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Review

Sesquiterpene lactones with unusual structure. Their biogenesis and biological activity

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ABSTRACT

The given review provides data on the new sesquiterpene lactones with unusual structure isolated from various natural sources, e.g. fungi, plants, marine growth; about their spread, biological activity, and the presumed biogenetic pathway of their formation. An attempt was made to biologically justify a wide structural formation variety of new sesquiterpene lactones with the unique structure.

1. Introduction

Secondary metabolism is a unique feature of higher plants. In this regard, the search and identification of new compounds, clarification of their synthesis and mechanisms of regulation are the most important and fundamental tasks of modern physiology and biochemistry of plants. In fact, crucial changes in the qualitative and quantitative content of secondary metabolites and the emergence of rare and unusual compounds are possible today.

It is well known that isoprenoids form the most multiple class of secondary metabolites (with over 35,000 known structures), many of which have high biological activity. In particular, sesquiterpene lactones synthesized by *Asteraceae* [1] family representatives hold a specific place among isoprenoids.

It is rather difficult to give a comprehensive analysis of recent work in the research area of sesquiterpene lactones chemistry. Furthermore, in the foreign countries, the long-term studies have been conducted aiming at the development of new generation anti-tumor drugs based on sesquiterpene lactones. Due to this fact, in recent years changes have occurred in the field of sesquiterpene lactones chemistry, and not only new biologically active compounds of this class but also unique, unusual lactones with a new carbon skeleton have been isolated, which was first and foremost promoted by the enhanced methods of isolation and analysis of natural compounds, in particular, the use of a gas-liquid and gas chromatography, nuclear magnetic resonance and proton magnetic resonance (NMR)-spectroscopy [2].

With respect to the Republic of Kazakhstan, over 6000 plant species grow in its territory, of which 667 are endemic ones, being the sources of new, previously not studied natural compounds. Overall, 133 plant species from the *Asteraceae* family were researched for the period from 1996 to 2015. These plants were chemically analysed, and, as a result, 61 sesquiterpene lactones were isolated and identified, including 15 compounds of germacrane type, 11 - eudesmane, 32 - guaiane, 3 of pseudoguaiane types, and also 3 dimeric lactones were derived. It is important to highlight that the majority of isolated lactones are guaianolides. Twelve out of the derived and identified sesquiterpene lactones are new, previously undescribed [3–4].

The aim of the given review is to analyse novel structural types of sesquiterpene lactones, their structures' elucidation, a biogenetic pathway of their formation, and a biological activity with the purpose to develop effective drugs with a wide range of pharmacological activity.

2. Discussion

It should be noted that the basic structural element of the isolated compounds molecules is the sesquiterpene skeleton which is formed biogenetically in a farnesyl pyrophosphate way. According to many authors, there is a certain plan of terpenoid molecules composition developed by nature in the early stages of evolution which plants and animals follow to undergo such biochemical transformations which result in a surprising variety of terpenes and their derivatives [5]. The distinction of separate molecules' structure can be explained by the intramolecular rearrangement and other biosynthetic transformations of intermediates formed at the enzymatic modifications in a plant body, sea metabolites, microorganisms [6–7].

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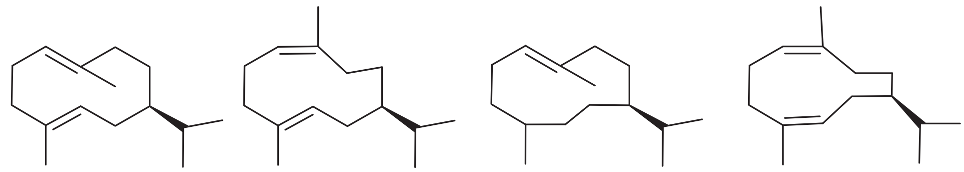

Trans-trans germacranolide Melampolide Heliangolide Cis-cis-germacradienolide

Scheme 1. Main types of sesquiterpene lactones.

The abundance of terpene carbon skeletons can be related to a variety of enzymes known as terpene synthases. These catalysts are capable of transforming prenyl diphosphates and squalene to a variety of cyclic and acyclic forms [8].

By 2015, more than 6000 sesquiterpene lactones belonging to various structural types had been discovered and described by various sources. From over 40 structural types of sesquiterpene lactones known to date the most widespread are germacrane, guaiane, eudesmane, and pseudoguaiane (Scheme 1), while elemanolides, xanthanolides, eremophilanolides, drimanolides, and bakkenolides are met less frequently [4].

