Design and Synthesis of Human Immunodeficiency Virus Entry Inhibitors: Sulfonamide as an Isostere for the α-Ketoamide Group

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The crystal structures of many tertiary α-ketoamides reveal an orthogonal arrangement of the two carbonyl groups. Based on the hypothesis that the α-ketoamide HIV attachment inhibitor BMS 806 (formally BMS378806, **26**) might bind to its gp120 target via a similar conformation, we designed and synthesized a series of analogs in which the ketoamide group is replaced by an isosteric sulfonamide group. The most potent of these analogs, **14i**, demonstrated antiviral potency comparable to **26** in the M33 pseudotyped antiviral assay. 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 conformations and thus suggest a possible binding conformation for each class.

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 recent approval of the first fusion inhibitor, enfuvirtide, has demonstrated the therapeutic potential of targeting these early stages in the virus lifecycle.[7] Additional evidence supporting virus entry as a target comes from several CCR5-binding inhibitors that have shown antiviral efficacy in the clinic[6] and from gp120-binding viral attachment inhibitors BMS 806 (formally BMS378806, **26**, Table 1) and BMS 043 (formally BMS488043, **27**, Table 1) that have demonstrated the ability to reduce viral loads in man.[8–10]

The small molecule attachment inhibitor, **26**, has been shown to bind within the CD4-binding pocket of the viral gp120 molecule.[11] Crystallographic analysis of compounds containing an Ar-(C═O)-(C═O)-NRR′ fragment[12] suggest a preferred conformation of the ketoamide group in which the two C═O bonds adopt a roughly orthogonal arrangement. This structural arrangement is likely to be an important component in the ability of this molecule to interfere with the CD4-binding pocket and thus prevent HIV infection. Based on the hypothesis that an SO_2 group could mimic the arrangement of the ketoamide oxygens in such a conformation, we undertook the synthesis of a series of analogs in which the two carbonyls of the previously reported ketoamide inhibitors are replaced by a sulfonyl group. This manuscript describes our discovery of sulfonamide HIV entry inhibitors exhibiting nanomolar potency and improved breadth of activity over related ketoamide analogs against clade B HIV-1 isolates. The isosteric replacement demonstrated in this work may prove generally useful in the optimization of lead structures containing the ketoamide group.

Synthesis. Indole-3-sulfonyl chlorides were prepared by sulfonylation of the corresponding indoles with pyridine−sulfur trioxide complex, followed by chlorination with thionyl chloride or phosphorus oxychloride, as described in Scheme 1 (method A). Azaindole-3-sulfonyl chlorides were prepared by chlorosulfonylation of the corresponding azaindole with a 5-fold or greater excess of chlorosulfonic acid (method C). The rates of the sulfonylation and chlorosulfonylation reactions are substrate-dependent, and the best results were obtained by performing the reactions at the lowest temperature at which a convenient reaction rate could be achieved. The sulfonyl chlorides thus obtained were treated with secondary amines in the presence of Hunig's base to provide sulfonamides (method B). Mono-*N*-acylated piperazines were prepared using literature protocols.[13] Many of the sulfonyl chlorides prepared in this work decomposed on storage, and were therefore normally converted

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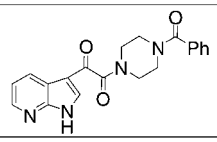
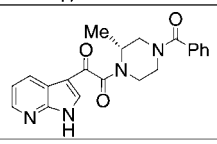
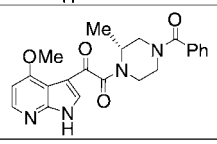
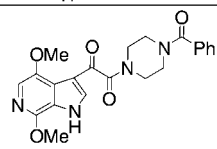
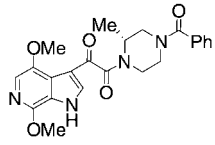
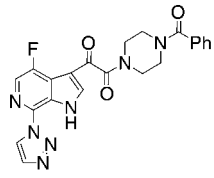
Table 1. M33 Pseudotyped Assay IC_{50} Values for Ketoamide Inhibitors

No.	Structure	IC_{50} (nM)
24		520
25		30
26		8
27		26
28		5
29		<5

to sulfonamides immediately without characterization. The indole and azaindole starting materials used in this work were commercially available or were prepared from nitropyridines using literature methods.[14]

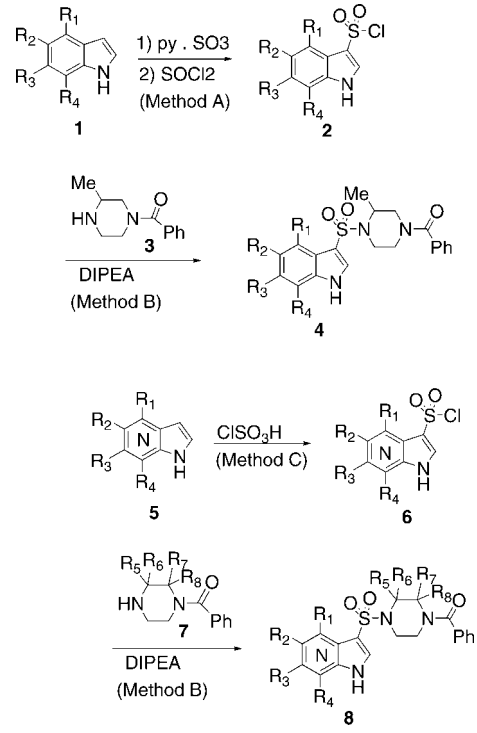
For SAR studies involving variation of the benzoyl group or substitution on the piperazine ring, certain compounds were prepared by acylation of intermediates of general structure **11**, as described in Scheme 2 (method E). These intermediates were in turn prepared by cleavage of the *tert*-butoxycarbonyl protecting group from intermediates of general structure **10** (method D). The mono-Boc piperazines used in this work were commercially available.

Nucleophilic aromatic substitution reactions were used to prepare a number of analogs of general structures **14** and **16** from intermediates of structures **13** and **15**, as described in Scheme 3. In this Scheme, Y-H is a five-member aromatic heterocycle having a free N-H group. Intermediates **13** and **15** were prepared according to Scheme 1.

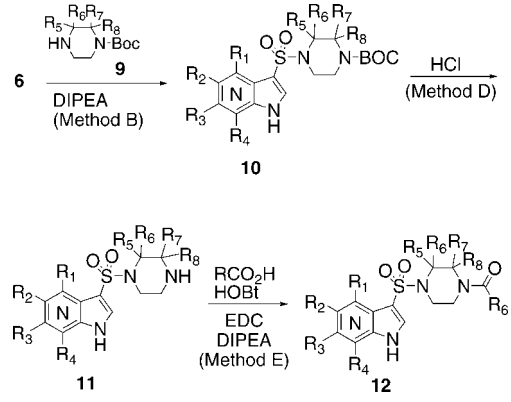
The palladium-catalyzed cyanation[15] of chloride **13a** provided the nitrile **17**, which was used to prepare a number of analogs having C-linked heterocycles attached to C-7 of the azaindole ring (Scheme 4). Alternatively, treating **13a** with sodium azide under microwave heating gave the aryl azide **21**, which was used to prepare certain analogs containing an N-linked 1,2,3-triazole substituent (Scheme 5).

