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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

Jacob J. Swidorski [a,*], Zheng Liu [a], Zhiwei Yin [a], Tao Wang [a], David J. Carini [a], Sandhya Rahematpura [b], Ming Zheng [b], Kim Johnson [b], Sharon Zhang [c], Pin-Fang Lin [c], Dawn D. Parker [b], Wenying Li [b], Nicholas A. Meanwell [a], Lawrence G. Hamann [a,†], Alicia Regueiro-Ren [a]

[a] Department of Discovery Chemistry, Bristol-Myers Squibb Research and Development, 5 Research Parkway, Wallingford, CT 06492, USA
[b] Department of Pharmaceutical Candidate Optimization, Bristol-Myers Squibb Research and Development, 5 Research Parkway, Wallingford, CT 06492, USA
[c] Department of Virology, Bristol-Myers Squibb Research and Development, 5 Research Parkway, Wallingford, CT 06492, USA

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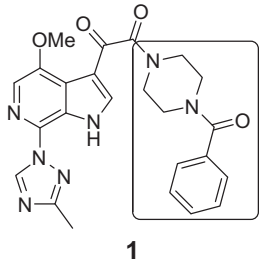
ABSTRACT

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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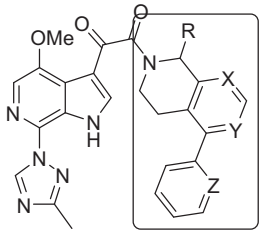

X, Y, Z = C, N; R = H, OH, alkyl

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

* Corresponding author.
† Current address: Novartis Institutes for BioMedical Research, 250 Massachusetts Ave., Cambridge, MA 02139, USA.

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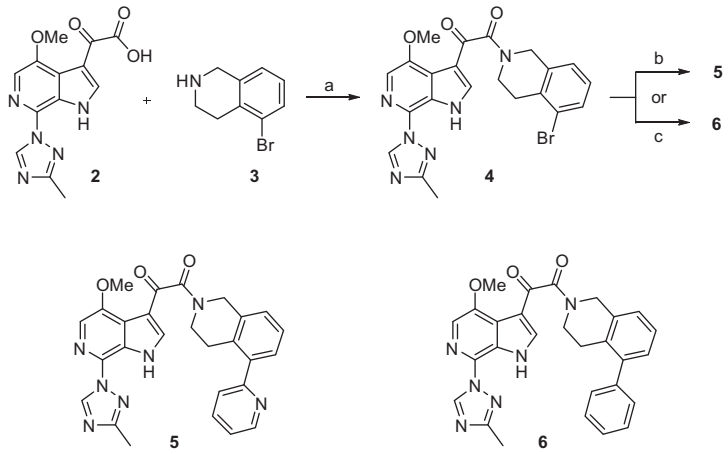


Scheme 1. Synthesis of 3-glyoxylyl azaindole phenyl and pyridyl tetrahydroisoquinolines. Reagents and conditions: (a) TBTU, DIEA, DMF, rt, 71 h, 88%; (b) 2-tri-*n*-butylstannylpyridine, $Pd(PPh_3)_4$, 1,4-dioxane, 100 °C, 4 days, 26%; (c) phenylboronic acid, $PdCl_2$(dppf)-CH_2Cl_2 adduct, K_2CO_3, 1,4-dioxane/water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

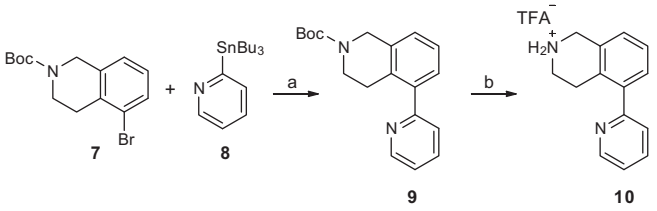
Table 1
Antiviral activity, cytotoxicity, in vitro metabolic stability, solubility properties and *c* Log *P* data for tetrahydroisoquinoline-based HIV-1 attachment inhibitors

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]

