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Thiazole and Imidazole Metabolites from the Ascidian *Aplydium pliciferum*.[1]

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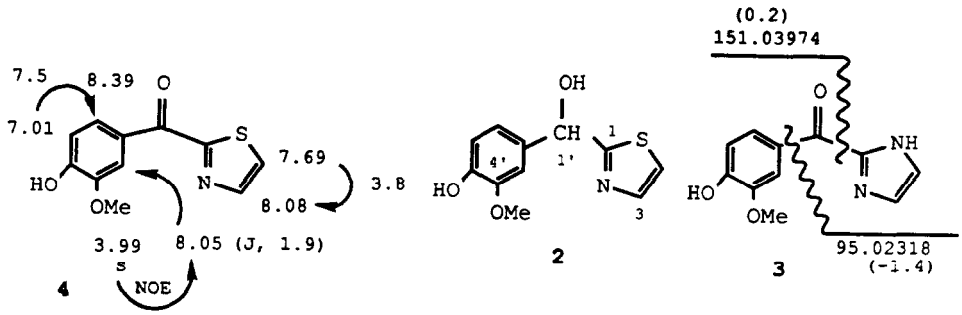
Abstract: Two thiazole- and one imidazole-containing metabolites have been isolated from the Australian ascidian *Aplydium pliciferum*. Their structures were established by spectral methods and synthesis.

Interest in the chemistry of ascidians has been stimulated by the novelty of the compounds isolated from them[2] and the promising anticancer and antiviral activity of some of the metabolites such as the didemnins[3] and the eudistomins[4]. Thiazole moieties are an integral part of a variety of cytotoxic cyclic peptides isolated from ascidians such as ulicyclamide[5], ulithiacyclamide[5], asciadiacyclamide[6] and the patellamides.[7] We report here the isolation of three novel thiazole and imidazole derivatives from the ascidian *Aplydium pliciferum*[8] collected at Rapid Bay, South Australia.

Successive methanol and methanol-chloroform extracts of one frozen specimen were chromatographed repeatedly over silica gel and then reverse phase high pressure liquid chromatography to give the three new metabolites, **1** (4 mg, mp 104° C), **2** (0.8 mg), and **3** (1.4 mg, mp 226° C).

The most abundant metabolite, **1**, $C_{11}H_9O_3NS$ (m/z 235.0295, -0.6 mmu), UV (100% EtOH) λmax (ε) 341 (5600), 300 (4800), 233 (4900) nm; FT IR 3526 (OH), 1637 (cross conjugated ketone) cm^{-1}, exhibited ^1H NMR data shown on the structure. These data confirmed the presence of a 1,2,4-trisubstituted benzene ring with the assigned locus of the methoxyl group. The low field position of two of the coupled benzenoid protons suggested they were ortho to a carbonyl group and the upfield position of one of the benzenoid protons (7.01 ppm) suggested that a hydroxyl group be located adjacent to the methoxyl group. High resolution mass spectral data (see structure **1**)

corroborated the substituted benzoyl speculation and established the elemental composition of the residual moiety. The latter was formulated as a 2-substituted thiazole to give structure **1** based on the remaining ^{1}H NMR signals. ^{13}C NMR data is also in agreement with structure **1**[9].

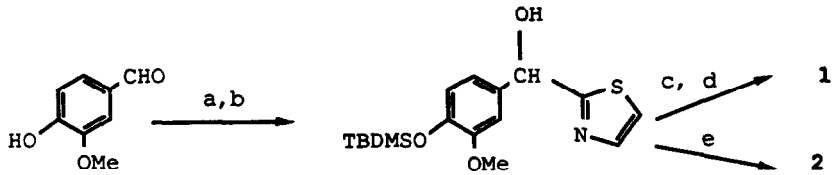


The lrms of the least abundant metabolite **2**, m/z 239 (M^{+} + 2, 4.7%), 237 (M^{+}, 100%), indicated the presence of nitrogen and sulfur and corresponded to the formula $C_{11}H_{11}O_3NS$. The proton spectrum[10] contained the same multiplets as observed for **1**, but all of the aromatic protons were shifted upfield somewhat indicating the absence of the electron-withdrawing effect of the carbonyl group. Consistent with this change was the occurrence of a one-proton singlet at 5.87 ppm corresponding to the methine proton of a -CH(OH)- group, and hence formula **2** was inferred.

The ^{1}H NMR spectrum[11] of the third metabolite, **3**, $C_{11}H_{10}O_3N_2$ (m/z 218.0709, +1.8 mmu), contained all the signals indicative of the hydroxymethoxybenzoyl moiety present in **1**. The remaining signal in the spectrum in $CDCl_3/CD_3OD$ was a broad, two-proton singlet at 7.25 ppm consistent with H-4 and -5 of a 2-substituted imidazole as shown in formula **3**. Mass spectral data supported this conclusion.

Structures **1** and **2** were confirmed by synthesis as outlined below. Hydrolysis of **4** gave **2** (mp 154-155° C) identical with the natural product by ^{1}H NMR and lrms analysis. Oxidation of **4** followed by aq. HF hydrolysis gave

1 in 91% overall yield.



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a) t-butyldimethylsilyl chloride, imidazole, DMF, rt (97 % yield); b) 2-lithiothiazole, Et_2O, -78° C; NH_4Cl/H_2O (95%); c) MnO_2, Et_2O, rt, 26 hr; d) CH_3CN-20% aq. HF(52-55%), rt, 30 hr; e) THF, $(n\text{-}Bu)_4NF$, rt, 2 hr (48%).

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9. **1**: ^{13}C NMR (75 MHz, $CDCl_3$) 182.0 (C-7'), 168.6 (C-2), 151.2 (C-5'), 146.4 (C-4'), 144.6 (C-4), 127.7 (C-7'), 127.4 (C-2'), 125.6 (C-5), 114.1 (C-6'), 113.0 (C-3'), 56.2 (OMe) (assignments by single frequency decouplings performed on synthetic material).

10. **2**: ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$) 7.60 (1 H, d, 2.9 Hz, H-4), 7.22 (1 H, d, 2.9 Hz, H-5), 6.91 (1 H, d, 2.1 Hz, H-3'), 6.81 (1 H, dd, 7.8, 2.1 Hz, H-7'), 6.73 (1 H, d, 7.8 Hz, H-6'), 3.90 (3 H, s, OMe).

11. **3**: ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$) 8.08 (1 H, dd, 8.5, 2.3 Hz, H-7'), 7.92 (1 H, d, 2.3 Hz, H-3'), 7.28 (2 H, br s, H-4,5), 6.90 (1 H, d, 8.5 Hz, H-6), 3.92 (3 H, s, OMe).

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