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Antagonists of the Human CCR5 Receptor as Anti-HIV-1 Agents. Part 2: Structure–Activity Relationships for Substituted 2-Aryl-1-[*N*-(methyl)-*N*-(phenylsulfonyl)amino]-4-(piperidin-1-yl)butanes

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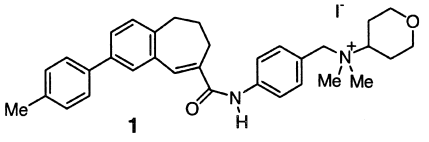
Abstract—(2*S*)-2-(3,4-Dichlorophenyl)-1-[*N*-(methyl)-*N*-(phenylsulfonyl)amino]-4-[spiro(2,3-dihydrobenzthiophene-3,4′-piperidin-1′-yl)]butane *S*-oxide (**3**) has been identified as a potent CCR5 antagonist lead structure having an $IC_{50} = 35$ nM. Herein, we describe the structure–activity relationship studies directed toward the requirement for and optimization of the C-2 phenyl fragment. The phenyl was found to be important for CCR5 antagonism and substitution was limited to small moieties at the 3-position (**13** and **16**: X = H, 3-F, 3-Cl, 3-Me). © 2001 Published by Elsevier Science Ltd.

Human immunodeficiency virus type-1 (HIV-1) is an enveloped virus that must fuse its envelope with the plasma membrane of its host cell to gain cell entry.[1] CCR5, a seven-transmembrane receptor for the β-chemokines MIP-1α, MIP-1β, and RANTES,[2] has been identified as a primary co-receptor with CD4 for cell entry of macrophage-tropic (M-tropic or R5) HIV-1 isolates.[3] Individuals homozygous for a 32-base pair deletion in the gene for CCR5 do not express functional receptor on their cell surfaces and have been identified as being highly resistant to HIV-1 infection,[4] while infected individuals heterozygous for the defective gene appear to exhibit delayed disease progression.[5] Given the importance of CCR5 for the establishment, and possible maintenance, of HIV-1 infection in vivo, and the lack of an overt detrimental phenotype in humans that do not express functional CCR5, numerous efforts have been initiated in an effort to identify suitable CCR5 antagonists for use as potential anti-HIV-1 therapeutic agents.[6–9]

Towards this end, there have now been several reports of CCR5 antagonists in the patent literature.[1,10] To date, the most established structure is TAK-779 (**1**),[11,12] which is actually a dual CCR5 and CCR2b antagonist having binding affinities of 1.4 and 27 nM, respectively.



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In our first manuscript in this series,[13] the discovery of several CCR5 selective (2*S*)-1-(*N*-alkyl-*N*-arylsulfonyl-amino)-2-phenyl-4-(piperidin-1-yl)butane structures (**2**) were identified through screening of the Merck sample collection and our initial structure–activity relationships (SARs) pertaining to the C-1 *N*-alkyl-*N*-arylsulfonamide moiety of **2** were reported. This work resulted in the identification of (2*S*)-2-(3,4-dichlorophenyl)-1-[(*N*-methyl-*N*-phenylsulfonyl)amino]-4-[spiro(2,3-dihydrobenzthiophene-3,4′-piperidin-1′-yl)]butane *S*-oxide (**3**, mixture of *R* and *S*-sulfoxides) as our initial key lead structure having an $IC_{50} = 35$ nM for inhibition of [^{125}I]-MIP-1α

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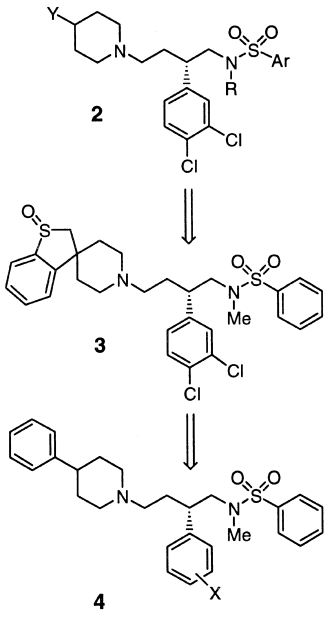
binding to CCR5.[14] Herein, the SAR for the central C-2-phenyl moiety will be described.

