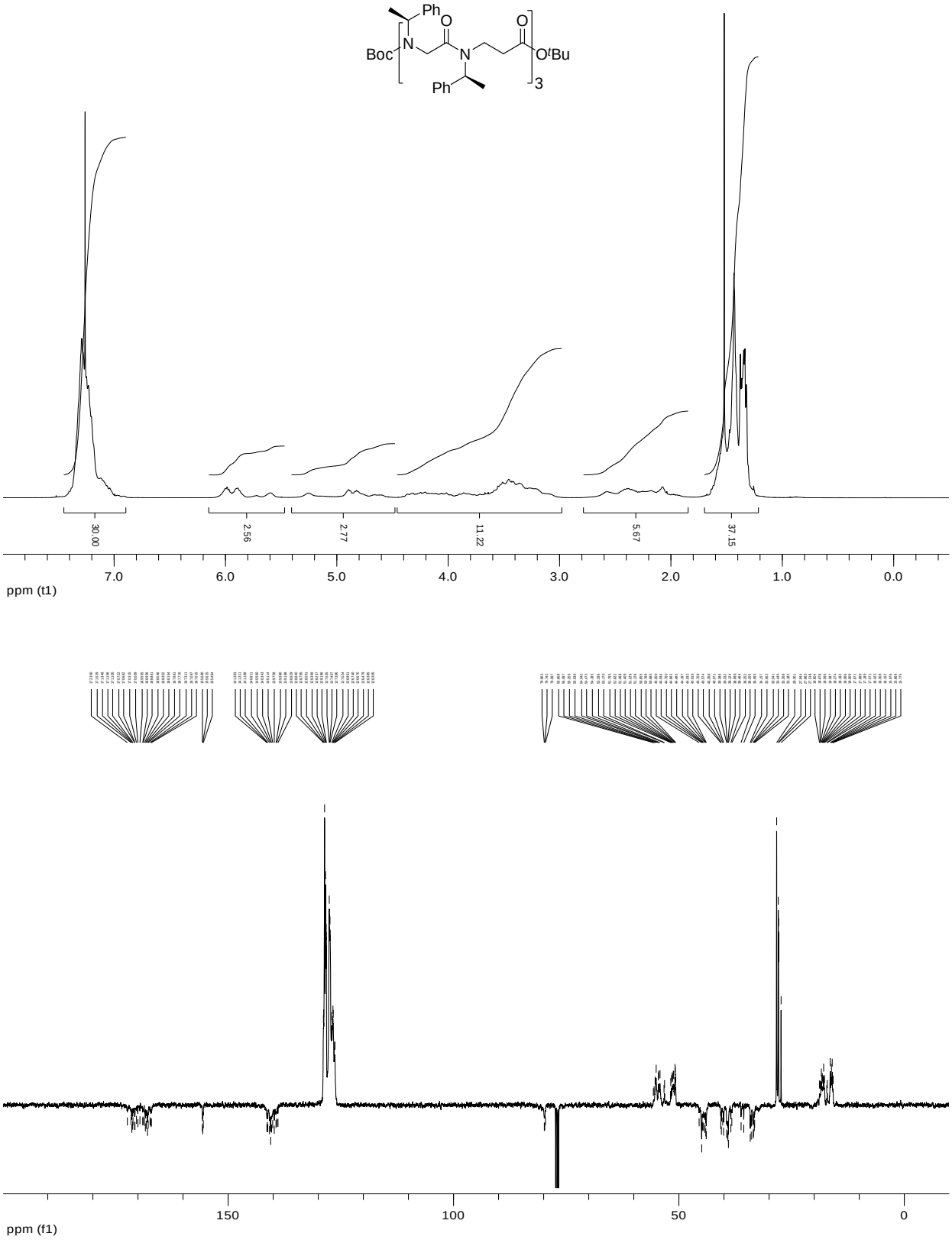
^{1}H NMR spectrum of compound **7** (CD_3CN)



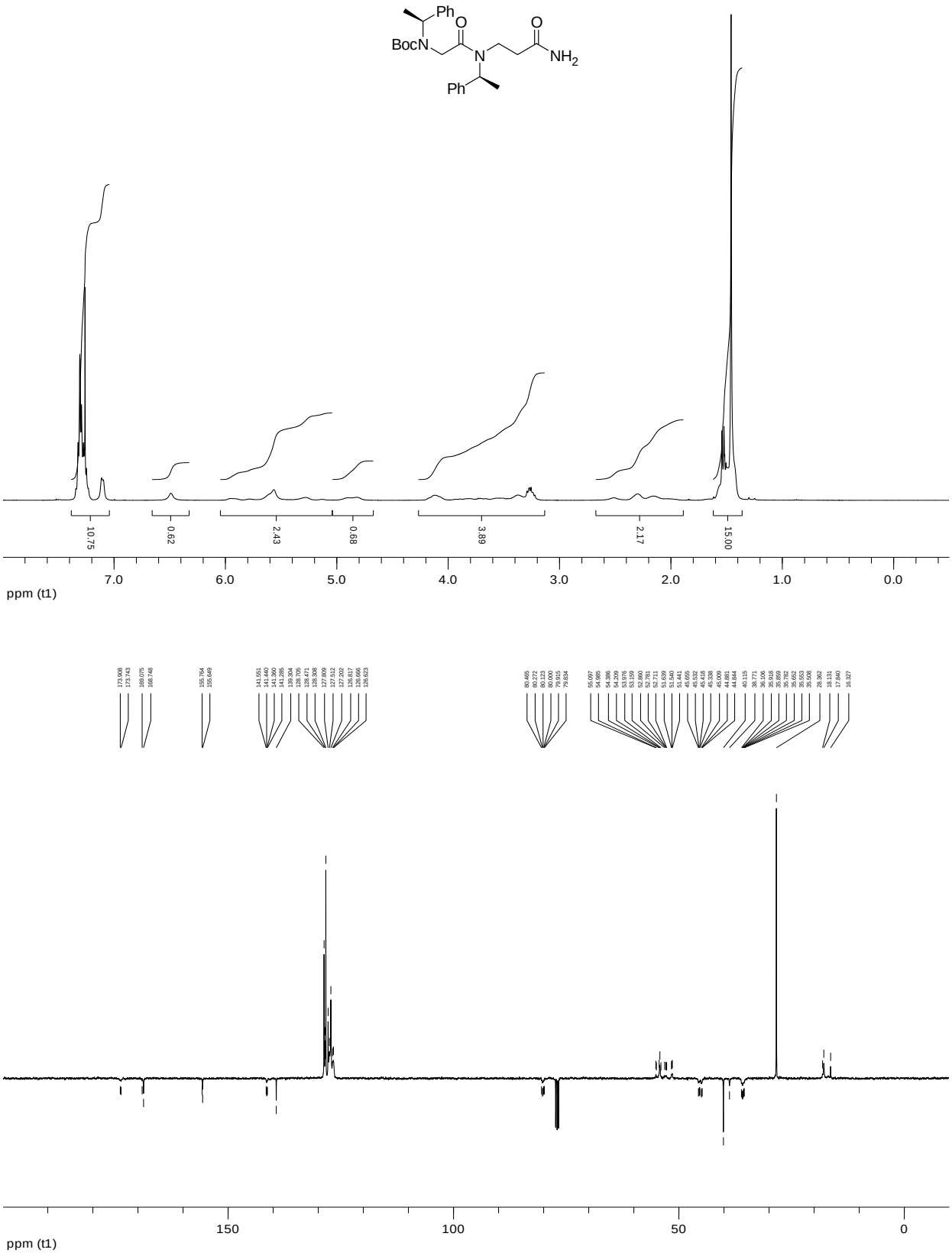
^{1}H and ^{13}C NMR spectra of compound **8** ($CDCl_3$)



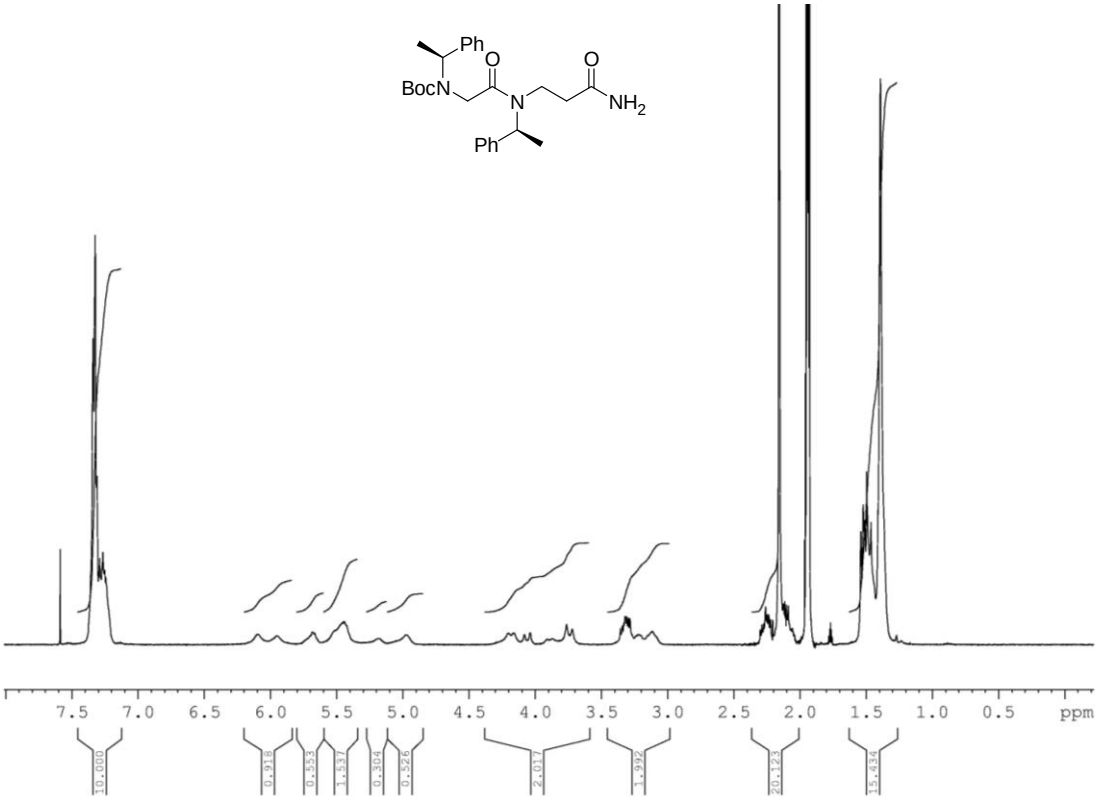
^{1}H and ^{13}C NMR spectra of compound **9** ($CDCl_3$)



