Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 17 (2007) 3010–3013
Bioorganic & Medicinal Chemistry Letters

Design, synthesis, and evaluation of tetrahydroquinoline and pyrrolidine sulfonamide carbamates as γ-secretase inhibitors

Tao Guo,[a,*] Huizhong Gu,[a] Doug W. Hobbs,[a] Laura L. Rokosz,[a] Tara M. Stauffer,[a] Biji Jacob[a] and John W. Clader[b]

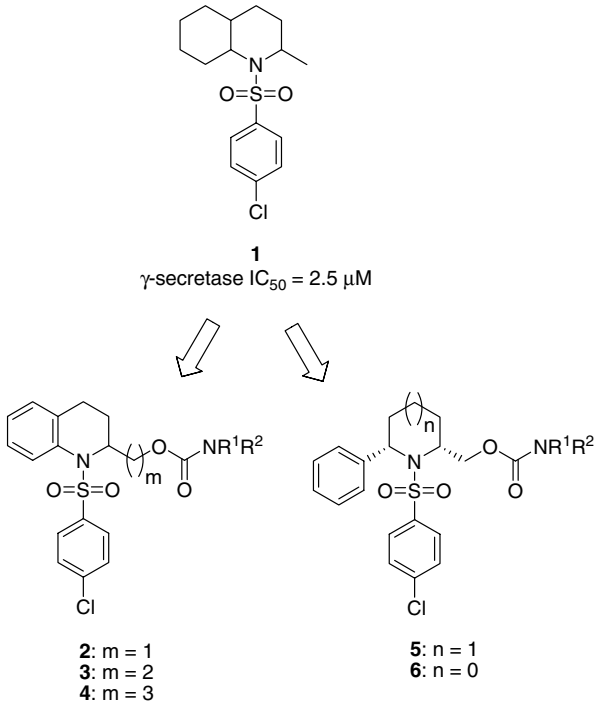
[a]*Pharmacopeia Drug Discovery, Inc., P.O. Box 5350, Princeton, NJ 08543-5350, USA*
[b]*Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA*

Received 27 February 2007; revised 15 March 2007; accepted 19 March 2007
Available online 23 March 2007

Abstract—γ-Secretase is a key enzyme involved in the production of β-amyloid peptides which are believed to play a critical role in the onset and progression of Alzheimer's disease (AD). As such, inhibition of γ-secretase has been an attractive approach to AD therapy. In this paper, the design, synthesis, and evaluation of tetrahydroquinoline and pyrrolidine sulfonamide carbamates as γ -secretase inhibitors are described.

Alzheimer's disease (AD) has become the most common cause of dementia in the elderly, affecting approximately 4.5 million people in the US and 15 million people worldwide.[1a,b] AD is a devastating disease characterized by a progressive loss in memory and cognitive function which ultimately leads to death. The pathological hallmark of AD includes extraneuronal amyloid plaques containing primarily aggregated β-amyloid peptides (Aβ) and intracellular neurofibrillary tangles (NFTs).[1a,b] Although both amyloid plaques and NFTs are thought to contribute to neuronal cell death and the symptoms observed in AD, the formation of amyloid plaques is unique to AD, whereas NFTs have been found in some other uncommon neurodegenerative diseases.[1c] Therefore, the production and deposition of Aβ peptides in the brain are believed to play a key role in the onset and progression of AD (the 'amyloid cascade hypothesis').[1d]

Aβ peptides are produced via the sequential cleavage of β-amyloid precursor protein (β-APP) by two proteases: β- and γ-secretases. Inhibition of either β- or γ-secretases has become an attractive approach to the treatment of AD. γ-Secretase is a novel membrane-bound aspartyl protease composed of presenilin-1/2, nicastrin, Aph-1, and pen-2, and to date a number of small molecule γ-secretase inhibitors have been reported.[2,3] In our search for novel γ-secretase inhibitors, various cyclic amine sulfonamide carbamates (**2**–**6**) were designed based on a screening hit **1** (IC_{50} = 2.5 μM).[3d] The SAR of tetrahydroquinoline sulfonamide carbamates **2** and piperidine



