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Discovery of an orally-bioavailable CC Chemokine Receptor 2 antagonist derived from an acyclic diaminoalcohol backbone

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ABSTRACT

We describe an isostere-driven approach to improve upon a previously-described series of capped dipeptide antagonists of CC Chemokine Receptor 2 (CCR2). Modification of the substitution around the isostere was combined with additional changes in a distal aromatic substituent to provide single-digit nanomolar antagonists of CCR2. These studies led to the identification of **18**, a compound that was suitable for studies in murine models of CCR2 activity.

Both monocyte chemoattractant protein-1 (MCP-1) and its cognate receptor CC Chemokine Receptor 2 (CCR2) have been the subject of a great deal of research, motivated by the apparently central role that they play in the biology of inflammatory monocytes.[1] Indeed, multiple pre-clinical studies in murine models have confirmed that blockade of the CCR2 axis via either genetic or pharmacologic intervention can substantially reduce disease score in murine models of rheumatoid arthritis, multiple sclerosis, insulin resistance, atherosclerosis, restenosis, and neuropathic pain.[2–4] A number of independent approaches to targeting CCR2 have been explored by the medicinal chemistry community, as discussed in recent reviews of the patent and primary literature.[5–7] However, despite this heavy investment, no clinical validation for the role of CCR2 in human disease has been described, and more clinical research with still-improved antagonists is required.[8,9]

As described in earlier reports from our laboratories, we have been engaged in the discovery and development of potent, selective, and orally bioavailable antagonists of CCR2.[10] Part of this program was focused on the structure–activity relationships around a series of capped dipeptides derived from diaminopropionic acid and glycine (Fig. 1, **A**).[11] Although potent and selective compounds were identified, we sought to improve the bioavailability in this series by reducing its peptidic character. Herein, we describe one successful approach to this objective, centered on replacing the C-terminal amide with a hydroxyethylene isostere (Fig. 1, **B**). We rationalized that this would allow us to retain the desired intramolecular hydrogen bonding motif[12] while eliminating an unnecessary NH moiety. The activity of the previously described[11] primary alcohol **1** gave us confidence to pursue this bioisostere approach.

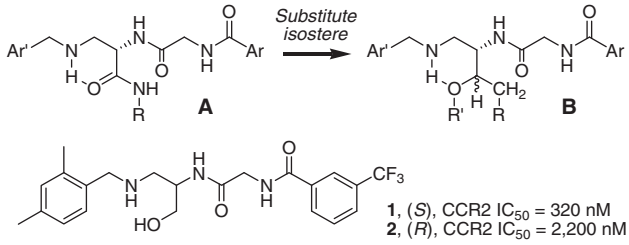

Figure 1. Replacement of the pendent amide moiety with a hydroxyethylisostere. The two previously described hydroxymethyl analogs are shown as a benchmark for the analogs described herein.

Scheme 1 illustrates the synthetic approach to the first set of compounds used to test the hypothesis.[13] The commercial N_{α}-Boc, N_{β}-Cbz diaminopropionic acid **3** was converted into its Weinreb amide **4**. Subsequent reaction of **4** with a Grignard reagent afforded the intermediate ketone, which was immediately reduced with sodium borohydride so as to avoid epimerization of the sensitive alpha-stereocenter. The alcohol diastereomers **5** were obtained in 1.5:1–6:1 dr for all substituents.

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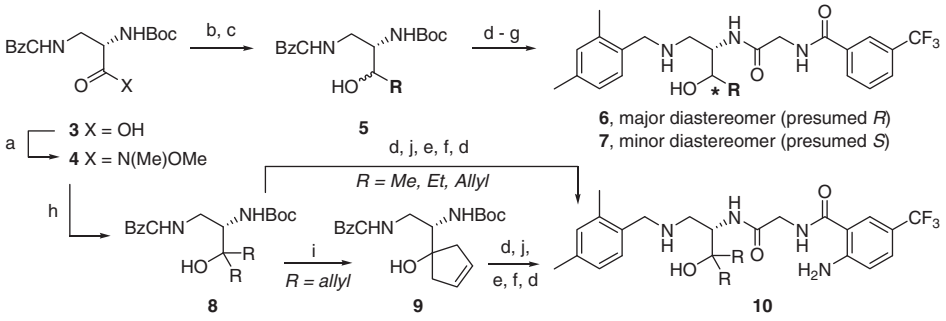
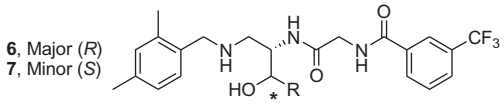


