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Aplyzanzine A, A new Dibromotyrosine derivative from a Verongida sponge

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Abstract: Aplyzanzine A (**1**), a novel bisdibromotyrosine derivative has been isolated from the Indo-Pacific sponge *Aplysina* sp. Its structure was elucidated mainly on the basis of 1D and 2D-NMR and MS spectroscopic data. A biomimetic synthesis, which might well be the biosynthesis of **1,** is suggested.

In connection with our long-standing interest in the chemistry of marine sponges, we have investigated Indo-Pacific sponges that were collected near the coast of Zanzibar. From one of the sponges, an *Aplysina* sp. we have isolated a new dibromotyrosine derivative (**1**) designated aplyzanzine A.

The genus *Aplysina* belonging to the Verongida sponges (order Verongida, family Aplysinidae) is well known for its dibromotyrosine metabolites [1-8]. The freshly collected sponge was frozen on site and kept frozen until needed. Freeze-dried sponge tissue (70g, dry wt) was extracted with ethyl acetate to give a brown gum (0.4g) after evaporation. The latter extract was subsequently partitioned between aqueous methanol and CCl_4, $CHCl_3$ and n-Butanol. The $CHCl_3$-phase was further fractionated by chromatography on Sephadex LH-20 (eluting with CH_2Cl_2:MeOH , 1:1) to afford aplyzanzine A (**1**, 15 mg, 0.02% dry wt).

Aplyzanzine A (**1**) [9], obtained as pale orange oil, analyzed for $C_{25}H_{33}Br_4N_3O_3$, from the CIMS and NMR data; the CIMS [10] showing a cluster of peaks at *m/z* 740/742/744/746/748, in a ratio of 1:4:6:4:1, characteristic for a tetrabrominated compound. The EIMS [11] showed a similar cluster of peaks at *m/z* 739/741/743/745/747 while the main peak (i.e. *m/z* 743) had the intensity of 4% only. The IR spectrum [12] revealed bands at 1036, 1678, 3222 and 2968 cm^{-1} suggesting an ethereal C−O, an amide and an aryl CH group, respectively. The presence of an amide group was confirmed by the d_C 170.8 s and d_H 8.67 br t resonances. Furthermore, the multiplicity of the NH signal suggested a CH_2NHCO group. Additional functionalities were two NMe_2 groups (d_H 2.26 s and 2.67 s, 6H each), one aromatic methoxy group (d_C 60.4 q, d_H 3.74 s, 3H), and two *para* substituted symmetric aromatic rings (Table 1) – accounting, together with the amide, for the nine degrees of unsaturation of **1**. From the multiplicity (DEPT experiment) and d_C - values it was clear that each ring is tetrasubstituted bearing an ethereal oxygen (d_C 152.3 s and 150.9 s, for C-4 and 15, respectively). The chemical shifts of the other ring carbon-atoms and especially the three and two bond CH-correlations, seen in a HMBC experiment (Table 1 and Figure 1) determined the alkyl-dibromophenolic structure of the two rings. A 1D INAPT experiment [13] assisted with the distinction between the close aromatic C-atom shifts. All chemical shifts of the aromatic rings are in good agreement with literature values [1]. Three additional spin systems were established by a COSY experiment (Figure 2), that is, one CH_2CH, one CH_2CH_2 and one $OCH_2CH_2CH_2N$ system (C-7, 8; C-10, 11 and C-18–20, respectively, Table 1). All the above functional groups accounted for all the molecule's atoms and the nine degrees of unsaturation. assemblage of the various moieties of

aplyzanzine A (**1**) was essentially achieved from the HMBC CH-correlations (Figure 1 and Table 1) and partially also confirmed by NOE measurements (Figure 2). ^{2}J and ^{3}J CH-correlations from 2H-7, H-8 and Me's 22, 23 to C-1, 2 (and 6), 8 and 9; and between 2H-11, H-13 (and 17), 2H-18 and the second aromatic ring C-atoms and, similarly, between 2H-10 and 11, 2H-18, 19, 20 and Me's 24, 25 to their adjacent C-atoms (Figure 1) established the full structure of **1**. The suggested structure was further confirmed by NOE measurements (Figure 2) and several MS fragments shown in Figure 3. All fragmentations agree well with known cleavages a to heteroatoms.

The structure of aplyzanzine A (**1**) point clearly to a bis-dibromotyrosine derivative. Parts of **1** are well known from other Verongida sponges metabolites (e.g. moloka'inamine [2], Figure 4). Closest in structure, however, is purealidin C reported by Kobayashi [1] from *Psammaplysilla purea* (Figure 4). Both **1** and the latter compound have in common the dibromotyrosine - dibromotyramine skeleton, however, they are differently substituted. To the best of our knowledge, the structure of a N,N-dimethyl tyrosine is without president as a marine natural product.

