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Modulators of the human CCR5 receptor. Part 3: SAR of substituted 1-[3-(4-methanesulfonylphenyl)-3-phenylpropyl]-piperidinyl phenylacetamides

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Abstract—SAR and PK studies led to the identification of *N*-(1-{(3*R*)-3-(3,5-difluorophenyl)-3-[4-methanesulfonylphenyl] propyl}piperidin-4-yl)-*N*-ethyl-2-[4-methanesulfonylphenyl]acetamide as a highly potent and selective ligand for the human CCR5 chemokine receptor with good oral pharmacokinetic properties.

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-base pair 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.[1,6]

We have previously reported our initial investigations into small molecule inhibitors of CCR5 which led to the identification of 1-(3,3-diphenylpropyl)-piperidinyl amides **1** as a suitable lead compound for further optimisation.[7] Further optimisation led to the identification of compound **2a** as a potent (IC_{50} 1.7 nM) and bioavailable CCR5 antagonist.[8] We now wish to report further optimisation of pharmacokinetics (PK) and potency in this series.[9]

In order to study the PK of **2a** in more depth, and to determine the absolute configuration that afforded greater potency, we developed an enantioselective synthesis of **2a** that could also be used to prepare analogues with different substitution on the undecorated phenyl ring. The route (Scheme 1) involved the diastereoselective conjugate addition of an aryl-cuprate species under the control of an imidazolidinone chiral auxiliary (**4**).[10] The substrate for the conjugate addition (**5**) was prepared by reaction of the acid chloride derived from cinnamic acid **3** with the imidazolidinone **4**. Addition of a cuprate prepared from an aryl Grignard to **5** mediated by di-*n*-butylboron triflate proceeded smoothly to give the product **6** as a single diastereoisomer (>95% dr by ^{1}H NMR). The auxiliary was removed either by reduction to the alcohol with subsequent oxidation to the aldehyde **7** using Dess–Martin periodinane, or by reduction directly to the aldehyde **7**

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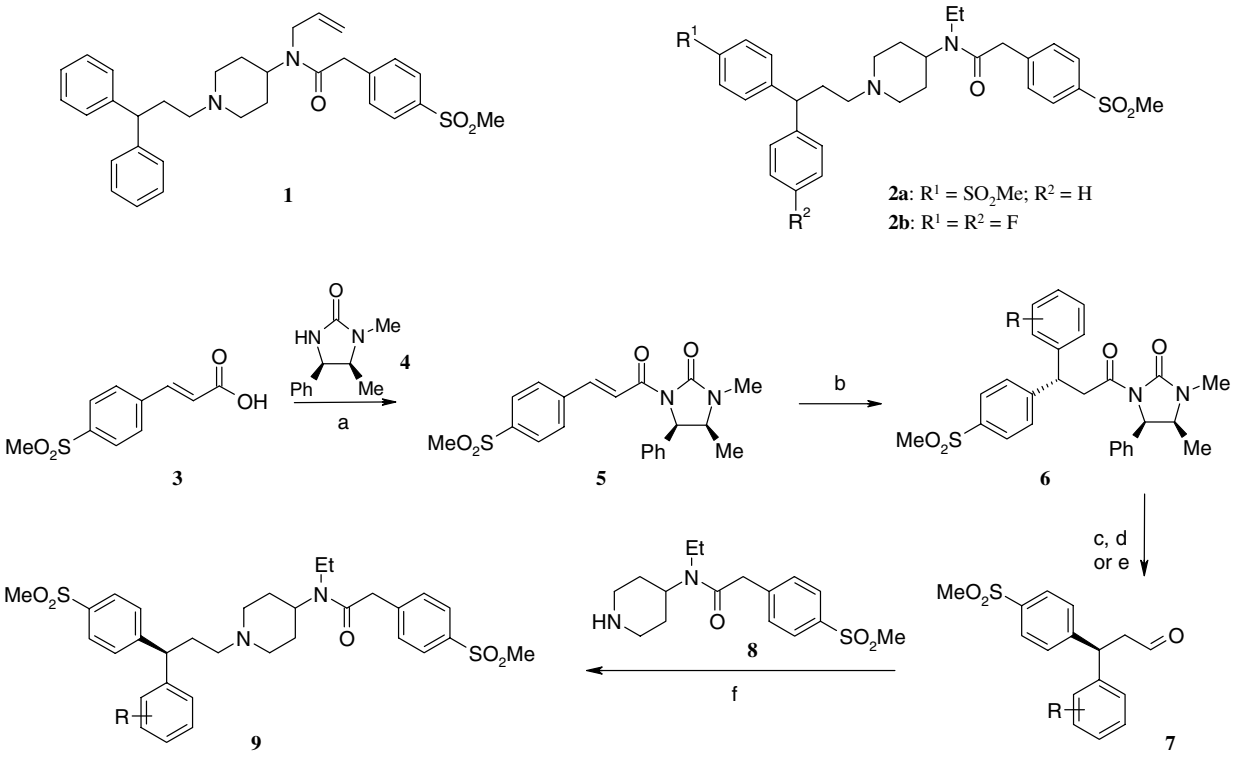
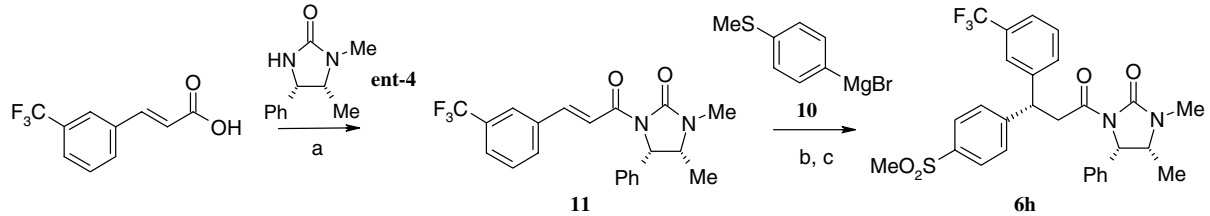


