Editorial

Challenging Organic Syntheses and Pharmacological Applications of Natural Products and their Derivatives – Part II

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Following the publication of the Part-1 Thematic Issue on "challenging organic syntheses and pharmacological applications of natural products and their derivatives" [1], a sequel is herein presented. Natural products continue to challenge and to stimulate scientists of multiple disciplines. A large part of the European scientific community involved in drug discovery with natural products met on 5-6 October 2015 in Roma (Sapienza University campus, Italy) for the first meeting of the CM1407 COST Action, organized by the Action chair Professor Bruno Botta. This successful initiative has been an unique opportunity to set the state of the art in natural products chemistry, therapeutic applications, and isolation/characterization techniques as well as to update on recent challenges and advancements in these fields. Some of the topics addressed during the CM1407 meeting are discussed and deepened in this Thematic Issue, which is composed of eleven review articles covering the broadest chemical classes of natural products, respective therapeutic targets and delivery systems.

First, Mascarello *et al.* reviewed the natural products with inhibitory activity against *Mycobacterium tuberculosis* (Mtb) protein tyrosine phosphatases (PTPs). These enzymes are attractive targets for the development of anti-TB therapeutics, mostly due to their key role in Mtb replication and survival as well as their localization outside Mtb wall. Structural features of Mtb PTPs and small molecule inhibitors from natural sources, also coming from authors' researches, are here reviewed with particular emphasis on a number of synthetic chalcone derivatives and a Diels-Alder-type adduct isolated from *Morus nigra* [2-4]. Karioti *et al.* updated the state of the art for natural products inhibitors of carbonic anhydrases (CAs), a class of intriguing targets for the development of anticancer drugs [5-9]. A synthetic sulfonamide inhibiting CAs developed by the authors is currently in clinical trials (namely SLC-0111) [10, 11]. The present article clearly highlights the relevance of naturally occurring chemotypes for CAs inhibition by means of multiple and different mechanisms of action. Structural, enzymatic, synthetic and biological activity data of coumarins, phenols, polyamines, terpenes, and natural sulfonamides inhibitors of CAs are herein reviewed. Grynkiewicz and Szeja addressed the key issue of primary and secondary metabolism of natural products, which is mostly carried out by means of glycosilation and may hamper the bioavailability or bioactivity of these small molecules. In their work, authors reviewed a large number of natural products and they glycoconjugates from a chemistry viewpoint, describing the challenging routes to synthesize these glycosilated derivatives and providing hints on the respective biological properties [12, 13]. Stanley and co-workers presented an overview of elegant and diverse syntheses of dimeric natural products carried out by means of key biomimetic dimerization reaction sequences. In particular, several total syntheses of complex natural product dimers are described, mostly coming from the own research of authors [14, 15]. The work of Iovine *et al.* revolves around a single molecules, namely the *Veratrum californicum* alkaloid cyclopamine, which inhibits the Hedgehog signalling pathway in cancer stem cells and exerts therefore anticancer effects. In this extensive review, total and semi-synthetic strategies to obtain cyclopamine as well as to design and synthesize a large number of cyclopamine derivatives with improved pharmacokinetics and pharmaceutical properties are deeply described. The work of Iovine *et al.* is a complete overview on this class of Hedgehog pathway inhibitors inspired by nature [16, 17]. Ladeiras and colleagues presented a review focusing on abietane diterpenoids, a class of natural products largely studied over the years, and endowed with multiple biological properties [18]. In particular, authors covered the sub-class of royleanones, namely abietane diterpenoids with hydroxy-*p*-quinone C ring, which correspond to one of their research topics [19, 20]. These molecules, beside their relevance in chemical biology, have been investigated also as therapeutics, mostly for their antimicrobial activity. The pharmaceutically relevant issue of natural products delivery has been addressed by D'Acquarica *et al.* [21]. Interestingly, authors focused on the resorc[4]arene scaffold as a suitable system for incorporating chemically diverse bioactive natural products such as amino acids, amphetamine, ethanolamine neurotransmitters, dipeptides, *vinca* alkaloids and nucleosides. These macrocycles, which are deeply investigated in authors own researches [22, 23], are herein described from synthetic and spectroscopic viewpoints. Natural products have played a remarkable leading role in the development of antibiotics, a class of drugs used to combat infections from different bacteria or other microorganisms. In his work, Prusov summarized recent advancements in the field of antibiotics, with particular emphasis on synthetic routes and structure-activity relationships, and suggested strategies to optimize pharmaceutical properties of these molecules up to clinical candidates [24]. Khan *et al.* deeply overviewed the endocannabinoid system from the molecular to the pathological level. Indeed, these neuromodulatory natural products and their receptors are attracting much attention within the scientific community, particularly for the development of novel anticancer therapeutics [25]. Šíša and Vaněk nicely updated the field of tetracyclic diterpenoids, one of the largest classes of natural products endowed with multiple biological activities [26]. Authors covered the literature from 2000 and emphasized challenging reactions and pitfalls in the synthesis of this scaffold. Finally, Ingallina and colleagues presented an interesting and personal viewpoint on the Pictet-Spengler two-component reaction, one of the most common synthetic and biosynthetic reaction that generates tetrahydroisoquinolines or tetrahydro-β-carbolines scaffolds [27-29]. In this review, authors provided an update of previous reports, devoting particular care in describing the technical aspects related to the chemical reaction.

Overall, the large participation to editorial and networking scientific initiatives focusing on natural products is a valuable confirmation of the renewed leading role of this type of small molecules in modern medicinal chemistry and drug discovery [30]. As guest editors, we are sincerely glad to all scientists that contributed to these issues with high quality reviews.

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