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Synthesis and evaluation of panaxatriol derivatives as Na^+, K^+-ATPase inhibitors

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ABSTRACT

Panaxatriol, a triterpene bearing a steroid-like structure similar to cardiac glycosides, was presumed to share the same bioactivity with cardiac glycosides, and may be a potential Na^+, K^+-ATPase inhibitor. In this paper, a series of panaxatriol derivatives were synthesized and evaluated for Na^+, K^+-ATPase inhibitory activities. The results of biological tests showed that more than half of the synthesized derivatives presented increased inhibitory activities compared with panaxatriol. Of these compounds, **13a** with a 3, 4-*seco* skeleton showed the most potent inhibitory activity, which was equal to that of the standard drug digoxin. To understand the binding mode of the most active compound, molecular docking study of **13a** with Na^+, K^+-ATPase was conducted. Therefore, **13a** may serve as a new lead compound for the development of novel Na^+, K^+-ATPase inhibitors.

Heart failure (HF) is a serious condition characterized by the incapability of the heart to supply sufficient blood flow to meet the body's needs.[1] Across the globe, about 26 million adults worldwide are living with HF.[2] However, survival rates remain poor and the five-year mortality rate for HF is nearly 50%.[3] Digitalis cardiac glycosides, such as digoxin, have been used as positive inotrope for the treatment of HF for more than 200 years. Their mechanism of action is digitalis reversibly inhibits the membrane bound alpha subunits of the Na^+, K^+-ATPase in cardiomyocytes.[4] Cardiac glycosides' aglycones, the steroidal structures, are considered to be responsible for their inhibitory activities.[5] Despite cardiac glycosides are extensively used in clinical therapy, its safety is still a big problem due to the life-threatening cardiac arrhythmias toxicity and the narrow therapeutic index.[6]

Panax ginseng has been widely used in Chinese medicine for the promotion of physical strength and resistance to diseases for thousands of years.[7] In addition, ginseng has been used for the treatment of HF,[8] and generally has a good safety profile and low adverse effects.[9,10] Ginsenosides are the main components of ginseng,[11] and have been reported to inhibit Na^+, K^+-ATPase.[12] However, ginsenosides were poorly absorbed in the gastrointestinal tract,[13] and were tend to be metabolized to their final aglycones by intestinal bacterial deglycosylation after oral administration.[14] The main aglycones of ginsenosides, such as protopanaxatriol (PPT) and protopanaxadiol, are dammarane-type tetracyclic triterpenes.

20(R)-panaxatriol (PT) is a pseudo-aglycone of PPT-type ginsenosides, and can be obtained by conversion of PPT during the acid hydrolysis.[15] PT was similar structurally to uzarigenin, which was a potent NKA inhibitor and 5αH-cardiotonic steroid.[16,17] Thus, we presumed that PT may share the same inhibitory activity towards Na^+, K^+-ATPase. To our best knowledge, the inhibitory activities of PT and its derivatives on Na^+, K^+-ATPase have not been reported yet. With the aim to search for novel Na^+, K^+-ATPase inhibitors with low toxicity and high affinity from natural resources, a series of PT derivatives were synthesized for Na^+, K^+-ATPase inhibitory activities evaluation (Fig. 1).

Panaxatriol was prepared by acid hydrolysis of total ginsenosides derived from the stem and leaf of *panax ginseng*. Whereas PT has three hydroxyl groups at C-3, C-6 and C-12, oxidation and etherification reactions were introduced to evaluate the role of hydroxyl groups as shown in Scheme 1. PT **1** was oxidized by equivalent Dess-Martin periodinane to produce 6-keto-PT **2** and 3-keto-PT **3**, which were further etherified by different haloalkanes to give the ethers **4a-4d** and **5a-5d**, respectively. Besides, treatment of **2** with ethoxycarbonyl isothiocyanate resulted in **4e**, which was followed by a ring closure reaction to afford **4f**.[18] The 3-keto-PT **3** was converted to 3, 12-keto-PT **6** in three steps (see supporting information). Oxidized compounds **7** and

