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Two Series of Synthetic Territrem B Analogues and their Biological Activities

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Abstract: Two series of territrem B analogues (**6**, **11**) were designed and synthesized from jujubogenin **2**. Compound **11c** inhibited AChE with the ratio of 70% at 10^{-4} mol/L. Compounds **5a**, **5b, 6a** and **11b** showed moderate cytotoxicity on cultured KB cells at 10^{-6} mol/L. Compounds **5c** and **6b** alleviated injury arising from oxygen-glucose deprivation (OGD).

Keywords: Territrem B analogues, acetylcholinesterase (AChE) inhibitor, cytotoxicity on KB cells, oxygen-glucose deprivation (OGD).

Acetylcholinesterase (AChE) inhibitors have become an important strategy for preventing and treating Alzheimer's disease (AD). To disclose more potential AChE inhibitors based on territrem B (**1**) (**Figure 1**), known as a new leading compound because of its potent AChE inhibitory activity (IC_{50}=7.8 nmol/L) yet rare from natural source[1~5], we conduct a series of investigations on the synthesis and biological evaluation of territrem B analogues. Previous preparation of its analogues with 2-en-1-one pharmacophore had afforded some active compounds with 50% inhibition at 10 μmol/L[6]. To further mimic the structure of **1**, we designed and synthesized two more series of territrem B analogues **6** and **11** containing an eight-bond linkage and a ten-bond linkage between the two pharmacophores of olefine ketone and aromatic ring starting from jujubogenin **2** enlightened by Chen's choking hypothesis[7].

Compound **3** was prepared from jujubogenin **2** (**Figure 1)** through four steps according to literature[6]. Then, oxidation of **3** with N-bromosuccinimide (NBS) under illumination following by treatment with substituted phenols, thiophenols, or arylamines to give corresponding esters, thiolesters, or amides **4** in 22.7~75.2% yield (**Scheme 1**)[8,9]. Compound **4** was treated with Li_2CO_3 in refluxed dimethylacetamide (DMAC) for 0.5 h to afford 2-en-ebesters, 2-en-ebethiolesters, or 2-en-ebeamides **5** in 28.3~83.9% yields[10]. Compound **5** was then oxidized with NBS in 1, 4-dioxane in the presence of $CaCO_3$ to

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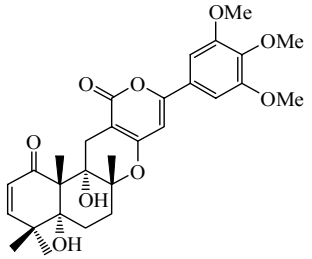
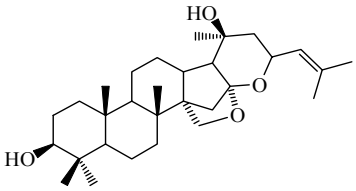
Figure 1

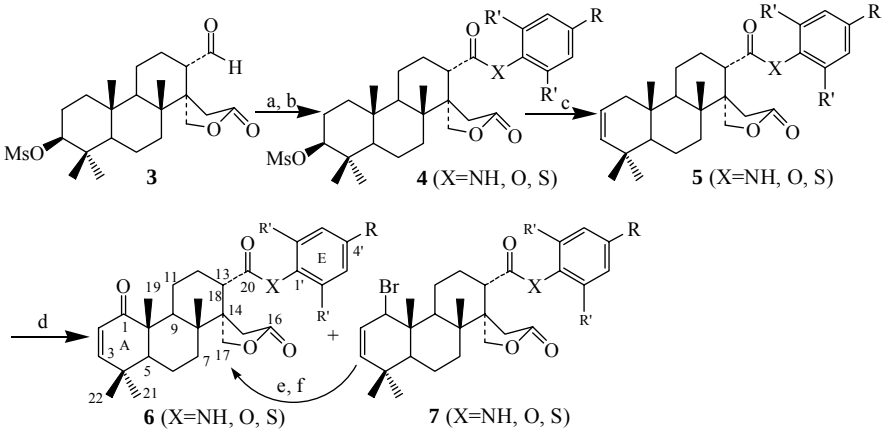


territrem B (**1**)



jujubogenin (**2**)