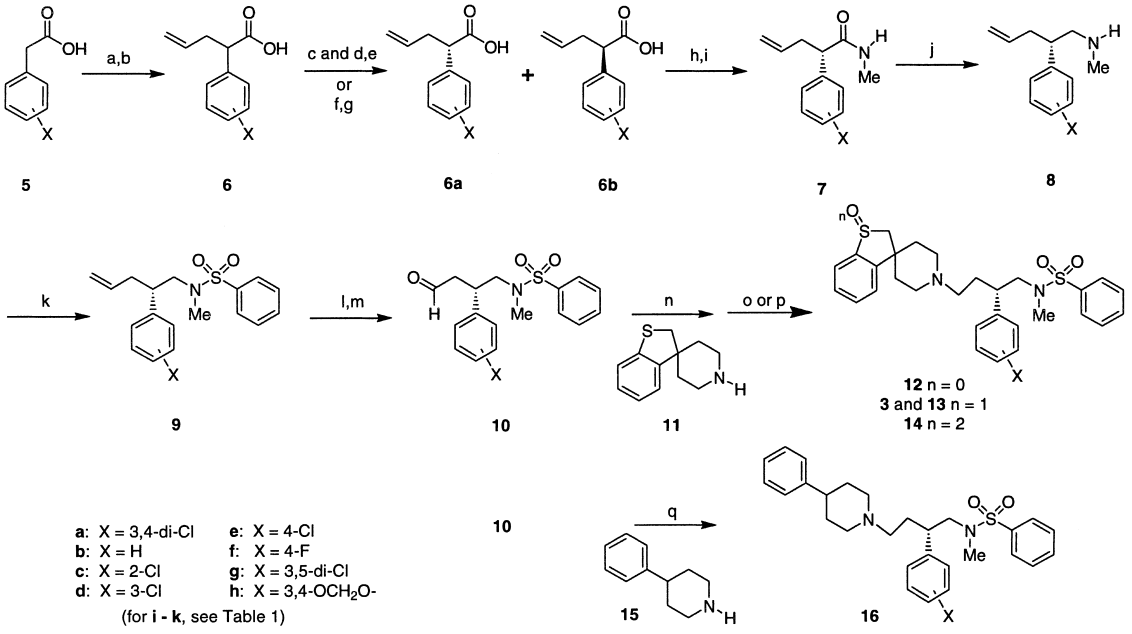
Using chemistry similar to that reported previously from these laboratories[13,15,16] (see Scheme 1) and several of the available intermediates, an initial SAR for the central phenyl ring was rapidly developed that indicated substitution on the phenyl could dramatically effect CCR5 inhibition, monosubstitution at the 3-position being preferred (see Table 1, compound **13d**). In addition, some early work on other piperidine derivatives indicated that the 4-phenylpiperidine as in **4** could replace the spiropiperidine of **3** while retaining most of the CCR5 binding potency, but with a greatly simplified structure.

Thus, in order to more easily explore the central phenyl ring substitution, a modified synthetic approach (see Scheme 2) was developed which could introduce a substituted aryl group at C-2 late in the synthesis rather than in the starting material as required in our established route. This new approach utilized an appropriately difunctionalized vinyl–tin intermediate **20**, which underwent Pd-catalyzed coupling[17] with a variety of aryl bromides to give the substituted styrenes **22**. Subsequent hydrogenation afforded the final racemic compounds in only two steps. The simplified piperidine moiety from above was employed in this alternate tin-coupling route.

