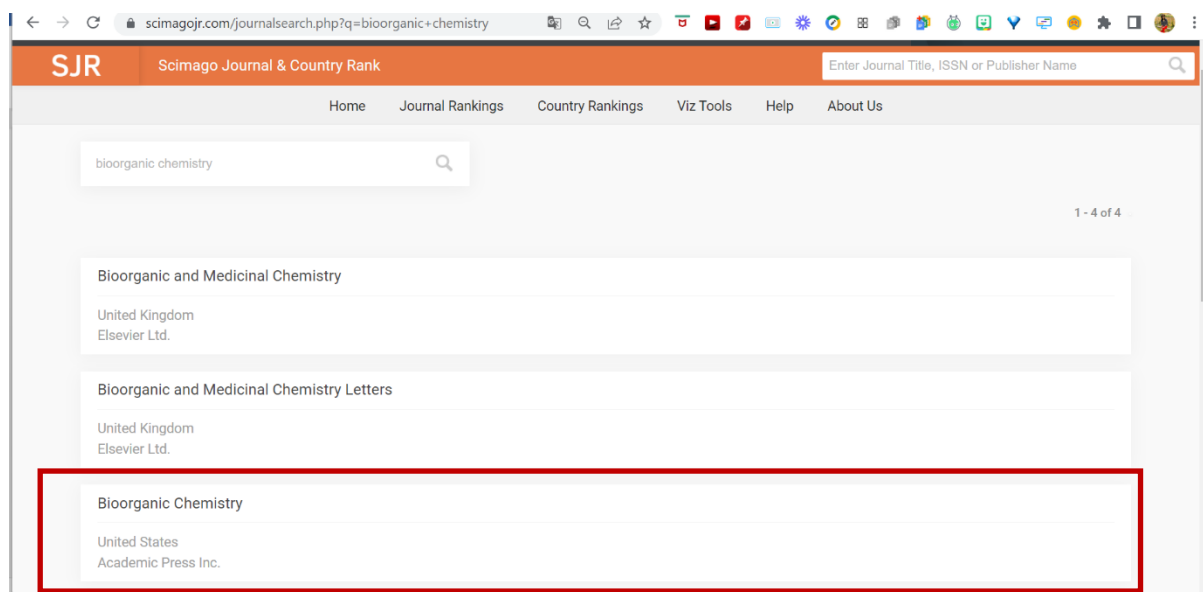
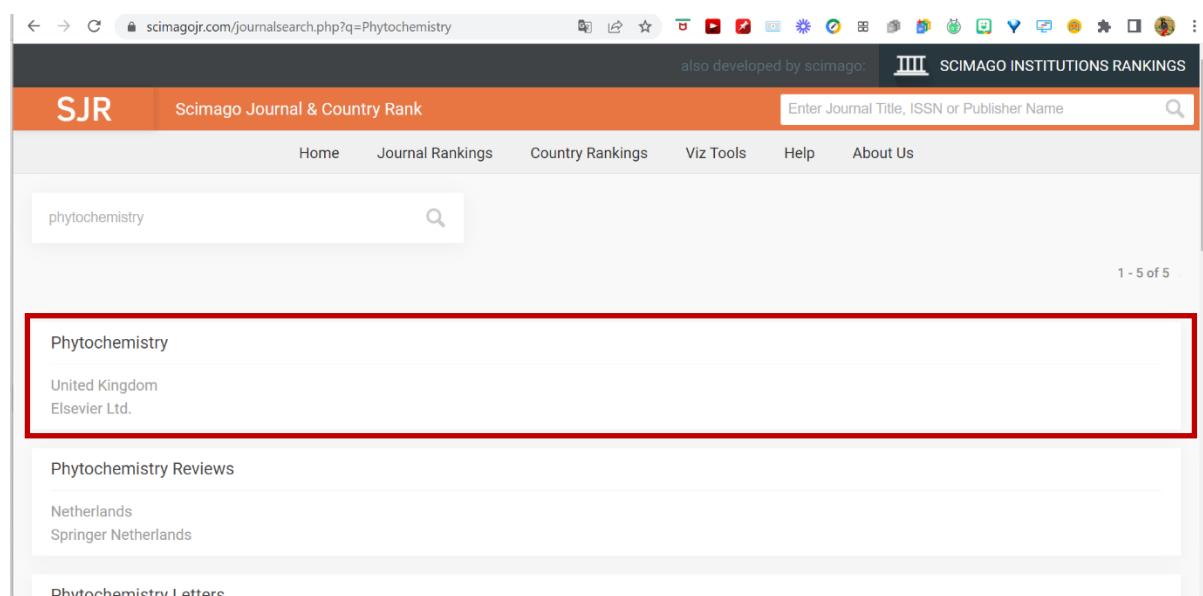


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1. Acylphloroglucinol trimers from *Callistemon salignus* seeds: Isolation, configurational assignment, hAChE inhibitory effects, and molecular docking studies. *Bioorganic Chemistry*. (2021) 117. 105404. (Oct 2021)



2. Phloroglucinol derivatives rhotomensones A-G from *Rhodomyrtus tomentosa*. *Phytochemistry*. (2021) 190. 112890. (Oct 2021)



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Acylphloroglucinols from *Callistemon lanceolatus* DC.

