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Bioorganic & Medicinal Chemistry Letters 15 (2005) 5012–5015
Bioorganic & Medicinal Chemistry Letters

Modulators of the human CCR5 receptor. Part 2: SAR of substituted 1-(3,3-diphenylpropyl)-piperidinyl phenylacetamides

John G. Cumming,[a,*] Anne E. Cooper,[b] Ken Grime,[b] Chris J. Logan,[b] Sharon McLaughlin,[a] John Oldfield,[a] John S. Shaw,[a] Howard Tucker,[a] Jon Winter[a] and David Whittaker[a]

[a]*Respiratory & Inflammation Research Area, AstraZeneca, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK*
[b]*AstraZeneca R&D Charnwood, Bakewell Road, Loughborough LE11 5RH, UK*

Received 27 July 2005; accepted 1 August 2005
Available online 9 September 2005

Abstract—SAR and DMPK studies led to the identification of substituted *N*-alkyl-*N*-[1-(3,3-diphenylpropyl)piperidin-4-yl]-2-phenylacetamides as potent and orally bioavailable ligands for the human CCR5 chemokine receptor.
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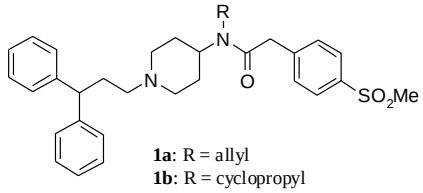
The chemokine receptor CCR5 is expressed on T-lymphocytes, monocytes, macrophages, dendritic cells, microglia and other cell types. These receptors detect and respond to several chemokines, principally "regulated on activation normal T-cell expressed and secreted" (RANTES) and macrophage inflammatory proteins (MIP) MIP-1α and MIP-1β, resulting in the recruitment of cells of the immune system to sites of disease. CCR5 is also a co-receptor for HIV-1 and other viruses, allowing these viruses to enter cells. Individuals who are homozygous for a 32-bp deletion in the gene encoding CCR5, whilst otherwise healthy, are strongly protected against HIV-1 infection.[1] Other studies indicate a role for CCR5 and its ligands in disorders such as rheumatoid arthritis,[2] multiple sclerosis,[3] transplant rejection[4] and inflammatory bowel disease.[5] These observations suggest that molecules that modulate the CCR5 receptor would have potential benefit in a wide range of diseases. The antagonism of CCR5 by small molecules has become an active area of research in many pharmaceutical companies.[1]

We have previously reported[6] our initial investigations into small molecule inhibitors of CCR5 which led to the identification of *N*-alkyl-*N*-[1-(3,3-diphenylpropyl)-piperidin-4-yl]phenylacetamides **1** as suitable lead compounds for further optimisation. Compounds **1**[6] had been shown to be functional antagonists at the human CCR5 receptor with binding IC_{50}'s below 100 nM. We now wish to report further improvements in CCR5 potency by SAR studies around the diphenylpropyl part of the structure.



1a: R = allyl
1b: R = cyclopropyl
1c: R = ethyl

We chose to fix on the amide *N*-ethyl substituent found in **1c** for our exploration of the SAR on the diphenyl portion.[7] A general scheme for the convergent synthesis of analogues **3** is shown in Scheme 1. Variously substituted 3,3-diphenylpropanals **4** were used in a reductive amination reaction with the piperidine **2**, which was prepared in three steps from 1-benzyl-4-piperidone. Aldehyde **4a** (used to prepare the di-(4-fluorophenyl) analogue **3a**) was prepared from the commercially available chlorobutyl compound **5** by elimination of the corresponding iodide followed by ozonolysis (Scheme 2). The other aldehydes **4** were prepared either from a substituted benzophenone **6** by Horner–Emmons

Keywords: CCR5; Chemokine receptor modulator.
* Corresponding author. Tel.: +44 0 1625517755; fax: +44 0 1625510823; e-mail: john.cumming@astrazeneca.com

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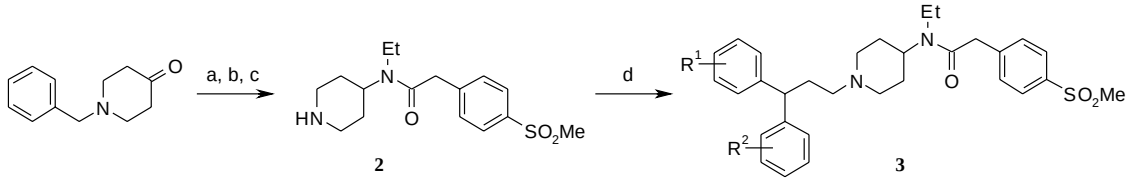
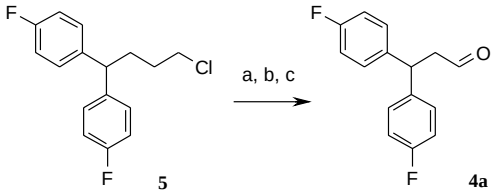
doi:10.1016/j.bmcl.2005.08.014



