Pergamon

Bioorganic & Medicinal Chemistry Letters 11 (2001) 3103–3106

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

# Design, Synthesis, and SAR of Heterocycle-Containing Antagonists of the Human CCR5 Receptor for the Treatment of HIV-1 Infection

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Received 19 June 2001; accepted 11 September 2001

**Abstract**—Replacement of the large hydantoin-indole moiety from our previous work with a variety of smaller heterocyclic analogues gave rise to potent CCR5 antagonists having binding affinity comparable to the hydantoin analogues. The synthesis, SAR, and biological profiles of this class of antagonists are described. 

The use of highly active anti-retroviral therapy (HAART) for the clinical control of HIV-1 infection has been highly successful at reducing disease progression as well as death rate. However, one can no longer assume that HAART will be consistently beneficial due to an alarming emergence of resistance (>30%) and the significant side effects associated with these treatments.[1] Thus, new, complementary, and better therapies are needed to help many patients whose treatment options are running out. The investigation of a new class of AIDS drug has been spurred by a series of recent reports on chemokines and chemokine receptors.[2,3] Recently, we reported the SAR of our early CCR5 benchmark compound (**I**), which was discovered by an extensive screening effort followed by SAR studies (Fig. 1).[4] Incorporation of a hydantoin-indole moiety together with a *N*-CBZ-group on the piperidine moiety led to potent CCR5 antagonists (**IIa**,**b**) as described previously (Table 1).[5] Even though this series of hydantoin-indole analogues (**IIa**,**b**) showed high CCR5 binding affinity, their relatively high molecular weight was a major drawback of that series. Thus, we turned our attention to relatively small-size heterocycles (e.g., B in **IIc**) as replacements of the large hydantoin-indole moiety.

Since the discovery of the importance of the *N*-CBZ group for both CCR5 binding and antiviral activity, this subunit has been employed throughout our SAR studies.[4,5] A general synthesis of several heterocyclic derivatives is shown in Schemes 1 and 2.

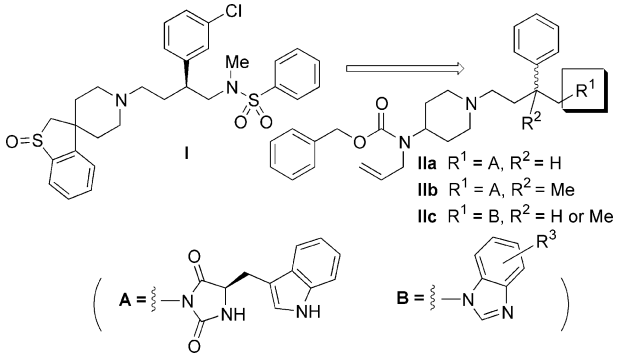


**Figure 1.** Replacement of the *N*-methylsulfonamide of **I** with heterocycles.

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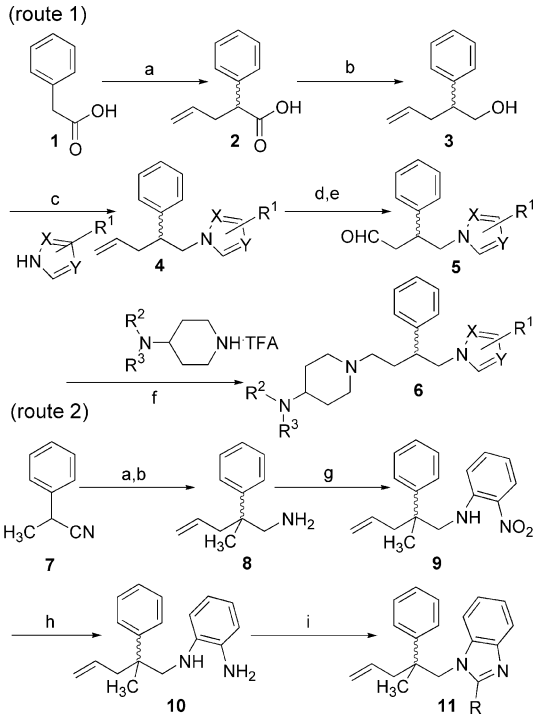
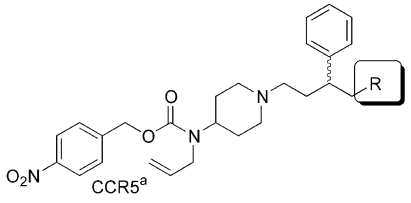
0960-894X/01/$ - see front matter 
PII: S0960-894X(01)00655-2

