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Cytotoxic bromotyrosine derivatives from a two-sponge association of *Jaspis* sp. and *Poecillastra* sp.

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ABSTRACT

Bioassay-guided chemical investigation of the lipophilic extract of a two-sponge association (*Jaspis* sp. and *Poecillastra* sp.) led to the isolation of two new bromotyrosine derivatives (**1** and **2**), along with known derivatives (**3–12**). Cyclobispsammaplin A (**1**) is a cyclic derivative of the previously reported bispsammaplin A (**13**), while psammaplin M (**2**) is composed of β-alanine (or aspartic acid) unit. Compounds **3**, **4**, **6**, **10**, and **12** are isolated for the first time from a sponge belonging to the subclass Tetractinomorpha. Structure elucidation was performed by a combination of high resolution mass and 2D NMR (principally COSY, HMBC, HSQC, and NOESY) spectroscopy. Compounds **1–4**, **6**, **10**, and **12** were evaluated for cytotoxicity against a small panel of five human solid tumor cell lines and their activity was compared in relevance to their structure.

Marine sponges are the most primitive multicellular animals and contain many pharmacologically important metabolites. A two-sponge association of *Jaspis* sp. and *Poecillastra* sp. collected from Korean waters was known to contain dihydroxystyrene metabolites[1] and steroidal glycosides.[2] As a part of our study on cytotoxic constituents from marine organisms of Korean waters, we previously reported the isolation of pectenotoxin II and several psammaplin analogs from the MeOH extract of a two-sponge association of *Jaspis* sp. and *Poecillastra* sp.[3,4] The two-sponge association of *Jaspis* sp. and *Poecillastra* sp. was collected again for our continued search for further cytotoxic constituents, and was found to contain apocarotenoids[5] and glycerides.[6] Further fractionation and purification of 90% aqueous MeOH extract led us to an isolation of 12 bromotyrosine derivatives (**1**–**12**). This report describes purification,[7] structural characterization, and cytotoxicity evaluation of these bromotyrosine derivatives.

Structural elucidation of cyclobispsammaplin A (**1**), a white, amorphous solid,[8] began from the isotopic clusters at *m/z* 1343/1345/1347/1349/1351 for $[M+Na]^+$, and at *m/z* 1319/1321/1323/1325/1327 for $[M-H]^-$ observed in a positive and negative mode ESIMS spectra, respectively. The exact mass of the pseudomolecular ions could not be measured by FABMS due to weak ion currents. So, the molecular formula, $C_{44}H_{44}N_8O_{12}S_4{}^{79}Br_2{}^{81}Br_2$, was determined on the basis of more sensitive but less accurate HRMALDITOFMS ($[M+Na]^+$ *m/z* 1344.8854, 1346.8811, 1348.8965, and 1350.8937) and NMR data (Table 1). The exact mass of the $[M+Na]^+$ ion (*m/z* 1346.8811) matched with the expected formula $C_{44}H_{44}N_8O_{12}S_4{}^{79}Br_2{}^{81}Br_2Na$ (Δ +26.0 mmu, 19 ppm). The ^{13}C NMR data revealed the presence of only 22 carbons, suggesting it to be a symmetric dimer. Five aromatic proton signals, two isolated methylene groups, and two pairs of coupled methylene groups were observed in ^1H NMR spectrum. These ^1H and ^{13}C NMR data were reminiscent of the data of bispsammaplin A.[4] Interpretation of the 2D NMR data including COSY, HSQC, and HMBC spectra enabled the construction of units **a–d** (Fig. 1). The partial structure **a**, comprised of 1,3,4,5-tetrasubstituted phenyl ring, was gauged by resonances at δ 7.21 (d, J = 2.0 Hz, H-2/H-2′) and 6.47 (d, J = 2.0 Hz, H-6/H-6′) and an isolated benzylic methylene at δ 3.70 (s, H_2-7/H_2-7′). While another unit **b** contained a phenyl ring with a 1,3,4-trisubstitution as indicated by the resonances at δ 7.56 (d, J = 2.0 Hz, H-2″/H-2‴), 6.65 (d, J = 8.0 Hz, H-5″/H-5‴), 7.16 (dd, J = 8.0, 2.0 Hz, H-6″/H-6‴) and an isolated benzylic methylene at δ 3.88 (s, H_2-7″/H_2-7‴). In addition to partial structures **a** and **b**, the NMR data also showed two more partial structures **c** and **d**, which consisted of two pairs of coupled methylenes as assigned from the resonances at δ 3.56 (m, H_2-11/H_2-11′)/2.90 (t, J = 7.0 Hz, H_2-12/H_2-12′) and δ 3.40 (t, J = 7.0 Hz, H_2-11″/H_2-11‴)/2.69 (t, J = 7.0 Hz, H_2-12″/H_2-12‴). Partial units **a** and **c** were connected as indicated by HMBC correlation (Fig. 2) from proton H_2-11/H_2-11′ (δ 3.56) to the amide carbon at δ 165.5