Scheme 1



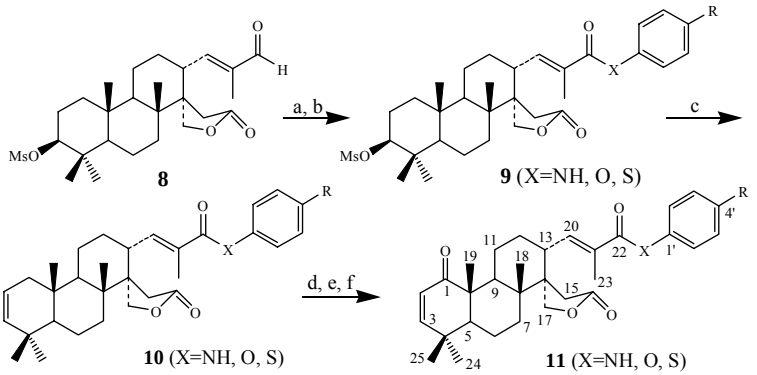
Reagents and conditions: a)NBS, CCl_4, hν, reflux 5 min; b) ArOH, ArSH or $ArNH_2$, Et_3N, r.t,1 h; c) Li_2CO_3, DMAC, reflux 0.5 h; d) $CaCO_3$, NBS, dioxane, H_2O, 50°, 6 h, hν; e) $CaCO_3$, H_2O, dioxane, reflux 5 h; f) PCC, CH_2Cl_2, reflux 6 h

form directly the target compounds 2-en-1-one-ebesters, 2-en-1-one-ebethiolesters, or 2-en-1-one-ebeamides **6** in 20~37% yield as well as by-products **7**[11], which could be transferred to **6** readily as shown in **Scheme 1**.

With the similar method, the other series of territrem B analogues 2,20-dien-1-one-ebesters, 2,20-dien-1-one-ebethiolesters, and 2,20-dien-1-one-ebeamides **11** and its derivatives could be prepared from α,β-unsaturated aldehyde **8** which was also from **2** (**Scheme 2**)[7]. The structures of **6**, **11** and the intermediates involved in **Scheme 1** and **Scheme 2** were confirmed by ^{1}H-NMR, ^{13}C-NMR and MS spectral data[12].

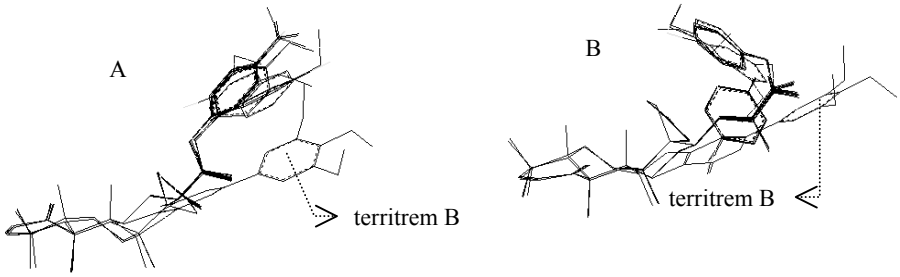
The target compounds and related intermediates were tested on various biological screening models, such as AChE inhibitory assay[13], cytotoxicity against cultured KB cells[14], protective activity on oxygen-glucose deprivation (OGD)-induced injury on rat primary neurons[15], and caspase-3 inhibitory assay[16], for evaluation of their biological activities. The results showed that 4′-chloro-2,20-dien-1-one-ebethiolester **11c** (X=S, R=Cl) inhibited 70% of AChE at 10^{-4} mol/L; 2-en-ebeamide **5a** (X=NH, R=R′=H), 4′-methoxy-2-en-ebester **5b** (X=O, R=OMe, R′=H)**,** 4′-chloro-2-en-1-one-ebeamide **6a**

Scheme 2



Reagents and conditions: a) NBS, CCl_4, hν, reflux 5 min; b) ArOH, ArSH or $ArNH_2$, Et_3N, r.t, 1 h; c) Li_2CO_3, DMAC, reflux 0.5 h; d) $CaCO_3$, NBS, dioxane, H_2O, 50°, 6 h, hν; e) $CaCO_3$, H_2O, dioxane, reflux 5 h; f) PCC, CH_2Cl_2, reflux 6 h

Figure 2



Superposition of compounds **6** and territrem B. Superposition of compounds **11** and territrem B.

(X=NH, R=Cl, R′=H), and 2,20-dien-1-one-ebester **11b** (X=O, R=H) showed moderate cytotoxicity on KB cells at 10^{-6} mol/L; while 2′,6′-dichloro-2-en-ebethiolester **5c** (X=S, R=H, R′=Cl) and 4′-methoxy-2-en-1-one-ebester **6b** (X=O, R=OMe, R′=H) showed statistically significant activity against OGD-induced injury on rat primary neurons compared with control at 0.1 μmol/L.

By superposition of the synthetic compounds (**6** and **11**) with territrem B based on their carbon atoms in the A and B rings with the SYBYL software, the corresponding aromatic E rings of **6** and **11** have been found to be apparently deviated from that in territrem B (**Figure 2**). This might be one of the factors of depressing the AChE inhibiton activities of these compounds. Therefore, subsequent modifications would focus on the synthesis of analogues possessing exactly the planar angle apart from the enone and the aromatic rings which were combined in the same molecule.

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