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CCR5 Antagonists: 3-(Pyrrolidin-1-yl)propionic Acid Analogues with Potent Anti-HIV Activity

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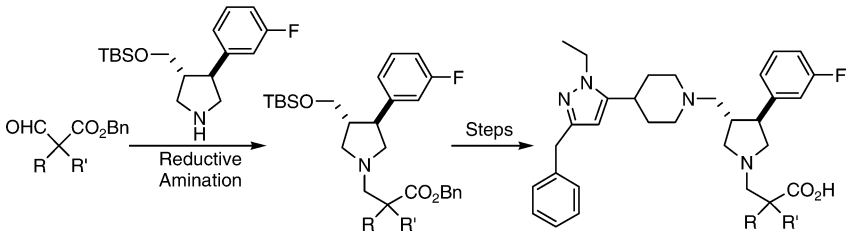
ABSTRACT



A novel approach to α,α-disubstituted-β-amino acids (β^{2,2}-amino acids) was employed in the synthesis of a series of 3-(pyrrolidin-1-yl)-propionic acids possessing high affinity for the CCR5 receptor and potent anti-HIV activity. The rat pharmacokinetics for these new analogues featured higher bioavailabilities and lower rates of clearance as compared to cyclopentane 1.

Recently a series of zwitterionic cyclopentane CCR5 antagonists were disclosed bearing a 4-(3-benzyl-pyrazol-5-yl)piperidine side chain and possessing both potent antiviral activity and acceptable pharmacokinetics (e.g. **1**).[1] Since these structures were inspired by the previously reported 1,3,4-trisubstituted pyrrolidines,[2] we envisioned a new series of antagonists by transposing the α-amino functionality of **1** into the cyclopentyl scaffold, thus producing a 3-(pyrrolidin-1-yl)propionic acid (e.g. **2**). This approach simplified the structure of **1** by replacing two stereocenters with symmetrical substituents. This paper presents the novel synthesis and the initial structure−activity relationships (SAR) of these new β-pyrrolidinyl acids as CCR5 antagonists with potent anti-HIV activity.

Previous approaches to β^{2,2}-amino acids have included dialkylation of cyanoacetates and β-alanine esters, Mannich reactions with silyl ketene acetates, aminations of β-halopropionates, and Reformatsky reactions with benzotriazole derivatives.[3] Our general route utilizes a reductive amination

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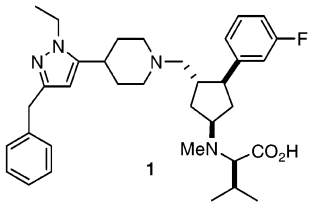


CCR5 (MIP 1α) IC_{50} = 1.1 nM
HeLa (BAL) $IC_{90} \leq 0.14$ nM
PBMC $IC_{95} \leq 8$ nM

Rat Pharmacokinetics
Cl_p = 5.2 mL/min/kg
$t_{1/2}$ = 1.1 h; %F = 15

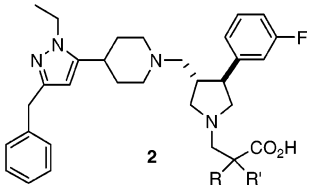
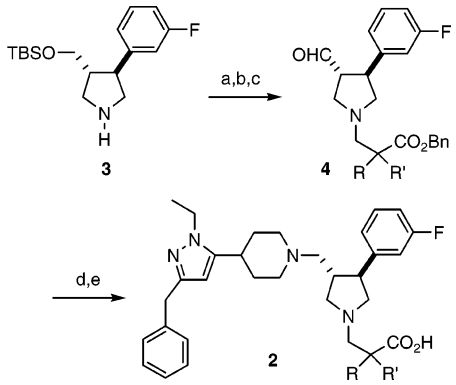


Figure 1. CCR5 antagonist **1** and 3-(pyrrolidin-1-yl)propionic acid analogue **2**.

with α-formyl esters derived from disubstituted malonates (Schemes 1 and 2). Although a related reductive amination has been reported for the preparation of an α,α-dimethyl-β-amino peptide mimetic,[4] the current method allows a novel and efficient manner to vary the side chains of the amino acids. In this paper a series of 3-(pyrrolidin-1-yl)propionic acids is synthesized that illustrate the utility of this chemistry in studying the SAR of β[2,2]-amino acids.