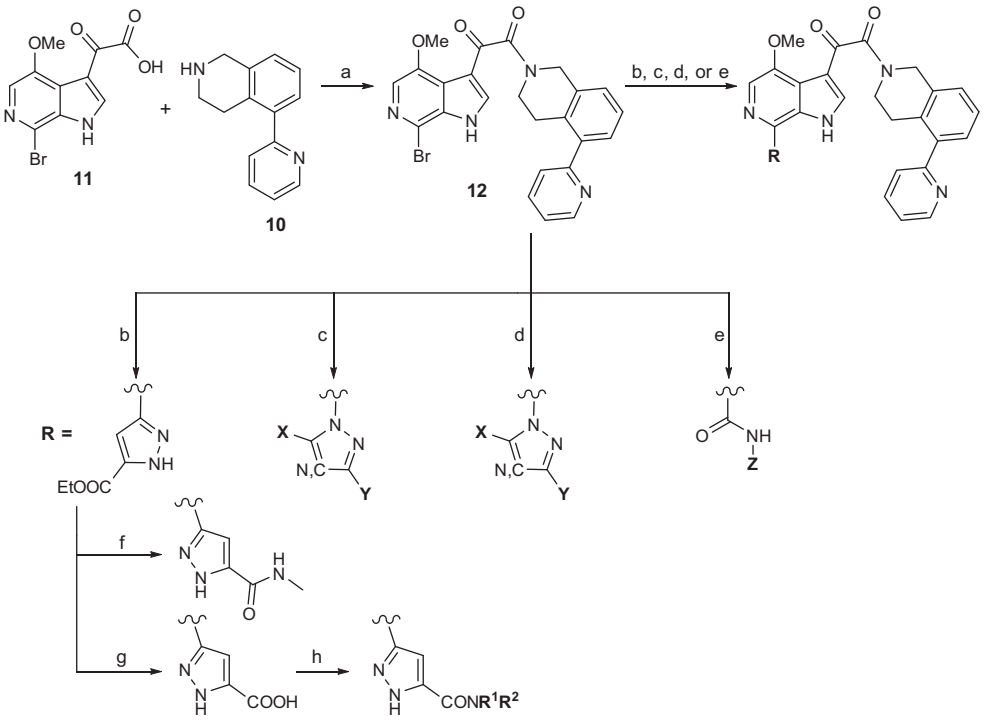
In previous communications, we have detailed chemical approaches to HIV-1 AIs that developed structure–activity relationships (SARs) and which delivered several compounds into clinical trials.[9–21] Recently we have detailed the discovery of **1** as a potent HIV-1 attachment inhibitor and the clinical 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**.

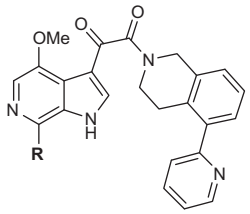


Scheme 3. Synthesis of C-7 modified 3-glyoxylyl azaindole pyridyl tetrahydroisoquinolines. Reagents and conditions: (a) TBTU, DIEA, DMF, rt, 70 h, 75%; (b) 3-(tributylstannyl)-1*H*-pyrazole-5-carboxylate, $Pd(PPh_3)_4$, 1,4-dioxane, 110 °C, 17 h, 30%; (c) **14**, **17**, and **18**; heterocycle, copper (0), pyridine, 145 °C; (d) compounds **15**, **16**, **19**, and **20**; heterocycle, Cu(I)iodide, K_2CO_3, (*1R,2S*)-N^1,N^2-dimethylcyclohexane-1,2-diamine, 1,4-dioxane, 100 °C; (e) compounds **26** and **27**; amine, CO (80 psi), $Pd(PPh_3)_4$, water, triethylamine, 80 °C, 16 h; (f) compound **23**; methylamine (2 M in THF), 40–60 °C, 6.5 days; (g) compound **22**; methanol, water, K_2CO_3, 60 °C, 2 h; (h) compounds **24** and **25**; amine, TBTU, DIEA, DMF, rt.

