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4,4-Disubstituted cyclohexylamine based CCR5 chemokine receptor antagonists as *anti*-HIV-1 agents

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ABSTRACT

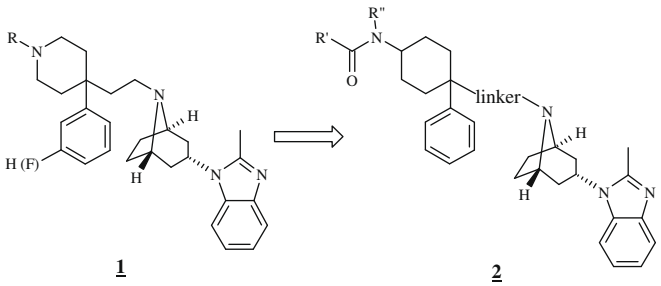
A series of 4,4-disubstituted cyclohexylamine based CCR5 antagonists has been designed and synthesized. Their antiviral structure–activity relationship has been extensively explored.

HIV/AIDS continues to be a threat to public health care. While current anti-HIV therapies have dramatically increased life expectancy of AIDS patients, issues arising from these treatments, such as the emergence of drug resistant HIV-1 strains and long-term treatment side effects, have brought significant challenges to current treatment and patient satisfaction. A need for new therapies with novel mechanism of action has become increasingly urgent. The discovery of chemokine receptor 5 (CCR5) as a co-receptor for HIV-1 infection opened a new avenue to anti-HIV treatment and prevention.[1] CCR5 antagonists as viral entry inhibitors have recently emerged as an important class of anti-HIV medicines.[2]

Several series of 4,4-disubstituted piperidine based CCR5 antagonists have previously reported from our laboratories, which demonstrated potent anti-HIV-1 activity (Fig. 1).[3] To explore the scope of the central ring system and diversify current scaffolds, we replaced the piperdine ring, leading to the discovery of a series of 4,4-disubstituted cyclohexylamine based CCR5 antagonists. Herein, we report the syntheses and structure–activity relationship of this novel series of the compounds.

Syntheses of 4,4-disubstituted cyclohexylamine analogues with C2-linker started with commercially available 4-oxo-1-phenylcyclohexanecarbonitrile and benzylamine by a non-stereoselectively reductive amination. The resulting secondary amine **3** was either *cis*- or *trans*- to the cyano group at the quaternary centre. Subsequent protection of this newly generated amine with Cbz made the *cis*- and *trans*-isomers **4** easily separable.[4] Next, identical synthetic sequences were carried out on both *cis* and *trans* isomers. Thus, Dibal-H reduction of the cyano group led to aldehyde **5**, serving as a precursor for Wittig olefination. The resulting *Z*/*E* enol ether mixture **6** was then treated with 90% formic acid at ambient temperature to afford the homologated aldehyde **7**. Subsequent reductive amination of aldehyde **7** with 1-(8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole **8** arrived at the stage to free the doubly protected amine in **9**. Finally, the unmasked amine **10** was coupled with carboxylic acids under HATU conditions to afford C2-linker analogues (**11a–j,** Tables 1 and 2) (Scheme 1).

To determine the optimum length of the linker between the cyclohexyl and the tropane rings, *cis*-C3, C1 and C0-linker analogues were synthesized. For C3-linker, *cis*-aldehyde **5** was coupled



1 2

Fig. 1. 4,4-Disubstituted piperidine (**1**) and cyclohexylamine (**2**) based CCR5 antagonists.

