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γ-Lactams as glycinamide replacements in cyclohexane-based CC chemokine receptor 2 (CCR2) antagonists

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ABSTRACT

We describe the design, synthesis, and evaluation, of γ-lactams as glycinamide replacements within a series of di- and trisubstituted cyclohexane CCR2 antagonists. The lactam-containing trisubstituted cyclohexanes proved to be more potent than the disubstituted analogs, as trisubstituted analog, lactam **13**, displayed excellent activity (CCR2 binding IC_{50} = 1.0 nM and chemotaxis IC_{50} = 0.5 nM) and improved metabolic stability over its parent glycinamide.

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Chemokines are a large family of chemotactic cytokines that assist in the activation and migration of leukocytes.[1] In many autoimmune and inflammatory conditions, chemokines are over expressed with a concomitant influx of leukocytes into the inflamed tissues.[2] We have been interested in the chemokine, monocyte chemoattractant protein-1 (MCP-1 or CCL2), that is expressed by monocytes, T cells, fibroblasts, and others.[3] MCP-1 generates a response by binding to CC chemokine receptor 2 (CCR2),[4] which is a member of the G protein-coupled receptor family. CCR2 and MCP-1 have been implicated in several diseases, including rheumatoid arthritis,[5] atherosclerosis,[6] multiple sclerosis[7] and insulin resistance.[8] As a result, there has been significant interest in the design and synthesis of CCR2 antagonists.[9] In this communication, we describe the use of lactams as glycinamide replacements within a series of cyclohexane-based CCR2 antagonists.

As shown in Figure 1, we have recently described di- and trisubstituted cyclohexanes **1** and **2** as potent and selective CCR2 antagonists.[10] These antagonists share the glycinamide unit as a common motif for placement of the critical trifluoromethyl group. However, as a *bis*-amide, the glycinamide possess the potential for proteolysis in vivo. Glycinamides are also known to exhibit poor physical characteristics such as low water solubility and poor intestinal permeability; hence, for the optimization of **1** and **2**, it was our desire to explore glycinamide replacements. We were restricted by results from a previous study that found substitution of the imbedded glycine by other amino acids (*R* or *S*) produced analogs with poor CCR2 binding (data not shown). To circumvent this, we investigated γ-lactams, which are known to be excellent conformation constraints within peptides.[11] Hence, γ-lactams, like **3**, **4** and **5** could stabilize our compounds toward proteolysis in vivo, improve intestinal permeability (by eliminating an amide NH),[12] and reduce CYP-mediated oxidative metabolism via rigidification.[13]

The newly synthesized lactams were evaluated in vitro, using a radiolabeled MCP-1 displacement assay with peripheral blood mononuclear cells (PBMCs).[14] Compounds with good activity in the CCR2 binding assay were also evaluated in a chemotaxis assay[14] for CCR2 functional antagonism and a CCR3 binding assay[15] for selectivity. As shown in Table 1, the *S*-lactam **8** (mixture of diastereomers) was more active than the *R*-lactam **9** (mixture of diastereomers); however, **8** still displayed ninefold less affinity for CCR2 as compared to its parent **6**. From this result, we progressed to the benzyl amine and found that **10** (again the *S*-lactam) had more CCR2 affinity than its diastereomer **11**,[16] and that lactam **10** was equipotent with its parent glycinamide **7**.

This confirmed that the *S*-lactams were viable glycinamide replacements, and we moved to the more potent sulfone-containing trisubstituted cyclohexanes that we recently reported.[10c] As shown in Table 2, not only was lactam **13** potent (CCR2 binding IC_{50} = 1.0 nM and chemotaxis IC_{50} = 0.5 nM), but it was also equipotent to its parent glycinamide **12**. As mentioned above, it

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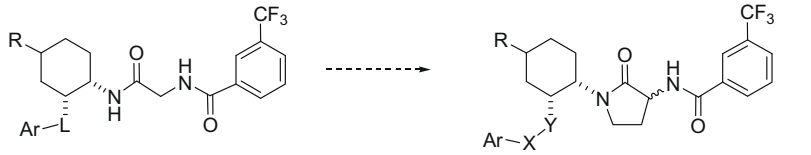
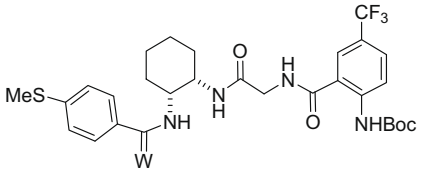


