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# 1,3,4-Trisubstituted Pyrrolidine CCR5 Receptor Antagonists: Modifications of the Arylpropylpiperidine Side Chains

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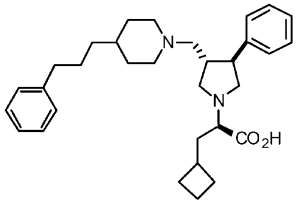
**Abstract**—The 4-(3-phenylprop-1-yl)piperidine moiety of the 1,3,4-trisubstituted pyrrolidine CCR5 antagonist **1** was modified with electron deficient aromatics as well as replacement of the benzylic methylene with sulfones, *gem*-difluoromethylenes and alcohols in an effort to balance the antiviral potency with reasonable pharmacokinetics.


Since the discovery of the chemokine receptor CCR5 as a co-receptor for HIV infection, numerous research groups have pursued CCR5 antagonists as novel agents for the treatment and/or prevention of HIV infection.[1–3] Previous reports from these laboratories described a series of 1,3,4-trisubstituted pyrrolidine[4] and bicyclic isoxazolidine[5] CCR5 antagonists as potent antivirals against HIV. Recently, we disclosed zwitterionic pyrrolidines as bioavailable and selective CCR5 antagonists.[6,7] For example, pyrrolidine **1**, which contains the 4-(3-phenylprop-1-yl)piperidine moiety and the 3-(cyclobutyl)propionic acid *N*-1 substituent, possessed potent antiviral activity and a good pharmacokinetic profile in rodents. To further explore the balance of pharmacokinetics with antiviral activity, this paper will present analogues containing electron deficient 4-(3-phenylprop-1-yl)piperidine subunits as well as compounds incorporating oxygen, sulfur, fluorine, and phosphorous functionality at the benzylic position of the propyl linker within the piperidine side chain.




**1**

CCR5 (MIP 1α) $IC_{50}$ = 0.1 nM
HeLa (BAL) $IC_{90}$ = 1.2 nM
PBMC $IC_{95}$ = <8 nM

Rat Pharmacokinetics
$Cl_p$ = 26.5 mL/min/kg
$t_{1/2}$ = 3.0 h
%F = 29

The synthetic approach for assembling these compounds through a reductive amination with the desired piperidine has previously been described.[7] The required piperidines were synthesized using chemistry presented in Schemes 1–7. Since it had previously been demonstrated that electron withdrawing substituents could enhance the CCR5 receptor affinity and antiviral activity of the pyrrolidine series,[4] *para*-substituted electron deficient 4-(3-phenylprop-1-yl)piperidine analogues were initially pursued. Two complimentary synthetic routes for the preparation of the 4-(3-phenylprop-1-yl)-

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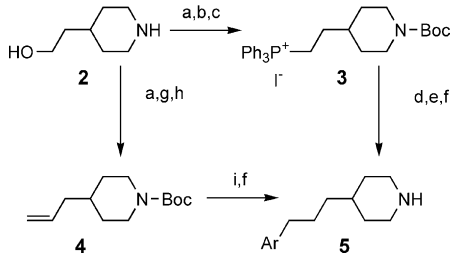
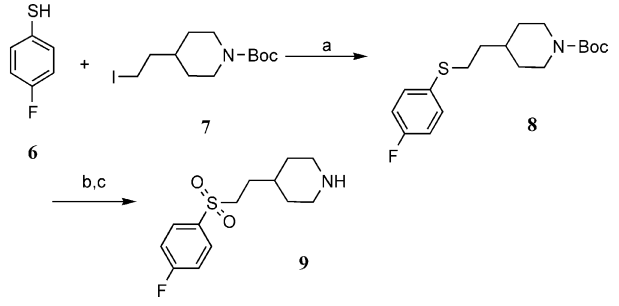
piperidine derivatives were developed (Scheme 1). Commercially available 4-hydroxyethylpiperidine **2** was protected as the Boc derivative, followed by conversion to the iodide and subsequently to the phosphonium salt **3**. Wittig olefination, followed by catalytic hydrogenation and deprotection, afforded the desired piperidine derivative **5**. The second route involved the oxidation of the 4-hydroxyethylpiperidine to an intermediate aldehyde, followed by a Wittig olefination with methyltriphenyl phosphonium bromide to provide **4**. Hydroboration of olefin **4** with 9-BBN, followed by a Suzuki coupling with the requisite aryl halide or triflate[8] and finally treatment with HCl in MeOH, gave the desired piperidine derivative **5**.