The synthesis of **3** and several initial substituted C-2 phenyl derivatives (Scheme 1) began with the phenylacetic acids **5**. Alkylation of **5** with allyl bromide using lithium hexamethyldisilylamide (LiHMDS) provided racemic **6** that, if desired, could usually be resolved by repeated crystallization of the (*S*)-(−)-α-methylbenzylamine salts



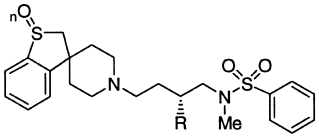
to afford the desired chiral (2*S*) enantiomer **6a**. Use of (*R*)-(+)-α-methylbenzylamine afforded the (2*R*) enantiomer **6b**. Alternatively, chemical resolution was possible by conversion of **6** to the diastereomeric (*S*)-(−)-4-benzyl-2-oxazolidinone derivatives, separation on silica gel, and hydrolysis with lithium hydroxide/hydrogen peroxide in THF.[16] Thus, the C-2 stereochemistry and phenyl substitution were set at the start. Conversion of **6a** to the amides **7** was done via the acid chlorides followed by treatment with methylamine. Reduction of **7** with DIBAL-H provided the *N*-methylamine intermediates **8**, which



Scheme 1. Reagents: (a) LiHMDS, THF, −70°C; (b) allyl bromide, −70°C to rt; (c) (*S*)-(−)-α-methylbenzylamine (0.6 equiv), *i*-PrOH, then two recrystallizations affords **6a**; (d) (*R*)-(+)-α-methylbenzylamine (1 equiv), *i*-PrOH, then two recrystallizations affords **6b**; (e) 2 N HCl, water, EtOAc (three extractions); (f) $(Me_3CCO)_2O$, TEA, THF, −70 °C to rt, then lithium salt of (*S*)-4-benzyl-2-oxazolidine in THF, −70 °C to rt; (g) LiOH, H_2O_2, 2:1 v/v THF/water, 0 °C, then Na_2SO_3 (aq), rt; (h) oxalyl chloride, DMF (cat), DCM, rt; (i) $MeNH_2$ (40% aq, 5 equiv), THF, 0 °C to rt; (j) DIBAL-H, THF, rt; (k) $PhSO_2Cl$, DIPEA, DCM, rt; (l) OsO_4 (cat), NMO, 2:1:1 v/v/v acetone/*t*-butanol/water, rt; (m) $NaIO_4$, 4:1 v/v THF/water, rt; (n) **11**-HCl, DIPEA, $NaBH(OAc)_3$, DCE, rt; (o) Oxone® (1.2 equiv), MeOH, −20 °C, 2–5 min; (p) Oxone® (3 equiv), MeOH, rt; (q) **15**, AcOH, $NaBH(OAc)_3$, DCE, rt.

were then sulfonylated with benzenesulfonyl chloride to afford the functionalized right hand portion (**9**). A two-step oxidation of the allyl group with osmium tetroxide/*N*-methylmorpholine-*N*-oxide (NMO) followed by sodium periodate cleavage of the intermediate diols afforded the aldehydes **10**. Reductive amination[18] of the spiropiperidine **11** with **10** using sodium triacetoxyborohydride in dichloroethane (DCE) provided the sulfide derivatives **12a–k**. Final oxidation of the sulfur with 1 equiv of Oxone®[19] at −20 °C afforded the sulfoxides **3** and **13b–k** (as 1:1 mixtures of sulfoxide diastereomers), while oxidation with excess Oxone® at room temperature afforded the corresponding sulfones **14a–k** (see Table 1). Alternatively, reductive alkylation of 4-phenylpiperidine (**15**) with aldehydes **10** resulted in the corresponding substituted central phenyl derivatives **16a–k** (see Table 2).

