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From rigid cyclic templates to conformationally stabilized acyclic scaffolds. Part II: Acyclic replacements for the (3*S*)-3-benzylpiperidine in a series of potent CCR3 antagonists☆

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Abstract—Conformational analysis of the 3-benzylpiperidine in CCR3 antagonist clinical candidate **1** (BMS-639623) predicts that the benzylpiperidine may be replaced by acyclic, conformationally stabilized, *anti*-1,2-disubstituted phenethyl- and phenpropylamines. Ab initio calculations, enantioselective syntheses, and evaluation in CCR3 binding and chemotaxis assays of *anti*-1-methyl-2-hydroxyphenethyl- and phenpropylamine-containing CCR3 antagonists support this conformational correlation.

In our previous letter, we disclosed the discovery of clinical candidate BMS-639623 (**1**), a small molecule CCR3 receptor antagonist indicated for the treatment of asthma.[1] It is believed that antagonism of the CCR3 receptor on eosinophils should prevent their chemotaxis into the lungs where they cause bronchial mucosal damage by releasing major basic protein, membrane-derived lipid mediators, and a host of other proteins and toxic substances. This damage is thought to give rise to the clinical features of asthma—bronchial hyperresponsiveness and airway obstruction.[2]

Given our previous success[1] in predicting the stereochemistry of **1** from the conformational analysis of the cyclohexane ring of lead molecule **2** (Fig. 1), we wanted to see if we could extend that analysis to the 3-benzyl-substituted piperidine ring. We envisioned that by introducing R^1 and R^2 onto phenpropylamine **3** (Fig. 2), we could discover a conformationally rigid acyclic isostere for the

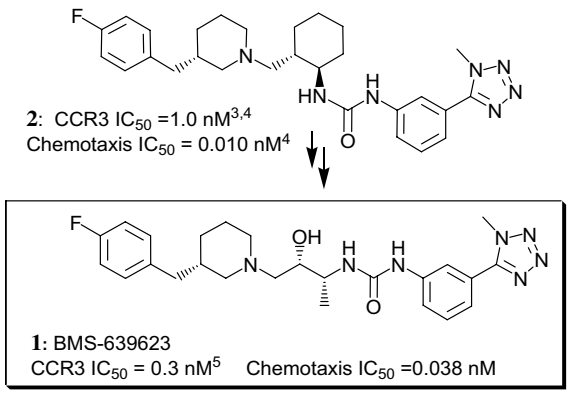

Figure 1. The discovery of **1** via conformational analysis of **2**.

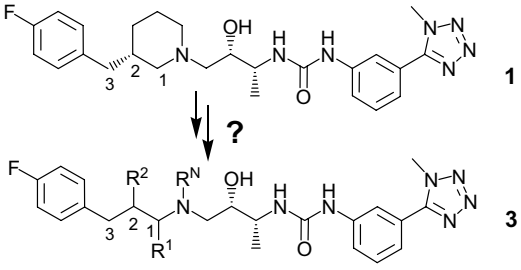

Figure 2. Can the R^1- and R^2-substituted phenpropylamine of **3** mimic the 3-benzylpiperidine of **1**?

Keywords: CCR3 antagonist; Eosinophil chemotaxis; Acyclic scaffold; Conformational analysis; Ab initio; Asthma; 3-Benzylpiperidine.

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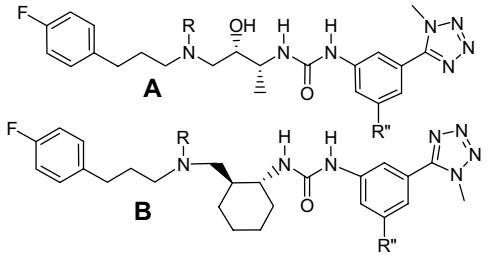
3-benzylpiperidine. Conformational analysis would dictate the stereochemistry of the R^1 and R^2 groups.

Before we introduce our R^1 and R^2 substituents onto a phenpropylamine, we first must investigate the SAR of the unsubstituted phenpropylamine itself (**3**: R^1, R^2 = H). We find in Table 1 that all of the compounds with only one tetrazole substituent on the phenylurea (R″ = H) exhibit weaker chemotaxis IC_{50} values (compounds **4a**–**8a**). However, in the presence of a 3,5-disubstituted phenylurea (in this case a [3-ethyl-5-(1-methyltetrazol-5-yl)phenyl]urea) we observe an increase in potency, as seen in other series of CCR3 antagonists.[1] In this 3,5-disubstituted phenylurea series, substituents on the basic nitrogen larger than R = methyl (**4b**), such as R = ethyl (**5b**) and R = cyclopropylmethyl (**8b**), yield compounds exhibiting single-digit picomolar chemotaxis IC_{50} values.

Substituents larger than a cyclopropylmethyl on the basic nitrogen are less potent. Substituents lowering the basicity on the nitrogen, such as CF_3CH_2, Ac, and $MeSO_2$, decrease binding potency. As described separately in greater detail, cyclic linker analogs were also investigated (see representative examples **16**–**18**).[6] These seem to be much more potent than their acyclic counterparts when we compare the chemotaxis potencies of **17** and **4a**. For all of the more potent compounds, we notice a disconnect between binding IC_{50} and chemotaxis IC_{50} potencies which has previously been observed in the acyclic[1] and cyclic linker[4] 3-benzylpiperidine series of CCR3 antagonists.

