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Synthesis and evaluation of CCR5 antagonists containing modified 4-piperidinyl-2-phenyl-1-(phenylsulfonylamino)-butane

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Abstract—Synthesis of analogs containing more rigid bicyclic piperidine replacements for the 4-benzyloxycarbonyl-(ethyl)amino-piperidine moiety of the CCR5 antagonist structure, **1**, is described. Although similar binding affinity to the lead was achieved with some analogs they were overall less potent anti-HIV agents suggesting that other features besides CCR5 binding are required for good anti-viral activity.

The chemokine receptor CCR5 is the primary co-receptor used by M-tropic (or R5) strains of human immunodeficiency virus (HIV) along with CD4 to gain entry into immune system cells. CXCR4, another member of the chemokine receptor family, is utilized by the T-tropic (or X4) strains.[1] The R5 virus predominates in the early stages of HIV infection in vivo and is present throughout the course of the disease, whereas the X4 virus is present only during the later stage of the disease. The beneficial effect of blocking CCR5 as a treatment for HIV infection has been inferred from human genetic studies. Individuals who lack functional CCR5 receptors on their cell surfaces, due to a 32 bp deletion in their CCR5 gene, are highly resistant to HIV infection[2] and infected heterozygous patients display a significantly delayed progression to clinical AIDS.[3] More recently efficacy of CCR5 antagonists was demonstrated in human clinical studies.[4] CCR5 is a member of the seven transmembrane G-protein coupled receptor family, which has provided many important targets for drug discovery. These observations have led to efforts in many laboratories to identify CCR5 antagonists as new therapies for HIV infection.[5]

Previous reports from these laboratories have described the discovery of low molecular weight CCR5 antagonists containing a 4-(piperidin-1-yl)-2-phenyl-1-(phenylsulfonylamino)butane framework.[6] SAR studies around this lead identified **1** with an IC_{50} = 2 nM in a CCR5 binding assay, which had minimal anti-viral activity in an in vitro HIV replication assay.[7] However, introduction of a benzylic methyl at C-2 and modification of the ethylamino-CBZ to an allylamino-4-nitro-CBZ group afforded **2**, which had good anti-viral activity.[8] In order to improve the potency, selectivity, and pharmacokinetic properties, analogs where the backbone was restrained as a pyrrolidine ring have been prepared.[9] Herein we report on an alternative approach (**3**) where the carbamate of **2** is constrained by linking the *N*-alkyl group (a) with the benzylic carbon atom or (b) with the piperidine ring and discuss the synthesis, CCR5 affinity, and anti-viral activity of these novel analogs.

The general synthesis of this class of compounds (Scheme 1) was described recently and was based on

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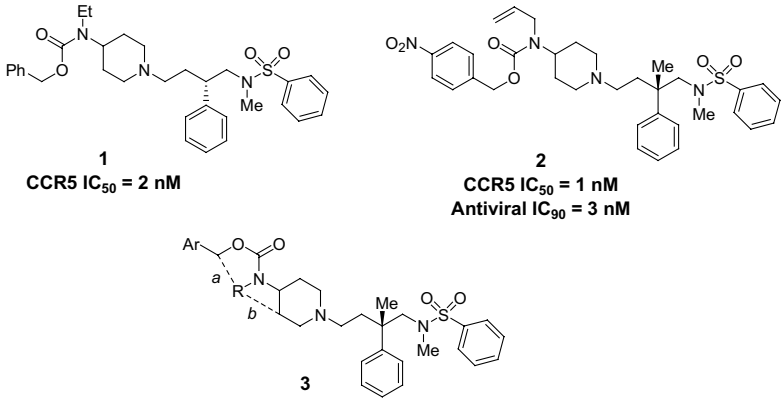
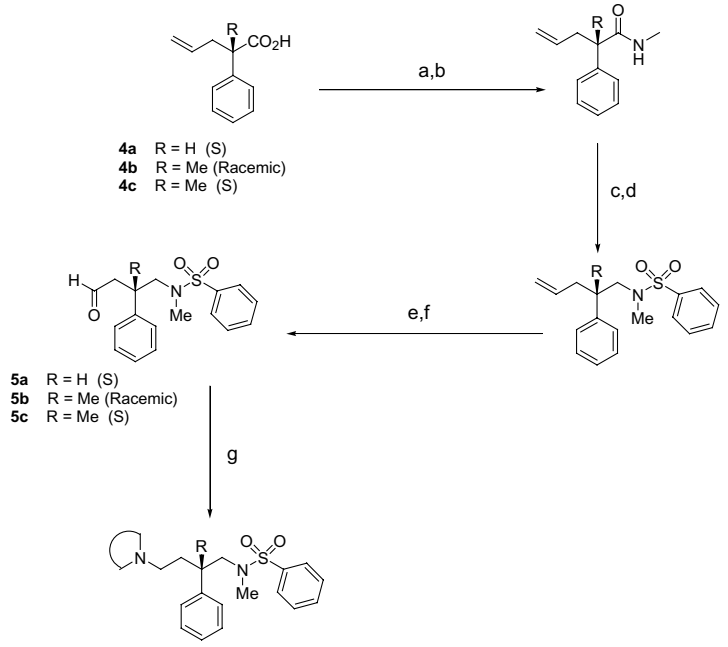


