Bioorganic & Medicinal Chemistry Letters 19 (2009) 1610–1613

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

[2-(4-Phenyl-4-piperidinyl)ethyl]amine based CCR5 antagonists: derivatizations at the N-terminal of the piperidine ring

Maosheng Duan [a,*], Christopher Aquino [b], Robert Ferris [a], Wieslaw M. Kazmierski [a], Terry Kenakin [c], Cecilia Koble [a], Pat Wheelan [a], Chris Watson [c], Michael Youngman [a]

[a] Infectious Diseases Center for Excellence in Drug Discovery, GlaxoSmithKline, Five Moore Drive, Research Triangle Park, NC 27709, United States
[b] Metabolic Pathways Center for Excellence in Drug Discover, GlaxoSmithKline, Five Moore Drive, Research Triangle Park, NC 27709, United States
[c] Molecular Discovery Research, GlaxoSmithKline, Five Moore Drive, Research Triangle Park, NC 27709, United States

ARTICLE INFO

Article history:
Received 9 January 2009
Revised 30 January 2009
Accepted 3 February 2009
Available online 10 February 2009

Keywords:
CCR5
Antagonist
Derivatization
Antiviral

ABSTRACT

Several series of CCR5 antagonists have been discovered by derivatization at the N-terminal of the piperidine ring of the core template **2**. Some derivatives exhibited potent inhibition against HIV-1infection. The pharmacokinetic properties of the lead compounds **11a**, **14a**, **15b**, and **16b** have been evaluated in vivo.

Discovery of the Chemokine Receptor R5 (CCR5) as a co-receptor for HIV-1 infection revealed a novel approach to HIV-1 epidemic prevention and treatment.[1] CCR5, a member of the 7TM G-protein coupled receptor (GPCR) family, thus, became an attractive target pursued by the pharmaceutical industry. Significant research and development efforts have led to several small molecule clinic candidates[2] and one FDA approved drug.[3] CCR5 antagonists, a new class of viral entry inhibitors, offer great promise to be the next generation of anti-HIV medicines.

Our laboratories have previously reported the identification of a class of 4,4-disubstituted piperidine carboxamide CCR5 antagonists exemplified by **1**, demonstrating anti HIV-1 activity (Fig. 1).[4] In order to further explore the structure–activity relationship (SAR) of this class, we then derivatized the core template **2** at the N-terminal of its piperidine ring with a variety of functionalities, leading to the discovery of several potent series of CCR5 antagonists. Herein, we wish to report the syntheses and structure-activity relationship of these series.

Synthesis of **2** was initiated by preparations of 1-(8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (**3**) and Boc protected 4-(2-oxoethyl)-4-phenyl-1-piperidine (**4**) as depicted in Scheme 1. Following the literature procedures,[4] **3** was conveniently obtained from readily accessible materials. Preparation of **4** started from commercially available 4-phenyl-4-piperidinecarbonitrile hydrochloride (**5**). Boc protection of the piperdine ring, followed by Dibal-H reduction, afforded aldehyde **6**, thus, setting the stage for Wittig olefination with Ph_3PCH_2OMe. The resulting *Z/E* enol ether mixture **7** was then stirred with 90% formic acid at ambient temperature to produce the homologated aldehyde **4**. Its subsequent reductive amination with **3**, and the removal of Boc group made the core template **2** available (see Ref. 4 for *m*-F analog of **2**).

