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

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Abstract—The synthesis and γ-secretase inhibition data for a series of carbamate-appended *N*-alkylsulfonamides are described. Carbamate **54** was found to significantly reduce brain Aβ in transgenic mice. **54** was also found to possess markedly improved brain levels in transgenic mice compared to previously disclosed **1** and **2**.

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 Aβ.[1] The evidence is mounting that it is the soluble oligomeric forms of Aβ that are the primary neurotoxic agents in AD.[2] The sequential action of β- and γ-secretases is responsible for the cleavage of β-amyloid precursor protein (APP) to release Aβ peptides.[3] We have been focusing on the identification of small molecules that inhibit γ-secretase cleavage of the C-terminal fragments of β-APP. The resulting inhibition of Aβ production has the potential to offer a therapy that would slow or halt the progression of AD.[4]

In a previous communication,[5] we described the identification of nitrogen-appended *N*-alkylsulfonamides **1** and **2** as potent inhibitors of γ-secretase, using a cell-based assay.[6] Compounds **1** and **2** were both selected for oral administration in Tg2576 βAPP-Swedish transgenic mice at a single 200 μmol/kg dose.[7] Three hours after dosing methyl sulfonamide **1**, a 27% reduction in brain Aβ was observed. Similarly, 3 h after dosing tetrazole **2**, a 41% reduction in brain Aβ was observed. It was speculated that the improved Aβ reduction demonstrated by tetrazole **2** was directly related to its higher mean brain concentration compared to methyl sulfonamide **1**. For this reason we continued to examine this sulfonamide chemotype in an attempt to identify analogs possessing both improved absolute brain levels and improved brain to plasma ratios (Fig. 1).

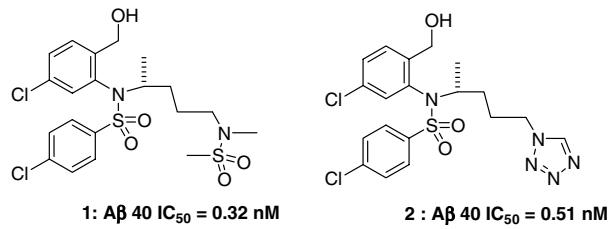

Figure 1.

Keywords: Alzheimer's disease; Secretase; Amyloid-β; Sulfonamides.
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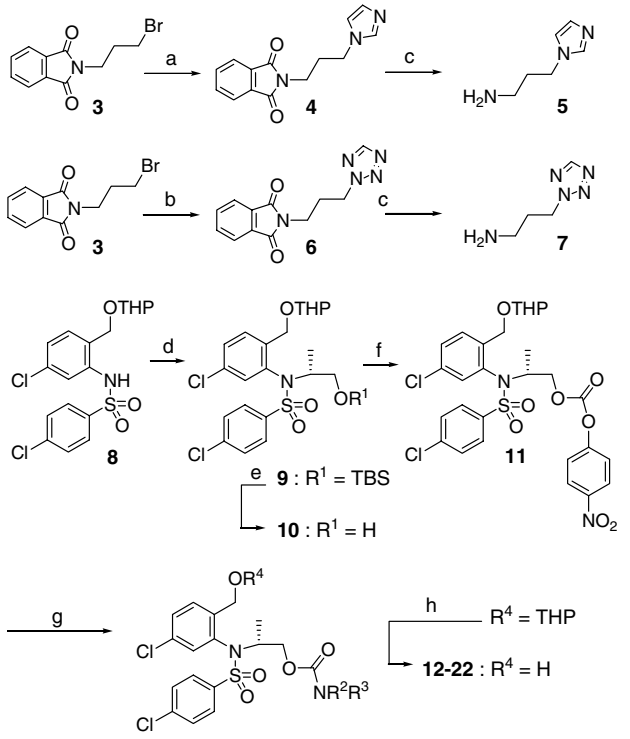
One of many strategies explored to achieve this goal was to study carbamates that are structurally closely related to the nitrogen-appended *N*-alkylsulfonamides **1** and **2**. Herein we report the SAR for this series of γ-secretase inhibitors.

Aryl carbonate **11** was selected as the key synthon for the synthesis of a targeted set of carbamates. Mitsunobu[8] conditions were employed to effect the coupling of arylsulfonamide **8** with (*S*)-4-[[dimethyl(1,1-dimethylethyl)-silyl]oxy]-2-propanol.[9] The resulting silyl ether **9** was deprotected with TBAF to produce alcohol **10**, which was then acylated with 4-nitrophenyl chloroformate to produce **11** (Scheme 1).

