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Synthesis and biological evaluation of phenyl piperidine derivatives as CCR2 antagonists

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Abstract—A series of phenyl piperidine derivatives possessing potent and selective CCR2 antagonist activity is reported. Structure–activity relationship (SAR) studies have established that incorporation of a second ring system adjacent to the aryl piperidine plays an important role in determining the CCR2 potency. Both a second piperidine ring and a 1,3-substituted cyclopentylamine have been probed as linkers. For the cyclopentylamine series, the 1*S*,3*R*-configuration exhibits much higher affinity for hCCR2 than the 1*R*,3*S*-configuration. Compound **3g** shows good selectivity over CCR1, CCR3, 5-HT and has an excellent P450 profile.

Chemokines, a large sub-family of chemoattractant cytokines, are small secreted proteins that attract and activate immune and non-immune cells.[1,2] They are generally classified into four sub-families: CXC, CC, CX3C and C chemokines, based on the configuration of conserved cysteine residues.[3] Monocyte chemoattractant protein-1 (MCP-1) is a CC chemokine and a potent chemoattractant or activator for monocytes. It is postulated to be primarily responsible for the selective recruitment of leukocytes from the circulation to the site of inflammation by binding to its seven transmembrane GPCR (CCR2) on the surface of monocytes and macrophages.[4,5] The evidence in favor of CCR2 and MCP-1 having dominant roles in monocyte chemotaxis and chronic inflammation was provided by CCR2 and MCP-1 knockout mice.[6,7] It has been recognized that CCR2 antagonists are potential therapeutic agents for various pathological conditions, such as psoriasis, uveitis, rheumatoid arthritis, multiple sclerosis, asthma, obesity, Chronic Obstructive Pulmonary Disease (COPD) and Crohn's Disease.[8–16]

Over the past few years, several series of CCR2 antagonists have been reported.[17–24] Among them, Forbes et al. disclosed indolopiperidine derivatives[22] (**1**, Fig. 1) that were not progressed due to unwanted 5-HT receptor affinities. Based on this structure, we made a series of

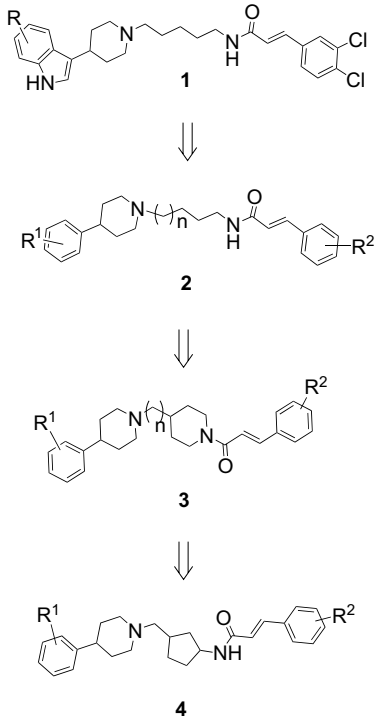

Figure 1. Evolution of Forbes indolopiperidine open chain derivatives (**1**) to closed ring analogs (**3** and **4**).

Keywords: CCR2 antagonist; MCP-1.
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modifications including changing the indole ring to a substituted phenyl, optimizing the linker length between the two nitrogens, and switching from the pentylamine chain to more rigid ring systems such as cyclopentylamine or piperidine.

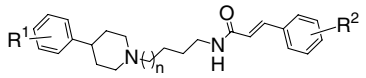
Initial SAR studies of the straight-chain series indicated that 4-(4-methoxyphenyl) piperidine and 4-(4-chlorophenyl) piperidine were good functional groups, with the optimized linker length between the nitrogens being four or five-carbons. Table 1 lists the CCR2 binding affinities for four-carbon and five-carbon analogs, respectively.[25] Binding affinity was diminished with linkers containing less than four carbons or greater than five carbons.

The affinity of these analogs generally was in the low single-digit micromolar range. It was reasoned that the phenyl-piperidine analogs would not possess the unwanted 5-HT activity that plagued the indolopiperidine analog, structure **1**. Based on this premise and the binding affinities of the phenyl-piperidine analogs we believed these were viable lead structures.

It was reasoned that increasing the rigidity of the linking sub-unit would hold the distance between the two nitrogens more constant and that decreasing the number of rotatable bonds might improve potency. In an effort to increase binding affinity of the phenyl-piperidine analogs the linking carbon chain was tied back to the amide nitrogen to form a ring.

