Pergamon

Tetrahedron Letters 40 (1999) 695–696

TETRAHEDRON LETTERS

Lyngbyapeptin A, a modified tetrapeptide from *Lyngbya bouillonii* (Cyanophyceae)

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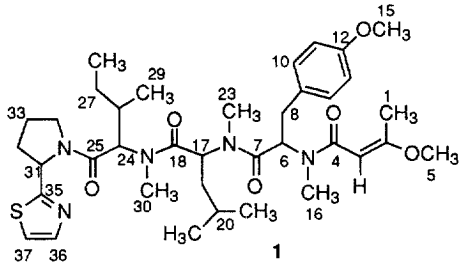
Received 16 October 1998; accepted 13 November 1998

Abstract. Lyngbyapeptin A **1**, a novel tetrapeptide containing the rare 3-methoxy-2-butenoyl moiety was isolated from the cyanobacterium *Lyngbya bouillonii*, collected in Papua New Guinea. Its structure (without stereochemistry) was established by mass spectral- and two-dimensional NMR studies.

In the course of a screening program to evaluate cyanobacteria as a source of new interesting bioactive compounds, we recently reported the isolation of two unusual secondary metabolites, laingolide[1] and lyngbyaloside[2] from *Lyngbya bouillonii*, collected on the North coast of Papua New Guinea (Laing Island, Nagada Harbour). During the course of our study, we found that this organism also produces a series of peptides in trace amounts, and we now report on the structure determination of the first of them, lyngbyapeptin A **1**.



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Lyngbyapeptin A **1** (1.05 mg, amorphous solid, HREIMS: $M^{+\cdot}$ at *m/z* 697.3869; calc. for $C_{37}H_{55}N_5O_6S$: 697.3873; Δ=0.4 mDa) displayed signals in its ^1H NMR spectrum (600 MHz, $CDCl_3$, Table 1), indicating the presence of ten methyl groups: one primary (t at δ 0.74, *J* = 6.0 Hz), three secondary (d at δ 0.81, *J* = 6.5 Hz, 0.90, *J* = 6.5 Hz, and 0.92, *J* = 6.5 Hz), one tertiary (s at δ 2.18), three NCH_3 (s at δ 2.59, 2.79 and 2.98), and two OCH_3 (s at δ 3.62 and 3.72). The ^1H NMR spectrum also showed the presence of four 1H signals attributable to α-H of amino acids (δ 4.96, d, *J* = 11.0 Hz; 5.42, m; 5.43, m; 5.80, dd, *J* = 9.7 and 5.3 Hz), of a singlet of 1H linked to a carbon atom at δ 90.5, of a thiazole ring (δ 7.65, 1H, d, *J*=3.0 Hz; 7.19, 1H, d, *J*=3.0 Hz), and of a tyrosine residue (δ 6.73, 2H, m and 7.18, 2H, m). The ^{13}C NMR spectrum, together with HMQC and HMBC data, allowed us to identify the four constitutive amino acid residues of **1** as *N,O*-dimethyltyrosine, *N*-methylleucine, *N*-methylisoleucine and proline. The ^{13}C NMR data also confirmed the presence of a 2-substituted thiazole ring (Table 1), and, moreover, permitted the identification of a 3-methoxy-2-butenoyl moiety. Particularly noteworthy were the HMBC correlations between the vinyl H at δ 5.15 and the C atoms at δ 170.2 and 18.5, between the CH_3 at δ 2.18 and the C atoms at δ 90.5 and 170.2, as well as between the OCH_3 at δ 3.62 and the C atom at δ 170.2 (Table 1). This was confirmed by comparison of the values observed for **1** with those reported for barbamide[3]. The sequence of the four *N*-methyl amino acids was established by HMBC correlations (see Table 1), and confirmed by a high-resolution mass spectral study. The positioning of the thiazole ring and of

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0040-4039/99/$ - see front matter
PII: S0040-4039(98)02451-4

the 3-methoxy-2-butenoyl moiety as shown in **1** was deduced on the basis of mass spectral fragmentations [e. g. fragment ions at *m/z* 544.3379 ($C_{30}H_{46}N_3O_6$), corresponding to the loss of the proline-thiazole fragment, *m/z* 417.2397 ($C_{23}H_{33}N_2O_5$), corresponding to the loss of the thiazole-proline-*N*-methylisoleucine fragment and *m/z* 290.1393 ($C_{16}H_{20}NO_4$), corresponding to the *N,O*-dimethyltyrosine-3-methoxy-2-butenoyl moiety].

