Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Efficient and versatile COMU-mediated solid-phase submonomer synthesis of arylopeptoids [oligomeric *N*-substituted aminomethyl benzamides]

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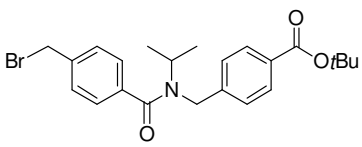
Contents

Synthesis of halomethyl-intermediates *p*-2 and *p*-3

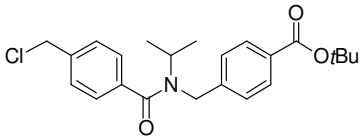
General Experimental Methods

THF and Et_3N were dried over 4Å molecular sieves. All other chemicals obtained from commercial sources (Alfa Aesar, Fluka, Merck and Sigma-Aldrich) were used as received. Melting points were determined on a Mettler Toledo MP70 melting point system and are referenced to the melting points of benzophenone and benzoic acid. NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer. Chemical shifts are referenced to the residual solvent peak and *J* values are given in Hz. The following multiplicity abbreviations are used: (s) singlet, (m) multiplet, and (br) broad. Where applicable, assignments were based on COSY, HMBC, HSQC and *J*-mod-experiments. IR spectra were recorded on a Shimadzu FTIR-8400S spectrometer equipped with a Pike Technologies MIRacle^{TM} ATR and wavenumbers (ν) are expressed in cm^{-1}. TLC was performed on Merck TLC aluminum sheets, silicagel 60, F_{254}. Progression of reactions was, when applicable, followed by HPLC, NMR and/or TLC. Visualising of spots in TLC was effected with UV-light and/or ninhydrin in EtOH/AcOH. Flash chromatography was performed with Merck silica gel 60, 40-63 µm. Unless otherwise stated, flash chromatography was performed in the eluent system for which the R_f values are given. HRMS were recorded on a Micromass LCT apparatus equipped with an AP-ESI probe calibrated with Leu-Enkephalin.



Bromomethyl-intermediate *p*-2. To a solution of *tert*-butyl 4-[(propan-2-ylamino)methyl]benzoate ***p*-1**[S1] (300 mg, 1.20 mmol) in THF (6.0 mL) at 0 °C under N_2 was added Et_3N (0.176 mL, 1.26 mmol) and then 4-(bromomethyl)benzoyl bromide (351 mg, 1.26 mmol). After stirring for 1 h at 0 °C, the resulting mixture was concentrated under reduced pressure at rt. The residue was taken up in EtOAc (30 mL) and the mixture was washed with satd. aq. $NaHCO_3$ (15 mL) and brine (15 mL). The combined aqueous layers were extracted with EtOAc (10 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography of the residue yielded ***p*-2** (490 mg, 91%) as a colorless solid. R_f (heptane/EtOAc 70:30) = 0.27. mp = 119.7-120.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96-7.90 (m, 2H), 7.50-7.18 (br m, 6H), 4.80-4.52 (br s, 2H, CONCH_2Ar), 4.52-4.39 (br s, 2H, BrCH_2Ar), 4.25-4.00 (br m, 1H, CONCH(CH_3)$_2$), 1.57 (s, 9H), 1.27-0.96 (br m, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.5 (C_q), 165.4 (C_q), 143.9 (C_q), 138.9 (C_q), 137.0 (C_q), 130.7 (C_q), 129.5 (2CH), 129.1, 126.6 (3×2CH), 80.8 (C_q), 50.6 (br, CH, CONCH(CH_3)$_2$), 43.4 (br, CH_2, CONCH_2Ar), 32.5 (CH_2, BrCH_2Ar), 28.1 ($3CH_3$), 21.3 ($2CH_3$) ppm. ν_{max}/cm^{-1} (ATR) 2977, 1709 (C=O), 1634 (C=O), 1436 (CH), 1410, 1368, 1293, 1165, 1118, 849.

HRMS (TOF MS ES$^+$) calcd for $C_{23}H_{29}BrNO_3$ $[M + H]^+$ *m*/*z* 446.1325, found 446.1320. HPLC purity = 99.9%.



Chloromethyl-intermediate *p*-3. Reaction of *tert*-butyl 4-[(propan-2-ylamino)methyl]benzoate ***p*-1**[S1] (300 mg, 1.20 mmol) with 4-(chloromethyl)benzoyl chloride (239 mg, 1.26 mmol) otherwise following the same procedure as in the synthesis of ***p*-2** yielded ***p*-3** (460 mg, 95%) as a colorless solid. R_f (heptane/EtOAc 70:30) = 0.30. mp = 122.4-123.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96-7.91 (m, 2H), 7.54-7.10 (br m, 6H,), 4.77-4.40 (2×br s, 2×2H, CONC*H*$_2$Ar and ClC*H*$_2$Ar), 4.22-4.98 (br m, 1H, CONC*H*$(CH_3)_2$), 1.57 (s, 9H), 1.27-0.95 (br m, 6H, CONCH$(CH_3)_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.5 (C_q), 165.4 (C_q), 144.0 (C_q), 138.5 (C_q), 137.0 (C_q), 130.6 (C_q), 129.5 (2CH), 128.7 (2CH), 126.6 (2CH), 126.5 (2CH), 80.8 (C_q), 50.7 (br, CH, CONC*H*$(CH_3)_2$), 45.5 (CH_2, Cl*C*H$_2$Ar), 43.4 (br, CH_2, CONC*H*$_2$Ar), 28.1 ($3CH_3$), 21.3 ($2CH_3$) ppm. ν_{max}/cm^{-1} (ATR) 2976, 1704 (C=O), 1629 (C=O), 1438, 1409, 1368, 1310, 1292, 1161, 1116, 1057, 841. HRMS (TOF MS ES$^+$) calcd for $C_{23}H_{29}ClNO_3$ $[M + H]^+$ *m*/*z* 402.1830, found 402.1838. HPLC purity = 99.9%.

Analytical and preparative HPLC

General Experimental Methods

Analytival and preparative HPLC was performed on a Waters 2525 binary gradient module equipped with a Waters 2767 sample manager, a column fluidic organiser, a Gemini 110 column (C18, 5 µm, 110 Å, 4.6×100 mm) with flow = 1.0 mL/min for analytical HPLC or a Gemini 110 column (C18, 5 µm, 110 Å, 21.2×100 mm) with flow = 10.0 mL/min for preparative HPLC, and a UV fraction manager coupled with a Waters 2996 PDA detector; detection range = 210-400 nm; solvent A = MeOH/water/TFA 5:95:0.1 and solvent B = MeOH/water/TFA 95:5:0.1.

Loading of the 2-chlorotrityl chloride polystyrene resin

The loading of the 2-chlorotrityl chloride resin (listed loading of 1.50 mmol/g) was estimated by measuring the content of unreacted 3- or 4-(chloromethyl)benzoic acid present in the washings collected after the attachment reaction. Thus, the CH_2Cl_2 washings were acidified with TFA and concentrated under reduced pressure. The residue was diluted with a known amount of MeOH and the resulting sample was then subjected to HPLC analysis using a 10 min gradient (0-2 min: 30% B; 2-7 min: 30→100% B; 7-9 min: 100→30% B; 9-10 min: 30% B). The HPLC profile was compared to a sample containing a known concentration of 3- or 4-(chloromethyl)benzoic acid and the amount of unreacted 3- or 4-(chloromethyl)benzoic acid and therefore the loading of the resin could then be estimated. We found that a constant loading of 1.23±0.03 mmol/g was obtained when the 2-chlorotrityl chloride polystyrene resin was reacted with 3 or 4-(chloromethyl)benzoic acid (1.2 equiv with respect to theoretical loading) in the presence of DIPEA (6.0 equiv) in CH_2Cl_2 at rt for 1 h.

HPLC programs used for analysis and purification of synthesised arylopeptoids

Analytical (10 min)	0-2 min:	2-7 min:	7-9 min:	9-10 min:
Preparative (20 min)	0-5 min:	5-15 min:	15-16 min:	16-20 min:
Prg. 1:	10→25% B;	25→40% B;	40→10% B;	10% B.
Prg. 2:	40% B;	40→80% B;	80→40% B;	40% B.
Prg. 3:	40→60% B;	60→90% B;	90→40% B;	40% B.
Prg. 4:	50% B;	50→100% B;	100→50% B;	50% B.
Prg. 5:	70% B;	70→100% B;	100→70% B;	70% B.
Prg. 6:	80→100% B;	100% B;	100→80% B;	80% B.

Retention times

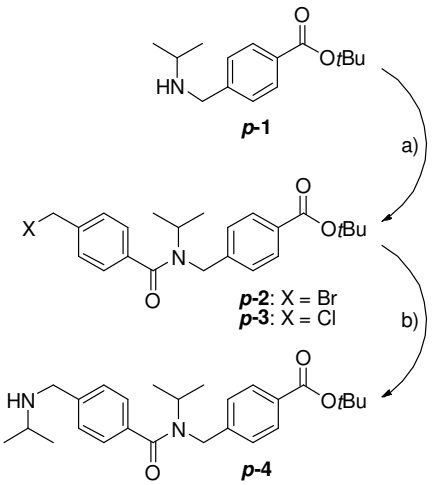
Arylopeptoids with free acids at the *C*-terminus.

Entry	Arylopeptoid	Side chains	Prg.	t_r, analytical (min)	t_r, prep. (min)
1	***p*-5**	Isopropyl	4	6.99	13.7
2	***p*-6a**	Isopropyl	5	6.13	-
3	***m*-6a**	Isopropyl	5	6.35	12.2
4	***p*-6b**	Ethyl	3	7.06	-
5	***m*-6b**	Ethyl	3	7.44	14.3
6	***p*-6c**	4-Phenylbutyl	6	5.99	9.9
7	***m*-6c**	4-Phenylbutyl	6	6.42	10.8
8	***p*-6d**	2-Morpholinoethyl	1	5.44	10.1
9	***m*-6d**	2-Morpholinoethyl	1	7.13	10.1
10	***p*-6e**	Pyridinylmethyl	1	6.75	12.2

Arylopeptoids with free amides at the *C*-terminus.

Entry	Arylopeptoid	Side chains	Prg.	t_r, analytical (min)	t_r, prep. (min)
1	***p*-7a**	Isopropyl	5	5.62	10.9
2	***m*-7a**	Isopropyl	5	5.81	11.3
3	***p*-7b**	Ethyl	3	6.52	12.7
4	***p*-7c**	4-Phenylbutyl	6	5.84	9.4
5	***m*-7c**	4-Phenylbutyl	6	5.73	9.1
6	***p*-7d**	2-Morpholinoethyl	1	5.03	9.4
7	***m*-7d**	2-Morpholinoethyl	1	6.57	12.2
8	***p*-7e**	Pyridinylmethyl	1	5.95	10.9
9	***p*-7f**	4-Aminobutyl	1	5.73	10.3
10	***p*-7g**	Carboxymethyl	2	5.59	11.0
11	***p*-8**	4-Phenylbutyl Isopropyl 2-Morpholinoethyl	5	5.23	9.3
12	***m*-8**	4-Phenylbutyl Isopropyl 2-Morpholinoethyl	5	5.41	10.1

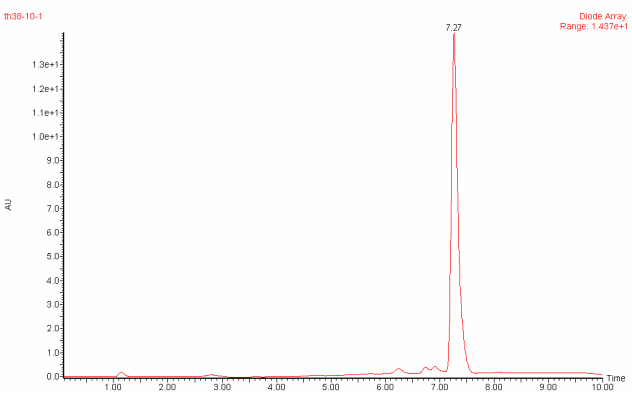
Optimisation of acylation and substitution steps using HPLC



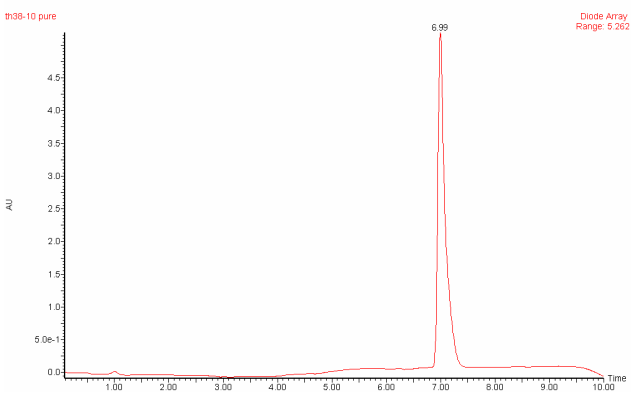
The solution phase study of acylation step (a) was carried out as outlined in the paper on a scale of 12.5 mg, 0.050 mmol ***p*-1**. The study of substitution step (b) was likewise carried out as described in the paper, on a scale of 11.2 mg, 0.025 mmol ***p*-2** or 10.2 mg, 0.025 mmol ***p*-3**. The reactions were followed by taking out a tiny drop of the reaction mixture at set timings and diluting it with 1.0 mL HPLC solvent B (MeOH/water/TFA 95:5:0.1) in order to quench the reactions. The resulting sample was then subjected to HPLC analysis using a 10 min gradient (0-2 min: 30% B; 2-7 min: 30→100% B; 7-9 min: 100→30% B; 9-10 min: 30% B). The following retention times were observed: ***p*-1**: t_r = 5.69 min; 4-(chloromethyl)benzoic acid: t_r = 6.73 min; ***p*-4**: t_r = 6.76 min; ***p*-3**: t_r = 8.72 min; ***p*-2**: t_r = 8.81 min.

Conversions in acylation step (a) were calculated by comparing the areas of starting material ***p*-1** with those of ***p*-2** and ***p*-3**. HPLC of a mixture of ***p*-1** and ***p*-2** in known concentrations showed ***p*-2** to have an area 2.18 times larger per mole than ***p*-1**. In the same manner, ***p*-3** was found to have an area 1.92 times larger per mole than ***p*-1**.

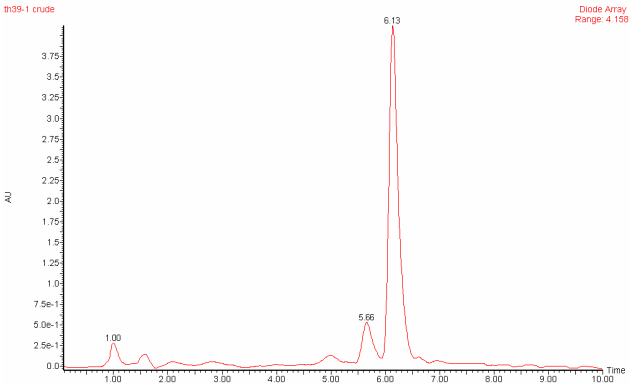
HPLC profiles of synthesised arylopeptoids



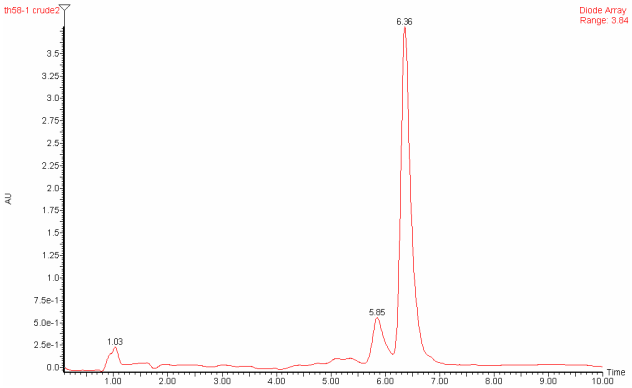
Arylopeptoid ***p*-5** crude (prg. 4).



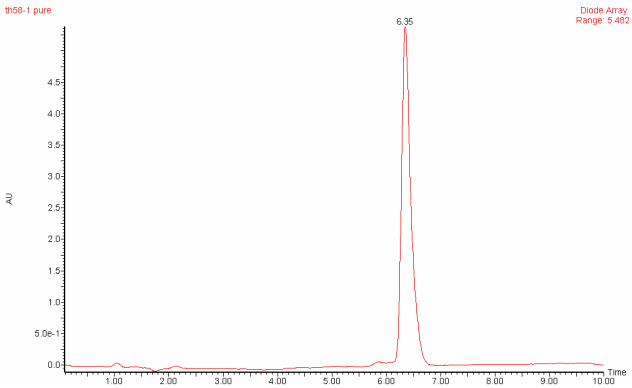
Arylopeptoid ***p*-5** pure (prg. 4).



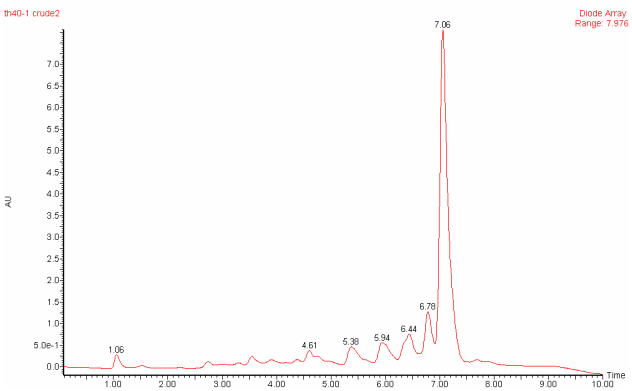
Arylopeptoid ***p*-6a** crude (prg. 5).



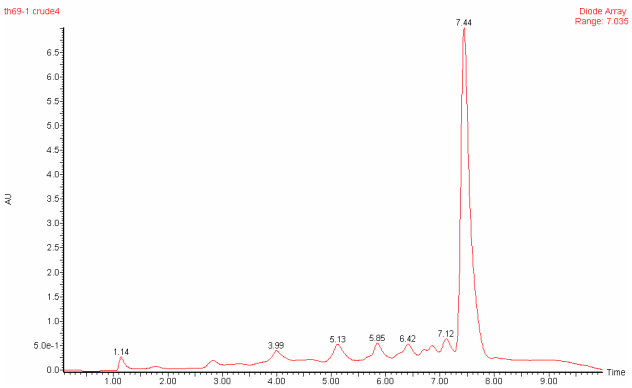
Arylopeptoid ***m*-6a** crude (prg. 5).



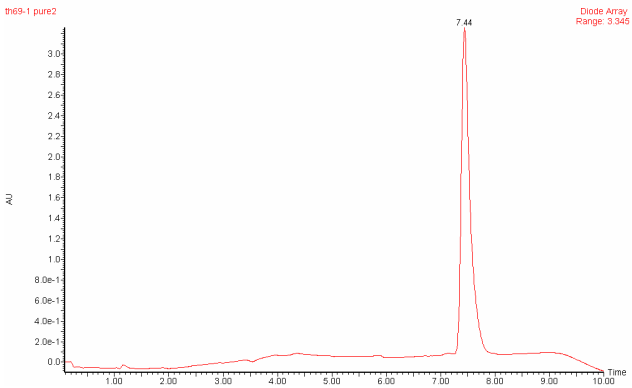
Arylopeptoid ***m*-6a** pure (prg. 5).



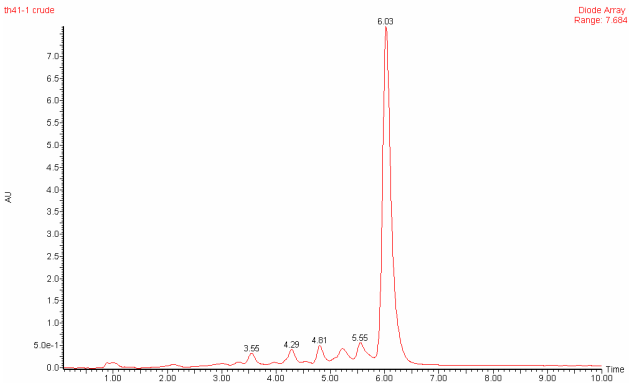
Arylopeptoid ***p*-6b** crude (prg. 3).



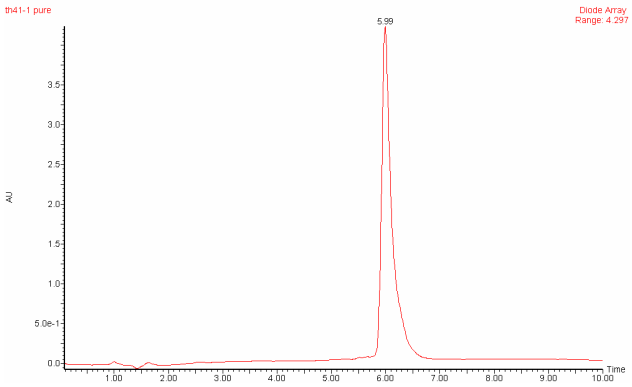
Arylopeptoid ***m*-6b** crude (prg. 3).



Arylopeptoid ***m*-6b** pure (prg. 3).



Arylopeptoid ***p*-6c** crude (prg. 6).