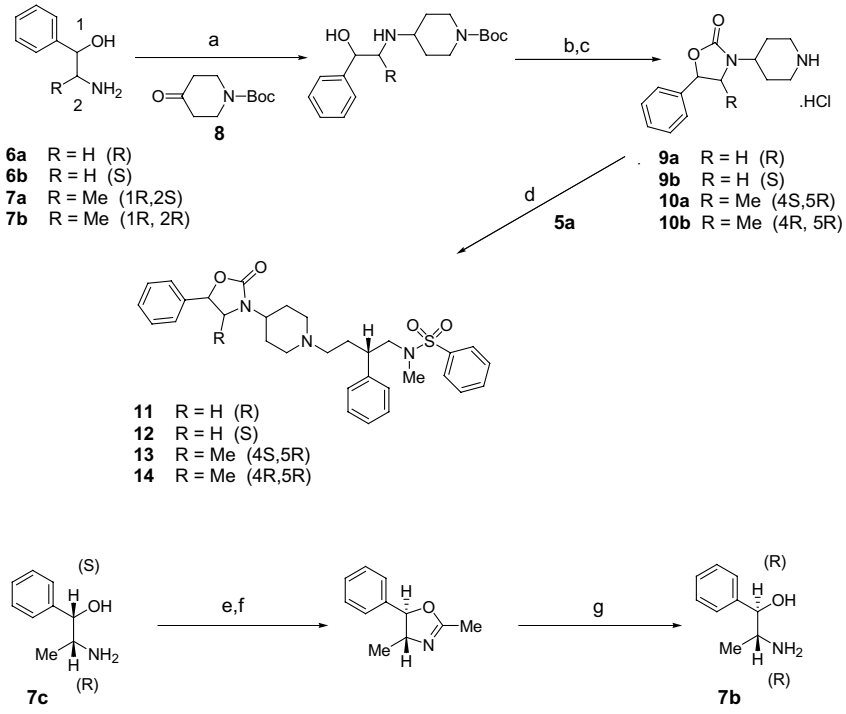
reductive amination of the key aldehyde intermediates, **5**, with 4-substituted piperidines.[6] This convergent approach was very useful for the present work because we only had to synthesize the desired bicyclic piperidine prior to the final coupling step. Initially, some of the analogs were made using the racemic aldehyde **5b**, with the compounds having good activity being remade using the chiral aldehyde **5c**, which then allowed separation of the individual diastereomers by chromatography. The starting chiral acids (**4a** and **4c**) were obtained by resolution of the racemic acids with (*S*)-(−)-α-methylbenzylamine.[6,8]

The preparation of piperidines with a cyclic carbamate substituent at C-4 is depicted in Scheme 2. Both (*R*)- and (*S*)-1-phenylethanolamine (**6a** and **6b**) were individually reacted with Boc-piperidone (**8**) and each aminoalcohol product was cyclized using phosgene. Removal of the Boc protecting group gave **9a** and **9b**. Reductive amination of **9a** and **9b** with **5a** furnished the test compounds **11** and **12**, respectively. Since **11** with (*R*) stereochemistry was preferred, only (*R*) isomers were prepared in the subsequent disubstituted series. The same three step sequence starting with (1*R*,2*S*)-norephidrine (**7a**) gave (4*S*,5*R*) oxazolinone (**10a**), which upon reaction with **5a** yielded **13**. The (1*R*,2*R*) isomer **7b** was prepared by inversion of the hydroxyl center of (1*S*,2*R*)-norephidrine (**7c**) in a three step procedure.[10] **7b** was converted to **10b**, which was reacted with **5a** to provide the (4*R*,5*R*) isomer **14**.

