Letters

Discovery of Oxadiazoyl Tertiary Carbinamine Inhibitors of β-Secretase (BACE-1)†

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Received September 1, 2006

Abstract: We describe the discovery and optimization of tertiary carbinamine derived inhibitors of the enzyme β-secretase (BACE-1). These novel non-transition-state-derived ligands incorporate a single primary amine to interact with the catalytic aspartates of the target enzyme. Optimization of this series provided inhibitors with intrinsic and functional potency comparable to evolved transition state isostere derived inhibitors of BACE-1.

Aging populations worldwide continue to increase the prevalence and social burden of Alzheimer's disease (AD).[1] Currently marketed treatments have limited efficacy, leaving a large unmet medical need in terms of true disease-modifying therapies. The amyloid cascade has emerged as a widely accepted hypothesis for the cause of AD. According to this theory, processing of the amyloid precursor protein (APP) by β-secretase (BACE-1) followed by γ-secretase releases the peptide Aβ, which is thought to play a central role in the events leading to the dementia and inevitable mortality associated with AD.[2] Given its upstream position in the amyloid cascade and absence of known mechanism-based toxicity, BACE-1 appears to be an attractive target for the treatment of AD.[3]

BACE-1 is a type I membrane associated aspartyl protease. The inhibition of aspartyl proteases with druglike small molecules remains a formidable challenge.[4] Transition state isosteres such as hydroxyethylamines, reduced amides, statines, and aminostatines are the most commonly utilized "warhead" fragments that interact with the catalytic aspartates.[5] The large active sites of aspartyl proteases typically require high molecular weight inhibitors to achieve acceptable levels of inhibition, and pharmacokinetic optimization of such large structures often proves challenging. While intense research efforts have focused on aspartyl proteases as therapeutic targets, the only marketed treatments are for the inhibition of HIV protease. Therapeutically useful inhibition of BACE-1 is further complicated by the requirement for CNS penetration, which effectively necessitates the development of novel inhibitors because of the poor brain penetration properties usually associated with transition state isosteres.[6] While potent inhibitors of renin and plasmepsin based on piperidine templates have been reported, such non-transition-state isostere derived inhibitors for BACE-1 inhibition remain scarce.[7]

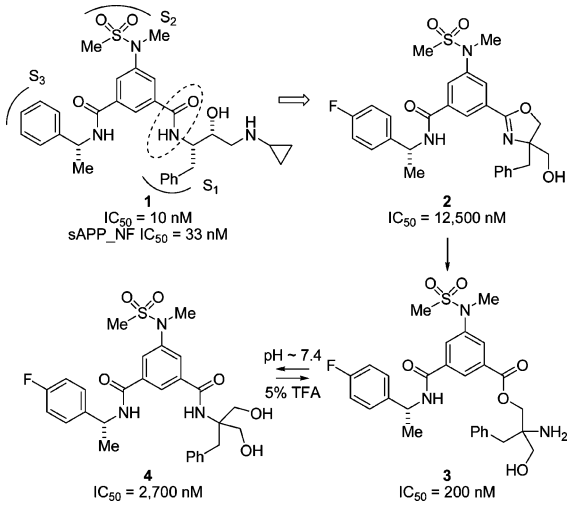

Figure 1. Discovery of tertiary carbinamine derived inhibitors of BACE-1.

The discovery of intrinsically and functionally active hydroxyethylamine derived inhibitors of BACE-1, exemplified by structure **1**, has been reported in the literature (Figure 1).[8,9] Because of the large number of hydrogen bond donors and acceptors, **1** was susceptible to efflux by P-glycoprotein (P-gp), and its passive permeability was not consistent with a brain penetrant compound.[10] As a result, we focused on systematically replacing the amide and sulfonamide components with substituents compatible with CNS penetration while maintaining acceptable potency. Recently reported studies have shown that the P_3 amide could be replaced while maintaining high levels of enzyme inhibition.[11] The right-hand P_1 amide was critical for the observed BACE-1 activity and could not be deleted without significant loss of potency because it formed two important interactions with the enzyme: the amide carbonyl with the Gln73 flap residue and the amide NH with the backbone Gly230 carbonyl.

