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Structures of Monodontamides A, B, C, D, E, and F, Six New Alkaloids Isolated from the Marine Gastropod Mollusc *Monodonta labio* (Linné)

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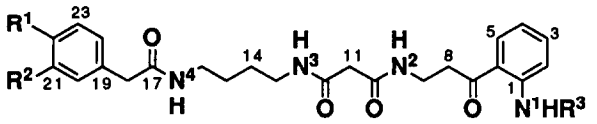
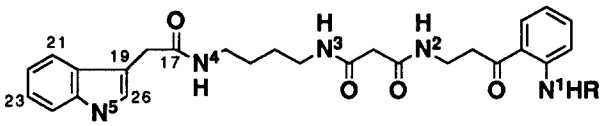
***Abstract*:** Six new alkaloids monodontamides A (**1**), B (**2**), C (**3**), D (**4**), E (**5**), and F (**6**) were isolated from the marine gastropod mollusc *Monodonta labio* (Linné). The structures of monodontamides were established on the basis of spectral data and unambiguous synthesis. Monodontamides exhibited weak inhibitory activity against a serine protease.

INTRODUCTION

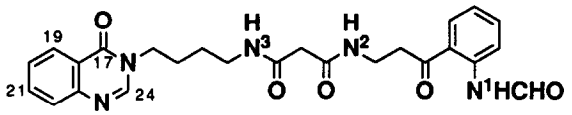
Marine organisms have yielded a variety of structurally novel and pharmacologically interesting compounds.[1] In connection with our research on the isolation of biologically active marine natural products, we have examined the constituents of the gastropod mollusc *Monodonta labio* (Linné) collected off the coast of Koka, Mie Prefecture, Japan and isolated five new putrescine alkaloids monodontamides A (**1**), B (**2**), C (**3**), D (**4**), and E (**5**) together with a new quinazoline alkaloid monodontamide F (**6**), all containing an N^3-malonylated



1 monodontamide A ($R^1 = R^2 = H$, $R^3 = CHO$)
2 monodontamide B ($R^1 = OH$, $R^2 = OMe$, $R^3 = CHO$)
3 monodontamide C ($R^1 = OH$, $R^2 = OMe$, $R^3 = H$)



4 monodontamide D (R = CHO)
5 monodontamide E (R = H)



6 monodontamide F

2',3-diaminopropiophenone (kynuramine) moiety as the common structural part. Described is a full account of the isolation of these alkaloids and their structure determination by means of spectral analysis and chemical synthesis.[2]

RESULTS AND DISCUSSION

Isolation of Monodontamides

The EtOAc-soluble material obtained from the MeOH extract of the mollusc *M. labio* was partitioned between hexane and MeOH–H_2O (9:1 v/v). The MeOH–H_2O soluble material was then subjected to repeated chromatography on silica gel followed by reversed-phase HPLC to afford monodontamides A (**1**), B (**2**), C (**3**), D (**4**), E (**5**), and F (**6**).

Structures of Monodontamides

Monodontamides C (3). The molecular formula of monodontamide C (**3**), $C_{25}H_{32}N_4O_6$, was determined from the ^{13}C NMR spectrum (Table **2**) and the high-resolution FABMS measurement [*m/z* 485.2419 [$(M+H)^+$], Δ +1.9 mmu]. The IR, ^1H NMR (Table **1**), and ^{13}C NMR spectra strongly suggested that **3** has an OH group [ν_{max} 3550 (br) and 3450 cm^{-1}; δ_H 5.70 (1 H, br s, a D_2O exchangeable signal)], an NH_2 group [δ_H 6.28 (2 H, br s, a D_2O exchangeable signal)], an OMe group connected to a benzene ring [δ_H 3.88 (3 H, s); δ_C 56.0 (q)], three secondary amides [ν_{max} 3350 (br), 1670, and 1510 cm^{-1}; δ_H 5.61 (1 H, a broad signal, N^4H), 7.16 (1 H, a broad signal, N^3H), and 7.03 (1 H, br *t*, J = 5.9 Hz, N^2H); δ_C 167.0 (s, C–10 or 12), 167.6 (s, C–10 or 12), and 171.6 (s, C–17)]. The presence of an aromatic ketone was implied from the ^{13}C NMR spectrum [δ_C 200.7 (s, C–7)] and the IR spectrum lacked an absorption band for aliphatic ketone. The ^1H and ^{13}C NMR spectra also indicated the presence of a 1,2-disubstituted benzene ring with an electron-withdrawing group and an electron-donating group [δ_H 6.66 (1 H, dd, J = 7.9, 1.3 Hz, H–2), 7.27 (1 H, ddd, J = 7.9, 7.9, 1.3 Hz, H–3), 6.64 (1 H, ddd, J = 7.9, 7.9, 1.3 Hz, H–4), and 7.67 (1 H, dd, J = 7.9, 1.3 Hz, H–5); δ_C 150.4 (s, C–1), 117.5 (d, C–2), 134.7 (d, C–3), 115.9 (d, C–4), 130.9 (d, C–5), 117.4 (s, C–6)], and a 1,3,4-trisubstituted benzene ring with three electron-donating groups [δ_H 6.77 (1 H, d, J = 2.0 Hz, H–20), 6.89 (1 H, d, J = 7.9 Hz, H–23), and 6.73 (1 H, dd, J = 7.9, 2.0 Hz, H–24); δ_C 126.6 (s, C–19), 111.9 (d, C–20), 147.0 (s, C–21), 145.0 (s, C–22), 114.9 (d, C–23), and 122.2 (d, C–24)]. The ^1H and ^{13}C NMR spectra also suggested the presence of an *N,N'*-diacylated putrescine (1,4-diaminobutane) moiety [δ_H 3.20 (4 H, m, H–13 and 16) and δ_H 1.46 (4 H, m, H–14 and 15); δ_C 39.0 (t, C–13 or 16), δ_C 26.5 (t, C–14 or 15), δ_C 26.8 (t, C–14 or 15), and δ_C 39.1 (t, C–13, or 16)] and a malonamide moiety [δ_H 3.11 (2 H, s, H–11); δ_C 42.9 (t, C–11)]. This inference was confirmed by the comparison of the ^1H NMR spectral data of **3** with those of *N,N'*-diacetylputrescine and malonamide. The two protons appeared at δ_H 3.48 (2 H, a sharp singlet, H–18) and one carbon at δ_C 43.4 (t, C–18) in **3** were assigned to those of a methylene group directly connected to two sp^2 carbons such as phenyl and carbonyl groups. Further analysis of the ^1H NMR , ^{13}C NMR, ^1H–^1H COSY, and ^1H–^{13}C COSY spectra coupled with the above spectral evidence revealed the presence of the partial structures A–G in **3**. The partial structures A–G account for all atoms present in **3** without any overlapping. In order to determine the connectivity of these partial structures, difference NOE experiments were performed (Figure **1**). Thus, the structure of monodontamide C was elucidated to be as depicted in the formula **3**.

Table 1. ^{1}H NMR Spectral Data of Monodontamides A (1), B (2), C (3), D (4), E (5), and F (6)[a]

