

## Discovery of BIIB042, a Potent, Selective, and Orally Bioavailable $\gamma$ -Secretase Modulator

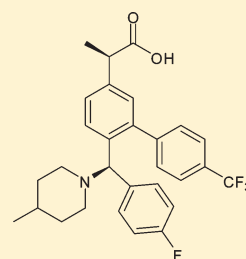
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**S** Supporting Information

**ABSTRACT:** We have investigated a novel series of acid-derived  $\gamma$ -secretase modulators as a potential treatment of Alzheimer's disease. Optimization based on cellular potency and brain pharmacodynamics after oral dosing led to the discovery of **10a** (BIIB042). Compound **10a** is a potent  $\gamma$ -secretase modulator, which lowered  $A\beta_{42}$ , increased  $A\beta_{38}$ , but had little to no effect on  $A\beta_{40}$  levels both in vitro and in vivo. In addition, compound **10a** did not affect Notch signaling in our in vitro assessment. Compound **10a** demonstrated excellent pharmacokinetic parameters in multiple species. Oral administration of **10a** significantly reduced brain  $A\beta_{42}$  levels in CF-1 mice and Fischer rats, as well as plasma  $A\beta_{42}$  levels in cynomolgus monkeys. Compound **10a** was selected as a candidate for preclinical safety evaluation.

**KEYWORDS:** Secretase, GSM, Alzheimer's, amyloid, Mannich reaction



BIIB042 (**10a**)

$A\beta_{42}$  EC<sub>50</sub> = 70–170 nM  
40% brain  $A\beta_{42}$  reduction  
in mice at 10 mg/kg p.o.

Alzheimer's disease (AD) is a devastating neurodegenerative disorder for which there is no disease-modifying therapy currently available.<sup>1</sup> Multiple lines of evidence suggest that amyloid- $\beta$  ( $A\beta$ ) peptide plays a pivotal role in the pathogenesis of AD. Preventing the accumulation and aggregation of  $A\beta$  peptide has been one of the major strategies in developing disease-modifying AD therapies.<sup>2–4</sup>  $A\beta$  peptides are produced from sequential cleavage of amyloid precursor protein (APP) by  $\beta$ -secretase and  $\gamma$ -secretase in the brain.<sup>5</sup> Cleavage by  $\gamma$ -secretase produces  $A\beta$  peptides that generally range from 37 to 42 amino acids in length.  $A\beta_{42}$  is more amyloidogenic as compared to the shorter  $A\beta$  isoforms and may serve as a key seed in the formation of senile plaques and may be at least partially responsible for mediating cognitive impairment in AD.<sup>6–8</sup>  $\gamma$ -Secretase modulators (GSMs) preferentially shift the carboxy-terminal cleavage pattern on the  $\beta$ -secretase-processed APP (C99) to bias production away from longer isoforms such as  $A\beta_{42}$  in favor of shorter, less toxic  $A\beta$  isoforms, such as  $A\beta_{38}$ . Because GSMs do not inhibit the enzymatic activity of  $\gamma$ -secretase, they are much less likely to interfere with processing and subsequent signaling activities of other important substrates, such as Notch, and could, therefore, potentially provide a better safety profile as compared to the  $\gamma$ -secretase inhibitors (GSIs).<sup>9,10</sup>

The first generation of GSMs originated from an epidemiological analysis, which showed that certain nonsteroidal anti-inflammatory drugs (NSAIDs) lowered the risk of developing AD, and the effect was independent of COX inhibition.<sup>11</sup> NSAID-derived

