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Syntheses and biological evaluation of 5-(piperidin-1-yl)-3-phenylpentylsulfones as CCR5 antagonists

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Abstract—Cellular proliferation of HIV-1 requires the cooperative assistance of both the CCR5 and CD4 receptors. Our medicinal chemistry efforts in this area have resulted in the identification of *N*-alkyl piperidine sulfones as CCR5 antagonists. These compounds display potent binding and show antiviral properties in HIV-1 spread cell-based assays.

1. Introduction

The plethora of drugs introduced during the past decade to confront the AIDS crisis have resulted in an improved quality of life for many individuals. Despite these impressive gains, the disease, after stabilizing in the US, is on the rise again with increasing numbers of people infected with drug resistant stains of the virus. Thus new therapeutic options, which tackle the replication of this insidious virus in novel ways are highly desirable.

Earlier work with HIV-1 has established that the virus uses CD4 as the primary receptor for cell entry. However, it was also recognized that while the CD4 receptor was necessary, it was not sufficient for HIV-entry and a secondary receptor was also involved. In 1995 it became clear that the chemokines MIP-1α, MIP-1β, and RANTES were active in suppressing of growth of HIV-1 in immune cells.[1,2] The following year, CCR5 and CXCR4 were identified as coreceptors along with CD4 for the entry of HIV into macrophages and T-cells.[3] Subsequently it was discovered that certain individuals homozygous for a 32-base pair deletion in the gene for CCR5 show no expression of this receptor on cell surfaces and are highly resistant to HIV infection.[4] HIV-infected individuals heterozygous for this variation show delayed progression to clinical AIDS.[5] These observations provided compelling evidence that a suitable small molecule CCR5 antagonist might have potential in the therapeutic treatment of HIV infection.[6]

Toward this end, medicinal chemistry efforts aimed at the development of CCR5 antagonists have resulted in several publications from this and other laboratories.[7] *N*-methylsulfonamides **1** and **2** along with related analogs, are potent CCR5 antagonists displaying antiviral activities[7b,h] in a cell-based assay. The amide **2**, our lead compound of interest in the present investigation, showed low serum levels following an oral dosing in dog.[7h] We reasoned that perhaps the replacement of the sulfonamide group of **1** by the sulfone functionality, as shown in **3** (Fig. 1), might lead to analogs with enhanced metabolic stability. This communication details the

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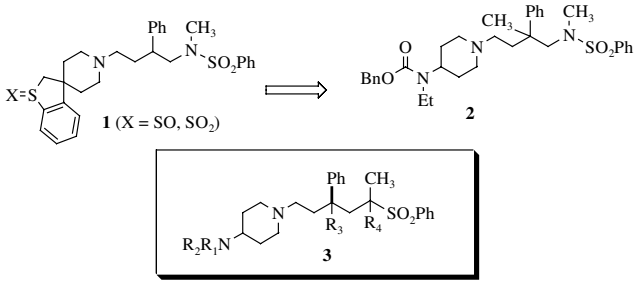


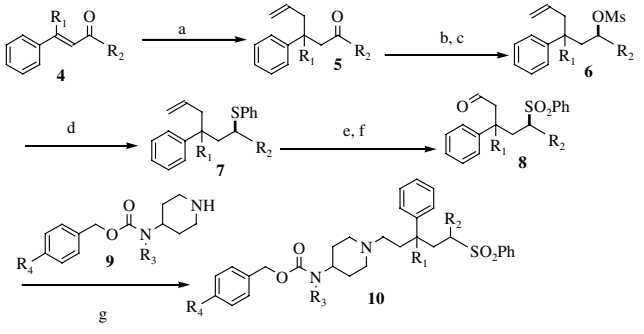
Figure 1.

preparation, SAR, and biological profile of such analogs.

