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METABOLITES FROM THE MARINE ACTINOBACTERIUM *Streptomyces* sp. KMM 7210

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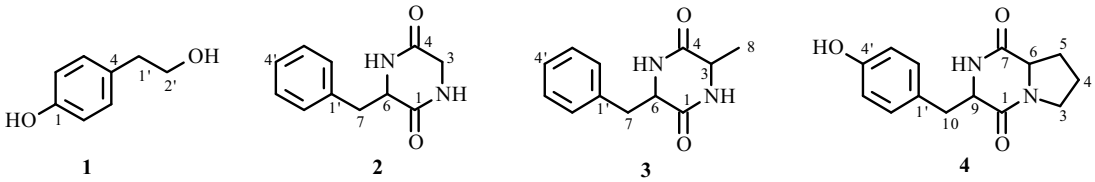
In continuation of the search for biologically active metabolites from marine actinobacteria, we studied the strain *Streptomyces* sp. KMM 7210 that was isolated from sediment samples of Troits Bay (Poset Gulf, Sea of Japan). Cultivation of this strain in medium consisting of edible potato starch (10 g/L), peptone (2 g/L), yeast extract (2 g/L), $CaCO_3$ (1 g/L), pH 7.7, and distilled water:seawater (1:1) for 6 d at ~20°C produced compounds with cytotoxic activity against sea urchin *Strongylocentrotus intermedius* embryos.

The cultivation liquid (20 L) was centrifuged for 30 min at 500 g. The resulting cells were suspended in distilled H_2O (100 mL) and destroyed with cooling by ultrasound for 2 min at 20-second intervals. The suspension of destroyed cells was extracted (3×) successively with EtOH and acetone. The supernatant was extracted with EtOAc (3×). The resulting extracts were combined and evaporated to dryness. The dry solid (600 mg) was chromatographed over a column of SiO_2 using a gradient of hexane:EtOAc (10:1, 5:1, 2:1, 3:2, 1:1), EtOAc, and EtOAc:EtOH (20:1, 10:1). This produced pure **1** (3 mg), **2** (2 mg), **3** (2.2 mg), and **4** (2.5 mg).



1 **2** **3** **4**

4-(2′-Hydroxyethyl)phenol (1), $C_8H_{10}O_2$. Mass spectrum (EI, 70 eV, *m*/*z*): 138 (30) $[M]^+$, 107 (100), 77 (22), 32 (19). PMR spectrum (500 MHz, CD_3OD, δ, ppm, J/Hz): 6.70 (2H, d, J = 8.6, H-2,6), 7.02 (2H, d, J = 8.6, H-3,5), 2.70 (2H, t, J = 7.1, H-1′), 3.67 (2H, t, J = 7.1, H-2′). ^{13}C NMR spectrum (125 MHz, CD_3OD, δ, ppm): 154.9 (C-1), 114.2 (C-2,6), 129.0 (C-3,4,5), 37.5 (C-1′), 62.7 (C-2′).

This compound was obtained earlier from the bacterium *Rhodosporillum rubrum* [1] and yeast *Candida albicans* [2].

Cyclo-(L-phenylalanylglycine) (2), $C_{11}H_{12}N_2O_2$, $[\alpha]_D^{22}$ +26° (*c* 0.95, DMSO). Mass spectrum (EI, 70 eV, *m*/*z*): 204 (41) $[M]^+$, 91 (100), 32 (81). PMR spectrum (700 MHz, CD_3OD, δ, ppm, J/Hz): 2.65 (1H, dd, J = 1.2, 17.7, H-3), 3.41 (1H, dd, J = 0.7, 17.7, H-3), 4.22 (1H, t, J = 7.1, H-6), 2.99 (1H, dd, J = 4.7, 13.7, H-7), 3.23 (1H, dd, J = 4.2, 13.9, H-7), 7.20 (2H, m, H-2′,6′), 7.29 (3H, m, H-3′,4′,5′). ^{13}C NMR spectrum (175 MHz, CD_3OD, δ, ppm): 170.6 (C-1), 45.3 (C-3), 169.3 (C-4), 58.1 (C-6), 41.5 (C-7), 137.0 (C-1′), 132.1 (C-2′,6′), 130.2 (C-3′,5′), 129.0 (C-4′). HMBC correlations (H/C): H-2′,6′ (7.20 ppm)/C-7, C-4′; H-3′,4′,5′ (7.20 ppm)/C-1′, C-2′, C-3′, C-5′, C-6′; H-3/C-1, C-4; H-6/C-4, C-7, C-1′; H-7/C-1, C-6, C-1′ C-2′, C-6′.