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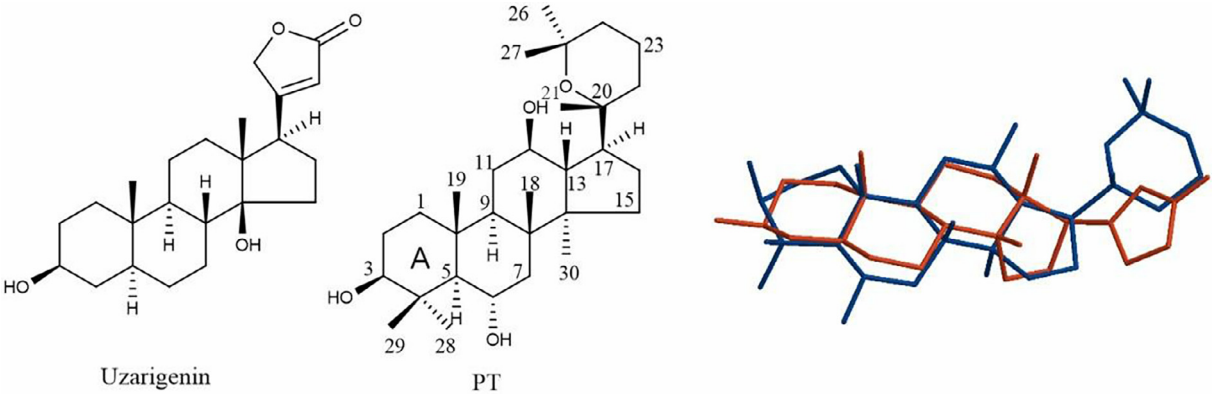
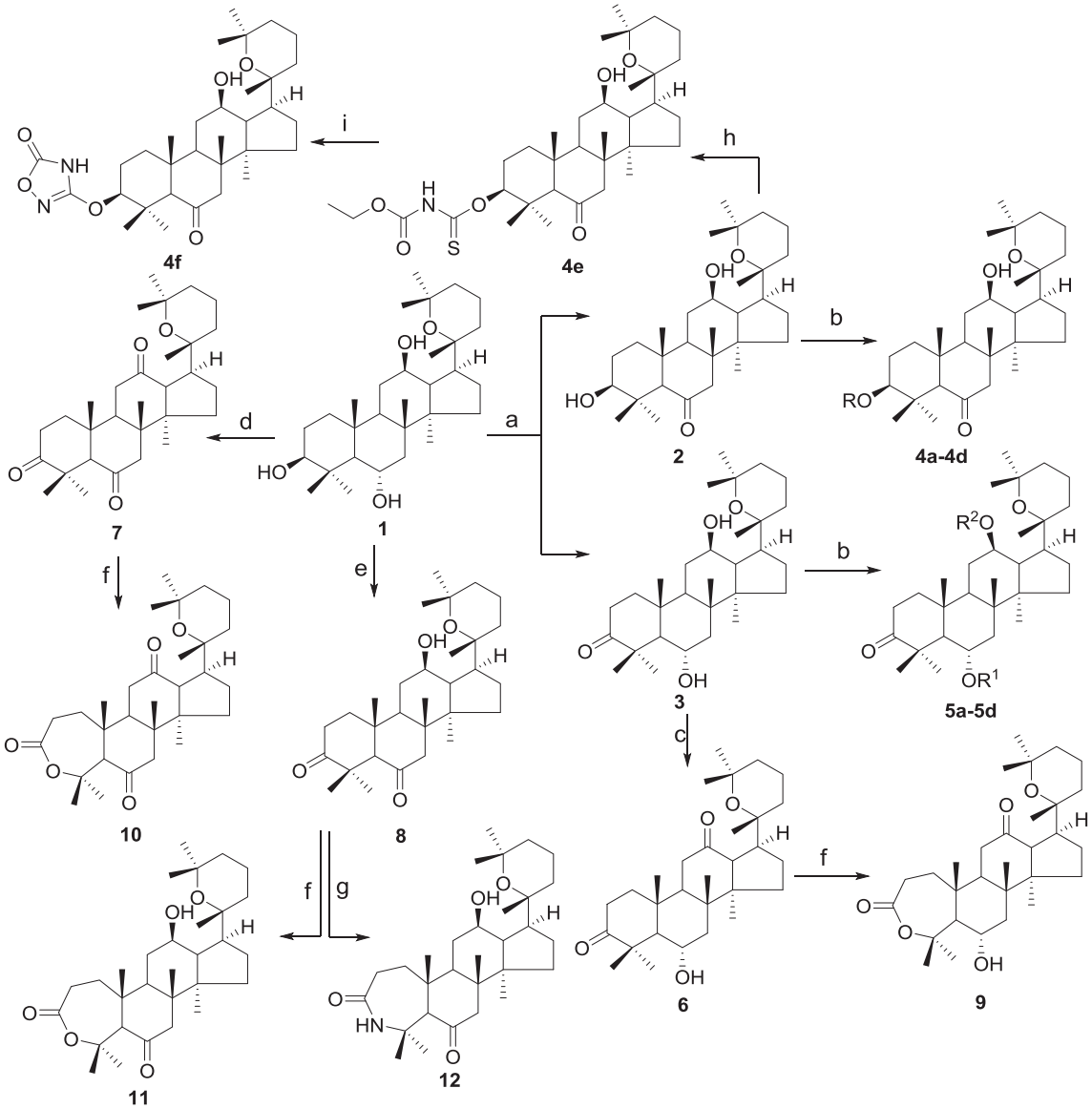


Fig. 1. Structures and stereo 3D stick model of the superposition of uzarigenin (red) and PT (blue).



Scheme 1. Reagents and conditions: (a) Dess-Martin Periodinane, DCM, rt, 3 h; (b) (i) NaH, THF, rt, 0.5 h; (ii) RBr, 70 °C, 12 h; (c) (i) Ac_2O, pyridine, reflux, 12 h; (ii) Jones reagent, 3 h; (iii) KOH, MeOH/H_2O, 1 h; (d) Jones reagent, rt, 12 h; (e) PCC, rt, 6 h; (f) m-CPBA, Li_2CO_3, DCM, 12 h; (g) (i) $NH_2OH{\cdot}HCl$, $NaHCO_3$, reflux, 8 h; (ii) $SOCl_2$, DCM, 0 °C, 1 h; (h) ethoxycarbonyl isothiocyanate, $CHCl_3$, 60 °C, 13 h; (i) $NH_2OH{\cdot}HCl$, LiOH, EtOH, rt, 5 h.