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Antagonists of the Human CCR5 Receptor as Anti-HIV-1 Agents. Part 4: Synthesis and Structure–Activity Relationships for 1-[*N*-(Methyl)-*N*-(phenylsulfonyl)amino]-2-(phenyl)-4-(4-(*N*-(alkyl)-*N*-(benzyloxycarbonyl)amino)piperidin-1-yl)butanes

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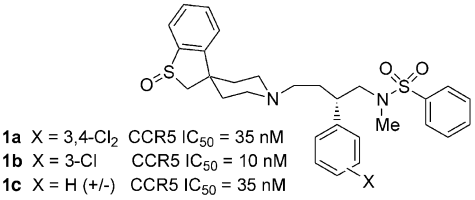
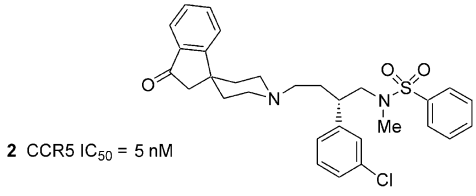
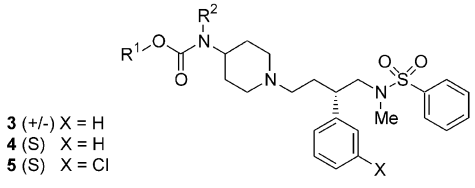
Abstract—(2*S*)-2-(3-Chlorophenyl)-1-[*N*-(methyl)-*N*-(phenylsulfonyl)amino]-4-[spiro(2,3-dihydrobenzthiophene-3,4′-piperidin-1′-yl)]butane *S*-oxide (**1b**) has been identified as a potent CCR5 antagonist having an $IC_{50} = 10$ nM. Herein, structure–activity relationship studies of non-spiro piperidines are described, which led to the discovery of 4-(*N*-(alkyl)-*N*-(benzyloxycarbonyl)amino)piperidine derivatives (**3**–**5**) as potent CCR5 antagonists.

The chemokine receptor CCR5, a member of the seven-transmembrane G-protein coupled family of receptors,[1] has been identified as a primary co-receptor with CD4 by which macrophage tropic HIV-1 virus strains infect their host cells.[2] These CCR5 utilizing HIV-1 strains, now called R5 variants, have been associated with the initial and early phases of HIV-1 infection, although they are generally present throughout the course of the disease AIDS. Given the importance of CCR5 for the establishment, and possible maintenance, of HIV-1 infection in vivo,[3] numerous efforts have been initiated in an effort to identify suitable CCR5 antagonists for use as potential therapeutic agents for the treatment of HIV-1 infection.[4–7]

In our previous manuscripts in this series,[8–10] the discovery 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 (**1a**), having an $IC_{50} = 35$ nM for inhibition of [^{125}I]-MIP-1α binding to CCR5, was described.[8] Subsequent investigation of the 2-phenyl substitution afforded **1b** ($IC_{50} = 10$ nM)[9] and then optimization of the spiropiperidine led to the spiro(indan-1-one-2,4′-piperidin-1′-yl) derivative **2** with







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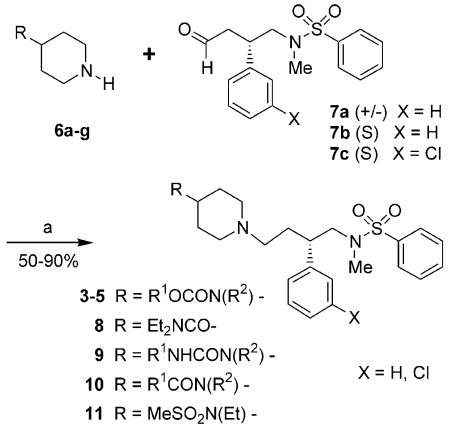
a CCR5 binding affinity of 5 nM.[10] Based on two possible models of the spiro portion of **2**,[10] further structure–activity relationship (SAR) studies as herein described led to the discovery of a new class of non-spiro piperidine CCR5 antagonists (**3**–**5**) containing the 4-(*N*-(alkyl)-*N*-(alkoxycarbonyl)amino)piperidine moiety.

