

## Supporting Information

### Structure-Activity Relationships of Cyclic Lactam Analogues of $\alpha$ -Melanocyte Stimulating Hormone ( $\alpha$ -MSH) Targeting the Human Melanocortin-3 Receptor.

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#### Contents:

1. NMR procedures
2. The list of the sequences of peptides **4-15**
3.  $^1\text{H}$  NMR spectra of peptide analogues **4-15** in  $\text{DMSO-d}_6$  and the list of chemical shifts and coupling constants.

## NMR experiments.

NMR samples were prepared in DMSO-*d*<sub>6</sub> with an approximate peptide concentration of 3.0 mM. The <sup>1</sup>H spectra were recorded on a Varian Inova 600 spectrometer at 599.6995 MHz and 25°C using a Varian 5mm inverse HCN cryogenic probe with single axis gradient, and were processed using the VNMR (Varian) and the Mestre-C (Mestrelab Research, Spain) software packages. Chemical shifts are referenced to the DMSO signal at 2.50 ppm.

- 4 c[CO-*o*-C<sub>6</sub>H<sub>4</sub>-CO-Pro-*D*-Phe-Arg-Trp-Lys]-NH<sub>2</sub>
- 5 c[CO-*o*-C<sub>6</sub>H<sub>4</sub>-CO-Pro-*D*-Nal(2')-Arg-Trp-Lys]-NH<sub>2</sub>
- 6 c[CO-(CH<sub>2</sub>)<sub>3</sub>-CO-Pro-*D*-Phe-Arg-Trp-Lys]-NH<sub>2</sub>
- 7 c[CO-(CH<sub>2</sub>)<sub>3</sub>-CO-Pro-*D*-Nal(2')-Arg-Trp-Lys]-NH<sub>2</sub>
- 8 c[CO-*cis*-CH=CH-CO-Pro-*D*-Phe-Arg-Trp-Lys]-NH<sub>2</sub>
- 9 c[CO-*cis*-CH=CH-CO-Pro-*D*-Nal(2')-Arg-Trp-Lys]-NH<sub>2</sub>
- 10 c[CO-2,6-pyridine-CO-*D*-Phe-Arg-Trp-Lys]-NH<sub>2</sub>
- 11 c[CO-2,6-pyridine-CO-*D*-Nal(2')-Arg-Trp-Lys]-NH<sub>2</sub>
- 12 c[CO-2,3-pyrazine-CO-*D*-Phe-Arg-Trp-Lys]-NH<sub>2</sub>
- 13 c[CO-2,3-pyrazine-CO-*D*-Nal(2')-Arg-Trp-Lys]-NH<sub>2</sub>
- 14 c[CO-(CH<sub>2</sub>)<sub>2</sub>-CO-Nle-*D*-Phe-Arg-Trp-Lys]-NH<sub>2</sub>
- 15 c[CO-(CH<sub>2</sub>)<sub>2</sub>-CO-Nle-*D*-Nal(2')-Arg-Trp-Lys]-NH<sub>2</sub>

Pro<sup>5</sup>-ω *cis/trans* rotamers were observed for the analogues 4 through 8 with the following ratios:

- 4: 13% (1:0.15)
- 5: 7% (1:0.07)
- 6: 50% (1:1)
- 7: 50% (1:1)
- 8: 41% (1:0.7)

**4 c[CO-*o*-C<sub>6</sub>H<sub>4</sub>-CO-Pro-*D*-Phe-Arg-Trp-Lys]-NH<sub>2</sub>** (56 observable hydrogens)

$\alpha$ -Hydrogens (5):

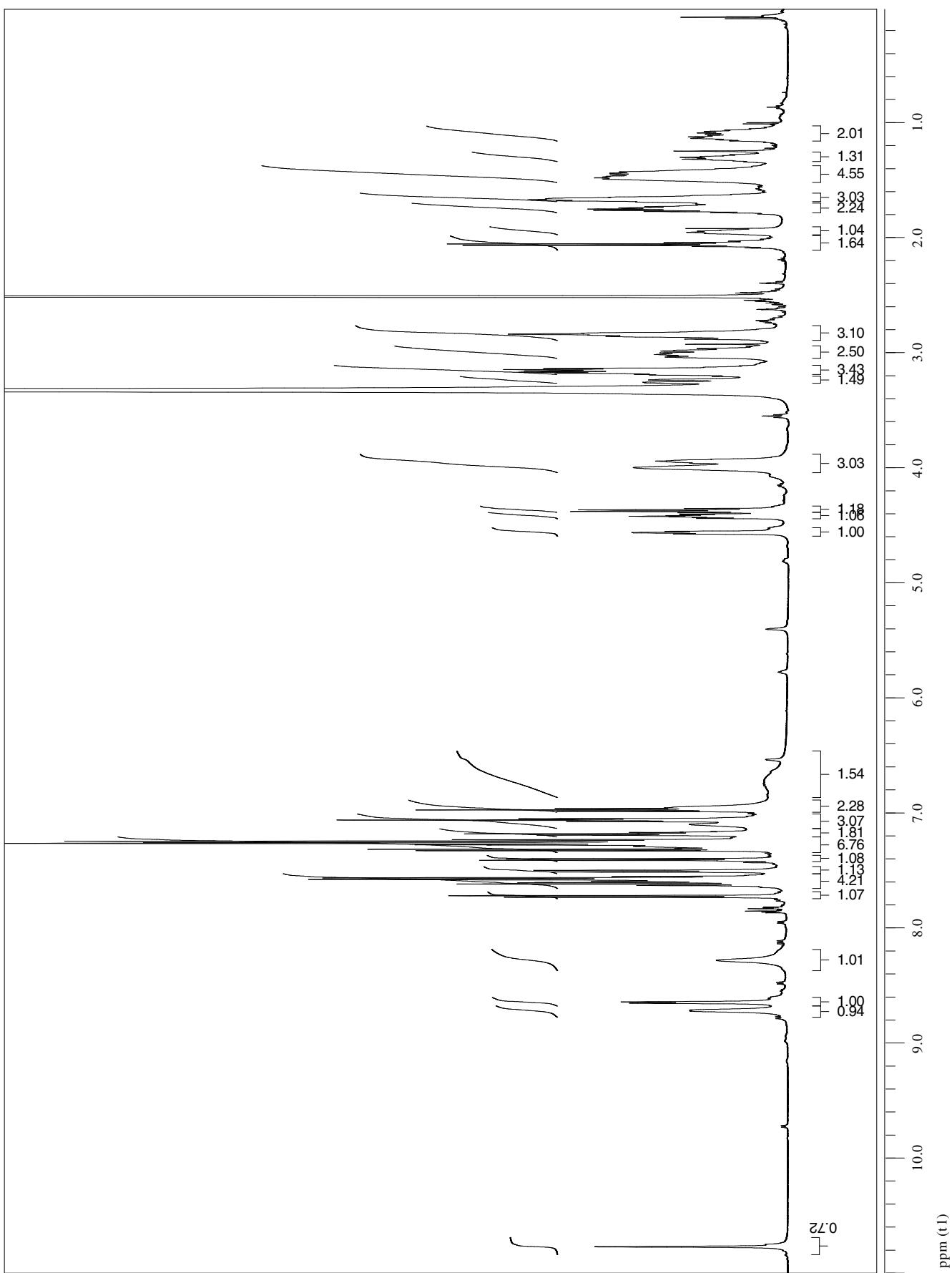
3.99 (2H, m)  
4.36 (1H, dd, *J*=7.0, 15.1 Hz)  
4.41 (1H, ddd, *J*=4.2, 7.9, 11.8 Hz)  
4.55 (1H, dd, *J*=1.4, 5.7 Hz)

Side chain hydrogens (24):

1.09 (2H, m)  
1.30 (1H, m)  
1.45 (4H, m)  
1.67 (3H, m)  
1.74 (2H, m)  
1.94 (1H, m)  
2.05 (1H, m)  
2.83 (3H, m)  
3.00 (2H, m)  
3.15 (3H, m)  
3.24 (1H, dd, *J*=2.6, 14.6 Hz)  
3.93 (1H, m)

Amide and aromatic hydrogens (27):

6.26-7.50 (3H, broad singlets)  
6.97 (1H, t, *J*=7.4 Hz)  
7.06 (2H, t, *J*=7.5 Hz)  
7.09 (1H, s)  
7.17 (2H, m)  
7.23-7.30 (6H, m)  
7.32 (1H, d, *J*=8.1 Hz)  
7.40 (1H, dd, *J*=0.7, 7.5 Hz)  
7.50 (1H, d, *J*=7.8 Hz)  
7.57 (3H, m)  
7.61 (1H, dt, *J*=1.0, 7.5 Hz)  
7.72 (1H, d, *J*=7.6 Hz)  
8.28 (1H, s)  
8.64 (1H, d, *J*=6.5 Hz)  
8.71 (1H, d, *J*=5.3 Hz)  
10.77 (1H, s)



