Bioorganic & Medicinal Chemistry Letters 23 (2013) 213–217

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Inhibitors of HIV-1 attachment. Part 10. The discovery and structure–activity relationships of 4-azaindole cores

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ARTICLE INFO

Article history:
Available online 7 November 2012

Keywords:
HIV-1
Entry
Attachment
4-Azaindole
BMS-378806

ABSTRACT

A series of 4-azaindole oxoacetic acid piperazine benzamides was synthesized and evaluated in an effort to identify an oral HIV-1 attachment inhibitor with the potential to improve upon the pre-clinical profile of BMS-378806 (**7**), an initial clinical compound. Modifications at the 7-position of the 4-azaindole core modulated potency significantly and SAR showed that certain compounds with a 5-membered ring heteroaryl group at that position were the most potent. Four of the compounds with the best profiles were evaluated in a rat pharmacokinetic model and all had superior oral bioavailability and lower clearance when compared with **7**.

An array of single antiviral agents and fixed-dose combinations representing six mechanistic classes is now available for use in the treatment of HIV-1 infection.[1] HIV-1 has been transformed from an acute to a chronic disease but, unfortunately, a cure is not on the horizon and there is an expanding population of HIV-1 patients relying on existing therapies whose medical needs are not completely satisfied.[2] The need for new, mechanistically distinct, non cross-resistant drugs remains due to the occurrence of drug-resistant strains and the emergence of comorbidities associated with long-term usage of highly active combination antiretroviral therapy (cART).[3] The initial entry step, HIV-1 attachment, involves the binding of viral envelope gp120 to CD-4 receptors on T-cells.[4] This binding event effects a conformational change that facilitates binding of the viral envelope to co-receptors. This step triggers a rearrangement of the fusion protein gp41 which then mediates host and viral membrane coalescence and virion entry to the cell.[5] Two drugs that inhibit the HIV-1 entry process have been approved: maraviroc, a CCR5 chemokine co-receptor antagonist, and enfuvirtide, an injectible polypeptidic inhibitor of gp41-mediated fusion. HIV-1 attachment inhibitors (AIs) are a previously disclosed class of orally bioavailable, small molecules that bind to and induce conformational changes within the HIV-1 viral envelope gp120 protein. These changes interfere with binding to the cellular CD4 receptor, thus inhibiting entry at the initial point of host cell engagement by the virus.[6–11] Potent and selective inhibition has been observed in vitro against macrophage-, T-, and dual-tropic HIV-1 strains by members of this class.[9,12,13] Mechanistically, HIV AIs are attractive because they target a viral, not a host receptor, they inhibit HIV-1 independent of viral co-receptor usage, and they lack cross resistance with existing drug classes. In addition, several preclinical in vitro studies suggest the potential for this class of compound to exhibit benefits beyond reduction in viral load, including T-cell protection, although the potential for these effects to manifest in the clinic will need to be determined experimentally.[14–16]

Indole diketo benzoylpiperazines such as **1** (Fig 1) represent the initial lead chemotype that was discovered through high throughput compound screening of the Bristol-Myers Squibb corporate collection. The structure–activity relationship (SAR) data that has been published on indole-based HIV-1 attachment inhibitors defines basic aspects of the pharmacophore and also highlights marginal pharmaceutical and metabolic stability properties.[17–19] These observations led to a focused effort on azaindole inhibitors, all of which offered improved physical properties.[13] Unsubstituted analogs of the 4-azaindole **2** and 7-azaindole **3** series demonstrated moderate potency improvements over the unsubstituted indole chemotype, while the 5-azaindole **4** and 6-azaindole **5** analogs exhibited reduced potency. Incorporation of a 4-methoxy substituent led to a 6-fold boost in potency in the indole **6** series and a ~two fold improvement in the 7-azaindole series **7** (BMS-378806). BMS-378806 (**7**) was the first small molecule inhibitor of HIV-1 attachment to enter into clinical trials, but failed to show sufficient exposure to merit proceeding into an efficacy trial.[12,20] The 4-methoxy substituent also provided a substantial (17-fold) improvement in potency in the 6-azaindole (**8**) series which lead

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http://dx.doi.org/10.1016/j.bmcl.2012.10.120