Replacement of the benzylic methylene with sulfur analogues was accomplished through an alkylation of 4-fluorobenzenethiol **6** with iodide **7** to provide thioether **8** (Scheme 2). Oxidation of the thioether linkage could be controlled by the stoichiometry of Oxone® yielding either the sulfoxide or the sulfone. In addition, the sulfoxide enantiomers could be separated with preparative chiral HPLC (Chiralpak-AS). Lastly, the Boc-group was cleaved with TFA to give **9**.

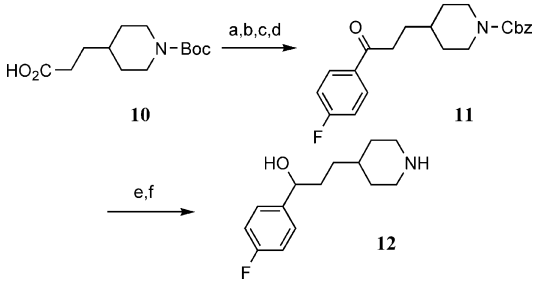
Oxygen-containing functionality was obtained along several synthetic pathways (Schemes 3–5). Initially, the



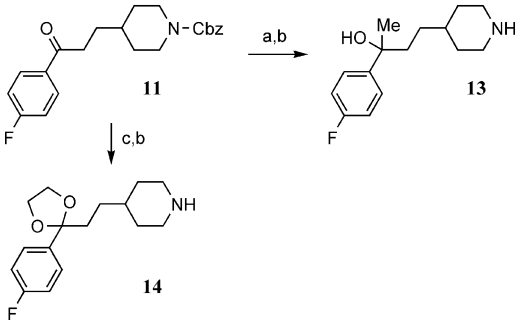

**Scheme 1.** Reagents: (a) $Boc_2O$, $CH_2Cl_2$; (b) $I_2$, $PPh_3$, imidazole, $Et_2O$, $CH_3CN$; (c) $PPh_3$, $CH_3CN$, reflux; (d) KHMDS, THF then ArCHO; (e) $H_2$, Pd/C, MeOH; (f) HCl, MeOH; (g) $(COCl)_2$, DMSO, DIEA, $CH_2Cl_2$; (h) KHMDS, $CH_3PPh_3Br$, THF; (i) 9-BBN, THF, then aryl halide, $Pd(dppf)Cl_2$, $K_2CO_3$, DMF, 50 °C.



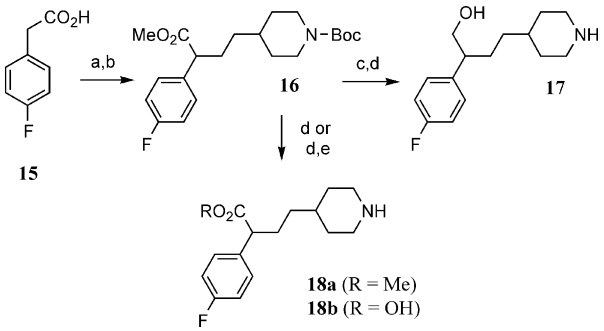

**Scheme 2.** (a) NaH, THF; (b) Oxone®, $MeOH_{(aq)}$; (c) TFA, $CH_2Cl_2$.



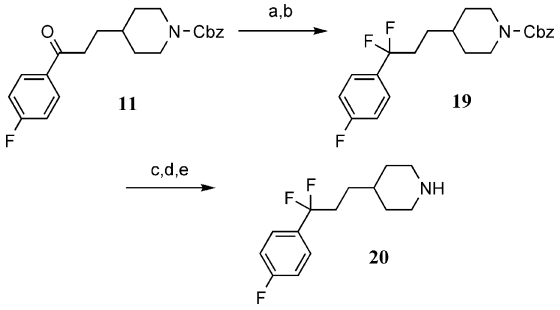

**Scheme 3.** (a) NMM, *i*BuOCOCl, $CH_2Cl_2$, 0 °C; NMM, MeONH-Me·HCl; (b) 4-F-phenyl-MgBr, THF, $Et_2O$, 0 °C; (c) TFA, $CH_2Cl_2$; (d) Cbz–Cl, NaOH, THF; (e) $NaBH_4$, THF; (f) $H_2$, Pd/C, MeOH.



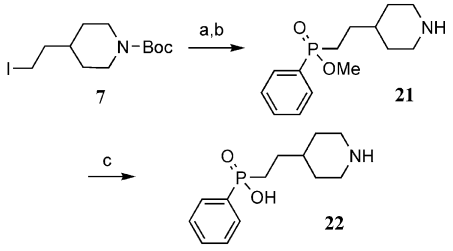

**Scheme 4.** (a) MeMgBr, $Et_2O$, 0 °C; (b) $H_2$, Pd/C, MeOH; (c) ethylene glycol, $TsOH_{(cat)}$, toluene.




**Scheme 5.** (a) $TMSCHN_2$, MeOH, THF; (b) NaH, iodide **7**, DMF; (c) $LiBH_4$, THF; (d) HCl, MeOH; (e) 1 N NaOH, MeOH.




