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Communication

Boronic acid-containing diarylpyrimidine derivatives as novel HIV-1 NNRTIs: Design, synthesis and biological evaluation

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ABSTRACT

Drug resistance remains to be a serious problem with type I human immunodeficiency virus (HIV-1) non-nucleoside reverse transcriptase inhibitors (NNRTIs). A series of novel boronic acid-containing diarylpyrimidine (DAPY) derivatives were designed *via* bioisosterism and scaffold-hopping strategies, taking advantage of the ability of a boronic acid group to form multiple hydrogen bonds. The target compounds were synthesized and evaluated for their anti-HIV activities and cytotoxicity in MT-4 cells. Compound **10j** yielded the most potent activity and turned out to be a single-digit nanomolar inhibitor towards the HIV-1 IIIB [wild-type (WT) strain], L100I and K103N strains, with 50% effective concentration (EC_{50}) values of 7.19–9.85 nmol/L. Moreover, **10j** inhibited the double-mutant strain RES056 with an EC_{50} value of 77.9 nmol/L, which was 3.3-more potent than that of EFV (EC_{50} = 260 nmol/L) and comparable to that of ETR (EC_{50} = 32.2 nmol/L). **10j** acted like classical NNRTIs with high affinity for WT HIV-1 reverse transcriptase (RT) with 50% inhibition concentration (IC_{50}) value of 0.1837 μmol/L. Furthermore, molecular dynamics simulation indicated that **10j** was proposed as a promising molecule for fighting against HIV-1 infection through inhibiting RT activity. Overall, the results demonstrated that **10j** could serve as a lead molecule for further modification to address virus-drug resistance.

With the morbidity and mortality increasing rapidly worldwide, the acquired immunodeficiency syndrome (AIDS) keeps to be one of the most serious global public health problems, and the type I human immunodeficiency virus (HIV-1) is the main causative agent for it [1]. In the life cycle of HIV-1, the reverse transcriptase (RT) utilizes RNA genome to synthesize double-stranded viral DNA, which was one of the most important enzymes in viral infection and a major target for antiretroviral therapies [2,3]. RT inhibitors can be divided into the nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). NNRTIs distort the enzyme's active site and perturb the alignment of the primer terminus by interacting in a noncompetitive manner with the allosteric site (NNRTIs binding pocket, NNIBP) about 10 angstroms distant from the polymerase active site of RT, resulting in inhibition of the reverse transcription step of HIV-1 replication [4,5]. NNRTIs are a component of highly active antiretroviral therapy (HAART) regimens used to fight HIV-1 due to their potent antiviral activity, high selectivity and modest toxicity [6].

Up to now, six NNRTIs have been approved by the U.S. Food and Drug Administration (FDA). Nevirapine (NVP), delavirdine (DLV) and efavirenz (EFV) constitute the first-generation, but the rapid emergence of drug-resistance and toxicities limit their clinical use [7]. Etravirine (ETR), rilpivirine (RPV) and doravirine (DOR) are the second-generation NNRTIs (Fig. 1), in which ETR and RPV belong to the diarylpyrimidine (DAPY) family and exhibit a broad spectrum of activity against the clinically relevant NNRTIs-resistance strains. However, their clinical application has also been complicated by

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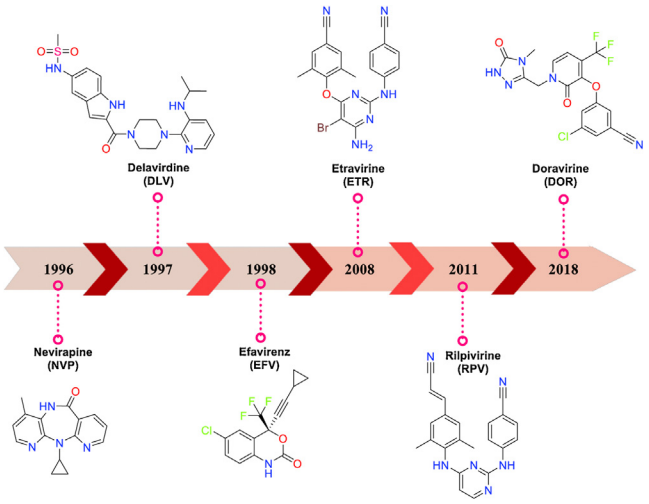