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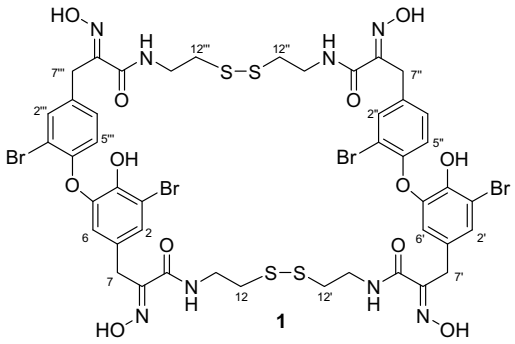
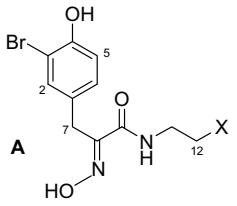


1

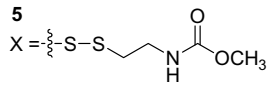


A

2 X = -S-COOCH$_3$

3 X = -S-SO$_2$CH$_3$

4 X = -S-SCN



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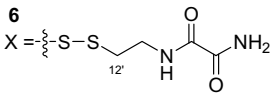

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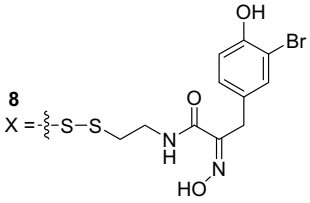

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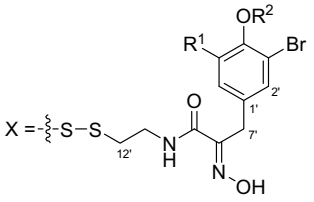
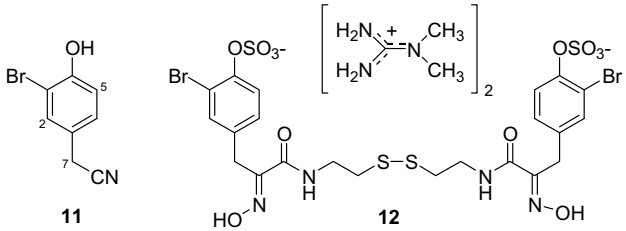
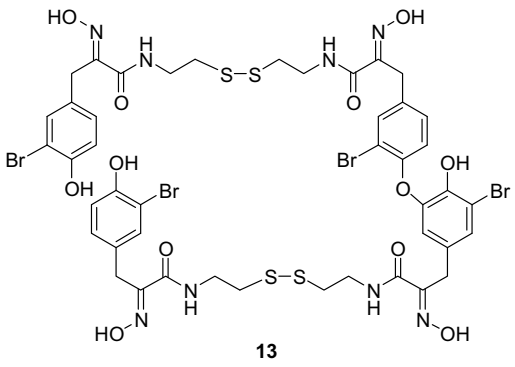


7 R^1 = H R^2 = H
9 R^1 = Br R^2 = H
10 R^1 = H R^2 = SO_3Na



11 **12**



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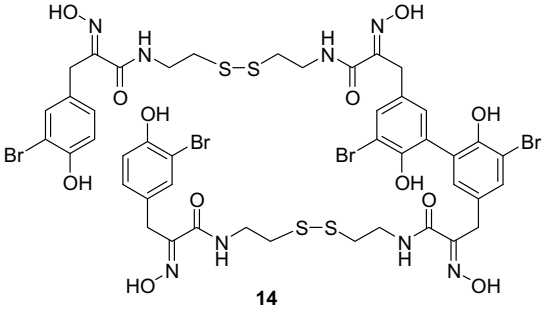

