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Research Article

Pharmacophore based 3D-QSAR modeling, virtual screening and docking for identification of potential inhibitors of β-secretase

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ABSTRACT

The enzyme β-secretase-1 is responsible for the cleavage of the amyloid precursor protein, a vital step in the process of the formation of amyloid-β peptides which are known to lead to neurodegeneration causing Alzheimer's disease. Challenges associated with toxicity and blood brain permeation inability of potential inhibitors, continue to evade a successful therapy, thus demanding the search and development of highly active and effective inhibitors. Towards these efforts, we used a ligand based pharmacophore model generation from a dataset of known inhibitors whose activities against β-secretase hovered in the nano molar range. The identified 5 feature pharmacophore model, AHHPR, was validated via three dimensional quantitative structure activity relationship as indicated by r^2, q^2 and Pearson R values of 0.9013, 0.7726 and 0.9041 respectively. For a dataset of compounds with nano molar activity, the important pharmacophore features present in the current model appear to be similar with those observed in the models resulting from much wider activity range of inhibitors. Virtual screening of the ChemBridge CNS-Set™, a database having compounds with a better suitability for central nervous system based disorders followed by docking and analysis of the ligand protein interactions resulted in the identification of eight prospective compounds with considerable diversity. The current pharmacophore model can thus be useful for the identification, design and development of potent β-secretase inhibitors which by optimization can be potential therapeutics for Alzheimer's disease.

1. Introduction

β-secretase (BACE1), a membrane associated aspartate protease is one of the most important protein targets for the treatment of Alzheimer's disease (Kandalepas and Vassar, 2012; Ghosh et al., 2012, 2008; Kwak et al., 2011; Yan and Vassar, 2014). Inhibition of BACE1 can lead to cessation of the formation of β-amyloid (Aβ) peptide in Alzheimer's disease (AD) (Kwak et al., 2011; Yan and Vassar, 2014; Ghosh et al., 2008). The development of β-secretase inhibitors being pursued for more than a decade has still not resulted in an effective therapy (Ghosh et al., 2012). However, steady progress in this field, has led to the development of inhibitors that show a wide range of activities, from nano to micro molar. Gene knock-out studies, highlight the advantage of the inhibition of β-secretase as a therapeutic intervention as it only results in minor physiological consequences (Luo et al., 2003; Roberds et al., 2001). Therefore, the development of inhibitors for β-secretase has been a valid therapeutic strategy towards the drug discovery efforts for AD.

Numerous studies resulted in the accumulation of large amount of experimental data in the form of identified potential inhibitors from several research groups (Kaller et al., 2012; Dineen et al., 2012; Weiss et al., 2012; Rueeger et al., 2012; Cole et al., 2008, 2006; Fobare et al., 2007; Swahn et al., 2012; Malamas et al., 2010a, 2010b, 2011; Nowak et al., 2010; Tresadern et al., 2011; Huang et al., 2012; Zuo et al., 2005; Niu et al., 2012). This repository of the existing inhibitors and their activity can be used for further understanding the common feature pharmacophore models for the identification of new lead compounds as well as optimization of the existing leads for enhanced activity and selectivity. Previous ligand based pharmacophore modeling studies on BACE1 identified the important features necessary for BACE1 inhibitors using data sets of compounds from a wide data range of activity, 0.01 μM to 140 μM (Zuo et al., 2005; John et al., 2011). Modeling studies from these datasets resulted in the identification of pharmacophores with features DHHPR (John et al., 2011), AADH (Niu et al., 2012) and AHH (Zuo et al., 2005) etc., containing hydrogen bond

Abbreviations: BACE1, β-secretase; AD, Alzheimer's disease; Aβ, amyloid-β; BBB, blood brain barrier; PDB, protein data bank; rmsd, root mean square deviation; IC_{50}, inhibitory concentration.

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acceptor (A), hydrogen bond donor (D), positive ionizable (P), ring aromatic (R) and hydrophobic features (H) as predominant features (Niu et al., 2012; John et al., 2011).

In the current study we aspired to build and explore the common feature pharmacophore hypothesis from BACE1 inhibitors with an activity range of 1 nm to 1000 nM to understand the distinct contributing features for their high potency. Typically the selection of known inhibitors, for relating quantitatively the structure and activity, covers a range of at least one, two or three logarithmic units of activity (Veerasamy et al., 2011). The nanomolar range of chosen inhibitors falls within one order of magnitude. Thus, we have employed this approach to identify and explore the contributing features of inhibitors in the sub micro molar range (<1 μM) with a dataset of reported BACE1 inhibitors. This order of magnitude of activity data may be useful in identifying the most critical features necessary for the identification of highly specific BACE1 inhibitors.