Fig. 1. Chemical structures of six NNRTIs approved by the U.S. FDA.

emergence of drug-resistance mutations (such as E138K and RES056) [7]. Besides, multiple lipophilic aromatic rings in their structure led to their poor solubility and lower oral bioavailability [7]. In 2017, elsulfavirine was marketed as a prodrug in Russia for the treatment of HIV, which displayed antiviral nanomolar potency [EC_{50} wild-type (WT) HIV-1 strain (IIIB) = 1.2 nmol/L] [7,8]. Therefore, it is imperative to discover novel NNRTIs with improved drug resistance profiles and favorable solubility.

Our previous studies have discovered a series of novel DAPY derivatives with more potent activity against the WT and mutant HIV-1 strains than the approved drug ETR [9–14]. Especially, the two piperidine-substituted thiophene[3,2-*d*]pyrimidine derivatives, **K-5a2** and **25a** (Fig. 2A), exhibited highly effective anti-HIV-1 activities and improved resistance profiles [15]. The co-crystal structure of HIV-1 RT in complex with **K-5a2** confirmed the "four-point pharmacophore model" of DAPY in NNIBP, which includes the hydrophobic domain, the hydrogen bonding domain, tolerant region I and tolerant region II (Fig. 2B) [15]. Specifically, the interactions between **K-5a2** and RT were elucidated. As depicted in Fig. 2C, the central thiophene[3,2-*d*]pyrimidine core could

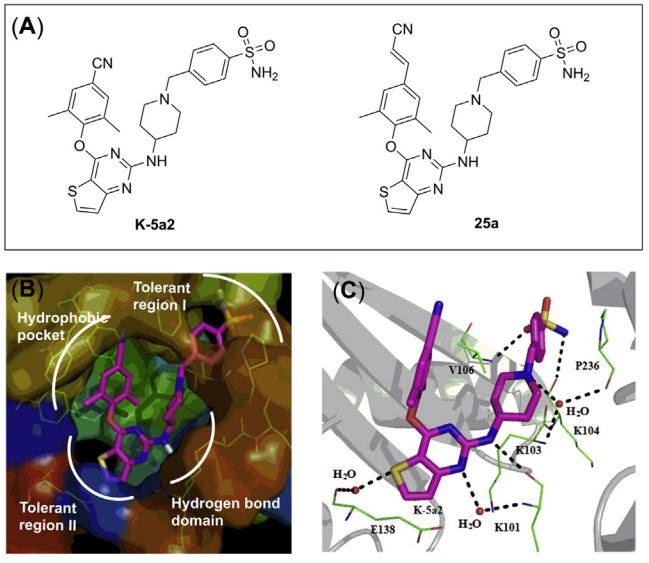


Fig. 2. (A) Chemical structures of our previously reported potent HIV-1 NNRTIs; (B) The co-crystal structure of **K-5a2**/RT complexes (PDB code: 6c0J) and the four-point pharmacophore model; (C) The detailed interactions with WT RT of **K-5a2**.

establish hydrogen bond with K101 and E138 directly or through a bridging water molecule; the piperidine nitrogen develops water-mediated hydrogen bonds with K103 and P236; and the surface-positioned sulfonamide group of the right wing developed a double-hydrogen bond with the carbonyl oxygen of K104 and the backbone nitrogen of V106. These extensive hydrogen-bonding networks between the inhibitor and the backbone of residues proved to be responsible for the stabilization of **K-5a2** to the NNIBP.