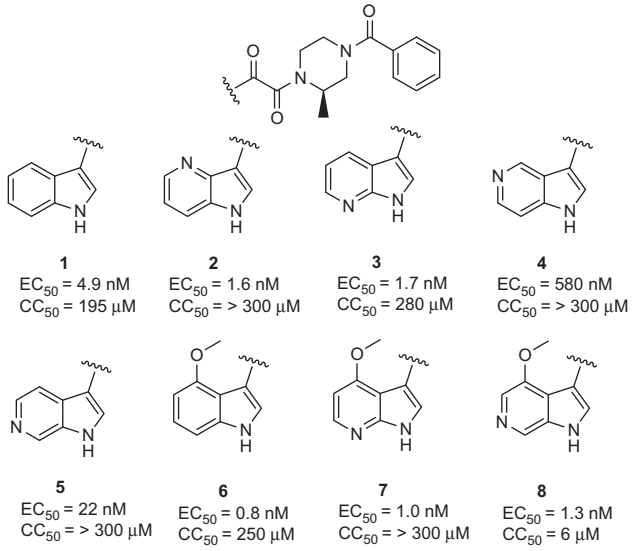
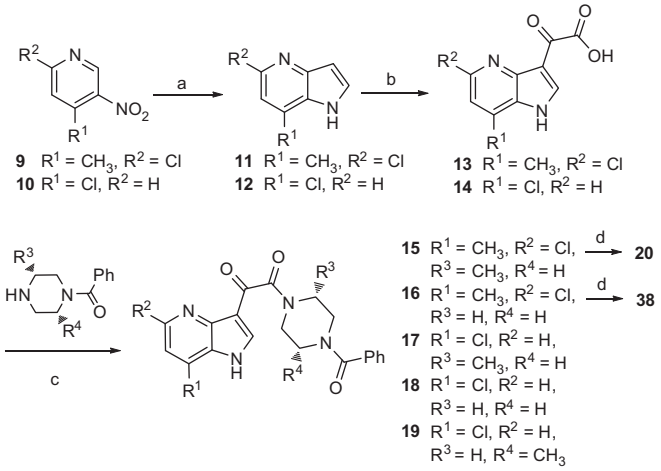


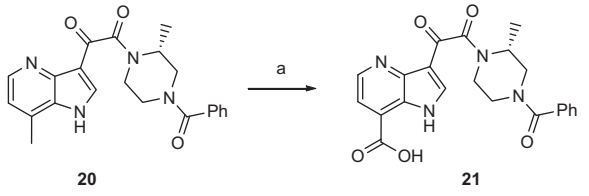
Figure 1. Lead HIV attachment molecules, azaindole comparison.

to the discovery of BMS-488043, the molecule that first demonstrated clinical proof-of-concept for the HIV-1 attachment mechanism.[13] Since the 4-azaindole **2** exhibited potency comparable to the 4-methoxyindole **6** and the 4-methoxy-6-azaindole **8** and emerging SAR indicated that significant potency enhancements were attainable by substitution at the 7-position, a survey of this aspect of structural modification was pursued as part of the search for molecules with both improved potency and in vivo exposure compared to **7**.

The synthetic approach for preparing the key intermediates is illustrated in Scheme 1. The 4-azaindole cores **11** and **12** were prepared from the commercially available 3-nitropyridines **9** and **10** via a Bartoli reaction using an excess of vinyl Grignard reagent.[21,22] The 3-position of the 4-azaindole was selectively acylated with methyl chlorooxoacetate using $AlCl_3$ to yield **13** or **14**. This Friedel–Crafts acylation could be done traditionally to yield a ketoester intermediate which was then hydrolyzed to the carboxylic acid, or the reaction could be performed using an ionic liquid as solvent, which afforded the acid product directly.[23] Coupling the β-keto-



Scheme 1. Reagents and conditions: (a) CH_2=CHMgBr, THF, −20 °C, 20–40% (b) (i) $ClCOCO_2CH_3$, $AlCl_3$, CH_2Cl_2 (ii) K_2CO_3, MeOH, H_2O 82% (for **13**) or $ClCOCO_2CH_3$, $AlCl_3$, 1-ethyl-3-methyl-1*H*-imidazol-3-ium chloride, 80% (for **14**) (c) DEBPT, iPr_2EtN, DMF, 50–80% d) 10% Pd/C, H_2, 40 psi, 90%.