Models based on the X-ray cocrystal structure of **1** in the BACE-1 active site indicated that replacement with an amide mimic in the form of an oxazoline could maintain the flap interaction.[12] Accordingly, **2** was synthesized with a simplified primary hydroxyl aspartate ligand and was shown to have weak activity in the BACE-1 primary assay. Given the oxazoline's instability to mild aqueous acid, we hypothesized that an impurity could be causing the observed β-secretase inhibition. When **2** was subjected to catalytic aqueous TFA, clean conversion to the tertiary carbinamine ester **3** occurred. Much to our surprise, this unique aspartyl protease inhibitor motif displayed significant enzyme inhibition.[13] However, **3** proved to be stable only at mildly acidic pH. Rearrangement to amide **4** occurred

† PDB files for the BACE-1/inhibitor **3** complex (PDB identifier 2lSO) and the BACE-1/inhibitor **8** complex (PDB identifier 2lRZ) have been deposited with the Protein Data Bank.

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10.1021/jm061046r CCC: $33.50
Published on Web 11/10/2006

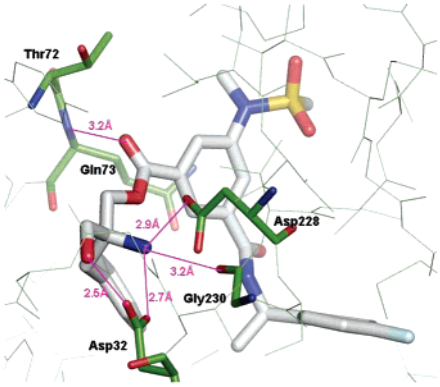


Figure 2. BACE-1/inhibitor **3** complex with relevant enzyme amino acid residue depicted in green.

at physiological pH, and cleavage of the ester bond readily took place at pH 1 and pH 10.

An X-ray crystal structure of **3** bound to the BACE-1 active site was obtained via the soaking exchange of a weak ligand (Figure 2).[14] The central tertiary carbinamine formed interactions with catalytic aspartates Asp32 and Asp228, as well as the Gly230 residue of the BACE-1 enzyme (the heavy atom distances are 2.7, 2.9, and 3.2 Å, respectively). The primary hydroxyl group was within hydrogen-bonding distance of Asp32 (2.5 Å). The ester carbonyl was in proximity to the flap residue Gln73 (3.2 Å). While simple amines have been reported as BACE-1 inhibitors,[5] the connectivity of the benzylic appendage filling the S_1 pocket is transposed by one atom for inhibitor **3**, which represents an unprecedented vector for filling this pocket of BACE-1. Comparing the bioactive conformations of inhibitors **1** and **3** illustrated that the P_1 phenyl rings were overlaid closely, filling identical space in the enzyme active site despite the differing trajectories.

Further inspection of the BACE-1 protein complexed with **1** and **3** revealed the gross enzyme structure to be highly conserved except for one key difference: the catalytic aspartic acid residue Asp32 was rotated out of the plane defined by the second catalytic aspartate Asp228 in the tertiary carbinamine enzyme complex. The angle defined by Asp32,OD1−Asp,32Cγ−Asp,-228Cγ−Asp228,OD2 was 84°. To the best of our knowledge, this is the only reported example of a BACE-1 enzyme inhibitor complex involving noncoplanar aspartates. This phenomenon is highly unusual in the apo or inhibitor bound structures of aspartyl proteases, as the usual coplanar orientation of the catalytic aspartates results in an intermolecular hydrogen bond.[15]

We sought to improve the stability and potency of this novel class of inhibitors (Figure 3). Deletion of the ester carbonyl provided the stable ether analogue **5**. Predictably, the absence of the ester carbonyl resulted in a potency loss. Surprisingly, excision of the primary alcohol presumed to interact with Asp32 gave **6** with a 3-fold potency *gain*.[16] Examination of the enzyme inhibitor complex of **3** revealed that isomeric ester **7** could access the flap residue. Ester **7** did recoup the potency, but the α-amino ester motif proved to be unstable at physiological pH. The superior potencies of **3** and **7** suggested that the optimal avenue for improving potency without drastically increasing molecular weight was to incorporate a flap interaction. In addition, cocrystal structures of inhibitors **3**, **5**, **6**, and **7** in the BACE-1 active site consistently revealed that the C_1-C_4 region of the linker was coplanar in the bioactive conformation. Therefore, we hypothesized that a heterocyclic constraint of the C_1-C_3 region could provide a more stable structure capable of interacting with Thr72 and Gln73.

