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Synthesis and SAR Studies of Fused Oxadiazines as γ-Secretase Modulators for Treatment of Alzheimer's Disease

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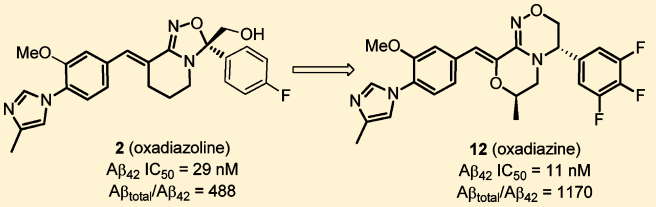
Supporting Information

ABSTRACT: Fused oxadiazines (**3**) were discovered as selective and orally bioavailable γ-secretase modulators (GSMs) based on the structural framework of oxadiazoline GSMs. Although structurally related, initial modifications showed that structure−activity relationships (SARs) did not translate from the oxadiazoline to the oxadiazine series. Subsequent SAR studies on modifications at the C3 and C4 positions of the fused oxadiazine core helped to identify GSMs such as compounds **8r** and **8s** that were highly efficacious in vitro and in vivo in a number of animal models with highly desirable physical and pharmacological properties. Further improvements of in vitro activity and selectivity were achieved by the preparation of fused morpholine oxadiazines. The shift in specificity of APP cleavage rather than a reduction in overall γ-secretase activity and the lack of changes in substrate accumulation and Notch processing as observed in the animal studies of compound **8s** confirm that the oxadiazine series of compounds are potent GSMs.



KEYWORDS: *Alzheimer's disease, oxadiazine, amyloid precursor protein, γ-secreatase modulator, Notch processing, morpholine*

Alzheimer's disease (AD) is an age-related neurodegenerative disorder that affects millions of elderly people in the United States. It is estimated that more than 35 million people suffer from AD worldwide, with an annual cost of over $600 billion, and the population may increase to more than 115 million by 2050.[1] Because of clear unmet medical need, both academic and industrial laboratories are working very aggressively to develop therapies to halt or even reverse AD. It is believed that the accumulation of amyloid-β (Aβ) peptide and hyperphosphorylated protein τ contributes to AD progression.[2−6] Aβ peptide is formed from a larger amyloid precursor protein (APP) via sequential proteolytic cleavage by β- and γ-secretases (Figure 1).[7] γ-Secretase cleaves the APP C-terminal fragment at multiple sites leading to Aβ peptides of 37−42 amino acids of which $Aβ_{42}$, the more hydrophobic form, is the most amyloidogenic and neurotoxic. Although the molecular mechanism of action remains largely unknown, γ-secretase modulators (GSMs) are believed to act at an allosteric site to shift the predominant site of γ-secretase cleavage toward shorter, nonamyloidogenic peptides (e.g., $Aβ_{38}$) by selectively inhibiting $Aβ_{42}$ formation without blocking overall γ-secretase function. This potentially offers a better selectivity window over γ-secretase inhibitors (GSIs)[8−10] versus, for example, notch processing.[11] From an in vitro point of view, the $Aβ_{total}/Aβ_{42}$ ratio can be used to distinguish GSMs from GSIs with a ratio of

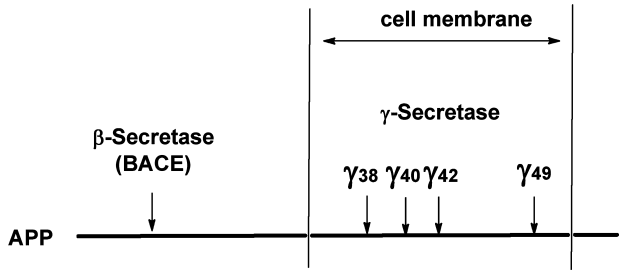


Figure 1. Sequential cleavage of APP by β- and γ-secretases.

