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Discovery of amide and heteroaryl isosteres as carbamate replacements in a series of orally active γ-secretase inhibitors

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Abstract—The design of amide and heteroaryl amide isosteres as replacements for the carbamate substructure in previously disclosed 2,6-disubstituted piperidine *N*-arylsulfonamides is described. In several cases, amides lessened CYP liabilities in this class of γ-secretase inhibitors. Selected compounds showed significant reduction of Aβ levels upon oral dosing in a transgenic murine model of Alzheimer's disease.

Alzheimer's disease (AD) is the most common form of neurodegeneration and has become a major healthcare issue with the aging population in the United States.[1] Though treatments exist, efficacy is observed in a palliative sense rather than halting the progression of AD, providing the patient with only a temporarily improved quality of life. Pathologically, overproduction of β-amyloid (Aβ) and deposition thereof in the form of plaques in the cortex of AD patients has been observed.[2] Due to the central role of γ-secretase in the generation of the Aβ peptides via cleavage of amyloid precursor protein (APP), inhibition of γ-secretase has been identified as an important target in the discovery of novel AD treatments.[3]

Recent reports from our laboratories demonstrate that the 2,6-disubstituted piperidine sulfonamide core serves as an excellent template for the synthesis of γ-secretase inhibitors.[4–8] Early studies indicated that aryl and cyclopropyl carbamate appendages such as in compound **1** provided oral efficacy in a transgenic mouse model of AD via lowering of Aβ levels (Fig. 1). Further studies aimed at remediation of CYP liabilities of **1** demonstrated that low molecular weight alkyl substitution at C(6) in lieu of an aryl group provided compounds such

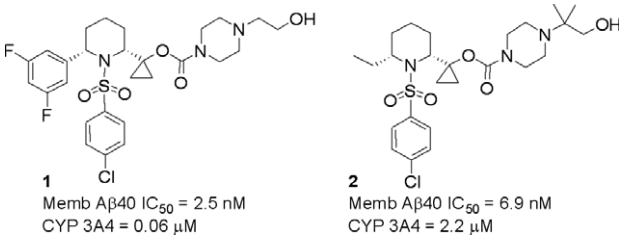
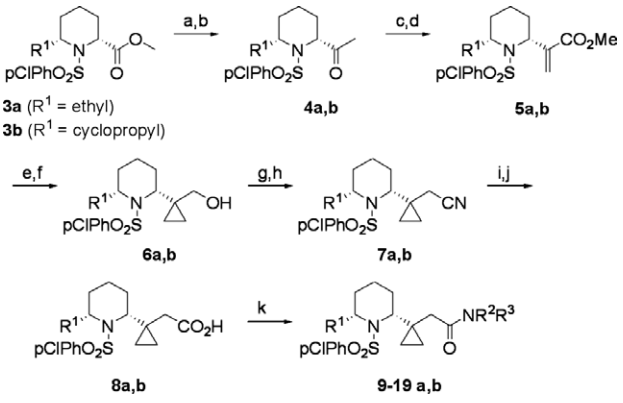


Figure 1. Representative piperidine sulfonamide γ-secretase inhibitors.



Scheme 1. Reagents: (a)HCl·HNCH$_3$(OCH$_3$), *i*-PrMgCl, THF; (b) MeMgBr, THF; (c) KHMDS, Commins' Rgt, THF; (d) CO(g), *n*Bu$_3$N, Pd(dba)$_2$, Ph$_3$P, LiCl, MeOH, CH$_3$CN; (e) DIBAL, THF; (f) Et$_2$Zn, ClCH$_2$I, DCE; (g) Ph$_3$P, I$_2$, imid., CH$_3$CN/tol.; (h) *n*Bu$_4$NCN, CH$_3$CN; (i) DIBAL, CH$_2$Cl$_2$; (j) NaClO$_2$, NaH$_2$PO$_4$, *t*-BuOH/H$_2$O; (k) Amine, HATU, iPr$_2$NEt, CH$_2$Cl$_2$.