Lyngbyapeptin A **1** is unstable and decomposed at the end of the NMR measurements, thus preventing us to determine the relative configuration of its C2-C3 double bond by nOe measurements. This configuration is proposed to be *E*, by comparison of the ^{1}H NMR data of **1** with those of model compounds[4]. The small amount available precluded the establishment of the relative and absolute configuration of stereogenic centres of **1**, as well as a study of its biological activity. These questions will be addressed in the future.

Position	δC^a	δH^b	HMBC (H to C)[c]
1	18.5	2.18, 3H, s	170.2, 90.5
2	170.2	-	-
3	90.5	5.15, 1H, s	170.2, 18.5
4	167.8	-	-
5	54.9	3.62, 3H, s	170.2
6	54.0	5.80, 1H, dd, 9.7, 5.3	169.6, 167.8, 34.5, 31.0
7	169.6	-	-
8	34.5	3.24, 1H, dd, 13.0, 9.8	54.0
8'		2.68, 1H, dd, 13.0, 5.3	169.6, 130.5, 129.3, 54.0
9	129.3	-	-
10,14	130.5	7.18, 2H, m	158.5, 34.5
11,13	113.7	6.73, 2H, m	158.5, 129.3
12	158.5	-	-
15	55.2	3.72, 3H, s	158.5
16	31.0	2.98, 3H, s	167.8, 54.0
17	51.4	5.43, m	171.2, 38.0, 29.5, 24.5
18	171.2	-	-
19	38.0	1.58, 1H, m; 1.52, 1H, m	-
20	24.5	1.32, 1H, m	-
21	22.2	0.92, 3H, d, 6.5	38.0, 24.5
22	23.3	0.90, 3H, d, 6.5	38.0, 24.5
23	29.5	2.79, 3H, s	169.6, 51.4
24	58.0	4.96, 1H, d, 11.0	171.2, 169.8, 33.0, 30.0
25	169.8	-	-
26	33.0	1.92, m	-
27	23.3	0.98, 1H, m; 0.77, 1H, m	-
28	10.2	0.74, 3H, t, 6.5	23.3
29	15.0	0.81, 3H, d, 6.5	58.0, 33.0, 23.3
30	30.0	2.59, 3H, s	171.2, 58.0
31	58.4	5.42, 1H, m	169.8
32	31.5	2.22, 1H, m; 2.16, 1H, m	-
33	24.0	2.15, 1H, m; 1.96, 1H, m	-
34	47.2	3.92, 1H, m; 3.72, 1H, m	-
35	171.7	-	-
36	142.0	7.65, 1H, d, 3.0	-
37	119.0	7.19, 1H, d, 3.0	-

[a]125.72 MHz, nanoprobe; [b]600 MHz; [c]Optimized for $^nJ_{CH}$ = 5 and 10 Hz

Table 1. NMR data of lyngbyapeptin A **1** ($CDCl_3$, δ, *J* in Hz).

Acknowledgements: We thank the Belgian FRFC for financial support (contracts n° 2.4570.93-98, 2.4502.95 and 2.4521.96). Particular thanks are due to Dr P. A. Keifer (Varian Application Lab, Palo Alto) who ran ^{13}C NMR, HMQC and HMBC spectra of **1**. We also thank Mr C. Maerschalk for NMR spectra and Mr C. Moulard for the HREIMS. L. H. is Research Associate of the Belgian National Fund for Scientific Research.

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