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Potent 1,3,4-trisubstituted pyrrolidine CCR5 receptor antagonists: effects of fused heterocycles on antiviral activity and pharmacokinetic properties

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Abstract—A series of 1,3,4-trisubstituted pyrrolidine CCR5 receptor antagonists containing a variety of fused heterocycles at the 4-position of the piperidine side chain has been discovered, which are orally bioavailable with potent anti-HIV activity.

The discovery of the β-chemokine receptor CCR5 as a co-receptor for HIV-1 infection has spurred recent intense research efforts directed toward the development of CCR5 antagonists as potential anti-HIV agents.[1] Furthermore, recent human genetic evidence supports CCR5 as a therapeutic target. Individual homozygous for a 32-base pair deletion in the gene for CCR5 lack this receptor on cell surfaces and are highly resistant to HIV-1 infection, while infected heterozygous individuals show significantly delayed progression to AIDS.[2]

Progress has already been made in identifying potent small-molecule CCR5 antagonists for use as therapeutic agents for the treatment of HIV-1.[3] Several CCR5 antagonists are currently under investigation as potential drugs. Recent reports from these laboratories have described 1,3,4-trisubstituted pyrrolidines containing acidic functionality at the *N*-position as potent CCR5 receptor antagonists with excellent anti-HIV activity in vitro.[4e] We have demonstrated that this class of zwitterionic pyrrolidines can display excellent antiviral activity, although with modest pharmacokinetic profiles, as exemplified by **1** (Fig. 1).[4]

Encouraged by these results, our efforts focused on modification of the phenylpropyl side chain in compound **1**. Of particular interest was the replacement of the phenylpropyl side chain with metabolically more stable heterocycles. The beneficial effect of heterocycles at this site on antiviral activity and pharmacokinetic properties has already been demonstrated.[5] Thus, we further developed the SAR of this series with a variety of fused heterocycles, which were expected to give more versatile positioning of nitrogen atoms around the rings. The effect of the spacer length between the fused heterocycle and the piperidine moiety on antiviral activity and pharmacokinetic properties was also examined herein (Fig. 1).

All of the pyrrolidine acid derived compounds in this paper were prepared by coupling pyrrolidine aldehydes through a reductive amination strategy with piperidines as reported earlier.[4] The synthesis of the pyrrolidine

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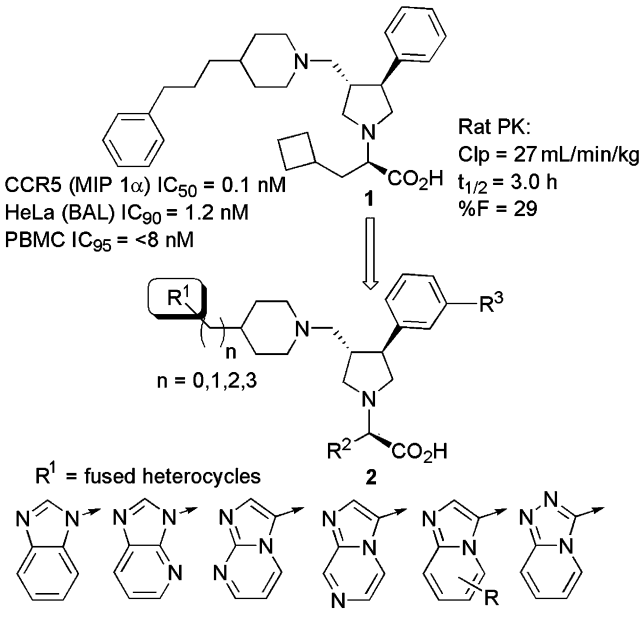


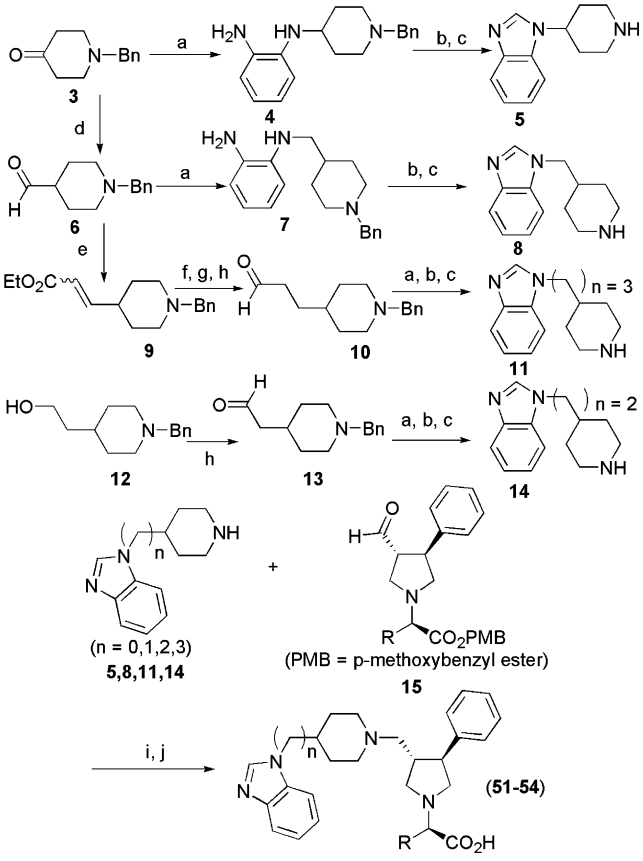
Figure 1. 1,3,4-Trisubstituted pyrrolidine CCR5 antagonists.