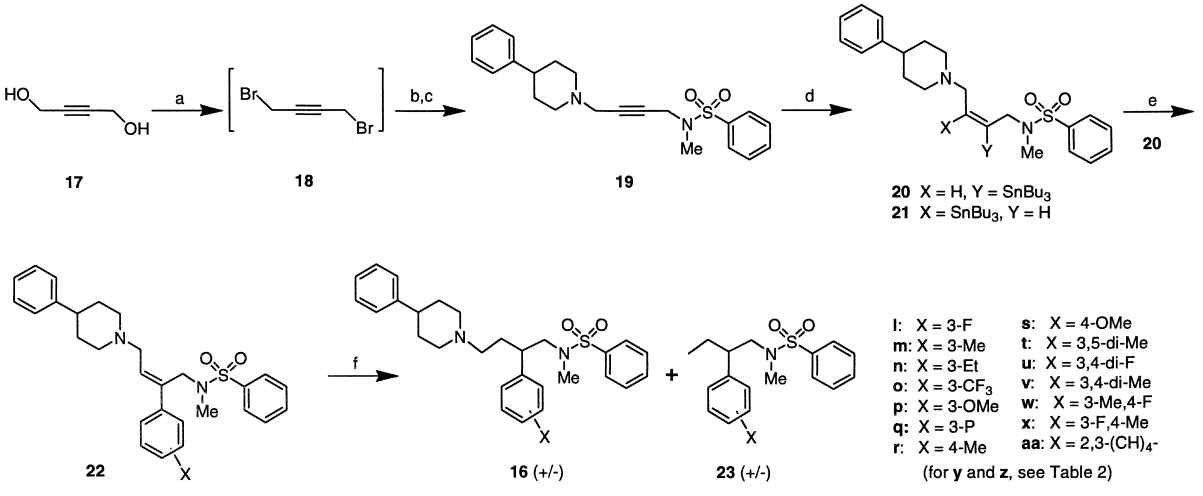
Table 1. Structures and CCR5 binding activities for the spiropiperidine derivatives **3**, **12**, **13**, and **14**



Compound	Structure		CCR5[a]
	n	R	IC_{50} (nM)[b]
12a	0	(*S*)-3,4-diCl-Phenyl	1000
3	1	(*S*)-3,4-diCl-Phenyl	35
14a	2	(*S*)-3,4-diCl-Phenyl	100
12b	0	(*R*/*S*)-Phenyl	450
13b	1	(*R*/*S*)-Phenyl	35
14b	2	(*R*/*S*)-Phenyl	30
13c	1	(*R*/*S*)-2-Cl-Phenyl	2000
14c	2	(*R*/*S*)-2-Cl-Phenyl	1300
12d	0	(*S*)-3-Cl-Phenyl	270
13d	1	(*S*)-3-Cl-Phenyl	10
14d	2	(*S*)-3-Cl-Phenyl	15
13e	1	(*S*)-4-Cl-Phenyl	270
13f	1	(*S*)-4-F-Phenyl	570
13g	1	(*R*/*S*)-3,5-diCl-Phenyl	90
14g	2	(*R*/*S*)-3,5-diCl-Phenyl	110
13h	1	(*S*)-3,4-OCH_2O-Phenyl	200
14h	2	(*S*)-3,4-OCH_2O-Phenyl	80
13i	1	(*R*/*S*)-2-Thienyl	180
14i	2	(*R*/*S*)-2-Thienyl	110
13j	1	(*R*/*S*)-3-Thienyl	100
14j	2	(*R*/*S*)-3-Thienyl	50
13k	1	(*R*/*S*)-Cyclohexyl	>1000 (36%)[c]
14k	2	(*R*/*S*)-Cyclohexyl	>1000 (42%)[c]

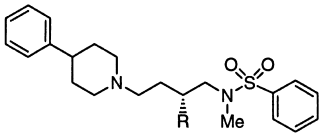
[a]See ref 13 for procedures.
[b]The IC_{50} results are an average of three independent titrations having calculated standard errors below 15%. The assay-to-assay variation was generally ±2-fold based on the results of the standard compound **13d**.
[c]These compounds gave the indicated % inhibition at 1000 nM.

