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Design, synthesis, and structure–activity relationship studies of *N*-arylsulfonyl morpholines as γ-secretase inhibitors

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ABSTRACT

Design and synthesis of *cis*-2,6-disubstituted *N*-arylsulfonyl morpholines as novel γ-secretase inhibitors for the potential treatment of Alzheimer's disease (AD) is reported. Several different small alkyl groups are installed on the left-hand side to lower the CYP3A4 liability while maintaining excellent in vitro potency.

Alzheimer's disease (AD) is the most common form of neurodegenerative disease characterized by cognitive and memory deterioration, and impairment of language and other daily activities. It is estimated that about 5 million Americans currently suffer from this disease, and an additional 360,000 people are newly diagnosed every year.[1] Due to its enormous burden on patients and the healthcare system, research on the treatment of AD has drawn tremendous attention from both academia and industry. At the moment, one of the major hypotheses to explain the etiology of AD is a chronic imbalance between β-amyloid peptide (Aβ) production and clearance, which results in the extracellular accumulation of Aβ. An excess of extracellular Aβ results in the aggregation of Aβ into oligomers and plaques in the brain, which leads to neurodegeneration, dementia, and ultimately death. The formation of Aβ is the result of sequential cleavage of the β-amyloid precursor protein (APP) by two proteases, β-secretase (BACE) and γ-secretase.[2] Thus both β- and γ-secretase are proposed as effective targets for treatment of AD because of their central role in the production of Aβ peptide. To date, several series of γ-secretase inhibitors have been reported.[3]

Previous reports from our laboratories showed that 2,6-disubstituted piperidine sulfonamides (**1**) are potent γ-secretase inhibitors.[4] Installation of a 4-OH on the piperidine ring (**2**) effectively reduced CYP3A4 inhibition seen in (**1**) while maintaining good γ-secretase activity (Fig. 1).[5] To extend the SAR study of the 2-,4,6-trisubstituted piperidine sulfonamides, the 4-OH substitution on the piperidine ring was brought into the ring to generate the morpholine core (**8b**) (Fig. 1). Previous work on the morpholine core focused on 5-aryl and 5-cyclopropyl substituted compounds and showed that they have reduced CYP3A4 inhibition relative to the corresponding piperidines.[6]

In addition, previous studies on the piperidine series have shown that low molecular weight alkyl groups can replace the aryl or cycloproyl group and retain good γ-secretase inhibition.[4] Herein, we report additional SAR studies on this morpholine sulfonamide core. Small alkyl groups such as isopropyl, *t*-butyl, 1-methylcyclopropyl and cyclopropylmethyl were installed separately on the left-hand side at C-5 position, then the right-hand side groups were varied systematically.

First, the isopropyl group was introduced on the left-hand side as shown in Scheme 1. D-Valinol was reacted with allyl bromide, followed by reaction with di-*tert*-butyl dicarbonate in dichloromethane (DCM) to provide compound **3**.[7] After dihydroxylation of the allyl group,[8] selective protection of the primary alcohol with TBDPSCl and oxidation of the secondary alcohol with Dess–Martin periodinane in DCM afforded ketone **4**. Compound **4** was treated with TFA to free the amine, and the in situ formed imine was reduced with $NaBH(OAc)_3$ to afford *cis*-morpholine **5** exclusively. Morpholine **5** was reacted with 4-chlorobenzenesulfonyl chloride in a mixture of pyridine/DCM, followed by deprotection with TBAF in THF, oxidation of the alcohol to acid with $NaIO_4$ and $RuCl_3{\cdot}nH_2O$, and methylation of the acid to give methyl ester **6**. Methyl ester **6** was converted to the cyclopropyl alcohol using the Kulinkovich reaction,[9] and the alcohol was treated with $COCl_2$ in DCM to

