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Discovery of *N*-benzyl-*N*′-(4-pipyridinyl)urea CCR5 antagonists as anti-HIV-1 agents (I): Optimization of the amine portion

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ABSTRACT

Several series of carbamate, urea and carboxamide-based CCR5 antagonists have been discovered via optimizations at the amine portion of lead compound **2**. All compounds were evaluated for their antiviral activities. Lead urea **29** showed good pharmacokinetic properties, justifying further development of this series.

The Chemokine Receptor R5 (CCR5) plays a critical role as viral entry co-receptor in the early stage of HIV-1 infection. Preventing its interaction with viral envelope protein gp120 ultimately blocks viral entry thus shutting down viral replication.[1] Maraviroc is the first marketed CCR5 inhibitor used as part of highly active antiretroviral therapy (HAART) in anti HIV-1 therapy.[2]

We previously reported several series of 4,4-disubstituted piperidine and cyclohexylamine based CCR5 antagonists,[3] exemplified by compound **1** (Fig. 1). The structure–activity relationship (SAR) in these series revealed that the central piperidine and a phenyl substituted quaternary carbon were critical for antiviral activity, and two-carbon linker between the piperidine and tropane was optimal length. These observations led us to continue the explorations of novel CCR5 antagonists by retaining the 4,4-disubstituted piperidine as a central scaffold and diversifying both the amine and the acyl termini.

Our efforts began with the synthesis of a small library varying amine substituents while keeping the acyl moiety unchanged (Fig. 2). Carbamate **3** was quickly identified as our initial hit,[4] and showed attractive potency in both HOS and PBL antiviral assays.

With this result in hand, we decided to further optimize the amine portion by expanding the carbamates to urea and carboxamides. Herein, we wish to describe the syntheses of this set of analogues and report their structure–activity relationship.

The synthesis was initiated by preparing key intermediate **11**. 2-Chloro-5-{[(1,1-dimethylethyl) amino]sulfonyl}-4-fluorobenzoic acid **6,** was first obtained in two steps from the commercially available 2-chloro-4-fluorobenzoic acid **4** (Scheme 1). Aldehyde **7,** prepared as previously described,[5] was converted into alcohol **8** with $NaBH_4$. Removal of Boc, followed by HATU coupling with **6**, resulted in alcohol **10**, setting the stage for the Swern oxidation towards intermediate **11**.

With intermediate **11** in hand, we next derivatized the carbamate moiety. Reductive amination of Boc protected piperidinone with allyl amine yielded **13**, which was then reacted with the in situ generated benzyl chloroformates **15**, affording intermediates **16**. Subsequent removal of Boc followed by reductive amination with the aldehyde **11** furnished the carbamate series **17a–f** (Scheme 2).

Preparation of the urea series was achieved by using the synthetic sequence in Scheme 3. Thus, isocyanates **19** were generated by treating amines **18** with slight excess of phosgene in presence of pyridine. Next, reaction with **13** yielded intermediate **20**. Upon Boc removal from **20**, the urea series **21a–l** was synthesized by reductive alkylation with aldehyde **11**.

The synthesis of the final amide series began with coupling amine **13** under HATU condition with phenyl acetic acid **22**. After Boc deprotection of amide **23**, the resulting piperidine **24** was reductively alkylated with **11**, yielding the carboxamide series **25a–e** (Scheme 4).

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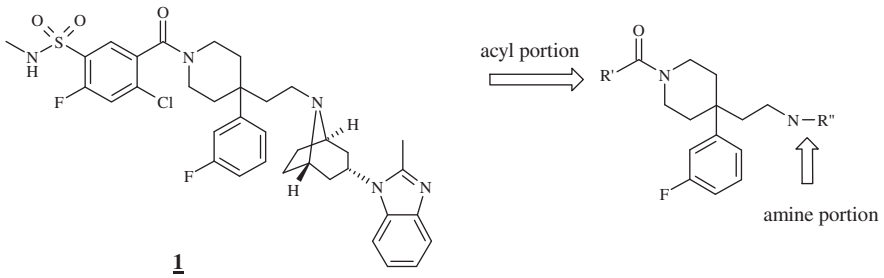


Figure 1. The piperidine based CCR5 antagonist and the central core template.