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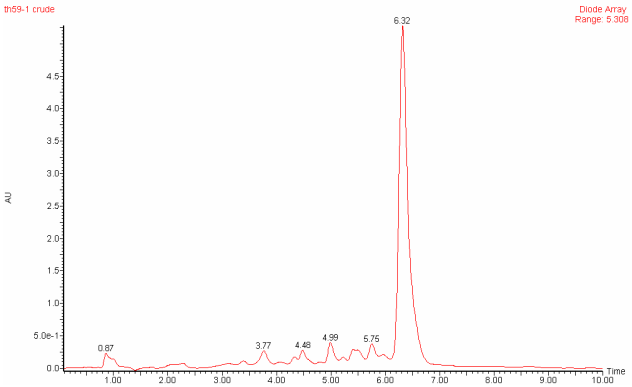
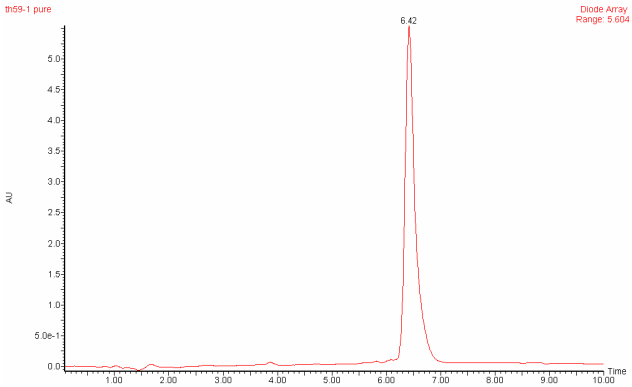


Arylopeptoid ***m*-6c** crude (prg. 6).



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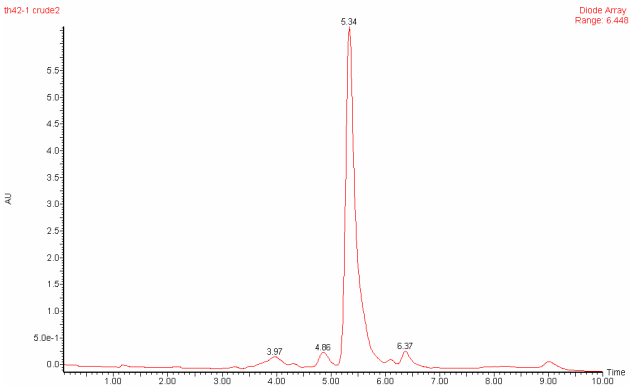

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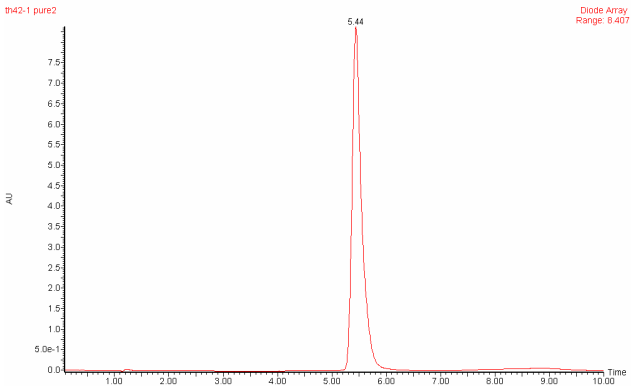

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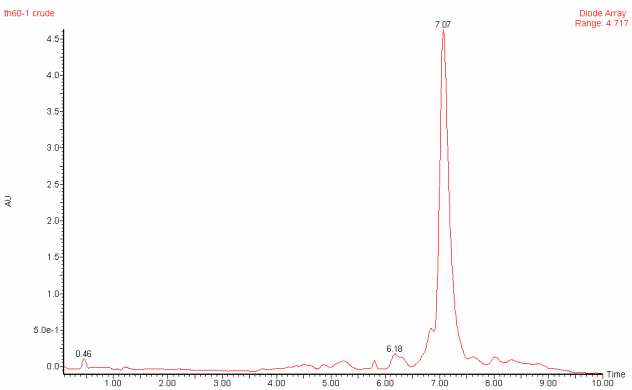
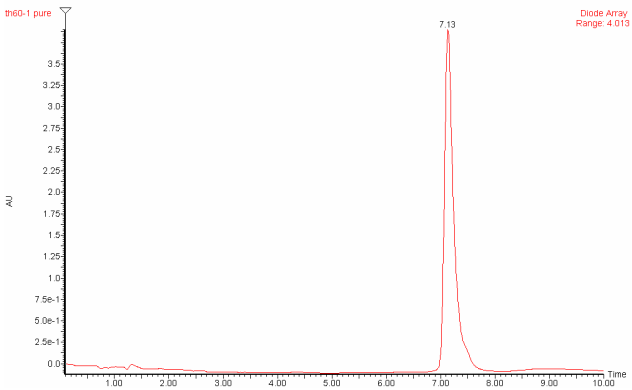


Arylopeptoid ***m*-6d** crude (prg. 1).



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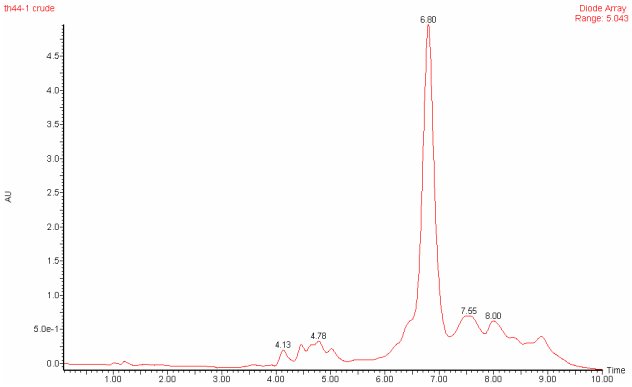

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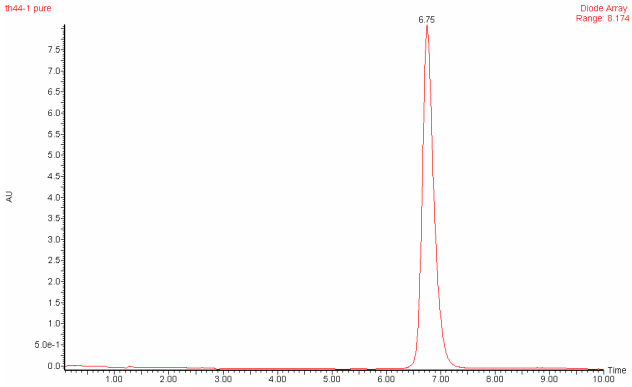

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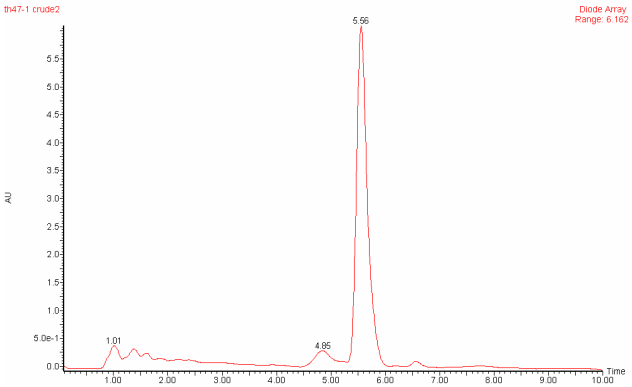
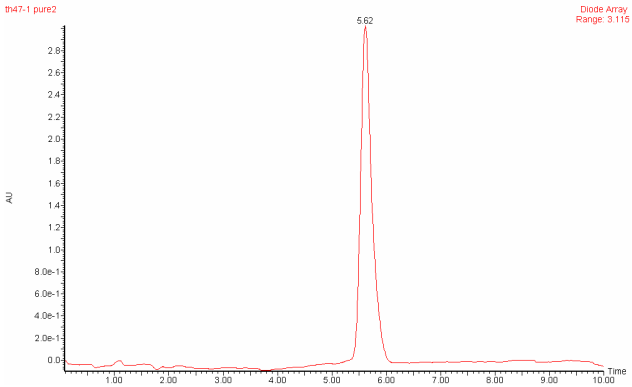
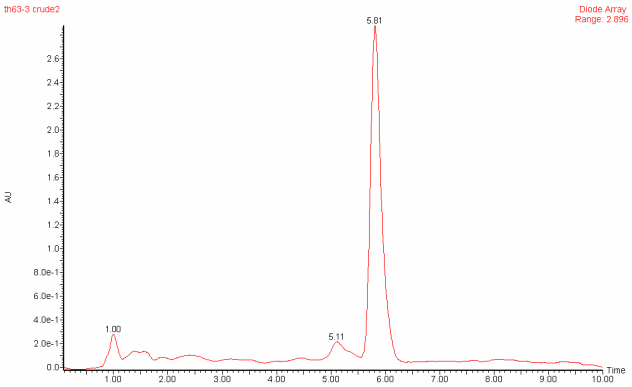


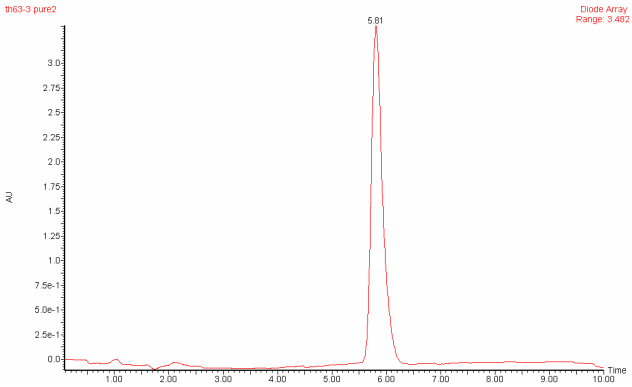
Arylopeptoid ***p*-7a** crude (prg. 5).



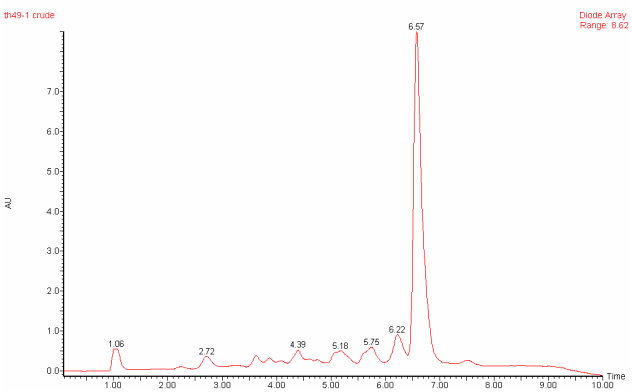
Arylopeptoid ***p*-7a** pure (prg. 5).



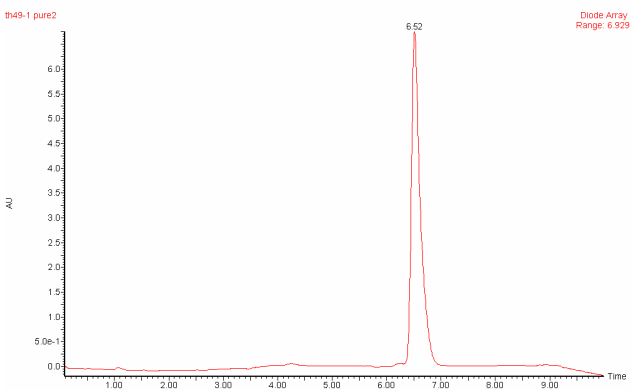
Arylopeptoid ***m*-7a** crude (prg. 5).



Arylopeptoid ***m*-7a** pure (prg. 5).



Arylopeptoid ***p*-7b** crude (prg. 3).



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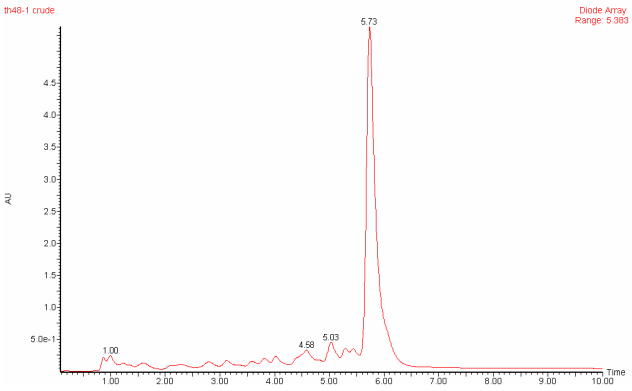
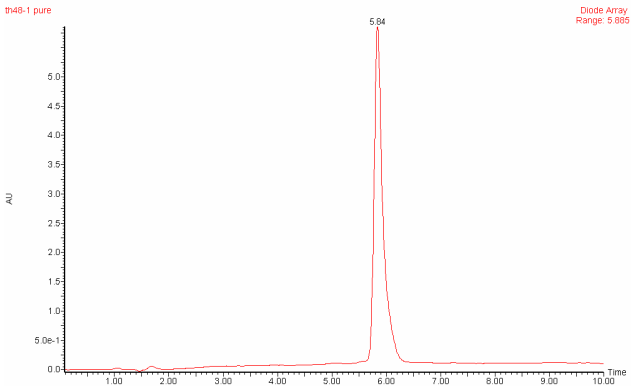


Arylopeptoid ***p*-7c** crude (prg. 6).



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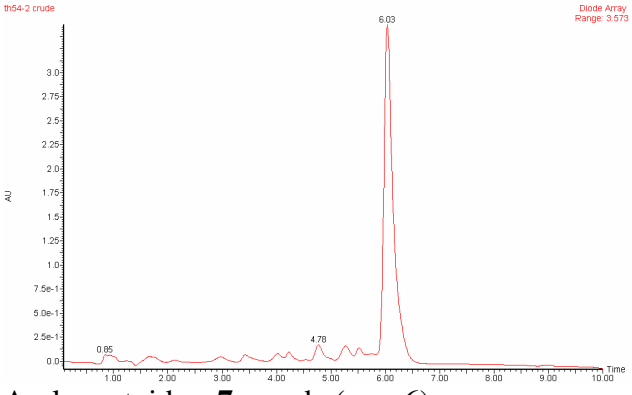
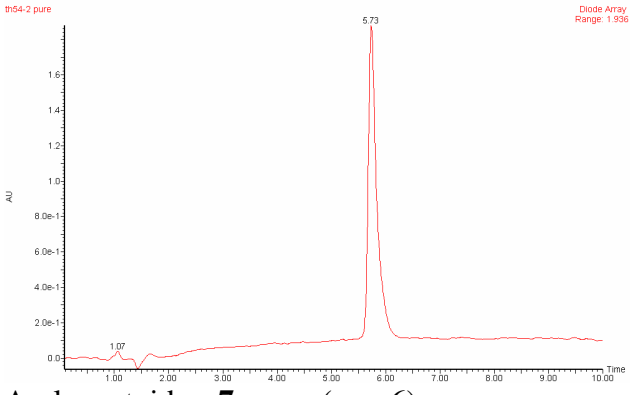
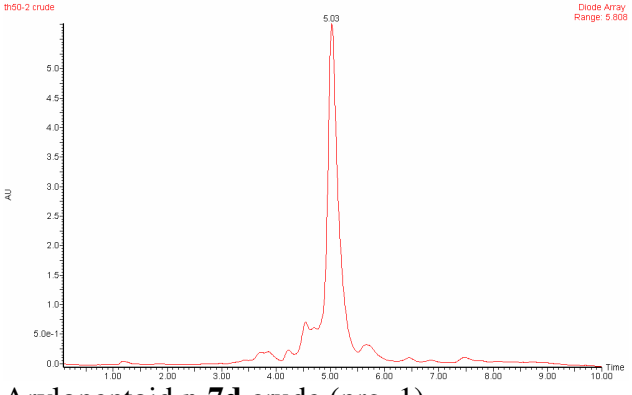


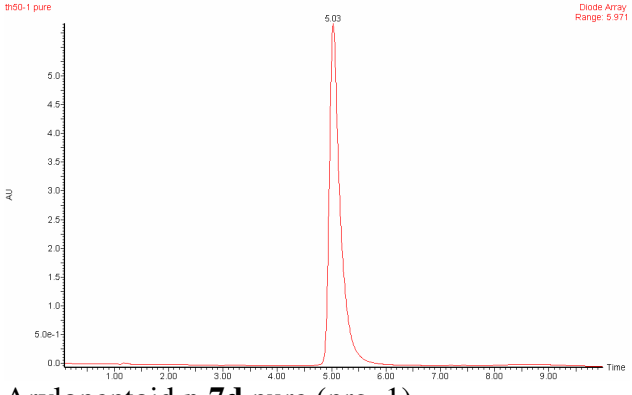
Arylopeptoid ***m*-7c** crude (prg. 6).



Arylopeptoid ***m*-7c** pure (prg. 6).



Arylopeptoid ***p*-7d** crude (prg. 1).



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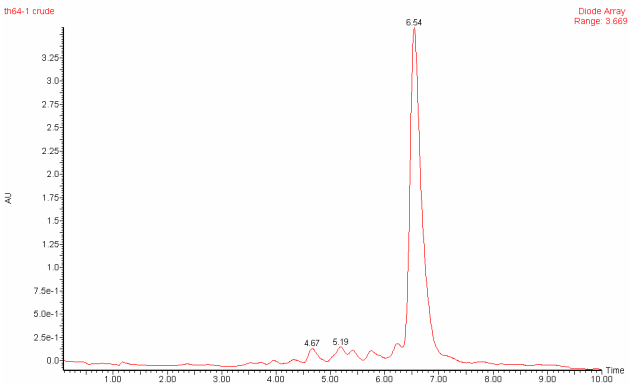

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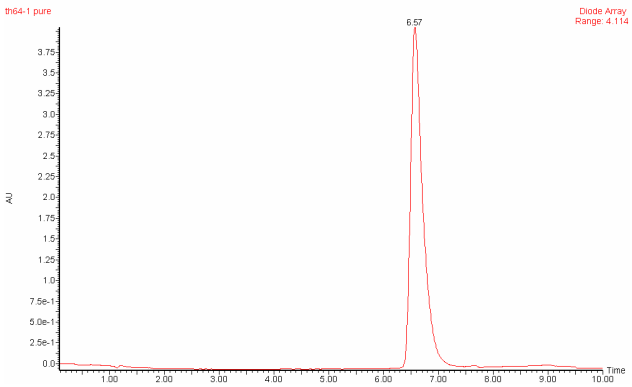

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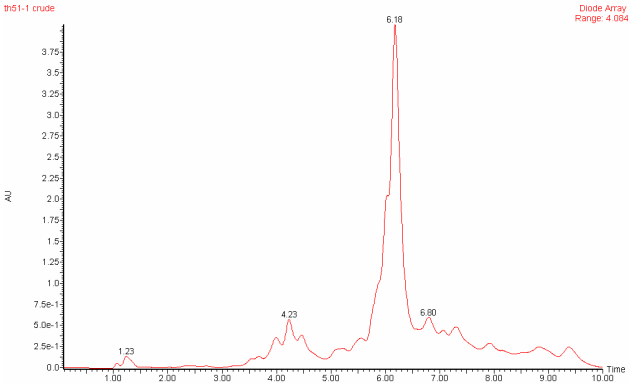

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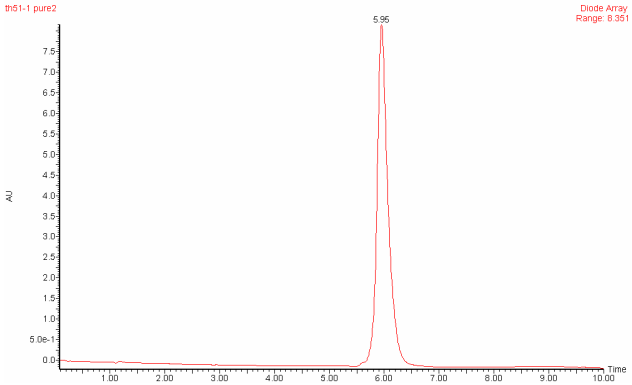

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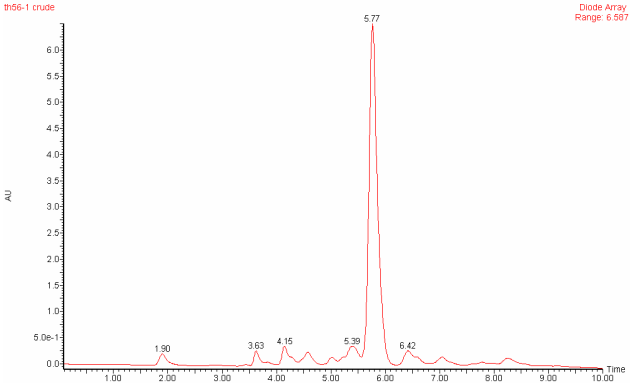
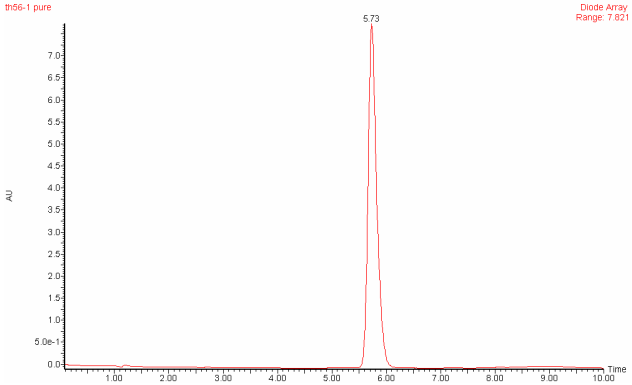
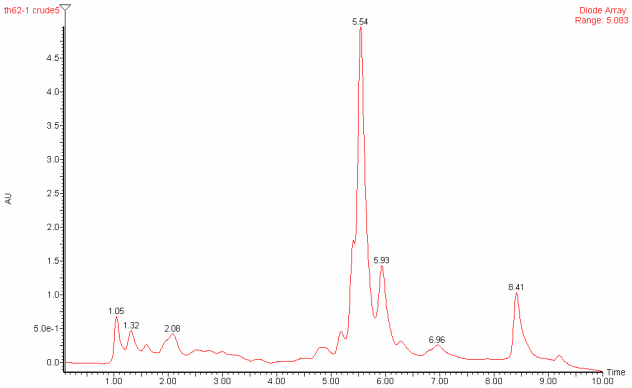


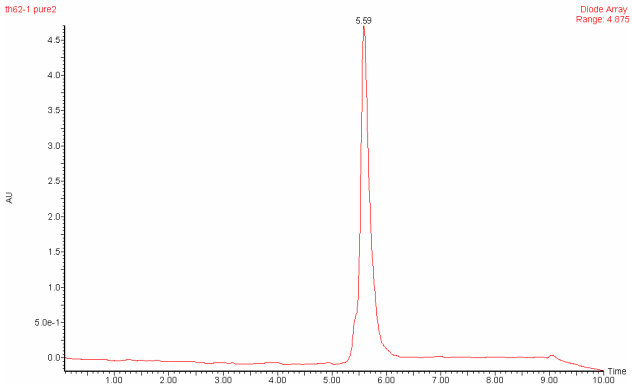
Arylopeptoid ***p*-7f** crude (prg. 1).



