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Syntheses and SAR studies of 4-(heteroarylpiperdin-1-yl-methyl)-pyrrolidin-1-yl-acetic acid antagonists of the human CCR5 chemokine receptor

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Abstract—Efforts toward the exploration of the title compounds as CCR5 antagonists are disclosed. The basis for such work stems from the fact that cellular proliferation of HIV-1 requires the cooperative assistance of both CCR5 and CD4 receptors. The synthesis and SAR of pyrrolidineacetic acid derivatives as CCR5 antagonists displaying potent binding and antiviral properties in a HeLa cell-based HIV-1 infectivity assay are discussed.

1. Introduction

During the past two decades the global HIV/AIDS epidemic has had a devastating impact both in social and economic terms. The current multiple drug-cocktail therapies have stabilized AIDS in the US, but a resurgence is being experienced today due to increasing incidences of drug resistant viruses. Thus, there is genuine need to explore newer strategies to confront HIV-1 infection and proliferation.

Earlier work had identified the two chemokine receptors, CCR5 and CXCR4, as co-receptors along with CD4 for the entry of macrophage-tropic and T-cell tropic strains of HIV-1, respectively.[1–3] It was subsequently discovered that certain individuals homozygous for a 32-base pair deletion in the gene for CCR5 show no expression of this receptor on their cell surfaces and are thus highly resistant to HIV-1 infection.[4,5] These observations provided compelling evidence that a suitable small molecule CCR5 receptor antagonist might have potential in the treatment of HIV-1 infection and/or prevention.

Rapid strides made during the past few years toward the development of CCR5 receptor antagonists have resulted in several publications from many laboratories.[6,7] A recent communication from this laboratory showed that compounds incorporating a 1,3,4-trisubstituted pyrrolidine ring scaffold (**1**) were potent CCR5 antagonists.[8a] During further development of this lead class we sought a more selective agent by restricting the free movement of the propyl side chain in **1a** by incorporation of several heterocyclic spacers. It was hoped that such a modification (**2**) might provide agents with better antiviral and pharmacokinetic properties. Evidence of the beneficial aspects of a heterocyclic spacer was seen the case of pyrazoles (**1b**) as recently reported.[8b–d]

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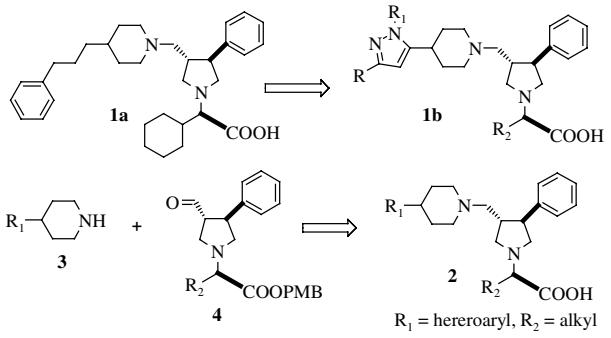


2. Chemistry

The strategy for the synthesis of derivatives related to **2** involved the reductive amination of novel 4-heterocyclic piperidines **3** with the requisite pyrrolidine aldehydes **4** in the key step as previously reported for **1**.[8] The syntheses of several piperidine analogs **3** bearing a variety of heterocyclic rings at C-4 are briefly discussed below.

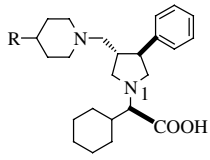
The preparation of the isomeric 3- and 5-phenyl-1,2-oxazole derivatives **6** and **7** (entries **30** and **31**, Table 1) was straightforward by literature methods.[9] The 1,3-dipolar addition of the respective nitrile oxide (derived from oxime **5**) and the requisite acetylene as shown in Scheme 1 gave either **6** or **7** after deprotection of the *N*-Boc with HCl in methanol.

Scheme 2 details the preparation of the 4-phenyl imidazole **11** (entry **32**, Table 1) by a literature method,[10] which involved lithiation of **8** followed by reaction with *N*-Boc piperidone to afford **9**. Dehydration of **9** followed by catalytic hydrogenation resulted in **10**. Removal of the protecting groups on **10** using standard protocols then afforded **11**.

