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Bioactive acetylenic metabolites

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ABSTRACT

This article focuses on anticancer, and other biological activities of acetylenic metabolites obtained from plants and fungi. Acetylenic compounds belong to a class of molecules containing triple bond(s). Naturally occurring acetylenics are of particular interest since many of them display important biological activities and possess antitumor, antibacterial, antimicrobial, antifungal, and immunosuppressive properties. There are of great interest for medicine, pharmacology, medicinal chemistry, and pharmaceutical industries. This review presents structures and describes cytotoxic activities of more than 100 acetylenic metabolites, including fatty alcohols, ketones, and acids, acetylenic cyclohexanoids, spiroketal enol ethers, and carotenoids isolated from fungi and plants.

Introduction

Acetylenic metabolites display important biological activities, namely antitumor, antibacterial, antimicrobial, antifungal, phototoxic, and other chemical and medicinal properties (Dembitsky 2006; Dembitsky and Levitsky 2006; Dembitsky et al. 2006; Carballeira 2008; Minto and Blacklock 2008; Siddiq and Dembitsky 2008; Bador and Paris 1990).

Plants have been used worldwide for treatment of various human ailments since antiquity. Their use is still quite prevalent in developing countries in the form of traditional/folkloric medicine (Bero et al. 2009; Fabricant and Farnsworth 2001; Nirmal et al. 2012). Intensive chemical and pharmacological studies during the last five decades have led in many cases to validation of traditional claims and facilitated identification of the traditional medicinal plants and of their active principles (Minto and Blacklock 2008; Siddiq and Dembitsky 2008). More than 1000 acetylenic metabolites have been isolated and identified from plant and animal species (Christensen and Jakobsen 2008; Minto and Blacklock 2008; Siddiq and Dembitsky 2008).

Thousands of herbal and traditional compounds are being screened worldwide to validate their use as anti-cancer, antifunal drugs, but terrestrial acetylenic compounds comprise an especially interesting group of the anticancer, antibacterial and antifungal agents (Dembitsky 2006; Dembitsky and Levitsky 2006; Siddiq and Dembitsky 2008). Their structure and biological activities, modes of action, and future prospects are discussed.

Fungal acetylenic metabolites

Fungi species produce many different acetylenic metabolites, but only some of them show cytotoxic, antitumor, antifungal, antibacterial and/or related activities (Siddiq and Dembitsky 2008; Dembitsky 2003; Dembitsky and Levitsky 2006; McAfee and Taylor 1999; Reisch et al. 1967; Stickings and Raistrick 1956; Jones 1966; Herbst 1960; Anchel 1952).

Repandiol (**1**, Fig. 1), a cytotoxic diepoxide, (2*R*,3*R*,8*R*,9*R*)-4,6-decadiyne-2,3:8,9-diepoxy-1,10-diol, was isolated from the mushrooms *Hydnum repandum* and *H. repandum* var. *album* (Takahashi et al. 1992; Nozoe et al. 1993). Repandiol demonstrated pronounced cytotoxic effects against various tumor cells. It was found to form interstrand cross-links of DNA, linking deoxyguanosines on opposite strands primarily within the 5′-GNC and 5′-GNNC sequences preferred by diepoxyoctane. However, repandiol was a significantly less efficient cross-linker than diepoxyalkanes (diepoxyoctane and diepoxybutane) (Millard et al. 2004).

Two antibiotics, biformin (or polyacetylenic 9-carbon glycol, **2**) and bioforminic acid (**3**) were obtained from fungus *Polyporus biformis* (syn: *Trichaptum biforme*, Basidiomycetes) grown on a modified Czapek-Dox liquid medium (Robbins et al. 1947; Anchel and Cohen 1954). Both compounds showed antibacterial activity *Bacillus subtilis*, *Bacillus subtilis*, and *Photobacterium fischeri* and *Pseudomonas aeruginosa* (Kavanagh 1947). Same compound,

