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Heterobiaryl Human Immunodeficiency Virus Entry Inhibitors

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Previously disclosed HIV (human immunodeficiency virus) attachment inhibitors, exemplified by BMS 806 (formally BMS378806, **1**), are characterized by a substituted indole or azaindole ring linked to a benzoylpiperazine via a ketoamide or sulfonamide group. In the present report, we describe the discovery of a novel series of potent HIV entry inhibitors in which the indole or azaindole ring of previous inhibitors is replaced by a heterobiaryl group. Several of these analogues exhibited IC_{50} values of less than 5 nM in a pseudotyped antiviral assay, and compound **13k** was demonstrated to exhibit potency and selectivity similar to those of **1** against a panel of clinical viral isolates. Moreover, current structure−activity relationship studies of these novel biaryl gp120 inhibitors revealed that around the biaryl, a fine crevice might exist in the gp120 binding site. Taken in sum, these data reveal a hitherto unsuspected flexibility in the structure−activity relationships for these inhibitors and suggest new avenues for exploration and gp120 inhibitor design.

Introduction

In highly active antiretroviral therapy (HAART), potent combinations of three or more reverse transcriptase and protease inhibitors are used to suppress replication of the human immunodeficiency virus (HIV).[1] HAART has provided an effective means of prolonging the survival of AIDS patients and controlling disease progression of HIV-infected patients.[2] Nonetheless, HAART has important limitations including incomplete efficacy,[2] toxicity[3] of the component antiviral agents, and the eventual emergence of resistant virus.[4] There is therefore an urgent need for the development of anti-HIV agents with novel mechanisms of action.

One promising area of investigation is the identification of agents that inhibit viral attachment and entry into host cells.[5] HIV-1 entry is a dynamic process beginning with viral attachment to the host cell via interactions between the viral gp120 molecule and its primary (CD4) and secondary receptors (typically the CCR5 and CXCR4 members of the chemokine receptor family). Following gp120 attachment to CD4 and coreceptor binding, the viral gp41 molecule undergoes a series of structural rearrangements leading ultimately to fusion between viral and host cell membranes. Drugs targeting attachment to either CD4 or the CCR5 coreceptor or fusion have been shown to inhibit viral infection both in vitro and in vivo.[6] The approval of the first fusion inhibitor, enfuvirtide, demonstrated the therapeutic potential of targeting these early stages in the virus life cycle.[7] Additional evidence supporting virus entry as a target comes from several CCR5-binding inhibitors that have shown antiviral efficacy in the clinic,[6] including maraviroc, which was approved in 2007. A third class of viral entry inhibitors that has been shown to reduce viral load in man is represented by BMS[a] 806 (formally BMS378806, **1**, Table 1) and BMS 043 (formally BMS488043, **2**, Table 1).[8−10] **1** has been shown to prevent viral attachment by binding within the CD4-binding pocket of the viral gp120 molecule.[11]

In spite of the high level of interest in **1** and its analogues as the only known family of potent small molecule viral attachment inhibitors that act through binding to gp120, relatively little detailed structure−activity relationship data have been published. Potent inhibitors have been described that are derived from **1** by relatively conservative changes such as replacing the 4-azaindole ring with an indole or isomeric azaindole ring.[10] Certain variations in the substitution pattern of the azaindole or indole ring are tolerated, and in some cases elimination of the methyl substituent from the piperazine ring has been shown to result in only a modest decrease in potency.[12] A recent publication from these laboratories disclosed a series of potent inhibitors in which the α-ketoamide group of the aforementioned compounds is replaced by a

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[a] Abbreviations: BMS, Bristol-Myers Squibb; ELISA, enzyme-linked immunosorbent assay; ELSD, evaporative light scattering detection; NaHMDS, sodium bis(trimethylsilyl)amide; LiHMDS, lithium bis-(trimethylsilyl)amide; MCPBA, 3-chloroperoxybenzoic acid; DME, ethylene glycol dimethyl ether; DCM, dichloromethane; Tosmic, tosylmethyl isocyanide; DMSO, dimethyl sulfoxide.