aldehydes **15** has been reported previously.[4e] Benzimidazole was chosen as the first fused heterocycle for examination and the requisite piperidine moieties bearing benzimidazoles with different spacer lengths were synthesized as described in Scheme 1.

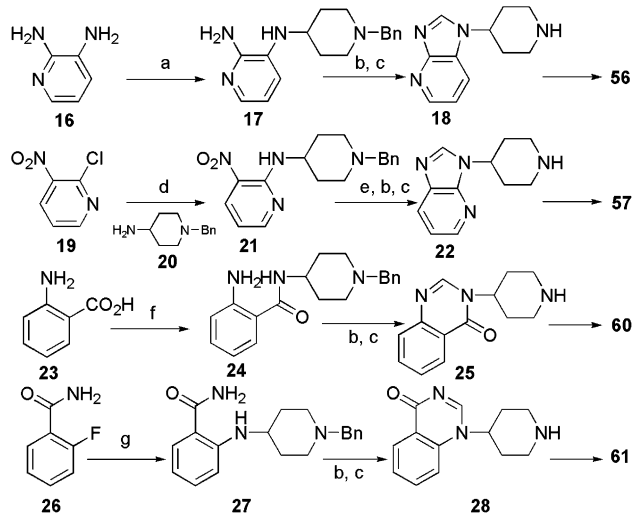
Reductive amination of *N*-benzylpiperidone **3** with 1,2-phenylenediamine followed by cyclization of **4** with trimethylorthoformate and debenzylation afforded the desired piperidine **5**. Treatment of *N*-benzylpiperidone **3** with TMS–diazomethane gave aldehyde **6**,[6] which was converted to ester **9** by the Horner–Emmons–Wittig reaction. Hydrogenation of **9** followed by LAH reduction and subsequent Swern oxidation of the resulting alcohol gave the two carbon extended aldehyde **10**. Swern oxidation of the commercially available alcohol **12** afforded aldehyde **13**. Aldehydes **6**, **10**, and **13** were converted to **8**, **11**, and **14**, respectively, following the same sequence as in the synthesis of **5**.

Next, our synthetic efforts focused on other fused heterocycles, which were directly attached to the piperidine moiety. The synthesis of the two sets of regioisomers, imidazopyridines (**56** and **57**)[7] and quinazolinones (**60** and **61**), are summarized in Scheme 2. Reductive amination of *N*-benzylpiperidone **3** with 1,2-diaminopyridine afforded **17**. Subsequent cyclization followed by debenzylation afforded imidazopyridine **18**. Displacement of the chlorine of **19** with **20** followed by reduction and the same sequence as above gave imidazopyridine **22**, the regioisomer of **18**. For the synthesis of quinazolinone analogs, acid **23** was coupled with **20** to afford **24** and displacement of the fluorine of **26** with **20** gave **27**. Cyclization of both **24** and **27** following the same sequence as above gave quinazolinones **25** and **28**, respectively.

The synthesis of fused heterocyclic analogs containing a nitrogen atom at the ring junction is described in