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Table 1
Inhibitory potency of C2-linker *cis*/*trans* analogues**11a–f** and maraviroc in the HOS cell assay (Scheme 1)

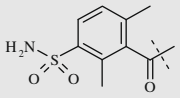
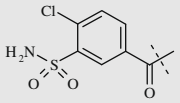
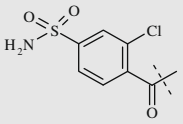
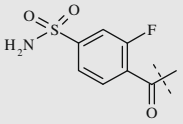
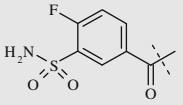
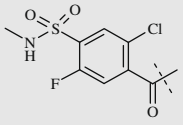
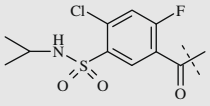
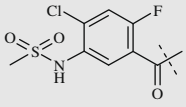
Compds	R	*cis*/*trans*	HOS IC_{50} (μM)
11a		*trans*	2.550
11b		*cis*	1.070
11c		*trans*	1.630
11d		*cis*	0.058
	maraviroc		0.002

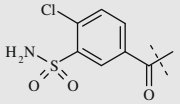
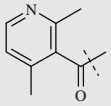
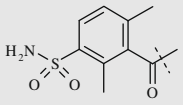
Table 2
Inhibitory potency of C2-linker *cis* analogues**11** *cis*- in the HOS cell assay (Scheme 1)

Compds	R	HOS IC_{50} (μM)
11e		0.23
11f		1.80
11g		0.48
11h		0.51
11i		0.59
11j		1.48

with methyl [bis(ethyloxy)phosphoryl]acetate anion to yield α,β-unsaturated ester **12**. Hydrogenation, amine reprotection and Dibal-H reduction gave aldehyde **14**. Subsequent reductive amination of **14**, followed by deprotection and amide formation furnished syntheses of *cis*-C3-linker analogues (**15a–c**, Table 3) (Scheme 2).

Syntheses of both *cis*-C1 and *cis*-C0-linker analogues encountered significant challenges due to steric hindrance. Modifications of the designed targets were made to achieve their syntheses. Therefore, *des*-phenyl C1-linker analogues (**18a** and **18b**) were obtained in three steps from 1-(8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole **8** and Boc protected *cis*-4-amino cyclohexanecarbaldehyde **16** via similar sequences as shown in the scheme (Scheme 3).

Table 3
Inhibitory potency of *cis* C3-linker analogues**15a–c** and in the HOS cell assay (Scheme 2)

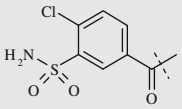
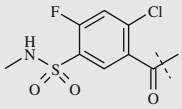
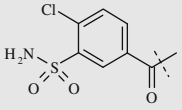
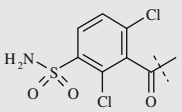
Compds	R	HOS IC_{50} (μM)
15a		0.38
15b		2.19
15c		2.45