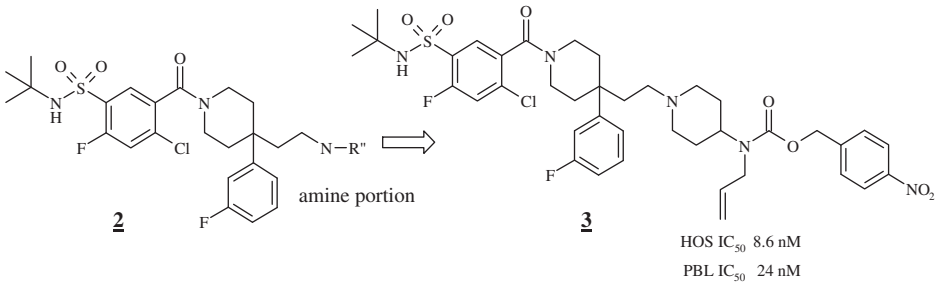
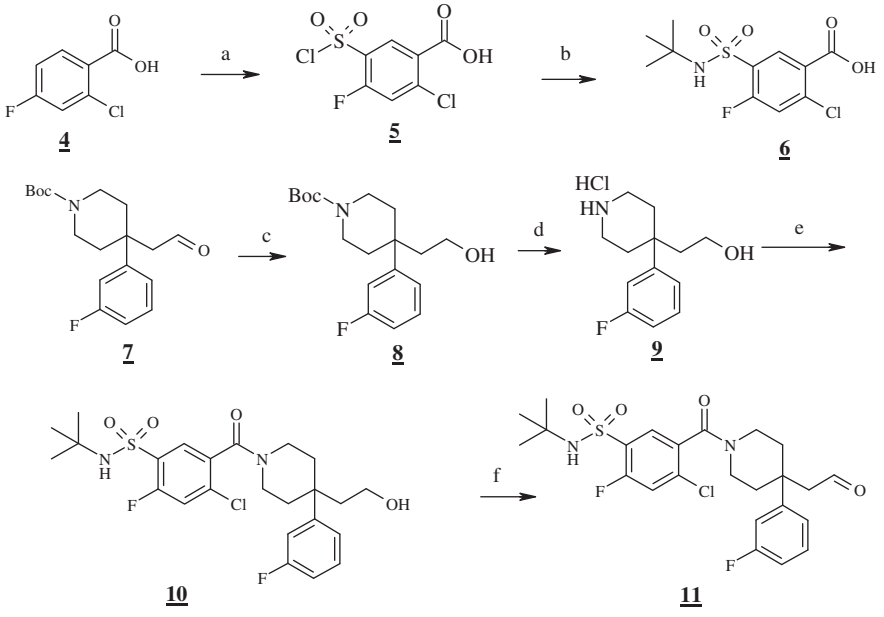


Figure 2. The initial library design and the hit.

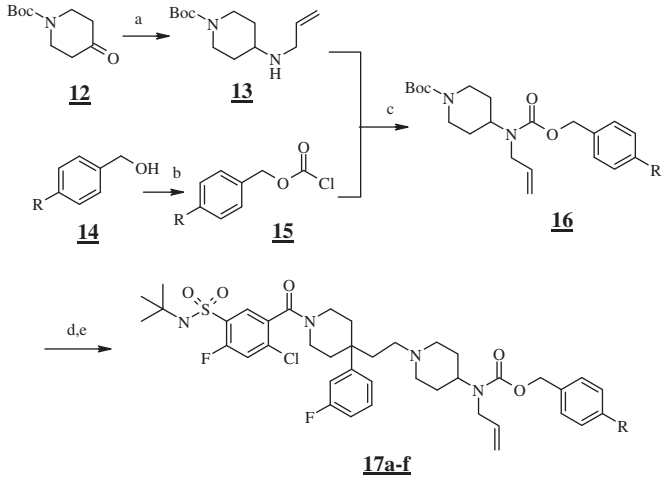


Scheme 1. Reagents and conditions: (a) HSO_3Cl, 150 °C, 6 h, 85%; (b) *t*-$BuNH_2$, $NaHCO_3$, dioxane/H_2O, 70%; (c) $NaBH_4$, MeOH, rt, 86%; (d) 4 M HCl, rt, quant.; (e) **6**, HATU, Et_3N, DMF, rt, 65%; (f) Swern oxidation, 22%.

