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Tetrahydroquinoline sulfonamides as γ-secretase inhibitors

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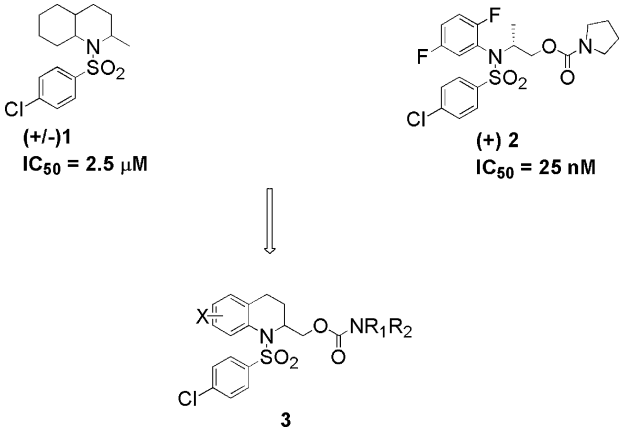
Abstract—The development of a novel series of tetrahydroquinoline-derived γ-secretase inhibitors for the potential treatment of Alzheimer's disease is described.

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by memory loss and cognitive decline. AD is the third largest cause of death and the leading cause of dementia in the United States.[1] A large body of evidence strongly suggests that overproduction, aggregation, and/or plaque deposition of the Aβ peptides, particularly Aβ 42, are central to the pathogenesis of AD.[2] The Aβ-peptides are produced by the sequential proteolytic cleavage of the amyloid precursor protein (APP) by β- and γ-secretases, respectively. Because of the essential role of γ-secretase in the generation of Aβ peptides, γ-secretase inhibition may be useful in the treatment of AD. Selective regulation of APP cleavage remains a critical issue because γ-secretase is also known to mediate a range of alternative transmembrane peptides most notably the Notch receptor, a large single-pass membrane protein that is implicated in development and differentiation.[3] To date, several γ-secretase inhibitors have been identified that lower Aβ production in intact cells and cell-free systems.[4]

Screening of an in-house database provided several hits with modest γ-secretase inhibitory activity, one of which was the bicyclic sulfonamide **1** (IC_{50} = 2.5 μM).

We presumed that the perhydroquinoline ring system in **1** could represent a ring constrained version of sulfonamide **2**, a recently reported γ-secretase inhibitor (IC_{50} = 25 nM).[5] We further surmised that the ring system in **1** could be simplified by elimination of the two asymmetric centers at the ring junction, and subsequent installation of an appropriate carbamate side chain at the 2-position could provide a novel tetrahydroquinoline γ-secretase inhibitor as represented by **3**. This communication describes the synthesis of tetrahydroquinoline analogues which illustrate how substituents on the heterocyclic and aromatic rings of the tetrahydroquinoline core relate to in vitro γ-secretase activity.[6]



Synthesis of the tetrahydroquinoline analogues[7] started with reduction of quinaldic acid **4** followed by esterification to give ester **5** (Scheme 1). The ester was reduced with LAH to give amino-alcohol **6**. The sulfonamide **7**

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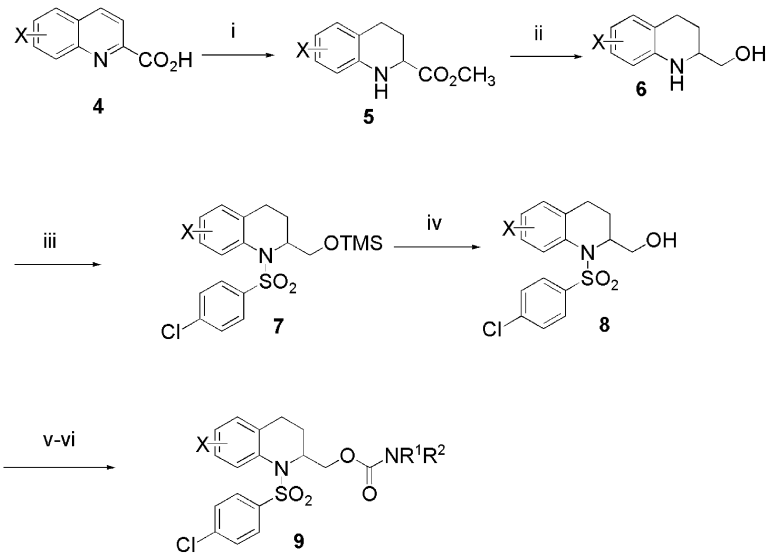


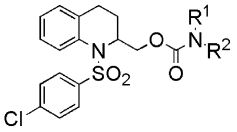
Scheme 1. Reagents and conditions: (i) a—H_2, PtO_2, MeOH; b—$SOCl_2$; (ii) LAH, THF; (iii) a—TMSCl, Et_3N, DCM, 0°C; b—$ArSO_2Cl$, Et_3N, THF, reflux; (iv) K_2CO_3, MeOH, 0°C; (v) *p*-NO_2–PhCOCl, CH_3CN, pyr; (vi) R_1R_2NH, MeOH.

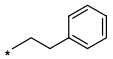
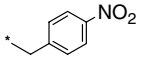
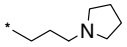
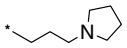
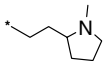
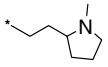
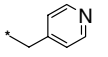
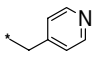
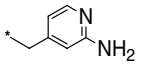
was prepared in a two-step, one-pot process by first protecting the alcohol as the silylether followed by sulfonylation. Deprotection provided the alcohol **8**. After activation as a *p*-nitrophenyl carbonate, the hydroxymethyl side chain was converted to carbamate **9**, in modular fashion, with a set of amines.

