

***Daucus carota* mediated-reduction of cyclic 3-oxo-amines**

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Supporting information

Table of contents

INFORMATION	2
PREPARATION OF SUBSTRATES	2
METHYL <i>N</i> -BENZYL-4-OXOPIPERIDINE-3-CARBOXYLATE (1)	2
ETHYL <i>N</i> -BOC-4-OXOPIPERIDINE-3-CARBOXYLATE (2)	2
3-PIPERIDONE HYDROCHLORIDE (5) AND <i>N</i> -BENZYL-3-PIPERIDONE (6)	3
<i>N</i> -BENZOYL-3-PIPERIDONE (7)	4
<i>N</i> -TOSYL-3-PIPERIDONE (8)	4
<i>N</i> -TRIFLUOROACETYL-3-PIPERIDONE (9)	5
<i>N</i> -ACETYL-3-PIPERIDONE (10)	6
<i>N</i> -BOC-3-PIPERIDONE (11) AND <i>N</i> -BOC-3-PYRROLIDONE (12)	7
(<i>R</i>)- <i>N</i> -BOC-2-METHOXYCARBONYL-3-PYRROLIDONE (13)	7
METHYLISATINE (14)	8
GENERAL PROCEDURE : DAUCUS CAROTA MEDIATED-REDUCTION OF CYCLIC OXO-AMINES	8
(4 <i>S</i> , 3 <i>R</i>) <i>N</i> -BENZYL-4-HYDROXY-3-ETHOXYCARBONYLPIPERIDINE (3') AND (4 <i>S</i> , 3 <i>S</i>) <i>N</i> -BENZYL-4-HYDROXY-3-ETHOXYCARBONYLPIPERIDINE (3'').	9
(4 <i>S</i> , 3 <i>R</i>) <i>N</i> -BOC-4-HYDROXY-3-ETHOXYCARBONYLPIPERIDINE (4') AND (4 <i>S</i> , 3 <i>S</i>) <i>N</i> -BOC-4-HYDROXY-3-ETHOXYCARBONYLPIPERIDINE (4'')	10
(<i>S</i>)- <i>N</i> -BENZYL-3-HYDROXYPIPERIDINE (16)	12
(<i>S</i>)- <i>N</i> -BENZOYL-3-HYDROXYPIPERIDINE (17)	12
(<i>S</i>)- <i>N</i> -TOSYL-3-HYDROXYPIPERIDINE (18)	13
(<i>S</i>)- <i>N</i> -TRIFLUOROACETYL-3-HYDROXYPIPERIDINE (19)	14
<i>N</i> -ACETYL-(<i>S</i>)-3-HYDROXYPIPERIDINE (20)	15
(<i>S</i>)- <i>N</i> -BOC-3-HYDROXYPIPERIDINE (21)	16
(<i>S</i>)- <i>N</i> -BOC-3-HYDROXYPYRROLIDINE (22)	16
<i>N</i> -BOC- <i>CIS</i> -4-HYDROXY- <i>L</i> -PROLINE METHYL ESTER (23)	17
3- HYDROXY-1-METHYL-1,3-DIHYDRO-INDOL-2-ONE (24)	18
FORMAL SYNTHESIS OF CAPROMORELIN	19
(4 <i>R</i> , 3 <i>S</i>) <i>N</i> -BOC-3-BENZYL-3-ETHOXYCARBONYL-4-HYDROXYPIPERIDINE (25)	19
(4 <i>R</i> , 3 <i>S</i>) 3-BENZYL-3-ETHOXYCARBONYL-4-HYDROXYPIPERIDINE (25')	19
(<i>S</i>)- <i>N</i> -BOC-3-BENZYL-3-ETHOXYCARBONYL-4-PIPERIDONE (26)	21
(<i>S</i>)- <i>N</i> -BOC-3-BENZYL-3-ETHOXYCARBONYL-4-PIPERIDONE (26')	22

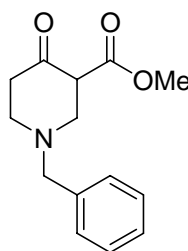
Information

TLC was performed on Merck 60F₂₅₄ silica gel plates and visualized with a UV lamp (254 nm), or by using a solution of KMnO₄/K₂CO₃/NaOH in water followed by heating. Column chromatography was performed with Merck Geduran Si 60 silica gel (40–63 μm). Infrared (IR) spectra were recorded on a Bruker TENSORTM 27 (IRFT), wave-numbers are indicated in cm⁻¹. ¹H NMR spectra were recorded on a Bruker AVANCE 400 at 400 MHz and data are reported as follows: chemical shift in ppm from tetramethylsilane as internal standard, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of non-equivalent resonances, integration). ¹³C NMR spectra were recorded on a Bruker AVANCE 400 at 100 MHz and data are reported as follows: chemical shift in ppm from tetramethylsilane with the solvent as internal standard (CDCl₃, δ 77.0 ppm or DMSO D₆, δ 40.4 ppm), multiplicity with respect to proton (deduced from DEPT experiments, s = quaternary C, d = CH, t = CH₂, q = CH₃). Mass spectra with electronic impact (MS-EI) were recorded from a Hewlett-Packard tandem 5890A GC (12 m capillary column) -5971 MS (70 eV). Enantiomeric excess were determined by supercritical fluid chromatography BERGER under 100 bars pressure with a UV detector (λ = 254 nm). Compounds **19**, **20**, **21**, **22** were benzylated (NaH 1.1 equiv., BnBr 1.2 equiv., CH₂Cl₂, rt) to be detected by the UV detector.

Preparation of substrates

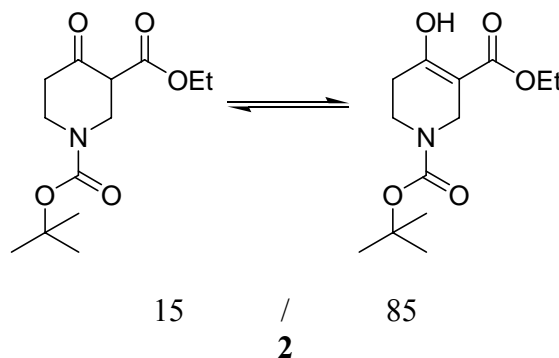
Methyl *N*-benzyl-4-oxopiperidine-3-carboxylate (**1**)

1 is commercially available (Aldrich).



1

Ethyl *N*-Boc-4-oxopiperidine-3-carboxylate (**2**)¹



¹ Knight, D.W.; Lewis, N.; Share, A.C.; Haigh, D. *Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972–1999)* **1998**, 3673–3684.

Ethyl 4-oxopiperidine-3-carboxylate hydrochloride (5.00 g, 24.07 mmol, 1 equiv.) and di-*tert*-butyl dicarbonate (5.78 g, 26.47 mmol, 1.1 equiv.) were dissolved in CH₂Cl₂. Et₃N (7.09 mL, 50.55 mmol, 2.1 equiv.) was then added dropwise under stirring. After 2 h, the solvent was evaporated *in vacuo* and the crude residue was purified by silica gel column chromatography, using EtOAc/hexane = 1:3 as eluent, to give a colourless oil crystallized in hexane to give a colourless solid (6.39 g, 23.6 mmol, 98%).

Formula : C₁₃H₂₁NO₅

mp 64–65 °C (hexane)

IR (neat) 2977, 1695, 1661, 1620, 1418, 1365, 1306, 1227, 1162, 1060 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) (enol, major tautomer) δ 12.05 (br s, 1H), 4.23 (q, *J* = 6.8 Hz, 2H), 4.06 (s, 2H), 3.56 (t, *J* = 5.8 Hz, 2H), 2.36 (t, *J* = 6.1 Hz, 2H), 1.48 (s, 9H), 1.31 (t, *J* = 6.6 Hz, 3H).

¹H NMR (400 MHz, CDCl₃) (ketone, minor tautomer) δ 4.12 (q, *J* = 7.8 Hz, 2H), 3.92–3.85 (m, 2H), 3.41 (t, *J* = 7.1 Hz, 2H), 2.63 (dt, *J* = 14.8, 5.8 Hz, 1H), 2.48 (m, 1H), 1.78 (m, 1H), 1.49 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H).

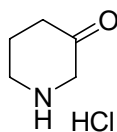
¹³C RMN (100 MHz, CDCl₃) (enol, major tautomer) δ 170.7 (s), 168.0 (s), 154.5 (s), 80.0 (s), 61.5 (t), 60.5 (t), 56.4 (d), 40.2 (t), 28.9 (t), 28.4 (q, 3C), 14.2 (q).

¹³C RMN (100 MHz, CDCl₃) (ketone, minor tautomer) δ 202.7 (s), 171.1 (s), 154.2 (s), 80.8 (s), 61.5 (t), 60.3 (t), 56.4 (d), 40.6 (t), 28.9 (t), 28.3 (q, 3C), 14.1 (q).

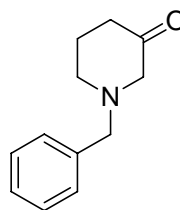
MS (EI) : *m/z* 214 (M⁺ - *t*-Bu[•], 5), 168 (8), 142 (6), 124 (9), 98 (32), 57 (100), 56 (22), 55 (29).

3-Piperidone hydrochloride (5) and *N*-benzyl-3-piperidone (6)

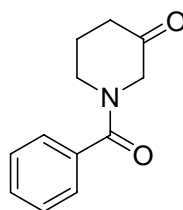
5 and 6 are commercially available (Aldrich).



5



6

***N*-Benzoyl-3-piperidone (7)²**

7

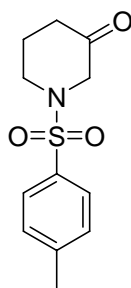
N-Benzoyl-3-hydroxypiperidine (820 mg, 4.0 mmol, 1 equiv.) was dissolved in CH₂Cl₂ (40 mL) and pyridinium chlorodichromate (PCC) (881 mg, 4.1 mmol, 1.03 equiv.) was added under stirring. The orange-red solution turned to a dark colour and was stirred at rt for 24 h. The solution was then filtrated on Celite under *vacuo* and the solid was washed with CH₂Cl₂ (3 x 50 mL). The filtrate was evaporated *in vacuo* and the crude product was purified by silica gel column chromatography, using EtOAc/hexane = 1:3 as eluent, to give a colourless oil (609 mg, 3 mmol, 75%).

Formula : C₁₂H₁₃NO₂

IR (neat) 2918, 2850, 1741, 1662, 1446, 1307, 1242, 1190, 1163 cm⁻¹.

¹H NMR (400 MHz, DMSO D₆, 144 °C) δ 7.45–7.34 (m, 5H), 3.79 (ddm, *J* = 12.7, 3.4 Hz, 1H), 3.60 (m, 1H), 3.19 (ddd, *J* = 12.9, 9.2, 3.6 Hz, 1H), 3.01 (dd, *J* = 12.8, 7.8 Hz, 1H), 1.90 (m, 1H), 1.75 (m, 1H), 1.55–1.37 (m, 2H).

MS (EI) : *m/z* 203 (M⁺, 22), 174 (21), 146 (9), 105 (100), 98 (13), 84 (11), 77 (41), 51 (9).

***N*-Tosyl-3-piperidone (8)³**

8

N-Tosyl-3-hydroxypiperidine (1.02 g, 4 mmol, 1 equiv.) was dissolved in CH₂Cl₂ (40 mL) and pyridinium chlorodichromate (PCC) (881 mg, 4.1 mmol, 1.03 equiv.) was added under stirring. The orange-red solution turned to a dark colour and was stirred at rt for 24 h. The

² (a) Hirsch, J.A. *J. Org. Chem.* 44, **1979**, 3225–3229. (b) Hirsch, J.A.; Jarmas, A.A. *J. Org. Chem.* **1978**, 4106–4110.

³ Brosius, A.D.; Overman, L.E.; Schwink, L. *J. Am. Chem. Soc.* **1999**, 700–709.

solution was then filtrated on Celite under *vacuo* and the solid was washed with CH₂Cl₂ (3 x 50 mL). The filtrate was evaporated *in vacuo* and the crude product was purified by silica gel column chromatography, using EtOAc/hexane = 1:3 as eluent, to give a colourless solid (704 mg, 2.78 mmol, 69%).

Formula: C₁₂H₁₅NO₃S

mp = 100 °C.

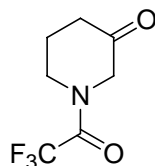
IR (neat) 2865, 2360, 1720, 1596, 1342, 1160, 944, 664 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.66 (dm, *J* = 8.3 Hz, 2H), 7.34 (dm, *J* = 8.6 Hz, 2H), 3.61 (s, 2H), 3.32–3.27 (m, 2H), 2.53 (s, 3H), 2.36 (t, *J* = 7.0 Hz, 2H), 2.05–1.97 (m, 2H).

¹³C NMR (100 MHz, CDCl₃) δ 202.6 (s), 144.2 (s), 132.8 (s), 129.9 (d, 2C), 127.7 (d, 2C), 55.7 (t), 44.5 (t), 37.9 (t), 22.7 (t), 21.5 (q).

MS (EI) : *m/z* 253 (M⁺, 2), 224 (4), 155 (7), 98 (70), 91 (51), 70 (100), 65 (46).

***N*-Trifluoroacetyl-3-piperidone (9)⁴**



9

N-Trifluoroacetyl-3-hydroxypiperidine (788 mg, 4 mmol, 1 equiv.) was dissolved in CH₂Cl₂ (40 mL) and pyridinium chlorodichromate (PCC) (881 mg, 4.1 mmol, 1.03 equiv.) was added under stirring. The orange-red solution turned to a dark colour and was stirred at rt for 24 h. The solution was then filtrated on Celite under *vacuo* and the solid was washed with CH₂Cl₂ (3 x 50 mL). The filtrate was evaporated *in vacuo* and the crude product was purified by silica gel column chromatography, using EtOAc/hexane = 1:3 as eluent, to give a slightly yellow oil (554 mg, 2.84 mmol, 71%).

Formula : C₇H₈F₃NO₂

IR (neat) 2930, 1730, 1690, 1200 cm⁻¹.

Rotamer ratio: 60/40.

¹H NMR (400 MHz, CDCl₃) (major rotamer) δ 4.22 (s, 2H), 3.85–3.78 (m, 2H), 2.61–2.55 (m, 2H), 2.15–2.06 (m, 2H).

⁴ Garst, M.E.; Bonfiglio, J.N.; Grudoski, D.A.; Marks, J. *J. Org. Chem.* **1980**, 2307–2315.

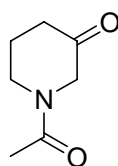
¹H NMR (400 MHz, CDCl₃) (minor rotamer) δ 4.15 (s, 2H), 3.85–3.78 (m, 2H), 2.61–2.55 (m, 2H), 2.15–2.06 (m, 2H).

¹³C NMR (100 MHz, CDCl₃) (major rotamer) δ 202.2 (s), 155.9 (sq, $J = 36.4$ Hz), 116.3 (sq, $J = 285.8$ Hz), 53.7 (t), 44.0 (tq, $J = 3.5$ Hz), 38.1 (t), 22.8 (t).

¹³C NMR (100 MHz, CDCl₃) (minor rotamer) δ 201.9 (s), 156.0 (sq, $J = 36.6$ Hz), 116.1 (sq, $J = 285.9$ Hz), 54.8 (tq, $J = 3.4$ Hz), 42.5 (t), 37.7 (t), 21.2 (t).

MS (EI) : m/z 195 (M⁺, 56), 167 (100), 139 (31), 126 (41), 98 (47), 69 (38), 55 (36).

N-Acetyl-3-piperidone (10)^{1,5}



10

N-Acetyl-3-hydroxypiperidine (572 mg, 4 mmol, 1 equiv.) was dissolved in CH₂Cl₂ (40 mL) and pyridinium chlorodichromate (PCC) (881 mg, 4.1 mmol, 1.03 equiv.) was added under stirring. The orange-red solution turned to a dark colour and was stirred at rt for 24 h. The solution was then filtrate on Celite under *vacuo* and the solid was washed with CH₂Cl₂ (3 x 50 mL). The filtrate was evaporated *in vacuo* and the crude product was purified by silica gel column chromatography, using EtOAc/hexane = 1:3 as eluent, to give a colourless oil (349 mg, 2.48 mmol, 62%).

Formula : C₇H₁₁NO₂

IR (neat) 3025, 1732, 1626, 938, 890 cm⁻¹.

¹H NMR (400 MHz, DMSO D₆, 144 °C) δ 4.02 (s, 2H), 3.62 (dd, $J = 7.05, 7.05$ Hz, 2H), 2.43 (dd, $J = 9.7, 9.7$, 2H), 1.98 (s, 3H), 1.89–1.80 (m, 2H).

¹³C NMR (100 MHz, CDCl₃) (First rotamer) δ 204.2 (s), 169.4 (s), 53.9 (t), 46.8 (t), 32.1 (t), 24.4 (t), 15.3 (q).

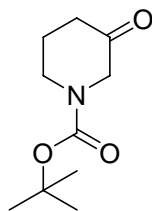
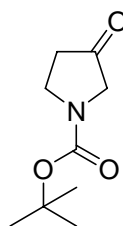
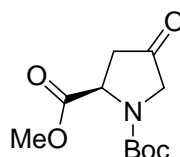
¹³C NMR (100 MHz, CDCl₃) (Second rotamer) δ 204.6 (s), 169.8 (s), 54.8 (t), 45.9 (t), 32.7 (t), 24.3 (t), 15.2 (q).

MS (EI) : m/z 141 (M⁺, 15), 112 (4), 99 (30), 98 (57), 85 (26), 70 (100), 56 (14).

⁵ Masamune, T.; Hayashi, H.; Fukuoka, T.S. *J. Org. Chem.* **1972**, 2343–2345.

***N*-Boc-3-piperidone (11) and *N*-Boc-3-pyrrolidone (12)**

11 and 12 are commercially available (Aldrich).

**11****12*****(R)*-*N*-Boc-2-Methoxycarbonyl-3-pyrrolidone (13)⁶****13**

N-Boc-*trans*-4-Hydroxy-L-proline methyl ester (980 mg, 4 mmol, 1 equiv.) was dissolved in CH₂Cl₂ (40 mL) and pyridinium chlorodichromate (PCC) (881 mg, 4.1 mmol, 1.03 equiv.) was added under stirring. The orange-red solution obtained turned to a dark colour and was stirred at rt for 24 h. The solution was then filtrated on Celite under *vacuo* and the solid was washed with CH₂Cl₂ (3 x 50 mL). The filtrate was evaporated *in vacuo* and the crude product was purified by silica gel column chromatography, using EtOAc/hexane = 1:3 as eluent, to give a colourless solid crystallized in EtOAc (700 mg, 2.88 mmol, 72%).

Formula : C₁₁H₁₇NO₅

[α]_D = + 23 (*c* 1, MeOH).

IR (neat) 2978, 1765, 1703, 1394, 1367, 1153 cm⁻¹.

Rotamer ratio: 80/20.

¹H NMR (400 MHz, CDCl₃) (major rotamer) δ 4.78 (dd, *J* = 9.9, 3.1 Hz, 1H), 3.90 (d, *J* = 7.8 Hz, 2H), 3.76 (s, 3H), 2.90 (m, 1H), 1.70 (m, 1H), 1.46 (s, 9H).

¹H NMR (400 MHz, CDCl₃) (minor rotamer) δ 4.36 (dm, *J* = 9.9 Hz, 1H), 3.72 (s, 3H), 3.55–3.41 (m, 2H), 2.58 (dd, *J* = 121.5, 2.1 Hz, 1H), 2.35 (m, 1H), 1.41 (s, 9H).

¹³C NMR (100 MHz, CDCl₃) (major rotamer) δ 207.5 (s), 172.3 (s), 154.9 (s), 81.4 (s), 57.9 (t), 55.5 (d), 52.8 (q), 41.2 (t), 28.3 (q, 3C).

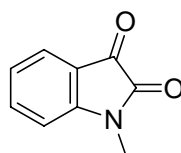
⁶ Cheng, M.; De, B.; Almstead, N.G.; Pikul, S.; Dowty, M.E.; Dietsch, C.R.; Dunaway, C.M.; Gu, F.; Hsieh, L.C.; Janusz, M.J.; Taiwo, Y.O. *J. Med. Chem.* **1999**, 5426–5436.

^{13}C NMR (100 MHz, CDCl_3) (minor rotamer) δ 208.6 (s), 172.3 (s), 153.6 (s), 80.1 (s), 57.7 (t), 56.3 (d), 52.5 (q), 40.8 (t), 28.4 (q, 3C).

MS (EI) : m/z 228 (M^+ , 13), 186(23), 142 (80), 57 (100).

Methylisatine (14)

14 is commercially available (Aldrich).



14

General procedure: *Daucus carota* mediated-reduction of cyclic oxo-amines

To a suspension of healthy freshly peeled carrot roots (140 g) in water (600 mL), kept under vigorous stirring (Figure 1), a solution of substrate (2 mmol) in methanol or ethanol (10 mL) was dropwise added in the vortex and then stirred at rt for 48 h. The mixture was filtered on cotton. For Compounds **3'**/**3''** and **16** a saturated solution of K_2CO_3 in water was added until pH = 10 was obtained. The resulting mixture was extracted with EtOAc (3 x 100 mL) and the organic extracts were combined, dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude residue was purified on silica gel column chromatography to give the corresponding optically active alcohol.

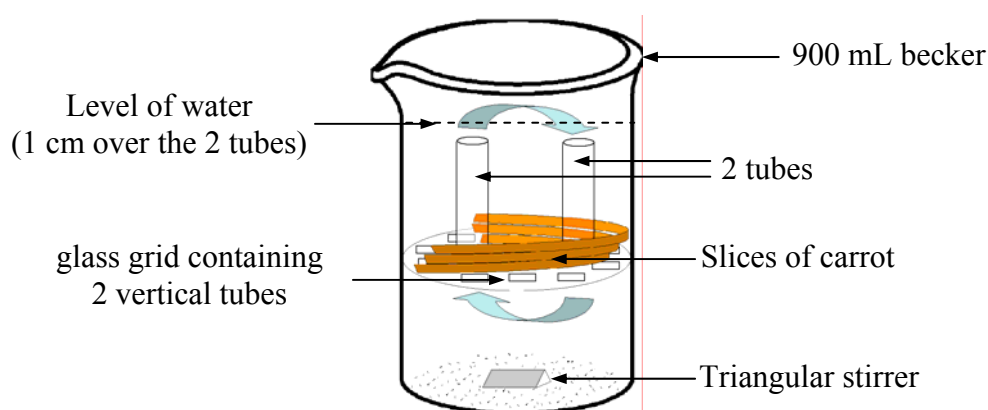
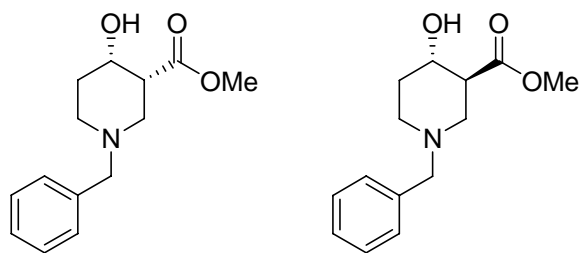


Figure 1

The grid separates the stirring bar and the carrot slices to avoid mashing the carrots during the reaction. The stirring could be increased from 120 rpm to 1100 rpm. However, the thickness of carrot slices avoids the surface to be stirred and the organic substrate (lower density than water) accumulates on surface. Two tubes have been added to generate a vortex and keep the substrate in suspension in water. This method allows increasing the stirring and then increasing the availability of the substrate to the carrots. By using this device, we have improved the yield by 30% from standard stirring and reduced the reaction time from 5 to 2 days. Only one batch of carrot is needed.

(4*S*,3*R*) *N*-Benzyl-4-hydroxy-3-ethoxycarbonylpiperidine (3') and (4*S*,3*S*) *N*-benzyl-4-hydroxy-3-ethoxycarbonylpiperidine (3'').⁷



3'

3''

Both diastereomers **3'** and **3''** in a ratio of 30/70 in favor of **3''** were separated by silica gel column chromatography, using EtOAc/CH₂Cl₂ = 1:3 as eluent, (398 mg, 1.6 mmol, 80%).

Formula : C₁₄H₁₉NO₃

(4*S*,3*R*) *N*-Benzyl-4-hydroxy-3-ethoxycarbonylpiperidine 3'

R_f = 0.25 (EtOAc/CH₂Cl₂, 1:3)

ee = 94%. Determined by supercritical fluid chromatography on OD-H column (MeOH 5%, flow rate = 5 mL/min, retention time = 10 min).

[α]_D = +10.4 (*c* 0.86, CH₂Cl₂)

IR (neat) 3356, 2985, 1726, 1444, 1360, 1300, 1197, 1157, 1049, 736 cm⁻¹.

¹H NMR (400MHz, CDCl₃) δ 7.34–7.22 (m, 5H), 4.10 (m, 1H), 3.69 (s, 3H), 3.57 (d, *J* = 13.2 Hz, 1H), 3.49 (d, *J* = 13.2 Hz, 1H), 3.10 (br s, 1H), 2.78 (m, 1H), 2.75–2.59 (m, 2H), 2.59–2.40 (m, 2H), 1.90 (m, 1H), 1.80 (m, 1H).

¹³C NMR (100 MHz, CDCl₃) δ 174.3 (s), 138.4 (s), 129.0 (d, 2C), 128.2 (d, 2C), 127.1 (d), 65.7 (d), 62.8 (t), 51.8 (q), 50.7 (t), 48.7 (t), 46.4 (d), 31.8 (t).

MS (EI) : *m/z* 249 (M⁺, 14), 218 (2), 190 (5), 158 (12), 140 (15), 132 (9), 120 (6), 91(100), 65 (18), 55 (10).

⁷ Ali, F.E.; Bondinell, W.E.; Dandridge, P.A.; Frazee, J.S.; Garvey, E. et al. *J. Med. Chem.* **1985**, 653–660.

(4*S*,3*S*) *N*-benzyl-4-hydroxy-3-ethoxycarbonylpiperidine 3''

$R_f = 0.20$ (EtOAc/CH₂Cl₂, 1:3)

ee = 94%. Determined by supercritical fluid chromatography on OD-H column (MeOH 5%, flow rate = 5 mL/min, retention time = 8.5 min).

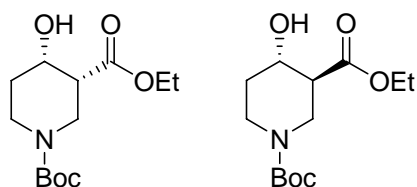
$[\alpha]_D = -10.6$ (*c* 1.05, CH₂Cl₂).

IR (neat) 3355, 2805, 1728, 1435, 1361, 1307, 1196, 1159, 1048, 736, 698 cm⁻¹.

¹H NMR (400MHz, CDCl₃) δ 7.30–7.20 (m, 5H), 3.79 (ddd, *J* = 10.6, 10.6, 4.8 Hz, 1H), 3.65 (s, 3H), 3.55 (d, *J* = 14.2 Hz, 1H), 3.55 (d, *J* = 14.2 Hz, 1H), 3.11 (ddd, *J* = 11.5, 4.1, 2.2 Hz, 1H), 3.00 (br s, 1H), 2.87 (dm, *J* = 11.6 Hz, 1H), 2.61 (ddd, *J* = 11.2, 9.8, 4.1 Hz, 1H), 2.07 (dd, *J* = 11.4, 11.4 Hz, 1H), 2.05 (ddd, *J* = 12.0, 12.0, 2.7 Hz, 1H), 1.95 (dddd, *J* = 12.8, 4.8, 2.9, 2.9 Hz, 1H), 1.63 (dddd, *J* = 12.3, 12.3, 11.1, 4.2 Hz, 1H)

¹³C NMR (100 MHz, CDCl₃) δ 174.0 (s), 138.1 (s), 128.9 (d, 2C), 128.3 (d, 2C), 127.2 (d), 69.8 (d), 62.3 (t), 53.4 (t), 51.9 (q), 51.5 (t), 49.8 (d), 32.8 (t).

