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Review

Recent advances in design, synthesis and bioactivity of paclitaxel-mimics

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ABSTRACT

Taxane-type anticancer drugs, including paclitaxel and its semi-synthetic derivatives docetaxel and cabazitaxel, are widely applied to chemotherapy of malignancy like breast cancer, ovarian cancer, non-small cell lung cancer and prostate cancer. However, their clinical applications are generally limited by scarce natural resources, various side effects and multidrug resistance. Therefore, it is significant to develop paclitaxel-mimics with simplified structure, fewer side effects and improved pharmaceutical properties. Based on our investigation on chemistry of paclitaxel, the current review summarized the most recent advances in the design, synthesis and biological activities of paclitaxel-mimics, which could be appealing to researchers in the field of medicinal chemistry and oncology. Meanwhile, smart design, interesting synthesis and potential bioactivities of these novel compounds may also provide valuable reference for the wider scientific communities.

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1. Introduction

Paclitaxel **(1)** [1], a natural diterpenoid isolated from the stem bark of Taxus, has been a research focus for decades due to its complex structure, unique therapeutic mechanism and excellent anticancer activities. By promoting tubulin assembly and stabilizing microtubules, paclitaxel can inhibit mitosis and finally leads to apoptosis of tumor cell [2]. Paclitaxel, along with its semi-synthetic derivatives docetaxel **(2)** [3] and cabazitaxel **(3)** [4] (Fig. 1), have been approved as anticancer drugs in clinical treatment of ovarian cancer [5,6], breast cancer [7], non-small cell lung cancer [8], small cell lung cancer [9], prostate cancer [10], head and neck neoplasm [11], leukemia [12], gastric cancer [13], etc. Although promising, clinical applications of taxane anticancer drugs are limited by their scarce natural resources, synthetic difficulty, poor aqueous solubility, clinical neurotoxicity, neutropenia [14] and multidrug resistance [15,16].

Paclitaxel is composed of a [6 + 8 + 6] tricyclic diterpenoid core and a C-13 side chain. Through in-depth SAR (structure–activity relationship) studies on paclitaxel, the C-13 side chain is revealed to be indispensable active groups [17–20], while its activity could be partly maintained with an open-loop diterpenoid core [21–25]. Early studies suggested that the unique diterpenoid core of paclitaxel is crucial to its anticancer activity [17,18]. However, with the discovery of new microtubule stabilizers [26–31], such as epothilone A, which have entirely different structures but share the same mechanism and binding site with paclitaxel [32], a new theory was proposed, suggesting the function of rigid diterpenoid scaffold in maintaining the special conformation of paclitaxel and stabilizing the orientation of C-2, C-13, C-3′ active substituents [33]. Therefore, it is promising for researchers to develop simplified paclitaxel analogs with potent anticancer activities.

At present, more than 200 simplified paclitaxel analogues derived from conformation or pharmacophore of paclitaxel have been reported. In our ongoing research on the modification of paclitaxel [25,34–36], we summarized the advances in design, synthesis and biological activity investigations of paclitaxel mimics, to provide reference for the development of paclitaxel mimics with simplified structures, higher efficacy and lower toxicity. It should be noted that based on Taxol conformation, Kingston and Snyder [37] presented a quite informative review by comparing various intermolecular distances (Å) of paclitaxel and its mimics. In this current review, a wider range of paclitaxel analogues were classified into four groups, including Core-simplification mimics, Core-replacement mimics, Macro-ring mimics and Microtubule-bound mechanism mimics. We will discuss their design ideas and chemical synthesis, compare and summarize their anti-cancer activities, which will significantly aid in future studies.

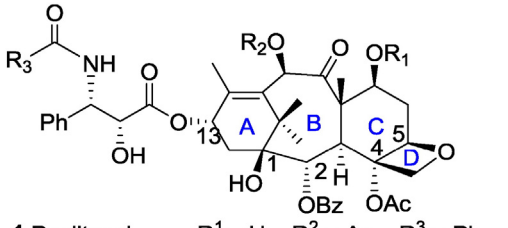

Fig. 1. Structures of paclitaxel, taxotere, and cabazitaxel.

2. Core-simplification mimics

Paclitaxel [6 + 8 + 6] tricyclic diterpenoid core is featured by multi-chiral carbons, rigid bridge double bonds and unstable quaternary epoxypropane, which make it difficult to synthesize. Thus, in pharmaceutical industry, semi-synthetic method requiring diterpenoid scaffold isolated from taxus are commonly adopted to afford paclitaxel and its derivatives [38].

C-13 side chain is proved to be indispensable active groups by in-depth SAR studies [17–20]: large side chain-free diterpenoid compounds isolated from taxus failed to demonstratedecent activities. Meanwhile, structural modifications on paclitaxel diterpenoid core indicated that most of its open-loop derivatives still showed certain cytotoxicities or microtubule stabilizing activity [21–25]. Therefore, the diterpenoid core is thought to act mainly by stabilizing the active conformation of paclitaxel. In addition, the discovery of new microtubule stabilizers, represented by Epothilones [26], further confirmed that the diterpenoid core is not an essential part for activities. Based on this observation, various simplified skeletons were designed to replace paclitaxel diterpenoid core and link with side chain, which created a class of Core-simplification mimics. We then divided this type of mimics into four subtypes, including Core-rearrangement mimics, AB-ring mimics, ABC-ring mimics, D-ring mimics, which will be discussed respectively.

2.1. Core-rearrangement mimics

Although complicated, elegant routes developed in the total synthesis of paclitaxel still contribute to the preparation of paclitaxel mimics in some ongoing efforts. Klar et al. [39] adopted the Wender's pinene route for the preparation of a tricyclic taxane scaffold [40–43]. In the purification process, a rearrangement product borneol ester **7** was obtained from intermediate **5**, which was prepared by the epoxidation of **4** (Scheme 1). Then, through esterification of **7** with docetaxel side chain, compound **8b** was prepared and tested to show weak but significant microtubule stabilizing activity, while its corresponding analogue **8a** with paclitaxel side chain was tested to be inactive.

Later, further structural modification studies were conducted, and the results of which indicated that the α-methyl isomer **9b** showed much better microtubule stabilizing activity, while its β-methyl epimer **9a** was inactive (Fig. 2). On this basis, side chain modified products **10–13** were obtained and tested to be active, which further supported that α-methylation was beneficial to activities. Interestingly, **12a** was proved to have better microtubule stabilizing activity than paclitaxel.

2.2. AB-ring mimics

The following research focus mainly on the simulation of paclitaxel AB ring. As is known, the [6 + 10] ring of antitumor antibiotics Calicheamicin **14** [44] is similar to paclitaxel AB ring. Therefore, Fallis et al. [45] designed paclitaxel mimic **15** (Fig. 3) by replacing paclitaxel diterpenoid core with Calicheamicin. Unfortunately, its cytotoxic activity was five orders of magnitude less potent than that of paclitaxel.

Bicyclo [3.3.1] nonanes skeleton exists in many natural products [46–48] and was generally used as the synthetic precursor of paclitaxel diterpenoid core [49–51]. Olga N. Zefirova et al. [52,53] selected this structure skeleton to replace diterpenoid core. SAR studies on paclitaxel demonstrated that the side chain [17–20], especially the benzoyloxy at C-2 [54–57] plays significant roles in tubulin assembly, but minor changes on C-2 are tolerable [58]. While acetoxyl group at C-4 can be

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