In Table 1, we see a dramatic increase in chemotaxis inhibition potency of about 3 orders of magnitude going from R = methyl to R = ethyl or cyclopropylmethyl (cf. **4a** and **5a**; **4b** and **5b**, **8b**). This large difference in potency is unlikely due to a simple increase in van der Waals interactions of ethyl versus methyl with the receptor site. Ab initio calculations on fragments **4aa** and **5aa** show that for R = Et, there is an increase in energy relative to R = Me of about 2 kcal/mol when bond angle ψ

Table 1. Binding and eosinophil chemotaxis inhibition activities of the unsubstituted phenpropylamines in both the 'acyclic linker' (A) and 'cyclic linker' series (B)



Compound	Structure A/B	R	R″	CCR3 IC_{50}[a] (nM)	Chemotaxis IC_{50}[b] (nM)
4a	A	Me	H	0.4	0% at 30 nM
5a	A	Et	H	0.2	34% at 0.3 nM
6a	A	Pr	H	0.2	43% at 3 nM
7a	A	*c*-Pr	H	0.4	—
8a	A	*c*-Pr–CH_2	H	0.4	44% at 3 nM
9a	A	*c*-Hex	H	2.5	—
10a	A	CF_3CH_2	H	59	—
11a	A	$AdCH_2$[c]	H	421	—
12	A	H	Et	0.3	55% at 30 nM 42% at 3 nM
4b	A	Me	Et	0.3	2.6
5b	A	Et	Et	0.4	0.004
6b	A	Pr	Et	0.5	62% at 0.3 nM 42% at 0.03 nM
7b	A	*c*-Pr	Et	0.6	—
8b	A	*c*-Pr–CH_2	Et	0.6	0.005
9b	A	*c*-Hex	Et	3.2	58% at 30 nM 0% at 3 nM
10b	A	CF_3CH_2	Et	9.0	—
11b	A	$AdCH_2$	Et	211	—
13	A	$PhCH_2$	Et	2.5	61% at 0.3 nM 9% at 0.03 nM
14	A	Ac	Et	6.0	—
15	A	SO_2Me	Et	21.6	—
16	B	H	H	3.7	—
17	B	Me	H	0.6 ± 0.3	0.6 ± 0.8
18	B	CF_3CH_2	H	60	—

[a] See Ref. 5 for CCR3/CCR2 chimera binding assay.
[b] See Ref. 4 for chemotaxis assay. Values without standard deviations represent a single determination.
[c] Ad = adamant-1-yl.

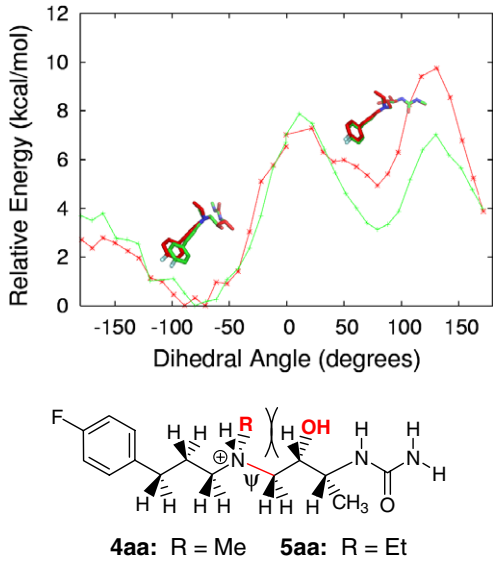


Figure 3. Dihedral drive of **4aa** (green) and **5aa** (red). Shown is the relevant diastereomer which was used in the ab initio calculations.

is rotated to eclipse R and OH (ψ = 130°, Fig. 3). Thus R = Et results in a more restricted bond angle ψ compared to R = Me. Apparently, this restricted bond angle permits better alignment of functional groups leading to increased chemotaxis inhibition potency. R = cyclopropylmethyl is similar enough to R = Et to share the same enhancement in potency. Other groups such as *n*-propyl, cyclohexyl, and benzyl are less potent, most likely due to increased rotational degrees of freedom and/or increased steric hindrance with the receptor site.

Having found that *N*-ethyl is optimal on phenpropylamine **3** where R^1 and R^2 = H, we are now ready to make conformationally rigid acyclic isosteres for the 3-benzylpiperidine of **1**. Conformational analysis of the 3-benzylpiperidine and its fragments will allow us to determine the stereochemistry of R^1 and R^2 in phenpropylamine **3** that is needed to impart conformational rigidity while simultaneously mimicking the binding conformation of the piperidine. The piperidine, like a cyclohexane, is a six-membered ring and therefore exists in a chair in its lowest energy conformation, which we assume is the binding conformation. Varnes et al. had earlier discovered via the synthesis of rigidized piperidine-containing CCR3 antagonists, that an equatorial benzyl group imparts more potency than an axial one.[7] Thus, we can draw a (3*S*)-3-benzylpiperidine in a chair conformation as shown in Figure 4 (**20a** or **20e**) with the benzyl in the equatorial position. Before we break up the piperidine ring and convert it into a disubstituted phenpropylamine, we must add a substituent at the 2-position which will eventually become R^1. The substituent R^1 may be substituted either axially (**20a**) or equatorially (**20e**). Taking **20e** and cutting out a methylene group at the piperidine 5-position yields an acyclic 1,2-disubstituted phenylpropylamine which can reside in three low energy conformers, **21**, **22**, and **23**. Conformer **21** is preferred since it has only 2 non-bond-

