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N-(5-Chloro-2-(hydroxymethyl)-*N*-alkyl-arylsulfonamides as γ-secretase inhibitors

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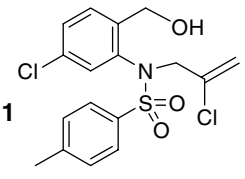
Abstract—A series of *N*-alkylbenzenesulfonamides were developed from a high throughput screening hit. Classic and parallel synthesis strategies were employed to produce compounds with good in vitro and in vivo γ-secretase activity.

Alzheimer's disease (AD) is a chronic, neurodegenerative disorder with pathology characterized by the accumulation of senile (neuritic) plaques, neurofibrillary tangles, amyloid deposition in neural tissues and vessels, synaptic loss, and neuronal death.[1a,b,2] Evidence suggests the accumulation of Aβ peptides is responsible for the neuronal toxicity that is associated with AD.[3] Aβ peptides are generated by sequential proteolytic cleavage of a 695–770 amino acid β-amyloid precursor protein (β-APP)[4] by the action of both β and γ-secretases, leading to elevated levels of Aβ peptides. We have been engaged in the identification of small molecules that inhibit the production of β-amyloid peptide (Aβ) from β-APP, particularly via inhibition of the cleavage mediated by γ-secretase. This approach has potential to provide a therapy that would prevent the progression of AD by the inhibition of Aβ production.[5]

A cell-based assay measuring Aβ production[6] was performed on our internal compound collection and the 3-chloro-2-hydroxymethy-benzenesulfonamide derivative **1**[7] (Fig. 1) was found to be a modest inhibitor of γ-secretase (IC_{50} = 850 nM). A cell free assay that specifically detects γ-secretase cleavage of membrane bound precursors was used to profile select compounds from this screen.[8,9] These compounds exhibited a profile consistent with the inhibition of γ-secretase. Herein, we report the SAR within this series of substituted benzene sulfonamides γ-Secretase inhibitors.



1

Figure 1.

Keywords: γ-Secretase; Alzheimers; *N*-alkyl-arylsulfonamides.
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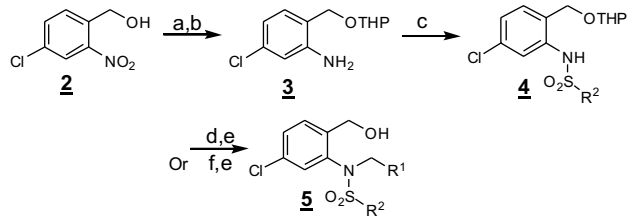
The key intermediate 5-chloro-2-((tetrahydro-2H-pyran-2-yloxy) methyl) aniline **3** was prepared from the commercially available (4-chloro-2-nitrophenyl) methanol **2** by protection of the alcohol and reduction of the nitro group. Aniline **3** was elaborated to various sulfonamides by acylation with an array of sulfonyl chlorides.

The resulting sulfonamide **4** was amenable to Mitsunobu coupling with various alcohols or alkylation with alkyl or benzyl halides to yield target molecules **5**.

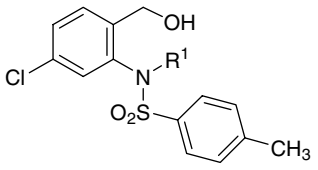


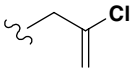
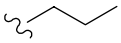
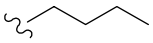
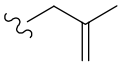
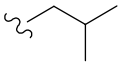
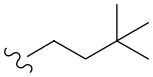
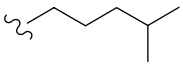
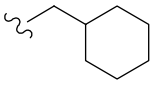
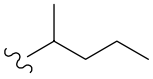
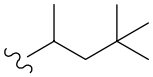
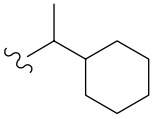
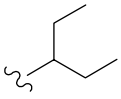
[a]Reagents: (a) 3,4-dihydro-2H-pyran, PPTS, DCM (62%) (b) Raney nickel, H_2, EtOH (98%) (c) R^2- sulfonyl chloride, anhydrous pyridine, 0^0C, (d) triphenylphosphine, R^1- OH, diisopropylazodicarboxylate, THF (e)1N HCl, THF, 6H, (f) NaH, THF, R^1-X.