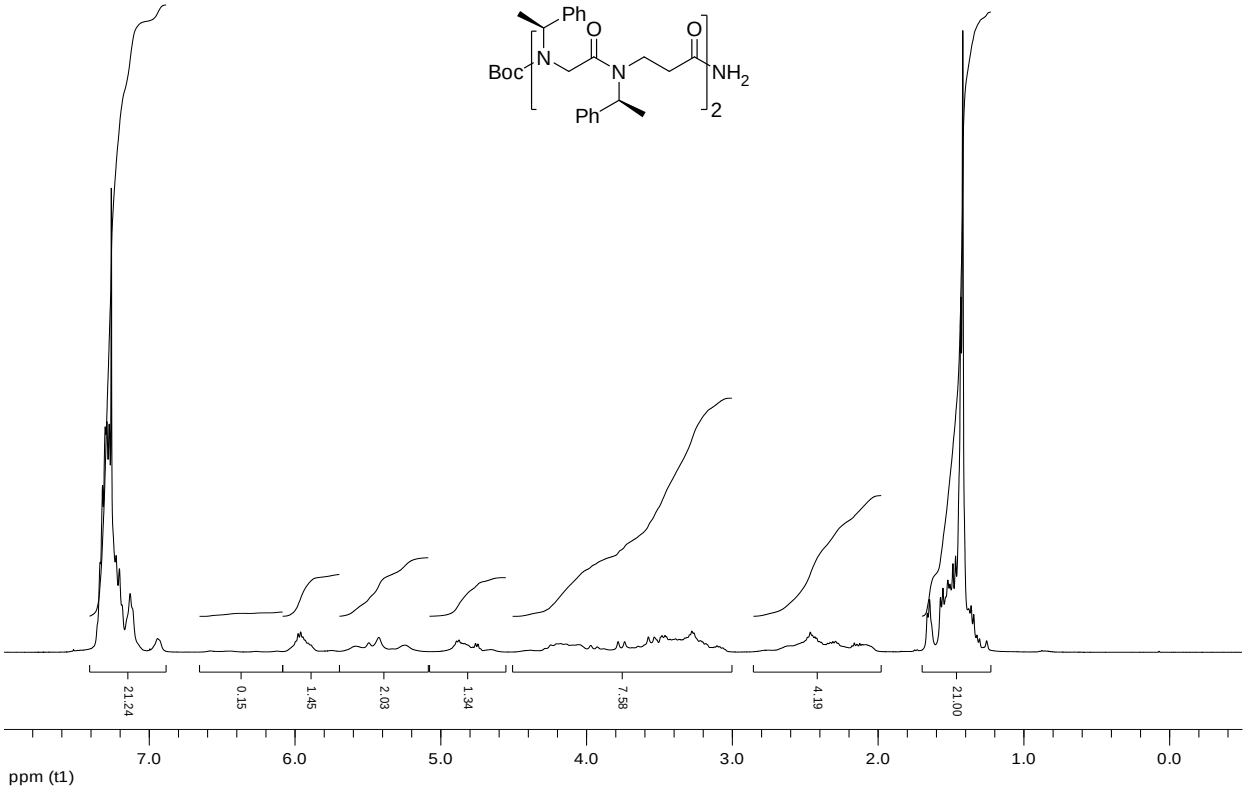
^{1}H and ^{13}C NMR spectra of compound **10** ($CDCl_3$)

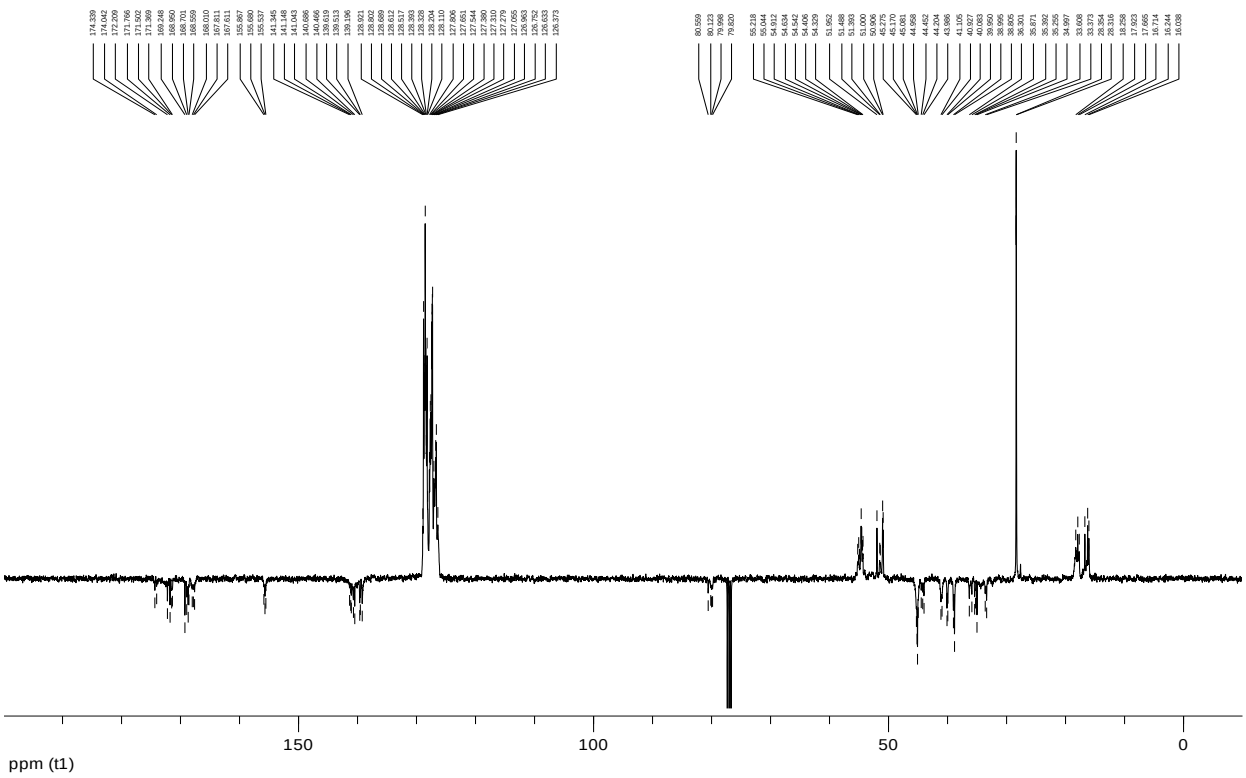


^{1}H NMR spectrum of compound **10** (CD_3CN)

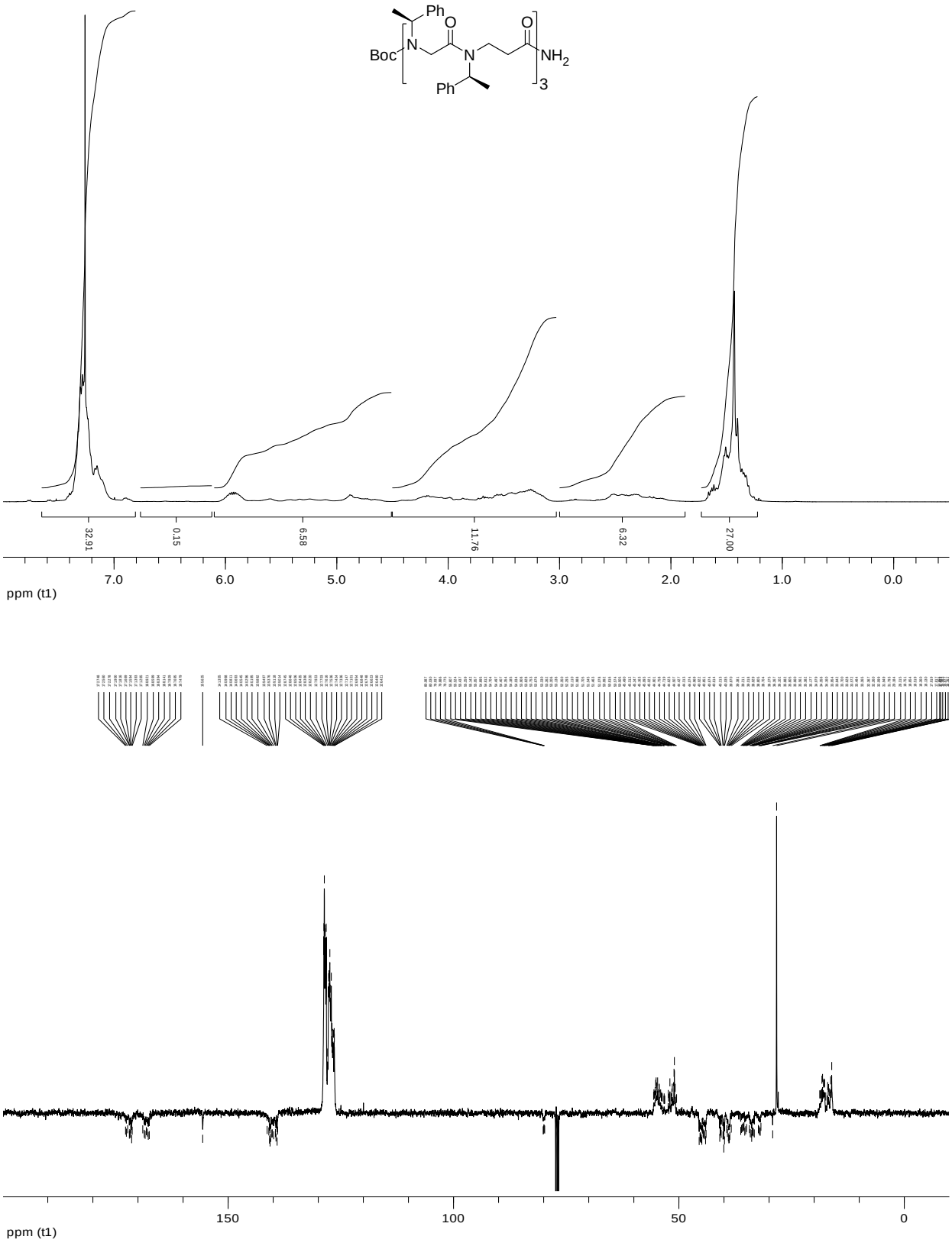


^{1}H and ^{13}C NMR spectra of compound **11** ($CDCl_3$)