Keywords: γ-Secretase; Alzheimer's disease.
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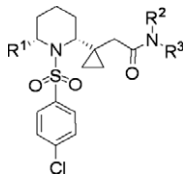
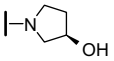
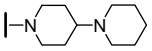
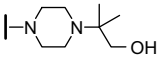
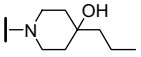
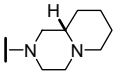
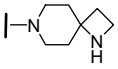
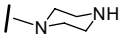
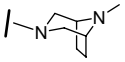
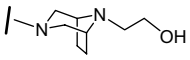
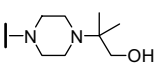
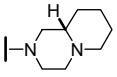
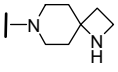
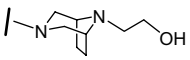
Table 1. 6-Alkyl piperidine amide SAR[a]



Compound	R^1	NR^2R^3	Memb Aβ40 IC_{50}[b] (nM)	Cell Aβ40 IC_{50}[b] (nM)	CYP 3A4 IC_{50}[c] (μM)	Rat AUC_{0-6h}[d] (ng h/mL)
9a	Ethyl		27 ± 0.8		2.6 ± 0.9	—
10a	Ethyl		35 ± 5.6		11.9 ± 4.2	116
11a	Ethyl		2.5 ± 0.07	5.6 ± 1.0	1.2 ± 0.2	93
12a	Ethyl		2.2 ± 0.01	2.4 ± 0.1	4.7 ± 0.6	1616
13a	Ethyl		28 ± 4.0		9.0 ± 2.7	58
14a	Ethyl		6.7 ± 2.6	65 ± 30	5.0 ± 0.9	
15a	Ethyl		4.5 ± 0.3	4.0 ± 0.6	4.2	419
16a	Ethyl		11.5 ± 0.4	72 ± 1.0	5.6	
17a	Ethyl		29 ± 0.7		0.3	
18a	Ethyl		5.9 ± 0.7	11.9 ± 2.0	4.7	2651
19a	Ethyl		3.1 ± 0.1	7.4 ± 1.0	2.2	3224
12b	*c*-Propyl		9.9 ± 1.5	9.7 ± 2.0	1.5 ± 0.6	1353
15b	*c*-Propyl		13.5 ± 0.3	24 ± 1.0	1.8 ± 0.3	673
16b	*c*-Propyl		20 ± 5.0		7.0	
19b	*c*-Propyl		8.5 ± 1.0	21 ± 5.0	1.0	5810

[a] All compounds are racemic.
[b] Mean values ($n = 2$) ± SEM.
[c] Values determined following 30-min pre-incubation. Mean values ($n = 3$) ± SEM.
[d] Mean values ($n = 3$). Dosed at 10 mg/kg po.

as **2**, which retained good inhibitory activity and improved CYP properties relative to **1**.

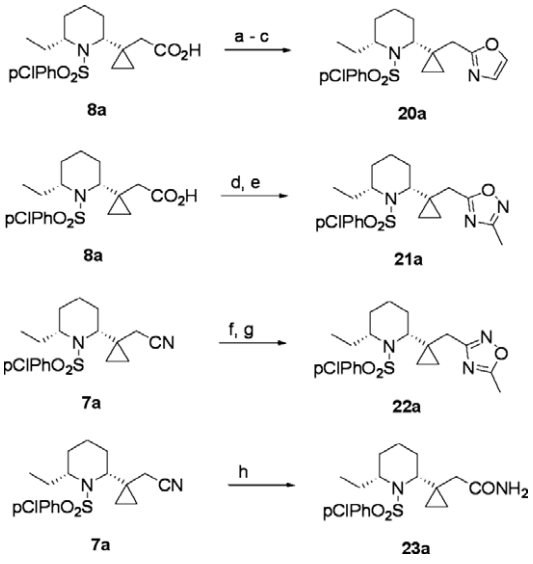
In an effort to extend the SAR of these piperidine sulfonamides, modifications were designed in order to further reduce molecular weight and clogP, while maintaining inhibitory activity and in vivo efficacy. Though the carbamate moiety can be a liability with respect to pharmacokinetic properties, previous studies indicated that the adjacent cyclopropyl group adequately retarded metabolism of the carbamate in this series.[6] Unanticipated improvements in γ-secretase inhibition were also achieved relative to non-cyclopropanated analogs. One focus became the identification of carbamate replacements in the 6-alkyl piperidine sulfonamide series typified by compound **2**. Amides and heteroaryl amide isosteres would assist in further reducing clogP, and potentially offer improvements in pharmacokinetic properties relative to carbamates. Synthesis and biological evaluation of these analogs is detailed herein.

