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Discovery of (*S*)-2-((*S*)-2-(3,5-difluorophenyl)-2-hydroxyacetamido)-*N*-((*S*,*Z*)-3-methyl-4-oxo-4,5-dihydro-3*H*-benzo[*d*][1,2]diazepin-5-yl)propanamide (BMS-433796): A γ-secretase inhibitor with Aβ lowering activity in a transgenic mouse model of Alzheimer's disease

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Abstract—We report on the design of benzodiazepinones as peptidomimetics at the carboxy terminus of hydroxyamides. Structure–activity relationships of diazepinones were investigated and orally active γ-secretase inhibitors were synthesized. Active metabolites contributing to Aβ reduction were identified by analysis of plasma samples from Tg2576 mice. In particular, (*S*)-2-((*S*)-2-(3,5-difluorophenyl)-2-hydroxyacetamido)-*N*-((*S*,*Z*)-3-methyl-4-oxo-4,5-dihydro-3*H*-benzo[*d*][1,2]diazepin-5-yl)propanamide (BMS-433796) was identified with an acceptable pharmacodynamic and pharmacokinetic profile. Chronic dosing of BMS-433796 in Tg2576 mice suggested a narrow therapeutic window and Notch-mediated toxicity at higher doses.

Alzheimer's disease (AD) is the major cause of dementia in the aging population. Autopsy of brains from AD patients reveals the presence of extracellular plaques and intracellular tangles, pathological hallmarks which are used to confirm diagnosis of the disease.[1] Over 20 years ago, it was discovered that plaques are largely composed of beta amyloid peptides (Aβ).[2] Although it was originally suspected that plaques were themselves the primary neurotoxic agents in AD, the focus has now shifted to soluble oligomeric forms of Aβ.[3] Although

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the majority of Aβ is the 40 amino acid form (Aβ40), Aβ42 is more prone to oligomerization and is associated with AD through rare mutations that lead to increased Aβ42 production.[3,4] Aβ is generated from a precursor protein through sequential cleavages by BACE and γ-secretase, both of which are being actively pursued as targets for the treatment of AD.[5,6] γ-Secretase is a complex of either presenilin-1 (PS-1) or PS-2 with nicastrin, Aph-1, and Pen-2, and is an unusual aspartyl protease requiring two Asp residues in PS.[6,7]

Several structurally diverse small molecule inhibitors of γ-secretase have been reported in the literature using whole-cell γ-secretase inhibition assays. These inhibitors include peptidic PS1 inhibitors,[8,9] semi-peptidic inhibitors from the Elan/Lilly group,[10,11] diaryl sulfonamides,[12,13] succinoyl-caprolactam derivatives,[14] substituted cyclohexyl sulfones,[15–20] *N*-(oxoazepanyl)benzenesulfonamides, aminothia-zoles[21], and 1,4-benzoxazepin-3-ones.[22] Several compounds are entering clinical trials.[10,23]

In two previous communications,[24,25] we chronicled our research efforts exploring potent γ-secretase inhibitors **1**–**3** using a cell based assay that measures Aβ40 levels.[26] In an attempt to improve the exposure of **1** in Tg2576 mice, the carboxy terminus of **1** was constrained. This effort led to the discovery of diazepinedione peptidomimetic **3**. Diazepinedione based compounds exhibited improved efficacy in Tg2576 transgenic mice over their triamide congeners, but were still inadequate due to poor pharmacokinetic profiles and/or brain penetration.[24] The potencies of **1** and **3** (Fig. 1) suggest that the newly introduced tertiary amide bond in **3** may not be involved in a productive interaction with the γ-secretase complex. Since the extra amide bonds may be detrimental to brain penetration, our starting point for peptidomimetic design began with the diazepinedione moiety. Removal of the carbonyl of **3** would yield dihydro benzodiazepinone **4** or benzodiazepinone **5** which still maintain all the suspected necessary hydrogen-bond interactions with γ-secretase. A convergent approach to the synthesis of the dihydro benzodiazepinone ring system in **4** is shown in Scheme 1. Our initial attempts to prepare **4** from the diazepinedione of **3** failed as the aromatic carbonyl group could not be reduced selectively. A successful approach to the synthesis of **4** was based on an intramolecular Mitsunobu reaction shown in Scheme 1.

