Editorial

Challenging Organic Syntheses and Pharmacological Applications of Natural Products and their Derivatives

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Natural products have had a major impact on chemistry, chemical biology and drug discovery and have been part of medical remedies since ancient times. Based on a recent survey, about one third of all new molecular entities approved by the FDA are natural products or their derivatives, most of them being used as antibacterial agents [1]. However, starting from 1990s, research aiming at exploiting natural products as a resource for drug discovery seriously declined. Many pharmaceutical companies concentrated their efforts on new technologies such as combinatorial chemistry, metagenomics and high-throughput screening to generate new drug candidates. Nevertheless, these new strategies have not delivered the expected results and recently there has been a renewed interest in the use of natural products in drug design and discovery. Nowadays, natural products still represent a unique source of lead structures for the creation of new medicines and, in addition, they are powerful tools in the hands of pharmacologists to modulate biomolecular systems.

A number of research initiatives have been recently undertaken at National or European level to support the use of natural products as a source of new drugs or drug candidates. Just as example, the CM1407 COST Action granted by the European Union (COST networking programme), and focusing on the synthesis and biological application of natural products in multiple therapeutic fields, has recently started [2]. The Action is chaired by Professor Bruno Botta from Sapienza University of Roma, a leading expert in natural products chemistry and drug discovery [3], and currently involves 30 different EU countries.

This thematic issue, which is the first of two foreseen on this topic, aims to present an overview of relevant classes of natural products that are currently under investigation as potential therapeutics, as well as the methods for total synthesis, high-throughput screening and pharmacological evaluation. First, Solum *et al.* summarized the synthesis and pharmacological applications of 2-methoxyestradiol, a metabolite of 17β-estradiol that captured the attention of the scientific community for its anticancer, antivascular, and antiangiogenic effects and lack of toxicity [4]. Betschart and Altmann reviewed the xenicanes, a large class of marine diterpenoids endowed with antiproliferative and anti-inflammatory activity *in vitro*. Authors also addressed the challenging synthesis of xenicanes and described recent efforts and advances [5]. Non-taxifolin derived flavolignans are a class of relatively unexplored natural products, which are systematically reviewed by Chambers *et al.* The authors also described the several biological activities *in vitro* and/or *in vivo* experienced by these molecules [6]. Doan and Christensen focused their research article on thapsigargins, a small family of highly bioactive compounds that also corresponds to authors' research interest. Particularly, a wide range of chemical transformations to afford thapsigargins structure activity relationships is described, up to the design and synthesis of a thapsigargins derivative (G202) that is currently in phase II clinical trials as therapeutics against hepatocellular carcinoma [7]. Pérez *et al.* reviewed recent efforts in developing novel synthetic strategies to obtain indoloquinolizidines and their derivatives, which showed noticeable biological activity as analgesic, anti-inflammatory, antihypertensive, and antiarrhythmic agents. Moreover, these molecules proved to be effective against the *Leishmania* parasites [8]. In the second part of the Issue, Marucci *et al.* deeply reviewed the several natural compounds providing modulation of cancer stem cells (CSCs), a subpopulation of cancer cells that is generally resistant to chemotherapy and is endowed with clonogenic capacity and stemness features. In this work, natural compounds from significantly different classes are discussed, thus proving the reader with multiple hints for further developments or medicinal chemistry studies [9]. In the review of Coman and Parvulescu, the well-known biological modulators prostaglandins are used as case study to perform a critical analysis of chemo- and diastereoselective hydrogenation reactions. In particular, examples of hydrogenation of a carbonyl group in the presence of a C=C double bond are reviewed, with particular emphasis on the synthesis of a $PGF_{2\alpha}$ analogue [10]. The review of Sencanski *et al.* focused on the use of natural compounds as leads for the treatment of influenza viruses infection. Authors examined the druggability of some key targets, including hemagglutinin, neuraminidase, non-structural protein 1, and a polymerase. All targeting natural products were reviewed and divided in structural classes [11]. Dinić *et al.* discussed on the role of natural products in preventing or modulating multidrug resistance (MDR) in cancer. In particular, authors addressed the topic at the molecular level and classified natural compounds active against MDR cancers into two classes, depending on the mechanism of action [12]. Finally, Wrzesinski and Fey presented a critical view of pros and cons of using cells grown in 3D cultures as tool for monitoring the efficacy of natural products. Indeed, 3D cultures mimic functions of human tissues significantly better than cells grown using classical 2D culture systems, even though they require higher manipulation costs [13].

In summary, we feel that this thematic issue is timely and may be of widespread interest for the scientific community. We also hope to contribute to the field by serving as forum for dissemination and discussion on recent relevant results and technological advances, covering the fields of drug design and discovery, natural products chemistry and pharmacology.

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