The synthesis of the isomeric 2-phenyl imidazole **14** is shown in Scheme 3 (entry **33**, Table 1). A three-step sequence starting from acid **12a**, which involved formation of the acid chloride, reaction with diazomethane, and then decomposition of the intermediate diazoketone with hydrogen bromide (gas) afforded α-bromoketone **13**. Reaction of **13** with benzamidine, followed by saponification of the benzoyl, afforded **14**.

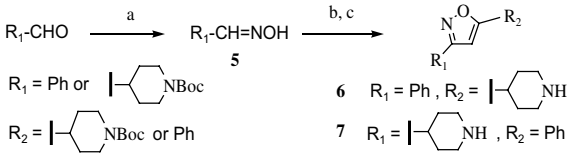
Interestingly, an analogous reaction of **13** with phenylacetamidine followed by saponification failed to yield the homologous 2-benzyl imidazole product. Alternatively, the imidazole **17** (entry **35**, Table 1) was synthesized (Scheme 4) via the *N*-Boc protected α-bromo compound **15**. We anticipated that the *N*-Boc in **15** would allow for easier N-deprotection in the final step. The three-step procedure from acid **12b** (as the *N*-Boc) involving Weinreb amide formation, addition of methyl Grignard, and α-bromination yielded **15**. Reaction of **15** with commercially available 2,6-diclorophenylacetamidine gave benzyl **16** after transfer hydrogenation to remove the chloro substituents. Finally, the *N*-Boc removal, now under standard acidic conditions, afforded the desired **17**.

Table 1. CCR5 binding/antiviral activity of heterocycle modified pyrrolidineacetic acid analogs[14]



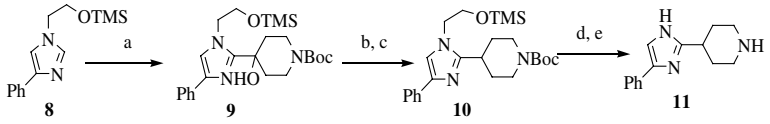
R	Entry	Binding IC_{50} (nM)	HeLa IC_{90} (nM)
	**30**	18.1	ND
	**31**	27	ND
	**32**	23	ND
	**33**	6.2	33
	**34**	1.1	100
	**35**	0.67	ND
	**36**	1.3	33
	**37**	2.0	33
	**38**	0.29	0.14
	**39**	1.5	100

ND = Not determined.

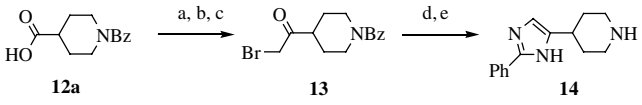


Scheme 1. Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, Py, rt; (b) $(n\text{-}Bu_3Sn)_2O$, *t*-BuOCl, and R_2CCH; (c) HCl, MeOH.

The *N*-Boc imidazole **16** was further functionalized (Scheme 5) to yield **18** and **20**, which were necessary to complete the SAR within this imidazole class (entries **49** and **50**, Table 3) Thus, **16** underwent electrophilic substitution with either NCS or iodine to furnish **18** (after *N*-Boc removal) or **19**. The iodo compound **19** under-



Scheme 2. Reagents and conditions: (a) *n*-BuLi/THF, then *N*-Boc-piperidone; (b) MsCl, DIPEA, CH_2Cl_2; (c) PtO_2/EtOH, H_2; (d) TBAF, THF; (e) HCl, MeOH.



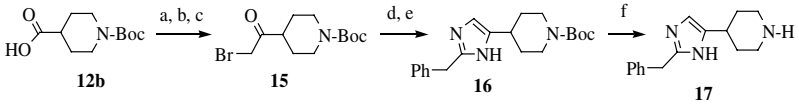
Scheme 3. Reagents and conditions: (a) $SOCl_2$; (b) CH_2N_2/ether; (c) HBr (gas); (d) benzamidine, $CHCl_3$, reflux; (e) KOH, MeOH.

went a three-step sequence that involved vinylation, catalytic reduction, followed by deprotection to furnish **20**.