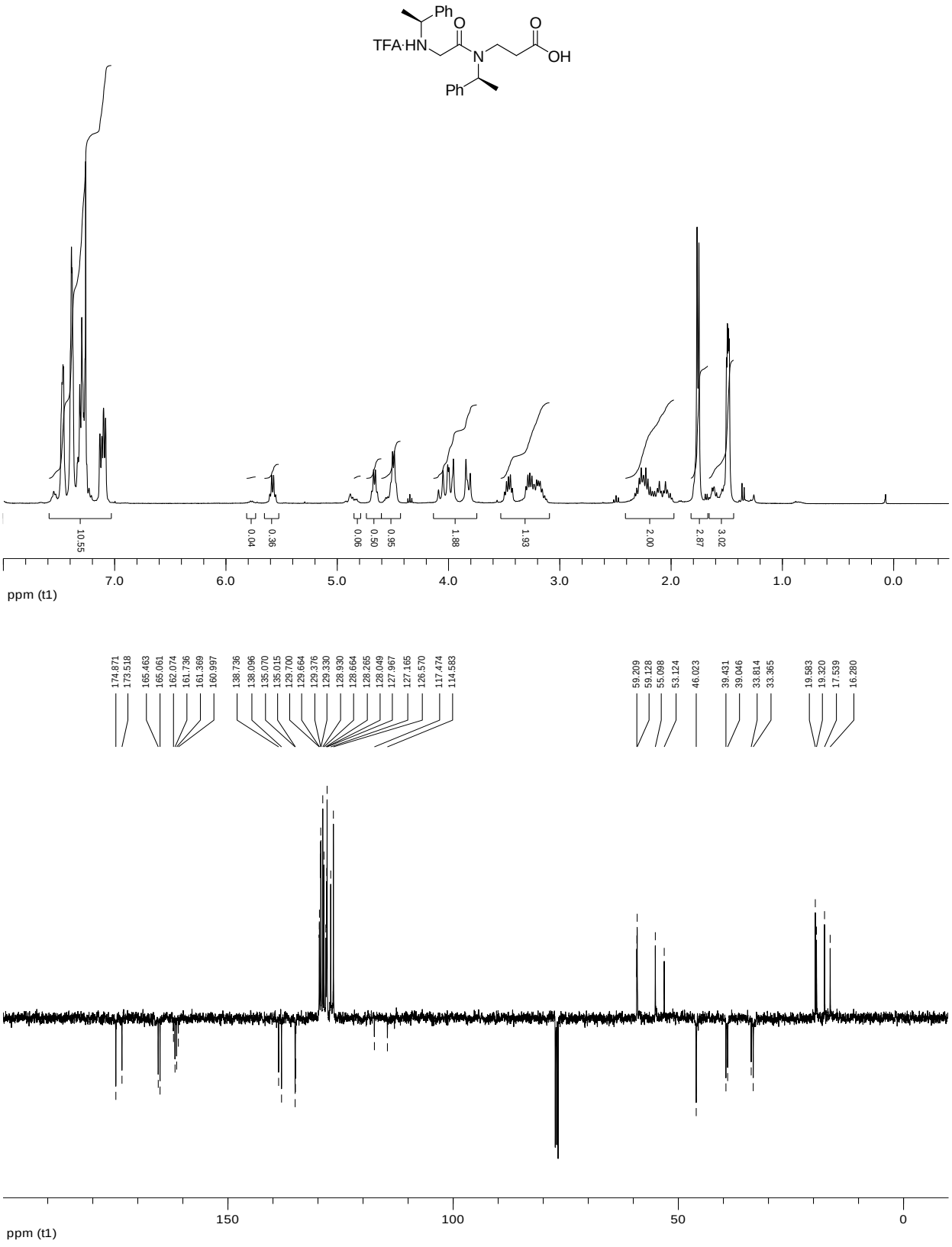




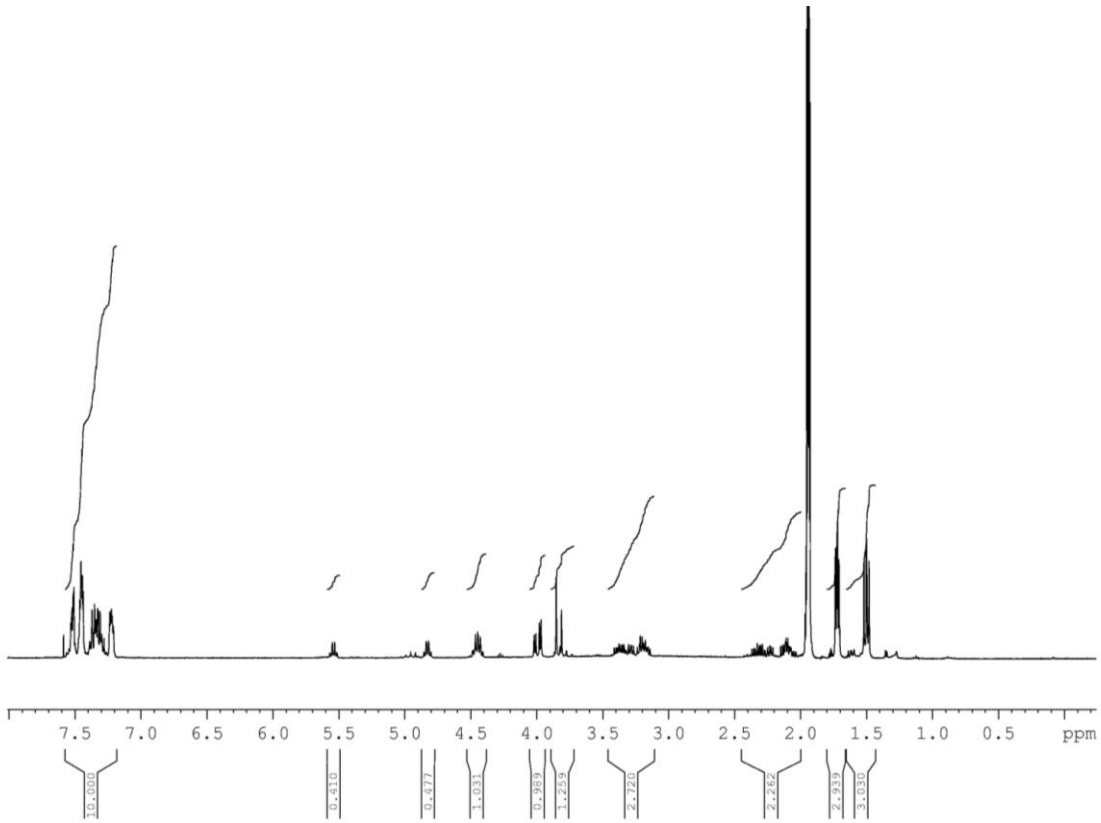
^{1}H and ^{13}C NMR spectra of compound **12** ($CDCl_3$)



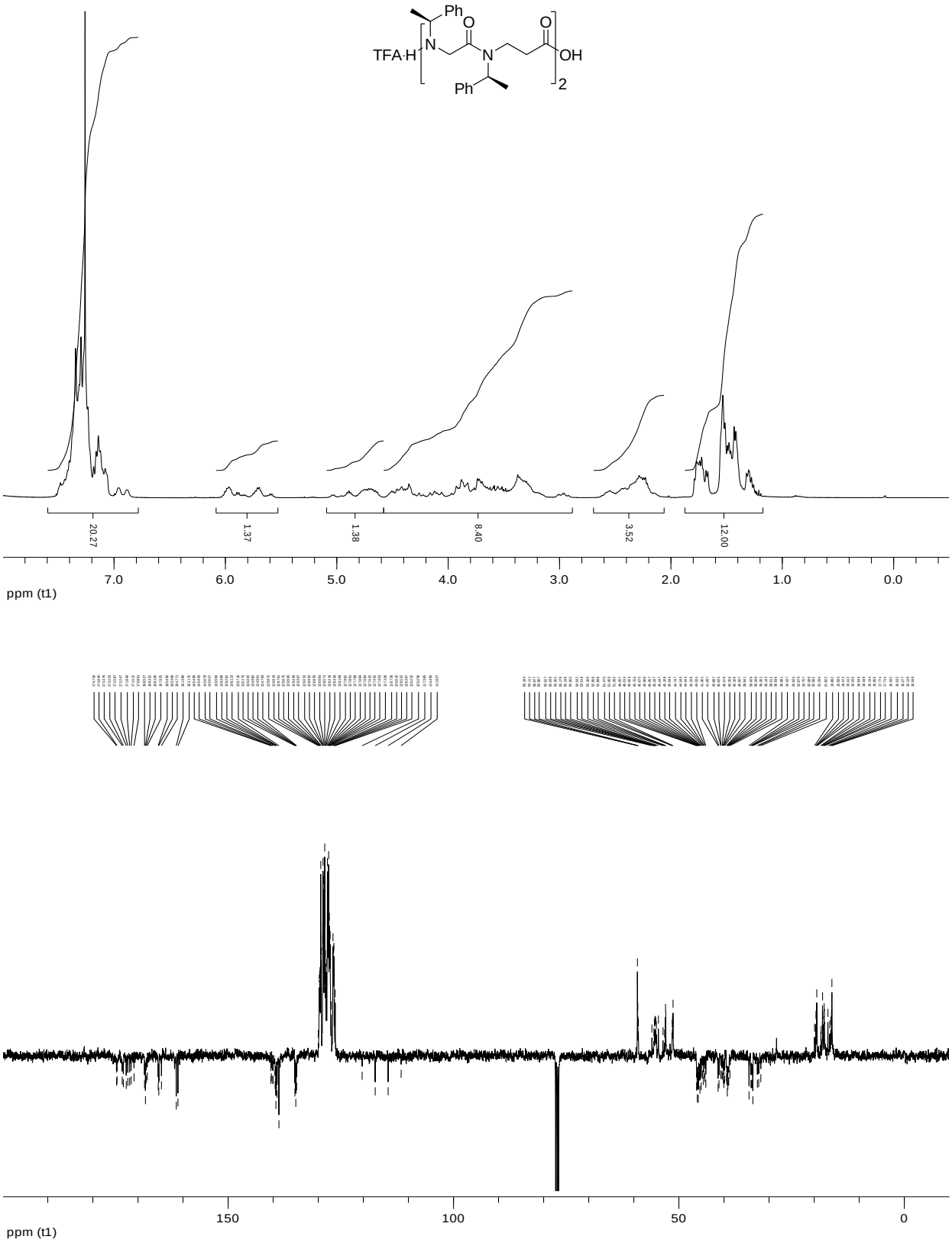
^{1}H and ^{13}C NMR spectra of compound **13** ($CDCl_3$)



