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Review

Biologically active fungal depsidones: Chemistry, biosynthesis, structural characterization, and bioactivities

Sabrin R.M. Ibrahim[a,b,*], Gamal A. Mohamed[c,d], Rwaida A. Al Haidari[a], Amal A. El-Kholy[e,f], Mohamed F. Zayed[a,g], Maan T. Khayat[h]

[a] Department of Pharmacognosy and Pharmaceutical Chemistry, College of Pharmacy, Taibah University, Al Madinah Al Munawwarah 30078, Saudi Arabia
[b] Department of Pharmacognosy, Faculty of Pharmacy, Assiut University, Assiut 71526, Egypt
[c] Department of Natural Products and Alternative Medicine, Faculty of Pharmacy, King Abdulaziz University, Jeddah 21589, Saudi Arabia
[d] Department of Pharmacognosy, Faculty of Pharmacy, Al-Azhar University, Assiut Branch, Assiut 71524, Egypt
[e] Department of Clinical and Hospital Pharmacy, College of Pharmacy, Taibah University, Al Madinah Al Munawwarah 30078, Saudi Arabia
[f] Department of Clinical Pharmacy, Faculty of Pharmacy, Ain-Shams University, Cairo 11566, Egypt
[g] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt
[h] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, King Abdulaziz University, Jeddah 21589, Saudi Arabia

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ABSTRACT

Fungi produce a wide range of structurally unique metabolites. Depsidones represent one of the most interesting classes of metabolites, consisting of two 2,4-dihydroxybenzoic acid rings linked together by both ether and ester bonds. Naturally occurring depsidones are produced by lichen, fungi, and plants. They possessed a wide array of bioactivities, including antioxidant, antiproliferative, antimalarial, cytotoxic, antibacterial, radical scavenging, antihypertensive, anti-inflammatory, antifungal, and aromatase and protein kinase inhibitory. In order to point out the potential of this class of compounds, the present review focuses only on the depsidones that have been isolated from fungal source and published from 1978 to 2018. This review outlined the research on the biosynthesis, source, isolation, spectral and physical data, and bioactivities of the naturally occurring fungal depsidones. On the basis of 88 references, > 80 compounds have been described.

