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Review

Naphthylisoquinoline alkaloids potential drug leads

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ABSTRACT

Naphthylisoquinolines are a group of structurally diverse secondary metabolites, consisting of naphthalene and isoquinoline moieties. Naturally occurring naphthylisoquinolines have so far been found only in the small palaeotropic families Dioncophyllaceae and Ancistrocladaceae. They have been shown to exhibit a diverse array of biological activities. Herein, we review the research on the occurrence, isolation, identification, biological activities, and biosynthesis of this class of compounds published from 1995 till now. Moreover, their chemotaxonomic relevance and molecular targets of action have been discussed. More than 125 metabolites are described and 99 references are cited.

Contents

Abbreviation: A, Ancistrocladus; 1,8 DHMN, 1,8-dihydroxy-3-methylnaphthalene; 3D7, chloroquine-sensitive strain of *P. falciparum*; CD, circular dichroism; D, *Dioncophyllum*; EC_{50}, effective concentration; GI_{50}, the concentration needed to reduce the growth of treated cells to half that of untreated cells; HIV, human immunodeficiency virus; HL-60, human promyelocytic leukemia cells; IC_{50}, inhibition concentration; INA-6, derived from a patient with multiple myeloma; J774.1, murine macrophage cell lines; K1 strain, chloroquine and pyrimethamine resistant strain of *P. falciparum*; K562, human erythromyeloblastoid leukemia cell line; L-6, rat skeletal muscle myoblast; LC_{50}, lethal concentration of a substance killing 50% of an exposed organisms at a specific time interval; NF54 strain, an airport strain of *Plasmodium falciparum* susceptible to standard antimalarials; NOE, nuclear overhauser effect; PKS, polyketide synthase; ROE, rotating-frame overhauser enhancement; RTs, reverse transcriptases; ppm, parts per million; *T*, *Triphyophyllum*; TDR/WHO, tropical diseases research/world health organization; U937, human leukemic monocyte lymphoma cell line.

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1. Introduction

Naphthylisoquinolines are a unique class of structurally diverse secondary metabolites. They are of high interest due to their unprecedented structures, remarkable chemotaxonomical implications, and promising biological activities. Structurally, they are chiral compounds characterized by the presence of *C,C* or *C,N* biaryl axis between naphthalene and isoquinoline moieties [1,2]. Many of these alkaloids display atropisomerism, since the biaryl axis usually is rotationally hindered due to the presence of bulky *ortho*-substituents. Biosynthetically, they are acetogenic isoquinoline alkaloids, both parts of the molecule originating from acetate-malonate units [3–5]. Also, dimers have been found, which can have up to three consecutive stereogenic biaryl axes [6,7]. These natural products are divided into different subclasses according to the location of biaryl axis between naphthyl and isoquinoline moieties: 5-1′, 5-3′, 5-8′, 7-1′, 7-3′, 7-6′, 7-8′, and C–*N* [8]. The structural variety of naphthylisoquinoline alkaloids arises from their probable biosynthetic formation through oxidative phenolic coupling of the two bicyclic systems [2]. Naturally occurring naphthylisoquinolines are derived from plants belonging to small palaeotropical plant families Dioncophyllaceae and Ancistrocladaceae [2]. Dioncophyllaceae consists of three monotypic genera, *Habropetalum*, *Dioncophyllum*, and *Triphyophyllum* [9], and the closely related Ancistrocladaceae has only one genus, *Ancistrocladus* [10]. Ancistrocladaceae and Dioncophyllaceae families are mainly occurring in Africa and also Southern and Southeastern Asia. The plants of these families have been widely used in the traditional medicine to treat dysentery, malaria, elephantiasis, and other diseases [11]. Naphthylisoquinolines exhibited strong inhibitory activities towards *Plasmodium* [12], *Leishmania* [12], and *Trypanosoma* species [13,14]. Thus, they are considered as lead structures for anti-parasitic drugs. Naphthylisoquinoline alkaloids have been demonstrated to exhibit remarkable biological activities such as anti-malarial, anti-trypanosomal, anti-leishmanial, fungicidal, molluscicidal, larvicidal, insecticidal, spasmolytic, and anti-HIV [12–18]. They are of great interest as potent lead compounds for medicinal chemistry. Furthermore, from the viewpoint of synthetic organic chemistry, the naphthylisoquinolines are challenging and interesting targets to test novel synthetic strategies and asymmetric reactions or novel chiral reagents. The chemistry, isolation, and structural elucidation of naphthylisoquinolines up to the year 1995 have been previously reviewed [1]. However, naphthylisoquinoline alkaloids constitute a rapidly growing class of natural products that the need for an updated overview seemed urgent. This review focuses on the occurrence, isolation, identification, biological activities, and biosynthesis of this class of compounds (Fig. 1). Herein, 128 naturally occurring naphthylisoquinoline derivatives have been listed. For each compound these data were listed in the following order: name, structure, molecular