Palladium-catalyzed coupling reactions between chloride **13a** and heteroaromatic boronic acids and trialkyltin derivatives were used to prepare several analogs, as described in Scheme 6.[16]

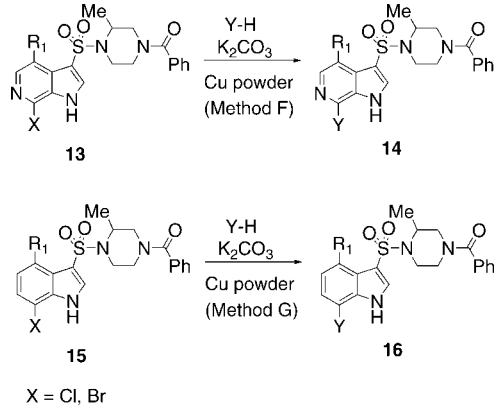
Scheme 1



Scheme 2



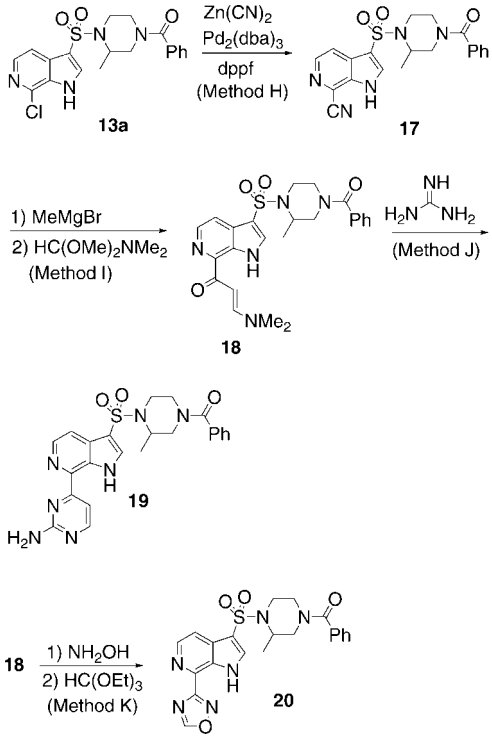
Scheme 3



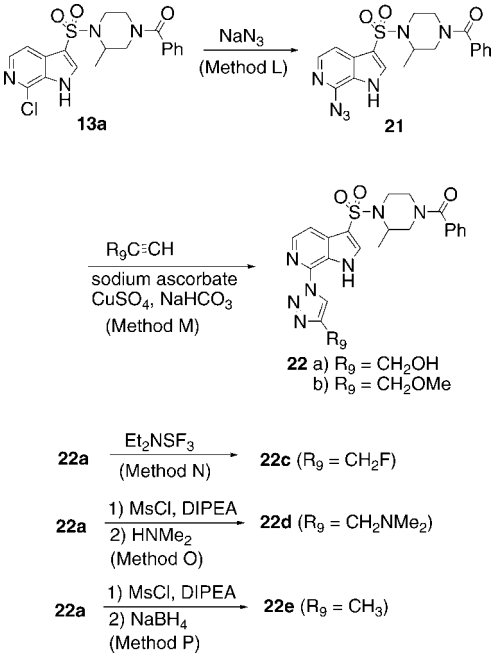
Ketoamide inhibitors **24**–**29** (Table 1) were prepared using methods described previously by others.[10]

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.[17] In

Scheme 4

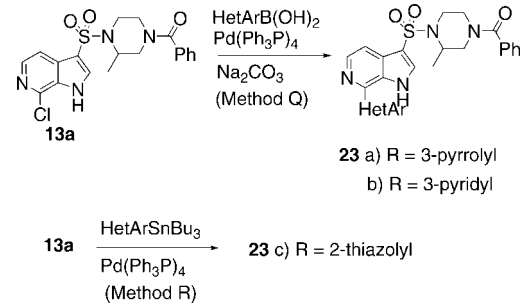


Scheme 5



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

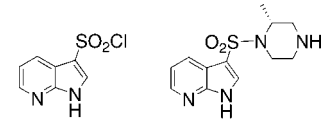
Scheme 6



assessed against U87, CD4, and CXCR4 cells. None of the compounds showed noticeable toxicity (CC_{50} > 40000 nM).

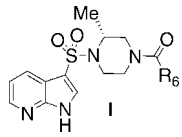
To facilitate comparison between the sulfonamides prepared in the course of this work and compounds reported previously by others,[10] we first examined the series of ketoamide inhibitors described in Table 1. Compounds **26** and **27** are clinical development compounds from Bristol-Myers-Squibb. Compound **25** differs from **24** by the addition of an (*R*)-configured methyl group to the piperazine ring adjacent to the ketoamide linker. This change led to a 17-fold enhancement in potency. Other comparisons, for example, **28** versus **27**, indicate that the effect of adding an (*R*)-methyl substituent on the piperazine ring is dependent on the nature of the azaindole ring. The addition of a methoxy group to the 4-position of the azaindole ring of **25** as in compound **26** provides a 4-fold improvement in potency in the psuedotype assay. Compound **29** and its prodrugs are the subject of several recently published patent applications from Bristol- Myers-Squibb.[10]

In the original test of our hypothesis that a sulfonyl group could replace the ketoamide group of the Bristol-Myers-Squibb entry inhibitors, we synthesized compound **12a** (Table 2) and examined its activity in the pseudotype assay. Compound **12a** exhibits an IC_{50} value of 860 nM, approximately 30-fold less potent than the corresponding ketoamide **25**. To explore SAR differences that might potentially arise from replacing the two atom linker of the ketoamide series with a single atom linker, as in the sulfonamides, two parallel synthesis libraries were prepared. In the first of these, more than 150 sulfonamides were prepared by treating the sulfonyl chloride **6a** with a diverse set of cyclic secondary amines. None of the resulting sulfonamides exhibited IC_{50} < 15000 nM.

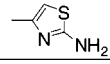
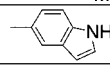
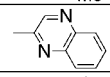
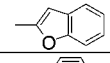
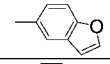
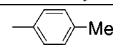
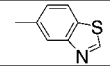


A second library was prepared by acylation of the amine **11a** (or its racemate) with a set of 285 carboxylic acids. The set of carboxylic acid building blocks for this library contained a diverse set of optionally substituted aromatic, heteroaromatic, arylalkyl, heteroarylalkyl, heterocyclic, alkyl, and cycloalkyl carboxylic acids. Representative analogs from this library exhibiting IC_{50} < 20000 nM are shown in Table 2. Most of the analogs from this library exhibiting measurable activity were derived from five-member heteroaromatic carboxylic acids having one or no substituents attached to the heteroaromatic ring. Only representative examples of these five-membered heteroaromatic analogs are shown in the table. Other active analogs were derived from fused heteroaromatic rings or optionally substituted six-member aromatic and heteroaromatic

Table 2. M33 Pseudotyped Assay IC_{50} Values for Compounds of the General Structure **I**



I

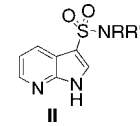
No.	R_6	IC_{50} (nM)
12a		860
12b		420
12c		520
12d		1900
12e		2,300
12f		4,600[a]
12h		4,600[a]
12i		2,400
12j		5,400[a]
12k		3,000
12l		3,300
12m		10,000[a]
12n		12,400[a]
12o		12,600[a]
12p		8,400
12q		9,100

[a] Racemic analog.

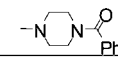
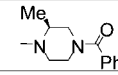
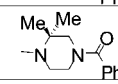
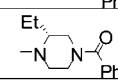
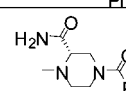
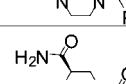
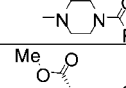
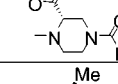
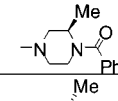
rings. Notably, none of these analogs is significantly more potent than **12a**, and the most potent analogs contain acyl groups that are approximately isosteric with benzoyl.