Similar to the sulfonamide group, the boronic acid group proves to have the distinct ability to form hydrogen bonds [16,17]. Recently, boronic acid have been extensively used for the purposes of biological probe development and drug discovery [18], especially for antiviral drugs, such as HIV-1 protease and hepatitis C virus (HCV) non-nucleoside polymerase (NS5B) inhibitors [16,19,20]. In boronic acid, there are two hydroxy groups acting as both donors and acceptors of hydrogen bonds. The hydroxy groups display four lone pairs and two hydrogen-bond donors, which provide six opportunities to form hydrogen bonds with one group [16]. Inspired by this, we tried boronic acid to replace the sulfonamide group in the lead **K-5a2** by utilizing the bioisosterism strategy in this work. We anticipated that the hydroxy groups of boronic acid could form interactions with K104 and V106. Meanwhile, bioisosterism and scaffold-hopping strategies were also employed to displace the center core of **K-5a2** with different fused pyrimidine rings and yielded twelve novel boronic acid-containing DAPY derivatives [21]. Moreover, the privileged 4-cyanovinyl-2,6-dimethylphenyl structure was introduced to the left wing of the most potent inhibitor **5j** (Fig. 3). The detailed structure – activity relationship (SAR) study of the derivatives and molecular dynamics simulation were also studied.

The synthetic protocols for the newly designed compounds **5a–k** and **10j** are outlined in Schemes 1 and 2, respectively. All derivatives were prepared by well-established methods as described in our previous articles [10–13]. Commercially available 2,4-dichloropyrimidines **1a–k** were selected as the starting materials, which were reacted with 4-hydroxy-3,5-dimethylbenzonitrile or 4-hydroxy-3,5-dimethylbenzaldehyde through nucleophilic substitution to afford **2a–k** and **6j.** Then, **6j** was treated with $(EtO)_2P(O)CH_2CN$ in the presence of *t*-BuOK to give **7j**. Next, **2a–k** or **7j** were reacted with 4-amino-1-Boc-piperidine to afford **3a–k** or **8j** *via* Buchwald-Hartwig reaction. Removal of the Boc protecting group gave the corresponding key analogues **4a–k** or **9j**, which led to the desired compounds by nucleophilic substitution with (4-(chloromethyl)phenyl)boronic acid.

The antiviral potency of the synthesized compounds was evaluated in cultured MT-4 cells infected with WT HIV-1 strain (IIIB) or a panel of NNRTIs-resistant single and double mutant strains, including L100I, K103N, Y181C, Y188L, E138K, F227L + V106A and K103N + Y181C (RES056). ETR and EFV were selected as control drugs. The values of 50% effective concentration (EC_{50}, anti-HIV potency), 50% cytotoxicity concentration (CC_{50}, cytotoxicity) and selectivity index (SI, CC_{50}/EC_{50} ratio) are summarized in Table 1 and Table S1 (Supporting information).

As shown in Table 1, compounds containing sulfur atom in the central ring (**5a–d**) exhibited nanomolar antiviral activity against HIV-1 IIIB, L100I, K103N, Y181C, Y188L and E138K. For the K103N mutation, **5a–d** displayed the most potent activities with EC_{50} values of 6.19, 8.18, 11.3 and 14.6 nmol/L, they were 12-, 9-, 7-, and 5-fold more potent than the reference drug EFV (EC_{50} = 75.4 nmol/L) but a little bit lower than ETR (EC_{50} = 3.33 nmol/L). However, all derivatives showed weaker efficacy against the double-mutant strain RES056.

With the aim to effectively occupy the tolerant region II and establish more interactions with NNIBP, the five-membered thiophene ring of **K-5a2** was changed to six-membered aromatic and alicyclic rings, yielding derivatives **5e–g** and **5h–k**. Among

