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Racemic and chiral lactams as potent, selective and functionally active CCR4 antagonists

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Abstract—A series of racemic and chiral, nonracemic lactams that display high binding affinities, functional chemotaxis antagonism, and selectivity toward CCR4 are described. Compound **41**, which provides reasonably high blood levels in mice when dosed intraperitoneally, was identified as a useful pharmacological tool to explore the role of CCR4 antagonism in animal models of allergic disease.

Chemokines are a group of secreted proteins that attract and activate a variety of cell types. To date, there appear to be 18 chemokine receptors and over 45 chemokine ligands known. There are two main subfamilies of chemokines based on the position of the first two of four conserved cysteine residues. The CC family, which constitutes the largest subfamily, has its cysteine residues adjacent to one another, while the CXC family has one amino acid separating the cysteine residues.[1] These chemokines exert their influence through G-protein coupled receptors, which bind specific ligands with high affinity and selectivity. CCR4 was recently reported to have two specific ligands: TARC (thymus and activation regulated chemokine)[2] and MDC (macrophage derived chemokine).[3] In vivo studies support the role of CCR4 and its ligands in Th2 mediated inflammation.[4] Thus, we undertook an effort to identify small molecule CCR4 receptor antagonists as potential therapeutics for allergic disease.

In a preceding report,[5] a series of diastereomerically pure, racemic thiazolidinones were identified that displayed good receptor affinity toward CCR4 along with functional inhibition of chemotaxis in vitro; however, there were concerns that the molecules lacked sufficient drug-like properties needed for good in vivo exposure (see Fig. 1). Indeed early pharmacokinetic analyses of these thiazolidinones showed them to be poorly absorbed and/or rapidly cleared upon p.o. or i.v. dosing (data not shown). Still, the early SAR and functional activity of these thiazolidinones was encouraging and the demonstrated importance of stereochemistry and enantiopurity spurred us to try and identify more potent CCR4 antagonists that might possess suitable pharmacokinetic profiles for animal model studies. Accordingly, a strategy was put in place to switch the core structure from thiazolidinones to lactams for the following reasons:

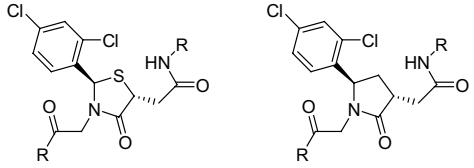

Figure 1. Previously explored thiazolidinones (**1**) and proposed analog lactams (**2**).

Keywords: Lactams; CCR4; Antagonists.
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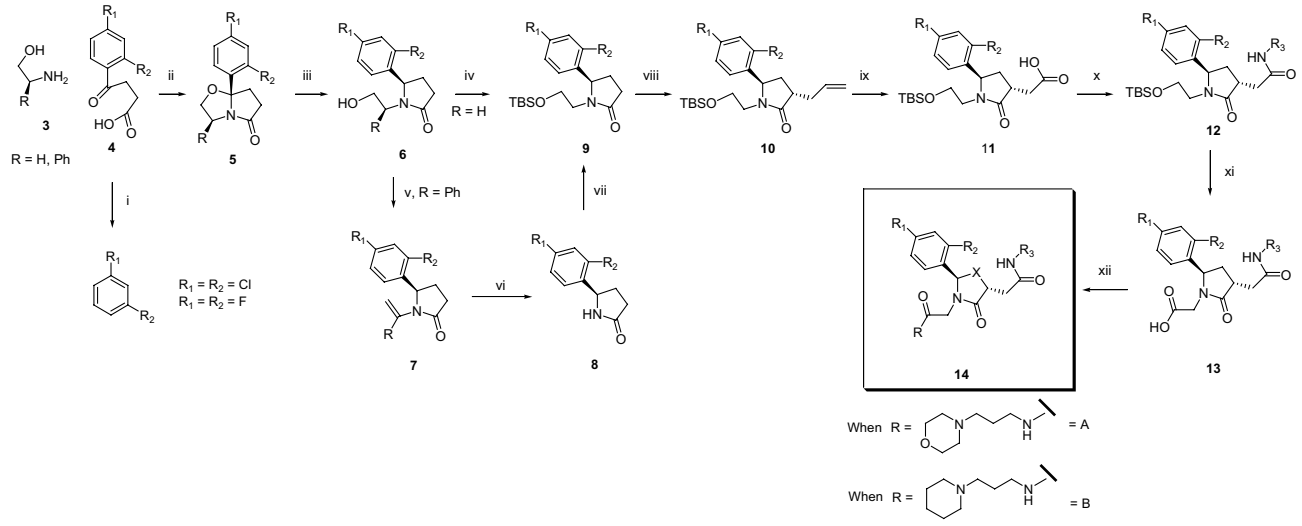