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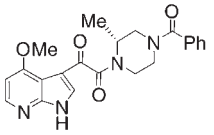
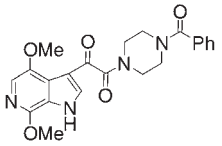
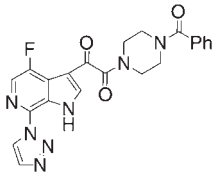
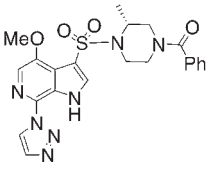
Table 1. Previously Disclosed Inhibitors

No.	Structure	M33 IC50 [b] (nM)	HIV (IIIB) ELISA IC_{50} (nM)[a]
1		8	930
2		26	2,400
3		<5	<80
4		7	215

[a] Reference 11. [b] M33 pseudotyped assay.[14]

sulfonamide group.[13] Flexible overlay calculations of a ketoamide inhibitor with a sulfonamide inhibitor revealed a single conformation of each that gave significantly better overlap of key pharmacophore features than other low energy conformations, thus suggesting a possible binding conformation for each class of inhibitor.

In the present manuscript we describe our discovery of potent HIV entry inhibitors in which the azaindole ring of previously described inhibitors is replaced by a heterobiaryl group. Among these, compound **13k** was shown to exhibit potency comparable to that of **1** against a panel of clinical viral isolates.

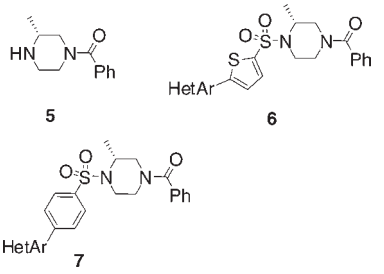
Structure−Activity Relationships

The potency of the compounds described in this work was examined using an anti-HIV-1 pseudotyped viral assay as described previously.[14] In brief, the anti-HIV-1 activity of inhibitors was determined by measuring the 50% inhibitory dose against pseudovirions containing an R5-using envelope that was cloned from a primary virus isolate. The specificity of inhibitors was assessed by their ability to prevent infection of pseudotyped viruses expressing a CD4-independent amphotropic murine leukemia virus (AMLV) envelope. Inhibitors that were shown to prevent infection of the M33 pseudovirus but were not able to inhibit AMLV pseudovirus infection at concentrations more than 100× their M33 IC_{50} were considered to be specific for inhibition of HIV. The toxicity of the compounds described in this work was assessed against U87, CD4, and CXCR4 cells. None of the compounds showed noticeable toxicity (CC_{50} > 40 000 nM). Selected compounds were also examined in a competitive ELISA format to assess their ability to inhibit the binding interaction between soluble CD4 and gp120 from the IIIB subtype of HIV. The activity was determined by measuring the 50% inhibitory dose against CD4 allowed to bind to gp120 (IIIB) via an anti-CD4 monoclonal antibody followed by a peroxidase-labeled antimouse antibody.

The activities of several previously reported inhibitors in our assays are shown in Table 1. Compound **1** exhibits single digit nanomolar potency in the M33 assay. The second generation inhibitor **2**, having an isomeric azaindole ring and a second methoxyl substituent, is slightly less potent in this assay. The incorporation of a triazole ring in the 7-position of the azaindole ring (BMS compound **3**[10b]) provided a compound with an IC_{50} less than 5 nM in the M33 assay. In the ELISA this compound was >11-fold more potent than the clinical development compounds **1** and **2**. Compound **4**, the most potent inhibitor identified in our recent study of analogues having a sulfonamide replacement for the ketoamide linker of the Bristol-Myers-Squibb compounds, exhibited potency greater than that of **1** and **2** but less than that of **3**.

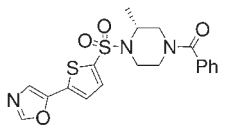
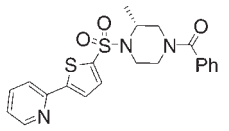
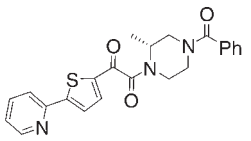
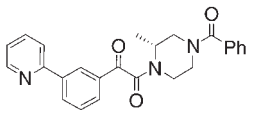
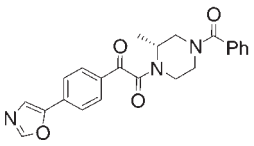
As part of our exploration of the structure−activity relationships of sulfonamide inhibitors related to **4**,[13] we undertook the preparation of a parallel synthesis library in which the amine **5** was treated with a diverse set of 90 commercially available sulfonyl chlorides. Among the most promising analogues arising from this effort were compounds **6a** and **6b**, which exhibit IC_{50} values of 1−5 μM in the M33 pseudotyped assay. In an effort to exploit these initially promising results, we then synthesized a series of 57 analogues of general structure **6** and 20 analogues of general structure **7**, but this effort did not lead to the discovery of compounds having significantly improved potency.

