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# Inhibition of β-site amyloid precursor protein cleaving enzyme 1 and cholinesterases by pterosins via specific structure-activity relationship with a strong BBB permeability

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We extracted 15 pterosin derivatives from *Pteridium aquilinum* inhibiting β-site amyloid precursor protein cleaving enzyme 1 (BACE1) and cholinesterases involved in the pathogenesis of Alzheimer's disease (AD). (2R)-Pterosin B inhibited BACE1, acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) with IC50 of 29.6, 16.2 and 48.1 μM, respectively. Ki values and binding energies (kcal/ mol) between pterosins and BACE1, AChE and BChE corresponded to the respective IC50 values. (2R)-Pterosin B was a noncompetitive inhibitor against human BACE1 and BChE and a mixed-type inhibitor against AChE, binding to the active sites of corresponding enzymes. Molecular docking simulation of mixed-type and noncompetitive inhibitors for BACE1, AChE and BChE revealed the novel binding site-directed inhibition of the enzymes by pterosins and structure-activity relationship. (2R)-Pterosin B exhibited a strong BBB permeability with the effective permeability (Pe) of 60.3 × $10^{-6}$ cm/s on PAMPA-BBB. (2R)-Pterosin B and (2R,3R)-pteroside C significantly decreased the secretion of Aβ peptides from neuroblastoma cells overexpressing human β-Amyloid Precursor Protein at 500 μM. Conclusively, our study suggested that a few pterosins are potential scaffolds for multi-target-directed ligands (MTDLs) for AD therapeutics.

**Biography**

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