Keywords: Alzheimer's disease; γ-Secretase inhibitors.
* Corresponding author. Tel.: +1 609 452 3746; fax: +1 609 452 3699; e-mail: tguo@pcop.com

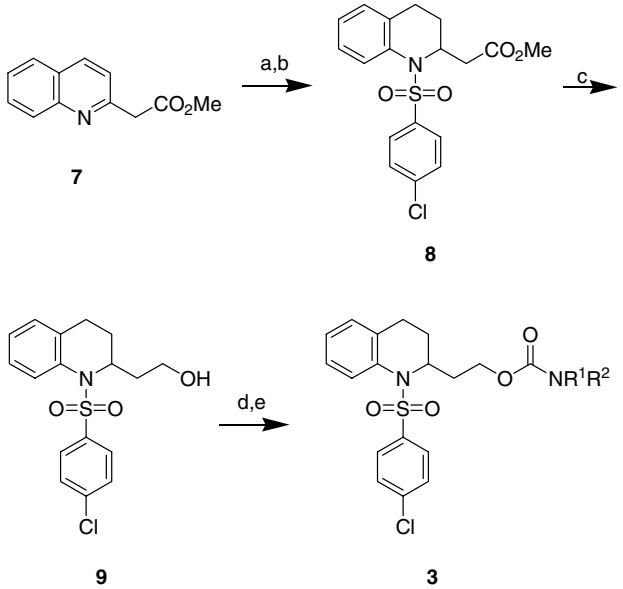
0960-894X/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2007.03.055

sulfonamide carbamates **5** have been recently disclosed.[3d–f] In this paper, the synthesis and SAR of tetrahydroquinoline sulfonamide carbamates **3**, **4**, and pyrrolidine sulfonamide carbamates **6** are described.

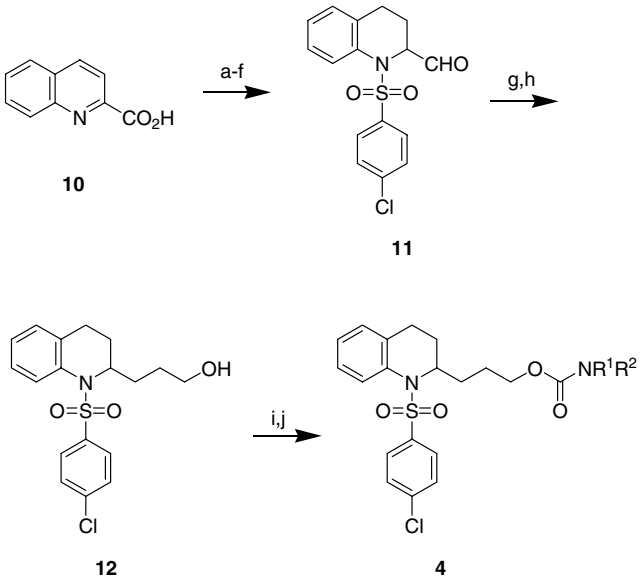
The synthesis of carbamates **3** is illustrated in Scheme 1. Hydrogenation of quinoline-2-acetic acid methyl ester **7**[4] (prepared from quinoline-N-oxide according to the literature procedure in Ref. 4) using H_2/PtO_2 followed by sulfonylation with 4-chlorobenzenesulfonyl chloride gave sulfonamide **8**. Then, reduction of **8** using DIBAL-H provided alcohol **9**. Finally, conversion of **9** to 4-nitrophenylcarbonate followed by treatment with various amines yielded target compounds **3**.

The preparation of carbamates **4** is shown in Scheme 2. The synthesis began with hydrogenation of quinaldic acid **10**, followed by LAH reduction, TMS-protection of the resulting alcohol, sulfonylation, TMS-deprotection, and Swern oxidation to provide aldehyde **11**. Next, after Wittig coupling of **11** with methyl (triphenylphosphoranylidene)acetate, DIBAL-H reduction gave propanol **12**. Finally, conversion of **12** to 4-nitrophenylcarbonate followed by reactions with various amines furnished target compounds **4**.

