Aryl Substituted Benzimidazolones as Potent HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitors

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Supporting Information

ABSTRACT: Since the discovery of HIV as the etiological agent of AIDS, the virus has infected millions of people each year. Fortunately, with the use of HAART, viremia can be suppressed to below detectable levels in the infected individuals, which significantly improves their quality of life and prevents the onset of AIDS. However, HAART is not curative and issues relating to adherence and drug resistance may lead to the re-emergence of viremia, the development of AIDS, and ultimately death. To address a pressing need for the development of new and efficacious antiretroviral agents with activity against viruses bearing prevalent resistant mutations, we have designed two generations of benzimidazolone derivatives as HIV non-nucleoside reverse transcriptase inhibitors. The first generation benzimidazolone inhibitors were found to be potent inhibitors of wild-type HIV reverse transcriptase but were ineffective in the presence of common resistance mutations such as K103N and Y181C. A second generation benzimidazolone inhibitor (compound 42) not only showed inhibitory activity against wild-type HIV but also remained active against HIV containing the K103N, Y181C, and K103N/Y181C drug resistance mutations.

KEYWORDS: HIV, NNRTI, indole, benzimidazolone, reverse transcriptase

Over the past 30 years, significant progress has been made in the treatment of people infected with the human immunodeficiency virus (HIV), the known causative agent of acquired immunodeficiency syndrome (AIDS).¹ However, no cure has been found for HIV infection. There are currently close to 40 million people living with HIV/AIDS, and just under 1 million AIDS related deaths were estimated to have occurred in 2017.²

Currently, there are six main classes of antiretroviral drugs which target different stages of the viral life cycle.³ HIV sufferers receiving treatment will normally receive a combination of these drugs, known as highly active antiretroviral therapy (HAART).⁴ Typically in low-to-middle income countries, treatment naïve patients receiving HAART will be taking two nucleoside reverse transcriptase inhibitors (NRTIs) and a non-nucleoside reverse transcriptase inhibitor (NNRTI).⁵ NNRTIs are an important component of HAART given their potent antiviral activity, high selectivity, favorable pharmacokinetics, and structural diversity.⁶ However, NNRTIs are vulnerable to the onset of resistance due to mutations in the reverse transcriptase (RT) allosteric binding pocket. First-generation NNRTIs such as Nevirapine (NVP) and Efavirenz (EFV) are especially susceptible to the onset of resistance through single point mutations, such as K103N and

Y181C.^{7,8} Although second-generation NNRTIs such as Etravirine (ETV) and Rilpivirine (RPV) display a higher genetic barrier to the development of resistance, they unfortunately have their own associated problems. For example, the K101P mutation confers high level resistance to RPV,⁹ while Y181I and Y181V mutations confer high levels of resistance to both RPV and ETV.⁸ Despite these shortcomings, NNRTIs remain a critical component of HIV therapy. Thus, there is a need to develop new therapeutic agents that remain effective against these mutants.

Our previous research into the development of novel NNRTIs that are effective against the problematic resistant strains identified a series of indole methyl ether and methyl sulfide compounds (1–4) as potent inhibitors of HIV RT (Figure 1).^{10,11} Compound 2 in particular not only exhibited low-nanomolar activity against wild-type HIV but also was able to maintain efficacy in the presence of clinically prevalent single point mutations such as K103N.¹⁰ However, due to the presence of ubiquitous cellular esterases *in vivo*, the ester

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Figure 1. A series of indole methyl ether and methyl sulfide compounds identified in previous publications were found to be potent inhibitors of wild-type HIV-1.^{10,11}

functionality at the 2-position on the indole scaffold was identified as a potential liability.

Although there exists a variety of less-labile bioisosteric replacements for the ester functionality, it was decided to address this issue through a scaffold-hopping approach. This approach, with the aid of molecular modeling, led to the identification of the benzimidazolone heterocycle as a suitable isofunctional replacement for the indole scaffold (Figure 2a).

