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Small conformationally restricted piperidine *N*-arylsulfonamides as orally active γ-secretase inhibitors

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Abstract—The design and development of a new class of small 2,6-disubstituted piperidine *N*-arylsulfonamide γ-secretase inhibitors is reported. Lowering molecular weight including the use of conformational constraint led to compounds with less CYP 3A4 liability compared to early leads. Compounds active orally in lowering Aβ levels in Tg CRND8 mice were identified as potential treatments for Alzheimer's disease.

Alzheimer's disease (AD), the most common form of neurodegenerative disorders, is progressively moving to the forefront of our public health agenda as our population age.[1] An incurable illness that mostly affects the elderly, AD is characterized by a loss of cognitive functions that ultimately results in death within 8–10 years of onset. Although AD has many histological features,[2] convergent lines of evidence suggest that aberrant production of β-amyloid (Aβ), aggregation, and/or plaque deposition in the brain of affected individuals are central to the evolution of the disease.[3] Current avenues of intervention seek to stop or reverse its course by inhibiting Aβ production and/or aggregation.[2,4] Aβ, in its form Aβ40 or Aβ42, the latter being the most amyloidogenic, is the result of proteolytic cleavage of the Aβ precursor protein (APP) by β-secretase and γ-secretase.[5] Despite its complexity and involvement in other regulatory pathways such as Notch processing, γ-secretase has been proposed as a valuable target for a drug-discovery program.[6] Structurally diverse γ-secretase inhibitors have now been reported[7] and early clinical results seem to suggest that a therapeutic window might exist for several classes of compounds.[8]

We previously reported our explorations into a series of 2,6-disubstituted piperidine sulfonamide γ-secretase inhibitors.[7b] Those compounds proved to be efficacious at lowering Aβ levels in a transgenic mice model of AD but unfortunately, further testing showed that many analogs in this series, such as our lead **1**, are also potent inhibitors of the CYP 3A4 liver co-enzyme (Fig. 1).

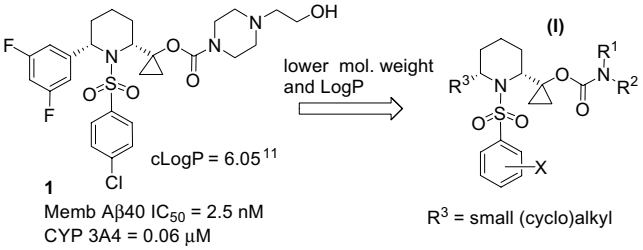

Figure 1. Compound **1** and strategy for smaller less lipophilic analogs. (See above-mentioned references for further information).

Keywords: Alzheimer's disease; γ-Secretase; Inhibitor; CYP 3A4; Sulfonamide; Piperidine; Conformational constraint.
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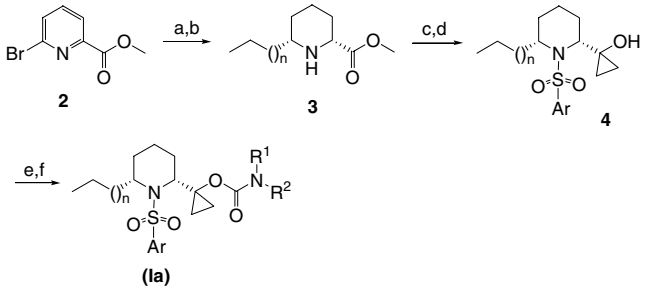
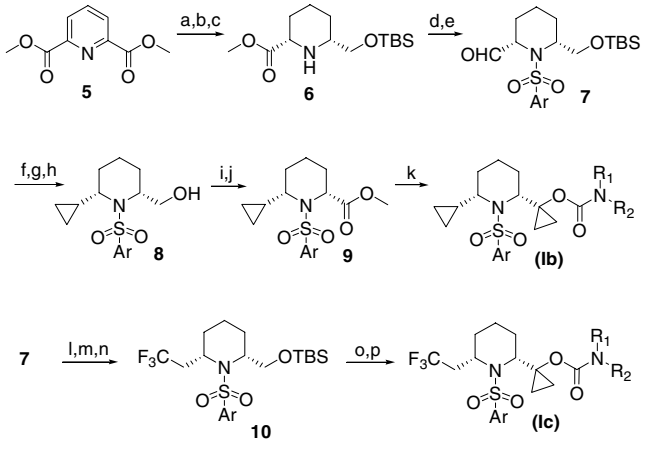
Drug–drug interaction due to CYP inhibition is a concern, especially in the context of an aging population often under multiple treatments.[9] We thus sought to identify and address the factors contributing to this liability, while preserving oral Aβ lowering activity. Interaction with CYP 3A4 has been linked to lipophilicity and the presence of basic amines,[10] two hallmarks of our series in addition to its quite high molecular weight (~600). We thus envisioned a series of analogs (**I**) where the aryl moiety at R^3 has been substituted with smaller alkyls and where the amine has been reengineered, all the while preserving the structurally important cyclopropyl carbamate moiety.[12] We chose R^3 > Me since earlier results suggested that analogs bearing this moiety would likely be less potent than others.[12]