The effect of varying the piperazine ring substituents is described in Table 3. Compound **8b** is the enantiomer of **12a**. It exhibits an IC_{50} > 20000 nM, demonstrating that the preferred configuration of the piperazine methyl group is the same as that previously reported for ketoamide entry inhibitors. Complete elimination of the piperazine methyl substituent led to a 25-fold reduction in potency (compound **8a**), similar to the 17-fold potency difference between ketoamide inhibitors **24** and **25**. These results, combined with those described in the previous paragraph, suggest a similar binding mode for the two series. Increasing the size of the substituent, as in compounds **8d**–**8g**, adding a second methyl group, as in compound **8c**, or moving the methyl group to a different position on the piperazine ring (compounds **8h**, **8i**) had a negative effect on potency, which might indicate limited binding space in the corresponding pocket area of gp120.

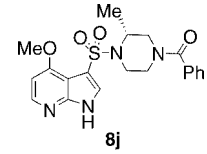
Table 3. M33 Pseudotyped Assay IC_{50} Values for Analogs of the General Structure **II**



II

No.	-NRR'	IC_{50} (nM)
8a		22,000
8b		>20,000
8c		>20,000
8d		16,000
8e		>20,000
8f		>20,000
8g		>20,000
8h		13,000
8i		>20,000

We then turned our attention to the more synthetically challenging task of evaluating changes to the azaindole ring. Our first effort in this arena was to synthesize compound **8j**, the sulfonamide analog of the BMS clinical compound **26**. We were disappointed to find that **8j** is substantially less active than the prototype **12a**, a result that contrasts with the potency-enhancing effect of this substitution in the ketoamide series.

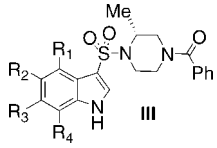


8j
IC_{50} = 9,200 nM

Table 4 shows the SAR of a series of analogs in which the 7-azaindole ring of **12a** is replaced by an indole ring. The unsubstituted indole ring of **4a** gave a 2-fold improvement in potency relative to **12a**, and the addition of a fluorine substituent in the 4-position gave a further reduction of the IC_{50} to 200 nM (compound **4b**). Examining a variety of other indole ring substitution patterns failed to provide significant improvements in potency. Compounds **4c** and **16a**−**c**, having a fluorine in the 4-position and a fluorine or heterocyclic group in the 7-position, exhibited potency approximately similar to or less than that of **4a**. The 4-methoxy indole derivative **4e** exhibited a dramatically reduced potency relative to the unsubstituted indole **4a**, in close analogy to what was observed in the 7-azaindole series.

The SAR of 6-azaindole sulfonamide analogs is described in Table 5. Analogs **8j** and **8k**, substituted in the 5-position of

Table 4. M33 Pseudotyped Assay IC_{50} Values for Analogs of the General Structure **III**



III

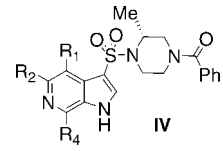
No.	R_1	R_2	R_3	R_4	IC_{50} (nM)
4a	H	H	H	H	430
4b	F	H	H	H	200
4c	F	H	H	F	370
4d	F	F	F	F	4,700
4e	OMe	H	H	H	4,200
4f	H	F	H	H	3,600
4g	H	CN	H	H	>20,000
4h	H	F	H	CN	10,000
16a	F	H	H		150
16b	F	H	H		200
16c	F	H	H		500

the azaindole ring, failed to exhibit detectable activity. Analog **8l**, which is monosubstituted with chlorine in the 7-position, gave only marginally better results. We then decided to direct our efforts toward the synthesis of analogs having a heteroaromatic substituent in the 7-position of the 6-azaindole ring. Among the C-linked heteroaromatic rings examined, the best results were obtained with a pyrazol-3-yl substituent (compound **23a**), which provided an IC_{50} value of 140 nM. Several N-linked heteroaromatic substituents were then examined. Pyrazole, imidazole, 1,2,4-triazole, and 1,2,3-triazole substituents in the 7-position of the azaindole ring increased potency from 4-fold to 32-fold relative to **12a**, with 1,2,3-triazole providing an IC_{50} value of 27 nM (compound **14e**). In hope of building on this result, we prepared a series of analogs **22a**–**22e** bearing a functionalized 1,2,3-triazole substituent. None of these analogs exhibited properties superior to those of **14e**. Lastly, we examined the effect of combining 4-fluoro and 7-heterocycle substitution on the azaindole ring. Fluorinated compounds **14f**–**14i** exhibit potency improvements of 2- to 4-fold relative to their nonfluorinated counterparts. The best of these, compound **14i** exhibits an IC_{50} of 7 nM.

The racemic version of compound **14e** was evaluated against a panel of laboratory-adapted strains in a viral replication assay. The data from this study are presented along with the Bristol-Myers-Squibb clinical development compound **26** in Table 6. Overall, racemic **14e** is somewhat less potent than **26** and exhibits a slightly different profile, with up to 2∼10× improved potency against certain individual strains.

Conformational Modeling of Sulfonamide and Ketoamide Entry Inhibitors. To obtain a better understanding of the structural features required for binding, flexible overlay calculations were performed for the sulfonamide inhibitor **12a** and the ketoamide inhibitor **25** using the algorithm and default parameters incorporated in the MOE software suite.[18,19] In this protocol, each atom is assigned a pharmacophore descriptor

Table 5. M33 Pseudotype Assay IC_{50} Values for Analogs of the General Structure **IV**[a]



IV

No.	R_1	R_2	R_4	IC_{50} (nM)
8j	H	OMe	H	>40,000[a]
8k	H	Cl	Cl	>40,000[a]
8l	H	H	Cl	11,000[a]
14a	H	H		80 160[a]
14b	H	H		300[a]
14c	H	H		150 200[a]
14d	H	H		240[a]
14e	H	H		27 54[a]
14f	F	H		620
14g	F	H		36
14h	F	H		80[a]
14i	F	H		7
19	H	H		500[a]
20	H	H		1,240[a]
22a	H	H		250
22b	H	H		580[a]
22c	H	H		240
22d	H	H		1,100[a]
22e	H	H		860[a]
23a	H	H		140[a]
23b	H	H		640[a]
23c	H	H		500[a]

[a] Racemic analog.

(aromatic, donor, acceptor, hydrophobe) according to the PATTY rules,[20] and the overlay scoring function is based on a method that approximates molecular shape as a sum of Guassian densities. The conformation of each molecule is randomly perturbed and then optimized against a function that includes terms describing both the extent of overlap of pharmacorphore features and the conformational energy of the individual molecules. Conformational searching is continued until a

Table 6. IC_{50} Values (nM) for Compounds **26** and (+/−)-**14e** in Viral Replication Assays vs a Panel of Laboratory-Adapted HIV Strains

entry	virus	**26**	**14e**
1	584.000220	4	2
2	584.000063P1B	37	460
3	208.000923	1400	465
4	589.000049	6	46
5	589.000821	2800	330
6	589.000033	28	492
7	584.000016	40	513
8	584.000030	31	267
9	584.000039	400	1800
10	584.000058	58	1400
11	584.000088	14	116
12	584.000241	118	8
	geometric mean	64	178

predetermined (in this case, 1000) number of successive attempts to generate novel overlays provides only duplicates of previously identified configurations.

The highest-ranked overlay between **12a** and **25** is shown in Figure 1. In this alignment, the piperazine ring and the benzamide groups of the two compounds are tightly overlaid. The sulfonamide group of **12a** is in close proximity to the ketoamide group of **25**, with one sulfonamide oxygen tightly overlaid on the amide oxygen. The other sulfonamide oxygen lies about 1.1 Å from the ketone oxygen. The azaindole rings of the two molecules are closely superimposed. A second highly ranked overlay differs from the one shown only in that there is a 180° rotation around the bond between the piperazine ring and the benzoyl group in each inhibitor. Other overlays provided a much poorer overlap of the azaindole rings, of the benzoylpiperazine groups, or of the piperazine ring methyl substituents. These results are congruent with the close similarity of the SAR trends observed in the two series.

