Bioorganic & Medicinal Chemistry Letters 20 (2010) 3026–3030

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Synthesis and SAR of novel isoquinoline CXCR4 antagonists with potent anti-HIV activity

John F. Miller [a,*], Kristjan S. Gudmundsson [a], Leah D'Aurora Richardson [a], Stephen Jenkinson [d], Andrew Spaltenstein [a], Michael Thomson [b], Pat Wheelan [c]

[a] Department of Medicinal Chemistry, Infectious Diseases Center for Excellence in Drug Discovery, GlaxoSmithKline Research and Development, Five Moore Drive, Research Triangle Park, NC 27709-3398, USA
[b] Department of Virology, Infectious Diseases Center for Excellence in Drug Discovery, GlaxoSmithKline Research and Development, Five Moore Drive, Research Triangle Park, NC 27709-3398, USA
[c] Department of DMPK, Infectious Diseases Center for Excellence in Drug Discovery, GlaxoSmithKline Research and Development, Five Moore Drive, Research Triangle Park, NC 27709-3398, USA
[d] Department of Biochemical and Analytical Pharmacology, Infectious Diseases Center for Excellence in Drug Discovery, GlaxoSmithKline Research and Development, Five Moore Drive, Research Triangle Park, NC 27709-3398, USA

ARTICLE INFO

Article history:
Received 10 March 2010
Revised 30 March 2010
Accepted 31 March 2010
Available online 3 April 2010

Keywords:
CXCR4
Isoquinoline
Tetrahydroquinoline
AMD070
HIV
Antiviral

ABSTRACT

Using AMD070 as a starting point for structural modification, a novel series of isoquinoline CXCR4 antagonists was developed. A structure–activity scan of alternate lower heterocycles led to the 3-isoquinolinyl moiety as an attractive replacement for benzimidazole. Side chain optimization in the isoquinoline series led to a number of compounds with low nanomolar anti-HIV activities and promising rat PK properties.

In recent years the medicinal chemist's focus in the battle against HIV/AIDS has broadened to include molecular targets beyond the HIV reverse transcriptase and protease enzymes, which are the cornerstones of the highly active antiretroviral therapy (HAART).[1] One area that has received a great deal of attention is the concept of blocking viral entry by targeting the chemokine receptors CCR5 and CXCR4, which function as co-receptors, along with CD4, to facilitate fusion of the viral membrane with the host cell.[2] CXCR4 is a G-protein coupled 7-transmembrane receptor utilized by T-tropic HIV strains to gain entry into T-cells. The appearance of CXCR4 utilizing strains of HIV is associated with a decrease in the number of T-cells and accelerated disease progression.[3] In vitro studies have shown that addition of the natural CXCR4 ligand, SDF-1, or small molecule antagonists, can block HIV infection.[2e] SDF-1 is a highly basic protein with about 20% of its 68 amino acids (for SDF-1α) being arginine, lysine or histidine. This observation, along with the fact that the extracellular binding regions of the CXCR4 receptor are particularly rich in aspartic acid and glutamic acid residues, points to a receptor–ligand binding model in which charge-charge interactions play a prominent role.[4] Not surprisingly, the currently known small molecule CXCR4 antagonists are also highly basic in nature. A particularly notable example is the tetrahydroquinoline derivative AMD070 (Fig. 1) which was recently shown to possess significant anti-HIV efficacy in human clinical studies.[5] Key features of the AMD070 pharmacophore include a triad of basic nitrogen atoms and a distal amino group attached to the central nitrogen by a 4-carbon tether.

We recently reported a structure–activity study toward improving the antiviral potency and/or ADME properties of AMD070 through iterative structural modifications. Specifically, we showed that it was possible to shift the distal amine side chain from the central nitrogen to either ring of the benzimidazole with retention of potent antiviral activity (Fig. 1, compounds **1** and **2**).[6] In a separate report we described related efforts in which we replaced the benzimidazole with an imidazopyridine in combination with the side chain shift.[7] The results of these studies prompted us to explore the possibility of replacing the benzimidazole with other heteroaromatic ring systems capable of maintaining the required basic nitrogen triad.

* Corresponding author. Tel.: +1 919 483 2750; fax: +1 919 315 6923.
E-mail address: john.6.miller@gsk.com (J.F. Miller).

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doi:10.1016/j.bmcl.2010.03.118

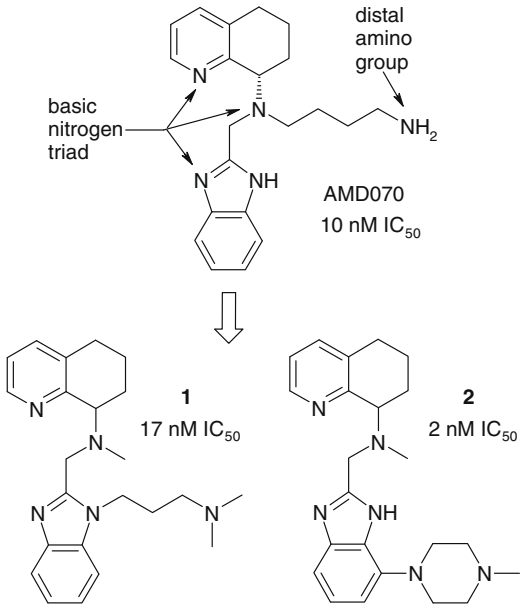
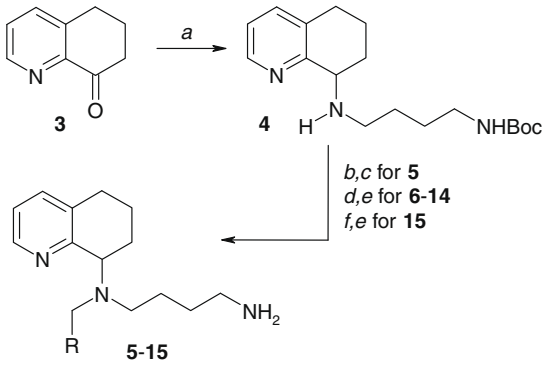


