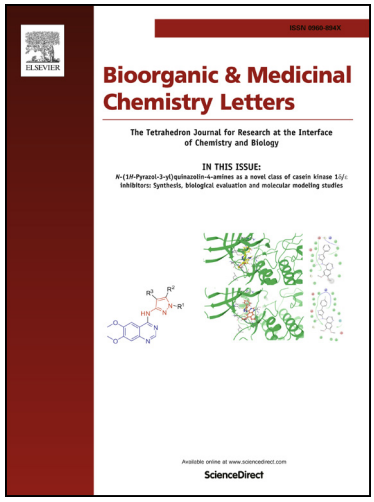

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PII: S0960-894X(17)30754-0
DOI: http://dx.doi.org/10.1016/j.bmcl.2017.07.047
Reference: BMCL 25160

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 22 May 2017
Revised Date: 3 July 2017
Accepted Date: 18 July 2017

Please cite this article as: Sun, W-X., Ji, Y-J., Wan, Y., Han, H-W., Lin, H-Y., Lu, G-H., Qi, J-L., Wang, X-M., Yang, Y-H., Design and synthesis of piperazine acetate podophyllotoxin ester derivatives targeting tubulin depolymerization as new anticancer agents, *Bioorganic & Medicinal Chemistry Letters* (2017), doi: http://dx.doi.org/10.1016/j.bmcl.2017.07.047

Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

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ABSTRACT

In this paper, a series of podophyllotoxin piperazine acetate ester derivatives were synthesized and investigated due to their antiproliferation activity on different human cancer cell lines. Among the congeners, **C5** manifested prominent cytotoxicity towards the cancer cells, without causing damage on the non-cancer cells through inhibiting tubulin assembly and having high selectively causing damage on the human breast (MCF-7) cell line (IC_{50} = 2.78 ± 0.15 μM). Treatments of MCF-7 cells with **C5** resulted in cell cycle arrest in G2/M phase and microtubule network disruption. Moreover, regarding the expression of cell cycle relative proteins CDK1, a protein required for mitotic initiation was up-regulated. Besides, Cyclin A, Cyclin B1 and Cyclin D1 proteins were down-regulated. Meanwhile, it seems that the effect of **C5** on MCF-7 cells apoptosis inducing was observed to be not obvious enough. In addition, docking analysis demonstrated that the congeners occupy the colchicine binding pocket of tubulin.

Keywords:
Podophyllotoxin piperazine acetate ester derivatives;
Cytotoxicity
Cell cycle
Microtubule network
Modeling

Microtubules (MTs), composed of α/β-tubulin, are found around the cytoplasm, which are also crucial component of the cytoskeleton. The α-tubulin and β-tubulin are the important members of the tubulin family and the most highly conserved eukaryotic proteins[1]. MTs are multiformity in their function such as maintaining structure of the cell, chromosomal segregation, protein trafficking and mitosis[2]. In most cases, MTs are continuously experiencing the process of polymerization and de-polymerization, and thus in dynamic equilibrium with tubulin dimer[3]. Disruption of the dynamic equilibrium blocks the cell division machinery at mitosis and subsequently programmed cell death. Therefore, microtubules have been considered as being a promising target of antitumor drugs[1]. At present, it is admitted that microtubule possess three binding sites, respectively, the taxane domain, the colchicine domain and the vinca domain[4]. Colchicine was the first drug known to bind to tubulin, and indeed tubulin was originally isolated through its ability to bind colchicine[4]. Literature searching shows that hundreds of potential colchicine binding site inhibitors have been synthesized and tested in the hope to find a better clinical drug for cancer therapy. A large number of structurally diverse colchicine binding site inhibitors molecules display their anticancer activity based on their abilities to arrest cell[5].

Due to the number of cancer cases increases rapidly in the world, it is essential to investigate several successful and affordable cure approaches for the fatal disease, which is also one of the important contributors to the deaths worldwide. Among a variety of ways, the improvement of natural products have been one of the most effective approaches to confirm new points and pipelines[6, 7]. Natural products are an considerable source of various bioactive principal compounds for the antitumor drugs, which have excellent significance to the development of the pharmacon [6].

As a naturally occurring cyclolignan, Podophyllotoxin (PPT, 1, **Fig.1**) displays cytotoxic activity by inhibition of