Compounds of formula (**Ia**) were prepared according to a modification of our original scheme, using Stille coupling to install the alkyl side chain and Kulinkovich reaction[13] to functionalize the methyl ester into the cyclopropyl carbinol **4**. Conversion to the carbamate was performed using previously reported methods (Scheme 1).[7b]

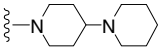
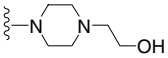
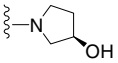


Scheme 1. Reagents: (a) $AllylSnBu_3$/$vinylSnBu_3$, $PdCl_2(PPh_3)_2$; (b) H_2, Pd/C; (c) $ArSO_2Cl$, Et_3N; (d) $Ti(O\text{-}i\text{-}Pr)_4$, EtMgBr; (e) *p*-$NO_2PhO$-C(O)Cl, pyridine; (f) R_1R_2NH.



Scheme 2. Reagents: (a) $NaBH_4$; (b) H_2, Pd/C; (c) TBSCl, imidazole; (d) 4-Cl–$PhSO_2Cl$, Et_3N; (e) DIBAH; (f) $Ph_3P{=}CH_2$; (g) CH_2I_2, Et_2Zn; (h) TBAF; (i) $NaIO_4$, $RuCl_3$; (j) $SOCl_2$, MeOH; (k) steps d–f; (l) CF_3TMS, $BF_3{\cdot}OEt_2$; (m) *n*-BuLi, PhOC(S)Cl; (n) Bu_3SnH, AIBN; (o) TBAF; (p) steps i–k.

Table 1. Membrane γ-secretase inhibition and CYP3A4 profile across 6-substituted piperidine series using standard carbamates (**I**, X = 4-Cl)[a]

Compound	R^3	NR^1R^2	Memb Aβ40 IC_{50}[b] (nM)	CYP 3A4[c] (μM)
11	3,5-diF–Ph		0.3	<0.8
12	*c*-Pr		2.8	2.2
13	*n*-Pr		2.5	0.7
14	Et		3.5	0.8
15	CF_3CH_2		3.5	—
1[d]	3,5-diF–Ph		2.4	0.06
16[d]	*c*-Pr		27	0.5
17[d]	Et		12	0.4
18[d]	CF_3CH_2		14	<0.3
19	3,5-diF–Ph		17	1.3
20	*c*-Pr		46	3.5
21	*n*-Pr		47	2.4
22	Et		56	11

[a] All compounds are racemic.
[b] Values are means of two experiments.
[c] Values determined after 30 min pre-incubation with compound.
[d] *c* log *P* = 6.05 (**1**); 4.92 (**16**); 5.02 (**17**); 4.81 (**18**).[11]

Preparation of cyclopropyl analogs (**Ib**) required selective functionalization of diester **5** into aldehyde **7** as precursor of the left-hand side cyclopropyl. Oxidation of alcohol **8** to give ester **9** set the stage for the final steps as before. Similarly, addition of trifluoromethyltrimethylsilane on aldehyde **7** followed by Barton–McCombie deoxygenation[14] provided the 2,2,2-trifluoroethyl analogs (**Ic**) after functionalization (Scheme 2).