The calculated steric energies of the sulfonamide and ketoamide conformers in Figure 1 are 9.5 and 10.5 kcal/mol, respectively, relative to their global conformational minima. When these conformers are individually minimized without similarity constraints, the resulting local conformational minima exhibit E_{rel} values of 0.2 and 0.6 kcal/mole compared to their respective global conformational energy minima. An overlay of these minimized structures is shown in Figure S1 (Supporting Information). Overall, the results of these calculations support the hypothesis that certain energetically accessible conformations of the sulfonamide **12a** and the ketoamide **25** have similar dispositions of potentially pharmacophoric aromatic, lipophilic, and hydrogen bond-acceptor groups. The single atom SO_2 linker of the sulfonamide is able to direct its attached azaindole and piperazine rings in a manner remarkably similar to that of the two-atom ketoamide group. These results provide a rationale for the activity of the sulfonamide compounds prepared in this work and suggest plausible binding conformations for the sulfonamide **12a** and the ketoamide **25**.

Conclusions

Based on the hypothesis that the α-ketoamide linker of previously reported HIV entry inhibitors adopts a twisted conformation similar to that observed in the crystal structures of related compounds, we designed and synthesized a series of analogs in which the ketoamide group is replaced by a sulfonamide group. The most potent of these analogs, compound **14i**, exhibits an IC_{50} value of 7 nM in the M33 pseudotyped viral attachment assay. A related analog, **(+/−)-14e**, exhibited approximately one-half the potency of the Bristol-Myers-Squibb clinical development compound **26** in viral replication assays

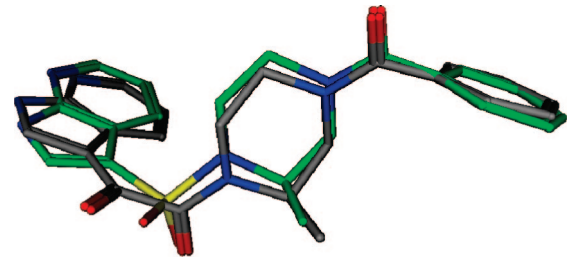


Figure 1

against a panel of laboratory-adapted strains. Parallels between the structure–activity relationship of the sulfonamides described in the present work and that of the ketoamide inhibitors described previously suggest a similar binding mode for the two series. Flexible overlay calculations revealed essentially a single conformer of each series that can mutually overlay and thus suggest possible binding conformations for each inhibitor type.

In addition to the implications of this work for the development of novel HIV entry inhibitors, our demonstration of the successful application of a sulfonamide group as an isosteric replacement for the α-ketoamide group may prove useful in other drug discovery programs. A search of the MDDR[21] for α-ketoamides that are currently marketed or in clinical development as human therapeutics revealed only compounds in which the ketone carbonyl of the ketoamide group is sterically hindered or conjugated to a strongly electron-donating aromatic ring. A possible explanation for this result is that the electrophilic carbonyl group of other α-ketoamides has prevented their advancement through preclinical development. The isosteric replacement demonstrated in this work may prove generally useful in the optimization of lead structures containing this group.

Experimental Section

General Chemistry. HPLC purification: Compounds requiring HPLC purification were purified on a system using a Sedex 75 ELSD as the fraction-determining detector, the Gilson 215 as autosampler and fraction collector, and Gilson 321 pumps. Mobile phases used were one of the following: (1) water/acetonitrile/0.05% trifluoroacetic acid; (2) 20 mM ammonium formate at pH 4–6 and acetonitrile; or (3) 0.1% ammonium hydroxide and acetonitrile at pH 9.0. Columns used were either Phenomenex Gemini, 5 μm, 21.2 × 50 mm or Peeke Scientific Ultro 60 C18 5 μm, 20 mm × 50 mm.

Analytical LCMS. Compounds were analyzed on an Applied Biosystems/Sciex 150EX single quad mass spectrometer in positive ion mode using either an ESI (electrospray ionization) source or an APCI (atmospheric pressure chemical ionization) source. The scan range is 100–1000 amu. The mobile phase used was one of the above, as described in General Chemistry. Sedex 75 ELSD and Agilent PDA (photodiode array) UV detection was used. The column most commonly used was the Phenomenex Gemini, 5 μm, 4.6 × 50 mm. When necessary to achieve greater separation of close-eluting impurities, other columns were used, including the Phenomenex Gemini, 5 um, 4.6 × 100 or 250 mm, the Kromasil 100, C18, 5 μm, 4.6 × 100 or 250, and the DuraGel HS, 5 μm, phenyl 4.6 × 250 mm from Peeke Scientific. Mass calculations were made using the monoisotopic mass for the compound.

7-Bromo-4-fluoro-1*H*-indole-3-sulfonyl Chloride (Method A). A mixture of 7-bromo-4-fluoro-1*H*-indole (3.71 g, 0.017 mol) and sulfur trioxide−pyridine complex (2.76 g, 0.017 mol) in anhydrous pyridine (200 mL) was refluxed under stirring for 2 h and then was cooled to RT, diluted with water (400 mL), and washed with Et_2O (2 × 250 mL). The aqueous phase was

evaporated to give crude 7-bromo-4-fluoro-1*H*-indole-3-sulfonic acid pyridinium salt, which was used in the next step without further purification.

Crude 7-bromo-4-fluoro-1*H*-indole-3-sulfonic acid pyridinium salt from the previous step was dissolved in 30 mL of a 1:1 sulfolane−acetonitrile mixture. The solution was cooled to 0 °C, and phosphorus oxychloride (3.5 mL) was added dropwise under stirring. Then the reaction mixture was heated to 70 °C, kept under stirring for 40 min, and then cooled to 0 °C. Cold water (50 mL) was added dropwise. The precipitate was filtered, washed with water, and dried under reduced pressure to afford 7-bromo-4-fluoro-1*H*-indole-3-sulfonyl chloride (2.84 g, 53% per two steps). ^{1}H NMR ($CDCl_3$): δ 9.06 (s, 1H, H-indole), 8.04 (d, J = 3.2 Hz, 1H), 7.49 (dd, $J_{H\text{-}H}$ = 8.6 Hz, $J_{H\text{-}F}$ = 4.7 Hz, 1H) 7.02 (dd, $J_{H\text{-}H}$ = 8.6 Hz, $J_{H\text{-}F}$ = 9.8 Hz, 1H).

(+/−)-[4-(7-Chloro-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl)-3-methyl-piperazin-1-yl]-phenyl-methanone (Method B). A mixture of 7-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl chloride (1.5 g, 6.0 mmol), (3-methyl-piperazin-1-yl)-phenyl-methanone (1.33 g, 6.5 mmol), and NEt_3 (0.66 g, 6.5 mmol) in CH_2Cl_2 (50 mL) was refluxed under stirring until the starting sulfonyl chloride disappeared (TLC monitoring, MeOH/$CHCl_3$ 5:95). The solution was cooled to RT, washed with brine, and dried with Na_2SO_4. The solvent volume was reduced by 75% by evaporation at reduced pressure. The residue was passed through a thin layer of silica gel (eluent: 10% MeOH/$CHCl_3$). The solvent was evaporated to give [4-(7-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl)-3-methyl-piperazin-1-yl]-phenyl-methanone (2.0 g, 81%). ^{1}H NMR (DMSO-d_6): δ 13.11 (s, 1H, H-indole), 8.29 (s, 1H), 8.11 (d, J = 5.4 Hz, 1H), 7.73 (d, J = 5.4 Hz, 1H), 7.40 (m, 3H, C_6H_5), 7.30 (m, 2H, C_6H_5), 4.37–3.87 (br signal, 2H), 3.79–3.38 (br signal, 2H), 3.22–3.09 (m, 1H), 3.06–2.64 (br signal, 2H), 1.08–0.79 (br signal, 3H, CH_3). LCMS: calcd for $C_{19}H_{19}ClN_4O_3S\cdot H^+$, 419.1; found, 419.0.

