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# 15-ACETYLTHIOXY-FURODYSININ LACTONE, A POTENT $LTB_4$ RECEPTOR PARTIAL AGONIST FROM A MARINE SPONGE OF THE GENUS DYSIDEA

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Summary: A novel sesquiterpene thioacetate with high binding-affinity for the human leukotriene $B_4$ ($LTB_4$) receptor has been isolated from the sponge Dysidea sp. collected in Palau. The structure of the new compound was determined on the basis of spectral data and the compound was prepared semi-synthetically by photo-oxidation of the known metabolite, thiofurodysin acetate.

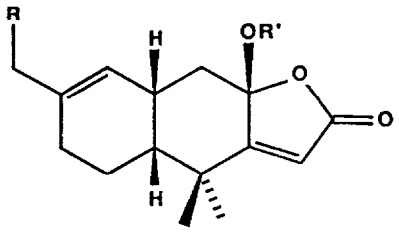
A decade ago, investigations of a marine sponge of the genus Dysidea from Australia yielded the furanoid sesquiterpenes furodysin and furodysinin along with their related thioacetates, which were the first reported naturally occurring terpene thiol derivatives[1]. Since this original study, reports on the isolation of oxidation products of furodysin and furodysinin from the dorid nudibranchs Chromodoris funerea[2] and Hypselodoris zebra[3] have appeared, but oxidation products of the related thioacetates were not reported. During our search for antagonists of leukotriene receptors, the crude extract of a Dysidea sp. sponge collected in Palau was shown to be active ($IC_{50}$ = 30 µg/mL) in a $LTB_4$ receptor binding assay[4]. This activity was shown to be due to furodysinin lactone thioacetate (1), the first reported oxidation product of thiofurodysinin acetate.

Dysidea sp. (specimen no. 81-057, 500 grams dry wt.) was collected by hand using SCUBA along the outer reef (-30 m) due west of Malakal harbor in the Palau Islands. The crude methanol extract was partitioned between water and $CH_2Cl_2$. The organic layer was chromatographed on silica using the $LTB_4$ radioligand binding assay[4] to monitor biological activity, yielding 5.0 mg (0.01% dry wt) of 1 (mp 144-145°C; $[\alpha]^{CHCl_3}$ = -178°). The HRMS of 1 established the formula as $C_{17}H_{22}O_4S$ [found m/z = 323.1305, $C_{17}H_{23}O_4S$(M+H) requires m/z = 323.1317] and the IR (KBr, 3300, 1744, 1693 $cm^{-1}$) suggested the presence of a thioacetate and a γ-hydroxy-γ-lactone. $^1H$ and $^{13}C$ NMR data[5] were almost identical with the published spectra of furodysinin lactone[3] (2) and O-methylfurodysinin lactone[2] (3) with replacement of the vinylic methyl group signals with those indicative of a $CH_2$-S-Ac group. The foregoing data allowed assignment of the structure as 1, which was supported in turn by extensive 2D NMR analysis and verified by photo-oxidation of furodysinin thioacetate to furodysinin lactone thioacetate (1) in the presence of a polymer-bound rose bengal catalyst using previously published conditions[2]. This semi-synthetic compound was identical in all respects to the natural product.

1: R = AcS, R' = H

2: R = R' = H

3: R = H, R' = Me




In an isolated U-937 cell membrane [$^3$H]LTB$_4$ receptor binding assay[4], LTB$_4$ and furodysinin lactone thioacetate (1) have binding affinities ($K_i$) of 0.1 nM and 0.2 μM respectively. In a human lung membrane [$^3$H]LTB$_4$ receptor binding assay[6], LTB$_4$ and 1 have binding affinity at 0.2 nM and 0.1 μM respectively. In differentiated human U-937 cells, furodysinin lactone thioacetate (1) exhibited partial agonist-like activity and induced LTB$_4$-receptor mediated $Ca^{2+}$ mobilization with an $ED_{50}$ of 4.0 μM[7]. The maximal extent of the $Ca^{2+}$ mobilization activity, however, was only 50-60% of that induced by 1 μM LTB$_4$. These results indicate that 1 could bind to human lung and U-937 cell membrane LTB$_4$ receptors and promote LTB$_4$ receptor mediated calcium mobilization in U-937 cells[8].

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5. $^1$H-NMR ($CDCl_3$) δ 1.24 (s, 3H), 1.41 (s, 3H), 1.55 (t, 1H, J = 13.5 HZ), 1.70 (2H, m), 2.04 (bd, 2H, J = 8 HZ), 2.32 (dd, 1H, J = 13.5, 3.6 HZ), 2.35 (s, 3H), 2.90 (m, 1H), 3.48 (s, 2H), 5.67 (bd, 1H, J = 8 HZ), 5.69 (s, 1H); $^{13}$C-NMR ($CDCl_3$) δ 18.4 (t), 25.4 (q), 26.8 (q), 28.1 (t), 30.4 (d), 30.5 (q), 35.4 (t), 38.4 (s), 40.5 (t), 47.2 (d), 104.9 (s), 115.2 (d), 127.4 (d), 137.8 (s), 170.1 (s), 174.6 (s), 195.5 (s).
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8. A QSAR study involving 10-15 furodysinin related compounds is in progress and will be published at a later date.

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