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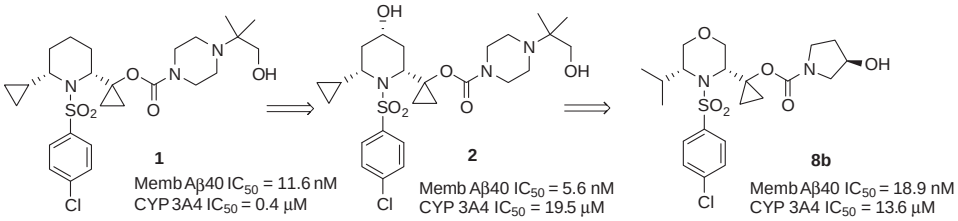
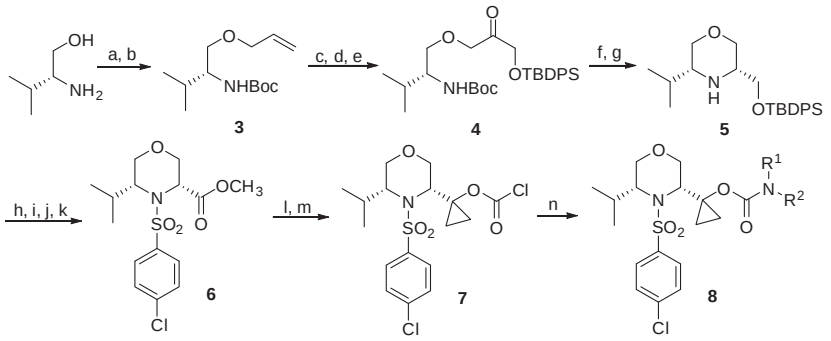


Figure 1. Introduction of 4-OH on piperidine ring to reduce CYP3A4 inhibition.

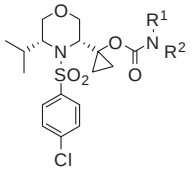


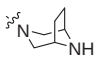
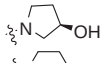
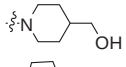
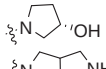
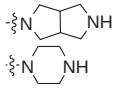
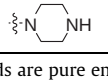
Scheme 1. Reagents and conditions: (a) NaH, allyl bromide, THF; (b) di-*tert*-butyl dicarbonate, DCM, 58% for two-steps; (c) NMO, OsO_4, *t*-BuOH/THF/H_2O (10/3/1); (d) TBDPSCl, imidazole, DMF, 70% for two-steps; (e) Dess–Martin periodinane, pyr., DCM, 57%; (f) TFA, DCM, 0 °C; (g) $NaBH(OAc)_3$, DCM, 0 °C, 57% for two-steps; (h) 4-chlorobenzenesulfonyl chloride, DMAP, pyr., 74%; (i) TBAF, THF; (j) $NaIO_4$, $RuCl_3{\cdot}nH_2O$, EtOAc/CH_3CN/H_2O (1/1/2), 95% for two-steps; (k) $TMSCHN_2$, toluene/CH_3OH (4/1), 75%; (l) Ti(O*i*Pr)$_4$, EtMgBr, THF, 0 °C, 85%; (m) $COCl_2$, pyr., DCM, 73%; (n) amine, DCM.

provide carbonochloridate **7**. By reacting with selected amines, carbamates **8** were obtained.

As shown in Table 1, this series of compounds has good in vitro activity in general. The compounds with free basic amines on the right-hand side (**8a**, **8e**, and **8f**) still have undesirable CYP3A4 inhibition, although they have good rat AUC values. On the other hand, the compounds without basic amines on the right-hand side (**8b**, **8c**, and **8d**) have a much better CYP3A4 inhibition profile. Unfortunately, these compounds also have low rat AUC values.

Table 1
Structure–activity relationship of 5-isopropylmorpholine series

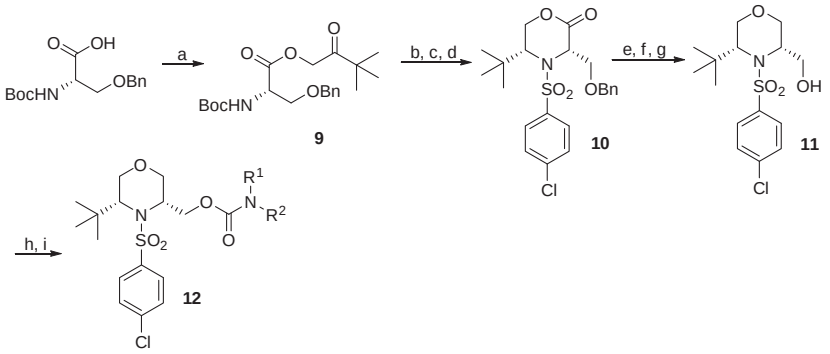


Compound[a]	NR^1R^2	Membr Aβ40 IC_{50}[b] (nM)	CYP3A4[c] (nM)	Rat $AUC_{0-6\ h}$[d] (h nM h)
8a		2.0	0.5	4970
8b		18.9	13.6	36
8c		6.5	13.8	0
8d		17.0	30.0	0
8e		9.3	6.4	1120
8f		14.5	0.3	3928

[a] All compounds are pure enantiomers.
[b] Data for inhibition of Aβ40 were measured by use of a membrane-based preparation of γ-secretase, and values are the mean of two experiments.
[c] Values are determined after 30 min pre-incubation with compound.
[d] Measured over 0–6 h after 10 mg/kg oral dosing in rat.

