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Discovery of 2,4,6-trisubstituted *N*-arylsulfonyl piperidines as γ-secretase inhibitors

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Abstract—Development of *cis*-2,4,6-trisubstituted piperidine *N*-arylsulfonamides as γ-secretase inhibitors for the potential treatment of Alzheimer's disease (AD) is reported.

Alzheimer's disease (AD), the most common form of dementia, is progressive and irreversible. It is estimated that about five million Americans suffer from this disease, and about 360,000 people are newly diagnosed every year.[1] Due to its significant financial burden on the healthcare system, research on the treatment of AD has drawn increasing attention from academia and industry. At the moment, one of the major hypotheses for the progression of AD is the chronic imbalance between β-amyloid peptide (Aβ) production and Aβ clearance resulting in the extracellular accumulation of Aβ. Subsequent plaque formation in the brain leads to neurodegeneration, dementia, and ultimately death. The release of Aβ is the result of sequential cleavage of β-amyloid precursor protein (APP) by two proteases, β-secretase and γ-secretase.[2] Because of its central role in the production of Aβ peptide, γ-secretase was proposed as an effective target for treatment of AD. To date, several series of γ-secretase inhibitors have been identified.[3]

The preceding papers from our research group disclosed cyclic sulfonamides and 2,6-disubstituted *N*-arylsulfonylated piperidines as potent γ-secretase inhibitors.[4,5] However, potential drug–drug interactions caused by CYP inhibition remained an issue in these series, since aging patients are often under multiple medications. Interaction of drugs with CYP3A4 has been linked to lipophilicity and the presence of basic amines.[6] During SAR studies, introduction of small alkyls at the R_1 position and modification of right-hand side chains substantially reduced CYP3A4 inhibition (Fig. 1). However, these improvements were still not sufficient to alleviate the undesired interactions. We envisioned that decreasing *c*log*P* by introducing substitution such as $-OCH_3$

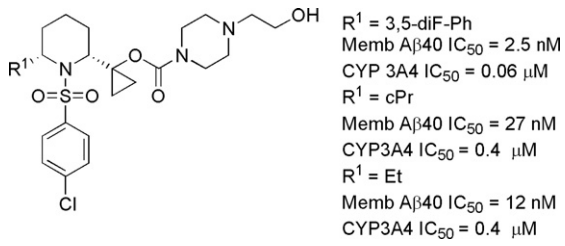

Figure 1. Introduction of small alkyls to reduce CYP3A4 inhibiton.

Keywords: Alzheimer's disease; *N*-Arylsulfonamide; γ-Secretase inhibitor.
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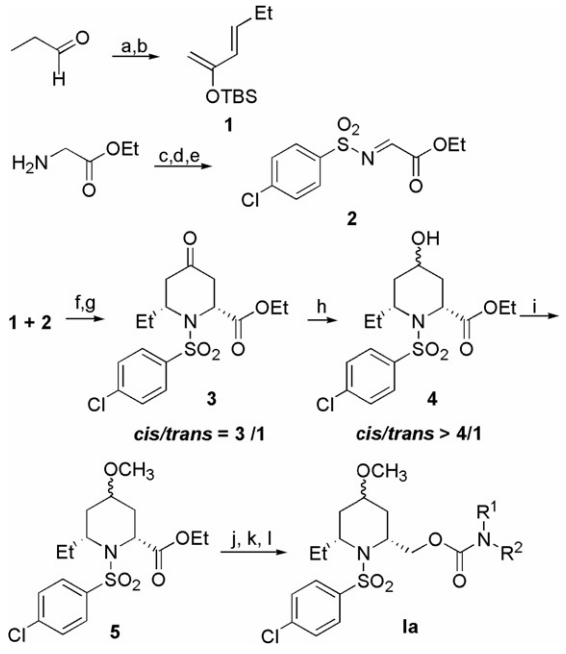
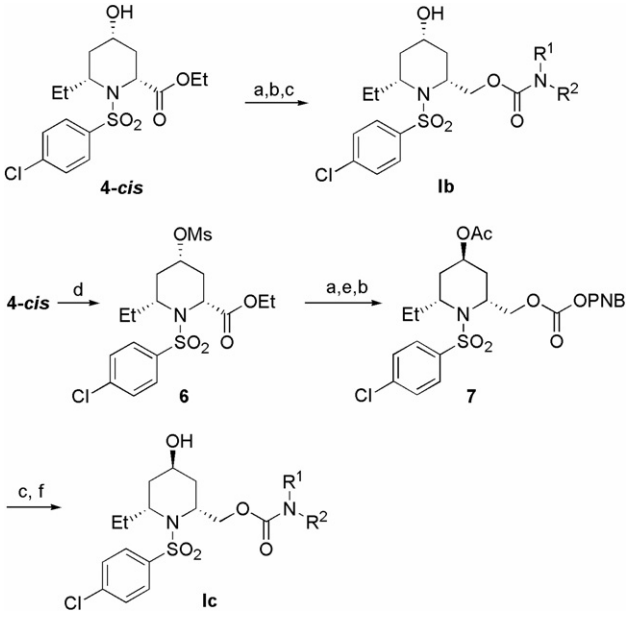
or –OH, on the piperidine ring could reduce the CYP3A4 inhibition in the piperidine sulfonamide series.

