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2,6-Disubstituted *N*-arylsulfonyl piperidines as γ-secretase inhibitors

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Abstract—A novel piperidine series of γ-secretase inhibitors, potentially useful for the treatment of Alzheimer's disease, is disclosed. SAR investigation revealed the requirement for *cis*-stereochemistry of the substituents attached to the core, which resulted in the chair-like diaxial conformation of the piperidine ring. The series was optimized to provide inhibitors with IC_{50}'s in the single-digit nanomolar range. Absolute stereochemistry of the active enantiomer was assigned.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder accompanied by memory decline, cognitive impairment, and visual-spatial disorientation, for which no effective treatment exists today. Postmortem brain analysis of AD patients reveals extensive formation of neurofibrillary tau protein tangles and amyloid plaques. The latter are formed by the aggregation of a highly insoluble amyloid-β peptide (Aβ) which is predominantly composed of a sequence of 40 or 42 amino acids. Over-expression of Aβ in the brain of AD patients is thought to be the major cause of AD pathology.[1,2] Aβ is formed from a larger amyloid precursor protein (APP) by the action of two proteolitic enzymes, termed β- and γ-secretases. Accordingly, an inhibitor of either β- or γ-secretase[3] may serve as a treatment of AD.

Several types of γ-secretase inhibitors have been reported recently.[4] At least one compound entered in the Phase I clinical trials for AD was well tolerated at the studied doses.[5] These encouraging results prompted us to disclose our SAR studies on cyclic sulfonamides. The preceding paper[6] described the discovery of a tetrahydroquinoline series **I** of γ-secretase inhibitors starting from a moderately active lead **1** (Fig. 1). Presently, we describe a related series **II** based on a sulfonylated piperidine core.

One of the synthetic complications of piperidines **II** is a possibility of *cis*- and *trans*-relative stereochemistry between the R^3 group and the carbamate side chain. At the outset, a few members of the *trans*-series **5a** and **b** and *cis*-series **7a** and **b** with a methyl substituent as the R^3 group were prepared according to Scheme 1.

For the synthesis of **5a** and **b**, *N*-Boc-2-methylpiperidine was deprotonated using Beak's conditions[7] and quenched with dimethylformamide to furnish *trans*-2,5-disubstituted piperidinyl aldehyde **2**.[8] After reduction of the aldehyde to primary alcohol, the Boc group was cleaved and the resulting alcohol was protected as a TBS ether, providing **3**. The amino group of **3** was sulfonylated using 4-chlorobenzenesulfonylchloride and triethylamine as the base, TBS group was removed

Keywords: γ-Secretase; Alzheimer's disease; Inhibitor; Sulfonamide; Piperidine; Carbamate; Mosher ester.
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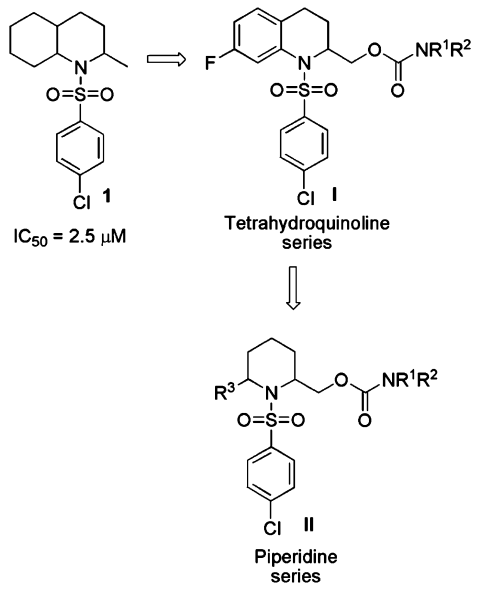
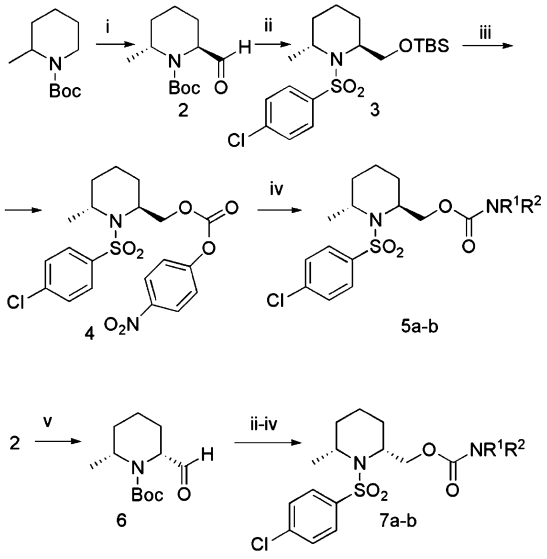