14

(C-9/C-9′). This connection between **a** and **c** constructed a structure of psammaplin A[3,4] analog. Similarly, HMBC correlation from protons H_2-11″/H_2-11‴ (δ 3.40) to the amide carbon at δ 165.5 (C-9″/C-9‴) confirmed connection between partial units **b** and **d**, comprising another structure of psammaplin A (**7**).[3,4] Chemical shift values for methylene protons are very typical when attached to tetrasubstituted (δ 3.56, H_2-11/H_2-11′ and 2.90, H_2-12/H_2-12′) and trisubstituted (δ 3.40, H_2-11″/H_2-11‴ and 2.69, H_2-12″/H_2-12‴) phenyl rings as observed in bispsammaplin A (**13**).[4] The stereochemistry of the oxime groups was assigned as *E* on the basis of the characteristic ^{13}C chemical shifts of the benzylic carbons (*E*: δ 28.6, 28.2; *Z*: δ 37.5).[4] Hence, from the careful study of these assignments, the structure of **1** was elucidated as a cyclic bispsammaplin A.

But still there were two possibilities for its structure (**1A** or **1B**), considering the symmetric nature of the planar structure of **1** (Fig. 3). The structure **1A** possesses a plane of symmetry, while **1B** has an axis of symmetry. For **1A**, the magnetic environment of H-11/H-12 and H-11′/H-12′ are expected to be equivalent. But, the magnetic environment of H-11/H-12 and H-11‴/H-12‴ would be non-equivalent. Therefore, these methylenes may be assigned as δ 3.56, H_2-11(H_2-11′); δ 2.90, H_2-12(H_2-12′); δ 3.40, H_2-11″(H_2-11‴); and δ 2.69, H_2-12″(H_2-12‴) (assignment aided by NMR simulation using Chemdraw ultra). However, for **1B**, the magnetic environment of H-11/H-12 and H-11′/H-12′ would be non-equivalent. But the magnetic environment of H-11/H-12 and H-11″/H-12″ would be equivalent. Therefore, these methylenes may be assigned as δ 3.56, H_2-11(H_2-11″); δ 2.90, H_2-12(H_2-12″); δ 3.40, H_2-11′(H_2-11‴); and δ 2.69, H_2-12′(H_2-12‴). If **1B** is the right structure for compound **1**, then we expect a NOE between the non-equivalent pair of nuclei H_2-12(H_2-12″) (δ 2.90) and H_2-12′(H_2-12‴) (δ 2.69). ROESY and NOESY experiments were carried out, but no NOE was observed between these pairs of nuclei H-12(H-12″) and H-12′(H-12‴). The reason for the absence of NOE between these nuclei might be either **1B** was not the right structure or distances between these nuclei were not close enough to observe NOE. To find out the possible reason, study on 3D model of **1B** was performed using Chem3D Pro software. For the structure of minimum-energy **1B**, the distances between these nuclei were calculated as 2.1 and 2.7 Å (Fig. 4). It is well-known that NOE can be usually detected if the distance between the dipolar-coupled nuclei is less than 3 Å.[9] Considering the absence of any NOE between these nuclei, just as an indirect clue, structure **1A** was proposed as the structure for cyclobispsammaplin A.

Psammaplin M (**2**) was isolated as an amorphous, white solid. The LRFABMS spectrum of **2** showed a pair of $[M+Na]^+$ ion peaks at *m/z* 381/383 suggesting the presence of one bromine atom in the molecule. The HRFABMS and ^{13}C NMR data[10] of **2** supported the molecular formula $C_{13}H_{15}N_2O_5Br$. The exact mass of the $[M-H]^-$ ion (*m/z* 357.0070) matched well with the expected formula $C_{13}H_{14}N_2O_5Br$ (Δ 1.6 mmu). Analysis of the ^{1}H and ^{13}C NMR data[10] revealed the presence of a 1,2,4-trisubstituted phenyl ring (δ 7.35/134.2, 6.75/117.0, and 7.05/130.6) and an isolated benzylic methylene (δ 3.77/28.2). Furthermore, ^{13}C NMR data showed the presence of an oxime (δ 153.0, C-8) and an amide (δ 165.5, C-9) groups. In addition, one carbonyl carbon (δ 173.5, C-13), one methoxyl singlet at (δ 3.63/52.5, OCH_3), and a pair of coupled