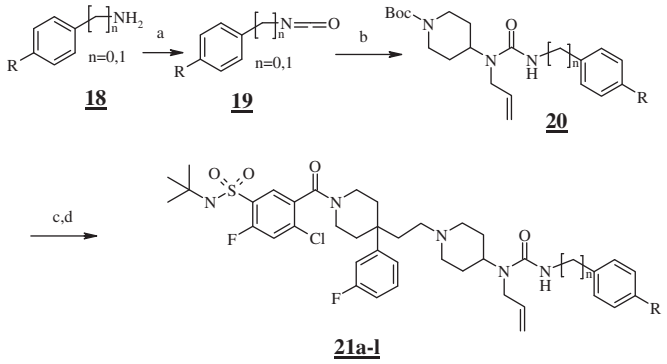
All compounds were tested for antiviral activity in both Human OsteoSarcoma (HOS) ($n = 2$) and peripheral blood lymphocytes (PBL) cells ($n \geqslant 4$) against the Ba-L strain of HIV-1.[6] Compound induced cellular toxicity was also investigated using CellTiter-Glo reagent (Promega). None of the compounds induced cell killing up to 1 μM (data not shown) indicating that the observed potency is the result of an antiviral effect and not toxicity (Tables 1–4).

We initially hypothesized from the *p*-nitro group in hit **3** that a hydrogen bonding acceptor may be required for antiviral activity. In addition, the strong electron-withdrawing nature of the nitro substituent could potentially improve metabolic stability of the benzyl moiety. Thus, a series of benzyl carbamates (**17a**–**f**) carrying substitutes at the *para* position with similar properties (hydrogen bonding acceptor and electron withdrawing) were synthesized. All except cyano-bearing **17e** turned out to be less potent in the HOS assay than the initial lead **3**. The cyano group (**17e**) improved the potency by ~twofolds. (Table 1).

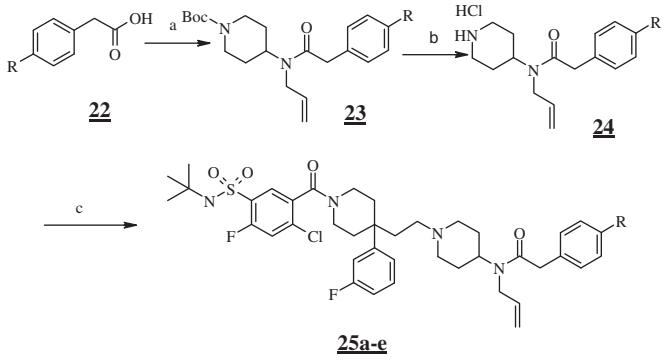
As bioisosteres of the carbamates, both phenyl and benzyl urea analogues were synthesized to further optimize the amine portion. As the data show in Table 2, the benzyl urea demonstrated better antiviral profiles than its phenyl counterparts though this was not true for the F substituent (**21d** vs **21c**). CF_3 substituted **21b** is 9 times more potent than **21a** in HOS cell assay, however, the relative potency of **21b** in the PBL assay is lower. Again, cyanobenzyl



Scheme 2. Reagents and conditions: (a) $NaBH(OAc)_3$, CH_2Cl_2, rt, quant.; (b) phosgene, K_2CO_3, CH_2Cl_2, rt; (c) *i*-Pr_2EtN, CH_2Cl_2, rt, 35–90%; (d) HCl, rt, quant.; (e) **11**, $NaBH(OAc)_3$, *i*-Pr_2EtN, CH_2Cl_2, rt, 30–60%.



Scheme 3. Reagents and conditions: (a) phosgene, pyridine, CH_2Cl_2, rt; (b) **13**, *i*-Pr_2EtN, CH_2Cl_2, rt, 50–81%; (c) HCl, rt, quant.; (d) **11**, $NaBH(OAc)_3$, *i*-Pr_2EtN, CH_2Cl_2, rt, 52–69%.