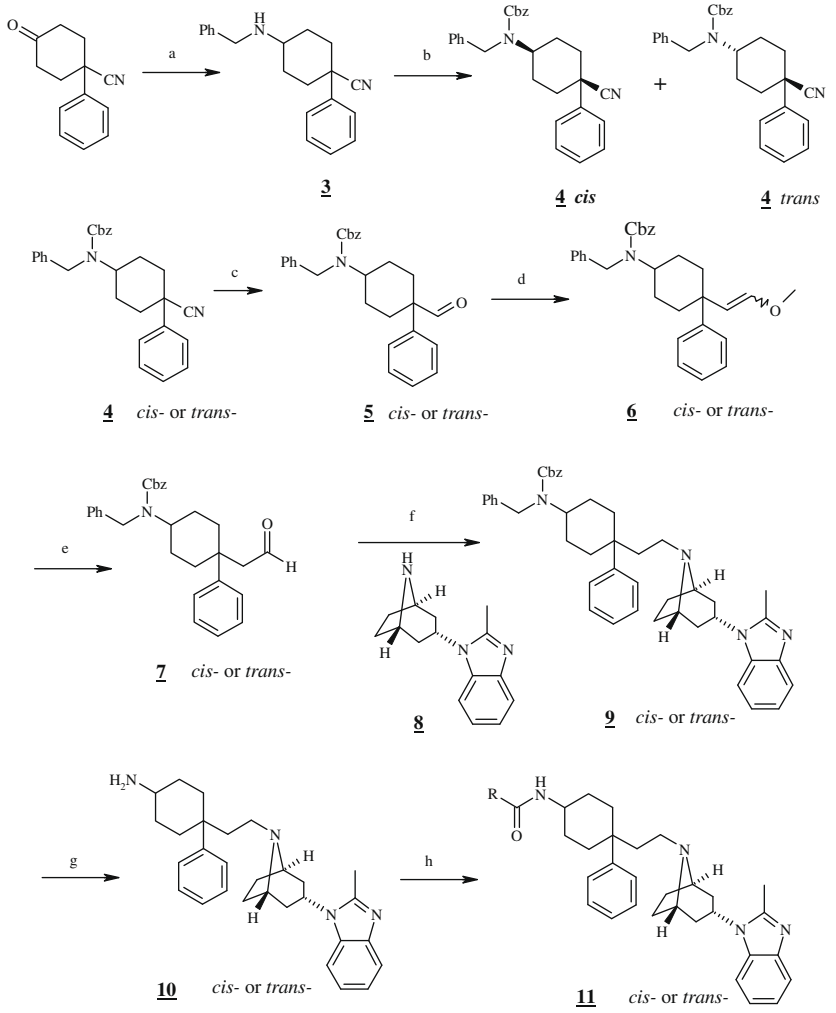
Me-C0-linker analogues were prepared differently. Boc protected 4-aminocyclohexaneone **19** condensed with 1-(8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole **8** in the presence of $Ti(OiPr)_4$. The in-situ generated imnium species reacted with Et_2AlCN to provide **20**. Subsequent treatment with methyl magnesium bromide afforded the separable *cis*-/*trans*- mixture **21**.[5] After deprotection of **21***cis*,[6] the free amine was coupled with acids to deliver the Me-C0-linker analogues (**23a** and **23b**, Table 4) (Scheme 4).

All synthesized compounds were tested for their antiviral activity in HOS cell against the Ba-L strain of HIV-1.[7] The data are presented in Tables 1–4.

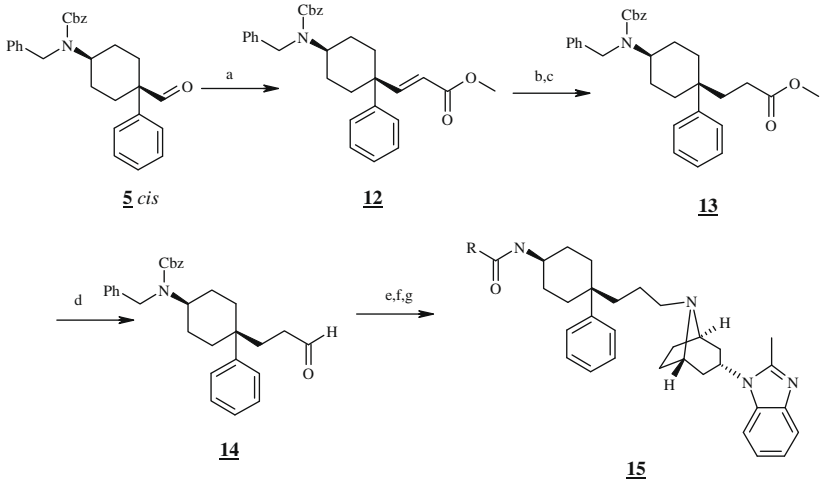
Two pairs of *cis*-/*trans*- C2-linker analogues (**11a** vs**11b** and **11c** vs **11d**) were first compared to address stereochemistry preference. As shown in Table 1, *cis*- isomers were more active than their *trans*- partners. Most notably, **11d** *cis* demonstrated a highly potent inhibition against HIV-1 virus infection in the HOS cell assay (IC_{50} = 58 nM) and improved antiviral activity substantially (~28-fold) over **11c** *trans*. In addition, significant SAR on phenyl substitution emerged as evidenced by comparison of potencies of **11d** and **11b**. With the aim to establish a more precise SAR and improve the potency, we synthesized a number of carboxylic acids and incorporated them into **10** *cis*- to yield **11e–j** *cis*-(Table 2). Interestingly, although these compounds exhibited moderate activities, Cl