Herein, we report 2,4,6-trisubstituted piperidine *N*-arylsulfonamides with reduced CYP3A4 liability. Based on the previous results,[5] the ethyl group was chosen as the left-hand side chain. Synthesis of compounds **Ia** started with preparation of diene **1** and dienophile **2** separately (Scheme 1). Propionaldehyde was reacted with (acetylmethylene) triphenylphosphorane,[7] followed by reaction with NaHMDS, and TBSCl in THF to provide diene **1**. Glycine ethyl ester was reacted with 4-chlorobenzenesulfonyl chloride in a mixture of pyridine/DCM, followed by bromination and elimination of HBr to generate dienophile **2**.[8] Diene **1** and dienophile **2** were combined in THF and stirred at rt overnight, and the Diels–Alder adduct was treated with concentrated HCl in DCM to regioselectively afford **3** as a separable mixture of diastereomers in favor of the *cis*-adduct (*cis*/*trans* = 3/1). The *cis*-diastereomer was reduced to alcohol **4** with $NaBH_4$ as a mixture of diastereomers at *C*-4 (*cis*/*trans* > 4/1), which were separated by column chromatography and methylated with CH_3I in the presence of Ag_2O.[9] Reduction of the ethyl ester with LAH, conversion of the alcohol to *p*-nitrophenyl carbonate, and reaction with different optimized right-hand sides[5] provided carbamates **Ia**.

Alternatively, the alcohol **4-*cis*** was reduced with LAH directly, followed by transformation of the primary alcohol selectively as in Scheme 1, giving compounds



Scheme 1. Reagents and conditions: (a) (acetylmethylene)triphenylphosphorane, reflux, DCM, 60 °C, overnight; (b) NaHMDS, TBSCl, THF, −78 °C–rt; (c) 4-chlorobenzenesulfonyl chloride, Py/DCM (1/1), 0 °C–rt; (d) Br_2, CCl_4, reflux; (e) NaH, THF, 0 °C; (f) overnight, rt, THF; (g) concd HCl, DCM; (h) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, EtOH; (i) Ag_2O, CH_3I, Et_2O, 80 °C; (j) LAH, THF, 0 °C; (k) *p*-NO_2-PhCOCl, CH_3CN, py; (l) R_1R_2NH, DCM.



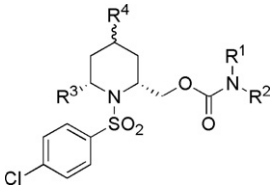
Scheme 2. Reagents and conditions: (a) LAH, THF, 0 °C; (b) *p*-NO_2-PhCOCl, CH_3CN, Py; (c) R_1R_2NH, DCM; (d) MsCl, Et_3N, DCM; (e) CsOAc, DMAP, toluene, reflux; (f) K_2CO_3, CH_3OH.

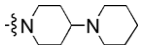
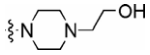
Ib (Scheme 2). Also, the alcohol **4-*cis*** was treated with MsCl, and the ethyl ester was reduced to alcohol with LAH. The mesylate was displaced with CsOAc in toluene under reflux,[10] and the primary alcohol was converted to *p*-nitrophenyl carbonate **7**. Carbonate **7** was reacted with amines, followed by hydrolysis of the acetate with K_2CO_3 providing compounds **Ic** (Scheme 2).

The influence of 4-substitution on γ-secretase inhibition and CYP3A4 is summarized in Table 1. Comparing with similar 2,6-disubstituted analogs, the γ-secretase inhibition was lost completely upon introduction of 4-OCH_3 (**11**, **12**, **16**, and **17**). The free hydroxyl at z*C*-4 resulted in a similar γ-secretase inhibition (**13**, **18**, and **19**). In both cases, CYP3A4 inhibition was decreased, with the more polar hydroxyl analog providing a dramatic reduction in CYP inhibition, validating our hypothesis.

