

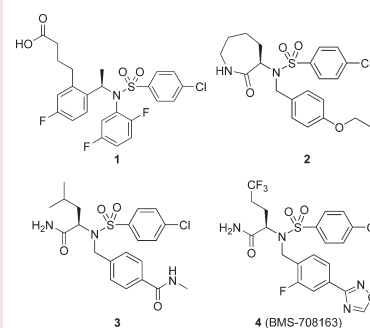
# Discovery and Evaluation of BMS-708163, a Potent, Selective and Orally Bioavailable $\gamma$ -Secretase Inhibitor

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**ABSTRACT** During the course of our research efforts to develop a potent and selective  $\gamma$ -secretase inhibitor for the treatment of Alzheimer's disease, we investigated a series of carboxamide-substituted sulfonamides. Optimization based on potency, Notch/amyloid- $\beta$  precursor protein selectivity, and brain efficacy after oral dosing led to the discovery of **4** (BMS-708163). Compound **4** is a potent inhibitor of  $\gamma$ -secretase ( $A\beta_{40}$   $IC_{50}$  = 0.30 nM), demonstrating a 193-fold selectivity against Notch. Oral administration of **4** significantly reduced  $A\beta_{40}$  levels for sustained periods in brain, plasma, and cerebrospinal fluid in rats and dogs.

**KEYWORDS**  $\gamma$ -Secretase, brain penetrant, oxadiazole, Alzheimer's, amyloid, clinical candidate



Histopathological and genetic evidence suggest that the amyloid- $\beta$  ( $A\beta$ ) peptide plays a key causative role in Alzheimer's disease (AD).<sup>1</sup>  $A\beta$  is generated by the proteolytic processing of the amyloid- $\beta$  precursor protein (APP) through consecutive cleavages by  $\beta$ -site APP-cleaving enzyme (BACE) and  $\gamma$ -secretase. APP is cleaved by BACE to form a  $\beta$ -secretase-derived C-terminal fragment of APP ( $\beta$ CTF), which undergoes further cleavage by  $\gamma$ -secretase to form  $A\beta$ .<sup>2</sup> Most  $A\beta$  isoforms contain a common N terminus, formed by BACE cleavage, while heterologous cleavage by  $\gamma$ -secretase creates  $A\beta$  isoforms ranging from 37 ( $A\beta_{37}$ ) to 42 ( $A\beta_{42}$ ) amino acid residues.  $A\beta_{40}$  is the most abundant isoform, while  $A\beta_{42}$  is most tightly linked with AD pathogenesis.

In our laboratories, one approach for the treatment of AD has been to identify potent and selective  $\gamma$ -secretase inhibitors to lower the production of  $A\beta$  in the brains of affected and at-risk patients. Because of the role of  $\gamma$ -secretase in Notch processing, the identity of secretase inhibitors with minimal impact on Notch signaling was also an important feature of our strategy. Our first  $\gamma$ -secretase clinical candidate, the 4-chloro-*N*-(2,5-difluorophenyl)phenylsulfonamide **1** (Figure 1),<sup>3</sup> progressed to phase I clinical trials. However, clinical progression of **1** was halted due to significant pharmacokinetic liabilities and lack of significant  $A\beta$  lowering in both single-ascending and multiple-ascending dose studies in man.<sup>4</sup> In addition to our efforts in the clinic, Wyeth

