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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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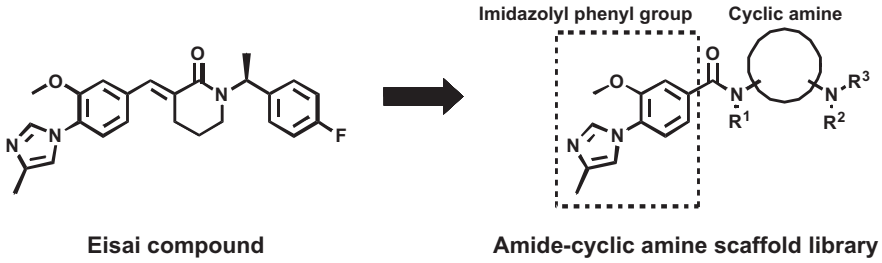
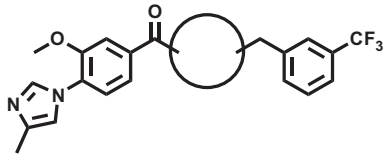
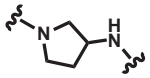
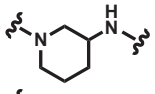
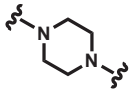
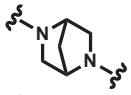
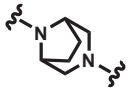
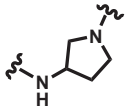
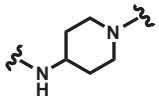
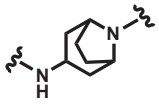
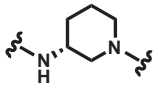
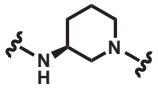
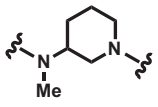


Figure 1.

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**

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