Figure 2. (a) A scaffold-hopping approach led to the identification of benzimidazolone 5 as an isofunctional alternative to the parent indole compound 1. (b) An overlay of indole compound 1 (white) with the benzimidazolone compound 5 (orange) illustrates that both compounds maintain a similar binding orientation in the allosteric site. Docking studies were conducted using the receptor PDB ID 2RF2. Note, although the modeling predicts a slightly better binding energy for the *R*-enantiomer (as shown in figure b), all compounds synthesized and assayed were racemic.

Docking studies comparing the binding mode of the benzimidazolone compound 5 against the indole series indicated that this new scaffold would maintain a similar binding orientation in the non-nucleoside inhibitor binding pocket (NNIBP) to the parent indole compound 1 by retaining interactions with Tyr181 and the backbone of

Lys101 and by occupying the small hydrophobic Val179 pocket (Figure 2b).

To validate this hypothesis, compound 5 was synthesized starting with the alkylation of commercially available 5-chloro-2-nitroaniline 9 (Scheme 1). The required alkylating agent, (1-iodopropyl)benzene 8, was synthesized by way of a Grignard reaction between ethylmagnesium iodide and benzaldehyde 6 to afford the secondary alcohol 7, which was subsequently converted into the corresponding iodide 8 in the presence of $BF_3 \cdot Et_2O$ and potassium iodide. With the desired alkylating agent 8 in hand, alkylation of 9 proceeded readily to afford compound 10. Reduction of the nitro compound 10 yielded the substituted *o*-phenylenediamine 11, which was converted into the benzimidazolone 5 using CDI.

Scheme 1^a

^aReagents and conditions: (a) EtI, Mg, Et_2O , 0 °C – rt, 2 h, 84%; (b) $BF_3 \cdot Et_2O$, KI, dioxane, rt, 18 h, 67%; (c) 8, NaH, THF, 0 °C – rt, 18 h, 88%; (d) Fe, AcOH, EtOH/ H_2O , sonication, 2 h, 78%; (e) CDI, THF, rt, 18 h, 73%.

Compound 5 was evaluated in a whole-cell nonreplicative HIV-1 phenotypic assay.^{12–14} The resulting biological data revealed that compound 5 exhibited similar potency to lead indole compounds 1–4, with an IC_{50} value of 36 nM (Figure 3). Unfortunately, further evaluation of compound 5 against

Figure 3. Biological evaluation of compound 5 in a whole-cell phenotypic HIV-1 assay revealed that, while a potent inhibitor of wild-type HIV, compound 5 was not effective against the K103N and Y181C resistance mutations.

clinically relevant resistant strains such as K103N and Y181C showed that this compound was very sensitive to these mutations and resulted in a significant loss in potency (>10-fold). The susceptibility of compound 5 to the Y181C mutation could be attributed to the fact that the binding affinity of compound 5 in the NNIBP most likely relies heavily on π – π interactions of the aryl group at the 1N-position with the side chain of Tyr181 (Figure 2). The mutation of the aromatic tyrosine into the aliphatic cysteine residue therefore results in a loss of this interaction and, consequently, a loss in binding affinity for the NNIBP. On the other hand, the mechanism by which the K103N mutation is thought to confer resistance is not yet fully understood. In one instance resistance is thought to occur through stabilization of the

closed-pocket form of the NNIBP in the absence of an inhibitor. This consequently hinders inhibitor accessibility to the NNIBP.¹⁵ Alternatively, changes in hydrophobic and electrostatic interactions as a result of the mutation of lysine into asparagine have been hypothesized to reduce the binding affinity of inhibitors to the NNIBP.¹⁶

Going forward, we envisaged that in order to overcome susceptibility to the Y181C mutation, reliance on π - π interactions with Tyr181 would have to be eradicated, without compromising the affinity for the NNIBP. To this end, it was decided to transpose the phenyl ring from the 1*N*-position on the benzimidazolone core to the 7-position (Figure 4a).

