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# Eurypongins A–C, three new unique sesquiterpenes from a marine sponge *Eurypongia* sp.

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ABSTRACT

Three new unique sesquiterpenes, eurypongins A–C (**1**–**3**), were isolated from a marine sponge *Eurypongia* sp. collected at Iriomote Island, Okinawa, Japan. Compound **1** possessed a bicyclic furanosesquiterpene structure with six- and eight-membered rings, whereas compounds **2** and **3** had an α,β-unsaturated-γ-lactone ring instead of the furan ring in **1**. Only five natural products in this class have been reported, and compounds **1**–**3** are the sixth–eighth examples of natural products. Compounds **1**–**3** had no inhibition effect against PTP1B, an important target enzyme for the treatment of diabetes, while the dehydro derivative of **1** [dehydroeurypongin A (**4**)] exhibited inhibitory activity ($IC_{50}$ = 3.6 μM).



Marine sponges have been shown to be an important resource for the discovery of bioactive natural products. Many metabolites isolated from marine sponges possess unique structural features and potent biological activities.[1] Sponges of the genus *Eurypongia* have been shown to contain various types of secondary metabolites, including steroidal sulfates,[2] secosteroids,[3] hydroquinones,[4] sesquiterpene quinones,[5] and furanoterpenoids.[6] During our search program for novel and useful metabolites from marine organisms, three new unique sesquiterpenes, named eurypongins A–C (**1**–**3**), were isolated from a marine sponge *Eurypongia* sp. collected at Iriomote Island, Okinawa, Japan (Fig. 1). The structures of **1**–**3** were assigned on the basis of their spectroscopic data as unique sesquiterpenes possessing a six- and eight-membered bicyclic skeleton. Only five compounds, pallescensin B (**5**),[7a] nakafuran-8 (**6**),[7b] 5-hydroxynakafuran-8 (**7**),[7c] 5-acetoxynakafuran-8 (**8**),[7c] and *O*-methyl nakafuran-8 lactone (**9**),[7d] have thus far been reported as natural products in this class (Fig. 1). The natural products **1**–**3** did not show inhibitory activity against protein tyrosine phosphatase 1B (PTP1B), an important target for the treatment of type-II diabetes, while the dehydrated product of **1** [dehydroeurypongin A (**4**)] inhibited the activity of this enzyme ($IC_{50}$ = 3.6 μM). We describe herein the isolation, structure elucidation including stereochemistry, and biological activity of compounds **1**–**4**.

The marine sponge (306.6 g, wet weight)[8] was extracted with ethanol, and the extract (1.1 g) was separated by an ODS column (100 g) followed by repeated HPLC to give compounds **1** (12.7 mg), **2** (0.90 mg), and **3** (1.55 mg) as colorless oil.[9]

The molecular formula, $C_{15}H_{20}O_2$, of eurypongin A (**1**)[10] was assigned from HREIMS (*m/z* 232.1462 $[M]^+$, Δ −0.1 mmu) and NMR data (Table 1). $^1H$ and $^{13}C$ NMR spectra of **1** showed 19 proton and 15 carbon signals, which were classified into three methyls, two methylenes, two $sp^3$ methines, one $sp^3$ oxygenated methine, one $sp^3$ quaternary carbon, two $sp^2$ methines, one $sp^2$ oxygenated methine, two $sp^2$ quaternary carbons, and one $sp^2$ oxygenated quaternary carbon from HMQC data. The presence of an OH group was revealed from IR absorption at 3402 $cm^{-1}$ and the molecular formula of **1**. Three partial structures (I–III), shown as bold lines in Figure 2, were elucidated from the $^1H$–$^1H$ COSY spectrum of **1**. An α,β-disubstituted furan ring in partial structure I was assigned from HMBC correlations from H-1 (δ 7.15) and H-2 (6.37) to C-3 (122.6) and C-10 (150.1) (Fig. 2) and UV absorption at 220 nm.[7b] HMBC correlations from $H_3$-13 (δ 0.78) to C-11 (44.2), C-12 (33.4), and C-14 (30.1), from $H_3$-14 (0.90) to C-6 (48.1), C-12, and C-13 (36.3), and from $H_3$-15 (1.87) to C-6, C-7 (141.5), and C-8 (120.2) connected partial structures II and III by forming a six-membered ring. The connections of a furan ring and, consequently, an eight-membered ring were elucidated from HMBC correlations from H-4 (δ 4.59) to C-3 and C-10, from $H_2$-5 (2.16 and 2.27) to C-3, from H-9 (3.45) to C-10, and from $H_2$-11 (1.56 and 1.64) to

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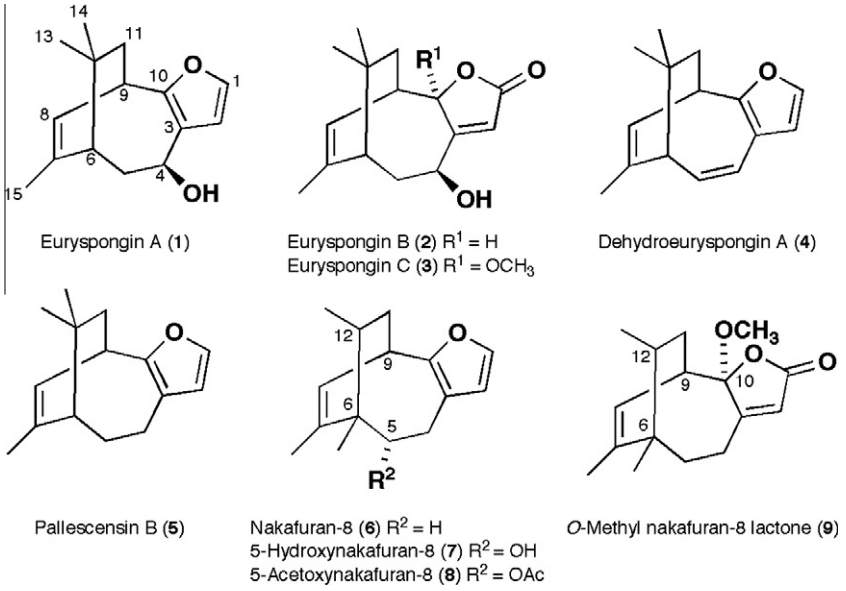


