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Coumarins with an unprecedented tetracyclic skeleton and coumarin dimers from chemically engineered extracts of a marine-derived fungus

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ABSTRACT

The unprecedented tetracyclic coumarin derivatives **1** and **2** and the coumarin dimers **3**–**5** were isolated from chemically engineered extracts (coumarin dimerization of natural extract) of the marine-derived fungus *Eurotium rubrum*. The structures of these compounds were established using NMR, MS and IR methods. The absolute configuration of **1** was determined by ECD calculations. The unprecedented tetracyclic coumarin skeleton was generated by domino-Knoevenagel-Diels-Alder reactions. Compounds **1**–**5** showed tyrosinase inhibitory activity (IC_{50} = 1.7, 1.2, 4.9, 1.8 and 2.9 μM, respectively). The isolated coumarin derivatives **1**–**5** were not observed by HPLC analysis in crude extracts of *E. rubrum*, suggesting that chemically engineered extract generated these new coumarin derivatives with tyrosinase inhibitory activity.

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1. Introduction

Small molecule compound libraries are valuable for developing new medicinal lead compounds.[1] Investigations of structural diversity typically focus on obtaining new compounds. Scaffold diversity synthesis (SDS) targets three dimensional structures that can interact with biological targets[2,3] whereas the aim of diversity oriented synthesis (DOS) is to generate small molecule compounds with high degrees of structural and functional diversity that interrogate large areas of chemical space, including known or unknown bioactive spaces.[4,5] Applying SDS and/or DOS to natural products is an attractive approach for discovering new compounds with unprecedented skeletons. Natural products are biosynthesized by a wide variety of mechanisms and exhibit wide structural diversity.[6] Consequently, the application of SDS and/or DOS to natural products holds promise for expanding our knowledge of their structural frameworks and aiding access to unique structures.[7,8]

Chemically engineered extracts (CEEs) are an ideal tool for obtaining semisynthetic natural compounds.[9,10] CEEs are natural crude extracts directly derivatized by chemical reactions and thus can yield various novel compounds at once. In our previous study, CEE of a marine-derived fungus *E. rubrum* enhanced their tyrosinase inhibitory activity and unnatural coumarin derivatives were isolated from these CEEs as tyrosinase inhibitors.[11]

We continue to focus our research on the dimerization of natural products. Natural product dimers have potential as new lead compounds. For example, dicoumarol, the lead compound of warfarin®, is a coumarin dimer and has both strong antithrombotic activity and anti-proliferative effects on cancer cells.[12] Another example is carthamin, the dimer of chalcone which is a natural red pigment[13] whose color is due to the long conjugated double bond system generated by dimerization.

Herein we report the coumarin dimerization of hydroquinones in the crude extract of the marine-derived fungus *E. rubrum* and the isolation of two tetracyclic coumarin derivatives (**1** and **2**) and three coumarin dimers (**3**–**5**) (Fig. 1).

