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CRAMBESCIDIN ACID FROM THE FRENCH POLYNESIAN *Monanchora* n. sp. MARINE SPONGE

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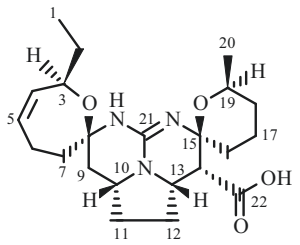
Marine natural products continue to be rich reservoirs for pharmacological lead compounds [1, 2]. Marine sponges are a distinct multicellular phylum and represent the biggest class of marine invertebrates with approximately 8,900 registered species, though 15,000 species are distributed over seas and oceans [3–5]. *Monanchora* marine sponges are well recognized for producing a high number of structurally divergent bioactive secondary metabolites [6], including acyclic and polycyclic guanidine alkaloids [7–9], steroids [10], terpenoids [11, 12], and long chain fatty acids [13]. These compounds display a myriad of biological potentialities as antimalarial [14], anticancer [15], anti-infective [16], and antiviral [17]. As a part of our ongoing program on bioactive natural products from marine sponges [18–21], we report herein the isolation and identification of five natural products **1–5** for the first time from the *n*-BuOH fraction of *Monanchora* n. sp. sponge.

Chemical investigation of the French Polynesia *Monanchora* sp. marine sponge led to the isolation and identification of one pentacyclic guanidine alkaloid crambescidin acid (**1**) along with four simple nitrogenous compounds, including one nucleoside thymidine (**2**) and three amino acid derivatives, namely phenylethylamine (**3**), tryptophan (**4**). and phenylalanine (**5**).

Compound **1** (11.5 mg) was purified as a viscous pale yellow oily material. It has the molecular formula $C_{22}H_{33}N_3O_4$ as established from its positive HR-ESI-MS *m/z* 404.2461 $[M + H]^+$ (calcd 404.2549), indicating eight degrees of unsaturation. A preliminary inspection of its ^{1}H NMR recorded in MeOH-d_4 showed characteristic signals with similar chemical shifts to those reported previously for crambescidine pentacyclic guanidine alkaloids, confirming the presence of a pentacyclic guanidinic core (vessel), which accounts for five degrees of unsaturation. A detailed analysis of the ^{13}C NMR and HSQC spectra disclosed 22 resonances, which were attributed to two methyls at δ_C 10.9 (C-1) and 22.1 (C-20), two oxymethines at δ_C 72.3 (C-3) and 68.3 (C-19), two azamethines at δ_C 55.6 (C-10) and 54.9 (C-13), two olefinic methines at δ_C 134.5 (C-4) and 131.6 (C-5) within the seven membered ring, giving the sixth degree of unsaturation, one methine at δ_C 54.1 (C-14), and nine methylene groups at δ_C 30.4 (C-2), 24.6 (C-6), 38.4 (7), 38.7 (C-9), 31.0 (C-11), 31.0 (C-12), 33.6 (C-16), 19.7 (C-17), and 32.9 (C-18). Four quaternary resonances, including two sp^3 spiro-carbons at δ_C 85.1 (C-8) and 82.8 (C-15) and two downfield resonances at δ_C 150.8 (C-21) and 181.6 (C-22), are attributed to the guanidinic and free carboxylic acid functionalities, giving the remaining two degrees of unsaturation and satisfying the eight degrees required by HR-MS. The 2D NMR spectral data interpretations, including ^{1}H–^{1}H COSY, and ^{1}H–^{13}C HMBC, enabled us to establish and confirm the total structure of **1** and supported its identification as crambescidin acid, a pentacyclic guanidine alkaloid previously isolated from another species, *Monanchora unigiculata* [22]; however, it is recorded here for the first time from *Monanchora* n. sp. Compound **1** displayed promising cytotoxicity against Kb cell lines with inhibitory activities of (100 ± 1) and (80 ± 1) at concentrations of 10 and 1 μM, respectively.

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1

The co-isolated simple nitrogenous compounds **2–5** were identified by matching their ^{1}H NMR and HR-MS spectral data with the literature [23, 24].

General experimental procedures, extraction, isolation, and cytotoxic activity, were performed according to previously published protocol [7].

Animal Material. The sponge was collected off the coast of Hiva Oa (9°45.421′S–139°08.275′W) at 20 m depth using Scuba on 07.09.2009. It was identified as *Monanchora* n. sp. (OTU QM4696) and a reference specimen was deposited at the Queensland Museum (Brisbane, Australia) under accession number QM G331116 [25].

Crambescidin acid (1), pale yellow oil (11.5 mg). HR-ESI-MS *m/z* 404.2461 $[M + H]^+$ (calcd for $C_{22}H_{34}N_3O_2$, 404.2549). UV (MeOH, λ_{max}, nm) (log ε): 276.4 (0.05). IR (neat, ν_{max}, cm^{-1}): 3230, 2967, 2932, 1630, 1542, 1448, 1343, 1114, 1054, 1010, 965, 844, 754. ^{1}H NMR (500 MHz, CD_3OD, δ, ppm, J/Hz): 5.71 (1H, m, H-5), 5.51 (1H, dd, J = 11, 2.0, H-4), 4.35 (1H, m, H-3), 4.23 (1H, m, H-13), 4.03 (1H, m, H-10), 3.82 (1H, m, H-19), 2.69 (1H, d, J = 5.0, H-14), 2.59 (1H, dd, J = 5.0, 4.5, H-9a), 2.42 (1H, m, H-7a), 2.40 (1H, m, H-6a), 2.32 (4H, m, H-11, 12), 2.13 (1H, m, H-6b), 1.95 (1H, dd, J = 6.5, 6.0, H-7b), 1.76 (2H, m, H-17), 1.71 (2H, m, H-16), 1.68 (2H, m, H-18), 1.54 (1H, m, H-2a), 1.46 (1H, m, H-2b), 1.25 (1H, m, H-9b), 1.08 (3H, d, J = 6.5, H-20), 0.86 (3H, t, J = 7.5, H-1). ^{13}C NMR (125 MHz, CD_3OD, δ, ppm): 181.6 (C-22), 150.8 (C-21), 134.5 (C-4), 131.6 (C-5), 85.1 (C-8), 82.8 (C-15), 72.3 (C-3), 68.3 (C-19), 55.6 (C-10), 54.9 (C-13), 54.1 (C-14), 38.7 (C-9), 38.4 (C-7), 33.6 (C-16), 32.9 (C-18), 31.0 (C-11, 12), 30.4 (C-2), 24.6 (C-6), 22.1 (C-20), 19.7 (C-17), 10.9 (C-1).

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