Compounds **5** (EC_{50} = 0.09 nM) and **6** (EC_{50} = 0.02 nM) were examined in the pseudotype assay and both showed improved potency when compared to **1** (EC_{50} = 0.10 nM). Additionally, **5** demonstrated improved solubility (19 μg/mL as a crystalline solid) over **6** (<1 μg/mL as an amorphous solid) and similar solubility to **1** (22 μg/mL at pH 5.7 as a crystalline solid). Unfortunately, both **5** and **6** were quickly metabolized upon incubation with human or rat liver microsomes, with only 5–11% of parent drug remaining after the 10 min incubation period (Table 1). We have shown previously that solubility and metabolic stability, as well as potency can be affected by the substituent in the 7-position of the azaindole moiety.[20] Therefore, we designed a series of compounds that would vary the lipophilicity of the molecule through modifications of the substituent at the C-7 position of the 6-azaindole ring. Earlier SAR developed in the program led us to focus on introducing triazoles and pyrazoles preferentially bearing polar substituents, as well as direct attachment of amides to the azaindole core. Because the initial assembly of **5** and **6** installed the THIQ late in the synthesis, an alternative approach was developed to enable C-7 substitution late in the synthetic sequence. The 5-pyridyl THIQ **9** was assembled via a Stille coupling of **7** with **8** (Scheme 2). The Boc group was removed by treatment with TFA in dichloromethane to give **10**. Amide formation was accomplished through a TBTU-mediated coupling of **10** with **11**[28] to yield the C-7 azaindole bromide **12** that proved to be a useful intermediate for subsequent modifications. The brominated core could be elaborated using Ullman conditions to introduce N-linked heterocycles (**13**–**20**), Stille conditions for the C-linked pyrazoles **21**–**25**, or carbonylation conditions to prepare the C-7 amides **26** and **27** (Scheme 3). The C-7 pyrazole **21** was formed by elaborating the pyrazole prior to the Stille coupling by reducing the ethyl ester of 3-(tributylstannyl)-1*H*-pyrazole-5-carboxylate with LAH. The other C-linked pyrazoles were further modified post-coupling through amination of the ester with methylamine (**23**), hydrolysis (**22**), or hydrolysis followed by TBTU-mediated coupling of the free carboxylic acid (**24** and **25**).

Substitution of the C-7 position of the azaindole (Table 2) with a 1,2,3 triazole, as in **13**, did not improve the in vitro metabolic stability or aqueous solubility compared to the prototype **5**. Examples **14**–**18** explored variation of the lipophilicity by changing the substituents attached to the triazole. The more lipophilic compounds **15** and **16** showed very poor solubility along with a poor in vitro metabolic profile. The less lipophilic compounds **14** and **18** exhibited better solubility and slightly improved metabolic stability. Consistent with previous SAR, the unsubstituted 1,2,4-triazole **14** lost potency. The methoxymethyl-substituted triazole **17** did not benefit from the decreased lipophilicity as HLM and RLM stability for this compound was still very poor; however, solubility was slightly improved. Substitution at the 5-position of the triazole in **18** did improve metabolic stability slightly, but potency decreased dramatically due to disruption in the planarity of the heterocyclic ring and the azaindole.[20] The N-linked pyrazoles **19** and **20** also probed variation of lipophilicity but failed to show an improvement in metabolic stability. Variations of C-linked pyrazoles were examined in the context of compounds **21**–**25**. Although improved compared to **5**, the in vitro metabolic stability of **21** (18/17% parent remaining after a 10 min incubation with microsomes) was still too low to progress into more advanced studies. Carboxylic acid **22** showed a great improvement in metabolic stability (95/91% parent remaining after 10 min incubation with microsomes), but the solubility of the compound was still less than ideal. Methyl amide **23** showed a slight loss of potency and solubility while amides **24** and **25** had solubility so low that the metabolic stability wasn't determined. The series of C-7 substitutions concluded with the two C-7 amides **26** and **27**. While HLM stability improved slightly, and methyl amide **26** did show an improvement in

Table 2
Antiviral activity, cytotoxicity, in vitro metabolic stability and calculated Log *P* data for C-7 substituted azaindole HIV-1 attachment inhibitors