1 R = H, L = varied linker
2 R = NR^1R^2, L = varied linker

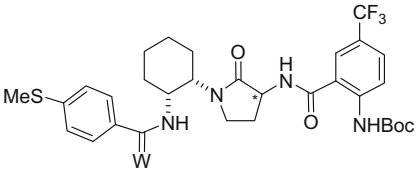
3 R = H, X = CO, Y = NH
4 R = H, X = CH_2, Y = NH
5 R = NR^4R^5, X = SO_2, Y = CH_2

Figure 1. Investigation of lactams as glycinamide replacements.

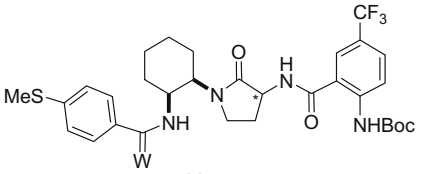
Table 1
Evaluation of lactam-containing disubstituted cyclohexane derivatives



6-7



8-10



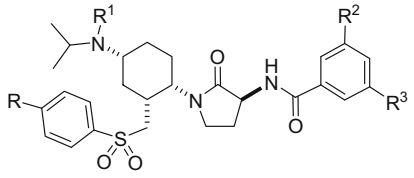
11

Compd #	W	Lactam configuration C(*)	CCR2 binding IC_{50}[c] (nM)
6[a]	O	No lactam	50.0 ± 11.3 (2)
8[b]	O	*S*	460.0 (1)
9[b]	O	*R*	14% @ 1 μM
7[a]	H,H	No lactam	311.5 ± 78.5 (2)
10	H,H	*S*	278.0 (1)
11	H,H	*S*	11% @ 1 μM

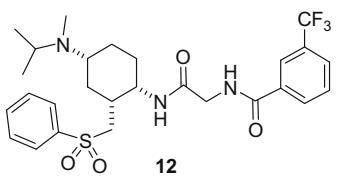
[a] Compound is racemic (relative stereochemistry shown).
[b] Compound is a mixture of diastereomers (relative stereochemistry shown on cyclohexane).
[c] IC_{50} values are reported as mean ± SD (n = 2).

was our desire to use the lactams to reduce CYP-mediated metabolism, and, as shown by the microsomal incubation data, lactam **13** was more stable when compared to its parent glycinamide **12** (88% remaining for **13** vs 61% remaining for **12**). Further analysis of **12** and **13** showed that both were selective versus CCR3 and both had no measurable permeability in Caco-2. However, lactam **13** displayed an increase in hERG channel inhibition as compared to **12**. For these trisubstituted cyclohexane-based antagonists, lactam incorporation preserved all the SAR trends we have previously reported for glycinamide-based compounds.[10b,c] For example,

Table 2
[a]Evaluation of lactam-containing trisubstituted cyclohexane derivatives



13-19

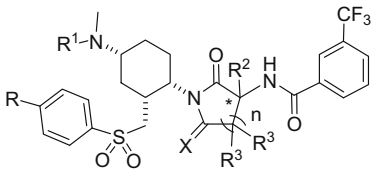


12

#	R	R^1	R^2	R^3	CCR2 Binding THP-1 IC_{50} (nM)	Chemotaxis[b] IC_{50} (nM)	CCR3 Binding %inh @ 10 μM	Human microsomal stability[d] (% remaining)	hERG[e] IC_{50} (μM)	Caco-2 P_{AP-BL} (nm/s)
12	See above				0.8 ± 0.0 (2)	1.3	19%	61	>80	<15
13	H	Me	CF_3	H	1.0 ± 0.2 (7)	0.5	17%	88	30	<15
14	Me	Me	CF_3	H	0.4 ± 0.1 (6)	0.8	8%	100	3	<15
15	H	Me	H	H	151 ± 11.3 (2)	NT	NT	100	>80	NT
16	H	Me	CF_3	CF_3	3.5 ± 2.4 (2)	2.4	NT	99	4	<15
17	H	Me	CF_3	F	0.8 ± 0.4 (2)	<0.4	NT	91	22	<15
18	H	Et	CF_3	H	0.3 ± 0.2 (2)	1.6[c]	12%	NT	NT	<15
19	H	Pr	CF_3	H	51 (1)	NT	NT	NT	NT	NT

NT = not tested.
[a] IC_{50} values (n) are displayed as mean ± SD (n = 2) and mean ± SEM (n >2).
[b] Chemotaxis in human monocytes (n = 1) with 0.1 M BSA.
[c] Chemotaxis in human monocytes (n = 1) with 0.5 M BSA.
[d] Percent remaining after 10 minute incubation in human hepatic microsomes.
[e] hERG FLIPR assay (n = 1).

