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Imidazopyridine-5,6,7,8-tetrahydro-8-quinolinamine derivatives with potent activity against HIV-1

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ABSTRACT

Synthesis of several novel imidazopyridine-5,6,7,8-tetrahydro-8-quinolinamine derivatives with potent activity against HIV are described. Synthetic approaches allowing for variation of the substitution pattern are outlined and resulting changes in antiviral activity and pharmacokinetics are highlighted. Several compounds with low nanomolar anti-HIV activity and oral bioavailability are described.

CXCR4 is a 7-transmembrane chemokine receptor.[1] Unlike most of the other receptors within the chemokine family, CXCR4 has only one known natural ligand, stromal cell-derived factor (SDF-1). The interaction of SDF-1 with CXCR4 has been shown to play a role in a number of physiological processes. CXCR4 is involved in the homing of immune cells to sites of inflammation[2] and the interaction of CXCR4 and SDF-1 helps maintain the cellular micro-environment of the bone marrow.[3] CXCR4/SDF-1 interaction has been shown to play a role in metastatic spread and in directly regulating the growth and/or survival of several types of cancer.[4] CXCR4 is a co-receptor for some strains of HIV-1 that are associated with late stage disease and progression to AIDS.[5] The CCR5 (R5) utilizing HIV-1 strains are generally associated with the initial infection and asymptomatic phase. As the disease progresses towards AIDS variant forms of the virus emerge that utilize both CCR5 and CXCR4 chemokine receptors (dual tropic viruses) or solely the CXCR4 chemokine receptor (CXCR4 tropic) to gain entry and infect new host cells.[6]

CXCR4 antagonists have potential therapeutic uses in HIV infection and several other indications, including mobilization of hematopoietic stem cells from the bone marrow.[7] CXCR4 antagonists may be of value in the treatment of rheumatoid arthritis by blocking the homing of inflammatory cells to inflamed joints.[8]

Both peptidic and small molecule CXCR4 antagonists have been described. Peptides that are CXCR4 antagonists include ALX-40-4C,[9] CTCE-9908,[10] FC131[11] and POL3026.[12] Small molecule CXCR4 antagonists have been developed by Kureha (KRH1636)[13] and

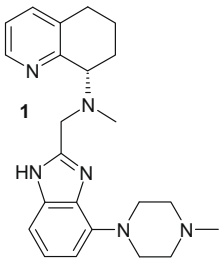

Figure 1.

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AnorMED (AMD3100, Plerixafor, Mozobil[14] and AMD070[15]). AMD3100 was recently approved by the FDA for stem cell mobilization.

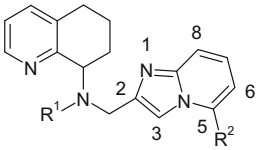
We recently described benzimidazole analogs, such as **1** (Fig. 1), that showed very potent anti-HIV activity (IC_{50} 0.6 nM against HIV-1).[16]

However, upon further investigation it became evident that benzimidazole **1** was highly protein bound and suffered significant protein shift (80-fold) in the antiviral assay (Table 1). We were therefore interested in synthesizing compounds in which the benzimidazole portion of **1** was replaced with an imidazopyridine and exploring the effect on antiviral activity and protein shift. Herein, we describe the synthesis and antiviral activity of several imidazopyridine-5,6,7,8-tetrahydro-8-quinolinamine derivatives.

For the synthesis of the desired imidazopyridine derivatives containing the piperazine linked to the C5-position, the first steps involved synthesis of a suitable imidazopyridine building block (Scheme 1). Condensation of commercially available 2-amino-6-fluoropyridine **2** and trichloroacetone gave the dichloromethyl imidazopyridine **3**. Treatment of **3** with aqueous sodium acetate yielded the aldehyde **4**.

Condensation of **4** and chiral tetrahydroquinoline amine **5**[16] via reductive amination gave the 5-fluoroimidazopyridine derivative **6**. Treatment of **6** with *N*-methylpiperazine under relatively mild

Table 1
Anti-HIV activity and cytotoxicity of imidazopyridine-tetrahydro-8-quinolinamines