Scheme 1. Synthesis of aminoalcohol-based CCR2 antagonists: glycinamide series. Reagents: (a) HCl*HN(Me)OMe, HATU, *i*Pr$_2$NEt, CH_2Cl_2/DMF; (b) **R**MgBr, THF; (c) $NaBH_4$, THF/EtOH; (d) TFA, CH_2Cl_2; (e) HO_2CCH_2NHCO(3-CF_3Ph), BOP, *i*Pr$_2$NEt, CH_2Cl_2/DMF; (f) H_2, 5% Pd/C (Degussa), MeOH; (g) 2,4-Me_2PhCHO, $NaCNBH_3$, MeOH; (h) RMgBr (or MeLi for R = Me), THF; aq workup; then repeat RMgBr; (i) Grubb's-I, DCM; (j) HO_2CCH_2NHCO(2-NHBoc-3-CF_3Ph), BOP, *i*Pr$_2$NEt, CH_2Cl_2/DMF.

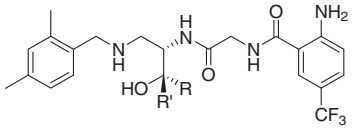
Table 1
Initial test of the hypothesis shown in Figure 1 through probing of side chain identity and relative stereochemistry



Series, R group	CCR2 binding IC_{50}[a] (nM)	
	6, major diastereomer	**7**, minor diastereomer
a, CH_2Me	390	64
b, CH_2Et	31	5
c, CH_2*n*-Pr	180	5
d, $CHMe_2$	100	65
e, CH_2*i*-Pr	350	19
f, CH_2*t*-Bu	600	19
g, Ph	>1000	100
h, CH_2Ph	2400	6400

[a] Binding was performed with 0.3 nM [^{125}I]MCP-1 and human peripheral blood mononuclear cells at rt (Ref. 13). IC_{50} values reported as the average of two or more determinations.

Table 2
Comparison with tertiary alcohol side chains



Compound	R′	R	CCR2 Binding IC_{50} [a] (nM)
10a	Me	Me	160
11	H	Et	17
10b	Et	Et	41
13	H	*n*-Pr	3.4
14	*n*-Pr	H	7
10c	*n*-Pr	*n*-Pr	27
10d	–$(CH_2)_4$–		87

[a] Binding was performed with 0.3 nM [^{125}I]MCP-1 and human peripheral blood mononuclear cells at rt (Ref. 13). IC_{50} values reported as the average of two or more determinations.

In some instances, it was possible to separate the diastereomers with repeated flash chromatography; and, in other examples, they were carried forward as a mixture. Deprotection of **5** and coupling with a substituted hippuric acid, followed by hydrogenolysis of the Cbz, and reductive amination with 2,4-dimethylbenzaldehyde provided final products. If separation had not been achieved at intermediate **5**, it was achieved at this point through either (1) HPLC separation, or (2) derivatization as a *t*-butyl carbamate, flash chromatography, and deprotection of the separated diastereomers with TFA.[14] The stereochemistry of the diastereomers was tentatively assigned assuming addition anti-periplanar to the CH_2NHBoc group in a classical Cram transition state in which the α-amine group occupies the 'inside' position and the hydrogen is positioned 'outside,' so as to minimize interactions with the ketone substituent.[15] This tentative assignment was later confirmed for R = Et and *n*-Pr (*vide infra*), and is also consistent with results obtained by other authors for the related reduction of a DAP-derived ketone.[16]

We also synthesized compounds containing achiral tertiary alcohol side chains. Subjection of Weinreb amide **4** to sequential organometallic additions afforded the tertiary alcohol **8** (Scheme 1). These disubstituted compounds **8** (R = Me, Et, or allyl) were brought forward to final compounds **10** (R = Me, Et, or *n*-Pr) as before, with only two minor modifications: the hippurate containing the Boc-protected 2-amino-5-trifluoromethylbenzamide was employed, and a final deprotection step (TFA/DCM) was utilized. These modifications permitted us to scan the impact of the tertiary alcohol in the context of the more potent 2-amino-5-trifluoromethyl-benzamide. Alternatively, compound **8** (R = allyl) could be subjected to ring-closing metathesis conditions, providing cyclopentene **9**. This material was advanced as above to give the cyclopentyl **10d** (Table 2).