Scheme 1. (i) (a) Aluminum chloride, 3-carbomethoxypropionyl chloride, 0 °C then 80 °C, 80%; (b) aq LiOH, H_2O, THF, 90%; (ii) toluene, reflux, Dean–Stark, 16 h, 100%; (iii) $TiCl_4$, DCM, Et_3SiH, −78 °C to rt, 16 h, 80%; (iv) TBDMSCl, imidazole, DMF, 95%; (v) (a) $SOCl_2$, THF, 0 °C to rt, 95%, (b) NaOEt, EtOH, 45 °C, 80%; (vi) 1 N HCl (aq), THF, reflux, 85%; (vii) KH, DMF, (2-bromoethoxy)-*tert*-butyldimethylsilane, rt, 1 h, 75%; (viii) LDA, THF, −78 °C then allyl bromide, 70%; (ix) (a) ozone, CH_2Cl_2, −78 °C, then PS–PPh_3, 90%; (b) $KMnO_4$, NaH_2PO_4, *t*-BuOH, 90%; (x) EDCI, HOBt, H_2O, amine, 65%; (xi) Jones rgt., acetone, 80%; (xii) CDI, CH_2Cl_2, amine, 20%.

- Replacing a sulfur atom with a carbon atom removes a potential oxidative metabolic liability from the compounds.[6]
- A simple carbon-for-sulfur substitution may have a minimal effect on the binding conformation of the antagonists and thereby allow us to build upon the SAR already established for the thiazolidinones.[7]
- The facile preparation and characterization of enantiopure lactams is well established in the synthetic organic literature.[8]
- The pyrrolidine scaffold is very well represented in the pharmaceutical literature and certain pyrrolidinones possess excellent in vivo properties.[9]

As shown previously in the thiazolidinone series, the *trans* diastereomer proved to be more potent than its *cis* counterpart so it became necessary to develop a synthetic route to the *trans* lactam diastereomer in both racemic and enantiopure forms (Scheme 1). Ultimately, the chosen synthetic route was based upon a series of literature reports.[8] The method of preparation for the enantiopure and racemic analogs were almost identical except for a three-step modified sequence for removal of the chiral auxiliary in the former series.[10] Bicyclic lactam **5** was readily prepared from precursors **3** and **4** with subsequent reductive opening to substituted lactam **6** in overall yields approaching 80%. Compound **6** could be readily chlorinated and eliminated to enamide **7**, followed by hydrolysis to provide the free pyrroldinone **8** in 65% overall yield. This procedure was compatible with other functionality. Additionally, it is worthy to note the excellent diastereoselectivity in the lactam allylation (**9** to **10**) that provided the requisite *trans* disposition (the other diastereomer in this alkylation was not observed). It appears from calculations and experiments[11] that the diastereoselectivity is due to the lone pair of the lactam nitrogen imparting a strong stereoelectronic effect. Subsequent manipulation of the olefin and amide formation took place without event to provide the desired series of analogs.

In an effort to verify that the SAR of the lactam series was congruent to the earlier reported thiazolidinone series, a relatively small number of lactam analogs were prepared for comparison in receptor binding[12] and microsomal stability assays (see Table 1). In general,

Table 1. Comparison of previously reported thiazolidinone-based with lactam-based CCR4 antagonists