Scheme 2. Reagents and conditions: (a) SeO_2, pyridine, dioxane, H_2O, reflux, 35%.

carboxylic acids **13** and **14** with known benzoyl piperazines using DEPBT resulted in the desired diketobenzoyl piperazine 4-azaindole derivatives **15**–**19**.[24,25] Dehalogenation of **15** and **16** under hydrogenation conditions yielded **20** and **38**, respectively.

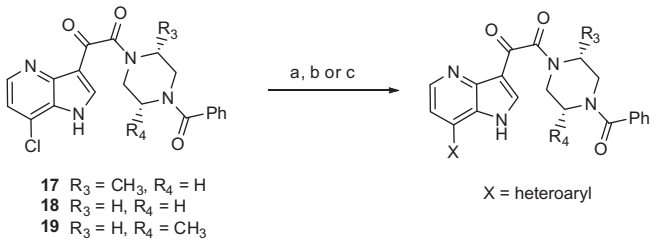
The 7-methyl compound **20** was oxidized with selenium dioxide in the presence of pyridine to yield the 7-carboxylic acid compound **21** (Scheme 2). The acid was converted directly to amides **22** and **30** using standard amine coupling conditions, or to a pentafluorophenyl ester intermediate which was reacted with heteroaryl amines to form compounds **28** and **29**.

The 7-chloro functionality in compounds **17–19** was converted to a 7-alkoxy substituent to afford **23** and **40** by displacement with potassium alkoxide under microwave irradiation conditions (Scheme 3). Similarly, all C-linked heterocycles were prepared via a $Pd(PPh_3)_4$-catalyzed cross-coupling reaction using the appropriate stannane or boronic acid at elevated temperatures. The N-linked heterocycles were prepared by nucleophilic displacement of the 7-chloro substituent with the appropriate heterocycle either directly or via copper(0) catalysis at 160 °C, again under microwave irradiation conditions.

All compounds were tested using a single cycle, HIV-1 pseudovirus assay which included an envelope DNA expression vector and a proviral cDNA (JR-FL) containing an envelope deletion mutation and a luciferase reporter gene.[7–9] This assay was designed to detect inhibition of early steps in the HIV-1 life cycle up to and including integration of viral DNA into the cell genome. All compounds were also tested for cytotoxicity. All potency and cytotoxicity assays were performed at a minimum in duplicate and the data are reported as an average. Analogs that demonstrated targeted potency and exhibited a therapeutic index equal to or greater than that of **7** were further evaluated using in vitro assays designed to assess their potential for a good pharmacokinetic profile or to manifest off-target liabilities. Molecules judged to display the potential for a profile superior to **7** were subsequently evaluated in a rat pharmacokinetic model.

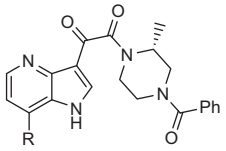
Compound **2** was the starting point in the 4-azaindole research effort. Since SAR development in the indole and 6-azaindole series had typically noted a moderate potency improvement with the 2*R*-methyl piperazine over the unsubstituted piperazine this moiety was initially employed (Table 1).[19]

Small modifications at the 7-position of the 4-azaindole from hydrogen (**2**) to chloro (**17**), methyl (**20**), carboxylic acid (**21**) or the simple amide **22** resulted in no or minimal losses in potency in the HIV-1 pseudotype assay. However, the 7-methoxy compound **23** exhibited subnanomolar potency. It is also worth noting that methylation of the indole NH, as in compound **24**, resulted in a >10-fold loss in potency. Introduction of a 4-methoxyphenyl (**25**) also resulted in an increase in potency when compared with **2**, as did other 6-membered heteroaromatics, represented by **26** and **27**. Cytotoxicity in the initial assay became measurable for the heteroaromatics **26** and **27** but at a level not considered to preclude further study in compounds with otherwise compelling profiles. Amides such as **28**, **29** and **30** demonstrated a wide range of potency, but the best molecule in this series (**28**) was only slightly more potent than the unsubstituted compound **2**. The incorporation of



Scheme 3. Reagents and conditions: (a) R_3Sn-heteroaryl, $Pd(Ph_3)_4$, dioxane 140 °C; (b) $(HO)_2B$-heteroaryl, $Pd(Ph_3)_4$, dioxane 140 °C; (c) heteroaryl (free NH), Cu(0), K_2CO_3, 160 °C.

