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Letters

2-Amino-3,4-dihydroquinazolines as Inhibitors of BACE-1 (β-Site APP Cleaving Enzyme): Use of Structure Based Design to Convert a Micromolar Hit into a Nanomolar Lead

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Abstract: A new aspartic protease inhibitory chemotype bearing a 2-amino-3,4-dihydroquinazoline ring was identified by high-throughput screening for the inhibition of BACE-1. X-ray crystallography revealed that the exocyclic amino group participated in a hydrogen bonding array with the two catalytic aspartic acids of BACE-1 (Asp_{32}, Asp_{228}). BACE-1 inhibitory potency was increased (0.9 μM to 11 nM K_i) by substitution into the unoccupied S_1' pocket.

Alzheimer's disease (AD) is a chronic degenerative disorder of the central nervous system, resulting in severe cognitive deficits along with psychiatric complications.[1] More than 20 million individuals suffer from this condition worldwide, and this number is expected to grow dramatically. The current standards of care are the cholinesterase inhibitors such as galantamine, which are indicated for mild to moderate AD, and the NMDA receptor antagonist memantine for the moderate to severe form of the disease. A compelling molecular target among the various strategies being pursued[2] is the aspartic protease BACE-1.[3] This membrane bound type 1 protein catalyzes the initial proteolytic cleavage of the amyloid precursor protein (APP^a) en route to the β-amyloid$_{1-40(42)}$ peptides. The mouse homozygous knock-out shows significant reduction of β-amyloid levels,[4] and this gene deletion in the Tg2576 animal model of β-amyloid overexpression results in the attenuation of the cognitive deficit.[5] BACE-1 has also recently been shown to play a role in myelination in the peripheral and central nervous system during development and may have cognitive and synaptic functions independent of APP processing.[6] Nevertheless, BACE-1 inhibitors have been shown to lower β-amyloid levels in the brains of mice[7] and thus may treat the etiology of the disease and not just the symptoms.

Table 1. Inhibition of BACE by **1**−**3a**

cmpd	K_i (nM)
1	900
2	158
3	30
3a	11

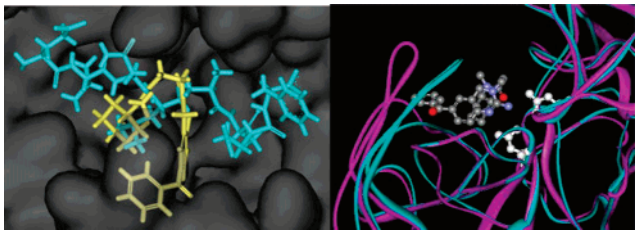
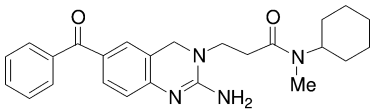


Figure 1. Left: superposition of OM99-2 (peptidic inhibitor) and **1** in the active site of BACE-1. Right: ribbon diagram representation of **1** with the two catalytic aspartic acids highlighted bound into BACE-1 (maroon), showing the flap over the active site moved when compared with BACE-1 when OM99-2 is bound in (turquoise).



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A screen of our corporate compound collection resulted in the identification of a variety of hits in the 1−10 μM range. We focused SAR development on 2-aminoquinazoline **1**, which

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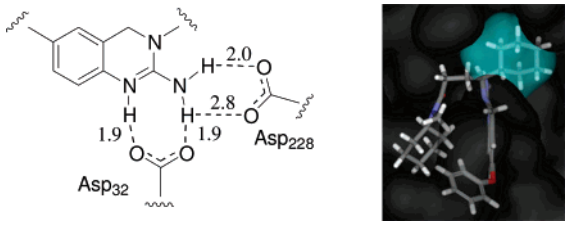
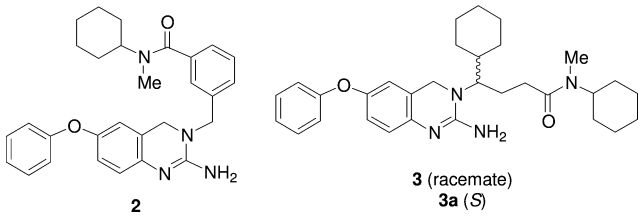