2. Results and discussion

Components in the crude $CHCl_3$ extract of *E. rubrum* was treated

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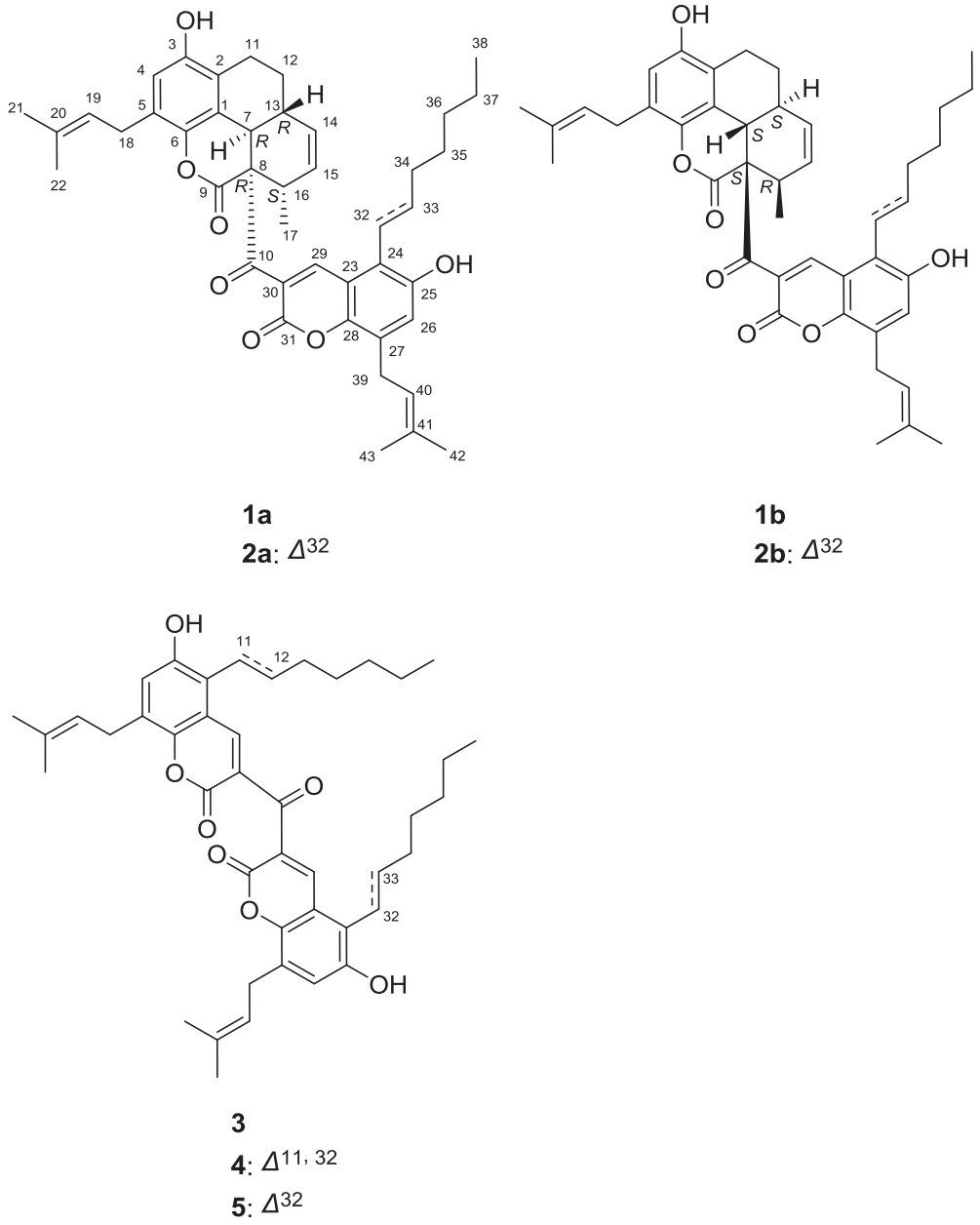

Fig. 1. Structures of the isolated compounds.

with diethyl 1,3-acetonedicarboxylate and piperidine in $CHCl_3$ under reflux for 2 h. This condensation of methylene and 2-hydroxybenzaldehyde could yield coumarin derivatives.[14] *E. rubrum* is a rich source of 2-hydroxybenzaldehyde derivatives[11] and therefore coumarin dimers could be generated by the condensation of two 2-hydroxybenzaldehyde derivatives with the two active methylenes in diethyl 1,3-acetonedicarboxylate (Fig. 2).

The tyrosinase inhibitory activity of CEE was higher than that of the natural crude extract (Fig. 3). Comparison of the HPLC profiles of the CEE and crude extract showed that the peaks arising from the known hydroquinone compounds flavoglaucin (**6**),[15] tetrahydroauroglaucin (**7**),[15] and isodihydroauroglaucin (**8**)[16] decreased and several new peaks appeared in the CEE (Fig. 4). These new peaks likely corresponded to coumarin dimers responsible for the enhanced tyrosinase inhibitory activity. This coumarin dimerization reaction mixture was subjected to silica-gel column chromatography (CC), octadecylsilyl (ODS) silica-gel CC, and preparative HPLC. Two tetracyclic coumarin derivatives (**1** and **2**) and three coumarin dimers (**3**–**5**) were isolated (Fig. 1).

Compound **1** was obtained as a yellow powder and the molecular formula was deduced to be $C_{43}H_{50}O_7$ by HRFABMS (*m/z* 679.3640 $[M+H]^+$). The IR spectrum showed absorptions attributable to hydroxyl (3366 cm^{-1}) and carbonyl (1715 cm^{-1}) groups. The UV spectrum exhibited absorption maxima at 205, 250 (shoulder), 334 and 415 (shoulder) nm.

The ^{13}C NMR spectrum showed the following: two benzene rings at δ_C 125.2, 119.9, 149.2, 114.3, 126.8, 140.8 (C-1 to C-6) and δ_C 117.5, 125.2, 149.8, 123.0, 128.0, 148.2 (C-23 to C-28), side chain derived carbons at δ_C 25.1, 30.9, 29.1, 29.6, 31.8, 22.6, 14.1 (C-32 to C-38), two prenyl groups at δ_C 27.2, 121.6, 133.5, 25.8, 17.8 (C-18 to C-22), and δ_C 26.7, 120.1, 134.8, 25.7, 17.9 (C-39 to C-43), two carboxyl groups at δ_C 166.4, 159.6 (C-9 and C-31), a carbonyl group at δ_C 190.0

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