Scheme 1. Reagents and conditions: (a) $SOCl_2$, CH_2Cl_2, rt; **4**, $^{i}Pr_2NEt$, rt; (b) ArMgBr, CuI, TMEDA, THF, −78 °C; $^{n}Bu_2BOTf$, **5**, −78 °C to rt; (c) $LiAlH_4$, THF, 0 °C; (d) DMP, CH_2Cl_2, rt; (e) DIBAL-H, CH_2Cl_2, −78 °C; (f) **8**, $NaBH(OAc)_3$, CH_2Cl_2, rt.

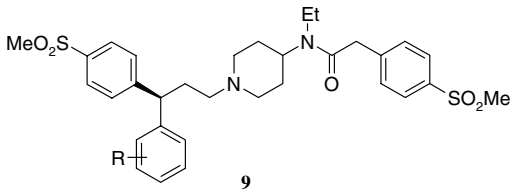
with di-*iso*-butylaluminium hydride. Reductive amination of **7** with 4-substituted piperidine **8**[8] gave the target compounds **9**. The 3-trifluoromethyl analogue **9h** was accessed[11] by the conjugate addition of 4-thioanisolemagnesium bromide (**10**) to the 3-trifluoromethylcinnamoyl derivative (**11**) of the opposite enantiomer of the auxiliary, with subsequent S-oxidation to the methanesulfonyl intermediate **6h** (Scheme 2).

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.[12] The results are shown in Table 1. Compound **9a** was approximately twice as potent as its racemate, **2a**, suggesting that it was the more active enantiomer. The rat PK of compound **9a**, the lead compound **1** and the di-4-fluorophenyl analogue **2b** was studied. Data for clearance (Cl), volume of distribution (V_{ss}) and terminal half-life ($t_{1/2}$) determined from iv dosing, and oral bioavailability (F%) are shown in Table 2. Compound **9a** had a moderately high clearance and was 13% bioavailable. The PK parameters of the lead compound **1** were similar to those of **9a**. In contrast, the di-4-fluorophenyl analogue **2b** had a low clearance, a longer half-life and was 56% bioavailable. It appears that the fluoro groups are acting to block oxidative metabolism at the 4-position of the phenyl rings, however this substitution pattern is also associated with loss of potency (IC_{50} 780 nM). We decided to try to reduce metabolism of **9a** without a loss of potency by exploring substitution of the undecorated phenyl. The results (Table 1) demonstrate clear SAR around this phenyl ring. The 3-chloro (**9d**) analogue maintained the potency of **9a** and the 3-fluoro (**9b**) analogue gave an increase in potency. Other small 3-substituents such as trifluoromethyl (**9h**), cyano (**9p**) and methoxy (**9q**) were somewhat less potent. More bulky groups such as isopropyl (**9o**) and *tert*-butyl (**9n**) led to a bigger drop in potency. The 4-fluoro analogue (**9c**) was around 50-fold less potent than **9a**, while other 4-substituents such as methoxy (**9f**) gave a large drop in potency. The 3,4-di-fluoro (**9e**) and 3,4,5-tri-fluoro (**9i**)