Tarenflurbil (**1**, EC<sub>50</sub> = 300  $\mu$ M, Figure 1)<sup>12</sup> was progressed through phase III clinical trials for AD but failed to achieve efficacy, potentially due to weak GSM activity and poor brain penetration. Chiesi has recently advanced CHF5074 (**2**, EC<sub>50</sub> = 40  $\mu$ M, Figure 1) into a phase II clinical trial. Cognitive benefits and plaque load reduction in the brain were reported after chronic treatment of Tg2576 transgenic mice with CHF5074.<sup>13</sup> This compound is about 7-fold more potent than Tarenflurbil and has improved brain exposure after prolonged dosing. There has been an intensive effort to further improve potency and brain exposure as exemplified by Merck's recent publications on a series of carboxylic acid-derived GSMs (e.g., **3**, EC<sub>50</sub> = 0.6  $\mu$ M, Figure 1).<sup>14</sup> Eisai's GSM (**4**, EC<sub>50</sub> = 0.08  $\mu$ M, Figure 1) represents a different class of GSMs that contain an aryl imidazole moiety instead of the carboxylic acid.<sup>15</sup> Additional patent literature in this field has been extensively reviewed recently.<sup>15</sup>

Our program aimed to identify potent GSMs with favorable brain exposure. As shown in Figure 2, our early lead **5** was designed to test the idea if an amino nitrogen atom was tolerated when introduced off the biaryl acetic acid scaffold that is similar to those of NSAIDs. Compound **5** was active in APP CHO cellular assay (EC<sub>50</sub> = 1  $\mu$ M). However, brain exposure was limited (0.6  $\mu$ M, 4 h) in mice after 50 mg/kg oral dosing, even though the plasma

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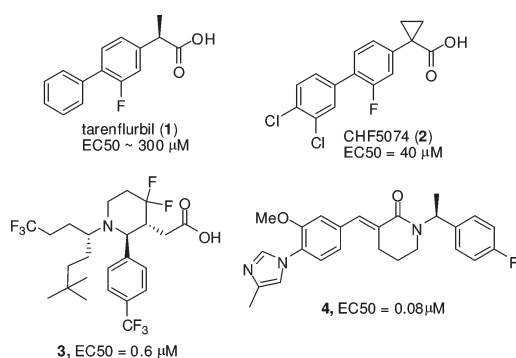


Figure 1. Structures of GSMs.

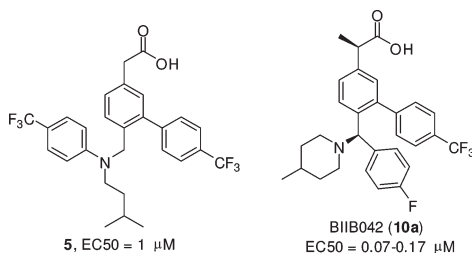
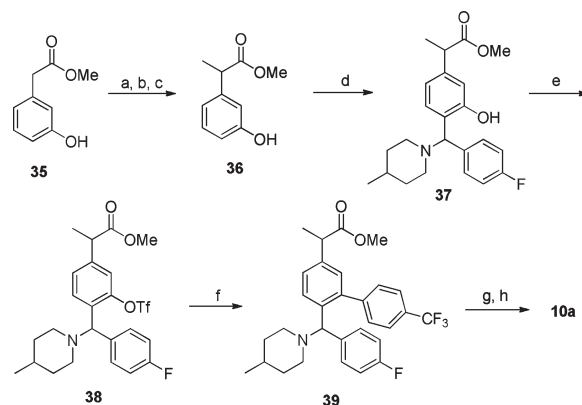


Figure 2. Structures of early lead 5 and BIIB042.

concentration was excellent (14.9 μM). We then decided to constrain the side chain into a more rigid structure and incorporate a basic nitrogen atom, in an effort to improve brain penetration. Mannich reaction on 3-hydroxyphenyl acetic acid (35, Scheme 1) provided an interesting and facile route to construct a compact framework and incorporate amines such as piperidine. Multipoint optimization based on cellular potency and brain pharmacodynamic (PD) response in wild type mice after oral dosing lead to the discovery of the preclinical candidate BIIB042 (10a). Herein, we describe the syntheses, structure–activity relationships (SARs), and profiles of this novel series of carboxylic acid-derived GSMs.