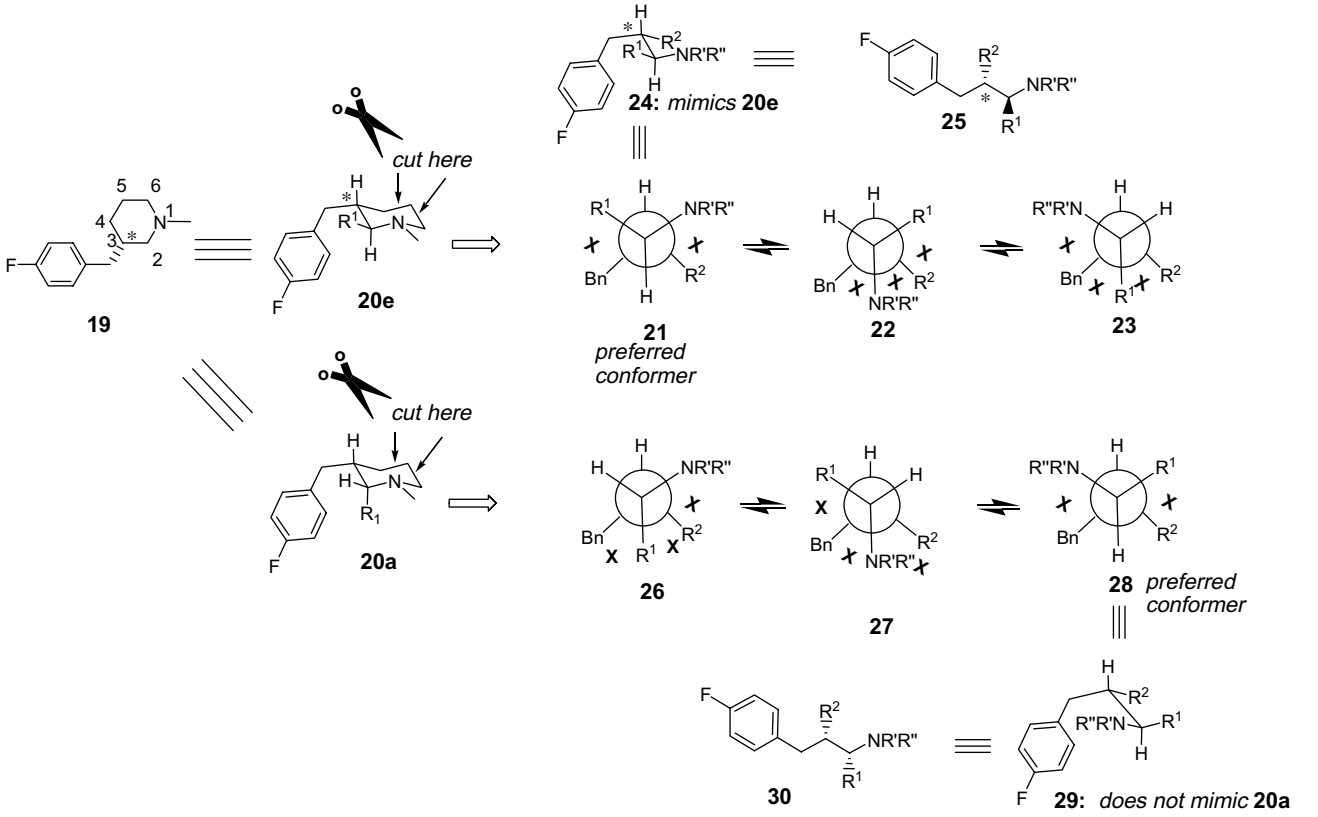


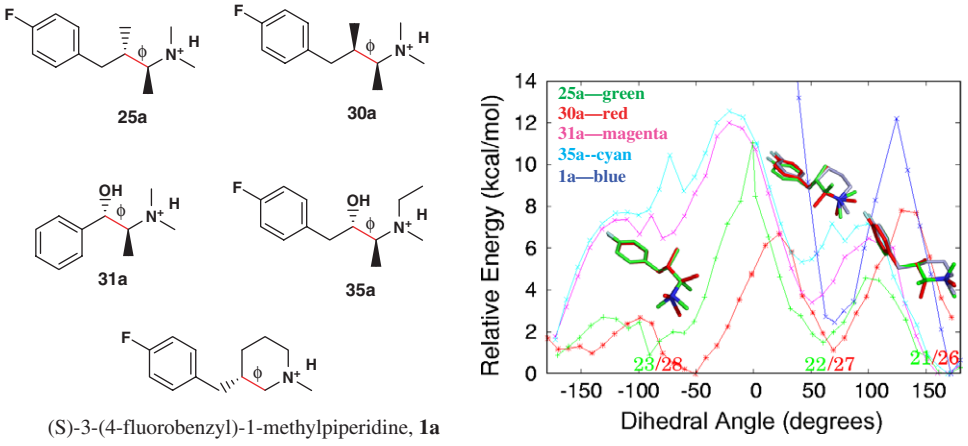
Figure 4. Conformational analysis of *S*-3-benzylpiperidine **19** leading to structures **25** and **30**. '**X**' denotes unfavorable gauche interactions. '*' denotes the position in the acyclic phenpropylamine which mimics the 3-position of 3*S*-3-benzylpiperidine **19**.

ing gauche interactions, while conformers **22** and **23** have three. Redrawing conformer **21** leads to structure **24** which clearly shows the identical relative stereochemistry as in benzylpiperidine **20e** between the benzyl and amine groups. Further redrawing **24** yields *anti*-1,2-disubstituted 3-phenylpropylamine **25** which theoretically should mimic the equatorial conformer of 3-benzylpiperidine. Since *S*-3-benzylpiperidine **19** has been shown[3] to be the more potent enantiomer, the enantiomer drawn for isostere **25** should be the more potent one also. On the other hand, if we substitute an axial R^1 group as in **20a**, the preferred conformer is **28**. When we redraw **28** as **29**, we clearly see that the relative orientation of the benzyl and amino groups is different from that found in 3-benzylpiperidine **20a**. Redrawing **29** as **30**, we obtain a *syn*-1,2-disubstituted 3-phenylpropylamine. Thus, only the *anti*- and not the *syn*-1,2-disubstituted-3-phenylpropylamine mimics the equatorial conformer of 3-benzylpiperidine.

The question now arises what should R^1 and R^2 be in our acyclic *S*-3-benzylpiperidine replacement **25**? In our previous letter[1] we showed that the cyclohexane group of **2** can be mimicked by a *syn*-1,2-disubstituted propyl chain as found in **1** where R^1 = Me and R^2 = OH. Can we also substitute R^1 = Me and R^2 = OH in structure **25**? The synthesis would be much simpler than when R^1, R^2 = Me. The 1-methyl-2-hydroxy substitution pattern is also shared by the well-known phenethylamine, pseudoephedrine. Although pseudoephedrine is not a phenpropylamine, we felt it was sufficiently close in structure to merit investigation as a 3-benzylpiperidine replacement, especially when all four diastereomers are commercially available to test our conformational analysis. It is also known that conformer **21** of pseudoephedrine (replace Bn with Ph) predominates for both the non-protonated and protonated forms in D_2O with intramolecular H-bonding not occurring.[8]

Ab initio calculations[7] confirm our conformational analysis (Fig. 5). For *anti*-diastereomer **25** when R^1 = R^2 = Me (fragment **25a**), the most preferred conformer is **21** and it is favored over **22** and **23** by about 1–1.5 kcal/mol. For *syn*-diastereomer **30** when R^1 = R^2 = Me (fragment **30a**), the most preferred conformer is **28** and it is favored over **26** and **27** by approximately the same amount. We will now see that in addition to being easier to synthesize, substitution of R^2 = OH instead of Me has a second benefit: the energy gap widens even further between the preferred and non-preferred conformers! Thus, for *anti*-diastereomer **25** when R^1 = Me, R^2 = OH (fragment **35a**), the most preferred conformer is again **21**, but it is now favored over **22** and **23** by about 5–7 kcal/mol. A similar energetic profile is seen with pseudoephedrine fragment **31a** where preferred conformer **21** is more favored over **22** and **23** by 3–6 kcal/mol. Thus, substitution of R^2 = OH seems to enhance the preference for conformer **21** in both the phenpropylamine and phenethylamine series. The reason for this is that when R^2 = OH in lowest energy conformer **21**, there is a stabilizing electrostatic interaction between the partially positive NH proton and the partially negative oxygen of the OH (a positive dipole–dipole interaction). In higher energy conformers **22** and **23**, there is a destabilizing steric interaction and repulsion between the OH and methyl groups (a negative dipole–dipole interaction) (see Supplemental information where ab initio calculation results are summarized for the positive and negative dipole–dipole interactions).