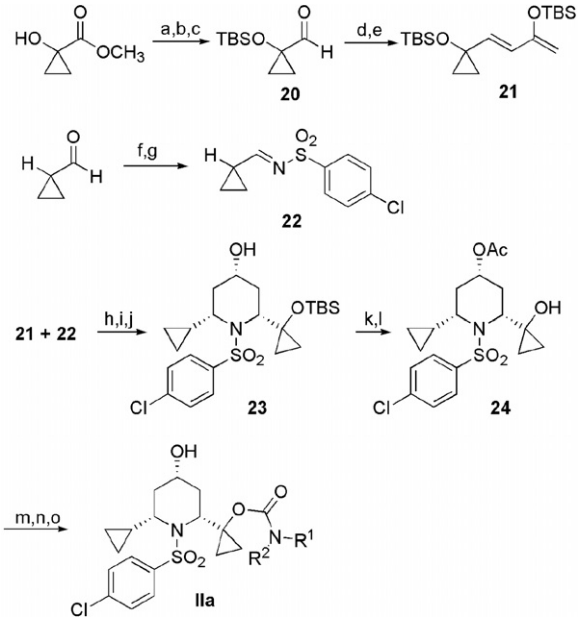
Encouraged by the results, the 4-OH was also introduced in both cyclopropyl carbamate and cyclopropyl amide series, based on previous observation that introduction of cyclopropyl group helped boost the γ-secretase inhibition ~5- to 20-fold.[4,5] Preparation of compounds **IIa** also began with the synthesis of diene **21** and dienophile **22** (Scheme 3).[11] The Diels–Alder product was obtained favoring the *cis*-adduct (*cis*/*trans* = 5/1) with desired regioselectivity. It was treated with concentrated HCl in DCM, followed by reduction with $NaBH_4$ in the presence of $CeCl_3{\cdot}7H_2O$ to provide 2,4,6-*cis*-trisubstituted alcohol **23** exclusively. Alcohol **23** was acetylated, followed by desilylation of the tertiary alcohol to provide **24**. The cyclopropyl alcohol **24** was converted to carbamate via the method described in Scheme 1, followed by deacetylation to provide compounds **IIa**.

Table 1. Structure–activity relationships of carbamates[a]



Compound	NR^1R^2	R^3	R^{4b}	Memb Aβ40[c] IC_{50} (nM)	CYP3A4[d] IC_{50} (μM)
8		Et	H	34.0	N/A
9		*c*-Pr	H	5.2	1.2
10		*i*-Pr	H	18.5	1.3
11		Et	*cis*-OCH_3	783	5.0
12		Et	*trans*-OCH_3	>1000	3.4
13		Et	*cis*-OH	28.4	24.3
14		*c*-Pr	H	71.1	0.3
15		*i*-Pr	H	103.5	0.3
16		Et	*cis*-OCH_3	>1000	30.0
17		Et	*trans*-OCH_3	>1000	10.1
18		Et	*cis*-OH	154.5	15.6
19		Et	*trans*-OH	310.1	30.0

[a] All compounds are racemic mixtures.
[b] *cis*- and *trans*- relative to 2,6-disubstitution on the piperidine ring.
[c] Data for inhibition of Aβ40 were measured by use of membrane-based preparation of γ-secretase.
[d] Values were determined after 30 min pre-incubation with compound.

