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Original article

Optical evodiamine derivatives: Asymmetric synthesis and antitumor activity

Zhen-Gang Li [1], Guo-Qiang Dong [1], Sheng-Zheng Wang, Zhen-Yuan Miao, Jian-Zhong Yao, Wan-Nian Zhang, Chun-Quan Sheng *

School of Pharmacy, Second Military Medical University, Shanghai 200433, China

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ABSTRACT

Evodiamine and its derivatives have an asymmetric center at the C13b position. Herein, isomers of evodiamine derivatives **2** and **3** were obtained by straightforward asymmetric total synthesis. Their inhibitory activities toward topoisomerases I and II and their cytotoxicities in cancer cell lines were evaluated. All the four isomers exhibited good to excellent antitumor potency and the (*S*)-isomers were generally more active than the (*R*)-isomers. The binding modes of (*S*)-**2** with topoisomerases I and II were also clarified by molecular docking.

1. Introduction

Natural products have played an important role in the discovery and development of clinically useful antitumor agents [1]. It is reported that 79.8% of the marketed antitumor agents are derived from natural products or their synthetic derivatives from the year 1981 to 2010 [2]. For example, vinblastine, vincristine, campthothecin derivatives (*e.g.* topotecan and irinotecan), etoposide and paclitaxel are widely used in current antitumor chemotherapy. Currently, natural products inspired novel antitumor drug discovery continues to be an active area of research interests [3]. Numerous antitumor natural products have been reported and several of them (*e.g.* flavopiridol and combretastin A4 phosphate) are under clinical evaluation.

Evodiamine is a quinazolinocarboline alkaloid isolated from the fruit of *Evodia rutaecarpa* Bentham. Evodiamine was reported to be a multi-targeting antitumor lead compound with cytotoxicity against various human cancer cell lines [4,5]. In our previous studies, topoisomerase I (Top1) was identified as one of molecular target of evodiamine by a structure-based virtual screening study [6]. Moreover, a number of evodiamine derivatives were designed and synthesized [7]. Several evodiamine derivatives, such as 3-fluoroevodiamine (**2**) and 10-hydroxylevodiamine (**3**), showed excellent antitumor activity against a variety of cancer cell-lines. Furthermore, in silico target identification in combination with biological assays confirmed that these highly active evodiamine derivatives acted by dual inhibition of topoisomerases I and II [7].

Chirality is a key feature of natural products, and stereochemistry is often important for a specific biological activity [8]. Evodiamine and its derivatives have an asymmetric center at the C13b position (Fig. 1). It is interesting to know the effects of the C13b chiral center on the antitumor activity. Herein, isomers of evodiamine derivatives **2** and **3** were obtained by asymmetric synthesis and their antitumor activity was investigated.

2. Experimental

Nuclear magnetic resonance (NMR) spectra were generated on a Bruker AVANCE300 and AVANCE500 spectrometer (Bruker Company, Germany), using $CDCl_3$ as the reference standard or DMSO-d_6. Chemical shifts (δ values) and coupling constants (J values) are expressed in ppm and Hz, respectively. ESI mass spectra were gathered on an API-3000 LC–MS spectrometer. TLC analysis was carried out on silica gel plates GF254 (Qindao Haiyang Chemical, China). Silica gel column chromatography was performed with Silica gel 60 G (Qindao Haiyang Chemical, China). Commercial solvents were used without any pretreatment.

* Corresponding author.
E-mail address: shengcq@hotmail.com (C.-Q. Sheng).
[1] These authors contributed equally to this article.

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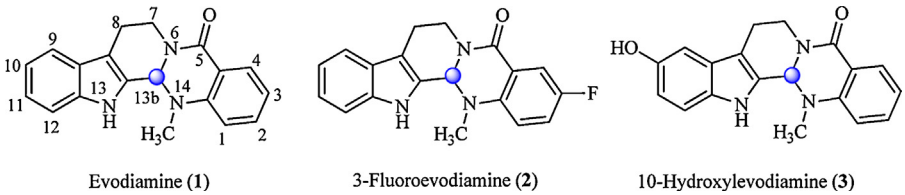


Fig. 1. Chemical structures of evodiamine and its derivatives.