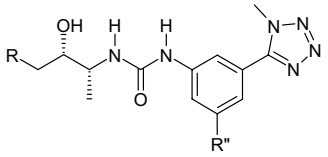
Using what we learned from Table 1, namely that the *N*-ethyl group together with a 3-ethyl-5-(1-methyltetrazol-5-yl)phenylurea is optimal for chemotaxis inhibition, we synthesized the 1-methyl-2-hydroxyphenpropylamine and pseudoephedrine/ephedrine analogs in Table 2. As predicted from the conformational analysis in Figure 4, incorporation of (1*S*,2*S*)-(+)-pseudoephedrine leads to **31H**, the most potent of all of the isomers possessing a (1-methyltetrazol-5-yl)phenylurea tail piece. It contains *anti*-stereochemistry, as does **25**, which we predicted to best mimic a 3-benzylpiperidine. We also expected the (1*S*,2*S*)-(+)-enantiomer of pseudoephedrine (**31H**) and not the (1*R*,2*R*)-(−)-enantiomer (**32H**) to lead to the more potent diastereomer since it embodies the same absolute stereochemistry as in **25**. Interestingly, *syn*-diastereomer **33H** is only 10-fold less potent

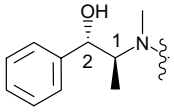
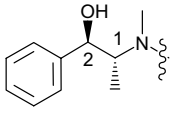
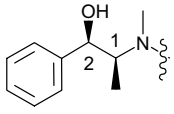
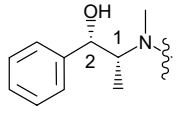
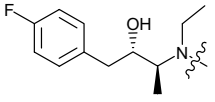
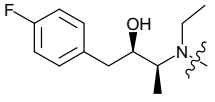
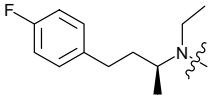
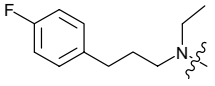
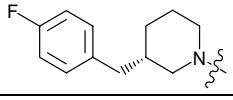


(S)-3-(4-fluorobenzyl)-1-methylpiperidine, **1a**

Figure 5. Energetic profiles obtained from ab initio calculations for fragments **25a** (green), **30a** (red), **31a** (magenta), **35a** (cyan), and (*S*)-3-(4-fluorobenzyl)-1-methylpiperidine **1a** (blue). Numbers **21/26**, **22/27**, **23/28** correspond to the conformers shown in Figure 3.

Table 2. Replacement of *S*-3-benzylpiperidine of **1** with 1-methyl-2-hydroxyphenethyl- and phenpropylamines, together with their corresponding CCR3 binding and eosinophil chemotaxis IC_{50} values



Compound	R	R″	CCR3 IC_{50}[a] (nM)	Chemotaxis[b] (nM)
31H	 (1S,2S)-(+)-pseudoephedrine	H	0.4	22, 67% at 30 nM
31Et		Et	0.5	78% at 0.03 nM
32H	 (1R,2R)-(-)-pseudoephedrine	H	577	—
33H	 (1R,2S)-(-)-ephedrine	H	5.7	—
34H	 (1S,2R)-(+)-ephedrine	H	238	—
35H		H	19	
35Et		Et	1.2	
36H		H	88	—
36Et		Et	3.4	
37H		H	2.5	—
37Et		Et	0.2	
5H		H	0.2	55% at 0.3 μM
5Et		Et	0.4	0.004
1H		H	0.3	0.04 ± 0.01
1Et		Et	1.8 ± 0.6	0.013

[a] See Ref. 5 for CCR3/CCR2 chimera binding assay.
[b] See Ref. 4 for chemotaxis assay. Values without standard deviations represent a single determination.

than *anti*-**31H**, and it is more potent than the *anti*-**32H**. In addition, *syn*-isomer **34H** contains the correct absolute chirality at C-2 as in **25**, but it is greater than 100-fold less potent than *syn*-**33H**, which does not. We may infer from this that the chirality about C-1 is a more important determinant for potency than is the chirality about C-2, the chiral center that is positionally equivalent to the chiral center of *S*-3-benzylpiperidine (see Fig. 4 and follow the asterisks). Once the chirality about C-1 is set, then additional increases in potency

arise from *anti*-substitution at C-2. Although sharing similar binding potencies, **31H** and **31Et** differ considerably in chemotaxis inhibition potency. Here again we see in **31Et** the increase in potency from 3,5-disubstitution on the phenyl urea where the chemotaxis IC_{50} is less than 30 pM, similar to that of 3-benzylpiperidine **1H**. It is not clear whether **31Et** is as potent as unsubstituted phenpropylamine **5Et** or the 3,5-disubstituted benzylpiperidine **1Et**,[9] but it is close. Thus the (1*S*,2*S*)-1-methyl-2-hydroxyphenethylamine moiety is an excellent isostere for the (3*S*)-3-benzylpiperidine.

We were a bit surprised at the nanomolar binding potency of *syn*-**33H**, expecting it to be much less potent. Seeking an explanation, we performed ab initio calculations on *syn*-fragment **33a** (Fig. 6) and found that both conformers **26** and **28** (replace Bn with Ph in Fig. 4) are actually of equal energy unlike what we had predicted. Thus **33H** not only exists in the inactive conformation **28**, but also in the active binding conformation **26**. One can rationalize the observed energetics as follows. Even though conformer **26** has 3 gauche interactions, only one of them involves the bulky phenyl and there is a positive dipole–dipole interaction between the partially positive NH proton and the partially negative oxygen of the OH group. In our previously predicted 'favored conformer' **28**, there is one gauche interaction with the phenyl and one repulsive dipole–dipole interaction between the R^1 = Me and the OH oxygen. In conformer **27**, there are two gauche interactions involving the phenyl and one repulsive methyl/oxygen interaction to make it the highest in energy.