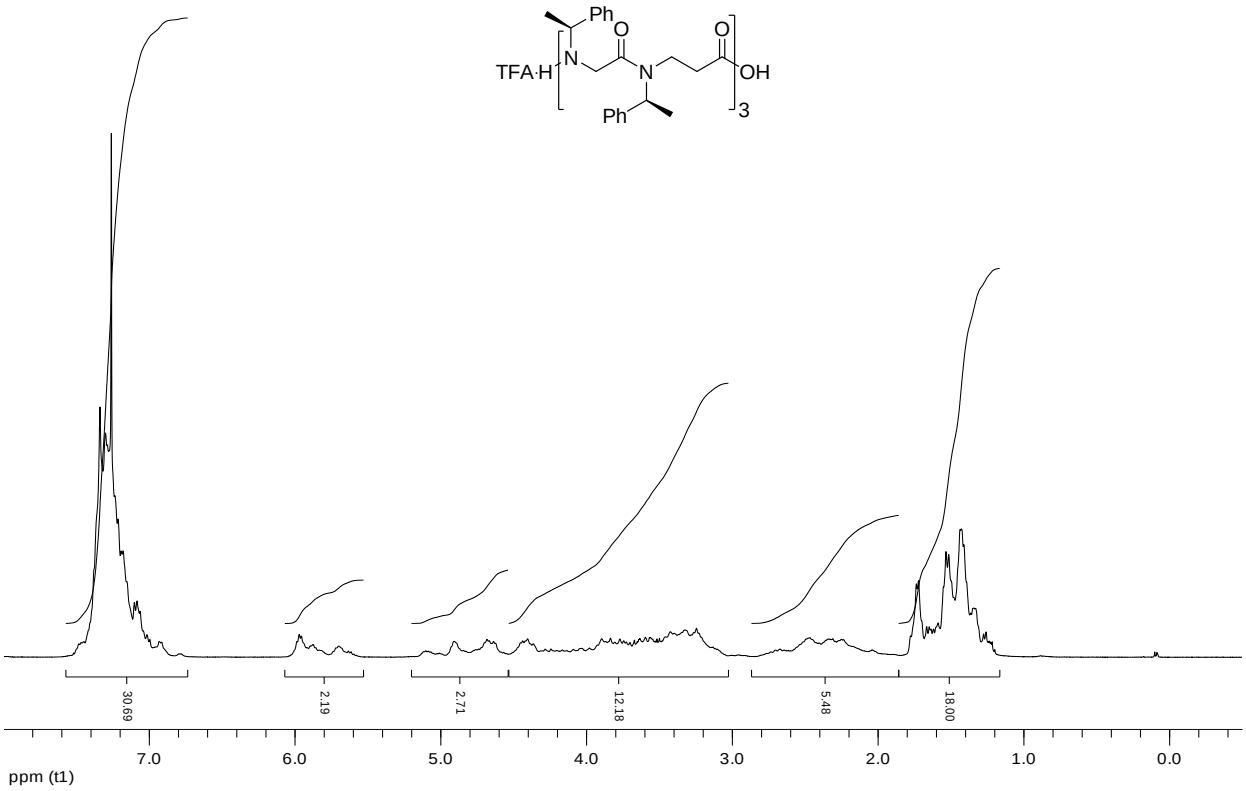
^{1}H NMR spectrum of compound **13** (CD_3CN)



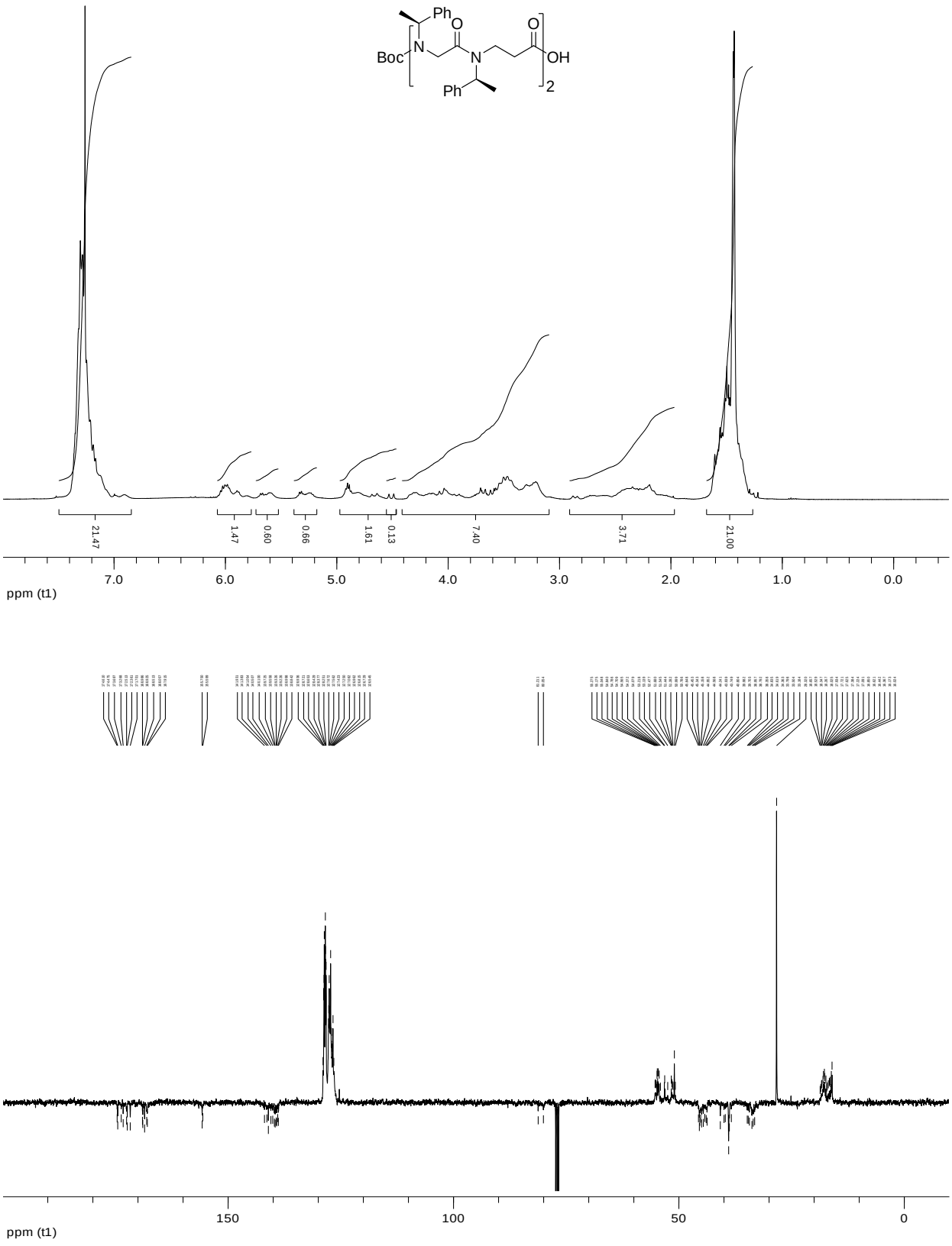
^{1}H and ^{13}C NMR spectra of compound **14** ($CDCl_3$)



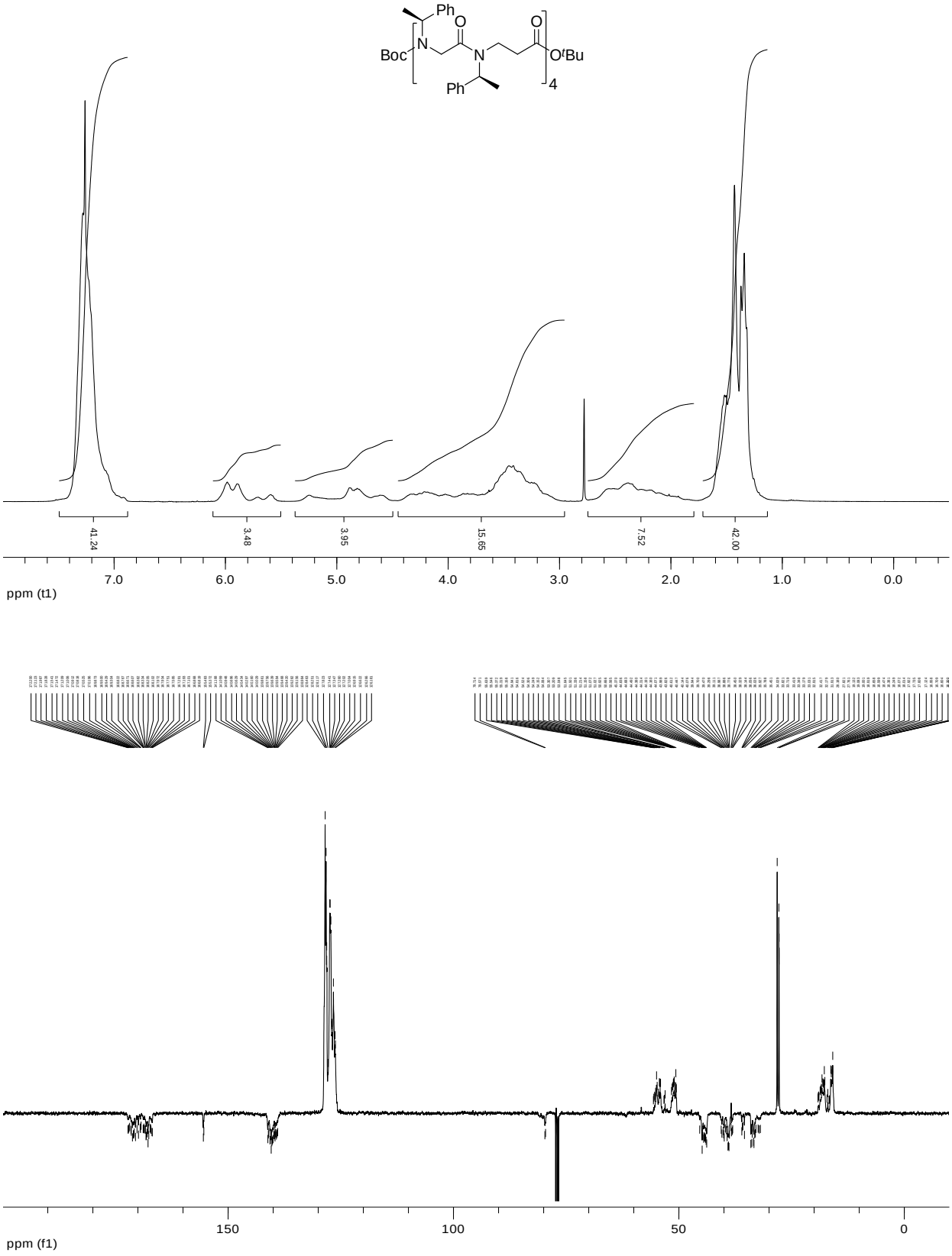
^{1}H NMR spectrum of compound **15** ($CDCl_3$)