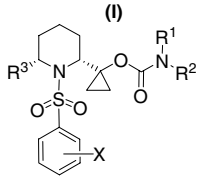
Series were first evaluated for the impact of R^3 substitution on γ-secretase inhibitory potency and CYP 3A4 liability, using standard amines and 4-chlorophenyl sulfonamide from our previous SAR (Table 1).[7b] Our initial results indicated that: (i) significant improvement in CYP profile was observed with small alkyls at R^3 versus the corresponding 3,5-difluorophenyl. It was accompanied by a drop in γ-secretase potency to some degree, but compounds in the single-digit nanomolar range could still be obtained; (ii) linear groups were slightly favored over cyclopropyl in lower molecular eight series (e.g., **17** vs **16**), while the opposite was true in higher molecular weight series (**12** vs **14**)[15]; (iii) while lipophilicity played a role in CYP liability, comparison of non-basic to (un)hindered basic amines also showed that the right-hand side contributed significantly to CYP liability.

In our most orally active series **1**,[7b] ethyl at R^3 (**17**) offered the most optimal properties (potency, CYP liability) and the series was progressed further, introducing various arylsulfonamides and de novo amines (a few R^3 = c-Pr were also prepared for comparison). Pharmacokinetic (PK) data for individual compounds were measured in the rat following oral administration at 10 mpk (Table 2).

We steered our efforts toward keeping the molecular weight as low as possible (<550). In our previous

Table 2. In vitro and AUC data in rat for series (**I**)[a]

(I)



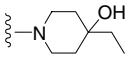
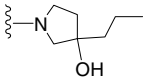
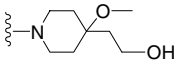
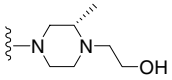
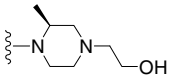
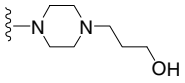
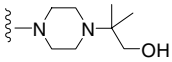
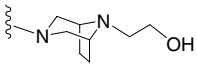
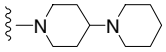
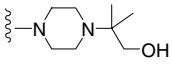
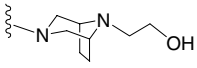
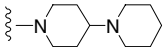
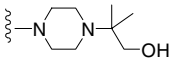
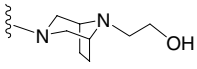
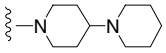
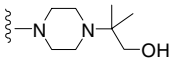
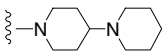
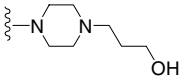
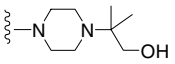
Compound	R^3	X	NR^1R^2	Memb Aβ40 IC_{50}[b] (nM)	Cell Aβ40 IC_{50}[b] (nM)	CYP 3A4[c] (μM)	AUC_{0-6h}[d] (h ng/mL)
23	Et	4-Cl		3.2	4.3	1.1	0
24	Et	4-Cl		28	190	3.3	—
25	Et	4-Cl		9.0	20	1.7	81
26	Et	4-Cl		13	10	1.0	1869
27	Et	4-Cl		12	14	<0.3	3414
28	Et	4-Cl		17	15	1.2	1784
29	Et	4-Cl		6.9	8.3	2.2	892
30	Et	4-Cl		3.5	7.7	2.5	939
14	Et	4-Cl		3.5	9.1	0.8	476
31	Et	4-F		10	25	4.6	405
32	Et	4-F		25		3.9	1780
33	Et	4-F		16	115	5.8	102
34	Et	3,4-di-F		9.6	20	1.6	323
35	Et	3,4-di-F		27		1.7	1332
36	Et	3,4-di-F		6.9	45	1.6	91
37	Et	3,5-di-F		81		2.6	580
38	Et	3,5-di-F		29	144	1.2	296

Table 2 (*continued*)

Compound	R^3	X	NR^1R^2	Memb Aβ40 IC_{50}[b] (nM)	Cell Aβ40 IC_{50}[b] (nM)	CYP 3A4[c] (μM)	AUC_{0-6h}[d] (hng/mL)
39	*c*-Pr	4-Cl		16	32	0.6	491
40	*c*-Pr	4-Cl		12	39	0.4	—

[a] All compounds are racemic.
[b] Values are means of two experiments.
[c] Values determined after 30 min pre-incubation with compound.
[d] Measured over 0–6 h after 10 mpk oral dosing in rat.

series, the *N*-(2-hydroxyethyl)-piperazine amine moiety resulted in many interesting compounds,[7b] but those were also among the worst offenders in terms of CYP 3A4 liability (compounds **1**, **16**–**18**). As previously mentioned, the presence of a basic amine can lead to CYP 3A4 liability.[10] We thus implemented several strategies to replace the above moiety with improved surrogates. In one of those, the basic amine was replaced with a substituted carbon but the PK of the resulting compound (**25**) proved to be quite low, as observed in other non-basic compounds (**23** and **24**) and in related series as well.[7b] In another approach, the length of the hydroxyl-ethyl tether was modified (**28**) to beneficial outcome in terms of CYP profile. The resulting compound also had good PK, although cellular potency remained in the double-digit nanomolar range.

