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Evaluation of a 3-amino-8-azabicyclo[3.2.1]octane replacement in the CCR5 antagonist maraviroc

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ABSTRACT

The bicyclic 5-amino-3-azabicyclo[3.3.0]octanes were shown to be effective replacements for the 3-amino-8-azabicyclo[3.2.1]octane found in the CCR5 antagonist maraviroc.

In addition to its role as a chemokine receptor on inflammatory leukocytes, CCR5 is also the primary co-receptor for macrophage-tropic HIV-1. Since its discovery, CCR5 has proven to be an extraordinary target for the pharmaceutical industry, with demonstrated therapeutic applications in HIV-treatment, as well as potential applications in various chronic or acute inflammatory diseases. Over the last 10 years or so, many CCR5 antagonists chemotypes have been explored.[1] These efforts led to the discovery, optimization, and clinical development of several compounds. For example, maraviroc (Selzentry®) was the first CCR5 antagonist approved for the treatment of HIV-1 infection. Maraviroc contains the four pharmacophore elements found in most series of CCR5 antagonists: a tertiary amine, two hydrophobic groups in the western portion of the molecule (henceforth referred to as the tail), and one head heteroaryl group in the eastern portion of the molecule (the head). In maraviroc, the basic amine is part of the rigid 8-azabicyclo[3.2.1]octane bicyclic system. In our efforts to identify a new series of CCR5 antagonists, we were, in part, interested in finding a replacement of this system. Synthetically, maraviroc's triazole ring was derived from a free amine group at position 3, so, we focused our search on systems that would have a free amine group appropriately positioned. We identified the exo-6-amino-3-azabicyclo[3.1.0]hexane (**template 1**) and the 5-amino-3-azabicyclo[3.3.0]octane (**template 2**) as possible replacements for the 3-amino-8-azabicyclo[3.2.1]octane (Fig. 1).

Conformational analysis showed that the 4-substituted 3-[1,2,4]triazole system derived from 3-aminotropane and the equivalent triazole system derived from **template 1** did not overlap well (Fig. 2). Indeed, its lowest energy conformation presented the triazole ring almost in the same plane as that of the pyrrolidine ring while in the tropane series, the triazole ring was almost perpendicular to the piperidine ring. Sampling of higher energy conformations identified conformations in which the triazole ring and the pyrrolidine ring were close to the adequate perpendicular orientation. However, they were at least 5.6 kcal higher in energy than the lowest energy parallel conformation, an energy barrier that was assumed to be too high to overcome.

The 4-substituted endo- or exo-5-[1,2,4]triazole systems derived from **template 2** showed decent overlap with the equivalent triazole derived from 3-aminotropane (Fig. 2), with the triazole rings almost perpendicular to the pyrrolidine ring. Since one of the key interactions between CCR5 and an antagonist involves a salt bridge between the tertiary amine of the antagonist and a glutamic acid in the CCR5 binding site, we wanted to evaluate the possibility of a difference in pK_a between the basic amine of the tropane ring and that of **template 2** that would affect the binding energy. The calculated pK_a values[4] of the tertiary amine of the 4-substituted dimethyl-1,2,4-triazole derived from 3-aminotropane and that derived from

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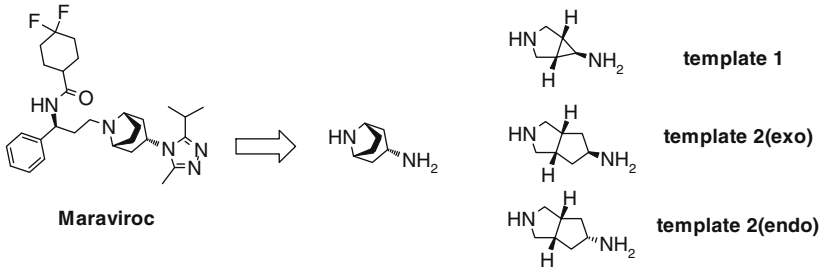


Figure 1. The 3-amino-8-azabicyclo[3.2.1]octane core in maraviroc and its potential replacements, **template 1** and **template 2**.

