Supporting Information

Design and Microwave-Assisted Synthesis of Novel Macrocyclic Peptides Active at Melanocortin Receptors: Discovery of Potent and Selective hMC5R Receptor Antagonists

Paolo Grieco[a,b ≠], Minying Cai[a ≠], Lu Liu[a], Alexander Mayorov [a], Kevin Chandler[a], Dev Trivedi[a], Guanxin Lin[a], Pietro Campiglia[c], Ettore Novellino[b] and Victor J. Hruby[a]*

[a]*Department of Chemistry, University of Arizona, Tucson, AZ 85721 USA*

[b]*Department of Pharmaceutical Chemistry and Toxicology, University of Napoli "Federico II", Naples, Italy*

[c]*Department of Pharmaceutical Science, University of Salerno, Fisciano, Salerno, Italy*

PG29N (45 observable hydrogens)

Amide and aromatic hydrogens (26)

9.13 (d, *J* = 8.39 Hz, 1H)

8.97 (broad s, 1H)

8.59 (d, *J* = 9.02 Hz, 1H)

8.50 (d, *J* = 4.71 Hz, 1H)

8.26 (dd, *J* = 8.77, 2.57 Hz, 1H)

8.04 (d, *J* = 8.21 Hz, 1H)

7.89 (d, *J* = 2.60 Hz, 1H)

7.79 (d, *J* = 6.57 Hz, 1H)

7.76 (d, *J* = 8.94 Hz, 1H)

7.58 (s, 1H)

7.42 (s, 1H)

7.30 (m, 2H)

7.24 (m, 6H)

7.20-7.16 (m, 5H)

7.14 (m, 2H)

α-Hydrogens (8)

4.81 (dt, *J* = 8.86, 5.31 Hz, 1H)

4.74 (q, *J* = 7.32 Hz, 1H)

4.50-4.44 (m, 1H)

4.43-4.36 (m, 1H)

3.75 (q, *J* = 7.18 Hz, 1H)

3.55-3.47 (m, 1H)

3.31-3.23 (m, 1H)

3.20 (dd, *J* = 15.26, 4.88 Hz, 1H)

Side chain hydrogens (11)

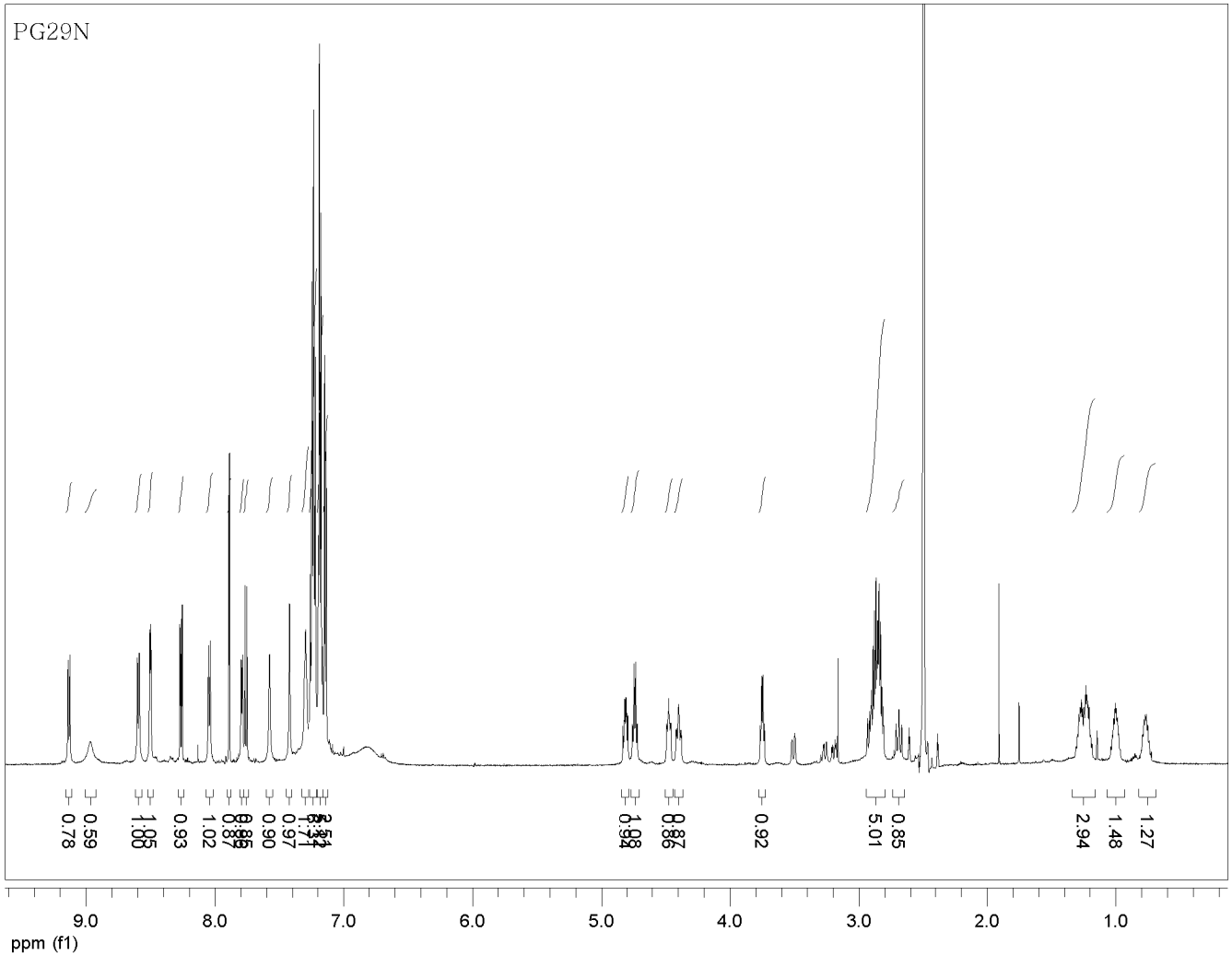
2.94-2.80 (m, 5H)

2.74-2.65 (m, 1H)

1.34-1.16 (m, 3H)

1.00 (m, 1H)

0.77 (m, 1H)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0.59
1.00
0.93
1.02
0.90
0.97
1.94
0.86
0.92
5.01
0.85
2.94
1.48
1.27
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

PG28N (52 observable hydrogens)

Amide and aromatic hydrogens (32)

8.97 (broad s, 1H)

8.82 (d, *J* = 8.05 Hz, 1H)

8.61 (d, *J* = 5.94 Hz, 1H)

8.39 (d, *J* = 7.18 Hz, 1H)

8.27 (dd, *J* = 8.85, 2.54 Hz, 1H)

8.15 (d, *J* = 2.54 Hz, 1H)

7.95 (d, *J* = 7.74 Hz, 1H)

7.84 (d, *J* = 7.50 Hz, 1H)

7.74 (m, 5H)

7.63 (s, 1H)

7.46 (m, 4H)

7.31 (m, 5H)

7.24 (m, 4H)

7.18 (m, 2H)

7.13 (m, 3H)

α-Hydrogens (6)

4.90 (q, *J* = 7.15 Hz, 1H)

4.47 (m, 1H)

4.38 (m, 2H)

3.89 (m, 1H)

3.65 (m, 1H)

Side chain hydrogens (14)

3.12 (m, 2H)

3.06 (m, 1H)

2.98 (m, 1H)

2.89 (d, 2H)