Looking at the 1,2-disubstituted phenpropylamines in Table 2, we see that the *anti*-substituted **35H** and **35Et** are again more potent than their *syn*-counterparts **36H** and **36Et** as predicted by conformational analysis. However, compounds **35H**, **35Et**, **36H**, and **36Et** are all for the most part less potent than their phenethylamine pseudoephedrine/ephedrine counterparts. They are also less potent than their des-OH counterparts **37H** and **37Et**. Not only does a single OH group have a negative impact on binding, but so does a single methyl group (compare **37H** with **5H**)—although the '3,5-disubstitution effect' seems to make up the difference in compound **37Et**. Unfortunately, we do not have a chemotaxis IC_{50} value for **37Et** to prove or disprove that.[9] We would expect **37H** to be more potent than **5H** since conformational analysis predicts the correct rotamer **21a** to be populated roughly 50% of the time (Fig. 7), the other 50% being populated by rotamer **22a**. Monosubstituted propylamine **37H** is also less potent than pseudoephedrine **31H** although **37Et** and **31Et** have equal and potent binding affinities due to the '3,5-disubstitution effect'.

To explain the decreased binding potency of the substituted phenpropylamines we once again performed ab initio calculations shown in Figure 8. Unsubstituted propylamine fragment **5aaa**'s lowest energy conformers occur at $\theta = 60°$ (60–80°), 140°, and 180°. Pseudoephedrine fragment **31aaa** shares a low energy conformer with **5aaa** at 60°, thereby possibly making this low energy conformer the binding conformer. Monosubstituted and disubstituted phenpropylamine fragments **37aaa** and **35aaa**, respectively, do not share an energy minimum at this dihedral angle. This explains the near equivalence in potency of **31H** with **5H**, **31Et** with **5Et** and their greater potency than **35H**, **35Et**, **37H**, and possibly **37Et**.[9] At 60°, both **35aaa** and **37aaa** have a gauche interaction between the α-methyl group and the *N*-ethyl group which apparently is severe enough to disallow an energy minima to occur. On the other hand, **5aaa** at 60° has a gauche interaction between a small hydrogen and the *N*-ethyl group, while **31aaa** between the α-methyl group and the *N*-methyl group. These are apparently less severe than the *N*-ethyl interactions in **35aaa** and **37aaa** thus allowing for low energy minima to occur.

Another interaction favors the increased potency found for the pseudoephedrines **31H** and **31Et**. The $\theta = 180°$ conformer represents the 'fully extended' conformation where the longest chains are opposite one another in a Newman projection (not drawn). Both unsubstituted

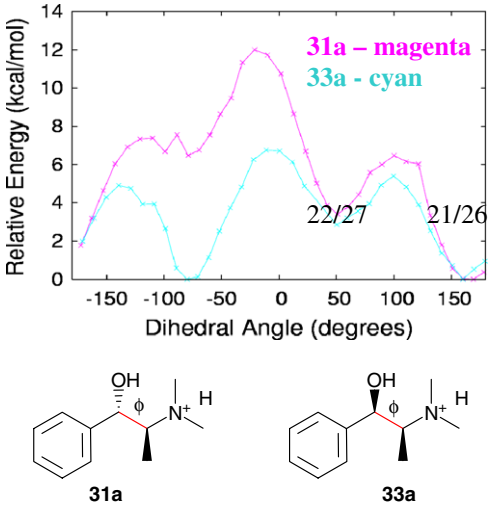


Figure 6. Energetic profile of compounds **31a** and **33a**. The inlaid numbers indicate the conformation depicted in the Newman projections from Figure 4.

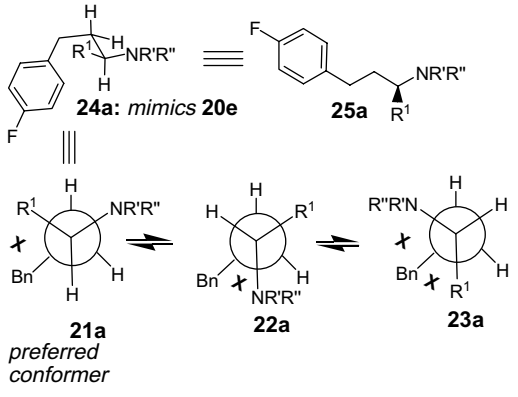


Figure 7. Conformational analysis of **25** when R^2 = H (**25a**). '**X**' denotes unfavorable gauche interactions. There is only one non-bonding gauche interaction in conformers **21a** and **22a**. There are two in conformer **23a**. Therefore both conformers **21a** and **22a** are favored nearly equally.

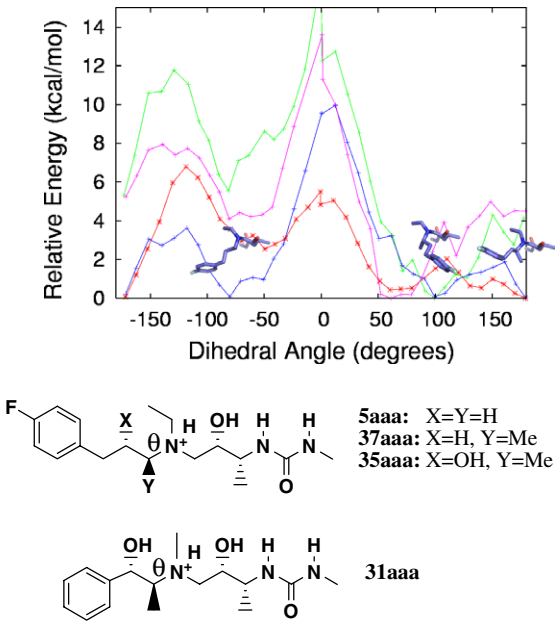


Figure 8. Dihedral drive of fragments **5aaa** (red), **37aaa** (blue), **35aaa** (green), and **31aaa** (magenta).