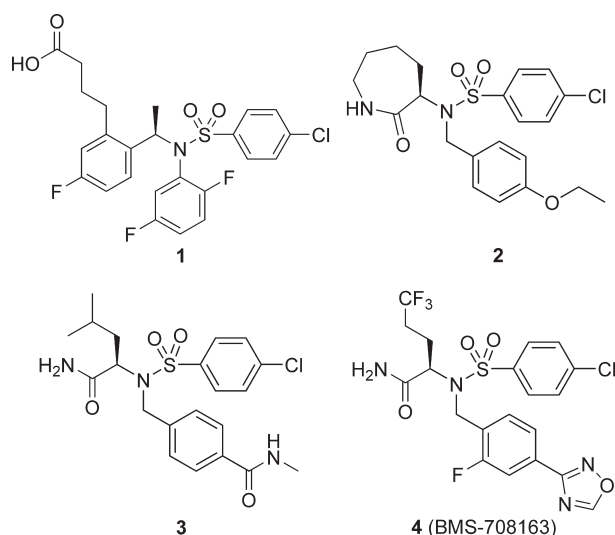
recently reported preclinical<sup>5</sup> results with the  $\gamma$ -secretase inhibitor begacestat, and Eli Lilly presented clinical evidence indicating reductions in plasma  $A\beta_{40}$  with the small molecule  $\gamma$ -secretase inhibitor LY450139.<sup>6</sup> The phase I clinical trials with **1** provided specific information to guide our efforts to develop an improved second-generation compound for clinical evaluation. Compound **1** demonstrated significant human Pregnane-X Receptor (PXR) transactivation ( $EC_{60}$  = 2.4  $\mu$ M), indicating potential for autoinduction in man. In addition, **1** had a modest brain to plasma ratio (B/P = 0.2) in Tg2576 mice. We reasoned that improvement in the brain to plasma ratio should increase central exposure and efficacy and decrease side effects associated with peripheral exposure such as autoinduction and Notch-related toxicities. Furthermore, **1** showed limited ability to lower brain  $A\beta_{40}$  in rats, which may be related to lower levels of APP-derived secretase substrate in this model.<sup>7</sup>

The discovery of a second-generation compound with improved pharmacokinetic properties commenced with the identification of the novel 2-oxoazepan-3-yl-benzenesulfonamide **2** ( $A\beta_{42}$   $IC_{50}$  = 9.0 nM) from a high-throughput screen of the BMS corporate compound deck.<sup>8</sup>

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**Figure 1.** Novel sulfonamide-based  $\gamma$ -secretase inhibitors.

**Table 1.** Summary of GS H4-8 SW1-40  $IC_{50}$  Values and Notch (mNotch1- $\Delta E$ )  $IC_{50}$  Values for Selected Sulfonamide-Based  $\gamma$ -Secretase Inhibitors<sup>a</sup>

compound	$IC_{50} \pm SD$ (nM)		Notch/APP ratio
	A $\beta$	Notch	
1	1.4 $\pm$ 1.2	540 $\pm$ 230	390
2	4.1 $\pm$ 1.2 <sup>b</sup>	960 $\pm$ 420	230
3	0.14 $\pm$ 0.05	26 $\pm$ 9.1	190
4	0.30 $\pm$ 0.15	58 $\pm$ 23	193

<sup>a</sup>  $IC_{50}$  and standard deviation values were calculated on the basis of a minimum of three independent experiments. <sup>b</sup>  $IC_{50}$  values measured using a GS H4-8 SW1-42 assay ( $n = 3$ ).

Early structure–activity relationship (SAR) exploration identified an improvement in A $\beta$ 40 in vitro potency by deannulation of the caprolactam ring of **2** (Table 1), which afforded a variety of acyclic amino acid amide analogues that were initially optimized based on potency, selectivity, and desirable physicochemical properties. The (*R*)-derived amino acid sulfonamides consistently provided higher potency. Further exploration into the SAR of the acyclic carboxamide series led to *N*-methyl-substituted benzene-carboxamide **3**, which was identified as potent inhibitor of A $\beta$ 40 formation ( $IC_{50} = 0.14$  nM).

