European Journal of Medicinal Chemistry 128 (2017) 219–236

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Review article

Pterocarpan scaffold: A natural lead molecule with diverse pharmacological properties

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ARTICLE INFO

Article history:
Received 21 December 2016
Received in revised form
12 January 2017
Accepted 13 January 2017
Available online 17 January 2017

Keywords:
Pterocarpan
Natural product chemistry
Pharmacological activity

ABSTRACT

Phytoalexins are substances produced by plants that act as potent inhibitors of pathogens. Pterocarpans are biologically active isoflavonoids most commonly found in the family Fabaceae that have the ability to act as phytoalexins. It is made up of a tetracyclic ring system possessing benzofuran-benzopyran. A very great number of pterocarpans have been isolated from natural sources and they are proved to have significant biological activities such as anti-microbial, anti-cancerous, anti-inflammatory and anti-malarial activities. Recently, pterocarpans gained lot of attention because of the broad range of anti-cancer activities in various cancer cell lines such as breast, leukemia, cervical, lung, colon and melanoma. Interestingly, pterocarpans exhibited inhibitory potency against many enzymes such as PTP1B, Neuraminidase, and α-glycosidase. In addition, they were shown to have anti-estrogenic and anti-diabetic activities. This review is a comprehensive inventory of the structures and sources of pterocarpans and it emphasizes on the biological evaluations of pterocarpans from various plant sources and their scope as a lead molecule.

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Contents

1. Introduction

Plant based compounds provide diverse scaffolds in the discovery of novel lead compounds [1,2]. Globally, the overall

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http://dx.doi.org/10.1016/j.ejmech.2017.01.023
0223-5234/Published by Elsevier Masson SAS.

botanical and plant-derived drugs market was valued at $25.6 billion in 2015. In 2010, of the 20 drugs approved by FDA, 50% of them were natural products and their derivatives. Large pharma companies such as Sanofi, Novartis and Pfizer work with plant-derived compounds that are in the development pipeline. The reasons behind the remarkable growth of use of naturally-derived compounds include: the belief among the public that these are safer than the synthetic drugs and lower developmental cost.

Natural products have tremendous potential to be a rich source for drug discovery and offer structural diversity. One of the major breakthroughs in the search for natural anticancer agents is the discovery of two life saving compounds, Taxol and camptothecin by the scientists from the Research Triangle Institute [3]. These natural products have been approved for the treatment of ovarian, breast, lung, and colon cancer and Kaposi's sarcoma [4]. Despite the continuous efforts in the discovery and development of novel drug molecules, cancer is still a highly challenging disease to be treated.

Naturally occurring pterocarpans constitute the second largest group of isoflavonoids and are often used in folklore medicine as an alternative and supplementary therapy. These pterocarpans have a tetracyclic ring system of benzofuran-benzopyran which contains two chiral centres in the 6a and 11a positions derived from the flavonoid skeleton (Fig. 1) [5,6].

Pterocarpans are potent phytoalexins (plant defensive agents) and are synthesized *de novo* by plants upon the action of stress factors such as pathogens, UV radiation and high metal salts. Phytoalexins protect plants from fungal and other microbial pathogens. Through solvent extraction, over hundred new pterocarpans have been identified and evaluated for their pharmacological activities from a variety of plants belonging to the families Leguminosae, Fabaceae, Papilionaceae, and Bituminaria. Based on the structure, pterocarpans are classified as pterocarpans containing core skeleton, O-glycosylated pterocarpans, dimethylpyranopterocarpans, furanopterocarpans and 6a-hydroxypterocarpans. Numerous methods are suggested for the synthesis of pterocarpans like sodium borohydride reduction of 2′ hydroxy-isoflavones, Heck arylation of 2H-Chromenes, Claisen rearrangement of aryl allyl ethers, aldol condensation between phenylacetates and benzaldehydes, 5-endo−trig radical cyclization, alkene metathesis and many other. UV spectral studies of pterocarpans showed three absorption peaks in the range of 280−335 nm [5].