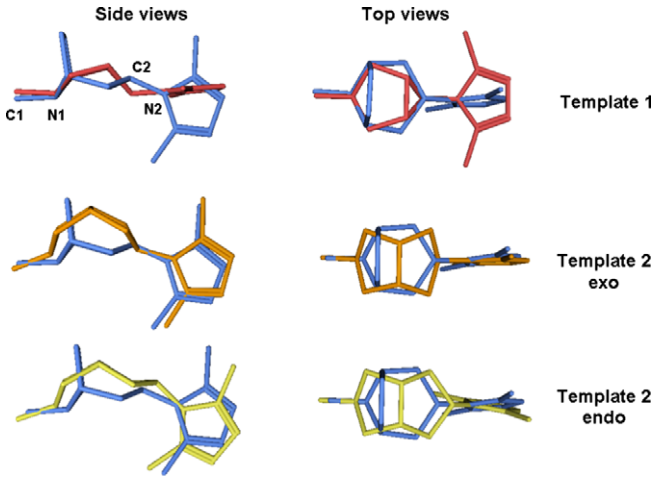
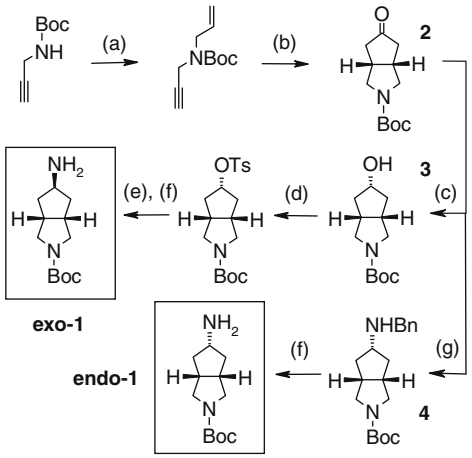


Figure 2. Overlaps (overlaps were performed in MOE[2] using C1, N1, C2 and N2 as anchoring points and were not manually modified) of the lowest energy conformations (conformations generated in MAESTRO[3] (OPLS-2005 force field, $CHCl_3$ as solvent and distance-dependent dielectric constant of 2 to mimic the hydrophobic nature of the CCR5 binding site) and processed using MOE) of the 4-substituted 3,5-dimethyl-[1,2,4]triazole derived from the 3-aminotropane system (blue), the *N*-methyl exo **template 1** (red), the *N*-methyl exo **template 2** (orange) and the *N*-methyl endo **template 2** (yellow).



Scheme 1. Reagents and conditions: (a) allyl bromide, NaH, DMF, 0 °C to rt, overnight (73%); (b) $Co_2(CO)_8$, H_2O, DME, reflux, 4 h (74%); (c) $NaBH_4$, MeOH, 0 °C, 1 h (>95%); (d) TsCl, DMAP, pyridine, CH_2Cl_2, reflux, 36 h (52%); (e) NaN_3, DMF, 50 °C (78%); H_2 (1 atm), $Pd(OH)_2$, MeOH, rt, overnight (>95%); (f) H_2 (1 atm), $Pd(OH)_2$, MeOH, rt, overnight (>95%); (g) $BnNH_2$, $NaBH(OAc)_3$, CH_2Cl_2, RT (43% after recrystallization with isopropylacetate/heptane 60/40).

the *N*-methyl **template 2** were virtually the same (9.47 ± 0.48, 9.42 ± 0.48, respectively). So, we anticipated that the only difference between the two ring systems would be structural and conformational. From our conformational analysis, it seemed that the major differences between the two systems were in the distances between the basic nitrogen and the triazole system, and the orientation of both exocyclic exit vectors. However, we hypothesized that the entropic character of the linker propyl chain could ultimately compensate for the differences in conformational overlap, by allowing an adjustment of the three-dimensional positions and relative orientations of the pharmacophores in the somewhat flexible CCR5 receptor binding site.

Conformational analysis alone was not enough to determine which of the two **template 2** amines (exo or endo) would be the best replacement for the 3-amino-8-azabicyclo[3.2.1]octane, therefore, compounds in both sub-series were prepared.