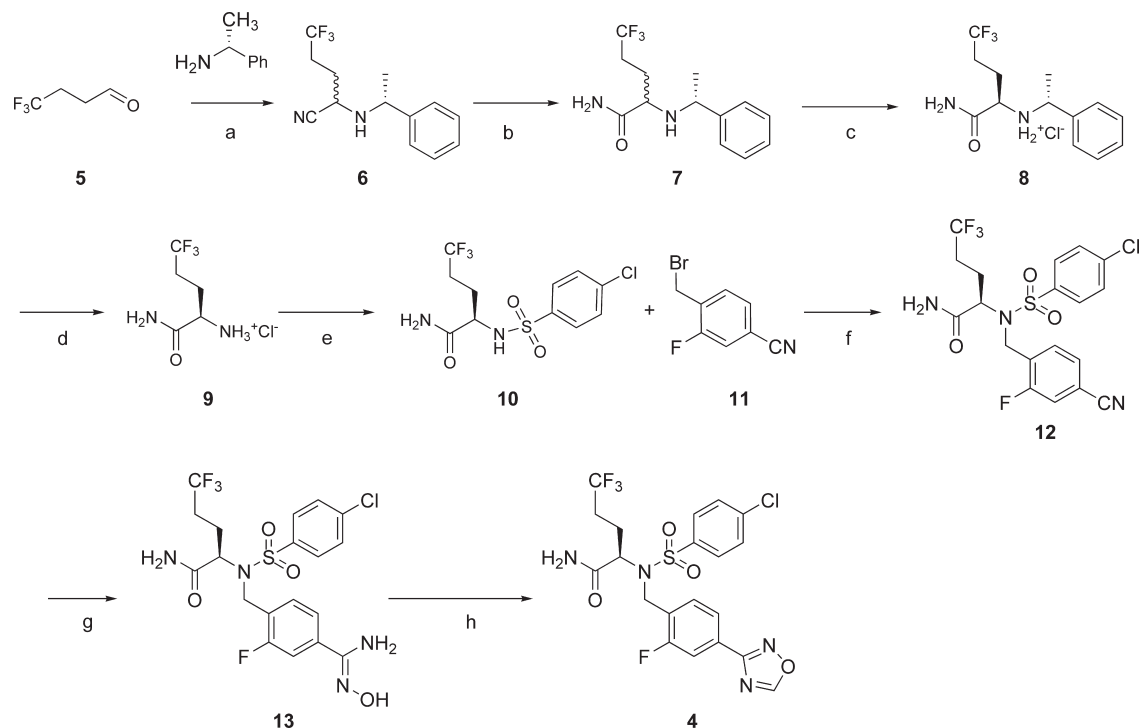
Compound **3** was tested in female wild-type rats to determine central and peripheral efficacy following oral administration at 1, 3, 10, and 30 mg/kg. Animals were sacrificed at 5 h postdose, and brain and plasma samples were collected for analyses of both drug exposure and A $\beta$ 40 levels.<sup>9</sup> A single dose of compound **3** at 30 mg/kg significantly reduced both plasma A $\beta$ 40 and brain A $\beta$ 40 to levels of 14  $\pm$  21 and 59  $\pm$  12 % (% of vehicle control  $\pm$  SEM), respectively. However, no significant reductions in brain A $\beta$ 40 were observed at 1, 3, and 10 mg/kg. Although we were encouraged by this preliminary finding, this series required further optimization to reduce the dose necessary

for A $\beta$ 40 reduction in the brain. Consistent with the discrepancy between central and peripheral efficacy, analysis of plasma and brain exposures of **3** revealed that the brain to plasma ratio was very low (brain<sub>concn</sub>/plasma<sub>concn</sub> = 0.01). In addition, **3** had poor in vitro microsomal stability [% remaining after 10 min of incubation in liver microsomes = 19 % (rat) and 44 % (human)],<sup>10</sup> indicating the potential for rapid clearance in vivo. In an effort to improve brain penetration and metabolic stability, a variety of substituents on the benzenecarboxamide nitrogen were tested.<sup>11</sup>

1,2,4-Oxadiazoles have been successfully employed as amide and ester bioisosteres for the optimization of brain-penetrant molecules.<sup>12–14</sup> We utilized this approach for optimizing **3** and prepared a number of oxadiazole analogues of **3**. From this effort, the novel oxadiazole (*R*)-2-(4-chloro-*N*-(2-fluoro-4-(1,2,4-oxadiazol-3-yl)benzyl)phenyl)sulfonamido)-5,5,5-trifluoropentanamide (**4**; BMS-708163)<sup>15</sup> was synthesized and subsequently evaluated in vitro and in vivo. The Cytochrome P-450 (CYP) inhibition in human recombinant CYP enzymes for compound **2** was reported to be in the nanomolar range for CYP isoforms 3A4 and 2C19.<sup>8</sup> SAR was not performed on CYP inhibition per se; however, this liability was continually monitored in subsequent analogues. Compound **4** was evaluated in vitro as an inhibitor of human recombinant CYPs. Weak inhibition ( $IC_{50} = 20$   $\mu$ M) was observed for CYP2C19. No inhibition was observed for the other isoforms up to the maximum tested concentration of 40  $\mu$ M.