Table 1
1D and 2D NMR data of **1** in CD_3OD at 500 MHz.[a]

Position	δ_H	δ_C[b]	COSY	HMBC
1 (1′)		129.8		
2 (2′)	7.21 (d, 2.0)	130.0	H-6 (H-6′)	C-6 (C-6′)
3 (3′)		c		
4 (4′)		c		
5 (5′)		c		
6 (6′)	6.47 (d, 2.0)	118.8	H-2 (H-2′)	C-2 (C-2′)
7 (7′)	3.70 (s)	28.2		C-9, 8, 2 (C-9′, 8′, 2′)
8 (8′)		152.4		
9 (9′)		165.5		
11 (11′)	3.56 (m)	39.6	H-12 (H-12′)	C-9, 12 (C-9′, 12′)
12 (12′)	2.90 (t, 7.0)	39.4	H-11 (H-11′)	C-11 (C-11′)
1″ (1‴)		129.8		
2″ (2‴)	7.56 (d, 2.0)	135.0	H-6″ (H-6‴)	C-4″ (C-4‴)
3″ (3‴)		114.0		
4″ (4‴)		154.0		
5″ (5‴)	6.65 (d, 8.0)	120.0	H-6″ (H-6‴)	C-4″, C-2″, C-3″ (C-4‴, 2‴, 3‴)
6″ (6‴)	7.16 (d, 8.0, 2.0)	130.8	H-5″, 2″ (H-5‴, 2‴)	
7″ (7‴)	3.88 (s)	28.6		C-9″, 8″, 6″ (C-9‴, 8‴, 6‴)
8″ (8‴)		153.0		
9″ (9‴)		165.5		
11″ (11‴)	3.40 (t, 7.0)	39.2	H-12″ (H-12‴)	C-9″, 12″ (C-9‴, 12‴)
12″ (12‴)	2.69 (t, 7.0)	38.0	H-11″ (H-11‴)	C-11″ (C-11‴)

[a] Multiplicities and coupling constants are in parentheses.
[b] Assignments based on HMBC and HSQC spectroscopic data.
[c] Not observed due to small amount.

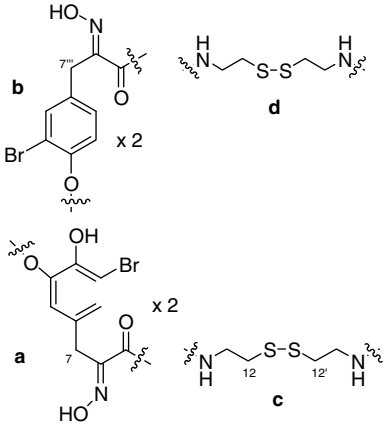

Figure 1. Partial structures of compound **1**.

methylenes at δ 3.48/35.7 (H_2-11/C-11) and at δ 2.53/34.3 (H_2-12/C-12) were observed in ^1H and ^{13}C NMR data. These data indicated the presence of the substructure **A**, which also formed the half structure of psammaplin A.[4] In the HMBC spectrum, the signals of H_2-12 (δ 2.53) and OCH_3 (δ 3.63) showed correlations with C-13 (δ 173.5). The stereochemistry of the oxime group was assigned as *E* on the basis of the characteristic ^{13}C chemical shift of the benzylic carbon (C-7, δ 28.2).[4] Psammaplin M (**2**) might be derived from a tyrosine and aspartic acid or β-alanine. This is the first psammaplin analog which does not contain a cysteine-derived sulfur moiety.

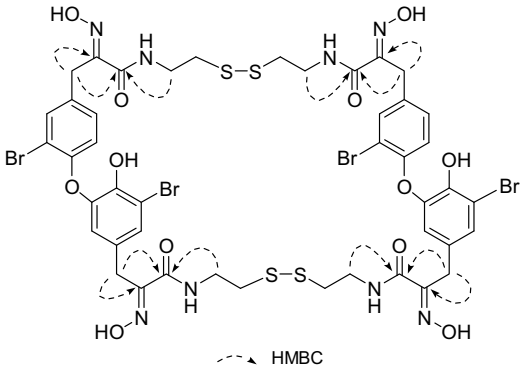

Figure 2. Key HMBC correlations of compound **1**.

