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Design and synthesis of an aminopiperidine series of γ-secretase modulators

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ABSTRACT

The design, synthesis, and SAR of cyclic diamines as novel γ secretase modulators (GSMs) are presented in this Letter. Starting from information in the literature and in-house cyclic diamines library, we have found a 3(*S*)-aminopiperidine as a potent structure for lowering Aβ42 production both in vitro and in vivo.

A widely pursued strategy for the treatment of Alzheimer's disease is based on inhibition of the production of neurotoxic amyloid β (Aβ) peptides, especially Aβ42.[1] Aβ peptides are generated by initial cleavage of the amyloid precursor protein (APP) by β-secretase to form a C-terminal fragment (CTF), which is subsequently cleaved by γ-secretase to produce Aβ peptides having 37–42 amino acids in length.[2] γ-Secretase inhibitors (GSIs) have been shown to reduce corticospinal fluid Aβ42 in humans; however, significant off-target liabilities have emerged during clinical development. In addition to APP, γ-secretase has multiple substrates including the Notch receptor. Notch cleavage by γ-secretase is critical for regulating neuronal development and cell differentiation. Recently, a phase III clinical trial with the GSI semagacestat was halted due to adverse events, including increased incidence in skin tumors and worsening of cognition.[3] On the other hand, γ-secretase modulators (GSMs) selectively inhibit the production of Aβ42 without blocking the overall function of γ-secretase on CTF and other substrates, such as Notch.[4] Therefore this class of molecules should not cause Notch-related side effects and could offer a better safety profile than GSIs. Herein, we discuss the synthesis and structure–activity relationship (SAR) of a series of novel aminopiperidine derived GSMs with good in vitro and in vivo suppression of Aβ42 production.

Eisai Co., Ltd has previously reported a GSM containing a cyclic cinnamide motif (Fig. 1).[5] Based on this structure, a number of other GSMs have subsequently been reported, revealing that the imidazolyl methoxy phenyl structure is a key pharmacophore for GSM activity.[6] Using a scaffold hopping strategy, we designed and prepared a focused library of compounds with the imidazolyl methoxy phenyl carboxamide moiety (Fig. 1). The olefinic double bond in Eisai's compound was replaced with amides, which are well-known to provide more polarity and to avoid the potential for Michael addition. Structural rigidity of the lactam was provided with cyclic diamines that are often seen in another class of GSMs.[7] We, thus, combined our cyclic diamine library with the imidazolyl methoxy phenyl carboxylic acids to obtain about 200 compounds. Using rat-fetus primary neuronal cell-based assay with Aβ42 ELISA, we measured in vitro Aβ42 lowering activity of the prepared compounds (Table 1).[8] At the screening stage, the substituent of the nitrogen atom on the right hand side of the cyclic amines was fixed by a 3-trifluoromethylbenzyl group. The secondary amide derivatives **1**–**5** displayed weak activity, whereas compounds **6**-**10** with primary amide groups showed strong activity. Especially, the 3(*S*)-aminopiperidine **10** exhibited the most potent activity. The (*S*) enantiomer **10** was more potent than the (*R*) enantiomer **9**. Substitution of the amide nitrogen in 3-aminopiperidine with a methyl (**11**), ethyl (**12**) or isopropyl (**13**) group resulted in complete loss of activity, indicating that the hydrogen atom is indispensable for GSM activity.

Next, we explored the right hand side moiety of the 3-aminopiperidine derivatives (Table 2). We first investigated the effect of substitution of the benzyl groups. The use of methyl groups

