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The semi-synthesis of novel andrographolide analogues and anti-influenza virus activity evaluation of their derivatives

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ABSTRACT

Two novel andrographolide analogues with the structural motif of $\Delta^{8,17}$-alkene *exo*-to-*endo* isomerization, **AI78** and **AI89**, were semi-synthesized firstly. Two series of derivatives were designed and synthesized based on the synthetic pathway (including series I: olefin isomerizing to endocyclic $\Delta^{8,9}$ and series II: olefin isomerizing to endocyclic $\Delta^{7,8}$). The anti-influenza virus activity in vitro for all derivatives was evaluated. Among the compounds synthesized, compound **38** with benzyl amino group showed the greatest potency against H3N2 and was approximately 1.5-fold more potent than that of Lianbizhi, andrographolide analogue used clinically in China. Adamantyl derivative, **43**, presented the lowest toxicity, with a higher TC_{50} and TI values than Lianbizhi. The structure–activity relationships studies of the synthetic analogues indicated that the endocyclic $\Delta^{7,8}$-double bond is preferable for anti-viral effect. Furthermore, the introduction of the fatty amino attached to the rigid skeleton at C-17 is beneficial for activity.

Influenza viruses are respiratory pathogens that affect humans and are responsible for substantial morbidity, mortality and decreased productivity around the world.[1–3] To date, only two classes of drugs are available for clinical use: M2 ion channel blockers (amantadine and rimantadine) and neuraminidase inhibitors (zanamivir and oseltamivir).[4–6] Nevertheless, the utility of both groups of compounds has been limited by significant drawbacks and emergence of resistant viral strains. Therefore, there is an urgent need to develop novel, effective antiviral agents against the influenza virus.

Andrographolide (Fig. 1) is one of the major labdane diterpenoids isolated from *Andrographis paniculata*.[7,8] Andrographolide exhibits extensive therapeutic potential for a wide range of diseases.[9] Andrographolide and its derivatives, such as Chuanhuning, Yanhuning and Lianbizhi (Fig. 1) have been used clinically for treating paediatric pneumonia and upper respiratory infections for decades.[10–14]

In view of the great therapeutic value, various semi-synthetic andrographolide analogues have been developed and evaluated in order to search for a better candidate compound compared to the parent molecule.[15–17] Most structure modifications were focused on the functionalization of 3,14,19-hydroxyl groups. Meanwhile, such epoxidation at $\Delta^{8,17}$, C-15 substitution with alkylidenyl group and $\Delta^{12,13}$-alkene isomerization were also main modifying method.[18]

In our previous work, **AI78** and **AI89** were obtained by microbial transformation (Fig. 2).[19] The structural motif of $\Delta^{8,17}$-alkene *exo*-to-*endo* isomerization in them never appeared in other andrographolide analogues. The key moiety in **AI78** and **AI89** brought a novel structural lead for modification and widened the structural diversity of andrographolide.

In this paper, we completed the semi-synthesis of **AI78** and **AI89** for the first time. Eighteen derivatives were designed and synthesized based on the semi-synthetic method. All of the compounds were bio-assayed in vitro to determine their activities against influenza A (H3N2).

The synthetic plan for the synthesis of **AI78** and **AI89** is described in Scheme 1. Starting from widely available andrographolide, compound **1** was prepared in high yield using a protocol modified from literature.[20] In view of the two allylic reactive sites around 8, 17-olefin, we choose SeO_2/cumene hydroperoxide (CHP) system to construct the pivotal scaffold, the 17-hydroxyl substituted allylic alcohol moiety, in **AI78** and **AI89** in one step. Subsequent hydrolysis with 2 N NaOH afforded the target compounds **AI78** and **AI89**, respectively. The spectral and physical properties of the synthetic samples are identical with those reported for the biotransformation products.[19]

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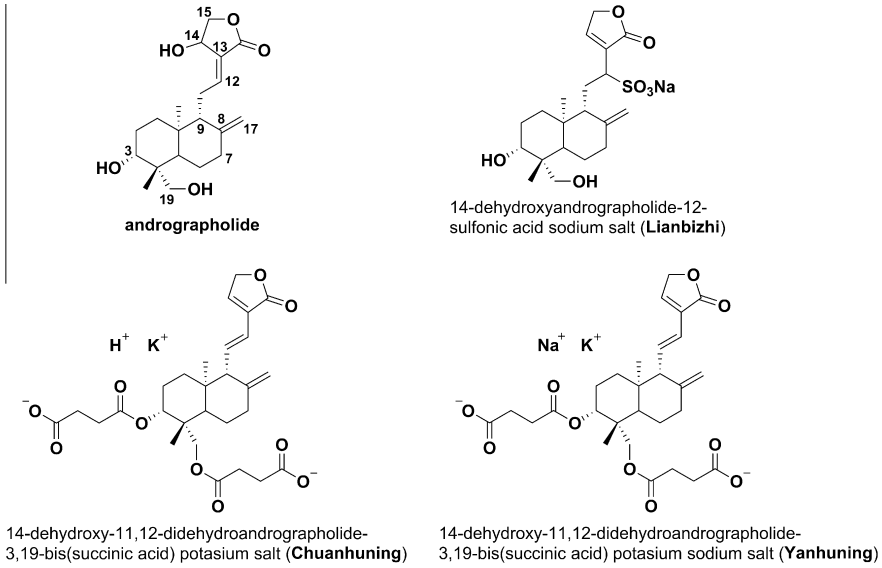


Figure 1. Structures of andrographolide and related derivatives.