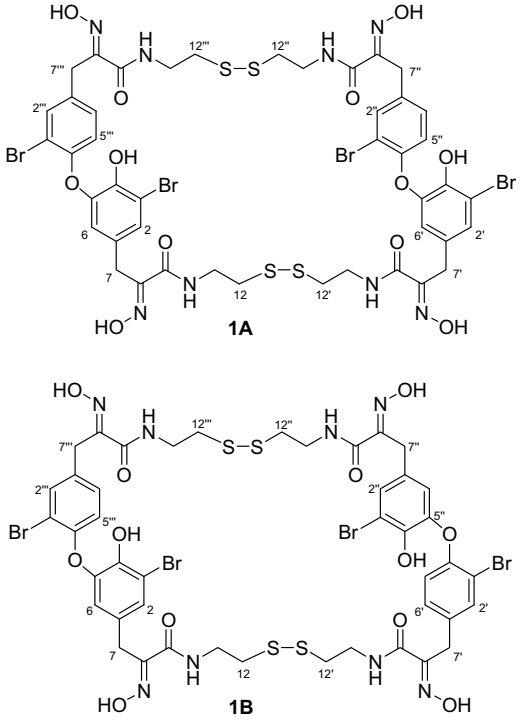

Figure 3. Two possible structures for compound **1**.

Table 2
Cytotoxicity data of bromotyrosine derivatives.[a]

Compound	A-549	SK-OV-3	SK-MEL-2	XF-498	HCT-15
1 (cyclobispsammaplin A)	1.95	1.21	1.14	2.88	3.82
6 (psammaplin E)	1.47	0.19	0.21	1.63	1.92
12 (diguanidium salt of psammaplin A sulfate)	12.27	1.79	4.48	16.92	43.17
doxorubicin	0.01	0.01	0.01	0.03	0.03
2 (psammaplin M)	>30	>30	>30	>30	>30
3 (psammaplin I)	4.15	1.76	2.84	2.96	6.51
4 (psammaplin B)	12.84	9.27	19.43	10.92	>30
10 (sodium salt of psammaplin A sulfate)	0.18	0.16	1.13	0.18	1.25
doxorubicin	0.02	0.07	0.10	0.10	0.33
5 (psammaplin D)[b]	0.80	0.17	0.20	0.60	1.23
7 (psammaplin A)[b]	0.57	0.14	0.13	0.57	0.68
9 (bromopsammaplin A)[b]	1.34	1.38	0.90	0.92	3.31
13 (bispsammaplin A)[b]	1.53	1.52	1.02	1.10	3.35
14 (bisaprasin)[b]	3.40	2.78	2.94	2.44	6.00
doxorubicin	0.04	0.15	0.003	0.10	0.09

[a] Data expressed in ED_{50} values (μg/mL). A-549, human lung cancer; SK-OV-3, human ovarian cancer; SK-MEL-2, human skin cancer; XF-498, human CNS cancer; HCT-15, human colon cancer.
[b] Data from Ref. [4].

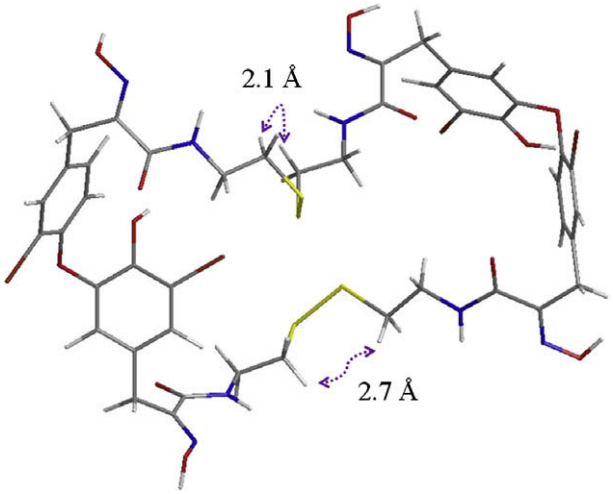

Figure 4. Energy-minimized structure of **1B**.