Scheme 2. Reagents and conditions: (a) $SOCl_2$, CH_2Cl_2, rt; **ent-4**, $^{i}Pr_2NEt$, rt; (b) **10**, CuI, TMEDA, THF, −78 °C; $^{n}Bu_2BOTf$, **11**, −78 °C to rt; (c) *m*-CPBA, CH_2Cl_2, rt.

Table 1. CCR5 binding data for diphenylpropylpiperidine compounds



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Compound	R	IC_{50}[a] (nM)
2a	—	1.7
2b	—	780
9a	H	0.76
9b	3-F	0.22
9c	4-F	46
9d	3-Cl	1.0
9e	3,4-Di-F	21
9f	4-OMe	132
9g	3,5-Di-F	0.32
9h	3-CF_3	20
9i	3,4,5-Tri-F	25
9j	2,3-Di-F	20
9k	2,6-Di-F	560
9l	2,5-Di-F	32
9m	3-F-5-Cl	1.1
9n	3-^{t}Bu	500
9o	3-^{i}Pr	110
9p	3-CN	56
9q	3-OMe	25

[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 **1**.

Table 2. Rat in vivo PK parameters for selected compounds

Compound	Cl[a] (mL/min/kg)	V_{ss}[a] (L/kg)	$t_{1/2}$[a] (h)	F%[b]
1	54	2.7	0.9	11
2b	10	1.7	2.4	56
9a	43	5.1	0.8	13
9b	54	5.3	1.8	nt
9g	28	5.3	2.6	38
9m	20	7.1	5.2	32

nt, not tested.
[a] Compounds dosed 1–2 mg/kg iv, $n = 3$ animals.
[b] Compounds dosed 5–10 mg/kg po, $n = 3$ animals.

analogues were intermediate in potency between the 3- and 4-fluoro compounds. *ortho*-Substitution with fluoro (**9j** and **9l**) led to a similar reduction in potency, while the analogue with a fluorine in both *ortho* positions (**9k**) was substantially less potent. However, the 3,5-di-fluoro analogue (**9g**) showed a significant increase in potency (IC_{50} 0.32 nM). The 3-fluoro-5-chloro analogue (**9m**) had similar potency to **9a**.

The rat PK of compounds **9b**, **9g** and **9m** was studied. **9b** had a high clearance and short half-life suggesting that the 3-fluoro was not having an effect on the metabolism. However, the 3,5-di-halo compounds (**9g** and **9m**) had a lower clearance, longer half-lives and good bioavailability. It appears that the incorporation of a halogen into both *meta* positions reduces oxidative metabolism of the phenyl ring. On the basis of its excellent potency and good rat PK, compound **9g** was selected for further studies. The (*S*)-enantiomer of **9g** was prepared via the same synthetic route (Scheme 1) but using the opposite enantiomer of the chiral auxiliary. The chiral purities of **9g** and **ent-9g** were determined by analytical chiral HPLC to be >97% ee and 96% ee, respectively. The CCR5 binding IC_{50} of **ent-9g** (which contained 2% of the (*R*)-isomer) was 40 nM, showing that essentially all the potency resides in the (*R*)-isomer. The absolute configuration of **9g** was confirmed as (*R*) by single crystal X-ray of the product from the conjugate addition reaction, **6g** (Fig. 1). Compound **9g** was tested for its ability to inhibit MIP-1β-stimulated calcium transients in human AlloT cells and was found to have an IC_{50} of 0.12 nM. Also **9g** was shown to have an IC_{50} of 2.8 nM in an assay measuring the inhibition of chemotaxis of human AlloT cells in response to MIP-1β. **9g** was found to be extremely selective for binding to CCR5 over other chemokine receptors (human CCR1, CCR2b, CCR3, CXCR1 and CXCR2) and other GPCRs (human M_1, M_2 and 5-HT_{2A}): it showed less than 50% inhibition at 10 μM in all cases, implying that its selectivity for CCR5 versus these other receptors is of the order of 30,000-fold or better. Compound **9g** had acceptable physicochemical properties: $\log D_{7.4} = 2.2$, plasma protein binding = 72% and 82% in rat and human plasma, respectively, thermodynamic aqueous solubility at pH 7.4 = 160 μM, $pK_a = 7.5$. Compound **9g** showed excellent oral bioavailability in the dog (Table 3). The iv and po PK profiles for **9g** in the rat and dog are shown in Figures 2 and 3, respectively.