The best results were obtained when introducing steric hindrance near the piperazine amine, in parallel to what has been reported by other investigators.[10] Introduction of a substituent directly on the piperazine ring (**26**) gave promising data, but our most optimal compounds were obtained via introduction of a *gem*-dimethyl next to the amine, or the use of a bridged piperazine derivative.[16] Compounds **29** and **30** showed reasonable PK while featuring nanomolar cellular γ-secretase inhibition and >2 μM CYP 3A4 potency. Replacement of the 4-chloro-arylsulfonamide with fluorinated arylsulfonamides, by contrast, did not significantly alter CYP liability or PK and often resulted in somewhat less potent analogs, an unsurprising result considering that those modifications do not significantly affect lipophilicity, molecular weight, and/or basicity at the right-hand side amine.

In the course of this study, NMRs of intermediates and products were collected to confirm that the chair-like conformation of the piperidine ring and di-axial orientation of the 6-substituent and 2-cyclopropylcarbamate observed in previous series were maintained.[7b] We also advantageously had a closer look at the X-ray structure of a related intermediate (Fig. 2, R^3 = aryl) in which we noticed: (i) close proximity of the cyclopropyl ring and R^3 group; (ii) alignment of the S–C(aryl) and C(cyclopropyl)–O bonds of the arylsulfonamide and carbamates, respectively, two important contributors of γ-secretase inhibition.

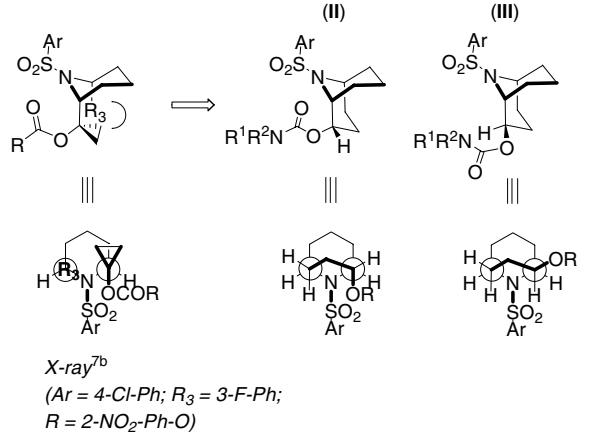
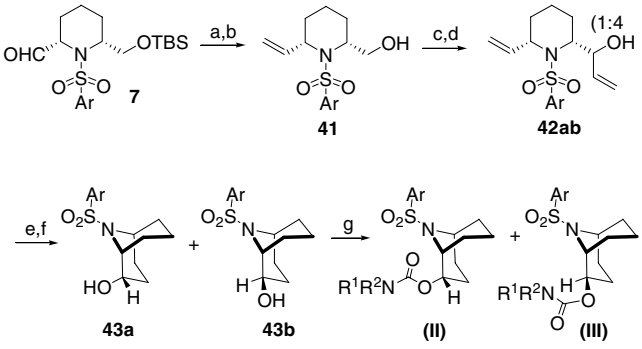


Figure 2. Conformational analysis and 2,6-diaxial lock.



Scheme 3. Ar = 4-Cl–Ph. Reagents and condition: (a) CH_3PPh_3Br, *n*-BuLi; (b) TBAF; (c) Dess–Martin periodinane; (d) AllylMgBr; (e) Grubbs's second generation catalyst; (f) H_2, 1 atm, PtO_2; (g) Scheme 1 steps e–f.

Those observations led us to environ a series of bridged analogs 'linking' the 6-ethyl and 2-cyclopropyl side chains (Fig. 2). Modifications brought to those moieties might also bring additional benefits in the form of better CYP 3A4 profile and/or metabolism. As shown below, although two different isomers (**II**) or (**III**) could be designed by branching out of the cyclopropyl, only (**II**) could conceivably lock the bond alignment observed in the X-ray structure.

Access to series (**II**) and (**III**) was relatively straightforward from intermediate **7** (Scheme 3, Ar = 4-Cl–Ph).