7-Chloro-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl Chloride (Method C). 7-Chloro-6-azaindole (8.0 g, 0.0524 mol) was added in small portions to chlorosulfonic acid (40 mL) at 0 °C under stirring. Then the reaction mixture was slowly heated to 120 °C (higher temperatures reduced the yield) and kept until the starting 7-chloro-6-azaindole disappeared (1.5–2 h). The reaction was monitored by TLC (5% MeOH/$CHCl_3$). To do this, a sample of the reaction mixture was treated with ice–water. The precipitate was filtered, washed with water, dissolved in methanol and analyzed by TLC. The reaction mixture was cooled and poured into ice–water. The precipitate was separated by filtration, washed with water several times, and vacuum-dried under P_2O_5 to give 7-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl chloride (8.3 g, 62%). ^{1}H NMR (DMSO-d_6): δ 12.46 (s, 1H, H-indole), 8.02 (d, J = 5.9 Hz, 1H), 7.81 (m, 2H).

Parallel Synthesis of Amides (Method D and E), (+)-[4-((7-Azaindole)-1*H*-3-sulfonyl)-3-methyl-piperazin-1-yl]-*t*-butyl-carboamide. Compound **10** from method B was dissolved in 20 mL of 4 M HCl in dioxane and stirred at room temperature for 2 h. The mixture was concentrated to ¼ the original volume and diluted with 12 mL of diethyl ether. The precipitate was filtered and dried under high vacuum to offer amine HCl salt (compound **11**). LCMS: calcd for $C_{12}H_{16}N_4O_2S\cdot H^+$, 281.1; found, 281.3. Purity (ELSD): 98%. The above compound was dissolved in DMF to give ~0.5 M solutions. The acids (95 uMol) were placed in 48-well plates. *N*-methylmorpholine (75 uL), a 0.5 M solution of HBTU in DMF (95 uM), and a 0.5 M solution of amine **1** in DMF (80 uM) were added sequentially into each tube. The plates were covered with a Cap Mat. The reaction mixtures were agitated for 10–20 s with the use of a Vortex shaker and kept at 40 °C for 24 h on a J-Chem heater. Water (50 uL) was added to each well, and the solvents were evaporated in a Savant evaporator for ~5 h at 65 °C. DCM (2 mL) and 5% NaOH in water (500 uL) were added to each well. The reaction mixtures were thoroughly stirred on a Vortex shaker and then passed through Celite columns packed in DCM. The DCM solutions were evaporated in an oven at 45 °C for 5 h. The residues were dissolved in DMSO and purified by reverse-phase chromatography.

[3-Methyl-4-(7-[1,2,3]triazol-1-yl-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl)-piperazin-1-yl]-phenyl-methanone and [3-Methyl-4-(7-[1,2,3]triazol-2-yl-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl)-piperazin-1-yl]-phenyl-methanone, Method F. A mixture of 4-(7-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl)-3-methyl-piperazin-1-yl]-phenyl-methanone (0.21 g, 0.5 mmol), Cu powder (0.064 g, 1 mmol), 1,2,3-triazole (1.04 g, 0.87 mL, 15 mmol), and powdered KOH (0.056 g, 1 mmol) was heated to 160 °C and kept (under an argon atmosphere) under stirring at this temperature until the starting sulfonamide disappeared (~3 h, TLC monitoring, 5% MeOH/$CHCl_3$). The reaction mixture was then cooled to RT, diluted with EtOAc (~2 mL), placed onto a silica gel column, and eluted with EtOAc/hexane (9:1). Fractions containing the first product (together with 1,2,3-triazole) were collected, evaporated, and diluted with water. The precipitate was filtered, washed with water and ether, and dried to give [3-methyl-4-(7-[1,2,3]triazol-1-yl-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl)-piperazin-1-yl]-phenyl-methanone (0.075 g, 30%). Then eluent was changed to 10% MeOH/$CHCl_3$ and fractions containing the second product were collected, and evaporated to give [3-methyl-4-(7-[1,2,3]triazol-2-yl-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl)-piperazin-1-yl]-phenyl-methanone (0.075 g, 30%). [3-Methyl-4-(7-[1,2,3]triazol-1-yl-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl)-piperazin-1-yl]-phenyl-methanone: ^{1}H NMR (DMSO-d_6): δ 12.68 (s, 1H, H-indole), 9.05 (d, J = 1.0 Hz, 1H), 8.30 (d, J = 5.6 Hz, 1H), 8.15 (s, 1H), 8.12 (d, J = 1.0 Hz, 1H), 7.87 (d, J = 5.6 Hz, 1H), 7.39 (m, 3H, C_6H_5), 7.30 (m, 2H, C_6H_5), 4.40–4.00 (br signal, 2H), 3.84–3.39 (br signal, 2H), 3.25–3.14 (m, 1H), 3.10–2.69 (br signal, 2H), 1.06–0.89 (br signal, 3H, CH_3). LC/MS calcd for $C_{21}H_{21}N_7O_3S$ $[M + 1]^+$, 452; found, 452. [3-Methyl-4-(7-[1,2,3]triazol-2-yl-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl)-piperazin-1-yl]-phenyl-methanone: ^{1}H NMR (DMSO-d_6): δ 12.50 (s, 1H, H-indole), 8.33 (s, 2H), 8.28 (d, J = 5.4 Hz, 1H), 8.15 (s, 1H), 7.84 (d, J = 5.4 Hz, 1H), 7.39 (m, 3H, C_6H_5), 7.30 (m, 2H, C_6H_5), 4.38–4.00 (br signal, 2H), 3.84–3.35 (br signal, 2H), 3.24–3.10 (m, 1H), 3.07–2.69 (br signal, 2H), 1.10–0.89 (br signal, 3H, CH_3). LC/MS calcd for $C_{21}H_{21}N_7O_3S$ $[M + 1]^+$, 452; found, 452.

[4-(4-Fluoro-7-[1,2,4]triazol-1-yl-1*H*-indole-3-sulfonyl)-3-methyl-piperazin-1-yl]-phenyl-methanone, Method G. [4-(4-Fluoro-7-[1,2,4]triazol-1-yl-1*H*-indole-3-sulfonyl)-3-methyl-piperazin-1-yl]-phenyl-methanone (55.6%) was prepared according to the procedure above, using [4-(7-bromo-4-fluoro-1*H*-indole-3-sulfonyl)-3-methyl-piperazin-1-yl]-phenyl-methanone and 1,2,4-triazole, and 0→3% MeOH in CH_2Cl_2 as eluent. ^{1}H NMR (DMSO-d_6): δ 12.25 (s, 1H, H-indole), 9.25 (s, 1H), 8.38 (s, 1H), 7.94 (s, 1H), 7.70 (dd, $J_{H\text{-}H}$ = 8.6 Hz, $J_{H\text{-}F}$ = 3.9 Hz, 1H), 7.39 (m, 3H, C_6H_5), 7.30 (m, 2H, C_6H_5), 7.19 (dd, $J_{H\text{-}H}$ = 8.6 Hz, $J_{H\text{-}F}$ = 10.3 Hz, 1H), 4.58–3.85 (br signal, 2H), 3.81–3.40 (br signal, 2H), 3.22–2.64 (br signal, 3H), 1.05 (br signal, 3H, CH_3). LC/MS calcd for $C_{22}H_{21}FN_6O_3S$ $[M + 1]^+$, 469; found, 469.