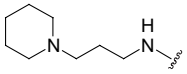
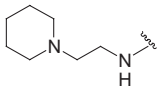
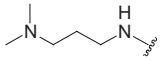
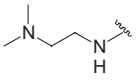
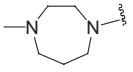
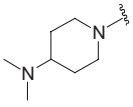
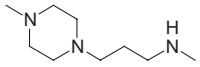
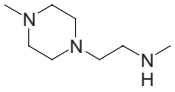
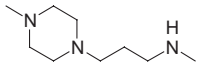
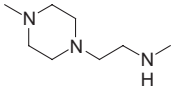
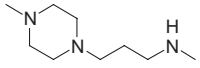
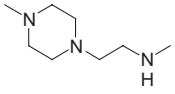
Compd[a]	R	X	R_1	R_2	R_3	MDC IC_{50} (μM)	HLM $t_{1/2}$ (min)
14	A	CH_2	Cl	Cl	1-Methylnaphthalene	2	3.3
15	A	S	Cl	Cl	1-Methylnaphthalene	0.69	8.2
16	A	CH_2	F	F	1-Methylnaphthalene	2.2	2.5
17	A	CH_2	Cl	Cl	3-Cl, 2-Me benzyl	0.88	4.8
18	A	S	Cl	Cl	3-Cl, 2-Me benzyl	0.40	11
19	A	CH_2	Cl	Cl	3-Cl, 2-Me benzyl	0.24[b]	3.0
20	A	CH_2	F	F	3-Cl, 2-Me benzyl	3	2.3
21	A	CH_2	Cl	Cl	2,3-Dimethyl benzyl	1.3	4.3
22	A	S	Cl	Cl	2,3-Dimethyl benzyl	0.44	3.1
23	A	CH_2	F	F	2,3-Dimethyl benzyl	3	2.3

[a] All compounds are racemic *trans* diastereomer unless otherwise noted.
[b] Pure enantiomer.

the *trans* racemic lactam analogs were 2–4 fold less potent than the corresponding *trans* racemic thiazolidinones (**14** vs **15**; **17** vs **18**; **21** vs **22**), but trends within each series remained the same and we still felt that certain advantages were inherent in the lactams. Fluorine substitution on the central aromatic ring failed to improve potency (**16**, **20**, and **23**), although we were encouraged by enantiopure compound **19**, which provided a threefold enhancement in binding affinity over its corresponding racemate, compound **17**. Unfortunately, these lactams showed poor in vitro stability in pooled human liver microsomes preparations (HLM) as evidenced by their relatively short half-lives (most $t_{1/2} < 5$ min).[13] Subsequent metabolic profiling revealed the morpholine moiety as a site of hydroxylation. Furthermore, in vivo pharmacokinetic data indicated that poor absorption and rapid clearance were still issues with these compounds (data not shown).

In an effort to engender more metabolic stability, enhance the physiochemical properties (clog *P*, molecular weight,[14] rotatable bonds[15]), and improve the binding affinity of these compounds, we next focused on morpholine replacements and other left side modifications in addition to enantiopurity (see Table 2).[16] Initially compounds were prepared that incorporated 4-monosubstitution on the central aromatic ring (R_2 = H; compounds **24**–**31**) because, while it has been shown that 2,4-disubstitution (R_2 = Cl) results in a slight increase in binding affinity, it also adds to the overall lipophilicity of the molecule as well as molecular weight. Although the right hand side aromatic ring seemed to favor a 3-chloro-2-methyl substitution pattern for optimal receptor binding affinity as evidenced by a concurrent SAR study (see Table 3), the 3-chloro substitution pattern was chosen here because it resulted in lower molecular weight, lower clog *P*'s, and did not

Table 2. Modifications of the left side chain in the enantiopure series of lactams (see compound **14** X = CH_2)

Compound[a]	R	R_1	R_2	R_3	MDC IC_{50} (μM)[b]	HLM $t_{1/2}$ (min)
24		Cl	H	3-Cl benzyl	1	
25		Cl	H	3-Cl benzyl	1.3	3.4
26		Cl	H	3-Cl benzyl	3	8
27		Cl	H	3-Cl benzyl	3	5.8
28		Cl	H	3-Cl benzyl	5.5	2.6
29		Cl	H	3-Cl benzyl	1	
30		Cl	H	3-Cl benzyl	0.98	4
31		Cl	H	3-Cl benzyl	3.3	
32		Cl	Cl	3-Cl benzyl	0.82	
33		Cl	Cl	3-Cl benzyl	1.3	
34		Cl	Cl	3-Cl, 2-Me benzyl	0.340 (0.630)	3.8
35		Cl	Cl	3-Cl, 2-Me benzyl	0.400 (1.0)	2.3

[a] All compounds are single enantiomers unless otherwise noted.
[b] Figures in parentheses represent IC_{50}'s for the corresponding racemic compounds.