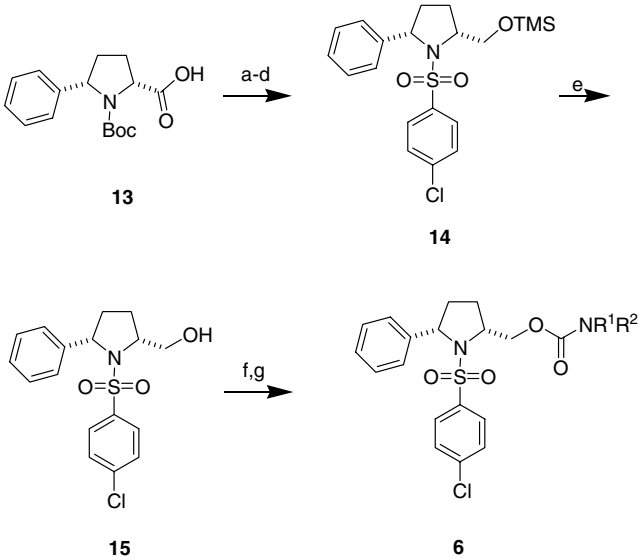
The synthesis of carbamates **6** is illustrated in Scheme 3. Commercially available (2*R*,5*S*)-Boc-5-phenyl-pyrrolidine-2-carboxylic acid **13** (SNPE North America LLC) was treated with HCl to remove Boc, followed by LAH reduction, TMS-protection of the resulting alcohol, and sulfonylation to give pyrrolidine sulfonamide silylether **14**. The TMS protecting group in **14** was then removed using K_2CO_3 in MeOH to provide alcohol **15**.[5] Finally, conversion of alcohol **15** to 4-nitrophenylcarbonate followed by reactions with various amines gave target compounds **6**.



Scheme 1. Preparation of tetrahydroquinoline sulfonamides **3**. Reagents and conditions: (a) H_2, PtO_2, MeOH, rt, 4 h; (b) 4-chlorobenzenesulfonyl chloride, Et_3N, $ClCH_2CH_2Cl$, 70 °C, 16 h, 28% (steps a–b); (c) DIBAL-H, toluene/hexane, rt, 16 h, 60%; (d) 4-nitrophenyl chloroformate, Et_3N, CH_2Cl_2, rt, 16 h; (e) R^1R^2NH, Et_3N, CH_2Cl_2, rt, 6 h, 50–95% (steps d-e).



Scheme 2. Preparation of tetrahydroquinoline sulfonamides **4**. Reagents and conditions: (a) H_2, PtO_2, MeOH, rt, 6 h, 100%; (b) $LiAlH_4$, THF, reflux, 4 h, 87%; (c) TMSCl, Et_3N, CH_2Cl_2, 0 °C, 15 min, 93%; (d) 4-chlorobenzenesulfonyl chloride, Et_3N, $ClCH_2CH_2Cl$, 70 °C, 16 h, 47%; (e) K_2CO_3, MeOH, 0 °C, 30 min, 96%; (f) Swern oxidation, 61%; (g) methyl (triphenyl-phosphoranylidene)acetate, THF, rt, 16 h, 100%; (h) DIBAL-H, toluene/hexane, rt, 3 h, 95%; (i) 4-nitrophenyl chloroformate, Et_3N, CH_2Cl_2, rt, 16 h; (j) R^1R^2NH, Et_3N, CH_2Cl_2, rt, 6 h, 50–95% (steps i–j).