Derivatization of **2** started with nucleophilic displacements (Scheme 2). Thus, the treatment of **2** with 2-bromopyrimidine and *N,N*-diisopropylethylamine at elevated temperature gave **8a**. Tetrazole **8b** was synthesized via a two-step sequence. After installation of the cyano group to the nitrogen of the piperidine, efficient Bu_2SnO-catalyzed cyclization of the resulting nitrile with $TMSN_3$[5]

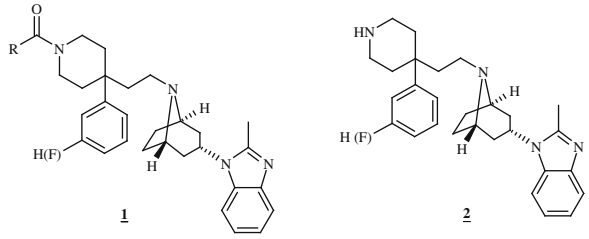
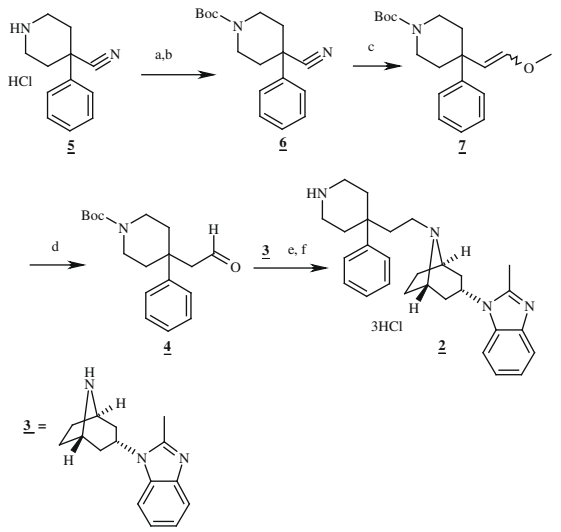


Figure 1. The carboxamide analog and the core template.

* Corresponding author. Fax: +1 919 483 6053.
E-mail addresses: maosheng.a.duan@gsk.com, duanmaosheng@hotmail.com (M. Duan).

0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.02.014



Scheme 1. Reagents and conditions: (a) Boc_2O, iPr_2NEt, CH_2Cl_2, rt, overnight, 99%; (b) *i*-Bu_2AlH, CH_2Cl_2, 0 °C, 1 h, then methanol, citric acid, 88%; (c) $Ph_3P^+CH_2OCH_3Cl^-$, NaHMDS, THF, −78 °C to 0 °C, 68%; (d) 90% formic acid, rt, 2 h, 99%; (e) **3**, $NaBH(OAc)_3$, CH_2Cl_2, rt, 3.5 h, 82%; (f) HCl, CH_2Cl_2, rt, 1 h, 99%.

led to **8b**. Methylene insertion analogues **8c–e** were secured by reductive amination of **2** with corresponding aldehydes (Scheme 2).

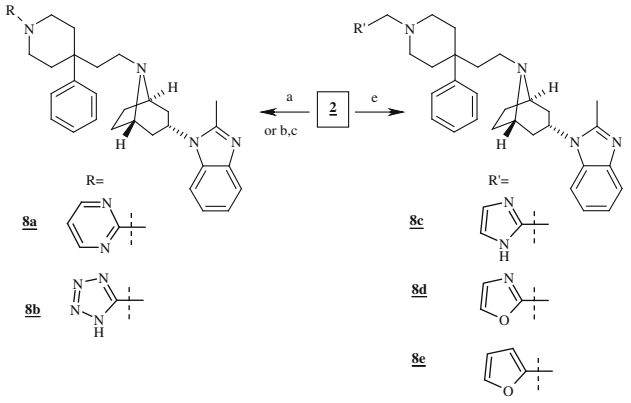
Syntheses of trisubstituted ureas were straightforward (Scheme 3). Commercially available isocyanates were reacted with **2** to give **9a–d**. *N,N,N′,N′*-tetrasubstituted ureas were obtained in a one-pot, two-step syntheses using phosgene. The in situ generated 4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinecarbonyl chloride was treated with secondary amines, delivering compounds **9e–f**. For the bulky *N,N*-diisopropyl amine derivative **9g**, the reaction sequence was reversed (Scheme 3).

