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Nitrogen-appended *N*-alkylsulfonamides as inhibitors of γ-secretase

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Abstract—The synthesis and γ-secretase inhibition data for a series of nitrogen-appended *N*-alkylsulfonamides (**11**–**47**) are described. Inhibition of brain Aβ in transgenic mice was demonstrated by two of these compounds (**23** and **44**).

Alzheimer's disease (AD) is a progressive dementing neurodegenerative disorder characterized pathologically by the presence of plaques composed of the 40–42 amino acid peptide amyloid-β (Aβ) and by increased levels of soluble oligomeric Aβ.[1] The actions of both β- and γ-secretases are responsible for the cleavage of β-amyloid precursor protein (APP) to release Aβ peptides.[2] Human genetics suggests a link between elevated levels of Aβ42 and early-onset familial AD.[3] Furthermore, soluble oligomeric Aβ has been shown to be neurotoxic in vitro.[4] Structurally diverse small molecule inhibitors of γ-secretase have been described in the literature.[5] For these reasons, we have targeted the inhibition of γ-secretase, as one of the proteases responsible for the unfavorable cleavage of APP, as a therapeutic approach to treat the underlying pathology of AD.

In a previous communication,[6] we described the identification of screening hit **1**, an inhibitor of γ-secretase, using a cell-based assay.[7] Compound **1** provided an attractive lead and subsequent analogs such as **2** exhibited more potent inhibition of γ-secretase (Fig. 1). Compound **2** was selected for oral administration in Tg2576 βAPP-Swedish transgenic mice at a single 500 μmol/kg dose.[8] Three hours after dosing, a 25% reduction in brain Aβ was observed. This modest reduction in brain Aβ, despite achieving robust brain concentrations, suggested that we needed to design even more potent inhibitors of γ-secretase.

Toward this end, we decided to further examine the role of the hydrophobic 2-pentyl sidechain by synthesizing a series of nitrogen-appended analogs of *N*-alkylsulfonamide **2**. Herein we report the SAR of this series of γ-secretase inhibitors.

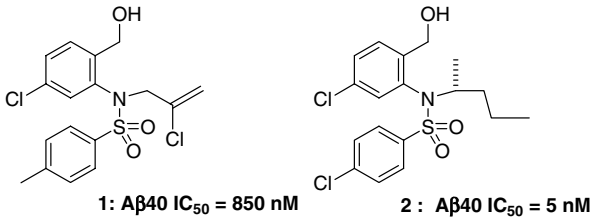

Figure 1.

Keywords: Alzheimer's disease; γ-Secretase; Aryl sulfonamides.
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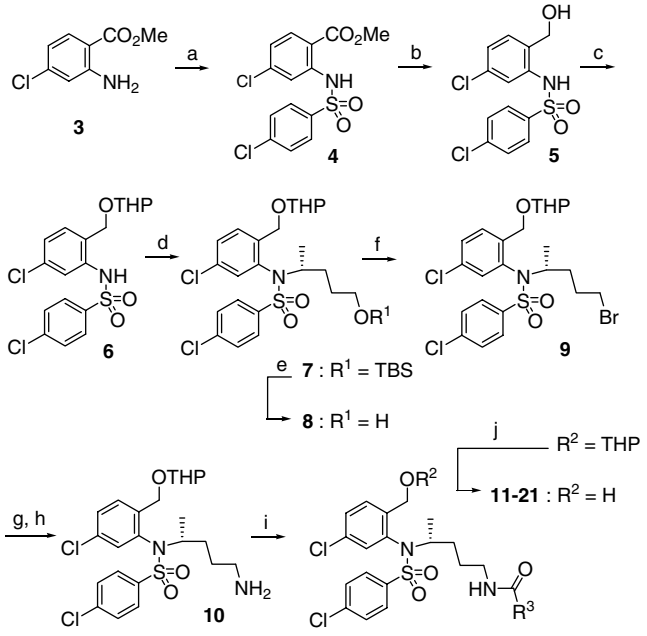
We targeted alkyl bromide **9** and primary amine **10** as versatile intermediates for the synthesis of nitrogen-appended *N*-alkylsulfonamides. A convergent approach for the synthesis of these intermediates is shown in Scheme 1. The key strategic feature of this approach involves a Mitsunobu[9] coupling of arylsulfonamide **6** and (*S*)-5-[[dimethyl(1,1-dimethylethyl)-silyl]oxy]-2-pentanol.[10] The resulting silyl ether **7** was deprotected with TBAF to produce alcohol **8**, which was converted to primary amine **10** using a standard three-step procedure.

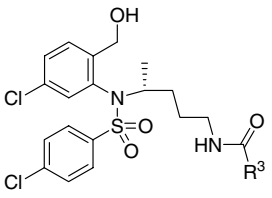
Primary amine **10** was acylated using array synthesis to determine if heteroatoms would be tolerated at the terminus of the 2-pentyl sidechain and to investigate the steric requirements of this sidechain for γ-secretase inhibition. The steric requirements did not appear to be stringent as formamide **11** was nearly equipotent to mandelamides **19** and **20** as shown in Table 1. Overall this group of amides did not achieve a significant increase in potency compared to previous lead **2**.