The structure–activity relationships of carbamate substituents are summarized in Table 1. Simple aliphatic carbamates show modest γ-secretase activity. However, inhibition of γ-secretase is significantly enhanced by the incorporation of a nitrogen heteroatom in the side chain (**13** and **15**). Furthermore, disubstituted carbamates with side chain bearing terminal amines showed up to twofold improvement in potency compared with the corresponding mono-substituted carbamates (**13** vs **14**, **15** vs **16**, and **17** vs **18**). Carbamates bearing amine substituents bulkier than ethyl (R^2 = benzyl, isopropyl) suffered in potency. The disubstituted 4-picolinyl carbamate (**18**) gave the best activity in this study. Introduction of a second amine on the pyridine ring resulted in a substantial loss in potency (**19**). Having identified potent inhibitors, attention was directed toward the synthesis of analogues with diverse substitution at the terminus of the side chain.

As shown in Table 2, terahydroquinoline analogues derived from piperazine (**20**–**22**) and simple 4-amino piperidine (**23** and **24**) provide comparable potency to the open chain carbamate analogues. A number of 4-amino piperidine analogues bearing cyclic distal amines were investigated. Piperidino-pyrolidine (**25**) and piperidino-homopiperidine (**29**) were modestly equipotent whilst piperidino-piperidine (**26**) proved to be most potent. Compound (**26**) was selected for further evaluation and was prepared in its enantiomerically pure form from the chromatographically resolved alcohol (**8**).[9] The relative potencies of the two enantiomers (**27** and **28**) indicate enantiospecificity with respect to γ-secretase inhibition.

Table 1. Structure–activity relationships of carbamates

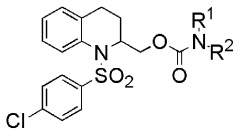


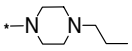
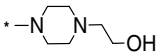
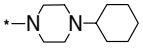
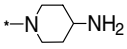
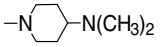
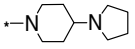
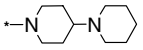
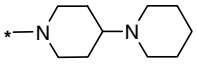
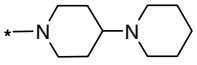
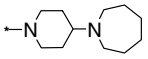
Compound	R^1	R^2	IC_{50} (nM)[8]
10		H	1096
11		H	4488
12		H	2959
13		H	394
14		Et	172
15		H	504
16		Et	253
17		H	1644
18		Et	88
19		Et	580

All compounds are racemic.

The effect of introducing fluorine substituents on the phenyl ring of the tetrahydroquinoline was investigated as outlined in Table 3. The compounds were prepared as piperidino-piperidine carbamates.[10] Introduction of two fluorine atoms at the 5,7- and 5,8-positions of the phenyl ring resulted in some loss of inhibitory activity (**30** and

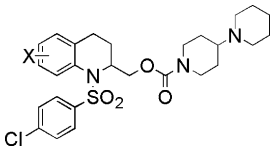
Table 2. Structure–activity relationships of cyclic carbamates



Compound	NR^1R^2	IC_{50} (nM)[8]
20		440
21		299
22		540
23		680
24		629
25		290
26		73
27	 enantiomer a	39
28	 enantiomer b	>1000
29		255

All compounds are racemic unless otherwise stated.

Table 3. Structure–activity relationship of fluorine substitution on aromatic ring of tetrahydroquinoline



Compound	X	IC_{50} (nM)[8]
26	H	73
30	5,7-F_2	219
31	5,8-F_2	217
32	6-F	>1000
33	7-F	56

All compounds are racemic.

31) and fluorine substitution at the 6-position (**32**) proved to be highly detrimental. Incorporation of a fluorine substituent at the 7-position, however, gave rise to the most potent compound (**33**). Selected tetrahydroquinoline sulfonamides displayed poor pharmacokinetic properties and further work was differed to the related 2,6-disubstituted *N*-arylsulfonyl piperidine class of compounds which showed promising pharmacokinetic properties.[11]

In conclusion, a novel series of tetrahydroquinoline sulfonamides that inhibit γ-secretase has been discovered. It was found that the potency of the screening hit **1** could be enhanced first by structural simplification to a tetrahydroquinoline core and subsequently by the introduction of appropriate substituents both on the heterocyclic and phenyl rings of the tetrahydroquinoline leading to compound **33**.

References and notes

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5. Smith, D. W.; Munoz, B. WO 50391, 2000 CAN 133:207678.
6. Preliminary SAR studies carried out on the perhydroquinoline lead series **1** established sulfonamide as optimum substituent on the ring nitrogen (unpublished result).
7. Asberom, T.; Guzik, H.; Josien, H.; Pissarnitski, D. WO 14075, 2003 CAN 138:187649.
8. Zhang, L.; Song, L.; Terracina, G.; Liu, Y.; Pramanik, B.; Parker, E. *Biochemistry* **2001**, *40*, 5049, all IC_{50} data shown are average of minimum of three independent results..
9. The two enantiomers of **8** (X = H) were separated by preparative HPLC. The following conditions were used for AS Chiralpack column: hexane/isopropanol, 90/10, 45 mL/min, 254 nM, 117.41 min (isomer A), 256.51 min (isomer B). Each enantiomer was independently converted to the enantiomerically pure carbamate.
10. The compounds listed in Table 3 were prepared in analogous fashion to the compounds listed in Table 1. The requisite fluorinated 2-methyl Quinoline starting materials were prepared using Doebner–Miller quinoline synthesis as modified by Matsugi, M.; Tabusa, F.; Minimikawa, J. *Tetrahedron Lett.* **2000**, 8523.
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