Figure 4. (a) A schematic representation illustrating the strategy to reduce susceptibility to the Y181C resistant strain by transposing the aryl functionality from the 1*N*-position on the benzimidazolone core to the 7-position. (b) An overlay of the two benzimidazolone scaffolds in the NNIBP showing that both compounds maintain a similar binding orientation. Docking studies were conducted using the receptors PDB ID 2RF2 and 2JLE.

Not only would this eliminate reliance on π - π interactions with Tyr181 but, based on docking studies, it also would result in creating new π - π interactions with Tyr188 and, importantly, π interactions with the highly conserved Trp229 residue in the NNIBP.¹⁷ Furthermore, molecular modeling studies indicated that the transposition of the aryl ring system would not adversely affect the key hydrogen bonding interaction with the backbone of Lys101, and with a suitably small alkyl group located at the 1*N*-position, occupation of the small Val179 pocket could also be maintained (Figure 4b). It is also worth noting that with the aryl functionality removed from the 1*N*-position on the benzimidazolone scaffold, Tyr181, would be able to adopt the energetically favored "down" position, as found in the apo RT enzyme (Figure 4b).^{18,19} An attractive feature from a synthetic point of view is that the new scaffold would not contain a stereogenic carbon.

To evaluate the effectiveness of this strategy, a small library of second-generation benzimidazolone compounds featuring

various substituted and unsubstituted aryl and heteroaryl groups at the 7-position was synthesized.

Synthesis of these second-generation compounds began with the chemoselective introduction of a benzyl group onto commercially available 2-amino-3-nitrophenol **13** (Scheme 2),

Scheme 2^a

^aReagents and conditions: (a) BnBr, K₂CO₃, DMF, -10 °C – rt, 18 h, 95%; (b) diethyl sulfate (DES), MeI or PrBr, NaH, DMF, or THF, 0 °C – rt, 18 h, 68% – 97%; (c) SnCl₂·2H₂O, EtOH, sonication, 15 min; (d) CDI, MeCN, rt, 18 h, 75% – 89%; (e) SEM-Cl, NaH, DMF, 0 °C – rt, 18 h, 67% – 82%; (f) Pd/C, H₂ (1 atm), EtOH, rt, 18 h, 79% – 85%; (g) aryl halide, CuI, K₃PO₄, picolinic acid, DMSO, 85 °C, 18 h, 61% – 91%; (h) aryl halide, Cs₂CO₃, DMF, 100 °C, 2 h, 62% – 94%; (i) BF₃·OEt₂, DCM, 0 °C – rt, 3 h then NaOH, THF/H₂O, rt, 18 h, 16% – 90% over 2 steps.

delivering **14**. This was followed by the mono *N*-alkylation of **14** with an appropriate alkyl halide to afford compounds **15**–**17**. A subsequent reduction of the nitro group in the presence of tin(II) chloride with ultrasonic irradiation yielded substituted *o*-phenylenediamines **18**–**20**, which were then subjected to a ring-closing reaction with CDI to afford compounds **21**–**23**. With the desired benzimidazolone core constructed, the remaining benzimidazolone nitrogen was protected using 2-(trimethylsilyl)ethoxymethyl chloride. The resulting compounds **24**–**26** were then subjected to palladium-catalyzed hydrogenation conditions to remove the benzyl protecting group, affording **27**–**29**. The resulting phenols were coupled to various aryl and heteroaryl halides by way of a nucleophilic aromatic substitution reaction (S_NAr) or under Ullmann coupling conditions to give compounds **30**–**39**. The final step in this synthesis involved a two-step removal of the SEM protecting group with BF₃·OEt₂ and then NaOH, to afford the desired second-generation benzimidazolone compounds **40**–**49**.

Before evaluating whether our strategy to overcome susceptibility to the Y181C resistant strain was successful, the compounds in this library were profiled for antiviral activity against wild-type HIV in our phenotypic assay (Table 1).