Table 4
HOS IC_{50} of *cis*-C0, and C1-linker analogues (Schemes 3 and 4)

Compds	R	Linker	HOS IC_{50} (μM)
18a		C1	>20
18b		C1	>20
23a		C0	0.87
23b		C0	20.00

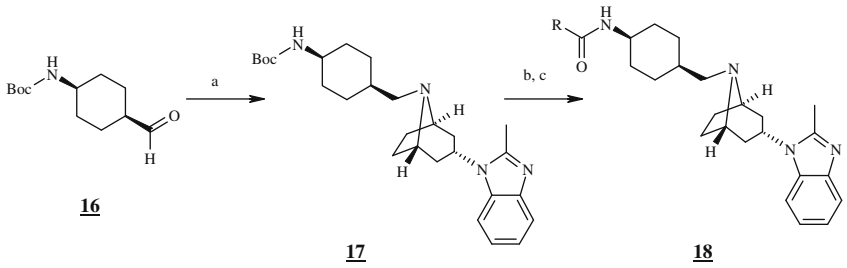


Scheme 1. Reagents and conditions: (a) $BnNH_2$, $NaBH(OAc)_3$, CH_2Cl_2, rt, overnight; (b) CbzCl, $NaHCO_3$ (aq), THF, rt, silica chromatography, 93% over two steps; (c) *i*-Bu_2AlH, CH_2Cl_2, −78 °C, 5 h; then 20% citric acid, 69%; (d) $Ph_3P^+CH_2OCH_3Cl^-$, NaHMDS, THF, −78 °C–0 °C, 6 h, 67%; (e) 90% formic acid, rt, 6 h, quant.; (f) **8**, $NaBH(OAc)_3$, CH_2Cl_2, rt, 4 h, 84%; (g) $Pd(OH)_2$, HCO_2NH_4, EtOH, reflux, 2 h, 63%; (h) RCOOH, HATU, *i*Pr_2EtN, rt, 2 h, 45–69%.

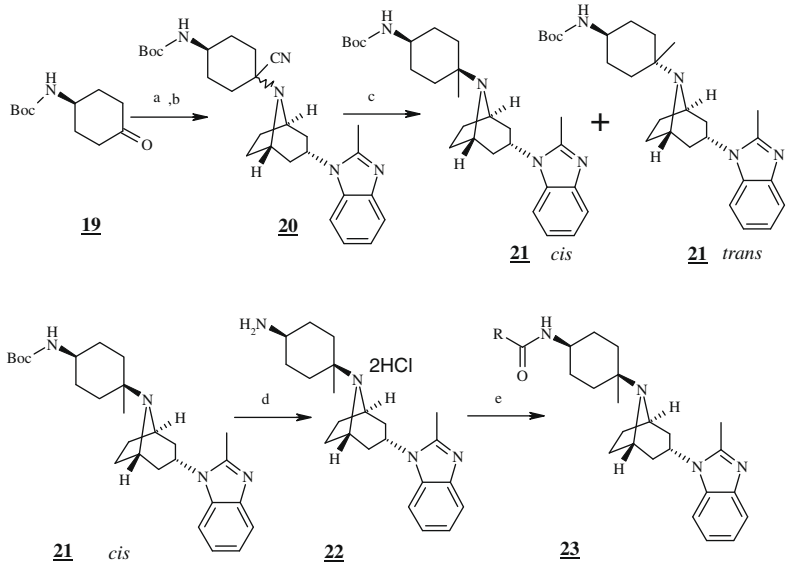


Scheme 2. Reagents and conditions: (a) $(EtO)_2P(O)CH_2COOCH_3$, NaH, THF, 0 °C, 4 h, 46%; (b) Pd/C, H_2, EtOH, 5 h; (c) CbzCl, $NaHCO_3$ (aq), THF, rt, 60% over two steps; (d) *i*Bu_2AlH, CH_2Cl_2 ,−78 °C, 5 h, quant.; (e) **8**, $NaBH(OAc)_3$, *i*Pr_2NEt, CH_2Cl_2, rt 3 h, 73%; (f) $Pd(OH)_2$, HCO_2NH_4, EtOH, reflux, 2 h, quant.; (g) RCOOH, HATU, *i*Pr_2EtN, CH_2Cl_2 , rt, 2 h, 60–83%.