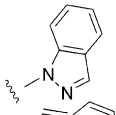
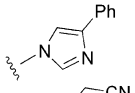
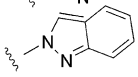
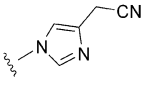
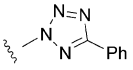
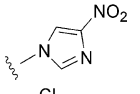
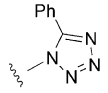
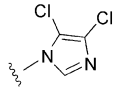
Allylation of phenylacetic acid **1** followed by reduction with LAH gave the primary alcohol **3**, which was coupled to a variety of heterocycles to give **4**. Cleavage of the olefin with ozone or catalytic $OsO_4$, followed by $NaIO_4$, gave the desired aldehyde **5**, which was used to reductively alkylate a variety of piperidines to give **6**. In the presence of the α-methyl group at the benzylic position, route 1 employing an $S_N2$ substitution of the triflate from alcohol **3** with heterocycles could not be used due to steric hindrance. Instead, neo-pentyl type amine **8** was used in a benzimidazole synthesis. Allylation of the α-methylbenzyl cyanide **7** followed by reduction afforded the primary amine **8**, which was reacted with *o*-fluoronitrobenzene to give the nitro compound **9**. Reduction of the nitro group followed by cyclization using orthoesters gave the benzimidazoles **11**. The synthesis of benzothiazepine **18** and isoindolone **21** is summarized in Scheme 2. Allylation of **12** followed by DIBAL reduction afforded aldehyde **13**. Reduction of the aldehyde **13** was followed by TBDMS protection to give **14**. Cleavage of the olefin followed by reductive amination gave the compound **16**. Deprotection of the TBDMS group followed by Swern oxidation gave the aldehyde **17**. Cyclization of **17** with 2-aminobenzenesulfonamide gave a diastereomeric mixture **18**, which was separated by flash chromatography. Isoindolone **21** was prepared following a procedure similar to that described in the literature.[6] The olefinic compounds (**11** and **21**) were cleaved and the resulting aldehydes were coupled to a variety of piperidines to give the desired compounds in Tables 2 and 3.



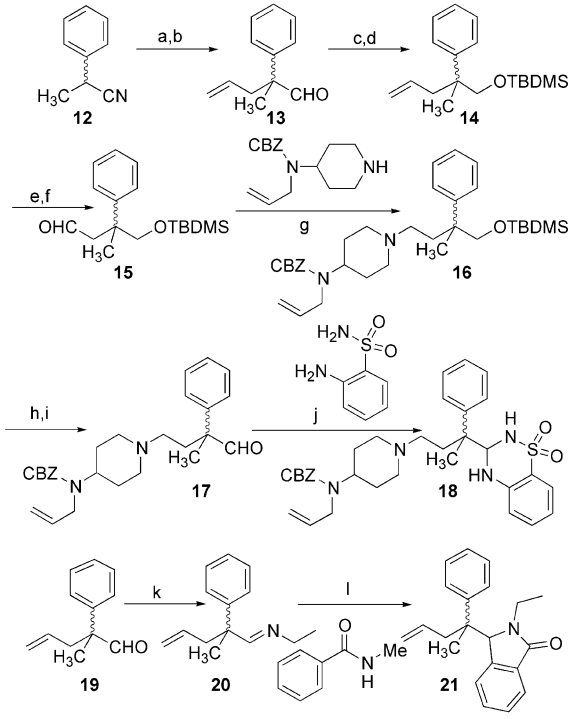

**Scheme 1.** Reagents: (a) LiHMDS, THF, −78 °C, then allyl bromide; −78 °C to rt; (b) LAH, THF; (c) $(CF_3SO_2)_2O$, 2,6-lutidine, $CH_2Cl_2$; (d) cat $OsO_4$, 4-methylmorpholine *N*-oxide, *t*-BuOH, $H_2O$, acetone; (e) $NaIO_4$, THF; (f) $NaBH(OAc)_3$, DIPEA, THF, molecular sieves, THF, rt; (g) 1-Fluoro-2-nitrobenzene, $K_2CO_3$, DMF, rt, 18 h; (h) $SnCl_2$, concd HCl, THF; (i) $CR(OMe)_3$, concd HCl.

