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Discovery of tetrahydroindazoles as a novel class of potent and *in vivo* efficacious gamma secretase modulators

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ABSTRACT

The identification and optimization of a novel series of centrally efficacious gamma secretase modulators (GSMs) offering an alternative to the privileged aryl imidazole motif is described. Chiral bicyclic tetrahydroindazolyl amine substituted triazolopyridines were identified as structurally distinct novel series of GSMs. Representative compound **BI-1408** (**(*R*)-42**) was demonstrated to be centrally efficacious in rats at a 30 mg/kg oral dose.

1. Introduction

Alzheimer's disease (AD) is a chronic and progressive neurodegenerative disease resulting in cognitive decline and memory loss. One of the hallmarks of this disease is the deposition of extracellular senile plaques comprised of amyloid-beta (Aβ) peptides.[1] The Aβ peptide derives from the sequential proteolytic cleavage of the amyloid precursor protein (APP) by BACE1, yielding a short membrane-bound C-terminal fragment (C99). Subsequently, C99 is cleaved via γ-secretase. While cleavage by γ-secretase yields Aβ peptides ranging from 37 to 43 amino acids long,[2] the hydrophobic Aβ 42 peptide ($Aβ_{42}$) appears most prone to aggregation. These aggregates form not only the nucleus of the senile plaques,[3] but also soluble oligomers, which are considered to be the primary neurotoxic agent in AD and have been proposed to play a central role in both the cause and progression of the disease.[4] Supporting this, mutations in presenilin 1 or 2, the catalytic subunits of γ-secretase, are associated with increased production of $Aβ_{42}$ and result in early onset AD.[5] Therefore, therapeutic approaches aimed at lowering the production of $Aβ_{42}$ represent an attractive pharmacological strategy to slow the progression of the disease. Gamma secretase modulators (GSMs), *i.e.* compounds that do not block gamma secretase cleavage but specifically lower $Aβ_{42}$ production while leaving total Aβ levels unchanged, were first identified in 2001.[6] Since then, GSMs have been demonstrated to lower $Aβ_{42}$ levels in both *in vitro* as well as *in vivo* studies. Furthermore, GSMs have been demonstrated to lower plaque load as well as rescue cognitive behavior in transgenic mice.[7]

From a chemistry perspective, GSMs can be divided into two main series: 1) NSAID-derived lipophilic carboxylic acids and 2) aryl imidazole compounds. In addition, Satori has reported natural product derived triterpenoid GSMs as an independent third chemical class.[8] Several reviews have been published on that matter and cover work of research teams in the GSM field of an entire decade.[9] The beginnings of aryl imidazole type GSMs can be traced back to an early report by Neurogenetics in 2004,[10] claiming compounds of a general structure represented by the molecule in Fig. 1. The compounds show four consecutively arranged (hetero)aromatic rings that became known as

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid β peptide; APP, amyloid precursor protein; BACE1, β-amyloid cleavage enzyme 1, β-secretase 1; GSM, gamma secretase modulator; LHS, left hand side; NSAID, non-steroidal anti-inflammatory drug; SAR, structure activity relationships; HLM, human liver microsomes; RLM, rat liver microsomes; PPB, plasma protein binding, MDCK cells, Madin-Darby canine kidney epithelial cells; pgp, p-glycoprotein; MDR1, multidrug resistance protein 1; MRT, mean residence time; psi, pounds per square inch.

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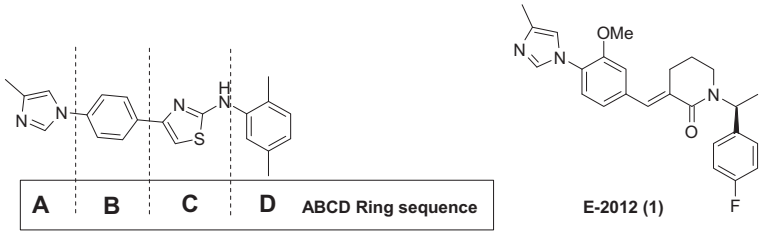

Fig. 1. Generic structure of aryl imidazole type GSMs.

the A-B-C-D ring motif.[9a] Later, Eisai described a similar, more elaborated compound E-2012 (**1**),[11] the first aryl imidazole type GSM to reach clinical trials.[12]