MS (EI) : *m/z* 249 (M⁺, 2), 218 (1), 190 (4), 158 (11), 140 (13), 132 (8), 120 (7), 91(100), 65 (17), 55 (10).

(4*S*,3*R*) *N*-Boc-4-Hydroxy-3-ethoxycarbonylpiperidine (4') and (4*S*,3*S*) *N*-Boc-4-hydroxy-3-ethoxycarbonylpiperidine (4'')⁸

4'

4''

Both diastereomers 4' and 4'' in a ratio of 60/40 in favor of 4' were separated by silica gel column chromatography, using EtOAc/hexane = 1:3 as eluent, (496 mg, 1.81 mmol, 91%).

Formula : C₁₃H₂₃NO₅

⁸ Knight, D.W.; Lewis, N.; Share, A.C.; Haigh, D. *Tetrahedron Asymmetry* **1993**, 625–628.

(4*S*,3*R*) *N*-Boc-4-Hydroxy-3-ethoxycarbonylpiperidine 4'

$R_f = 0.40$ (EtOAc/hexane, 1:3)

ee = 91%. Determined by supercritical fluid chromatography on OD-H column (MeOH 3%, flow rate = 5 mL/min, retention time = 22 min).

$[\alpha]_D = +56.0$ (c 1, CH₂Cl₂).

IR (neat) 3378, 2921, 2806, 1729, 1453, 1435, 1361, 1307, 1197, 1160, 1049, 739, 699 cm⁻¹.

¹H NMR (400 MHz, CDCl₃, 51 °C) δ 4.27 (m, 1H), 4.19 (q, $J = 7.1$ Hz, 2H), 3.98 (m, 1H), 3.70 (ddd, $J = 13.4, 4.0, 4.0$ Hz, 1H), 3.43 (t, $J = 11.4$ Hz, 1H), 3.29 (ddd, $J = 13.8, 11.3, 3.2$ Hz, 1H), 2.95 (br s, 1H), 2.62 (ddd, $J = 10.5, 4.3, 2.7$ Hz, 1H), 1.83 (ddd, $J = 13.7, 8.4, 4.8$ Hz, 1H), 1.65 (m, 1H), 1.47 (s, 9H), 1.28 (t, $J = 7.2$ Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 172.6 (s), 154.5 (s), 80.1 (s), 69.7 (d), 61.1 (t), 49.4 (d), 43.7 (t), 42.5 (t), 32.6 (t), 28.4 (q, 3C), 14.1 (q).

MS (EI) : m/z 273 (M⁺, 2), 216 (32), 200 (13), 172 (23), 154 (37), 126 (50), 100 (24), 82 (79), 57 (100), 41 (21).

(4*S*,3*S*) *N*-Boc-4-hydroxy-3-ethoxycarbonylpiperidine 4''

$R_f = 0.35$ (EtOAc/hexane, 1:3).

ee = 91%. Determined by supercritical fluid chromatography on OD-H column (MeOH 3%, flow rate = 5mL/min, retention time = 19 min).

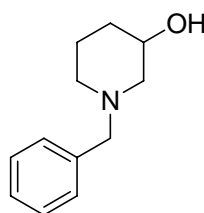
$[\alpha]_D = -24.3$ (c 1, CH₂Cl₂).

IR (neat) 3378, 2921, 2806, 1729, 1453, 1435, 1361, 1307, 1197, 1160, 1049, 739, 699 cm⁻¹.

¹H NMR (400 MHz, CDCl₃, 51 °C) δ 4.30 (m, 1H), 4.21 (q, $J = 7.0$ Hz, 2H), 4.10 (m, 1H), 3.92 (ddd, $J = 10.1, 10.1, 4.6$ Hz, 1H), 2.77 (ddd, $J = 13.1, 13.1, 2.4$ Hz, 2H), 2.40 (ddd, $J = 11.0, 9.5, 4.2$ Hz, 1H), 1.97 (dddd, $J = 12.8, 4.2, 3.0, 3.0$ Hz, 1H), 1.47 (s, 9H), 1.29 (t, $J = 7.0$ Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 174.3 (s), 154.7 (s), 79.9 (s), 68.5 (d), 61.1 (t), 53.4 (t), 45.9 (d), 41.5 (t), 39.0 (t), 28.4 (q, 3C), 14.1 (q).

MS (EI) : m/z 273 (M⁺, 4), 216 (67), 200 (32), 172 (66), 154 (37), 126 (72), 100 (65), 82 (82), 57 (100), 41 (51).

(S)-N-Benzyl-3-hydroxypiperidine (16)⁹**16**

A large emulsion was obtained and only low amount of **16** could be recovered. The crude product was purified by silica gel column chromatography, using EtOAc/CH₂Cl₂ = 1:3 as eluent, to give a colourless oil (42 mg, 0.22 mmol, 11%).

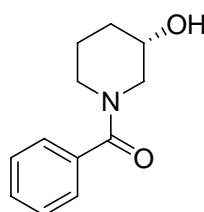
Formula : C₁₂H₁₇NO

IR (neat) 3253, 2933, 2793, 1452, 1153, 1100, 1058, 1025, 972, 735, 697 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.34–7.22 (m, 5H), 3.80 (m, 1H), 3.50 (s, 2H), 2.55–2.40 (m, 4H), 2.25 (t, *J* = 8.2 Hz, 1H), 1.90 (m, 1H), 1.85–1.45 (m, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 138.0 (s), 129.0 (d, 2C), 128.3 (d, 2C), 127.1 (d), 66.2 (d), 63.0 (t), 60.2 (t), 53.5 (t), 31.7 (t), 21.5 (t).

MS (EI) : *m/z* 191 (M⁺, 7), 146 (4), 134 (13), 114 (12), 91 (100), 71 (13), 65 (21).

(S)-N-Benzoyl-3-hydroxypiperidine (17)¹⁰**17**

17 was purified by silica gel column chromatography, using EtOAc/ CH₂Cl₂ = 1:3 as eluent, to give a colourless solid (270 mg, 1.13 mmol, 66%).

Formula : C₁₂H₁₅NO₂

mp = 88 °C

⁹ Iwakubo, M.; Takami, A.; Okada, Y.; Kawata, T.; Tagami, Y.; Ohashi, H.; Sato, M.; Sugiyama, T.; Fukushima, K.; Iijima, H.; *Bio. Med. Chem.* **2007**, 350–364.

¹⁰ Tomori, H.; Shibatani, K.; Ogura, K. *Bull. Chem. Soc. Jap.* **1996**, 207–216.

ee = 88%. Determined by supercritical fluid chromatography on OD-H column (MeOH 3%, flow rate = 7 mL/min, retention time = 8.5 min).

$[\alpha]_D = +124.3$ (c 0.8, MeOH).

IR (neat) 3373, 2930, 2860, 1611, 1441, 1277, 1075, 970, 701 cm^{-1} .

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ could not be determined due to rotamers.

$^{13}\text{C NMR}$ (100 MHz, CDCl_3) (First rotamer) δ 171.3 (s), 136.0 (s), 129.7 (d), 128.5 (d, 2C), 127.0 (d, 2C), 66.0 (d), 53.4 (t), 49.2 (t), 32.8 (t), 23.0 (t).

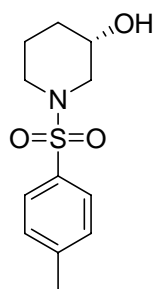
$^{13}\text{C NMR}$ (100 MHz, CDCl_3) (Second rotamer) δ 171.3 (s), 136.0 (s), 129.7 (d), 128.5 (d, 2C), 127.0 (d, 2C), 66.0 (d), 53.4 (t), 48.2 (t), 32.2 (t), 22.0 (t).

MS (EI) : m/z 205 (M^+ , 54), 187 (18), 148 (12), 105 (100), 100 (16), 77 (44).

17 was reduced to 16 in order to confirm the structure.

In a dry 25 mL flask, 17 (60mg, 0.3 mmol) was dissolved in THF (5 mL). LiAlH_4 (0.33 mmol, 12.5 mg, 1.1 equiv.) was added under stirring at 0 °C. The mixture was then heated at reflux for 2h and then cooled down at 0 °C. The reaction was quenched by adding water (12.5 μL , 2.1 equiv), a solution of NaOH 15% in water (12.5 μL , 2.1 equiv.) and water (31.3 μL , 5.3 equiv.). The mixture was kept under stirring for 30mn and then filtrated. The filtrate was evaporated and the crude product was purified by silica gel column chromatography, using EtOAc / CH_2Cl_2 = 1:3 as eluent, to give a colourless oil (45 mg, 0.24 mmol, 80%). The product was determined to be **16** and then confirmed the structure of **17**.

(S)-N-Tosyl-3-hydroxypiperidine (18)¹¹



18

18 was purified by silica gel column chromatography, using EtOAc/hexane = 1:3 as eluent, to give a colourless solid (397 mg, 1.56 mmol, 78%).

Formula : $\text{C}_{12}\text{H}_{17}\text{NO}_3\text{S}$

mp = 102 °C

¹¹ Brosius, A.D.; Overman, L.E.; Schwink, L. *J. Am. Chem. Soc.* **1999**, 700–709.

ee = 92%. Determined by supercritical fluid chromatography on OD-H column (MeOH 2%, flow rate = 4 mL/min, retention time = 11 min).

$[\alpha]_{\text{D}} = +20.2$ (*c* 1.1, CH₂Cl₂).

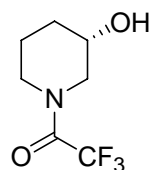
IR (neat) 3451, 2924, 2848, 1337, 1162, 1091, 941, 750, 657 cm⁻¹.

¹H NMR (400MHz, CDCl₃) δ 7.64 (dm, *J* = 8.6 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 3.86 (dddd, *J* = 7.6, 7.6, 3.9, 3.9 Hz, 1H), 3.32 (dd, *J* = 11.3, 3.2 Hz, 1H), 3.11 (ddd, *J* = 10.8, 6.0, 3.9 Hz, 1H), 2.77 (ddd, *J* = 11.6, 8.6, 3.2 Hz, 1H), 2.69 (dd, *J* = 11.2, 7.4 Hz, 1H), 2.43 (s, 3H), 2.35–2.10 (br s, 1H), 1.90–1.80 (m, 1H), 1.80–1.70 (m, 1H), 1.67–1.55 (m, 1H), 1.44–1.33 (m, 1H).

¹³C NMR (100 MHz, CDCl₃) δ 143.7 (s), 133.1 (s), 129.7 (d, 2C), 127.6 (d, 2C), 65.7 (d), 52.6 (t), 46.2 (t), 31.6 (t), 21.8 (t), 21.5 (q).

MS (EI) : *m/z* 255 (M⁺, 1), 198 (1), 155 (5), 100 (100), 91 (46), 71 (54), 65 (32), 55 (14).

(S)-N-Trifluoroacetyl-3-hydroxypiperidine (19)¹²



19

19 was purified by silica gel column chromatography, using EtOAc/hexane = 1:3 as eluent, to give a colourless solid (295 mg, 1.5 mmol, 75%).

Formula : C₇H₁₀F₃NO₂

ee = 75%. Determined by supercritical fluid chromatography on OD-H column (MeOH 4%, flow rate = 5 mL/min, retention time = 4.5 min).

$[\alpha]_{\text{D}} = + 4.70$ (*c* 1, CH₂Cl₂).

IR (neat) 3393, 2932, 2359, 1683, 1449, 1182, 1141 cm⁻¹.

¹H NMR (400 MHz, DMSO D₆, 120 °C) δ 4.42 (br s, 1H), 3.80 (m, 1H), 3.70–3.57 (m, 2H), 3.35 (m, 1H), 3.20 (dd, *J* = 12.84, 7.72 Hz, 1H), 1.96–1.77 (m, 2H), 1.60–1.41 (m, 2H).

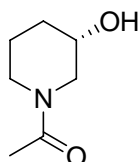
¹³C NMR (100 MHz, CDCl₃) (major rotamer) δ 156.5 (sq, *J* = 36 Hz), 116.5 (sq, *J* = 286 Hz), 65.6 (d), 51.9 (t), 43.8 (t), 32.9 (t), 22.8 (t).

¹² Garst, M.E.; Bonfiglio, J.N.; Grudoski, D.A.; Marks, J. *J. Org. Chem.* **1980**, 2307–2315.

^{13}C NMR (100 MHz, CDCl_3) (minor rotamer) δ 156.5 (sq, $J = 36$ Hz), 116.5 (sq, $J = 286$ Hz), 66.1 (d), 51.9 (t), 46.2 (t), 32.5 (t), 21.7 (t).

MS (EI) : m/z 195 (M^+ , 15), 179 (5), 154 (6), 140 (32), 128 (19), 126 (19), 100 (54), 72 (42), 69 (100), 56 (38).

N-acetyl-(*S*)-3-hydroxypiperidine (**20**)¹³



20

20 was purified by silica gel chromatography, using EtOAc/ $\text{CH}_2\text{Cl}_2 = 1:3$ as eluent, to give a colourless oil (217 mg, 1.51 mmol, 76%).

Formula : $\text{C}_7\text{H}_{13}\text{NO}_2$

ee = 89%. Determined by supercritical fluid chromatography on OD-H column (MeOH 3%, flow rate = 5 mL/min, retention time = 5 min).

$[\alpha]_{\text{D}}$ = + 20.4 (c 1, CH_2Cl_2).

IR (neat) 3381, 2923, 2859, 1620, 1444, 1257, 1075 cm^{-1} .

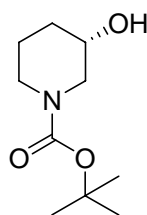
^1H NMR (400 MHz, DMSO D_6 , 144 $^\circ\text{C}$) δ 3.75 (m, 1H), 3.60–3.49 (m, 3H), 3.15 (m, 1H), 1.98 (s, 3H), 1.85 (m, 1H), 1.70 (m, 1H), 1.49–1.30 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3) (First rotamer) δ 169.8 (s), 65.7 (d), 48.6 (t), 46.8 (t), 32.10 (t), 23.0 (t), 21.4 (q).

^{13}C NMR (100 MHz, CDCl_3) (second rotamer) δ 169.8 (s), 66.3 (d), 53.2 (t), 45.9 (t), 32.7 (t), 21.9 (t), 21.5 (q).

MS (EI) : m/z 143 (M^+ , 42), 125 (26), 100 (79), 86 (44), 83 (71), 71 (82), 57 (100).

¹³ McManus, J.M. et al. *J. Med. Chem.* **1965**, 766–776.

(S)-N-Boc-3-hydroxypiperidine (21)¹⁴**21**

21 was purified by silica gel column chromatography, using EtOAc/ CH₂Cl₂ = 1:3 as eluent, to give a colourless solid (293 mg, 1.45 mmol, 73%).

Formula : C₁₀H₁₉NO₃

mp = 56 °C.

ee = 95%. Determined by supercritical fluid chromatography on OD-H column (MeOH 4%, flow rate = 5 mL/min, retention time = 6 min).

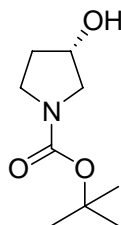
[α]_D = + 23.8 (*c* 0.9, EtOH).

IR (neat) 3401, 2925, 2859, 1663, 1420, 1365, 1265, 1234, 1170, 1145, 734 cm⁻¹.

¹H NMR (400 MHz, CDCl₃, 51 °C) δ 3.77–3.67 (m, 2H), 3.50 (m, 1H), 3.12 (ddd, *J* = 13.0, 8.7, 3.4 Hz, 2H), 3.06 (q, *J* = 7.7 Hz, 1H), 2.10 (br s, 1H), 1.90 (m, 1H), 1.75 (m, 1H), 1.50 (m, 1H), 1.46 (s, 9H).

¹³C NMR (100 MHz, CDCl₃) δ 155.2 (s), 79.7 (s), 66.2 (d), 50.8 (t), 44.2 (t), 32.6 (t), 28.4 (q, 3C), 22.3 (t).

MS (EI) : *m/z* 201 (M⁺, 14), 145 (33), 128 (39), 101 (22), 88 (20), 57 (100).

(S)-N-Boc-3-hydroxypyrrolidine (22)¹⁵**22**

¹⁴ Reddy, M.S.; Narender, M.; Rao, K.R. *Tetrahedron* **2007**, 331–336.

¹⁵ Kocalka, P.; Pohl, R.; Rejman, D.; Rosenberg, I. *Tetrahedron* **2006**, 5763–5774.

22 was purified by silica gel column chromatography, using EtOAc/ CH₂Cl₂ = 1:3 as eluent, to give a colourless oil (284 mg, 1.52 mmol, 76%).

Formula : C₉H₁₇NO₃

ee = 96%. Determined by supercritical fluid chromatography on OD-H column (MeOH 4%, flow rate = 5 mL/min, retention time = 6 min).

[α]_D = + 23.2 (*c* 0.9, CHCl₃).

IR (neat) 3392, 2975, 1663, 1403, 1162, 1119, 1101, 878 cm⁻¹.

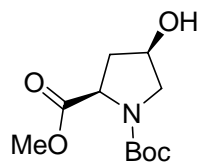
¹H NMR (400 MHz, CDCl₃, 51 °C) δ 4.40 (m, 1H), 3.54–3.38 (m, 3H), 3.30 (m, 1H), 2.60 (br s, 1H), 2.04–1.83 (m, 2H), 1.46 (s, 9H).

¹³C NMR (100 MHz, CDCl₃) (First rotamer) δ 154.9 (s), 79.4 (s), 69.9 (d), 54.0 (t), 44.0 (t), 33.9 (t), 28.5 (q, 3C).

¹³C NMR (100 MHz, CDCl₃) (second rotamer) δ 154.9 (s), 79.4 (s), 70.7 (d), 54.2 (t), 43.5 (t), 33.4 (t), 28.5 (q, 3C).

MS (EI) : *m/z* 187 (M⁺, 8), 132 (32), 114 (47), 103 (5), 87 (17), 57 (100).

***N*-Boc-*cis*-4-hydroxy-*L*-proline methyl ester (**23**)**¹⁶



23

23 was purified by silica gel column chromatography, using EtOAc/ CH₂Cl₂ = 1:3 as eluent, to give a colourless solid (328 mg, 1.34 mmol, 67%).

Formula : C₁₁H₁₉NO₅

mp = 76 °C.

de = 98%.

[α]_D = + 26.2 (*c* 0.6, MeOH).

IR (neat) 3431, 2977, 1751, 1675, 1477, 1395, 1365, 1157, 1085, 732 cm⁻¹;

¹⁶ Merino, P.; Anoro, S.; Franco, S.; Merchan, F.L.; Tejero, T.; Tunon, V. *J. Org. Chem.* **2000**, 1590–1596.

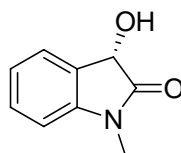
¹H NMR (400 MHz, CDCl₃, 51 °C) δ 4.41–4.26 (m, 2H), 3.78 (s, 3H), 3.72–3.50 (m, 2H), 3.10 (m, 1H), 2.33 (br s, 1H), 2.08 (br d, J = 14.4 Hz, 1H), 1.45 (s, 1H).

¹³C NMR (100 MHz, CDCl₃) (First rotamer) δ 175.5 (s), 153.7 (s), 80.5 (s), 70.3 (d), 57.9 (d), 55.5 (t), 52.5 (q), 38.6 (t), 28.3 (q, 3C).

¹³C NMR (100 MHz, CDCl₃) (second rotamer) δ 175.8 (s), 153.5 (s), 80.5 (s), 71.4 (d), 57.7 (d), 56.0 (t), 52.8 (q), 37.7 (t), 28.4 (q, 3C).

MS (EI) : m/z 227 (M⁺-H₂O, 1), 186 (5), 144 (13), 130 (32), 86 (57), 68 (28), 57 (100).

3- Hydroxy-1-methyl-1,3-dihydro-indol-2-one (**24**)¹⁷



24

24 was purified by flash silica gel column chromatography, using EtOAc/hexane = 1:3 as eluent, to give a colourless solid (270 mg, 1.65mmol, 83%). This compound is air sensitive and can be degraded on silica gel.

Formula : C₉H₉NO₂

mp = 133 °C.

ee = 82%. Determined by supercritical fluid chromatography on OD-H column (MeOH 2%, flow rate = 4 mL/min, retention time = 10 min).

[α]_D = + 25.33 (c 0.6, MeOH).

IR (neat) 3343, 2890, 2360, 2341, 1715, 1615, 1470, 1351, 1107, 754 cm⁻¹.

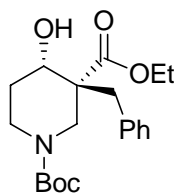
¹H NMR (400 MHz, CDCl₃) δ 7.45 (dm, J = 7.3 Hz, 1H), 7.32 (dddd, J = 7.8, 7.8, 1.2, 0.8 Hz, 1H), 7.11 (ddd, J = 7.6, 7.6, 0.9 Hz, 1H), 6.83 (d, J = 7.8 Hz, 1H), 5.06 (d, J = 2.8 Hz, 1H), 3.19 (s, 3H), 3.08 (br s, 1H).

¹³C NMR (100 MHz, CDCl₃) δ 176.6 (s), 144.0 (s), 129.9 (d), 126.7 (s), 125.1(d), 123.2 (d), 108.5 (d), 69.9 (d), 26.3 (q).

¹⁷ Carpentier, J.-F.; Mortreux, A. *Tetrahedron Asymmetry* **1997**, 1083–1099.

Formal synthesis of Capromorelin

(4*R*,3*S*) *N*-Boc-3-Benzyl-3-ethoxycarbonyl-4-hydroxypiperidine (**25**)



25

The mixture of *N*-Boc-(*S*)-4-hydroxy-3-ethoxycarbonylpiperidine **4'** and **4''** (2 mmol, 542 mg, 1 equiv.) was dissolved in dry THF (20 mL) under argon and then stirred at -78 °C. LDA 1 M (5 mL) was dropwise added and the mixture was warmed to 0 °C for 20 min. The mixture was then cooled to -78 °C and benzylbromide (2.6 mmol, 310 μ L, 1.3 equiv.) was added. The solution was stirred at -78 °C to 0 °C for 2 h. The mixture was quenched with water at 0 °C and then evaporated under *vacuo*. The crude product was then purified by silica gel chromatography, using EtOAc/hexane = 1:3 as eluent, to give this diastereomer as a colourless oil (435 mg, 60%).

Formula : C₂₀H₂₉NO₅

[α]_D = + 23.5 (*c* 1.1, CH₂Cl₂).

IR (neat) 3439, 2919, 2850, 2359, 2341, 1692, 1425, 1366, 1279, 1244, 1167, 1136, 971, 702 cm⁻¹.

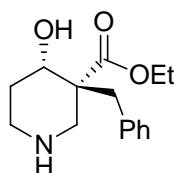
¹H NMR (400 MHz, CDCl₃) δ 7.30–7.16 (m, 5H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.05 (m, 1H), 3.81–3.57 (m, 2H), 3.35–3.00 (m, 2H), 3.02 (d, *J* = 13.4 Hz, 1H), 2.95 (d, *J* = 13.3 Hz, 1H), 1.90 (m, 1H), 1.68 (m, 1H), 1.46 (s, 9H), 1.25 (m, 1H), 1.13 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 175 (s), 154 (s), 135.7 (s), 130.3 (d, 2C), 128.2 (d, 2C), 126.9 (d), 79.8 (s), 71.0 (d), 60.9 (t), 52.5 (s), 46.2 (t), 39.2 (t), 29.7 (t), 28.8 (q, 3C), 13.9 (q).

HRMS: calcd for C₂₀H₂₉NO₅Na (MNa⁺) 386.19434, found 386.19379.

In order to confirm the structure, the nitrogen atom of **25** has been deprotected to give **25'**.

(4*R*,3*S*) 3-Benzyl-3-ethoxycarbonyl-4-hydroxypiperidine (**25'**)



25'

The nitrogen atom of **25** have been deprotected to obtain the corresponding secondary amine **25'** in order to determine the absolute configuration at C3 and avoid rotamers. In a dry flask, **25** (60 mg, 0.2mmol, 1 equiv.) was dissolved in CH₂Cl₂ (3 mL) and trifluoroacetic acid was added (TFA) (1.4 mmol, 7 equiv). The mixture was stirred for 1h at rt. The mixture was quenched with 5 mL of a saturated solution of K₂CO₃ at 0 °C. The organic layer was extracted and evaporated under *vacuo*. The crude product was purified by a silica gel chromatography, using EtOAc/CH₂Cl₂ = 1:3 as eluent, to give **26'** as a slightly yellow oil (52 mg, 95%).

Formula : C₁₅H₂₁NO₃

IR (neat) 3300, 2919, 2360, 1706, 1198, 701cm⁻¹.

¹H NMR (400 MHz, DMSO D₆) δ 7.25 (t, *J* = 5.7 Hz, 2H), 7.20 (t, *J* = 5.5 Hz, 2H), 7.13 (d, *J* = 5.7 Hz, 1H), 4.89 (dm, *J* = 4.1 Hz, 1H), 4.01–3.93 (m, 2H), 3.90 (m, 1H), 3.40 (br s, 1H), 3.20 (d, *J* = 13.1 Hz, 1H), 2.92 (d, *J* = 13.1 Hz, 1H), 2.85 (ddd, *J* = 12.1, 12.1, 3.4 Hz, 1H), 2.76 (d, *J* = 13.1 Hz, 1H), 2.68 (m, 1H), 2.54 (d, *J* = 12.6 Hz, 1H), 1.90 (m, 1H), 1.48 (m, 1H), 1.13 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (400 MHz, DMSO D₆) δ 173.4 (s), 137.0 (s), 129.8 (d, 2C), 127.9 (d, 2C), 126.4 (d), 69.4 (d), 59.5 (t), 51.3 (s), 43.5 (t), 40.5 (t), 37.0 (t), 29.4 (t), 13.9 (q).

MS (EI) : *m/z* 263 (M⁺, 33), 216 (17), 200 (27), 172 (28), 154 (100), 115 (24), 91 (46).

HRMS: calcd for C₁₅H₂₂NO₃ (MH⁺) 264.34008, found 264.15942.

NOESY : the axial and the equatorial hydrogens at C5 have been determined by using coupling constant in ¹H NMR and by nOe (thin blue lines). The *cis* relationship between the axial hydrogen at C5 and the benzylic group at C3 have been confirmed thanks to the nOe (thick blue line) (Figure 2).

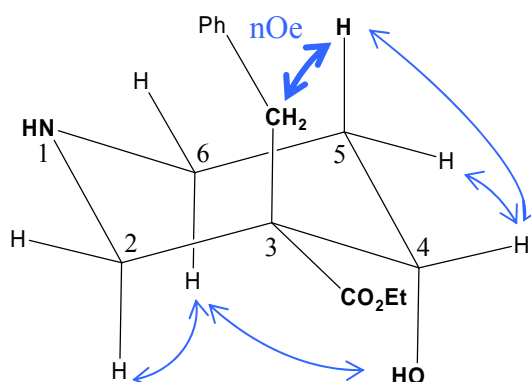
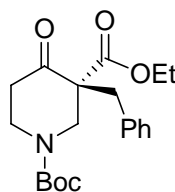


Figure 2.