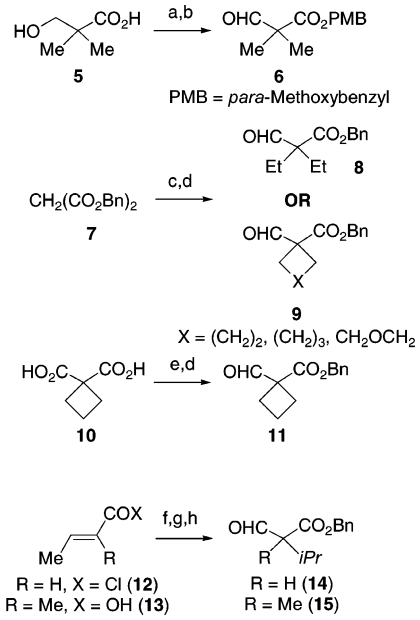
Scheme 1. General Synthesis of the 3-(Pyrrolidin-1-yl)propionic Acid Analogues[a]



[a] Reagents and conditons: (a) $NaB(OAc)_3H$, aldehyde from Scheme 2, CH_2Cl_2 (31−85%); (b) TBAF, THF (86−99%); (c) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; DIEA (70−88%); (d) $NaB(OAc)_3H$, 4-(3-benzyl-1-ethyl-pyrazol-5-yl)piperidine, CH_2Cl_2 (52−84%); (e) H_2, Pd−C, MeOH (benzyl esters; 37−99%) or HCO_2H, Δ, (PMB-esters; 66%).

In the execution of the chemistry, the desired analogues were obtained through a reductive amination between pyrrolidine **3**[5] and an α-formyl ester from Scheme 2, followed by treatment with TBAF and a Swern oxidation, to provide aldehydes **4** (Scheme 1). A reductive amination with 4-(3-benzyl-1-ethyl-pyrazol-5-yl)piperidine, followed by unmasking of the carboxylic acids, gave the final targets.

Scheme 2. Syntheses of the α-Formyl Esters Required for the Reductive Amination in Scheme 1[a]



[a] Reagents and conditions: (a) TEA, PMB−Cl, DMF (56%); (b) $(COCl)_2$, DMSO, DIEA, CH_2Cl_2, −78 to 0 °C (99%); (c) Cs_2CO_3, Et−I, DMF (99%) or K_2CO_3, dihalide, DMSO (67−99%); (d) DIBAL, CH_2Cl_2, −78 °C (54−98%); (e) TEA, Bn−Br, DMF (31%); (f) DMAP, Bn−OH, K_2CO_3, CH_2Cl_2, (R = H; 64%) or TEA, Bn−Br, DMF (R = Me; 44%); (g) LDA, HMPA, THF, −78 °C; *i*Pr−I, THF, −78 to −25 °C (45−60%); (h) O_3, CH_2Cl_2, −78 °C; Me_2S (58−66%).

The required aldehydes were obtained through a variety of routes (Scheme 2). The *gem*-dimethyl aldehyde **6** was synthesized in a two-step sequence of esterification and Swern oxidation of the commercially available hydroxy propionic acid **5**. The *gem*-diethyl **8** and cyclic side chains **9** (ring sizes greater than or equal to 5 atoms) were synthesized from dibenzyl malonate **7** and the appropriate dihalide in the presence of cesium carbonate or potassium carbonate. The intermediate diester was reduced to the α-formyl ester by DIBAL, using the method of Burton.[6] The cyclobutane **11** was obtained from the commercially available diacid **10**, using chemistry analogous to that used to prepare **8** and **9**. The isopropyl side chain in **14** and **15** was introduced by an alkylation of a cinnamate or tiglate ester with isopropyl iodide,[7] followed by ozonolysis of the resulting β,γ-unsaturated ester.