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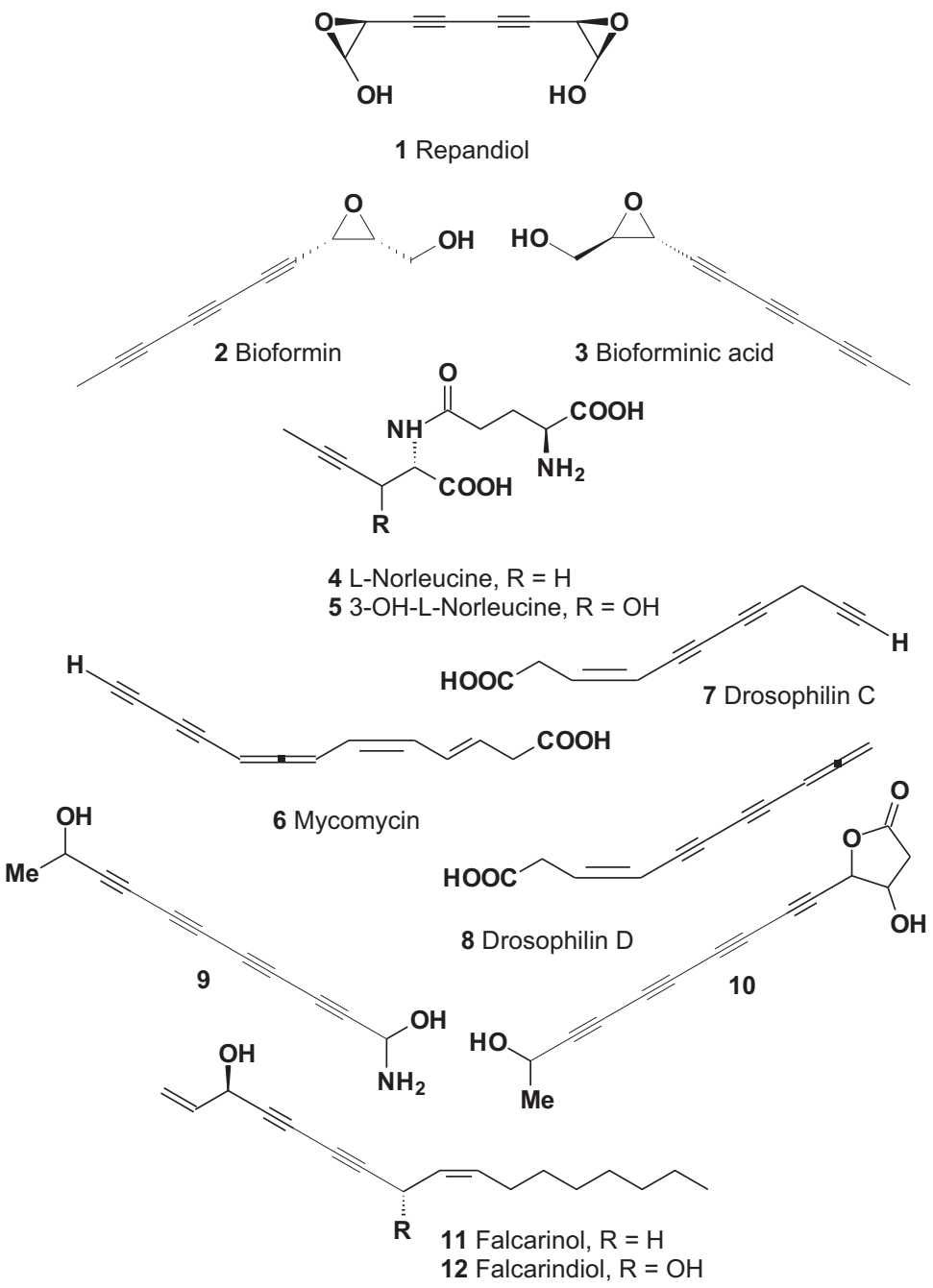

Fig. 1. Acetylenic metabolites produced by fungal endophytes.

trans-2,3-epoxydeca-4,6,8-triyn-l-ol, has been isolated from the culture filtrate of the fungus *Tramtes pubescens* (Dagne et al. 1994). It showed antifungal activity against *Aspergillus niger* and *Aspergillus ochraceus*.

Two glutamyl-peptides, γ-glutamyl-L-2-aminohex-4-ynoic acid (**4**) and γ-L-glutamyl-L-erythro-2-amino-3-hydroxyhex-4-ynoic acid (**5**), were isolated from the fruit bodies of *Tricholomopsis rutilans* (Niimura and Hatanaka 1977; Okishi 1977; Hatanaka et al. 1973). Derivatives of these amino acids showed antiviral, anticholesterol and anticancer activities (Patel 2001; Sung et al. 1969; Takada et al. 1991; Whitehead 1999).

Mycomycin (**6**) isolated in 1950 by Jenkins (Jenkins 1950), is used not only as a therapeutic agent for tuberculosis (King 1950; Chain 1958; Beer 1955), but for treatment of late-stage inoperable primary hepatocellular carcinoma (Du and Hu 1997; Veljkovic and Lalovic 1978). More recently, antibiotic 07F275 (also known as mycomycin, **6**), is produced by submerged fermentation of fungal culture LL-07F275, and belonging to the allenic polyacetylene family (Schlingmann et al. 1995).

Acetylenic metabolites named drosophilin C (**7**), and D (**8**) have been isolated from fungus culture of *Drosophila subatrata* (now classified as *Psathyrella subatrata*) (Jones et al. 1960; Kavanagh et al. 1952; Ahmed et al. 1977). These compounds showed antibacterial, antimicrobial and antifungal activities, and they inhibited bacteriophage growth (Anchel 1953, 1954; Asheshov et al. 1954; Kavanagh et al. 1952).

Two bioactive polyynes, 10-hydroxyundeca-2,4,6,8-tetraynamide (**9**) and 3,4,13-trihydroxy-tetradeca-5,7,9,11-tetraynoic acid-γ-lactone (**10**) were isolated from cultures of the fungus *Mycena viridimarginata*. Compound (**9**) was highly