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Seagrass-derived fungi as a source of bioactive compounds

*Five new eudesmane-type sesquiterpenes – thomimarines A-E (**1-5**) and 12 new polyketides with "decalin" moiety – zosteropenillines A-L (**6-17**) were isolated from the ethylacetate extract of the fungi Penicillium thomii associated with the seagrass Zostera marina. Their structures were established based on spectroscopic methods. The absolute configurations of **1**–**5** and **7-10** were determined by time-dependent density functional theory (TD-DFT) calculations of ECD spectra. The absolute configuration of zosteropenilline A (**6**) was determined by a combination of the modified Mosher's method, X-ray analysis, and NOESY data. The effect of selected compounds on the viability of human drug-resistant prostate cancer cells PC3 as well as on autophagy in these cancer cells and inhibitory effects of selected compounds on NO production in LPS-induced RAW 264.7 murine macrophages were evaluated.*

Key words: Penicillium thomii, Zostera marina, NMR, X-ray, ECD spectra,TD-DFT, Mosher's method, autophagy, NO, sesquiterpenes, polyketides.

Marine-derived fungi are a prolific source of new secondary metabolites many of which are biologically active [4-6].As part of our ongoing search for structurally novel and bioactive metabolites we have isolated 17 new compounds from two fungi *Penicillium thomii*, associated with seagrass *Zostera marina* (Troitsa bay, Sea of Japan), including five new eudesmane-type sesquiterpenes – thomimarines A-E (**1-5**) [1, 2] (Figure 1) from the *P. thomii* KMM 4667 and 12 new polyketides with "decalin" moiety – zosteropenillines A-L (**6-17**) (Figure 2) from the *P. thomii* KMM 4674 [3] (Figure 1). Their structures were established based on spectroscopic methods. The absolute configurations of thomimarines A-E (**1-5**) and zosteropenillines B-D (**7-9)** were determined by time-dependent density functional theory (TD-DFT) calculations of ECD spectra. The absolute configuration of zosteropenilline A (**6**) was determined by a combination of the modified Mosher's method, X-ray analysis and NOESY data (Figure 3).

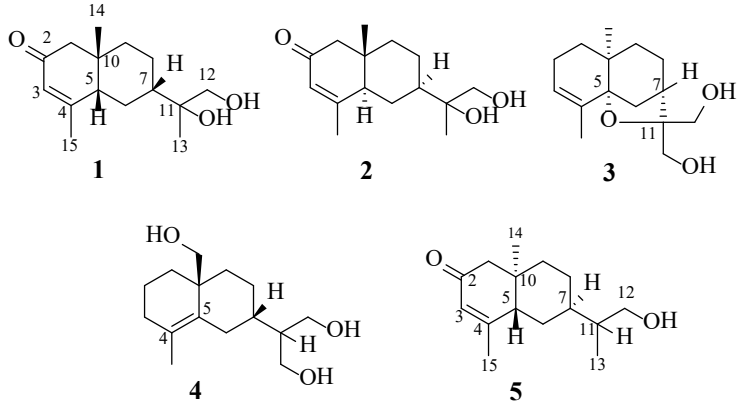

Figure 1. Chemical structures of thomimarines A-E (**1-5**)

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It was found that compounds **1**, **4**, **5**, **6**, **13** and **15** at concentration of 10.0 μM induced a moderate down-regulation of NO production in macrophages stimulated with LPS. NO level in these cells was decreased by 24.9%±0.9, 20.9%±5.7, 22.5±5.1%, 27.7%±1.8, 20.6%±1.2 and 22.3%±3.8, respectively, compare to control cells pretreated with LPS.

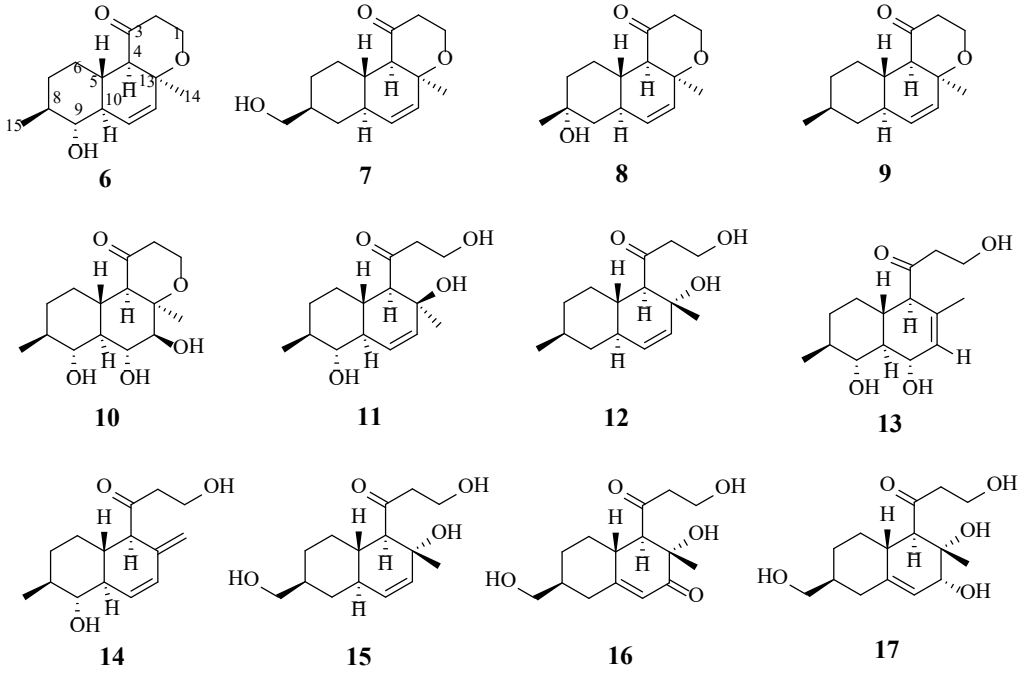

Figure 2. Chemical structures of zosteropenillines A-L (**6-17**)

The most effective substance was compound **2** exhibited the maximal pronounced inhibition of NO formation in LPS-stimulated RAW 264.7 cells by 43.4%±1.5. The effect of zosteropenillines **6-8**, **12**, **13**, **15** and **16** on the viability of human drug-resistant prostate cancer cells PC3 as well as on autophagy in these cancer cells was examined. The results suggest that the investigated compounds are able to inhibit autophagy at non-cytotoxic concentrations and may sensibilize human cancer cells to cytotoxic anticancer drugs.

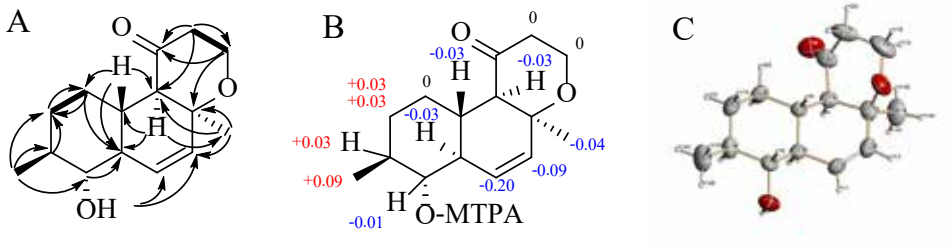

Figure 3. (A) Key HMBC and COSY correlations of **6**; (B) $\Delta\delta(\delta_S - \delta_R)$ values (in ppm) for the (*S*)- and (*R*)-MPTA esters of **6**; (C) Crystal structure of **6**

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