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Inhibitors of HIV-1 attachment. Part 7: Indole-7-carboxamides as potent and orally bioavailable antiviral agents

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ABSTRACT

A series of substituted carboxamides at the indole C7 position of the previously described 4-fluoro-substituted indole HIV-1 attachment inhibitor **1** was synthesized and the SAR delineated. Heteroaryl carboxamide inhibitors that exhibited pM potency in the primary cell-based assay against a pseudotype virus expressing a JRFL envelope were identified. The simple methyl amide analog **4** displayed a promising in vitro profile, with its favorable HLM stability and membrane permeability translating into favorable pharmacokinetic properties in preclinical species.

Although the mortality rate resulting from human immunodeficiency virus-1 (HIV-1) infection/AIDS has been reduced by highly active anti-retroviral therapy (HAART),[1] which uses drug combinations containing nucleoside and non-nucleoside reverse transcriptase inhibitors, as well as protease and integrase inhibitors, the emergence of drug-resistant HIV-1 mutant viruses, drug toxicity and patient non-compliance associated with long-term therapy remain significant medical challenges.[2] Inhibitors of new viral targets that are not cross-resistant to the current drugs thus continue to be pursued in order to surmount these major obstacles to the treatment of HIV-1 infection.[3]

Indole- and azaindole-oxoacetic piperazinyl benzamide-based HIV-1 attachment inhibitors, as exemplified by an early indole lead compound **1** and a development candidate 6-azaindole BMS-488043 (**2**) (Table 1), have previously been described by these laboratories.[4–9] These inhibitors interfere with the attachment of the viral envelope glycoprotein gp120 to host cell receptor CD4, which is an essential first step in the process of HIV-1 entry into host cells. The binding of gp120 to CD4 and the ensuing association of this binary complex with a co-receptor (CCR5 or CXCR4) triggers the membrane fusion process that proceeds via the formation of a six helical bundle of the viral transmembrane protein gp41, ultimately culminating in the release of the viral genetic material into the host cell cytosol to initiate viral replication.[10] Clinical proof-of-concept for an antiviral effect by inhibition of binding of gp120 to CD4 was established by **2** during a Phase-1b, 8-day monotherapy trial in HIV-1-infected patients.[6e,7]

One aspect of the early stage lead optimization in the medicinal chemistry program of HIV-1 attachment inhibitors was aimed at exploring the SAR associated with substitution at the indole C7 position of the early lead compound **1** with various carboxamide moieties.[6b] It was anticipated that substitutions on the amide element may offer additional interactions with gp120 and that the amide group may also modulate the physicochemical property of these compounds. In this Letter, the SAR resulting from a survey of substituted amides in the 4-substituted indole series is described along with the in vitro and in vivo profiles of key compounds.

As shown in Table 2, the introduction of a primary amide to the C7 position of **1** maintained potency as exemplified by **3**, while the secondary methyl amide analog **4** was slightly more potent than **1**. A tertiary *N*,*N*-dimethyl amide **5** was poorly tolerated, although potency appeared to be restored in a tertiary amide with a larger substitutent, as noted for the C7 piperazinyl benzamide **6**. The methoxy amide **7** and the hydrazide analog **8** were equipotent to **1**; however, erosion of potency was observed in analogs of these two compounds (**9**–**13**) that contained a basic amine or a more extended amide moiety. This trend also holds for the benzyl amide **14** which showed a >80-fold reduction in potency compared to **1**. Interestingly, replacing the phenyl ring in **14** with heterocycles (**15**–**18**) improved potency to be comparable to **1**. It appeared from this survey that the presence of a heteroatom coupled with an aromatic ring deployed at the correct position with respect to the

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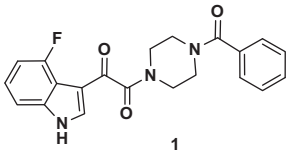
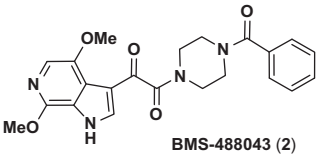
Table 1
Antiviral activity of HIV-1 attachment inhibitors



1



BMS-488043 (2)

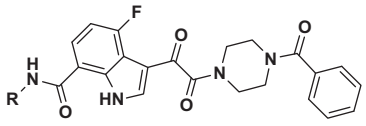
Compound	EC_{50} (nM)[11]	CC_{50} (μM)[11]
1	1.24	>300
2	0.75	>300