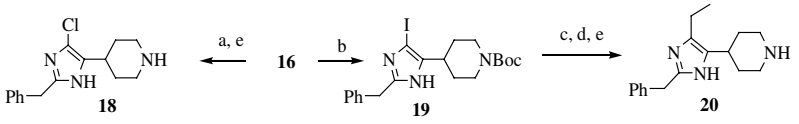
The preparation of the 1,3-thiazoles (entries **34** and **36**, Table 1) was accomplished by literature methods[11] starting from the appropriate α-bromoketone and thioamide as was accomplished in Scheme 4. The isomeric thiazole analog **24** (entry **37**, Table 1) and its 4-ethyl analog **25** (entry **52**, Table 3) were prepared (Scheme 6) by nitroaldol reaction of **21** with nitromethane or 1-nitropropane to furnish aminols **22** after catalytic reduction. The aminols **22** were then acylated and oxidized to afford **23**. The ketoamides **23** underwent smooth cyclodehydration with Lawesson's reagent to furnish **24** and **25** after the usual Boc deprotection.

General approaches to the preparation of the 2-benzyl-1,3-oxazoles **28** and **29** (entries **39**, Table 1, and **51**, Table 3) are shown in Scheme 7.[12] Addition of vinyl magnesium bromide to aldehyde **21** followed by reaction with phenylacetic acid under DCC/DMAP conditions provided the ester **26**. Ozonolysis of **26** followed by a reductive workup gave the intermediate aldehyde or ketone, which on refluxing with ammonium acetate afforded the oxazoles **27**. Removal of the *N*-Boc protection of **27** then gave desired products **28** and **29**.

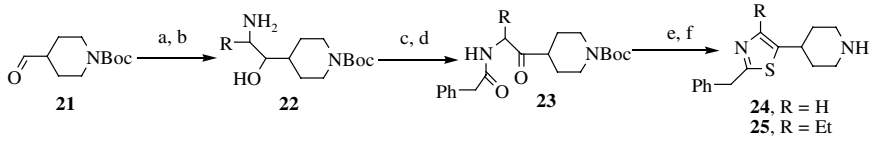
The synthesized heterocyclic compounds discussed above were reductively aminated with **4** and in one or



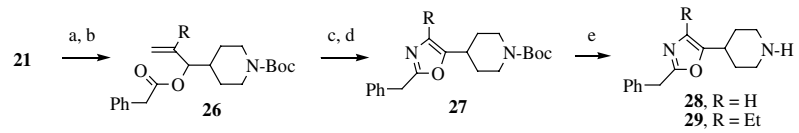
Scheme 4. Reagents and conditions: (a) DCC, DMAP, NHMeOMe; (b) MeMgI/ether; (c) LDA/TMSCl, then NBS; (d) 2,6-dichloro-phenylacetamidine, $CHCl_3$, reflux; (e) Pd/C, ammonium formate, AcOH/water; (f) EtOAc/HCl.



Scheme 5. Reagents and conditions: (a) NCS, $CHCl_3$, reflux; (b) I_2/NaOH, THF; (c) vinyltin, $Pd(PPh_3)_4$, DMF, 110 °C; (d) Pd/C, H_2, MeOH; (e) EtOAc/HCl.

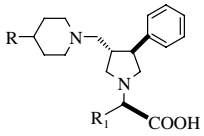


Scheme 6. Reagents and conditions: (a) RCH_2NO_2, DBU THF; (b) Pd/C, MeOH, H_2; (c) $PhCH_2COOH$, DCC/DMAP, CH_2Cl_2; (d) chromic acid/ether; (e) Lawesson's reagent; (f) EtOAc/HCl.



Scheme 7. Reagents and conditions: (a) vinyl grignard, THF; (b) phenylacetic acid, DCC/DMAP, THF; (c) O_3, MeOH/CH_2Cl_2, −78 °C, then PPh_3, rt; (d) ammonium acetate, AcOH, reflux; (e) EtOAc/HCl.