(S)-N-Boc-3-Benzyl-3-ethoxycarbonyl-4-piperidone (26)¹⁸**26**

(4*R*, 3*S*) *N*-Boc-3-benzyl-3-ethoxycarbonyl-4-hydroxypiperidine **25** (1 mmol, 360 mg, 1equiv.) was dissolved in CH₂Cl₂ (20 mL) under stirring at rt and under argon atmosphere. Dess Martin reagent (1.2 mmol, 508 mg, 1.2 equiv.) was then added and the solution was kept under stirring for 24 h. The mixture was evaporated under *vacuo* and the crude product was purified by a silica gel chromatography, using EtOAc/hexane = 1:3 as eluent, to slightly yellow oil (325 mg, 90%).

Formula : C₂₀H₂₇NO₅

[α]_D = - 45.8 (*c* 3, CH₂Cl₂).

IR (neat) 2976, 2929, 1693, 1454, 1365, 1277, 1244, 1227, 1163, 1126, 701 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.28–7.12 (m, 5H), 4.60 (m, 1H), 4.07 (q, *J* = 7.0 Hz, 2H), 4.10 (m, 1H), 3.24 (d, *J* = 13.9 Hz, 1H), 3.15 (m, 1H), 3.01 (d, *J* = 13.5 Hz, 1H), 3.05 (m, 1H), 2.69 (ddd, *J* = 14.7, 10.5, 6.6 Hz, 1H), 2.40 (m, 1H), 1.44 (s, 9H), 1.15 (t, *J* = 7.1 Hz, 3H).

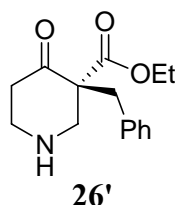
¹³C NMR (100 MHz, CDCl₃) δ 204.5 (s), 169.8 (s), 154.2 (s), 135.6 (s), 130.4 (d, 2C), 128.2 (d, 2C), 127.0 (d), 80.5 (s), 62.2 (s), 61.7 (t), 43.1 (t), 40.0 (t), 37.3 (t), 28.2 (q, 3C), 13.9 (q).

HRMS : calcd for C₂₀H₂₇NO₅Na (MNa⁺) 384.17814, found 384.17814.

¹⁸ Carpino, P. A.; Lefker, B. A.; Toler, S. M.; Pan, L. C.; Hadcock, J. R.; Cook, E. R.; DiBrino, J. N.; Campeta, A. M.; DeNinno, S. L.; Chidsey-Fink, K. L.; Hada, W. A.; Inthavongsay, J.; Mangano, M. F.; Mullins, M. A.; Nickerson, D. F.; Ng, O.; Pirie, C. M.; Ragan, J. A.; Rose, C. R.; Tess, D. A.; Wright, A. S.; Yu, L.; Zawistoski, M. P.; DaSilva-Jardine, P. A.; Wilson, T. C.; Thompson, D. D. *Bio. Med. Chem* **2003**, *11*, 581–590.

In order to confirm the structure, the nitrogen atom of **26** was deprotected (TFA 5 equiv, CH₂Cl₂, 95%) to give **26'**.

(S)-N-Boc-3-Benzyl-3-ethoxycarbonyl-4-piperidone (26')



The nitrogen atom of **26** have been deprotected to obtain the corresponding secondary amine **26'** (TFA 5 equiv, CH₂Cl₂, 95%) in order to avoid rotamers. In a dry flask, **26** (60 mg, 0.2mmol, 1 equiv.) was dissolved in CH₂Cl₂ (3 mL) and trifluoroacetic acid was added (TFA) (1.4 mmol, 7 equiv). The mixture was stirred for 1h at rt. The mixture was quenched with 5 mL of a saturated solution of K₂CO₃ at 0 °C. The organic layer was extracted and evaporated under *vacuo*. The crude product was purified by a silica gel chromatography, using EtOAc/CH₂Cl₂ = 1:3 as eluent, to give **26'** as a slightly yellow oil (51 mg, 95%).

Formula : C₁₅H₁₉NO₃

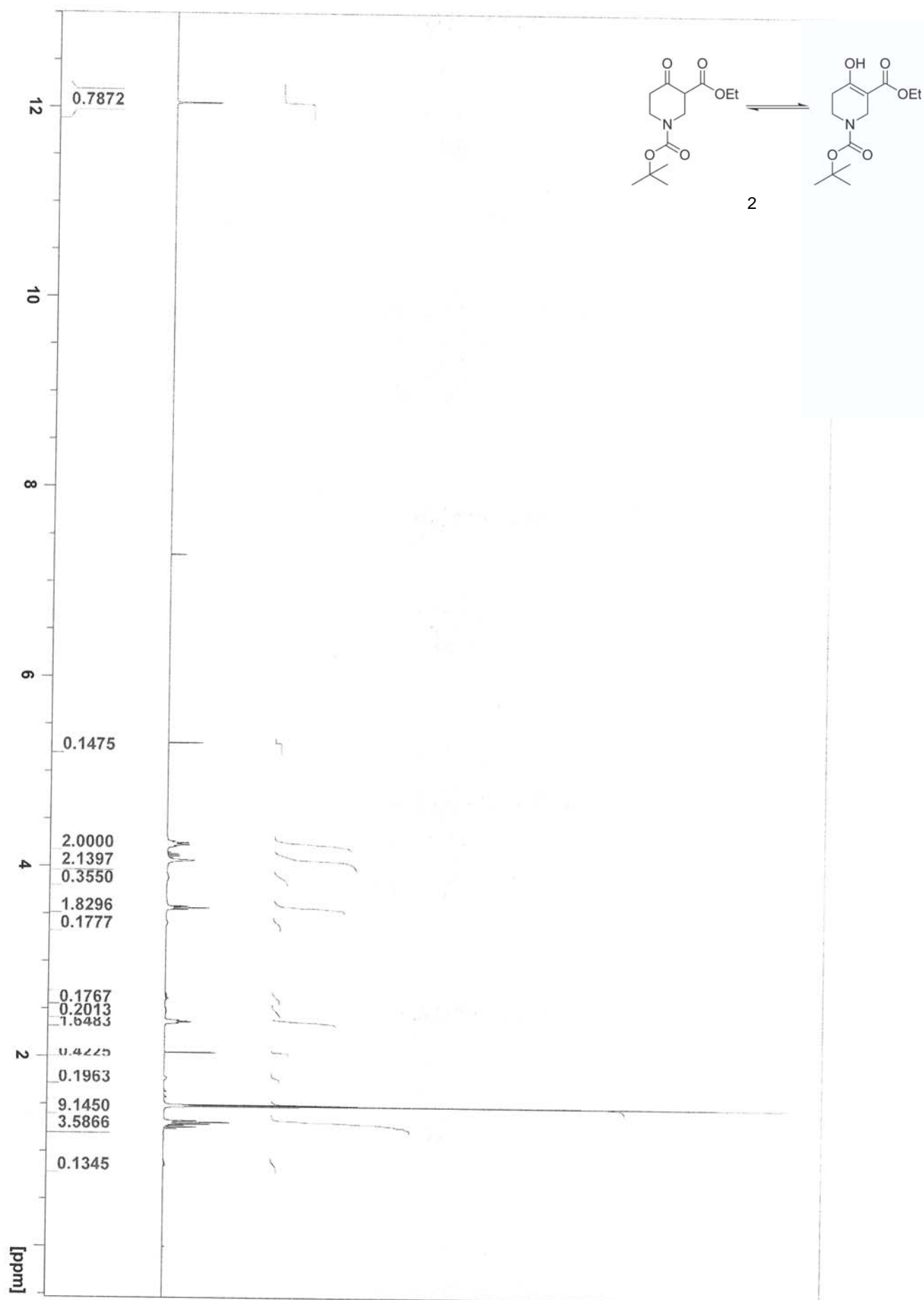
IR (neat) 2976, 2362, 1693, 1421, 1226, 1162, 1125, 701 cm⁻¹.

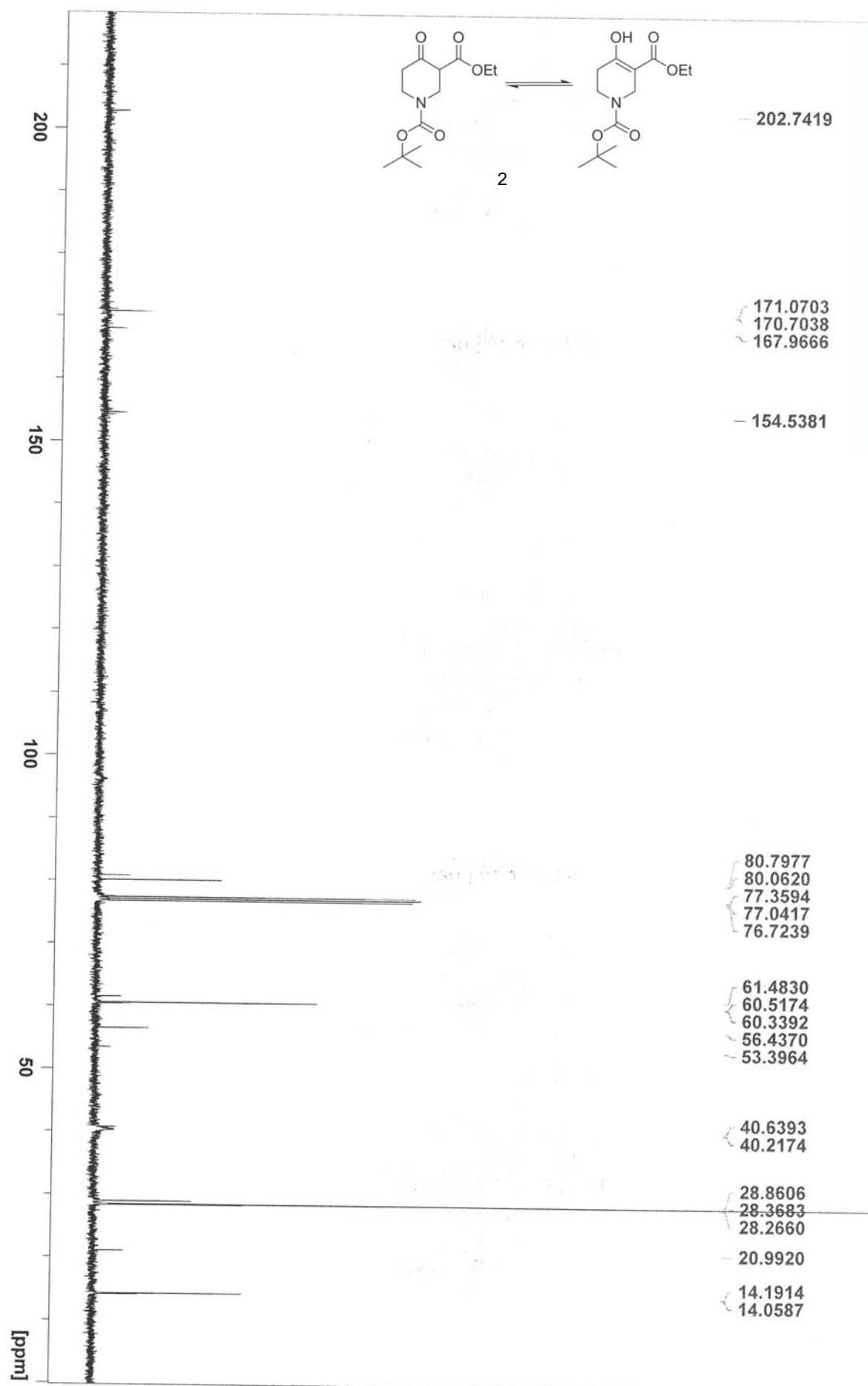
¹H NMR (400 MHz, CDCl₃) δ 7.19-7.12 (m, 3H), 7.04–6.99 (m, 2H), 4.14–3.97 (m, 2H), 3.61 (dd, *J*= 13.4, 2.4 Hz, 1H), 3.31 (dm, *J*= 14.0 Hz, 1H), 2.81 (ddd, *J*= 13.2, 11.2, 4.4 Hz, 1H), 2.75 (d, *J*= 14.0 Hz, 1H), 2.55 (d, *J*= 13.5 Hz, 1H), 2.45–2.30 (m, 2H), 1.87 (br s, 1H), 1.12 (t, *J*= 7.16 Hz, 3H).

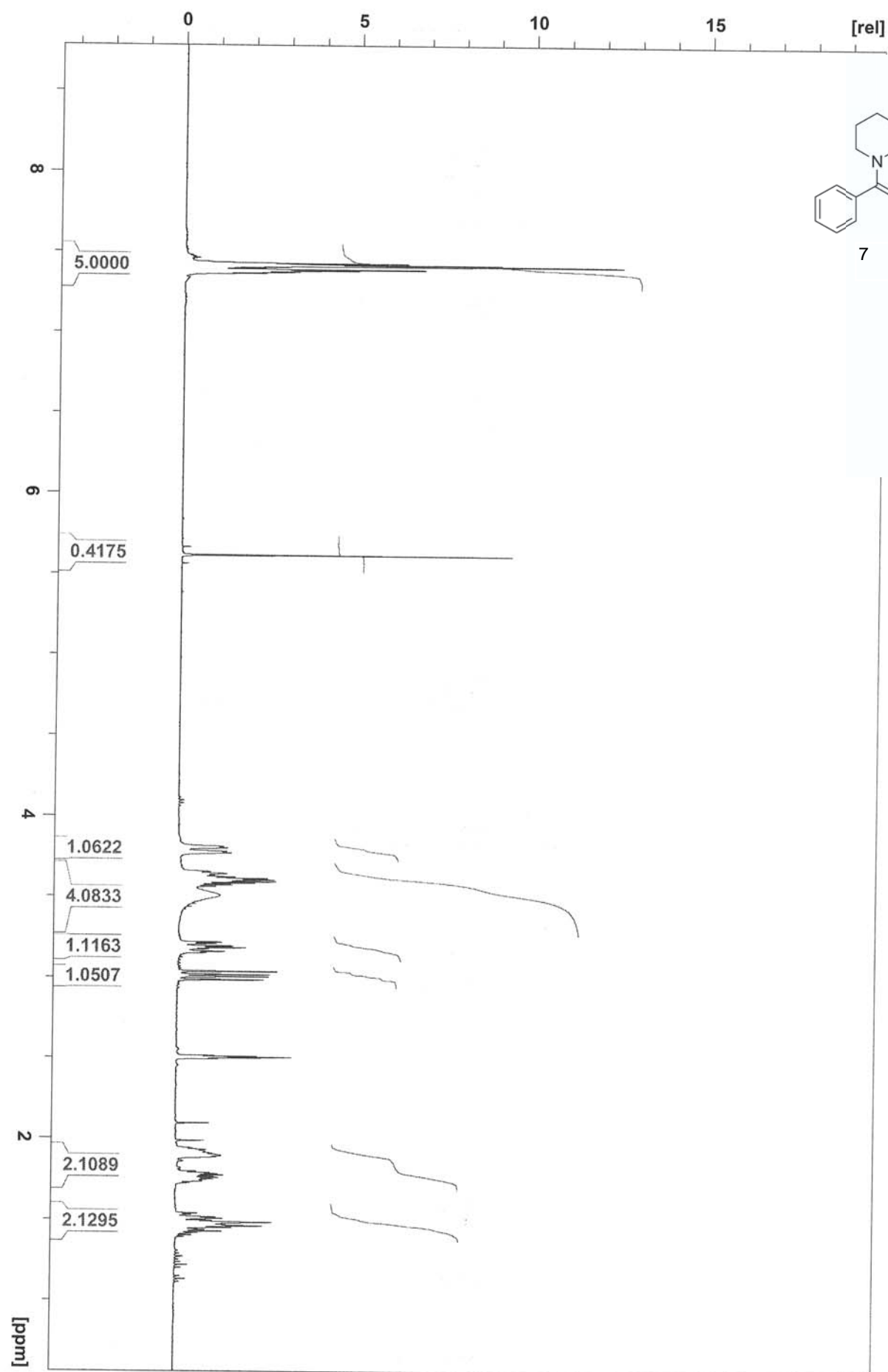
¹³C NMR (100 MHz, CDCl₃) δ 204.6 (s), 170.6 (s), 136.0 (s), 130.1 (d, 2C), 128.2 (d, 2C), 126.2 (d), 64.4 (s), 61.6 (t), 55.3 (t), 48.0 (t), 43.5(t), 37.5 (t), 14.0 (q).

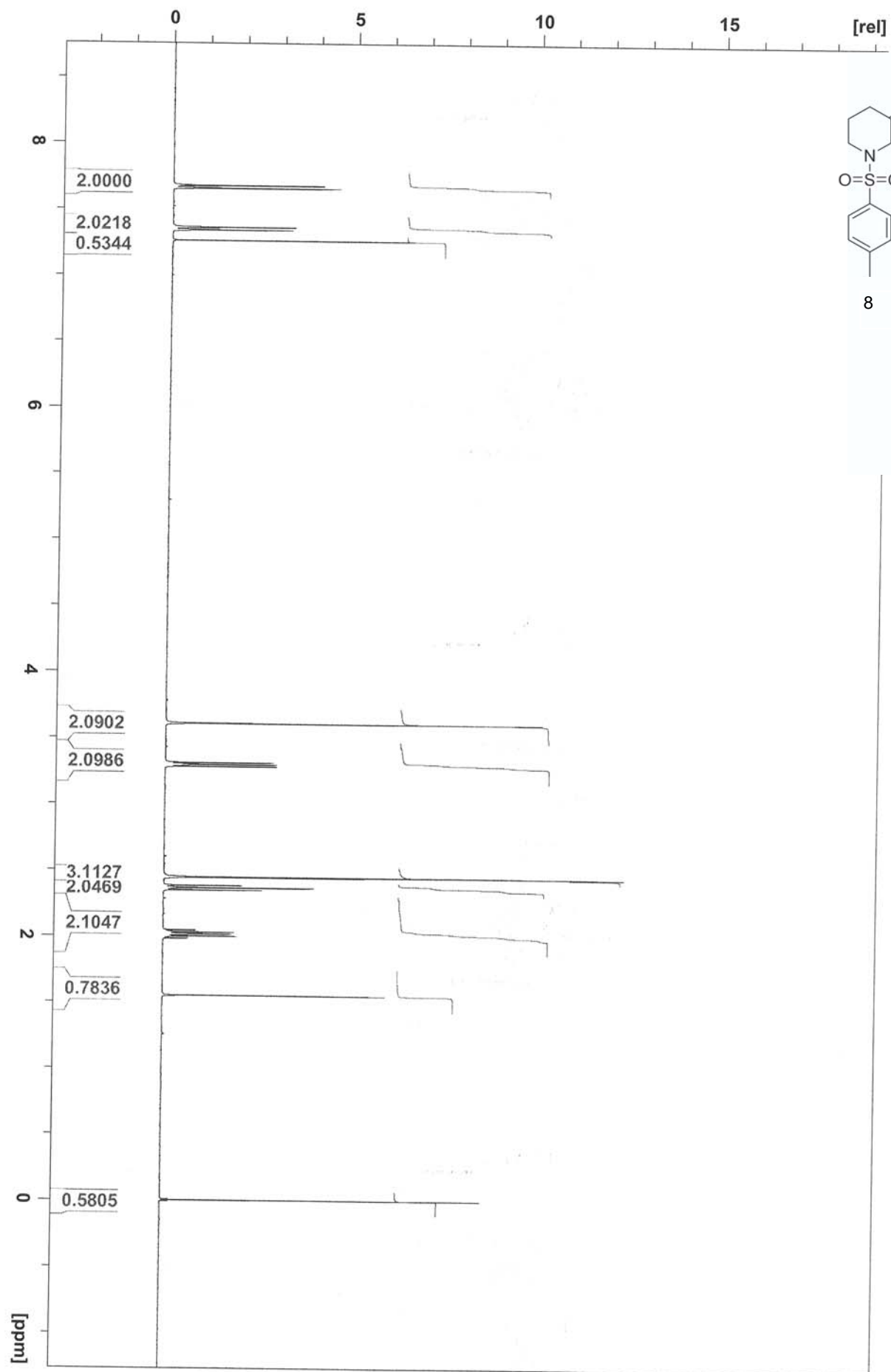
MS (EI) : *m/z* 233 (M⁺-Et, 2), 216 (14), 188 (10), 170 (96), 159 (11), 131 (15), 124 (100), 115 (22), 91 (40).

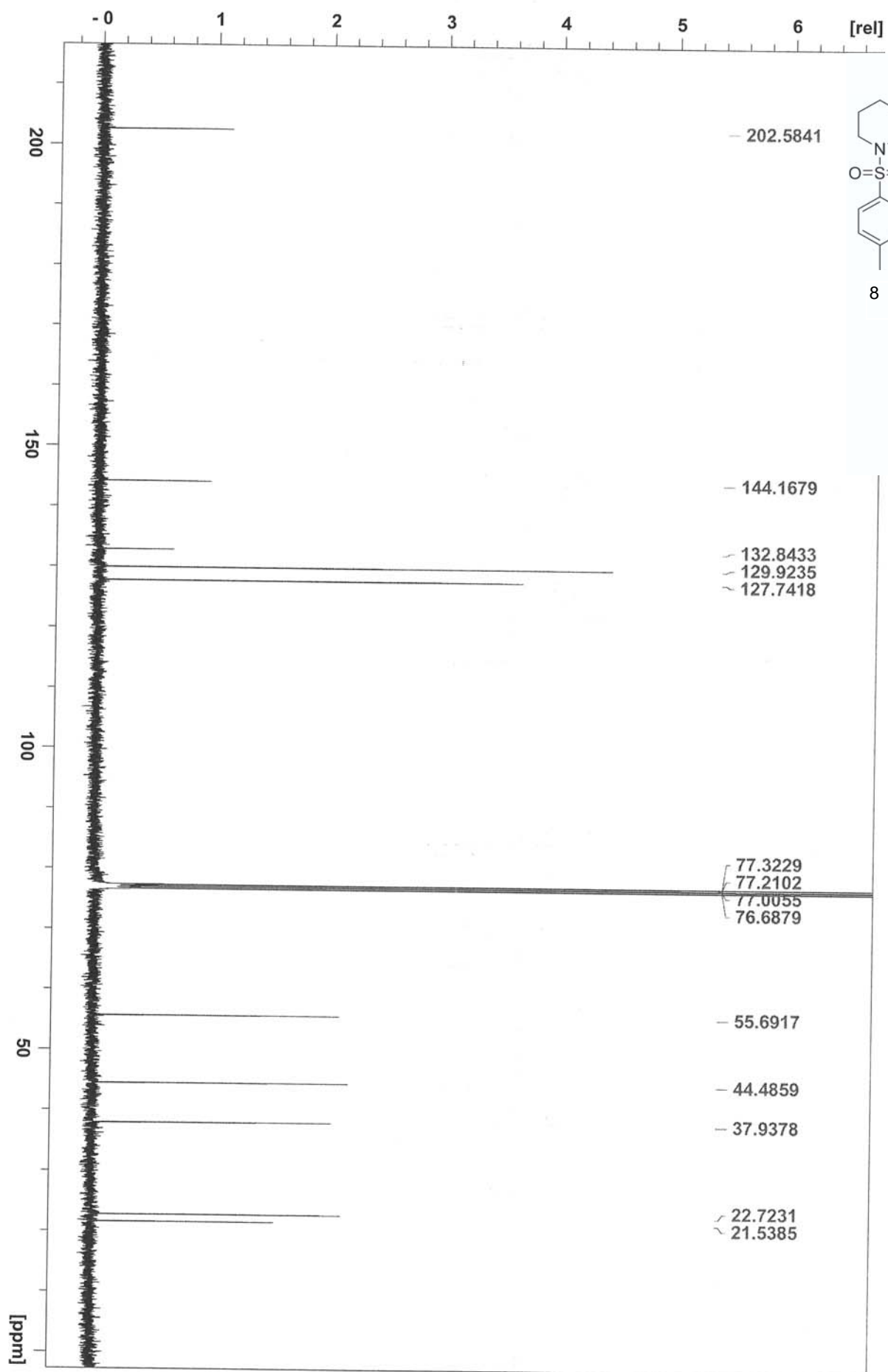
HRMS : calcd for C₁₅H₂₀NO₃ (MH⁺) 262.14377. found. 262.14377.