Compound **40**, which was an obvious analogue of the first-generation benzimidazolone compound **5**, exhibited very poor activity against HIV with an IC₅₀ value of only 4 μM. However,

Table 1. HIV-1 Phenotypic Assay against Wild-Type HIV (IC₅₀) and Toxicity (CC₅₀) Data

Com- pound	R ¹	R ²
			IC ₅₀ WT (μM)	CC ₅₀ (μM)
40	Et	Ph	3.88±0.736	55.0
41	Et		0.303±0.075	7.16
42	Et		0.026±0.007	24.1
43	Me		0.029±0.008	53.4
44	Pr		0.050±0.003	24.8
45	Et		0.063±0.006	96.6
46	Et		2.27±0.033	31.3
47	Et		>44.1	95.1
48	Et		13.3±1.465	>100
49	Et		1.36±0.082	>100
NVP			0.105±0.020	92.7

typically for compounds with an aryl ring system situated in the vicinity of Tyr188, the introduction of functional groups such as a methyl, chloro, or nitrile has been shown to significantly improve potency against wild-type and resistant HIV strains.^{20–22} The introduction of two methyl groups on compound **41** unfortunately only salvaged some activity against wild-type HIV (IC₅₀ = 303 nM). It was only with the introduction of chloro and nitrile substituents onto the aryl ring system (**42–45**) that we observed a drastic improvement in potency. Quite possibly, this marked improvement in potency could be attributed to the theory that the introduction of electron-withdrawing groups results in an improvement in the edge-to-face π -interactions with Trp229.²³ A larger aryl group in the form of a naphthalene was not tolerated in the NNIBP (compound **46**) and exhibited poor activity against wild-type HIV. Similarly, substituted heteroaryl groups (compounds **47–49**) were found not to be efficacious. In

general, all the compounds investigated contained an ethyl group at the 1*N*-position, which molecular modeling found to be optimal for occupying the small Val179 pocket. However, in the case of compounds **43** and **44**, methyl and propyl groups at this position were also found to be effective, although the propyl group exhibited a slight drop in potency, most likely due to the fact that the limit of the size of the alkyl group optimally occupying this pocket has been reached.

Having identified compounds **42** and **43** as the most potent compounds in this series, we now compared their activities against a panel of resistant strains (Table 2).

Table 2. Evaluation of Compounds 42 and 43 in a Phenotypic Assay against a Panel of Clinically Relevant Resistant Strains of HIV

	IC ₅₀ (μM)	
	42	43
WT	0.026 ± 0.007	0.029 ± 0.008
K103N	0.111 ± 0.030	0.126 ± 0.006
Y181C	0.018 ± 0.006	0.055 ± 0.013
V106M	0.293 ± 0.040	0.494 ± 0.130
G190A	0.126 ± 0.001	0.107 ± 0.013
Y188C	0.007 ± 0.004	0.236 ± 0.017
Y188H	0.415 ± 0.001	0.074 ± 0.005
K103N/Y181C	0.052 ± 0.005	ND

Pleasingly, transposition of the aryl ring to the 7-position on the benzimidazolone core was indeed found to be a successful strategy, as compounds **42** and **43** were able to maintain complete potency against the Y181C resistant strain. Furthermore, where first-generation compound **5** experienced high levels of resistance in the presence of the K103N mutation, compounds **42** and **43** experienced only low levels of resistance with a 4-fold loss in potency. Similarly, low levels of resistance were also observed for the G190A mutation. Unfortunately, in the presence of V106M, a single-point mutation commonly observed among patients receiving EFV,⁷ compounds **42** and **43** experienced high levels of resistance (>10-fold). Interestingly, point mutations at Tyr188 affected the activity of the two compounds differently. Compound **42** was able to maintain potency in the presence of the Y188C mutation but experienced high levels of resistance in the presence of Y188H. The opposite was observed for compound **43**. Compound **42** was also tested against a clinically common double mutant K103N/Y181C, which is known to cause high-levels of resistance to approved first-generation NNRTIs NVP and EFV.²⁴ Pleasingly, compound **42** was found to perform very well with only a 2-fold loss in potency.

Although second-generation compounds **42** and **43** were potent inhibitors of wild-type HIV and displayed a promising resistance profile, molecular modeling studies identified an opportunity to possibly further boost activity by increasing the binding affinity of these compounds for the NNIBP through increased interactions within this pocket.