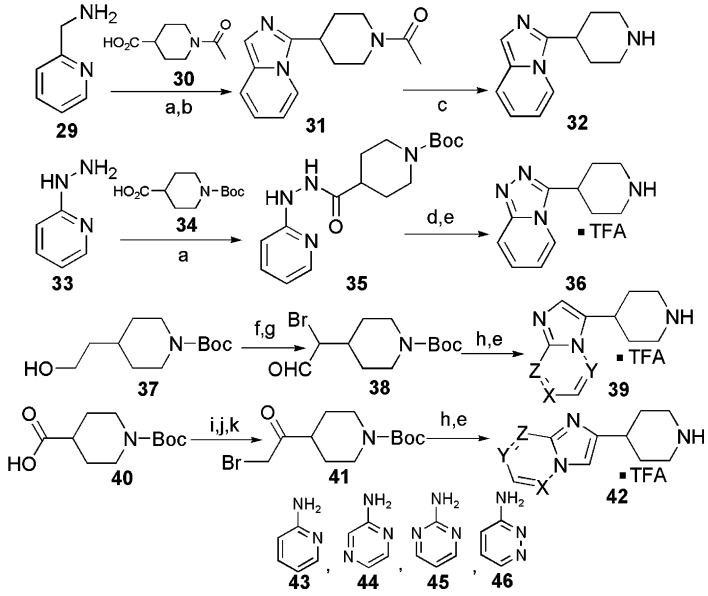


Scheme 1. Reagents and conditions: (a) 1,2-phenylenediamine, $NaBH(OAc)_3$, molecular sieves, CH_2Cl_2; (b) $CH(OMe)_3$, concd HCl, Δ; (c) 10% Pd/C, NH_4^+ $HCOO^-$, MeOH; (d) TMS–CHN_2, LDA, DIPEA; (e) $(EtO)_2POCH_2CO_2Et$, NaHMDS, THF; (f) 10% Pd/C, H_2 42 psi, EtOH; (g) LAH, THF; (h) Swern oxidation; (i) $NaBH(OAc)_3$, molecular sieves, CH_2Cl_2; (j) anisole, TFA.



Scheme 2. Reagents and conditions: (a) **3**, $NaBH(OAc)_3$, molecular sieves, CH_2Cl_2; (b) $CH(OMe)_3$, concd HCl, Δ; (c) 10% Pd/C, NH_4^+ $HCOO^-$, MeOH; (d) DIPEA, THF; (e) $SnCl_2$, concd HCl; (f) **20**, HOBT, EDC, CH_2Cl_2; (g) **20**, Na_2CO_3, DMSO.

Scheme 3. Amide coupling of **29** with acid **30** followed by cyclization in PPA at elevated temperature gave the



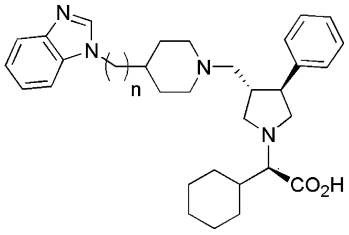
Scheme 3. Reagents and conditions: (a) HOBT, EDC, CH_2Cl_2; (b) PPA, 120 °C, 18 h; (c) 45% KOH, EtOH; (d) Ph_3PCl_2, Et_3N, CH_3CN; (e) TFA; (f) Swern oxidation; (g) $C_6H_5N(CH_3)_3Br{\cdot}Br_2$, THF, 0 °C, 45 min, 50%; (h) EtOH, reflux; (i) DCC, DMAP, NHMeOMe; (j) MeMgBr/ether; (k) LDA/TMSCl, then NBS.

desired imidazopyridine **31**.[8] Hydrazinopyridine **33** was coupled with acid **34**, then cyclized to give triazolopyridine **36**, according to a literature procedure.[9] While bromoaldehyde **38** afforded the fused heterocycle **39** with a variety of amino-substituted heterocycles **43–46**, bromoketone **41**[5b] gave the regioisomer **42**.[10]

For the synthesis of compound **68**, bromo-pyrazolopyrimidine **47**, prepared according to a known procedure,[11] was coupled with the vinyltin intermediate **48** to give **49**, which was reduced, then deprotected to give the target **50** as shown in Scheme 4.

Coupling of these piperidine intermediates (Schemes 1–4) with aldehyde followed by deprotection as described in Scheme 1 afforded the target compounds in Tables 1–4. Since previous work demonstrated that the cyclohexyl and cyclobutyl methylene (R^2) in structure **2** were essentially equivalent, our new piperidines were evaluated in either series.[4e] In addition, improved pharmacokinetics and activity of some 3-fluorophenyl analogs over phenyl analog (R^3 = F vs R^3 = H in structure **2**) led us to incorporate the 3-fluorophenyl group into the compounds shown in Tables 3 and 4.[4f,g,5b] The synthesized compounds were evaluated for CCR5 binding affinity in an assay that tested their ability to displace ^{125}I-MIP-1α from the human CCR5 receptor expressed on CHO cell membranes.[4a] The IC_{90} of selected compounds was evaluated in a 48 h single-cycle infection assay using HIV-1 (BAL) and utilizing HeLa Magi cells expressing both CXCR4 and CCR5 as previously described.[12] The CCR5 affinity and antiviral data for these compounds are presented in Tables 1–4. Table 1 shows the results for the benzimidazole analogs incorporating