Table 1
Potency and cytotoxicity of 4-azaindole analogs with 2*R*-methyl benzoyl piperazine

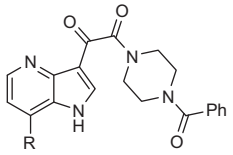


Compd	R	HIV EC_{50} (nM)	CC_{50} (uM)
2	H	1.56	>300
17	Cl	1.22	>300
20	CH_3	3.06	>300
21	COOH	3.38	>300
22	CONHMe	2.48	>300
23	CH_3O	0.63	>300
24	CH_3O (w/NMe)	7.37	>300
25	4-Methoxyphenyl	0.32	>300
26	Pyrimidin-5-yl	0.68	35.3
27	Pyrazin-2-yl	0.27	15.3
28	thiazol-2-ylcarbamoyl	0.43	>300
29	4-Methylthiazol-2-ylcarbamoyl	3.4	>300
30	Methoxy(methyl)carbamoyl	61.1	>300
31	Thiophen-2-yl	0.02	>300
32	Thiophen-3-yl	0.18	94.5
33	Benzo[*b*]thiophen-2-yl	0.10	170.5
34	4-Methylthiophen-2-yl	0.04	48.9
35	Thiazol-2-yl	0.10	>300
36	Oxazol-2-yl	0.18	>300
37	3,5-Dimethylisoxazol-4-yl	1.05	>300

C-linked 5-membered heteroaromatic rings provided the first significant enhancement in potency. The 2-thiophenyl compound **31** displayed an EC_{50} of 20 pM in the pseudotype assay, representing a 75-fold potency increase compared to **2**. Replacing the 2-thiophene with 3-thiophene (**32**), 2-benzothiophene (**33**) or 4-methyl-2-thiophene (**34**) resulted in compounds that were still several fold more potent than **2**. The 2-thiazolyl derivative **35** and 2-oxazolyl analog **36** each provided an EC_{50} value that was a >10-fold improvement over compound **2** and had no notable cytotoxicity. Interestingly, when the 3,5-dimethylisoxazol-4-yl moiety was attached to the 7-position (**37**), the improved potency that had been observed with other 5-membered ring heteroaromatics was no longer apparent. A possible explanation for this result is that substituents on the heteroaryl ring adjacent to the point of attachment to the 4-azaindole may prevent the heteroaromatic from achieving coplanarity with the 4-azaindole due to allylic 1,3-strain.[26] Although the bound conformation of attachment inhibitors has not been definitively established, a mnemonic in which substitution around the attached heteroaromatic that allows coplanarity with the 4-azaindole has generally proven to be a useful guide as a predictor of optimal potency within a series.[27–30]