Analogs of the initial screening hit **1** were accessible via classic and parallel synthesis strategies. Our early focus was on the exploration of the *N*-alkyl side chain. From a moderate sized library of diverse compounds bearing *N*-alkyl or *N*-alkylaryl substituents (Table 1), a few key characteristics emerged. A variety of alkyl groups conferred potency within twofold of the initial lead **1**, including the straight chain alkyls (e.g., **6**–**8**), terminally branched alkyls (e.g., **9**–**12**), and cycloalkyls (e.g., **13**). The most interesting outcome from this set of compounds was the significant enhancement in potency that resulted from branching with an α-methyl group at the point of attachment to the sulfonamide nitrogen. This increase was found to be on average about 10-fold, as in the case of **11**/**15** and **13**/**16**. A more pronounced effect was seen in the comparison of the *n*-butyl analogue **8** with the α-methyl butyl (2-pentyl) derivative **14**, where a 30-fold improvement in potency was realized. As can be seen with example **17**, this branching effect was limited to one carbon.

With the α-methyl butyl side chain fixed, a library focused on the sulfonamide aryl group was synthesized. As shown in Table 2, this region of compound **1** was quite sensitive to structural modification. The simple unsubstituted benzene sulfonamide **18** was significantly less potent than the 4-methyl derivative **9**. However, extension to larger 4-alkyl groups such as ethyl (**19**) and isopropyl (**20**) resulted in diminished potency. Transposition of the methyl group to the 3-position, as in **21**, also lead to significantly decreased potency relative to **9**. Within a series of 4-substituted phenyl analogues, halogens were well tolerated, with the 4-chlorophenyl compound **24** being most potent. Other small electron-withdrawing groups were acceptable such as trifluoromethyl (**25**) and nitrile (**26**). However, incorporation of an electron rich 4-methoxy group, as in **27**, was detrimental to potency. Inclusion of additional chlorines on the 4-chlorophenyl group gave analogues **28**–**30** that were all less potent than the 4-chloro analog **24**. Based on the potency of sulfonamide **24** (Aβ40 IC_{50} = 19 nM), the 4-chloro group appeared to be the optimal substituent on the aryl sulfonamide portion of the molecule.

Table 1. Modification of R^1 in the 4-MePh sulfonamide series

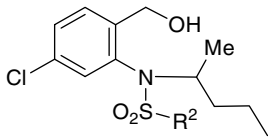


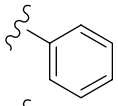
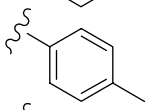
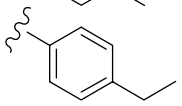
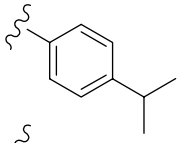
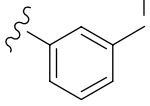
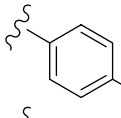
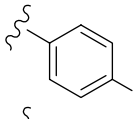
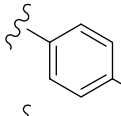
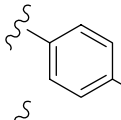
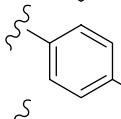
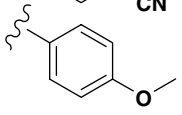
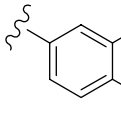
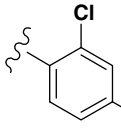
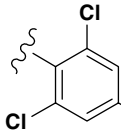
Exp. #	R^1	Aβ40 IC_{50}[a] (nM)
1		850
6		1100
7		750
8		1300
9		400
10		700
11		2000
12		920
13		1000
14		40
15		350
16		190
17		1000

[a] Values are means of two experiments, with 12 drug concentrations in each exp.; intra-assay variance <10%.