**5 c[CO-o-C<sub>6</sub>H<sub>4</sub>-CO-Pro-D-Nal(2')-Arg-Trp-Lys]-NH<sub>2</sub>** (58 observable hydrogens)

$\alpha$ -Hydrogens (5):

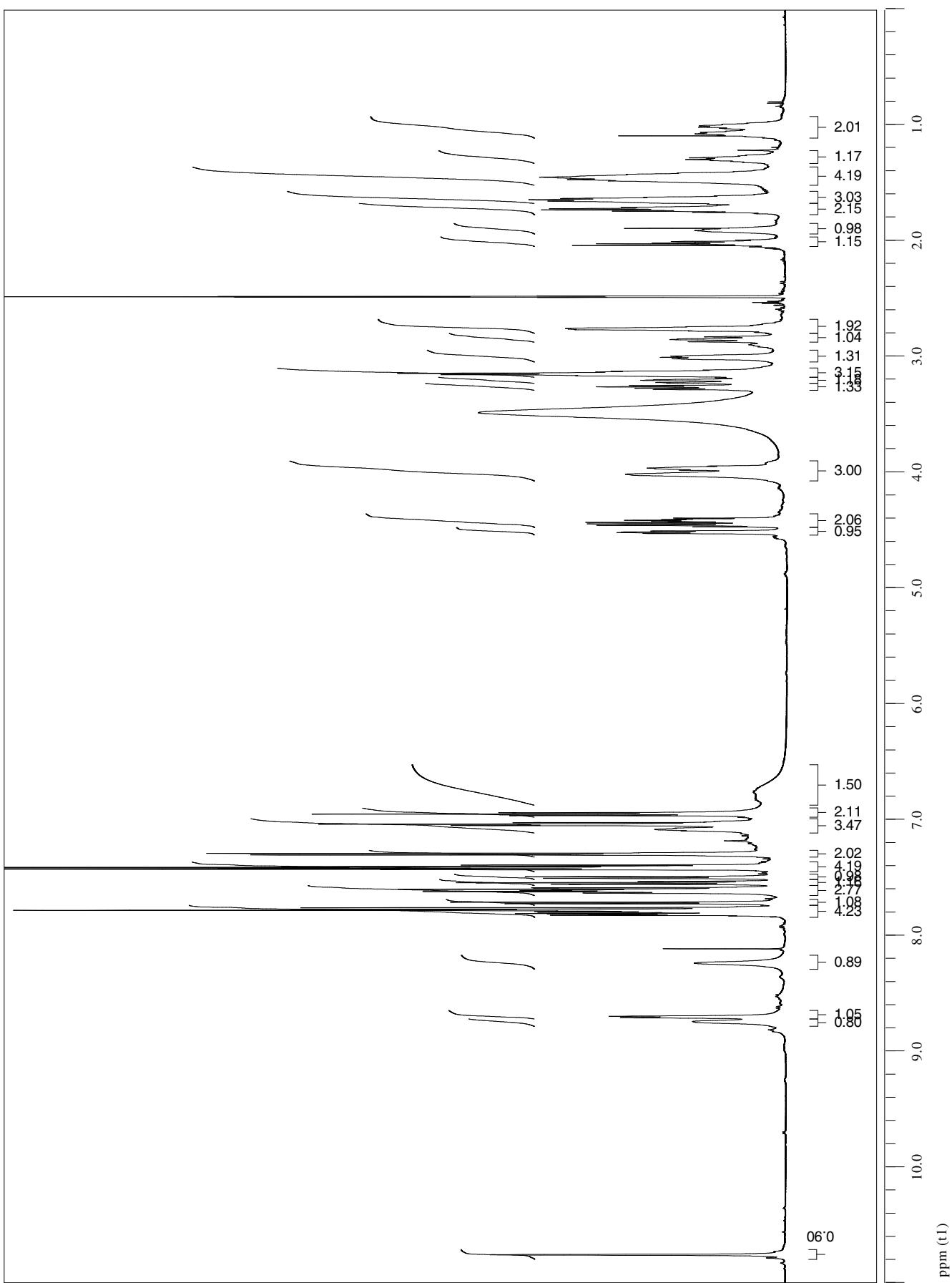
4.01 (2H, m)  
4.41 (1H, m)  
4.45 (1H, dd,  $J=7.2, 15.3$  Hz)  
4.51 (1H, dd,  $J=5.0, 7.8$  Hz)

Side chain hydrogens (24):

1.00 (1H, m)  
1.07 (1H, m)  
1.28 (1H, m)  
1.45 (4H, m)  
1.64 (3H, m)  
1.72 (2H, m)  
1.91 (1H, m)  
2.01 (1H, m)  
2.76 (2H, m)  
2.84 (1H, dd,  $J=11.1, 14.1$  Hz)  
3.00 (1H, m)  
3.14 (3H, m)  
3.21 (1H, dd,  $J=3.3, 14.4$  Hz)  
3.26 (1H, dd,  $J=6.1, 13.7$  Hz)  
3.96 (1H, m)

Amide and aromatic hydrogens (29):

6.23-7.88 (4H, broad singlets)  
6.95 (2H, t,  $J=7.4$  Hz)  
7.04 (2H, m)  
7.08 (1H, m)  
7.30 (1H, br.s)  
7.30 (1H, d,  $J=8.1$  Hz)  
7.39-7.43 (4H, m)  
7.50 (1H, d,  $J=7.9$  Hz)  
7.54 (1H, dt,  $J=1.2, 7.6$  Hz)  
7.60 (1H, dt,  $J=1.1, 7.5$  Hz)  
7.62 (2H, t,  $J=7.4$  Hz)  
7.72 (1H, d,  $J=7.6$  Hz)  
7.77 (1H, d,  $J=8.6$  Hz)  
7.78 (1H, s)  
7.79 (1H, dd,  $J=2.9, 6.2$  Hz)  
7.82 (1H, dd,  $J=3.5, 6.0$  Hz)  
8.24 (1H, s)  
8.70 (1H, d,  $J=6.7$  Hz)  
8.74 (1H, m)  
10.76 (1H, s)



**6 c[CO-(CH<sub>2</sub>)<sub>3</sub>-CO-Pro-D-Phe-Arg-Trp-Lys]-NH<sub>2</sub>** (58 observable hydrogens)

$\alpha$ -Hydrogens (5):

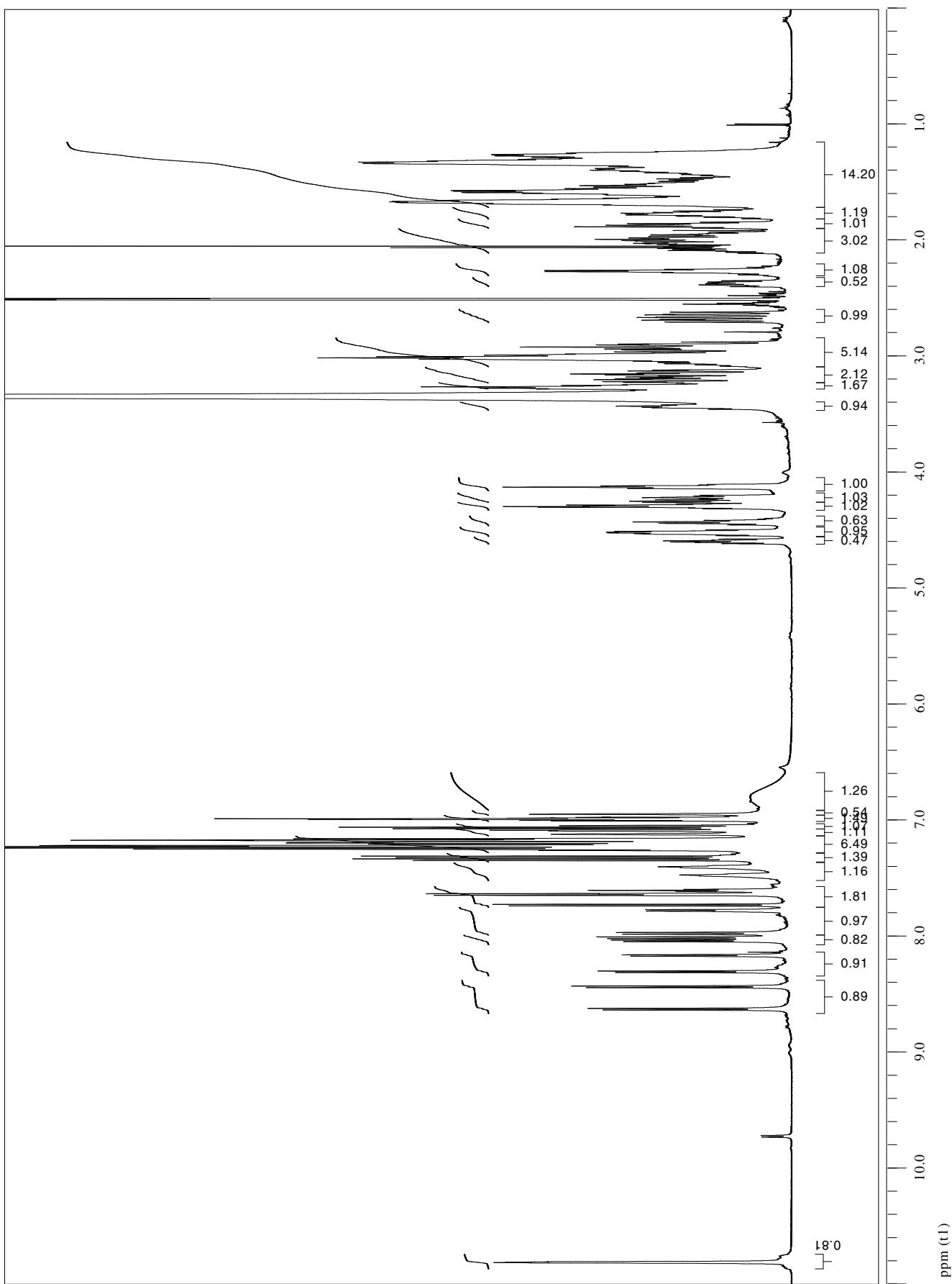
4.12 (1H, m)  
4.21 (m) and 4.25 (dd,  $J=5.7, 13.2$  Hz) (1H)  
4.29 (1H, m)  
4.51 (1H, m)  
4.43 (dd,  $J=8.2, 15.2$  Hz) and 4.59 (dt,  $J=5.8, 9.2$  Hz) (1H)