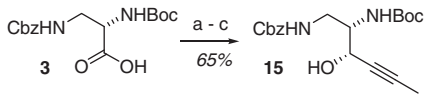
Table 1 lists the CCR2 binding data obtained with a pilot set of compounds derived from DAP. Both the 2,4-dimethylbenzylamine and 3-trifluorobenzamide groupings were standardized for the initial study. Notably, in all pairs but one (series **h**), the analog **7** derived from the minor diastereomer of **5** was more potent than that from the major diastereomer, and was also more potent than the primary alcohol **1**. In the alkyl series **7a**–**7f**, the unbranched propyl and butyl appeared to be equivalent or superior to the isobutyl and neopentyl compounds. This was *not* expected based on the structure–activity relationships in the earlier amide series. In the aryl series **7g**–**7h**, a notable dependence on chain length was discovered, with benzyl being much less potent than phenyl.

As shown in Table 2, the potency of achiral tertiary alcohols increased incrementally with the size of the alkyl substituent (compare **10a**, **10d**, **10b**, and **10c**). However, in each instance, the tertiary alcohol was less potent than the secondary alcohol with the comparable alkyl substituent (cf. **11** and **10b**, as well as **13**, **14**, and **10c**). Although this scan did not identify a more potent side chain substituent, it did allow us to confirm both (1) the modestly improved binding affinity of the 2-amino-5-trifluoromethyl benzamide substituent relative to the 3-trifluoromethyl benzamide (cf. **7a** and **11**; **7b** and **13**; **6b** and **14**); and (2) the superiority of *n*-propyl to ethyl as the side chain substituent. Accordingly, we focused

additional work on derivatives of compound **13**, which contained both of these key groups.

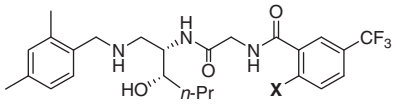
Since the diastereoselectivity of the ketone reduction used to generate **5** (R = *n*-Pr) produced the desired diastereomer with an unfavorable ratio (>5:1 *R*:*S*), it was critical to address the synthetic issue inherent in the production of analogs. One successful approach to this problem entailed simply switching the order of operations, such that the amide **4** was first converted to the aldehyde, and then this was then treated with an alkyl Grignard. Although this did provide the desired diastereomer as the major product,[16] it also introduced the epimerization of the aldehyde as an obstacle for scale-up. Accordingly, we pursued a more secure approach and employed a chiral reducing agent to overcome the inherent substrate bias of the ketone. As shown in Scheme 2, a three-step sequence from the commercially available **3** provided the desired diastereomer **15** when *R*-Alpine Borane® was utilized as the reducing agent. Given the known stereoinduction of Alpine Borane reductions of propynyl ketones,[17] this result is consistent with the assignment of the previously-minor diastereomer of **5** as the 2*S*,3*S*-diastereomer. We corroborated this inference through the analysis of the NOESY spectra of the N,O-cyclized derivatives of the individual isomers of **5** (R = Et). For purposes of analog generation, this *tert*-butyl (2*S*,3*S*)-3-hydroxy-1-(2-oxo-2-phenylethylidene-amino)hex-4-yn-2-ylcarbamate **15** (Scheme 2) could be advanced through the sequence shown in Scheme 1, in which the propyne was reduced to *n*-propyl as part of the hydrogenolysis of the Cbz group.

With a stereoselective route to the key intermediate **15** in hand, we turned back to expand our SAR investigations. Initially, we explored derivitization of the anthranilic acid, as this had been shown to improve potency in both our cyclohexyl[18] and capped dipeptide[11] series, whereas modification of the benzyl amine in the dipeptide series had been less fruitful. As shown in Table 3, a wide variety of substitutions at the 2-amino position of the benzamide were compatible with potent binding to CCR2. Furthermore, relative to the parent **7b** and simple 2-amino-5-trifluormethylbenzamide **13**, many of these more elaborate derivatives exhibited improved potency in the monocyte chemotaxis assay. Consistent with our previous observations in the CCR2 and CCR3 projects,[11,19] it appeared that the chemotaxis potency depended on specific structural features, as opposed to simply tracking linearly with receptor binding. For example, the installation of the *ortho*-amine itself was beneficial (cf. **7b** and **13**, for which the chemotaxis improves more than indicated in the comparison of binding affinities). However, specific aniline substituents increased chemotaxis potency even further, despite failing to improve the binding potency (cf. **13**, **21**, and **26**).