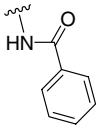
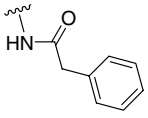
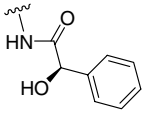
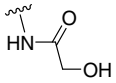
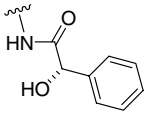
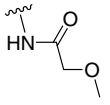
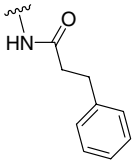
It is worth noting that the added hydroxyl group of the mandelamides **19** and **20** resulted in roughly an order of magnitude greater potency as compared to phenylacetamide **18**. For this reason, we synthesized a small group of sulfonamides from bromo intermediate **9** (Scheme 2) to determine if a sulfonamido moiety would be a reasonable isostere for the mandelamide. Benzenesulfonamide **25** was found to have similar potency to mandelamides **19** and **20**, suggesting that these terminal moieties interact with γ-secretase in a similar fashion. Methyl sulfonamide **22** was the first compound in this series to exhibit



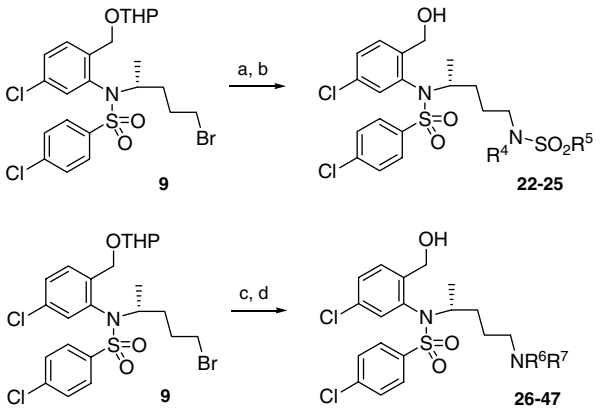
Scheme 1. Reagents and conditions: (a) *p*-ClPhSO$_2$Cl, pyr, CH$_2$Cl$_2$, rt, 8 h, 91%; (b) LiAlH$_4$, THF, 0 °C, 4 h, 77%; (c) DHP, PPTS, CH$_2$Cl$_2$, rt, 6 h, 98%; (d) (*S*)-5-[[dimethyl(1,1-dimethylethyl)-silyl]oxy]-2-pentanol10, DIAD, PPh$_3$, THF, rt, 16 h, 64%; (e) TBAF, THF, rt, 3 h, 96%; (f) CBr$_4$, PPh$_3$, CH$_2$Cl$_2$, rt, 8 h, 62%; (g) NaN$_3$, K$_2$CO$_3$, DMF, rt, 6 h, 83%; (h) H$_2$ (1 atm), 10% Pd–C, EtOAc, rt, 8 h, 86%; (i) R^{3}C(O)Cl, pyr, CH$_2$Cl$_2$, rt, 8 h; (j) 1 M HCl, THF, rt, 6 h.

Table 1. γ-Secretase inhibition for amides **11**–**21**



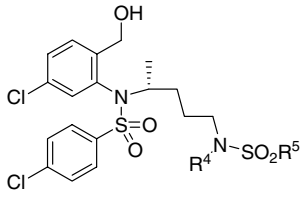
Compound	HN(O)R^3	Aβ40 IC$_{50}$[11] (nM)	Compound	HN(O)R^3	Aβ40 IC$_{50}$[11] (nM)
11		5.1	**17**		15
12		7.3	**18**		26
13		13	**19**		1.6
14		8.1	**20**		2.9
15		6.9	**21**		72
16		14			

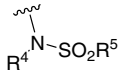
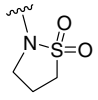
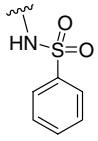
picomolar potency as shown in Table 2. In fact, **22** was an order of magnitude more potent than **2**. Furthermore, the *N*-methyl analog **23** was nearly equipotent to **22**, demonstrating that the sulfonamide hydrogen of **22** was not critical for inhibition of γ-secretase. In further studies, compound **23** was selected for oral administration in Tg2576 βAPP-Swedish transgenic mice at a single 200 μmol/kg dose. Three hours after dosing, a 27% reduction in brain Aβ was observed. The plasma level of this compound was 12,302 ± 11,323 nM and the brain level was 759 ± 459 nM. This represents a similar reduction in brain Aβ at less than one-half the dose of **2**.



Scheme 2. Reagents and conditions: (a) $HN(R^4)SO_2R^5$, NaH, DMF, 60 °C, 8 h; (b) 1 M HCl, THF, rt, 6 h; (c) HNR^6R^7, K_2CO_3, DMF, rt, 18 h; (d) 1 M HCl, THF, rt, 6 h.