Table 3. Modifications of the right side amide in the racemic series of lactams (see compound **14** X = CH_2)

Compd	R	R_1	R_2	R_3	MDC IC_{50} (μM)	HLM $t_{1/2}$ (min)
36	B	Cl	Cl	1-Methylnaphthalene	0.50	29.1
37	B	F	F	1-Methylnaphthalene	0.52	
38	B	Cl	Cl	3-Cl, 2-Me benzyl	0.50	16.6
39	B	Cl	Cl	3-Cl, 2-Me benzyl	0.09[a]	11.6
40	B	F	F	3-Cl, 2-Me benzyl	0.50	5.5
41	B	F	F	3-Cl, 2-Me benzyl	0.13[a]	17.4
42	B	F	F	3-Cl, 2-Me benzyl	12.0[b]	10.0
43	B	Cl	Cl	2,3-Di-Cl benzyl	0.60	4.2
44	B	Cl	Cl	3-Cl benzyl	0.61	9.4
45	B	Cl	Cl	4-Cl benzyl	0.16	4.1
46	B	Cl	Cl	(*S*)-α-Me benzyl	1.2[c]	35.3
47	B	Cl	Cl	(*R*)-α-Me benzyl	2.2[c]	19.4
48	B	Cl	Cl	Benzyl	1.0	57.4
49	B	Cl	Cl	4-F benzyl	1.0	34.8
50	B	Cl	Cl	3-F benzyl	2.0	11.3
51	B	Cl	Cl	3,4-Di-Cl benzyl	0.57	19.4
52	B	Cl	Cl	4-OMe benzyl	3.0	15.6
53	B	Cl	Cl	3-Cl-2-F benzyl	0.42	10.1
54	B	Cl	Cl	3-CF_3-2-F benzyl	0.50	10.1
55	B	Cl	Cl	2,3,4-Tri-fluoro benzyl	0.50	17.9
56	B	Cl	Cl	2-Cl-6-F-3-Me benzyl	4.0	5.6
57	B	Cl	Cl	2-CF_3 benzyl	1.8	4.5
58	B	Cl	Cl	2,3-Di-OMe benzyl	3.3	3.2
59	B	Cl	Cl	3-Chloro-2-CF_3 benzyl	0.89	3.9

[a] *R*,*R*-enantiomer.
[b] *S*,*S*-enantiomer.
[c] Mixture of diastereomers.

incorporate a potential site of metabolism (i.e., an *ortho*-methyl group). Changes in chain length to the basic amine, conformational restriction, and the addition of a second basic amine were studied on the left side of the molecule. All compounds were enantiomerically pure and prepared as outlined in Scheme 1. Compound **24** compared to **25** shows the lack of an effect when removing a single methylene group from the left side tether. To remove molecular weight from the molecule, the dimethylamine was used at the basic amine moiety and, again, no change in potency was observed between **26** and **27**, but compared to **24** and **25**, the piperidine is preferred. Compound **28** illustrates a hybrid of **26** and **27** that incorporates a homopiperazine group. In this molecule, rotatable bonds are removed at the expense of molecular weight, but binding affinity suffers. Compound **29** is a conformationally restricted version of **26** and showed slightly improved binding. We next looked at the addition of a second basic site on the left side by using an *N*-methyl piperazine group as a way to optimize physiochemical properties (log *D* and log *P* calculations on these piperazine analogs suggested that they are in the desired range for gut permeability). While no improvement in potency was observed over the piperidine containing compounds (compare **30** with **24**), chain shortening proved to be detrimental as potency dropped when going from three to two methylenes (compare **30** to **31**), counter to what was observed in compounds **24** and **25**. Although we improved clog *P* values, molecular weights, and, in some cases, reduced the number of rotatable bonds, potencies were not acceptable. To regain binding affinity, we reintroduced preferred groups at the R_2 and R_3 positions on the molecule. Accordingly, compounds **32**–**35** have R_2 as chlorine and improvements in binding potency were observed in compounds **32** and **33** over **30** and **31**. Replacing R_4 with a methyl group (compounds **34** and **35**) results in a two- to threefold boost in potency over **32** and **33**. Unfortunately, these changes failed to improve the metabolic stability (HLM $t_{1/2} < 5$ min) of the molecules and poor absorption and rapid clearance were still issues in pharmacokinetic experiments.