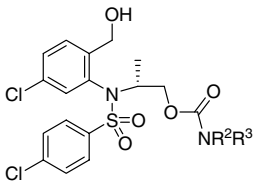
A small collection of commercially available amines along with 3-(*1H*-imidazol-1-yl)propan-1-amine **5** and 3-(*2H*-tetrazol-2-yl)propan-1-amine **7** were acylated with aryl carbonate **11**. The THP protecting group on the benzyl alcohol was then removed as shown in Scheme 1 to produce carbamates **12–22**. The steric requirements for γ-secretase inhibition did not appear to be stringent as methyl carbamate **12** was nearly equipotent to *tert*-butyl carbamate **20** as shown in Table 1. The most potent carbamates in this set were imidazole-appended **15** and tetrazole-appended **16.**

Imidazole **15** was selected for further analog studies due to its basic properties that allowed for salt formulations.



Scheme 1. Reagents and conditions: (a) Imidazole, K_2CO_3, CH_3CN, reflux, 16 h, 74%; (b) Tetrazole, K_2CO_3, CH_3CN, reflux, 12 h, 47%; (c) Hydrazine, aq EtOH, reflux, 16 h, 83%; (d) (*S*)-1-[[Dimethyl(1,1-dimethylethyl)-silyl]oxy]-2-propanol9, DIAD, PPh_3, THF, rt, 16 h, 68%; (e) TBAF, THF, rt, 3 h, 94%; (f) 4-Nitrophenyl chloroformate, py, THF, rt, 6 h, 85%; (g) HNR2R3, DMF, rt, 8 h; (h) 1 M HCl, THF, rt, 6 h.

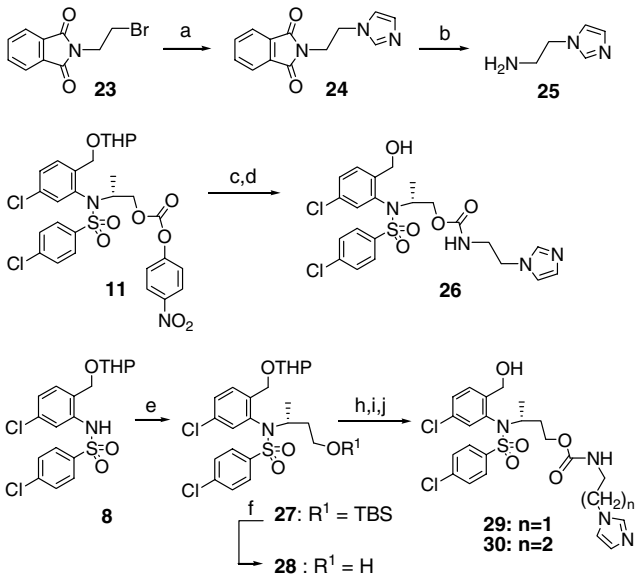
Table 1. γ-Secretase inhibition for carbamates **12–22**



Compound	NR^2R^3	Aβ40 IC_{50} (nM)[10]
12	HN—	15
13	HN—	10
14	HN—	10
15	HN—	2.3
16	HN—	2.1
17	HN—	12
18	HN—	15
19	HN—	5.6
20	HN—	12
21	N—	18
22	N—	1.8

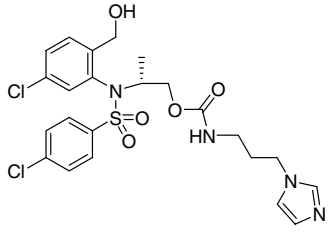
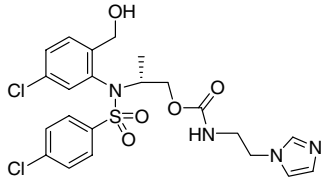
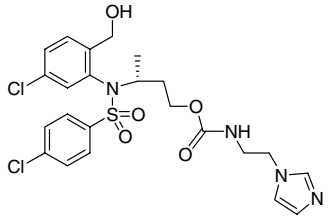
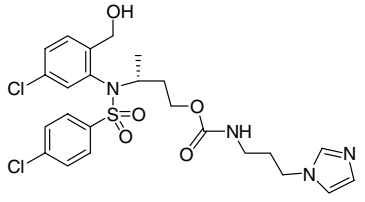
Initially, chain length analogs of **15** were examined to determine whether its potency could be improved. As part of this objective, imidazole **26** was synthesized from 2-(*1H*-imidazol-1-yl)ethanan-1-amine **25** as shown in Scheme 2. **26** was found to be modestly more potent than **15** as shown in Table 2.[11] Chain length analogs **9** and **30** were also synthesized (Scheme 2) and found to be no more potent than **15** (Table 2).

