Discovery of Begacestat, a Notch-1-Sparing γ-Secretase Inhibitor for the Treatment of Alzheimer's Disease

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Abstract: SAR on HTS hits **1** and **2** led to the potent, Notch-1-sparing GSI **9**, which lowered brain Aβ in Tg2576 mice at 100 mg/kg po. Converting the metabolically labile methyl groups in **9** to trifluoromethyl groups afforded the more stable analogue **10**, which had improved in vivo potency. Further side chain modification afforded the potent Notch-1-sparing GSI begacestat (**5**), which was selected for development for the treatment of Alzheimer's disease.

Alzheimer's disease (AD[a]) is the most devastating human disease for which there is no highly effective therapy.[1] Currently available therapies for AD only treat disease symptoms and do not address the underlying disease processes.[2] The increasing incidence of AD with age coupled with the increase in age of the general population is projected to lead to epidemic levels of this disease unless a disease-modifying anti-Alzheimer's drug (DMAAD) can be found.[3]

The key to the discovery of a DMAAD is an understanding of the etiology of AD.[4] Great strides have been made in the area in the past 25 years leading to the current prevailing hypothesis of AD disease causation: the $A\beta_{42}$ hypothesis.[5] In this model, $A\beta_{42}$, produced by sequential cleavage of APP (amyloid precursor protein) by β-secretase and γ-secretase, aggregates into synaptotoxic oligomers that are responsible for the early cognitive impairment of AD.[6] Thus, targeting $A\beta_{42}$ by blocking its synthesis, inhibiting its oligomerization, or enhancing its metabolism and/or clearance is a strategy that could afford DMAADs.[7−10]

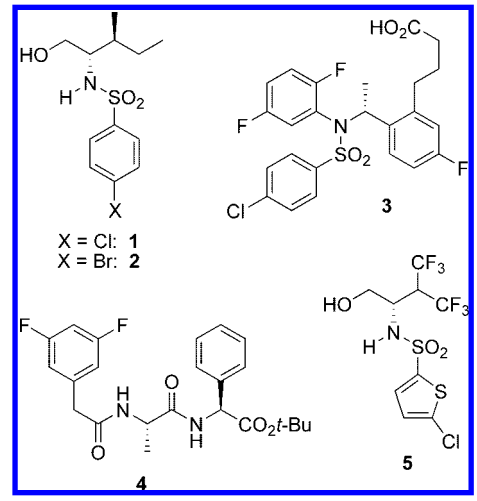

Figure 1. γ-Secretase inhibitors.

Table 1. $A\beta_{40}$ Inhibition Data and Notch Selectivity

compd	$A\beta_{40}IC_{50}$ (nM)	fold selectivity vs Notch inhibition
1	5449	3.7
2	2214	9
5	15	14
7	294	14
8	297	NT[a]
9	25	10
10	16	15
16	10670	NT[a]

[a] NT = not tested.

When we began our work on Aβ-lowering agents, no structural information was available on the β-secretase[11] and γ-secretase[12] enzymes, which precluded a structure-based design approach. Therefore, we employed high-throughput screening (HTS) screening of the Wyeth and ArQule compound collections in a cellular assay (hAPPCHO cells) of Aβ production to furnish the closely related lead molecules **1** ($IC_{50}A\beta_{40}$ = 5449 nM) and **2** ($IC_{50}A\beta_{40}$ = 2214 nM, Figure 1 and Table 1). That these compounds were γ-secretase inhibitors (GSIs) was established by their ability to elevate C99 (the product of β-secretase cleavage of APP) levels in a human APP reporter construct containing the Swedish KM to NL mutation.[13]

Subsequent to the discovery of APP processing by γ-secretase to form the various Aβ monomers was the discovery that other substrates such as Notch-1 are processed by this enzyme.[14] Because Notch-1 processing to generate NICD (Notch intracellular domain) is involved in key physiological processes such as T cell and GI cell differentiation, selectivity for APP processing over Notch-1 processing was desired in a GSI targeting the chronic treatment of AD. In fact, GSIs that lack this selectivity show in vivo goblet cell hyperplasia and untoward effects on T cell differentiation in CRND8 mice.[15] As far as how much Notch-1-sparing selectivity is required for

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[a] Abbreviations: AD, Alzheimer's disease; DMAAD, disease-modifying anti-Alzheimer drug; APP, amyloid precursor protein; HTS, high throughput screening; CHO, Chinese hamster ovary; GSI, γ-secretase inhibitor; NICD, Notch-intracellular domain; Tg, transgenic; CFC, contextual fear conditioning; PAMPA, parallel artificial membrane permeability assay; BSA, bistrimethylsilylamine.