Figure 2. Left: the 2-amino-3,4-dihydroquinazoline fragment of **1** and the Asp_{32} and Asp_{228} sidechains of BACE-1, with H-bond distances in Å between the Asp carboxylate oxygens and the hydrogens. Right: the X-ray structure of **3a** bound in to BACE-1, showing the α-cyclohexyl substituent filling the S_1' pocket.

inhibited BACE-1 with a 0.9 μM K_i (Table 1). An X-ray structure of **1** bound into the BACE-1 protein was obtained as part of a collaboration with Astex Therapeutics. The BACE-1 protein used in the crystallography studies was prepared by recombinant insect cell expression.[8] The structure of **1** in the active site of BACE-1 was compact, with the side chain bending back onto itself in a hairpin turn orientation (Figure 1). This allowed the *N*-cyclohexyl substituent to occupy the critical S_1 binding pocket. In addition, the flap region of the protein adopted an "open" structure in which the $Tyr^{71}C_\alpha$ carbon is displaced by 4 Å relative to the peptidic OM99-2[9] bound into BACE-1. Similar flexibility has been observed for the flap region of other aspartyl proteases such as renin and HIV-1 protease.

An especially intriguing feature of this structure is the exquisite hydrogen bonding array that **1** forms with the two catalytic aspartates (Asp_{32}, Asp_{228}; Figure 2). Related 2-aminopyridines, 2,3-diaminopyridines, 1-aminoisoquinolines, and 2-aminoquinolines have been identified by the use of a fragment-screening approach as BACE-1 inhibitors.[10]

To reinforce the hairpin conformation in the side chain, we prepared **2**, which bears a 1,3-disubstituted phenyl ring in the side chain. This modification also incorporated 6-phenoxy substitution instead of the 6-benzoyl group present in **1**. A 6-fold increase in potency for BACE-1 inhibition was observed for **2** (158 nM K_i) when compared with **1**. Further examination of

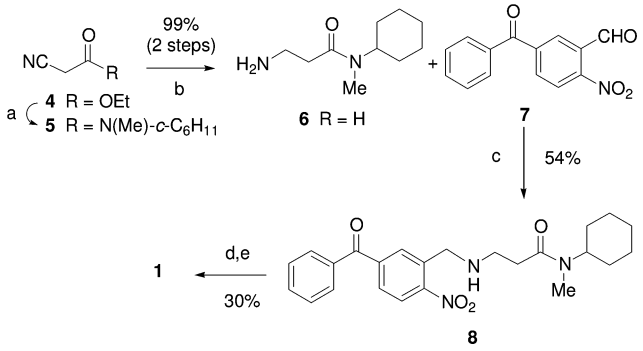


the X-ray structure of **1** bound into BACE-1 revealed that the vacant hydrophobic S_1' pocket could be filled by substitution with *S* stereochemistry on the α-carbon of the side chain. Compound **3** was prepared as a racemate initially and was found to be a potent BACE-1 inhibitor (30 nM K_i). The enantiomers of **3** were obtained independently, and the activity resided predominantly in the *S* enantiomer as predicted (**3a**, 11 nM K_i, Figure 2).

Chemistry. 2-Amino-3,4-dihydroquinazoline **1** was prepared starting with the conversion of ethyl cyanoacetate **4** into amide **5**, which afforded amine **6** after reduction (Scheme 1). Reductive amination of 3-benzoyl-6-nitrobenzaldehyde **7**[11] and **6** provided benzyl amine **8**. Reduction of the nitro group of **8** followed by

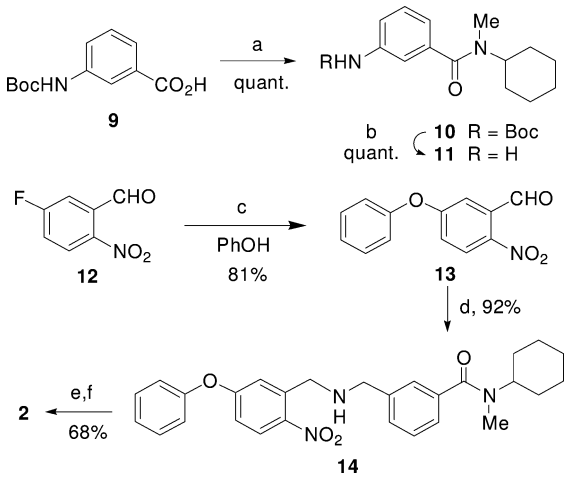
[a] Abbreviations: APP, amyloid precursor protein; BACE-1, β-site APP cleaving enzyme or Asp-2 or memapsin-2; NEM, *N*-ethylmorpholine.