Figure 1. The origin of the piperidine series of γ-secretase inhibitors.

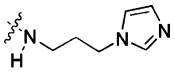
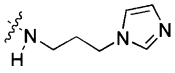
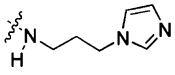
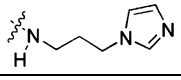


Scheme 1. Synthesis of *trans*- and *cis*-2,6-disubstituted piperidines. Reagents and conditions: (i) *sec*-BuLi, Et_2O, TMEDA, −78 °C, then DMF; (ii) a—$NaBH_4$, THF; b—TFA, DCM; c—TBSCl, imidazole, THF; d—4-chlorobenzenesulfonylchloride, DCM, Et_3N; (iii) a—TBAF, THF; b—4-NO_2–C_6H_4–O(CO)Cl, Py (3 equiv), THF/CH_3CN = 2:1; (iv) HNR_1R_2, THF or DCM; (v) K_2CO_3, MeOH.

with TBAF, and the primary alcohol was converted to 4-nitrophenylcarbonate. The resulting intermediate **4** could be stored for months at room temperature without signs of decomposition and conveniently provided the final carbamates **5a** and **b** by the displacement of 4-nitrophenol with amines. For the preparation of *cis*-disubstituted piperidines **7a** and **b**, aldehyde **2** was epimerized using potassium carbonate in methanol to provide **6**, which was processed in the analogous fashion.

Compounds **5a**,**b** and **7a**,**b** showed bioactivity in the γ-secretase assay[9] albeit were less potent than corresponding tetrahydroquinoline analogs **8a** and **b** with identical NR^1R^2 groups[6] (Table 1). Interestingly, *cis*-disubstituted piperidines **7a** and **7b** were approximately 5- to 10-fold more active than their *trans*-congeners **5a** and **5b**. Both **5a**,**b** and **7a**,**b** were much more active than piperidine **9** which lacked the R^3 group, thus underlining the importance of this substituent for the binding interaction with the enzyme. Based on the activity, the *cis*-disubstituted series was selected for further advancement (Table 2).

Table 1. Preference of *cis*-substitution at the piperidine ring

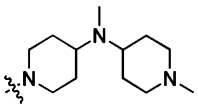
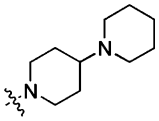
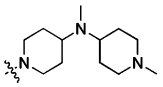
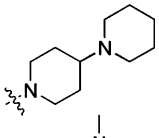
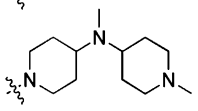
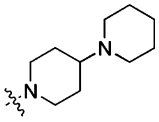
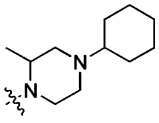
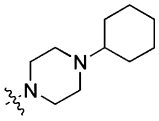
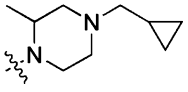
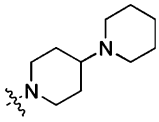
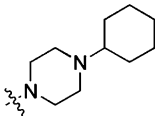
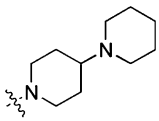
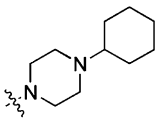
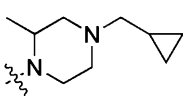
Compound	Series	NR^1R^2	R^3	$A\beta_{40}$ IC_{50} (μM)
5a	**II**-*trans*		Me	10.62
7a	**II**-*cis*		Me	1.97
8a	**I**		N/A	0.68
5b	**II**-*trans*		Me	6.42
7b	**II**-*cis*		Me	0.57
8b	**I**		N/A	0.27
9	**II**		H	15.42

N/A, not applicable.