Tables 1–3 summarize the SAR at various positions of the molecule. CHO cells overexpressing the APP V717F mutation were used to measure the effect of GSM compounds on Aβ peptide (Aβ<sub>42</sub>, Aβ<sub>40</sub>, and Aβ<sub>38</sub>) production using a multiplex Aβ ELISA assay to detect all isoforms simultaneously in a single well. In our investigation, compounds that lowered the levels of Aβ<sub>42</sub> concomitantly elevated the levels of Aβ<sub>38</sub>, while leaving Aβ<sub>40</sub> levels generally unchanged. The PD response of these compounds was measured in wild-type mice following oral administration. Animals were sacrificed 4 h after dosing, and brain and plasma samples were collected for analyses of both drug exposure and Aβ levels.

As shown in Table 1, with a much more rigid and compact structure and a basic amine as compared to the early lead 5, compound 6 maintained moderate potency (EC<sub>50</sub> = 1.1 μM) for lowering Aβ<sub>42</sub> in the APP CHO cellular assay. This was accompanied by a 10-fold improvement in brain exposure (brain concn = 7.4 μM, 4 h, po, 50 mg/kg) and a detectable PD response (20% Aβ<sub>42</sub> reduction). At the R3 position, 4-CF<sub>3</sub> phenyl was found to be optimal. As exemplified in Table 1, compound 7 (*p*-F-phenyl, EC<sub>50</sub> = 2.3 μM) was less potent as compared to 6. Compound 8 (4-*t*-butyl phenyl, EC<sub>50</sub> = 0.56 μM)

Scheme 1. Synthesis of Compound 10a<sup>a</sup>

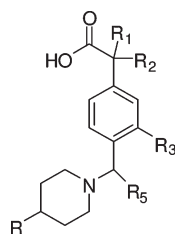
<sup>a</sup> (a) BnBr, K<sub>2</sub>CO<sub>3</sub>, acetonitrile, room temperature, 6 h, 87%. (b) LiHMDS, THF, CH<sub>3</sub>I, −78 °C to room temperature, 76%. (c) Pd/C, H<sub>2</sub>, MeOH, 3 h, 87%. (d) 4-Fluorobenzaldehyde, 4-methylpiperidine, trifluoro toluene, microwave, 120 °C, 1 h, 42%. (e) Tf<sub>2</sub>O, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, 75%. (f) 4-(Trifluoromethyl)phenyl boronic acid, Pd(PPh<sub>3</sub>)<sub>4</sub>, 1,2-dimethoxyethane/ethanol/saturated Na<sub>2</sub>CO<sub>3</sub>, microwave, 120 °C, 0.5 h, 67%. (g) NaOH, MeOH/THF (1:1), microwave, 100 °C, 10 min, 86%. (h) SCF chiral separation, Chiralpak AD-H (2 cm × 15 cm), 10% isopropanol (0.1% DEA)/CO<sub>2</sub>, 100 bar, 60 mL/min, 220 nm.

demonstrated improved cellular potency; however, it had much lower brain exposure (1.0 μM, 4 h) as compared to 6 and did not reduce brain Aβ<sub>42</sub> when dosed at 50 mg/kg orally. Heterocyclic moieties were not well tolerated at the R3 position as exemplified by compound 9 (EC<sub>50</sub> = 4.5 μM).

Compounds 10–19 highlight the SAR at the R1/R2 position. Substitution at this position appeared to greatly improve cellular potency. As compared to compound 11, a simple methyl substitution at the R1/R2 position improved the cellular potency by 8-fold (Table 1, compound 10, EC<sub>50</sub> = 0.39 μM). There was a trend that bulkier groups at the R1/R2 position provided more potent cellular activity as demonstrated by compounds 12, 13, and 15–17, with compound 17 achieving 40 nM EC<sub>50</sub> in the APP CHO cellular assay. However, brain penetration tended to diminish as the number of rotatable bonds increased and the molecular weight passed 500. For example, compound 14 (EC<sub>50</sub> = 0.12 μM) only achieved 30% Aβ<sub>42</sub> reduction and 5.7 μM drug concentration in the brain when dosed at 50 mg/kg, while the methyl analogue 10 resulted in 45% Aβ<sub>42</sub> lowering and 18.4 μM drug concentration in the brain when dosed at 30 mg/kg. Compounds 18 and 19 have an advantage of simplifying the stereochemistry. Unfortunately, the cyclopropyl analogue 19 was weaker in lowering Aβ<sub>42</sub> in the cell-based assay (EC<sub>50</sub> = 2.2 μM). The gem dimethyl analogue (18) showed reasonable cellular potency (EC<sub>50</sub> = 0.45 μM), however, had only moderate brain PD response (30% Aβ<sub>42</sub> reduction) in mice at 30 mg/kg and did not show PD response in the brain after oral dosing at 30 mg/kg in rat (data not shown).

The key SAR at the R5 position is highlighted by compounds 20–24. Various substitution patterns on the phenyl were explored; 4-F phenyl appeared to be the best as in compound 10. For reasons not clear to us, compound 20 did not achieve a PD response in the brain even though the cellular potency was better, and the brain exposure was significant. A heterocyclic moiety appeared to be not as well tolerated at the R5 position, as exemplified by compound 23. The best heterocyclic analogue

Table 1. SAR at the R1/R2, R3, and R5 Positions



Cmpd	R1, R2	R3	R	R5	A $\beta$ 42 EC <sub>50</sub> ( $\mu$ M) <sup>a</sup>	A $\beta$ 42 Red. brain <sup>b</sup>	Brain/plasma Conc. ( $\mu$ M)
<b>6</b>	H, H	<i>p</i> -CF <sub>3</sub> Ph	CF <sub>3</sub>	<i>p</i> -FPh	1.1	20% <sup>c</sup>	7.4/26
<b>7</b>	H, H	<i>p</i> -FPh	CF <sub>3</sub>	<i>p</i> -FPh	2.3	NT <sup>f</sup>	
<b>8</b>	H, H		CF <sub>3</sub>	<i>p</i> -FPh	0.56	NS <sup>c,e</sup>	1.0/6.3
<b>9</b>	Me, H		Me	<i>p</i> -FPh	4.5	NT	
<b>10</b>	Me, H	<i>p</i> -CF <sub>3</sub> Ph	Me	<i>p</i> -FPh	0.39	45% <sup>d</sup>	18.4/27.2
<b>11</b>	H, H	<i>p</i> -CF <sub>3</sub> Ph	Me	<i>p</i> -FPh	2.9	NT	
<b>12</b>	Et, H	<i>p</i> -CF <sub>3</sub> Ph	Me	<i>p</i> -FPh	0.33	40% <sup>d</sup>	13.0/20.4
<b>13</b>	n-Pr, H	<i>p</i> -CF <sub>3</sub> Ph	Me	<i>p</i> -FPh	0.25	NT	
<b>14</b>	i-Pr, H	<i>p</i> -CF <sub>3</sub> Ph	Me	<i>p</i> -FPh	0.93	NT	
<b>15</b>	, H	<i>p</i> -CF <sub>3</sub> Ph	H	<i>p</i> -FPh	0.12	30% <sup>c</sup>	5.7/32.2
<b>16</b>	, H	<i>p</i> -CF <sub>3</sub> Ph	Me	<i>p</i> -FPh	0.11	40% <sup>d</sup>	11.8/29.6
<b>17</b>	, H	<i>p</i> -CF <sub>3</sub> Ph	H	<i>p</i> -FPh	0.04	NT	
<b>18</b>	Me, Me	<i>p</i> -CF <sub>3</sub> Ph	Me	<i>p</i> -FPh	0.45	30% <sup>d</sup>	16.1/22.8
<b>19</b>		<i>p</i> -CF <sub>3</sub> Ph	Me	<i>p</i> -FPh	2.2	NT	
<b>20</b>	Me, H	<i>p</i> -CF <sub>3</sub> Ph	Me	<i>p</i> -CF <sub>3</sub> Ph	0.18	NS <sup>d,e</sup>	14.0/20.5
<b>21</b>	Me, H	<i>p</i> -CF <sub>3</sub> Ph	Me		0.25	40% <sup>d</sup>	12.0/20.8
<b>22</b>	Me, H	<i>p</i> -CF <sub>3</sub> Ph	Me	<i>p</i> -ClPh	0.42	25% <sup>d</sup>	19.4/27.1
<b>23</b>	Me, H	<i>p</i> -CF <sub>3</sub> Ph	Me		3.7	NT	
<b>24</b>	Me, H	<i>p</i> -CF <sub>3</sub> Ph	Me		0.58	23% <sup>d</sup>	10.9/25.2