Abbreviations: 17-AAG, 17-allylamino-demethoxygeldamycin; ABCA1, ATP-binding cassette transporter A1; ABCG1, ATP-binding cassette transporter G1; ABCA1, ATP-binding cassette sub-family A1; ACS, American Chemical Society; A-549, human lung carcinoma; ApoA1, apolipoprotein A1; AcOH, acetic acid; BC, human breast cancer cells; BC1, human breast cancer cell line; BCA, binding cassette sub-family A; Bre04, human breast cancer cell line; BAF, human primary breast adipose fibroblasts; CAM, chick embryo chorioallantoic membrane assay; CC, column chromatography; CC_{50}, cytotoxic concentration 50; CD36, cluster of differentiation 36; CDA, chiral derivatizing agent; CE, cholesteryl ester; CHO, Chinese hamster ovary; CMeT, *C*-methyltransferase; CYP19, aromatase; CXCR4, C-X-C motif chemokine receptor 4; DPPH, 2-diphenyl-1-picrylhydrazyl; 2D, two dimensional; EtOAc, ethyl acetate; Et_2O, diethyl ether; GFP, green fluorescent protein; GI_{50}, 50% growth inhibition; HDL, high-density lipoprotein; HL-60, human promyelocytic leukemia cell line; HepG2, human liver cancer; HeLa, human cervix cancer cell line; HepG2, human hepatocellular liver carcinoma; HPLC, High Pressure Liquid Chromatography; Hsp90, heat shock protein 90; HUVEC, human umbilical vein endothelial cell lines; HuCCA-1, human lung cholangiocarcinoma; IC_{50}, concentration required to inhibit cell growth by 50%; IL, interleukin; IR, infrared; iNO, inducible nitric oxide; IXO, inhibited xanthine oxidase; IV, intravenous; K-562, human erythroleukaemic; KB, human epidermoid carcinoma cell; KKU-100, KKU-M139, KKU-M156, KKU-M213, and KKUM214, cholangiocarcinoma cell lines; L5178Y, mouse lymphoma; LC_{50}, lethal concentration required to kill 50% of cells; LPS, lipopolysaccharide; LXRα, liver X receptor alpha; Lu04, human lung cell line; MABA, microplate Alamar Blue assay; MCF-7, human breast adenocarcinoma; MDR, multidrug-resistant; MDA-MB-435, human breast cancer cell line; MIC, minimum inhibitory concentration; MOLT-3, acute lymphoblastic leukemia; MRC-5, normal embryonic lung cells; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; MSSA, methicillin-sensitive *Staphylococcus aureus*; MSSE, methicillin-sensitive *Staphylococcus epidermidis*; MptpB, tyrosine phosphatase B; MTPA, methoxy trifluoromethyl phenyl acetic acid; MTT, (3-(4,5-dimethylthiazol-2-yl))-2,5-diphenyl-2H-tetrazolium bromide; N04, human neuroma cell line; NCI-H187, human small cell lung cancer cell line; NMR, nuclear magnetic resonance; NR-PKS, non-reduced polyketide synthase; oxLDL, oxidized low-density lipoprotein; P388, murine leukemia cell; PE, petroleum ether; PKS, polyketide synthase; PR, progesterone receptor; PPDK, pyruvate phosphate dikinase; $PPAR\gamma$, peroxisome proliferator-activated receptor gamma; Raji, Burkitt's lymphoma; RAW264.7, murine macrophage cell line; REMA, resazurin microplate assay; RNS, reactive nitrogen species; ROS, reactive oxygen species; S102, human liver cancer cell line; SR-A1, scavenger receptors-A1; SR-A2, scavenger receptors-A2; SI, selectivity index; SRB, sulforhodamine B; SOAT, sterol *O*-acyltransferase; T47D, human breast carcinoma cell line; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TLC, thin layer chromatography; TNF-α, tumor necrosis factor-α; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; UV, ultraviolet; Vero, African green monkey kidney fibroblast; VRE, vancomycin-resistant enterococci; VSE, vancomycin-sensitive enterococci; XTT, (2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2*H*-tetrazolium-5-carboxanilide); XXO, xanthine/xanthine oxidase

* Corresponding author at: Department of Pharmacognosy and Pharmaceutical Chemistry, College of Pharmacy, Taibah University, Al Madinah Al Munawwarah 30078, Saudi Arabia.
E-mail address: sribrahim@taibahu.edu.sa (S.R.M. Ibrahim).

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1. Introduction

Fungi are a wealthy pool of bio-metabolites with varied structures and bioactivities, as well as agricultural and pharmacological importance [1–7]. Depsidones are aromatic compounds, consisting of two 2,4-dihydroxybenzoic acid rings linked together by both ether and ester bonds, giving the rigid 11*H*-dibenzo[b,e] [1,4] dioxepin-11-one ring [8]. Also, they are known to be cyclic ethers of polyphenolic depsides. Their rings rely on the orsellinic acid's structure, where the one with the esterified-carbonyl is specified as A and the other as B. The joined rings may have different or similar substituents. Depsidones and depsides are classified into β-orcinol or orcinol series, depending on the existence of a methyl group on the C_3 carbon of both rings (Fig. 1).