Cyclic amines bearing a basic nitrogen center at the right-hand side provided more active compounds (**7c**,**d** vs **7b**). Additional improvement in potency was achieved by applying ethyl as the R^3 substituent (**13a** and **b**). Synthesis of compounds **13a** and **b** started from the coupling of the methyl ester of commercial 6-bromo-2-pyridinecarboxylic acid with vinyltributyltin under Stille conditions (Scheme 2).[10] Resulting pyridine **10** was hydrogenated over platinum dioxide followed by sulfonylation, reduction of the ester group with LAH to the alcohol, and conversion of the latter to the carbonate **12**. Transformation of **12** to the carbamates **13a** and **b** was accomplished as previously described.

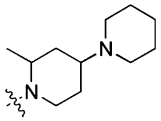
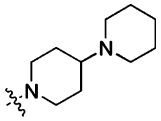
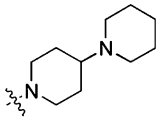
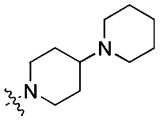
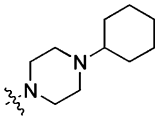
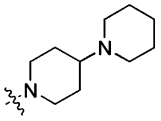
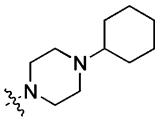
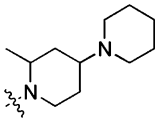
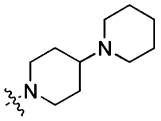
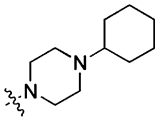
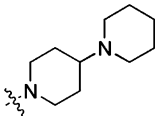
Since tetrahydroquinolines **I** contain an aromatic region on the left-hand side of the molecule which is important for activity, we chose to append an aromatic R^3 off the piperidine scaffold. The syntheses of benzyl- and phenyl-substituted compounds **18a**,**b** and **21a**–**d** are shown in Scheme 3. Commercial 2,6-dibromopyridine and known[11] 6-bromo-pyridine-2-carboxaldehyde were used as the starting materials. Both sequences utilized selectivity in catalytic hydrogenation of the pyridine over the phenyl when atmospheric pressure of hydrogen was used (rubber balloon).

Table 2. SAR of piperidine series **II**-*cis*[a]

Compound	NR^1R^2	R^3	$A\beta_{40}$ IC_{50} (μM)
7c		Me	0.219
7d		Me	0.076
13a		Et	0.159
13b		Et	0.034
18a		Bn	12.30
18b		Bn	4.77
21a		Ph	0.071
21b		Ph	0.067
21c		Ph	0.037
21d		Ph	0.016
22a		2-F–Ph	0.017
22b		2-F–Ph	0.008
23a		3-F–Ph	0.038
23b		3-F–Ph	0.026

(*continued on next page*)

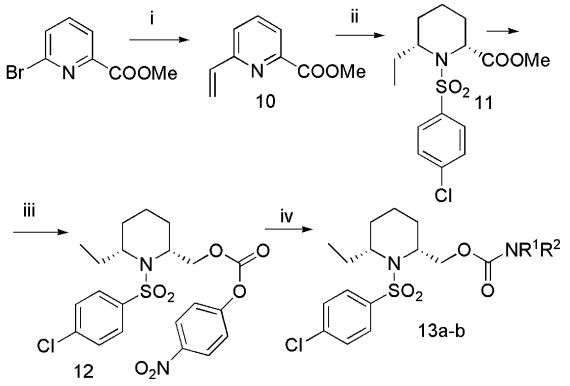
Table 2 (*continued*)

