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Xanthones and sesquiterpene derivatives from a marine-derived fungus *Scopulariopsis* sp.

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ABSTRACT

Two new xanthone derivatives, 12-dimethoxypinselin (**1**) and 12-*O*-acetyl-AGI-B4 (**2**), as well as two new phenolic bisabolane-type sesquiterpenes, 11,12-dihydroxysydonic acid (**15**) and 1-hydroxyboivinianic acid (**16**), together with one new alkaloid, scopulamide (**21**) and one new α-pyrone derivative, scopupyrone (**26**), in addition to twenty-three known compounds (**3**–**14**, **17**–**20**, **22**–**25**, **27**–**29**) were isolated from solid rice cultures of the marine-derived fungus *Scopulariopsis* sp. obtained from the Red Sea hard coral *Stylophora* sp. All compounds were unambiguously identified through extensive NMR spectroscopic analyses, and by comparison with the literature. Marfey's reaction was performed to determine the absolute configuration of scopulamide (**21**) and TDDFT-ECD calculations were used to assign the configuration of AGI-B4 (**3**) and scopupyrone (**26**). All isolated compounds were evaluated for their cytotoxicity against L5178Y mouse lymphoma cells and the structure-activity relationships were discussed.

1. Introduction

Marine microorganisms have been recognized as an important source of bioactive secondary metabolites.[1] For example, phomactins,[2] a class of fungal diterpenoids, which were initially found in the fungus *Phoma* sp. obtained from the shell of the crab *Chionoecetesopilio*, attracted attention due to their pronounced platelet activating factor antagonizing activity. Moreover, peribysins[3] isolated from the sea hare-derived fungus *Periconia byssoides* are well-known as cell-adhesion inhibitors, and tryptostatins,[4] structurally unique indole alkaloids, which were firstly isolated from *Aspergillus fumigatus*, a fungus obtained from a sea sediment sample, exhibit mammalian cell cycle inhibition activity. In addition, some of these metabolites have advanced to clinical trials and may potentially be launched as pharmaceutical drugs in the future. One of the most prominent examples of fungal derived bioactive compounds is plinabulin (NPI-2358), a synthetic analogue of the diketopiperazine alkaloid halimide which is produced by *Aspergillus* sp. CNC-139 isolated from the alga *Halimeda lacrimosa*. Plinabulin acts as a vascular disrupting agent (VDA) and inhibits tubulin polymerization, resulting in selective collapse of tumor endothelial vasculature. It is currently undergoing phase II clinical trials for patients with advanced non-small-cell lung cancer.[5]

In continuation of our ongoing efforts to identify new fungal products from rare and unusual econiches,[6–11] we investigated the marine-derived fungus *Scopulariopsis* sp., which was isolated from the inner tissues of the Red Sea hard coral *Stylophora* sp. collected in Egypt. The ethyl acetate extract of this fungus when grown on solid rice medium was found to exhibit cytotoxicity against the mouse lymphoma cell line L5178Y in a preliminary bioassay. Moreover, a literature survey revealed that chemical studies on fungi of this genus have rarely been conducted. So far two cytotoxic cyclodepsipeptides,[12] two naphthalene derivatives,[13] and one alkaloid named fumiquinazoline L[14] had been reported. In the present study, 29 compounds including 11 xanthones (**1**–**11**), 5 sesquiterpene derivatives (**12**–**16**), 4 phenyl ethers (**17**–**20**), 5 alkaloids (**21**–**25**), and 4 miscellaneous compounds (**26**–**29**) were isolated from solid rice cultures of *Scopulariopsis* sp.. Among them, 12-

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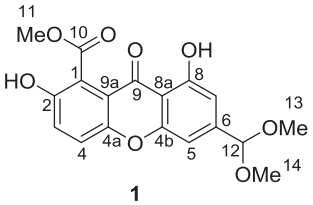

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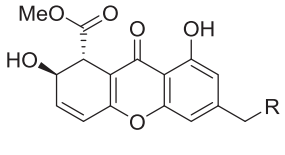
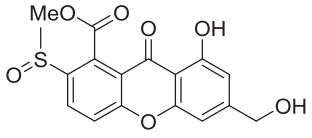