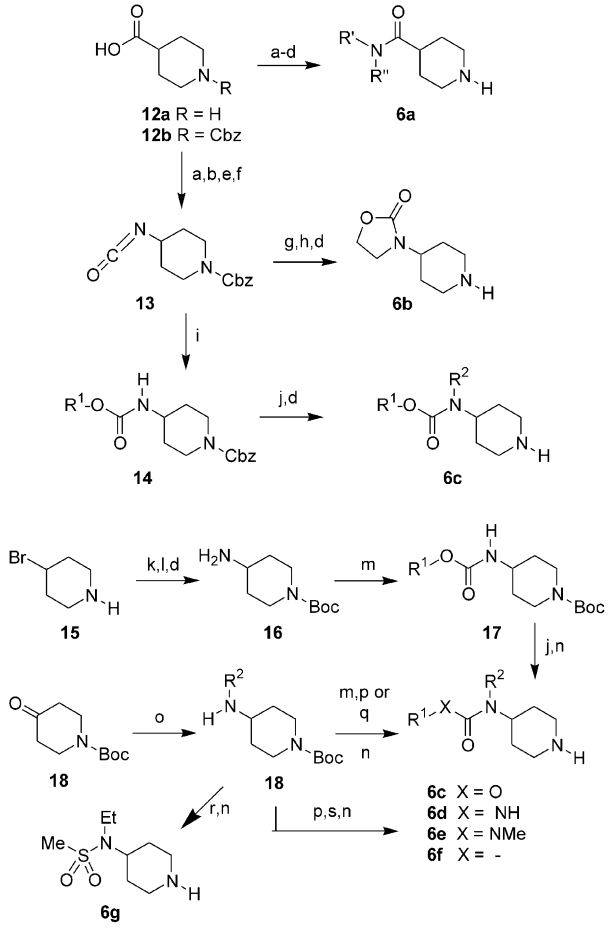
The synthesis of these modified piperidine derivatives was based on our previously described routes[9–12] (Scheme 1) and initially utilized the unsubstituted, racemic 3-phenyl-4-(*N*-methyl-*N*-phenylsulfonylamino)butanal (**7a**). In addition, selected compounds were also prepared in the chiral (*S*) and/or the (*S*)-3-chlorophenyl series (**4** and **5**) from **7b** and/or **7c**, respectively. The reductive amination of appropriately substituted piperidines **6a**–**g** (Scheme 2) using sodium triacetoxyborohydride in dichloroethane (DCE) afforded the coupled products **3**–**5**, **8**, and **9**–**11** (see Tables 1 and 2 for structures) in 50–90% yields.

The preparations of the piperidines that were utilized in Scheme 1 were carried out in several ways depending on the substitution pattern (Scheme 2). Some initial 4-carboxamide substituted piperidines **6a** (e.g., $R' = R'' = Et$) were prepared from piperidine-4-carboxylic acid (**12a**) by reaction of the *N*-Cbz protected acid chloride with various amines followed by hydrogenation to remove the Cbz. Placing the carbonyl *beta* to the piperidine as in **2** was first accomplished by Curtius rearrangement of the acyl azide of **12b** to give the isocyanate **13**. Reaction with methanol or *t*-butanol afforded the carbamate derivatives **14** ($R^1 =$ Me or *t*-Bu). *N*-Alkylation and/or Cbz removal then afforded the *N*-alkyl or *N*-H carbamate derivatives **6c**. The cyclic carbamate derivative **6b** was also obtained by reacting the intermediate isocyanate **13** with 2-chloroethanol followed by internal alkylation of the nitrogen using NaH in DMF. Two more direct routes were also developed depending on the alkoxy and *N*-alkyl substitution. Starting with commercial 4-bromopiperidine (**15**), the amine **16** was prepared via reduction of the azide obtained by displacement of the bromide in DMF after first Boc protection of the piperidine nitrogen. Acylation with various chloroformates afforded the *N*-H carbamates **17** which were then *N*-alkylated with an appropriate alkyl halide and sodium hydride in DMF. Final Boc removal was performed with HCl in methanol or with TFA. Alternatively, the *N*-alkyl moiety could be installed first by reductive amination of the corresponding alkylamine with Boc-piperidone (**18**). Acylation of **19** ($R^2 =$ Et, *n*-Pr, allyl) could then be done with a variety of chloroformates, acid chlorides, isocyanates, and methanesulfonyl chloride to afford other carbamate (**6c**), urea (**6d**), amide (**6f**), and sulfonamide (**6g**) substituted piperidines. A second alkylation of the distal urea N–H with methyl iodide prior to the Boc removal afforded the dialkyl ureas **6e**.

