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Oximino-Piperidino-Piperidine-Based CCR5 Antagonists. Part 2: Synthesis, SAR and Biological Evaluation of Symmetrical Heteroaryl Carboxamides

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Abstract—The synthesis, SAR and biological evaluation of symmetrical amide analogues of our clinical candidate SCH 351125 are described. A series of potent and orally bioavailable CCR5 antagonists containing symmetrical 2,6-dimethyl isonicotinamides and 2, 6-dimethyl pyrimidines amides were generated with enhanced affinity for the CCR5 receptor.

The process of HIV-1 entry into target cells is an attractive target for antiviral intervention. One stage in the HIV-1 entry process that is a particularly plausible site for pharmacological intervention is the CD4-dependent interaction between the HIV-1 glycoprotein-120 complex and the CCR5 chemokine receptor, which serves as a viral coreceptor.[1,2] The CCR5 receptor is a member of the seven transmembrane G-protein coupled receptor family, and its natural ligands are the chemokines RANTES, MIP-1α and MIP-1β.[3] Individuals who are homozygous for a 32-base pair deletion in the gene encoding CCR5, are immunologically normal, and are strongly protected against HIV-1 infection. Furthermore, heterozygous individuals, who possess only one intact CCR5, allele advance more slowly to AIDS, relative to patients having no deletion.[4,5] These observations strongly suggested that inhibiting CCR5 receptor with a small molecule antagonist would provide protection against HIV-1 infection.

Over the past 2 years numerous publications from our labs as well as others have appeared describing the anti-HIV activity of small molecule CCR5 antagonists.[6] Recent reports from our laboratories have shown that the small molecule CCR5 antagonist SCH 351125 (**1**) (Sch-C) is a novel and effective agent for the treatment or prevention of HIV infection.[7] In the preceding paper, we described the physico-chemical properties and biological evaluation of the rotamers of compound **1**. Although the presence of two restricted bond rotations present in **1** has no impact on antiviral activity, it creates significant challenges for development. Therefore, in order to prepare compounds with a reduced number of rotamers, we envisioned replacing the unsymmetrical nicotinamide *N*-oxide with a symmetrical isonicotinamide *N*-oxide. In this paper, we will describe the design, synthesis and structure activity studies of various symmetrical amide analogues of **1**.[8]

We began our studies with the synthesis of 2,6-dimethyl isonicotinic acid, and the corresponding *N*-oxide. Starting with commercially available 3,5-lutidine, *N*-aminopyridinium iodide **2** was prepared by treatment with NH_2OSOK and HI (Scheme 1).[9a] Acylation with acetic anhydride followed by treatment with amberlite resin and NaOH yielded **3**. Alkylation of **3** with MeI followed by treatment with KCN provided the 4-cyanopyridine **5**.[9b] Hydrolysis of the nitrile with concentrated HCl gave carboxylic acid **6**, which was allowed to undergo *N*-oxidation (H_2O_2 and AcOH) to afford product **7**.

The synthesis of the 2,6-dichloro and the 2,6-dibromo isonicotinic acid-*N*-oxides (Scheme 2) started with the 3,5-dihalo pyridines, which were converted to the carboxylic acids **8** by treatment with LDA followed by

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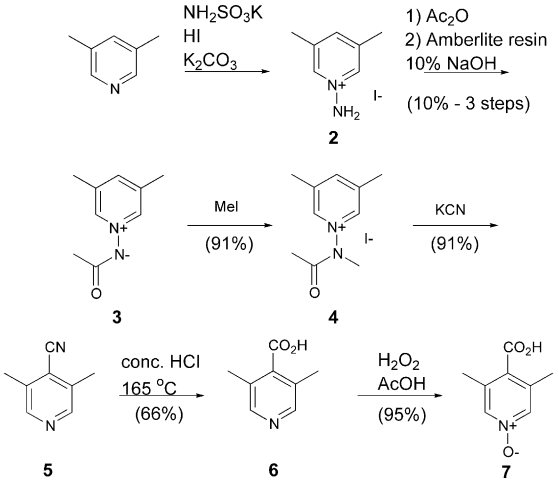
solid CO_2.[10] The nicotinic acids **8** were then oxidized to the *N*-oxides **9** by treatment with *m*-CPBA.

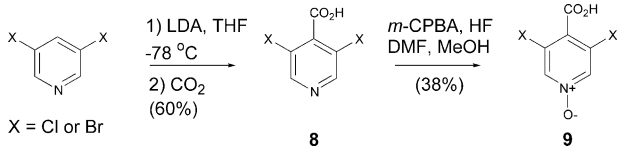
The carboxylic acids **7** and **9** were then coupled under standard conditions with the piperidino-piperidine core **10**, synthesized using the method described previously,[7b] to afford the targets **11a**–**11f** (Scheme 3).