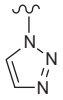
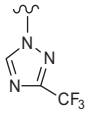
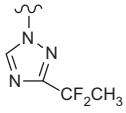
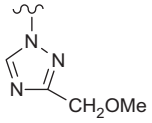
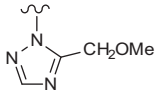
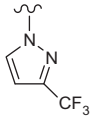
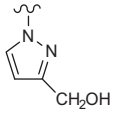
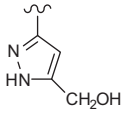
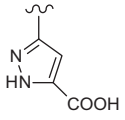
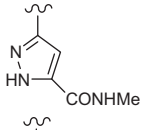
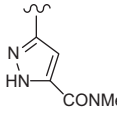
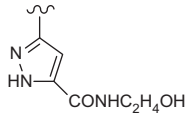
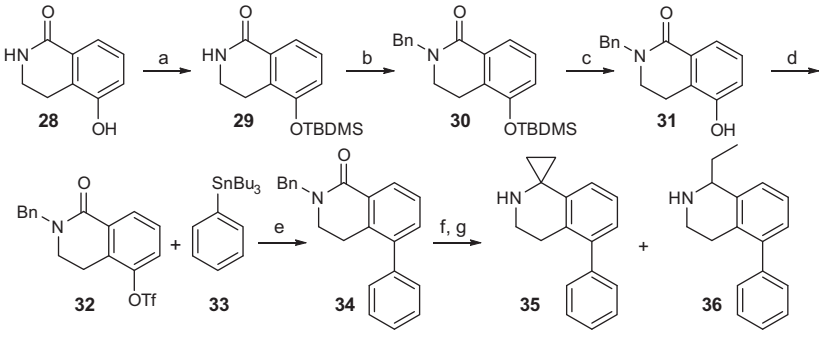
Compound	R	EC_{50} (nM)	CC_{50} (μM)	HLM/RLM% remaining at 10 min	Solubility* (μg/mL)	*c* Log *P*
13		0.06	37.5	7/0	18	3.14
14		0.48	162	9/20	30	1.99
15		0.14	>3.7	7/8	<1	3.01
16		0.14	>11.1	7/5	3	2.71
17		0.54	>100	5/9	27	1.79
18		53.4	119	29/33	37	1.79
19		0.41	>1.23	1/1	<1	4.28
20		0.13	>33.3	3/1	ND	2.31
21		0.08	190	18/17	20	2.51
22		0.15	>300	95/91	7	3.77
23		0.14	28.4	6/6	8	3.42
24		0.37	>33.3	ND	2	2.57

Table 2 (*continued*)

Compound	R	EC_{50} (nM)	CC_{50} (μM)	HLM/RLM% remaining at 10 min	Solubility* (μg/mL)	*c* Log *P*
25		0.10	>33.3	ND	1	2.86
26		0.62	>100	20/3	33	2.74
27		0.44	>33.3	24/28	4	2.18

* Solubility of amorphous solids measured at pH = 6.5.



Scheme 4. Synthesis of 1- and 1,1′-modified tetrahydroisoquinolines. Reagents and conditions: (a) TBDMS-Cl, 1*H*-imidazole, DMAP, DMF, rt, 22.5 h, 97% (b) NaHMDS, benzyl bromide, THF, rt, 41 h; (c) TBAF (1 M in THF), THF, rt, 45 min; (d) Tf_2O, pyridine, CH_2Cl_2, 0 °C-rt, 1 h, 11% over three steps; (e) tri-2-furylphosphine, LiCl, $Pd_2(dba)_3$, NMP, 85 °C, 15.5 h, 77%; (f) methyltitanium triisopropoxide (1 M in THF), EtMgBr (1 M in THF), THF, −78 °C to 50 °C, 23 h, 23%; (g) 10% Pd/C, MeOH, H_2 (1 atm), 4.5 h, 1:0.57 ratio based on ^{1}H NMR integration, 100%.

solubility, both compounds showed diminished antiviral potency. Although this series of compounds did not improve metabolic stability as much as initially hoped, there seemed to be a general trend that compounds with lower *c* Log *P* values had improved metabolic stability. The only compound with a major improvement in metabolic stability, acid **22**, lacked the potency of the best compounds and also had inadequate passive membrane permeability with PAMPA assay values of 0 nm/s at pH = 7.4 and 32 nm/s at pH = 5.5. Based on these results, we decided to pursue in vitro biotransformation studies with **5** in an effort to determine where the metabolic soft spots in the molecule were located (see Fig. 1).

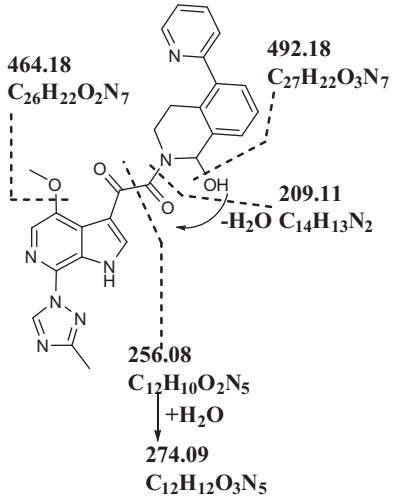
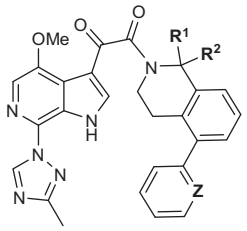


Figure 1. In vitro biotransformation analysis of **5**.