Thus, treatment of **6** (prepared from isochroman-3-one) with triphenylphosphine and diisopropylazo-dicarboxylate furnished the desired compound **7** in 60% yield. Introduction of azide functionality followed by its reduction under controlled conditions proceeded in excellent yield to give the amine **9**. The amine was then coupled to *N*-3,5-(difluorophenylacetyl)-alanine using EDC to give **10** in 75% yield. Exposure of **10** to trifluoroacetic acid resulted in removal of the N-terminal *tert*-butoxycarbonyl group to afford **11** as an amine salt in almost quantitative yield. Inhibitors **10** (IC_{50} = 24 nM) and **11** (IC_{50} = 9.0 nM) displayed excellent potencies thereby confirming the hypothesis that the aromatic carbonyl group of diazepinediones plays a passive role in the enzyme–inhibitor interaction. In further studies, compound **11** was selected for oral administration to Tg2576 mice (Table 1). The brain and plasma ED_{50} values for Aβ reductions 3 h after dosing were 26 and 5 μmol/kg, respectively.

Low compound levels of **11** were observed in the brain relative to the in vitro IC_{50} value, which suggested that there might be an active metabolite responsible for Aβ reduction. Mass spectral analysis of plasma and brain samples from Tg2576 mice detected metabolite **15** (Table 2) which results from oxidation of the diazepinone ring in **11**. Brain and plasma concentrations of **15** were similar to the levels of **11** in these samples

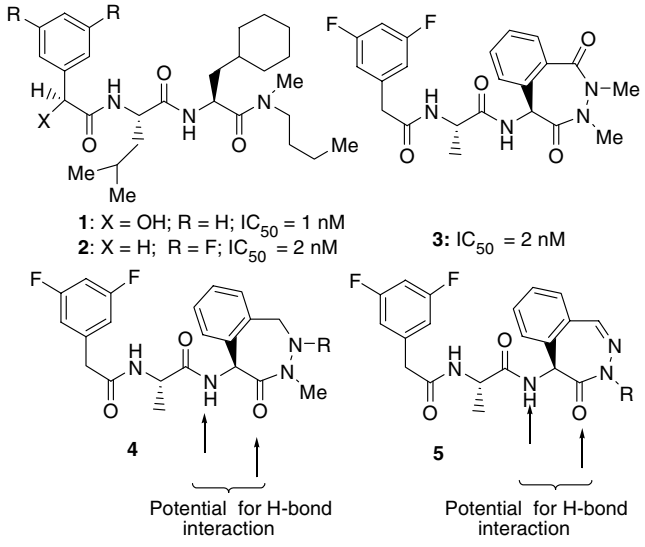
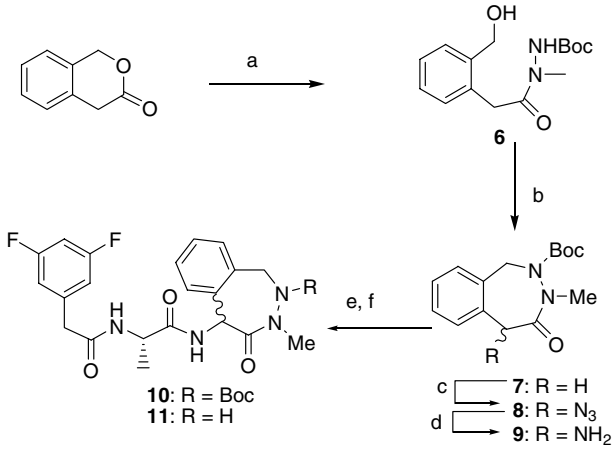


Figure 1. Design considerations of diazepinediones based on H-bond motif recognition.



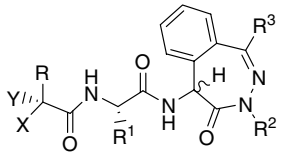
Scheme 1. Reagents and conditions: (a) (Me)HNNHBoc, catalytic HOAc, 100 °C, 12 h, 54%; (b) diisopropyl azodicarboxylate, PPh_3, THF, rt, 12 h, 60%; (c) $KN(SiMe_3)_2$, −78 °C, THF, trisyl azide, then HOAc, 61%; (d) 10% Pd–C, EtOAc, H_2 (1 atm), 40 min, 98%; (e) *N*-(3,5-difluorophenylacetyl)-L-alanine, EDC, HOBt, Et_3N, DMF, rt, 2 h, 75%; (f) CF_3CO_2H–CH_2Cl_2, rt, 2 h, 98%.