Analogues **11a**, **11c** and **11e** as shown in Table 1 are very potent CCR5 antagonists, with IC_{50} values less than or equal to 1 nM. The oral plasma levels observed in rats were 2–10-fold lower for the nicotinamides than for the corresponding *N*-oxides, which is expected from our previous studies showing that the nicotinamides are readily oxidized to the *N*-oxides in vivo.[7b] The symmetrical *N*-oxides (**11b**, **11d** and **11f**) also provided potent CCR5 antagonists which are comparable to our lead antagonist **1**. After oral administration to rats, the pyridine *N*-oxides achieved plasma levels higher than those for the corresponding pyridines, but still lower than those for **1**.

Next, we investigated symmetrically substituted pyrimidines as replacements for the nicotinamide-*N*-oxide in **1**. The synthesis of the substituted pyrimidines is outlined in Scheme 4. The diketone **12** was converted to the enol ether **13** by generation of the cesium salt followed by subsequent quenching with methyl triflate.[11a] No evidence of C-alkylation was observed although starting material was recovered. Condensation of **13** with various amidines generated the desired heterocyclic

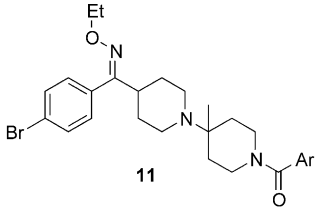


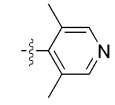
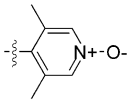
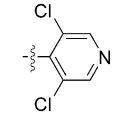
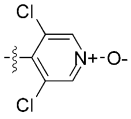
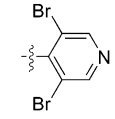
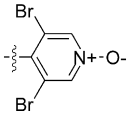
Scheme 1. Synthesis of 2,6-dimethyl isonicotinamides.



Scheme 2. Synthesis of 2,6-disubstituted isonicotinamides.

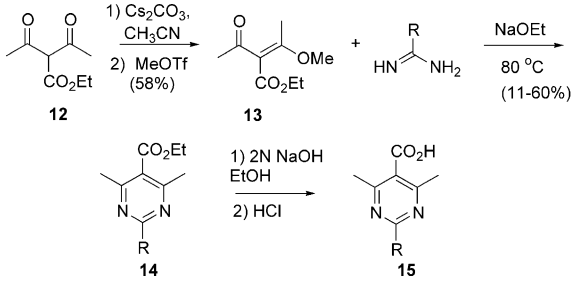
Table 1. SAR and pharmacokinetic properties of 2,6-disubstituted isonicotinic amides



	Ar	K_i (nM)[a,b]	IC_{50} (nM)[c]	Rat PK (10 mg/kg·po)[d] $AUC_{0-6\ h}$ (h μg/mL)
1		2.1	0.6	6.5
11a		2.3		1.3
11b		8.8	0.40	1.6
11c		0.4	0.69	0.5
11d		1.2	0.15	3.9
11e		0.3	1.04	0.5
11f		0.7	1.24	4.4

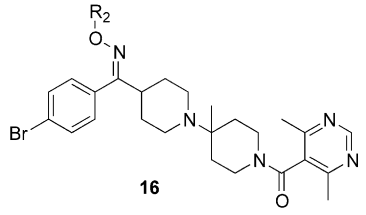
[a]Data for the inhibition of RANTES binding and 23 °C for 60 min.
[b]The standard error was 10% and variability was 2–3-fold from assay to assay.
[c]Concentration required to inhibit by 50% the entry of HIV-1 reported virus (ADA) into U-87 cells; see ref 7c for assay procedures. For IC_{50} values, 95% confidence limit was within 1 log and intraassay variation less than 0.5 log.
[d]See ref 12 for procedure.

Scheme 3. Synthesis of symmetrical amide analogues of **1**.



Scheme 4. Synthesis of substituted pyrimidines.

Table 2. SAR and pharmacokinetic properties of compounds with a 4,6-dimethyl pyrimidine amide



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	R2	K_i (nM)[a,b]	IC_{50} (nM)[c]	Rat PK (10 mg/kg·po)[d] $AUC_{0-6\ h}$ (h μg/mL)
1		2.1	0.6	6.5
16a	Me	4.7	1.83	4.1
16b	Et	2.2	0.36	3.1
16c	Pr	2.0	0.89	1.6
16d		14	3.80	6.9
16e		8.1	1.17	0.6
16f		11		3.7
16g	iPr	3.3	0.28	2.4

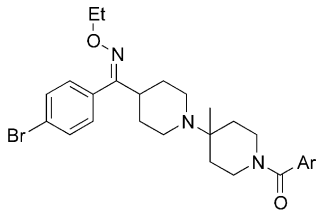
[a]Data for the inhibition of RANTES binding and 23 °C for 60 min.
[b]The standard error was 10% and variability was 2-3 fold from assay to assay.
[c]Concentration required to inhibit by 50% the entry of HIV-1 reported virus (ADA) into U-87 cells. see ref 7c for assay procedures. For IC_{50} values, 95% confidence limit was within 1 log and intraassay variation less than 0.5 log.
[d]See ref 12 for procedure.