Table 3
[a]Evaluation of lactam modifications



13 and **20-25**

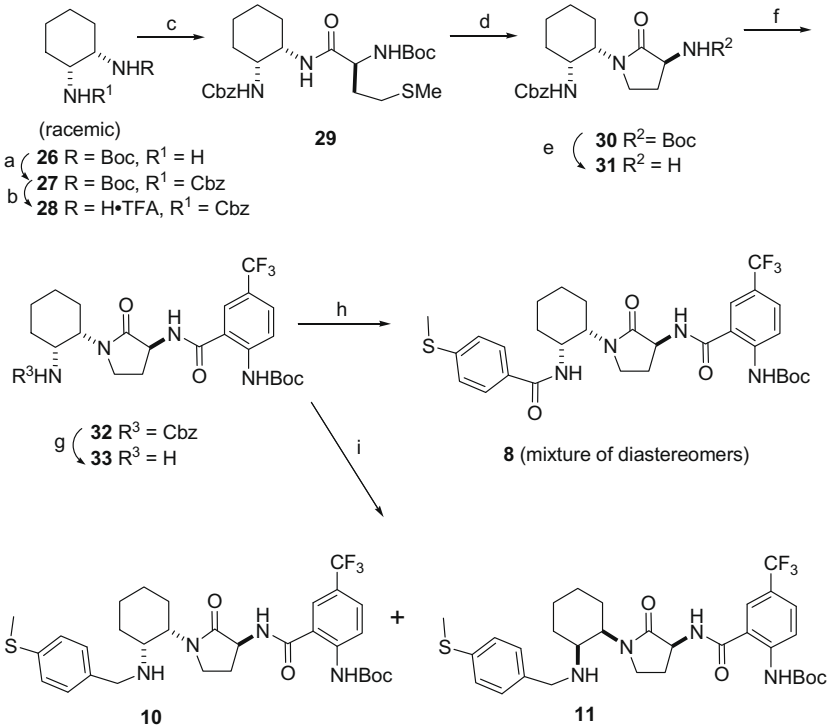
#	R	R^1	X	R^2	Lactam configuration C(*)	R^3	*n*	CCR2 Binding THP-1 IC_{50} (nM)	Caco-2 P_{AP-BL} (nm/s)
13	H	*i*-Pr	H,H	H	*S*	H	1	1.0 ± 0.2 (7)	<15
20[b]	SMe	*i*-Pr	H,H	Me	*S*/*R*	H	1	4500 (1)	NT
21[c]	SMe	*i*-Pr	H,H	Me	*S*/*R*	H	1	56.5 ± 45.9 (2)	<15
22[d]	H	*i*-Pr	H,H	H	*S*	Me	1	>1000 (1)	<15
23[d]	H	Me	H,H	H	*S*	H	2	284.0 ± 31.1 (2)	NT
24[d]	H	*i*-Pr	H,H	H	*S*	H	3	>1000 (1)	NT
25[d]	H	*i*-Pr	O	H	*S*	H	1	99.0 ± 19.8 (2)	22

NT = not tested.
[a] IC_{50} values (*n*) are displayed as mean ± SD (*n* = 2) and mean ± SEM (*n* >2).
[b] First diastereomer (racemic) from reverse phase HPLC (pair with **21**).
[c] Second diastereomer (racemic) from reverse phase HPLC (pair with **20**).
[d] Mixture of diastereomers (relative stereochemistry shown on cyclohexane).