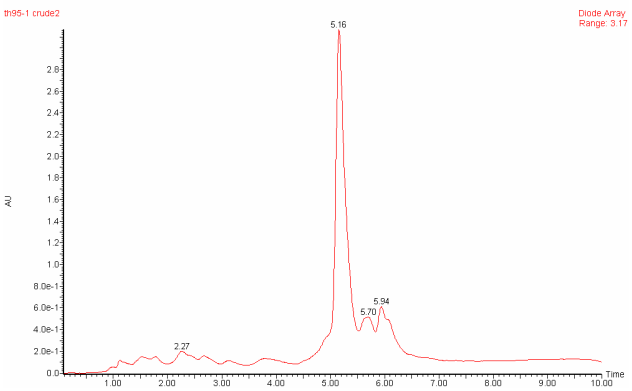
Arylopeptoid ***p*-7f** pure (prg. 1).



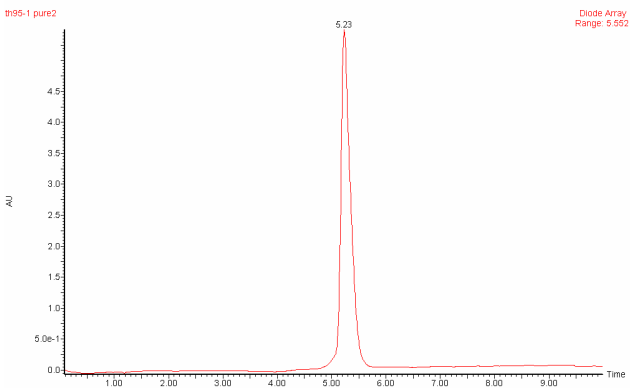
Arylopeptoid ***p*-7g** crude (prg. 2).



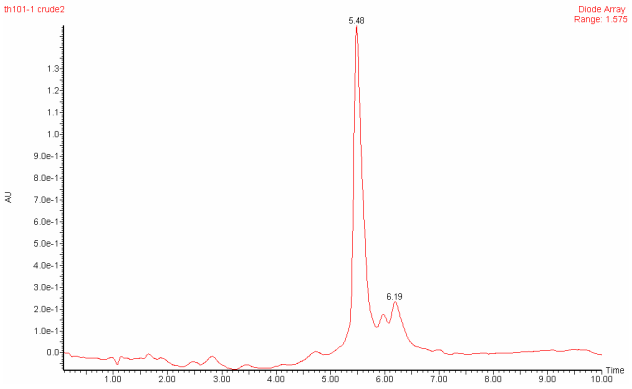
Arylopeptoid ***p*-7g** pure (prg. 2).



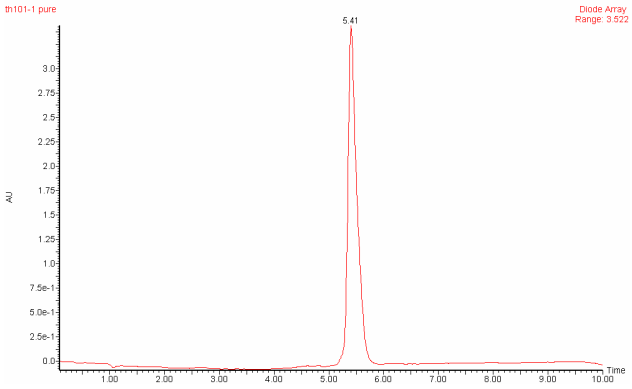
Arylopeptoid ***p*-8** crude (prg. 5).



Arylopeptoid ***p*-8** pure (prg. 5).

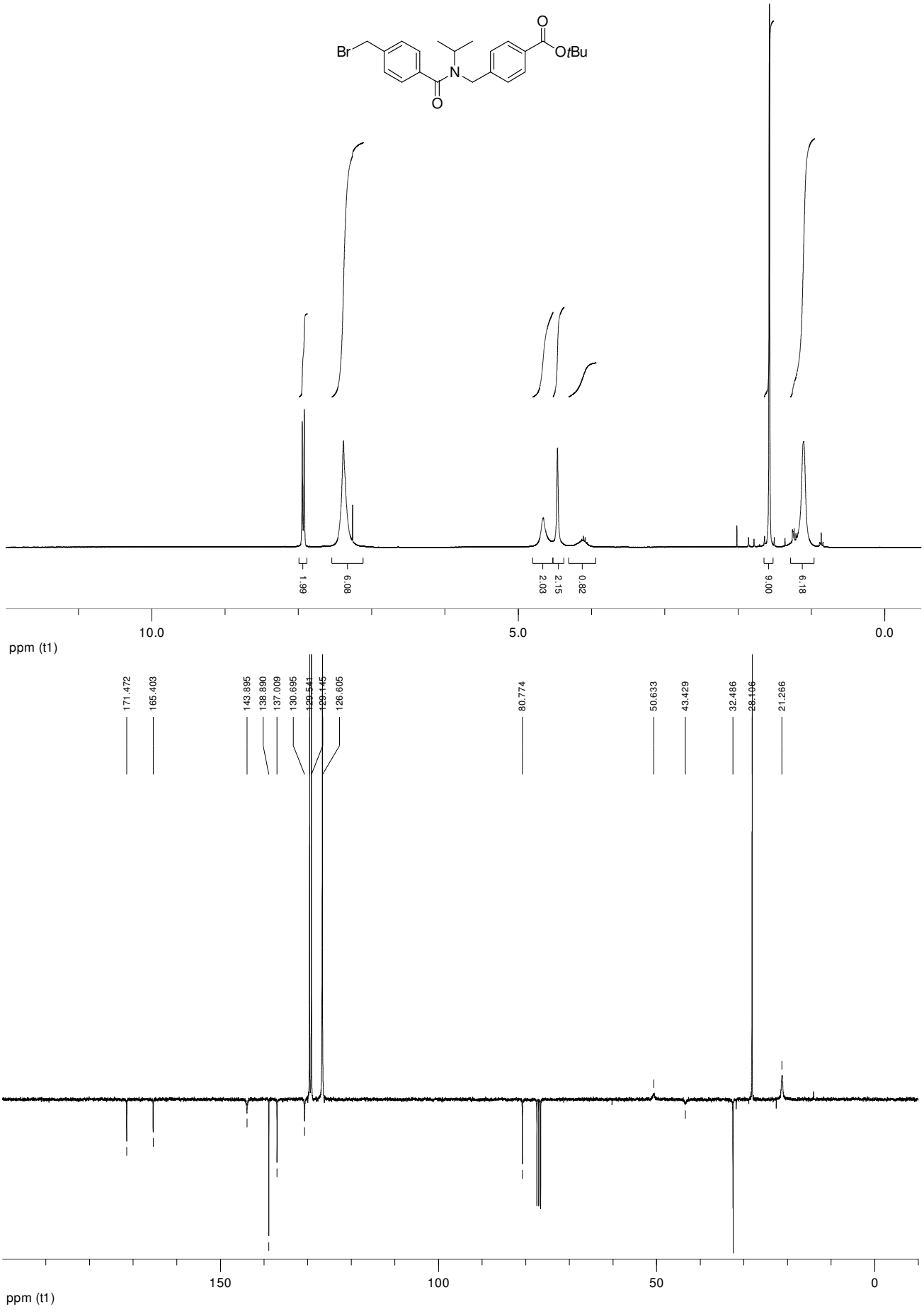


Arylopeptoid ***m*-8** crude (prg. 5).

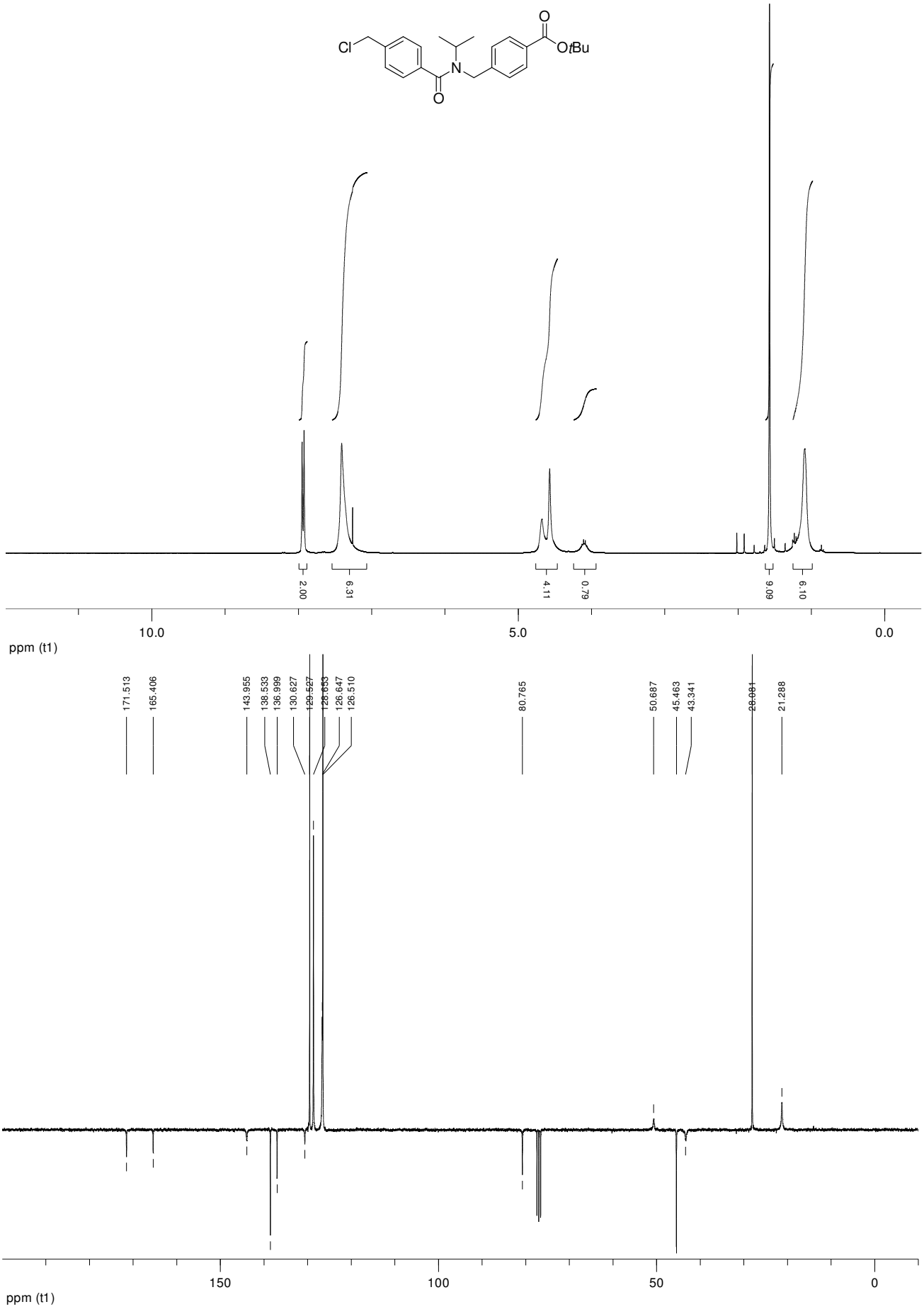


Arylopeptoid ***m*-8** pure (prg. 5).

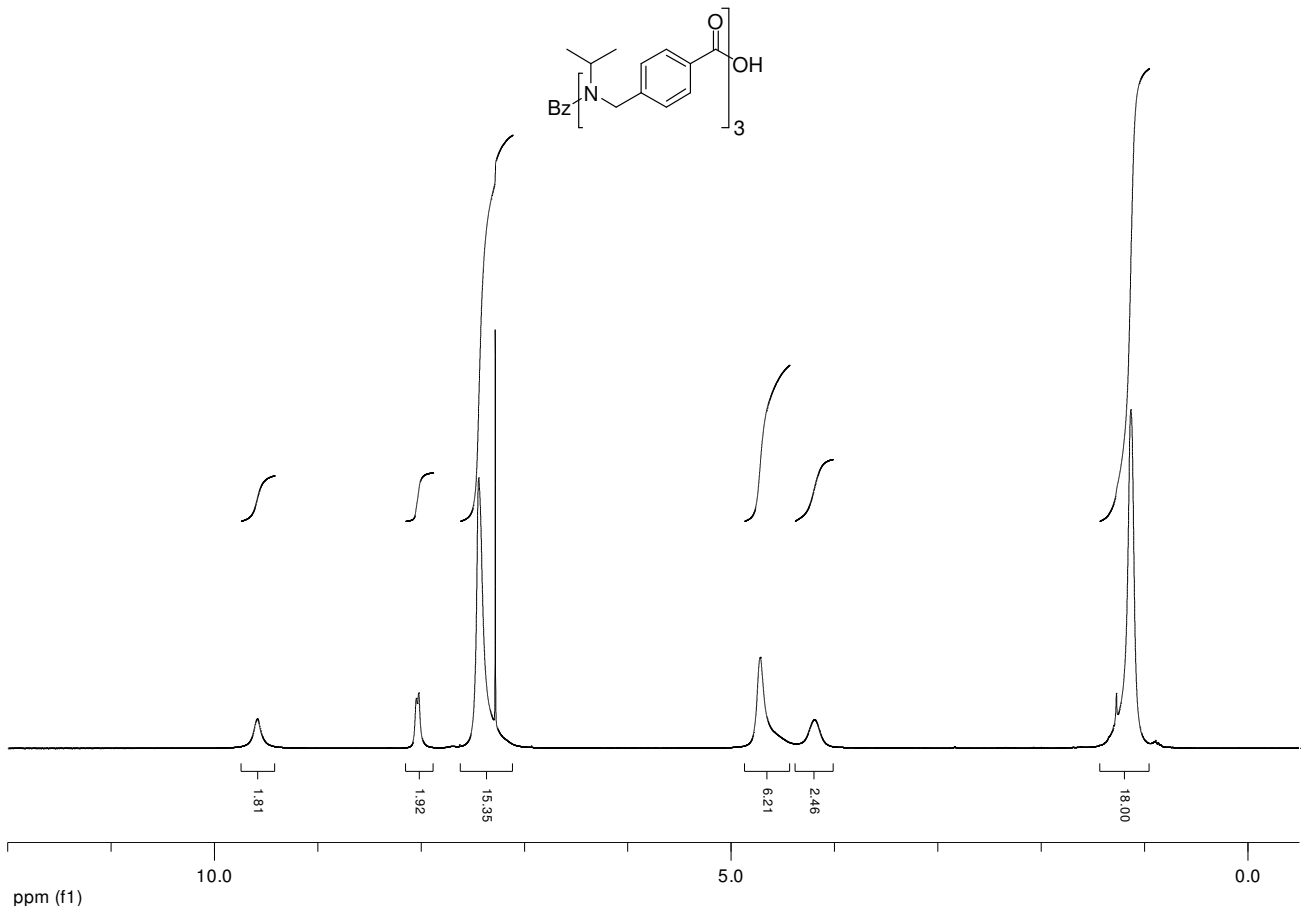
NMR spectra of *p*-2 ($CDCl_3$)

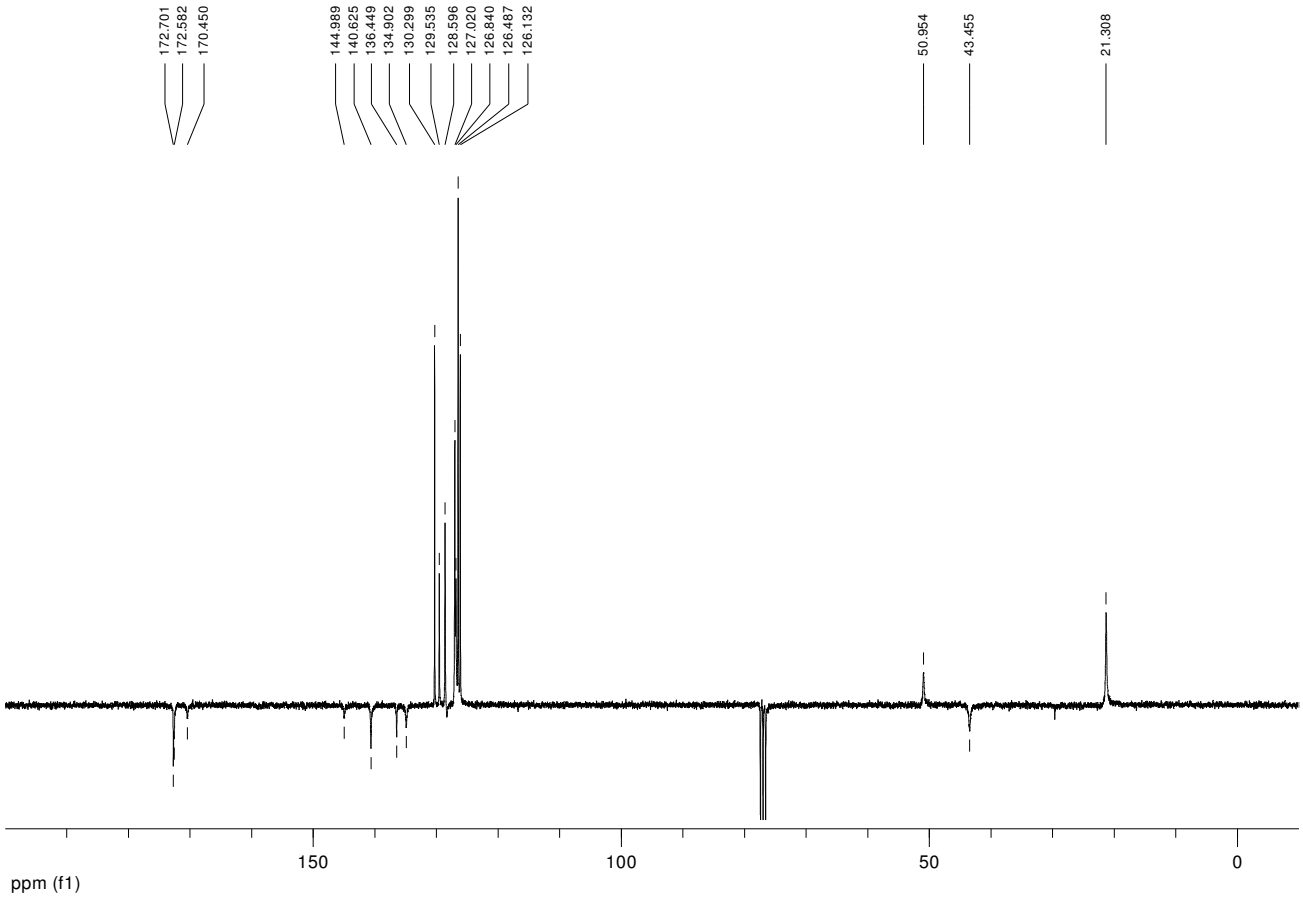


NMR spectra of *p*-3 ($CDCl_3$)

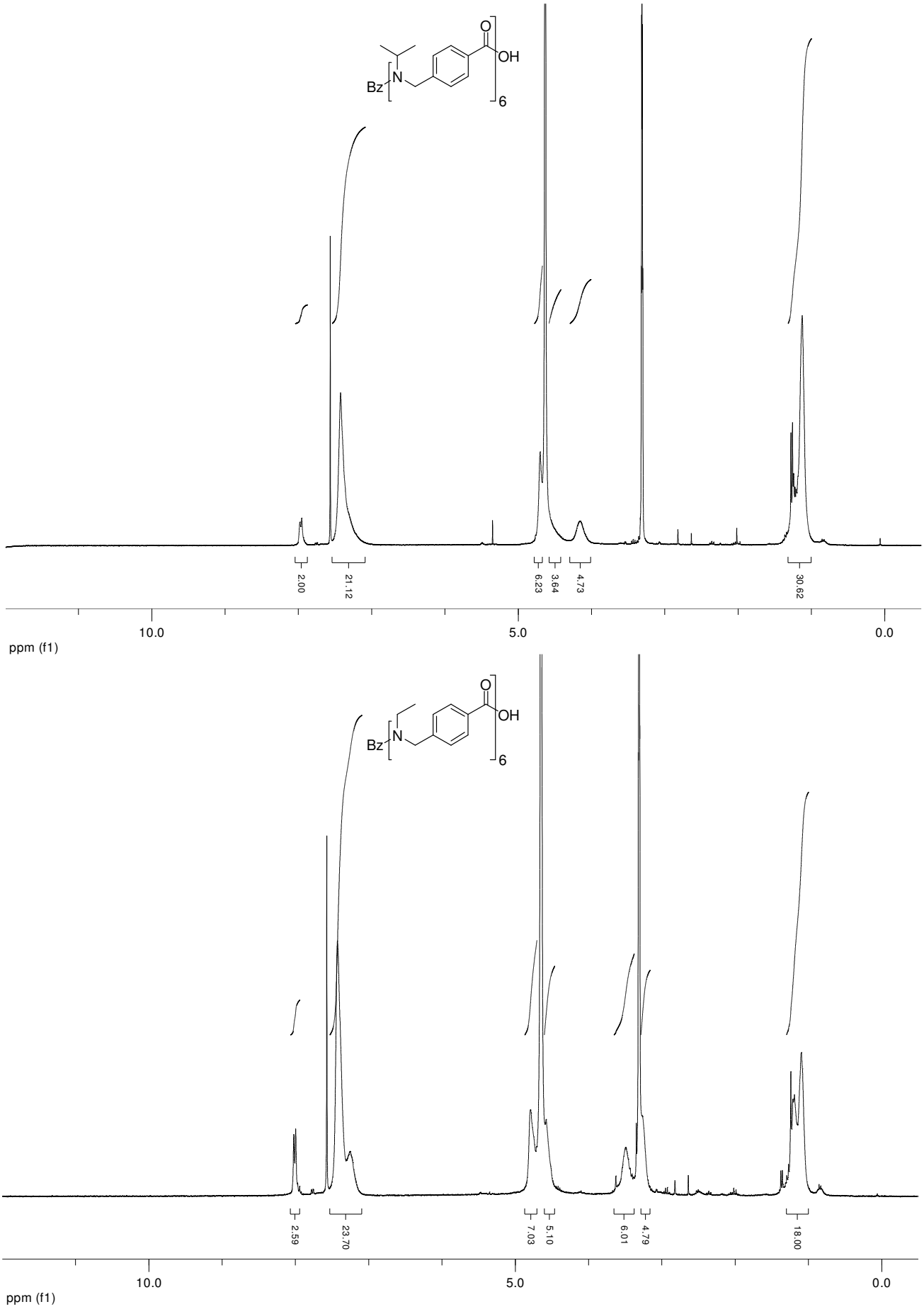


NMR spectra of *p*-5 ($CDCl_3$)