**Scheme 6.** (a) 1,2-Ethanedithiol, $BF_3{\cdot}2HOAc$, $CH_2Cl_2$; (b) 1,3-dibromo-5,5-dimethylhydantoin, HF·pyr, $CH_2Cl_2$, −78 °C; (c) $H_2$, $Pd(OH)_2/C$, 95% EtOH; (d) $Boc_2O$, $CH_2Cl_2$; (e) TFA, $CH_2Cl_2$.




**Scheme 7.** (a) PhPOH(OMe), NaHMDS, THF; (b) HCl, MeOH; (c) TMS-I, $CHCl_3$.

propionic acid **10** was converted into the Weinreb amide and reacted with 4-fluorophenylmagnesium bromide, followed by a protecting group switch to Cbz providing ketone **11** (Scheme 3). Reduction with $NaBH_4$, followed by hydrogenation, yielded piperidine **12**. In addition, further elaboration of ketone **11** gave either piperidine **13** or **14** (Scheme 4).

Assembly of an intermediate ester is presented in Scheme 5. Esterification of 4-fluorophenylacetic acid **15**, followed by alkylation with iodide **7**, gave **16**. Intermediate ester **16** was reduced with $LiBH_4$ and deprotected with HCl in MeOH to yield **17**. Alternatively, **16** was deprotected to provide the piperidinyl-ester **18a**, which was subsequently saponified to yield piperidinyl-acid **18b**.

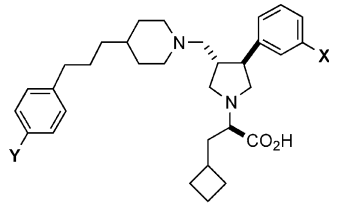
The desired benzylic *gem*-difluoro compounds were obtained through the fluorination method of Katzenellenbogen (Scheme 6).[9] Ketone **11** was initially converted to the 1,3-dithiolane. The resulting thioketal was activated by 1,3-dibromo-5,5-dimethylhydantoin in the presence of HF-pyridine to give the *gem*-difluoride **19**. However, separation of the desired product from an impurity could only be accomplished through a Cbz to Boc protecting group switch. The piperidine was finally deprotected with TFA in $CH_2Cl_2$ yielding **20**.

Lastly, the phosphinates were pursued as polar substituents at the benzylic position. Alkylation of methyl phenylphosphinate with iodide **7**, followed by treatment with HCl in MeOH, provided phosphinic ester **21**. Subjecting ester **21** to TMS-I gave phosphinic acid **22**.

The CCR5 receptor affinity and antiviral data for the compounds are presented in Tables 1–5. Initially, the analogues were screened for their ability to displace [$^{125}$I]-labeled MIP-1α from the CCR5 receptor expressed on CHO cell membranes[10] and for their antiviral properties in a HeLa cell anti-infectivity single cycle assay versus the BAL strain of HIV.[11] The most potent analogues were further evaluated in a 7-day PBMC viral assay (see Table 6).[11]

Since previous work demonstrated that compound **1** possessed a reasonable balance of activity and pharmacokinetics, the cyclobutylmethylene or cyclopropylmethylene side chain and the 4-(3-arylpropyl)-piperidine architecture was generally maintained throughout our SAR studies. In addition, we had observed the incorporation of the 3-fluorophenyl at the 4-position of the pyrrolidine led to improved pharmacokinetics and activity for some analogues (unpublished). A brief look at electron deficient aryl rings produced the 4-fluorophenyl analogue **24** which maintained the activity of **1** and possessed a longer half life and a lower clearance in the rat (Table 1). Although nitrile **25** exhibited potent antiviral properties, the pharmacokinetics failed to improve. The trifluoromethyl derivative **26** demon-