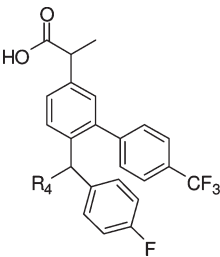
<sup>a</sup> EC<sub>50</sub> values were calculated as an average of at least two determinations. <sup>b</sup> PD responses were measured at 4 h after oral administration of compounds in a solution formulation (ethanol:propylene glycol:10% solutol = 1:1:8). <sup>c</sup> Oral dosing at 50 mg/kg. <sup>d</sup> Oral dosing at 30 mg/kg. <sup>e</sup> NS, not significant. <sup>f</sup> NT, not tested.












(**24**, EC<sub>50</sub> = 0.58  $\mu$ M) in our collection achieved favorable brain exposure (brain concn = 10.9  $\mu$ M), likely benefiting from a 4-CF<sub>3</sub> substituted pyridyl group at the R5 position. However, the PD response of **24** was rather moderate (23% A $\beta$ 42 reduction, 30 mg/kg).

We then fixed R1/R2, R3, and R5 and explored the R4 position. As shown for compound **25** in Table 2, a piperazine

moiety at this position led to much weaker cellular activity. However, hydrophobic substitution on the piperidine was beneficial in improving cellular potency. For example, the 4-CF<sub>3</sub> substitution on piperidine rendered compound **26** 2-fold more potent in the cell-based assay (EC<sub>50</sub> = 0.18  $\mu$ M) as compared to compound **10**. Interestingly, the improved in vitro potency did not translate into a better PD response in the brain despite

Table 2. SAR at the R4 Position



Cmpd	R4	A $\beta$ 42 EC <sub>50</sub> ( $\mu$ M) <sup>a</sup>	A $\beta$ 42 Red. Brain <sup>b</sup>	brain/plasma Conc. ( $\mu$ M)
<b>10</b>		0.39	45%	18.4/27.2
<b>25</b>		> 10	NT	
<b>26</b>		0.18	40%	14.4/21.7
<b>27</b>		1.4	NT	
<b>28</b>		2.0	NT	
<b>29</b>		2.3	NT	
<b>30</b>		0.3	30%	25.3/27.2
<b>31</b>		0.17	25%	2.5/5.3
<b>32</b>		0.4	NT	
<b>33</b>		0.39	25%	3.1/10.7
<b>34</b>		0.62	30%	12.1/16.3

<sup>a</sup>EC<sub>50</sub> values were calculated as an average of at least two determinations. <sup>b</sup>PD responses were measured at 4 h after oral administration of compounds at 30 mg/kg in a solution formulation (ethanol:propylene glycol:10% solutol = 1:1:8).

comparable brain exposures (Table 2). In the absence of a methyl substitution on the piperidine, compound **27** was about 4-fold less potent as compared to **10** in the cell-based assay. 4-Fluoro substitutions, as in **28** (EC<sub>50</sub> = 2  $\mu$ M), was not beneficial. The pyrrolidine analogue **29** was also weaker in the cell-based assay (EC<sub>50</sub> = 2.3  $\mu$ M). Compound **31** exhibited better cellular potency (EC<sub>50</sub> = 0.17  $\mu$ M); however, the brain exposure was much lower (2.5  $\mu$ M), resulting in a weak PD response. As exemplified by compounds **32**–**34**, spiro, bridged, and fused cyclic amines were well tolerated at the R4 position. The PD responses for these compounds were moderate (Table 2). Overall, compound **10** provided the most robust PD response in the brain.

