Bioorganic & Medicinal Chemistry Letters 20 (2010) 2279–2282

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Purine derivatives as potent γ-secretase modulators

Alexey Rivkin [a,*], Sean P. Ahearn [a], Stephanie M. Chichetti [a], Christopher L. Hamblett [a], Yudith Garcia [a], Michelle Martinez [a], Jed L. Hubbs [a], Michael H. Reutershan [a], Matthew H. Daniels [a], Phieng Siliphaivanh [a], Karin M. Otte [a], Chaomin Li [a], Andrew Rosenau [a], Laura M. Surdi [a], Joon Jung [a], Bethany L. Hughes [a], Jamie L. Crispino [a], George N. Nikov [a], Richard E. Middleton [a], Christopher M. Moxham [a], Alexander A. Szewczak [a], Sanjiv Shah [b], Lily Y. Moy [b], Candia M. Kenific [b], Flobert Tanga [b], Jonathan C. Cruz [b], Paula Andrade [c], Minilik H. Angagaw [c], Nirah H. Shomer [c], Thomas Miller [a], Benito Munoz [a], Mark S. Shearman [b]

[a] Department of Drug Design and Optimization, Merck Research Laboratories, 33 Avenue Louis Pasteur, Boston, MA 02115, USA
[b] Department of Neuroscience Drug Discovery, Merck Research Laboratories, 33 Avenue Louis Pasteur, Boston, MA 02115, USA
[c] Department of Laboratory Animal Resources, Merck Research Laboratories, 33 Avenue Louis Pasteur, Boston, MA 02115, USA

ARTICLE INFO

Article history:
Received 19 November 2009
Revised 31 January 2010
Accepted 2 February 2010
Available online 6 February 2010

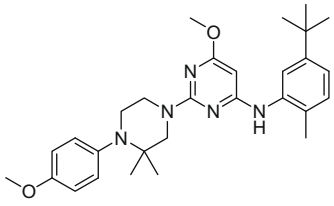
ABSTRACT

The development of a novel series of purines as γ-secretase modulators for potential use in the treatment of Alzheimer's disease is disclosed herein. Optimization of a previously disclosed pyrimidine series afforded a series of potent purine-based γ-secretase modulators with 300- to 2000-fold in vitro selectivity over inhibition of Notch cleavage and that selectively reduces Aβ42 in an APP-YAC transgenic mouse model.

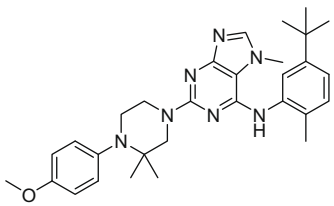
Alzheimer's disease (AD) is a debilitating illness with unmet medical needs.[1] The number of people afflicted with the disease worldwide is expected to triple by the year 2050.[2] While there are symptomatic treatments available, there is currently no treatment that is considered disease-modifying.[3] The primary pathological event in sporadic and familial AD is the extracellular accumulation of amyloid-β (Aβ) peptides and formation of amyloid plaques.[4] One strategy for developing a disease modifying AD therapy has been to reduce or eliminate the production of Aβ peptides through inhibition of γ-secretase, which generates Aβ peptides from the amyloid precursor protein (APP).

Several γ-secretase inhibitors are currently in clinical trials.[5] The major side effects observed with γ-secretase inhibitors are thought to be associated with blocking the processing of Notch, a transmembrane receptor which is also a substrate of γ-secretase.[6] To avoid Notch-related toxicity we pursued a strategy that focused on the discovery of a small molecule that modulates the processing of γ-secretase substrates, specifically targeting reductions in Aβ42. The pathogenic Aβ42 peptide fragment is thought to play a more significant role in AD pathology.[4] This approach was supported by recent reports that non-steroidal anti-inflammatory drugs reduce Aβ42 generation and spare Notch processing and Aβ40 production.[7,8]

We have previously disclosed a novel series of piperazinyl pyrimidines, which selectively inhibits the production of Aβ42 over Aβ40 (e.g., **1**; IC_{50}-Aβ42 = 260 nM and IC_{50}-Aβ40 = 5700 nM) and shows >180-fold selectivity over inhibition of Notch cleavage (Fig. 1).[9] Herein, we describe the subsequent optimization of this series resulting in the identification of a novel purine series (e.g., **2**) possessing low nanomolar potency for the selective in vitro inhibition of Aβ42 and proof of activity in vivo.



1 (IC_{50}(nM) - Aβ42/40 = 260/ 5700 nM)



2 (IC_{50}(nM) - Aβ42/40 = 21/ 350 nM)

Figure 1. Novel class of purine-based γ-secretase modulators.

* Corresponding author. Tel.: +1 617 992 2295; fax: +1 617 992 2403.
E-mail address: alexey_rivkin@merck.com (A. Rivkin).