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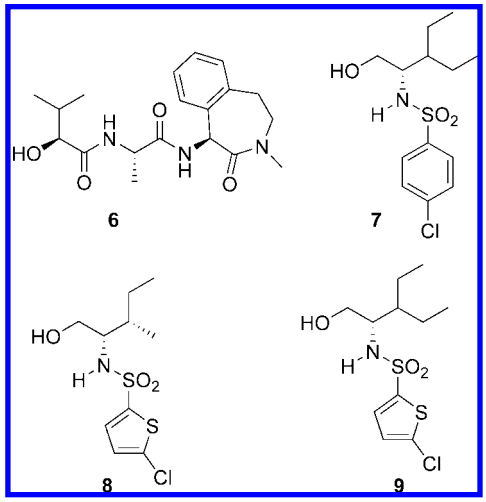


Figure 2. Additional γ-secretase inhibitors.

Table 2. In Vivo Efficacy

compd	dosage (mg/kg po)	% Aβ_{40} reduction @ 4 h	% Aβ_{42} reduction @ 4 h
4	100	~25	~25
5	5	37	25
9	100	~25	~25
10	5	27	22

a GSI to avoid Notch-1-related side effects, a recent report on the clinical GSI BMS-299897 (**3**) revealed that 15-fold Notch-1-sparing selectivity avoided in vivo Notch-1 related side effects while significantly lowering Aβ in Tg2576 mouse brain.[16] In a related study using other transgenic mouse models it was found that 30% reduction of γ-secretase activity could be tolerated without Notch-1-related side effects.[17]

As far as how much Aβ_{42} lowering is required to reverse cognitive deficits due to Aβ_{42}, we have recently reported that the GSI DAPT (**4**), a compound that lacks Notch-sparing selectivity, lowers brain Aβ_{42} by ~25% in the Tg2576 mouse model at 4 h dosed at 100 mg/kg po (Table 2) and is able to reverse cognitive deficits due to excess Aβ production in the contextual fear conditioning (CFC) model in this transgenic mouse model.[18] Therefore, it is hoped that partial inhibition of γ-secretase will lower Aβ_{42} sufficiently to reverse cognitive effects while avoiding Notch-1-related side effects by allowing a small amount of NICD to be generated to enable physiologically important signaling. This partial inhibition approach has a successful precedent in the use of statins to partially block chlolesterol synthesis.[19]

Therefore, our goal was to modify our HTS hits **1** and **2** to obtain potent GSIs with ~15-fold Notch-1-sparing selectivity that lower brain Aβ_{42} by ~25% and reverse cognitive deficits in the CFC model at ~10 mpk po. Herein we report how we successfully reached this goal leading to begascestat (**5**), which has entered clinical trials for the treatment of AD.

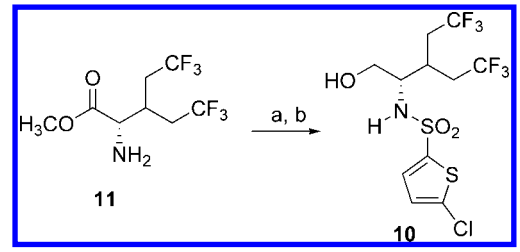
We were gratified to learn that our initial HTS hits **1** and **2** did show comparable or better Notch-1-sparing selectivity relative to the GSI LY450139 (**6**, Figure 2) (Notch-sparing selectivities: 3.7-fold, 9-fold, and 2.3-fold, respectively) that is in phase 3 clinical trials for the treatment of AD.[20] Our first task was to improve upon the modest GSI potency toward APP processing of our HTS hits **1** and **2**. We have recently reported that replacing the 2-butyl side chain of **1** with the 3-pentyl group to afford **7** significantly improved GSI potency (IC$_{50}$Aβ_{40} = 5449 and 294 nM, respectively) and Notch-1-sparing selectivity (3.7-fold and 14-fold, respectively).[13] We subsequently reported that replacing the 4-chlorophenyl moiety in **1** or **7** with the 5-chlorothiophene group to afford **8** or **9** also significantly improved GSI potency (IC$_{50}$Aβ_{40} = 297 and 25 nM, respectively).[21]

Table 3. Analysis of Metabolic Stability

species	in vitro $t_{1/2}$ (min) **9**[a]	**10**[a]	**5**[a]
Tg2576 mouse	2	24	48
rat	1	8	3
human	8	8	>90
dog	NT[b]	13	31
monkey	NT[b]	5	26

[a] pK_a values: **9**, 9.6; **10**, 8.9; **5**, 8.3. [b] NT = not tested.

