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BACE-1 hydroxyethylamine inhibitors using novel edge-to-face interaction with Arg-296

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ABSTRACT

Inhibition of the aspartyl protease BACE-1 has the potential to deliver a disease-modifying therapy for Alzheimer's disease. Herein, is described a series of potent inhibitors based on an hydroxyethylamine (HEA) transition state mimetic template. These inhibitors interact with the non prime side of the enzyme using a novel edge-to-face interaction with Arg-296.

Alzheimer's disease is a devastating neurodegenerative disorder for which no disease-modifying therapy is currently available.[1] An increasing body of evidence suggests this disease is triggered by the formation of amyloid plaques in the brain, mainly constituted of amyloid-beta peptides (Aβ-40, Aβ-42).[2] The aspartyl protease BACE-1[3] (for β-site APP cleaving enzyme, also known as β-secretase, memapsin-2 or Asp-2) plays a key role in the formation of these peptides and has therefore been the subject of intensive medicinal chemistry efforts.[4] Indeed, it has been shown that BACE-1 inhibitors can reduce amyloid-beta formation in pre-clinical species.[5]

We have recently disclosed our medicinal chemistry effort starting from the hydroxyethylamine transition state mimetic[6] **1** (Fig. 1) which led to GSK188909 **2**-[7] the first BACE-1 inhibitor shown to reduce brain amyloid levels in transgenic mice following oral administration.[8] Further optimization led to inhibitors such as **3** with improved pharmacokinetic profiles.[9]

In parallel with this Lead Optimization effort, and bearing in mind the inherent difficulties associated with identifying an orally efficacious and brain penetrant BACE-1 inhibitor derived from a transition state mimetic, we were keen to identify alternative starting points that might address some of these issues.

The compounds highlighted above all make an important hydrogen bonding interaction with Asn-294 on the non prime side of the enzyme, either via a lactam (compound **1**) or a sulfonamide (compounds **2**–**3**) oxygen atom. Removing this interaction generally led to very significant (>100-fold) losses of potency. Therefore we prepared a series of analogs varying the side chain and incorporating groups with the capacity to interact through an hydrogen bond with Asn-294, using the available GSK proprietary acid collection (Fig. 2).

This effort lead to the identification of compound **4**, markedly more active (350-fold) than our first hit **1** (Table 1) and showing some selectivity against BACE-2 and cathepsin D (Cat-D), the two aspartic proteases most closely related to BACE-1 and which comprised our primary selectivity panel.

The first round of SAR around this hit demonstrated the importance of the presence and nature of the H-bond acceptor (compare activity of **5** and **6** vs **4**) and of the distal aromatic (compares activity of **7** and **8** with **4**). All other substitution patterns tested led to significant decrease in potency (see representative examples **9**–**14**).

Intensive efforts were directed towards obtaining a co-crystal of inhibitor **4** with a BACE-1 construct in order to aid the prioritization of our chemistry efforts around this hit. Interestingly, the X-ray co-crystal structure succeeded in demonstrating that inhibitor **4** interacts with the non prime side of the enzyme not only via

