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# Anti-HIV-1 entry optimization of novel imidazopiperidine-tropane CCR5 antagonists

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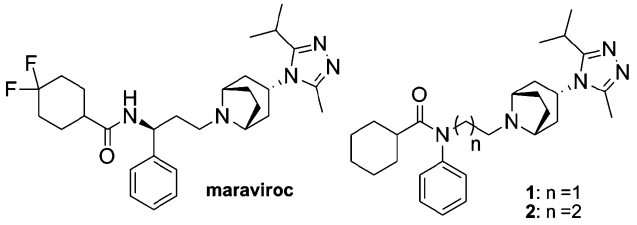
**Abstract**—A novel series of imidazopiperidine-tropane CCR5 antagonists is described. The series was optimized for anti-HIV-1 potency using a set of phenotypic viral entry assays. This strategy resulted in the identification of several very potent ($IC_{50}$ < 10 nM) inhibitors of HIV-1 entry. One compound (**40**) was further profiled and was found to have attractive selectivity, pharmacokinetic, and antiviral properties.


The chemokine receptor CCR5 has proven to be an exciting target for the pharmaceutical industry in the HIV-1 and inflammation therapeutic areas. CCR5 plays an integral role in the R5-tropic HIV-1 entry process by serving as a critical co-receptor for the viral envelope protein gp120.[1,2] Homozygous individuals with a 32-base pair deletion in the gene encoding CCR5 do not express the functional receptor and are ultimately resistant to R5-tropic HIV-1 infection.[3] These facts have inspired a great amount of research over the past decade to identify anti-HIV-1 therapeutics targeting the CCR5-mediated entry mechanism.[4–8] These efforts have resulted recently in the FDA approval of the first small molecule CCR5 antagonist, maraviroc (Selzentry®),[9,10] for the treatment of HIV-1 infection. Despite this considerable milestone, there is still much interest in the development of second generation CCR5 antagonists with improved properties.

Our chemistry program began with the observation that a wide variety of templates sharing a basic pharmacophore were reported to bind to CCR5 and to possess antiviral properties.[5,6,11] We designed chemical scaffolds that combined the attractive features of reported templates, including maraviroc, with the goal of identifying novel compounds that could be optimized to have superior properties to compounds reported to be in clinical development. Using this approach, compound **1** was identified via a Mip1-β competition binding assay as a modest starting point ($IC_{50}$ = 0.97 μM) for further optimization.[12]




Elongating the *N*-ethyl spacer of **1** by one carbon resulted in **2**, which is a threefold more potent inhibitor of chemokine binding ($IC_{50}$ = 0.31 μM). Modification of the cyclohexylamide moiety of **2** to a urea proved to be quite beneficial, resulting in a 10-fold increase in potency (compound **3** in Table 1). At this stage a series of urea derivatives was made to assess the optimal hydrophobic group at this position (Table 1). Replacement of the cyclohexyl ring with a smaller ring (**4**) or alkyl chain (**5**, **6**) resulted in a slight loss of potency. A phenyl replacement (**7**) was found to be equipotent to **3**; however, replacement with a benzyl group (**8**)

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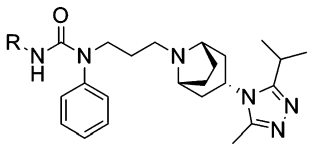
**Table 1.** $IC_{50}$ values for compounds **3**–**19** in a Mip1-β binding assay



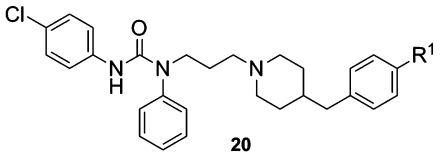
| Compound | R | $IC_{50}$[a] (μM) |
|---|---|---|
| **3** | Cyclohexyl | 0.031 |
| **4** | Cyclopentyl | 0.078 |
| **5** | *n*-Propyl | 0.271 |
| **6** | *i*-Propyl | 0.096 |
| **7** | Phenyl | 0.020 |
| **8** | Benzyl | 0.323 |
| **9** | 2-Me-phenyl | 0.271 |
| **10** | 3-Me-phenyl | 0.029 |
| **11** | 4-Me-phenyl | 0.004 |
| **12** | 2-OMe-phenyl | 0.381 |
| **13** | 3-OMe-phenyl | 0.053 |
| **14** | 4-OMe-phenyl | 0.027 |
| **15** | 2-Cl-phenyl | 0.100 |
| **16** | 3-Cl-phenyl | 0.015 |
| **17** | 4-Cl-phenyl | 0.004 |
| **18** | 2,6-Cl-phenyl | 0.539 |
| **19** | 2,3-Cl-phenyl | 0.048 |