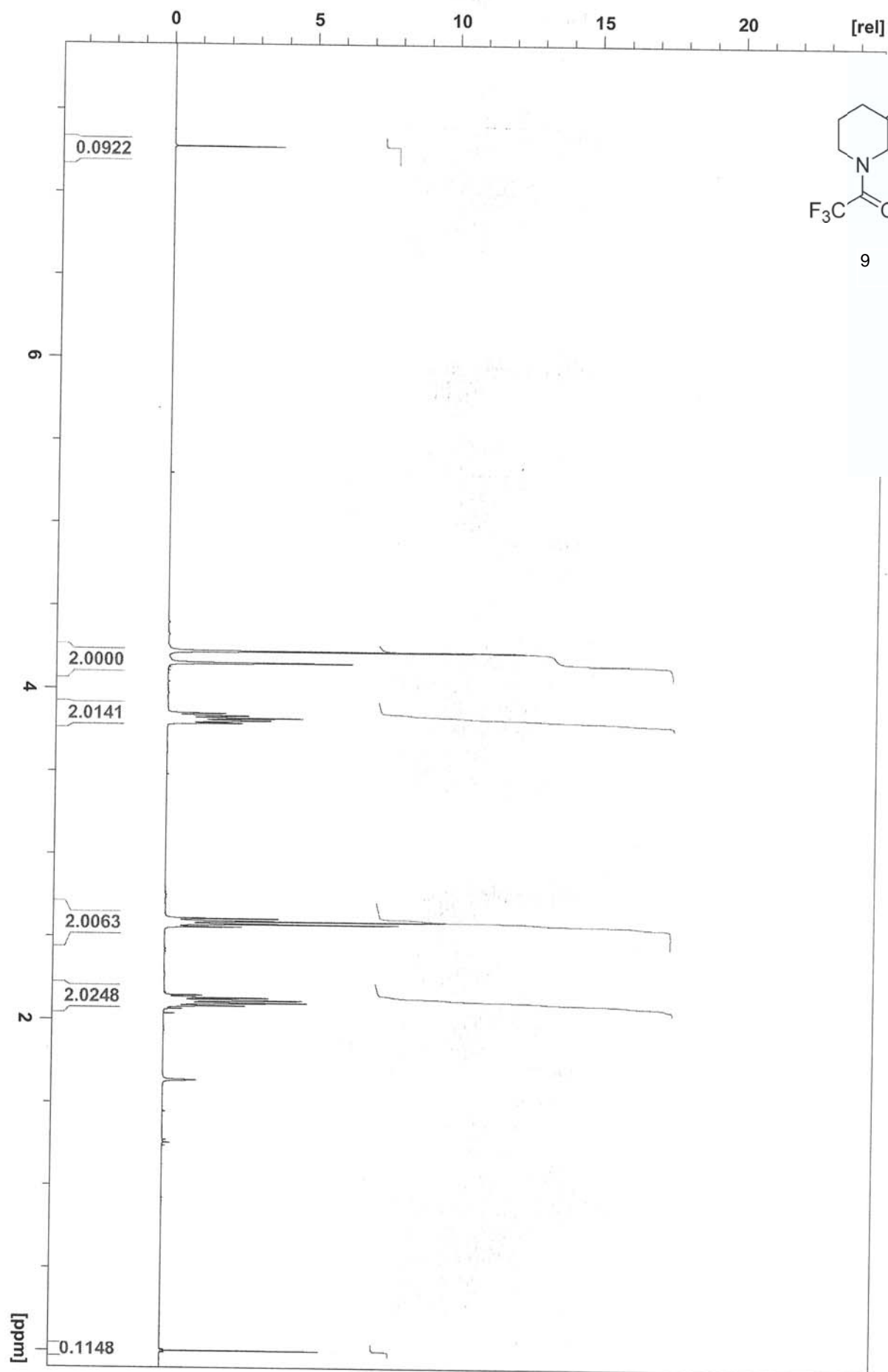


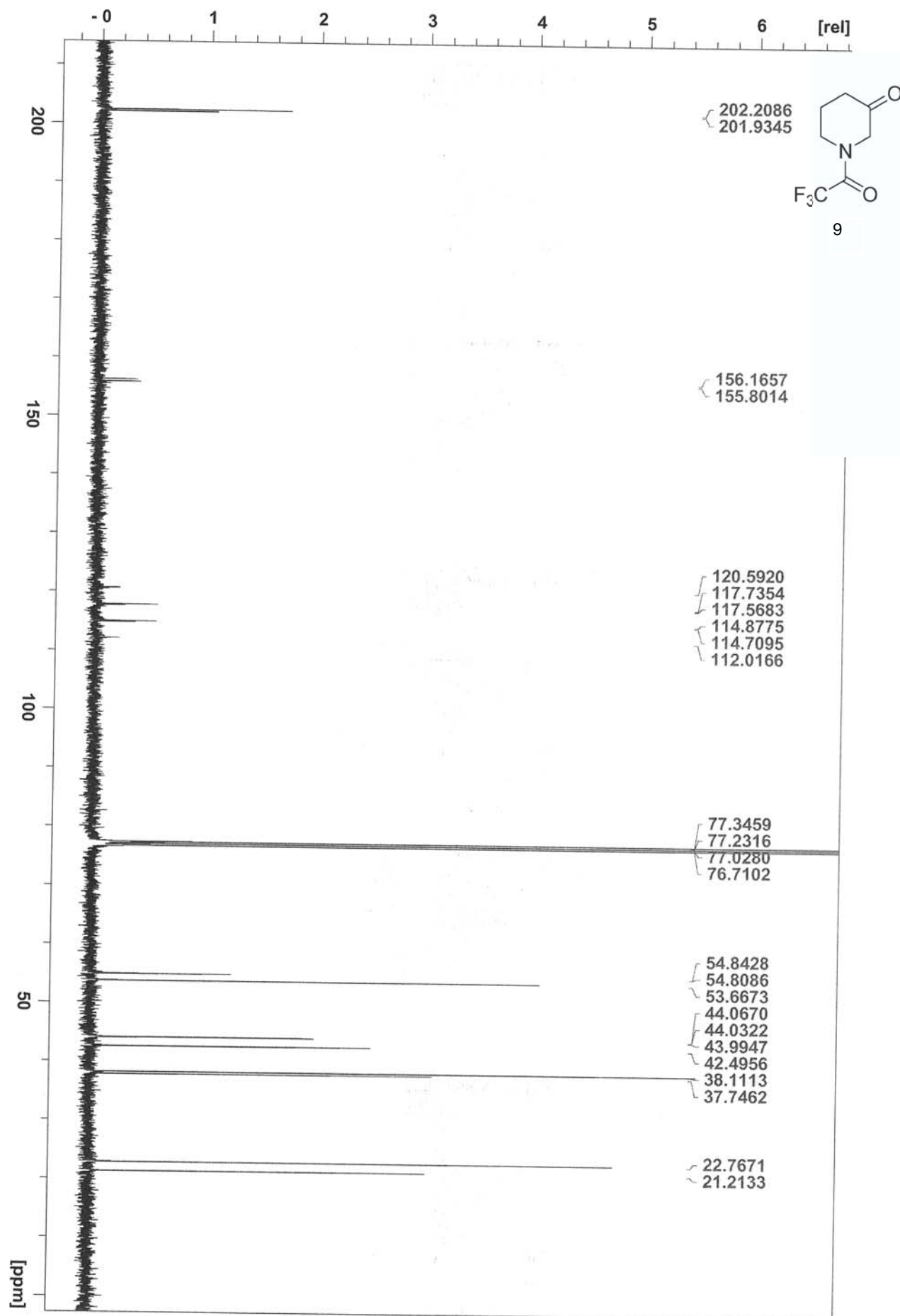


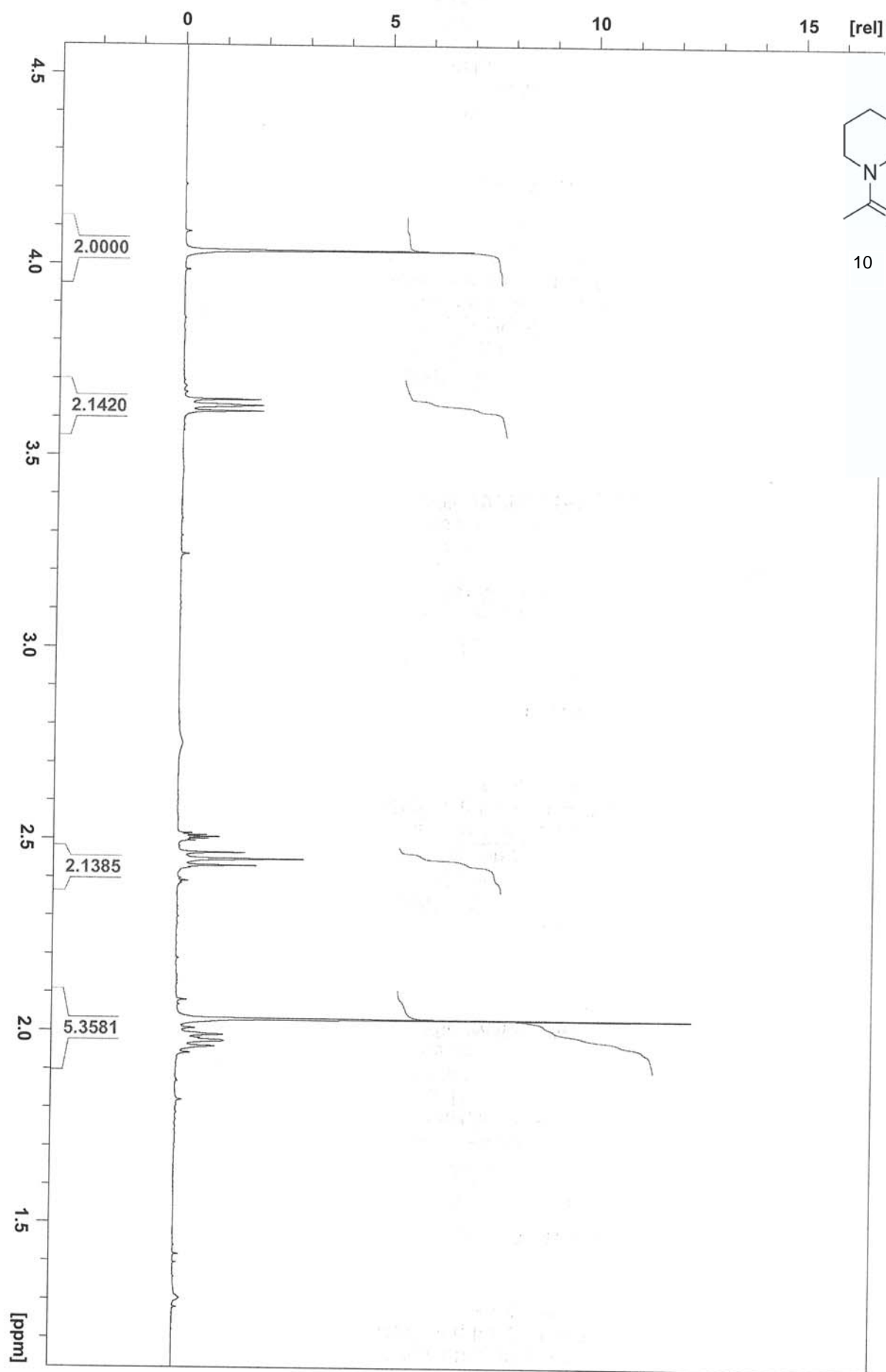


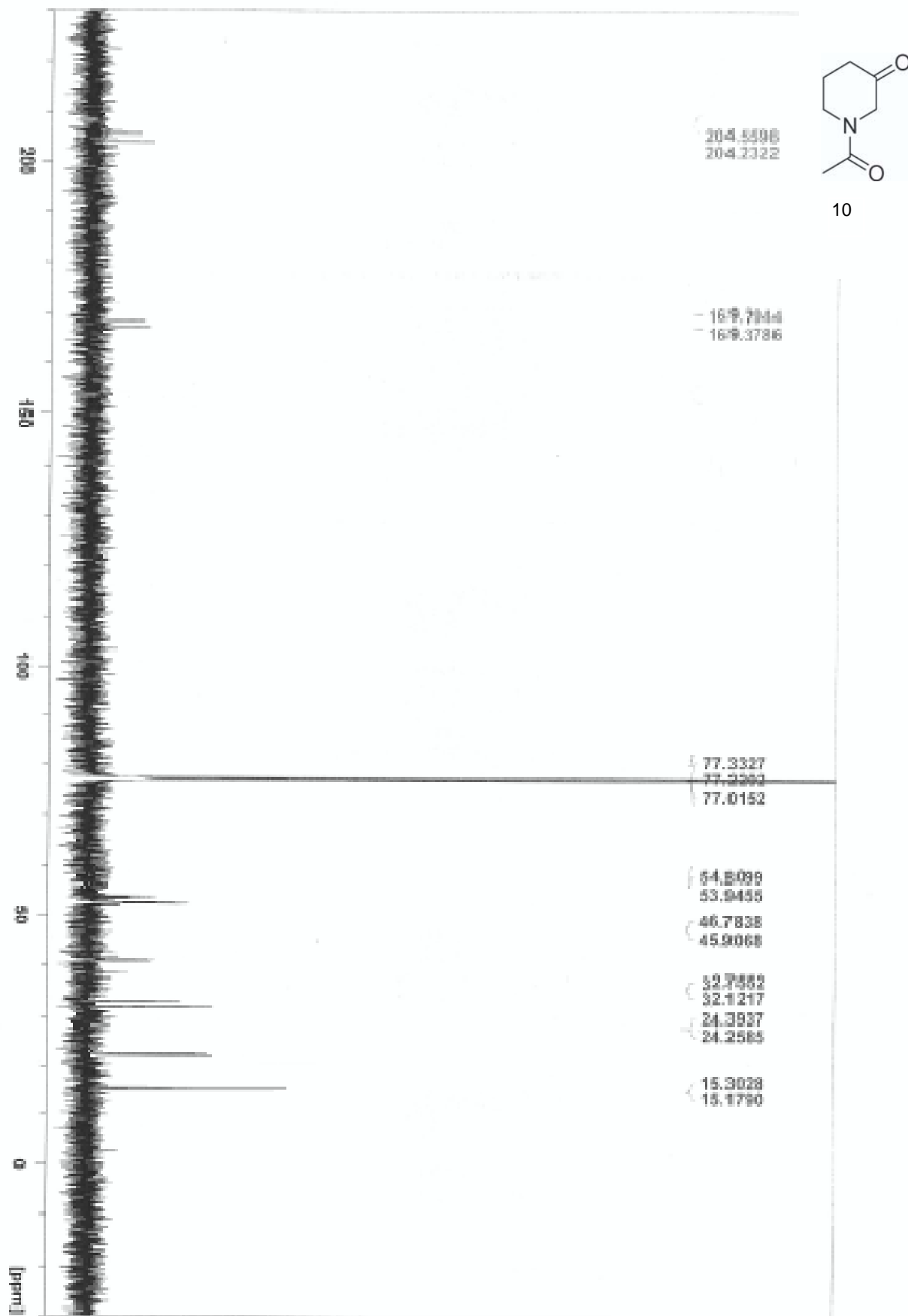


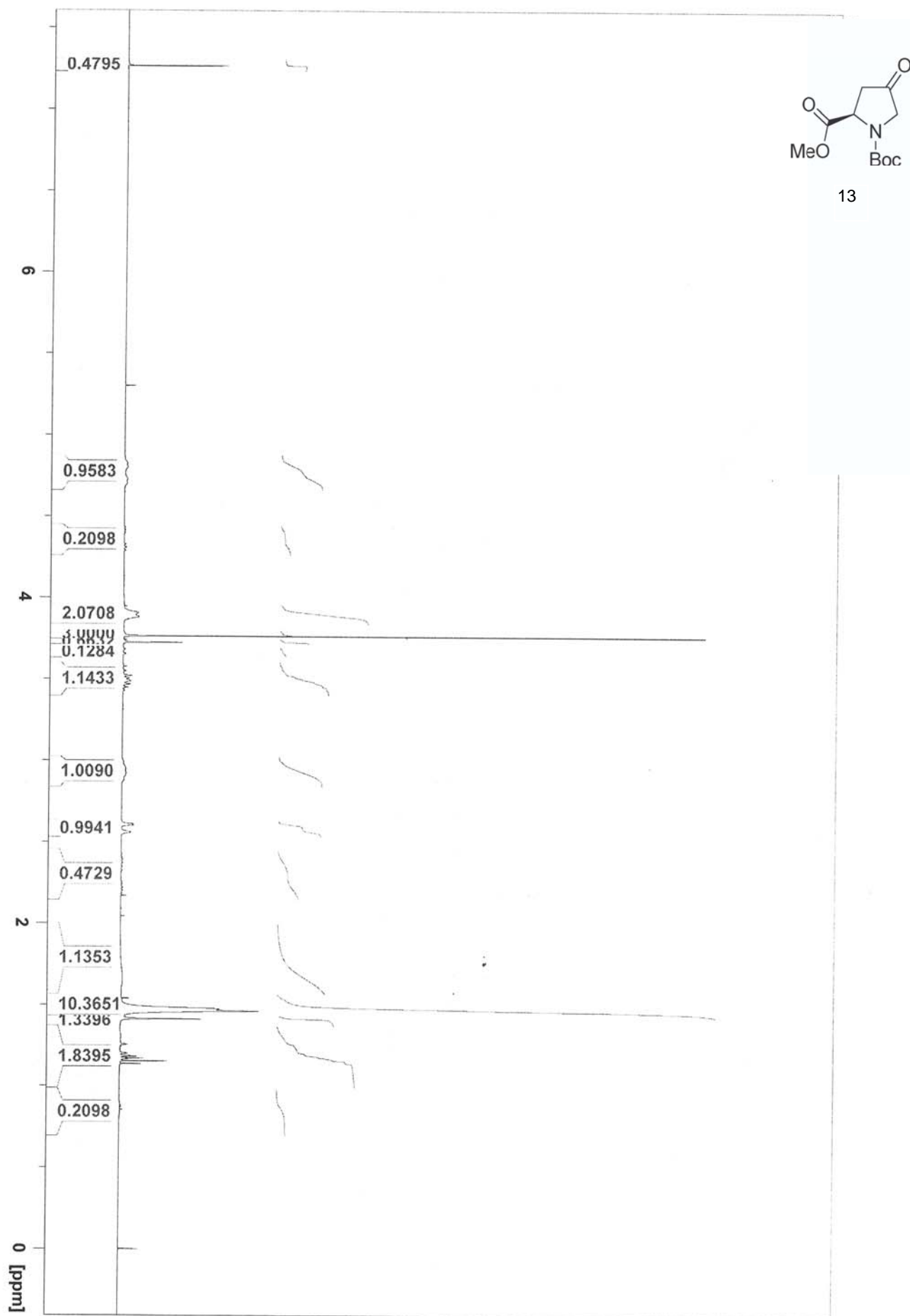


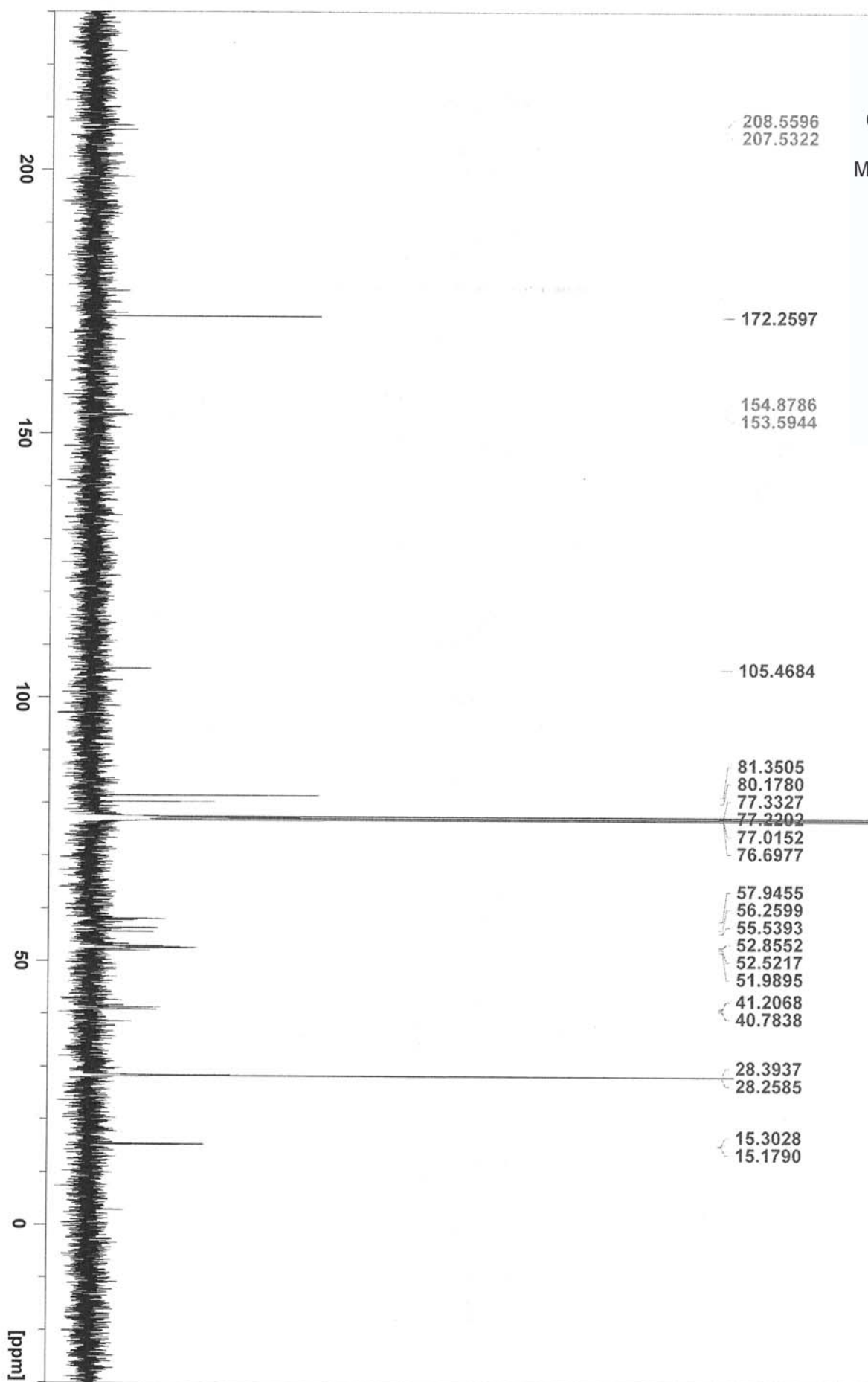


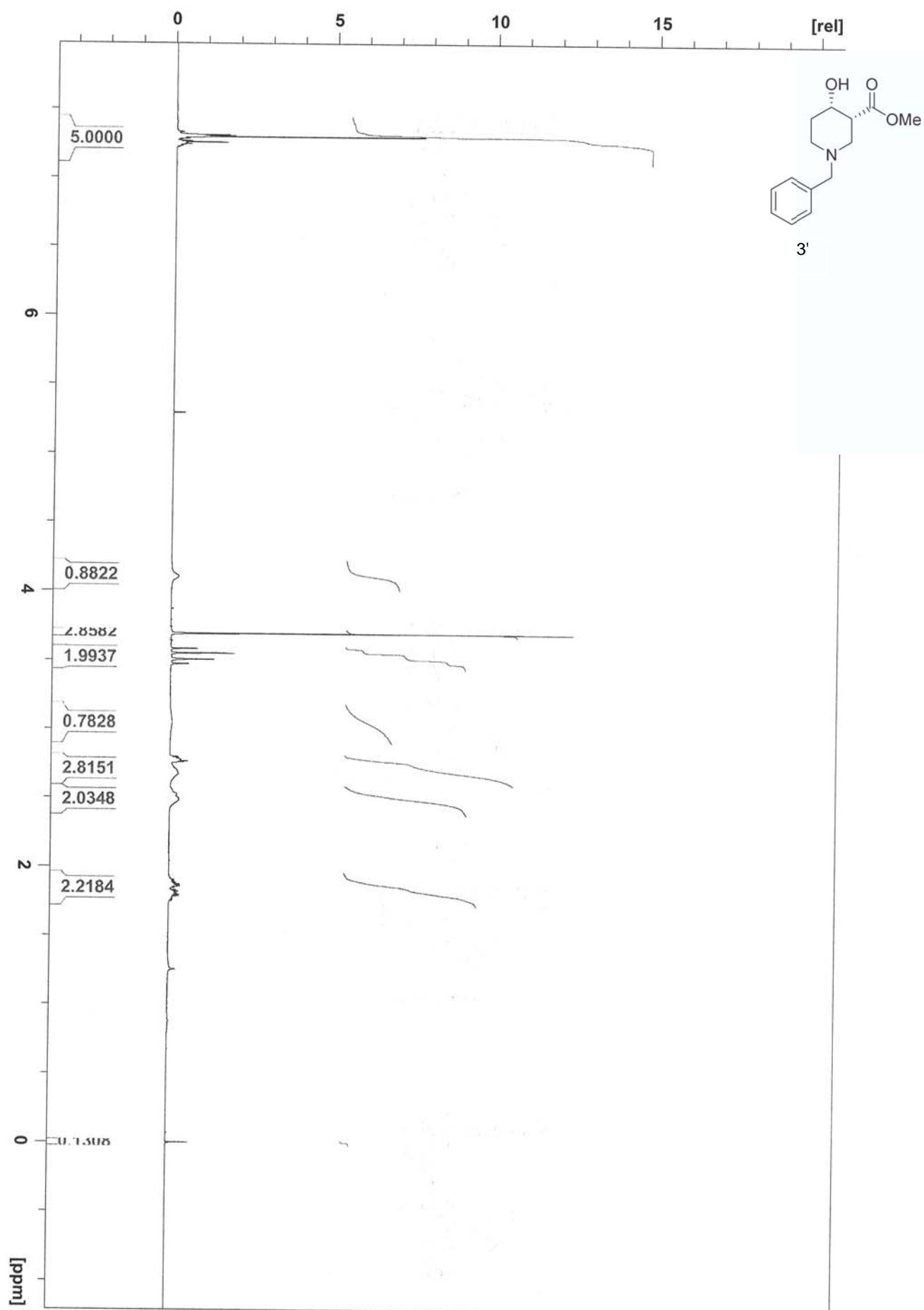


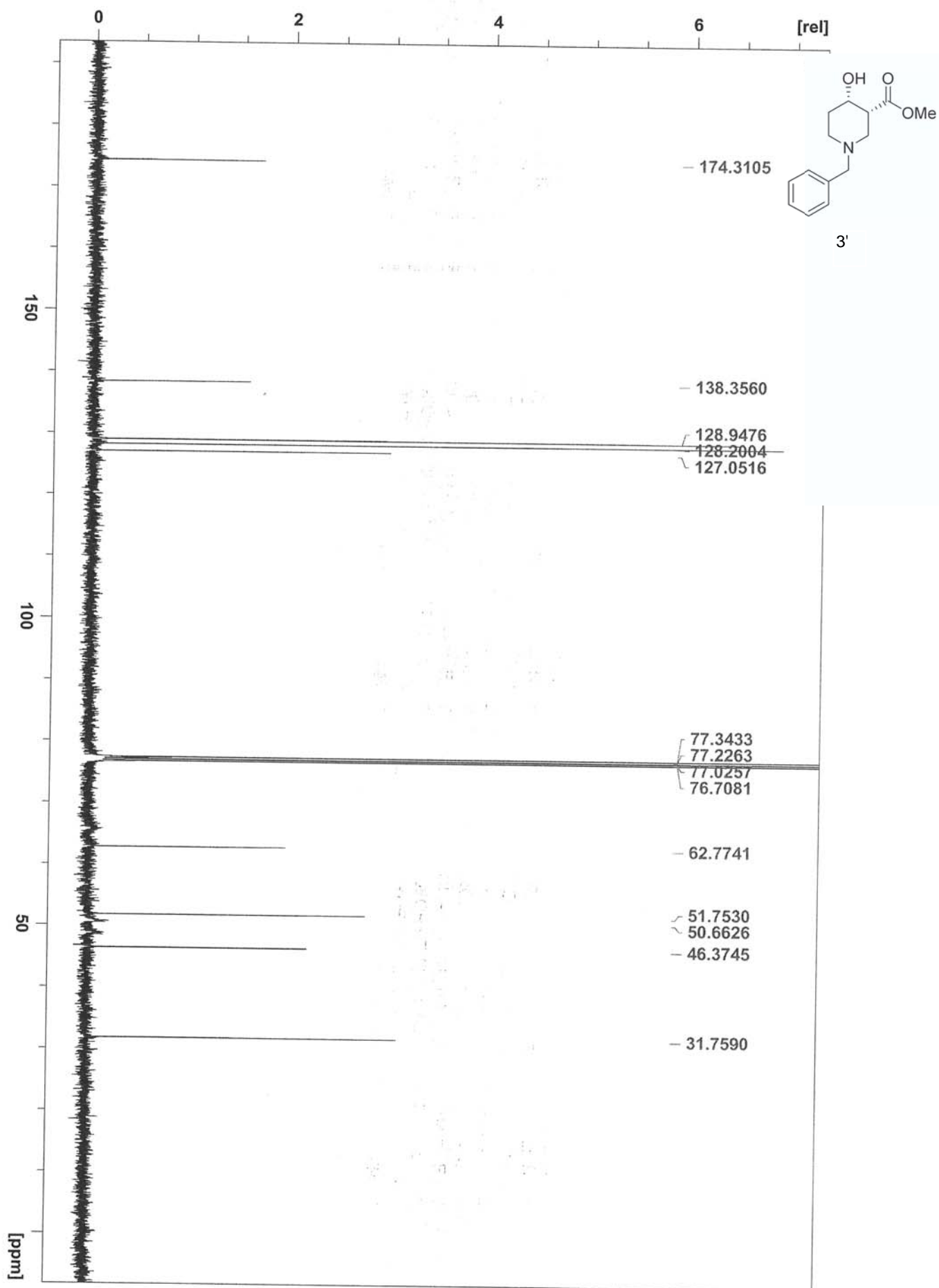


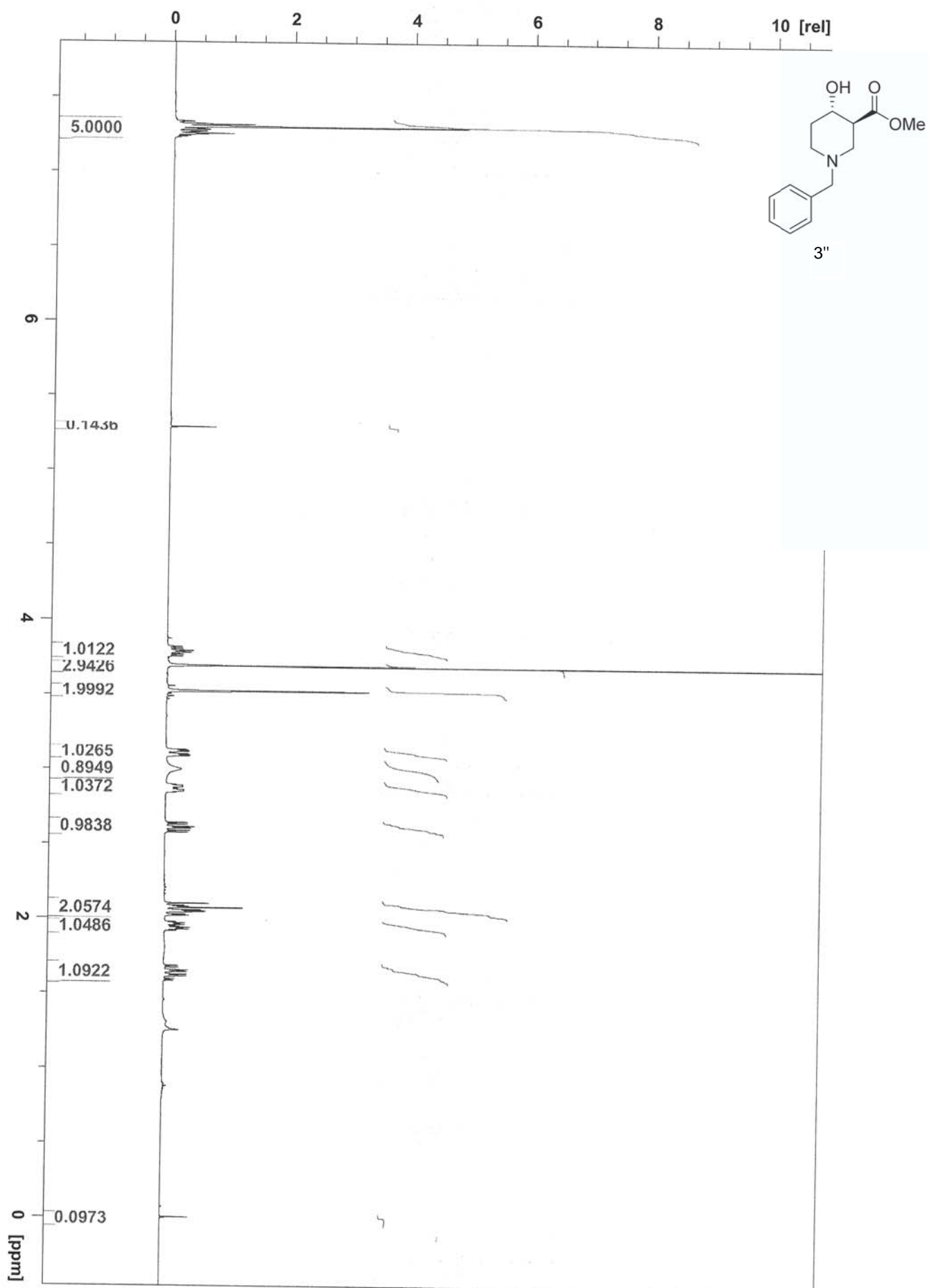