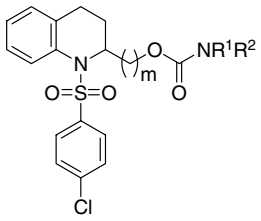


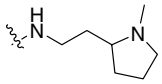
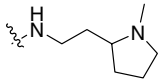
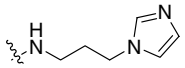
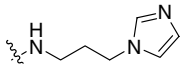
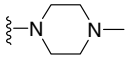
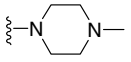
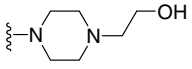
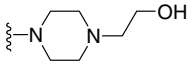
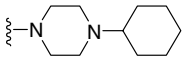
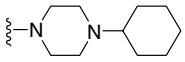
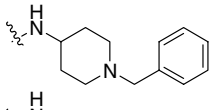
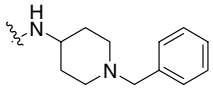
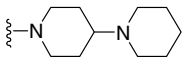
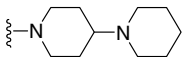
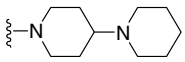
Scheme 3. Preparation of pyrrolidine sulfonamides **6**. Reagents and conditions: (a) 4N HCl, dioxane, rt, 2 h; (b) $LiAlH_4$, THF, reflux, 4 h; (c) TMSCl, Et_3N, CH_2Cl_2, 0 °C, 45 min, 100% (steps a–c); (d) 4-chlorobenzenesulfonyl chloride, Et_3N, $ClCH_2CH_2Cl$, 70 °C, 16 h, 52%; (e) K_2CO_3, MeOH, rt, 30 min, 96%; (f) 4-nitrophenyl chloroformate, Et_3N, CH_2Cl_2, rt, 16 h; (g) R^1R^2NH, Et_3N, CH_2Cl_2, rt, 6 h, 50–95% (steps f–g).

Table 1 lists the SAR[6,7] of tetrahydroquinoline sulfonamide carbamates **3** and **4**. For the two carbon chain

linked carbamates (**3a–g**, $m = 2$), IC_{50} values ranging from 280 nM (**3b**) to 1900 nM (**3c**) were achieved. For the three carbon chain linked carbamates (**4a–g**, $m = 3$), potency enhancements of ~5-fold were observed for carbamates of piperazine and piperidine with bulky side chains as compared to the corresponding two carbon chain carbamates (**4e–g** vs. **3e–g**). In contrast, little change in potency was observed for primary amine carbamates (**4a,b** vs. **3a,b**) or for carbamates of piperazine and piperidine with small side chains (**4c,d** vs **3c,d**). The potency levels observed for the three carbon chain linked carbamates are similar in magnitude to those found for the one carbon chain linked carbamates (**2**, $m = 1$).[3d] As an example, carbamate **4g** (IC_{50} = 60 nM, $m = 3$) is almost equipotent to carbamate **2g**[3d] (IC_{50} = 73 nM, $m = 1$). It should be noted that all the compounds shown in Table 1 are racemic mixtures. The two enantiomers of **2g** had been separated by chiral preparative HPLC, with one enantiomer displaying an IC_{50} of 39 nM, while the other enantiomer showing an IC_{50} of >1000 nM (see Ref. 3d). However, the absolute stereochemistry for the active enantiomer was not established.

Table 1. SAR of tetrahydroquinoline sulfonamide carbamates

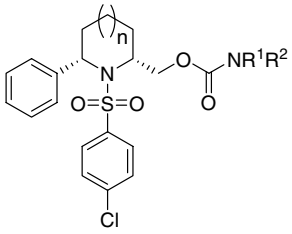


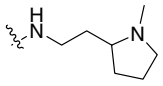
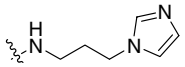
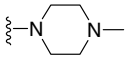
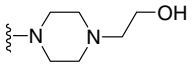
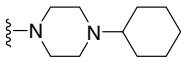
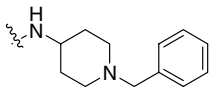
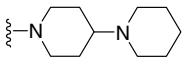
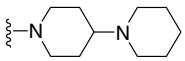
Compound	m	NR^1R^2	IC_{50} (nM)[a]
3a	2		530
4a	3		220
3b	2		280
4b	3		86
3c	2		1900
4c	3		780
3d	2		880
4d	3		680
3e	2		1000
4e	3		180
3f	2		900
4f	3		190
3g	2		360
4g	3		60
2g[3d]	1		73[3d]