2. Chemistry

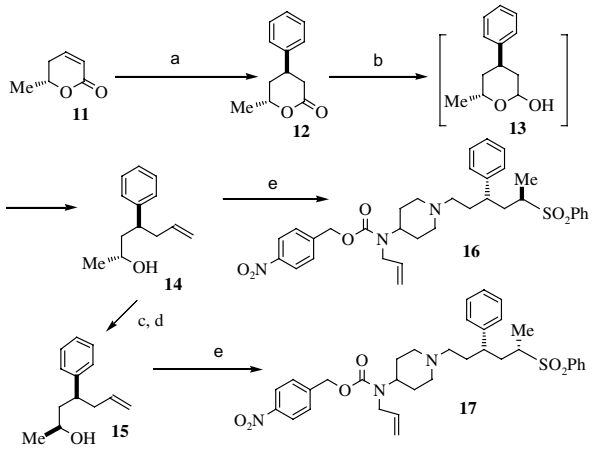
General routes for the synthesis of sulfones are shown in Scheme 1. A smooth 1,4-addition of allyltrimethylsilane to enone **4** gave **5**.[8] Ketone **5** was reduced to give a mixture of alcohols that in a subsequent step was transformed to the mesylate **6**. The mesylate **6** underwent a facile nucleophilic displacement by thiophenol to afford the sulfide **7**. The vinyl group in sulfide **7** was then transformed to aldehyde **8** in a two step oxidative sequences that initially involved the transformation of the sulfide to the sulfone, followed by ozonolysis of the double bond to give **8**. Reductive amination[9] of **8** with select amines (**9**) furnished the sulfones **10** as a mixture of diastereomers.

The synthesis of sulfones described above generated stereochemical mixtures, which were not separated before initial screening in the CCR5 binding assay. Mixtures, which showed good activity were prepared in stereochemically pure form as shown in Scheme 2. In this route, the palladium-catalyzed Michael addition of iodobenzene to the known chiral lactone **11**[10] gave exclusively **12**.[11] During this reaction it was expected that the addition of the phenyl group to the double bond would be from the side opposite to the methyl group. The lactone **12** was transformed to the carbinol **14** in a



R_1 = H, Me, R_2 = H, Me, Et, R_3 = Et, allyl, R_4 = H, NO_2

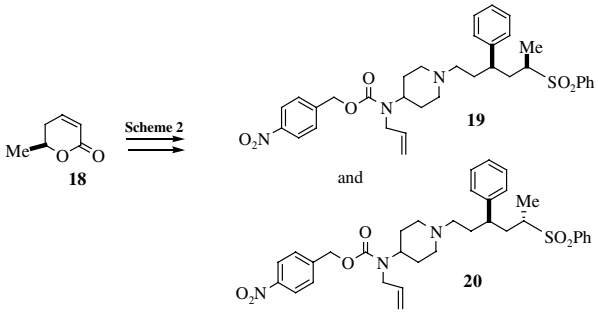
Scheme 1. Reagents and conditions: (a) allyltrimethylsilane, $TiCl_4$, CH_2Cl_2; (b) $NaBH_4$, MeOH; (c) MsCl, NEt_3, CH_2Cl_2; (d) PhSH, CsF, DMF; (e) H_2O_2, AcOH; (f) O_3, $MeOH/CH_2Cl_2$ at −78 °C, and then PPh_3 to rt; (g) $Na(OAc)_3BH$, CH_2Cl_2.



Scheme 2. Reagents and conditions: (a) PhI, Et_3N, $Pd(PPh_3)_4$, 80 °C; (b) DIBAL, THF, −78 °C, and then PPh_3Me/*n*-BuLi, −78 °C to rt; (c) DEAD, PPh_3, *p*-nitrobenzoic acid, benzene, rt; (d) K_2CO_3, CH_3OH, rt; (e) Scheme 1 and steps c–f.

one-pot reaction that initially involved DIBAL reduction of **12** to the intermediate lactol **13**, which subsequently underwent a Wittig reaction to afford **14**. To access the other diastereomer, **15**, we carried out an inversion at the carbinol carbon via Mitsunobu reaction[12] on **14** to give a *p*-nitrobenzoyl ester that was subjected to saponification to give **15**. Eventual transformation of **14** and **15** to the chiral sulfones **16** and **17** was analogous to the transformation of **6** to **10** described in Scheme 1.

A similar sequence starting from the enantiomeric lactone **18**[13] and following the protocol described for **16** and **17** in Scheme 2, produced sulfones **19** and **20**, shown below.

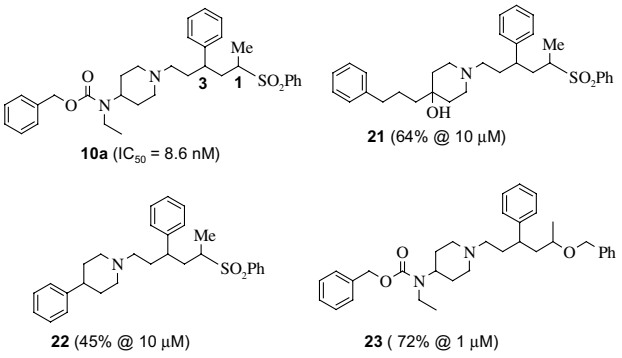


Finally, other miscellaneous sulfone analogs described in this communication that were necessary to complete the SAR were prepared from other sulfone intermediates via known chemistry.[14]