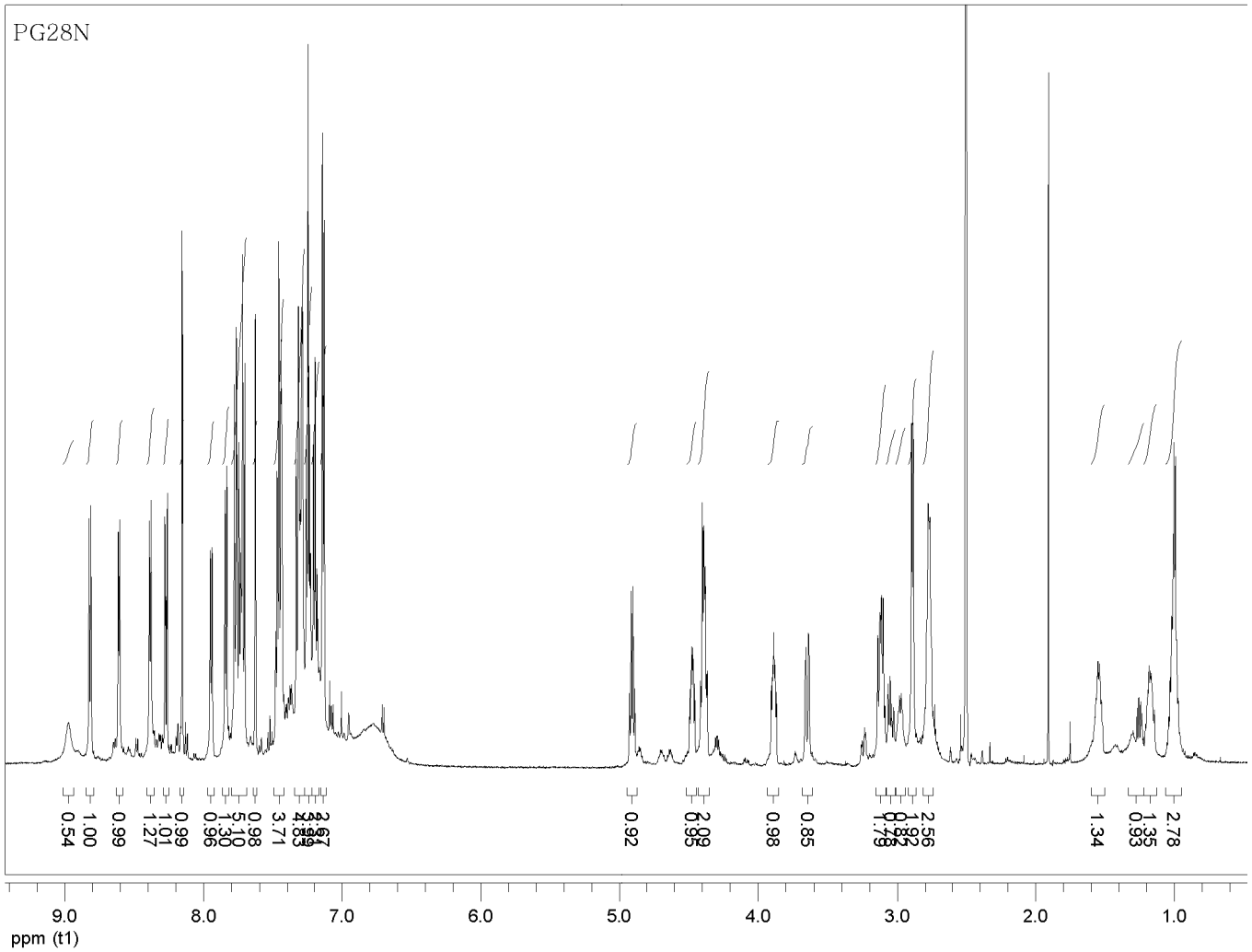
2.77 (m, 2H)

1.54 (m, 1H)

1.28 (m, 1H)

1.17 (m, 1H)

1.01 (m, 3H)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0.54
1.00
0.99
1.27
1.01
0.99
0.96
1.30
5.10
0.98
3.71
0.92
0.98
0.85
1.79
2.56
1.34
0.93
1.35
2.78
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

PG26N (61 observable hydrogens)

Amide and aromatic hydrogens (34)

9.01 (d, *J* = 4.95 Hz, 1H)

8.76 (t, *J* = 6.90 Hz, 1H)

8.72 (d, *J* = 6.03 Hz, 1H)

8.68 (d, *J* = 5.96 Hz, 1H)

8.48 (d, *J* = 7.92 Hz, 1H)

8.44 (d, *J* = 8.11 Hz, 1H)

8.24 (dt, *J* = 2.56, 9.00 Hz, 1H)

8.11 (t, *J* = 2.28Hz, 1H)

7.83 (d, *J* = 7.43 Hz, 1H)

7.77 (d, *J* = 7.67 Hz, 1H)

7.74 (d, *J* = 7.86 Hz, 1H)

7.68 (dd, *J* = 9.06, 4.52 Hz, 1H)

7.63 (m, 4H)

7.44 (s, 1H)

7.36 (m, 2H)

7.29 (m, 4H)

7.21 (m, 6H)

7.05 (m, 1H)

6.96 (m, 1H)

6.90 (m, 1H)

6.59 (m, 2H)

α-Hydrogens (7)

4.85 (q, *J* = 7.83 Hz, 1H)

4.39 (m, 3H)

4.25 (m, 1H)

4.14 (m, 1H)

3.63 (m, 1H)

Side chain hydrogens (20)

3.09 (m, 3H)

2.97 (m, 2H)

2.91 (m, 1H)

2.64 (m, 3H)

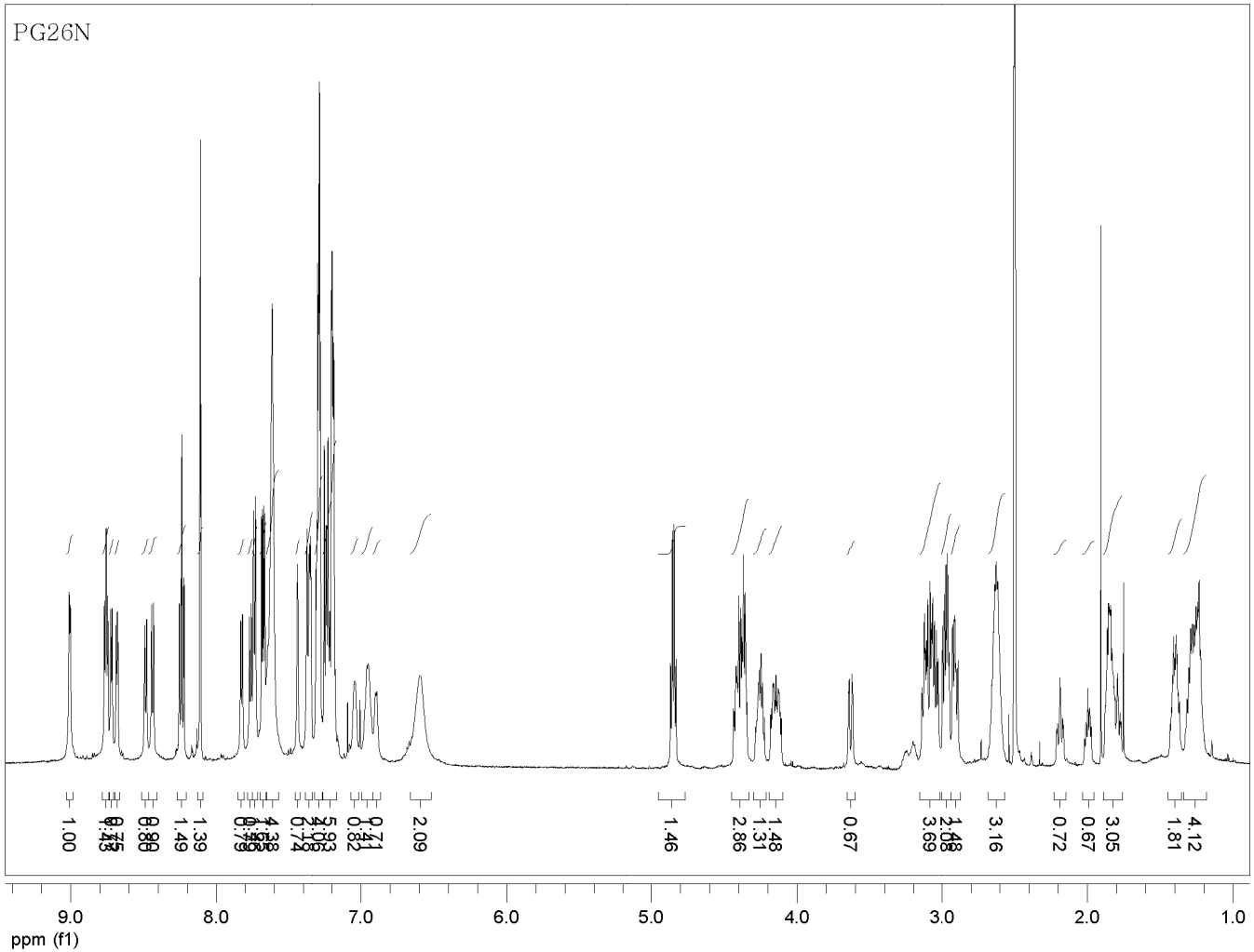
2.19 (m, 1H)

2.00 (m, 1H)

1.84 (m, 3H)

1.40 (m, 2H)

1.26 (m, 4H)


PG26N
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1.49
1.39
2.09
1.46
2.86
1.31
0.67
3.69
3.16
0.72
0.67
3.05
1.81
4.12
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