These compounds were then evaluated in a [^{125}I]-MIP-1α based binding assay of CCR5 stably expressed in Chinese hamster ovary (CHO) cells [8,13] (Tables 1 and 2). The initial investigation of non-spiro derivatives was done in the racemic, des-chloro series **3**. As previously reported,[10] the best spiropiperidine was the ketone **2** ($IC_{50} = 5$ nM) in which the carbonyl oxygen was *beta* to the C-4 piperidine position. Not surprisingly, the 4-amides, such as **8**, were not active in the CCR5 binding



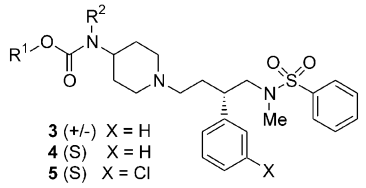
Scheme 1. Reagents: (a) HOAc or DIPEA (if **6** was an HCl salt), $NaBH(OAc)_3$, DCE.



Scheme 2. Reagents: (a) Cbz-Cl, NaOH, water/acetone; (b) oxalyl chloride, DMF (cat), DCM, rt; (c) R′R″NH, DCM, rt; (d) 10% Pd/C, H_2 (40 psi), MeOH; (e) NaN_3, acetone/water, 0 °C; (f) toluene, 80 °C; (g) 2-chloroethanol, DIPEA, rt; (h) NaH, DMF, rt; (i) MeOH, DIPEA or *t*-BuOH, $CuCl_2$, rt; (j) R^2X, NaH, DMF, rt; (k) $(Boc)_2O$, DIPEA, DCM; (l) NaN_3, DMF, rt; (m) R^1OCOCl, DIPEA, DCM, rt; (n) HCl, MeOH, rt or TFA, rt; (o) R^2NH_2, HOAc, $NaBH(OAc)_3$, DCE, rt; (p) R^1NCO, DIPEA, DMAP (cat), DCM, rt; (q) R^1COCl, DIPEA, rt; (r) $MeSO_2Cl$, DIPEA, DCM, rt; (s) MeI, NaH, DMF, rt.

assay ($IC_{50} > 10{,}000$ nM for several primary and secondary amides). However, the carbamates with their carbonyl now *beta* to the piperidine as in **2** showed interesting activity without the spiro structure. The *N*-ethyl Boc derivative **3d** was found to have an $IC_{50} = 30$ nM, being equipotent to the corresponding racemic deschloro analogue **1c**.[9] Since the N–H derivatives **3b–c** were only 1000 nM, the *N*-alkyl appeared to also play a critical role in the observed activity of **3d**. The *N*-methyl-*N*-(methoxycarbonyl)amino compound **3e** was found to be the minimal carbamate structure and was comparable to the simple 4-phenylpiperidine derivative ($IC_{50} = 150$ vs 120 nM).[9] Interestingly, **3a**, the cyclic version of **3e**, was essentially inactive (37% I@1000 nM), suggesting that the preferred orientation of the carbonyl is precluded with this cyclic constraint. Thus, configurations **A** and **B** of the carbamate moiety (Fig. 1) are not likely to be the active species, leaving configurations **C** and **D**, with **C** placing the carbonyl in the same position as the carbonyl of **2** (see structure **2**) in a proposed model.[10] The preferred orientation of the carbamate (either **C** or **D**) was the subject of further investigation and will be reported elsewhere.