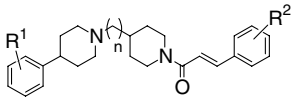
We were delighted to see that replacing the pentylamine linker with piperidin-4-yl methyl gave compounds with improved binding affinity. Table 2 lists the IC_{50} data for structure **3** containing a second piperidine ring as a linker. The compound with piperidin-4-yl methyl (**3g**) had higher CCR2 binding affinity than the compound with piperidin-4-yl ethyl (**3n**). For R^1, *para*-substituents gave better potency than *ortho*- or *meta*-substituents (**3c** vs **3a** and **3b**). For R^2, dichloro was favored over dimethoxy (**3g** vs **3j**).

Table 1. Open chain, four-carbon linkage analogs (structure **2**, Fig. 1)



Compound	R^1	R^2	*n*	CCR2B binding IC_{50} (μM)
2a	4-Chloro	4-Fluoro	1	3.1
2b	4-Chloro	3,4-Dichloro	1	2.9
2c	4-Chloro	3,5-Difluoro	1	4.5
2d	4-Chloro	3,4,5-Trifluoro	1	1.9
2e	4-Methoxy	4-Fluoro	1	2.3
2f	4-Methoxy	3,4-Dichloro	1	2.6
2g	4-Methoxy	3,5-Difluoro	1	3.8
2h	4-Methoxy	3,4,5-Trifluoro	1	3.4
2i	4-Chloro	4-Fluoro	2	1.8
2j	4-Chloro	3,4-Dichloro	2	1.2
2k	4-Methoxy	4-Fluoro	2	2.1
2l	4-Methoxy	3,4-Dichloro	2	1.5
2m	4-Hydroxy	3,4-Dichloro	2	12.6

Table 2. Analogs containing a second piperidine ring of structure **3** from Figure 1



Compound	R^1	*n*	R^2	CCR2B binding IC_{50} (μM)
3a	2-Methoxy	1	3,4-Dichloro	11.1
3b	3-Methoxy	1	3,4-Dichloro	4.0
3c	4-Methoxy	1	3,4-Dichloro	0.32
3d	4-Dimethylamino	1	3,4-Dichloro	0.95
3e	4-Hydroxy	1	3,4-Dichloro	0.51
3f	4-Methyl	1	3,4-Dichloro	2.2
3g	4-Chloro	1	3,4-Dichloro	0.30
3h	4-Chloro	1	3,4-Difluoro	2.0
3j	4-Chloro	1	3,4-Dimethoxy	5.9
3k	4-Chloro	1	3-Trifluoromethyl	1.4
3l	4-Chloro	1	4-Bromo	5.2
3m	4-Chloro	1	2-Fluoro-4-bromo	17% at 25 μM
3n	4-Chloro	2	3,4-Dichloro	2.9

Table 2 shows that the piperidine–methylene–piperidine compounds **3c**, **3e**, and **3g** possess binding affinities in the sub-micromolar range. The 4-chlorophenyl analog **3g** was chosen for further biological evaluation. The results are shown in Table 3 below.

It may be seen from the results shown in Table 3 that compound **3g** does not show 5-HT inhibition at 1 μM as compared with structure **1** which does have 5-HT activity. Furthermore compound **3g** is selective against CCR1 and CCR3 and possesses acceptable oral bioavailability of 19%. This compound was tested for in vivo efficacy. In the thioglycollate-induced peritonitis model in mice, compound **3g** inhibited monocyte influx by 58% when dosed at 30 mg/kg (ip).

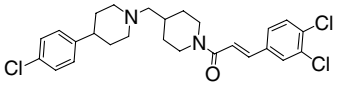
The synthetic route to prepare compounds of structure **3** is shown in Scheme 1. An appropriate piperidin-4-yl-alcohol was acylated with the desired acid chloride. The resulting alcohol was treated with methanesulfonyl chloride, then reacted with a substituted phenyl piperidine to give compound **3**.

The effect of replacing the second piperidine ring with a 5-membered carbocyle was also investigated. To this end cyclopentylamine analogs (**4** in Fig. 1) were synthesized using a similar synthetic route as Scheme 1. Table 4 lists binding data for a select group of these analogs.

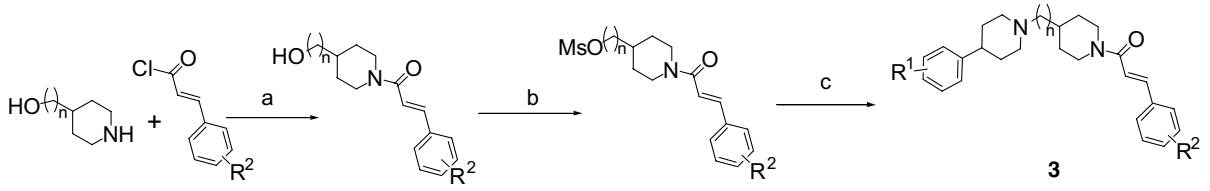
It is interesting to note that for the diastereomers shown in Figure 2, the 1*S*,3*R*-configuration is far more potent than the 1*R*,3*S*-configuration (**4c** vs **4d**, **4f** vs **4g**, **4i** vs **4j**). Compound **4i** was found to be the most potent with an IC_{50} of 80 nM in hCCR2 membrane binding assay.