Table 1. Aβ and compound levels 3 h after a single oral dose of 30 μmol/kg to Tg2576 mice, $n = 7–10$

Compound	Cell IC_{50} (nM)	Brain Aβ (% inhibition)	Brain conc (nM)	Plasma Aβ (% inhibition)	Plasma conc (nM)
11	9	51 ± 4	6 ± 0.5	80 ± 1	205 ± 42
15	6	54 ± 3	12 ± 3	75 ± 3	199 ± 57
25	1	92 ± 2	280 ± 29	98 ± 1	2091 ± 162
40	0.3	90 ± 5	133 ± 12	88 ± 2	1959 ± 190
41	10	91 ± 6	202 ± 8	86 ± 2	2750 ± 322
42	30	29 ± 4	72 ± 10	Not determined	546 ± 49
43	750	Not dosed			

Means ± SEM.

Table 2. Aβ lowering activity in H4 cells following modifications at the amino acid and at the carboxy terminus



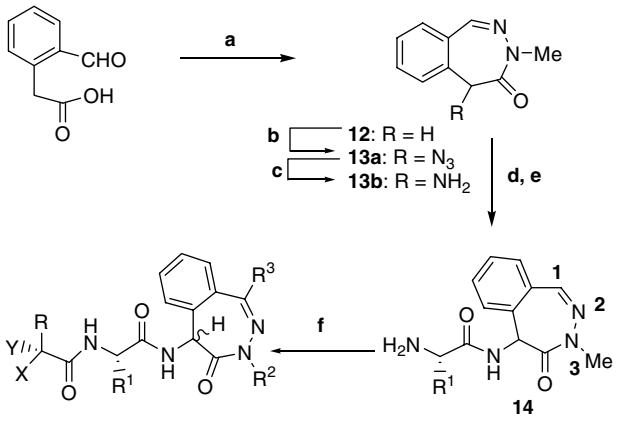
Compound	X	Y	R	R^1	R^2	R^3	IC_{50}[a] (nM)
15	H	H	3, 5-Difluorophenyl	CH_3	CH_3	H	6
16	H	H	3-Fluorophenyl	CH_3	CH_3	H	8
17	H	H	4-Fluorophenyl	CH_3	CH_3	H	59
18	H	H	3-Chlorophenyl	CH_3	CH_3	H	10
19	H	H	3-Pyridyl	CH_3	CH_3	H	162
20	H	H	Cyclohexyl	CH_3	CH_3	H	43
21	H	H	2-Naphthyl	CH_3	CH_3	H	269
22	H	H	2-Thienyl	CH_3	CH_3	H	3
23	H	H	3-Thienyl	CH_3	CH_3	H	1
24	H	H	2-Furyl	CH_3	CH_3	H	24
25	O	O	3,5-Difluorophenyl	CH_3	CH_3	H	1
26	H	H	3,5-Difluorophenyl	CH_3	$CH(CH_3)_2$	H	4
27	H	H	3,5-Difluorophenyl	CH_3	CH_3	CH_3	1.3
28	OH	H	3,5-Difluorophenyl	CH_3	CH_3	CH_3	0.2
29	H	H	3-Furanyl	CH_3	CH_3	CH_3	2
30	H	H	3,5-Difluorophenyl	$CH_2CH(CH_3)_2$	CH_3	H	0.5
31	H	H	3-Fluorophenyl	$CH_2CH(CH_3)_2$	CH_3	H	2
32	H	H	4-Fluorophenyl	$CH_2CH(CH_3)_2$	CH_3	H	14
33	H	H	2-Fluorophenyl	$CH_2CH(CH_3)_2$	CH_3	H	22
34	H	H	3-Thienyl	$CH_2CH(CH_3)_2$	CH_3	H	0.7
35	H	H	2-Thienyl	$CH_2CH(CH_3)_2$	CH_3	H	1.9
36	H	H	Cyclohexyl	$CH_2CH(CH_3)_2$	CH_3	H	14
37	H	OH	Phenyl	$CH_2CH(CH_3)_2$	CH_3	H	56
38	OH	H	Phenyl	$CH_2CH(CH_3)_2$	CH_3	H	0.4

[a] Values are obtained for diastreomeric mixture. Values are means of two experiments, with 16 data points in each experiment; intra-assay variance <10% (na = not applicable). IC_{50}s were determined using a cell based assay.[24]

(data not shown). The efficacy observed after dosing **15** (Table 1) supports the conclusion that it contributes to the efficacy observed upon administration of **11**.