For the period from 1995 to 2015, 2768 new sesquiterpene lactones were isolated, 764 of which are new guaianolides, 603 - germacranolides, 455 - eudesmanolides (Fig. 1).

Over the last 20 years, more than 160 new sesquiterpene lactones were derived with an unusual carbon carbocyclic skeleton. Some individual cases are reported about the isolation of sesquiterpene lactones of cuparane, sterpurane, hirsutane, illudane, carabrane, aristolane, aromandrane, valerane, botrydiane and other types (Fig. 2). There are lactones of a mixed type - 60 new and 34 - unique, i.e. exclusive and exceptionally rare.

A major breakthrough in the Chemistry of Natural Compounds has been determined by the following factors:

- the mastering of new isolation methods from natural raw materials, which allow the tracing of rather labile compounds;
- the application of new physical and physical-chemical methods of high resolution to conduct compositional analysis of complex mixtures of this class and composition of individual products in low quantities.

It is still evident that even a larger quantity remains unstudied and will be identified later. However, it is due to the improvement of extraction and analysis methods of natural compounds that allows us to receive representatives of sesquiterpene lactones with new structural types.

Therefore, to date three ways of a single isoprenyl fragment formation have been confirmed, where the mevalonate pathway is the main one. The second by importance is mevalon-independent (Methyl Erythritol Phosphate (MEP)) synthesis. The third and far less frequent way is when isoprenoids are formed from amino acids. Thus, mevalonic acid becomes a building block for creation of terpenoids after its transformation into isopentenyl diphosphate. Then the carbon chain is extended by condensation of isopentenyl diphosphate molecules into geranyl diphosphate, farnesyl diphosphate, among others. Besides, prenyl transferase enzymes catalyze this process. As a rule, terpenoid monomers are bound according to "head-to-tail" type, for instance, at formation of geranyl - and farnesyl diphosphates [9–11].

Accordingly, the Biogenetic theory, proposed by Ruzicka L., has gained further development. Every year the amount of experimental data grows which confirms the idea that sesquiterpenoids biosynthesis goes through a mevalonate-isopentyl pyrophosphate-farnesyl pyrophosphate pathway. The peculiar fact in terpenoids biosynthesis is that early biosynthetic stages result in recovery processes, whereas the subsequent biomodifications are mainly presented by oxidizing reactions. Moreover, the sesquiterpene lactones hydroperoxides isolated by R.W. Doskotch [12] and El-Feraly [13] confirm that hydroperoxides can be intermediates in the biosynthesis of various skeleton types of the hydroxylated terpenoids, which usually lead to allylic oxidations. Besides, the extraction of sesquiterpene lactones epoxides from plants implies their participation in the main biosynthetic sequences of natural compounds, in particular, in cyclization (ring closure reactions). On the basis of biogenetic premises, it is established today that sesquiterpene lactones are the derivatives of farnesyl or nerolidyl pyrophosphates [9–11].

This can be illustrated by the general scheme of terpenoids biogenesis, presented below (Scheme 2), which is the joint work of many scientists, including Ruzicka, Cornforth, Bloch, Lynen. Russian and

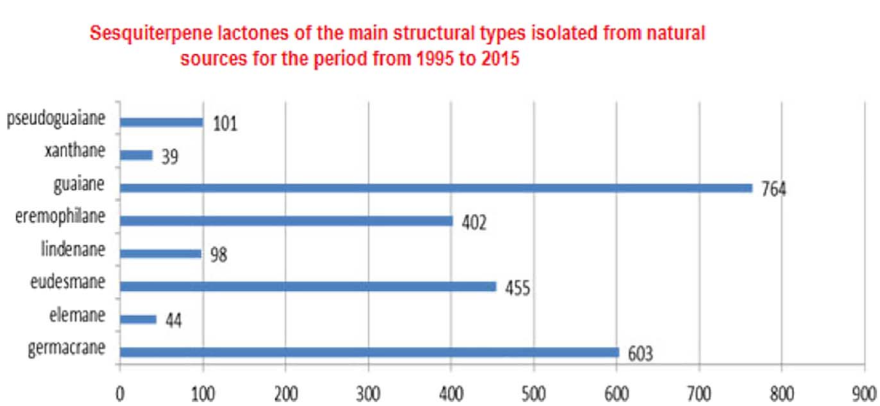

Fig. 1. Sesquiterpene lactones of the main structural types isolated from natural sources for the period from 1995 to 2015.