2; R= OAc
3; R= OH



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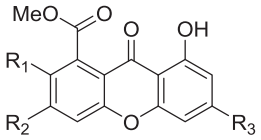
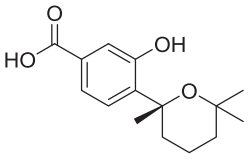


5; R_1= OH, R_2=H, R_3=CH_3
6; R_1= OH, R_2=H, R_3=CH_2OH
7; R_1= OH, R_2=H, R_3=CH_2OAc
8; R_1= OH, R_2=H, R_3=COOH
9; R_1= H, R_2=H, R_3=CH_2OH
10; R_1= H, R_2=H, R_3=COOH
11; R_1= H, R_2=OH, R_3=CH_3



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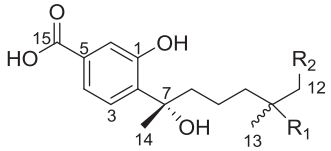
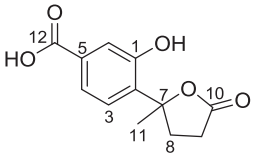


13; R_1= H, R_2=H
14; R_1= OH, R_2=H
15; R_1= OH, R_2=OH



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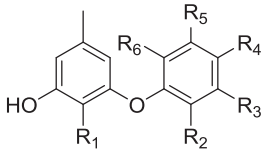
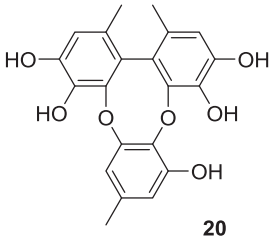


17; R_1,R_2,R_3 = OH, R_4,R_6 = H, R_5= CH_3
18; R_1,R_2,R_6 = OH, R_3,R_5 = H, R_4= CH_3
19; R_1,R_2,R_4,R_6 = H, R_3 = OH, R_5= CH_3



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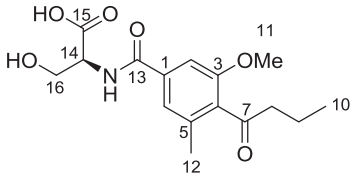

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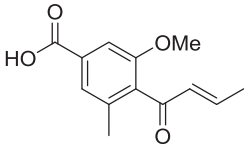

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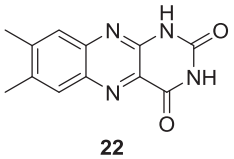

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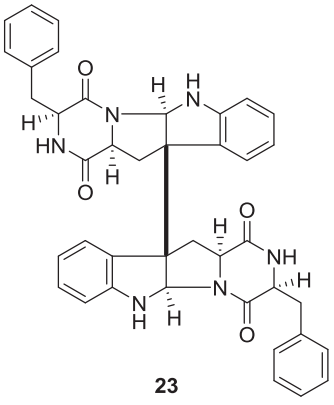

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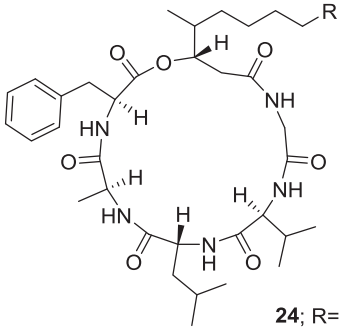
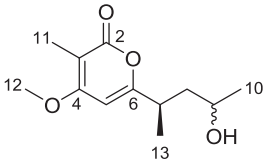


24; R= C_2H_5
25; R= H



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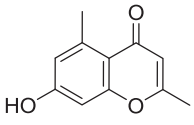

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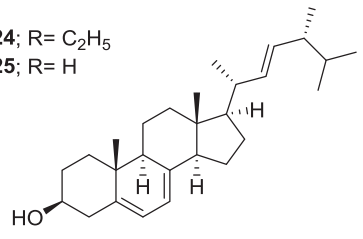

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