PG23N (53 observable hydrogens)

Amide and aromatic hydrogens (27)

9.01 (d, *J* = 5.32 Hz, 1H)

8.79 (t, *J* = 6.96 Hz, 1H)

8.68 (d, *J* = 6.02 Hz, 1H)

8.63 (d, *J* = 5.97 Hz, 1H)

8.42 (d, *J* = 7.44 Hz, 1H)

8.35 (d, *J* = 7.85 Hz, 1H)

8.24 (dt, *J* = 2.58, 9.14 Hz, 1H)

8.12 (d, *J* = 2.34 Hz, 1H)

7.88 (d, *J* = 7.33 Hz, 1H)

7.79 (t, *J* = 6.94 Hz, 2H)

7.67 (dd, *J* = 9.07, 2.51 Hz, 1H)

7.37 (m, 2H)

7.29 (m, 5H)

7.22 (m, 2H)

7.17 (m, 4H)

7.06 (m, 1H)

7.01 (m, 1H)

α-Hydrogens (6)

4.86 (m, 1H)

4.39 (m, 2H)

4.34 (m, 1H)

4.24 (m, 1H)

4.10 (m, 1H)

Side chain hydrogens (20)

3.12 (m, 2H)

3.06 (m, 1H)

2.96 (m, 2H)

2.90 (m, 1H)

2.75 (m, 3H)

2.23 (m, 1H)

2.03 (m, 1H)

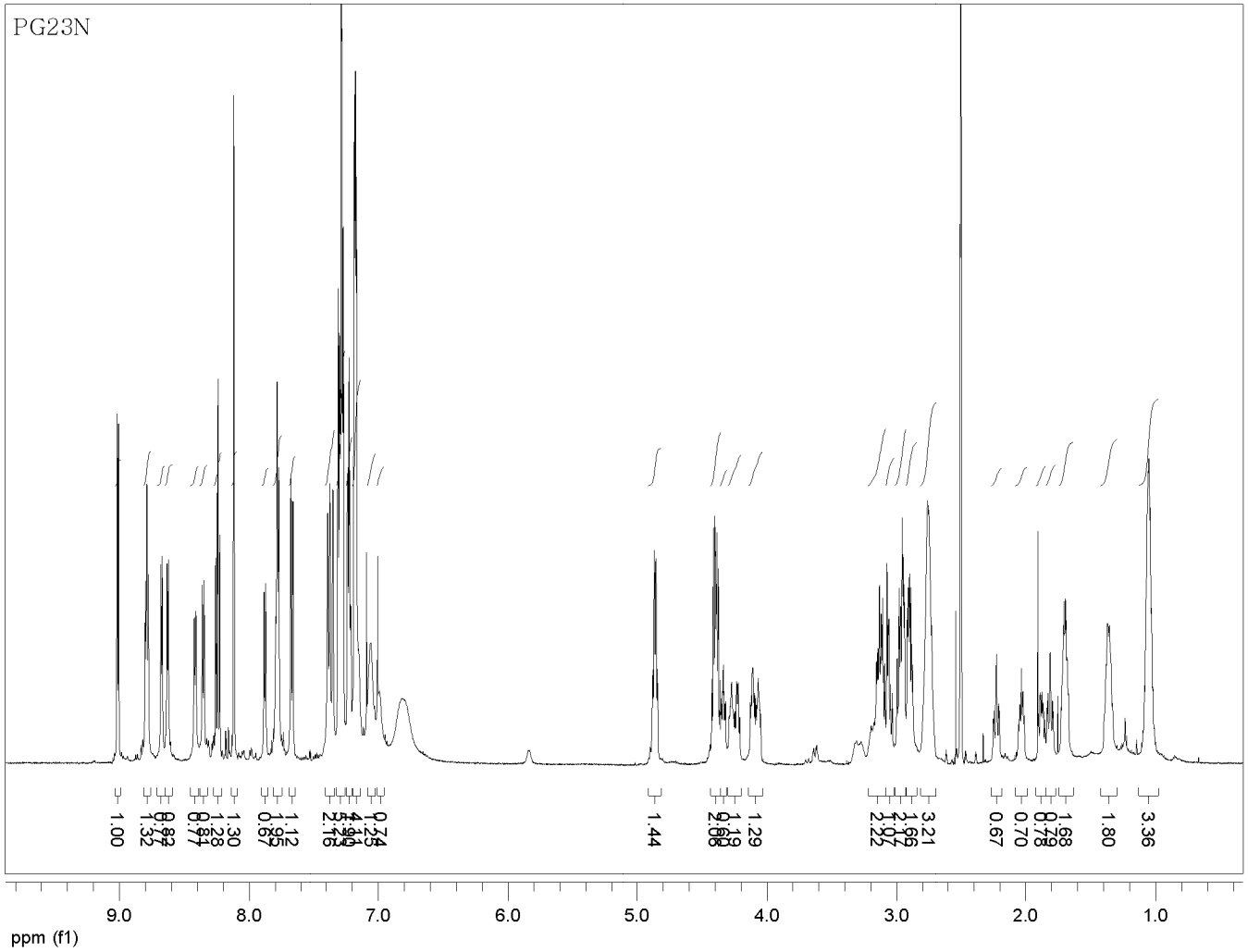
1.91 (m, 1H)

1.81 (m, 1H)

1.69 (m, 2H)

1.36 (m, 2H)

1.05 (m, 3H)


PG23N
1.00
1.32
1.28
1.30
0.67
1.12
1.44
1.29
3.21
0.67
0.70
1.68
1.80
3.36
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

PG27N (42 observable hydrogens)
Amide and aromatic hydrogens (26)
9.12 (1H, d, *J*=8.43 Hz)
8.99 (1H, s)
8.60 (1H, d, *J*=8.92 Hz)
8.47 (1H, d, *J*=4.85 Hz)
8.28 (1H, dd, *J*=2.53, 8.75 Hz)
8.08 (1H, d, *J*=7.89 Hz)
7.90 (1H, d, *J*=2.55 Hz)
7.85 (1H, d, *J*=7.79 Hz)
7.80 (3H, d, *J*=8.27 Hz)
7.76 (1H, d, *J*=8.94 Hz)
7.67 (1H, s)
7.55 (1H, s)
7.46 (3H, m)
7.36 (1H, d, *J*=8.39 Hz)
7.29 (1H, t, *J*=5.12 Hz)
7.22 (4H, m)
7.17 (1H, m)
7.12 (2H, d, *J*=7.11 Hz)

α-Hydrogens (7)
4.82 (1H, dt, *J*=5.42, 8.95 Hz)
4.68 (1H, q, *J*=7.33 Hz)
4.47 (2H, t, *J*=9.74 Hz)
3.74 (1H, dd, *J*=6.97, 12.41 Hz)
3.26 (1H, dd, *J*=10.77, 14.58 Hz)
3.19 (1H, dd, *J*=4.99, 15.19 Hz)

Side chain hydrogens (9)
2.92 (2H, m)
2.84 (1H, m)
2.60 (2H, m)
1.26 (1H, m)
1.14 (1H, m)
0.94 (1H, m)
0.73 (1H, m)

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
1.00
0.73
1.00
1.16
0.96
1.07
2.44
1.04
1.16
1.69
0.77
0.07
0.11
0.40
0.80
2.32
1.86
2.76
0.12
0.06
1.37
1.46
1.51
1.24

PG11N (66 observable hydrogens)

Amide and aromatic hydrogens (38)

10.79 (1H, d, *J*=1.79 Hz)

9.41 (1H, s)

8.43 (1H, d, *J*=6.17 Hz)

8.27 (1H, dd, *J*=2.55, 8.82 Hz)

8.21 (1H, d, *J*=2.54 Hz)

7.90 (1H, d, *J*=6.77 Hz)

7.78 (1H, d, *J*=8.95 Hz)

7.76 (1H, d, *J*=7.25 Hz)

7.58 (1H, d, *J*=7.02 Hz)

7.54 (1H, d, *J*=8.32 Hz)

7.33 (1H, d, *J*=8.21 Hz)

7.28 (5H, m)

7.21 (4H, m)

7.17 (12H, m)

7.13 (2H, m)

7.07 (3H, m)

6.99 (1H, t, *J*=7.74 Hz)

α-Hydrogens (7)

4.59 (1H, q, *J*=7.05 Hz)

4.49 (1H, m)

4.33 (1H, m)

4.24 (1H, ddd, *J*=3.46, 7.35, 10.78 Hz)

3.90 (1H, dd, *J*=5.49, 9.43 Hz)