However, almost all non-NSAID-derived GSMs reported to date – including our own initial GSMs[13] – still share the same general characteristics such as a very high degree of aromaticity and the presence of an aryl imidazole left-hand side (LHS) moiety, which was often incorporated as aniline substructure into the compounds. While the privileged aryl imidazole A-B ring sequence seems to be particularly necessary to achieve good potency, we thought that a structural element lacking (*a*) the imidazole and (*b*) the electron rich aniline substructures would be desirable in order to avoid both CYP inhibition and potential formation of reactive metabolites.[14,15]

Several efforts have therefore been directed at reducing electron density of the B-ring by the introduction of electron-withdrawing groups, replacing the central aniline with heteroaromatics or more recently using benzoic acids and their conjugates as more polar B-C ring fragments.[16–19]

Researchers at Merck & Co reported on benzoazepinones where the imidazole was replaced by other heterocycles and the B-ring aromatic moiety was substituted or replaced by other aromatics or a triple bond linker.[20] A small number of patent applications deal with compounds that demonstrated the successful replacement of the A-Ring imidazole by a nitrile moiety (Fig. 2). First introduced by Roche[21] in 2009 (compound **2**), the research team at Bristol-Myers Squibb[22] highlighted amino benzonitriles (e.g. **3**) as a specific structural class of GSMs in two patent applications in 2012. Additionally, cyano indoles (e.g. **4**) were claimed as even further advanced analogues of the original motif by the research team at Janssen with C-linked connectivity towards the C-D fragment.[23] Sekioka et al. recently reported the identification of isoindolinone **5** as replacement for the aryl imidazole motif on an imidazopyridine scaffold as weakly active GSM.[24]

However, only a handful of reports dealt with finding non-aromatic B ring replacements, which in turn highlights the difficulties in identifying novel GSMs showing a lower degree of aromaticity: methoxyphenyl piperazines (e.g. **6**) were reported first by Merck & Co[25] and subsequently utilized on a different core by the research team from Janssen,[26] whereas heteroaromatic piperidinyl amines were published in 2011 and 2012 by Roche[27] (e.g. **7** and **8**) (Fig. 3).

While there is structural freedom to annellate the B-C ring sequence[28] as well as using bicyclic core systems as C-ring elements there is yet no evidence in literature that more flexible, partially saturated bicyclic amines can be used as A-B ring system.[29]

Herein, we report our work leading to a novel class of potent and *in vivo* efficacious gamma secretase modulators that comprise tetrahydroindazolyl amines as a replacement of the prominent aryl imidazole motif. To our best knowledge, this is the first disclosure of highly potent GSMs with partially saturated bicyclic amines as A-B ring fragments.

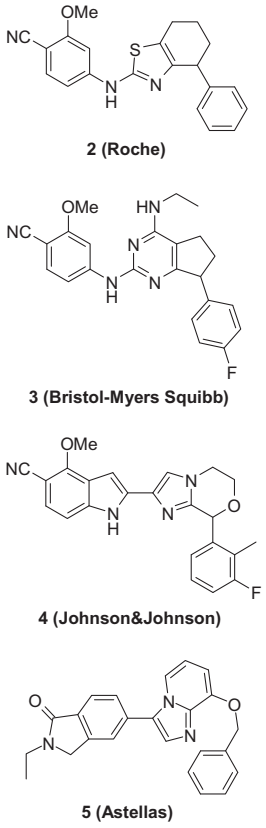

Fig. 2. Literature-known structural alternatives to the aryl imidazole moiety: benzonitriles and conjugates.

2. Design and synthesis

2.1. Design

When looking for promising starting points to identify such novel A-B entities we recognized[30] the marked tolerance of the [1,2,4]triazolo[1,5-*a*]pyridine core to non-aromatic B ring modifications (e.g. compound **7**, Fig. 4). We therefore hypothesized the triazolopyridine core to be a good probe for the identification of novel A-B structures. To this end, we chose a diverse set of primary and secondary amines of commercial and internal origin including numerous bicyclic amines as left-hand side elements for combination with a suitable triazolopyridine scaffold.

In the amine selection process, we acknowledged the necessity of keeping a terminal hydrogen bond acceptor as a key pharmacophore (see Fig. 4, pink ellipse) as well as the presence of at least one ring system to limit conformational flexibility. Apart from that, we allowed all kinds of mono- or bicyclic aromatic, saturated, or partially saturated ring systems.