Figure 1. Tetrahydroquinolines with potent anti-HIV activity.

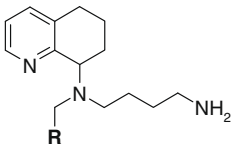
In order to identify viable alternative ring systems, we conducted a scan of various heteroaryl fragments with the distal amine side chain attached to the central nitrogen analogous to AMD070, with the exception that this study was done in the racemic series. Our synthetic approach is illustrated in Scheme 1. The key secondary amine intermediate **4** was synthesized by reductive amination of ketone **3**[8] with *N*-Boc-1,4-diaminobutane. The benzimidazole derivative **5** was prepared via alkylation with *N*-Boc-2-(chloromethyl)benzimidazole followed by TFA deprotection. Compounds **6**–**14** were prepared by reductive alkylations with the appropriate heteroaryl aldehydes followed by HCl mediated cleavage of the Boc protecting group. The benzothiazole analog **15** was synthesized by alkylation with 2-(bromomethyl)-1,3-benzothiazole followed by acidic deprotection.

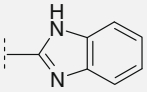
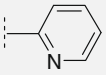
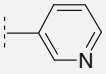
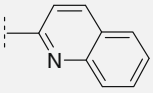
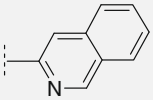
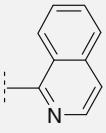
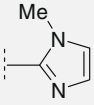
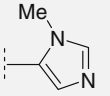
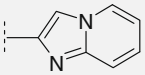
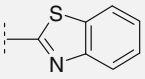
Antiviral and cytotoxicity data for the alternate lower heterocycle derivatives is shown in Table 1. Most of the ring systems studied retain appreciable antiviral activity with several in the same potency range as the benzimidazole derivative **5** (racemic version of AMD070). Exceptions include the 3-pyridyl and imidazole derivatives **7** and **12**, which due to the position of the basic ring nitrogens, are incapable of maintaining the required nitrogen triad



Scheme 1. Reagents and conditions: (a) *N*-Boc-1,4-diaminobutane, $NaBH(OAc)_3$, AcOH, 1,2-dichloroethane (73%); (b) *N*-Boc-2-(chloromethyl)benzimidazole, KI, $(iPr)_2EtN$, MeCN, rt (83%); (c) TFA, CH_2Cl_2 (71%); (d) RCHO, $NaBH(OAc)_3$, AcOH, 1,2-dichloroethane (55% for **6**); (e) 4 N HCl/dioxane, MeOH (62% for **6**); (f) 2-(bromomethyl)-1,3-benzothiazole, KI, $(iPr)_2EtN$, MeCN, 80 °C (59%).

Table 1
Anti-HIV IC_{50}s ± standard deviation (n) and CC_{50}s for alternate lower heterocycle derivatives



Compound	R	IC_{50}[a] (nM)	CC_{50}[b] (nM)
5[c]		23 ± 2 (4)	13,000
6[d]		70 ± 8 (4)	11,000
7		>20,000 (1)	>20,000
8[d]		34 ± 7 (2)	12,000
9		12 ± 1 (2)	13,000
10		11 ± 1 (2)	8200
11[e]		120 ± 3 (2)	>20,000
12		>20000 (2)	>20,000
13		42 ± 8 (2)	>20,000
14[d]		340 ± 29 (2)	9700
15[d]		200 ± 12 (2)	13,000

[a] HOS cells expressing hCXCR4/hCCR5/hCD4/pHIV-LTR-luciferase, HIV-1, CXCR4 strain (IIIB). Compounds were tested for their ability to block infection of the HOS cell line. IC_{50} is the concentration at which 50% efficacy in the antiviral assay was observed.[9]

[b] CC_{50} is the concentration at which 50% cytotoxicity is observed in the HOS cell line.

[c] Compound previously reported in Ref. 10.

[d] Compound previously reported in Ref. 11.

[e] Compound previously reported in Ref. 12.

geometry. The isoquinoline derivatives **8**–**10** were particularly interesting with antiviral activities in the 10–30 nM range. A comparison of these compounds with the pyridyl derivative **6**, shows that benzo ring fusion confers a consistent improvement in activity. Compounds **14** and **15** show reduced activities relative to the corresponding nitrogen analogs (i.e., **15** compared to **5**), perhaps due to the reduced basicity of the thiazole and benzothiazole ring nitrogens.