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Viewpoint

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ACS Chemical Neuroscience Molecule Spotlight on Begacestat (GSI-953)

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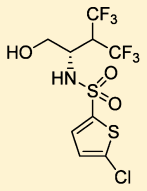
ABSTRACT: A "second generation" γ-secretase, Begacestat (GSI-953), which is more selective against Notch-signaling, has shown promise in recent Phase I clinical trials. Begacestat, a novel, 2,5-disubsitituted thiophene sulfonamide from Wyeth (now Pfizer) is under evaluation for the treatment of Alzheimer's disease.



Begacestat (GSI-953)
γ-secretase inhibitor

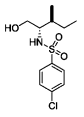
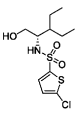
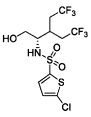
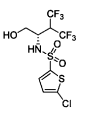
KEYWORDS: *Alzheimer's disease, γ-secretase inhibitors, GSI, Aβ-peptides*

Alzheimer's disease (AD) is the most common form of dementia and the most common neurodegenerative disorder, affecting nearly 25 million people worldwide. AD is a progressive disease and current treatments can only temporarily slow the worsening of the dementia symptoms and improve quality of life for a short period of time. There is no known cure for AD; however, there is a massive research effort ongoing in the academic, nonprofit association, and pharmaceutical industry looking for better treatment options and, hopefully, a cure for this devastating disease. Over the past several years, one of the leading hypotheses into the cause and progression of AD is the so-called "amyloid hypothesis".[1] This hypothesis, although not the only hypothesis, nor far from being universally accepted, states that the primary cause of the disease is the accumulation of amyloid β-peptides in the CNS. These Aβ-peptides are thought to initiate the disease progression that ultimately leads to the clinical observations of AD.[1c] Thus, an appropriate therapeutic intervention would be to inhibit or reverse the accumulation of Aβ-peptides.

One of the more advanced therapeutic avenues for blocking Aβ-peptide formation (namely, $A\beta_{42}$) studied thus far is selective inhibition of γ-secretase. γ-Secretase (along with β-secretase) produces $A\beta_{42}$ by cleavage of amyloid precursor protein (APP), thus targeting inhibition of γ-secretase should lead to an overall reduction in $A\beta_{42}$ levels.[2] The pharmaceutical industry has put forth a significant research effort in bringing γ-secretase inhibitor (GSI) compounds into clinical development. Unfortunately, two of the more advanced compounds have failed in the clinic: ELND006 showed significant side effects in the liver, and semagacestat (LY450139) performed worse than placebo in cognition and patients' ability to complete routine daily tasks.[3] Despite these setbacks, a number of compounds remain in the clinic and one of these compounds is being developed by Pfizer, begacestat (GSI-953).

Researchers at Wyeth (now Pfizer) started from a high-throughput screening hit,[4] **1**, and after extensive optimization discovered compounds **9** and **10**, with much improved potency against Aβ production (Table 1).[5] Both compounds were >200-fold more potent than the lead compound **1** and showed improved selectivity against Notch, an important protein involved in cell development and differentiation. Unfortunately, these compounds displayed poor stability in human microsomes ($t_{1/2}$ < 10 min). The metabolic instability was thought to be mainly due to oxidation of the alkyl groups; thus, contraction of the side chain of **10** led to the discovery of GSI-953 (begacestat, **5**). GSI-953 displayed significant improvement in human stability ($t_{1/2}$ > 90 min.) while maintaining potency against Aβ production and selectivity versus Notch.[5]

Table 1. Lead Optimization of GSI-953, 5

	 **1**	 **9**	 **10**	 **GSI-953, 5**
$A\beta_{40}$ IC_{50} (nM)	5449	25	16	15
Notch selectivity	3.7	10	15	16.8
Human in vitro $t_{1/2}$ (min)		8	8	>90

Begacestat was further characterized in a number of preclinical assays and has been dosed in healthy human volunteers.[6] As was reported in the lead optimization paper,[5] begascestat was shown to inhibit Aβ production in the low nanomolar range ($A\beta_{40}$ EC_{50} = 14.8 nM and $A\beta_{42}$ EC_{50} = 12.4 nM) in both cellular and cell-free assays. The group also reported on a close analogue of GSI-953 (WAY-210952, the (*R*)-isomer), which was shown to have much reduced potency

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(>10 μM) for Aβ production inhibition. Evaluation in the APP-overexpressing Tg2576 transgenic mice showed that begacestat, when dosed orally, produced significant reduction of Aβ levels in plasma, brain and CSF levels.[6] When dosed at 100 mg/kg, begacestat produced an ∼88% reduction in CSF and plasma at 2−6 h time points, and produced an ∼60% reduction in brain levels at 6 h. In addition, a 30 mg/kg dose of begacestat displayed a maximal reduction of A$\beta_{40/42}$ levels between 4 and 6 h when studied in a 24 h time course study in the brain. Using the same Tg2576 mice, the minimal effective dose (MED) was determined to be 1 mg/kg for Aβ_{40} reduction, with significant reduction in both A$\beta_{40/42}$ at 2.5 mg/kg.[6] The group also looked at the reversal of contextual memory deficits in Tg2576 mice, a test of hippocampal dependent learning in preplaque animals, and found that begacestat reversed these deficits in a dose-dependent manner from 2.5−10 mg/kg, whereas the (*R*)-isomer showed no effect (30 mg/kg). Lastly, the group reported the initial study in healthy human volunteers. The study looked at single dose administration (3−600 mg) in young subjects (18−55 years old) and found the compound produced dose-dependent changes in plasma Aβ demonstrating target engagement in humans.[6]

Based on these exciting preclinical and first-in-human studies, and the lack of Notch-related toxicity in rats and dogs,[6] begacestat has been progressed to more advanced clinical trials.[7] Although the promise of this molecule is high due to the preliminary results, it still remains to be seen if begacestat can be the first γ-secretase inhibitor to be approved for the treatment of AD.

AUTHOR INFORMATION

Notes

The authors declare no competing financial interest.

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