Table 1. Structures and CCR5 binding activities for compounds **3–5**



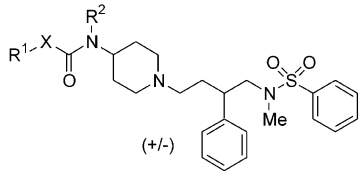
3 (+/-) X = H
4 (S) X = H
5 (S) X = Cl

Compd	R^1	R^2	CCR5[a] IC_{50} (nM)[c]	PBMC[b] IC_{95} (μM)[d]
3a	$-CH_2CH_2-$		>1000	nd[e]
3b	Me	H	1000	nd
3c	*t*-Bu	H	1000	nd
3d	*t*-Bu	Et	30	nd
3e	Me	Me	150	nd
3f	Me	Et	40	nd
3g	Me	*n*-Pr	20	nd
3h	Me	*n*-Bu	15	nd
3i	Me	*n*-C_6H_{13}	10	nd
3j	Me	*c*-C_6H_{11}–CH_2	6	25
3k	Me	Bn	100	nd
3l	Et	*c*-C_6H_{11}–CH_2	35	nd
3m	Bn	*c*-C_6H_{11}–CH_2	800	nd
3n	Et	Et	40	nd
3o	*t*-Bu	Et	25	nd
3p	*c*-C_6H_{11}–CH_2	Et	15	nd
3q	Ph	Et	10	nd
3r	Bn	Et	2	13
5r	Bn	Et	2	13
3s	Bn	Me	5	25
3t	Bn	*n*-Pr	2	25
5t	Bn	*n*-Pr	4	nd
3u	Bn	*n*-Bu	5	>13
3v	Bn	Allyl	2	0.8
4v	Bn	Allyl	1.5	0.8
3w	2-Me–C_6H_4–CH_2	*n*-Pr	4	nd
3x	3-Me–C_6H_4–CH_2	*n*-Pr	3	nd
3y	4-Me–C_6H_4–CH_2	*n*-Pr	3	nd
3z	4-CF_3–C_6H_4–CH_2	*n*-Pr	6	nd
3aa	4-NO_2–C_6H_4–CH_2	*n*-Pr	1.5	nd
4aa	4-NO_2–C_6H_4–CH_2	*n*-Pr	1.5	0.1–0.4[f]
3bb	4-NO_2–C_6H_4–CH_2	Allyl	2	0.2
5bb	4-NO_2–C_6H_4–CH_2	Allyl	2	0.2
5cc	3-$NH_2COC_6H_4$–CH_2	*n*-Pr	0.8	3
4dd	4-$NH_2COC_6H_4$–CH_2	*n*-Pr	2	nd
5dd	4-$NH_2COC_6H_4$–CH_2	*n*-Pr	3	0.4

[a]See refs 8 and 13 for a description of the binding assay.
[b]See ref 14 for a description of the PBMC antiviral assay.
[c]The IC_{50} values are an average of three independent titrations having calculated standard errors usually less than 15%. The assay-to-assay variation was generally less than ±2-fold based on the results for the standard compound **1b**.
[d]Usually, the result of a single experiment. For derivatives **j**, **r–t**, and **v**, **1b** was used as a standard and was 13–25 μM in these assays.
[e]No data.
[f]The range of three determinations.

The developing SAR for these carbamates (Table 1) in fact did indicate two distinct binding motifs. Increasing the size of the *N*-alkyl in the methoxycarbonyl series (**3e–k**) gave increasing activity, the optimum size being about that of the cyclohexylmethyl group of **3j**; however, the benzyl derivative **3k** was significantly poorer. With larger alkoxy groups, the activity rapidly diminished (**3l–m**). Conversely, keeping the *N*-alkyl constant with an ethyl moiety and increasing the size of the alkoxy group again led to enhanced activity as seen with the series **3f,n–r**, the best now being the benzyloxy compound **3r**. The optimum size of the *N*-alkyl group (**3r–v**) was determined to be between ethyl, *n*-propyl, or allyl ($IC_{50} = 2$ nM). While moderate sized groups afforded the expected intermediate binding activity (data not shown), the incompatibility of two large groups in the same molecule is highlighted with compound **3m**. A tentative hypothesis is that the latter benzyloxy compounds adopt conformation **C** in which the smaller *N*-alkyl group is adjacent to the piperidine,

Table 2. Structures and CCR5 binding activities for compounds **9** and **10**



Compd	X	R^1	R^2	CCR5[a] IC_{50} (nM)[b]
3s	O	Bn	*n*-Pr	2
9a	N–H	Me	H	1000
9b	N–H	Me	Et	120
9c	N–H	Bn	H	100
9d	N–H	Bn	*n*-Pr	2.5
9e	N–H	Ph	*n*-Pr	4
9f	N–Me	Bn	*n*-Pr	20
9g	N–H	(*R*)-α-Me–Bn	*n*-Pr	6
9h	N–H	(*S*)-α-Me–Bn	*n*-Pr	75
9i (*S*)	N–H	4-NO_2–Bn	Allyl	0.75
10a	—	Me	Et	120
10b	—	Ph	*n*-Pr	100
10c	—	Bn	*n*-Pr	3
10d	—	$PhOCH_2$	*n*-Pr	4
10e	—	$PhCH_2CH_2$	*n*-Pr	20
10f	—	4-NO_2–Bn	Allyl	2

[a]See ref 8 for a description of the binding assay.
[b]The IC_{50} values are an average of three independent titrations having calculated standard errors usually less than 15%. The assay-to-assay variation was generally less than ±2-fold based on the results for the standard compound **1b**.