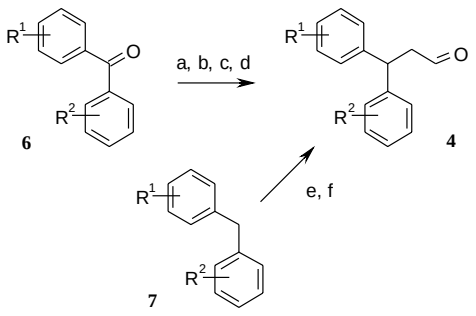
Scheme 1. Reagents and conditions: (a) $EtNH_2{\cdot}HCl$, $NaBH(OAc)_3$, MeOH, rt; (b) 4-SO_2Me-$C_6H_4CH_2CO_2H$, $^iPr_2NEt$, DCCI, DMAP, CH_2Cl_2, rt; (c) $HCOONH_4$, 30%Pd/C, EtOH, rt; (d) **4**, $NaBH(OAc)_3$, CH_2Cl_2, rt.



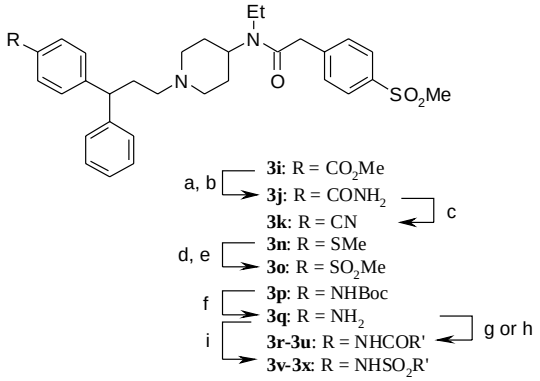
Scheme 2. Reagents and conditions: (a) NaI, acetone, reflux; (b) KO^tBu, THF, rt; (c) O_3, CH_2Cl_2, −78 °C; PPh_3, rt.

reaction followed by reduction of the alkene and two-step conversion of the ester group to an aldehyde, or from a substituted diphenylmethane **7** by C-alkylation with allyl bromide followed by ozonolysis (Scheme 3). Further compounds **3** were prepared by functional group interconversion of compounds prepared via these routes (Scheme 4). Thus, ester **3i** was converted to primary amide **3j** which was in turn dehydrated to give nitrile **3k**. Sulfide **3n** was oxidized with *m*-CPBA with subsequent reduction of the piperidine *N*-oxide to give sulfone **3o**. Aniline **3q** was obtained by removal of the *t*-butyloxycarbonyl group from **3p** and served as the precursor to amides **3r**–**3u** and sulfonamides **3v**–**3x**. CCR5 binding potency was assayed by displacement of the binding of [^{125}I]MIP-1α to membranes prepared from Chinese hamster ovary (CHO) cells stably expressing recombinant human CCR5.[8] The results are shown in Table 1.

Addition of fluorine in the 4-position of both phenyl rings (**3a**) resulted in a dramatic loss of potency. Incorporation of fluorine in the 4-position of just one phenyl ring (**3b**) also gave a drop in potency. In contrast, the addition of chlorine in the 4-position of one ring (**3c**)



Scheme 3. Reagents and conditions: (a) $LiN(SiMe_3)_2$, $(EtO)_2P(O)CH_2CO_2Et$, THF, 0 °C to rt; (b) $Pd(OH)_2$, H_2, EtOH, rt; (c) $LiAlH_4$, THF, 0 °C; (d) DMP, CH_2Cl_2, rt; (e) LDA, allyl bromide, −78 °C to rt; (f) O_3, CH_2Cl_2, −78 °C; Me_2S, rt.



