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Synthesis and biological evaluation of 4β-(thiazol-2-yl)amino-4′-*O*-demethyl-4-deoxypodophyllotoxins as topoisomerase-II inhibitors

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ABSTRACT

A series of 4β-(thiazol-2-yl)amino-4′-*O*-demethyl-4-deoxypodophyllotoxins were synthesized, and their cytotoxicities were evaluated against four human cancer cell lines (A549, HepG2, HeLa, and LOVO cells) and normal human diploid fibroblast line WI-38. Some of the compounds exhibited promising antitumor activity and less toxicity than the anticancer drug etoposide. Among them, compounds **15** and **17** were found to be the most potent synthetic derivatives as topo-II inhibitors, and induced DNA double-strand breaks via the p73/ATM pathway as well as the H2AX phosphorylation in A549 cells. These compounds also arrested A549 cells cycle in G2/M phase by regulating cyclinB1/cdc2(p34). Taken together, these results show that a series of compounds are potential anticancer agents.

Cancer has become one of the leading causes of death worldwide, according to information from the World Health Organization (WHO), it is estimated that there will be 12 million deaths from cancer in 2030. Among them, it is estimated that more than 1 million people die of lung cancer annually and approximately 1.4 million individuals are diagnosed per year, 12% of whom are new cases.[1] Thus, there is an unmet need for novel therapies to improve the prognosis of patients with lung cancer. Plant-derived compounds are known to have curative potential.

DNA is the most vulnerable material in the cell, and DNA damage induces a prominent route of cell death known as apoptosis.[2] In clinical treatment, other than surgery, the mainstay of cancer treatment to date has involved the use of DNA-damaging agents in the form of radiation and systemic chemotherapy. Radiation is responsible for approximately 40% of all cures achieved in cancer patients.[3] Commonly used DNA-damage-inducing chemotherapies include platinum salts (carboplatin, cisplatin, and oxaliplatin) that generate covalent cross-links between DNA bases,[4] and topoisomerase-II (topo-II) inhibitors (etoposide and doxorubicin) that generate topo–DNA adducts and DNA strand breaks.[5] Topo-I inhibitors induce DNA single-strand breaks, while topo-II inhibitors induce DNA double-strand breaks (DSBs). H2AX, an evolutionarily conserved variant of histone H2A, is a key histone that undergoes various posttranslational modifications in response to DSBs.[6] By virtue of phosphorylation, H2AX marks the damaged DNA double helix to facilitate local recruitment and retention of DNA repair and chromatin remodeling factors and thus restore genomic integrity.

Podophyllotoxin (PPT, **1**), derived from the roots and rhizomes of *Podophyllum* species, has cathartic, antirheumatic, and antiviral properties, and pesticidal and antimitotic activity.[7] Etoposide (VP-16, **2**) and teniposide (VM-26, **3**, Fig. 1) are semisynthetic glucosidic cyclic acetals of PPT currently used in chemotherapy for various types of cancer, including small-cell lung cancer, testicular carcinoma, lymphoma, and Kaposi's sarcoma.[8] Both of these compounds block the catalytic activity of DNA topo-II by stabilizing a cleavable enzyme–DNA-complex in which the DNA is cleaved and covalently linked to enzyme.[9] Although they are widely used in the clinic, several problems hinder their clinical efficacy such as drug resistance and poor water solubility. Therefore, there remains a need for new PPT derivatives with anticancer activity and improved water solubility. Extensive efforts have been made researchers to address these limitations.[10] Structure–activity relationship (SAR) experiments have unambiguously demonstrated that C4 is the major molecular site tolerant to significant structural diversification.[11] Furthermore, the comparative molecular field analysis ('CoMFA') models generated by Lee and coworkers

