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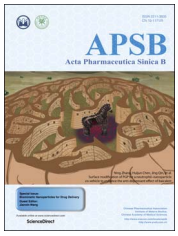

ORIGINAL ARTICLE

Synthesis and biological evaluation of novel tricyclic matrinic derivatives as potential anti-filovirus agents

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Abstract Twenty-six novel tricyclic sophoridinic and matrinic derivatives containing a common chlorinated benzene fragment were designed, synthesized and evaluated for their anti-ebolavirus (EBOV) activities. Structure–activity relationship analysis indicated: (i) 12*N*-dichlorobenzyl motif was beneficial for the activity; (ii) the chiral configuration at C5 atom might not affect the activity much. Among the target compounds, compound **7d** exhibited the most potent potency against EBOV with an IC_{50} value of 5.29 μmol/L and an SI value of over 37.8. Further *in vivo* anti-EBOV assay of **7d** identified its high effectiveness, and *in vivo* anti-MARV assay of **7d** suggested its inspiring broad-spectrum anti-filovirus activity. The results provided powerful information on further strategic optimization and development of this kind of compounds against filoviruses.

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1. Introduction

Ebola virus (EBOV), the most well known filamentous virus discovered, along with the marburg virus (MARV), constitutes the filovirus family. Members of the filovirus can cause an acute lethal hemorrhagic fever in humans.[1–4] The 2014–2015 EBOV breakout in West Africa caused more than 28,600 human infections and killed 11,300 people.[5,6] Worse still, new flare-ups have occurred several times after the EBOV breakout was over.[6] Several outbreaks of Marburg hemorrhagic fever were also reported,[7] the mortality rate for the 2004–2005 Angola outbreak even reached 90%.[8,9] Although outbreaks have predominantly occurred in central Africa to date, the potential for imported cases or bioterrorism in non-African countries cannot be ignored.[10] In light of this, a lot of efforts have been made to treat EBOV and MARV infections, disappointingly, currently there are still no approved therapeutics (small molecule or biologic agents) for prophylaxis or treatment available, so an approach to effectively treat the infection caused by filovirus is still highly desirable.

Over the past few years, our group has been dedicating to the search and discovery of new antiviral candidates from Tradition Chinese Medicine, such as matrine, sophocarpine and sophoridine (5*R*-matrine) as shown in Fig. 1, and then a compound library of tricyclic matrinic derivatives has been constructed.[11–20] In order to obtain the lead compounds against EBOV, the library was screened in a pseudotyped EBOV virus model (namely pHIV-EBOVGP-Fluc)[21] taking sertraline (Fig. 1) as the positive control.[22] The compound, methyl 12*N*-*p*-chlorobenzyl sophoridinate dihydrochloride (**1**, Fig. 1), displayed a good anti-EBOV activity with an IC_{50} value of 5.07 μmol/L and a CC_{50} value of 22.20 μmol/L.

Interestingly, compared with the structure of sertraline as displayed in Fig. 1, compound **1** also has a similar chlorinated benzene structural fragment at the 12-position, suggesting that chlorinated benzene fragment might be helpful for the potency against EBOV. Based on this strategy, in the present paper, the chlorinated benzene fragment as a pharmacophore was then retained on position 12, and a series of novel tricyclic 12*N*-substituted sophoridinic and matrinic derivatives were generated and evaluated for their activities against EBOV *in vitro*, taking compound **1** the lead. Furthermore, the *in vivo* anti-EBOV and anti-MARV efficacy of the representative compounds were carried out as well.

2. Results and discussion

2.1. Synthetic routes

Totally twenty-six new tricyclic sophoridinic and matrinic derivatives were prepared from commercially available sophoridine, matrine or sophocarpine with purity over 95% as the starting materials as described in Schemes 1–3, respectively. The synthesis of sophoridinic derivatives including methyl sopharidinates (**4a–c**) and sopharidinic acids (**5a–c**) was illustrated in Scheme 1. The key intermediate **3** was obtained by a two-step procedure of hydrolyzation and esterification with sophoridine as the staring material.[16] In the formation of compound **4a**, the condensation of **3** and 3′,4′-dichlorobenzaldehyde achieved a Schiff base, which was then reduced selectively by sodium triacetoxyborohydride (STB).[16] The desired products **4b** and **4c** were produced from the 12*N*-acylation or 12*N*-sulfonylation of **3** with the corresponding benzoyl chloride or benzenesulfonyl chloride with yields of 55% and 57%, respectively. Products **5a–c** were obtained *via* hydrolysis of **4a–c** in 3 mol/L HCl with yields of 54–55%.