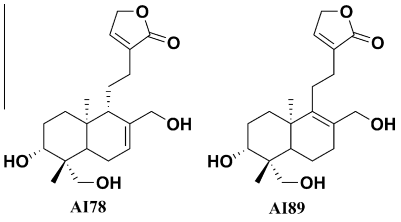


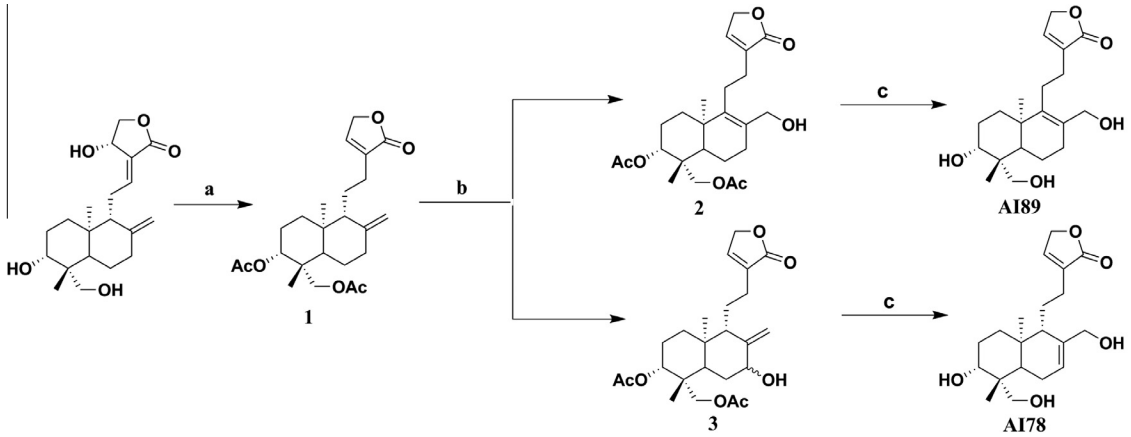
Figure 2. Structures of **AI78** and **AI89**.

Because **2** and **3** were two key intermeditates, the extensive investigations were carried out to define the optimal reaction conditions in the critical SeO_2 oxidation step (Table 1). During the course of our initial investigation, treatment of **1** with different oxidation system such as SeO_2, SeO_2/TBHP and SeO_2/CHP in DCM at 35 °C for 12 h exclusively produces **3** in a range of 60–75% yield. Next, neither prolonging reaction time nor increasing the temperature changed the product species. When 1,2-dichloroethane (1,2-DCE) was used as solvent, the other desired product **2** was obtained along with **3** and the diol side product **4**. In light of these results, other reaction parameters were further examined. Finally, the best results were obtained using SeO_2/CHP in 1,2-DCE at 60 °C for 24 h to deliver **2** and **3** in 41.7% and 49.5% yield, respectively (entry 10).

The structures of **2** and **3** were established by ^{1}H NMR and ^{13}C NMR spectroscopy. In the ^{1}H NMR spectrum, the terminal olefinic protons and 7-oxygenated methine signals appeared at δ_H 5.13, 4.77 and 4.39 in **3**, respectively. Whereas, no terminal double bond signals were observed in the ^{1}H NMR spectrum of **2**. The presence of two allylic oxygenated methylene protons was determined by the triplet at δ_H 4.17 for **2**. The ^{13}C NMR spectrum displayed four olefinic carbon signals for **2** and **3**, respectively. The olefinic resonance signal appeared at δ_C 110.28 in **3** revealed the presence of a terminal double bond.

In the process of the semi-synthesis of **AI89**, the hydroxyl group should be installed at C-9 to furnish **5** according to the mechanism of the SeO_2 oxidation.[21] Surprisingly, 8, 17-double bond isomerization straightly gave **2**. It was presumed that **5** probably isomerized to the more stable **2** under the reaction conditions (Scheme 2).

Previous studies of the structure–activity relationships (SARs) of andrographolide have revealed that the α-alkylidene-γ-butyrolactone moiety of andrographolide plays a crucial role in the activity profile.[15] However, the structural modification involved in the 8, 17-double bond *exo*-to-*endo* isomerization and 17-substituted



Scheme 1. Reagents and conditions: (a) (i) $Ac_2O/ZnCl_2$, rt, 91.8%; (ii) $NaBH_4$, MeOH, rt, 65%; (b) SeO_2/CHP, 1, 2-DCE, for **2**: 41.7%; for **3**:49.5%; (c) 2 N NaOH, EtOH, reflux, for **AI78**: 97.8%; for **AI89**: 95.8%.