Table 2. CCR5 binding activity of alkyl substituted pyrrolidineacetic acid analogs[14]



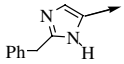
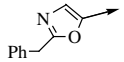
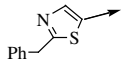
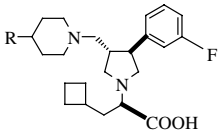
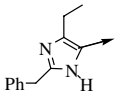
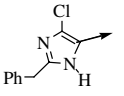
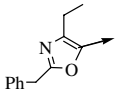
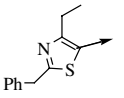
R	R_1	Entry	Binding IC_{50} (nm)	HeLa IC_{50} (nM)
	i-Pr	**40**	7.0	300
		**41**	0.73	100
		**42**	0.38	100
	i-Pr	**43**	3.8	300
		**44**	1.6	3.7
		**45**	0.34	3.7
	i-Pr	**46**	0.51	11
		**47**	0.23	0.13
		**48**	0.23	0.13

Table 3. CCR5 binding activity of cyclobutylmethyl substituted pyrrolidineacetic acid analogs[14]



R	Entry	Binding IC_{50} (nM)	HeLa IC_{50} (nM)
	**49**	0.57	0.4
	**50**	0.60	0.13
	**51**	0.89	0.13
	**52**	0.76	0.13

more subsequent steps[8] (i.e., deprotection of pyrrolidineacetic acid) afforded the products listed in Tables 1–3, the SAR of which are discussed below.

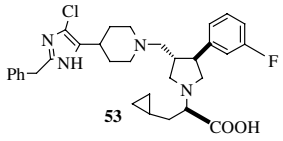
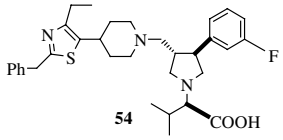
3. Results and discussion

The synthesized compounds were routinely screened for both CCR5 binding affinity and inhibition of viral infectivity (HeLa assay) and the results are summarized in Tables 1–3. The CCR5 receptor binding assay utilized ^{125}I-MIP-1α as the ligand and the results are given as IC_{50}'s (nM).[12,13] The HIV-1 infectivity assay utilized HeLa Magi cells that expressed both CXCR4 and CCR5 receptors and the results are expressed with the more stringent IC_{90}'s (nM).[14,15] The SAR for these analogs was initially centered on the modification of the heterocyclic moiety at C-4 of the piperidine and selected alkyl substituents at the acetic acid appendage on the pyrrole nitrogen. The results of these two modifications were then later incorporated to generate hybrid analogs that also incorporated additional substituents at the heterocyclic ring. Accordingly, initial results from the placement of various heterocycles on the piperidine ring at C-4 are shown in Table 1. Notice that all the compounds displayed in Table 1 had the cyclohexylacetic acid substituent at the pyrrolidine nitrogen.

Relative comparison of the binding potency among the first 4 entries (**30**–**33**) in Table 1 clearly indicates that the 2-phenylimidazole analog (**33**) was 3–4-fold more potent than the other analogs. The imidazole **33** also exhibited a modest activity in the HeLa antiviral assay ($IC_{90} = 33$ nM). The surprising result was the 2-phenyl-1,3-thiazole (**34**), which showed binding affinity that was significantly better than **33**, however, it was 3-fold less potent in HeLa antiviral assay. Both oxazole isomers **30** and **31**, as well as the isomeric 4-phenylimidazole analog **32** were comparatively less potent. The impressive binding potencies observed for **33** and **34** led us to explore these derivatives further with the preparation of the benzyl analogs **35**–**36**, the isomeric benzyl thiazoles **37**–**38**, and 1,3-oxazole **39**. These benzylic analogs uniformly displayed superior binding affinity with the imidazole **35** and thiazole **38** now displaying binding affinities in the sub-nanomolar range. Relative comparison of the thiazole analogs **34** and **36** indicated that going from the phenyl to benzyl did not make much difference in the binding affinity, but the antiviral activity for **36** was 3-fold better. The beneficial effect on the binding affinity of the benzyl replacement for phenyl appeared to also be borne out by the other isomeric thiazole analogs **37** and **38** and the 5-benzyl-1,3-oxazole **39**.