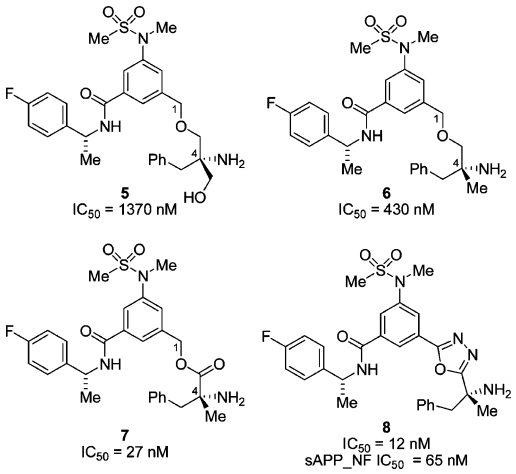


Figure 3. Optimization of the tertiary carbinamines.

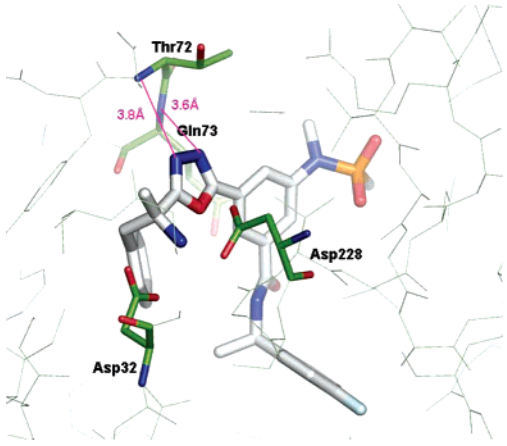


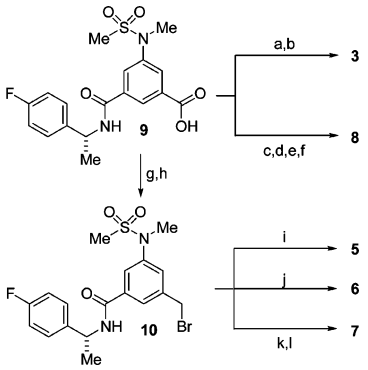
Figure 4. Inhibitor **8** complexed with BACE-1, with relevant enzyme amino acid residue depicted in green.

We chose to incorporate a 1,3,4-oxadiazole, a well-known ester mimic,[17] into the linker of our inhibitors. The resulting oxadiazole tertiary carbinamine inhibitor **8** displayed excellent intrinsic and functional potency in our BACE-1 assays and proved to be a stable entity. An X-ray crystal structure of **8** complexed with BACE-1 was obtained (Figure 4), and we observed close homology between the tertiary carbinamine and the P_1, P_2, and P_3 substituents for inhibitors **3** and **5**−**8**. The incorporation of a five-membered heterocycle did result in minor distortions of the linker region, but this was fortunately tolerated from the potency perspective.

The closest distance from the oxadiazole nitrogen atoms to flap residues Thr72 and Gln73 were observed to be 3.8 and 3.6 Å, respectively. While the distance and the geometry were not optimal for a true hydrogen bond, we observed that the oxadiazole ring was rotated out of the plane defined by the central aryl scaffold with a dihedral angle of approximately 29°. Calculations show that the lowest energy conformation places the two aryl rings in the same plane.[18] Hence, we hypothesize that a weak interaction of the oxadiazole and the flap region could be present. The observed potency enhancement could also be attributed in part to rigidification of the linker.