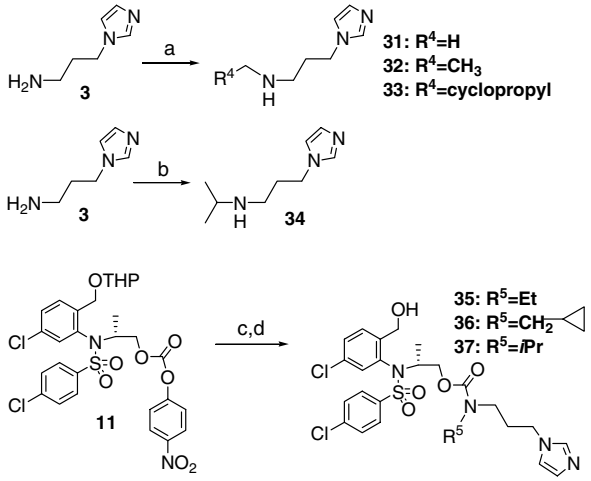
After exploring the ether length of imidazole-appended carbamate **15**, a small set of tertiary carbamates were synthesized in order to compare to secondary carbamate **15**. Amine **5** was reductively alkylated to form secondary amines **32–34** according to Scheme 3. These amines were acylated with carbonate **11** using standard condi-



Scheme 2. Reagents and condtions: (a) Imidazole, K_2CO_3, CH_3CN, reflux, 16 h, 69%; (b) Hydrazine, aq EtOH, reflux, 16 h; 74%; (c) **25**, DMF, rt, 8 h, 69%; (d) 1 M HCl, THF, rt, 6 h, 76%; (e) (*S*)-4-[[Dimethyl(1,1-dimethylethyl)-silyl]oxy]-2-butanol[9], DIAD, PPh_3, THF, rt, 16 h, 67%; (f) TBAF, THF, rt, 3 h, 93%; (h) 4-Nitrophenyl chloroformate, py, THF, rt, 6 h, 86%; (i) **5/25**, DMF, rt, 8 h; (j) 1 M HCl, THF, rt, 6 h.

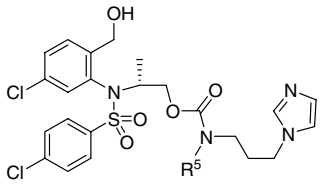
Table 2. γ-Secretase inhibition for imidazoles **15**, **26**, **29**, **30**

Compound		Aβ40 IC_{50} (nM)[10]
15		2.3
26		0.93
29		4.0
30		7.7



Scheme 3. Reagents and conditions: (a) $RCH_2C(O)H$, $Na(CN)BH_3$, HCl/MeOH, reflux, 16 h; (b) Acetone, $Na(OAc)_3BH$, AcOH, CH_2Cl_2, rt, 16 h; 31%; (c) **32–34**, DMF, rt, 8 h; (d) 1 M HCl, THF, rt, 6 h.

Table 3. γ-Secretase inhibition for imidazoles **15**, **35–37**

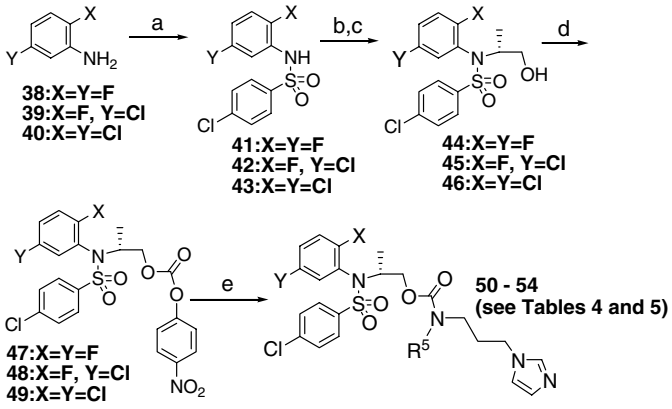


Compound	R^5	Aβ40 IC_{50} (nM)[10]
15	H	2.3
35	Et	0.06
36	CH_2–cyclopropyl	0.06
37	*i*Pr	19

tions to produce tertiary carbamates **35–37**. The most potent of these inhibitors were ethyl carbamate **35** and methylene cyclopropyl carbamate **36** (Table 3).

