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Design, synthesis and evaluation of novel sophoridinic imine derivatives containing conjugated planar structure as potent anticancer agents

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ABSTRACT

Based on our previous study and the binding mode of camptothecin with Topo I, a series of novel sophoridine imine derivatives containing conjugated planar structure were designed, synthesized and tested for their *in vitro* anticancer activity. The results showed that most of the derivatives displayed potent activity. In particular, compounds **10b** exhibited excellent anti-proliferative activities with IC_{50} 5.7 μM and 8.5 μM against HepG-2 and HeLa cell lines, respectively. Molecular docking studies revealed that the introduction of conjugated planar structure could form π-π stacking interaction with DNA, leading to the improvement of biological activity. Its mode of action was to inhibit the activity of DNA Topo I, followed by the G0/G1 phase arrest. This work provides a theoretical basis for structural optimizations and exploring anticancer pathways of this kind of compound and **10b** could emerge as promising lead compounds for the development of novel Topo I inhibitors.

1. Introduction

Cancer continues to be a serious threat to human health.[1] Presently, chemotherapy is the main modality for cancer therapy.[2] Although it can effectively control the spread and metastasis of tumors, there still exists new issues, such as low selectivity, side effects. Thus, the targeted therapy has received more widespread attention.[3,4] With the target of topoisomerase for designing new drugs via traditional Chinese medicine, it could inhibit the DNA replication selectively, kill tumor cells intensively and reduce untoward effects.[5,6,7,8]

Sophoridine, a kind of monomer alkaloid purified from *Sophora alopecuroides* L., has been widely used to treat live cancer, gastric cancer and lung cancer in China for decades with low side-effects.[9] The mechanism of action of Sophoridine is to inhibit the DNA topoisomerase I (Topo I) activity, induce cell cycle arrest at the G0/G1 phase, and cause apoptotic cell death.[10,11] But the moderate antitumor activity of sophoridine limits its use as a drug for clinical applications. Furthermore, various druggable advantages of sophoridine, such as special chemical scaffold, flexible structure, high solubility, and good safety profiles, also provoked our strong interest for further modifications and optimizations.

The structure-activity relationship study (SAR) of sohporidine as anticancer agent was carried out via the modifications at 14-position in our laboratory, and SAR results revealed that introduction of the plannar aromatic group could enhance the anticancer activity by improving the binding affinity with the base-pairs of DNA through π-π stacking interaction.[12] Herein, we hypothesize that similar modifications at nearby position might also be valuable for improving anticancer activity. In addition, C═N functional group, as the necessary component of Schiff base, is present in a number of bioactive molecules, and is recognized as a key building block for the synthesis of small-molecules with potential pharmaceutical activities such as antibacterial,[13,14] antihypertensive,[15] anti-inflammatory[16,17] and anticancer,[18–20] etc. Besides, some researchers demonstrated that the D-ring was not necessary for activity.[21] In consideration of above conditions, our present study was focused on the modification at 15-position of sophoridine involving the transformation of C═O to C═N group, followed by the introduction of a variety of aromatic rings. The strategy adopted for the synthesis target compounds, is depicted in Fig. 1.

Camptothecin (CPT), another cytotoxic quinoline alkaloid, is a potent anticancer agent, especially for leukemia and solid tumors.[22,23] Currently, it's one of the most widely studied anticancer agents among

