Bioorganic & Medicinal Chemistry Letters 19 (2009) 3418–3422

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Novel sulfone-containing di- and trisubstituted cyclohexanes as potent CC chemokine receptor 2 (CCR2) antagonists

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ARTICLE INFO

Article history:
Received 13 March 2009
Accepted 11 May 2009
Available online 18 May 2009

Keywords:
CCR2
CCR2 antagonist
Chemokine
GPCR

ABSTRACT

Potent sulfone-containing di- and trisubstituted cyclohexanes were synthesized and evaluated as CC chemokine receptor 2 (CCR2) antagonists. This led to the trisubstituted derivative **54**, which exhibited excellent binding (CCR2 IC_{50} = 1.3 nM) and functional antagonism (calcium flux IC_{50} = 0.5 nM and chemotaxis IC_{50} = 0.2 nM). The superiority of the trisubstituted scaffold was rationalized to be the result of a conformational rigidification, which provided insight into the bioactive conformation of this chemotype.

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Chemokines are endogenous proteins that assist in the activation and migration of leukocytes.[1] In many autoimmune and inflammatory conditions, high levels of chemokines have been detected and are associated with the uncontrolled delivery of inflammatory cells into the tissues and joints.[2] We have been interested in a CC chemokine, monocyte chemoattractant protein-1 (MCP-1 or CCL2),[3] which binds to its cognate receptor, CC chemokine receptor 2 (CCR2),[4] a member of the G-protein coupled receptor (GPCR) family. This pair has been associated with several diseases that are characterized by monocyte accumulation, including rheumatoid arthritis,[5] atherosclerosis,[6] and multiple sclerosis[7] and insulin resistance.[8] As a result, there has been a substantial interest in the design and synthesis of CCR2 antagonists.[9] In this Letter, we describe a series of novel, sulfone-containing di- and trisubstituted cyclohexanes as potent CCR2 antagonists.

As shown in Figure 1, we recently described the disubstituted cyclohexane **1** as a potent and selective CCR2 antagonist.[10] In an attempt to reduce the number of hydrogen bond donors, we began to explore sulfones **2a** and **2b** as possible antagonists. As shown in Scheme 1, the disubstituted cyclohexanes (**10–11** and **22–29**) were synthesized in racemic form, starting from the commercial, racemic alcohol **3**. After carbamate formation, sulfide installation was accomplished via a displacement reaction[11] to give **5**. Sulfide oxidation was followed by a S_NAr reaction to deliver compound **7**. An initial target was then realized by direct coupling of **8** with glycinamide **9** to yield **10**. Amine **8** could also be coupled with *N*-Boc-glycine to afford **12**. After carbamate removal, the functionalized anthralinic acids **14–21** (synthesis shown in Scheme 2) were attached via BOP coupling to yield targets **22–29**.

The functionalized anthranilic acids were synthesized as shown in Scheme 2. Carboxylate **30** was protected as an allyl ester by exposure to allyl bromide and potassium carbonate in DMF to afford **31**. Standard deprotection of the carbamate gave aniline **32**. Treatment with triphosgene and the amine of choice gave a urea,[12] which only needed the allyl ester removed to afford the functionalized anthranilic acids **14–21**.

As shown in Scheme 3, synthesis of the racemic trisubstituted scaffold commenced with the racemic epoxide **33**.[13] A Lewis acid-promoted epoxide opening was used in conjunction with a lithiated methyl phenyl sulfone to provide the alcohol **34**.[14] The secondary alcohol was converted to azide **35** through the intermediacy of the mesylate. The benzyl group of **35** was removed with BCl_3[15] prior to the reduction of azide **36** to amine **37**. After the amine was protected as carbamate **38**, a mesylate displacement reaction provided azide **39**. Carbamate removal was followed by amide formation to give either glycinamide **42** or **43**, depending on the carboxylate (**41** or **9**) used. In each case, the azide was reduced to the amine (**44** or **45**) and then elaborated to the targets, as shown in Scheme 2.