1-[3-(4-Benzoyl-2-methyl-piperazin-1-sulfonyl)-1*H*-pyrrolo[2,3-*c*]pyridin-7-yl]-ethanone, Method H. [4-(7-Chloro-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl)-3-methyl-piperazin-1-yl]-phenyl-methanone (0.6 g, 1.4 mmol), $Zn(CN)_2$ (0.089 g, 0.76 mmol), Zn dust (0.01 g, 0.15 mmol), $Pd_2(dba)_3$ (0.023 g, 0.025 mmol), dppf (0.028 g, 0.038 mmol), and anhydrous dimethylacetamide (6.5 mL) were placed into a pressure-capped glass reactor (10 mL) filled with argon. The mixture was kept in a microwave oven (CEM Discovery System, 908010) at 130 °C for 1 h, cooled to RT, and diluted with water (50 mL). The precipitate was filtered, washed with water and then Et_2O, and dried under reduced pressure to give 3-(4-benzoyl-2-methyl-piperazin-1-sulfonyl)-1*H*-pyrrolo[2,3-*c*]pyridine-7-carbonitrile (0.45 g, 71%), which was used for the next step without additional purification. LC/MS calcd for $C_{20}H_{19}N_5O_3S\cdot H^+$, 410.1; found, 410.1. ^{1}H NMR (DMSO-d_6): δ 13.58 (s, 1H, H-indole), 8.47 (d, J = 5.4 Hz, 1H), 8.44 (s, 1H), 8.05 (d, J = 5.4 Hz, 1H), 7.40 (m, 3H), 7.30 (m, 2H), 4.37–3.36 (br signal, 4H), 3.20–2.82 (br signal, 3H), 0.98 (br signal, 3H, CH_3).

1-[3-(4-Benzoyl-2-methyl-piperazin-1-sulfonyl)-1*H*-pyrrolo[2,3-*c*]pyridin-7-yl]-3-dimethylamino-propenone, Method I. To a suspension of 3-(4-benzoyl-2-methyl-piperazin-1-sulfonyl)-1*H*-pyrrolo[2,3-*c*]pyridine-7-carbonitrile (1.78 g, 4.3 mmol) in anhydrous

THF (40 mL) cooled to −20 °C, a 22% solution of MeMgBr (5.9 mL, 17.4 mmol) in THF was slowly added dropwise. The reaction mixture was stirred at this temperature for 40 min, treated (at the same temperature) with a 5% solution of H_2SO_4 until complete precipitate dissolution, allowed to warm to RT, evaporated to $^1/_3$ of the volume, made basic with aqueous NH_3, and extracted with $CHCl_3$ (4 × 50 mL). The organic phase was washed with water and brine, dried with Na_2SO_4, and evaporated. The residue was purified by chromatography (silica gel, eluent $CHCl_3$/MeOH 50:1) to afford 1-[3-(4-benzoyl-2-methyl-piperazin-1-sulfonyl)-1*H*-pyrrolo[2,3-*c*]pyridin-7-yl]-ethanone (0.66 g, 36%). LC/MS calcd for $C_{21}H_{22}N_4O_4S$ $[M + 1]^+$, 427.5; found, 427, 428. ^{1}H NMR (DMSO-d_6): δ 12.56 (s, 1H, H-indole), 8.48 (d, J = 5.4 Hz, 1H), 8.10 (m, 1H), 8.02 (d, J = 5.4 Hz, 1H), 7.40 (m, 3H), 7.31 (m, 2H), 4.38–3.37 (br signal, 4H), 3.17–2.82 (br signal, 3H), 2.76 (s, 3H, CH_3), 0.94 (br signal, 3H, CH_3).

A solution of 1-[3-(4-benzoyl-2-methyl-piperazin-1-sulfonyl)-1*H*-pyrrolo[2,3-*c*]pyridin-7-yl]-ethanone (0.78 g, 1.8 mmol) and dimethylformamide dimetylacetal (6.3 mL) in anhydrous DMF (6.5 mL) was stirred at 55–60 °C for 6 h (TLC-monitoring, $CHCl_3$/MeOH 9:1) and evaporated to give crude 1-[3-(4-benzoyl-2-methyl-piperazine-1-sulfonyl)-1*H*-pyrrolo[2,3-*c*]pyridin-7-yl]-3-dimethylamino-propenone (quantitative yield), which was used for the next step without additional purification. LC/MS calcd for $C_{24}H_{27}N_5O_4S \cdot H^+$, 482.5; found, 482.1. ^{1}H NMR (DMSO-d_6): δ 11.05 (s, 1H, H-indole), 8.38 (d, J = 5.4 Hz, 1H), 8.00 (s, 1H), 7.85 (d, J = 5.4 Hz, 1H), 7.40–7.30 (m, 6H), 6.53 (m, 1H), 4.44–3.51 (br signal, 4H), 3.29–3.03 (br signal, 3H), 3.22 (s, 3H, NCH_3), 2.97 (s, 3H, NCH_3), 0.94 (br signal, 3H, CH_3).

{4-[7-(2-Amino-pyrimidin-4-yl)-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl]-3-methyl-piperazin-1-yl}-phenyl-methanone, Method J. {4-[7-(2-Amino-pyrimidin-4-yl)-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl]-3-methyl-piperazin-1-yl}-phenyl-methanone (15%) was removed according to the procedure above, using 1-[3-(4-benzoyl-2-methyl-piperazin-1-sulfonyl)-1*H*-pyrrolo[2,3-*c*]pyridin-7-yl]-3-dimethylamino-propenone and guanidine hydrochloride. The product was purified by chromatography (silica gel, first column, eluent $CHCl_3$/MeOH 20:1→9:1; second column, eluent Et_2O/MeOH 9:1). ^{1}H NMR (DMSO-d_6): δ 12.50 (s, 1H, H-indole), 8.46 (d, J = 5.4 Hz, 2H), 8.23 (m, 1H), 7.88 (d, J = 5.4 Hz, 1H), 7.63 (d, J = 5.1 Hz, 1H), 7.41–7.29 (m, 5H), 6.97 (br s, 2H), 4.34–4.04 (br signal, 2H), 3.79–3.33 (br signal, 2H), 3.18–2.91 (m, 3H), 3.07–2.69 (br signal, 2H), 0.98 (br signal, 3H, CH_3). LC/MS calcd for $C_{23}H_{23}N_7O_3S$ $[M + 1]^+$, 478; found, 478.

[3-Methyl-4-(7-[1,2,4]oxadiazol-3-yl-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl)-piperazin-1-yl]-phenyl-methanone, Method K. Hydroxylamine hydrochloride (0.03 g, 4.3 mmol), Na_2CO_3 (0.023 g, 2.2 mmol), and $BF_3 \cdot Et_2O$ (two drops) were added to a suspension of 3-(4-benzoyl-2-methyl-piperazin-1-sulfonyl)-1*H*-pyrrolo[2,3-*c*]pyridine-7-carbonitrile (0.17 g, 4.2 mmol) in a water−ethanol mixture (1:1, 10 mL). The mixture was stirred for 3 h at RT, then diluted with water (10 mL), and extracted with DCM (3 × 10 mL), the organic layers were combined, dried over sodium sulfate, and concentrated to give crude 3-(4-benzoyl-2-methyl-piperazin-1-sulfonyl)-*N*-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-7-carboxamidine, which was used for the next step without further purification. LC/MS calcd for $C_{21}H_{20}N_6O_4S$ $[M + 1]^+$, 443; found, 443.

A mixture of the product from the previous step and $BF_3 \cdot Et_2O$ (5 drops) in triethyl orthoformate (10 mL) was refluxed under stirring for 1 h and then evaporated. The residue was purified by HPLC to give [3-methyl-4-(7-[1,2,4]oxadiazol-3-yl-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl)-piperazin-1-yl]-phenyl-methanone (0.06 g, 32% per two steps). ^{1}H NMR (DMSO-d_6): δ 12.35 (s, 1H, H-indole), 9.97 (s, 1H), 8.53 (d, J = 5.4 Hz, 1H), 8.15 (m, 1H), 7.96 (d, J = 5.4 Hz, 1H), 7.39 (m, 3H, C_6H_5), 7.30 (m, 2H, C_6H_5), 4.46–3.92 (br signal, 2H), 3.89–3.40 (br signal, 2H), 3.20–2.67 (br signal, 3H), 0.98 (br signal, 3H, CH_3). LC/MS calcd for $C_{21}H_{20}N_6O_4S$ $[M + 1]^+$, 453; found, 453.