Scheme 2. Synthesis of key propynyl intermediate. Reagents: (a) HCl*HN(Me)OMe, HATU, *i*Pr$_2$NEt, CH_2Cl_2/DMF; (b) MeCCMgBr, THF; (c) R-alpine borane, neat, 7 days.

Table 3
Anthranilic acid derivatives



Compd	X	CCR2 Binding IC_{50} [a] (nM)	Monocyte Chemota xis IC_{50} [b] (nM)
7b	H	5	240
13	NH_2	3.4	32
16	$NHCO_2t$-Bu	4	17
17	NHCONHMe	6.7	5
18	NHCONHEt	3.6	24
19	NHCONH*i*-Pr	4.7	9.9
20	NHCO(c-NC_3H_6)	2.1	4.3
21	NHCO(c-NC_4H_8)	5.8	5.2
22	NHCOmorpholine	3.8	13
23	NHCOpiperazine	2.5	10
24	NH*i*-Pr	5.3	9
25	NH*t*-Bu	7.4	33
26	$NHCH_2Ph$	9.3	7.2

[a] Binding was performed with 0.3 nM [^{125}I]MCP-1 and human peripheral blood mononuclear cells at rt (Ref. 13). IC_{50} values reported as the average of two or more determinations.

[b] Antagonism of chemotaxis of human PBMCs induced by 10 nM MCP-1 at 37 °C (Ref. 13).

One hypothesis related to the improvement in potency engendered by the anthranilic amide was that the *ortho*-amine reinforced the internally H-bonded conformation shown in Figure 2. We tested this directly through the synthesis[20] of the indazole analog **27**, which proved to be about twofold weaker in both binding and chemotaxis relative to the anthranilic amide **13** (Fig. 2).[21] The potencies of **13** and **27** were similar enough to suggest that the internally H-bonded conformation of the anthranilic amide was the biologically active one, especially since the chemotaxis was improved relative to the unconstrained **7b**. Unfortunately, alkylation of the indazole to remove the proton donor reduced binding potency further (data not shown), thereby eliminating the path to potency enhancement utilized in the anthranilic amide series (see Table 3). In this context, it was surprising to us that the conformationally unconstrained 3-amino-5-trifluoro-methyl benzamide **28** had essentially the same binding and chemotaxis potencies as the anthranilamide **13** (Fig. 2). These data suggested that the chemotaxis potency could also be improved through the addition of a receptor-specific interaction. Accordingly, we explored other methods for presenting the amine moiety in an attempt to enhance potency further, and focused on the use of a 'retro-amide' substitution.

The 'retro-amides' (malonamides) were synthesized as described in Scheme 3. In brief, the enantiopure **15** was coupled to a hemi-malonamide, and the product was then hydrogenated and subjected to reductive amination with 2,4-dimethylbenzaldehyde.[22] In the case of the 3-amino-5-trifluoromethyl series, additional steps were required, either in the form of a final deprotection (**30** → **31**, Scheme 3) or in the context of a re-ordering of steps to allow for a selective functionalization of the amine on the phenylamide (see **5** → **32** → **34**, Scheme 3). Benzimidazole isosteres **35** and **36** were synthesized through the HATU-mediated coupling of the lithium salt of either 4-or 5-trifluoromethyl-1*H*-benzoimidazol-2-yl)-acetic acid with (2*S*,3*S*)-2-amino-3-hydroxy-hex-4-ynyl]-carbamic acid benzyl ester **15**, followed by deprotection and reductive amination, in direct analogy to Scheme 3.[22]

Table 4 summarizes the data with an exploratory set of 'retroamides' based on the 3-CF_3 phenylamide **37** (CCR2 Binding IC_{50} = 28 nM). This compound was selected as the parent for our investigations because it was more potent than the 2-CF_3 or 4-CF_3 isomers (IC_{50} values 3200 and 1100 nM, respectively; data not shown), as well as the 3-OCF_3 analog (IC_{50} = 59 nM). The 2-NH_2 and 2-NHBoc compounds were less potent than expected based on our results in the 'forward' amide series (cf. **7b**/**13**/**16** and **37**/**38**/**39**); however, the 3-NH_2 substitution was potency enhancing, in line with expectations (cf. **31**/**37** and **28**/**7b**). Small aminoalkyl groups (NHMe, NHEt) appeared to enhance binding potency and retain chemotaxis potency (see **40** and **34**), but potency started to drop off for *n*-propyl (**41**).