Compound **3** was identified as psammaplin I, previously reported from a sponge *Pseudoceratina purpurea*.[11] Compound **4** was identified as a psammaplin B, which was previously isolated from marine sponges *Psammaplysilla purpurea*[12] and *Pseudoceratina purpurea*.[11] Compound **5** was identified as psammaplin D, which was previously isolated from a marine sponge *P. purpurea*.[12] Compound **6** was identified as psammaplin E, previously isolated from a marine sponge *Pseudoceratina purpurea*.[11] Compound **7** was identified as (*E*,*E*)-psammaplin A, the well-known metabolite of marine sponges *Psammaplysilla* sp.,[12,14] *Thorectopsamma xana*,[15] *Pseudoceratina purpurea*,[11] *Aplysinella rhax*.[16–18] Compounds **8** and **9** were identified as (*E*,*Z*)-psammaplin A and bromopsammaplin A, respectively, which were previously isolated from the previous collection of the same specimen.[4] Compound **10** was identified as a sodium salt of psammaplin A sulfate, which was reported from a marine sponge *A. rhax*.[16] Compound **11** was a known metabolite of several marine sponges.[4,12,13] Compound **12** was identified as a bis-*N*, *N*-dimethylguanidium salt of psammaplin A sulfate, which was previously isolated from a marine sponge *A. rhax*.[18] This is the first report on the isolation of compounds **3**, **4**, **6**, **10**, and **12** from an association of sponges *Jaspis* sp. and *Poecillastra* sp. Compounds **13** (bispsammaplin A) and **14** (bisaprasin A) were reported in our previous letter.[4]

Many bromotyrosine-derived metabolites with diverse structural features have been reported from marine sponges. Apart from sponges, there is only one report on the isolation of bromotyrosine derivatives from an ascidian *Botryllus* sp.[19] Bromotyrosine alkaloids are considered as the chemotaxonomic markers for the sponges belonging to the order Verongida.[20] However, they are also encountered in sponges belonging to other orders, such as *Pachychalina*,[21] *Oceanapia*,[22] (both genera belong to the order Haplosclerida), *Latrunculia*,[23] *Iotrochota*[24] (both genera belong to the order Poecilosclerida), and a sponge of order Dendroceratida, *Dendrilla cactos*.[25] Orders, Verongida, Haplosclerida, Poecilosclerida, and Dendroceratida belong to the subclass Ceractinomorpha, but sponges *Jaspis* and *Poecillastra* belong to the order Astrophorida (subclass Tetractinomorpha). To the best of our knowledge, two-sponge association of *Jaspis* sp. and *Poecillastra* sp. is the only sponge specimen from the subclass Tetractinomorpha containing bromotyrosine alkaloids.[3,4]

The wide spectrum of biological activities has been reported for psammaplin derivatives.[26–34] The cytotoxicity of the isolated compounds (**1–4**, **6**, **10**, and **12**) against A-549, SK-OV-3, SK-MEL-2, XF-498, and HCT-15 solid tumor cell lines was studied (Table 2). In general, the dimeric forms (**7**, **9**, **10**, and **12**) exhibited more potent cytotoxicity to cancer cell lines. Dimers containing trisubstituted phenyl rings at both ends (**7** and **10**) displayed the most potent cytotoxicity. The diguanidium salt of psammaplin A sulfate (**12**) showed a rather weak cytotoxicity but was selective against human ovarian cancer cells (SK-OV-3). It appears that monomeric forms containing amide terminal group (**5** and **6**) also show high potency. The disulfide moiety in these bromotyrosine derivatives also plays an important role as monomers (**2–4**) lacking it exhibited less potency. In case of tetramers, ether forms (**1** and **13**) were twice as potent as compared to condensed form (**14**).

Acknowledgments

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References and notes

1. Chang, Y. H.; Shin, D.; Na, Z.; Lee, H. S.; Kim, D. D.; Oh, K. B.; Shin, J. *J. Nat. Prod.* **2008**, *71*, 779.
2. Ryu, G.; Choi, B. W.; Lee, B. H.; Hwang, K. H.; Lee, U. C.; Jeong, D. S.; Lee, N. H. *Tetrahedron* **1999**, *55*, 13171.
3. Jung, J. H.; Sim, C. J.; Lee, C. O. *J. Nat. Prod.* **1995**, *58*, 1722.