The synthesis of matrinic derivatives including methyl matrinic butyrate compounds (**7a–d**) and matrinic butyric acids (**8a–c**) was illustrated in Scheme 2. The key intermediate methyl butyrate **6** was acquired from matrine through hydrolysis, and methyl esterification in an over yield of 85% as reported previously.[13] The target compounds **7a–d** were acquired from the alkylation, acylation or sulfonylation on the 12 N atom of **6** with yields of 50–62%. The hydrolysis of **7a–c** produced **8a–c** with yields of 55–60% in 3 mol/L HCl.

Scheme 3 depicted the synthesis of matrinic acetic acid derivatives, including methyl matrinic acetates **10a–d** and matrinic acetic acids **11a–c** and **15a–f**. The intermediate **9** was acquired *via* the oxidation and esterification reaction using $KMnO_4$ as an oxidizing agent in acidic condition from sophocarpine.[13] The alkylation, acylation or sulfonylation on the 12 N atom of **9** achieved the target compounds **10a–d** with yields of 45–54%. Compounds **11a–c** were gained from the hydrolysis of **10a–d** in a 48–55% yield in 3 mol/L HCl. Dess-Martin oxidation of commercially available phenethylalcohols or phenylpropanols **12a–f** generated key intermediates **13a–f** as phenylacetaldehydes or phenylpropion aldehydes,[23] which were then condensed with **9** in alkaline condition followed by a selective reduction with STB to give intermediates **14a–f**. The final products **15a–f** were obtained *via* acidic hydrolysis of **14a–f** with yields of 42%–50%.

All the final products were purified by flash column chromatography on silica gel with CH_2Cl_2/CH_3OH as the eluents.

2.2. SAR analysis for anti-EBOV activity

All the target compounds were measured for their *in vitro* anti-EBOV activities in human embryonic kidney (HEK) 293 T cells. The potency against EBOV of each tested compound was evaluated by the combination of its IC_{50} and selectivity index (SI) value as the important therapeutic indication. The structures and anti-EBOV activities of all target compounds were displayed in Table 1.

First, mono-chlorobenzene or di-chlorobenzene group was selected as an active substituent at the 12-position, a series of chlorobenzoyl, chlorobenzyl or chlorobenzenesulfonyl sophoridinic derivatives (**4a–c** and **5a–c**) were then generated. As displayed in Table 1, methyl sopharidinates **4a–c** gave 4–29 times lower IC_{50} values than their counterparts sopharidinic acids **5a–c**, consistent with our previous report.[11] Interestingly, among the methyl sopharidinates, 3′,4′-dichlorobenzyl **4a** and *p*-chlorobenzenesulfonyl **4c**, with IC_{50} values of 2.68 and 2.90 μmol/L respectively, displayed comparably higher anti-EBOV activities than *p*-chlorobenzyl **1** and *p*-chlorobenzyl **4b**. Similarly, among the sopharidinic acids, 3′,4′-dichlorobenzyl **5a** and *p*-chlorobenzenesulfonyl **5c** displayed obviously higher anti-EBOV activities than *p*-chlorobenzoyl **5b**. These results hinted that 3′,4′-dichlorobenzyl and *p*-chlorobenzenesulfonyl might be more favorable 12*N*-substitutions than *p*-chlorobenzyl and *p*-chlorobenzoyl groups.

Then, SAR was moved on the effect of chiral configuration on the 5-carbon atom, a group of matrinic compounds with 5*S*-configuration (**7a–d** and **8a–c**) were generated correspondingly. As expected, an obvious advantage of methyl matrinic butyrates over their matrinic butyric acids was revealed in Table 1, **7a–d** gave much higher potencies than their counterparts **8a–c**. *p*-Chlorobenzenesulfonyl **7c** and 3′,4′-dichlorobenzyl **7d** displayed the most potent activities with IC_{50} values of 8.23 and 5.29 μmol/L and SI values of 24.3 and over

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