**Figure 1.** Structures of compounds **1**–**9**.

**Table 1**
$^{1}H$ and $^{13}C$ NMR data for eurypongins A–C (**1**–**3**) in $CDCl_3$

| Position | Eurypongin A (**1**) | | Eurypongin B (**2**) | | Eurypongin C (**3**) | |
|---|---|---|---|---|---|---|
| | $\delta_C$ | $\delta_H$ ($J$ in Hz) | $\delta_C$ | $\delta_H$ ($J$ in Hz) | $\delta_C$ | $\delta_H$ ($J$ in Hz) |
| 1 | 138.8 | 7.15 d (1.9) | 172.5 | – | 166.8 | – |
| 2 | 109.3 | 6.37 d (1.9) | 118.0 | 6.26 s | 119.9 | 6.30 d (1.0) |
| 3 | 122.6 | – | 176.1 | – | 170.1 | – |
| 4 | 65.9 | 4.59 dd (11.1, 4.8) | 67.0 | 4.32 dd (10.6, 5.5) | 65.7 | 4.32 ddd (10.0, 5.6, 1.0) |
| 5a | 40.8 | 2.27 ddd (14.0, 9.2, 4.8) | 34.9 | 2.22 ddd (14.1, 8.6, 5.7) | 35.6 | 2.22 ddd (14.0, 8.2, 5.8) |
| 5b | | 2.16 ddd (13.9, 11.0, 1.1) | | 1.95 dd (13.9, 10.6) | | 1.98 dd (14.0, 10.6) |
| 6 | 48.1 | 2.08 d (8.7) | 47.2 | 1.89 d (8.8) | 47.5 | 1.90 d (8.7) |
| | 141.5 | – | 142.5 | – | 140.4 | – |
| 8 | 120.2 | 5.74 dq (7.3, 1.4) | 118.8 | 5.61 d (6.6) | 119.4 | 5.60 dq (7.3, 1.0) |
| | 150.1 | | | | | |
| 9 | 33.8 | 3.45 ddd (7.3, 6.0, 2.2) | 33.9 | 2.96 br t | 37.2 | 2.97 br t |
| 10 | 150.1 | – | 83.5 | 4.85 s | 109.4 | – |
| 11 | 44.2 | 1.56 dd (13.3, 6.0) | 30.2 | 1.25 m | 33.8 | 1.25 m |
| | | 1.64 dd (13.3, 2.2) | | 1.35 dd (15.0, 9.5) | | 1.53 dd (15.5, 10.1) |
| 12 | 33.4 | – | 34.0 | – | 33.1 | – |
| 13 | 36.3 | 0.78 s | 29.3 | 0.93 s | 29.8 | 0.92 s |
| 14 | 30.1 | 0.90 s | 33.7 | 0.95 s | 34.7 | 0.96 s |
| 15 | 23.5 | 1.87 d (1.4) | 24.0 | 1.81 s | 24.0 | 1.82 d (1.0) |
| 10-$OCH_3$ | | | | | 51.1 | 3.23 s |

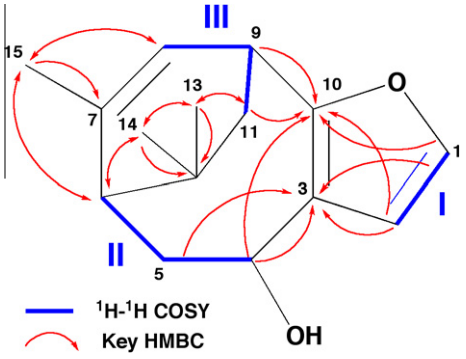


**Figure 2.** $^{1}H$–$^{1}H$ COSY and HMBC correlations for eurypongin A (**1**).

C-10 (Fig. 2). Thus, the skeletal structure of **1** was assigned as shown in Figure 2.

The relative stereochemistry of **1** was elucidated by the analysis of NOESY data ($CDCl_3$) and 1D NOE difference experiments in $C_6D_6$ (Fig. 3). Correlations between H-4 ($\delta$ 4.59)/$H_3$-15 (1.87), H-5b (2.16)/$H_3$-13 (0.78), H-6 (2.08)/$H_3$-14 (0.90), $H_3$-15/H-8 (5.74), and H-8/H-9 (3.45) were observed in the NOESY spectrum of **1** measured in $CDCl_3$ (Fig. 3). Assignment of the stereochemistry at C-4 to C-6 was also confirmed by NOE difference experiments in $C_6D_6$ (Fig. 3) because $^{1}H$ signals were observed closely to each other in $CDCl_3$. NOE difference spectra in $C_6D_6$ exhibited strong enhancements between H-4 ($\delta$ 4.45)/$H_3$-15 (1.47), H-6 (1.80)/$H_3$-14 (0.78), and H-6/$H_3$-15. Considering these NOE data, the Monte Carlo conformational analysis was performed with an