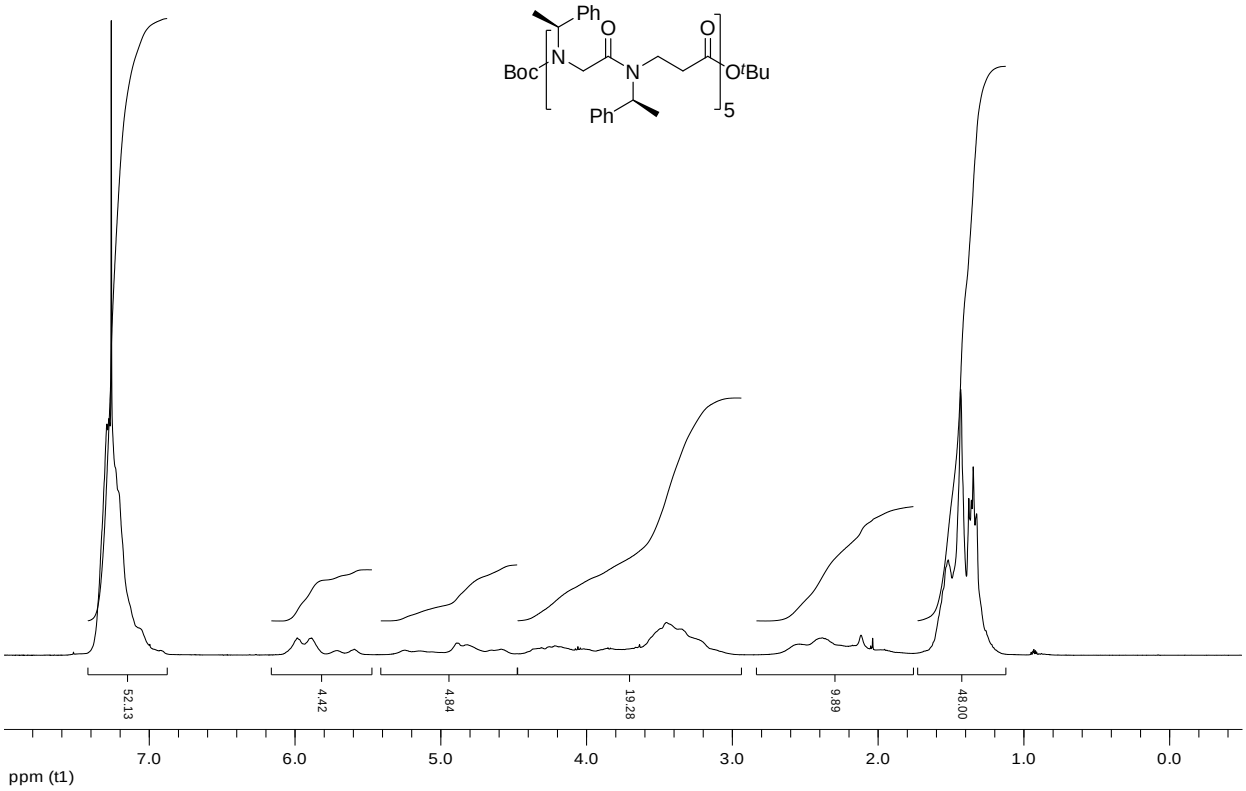
^{1}H and ^{13}C NMR spectra of compound **16** ($CDCl_3$)

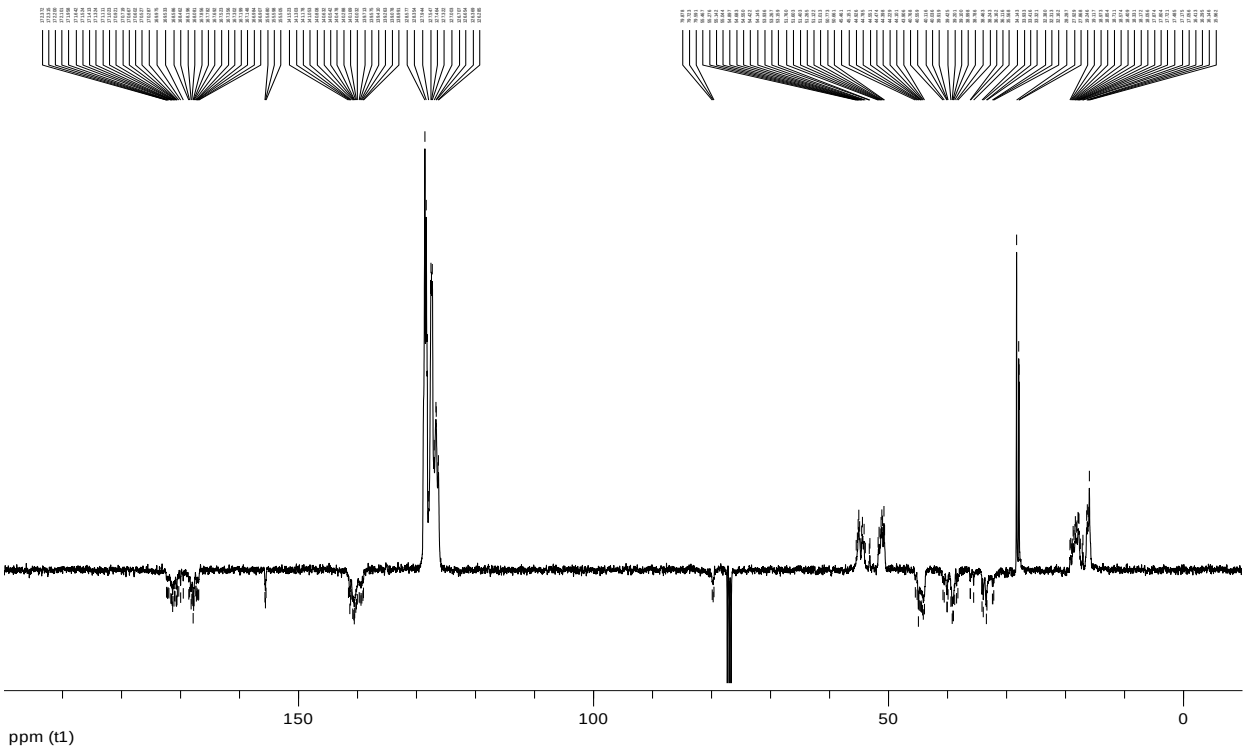


^{1}H and ^{13}C NMR spectra of compound **17** ($CDCl_3$)