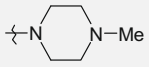
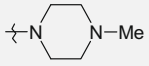
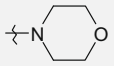
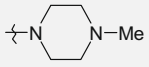
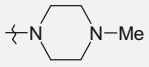
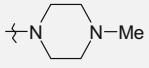
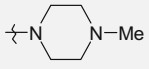
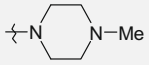
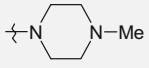
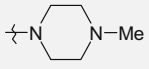
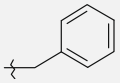
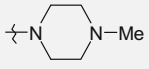
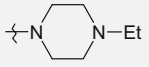
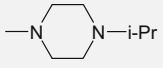
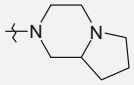
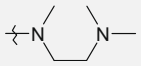
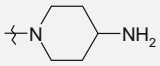
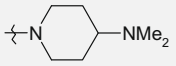
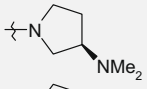
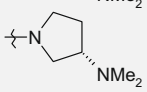
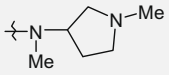
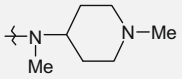
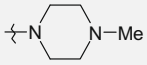
Compd[a]	R^1	R^2	IC_{50}[b] (μM)	Protein[c] shift	CC_{50}[d] (μM)
8	Me		0.002	1.5	4.5
10 R	Me		0.084	—	12.6
11 (rac)	Me		0.69		>10
12	Et		0.002	1.5	8.1
13 (rac)	CH_2CF_3		0.127	—	>5
14	*n*-Pr		0.003	5	6.7
15	*i*-Pr		0.005	5	8.9
16			0.004	6	8.0
17	*n*-Bu		0.003	—	5.3
18			0.023	—	20
19			0.028	—	9.3
20	Me		0.004	10	3.9
21	Me		0.003	3.3	7.1
22	Me		0.004	—	3.9
23	Me		0.017	—	2.2

Table 1 (*continued*)

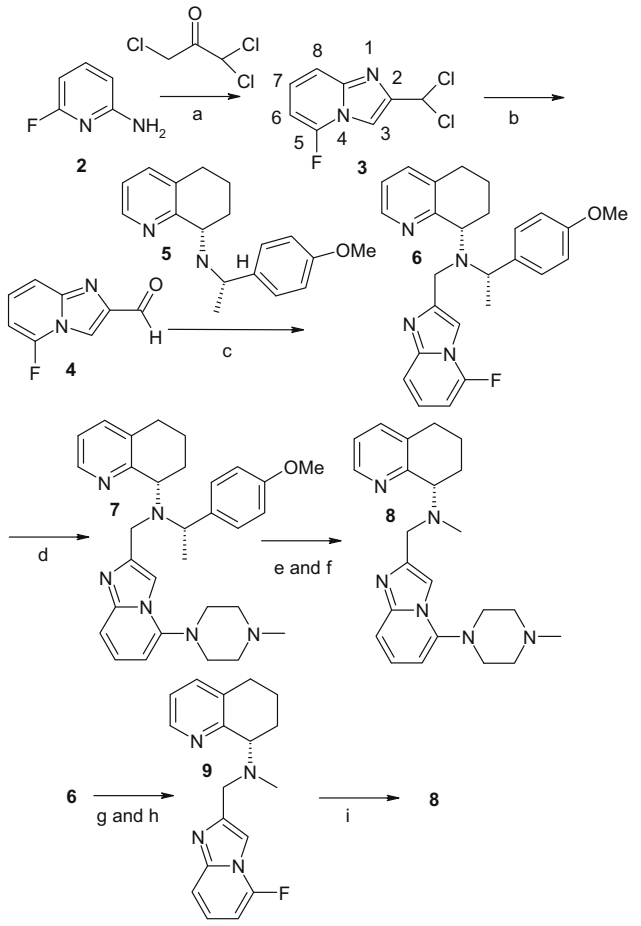
Compd[a]	R^1	R^2	IC_{50}[b] (μM)	Protein[c] shift	CC_{50}[d] (μM)
24	Me		0.004	—	6.3
25	Me		0.004	8	3.4
26	Me		0.008	3	2.1
27	Me		0.043	5	4.9
28	Me		0.030	1.3	10.8
29	Me		0.049	—	12.5
35[e]	Me		0.640	—	>5
1[f]			0.0006	80	>5

[a] Compounds have *S*-stereochemistry at 8-position of the tetrahydroquinoline unless otherwise noted, (rac) is racemic.
[b] HOS cells (expressing hCXCR4/hCCR5/hCD4/pHIV-LTR-luciferase), HIV-1, CXCR4-tropic strain (IIIB). Compounds were tested for their ability to block infection of the HOS cell line. IC_{50} is the concentration at which 50% efficacy in the antiviral assay is observed.[19]
[c] Protein shift is the shift in concentration at which 50% efficacy in the antiviral assay is observed in the presence of human serum albumin (45 mg/mL) and α-acid glycoprotein (1 mg/mL).
[d] CC_{50} is the concentration at which 50% cytotoxicity is observed in the HOS cell line.
[e] Compound **35** is methylpiperazine substituted at C-8 position (Scheme 2).
[f] Compound **1** is benzimidazole, from Ref. 16 included for comparison.

