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Barettin, revisited?

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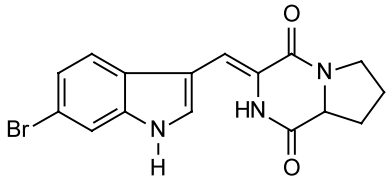
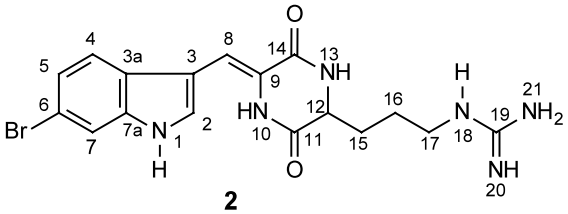
Abstract—A new indole derivative representing a condensation product of 6-bromotryptophan and arginine is the major diketopiperazine produced by the sponge *Geodia baretti*. Strong evidence is provided that this compound represents the correct structure of barettin, which had been described earlier.

Sponges of the family Geodiidae are sources of interesting natural products.[1,2] Lidgren et al. have described the isolation of a pharmacologically active indole alkaloid from the cold water sponge *Geodia baretti*.[3,4] On the basis of spectral data they proposed the compound to be the diketopiperazine **1** which they called barettin. An independent synthesis of **1**, however, disproved this structure.[5] Here we describe the isolation and structure elucidation of the novel diketopiperazine **2** from *G. baretti*, showing spectral data similar to those reported for barettin. We do not suggest a trivial name for **2**, but we believe it to represent the compound that has been originally termed barettin.

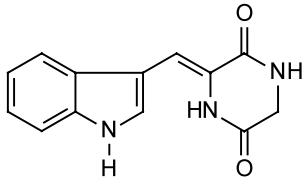


1

The material was collected by submersible at the sula-ridge (Norway) at 300 m depth. The sponge (200 g wet weight) was immediately frozen and kept at −18°C until extraction with acetone. Under reduced pressure, the organic solvent was removed from the aqueous acetone extract. The remaining aqueous solution was extracted with 1-butanol, and the organic layer was concentrated to dryness. The residue was subjected to column chromatography (Merck silica 60, 230–400 mesh, 15% CH_2Cl_2 in MeOH, 0.5 bar overpressure) to yield **2** (0.02% wet weight).



2



3

Investigations of **2** by HR-ESI-MS gave $[M+H]^+$ at m/z 419.0833 corresponding to the molecular formula of $C_{17}H_{20}BrN_6O_2$ (calcd 419.0831). This shows the molecular weight of **2** to be 59 g/mol (CH_5N_3) higher than that of **1**. Screening for the presence of **1** in the crude extract of *G. baretti* proved to be negative. Investigations by MALDI-TOF did not show any mass signal at m/z 360 ($[M+H]^+$ of **1**); however, a molecular ion cluster at m/z 419, 421 $[M+H]^+$ (ratio 1:1), characteristic of a monobrominated compound (like **2**) could be detected.

The ^1H NMR of the new compound showed characteristic signals in the lowfield region indicating a disubstituted indole system.[6] ^1H–^1H coupling as well as NOE

Keywords: diketopiperazine; barettin; sponge; *Geodia*.
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Table 1. ^{1}H NMR (Bruker DRX 500, 500 MHz, DMSO-d_6) and ^{13}C NMR (Bruker AMX 400, 101 MHz, D_3COD) data of barettin

Carbon	δ (ppm)	Proton	δ (ppm)	J (Hz)	COSY[a]	HMBC[b]	NOE[c]
		1-H	12.12	d, $J_{1,2}=2.5$	2-H	C-2, C-3, C-3a	2-H, 7-H, 10-H
C-2	127.45	2-H	7.99	d, $J_{1,2}=2.5$	1-H, 8-H	C-3, C-3a, C-7a, C-8	1-H, 10-H
C-3	109.87						
C-3a	127.55						
C-4	120.87	4-H	7.62	d, $J_{4,5}=8.5$	5-H, 7-H	C-3, C-6, C-7a	5-H, 8-H
C-5	224.52	5-H	7.24	dd, $J_{4,5}=8.5$; $J_{5,7}=1.6$	4-H, 7-H	C-3a, C-7	4-H
C-6	117.03						
C-7	115.69	7-H	7.67	d, $J_{5,7}=1.6$	4-H, 5-H	C-3a, C-5	1-H
C-7a	138.42						
C-8	110.95	8-H	6.99	s	2-H, 10-H	C-2, C-3a, C-11, C-14	2-H, 4-H
C-9	123.35						
		10-H	9.63	s	8-H	C-8, C-9, C-11, C-12, C-14	1-H,2-H
C-11	168.61						
C-12	56.48	12-H	4.07	m	13-H, 15-H	C-11, C-14, C-15, C-16	13-H
		13-H	8.45	d, $J_{12,13}=2.5$	12-H	C-9, C-11, C-12	12-H
C-14	163.36						
C-15	32.62	15-H_2	1.76–1.84	m	12-H, 16-H	C-11, C-12, C-16	–
C-16	25.11	16-H_2	1.50–1.63	m	15-H, 17-H	C-12, C-17	17-H
C-17	41.98	17-H_2	3.16–3.20	m	16-H, 18-H	C-15, C-16, C-19	16-H
		18-H	8.01	t, $J_{17,18}=6.0$	17-H	C-17, C-19	–
C-19	158.61						
		20-/21-H_3	7.00–7.78	br	–	–	–

[a] Correlations of protons in COSY spectra (500 MHz, DMSO-d_6).
[b] Correlations of protons in HMBC spectra (500 MHz, DMSO-d_6).
[c] Correlations of protons in NOESY spectra (500 MHz, DMSO-d_6).

data suggested 3,6-substitution of the indole nucleus, positioning a bromo substituent at C-6 (similar to many other indole derivatives identified in marine organisms).[7] An additional signal at 6.99 ppm indicated a methine group in the 3-position of the indole system (consequently conjugated with another double bond). HMBC spectra showed the presence of a diketopiperazine system attached to the bromoindole via this methine group. NOE data proved the corresponding double bond to be *cis*-configurated. All data fitted perfectly those reported for barettin and those of dipodazine **3**, a secondary metabolite isolated from *Penicillium dipodomyis*.[2,8] In the upfield region, signals caused by protons of a continuous spinsystem (12-H, 13-H, 15-H to 18-H) were found. Chemical shifts of carbon atoms belonging to an aliphatic side chain linked to the diketopiperazine strongly pointed to an arginine substructure.[9] This assignment was further supported by a broad signal between 7.00 and 7.78 ppm (^{1}H NMR) representing the terminal amino groups of the guanidino moiety which typically exchange protons. ^{1}H and ^{13}C NMR data as well as couplings resulting from ^{1}H–^{1}H-COSY, HMBC and NOESY experiments are listed in Table 1.

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