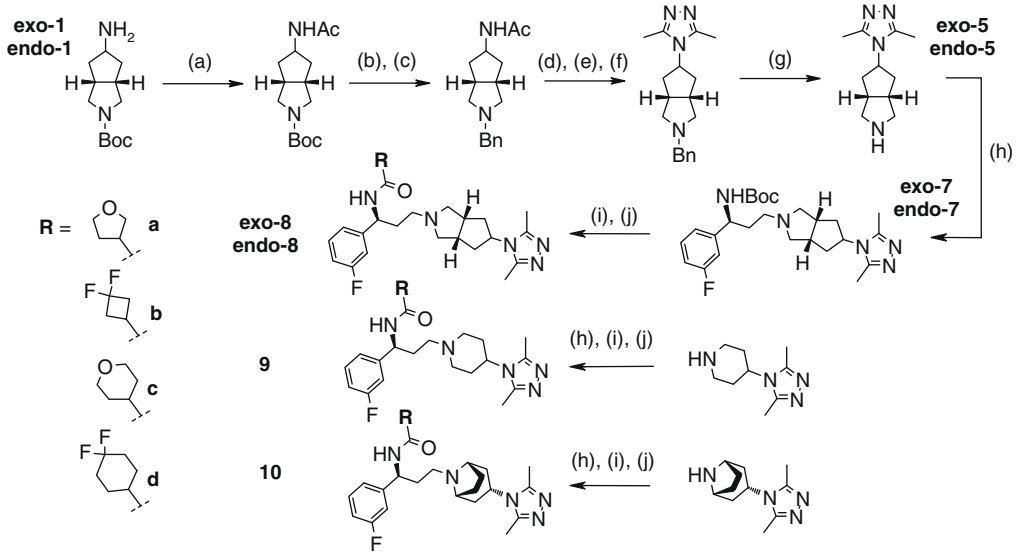
Amines exo-**1** and endo-**1** were prepared (Scheme 1) from a common intermediate, ketone **2**, which itself was synthesized through a reductive Pauson–Khand cyclization[5] of *N*-boc-*N*-allylpropargylamine. Reduction of ketone **2** with sodium borohydride gave selectively the endo alcohol **3**. Conversion of the alcohol to the tosylate, displacement of the tosylate with sodium azide and subsequent hydrogenolysis of the azide gave amine exo-**1**. It is noteworthy to point out that the tosylation required more drastic conditions than usual and gave the tosylate only in 52% yield indicating a substantial steric hindrance of the endo alcohol **3**. After noticing the selectivity of the ketone reduction we formed the amine endo-**1** by reacting ketone **2** with benzylamine under reductive N-alkylation conditions to give *N*-benzylamine **4** as a 90/10 mixture of endo/exo isomers. The pure endo *N*-benzylamine was obtained after two recrystallizations. The *N*-benzyl group was then hydrogenolyzed to give endo-**1**.

Triazoles exo-**5** and endo-**5** were prepared in six steps (Scheme 2). The exo-**1** and endo-**1** amines were acylated, the pyrrolidine nitrogen protecting group was exchanged from a boc group to an *N*-benzyl group, the acetamides were treated with phosphorous pentachloride to give the chloroimidate adducts, which reacted with acetic hydrazide to give the corresponding acylhydrazidoimidate intermediates. These were cyclized under acidic conditions to give the 4-substituted 1,2,4-triazoles. Finally, the *N*-benzyl groups were hydrogenolyzed to give exo-**5** and endo-**5**.

The pyrrolidine was treated under reductive conditions with *N*-boc-(*S*)-3-amino-3-(3-fluoro-phenyl)-propionaldehyde **6** prepared according to literature procedures[6] to give exo-**7** and endo-**7**. The boc group was hydrolyzed and the amine was acylated with tetrahydrofuran-3-carboxylic acid, 4-tetrahydropyrancarboxylic acid, 3,3-difluorocyclobutanecarboxylic acid or 4,4-difluoro-cyclohexanecarboxylic acid to give exo-**8**(**a**–**d**), and endo-**8**(**a**–**d**).

For comparative purposes, we prepared the piperidine compounds **9a,d**, and the tropane compounds **10**(**a**–**d**), following the same sequence.