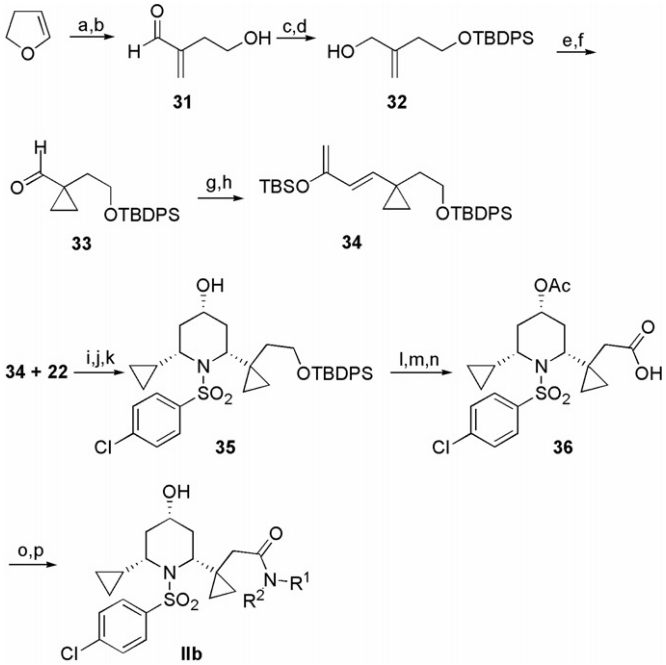


Scheme 3. Reagents and conditions: (a) imidazole, TBSCl, DMF/DCM; (b) DIBAL, THF, 0 °C; (c) $(COCl)_2$, DMSO, DCM, −78 °C; (d) (acetylmethylene) triphenylphosphorane, reflux, DCM, 60 °C, overnight; (e) NaHMDS, TBSCl, THF, −78 °C–rt; (f) 4-chlorobenzenesulfonamide, sodium *p*-toluenesulfinate, HCO_2H, H_2O; (g) sat. Na_2CO_3, DCM; (h) reflux, toluene, overnight; (i) concd HCl, DCM, 0 °C; (j) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, EtOH, 0 °C; (k) Ac_2O, DMAP, Py; (l) TBAF, THF, 0 °C; (m) *p*-NO_2-PhCOCl, CH_3CN, pyridine; (n) R_1R_2NH, DCM; (o) K_2CO_3, CH_3OH.

The synthesis of the cyclopropyl amide is shown in Scheme 4. Commercially available 2,3-dihydrofuran was treated with concentrated HCl in water,[12] and the resultant lactol was reacted with formaldehyde to generate **31**.[13] Protection of the alcohol and reduction of aldehyde provided compound **32**. After cyclopropanation[14] and Swern oxidation,[15] cyclopropyl aldehyde **33** was obtained. Wittig reaction with **33** provided the α,β-unsaturated ketone,[7] which was transformed to diene **34** by using the previous protocol. Again, the Diels–Alder reaction followed by hydrolysis gave the correct 2,6-disubstituted piperdine regioisomer, favoring the *trans*-diastereomer (*trans*/*cis* = 2/1). Following chromatographic separation, the *cis*-isomer was reduced with $NaBH_4$ to provide compound **35** as a single diastereomer. The 4-OH was protected with the acetate, followed by removal of TBDPS, and oxidation of the primary alcohol gave the acid **36**. Then the 4-OH was unmasked, and the acid was coupled with amines in the presence of HATU and *i*-Pr_2EtN to afford amides **IIb**.

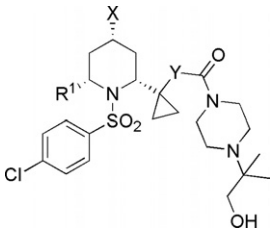
The biological results are shown in Table 2. As expected, in either series, the introduction of 4-OH substitution on piperidine ring helped decrease the CYP3A4 inhibition while maintaining high γ-secretase inhibition.

In conclusion, by introducing 4-OH on the piperidine ring with small alkyl groups on the left-hand side and modified non-basic amines on the right-hand side, we were able to substantially lessen CYP3A4 inhibition, while maintaining good γ-secretase inhibition in our previously identified piperidine sulfonamide series.



Scheme 4. Reagents and conditions: (a) concd HCl, water; (b) butyric acid, dibutylamine, HCHO in water, *i*-PrOH; (c) imidazole, TBDPSCl, DMAP, DMF; (d) $NaBH_4$, EtOH, 0 °C; (e) Et_2Zn, CH_2ICl, DCM, 0 °C–rt; (f) $(COCl)_2$, DMSO, DCM, −78 °C; (g) (acetylmethylene) triphenylphosphorane, reflux, DCM, overnight; (h) NaHMDS, TBSCl, THF, −78 °C–rt; (i) THF, 100 °C, 16 h; (j) concd HCl, DCM, 0 °C; (k) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, THF; (l) Ac_2O, *p*-TsOH (cat.); (m) TBAF, THF; (n) AcNH·TEMPO, NaCOCl, $NaBr/Bu_4N^+H \cdot HSO_4^-$, DCM/H_2O; (o) K_2CO_3, CH_3OH; (p) Amine, HATU, *i*-Pr_2NEt, DMF.

Table 2. Structure–activity relationships of carbamates and amides[a]



Compound	R^1	X	Y	Memb Aβ40 IC_{50}[b] (nM)	CYP3A4 IC_{50}[c] (μ)
25	3,5-diF-Ph	H	O	4.4	0.4
26	CH_3	H	O	48.8	0.8
27	Et	H	O	6.9	2.2
28	*i*-Pr	H	O	2.4	0.5
29	*c*-Pr	H	O	11.6	0.4
30	*c*-Pr	OH	O	5.6	19.5
37	*c*-Pr	H	CH_2	9.9	1.5
38	*c*-Pr	OH	CH_2	8.1	11.0

[a] All compounds are racemic mixtures.
[b] Data for inhibition of Aβ40 were measured by use of membrane-based preparation of γ-secretase.
[c] Values were determined after 30 min pre-incubation with compound.

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