The newly synthesized sulfones were evaluated in vitro, using a radiolabeled MCP-1 displacement assay with peripheral blood mononuclear cells (PBMCs).[16] We were interested in selective CCR2 antagonists, and therefore, we used a CCR3 binding assay[17] for an initial assessment of selectivity. Compounds with good

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doi:10.1016/j.bmcl.2009.05.041

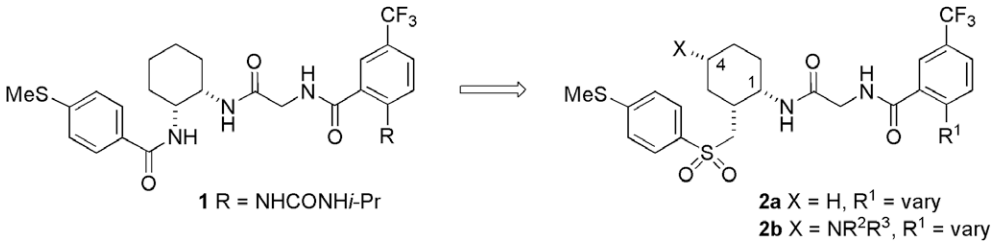
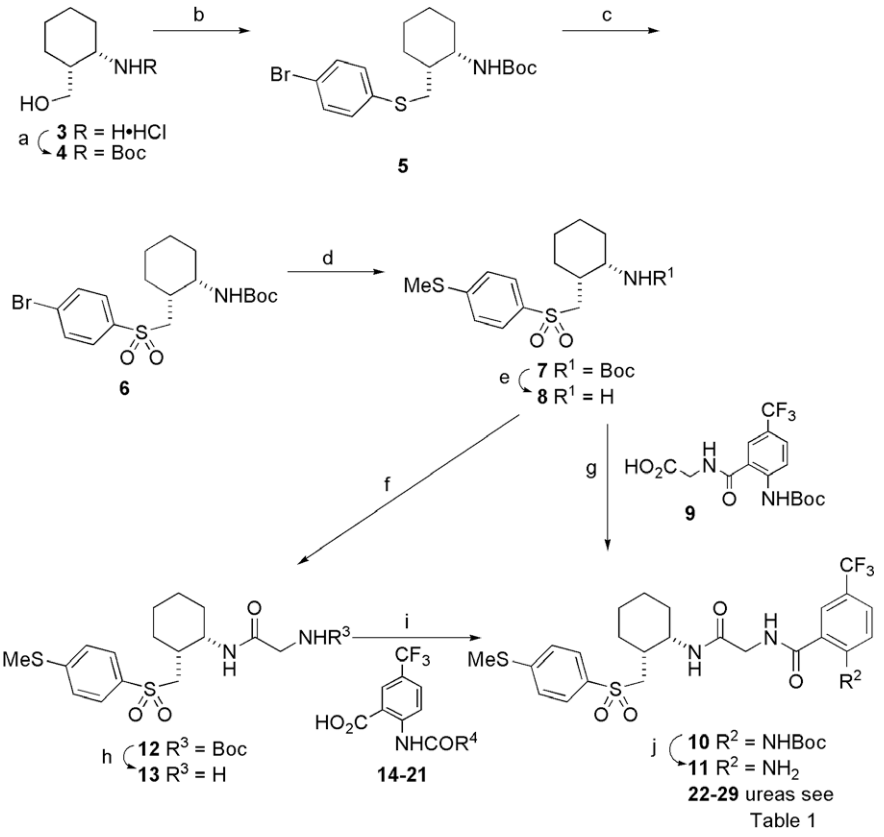


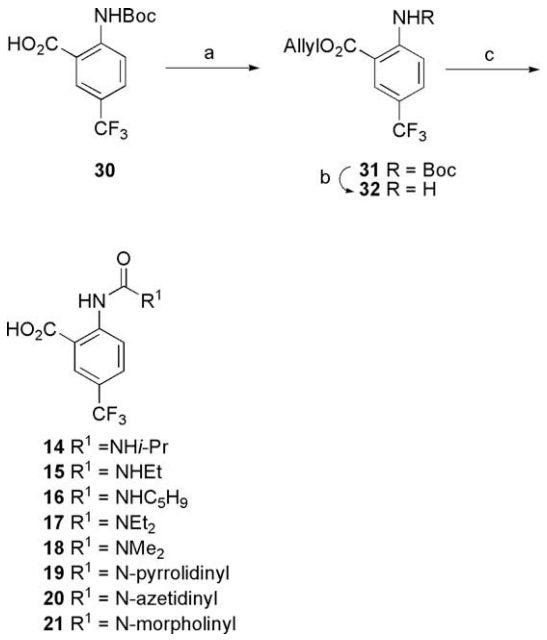
Figure 1. Investigation of sulfone-containing di- and trisubstituted cyclohexanes.