To this end, two promising strategies were identified. In the first instance, we decided to investigate targeting a lysine residue (Lys223) situated at the top of a small hydrophobic chimney formed by the amino acid residues Trp229, Tyr188, and Phe227. In order to facilitate a sufficiently strong hydrogen bond with Lys223, a substituent of a suitable length would have to be installed onto the phenyl ring system of the benzimidazolone scaffold. With the aid of molecular modeling

we identified the cyanovinyl group, as shown on compound **50**, as an appropriate substituent to fulfill these requirements, while not adversely affecting the binding orientation of the benzimidazolone core in the NNIBP (Figure 5). Interestingly, the use of the cyanovinyl group is not without precedent as it is found on other NNRTIs, including the second-generation NNRTI, RPV.^{25–27}

Figure 5. (a) In order to facilitate a hydrogen bond with Lys223 situated at the top of a small hydrophobic chimney, a cyanovinyl group would be installed onto the “upper” aryl ring system of the benzimidazolone scaffold. (b) Even with the introduction of the cyanovinyl group, compound **50** would still retain other important interactions within the NNIBP. Docking studies were conducted using the receptor PDB ID 2JLE.

With this promising compound in mind we set about the synthesis of **50**, starting from the SEM-protected benzimidazolone precursor **27** described previously in Scheme 2. Installation of the required 3-bromo-5-cyanophenyl functionality by way of an S_NAr reaction was readily achieved with 3-bromo-5-fluorobenzonitrile in the presence of Cs_2CO_3 to afford **51** in excellent yield (Scheme 3). A subsequent Heck

Scheme 3^a

^aReagents and conditions: (a) 3-bromo-5-fluorobenzonitrile, Cs_2CO_3 , DMF, 100 °C, 2 h, 96%; (b) acrylamide, K_2CO_3 , *N*-phenylurea, $Pd(OAc)_2$, DMF, 130 °C, 2 h, 89%; (c) TBAF, 60 °C, 18 h, 32%; (d) $POCl_3$, 0 °C – rt, 2 h, 41%.

reaction employing phosphine-free conditions between **51** and acrylamide afforded **52**, with the acrylamide in the desired *trans* configuration. It is worth noting that during the synthesis of **50**, we found that the SEM group had to be removed prior to the dehydration of the vinyl amide to the corresponding nitrile. Therefore, SEM deprotection of the benzimidazolone NH was carried out in the presence of TBAF, affording the deprotected benzimidazolone **53**, which then underwent a dehydration of the amide with $POCl_3$, to finally arrive at the desired compound, **50**.

Our second strategy to further bolster activity involved an attempt to reintroduce the additional hydrogen bond acceptor which interacts with the backbone of Lys101 (a feature exhibited by indole compounds **1–4**, discussed previously and shown in Figure 1). It was envisaged that by way of a molecular hybridization approach, guided by molecular modeling, a hybrid of our lead second-generation benzimidazolone compound **42**, and known NNRTI EFV, would furnish the novel benzoxazin-2-one compound **54**. This novel scaffold would reposition the carbonyl at position 2 in such a way that it would favor the formation of a hydrogen bond with the backbone of Lys101 (Figure 6a), without significantly altering

Figure 6. (a) Compound **54** was designed using a molecular hybridization approach between **42** and EFV. (b) Docking studies suggested that the new benzoxazin-2-one scaffold would be able to facilitate the formation of an additional hydrogen bond to the backbone of Lys101 due to the repositioning of the carbonyl at the 2-position. Modeling studies were conducted using the receptor PDB ID 2JLE

the binding orientation in the NNIBP, so as not to lose crucial interactions with Tyr188 and Trp229 (Figure 6b). In order to avoid synthetic complexity, it was decided to install two methyl groups at position 4 on the benzoxazin-2-one scaffold. Docking studies had demonstrated that this particular compound would be well accommodated in the NNIBP.