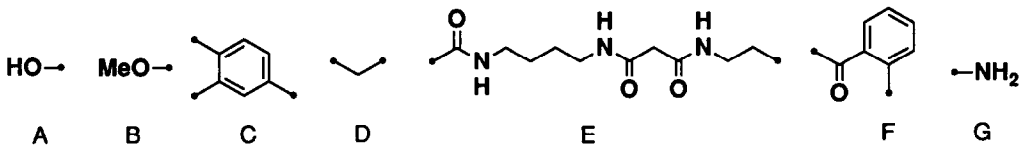
No.	1	2	3	4	5	6
2	7.89 (dd) (7.9, 1.3)	7.89 (dd) (7.9, 1.3)	6.66 (dd) (7.9, 1.3)	7.87 (dd) (7.9, 1.3)	6.64 (dd) (7.9, 1.3)	7.89 (dd) (7.9, 1.3)
3	7.15 (dd) (7.9, 7.9)	7.16 (dd) (7.9, 7.9)	7.27 (ddd) (7.9, 7.9, 1.3)	7.15 (dd) (7.9, 7.9)	7.26 (ddd) (7.9, 7.9, 1.3)	7.16 (dd) (7.9, 7.9)
4	7.56 (ddd) (7.9, 7.9, 1.3)	7.57 (ddd) (7.9, 7.9, 1.3)	6.64 (ddd) (7.9, 7.9, 1.3)	7.56 (ddd) (7.9, 7.9, 1.3)	6.62 (ddd) (7.9, 7.9, 1.3)	7.57 (ddd) (7.9, 7.9, 1.3)
5	8.73 (d) (7.9)	8.74 (d) (7.9)	7.67 (dd) (7.9, 1.3)	8.73 (d) (7.9)	7.66 (dd) (7.9, 1.3)	8.75 (d) (7.9)
8	3.28 (t) (5.9)	3.30 (t) (5.9)	3.20 (m)[q]	3.28 (t) (5.9)	3.14 (t) (5.9)	3.30 (t) (5.9)
9	3.66 (dt) (5.9, 5.9)	3.66 (dt) (5.9, 5.9)	3.66 (dt) (5.9, 5.9)	3.66 (dt) (5.9, 5.9)	3.64 (dt) (5.9, 5.9)	3.68 (dt) (5.9, 5.9)
11	3.13 (s)	3.13 (s)	3.11 (s)	3.10 (s)	3.07 (s)	3.15 (s)
13	3.21 (m)[b]	3.21 (m)[e]	3.20 (m)[g]	3.15 (m)[i]	3.15 (m)[k]	3.35 (dt) (6.8, 6.8)
14	1.45 (m)[c]	1.45 (m)[f]	1.46 (m)[h]	1.37 (m)[j]	1.35 (m)[l]	1.64 (m)
15	1.45 (m)[c]	1.45 (m)[f]	1.46 (m)[h]	1.37 (m)[j]	1.35 (m)[l]	1.83 (m)
16	3.21 (m)[b]	3.21 (m)[e]	3.20 (m)[g]	3.15 (m)[i]	3.15 (m)[k]	4.02 (t) (7.3)
18	3.55 (s)	3.47 (s)	3.48 (s)	3.72 (s)	3.71 (s)	—
19	—	—	—	—	—	8.30 (dd) (8.1, 1.3)
20	7.30 (m)[d]	6.76 (d) (2.0)	6.77 (d) (2.0)	—	—	7.51 (ddd) (8.1, 6.8, 1.3)
21	7.30 (m)[d]	—	—	7.41 (d) (7.9)	7.40 (dd) (7.9, 1.3)	7.76 (ddd) (8.1, 6.8, 1.3)
22	7.30 (m)[d]	—	—	7.23 (dd) (7.9, 7.9)	7.24 (dd) (7.9, 7.9)	7.70 (dd) (8.1, 1.3)
23	7.30 (m)[d]	6.88 (d) (7.9)	6.89 (d) (7.9)	7.17 (dd) (7.9, 7.9)	7.18 (ddd) (7.9, 7.9, 1.3)	—
24	7.30 (m)[d]	6.72 (dd) (7.9, 2.0)	6.73 (dd) (7.9, 2.0)	7.55 (d) (7.9)	7.55 (d) (7.9)	8.04 (s)
26	—	—	—	7.14 (s)	7.20 (s)	—
CHO	8.43 (s)	8.49 (s)	—	8.47 (s)	—	8.51 (s)
N^1H	11.50 (br s)	11.50 (br s)	6.28 (br s)	11.50 (br s)	6.27 (br s)	11.50 (br s)
N^2H	7.54 (br)	7.43 (br t) (5.9)	7.03 (br t) (5.9)	7.57 (br)	7.19 (br)	7.27 (br)
N^3H	7.17 (br)	7.04 (br t) (5.9)	7.16 (br)	6.91 (br t) (5.9)	7.05 (br t) (5.9)	6.97 (br)
N^4H	5.67 (br)	5.63 (br t) (5.9)	5.61 (br)	5.81 (br t) (5.9)	5.77 (br t) (5.9)	—
N^5H	—	—	—	8.48 (br s)	8.60 (br s)	—
OH	—	5.78 (br s)	5.70 (br s)	—	—	—
OMe	—	3.88 (s)	3.88 (s)	—	—	—

a) Spectra were taken in $CDCl_3$ at 270 MHz. Chemical shifts are in δ values from internal TMS and coupling constants (lower parentheses) in Hz.
b-l) Signals with identical superscripts are overlapped.

Table 2. ^{13}C NMR Spectral Data of Monodontamides A (1), B (2), C (3), D (4), E (5), and F (6)[a]

No.	1	2	3	4	5	6
1	139.9 (s)	139.9 (s)	150.4 (s)	139.8 (s)	150.4 (s)	139.7 (s)
2	130.8 (d)	130.8 (d)	117.5 (d)	130.8 (d)	117.4 (d)	130.7 (d)
3	123.2 (d)	123.2 (d)	134.7 (d)	123.2 (d)	134.7 (d)	123.1 (d)
4	135.4 (d)	135.4 (d)	115.9 (d)	135.4 (d)	115.9 (d)	135.3 (d)
5	121.8 (d)	121.7 (d)	130.9 (d)	121.7 (d)	130.9 (d)	121.7 (d)
6	121.6 (s)	121.6 (s)	117.4 (s)	121.6 (s)	118.7 (s)	121.9 (s)
7	203.1 (s)	203.0 (s)	200.7 (s)	203.1 (s)	200.7 (s)	202.9 (s)
8	39.4 (t)	39.3 (t)	38.2 (t)	39.3 (t)	38.3 (t)	39.2 (t)
9	34.5 (t)	34.5 (t)	34.7 (t)	34.5 (t)	34.7 (t)	34.5 (t)
10	167.2 (s)[b]	167.3 (s)[e]	167.0 (s)[g]	167.0 (s)[j]	167.0 (s)[m]	167.4 (s)[p]
11	42.9 (t)	42.7 (t)	42.9 (t)	42.8 (t)	42.9 (t)	42.8 (t)
12	167.3 (s)[b]	167.5 (s)[e]	167.6 (s)[g]	167.3 (s)[j]	167.5 (s)[m]	167.5 (s)[p]
13	39.1 (t)[c]	39.1 (t)	39.0 (t)[h]	38.9 (t)[k]	38.9 (t)[n]	38.7 (t)
14	26.3 (t)[d]	26.3 (t)[f]	26.5 (t)[i]	26.0 (t)[l]	26.3 (t)[o]	26.3 (t)[q]
15	27.1 (t)[d]	27.0 (t)[f]	26.8 (t)[i]	27.0 (t)[l]	26.8 (t)[o]	26.6 (t)[q]
16	39.2 (t)[c]	39.1 (t)	39.1 (t)[h]	39.1 (t)[k]	39.0 (t)[n]	46.3 (t)
17	171.3 (s)	171.7 (s)	171.6 (s)	171.8 (s)	171.8 (s)	161.1 (s)
18	43.8 (t)	43.4 (t)	43.4 (t)	33.4 (t)	33.4 (t)	121.5 (s)
19	136.4 (s)	126.6 (s)	126.6 (s)	109.1 (s)	109.0 (s)	126.6 (d)
20	129.4 (d)	111.9 (d)	111.9 (d)	127.0 (s)	127.0 (s)	134.2 (d)
21	129.1 (d)	147.0 (s)	147.0 (s)	111.5 (d)	111.5 (d)	127.3 (d)
22	127.4 (d)	145.0 (s)	145.0 (s)	122.6 (d)	122.5 (d)	127.4 (d)
23	129.1 (d)	114.9 (d)	114.9 (d)	120.1 (d)	119.9 (d)	148.0 (s)
24	129.4 (d)	122.2 (d)	122.2 (d)	118.7 (d)	118.7 (d)	146.5 (d)
25	—	—	—	136.4 (s)	136.4 (s)	—
26	—	—	—	123.8 (d)	123.9 (d)	—
CHO	159.8 (d)	160.0 (d)	—	160.0 (d)	—	160.0 (d)
OMe	—	56.0 (q)	56.0 (q)	—	—	—

a) Spectra were taken in $CDCl_3$ at 67.8 MHz. Chemical shifts are in δ values from internal TMS.
b-q) Signals with identical superscripts may be interchaged.