3.87 (1H, d, *J*=16.63 Hz)

3.69 (1H, dd, *J*=3.05, 13.64 Hz)

Side chain hydrogens (21)

3.26 (1H, d, *J*=16.57 Hz)

3.19 (3H, m)

3.08 (2H, m)

3.00 (2H, dd, *J*=7.71, 13.83 Hz)

2.88 (3H, m)

2.54 (1H, s)

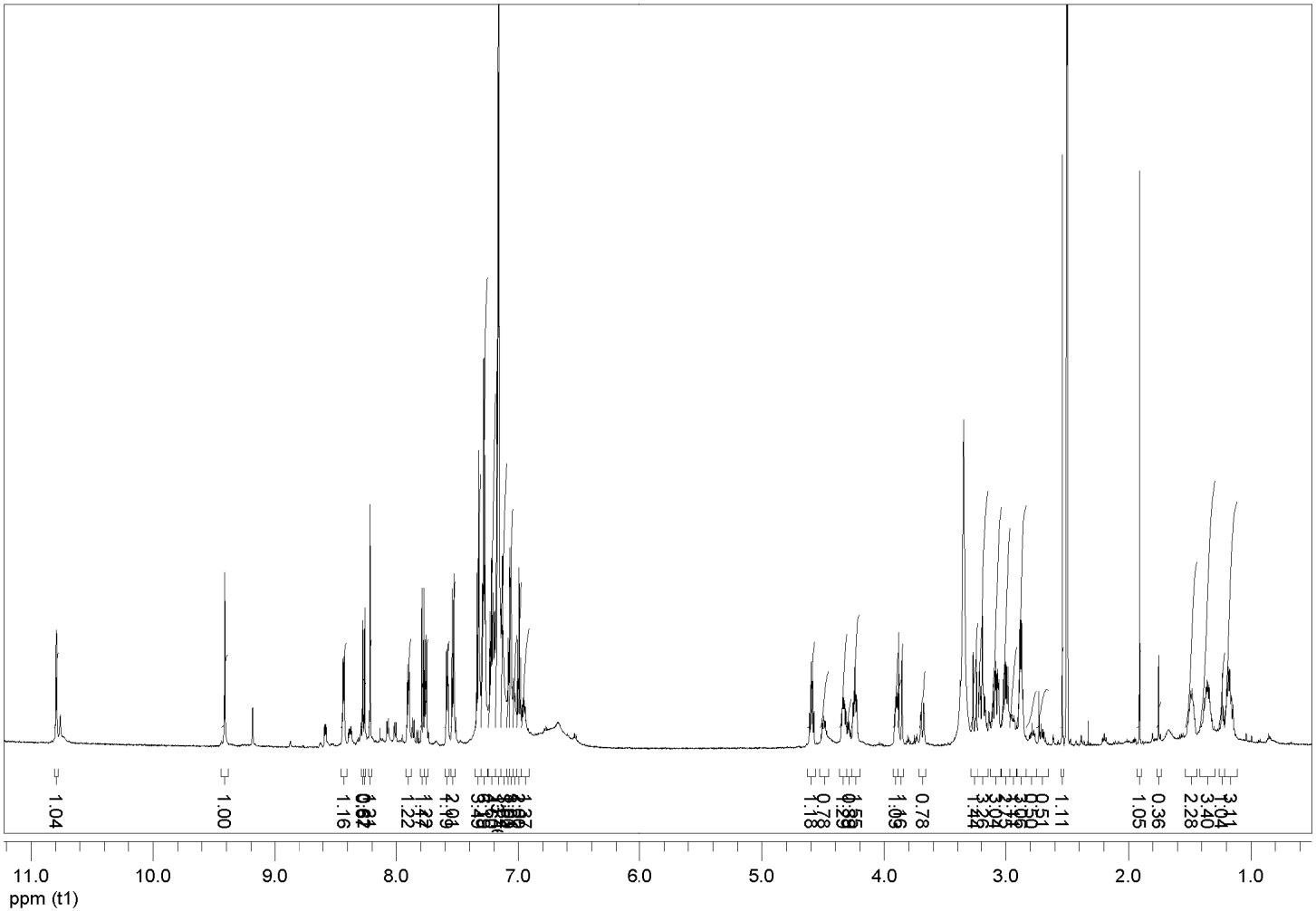
1.91 (1H, s)

1.49 (2H, m)

1.36 (3H, m)

1.24 (1H, m)

1.17 (2H, m)


1.04
1.00
1.16
1.22
1.18
0.78
1.11
1.05
0.36
2.28
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

PG13N (96 observable hydrogens)

Amide and aromatic hydrogens (38)

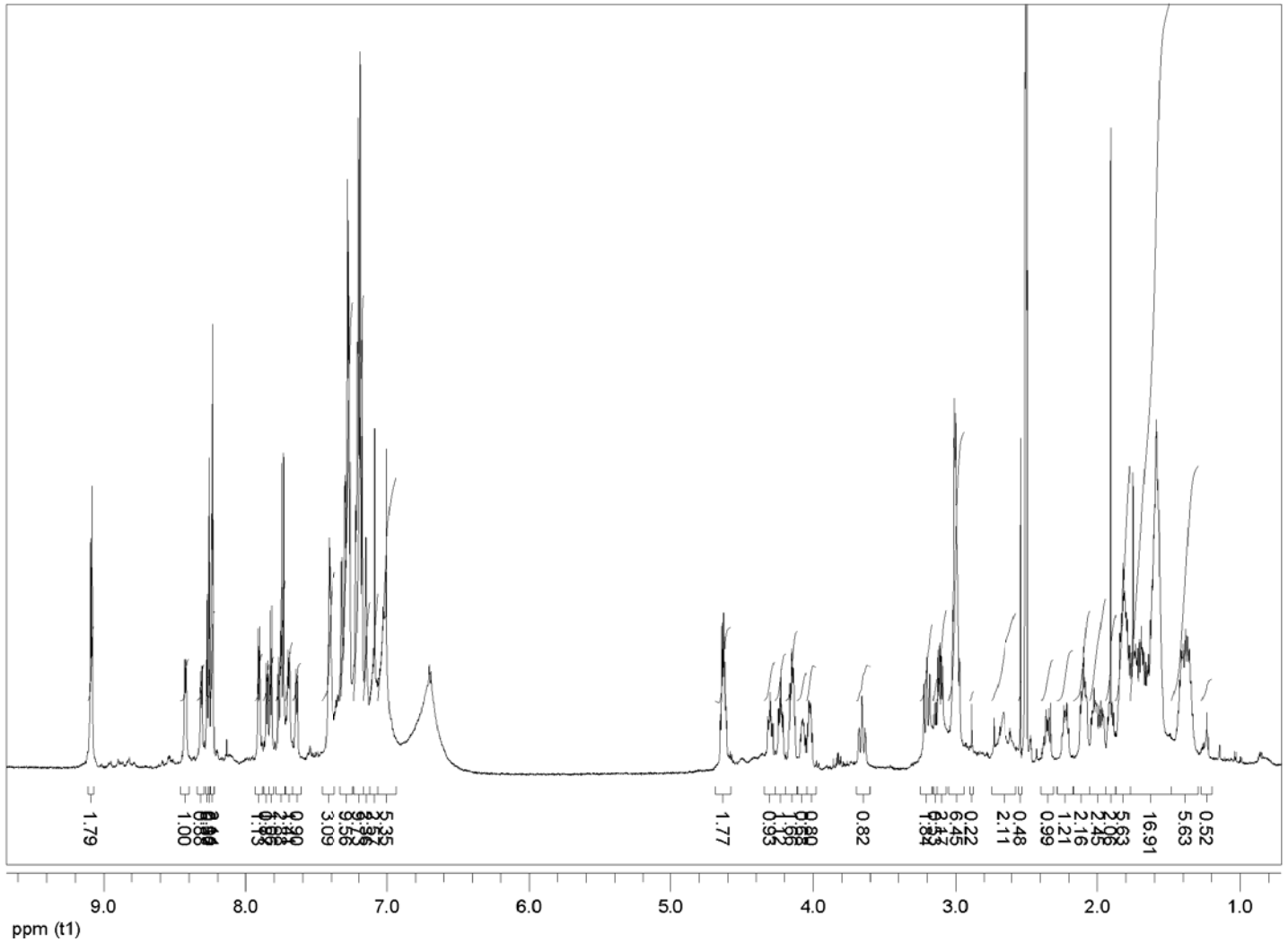
9.09 (2H, d, *J*=6.12 Hz)
8.43 (1H, d, *J*=6.09 Hz)
8.31 (1H, d, *J*=6.44 Hz)
8.27 (1H, d, *J*=2.53 Hz)
8.26 (1H, d, *J*=2.52 Hz)
8.24 (2H, m)
7.91 (1H, d, *J*=6.82 Hz)
7.85 (1H, d, *J*=7.47 Hz)
7.82 (1H, d, *J*=7.29 Hz)
7.76 (1H, d, *J*=7.74 Hz)
7.74 (2H, d, *J*=8.88 Hz)
7.70 (1H, d, *J*=6.91 Hz)
7.64 (1H, d, *J*=7.10 Hz)
7.41 (2H, m)
7.29 (8H, m)
7.20 (8H, m)
7.15 (2H, s)
7.09 (2H, s)
7.00 (2H, s)