Side chain hydrogens (30):

1.16-1.72 (14H, m)  
1.77 (1H, m)  
1.86 (1H, m)  
1.90-2.11 (m) and 2.36 (m) (3H)  
2.26 (1H, m)  
2.66 (1H, ddd,  $J=10.6, 13.8, 25.7$  Hz)  
2.91 (2H, m)  
3.01 (3H, m)  
3.17 (2H, m)  
3.26 (1H, m)  
3.43 (1H, m)

Amide and aromatic hydrogens (23):

6.70-7.50 (4H, broad singlets)  
6.95 (1H, br. s)  
6.99 (1H, m)  
7.06 (1H, m)  
7.10 (1H, d,  $J=17.2$  Hz)  
7.14-7.28 (6H, m)  
7.33 (1H, dd,  $J=8.1, 14.7$  Hz)  
7.40 (m) and 7.47 (m) (1H)  
7.62 (1H, dt,  $J=5.7, 20.0$  Hz)  
7.64 (d,  $J=7.9$  Hz) and 7.73 (d,  $J=7.9$  Hz) (1H)  
7.78 (d,  $J=7.3$  Hz) and 7.97 (d,  $J=8.8$  Hz) (1H)  
8.02 (1H, dd,  $J=8.2, 16.2$  Hz)  
8.16 (d,  $J=7.4$  Hz) and 8.30 (d,  $J=7.4$  Hz) (1H)  
8.43 (d,  $J=8.6$  Hz) and 8.63 (d,  $J=8.3$  Hz) (1H)  
10.81 (1H, dd,  $J=2.1, 4.2$  Hz)



**7 c[CO-(CH<sub>2</sub>)<sub>3</sub>-CO-Pro-D-Nal(2')-Arg-Trp-Lys]-NH<sub>2</sub>** (60 observable hydrogens)

$\alpha$ -Hydrogens (5):

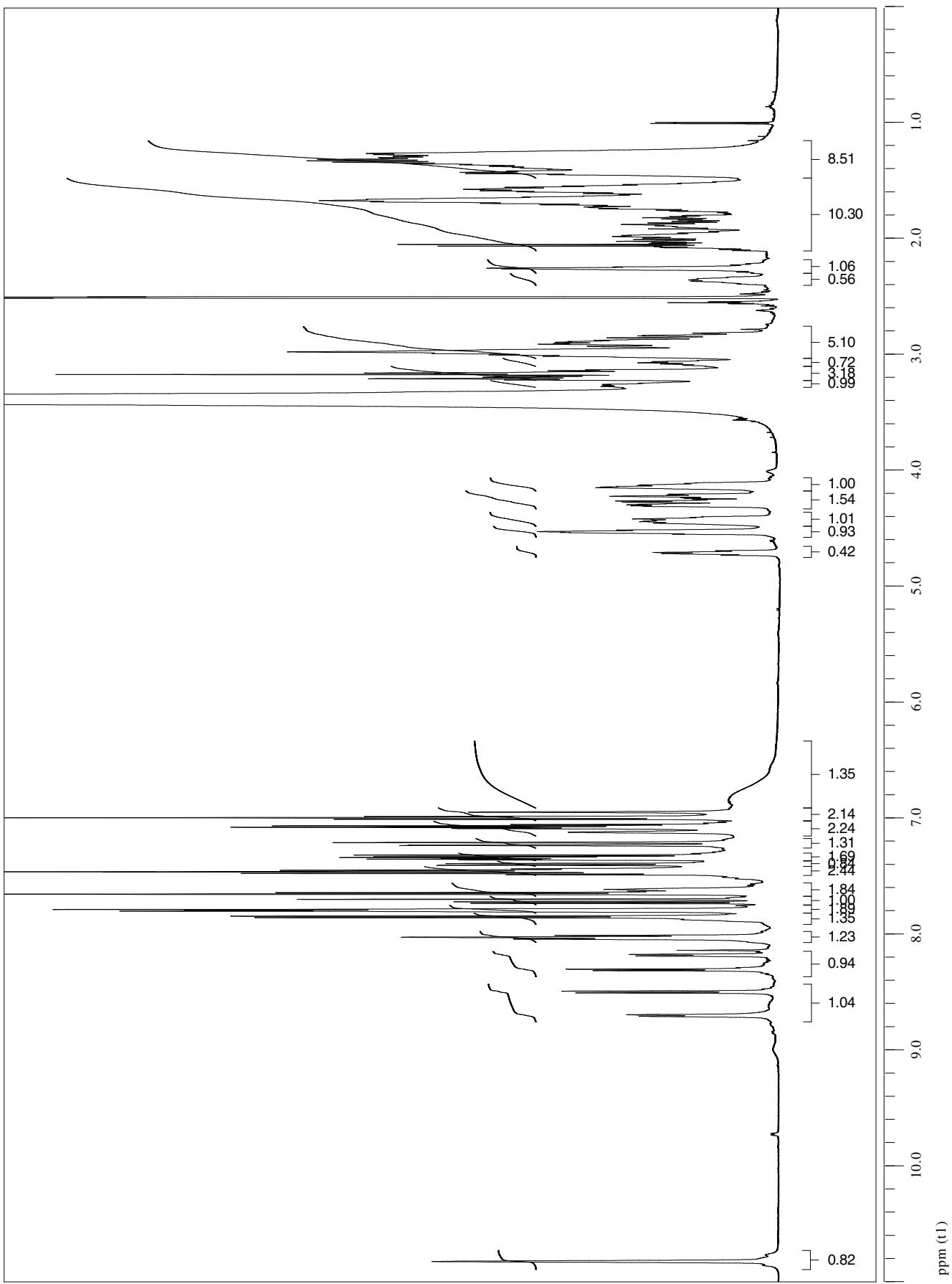
4.12 (1H, m)  
4.22 (m) and 4.30 (1H, m) (1H)  
4.26 (dd, *J*=7.4, 13.7 Hz) and 4.71 (dd, *J*=8.8, 14.6 Hz) (1H)  
4.42 (1H, m)  
4.52 (1H, m)

Side chain hydrogens (30):

1.09-2.12 (19H, m)  
2.06 (m) and 2.35 (m) (1H)  
2.25 (1H, m)  
2.76-3.04 (5H, m)  
3.07 (m) and 3.26 (m) (1H)  
3.10-3.23 (3H, m)

Amide and aromatic hydrogens (25):

6.70-7.50 (4H, broad singlets)  
6.95 (1H, br. s)  
6.99 (1H, t, *J*=7.3 Hz)  
7.07 (2H, dd, *J*=7.0, 14.2 Hz)  
7.12 (1H, br. s)  
7.22 (1H, m)  
7.32 (1H, d, *J*=8.2 Hz)  
7.35 (1H, dd, *J*=4.4, 8.2 Hz)  
7.40 (1H, d, *J*=8.4 Hz)  
7.46 (2H, m)  
7.61 (1H, m)  
7.65 (1H, d, *J*=8.1 Hz)  
7.70 (s) and 7.73 (d, *J*=7.9 Hz) (1H)  
7.79 (2H, m)  
7.85 (1H, d, *J*=7.7 Hz)  
8.03 (1H, t, *J*=9.4 Hz)  
8.18 (d, *J*=7.2 Hz) and 8.31 (d, *J*=7.4 Hz) (1H)  
8.50 (d, *J*=8.5 Hz) and 8.70 (d, *J*=8.0 Hz) (1H)  
10.83 (1H, m)