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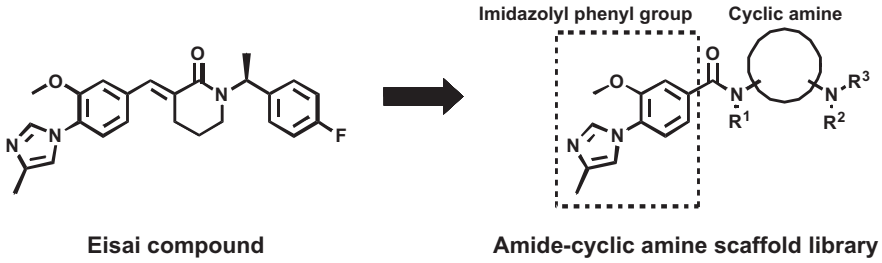
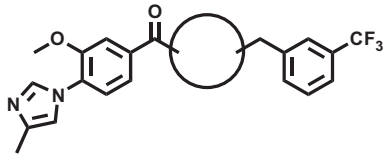
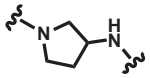
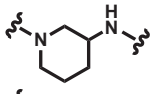
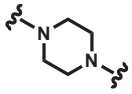
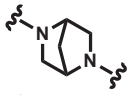
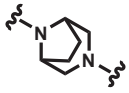
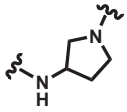
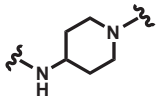
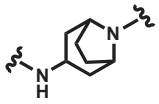
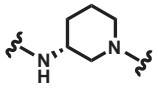
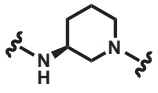
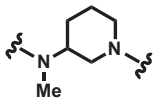


Figure 1.

Table 1

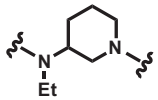
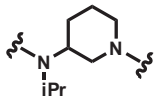
Diamine



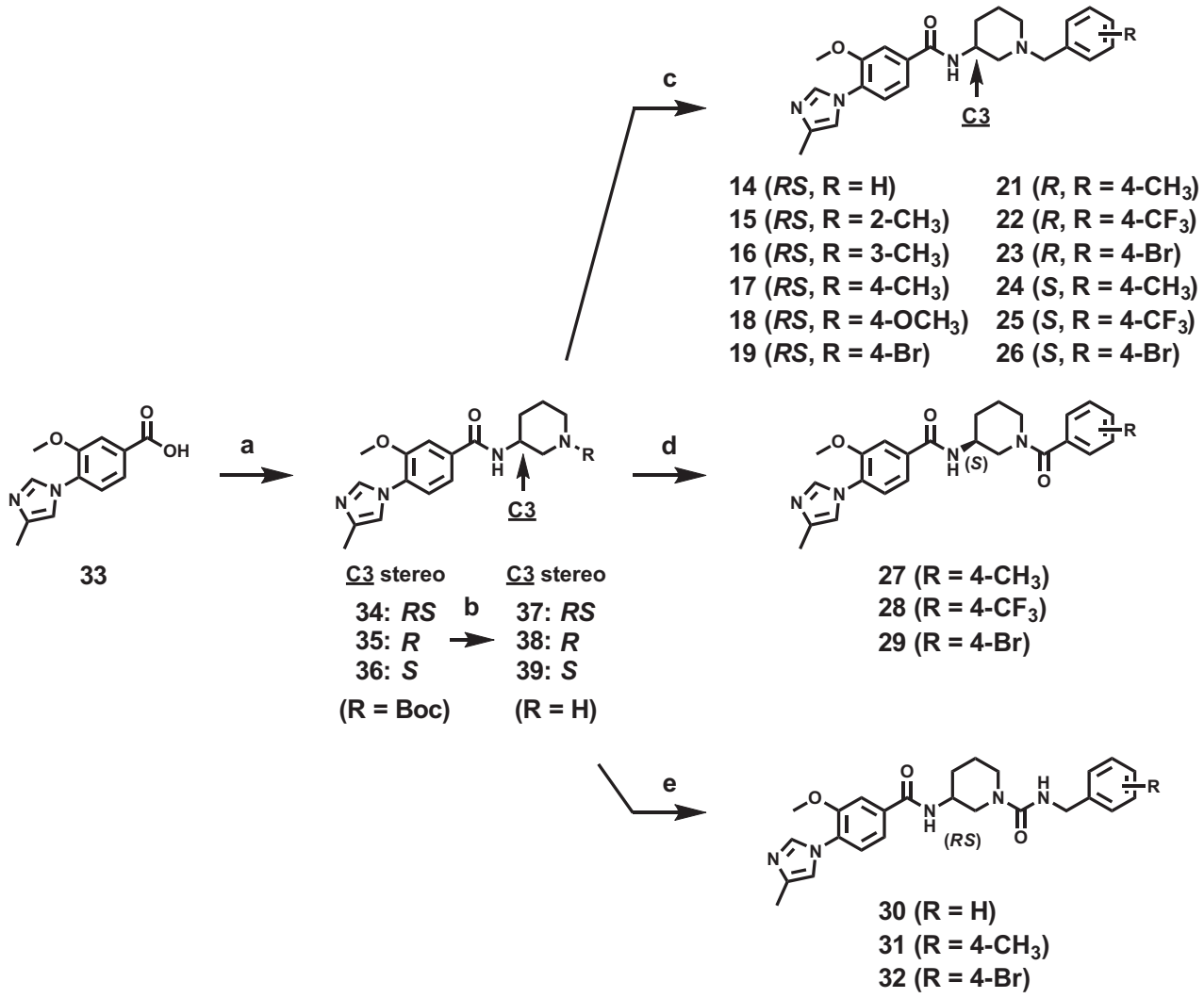
Compound	Diamine	Aβ42 inhibition[a] (%)
1		**39**
2		**17**
3		**18**
4		**51**
5		**19**
6		**31**
7		**78**
8		**40**
9		**72**
10		**82**
11		**<1**