Since the activities of the above 4-phenylpiperidine derivatives had only a 3-fold or less reduction in CCR5 binding affinity compared to the corresponding sulfoxide compounds (see below), this simplified left-hand moiety was utilized for further exploration of the central phenyl in the following modified synthetic route (Scheme 2). 2-Butyn-1,4-diol (**17**) was treated with 2.5 equiv of triphenylphosphine-dibromide to form the dibromide **18**. In a one-pot double displacement sequence, first with 0.75 equiv of the preformed sodium salt of *N*-methylbenzenesulfonamide followed by excess 4-phenylpiperidine (**15**), the crude **18** afforded the disubstituted alkyne **19** in 42% yield. Hydrostannylation[20] of **19** was carried out with $PdCl_2(Ph_3P)_2$ in THF to give primarily the desired readily separable regioisomer **20** over **21** in a 4:1 ratio (55 and 17%, 32% recovered **19**).[21] The best conditions found for the coupling of **20** to a variety of substituted phenyl bromides and 2- and 3-bromopyridine utilized $PdCl_2(Ph_3P)_2$ in *N*-methylpyrrolidine (NMP) at 70 °C in the presence of potassium carbonate. The inclusion of potassium carbonate neutralized any acid formed and served to provide a more reactive ligand for the Pd.[17] Yields of the coupled styrene products **22** were between 20 and 40%. Hydrogenation of **22** to the final racemic products **16** was done with $Pd(OH)_2$ in methanol and required the addition of acetic acid. Unfortunately, these conditions also promoted the partial hydrogenolysis of the allylic piperidine to give **23** and resulted in lower yields of **16**, usually about 50%. The



Scheme 2. Reagents: (a) (Ph_3P)-Br_2 (2.25 equiv), MeCN, 0 °C to rt; (b) $PhSO_2NHMe$ (0.75 equiv), NaH (60%), DMF, 0 °C; (c) crude **18** in DMF, 0 °C, addition of $PhSO_2NMe$-Na (0.75 equiv) from (b), 0 °C, 2 h; then **15** (1.5 equiv), DIPEA, rt; (d) Bu_3SnH, $PdCl_2(Ph_3P)_2$ (2 mol%), THF, rt; (e) X-PhBr, $PdCl_2(Ph_3P)_2$ (3 mol%), K_2CO_3, *N*-methylpyrrolidine, 70 °C, 16 h; (f) H_2 (50 psi), 20% $Pd(OH)_2$ (cat), HOAc, MeOH, rt.

Table 2. Structures and CCR5 binding activities for the 4-phenylpiperidine derivatives **16** and **27**



Compound	Structure R	CCR5[a] IC_{50} (nM)[b]
16b	(*R*/*S*)-Phenyl	120
16c	(*R*/*S*)-2-Cl-Phenyl	3000
16d	(*S*)-3-Cl-Phenyl	30
16f	(*S*)-4-F-Phenyl	~1000
16g	(*R*/*S*)-3,5-diCl-Phenyl	300
16h	(*S*)-3,4-OCH_2O-Phenyl	300
16i	(*R*/*S*)-2-Thienyl	400
16j	(*R*/*S*)-3-Thienyl	100
16k	(*R*/*S*)-Cyclohexyl	>1000 (26%)[c]
16l	(*R*/*S*)-3-F-Phenyl	100
16m	(*R*/*S*)-3-Me-Phenyl	80
16n	(*R*/*S*)-3-Et-Phenyl	110
16o	(*R*/*S*)-3-CF_3-Phenyl	500
16p	(*R*/*S*)-3-OMe-Phenyl	>1000 (45%)[c]
16q	(*R*/*S*)-3-Biphenyl	~10,000 (76%)[d]
16r	(*R*/*S*)-4-Me-Phenyl	200
16s	(*R*/*S*)-4-OMe-Phenyl	>1000 (40%)[c]
16t	(*R*/*S*)-3,5-diMe-Phenyl	160
16u	(*R*/*S*)-3,4-diF-Phenyl	570
16v	(*R*/*S*)-3,4-diMe-Pphenyl	60
16w	(*R*/*S*)-3-Me,4-F-Phenyl	180
16x	(*R*/*S*)-3-F,4-Me-Phenyl	110
16y	(*R*/*S*)-2-Pyridyl	~10,000 (61%)[d]
16z	(*R*/*S*)-3-Pyridyl	>10,000 (43%)[d]
16aa	(*R*/*S*)-2-Naphthyl	720
27a,b	(*R*/*S*) Benzyl	~10,000 (68%)[d]