**8 c[CO-*cis*-CH=CH-CO-Pro-D-Phe-Arg-Trp-Lys]-NH<sub>2</sub>** (54 observable hydrogens)

$\alpha$ -Hydrogens (5):

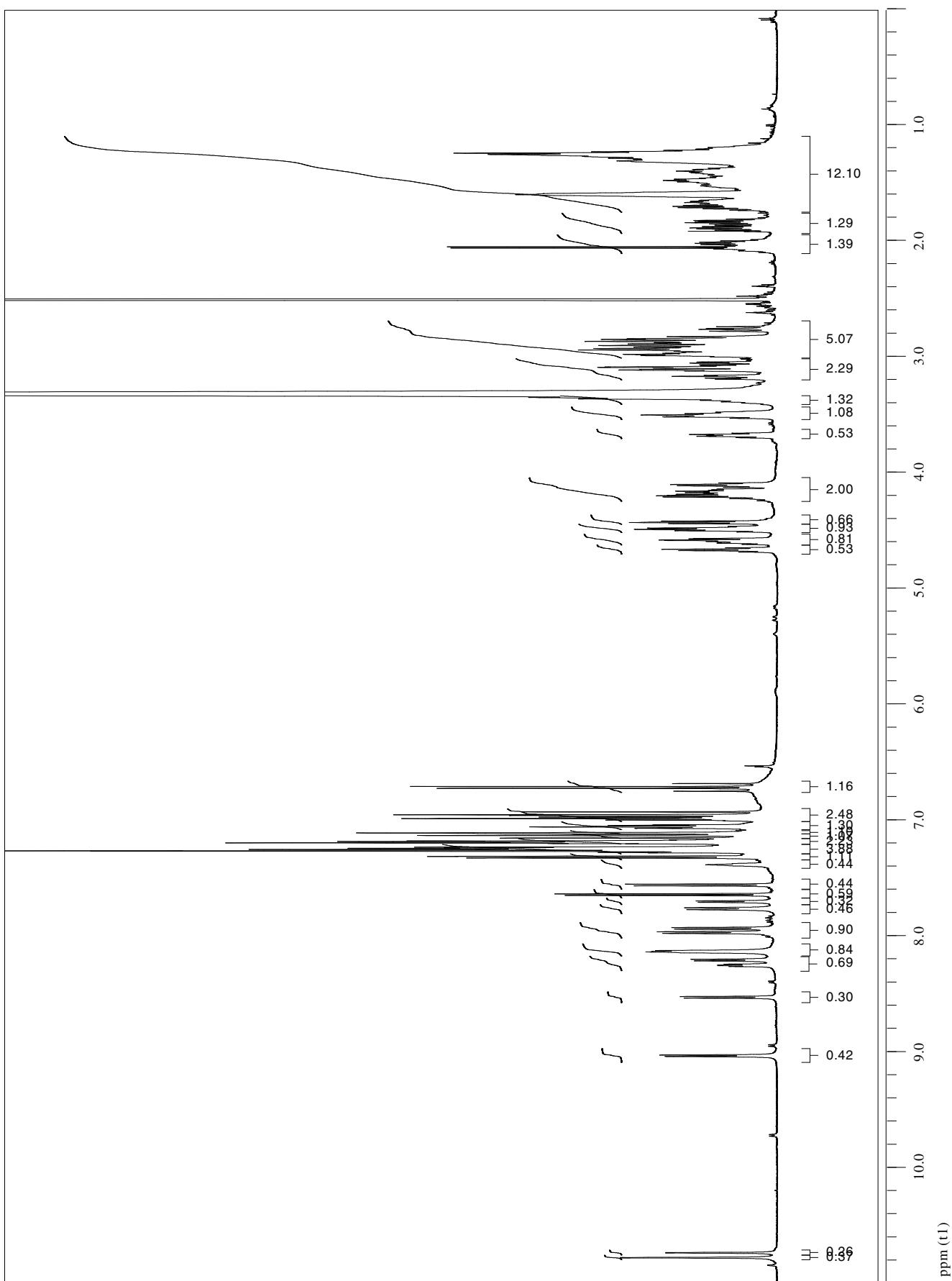
4.10 (dd,  $J=7.9, 14.2$  Hz) and 4.17 (m) (2H)  
4.42 (dd,  $J=5.5, 7.5$  Hz) and 4.60 (dd,  $J=6.5, 8.5$  Hz)  
4.48 (1H, m)  
4.57 (dd,  $J=2.4, 8.2$  Hz) and 4.66 (dd,  $J=7.4, 14.3$  Hz) (1H)

Side chain hydrogens (24):

1.12-1.75 (12H, m)  
1.86 (m) and 1.88 (ddd,  $J=6.9, 12.0, 13.7$  Hz) (1H)  
2.01 (sxt,  $J=6.5$  Hz) and 2.05 (m) (1H)  
2.69-3.02 (5H, m)  
3.06 (dd,  $J=5.5, 13.7$  Hz) and 3.17 (dd,  $J=5.0, 14.6$  Hz) (1H)  
3.10 (1H, m)  
3.38 (1H, m)  
3.50 (m) and 3.67 (dt,  $J=6.7, 9.6$  Hz) (2H)

Amide and aromatic hydrogens (25):

6.30-7.50 (4H, broad singlets)  
6.72 (1H, q,  $J=15.0$  Hz)  
6.94 (1H, d,  $J=15.0$  Hz)  
6.96 (1H, s)  
6.98 (1H, t,  $J=7.9$  Hz)  
7.05 (1H, m)  
7.11 (1H, s)  
7.14 (1H, d,  $J=13.3$  Hz)  
7.19 (2H, m)  
7.25 (4H, m)  
7.32 (1H, d,  $J=8.0$  Hz)  
7.56 (d,  $J=7.9$  Hz) and 7.64 (d,  $J=7.9$  Hz) (1H)  
7.70 (d,  $J=7.1$  Hz) and 7.76 (d,  $J=9.1$  Hz) (1H)  
7.93 (d,  $J=8.4$  Hz) and 7.97 (d,  $J=8.0$  Hz) (1H)  
8.13 (1H, m)  
8.21 (d,  $J=8.1$  Hz) and 8.25 (dd,  $J=4.7, 7.2$  Hz) (1H)  
8.53 (d,  $J=7.8$  Hz) and 9.03 (d,  $J=7.3$  Hz) (1H)  
10.74 (d,  $J=1.9$  Hz) and 10.78 (d,  $J=1.8$  Hz) (1H)



**9 c[CO-*cis*-CH=CH-CO-Pro-*D*-Nal(2')-Arg-Trp-Lys]-NH<sub>2</sub>** (54 observable hydrogens)

$\alpha$ -Hydrogens (5):