Scheme 1. Reagents and conditions: (a) $(Boc)_2O$, TEA, THF/H_2O, 97%; (b) bis(4-bromophenyl) disulfide, PBu_3, CH_2Cl_2, 43%; (c) *m*-CPBA, CH_2Cl_2, 77%; (d) NaSMe, DMF, quant.; (e) TFA, CH_2Cl_2, quant.; (f) BOP, *N*-Boc-Gly-OH, DIEA, DMF, quant.; (g) BOP, **9**, DMF, 53%; (h) TFA, CH_2Cl_2, quant.; (i) BOP, **14**–**21**, DIEA, 11–55%; (j) TFA, CH_2Cl_2, quant.

activity in the CCR2 binding assay were also evaluated in two functional assays: a calcium flux assay[16,18] and a chemotaxis assay.[16] As shown in Table 1 for the disubstituted case, a direct comparison of the previously published[10] amide **1** to sulfone **22** showed a fivefold loss of CCR2 affinity for the sulfone. In order to discover CCR2 affinity for the sulfones, we probed the 2-amino position of the anthranilic amide. The *t*-butyl carbamate **10**, the amino derivative **11**, the ethyl urea **23** or cyclopentyl urea **24** all failed to demonstrate any additional CCR2 affinity when compared to **22**. However, the diethyl urea **25** gained fourfold in affinity for CCR2 as compared to **22**, without affecting its selectivity versus CCR3. Likewise, the dimethyl urea **26** also demonstrated this increase in CCR2 binding affinity. This trend was improved with the cyclic cases of pyrrolidinyl **27**, azetidinyl **28**, and morpholinyl **29**, as they displayed both excellent binding and functional activity. However, these large ureas added significant molecular weight, and we sought ways to circumvent this.

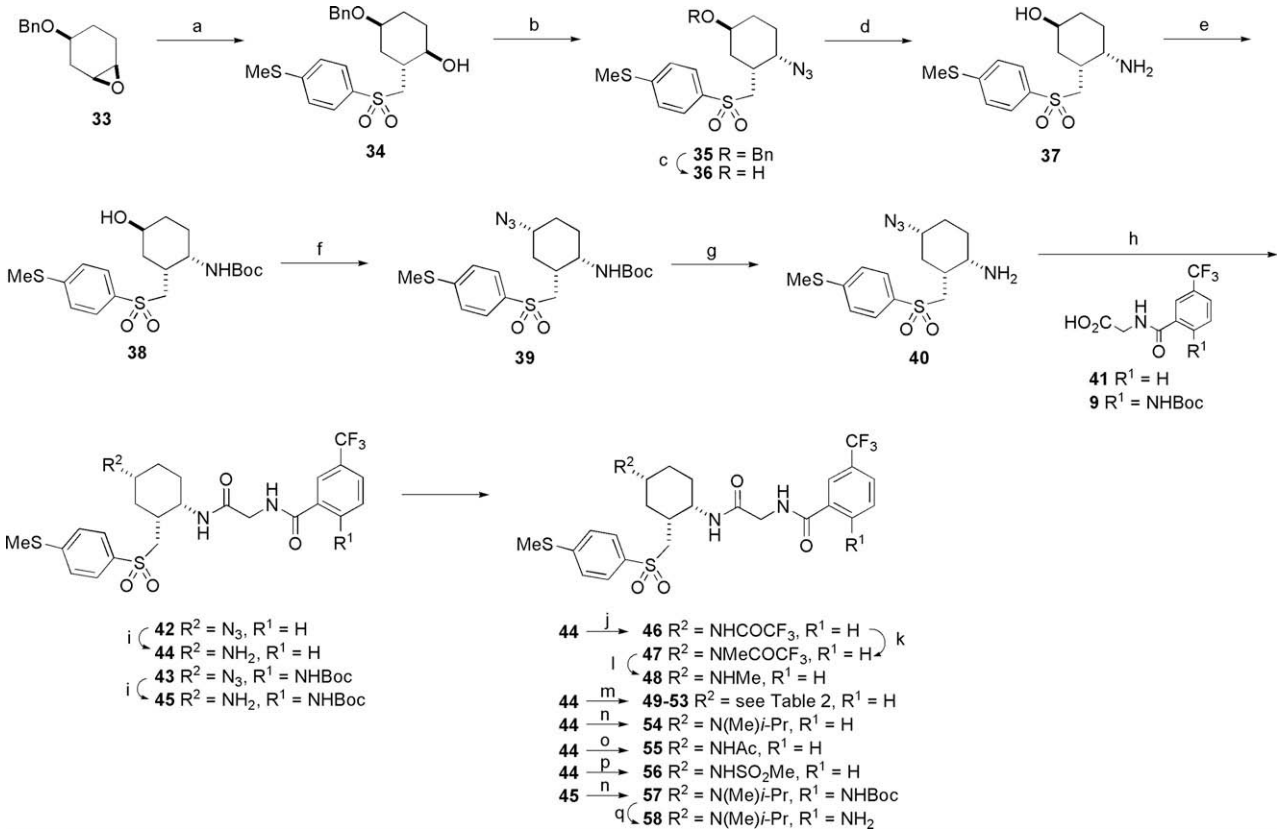
Recently, we described[19] a series of potent trisubstituted CCR2 antagonists, which featured exocyclic amines in the 4-position of the cyclohexane, and these antagonists did not need the large ureas for activity. In an attempt to reduce our requirement for the large ureas in the present case (Table 1), we investigated the installation of exocyclic amines in the C-4 position of the cyclohexyl sulfone antagonists. As shown in Table 2, the primary amine **44** displayed excellent CCR2 activity without the need for an urea on the anthranilic amide, thus lowering molecular weight. In addition, the primary amine **44** was a potent functional antagonist while remaining selective versus CCR3. The mono-methyl amine **48** showed a threefold increase in binding affinity with a corresponding fivefold increase in calcium flux potency as compared to **44**. Other secondary amines (benzyl **49** and *i*-propyl **50**) were also active in the binding assay with similar functional activity. Small tertiary amines like the dimethyl **51**, diethyl **52**, and *i*-propyl methyl **54** displayed