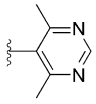
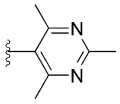
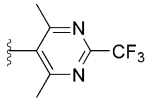
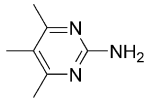
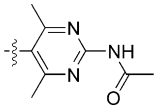
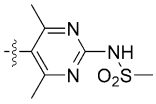
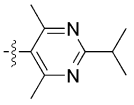
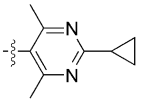
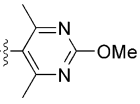
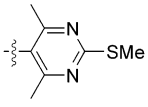
esters **14** in 11–60% yield.[11b] Hydrolysis followed by acidification gave the desired acids **15** in quantitative yield.

The pyrimidine acids **15** were then coupled with amine **10** under standard conditions. The biological data for the resulting amides are summarized in Tables 2 and 3. These amides showed receptor binding profiles similar to those of the nicotinic acid *N*-oxide amides;[7b] compounds with small *O*-alkyl substituents on the oxime (**16b**) and (**16c**) were optimal. These antagonists showed CCR5 binding affinity simillar to that of our lead antagonist **1** and also gave comparable plasma levels in rats following oral administration.

In order to address potential metabolism at the 2-position of the pyrimidine moiety, as well as to improve the

Table 3. SAR and pharmacokinetic properties of 2-substituted-4,6-dimethyl pyrimidine amides



	Ar	K_i (nM)[a,b]	IC_{50} (nM)[c]	Rat PK (10 mg/kg·po)[d] $AUC_{0-6\ h}$ (h μg/mL)
1		2.1	0.6	6.5
16b		2.2	0.36	3.1
17a		2.1	0.93	2.7
17b		3.2	0.26	2.0
17c		5.7	0.35	3.1
17d		60		
17e		315		
17f		43		
17g		25		
17h		5.3	0.13	1.8
17i		1.3		0.4

[a]Data for the inhibition of RANTES binding and 23 °C for 60 min.
[b]The standard error was 10% and variability was 2–3 fold from assay to assay.
[c]Concentration required to inhibit by 50% the entry of HIV-1 reported virus (ADA) into U-87 cells; see ref 7c for assay procedures. For IC_{50} values, 95% confidence limit was within 1 log and intraassay variation less than 0.5 log.
[d]See ref 12 for procedure.

overall profile, several 2-substituted 4,6-dimethyl 5-pyrimidine carboxylic acid derivatives were prepared. Small alkyl groups at the 2-position of pyrimidine are tolerated. For example, compounds with methyl (**17a**), trifluoromethyl (**17b**), methoxy (**17h**) substituents exhibited good CCR5 binding affinity. 2-Amino substitution as in **17c** was also acceptable, but amido and sulfonamido pyrimidines (**17d**, **17e**) were found to be less active. Clearly, analogues with substitution at the 2-position provided no improvement in overall pharmacokinetic profile.

The inhibition of binding at the CCR5 receptor correlated well with inhibition of viral entry for both pyrimidine and isonicotinic *N*-oxide analogues of **1**. In both series, in general methoxime analogues are less potent in the RANTES binding assay than the ethoximes. In addition, all compounds with ADA viral entry data listed (Table 2 and 3) inhibited the entry of HIV-1 isolate YU-2 in U-87 cells with IC_{50} values less than 1 nM. Furthermore, compounds **16a** and **16b** inhibited the replication of a primary HIV-1 isolate (US-1) in PBMCs with IC_{50} values comparable to that of antagonist **1** ($IC_{50} = 2.6$ nM for **16a**).[7b,7c] Despite meeting all the criteria for a possible preclinical candidate, the potential liability of **16a** was a lack of consistent antiviral activity against a wide range of genetically diverse HIV-1 isolates, relative to antagonist **1**.

In summary, we have described the results of our SAR investigation of the right-hand side nicotinamide *N*-oxide moiety in the lead antagonist **1**. Symmetrical pyrimidines, 2-substituted pyrimidines and 2,6-disubstituted isonicotinamides and their corresponding *N*-oxides are all well tolerated, providing potent CCR5 receptor antagonists with comparable efficacy in both binding and viral entry assays to our lead antagonist **1**, while reducing the number of rotational isomers. Our continuing efforts to improve the overall profile of these compounds will be published in due course.

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