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Bioorganic & Medicinal Chemistry Letters 15 (2005) 2685–2688
Bioorganic & Medicinal Chemistry Letters

Aryl sulfones: a new class of γ-secretase inhibitors

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Received 27 September 2004; revised 23 November 2004; accepted 8 December 2004
Available online 12 April 2005

Abstract—The development of a novel series of 4-aryl, 4-phenylsulfonyl cyclohexananone-derived γ-secretase inhibitors for the potential treatment of Alzheimer's disease is described.

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by memory loss and cognitive decline. AD is the most common form of dementia and affects up to 50% of the population over 85 years of age.[1] The amyloid-β (Aβ) peptide is the major component of extracellular proteinaceous plaques found in Alzheimer's brains, and soluble Aβ has been shown to be neurotoxic in vitro.[2] Cleavage of amyloid precursor protein (APP) by both β- and γ-secretases[3] releases Aβ peptides and it is these cleavage events that are thought to play a key role in the neurodegenerative pathways responsible for the progressive cognitive decline observed in AD patients. Inhibition of the proteases responsible for the unfavourable cleavage of APP therefore becomes an attractive pharmaceutical point of intervention, which could alter the underlying pathophysiology[4] of the disease rather than act as a palliative treatment.

A recent published patent application[5] exemplified a series of sulfonamides (e.g., **1**–**4**, Table 1) that inhibit the production of Aβ peptides in vitro.[6]

Based on the simplicity and relatively high potency of these molecules we targeted the structurally novel carbon analogues for synthesis.[7,8] Thus 4-chlorobenzenethiol was reacted with 2,5-difluorobenzyl bromide followed by oxidation of the sulfide to give the intermediate sulfone (**5**). This could be readily alkylated with substituted bromides, and the esters reduced with lithium aluminium hydride to give the alcohols (Scheme 1).

The unsubstituted sulfone (**5**) was a weak γ-secretase inhibitor as measured in a whole cell inhibition assay using SH-SY5Y cells,[6] however a significant improvement in potency was observed as the size of the lipophilic group at the benzylic position was increased (e.g., **6**–**7**). Introduction of the ester (**8**) or the alcohol (**9**) gave a slight reduction in potency, but potency was re-established when the homologated alcohol was introduced (**10**) (Table 2).

To explore the effects of restricting the conformational freedom of the two aryl groups and to remove the chiral centre, a geminally-fused cyclohexane ring was introduced. The sulfone (**5**) underwent a double Michael addition followed by a Dieckmann cyclization to give the β-keto ester (**11**),[9] which underwent decarboxylation under Krapcho conditions to give the 4-aryl-4-phenylsulfonyl cyclohexanone (**12**, Scheme 2). The cyclohexanone was reduced with $NaBH_4$ to give a separable mixture of *cis* and *trans* alcohols (**13** and **14**). The sulfone (**5**) also underwent double alkylation with 1,5-diiodopentane to give the unsubstituted cyclohexane (**15**).[10]

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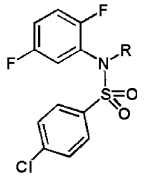
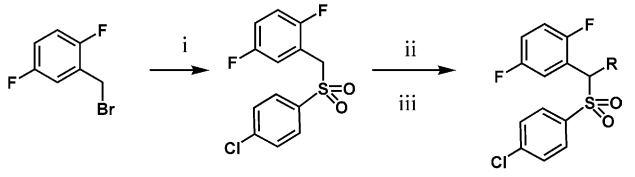
doi:10.1016/j.bmcl.2004.12.017

Table 1. γ-Secretase inhibition for sulfonamides **1**–**4**



Entry	R	IC_{50} (nM)[6]
1	H	>10,000
2	Me	1900
3	^{i}Pr	170
4		27

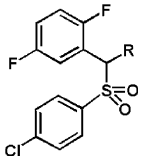
IC_{50} concentration to inhibit production of 50% of Amyloid (Aβ) peptide.