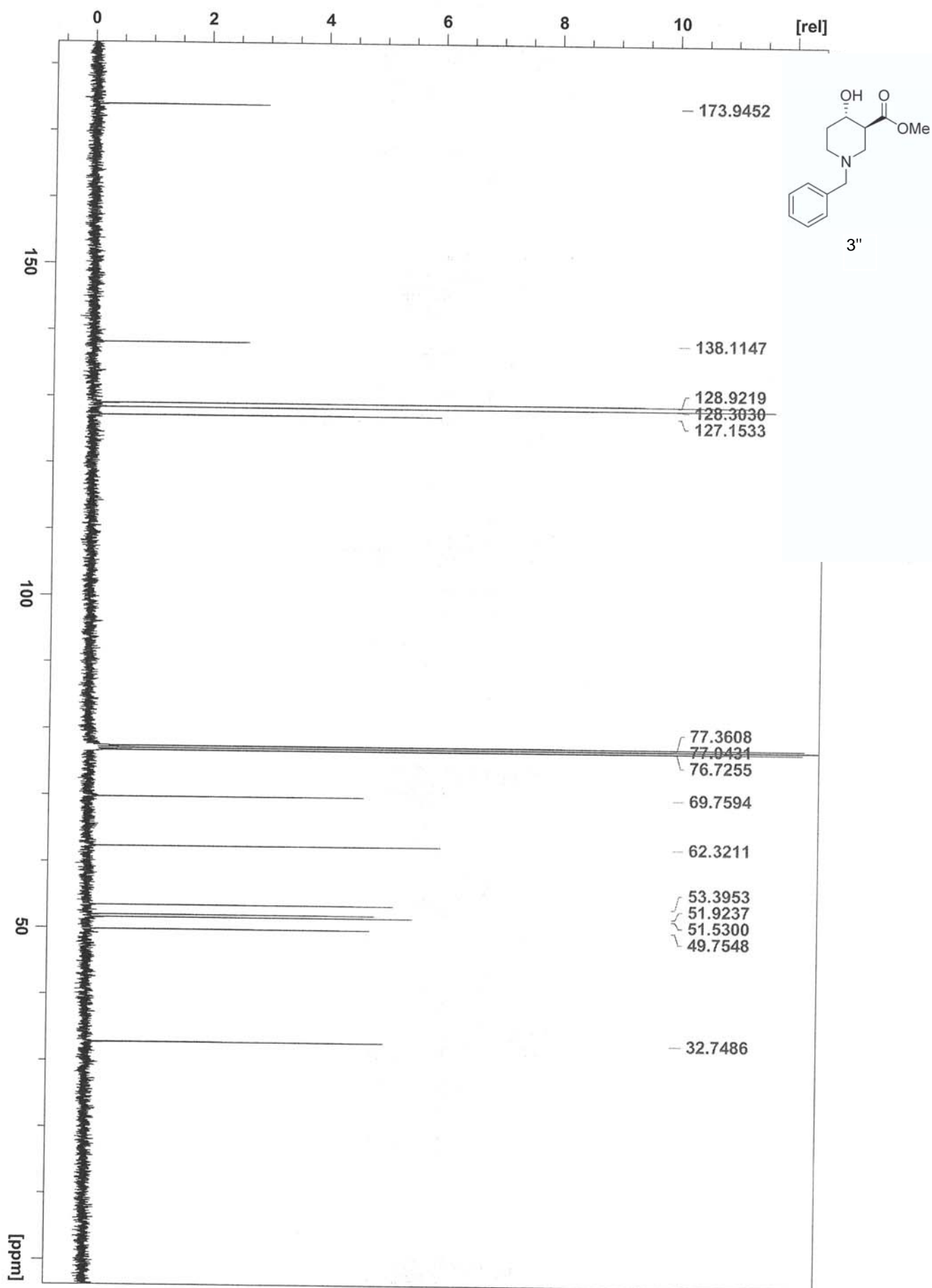


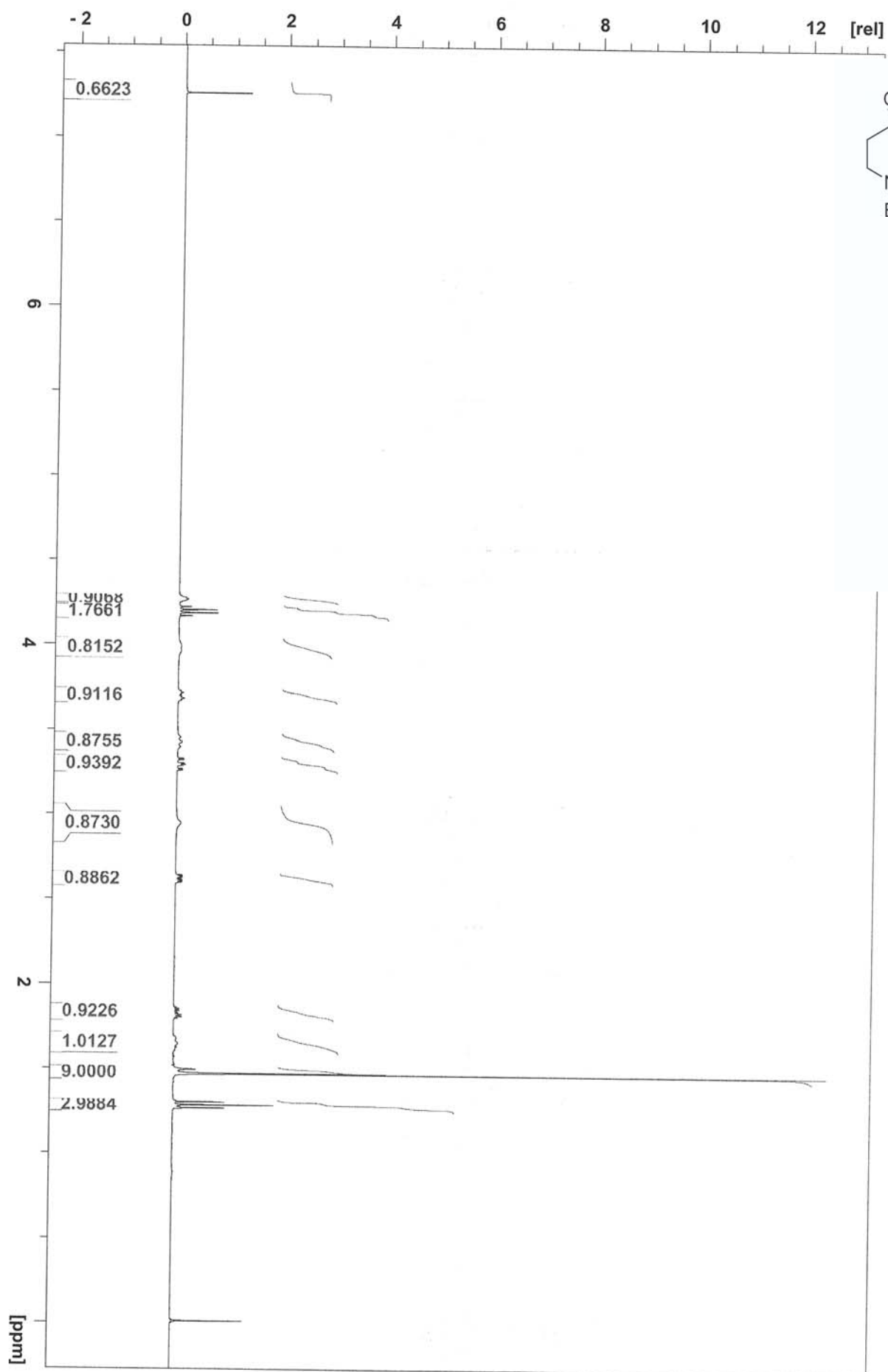


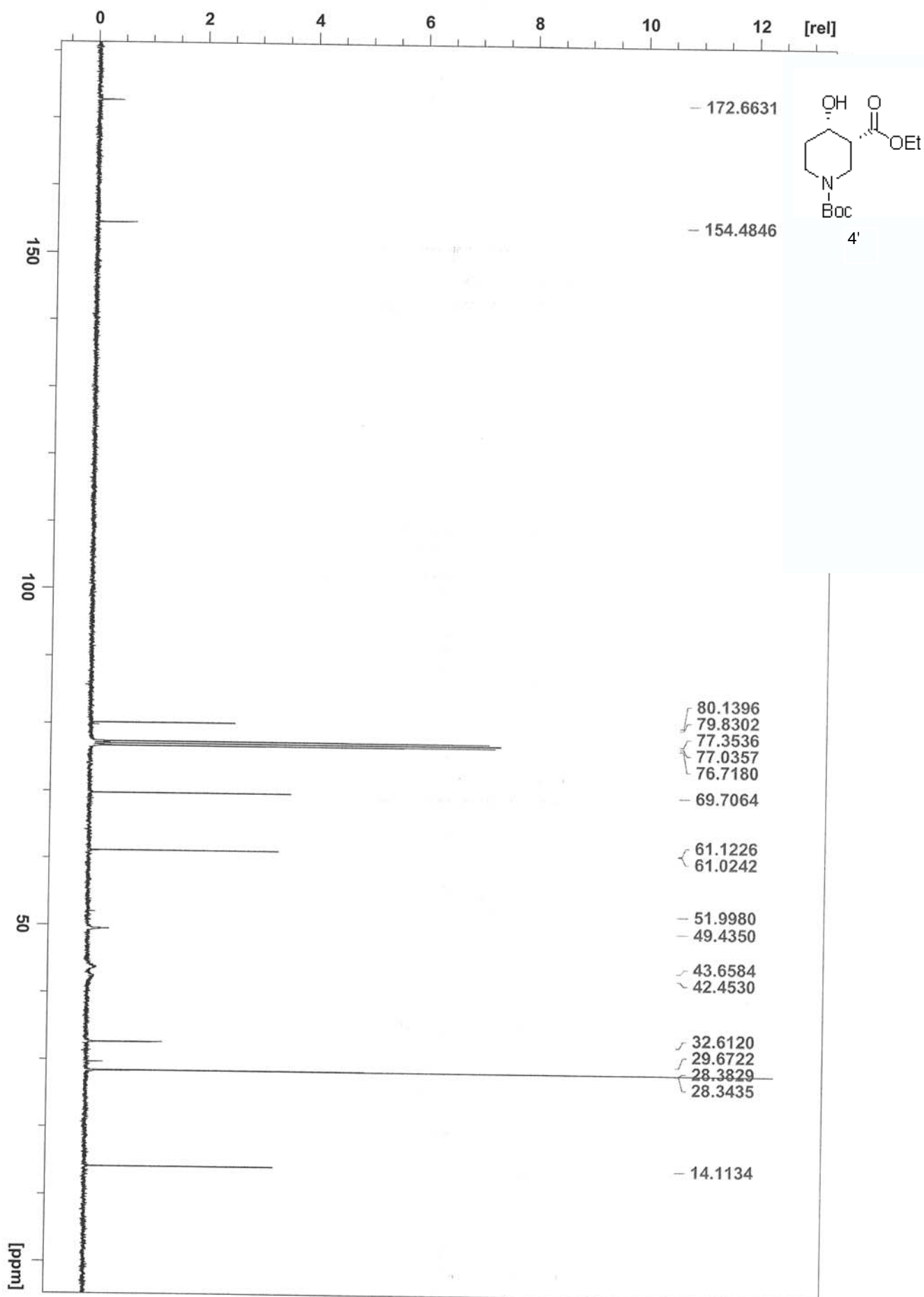


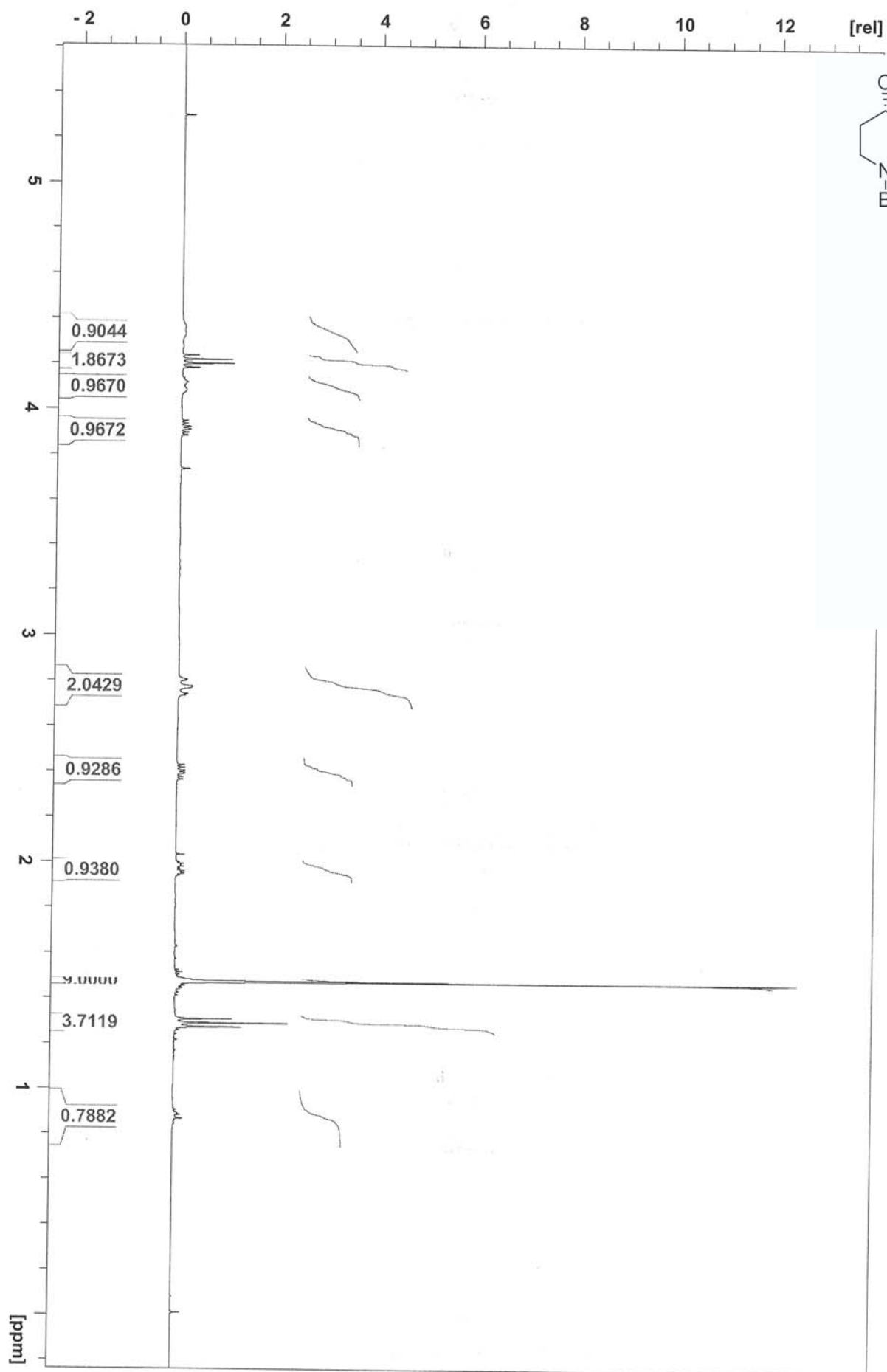


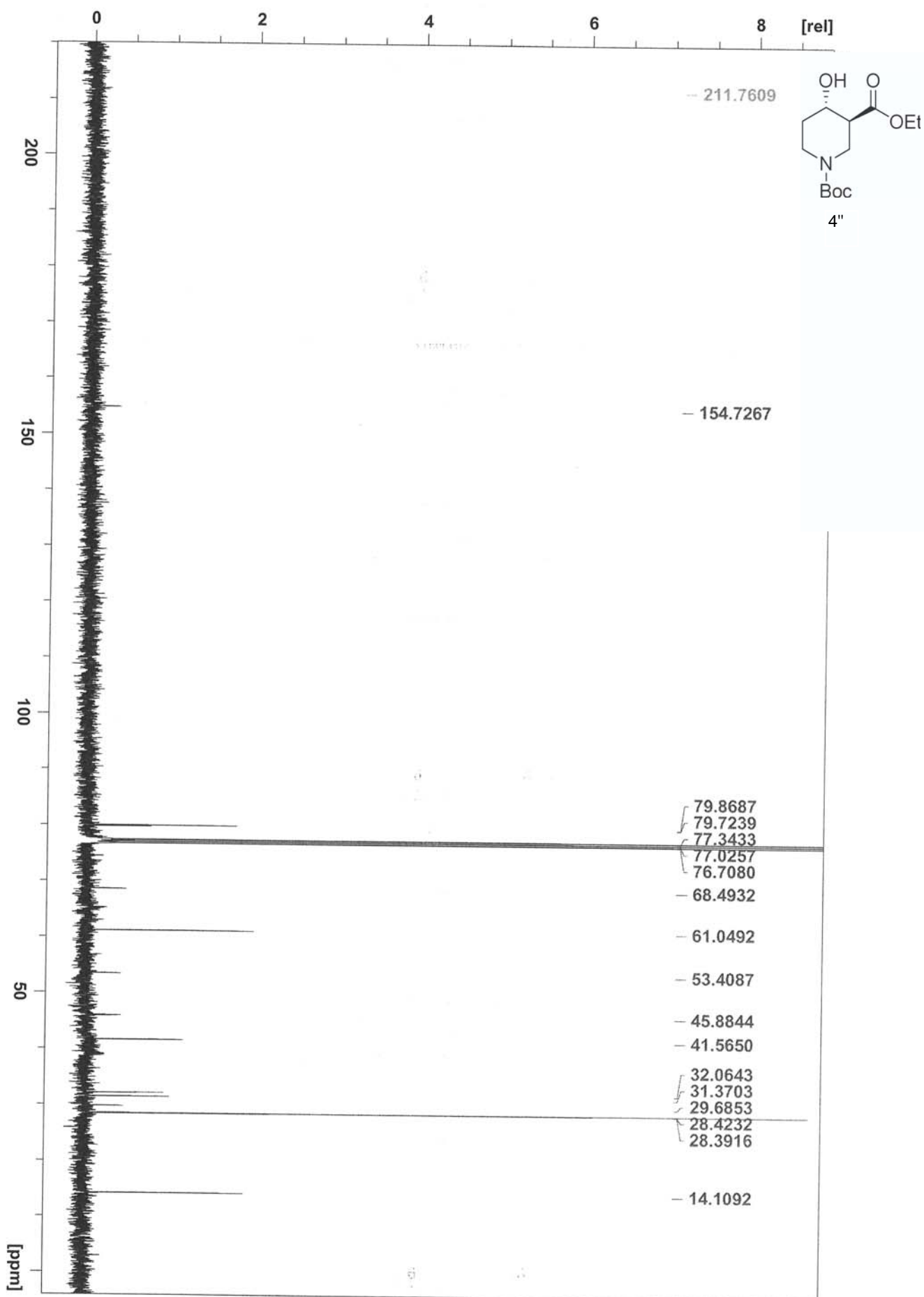


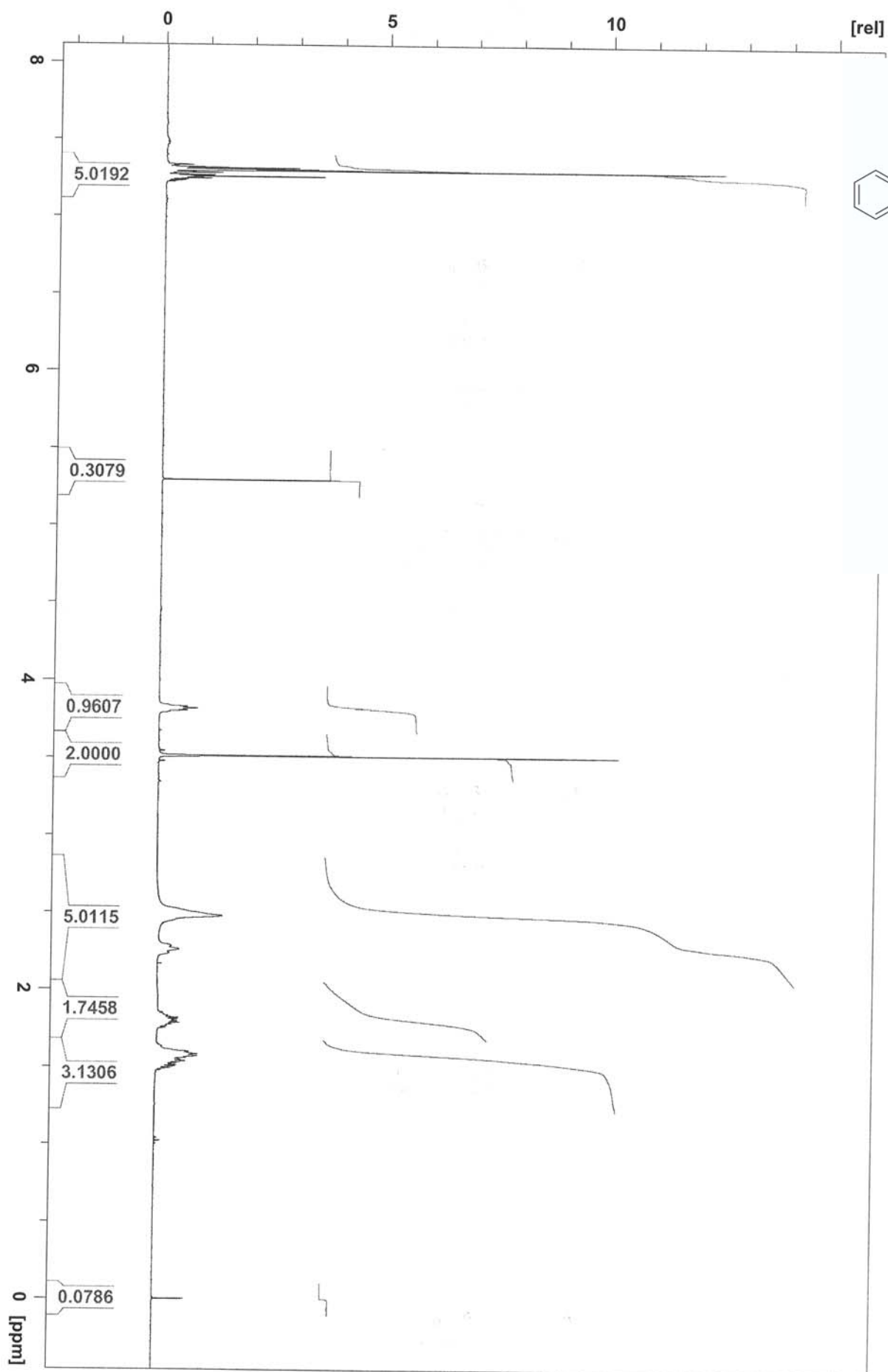


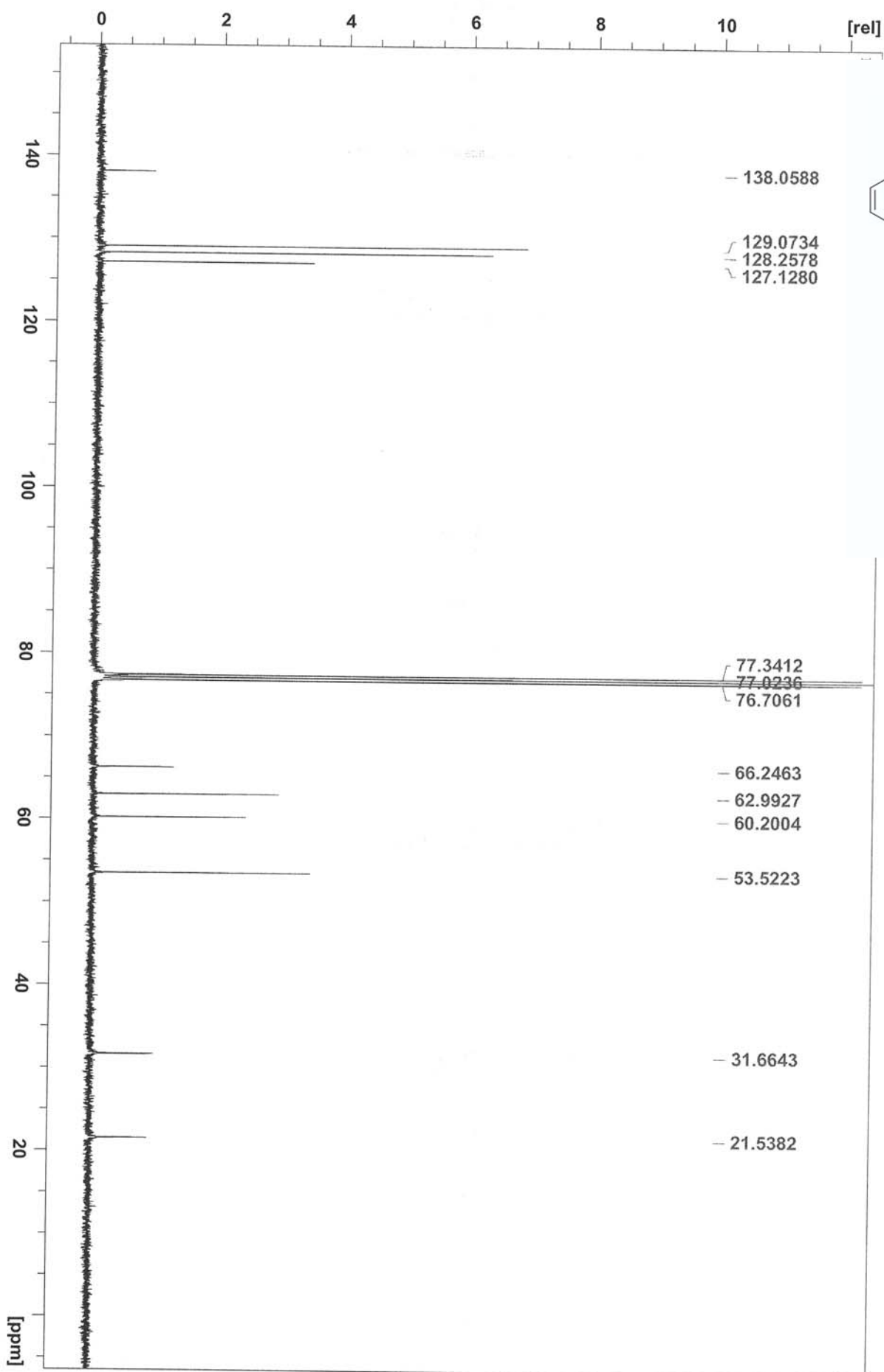


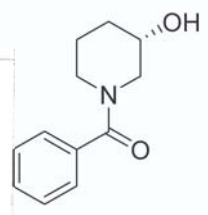