propylamine **5aaa** and monosubstituted phenpropylamine fragment **37aaa** display a low energy conformer in the 'fully extended' conformation when $\theta = 180°$. What happens to **31aaa** and **35aaa** at 180°? When $\theta = 180°$, the X = OH and the *N*-alkyl groups in this fully extended conformation become eclipsed resulting in higher energy (negative dipole–dipole interaction) similar to when the *N*-ethyl group eclipsed the other OH in the molecule (Fig. 3, $\psi = 130°$). Recall that the *N*-ethyl group enhanced potency in the unsubstituted phenpropylamines by favoring a restricted bond angle ψ. For **31aaa** and **35aaa**, a similar situation also occurs with bond angle θ. The *N*-alkyl—OH negative dipole–dipole interaction disfavors the bond angle $\theta = 180°$. Thus a restricted bond angle is induced, favoring a low energy conformer where $\theta = 60°$ for **31aaa** and $\theta = 100°$ for **35aaa**. Since unsubstituted propylamines **5H** and **5Et** also share the low energy conformer with $\theta = 60°$, compounds **31H** and **5H**, **31Et** and **5Et** are similar in binding potency and **31Et** and **5Et** are similar in chemotaxis inhibition potency. Unfortunately for **35H**, **35Et**, **37H**, and **37Et**, the *N*-ethyl gauche interaction with the α-methyl group disallows a low energy conformation at $\theta = 60°$ and thus **35H**, **35Et**, **37H**, and possibly **37Et**[9] are all less potent.

Incorporating what we have learned about angles ϕ, θ, and ψ, we performed ab initio calculations on the entire molecules of **31Et**, **5H**, and BMS-639623 (**2**) (Fig. 9). In Figure 9a, the α-methyl-β-hydroxypropylurea of **31Et** is in a conformation which mimics that of the cyclohexyl linker of **2** and which was calculated in our previous letter[1] (see also Fig. 9b). Angles ϕ, θ, and ψ are 161°, 80°, and −79°, respectively. These angles are all close to the ones found earlier when the calculations were done for discrete bond angles only: angle ϕ in conformer **21** (160° to 170°—the benzyl and amino groups are nearly opposite one another), angle θ (60–80°) in **31aaa** in Figure 8, and angle ψ (−75 to −90°) in **5aaa** in Figure 3. Ab initio calculations on the entire molecule of **31Et** also show an intramolecular H-bond that we did not anticipate: an H-bond between the two OH groups. *Thus, not only does the pseudoephedrine OH group stabilize conformer* **21** *more than a methyl group as discussed previously, but it also 'locks up' half of the molecule in a stable conformation via an intramolecular H-bond. Since the* α*-methyl group to the urea has been shown to control the conformation of the other half of the molecule,*[1] *one can say that* **31Et***'s entire scaffold is essentially rigid and favors the one conformation shown.*[10] Overlap of **31Et** with the minimized structure of BMS-639623 (**2**) in Figure 9b shows that the benzylpiperidine of **2** provides a scaffold in which θ is locked at an angle of 180°, yielding a fully extended 'phenylpropylamine' backbone which is different from that of **31Et**. Fortunately, pseudoephedrine's phenyl group in **31Et** resides in the same general area as the phenyl in the benzylpiperidine of **2** resulting in outstanding binding affinity and chemotaxis inhibition potency. When we overlap a minimized structure of **5H** as in Figure 9c, we see that the phenylpropylamine moiety can follow the same extended backbone conformation ($\theta = 180°$) as found in the benzylpiperidine of **2**. However, we can also make $\theta = 80°$ in **5H** and induce the phenpropylamine's carbon backbone to align itself with that of **31Et** (Fig. 9d) and this conformation also turns out to be an energy minimum. Thus for phenpropylamine **5H**, the phenpropylamine portion appears to have at least two different binding conformations: either that of pseudoephedrine **31H** or that of benzylpiperidine **2** thereby making it very potent, even though it is not as conformationally rigid as **2** or **31Et**. As mentioned earlier, since both **35H** and **37H** cannot have $\theta = 60$–80° or 180°, they are less potent.

Compounds in Tables 1 and 2 were synthesized by the methods shown in Scheme 1. Epoxide **41** was synthesized by the method of Beaulieu.[11] Subsequent epoxide opening with pseudoephedrine or a phenpropylamine **48** yields **42**. Hydrogenolysis of the benzyl groups followed by reaction with carbamate **44**[1] yields urea **45**. Compounds in Table 1, structure B were synthesized according to the method of De Lucca[4] using the appropriate phenpropylamine. Compounds in Table 2 were made by the methods disclosed in Scheme 2. Wittig reaction of BOC-L-alaninal[12] yields chiral styrene **53**. Asymmetric Sharpless dihyroxylation[13] with AD-mix-β yields glycol **54**. Absolute stereochemistry was assigned based on precedent with a similar substrate where the 1-CH_3 group in **53** is replaced by a 1-CH_2OH.[14] The chiral center at C-1 is reported not to play a role in determining the outcome of the asymmetric dihydroxylation.[14] Benzylic hydroxyl removal via hydrogenation, followed by deprotection, benzylation, reductive amination with acetaldehyde, and debenzylation yields, amine **57**. Reaction with epoxide **58**,[15] followed by deprotection and reaction with carbamate **44**,[1] yields ureas **35H** and **35Et**. Compounds **36H** and **36Et** may be synthesized by repeating the sequence using AD-mix-α.[13] Monomethyl-substituted compounds **37H** and **37Et** may be synthesized by hydrogenating styrene **53** and completing