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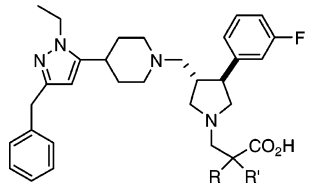
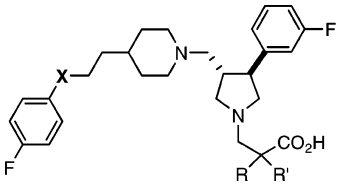
Table 1. CCR5 Receptor Affinity, Antiviral Activity, and Rat Pharmacokinetics



compd no.	R	R′	MIP-1α[a] (HeLa)[b]	Clp (mL/min/kg)	$t_{1/2}$ (h)	% F
16	Me	Me	0.7 (33)	1.4	0.9	27
17	Et	Et	0.8 (0.4)	7.9	1.1	22
18[c]	*i*-Pr	H	0.6 (11)	3.4	1.5	48
19[c]	*i*-Pr	Me	0.8 (0.13)	1.4	1.6	16
20	$(CH_2)_3$		0.6 (33)	1.8	0.8	36
21	$(CH_2)_4$		0.4 (0.13)	1.0	0.9	35
22	$(CH_2)_5$		0.2 (0.13)	NT[d]	NT[d]	NT[d]
23	$(CH_2CH_2OCH_2CH_2)$		1.5 (11)	NT[d]	NT[d]	NT[d]

[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 8 for assay protocol. [b] IC_{90} values obtained in the HeLa cell anti-infectivity assay vs BAL (nM). See ref 9 for assay protocol. [c] Racemic. [d] Not tested.

Table 2. CCR5 Receptor Affinity and Antiviral Activity for the *gem*-Difluoro and Sulfone Analogues



compd no.	R	R′	X	MIP-1α[a] (HeLa)
24	Me	Me	CF_2	0.6 (100)
25	Me	Me	SO_2	1.4 (33)
26	Et	Et	SO_2	0.2 (1.2)
27	$(CH_2)_3$		CF_2	0.2 (33)
28	$(CH_2)_3$		SO_2	0.5 (33)
29	$(CH_2)_4$		CF_2	0.1 (NT)[b]
30	$(CH_2)_4$		SO_2	0.2 (NT)[b]

[a] See Table 1, footnotes a and b. [b] Not tested.

The CCR5 receptor affinity and antiviral data for the compounds are presented in Table 1. Initially, the analogues were screened for their ability to displace [^{125}I]-labeled MIP-1α from the CCR5 receptor expressed on CHO cell membranes[8] and for their antiviral properties in a HeLa cell anti-infectivity single cycle assay versus the BAL strain of HIV.[9] All of the compounds in this series possessed subnanomolar affinity for the CCR5 receptor (**16**−**22**), with the exception of pyran **23**. Analogues with side chains greater than or equal to 4 carbon atoms (**17**, **19**, **21**, and **22**) also possessed subnanomolar antiviral activity in the HeLa cell antiviral assay. These 3-(pyrrolidin-1-yl)propionic acids were further evaluated to determine their rat pharmacokinetics. In general, these $\beta^{2,2}$-amino acids had lower clearance rates and comparable half-lives to **1**. Oral bioavailability was acceptable across this series of antivirals.

To further examine the 3-(pyrrolidin-1-yl)propionic acids, some other previously described piperidine subunits[10] were incorporated into this new scaffold (Table 2). These hybrid molecules possessed high affinity for the CCR5 receptor as judged by their IC_{50}'s in the MIP-1α assay. Unfortunately, this potency did not translate into better antiviral activity as compared to the corresponding benzyl pyrazole analogues of Table 1. The best compound from Table 2 (**26**) was 10-fold less active in the HeLa assay as compared to the most active compounds of Table 1 (**19**, **21**, and **22**). As a result of this decline in antiviral activity, pharmacokinetic studies were not carried out with the hybrid analogues.

In conclusion, a novel approach to studying the side chain SAR of $\beta^{2,2}$-amino acids was developed in the synthesis of the 3-(pyrrolidin-1-yl)propionic acids. These analogues possessed high affinity for the CCR5 receptor and potent anti-HIV activity. In addition, the rat pharmacokinetics for this class of antivirals featured enhanced bioavailabilities and lower rates of clearance as compared to **1**. This new series of antagonists departed from the previously reported α-amino acids,[2,10] which never rivaled the potency of the cyclopentane-based analogues, and allowed access to pyrrolidine-derived CCR5 antagonists comparable to **1**.

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