Compound	NR^1R^2	R^3	$A\beta_{40}$ IC_{50} (μM)
23c		3-F–Ph	0.013
23d		3-F–Ph	0.011
(−)-**23d**		3-F–Ph	0.003
(+)-**23d**		3-F–Ph	0.083
24a		2,5-Di-F–Ph	0.028
24b		2,5-Di-F–Ph	0.010
25a		3,5-Di-F–Ph	0.036
25b		3,5-Di-F–Ph	0.007
25c		3,5-Di-F–Ph	0.004
26a		3,4-Di-F–Ph	0.026
26b		3,4-Di-F–Ph	0.008

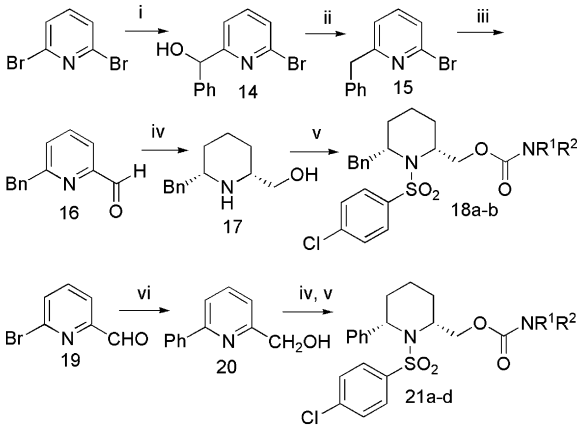
[a] All compounds are racemic unless stated otherwise.

While the activity of benzyl-substituted compounds **18a** and **b** dropped precipitously (Table 2), corresponding phenylpiperidines **21a**–**d** showed an improvement in potency, reaching the double-digit nanomolar level. Since introduction of a fluorine atom in the aromatic region of **I** led to an improvement of potency,[6] the same substituent was introduced into various positions of the phenyl ring of **21a**–**d**. As was expected, the resulting mono- and difluorinated compounds **22**–**26** showed improved potency with IC_{50}'s in the single-digit nanomolar range.

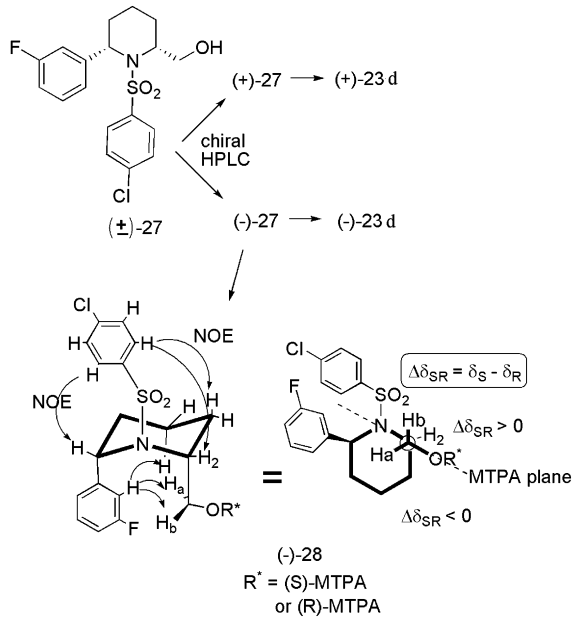
In order to elucidate the requirements of the absolute stereochemistry, synthetic intermediate **27** was resolved by chromatography on a Chiralpak™ OD column[12] using 15% IPA in hexanes, and both enantiomers of **23d** were prepared in a pure form (Fig. 2). The early eluting enantiomer of **27** gave rise to the (−)-enantiomer of **23d** which was more active (Table 2) with eudismic ratio of approximately 27. The absolute stereochemistry of (−)-**27**, and therefore (−)-**23d**, was assigned using Mosher's method, which relies upon the assessment of proton NMR chemical shift differences



Scheme 2. Synthesis of compounds **13a** and **b**. Reagents and conditions: (i) (a) vinyltributyltin, $Pd(PPh_3)_4$, DMF, 90 °C; (ii) a—H_2, cat PtO_2, 50 psi, MeOH; b—4-chlorobenzenesulfonylchloride, Py; (iii) a—LAH, THF, 0 °C; b—4-NO_2–C_6H_4–O(CO)Cl, Py (3 equiv), THF/CH_3CN = 2:1; (iv) HNR_1R_2, THF or DCM.