(*continued on next page*)

Table 1 (*continued*)

12		<1
13		<1

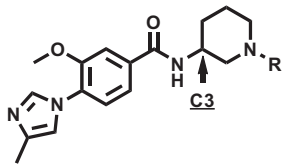
[a] Aβ42 inhibition was assayed at 2.5 μM. Each value is the average of two determinations.



Scheme 1. Reagents and conditions: (a) 3-Amino NBoc piperidine, WSCD, HOBT, DMF, rt,; (b) HCl, 1,4-dioxane, rt,; (c) The corresponding benzylbromide, K_2CO_3, DMF, rt.; (d) the corresponding benzoic acid, WSCD, HOAt, DMF, rt.; (e) the corresponding isocyanate, THF, rt.

(*o*-, *m*-, and *p*-), giving compounds **15**–**17,** increased GSM activity compared to the use of no substituent (compound **14**), with substitution at the *p*-position providing the best activity. A hydrophilic methoxy group at the *p*-position (**18**) did not affect the activity, whereas the use of a hydrophobic trifluoromethyl group (**19)** or a bromo group (**20)** resulted in strong activity. This trend was also seen in other Eisai-type GSMs.[6b] We prepared the enantiomerically pure 3(*R*) and 3(*S*) derivatives (**21**–**23** and **24**–**26**, respectively). 3(*S*) derivatives displayed stronger activity (>90% inhibition at 2.5 μM) than their enantiomers. Although there is little structural information about interaction of Eisai-type GSMs with γ-secretase, it is reported that stereochemistry in the right hand side moiety has strong influence on GSM activity in some cases.[6b–e] In our 3-aminopiperidine scaffold, 3(*S*) enantiomers might provide more favorable interaction to the active site than their enantiomers. Next, we investigated linker moiety that connects the piperidine nitrogen to the phenyl or benzyl group. The amide **27**–**29** and urea **30**–**32** derivatives showed decreased activity than the corresponding derivatives with a methylene linker. Based on these findings, we considered that the basicity of the nitrogen atom at the piperidine and the hydrophobic interaction at this region are important for high GSM activity. Then, we carried out metabolic stability tests in human liver microsome with highly active compounds (**24**–**26**). As a result, only **26** had acceptable pharmacokinetic properties for

Table 2



Compound	C3 stereo	R	Aβ42 inhibition[a] (%)
14	RS	Benzyl	**37**
15	RS	2-CH_3 benzyl	**62**
16	RS	3-CH_3 benzyl	**54**
17	RS	4-CH_3 benzyl	**82**
18	RS	4-OCH_3 benzyl	**45**
19	RS	4-CF_3 benzyl	**90**
20	RS	4-Br benzyl	**93**
21	R	4-CH_3 benzyl	**36**
22	R	4-CF_3 benzyl	**57**
23	R	4-Br benzyl	**55**
24	S	4-CH_3 benzyl	**90**
25	S	4- CF_3 benzyl	**92**
26	S	4-Br benzyl	**97**
27	S	4-CH_3 benzoyl	**55**
28	S	4-CF_3 benzoyl	**34**
29	S	4-Br benzoyl	**64**
30	RS	–CONH- benzyl	**25**
31	RS	–CONH- 4-CH_3 benzyl	**28**
32	RS	–CONH-4-Br benzyl	**47**