Since potency of less than 200 pM had been demonstrated in a number of compounds in the 4-azaindole series, the necessity of the methyl group on the piperazine ring as a potency-enhancing substituent was next investigated. An unsubstituted piperazine in this series would be synthetically more accessible than a methyl-substituted piperazine if the potency could be maintained (Table 2). Once again, simple 7-substituents such as methyl (**38**), chloro (**39**) and methoxy (**40**) were prepared and tested. All showed significant decreases in potency, exemplifying the importance of the 2*R*-methyl group on the piperazine. However, once 5-membered heteroaryls were installed at the 7-position, the beneficial impact of this methyl group on potency was muted. In fact, the 4-methyl-2-thiophenyl **41**, 2-thiazole **43** and 2-oxazole **44** analogs were equipotent in the desmethyl series when compared with the 2*R*-methylpiperazine series (**34**, **35**, and **36**, respectively). Introducing an acetyl group to the thiophene (**42**) resulted in an improved CC_{50} but reduced potency compared with **41**. Additionally, shifting the attachment point of the 2-thiazole **43** to the 5-position (**45**) produced a molecule with an EC_{50} of 90 pM and a CC_{50} of >300 μM. A methyl group on the 4-position of the 2-substituted thiazole (**46**) maintained the potency of the unsubstituted 2-thiazole, but with a measurable increase in cytotoxicity. Moving the methyl group to the 5-position (**47**) decreased the cytotoxicity, but potency was also moderately reduced. 6-Membered heteroaromatics were also investigated and analogs such as pyridin-2-yl (**48**), pyrazin-2-yl (**49**) and 6-methoxypyridin-2-yl (**50**) were generally found to be less potent than *C*-linked 5-membered heteroaromatics. The N-linked heteroaromatics were explored for the first time in this series. The most potent molecules within this group were the 2-linked, 1,2,3 triazole **51** and the 2-linked 1,2,3-benzotriazole **55**. These molecules have nitrogen atoms flanking the site of attachment to the core. Consequently, there is no steric encumbrance that would hinder coplanarity between the two heteroaromatic rings. Replacing one of these flanking nitrogens with a CH, as in **52**, **53**, or **54** lead to a moderate loss in potency across the series, consistent with the coplanarity argument. If a fused aromatic ring was placed into one of these flanking positions, as in **56** or **57**, significant, 50 to 100-fold reductions in potency were observed.

Table 2
Potency and cytotoxicity of 4-azaindole analogs with an unsubstituted benzoyl piperazine

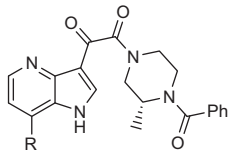


Compd	R	HIV-1 EC_{50} (nM)	CC_{50} (uM)
38	CH_3	46.3	>300
39	Cl	18.4	>300
40	CH_3O	12.3	>300
41	4-Methylthiophen-2-yl	0.02	85
42	5-Acetylthiophen-2-yl	0.29	268
43	Thiazol-2-yl	0.21	150
44	Oxazol-2-yl	0.39	>300
45	Thiazol-5-yl	0.09	>300
46	4-Methylthiazol-2-yl	0.20	23
47	5-Methylthiazol-2-yl	0.52	251
48	Pyridin-2-yl	0.93	231
49	Pyrazin-2-yl	1.71	>300
50	6-Methoxypyridin-2-yl	7.40	174
51	2*H*-1,2,3-Triazol-2-yl	0.32	>300
52	1*H*-1,2,4-triazol-1-yl	0.64	>300
53	1*H*-1,2,3-triazol-1-yl	0.88	>300
54	pyrazol-1-yl	0.89	>300
55	2*H*-benzo[*d*][1,2,3]-triazol-2-yl	0.21	124
56	1*H*-benzo[*d*][1,2,3]-triazol-1-yl	23.6	246
57	3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl	10.6	>300

Analogs with a 3*R*-methyl-piperazine were prepared and evaluated to determine if they offered potency (Table 3) and/or pharmacokinetic advantages.[31] Within this series, the 2-thiophene **59** and the 4-methyl-2-thiophene **60** each resulted in good EC_{50} values of ~200 pM. The 2-oxazole **61** and the 2-thiazole **62** derivatives were each about equipotent with the desmethyl and 2*R*-methyl piperazine analogs. Methyl substitution on the 2-thiazole was also tolerated, although the 4-methyl **64** was slightly more potent than the 5-methyl isomer **63**. Interestingly, a similar shift of the methyl group from the 3-methylpyrazol-1-yl analog **66**, which had an EC_{50} value of 460 pM, to the 4-methylpyrazol-1-yl **67**, again afforded a loss of potency. As anticipated based on the coplanarity mnemonic, within the N-linked 5-membered heteroaryl analogs, the 2-linked 1,2,3-triazole **65** and the 2-linked 1,2,3-benzotriazole **68** proved to be the most potent, but within the 3*R*-methyl series the 3-methylpyrazo-l-yl analog **66** was equal in potency to **68**. The importance of avoiding allylic 1,3-strain between the 7-heteroaryl and the 4-azaindole was again demonstrated in this series.[26] When comparing the 2-benzotriazole **68** to the 1-benzotriazole **69** and the 3-methyl-1,2,4-triazol-1-yl **70** to 5-methyl-1,2,4-triazol-1-yl **71**, the more sterically encumbered molecule was nearly 20-fold less potent. This loss in potency may be attributed to interference with a coplanar conformation between the heteroaryl ring and the 4-azaindole. Although collectively the 3*R*-methyl piperazine series displayed slightly diminished potency when compared with the desmethyl or 2*R*-methyl series, this series generally demonstrated superior predicted and balanced properties from in vitro assays (including metabolic stability and permeability) (unpublished results). Overall, optimal potency in all three 4-azaindole series at the key 7-position was obtained using 5-membered ring heteraromatics which possessed structural elements that would enhance (or not hinder) coplanarity between the heteroaromatic elements. Also, the 2*R*-methyl-piperazine did not offer a significant potency advantage over the unsubstituted piperazine or the 3*R*-methyl-piperazine in the most potent analogs.

