ChemMedChem 2015 vol.10 N11, pages 1863-1874

6-methyluracil derivatives as bifunctional acetylcholinesterase inhibitors for the treatment of Alzheimer's disease

Semenov V., Zueva I., Mukhamedyarov M., Lushchekina S., Kharlamova A., Petukhova E., Mikhailov A., Podyachev S., Saifina L., Petrov K., Minnekhanova O., Zobov V., Nikolsky E., Masson P., Reznik V.

Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

© 2015 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. Novel 6-methyluracil derivatives with ω-(substituted benzylethylamino)alkyl chains at the nitrogen atoms of the pyrimidine ring were designed and synthesized. The numbers of methylene groups in the alkyl chains were varied along with the electron-withdrawing substituents on the benzyl rings. The compounds are mixed-type reversible inhibitors of cholinesterases, and some of them show remarkable selectivity for human acetylcholinesterase (hAChE), with inhibitory potency in the nanomolar range, more than 10 000-fold higher than that for human butyrylcholinesterase (hBuChE). Molecular modeling studies indicate that these compounds are bifunctional AChE inhibitors, spanning the enzyme active site gorge and binding to its peripheral anionic site (PAS). In vivo experiments show that the 6-methyluracil derivatives are able to penetrate the blood-brain barrier (BBB), inhibiting brain-tissue AChE. The most potent AChE inhibitor, 3 d (1,3-bis[5--o-nitrobenzylethylamino)pentyl]-6-methyluracil), was found to improve working memory in scopolamine and transgenic APP/PS1 murine models of Alzheimer's disease, and to significantly decrease the number and area of β-amyloid peptide plaques in the brain. Head-AChE relief! In our efforts to identify compounds to treat Alzheimer′s disease, we found that 1,3-bis[--(substituted benzylethylamino)alkyl]-6-methyluracils bind to the active site gorge and peripheral anionic site of acetylcholinesterase (AChE). These compounds can cross the blood-brain barrier, and decrease the number and area of β-amyloid plaques in the brain.

http://dx.doi.org/10.1002/cmdc.201500334

Keywords

6-methyluracil, acetylcholinesterase, Alzheimer's disease, molecular modeling, reversible inhibitors