They are mostly present in lichens. Also, they have been found in some fungi and higher plants [9–11]. In contrast to the lichen depsidones, fungal depsidones are not widely distributed. They are reported only from a limited number of fungi (Tables 1–29). They belong to the "mixed" series of depsidones. They play a considerable role in the protection of plants against microbes and insects or sunlight. They have beneficial effects on humans' health because of their structures resemblance to humans' leukotrienes and prostaglandins [12]. On the other hand, some depsidones may induce weak allergic reactions in humans [13,14]. It was reported that naturally occurring depsidones possessed remarkable bioactivities: antiproliferative, antimalarial, cytotoxic, antibacterial, radical scavenging, antihypertensive, anti-trypanosomal, anti-malarial, anti-leishmanial, herbicidal, larvicidal, aromatase and cholinesterase inhibitor, antioxidant, and antifungal [15–20]. Thus, they are of substantial interest as a potential lead motif for medicinal chemistry. Moreover, from the organic chemists' viewpoint, depsidones are interesting and challenging goals to assess novel synthetic strategies. The biosynthesis of depsidones has been previously reported [21]. Moreover, depsidones comprise a rapidly increasing class of natural metabolites that need to be overviewed. In spite of their significance, this class of natural metabolites wasn't paid much attention. Surveying the currently available literature revealed that no separate review for the naturally occurring depsidones is available. The present work focused on naturally occurring depsidones, especially those of fungal origin that have been published from 1978 to 2018 and gave a summary of their biosynthesis, identification, isolation, bioactivities, sources, and references (Tables 1–30, Figs. 2–13). A literature search of studies published was conducted over different databases: MedLine (PubMed), Web of Science, Scopus, Google Scholar, SpringerLink, SciFinder, ACS Publications, and Wiley search was done using keywords (depsidone, endophytic fungi, isolation + NMR, and biological activities). Additionally, the following databases for patents were analyzed: United States Patent, Google Patents, and Theses Full-text database. During our search we found that some of the published compounds had the same molecular formulae and chemical structures, but they had different nomenclature e.g. botryorhodine A/botryosphaerone A, botryorhodine B/botryosphaerone B, botryorhodine C/botryosphaerone

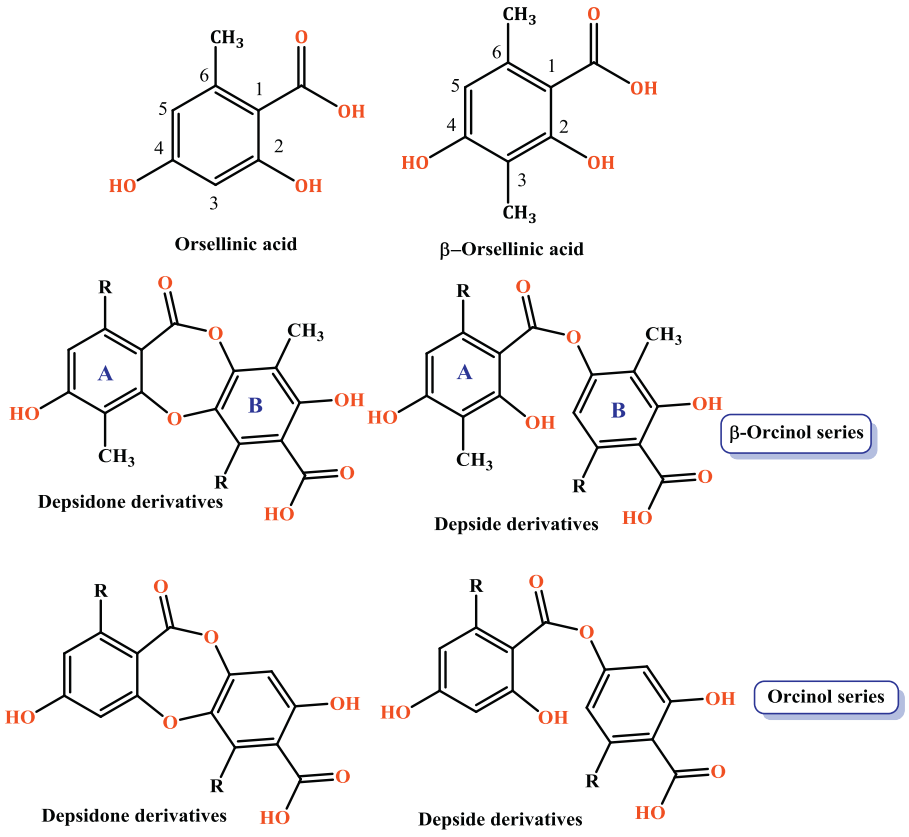

Fig. 1. Structures of orsellinic acid, β-orsellinic acid, depsides, and depsidones derivatives (orcinol and β-orcinol series).