Reaction of **2** with diphenylcyanocarbonimide under mild conditions afforded piperidinecarboximidoate **10**, which served as a precursor toward two different classes of compounds. Thus, in RONa/ROH (or RSNa/RSH) medium, displacement of the remaining phenoxy in **10** readily occurred to yield compounds **11a–c** and **12a–c**, respectively. Meanwhile, stirring **10** with amines produced *N*-cyano-*N′*-alkyl-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidine carboximidamides **13a–b** (Scheme 4).

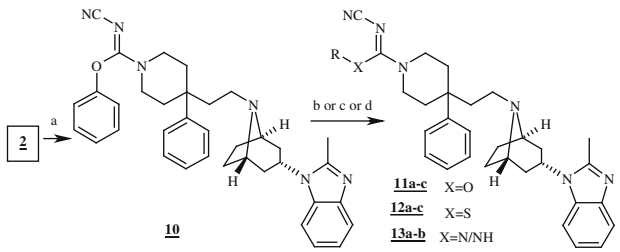
Amino acids **14a–g** were obtained by a three-component coupling from **2**, glycoxylic acid and aryl boronic acids under Petasis conditions.[6] Resulting amino acids were converted either into esters **15a–c** or amides **16a–c** by standard methods (Scheme 5).

All synthesized compounds were tested for both their ability to displace [^{125}I]-labeled MIP-1β from the CCR5 receptor expressed on CHO cell membrane[7] and their antiviral activity in HOS cell against the Ba-L strain of HIV-1.[8] The data are presented in Tables 1–5.

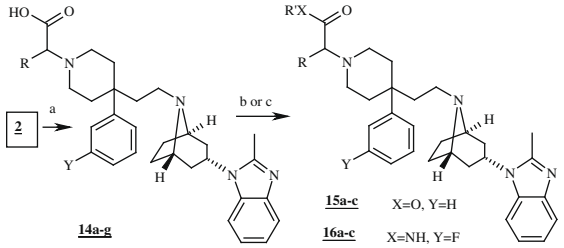
Installation of pyrimidine (**8a**) or tetrazole (**8b**) to the N-terminal of the piperidine ring in **2** decreased activities by ~10-fold as compared to the reported carboxamides,[4] while the analogues obtained via reductive amination (**8c–e**) showed improved binding potencies. Notably, **8e** had an IC_{50} = 3.0 nM in the MIP-1β binding



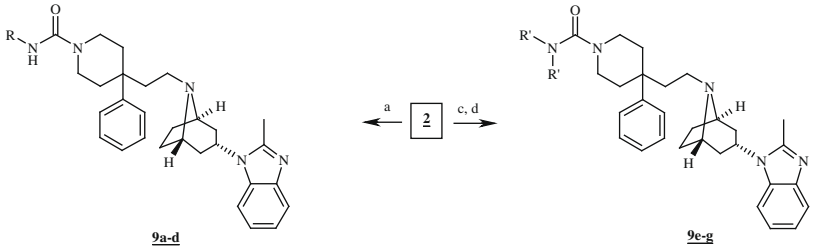
Scheme 2. Reagents and conditions: (a) 2-bromopyrimidine, iPr_2NEt, DMF, 80 °C, 2.5 h, 65%; (b) BrCN, K_2CO_3, $CHCl_3$, 61 °C, 4 h, 99%; (c) $TMSN_3$, Bu_2SnO, toluene, 90 °C, 6 h, 75%; (e) R′CHO, $NaBH(OAc)_3$, iPr_2NEt, CH_2Cl_2, rt, 3–4 h, 39–87%.



Scheme 4. Reagents and conditions: (a) diphenylcyanocarbonimide, Et_3N, CH_2Cl_2, rt, 4 h, 94%; (b) ROH/NaOR, rt, 1 h, 71–91%; (c) RSH/NaSR, rt, 1 h, 68–99%; (d) amine, MeOH, rt, overnight, 26–91%.



Scheme 5. Reagents and conditions: (a) glyoxylic acid monohydrate, $RB(OH)_2$, Et_3N, THF, rt to 50 °C, 4 h to 2 d, 71–94%; (b) $TMSCHN_2$, MeOH, rt, 1 h, 81–96%, (c) amine, HATU, Et_3N, DMF, rt, 2 h, 33–85%.