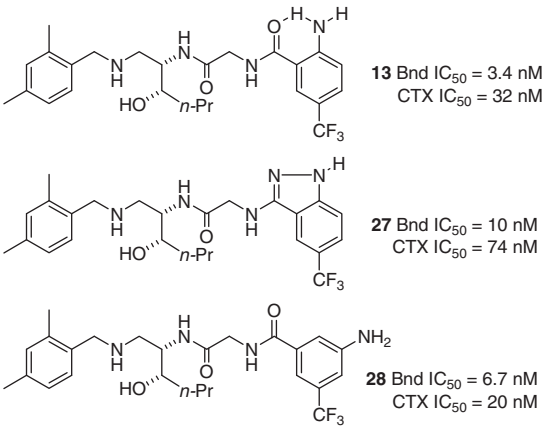


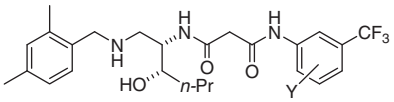
Figure 2. Comparison of different presentations of NH donor. The CCR2 binding and chemotaxis IC_{50} values are shown (see Ref. 13).

Notably, modifications of the aniline that had been successful in the anthranilic amide series (Boc, Et urea) were deleterious here (see **30**, **42**). Also, whereas the substitution of methoxy at the 2-position was inferior to the amine (**43** vs **38**), the two groups were nearly equivalent at the 3-position (**44** vs **31** and **40**). A brief scan of other functionality (see **45**–**47**) failed to identify something that was even equivalent to the parent **37**. Likewise, substitution on the central carbon of the malonamide (dimethyl, monomethyl, difluoro) reduced binding >10-fold (not shown). Overall, the malonamide was a sub-optimal replacement for the glycinamide, with the exception of the 3-aminophenylamide and its small alkyl analogs.

Given the distinct SAR between the glycinamide and malonamide series (cf. Tables 3 and 4), we explored the preferred conformation of the malonamide through the use of a benzimidazole isostere (Scheme 3). In the event, compound **35** was substantially more potent than the isomeric **36**, although benzimidazole **35** was not more potent than the parent malonamide **37** (Table 4). Given the aforementioned aminoindazole analog **27**, the data collectively suggest that the benzimidazole **35** prefers the tautomer illustrated in Scheme 3.

Based on the optimization activities described above (Tables 3 and 4), the best compounds contained benzamide or phenylamide groups with at least one hydrogen bond donor. Moreover, although the change in the side chain moiety from an amide to its hydroxyethyl isostere did reduce the overall heteroatom count by one atom, this change did not reduce the number of hydrogen bond donors. Since masking of proton donors is often helpful for improving the absorption of molecules that would otherwise be too polar, we investigated this strategy in the acyclic amino alcohol series. As shown in Figure 3, alkylation of the amine reduced potency at