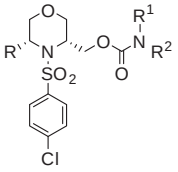
Next, we introduced *t*-butyl and 1-methylcyclopropyl as the left-hand side chain. Both groups were introduced by use of a similar procedure as shown in Scheme 2. The condensation of *N*-Boc-*O*-benzyl-L-serine with 1-bromopinacolone provided compound **9**. This compound was then reacted with TFA in DCM to give free amine, the in situ generated imine was reduced with $NaBH(OAc)_3$ to afford the morpholinone core, which was reacted with 4-chlorobenzenesulfonyl chloride to give **10**. Morpholinone **10** was reduced to the diol, followed by intramolecular Mitsunobu reaction to close the morpholine ring and hydrogenation to provide alcohol **11**. Due to the steric hindrance from the left-hand side, the attempted conversion of the primary alcohol **11** to a cyclopropyl alcohol through the formation of an ester followed by the Kulinkovich reaction as shown in Scheme 1 was not successful here. Therefore, the primary alcohol was treated with 4-nitrophenyl chloroformate and pyridine in THF/CH_3CN directly, followed by reacting with different amines to provide the carbonates. The biological results for those compounds are shown in Table 2. Due to the absence of cyclopropyl on the right-hand side, the in vitro activities for this series of compounds decreased as expected.[5] However, the CYP3A4 inhibition data for these compounds suggested that the *t*-butyl group on the left-hand side could help to improve the CYP3A4 profile compared to 1-methylcyclopropyl.

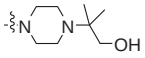
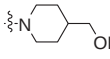
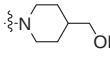
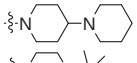
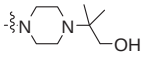
A cyclopropylmethyl group was also introduced as the left-hand side group on the morpholine core. Allylation of Boc-D-serine methyl ester provided allyl ether **13**,[10] followed by ozonolysis of the alkene and capture of the iminium cation with methanol to give morpholine **14**. This was reacted with allytrimethylsilane in the presence of $BF_3{\cdot}Et_2O$ to introduce the *cis*-allyl group on the left-hand side.[11] After reacting with 4 N HCl in dioxane, treatment with 4-chlorobenzenesulfonyl chloride in a mixture of pyridine



Scheme 2. Reagents and conditions: (a) 1-bromopinacolone, KOH, KI, CH_3OH/DCM (2/1), 92%; (b) TFA, DCM; (c) $NaBH(OAc)_3$, DCM, 54% for two-steps; (d) 4-chlorobenzenesulfonyl chloride, DMAP, pyr.; (e) $NaBH_4$, $CaCl_2$, THF/EtOH, 60 °C, 29% for two-steps; (f) DIAD, PPh_3, toluene, 60 °C, 84%; (g) H_2, PtO_2, EtOH; (h) 4-nitrophenyl chloroformate, pyr., THF/CH_3CN (1/1), 67% for two-steps; (i) amine, DCM.

Table 2
Structure–activity relationship of 5-*t*-butylmorpholine series



Compound[a]	R	NR^1R^2	Membr Aβ140 IC_{50}[b] (nM)	CYP3A4[c] (nM)
12a			34.7	23.8
12b			107.9	7.1
12c			131.1	5.5
12d			20.4	1.5
12e			39.3	0.5

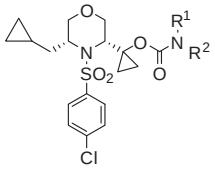
[a] All compounds are pure enantiomers.
[b] Data for inhibition of Aβ40 were measured by use of a membrane-based preparation of γ-secretase, and values are the mean of two experiments.
[c] Values are determined after 30 min pre-incubation with compound.