3. Results and discussion

The synthesized compounds were screened for CCR5 binding affinity employing the ^{125}I-MIP-1α binding assay.[15] The initial IC_{50} data for the compounds shown below (**10a**, **21**, **22**, and **23**) clearly indicated to us that the carbamate-based sulfone analog (**10a**) displayed potency that was several magnitudes better than that of

the others. The sulfones with the 3-phenylpropyl (**21**) and phenyl (**22**) piperidines showed weak affinity for the receptor. The results for **21** and **22** are to be contrasted with those obtained for the pyrrolidine and *N*-sulfonamide based CCR5 antagonists, wherein the presence of such a subunit resulted in analogs with superb binding potency.[7b,h]

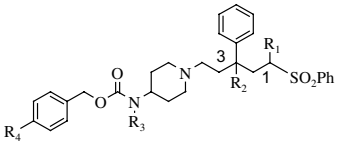


Ethers such as **23** that still retained the carbamate unit (as in **10a**) but lacked the sulfone moiety were not active. These results clearly underscore the beneficial effect of both the sulfonyl and carbamate group in the present lead class.

Further efforts in this lead class probed ways to modify the sulfone **10a**. This involved the placement of alkyl substituents at C-1/C-3 of *n*-pentyl backbone, change in carbamate substitution on the piperidine ring and finally the replacement of the phenylsulfone moiety by other sulfones. The results from the binding assay for the synthesized analogs are compared with **10a** and are displayed in Tables 1 and 2.

As is evident from Table 1, replacement of the C-1 methyl group (**10a**) by the ethyl analog (**10b**), resulted in a 10-fold loss in the binding activity. The analog **10c**,

Table 1. CCR5 binding activity of sulfones[a]

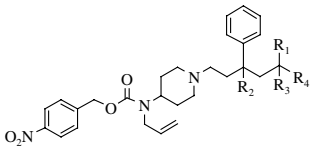


Entry	R_1	R_2	R_3	R_4	IC_{50} (nM)[b]
10a	Me	H	Et	H	8.6
10b	Et	H	Et	H	88
10c	Me	Me	Et	H	6.8
10d	H	Me	Et	H	24
10e	Et	H	Allyl	NO_2	7.2
10f	Me	Me	Allyl	NO_2	3.8
10g	H	Me	Allyl	NO_2	4.4

[a] The examples shown are diastereomeric mixtures and prepared according to Scheme 1.

[b] The IC_{50} results are an average of three independent titrations having calculated standard error below 15% and the variability was generally ±3-fold.

Table 2. CCR5 binding activity of miscellaneous sulfones[a]



Entry	R_1	R_2	R_3	R_4	IC_{50} (nM)[b]
10h	Me	Me	Me	SO_2Ph	11
10i	Me	H	H	SO_2Me	6
10k	Me	H	H	SO_2Et	6
10l	Me	H	H	SO_2Pr^i	5
10m	H	H	H	COPh	15

[a] The examples shown are diastereomeric mixtures and prepared according to Scheme 1.

[b] The IC_{50} results are an average of three independent titrations having calculated standard error below 15% and the variability was generally ±3-fold.

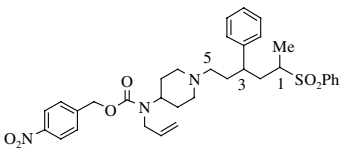
with an additional methyl group at C-3, is equipotent to **10a**. The sulfone analog **10d**, lacking the methyl substituent at C-1, displayed a 4-fold loss of potency compared to **10a**. These results clearly suggest that a small alkyl group at C-1 is highly desirable. An impressive 12-fold gain in binding potency was further achieved for the sulfone analogs upon replacement of the O-benzyl/*N*-ethyl carbamate subunit (**10b**) with O-(4-nitro-benzyl)/*N*-allyl (**10e**). This was also seen for the analogs **10f** and **10g**. Analogous results have been observed for the *N*-sulfonamide compounds[7h] reported from these laboratories.

Since the combination of the 4-nitrobenzyl and *N*-allyl substituents resulted in enhanced potency, the rest of the SAR in this series was completed retaining these subunits as shown below in Table 2. The sulfone **10h** with a geminal methyl at C-1 showed loss of potency in comparison to either **10a** or **10f**. Interestingly, the alkyl sulfone analogs **10i–l** were all equipotent to **10a**. The replacement of the sulfone moiety by ketone leading to **10m** resulted in moderate loss of potency.

