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Review

Epoxy acetylenic lipids: Their analogues and derivatives

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ABSTRACT

Currently, approximately 250 natural acetylenic epoxy structures are known. The present review describes research concerning biologically active epoxy acetylenic lipids and related compounds isolated from different sources. Intensive searches for new classes of pharmacologically potent agents produced by living organisms have resulted in the discovery of dozens of such compounds that possess high anti-cancer, cytotoxic, antibacterial, antiviral, and other activities. Acetylenic epoxides primarily belong to a class of molecules containing triple bond(s) and epoxy group(s) belonging to different lipid classes and/or other groups. This review emphasises natural and synthetic acetylenic epoxides and other related compounds as important sources of leads for drug discovery. The present review is the first article devoted to natural acetylenic epoxides.

Contents

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1. Introduction

Natural acetylenic epoxides and related compounds display important biological activities, including antitumour, antibacterial, antimicrobial, antifungal, phototoxic, and other chemical and medicinal properties [1–7]. Compounds with acetylene, vinyl–acetyl, and acetylene–allene type bond systems were first discovered in the late 19th century in some mushrooms. Because molecules containing these fragments are most often unstable, their presence in natural objects appeared unusual. However, as experimental findings have been accumulated, it has become evident that compounds of this type that are characteristic of natural life are widely represented and perform important functions; in particular, these compounds act as antibiotic, anticancer, antibacterial and other agents.

Acetylenic epoxides and related lipophilic metabolites that contain a [—C≡C—] bond(s) and an ethylene oxide group (also called oxirane) are interesting metabolites and are found in both terrestrial and marine organisms [7,8]. Graphic chemical structures are shown in Fig. 1.

In many cases, intensive chemical and pharmacological studies during the last five decades have led to the validation of traditional claims and have facilitated the identification of traditional medicinal plants and of their active principles [4,7]. More than 1300 acetylenic metabolites have been isolated and identified from plant and animal species [1–3,7–14].

Thousands of terrestrial and marine epoxy and acetylenic compounds are being screened worldwide to validate their use as anticancer drugs; however, terrestrial acetylenic compounds compose a particularly interesting group of anticancer agents and other biologically active compounds [1–4,7].

The present review is the first article devoted to natural epoxy acetylenic lipids. This review focuses on the origin, structures, and biological activities of natural epoxy acetylenic lipids and selected semi- and/or synthetic-related compounds. Their modes of action and future prospects are also discussed.

2. Fatty acids and glycerides

The aerial parts of *Erigeron philadelphicus* were found to produce the isomeric methyl esters of 7-(3-methyl-oxiranyl)-2-heptene-4,6-diynoic acid (**1** and **2**) [15]. The same compounds were detected along with polyacetylenes in *Chrysoma pauciflosculosa* [16]. Two derivatives of matricaria esters, 2(*Z*)-10-hydroxy- and 2(*Z*)-10-acetoxy-8,9-epoxydecen-4,6-diynoate (**3** and **4**, respectively), were detected in extracts of the rabbitbrush *Chrysothamnus nauseosus* (family Asteraceae) [17,18], and these derivatives were found to inhibit the feeding of 3rd instar Colorado potato beetle larvae. Compound **4** was isolated from *Chrysothamnus parryi* [19].

A fatty acid that was identified as 8-(3-oct-2-ynyl-oxiranyl)-octanoic acid (**5**) composes 60% of the seed oil of *Crepis foetida* (family Compositae) [20]. Acetylenic acid and methyl ester (**6** and **7**, respectively), which are inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase, were found in the root bark of *Paramacrolobium caeruleum* [21]. Acetylenic acid (**8**) was prepared as an inhibitor of human neutrophil LTA_4 hydrolase [22].