Scheme 1[a]



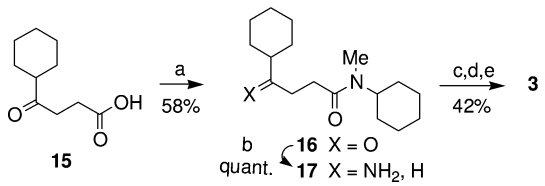
[a] Reagents and conditions: (a) MeNH-*c*-C_6H_{11}, EtOH, reflux; (b) H_2, Raney Ni, NH_3/MeOH; (c) $NaBH(OAc)_3$, CH_2Cl_2; (d) H_2, Pd/C, thiophene, MeOH; (e) BrCN, EtOH, reflux.

Scheme 2[a]



[a] Reagents and conditions: (a) MeNH-*c*-C_6H_{11}, HBTU, NEM, DMF; (b) TFA, CH_2Cl_2; (c) K_2CO_3, DMF, 120 °C, 1 h; (d) $NaBH(OAc)_3$, CH_2Cl_2, **11**; (e) $SnCl_2$ $2H_2O$, EtOH, reflux; (f) BrCN, EtOH.

Scheme 3[a]

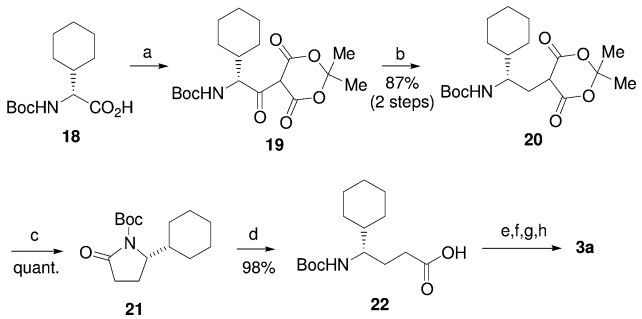


[a] Reagents and conditions: (a) MeNH-*c*-C_6H_{11}, *i*-BuOCOCl, TEA, CH_2Cl_2; (b) NH_4OAc,$NaBH_3CN$, MeOH; (c) $NaBH_3CN$, HOAc, **13**, MeOH; (d) H_2, 10% Pd/C, MeOH; (e) BrCN, EtOH, reflux.

treatment with cyanogen bromide led to 2-amino-3,4-dihydroquinazoline **1**.

The preparation of **2** was initiated by conversion of **9** to amide **10** and deprotection to provide **11** (Scheme 2). Nitrobenzaldehyde **12** was converted to phenoxy derivative **13**.[12] Reductive amination of **13** and **11** afforded benzylamine **14**, which was converted to aminoquinazoline **2**. The chemistry to prepare **3** (racemic) started with amidation of ketoacid **15**[13] to give **16**, followed by reductive amination to afford primary amine **17** (Scheme 3). Conversion to target **3** was conducted by the use of the same sequence as for **1** and **2**. The single enantiomers of **3** were obtained via a synthetic strategy to prepare γ-substituted-γ-aminoacids devised by Smrcina and Majer,[14] which resulted in no detectable epimerization on a reaction scale of up to 200 g.

Scheme 4[a]



[a] Reagents and conditions: (a) Meldrum's acid, DMAP, EDCI, CH_2Cl_2; (b) $NaBH_4$, HOAc; (c) tol, reflux; (d) NaOH, acetone; (e) MeNH-*c*-C_6H_{11}, HOBT, EDCI, TEA, DMF; (f) TFA, CH_2Cl_2; (g) **13**, $NaBH(OAc)_3$, CH_2Cl_2; (h) H_2, Pd/C; (i) BrCN, EtOH.