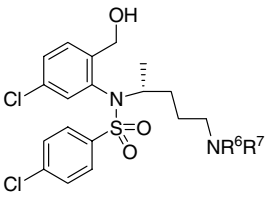
Table 2. γ-Secretase inhibition for sulfonamides **22–25**

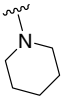
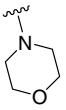
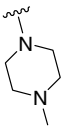
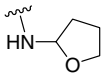
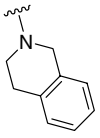
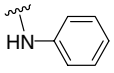


Compound		Aβ40 IC_{50}[11] (nM)
22		0.23
23		0.32
24		1.1
25		7.4

In an effort to design a compound with improved brain levels compared to methyl sulfonamide **23**, we decided to synthesize (Scheme 2) a set of amines and heterocycles at the terminus of the 2-pentyl sidechain. Table 3 shows that the majority of the resulting amino compounds exhibited reduced potency as compared to des-amino compound **2**, although dimethylamino compound **28** and morpholino compound **32** were essentially equipotent to **2**.

Table 3. γ-Secretase inhibition for amines **26–34**

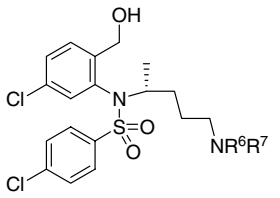


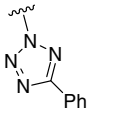
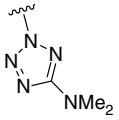
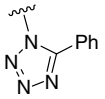
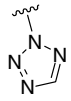
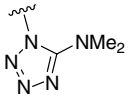
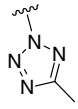
Compound		Aβ40 IC_{50}[11] (nM)	Compound		Aβ40 IC_{50}[11] (nM)
26		288	**31**		50
27		262	**32**		3.1
28		6.5	**33**		29
29		29	**34**		84
30		36			

A set of nitrogen based heterocyclic derivatives, including pyrazoles, imidazoles, and triazoles, exhibited better potency than their amino analogs **26–34** as shown in Table 4. Some of the most promising of these heterocycles were the tetrazole analogs, with **44**, **45**, and **47** possessing subnanomolar potency. Compound **44** was selected for oral administration in Tg2576 mice at a single 200 μmol/kg dose. Three hours after dosing, a 41% reduction in brain Aβ was observed. The plasma level of this compound was 5473 ± 1083 nM and the brain level was 1155 ± 279 nM. Tetrazole **44** shows an improved brain Aβ lowering activity and an improved brain-to-plasma ratio compared to methyl sulfonamide **23**.

In summary, we have described the SAR for a series of nitrogen-appended analogs of sulfonamide **2**. Heteroatom substitution is clearly preferred at the terminus of the 2-pentyl sidechain as compounds **22**, **23**, **44**, and **47** are roughly an order of magnitude more potent than **2**. Furthermore, compounds **23** and **44** were more effective than compound **2** in reducing brain Aβ in transgenic mice. Subsequent communications will describe our continued efforts to design analogs with improved in vivo profiles.

Table 4. γ-Secretase inhibition for heterocycles **35**–**47**



Compound	NR^6R^7	Aβ40 IC_{50}[11] (nM)	Compound	NR^6R^7	Aβ40 IC_{50}[11] (nM)
35		18	**42**		61
36		11	**43**		5.6
37		12	**44**		0.51
38		0.9	**45**		0.75
39		4.8	**46**		15
40		1.2	**47**		0.53
41		6.1			

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References and notes

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7. H4 human neuroglioma cells expressing HPLAP-βAPP^{164SFAD} were grown in high glucose (4.5 g/L) DMEM (Invitrogen) media supplemented with 10% FBS, 100 μg/mL pen-strep, 2 mM glutamine, and 100 μg/mL geneticin. Cells were aliquoted into a 96-well plate, and after attachment the medium was replaced with Ultraculture (Whittaker Bioproducts) containing individual compounds of interest (final DMSO concentration of 1%). After an overnight incubation, the conditioned medium was removed and evaluated for the presence of Aβ in a sandwich ELISA using a monoclonal C-terminal Aβ40 specific capture antibody and an HRP labeled monoclonal antibody to the N-terminus of Aβ for detection. The endpoint measurement of Aβ1–40 level was developed using TMB reagent followed by the addition of 1 M phosphoric acid. The plates were read at 450 nm.
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10. (*S*)-5-[[Dimethyl(1,1-dimethylethyl)-silyl]oxy]-2-pentanol was synthesized via the following procedure: commercially available (*S*)-1,4-pentanediol (2.86 g, 27.5 mmol) was stirred with TBSCl (4.55 g, 30.2 mmol), TEA (4.59 mL, 33.0 mmol), and DMAP (0.335 g, 2.75 mmol) in CH_2Cl_2 (55 mL) at 0 °C for 4 h. The resulting mixture was concentrated and purified by silica gel column chromatography eluting with 4:1 hexanes/ethyl acetate to isolate the title compound in 86% yield.
11. IC_{50}s were determined using a cell-based assay (see Ref. 6). Values are means of two experiments, with 12 drug concentrations in each experiment; intra-assay variance was <10%.