α-Hydrogens (9)

4.63 (2H, m)
4.30 (1H, ddd, *J*=3.40, 7.68, 10.89 Hz)
4.23 (1H, ddd, *J*=3.52, 7.32, 10.85 Hz)
4.15 (2H, m)
4.07 (1H, m)
4.02 (1H, td, *J*=6.00, 9.85 Hz)
3.66 (1H, dt, *J*=2.93, 14.32 Hz)

Side chain hydrogens (49)

3.20 (2H, m)
3.12 (3H, m)
3.00 (6H, m)
2.67 (2H, m)
2.35 (1H, m)
2.22 (1H, td, *J*=7.94, 13.15 Hz)
2.10 (1H, m)
2.00 (2H, m)
1.91 (2H, m)
1.82 (6H, m)
1.64 (17H, m)
1.39 (6H, m)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0.22
0.48
2.11
0.99
16.91
5.63
0.52
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

PG14N (56 observable hydrogens)

Amide and aromatic hydrogens (24)

10.76 (1H, d, *J*=1.83 Hz)

8.86 (1H, d, *J*=5.05 Hz)

8.72 (1H, d, *J*=7.37 Hz)

8.33 (1H, d, *J*=7.24 Hz)

8.27 (2H, m)

7.94 (1H, d, *J*=7.00 Hz)

7.63 (2H, d, *J*=8.68 Hz)

7.50 (1H, d, *J*=7.92 Hz)

7.38 (1H, s)

7.29 (1H, d, *J*=8.10 Hz)

7.25 (5H, m)

7.20 (3H, m)

7.11 (2H, d, *J*=1.27 Hz)

7.04 (1H, t, *J*=7.45 Hz)

6.94 (1H, t, *J*=7.47 Hz)

α-Hydrogens (6)

4.62 (1H, q, *J*=7.54 Hz)

4.38 (1H, q , *J*=7.19 Hz)

4.33 (1H, m)

4.27 (1H, m)

3.94 (1H, m)

3.61 (1H, m)

Side chain hydrogens (26)

3.12 (1H, d, *J*=7.41 Hz)

3.08 (1H, dd, *J*=9.89, 14.01 Hz)

2.95 (2H, m)

2.73 (2H, m)

1.77 (1H, m)

1.62 (6H, m)

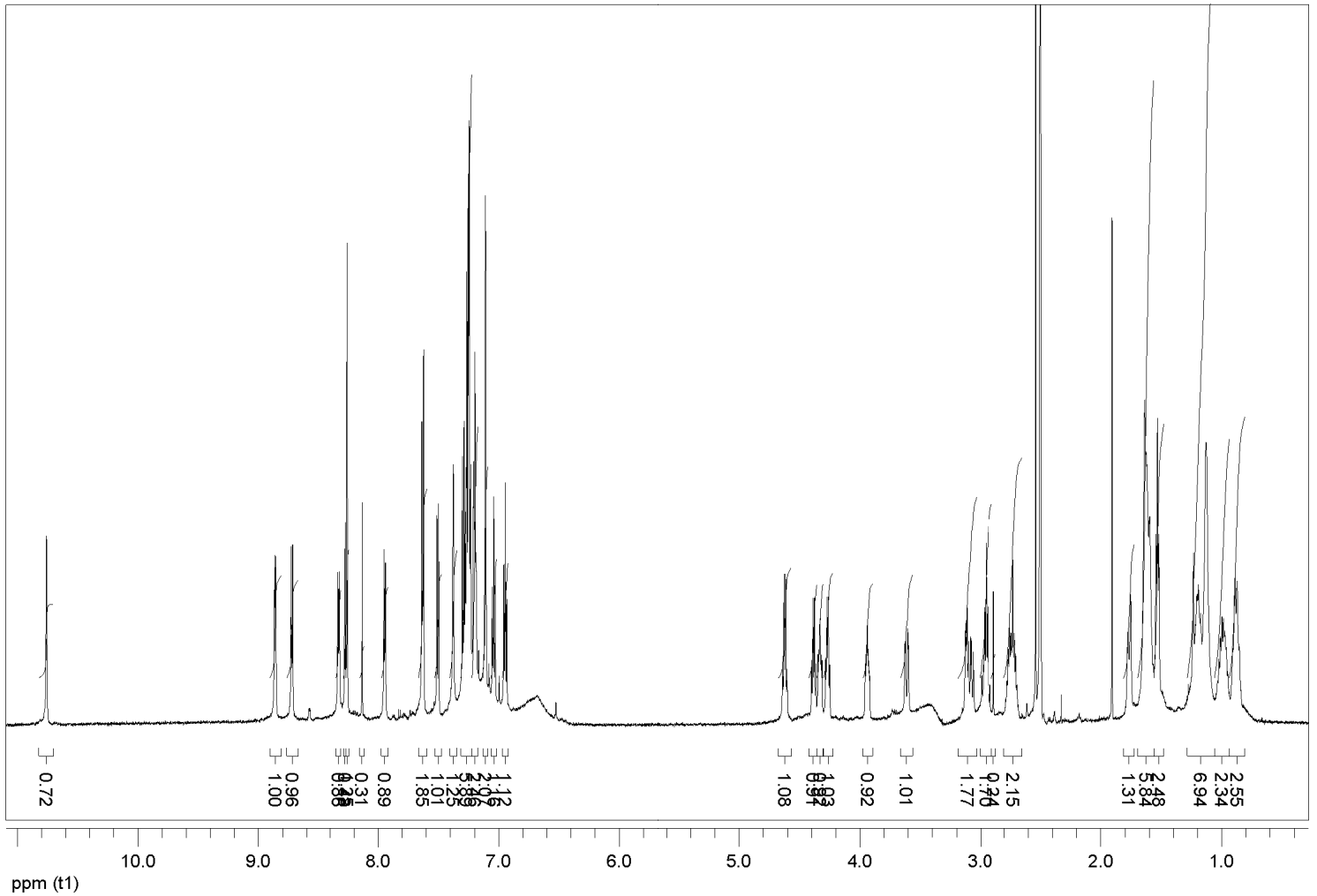
1.53 (2H, t, *J*=7.13 Hz)

1.21 (3H, m)

1.13 (4H, m)

0.99 (2H, m)