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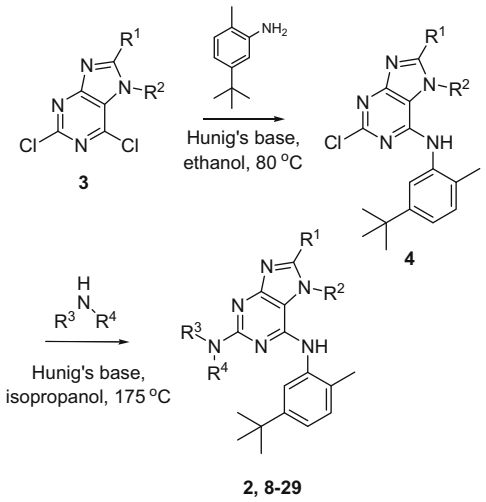
doi:10.1016/j.bmcl.2010.02.008

The general synthetic approach employed to prepare analogs of **2** is outlined in Scheme 1. Regioselective nucleophilic addition of 5-*tert*-butyl-2-methylaniline to 2,6-dichloropurine **3** in the presence of base afforded the corresponding 6-aminopurine **4**. A second addition of a variety of amines to **4** using microwave irradiation gave the corresponding purines **2**, **8**–**29**.

During the course of our SAR studies with the previously disclosed pyrimidine series (e.g., **1**), we discovered that polar groups were well tolerated in the 6-position of the pyrimidine ring with retained or enhanced potency and improved physical properties. The enhancement of potency in certain cases was thought to be partially attributed to a hydrogen bond interaction. With this hypothesis in mind, we continued to explore the SAR of the pyrimidine ring with the goal of enhancing this interaction in order to improve the potency. While exploring a variety of fused pyrimidine analogs, we discovered purine **2** that was 10-fold more potent than **1** and equally selective, thus supporting the hypothesis that a hydrogen bond interaction may be important (Table 1). This hypothesis is reinforced by the loss in potency of regioisomer **5**, pyrrolopyrimidine **6** (see also **6** vs **8**), and pyridopyrimidine **7**. Further SAR studies with **2** showed that the purine ring is tolerant of minor substitution, with subtle changes often leading to small fluctuations in potency (**8**–**12**).

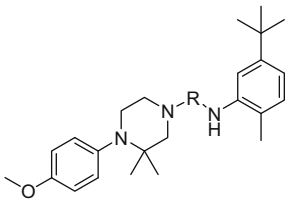
We then turned our attention to exploring the SAR profile of the 4-methoxyphenyl piperazine of **2** with the goal of improving the potency and replacing this moiety with something less prone to metabolism (Table 2). Survey of the SAR showed that this region is tolerant to a wide variety of substitutions, which is in stark contrast to the lack of tolerability that this same region showed in the previously disclosed pyrimidine series (e.g., **1**).[9] Interestingly, the enhancement of selectivity by the *gem*-dimethyl substitution, which we observed in the pyrimidine series, is not present in the purine series (**2** vs **14**). These differences in SAR may be attributed to a shift in the binding mode of the purine series where the 4-methoxyphenyl is situated in a less constrained location. The replacement of the oxygen atom with a carbon atom (**14** vs **15**) led to a 20-fold loss in potency, which may be partially due to the loss of a hydrogen bond interaction between the 4-methoxy group and the enzyme. As a result, we continued our SAR studies while attempting to preserve this presumable hydrogen bond interaction. Variation of the phenyl or piperazine rings led to a substantial loss in potency (**16**–**18**). Introduction of an imidazolyl or pyridyl piperidine led to loss of potency that could be recovered in the pyridyl piperidine case by addition of a carbon spacer (**19**–**21**). SAR studies of 4-(piperidin-4-ylmethyl)pyridine of **21** led to further improvement of potency (**22**–**24**). Interestingly, replacement of the piperidine ring with a phenyl ring led not only to a loss of potency but also to a reduction in selectivity (**21** vs **25**). Introduction of a tetrahydropyran in place of the pyridine ring led to loss of potency as well but without a substantial impact on selectivity (**22** vs **26**). While introduction of pyridyl piperidine led to a 17-fold loss in potency relative to **2**, the incorporation of a pyridyl pyrrolidine led only to a threefold loss (**20** vs **27**). Maintaining the pyrrolidine ring system was not required for retention of potency (**28**, **29**), which is in contrast to what was observed in the SAR of 4-methoxyphenyl piperazine (**14** vs **17**).

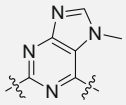
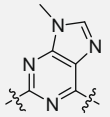
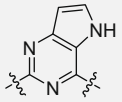
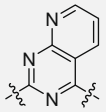
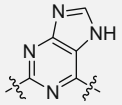
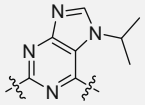
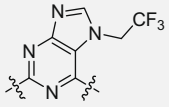
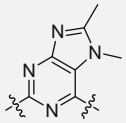
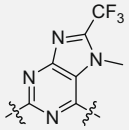
Several lead compounds were further profiled in a Notch cleavage assay[11] and found to have at least a 300-fold selectivity ratio between inhibition of Aβ42 and Notch cleavage (Table 3).



Scheme 1. Synthetic strategy for the preparation of the purine series.

Table 1
In vitro activity of the purine series against Aβ42 and Aβ40



Compound	R	Aβ42 IC_{50}[10] (nM)	Aβ40 IC_{50}[10] (nM)
2		21	350
5		130	2600
6		750	3000
7		210	3100
8		68	1000
9		50	350
10		55	420
11		22	160
12		50	1000