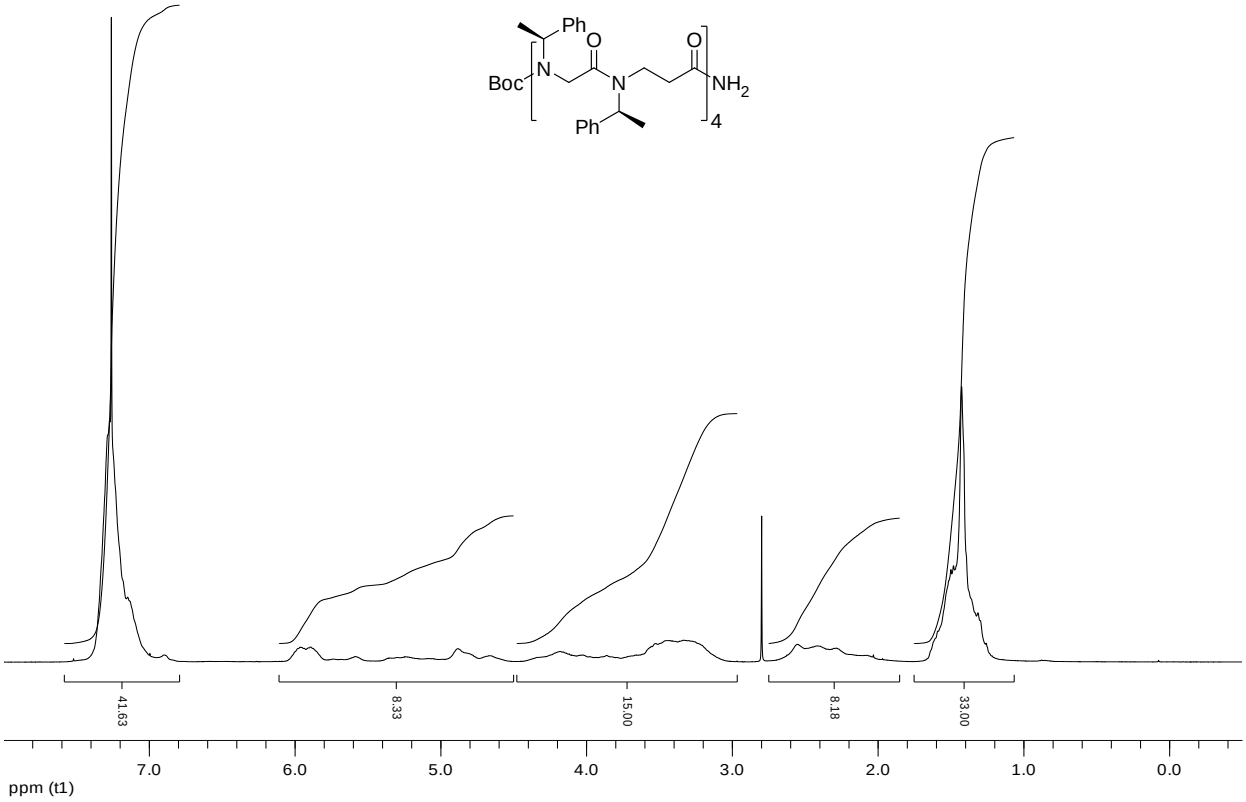


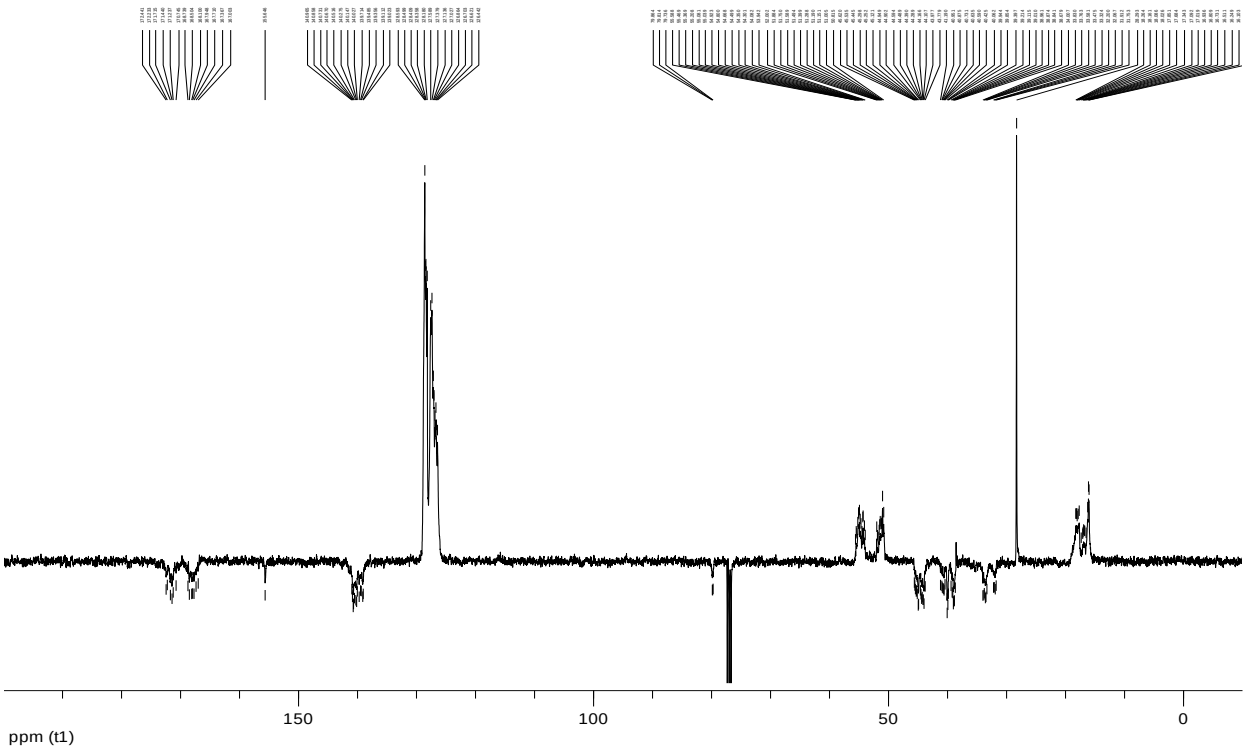
^{1}H and ^{13}C NMR spectra of compound **18** ($CDCl_3$)



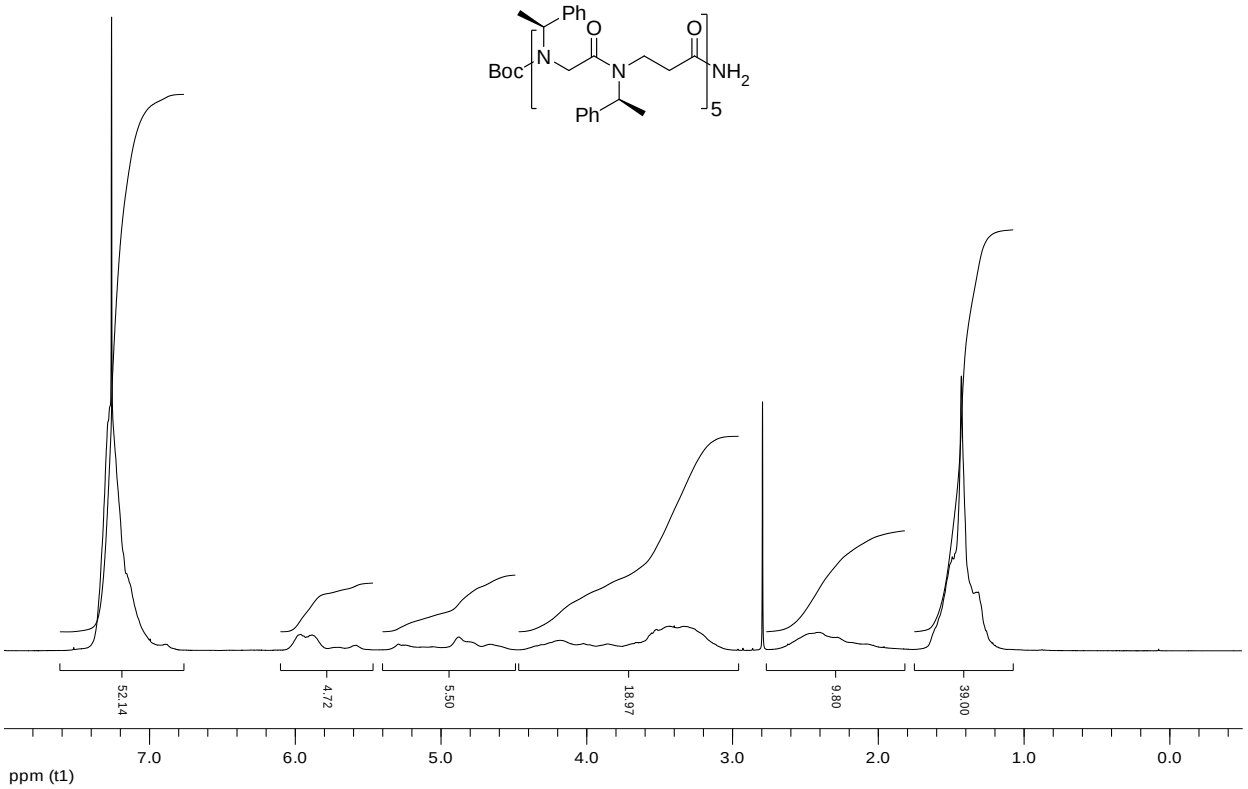


^{1}H and ^{13}C NMR spectra of compound **19** ($CDCl_3$)



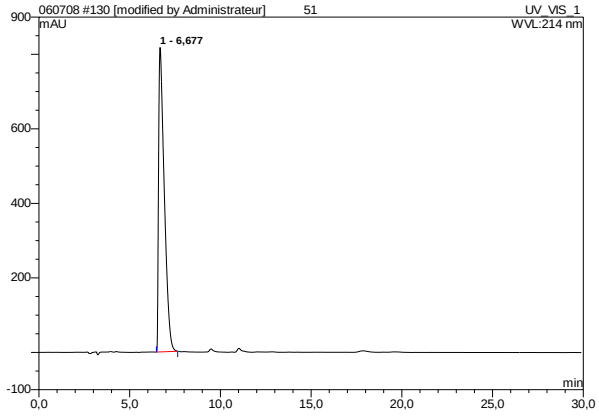


^{1}H NMR spectrum of compound **20** ($CDCl_3$)

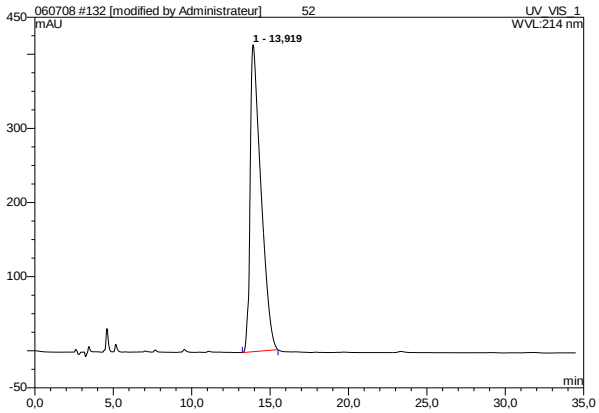


Analytical HPLC analysis of peptoids

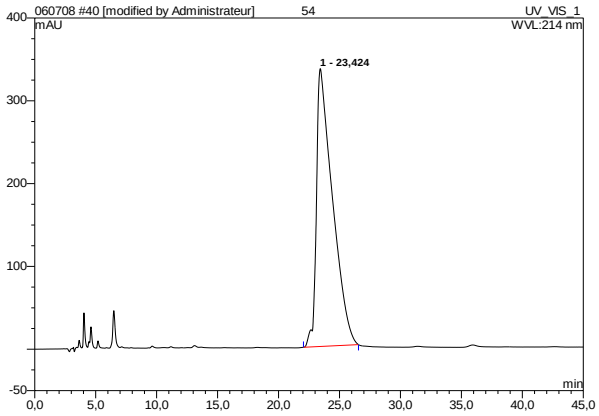
General conditions: Solvent A: water (1% TFA); solvent B: MeCN; solvent C: MeOH; 214 nm.



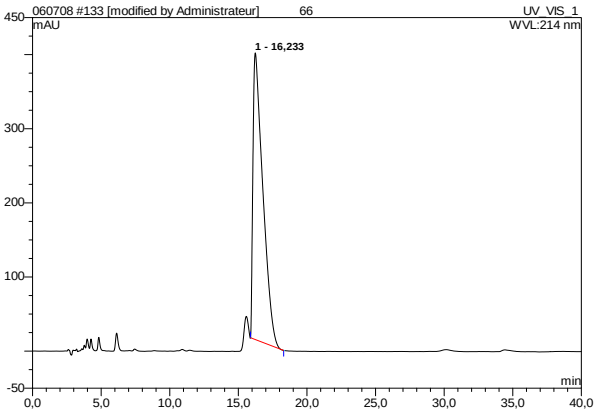
Peptoid **1** (A/B 40:60, flow = 0.80).



