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Letters

Novel, Orally Bioavailable γ-Aminoamide CC Chemokine Receptor 2 (CCR2) Antagonists

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Abstract: Through modification of a screening hit we have discovered a structurally distinct new lead, (2*S*)-*N*-[3,5-bis(trifluoromethyl)benzyl]-2-(4-fluorophenyl)-4-(4-phenylpiperidin-1-yl)butanamide (**11**), which has subsequently served as the departure point for an ongoing program targeting CCR2 antagonists. Optimization of **11** leading to antagonists **26** and **37** is described. Antagonist **26** was shown to have good oral bioavailability in rats. Antagonist **37** had a CCR2 IC_{50} of 59 nM and excellent potency in a functional assay measuring inhibition of MCP-1 induced monocyte chemotaxis (IC_{50} of 41 nM).

Chemokines (chemotactic cytokines) are structurally related small proteins that play an important role in leukocyte migration and activation.[1] Most chemokines are classified as belonging to one of two major subfamilies that are distinguished on the basis of the arrangement of the first two conserved cysteines in their sequences: the CC family that contains adjacent cysteines; the CXC family in which the cysteines are separated by a single intervening amino acid. Monocyte chemoattractant protein-1 (MCP-1, CCL2), included within the CC subfamily of chemokines, mediates chemotaxis of monocytes to inflammatory sites primarily through interactions with its CC chemokine receptor 2 (CCR2).[2] CCR2 is a member of the G-protein-coupled seven-transmembrane receptor superfamily and is expressed on most blood borne monocytes. Recent studies have linked MCP-1 and CCR2 to various inflammatory diseases[3] including rheumatoid arthritis (RA), atherosclerosis, and multiple sclerosis. Notably, MCP-1 expression is elevated in RA inflamed synovium,[4] and this elevated expression can be reduced by administration of antiarthritic drugs.[4b] Relating to atherosclerosis, studies conducted with MCP-1 and CCR2 knockout mice maintained on high-fat diets showed reductions in aortic lesion size, macrophage content, and necrosis.[5] Consequently, the therapeutic potential of CCR2 antagonists for treating inflammatory diseases has stimulated considerable interest. Several CCR2 antagonists have already been described in the literature.[6] Most of these have one or more disadvantages, such as poor binding affinity and/or functional activity,[6e] undisclosed pharmacokinetic properties,[6b−e] and off-target activities.[6b,c] This communication describes the discovery of a new class of potent, orally bioavailable CCR2 antagonists based on a γ-aminoamide core **4** (Figure 1).

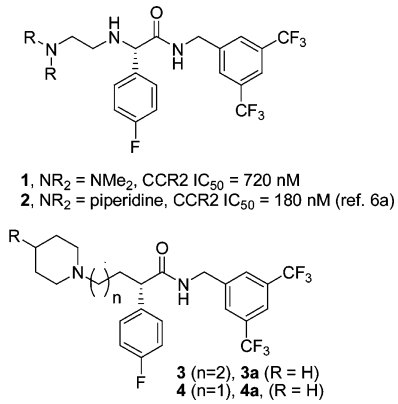

Figure 1. Leads **1** and **2** and target analogues **3** and **4**.

Screening of the Merck sample collection identified **1** as a potential lead with a CCR2 IC_{50} of 720 nM.[7] Subsequent modification of **1** revealed that incorporation of a piperidine moiety in place of *N*,*N*-dimethylamine results in improved binding affinity (**2**, IC_{50} = 180 nM).[6a] Further optimization of **2** led to additional potency enhancements, but pharmacokinetic studies in rats revealed rapid clearance as an issue for this series.[6a] To address this concern, we set out to explore modifications to the backbone of **2** by replacing the α-amine with a carbon atom (**3a**) or by removing it entirely with an associated shortening of the amide to amine chain length (**4a**). In addition, because of the structural similarity of the resulting analogues with CCR5 antagonists studied within our laborato-