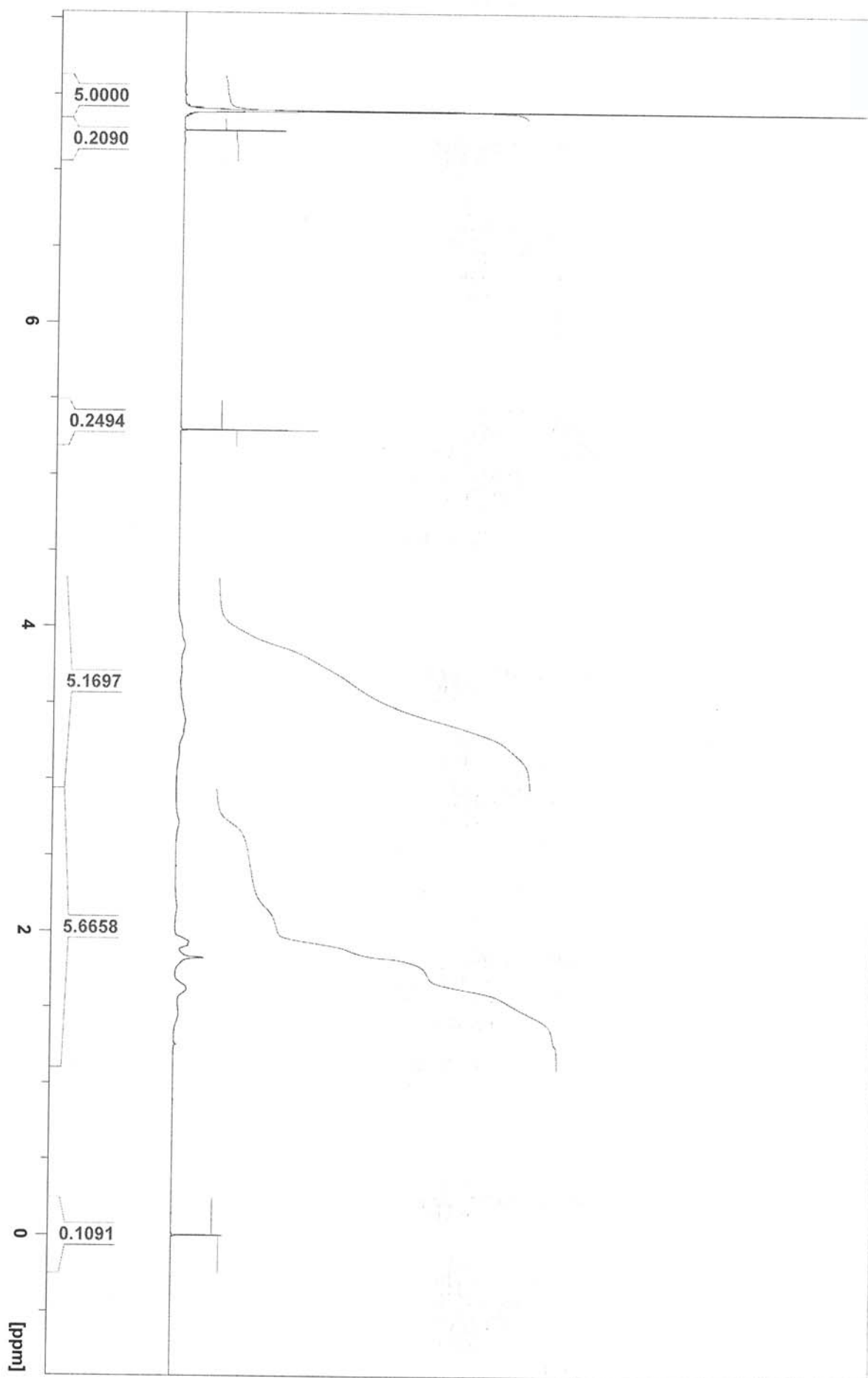




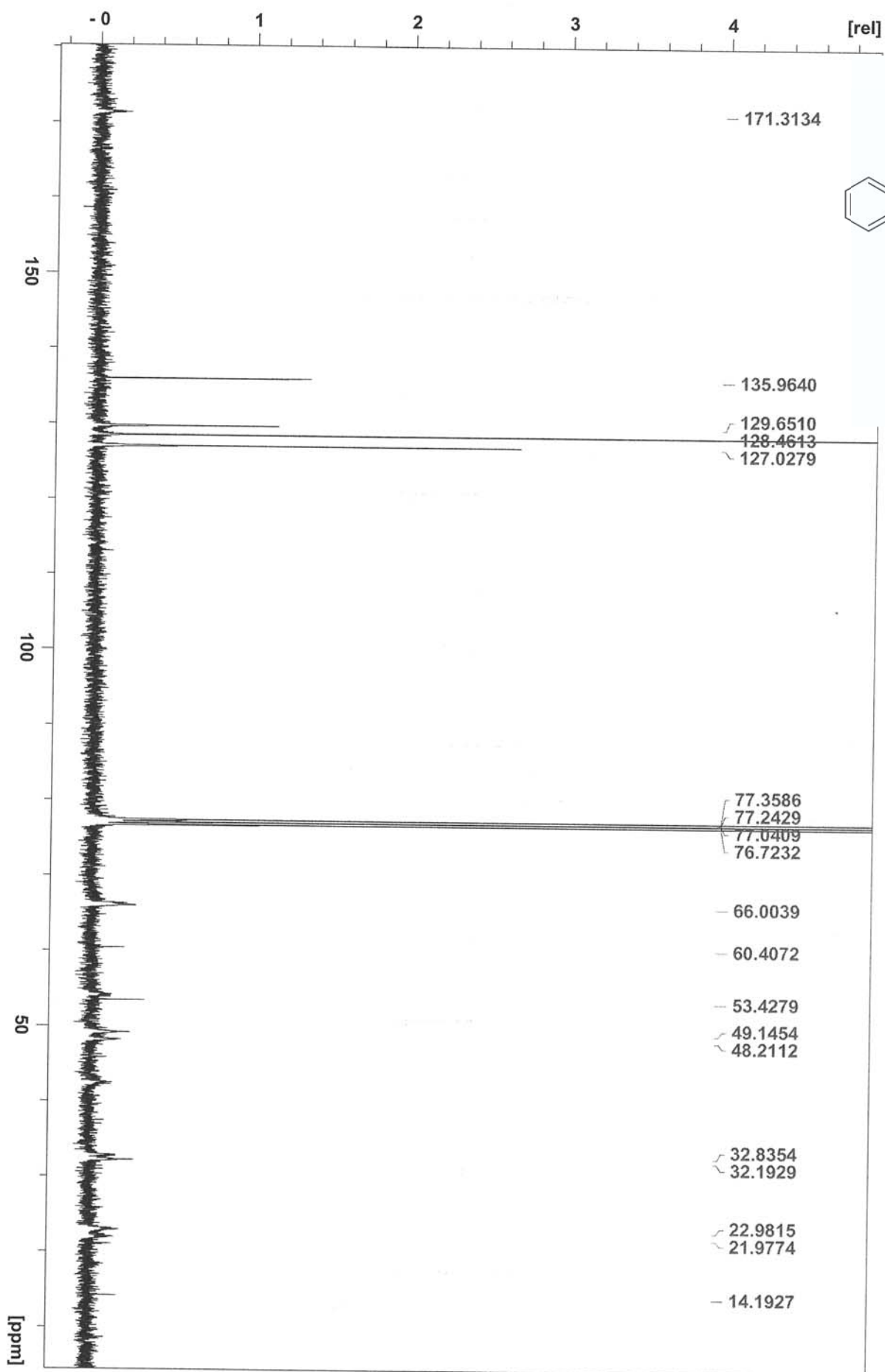


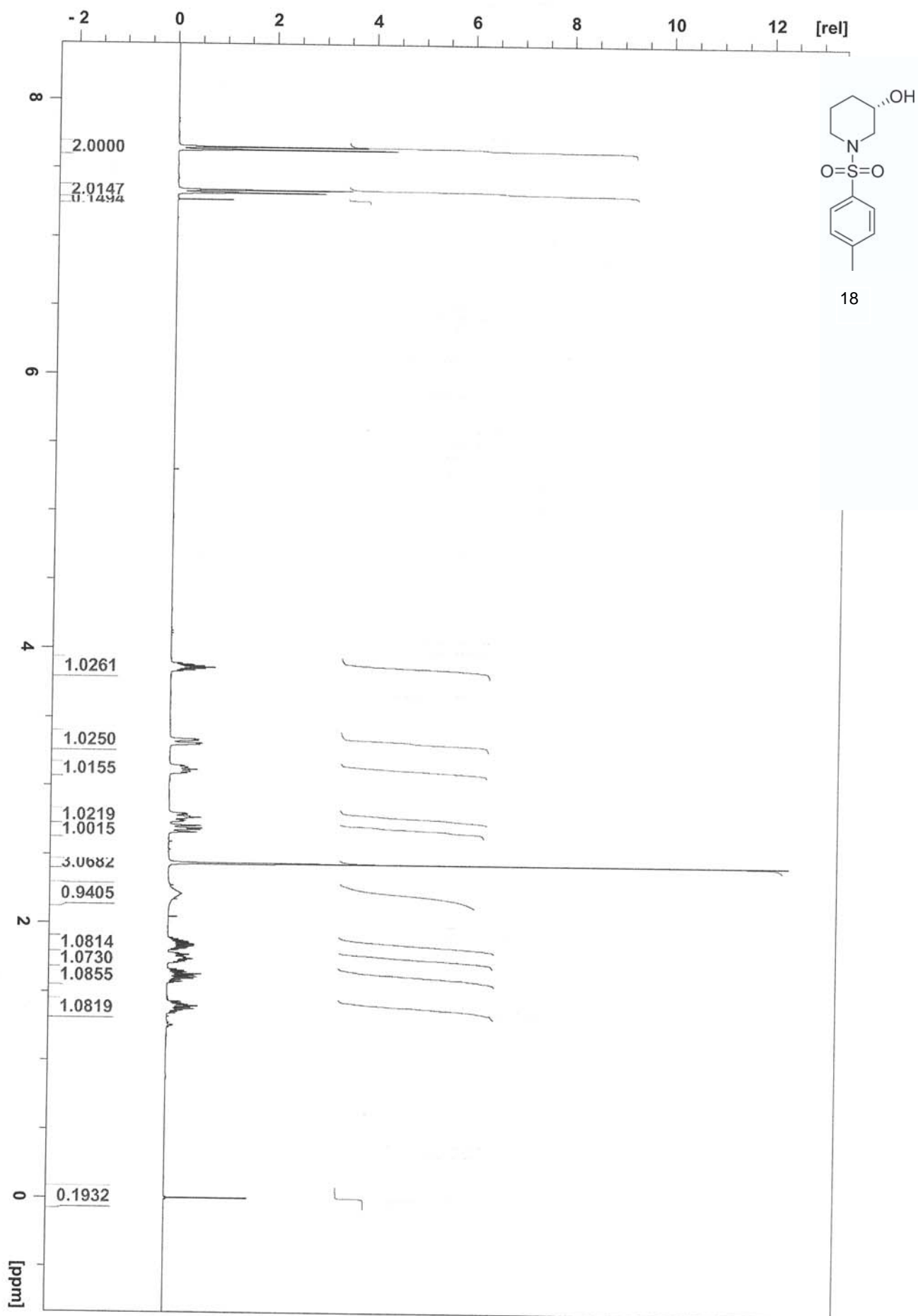


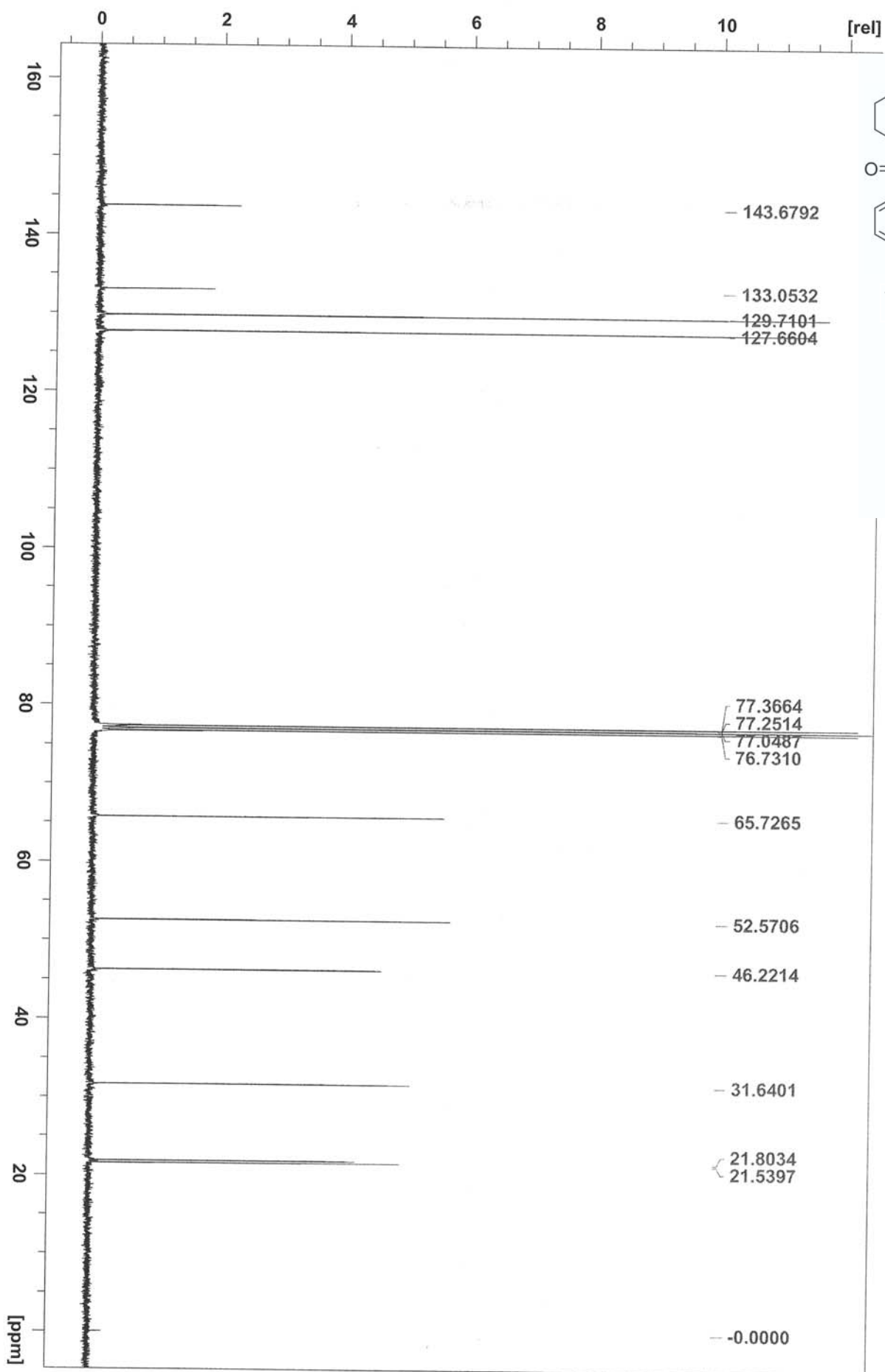


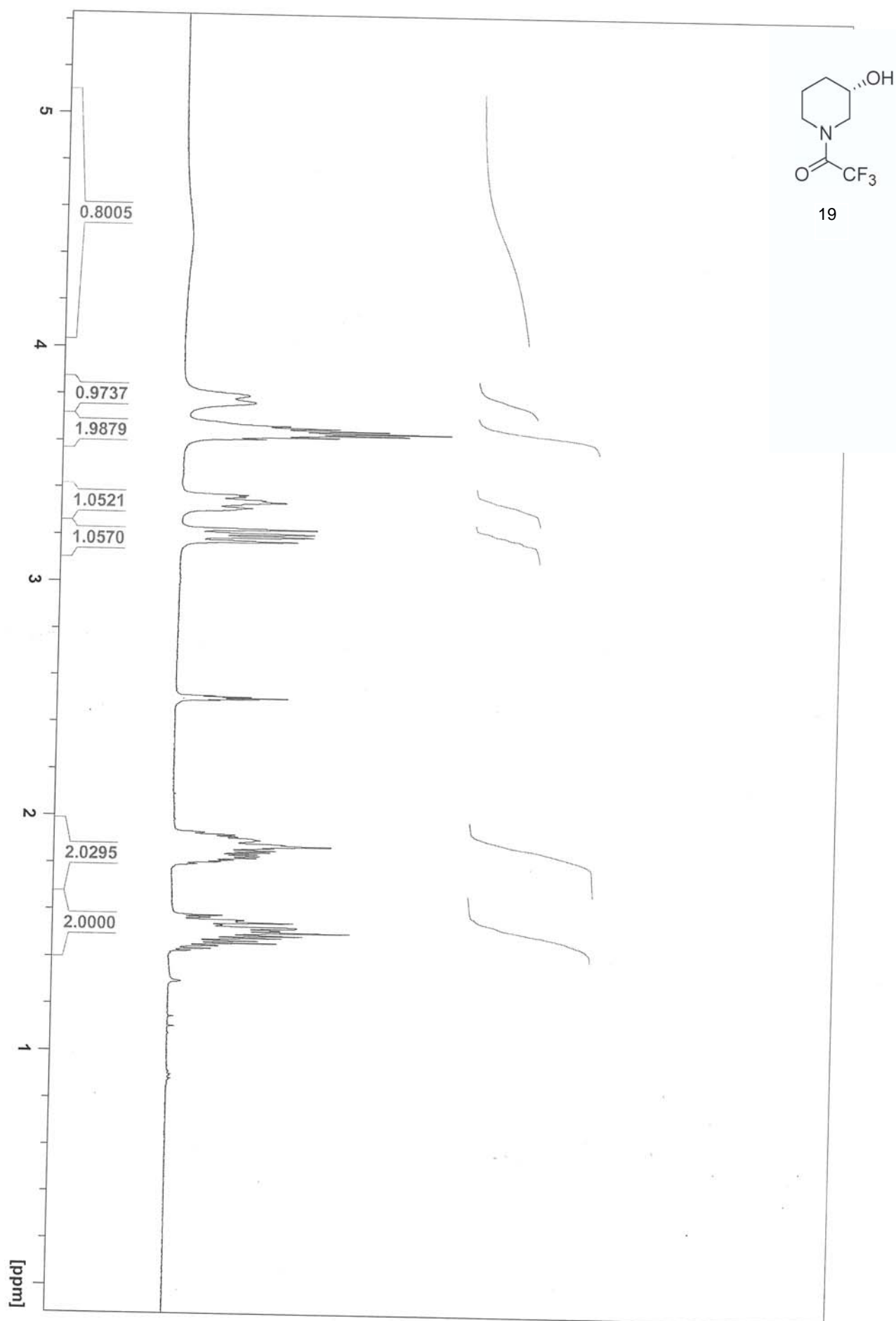


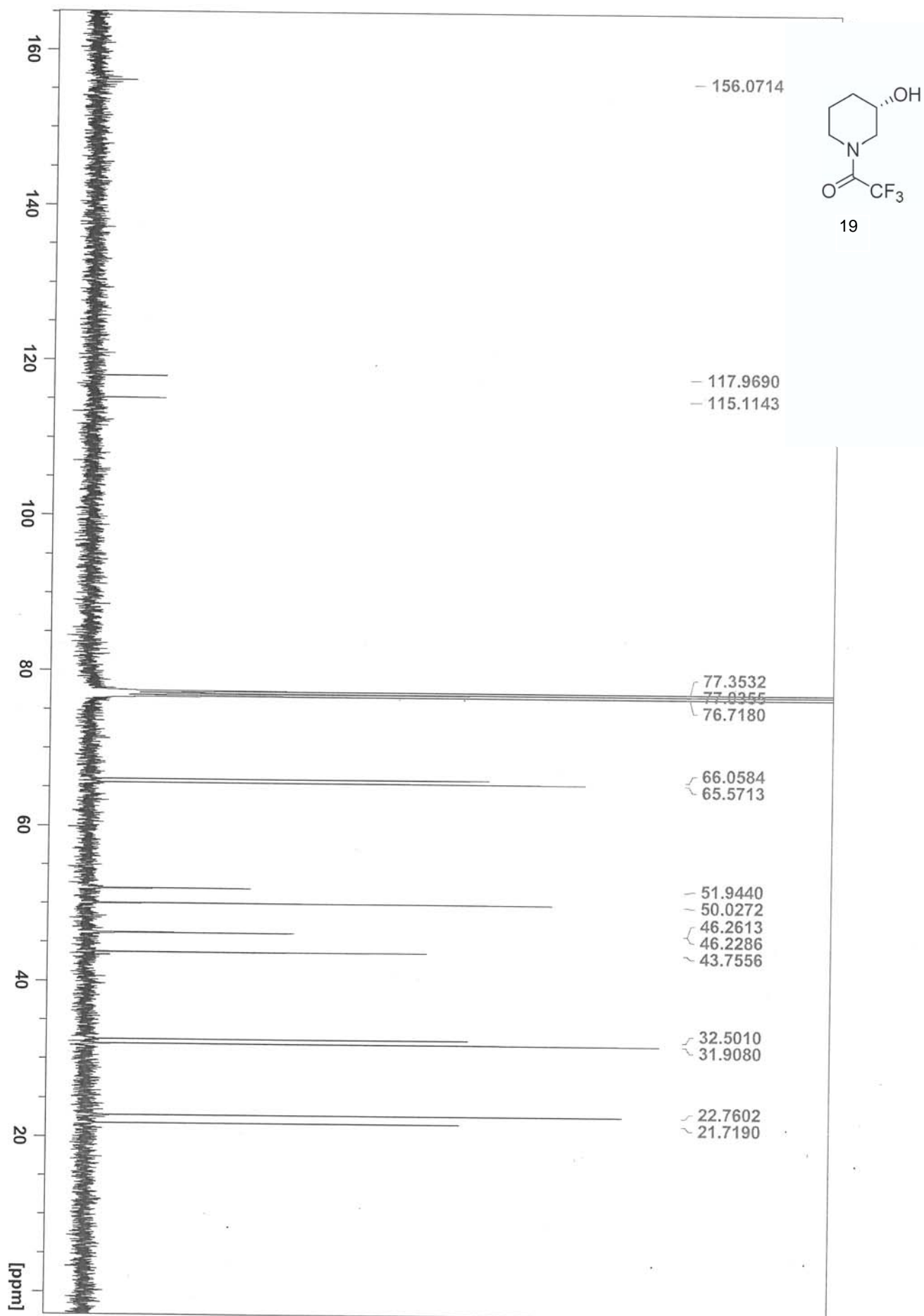
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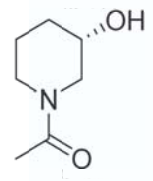
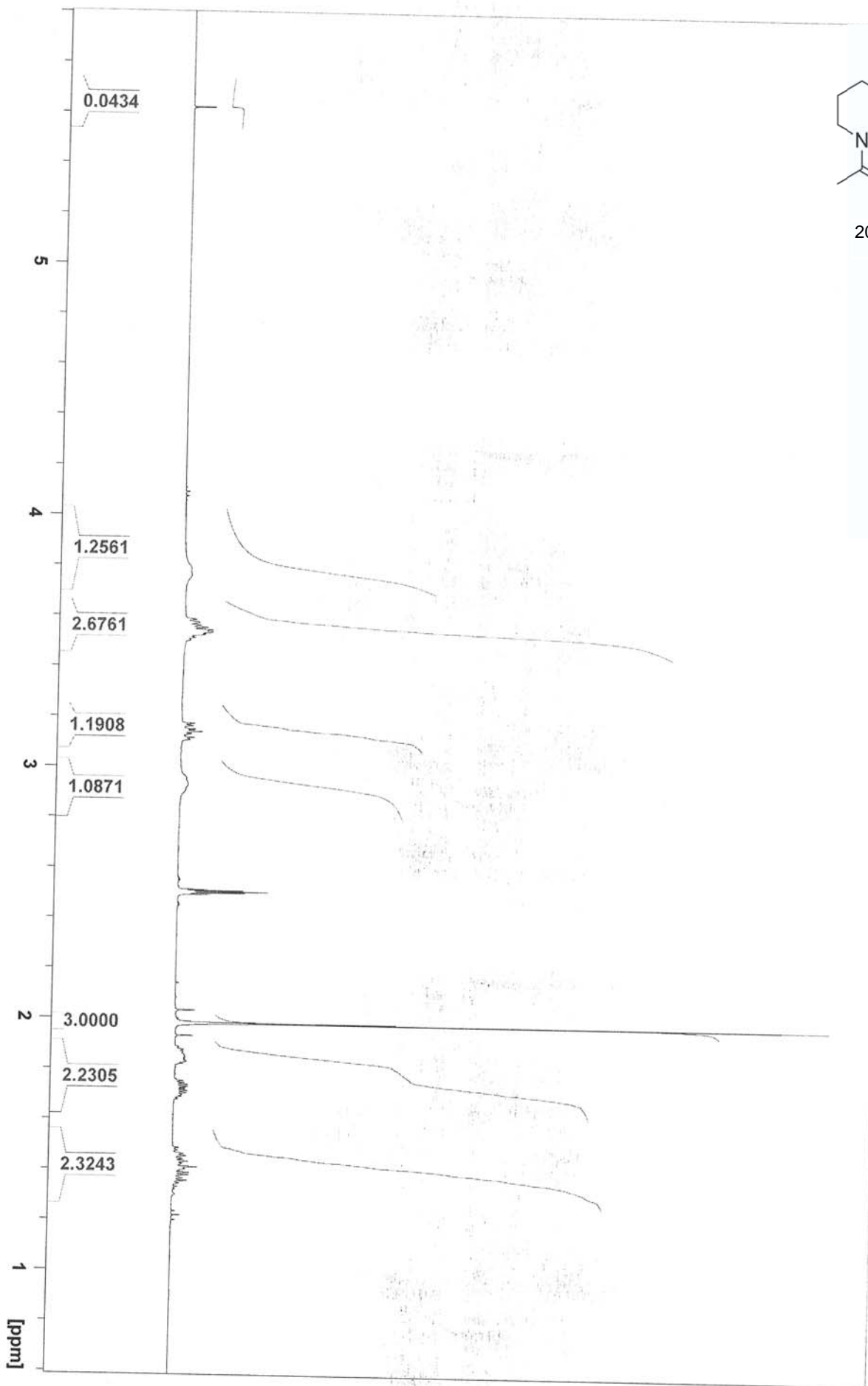