Further, using structural alignment docking followed by pharmacophore based QSAR generation, the field distributions of the various features in the pharmacophore models were analyzed using partial least square (PLS) factor analysis as a step towards validation of the identified pharmacophore model. The common features of the dataset compounds were aligned with the pharmacophore features and the resulting pharmacophore model was used for virtual screening of ChemBridge CNS-Set™ database.

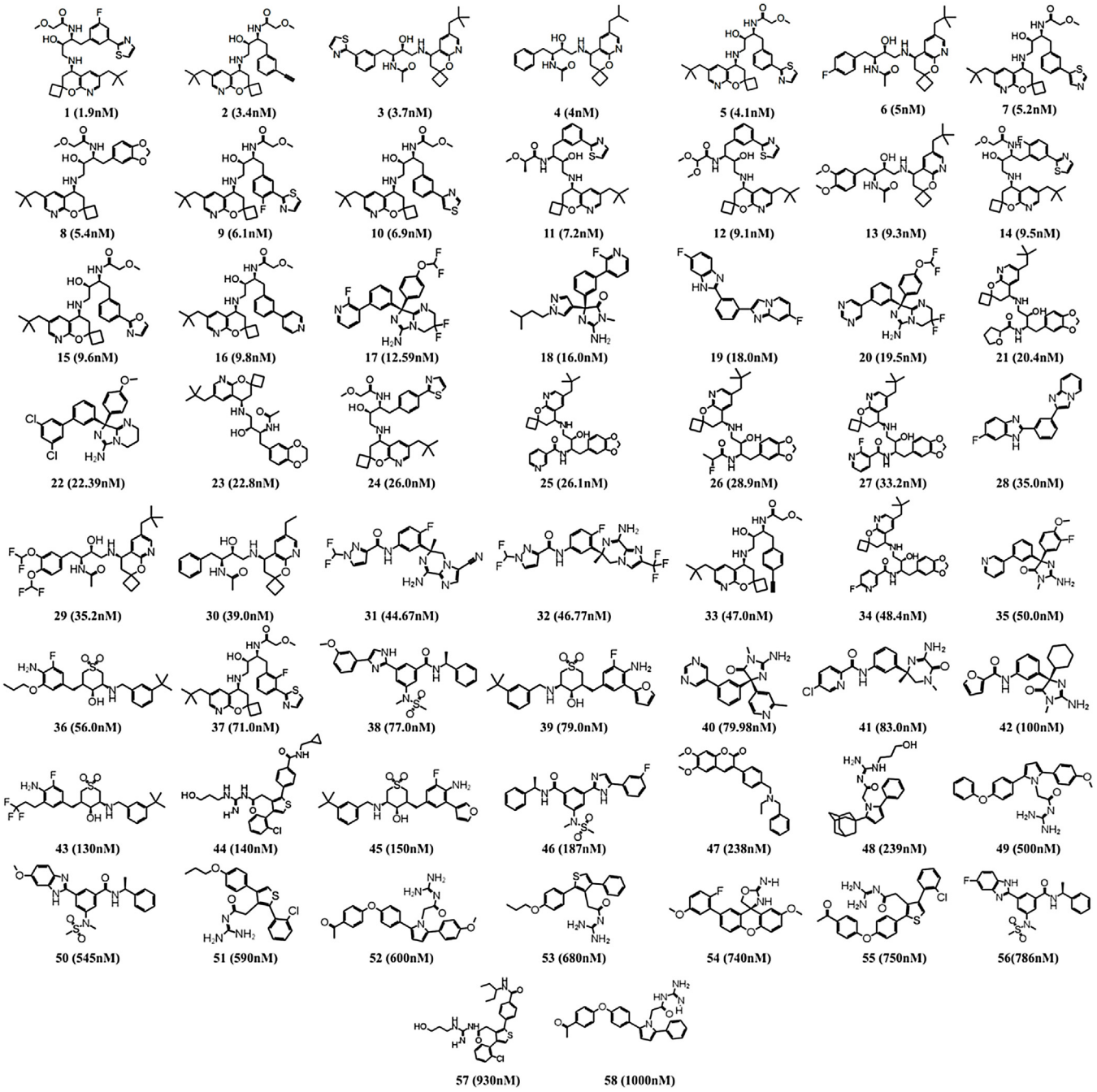

Fig. 1. The 2D structures of the dataset compounds indicating the experimentally reported inhibitory activity (in parentheses) against BACE1.