[a] IC_{50}'s are mean values of two or more determinations with the standard deviations no greater than 50% from the mean.[6]

Table 2 summarizes the SAR[6,7] of pyrrolidine sulfonamide carbamates **6**. As can be seen from Table 2,

Table 2. SAR of pyrrolidine sulfonamides



Compound	n	NR^1R^2	IC_{50} (nM)[a]
6a	0		600
6b	0		650
6c	0		450
6d	0		540
6e	0		120
6f	0		140
6g	0		180
5g[3e]	1		16[3e]

[a] IC_{50}'s are mean values of two or more determinations with the standard deviations no greater than 50% from the mean.[6]

carbamates bearing piperazines and piperidines with bulky side chains (**6e–g**) are more active than carbamates bearing acyclic amines (**6a–b**) or piperazines and piperidines with small side chains (**6c–d**). Compound **6e** showed the highest potency in this series with an IC_{50} value of 120 nM. It should be noted that compounds **6a–g** were prepared as pure (2*R*,5*S*)-enantiomers.[5] The antipodes, (2*S*,5*R*)-enantiomers, were also prepared but all gave $IC_{50} > 10{,}000$ nM (data not shown).[5] As a result, the strong preference for (2*R*,5*S*)-configuration in γ-secretase inhibition is clearly established. It should also be noted that the pyrrolidine carbamates **6** are in general ~10-fold less potent than the corresponding piperidine carbamates **5**.[3e] For example, pyrrolidine analog **6g** ($IC_{50} = 180$ nM) is 11-fold less potent than piperidine analog **5g**[3e] ($IC_{50} = 16$ nM). Interestingly, using chiral HPLC and Mosher's method, the absolute stereochemistry required for γ-secretase inhibition by the piperidine carbamates **5** had been established to have the (2*R*,6*S*)-configuration (see Ref. 3e), consistent with that for pyrrolidine carbamates **6**. Based on these results, the absolute stereochemistry for the active enantiomers in the tetrahydroquinoline carbamates could be inferred as the (2*R*)-configuration. However, this hypothesis needs further experimental confirmation.

In summary, novel cyclic amine sulfonamide carbamates have been discovered as potent γ-secretase inhibitors. Tetrahydroquinoline sulfonamide carbamates with one and three carbon chain linkers are more potent than those with a two carbon chain linker. Pyrrolidine sulfonamide carbamates are in general less potent than the corresponding piperidine sulfonamide carbamates. A clear preference for the (2*R*,5*S*)-configuration was firmly established for the pyrrolidine sulfonamide carbamate γ-secretase inhibitors.

Acknowledgment

The authors thank Dr. William J. Greenlee of Schering-Plough Research Institute for helpful discussions, support, and encouragement.

