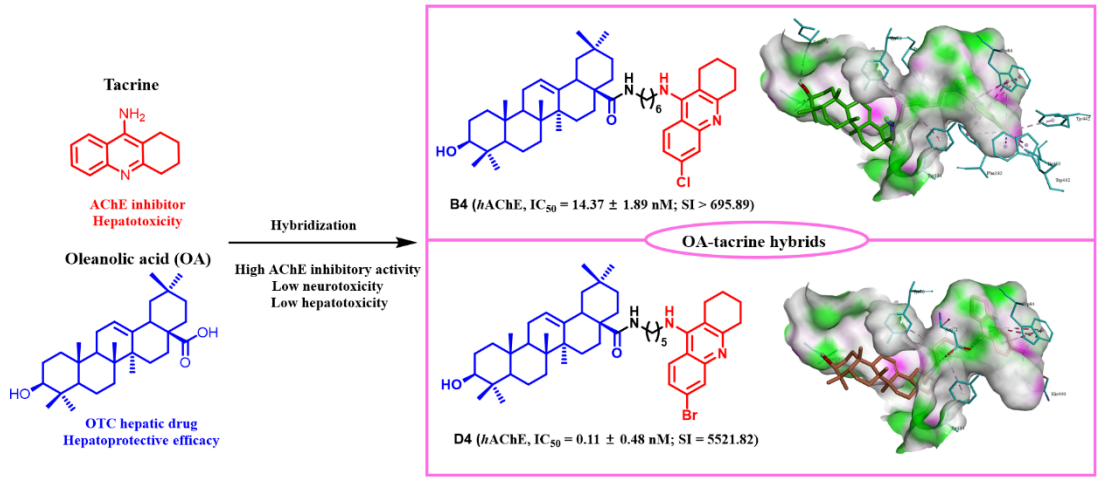
Design, synthesis and evaluation of OA-tacrine hybrids as cholinesterase inhibitors with low neurotoxicity and hepatotoxicity against Alzheimer's disease

ABSTRACT

A series of OA-tacrine hybrids with the alkylamine linker were designed, synthesized and evaluated as effective cholinesterase inhibitors for the treatment of Alzheimer's disease (AD). Biological activity results demonstrated that some hybrids possessed significant inhibitory activities against acetylcholinesterase (AChE). Among them, compounds B4 (*h*AChE, IC_{50} = 14.37 ± 1.89 nM; SI > 695.89) and D4 (*h*AChE, IC_{50} = 0.18 ± 0.007 nM; SI = 3374.44) showed excellent inhibitory activities and selectivity for AChE as well as low nerve cell toxicity. Furthermore, compounds B4 and D4 exhibited lower hepatotoxicity than tacrine in cell viability, apoptosis and intracellular ROS production for HepG2 cells. These properties of compounds B4 and D4 suggest that they deserve further investigation as promising agents for the prospective treatment of AD.



Keywords: Oleanolic acid, Tacrine, Cholinesterase inhibitors, Low-toxicity, Alzheimer's disease.