The synthesis of **4** was initiated via an asymmetric Strecker reaction with trifluorobutyraldehyde **5** and (*R*)- $\alpha$ -methylbenzylamine,<sup>16</sup> affording nitrile **6** as a 3.65:1 mixture of diastereomers (Scheme 1). Subsequent hydrolysis of nitrile **6** directly to the carboxamide **7**, followed by fractional crystallization of the HCl salt, afforded **8** in a > 99:1 ratio of the desired (*R,R*) vs the (*S,R*) diastereomer. Removal of the chiral auxiliary under hydrogenolysis conditions with catalytic palladium hydroxide gave the amine hydrochloride salt **9**, followed by conversion of the amine to the corresponding sulfonamide under standard conditions afforded **10** in 84 % yield over the two steps. Alkylation of **10** with cesium carbonate and 4-cyano-2-fluorobenzyl bromide **11** afforded **12** in 68 % yield with no loss of stereochemical purity as determined by chiral high-performance liquid chromatography. Lastly, conversion of **12** to oxadiazole **4** was accomplished via a two-step procedure starting with the addition of hydroxylamine to the aryl nitrile, affording the intermediate amide-oxime **13**. Annulation of the amide-oxime **13** with triethyl orthoformate and a catalytic amount of boron trifluoride etherate gave the oxadiazole **4** in 69 % yield over two steps.<sup>17</sup> The overall conversion of aldehyde **5** to oxadiazole **4** was amenable to scale-up as needed for in vivo testing.

In vitro, **4** demonstrated an improved metabolic stability profile relative to **3** across species [% remaining after 10 min of incubation = 32 % (rat), 75 % (dog), and 97 % (human)], as well as a significantly diminished PXR transactivation profile ( $EC_{60} > 16.7$   $\mu$ M) relative to compound **1**. Compound **4** potently inhibited the formation of A $\beta$ 40 and A $\beta$ 42 in H4-8Sw cells. Analysis of multiple experiments yielded an  $IC_{50} = 0.30 \pm 0.15$  nM (mean  $\pm$  SD,  $n = 50$ ) for A $\beta$ 40

Scheme 1. Synthesis of Compound 4<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) NaCN, AcOH, MeOH, 3.65:1 *de*, 89%. (b) H<sub>2</sub>SO<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>. (c) HCl, Et<sub>2</sub>O/MeOH recrystallization, >99% *de*, 23%. (d) Pd(OH)<sub>2</sub>, H<sub>2</sub> (50 psi), EtOH/H<sub>2</sub>O. (e) 4-Chlorobenzene-1-sulfonyl chloride, DIPEA, CH<sub>2</sub>Cl<sub>2</sub>, 84% (two steps). (f) Cs<sub>2</sub>CO<sub>3</sub>, DMF, 68%. (g) NH<sub>2</sub>OH, EtOH. (h) BF<sub>3</sub>·OEt<sub>2</sub>, CH(OMe)<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub> 69% (two steps).

Table 2. Single-Dose Pharmacokinetic Parameters of 4 in Rats and Dogs<sup>a</sup>

species	route	dose (mg/kg)	C <sub>max</sub> (μM)	T <sub>max</sub> (h)	AUC (0–24 h) (μM h)	T <sub>1/2</sub> (h)	CLTp (mL/min/kg)	V <sub>ss</sub> (L/kg)	F (%)
rat (female)	IV	1			2.60 ± 0.42	6.90 ± 2.20	11.7 ± 2.48	5.34 ± 0.74	105
	PO	10	2.29 ± 1.1	14.0 ± 9.2	27.2 ± 7.39				
dog (male)	IV	1			6.04 ± 1.12	11.4 ± 1.76	4.20 ± 0.93	3.87 ± 0.56	42
	PO	2.5	0.58 ± 0.24	0.75 ± 0.25	6.35 ± 2.07				

<sup>a</sup> Mean ± SD. Compound 4 (10 μM) was 97.0 ± 0.7% bound to human serum proteins and 96.3–97.9% bound to serum proteins in the animal species studied.

inhibition and an IC<sub>50</sub> = 0.27 ± 0.12 nM (mean ± SD, *n* = 45) for Aβ<sub>42</sub> inhibition.