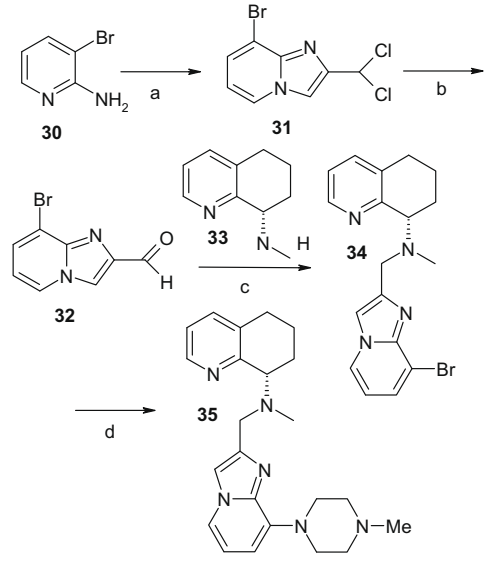
conditions resulted in displacement of the 5-fluorine and formation of **7**.[17] Displacement of the fluorine has to be carried out under mild conditions as the 8-aminotetrahydroquinoline is labile to racemization[18] at higher temperature. Finally, removal of the (*S*)-4-methoxyphenylethylgroup, followed by alkylation under reductive amination conditions gave the desired compound **8**. Alternatively, **8** could be prepared from **6** via deprotection and alkylation to give **9**, followed by displacement of the 5-fluorine with *N*-methylpiperazine, again using only mildly elevated temperature to avoid racemization of the 8-aminotetrahydroquinoline.

The *R*-enantiomer **10** was prepared in a similar fashion as the *S*-enantiomer **8**. The *S*-enantiomer **8** was about 50-fold more potent than the *R*-enantiomer **10** against HIV-1 (Table 1). Replacing the *N*-methylpiperazine with morpholine (**11**) resulted in greatly reduced anti-HIV activity (345-fold reduction in activity), highlighting the importance of the basic piperazine nitrogen. We then explored changing the 8-aminotetrahydroquinoline alkyl substituent, while keeping the *N*-methylpiperazine intact. Compounds **12–19** were prepared from **7** in a similar fashion as outlined in Scheme 1. In general smaller alkyl substituents gave potent compounds, as long as they did not affect the basicity of the 8-aminotetrahydroquinoline nitrogen. Thus, the ethylamine **12** was equipotent to the methylamine **8**, whereas the trifluoroethylamine **13** showed significantly reduced anti-HIV activity (60-fold less activity), presumably due to the altered basicity of the 8-amine. The *n*-propylamine **14**, isopropylamine **15**, cyclopropylmethylamine **16** and *n*-butylamine **17** showed promising anti-HIV activity while the *sec*-butylamine **18** and the still bulkier benzylamine **19** were less preferred (about fivefold less potent). We then looked at the effect that human serum protein would have on antiviral activity (protein shift) by adding human albumin and α-acid glycoprotein to the antiviral assay (Table 1). The methylpiperazine analogs (**8**, **12**–**19**), in which the 8-aminotetrahydroquinoline alkyl substituent (R^1) is a small alkyl group (e.g., **8** and **12**), were not generally affected by protein addition. However, piperazine analogs with larger alkyl substituents at R^1 (e.g., **14–16**) showed a more significant protein shift, up to 10-fold. Next we looked at replacing the *N*-methylpiperazine with *N*-ethylpiperazine (**20**) and *N*-isopropylpiperazine (**21**). Both analogs were potent in the anti-HIV assay, but both suffered significant protein shift (>3-fold).

We then explored replacing the piperazine with other heterocycles and basic amines. The C5-fluoroderivative **9** provided easy access to a number of nitrogen linked C5-substituted derivatives via an addition elimination reaction and compounds **22**–**29** were prepared in this fashion. The hexahydropyrrolo[1,2-*a*]pyrazine derivative **22** had similar potency to **8**. The trimethyl ethylenediamine derivative **23**, a flexible analog of **8**, had almost 10-fold reduced activity against HIV-1. The 4-aminopiperidine derivatives **24** and **25**, as well as the (3*R*)-3-dimethylamino-1-pyrrolidinyl derivative **26**, had good anti-HIV activity. Both **25** and **26** were more protein shifted (3–10-fold) than comparable piperazine analogs. Interestingly, the (3*S*)-3-dimethylamino-1-pyrrolidinyl derivative **27** demonstrated fivefold less anti-HIV activity than the closely related (3*R*)-3-dimethylamino-1-pyrrolidinyl derivative **26**. Finally, pyrrolidinyl derivative **28** and piperidinyl derivative **29** had reduced anti-HIV activity and appeared less attractive. Thus, while several heterocycles were identified (e.g., **25** and **26)** that could potentially replace the piperazine, none showed better anti-HIV activity and protein shift profile than the *N*-methylpiperazines. To this point we had only looked at C-5 substituted imidazopyridines, whereas the piperazine could be attached to the C-8 position of the imidazopyridine and still occupy similar space by rotating the imidazopyridine. To confirm that the C-5 was the optimal site for the piperazine substituent we synthesized the C-8 substituted imidazopyridine (Scheme 2). Condensation of 2-amino-3-bromopyridine (**30**) with trichloroacetone gave the