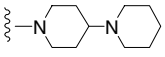
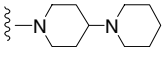
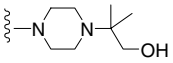
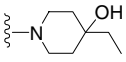
Key steps involved allyl Grignard condensation on an aldehyde derived from **41** followed by a ring closure metathesis using Grubs second generation catalyst (yields were substantially lower using the first generation).[17] The unsaturated diastereoisomeric alcohols were separated at this stage and, after reduction of the alkene bond under reduced pressure, processed to the carbamates according to previous methods. The Grignard addition proceeded in a 4:1 ratio in favor of the preferred series (**II**). Key intermediates were unambiguously assigned by NMR.

Assessment of the new series in the γ-secretase membrane assay confirmed the X-ray analysis (Table 3): we were pleased to observe that series (**II**) bearing the standard 4-piperidinopiperidine produced a potent analog (**44**), whereas series (**III**) where arylsulfonamide and carbamate were locked away from the X-ray conformation was essentially inactive (**45**). In a related study, trimmed 5-membered analogs of (**II**) and (**III**) were also synthesized and did not show any potency.[18] Series (**II**) was further explored and provided several analogs in the low to mid-single-digit nanomolar activity such as **46**. However, the CYP 3A4 profile did not differ significantly from the one observed in the des-cyclic series. Although this series appears to be somewhat less potent than its non-bridged predecessor (**I**, R^3 = Et), on closer look it is actually more related to series (**I**, R^3 = Me). Accordingly, further substitution of the methylene attached to the bridge might conceivably improve potency.

Table 4 summarizes in vivo results obtained after dosing selected analogs to young transgenic pre-plaque Tg CRND8 mice model of AD. Reduction in plasma Aβ40 levels was measured after 3 h following oral or sub-cutaneous administration. In this model, compound **29** led to near-complete abolition of plasma Aβ40 levels when administered at 30 mpk either orally or sub-cutaneously. Close analog **31** also significantly lowered plasma Aβ40 levels when administered sub-cutaneously. Efficacy in lowering brain Aβ40 levels was not measured since we had found a better related series but it is expected to be significant based on high brain penetration (one example).

In summary by lowering the molecular weight of an early lead and modifying its right-hand side basic amine, we were able to substantially lessen CYP3A4 liability while retaining significant Aβ40 lowering capability. Further improvement in that direction including the recourse to reengineering of the core will be reported in the near future.

Table 3. Membrane γ-secretase inhibition and CYP3A4 profile across bridged piperidine series using standard carbamates (Ar = 4-Cl–Ph)[a]

Compound	Core	NR_1R_2	Memb Aβ40 IC_{50}[b] (nM)	CYP 3A4[c] (μM)
44	II		15	1.1
45	III		2425	—
46	II		57	0.5
47	II		104	0.6

[a] All compounds are racemic.
[b] Values are means of two experiments.
[c] Values determined after 30 min pre-incubation with compound.

Table 4. In vivo profile following acute dosing for selected compounds in vivo efficacy

Compound	Memb Aβ40 IC_{50}[a] (nM)	Tg CRND8 mice reduction in plasma $Aβ_{40}$ (30 mpk, 3 h) (%)
29	6.9	−96[b] −91[c]
30	3.5	−85[c,d]
31	10	−59[c]

[a] Values are means of two experiments.
[b] Oral dosing.
[c] Sub-cutaneous dosing.
[d] Brain concentration/plasma concentration = 3:1.

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11. *c*log *P*s were calculated using Sybyl 7.1 from Tripos, using *c*log *P* version 4.3 from BioByte, and were within <49 error.
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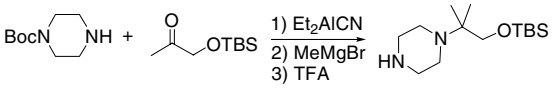
15. In a related series, 2′,2′-difluorocyclopropyl analogs proved to be less potent (synthesis not shown).
16. The precursor of the *gem*-dimethyl amine was prepared according to the following scheme:



preparation of the bridged piperazine amine used synthetic routes derived from Cignarella, G.; Nathansohn, G.; Occelli, E. *J. Org. Chem.* **1961**, *26*, 2747, followed by N-alkylation with $BrCH_2CH_2OTBS$ and N-debenzylation.

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18. Synthesis not shown. In such scaffolds, S–C(aryl) and C(cyclopropyl)–O bonds of arylsulfonamide and carbamates, respectively, are not aligned: