Bioorganic & Medicinal Chemistry Letters 26 (2016) 3928–3937

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Design and synthesis of aminothiazole modulators of the gamma-secretase enzyme

Kevin D. Rynearson [a], Ronald N. Buckle [b], Keith D. Barnes [b], R. Jason Herr [b], Nicholas J. Mayhew [b], William D. Paquette [b], Samuel A. Sakwa [b], Phuong D. Nguyen [a], Graham Johnson [c], Rudolph E. Tanzi [d], Steven L. Wagner [a,*]

[a] Department of Neurosciences, University of California, San Diego, 9500 Gilman Drive MC 0624, La Jolla, CA 92093-0624, United States
[b] Department of Medicinal Chemistry, AMRI, East Campus, 3 University Place, Rensselaer, NY 12144, United States
[c] NuPharmAdvise, 3 Lakeside Drive, Sanbornton, NH 03269, United States
[d] Genetics and Aging Research Unit, Department of Neurology, Massachusetts General Hospital, Charlestown, MA 02129, United States

ARTICLE INFO

Article history:
Received 4 May 2016
Revised 1 July 2016
Accepted 4 July 2016
Available online 6 July 2016

Keywords:
Alzheimer's disease
γ-Secretase modulators
Aminothiazoles

ABSTRACT

The design and construction of a series of novel aminothiazole-derived γ-secretase modulators is described. The incorporation of heterocyclic replacements of the terminal phenyl D-ring of lead compound **1** was conducted in order to align potency with favorable drug-like properties. γ-Secretase modulator **28** displayed good activity for in vitro inhibition of Aβ42, as well as substantial improvement in ADME and physicochemical properties, including aqueous solubility. Pharmacokinetic evaluation of compound **28** in mice revealed good brain penetration, as well as good clearance, half-life, and volume of distribution which collectively support the continued development of this class of compounds.

© 2016 Published by Elsevier Ltd.

Alzheimer's disease (AD) is a devastating neurological disorder and is currently estimated to affect 5.3 million Americans. In 2015, AD and other related dementias will cost the United States $226 billion, and if the current disease trajectory is maintained, the associated costs could rise to as high as $1.1 trillion by 2050.[1] AD is the only top ten cause of death in America that cannot be prevented, cured or slowed, and thus there is an urgent medical need for disease modifying therapeutic agents.[1]

AD is an irreversible and progressive neurodegenerative disease affecting the brain which insidiously destroys memory, thinking skills and cognition. Originally described in 1906 by German physician Alois Alzheimer, AD is characterized by the presence of intraneuronal neurofibrillary tangles of hyperphosphorylated microtubule associated protein tau and extraneuronal neuritic plaques primarily composed of amyloid β-42 (Aβ42).[2] A large body of histopathological and genetic evidence implicates that the processing and deposition of Aβ peptides within the brain is the primary driver of AD progression ultimately leading to dementia.[3] The Aβ peptides are formed as the result of sequential proteolytic cleavages of the amyloid precursor protein (APP) by two aspartyl proteases, β-secretase (BACE-1) and γ-secretase, respectively.[4] APP is first cleaved by BACE-1 which yields membrane bound carboxy-terminal fragment-β (CTF-β) known as C99. Further cleavages of the C99 fragment by γ-secretase releases the APP intracellular domain (AICD) and produces extracellular Aβ peptides which vary in length from 37 to 43 amino acids.[5]

Directly implicated in the production of Aβ peptides, BACE-1 and γ-secretase represent attractive targets for the development of AD therapies.[3–5] Consequentially, small molecule compounds which curtail the formation of all Aβ species by inhibition of either BACE-1 or γ-secretase have been intensely pursued.[6] Potent γ-secretase inhibitors (GSI) such as semagacestat and avagacestat were developed and demonstrated robust reduction of Aβ peptides.[7] Unfortunately, these GSIs also displayed severe side effects and counter efficacy which resulted in accelerated cognitive decline during clinical evaluation, and thus γ-secretase inhibition strategies were abandoned.[8] As an alternative to inhibition, γ-secretase modulation offers an attractive approach with the goal of attenuating the production of the neurotoxic and aggregation prone Aβ42 isoform, the primary component of neuritic plaques, while not affecting endogenous γ-secretase function.[9] Based on the fact that the vast majority of the more than 200 FAD-linked genetic mutations appear to cause a 2-fold increase in the ratio of the longer Aβ42 peptide to the shorter Aβ40 peptide, and a large body of data pointing specifically to Aβ42 in pathogenesis, a therapeutic rationale that modulates γ-secretase activity to reduce the level of

* Corresponding author.
E-mail address: slwagner@ucsd.edu (S.L. Wagner).

http://dx.doi.org/10.1016/j.bmcl.2016.07.011
0960-894X/© 2016 Published by Elsevier Ltd.

Aβ42 relative to the shorter Aβ peptides (i.e., Aβ40, Aβ38 and Aβ37) without affecting overall γ-secretase function may prove to be an efficacious course for interrupting AD progression.[10] Several classes of γ-secretase modulators have been discovered which alter the Aβ cleavage pattern in favor of shorter Aβ peptides, including compounds derived from non-steroidal anti-inflammatory drugs (NSAIDs),[11] aryl imidazoles[5,12] and triterpenes.[13]

Previously our lab discovered a series of aminothiazole-derived γ-secretase modulators (AGSMs) through rational hit to lead optimization efforts which demonstrate remarkable potency for lowering Aβ42 (>1000-fold more potent than the NSAID-like GSM tarenflurbil) and exhibit moderate brain penetrance.[14] This novel class of compounds is characterized by a tetracyclic scaffold composed of bridged linear aromatics (Fig. 1). Compounds within this series have been shown to specifically reduce the levels of Aβ42 and Aβ40 production while simultaneously increasing the levels of Aβ38 and Aβ37, thereby leaving the total amount of Aβ produced unchanged. Importantly, AGSMs do not affect γ-secretase-mediated cleavage of other critical substrates, including Notch and E-cadherin. The selectivity for Aβ products likely stems from the observed binding of AGSMs to Pen-2 and PS-1 NTF of the γ-secretase enzymatic complex which shifts rather than inhibits endogenous function. Additionally, in vivo studies showed AGSMs were potent and effective at decreasing the levels of Aβ42 and Aβ40 in the plasma and brain of APP transgenic mice. Chronic administration of AGSMs to Tg2576 APP transgenic mice resulted in dramatic reduction of AD-like pathology in the absence of GSI-related effects such as intestinal goblet cell hyperplasia due a distinct mode of action.[14] Despite the overall efficacy of these compounds, the poor aqueous solubility (<0.1 μM at neutral pH) of the AGSMs presents a significant liability especially when attempting to achieve the supraefficacious exposures required for safety and toxicology studies during preclinical development.

Herein, we describe the development of second generation GSM compounds aimed at improving critical physicochemical properties while maintaining the potent activity of the parent AGSM. Ligand design focused on identifying heterocyclic replacements for the hydrophobic D-ring as a means to improve ADME (absorption, distribution, metabolism and excretion) parameters, as well as aqueous solubility. Replacement of the alkyl rich phenyl D-ring by a pyrazole containing scaffold was anticipated to ameliorate the property related shortcomings of the AGSMs. Based on the spatial arrangement of the substituents within AGSM **1**, as well as molecular modeling overlays, tetrahydroindazole, 3-*tert*-butylpyrazole and cyclopentapyrazole D-ring analogs were selected for preparation. The construction of the three unique series would be accomplished utilizing established Hantzsch chemistry from a common bromoacetophenone precursor enabling the rapid preparation of a diverse set of pyrazole containing scaffolds permitting rigorous evaluation of these novel D-ring substitutions (Scheme 1).[15]

A series of 3-aminotetrahydroindazole analogs were synthesized in order to explore the local spatial constraints of the γ-secretase binding cavity with respect to this novel D-ring substitution. The fused ring system of the 2-substituted tetrahydroindazole **5** was envisioned to mirror the alkyl functionalization of AGSM **1** while rigidifying the D-ring and preserving favorable hydrophobic interactions of the parent molecule. 2-Substituted tetrahydroindazoles **5**–**9** displayed modest activity for the reduction of Aβ42 in a SHSY5Y neuroblastoma cell line stably over-expressing human APP and demonstrated a slight gain in potency as the alkyl chain increases in size (compounds **5**–**7** Table 1).[16,17] However, the alteration in *N*-alkyl connectivity of tetrahydroindazole **7** providing isopropyl derivative **8**, as well as the introduction of a *tert*-butyl group in compound **9** led to a slight reduction in activity. Removal of the 2-postion substituent as illustrated by tetrahydroindazole **10** abrogates activity, underscoring the importance of the alkyl functionality with respect to Aβ modulation.