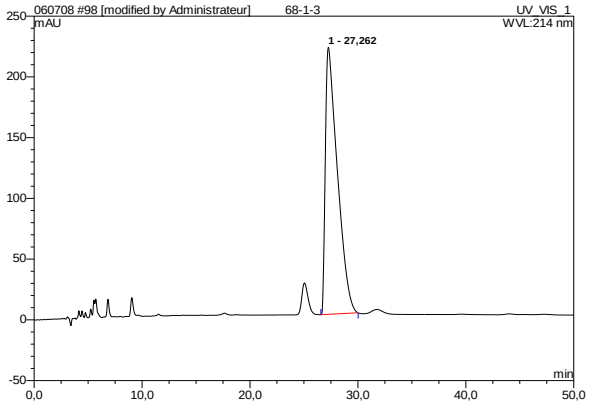
Peptoid **1a** (A/B 40:60, flow = 0.80).



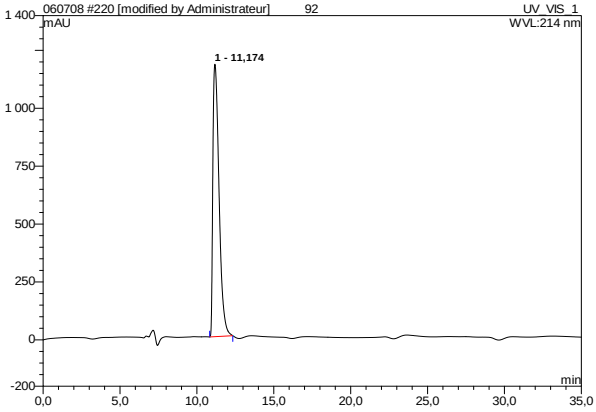
Peptoid **2** (A/B 40:60, flow = 0.80).



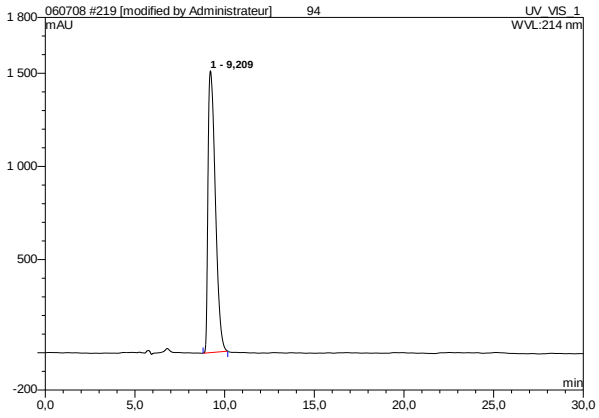
Peptoid **2a** (A/B 30:70, flow = 0.80).



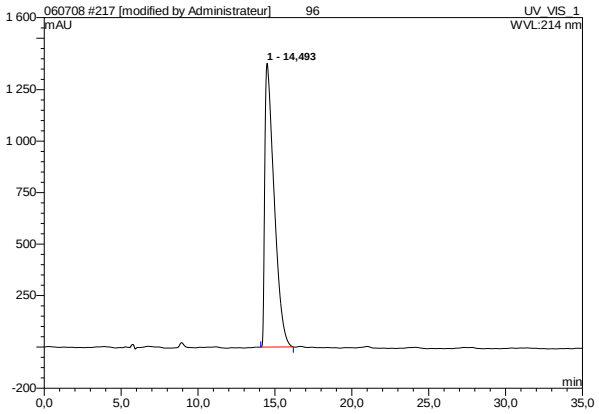
Peptoid **3** (A/B 30:70, flow = 0.80).



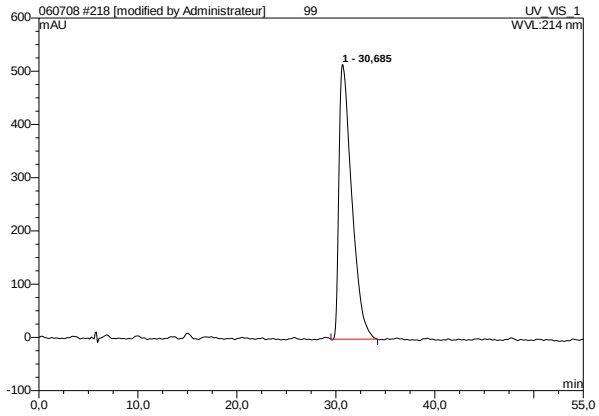
Peptoid **4** (A/C 40:60, flow = 0.40).



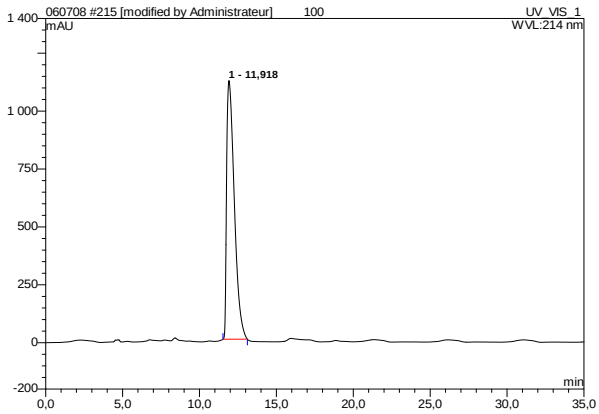
Peptoid **4a** (A/C 30:70, flow = 0.50).



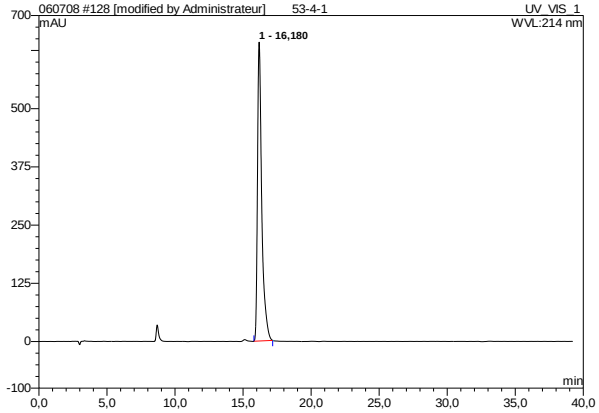
Peptoid **5** (A/C 30:70, flow = 0.50).



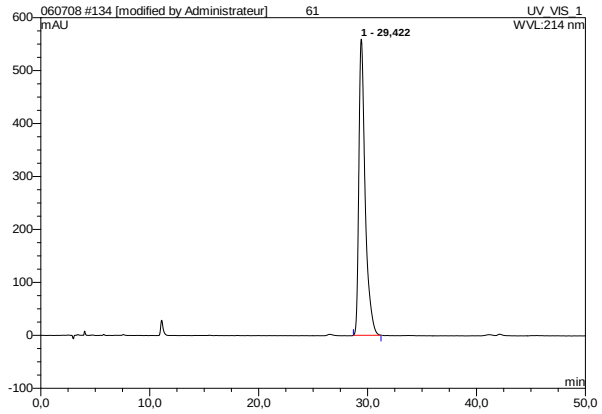
Peptoid **5a** (A/C 30:70, flow = 0.50).



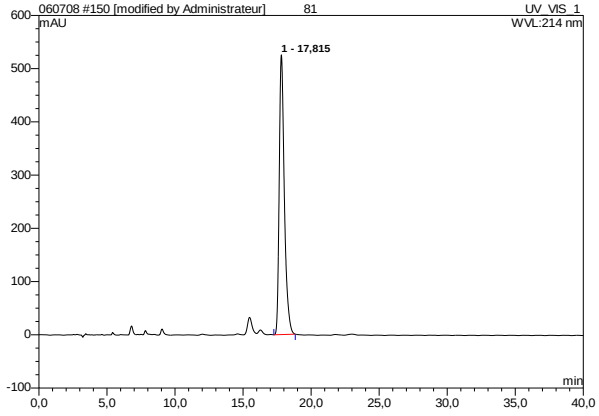
Peptoid **6** (A/C 20:80, flow = 0.60).



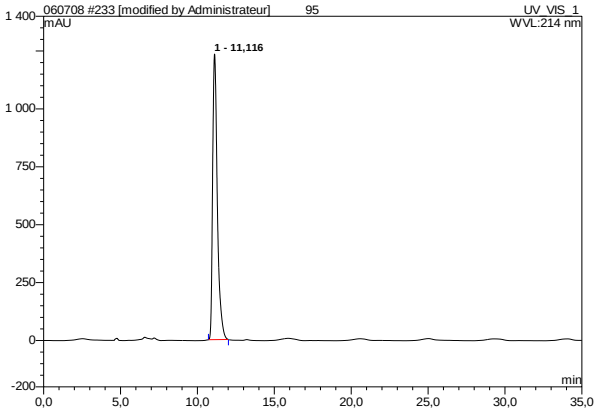
Peptoid **7** (A/B 20:80, flow = 0.80).



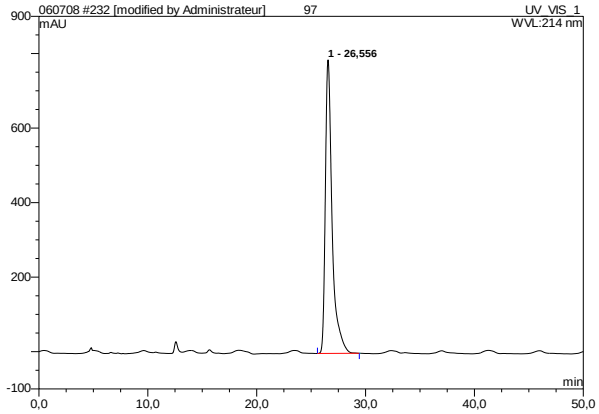
Peptoid **8** (A/B 20:80, flow = 0.80).



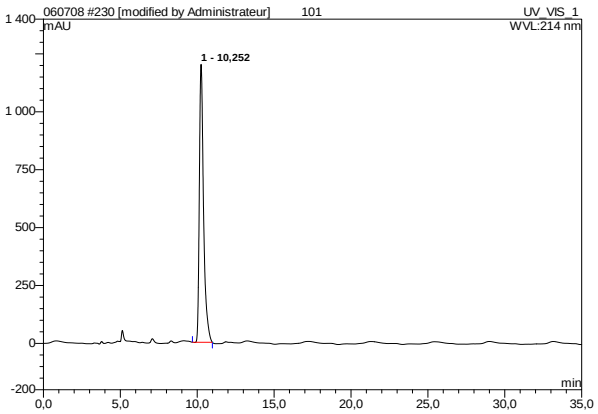
Peptoid **9** (A/B 10:90, flow = 0.80).