In addition to APP processing, γ-secretase activity is required for signaling by the Notch family of transmembrane receptors.<sup>18,19</sup> Because inhibition of Notch signaling causes undesired, mechanism-based side effects, a cellular assay for Notch1-ΔE signaling was used to counterscreen γ-secretase inhibitors.<sup>20–22</sup> Compound 4 exhibited weaker potency for inhibition of Notch processing, IC<sub>50</sub> = 58 ± 23 nM (mean ± SD, *n* = 58), as compared to its inhibition potency for APP cleavage. On the basis of the cellular potencies for inhibiting Aβ<sub>40</sub> generation (0.30 nM) and Notch signaling (58 nM) in these assays, 4 demonstrated a Notch/APP selectivity ratio of 193X (95% CI = 163–232). With compound 4, there were no dose-limiting effects in dogs with QD/PO dosing for 6 months at 3 mg/kg.

Table 2 illustrates the pharmacokinetic parameters of 4 in female rats and male dogs.<sup>23</sup> In both rats and dogs following

an IV dose, plasma concentrations exhibited a multiexponential decline. The total body clearance of 4 was low in both species (rat = 11.7 ± 2.48 mL/min/kg; dog = 4.20 ± 0.93 mL/min/kg). The volume of distribution at steady state (V<sub>ss</sub>) was high, indicating extensive extravascular distribution (rat = 5.34 L/kg; dog = 3.87 L/kg). Oral bioavailability from solution formulations of 4 was 105 and 42% in rats and dogs, respectively. In addition, 4 demonstrated a high brain to plasma ratio (brain<sub>concn</sub>/plasma<sub>concn</sub> = 2.4) in dogs.

On the basis of favorable oral bioavailability and sufficient half-life for QD dosing, 4 was dosed orally in female rats and analyzed for its potential to reduce Aβ<sub>40</sub> in plasma and brain over a time course of 24 h at doses of 1, 10, and 100 mg/kg. Compound 4 significantly reduced both plasma and brain Aβ<sub>40</sub> levels relative to control at 10 and 100 mg/kg for the entire dosing interval (Figure 2A,B). The increase in plasma Aβ levels observed at the 1 mg/kg dose is related to an intrinsic characteristic of γ-secretase pharmacology and is

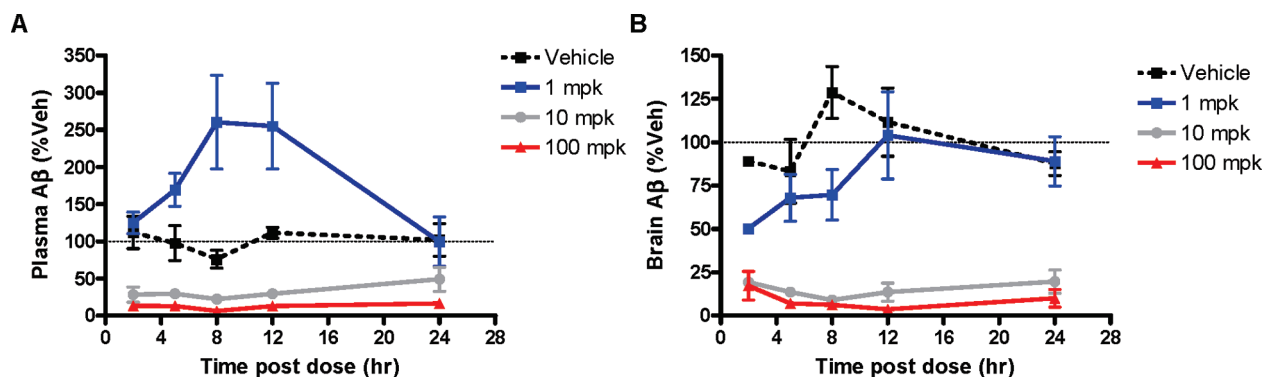


Figure 2. Plasma and brain Aβ40 following a single dose of 4 in female rats. The time course of changes in (A) plasma Aβ40 and (B) brain Aβ40. Mean ± SEM (*n* = 3 animals) for each time point shown.