Examples in Table 3 illustrate variation of the *N*-alkyl substituent with the optimized 4-chlorosulfonamide substituent held constant. Simple unbranched alkyl analogues **31** and **32** showed improved potency relative to their 4-methylphenyl sulfonamide counterparts **6** and

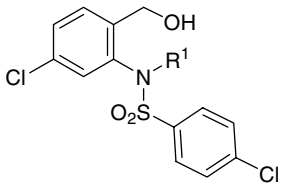
Table 2. Modification of R^2 in the *N*-(2-pentyl)sulfonamide series



Exp. #	R^2	Aβ40 IC_{50}[a] (nM)
18		1200
9		40
19		360
20		720
21		1200
22		66
23		56
24		19
25		72
26		180
27		1300
28		240
29		560
30		>25,000

[a] Values are means of two experiments, with 12 drug concentrations in each exp.; intra-assay variance <10%.

Table 3. Modification of R^1 in the 4-ClPh sulfonamide series



Exp. #	R^1	Aβ40 IC_{50}[a] (nM)
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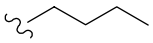
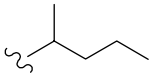
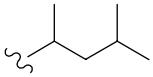
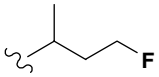
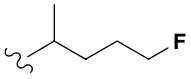
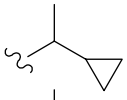
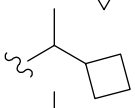
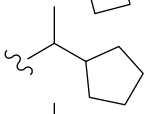
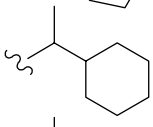
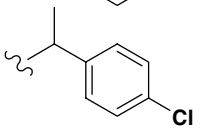
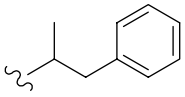
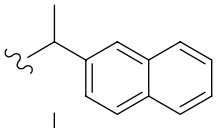
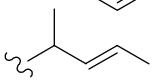
32		140
24		19
33		23
34		25
35		7
36		49
37		12
38		14
39		33
40		22
41		41
42		100
43		140

[a] Values are means of two experiments, with 12 drug concentrations in each exp.; intra-assay variance <10%.

8, respectively. A variety of α-methyl alkyl groups were well tolerated as seen with examples **24** and **33**–**41**. Comparison of the *n*-butyl analogue **32** with the 2-pentyl derivative **24** illustrates the positive effect of branching adjacent to the sulfonamide nitrogen, with the α-methyl

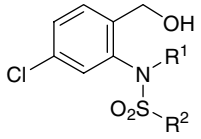
group giving a sevenfold increase in potency. The 5-fluoro-2-pentyl analogue **35** was particularly potent with an IC_{50} of 7 nM. In the series of α-methyl cycloalkyl derivatives **36**–**39**, ring size played a role, with the cyclobutyl **37** and the cyclopentyl **38** compounds having the best potency. Unsaturated groups were also examined as in **40**–**43**. Surprisingly, the alkene **43** was approximately sevenfold less potent than its saturated counterpart **24**. Aromatic substituents were tolerated, although phenyl groups (e.g., **40**, **41**) were preferred over naphthyl **42**. Our conclusion from this part of our SAR study was that α-methyl branching was critical for good potency and that a variety of alkyl groups gave reasonable potency within a narrow range of IC_{50}'s.