It is interesting to observe from Table 1 that high binding affinity was not sufficient for good antiviral activity, or at least not until sub-nanomolar binding was achieved as with **38**. This suggests that additional factors such as protein binding, cell wall penetration or other mechanisms may also be involved. The observation was also made that a nitrogen lone pair at the 3 position relative to the piperidine linkage, as well as the benzylic substitution at the 4 position, was critical for both binding and antiviral activities.[8b] In light of these observations and the impressive CCR5 binding and HeLa antiviral activity of **38**, we were encouraged to further optimize the antiviral activity based on the pyrrolidineacetic acid substitution. These efforts led to the preparation of analogs in the 2-benzylimidazole, 2-benzyl-1,3-oxazol-5-yl, and 2-benzylthiazol-5-yl series as shown in Table 2.

Modification at the acetic acid end for each heterocycle involved the incorporation of three specific substituents: namely, the *iso*-propyl, cyclopropylmethyl, and cyclo-

	Binding IC_{50} (nM)	HeLa IC_{50} (nM)	Cl*p* (mL/min/kg)	V_{dss} (L/kg)	$t_{1/2}$ (h)	% *F*
 **53**	0.7	0.4	60.5	1.05	0.53	1.1
 **54**	1.0	0.13	10.15	0.54	0.84	19

butylmethyl groups, respectively. The results for these analogs (**40**–**48**, Table 2) were compared with the analogous heterocyclic compounds in the cyclohexyl series (Table 1).[8a] In the imidazole series, while the *iso*-propyl analog **40** lost potency in both the binding and antiviral assays, the cyclopropylmethyl **41** and cyclobutylmethyl **42** by and large retained the binding potency of **35** and showed moderate antiviral activity in the HeLa assay. The *iso*-propyl oxazole analog **43** mimicked the imidazole **40** with respect to loss of binding potency. However, the analogs **44** and **45** displayed both good affinity and an impressive 25-fold gain in the anti-HIV activity. The gain in the antiviral potency for the corresponding thiazole analogs **47** and **48** was even more dramatic by two orders of magnitude. Interestingly, even the *iso*-propyl **46** showed desirable activity. This result would prove important for PK reasons as discussed below. Thus, it appeared from Table 2 that the presence of the smaller alkyl groups of these analogs lead to significant enhancement in antiviral activity with little or no compromise in the binding activity. These results were then incorporated into additional analogs wherein the heterocyclic ring was further derivatized with a chloro or ethyl as shown in Table 3.[8b] We also replaced the unsubstituted phenyl group on the pyrrolidine ring with a 3-fluorophenyl, which had been demonstrated to enhance the metabolic stability for this pyrrolidine scaffold.[8a,b]

A comparison of the imidazole analogs **49** and **50** with **42** (Table 2) indicates that both the ethyl and chloro substituents had remarkable effects (several fold!) in enhancing the antiviral properties that we had not seen previously for these compounds. The oxazole compound **45** also benefited by the placement of an ethyl substituent as in **51**. However, the presence of ethyl group on the thiazole compound **52** was not able to further enhance the antiviral properties of **47** and **48**. Subsequently, we realized that these substituted heterocycles in combination with an *iso*-propyl or cyclopropylmethyl moiety would suffice to generate potent analogs with improved PK properties. Shown above are two additional compounds, **53** and **54**, that were subsequently evaluated for their PK profiles in the rat.

Both **53** and **54** had comparable potency and are perhaps much more potent than other leading CCR5 antagonists in the literature. The rat pharmacokinetics studies (IV and PO) indicated that the imidazole **53** still suffered from a high clearance and short half-life. However, **54** appeared better as characterized by its lower clearance and good oral bioavailability.

In conclusion, in lieu of the 3-phenylpropyl-side chain of **1a**, a variety of heterocyclic scaffolds, in addition to the pyrazole of **1b**, were found to afford very potent compounds in both CCR5 binding and in a HIV-1 HeLa cell-based infectivity assay. Furthermore, we have confirmed that with the placement of appropriate substituents on the heterocycle and with the proper choice of alkyl substitution at the acetic acid side chain increased antiviral potency and improved pharmacokinetics can be achieved.

Acknowledgements

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