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MEETING ABSTRACTS

TACRINE-SQUARAMIDE DERIVATIVES AS POTENT CHOLINESTERASE INHIBITORS

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Tacrine was the first drug to be approved for Alzheimer´s disease (AD) treatment, acting as a cholinesterase inhibitor. The neuropathological hallmarks of AD are amyloid-rich senile plaques, neurofibrillary tangles, and neuronal degeneration. Squaramides (SQ) are derivatives of squaric acid that are widely used in a variety fields of experties. Examples of small molecules with incorporated squaramide scaffold are Perzinfotel or Navarixin. Considering the relatively simple synthesis approach and other interesting properties (rigidity, aromatic character, H-bond formation) of squaramide motif, we developed 21 novel dimers amalgamating squaric acid with either tacrine, 6-chlorotacrine or 7-methoxytacrine representing various acetylcholinesterase inhibitors (AChEIs). All new derivatives were evaluated for their anti-cholinesterase activities, hepatotoxicity and screened to predict their ability to cross the blood-brain barrier. In ongoing study, we also demonstrate that a common butyrylcholinesterase variant confers resistance to tacrine, which can be overcome by using derivatives from tacrine-squaramaide family. These findings underscore the importance of genetic drug target variability for personalized medicine.

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Keywords: Alzheimer´s disease; squaramides; tacrine

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