Scheme 3. Reagents and conditions: (a) RNCO, CH_2Cl_2, rt, overnight, 63–99%; (c) phosgene, iPr_2NEt, CH_2Cl_2, rt, 4 h; (d) R'_2NH, rt, overnight, 57–63%.

Table 1
Inhibitory potency of heterocycle analogues **8a–d** in the ^{125}I-[MIP-1β] binding assay and HOS cell assay (Scheme 2)

Compds	R	R′	MIP-1β IC_{50} (μM)	HOS IC_{50} (μM)
8a			0.32	1.91
8b			0.129	2.86
8c			0.074	1.79
8d			0.013	0.059
8e			0.003	0.035

Table 2
Inhibitory potency of urea analogues **9a–g** in the ^{125}I-[MIP-1β] binding assay and HOS cell assay (Scheme 3)

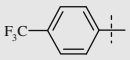
Compds	R	R′	MIP-1β IC_{5O} (μM)	HOS IC_{50} (μM)
9a			0.0040	0.0420
9b			0.0070	0.0270
9c			0.0060	0.1030
9d			0.2650	2.5690
9e		CH_3	0.0210	0.1220
9f		CH_3CH_2	0.0240	0.2400
9g			0.0180	0.1370

Table 3
Inhibitory potency of cyano-imido(thio)carbamates (**11a–c** and **12a–c**) and guanidines **13a–b** in the ^{125}I-[MIP-1β] binding assay and HOS cell assay[a] (Scheme 4)

Compds	R	X	MIP-1βIC_{50} (μM)	HOS IC_{50} (μM)
11a	CH_3	O	0.0020	0.0075
11b		O	0.0030	0.0255
11c		O	0.0070	0.0371
12a	CH_3	S	0.0230	n.t.
12b		S	0.0130	0.1014
12c		S	0.0400	0.0.094
13a	CH_3	NH	0.0110	0.1086
13b		N	0.0050	0.0207

[a] n.t.: not tested.

Table 4
Inhibitory potency of amino acid analogues **14a–g** in the ^{125}I-[MIP-1β] binding assay and HOS cell assay (Scheme 5)

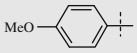
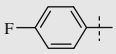
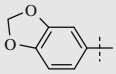
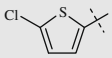
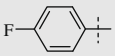
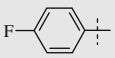
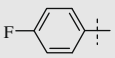
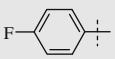
Compds	R	Y	MIP-1βC_{50} (μM)	HOS IC_{50} (μM)
14a		H	0.0080	0.0097
14b		H	0.0070	0.0248
14c		F	0.0040	0.0220
14d		H	0.0070	0.0292
14e		H	0.0050	0.0150
14f		H	0.0030	0.0068
14g		H	0.0230	0.0060

Table 5
Inhibitory potency of amino acid derivatives **15a–c** and **16a–c** in the ^{125}I-[MIP-1β] binding assay and HOS cell assay[a] (Scheme 5)

Compds	R	R′	MIP-Iβ IC_{50} (μM)	HOS IC_{50} (μM)
15a		CH_3	0.0050	0.0103
15b		CH_3	0.0009	0.0150
15c		CH_3	0.0130	0.2160
16a		H	n.t.	0.0520
16b		CH_3	n.t.	0.0202
16c		n-Bu	n.t.	0.7879

assay. This suggests that a direct attachment with rings may affect the conformation of the central piperidine for bindings. More flexible appendage may favor such interactions, which translate into improved antiviral activity (Table 1).

