INHIBITION OF BACE-1 BY HYDROXYETHYLAMINE AND HYDROXYETHYLSULFIDE ISOSTERIC REPLACEMENTS

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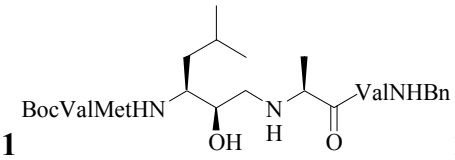
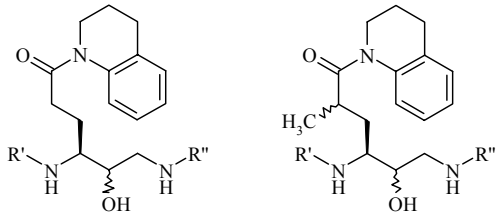
An abnormal extraneuronal deposition of the polypeptide β-Amyloid Peptide (Aβ) has an important role in the development of Alzheimer desease (AD). Aβ derives from the cleavage of a transmembrane protein APP by two proteases BACE-1 (β-site APP cleaving enzime) and γ-Secretase. BACE-1 inhibition, causing a reduction in the formation of the γ-Secretase substrate from which is obtained Aβ, is a promising therapeutic approach to prevent AD progression. BACE1 is a membrane-bound aspartyl protease and potent inhibitors have been synthesized.[1] In order to obtain new inhibitors we have synthesized as epimeric mixtures two structures containing the hydroxyehtylamine (HEA) and the hydroxyethylsulfide (HES) isosters. These molecules resulted BACE-1 inhibitors with nanomolar IC_{50} for the HEA mimetic (IC_{50}=120 nM) and micromolar IC_{50} for the HES compound (IC_{50}=1.85 μM).[2] Following these promising data stereoselective synthesis of the HEA and the HES transition-state mimetics were conducted and biological evaluation has shown that while the HES shows the usual *anti* stereopreference of aspartyl proteases the HEA *syn* isoster **1** resulted 100 times more active than the *anti* epimer (IC_{50}=14 nM vs IC_{50}=1.57 μM).



1 IC_{50}=14 nM (BACE-1)

These compounds were also tested on BACE-2, murine BACE, Pepsin and Cathepsin D. Molecular modelling studies have suggested that the HEA *syn* epimer has a binding mode different from the published crystal structure of the hydroxyethyl isoster.[3]
Aiming to reduce the peptidic character of these compounds we have also modified the P region of the HEA isoster by introducing a large hydrophobic residue in P_1 that should interact also with the S_3 pocket. This modification was introduced based on the observation that the S region of BACE is characterized by a very large hydrophobic pocket spanning the S_1-S_3 subsites.



[1] Varghese, J., Beck, J.P., Bienkowski, M.J., Sinha, S., Heinrikson, R.L., *J. Med. Chem.* **2003**, *46*, 4625
[2] Rizzi, L.; Romeo, S., *Letters in Drug Design & Discovery*, **2005**, *2*, 184
[3] Hong, L. Turner III, R.T., Koelsch, G., Shin, D., Ghosh, A.K., Tang, J.,*Biochem.*, **2002**, *41*, 10963