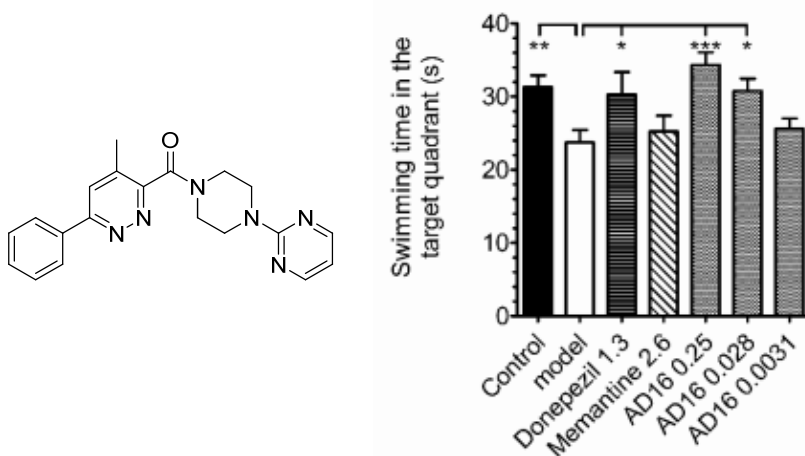


28AB-ISMS23 Identification of Anti-Neuroinflammatory Agent Effective in Alzheimer's Disease Animal Model

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Alzheimer's disease (AD), a devastating age-related neurodegenerative disorder, is in great need of disease-modifying therapies to slow or stop the neuronal loss and the associated cognitive decline. Current target-based drug discovery approach in the field of Alzheimer's disease seems to carry risks of high failure rate and low productivity. Regardless of the cause of AD, neuronal death and inflammation in the brain play key roles in AD progression and are directly related with neuroinflammation. Inspired by the important role of microglia-driven neuroinflammation played in the progress of AD, our anti-AD drug discovery approach was reoriented to the conventional phenotypic screenings approach to identify small molecules that can modulate neuroinflammation cycle with promising in vivo efficacy. With structural optimization of drug-like, we identified a novel neuroinflammatory inhibitor GIBH130 that could significantly suppress the expression of proinflammatory factors of interleukin 1beta (IL-1 β) and TNF- α in lipopolysaccharide (LPS)-stimulated microglia. It can remarkably counteract memory impairment and cognitive defects dose-dependently in three different Alzheimer animal models, including β amyloid-induced and APP/PS1 double transgenic Alzheimer animal models with age of 3 months and 8 months (effective dose: 0.25 mg/kg) and acquires the equivalent therapeutic effect in contrast with the top market drug donepezil (1.3 mg/kg) and memantine (2.6 mg/kg), and GIBH130 can effectively reduce approximately 60% A β deposition and protect neurons and synapses. It also could easily cross blood-brain barrier and had no cardiac toxicity or acute toxicity. Preclinical studies of proof-of-concept in industry-standard models of AD have been completed under the collaboration with South China Center for Innovative Pharmaceuticals.

Figure 1: Structure of GIBH130



Note: GIBH130 is Comparable with Donepezil and Memantine on 3 type of AD animal models, such as APP/PS1 double transgenic dementia mice at low dose.