Table 4
Malonamide derivatives as 'retro-amide' analogs



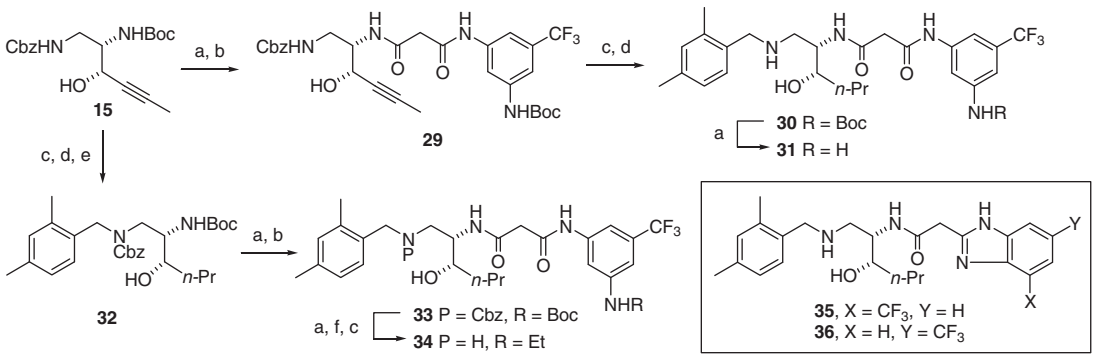
Compd	Y	CCR2 Binding IC_{50} [a] (nM)	Monocyte Chemota xis IC_{50} [b] (nM)
37	H	28	81
38	2-NH_2	43	
39	2-$NHCO_2t$-Bu	240	
31	3-NH_2	3.8	14
40	3-NHMe	7.1	23
34	3-NHEt	4.5	12
41	3-NHPr	20	
30	3-$NHCO_2t$-Bu	340	
42	3-NHC(O)NHEt	40	
43	2-OMe	217	
44	3-OMe	24	23
45	3-Br	710	
46	3-CF_3	690	
47	3-C(O)NHEt	158	
35	See Scheme 3	49	
36	See Scheme 3	6% Inh @ 1 μM	

[a] Binding was performed with 0.3 nM [^{125}I]MCP-1 and human peripheral blood mononuclear cells at rt (Ref. 13). IC_{50} values reported as the average of two or more determinations.
[b] Antagonism of chemotaxis of human PBMCs induced by 10 nM MCP-1 at 37 °C (Ref. 13).

CCR2 (cf. **19** and **48**, **49**). In contrast, methylation of the alcohol did not dramatically reduce potency, either in binding (3.4 vs 11 nM) or chemotaxis (32 vs 30 nM for alcohol **13** and methyl ether **50**, respectively). These observations are consistent with our previously proposed model of the side chain moiety participating in an intramolecular H-bonding interaction with the proton from the amine (Fig. 1).[11]

We also examined the masking of the central amide moiety via its Friedlander lactam.[23] Although the *S*-lactam was more potent than the *R*-lactam (cf. **53** and **54**), both were >200-fold weaker than their glycinamide counterpart **13**, even with optimal substitutions (see **51** and **52**, Fig. 3). Thus, relative to our cyclohexyl series of CCR2 antagonists,[24] the acyclic amino alcohol series was much less tolerant of the lactam as a linking group, but displayed the same stereochemical preference for lactam substitution.

In order to determine the suitability of these acyclic amino alcohols for evaluation in vivo, we studied their pharmacology and



Scheme 3. Synthesis of aminoalcohol-based CCR2 antagonists: malonamide series. Reagents: (a) TFA, CH_2Cl_2; (b) $HO_2CCH_2C(O)NH$(3-NHBocPh), HATU, iPr_2NEt, 3:1 CH_2Cl_2/DMF; (c) H_2, 5% Pd/C (Degussa), MeOH; (d) 2,4-Me_2PhCHO, $NaCNBH_3$, MeOH; (e) Cbz_2O, Et_3N, THF; (f) $NaCNBH_3$, MeCHO, MeOH.

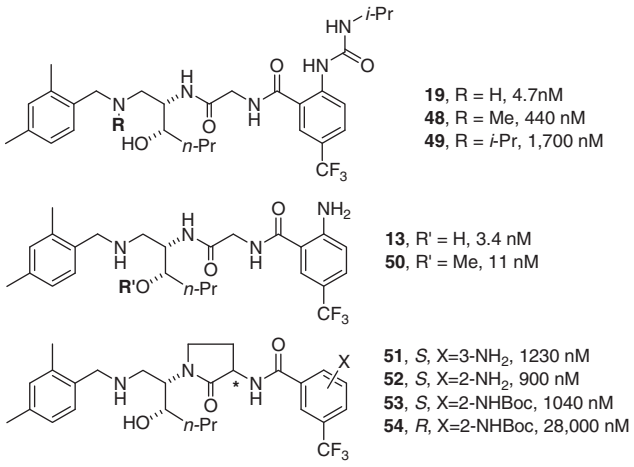


Figure 3. Masking proton donors. The CCR2 binding IC_{50} values are shown (see Ref. 13).