The synthesis of carbamate derivatives commenced with intermediates **3a**,**b** (Scheme 1).[7] Amidation according to the procedure of Weinreb was followed by treatment with methyl Grignard to provide methyl ketones **4a**,**b**. Enolization and subsequent treatment with Commins' reagent provided the vinyl triflates, which were smoothly carbonylated in the presence of methanol to provide methyl esters **5a**,**b**. Reduction to the allylic alcohols and application of Denmark's cyclopropanation protocol[9] installed the cyclopropyl moiety. Homologation was achieved via iodide formation and displacement with cyanide to afford nitriles **7a**,**b**, which were in turn converted to the acids by reduction followed by oxidation of the aldehyde intermediates. Coupling with appropriate amines was achieved under standard conditions to complete the amide targets. Though circuitous, this route required only four chromatographic purifications and was easily scaled.

Representative 6-alkyl piperidine amides are shown in Table 1. Sidechain substituents which proved beneficial in the carbamate series were incorporated in the current study.[7] As shown, amides served as suitable replacements for the carbamate group, and in many cases showed improved potency relative to the carbamates, while negating the possibility of a cyclopropyl alcohol metabolite. As anticipated, the general CYP 3A4 profiles of the amides were also modestly improved relative to those of the C(6)-alkyl carbamate series.[10] While pharmacokinetic properties of the amides were not significantly improved, overall profile of the amides was promising. In general, the 6-ethyl derivatives showed decreased CYP P450 liability relative to the cyclopropyl series and were 3- to 4-fold more potent.

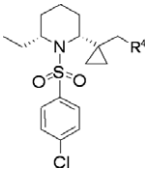
In order to further explore the SAR, several heteroaryl derivatives were synthesized as isosteric amide replacements. Initially targeted were N,O-heteroaryl derivatives devoid of amine sidechains, the synthesis of which is described in Scheme 2. Using acid **8a** as a point of departure, coupling with ethanolamine followed by oxidation and dehydrative cyclization[11] provided oxazole **20a**. Alternatively, activation of the acid followed by treatment with acetamidoxime afforded oxadiazole **21a**. The regioisomeric oxadiazole **22a** was synthesized via treatment of nitrile **7a** with hydroxylamine, subsequent acylation and dehydration. The primary amide **23a** was obtained via hydrolysis of nitrile **7a**.

Inhibition data for the truncated heteroaryl piperidine sulfonamides are shown in Table 2. As a point of reference, the primary amide **23a** containing no amine-containing sidechain provided an $IC_{50} = 124$ nM and showed modest CYP 3A4 inhibition. Oxazole **20a** pro-



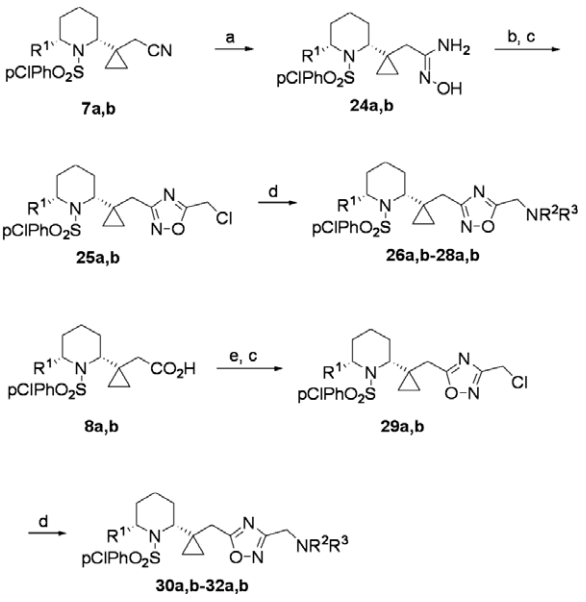
Scheme 2. Reagents: (a) ethanolamine, BOP, CH_2Cl_2; (b) Dess-Martin Periodinane, Et_3N, CH_2Cl_2; (c) Ph_3P, C_2Cl_6, pyr; (d) CDI; (e) NaH, acetamidoxime; (f) NaOMe, NH_2OH; (g) AcCl; (h) KOH.

Table 2. Truncated amide isosteres[a]



Compound	R^4	Memb Aβ40 IC_{50}[b] (nM)	CYP3A4 IC_{50}[c] (μM)
23a		124 ± 21	11.5
20a		194 ± 9.7	<0.03
21a		173 ± 1.7	>30
22a		165 ± 1.3	16.9

[a] All compounds are racemic.
[b] Mean values ($n = 2$) ± SEM.
[c] Values determined following 30-min pre-incubation.