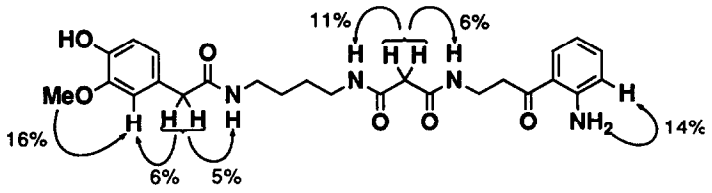
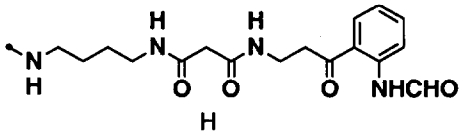


Figure 1. Difference NOE Experiments of Monodontamide C (3).

Monodontamide B (2). Monodontamide B (**2**) has the molecular formula $C_{26}H_{32}N_4O_7$, which was determined from the ^{13}C NMR spectrum (Table **2**) and the high-resolution FABMS measurement [*m/z* 513.2326 [(M+H)$^+$], Δ –2.3 mmu]. Comparison of the spectral properties of **2** with those of **3** suggested that their structures were closely related and **2** was deduced to be an *N*-formyl derivative of **3**. The presence of the *N*-formyl group in **2** was implied from the ^1H NMR and ^{13}C NMR spectral data [δ_H 8.49 (1 H, s, CHO) and 11.50 (1 H, br s, N^{1}H); δ_C 160.0 (d, CHO)]. The detailed analysis of the ^1H NMR, ^{13}C NMR, ^1H–^1H COSY, and ^1H–^{13}C COSY spectra coupled with difference NOE experiments defined the assignments of all protons and carbons, and the connectivity of all atoms in **2**, elucidating the structure of monodontamide B to be as depicted in the formula **2**.

Monodontamide A (1). Monodontamide A (**1**) has the molecular formula $C_{25}H_{30}N_4O_5$, which was determined from the ^{13}C NMR spectrum (Table **2**) and the high-resolution FABMS measurement [*m/z* 467.2301 [(M+H)$^+$], Δ +0.7 mmu]. The detailed analysis of the IR, ^1H NMR, ^{13}C NMR, ^1H–^1H COSY, and ^1H–^{13}C COSY spectra indicated that **1** has the same structural part H ($C_{17}H_{23}N_4O_4$) as **2** has. The remaining C_8H_7O moiety was assigned to be a phenylacetyl group from the ^1H and ^{13}C NMR spectral data [δ_H 7.30 (5 H, m, H–20, 21, 22, 23, and 24) and 3.55 (2 H, s, H–18); δ_C 171.3 (s, C–17), 43.8 (t, C–18), 136.4 (s, C–19), 129.4 (2 x d, C–20 and 24), 129.1 (2 x d, C–21 and 23), and 127.4 (d, C–22)], thereby revealing the structure of monodontamide A to be as depicted in the formula **1**.

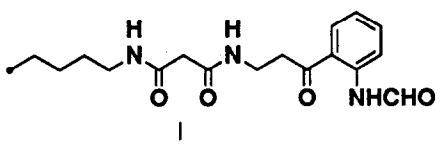


Monodontamide D (4). The molecular formula of monodontamide D (**4**), $C_{27}H_{31}N_5O_5$, was determined from the ^{13}C NMR spectrum and the high-resoution FABMS measurement [*m/z* 506.2420 [(M+H)$^+$], Δ +1.7 mmu]. The detailed analysis of the ^1H NMR, ^{13}C NMR, ^1H–^1H COSY, and ^1H–^{13}C COSY spectra suggested that **4** has the same structural part H ($C_{17}H_{23}N_4O_4$) as **1** and **2** have. The remaining $C_{10}H_8NO$ moiety was supposed to be a 3-indolylacetyl group from the ^1H and ^{13}C NMR spectral data [δ_H 3.72 (2 H, s, C–18), 7.41 (d, *J* = 7.9 Hz, H–21), 7.23 (dd, *J* = 7.9, 7.9 Hz, H–22), 7.17 (dd, *J* = 7.9, 7.9 Hz, H–23), 7.55 (d, *J* = 7.9 Hz, H–24), 7.14 (s, H–26), and 8.48 (1 H, br s, N^{5}H); δ_C 171.8 (s, C–17), 33.4 (t, C–18), 109.1 (s, C–19), 127.0 (s, C–20), 111.5 (d, C–21), 122.6 (d, C–22), 120.1 (d, C–23), 118.7 (d, C–24), 136.4 (s, C–25), and 123.8 (d, C–26)]. This inference was confirmed by the comparison of the ^1H NMR spectrum of **4** with that of indole-3-acetic acid. Thus, the structure of monodontamide D was revealed to be as depicted in the formula **4**.

Monodontamide E (5). Monodontamide E (**5**) has the molecular formula $C_{26}H_{31}N_5O_4$, which was determined from the ^{13}C NMR (Table 2) and high-resolution FABMS measurement [*m/z* 478.2435 [(M+H)$^+$], Δ –1.9 mmu]. Comparison of the spectral properties of **5** with those of **4** suggested that **5** was a deformyl compound of **4**. The detailed analysis of the ^1H NMR, ^{13}C NMR, ^1H–^1H COSY, and ^1H–^{13}C COSY spectra of **5** coupled with difference NOE experiments defined the assignments of all protons and carbons, and the connectivity of all atoms, elucidating the structure of monodontamide E to be as depicted in the formula **5**.

Monodontamide F (6). The molecular formula of monodontamide F (**6**), $C_{25}H_{27}N_5O_5$, was determined from the ^{13}C NMR spectrum and the elemental analysis. The detailed analysis of the IR, ^1H NMR, ^{13}C NMR,

^{1}H–^{1}H COSY, ^{1}H–^{13}C COSY indicated that **6** has the same structural part I ($C_{17}H_{22}N_3O_4$) as **1**, **2**, and **4** have. The remaining $C_8H_5N_2O$ moiety was supposed to be a 4(3*H*)-quinazolinon-3-yl group from the ^{1}H and ^{13}C NMR spectral data [δ_H 8.30 (dd, J = 8.1, 1.3 Hz, H–19), 7.51 (ddd, J = 8.1, 6.8, 1.3 Hz, H–20), 7.76 (ddd, J = 8.1, 6.8, 1.3 Hz, H–21), 7.70 (dd, J = 8.1, 1.3 Hz, H–22), and 8.04 (s, H–24); δ_C 161.1 (s, C–17), 121.5 (s C–18), 126.6 (d, C–19), 134.2 (d, C–20), 127.3 (d, C–21), 127.4 (d, C–22), 148.0 (s, C–23), and 146.5 (d, C–24)]. This inference was confirmed by the comparison of ^{1}H NMR spectrum of **6** with that of authentic 3-butyl-4(3*H*)-quinazolinone (**7**)[3,8] [δ_H 8.31 (dd, J = 7.9, 1.3 Hz, H–5), 7.49 (ddd, J = 7.9, 6.6, 1.3 Hz, H–6), 7.74 (ddd, J = 7.9, 6.6, 1.3 Hz, H–7), 7.69 (dd, J = 7.9, 1.3 Hz, H–8), and 8.02 (s, H–2)]. Thus, the structure of monodontamide F was elucidated to be as depicted in the formula **6**.



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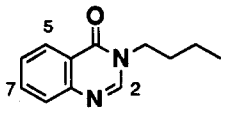

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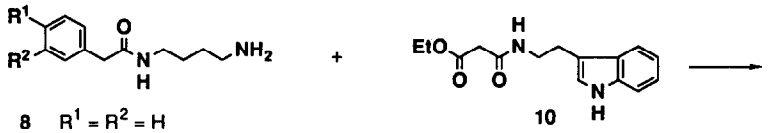
Synthesis of Monodontamides

In order to establish the structures of monodontamides A, B, C, D, E, and F, the unambiguous synthesis of the compounds having the structures as shown in the formulas **1**, **2**, **3**, **4**, **5**, and **6** was performed.

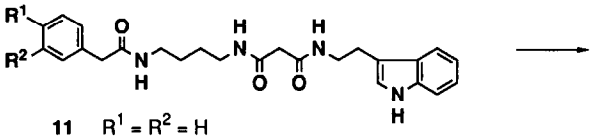
Thus, coupling of malonylated tryptamine **10**[4] and *N*-phenylacetylputrescine (**8**) prepared from putrescine (1,4-diaminobutane) and ethyl phenylacetate gave triamide **11** (79% from **10**) (Scheme 1). Ozonolysis[5] of the indole ring in **11** in MeOH followed by reductive workup provided **1** (63%), whose spectral and chromatographic properties were completely identical with those of natural monodontamide A.

Scheme 1.

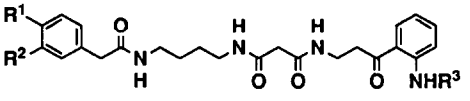


8 $R^1 = R^2 = H$
9 R^1 = OH, R^2 = OMe

10



11 $R^1 = R^2 = H$
12 R^1 = OH, R^2 = OMe
13 R^1 = OAc, R^2 = OMe

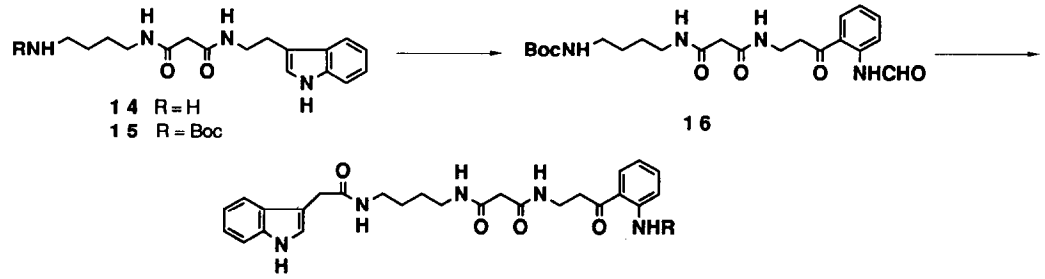


1 monodontamide A ($R^1 = R^2 = H$, R^3 = CHO)
2 monodontamide B (R^1 = OH, R^2 = OMe, R^3 = CHO)
3 monodontamide C (R^1 = OH, R^2 = OMe, R^3 = H)

Coupling of **10** and *N*-homovanilloylputrescine (**9**) prepared from putrescine and methyl homovanillate gave triamide **12** (80% from **10**) (Scheme 1). After acetylation of the hydroxyl group in **12** (96%), the resulting acetate **13** was subjected to ozonolysis in MeOH in the presence of $NaHCO_3$[13] followed by reductive workup to provide **2** (87%), which upon acidic hydrolysis afforded **3** (90%). Spectral and chromatographic properties of synthetic **2** and **3** were completely identical with those of natural monodontamides B and C, in all respects, respectively.

Reaction of **10** with a large excess of putrescine gave amine **14** (96% from **10**) (Scheme 2). After protection of the amino group in **14** with the Boc group (93%), the resulting urethane **15** was subjected to ozonolysis in MeOH in the presence of $NaHCO_3$ followed by reductive workup to provide formamide **16** (73%). Deprotection of the *N*-Boc group in **16** and subsequent coupling of the resulting amine with indole-3-acetic acid using diethyl cyanophosphonate[6] afforded **5** (90%), which upon formylation with ethyl formate[7] provided **4** (45%). Spectral and chromatographic properties of synthetic **4** and **5** were completely identical with those of natural monodontamides D and E, in all respects, respectively.

Scheme 2.

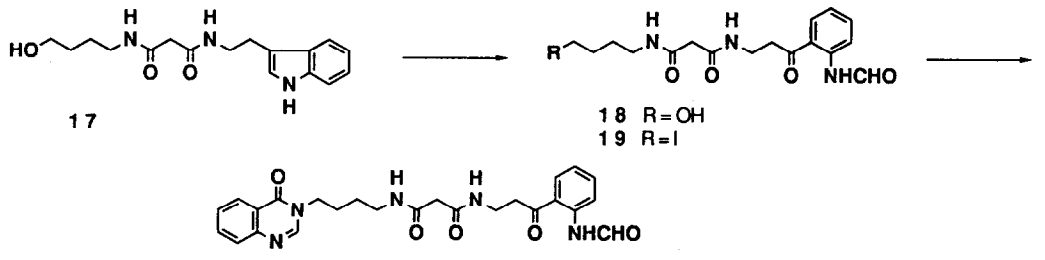


14 R=H
15 R=Boc
16

4 monodontamide D (R = CHO)
5 monodontamide E (R = H)

Reaction of **10** with a large excess of 4-amino-1-butanol gave alcohol **17** (90% from **10**) (Scheme 3). Ozonolysis of **17** in MeOH in the presence of $NaHCO_3$ followed by reductive workup provided formamide **18** (62%), which was converted into iodide **19** (95% from **18**) by conventional manner. Finally, *N*-3 alkylation of quinazoline[8] with **19** was effected using KOH as a base, yielding **6** (45% from **19**). The spectral and chromatographic properties of synthetic **6** were completely identical with those of natural monodontamide F in all respects.

Scheme 3.



17
18 R=OH
19 R=I

6 monodontamide F

CONCLUSION

Monodontamides A–E (**1–5**) are new putrescine alkaloids. Putrescine is among the biologically important aliphatic amines such as cadaverine, spermidine, and spermine.[9] Although a number of putrescine derivatives have been isolated from various plants, animals, and microorganisms,[9] the isolation of putrescine-containing secondary metabolites from marine sources is quite rare.[1] To our knowledge this is the first example on the isolation of natural products containing malonylated putrescine from a marine source. Monodontamide F (**6**) is a new quinazoline alkaloid. Although a number of quinazoline alkaloids have been isolated from various plants, animals, and microorganisms,[10,11] the isolation of quinazoline alkaloids from marine sources is also quite rare.[1] This presents the first isolation of a 4(3*H*)-quinazolinone compound from a marine source. It is also noteworthy that monodontamides isolated in the present study all contain an N^3-malonylated 2'3-diaminopropiophenone (kynuramine) moiety as the common structure part. Biogenetically, monodontamides may be derived from the corresponding malonylated tryptamine compounds through oxidative cleavage of the indole ring as the well-known tryptophan metabolism leading to kynurenine.[12]

Monodontamides exhibited weak inhibitory activity against a serine protease, rat eosinophil chymase. Their activities are as follows: monodontamide A (**1**), 23% inhibition at 1.5×10^{-5} M; monodontamide B (**2**), 30% inhibition at 4.1×10^{-5} M; monodontamide C (**3**), 58% inhibition at 4.3×10^{-5} M.

EXPERIMENTAL

Melting points are uncorrected. UV spectra were taken on a JASCO UVIDEC-510 spectrophotometer. IR spectra were taken on a JASCO IR-810 spectrophotometer. ^{1}H NMR spectra were recorded on either JEOL JNM EX-270 (270 MHz) or JEOL JNM-C675 (270 MHz) spectrometer in $CDCl_3$: Chemical shifts (δ) are reported in ppm downfield from internal tetramethylsilane in $CDCl_3$, and coupling constants in Hz. Low-resolution (EIMS, DCIMS, and FABMS) and high-resolution mass spectra (HREIMS and HRFABMS) were measured on a JEOL JMS-LG2000 instrument. Fuji-Davison silica gel BW-820MH was used for column chromatography. Merck precoated silica gel 60 F_{254} plates, 0.25 mm thickness were used for analytical thin layer chromatography (TLC) and Merck silica gel 60 $F_{254\ s}$ for preparative TLC. Dichloromethane (CH_2Cl_2), pyridine, and triethylamine (Et_3N) were distilled from calcium hydride (CaH_2) under nitrogen. *N,N*-Dimethylformamide (DMF) was distilled from CaH_2 under reduced pressure. Methanol (MeOH) was distilled from $Mg(OMe)_2$ under nitrogen. Acetone was distilled from anhydrous K_2CO_3 under nitrogen. Unless otherwise stated, the organic solutions obtained by extractive workup were washed with saturated aqueous NaCl solution, dried over anhydrous sodium sulfate (Na_2SO_4) and concentrated under reduced pressure by a rotary evaporator.