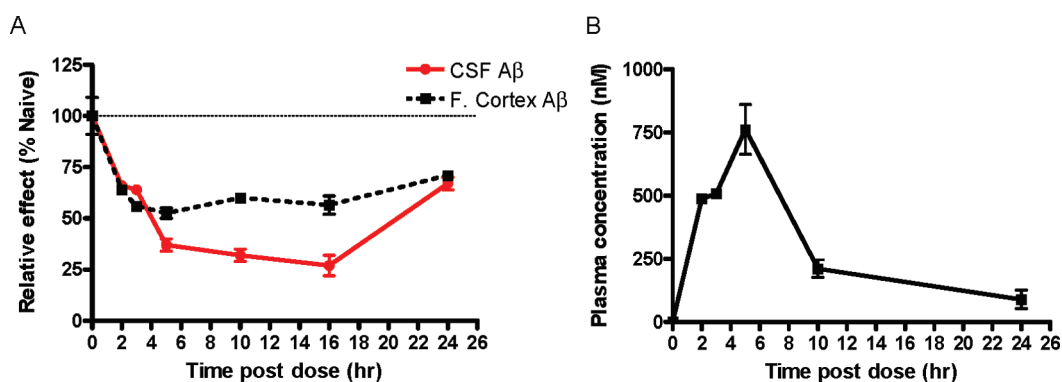


Figure 3. (A) Brain and CSF Aβ40 % reduction and (B) plasma concentration by 4 dosed PO 2 mg/kg in male dogs. Mean ± SEM (*n* = 1 or 2 animals) for each time point shown.

observed with low levels of  $\gamma$ -secretase inhibition (Figure 2A).<sup>7</sup> In brain, 4 demonstrated significant Aβ40 lowering for 8 h after an oral dose of 1 mg/kg (Figure 2B). In a separate study, when measured 5 h after single oral doses ranging from 3 to 100 mg/kg, 4 significantly lowered CSF Aβ40 levels in rats (data not shown).

In addition to the *in vivo* studies performed in rats, 4 was administered orally to male beagle dogs to measure Aβ40 lowering in brain and CSF. In this study, dogs were administered a single oral dose of 2 mg/kg of 4 and euthanized 2, 3, 5, 10, 16, and 24 h postdose (*n* = 1 or 2 per time point). Aβ40 measurements from the frontal cortex and CSF showed a rapid and sustained reduction in brain and CSF Aβ40 levels (Figure 3). In this experiment, CSF Aβ reductions measured in the dog correlated with Aβ reductions measured in the frontal cortex. Because it is not possible to directly measure human brain Aβ, a pharmacologic proof of concept of Aβ reductions in humans will rely primarily on measurement of a surrogate biomarker(s). On the basis of the correlation observed between brain and CSF Aβ40 lowering activity in dogs, our results suggest that CSF Aβ40 may serve as a surrogate biomarker for brain Aβ40 levels in humans.

In summary, we designed and synthesized the novel oxadiazole-substituted sulfonamide 4 as a potent and selective  $\gamma$ -secretase inhibitor for the potential treatment of Alzheimer's disease. Replacement of the benzamide functionality in compound 3 with a bioisosteric oxadiazole

as well as incorporation of a trifluoromethyl group<sup>24</sup> in the side chain improved brain penetration and significantly increased the ability of this class of compounds to lower brain Aβ40. Compound 4 is currently undergoing clinical evaluation to determine its potential to act as a disease-modifying agent for the treatment of Alzheimer's disease. Results from these studies and a more detailed SAR summary surrounding the discovery of 4 will be presented in due course.

**SUPPORTING INFORMATION AVAILABLE** Experimental details for synthetic procedures and associated chemical data for compounds 3–13 as well as experimental details on the Aβ40 and mNotch1-ΔE assays. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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