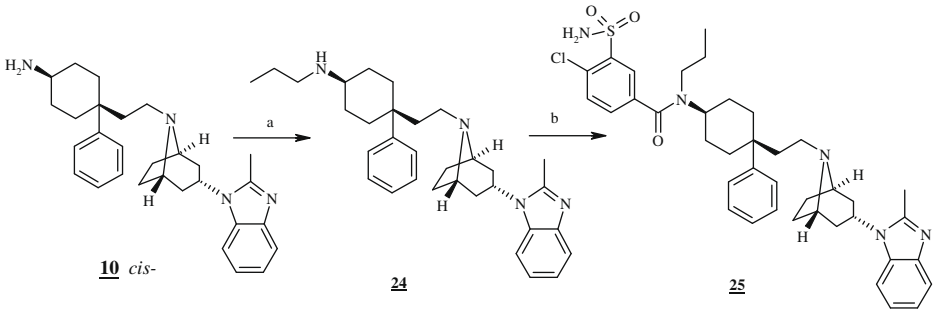
was a better substituent than F (**11e** vs **11f** and **11d** vs **11g**). *Meta*-sulfonamides (**11d** and **11g**) were more potent than the *para* (**11e** and **11f**). In addition, benzenesulfonamides (**11d–i** not **11f**) seemed to be more active than the methanesulfonamide **11j**. Final-



Scheme 3. Reagents and conditions: (a) **8**, $NaBH(OAc)_3$, CH_2Cl_2, rt, overnight, 52%; (b) HCl, CH_2Cl_2, quant.; (c) RCOOH, HATU, iPr$_2$EtN, rt, 2 h, 40–67%.



Scheme 4. Reagents and conditions: (a) **8**, Ti(OiPr)$_4$, CH_2ClCH_2Cl, 80 °C, 1 h, then rt, 18 h; (b) Et_2AlCN, THF, rt, 24 h; (c) MeMgBr, THF, rt, 5 h, *cis*- 24%, *trans*- 13% over three steps; (d) HCl, CH_2Cl_2, rt, quant.; (e) RCOOH, HATU, iPr$_2$EtN, CH_2Cl_2 rt, 2 h, 64–94%.



Scheme 5. Reagents and conditions: (a) propanal, $NaBH(OAc)_3$, CH_2Cl_2 72%; (b) 3-(aminosulfonyl)-4-chlorobenzoic acid, HATU, Et_3N, DMF, rt, 51%.

ly, the benzenesulfonamide acyl derivatives had relatively better activity than heteroaryl or aliphatic acyl derivatives (data not shown).

C2-linker series suggested *cis*-geometry was preferred. In the C3-linker series, only *cis* C3-linker analogues were synthesized. It turned out that with the C3 linkage, the potency of C3-linker compounds (**15a**–**c**) decreased 2 to 5 fold as compared to their *cis* C2-linker counterparts. (Table 3).

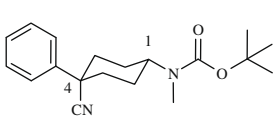
The *cis*-C0 and C1-linker analogues did not contain the phenyl group found in C2 and C3 analogues. Disappointingly, the *des*-phenyl C1-linker analogues (**18a** and **18b**) lost potency completely. However, the Me C0-linker analogue (**23a**) inhibited HIV-1 at sub-micromolar levels. This suggests that a quaternary carbon centre could be critical for locking the 'bioactive' conformation of the cyclohexyl ring. Additionally, bulky phenyl is preferred over methyl (**11d** vs **23a**) (Table 4).