>10 for GSMs and <3 for GSIs. There are two major classes of GSMs in clinical trials: one is the nonsteroidal anti-inflammatory acids (NSAIDs),[12,13] and the other is the non-NSAIDs class such as lactam **1** from Eisai. In our effort in the AD area, we have recently identified multiple structural classes[14−18] of GSMs with good in vitro potency and selectivity. Herein, we report our continued structure−activity relationship

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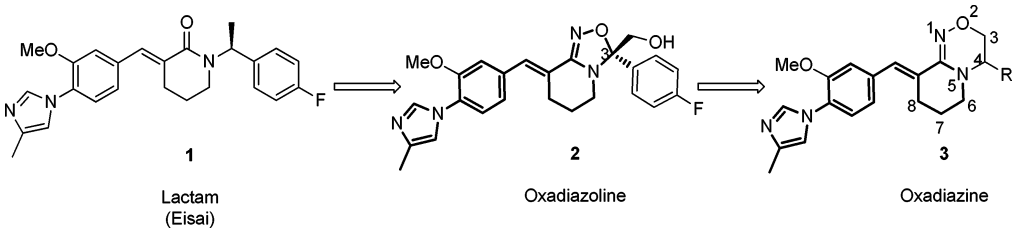


Figure 2. Design rationale of oxadiazine GSMs.

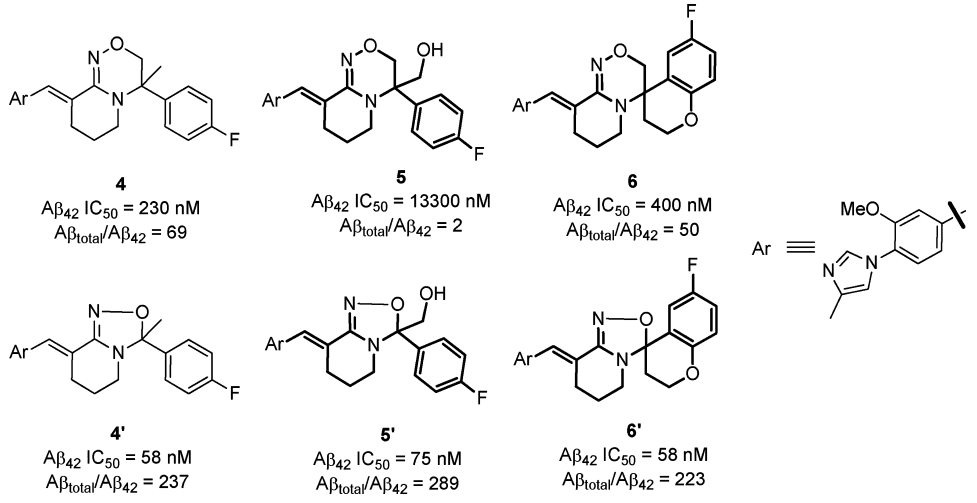
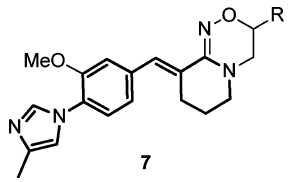
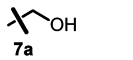
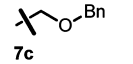
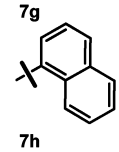
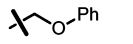
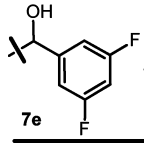
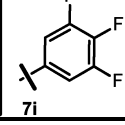
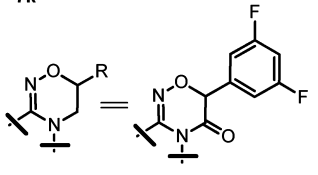


Figure 3. Comparison between oxadiazoline/oxadiazine of initial SAR studies. Each IC_{50} value is an average of at least two determinations.

Table 1. SAR Studies of C3-Monosubstituted Oxadiazines[a]



R	$A\beta_{42}$ IC_{50} (nM)	$A\beta_{total}/A\beta_{42}$	R	$A\beta_{42}$ IC_{50} (nM)	$A\beta_{total}/A\beta_{42}$	R	$A\beta_{42}$ IC_{50} (nM)	$A\beta_{total}/A\beta_{42}$
 **7a**	5400	4	 **7f**	83	241	 **7j**	9000	2
 **7b**	56	80	 **7g**	210	91	 **7k**	6700	3
 **7c**	250	80	 **7h**	130	158			
 **7d**	140	147						
 **7e**	76	265	 **7i**	48	328	 **7l**	1100	18

[a]Each IC_{50} value is an average of at least two determinations. Racemic at C3 except **7i**, which was the *S*-isomer as prepared from chiral starting material.

(SAR) effort focusing on novel fused oxadiazine core structures, which resulted in the identification of compounds with potent in vitro and in vivo activity and highly desirable physicological and physical properties.