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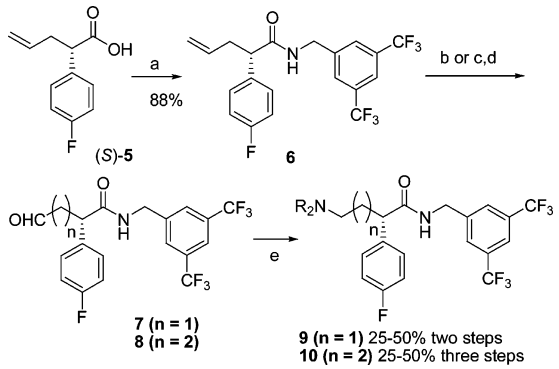
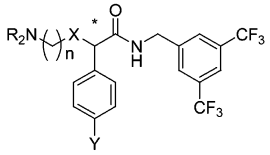
Scheme 1. Preparation of Three-Carbon- and Four-Carbon-Chain Analogues[a]



[a] (a) 3,5-Bis(trifluoromethyl)benzylamine, EDC, HOBt, DIEA, DCM, room temp; (b) O_3, DCM, −78 °C; DMS, −78 °C to room temp; (c) BH_3, THF; $NaBO_3$; (d) $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C; (e) HNR_2, $NaB(OAc)_3H$, 4 Å molecular sieves powder, room temp.

Table 1. Binding Affinities[7] for **1**, **2**, and Carbon Chain Analogs with and without Piperidine 4-Substitution



Cmpd	NR_2	Y	*	n	X	CCR2 IC_{50} (μM)[a]
1	NMe_2	F	*S*	2	NH	0.72 ± 0.03
2	piperidine	F	*S*	2	NH	0.18 ± 0.03
3a	piperidine	F	*S*	2	CH_2	1.0
4a	piperidine	F	*S*	1	CH_2	1.1
11	4-phenylpiperidine	F	*S*	1	CH_2	0.15 ± 0.01
12	4-phenylpiperidine	F	*S*	2	CH_2	1.1
13	benzyl allyl(piperidin-4-yl)carbamate	F	*S*	1	CH_2	14%[c]
14	benzyl allyl(piperidin-4-yl)carbamate	F	*S*	2	CH_2	-18%[c]
15[b]	4-phenylpiperidine	H	*S*	2	NH	0.83
16	4-phenylpiperidine	F	*R*	1	CH_2	0.93

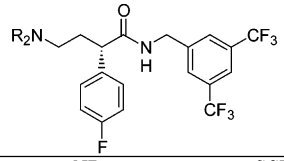
[a] SD given when IC_{50} is an average of three or more determinations. Otherwise one to two determinations were performed. [b] H in place of F has little effect on IC_{50}; replacing F with H in **2** gives an IC_{50} of 0.22 μM. [c] % inhibition at 1 μM.

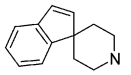
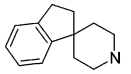
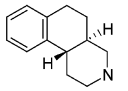
ries, we decided to incorporate several of the optimized substituted piperidines found in those antagonists.[8]

Analogues were prepared as described in Scheme 1. The requisite scalemic acid (*S*)-**5** was synthesized according to known methodology.[9] Standard peptide coupling of (*S*)-**5** with 3,5-bis(trifluoromethyl)benzylamine provided amide **6**. Elaboration into homologous aldehydes **7** and **8** was accomplished by ozonolysis and by a hydroboration−oxidation, Swern oxidation sequence, respectively. Compounds **7** and **8** are unstable and slowly decompose, even when stored in a freezer. Reaction of **7** and **8** with various amines in the presence of sodium triacetoxyborohydride gave the target analogues **9** and **10** in modest yields.

Neither **3a** nor **4a** (Table 1), which directly correspond to lead **2** with four- and three-carbon amine to amide chain lengths, respectively, was as potent as **2**. Two optimized 4-substituted piperidines from our CCR5 program (4-phenylpiperidine[8a] and benzyl allyl(piperidin-4-yl)carbamate[8b]) were incorporated in both chain length series to make analogues **11**−**14**. Only **11**, with 4-phenylpiperidine in the three-carbon chain length series, had improved potency over its unsubstituted piperidine predecessor **4a**. No potency enhancement was observed in the four-carbon chain length series (**12**), having the same chain length as our original lead **1**. Similarly, incorporation of 4-phenylpiperidine into the diamine lead decreased potency relative to simple piperidine analogue **2**, suggesting a different SAR pattern (**15**). Both analogues prepared using benzyl allyl(piperidin-4-yl)carbamate (**13**, **14**) were inactive, implying divergent SAR from the CCR5 program. Interestingly, despite the structural similarity of **11** with some of the CCR5 compounds studied at Merck, no hits from the CCR5 program were found in our original screening for CCR2. Finally, we evaluated the importance of stereochemistry α to the amide carbonyl by preparing **16** (Table 1) and found that, as with the original lead, the preferred absolute stereochemistry is *S*.

