European Journal of Medicinal Chemistry xxx (2014) 1–12

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Invited review

Selected hybrid natural products as tubulin modulators☆

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ARTICLE INFO

Article history:
Received 3 June 2014
Received in revised form
10 October 2014
Accepted 20 October 2014
Available online xxx

Keywords:
Tubulin activators and de-activators
Epothilone and related compounds
Eribulin and related compounds
Signaling pathways
Protein–protein interactions

ABSTRACT

Modulators of microtubule dynamics have received increasing attention because of their potential to stop cancer growth. Although it belongs to the category of complex protein–protein interactions (PPIs), which are generally considered difficult to modulate through small molecules, the use of microtubule is considered a well-validated target. There are a number of bioactive natural products and related compounds that are currently in use as drugs or in clinical trials as next generation anti-cancer agents. The present review article is focused on two such bioactive natural products, epothilone and halichondrin B, and covers some of the key papers published after 2005 that outline various synthetic approaches to obtain next generation structural analogs as well as the synthesis of hybrid compounds.

1. Introduction

The post-genomic drug discovery era is challenging the scientific community to tackle biological targets still considered "undruggable" and it is also demanding a call to build new sets of tool compounds that may be better suited to modulate such targets [1]. A paradigm shift from enzyme inhibition to pathway driven targets is underway [1d,2]. Signaling pathways are the central cellular machinery and are highly regulated in the normal state; however, under disease conditions, they seem to undergo deregulation and cause dysfunctioning at the cellular level [3]. Signaling pathways work through multiple dynamic protein–protein interactions (PPIs) and restoring the normal state by modulating these interactions with small molecules is receiving increasing interest. Unlike enzymes, PPIs generally do not involve deep pockets, but rather shallow and large surface-to-surface interactions that lead to significant challenges for their modulation by small molecules [4]. Most PPIs belong to the category of "undruggable targets" but in the past several years we have witnessed a significant progress in the design and synthesis of active small molecules as PPIs modulator. *Where can we find small molecules that are capable of modulating PPIs?* Natural products have a proven track record in this arena [5]. For example, in cancer research, there are several well-known natural products that are known to modulate microtubule dynamics, thereby stopping the growth of cancerous cells [5a,5b,6].

2. Microtubule dynamics and cancer

Microtubules are dynamic filamentous sub-cellular proteins that are an important for cell proliferation, intracellular transportation, signaling and some other cellular processes [5b,6b]. In mitosis, the microtubule undergoes to form mitotic spindle. These mitotic spindles are highly dynamic so that microtubules are an important therapeutic target for the development of anti-cancer agents [7]. Several microtubule stabilizing agents have been identified, and among those, a polycyclic natural product called paclitaxel (Taxol®) is one of the most promising compounds known to kill cancer cells by stabilizing the microtubule polymerization [8].

3. Epothilone and related analogs and hybrid compounds

In 1996, Höfle and his co-workers isolated 16-membered macrocyclic natural products called epothilone A/B (Fig. 1) [9]. Like taxanes, epothilones are shown to interrupt cell mitosis by stabilizing microtubules, and thus exhibit an excellent cytotoxic activity. Another interesting fact is that epothilones are known to bind microtubules [10] at a site closer to the one where taxol binds. The advantages of epothilones over paclitaxol are the structurally simplicity and their easy structural modification.

☆ For a Special Issue on "Novel Chemistry for Undruggable Targets".

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http://dx.doi.org/10.1016/j.ejmech.2014.10.062
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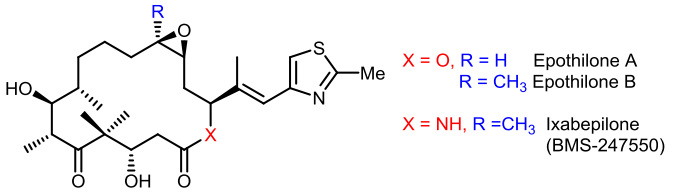

Fig. 1. Structures of epothilone A, B and ixabepilone.

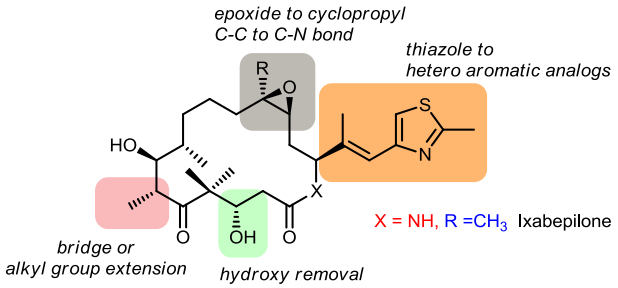

Fig. 2. Different structural modification sites to obtain epothilone analogs and hybrids.