Focusing on the non-NSAID GSM class represented by compound **1** to further optimize its overall pharmacological and pharmacokinetic (PK) profile and address its lenticular toxicity issue,[7] we have recently identified cyclic hydroxyamidines such

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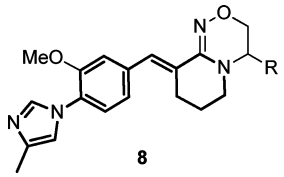
Table 2. SAR Studies of C4-Monosubstituted Oxadiazines[a]



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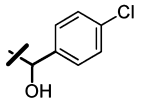
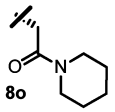
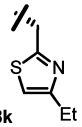
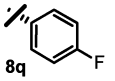
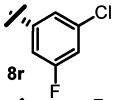
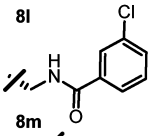
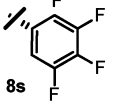
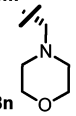
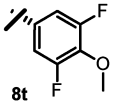
R	$A\beta_{42}$ IC_{50} (nM)	$A\beta_{total}/A\beta_{42}$	R	$A\beta_{42}$ IC_{50} (nM)	$A\beta_{total}/A\beta_{42}$	R	$A\beta_{42}$ IC_{50} (nM)	$A\beta_{total}/A\beta_{42}$
H **8a**	3100	7	 **8i**	300	49	 **8o**	1500	13
 **8b**	2500	8	 **8j**	80	238	 **8p**	87	210
 **8c**	530	34	 **8k**	6400	3	 **8q**	37	385
 **8d**	73	149	 **8l**	19000	1	 **8r**	39	507
 **8e**	120	162	 **8m**	820	24	 **8s**	33	607
 **8f**	1900	11						
 **8g**	3300	6	 **8n**	3700	5	 **8t**	44	459
 **8h**	100	120						

[a]Each IC_{50} value is an average of at least two determinations. The stereochemistry of the more active enantiomer is as shown in the table. The absolute stereochemistry was confirmed by synthesis from chiral starting material.

as oxadiazolines (**2**, Figure 2) as highly efficacious GSMs in both in vitro studies and in vivo animal models. These oxadiazolines were designed as novel isosteric replacements of amides with a consideration of hydrogen-bonding characteristics and lack of strong basicity. They were found to not only be chemically stable but also possess highly desirable PK and toxicological profiles.[17] With the validation of five-membered cyclic hydroxyamidines as lactam carbonyl isosteric replacements and to further improve properties of this series of compounds, we became interested in fused oxadiazines (**3**), which are modestly basic and could offer opportunities to improve activity and enable salt formation for ease of formulation for rapid absorption.

Equipped with SAR information from the oxadiazoline series, we believed that it would be possible to identify a lead compound from the oxadiazine series considering the similarity of the two core structures. Because the left-hand imidazolylphenyl unit is necessary for potency,[17] we chose to focus our SAR studies on the modification of the right-hand side. Because of better activity of C3-disubstituted compound to monosubstituted oxadiazolines,[17] we first prepared C4-disubstituted oxadiazine compounds **4**–**6** (racemic, Figure 3). To our surprise, it turned out that the SAR clearly did not translate from the oxadiazoline to the oxadiazine series. C4 methyl 4-fluorophenyl-substituted compound **4** lost in vitro potency by 4-fold vs **4′**, and the spiro compound **6** was about 7-fold less active as compared to **6′**. More dramatically, hydroxylmethyl oxadiazine **5** was much less active than oxadiazoline compound **5′**. This SAR trend prompted us to consider that the two series might have different conformational interactions with the enzyme such that substitution at C3 of the oxadiazine core was preferred. Therefore, we decided to turn our effort to C3 modifications and carry out focused SAR studies (third degree SAR studies).[19]

Indeed, more tractable SAR was realized with the modifications at C3 (Table 1). We first introduced a hydroxymethyl group for ease of functionalization. Although this compound (**7a**) was not very potent, its TBDPS protected form (**7b**) caught our attention due to its much improved $A\beta_{42}$ inhibition even though the $A\beta_{total}/A\beta_{42}$ selectivity was not desirable. We then explored the benzyl (**7c**) and phenyl (**7d**) ethers, which displayed moderated activity, with **7d** having improved selectivity as compared to compound **7b**. This suggested that the aromatic ring might be playing a role in the activity. By moving the aryl group closer to the oxadiazine ring (**7e**), we saw much improved binding activity and selectivity as compared to the primary alcohol **7a**. The hydroxyl group did not appear to be crucial for activity. Compound **7f** retained similar potency and selectivity. When the methylene group of **7f** was eliminated, a slightly decreased activity was observed (**7g**). Aryl modifications such as naphthyl (**7h**) were tolerated and retained good activity and selectivity. Further improvement of potency was achieved by introduction of the trifluorophenyl group, and compound **7i** showed very good $A\beta_{42}$ activity and good selectivity. With this improved in vitro profile, **7i** was further studied in in vivo, PK, and ancillary profile evaluations. Compound **7i** displayed 45% inhibition of $A\beta_{42}$ in the rat cerebrospinal fluid (CSF) at the 3 h time point following acute