4. Park, Y.; Liu, Y.; Hong, J.; Lee, C. O.; Cho, H.; Kim, D. K.; Im, K. S.; Jung, J. H. *J. Nat. Prod.* **2003**, *66*, 1495.
5. Shinde, P. B.; Kim, M. A.; Son, B. W.; Lee, C. O.; Jung, J. H. *Nat. Prod. Sci.* **2007**, *13*, 365.
6. Shinde, P. B.; Park, T.; Hong, J.; Kim, D. K.; Jung, J. H. *Pharm. Biol.*, in press.
7. The sponges, collected in November 2002, offshore Jeju Island, South Korea, were frozen immediately after collection and stored at 20 °C until extraction. The frozen animal material was cut into small pieces and extensively extracted with MeOH at room temperature. The MeOH extract was partitioned between CH_2Cl_2 and H_2O, and the CH_2Cl_2 layer was further partitioned between 90% aq MeOH and *n*-hexane. The aqueous MeOH fraction was selected for further separation on the basis of its lethality to brine shrimp larvae and subjected to a reversed-phase flash column chromatography (YMC Gel ODS-A, 60 Å 500/400 mesh), eluting with gradient solvent system of 50–100% MeOH/H_2O to yield 19 fractions. Fractions containing bromotyrosines (1–8) were selected for further separation from their potent activity (LD_{50} ~20 μg/mL) in the brine shrimp lethality assay and were subjected to repeated reversed-phase chromatographic separation to afford 12 compounds. Compound **1** was obtained by purification of fraction 8 by reversed-phase HPLC. Fraction 1 was subjected to MPLC, eluting with gradient solvent system of 0–70% MeOH/H_2O to yield 10 subfractions. These subfractions were subjected to reversed-phase HPLC to obtain compounds **2**–**5** and **7**–**11**. The H_2O layer was also abundant in psammaplin derivatives. The H_2O layer was partitioned between *n*-BuOH and H_2O. The *n*-BuOH layer was subjected to MPLC to yield 12 fractions (1–12). Compounds **6** and **12** were obtained by purification of fraction 3 by repeated HPLC separation.
8. ***Cyclobispsammaplin A (1):*** Amorphous, white solid; LRESIMS (+ve mode) *m/z* 1343, 1345, 1347, 1349, 1351 $[M+Na]^+$, (−ve mode) *m/z* 1319, 1321, 1323, 1325, 1327 $[M-H]^-$; HRMALDITOFMS *m/z* 1344.8854, 1346.8811, 1348.8965, 1350.8937 $[M+Na]^+$ (Calcd for $C_{44}H_{44}N_8O_{12}S_4{}^{79}Br_2{}^{81}Br_2Na$, 1346.8551); ^1H and ^{13}C NMR data, see Table 1.
9. Friebolin, H. *Basic One- and Two-Dimensional NMR Spectroscopy;* translated by Becconsall, J. K.; Wiley-VCH, 1998, Chapter 10.
10. ***Psammaplin M (2):*** Amorphous, white solid; LRFABMS (+ve mode) *m/z* 381/383 $[M+Na]^+$; HRFABMS (−ve mode) *m/z* 357.0070 $[M-H]^-$ (Calcd for $C_{13}H_{14}N_2O_5Br$, 357.0086); ^1H NMR (CD_3OD, 500 MHz) δ 7.35 (1H, d, J = 2.0 Hz, H-2), 7.05 (1H, dd, J = 8.0, 2.0 Hz, H-6), 6.75 (1H, d, J = 8.0 Hz, H-5), 3.77 (2H, s, H-7), 3.63 (3H, s, OCH_3), 3.48 (2H, t, J = 7.0 Hz, H-11), 2.53 (2H, t, J = 7.0 Hz, H-12); ^{13}C NMR (CD_3OD, 500 MHz, based on HMBC and HSQC data) δ 173.5 (C-13), 165.5 (C-8), 153.5 (C-4), 153.0 (C-8), 134.2 (C-2), 130.6 (C-1, C-6), 117.0 (C-5), 110.0 (C-3), 52.5 (OCH_3), 35.7 (C-11), 34.3 (C-12), 28.2 (C-7).