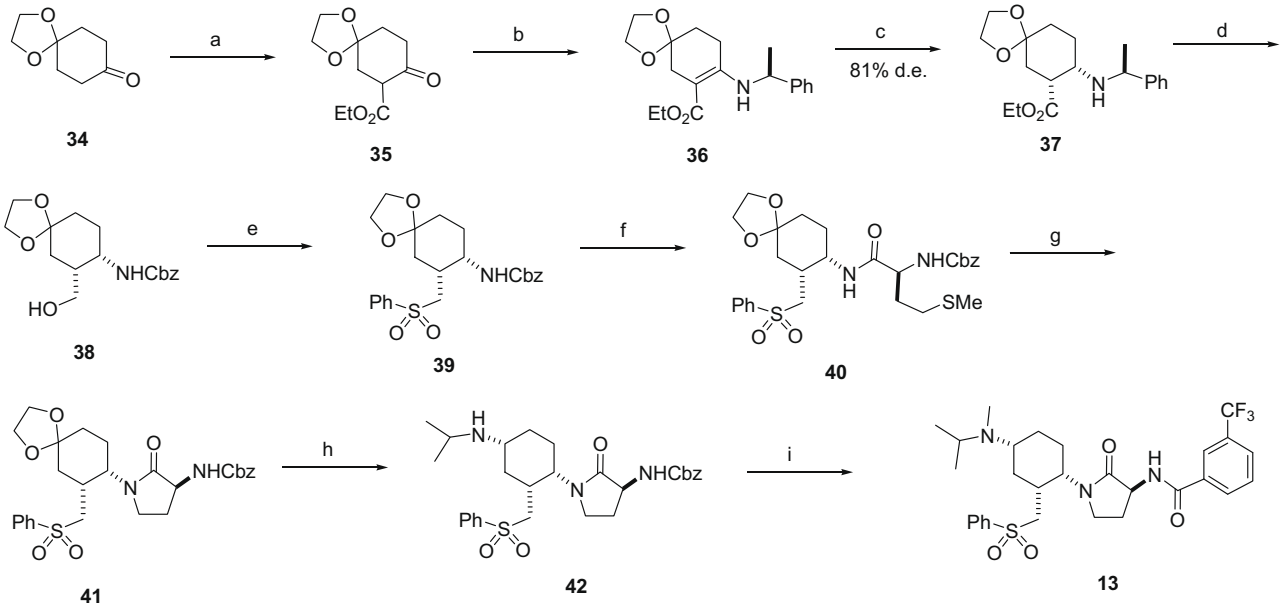
Table 4
Mouse and dog pharmacokinetic data for compound **13**

Species	Dose (*n*)	AUC 0–8 h (nM h)	CL (L/h/kg)	$T_{1/2}$ (h)	V_{ss} (L/kg)	C_{max} (nM)	*F*%
Mouse	iv, 1 mpk (*n* = 2)	99	11	0.7	10.2	200	—
Mouse	po, 10 mpk (*n* = 1)	40	—	5.2	—	13	3
Dog	iv, 1 mpk (*n* = 2)	2900	0.5	1.6	1	3900	—
Dog	po, 6 mpk (*n* = 1)	9100	—	2.0	—	2900	50

AUC, area under curve; C_{max}, maximum concentration; $t_{1/2}$, terminal half-life; V_{ss}, steady-state volume of distribution; *F*, oral bioavailability.



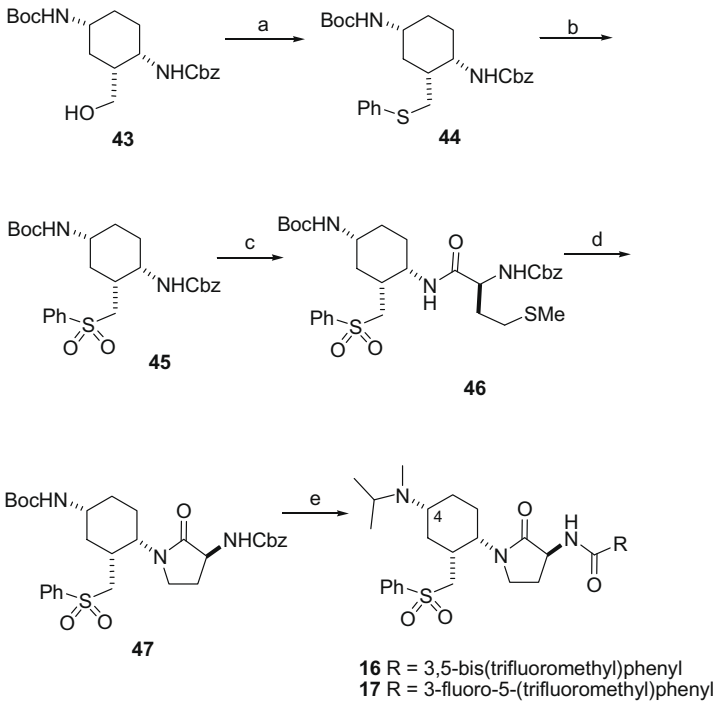
Scheme 1. Reagents and conditions: (a) Cbz_2O, TEA, DCM, 82%; (b) TFA, DCM, quant; (c) BOP, *N*-Boc-*L*-Met-OH, NMM, DMF, quant; (d) (i) MeI; (ii) NaH, DMF, DCM, 49%; (e) TFA, DCM, quant; (f) BOP, 5-trifluoromethyl-2-*N*-Boc-anthranilic acid, NMM, DMF, 52%; (g) H_2, Pd/C, MeOH, quant; (h) BOP, 4-(methylthio)benzoic acid, NMM, DMF, 85%; (i) $NaBH(OAc)_3$, AcOH, 4-(methylthio)benzaldehyde, DCE, 55%.