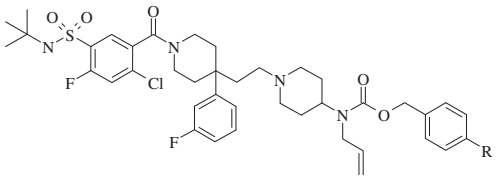


Scheme 4. Reagents and conditions: (a) **13**, HATU, *i*-Pr_2EtN, CH_2Cl_2, rt; (b) HCl, CH_2Cl_2, rt; (c) **11**, $NaBH(OAc)_3$, *i*-Pr_2EtN, CH_2Cl_2, rt, 52–69%.

urea **21f** exhibited much better activity than cyanophenyl urea **21e** in both HOS and PBL assays. Methyl sulfone (**21g**) and methyl ester (**21h**) behaved similarly as they did in the carbamate series. Surprisingly, the amide caused significant loss of potency (**21i**). Acetate **21j** also failed to improve the antiviral activity.

Carboxamides exhibited similar antiviral activity as the phenyl urea analogues except for **25a** (Table 3). The trifluoromethyl(CF_3) substituent provided a substantial potency improvement of **25a** in

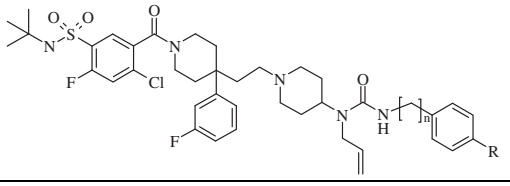
Table 1
Antiviral potency of carbamate analogues **17a–f** in HOS and PBL cell assays



Compound #	R	HOS IC_{50} (nM)	PBL IC_{50} (nM)
17a		15	40
17b		22	NA
17c		41	NA
17d		17	4.5
17e		4.5	NA
17f		27	NA

NA: not available.

Table 2
Antiviral potency of urea analogues **21a–j** in HOS and PBL cell assays



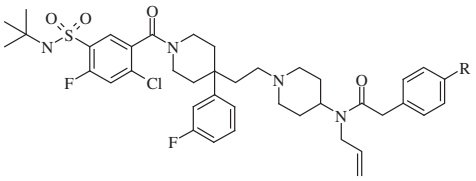
Compound #	R	*n*	HOS IC_{50} (nM)	PBL IC_{50} (nM)
21a		0	64	NA
21b		1	6.9	42
21c		0	34	NA
21d		1	46	NA
21e		0	20.5	25
21f		1	3.9	3.7
21g		0	11.5	35
21h		1	26	146
21i		1	3100	NA
21j		0	60	NA

NA: not available.

the HOS assay, however, its antiviral potency in the PBL assay was disappointing, presumably due to high *c* log *P* of **25a**. To best mimic the benzyl carbamate/urea, phenyl propanamides **26** and **27** were synthesized via a similar approach (Fig. 3). Surprisingly, both amides exhibited a dramatic loss of potency, which was not attributed to replacing *t*-But with methyl substituent in the benzenesulfonamide portion (see SAR in the follow-on communication).[7]

The described potency SAR identified the benzyl ureas as the lead scaffold and cyano (CN) as the best *para*-phenyl substituent. This observation led us to focus on the *p*-cyanobenzyl urea series and to further probe SAR on the allyl portion of *p*-cyanobenzyl

Table 3
Antiviral potency of amide analogues **25a–e** in HOS and PBL cell assays

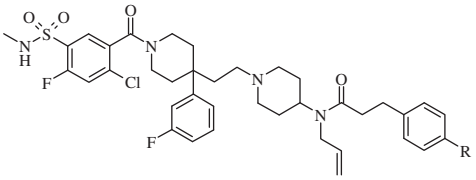


Compound #	R	HOS IC_{50} (nM)	PBL IC_{50} (nM)
25a		3.3	53
25b		52	NA
25c		65	NA
25d		18	87
25e		210	NA

NA: not available.

