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MEETING ABSTRACTS

PHENOTHIAZINE-TACRINE HETERODIMERS: PURSUING MULTITARGET DIRECTED APPROACH IN ALZHEIMER'S DISEASE

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Since 2002, no clinical candidate against Alzheimer's disease has reached the market; hence, an effective therapy is urgently needed. We followed the so-called "multitarget directed ligand" approach and designed 36 novel tacrine phenothiazine heterodimers which were *in vitro* evaluated for their anticholinesterase properties. The assessment of the structure–activity relationships of such derivatives highlighted compound **1dC** as a potent and selective acetylcholinesterase inhibitor with IC_{50} = 8 nM and **1aA** as a potent butyrylcholinesterase inhibitor with IC_{50} = 15 nM. Selected hybrids, namely, **1aC**, **1bC**, **1cC**, **1dC**, and **2dC**, showed a significant inhibitory activity toward τ(306–336) peptide aggregation with percent inhibition ranging from 50.5 to 62.1%. Likewise, **1dC** and **2dC** exerted a remarkable ability to inhibit self-induced $A\beta_{1-42}$ aggregation. Notwithstanding, *in vitro* studies displayed cytotoxicity toward HepG2 cells and cerebellar granule neurons; no pathophysiological abnormality was observed when **1dC** was administered to mice at 14 mg/kg (i.p.). **1dC** was also able to permeate to the CNS as shown by *in vitro* and *in vivo* models. The maximum brain concentration was close to the IC_{50} value for acetylcholinesterase inhibition with a relatively slow elimination half-time. **1dC** showed an acceptable safety and good pharmacokinetic properties and a multifunctional biological profile.

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Keywords: Alzheimer's disease; acetylcholinesterase; phenothiazine; tacrine; multitarget directed ligands

References

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