Goel and co-workers [5] published a review article that covers the synthesis, stereochemistry, classification and chemical reactivity of natural pterocarpans. Jiménez-González et al. [6] reported a review on antifungal activity and other biological properties in the year of 2008. We observed that soon after their publications, there are several research articles published on the diverse pharmacological properties of pterocarpans. Thus, we compiled the diverse pharmacological activities of the pterocarpans reported during the year 2008−2016 in this review. Moreover, the information provided in this review will give an insight on the importance of pterocarpans in the bio molecular pathway and their potential as lead-compounds.

2. Anticancer activity

The cytotoxic activity of four pterocarpans (**1**–**4**) isolated from the plant *Platymiscium floribundum* was investigated against human promyelocytic leukemia (HL-60) cell by Militao et al. [7,8] They reported that the pterocapans reduced cell viability by 52.5−72.1% at 12.5 μg/ml. The results revealed that the inhibition of DNA synthesis and disruption of membrane integrity towards HL-60 cells exhibited lower number of cell division and internucleosomal DNA breakdown [9] with these compounds (Table 1). In another study, Militao et al. [10] investigated 2, 3, 9-trimethoxypterocarpans (**1**) for its cytotoxic activity in four leukemia cell lines (HL-60, Molt-4, Jurkat, and K562). This pterocarpan showed anti-proliferative activity in K562 cell after 48 h incubation with IC_{50} = 0.8 μg/ml. Bioassay-guided fractionation of *Harpalyce brasiliana* yielded six bioactive pterocapan derivatives in which leiocarpin (**5**) with IC_{50} = 0.1−1.2 μg/ml exhibited the maximum anti-mitotic activity [11]. The presence of prenyl group at C2 and C4 position plays an important role in the increased antimitotic properties. All the six compounds were screened against three human cell lines, leukemia (HL-60), melanoma (MDA-MB-435) and colon (HCT-8) with 4-dehydroxycarbenegrin (**6**) being the most active at 3.1−8.5 μg/ml.

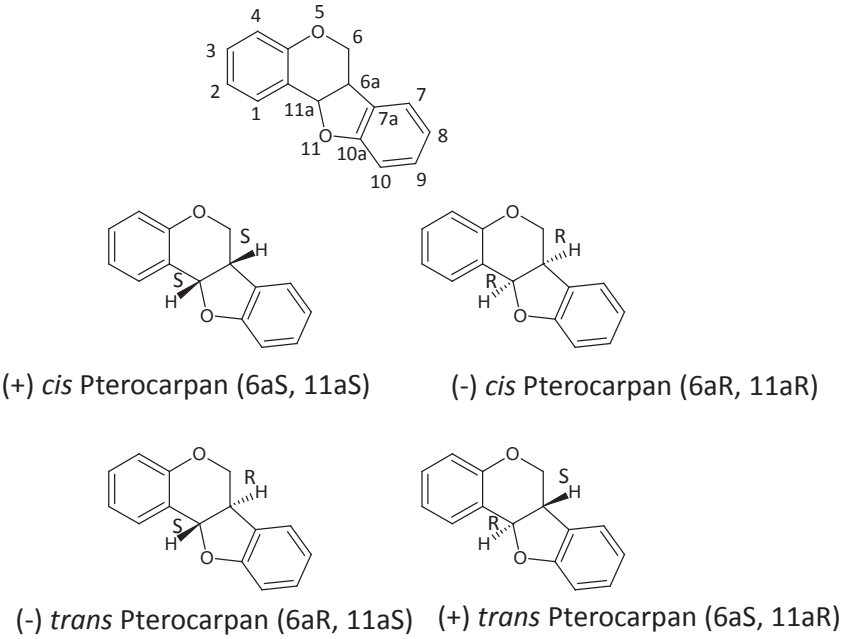

Fig. 1. Stereochemistry of Pterocarpan.