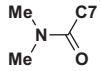
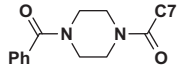
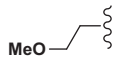
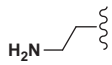
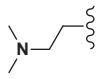
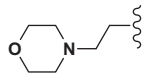
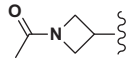
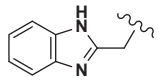
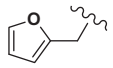
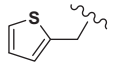
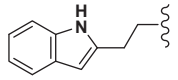
amide nitrogen was important for optimal potency. This observation is also reflected in the potency of the acyl sulfonamides **19** and **20**, with the latter about four-fold more potent than **1**. However, of particular note, was the approximately 800-fold increase in potency in methyl amide analog **4** compared to the dimethyl amide **5**. The co-planar conformation of **4**, stabilized by an intramolecular hydrogen-bond between the amide carbonyl and the indole NH as observed in its single crystal X-ray structure (Fig. 1), likely contributed significantly to the observed potency enhancement. The dimethyl amide moiety in **5** is likely to adopt an out of plane conformation due to the severe A(1,3) strain that would develop between the amide methyl group and the C6-H if it assumes a co-planar arrangement with the indole ring. An extensive review of structural information has revealed that this kind of highly stable, planar, conjugated system resulting from intramolecular, resonance-assisted hydrogen-bonding occurs with high frequency and often has an impact on molecular properties.[12]

Since the simple primary amide **3** and the secondary methyl amide **4** were the more potent analogs identified in this amide survey, analogs of these two compounds with modifications in other areas of the molecule were synthesized. As depicted in Table 3, the 4-methoxy group, another preferred substituent at C4,[6b] conferred increased potency over amide **3** but not the methyl amide **4** (compare **21** and **22**). Introduction of an (*R*)-methyl to the piperazine ring, a modification that was previously found to increase potency,[6d] also improved the potency of the primary amide **3** but not **4** (compare **23** and **24**). The picolinamide analogs **25** and **26**, prepared with the intent of increasing solubility, showed a 3- and 10-fold reduction in potency compared to **3** and **23**, respectively.

A hypothesis derived from the SAR studies presented in Table 2 was that heteroatom(s) in an aromatic ring within several atoms distance of the C7 carboxamide nitrogen appeared to contribute to good potency, exemplified by **16**–**18**. Heteroaryl carboxamides were therefore investigated and the results are shown in Table 4. Satisfyingly, a range of carboxamides incorporating heterocycles, including pyridine, tetrazole, thiadiazole, isoxazole, thiazole, benzothiazole and benzimidazole (**29**–**31** and **33**–**39**), showed subnanomolar to picomolar antiviral potency in the pseudotype infectivity assay. Heterocycles with a N atom α to the amide nitrogen were the most potent (compare **29** with **27** and **28**), with the thiazol-2-yl analogs **35**–**36** and the benzimidazol-2-yl analog **38** exhibiting half-maximal inhibition at pM concentrations. Moreover, the

Table 2
Antiviral activity of 4-fluoroindole-7-carboxamides and sulfonamides



Compound	R	EC_{50} (nM)[11]	CC_{50} (μM)[11]
1	—	1.24	>300
3		2.03	>300
4		0.52	>300
5		407	>300
6		2.68	145
7		3.83	>300
8		2.69	>300
9		18.82	298
10		12.83	135
11		315.7	>300
12		7.95	>300
13		11.24	>300
14		109.1	>300
15		6.73	>300
16		1.30	71
17		1.06	44
18		1.08	>300
19		2.64	>300
20		0.29	>300

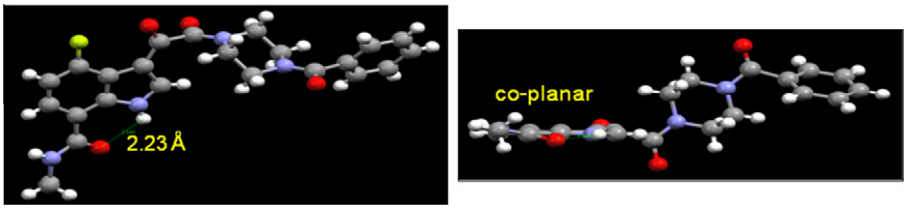


Figure 1. Single crystal X-ray structure of methyl amide **4**.