Trisubstituted ureas (**9a–c**) improved binding affinities dramatically, reaching single-digit nM levels. Surprisingly, **9d**, from the same group of the urea, had a binding IC_{50} 265 nM. The ~40-fold decrease in potency was presumably due to the replacement of aliphatic moiety with a highly hydrophobic *para*-trifluoromethyphe-

Table 6
Pharmacokinetics of the selected compounds **11a**, **14a**, **15b**, and **16b** in rat at 1 mg/kg

Compds	Cl (mL/min/kg)	$t_{1/2}$ (h)	V_{dss} (L/kg)	%F
11a	22.8	2.1	1	15
14a	117		3.5	0
15b	39.3	2.3	6.5	53
16b	43	6.1	16.5	37

nyl group. Despite their exceptional binding potency, the antiviral activity of the trisubstituted ureas need to be further enhanced. Meanwhile, the tetrasubstituted ureas (**9e–f**) were less impressive due to their relatively lower IC_{50}s in both the binding and antiviral assays (Table 2).

Cyano-imidocarbamates (**11a–c**) demonstrated comparable binding affinity to the trisubstituted ureas. Moreover, **11a** turned out to be highly potent in antiviral inhibition with HOS IC_{50} = 7.5 nM. Their thio counterparts (**12a–c**) and the cyano-guanidine analogues (**13a–b**) were, however, less active (Table 3).

Amino acids (**14a–g**) were a very promising series, which, in general, retained the binding potency in the single-digit nM range. Importantly, their potent binding affinities successfully translated into high antiviral activities as shown in Table 4 (**14a**, **14f**, and **14g**). In addition, it was observed that amino acid analogues helped to minimize hERG/QTc liabilities sometimes observed with related series discussed elsewhere (Kazmierski, Duan et al. manuscript in preparation) presumably due to the polarities of the amino acids. Conversion of selected amino acid analogues into esters (**15a–c**) or amides (**16a–c**) with the aim of improving cell permeability appeared to have no significant impact on the activity, except that relatively large amine was incorporated (**16c**) (Table 5).

The pharmacokinetics of lead compounds **11a**, **14a**, **15b**, and **16b** were evaluated in Sprague Dawley rats at 1 mg/kg using 5% mannitol with 0.05% acetic acid as dose vehicle. **11a** had acceptable clearance, but its bioavailability was moderate (15%). Disappointingly, **14a**, a representative of the most potent series had no oral exposure due to extremely high clearance and potentially poor permeability. Masking carboxylic acid functionality of **14c** either as an ester **15b** or as an amide **16b** did boost bioavailability, but their clearances remained high (Table 6).

In conclusion, several series of potent CCR5 antagonists have been discovered via derivatization at the N-terminal of the piperidine ring of **2**. All compounds were tested for both binding and antiviral activities. Amino acid derivatives have shown significant promise, but their PK properties need further improvement.

References and notes

1. Dragic, T.; Litwin, V.; Allaway, P. G.; Martin, R. S.; Huang, Y.; Nagashima, A. K.; Cayanan, C.; Maddaon, J. P.; Koup, A. R.; Morroe, P. J., et al *Nature* **1996**, *381*, 667.
2. Kazmierski, W. M.; Gudmundsson, K. S.; Piscitelli, S. C. *Annu. Rep. Med. Chem.* **2007**, *42*, 301.
3. Wood, A.; Armour, D. *Prog. Med. Chem.* **2005**, *43*, 239.
4. Kazmierski, W. M.; Aquino, C.; Chauder, B.; Deanda, F.; Ferris, R.; Jones-Hertog, D.; Kenakin, T.; Koble, C.; Watson, C.; Wheelan, P.; Yang, H.; Youngman, M. *J. Med. Chem.* **2008**, *51*, 6538.
5. Wittenberger, S. J.; Donner, B. G. *J. Org. Chem.* **1993**, *58*, 4139.
6. Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445.
7. Watson, C.; Jenkinson, S.; Kazierski, W.; Kenakin, T. *Mol. Pharmacol.* **2005**, *67*, 1268.
8. Jenkinson, S.; McCoy, D.; Kener, S.; Ferris, R.; Lawrence, W.; Fox, T.; Smith, C. *Recept. Channels* **2003**, *9*, 117.