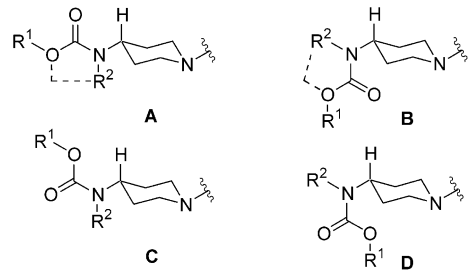


Figure 1. Four possible conformations of carbamate derivatives.

while the former series adopts conformation **D** in which the larger alkyl group is away from the piperidine and the smaller methoxy occupies the more restricted position. The better activity of the benzyloxy series then implies a superior interaction of the carbonyl of conformer **C** with the receptor. The extended conformation of the benzyl in conformation **C** was also in agreement with the good binding, but poor antiviral activity[14] (see below), previously seen with a 4-(3-phenylpropyl)piperidine compound ($IC_{50}=5$ nM, PBMC assay, $IC_{95}=50{,}000$ nM).[10]

Previously, the chiral, 3-chlorophenyl derivative **1b** had shown 3- to 4-fold improvement over the racemic unsubstituted compound **1c** in both the binding ($IC_{50}=10$ vs 35 nM) and antiviral assays. Unfortunately, for unknown reasons, neither the expected affinity enhancement nor any improvement in antiviral efficacy were realized for the chiral, 3-chlorophenyl analogues **5r** and **5t** with these non-spiro carbamate derivatives.

Substitution on the benzyl was also investigated. The isomeric 2-, 3-, and 4-methyl derivatives **3w**–**y** showed very little effect on binding, although the larger trifluoromethyl group of **3z** appeared to be detrimental, as well as 4-phenyl and 1- or 2-naphthyl (data not shown). However, the polar 4-nitro and 3- and 4-carboxamide moieties of **3aa**, **4aa**, **3bb**, and **4dd** showed equal or more potent binding which was also maintained in **5bb**–**dd**. Although not evident from the binding data ($IC_{50}=1$–2 nM), the 4-nitro and 4-carboxamide groups provided much improved antiviral activity (see below).

Other acyl groups were also investigated with the preparation of amides and ureas. The same SAR was seen regarding the relative size of the two groups with the best again being the benzyl related compounds as illustrated in the urea series **9a**–**e**. While neither showed improved activity over **9e**, the results of the α-methyl urea derivatives **9g** and **9h** showed that a stereochemical preference exists for the (*R*) isomer, thus indicating a preferred directionality for the benzyl moiety in the binding site. A second alkylation on the terminal nitrogen (**9f**) was always detrimental by at least 10-fold. Several amide derivatives were also quite potent as seen with **10a**–**e**; however, the benzamide **10b** was a considerably poorer inhibitor than **10c**, indicating that the binding site could not tolerate the extended confirmation of the planar benzamide, in agreement with the previously proposed binding model.[10] The effect of the 4-nitro substitution was also explored with **9i** and **10f**, which also afforded potent binding. The sulfonamide **11** (Scheme 1) was less active than **3f** ($IC_{50}=300$ vs 40 nM).

The more potent compounds were also tested in a PBMC cell-based assay using the R5 HIV-1 viral isolate YU-2.[14] Since considerable variation in results was obtained in this assay with only moderately potent inhibitors, **1b** was usually included as a standard during this assay period.[9] Disappointingly, the enhanced CCR5 binding seen for **3j**, **3s**–**t**, and amide **10c** did not translate into improved antiviral efficacy compared to **1b** ($IC_{95}=13$–25 μM vs 25 μM, respectively), although the ureas **9d** and **9e** did offer some improvement ($IC_{95}=3$ and 6 μM). Interestingly, while the CCR5 binding assay results were essentially the same, the allyl derivatives **3v** and **4v** finally showed significantly better antiviral activity compared to **3t** ($IC_{95}=$ both 800 nM vs 25 μM). Introduction of the polar 4-nitro and carboxamide groups of **4aa** and **5dd** also afforded enhanced antiviral activity in the PBMC assay ($IC_{95}=100$–400 nM). The combination of both the allyl and 4-nitro moieties in the carbamates **3bb** and **5bb** ($IC_{95}=200$ nM), urea **9i** ($IC_{95}=250$ nM), and especially amide **10f** ($IC_{95}=50$ nM) afforded the best efficacy in the PBMC assay with IC_{95}'s now in the lower nanomolar range.

Thus, with the synthesis of the initial carbamates, the spiro structure of **1** and **2** was found not to be required for potent CCR5 binding activity. Optimization of the two alkyl portions implicated two distinct binding motifs of which the *N*-alkyl-*N*-benzyloxycarbonylamino derivatives were the more potent. Further use of the *N*-allyl, substitution on the benzyl, and investigation of other linking functionality led to significantly enhanced antiviral activity of the *N*-allyl-4-nitrobenzyl compounds with IC_{95}'s of 50–200 nM in the PBMC assay. Further investigations of these findings in combination with other core structures will be reported in the near future.

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