[a] Aβ42 inhibition was assayed at 2.5 μM. Each value is the average of two determinations.

further pharmacological evaluation (data not shown). We determined the IC_{50} value of the most potent compound (**26**) as 250 nM, which is almost the same value as that of Eisai's compound (240 nM, in-house data). The synthesis of compound **26** is shown in Scheme 1. The imidazolyl methoxy phenyl carboxylic acid **33** was prepared according to the literature,[9] and then combined to the *N-tert*-butyloxycarbonyl (Boc)-protected 3(*S*)-amino piperidine to give **36**. Deprotection of the Boc group in **36** with a hydrogen chloride gave the free amine **39**, which was alkylated with 4-bromobenzylbromide to provide compound **26**.[10] Compound **26** showed acceptable *C*log*P* and polar surface area (PSA) values (3.93 and 59 $Å^2$, respectively) for CNS drugs and exhibited good water solubility (8.0 μg/mL, pH 7.4) and membrane permeability (50×10^{-6} cm/s, pH 7.4) in an artificial membrane permeability assay. Next, we evaluated the efficacy of compound **26** in suppressing the production of Aβ42 in vivo. Compound **26**, given orally at 100 mg/kg, reduced Aβ42 production in the hippocampus and plasma of wild-type mice by 55% and 66%, respectively.

In summary, cell-based screening of an in-house focused library resulted in the discovery of the 3(*S*)-aminopiperidine scaffold as a novel structure for a new class of GSMs. Compound **26** displayed good in vitro and in vivo Aβ42 lowering activity. Although there are many Eisai-type GSMs reported, our 3(*S*)-aminopiperidine scaffold provides a facile synthetic program (simple amide condensation and N-substitution) suitable for optimization study. Further optimization of this compound will be reported in due course.

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8. In vitro assay protocol for Aβ42 inhibition: Rat fetus primary neurons were treated with compounds at specified concentration for 1–3 days. The medium was collected and quantified Aβ42 with an enzymed-linked immunosorbent assay (ELISA) kit (Human/Rat β amyloid (42) ELISA kit, High-sensitive, Wako, Japan) by manufacturer's instructions.
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10. *Chemical properties of compound* ***26***: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.25 (1H, d, J = 7.8 Hz), 7.83 (1H, d, J = 1.4 Hz), 7.59 (1H, d, J = 1.8 Hz), 7.54–7.48 (3H, m), 7.44 (1H, d, J = 8.2 Hz), 7.27 (2H, d, J = 8.2 Hz), 7.18 (1H, t, J = 1.1 Hz), 4.02–3.88 (1H, m), 3.88 (3H, s), 3.57–3.39 (2H, m), 2.85 (1H, d, J = 7.3 Hz), 2.72 (1H, d, J = 10.5 Hz), 2.14 (3H, s), 2.01–1.77 (3H, m), 1.74–1.63 (1H, m), 1.60–1.46 (1H, m), 1.41–1.28 (1H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.2, 152.3, 138.1, 136.8, 134.8, 131.4, 130.6, 129.0, 124.5, 121.2, 118.6, 116.2, 120.0, 77.2, 62.1, 57.6, 56.1, 53.7, 45.4, 28.6, 21.7, 13.6.; HRMS (ESI) m/z calcd for $C_{24}H_{28}BrN_4O_2$ 483.1390; found 483.1394 (M+H); Anal. Calcd for $C_{24}H_{27}BrN_4O_2 \cdot 0.25H_2O$; C, 59.08; H, 5.68; N, 11.48; Br, 16.38. Found: C, 58.86; H, 5.55; N, 11.21; Br, 16.16.