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Substituted dipiperidine alcohols as potent CCR2 antagonists

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ABSTRACT

The synthesis and biological evaluation of a series of substituted dipiperidine alcohols are described. Structure–activity relationship studies led to the discovery of potent CCR2 antagonists displaying IC_{50} values in the nanomolar or subnanomolar range. The cinnamoyl compounds had higher binding affinities than the corresponding urea analogs.

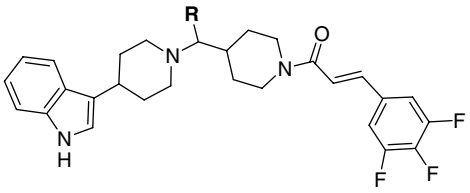
Chemokines (chemotactic cytokines) are small molecular weight proteins that play an important role in leukocyte migration and activation.[1] Chemokine receptors are mediators of inflammatory and immunoregulatory disorders and diseases including rheumatoid arthritis, asthma, and allergic diseases. Monocyte chemoattractant protein-1 (MCP-1) is a major chemoattractant for monocytes and memory T cells through binding to its specific cell-surface receptor, CC-chemokine receptor-2 (CCR2). CCR2 belongs to the G-protein-coupled seven-transmembrane receptor superfamily. MCP-1 and CCR2 knockout (KO) mice have demonstrated a phenotype of significantly decreased monocyte infiltration into inflammatory lesions.[2,3] In addition, such knockout mice are resistant to the development of experimental allergic encephalomyelitis, cockroach allergen-induced asthma, atherosclerosis, and uveitis. Many studies have implicated the importance of MCP-1 and CCR2 in a variety of inflammatory diseases. Rheumatoid arthritis and Crohn's disease patients have demonstrated a reduction in symptoms during the treatment with TNF-α antagonists at dose levels that correlate with decreases in MCP-1 expression and the number of infiltrating macrophages.[4] The therapeutic potential of CCR2 antagonists in preventing, treating, or ameliorating a CCR2-mediated inflammatory syndrome or disease has attracted considerable interest.[5–19]

In earlier reports,[20,21] we described both the phenyl piperidinyl derivatives as CCR2 antagonists with submicromolar binding affinity and the more potent carboxylic acid analogs with IC_{50} in the nanomolar range. The systematic structure–activity relationship studies on the CH_2 linker between the two piperidine moieties revealed that alcohol **1i** had much higher affinity for the human CCR2 receptor than the amine, ester, amide, and unsubstituted analogs (Table 1). We now report the identification of additional substituted dipiperidine alcohols as potent CCR2 antagonists and present details of our structure–activity relationship (SAR) studies.

The synthesis of compound **1i** and its analogs **6a–w** is outlined in Scheme 1.

Boc-protected piperidin-4-yl-acetic acid ethyl ester **2** was converted to α-bromoester **3** through bromination (LHMDS/TMSCl,

Table 1
Functional group effect on CCR2 binding affinity



Compound	R	CCR2 IC_{50} (nM)
1a	CH_2NMe_2	4800
1b	CO_2Me	3300
1c	$CH_2NHCONHEt$	2400
1d	$CONH_2$	1800
1e	H	470
1f	$CH_2NHCOMe$	80
1g	CH_2OCOMe	20
1h	CO_2H	5 ± 2
1i	CH_2OH	4 ± 2

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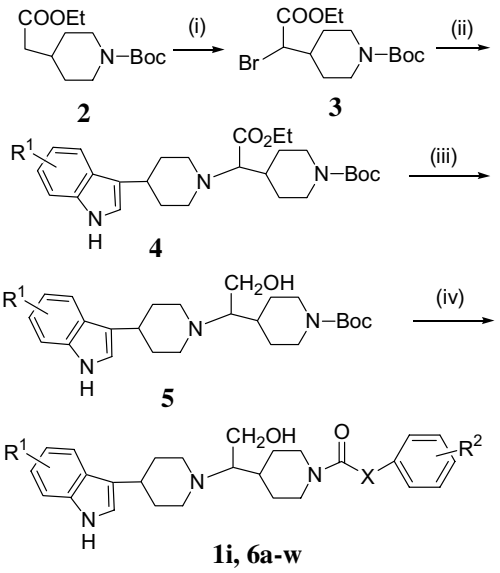
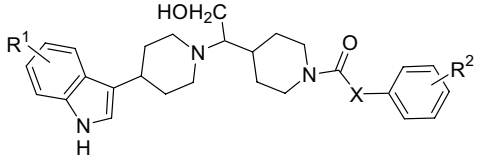


Scheme 1. Synthesis of alcohol analogs. Reagents and conditions: (i) LiHMDS, TMSCl, −78 °C, then Br_2 82%; (ii) substituted 4-(indol-3-yl)piperidine, CH_3CN, N(*i*-Pr)$_2$Et, reflux, 49–80%; (iii) LAH, 0 °C 80–90%; (iv) (a) TFA; (b) ArCH=CHCOCl or ArNCO, 21–82%.