The synthesis of bicyclic piperidine **16**, where the alkyl group is connected to the piperidine, is shown in Scheme 3. The indole N of 5-azaindole (**15**), prepared by a literature procedure,[11] was protected as a Boc derivative and the product was hydrogenated using PtO_2. Reductive amination of **16** with **5a** and **5b** furnished **17** and **18** as mixtures of diastereomers, respectively. Removal of the Boc group from **18** gave the free amine **19**, which was acylated to afford **20**–**22** also as mixtures of isomers. Reaction of **16** with chiral aldehyde **5c** formed two diastereomers, which could be separated by chromatogra-



Scheme 1. Reagents: (a) $(COCl)_2$, CH_2Cl_2; (b) $MeNH_2$, CH_2Cl_2; (c) DIBAL-H, THF; (d) $PhSO_2Cl$, iPr_2NEt, CH_2Cl_2; (e) OsO_4, NMO, *t*-BuOH, acetone, H_2O; (f) $NaIO_4$, THF, H_2O; (g) amine·HCl, $Na(OAc)_3BH$, iPr_2Net, DCE, or CH_2Cl_2.



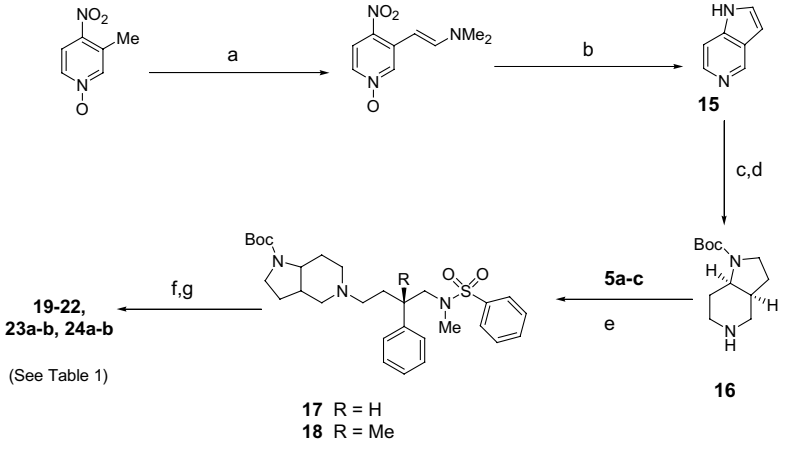
Scheme 2. Reagents: (a) $Na(OAc)_3BH$, DCE; (b) $COCl_2$, Et_3N; (c) HCl, EtOAc; (d) $Na(OAc)_3BH$, $i Pr_2Net$, DCE; (e) Ac_2O, toluene; (f) HCl, toluene; (g) 4 N HCl, H_2O, toluene.

phy to isolate individual stereoisomers **23a** and **23b**. Acid treatment of **23a** and **23b** individually and reacylation with 4-nitro-CBZ-Cl gave **24a** and **24b**, respectively.

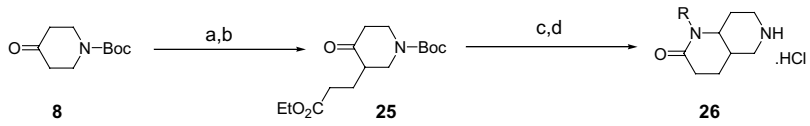
The fused piperidines **26** (Scheme 4) were prepared from Boc-piperidone (**8**). Michael addition of the pyrrolidine enamine of **8** to ethyl acrylate gave **25**. Reaction of **25** with an amine and $Na(OAc)_3BH$ formed the lactam and subsequently the protecting group was removed with HCl/ethyl acetate to yield **26**. Final reductive amination of **5b** with **26** using $Na(OAc)_3BH$ afforded the test compounds **27**–**29** as mixtures of diastereomers.

The receptor binding and anti-viral activities of the newly synthesized compounds along with the two leads (**1** and **2**) are listed in Table 1. Among the analogs with a cyclic carbamate (**11**–**14**) the stereoisomers **11** and **13** were preferred and had about a 10-fold better affinity than the other isomers. However, the best compound was still much less active than **1**, thus indicating that this construction did not allow the proper orientation of the pharmacophores for binding.

The perhydro azaindole series (**17**–**24b**) provided better orientation and both **18** and **21** had comparable activity to **2** in the binding assay. Since **18** and **21** each contained four stereoisomers, the individual isomers **23a**,**b** and **24a**,**b** with *S* stereochemistry at the quaternary center were synthesized. Both **23b** and **24b** were as good as **2** in the CCR5 binding assay but their anti-viral activity

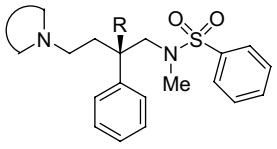


Scheme 3. Reagents: (a) $Me_2NCH(OMe)_2$, DMF, 90 °C; (b) H_2, 10% Pd/C, EtOH, 60 °C; (c) $(Boc)_2O$, DMAP, MeCN; (d) H_2, PtO_2, EtOH, HOAc; (e) $Na(OAc)_3BH$, $i Pr_2NEt$, DCE; (f) HCl, EtOAc; (g) chloroformate or acid chloride, Et_3N, CH_2Cl_2.