We then turned our efforts to the synthesis of biaryl analogues in the ketoamide series. Compound **8**, which is the ketoamide analogue of sulfonamide **6b**, failed to exhibit interesting activity in the M33 pseudotyped assay (Table 2). We then prepared the meta and para biaryls **9** and **12a**. We were gratified to find that **12a** exhibited potency approximately 5-fold greater than any previous compound in this series.

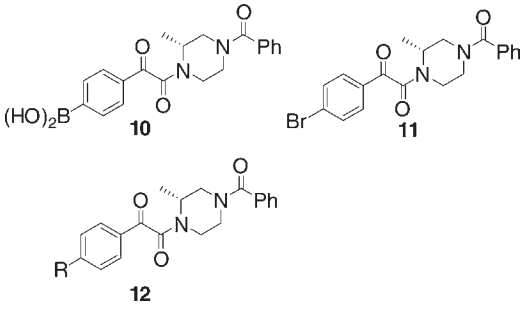


In order to rapidly map out the structure−activity relationships around the heteroaryl ring of **12a**, we prepared a library of 73 analogues of general structure **12** by performing palladium-catalyzed aryl−aryl coupling reactions on the boronic acid **10** or the aryl bromide **11**.[20,21] Each product was purified by HPLC. Purity (>95% by ELSD) and identity were established by LCMS. The 10 most active analogues from this library are shown in Table 3. These data suggest a relatively small binding pocket around

Table 2. M33 Pseudotyped Assay IC_{50} Values

No.	Structure	IC_{50} (nM)
6a		1,200
6b		5,400
8		13,000
9		23,000
12a		250

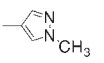
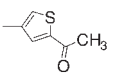
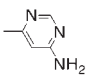
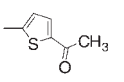
the oxazole ring of **12a** that prefers five-member rings with minimal substitution.



10 **11** **12**

Further evaluation of the SAR around the terminal heterocycle was performed by the synthesis of discrete analogues. The data for these analogues are shown in Table 4. Overall, these data support the results from the parallel synthesis-derived analogues, suggesting a relatively small binding pocket in this region. The results for compounds **12u** and **12v** suggest a preference for R to be an unsaturated ring. Small changes in the steric profile of this part of the molecule are demonstrated by the 10-fold potency difference between **12l** and **12r**. In spite of the negative effect observed for methyl substitution in this pair, similar substitution appears to be well-tolerated when the pyrazole has an isomeric mode of attachment to the phenyl ring, as in **12b**.

Table 3. M33 Pseudotyped Assay IC_{50} Values for Parallel Synthesis-Derived Analogues **12**

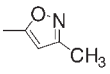
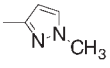
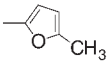
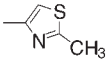
No.	-R	M33 PT IC50 (nM)
12b		110[a]
12c		320
12d		420
12e		440
12f		540
12g		910[a]
12h		1,400[a]
12i		1,600
12j		2,000
12k		2,500

[a] Racemic analogue.

In order to better understand the structure−activity relationships observed in this series, we compared the MM2-minimized structures of **12a** and the potent Bristol-Myers-Squibb inhibitor **3**. This overlay is shown in Figure 1. In this model we have assumed that the ketoamide and benzoylpiperazine groups of the two inhibitors interact with the gp120 protein in a similar manner. The trajectory of the aryl−carbonyl bond of **12a**, combined with the linear geometry of the para-substituted phenyl ring, places the oxazole ring of **12a** in a position similar to that occupied by the triazole ring of **3**. The phenyl ring closely overlays the pyrrole moiety of the azaindole ring. The model further suggests that substituents in the 2- or 3-position of the phenyl ring of **12a** could occupy a position similar to that of the pyridine moiety of the azaindole ring of **3**. We therefore decided to prepare a series of heterobiaryl analogues of general structure **13**. The screening data for these analogues are shown in Table 5.

