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Inhibitors of HIV-1 attachment: The discovery and structure–activity relationships of tetrahydroisoquinolines as replacements for the piperazine benzamide in the 3-glyoxylyl 6-azaindole pharmacophore

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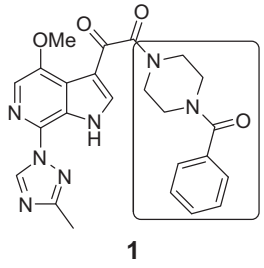
ABSTRACT

6,6-Fused ring systems including tetrahydroisoquinolines and tetrahydropyrido[3,4-*d*]pyrimidines have been explored as possible replacements for the piperazine benzamide portion of the HIV-1 attachment inhibitor BMS-663068. In initial studies, the tetrahydroisoquinoline compounds demonstrate sub-nanomolar activity in a HIV-1 pseudotype viral infection assay used as the initial screen for inhibitory activity. Analysis of SARs and approaches to optimization for an improved drug-like profile are examined herein.



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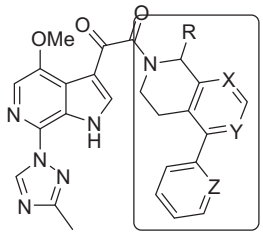

X, Y, Z = C, N; R = H, OH, alkyl

Despite the considerable advances in the treatment of HIV-1, in recent years HIV-1 drug resistance has become of increasing concern with antiretroviral (ARV) naïve patients infected with drug resistant virus at a rate of 10–17% in developed countries.[1] In addition to treatment-naïve patients with pre-existing virus mutations, acquired resistances are still emerging after treatment with the current standard of care regimens. Although rates of resistance development have slowed as combination antiretroviral therapy (cART) agents have been developed,[2] there is still a need for new ARV agents to treat patients who have developed resistance to current therapies, particularly the highly treatment experienced group. New ARV agents with mechanistically distinct modes of action that can offer complementary resistance profiles to marketed drugs will be essential to treat patients with resistant HIV-1infections.[3] HIV-1 attachment inhibitors (AIs) provide a differentiated target from the core cART agents currently being

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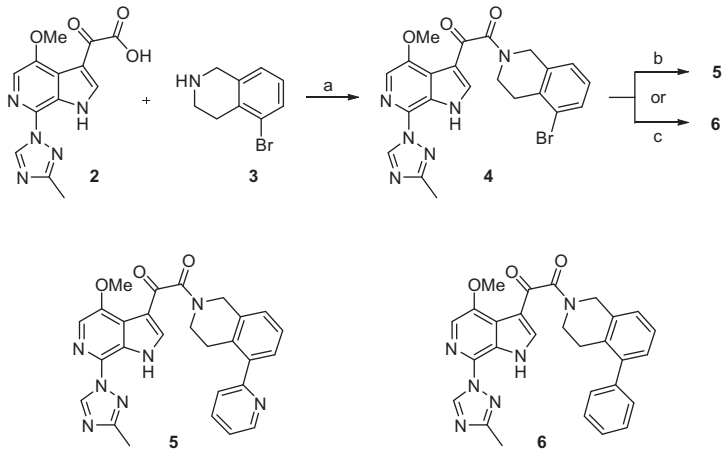


Scheme 1. Synthesis of 3-glyoxylyl azaindole phenyl and pyridyl tetrahydroisoquinolines. Reagents and conditions: (a) TBTU, DIEA, DMF, rt, 71 h, 88%; (b) 2-tri-*n*-butylstannylpyridine, $Pd(PPh_3)_4$, 1,4-dioxane, 100 °C, 4 days, 26%; (c) phenylboronic acid, $PdCl_2$(dppf)-CH_2Cl_2 adduct, K_2CO_3, 1,4-dioxane/water (4:1), 85 °C, 2 h, 48%.