The synthetic route to **10a** is outlined in Scheme 1. The  $\alpha$ -methyl group was installed by benzyl protection of methyl 2-(3-hydroxyphenyl)acetate (**35**) followed by methylation and

Table 3. Separated Single Isomers of Compound 10

compd	A $\beta$ 42 EC <sub>50</sub> ( $\mu$ M)	A $\beta$ 42 red. brain (10 mpk) (%)	brain/plasma concn ( $\mu$ M)	hERG EC <sub>50</sub> ( $\mu$ M)
<b>10a</b>	0.17	40	4.6/10	15
<b>10b</b>	0.15	38	6.6/7.4	4.6
<b>10c/10d</b>	0.89	NT		

deprotection to give intermediate **36**. Then, 4-fluorobenzaldehyde and 4-methylpiperidine were condensed with **36** in trifluorotoluene via a three components Mannich reaction to afford intermediate **37**. Triflation of **37** followed by Suzuki coupling with 4-(trifluoromethyl)phenyl boronic acid provided **39**, which was hydrolyzed to compound **10**. Using supercritical fluid (SCF) chiral method, racemate **10** was separated into two single isomers (**10a** and **10b**). The absolute configuration of **10a** was unambiguously established as *R,R* by a single crystal X-ray structure determination (Supporting Information). The other two isomers (**10c** + **10d**) were very difficult to separate and were tested as a mixture in the assays.

As shown in Table 3, isomers **10a** and **10b** showed similar cellular potency in lowering A $\beta$ 42 (EC<sub>50</sub> = 0.17 and 0.15  $\mu$ M, respectively). The A $\beta$ 40 levels were unchanged, and A $\beta$ 38 levels were increased (EC<sub>50</sub> = 0.15 and 0.11  $\mu$ M, respectively). The mixture of the other two isomers was much less active (EC<sub>50</sub> = 0.89  $\mu$ M) and was not profiled further at the time. Both **10a** and **10b** demonstrated a very good PD response in the brain in wild-type mice after oral administration at 10 mg/kg. At 4 h postdose, these compounds achieved 4.6 and 6.6  $\mu$ M brain concentrations, respectively, resulting in a 40 and 38% reduction in brain A $\beta$ 42 levels, as compared to the vehicle control. When tested in the FastPatch hERG assay, compound **10b** had an EC<sub>50</sub> of 4.6  $\mu$ M, while isomer **10a** had an EC<sub>50</sub> of 15  $\mu$ M. Therefore, we proceeded to profile **10a** more thoroughly.

Compound **10a** demonstrated excellent permeability in the Caco 2 assay [ $P_{app}(A - B) = 43.8 \times 10^{-6}$  cm/s,  $p$  ratio (B - A/A - B) = 0.8] and was not a substrate for efflux transporters. It did not inhibit any of the five major human CYP isoforms assayed (3A4, 2C9, 2C19, 2D6, and 1A2; IC<sub>50</sub> > 35  $\mu$ M), and there was no evidence for time-dependent inhibition of human CYP3A4. The in vitro microsomal stability of **10a** was good [Qh%: 27 (mouse), 24 (rat), 41 (dog), 25 (dog), and 34% (human)]. Compound **10a** was highly protein-bound across species in mouse, rat, dog, monkey, and human plasma ( $f_u$ % < 0.1%). The thermodynamic solubility was moderate and measured 20–30  $\mu$ g/mL for a crystalline HCl salt. In addition to the low risk hERG readout, compound **10a** was negative in the AMES mutagenicity assay.