[4-(7-Azido-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl)-3-methyl-piperazin-1-yl]-phenyl-methanone, Method L. A mixture of [4-(7-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl)-3-methyl-piperazin-1-yl]-phenyl-methanone (2.0 g, 4.78 mmol) and NaN_3 (1.6 g, 24.6 mmol) in HMPT (15 mL) was kept under stirring at 150–160 °C for 1 h using a Biotage microwave reactior, cooled to RT, and diluted with water (70 mL). The precipitate was filtered, washed with water, and dried under reduced pressure to give [4-(7-azido-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl)-3-methyl-piperazin-1-yl]-phenyl-methanone (1.7 g, 83%), which was used for the next step without additional purification. LC/MS calcd for $C_{19}H_{19}N_7O_3S \cdot H^+$, 426.1; found, 426.1. Purity (ELSD): 100%. ^{1}H NMR (DMSO-d_6): δ 14.05 (s, 1H, H-indole), 8.95 (m, 1H), 8.27 (s, 1H), 7.69 (m, 1H), 7.39 (m, 3H), 7.29 (m, 2H), 4.34–3.58 (br signal, 4H), 3.20–2.75 (br signal, 3H), 0.99 (br signal, 3H, CH_3).

{4-[7-(4-Hydroxymethyl-[1,2,3]triazol-1-yl)-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl]-3-methyl-piperazin-1-yl}-phenyl-methanone, Method M. A mixture of [4-(7-azido-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl)-3-methyl-piperazin-1-yl]-phenyl-methanone (0.4 g, 0.94 mmol), propargyl alcohol (0.5 g, 8.9 mmol), sodium ascorbate (0.04 g, 0.2 mmol), $CuSO_4$ (0.03 g, 0.47 mmol), and $NaHCO_3$ (0.079 g, 0.94 mmol) in DMF (6 mL) and water (2 mL) was kept under stirring at 100–120 °C for 40 min (TLC monitoring, $CHCl_3$/MeOH 9:1), cooled to RT, and evaporated. The residue was purified by chromatography (silica gel, eluent Et_2O/MeOH 9:1, then $CHCl_3$/MeOH 9:1) to give {4-[7-(4-hydroxymethyl-[1,2,3]triazol-1-yl)-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl]-3-methyl-piperazin-1-yl}-phenyl-methanone (0.36 g, 79%). ^{1}H NMR (DMSO-d_6): δ 12.64 (s, 1H, H-indole), 8.84 (s, 1H), 8.29 (d, J = 5.6 Hz, 1H), 8.13 (s, 1H), 7.85 (d, J = 5.6 Hz, 1H), 7.42–7.36 (m, 3H), 7.30 (m, 2H), 5.37 (t, J = 5.6 Hz, 1H, OH), 4.70 (d, J = 5.6 Hz, 2H), 4.34–3.37 (br signal, 4H), 3.21–2.74 (br signal, 3H), 0.98 (br signal, 3H, CH_3). LC/MS calcd for $C_{22}H_{23}N_7O_4S \cdot H^+$, 482.1; found, 482.1.

{(*R*)-4-[7-(4-Fluoromethyl-[1,2,3]triazol-1-yl)-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl]-3-methyl-piperazin-1-yl}-phenyl-methanone, Method N. To a solution of {4-[7-(4-hydroxymethyl-[1,2,3]triazol-1-yl)-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl]-3-methyl-piperazin-1-yl}-phenyl-methanone (0.23 g, 0.48 mmol) in DCM (40 mL) cooled to −80 °C, Et_2NSF_3 (0.3 mL, 2.27 mmol) was added dropwise. The reaction mixture was allowed to warm to RT (LC/MS monitoring). Water (40 mL) and DCM (20 mL) were added, the mixture obtained was filtered, the organic phase was separated, washed with water, dried with Na_2SO_4, and evaporated, and the residue was purified by chromatography (silica gel, eluent $CHCl_3$/MeOH 9:1) to afford {(*R*)-4-[7-(4-fluoromethyl-[1,2,3]triazol-1-yl)-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl]-3-methyl-piperazin-1-yl}-phenyl-methanone (0.015 g, 6.5%). ^{1}H NMR (DMSO-d_6): δ 12.70 (s, 1H, H-indole), 9.25 (m, 1H), 8.30 (m, 1H), 8.16 (s, 1H), 7.88 (m, 1H), 7.41 (m, 3H), 7.30 (m, 2H), 5.65 (d, $J_{H\text{-}F}$ = 48 Hz, 2H, CH_2F), 4.37–3.40 (br signal, 4H), 3.21–2.69 (br signal, 3H), 1.00 (br signal, 3H, CH_3). LC/MS calcd for $C_{22}H_{22}FN_7O_3S$ $[M + 1]^+$, 484; found, 484.

{4-[7-(4-Dimethylaminomethyl-[1,2,3]triazol-1-yl)-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl]-3-methyl-piperazin-1-yl}-phenyl-methanone, Method O. A solution of methanesulfonyl chloride (0.08 mL, 1.0 mmol) in DCM (2 mL) was added dropwise under stirring to a solution of {4-[7-(4-hydroxymethyl-[1,2,3]triazol-1-yl)-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl]-3-methyl-piperazin-1-yl}-phenyl-methanone (0.2 g, 0.41 mmol) and NEt_3 (0.15 mL, 1.0 mmol) in DCM (20 mL) at 0 °C. The reaction mixture was kept at 0 °C for 1 h and then allowed to warm to RT (TLC monitoring, $CHCl_3$/MeOH 9:1). Water (20 mL) was added, the product was extracted with DCM (20 mL), the organic phase was dried with Na_2SO_4 and evaporated, and the residue was purified by chromatography (silica gel, eluent EtOAc/*n*-hexane 9:1, then $CHCl_3$/MeOH 9:1) to afford methanesulfonic acid 1-[3-(4-benzoyl-2-methyl-piperazine-1-sulfonyl)-1*H*-pyrrolo[2,3-*c*]pyridin-7-yl]-1*H*-[1,2,3]triazol-4-ylmethyl ester (0.1 g, 43%). LC/MS calcd for $C_{23}H_{25}N_7O_6S_2$ $[M + 1]^+$, 560.5; found, 560, 561. ^{1}H NMR (DMSO-d_6): δ 12.69 (s, 1H, H-indole), 9.20 (s, 1H), 8.31 (m, 1H), 8.17 (s, 1H), 7.89 (m, 1H), 7.38 (m, 3H), 7.30 (m, 2H), 5.53 (s, 2H), 4.38–3.36 (br signal, 4H), 3.29 (s, 3H), 3.21–2.68 (br signal, 3H), 1.00 (br signal, 3H, CH_3).