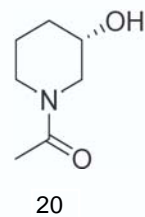
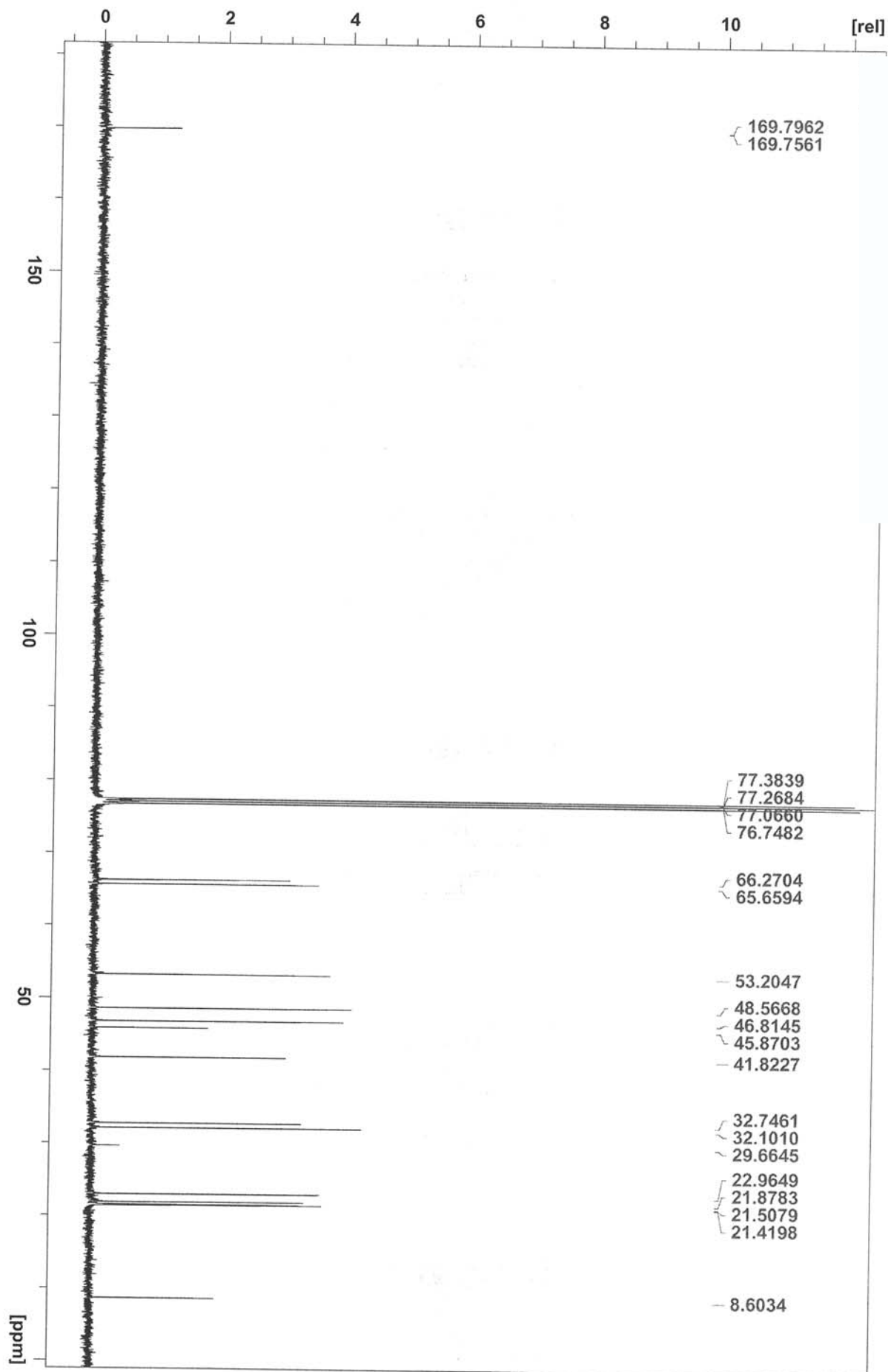


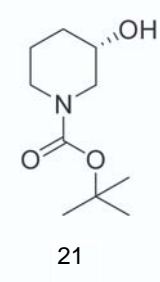
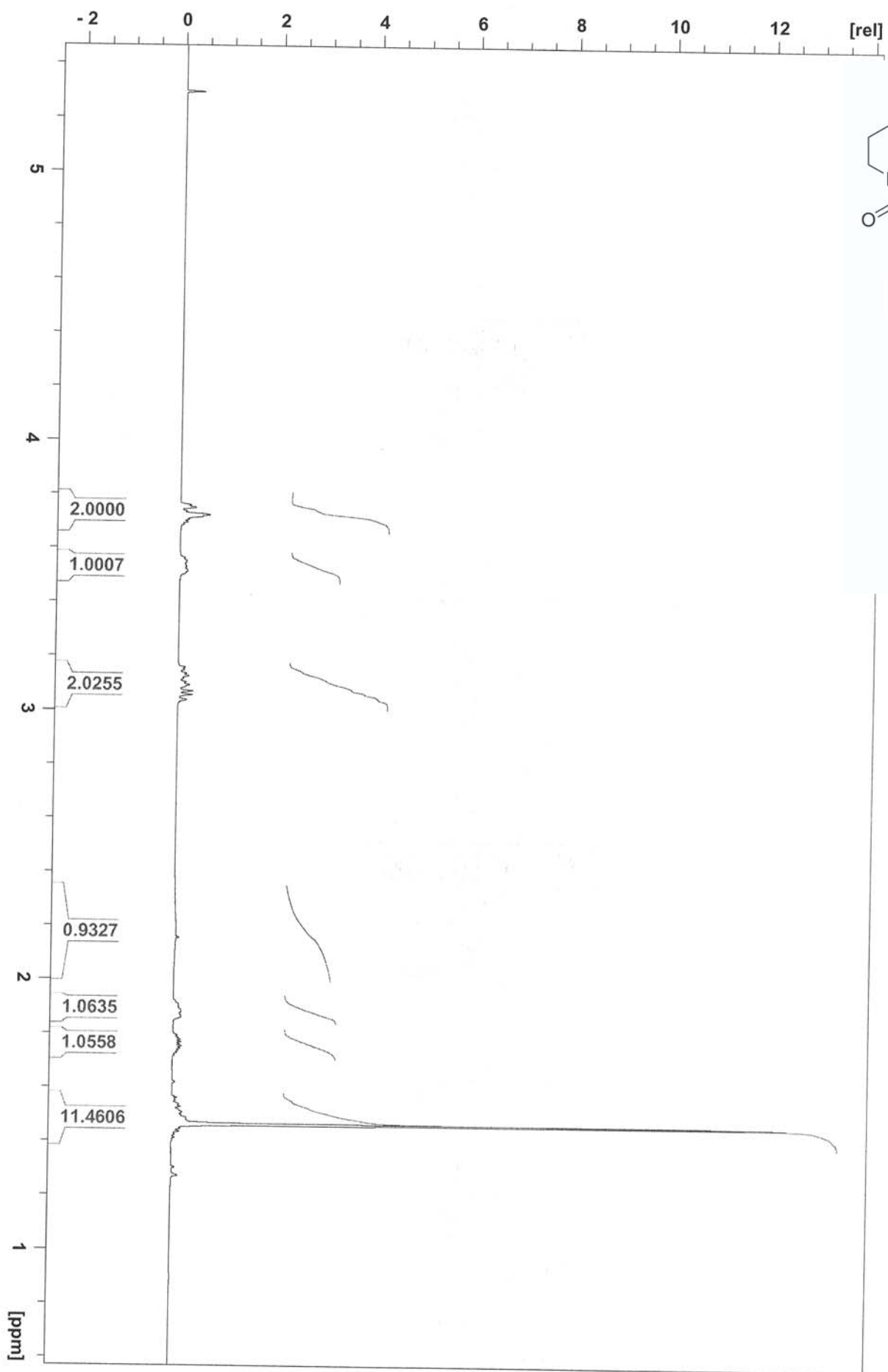


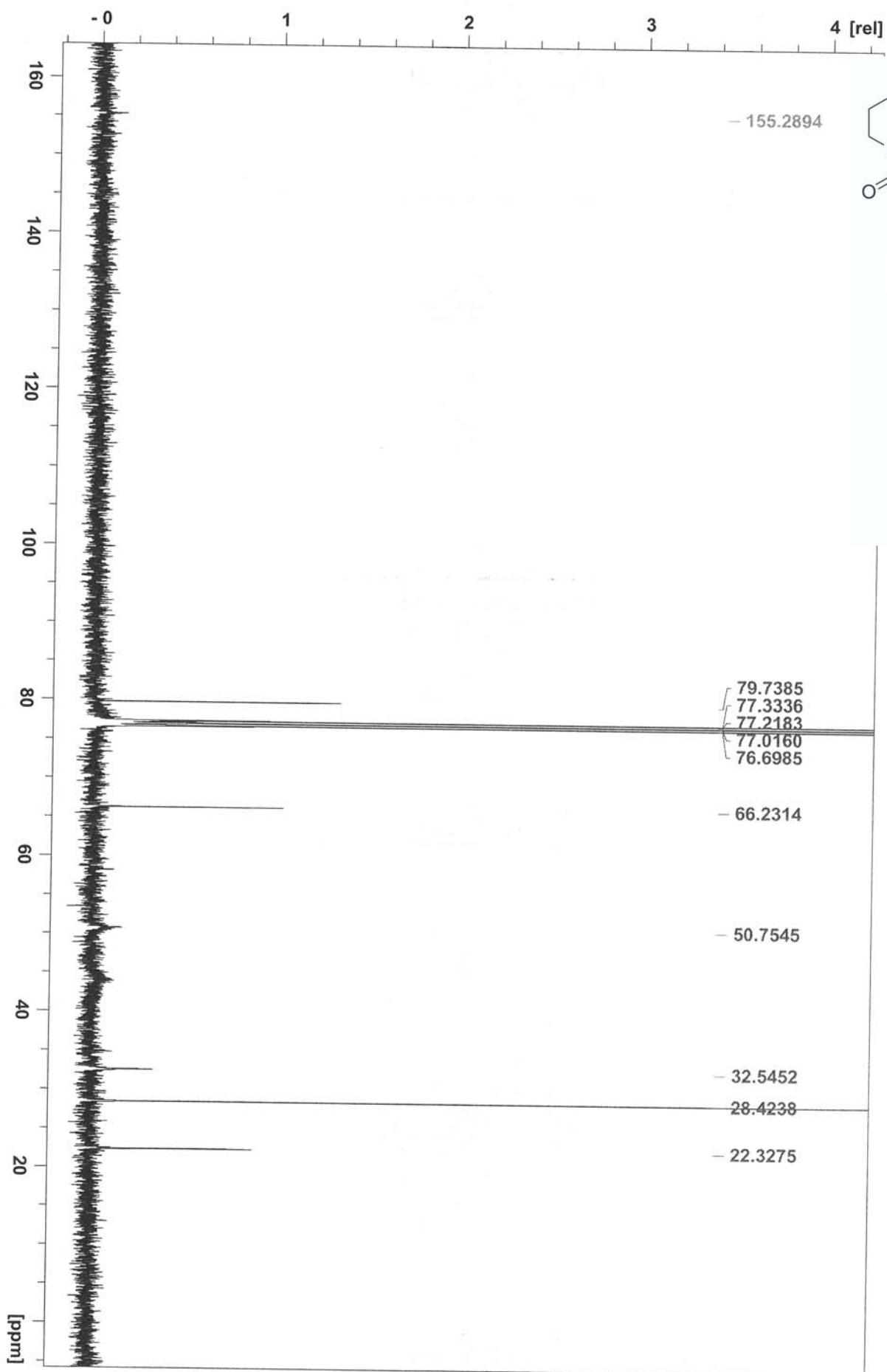


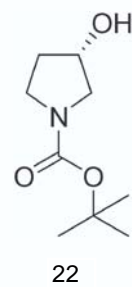
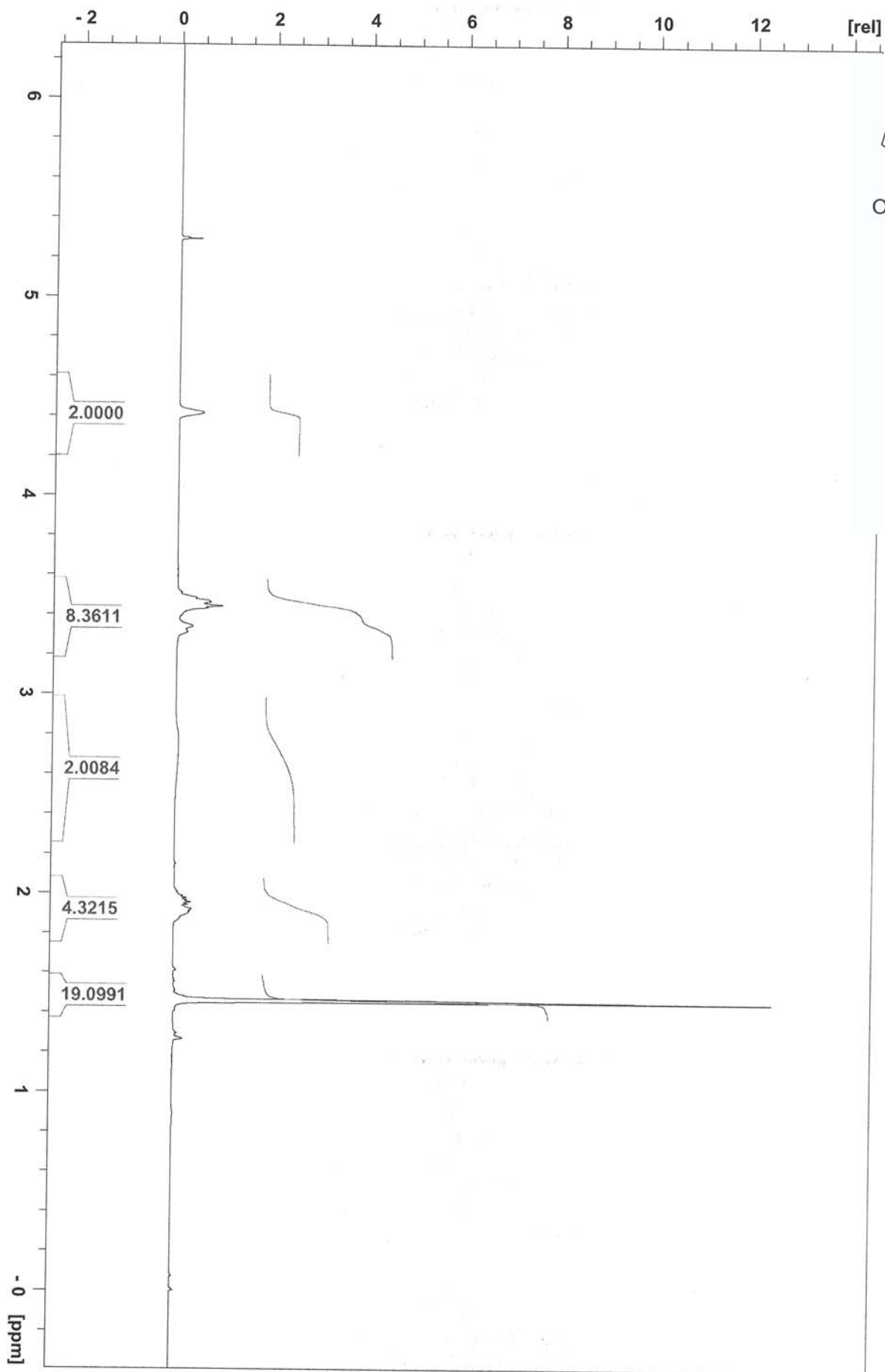


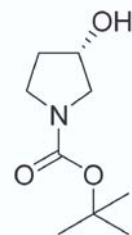
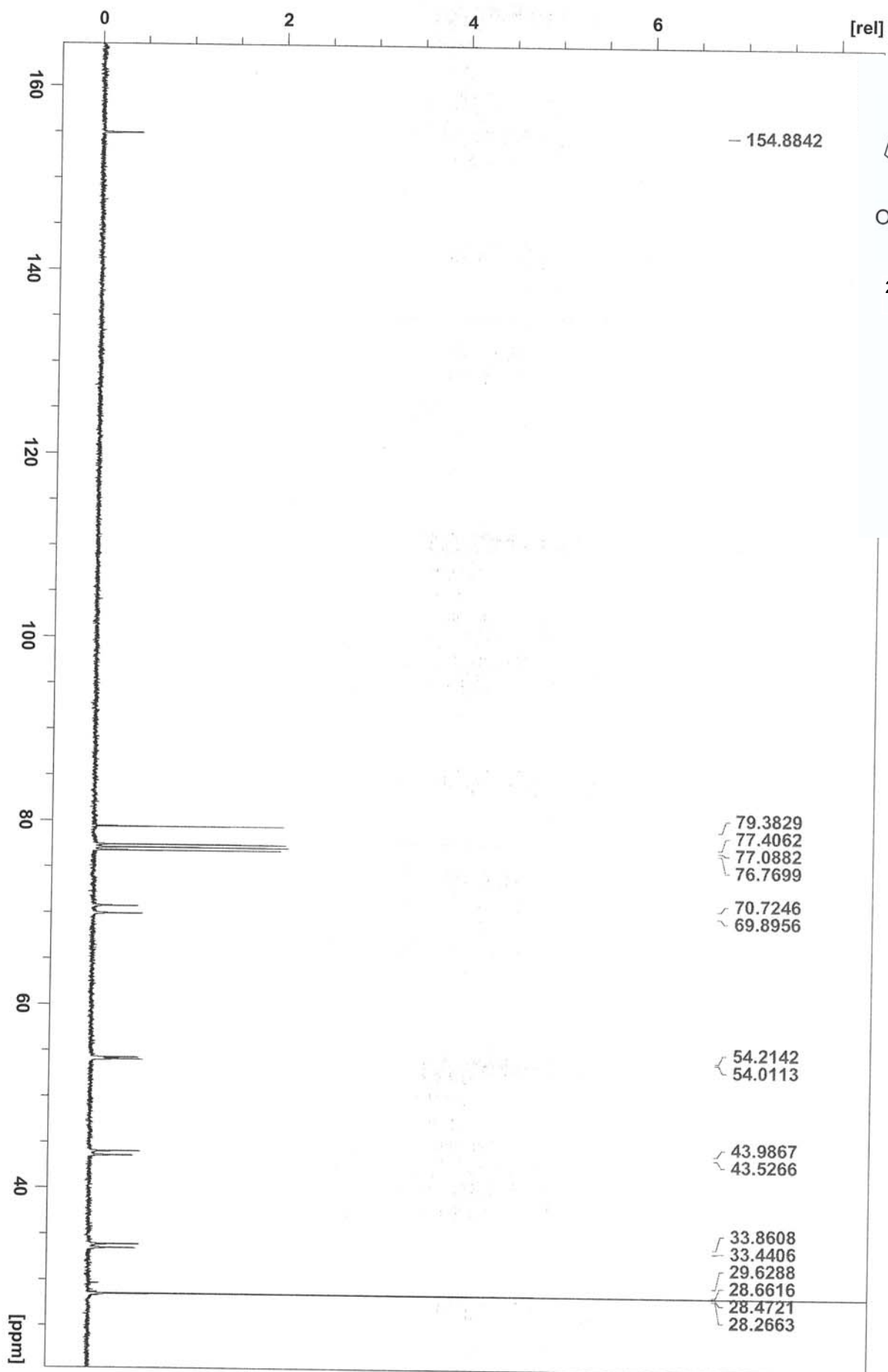
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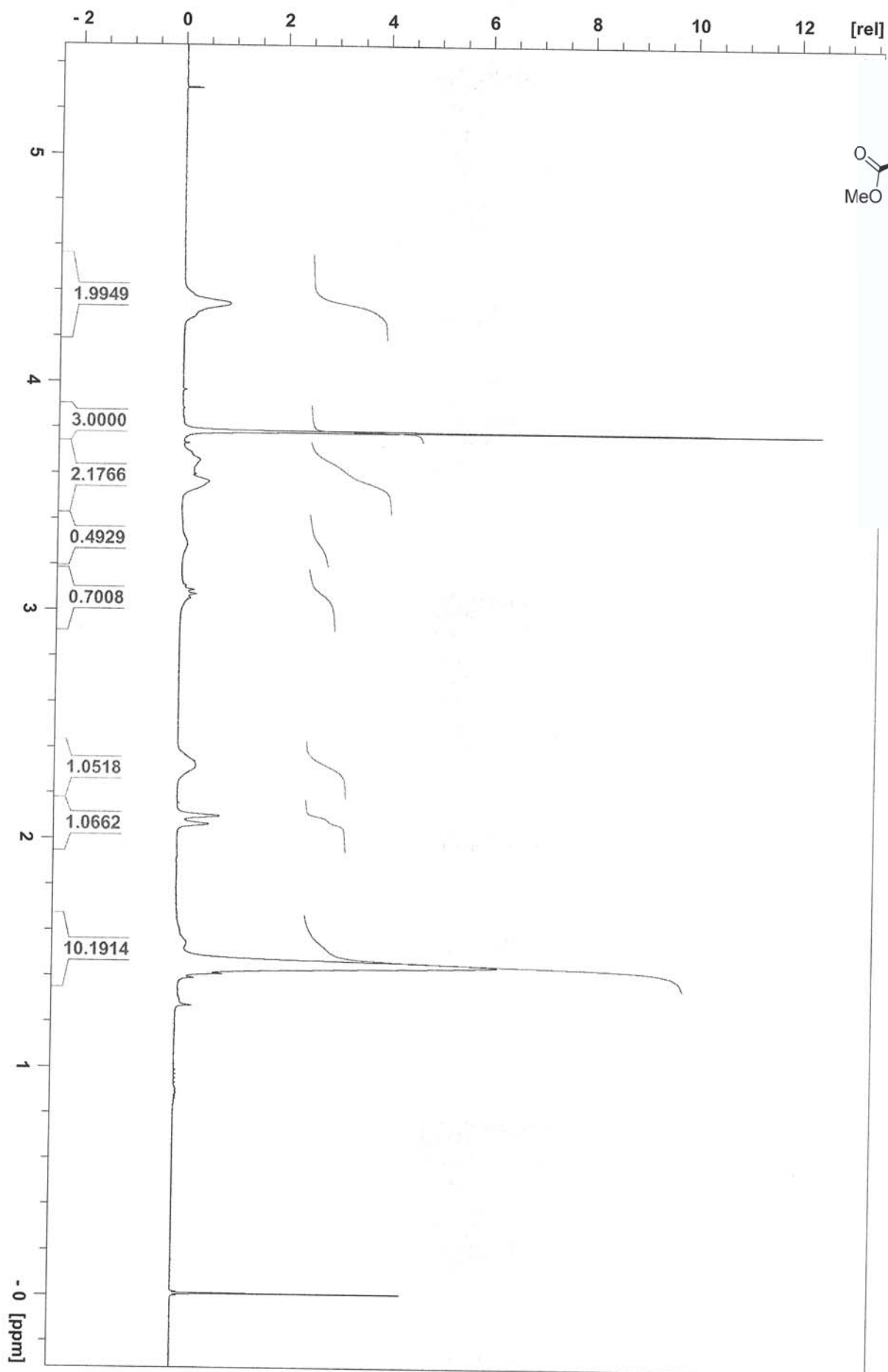


