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Short communication

Syntheses and biological evaluation of C-3′-N-acyl modified taxane analogues from 1-deoxybaccatin-VI

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ABSTRACT

A series of side-chain modified taxane analogues were synthesized and their *in vitro* anticancer activities against four human cancer cell lines: MDA-MB-231 (human breast cancer), PC-3 (human prostatic cancer), HepG2 and H460 (human hepatoma) were studied. The three hydroxyl groups at C-7, C-9 and C-10 enable the behavior of these compounds to be evidently distinct from other similar compounds. The strong cytotoxicity in the four cell lines showed by the newly synthesized taxane analogues **13a** and **13d** indicated them as potential lead compounds for anticancer drug design.

1. Introduction

Paclitaxel **1** (**Fig. 1**), a diterpenoid natural compound was isolated from the stem bark of *Taxus brevifolia*, has preeminent antitumor activities against a range of cancers, including breast, ovarian, germ cell, lung and esophageal cancers [1–5]. The activity is believed to be related to its binding to polymerize tubulin, to promote microtubule assembly and to stabilize microtubule by bundle formation [6]. Numerous structure-activity-relationship studies (SARs) indicated that the C-13 side chain is an indispensable part for its antitumor activity, Ojima et al. synthesized a variety of C-3′-N-acyl modified paclitaxel analogues by employing β-lactam four-membered ring which can be coupled to baccatin III through coupling reaction as a side chain precursor to produce paclitaxel analogues. Respectively, these C-3′-N-acyl (2-furyl, 2-thienyl, p-fluorophrnyl and p-methoxyphenyl) modified paclitaxel analogues exhibited similar or lower IC_{50} comparing with paclitaxel against J774.1 and J7.DEF3 [7–9]. The structure-activity-relationship studies (SARs) also showed that the 1-hydroxyl group is not crucial for the tubulin assembly activities of paclitaxel [10–13].

Starting from 1-deoxybaccatin-VI **3** (**Fig. 1**), which is readily available from *Taxus chinensis*, *Rehd. Var. mairei* in good yield [14,15], Kingston synthesized several 1-deoxybaccatin-VI analogues and reported that compound **4** (**Fig. 1**) ($IC_{50} = 0.0315$ μM) had an IC_{50} value 11-fold greater than that of paclitaxel ($IC_{50} = 0.0028$ μM) in the HCT116 cell line evaluated [16]. In our previous study, we also presented the detailed design and synthesis of 1-deoxypaclitaxel [17]; in the A549 cell line evaluated by us 1-deoxypaclitaxel **5** (Fig. 1) (IC50 = 0.062 μM) had an IC_{50} value 10-fold greater than that of paclitaxel (IC50 = 0.0063 μM). According to the two studies, both of the two compounds indicated a significant loss in cytotoxicity. However, in our further investigation of 1-deoxypaclitaxel analogues [18], we discovered that compound **6** (Fig. 1) ($IC_{50} = 0.11$ ng/mL) had the same IC_{50} value as that of paclitaxel ($IC_{50} = 0.13$ ng/mL) in the A2780 cell line evaluated, while this compound ($IC_{50} = 0.18$ ng/mL) even had an IC_{50} value 1.6-fold lower than that of paclitaxel ($IC_{50} = 0.29$ ng/mL) in the A549 cell line evaluated. Compared to the compound **4** and 1-deoxypaclitaxel **5**, compound **6** is structurally distinctive due to the three hydroxyls at the C-7, C-9 and C-10 positions.

As an ongoing part of our research on 1-deoxypaclitaxel analogues [17,18], we have become interested in developing the syntheses and biological activities of a series of 1-deoxypaclitaxel analogues bearing different substituted groups at the C-3′-N-Acyl position and three hydroxyls at the C-7, C-9 and C-10 positions from 1-deoxybaccatin VI. The activities of these newly synthesized compounds against four cancer cell lines and cell survival data are reported in this paper.

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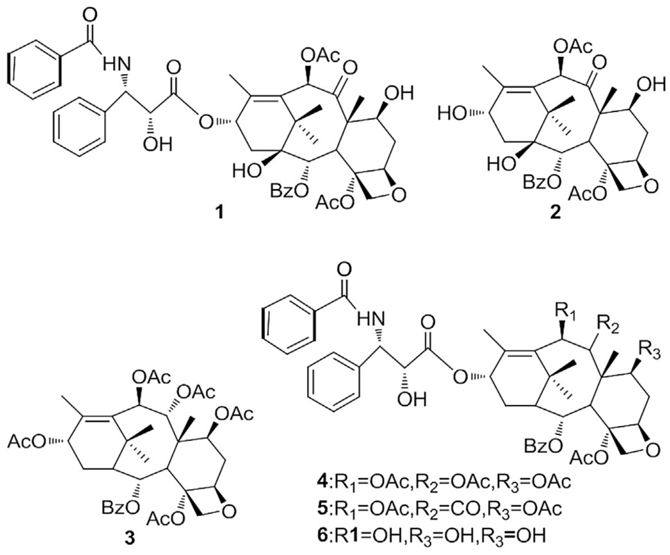


Fig. 1. Paclitaxel and 1-deoxybaccatin III analogues.