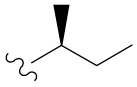
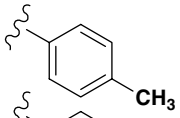
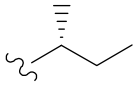
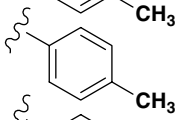
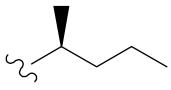
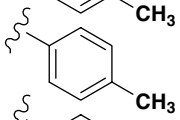
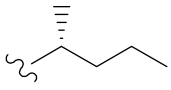
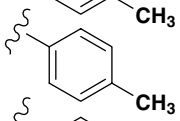
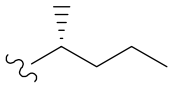
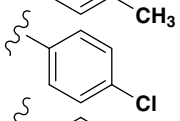
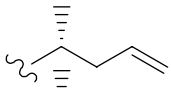
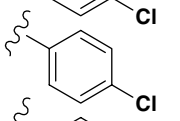
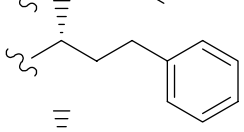
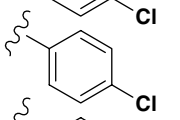
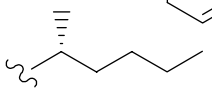
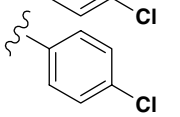
Further examination of the *N*-alkyl region focused on the influence of the chiral center at the α-branched position (Table 4). Examples **44**–**47** illustrate two comparisons of (*R*) versus (*S*) isomers in the 4-methylphenylsulfonamide series. For the 2-butyl substituent, the (*R*)-isomer **45** was >10-fold more potent than the (*S*)-isomer **44**. Likewise, with 2-pentyl analogues **46** and **47**, the (*R*)-isomer **47** was more potent, although in this case the difference in IC_{50} was >150-fold. In examples **48**–**51**, the chiral center is fixed in the (*R*)-configuration and the optimized 4-chlorosulfonamide substituent is held constant. Combination of the (*R*)-2-pentyl group with the 4-chlorophenyl sulfonamide substituent provided **48**, which proved to be one of the most potent compounds to emerge from this series. The 2-methyl-4-phenyl analogue **50** and the 2-hexyl derivative **51** had similar potency to **48**, while introduction of simple unsaturation in the side chain as in **49** resulted in a threefold reduction in potency. This is similar to the decrease in potency described for the alkene **43** compared with its saturated counterpart **24**.

Analog **48** was evaluated in in vivo[10] in Tg2576 βAPP-Swedish transgenic mice at a single 500 μmol/kg dose. Three hours after oral dosing, **48** produced a small, non significant (25%) reduction in brain Aβ, which was associated with a 2- to 3-fold increase in β and α cleaved C terminal fragments of APP. The plasma level of this compound was 1.6 μM and the brain level was 5.2 μM. Subcutaneous dosing of **48** for 5 days BID did lead to significant decreases in brain Aβ of 38%, associated with plasma levels of 21 μM in plasma and 14 μM in brain. The lack of robust efficacy in the in vivo model may be due to plasma protein binding of **48**, which is >99% in the mouse, rat, and human,[11] and presumably high protein binding in the brain as well.

In summary, potent γ-secretase inhibitors resulting from classic structure–activity relationship studies were

Table 4. Inhibitory activities of *N*-α-methylalkylsulfonamide enantiomers



Exp. #	R^1	R^1	Aβ40 IC_{50}[a] (nM)
44			1300
45			100
46			3700
47			24
48			5.0
49			14
50			4.0
51			5.0

[a] Values are means of two experiments, with 12 drug concentrations in each exp.; intra-assay variance <10%.

produced. These results demonstrate that a variety of arylsulfonamides can be produced with low nanomolar activities in a cell free assay. Compounds exemplified by (*R*)-2-pentyl **48**, were more than 100-fold more potent than the original screening hit. This molecule also reduced the concentration of Aβ in the brain in transgenic Tg2576 mice. Subsequent communications will describe our continued efforts to design compounds possessing both improved Aβ IC_{50}'s and in vivo efficacy.

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