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ACS Chemical Neuroscience Molecule Spotlight on BMS-708163

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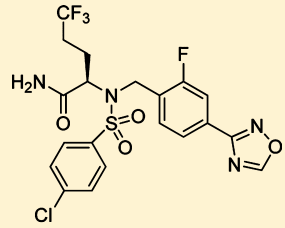
ABSTRACT: BMS-708163 is a novel, sulfonamide containing γ-secretase inhibitor from Bristol-Myers Squibb Co. currently in Phase II clinical trials for the treatment of Alzheimer's disease (AD).



BMS-708163
γ-secretase inhibitor

KEYWORDS: *Alzheimer's disease, amyloid hypothesis, gamma-secretase inhibitors, GSI*

As has been reported here[1−3] and elsewhere,[4,5] an exciting and popular mechanism of action for the potential treatment of Alzheimer's disease is the development of γ-secretase inhibitors (GSIs). This interest stems from the so-called "amyloid hypothesis" of AD[6] which postulates that accumulation of amyloid β-peptides in the CNS is the principal initiative cause of the disease which ultimately progresses to clinical diagnosis. In order to inhibit or reverse the accumulation of these Aβ-peptides, researchers have focused on two main areas for therapeutic intervention: inhibition of β-secretase (BACE)[7] or γ-secretase (GSI). Thus far, selective inhibitors of BACE have lagged far behind GSIs, although a recent report from Merck (MK-8931) has shown significant promise in this field.[8] However, despite being more advanced in clinical trials (and number of molecules), GSIs have yet to deliver a marketed drug, with two of the more advanced compounds actually failing in the clinic due to liver side effects[2] or poor performance in cognitive tasks.[1]

Despite these setbacks, the GSI field is still extremely active with numerous compounds still in clinical trials.[4] One such compound is BMS-708163, (*R*)-2-(4-chloro-*N*-(2-fluoro-4-(1,2,4-oxadiazol-3-yl)benzyl)phenylsulfonamido)-5,5,5-trifluoropentanamide, which has recently performed well in a Phase II clinical trial. The effort from Bristol-Myers Squibb started with the discovery of the first clinical candidate, **1** (Table 1), which showed potent $A\beta_{40}$ inhibition (1.4 nM) and >300-fold selectivity versus Notch (540 nM).[9] Unfortunately, the clinical trial of compound **1** was halted due to pharmacokinetic issues and the lack of Aβ lowering in humans. Following compound **1**, the researchers developed compound **2** from a high-throughput screening effort which produced a caprolactam series of compounds. This compound led to the discovery of **3** which showed a distinct improvement in $A\beta_{40}$ inhibition (in vitro, 0.14 nM); however, with a decreased selectivity versus Notch. In vivo evaluation of **3** showed significant $A\beta_{40}$ lowering in plasma and brain levels in mice at 30 mg/kg dosing (5 h postdose, p.o.). Unfortunately, **3** displayed poor pharmacokinetic properties: low brain levels (B:P ∼ 0.01) and poor microsomal stability.[9] Lastly, after exploration of amide bioisosteres, the researchers discovered their clinical candidate, BMS-708163, **4**. Like **3**, BMS-708163 displays potent in vitro inhibition of $A\beta_{40}$ inhibition (0.30 nM), however, with a modest selectivity versus Notch (193-fold). BMS-708163 displayed in vivo PK properties amenable to QD dosing (F > 40% in two species and sufficient half-life) and was shown to significantly reduce both plasma and brain $A\beta_{40}$ levels in female rats at 10 and 100 mg/kg up to 24 h. In addition to rodent studies, BMS-708163 demonstrated significant $A\beta_{40}$ reduction in brain and CSF in male beagle dogs up to 24 h post dose.[9] Based on these (and other) preclinical evaluations, BMS-708163 was advanced to clinical trials for potential disease-modifying in AD patients.

In 2011, Bristol-Myers Squibb released data on a phase II trial of BMS-708163 in patients with mild-to-moderate AD.[10] The study (CN156-013) was a randomized, double-blind, placebo-controlled study which was powered to identify a safe and tolerable dose of BMS-708163 which would provide a therapeutic window. Unfortunately, the study was not designed to determine efficacy of BMS-708163, but simply to determine a dose less than 100 mg/day that would warrant further testing. Of the doses tested, 25 and 50 mg/day showed tolerability that was acceptable, displaying discontinuation rates similar to placebo. However, doses at or above 100 mg/day displayed higher discontinuation rates than were acceptable, primarily due to GI and dermatological effects. As this study does not demonstrate efficacy for this new compound, it remains to be seen whether this lower dosing regimen will translate to the efficacy necessary for BMS-708163 to be approved for the treatment of AD.

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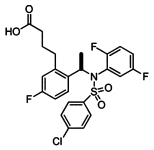
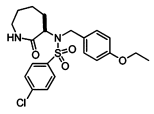
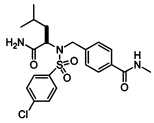
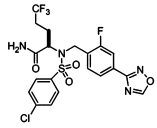
Table 1. Compound Progression to the Discovery of BMS-708163, 4

	 1	 2	 3	 4, BMS-708163
$A\beta_{40}$ IC_{50} (nM)	1.4 ± 1.2	4.1 ± 1.2	0.14 ± 0.05	0.30 ± 0.15
Notch selectivity	540 ± 230	960 ± 420	26 ± 9.1	58 ± 23
Notch/APP ratio	390	230	190	193

AUTHOR INFORMATION

Notes

The authors declare no competing financial interest.

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