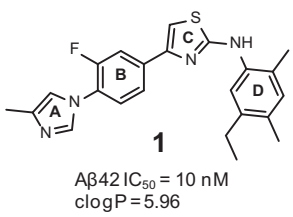
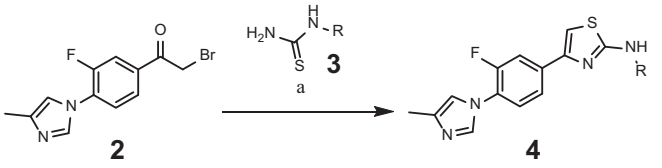


Figure 1. General scaffold of optimized lead aminothiazole-derived γ-secretase modulator (AGSM). The rings are labeled A–D for clarity.



Scheme 1. Reagents and conditions: (a) EtOH, reflux, overnight, 16–79%, R = tetrahydroindazole, 3-*tert*-butylpyrazole or cyclopentapyrazole containing scaffold.

Based on the pivotal role the 2-postion substituent plays with respect activity, in addition to the overall tolerance for alkyl substituents of various size, analogs **11**–**26** were prepared to thoroughly probe the chemical space for favorable interactions. The constrained and small 2-cyclobutyl tetrahydroindazole **11** displayed a 2-fold increase in activity when compared to isopropyl analog **8**, suggesting that this region of γ-secretase features a narrow hydrophobic pocket. This assertion is further supported by ligands **12**–**16** which illustrate that as the size of the substituent increases from the 2-cyclopropyl to the larger 2-cyclohexyl derivative (**12** vs **13**) the observed activity decreases. Moreover, increasing the polarity of the 2-position substituent through the incorporation of heteroatoms as exemplified by the tetrahydrofuran **14**, tetrahydropyran **15** and 1-methylpiperidine **16** significantly erodes potency. In general, deviation from linear *N*-alkyl substitution is deleterious to suppressing Aβ42 levels, and the introduction of heteroatoms served to exacerbate this trend.

Efforts to increase the flexibility of the heterocyclic substituent, as well as extend beyond the constrained hydrophobic region through the insertion of an ethyl or propyl linker failed to restore the loss of activity as evidenced by analogs **17**, **18** and **19**. Consequentially, the incorporation of smaller functionalities within the active 2-postion alkylated analogs was explored. 2-Trifluororethane **21** demonstrated similar activity to parent analog **6**, whereas 2-fluoroethane **20** displayed a slight increase in activity for the reduction of Aβ42. The insertion of oxygen with the alkyl chain was poorly tolerated as demonstrated by 2-methoxyethane **22**, 2-hydroxyethane **23**, and 2-hydroxypropane **24** which are approximately 2-fold less active than the corresponding aliphatic analog. However, increasing hydrophobicity of analog **23** through the addition of two flanking methyl groups resulting in 2-hydroxy-2-methylpropane compound **25** showed an unexpected 3-fold improvement over primary analog **7** thus reinforcing the strong preference for hydrophobic character within this region of the D-ring by the γ-secretase enzyme. Finally, an *N*-methyl derivative of compound **26** was synthesized in order to ascertain the role of the proton with respect to ligand affinity. Unfortunately, *N*-methylated analog **26** loses all activity suggesting either the presence of a hydrogen bond between the ligand and enzyme or an overall reduction in ligand flexibility stemming from the sterical interactions between the D-ring and the added methyl which restrict access to conformations required for target interaction.

Download English Version:

https://daneshyari.com/en/article/1369722

Download Persian Version:

https://daneshyari.com/article/1369722

Daneshyari.com