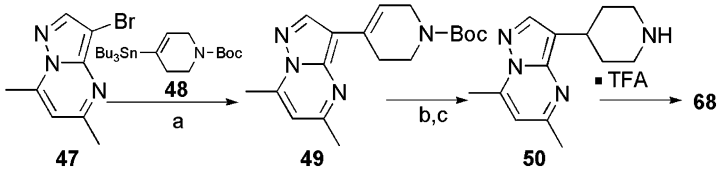
Table 1. Effect of spacer length on CCR5 antagonist activity and antiviral activity of benzimidazole analogs



Compd	*n*	CCR5[a] IC_{50} (nM)	HeLa[b] IC_{90} (nM)
51	0	2.5	11/100
52	1	6.3	100/>300
53	2	2.6	100/>300
54	3	0.84	1.2/33

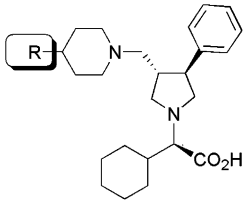
[a] The data are an average of three independent titrations having calculated standard errors below 15%. The assay-to-assay variation was generally ±2-fold. See Ref. 4a for assay protocol.

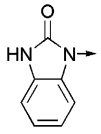
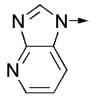
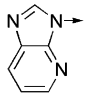
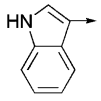
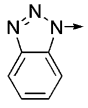
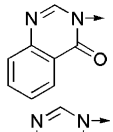
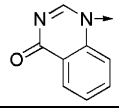
[b] IC_{90} values obtained in the HeLa cell antiinfectivity assay versus BAL in the absence and presence of 50% of human serum.[14]



Scheme 4. Reagents and conditions: (a) $Pd(II)(Ph_3P)_2Cl_2$, 1,4-dioxane; (b) H_2, 10% Pd/C, EtOH/EtOAc; (c) TFA, CH_2Cl_2.

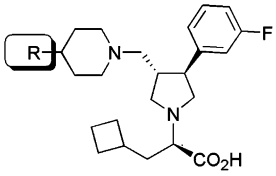
Table 2. CCR5 antagonist activity and antiviral activity of fused heterocyclic analogs

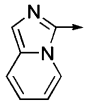
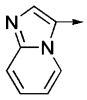
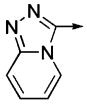
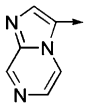
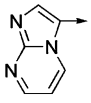
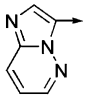
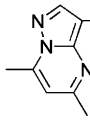
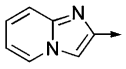
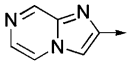
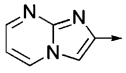


Compd	R	CCR5[a] IC_{50} (nM) (HeLa[b], IC_{90} (nM))
51		2.5 (11/100)
55		63 (ND)[c]
56		23 (ND)
57		2.8 (33/ND)
58		10 (ND)
59		8.2 (100/ND)
60		12 (ND)
61		100 (ND)

[a] See footnote a of Table 1.
[b] See footnote b of Table 1.
[c] ND = not determined.

Table 3. CCR5 antagonist activity and antiviral activity of fused heterocyclic analogs containing a nitrogen atom at the ring junction



Compd	R	CCR5[a] IC_{50} (nM) (HeLa[b], IC_{90} (nM))
62		13 (>300/>300)
63		0.42 (1.2/33)
64		12 (100/>300)
65		1.0 (11/100)
66		3.5 (33/100)
67		3.0 (11/300)
68		7.0 (>300/>300)
69		65 (ND)[c]
70		29 (300/300)
71		200 (ND)

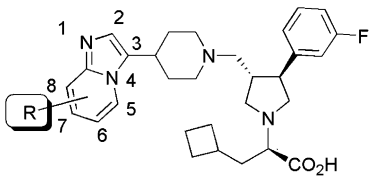
[a] See footnote a of Table 1.
[b] See footnote b of Table 1.
[c] ND = not determined.

various spacer lengths. Compound **54** ($n = 3$) showed excellent CCR5 antagonist activity ($IC_{50} = 0.84$ nM) as well as antiviral activity comparable to compound **1**. Interestingly, compound **51** without the spacer ($n = 0$) was found to possess the second best CCR5 and antiviral activity in this series, albeit less potent than compound **54**. Unfortunately, these two potent compounds (**51** and **54**) showed negligible oral bioavailability (<2%) in the rat.[13]

Encouraged by the results for **51**, fused heterocyclic systems directly attached to the piperidine moiety were investigated to further improve the CCR5 activity and PK profiles (Table 2). Among the seven new heterocyclic analogs in Table 2, only imidazo[4,5-*b*]pyridine analog **57** showed CCR5 affinity and antiviral activity comparable to benzimidazole **51**. Imidazopyridine **57** was ca. 8-fold more potent than its regioisomer **56**. Incorporation of a carbonyl into benzimidazole **51** resulted in substantial loss in activity (**60**, **61**).