Scheme 4. Reagents and conditions: (a) NaOH, MeOH, rt; (b) $(COCl)_2$, CH_2Cl_2, rt; NH_3/MeOH, rt; (c) $(CF_3CO)_2O$, pyridine, dioxane, 0 °C to rt; (d) *m*-CPBA CH_2Cl_2, rt; (e) $CH_3COOCHO$, CH_2Cl_2, 0 °C to rt; (f) TFA, rt; (g) R′CO_2H, CDI, Et_3N, CH_2Cl_2, rt; (h) R′COCl, Et_3N, CH_2Cl_2, rt; (i) R′SO_2Cl, Et_3N, CH_2Cl_2, rt.

gave an increase in potency (IC_{50} < 10 nM), although incorporation of chlorine in the 4-position of both rings (**3d**) was just as detrimental to potency as fluorine. We interpreted these results in terms of the two phenyl rings having differing SAR requirements; it appeared that 4-substitution with chlorine (though not with fluorine) in one ring led to an increase in potency but was not tolerated on the other ring. Separation of the two enantiomers of **3c** by chiral HPLC showed that the potency resided in one enantiomer (data not shown). Substitution of the 3-position of one ring with chlorine (**3e**, **3f**) led to a drop in potency. We decided to explore further substituents in the 4-position of one ring, keeping the other unsubstituted (**3g**–**3x**). In general, there is a trend for increasing potency with increasing electron-withdrawing power of the 4-substituent, as estimated by means of σ_p values[9] (Fig. 1). Compounds with strongly electron-withdrawing substituents such as cyano (**3k**), methanesulfonyl (**3o**) and trifluoromethyl (**3h**) were the most potent, while those with electron-donating substituents such as phenyl (**3m**) and amino (**3q**) were weakly active. However, the fluoro (**3b**) and carboxamido (**3j**) analogues seem to be less potent than expected on the basis of their electron-withdrawing power (Fig. 1). The receptor tolerates quite large substituents in this position, as shown by the phenylacetylamino (**3s**) and phenylacetylsulfonyl derivatives (**3w**). Interestingly, there is a marked drop in potency for the benzoylamino (**3t**) and benzenesulfonyl (**3x**) analogues relative to the acetylamino (**3r**, **3s**) and acetylsulfonyl (**3v**, **3w**) analogues, respectively. Clearly electronic effects alone are not sufficient to explain the SAR. A number of compounds with sub-

Table 1. CCR5 binding data for diphenylpropylpiperidine compounds

Compound	R^1	R^2	IC_{50}[a] (nM)
1a	—	—	13
1b	—	—	32
1c	—	—	18
3a	4-F	4-F	780
3b	4-F	H	310
3c	4-Cl	H	8.5
3d	4-Cl	4-Cl	760
3e	3-Cl	H	58
3f	3,4-di-Cl	H	78
3g	4-Me	H	28
3h	4-CF_3	H	2.3
3i	4-CO_2Me	H	7.1
3j	4-$CONH_2$	H	260
3k	4-CN	H	<1.0
3l	4-OMe	H	6.3
3m	4-Ph	H	85
3n	4-SMe	H	12
3o	4-SO_2Me	H	1.7
3p	4-NHBoc	H	200
3q	4-NH_2	H	200
3r	4-NHAc	H	26
3s	4-NHCOBn	H	5.9
3t	4-NHCOPh	H	130
3u	4-NHCO^{t}Bu	H	22
3v	4-$NHSO_2$Me	H	18
3w	4-$NHSO_2$Bn	H	11
3x	4-$NHSO_2$Ph	H	740
3y	4-Cl	3-F	19
3z	4-NHBoc	3-F	89
3aa	4-NH_2	3-F	105
3ab	4-NHAc	3-F	7.9
3ac	4-$NHSO_2$Me	3-F	9.1

[a] IC_{50}'s were derived from triplicate measurements whose standard errors were normally <5% in a given assay. Assay to assay variability was within ±2-fold based on the results of the standard compound **1a**.

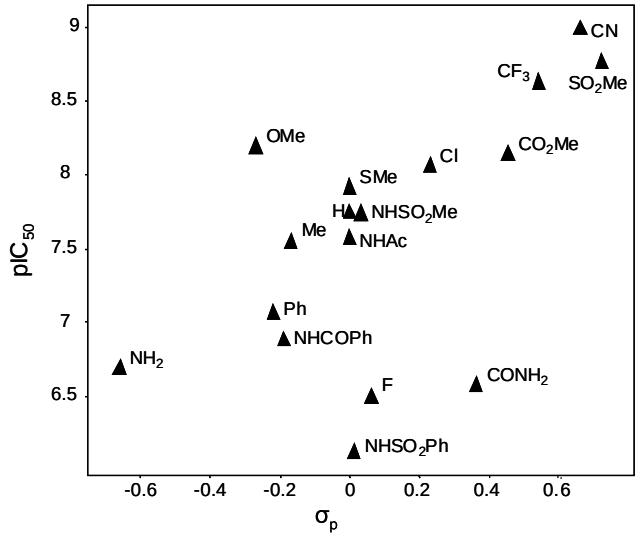


Figure 1. Plot of CCR5 potency ($-\log_{10}$ molar IC_{50}) versus σ_p values of R^1 for the compounds of Table 1 where R^2 = H.

stituents in the 4-position of one ring and fluorine in the 3-position of the other ring were also examined (**3y**–**3ac**). The SAR was parallel with that observed for the unsubstituted ring, with the IC_{50}'s of the fluoro analogues generally within about 2-fold of those of the corresponding des-fluoro analogues (e.g., compare **3y** with **3c**, **3aa** with **3q** and **3ac** with **3v**).