0.87 (2H, m)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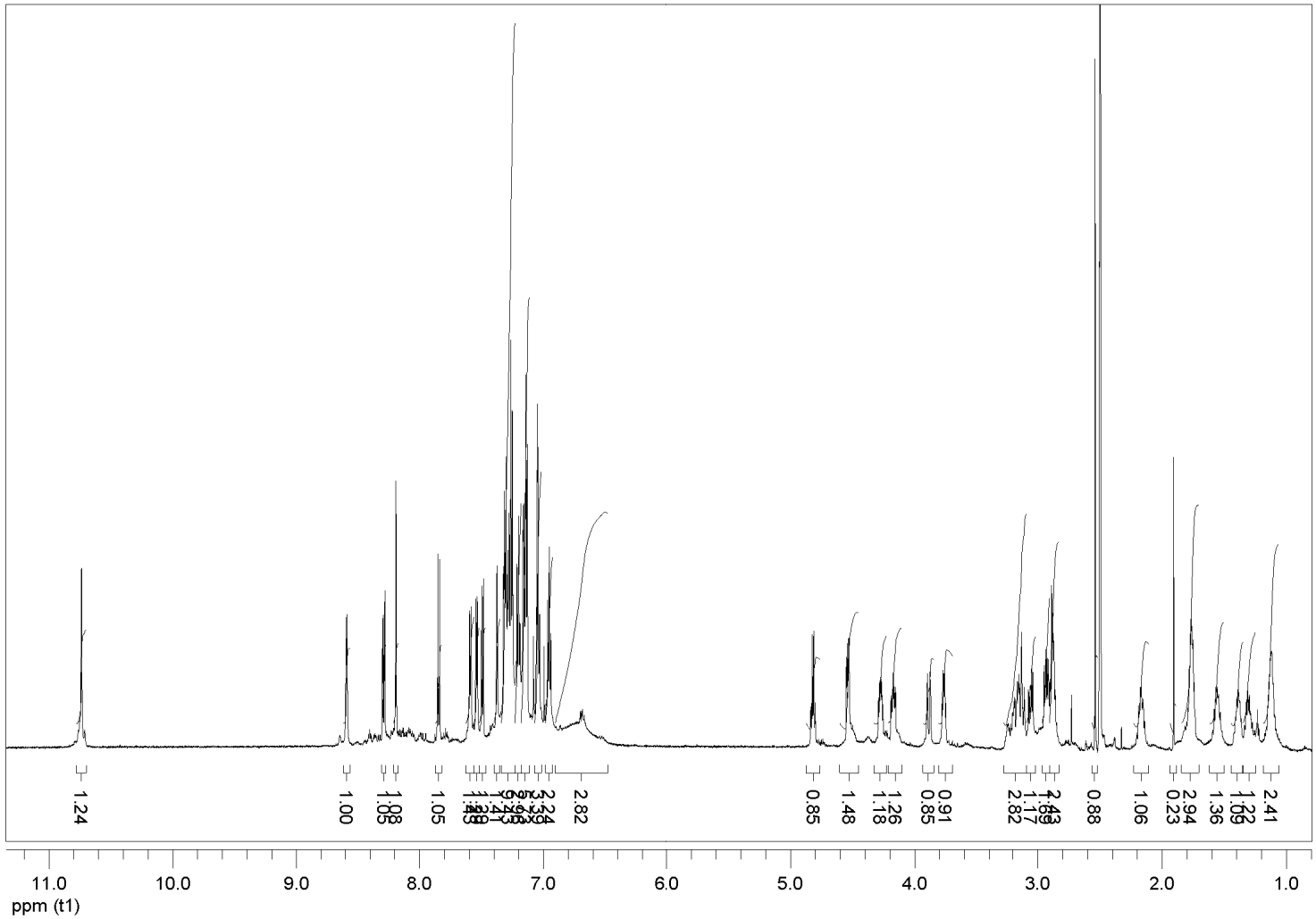
0.31
0.89
1.85
1.01
1.25
1.12
1.08
0.92
1.01
1.77
2.15
1.31
6.94
2.55
2.34
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

PG15N (49 observable hydrogens)
Amide and aromatic hydrogens (25)
10.74 (1H, d, *J*=1.78 Hz)
8.59 (1H, d, *J*=4.73 Hz)
8.29 (1H, dd, *J*=2.55, 8.80 Hz)
8.19 (1H, d, *J*=2.57 Hz)
7.85 (1H, d, *J*=8.94 Hz)
7.59 (1H, d, *J*=7.31 Hz)
7.54 (1H, d, *J*=6.45 Hz)
7.49 (1H, d, *J*=7.84 Hz)
7.37 (1H, s)
7.29 (7H, m)
7.20 (2H, t, *J*=7.29 Hz)
7.14 (4H, m)
7.05 (2H, m)
6.95 (1H, t, *J*=7.45 Hz)

α-Hydrogens (6)
4.82 (1H, q, *J*= 7.06 Hz)
4.54 (1H, dd, *J*=3.79, 8.98 Hz)
4.27 (1H, m)
4.17 (1H, m)
3.89 (1H, dd, *J*=2.78, 14.35 Hz)
3.76 (1H, m)

Side chain hydrogens (18)
3.19 (3H, m)
3.06 (1H, dd, *J*=6.79, 13.62 Hz)
2.93 (1H, dd, *J*=7.11, 13.78 Hz)
2.88 (3H, m)
2.17 (1H, m)
1.77 (3H, m)
1.55 (1H, m)
1.39 (1H, m)
1.30 (1H, m)
1.12 (3H, m)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1.00
1.08
1.05
2.82
0.85
1.48
1.26
1.18
0.85
0.91
2.82
0.88
1.06
0.23
2.94
1.36
2.41
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

PG10N (58 observable hydrogens)

Amide and aromatic hydrogens (34)

10.75 (d, *J* = 1.80 Hz, 1H)

8.84 (d, *J* = 7.91 Hz, 1H)

8.64 (d, *J* = 5.62 Hz, 1H)

8.43 (d, *J* = 7.12 Hz, 1H)

8.27 (dd, *J* = 8.84, 2.56 Hz, 1H)

8.15 (d, *J* = 2.52 Hz, 1H)

7.80 (d, *J* = 7.28 Hz, 1H)

7.75 (d, *J* = 6.41 Hz, 1H)

7.68 (d, *J* = 9.07 Hz, 1H)

7.49 (d, *J* = 7.87 Hz, 1H)

7.39 (s, 1H)

7.28 (m, 8H)

7.20 (m, 3H)

7.16 (m, 4H)

7.12 (s, 2H)

7.08 (s, 2H)

7.04 (t, *J* = 7.49 Hz, 2H)

6.95 (t, *J* = 7.37 Hz, 2H)

α-Hydrogens (7)

4.88 (q, *J* = 7.70 Hz, 1H)

4.36 (m, 4H)

3.92 (m, 1H)

3.62 (m, 1H)

Side chain hydrogens (17)

3.09 (m, 4H)

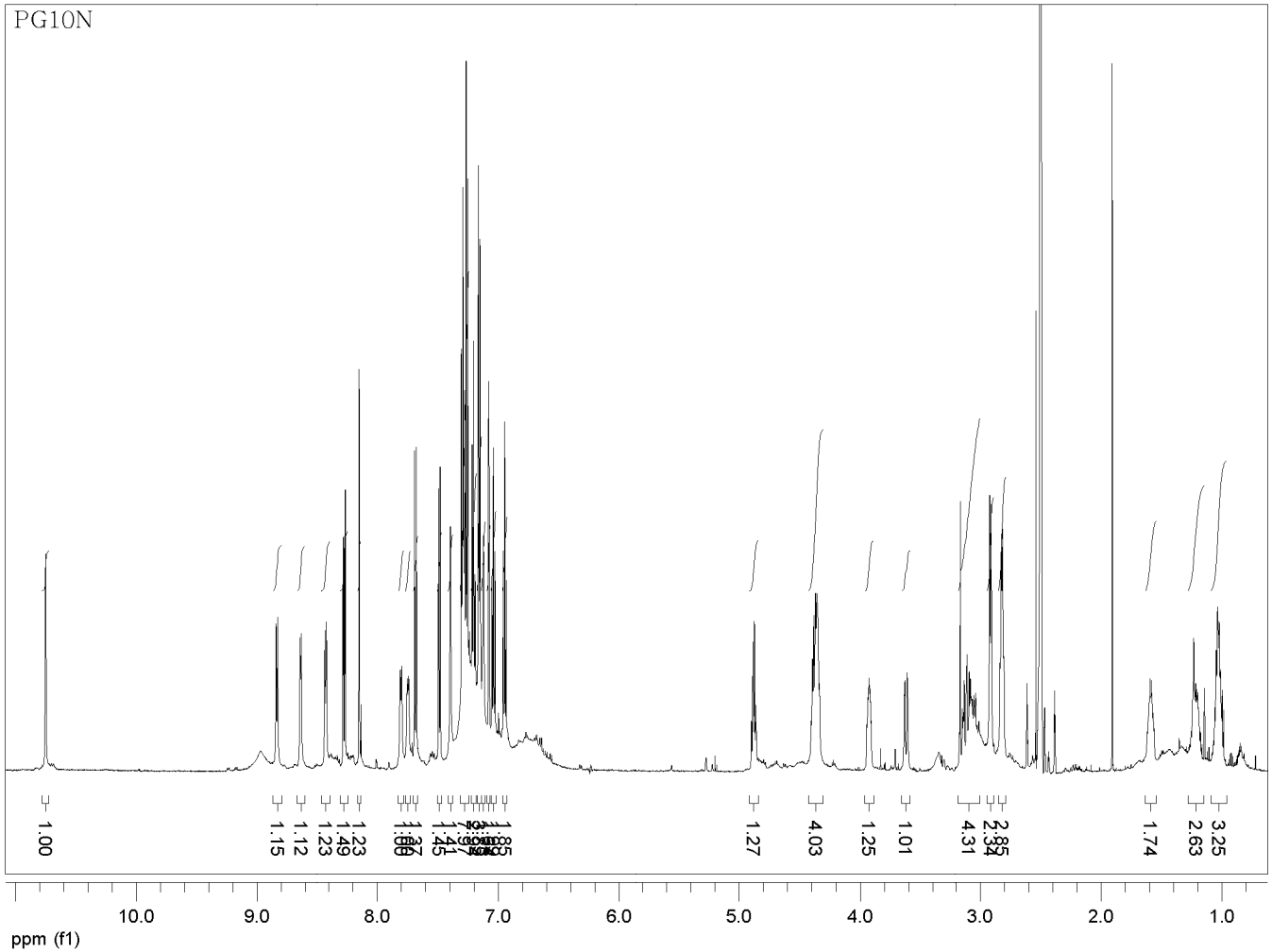
2.91 (d, *J* = 7.36 Hz, 2H)