Scheme 2. Reagents and conditions: (a) allyl-Br, K_2CO_3, DMF, 73%; (b) TFA, CH_2Cl_2, quant.; (c) (i) triphosgene, THF, (ii) amine of choice, THF, 48–87%, (iii) $Pd(PPn_3)_4$ pyrrolidine, MeCN, 27–53%.

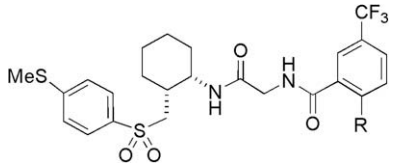
the best binding affinity, with **54** having excellent functional activity (calcium flux $IC_{50} = 0.5$ nM and chemotaxis $IC_{50} = 0.2$ nM). However, as shown by the dipropyl analog **53**, if the tertiary amine became too large, CCR2 binding affinity decreased. The CCR2 binding affinity also decreased for non-basic analogs like the acetamide **55** and the sulfonamide **56**. A direct comparison of the Boc carbamate **57** with its corresponding disubstituted case **10** demonstrated that the trisubstituted derivative **57** gained about fourfold in affinity for CCR2. Unexpectedly, removal of the carbamate to the trisubstituted **58** led to a *100-fold gain* in affinity for CCR2, as compared to the disubstituted case **11**.

Thus, the C-4 exocyclic amine proved to be a valuable substituent in the CCR2 driven optimization of these sulfone antagonists. It is likely that the exocyclic amine makes a new contact within the CCR2 receptor, however this exocyclic substituent has another role as well, conferring conformational rigidity to the cyclohexane core. As shown in Figure 2, disubstituted **11** has two conformations (see **11A** and **11B**) of essentially the same energy[20] that interconvert via a ring flip, as both substituents compete for the equatorial position. Installation of the C-4 exocyclic amine creates a 1,3-diaxial interaction between the C-4 and C-2 position (see conformation **58B**), thus forcing the cyclohexane to adopt a single chair, which places the C-4 and C-2 substituent in the equatorial position as shown by conformation **58A**. Hence, from these considerations, we presume that **58A** and **11A** repre-