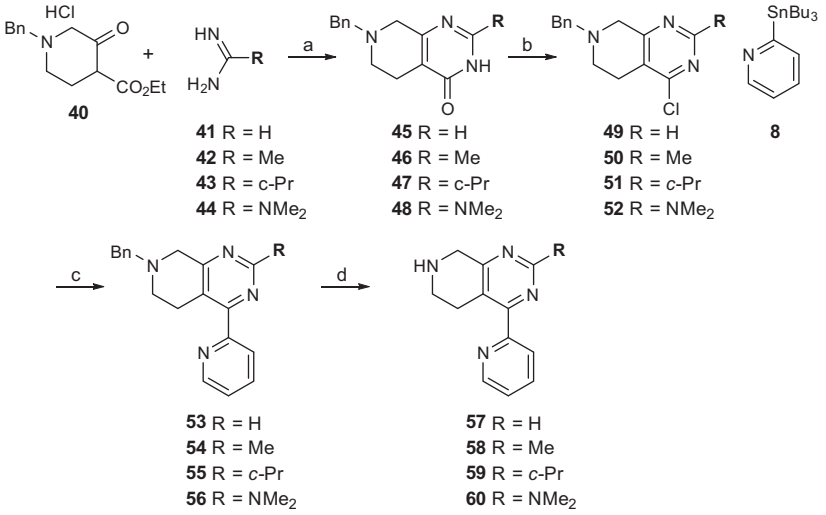
In vitro biotransformation studies with **5** and several related analogs identified the benzylic position adjacent to the *N* atom of the THIQ as the labile metabolic site for this chemotype. The hemiaminal **37** was the only metabolite produced after incubating **5** with human liver microsomes. In order to obtain a sufficient amount of **37** to test for biological activity and metabolic profiling, the biotransformation of **5** into **37** was accomplished preparatively using a liver S9 fraction from Aroclor 1254-induced rats incubated with compound at 37 °C for 4.5 h.[29] Hemiaminal **37** not only had a lower calculated *c* Log *P* than the parent (1.6 vs 2.26, Table 3), but both metabolic stability and solubility were greatly improved. Unfortunately, however, there was more than a 50-fold decrease in antiviral potency compared with **5**.

In an attempt to improve the metabolic stability by blocking the benzylic position, cyclopropyl analog **38** was prepared. Preparation of the substituted THIQ was accomplished by protecting the phenolic alcohol of the commercially available 5-hydroxy-3,4-dihydroisoquinolin-1(2*H*)-one (**28**) as the TBDMS ether followed by benzyl protection of the amide to give **30** (Scheme 4). The TBDMS ether was removed with TBAF and the phenol was converted into triflate **32**. Modified Stille conditions[30] allowed for efficient cross-coupling to install the phenyl ring. The benzyl-protected amide was then converted to the aminocylopropane **35** utilizing conditions developed by Kulinkovich and de Meijere followed by hydrogenolysis of the benzyl protecting group.[31] During the formation of the aminocylopropane **35**, the amino ethyl analog **36** was also formed. Since separation of these two compounds was difficult, the mixture of **35** and **36** was directly coupled to core **2** using a TBTU-mediated coupling and the fully elaborated products **38** and **39** were separable by preparative HPLC. While the stability of **38** in HLM was only marginally better than **6**, potency declined by 460-fold. Ethyl derivative **39**, which could in principle deter metabolism by increasing steric hindrance around the labile site, did not offer

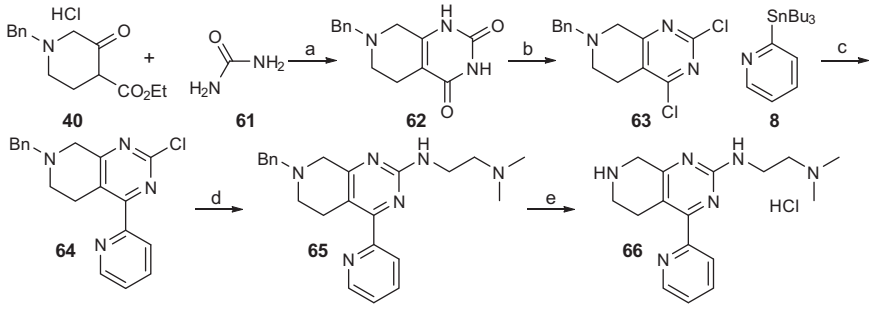
Table 3
Antiviral activity, cytotoxicity, in vitro metabolic stability and calculated Log *P* data for modifications to the 1-position of the THIQ ring