[a] Values are means of two experiments.

resulted in a 10-fold reduction in potency. *Mono*-substitution at the para position of the phenyl ring in **7** is clearly favored as evidenced by compounds **11**, **14**, and **17** ($IC_{50}$ values of 4, 27, and 4 nM, respectively). It is interesting to note that others have reported the importance of a *para*-substituted phenyl urea group for CCR5 binding (example **20**),[13] thus suggesting a strong pharmacophore overlap with our series. This observation suggested that the triazole moiety most likely interacts with a similar region of the receptor as the benzyl group of **20**.

Given the potency of **11** in the chemokine binding assay, this compound was tested in a luciferase-reporter phenotypic viral entry assay to assess its antiviral properties.[14] The compound was evaluated using a panel of viral stocks pseudotyped with envelop sequences derived from five different viral isolates representing a diversity of viral subtypes. Maraviroc was also tested as a control compound. The results of these studies are shown in Table 2.

Despite the potent effects of **11** in the CCR5 binding experiments, this compound was determined to be 5- to 10-fold less potent than our target profile for viral entry inhibition. Chemokine binding assays are often used for optimizing the potency of a chemical series in terms of receptor antagonism. However, chemokine inhibition often does not correlate well with viral entry inhibition. Many potent inhibitors of chemokine binding have been identified that have modest to no antiviral activity (data not shown). This fact highlights the subtle differences in the allosteric modes of inhibition for chemokine binding versus gp120 binding. Most CCR5 antagonists are believed to bind in the transmembrane region of the GPCR resulting in conformational changes in the extracellular loops of the receptor.[5] These conformational changes may differentially affect the binding of the various chemokines and gp120 to the receptor. Given the disconnect often observed between chemokine and viral entry inhibition, we chose to utilize viral entry assays for optimization of antiviral potency.



**20**

The SAR reported around **20** suggested that a polar substituent at $R^1$ (such as $SO_2Me$) greatly enhances the antiviral properties of this series.[13] Given the potential overlap of the benzyl group of **20** with the triazole moiety of our series we decided to modify the triazole group to incorporate a polar side chain that could potentially occupy the same space as that found in the case of $R^1$ in **20**. The initial results of this effort are shown in Table 3.

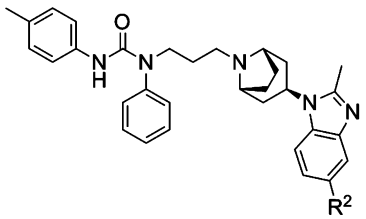
A benzimidazole scaffold was first utilized in an attempt to replace the triazole ring. It was hypothesized that this system would closely mimic the *para*-substituted benzyl group of **20**. A previous report in the literature on a related chemical series suggested that replacement of the 3-isopropyl-5-methyltriazole system with 2-methylbenzimidazole maintains antiviral potency.[15] The endo geometry of the tropane-benzimidazole was suggested to be preferred since the sterics of this system force the tropane ring into a boat conformation, thus positioning the imidazole ring in a similar orientation

**Table 2.** Viral entry inhibition, $IC_{50}$[a] (μM)

| Compound | Virus | | | | |
|---|---|---|---|---|---|
| | JRCSF | ASM80 | Ba-L | 97-ZA-003 | RU570 |
| **11** | 0.118 | 0.058 | 0.048 | 0.029 | 0.028 |
| Maraviroc | 0.005 | 0.006 | 0.004 | 0.008 | 0.002 |

[a] Values are means of two experiments.

**Table 3.** Viral entry inhibition, $IC_{50}$[a] (μM)



**21**: $R^2 = H$
**22**: $R^2 = SO_2Me$

| Compound | Virus | | | | |
|---|---|---|---|---|---|
| | JRCSF | ASM80 | Ba-L | 97-ZA-003 | RU570 |
| **21** | 0.019 | 0.022 | 0.050 | 0.015 | 0.018 |
| **22** | >10,000 | >10,000 | >10,000 | >10,000 | >10,000 |

[a] Values are means of two experiments.