Discovery of 4-Benzoyl-1-[(4-methoxy-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)oxoacetyl]-2-(*R*)-methylpiperazine (BMS-378806): A Novel HIV-1 Attachment Inhibitor That Interferes with CD4-gp120 Interactions[†]

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Abstract: Indole derivative **1** interferes with the interaction of the HIV surface protein gp120 with the host cell receptor CD4. The 4-fluoro derivative **2** exhibited markedly enhanced potency and was bioavailable in the rat, dog, and cynomolgus monkey when administered orally as a solution formulation. However, aqueous suspensions of **2** were poorly bioavailable, indicative of dissolution-limited absorption. The 7-azaindole derivative **3**, BMS-378806, exhibited improved pharmaceutical properties while retaining the HIV-1 inhibitory profile of **2**.

Introduction. The advent of highly active anti-retroviral therapy (HAART), a combination cocktail of inhibitors of HIV reverse transcriptase and protease, has provided an effective means of controlling viral load and disease progression in HIV-infected individuals.[1] However, compliance with drug dosing regimens can be challenging because of the severity of side effects and a significant pill burden, factors that have prompted examination of the concept of scheduled treatment interruptions (STI).[2] These limitations have contributed to the development and dissemination of resistant viruses, an emerging and significant problem that portends a need for new anti-retroviral agents that interfere with different targets in the replication cycle, are better tolerated and offer more convenient dosing schedules.[3,4] As the preliminary step toward that objective, a cell-based screening assay designed to capture inhibitors of HIV replication without mechanistic bias was implemented. The indole derivative **1**, a member of a purely prospective library of amides prepared largely from commercially available components, emerged from that exercise as a mechanistically novel and effective inhibitor of HIV that was devoid of overt cytotoxicity. It was quickly established that **1** was an inhibitor of a range of HIV-1 isolates and that the activity was independent of the coreceptor used by these viruses to enter host cells, data summarized in Table 1. The selectivity index based on the cytotoxicity associated with **1** in MT-2 and PM1 cells ranged from 28 (NL4−3) to 1686 (LAI). Moreover, at a concentration of 200 μM, indole **1** was without significant inhibitory activity toward a panel of viruses composed of HIV-2, simian immunodeficiency virus (SIV), murine leukemia virus (MuLV), respiratory syncytial virus (RSV), human cytomegalovirus (HCMV), bovine viral diarrhea virus (BVDV), vesicular stomatitis virus (VSV), and influenza virus. The cytotoxicity of **1** toward the panel of uninfected host cell types used to grow these viruses was minimal, with 50% inhibitory levels (CC$_{50}$) ranging from 99 to greater than 200 μM. Cytotoxicity was most evident in Hep-2 cells, a human larynx carcinoma cell line that is a particularly sensitive sentinel. A series of mechanistic studies deduced that **1** compromised the interaction of the viral surface protein gp120 with the host cell receptor CD4, providing the first example of a small molecule with a mode of action that has hitherto proven elusive.[5] As a mechanistically unique HIV-1 inhibitor with druglike qualities,[6,7] **1** offered a compelling point of departure, and in this communication optimization into the prototype BMS-378806 (**3**) is described.

The initial survey of structure−activity studies associated with indole **1** revealed that potency was exquisitely sensitive to substitution at C-4 of the heterocycle and the fluoro derivative **2** very quickly emerged as a molecule with a profile of considerable interest as a potential candidate for development. The inhibitory activity of **2** toward the panel of macrophage- and T cell-tropic HIV-1 strains is compared with **1** in Table 1. These viruses are laboratory strains that use either CCR5 (M-tropic) or CXR4 (T-tropic) coreceptors to enter cells and are classified as B subtypes. The fluoro analogue **2** is consistently more potent than the prototype **1**, with an advantage ranging from 10- to 1585-fold, dependent upon virus identity. In the presence of 40% human serum, the EC$_{50}$ values increased by 2−3-fold, reflecting modest protein binding that was subsequently determined by ultrafiltration to be 93% in human plasma. The profile of **2** in a series of in vitro assays designed to evaluate pharmacokinetic properties indicated good intestinal membrane permeability (Caco-2 permeability of 100 nm/s) and an intermediate clearance in man based on the stability of the compound in human liver microsomes. However, **2** was less stable in rat liver microsomes (RLM), a result that predicted high clearance in this species, and subsequently confirmed in vivo (vide infra). Of the human metabolizing enzymes, only CYP2C19 was significantly affected by