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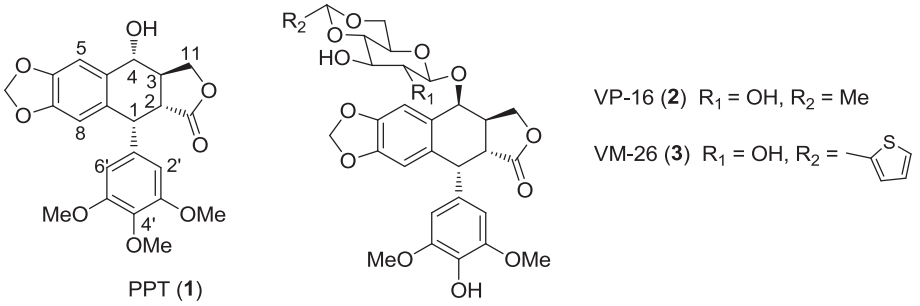


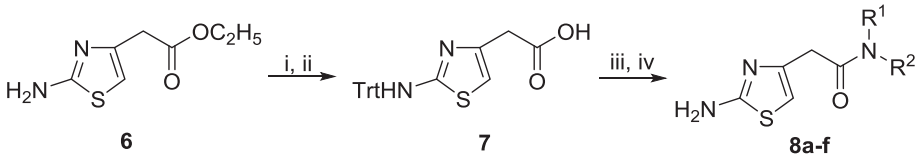
Fig. 1. The structures of podophyllotoxin (**1**), etoposide (**2**), and teniposide (**3**).

demonstrated that bulky substituent at C4 of PPT might favor DNA topo-II inhibition.[12]

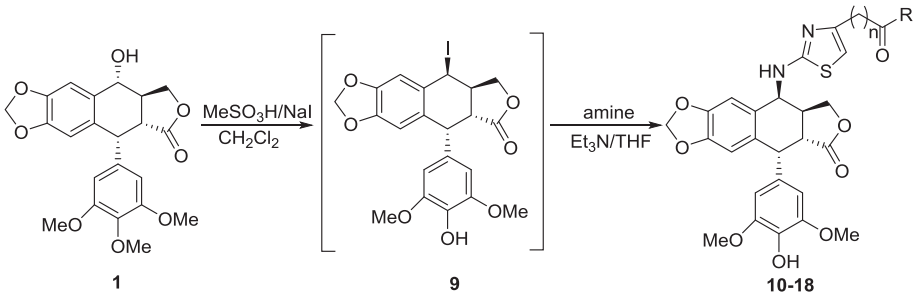
Recently, kinds of 4β-*N*-substituted 4′-*O*-demethyl-4-deoxypodophyllotoxins were generated and have been shown to exhibit more potent anticancer activity and better binding ability to DNA topo-II compared with etoposide.[13–16] As part of our ongoing efforts to develop new podophyllotoxin derivatives with potent biological activities,[17–23] herein we report the synthesis and cytotoxicities of a series of 4β-(thiazol-2-yl)amino-4′-*O*-demethyl-4-deoxypodophyllotoxins. Compound **15** and **17** were further evaluated for its effect on topo-II enzymes, H2AX phosphorylation as well as cell cycle progression.

The intermediates 2-(2-aminothiazol-4-yl)acetic carbamate **8a–f** were synthesized from ethyl 2-(2-aminothiazol-4-yl)acetate (compound **6**) using previously published methods[24] as outlined in Scheme 1. Briefly, the amino group of compound **6** was protected with trityl chloride (TrtCl) and then saponified to produce compound **7**, followed by reaction with different amines under 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDCI) in the presence of *N*-hydroxybenzotriazole (HOBT) in dichloromethane. Last, the protecting group was removed in the presence of acetic acid to provide the intermediates **8a–f**.

The target compounds **10–18** were synthesized from PPT according to previously published methods (Scheme 2).[22] Briefly,



Scheme 1. Synthesis of compounds **8a–f**. Reagents and conditions: (i) TrtCl, Et_3N, r.t (ii) NaOH, MeOH, reflux; (iii) amines, EDCI, HOBT, CH_2Cl_2, r.t; (iv) CH_3COOH, 60 °C.



Compounds	n	R	Compounds	n	R
10	1	HN–△	**11**	1	HN–⬠
12	1	HN–⬡	**13**	1	N⬡O
14	1	N⬡N–	**15**	1	N⬡N–⬠
16	1	OCH_2CH_3	**17**	0	OCH_2CH_3
18	1	OH			

Scheme 2. Synthesis of target compounds **10–18**.