Table 2. Binding Affinities[7] for Analogues of **11**



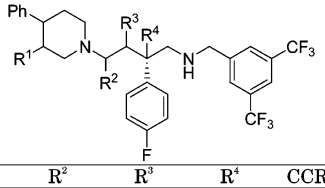
Compd	NR_2	CCR2 IC_{50} (μM)[a]
17	3-phenylazetidine	18%[b]
18[c]	3-phenylpyrrolidine	44%[b]
19[c]	4-phenylhexahydroazepine	3%[b]
20	4-phenylpiperazine	11%[b]
21[c]	3-methyl-4-phenylpiperazine	0.78
22	4-cyclohexylpiperidine	20%[b]
23	4-(3-thiophene)piperidine	0.16 ± 0.01
24[c]	3-benzylpiperidine	43%[b]
25	tetrahydroisoquinoline	15%[b]
26		0.08 ± 0.02
27		0.32
28[c]		6%[b]

[a] SD given when IC_{50} is an average of three or more determinations. Otherwise one to two determinations were performed. [b] % inhibition at 1 μM. [c] A mixture of two diastereomers.

We explored variations of **11**, focusing on the phenylpiperidine moiety (Table 2). Compounds **17**−**19** show that the piperidine ring size is best. The closely related piperazine-based **20** was inactive; however, installation of a 3-methyl group on the piperazine partially restored potency (**21**). The fully saturated form of **11** was inactive (**22**). Some analogues with heterocycles (**23**) were tolerated. Analogues in which the 4-phenyl group of **11** was relocated (**24**, **25**) were less potent. The conformationally locked spiroindenylpiperidine analogue **26** was 2-fold more potent than **11**. The closely related spiroindanylpiperidine **27** was less potent. The conformationally locked *trans*-1,2,3,4,-4a,5,6,10b-octahydrobenzo[*f*]isoquinoline[10] analogue **28** was inactive.

Concurrent with the phenylpiperidine SAR described above, we explored incorporation of methyl groups in positions along the γ-aminoamide backbone and on the piperidine ring to probe the effect of conformational changes (Table 3). Incorporation of methyl groups in all positions of the γ-aminoamide backbone (**29**−**31**) led to decreases in potency, even when taking into account the presence of multiple analogue isomers. When a methyl was incorporated into the 3-position of the piperidine, the potency depended on the relative stereochemistry; the mixture of two cis isomers (**32**) was less potent than **11**, but the mixture of two trans isomers (**33**) was at least equally potent to **11**.

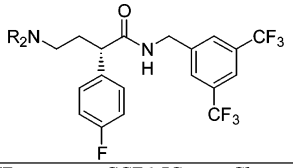
Table 3. Incorporation of Methyl at Various Positions

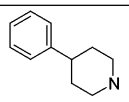
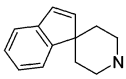
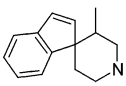
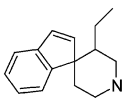
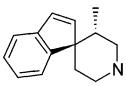
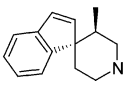


Compd	R^1	R^2	R^3	R^4	CCR2 IC_{50} (μM) [a]
11	H	H	H	H	0.15 ± 0.01
29[b]	H	H	H	CH_3	1.07 ± 0.31
30[c]	H	H	CH_3	H	0%[f]
31[c]	H	CH_3	H	H	1.5
32[d]	CH_3	H	H	H	0.7
33[e]	CH_3	H	H	H	0.14 ± 0.00

[a] SD given when IC_{50} is an average of three or more determinations. Otherwise one to two determinations were performed. [b] Racemate. [c] Mixture of all four diastereomers. [d] *cis*-Piperidine, mixture of two diastereomers. [e] *trans*-Piperidine, mixture of two diastereomers. [f] % inhibition at 1 μM.