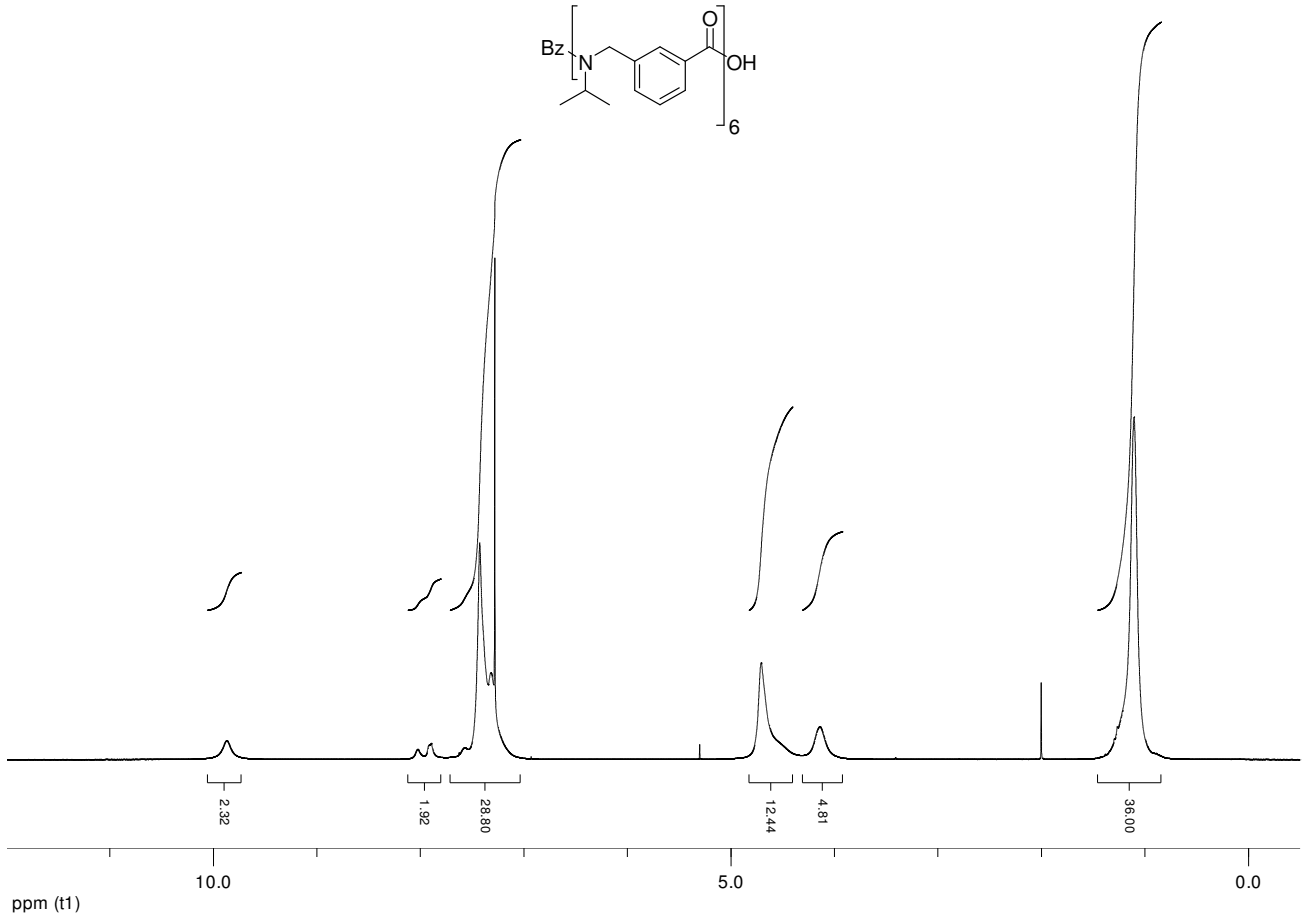


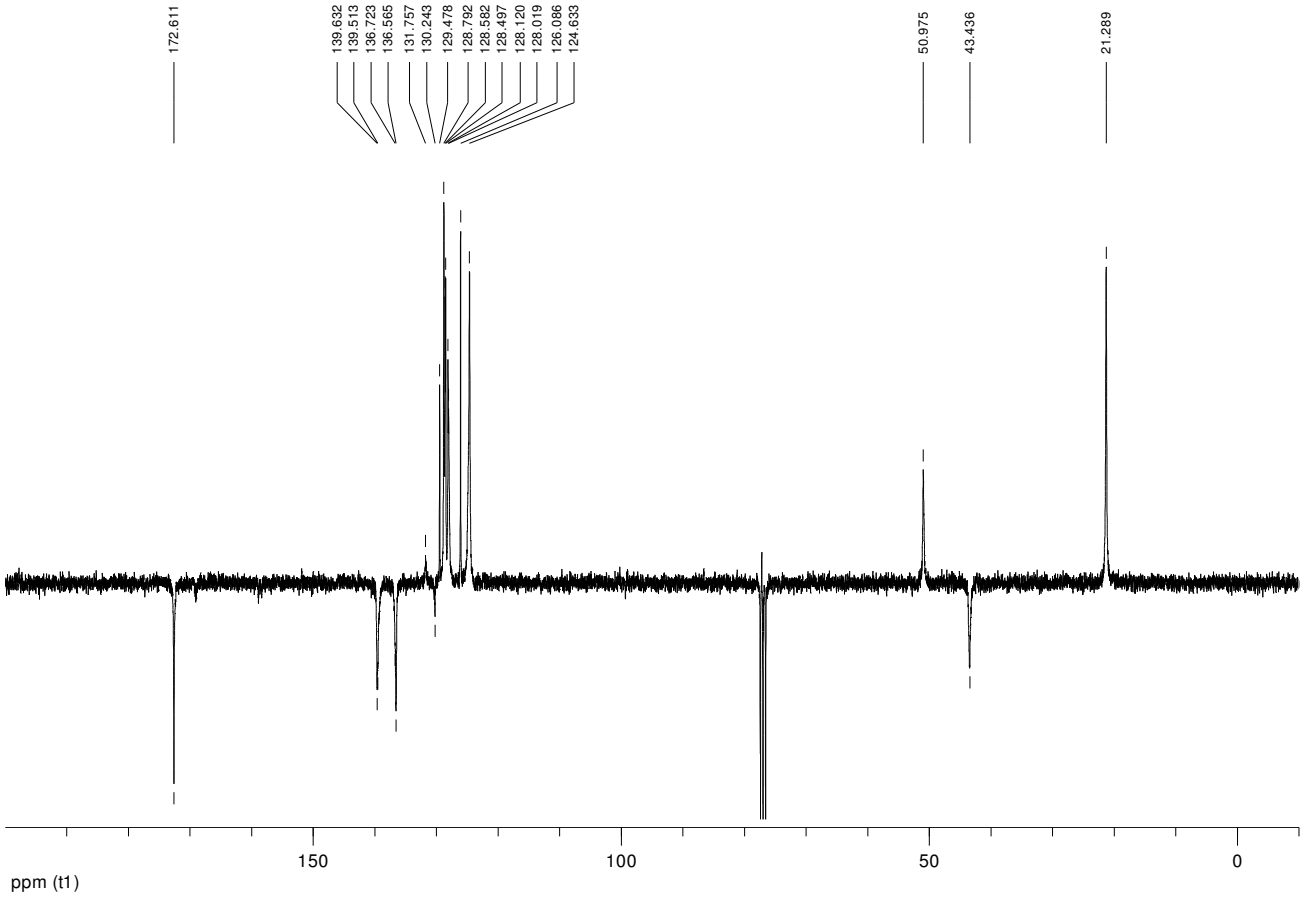


NMR spectra of crude *p*-6a ($CDCl_3$/MeOD) and crude *p*-6b ($CDCl_3$/MeOD)

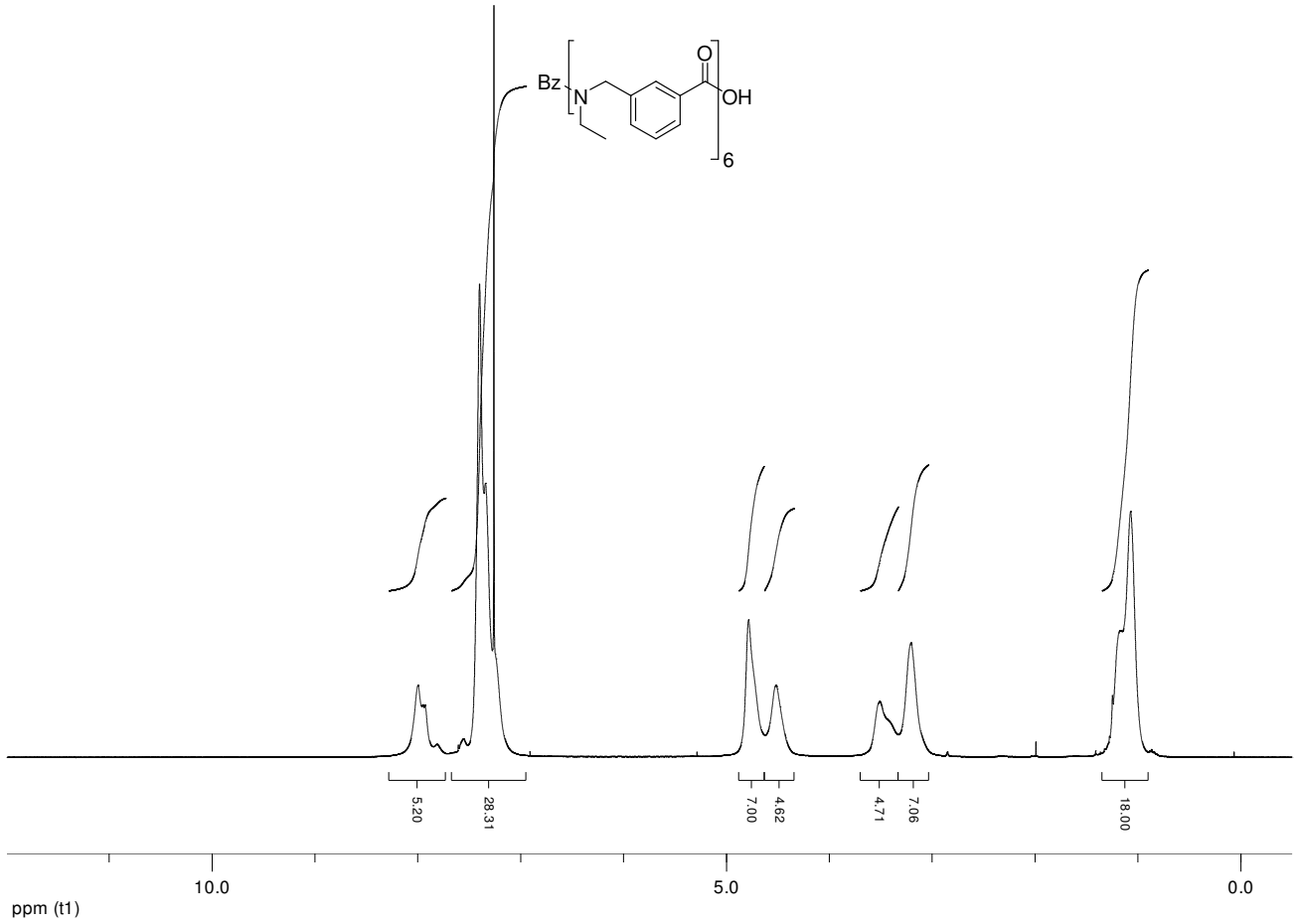


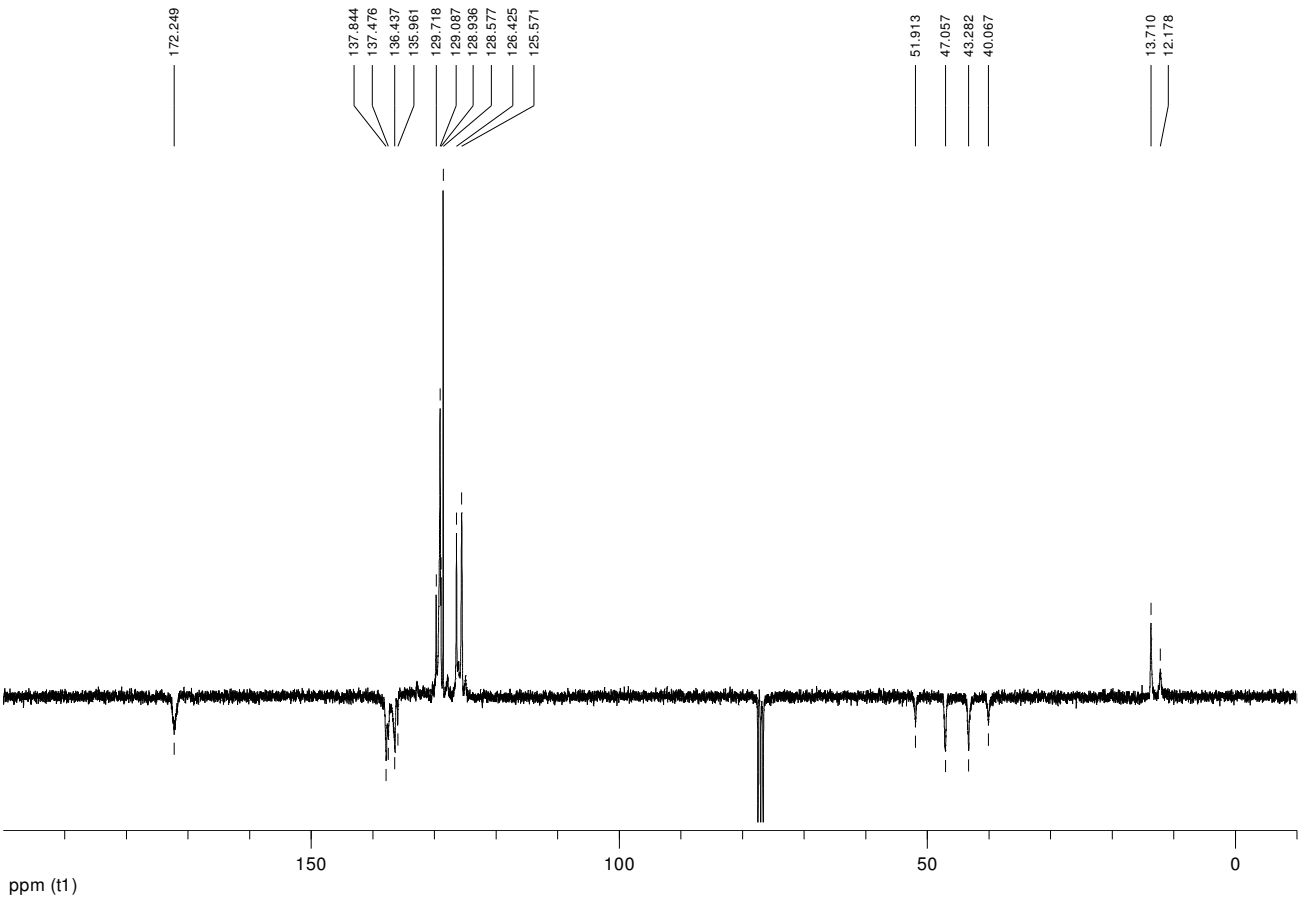
NMR spectra of *m*-6a ($CDCl_3$)



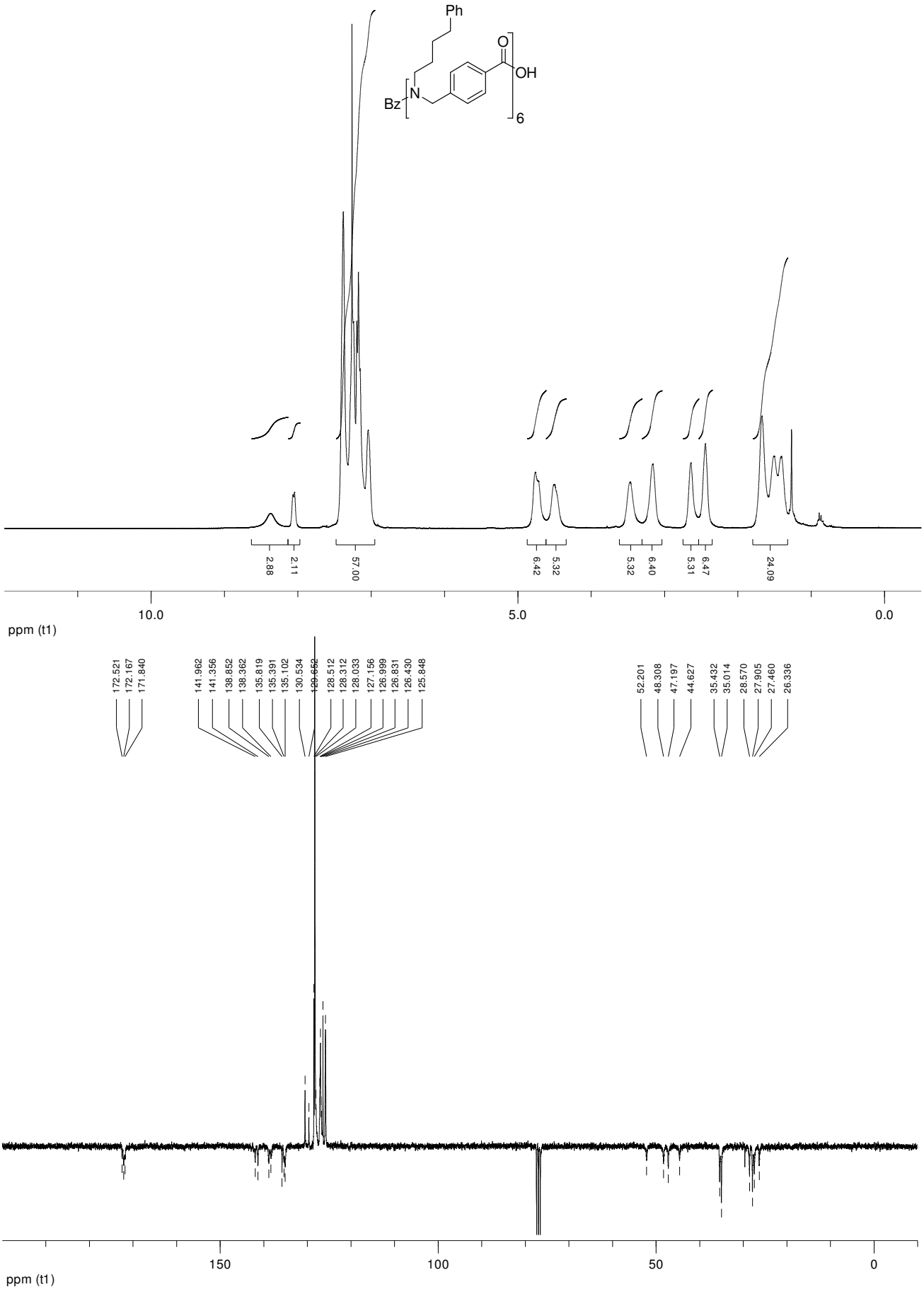


NMR spectra of *m*-6b ($CDCl_3$)