**Table 1.** CCR5 antagonist activity of heterocycle analogues




| Entry | R | CCR5[a] $IC_{50}$ (nM)[b] | Entry | R | CCR5[a] $IC_{50}$ (nM)[b] |
|---|---|---|---|---|---|
| **22** |  | 15 | **26** |  | 23 |
| **23** |  | 27 | **27** |  | 15 |
| **24** |  | 111 | **28** |  | 15 |
| **25** |  | 335 | **29** |  | 16 |
| | | | **30** |  | 28 |

[a]See ref 4a for the procedure.
[b]The $IC_{50}$ results are an average of three independent titrations having calculated standard errors below 15%. The assay-to-assay variation was generally ±2-fold based on the results of the standard compound **I** (Fig. 1).




**Scheme 2.** Reagents: (a) LiHMDS, THF, −78 °C, then allyl bromide; −78 °C to rt; (b) DIBAL, $CH_2Cl_2$; (c) $LiBH_4$; (d) TBDMSCl; (e) $OsO_4$, NMMO, *t*-BuOH, $H_2O$, acetone; (f) $NaIO_4$, THF; (g) $NaBH(OAc)_3$, DIPEA, THF, molecular sieves, THF, rt; (h) $Bu_4NF$, THF; (i) $(COCl)_2$, DMSO, DIPEA, $CH_2Cl_2$; (j) NMP, 100 °C, 18 h; (k) ethylamine, $Bu_2SnCl_2$, $Na_2SO_4$, molecular sieves, $CH_2Cl_2$; (l) *n*-BuLi, THF, $BF_3{\cdot}OEt$, then 150 °C.

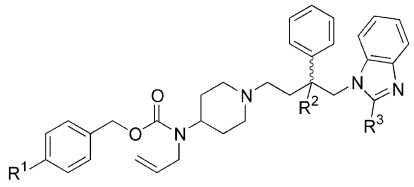
These compounds were then evaluated for CCR5 binding affinity utilizing a $^{125}$I-MIP-1α binding assay.[7] The $IC_{90}$s of selected compounds were evaluated in a 48 h single-cycle HIV (BAL) infection assay utilizing HeLa Magi cells expressing both CXCR4 and CCR5 as previously described.[8]

Tables 1–3 show the results for a series of compounds incorporating a variety of heterocycles in combination with the benzylic methyl group and the 4-$NO_2$ substitution on the *N*-CBZ, which showed potency enhancement in some cases.[4d,4e,5]

Indazole analogues (**22** and **23**) were found to possess activity comparable to that of the hydantoin analogue **IIa** ($IC_{50}$ = 7 nM), whereas the tetrazole analogues (**24** and **25**) showed sharply decreased activity. In both cases, the major isomers were more active than the minor isomers (**22** and **24**). Most of the imidazole analogues (**26**–**29**) were as active as the indazoles. It was notable that simple triazole analogue **30** also showed good CCR5 binding affinity.

The benzimidazole was chosen for further exploration (Table 2) with additional substitution at the benzylic position ($R^2$, Table 2) and on the imidazole ring. Incorporation of the 4-$NO_2$ group ($R^1$, in Table 2) on the CBZ moiety increased the binding affinity by 5- to 11-fold (**32**, **34**, and **36**), whereas introduction of either an α-methyl ($R^2$) or ethyl ($R^3$) resulted in a substantial loss of binding affinity (**33**–**35**, Table 2). While introduction of the benzylic methyl ($R^2$ = Me) was expected to give a substantial increase in CCR5 binding as seen in both the sulfonamide and hydantoin series (Fig. 1),[4e,5] in this situation the methyl resulted in a loss of binding affinity for both **35** and **36** compared to **31** and **32**. Presumably the closer proximity of the rigid benzimidazole to the methyl prevents its correct orientation in **35** and **36**, while the methyl beneficially orientates the more flexible sulfonamide moiety of **I** and the hydantoin of **IIa**,**b**. The viral spread assay results (Table 2) for selected compounds containing the heterocyclic moieties indicated that the nitro group in the *N*-CBZ increased the antiviral potency from > 3000 nM to 1000 nM (**31** vs **32**). Unfortunately, the previous beneficial effect of the benzylic methyl ($R^2$ = Me, Table 2) was not achieved for these benzimidazole