The synthesis of diazepine-based inhibitors is shown in Scheme 2. The synthetic scheme involved coupling aminodiazepine **14** with N-protected amino acid using amide bond coupling reagents. Amine functionality was introduced into the diazepinone moiety **12** using Evans' electrophilic azidation of enolates with 2,4,6-triisopropylbenzenesulfonyl azide (trisyl azide).[27] Reaction of *ortho*-formylphenylacetic acid and methylhydrazine in refluxing ethanol furnished the requisite diazepinone **12** in 50% yield (Scheme 2). Structural changes at position 1 and 3 of the constrained ring were also considered for structure–activity relationships. 3-Substituted diazepinones were synthesized from isopropylhydrazine and ethyl *o*-formylphenyl acetate in 65% yield. 1-Substituted diazepinones were synthesized from acetophenone and methylhydrazine in 50% yield. The amine salt **14** was coupled to various acid chlorides or carboxylic acids to furnish the desired products in 60–85% yield.

γ-Secretase inhibition data obtained for the inhibitors **15**–**38** are shown in Table 2. Comparison of the potency of peptidomimetic inhibitors to their triamide congeners **1**–**2** demonstrated that the diazepinone was an effective mimetic at the carboxy terminus. Within the series of diazepinone-based inhibitors carrying *N*-methyl substituents, modification of the N-terminal phenylacetyl group was performed. Introduction of halogens (e.g., 3,5-difluorophenylacetyl) improved potency. As the data

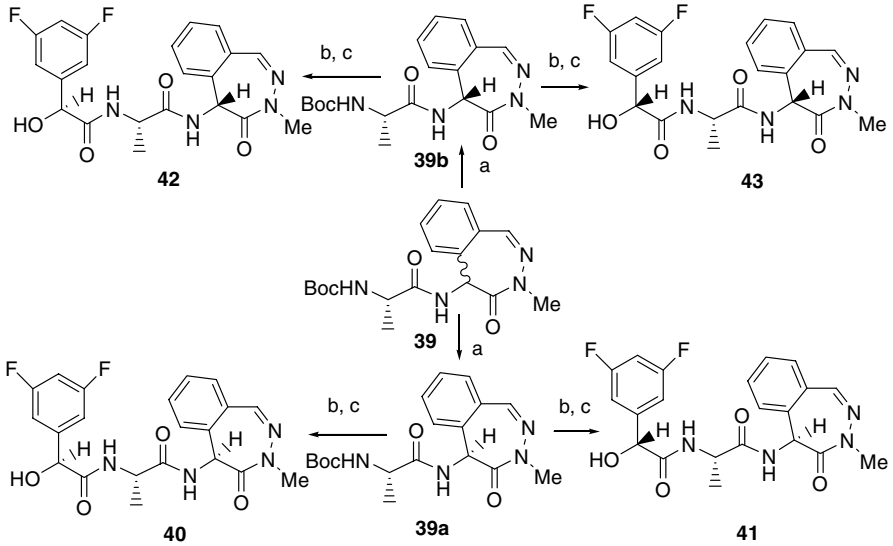


Scheme 2. Reagents and conditions: (a) $(Me)HNNH_2$, EtOH, reflux, 1 h; (b) vacuum sublimation at 140 °C, 1 h, 50% for two steps; (b) $KN(SiMe_3)_2$, −78 °C, THF, trisyl azide, then HOAc; (c) 10% Pd–C, EtOAc, H_2 (1 atm), 40 min; (d) Boc amino acid, EtOC(O)Cl, Et_3N, CH_2Cl_2, 0 °C, 3 h; (e) CF_3CO_2H–CH_2Cl_2, rt, 2 h; (f) RCH_2CO_2H, PyBop, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, 12 h, 60–85%.