In terms of selectivity, compound **10a** inhibited COX1 or COX2 very weakly (IC<sub>50</sub> = 35 and 27  $\mu$ M, respectively). Compound **10a** was tested in a cell-based assay in which the levels of HES1 protein were measured. HES1 expression is dependent upon an intact Notch signaling cascade and is mediated via cleavage of the Notch intracellular domain from the nascent transmembrane protein by  $\gamma$ -secretase.<sup>16</sup> Compound **10a** was found to have no effect on HES-1 after 24 h of incubation of the cell with 10  $\mu$ M compound in this assay.

Compound **10a** demonstrated very good pharmacokinetic characteristics. As summarized in Table 4, it achieved good oral bioavailability (44–106%) after a single oral dose at 10 mg/kg (crystalline HCl salt formulated in suspension) in rats, dogs, and

Table 4. Single Dose Pharmacokinetic Parameters of 10a in Rats, Dogs, and Cynomolgus Monkeys<sup>a</sup>

species	route	dose (mg/kg)	Clp (mL/min/kg)	Vss (L/kg)	t <sub>1/2</sub> (h)	AUC <sub>0–24h</sub> (μg/mL h)	C <sub>max</sub> (μg/mL)	T <sub>max</sub> (h)	F (%)
rat	iv <sup>b</sup>	1	1.5 ± 0.1	0.8 ± 0.2	7.2 ± 1.7	10.4 ± 0.8			
	po <sup>c</sup>	10			6.6 ± 0.6	49.7 ± 8.8	6.0 ± 0.4	1.7 ± 0.6	47 ± 9
dog	iv <sup>b</sup>	1	14 ± 1	0.9 ± 0.1	1.3 ± 0.2	1.2 ± 0.1			
	po <sup>c</sup>	10			2.3 ± 0.2	5.2 ± 1.8	1.4 ± 0.5	1.3 ± 0.6	44 ± 16
monkey	iv <sup>b</sup>	1	3.7 ± 1.2	1.7 ± 0.3	11.2 ± 4.3	4.7 ± 1.4			
	po <sup>c</sup>	10			25 ± 6	48 ± 14	5.9 ± 2.3	2.0 ± 1.7	106 ± 33

<sup>a</sup> Mean ± SD (n = 3). <sup>b</sup> Formulation iv EtOH:PEG400:water (10:40:50), 1 mL/kg. <sup>c</sup> Formulation po, 0.5% CMC, 0.2% Tween80, 5 mL/kg.

cynomolgus monkeys. Compound 10a had low clearance in rats and cynomolgus monkeys with a t<sub>1/2</sub> of 6 and 11 h, respectively. In dogs, the clearance was higher, and the t<sub>1/2</sub> was approximately 2 h.

Compound 10a was also tested in human H4 cells that express human wild-type APP. In this assay, the compound displayed the same Aβ modulating profile as it had in the CHO-based cellular assay with an EC<sub>50</sub> of 70 nM for the reduction of Aβ<sub>42</sub>. As discussed previously, compound 10a showed significant Aβ<sub>42</sub> lowering (40%) in the brain after acute oral dosing at 10 mg/kg in wild type mice (CF-1). At the same oral dose, compound 10a also achieved 30% Aβ<sub>42</sub> reduction in the brain in Fischer rats (4 h) and 30% Aβ<sub>42</sub> reduction in the plasma in cynomolgus monkeys (5 h). The shifting of cleavage to shorter Aβ peptide in all three species appeared to match what was observed in the in vitro cellular assay: lowering Aβ<sub>42</sub>, increasing Aβ<sub>38</sub>, while having no effect on Aβ<sub>40</sub> levels. The complete pharmacological data will be reported in due course.

In conclusion, we have designed a novel series of acid-based GSMs that are potent and have excellent brain exposure. On the basis of its potent lowering of brain Aβ, its lack of Notch activity, and its favorable pharmaceutical profiles, BIIB042 (10a) was selected as a candidate for preclinical safety evaluation.

## ■ ASSOCIATED CONTENT

Supporting Information. Experimental details for Aβ and Notch assays, synthetic procedures, and analytical data for compounds 6–34 and crystallographic data for compound 10a. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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