Compound	R^1	R^2	Z	EC_{50} (nM)	CC_{50} (μM)	HLM/RLM% remaining at 10 min	Solubility (μg/mL)	*c* Log *P*
37	H	OH	N	4.62	>100	79/72	70 (c)	1.60
38	Cyclopropyl		CH	9.20	5.45	30/6	<1 (a)	3.86
39	H	Ethyl	CH	0.71	24.7	21/5	<1 (a)	4.59



Scheme 5. Synthesis of 2-substituted-4-(pyridin-2-yl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidines. Reagents and conditions: (a) NaOMe, MeOH, rt; (b) $POCl_3$, DIEA, toluene, reflux; (c) Palladium(II)acetate, tri-2-furylphosphine, 1,4-dioxane, reflux; (d) DIEA, DCM, 1-chloroethyl chloroformate, 0 °C, 1 h then rt, isolated HCl salts.



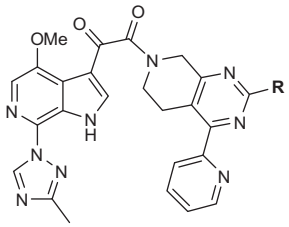
Scheme 6. Synthesis of 2-amino-substituted 4-(pyridin-2-yl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidines. Reagents and conditions: (a) sodium methoxide, MeOH, reflux 18 h, 58%; (b) $POCl_3$, reflux, 18 h, 11.5%, (c) palladium(II)acetate, tri-2-furylphosphine, 1,4-dioxane, reflux, 5 h, 71%; (d) *N*,*N*-dimethylethylenediamine, acetonitrile, reflux, 26 h, 68%; (e) 20% palladium hydroxide on carbon, 1 N HCl, methanol, H_2 (1 atm), rt, 5 days, 100%.

any advantage in terms of improving metabolic stability. Additionally, both **38** and **39** showed elevation in cytotoxicity (5.45 μM for **38** and 24.7 μM for **39**) in the assay. These compounds showed that even small structural changes at the 1-position of the THIQ ring can cause a dramatic loss in potency and that metabolism in these molecules can shift to other positions if a single soft spot is blocked.

Only two compounds, **22** and **37**, showed a significantly improved metabolic profile. Both of these compounds contained polar groups, with **22** containing a free carboxylic acid on the pyrazole at C-7 while **37** is hydroxylated at the 1-position of the THIQ ring. With these data in hand, we decided to pursue a series of compounds that would increase the polarity of the THIQ ring. Calculated *c* Log *P* values show a considerable decrease in lipophilicity when the THIQ ring is replaced by a tetrahydropyrido[3,4-*d*]pyrimidine heterocycle. Further adjustments in lipophilicity could then be realized via substitution at the 2-position of the bicyclic ring.

The synthesis of the bicyclic ring system is illustrated in Scheme 5.[32] Analogs **57**–**60** were constructed through cyclization

Table 4
Antiviral activity, cytotoxicity, *in vitro* metabolic stability and calculated Log *P* data for tetrahydropyrido[3,4-*d*]pyrimidine modifications



Compound	R	EC_{50} (nM)	CC_{50} (μM)	HLM/RLM% remaining at 10 min	Solubility (μg/mL)	*c* Log *P*
67	H	0.17	>33.3	79/81	3 (a)	0.12
68	Me	0.42	>11.1	ND	3 (a)	0.62
69	Cyclopropyl	0.02	>3.7	ND	<1 (a)	1.07
70	NMe_2	0.03	>3.7	ND	<1 (a)	1.04
71	$NHCH_2CH_2NMe_2$	69.2	52.8	ND	267 (c)	1.17