The addition of 2- or 3-substituents to the phenyl group of our heterobiaryl inhibitors had widely varying effects on potency. In the pyrazole and methylisoxazole series, the addition of a 2-methoxyl group (**13e**, **13k**) provided a >30-fold enhancement in potency to give analogues with M33 IC_{50} values of less than 5 nM. The effect of 3-methoxyl (**13i**) on pyrazole series with 3-fold potency enhancement is contrary to that on methylisoxazole series with >2.5-fold activity decrease (**13l**). In the oxazole series, the addition of a 3-chloro substituent provided a >50-fold enhancement in potency,

Table 4. M33 IC_{50} Data for Discretely Synthesized Analogues **12**

No.	-R	M33 PT IC50 (nM)	HIV IIIB ELISA IC_{50} (nM)
12l		160[a]	2,400
12m		330	>10,000
12n		630	>10,000
12o		870[a]	6,200
12p		940[a]	>10,000
12q		1,200	>7,500
12r		1,800[a]	*N.D.*
12s		2,800	>10,000
12t		5,400	*N.D.*
12u		6,700	>10,000
12v		12,000	>10,000

[a] Racemic analogue.

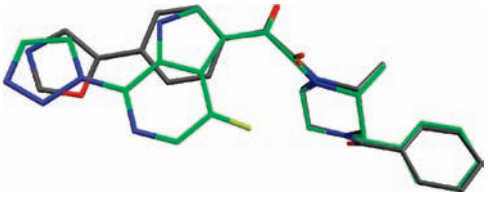


Figure 1

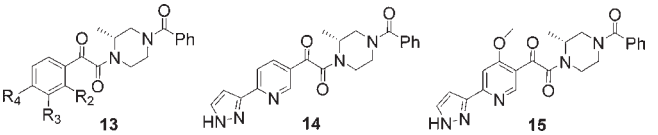
leading to a third analogue having IC_{50} < 5 nM in the M33 assay. The presence of a 2-hydroxyl group had a highly deleterious effect on potency in analogues **13d** and **13j**. Replacing the phenyl ring of inhibitor **12l** with a pyridine ring as in **14** led to a substantial reduction in potency, which might suggest an electron rich aromatic ring system is required for excellent potency. This is consistent with the presence of 2-MeO leading to a > 30-fold potency enhancement

Table 5. M33 PT and HIV IIIb ELISA IC_{50} Values for Analogues **13** and **14**

No.	R_2	R_3	R_4	M33 PT IC_{50} (nM)	HIV IIIb ELISA IC_{50} (nM)
12l	H	H		160[a]	2,400[a]
13a	CH_3	H		1,100	>10,000
13b	F	H		46	1,100
13c	Cl	H		250	4,600
13d	OH	H		2,200	>10,000
13e	OCH_3	H		<5	560
13f	NH_2	H		78	5,900
13g	$NHCH_3$	H		>10,000	*N.D.*
13h	H	CH_3		35	680
13i	H	OCH_3		56	2,500
12m	H	H		330	> 10,000
13j	OH	H		7,300	>10,000
13k	OCH_3	H		<5	230
13l	H	OCH_3		830	>10,000
13m	H	F		130	>10,000
12a	H	H		250	4,000
13n	H	Cl		<5	236
13o	H	OCH_3		50	780
14	-	-	-	1,000	>10,000

[a] Racemic analogue.

in the pyrazole and methylisoxazole series. To prove this hypothesis, we made compound **15** with MeO at position 6, which led to a 7.5-fold enhancement in potency with IC_{50} = 134nM.

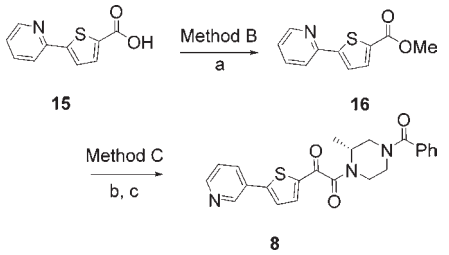


Compound **13k** was tested against a panel of clinical HIV isolate strains derived from phase II clinical trials of enfuvirtide. The derivation of the isolates for the panel and the method used for testing compound **13k** against the panel of primary isolates are described in the ref 14b. The activity of compound **13k** in a viral replication assay against a panel of clinical HIV isolate strains is shown in Table 6 along with similar data for **1** and **2**. The geometric mean IC_{50} values for **1**, **2**, and **13k** are 190, 83, and 155 nM, respectively. Heterobiaryl

Table 6. IC_{50} Values (nM) for Compounds **1**, **2**, and **13k** in Viral Replication Assays vs a Panel of Clinical HIV Isolates Strains

