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Antitumor aporphine alkaloids from *Thalictrum wangii*

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ABSTRACT

Nine new isoquinoline alkaloids, including two proaporphine (**1–2**), three aporphine (**3–5**), two oxoaporphine (**6–7**), and two *seco*-bisbenzylisoquinoline (**8–9**), together with three known alkaloids (**10 − 12**) were isolated from the whole plant of *Thalictrum wangii*. Their structures were established on the basis of spectroscopic data. The antitumor activities of the isolated compounds were evaluated *in vitro* against glioma stem cells. Compounds **3–8** showed the cytotoxicity with IC_{50} values 15–20 μg/mL.

1. Introduction

Isoquinoline alkaloids, as a group of natural products, are widely distributed in the plant kingdom [1]. Most, if not all, isoquinoline alkaloids have shown significant medicinal value to the betterment of mankind [2,3], exhibiting anti-inflammatory [4], anti-tumor [5], antihypertensive [6], and antibacterial activities [7]. In fact, human use of isoquinoline alkaloids as drugs can be traced back to the last century, with representatives morphine as a painkiller and berberine for intestinal infections [8,9]. Recent investigations show the role of isoquinoline alkaloids in anticancer therapy [10,11], such as berberine (BBR) targeted inhibition of prostate cancer [12], tetrandrine (Tet) exhibited anti-proliferation activity against hepatoma cell [13], and berbamine (BBM) inhibit leukemia [14], lymphoma [15], myeloma and lung cancer [16,17].

Glioblastoma multiforme (GBM) is one of the most aggressive primary brain malignancies, and accounts for more than half of all gliomas, which are currently incurable and confer a poor prognosis [18-20]. Surveys data from the Australian Genomics and Glioma Treatment Database (AGOG) showed that GBM patients have a median survival of approximately 1 year, with only a minority of GBM patients surviving 2 years or more [21]. Furthermore, clinical management of standard care in patients with GBM, including surgical resection, adjuvant radiotherapy, chemotherapy, and molecularly targeted drugs [22–24], had no significant effect on overall survival [21]. With rapid increase in the incidence of GBM, it is imminent to develop effective chemotherapeutic drugs to alleviate the disease. Fortunately, many natural-product compounds, such as isoquinolines, have therapeutic potential to stem cells cancer-fighting [25–29].

Thalictrum wangii B. Boivin is a perennial Chinese medicinal plant indigenous to cold alpine of the Southern Tibet and the regions of Lijiang county. The Tibetan people used it as a folk anti-inflammating herb and antidote drug [30]. Furthermore, isoquinoline alkaloids are regarded as the main active compounds in this genus [31–33]. Enlightened by the diverse bioactivities and intriguing structures of isoquinoline alkaloids, investigation of *Thalictrum wangii* led to the isolation of new isoquinoline alkaloids (**1–9**) and three known analogues (Fig. 1); prodensiflorin B (**10**) [34], thalidine (**11**) [35], and 4-methoxyoxohernandaline (**12**) [36]. Herein, All the isolates were evaluated against glioma stem cells (GSC-3$^{\#}$). The new compounds **3–8** showed *in vitro* cytotoxicity with IC_{50} values at 15–20 μg/mL.