Scheme 1. Reagents and conditions: (a) trichloroacetone, DME, 80 °C, 12 h (63%); (b) NaOAc, EtOH, H_2O, 60 °C, 12 h (55%); (c) $NaBH(OAc)_3$, AcOH, $ClCH_2CH_2Cl$, rt, 18 h (64%); (d) *N*-methylpiperazine, 100 °C, 72 h (93%; >20:1 de as determined by HNMR); (e) CF_3COOH, CH_2Cl_2, rt, 4 h; (f) CH_2O (aq), $NaBH(OAc)_3$, AcOH, $ClCH_2CH_2Cl$, rt, 18 h, (64% for two steps); (g) CF_3COOH, CH_2Cl_2, rt, 4 h; (h) CH_2O (aq), $NaBH(OAc)_3$, AcOH, $ClCH_2CH_2Cl$, rt, 18 h (60% for two steps); (i) *N*-methylpiperazine, 100 °C, 72 h (90%, 100% ee as determined by chiral supercritical fluid chromatography).



Scheme 2. Reagents and conditions: (a) trichloroacetone, DME, 15 h, rt. Then, precipitate collected by filtration, EtOH, 4 h, reflux (45%); (b) aq $CaCO_3$, 1.5 h, reflux (91%); (c) $NaBH(OAc)_3$, AcOH, $ClCH_2CH_2Cl$, rt, 15 h (89%); (d) *N*-methylpiperazine, $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, reflux, 12 h (27%).

Table 2
Pharmacokinetics in rats

Parameter	8	14	16	21	25	26
Cl (mL/min/kg)	14	8.9	9.9	31	5.7	9.5
$V_d$ss (L/kg)	4.9	6.2	6.0	10.6	5.1	4.5
$T_{1/2}$ (h)	5.5	10.7	8.8	3.9	10	7.9
F (%, solution)	11	41	31	29	7	2

Clearance (Cl), volume of distribution ($V_d$ss) and half life ($T_{1/2}$) calculated following a 1 mg/kg iv dose. Oral bioavailability (*F*) calculated following solution doses of 3 mg/kg.

Table 3
Pharmacokinetics of **8**

Parameter	Rat	Dog (beagle)	Monkey (cynomolgus)
Cl (mL/min/kg)	14	18	6
$V_d$ss (L/kg)	4.9	8.5	3.7
$T_{1/2}$ (h)	5.5	7.6	10
F (%, solution)	11	13	10

Clearance (Cl), volume of distribution ($V_d$ss) and half life ($T_{1/2}$) calculated following a 1 mg/kg iv dose. Oral bioavailability (*F*) calculated following solution doses of 3 mg/kg.

dichloromethyl derivative **31**. Aqueous base treatment of **31** yielded aldehyde **32**. Reductive amination of aldehyde **32** and (8*S*)-*N*-methyl-5,6,7,8-tetrahydro-8-quinolinamine **33** gave **34**. The C8-bromine in **34** could not be replaced via treatment of **34** with *N*-methylpiperazine at elevated temperature but required coupling under Buchwald amination conditions to give the desired C-8 *N*-methylpiperazine substituted **35**. Compound **35** was over 300-fold less potent than the corresponding C-5 substituted derivative **8**, highlighting the importance of the position of the imidazopyridine N1-nitrogen in relation to the piperazine.

A set of potent analogs were chosen for rat pharmacokinetic studies (Table 2).

With regard to bioavailability and half life, compounds **8**, **14** and **16** appeared promising. While compounds **14** and **16** showed better pharmacokinetic properties in rat studies than compound **8**, this benefit was outweighed by the higher protein shift of both **14** and **16** (>5-fold for both). Compound **21** showed good bioavailability but shorter half life and greater protein shift than **8**. Compounds **25** and **26** were less bioavailable and more protein shifted than **8**. This resulted in **8**[20] being chosen as the first compound for more detailed pharmacokinetic studies in dog and cynomolgus monkey (Table 3).

Compound **8** showed oral bioavailability in both dog and monkey. Furthermore, it displayed suitable cytochrome P450 profile and screening against a panel of enzymes and receptors (PanLab) revealed little risk of unwanted enzyme and receptor inhibition at concentrations close to those demonstrating anti-HIV activity (selectivity over 100-fold).

Because of the promising anti-HIV potency and oral bioavailability, **8** was progressed into toxicology studies and served as a template for the synthesis of additional analogs.

Acknowledgements

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