Table 1. HIV-1 Inhibitory Activity and Cytotoxicity Associated with Compounds **1**−**3**[a]

| | **1** | | **2** | | **3** (BMS-378806) | |
virus	EC$_{50}$ (nM)	CC$_{50}$ (μM)	EC$_{50}$ (nM)	CC$_{50}$ (μM)	EC$_{50}$ (nM)	CC$_{50}$ (μM)
LAI (T)	86 ± 24	145 ± 23 In MT-2 cells	2.93 ± 1.41	146 ± 74 in MT-2 cells	2.68 ± 1.64	>300 in MT-2 cells
SF-2 (T)	1030 ± 29		62.4 ± 33.7		26.5 ± 3.5	
NL4−3 (T)	5130 ± 2620		30.8 ± 18.6		2.94 ± 2.01	
Bal (M)	28 700 ± 4200	>200 in PM1 cells	18.1 ± 8.4	52.5 ± 1.2	15.5 ± 6.8	>300 in PM1 cells
SF-162 (M)	230 ± 140		ND		3.46 ± 0.81	
JRFL (M)	ND		2.39 ± 0.85		1.47 ± 0.63	
TLAV (dual)	149 ± 65	145 ± 23 in MT-2 cells	13.6 ± 7.8	146 ± 74 in MT-2 cells	0.85 ± 0.13	>300 in MT-2 cells

[a] ND: Not determined. T = T-tropic virus that utilizes the CXCR-4 coreceptor; M = macrophage-tropic virus that utilizes the CCR5 coreceptor; dual = virus utilizing both CXCR4 and CCR5 coreceptors for entry.

Table 2. Pharmacokinetic Parameters for Compounds **2** and **3**[a]

1: R = H
2: R = F
3

	2	**3**
	Rat	
iv/po dose (mg/kg)	5/5	1/5
F_{po} (%)	9.4	19
$C_{max,po}$ (μM)	0.15	0.22
CL$_{tot}$ (mL/min/kg)	48	32
V_{ss} (L/kg)	0.99	0.56
	Dog	
iv/po dose (mg/kg)	2/10	0.67/3.4
F_{po} (%)	∼100	77
$C_{max,po}$ (μM)	18	7.4
CL$_{tot}$ (mL/min/kg)	2.4	5.2
V_{ss} (L/kg)	1.8	0.47
	Monkey	
iv/po dose (mg/kg)	2/10	0.67/3.4
F_{po} (%)	∼100	24
$C_{max,po}$ (μM)	34	0.51
CL$_{tot}$ (mL/min/kg)	3.1	10
V_{ss} (L/kg)	0.24	0.39

[a] Administered as a solution in poly(ethylene glycol) 400/ethanol (90:10 v/v).

2, IC$_{50}$ = 7 μM, with half-maximal inhibition of the other major isoforms >10 μM. These data, when combined with the observation that **2** is metabolized by multiple P450 isoforms, anticipate minimal drug−drug interactions, of particular importance in the arena of HIV therapy where drug combinations are the standard of care.