Scheme 1. Synthesis of **10**[a]



[a] Reaction conditions: (a) pyr, CH_2Cl_2, 5-Cl-thiophene-2-sulfonyl chloride; (b) $LiBH_4$, THF, TMSCl.

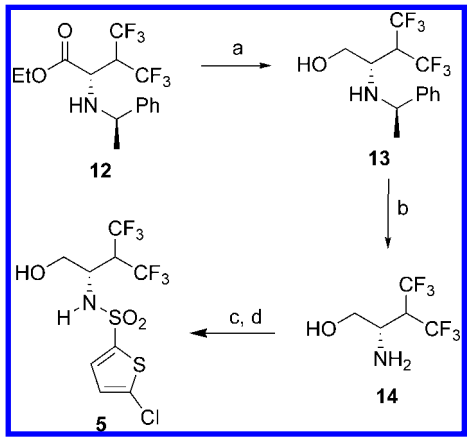
Not only is **9** a potent GSI but it also has promising Notch-1-sparing selectivity (10-fold). This compound was profiled for in vivo reduction of brain Aβ_{40} and Aβ_{42} in the Tg2576 mouse model at the 4 h time point when given 100 mg/kg po. Brain Aβ_{40} and Aβ_{42} in the Tg2576 mouse model were reduced by ~25% at this dose, which was comparable to what we observed with DAPT (**4**) at the same dose. However, the target dose for Aβ-lowering efficacy of **9** was off by an order of magnitude from our goal.

We investigated potential causes of the less than desired in vivo potency of **9**. This compound had excellent solubility (6.7 mg/mL) in the efficacy vehicle employed (Phosal PG 50/Tween-80/water in a ratio of 10:2:88) and exhibited high membrane permeability in the PAMPA assay ($P_e = 12.5 \times 10^6$ cm/s) and the CACO2 assay (A−B, $P_{app} = 50 \times 10^6$ cm/s; B−A, $P_{app} = 42 \times 10^6$ cm/s) and a good brain/plasma ratio (2.0) which eliminated solubility and membrane permeability concerns. However, the in vitro microsomal stability of **9** was low [$t_{1/2}$ = 1 min (rat), 2 min (mouse), 8 min (human)], indicating that rapid in vivo metabolism was a possible explanation for the less than desired in vivo potency (Table 3).

To improve the metabolic stability of **9**, we first identified the primary sites of metabolism, which were found to be oxidation of the terminal methyl groups of the 3-pentyl side chain and glucuronidation of the primary hydroxyl group. From our previous SAR studies, we knew that we could not block glucuronidation by alkylation of the hydroxyl or addition of alkyl groups on the primary hydroxyl-bearing carbon atom because these modifications drastically reduced GSI potency.[13] We therefore focused on blocking the oxidation of the terminal methyl groups in the side chain of **9** by replacing them with trifluoromethyl groups to afford **10**.

The synthetic route to **10** is outlined in Scheme 1. We have previously reported on the synthesis of **11**, the chiral precursor of **10**.[22] Treatment of **11** with 5-Cl-thiophene-2-sulfonyl chloride and pyridine in methylene chloride followed by reduction

Scheme 2. Synthesis of **5**[a]



[a] Reaction conditions:(a) (i) NaOH, toluene, (ii) DIBALH, toluene, −70 °C; (iii) HCl in Et_2O; (b) 10% Pd/C, H_2, MeOH; (c) BSA, CH_2Cl_2, Et_3N, DMAP; (d) 5-Cl-thiophene-2-sulfonyl chloride.

employing $LiBH_4$ and TMSCl in THF afforded **10** in 41% overall yield.

We were gratified to find that **10** not only had improved GSI potency ($IC_{50}A\beta_{40}$ = 16 nM) and Notch-1-sparing selectivity (15-fold) relative to **9** but also had increased in vitro metabolic stability in rat and mice microsomes [$t_{1/2}$ = 8 min (rat), 24 min (mouse), 8 min (human)]. When Tg2576 mice were dosed with 5 mg/kg po of **10**, brain $A\beta_{40}$ and $A\beta_{42}$ were significantly reduced at the 4 h time point (27% lowering of brain $A\beta_{40}$ and 22% lowering of $A\beta_{42}$ were observed). Thus, **10** is able to produce comparable lowering of transgenic mouse brain $A\beta$ levels at $\sim^1/_{20}$ of the dose of **9**, which is presumably largely due to its increased metabolic stability.