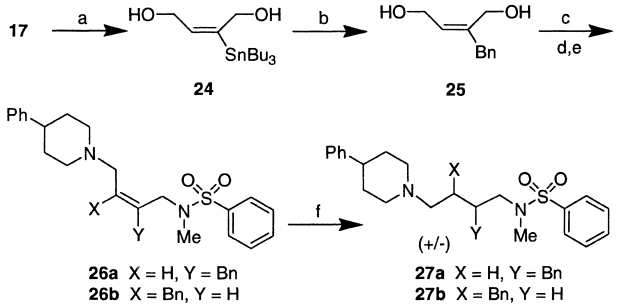
[a]See ref 13 for procedures.
[b]The IC_{50} results are an average of three independent titrations having calculated standard errors below 15%. The assay-to-assay variation was generally ±2-fold based on the results of the standard compound **13d**.
[c]These compounds gave the indicated % inhibition at 1000 nM.
[d]These compounds gave the indicated % inhibition at 10,000 nM.

final compounds **16l–aa** prepared by this route are also listed in Table 2.

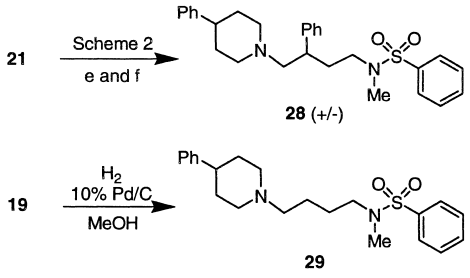
In order to prepare the C-2 benzyl derivative, the reaction of **20** with benzyl bromide was attempted. However, alkylation of the piperidine nitrogen occurred to give the quaternary amine. Thus, a modified route was utilized starting from the diol **17** (Scheme 3). Using analogous chemistry as above, the vinyl stannane **24** afforded 2-benzylbut-2-ene-1,4-diol (**25**). The incorporation of the sulfonamide and piperidine moieties was again achieved in a single reaction via the dibromide to afford **26a**,**b**. Final hydrogenation then afforded **27a**,**b** as a mixture of racemic regioisomers.

Finally, use of the isomeric stannane **21** afforded the isomerically pure racemic C-3 phenyl derivative **28** and hydrogenation of the alkyne **19** yielded the des-phenyl derivative **29** (Scheme 4).

These compounds were then evaluated for CCR5 affinity utilizing a [^{125}I]-MIP-1α binding assay.[14] An initial survey of monosubstitution at the 2-, 3-, and 4-phenyl



Scheme 3. Reagents: (a) Bu_3SnH, $PdCl_2(Ph_3P)_2$ (2 mol%), THF, rt; (b) benzyl bromide, $PdCl_2(Ph_3P)_2$ (3 mol%), K_2CO_3, NMP, 70 °C, 6 h; (c) (Ph_3P)-Br_2 (2.25 equiv), MeCN, 0 °C to rt; (d) $PhSO_2NHMe$ (0.75 equiv), NaH (60%), DMF, 0 °C; (e) crude dibromide in DMF, 0 °C, addition of $PhSO_2NMe$-Na (0.75 equiv) from (d), 0 °C, 2 h; then **15** (1.5 equiv), DIPEA, rt; (f) H_2 (50 psi), 20% $Pd(OH)_2$, HOAc, MeOH, rt.



Scheme 4.

positions resulted in a clear preference for substitution at the 3-position as seen in the chloro sulfoxide series **13c**, **13d**, and **13e** (IC_{50} = 2000, 10 and 270 nM, respectively). In agreement with previous results with **12a**, **3**, and **14a**,[13] in all cases the sulfides had the poorest CCR5 binding affinity (i.e. **12b** and **d**, IC_{50} = 450 and 270 nM) while the sulfone derivatives usually resulted in only slightly poorer binding than the corresponding sulfoxides (compare **13c** and **14c**, 10 and 15 nM, respectively). Thus, the following discussion deals mostly with the sulfoxide results. While it would have been of interest, any possible sulfoxide stereochemical preference for CCR5 interaction was not determined since the sulfoxide isomers were not separable. In agreement with the improved CCR5 binding seen with **13d** and **14d**, enhanced antiviral activity was also observed (see below).