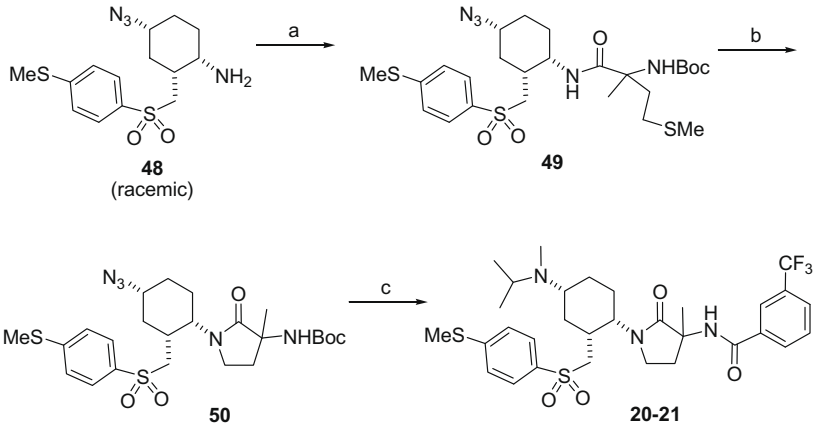
Scheme 2. Reagents and conditions: (a) EtO_2CCN, LDA, THF, 81%; (b) $Yb(OTf)_3$, (*S*)-1-methyl-2-propanamine, DCM, 91%; (c) $NaBH(OAc)_3$, AcOH, DCE, 78%; (d) (i) LAH, Et_2O; (ii) H_2, $Pd(OH)_2$/C, MeOH; (iii) Cbz_2O, Et_3N, THF/H_2O, 65% (three steps); (e) (i) *n*-Bu_3P, PhSSPh, Δ, THF; (ii) *m*-CPBA, DCM, 92% (two steps); (f) (i) H_2, Pd/C, MeOH; (ii) BOP, *N*-Cbz-*L*-Met-OH, NMM, DMF, 79% (two steps); (g) (i) MeI; (ii) Cs_2CO_3, DMF, 65%; (h) (i) HCl, THF, H_2O; (ii) Ti(O*i*-Pr)$_4$, $NaBH_4$, *i*-$PrNH_2$, 55%; (i) (i) 37% HCHO, $NaBH_3CN$; (ii) H_2, Pd/C, MeOH; (iii) HATU, 3-trifluoromethylbenzoic acid, NMM, DMF, 12% (three steps).

methyl substitution at the 4-position of the aryl sulfone gave compound **14** that was equipotent to **13** versus CCR2; however, **14** exhibited an increase in hERG potency as compared to **13**. The trifluoromethyl of the benzamide was still critical, as shown by the loss of CCR2 affinity with the *des*-trifluoromethyl compound **15**. Additional lipophilic groups could be placed *meta* to the existing trifluoromethyl; however, both **16** and **17** showed an increased in hERG channel inhibition. With the *iso*-propyl group installed on the *exo*-cyclic amine, the length of the second substituent was restricted to the ethyl of **18**, as the propyl compound **19** lost significant CCR2 affinity.