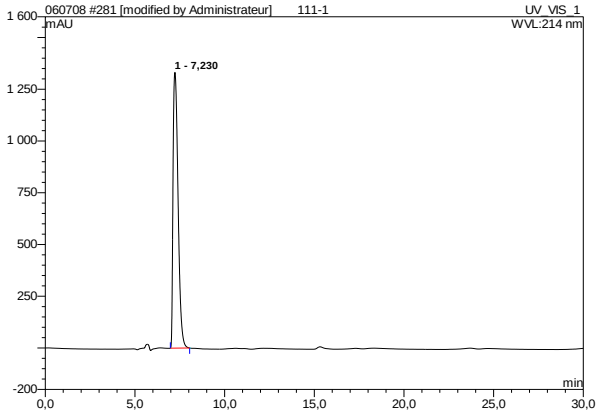
Peptoid **10** (A/C 20:80, flow = 0.60).



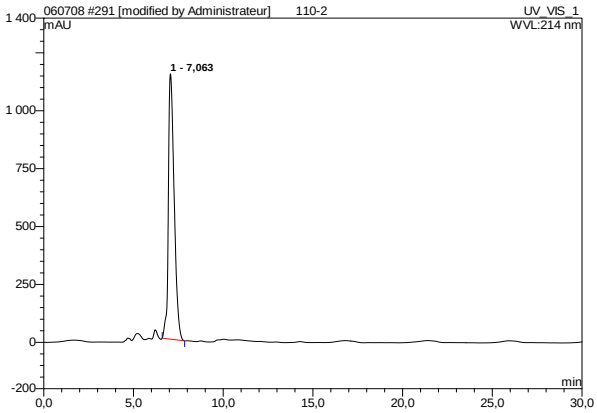
Peptoid **11** (A/C 20:80, flow = 0.60).



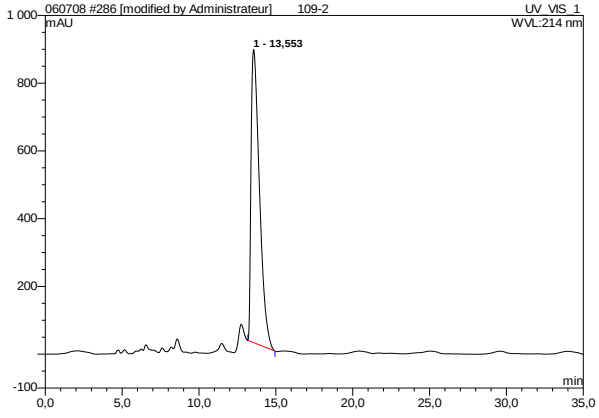
Peptoid **12** (A/C 10:90, flow = 0.75).



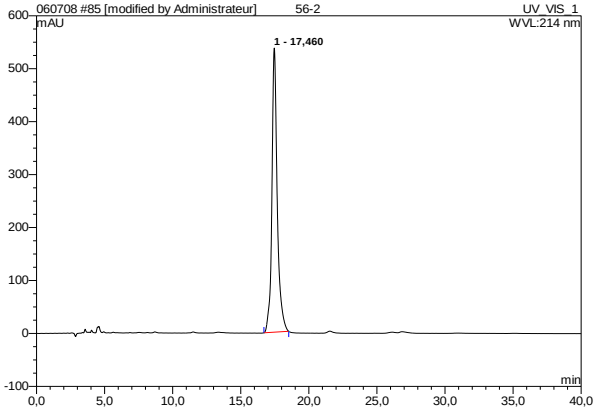
Peptoid **13** (A/C 30:70, flow = 0.50).



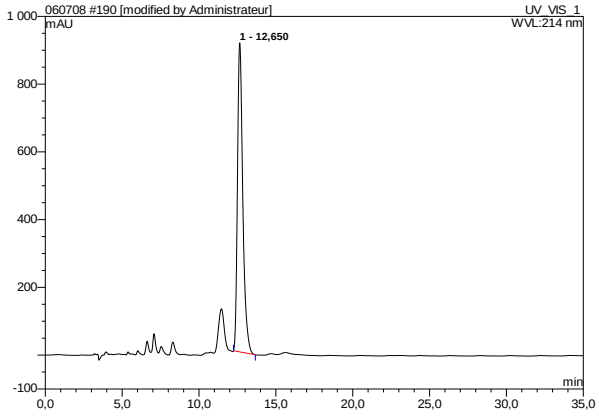
Peptoid **14** (A/C 20:80, flow = 0.60).



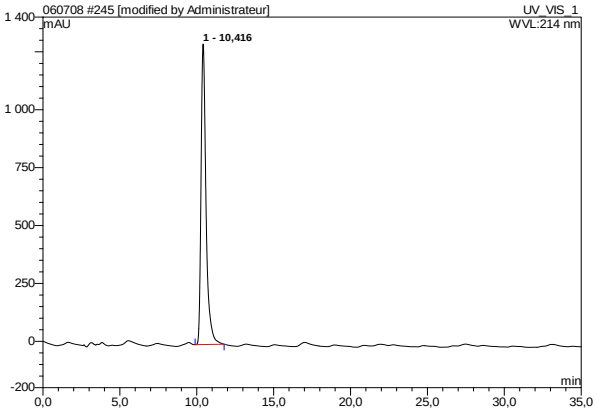
Peptoid **15** (A/C 20:80, flow = 0.60).



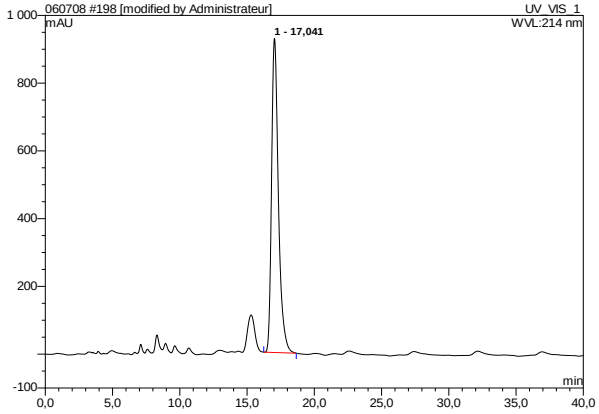
Peptoid **16** (A/B 30:70, flow = 0.80).



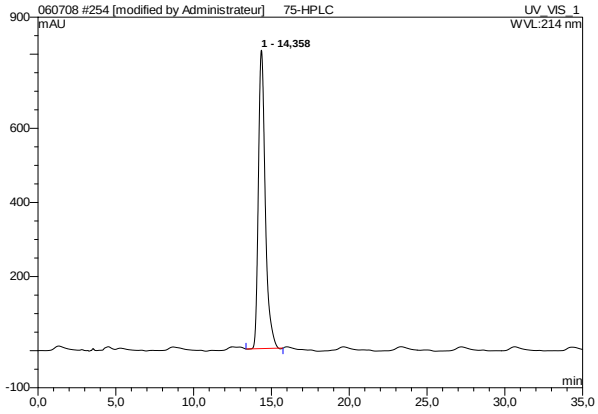
Peptoid **17** (A/C 5:95, flow = 0.80).



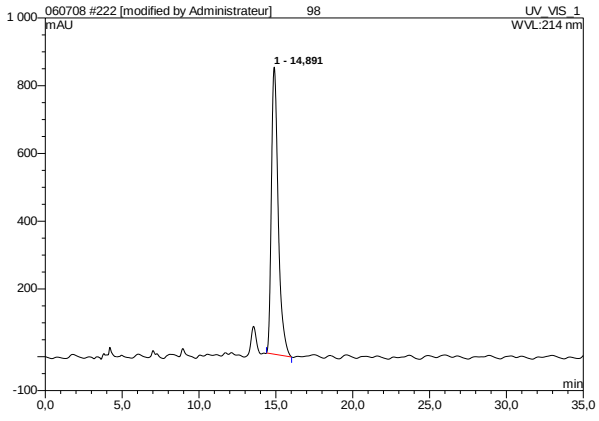
Peptoid **17** after purification by preparative HPLC (A/C 5:95, flow = 0.80).



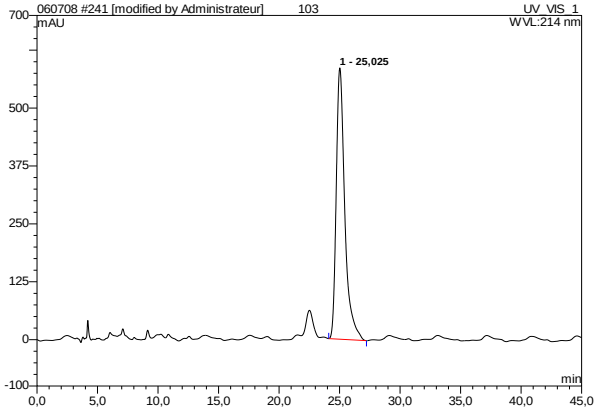
Peptoid **18** (A/C 5:95, flow = 0.80).



Peptoid **18** after purification by preparative HPLC (A/C 5:95, flow = 0.80).



Peptoid **19** (A/C 10:90, flow = 0.75).



Peptoid **20** (A/C 10:90, flow = 0.75).

References

1 Chemical Rubber Co, Robinson, James W, Handbook of spectroscopy, Boca Raton, Fla. CRC Press 1974.

2 Kamlet MJ, Abboud JL, Abraham MH and Taft RW (1983) Linear solvation energy relationships. 23. A comprehensive collection of the solvatochromic parameters, π*, α and β and some methods for simplifying the generalized solvatochromic equation. *J Org Chem* **48**: 2877-2887.

3 Kamlet MJ, Doherty RM, Abraham MH, Marcus Y and Taft RW (1988) Linear solvation energy relationship. 46. An improved equation for correlation and prediction of octanol/water partition coefficients of organic nonelectrolytes (including strong hydrogen bond donor solutes). *J Phys Chem* **92**: 5244-5255.

4 Besseau F, Laurence C and Berthelot M (1994) Hydrogen-bond basicity of esters, lactones and carbonates. *J Chem Soc , Perkin Trans 2* 485-489.

5 Le Questel JY, Laurence C, Lachkar A, Helbert M and Berthelot M (1992) Hydrogen-bond basicity of secondary and tertiary amides, carbamates, ureas and lactams. *J Chem Soc , Perkin Trans 2* 2091-2094.

6 Leo AJ (2000) Evaluating hydrogen-bond donor strength. *J Pharm Sci* **89**: 1567-1578.

7 Schwöbel J, Ebert RU, Kühne R and Schüürmann G (2009) Prediction of the intrinsic hydrogen bond acceptor strength of chemical substances from molecular structure. *J Phys Chem A* **113**: 10104-10112.