Finally, amide N substitution was also examined. To this end, *cis*-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo-[3.2.1]oct-8-yl]ethyl}-4-phenylcyclohexanamine **10** was reductively alkylated and the resulting secondary amine **24** was acylated with 3-(aminosulfonyl)-4-chlorobenzoic acid to give **25** (HOS IC_{50} = 2.8 μM) (Scheme 5). Unfortunately, this modification appeared to result in a 48-fold loss in activity compared to **11d**.

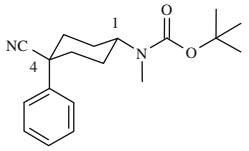
In summary, we have designed and synthesized novel cyclohexylamine based CCR5 antagonists. The structure–activity relationship suggested that *cis* is the preferred stereochemistry for the cyclohexyl ring, and C2 may be the optimal linker. Examination of many acyl moieties revealed that benzenesulfonamide is preferred and that halogen substitution on the benzene ring could further modulate potency. This work led to identification of the potent *cis* **11d** (HOS IC_{50} = 58 nM) and establishment of antiviral SAR of the cyclohexylamine series. Further optimisation will be published in due course.

References and notes

1. Dragic, T.; Litwin, V.; Allaway, P. G.; Martin, R. S.; Huang, Y.; Nagashima, A. K.; Cayanan, C.; Maddaon, J. P.; Koup, A. R.; Morroe, P. J., et al *Nature* **1996**, *381*, 667.
2. (a) Kazmierski, W. M.; Gudmundsson, K. S.; Piscitelli, S. C. *Annu. Rep. Med. Chem.* **2007**, *42*, 301; (b) Wood, A.; Armour, D. *Prog. Med. Chem.* **2005**, *43*, 239.
3. (a) Kazmierski, W. M.; Aquino, C.; Chauder, B.; Deanda, F.; Ferris, R.; Jones-Hertog, D.; Kenakin, T.; Koble, C.; Watson, C.; Wheelan, P.; Yang, H.; Youngman, M. *J. Med. Chem.* **2008**, *51*, 6538; (b) Duan, M.; Aquino, C.; Ferris, R.; Kazmierski, M. W.; Kenakin, T.; Koble, C.; Wheelan, P.; Watson, C.; Youngman, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1610.
4. The relative stereochemistry of **4** *cis*/*trans* was postulated based on **26a** and **26b** synthesized as in Scheme 1 to afford simple NMR molecules. ROESY experiments suggested cyclohexyl ring in both isomers adopted a chair conformation, and the carbamate group occupied an equatorial position. In *cis* isomer **26a**, the correlation between the *ortho*-protons on 4-phenyl and C-3/5 protons in the cyclohexyl ring (both axial and equatorial) was found. In addition, C-1 proton was a singlet, indicating its axial position (data acquired at 60 °C). In *trans* isomer **26b**, a ROESY correlation from the *ortho*-protons on 4-phenyl and C-2/6 axial protons was supportive of the phenyl being in an axial conformation. Furthermore, *N*-methyl from the carbamate had a correlation to C-2/6 axial protons. This assignment was consistent with the literature for analogous stereochemistry assignment. (Elliott, J.M.; *etc*, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1755–1758)



26a



26b

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5. Thoma, G.; Nuninger, F.; Schaefer, M. C.; Akyel, K. G.; Albert, R.; Beerli, C.; Bruns, C.; Francotte, E.; Luyten, M.; MacKenzie, D.; Oberer, L.; Streiff, M. B.; Wagner, T.; Walter, H.; Weckbecker, G.; Zerwes, H.-G. *J. Med. Chem.* **2004**, *47*, 1939.
6. The *cis* stereochemistry in **21** was determined by the similar NMR experiments conducted in the note 4.
7. Jenkinson, S.; McCoy, D.; Kener, S.; Ferris, R.; Lawrence, W.; Fox, T.; Smith, C. *Recept. Channels* **2003**, *9*, 117.