With the five-membered lactam proven to be a viable glycinamide replacement in this series, we turned our efforts toward its optimization by exploring different ring sizes and other substitutions as shown in Table 3. Substitution of a methyl on C(3) of the lactam (see **20** and **21**) or as a dimethyl on C(4) (see **22**) both failed



Scheme 3. Reagents and conditions: (a) *n*-Bu_3P, PhSSPh, Δ, THF, 82%; (b) oxone, IPA, H_2O, 92%; (c) (i) H_2, $Pd(OH)_2$, MeOH; (ii) EDC, HOBt, TEA, *N*-Cbz-*L*-Met-OH, DCM, 89%; (d) (i) MeI; (ii) Cs_2CO_3, DMF, 39%; (e) (i) TFA, DCM; (ii) acetone, $NaBH(OAc)_3$, DCM; (iii) 37% HCHO, $NaBH(OAc)_3$, DCM, 99%; (iv) H_2, $Pd(OH)_2$, MeOH, 92%; (v) HATU, NMM, benzoic acid of choice, DMF, 28–38%.



Scheme 4. Reagents and conditions: (a) HATU, *N*-Boc-α-methyl-*D*/*L*-methionine, *i*-PrNEt$_2$, DMF, 77%; (b) (i) MeI; (ii) Cs_2CO_3, DMF, 75%; (c) (i) TFA, DCM; (ii) 3-(trifluoromethyl)benzoyl chloride, TEA, 78% (two steps); (iii) H_2, Pd/$BaSO_4$, MeOH, 83%; (iv) acetone, AcOH, $NaBH(OAc)_3$, DCE, 73%; (v) 38% HCHO, $NaBH_3CN$, MeOH, 58%.

to increase CCR2 affinity or cellular permeability. A larger lactam ring size (see **23** and **24**) also proved to be detrimental for CCR2 activity, as did conversion to the imide **25**.

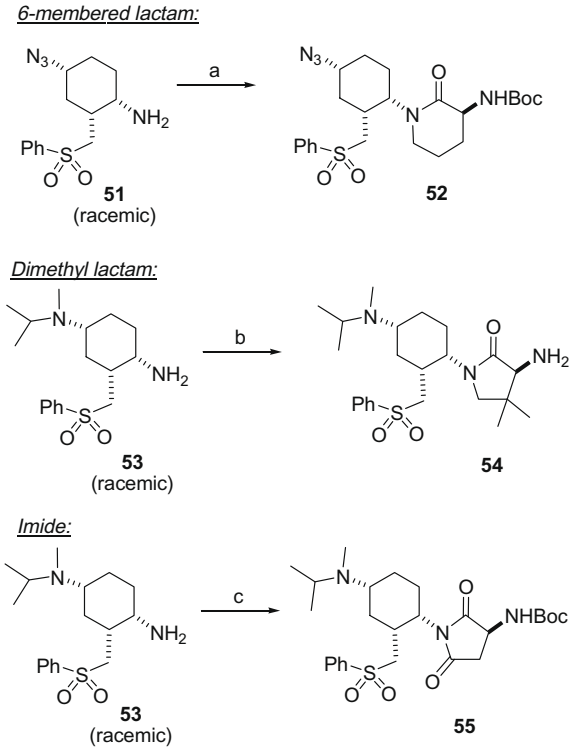
Lactam **13** had the best overall profile, so we advanced this compound into pharmacokinetic studies. As shown in Table 4, compound **13** was administered to mice; however, its high clearance limited its bioavailability. Compound **13** was also studied in dog and was found to have low clearance and good oral bioavailability.

As shown in Scheme 1, the synthesis of the disubstituted analogs began with the racemic mono-carbamate **26**.[17] Protecting group manipulation led to **28**, which was coupled with *N*-Boc-*L*-methionine to yield amide **29**. This was transformed into the γ-lactam **30**, using the Freidinger conditions (MeI and then NaH).[11b] Protecting group deprotection, benzamide formation, and Cbz removal gave compound **33**, which was used as a diversification point. The coupling of **33** with 4-(methylthio)benzoic acid gave benzamide **8** as a mixture of diastereomers. A reductive amination with **33** and 4-(methylthio)benzaldehyde gave the separated diastereomers **10** and **11**. The final disubstituted analog **9** was made by repeating the sequence with *N*-Boc-*D*-methionine (substituted into step c, Scheme 1) to give **9** (see Table 1) as a mixture of diastereomers.