2. Results and discussion

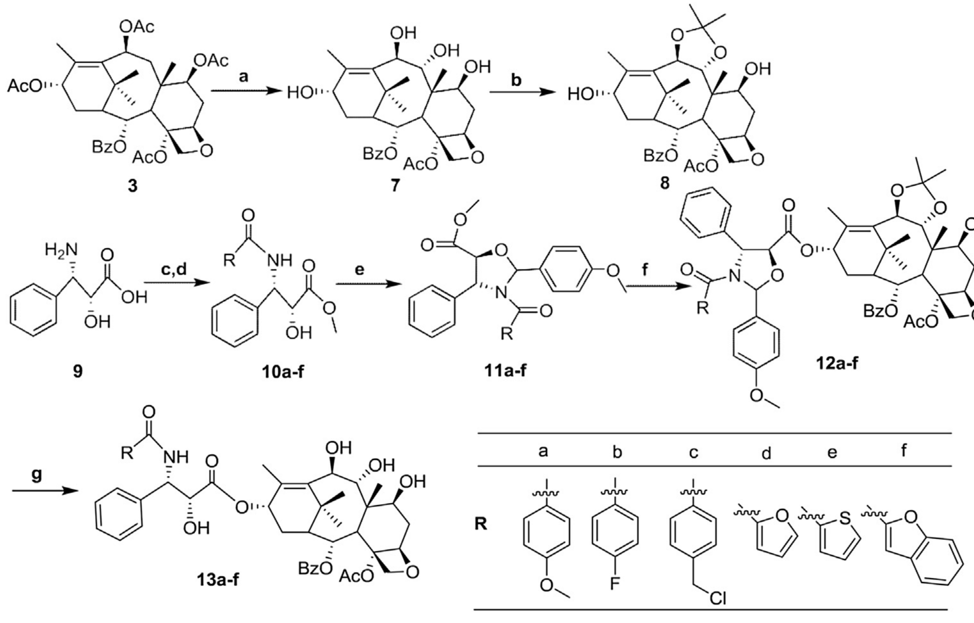
2.1. Chemistry

As previously reported, paclitaxel side chains were synthesized by different methods [19–26]. In this study, we applied the method which was recently described by Yoshio Hayashi et al. [25,26] to synthesize the oxazoline side chain precursor by using (2R,3S)-3-Phenylisoserine **9** with natural configuration (Scheme 1).

The synthesis of compounds **13a-f** is shown in Scheme 1. The starting material 1-deoxybaccatin VI **3** was selectively deacetylated at the C-7, C-9, C-10 and C-13 acetoxyl groups without concomitant deacylation of the C-2 and C-4 acyloxy groups. Subsequent protection of the C-9 and C-10 hydroxyl groups using 2,2-dimethoxypropane gave compound **8**, in which only two hydroxyls remained at the C-7 and C-13 positions after deprotection. However, the C-13 hydroxyl group is more active compared with the C-7 hydroxyl group due to the huge stereo-hindrance effect on the C-7 hydroxyl group caused by the acetal protection at the C-9 and C-10 positions. Therefore, the corresponding carboxylic acid can be immediately coupled with compound **8** by the DDC-DMAP method in toluene.

The key step is the synthesis of the corresponding carboxylic acid, starting from commercially available material (2R,3S)-3-Phenylisoserine **9** with natural configuration as outlined in Scheme 1. Compound **9** was first transformed into **10a-f** after protection of the amine moiety by the acyl chloride and formation of the methyl ester. The next cyclic protection used 4-methoxy benzaldehyde dimethyl acetal in the presence of a catalytic amount of pyridinium p-toluenesulfonate (PPTS), yielding compounds **11a-f**. Compounds **11a-f**, after saponification to the corresponding carboxylic acid without further purification, were then coupled with compound **8** in the present of DCC and DMAP to smoothly provide the corresponding cyclic ester intermediates **12a-f** with good to excellent yield (80–91%). After hydrolysis of the two acetonide protecting groups under strongly acidic conditions, the final products **13a-f** were afforded (Scheme 2).

Further investigation of the modification of the side chain revealed it is difficult to modify the C-3-N'-acyl position using the corresponding alkanoic acid, such as n-hexylic and n-butyric acid, through the DDC-DMAP coupling method. However, the novel taxoid bearing a n-hexane group at the C-3-N′-Acyl position was reported to exhibit excellent antitumor activities [27], which interested us in the design and synthesis of n-hexanoyl-modified 1-deoxypaclitaxel analogues via a β-lactam four-membered ring-opening coupling protocol [28–32]. The synthesis of the compound **18** is illustrated in Scheme 2. Starting from the commercially available β-lactam **14** with high enantiomeric purity, protection of the hydroxyl group of β-lactam **14** at low temperature as a triethylsilyl (TES) ether afforded 3-OTES-β-lactam **15** in 76% yield. Treatment of 3-OTES-β-lactam **15** with n-hexanoyl chloride in



Scheme 1. Reagents and conditions: (a) $NH_2NH_2 \cdot H_2O$, EtOH, rt, 82%; (b) 2,2-dimethoxypropane, montmorillonite K10, CH_2Cl_2, rt, 97%; (c) $SOCl_2$, MeOH, 0 °C to rt, overnight; (d) carbonyl chloride, THF, sat. $NaHCO_3$, 0 °C to rt, 3 h; (e) 4-methoxybenzaldehyde dimethyl acetal, PPTS, toluene, 110 °C, 90%; (f) (1) KOH, MeOH, rt, 2 h; (2) DCC, DMAP, CH_2Cl_2, 50 °C, 2 h; (g) PTS, MeOH, rt, 5 h, 20–30%.