2.82 (dd, *J* = 12.65, 6.68 Hz, 3H)

1.59 (m, 2H)

1.22 (m, 3H)

1.02 (m, 3H)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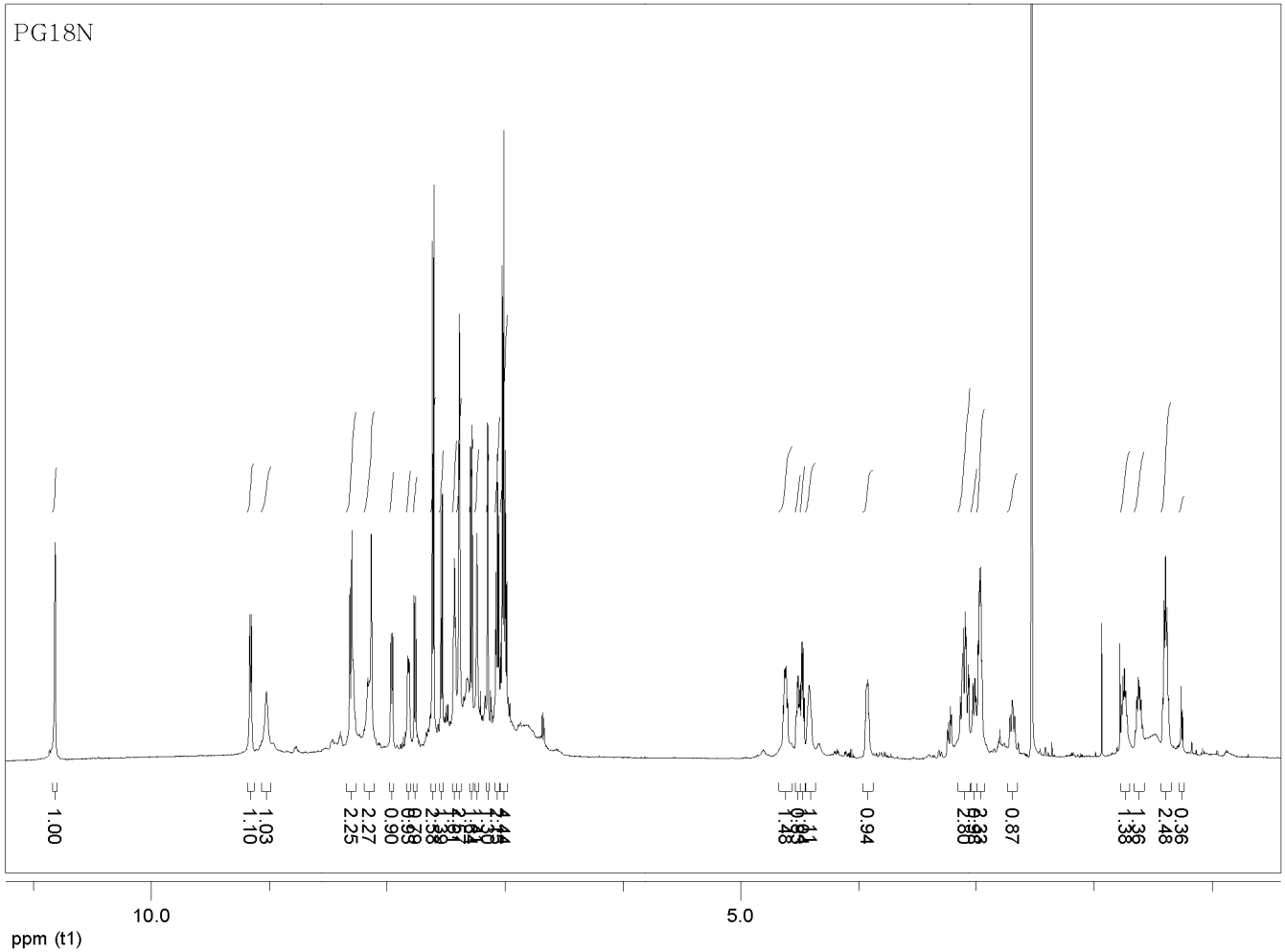
1.00
1.15
1.12
1.23
1.49
1.23
1.27
4.03
1.25
1.01
4.31
1.74
2.63
3.25
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

PG18N (44 observable hydrogens)
Amide and aromatic hydrogens (28)
10.81 (s, 1H)
9.16 (d, *J* = 7.49 Hz, 1H)
9.03 (s, 1H)
8.30 (m, 2H)
8.15 (m, 2H)
7.96 (d, *J* = 8.05 Hz, 1H)
7.82 (d, *J* = 6.20 Hz, 1H)
7.76 (d, *J* = 9.04 Hz, 1H)
7.61 (d, *J* = 8.14 Hz, 2H)
7.54 (d, *J* = 7.88 Hz, 1H)
7.43 (t, *J* = 4.99 Hz, 2H)
7.39 (s, 3H)
7.29 (d, *J* = 8.08 Hz, 2H)
7.24 (s, 1H)
7.15 (d, *J* = 1.84 Hz, 1H)
7.07 (m, 2H)
7.01 (m, 4H)

α-Hydrogens (5)
4.62 (q, *J* = 7.84 Hz, 1H)
4.52 (m, 1H)
4.48 (q, *J* = 7.03 Hz, 1H)
4.42 (s, 1H)
3.93 (m, 1H)

Side chain hydrogens (11)
3.10 (m, 3H)
3.01 (m, 1H)
2.97 (q, *J* = 6.63 Hz, 2H)
2.69 (m, 1H)
1.75 (m, 1H)
1.63 (m, 1H)
1.40 (m, 2H)


PG18N
1.00
1.10
1.03
2.25
2.27
0.90
1.48
0.94
0.87
1.38
2.48
0.36
10.0
5.0
ppm (t1)

PG19N (65 observable hydrogens)

Amide and aromatic hydrogens (38)

8.99 (s, 1H)

8.76 (d, *J* = 5.75 Hz, 1H)

8.73 (m, 2H)

8.51 (d, *J* = 7.48 Hz, 1H)

8.45 (d, *J* = 7.83 Hz, 1H)

8.24 (m, 2H)

8.07 (t, *J* = 2.22 Hz, 1H)

7.85 (m, 6H)

7.76 (m, 2H)

7.69 (m, 3H)

7.48 (m, 4H)

7.37 (m, 6H)

7.29 (m, 2H)

7.04 (m, 1H)

6.95 (m, 2H)

6.86 (m, 1H)

6.58 (m, 2H)

α-Hydrogens (7)

4.88 (dt, *J* = 8.30, 6.07 Hz, 1H)

4.50 (m, 1H)

4.39 (m, 1H)

4.32 (m, 1H)

4.22 (m, 1H)

4.09 (m, 1H)

3.65 (m, 1H)

Side chain hydrogens (20)

3.11 (m, 6H)

2.97 (m, 1H)

2.74 (m, 3H)

2.20 (m, 1H)

1.99 (m, 1H)