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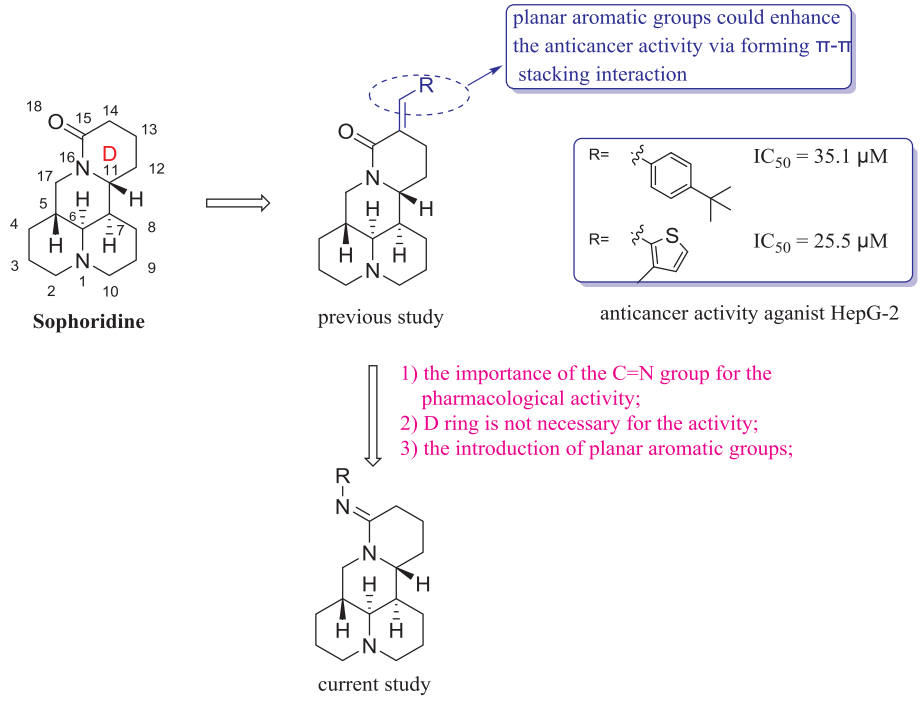

Fig. 1. The first modification strategy for the new compounds.

the Topo I inhibitors. Among its derivatives, 10-Hydrocamptothecin, Topotecan, Irinotecan and Belotecan were used in clinic mainly for the treatment of colon cancer, lung cancer and ovarian cancer.[24–27] An obvious characteristic of the Topo I inhibitors is their planar ring structure, which allows the poisons insert into the DNA and thereby form stacking interactions with base pairs.[28,29] Although the poisons exhibited potent anticancer activity, the side effects, such as myelosuppression, bladder toxicity, seriously limited the application of CPT and its derivatives as potent anticancer agents.[30,31] Besides, the instability caused by the lactonic ring and poor water solubility[32,33] are more limitations which make it an urgent need for designing novel Topo I inhibitors scaffold based on CPT structure. Further, considering the druggable advantages and good safety profiles of sophoridine, we hypothesize to introduce the necessary planar moiety of CPT on the sophoridine structure. The strategy for the design of novel scaffold Topo I inhibitors is described in Fig. 2.

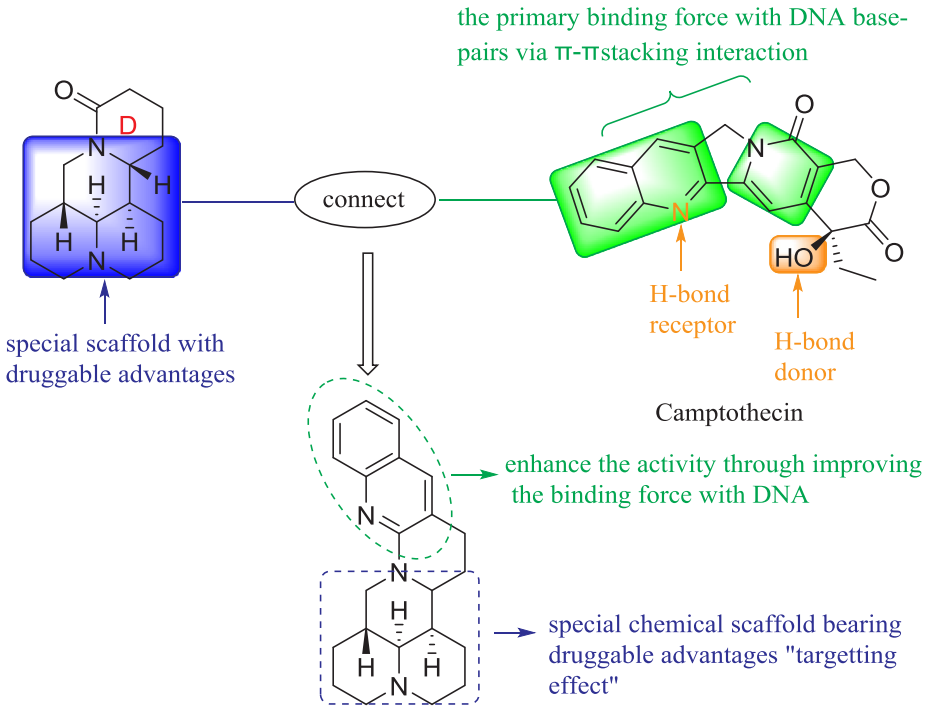

Fig. 2. The second modification strategy for the new compounds.