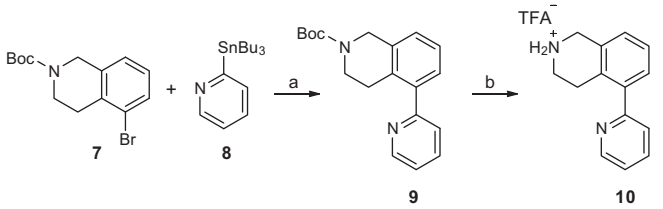
Table 1
Antiviral activity, cytotoxicity, in vitro metabolic stability, solubility properties and *c* Log *P* data for tetrahydroisoquinoline-based HIV-1 attachment inhibitors

Compound	EC_{50}[a] (nM)	CC_{50}[b] (μM)	HLM% rem at 10 min[c]	RLM% rem at 10 min[c]	Solubility pH 6.5[d] (μg/mL)	*c* Log *P*[e]
1	0.10	>300	97	96	22 (c, pH 5.7)	0.86
5	0.09	>33.3	11	8	19 (c)	2.26
6	0.02	>11.1	10	5	<1 (a)	3.54

[a] HIV-1 pseudotype assay performed at least in duplicate (averaged) utilizing HeLa CD4 CCR5 cells and HIV-1 JRFL virus envelope (Ref. 5). Experimental details are reported in the Supporting information.
[b] Concentration of drug associated with a 50% reduction in HeLa cell viability in the absence of pseudotype virus performed at least in duplicate (averaged) and in parallel with the pseudotype assay (Ref. 5).
[c] Metabolic stability experimental determination is detailed in the Supporting information. % Remaining at 10 min was extrapolated into low clearance (>85% remaining at 10 min), medium clearance (61–84% remaining at 10 min) and high clearance (<61% remaining at 10 min). Reference agents are referred to in the Supporting information.
[d] Solubility of crystalline (c) or amorphous (a) material at pH = 6.5 unless stated otherwise stated.
[e] *c* Log *P* values were calculated using Cambridgesoft ChemBioDraw version 12.0.

prescribed.[4] Attachment inhibitors have been shown to interfere with the first step of the HIV-1 entry process by binding to the viral glycoprotein (gp120) and stabilizing a conformation not recognized by CD4.[5] Attachment of gp120 to the cellular CD4 receptor is disrupted by the envelope changes and, consequently, the downstream processes which allow for viral genetic material to be released into the host cell cytosol are interfered with, hindering viral replication.[6–8]

In previous communications, we have detailed chemical approaches to HIV-1 AIs that developed structure–activity relationships (SARs) and which delivered several compounds into clinical trials.[9–21] Recently we have detailed the discovery of **1** as a potent HIV-1 attachment inhibitor and the clinical form of the molecule, a phosphate prodrug, BMS-663068.[22,23] The phosphate prodrug of **1** has progressed in the clinic through Phase IIb studies with encouraging results that support its continued development in Phase III trials.[24] In humans, benzamide hydrolysis was observed as a metabolic pathway, which spurred interest in preparing non-amides so we analyzed a full range of structural modifications in pursuit of a differentiated clinical candidate. Previous efforts communicated by our group[12] and, more recently, Tuyishime et al.[25,26] have shown that specific modifications to the piperazinamide moiety could afford compounds with excellent antiviral potency; however, all of these reports described amide derivatives that could potentially be hydrolyzed through similar metabolic processes. Alternatively, we found the tetrahydroisoquinoline (THIQ) to have a topology that could position an aromatic group in a similar position to the phenyl group of the benzamide of HIV AIs similar to **1**. We envisioned functionalization of either the THIQ or the core to improve solubility and perhaps preclude the use of a prodrug. THIQ



Scheme 2. Synthesis of pyridyl tetrahydroisoquinoline **10**, TFA salt. Reagents and conditions: (a) $Pd(PPh_3)_4$, 1,4-dioxane, 110 °C, 65 h, 91%; (b) TFA, CH_2Cl_2, rt, 6 h, 100%.

6 (EC_{50} = 0.02 nM) showed an improvement in potency in the in vitro HIV-1 pseudotype assay used as the initial screen for inhibitory activity in the program compared to the clinical candidate **1**, EC_{50} = 0.10 nM. In addition, the THIQ was an attractive motif because it allowed for modifications at several positions which could potentially modulate lipophilicity of the molecule and/or influence solubility, permeability and metabolic stability of the parent compound.[27]

Taking into account prior SARs, our initial molecules incorporated the 3-methyl-1,2,4-triazole at the 7-position of the 3-glyoxylyl azaindole core. The synthetic approach to construct the 3-glyoxylyl azaindole phenyl and pyridyl THIQs is illustrated in Scheme 1. With **2** in hand from previous efforts,[23] the amide was constructed utilizing an *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU)-mediated coupling with **3** to give the 5-bromo THIQ **4**. Installation of the pyridyl moiety was accomplished using Stille conditions to attain **5**, while the phenyl group was installed via a Suzuki coupling with the phenyl boronic acid to give **6**.