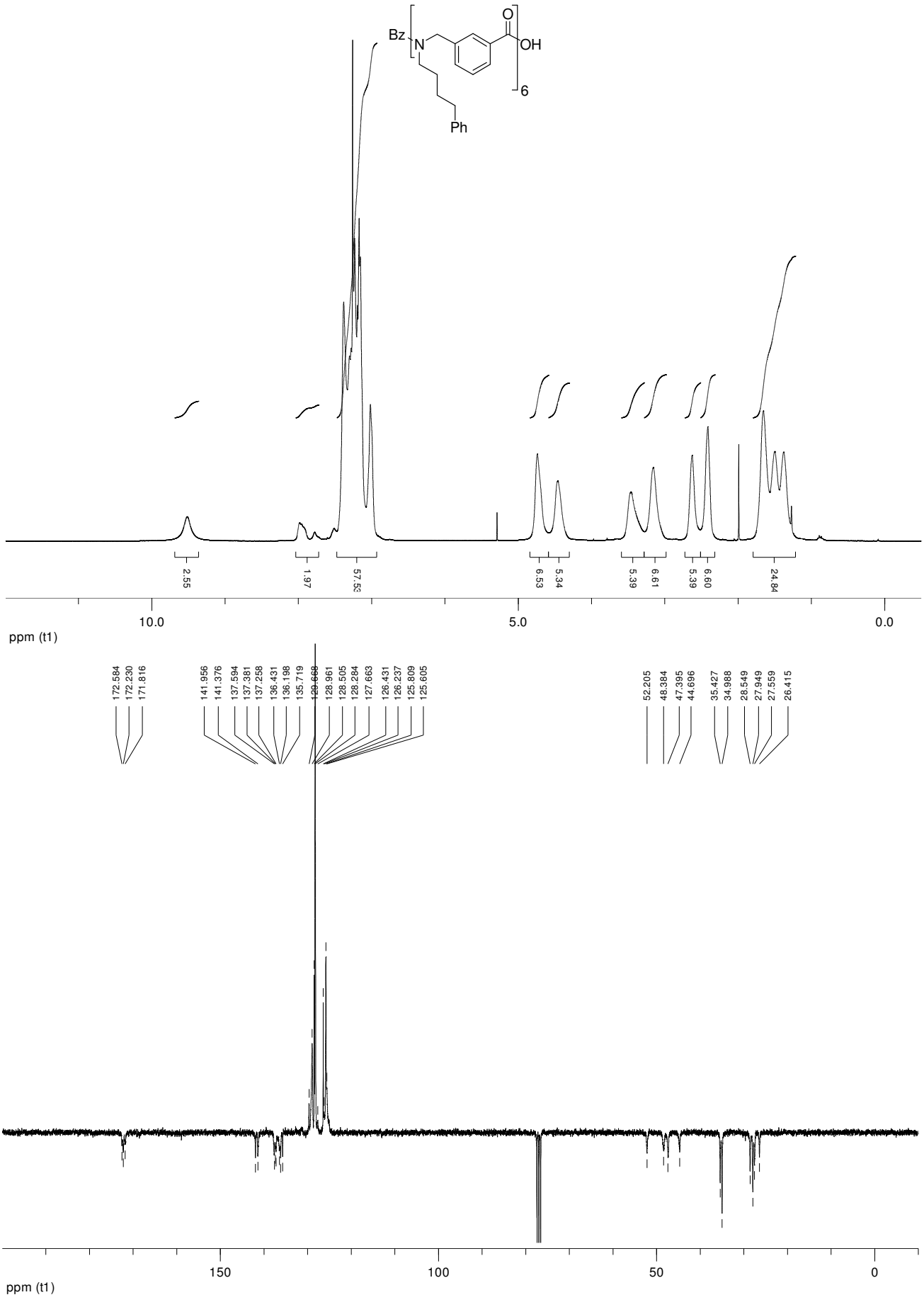




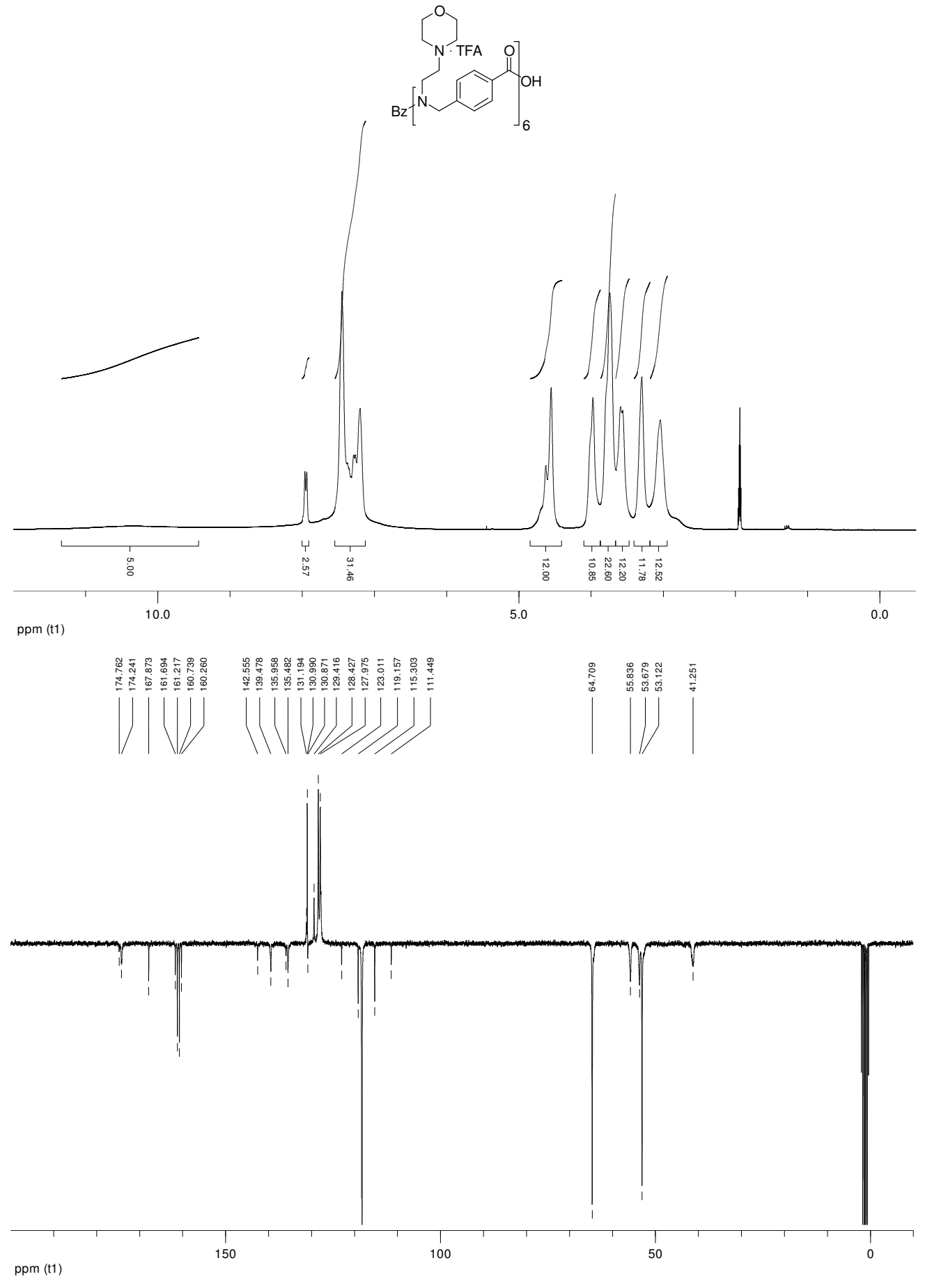
NMR spectra of *p*-6c ($CDCl_3$)



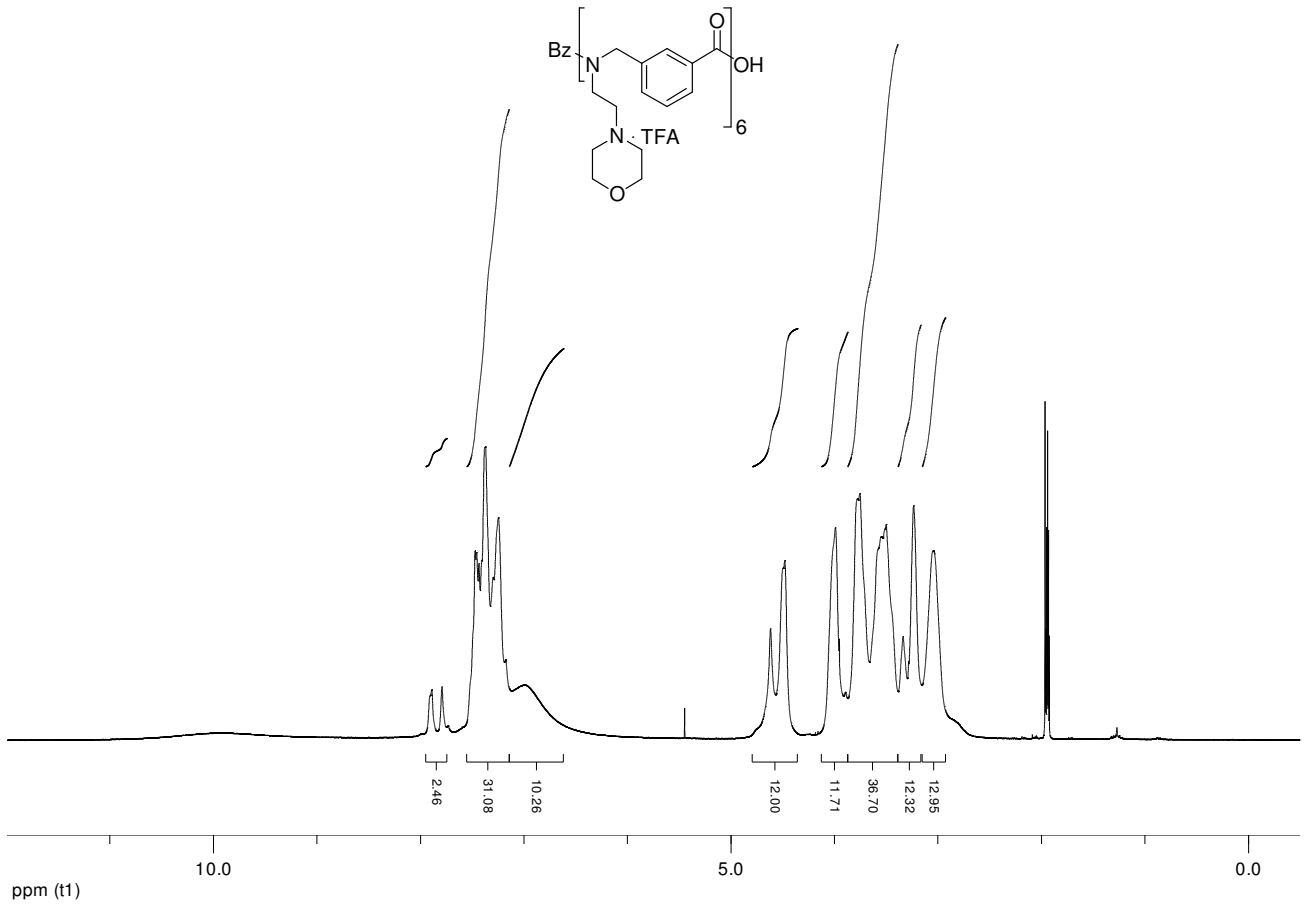
NMR spectra of *m*-6c ($CDCl_3$)

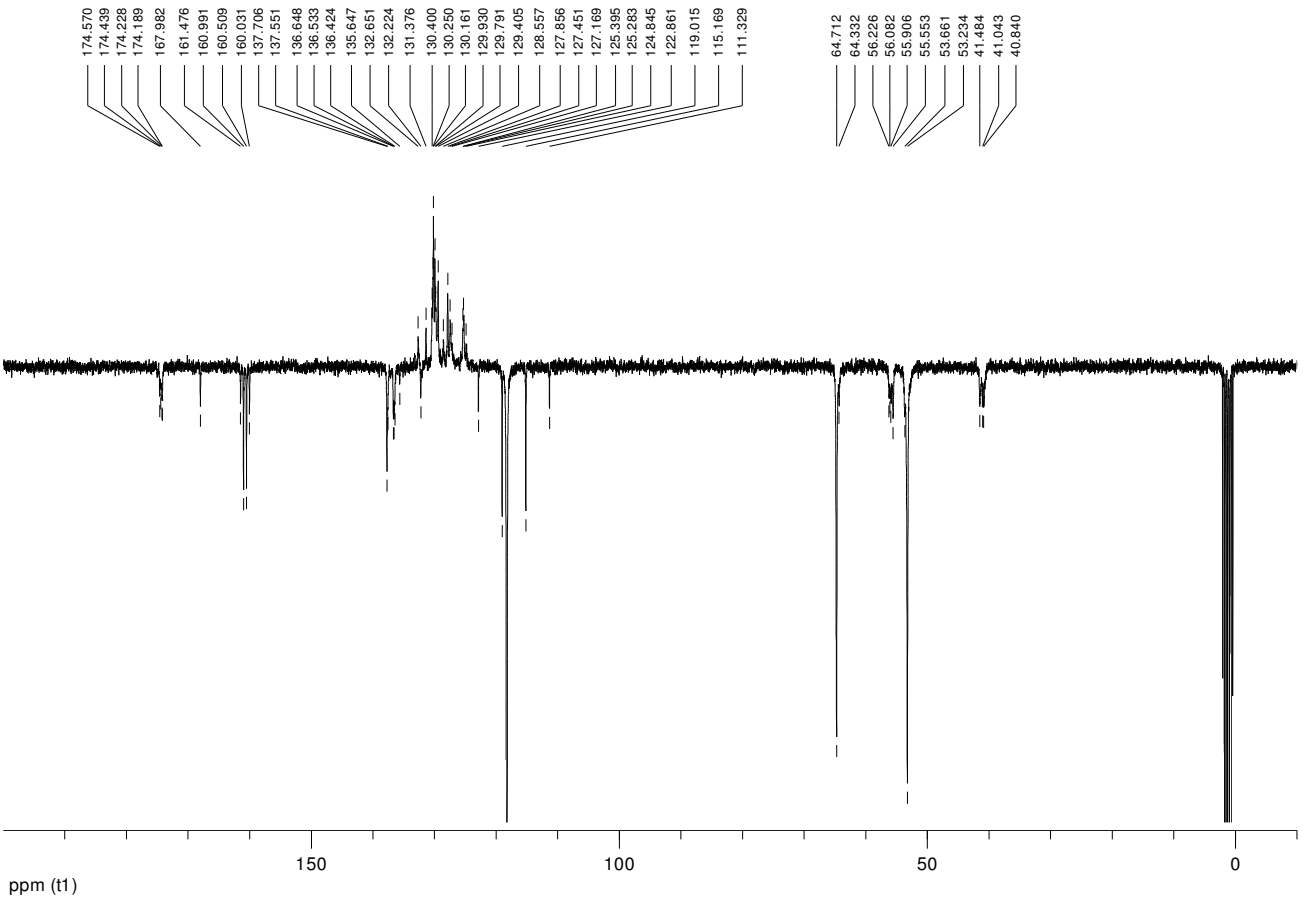


NMR spectra of *p*-6d (MeCN-d_3)

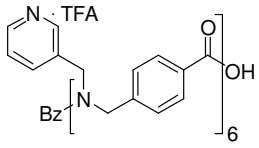


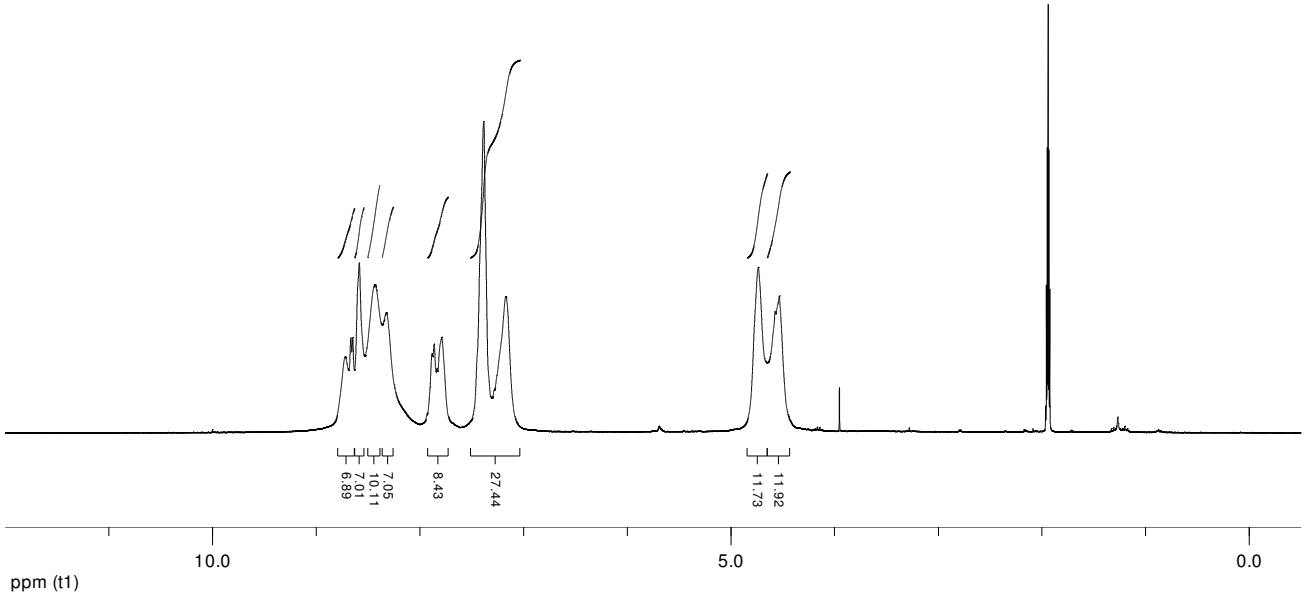
NMR spectra of *m*-6d (MeCN-d_3)

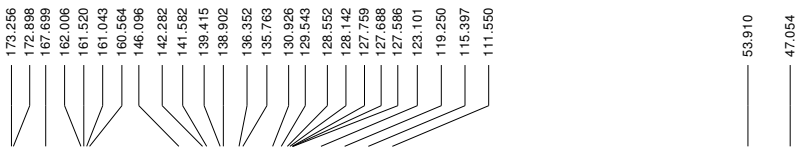


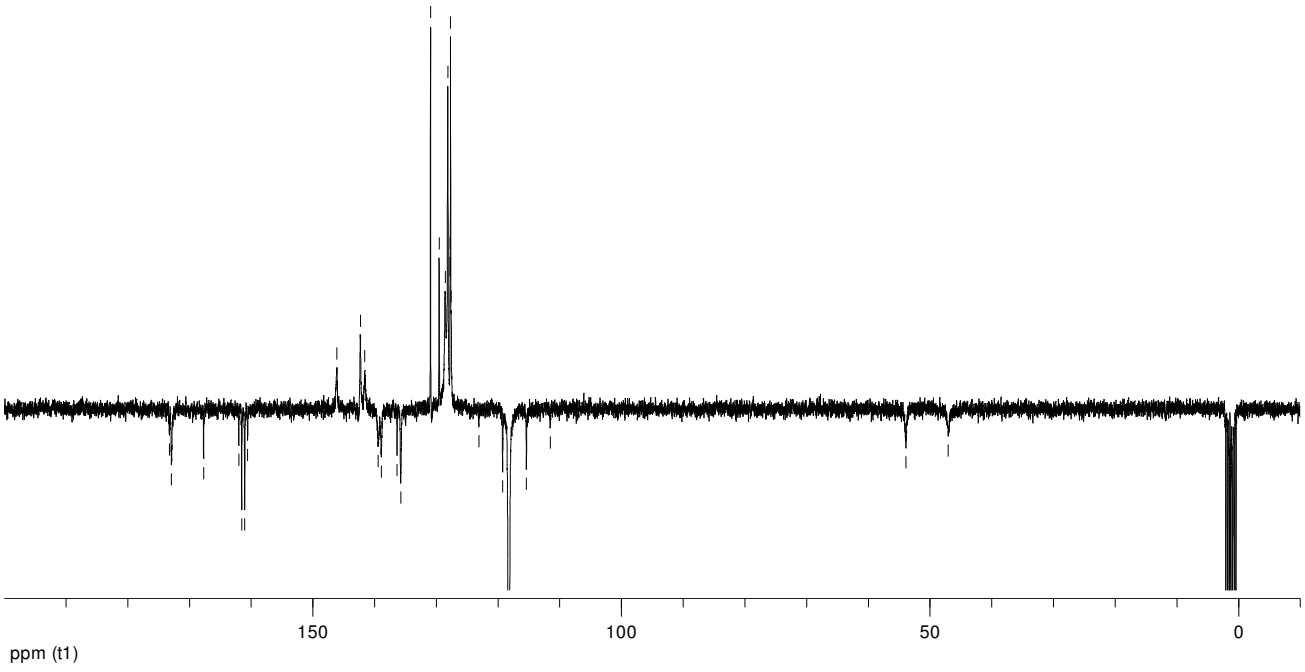


NMR spectra of *p*-6e (MeCN-d_3)