In terms of inhibition of other aspartyl proteases by this novel warhead, inhibitor **8** does show moderate selectivity versus highly homologous enzyme BACE-2 (IC_{50} = 620 nM) and shows little inhibition of renin at 20 μM inhibitor concentration. Related tertiary carbinamine analogues display no inhibition of

Scheme 1. Synthesis of Tertiary Carbinamine Inhibitors[a]



[a] (a) Benzylserinediol, *i*-Pr_2NEt, BOP reagent, CH_2Cl_2, 27%; (b) 5% TFA, CH_3CN/H_2O, 80%; (c) Boc-$NHNH_2$, EDC, HOAt, DMF, 95%; (d) HCl, CH_2Cl_2, 100%; (e) *N*-Boc-α-Me-Phe-OH, CDI, then CBr_4, Ph_3P, CH_2Cl_2, 75%; (f) HCl, CH_2Cl_2, 97%; (g) BH_3, THF, 95%; (h) CBr_4, Ph_3P, Im, CH_3CN/CH_2Cl_2, 53%; (i) benzylserine diol, NaHMDS, DMF, 79%, then ChiralPak AD separation; (j) (*R*)-α-Me-phenylalaninol, NaHMDS, DMF, 74%; (k) (*R*)-*N*-Boc-α-Me-Phe-OH, Cs_2CO_3, DMF, 86%; (l) HCl, CH_2Cl_2, 95%.

cathepsin D at 100 μM. We believe this selectivity is built into the isophthalimide scaffold, exploiting the hydrophilic nature of the BACE-1 S_2 pocket compared to BACE-2, renin, and cathepsin D.[19] Hence, the utility of tertiary carbinamines as a general "warhead" motif for aspartyl protease inhibition remains to be fully explored.

Synthesis of the inhibitors **3**−**8** began with the isophthalimide derivative **9** (Scheme 1). Coupling with benzylserine diol gave amide **4**, which underwent acid-catalyzed N,O acyl migration, providing an alternative route to inhibitor **3**. Coupling of **9** with Boc-hydrazine and acid mediated deprotection gave access to the benzoyl hydrazide derivative of **9**. Activation of (*R*)-*N*-Boc-α-Me-Phe-OH with CDI, addition of the benzoyl hydrazide, followed by dehydration with CBr_4/Ph_3P in the same pot provided desired the oxadiazole.[20] Deprotection of the Boc group gave inhibitor **8**. Acid **9** was transformed to the benzyl bromide derivative **10** via borane reduction and treatment of the resulting benzyl alcohol with CBr_4/Ph_3P. The ether bond of inhibitor **5** was constructed by the deprotonation of benzylserine diol with base, followed by treatment with intermediate **10**. Separation of the resulting diastereomeric mixture on a chiral stationary phase provided **5**. Etherification with (*R*)-α-Me-phenylalaninol under the same conditions provided **6**. Esterification of (*R*)-*N*-Boc-α-Me-Phe-OH with **10** utilizing Cs_2CO_3 as the base followed by acid mediated Boc deprotection afforded **7** in high yield.

In summary, we report the discovery of novel non-transition-state isostere derived inhibitors of BACE-1. The central tertiary carbinamine moiety interacts with three key residues of the target enzyme: the catalytic aspartates Asp32 and Asp228 and the carbonyl of Gly230. We also report a novel vector for accessing the S_1 pocket of BACE-1. Utilizing structure-based information, this series was optimized to the stable tertiary carbinamine oxadiazole **8**, which has intrinsic and functional potency comparable to evolved hydroxyethylamine inhibitors of BACE-1 exemplified by **1**.

The "warhead" fragment represented by the tertiary carbinamine oxadiazoles has been significantly simplified in terms of hydrogen bond donors and acceptors compared to transition state isostere derived inhibitors. Additionally, the tertiary carbinamine inhibitors cause a highly unusual "induced fit" of the BACE-1 catalytic aspartates, twisting Asp32 such that this residue is orthogonal to the plane defined by Asp228. The implications of this observation are not fully understood in terms of inhibitor design. Unfortunately, because of the presence of the P_2 sulfonamide and P_3 amide, **8** was not predicted to be brain penetrant based on our in vitro P-gp assay. The optimization of the tertiary carbinamine derived BACE-1 inhibitors toward achieving this goal is an ongoing effort.

Acknowledgment. The authors thank Joan Murphy for mass spectral data, Steve Pitzenberger for assistance with the structural assignment of **3**, Carl Homnick for chiral separations, B. Wesley Trotter and James C. Barrow for thoughtful proofreading of this manuscript, and Bryan T. Mott for the described second-generation synthesis of **8**. PyMol, version 0.99, distributed by DeLana Scientific LLC, was utilized to generate Figures 2 and 4.

Supporting Information Available: Experimental procedures for the synthesis of compounds **3**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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