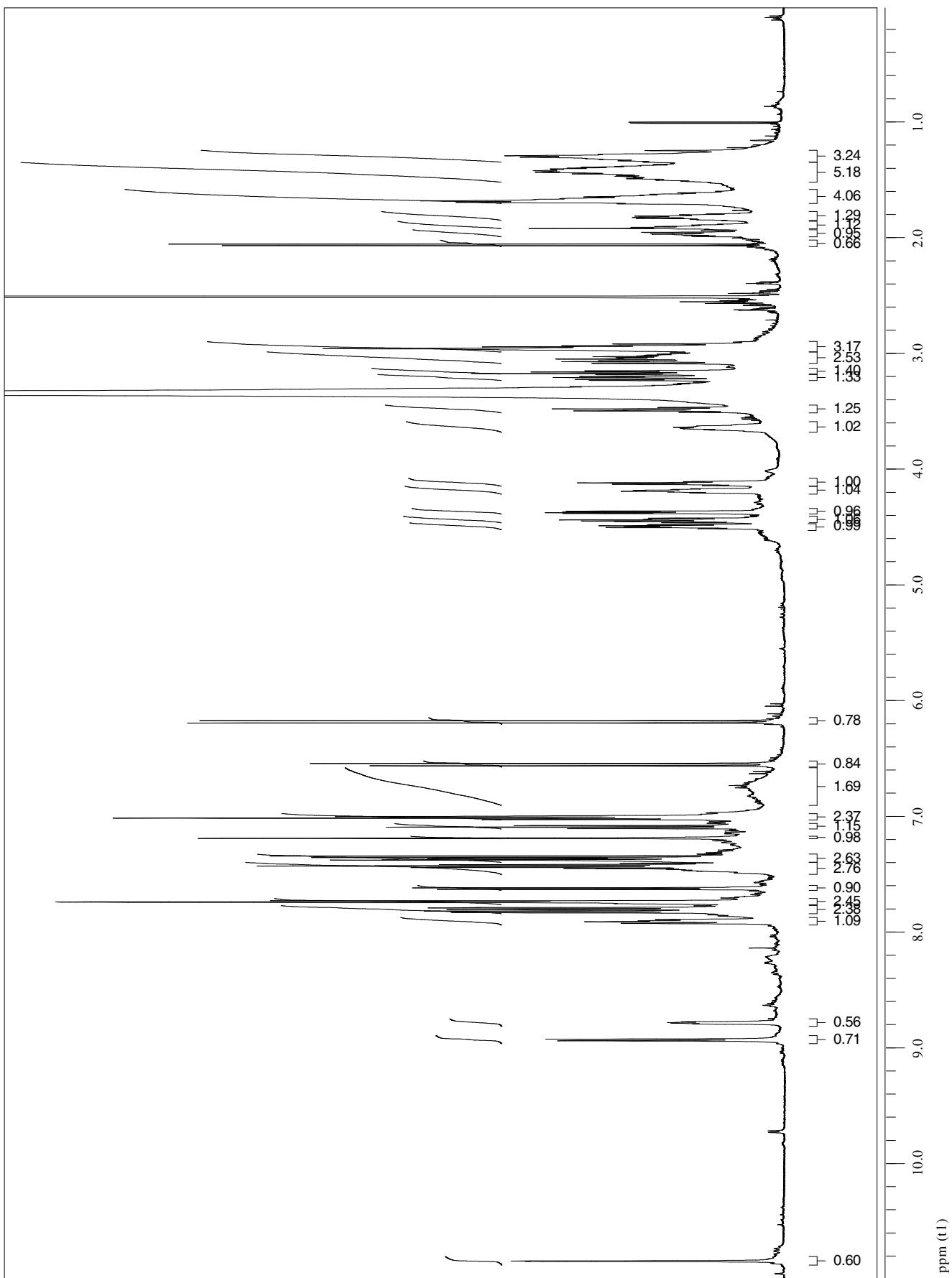
4.11 (1H, dd, *J*=6.8, 13.5 Hz)  
4.18 (1H, dt, *J*=4.3, 8.8 Hz)  
4.36 (1H, dd, *J*=3.7, 8.1 Hz)  
4.43 (1H, dt, *J*=6.2, 8.7 Hz)  
4.49 (1H, m)

Side chain hydrogens (24):

1.29 (3H, m)  
1.40 (4H, m)  
1.46 (1H, m)  
1.66 (4H, m)  
1.81 (1H, m)  
1.89 (1H, m)  
1.96 (1H, m)  
2.94 (3H, m)  
3.02 (1H, m)  
3.06 (1H, dd, *J*=9.1, 13.6 Hz)  
3.16 (1H, dd, *J*=5.6, 13.8 Hz)  
3.21 (1H, dd, *J*=5.1, 14.8 Hz)  
3.48 (1H, dt, *J*=7.5, 10.0 Hz)  
3.64 (1H, m)

Amide and aromatic hydrogens (25):

6.18 (1H, d, *J*=12.2 Hz)  
6.55 (1H, d, *J*=12.2 Hz)  
6.44-7.53 (4H, broad singlets)  
7.01 (2H, t, *J*=7.7 Hz)  
7.09 (1H, t, *J*=7.5 Hz)  
7.19 (1H, s)  
7.34 (1H, d, *J*=8.1 Hz)  
7.36 (1H, dd, *J*=1.5, 8.6 Hz)  
7.37 (1H, br.s)  
7.42 (2H, m)  
7.46 (1H, m)  
7.62 (1H, d, *J*=7.9 Hz)  
7.74 (2H, m)  
7.81 (2H, m)  
7.90 (1H, dd, *J*=7.2, 12.4 Hz)  
8.78 (1H, dd, *J*=3.9, 7.0 Hz)  
8.93 (1H, d, *J*=8.3 Hz)  
10.84 (1H, d, *J*=1.7 Hz)



**10 c[CO-2,6-pyridine-CO-*D*-Phe-Arg-Trp-Lys]-NH<sub>2</sub>** (48 observable hydrogens)

$\alpha$ -Hydrogens (4):

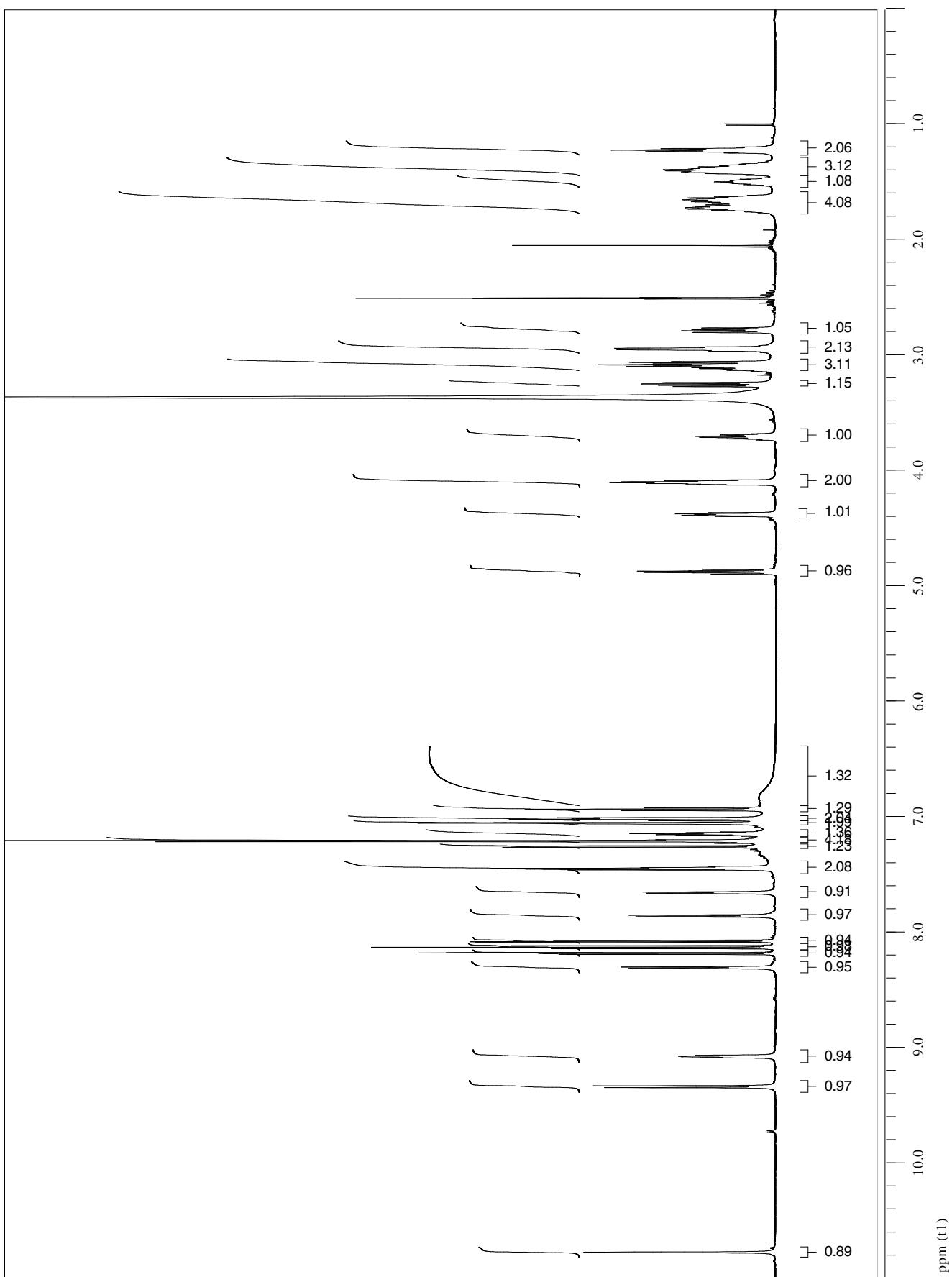
4.10 (2H, m)  
4.38 (1H, dt, *J*=5.9, 8.6 Hz)  
4.87 (1H, dt, *J*=6.7, 8.6 Hz)

Side chain hydrogens (18):

1.22 (2H, m)  
1.38 (3H, m)  
1.49 (1H, m)  
1.59-1.78 (4H, m)  
2.78 (1H, dd, *J*=8.6, 14.8 Hz)  
2.94 (2H, dd, *J*=6.1, 13.2 Hz)  
3.08 (3H, m)  
3.25 (1H, dd, *J*=6.4, 13.7 Hz)  
3.70 (1H, m)

Amide and aromatic hydrogens (26):