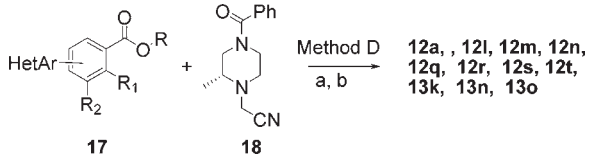
entry	virus	1	2	13k
1	584.000 017	> 10000	> 10000	> 10000
2	584.000 030	29	30	13
3	584.000 031	8016	240	8975
4	584.000 054	5533	7131	3514
5	584.000 058	38	60	22
6	584.000 060	24	14	17
7	584.000 063	46	17	25
8	584.000 066	190	11	273
9	584.000 098	394	425	301
10	584.000 220	5	4	3
11	584.000 227	423	22	1,817
12	589.000 033	27	34	11
geometric mean		190	83	155

Scheme 1[a]



[a] Reagents: (a) $(CH_3O)_2SO_2$, $LiOH \cdot H_2O$, THF; (b) NaHMDS, THF; (c) aq NaOCl.

Scheme 2[a]



[a] Reagents. D-1: (a) NaHMDS, THF; (b) aq NaOCl. D-2: (a) LiHMDS, THF; (b) MCPBA, THF.

inhibitor **13k** exhibits a spectrum of activity closely comparable to that of **1**. Bristol-Myers-Squibb's second generation inhibitor **2** exhibits better potency against several strains 3, 8, and 11 that are resistant to inhibition by **1** and **13k**.

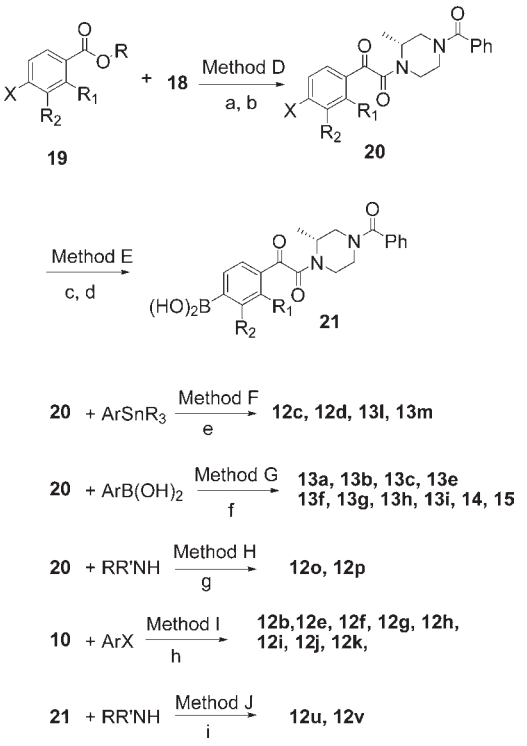
Synthesis

Compounds **6a** and **6b** were prepared by treating commercially available sulfonyl chlorides with the amine **5** (method A). Compound **8** was prepared by the route shown in Scheme 1.

Most of the other compounds described in this manuscript were prepared by one of two general strategies. The first of these involved preparing heterobiaryl carboxylic acid ester **17** and performing an oxidative coupling[15] with **18** as outlined in Scheme 2. Many of the heterobiaryl carboxylic esters were commercially available. The syntheses of others were performed using literature methods or relatively straightforward modifications of literature methods for the synthesis of related compounds.[16−18] These are described in detail in the Supporting Information.

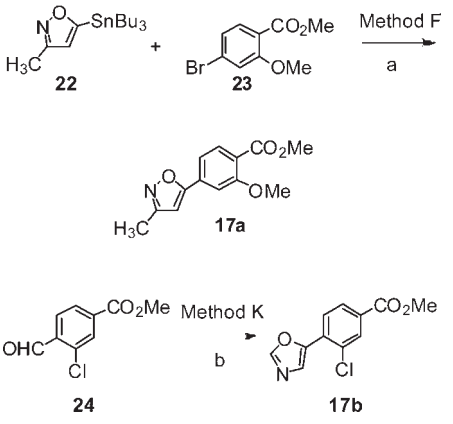
The second general strategy involved using this same oxidative coupling method to prepare a ketoamide of general structure **20** (Scheme 3). Palladium-catalyzed conversion of **20** to the corresponding boronic acids **21** was achieved

Scheme 3[a]



[a] Reagents: (a) NaHMDS, THF; (b) aq NaOCl; (c) 4,4,5,5,4′,4′,5′,5′-octamethyl[2,2′]bi[[1,3,2]dioxaborolanyl], KOAc, $PdCl_2$dppf, 75 °C; (d) $NaIO_4$, NH_4OAc, acetone/H_2O, room temp; (e) $PdCl_2(PPh_3)_2$, THF, reflex; (f) tetrakis(triphenylphosphine)palladium(0), 2 M Na_2CO_3 (aq), *t*-Bu_4NBr, toluene/H_2O (1:1); (g) Cu, KOH, 160 °C; (h) $Pd(OAc)_2$, *o*-Tol_3P, K_2CO_3, DME/H_2O 5:1; (i) $Cu(OAc)_2$, Et_3N, DCM, room temp.

