Simple Structure-Based Approach for Predicting the Activity of Inhibitors of Beta-Secretase (BACE1) Associated with Alzheimer's Disease, Research Article

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Beta-site amyloid precursor protein cleaving enzyme-1 (BACE1) is a target of interest for treating patients with Alzheimer's disease (AD). Inhibition of BACE1 may prevent amyloid-ß (Aß) plaque formation and the development or progression of Alzheimer's disease. Known BACE1 inhibitors were analyzed using computational chemistry and cheminformatics techniques to search for quantitative structure− activity relationships (QSAR). A remarkable relationship was found with only two simple descriptors with a square of the linear correlation coefficient r^2 of 0.75. The main descriptor is the number of hydrophobic contacts in the range 4−5 Å between the atoms of the ligand and active site. The other descriptor is the number of short (<2.8 Å) hydrogen bonds. Our approach uses readily available structural data on protein- inhibitor complexes in the Protein Data Bank (PDB) but would be equally applicable to proprietary structural biology data. The findings can aid structure-based design of improved BACE-1 inhibitors. If an inhibitor has less observed activity than predicted by our correlation, the compound should be retested because the first assay may have underestimated the compound's true activity.

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