Compound **9g** showed good stability to metabolism in human hepatocytes in vitro (Cl_{int} = 3 μL/min/10^6 cells)[8]

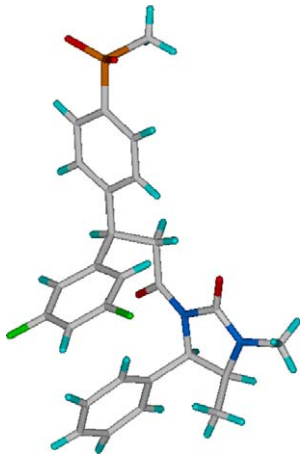

Figure 1. Single crystal X-ray structure of **6g** (R = 3,5-di-F) showing *R* absolute configuration at induced chiral centre.

Table 3. Dog in vivo PK parameters for compound **9g**

Cl (mL/min/kg)[a]	V_{ss}[a] (L/kg)	$t_{1/2}$[a] (h)	F%[b]
18	5.7	3.9	86

[a] Compound dosed 1 mg/kg iv, $n = 3$ animals.
[b] Compound dosed 4 mg/kg po, $n = 2$ animals.

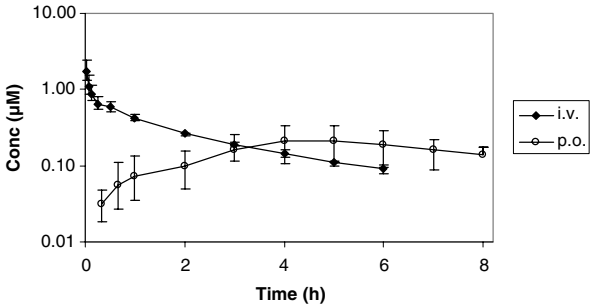

Figure 2. PK profile for compound **9g** in rat; dosing at 2 mg/kg iv ($n = 3$) and at 4 mg/kg po ($n = 3$).

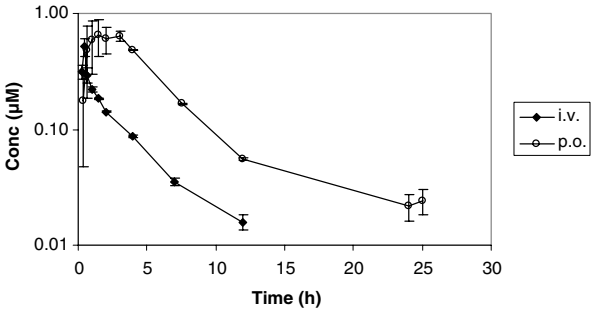

Figure 3. PK profile for compound **9g** in dog; dosing at 1 mg/kg iv ($n = 3$) and at 4 mg/kg po ($n = 2$).

and was tested for inhibition of human cytochrome P_{450} activity, achieving our target of IC_{50} >10 μM versus the 1A1, 2C19, 2C9 and 3A4 isoforms. However, **9g** gave an IC_{50} of 1.6 μM versus the 2D6 isoform and was found to have an IC_{50} of 7.3 μM in a hERG ion channel binding assay.[13] In view of the excellent potency and PK properties of **9g**, we predicted that an acceptable margin with respect to these two off-target activities could be achieved in humans.

In summary, SAR and PK studies in the homochiral 1-[3-(4-methanesulfonylphenyl)-3-phenylpropyl]piperidine series have led to the identification of **9g** as a highly potent antagonist at the human CCR5 receptor with good oral PK properties. This compound has potential as an oral treatment of diseases in which CCR5 plays a role.

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