11. Pina, C. I.; Gautschi, J. T.; Wang, G. Y. S.; Sanders, M. L.; Schmitz, F. J.; France, D.; Cornell-Kennon, S.; Sambucetti, L. C.; Remiszewski, S. W.; Perez, L. B.; Bair, K. W.; Crews, P. *J. Nat. Prod.* **2003**, *66*, 1495.
12. Jimenz, C.; Crews, P. *Tetrahedron* **1991**, *47*, 2097.
13. Quinoa, E.; Crews, P. *Tetrahedron Lett.* **1987**, *28*, 3229.
14. Arabshahi, L.; Schmi tz, F. J. *J. Org. Chem.* **1987**, *52*, 3584.
15. Rodriguez, A. D.; Akee, R. K.; Scheuer, P. J. *Tetrahedron Lett.* **1987**, *28*, 4989.
16. Pham, N. B.; Butler, M. S.; Quinn, R. J. *J. Nat. Prod.* **2000**, *63*, 393.
17. Tabudravu, J. N.; Eijsink, G. H.; Gooday, G. W.; Jaspars, M.; Komander, M. L.; Synstad, B.; Aalten, D. M. F. *Bioorg. Med. Chem.* **2002**, *10*, 1123.
18. Shin, J.; Lee, H. S.; Seo, Y.; Rho, J. R.; Cho, K. W.; Paul, V. J. *Tetrahedron* **2000**, *56*, 9071.
19. McDonald, L. A.; Swersey, J. C.; Ireland, C. M.; Carroll, A. R.; Coll, J. C.; Bowden, B. F.; Fairchild, C. R.; Cornell, L. *Tetrahedron* **1995**, *51*, 5237.
20. Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155.
21. Fernanda, D. O. M.; Luis, D. O. J. H. H.; Galetti, F. C. S.; Olivia, D. S. A.; Silva, C. L.; Hajdu, E.; Peixinho, S.; Berlink, R. G. S. *Planta Med.* **2006**, *72*, 437.
22. Nicholas, G. M.; Newton, G. L.; Fahey, R. C.; Bewley, C. A. *Org. Lett.* **2001**, *3*, 1543.
23. Perry, N. B.; Blunt, J. W.; McCombs, J. D.; Munro, M. H. G. *J. Org. Chem.* **1986**, *51*, 5476.
24. Costantino, V.; Fattorusso, E.; Mangoni, A.; Pansini, M. *J. Nat. Prod.* **1994**, *57*, 1552.
25. Reddy, A. V.; Ravinder, K.; Narasimhulu, M.; Sridevi, A.; Satyanarayana, N.; Kondapi, A. K.; Venkateswarlu, Y. *Bioorg. Med. Chem.* **2006**, *14*, 4452.
26. Ortlepp, S.; Sjoegren, M.; Dahlstroem, M.; Weber, H.; Ebel, R.; Edrada, R.; Thoms, C.; Schupp, P.; Bohlin, L.; Proksch, P. *Mar. Biotechnol.* **2007**, *9*, 776.
27. Ahn, M. Y.; Jung, J. H.; Na, Y. J.; Kim, H. S. *Gynecol. Oncol.* **2008**, *108*, 27.
28. Kim, D.; Lee, I. S.; Jung, J. H.; Yang, S. I. *Arch. Pharm. Res.* **1999**, *22*, 25.
29. Kim, D. H.; Shin, J.; Kwon, H. J. *Exp. Mol. Med.* **2007**, *39*, 47.
30. Jiang, Y. H.; Ahn, E. Y.; Ryu, S. H.; Kim, D. K.; Park, J. S.; Yoon, H. J.; You, S.; Lee, B. J.; Lee, D. S.; Jung, J. H. *BMC Cancer* **2004**, *4*, 70.
31. Kim, D.; Lee, I. S.; Jung, J. H.; Lee, C. O.; Choi, S. U. *Anticancer Res.* **1999**, *19*, 4085.
32. Jiang, Y. H.; Ryu, S. H.; Ahn, E. Y.; You, S.; Lee, B. D.; Jung, J. H.; Kim, D. K. *Nat. Prod. Sci.* **2004**, *10*, 277.
33. Shim, J. S.; Lee, H. S.; Shin, H. J. *Cancer Lett.* **2004**, *203*, 163.
34. Mora, F. D.; Jones, D. K.; Desai, P. V.; Panty, A.; Avery, M. A.; Feller, D. R.; Smillie, T.; Zhou, Y. D.; Nagle, D. G. *J. Nat. Prod.* **2006**, *69*, 547.