Extraction and Isolation Procedure. Specimens of *Monodonta labio* (Linné) were collected off the coast of Koka, Mie Prefecture, Japan in May 1992. Specimens (wet weight 19.2 kg) were crushed in MeOH using a blender. The crushed specimens were soaked in MeOH (40 l) at room temperature for 3 months. The mixture was filtered with suction. The filtration residue was washed with MeOH (2 x 5 l). The combined filtrate and washings were concentrated under reduced pressure to a volume of 1 l. The resulting aqueous mixture was extracted with EtOAc (4 x 1 l). The combined EtOAc extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a dark brown oil (26.3 g), which was partitioned between 9:1 MeOH–H_2O (100 ml) and hexane (3 x 100 ml). Concentration of the MeOH–H_2O layer afforded a dark brown oil (1.4 g), which was subjected to column chromatography on silica gel (42 g) using EtOAc (336 ml) and 1:1 EtOAc–MeOH (336 ml) as eluent. The fraction A (563 mg) eluted with 1:1 EtOAc–MeOH was further

chromatographed on silica gel (20 g) with EtOAc (400 ml), 9:1 EtOAc–MeOH (400 ml), and MeOH (120 ml). The fraction **B** (238 mg) eluted with 9:1 EtOAc–MeOH was then subjected to separation by preparative TLC on silica gel (200 mm x 200 mm x 2 mm x 2 plates, 10:1 $CHCl_3$–MeOH, two-times development) to give the less polar fraction **C** (52 mg) containing monodontamides A (**1**), B (**2**), C (**3**), and F (**6**), and the more polar fraction **D** (42 mg) containing monodontamides D (**4**) and E (**5**). Further separation of the less polar fraction **C** by HPLC [Develosil ODS-10/20 (250 mm x 20 mm i.d.), linear gradient from 50:50 MeOH–H_2O to 85:15 MeOH–H_2O over 45 min, flow rate 3 ml/min, UV detection at 254 nm] provided the fraction **E** (10 mg) containing monodontamides B (**2**) and C (**3**) and the fraction **F** (5.5 mg) containing monodontamides A (**1**) and F (**6**). The second extraction of other specimens (9. 3 kg) collected at the same place in September 1992, followed by separation as described above gave another fractions **D** (13 mg), **E** (2 mg), and **F** (3 mg). The combined fractions **D** (total 55 mg) were separated by repeated HPLC [Develosil ODS-10 (250 mm x 20 mm i.d.), linear gradient from 50:50 MeOH–H_2O to 100:0 MeOH–H_2O over 32 min, flow rate 3 ml/min, UV detection at 254 nm; Develosil ODS-HG-5 (250 mm x 10 mm i.d.), 50:50 MeOH–H_2O, flow rate 2 ml/min, UV detection at 254 nm], yielding monodontamides D (**4**) (2.8 mg, 9.8 x 10^{-6}% wet weight) and E (**5**) (0.5 mg, 1.8 x 10^{-6}% wet weight). The combined fractions **E** (total 12 mg) were separated by repeated HPLC [Develosil ODS-HG-5 (250 mm x 10 mm i.d.), 40:60 MeOH–H_2O, flow rate 2 ml/min, UV detection at 254 nm], yielding monodontamides B (**2**) (0.3 mg, 1.1 x 10^{-6}% wet weight) and C (**3**) (0.7 mg, 2.5 x 10^{-6}% wet weight). The combined fractions **F** (total 8.5 mg) were separated by HPLC [Develosil ODS-HG-5 (250 mm x 10 mm i.d.), 50:50 MeOH–H_2O, flow rate 2 ml/min, UV detection at 254 nm], yielding monodontamides A (**1**) (1.5 mg, 5.3 x 10^{-6}% wet weight) and F (**6**) (0.9 mg, 3.2 x 10^{-6}% wet weight).

Monodontamide A (**1**): $C_{25}H_{30}N_4O_5$; a colorless amorphous solid; UV (MeOH) λ_{max} (ε) 229 (15300), 258 (6020), 318 (2900), and 330 nm (sh, 2590); IR (KBr) 3300 (br), 3080, 1675, 1650, 1605, 1590, and 1525 cm^{-1}; ^1H NMR, Table **1**; ^{13}C NMR, Table **2**; FABMS *m/z* (relative intensity) 467 [$(M+H)^+$, 100]; HRFABMS calcd for $C_{25}H_{31}N_4O_5$ [$(M+H)^+$] 467.2294, found 467.2301.

Monodontamide B (**2**): $C_{26}H_{32}N_4O_7$; a colorless amorphous solid; UV (MeOH) λ_{max} (ε) 231 (26600), 259 (9830), 280 (sh, 3710), and 318 nm (3930); IR ($CHCl_3$) 3550 (br), 3450, 3300 (br), 3010, 1670, 1605, 1585, and 1510 cm^{-1}; ^1H NMR, Table **1**; ^{13}C NMR, Table **2**; FABMS *m/z* (relative intensity) 513 [$(M+H)^+$, 100]; HRFABMS calcd for $C_{26}H_{33}N_4O_7$ [$(M+H)^+$] 513.2349, found 513.2326.

Monodontamide C (**3**): $C_{25}H_{32}N_4O_6$; a colorless amorphous solid; UV (MeOH) λ_{max} (ε) 226 (32300), 256 (6990), 281 (3720), and 365 nm (6000); IR ($CHCl_3$) 3550 (br), 3450, 3350 (br), 3010, 1670, 1605, 1585, and 1510 cm^{-1}; ^1H NMR, Table **1**; ^{13}C NMR, Table **2**; FABMS *m/z* (relative intensity) 485 [$(M+H)^+$, 10]; HRFABMS calcd for $C_{25}H_{33}N_4O_6$ [$(M+H)^+$] 485.2400, found 485.2419.

Monodontamide D (**4**): $C_{27}H_{31}N_5O_5$; a colorless amorphous solid; UV (MeOH) λ_{max} (ε) 221 (37100), 260 (10900), 278 (sh, 5590), 287 (sh, 4720), and 320 nm (3350); IR ($CHCl_3$) 3470, 3300 (br), 3010, 1660, 1580, and 1520 cm^{-1}; ^1H NMR, Table **1**; ^{13}C NMR, Table **2**; FABMS *m/z* (relative intensity) 506 [$(M+H)^+$, 49]; HRFABMS calcd for $C_{27}H_{32}N_5O_5$ [$(M+H)^+$] 506.2403, found 506.2420.

Monodontamide E (**5**): $C_{26}H_{31}N_5O_4$; a colorless amorphous solid; UV (MeOH) λ_{max} (ε) 221 (41200), 258 (7950), 279 (5290), 287 (sh, 4400), and 363 nm (4790); IR ($CHCl_3$) 3430, 3350 (br), 3010, 1670, 1580, and 1510 cm^{-1}; ^1H NMR, Table **1**; ^{13}C NMR, Table **2**; FABMS *m/z* (relative intensity) 478 [$(M+H)^+$, 90]; HRFABMS calcd for $C_{26}H_{32}N_5O_4$ [$(M+H)^+$] 478.2454, found 478.2435.

Monodontamide F (**6**): $C_{25}H_{27}N_5O_5$; colorless plates; mp 129–132 °C (MeOH); UV (MeOH) λ_{max} (ε) 228 (45300), 260 (17900), 303 (sh, 6090), and 312 nm (6510); IR ($CHCl_3$) 3450, 3300 (br), 3010, 1670, 1580, and 1520 cm^{-1}; ^1H NMR, Table **1**; ^{13}C NMR, Table **2**; FABMS *m/z* (relative intensity) 478 [$(M+H)^+$, 100]; HRFABMS calcd for $C_{25}H_{28}N_5O_5$ [$(M+H)^+$] 478.2090, found 478.2087.

***N*-(4-Aminobutyl)phenylacetamide (8).** A stirred mixture of putrescine (1,4-diaminobutane) (2.7 g, 31 mmol) and ethyl phenylacetate (1.0 g, 6.1 mmol) under nitrogen was heated at 100 °C for 2.5 h. After cooling, the reaction mixture was concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel (30 g, 10:1 MeOH–conc. NH_3), affording **8** (883 mg, 70% from ethyl phenylacetate) as a colorless amorphous solid: IR ($CHCl_3$) 3430, 3300 (br), 3010, 1660, and 1520 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.17 (br s, 2 H, NH_2), 1.35–1.51 (m, 4 H), 2.64 (t, J = 6.6 Hz, 2 H), 3.22 (dt, J = 6.6, 6.6 Hz, 2 H), 3.56 (s, 2 H), 5.92 (br s, 1 H, NH), and 7.24–7.39 (m, 5 H); EIMS *m/z* (relative intensity) 206 (M^+, 50), 115 (46), and 92 (100); HREIMS calcd for $C_{12}H_{18}N_2O$ (M^+) 206.1419, found 206.1410.