More promising results were obtained with the fused heterocycle series containing a nitrogen at the ring junction (Table 3). Imidazo[1,2-*a*]pyridine **63**, the most potent CCR5 binding compound in this series, also showed an increase in the antiviral activity, compared to benzimidazole **51** and was the same as **54** (which contains the 3-carbon spacer). It was notable that the

Table 4. CCR5 antagonist activity, antiviral activity and pharmacokinetic parameters of imidazo[1,2-*a*]pyridine analogs[13]



Compd	R	CCR5[a] IC_{50} (nM)	HeLa[b] (BAL; IC_{90})	AUC (Norm)po (μM h kg/mg)	Clp (mL/min/kg)	$t_{1/2}$ (h)	%*F*
63	H	0.42	1.2/33	0.032	38	2.1	4
72	6-Ph	0.80	11/300	0.071	83	1.6	19
73	7-Et	0.35	0.13/11	0.053	67	2.5	11
74	6-Cl	0.89	1.2/100	0.524	16	0.7	26
75	6,8-Di-Cl	0.50	33/>300	0.576	20	0.4	39
76	6-F	0.30	3.7/300	0.660	19	0.8	38
77	6-CF_3	0.82	11/300	0.415	18	0.8	26
78	6-NO_2	0.60	100/300	0.178	120	0.2	61

[a] See footnote a of Table 1.
[b] See footnote b of Table 1.

imidazopyridine **63** was ca. 30-fold more potent than its regioisomer **62**. Incorporation of an additional nitrogen atom at various positions around the imidazopyridine ring resulted in a gradual loss in CCR5 activity (**64**–**67**). Regioisomers derived from bromoketone **41** exhibited decreased CCR5 activity compared to their corresponding analogs (**69**–**71**), suggesting that the angle between heterocycles and the piperidine ring plays an important role in the CCR5 binding. Pyrazolopyrimidine analog **68** showed disappointing antiviral activity despite its CCR5 potency (IC_{50} = 7 nM). Although the most potent imidazo[1,2-*a*]pyridine analog **63** lacked oral bioavailability (%F = 4), attractive features exhibited by the series, the extremely high CCR5 antagonist activity and antiviral activity, led us to further develop the SAR of this imidazo[1,2-*a*]pyridine series. As expected, most imidazo[1,2-*a*]pyridine analogs showed subnanomolar CCR5 activity as well as excellent antiviral activity (Table 4). Analogs with a phenyl-, ethyl-, or nitro-substituent (**72**, **73**, and **78**) suffered from rapid clearance, whereas analogs with halogens or a CF_3 group (**74**–**77**) showed somewhat lower clearance in the rat.[12] These four analogs (**74**–**77**) showed reasonable oral exposure and good oral bioavailability in the range between 26% and 39%, albeit with relatively short half-lives (<1 h). We had previously seen some off-target activity (L-type Ca^{2+} ion channel activity being representative) in pyrrolidine-based CCR5 antagonists.[4e,5c] Selected compounds from the current series (**63**, **74**, and **77**) were examined, with the results showing improved selectivity (IC_{50} or K_i > 10 μM) against the L-type Ca^{2+} channel over compound **1** (IC_{50} = 2.7 μM) as well as some related pyrazolylpiperidine analogs.[4e,5b,c] While compound **63** showed an IC_{50} of 2.7 μM in the hERG K^+ assay, improved selectivity was observed with trifluoromethyl substituted compound **77** (IC_{50} > 10 μM).

In conclusion, replacement of the phenylpropyl moiety of compound **1** was accomplished with the synthesis of a variety of fused heterocyclic analogs. These heterocyclic analogs were found to have binding affinity and antiviral activity comparable to **1**. Although the rat PK profiles of most of these compounds in these series were not adequate, analogs **74**–**77** exhibited promising PK profiles in the rat. Reports on further improvement of the pharmacokinetic profiles of pyrrolidine-derived CCR5 antagonists utilizing a different heterocyclic series will follow in due course.

Acknowledgements

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References and notes

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14. The data are generally the result of a single experiment and are the lowest test concentration for which >90% inhibition was observed. The assay-to-assay variation of a standard test compound was generally ±3-fold.