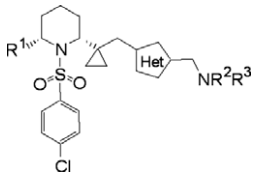


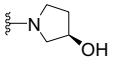
Scheme 3. Reagents: (a) NH_2OH, NaOEt; (b) chloroacetic acid, DCC; (c) xylenes, 130 °C; (d) HNR_2R_3; (e) chloroacetamide oxime, DCC.

vided γ-secretase inhibition similar to the amide, indicating that it was functioning as an acceptable amide isostere. However a marked increase in CYP 3A4 inhibition was noted. More promising results were seen with oxadiazoles **21a** and **22a**, which maintained similar γ-secretase inhibition to that of the amide and oxazole, in addition to mitigating the CYP liabilities seen with the amide. With these encouraging results in hand, the focus shifted to installing a basic sidechain on the oxadiazoles to improve potency with the aim of retaining the favorable CYP450 profiles seen with these amide surrogates.

Synthesis of the extended oxadiazole derivatives is detailed in Scheme 3. Conversion of nitriles **7a**,**b** to acetamidoximes **24a**,**b** was followed by coupling with chloroacetic acid. Cyclodehydration was achieved via heating in xylenes, and installation of the amines proceeded smoothly to provide the desired targets. Regioisomeric oxadiazoles were synthesized in a similar fashion commencing from acids **8a**,**b**. Coupling of the acids with chloroacetamide oxime[12] and cyclodehydration was followed by alkylation to install the amine sidechains.

Table 3. Oxadiazole SAR[a]



Compound	R^1	Het	NR^2R^3	Memb Aβ40 IC_{50}[b] (nM)	CYP 3A4 IC_{50}[c] (μM)	Rat $AUC_{0-6\ h}$[d] (ng h/mL)
26a	Ethyl			50 ± 4.0	4.0	
27a	Ethyl			95 ± 2.7	2.6	
26b	*c*-Propyl			9.2 ± 1.7	3.1	81
28b	*c*-Propyl			46 ± 1.9	1.2	20
30a	Ethyl			21 ± 1.3	0.3	973
31a	Ethyl			11 ± 0.9	0.7	26
30b	*c*-Propyl			25 ± 3.8	0.3	143
31b	*c*-Propyl			18 ± 1.7	0.3	
32b[e]	*c*-Propyl			34 ± 5.7	0.6	

[a] All compounds are racemic.
[b] Mean values ($n = 2$) ± SEM.
[c] Values determined following 30-min pre-incubation.
[d] Mean values ($n = 3$). Dosed at 10 mg/kg po.
[e] Mixture of 4 diastereoisomers.

Table 4. In vivo efficacy in CRND8 mice following acute oral dosing for selected amides and oxadiazoles

Compound	Plasma $A\beta_{40}$ reduction[a] (30 mpk, 3 h [%])
12b	−80
15a	−20
19a	−83
19b	−82

[a] Mean values ($n = 5$). Expressed as a percent relative to vehicle controls.

As exemplified in Table 3, installation of the amine side-chain significantly improved inhibition of γ-secretase in all cases, however CYP inhibition also returned. While oxadiazoles proved suitable isosteric replacements for the amides with respect to γ-secretase inhibition, no improvements were observed with respect to pharmacokinetic properties in this chemical series.

A set of compounds with the best overall profiles from these series was chosen for further evaluation in vivo (Table 4). In the transgenic CRND8 mouse, a model exhibiting rapid deposition of Aβ, oral dosing (30 mg/kg) significantly reduced plasma $A\beta_{40}$ levels at 3 h post-dosing. The efficacy observed with these series is similar to that observed with similar compounds derived from the carbamate series (cf. compound **2**).[7] Importantly, several of the compounds in the amide series show modest improvements in CYP 3A4 inhibition relative to the carbamates. The oral efficacy observed with these compounds provided further impetus to continue studies in this piperidine sulfonamide series in order to mitigate liabilities related to CYP inhibition and further improve pharmacokinetic properties.

In summary, we have extended the structure-activity relationship studies in the piperidine sulfonamide series to incorporate low molecular weight amides and amide isosteres. While maintaining γ-secretase inhibition and pharmacokinetic properties, modest improvements in CYP liabilities were observed with several compounds, though no general trend was observed. Oral efficacy was demonstrated with representative compounds from this series in a transgenic murine model for reduction of Aβ levels.

Acknowledgment

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