Generally, the isomers of evodiamine derivatives **2** and **3** were prepared according to the method described in Scheme 1. The anilines **4a**-**b** were treated with $NaNO_2$ to yield diazkonium compounds **5a**-**b**. Hydrolysis of ethyl 2-oxopiperidine-3-carboxylate (**6**) gave the compound **7**. The key β-carboline intermediates **9a**-**b** were synthesized by reacting **5a**-**b** with **7**, followed by treating with HCOOH at reflux [9]. In the presence of $POCl_3$, intermediates **9a**-**b** were reacted with methyl 2-(methylamino)benzoate **10a**-**b** in anhydrous THF to afford the dehydroevodiamine derivatives **11a**-**b**. Finally, asymmetric catalytic hydrogenation of **11a**-**b** by RuCl[(*S*,*S*)-Tsdpen](p-cymene) or RuCl[(*R*,*R*)-Tsdpen](p-cymene) gave (*S*)-**2**, (*S*)-**12**, (*R*)-**2** and (*R*)-**12** using Noyori's procedure [10]. After removal of the protection group, compounds (*S*)-**3** and (*R*)-**3** were obtained. The absolute configuration of the isomers were assigned according to the previous reports [7,10].

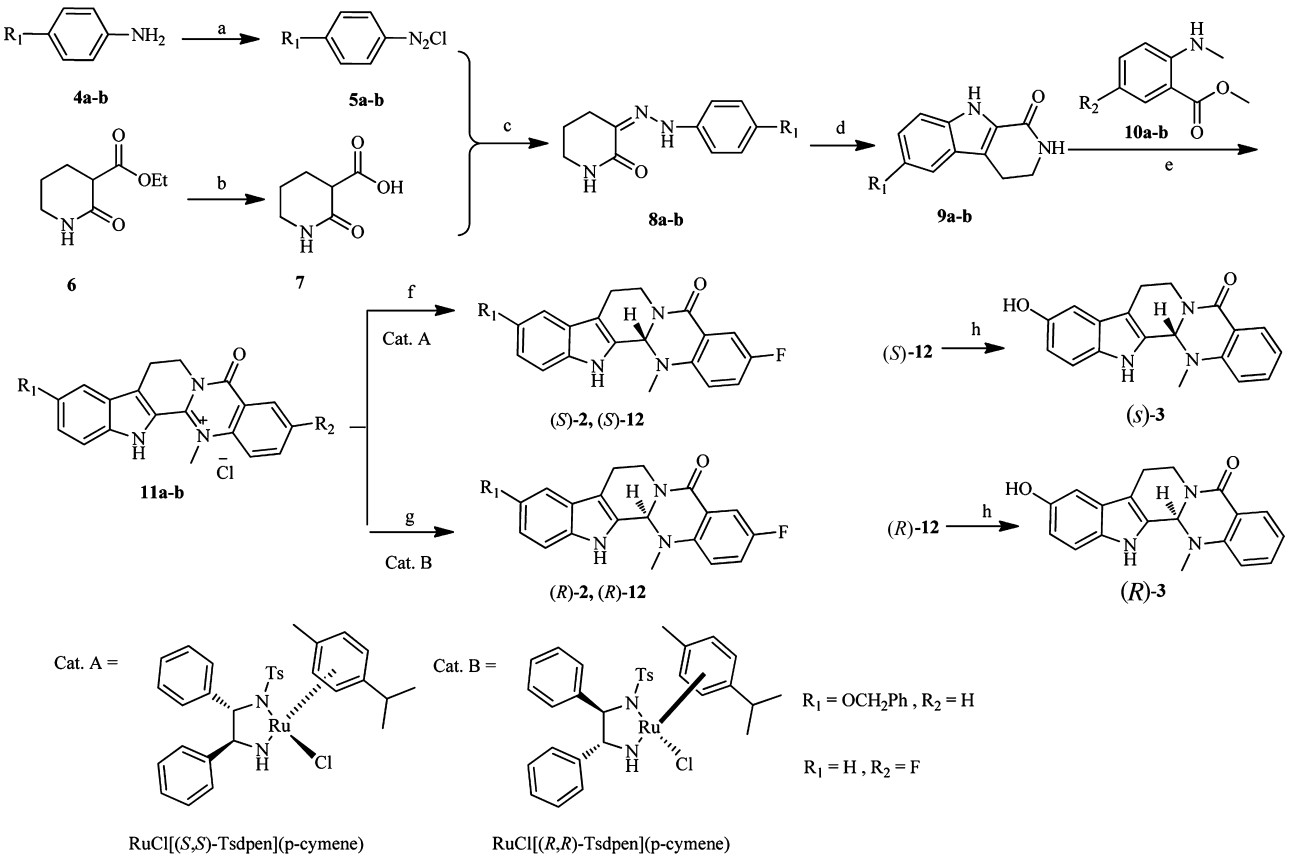
2.1. Synthesis of 3-fluorodehydroevodiamine (*11a*)