In conclusion, we have identified a series of phenyl piperidine derivatives as potent and selective CCR2 antagonists. Compound **3g** shows good to excellent selectivity over CCR1, CCR3, and 5-HT and has an excellent P450 profile. Further optimization of potency

Table 3. Additional biological data for compound **3g**

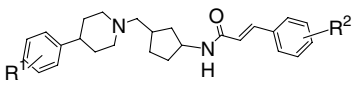


Assay	Condition	Parameter	Result
Binding	Whole cells	IC_{50}	0.3 μM
	Membranes	IC_{50}	0.3 μM
Chemotaxis	Cell based assay	IC_{50}	0.4 μM
Inhibition of cytochrome P450's	1A2 3A4 2C9 2C19 2D6	IC_{50}	>40 μM
Metabolism	Human liver microsomes	$T_{1/2}$	>100 min
CCR specificity	CCR1	% inhibition	0%
	CCR3	at 25 μM	29%
5-HT selectivity	5-HT1A, 5-HT1B, 5-HT2A, 5-HT3, 5-HT5A, 5-HT6	% inhibition at 1 μM	—
PK (rat)	1 mg/kg iv	C_{max}	3.4 μM
		T_{max}	0.1 h
		$T_{1/2}$	6.0 h
		Cl	0.22 mg/kg/μM h
	30 mg/kg po	C_{max}	1.4 μM
		T_{max}	17 h
		$T_{1/2}$	9.5 h
		Oral bioavailability	19%



Scheme 1. Synthesis of the compound **3**. Reagents: (a) Et_3N, CH_2Cl_2; (b) CH_3SO_2Cl, Et_3N, CH_2Cl_2; (c) substituted phenyl piperidines, CH_3CN, Et_3N, reflux.

Table 4. Cyclopentylamine analogs **4**



Compound	R^1	R^2	CCR2 binding IC_{50} (μM)
4a (*cis*-Racemate)	4-Methoxy	3,4-Dichloro	0.14
4b (*cis*-Racemate)	4-Methoxy	3,5-Dichloro	0.18
4c (1*S*,3*R*-Enantiomer)	4-Methoxy	3,5-Dichloro	0.16
4d (1*R*,3*S*-Enantiomer)	4-Methoxy	3,5-Dichloro	6.45
4e (*cis*-Racemate)	4-Methoxy	3,5-Difluoro	0.24
4f (1*S*,3*R*-Enantiomer)	4-Methoxy	3,5-Difluoro	0.16
4g (1*R*,3*S*-Enantiomer)	4-Methoxy	3,5-Difluoro	12.0
4h (*cis*-Racemate)	4-Methoxy	3,4,5-Trifluoro	0.13
4i (1*S*,3*R*-Enantiomer)	4-Methoxy	3,4,5-Trifluoro	0.08
4j (1*R*,3*S*-Enantiomer)	4-Methoxy	3,4,5-Trifluoro	8.40
4k (*cis*-Racemate)	3,4-Difluoro	3,5-Difluoro	0.79

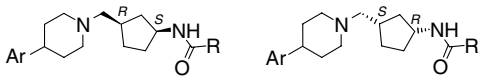


Figure 2. Cyclopentylamine diastereomers.

for these bioavailable CCR2 antagonists will be the subject of a future publication.

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25. The binding affinities were evaluated in THP-1 cells. THP-1 cells were incubated with 0.5 nM ^{125}I labeled MCP-1 (Perkin-Elmer Life Sciences, Inc., Boston, MA) in the presence of varying concentrations of either unlabeled MCP-1 (R&D Systems, Minneapolis, MN) or test compound for 2 h at 30 °C in a 96-well plate. Cells were then harvested onto a filter plate, dried, and 20 μL of Microscint 20 was added to each well. Plates were counted in a TopCount NXT, Microplate Scintillation & Luminescence Counter (Perkin-Elmer Life Sciences, Inc., Boston, MA). Blank values (buffer only) were subtracted from all values and drug treated values were compared to vehicle treated values. One micromolar cold MCP-1 was used for non-

specific binding. MCP-1 induced chemotaxis was run in a 24-well chemotaxis chamber. MCP-1 (0.01 μg/mL) was added to the lower chamber and 100 μL of THP-1 cells (1×10^{7} cell/mL) was added to the top chamber. Varying concentrations of test compound were added to the top and bottom chambers. Cells were allowed to chemotaxis for 3 h at 37 °C and 5% CO_2. An aliquot of the cells which had migrated to the bottom chamber was taken and counted then compared to vehicle. All data represent mean values.