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Acylphloroglucinol trimers from *Callistemon salignus* seeds: Isolation, configurational assignment, hAChE inhibitory effects, and molecular docking studies

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ABSTRACT

Alzheimer's disease (AD) diagnoses are greatly increasing in frequency as the global population ages, highlighting an urgent need for new anti-AD strategies. With the aim to search for human acetylcholinesterase (hAChE) inhibitors from the species of Myrtaceae family, ten acylphloroglucinol trimers (APTs), including eight new APTs, callistemontrimers A–H (1a, 1b, 2a, 2b, 3a, 3b, 4b, and 5b), and two naturally occurring ones (4a and 5a), along with one reported triketone–acylphloroglucinol–monoterpene adduct (6), were obtained and structurally characterized from the hAChE inhibitory acetone extract of *Callistemon salignus* seeds. The structures and their absolute configurations for new APTs were unequivocally established via the detailed interpretation of extensive spectroscopic data (HRESIMS and NMR), ECD calculations, and single crystal X-ray diffraction, whereas the absolute configurations of known APTs were determined by further chiral separation, and calculated ECD calculations. The results of hAChE inhibitory assay revealed that an enantiomeric mixture of 2a/2b, 2a, and 2b are good hAChE inhibitors with IC₅₀ values of 1.22 ± 0.23 , 2.28 ± 0.19 , and 4.96 ± 0.39 μ M, respectively. Molecular docking was used to uncover the modes of interactions for bioactive compounds with the active site of hAChE. In addition, 2 and 6 displayed moderate neurite outgrowth-promoting effects with differentiation rates of 6.16% and 6.19% at a concentration of 1.0 μ M, respectively.

1. Introduction

Alzheimer's disease (AD), one of the most common kinds of dementia, is an age-linked neurodegenerative disease seriously affecting approximately 24 million victims worldwide. As the global population ages, it is estimated that the number of people suffering from AD would total up to more than 100 million cases by the end of 2050 [1]. Despite a herculean effort, it is still a real challenge for the community to find a cure, or at very least, a treatment that delays the progression of this disease. With only four drugs approved to barely relieve the symptoms of AD, three of them are human acetylcholinesterase (hAChE) inhibitors named galantamine, donepezil, and rivastigmine. Given that one of hallmarks of the AD pathophysiology is high damage in the forebrain during the progression of AD [2,3], an increase of acetylcholine (ACh) level at the synapse region by means of inhibiting the hAChE could be an

advisable approach to slow down the progression of AD [4–8]. AChE inhibition is conducive to maintaining the normal neurotransmission mediated by ACh for healthy people. Additionally, it may prevent the occurrence of AD or decelerate the progression for AD patients [9]. In recent years, hAChE inhibitors have proven to share several benefits [10], such as reduced degradation of synaptic ACh as well as improvement of brain ACh levels in a dose dependent manner resulting in an enhanced cholinergic transmission for AD patients.

Acylphloroglucinol trimers (APTs) reported from the plants of Myrtaceae family, a class of Diels–Alder adducts, arise biosynthetically from one acylphloroglucinol and two triketone units [11–22]. These secondary metabolites are particularly attractive, not only due to their interesting chemical features, but also because of a broad range of biological effects, including anti-bacterial [12,20], α -glucosidase inhibitory [13], anti-malarial [16], anti-inflammatory [23–26], anti-proliferative

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bioorg.2021.105404>.

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Q.-H. Mo et al.

Phytochemistry 190 (2021) 112890

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Total syntheses of ericifolione and its analogues via a biomimetic inverse-electron-demand Diels–Alder reaction†

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ericifolione analogue **1i** was obtained in a good yield, irrespective of the ester functional group, as compared to **1c**, strengthening the excellent tolerance of functionalities during this biomimetic cascade process. Collectively, the aforementioned results revealed that this biomimetic approach held promise of rapid access to biologically meaningful ericifolione analogues or derivatives.

In conclusion, polycyclic polymethylated phloroglucinols encoded by potential biosynthetic pathways stimulated us to explore an efficient methodology featuring a biomimetic tautomerization/intermolecular inverse-electron-demand hetero Diels–Alder reaction cascade sequence, which allowed efficient access to sterically hindered dihydropyran scaffolds with excellent diastereoselectivity and facilitated the first biomimetic total syntheses of ericifolione along with its analogues. Taking the advantage of simplicity and efficiency, the well-established synthetic methodology will provide a generally practical protocol for the preparation of relevant PPPs or other natural products and derivatives in sufficient quantities to meet the needs of drug discovery. Further endeavors towards this goal will be reported in due course.

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Conflicts of interest

There are no conflicts to declare.

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- Ericifolione (**1a**) was discovered as an optically pure natural product in Nature, which suggested that the Diels–Alderase should be involved in the biosynthetic process of ericifolione (**1a**) to provide the potent enantioselectivity.