References and notes

1. (a) Selkoe, D. J. *Arch. Neurol.* **2005**, *62*, 192; (b) Selkoe, D. J. *Ann. Intern. Med.* **2004**, *140*, 627; (c) Spillantini, M. G.; Murrell, J. R.; Goedert, M.; Farlow, M. R.; Klug, A.; Ghetti, B. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 7737; (d) Hardy, J.; Selkoe, D. J. *Science* **2002**, *297*, 353.
2. (a) Churcher, I.; Beher, D. *Curr. Pharm. Des.* **2005**, *11*, 3363; (b) Josien, H. *Curr. Opin. Drug Discov.* **2002**, *5*, 513.
3. (a) Rishton, G. M.; Retz, D. M.; Tempest, P. A.; Novotny, J.; Kahn, S.; Treanor, J. J. S.; Lile, J. D.; Citron, M. *J. Med. Chem.* **2000**, *43*, 2297; (b) Smith, D.W.; Munoz, B.; Srinivasan, K.; Bergstrom, C.P.; Chaturvedula, P.V.; Deshpande, M.S.; Kevy, D.J.; Lau, W.Y.; Parker, M.F.; Sloan, C.P.; Wallace, O.B.; Wang, H.H. PCT Int. Appl. WO2000050391; (c) Churcher, I.; Beher, D.; Best, J. D.; Castro, J. L.; Clarke, E. E.; Gentry, A.; Harrison, T.; Hitzel, L.; Kay, E.; Kerrad, S.; Lewis, H. D.; Morentin-Gutierrez, P.; Mortishire-Smith, R.; Oakley, P. J.; Reilly, M.; Shaw, D. E.; Shearman, M. S.; Teall, M. R.; Williams, S.; Wrigley, J. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 280; (d) Asberom, T.; Bara, T. A.; Clader, J. W.; Greenlee, W. J.; Guzik, H. S.; Josien, H. B.; Li, W.; Parker, E. M.; Pissarnitski, D. A.; Song, L.; Zhang, L.; Zhao, Z. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 205; (e) Pissarnitski, D. A.; Asberom, T.; Bara, T. A.; Buevich, A. V.; Clader, J. W.; Greenlee, W. J.; Guzik, H. S.; Josien, H. B.; Li, W.; McEwan, M.; McKittrick, B. A.; Nechuta, T. L.; Parker, E. M.; Sinning, L.; Smith, E. M.; Song, L.; Vaccaro, H. A.; Voigt, J. H.; Zhang, L.; Zhang, Q.; Zhao, Z. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 57; (f) Asberom, T.; Zhao, Z.; Bara, T. A.; Clader, J. W.; Hyde, L. A.; Josien, H. B.; Li, W.; McPhail, A. T.; Nomeir, A. A.; Parker, E. M.; Rajagopalan, M.; Song, L.; Wong, G. T.; Zhang, L.; Zhang, Q.; Pissarnitski, D. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 511.
4. Gilchrist, T. L.; Rahman, A. *J. Chem. Soc. Perkin Trans. 1* **1998**, *7*, 1203.
5. The alcohol intermediate **15** was analyzed by chiral HPLC using analytical Chiralcel OD column, 10% isopropanol in hexane, 1 mL/min, 254 nm: $t_R = 9.9$ min, >99% e.e. The antipode, (2*S*,5*R*)-**15**, was also prepared (from (2*S*,5*R*)-Boc-5-phenyl-pyrrolidine-2-carboxylic acid) and analyzed: $t_R = 12.3$ min, >99% e.e. Each pure enantiomer was independently converted to the corresponding carbamates.
6. To measure γ-secretase activity, compounds were diluted serially in DMSO, followed by a 37.5-fold dilution in start buffer (Hepes, pH 7.5, and 5 mM EDTA). 10 μL of membranes (5.0 μg total protein) in 20 mM Hepes, pH 5.0, and 5 mM EDTA, prepared as described in Ref. 7, was mixed with 30 μL of start buffer containing either compound or 2.7% DMSO (2% final) in a black 96-well Corning Costar HTRF-compatible plate and incubated for 2 h at 37 °C. The enzymatic reaction was quenched with the addition of 40 μL of a mixture containing 100 mM Tris–HCl, pH 7.5, 50 mM NaCl, 0.5% BSA, 2.0% Triton X-100, 17 nM biotin-W02 (Aβ40-specific antibody), 85 nM allophycocyanin-streptavidin (Wallac), and ~2 nM Europilated-G2-10 (Aβ40-specific antibody labeled using Europium chelate from Wallac according to the manufacturers' procedures). The mixture was incubated for two to 16 h at room temperature to allow the signal to develop and the plate was read on a Wallac Victor. Fluorescence was recorded at 665 nm. The signal at 615 nm was also monitored to check for fluorescence interference or other artifacts. All IC_{50}'s represent the mean values of two or more determinations with the standard deviations no greater than 50% from the mean.
7. Zhang, L.; Song, L.; Terracina, G.; Liu, Y.; Pramanik, B.; Parker, E. *Biochemistry* **2001**, *40*, 5049.