As shown in Scheme 2, our first synthesis of a lactam-containing trisubstituted system started with the formation of keto ester **35** from **34**. Compound **35** was converted to enamine **36** prior to a diastereoselective reduction[18] (81% d.e.) to give **37**. The chiral auxiliary was removed, and the ester was reduced to alcohol **38**. Incorporation of **38** into a sulfide substitution reaction was followed by an oxidation to give sulfone **39**. Carbamate removal and amide coupling gave the single diastereomer **40**. Lactam formation was best accomplished by modified Freidinger conditions, namely methyl iodide followed by cesium carbonate in DMF. The resulting compound **41** was hydrolyzed to the ketone prior to a reductive amination. When sodium borohydride was used in the reductive amination, a 1:1 ratio of diastereomers resulted, and the desired secondary amine **42** was isolated by chromatography. Conversion to the tertiary amine, carbamate removal, and benzamide formation gave the desired derivative **13**. Other analogs were produced from this sequence as well. From the secondary amine **42**, other reductive aminations were performed to give the ethyl and propyl substitutions of **18** and **19**, respectively. The primary alcohol **38** was also converted to the tolyl derivative, which was used in the synthesis of **14**.

For a second generation synthesis, it was our desire to avoid the late-stage reductive amination (**41** to **42**), and install the *exo*-cyclic amine at C(4) as a single stereoisomer early in the synthesis. As a result, we developed and recently reported[19] the enantioenriched trisubstituted cyclohexane **43** (93% ee). Shown in Scheme 3, the new sequence commenced with a sulfide substitution reaction to yield **44**. Oxidation, carbamate removal, and amide formation gave **46**. Lactam formation using our standard conditions (methyl iodide followed by cesium carbonate) gave **47**. With the C(4) *exo*-cyclic amine in place, simple progression to a reductive amination and benzamide formation gave analogs **16** and **17**.

The lactam modifications of Table 3 were accomplished using similar chemistry to that described in Schemes 2 and 3. As shown in Scheme 4, racemic **48**[10c] was used in the formation of benzamide **49**, which contained the desired quaternary center. Our cesium



Scheme 5. Reagents and conditions: (a) (i) $NaBH(OAc)_3$, (*S*)-*N*-Boc-5-oxopentanoic acid methyl ester, DCM; (ii) LiOH, H_2O, THF; (iii) HATU, Et_2Ni-Pr, DMF, 35% (three steps); (b) (i) $NaBH(OAc)_3$, (*S*)-3,3-dimethyl-4-oxo-2-[(9-phenylfluoren-9-yl)-amino]-butyric acid methyl ester, DCM, 67%; (ii) TFA, DCM; (iii) Δ, toluene, 21%; (c) EDC, HOBt, TEA, *N*-Boc-*L*-Asp-OH, DCM, 6%.

carbonate cyclization conditions afforded lactam **50**, even in the presence of the aryl sulfide. Subsequent reduction of the azide followed by our standard transformations gave the desired racemic diastereomers **20** and **21**.

With the 'end game' chemistry firmly established (see Schemes 2–4), other core modifications were produced as shown in Scheme 5. The six-membered lactam necessary for analog **23** started from the racemic amine **51**.[10c] A reductive amination with (*S*)-2-*N*-*tert*-butoxycarbonyl-5-oxopentanoic acid methyl ester[20] followed by saponification and cyclization yielded **52**, which was taken to **23** using our standard chemistry. Following this same sequence, but substituting (*S*)-2-*N*-*tert*-butoxycarbonyl-5-oxohexanoic acid methyl ester[21] into the reductive amination, gave the seven-membered lactam analog of **52**, which was used to synthesize **24**. In a similar way, a reductive amination of **53** and (*S*)-3,3-dimethyl-4-oxo-2-[(9-phenylfluoren-9-yl)-amino]-butyric acid methyl ester[22] was followed by phenylfluorenyl removal and cyclization to yield **54**, which was used in the production of **22**. Finally, amine **53** was also coupled to *N*-Boc-*L*-aspartic acid, thus directly forming the imide **55**, which was used in the formation of analog **25**.

In summary, we have demonstrated that γ-lactams are viable glycinamide replacements within a series of cyclohexane-based CCR2 antagonists. Lactam-containing trisubstituted cyclohexanes were more promising, and this led to the potent and selective CCR2 antagonist **13**, which also showed oral bioavailability in dog. The five-membered lactam of compound **13** proved to be more active than the six- or seven-membered lactams, and additional substitution about the lactam ring of **13** was not tolerated. As glycinamide-based CCR2 antagonists are quite prevalent, these γ-lactams could find additional use in the design and development of future antagonists.

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