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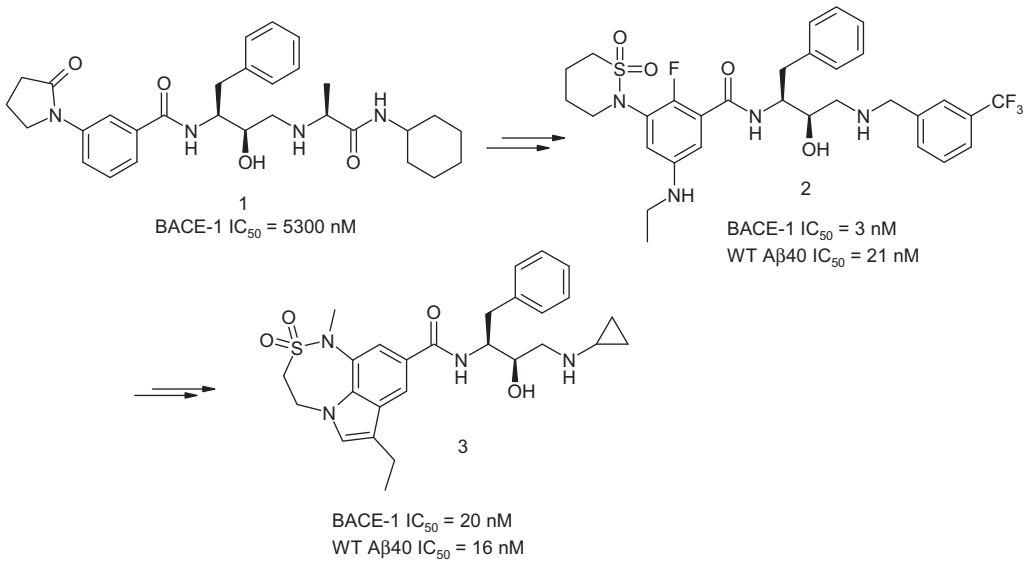


Figure 1. From micromolar hit to nanomolar orally bioavailable BACE-1 hydroxyethylamine inhibitors.

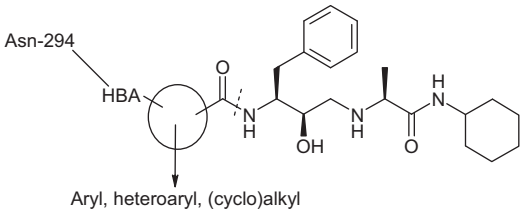
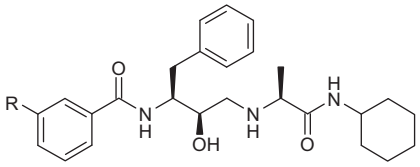


Figure 2. Design of novel HEA inhibitors susceptible of interacting with Asn-294.

Table 1
BACE-1 inhibition for compounds **1**, **4**–**14**



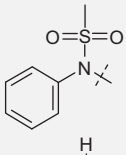
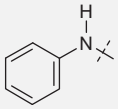
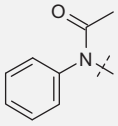
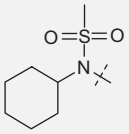
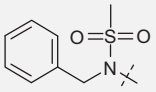
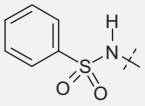
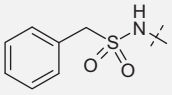
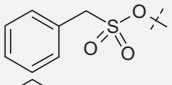
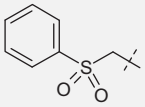
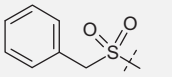
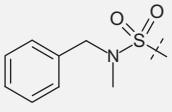
Compd	R^1	BACE-1[a] IC_{50} (μM)	BACE-2[a] IC_{50} (μM)	Cat-D[a] IC_{50} (μM)
1		5.3	79	26
4		0.015	0.655	0.660
5		6.3	0.6	1.7
6		1.3	8.9	6.2

Table 1 (*continued*)

Compd	R^1	BACE-1[a] IC_{50} (μM)	BACE-2[a] IC_{50} (μM)	Cat-D[a] IC_{50} (μM)
7		0.3	7.1	2.4
8		0.18	4.1	0.6
9		7.9	79.4	12.0
10		5.5	132	30
11		13	35	3.5
12		44	46	12
13		50	117	6.6
14		41	200	2.2

[a] In all tables, IC_{50}s reported are means of the values of three different experiments. Each IC_{50} is within threefold of the mean value.

the anticipated H-bond with Asn-294, but also via an unexpected edge-to-face interaction with Arg-296 (Fig. 3).[10,11] The increase of potency against BACE-2 and Cat-D may potentially be explained by a similar interaction but no co-crystallization was attempted in both cases.

With this information in hand, we were keen to expand the SAR around this diphenylamine sulfonamide template. The chemistry