Although we had significantly improved the profile of **9** by replacing the terminal methyl groups with trifluoromethyl groups to afford **10**, we were still concerned with the low metabolic stability of **10** in human microsomes. We hypothesized that by contracting the bis-CF_3-containing side chain to afford begacestat (**5**), we not only eliminated sites of metabolic oxidation in the side chain but also moved the CF_3 groups closer to the hydroxyl group, the site of glucuronidation, where they might exert steric and electronic effects on the glucuronidation reaction.

Begacestat (**5**) was prepared as depicted in Scheme 2. The known chiral α-amino ester hydrochloride **12** of *S* absolute configuration was reduced with DIBALH in toluene to afford an 80% yield of the *N*-benzylamino alcohol **13**.[23] Treatment of **13** with hydrogen using a palladium catalyst provided the amino alcohol **14**, which was converted to begacestat in 48% yield by sequential treatment with bistrimethylsilyl amine (BSA) in methylene chloride containing TEA and DMAP followed by 5-Cl-thiophene-2-sulfonyl chloride. An identical procedure employing the known chiral α-amino ester hydrochloride **15** of *R* absolute configuration was used to prepare **16**, the enantiomer of begacestat (Figure 3). The absolute configuration of begacestat was unambiguously established as *S* by a single crystal X-ray structure determination (Figure 4).

We were gratified to find that begacestat not only had comparable GSI potency ($IC_{50}A\beta_{40}$ = 15 nM) and Notch-1-sparing selectivity (14-fold) relative to **10** but also had increased in vitro metabolic stability in mice and human microsomes [$t_{1/2}$ = 3 min (rat), 48 min (mouse), >90 min (human)]. In contrast to the potent in vitro GSI activity of begacestat, the enantiomer **16** had very weak GSI activity ($IC_{50}A\beta_{40}$ = 10 670 nM), indicating the stereospecific nature of this inhibition. When

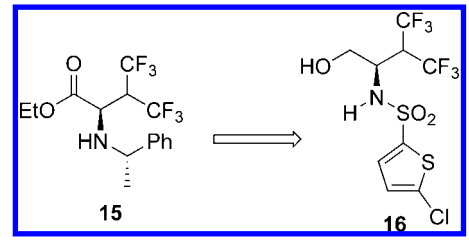


Figure 3. Enantiomer of begacestat (**16**).

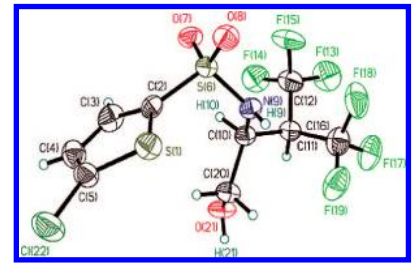


Figure 4. Single crystal X-ray structure of **5**.

Tg2576 mice were dosed with 5 mg/kg po of begacestat, brain $A\beta_{40}$ and $A\beta_{42}$ were significantly reduced at the 4 h time point (37% lowering of brain $A\beta_{40}$ and 25% lowering of $A\beta_{42}$ observed).[24] Importantly, begacestat was able to reverse the cognitive deficits in the Tg2576 CFC model at 10 mg/kg po whereas its enantiomer **16** was inactive in this model.[24] On the basis of its favorable profile and lack of Notch-1-based toxicity in several animal models, begacestat was selected for clinical evaluation in the treatment of AD.

In summary, after nearly 3000 new analogues, we have improved the in vitro potency and Notch-1-sparing selectivity of HTS hits **1** and **2** by replacing the 4-Cl-benzenesulfonamide group with the 5-Cl-thiophenesulfonamide group and by replacing the 2-butyl side chain with the 3-pentyl side chain. Incorporation of these two changes into one molecule led to the potent, Notch-sparing GSI **9** that demonstrated in vivo lowering of brain $A\beta$ levels in Tg2576 mice but unfortunately had low metabolic stability. Replacement of the metabolically labile terminal methyl groups in the side chain of **9** afforded **10**, which retained in vitro GSI potency and Notch-sparing selectivity but had improved metabolic stability and in vivo potency in lowering brain $A\beta$ levels in Tg2576 mice. Further research on the side chain afforded the potent Notch-1-sparing GSI begacestat, which not only lowered brain $A\beta$ levels in Tg2576 but also reversed cognitive deficits due to excess $A\beta$ levels in the CFC model.[18] On the basis of its potent lowering of brain $A\beta$, its ability to reverse cognitive deficits, and its lack of Notch-1-toxicity, begacestat was selected for development for the treatment of AD.

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Supporting Information Available: Experimental details for synthetic procedures, analytical data, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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