Bioorganic & Medicinal Chemistry Letters 22 (2012) 4404–4409

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Fused tricyclic indoles as $S1P_1$ agonists with robust efficacy in animal models of autoimmune disease

Daniel J. Buzard *, Sangdon Han, Luis Lopez, Andrew Kawasaki †, Jeanne Moody ‡, Lars Thoresen, Brett Ullman, Juerg Lehmann, Imelda Calderon, Xiuwen Zhu, Tawfik Gharbaoui §, Dipanjan Sengupta §, Ashwin Krishnan, Yinghong Gao ¶, Jeff Edwards ‖, Jeremy Barden, Michael Morgan, Khawja Usmani, Chuan Chen, Abu Sadeque, Jayant Thatte ††, Michelle Solomon, Lixia Fu ‡‡, Kevin Whelan, Ling Liu §§, Hussien Al-Shamma, Joel Gatlin, Minh Le, Charles Xing, Sheryll Espinola ¶¶, Robert M. Jones

Arena Pharmaceuticals, 6166 Nancy Ridge Drive, San Diego, CA 92121, USA

ARTICLE INFO

Article history:
Received 29 March 2012
Revised 26 April 2012
Accepted 27 April 2012
Available online 7 May 2012

Keywords:
Sphingosine-1 phosphate receptor
$S1P_1$ agonist
Immunomodulators
FTY720

ABSTRACT

Two series of fused tricyclic indoles were identified as potent and selective $S1P_1$ agonists. In vivo these agonists produced a significant reduction in circulating lymphocytes which translated into robust efficacy in several rodent models of autoimmune disease. Importantly, these agonists were devoid of any activity at the $S1P_3$ receptor in vitro, and correspondingly did not produce $S1P_3$ mediated bradycardia in telemeterized rat.

Fingolimod (**1**) is a potent immunosuppressant that was identified during a medicinal chemistry campaign aimed at dialing out the GI side effect profile associated with the secondary fungal metabolite ISP-1 (**2**, Fig. 1).[1] In vivo, (**1**) is phosphorylated to the (*S*)-isomeric mono-phosphate (**3**) which is an agonist at four of the five sphingosine-1-phosphate receptors ($S1P_1$, $S1P_{3-5}$).[2] The $S1P/S1P_1$ axis regulates the egress of lymphocytes from peripheral lymphoid tissue and (**3**) prevents this trafficking via sustained receptor internalization accompanied by proteasomal degradation.[3] Impaired lymphocyte trafficking reduces the circulation of auto-reactive immune cells, which has been found to slow the progression of disease in multiple sclerosis patients.[4] Fingolimod also may be acting directly on astrocytes to reduce inflammation in the CNS of these patients. $S1P_1$ expression in central MS lesions is dramatically increased, and mouse neural $S1P_1$ knockouts phenotypically show reduced disease severity, astrogliosis, demyelination and axonal loss when compared to their wild type littermates.[5] The precise role of the other S1P subtypes in the amelioration of disease is less well understood, although (**1**) may be acting on the $S1P_5$ and $S1P_3$ receptors expressed centrally on oligodendrocytes and astrocytes.[3]

Over the last decade, medicinal chemistry efforts have focused on identifying alternative agents with improved selectivity. Particular emphasis has been placed on the cardiac expressed $S1P_3$ receptor that is associated with bradycardia in rodents.[6] However, human trials of the $S1P_3$-sparing agonist BAF312, suggests that the transient effect on heart rate may not be attributable to $S1P_3$ activation in humans.[7] More recently, researchers have sought agonists with improved pharmacokinetic profiles given the long half-life of (**1**) in humans ($T_{1/2}$ = 8 days).[8] These efforts have also centered around developing non pro-drug agonists that can penetrate the CNS and act directly on astrocytes.[9] Development of

* Corresponding author.
E-mail address: dbuzard@arenapharm.com (D.J. Buzard).
† Present address: Focus Synthesis, 11475 Sorrento Valley Road, Suite 212, San Diego, CA 92121, USA.
‡ Present address: Regulus Therapeutics, 3545 John Hopkins Court, San Diego, CA 92121, USA.
§ Present address: Dart NeuroScience LLC, 7473 Lusk Boulevard, San Diego, CA 92121, USA.
¶ Present address: EMD Millipore, 10394 Pacific Center Court, San Diego, CA 92121, USA.
‖ Present address: Amylin Pharmaceuticals, 9360 Towne Center Drive, San Diego, CA 92121, USA.
†† Present address: PRESCOS LLC, 3550 General Atomics Court, M/S 02-422, San Diego, CA 92121, USA.
‡‡ Present address: Synthetic Genomics, 11149 North Torrey Pines Road, La Jolla, CA 92037, USA.
§§ Present address: Pfizer, 10646 Science Center Drive, San Diego, CA 92121-1150, USA.
¶¶ Present address: Genomics Institute of the Novartis Research Foundation, 10675 John Jay Hopkins Drive, San Diego, CA 92121, USA.