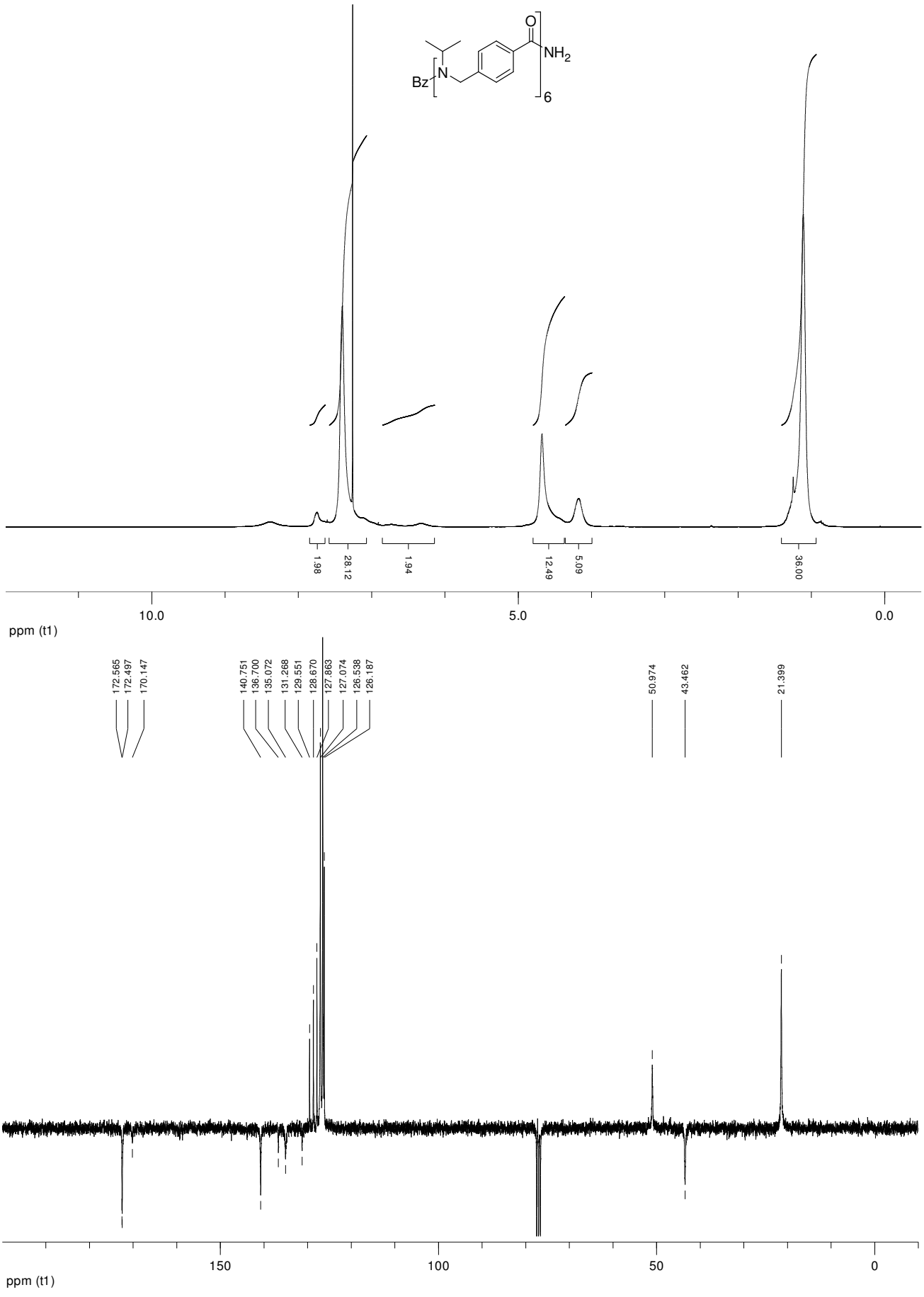




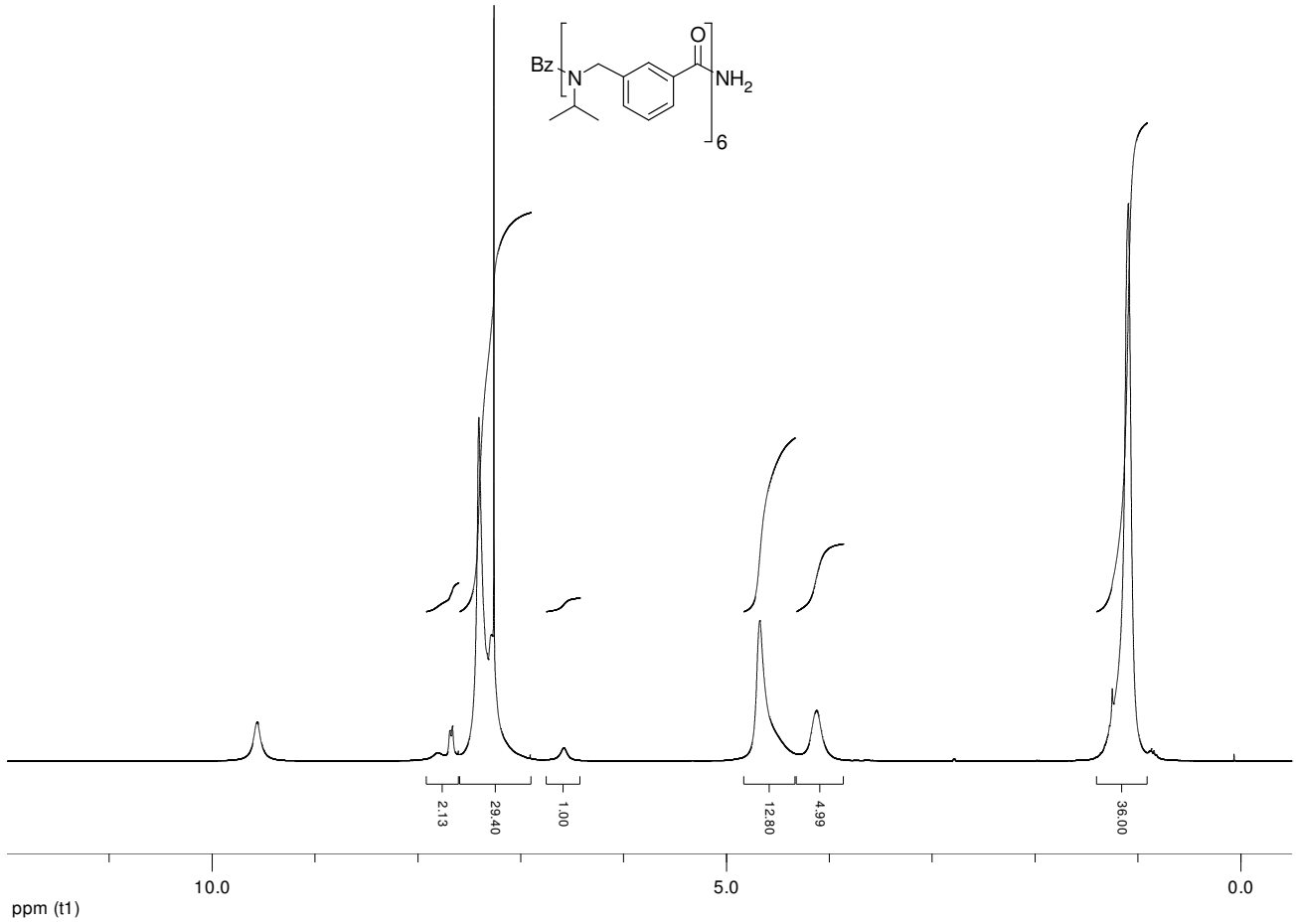


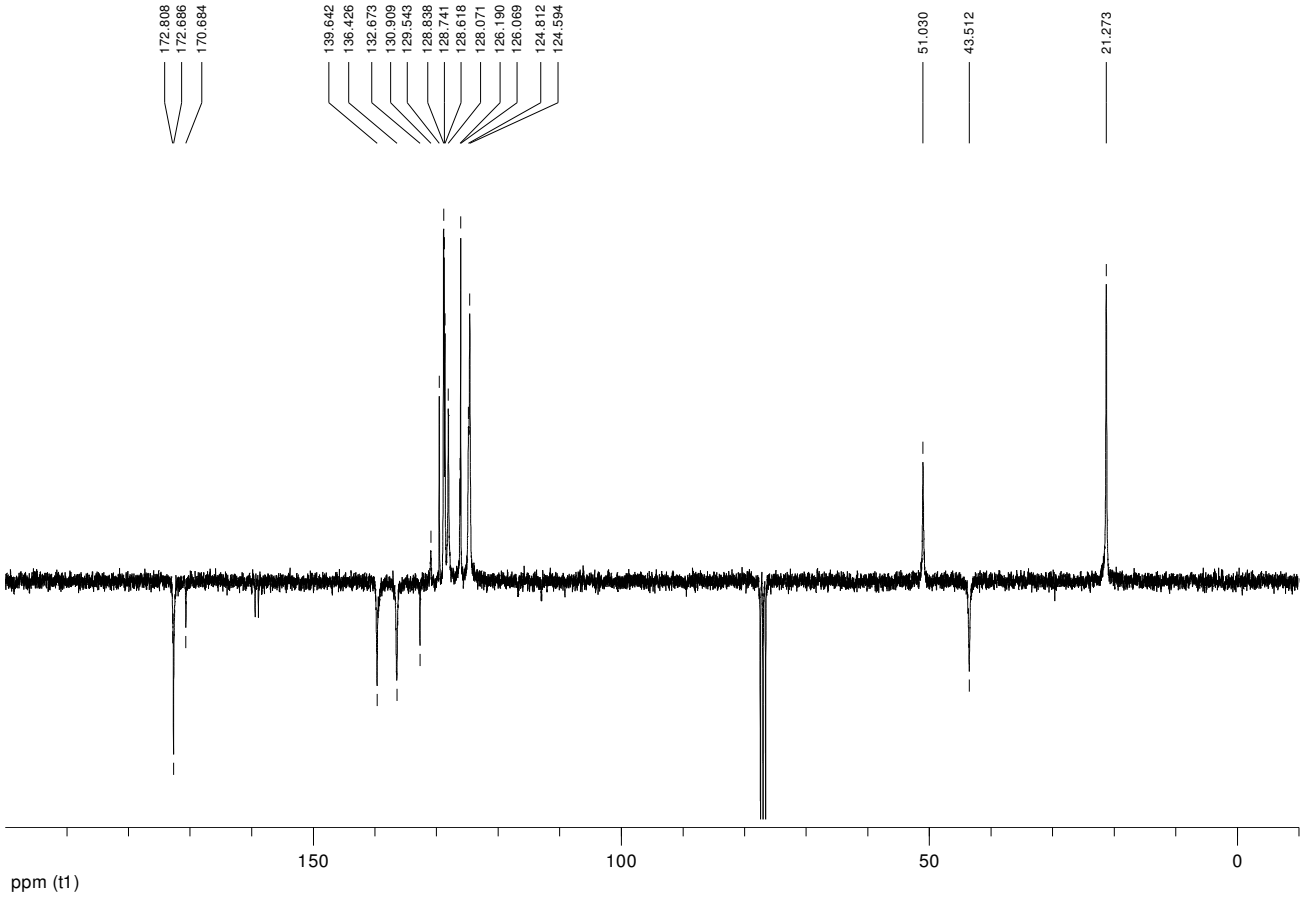


NMR spectra of *p*-7a ($CDCl_3$)

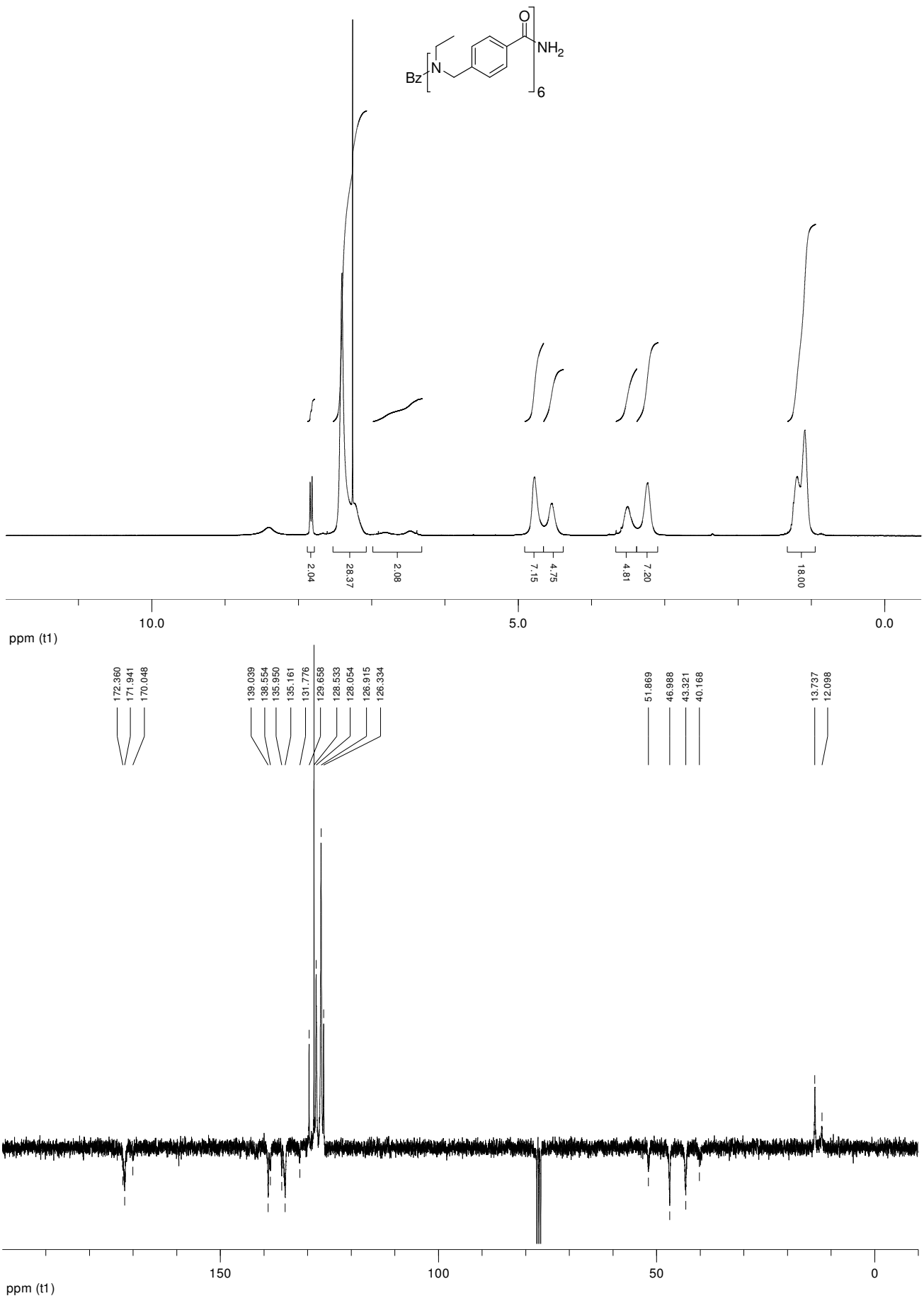


NMR spectra of *m*-7a ($CDCl_3$)

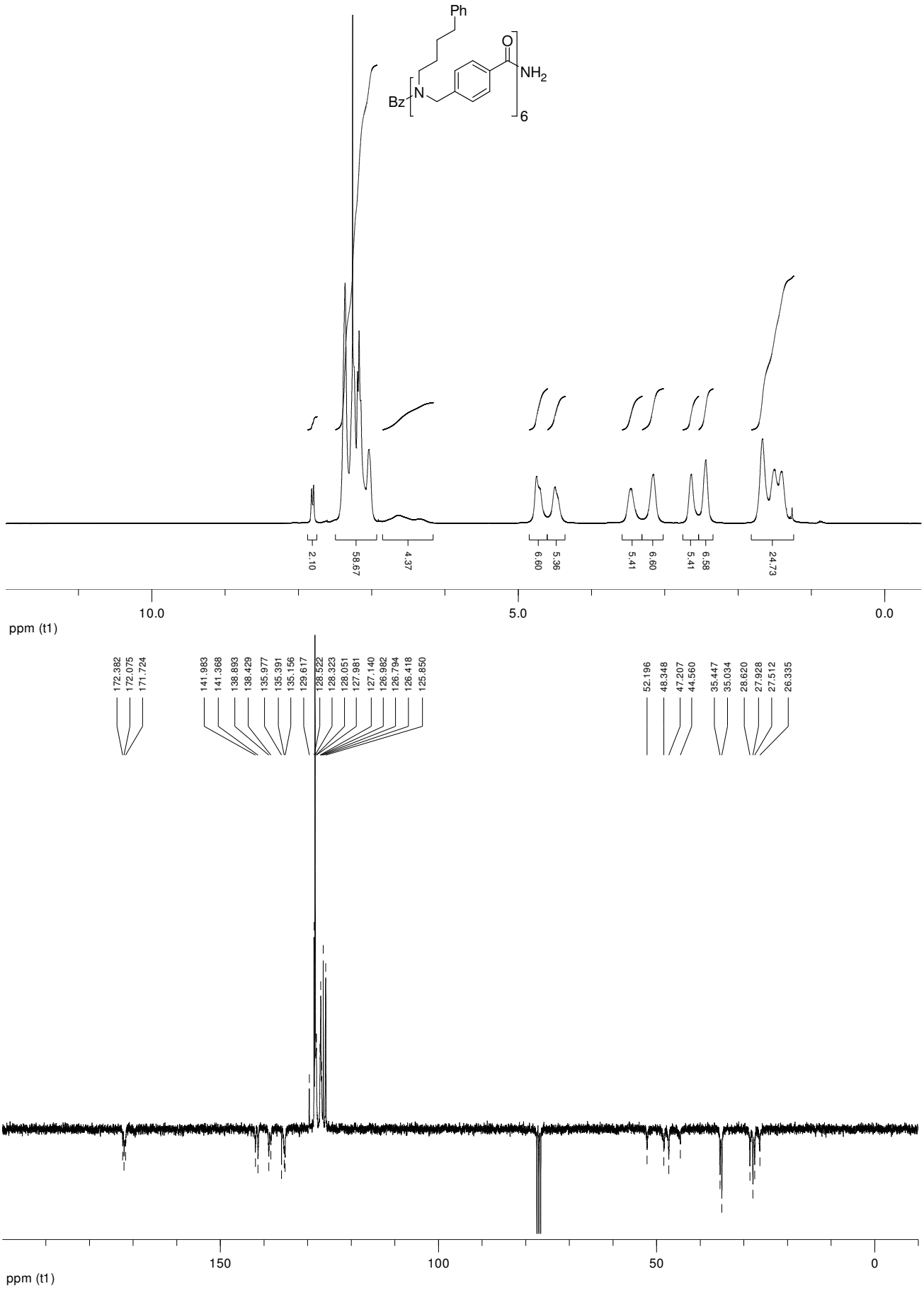




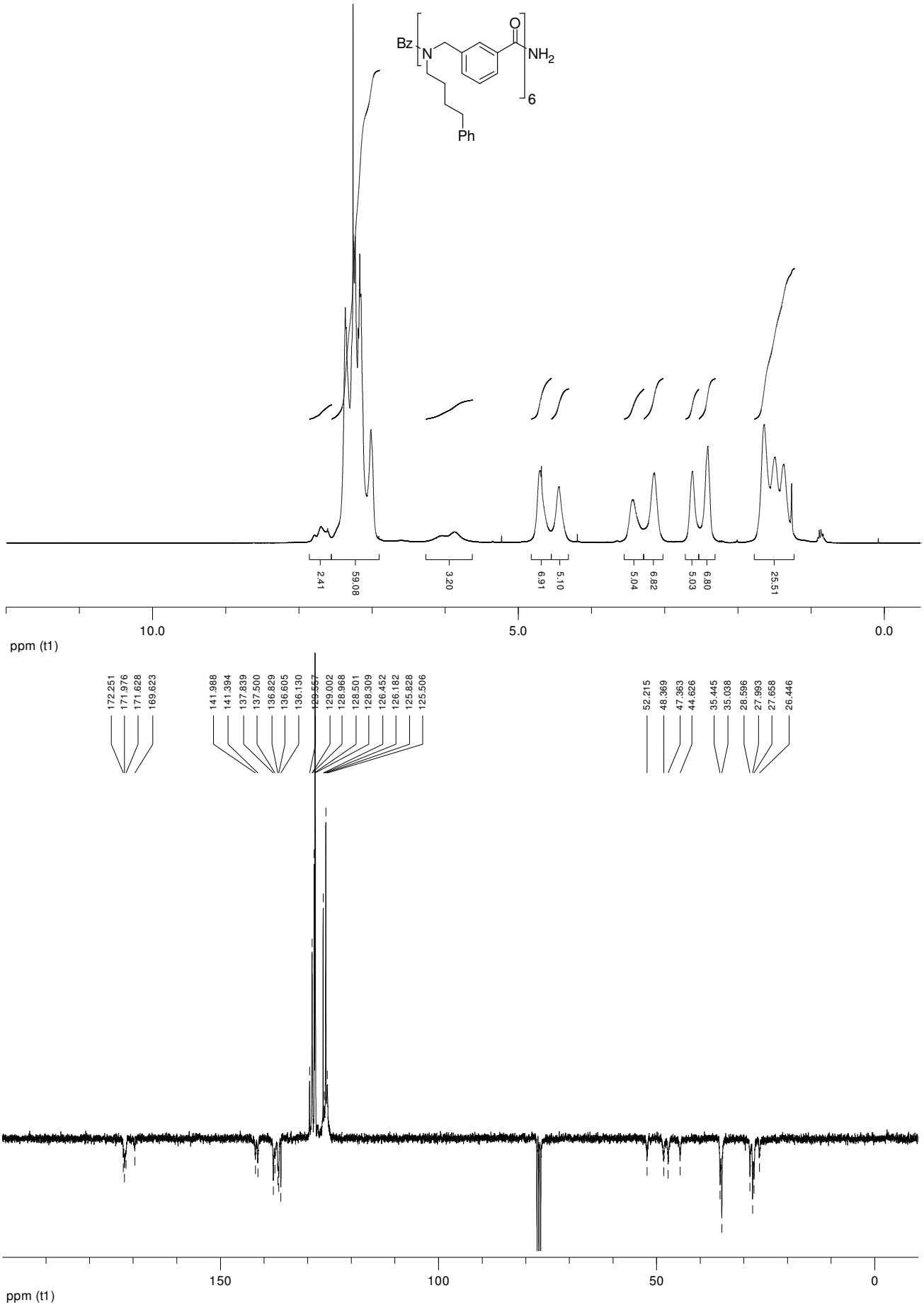
NMR spectra of *p*-7b ($CDCl_3$)