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oral administration at the 10 mg/kg dose. An oral rat PK study at a dose of 10 mpk showed high exposure with a plasma AUC of 24300 nM h, substantial brain concentration (1885 ng/g) at 6 h, and a brain/plasma ratio of 1.0. It did not inhibit CYP P450s or induce PXR in in vitro studies; however, 83% inhibition of hERG was observed in a function assay at a concentration of 10 μM. In an attempt to improve the hERG profile, we introduced polar groups such as heteroaryl substitutions at the C3 position. Compounds **7j** and **7k** showed much reduced Aβ_{42} activity. A carbonyl substitution at C4 (**7l**) also resulted in decreased activity.

To further improve the in vivo activity and overall profile of **7i**, we decided to revisit substitutions at the C4 position by systematically focusing on monosubstitution.[19] As summarized in Table 2, the absence of substitution at C3 and C4 (**8a**) resulted in loss of activity. The carbonyl group at C4 did not improve activity (**8b**). However, when small alkyl groups such as isopropyl (**8c**) were introduced, improved activity was observed. Steric bulk was tolerated as both isobutyl and *tert*-butyl substitutions gave compounds **8d** and **8e** with good activity and reasonable selectivity. Tetrahydropyran-substituted compound **8f** showed decreased activity, which might be due to the introduction of the polar oxygen atom. A similar SAR trend was observed with C3 modification. The hydroxyl group (**8g**) did not improve activity, but benzyl ether (**8h**), aryl-substituted secondary alcohol (**8i**), and simple benzyl substitution (**8j**) showed improved activity. To modify the physical properties of these compounds, polar groups were introduced at C4 position to decrease the clog *D* value. However, all of these changes resulted in much decreased activity [thiozole **8k** (6400 nM), sulfone **8l** (19000 nM), amide **8m** (820 nM), morpholine **8n** (3700 nM), and reverse amide **8o** (1500 nM)]. On the other hand, when aryl substitutions were introduced, consistently good activity and selectivity (**8p−t**) were achieved. In particular, the introduction of halogens to the aryl groups further improved the binding activity and Aβ_{total} to Aβ_{42} selectivity (**8q−t**). To differentiate these compounds for further profiling, they were characterized in PK and in vivo studies. As summarized in Table 3, compounds **8r** and **8s** showed highly potent in vivo activity with both compounds resulting in 62% reduction of CSF Aβ_{42} following oral dosing of 10 mg/kg. On the basis of the correlation between the decreased in vivo activity of compounds **8p** and **8t** and their lower brain exposure at the 6 h time point in rapid rat PK studies and at the 3 h time point in the PK/PD studies (for **8p**), sufficient brain exposure seemed important for improved CSF activity. Because of its potent in vitro and in vivo activity and excellent rat PK profile (bioavailability, 100%; $T_{1/2}$, 3.5 h; V_{dss}, 0.4 L/kg; and CL, 1.4 mL min^{-1} kg^{-1}), compound **8s** was further profiled. This compound was found to dose dependently reduce Aβ_{42} preferentially over Aβ_{total} and Aβ_{40} upon acute oral administration to rats,[17] thus confirming modulator activity in vivo. Compound **8s** displayed pK_a values of 7.4 and 2.7, indicating that the oxadiazine ring was modestly basic, which conferred to a highly desirable aqueous solubility of the HCl salt of >100 mM at pH 3.5. Compound **8s** was highly permeable in a Caco-2 membrane permeability assay and did not appear to be a substrate for PGP efflux. Even though a 76% inhibition of hERG activity was observed at 10 μM, no affect on QTc intervals in dogs at sufficient exposure multiples over exposures required for pharmacological effects were observed (data not shown). Compound **8s** did not affect Notch processing in HEK293 cells expressing the human Notch1 protein at concentrations up to 50 μM. There was no evidence of Notch-related side effects or biomarker changes following repeated administration of the highest tolerable doses of **8s** to rats.[17]