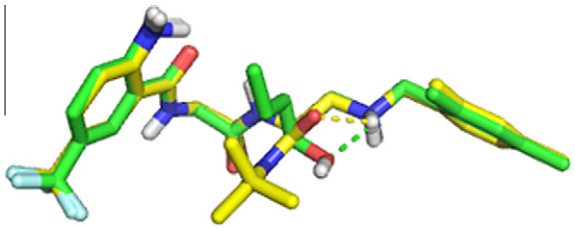


Figure 4. Shown is a comparison of the hypothetical receptor-bound conformations of analogous members of the original amide series (yellow, compound **50** in Ref. 11; CCR2 IC_{50} = 11 nM, CTX IC_{50} = 260 nM) and the 2*S*, 3*S*-hydroxyalkylisostere series (green, compound **13** in this manuscript; CCR2 IC_{50} = 3.4 nM, CTX IC_{50} = 32 nM).

pharmacokinetics in the murine context. Although the original capped dipeptide series did not shown substantial binding activity to the mouse receptor, the amino alcohols generally displayed measureable binding affinity. The structure–activity relationships from our limited survey suggested that both the propyl substituent and the *S*-alcohol stereochemistry favored mouse CCR2 binding, such that compounds like **6e**, **7e**, and **14** exhibited >10-fold reductions in affinity for mouse CCR2, whereas compounds like **7b**, **13**, **16**, and **18** were equipotent for binding mouse and human CCR2. We extended these observations by performing additional studies with **18**, and determined that it both blocked the chemotaxis of mouse monocytes (IC_{50} = 4 nM) and exhibited useful levels of oral bioavailability in the mouse (*F* = 29%), despite relatively high Cl values (5.1 L/h/kg). Additional screening of compounds in mouse PK models showed that a number of members of the series exhibited oral bioavailability in the mouse, albeit in the same modest range (data not shown).

The pharmacology of compound **18** was studied further. The compound was a full antagonist of multiple CCR2-mediated functions (chemotaxis, calcium flux, and cAMP depression), and was also an antagonist of all of the known CCR2 ligands. It was >1000-fold selective in a panel of 140 other GPCRs, enzymes, and transporters. Although it was selective versus CCR1 and CCR3, it did show measurable binding affinity for CCR5 (binding IC_{50} = 86 nM).

As described in the introduction, the hydroxyalkyl side chain was designed to act as an amide isostere. While the data described herein document that the compound series are indeed similar in many aspects of the SAR, there are also important divergences. Accordingly, we compared the modeled receptor-bound conformation of two representative compounds (Fig. 4).[25] As shown, the compounds are able to adopt very similar placements of the benyzlamine and benzamide functionalities, consistent with the similar SAR in these regions. Moreover, the amide carbonyl (yellow structure) and hydroxyl (green structure) are forming analogous intramolecular hydrogen bonds, as predicted. However, in the low energy conformations, the alkyl side chain is oriented quite differently in the 2*S*,3*S*-hydroxyalkyl series relative to the amide series, which may underpin the distinctions observed with regards to mouse activity and chemotaxis potency.

In conclusion, we have demonstrated that a hydroxyethyl isostere offers advantages over an amide side chain in a series of capped dipeptide CCR2 antagonists. Improvements in binding, chemotaxis potency, mCCR2 binding, and mouse pharmacokinetics were noted. Distinct structure–activity relationships within the glyincamide and malonamide sub-series were discovered. Additional studies that describe the detailed characterization of **18** will be published separately, as will studies to extend the SAR observations described herein.

Acknowledgments

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25. Initial conformations were generated using the conformational search module in Macromodel (v.9.9, Schrodinger LLC) with the OPLS2005 forcefield in vacuum. The secondary amine was protonated during the search. The low energy conformations for both compounds were found to possess intramolecular hydrogen bonds between the amino nitrogen and the carbonyl from the *t*-butyl amide or the hydroxyl moiety. A second hydrogen bond was present between the analino nitrogen and the benzamide carbonyl. Despite the stability of the hydrogen bonds, the flexible glycine linker adopted multiple conformations with similar energies resulting in variable relative positioning substituents on either side. Putative bound conformations were then selected by rigidly docking into a CCR2 homology model derived from the CXCR4 crystal structure (3ODU), constraining the basic amine to contact the glutamic acid on TM7, Glu 291 (modeling studies to be published separately). The conformation from a docking pose consistent with the SAR reported herein is shown in Figure 4.