Br_2). Then compound **3** was refluxed with the desired substituted 4-(indol-3-yl)piperidine in acetonitrile to give ester **4**, which was reduced to alcohol **5** with LAH. Alcohol **5** was converted to the target compounds **1i** and **6a–w** through deprotection of the Boc group with TFA, and acylation with appropriate acid chloride or isocyanate.

Table 2 lists the CCR2 binding affinities for the alcohol analogs **6a–w**. Halogen or trifluoromethyl substitution on the 3, 4, or 5-position of the cinnamoyl phenyl ring was preferred (less active 2-position substituted analogs were not listed). Substitution on the 5, 6, or 7-position of the indole ring was tolerated. Compounds with a 5-methoxy (**6o**) or a 7-methoxy group (**6n**) had higher affinity than the analog with a 6-methoxy group (**6k**). The urea analogs (**6t**, **6u**) had much lower affinity (67- and 45-fold, respectively) than the corresponding cinnamoyl compounds (**6e**, **6f**). Compounds **6e**, **6f**, and **6j** had subnanomolar binding affinities.

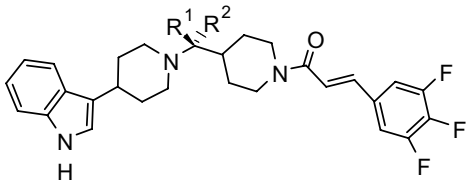
Table 2
CCR2 binding affinities of alcohol analogs



Compound	R^1	X[a]	R^2	CCR2 IC_{50} (nM)
6a	H	CH=CH	3-CF_3	10
6b	H	CH=CH	3-Br	9 ± 2
6c	H	CH=CH	3,4-diF	6 ± 2
6d	H	CH=CH	3-Br-4-F	2 ± 1
6e	H	CH=CH	3,5-diF	0.6 ± 0.3
6f	H	CH=CH	3,4-diCl	0.2 ± 0.2
6g	6-CH_3O	CH=CH	3,4-diCl	30
6h	5-F	CH=CH	3,4-diCl	20
6i	5-CH_3O	CH=CH	3,4-diCl	7 ± 3
6j	5-CH_3SO_2NH	CH=CH	3,4-diCl	0.6 ± 0.1
6k	6-CH_3O	CH=CH	3,4,5-triF	50
6l	5-F	CH=CH	3,4,5-triF	40
6m	5-CO_2CH_3	CH=CH	3,4,5-triF	20
6n	7-CH_3O	CH=CH	3,4,5-triF	10
6o	5-CH_3O	CH=CH	3,4,5-triF	6 ± 1
6p	5-CH_3CONH	CH=CH	3,4,5-triF	2 ± 2
6q	5-OH	CH=CH	3,4,5-triF	1 ± 1
6r	5-CH_3SO_2NH	CH=CH	3,4,5-triF	1 ± 1
6s	5-NH_2	CH=CH	3,4,5-triF	1 ± 1
6t	H	NH	3,5-diF	40
6u	H	NH	3,4-diCl	9 ± 5
6v	5-CO_2H	NH	3,4-diCl	10
6w	5-CO_2CH_3	NH	3,4-diCl	50

[a] All CH=CH are trans.

Table 3
CCR2 binding affinities of the different enantiomers



Compound	R^1	R^2	CCR2 IC_{50} (nM)
7a	H	CH_2OH	2.4 ± 2.0
7b	CH_2OH	H	10

Compounds **1i** and **6a–w** had one chiral center. The enantiomers were prepared from the known chiral intermediate through the same synthetic route outlined in Scheme 1. The biological data indicated that (*S*)-enantiomer was more potent than (*R*)-enantiomer. For example, compound **7a** had higher binding affinity than compound **7b** (Table 3). In a chemotaxis assay using the THP-1 cell line, compound **7a** effectively antagonized the MCP-1-induced effect with an IC_{50} of 3.5 nM. The IC_{50} was 0.38 nM when the MCP-1-induced flux of Ca^{2+} ions was measured instead of chemotaxis.

In summary, substituted dipiperidine alcohols have been synthesized and identified as potent CCR2 antagonists with IC_{50} values in the nanomolar or subnanomolar range. Alcohol **1i** had much higher affinity for the human CCR2 receptor than the amine **1a**, ester **1b**, amide **1d**, and unsubstituted analog **1e**. The cinnamoyl compounds had higher binding affinity than corresponding urea analogs and three analogs (**6e**, **6f**, and **6j**) had IC_{50} values below 1 nM. Further pharmacology studies on this series will be reported in due course.

Acknowledgments

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