with commercially-available **40** and the substituted amidine or guanidine **41**–**44** to provide the pyrimidinones **45**–**48**. The pyrimidinone intermediate was then treated with $POCl_3$ to give the chlorides **49**–**52**. Stille coupling with 3-(tributylstannyl)pyridine followed by deprotection of the amine gave the elaborated tetrahydropyrido[3,4-*d*]pyrimidines **57**–**60** as their respective HCl salts. Alternatively, the bicyclic ring was constructed by reacting **40** with urea to give the tetrahydropyridopyrimidinedione **62** (Scheme 6). The dione **62** was converted to dichloride **63** through treatment with $POCl_3$. Stille coupling was accomplished selectively at the 4-position which then allowed substitution of the remaining chloride with *N*,*N*-dimethylethylenediamine to give the fully elaborated tetrahydropyrido[3,4-*d*]pyrimidine **65**. Deprotection via hydrogenolysis gave **66** as the HCl salt. The final deprotected amines **57**–**60** and **66** were individually coupled with **2** using TBTU to give **67**–**71**.

The unsubstituted analog in the tetrahydropyrido[3,4-*d*]pyrimidine series, **67**, showed promise as the antiviral potency was retained (EC_{50} = 0.17 nM) and the metabolic profile was improved considerably (79/81% parent remaining after a 10 min incubation with microsomes), albeit with a decrease in solubility (3 μg/mL) when compared to **5** (Table 4). The lower *c* Log *P* of **67** (0.12) seems to correlate with an improvement in free fraction when compared with **5** (8% vs 2%). Methyl substitution at the 2-position of the tetrahydropyrido[3,4-*d*]pyrimidine ring in **68** showed lower antiviral potency (EC_{50} = 0.42 nM) while substitution with cyclopropyl (**69**) or dimethylamino (**70**) groups increased potency (EC_{50} = 0.02 and 0.03 nM, respectively) but showed even less desirable aqueous solubility (<1 μg/mL). Large polar substituents such as in **71** exhibited reduced antiviral activity (EC_{50} = 69 nM) associated with a significant improvement in aqueous solubility (267 μg/mL).

Further profiling of **67** showed adequate passive membrane permeability with PAMPA assay values of 294 nm/s at pH = 7.4 and 244 nm/s at pH = 5.5;[33] consequently, this compound was advanced into rat PK studies. IV plasma clearance and the volume of distribution of **67** were 5.2 mL/min/kg (indicating low clearance) and 0.33 L/kg, respectively, after dosing at 1 mg/kg. The resulting mean terminal half life was 1.1 h and **67** had good oral exposure, with AUC_{last} = 41 μM * h and C_{max} = 10.0 μM after dosing at 5 mg/kg using a poly(ethylene glycol) 400 (PEG 400) and ethanol (90:10 v/v) vehicle. Overall, the IV and PO profile is very promising although inferior to that of **1** which exhibited a $t_{1/2}$ = 5.9 h, an AUC_{last} = 52 μM * h and a C_{max} = 6.4 μM after oral dosing at 5 mg/kg.

In summary, with the continued emergence of resistance to current HIV-1 therapies, inhibitors with differentiated modes of action will be a critical component of new HIV-1 treatments. HIV-1 attachment inhibitors show a differentiated mode of action from the current standard of care, and could be a component, especially in the population of highly treatment-experienced patients where drug resistance is more prevalent. In this communication we have examined replacements for the piperazine benzamide moiety, a critical structural component in HIV-1 attachment inhibitors. With favorable in vitro antiviral potency, the THIQ ring system was a promising starting point for modifications that could potentially allow for a low dose formulation without the need for a prodrug. THIQ analogs with modified heterocycles at the C-7 position of the azaindole varied the lipophilicity of the molecule but were unable to achieve the desired improvements to aqueous solubility and had only modest improvements in metabolic stability. Modification of the THIQ ring aimed at sterically blocking metabolism only slightly improved the in vitro metabolic profile of the series as a consequence of redirected metabolism but did not improve aqueous solubility. Introducing heteroatoms into the THIQ heterocycle led us to explore the tetrahydropyrido[3,4-*d*]pyrimidine series which lowered the *c* Log *P* of the molecule substantially. This series retained targeted antiviral potency and **67** showed a remarkable improvement in metabolic stability. However, further profiling of **67** in vivo revealed properties inferior to **1**. With these studies, we have demonstrated that a series of 6,6 bicyclic systems is a suitable isosteric replacement for the piperazine benzamide moiety in HIV-1 attachment inhibitors. Ultimately, the superior overall profile of the clinical candidate **1** precluded any further development of these bicyclic analogs.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2015.11.009.

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33. Experimental details are reported in the Supporting information.