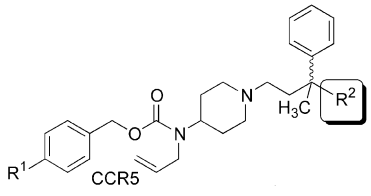
**Table 2.** CCR5 antagonist activity and antiviral activity of benzimidazole analogues

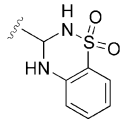
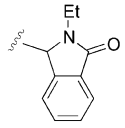
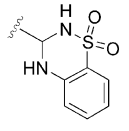
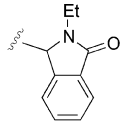


| Entry | $R^1$ | $R^2$ | $R^3$ | CCR5[a] $IC_{50}$ (nM)[b] | Viral Spread (nM) HeLa ($IC_{90}$)[c] |
|---|---|---|---|---|---|
| **31** | H | H | H | 25 | > 3000 |
| **32** | $NO_2$ | H | H | 4 | 1000 |
| **33** | H | H | Et | 246 | ND[d] |
| **34** | $NO_2$ | H | Et | 48 | 3000 |
| **35** | H | $CH_3$ | H | 112 | ND[d] |
| **36** | $NO_2$ | $CH_3$ | H | 10 | 1000 |

[a]See ref 4a for the procedure.
[b]The $IC_{50}$ results are an average of three independent titrations having calculated standard errors below 15%. The assay-to-assay variation was generally ±2-fold based on the results of the standard compound **I** (Fig. 1).
[c]See ref 8 for the procedure.
[d]Not determined.

**Table 3.** CCR5 antagonist activity of heterocycle analogues



| Entry | $R^1$ | $R^2$ | CCR5 $IC_{50}$[a] (nM)[b] | Entry | $R^1$ | $R^2$ | CCR5 $IC_{50}$[a] (nM)[b] |
|---|---|---|---|---|---|---|---|
| **37**[c] | H |  | 55 | **39**[c] | $NO_2$ |  | 10 |
| **38**[d] | H |  | 18 | **40**[d] | $NO_2$ |  | 18 |

[a]See ref 4a for the procedure.
[b]The $IC_{50}$ results are an average of three independent titrations having calculated standard errors below 15%. The assay-to-assay variation was generally ±2-fold based on the results of the standard compound **I** (Fig. 1).
[c]Higher $R_f$ isomer.
[d]Lower $R_f$ isomer.

derivatives. The viral spread assay results also indicated that the high potency in the CCR5 binding assay did not translate into high potency in the viral spread assay as in the previous case.[5] The origin of this discordant results is still under investigation.

Results on conformationally more restricted analogues, in which heterocycles were directly attached to the α-position, are shown in Table 3. High binding affinity was maintained in both benzothiazepine **38** and isoindolone **39**.

Compounds **31**–**36**, **38**, and **39** were all found to be selective CCR5 antagonists versus other chemokine receptors, such as CCR1, CCR2, CCR3, CCR4, and CXCR4 ($IC_{50}$ $>1000$ nM). Preliminary pharmacokinetic properties for the best benzimidazole compound **32** were determined in the rat and showed an improved 14% oral bioavailability and lower clearance rate of 49 mL/min/kg, compared to **IIb** (Fig. 1, 1% oral bioavailability and 84 mL/min/kg clearance),[9] one of the potent hydantoin analogues.

Replacement of the large hydantoin-indole moiety from our previous work was accomplished with the synthesis of a variety of smaller heterocyclic analogues. These heterocyclic derivatives were found to have binding affinity comparable to our hydantoin analogues **IIa**,**b**, with compound **32** being the most potent compound, having a 4-$NO_2$ in the *N*-CBZ group. Increasing antiviral activity in our series suggests that efficient inhibition of HIV-1 replication may be possible by further modification of potent heterocycle-based CCR5 antagonists with better understanding of the origin of the discordant results.

## References and Notes

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9. Average data generated after 2 mg/kg po and 0.5 mg/kg iv doses in $n=3$ animals/dose. The vehicle for iv and oral doses was PEG400/ethanol/water (20:20:60, v/v/v) and 20% hydroxypropyl β-cyclodextrin, respectively.