Removal of both of the chlorines as in **13b** (IC_{50} = 35 nM, racemic[22]) actually resulted in a possible 2-fold improvement in binding compared to the 3,4-dichloro lead compound **3** (IC_{50} = 35 nM, chiral[22]) and within a 2-fold reduction compared to **13d**. Dichloro substitution at the 3,5-positions (**13g**, IC_{50} = 90 nM, racemic) was not additive and actually showed a moderate loss in potency compared to **13d**. 3,4-Disubstitution as in the methylenedioxy derivative **13h** (IC_{50} = 200 nM, chiral) decreased affinity relative to **3**. Replacement of the phenyl with either a 2- or 3-thienyl (**13i** and **13j**, 180 and 100 nM, both racemic) led to a moderate loss in binding while the cyclohexane analogue **13k** resulted in very poor activity. Thus, from this initial survey of substitutions on the C-2 phenyl, limited substitution at the 3-position or even no substitution appeared to be preferred.

From our initial screening results, there had been hints that the spiro-piperidine was not required and that a simple 4-phenylpiperidine might have similar binding (data not shown). Indeed, this modification in the above cases afforded very similar results, being within a factor of three in all cases as exemplified with the best 3-chloro compounds **13d** and **16d** having IC_{50}s of 10 versus 30 nM. Also, the unsubstituted compound **16b** was only 2-fold lower in binding than **16d**, the best 3-substituted compound in this series (IC_{50} = 120 nM, racemic, versus 30 nM chiral). Thus, this simplified piperidine derivative was utilized in a more rigorous exploration of the phenyl substitution. From these additional derivatives, other small substituted analogues, such as 3-fluoro (**16l**, IC_{50} = 100 nM, racemic), 3-methyl (**16m**, IC_{50} = 80 nM, racemic), and even 3-ethyl (**16n**, IC_{50} = 110 nM, racemic), exhibited potency within 2-fold of **16d**. Larger groups, such as trifluoromethyl (**16o**), methoxy (**16p**), and phenyl (**16q**), all had diminished CCR5 affinity. Surprisingly, the binding of the 4-methyl compound **16r** (IC_{50} = 200 nM, racemic) was appreciably better than would be expected from the 4-Cl (**13e**) and 4-F (**13f** and **16f**) results, although the 4-MeO compound (**16s**) was inactive. The benign effect of the 4-methyl carried over to the 3,4-dimethyl derivative (**16v**, IC_{50} = 60 nM, racemic), which appeared to be equipotent with the 3-chloro **16d**, as well as the 3-F,4-Me compound **16x** (IC_{50} = 110 nM, racemic). However, other 3,4-disubstitution was generally detrimental as anticipated (see **16u** and **16w**). Replacement of the central phenyl ring with a 2- or 3-pyridyl (**16y** and **16z**) resulted in substantial loss of CCR5 activity. Extension of the phenyl by a methylene unit was not tolerated as seen with the benzyl derivatives **27a**,**b** for which there was no apparent activity for any of the four isomers. All the vinyl intermediates **22** and the des-piperidine compound **23** were inactive (Scheme 2, IC_{50} >4000 nM, data not shown). The importance of the phenyl was also demonstrated by the lack of CCR5 affinity for the C-3 phenyl isomer **28** and the des-phenyl compounds **19** and **29** (61, 5, and 20% I at 10,000 nM, respectively).