Scheme 3. Introduction of the aromatic groups to the piperidine core. Reagents and conditions: (i) BuLi (1 equiv), ether, −78 °C, then DMF; (ii) Et_3SiH, TFA, DCM, 80 °C, sealed tube; (iii) BuLi, THF, −78 °C, then DMF; (iv) 1 atm H_2, PtO_2, MeOH/AcOH = 2:1; (v) a—TMSOTf, Et_3N, DCM; b—4-chlorobenzenesulfonylchloride, DCM, Et_3N; c—HCl, MeOH; d—4-NO_2–C_6H_4–O(CO)Cl, Py (3 equiv), THF/CH_3CN = 2:1; e—HNR_1R_2, THF or DCM; (vi) a—$NaBH_4$, THF; b—$PhB(OH)_2$, cat $Pd(PPh_3)_4$, Na_2CO_3, toluene/EtOH = 6:3, 90 °C, 10 h.



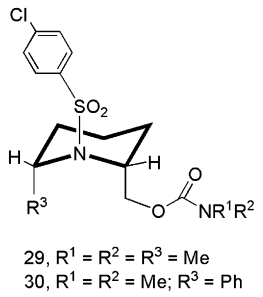


Figure 2. Stereochemical analysis of the series.

($\Delta\delta_{SR}$) between S and R esters of 2-methoxy-2-phenyl-2-(trifluoromethyl) acetic acid (MTPA) and the analyte.[13] Alcohol (−)-**27** was esterified using both (*R*)- and (*S*)-MTPA. Analysis of the vicinal proton–proton *J*-coupling constants and NOEs of the resulting MTPA esters (−)-**28** revealed a chair-like conformation of the piperidine ring, with the ester side chain and 3-fluorophenyl substituent both being axial. Complete NOE analysis (not shown) also led to the unambiguous assignment of protons H_a and H_b. The difference in chemical shifts $\Delta\delta_{SR}$ between the related protons of (*S*)- and (*R*)-MTPA derivatives was then evaluated. For the protons on the right of the MTPA plane (e.g., H_b and H_2) $\Delta\delta_{SR}$ was positive, while for the proton H_a on the left it was negative. Based on the empirical rules proposed in the literature,[13] this behavior of $\Delta\delta_{SR}$ is consistent with the absolute stereochemistry of **28** and **27** as drawn in Figure 2.

In order to assess the energy difference between the preferred and other conformations of the piperidine ring, ab initio calculations[14] for model compounds **29** and **30** (Fig. 2) were performed (B3LYP/6-31G** optimization; B3LYP/ CC_PVTZ(-F)++ single point energy). For **29** and **30**, the 2,6-diaxial chair-like conformation had the lowest energy in agreement with the NMR experiment, followed by twist-conformations which were 4 kcal/mol higher in energy. The 2,6-diequatorial chair-like conformation was 9 kcal/mol above the energy of the diaxial conformation. The preference for the diaxial conformation could be explained by the sp^2-character of the piperidine nitrogen.[15]

In conclusion, we discovered a novel series of γ-secretase inhibitors based on 2,6-disubstituted *N*-arylsulfonylpiperidine core **II**. *cis*-Relative stereochemistry of the substituents at the piperidine ring was established as a requirement for the potency. Absolute stereochemistry of the active enantiomer was assigned by Mosher's NMR analysis of a synthetic precursor **27**. Combination of NMR experiments and ab initio calculations points to

the chair-like 2,6-diaxial conformation of the inhibitors as being predominant.

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