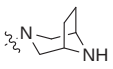
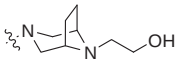
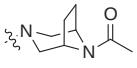
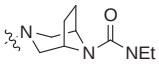
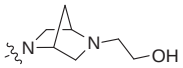
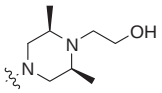
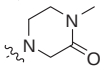
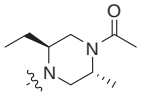
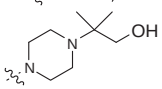
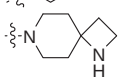
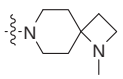
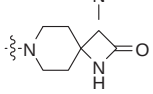
and DCM gave *N*-arylsulfonyl morpholine **15**. After cyclopropanation of the olefin and Kulinkovich reaction of the methyl ester,[9] cyclopropyl alcohol **17** was prepared. Again, this was converted to chlorocarbamate and reacted with amines to give carbamates **18** (Scheme 3). It should be noted that all final compounds were pure enantiomers and the compounds with this absolute configuration were more active as determined previously.[4b]

Extensive SAR studies on the right-hand side were carried out in this series, and the biological data for selected compounds was shown in Table 3. In general, the compounds with high CYP3A4 inhibition have high rat AUC values, and the ones with low CYP3A4 inhibition have low rat AUC values. Compared to the previous two series and the series with cyclopropyl or aryl substitution at C-5 on the left-hand side,[6] the cyclopropylmethyl substitution provided the best in vitro activity and compatible CYP profile. Compound **18j** has the best balance of good Aβ40 inhibition (3.1 nM) with reasonably good rat PK and acceptable CYP3A4 inhibition.

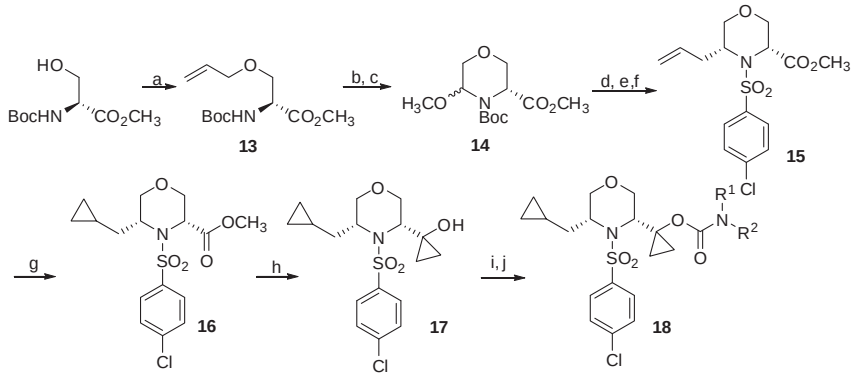
In summary, the proper combination of small alkyl groups on the left-hand side and amines on the right-hand side could provide

Table 3
Structure–activity relationship of 5-cyclopropylmethyl morpholine series



Compound[a]	NR^1R^2	Membr Ap40 IC_{50}[b] (nM)	CYP3A4[c] (nM)	Rat$AUC_{0-6\ h}$[d] (h nM h)
18a		0.8	0.8	4584
18b		0.9	2.3	1283
18c		4.4	>30	13
18d		5.5	>30	60
18e		3.6	3.2	1348
18f		11.6	2.0	1225
18g		5.7	1.4	1021
18h		29.3	>30.0	N.D.
18i		27.6	>30	77
18j		3.1	11.3	1343
18k		2.6	30.0	894
18l		7.4	>30	37

[a] All compounds are pure enantiomers.
[b] Data for inhibition of Aβ40 were measured by use of a membrane-based preparation of γ-secretase, and values are the mean of two experiments.
[c] Values are determined after 30 min pre-incubation with compound.
[d] Measured over 0–6 h after 10 mg/kg oral dosing in rat.



Scheme 3. Reagents and conditions: (a) carbonic acid allyl ethyl ester, $[AllylPdCl]_2$, PPh_3, THF, 70%; (b) O_3, SMe_2, CH_3OH; (c) CH_3OH, TsOH, 91% for two-steps; (d) allyltrimethylsilane, $BF_3{\cdot}OEt_2$, DCM, 48%; (e) 4 N HCl in dioxane; (f) 4-chlorobenzenesulfonyl chloride, pyr., 74% for two-steps; (g) $ZnEt_2$, TFA, CH_2I_2, THF, 87%; (h) $Ti(O\text{-}iPr)_4$, EtMgBr, THF, 50%; (i) $COCl_2$, pry., DCM, 78; (j) amine, DCM.

compounds with good in vitro activity and reduced CYP3A4 inhibition.

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References and notes

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