The pharmacokinetic properties of **2**, administered as a solution in poly(ethylene glycol) 400 (PEG 400) and ethanol (90:10 v/v), in the rat, dog and cynomolgus monkey are summarized in Table 2. Oral bioavailability was excellent in the dog and monkey, but poor in the rat, where the high clearance was anticipated based on the poor stability in RLM. The maximum plasma concentrations achieved in all three species were well in excess of the antiviral EC$_{50}$ values determined in the cell culture assays. However, while exposure in the rat and dog was responsive to dose escalation, nonlinear pharmacokinetic properties were observed in these species. In rats, the bioavailability increased 2-fold and C_{max} increased 10-fold when the dose was increased

from 5 to 25 mpk. In the dog, oral bioavailability was >100% at a dose of 10 mpk when compared to a 2 mpk dose administered intravenously. However, a marked reduction in exposure was encountered when dosing suspensions of **2** in 0.75% (w/w) Methocel A4M and 0.5% (w/w) Pluronic F68. In the rat, a dose of 5 mpk of **2** administered as a mean particle size of 46 μm resulted in no detectable oral exposure. Examination of material prepared as a nanosuspension in 1% (w/w) Pluronic F108 provided only a marginal improvement, with bioavailability determined to be 4% in the rat and 36% in the dog at a dose of 1 mpk. These results are indicative of problems associated with drug dissolution, a phenomenon reflected in the solubility profile of **2**, which was determined to be 5 μg/mL in water, 100 μg/mL in a mixture of 5% Tween 80 in water and 4.6 mg/mL in PEG 400, and related to the high melting point, 236 °C.

These findings prompted a search for a compound with a similar antiviral profile to **2** but with improved pharmaceutical properties, an objective fulfilled with the preparation of the azaindole derivative **3**, recognized as BMS-378806. The introduction of a nitrogen atom into the heterocycle and installation of a more polar and electron-donating methoxy substituent[8,9] at C-4 provided a compound with aqueous solubility from the crystalline form of 170 μg/mL, a 34-fold improvement compared to **2**. The solubility of **3** improves to 1.3 mg/mL at pH = 2.1 and 3.3 mg/mL at pH = 11, a solubility profile that reveals the amphoteric nature of the compound and estimates the pK_a of the protonated form as 2.9 while that of the free base is approximately 9.6.

The antiviral effects of the azaindole **3** are presented in Table 1 where it is readily apparent that all of the activity of indole **2** against the panel of B subtype HIV-1 strains is fully preserved. In MT-2 cells infected with HIV-1 LAI virus, the presence of 40% human serum increased the EC$_{50}$ value by a modest 1.2-fold while the addition of 1 mg/mL of α_1 acid glycoprotein was without effect. Consistent with this result, plasma protein binding, determined using an ultrafiltration method at a plasma concentration of 1 μg/mL, was found to be 73, 63, 44, and 54% in human, rat, dog and monkey plasma, respectively.

In a series of biochemical assays, **3** was not an effective inhibitor of HIV integrase, protease, or reverse transcriptase, but did compete with soluble CD4 binding to a monomeric form of gp120 in an ELISA assay with IC$_{50}$ = ∼100 nM. The generation and sequencing of resistant viruses identified M426L, M434I/V and M475I of gp120 as primary resistance mutations in the HIV-1 strains NL4−3 and LAI. Recombinant viruses contain-

Scheme 1[a]
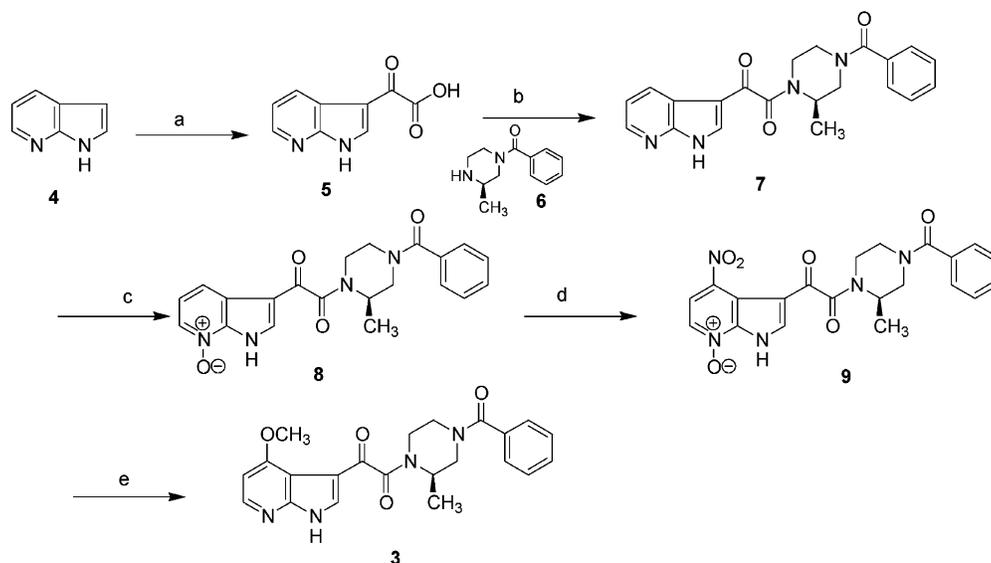
[a] (a) 1. ClCOCO$_2$Me/AlCl$_3$/CH$_2$Cl$_2$ (79%); 2. K$_2$CO$_3$/MeOH/H$_2$O (90%); (b) DEPBT/Pr$_2$EtN/DMF (81%); (c) mCPBA/acetone (91%); (d) HNO$_3$/CF$_3$CO$_2$H; (e) 1. MeONa/MeOH/Δ; 2. PCl$_3$/EtOAc (50% over three steps).