For the synthesis of **54**, commercially available 2-methyl-3-nitrophenol **55** was alkylated with methyl iodide in the presence of NaH to afford **56** (Scheme 4). Oxidation of the benzylic methyl to the carboxylic acid **57** was carried out in the presence of $KMnO_4$, albeit in a modest yield. Subsequent esterification of the acid to the corresponding methyl ester **58** was followed by reduction of the nitro group under standard palladium-catalyzed hydrogenation conditions to afford **59**. A

Scheme 4^a

^aReagents and conditions: (a) MeI, NaH, DMF, 0 °C – rt, 18 h, 93%; (b) KMnO₄, *t*-BuOH/H₂O, 100 °C, 18 h, 34%; (c) MeI, K₂CO₃, DMF, rt, 2 h, 96%; (d) Pd/C, H₂ (1 atm), EtOH, rt, 18 h, 93%; (e) MeMgBr, THF, 0 °C – rt, 4 h, 91%; (f) CDI, MeCN, rt, 30 min, 68%; (g) BBr₃, DCM, 0 °C, 4 h, 90%; (h) 3-chloro-5-fluorobenzonitrile, Cs₂CO₃, DMF, 70 °C, 18 h, 13%.

Grignard reaction with an excess of methylmagnesium bromide furnished the tertiary alcohol **60**, which could then undergo a ring-closing reaction with CDI to afford the desired benzoxazin-2-one core **61**. Deprotection of **61** in the presence of BBr₃ yielded the phenol **62**, which finally underwent an S_NAr reaction with 3-chloro-5-fluorobenzonitrile to afford the target compound, **54**.

With compounds **50** and **54** in hand we could investigate our strategy to improve activity through the introduction of additional electrostatic interactions and compare their activities against wild-type HIV, and the mutant panel described for lead compound **42**. From Table 3 it is evident that compound **50**

Table 3. Evaluation of Target Compounds **42, **50**, and **54** in a Phenotypic Assay against Wild-Type and Clinically Relevant Mutant Strains of HIV-1 (IC₅₀) and Toxicity Data (CC₅₀)**

	IC ₅₀ (μM)		
	42	50	54
WT	0.026 ± 0.007	0.049 ± 0.007	0.021 ± 0.008
K103N	0.111 ± 0.030	0.166 ± 0.022	0.798 ± 0.152
Y181C	0.018 ± 0.006	0.073 ± 0.011	0.028 ± 0.004
V106M	0.293 ± 0.040	0.926 ± 0.104	0.630 ± 0.059
G190A	0.126 ± 0.001	0.377 ± 0.096	2.759 ± 0.157
Y188C	0.007 ± 0.004	0.014 ± 0.003	0.007 ± 0.002
Y188H	0.415 ± 0.001	0.468 ± 0.029	1.150 ± 0.220
K103N/Y181C	0.052 ± 0.005	0.051 ± 0.001	0.894 ± 0.057
CC ₅₀ (μM)	24.1	9.70	82.7

maintains a similar potency to lead compound **42** with no noticeable improvement in activity against K103N, V106M, or the double mutant K103N/Y181C. Compound **50** does exhibit a lower therapeutic index due to increased toxicity. Unfortunately, compound **54** exhibited an inferior activity profile against the mutant panel with the K103N, G190A, and the double mutant K103N/Y181C exhibiting much higher levels of resistance against this compound.

In conclusion, a series of first- and second-generation benzimidazolones were synthesized and evaluated for their activity against wild-type and resistant strains of HIV. The first-

generation compound **5** was found to be effective against wild type HIV but suffered significantly in the presence of clinically relevant resistant strains such as K103N and Y181C. However, second-generation compound **42** was able to maintain efficacy in the presence of the Y181C as well as the problematic Y181C/K103N double mutant. Other commonly observed mutations such as K103N and G190A exhibited only low levels of resistance against compound **42**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmchemlett.8b00549.

Synthetic procedures, spectral data, and the *in vitro* protocol for test compound screening (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

AIDS, acquired immunodeficiency syndrome; EFV, efavirenz; ETV, etravirine; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; NNIBP, non-nucleoside inhibitor binding pocket; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; RPV, rilpivirine; RT, reverse transcriptase.

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