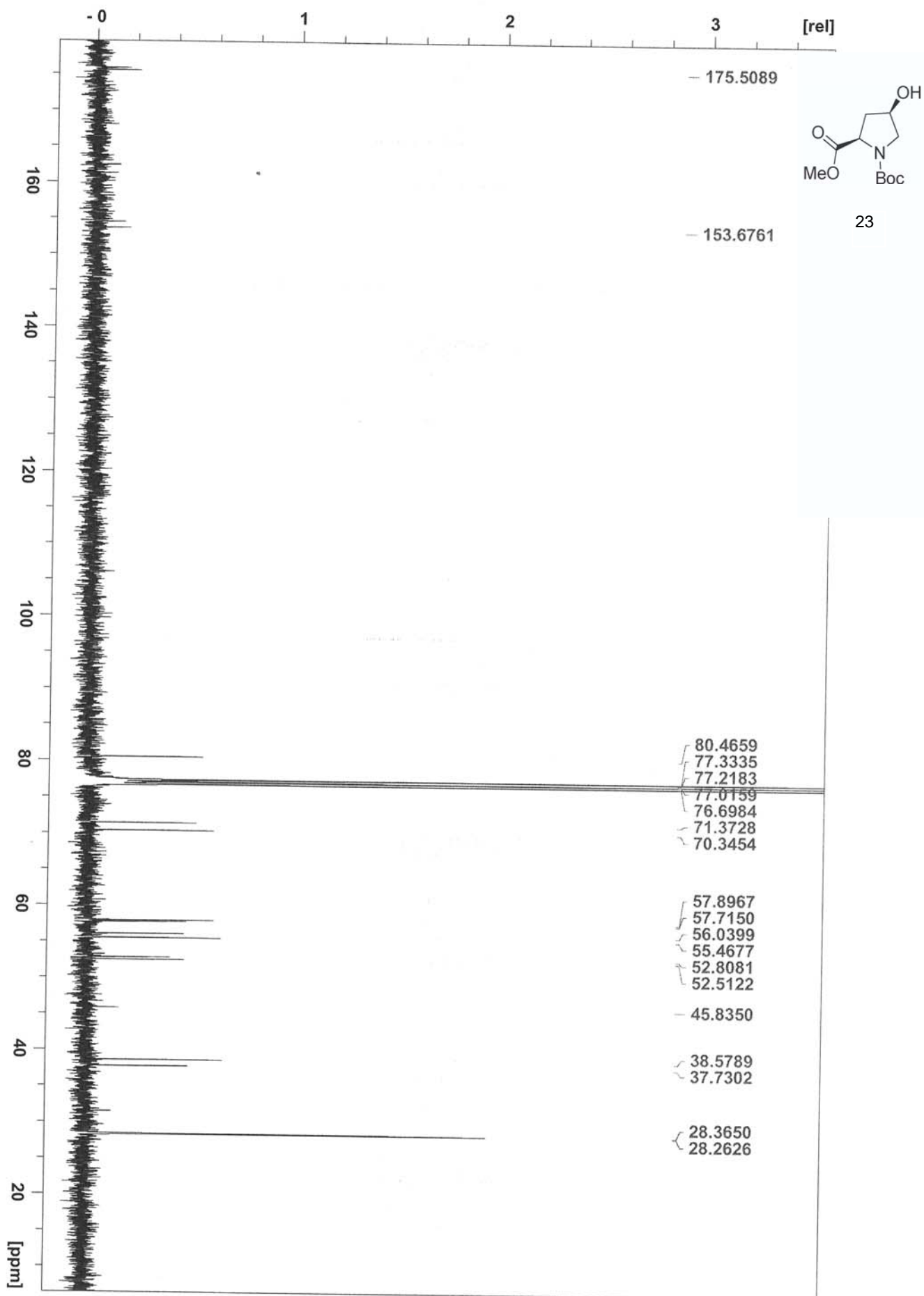


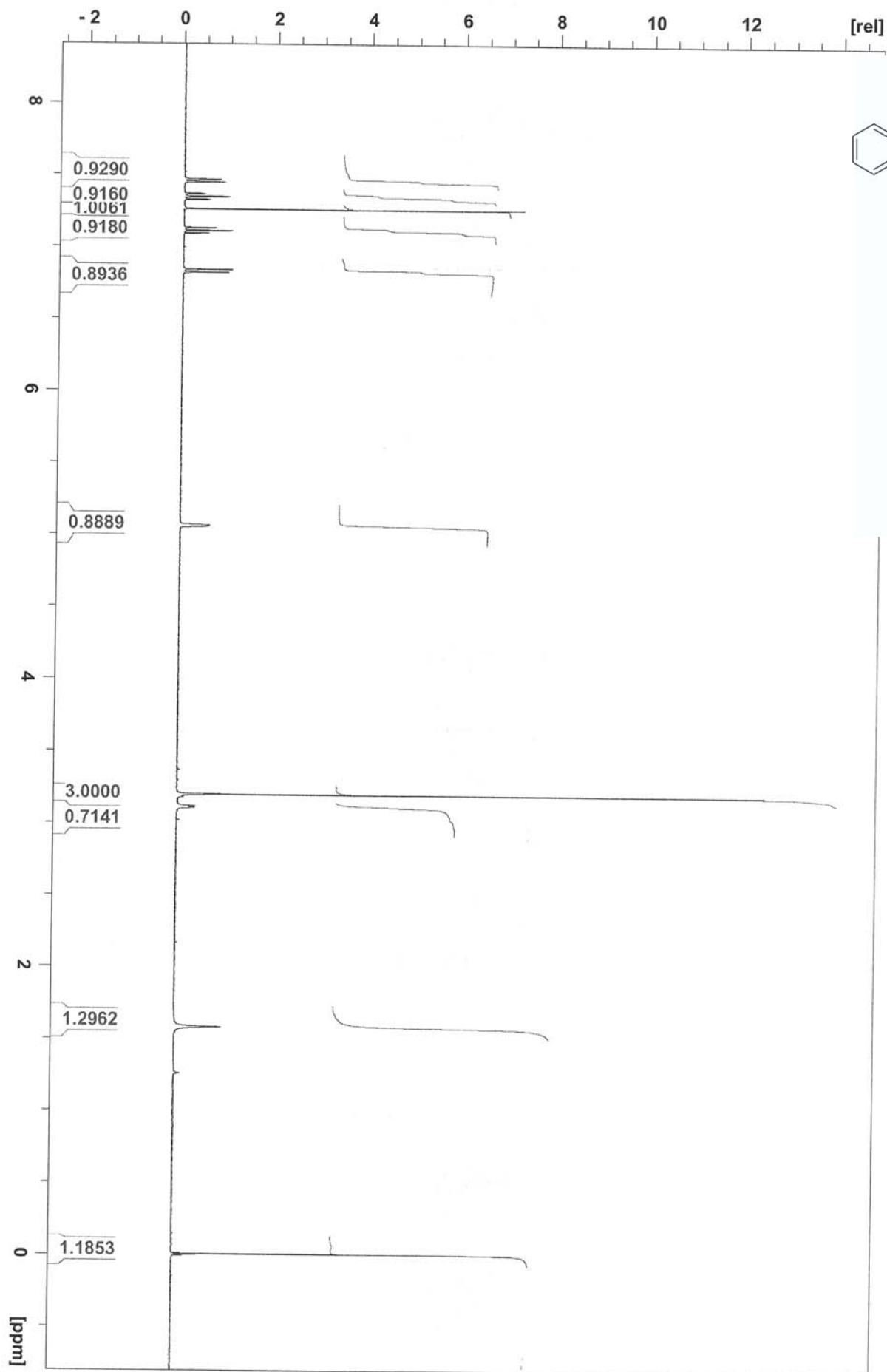


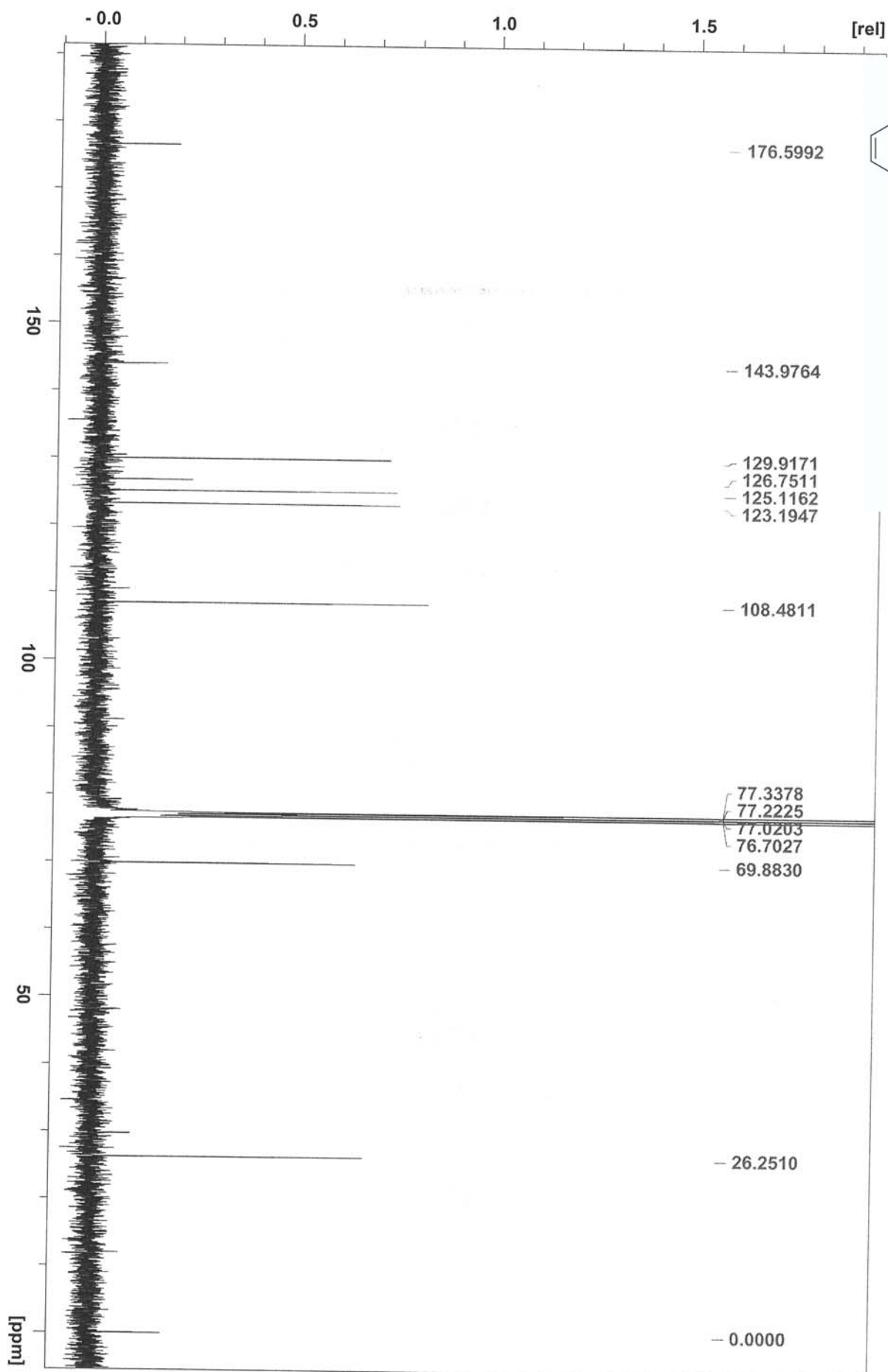


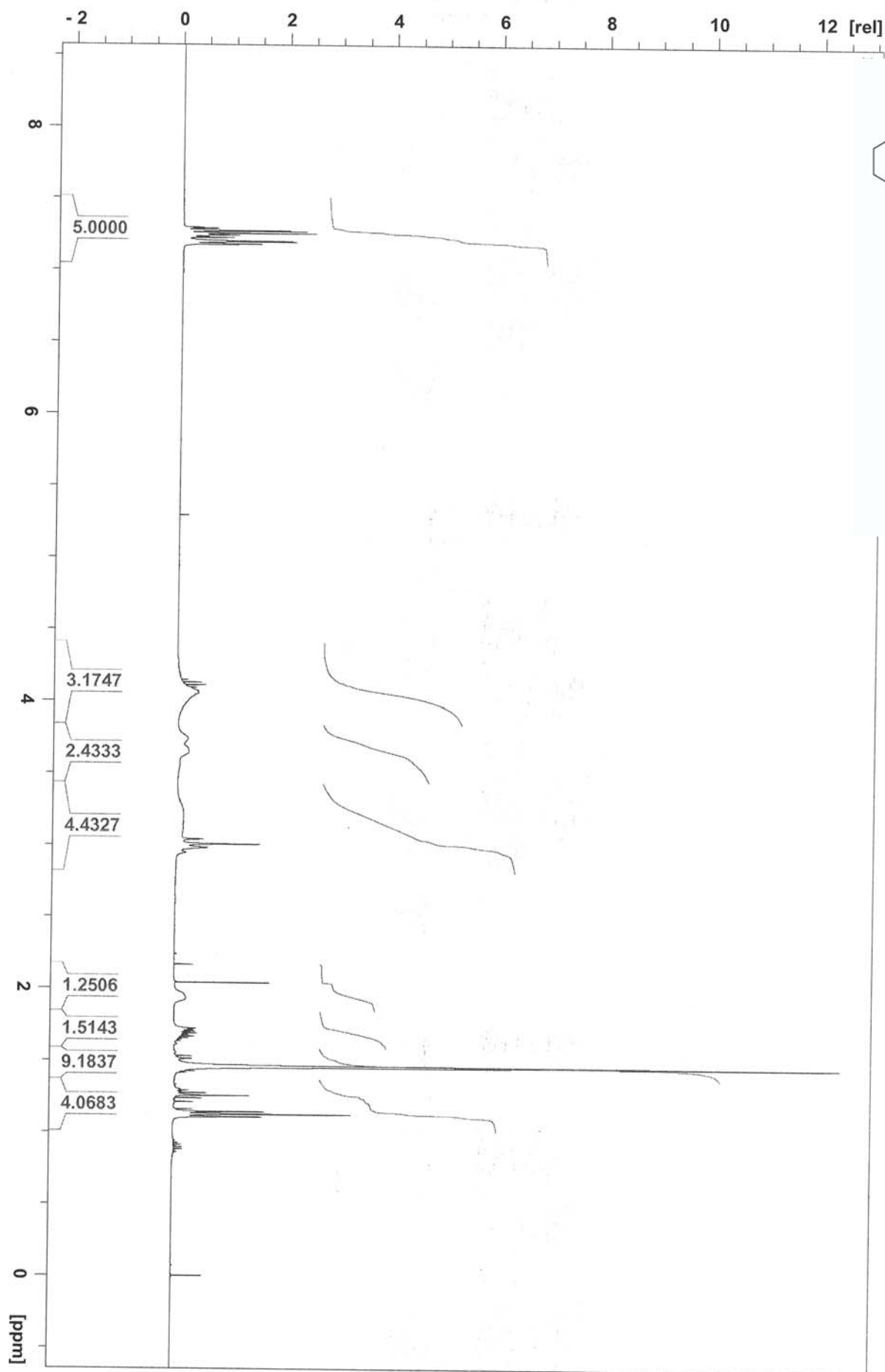
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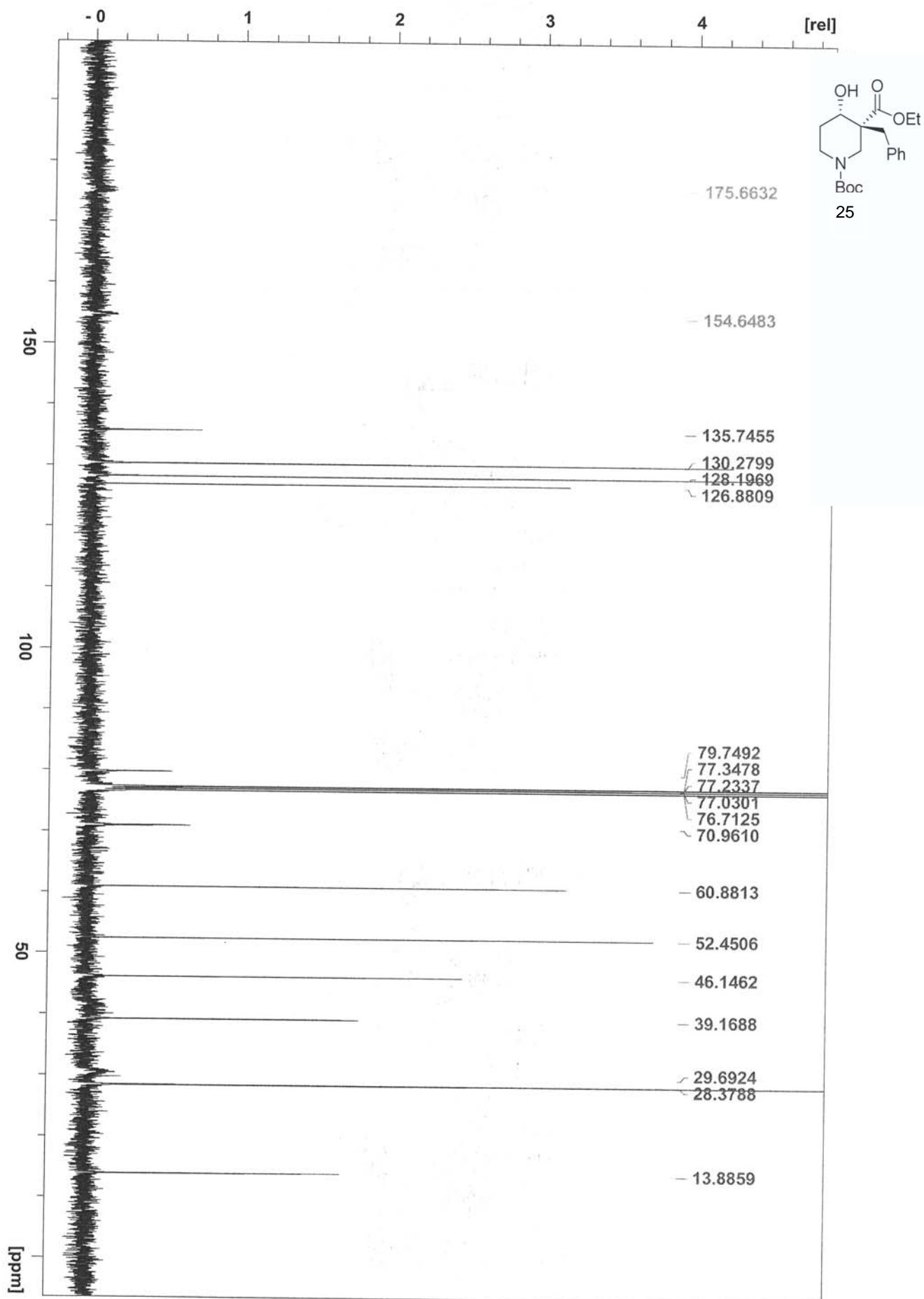


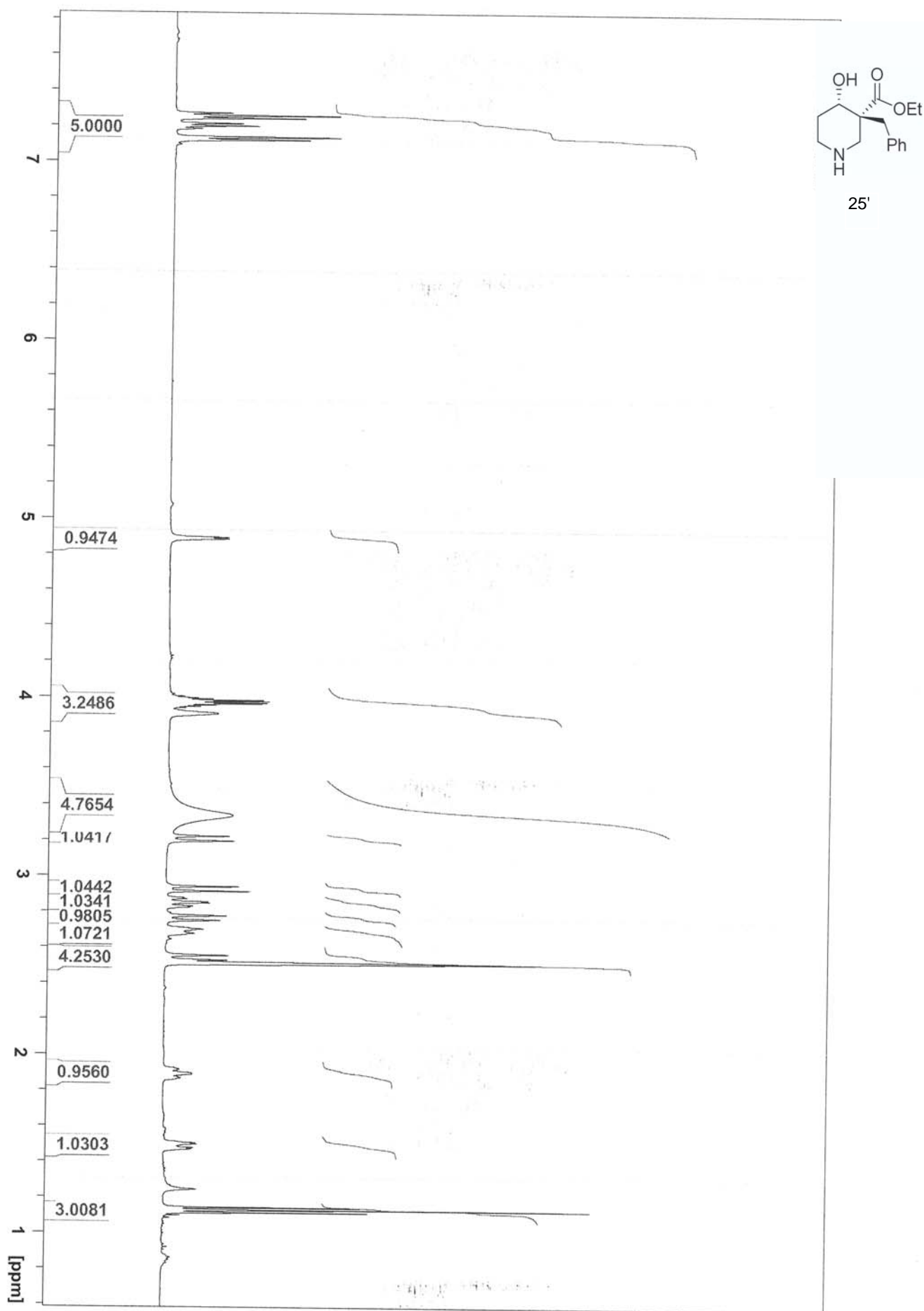


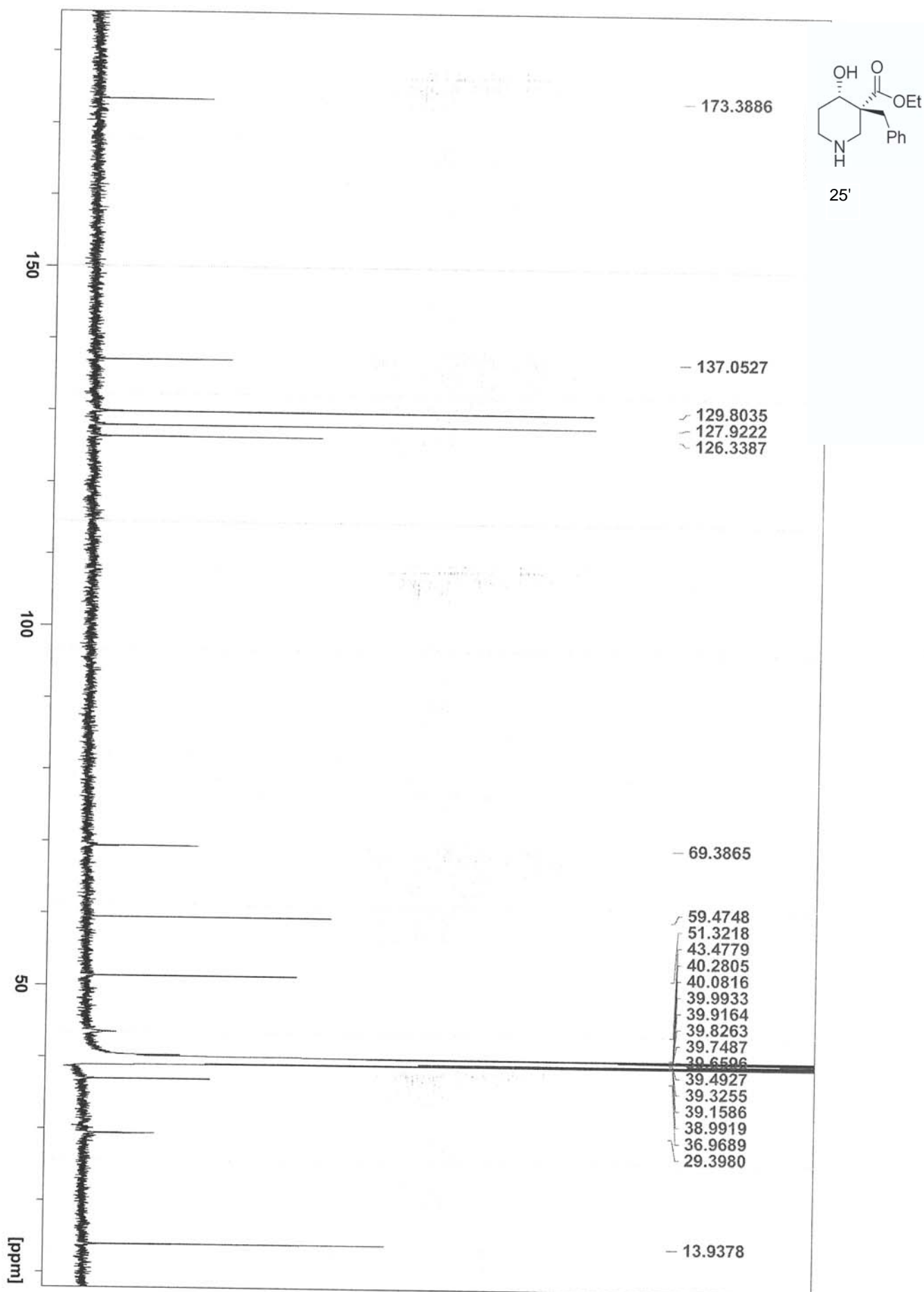


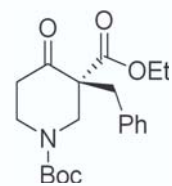
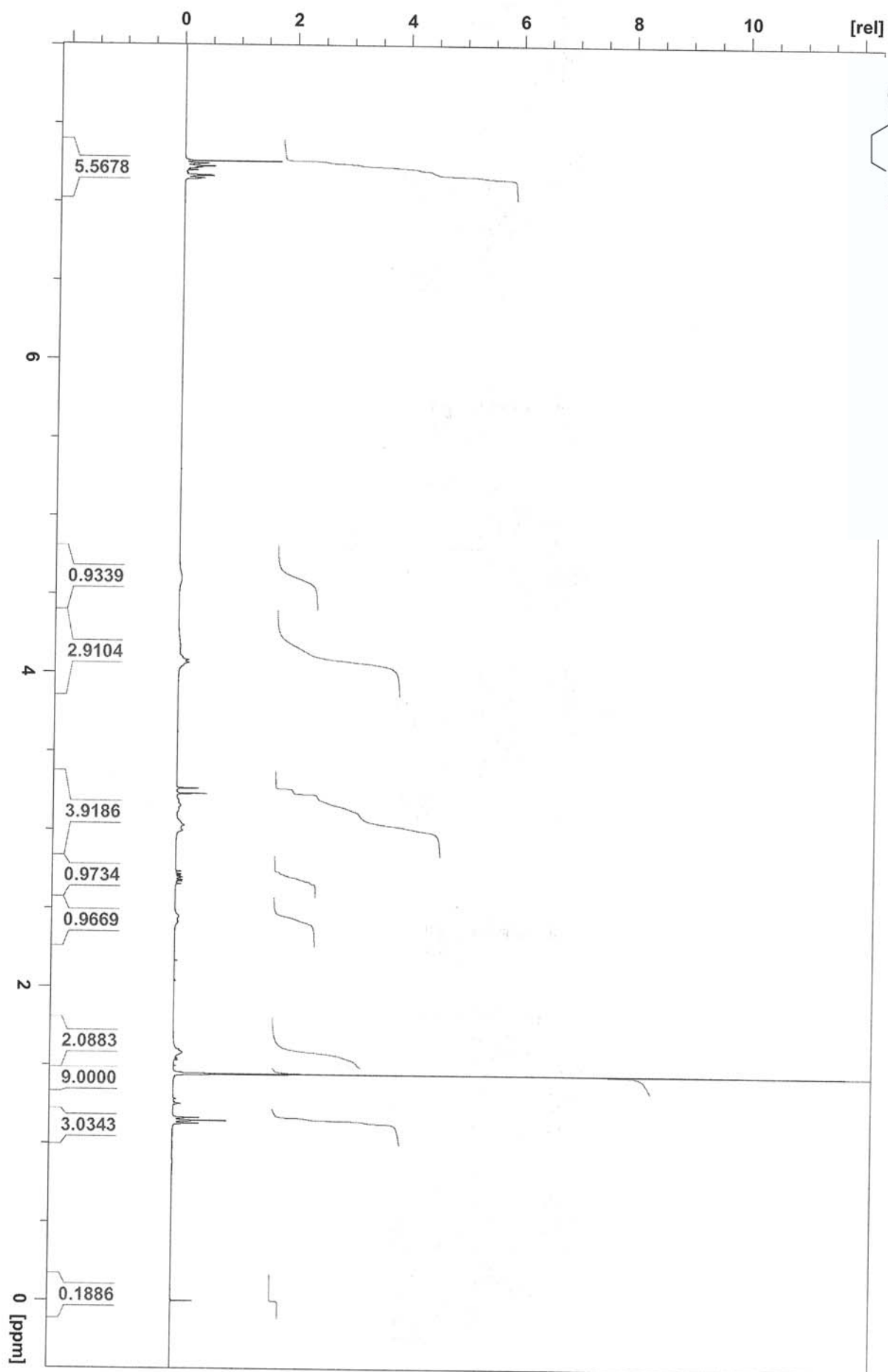












26