0960-894X/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmcl.2012.04.129

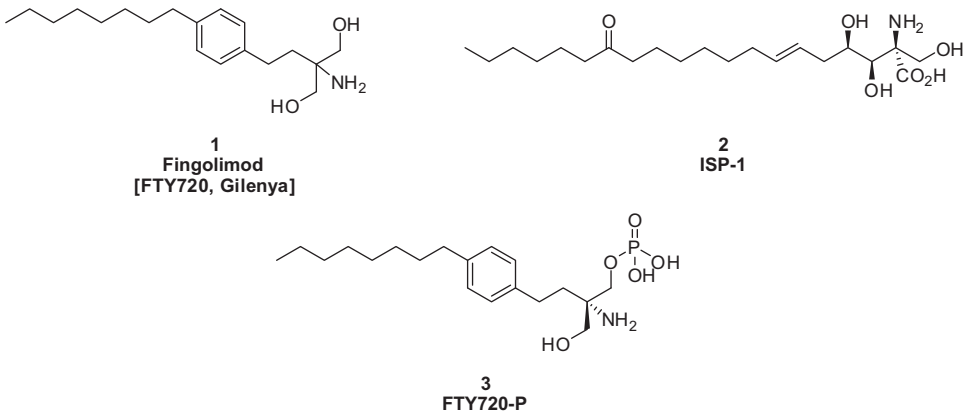


Figure 1. Fingolimod origin and mechanism.

agonists for other autoimmune indications such as psoriasis (Ponesimod),[10] polymyositis (BAF312),[11] and ulcerative colitis (KRP-203)[12] is also underway.

As part of our effort to identify superior $S1P_1$ agonists, we have expanded upon an early series of 3-(indolin-2-yl)propanoic acids (**4**, Fig. 2)[13] and herein disclose two fused tricyclic indole $S1P_1$ chemotypes (**5**, **6**).

The cyclopenta[*b*]indole ring system (**8**) was prepared via a palladium mediated cyclization utilizing aniline **7** and ethyl 2-(2-oxocyclopentyl)acetate as coupling partners (Scheme 1). Subsequent hydroxy-amidine formation (**9**), and treatment with an activated benzoic acid afforded the 5-phenyl-1,2,4-oxadiazole motif (**10**). Ester saponification was typically performed using LiOH, however, compound **17** (Table 1) required a milder procedure

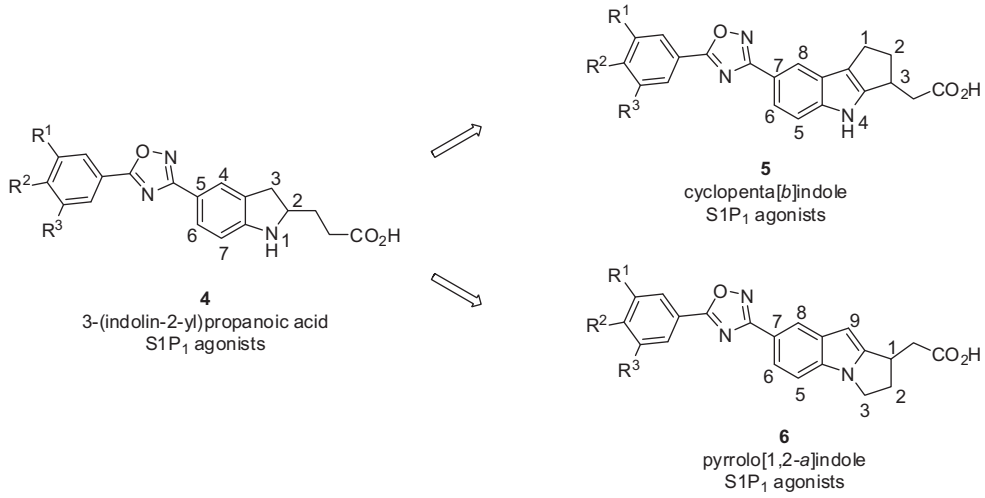
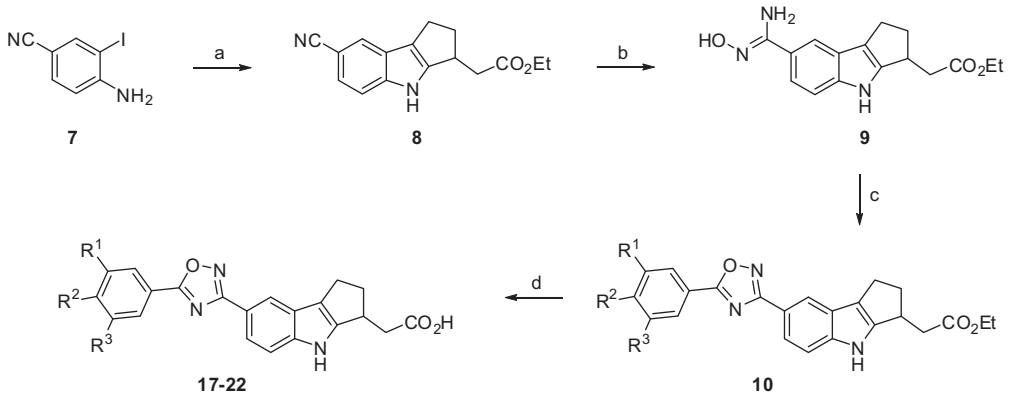


Figure 2. Cyclopenta[*b*]indole and Pyrrolo[1,2-*a*]indole $S1P_1$ agonists.



Scheme 1. Cyclopenta[*b*]indole synthesis. (a) Ethyl 2-(2-oxocyclopentyl)acetate, PPTS, $Si(OEt)_4$ then $Pd(OAc)_2$, DIEA (b) 50% aq hydroxylamine, EtOH (c) ArCOCl, Et_3N or $ArCO_2H$, CDI (d) NaOH or LiBr, Et_3N, MeCN, water.