Scheme 3. Reagents and conditions: (a) *p*-$MeSC_6H_4SO_2Me$, *n*-BuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C, 65–84%; (b) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C; (ii) NaN_3, DMSO, 85 °C, 70% (two steps); (c) BCl_3, CH_2Cl_2, 84%; (d) H_2, $Pd/BaSO_4$, MeOH, 98%; (e) $(Boc)_2O$, $NaHCO_3$, THF/H_2O, quant.; (f) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C; (ii) NaN_3, DMSO, 85 °C, 76%; (g) TFA, CH_2Cl_2, quant.; (h) **41** or **9** BOP, NMM, DMF, 96%; (i) H_2, $Pd/BaSO_4$, MeOH, 92%; (j) CF_3CO_2Et, TEA, CH_2Cl_2, quant.; (k) MeI, K_2CO_3, DMF, 18%; (l) 2 M K_2CO_3, MeOH, 89%; (m) aldehyde of choice (acetone for **50**), $NaBH_3CN$, MeOH, 17–36%; (n) (i) acetone, $NaBH_3CN$, MeOH; (ii) 38% HCHO $NaBH_3CN$, MeOH, 91%; (o) AcCl, TEA, $CHCl_3$, 37%; (p) MsCl, TEA, $CHCl_3$, 52%; (q) TFA, CH_2Cl_2, quant.

Table 1
Evaluation of disubstituted cyclohexane derivatives[a]



Compd #	R	IC_{50}[b] (nM)			CCR3 Binding % Inh@10 μM[c]
		CCR2 Binding	Ca^{2+} Flux	Chemotaxis	
1	See Figure 1	5.1 ± 3.6 (2)	18 ± 0.7 (2)	1.0 ± 0.2 (2)	37
22	NHCONH*i*-Pr	26.5 ± 3.5 (2)	38.0 (1)	NT	32.0
10	NHBoc	46.0 ± 2.8 (2)	NT	NT	9.4
11	NH_2	172.0 ± 108.9 (2)	NT	NT	NT
23	NHCONHEt	27.5 ± 2.1 (2)	21.0 (1)	NT	18.1
24	$NHCONHC_5H_9$	44.5 ± 4.9 (2)	64.0 (1)	NT	55.2
25	$NHCONEt_2$	6.5 ± 2.1 (2)	34.0 (1)	39.5 ± 20.5 (2)	3.0
26	$NHCONMe_2$	8.1 ± 4.0 (2)	21.0 (1)	43.5 ± 4 9 (2)	12.9
27	NHCON-pyrrolidinyl	3.8 ± 1.6 (2)	24.0 (1)	11.8 ± 7.2 (2)	0
28	NHCON-azetidinyl	5.8 ± 2.2 (2)	6.5 (1)	16.5 ± 9.2 (2)	24.6 ± 3.7 (2)
29	NHCON-morpholinyl	2.7 ± 2.2 (2)	16.0 (1)	7.0 ± 4.2 (2)	21.6 ± 7.5 (2)

[a] Compounds are racemic, one enantiomer is displayed for illustrative purposes.
[b] IC_{50} values (n) are displayed as mean ± SD (n = 2) and mean ± SEM (n > 2).
[c] CCR3% inhibition are n = 1, unless otherwise noted. NT = not tested.

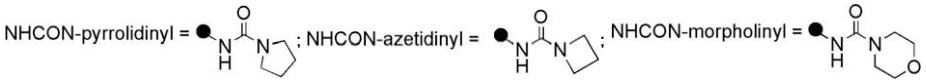
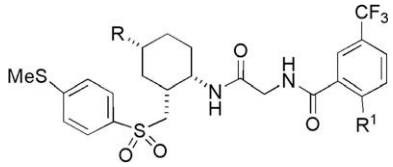


Table 2
Evaluation of trisubstituted cyclohexane derivatives[a]