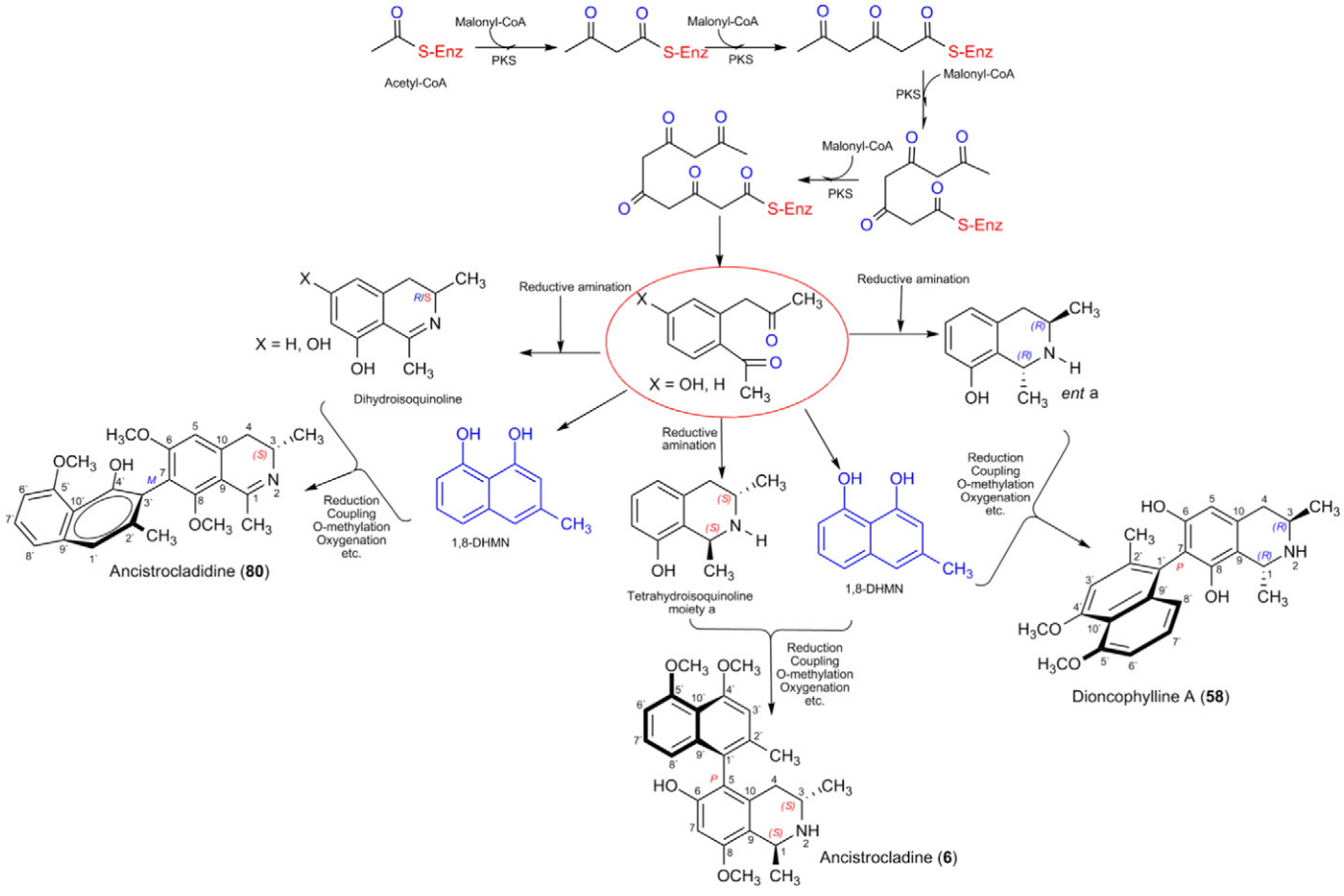

Fig. 1. Biosynthetic pathways of naphthylisoquinoline alkaloids.