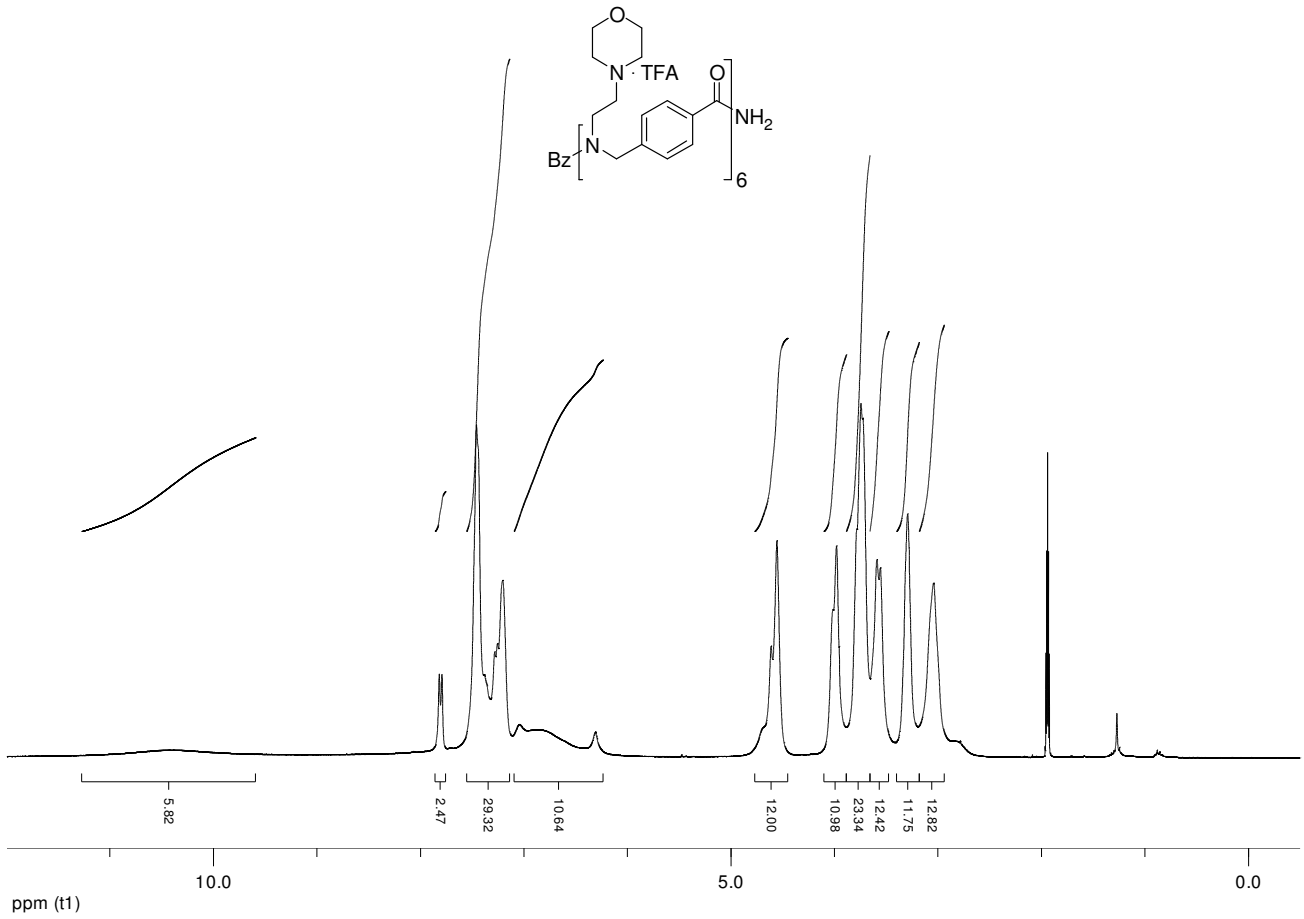
NMR spectra of *p*-7c ($CDCl_3$)

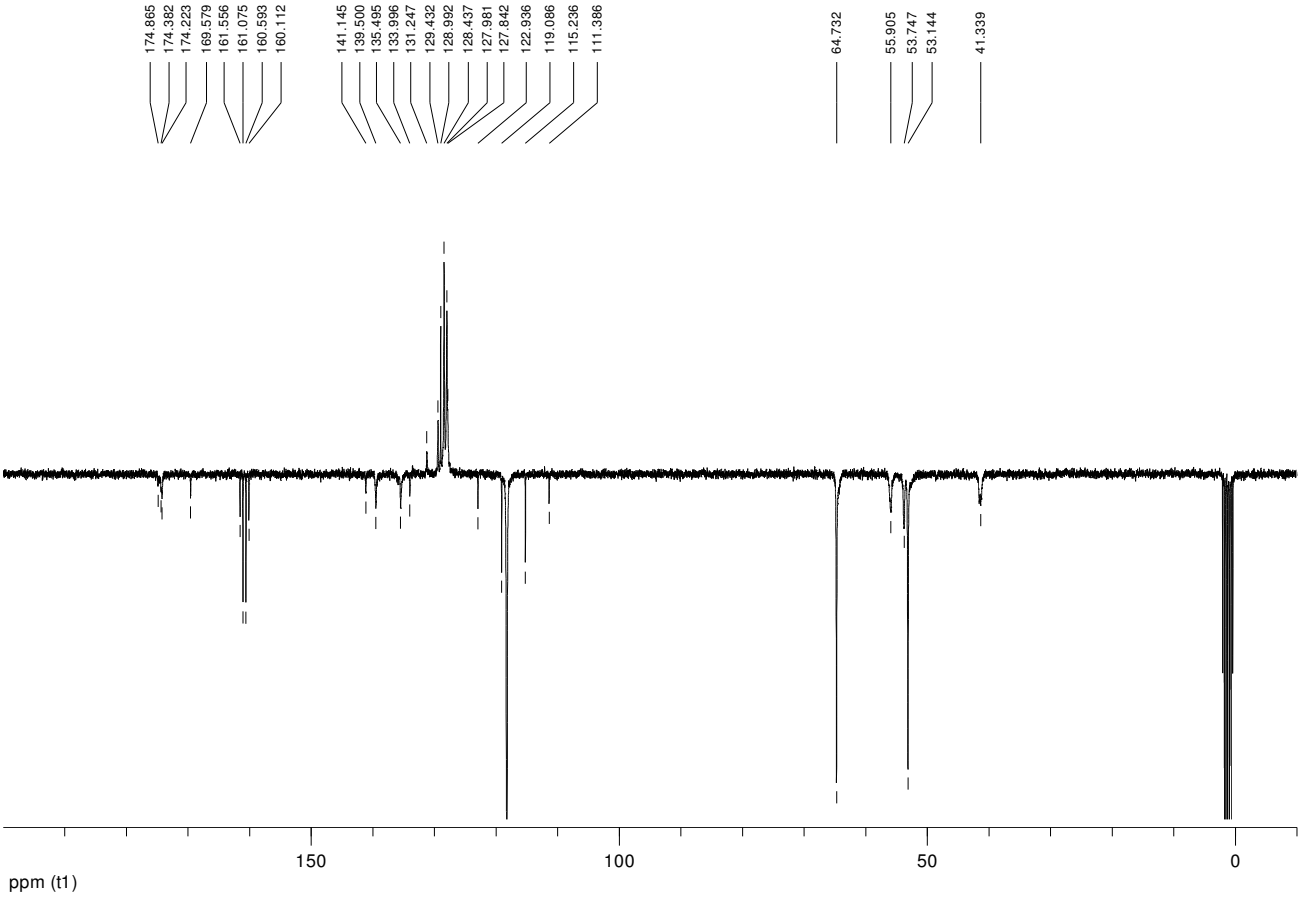


NMR spectra of *m*-7c ($CDCl_3$)

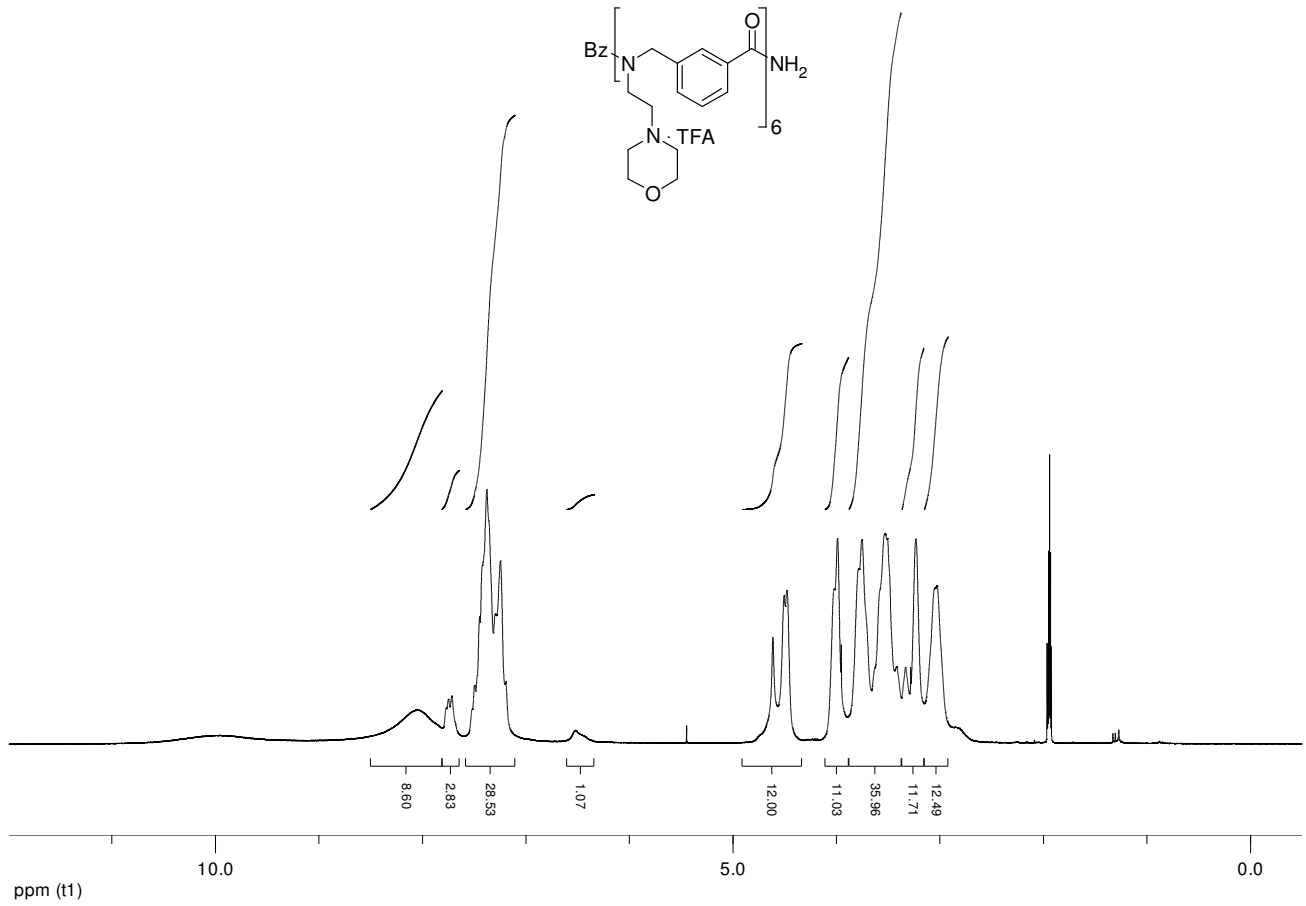


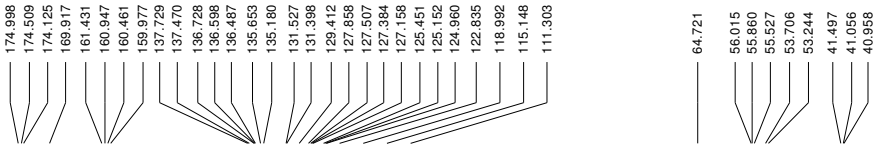
NMR spectra of *p*-7d (MeCN-d_3)

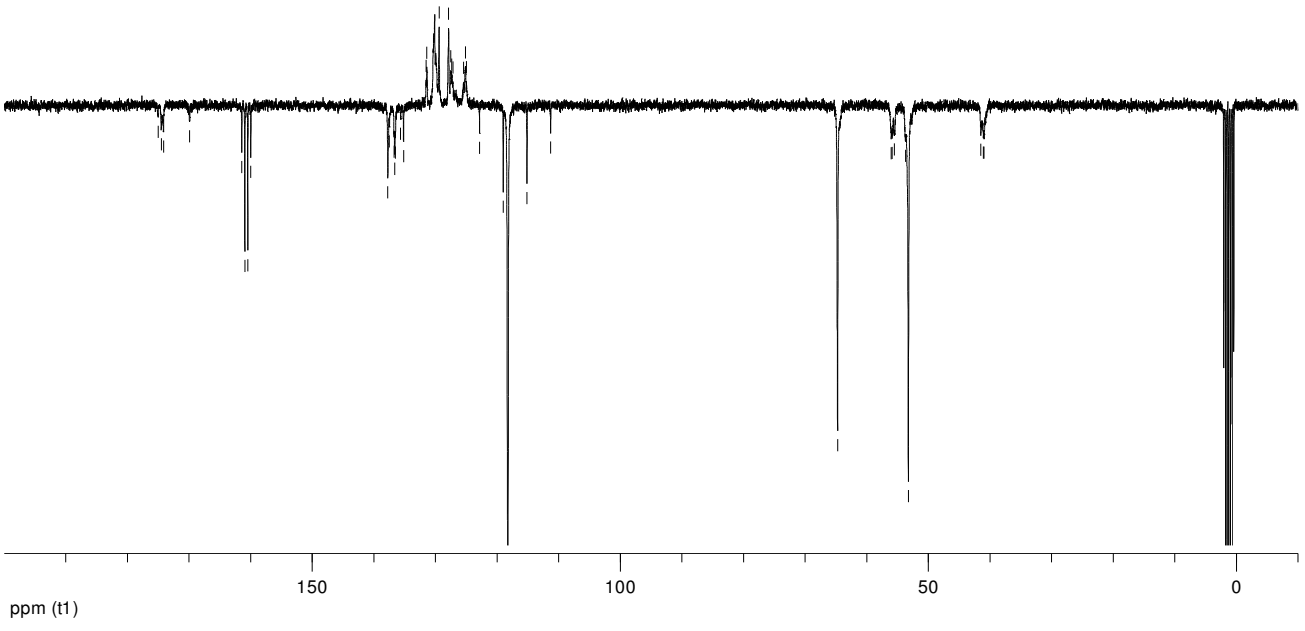




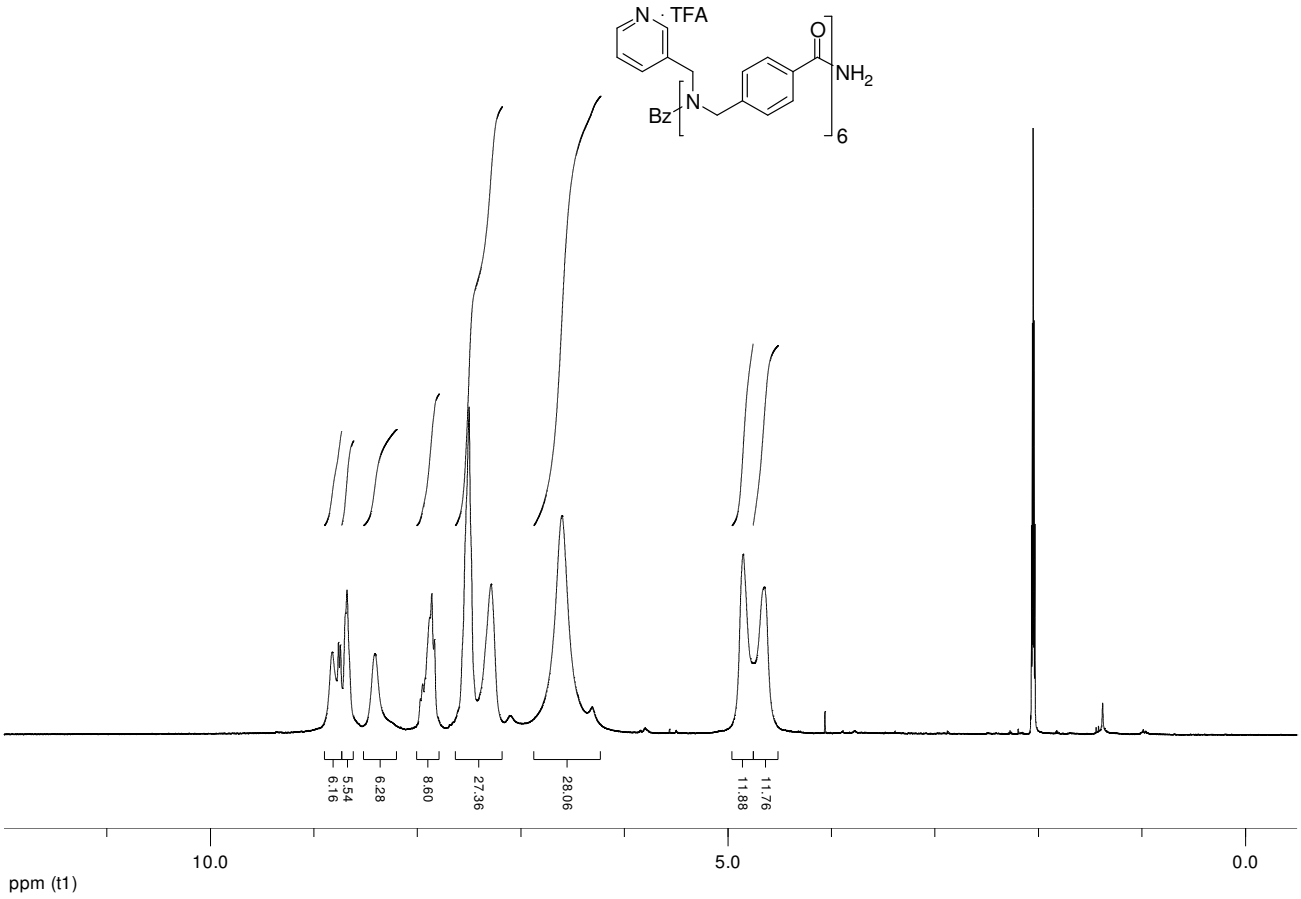
NMR spectra of *m*-7d (MeCN-d_3)

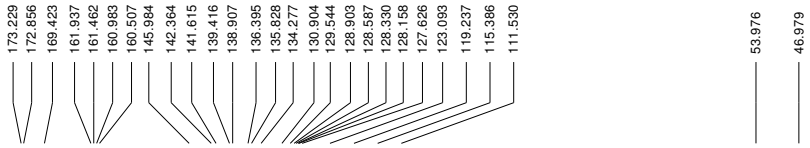


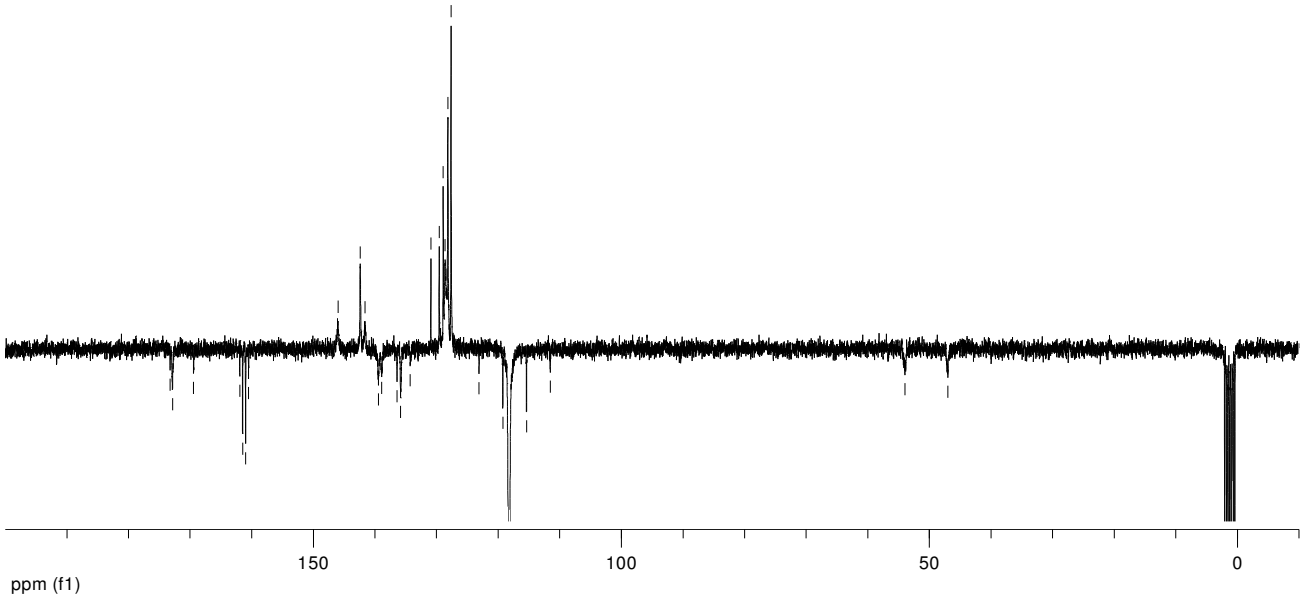




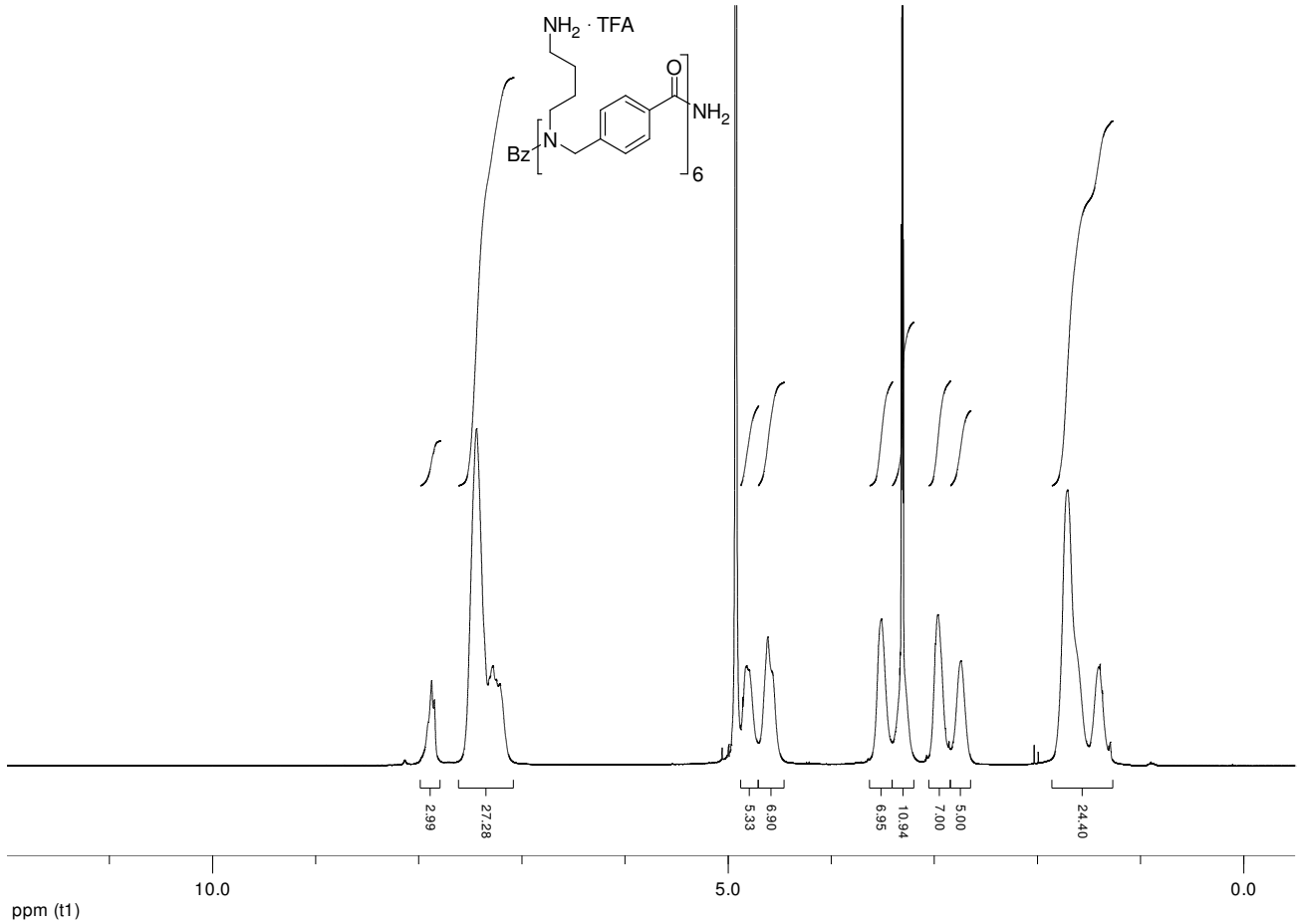
NMR spectra of *p*-7e (MeCN-d_3)