***N*-[4-(Phenylacetylamino)butyl]-*N'*-[2-(3-indolyl)ethyl]malonamide (11).** A stirred mixture of **8** (611 mg, 2.97 mmol) and ethyl *N*-[2-(3-indolyl)ethyl]malonamate (**10**)[4] (492 mg, 1.80 mmol) in dioxane (2.0 ml) under nitrogen was heated under reflux for 38 h. After cooling, the reaction mixture was concentrated under reduced pressure to leave a colorless solid. Recrystallization from MeOH afforded **11** (534 mg, 69% from **10**) as colorless powdery crystals: mp 151–154 °C (MeOH); IR ($CHCl_3$) 3300 (br), 3020, 1660, and 1520 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.45 (m, 4 H), 3.00 (t, J = 6.9 Hz, 2 H), 3.07 (s, 2 H), 3.22 (m, 4 H), 3.57 (s, 2 H), 3.61 (dt, J = 6.9, 6.9 Hz, 2 H), 5.22 (br, 1 H, NH), 6.55 (br, 1 H, NH), 6.97 (br, 1 H, NH), 7.04 (d, J = 2.3 Hz, 1 H), 7.12 (ddd, J = 7.9, 7.9, 1.0 Hz, 1 H), 7.20 (ddd, J = 7.9, 7.9, 1.0 Hz, 1 H), 7.24–7.39 (m, 6 H), 7.59 (d, J = 7.9 Hz, 1 H), and 8.29 (br s, 1 H, NH); DCIMS *m/z* (relative intensity) 435 [$(M+H)^+$, 60], 292 (80), and 143 (88). Anal. Calcd for $C_{25}H_{30}N_4O_3$: C, 69.08; H, 6.96; N, 12.90. Found: C, 69.06; H, 6.93; N, 12.78.

Monodontamide A (1). A stream of ozone gas was passed through a stirred solution of **11** (29.5 mg, 0.0680 mmol) in MeOH (3 ml) at –78 °C. The progress of the reaction was monitored by TLC (4:1 EtOAc–MeOH). After only a trace of **11** could be detected (ca. 7 min) by TLC, the ozone flow was discontinued, and nitrogen gas was bubbled through the solution (ca. 2 min). To the solution was added dimethyl sulfide (0.2 ml), and the mixture was allowed to warm to room temperature with continuous stirring. After stirring at room temperature for an additional 1 h, the mixture was concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel (4 g, 8:1→6:1 EtOAc–MeOH), providing monodontamide A (**1**) (28.0 mg, 63%) as a colorless amorphous solid: HRFABMS calcd for $C_{25}H_{31}N_4O_5$ [$(M+H)^+$] 467.2294, found 467.2310.

***N*-(4-Aminobutyl)-4-hydroxy-3-methoxyphenylacetamide (9).** Under nitrogen a stirred mixture of putrescine (1.3 g, 15 mmol) and methyl homovanillate (602 mg, 3.07 mmol) was heated at 100 °C for 2.5 h. After cooling, the reaction mixture was concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel (30 g, 10:1 MeOH–conc. NH_3), affording **9** (757 mg, 98% from methyl homovanillate) as a colorless amorphous solid: IR ($CHCl_3$) 3550 (br), 3420 (br), 3020, 1660, 1600, and 1520 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.17 (br s, 2 H, NH_2), 1.34–1.53 (m, 4 H), 2.17 (br s, 3 H, OH and NH_2), 2.66 (t, J = 6.6 Hz, 2 H), 3.21 (dt, J = 6.6, 6.6 Hz, 2 H), 3.48 (s, 2 H), 3.87 (s, 3 H), 5.79 (br s, 1 H, NH), 6.70 (dd, J = 7.9, 2.0 Hz, 1 H), 6.75 (d, J = 2.0 Hz, 1 H), and 6.86 (d, J = 7.9 Hz, 1 H); EIMS *m/z* (relative intensity) 252 (M^+, 82), 164 (60), 137 (100), and 115 (46); HREIMS calcd for $C_{13}H_{20}N_2O_3$ (M^+) 252.1474, found 252.1504.

***N*-[4-(4-Hydroxy-3-methoxyphenylacetylmino)butyl]-*N'*-[2-(3-indolyl)ethyl]malonamide (12).** A stirred mixture of **9** (633 mg, 2.51 mmol) and **10** (459 mg, 1.68 mmol) in dioxane (2.0 ml) under

nitrogen was heated at 90 °C for 46 h and then under reflux for 21 h. After cooling, the reaction mixture was concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel (50 g, 10:1→5:1 EtOAc–MeOH), affording **12** (646 mg, 80% from **10**) as a colorless amorphous solid: IR ($CHCl_3$) 3550 (br), 3330 (br), 3010, 1670, and 1520 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.44 (m, 4 H), 2.99 (t, *J* = 6.9 Hz, 2 H), 3.05 (s, 2 H), 3.20 (m, 4 H), 3.48 (m, 2 H), 3.60 (dt, *J* = 6.9, 6.9 Hz, 2 H), 3.86 (s, 3 H), 5.62 (br, 1 H, NH), 5.75 (br s, 1 H, OH), 6.71 (dd, *J* = 7.9, 2.0 Hz, 1 H), 6.72 (br, 1 H, NH), 6.76 (d, *J* = 2.0 Hz, 1 H), 6.88 (d, *J* = 7.9 Hz, 1 H), 7.03 (d, *J* = 2.3 Hz, 1 H), 7.09 (br, 1 H, NH), 7.11 (ddd, *J* = 7.9, 7.9, 1.0 Hz, 1 H), 7.19 (ddd, *J* = 7.9, 7.9, 1.0 Hz, 1 H), 7.38 (d, *J* = 7.9 Hz, 1 H), 7.58 (d, *J* = 7.9 Hz, 1 H), and 8.40 (br s, 1 H, NH); FABMS *m/z* (relative intensity) 481 [$(M+H)^+$, 11]; HRFABMS calcd for $C_{26}H_{33}N_4O_5$ [$(M+H)^+$] 481.2451, found 481.2463.

***N*-[4-(4-Acetoxy-3-methoxyphenylacetylamino)butyl]-*N'*-[2-(3-indolyl)ethyl]malonamide (13).** A mixture of **12** (390 mg, 0.813 mmol), acetic anhydride (1.0 ml), and pyridine (2.0 ml) under nitrogen was stirred ar room temperature for 2.5 h, and the reaction mixture was concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel (30 g, 10:1→5:1 EtOAc–MeOH), affording **13** (409 mg, 96%) as a colorless amorphous solid: IR ($CHCl_3$) 3480, 3320 (br), 3010, 1760, 1670, 1610, 1520, and 1510 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.41 (m, 4 H), 2.31 (s, 3 H), 3.03 (s, 2 H), 3.15 (dt, *J* = 6.3, 6.3 Hz, 2 H), 3.22 (dt, *J* = 6.3, 6.3 Hz, 2 H), 3.52 (s, 2 H), 3.58 (dt, *J* = 6.6, 6.6 Hz, 2 H), 3.74 (s, 3 H), 5.74 (br, 1 H, NH), 6.80 (dd, *J* = 7.9, 2.0 Hz, 1 H), 6.86 (d, *J* = 2.0 Hz, 1 H), 6.91 (br, 1 H, NH), 6.99 (d, *J* = 2.3 Hz, 1 H), 7.10 (ddd, *J* = 7.9, 7.9, 1.0 Hz, 1 H), 7.11 (br, 1 H, NH), 7.18 (ddd, *J* = 7.9, 7.9, 1.0 Hz, 1 H), 7.37 (d, *J* = 7.9 Hz, 1 H), 7.57 (d, *J* = 7.9 Hz, 1 H), and 8.50 (br s, 1 H, NH); FABMS *m/z* (relative intensity) 523 [$(M+H)^+$, 52]; HRFABMS calcd for $C_{28}H_{35}N_4O_6$ [$(M+H)^+$] 523.2556, found 523.2551.