To further improve the overall profile of this series of compounds, we also prepared fused morpholine oxadiazines (**9−12**) by replacing the C8 carbon with an oxygen atom. This modification could block potential metabolism at C8 and, by modifying the overall electronic proterties of the molecule, might also offer advantageous properties. On the basis of SAR studies of the morpholine oxadiazoline series,[21] the C7 methyl group was installed to further improve activity. As shown in Figure 4, difluorophenyl derivatives (**9** and **10**) showed comparable in vitro activity to the trifluorophenyl analogs (**11** and **12**). In both cases, the (4*S*,7*S*)-isomers had better Aβ_{42} inhibition and Aβ_{total}/Aβ_{42} selectivity than the (4*S*,7*R*)-isomers.[22] Compound **12** represented one of the most potent and selective GSMs that we identified. This compound displayed excellent in vivo activity, reducing Aβ_{42} in rat (60% reduction of CSF Aβ_{42} at 3 h with 10 mpk acute oral dosing), and provided opportunities for future SAR development.

In summary, in an effort to identify GSMs to treat AD, we discovered a series of fused oxadiazines (**3**) as selective and orally bioavailable GSMs based on the structural framework of oxadiazolines GSMs. Although structurally related, initial studies showed that SAR did not translate from the

Table 3. Rat PK Profile[20] and in Vivo Activity of Compounds 8p−t

compd	AUC$_{0-6h}$[a]	brain concn[b]	B/P ratio[c]	CSF Aβ42 reduction[d] (%)	brain level[e]	plasma level[e]
8p	17620	539	0.9	39	2.8	6.2
8q	86460	2846	0.8	53	7.7	6.7
8r	24580	1340	1.1	62	ND[f]	7.2
8s	87410	2907	0.4	62	ND[f]	10.7
8t	22680	268	1.1	26	ND[f]	6.3

[a]nM h with 10 mpk, po dosing. [b]ng/g at 6 h from rapid rat PK studies. [c]At 6 h from rapid rat PK studies. [d]Average of multiple testings at the 3 h time point with 10 mpk acute oral dosing in PD studies. [e]μM, average of multiple testings at the 3 h time point with 10 mpk acute oral dosing in PD studies. [f]Not determined.

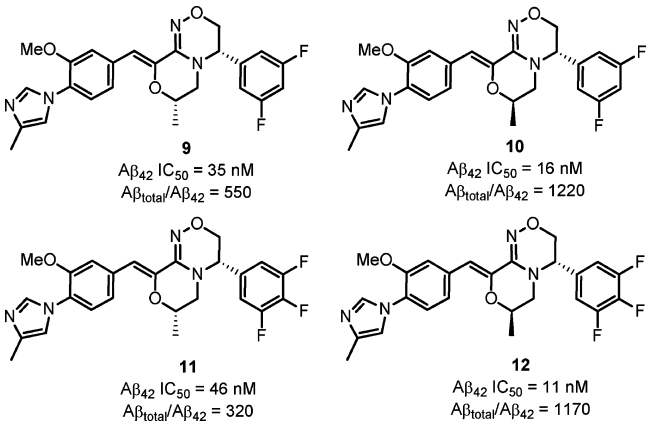

Figure 4. Identification of highly potent and selective fused morpholine oxadiazine GSMs. Each IC$_{50}$ value is an average of at least two determinations.

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oxadiazoline to the oxadiazine series. Subsequently, we focused our SAR studies on modifications at the C3 and C4 positions of the fused oxadiazine core and identified GSMs such as compounds **8r** and **8s** that were highly efficacious in vitro and in vivo in a number of animal models with highly desirable physical and physicological proterties. Further improvement of in vitro activity and selectivity was achieved by the preparation of fused morpholine oxadiazines, which provided opportunities for future SAR development. The shift in specificity of APP cleavage rather than a reduction in overall γ-secretase activity and the resulting lack of changes in substrate accumulation and Notch processing as observed in the animal studies of compound **8s** confirm that the oxadiazine series of compounds are potent GSMs. Further exploration of these compounds as potential drugs to treat AD is underway and will be the subject of future communications.

■ ASSOCIATED CONTENT

Supporting Information

Biological assay protocols, general experimental descriptions and procedures, and characterization of final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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