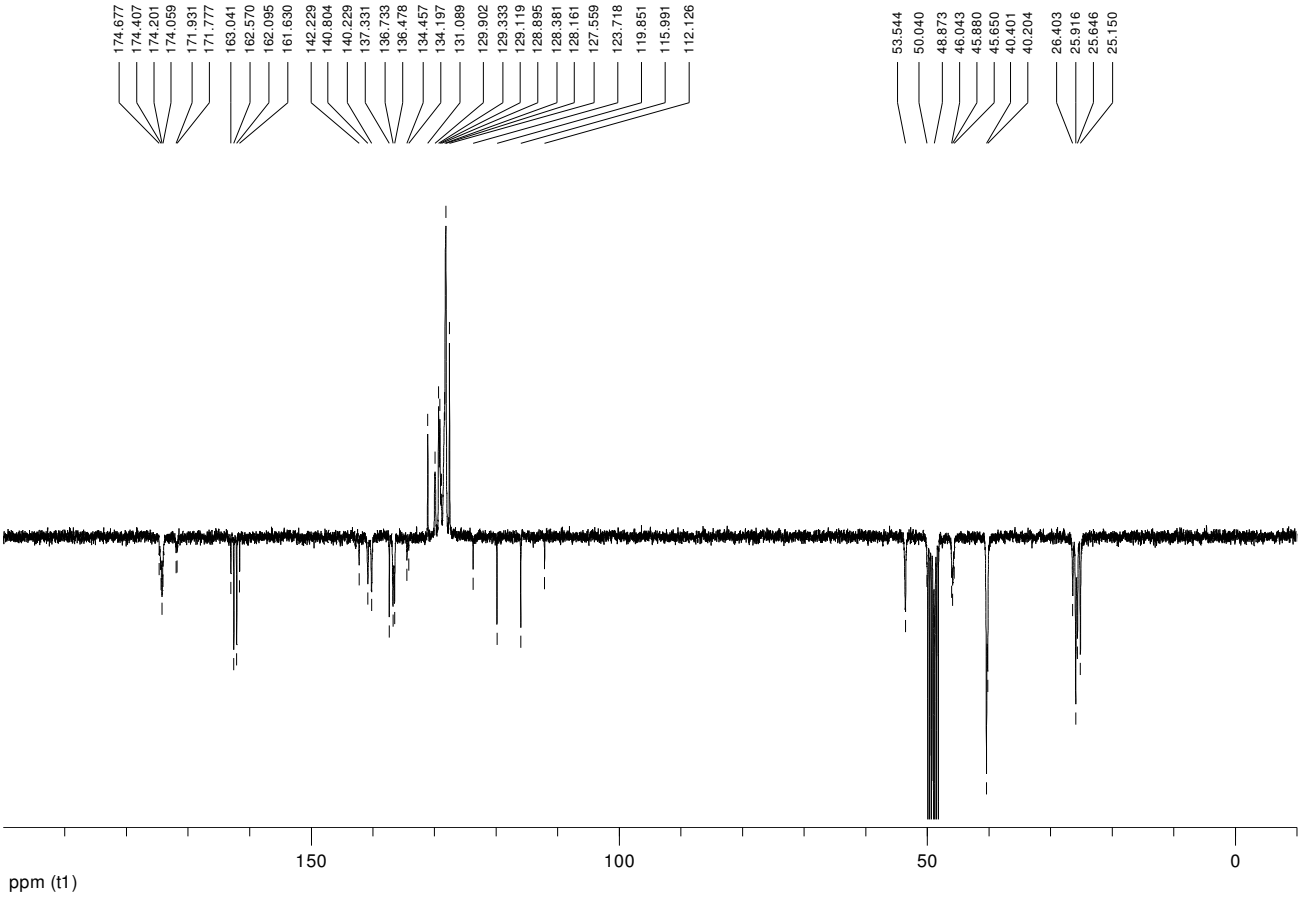




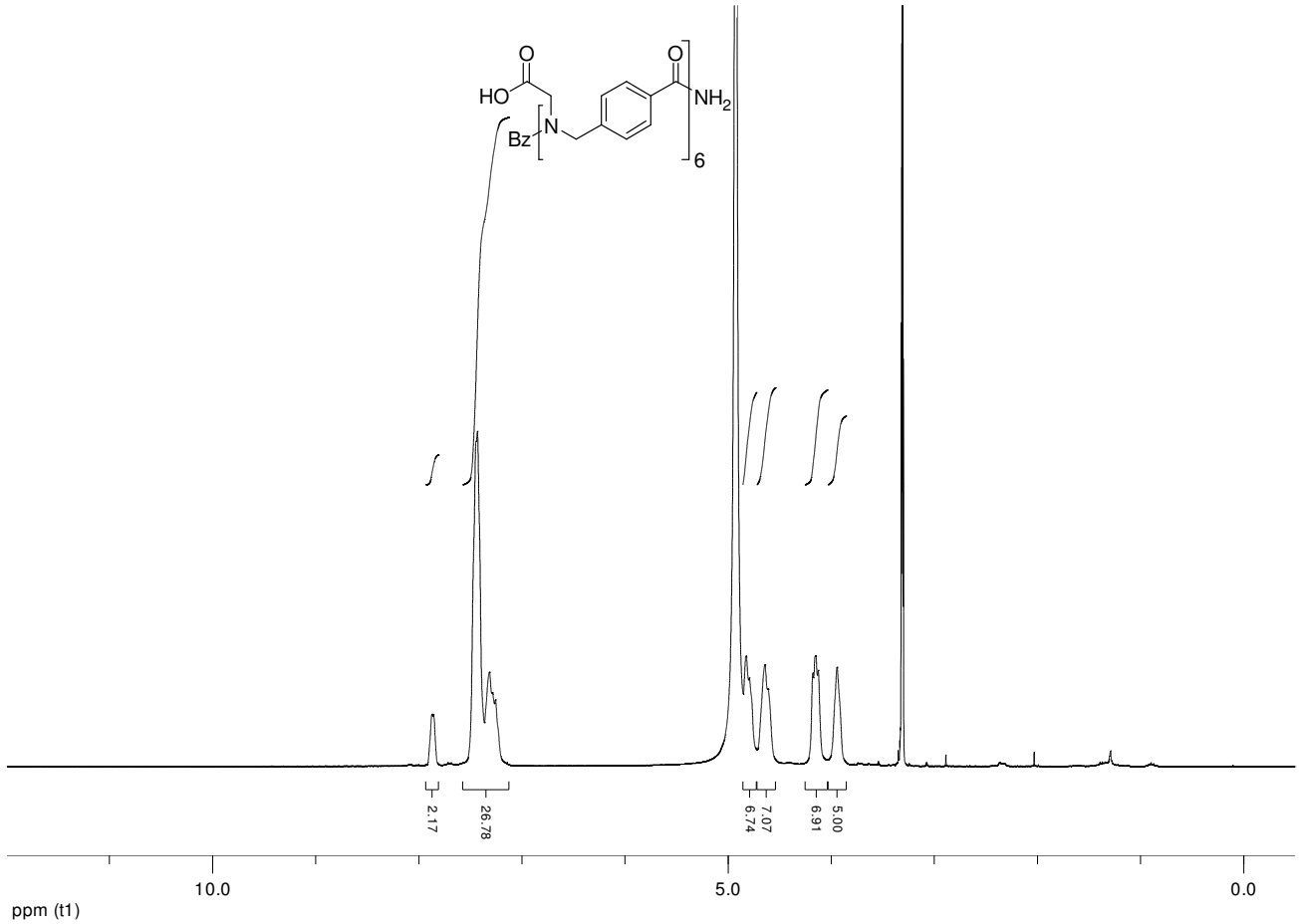


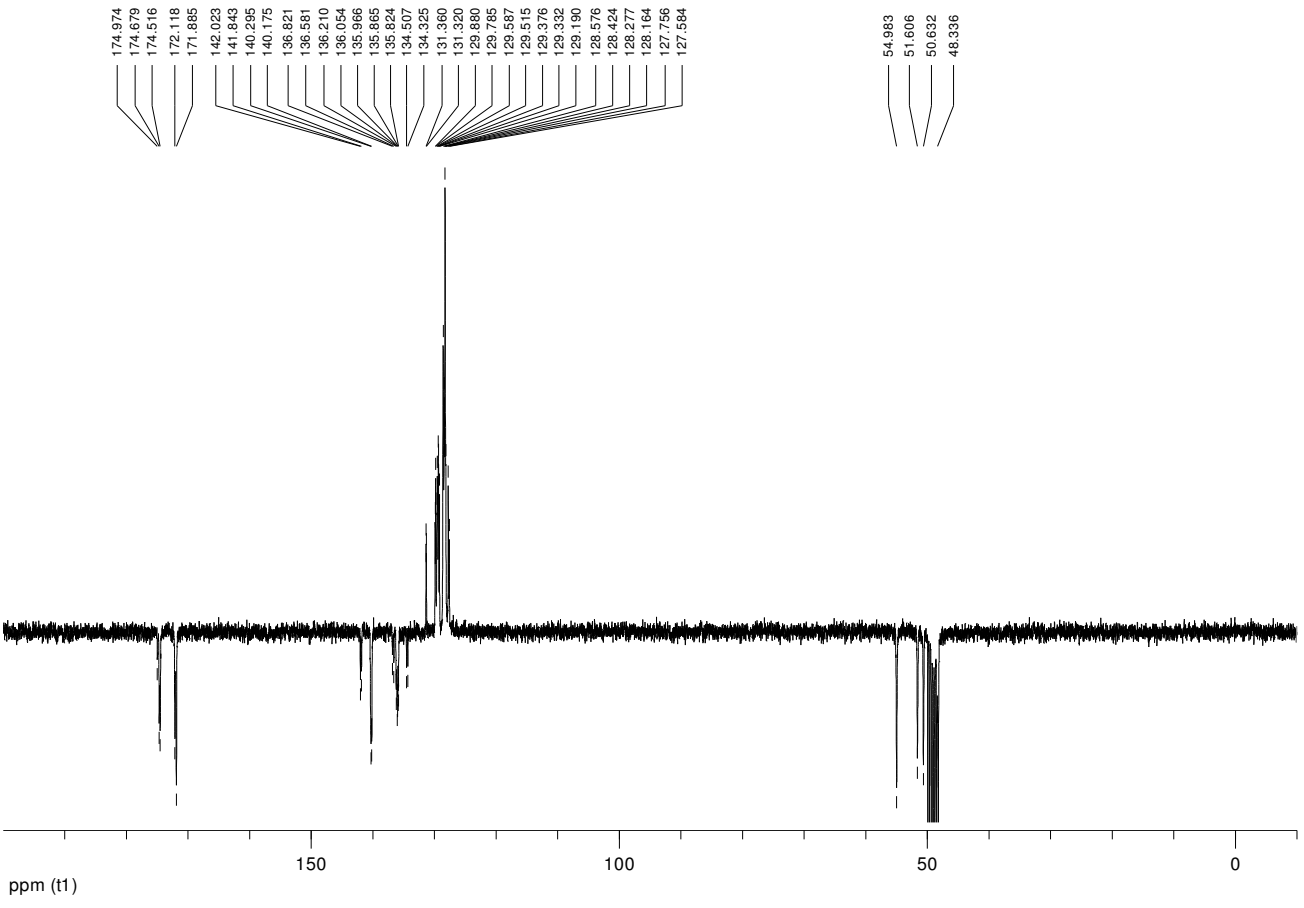
NMR spectra of *p*-7f (MeOD)



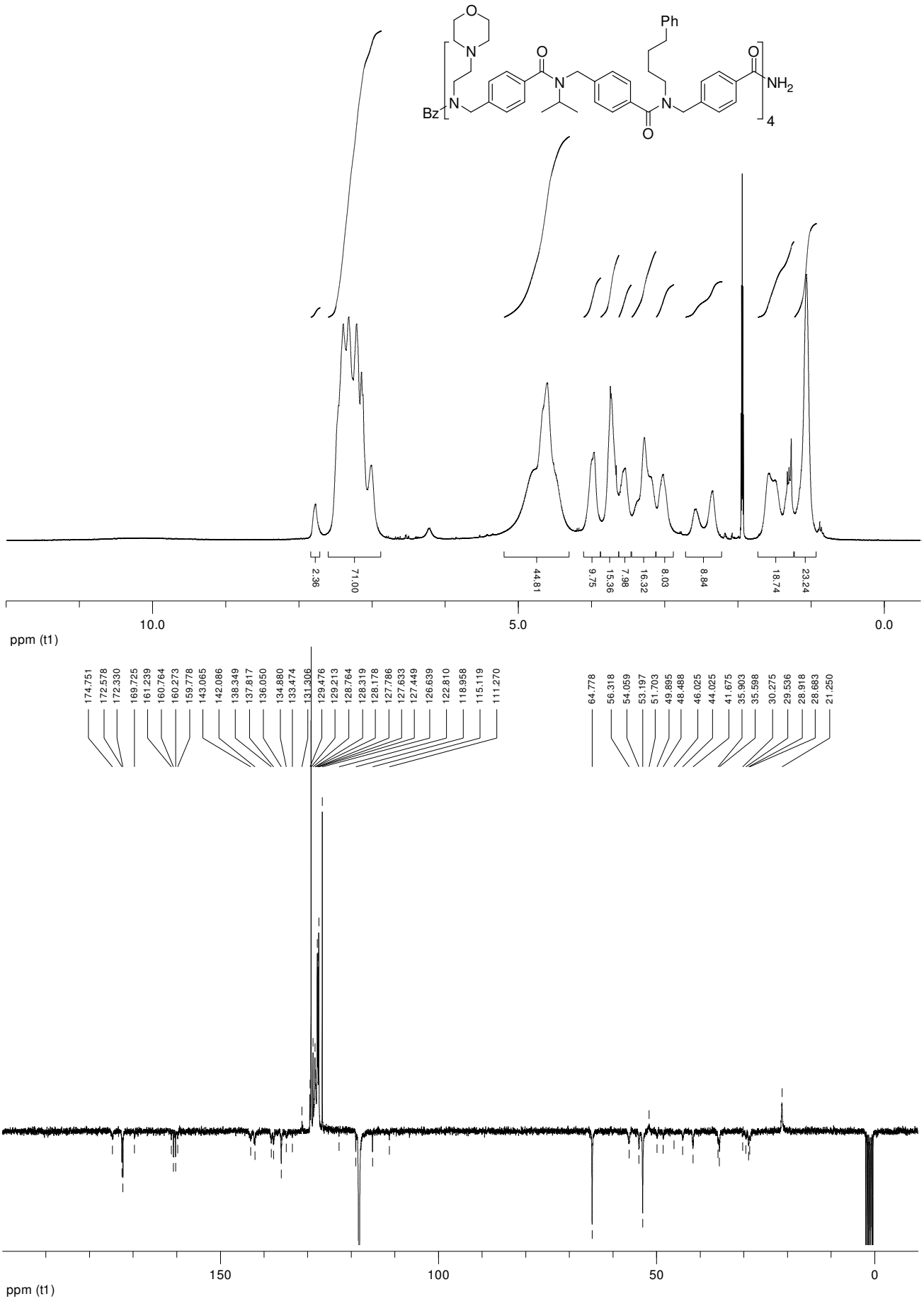


NMR spectra of *p*-7g (MeOD)

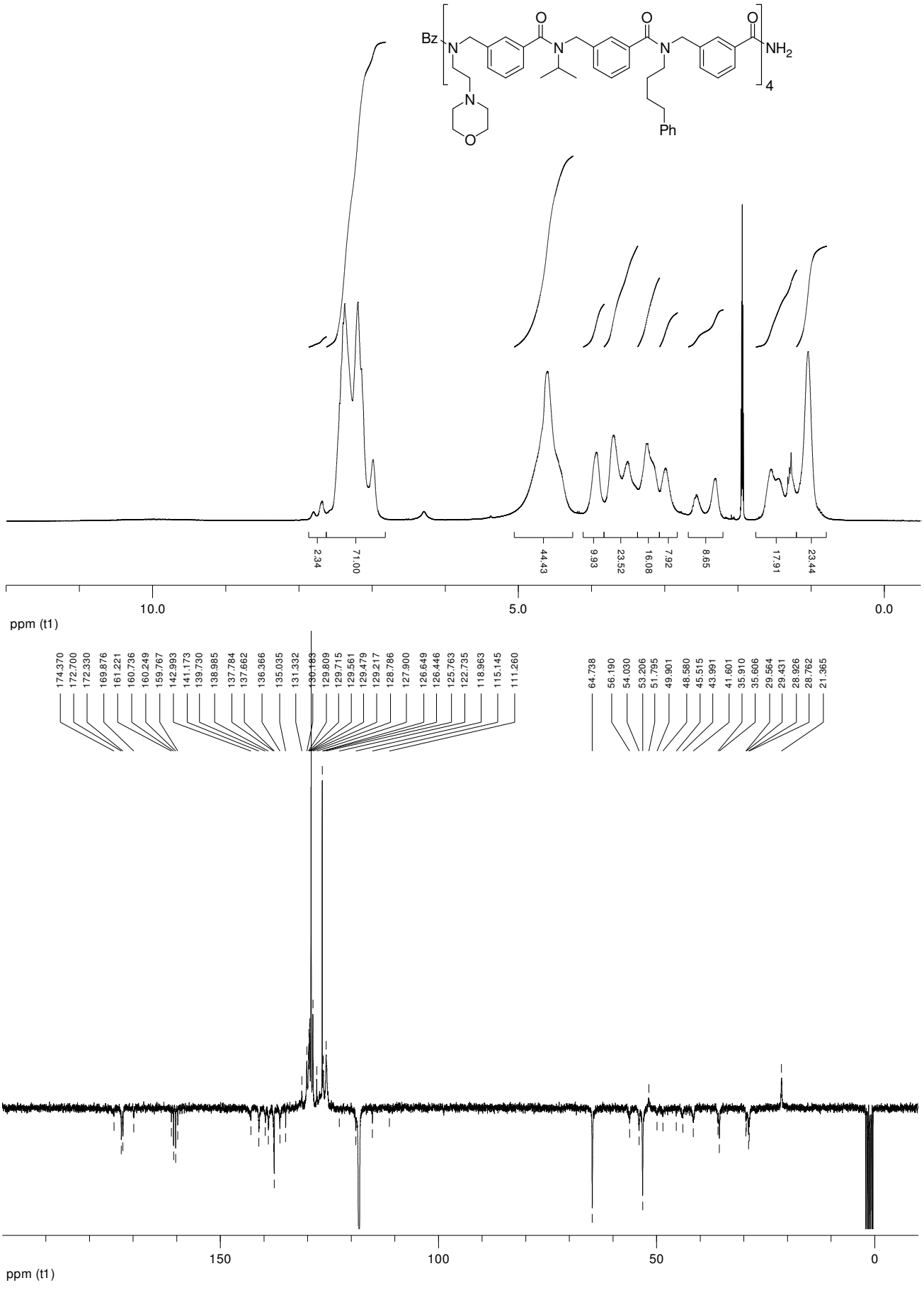




NMR spectra of *p*-8 (MeCN-d_3)



NMR spectra of *m*-8 (MeCN-d_3)



References

[S1] T. Hjelmgaard, S. Faure, D. Staerk, C. Taillefumier, J. Nielsen *Eur. J. Org. Chem.* **2011**, *accepted*.