Table 4. Spiroindenylpiperidine Analogues[a]

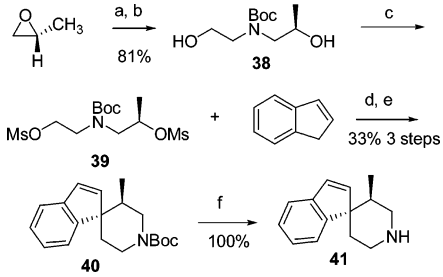


Compd	NR_2	CCR2 IC_{50} (μM) [b]	Chemotaxis IC_{50} (μM) [b]	NK1 IC_{50} (μM)
11		0.15 ± 0.01	40% @1 μM	0.024
26		0.08 ± 0.02	0.176	0.050
34[c]		0.045 ± 0.008	-	-
35[c]		0.44	-	-
36		0.12 ± 0.00	0.062	-
37		0.059 ± 0.017	0.041	0.028

[a] SD given when IC_{50} is an average of three or more determinations. Otherwise one to two determinations were performed. [b] Inhibition of MCP-1 stimulated monocyte chemotaxis.[13] [c] A mixture of two trans diastereomers.

We then decided to combine the two potency enhancing/retaining discoveries outlined above by incorporating the known *trans*-3-methyl-4,4′-spiroindenylpiperidine.[11] The resulting **34** (Table 4) was approximately 2-fold more potent than **26** and 4-fold more potent than lead **11**, suggesting an additive effect of combining the spiroindenylpiperidine with the *trans*-3-methyl substituent. Increasing the steric bulk at the piperidine 3-position (**35**) reduced potency.[12] The single enantiomers of *trans*-3-methyl-4,4′-spiroindenylpiperidine were prepared (Scheme 2) and incorporated into final target analogues **36** and **37** to determine the importance of absolute stereochemistry. According to Scheme 2, (*R*)-(+)-propylene oxide was treated with an excess of ethanolamine. The resulting ring-opened product was protected (Boc_2O) to give **38**. Conversion to bis-mesylate **39** followed by reaction with indene in the presence of 2 equiv of LHMDS gave **40** as a 3:1 mixture of trans/cis isomers (53% two steps). Crystallization from hot hexanes provided pure *trans*-**40**. Following Boc removal, piperidine **41** was incorporated according to Scheme 1 to make analogue **37**. The requisite piperidine for analogue **36** was prepared in an identical fashion starting from (*S*)-(−)-propylene oxide.

Scheme 2[a]



[a] (a) Ethanolamine (8 equiv) 0 °C to room temp; (b) Boc_2O, DCM, room temp; (c) MsCl, Et_3N, DMAP (cat.), DCM, 0 °C; (d) LHMDS (2.1 equiv), THF, 0 °C to room temp; (e) recrystallization from hot hexanes; (f) anhydrous 4 N HCl/dioxane, room temp.

Table 5. CCR2 and CCR5[15] Affinities of **11**, **26**, and **37**

Compd	CCR2 IC_{50} (μM)	CCR5 IC_{50} (μM)
11	0.15	0.072
26	0.080	0.030
37	0.059	26% @ 0.01 μM

Table 4 shows that the (*R*,*R*,*S*)-isomer **37** was more potent in our binding assay, but its diastereomer **36** retained significant potency. Table 4 also shows that milestone analogues **11**, **26**, and **37** are all functional antagonists of CCR2 in that they inhibit MCP-1 stimulated recruitment of monocytes.[13] Furthermore, in the progression from **11** to **26** and **37**, the potency enhancements are even more pronounced when measured in the chemotaxis functional assay. Compound **11** inhibits chemotaxis by only 40% at 1 μM, while optimized **37** inhibits chemotaxis with an IC_{50} of 41 nM. Later-generation analogues incorporating spiropiperidine **41** and its (*S*,*S*)-isomer confirmed that CCR2 antagonists containing the **41**-derived subunit are consistently more potent in binding and functional assays.[14]