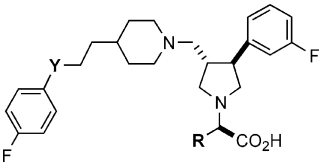
**Table 1.** CCR5 receptor affinity, antiviral activity and the rat pharmacokinetics of the electron deficient 4-(3-arylpropyl)piperidine analogues



| Compd | X | Y | MIP-1α[a] (HeLa)[b] | $Cl_p$ (mL/min/kg) | $t_{1/2}$ (h) | %F |
|---|---|---|---|---|---|---|
| **1** | H | H | 0.1 (1.2) | 26.5 | 3.0 | 29 |
| **23** | F | H | 0.5 (NT) | 32.0 | 3.4 | 24 |
| **24** | F | F | 0.8 (2.0) | 21.0 | 3.4 | 16 |
| **25** | F | CN | 0.3 (0.4) | 47.8 | 1.0 | 7 |
| **26** | F | $CF_3$ | 0.2 (11) | NT[c] | NT[c] | NT[c] |

[a]Displacement of [$^{125}$I]-labeled MIP-1α from the CCR5 receptor expressed on CHO cell membranes ($IC_{50}$, nM). Data are reported as a mean of three determinations. See ref 10 for assay protocol.
[b]$IC_{90}$ values obtained in the HeLa cell anti-infectivity assay versus BAL. See ref 11 for assay protocol.
[c]Not tested.

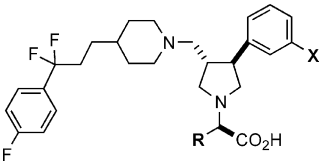
**Table 2.** CCR5 receptor affinity and antiviral activity of the sulfur analogues



| Compd | R | Y | MIP-1α[a] (HeLa)[b] |
|---|---|---|---|
| **27** | *i*-Pr | S | 0.8 (100) |
| **28** | *i*-Pr | $SO_2$ | 0.9 (4) |
| **29** | (c-Bu)$CH_2$ | S | 0.1 (4) |
| **30** | (c-Bu)$CH_2$ | SO[c] | 0.5 (33) |
| **31** | (c-Bu)$CH_2$ | SO[d] | 0.4 (0.8) |
| **32** | (c-Bu)$CH_2$ | $SO_2$ | 0.2 (0.4) |
| **33** | c-Hex | $SO_2$ | 1.1 (0.4) |

[a]See Table 1, footnote (a).
[b]See Table 1, footnote (b).
[c]More polar entantiomer (Chiralpak-AS; 85 hexane/15 *iso*-propanol).
[d]Less polar entantiomer (Chiralpak-AS; 85 hexane/15 *iso*-propanol).

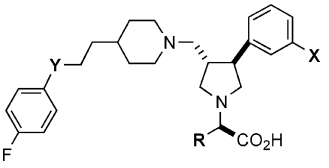
**Table 3.** CCR5 receptor affinity and antiviral activity of the gem-difluoro analogues



| Compd | R | X | MIP-1α[a] (HeLa)[b] |
|---|---|---|---|
| **34** | *i*-Pr | F | 0.5 (33) |
| **35** | (c-Pr)$CH_2$ | F | 0.06 (0.4) |
| **36** | (c-Bu)$CH_2$ | H | 0.2 (NT)[c] |
| **37** | (c-Bu)$CH_2$ | F | 0.3 (1.6) |
| **38** | c-Hex | H | 0.3 (4) |

[a]See Table 1, footnote (a).
[b]See Table 1, footnote (b).
[c]Not tested.

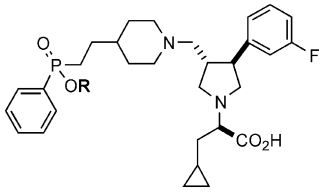
**Table 4.** CCR5 receptor affinity and antiviral activity of the oxygenated analogues



| Compd | R | X | Y | MIP-1α[a] (HeLa)[b] |
|---|---|---|---|---|
| **39** | (c-Pr)$CH_2$ | F | CHOH | 0.4 (1.2) |
| **40** | (c-Pr)$CH_2$ | F | $CH(OCH_2CH_2O)$ | 3.7 (100) |
| **41** | (c-Pr)$CH_2$ | F | $CHCH_2OH$ | 4.8 (33) |
| **42** | (c-Pr)$CH_2$ | F | $C(OH)CH_3$ | 1.6 (1.2) |
| **43** | (c-Pr)$CH_2$ | F | $CHCO_2H$ | 51 (NT)[c] |
| **44** | (c-Pr)$CH_2$ | F | $CHCO_2Me$ | 1.5 (33) |
| **45** | c-Hex | H | C=O | 1.6 (100) |

[a]See Table 1, footnote (a).
[b]See Table 1, footnote (b).
[c]Not tested.

**Table 5.** CCR5 receptor affinity and antiviral activity of the phosphinate analogues



| Compd | R | MIP-1α[a] (HeLa)[b] |
|---|---|---|
| **46** | Me | 19 (NT)[c] |
| **47** | H | ~1000 (NT)[c] |

[a]See Table 1, footnote (a).
[b]See Table 1, footnote (b).
[c]Not tested.

strated inferior activity. Since the 4-fluorophenyl moiety maintained the best balance of antiviral activity and pharmacokinetics within this limited set of analogues, it was maintained as the SAR of the benzyl methylene was explored.