Several recently reported additional dibromotyrosine derivatives are ceretinamine [4], ceratinamides A and B [5], 7-Hydroxyceratinamine [7], and other metabolites reported by Fattorusso [6].

A suggested biomimetic synthesis of **1** is shown in Scheme 1, starting from the suitable dibromotyrosine and dibromotyramine derivatives. This synthesis can also be suggested as the biosynthesis of **1** in the sponge.

Table 1. ^{1}H and ^{13}C NMR Data for 1[a]

No.	d_C (mult)	d_H[b] (mult, *J* in Hz)	COSY correlations	HMBC (H to C) correlations	Inapt	1D NOE
1	137.66 s					
2, 6	133.21 d	7.31 (s, 2H)		C2/C6, C3/C5, C4, C7	C2/C6, C3/C5, C4	H7a, H7b
3, 5	117.58 s					
4	152.34 s					
7a 7b	31.57 t	2.71 (dd, 1H, 4.5, 13.8) 2.94 (dd, 1H, 8.8, 13.5)	H7b, H8 H7a, H8	C2/C6, C8, C9	C1, C2/C6, C22/C23	H22/H23
8	69.84 d	3.14 (dd, 1H, 4.5, 8.8)	H7a, H7b	C1, C9, C22/C23		
9	170.82 s					
10	39.81 t	3.29 (dt, 2H, 2.8, 7.0)	H11a, H11b	C9, C11, C12		
11a	34.20 t	2.54 (m, 1H)	H10	C10, C13/C17		

11b		2.57 (m, 1H)				
12	137.94 s					
13, 17	132.78 d	7.23 (s, 2H)		C11, C13/C17, C14/C16, C15	C13/C17, C14/C16, C15	H11a, H11b
14, 16	117.74 s					
15	150.87 s					
18	69.71 t	3.96 (t, 2H, 5.5)	H19	C15, C19, C20		
19	25.38 t	2.18 (m, 2H)	H18, H20	C18, C20		
20	55.41 t	3.16 (m, 2H)	H19	C18, C19, C24/C25		
21	60.39 q	3.74 (s, 3H)		C3/C5, C4		
22, 23	41.51 q	2.26 (s, 6H)		C8, C22/C23	C8	H7a, H7b
24, 25	42.92 q	2.67 (s, 6H)		C20, C24/C25	C20	H20
N-1[c]		8.67 (br t, 1H)	H10			

a Data recorded in $CDCl_3$+CD_3OD (10:1) at 500 MHz (^1H) and 125 MHz (^{13}C) at 27 ^oC.

b CH assignments are based on the HMQC spectrum.

c Obtained from spectra taken in $CDCl_3$.

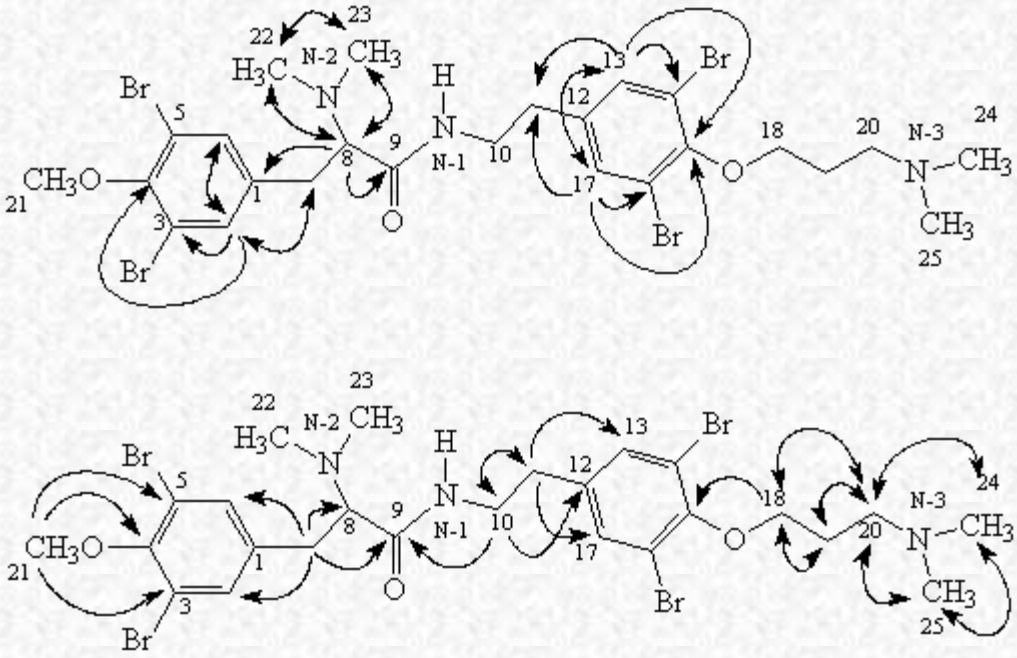


Figure 1. HMBC correlations of **1**.