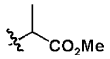
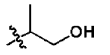
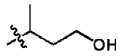


5 **6-10**

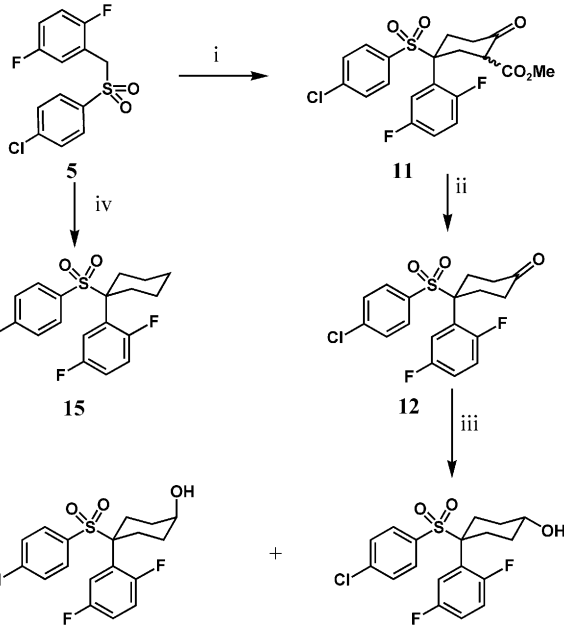
Scheme 1. Reagents and conditions: (i) (a) Et_3N, ClArSH, 90%, (b) 3-chloroperoxybenzoic acid; (ii) R–Br, ^{t}BuOK, 40–90% for **6**, **7** and **8**; (iii) lithium aluminium hydride, THF, 36% for **9** and **10**.

Table 2. γ-Secretase inhibition for sulfones **5**–**10**



Entry	R	IC_{50} (nM)[6]
5	II	4408
6	Me	2472[a]
7	^{i}Pr	70[a]
8		253[b]
9		304[b]
10		35[b]

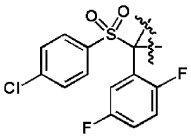
[a] Racemate.
[b] Racemic diastereoisomers (1:1).

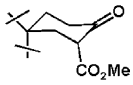
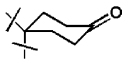
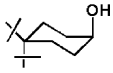
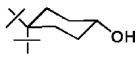
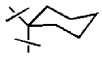


13 (*cis* alcohol) **14** (*trans* alcohol)

Scheme 2. Reagents and conditions: (i) KO^{t}Bu, methyl acrylate, 60%; (ii) NaCl/DMSO–H_2O, 150 °C, 30%; (iii) $NaBH_4$, 80%; (iv) $I(CH_2)_5I$, NaH, 29%.

Table 3. γ-Secretase inhibition for cyclic sulfones

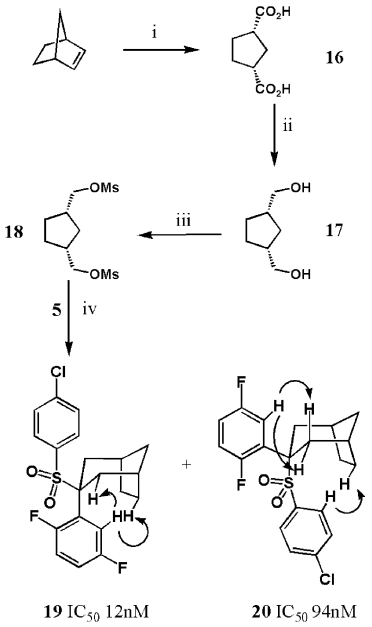


Entry	Cyclohexyl substitution	IC_{50} (nM)[6]
11		104
12		22
13		10
14		385
15		3

The cyclohexyl keto ester (**11**) had improved potency relative to the unsubstituted sulfone **5** (Tables 2 and 3). Removal of the ester gave the ketone (**12**) and provided a further increase in potency (IC_{50} 22 nM). The *cis* alcohol (**13**) retained potency, while the *trans* alcohol (**14**) was a weaker inibitor. Intriguingly, the unsubstituted cyclohexane (**15**) proved to be the most potent analogue prepared (IC_{50} 3 nM).

To further investigate the conformation of **15**, two bicyclic analogues were synthesized (Scheme 3) that hold the 2,5-difluoraryl group in either the axial or equatorial position.