In Table 2 it can be seen that substitution of sulfur functionality for the benzylic methylene was well tolerated by the receptor. However, the antiviral activity of this series was highly dependent on the oxidation state of the sulfur. The sulfones exhibited the most potent activity (e.g., **32** and **33**), while lower oxidation states of sulfur dropped in activity (e.g., **27** and **29**). Specifically, comparing **27** to **28** and **29** to **32** a $\geq$10-fold shift in the HeLa assay was observed. Although the sulfoxide enantiomers **30** and **31** possessed similar affinity for CCR5, interestingly the antiviral activity primarily resided with one of the enantiomers. As previously observed, receptor binding allowed a wide variation in the acetic acid side chain.[7] The most potent antivirals possessed the cyclobutylmethylene or the cyclohexyl side chain (**32** and **33**).

**Table 6.** PBMC antiviral activities and pharmacokinetic profiles of **32**, **35**, **37**, **39** and **42**

| | **32** | **35** | **37** | **39** | **42** |
|---|---|---|---|---|---|
| PBMC (BAL) $IC_{95}$ nM (*n*)[11] | 1.6 (2) | 12 (11) | 18 (19) | 15 (2) | NT[a] |
| Rat | | | | | |
| Clp (mL/min/kg) | 78 | 14 | 18 | 76 | 54 |
| $Vd_{ss}$ (L/kg) | 1.9 | 6.1 | 2.2 | 3.3 | 3.9 |
| $t_{1/2}$ (h) | 0.8 | 7.5 | 3.1 | 0.9 | 1.6 |
| %F | 16 | 39 | 32 | 2 | 10 |
| Dog | | | | | |
| Clp (mL/min/kg) | NT[a] | 24 | NT[a] | NT[a] | NT[a] |
| $Vd_{ss}$ (L/kg) | | 3.7 | | | |
| $t_{1/2}$ (h) | | 2.4 | | | |
| %F | | 37 | | | |
| Rhesus | | | | | |
| Clp (mL/min/kg) | NT[a] | 17.6 | 11 | NT[a] | NT[a] |
| $Vd_{ss}$ (L/kg) | | 2.8 | 1.8 | | |
| $t_{1/2}$ (h) | | 5.6 | 2.4 | | |
| %F | | 8 | 12 | | |

[a]Not tested.

The benzylic *gem*-difluoro analogues in Table 3 were initially prepared to mask the benzylic position against metabolism. This modification led not only to high receptor affinity for CCR5, but provided potent antivirals in the HeLa assay (**35** and **37**).

Since cyclopropylmethylene analogue **35** was one of the most potent antiviral analogues with excellent CCR5 affinity, the oxygenated analogues in Table 4 were prepared containing the cyclopropyl side chain. Within this series of analogues, benzylic alcohols **39** and **42** were the most potent analogues against HIV, analogous to sulfoxides **30** and **31**. Although other functionality possessed reasonable binding for CCR5, such as ester **44** and ketone **45**, the HeLa activity dropped off with these substituents. With the carboxylic acid **43**, the receptor affinity decreased by 30-fold as compared to ester **44** and ketone **45**. Phosphinate analogues **46** and **47** (Table 5) were considerably less active.

The best compounds from Tables 2–5 were tested in the PBMC assay and screened for their pharmacokinetic (PK) properties (Table 6). Sulfone **32** was one of the most potent antivirals prepared ($IC_{95}$ = 1.6 nM), but its poor rat PK with a high clearance and short half-life precluded it from higher species PK experiments. This trend of high clearance and short half-life was observed with benzylic alcohols **39** and **42** as well. The *gem*-difluoro analogues **35** and **37** possessed better PK profiles with lower rates of clearance and longer half-lives than the other series of analogues. These properties along with the data from the PBMC assay (**35** and **37**, $IC_{95}$ < 20 nM) demonstrated the possibility of balancing antiviral activity with pharmacokinetics better than **1**.

In our efforts to explore the SAR of the arylpropyl piperidine side chain, potent antiviral agents were prepared by introducing an electron deficient aryl moiety and replacing the benzyl methylene of **1** with sulfones, *gem*-difluoromethylenes and benzylic alcohols. In con-

clusion, we have been able to maintain the antiviral properties of **1** while improving the pharmacokinetic profile within the trisubstituted pyrrolidine CCR5 class of antagonists.

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