Compounds were tested in two assays, first as inhibitors of RANTES binding, one of the natural chemokine ligands of CCR5, then as inhibitors of HIV-1 entry (Table 1).[7]



Scheme 2. Reagents and conditions (yields in parentheses are first for the endo- and then for the exo-bicyclic systems): (a) Ac_2O, pyridine, CH_2Cl_2, rt, 3 h (51%, 38%); (b) HCl 4 M in dioxane, CH_2Cl_2, rt, 2 h; (c) PhCHO, $NaBH(OAc)_3$, CH_2Cl_2, rt, overnight (56%, 75% over two steps); (d) PCl_5, CH_2Cl_2, 0 °C, 2 h; (e) $AcNHNH_2$, THF/CH_2Cl_2, 0 °C to rt, overnight; (f) AcOH catalytic, $ClCH_2CH_2Cl$, reflux, 2 h (67%, 50% over three steps); (g) H_2 (1 atm), $Pd(OH)_2$, MeOH, rt, overnight; (h) **6**, $NaBH(OAc)_3$, CH_2Cl_2, rt, 2 h (53%, 54% over two steps); (i) HCl 4 M in dioxane, CH_2Cl_2, rt, 2 h; (j) **R**COOH, EDCI, HOBt, DIPEA (or Et_3N), CH_2Cl_2 (20–85% over two steps).

Table 1
RANTES binding inhibition, and antiviral activity of exo-**8**(**a**–**d**), endo-**8**(**a**–**d**), **9a**,**d**, and **10**(**a**–**d**)

Compounds	Binding[a,c] (nM)	Antiviral[b,c] (nM)
Maraviroc	1.4	2.8
Exo-**8a**	35	40
Exo-**8b**	6	200
Exo-**8c**	43	⩾625
Exo-**8d**	—	81
Endo-**8a**	18	210
Endo-**8b**	6	74
Endo-**8c**	30	⩾625
Endo-**8d**	8	41
9a	—	⩾625
9d	38	⩾625
10a	7	62
10b	5	24
10c	13	220
10d	5	5

[a] Binding inhibition (IC_{50}) of [^{128}I]-RANTES to CCR5-expressing CHO cells.
[b] Replication inhibition (IC_{50}) of R5 HIV_{NLBal} in JC53-BL cells.
[c] Values are means of at least two experiments.

It is noteworthy to point out the discrepancy between the RANTES binding inhibition and the activity in the antiviral assay. This indicated to us that binding inhibition was not necessarily correlated with functional inhibition. We hypothesized that upon binding, the antagonist induces a change of conformation in the receptor, which in turn prevents the binding of HIV_{NLBal} to CCR5. Mechanistically, it is still not clear to us why one antagonist would induce a conformational change leading to a better antiviral activity than another antagonist. The RANTES binding inhibition assay was thus used as the first line assay, while we only compared compounds with each other based on their functional antiviral activity.

The piperidine compounds **9a** and **9d** were devoid of any measurable antiviral activity (upper limit of the assay = 625 nM) while the direct maraviroc-like equivalents showed reasonable antiviral activity for **10a** (62 nM) and single digit nanomolar activity for **10d** (5 nM). Interestingly, exo/endo-**8a** and exo/endo-**8d** were still active in the antiviral assay. We attributed some of the activity to the increased rigidity of **template 2** compared to the piperidine ring. This was the first indication that, as we had anticipitated from modeling, **template 2** might be an effective replacement of the conformationally restricted 8-azabicyclo[3.2.1]octane found in maraviroc. It is known from the SAR that led to the discovery of maraviroc[8] and that of our own discovery program,[9] that as far as antiviral activity was concerned, hydrophobic groups in the tail were better tolerated than more polar ones (e.g., **10b** and **10d** compared to **10a** and **10c**), that a larger hydrophobic group was better tolerated than smaller ones (**10d** compared to **10b**), and that the tetrahydrofuran ring was better tolerated than the tetrahydropyran ring (**10a** compared to **10c**). We observed similar properties in the case of the compounds using **template 2** (i.e., exo/endo-**8a** compared to exo/endo-**8c**, and exo/endo-**8b** compared to exo/endo-**8d**). However, compounds with hydrophobic groups in the exo sub-series were surprisingly less potent than the compounds with polar groups. This indicated to us that the series had a slightly different binding mode than that maraviroc, and that more SAR exploration would be required to further optimize both the endo and the exo sub-series. However, no other compounds were prepared in this new series of CCR5 antagonists.

Based on functional activity, we showed that the bicyclic exo and endo 5-amino-3-azabicyclo[3.3.0]octanes were effective, but not equal, replacements for the conformationally restricted 3-amino-8-azabicyclo[3.2.1]octane of the CCR5 antagonist maraviroc. The introduction of this template into other series of CCR5 antagonists will be described in due course.

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