6.27-7.51 (5H, broad singlets)  
6.93 (1H, m)  
7.02 (2H, m)  
7.15 (2H, m)  
7.20 (4H, m)  
7.26 (1H, d, *J*=8.1 Hz)  
7.44 (2H, dd, *J*=6.7, 10.6 Hz)  
7.66 (1H, d, *J*=8.1 Hz)  
7.86 (1H, d, *J*=8.1 Hz)  
8.08 (1H, dd, *J*=1.2, 7.7 Hz)  
8.13 (1H, t, *J*=7.7 Hz)  
8.18 (1H, dd, *J*=1.2, 7.7 Hz)  
8.31 (1H, d, *J*=7.0 Hz)  
9.08 (1H, dd, *J*=4.8, 7.1 Hz)  
9.34 (1H, d, *J*=8.8 Hz)  
10.78 (1H, d, *J*=2.0 Hz)



**11 c[CO-2,6-pyridine-CO-*D*-Nal(2')-Arg-Trp-Lys]-NH<sub>2</sub>** (50 observable hydrogens)

$\alpha$ -Hydrogens (4):

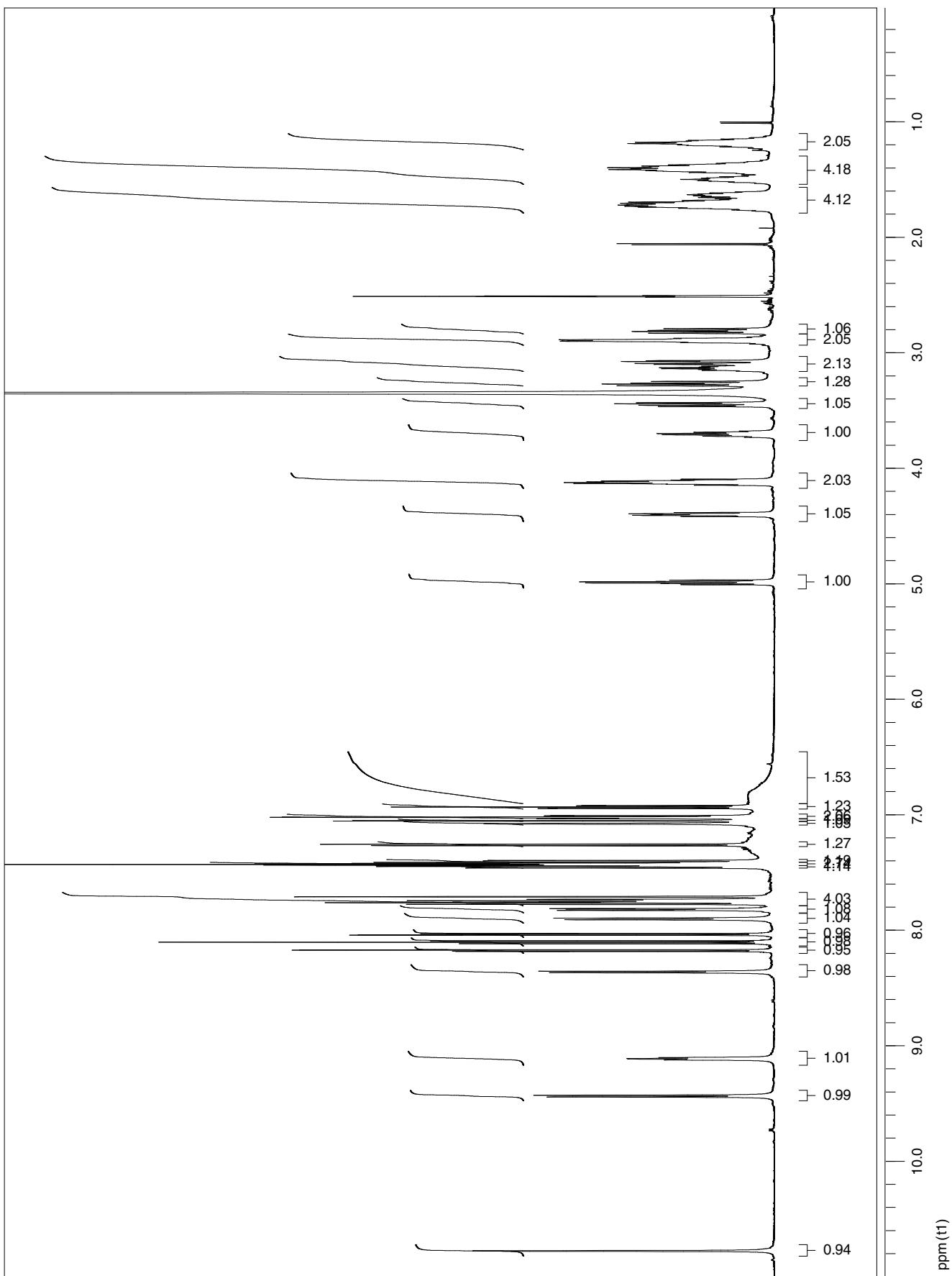
4.11 (2H, m)  
4.39 (1H, dt,  $J=6.2, 7.5$  Hz)  
4.98 (1H, dt,  $J=6.4, 8.7$  Hz)

Side chain hydrogens (18):

1.17 (2H, m)  
1.39 (3H, m)  
1.49 (1H, m)  
1.57-1.79 (4H, m)  
2.80 (1H, dd,  $J=8.6, 14.8$  Hz)  
2.88 (2H, dt,  $J=7.1, 9.2$  Hz)  
3.07 (1H, dd,  $J=4.8, 14.8$  Hz)  
3.12 (1H, dq,  $J=4.8, 9.5$  Hz)  
3.26 (1H, dd,  $J=8.6, 13.7$  Hz)  
3.44 (1H, dd,  $J=6.1, 13.8$  Hz)  
3.70 (1H, m)

Amide and aromatic hydrogens (28):

6.39-7.52 (5H, broad singlets)  
6.93 (1H, m)  
7.02 (2H, m)  
7.05 (1H, d,  $J=2.2$  Hz)  
7.07 (1H, m)  
7.26 (1H, d,  $J=8.1$  Hz)  
7.40 (1H, dd,  $J=1.6, 8.4$  Hz)  
7.43 (3H, m)  
7.45 (1H, d,  $J=7.5$  Hz)  
7.70 (1H, s)  
7.74 (2H, m)  
7.76 (1H, d,  $J=8.6$  Hz)  
7.90 (1H, dd,  $J=3.2, 6.1$  Hz)  
8.03 (1H, dd,  $J=1.1, 7.7$  Hz)  
8.10 (1H, t,  $J=7.7$  Hz)  
8.17 (1H, dd,  $J=1.2, 7.7$  Hz)  
8.36 (1H, d,  $J=7.0$  Hz)  
9.11 (1H, dd,  $J=5.1, 6.7$  Hz)  
9.43 (1H, d,  $J=8.9$  Hz)  
10.78 (1H, d,  $J=2.0$  Hz)



**12 c[CO-2,3-pyrazine-CO-*D*-Phe-Arg-Trp-Lys]-NH<sub>2</sub>** (47 observable hydrogens)

$\alpha$ -Hydrogens (4):

