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A Biosynthetic Numbering System for Diterpene Pyrones

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Abstract

Diterpene pyrones, spiroditerpenoids, and brevianes are names given to a series of fungal meroterpenoids that share common structural features and a common biosynthetic pathway elaborated by multiple oxidations, rearrangements, and cyclizations to produce the observed structural diversity. A unifying approach to the numbering of these fungal metabolites, based on a common biosynthetic progenitor, a geranylgeranyl-pyrone hybrid, is presented. This proposal will foster simplicity through a standardized numbering system that can be applied to the known members of this family, as well as to future metabolites.

Keywords

diterpene pyrones, biosynthesis, systematic numbering, fungal secondary metabolites

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Diterpene pyrones (DTPs) are a family of fungal meroterpenoids composed of more than 60 compounds that have attracted the attention of researchers in recent years.[1-3] They are referred to by various names, namely, pyrone diterpenes,[1] spiroditerpenoids,[4] and brevianes.[5] One common aspect, however, is the presence of a diterpene moiety with a *trans*-decalin core linked to a pyrone ring. Presented with a range of structural scaffolds, multiple stereocenters, and a wide variety of biological activities, it is not surprising that DTPs are a hot topic. Two new DTPs have been isolated in this laboratory, which brought attention to this steadily growing class of metabolites. A literature review disclosed that since 2015, 20 new DTPs were isolated from various fungal strains.[4,6-11] Despite the size of this family and their structural variety (Figure 1), they all share a similar biogenetic origin. However, there is a discrepancy in the way these compounds are classified and numbered since they are not viewed as one family. Herein, a uniform numbering system for this growing family of natural products, based on their biosynthetic pathway, is suggested.

The biosynthesis of DTPs was investigated using isotope labeling when the isolates were initially characterized,[12] and it was established that they arose from a terpenoid-acetate pathway through the key intermediate **1**. More recently, the biosynthetic gene cluster (BGC) responsible for the biosynthesis of subglutinols was identified in *Metarhizium robertsii* ARSEF23 and heterologously expressed in *Aspergillus nidulans* A1145.[7] The findings supported the biogenetic pathways in which DTPs are elaborated from the geranylgeranyl-pyrone intermediate **1**[5,13] (Figure 2). This metabolite was isolated from *A. nidulans* A1145 after the subglutinol BGC was expressed, unequivocally confirming the importance of **1** in subglutinol formation. Since all DTPs share the same primordial precursor **1**, by numbering it on the basis of its biosynthesis, a uniform system that can be applied to number all of the natural DTPs can be achieved (Figure 2). Using this system, tracking the fate of carbons between known and new DTP members is simplified, especially when referring to characteristic carbon atoms such as C-2, C-14, C-10, C-18, C-9, and C-20. Diterpene pyrones with a γ-pyrone ring can be numbered similar to the α-pyrones, and in all cases, the biogenetic origin of the skeletal carbon atoms traced directly.

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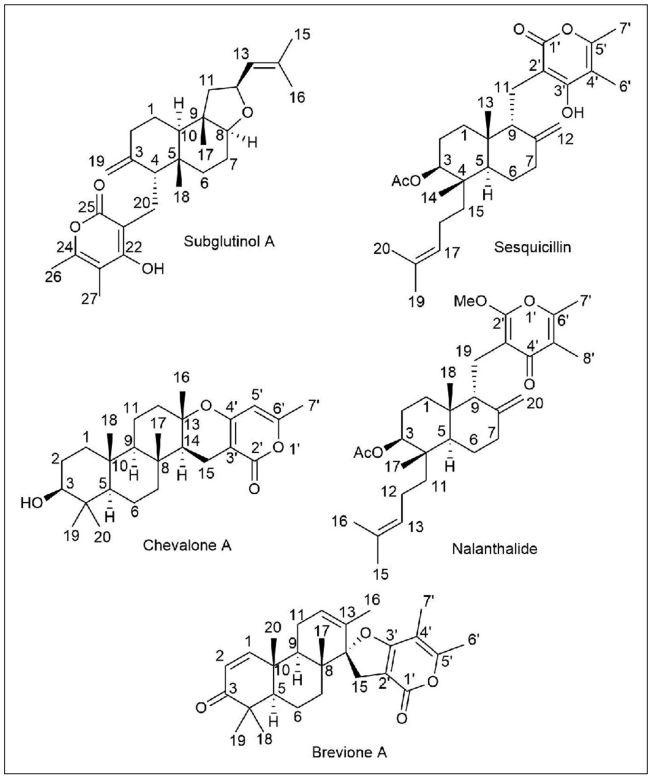

Figure 1. Selected diterpene pyrones with their original numbering.

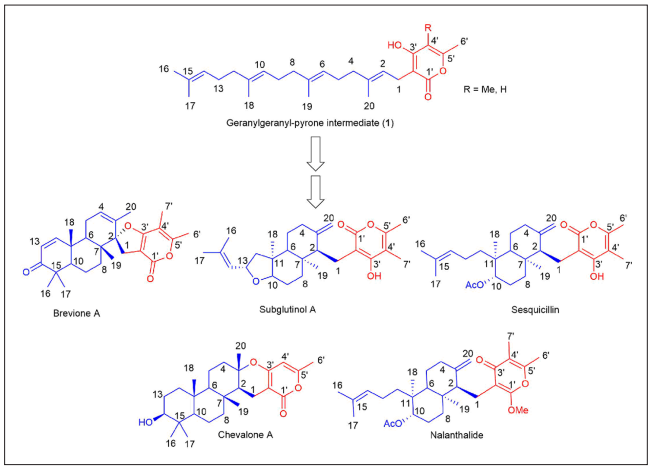

Figure 2. Proposed biosynthetic numbering system for representative diterpene pyrenes.

An extensive review of the isolation, biological activity, synthesis, and biosynthesis of this metabolite class is currently in progress.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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