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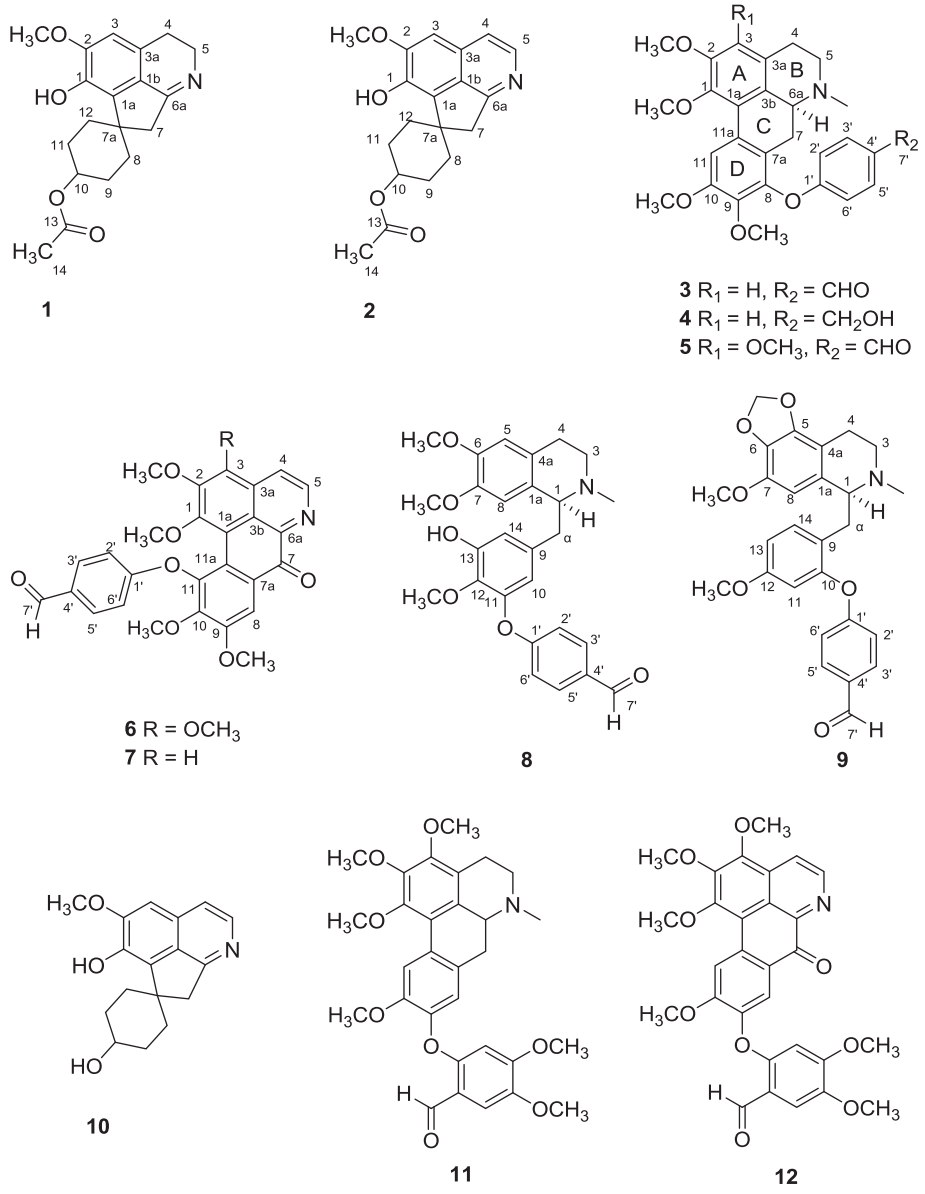

Fig. 1. Structure of compounds **1–12.**

2. Experimental

2.1. General experimental procedures

The optical rotations were obtained on a Jasco P-1020 automatic digital polarimeter. UV spectra were measured with a Shimadzu UV2401PC spectrometer. IR spectra were obtained on a Bruker FT-IR Tensor-27 infrared spectrometer (KBr pellets). NMR spectra were recorded on a Bruker DRX-600 and Bruker AMD-500 pectrometers, with tetramethylsilane as an internal standard. Unless otherwise specified, chemical shifts (δ) were expressed in ppm with reference to solvent signals. ESIMS and HRESIMS analyses were measured on Agilent 1290 UPLC/6540 Q-TOF mass spectrometer. Column chromatography (CC) was performed on silica gel (100–200 and 200–300 mesh, Qingdao Marine Chemical Co. Ltd., P.R. China), and MCI-gel CHP 20P (75–100 μm, Mitsubishi Chemical Co., Ltd). Sephadex LH-20 (GE Healthcare Bio-Sciences AB). Fractions were monitored by TLC (GF_{254}, Qingdao Marine Chemical Co., Ltd., P. R. China) and spots were visualized by Dragendorff's reagent.

2.2. Plant material

The whole plants of *T. wangii* were collected from Lijiang County of Yunnan Province, China. The plant was identified by Jun Zhang (Kunming Institute of botany, Chinese Academy of Science). A voucher specimen (No. 20161103) was deposited in Kunming Institute of Botany, Chinese Academy of Science.

2.3. Extraction and isolation

The milled dried whole plant (13 kg) of *Thalictrum wangii* was extracted with 90% methanol (25 L × 3, 3 h each) under reflux conditions, and the solvent was evaporated *in vacuum*. The residue was dissolved in 0.37% HCl and the solution was subsequently basified with 10% ammonia to pH 9–10. The basic solution was partitioned with ethyl acetate, affording a two-phase mixture including the aqueous phase and the ethyl acetate phase. Then, the ethyl acetate fraction (130 g) was dissolved in methanol, and the resulting solution was subjected to column chromatography over silica gel eluting with $CHCl_3/CH_3OH$ (from 15:1–0:1) to afford six fractions (Fr. A to F). Then,