suggest, introduction of water solubilizing group or larger hydrophobic groups at the N-termini led to loss of potency (**21** vs **19** and **22**). A similar trend was also seen in the SAR of the hydroxytriamides. Inhibitors **22**–**24** were equipotent to **15**, with a slight increase in potency observed for the diazepinone with the 3-furanyl and 3-thienyl N-capping groups. Thus, in addition to halogenated aryl moieties, 3-furylacetyl functionality was also desirable. Ketoamide **25** was found to have comparable potency as the parent compound **15** against γ-secretase. Replacement of the *N*-methyl group with a bulkier isopropyl group afforded an equipotent compound (**15** vs **26**). Introduction of a methyl group at the 1-position of the diazepine ring improved potency (**27** and **28**). The role of a hydrophobic amino acid at the central amide bond and introduction of an (*S*)-hydroxy group at the benzylic carbon were also investigated. As expected, the trend and improvement in inhibitor potencies were similar to those observed in triamide series. (**15** vs **30**, **38**, and **39**.) In addition, the role of the diazepinone asymmetric carbon on potency was investigated. Compound **15** was resolved into pure diastereoisomers, **15a** and **15b**, using chiral HPLC (absolute stereochemistry not determined). As expected, the isomers differed substantially in potency (**15a**: IC_{50} = 2 nM; **15b**: IC_{50} = 150 nM).

Both compound **11** and its metabolite **15** demonstrated similar efficacy after oral dosing in Tg2576 mice (Table 1). Again, low compound concentrations of **15** suggested that a metabolite(s) might be at least partly responsible for efficacy. Mass spectral analysis of plasma samples detected the formation of hydroxylated metabolites which can occur through oxidation at the benzylic position of the phenylacetyl moiety. As the oxidation process generates an additional chiral center, isolation of pure diastereiomers was necessary to determine the identity of the active species. The synthesis of each hydroxylated metabolite is shown in Scheme 3. Diastereomeric mixture **39** was easily separated using a chiral HPLC (Chiralcel OD 50 × 500 mm column, 20 μm particle size as a stationary phase and 5% EtOH in heptane as mobile phase) into pure diastereomers **39a** and **39b**. Each isomer was subjected to trifluoroacetic acid (TFA) mediated deprotection, followed by coupling with either (*R*) or (*S*) 3,5-difluoromandelic acid to furnish the desired hydroxylated compounds **40** (BMS-433796), **41**, **42**, and **43** in good yield. The diastereoisomers differed markedly in activity (Table 1). The stereochemistry of the most active diastereoisomer **40** was confirmed by X-ray crystallographic analysis (Fig. 2). The dependence of potency on stereochemistry of the hydroxyl functionality in **40**–**43** reflects a similar trend in the triamide series.[25]

Oral administration of **40** and **41** to Tg2576 mice showed that they were significantly more effective at lowering brain Aβ than **11** and **15** (Table 1). The brain Aβ ED_{50} values were similar for **40** and **41** at 4 and



Scheme 3. Reagents and conditions: (a) separation on chiral HPLC; (b) CF_3CO_2H, CH_2Cl_2, rt, 3 h; (c) (*R*) or (*S*)-3,5-difluoromandelic acid, CH_2Cl_2, PyBop, Et_3N, 6 h, 65–82%.

5 μmol/kg, respectively, compared with ED_{50} values for **11** and **15** of 26 and 48 μmol/kg, respectively. Compound **40** reduced Aβ in brain and plasma for 12 h after a single dose, with recovery to near baseline in brain by 24 h and a 60% increase in plasma Aβ at 24 h (Fig. 3). This rise in plasma Aβ occurred even at a time when plasma levels of compound were below the level of detection (<4 nM). Rises in plasma Aβ have been reported by others after administration of γ-secretase inhibitor in preclinical models and in humans.[10,28]

Tg2576 mice were also dosed with **40** for 14 days to determine the effect of multi-day dosing on Aβ lowering and exposure. In one experiment, brain Aβ was lowered by 25% and 38% after 1 or 14 days of once daily (QD) dosing at 4 μmol/kg. At a higher dose of 30 μmol/kg, 83%, 89%, and 98% inhibition was observed after a single dose, 14 days of QD or twice daily (BID) dosing, respectively. Along with no significant changes in activity, sub-chronic dosing did not lead to any accumulation or reduction in drug levels through 14 days (data not shown). In addition, when brain and plasma samples were examined for possible metabolites, an active ketoamide metabolite, **25** (Table 2), was detected at 20–40% of parent levels in brain and plasma. Metabolite **25** was observed to be active when directly dosed in Tg2576 mice as well (Table 1).