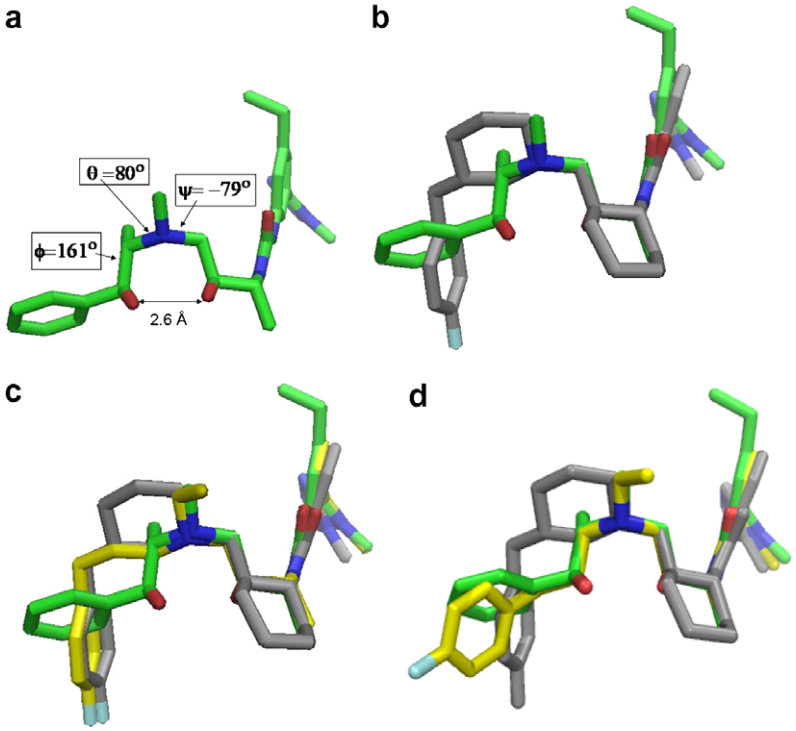
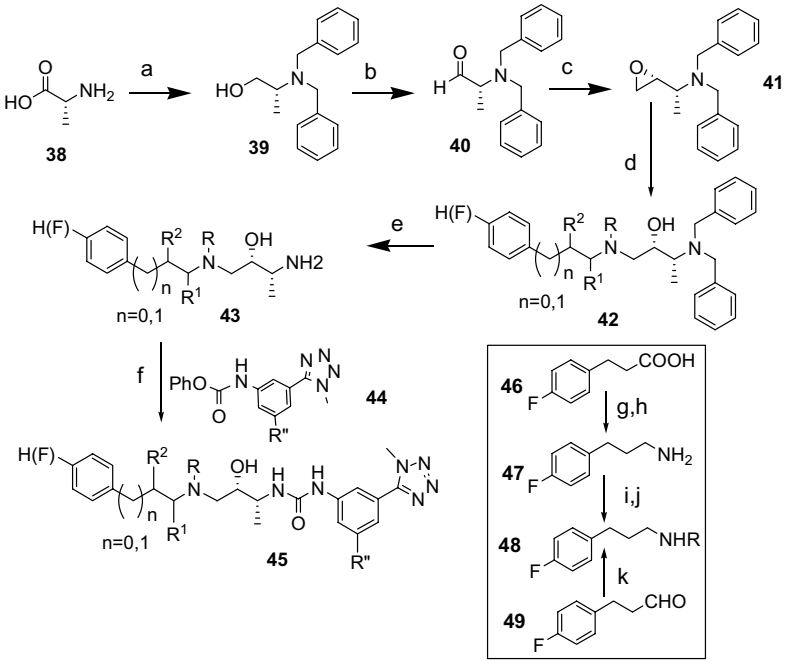


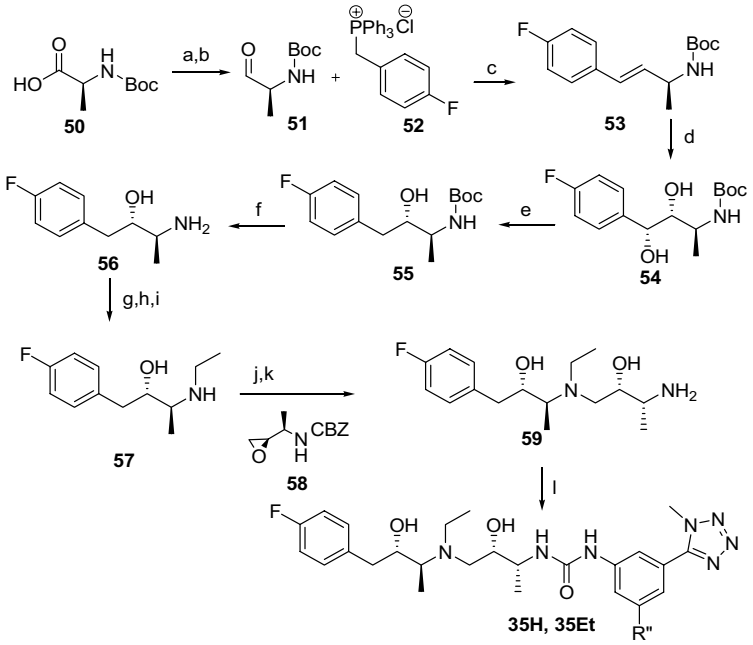
Figure 9. Ab initio minimized structures of (a) **31E**t (green); (b) **31Et** and **2** (gray); (c) **31Et**, **2**, and **5H** (yellow) where **5H** is in the fully extended conformation ($\theta = 180°$); (d) **31Et**, **2**, and **5H** where in **5H**, $\theta = 80°$.



Scheme 1. Reagents and conditions: (a) i—BnBr, K_2CO_3, EtOH, rt; ii—LAH, reflux, 24 h, 72%; (b) DMSO, Py–SO_3, 10–15 °C, 2 h, 96% crude; (c) CH_2Br_2, THF, *n*-BuLi, −55 °C, 95%, 6:1 mixture of diastereomers; (d) pseudoephedrine or **48**, EtOH, reflux, 20 h; (e) $Pd(OH)_2$, H_2, MeOH, HOAc; (f) **44** (R″ = H, Et), acetonitrile, 25 °C; (g) i—$SOCl_2$, $CHCl_3$; ii—NH_4OH; (h) LAH, THF 67% for two steps; (i) R′COCl, TEA, CH_2Cl_2; (j) LAH, THF; (k) RNH_2, STAB, CH_2Cl_2.

the reaction sequence in Scheme 2 omitting steps d and e.

In summation, we have found that unsubstituted phenpropylamines can effectively mimic a (*S*)-3-benzylpiperidine. In this unsubstituted phenpropylamine series, we found that substitution of groups on the basic nitrogen larger than methyl, such as ethyl, cyclopropyl, and cyclopropylmethyl, leads to molecules with chemotaxis IC_{50} values in the single-digit picomolar range.