Oxidation of norbornene was accomplished with ruthenium chloride and sodium periodate, and the resulting bis-acid (**16**)[11] reduced with lithium aluminium hydride to give the diol (**17**). This was activated as the bis-mesylate (**18**) and used in a double alkylation with the sulfone (**5**) to give a separable mixture of the bicyclic analogues **19** and **20** in low yield (24% and 4%, respectively). The structures were confirmed by ^{1}H NMR NOE



Scheme 3. Reagents and conditions: (i) $RuCl_3$, $NaIO_4$, $CHCl_3$–H_2O, rt, 70%; (ii) $LiAlH_4$, THF, 65%; (iii) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C, 92%; (iv) KO^{t}Bu, NaH, THF, **5**, 28%.

experiments[12]. In analogue **19** the *ortho*-fluorophenyl proton was shown to be in close proximity to the C-2 equatorial proton of the cyclohexane and the proton on the ethylene bridge. For analogue **20** NOE's were observed from the *ortho*-fluorophenyl proton to both the 2-axial and 2-equatorial protons and the *ortho*-chlorophenyl proton also showed an NOE to the proton on the ethylene bridge, indicating that the SO_2Ar group exists in the axial orientation (Scheme 3). In analogue **15** NOE's were observed between the *ortho*-fluorophenyl proton and the 2-equatorial and 3-axial protons on the cyclohexane. Taken together, these experiments suggest that the more potent bicyclic analogues (**19** IC_{50} 12 nM) and **15** (IC_{50} 3 nM) possess the 2,5-difluoroaryl group in the axial position. This suggestion is supported by the work of Eliel and Manoharan[13] who showed that the larger phenyl group in 1-methyl-1-phenylcyclohexane prefers to exist in the energetically favourable axial position. An X-ray structure was obtained compound **15**

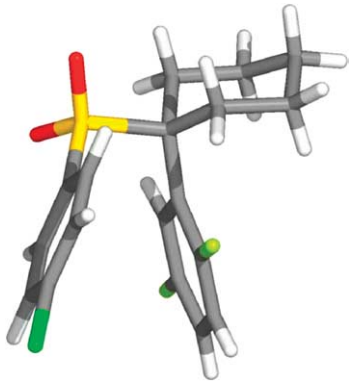
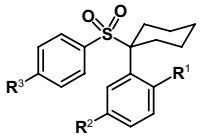


Figure 1. X-ray crystal structure of compound **15**.

Table 4. γ-Secretase inhibition for cyclic sulfons **15**, **21**–**24**



Entry	R^1	R^2	R^3	IC_{50} (nM)[5]
15	F	F	Cl	3
21	F	H	Cl	55
22	H	F	Cl	249
23	H	H	Cl	461
24	F	F	H	98

clearly depicted the 2,5-difluoroaryl group in the axial position (Fig. 1).[14]

To investigate the importance of the halogen substituents, a series of sulfones **21**–**24** were prepared (Table 4) following the general procedures outlined in Schemes 1 and 2.

A decrease in potency was observed with removal of the 5-fluoro (**21**), the 2-fluoro substituent (**22**) or both (**23**). Removal of the 4-chloro substituent in the aryl sulfone ring, as in analogue (**24**) also resulted in a decrease in potency (IC_{50} 98 nM). All substituents are therefore contributing to the high potency of the γ-secretase inhibitor **15**.

In conclusion, we have described a series of novel, aryl sulfone γ-secretase inhibitors, which possesses a simple pharmacophore, and requires only a three step synthesis to prepare potent compounds (e.g., **15**, IC_{50} 3 nM). The contribution of the halogen aromatic substituents was investigated, with the 2,5-difluorophenyl and 4-chlorophenyl groups found to be essential to maintain high potency. Finally, using NMR experiments, analogy with structurally defined analogues (**19** and **20**), and an X-ray it was concluded that the 2,5-difluoroaryl group resides in the axial position in the active conformer of **15**.

Acknowledgements

We thank Jonathan Wrigley, Dirk Beher, Earl Clarke and Huw Lewis for their support in obtaining the data.

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