ing these individual substitutions display a resistant phenotype. The M426L and M475I mutations map to the pocket on gp120 that interacts with phenylalanine 43 of CD4, a residue that has been shown to be critical to recognition and which provides additional support for the proposed mode of action.[10] The specificity of **3** toward inhibition of HIV-1 was confirmed by evaluation against HIV-2, SIV, MuLV, RSV, HCMV, BVDV, VSV, and influenza virus, with no significant inhibitory activity observed at concentrations ranging from 10 to 30 μM and no overt cytotoxicity toward the host cells, CC$_{50}$ values > 225 μM.

The pharmacokinetic properties of **3** in the rat, dog, and cynomolgus monkey are summarized in Table 2. The oral bioavailability of **3** in rats, administered as a solution in PEG 400/EtOH (90:10 v/v), was 19% at a dose of 5 mg/kg while an aqueous crystalline suspension of free base in 0.75% (w/w) Methocel A4M Premium administered orally at the same dose afforded a relative bioavailability of 61%. Importantly, dose-proportional increases in the AUC and C_{max} were observed between doses of 5 and 25 mpk, when **3** was administered either in the solution or suspension formulation. In all three species, plasma levels of drug exceeded the concentrations required to half-maximally inhibit virus replication in vitro. The volume of distribution of **3** ranged from 0.4 to 0.6 L/kg, indicative of partitioning beyond plasma; however, examination of brain levels in the rat revealed minimal CNS penetration.

Additional preclinical studies revealed that **3** is not a potent inhibitor of any of the five major human CYP isoforms, evaluated as recombinant preparations, with IC$_{50}$ values of >100 μM for CYP1A2 and CYP2C9, 23 μM for CYP2C19, 20 μM for CYP2D6, and 39 to 81 μM for CYP3A4. Moreover, since **3** is metabolized by CYP450 1A2, 2D6, and 3A4, it is unlikely to lead to severe drug−drug interactions in a clinical setting. Safety profiling of **3** provided no evidence of mutagenicity in an Ames reverse mutation assay at 1600 μg/plate and only weak inhibition of a cloned HERG channel (10.9% inhibition at 10 μM). The limited

Scheme 2
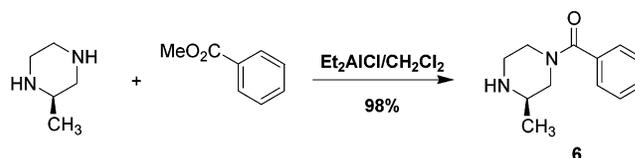
potential for cardiac problems was confirmed in a rabbit purkinje fiber assay, where no significant changes in action potential duration were seen at 30 μM, and in the dog, where no ECG abnormalities where were observed following doses as high as 200 mg/kg. In toxicology studies, **3** was well tolerated in rats at doses of 100 mg/kg/day for 2 weeks and in dogs at doses of 90 mg/kg for 10 days.

