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Molecular-modeling based design, synthesis, and activity of substituted piperidines as γ-secretase inhibitors

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Abstract—Alzheimer's disease (AD) is a debilitating disease widely thought to be associated with the accumulation of beta amyloid (Aβ) in the brain. Inhibition of γ-secretase, one of the enzymes responsible for Aβ production, may be a useful strategy for the treatment of AD. Described below is a series of γ-secretase inhibitors designed from a scaffold identified by a ROCS [*J. Comput. Chem.* **1996**, *17*, 1653] search of the corporate database.

Alzheimer's disease (AD) is a debilitating disease of the elderly, which ultimately leads to death. The disease is typically recognized by the gradual deterioration of mental ability; AD is the most common form of dementia—loss of memory—in the elderly.

AD is pathologically characterized by the presence of two major lesions in the brain: extracellular amyloid deposits of beta amyloid protein (Aβ) in the form of plaques and amyloid angiopathy; and intracellular neurofibrillary tangles of aggregated hyperphosphorylated tau protein.[2] Recent evidence suggests that elevated Aβ levels in the brain not only precede tau pathology but also correlate with cognitive decline.[3] Additional studies have also shown that aggregated Aβ is toxic to neurons in cell culture[4] and has a detrimental effect on memory.[5] Together, this evidence implicates Aβ in a causative role in AD and suggests that reducing Aβ levels is a viable therapeutic strategy for the treatment of AD.

Aβ is a 39–42 amino acid peptide that is produced from a larger precursor protein called amyloid precursor protein (APP) by the sequential action of β- and γ-secretase. Although rare, cases of early onset of AD have been attributed to genetic mutations in APP or in presenilins 1 and 2, components of the γ-secretase complex, that lead to an overproduction of either total Aβ or its more aggregation-prone 42 amino acid isoform.[6–8] Furthermore, people with Down's Syndrome possess an extra copy of the chromosome that contains the gene that encodes APP; these people have elevated Aβ levels and invariably develop AD later in life.[9]

A plausible strategy for the treatment of AD suggested from the above information is to inhibit Aβ production via the inhibition of γ-secretase. Several γ-secretase inhibitors have been designed based upon the amino acid sequence of the APP cleavage site.[10] Importantly, the γ-secretase inhibitor *N*-[*N*-(3,5-difluorophenacetyl)-L-alanyl]-*S*-phenylglycine *tert*-butyl ester (DAPT) has recently been shown to reduce Aβ protein levels in mice brains in vivo after oral administration.[11] Herein is described a series of γ-secretase inhibitors designed by molecular modeling and exhibiting some promising activity in our Aβ40/Aβ42 assay.

In our efforts to uncover new leads for the γ-secretase program, we chose to use the ROCS[1] program to find new scaffolds for lead development. The ROCS program identifies molecules that have a similar

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three-dimensional shape. The similarity search requires the input of a compound query to make comparisons against a compound database. In our search, the degree of shape similarity is scored by a Tanimoto coefficient.

As a starting point for the ROCS search, we used sulfonamide **1** (see Fig. 1), a recently reported potent inhibitor of Aβ production.[12] A conformational search based on the Monte Carlo method in Macromodel[13] was performed on **1**. The MMFF94 force field[14–18] was used in the energy minimization steps. The low-energy conformer of **1** was used as the query. Using a Tanimoto coefficient cut-off of 0.7, the search of an in-house database provided us with about 500 hits; one of these hits was compound **2**.

The hits were then analyzed to see which of them contained the chemical features believed to be important for γ-secretase activity or which could be readily modified to contain those features. We have identified, in particular, three features thought to be important for γ-secretase inhibition: two hydrophobes about 4 Å apart and a hydrogen bond acceptor about 6–8 Å from the hydrophobes (see Fig. 2).

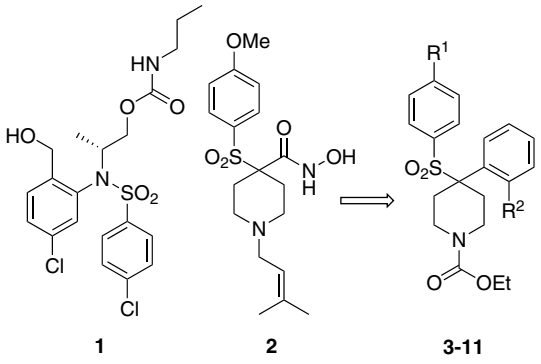

Figure 1. A ROCS search using the low-energy conformer of **1** identified hit **2** from the corporate database. Modification of hit **2** generated analogues **3**–**11**.