A mixture of 1-[3-(4-benzoyl-2-methyl-piperazine-1-sulfonyl)-1*H*-pyrrolo[2,3-*c*]pyridin-7-yl]-1*H*-[1,2,3]triazol-4-ylmethyl ester (0.1 g, 0.18 mmol) and 40% aqueous solution of dimethylamine (0.15 mL) in DMF (4 mL) was stirred at RT for 30 min (TLC monitoring, $CHCl_3$/MeOH 9:1). Solvent was evaporated, and the residue was purified by chromatography (silica gel, eluent $CHCl_3$/MeOH 9:1) to afford methanesulfonic acid {4-[7-(4-dimethylaminomethyl-[1,2,3]triazol-1-yl)-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl]-3-methyl-piperazin-1-yl}-phenyl-methanone (0.04 g, 43%). ^{1}H NMR (DMSO-d_6): δ 12.63 (s, 1H, H-indole), 8.87 (s, 1H), 8.28 (d, J = 5.4 Hz, 1H), 8.13 (s, 1H), 7.85 (d, J = 5.4 Hz, 1H), 7.41–7.35 (m, 3H), 7.29 (m, 2H), 4.38–3.92 (br signal, 2H), 3.83–3.37 (br signal 2H), 3.21–2.69 (br signal, 3H), 2.23 (s, 6H, $N(CH_3)_2$), 0.98 (br signal, 3H, CH_3). LC/MS calcd for $C_{24}H_{28}N_8O_3S$ $[M + 1]^+$, 509; found, 509.

{3-Methyl-4-[7-(4-methyl-[1,2,3]triazol-1-yl)-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl]-piperazin-1-yl}-phenyl-methanone, Method P. A solution of methanesulfonyl chloride (0.08 mL, 1.0 mmol) in DCM (2 mL) was added dropwise under stirring to a solution of {4-[7-(4-hydroxymethyl-[1,2,3]triazol-1-yl)-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl]-3-methyl-piperazin-1-yl}-phenyl-methanone (0.2 g, 0.41 mmol) and NEt_3 (0.15 mL, 1.0 mmol) in DCM (20 mL) at RT. The reaction mixture was kept at RT for 2 h (TLC monitoring, $CHCl_3$/MeOH 9:1). Water (20 mL) was added, the product was extracted with DCM (20 mL), and the organic phase was dried with Na_2SO_4, evaporated to give crude {4-[7-(4-chloromethyl-[1,2,3]triazol-1-yl)-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl]-3-methyl-piperazin-1-yl}-phenyl-methanone (~0.1 g), which was used for the next step without purification. LC/MS calcd for $C_{22}H_{22}ClN_7O_3S$ $[M + 1]^+$, 501; found, 501, 502.

Sodium borohydride (0.03 g, 0.79 mmol) was added to a solution of crude (from the previous step) {4-[7-(4-chloromethyl-[1,2,3]triazol-1-yl)-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl]-3-methyl-piperazin-1-yl}-phenyl-methanone (~0.1 g) in DMF (3.5 mL) under stirring at 0 °C. Then the mixture was heated to 50–60 °C, stirred for 6 h (TLC monitoring, $CHCl_3$/MeOH 2:1), and cooled to RT. A 15% aqueous solution of H_2SO_4 was added dropwise until a homogeneous solution was obtained. Solvent was evaporated, and the residue was purified by chromatography (silica gel, eluent $CHCl_3$/MeOH 9:1), followed by HPLC, to afford {3-methyl-4-[7-(4-methyl-[1,2,3]triazol-1-yl)-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl]-piperazin-1-yl}-phenyl-methanone (0.03 g, 32%). ^{1}H NMR (DMSO-d_6): δ 12.60 (s, 1H, H-indole), 8.78 (s, 1H), 8.27 (d, J = 5.4 Hz, 1H), 8.12 (s, 1H), 7.83 (d, J = 5.4 Hz, 1H), 7.41–7.36 (m, 3H), 7.30 (m, 2H), 4.41–3.42 (br signal, 4H), 3.20–2.67 (br signal, 3H), 2.42 (s, 3H, CH_3), 0.99 (br signal, 3H, CH_3). LC/MS calcd for $C_{22}H_{23}N_7O_3S$ $[M + 1]^+$, 466; found, 466.

[3-Methyl-4-(7-pyridin-3-yl-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl)-piperazin-1-yl]-phenyl-methanone, Method Q. Toluene (100 mL), EtOH (100 mL), and 2 M K_2CO_3 (16 mL) were added to a mixture of [4-(7-chloro-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl)-3-methyl-piperazin-1-yl]-phenyl-methanone (0.5 g, 1.2 mmol), 3-pyridylboronic acid (0.33 g, 2.0 mmol), and Bu_4NBr (0.5 g). Argon was bubbled within the reaction mixture for ~20 min. Then $Pd(PPh_3)_4$ (0.14 g, 0.12 mmol) was added. The reaction mixture was stirred under reflux (48 h; TLC monitoring, $CHCl_3$/MeOH 9:1), then cooled to RT, and diluted with water (50 mL). The product was extracted with benzene (2 × 50 mL). The organic solution was washed with water (3 × 100 mL), dried with Na_2SO_4, and evaporated, and the residue was purified by chromatography (silica gel, EtOAc/*n*-hexane 1:1, then 3:1, then EtOAc), then additionally by HPLC to afford [3-methyl-4-(7-pyridin-3-yl-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl)-piperazin-1-yl]-phenyl-methanone as TFA-salt (0.115 g, 16.7%). ^{1}H NMR (DMSO-d_6): δ 13.33 (br s, 1H, H-indole), 9.16 (s, 1H), 8.87 (m, 1H), 8.52 (m, 2H), 8.47 (m, 1H), 7.99 (m, 1H), 7.81 (m, 1H), ~7.50 (br signal, $CF_3COOH \cdot H_2O$), 7.42 (m, 3H, C_6H_5), 7.32 (m, 2H, C_6H_5), 4.49–3.91 (br signal, 2H), 3.88–3.33 (br signal, 2H), 3.20 (m, 1H), 3.10–2.70 (br signal, 2H), 1.02 (br signal, 3H, CH_3). LC/MS calcd for $C_{24}H_{23}N_5O_3S$ $[M + 1]^+$, 462.5; found, 462, 463.

[3-Methyl-4-(7-thiazol-2-yl-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl)-piperazin-1-yl]-phenyl-methanone, Method R. [4-(7-Chloro-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl)-3-methyl-piperazin-1-yl]-phenyl-methanone (0.1 g, 0.24 mmol), $Pd(PPh_3)_4$ (0.2 g, 0.17 mmol), 2-tributylstannylthiazole (0.2 mL, 0.63 mmol), and anhydrous dioxane (6.5 mL) were placed into a pressure-capped glass reactor (10 mL) filled with argon. The mixture was kept in a microwave oven (CEM Discover System, 908010) at 150 °C for 20 min, cooled to RT, diluted with water (50 mL), and extracted with EtOAc (3 × 40 mL). The organic solution was dried with Na_2SO_4 and evaporated, and the residue was purified by chromatography (silica gel, EtOAc/*n*-hexane 9:1) and then additionally by HPLC to afford [3-methyl-4-(7-thiazol-2-yl-1*H*-pyrrolo[2,3-*c*]pyridine-3-sulfonyl)-piperazin-1-yl]-phenyl-methanone (0.035 g, 31%). ^{1}H NMR (DMSO-d_6): δ 12.38 (s, 1H, H-indole), 8.39 (d, J = 5.6 Hz, 1H), 8.17 (d, J = 3.2 Hz, 1H), 8.10 (m, 1H), 7.99 (d, J = 3.2 Hz, 1H), 7.84 (d, J = 5.4 Hz, 1H), 7.39 (m, 3H, C_6H_5), 7.30 (m, 2H, C_6H_5), 4.40–3.63 (br signal, 4H), 3.19–2.72 (br signal, 3H), 0.97 (br signal, 3H, CH_3). LC/MS calcd for $C_{22}H_{21}N_5O_3S_2$ $[M + 1]^+$, 468; found, 468.

Supporting Information Available: Overlay of minimized structures of **12a** and **25**. Characterization data (NMR, LC-MS, and elemental analysis) for newly synthesized compounds and protocol for single cycle antiviral assay and cytotoxicity assay. This material is available free of charge via the Internet at http://pubs.acs.org.

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