The animals being dosed at 30 μmol/kg BID needed to be terminated at 10 days due to toxicity, including: lethargy, weight loss, diarrhea, alopecia (loss of fur on the back of the head), and mortality in a third of the animals. Histopathological analysis showed moderate to marked hyperplasia of intestinal goblet cells in this group. Although the 30 μmol/kg QD group did not show any clinical signs, some animals had mild intestinal hyperplasia. In addition to reducing Aβ production, γ-secretase inhibitors are known to block the cleavage of Notch, an important protein in development and differentiation pathways.[30] In vitro studies comparing the activity of **40** in Notch and Aβ assays[26] show little separation of activity with a Notch/APP(Aβ) IC_{50} ratio of 0.5. The clinical signs and histopathology are consistent with a Notch mediated mechanism of toxicity.[31]

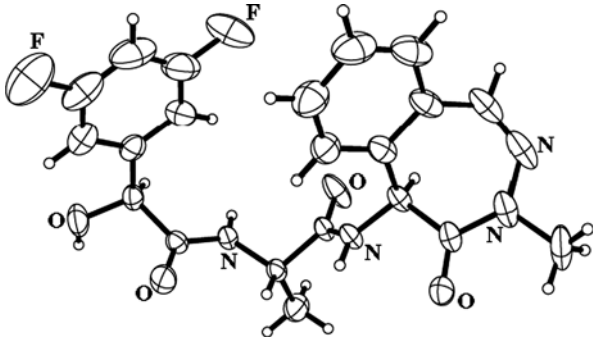


Figure 2. ORTEP drawing of **40** with ellipsoids drawn at 35% probability level and H atoms arbitrarily scaled. Carbon and hydrogen atoms are not labeled.[29]

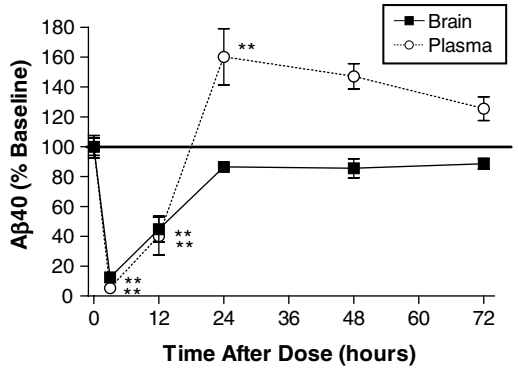


Figure 3. Changes in Aβ after a single oral dose of **40** at 30 μmol/kg in Tg2576 mice. $^{**}p < 0.01$.

Compound **40** was also characterized in pharmacokinetic studies in male Sprague–Dawley rats. Following a 10-min intravenous infusion at 2.3 μmol/kg in PEG-400, the total body clearance of **40** was 5.2 ± 0.82 mL/min/kg (means ± SEM; $n = 3$), indicating low clearance. The apparent terminal elimination half-life was 4.6 ± 0.48 h. Oral administration of a PEG-400 suspension at 35 μmol/kg showed an oral bioavailability of 31% with prolonged absorption. The compound had satisfactory metabolic stability in human liver microsomal preparations and was not an inhibitor of human CYPs ($IC_{50} > 100$ μM).

In summary, we have discovered a new constrained diazepine ring system as a peptidomimetic at the carboxy terminus of γ-secretase inhibitors. The diazepine ring system has fewer tertiary amide bonds over the previously disclosed 2,3-diazepin-1,4-dione ring system. Mass spectral analysis of in vivo samples from Tg2576 mice led to the identification of metabolites responsible for inhibition of Aβ production and to the design of a diazepinone as a metabolically stable peptidomimetic at the carboxy terminus. An inhibitor containing the new peptidomimetic diazepine moiety coupled with (*S*)-3,5-difluoromandelate at the amino terminus displayed improved inhibition of Aβ production in the brain over its triamide congeners. Although compound **40** showed excellent activity lowering brain Aβ, frank toxicity was observed with repeated dosing in mice. This toxicity, likely due to a Notch mediated mechanism, limits the usefulness of this compound as a therapeutic for the treatment of AD.

Acknowledgments

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