Four molecules within the 4-azaindole series demonstrated sufficiently potent antiviral activity and in vitro ADME properties along with limited off-target liabilities to merit investigation in a rat pharmacokinetic study. Compounds were administered as a single dose (IV at 1 mg/kg and PO at 5 mg/kg) and plasma concentrations assessed. All of the molecules displayed pharmacokinetic properties in rats that were superior to **7** (see Table 4). However, both the 1,2,3-triazol-2-yl compound in the desmethyl piperazine series (**51**) and the 2-oxazole in the 3*R*-methyl piperazine series (**61**) displayed higher AUC values and lower clearance than that exhibited by **62** and **65** in the 3*R*-methyl piperazine series.

Table 3
Potency and cytotoxicity of 4-azaindole analogs with 3*R*-methyl benzoyl piperazine.



Compd	R	HIV EC_{50} (nM)	CC_{50} (uM)
58	Cl	11.6	300
59	Thiophen-2-yl	0.24	168
60	4-Methylthiophen-2-yl	0.21	123
61	Oxazol-2-yl	0.34	135
62	Thiazol-2-yl	0.31	35
63	5-Methylthiazol-2-yl	0.71	28
64	4-Methylthiazol-2-yl	0.19	30
65	2*H*-1,2,3-Triazol-2-yl	0.44	300
66	3-Methyl-1*H*-pyrazol-1-yl	0.46	300
67	4-Methyl-1H-pyrazol-1-yl	1.59	>150
68	2*H*-Benzo[*d*][1,2,3]-triazol-2-yl	0.31	74
69	1*H*-Benzo[*d*][1,2,3]-triazol-1-yl	5.34	71
70	3-Methyl-1*H*-1,2,4-triazol-1-yl	0.59	>300
71	5-Methyl-1*H*-1,2,4-triazol-1-yl	10.8	>300

Table 4
Rat pharmacokinetic properties of compounds **51**, **61**, **62** and **65** compared with BMS-378806 (**7**)

	7	**51**	**61**	**62**	**65**
F%	19	65	60	41	78
AUC po.(uM*hr)	1.3	9.6	5.6	1.3	3.3
CL iv (mL/min/kg)	32	5.4	7.4	11.2	13.9

In summary, a series of novel and potent 4-azaindole core containing compounds was prepared and evaluated for potential utility as inhibitors of HIV-1 attachment and infection in vitro. Synthetic chemical approaches were successfully developed that allowed for the investigation of SAR around the key 7-position of this core. Many aromatic heterocyclic compounds that conformed to a model in which coplanarity between the C-7 substituent and the core heterocycle was accessible were found to have improved potency when compared with **7** from which two compounds, **51** and **61**, exhibited superior PK profiles in the rat. Thus, the goal of an improvement in combined potency and exposure was achieved in this series, and 4-azaindole core molecules were considered for advancement. Ultimately, however, more promising candidates were discovered in a related 6-azaindole core series a member of which provided clinical proof-of-concept for the attachment mechanism.[13,32–35] A prodrug of a second more potent compound within the 6-azaindole series has been advanced into Phase II clinical studies.[36–40]

Acknowledgments

The authors would like to gratefully acknowledge Dr. Gregory Yamanaka (deceased) for providing the antiviral data presented in this manuscript. Greg was both a thoughtful and thought-provoking scientist and he is dearly missed.

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