This compound was obtained earlier by cultivation of an endophytic fungus-micromycete isolated from mangrove tree leaves [3].

Cyclo-(L-phenylalanyl-L-alanine) (3), $C_{12}H_{14}N_2O_2$, $[\alpha]_D^{22}$ –20° (*c* 0.05, MeOH). Mass spectrum (EI, 70 eV, *m*/*z*): 218 (22) $[M]^+$, 91 (44), 32 (100). PMR spectrum (700 MHz, DMSO, δ, ppm, J/Hz): 3.6 (1H, m, H-3), 4.16 (2H, m, H-6), 2.85 (1H, dd, J = 5.2, 13.7, H-7), 3.12 (1H, dd, J = 3.8, 13.7, H-7), 0.48 (3H, d, J = 6.9, CH_3-8), 7.16 (2H, m, H-2′,6′), 7.27 (2H, m, H-3′,5′), 7.2 (2H, m, H-4′). ^{13}C NMR spectrum (175 MHz, DMSO, δ, ppm): 167.7 (C-1), 49.7 (C-3), 165.9 (C-4), 55.4

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(C-6), 39.6 (C-7), 19.7 (C-8), 136.0 (C-1′), 130.4 (C-2′,6′), 128.0 (C-3′,5′), 126.7 (C-4′). HMBC correlations (H/C): H-2′,6′ (7.16 ppm)/C-4′, C-7; H-3′,5′ (7.27 ppm)/C-2′, C-6′, C-1; H-4′/C-2′, C-6′; H-3/C-4; H-7/C-1′, C-2′, C-6′, C-6; H-8/C-1, C-4.

This compound was isolated earlier from the marine bacterium *Bacillus subtilis* [4].

Cyclo-(L-tyrosyl-D-proline) (4), $C_{14}H_{16}N_2O_3$, $[\alpha]_D^{22}$ +12° (*c* 0.05, MeOH). Mass spectrum (EI, *m*/*z*): 283 $[M + Na]^+$. PMR spectrum (700 MHz, CD_3OD, δ, ppm, J/Hz): 3.35 (1H, m, H-3), 3.56 (1H, m, H-3), 1.68 (2H, m, H-4,5), 1.93 (1H, m, H-4), 2.08 (1H, m, H-5), 2.62 (1H, m, H-6), 4.16 (1H, td, J = 0.7, 4,4, H-9), 2.90 (1H, dd, J = 4.6, 14.0, H-10), 3.13 (1H, dd, J = 4.3, 14.0, H-10), 6.99 (2H, d, J = 8.5, H-2′,6′), 6.74 (2H, d, J = 8.5, H-3′,5′). ^{13}C NMR spectrum (175 MHz, CD_3OD, δ, ppm): 172.0 (C-1), 46.7 (C-3), 23.0 (C-4), 30.4 (C-5), 59.7 (C-6), 168.2 (C-7), 60.5 (C-9), 40.8 (C-10), 127.7 (C-1′), 132.9 (C-2′,6′), 117.0 (C-3′,5′), 158.8 (C-4′). HMBC correlations (H/C): H-2′,6′ (6.99 ppm)/C-10, C-3′, C-5′; H-3/C-4, C-5, C-6; H-4/C-3, C-5; H-5/C-4, C-3, C-6; H-6/C-1, C-5; H-9/C-1′, C-1, C-7, C-10; H-10/C-1, C-6, C-1′, C-2′, C-6′.

This compound was isolated earlier from a bacterium *Bacillus* sp. associated with the marine sponge *Ircinia variables* [5].

The absolute configurations of **2**-**4** were determined by the Murphy method [6].

Compounds **2** and **4** exhibited cytotoxic activity against sea urchin *S. nudus* sperm (IC_{50} 56.0 and 37.0 μg/mL, respectively).

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