For the preparation of **3a**, (*R*)-cyclohexylglycine **18** (>97% e.e.) was treated with Meldrum's acid under basic conditions to afford **19**, and the ketone functionality of **19** was subsequently reduced with $NaBH_4$ to provide **20**. Thermolysis of **20** provided lactam **21**, which was saponified to **22**, suitable for further homologation to **3a** (Scheme 4).

Pharmacology. Compound **3a** was further examined in a variety of assays to probe selectivity and suitability for further consideration as a lead. It displayed modest selectivity for BACE-1 over the aspartic proteases renin (2.7 μM IC_{50}) and cathepsin D (0.11 μM IC_{50}) as well as the hERG channel (0.14 μM IC_{50}). The Caco-2 apparent permeability coefficients P_{app}A to B and P_{app}B to A values for compound **3a** were determined to be 0.28×10^{-6} cm/s and 3.38×10^{-6} cm/s, respectively. The efflux ratio of 12.2 suggests that this compound is a PgP substrate, although testing against PgP itself would need to be done to confirm this hypothesis. Compound **3a** exhibited excellent potency in a cellular assay, which measures the inhibition of $A\beta_{1-40}$ secretion in CHO cells transfected with the Swedish familial AD mutant APP (K670N/M671L). Additionally, **3a** lowered β-amyloid$_{1-40}$ in plasma by 40−70% in rats after p.o. administration (30 mg/kg), 3 h post-dosing.

Discussion. A variety of compounds have been reported that inhibit BACE-1.[3,15] Many of these are statine-like pseudo-transition state inhibitors, and others have more dramatically altered chemotypes such as the 2-aminoheterocycles recently reported[10] that are similar to the 2-amino-3,4-dihydroquinazolines disclosed here. Considerable computational work has also been conducted examining the BACE-1 active site in an effort to design more potent inhibitors or add suitable substitution to address ADME or other liabilities.[16] There were several very distinctive features of our 2-amino-3,4-dihydroquinazoline chemotype. The 2-amino-3,4-dihydroquinazolines adopted a compact structure bearing a hairpin turn of the side chain and anchored at the active site by virtue of an extensive hydrogen bonding array of the two catalytic aspartic acids with the exocyclic amino group. As a consequence, the protein flap over the active site was pushed away by a distance of about 4 Å when compared to the structure of OM99-2 (peptidic inhibitor) bound in to BACE-1. Because only the S_1 pocket of the protein was filled with initial 2-amino-3,4-dihydroquinazoline ligand **1** we were able to explicitly design several modifications that served to improve potency. The hairpin turn was accommodated by the incorporation of a structural constraint (e.g., **2**), and the S_1' pocket was filled by (*S*)-α-(*c*-C_6H_{12}) substitution.

Conclusion. The 2-amino-3,4-dihydroquinazoline substructure is a new fragment for aspartic protease inhibition such as against BACE-1, which is an important target in the search for new Alzheimer's disease treatments. The exocyclic amino group was shown to be involved in a hydrogen bonding array with the two aspartic acids at the BACE-1 active site. X-ray crystallography analysis of **1** (0.9 μM K_i) bound in to BACE-1 was critical in allowing us to design additional analogs with improved potency. For example, because the side chain of **1** adopted an energetically unfavored hairpin conformation, 1,3-phenyl disubstituted derivative **2** was prepared, which displayed improved potency (158 nM K_i) relative to **1**. Careful analysis of the structure of **1** bound into BACE-1 revealed that the S_1' pocket could be accessed by (*S*)-α-substitution off of the side chain, so we designed and prepared by (*S*)-α-(*c*-C_6H_{11}) derivative **3a**, which had excellent potency for BACE-1 inhibition (11 nM K_i). These structural modifications (**2** and **3a**) would not have been given high priority for synthesis without the insight provided by the crystal structure of **1** bound in to BACE-1. We were able to transition from a micromolar hit to a nanomolar lead suitable for extensive SAR development by the use of ligand−BACE-1 crystallographic analysis.

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Supporting Information Available: Chemistry experimentals for the preparation of **1**, **2**, **3** and **3a**. X-ray structure coordinates for **1** and **3a** bound in to BACE-1 have been deposited into the Protein Databank (www.pdb.org, file codes 2Q15 and 2Q11, respectively). This material is available free of charge via the Internet at http://pubs.acs.org.

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