Chemistry. The synthesis of BMS-378806 (**3**) is depicted in Scheme 1 and is initiated by acylating 7-azaindole (**4**) with methyl chlorooxoacetate in the presence of AlCl$_3$.[11,12] Hydrolysis of the resulting ester, using K$_2$CO$_3$ in aqueous MeOH, was followed by coupling with the benzoylated piperazine **6**, a reaction mediated by 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one[13] in the presence of N,N-diisopropylethylamine (^{i}Pr$_2$NEt, Hunig's base) in DMF, to afford **7** in an overall yield of 57%. The piperazine **6** was, in turn, obtained by exposing (R)-(−)-2-methylpiperazine and methyl benzoate to 1 mol equiv of diethylaluminum chloride in CH$_2$Cl$_2$, a reaction proceeding with excellent regiospecificity, as summarized in Scheme 2.[14] Incorporation of the methoxy substituent at the 4-position of **7** was accomplished by a serial process, initiated by oxidation of the nitrogen atom of the heterocycle[15] and followed by nitration with fuming HNO$_3$ in CF$_3$CO$_2$H, which afforded the 4-nitro N-oxide **9**.[16] Heating **9** with an excess of NaOMe in MeOH resulted an ipso displacement of nitrite,[17] setting the stage for the final transformation to **3**. This was accomplished in a straightforward fashion by reduction of the N-oxide using PCl$_3$ in EtOAc.[17] The yield of **3** from the unsubstituted N-oxide **8** was 50% for the three steps, with an overall yield of 26% from **4**. That nitration of N-oxide **8** had occurred

at C-4 was established by analysis of a $^1H-^{15}N$ HMBC 2D NMR experiment in which the N-7 atom of **3**, resonating at δ183 ppm showed a strong cross-peak with the C-6 proton resonating at δ 8.23, while the parameter of the experiment was optimized for a 8 Hz coupling constant. Literature precedent indicates that ^2J (HN) for pyridine and quinoline derivatives is approximately 11 Hz, falling off to less than 0.3 Hz for coupling across four bonds.[18] The strength of the cross coupling in the $^1H-^{15}N$ HMBC 2D NMR experiment is consistent with the methoxy substituent located at C-4 rather than C-2, regiochemistry subsequently confirmed by single-crystal X-ray analysis.[19] The C-2 proton of **3** resonated as two singlets at δ 8.09 and 8.15 that coalesced to a single singlet when the DMSO-d_6 solution was warmed to 120 °C, indicating that **3** exists as a pair of rotational conformers at room temperature.

The preparation of **2** was accomplished from 4-fluoroindole using a synthetic protocol similar to that used to secure **7** but more convenient, taking advantage of the enhanced reactivity of 4-fluoroindole toward oxalyl chloride in Et$_2$O, which allowed the corresponding acid chloride to be realized in a single procedure. Exposure of this acid chloride to *N*-benzoylpiperazine in the presence of ^{i}Pr$_2$NEt in THF afforded **2**.

In summary, optimization of a structurally elementary and effective inhibitor of HIV attachment (**1**) into a compound (**3**) with improved antiviral potency, attractive pharmaceutical and pharmacokinetic properties, and a safety profile appropriate for more advanced studies has been accomplished. These indole-based compounds represent the basic pharmacophore of a new class of HIV-1 inhibitor that are the first small molecules able to effectively and potently interfere with the interaction of the HIV surface protein gp120 and the primary host cell receptor CD4, the initial step of HIV entry. As such, they add to the emerging repertoire of HIV-1 inhibiting compounds that interfere with the viral entry process, providing an effective complement to the CCR5 and CXR4 coreceptor antagonists and enfuvirtide, the gp41 fusion inhibitor. A more detailed analysis of the profile of **3** as an inhibitor of HIV-1 clinical isolates will be presented in due course.[21]

Supporting Information Available: Experimental details and analytical data for the preparation of compounds **2**, **3**, and **5**–**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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