Scheme 4. Reagents: (a) pyrrolidine, *p*-TsOH, benzene, Dean–Stark trap, 80 °C; (b) ethyl acrylate, benzene, Dean–Stark trap, 80 °C; (c) H_2O, reflux; (d) RNH_2, $Na(OAc)_3BH$, DCE; (e) HCl, EtOAc.

Table 1. CCR5 binding affinity and anti-viral activity of synthesized compounds



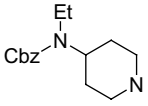
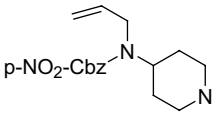
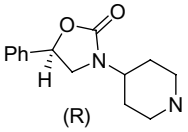
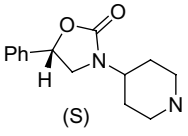
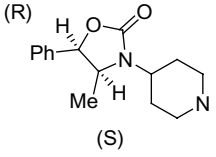
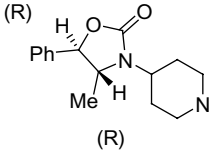
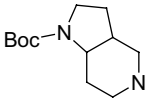
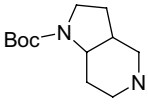
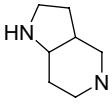
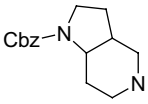
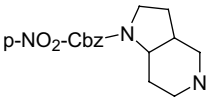
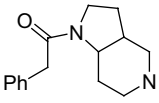
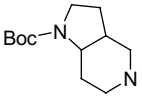
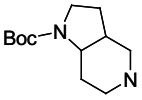
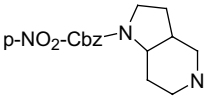
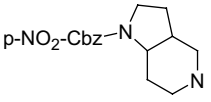
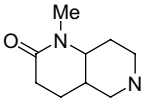
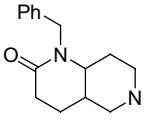
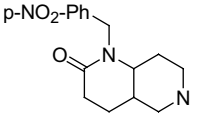
No.		R	CCR5 IC_{50} (nM)[a]	Anti-viral IC_{90} (nM)[b]
1		H	2	ND[c]
2		Me	1	3
11		H	31.9	ND
12		H	>100	ND
13		H	36.7	ND
14		H	350	ND
17		H	16	ND
18		Me (*R*/*S*)	11	111
19		Me (*R*/*S*)	>2000	ND

Table 1 (*continued*)

No.		R	CCR5 IC_{50} (nM)[a]	Anti-viral IC_{90} (nM)[b]
20		Me (*R*/*S*)	9	>300
21		Me (*R*/*S*)	3.6	111
22		Me (*R*/*S*)	6.4	111
23a	 Isomer A	Me	>2000	ND
23b	 Isomer B	Me	2	100
24a	 Isomer A	Me	21	300
24b	 Isomer B	Me	2	33
27		Me (*R*/*S*)	28	>300
28		Me (*R*/*S*)	10	333
29		Me (*R*/*S*)	5.3	333

[a] The assay used recombinant CCR5 receptors expressed on CHO cell membranes and ^{125}I-MIP-1α as the ligand. IC_{50} values are the average of three experiments, where standard errors were <15% in a single assay. See footnote 20 of Ref. 12 for assay protocol.
[b] The assay has been described in Ref. 13.
[c] ND = Not determined.

was significantly lower. This result clearly demonstrates that CCR5 binding affinity is not sufficient for anti-viral activity and other features such as rate of dissociation from the receptor or some physical property might be important. Among the fused lactams, **28** and **29** both displayed moderate CCR5 affinity, but also lacked anti-viral activity.

Three types of bicyclic replacements for the 4-alkyl-amino-piperidine moiety of the lead were evaluated for

their CCR5 activity and perhydro-5-azaindole derivatives were found to have low nanomolar affinity for the receptor. However, these compounds (**23b** and **24b**) were significantly less active as anti-viral agents suggesting that activity in the CCR5 binding assay is not the sole determinant of the anti-HIV activity. The lower affinity of these bicyclic analogs has also provided valuable insights about the preferred orientation of the alkyl and carbamate groups for chemokine binding and especially anti-HIV activity. We have used this information to design other rigid structures with improved potency and selectivity and these results were disclosed recently.[14]

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