Because our original lead **1** came from the Merck NK1 antagonist program, we wanted to evaluate if analogues **11**, **26**, and **37** retained NK1 binding affinity. Table 4 shows that all three retain significant potency in the NK1 assay. Encouragingly, in the progression from **11** to **26** and **37**, the selectivity shifts from much greater potency in NK1 to more evenly balanced activities. Subsequent reports from our laboratories will describe how we have tuned out the NK1 activity from later-generation analogues of **37**.[14]

Another consideration about selectivity involves the possible binding affinity of **11**, **26**, and **37** to other chemokine receptors. To evaluate this, we screened these three compounds against other chemokine receptors and found them to be highly selective against all the receptors tested (CCR1, CCR3, CXCR3, CCR4, CXCR4, CCR8) except CCR5, where they demonstrated significant potency (Table 5).[15] The difficulty in separating parallel CCR2 and CCR5 binding affinities is precedented.[6b,c] Although our aim was to find a completely selective antagonist of CCR2, a dual CCR2/CCR5 antagonist has intriguing possibilities in that both receptors are thought to play a role in RA pathogenesis.[4c] Later publications from our group will detail modifications of **37** leading to improved selectivity over CCR5.[14]

Of the three milestone CCR2 antagonists described herein, only one has been evaluated in a rat pharmacokinetic model. Compound **26** had good oral bioavailability in rats at 3 mpk

and excellent overall pharmacokinetic characteristics ($F = 38\%$, $AUC_{po} = 1.8\ \mu M\ h\ kg\ mg^{-1}$, $Cl = 6\ mL\ min^{-1}\ kg^{-1}$, $t_{1/2} = 8$ h).

In summary, through modification of a screening lead from our sample collection, we have discovered a structurally distinct new lead, **11**, which has subsequently served as the departure point for an ongoing program targeting CCR2 antagonists. Compound **11** was optimized by modifications to the 4-phenylpiperidine moiety to spiroindenylpiperidine analogue **26** and ultimately to *trans*-3-methyl-4,4′-spiroindenylpiperidine analogue **37**, which was potent in our CCR2 binding assay ($IC_{50} = 59$ nM) and in a functional assay measuring inhibition of MCP-1 induced monocyte chemotaxis ($IC_{50} = 41$ nM). CCR2 antagonists **11**, **26**, and **37** were selective against all other chemokine receptors assayed with the exception of the CCR5 receptor where they had similar potency. All three compounds also showed binding affinity for the NK1 receptor. Compound **26** had good oral bioavailability in rats. Subsequent reports from our laboratories will detail further SAR studies in this series that address enhancing potency and selectivity against NK1 and CCR5.[14]

Acknowledgment. We thank Marc M. Kurtz and Kwei-Lan C. Tsao for performing the NK1 assays on **11**, **26**, and **37**, and Bernard Kartsen Choi for HRMS analyses.

Supporting Information Available: Experimental details for the synthesis and characterization of representative CCR2 antagonists **11**, **26**, and **37**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Radioligand competition binding assay: CHO cells expressing human CCR2b. Assay experimental details provided in Supporting Information.

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(12) The required spiroindenylpiperidine was prepared in an analogous fashion to that shown in Scheme 2 starting with 1,2-epoxybutane.

(13) Human monocyte chemotaxis assay: details provided in Supporting Information. Known CCR2 antagonist 1-(3,4-dichlorobenzyl)-5-hydroxy-1*H*-indole-2-carboxylic acid was calculated to have an IC_{50} of 95 nM in this assay, in good agreement with the reported value of 60 nM (Faull, A. W.; Kettle, J. G. WO 2000046196, 2000).

(14) Subsequent publications from our group will detail next-generation CCR2 antagonists derived from **37** wherein the central *p*-fluorophenyl has been replaced/modified and/or the γ-aminoamide core has been cyclized. Their improved selectivity for CCR2 over the CCR5 and NK1 receptors and their favorable pharmacokinetic properties will be described.

(15) Refer to ref 9 for details about the CCR5 binding assay.

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