The lead structure **3** was initially characterized in an isolated peripheral blood mononuclear cell (PBMC) viral replication assay[23] using the R5-tropic HIV-1 YU-2 isolate and gave IC_{95} values of 6 to 12 μM.[13] This activity indicated that inhibition of viral entry was possible with these small molecule CCR5 antagonists. With the enhancement in the CCR5 binding assay obtained with the 3-chlorophenyl derivative **13d** in the spiro-piperidine series, better results were also seen in this antiviral assay, giving an IC_{95} as low as 1500 nM,[24] while the sulfone **14d** afforded an IC_{95} of 3000 nM in the same assay. Use of the different R5-tropic strain SF162 afforded IC_{95}'s of 800 and 6000 nM for **13d** and **14d**, respectively. The unsubstituted compound **13b** also afforded inhibition similar to **13d** in the same assay. The best thiophene derivative (**14j**, IC_{50} = 50 nM) was not active in this assay (IC_{95} >25,000 nM). As expected from the CCR5 binding data, the antiviral activity was poorer in the 4-phenylpiperidine series, again the best activity was seen with the 3-chloro derivative **16d**, as well as the 3-methyl **16m**, both having IC_{95} of 6000 nM against the YU-2 strain. As expected, **13d** failed to give any inhibition when the X4-tropic NL4-3 strain was used (data not shown).

Herein, the results of our SAR study of the central phenyl ring of lead compound **3** were described. In the spiro-piperidine series, the 3-chloro derivative **13d** was identified as a having a 4-fold improvement in CCR5 binding affinity and resulted in enhanced antiviral inhibition in a PBMC based assay with an IC_{95} as low as 1500 nM and served thereafter as a standard in this assay.[24] Selectivity for CCR5 was maintained by **13d** in that the IC_{50}'s for CCR1, CCR2, CCR3, and CXCR4 were all >10,000 nM. Both **13d** and **14d** showed modest pharmacokinetics in the rat at 1 mg/kg iv and 10 mg/kg oral ($t_{1/2}$ = 0.7 and 0.8 h, F = 3 and 2%, respectively). In addition, the unsubstituted compound **13b** was found to be nearly as potent an antagonist as **13d** and **14d**. Comparable affinity was also found in the 4-phenylpiperidine series which allowed identification of other small substituents, such as 3-F (**16i**) and 3-Me (**16m**), as being nearly equipotent to 3-Cl. These results allowed the simplification of the synthesis of further piperidine derivatives as well as other structural modifications which will be reported in the future.

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14. For a description of the binding assay, see ref 13, footnote 25. The CCR5 binding titrations were usually done in triplicate with standard errors of < 15%. Assay-to-assay variability was generally ±2-fold based on the standard compound **13d**.

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21. NMR data for the isomeric stannanes **20** and **21**. Higher R_f product **20**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.8–0.9 (m, 6H), 0.87 (t, J = 7 Hz, 9H), 1.25–1.35 (m, 6H), 1.35–1.5 (m, 6H), 1.6–1.85 (2 m, 4H), 1.94 (dt, J = 3 and 8 Hz, 2H), 2.43 (m, 1H), 2.69 (s, 3H), 3.01 (brt, J_{H-Sn} = 25 Hz, 2H), 3.78 (d, J = 6 Hz, 2H), 5.44 (brt, J = 1.5 and 6 Hz, J_{H-Sn} = 34 Hz, 1H), 7.1–7.3 (2 m, 5H), 7.5–7.65 (m, 3H), 7.77 (dd, J = 1.5 and 7.0 Hz, 2H). Lower R_f product **21**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 7 Hz, 9H), 0.95–1.05 (m, 6H), 1.25–1.4 (m, 6H), 1.45–1.6 (m, 6H), 1.7–1.85 (m, 4H), 1.92 (dt, J = 3 and 8 Hz, 2H), 2.42 (m, 1H), 2.48 (s, 3H), 2.96 (m, 2H), 3.74 (brt, J_{H-Sn} = 23 Hz, 2H), 5.88 (brt, J = 6 Hz, J_{H-Sn} = 32 Hz, 1H), 7.1–7.3 (2 m, 5H), 7.5–7.65 (m, 3H), 7.77 (dd, J = 1.5 and 7.0 Hz, 2H).
22. Since the C-2 (*R*) configuration was much less potent than the (*S*),[13] for comparison with chiral derivatives the effective IC_{50} activities for the racemic derivatives can be assumed to be essentially half that indicated in the tables.
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24. There was extensive variation in the results from this PBMC assay as seen in the results for **13d**, which varied from 1500 to 12,500 nM. Thus, **13d** was always used as a standard and the results for the other compounds are reported in relation to the result for **13d** in the same assay.