Compound #	R	R^1	IC_{50}[b] (nM)			CCR3 Binding % Inh@10 μM[c]
			CCR2 Binding	Ca^{2+} Flux	Chemotaxis	
44	NH_2	H	13.1 ± 5.1 (5)	7.5 ± 7.8 (2)	21.0 ± 8.7 (3)	50.2 ± 3.7 (2)
48	NHMe	H	3.7 ± 2.3 (2)	1.5 (1)	NT	51.2
49	NHBn	H	8.4 ± 3.7 (2)	NT	12.7 ± 6.1 (2)	83.6
50	NH*i*-Pr	H	2.05 ± 0.2 (2)	5.1 ± 7.7 (3)	10.4 ± 0.8 (2)	71.6
51	NMe_2	H	0.37 ± 0.07 (2)	0.3 ± 0 (2)	2.5 (1)	53.1
52	NEt_2	H	1.3 ± 0.7 (2)	0.7 ± 0.1 (2)	NT	69.6
53	N*n*-Pr_2	H	199.5 ± 72.8 (2)	NT	NT	NT
54	N*i*-PrMe	H	1.3 ± 0.5 (2)	0.5 ± 0.1 (2)	0.2 (1)	75.5
55	NHAc	H	153.0 ± 14.1 (2)	NT	NT	NT
56	$NHSO_2$-Me	H	41.3 ± 28.6 (2)	NT	NT	42.9
57	N*i*-PrMe	NHBoc	12.5 ± 3.5 (2)	NT	2.3 (1)	34.6
58	N*i*-PrMe	NH_2	1.4 ± 0 (2)	NT	1.1 ± 0.8 (2)	28.1

[a] Compounds are racemic, one enantiomer is displayed for illustrative purposes.
[b] IC_{50} values (n) are displayed as mean ± SD (n = 2) and mean ± SEM (n > 2).
[c] CCR3 % inhibition are n = 1, unless otherwise noted. NT = not tested.

sent the likely bioactive conformations for these tri- and disubstituted antagonists.

In summary, we have described the synthesis and evaluation of novel, sulfone-containing di- and trisubstituted cyclohexanes as potent CCR2 antagonists. The lower molecular weight and increased potency of the trisubstituted antagonists made them more attractive, with compound **54** having the best profile. The superiority of the trisubstituted platform was rationalized, in part, to be the

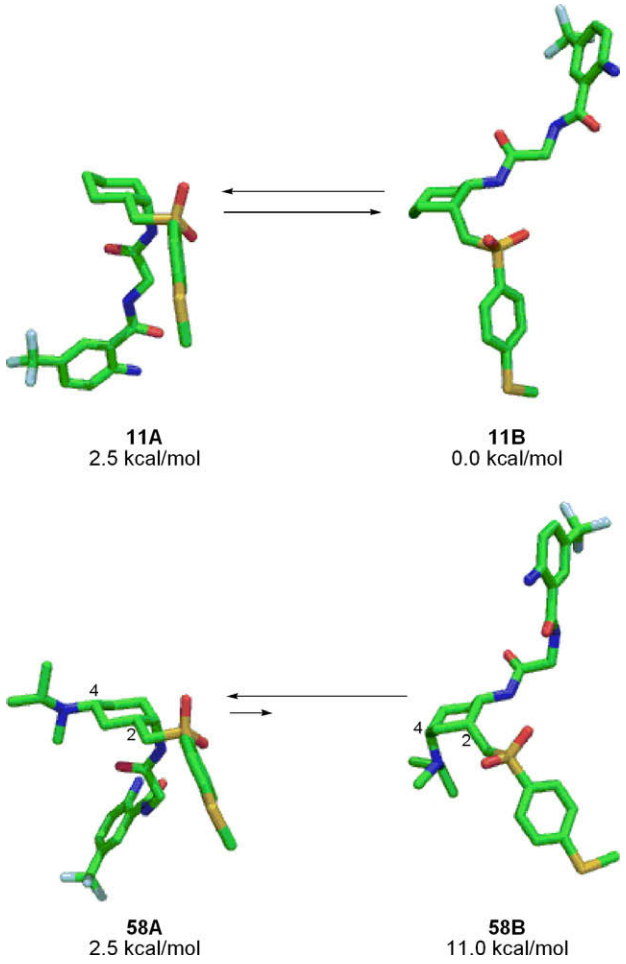


Figure 2. Energy-minimized[20] conformations of **11** and **58**.

result of a conformational rigidification inherent in the trisubstituted case. This provided structural information on the bioactive conformation of this chemotype, which should aid in the design of future CCR2 antagonists.

Acknowledgment

We also thank Dr. Joel C. Barrish for a critical review of the manuscript.

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