Scheme 2. Reagents and conditions: (a) EtOCOCl, Hunig's base, EtSH, CH_2Cl_2; (b) Et_3SiH, 10% Pd–C, acetone; (c) KHMDS, THF/toluene, 18% for three steps; (d) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH/H_2O, quant; (e) $Pd(OH)_2$, H_2, MeOH, 62%; (f) HCl/dioxane, 94%; (g) PhCHO, STAB, $ClCH_2CH_2Cl$, AcOH, 67%; (h) CH_3CHO, STAB, $ClCH_2CH_2Cl$, AcOH, quant; (i) H_2, $Pd(OH)_2$, MeOH, quant; (j) **58**, EtOH, reflux, 43%; (k) H_2, $Pd(OH)_2$, MeOH, quant; (l) **44** (R″ = H, Et), CH_3CN, 32%.

Through the use of conformational analysis of the 3-benzylpiperidine moiety of CCR3 antagonist **1**, together with ab initio calculations, we were able to predict that the *anti*-1,2-disubstituted phenethyl- and phenpropylamine isosteres should be more potent than their *syn*-counterparts. We could quickly test and validate our conformational analysis through the incorporation of the four commercially available pseudoephedrine diastereomers. It was found that (1*S*,2*S*)-(+)-pseudoephedrine is an excellent acyclic mimic of cyclic (*S*)-3-benzylpiperidine. The pseudoephedrine portion of **31Et** binds in a slightly different conformation than does the benzylpiperidine of **2**. However, pseudoephedrine's phenyl and benzylpiperidine's phenyl end up occupying the same space which most likely accounts for **31Et**'s outstanding binding and chemotaxis inhibition potencies. The presence of an intramolecular H-bond between the two OH groups in **31Et** essentially 'locks up' half of the molecule into a single conformation. Since the rest of the molecule has been previously shown to be rigid,[1] the entire scaffold of **31Et** is therefore rigid. We also found that *anti*-disubstituted phenpropylamines were more potent than *syn* but that both were less potent than the pseudoephedrine and unsubstituted phenpropylamines. We were able to explain the greater potency of the latter compounds using ab initio calculations.

In this letter and in our previous letter,[1] we have performed conformational analyses on both the cyclohexyl and the benzylpiperidine of lead **2**. This permitted us to discover potent CCR3 receptor antagonists such as **31Et** containing a totally acyclic but conformationally rigid scaffold as shown in Figure 10. *The opposite strategy is usually the norm in medicinal chemistry: acyclic scaffolds are rigidized into more potent cyclic ones*. We hope that

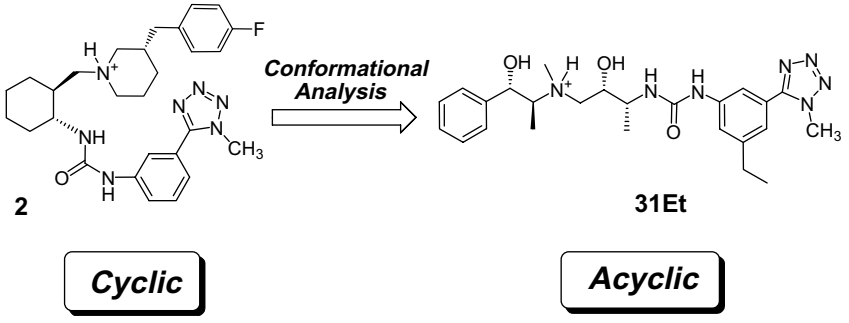


Figure 10. Via conformational analysis of the cyclohexane and benzylpiperidine moieties of lead molecule **2**, we eventually were able to design potent CCR3 antagonist **31Et**.

our two exercises in conformational analysis will inspire medicinal chemists to design conformationally stable acyclic alternatives to their heterocyclic and carbocyclic drug targets.[16]

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.11.087.

References and notes

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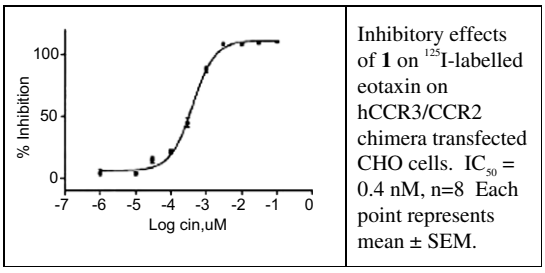
5. The binding assay was carried out using ^{125}I-labeled eotaxin and CHO cells stably transfected with a gene encoding a chimeric receptor, consisting of the intracellular domain of human CCR2 with the extracellular and transmembrane domains of human CCR3. This variation was found to give results nearly identical to those obtained using the native CCR3 receptor as shown below:



Inhibitory effects of **1** on ^{125}I-labelled eotaxin on hCCR3/CCR2 chimera transfected CHO cells. IC_{50} = 0.4 nM, n=8 Each point represents mean ± SEM.

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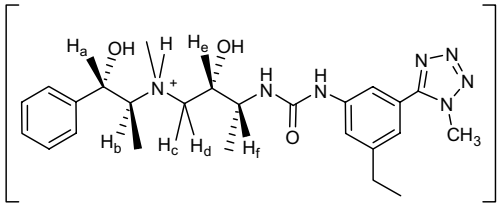
9. It was at this point when the CCR3 discovery research program was concluded. Thus there are no chemotaxis inhibition data.
10. An interpretable ^{1}H NMR spectrum of the TFA salt of **31Et** could only be obtained in CD_3OD. Other NMR solvents yielded spectra with broadened peaks. It can be envisaged, that H-bonding by CD_3OD could prevent the optimal conformer (Fig. 9a) from occurring. Surprisingly, the pseudoephedrine portion of **31Et** yielded coupling constants that matched those that were calculated from the conformation shown in Figure 9a (see Table below). However, observed coupling constants for H_e–H_f differed from those calculated. ^{1}H NMR spectra and selective ^{1}H–^{1}H decoupled NMR spectra were obtained at both 500 and 700 MHz. In addition, ^{1}H–^{1}H and ^{1}H–^{13}C 2D NMR spectra were obtained at 500 MHz.



H_x-H_y	Calculated J_{x-y}, (Hz)	Measured J_{x-y}, (Hz)
H_a-H_b	9.6	10
H_c-H_e	3.2	2.5
H_d-H_e	11.0	10
H_e-H_f	10.7	5

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