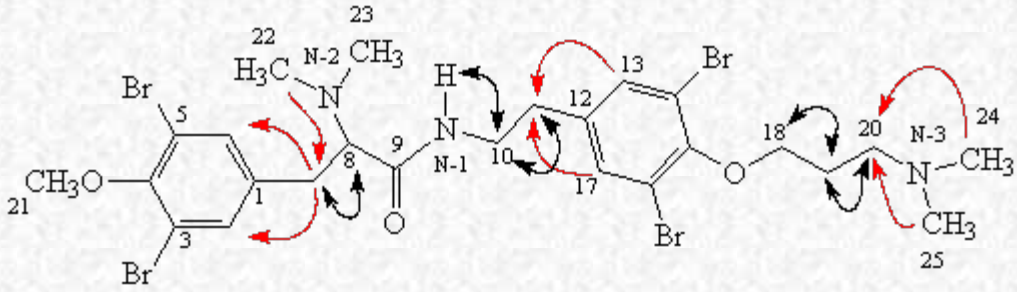


Figure 2. COSY and NOE correlations of **1**.

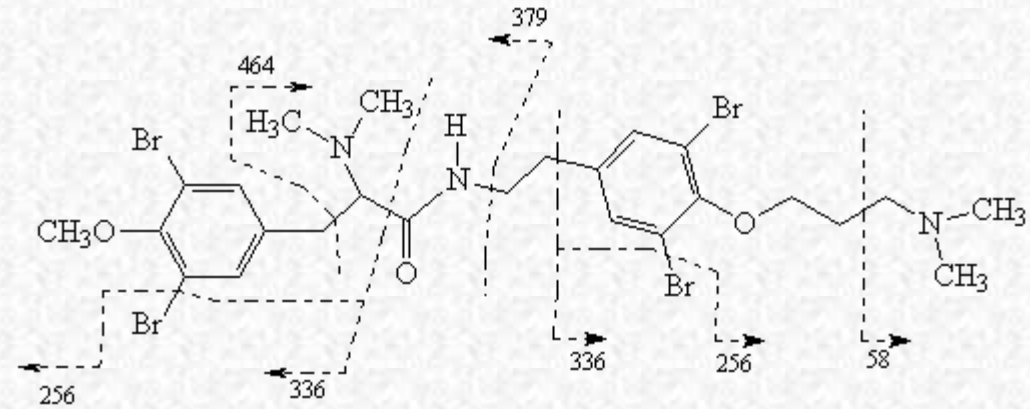
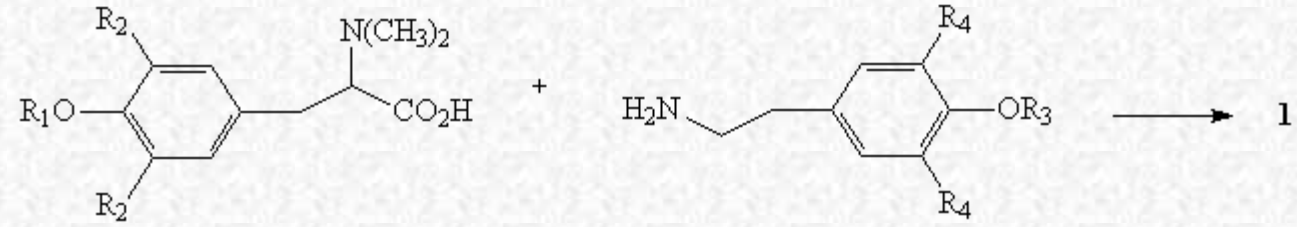


Figure 3. EIMS fragmentation of **1**.



R_1= H or Me
R_2= H or Br

R_3= H or $CH_2CH_2CH_2NMe_2$
R_4= H or Br

Scheme 1. Suggested biomimetic / biogenesis for **1**.