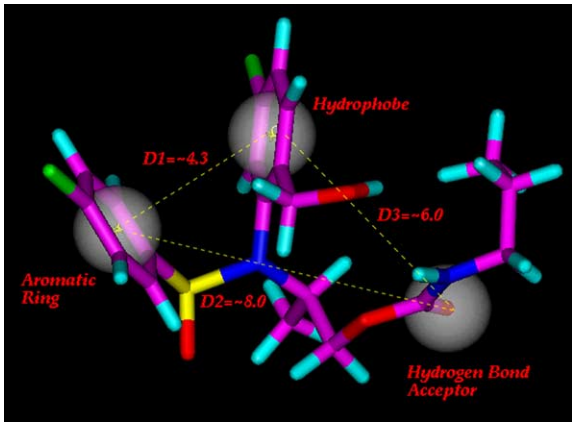

Figure 2. This figure depicts a schematic of the pharmacophore overlayed on compound **1**, shown as the low-energy conformer.

Overlap of the hydroxamic acid of **2** with one of the aromatic rings in **1** (see Fig. 3) suggested the replacement of the hydroxamic acid with a phenyl ring, satisfying the first requirement of our pharmacophore. Secondly, the replacement of the alkene moiety in **2** with a carbamate added the requisite hydrogen bond acceptor. These two modifications led us to compound **3**, which we also believed would be relatively straightforward to synthesize and would prove amenable to parallel synthesis if needed. Minimization of **3** with the MMFF94 force field and subsequent comparison with **1** (see Fig. 4) resulted in good overlap while maintaining the pharmacophore orientation and providing us with a potential new lead for our γ-secretase program.

While hit **2** was inactive in our Aβ40/Aβ42 assay, a sandwich ELISA employing 6E10 antibody for Aβ capture and Aβ40 or 42 C-terminal specific antibodies for

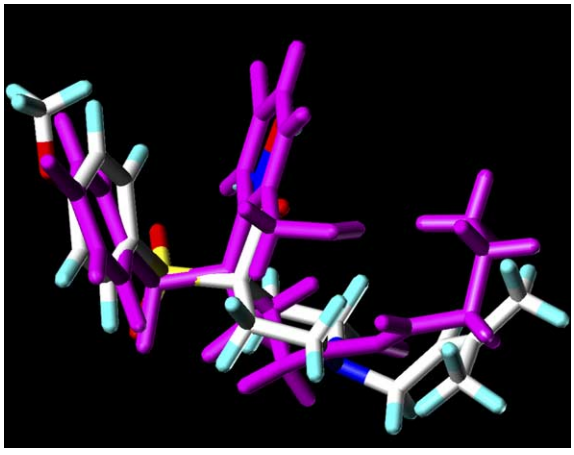

Figure 3. Overlay of compound **2** with compound **1** (magenta) generated from the ROCS software. Note the strong overlap of the aromatic rings and the tail portions. Also, note the close proximity of the hydroxamic acid to the aromatic hydrophobe of **1**.

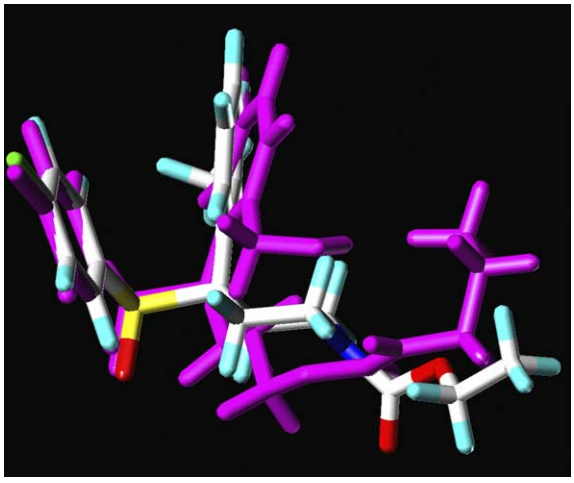

Figure 4. Overlay of compound **3** with compound **1** (magenta); these structures were minimized using the MMFF94 force field and then compared by mapping the aromatic regions, the sulfones, and the carbonyl oxygen of each molecule.