It was our intention to find the most active diastereomer and evaluate it in the viral infectivity assay and also subsequently for pharmacokinetic properties. To this end, we anticipated that the preparation of homochiral O-nitrobenzyl/*N*-allyl analogs (**10g**) might access even more potent analogs.

The binding and antiviral activities for these individual isomers are displayed in Table 3. As the table reveals, isomer **16** (1*R*,3*R*), and its mirror image analog **19** (1*S*,3*S*) were equipotent and at least 3–5-fold better than **17** and **20** in the binding assay. The sulfones **16**, **17**, **19**, and **20** were also evaluated for their antiviral properties and the data are shown below.[16,17] One notices that the results from the binding assay for **16**, **17**, **19**, and **20** stand in contrast to the data for the antiviral assay. The sulfone **16** was 3-fold more potent than **19**. Interestingly both **17** and **19** have very similar antiviral activity. More surprisingly **20** was 10-fold less active in Hela than **17**, despite having very similar binding potency.

Table 3. CCR5 binding/antiviral activity of chiral sulfones[a]

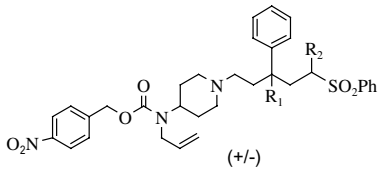


Entry	Configuration	IC_{50} (nM)[b]	Hela IC_{90} (nM)[b]
16	1*R*,3*R*	2.3	111
17	1*S*,3*R*	8.4	300
19	1*S*,3*S*	3.5	300
20	1*R*,3*S*	10.4	3000

[a] The examples shown are diastereomeric mixtures and prepared according to Scheme 1.

[b] The IC_{50} results are an average of three independent titrations having calculated standard error below 15% and the variability was generally ±3-fold.

Other select racemic sulfone analogs **10e** and **10g** that showed potent affinities were screened in the antiviral assay and the outcome (shown below) was substantially similar to **17** or **19**.



10e, R_1 = H, R_2 = Et, IC_{90} = >1000 nM
10g, R_1 = Me, R_2 = H, IC_{90} = 300 nM

The results shown in Table 3, taken with results for other analogs, suggest that the potent receptor affinities for these analogs were not manifested as activity in the antiviral assay. In general, the sulfones and the *N*-methyl sulfonamides have similar binding potency, the difference being that the sulfones are less potent in the antiviral assay. The sulfone analog **16** was further evaluated in a rat pharmacokinetic assay. Disappointingly, it had a moderately high rate of clearance ($Cl_p = 40$ mL/min/kg) and poor oral bioavailability (9%). For these reasons, additional efforts in pursuit of sulfone based CCR5 antagonists were curtailed.

In conclusion, a stereospecific synthesis of novel sulfones was developed and analogs thus produced were assessed for their CCR5 activity. Many of these compounds demonstrated potent binding affinity and modest antiviral properties. Among them the sulfone **16** had the best profile. It was, however, less active than the corresponding sulfonamide.

References and notes

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13. Lactone **18** was synthesized in a similar manner given under Ref. 10.
14. The sulfide **7** was oxidized to corresponding sulfone, deprotonated with *n*-BuLi and then quenched with MeI to give alkylated product, which was elaborated to the desired product.
15. The CCR5 binding assay utilized ^{125}I-MIP-1α as the ligand was carried out by mixing 200 μL of 50 nM Hepes buffer, pH 7.4 containing 5 mM $MgCl_2$, 1 mM $CaCl_2$, 0.5% BSA, 10 μg/mL each of the protease inhibitors aprotinin, chymostatin, and leupeptin, 0.1 mM PMSF, and 0.01 mM phosphoramidon with 5 μL of compound at increasing concentration or the DMSO for the background, 20 μL of ^{125}I-MIP-1α (2×10^4 cpm, 2000 Ci/mmol) and 10 μL of buffer or unlabeled MIP-1α (100 nM final concentration). Assays were initiated by adding CHO cells (3×10^4) stably expressing 10^6 CCR5 receptors/cell and incubated for 1 h at 24 °C. Separation of free from bound ^{125}I-MIP-1α was carried out on a Packard Filtermate 196 using GF/C filters pre-soaked in 0.33% PEI. IC_{50} values were calculated using standard methods from the binding results using final concentrations of test compound in the range from 0.13 to 10,000 nM.
16. The IC_{90}s of select compounds were evaluated in a 48 h single cycle HIV(BAL) infection assay that used HeLa Magi cells expressing both CXCR4 and CCR5, described previously (see Ref. 17).
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