Concurrent with the exploration of the left side analogs, a series of right side analogs were generated in the lactam series (see Table 3). As in the thiazolidinone series, when the piperidine group was incorporated into the lactam series, the resulting compounds showed greater potency and metabolic stability. All compounds are *trans* racemic diastereomers unless otherwise noted. As before, efforts were directed at replacing the naphthalene group due to issues with its metabolism and toxicity[17] and the 2,3-disubstituted phenyls emerged as excellent mimics. Where R_1 and R_2 are fluorine, no significant improvement in potency or chemotaxis was observed, although these analogs have more optimal physiochemical properties in terms of molecular weight and clog *P*. A 90-fold difference in potency was observed between enantiomers **41** and **42**, again demonstrating the importance of stereochemistry within this series. Various substitution around the right side aromatic ring (**36**, **37**, **41**–**45**, **48**–**59**) or methyl group substitution on the benzyl position (**46** and **47**) maintained or detracted from binding potency. Numerous analogs were also prepared where substitution on the central aromatic ring was varied. As in the thiazolidinone series, this resulted in

a rigid SAR wherein R_1 and R_2 were optimal as dichloro or difluoro substitution. Compound **38** was prepared in racemic form and displayed an IC_{50} of 0.5 μM. Subsequent preparation in enantiopure form (compound **39**; *R*,*R* stereochemistry) provided a 5–6 fold increase in potency to 0.09 μM, the most potent CCR4 binder we had identified so far. It is important to note that chiral HPLC analysis on intermediate **9** ($R_1 = R_2 = Cl$; see Scheme 1) revealed that the enantiomeric excess was >95% and no epimerization or diastereomer formation was observed by NMR during subsequent chemistry leading to **39**. This compound showed excellent chemotaxis inhibition in both MDC and TARC driven cell migration assays ($EC_{50} = 0.3$ and 0.1 μM, respectively). In general, the IC_{50}/EC_{50} ratio was closer to unity with the lactams series as compared to the thiazolidinone series. Compound **39** also displayed excellent selectivity for CCR4 versus CCR3, CCR5, CCR6, CCR8, and CX3CR1, as <20% inhibition of chemotaxis was observed at 10 μM concentrations of **39** against these chemokine receptors.

Ultimately, we proceeded to obtain mouse pharmacokinetic data on compound **41**.[18] This lactam showed promising blood levels when administered intraperitoneally ($C_{max} = 2445$ ng/ml; $t_{1/2} = 1.4$ h; AUC = 3473 ng h/ml at 10 mg/kg in the mouse) and provided an excellent pharmacological tool to study the validity of CCR4 antagonism in vivo. Results of these studies will be reported in due course.

In summary, we have prepared a series of lactams that show good binding potency, excellent chemotaxis inhibitory activity and selectivity over other chemokine receptors. The (*R*,*R*) enantiopure lactams were prepared in >95% ee and have about a two- to fivefold advantage in binding over their racemic counterparts. The lactams, although in general less potent than the original thiazolidinones, tracked well with the previously reported SAR and displayed enhanced chemotaxic antagonism. Preliminary in vitro and in vivo pharmacokinetic properties continues to be optimized and will be reported in due course along with pharmacodynamic results in animal models of allergic disease.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2004.09.001.

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13. In general, the human liver microsome stabilities of the compounds in Table 1 correlated well with the mouse liver

microsome (MLM) stabilities. For example, compounds **14**, **16**, **19**, and **20** gave MLM half-lives of 2.2, 2.0, 4.4, and 1.8 min, respectively.

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16. Another less than desirable feature of these antagonists, as pointed out by a reviewer, is the presence of two amide bonds which might limit permeability for a similar example, see: Boyd, S. A. et al. *J. Med. Chem.* **1992**, *35*, 1735. Unfortunately, bioisosteric replacement or removal of these linkages resulted in compounds devoid of affinity for the CCR4 receptor (data not shown).
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18. In general, the human and mouse liver microsome stabilities for compounds in Table 3 provided acceptable correlation but there were several anomalies. For example, compounds **36**, **41**, and **48** provided MLM half-lives of 9.9, 47.5, and 12.2 min, respectively.