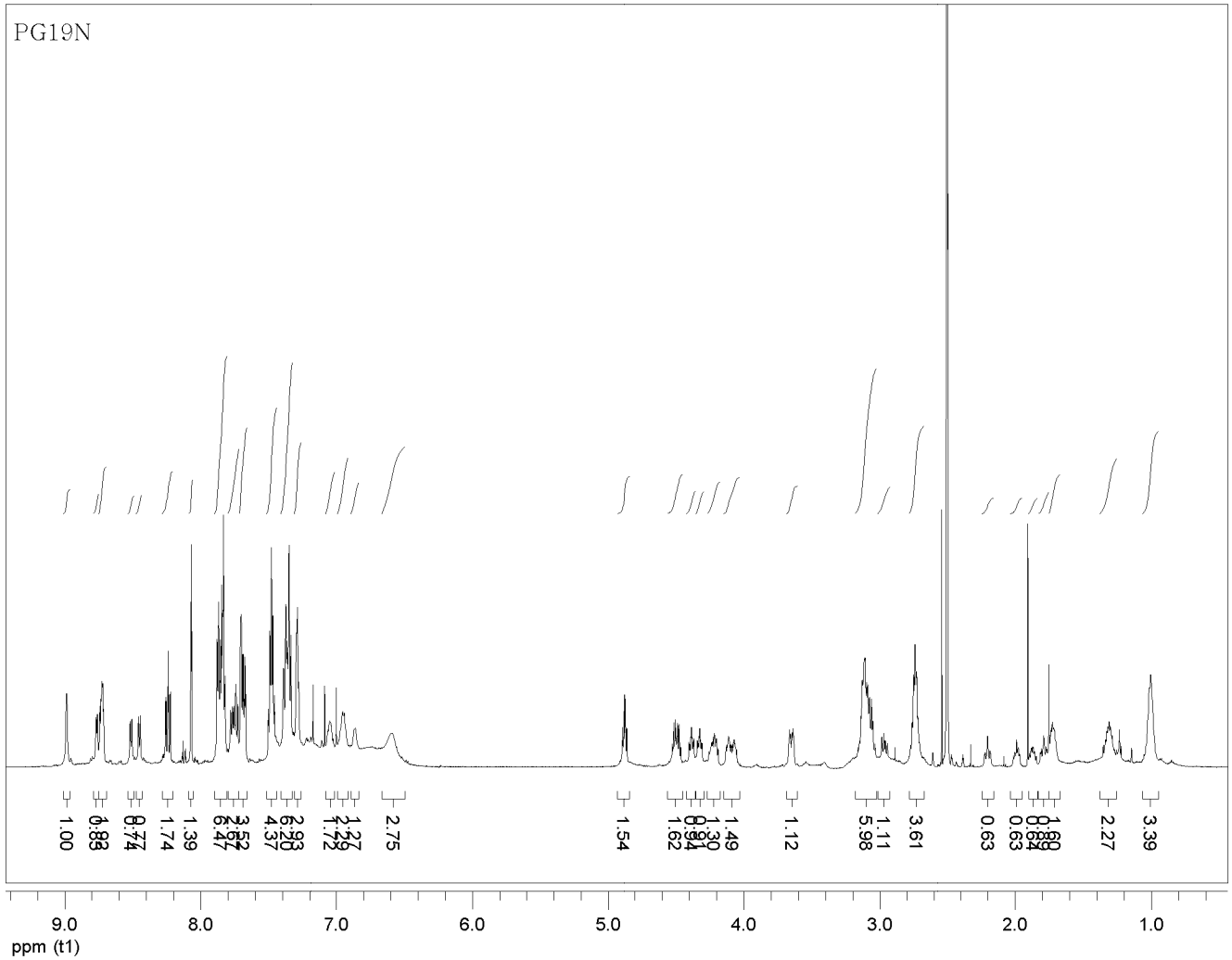
1.87 (m, 1H)

1.79 (m, 1H)

1.71 (m, 1H)

1.32 (m, 2H)

1.01 (m, 3H)


PG19N
1.00
1.74
1.39
2.75
1.54
1.62
1.49
1.12
5.98
1.11
3.61
0.63
0.63
2.27
3.39
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

PG30N (45 observable hydrogens)

Amide and aromatic hydrogens (27)

8.99 (broad s, 1H)

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

8.61 (d, *J* = 5.63 Hz, 1H)

8.40 (d, *J* = 7.01 Hz, 1H)

8.27 (dd, *J* = 8.84, 2.55 Hz, 1H)

8.15 (d, *J* = 2.56 Hz, 1H)

7.82 (d, *J* = 7.61 Hz, 1H)

7.75 (d, *J* = 7.39 Hz, 1H)

7.70 (d, *J* = 9.05 Hz, 1H)

7.41 (broad s, 1H)

7.36 (broad s, 1H)

7.33 (broad s, 1H)

7.23 (m, 8H)

7.15 (m, 7H)

α-Hydrogens (6)

4.90 (q, *J* = 7.88 Hz, 1H)

4.40 (q, *J* = 7.20 Hz, 1H)

4.34 (m, 2H)

3.89 (m, 1H)

3.65 (m, 1H)

Side chain hydrogens (12)

3.11 (m, 1H)

3.05 (m, 2H)

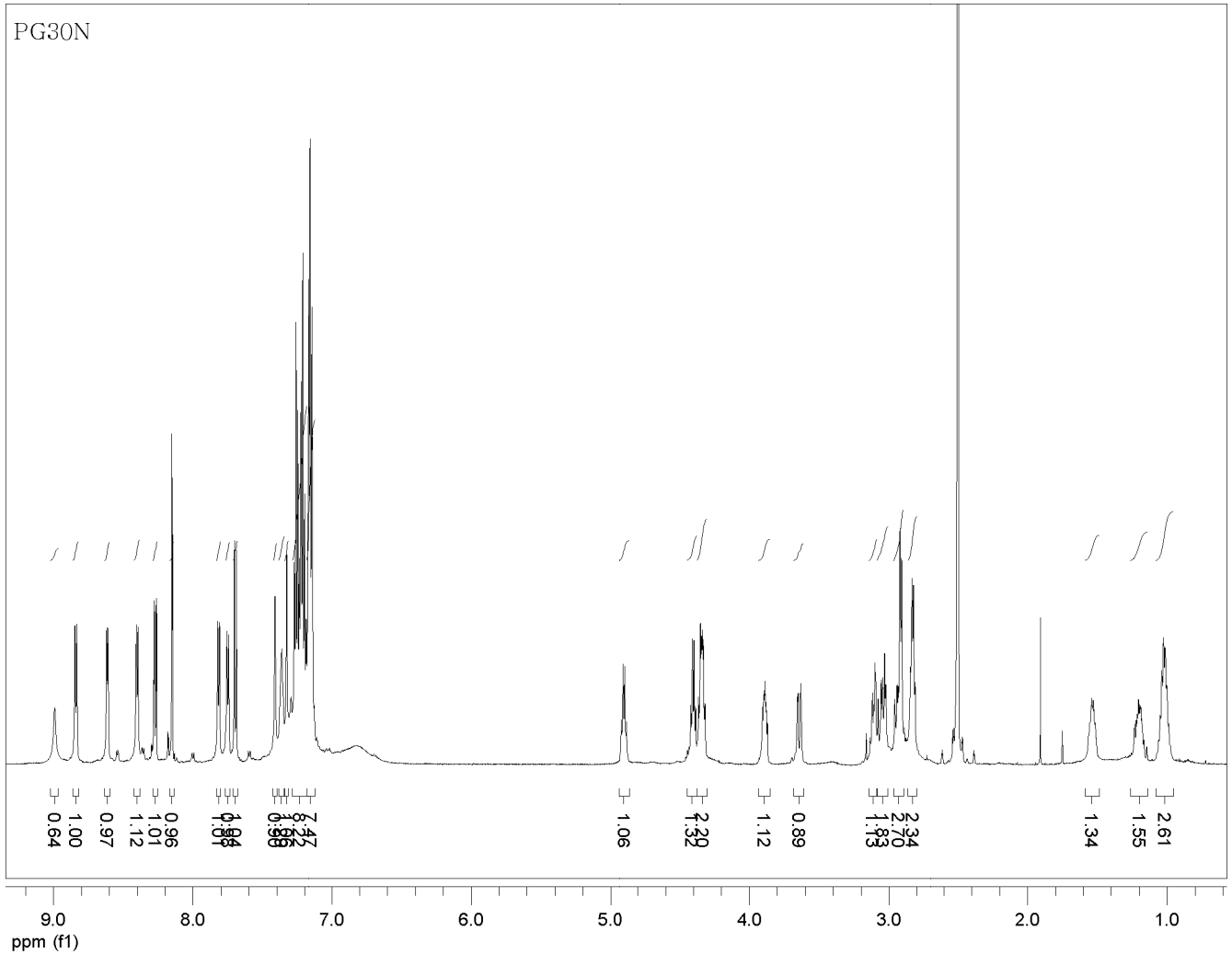
2.93 (m, 3H)

2.83 (q, *J* = 6.71 Hz, 2H)

1.54 (m, 1H)

1.21 (m, 1H)

1.02 (m, 2H)


PG30N
0.64
1.00
0.97
1.12
1.01
0.96
1.06
1.32
1.12
0.89
1.34
1.55
2.61
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)