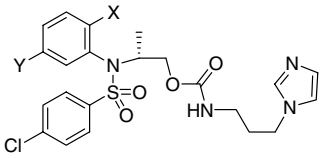
Carbamates **35** and **36** were selected for oral administration in Tg2576 mice at a single 200 μmol/kg dose. Three hours after dosing **35**, a 15% reduction in brain Aβ was observed. The plasma level of **35** was 730 ± 296 nM and the brain level was 227 ± 3 nM. Similarly, 3 h after dosing **36**, no reduction in brain Aβ was observed. The plasma level of **36** was 6830 ± 2898 nM and the brain level was 859 ± 49 nM. It was hypothesized that the combination of the polar imidazole and the benzyl alcohol functionalities may have been responsible for the reduced brain efficacies of **35** and **36** compared to **2**. For that reason, we sought to explore the removal of the benzyl alcohol functionality in the general chemotype represented by **35** and **36**.

Toward that end, the 2,5-difluoro, the 2-fluoro-5-chloro, and the 2,5-dichloro analogs of the arylsulfamido carbamate **15** were synthesized as shown in Scheme 4. The most potent of these new compounds was the 2,5-dichloro analog **52** (Table 4). It is worth noting that aryl



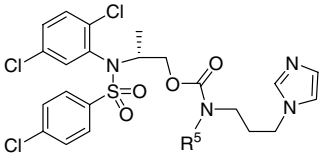
Scheme 4. Reagents and conditions: (a) p-ClPhSO$_2$Cl, py, CH$_2$Cl$_2$, rt, 8 h; (b) (*S*)-1-[[Dimethyl(1,1-dimethylethyl)-silyl]oxy]-2-propanol[9], DIAD, PPh$_3$, THF, rt, 16 h; (c) TBAF, THF, rt, 3 h; (d) 4-Nitrophenyl chloroformate, py, THF, rt, 6 h; (e) **5**, **31–32**, DMF, rt, 8 h.

Table 4. γ-Secretase inhibition for imidazoles **50–52**



Compound	X	Y	Aβ40 IC$_{50}$ (nM)[10]
50	F	F	1.2
51	F	Cl	0.66
52	Cl	Cl	0.41

Table 5. γ-Secretase inhibition for imidazoles **53–54**



Compound	R^5	Aβ40 IC$_{50}$ (nM)[10]
52	H	0.41
53	Me	0.48
54	Et	0.27

chloride **52** was roughly five times more potent than the benzyl alcohol analog **15**.

Next, N-alkylated analogs of **52** were synthesized, as described in Scheme 4, to determine whether a similar increase in potency could be achieved as had been previously observed with N-alkylated analogs of **15**. Table 5 shows that methyl carbamate **53** was roughly equipotent to **52**, while ethyl carbamate **54** was modestly more potent than **52**. Compound **54** was selected for oral administration in Tg2576 mice at a single 200 μmol/kg dose. Three hours after dosing, a 50% reduction in brain Aβ was observed. The plasma level of this compound was 98,942 ± 60,560 nM and the brain level was 41,171 ± 18,463 nM. This 50% reduction in brain Aβ was a significant improvement over what had been produced by benzyl alcohol analogs **35** and **36**.

In summary, we have described the SAR for a series of sulfonamide inhibitors γ-secretase exemplified by carbamate **12** and its analogs. Tertiary carbamates containing a tethered imidazole such as compounds **35**, **36**, and **54** are the most potent γ-secretase inhibitors identified thus far in this carbamate series. Aryl chloride **54** generated a more pronounced decrease in brain Aβ in transgenic mice relative to the benzyl alcohol analogs **35** and **36** despite the superior potency of **35** and **36**. This may be due to improved brain concentrations of **54** over **35** and **36**. **54** also achieved a significantly improved brain to plasma ratio and a higher absolute brain concentration compared to the previously disclosed sulfonamide **2**; accompanied by a similar reduction of brain Aβ in mice. Strategies for improved brain efficacy in this class are being pursued and will be discussed in future communications.

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6. H4 human neuroglioma cells expressing HPLAP-βAPP^{164SFAD} were grown in high glucose (4.5 g/L) DMEM (Invitrogen) 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 Ultracul-

ture (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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9. (*S*)-3-[[Dimethyl(1,1-dimethylethyl)-silyl]oxy]-2-propanol was synthesized as follows. Commercially available (*S*)-1,2-propanediol (2.09 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 74% yield. (*S*)-4-[[dimethyl(1,1-dimethylethyl)-silyl]oxy]-2-butanol was synthesized in an analogous fashion from (*S*)-1,3-butanediol in 81% yield.
10. 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%.
11. It was decided not to examine **26** further due to its instability in solution.