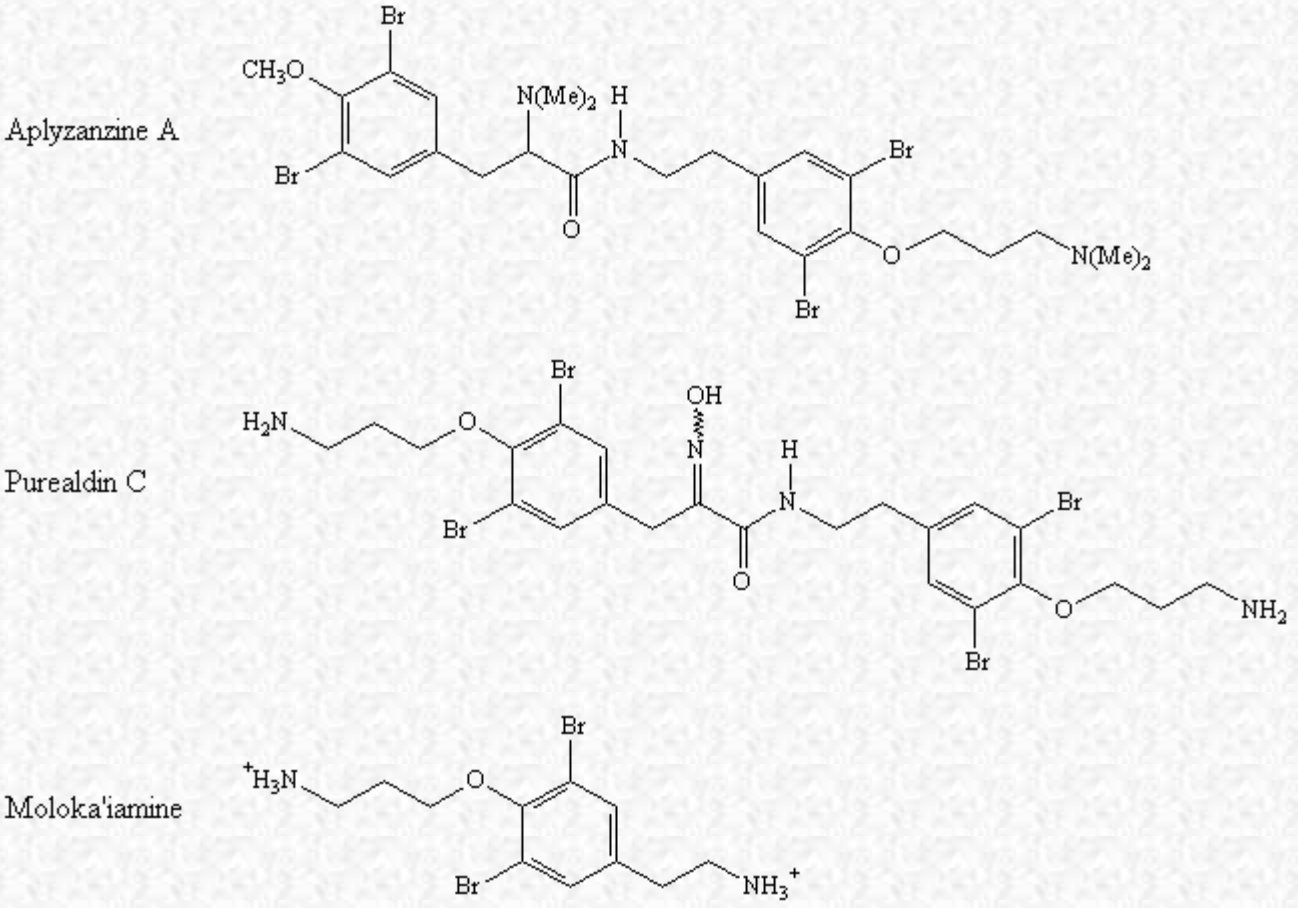


Figure 4. Aplyzanzine A (**1**) and the closely related purealidin C and moloka'iamine [2].

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[9] Aplyzanzine A exhibits a zero a_D value, suggesting easy racemization of the chiral a position of the tyrosine, in the sponge.

[10] CIMS *m/z* (relative intensity): 740(22)/742(70)/744(100)/746(64)/748(20) [MH^+], 696(1)/698(5)/700(7)/702(4)/704(1) [MH^+-Nme_2], 662(4)/664(10)/666(8)/668(2) [MH^+-Br], 582(3)/584(6)/586(3) [MH^+-Br_2], 462(3)/464(12)/466(12)/468(3), 334(15)/336(26)/338(15) [$C_{11}H_{14}Br_2NO^+$], 309(12)/311(21)/313(8), 118(22).

[11] EIMS *m/z* (relative intensity): 696(1)/698(3)/700(7)/702(3)/704(1) [MH^+-Nme_2], 462(4)/464 (9)/466(7) [$C_{17}H_{26}Br_2N_3O_2^+$], 377(5)/379(6)/381(3) [$C_{12}H_{15}Br_2N_2O_2^+$], 334(52)/336(99)/338(50) [$C_{11}H_{14}Br_2NO^+$], 256(20)/258(15) [$C_{11}H_{14}BrNO^+$], 84(17), 58(100) [$CH_2Nme_2^+$].

[12] IR ($CHCl_3$) n_{max} 997, 1036, 1211, 1221, 1259, 1420, 1465, 1473, 1545, 1678, 2450, 2969, 3023, 3222 cm^{-1}.

[13] Braun S.; Kalinowski H. O.; Berger S. In *100 and more Basic NMR Experiments*, VCH Publishers, **1996**, p 203.

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