Monodontamide B (2). A stream of ozone gas was passed through a vigorously stirred mixture of **13** (197 mg, 0.377 mmol) and $NaHCO_3$ (320 mg, 3.81 mmol) in MeOH (5 ml) at –78 °C. The progress of the reaction was monitored by TLC (4:1 EtOAc–MeOH). After only a trace of **13** could be detected (ca. 7 min) by TLC, the ozone flow was discontinued, and nitrogen gas was bubbled through the solution (ca. 2 min). To the solution was added dimethyl sulfide (0.8 ml), and the mixture was allowed to warm to room temperature with continuous stirring. After stirring at room temperature for an additional 4 h, the mixture was filtered through a cotton plug. The filtrate and washings were combined and concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel (20 g, 10:1→5:1 EtOAc–MeOH), providing monodontamide B (**2**) (168 mg, 87%) as a colorless amorphous solid: HRFABMS calcd for $C_{26}H_{33}N_4O_7$ [$(M+H)^+$] 513.2349, found 513.2320.

Monodontamide C (3). To a solution of **2** (92 mg, 0.18 mmol) in EtOH (12.5 ml) under nitrogen was added 1.5 M HCl (12.5 ml), and the mixture was stirred at room temperature for 1 h. The reaction mixture was neutralized by the addition of $NaHCO_3$ (1.7 g), and the mixture was filtered through a cotton plug. The filtrate and washings were combined and concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel (4 g, 10:1 EtOAc–MeOH), providing monodontamide C (**3**) (78 mg, 90%) as a colorless amorphous solid: HRFABMS calcd for $C_{25}H_{33}N_4O_6$ [$(M+H)^+$] 485.2400, found 485.2396.

***N*-(4-Aminobutyl)-*N'*-[2-(3-indolyl)ethyl]malonamide (14).** Under nitrogen a stirred mixture of **10** (133 mg, 0.485 mmol) and putrescine (214 mg, 2.43 mmol) was heated at 100 °C for 2 h. After cooling,

the reaction mixture was concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel (20 g, 20:1 MeOH–conc. NH_3), yielding **14** (147 mg, 96% from **10**) as a colorless amorphous solid: IR ($CHCl_3$) 3480, 3300 (br), 3010, 1670, and 1530 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.47–1.56 (m, 4 H), 1.60 (br s, 2 H, NH_2), 2.72 (t, J = 6.6 Hz, 2 H), 2.99 (t, J = 6.6 Hz, 2 H), 3.05 (s, 2 H), 3.23 (dt, J = 6.6, 6.6 Hz, 2 H), 3.60 (dt, J = 6.6, 6.6 Hz, 2 H), 6.91 (br, 1 H, NH), 7.04 (d, J = 2.3 Hz, 1 H), 7.10 (ddd, J = 7.9, 7.9, 1.3 Hz, 1 H), 7.19 (ddd, J = 7.9, 7.9, 1.3 Hz, 1 H), 7.35 (dd, J = 7.9, 1.3 Hz, 1 H), 7.44 (br t, J = 6.6 Hz, 1 H, NH), 7.58 (dd, J = 7.9, 1.3 Hz, 1 H), and 8.76 (br s, 1 H, NH); FABMS *m/z* (relative intensity) 317 [$(M+H)^+$, 100]; HRFABMS calcd for $C_{17}H_{25}N_4O_2$ [$(M+H)^+$] 317.1977, found 317.1976.

***N*-[4-(*t*-Butoxycarbonylamino)butyl]-*N'*-[2-(3-indolyl)ethyl]malonamide (15).** To a solution of **14** (178 mg, 0.563 mmol) in CH_2Cl_2 (2.0 ml) under nitrogen was added di-*t*-butyl dicarbonate (0.14 ml, 0.62 mmol). The mixture was stirred at room temperature for 4.5 h and concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel (20 g, 10:1→5:1 EtOAc–MeOH), yielding **15** (219 mg, 93%) as a colorless amorphous solid: IR ($CHCl_3$) 3480, 3450, 3320 (br), 3000, 1700, 1670, and 1510 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.45 (s, 9 H), 1.49–1.51 (m, 4 H), 2.99 (t, J = 6.6 Hz, 2 H), 3.06 (s, 2 H), 3.12 (m, 2 H), 3.23 (dt, J = 6.6, 6.6 Hz, 2 H), 3.60 (dt, J = 6.6, 6.6 Hz, 2 H), 4.61 (br s, 1 H, NH), 6.73 (br, 1 H, NH), 7.02 (br, 1 H, NH), 7.04 (d, J = 2.3 Hz, 1 H), 7.12 (ddd, J = 7.9, 7.9, 1.3 Hz, 1 H), 7.20 (ddd, J = 7.9, 7.9, 1.3 Hz, 1 H), 7.38 (dd, J = 7.9, 1.3 Hz, 1 H), 7.59 (dd, J = 7.9, 1.3 Hz, 1 H), and 8.34 (br s, 1 H, NH); FABMS *m/z* (relative intensity) 417 [$(M+H)^+$, 22]; HRFABMS calcd for $C_{22}H_{33}N_4O_4$ [$(M+H)^+$] 417.2502, found 417.2514.

***N*-[4-(*t*-Butoxycarbonylamino)butyl]-*N'*-[3-(2-formylamino)phenyl-3-oxopropyl]malonamide (16).** A stream of ozone gas was passed through a vigorously stirred mixture of **15** (204 mg, 0.490 mmol) and $NaHCO_3$ (412 mg, 4.90 mmol) in MeOH (8 ml) at –78 °C. The progress of the reaction was monitored by TLC (4:1 EtOAc–MeOH). After only a trace of **15** could be detected (ca. 15 min) by TLC, the ozone flow was discontinued, and nitrogen gas was bubbled through the mixture (ca. 2 min). To the mixture was added dimethyl sulfide (0.7 ml), and the mixture was allowed to warm to room temperature with continuous stirring. After stirring at room temperature for an additional 1.5 h, the mixture was filtered through a cotton plug. The filtrate and washings were combined and concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel (20 g, 30:1→10:1 EtOAc–MeOH), providing **16** (160 mg, 73%) as colorless plates: mp 132–135 °C (EtOAc); IR ($CHCl_3$) 3450, 3300 (br), 3010, 1700, 1660, 1610, 1580, and 1520 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.41 (s, 9 H), 1.49–1.51 (m, 4 H), 3.09 (dt, J = 5.9, 5.9 Hz, 2 H), 3.14 (s, 2 H), 3.24 (dt, J = 5.9, 5.9 Hz, 2 H), 3.28 (t, J = 5.9 Hz, 2 H), 3.65 (dt, J = 5.9, 5.9 Hz, 2 H), 4.69 (br, 1 H, NH), 7.15 (dd, J = 7.9, 7.9 Hz, 1 H), 7.24 (br, 1 H, NH), 7.55 (ddd, J = 7.9, 7.9, 1.3 Hz, 1 H), 7.65 (br t, J = 5.9 Hz, 1 H, NH), 7.88 (dd, J = 7.9, 1.3 Hz, 1 H), 8.49 (s, 1 H), 8.72 (d, J = 7.9 Hz, 1 H), and 11.50 (br s, 1 H, NH); FABMS *m/z* (relative intensity) 449 [$(M+H)^+$, 6]. Anal. Calcd for $C_{22}H_{32}N_4O_6$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.88; H, 7.16; N, 12.27.

Monodontamide E (5). To an ice-cooled solution of **16** (47.0 mg, 0.105 mmol) in CH_2Cl_2 (0.5 ml) under nitrogen was added trifluoroacetic acid (0.16 ml, 2.1 mmol). The mixture was stirred at 0 °C for 45 min and concentrated under reduced pressure. The resulting oily residue was dissolved in DMF (1.8 ml) under nitrogen. To the ice-cooled solution was added indole-3-acetic acid (27.6 mg, 0.158 mmol), diethyl cyanophosphonate (0.06 ml, 0.40 mmol), and triethylamine (0.10 ml, 0.72 mmol). The mixture was stirred at 0 °C for 30 min and then diluted with saturated $NaHCO_3$ solution (1.5 ml) and water (2 ml). The aqueous

mixture was extracted with EtOAc (4 x 5 ml). The extracts were combined, washed, dried, and concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel (10 g, 10:1→5:1 EtOAc–MeOH), providing monodontamide E (**5**) (48.1 mg, 90%) as a pale yellow amorphous solid: HRFABMS calcd for $C_{26}H_{32}N_5O_4$ [(M+H)$^+$] 478.2454, found 478.2473.