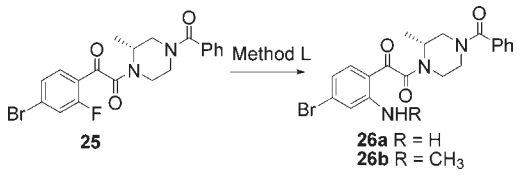
Scheme 4[a]



[a] Reagents: (a) $PdCl_2(PPh_3)_2$, THF, ref; (b) Tosmic, Na_2CO_3, MeOH.

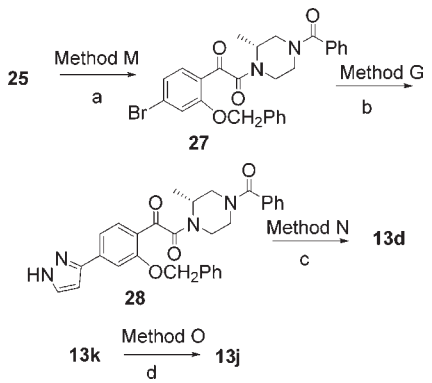
using method E.[19] Intermediates of types **20** and **21** were then used to prepare the final analogues using a variety of transformation types. In method F, halides **20** were coupled with arylstannanes under Stille conditions to provide final analogues.[20] In methods G and I aryl−aryl bonds were formed using the Suzuki protocol.[21] Compounds **12o**, **12p**, **12u**, and **12v** were prepared by copper-mediated coupling reactions between an aromatic or aliphatic amine and intermediates of general structure **20** or **21** using literature procedures (methods H and J).[22] All of the arylstannanes, arylboronic acid, aryl halides, and amines required for these transformations were commercially available or were synthesized using literature procedures.

Scheme 5[a]



[a] Reagents: (a) amines ($NH_3 \cdot H_2O$, **26a**; $MeNH_2$, **26b**), DMSO, 80 °C.

Scheme 6[a]



[a] Reagents: (a) BnOH, K_2CO_3, DMSO; (b) pyrazole-3-boronic acid, tetrakis(triphenylphosphine)palladium(0), 2 M Na_2CO_3(aq), *t*-Bu_4NBr, toluene/H_2O (1:1); (c) H_2/Pd−C, THF; (d) $AlCl_3$, DCM, room temp.

Most of the intermediates **17** used in this work are known in the literature, and many others were prepared by esterification of previously described carboxylic acids. The previously unknown ester **17a** was prepared by a Stille coupling, and previously unknown ester **17b** was prepared by formation of the oxazole ring.[17−18] These routes are shown in Scheme 4.

Intermediates **26a**,**b** were prepared by nucleophlic aromatic substitution reactions of **25** in DMSO at 80 °C (Scheme 5). Hydroxylated analogues **13d** and **13j** were formed by debenzylation and demethylation reactions, respectively (Scheme 6).

Conclusions

As part of a research effort directed at the discovery of novel inhibitors of viral entry that target the interaction of the viral gp120 protein with its primary coreceptor CD4, we have examined the utility of heterobiaryl groups as replacements for the indole and azaindole rings that are invariant motifs in previously described inhibitors. This effort led to the discovery of a novel series of inhibitors having a 4-heteroaryl-substituted phenyl in place of the azaindole ring of the previously described inhibitor. Optimization of the identity of the heteroaryl ring and of the substitution pattern on the phenyl ring led to several inhibitors with $IC_{50} < 5$ nM in the M33 pseudotyped antiviral assay. Compound **13k** exhibited potency and selectivity comparable to that of **1** against a panel of clinical viral isolates. Moreover, current structure−activity relationship studies of these novel biaryl gp120 inhibitors revealed that around the biaryl, a fine crevice might exist in the gp120 binding site. Taken in sum, these data reveal a hitherto unsuspected flexibility in the structure−activity relationships for these inhibitors and suggest new avenues for exploration and inhibitor design.

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Supporting Information Available: Experimental procedures and characterization data for newly synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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