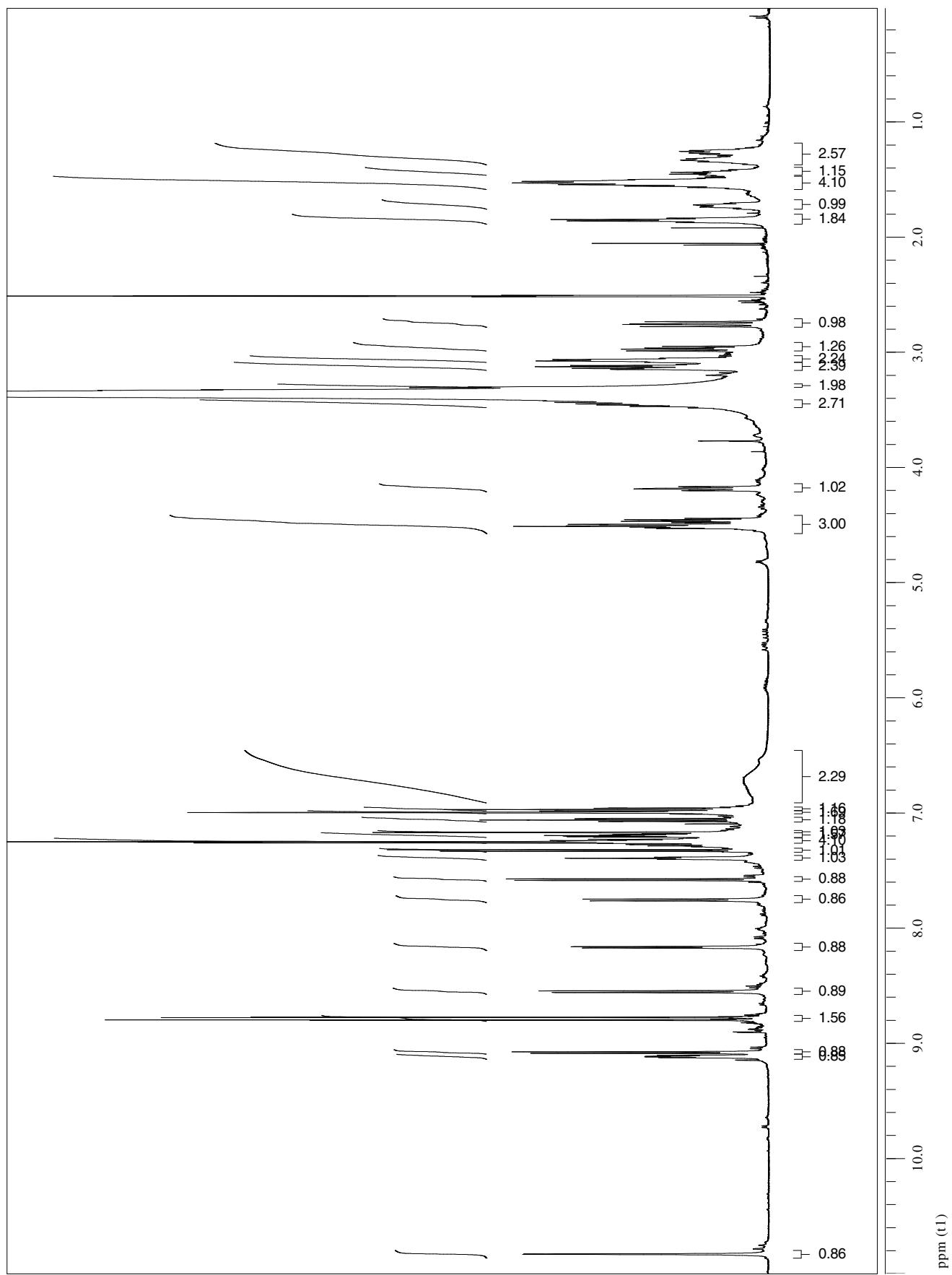
4.18 (1H, m)  
4.45 (1H, dt, *J*=6.5, 8.8 Hz)  
4.50 (2H, m)

Side chain hydrogens (18):

1.25 (1H, m)  
1.32 (1H, m)  
1.43 (1H, m)  
1.52 (4H, m)  
1.72 (1H, m)  
1.84 (2H, dd, *J*=7.4, 14.7 Hz)  
2.74 (1H, dd, *J*=11.1, 14.4 Hz)  
2.96 (1H, dd, *J*=8.9, 14.8 Hz)  
3.06 (2H, m)  
3.12 (2H, dd, *J*=5.8, 14.6 Hz)  
3.32 (1H, m)  
3.44 (1H, m)

Amide and aromatic hydrogens (25):

6.30-7.46 (5H, broad singlets)  
6.96 (1H, m)  
6.99 (1H, s)  
7.06 (1H, m)  
7.16 (1H, d, *J*=2.3 Hz)  
7.19 (1H, m)  
7.23 (1H, m)  
7.24 (2H, s)  
7.25 (1H, d, *J*=3.6 Hz)  
7.32 (1H, d, *J*=8.1 Hz)  
7.39 (1H, t, *J*=5.4 Hz)  
7.57 (1H, d, *J*=8.0 Hz)  
7.75 (1H, d, *J*=8.8 Hz)  
8.16 (1H, d, *J*=6.6 Hz)  
8.55 (1H, d, *J*=9.0 Hz)  
8.78 (2H, dd, *J*=2.5, 14.2 Hz)  
9.08 (1H, d, *J*=7.8 Hz)  
9.11 (1H, dd, *J*=4.5, 7.7 Hz)  
10.83 (1H, d, *J*=2.0 Hz)



**13 c[CO-2,3-pyrazine-CO-D-Nal(2')-Arg-Trp-Lys]-NH<sub>2</sub>** (49 observable hydrogens)

$\alpha$ -Hydrogens (4):

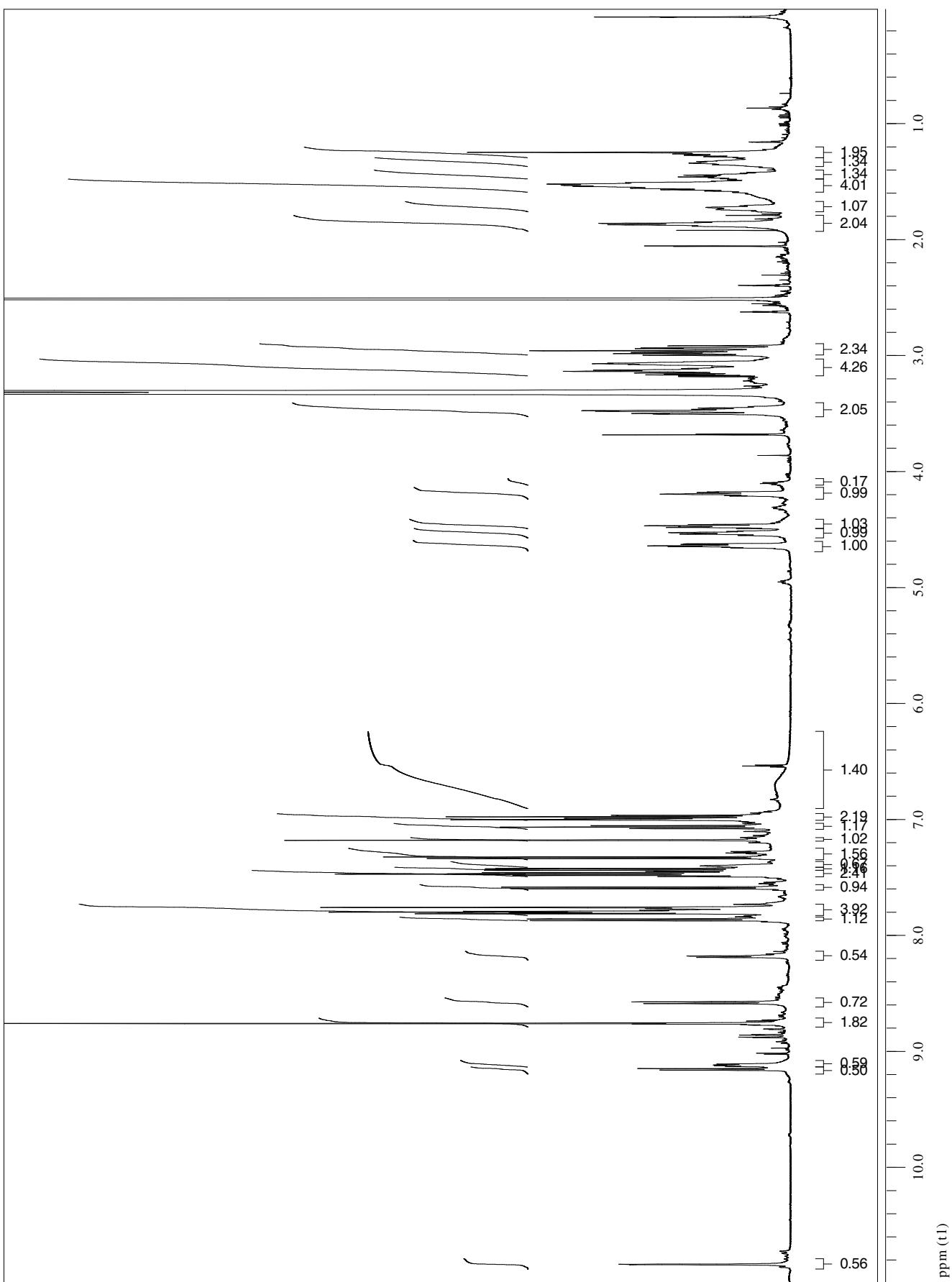
4.19 (1H, m)  
4.47 (1H, dt,  $J=5.8, 8.8$  Hz)  
4.52 (1H, m)  
4.63 (1H, m)

Side chain hydrogens (18):

1.25 (1H, m)  
1.35 (1H, m)  
1.44 (1H, m)  
1.53 (4H, m)  
1.72 (1H, m)  
1.85 (2H, dd,  $J=7.3, 14.3$  Hz)  
2.93 (1H, dd,  $J=11.1, 14.5$  Hz)  
2.97 (1H, dd,  $J=9.0, 14.8$  Hz)  
3.06 (2H, m)  
3.14 (2H, m)  
3.45 (1H, dd,  $J=6.9, 14.0$  Hz)  
3.48 (1H, dd,  $J=3.1, 14.6$  Hz)

Amide and aromatic hydrogens (27):