Table 4
Pharmacokinetics of **29** in rat at 1 mg/kg

Compound #	Cl (mL/min/kg)	$t_{1/2}$ (h)	Vdss (L/kg)	%F
29	18	10.8	11.6	22

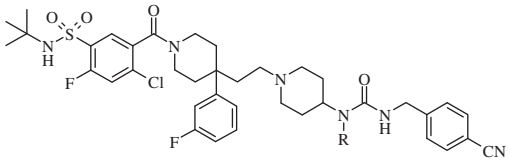


26 R = OCF_3 HOS IC_{50} = 420nM

27 R = CN HOS IC_{50} = 150nM

Figure 3. **3**-Phenyl propanamide derivatives **26** and **27** and their HOS IC_{50}.

urea. Compounds **28** and **29** were synthesized using the synthetic sequence in Schemes 3 and 4. The *n*-butyl analog **28** exhibited a similar potency to the allyl analogue **21f**. However, we were excited to discover that the replacement of allyl with a *m*-fluorophenyl moiety further improved the antiviral activity to subnano molar level (Fig. 4).



28 R = *n*-Bu HOS IC_{50} = 2.6nM, PBL IC_{50} =11nM

29 R = *m*-Fluorophenyl HOS IC_{50} = 0.4 nM, PBL IC_{50} = 1.7nM

Figure 4. *n*-Butyl and *m*-fluorophenyl derivatives **28** and **29** and their antiviral activity.

The pharmacokinetic profile of urea **29** was evaluated in Sprague Dawley rats at 1 mg/kg using 5% mannitol with 0.05% acetic acid as dose vehicle. Encouragingly, **29** showed acceptable clearance and bioavailability (22%).

In summary, starting from Lead **3**, we synthesized and evaluated carbamate, urea and carboxamide-based CCR5 antagonist scaffolds. Compounds in these series were generally very potent in both HOS and PBL antiviral assays. In particular, the *p*-cyanobenzyl urea motif enabled the most potent antiviral profiles across the series. Moreover, replacement of allyl in **21f** with *m*-fluorophenyl **29** dramatically enhanced its antiviral activity. Urea **29** was found to possess satisfactory in vivo properties in the rat PK model, suggesting that **29** is an interesting lead molecule for additional medicinal chemistry explorations. Subsequent optimization of the acyl portion will be reported in the follow-on communication.

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.; Moore, P. J., et al *Nature* **1996**, *381*, 667.
2. Price, D. A.; Armour, D.; De Groot, M.; Leishman, D.; Napier, C.; Perros, M.; Stamman, B. L.; Wood, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4633.
3. (a) 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; (b) Duan, M.; Aquino, C.; Ferris, R.; Kazmierski, M. W.; Wheelan, P. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4988.
4. Merck used the same carbamate motif in their CCR5 antagonists: Shankaran, K.; Donnelly, K. L.; Shah, S. K.; Caldwell, C. G.; Chen, P.; Finke, P. E.; Oates, B.; MacCoss, M.; Mills, S. G.; DeMartino, J. A.; Gould, S. L.; Malkowitz, L.; Siciliano, S. J.; Springer, M. S.; Kwei, G.; Carella, A.; Carver, G.; Danzeisen, R.; Hazuda, D.; Holmes, K.; Kessler, J.; Lineberger, J.; Miller, M. D.; Emini, E. A.; Schleif, W. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3589.
5. Kazmierski, W. M.; Aquino, C.; Chauder, B.; Deanda, F.; Ferris, R.; Jones-Hertzog, D.; Kenakin, T.; Koble, C.; Watson, C.; Wheelan, P.; Yang, H.; Youngman, M. *J. Med. Chem.* **2008**, *51*, 6538.
6. Muniz-Medina, V.; Jones, S.; Maglich, J.; Galardi, C.; Hollinggswirth, R.; Kazmierski, W.; Ferris, R.; Edelstein, M.; Chiswell, K.; Kenakin, T. *Mol. Pharmacol.* **2009**, *75*, 490.
7. Duan, M.; Peckhman, J.; Edelstein, M.; Ferris, R.; Kazmierski, K. M.; Wheelan, P.; Xiong, Z. *Bioorg. Med. Chem. Lett.* **2010**, *xx*, yyzz.