An unusual acetylenic amide (**9**) was isolated from the extract of *Spilanthes alba* [23]. Acetylenic N-alkylamide (**10a**), with evidence of immune stimulating properties, was isolated from the extract of *Spilanthes acmella* [24], in *S. acmella* flowers [25], in roots of *Acmella ciliata* [26], and in the aerial parts of *Salmea scandens* [27]; an identical metabolite (**10b**) was isolated from the leaves and flower heads of *Acmella radicans* var. *radicans* (family Asteraceae) [28].

An unusual methyl ester of fatty acid (**11**) was isolated from N-fixing lichens *Leptogium saturninum* and *Peltigera canina* [29]. *L. saturninum* (order Peltigerales) displayed strong multi-copper oxidase (e.g., tyrosinase) and heme-containing peroxidase activities [30,31]. *Peltigera* sp., which is a cyanolichen that contains *Nostoc* sp. as a cyanobiont, produced arginase and arginine [32,33], which are also produced from phycobiliprotein pigments [34], and displayed laccase activity [35]. Both lichen species were found to contain unusual lipids and fatty acids [36–38].

A panaxydol derivative (**12a**) was obtained from *Panax ginseng* [39]. Both compounds **12a** and **12b** showed IC_{50} values of 0.06 and 12.7 μg/mL for inhibiting the proliferation of L2110 leukaemia and HeLa cells, respectively. Panaxydol linoleate (**13**) and ginsenoyne A linoleate (**14**) were found in the extract of the root of *P. ginseng*; these compounds showed cytotoxic activities against murine and human malignant cells (DT, NIH/3T3, L-1210, HeLa, T24 and MCF7 cells) *in vitro* [40].

Several bioactive fatty acids (as Na salts) and their methyl and ethyl esters (**15a**, **b**, **c**-**17a**, **b**, and **c**) were prepared [41]. These acids are useful as anti-asthmatic, anti-allergic, anti-inflammatory, and cytoprotective pharmaceuticals.

The myxomycetes (plasmodial slime moulds) are a group of fungus-like organisms usually present and sometimes abundant in terrestrial ecosystems. The myxomycete lifecycle involves two extremely different trophic (feeding) stages, one consisting of uninucleate amoebae, with or without flagella, and the other consisting of a distinctive multinucleate structure, the plasmodium [42]. Their chemical constituents include more than 100 natural compounds; lipids, fatty acids, alkaloids, amino acids, peptides, terpenes, naphthoquinone pigments, and aromatic and carbohydrate compounds from 26 species of four orders from myxomycetes were reported in several review articles [43–45]. These constituents are fatty acids, amino acids, alkaloids, naphthoquinones, aromatic metabolites, terpenoids, esters, and their derivatives. Thus, slime moulds not only have become one of the important research objects for natural products but also are expected to be new bioactive resources for natural products.

The slime mould *Lycogala epidendrum*, commonly known as wolf's milk, is a cosmopolitan species. Recently, some interesting lipids were isolated from this myxomycete. Specifically, rare fatty acids (**18**–**21**) and three triacylglycerides (TAG), named lycogarides A (**22**), B (**23**), and C (**24**), were isolated from the myxomycete *L. epidendrum* [46,47]. More recently, two unusual TAG, lycogarides D (**25**) and E (**26** and **27**), and two diacylglycerols (DAG), lycogarides F (**28**) and G (**29**), were reported [48].

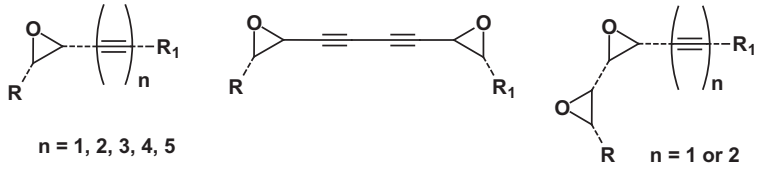

Fig. 1. Graphical display of chemical structures of natural acetylenic epoxides R, R_1=H, alkyl, phenolic, cyclic and/or heterocyclic moiety.