6.34-7.55 (5H, broad singlets)  
6.97 (1H, t,  $J=7.7$  Hz)  
7.00 (1H, s)  
7.06 (1H, t,  $J=7.5$  Hz)  
7.17 (1H, s)  
7.28 (1H, dd,  $J=3.9, 8.0$  Hz)  
7.33 (1H, d,  $J=8.1$  Hz)  
7.40 (1H, s)  
7.43 (1H, dd,  $J=1.6, 8.5$  Hz)  
7.47 (2H, m)  
7.59 (1H, d,  $J=7.9$  Hz)  
7.77 (2H, m)  
7.80 (1H, dd,  $J=3.3, 5.2$  Hz)  
7.87 (1H, m)  
8.18 (1H, d,  $J=6.6$  Hz)  
8.58 (1H, d,  $J=9.1$  Hz)  
8.76 (2H, m)  
9.12 (1H, dd,  $J=4.3, 7.8$  Hz)  
9.15 (1H, d,  $J=7.8$  Hz)  
10.84 (1H, d,  $J=1.9$  Hz)



**14 c[CO-(CH<sub>2</sub>)<sub>2</sub>-CO-Nle-D-Phe-Arg-Trp-Lys]-NH<sub>2</sub>** (60 observable hydrogens)

$\alpha$ -Hydrogens (5):

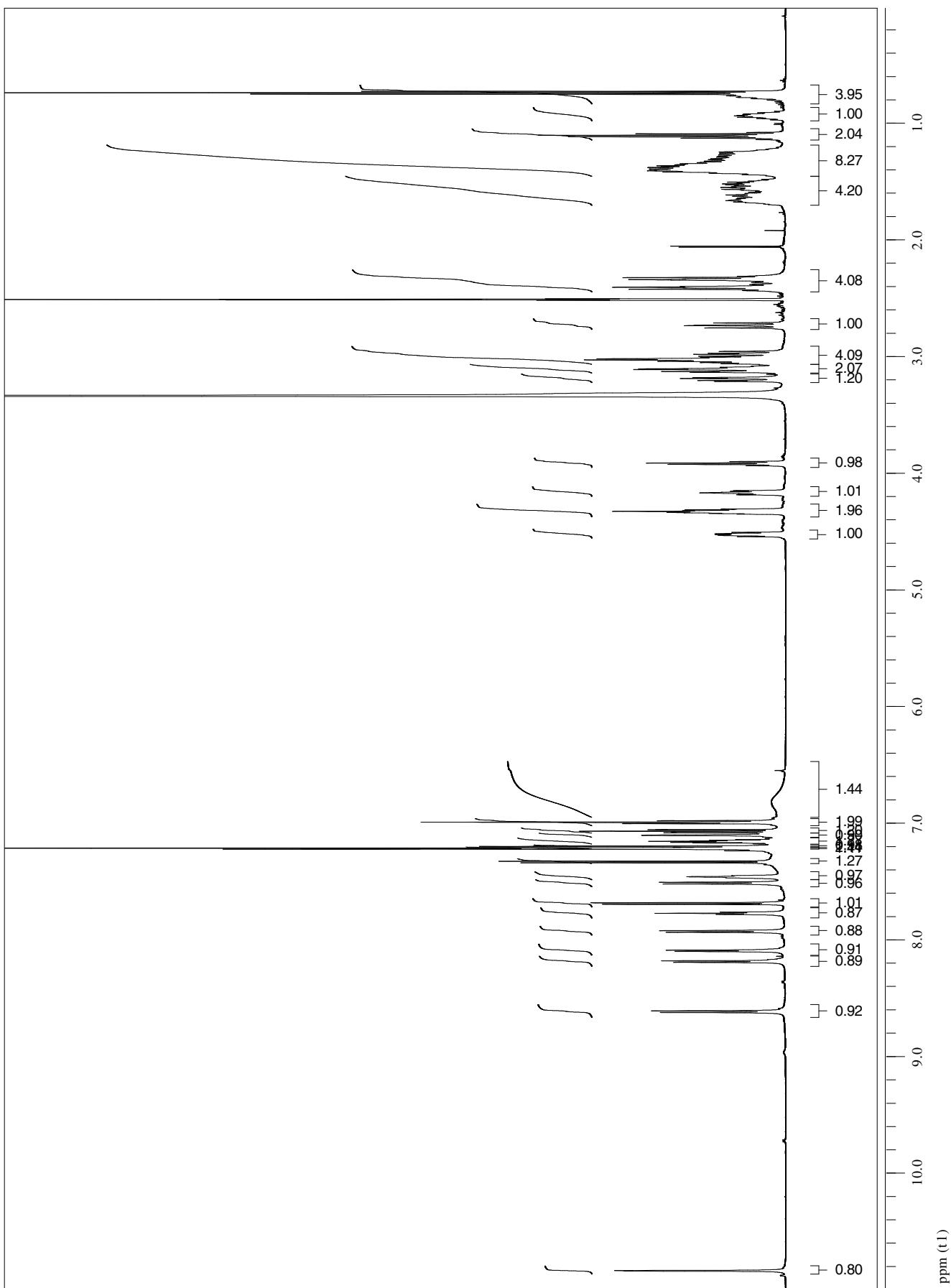
3.91 (1H, q,  $J=7.1$  Hz)  
4.16 (1H, m)  
4.32 (2H, m)  
4.52 (1H, m)

Side chain hydrogens (31):

0.73 (3H, t,  $J=7.4$  Hz)  
0.75 (1H, m)  
0.92 (1H, m)  
1.10 (2H, sxt,  $J=7.4$  Hz)  
1.19-1.70 (12H, m)  
2.36 (4H, m)  
2.72 (1H, dd,  $J=11.6, 13.8$  Hz)  
2.98 (1H, m)  
3.02 (3H, m)  
3.09 (1H, dd,  $J=4.8, 12.4$  Hz)  
3.11 (1H, dd,  $J=3.8, 14.0$  Hz)  
3.19 (1H, dd,  $J=4.6, 14.8$  Hz)

Amide and aromatic hydrogens (24):

6.47-7.59 (4H, broad singlets)  
6.99 (2H, m)  
7.06 (1H, m)  
7.10 (1H, br.s)  
7.15 (1H, m)  
7.19 (1H, d,  $J=2.0$  Hz)  
7.21 (2H, s)  
7.22 (2H, d,  $J=1.6$  Hz)  
7.33 (1H, d,  $J=8.1$  Hz)  
7.45 (1H, t,  $J=4.8$  Hz)  
7.51 (1H, d,  $J=8.4$  Hz)  
7.68 (1H, d,  $J=7.9$  Hz)  
7.77 (1H, t,  $J=6.4$  Hz)  
7.92 (1H, d,  $J=8.2$  Hz)  
8.09 (1H, d,  $J=6.4$  Hz)  
8.18 (1H, d,  $J=7.3$  Hz)  
8.61 (1H, d,  $J=8.3$  Hz)  
10.84 (1H, d,  $J=1.9$  Hz)



**15 c[CO-(CH<sub>2</sub>)<sub>2</sub>-CO-Nle-D-Nal(2')-Arg-Trp-Lys]-NH<sub>2</sub>** (62 observable hydrogens)

α-Hydrogens (5):

3.89 (1H, q, *J*=7.0 Hz)

4.17 (1H, m)

4.36 (1H, m)

4.44 (1H, m)

4.54 (1H, m)

Side chain hydrogens (31):

0.45 (3H, t, *J*=7.3 Hz)

0.53 (1H, m)

0.76 (1H, m)

1.10 (2H, spt, *J*=6.9 Hz)

1.15-1.71 (12H, m)

2.30 (2H, m)

2.40 (2H, m)

2.89 (1H, m)

2.97 (1H, dd, *J*=10.0, 15.0 Hz)

3.01 (2H, m)

3.07 (2H, m)

3.20 (1H, dd, *J*=4.7, 14.8 Hz)

3.28 (1H, m)

Amide and aromatic hydrogens (26):

6.38-7.60 (4H, broad singlets)

7.00 (2H, t, *J*=7.4 Hz)

7.07 (1H, t, *J*=7.6 Hz)

7.09 (1H, br.s)

7.20 (1H, s)

7.34 (1H, d, *J*=8.1 Hz)

7.38 (1H, br.s)

7.38 (1H, dd, *J*=1.4, 8.5 Hz)

7.44 (2H, dqnt, *J*=1.4, 6.8 Hz)

7.55 (1H, d, *J*=8.3 Hz)

7.69 (1H, d, *J*=7.9 Hz)

7.71 (1H, s)

7.77 (3H, m)

7.82 (1H, dd, *J*=1.4, 7.4 Hz)

7.95 (1H, d, *J*=8.2 Hz)

8.04 (1H, d, *J*=6.1 Hz)

8.20 (1H, d, *J*=7.2 Hz)

8.69 (1H, d, *J*=8.3 Hz)

10.83 (1H, d, *J*=2.0 Hz)