Natural products provide ideal starting points to initiate a drug discovery program. Most of the currently approved drugs are natural product-derived compounds or semi synthetic natural products. One of the strategies to identify lead compounds in drug discovery is to screen a large collection of natural products-based libraries. This generally provides information on the basic skeleton that can further lead to structural modifications to produce more focused, natural product-derived small molecules. In the case of epothilones, the bioactive conformation of epothilone–tubulin was well studied [11] and molecular mechanism also predicted using high resolution crystal structure [12]. Binding of epothilone to microtubules is also studied by utilizing biochemical and NMR techniques [13].

By these evidences the researchers made number of epothilone analogs and hybrids. Among all synthetic compounds, the aza-analog of epothilone, ixabepilone (BMS-247550) was approved by FDA in 2007 to treat breast cancer [14].

Several nicely written reviews that covered the chemistry and biology of epothilones appeared before 2005 [15]. To avoid any overlap, here we are covering the analogs and hybrid compounds of epothilones, and, to best of our knowledge, the impact of these structural modifications on various cancer cell lines is not covered before.

As shown in Fig. 2 (**2.1**), four important modification sites can led to different analogs. Initially many research groups focused on the aromatic thiazole ring i.e. side chain of epothilone and its replacement with various aromatic moieties. A second modification site was an epoxide, which can be replaced with a cyclopropyl ring, trifluoromethyl groups, and with other hetero-atom containing moieties, such as amides, substituted amines, triazole ring system to obtain different natural product mimics. The hydroxyl group removal was the third modification site, and the fourth one was the replacement of the methyl group with an allyl group to obtain further potent analogs. The remaining positions were also used to obtain several newer analogs but most these changes led to a decrease in the cytotoxic activity.

Altmann's group developed several novel biologically active epothilone analogs through extensive structural modifications in the existing natural product [16], and in 2005, they designed and synthesized the 3-deoxy analog of epothilone B (**F3.1**, Fig. 3A). In another series, they synthesized the aromatic thiazole side chain modified analogs (**F3.2** and **F3.3**) of compound **F3.1**. Another compound **F3.4**, having a *trans* epoxide in **F3.2** was also synthesized. In another study, to obtain novel hybrids of epothilones, they designed C12 aza-epothilones by substituting C12 with "nitrogen atom" (**F3.5**), and the other common side chain benzimidazole (**F3.6**) [17]. The structural features of these derivatives (Fig. 3) are unique, in that, they do not impose much change in the conformation of the parent natural product. The other major feature was that these modified compounds do not fit into the biosynthetic pathway which is used to synthesize polyketides. Thus, there is no program for the synthesis of aza analogs in the biosynthetic machinery.

Here we discussed Altmann's synthesis of C12-aza analog of epothilone (**F3.6**) is described in Scheme 1. The aldol reaction between a known aldehyde (**1.1**) and ethyl ketone (**1.2**) gave fragment **1.3**, which has the required stereocenters of an epothilone polyketide chain. In several simple reactions, then conversion compound **1.3** into an acid (**1.4**), having a terminal olefin at the other

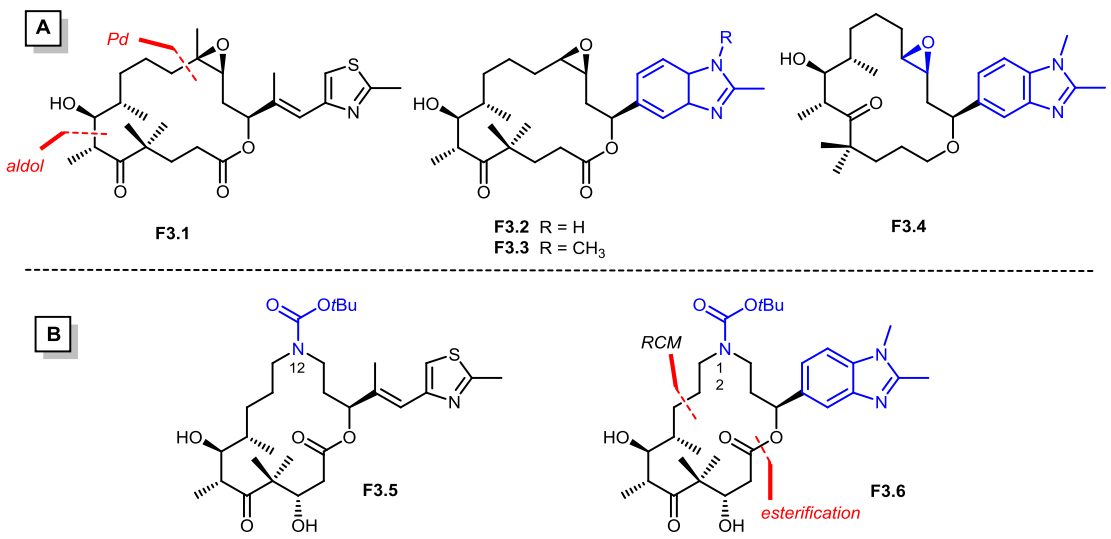

Fig. 3. Altmann's designed novel epothilone analogs.