Compounds with IC_{50}'s below 10 nM were tested for their stability to metabolism by rat hepatocytes in vitro (at 1 μM).[10] The results, expressed as intrinsic clearance (Cl_{int}) values,[11] are shown in Table 2.[12] The methyl ester (**3i**) and cyano (**3k**) analogues were very rapidly cleared in vitro. Compounds **3c**, **3h** and **3l** were also rather unstable to metabolism. However, compounds **3o**, **3ab**, and **3ac** were more stable and were evaluated for oral pharmacokinetics (PK) in the rat using a cassette dosing protocol (compounds were dosed at ~2 mg/kg in a propyleneglycol formulation, $n = 2$ animals).[13] The sulfonamido (**3ab**), acetamido (**3ac**) and phenylacetamido (**3s**) compounds showed very low plasma levels (Table 2); however, the methanesulfonyl analogue **3o** showed a respectable area under the curve (AUC). Since the intrinsic clearances of these compounds are similar, it is possible that the absorption of **3s**, **3ab** and **3ac** is lower, consistent with the presence of a hydrogen bond donor in these three compounds but not in **3o**.[14] The active enantiomer of **3c**, the lead compound **1a** and the weakly potent di-(4-fluorophenyl) analogue **3a** were also tested for in vitro and in vivo PK (Table 2). 4-Chloro analogue **3c** and the unsubstituted diphenyl **1a** had a high intrinsic clearance in vitro, high clearance in vivo and low bioavailability. Compound **3a** showed the best PK profile of those tested, being stable in vitro with a low in vivo clearance and good bioavailability. This seems likely to be due to the two fluorine atoms reducing oxidative metabolism on the phenyl rings of the diphenylpropyl moiety and indicated to us a possible approach to improving the oral PK in this series.

The compounds in this series are functional antagonists at the CCR5 receptor as shown by their ability to inhibit the effects of the ligands MIP-1α, MIP-1β and RANTES

Table 2. Rat in vitro and in vivo PK data for selected compounds

Compound	Cl_{int}[a] (μL/min/10^6 cells)	AUC[d] (μM h)	Cl[e] (mL/min/kg)	F%[f]
3c	34[b]	—	46[g]	3[g]
3h	37[b]	—	—	—
3i	>150[b]	—	—	—
3k	88[a]	—	—	—
3l	41	—	—	—
3o	20 (± 3)[c]	0.174	—	—
3ab	17 (± 5)[c]	0.008	—	—
3ac	15 (± 4)[c]	0.002	—	—
3s	nt	0.012	—	—
3a	4 (± 0.8)[c]	1.87	10	56
1a	54	0.132	54	11

[a] For procedure see Ref. 10; nt = not tested.
[b] Cl_{int} reported is mean of two separate experiments.
[c] Cl_{int} reported is mean of at least six separate experiments with standard error of the mean shown in brackets.
[d] Plasma AUC 0–6 h, cassette dosing at ~2 mg/kg p.o., $n = 2$ animals.
[e] Compounds dosed at 1 mg/kg i.v., $n = 3$ animals.
[f] Compounds dosed at 4–10 mg/kg p.o., $n = 3$ animals.
[g] Data for active enantiomer.

in functional systems at concentrations close to their binding IC_{50}'s. For example, compound **3v** (binding IC_{50} = 18 nM) inhibited MIP-1β-stimulated calcium transients in CCR5-expressing CHO cells with an IC_{50} of 24 nM and inhibited the chemotaxis of human AlloT cells in response to MIP-1β with an IC_{50} of 31 nM.

In summary, SAR studies around the diphenyl portion of compounds **1** have led to the identification of 4-methanesulfonyl analogue **3o** as a highly potent (IC_{50} 1.7 nM) CCR5 antagonist with significant oral exposure. Further SAR and pharmacokinetic studies on this series will be the subject of future publications.

Acknowledgments

The authors thank our colleagues Lucy Ashman, Susan Mellor and Lorraine Newboult for developing and carrying out the biological assays, and Anthony Atkinson, the late Craig Martin and Steve Trigg for carrying out the DMPK studies.

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