To a stirring solution of **9a** [7] (0.3 g, 1.6 mmol) in dry THF (20 mL), $POCl_3$ (0.22 mL, 2.4 mmol) was added, and the mixture was stirred under nitrogen atmosphere at 60 °C. After 40 min, methyl 5-fluoro-2-(methylamino)benzoate (0.45 g, 2.4 mmol) was added and the reaction mixture was stirred under reflux for 3 days. The mixture was diluted with water (100 mL) and then extracted with EtOAc (3× 100 mL). The combined organic layers were washed with saturated sodium chloride solution (3× 100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (gradient CH_2Cl_2:MeOH = 100:2–100:5) to give compound **11a** as a yellow solid (0.29 g, yield 55%). ^{1}H NMR (DMSO-d_6, 600 MHz): δ 3.32 (t, 2H, J = 6.6 Hz), 4.04 (s, 3H), 4.64 (t, 2H, J = 6.6 Hz), 7.25 t, 1H, J = 7.5 Hz), 7.51 (t, 1H, J = 7.5 Hz), 7.70 (d, 1H, J = 8.2 Hz), 7.86 (d, 1H, J = 8.2 Hz), 8.01–8.05 (m, 1H), 8.09 (dd, 1H, J = 7.8 Hz, 3.1 Hz), 8.28 (dd, 1H, J = 9.0 Hz, 3.9 Hz), 12.78 (s, 1H). MS (ESI, positive) m/z calcd. for $C_{19}H_{15}FN_3O^+$ (M): 320.34; found: 320.12.

The synthetic method for compound **11b** was similar to that of compound **11a**.

2.2. Synthesis of (S)-3-fluoroevodiamine ((S)-*2*)

To a stirred solution of **11a** (49 mg, 0.14 mmol) and RuCl[(*S*,*S*)-Tsdpen](p-cymene) (4 mg, 6 mmol%) in DMF (2.5 mL) was added



Scheme 1. Synthetic routes of the target compounds. Reagents and conditions: (a) $NaNO_2$, hydrochloric acid, H_2O, 0–5 °C, 2 h, yield 90%; (b) KOH, H_2O, r.t., 12 h, yield 93%; (c) r.t., 10 h, yield 85%; (d) HCOOH, reflux, 0.5 h, yield 55%–59%; (e) $POCl_3$, THF, reflux, 3 days, yield 55%; (f) Cat. A, HCOOH:Et_3N (5:2), 0 °C, 8 h, yield 78%–87%; (g) Cat. B, HCOOH:Et_3N (5:2), 0 °C, 8 h, yield 84%; (h) 10% Pd/C, H_2, DMF, r.t., 12 h, yield 83%–87%.