Monodontamide D (4). A solution of monodontamide E (**5**) (7.4 mg, 0.016 mmol) in ethyl formate (5 ml) was sealed in a pyrex tube under nitrogen. The sealed tube was heated at 100 °C for 15 h. After cooling, the reaction mixture was concentrated under reduced pressure. The oily residue was purified by preparative TLC on silica gel (4:1 EtOAc–MeOH), providing monodontamide D (**4**) (3.5 mg, 45%) as a colorless amorphous solid: HRFABMS calcd for $C_{27}H_{32}N_5O_5$ [(M+H)$^+$] 506.2403, found 506.2390.

***N*-(4-Hydroxybutyl)-*N'*-[2-(3-indolyl)ethyl]malonamide (17).** Under nitrogen a stirred mixture of **10** (323 mg, 1.18 mmol) and 4-amino-1-butanol (0.54 ml, 5.9 mmol) was heated at 70 °C for 1 h. After cooling, the reaction mixture was concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel (20 g, 10:1→5:1 EtOAc–MeOH), yielding **17** (334 mg, 90% from **10**) as colorless plates: mp 104–105 °C (EtOAc); IR ($CHCl_3$) 3480 (br), 3450 (br), 3320 (br), 3020, 1670, and 1520 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.60 (m, 4 H), 1.78 (br s, 1 H, OH), 2.99 (t, J = 6.9 Hz, 2 H), 3.07 (s, 2 H), 3.28 (m, 2 H), 3.60 (dt, J = 6.9, 6.9 Hz, 2 H), 3.67 (m, 2 H), 6.64 (br, 1 H, NH), 7.05 (d, J = 2.3 Hz, 1 H), 7.08 (br, 1 H, NH), 7.12 (dd, J = 7.9, 7.9 Hz, 1 H), 7.21 (dd, J = 7.9, 7.9 Hz, 1 H), 7.37 (d, J = 7.9 Hz, 1 H), 7.59 (d, J = 7.9 Hz, 1 H), and 8.21 (br s, 1 H, NH); FABMS *m/z* (relative intensity) 318 [(M+H)$^+$, 100]. Anal. Calcd for $C_{17}H_{23}N_3O_3$: C, 64.33; H, 7.30; N, 13.24. Found: C, 64.23; H, 7.18; N, 13.07.

***N*-4-(Hydroxybutyl)-*N'*-[3-(2-formylamino)phenyl-3-oxopropyl]malonamide (18).** A stream of ozone gas was passed through a vigorously stirred mixture of **17** (229 mg, 0.722 mmol) and $NaHCO_3$ (607 mg, 7.22 mmol) in MeOH (8 ml) at –78 °C. The progress of the reaction was monitored by TLC (4:1 EtOAc–MeOH). After only a trace of **17** could be detected (ca. 20 min) by TLC, the ozone flow was discontinued, and nitrogen gas was bubbled through the mixture (ca. 2 min). To the mixture was added dimethyl sulfide (1 ml), and the mixture was allowed to warm to room temperature with continuous stirring. After stirring at room temperature for an additional 5 h, the mixture was filtered through a cotton plug. The filtrate and washings were combined and concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel (30 g, 10:1→5:1 EtOAc–MeOH), providing **18** (157 mg, 62%) as colorless needles: mp 114–114.5 °C (EtOAc); IR ($CHCl_3$) 3450, 3300 (br), 3010, 1670, 1610, 1590, and 1520 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.60 (m, 4 H), 1.92 (br s, 1 H, OH), 3.13 (s, 2 H), 3.28 (m, 2 H), 3.30 (t, J = 5.9 Hz, 2 H), 3.67 (m, 2 H), 3.69 (dt, J = 5.9, 5.9 Hz, 2 H), 7.02 (br, 1 H, NH), 7.17 (dd, J = 7.9, 7.9 Hz, 1 H), 7.44 (br, 1 H, NH), 7.58 (ddd, J = 7.9, 7.9, 1.3 Hz, 1 H), 7.89 (dd, J = 7.9, 1.3 Hz, 1 H), 8.51 (br s, 1 H), 8.74 (d, J = 7.9 Hz, 1 H), and 11.50 (br s, 1 H, NH); FABMS *m/z* (relative intensity) 350 [(M+H)$^+$, 100]. Anal. Calcd for $C_{17}H_{23}N_3O_5$: C, 58.44; H, 6.63; N, 12.03. Found: C, 58.44; H, 6.59; N, 11.95.

***N*-4-(Iodobutyl)-*N'*-[3-(2-formylamino)phenyl-3-oxopropyl]malonamide (19).** To an ice-cooled solution of **18** (50.0 mg, 0.143 mmol) in pyridine (0.25 ml) was added *p*-toluenesulfonyl chloride (54.6 mg, 0.287 mmol) under nitrogen, and the mixture was stirred at 0 °C for 2 h. To the reaction mixture was added water (0.2 ml), and the mixture was stirred at 0 °C for an additional 15 min. The mixture was diluted with water (1 ml) and extracted with EtOAc (2 x 4 ml). The organic layers were combined, washed, dried, and concentrated under reduced pressure. The resulting crude tosylate was dissolved in dry acetone (1.5 ml) under nitrogen. To the solution were added NaI (221 mg, 1.48 mmol) and powdered $CaCO_3$ (26.5 mg, 0.295

mmol). The mixture was vigorously stirred at 50 °C in the dark for 12 h. After cooling, the reaction mixture was diluted with water (1 ml) and extracted with EtOAc (4 x 3 ml). The extracts were combined, washed, dried, and concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel (4 g, 10:1 EtOAc–MeOH), providing **19** (64.1 mg, 95% from **18**) as colorless needles: mp 111–112 °C (EtOAc); IR ($CHCl_3$) 3450, 3300 (br), 3010, 1670, 1610, 1580, and 1520 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.62 (m, 2 H), 1.83 (m, 2 H), 3.14 (s, 2 H), 3.17 (t, J = 6.6 Hz, 2 H), 3.26 (t, J = 5.6 Hz, 2 H), 3.27 (m, 2 H), 3.67 (dt, J = 5.6, 5.6 Hz, 2 H), 7.03 (br, 1 H, NH), 7.16 (dd, J = 7.9, 7.9 Hz, 1 H), 7.39 (br, 1 H, NH), 7.58 (dd, J = 7.9, 7.9 Hz, 1 H), 7.89 (d, J = 7.9 Hz, 1 H), 8.51 (s, 1 H), 8.74 (d, J = 7.9 Hz, 1 H), and 11.50 (br s, 1 H, NH); FABMS *m/z* (relative intensity) 460 [$(M+H)^+$, 100]. Anal. Calcd for $C_{17}H_{22}N_3O_4I$: C, 44.46; H, 4.83; N, 9.15. Found: C, 44.49; H, 4.78; N, 8.98.

Monodontamide F (6). To a solution of 4-hydroxyquinazoline (**20**) (30.4 mg, 0.208 mmol) in EtOH (0.5 ml) was added KOH (11.7 mg, 0.208 mmol) under nitrogen, and the mixture was stirred at room temperature for 20 min. To the resulting slurry was added a solution of **19** (47.8 mg, 0.104 mmol) in EtOH (0.5 ml), and the mixture was heated under reflux for 3.5 h. After cooling, the reaction mixture was diluted with saturated NH_4Cl solution and extracted with EtOAc (4 x 5 ml). The extracts were combined, washed, dried, and concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel (7 g, 10:1→5:1 EtOAc–MeOH), providing monodontamide F (**6**) (21.7 mg, 45% from **19**) as colorless plates: mp 130–134 °C (MeOH). Anal. Calcd for $C_{25}H_{27}N_5O_5$: C, 62.88; H, 5.70; N, 14.67. Found: C, 62.74; H, 5.35; N, 14.47.

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