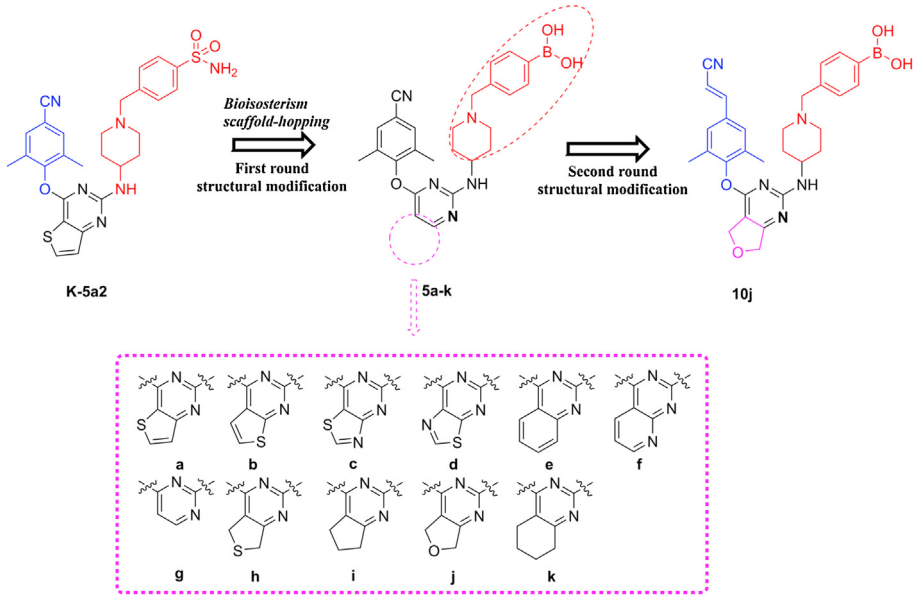
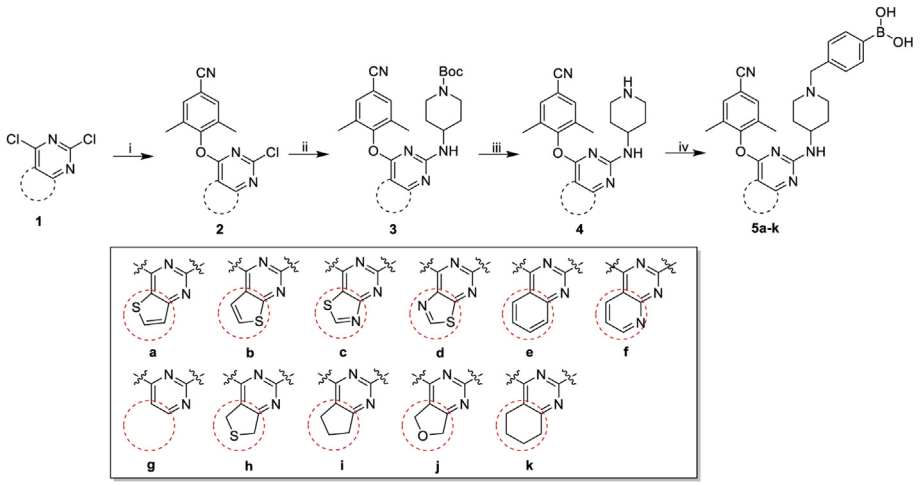
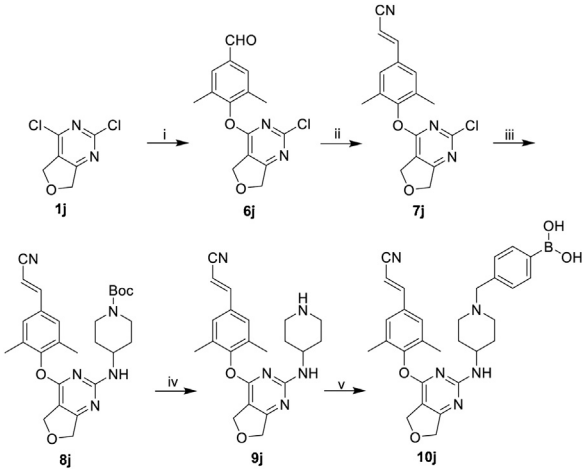


Fig. 3. Design and optimization of the boronic acid-containing DAPY derivatives.



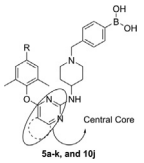
Scheme 1. Synthesis of **5a**–**k**[a]. [a]Reagents and conditions: i) 3,5-dimethyl-4-hydroxybenzonitrile, K_2CO_3, DMF, r.t.; ii) BINAP, $Pd_2(dba)_3$, Cs_2CO_3, 1,4-dioxane, 90 °C, N_2; iii) TFA, DCM, r.t.; iv) (4-(chloromethyl)phenyl)boronic acid, K_2CO_3, DMF, r.t.

them, **5e**–**g** turned out to be nanomolar inhibitors of HIV-1 IIIB, K103N and E138K, with EC_{50} values ranging from 2.73 nmol/L to 24.5 nmol/L. In addition, compound **5g**, with a single pyrimidine central core, displayed extremely potent activity against HIV-1 IIIB (EC_{50} = 2.73 nmol/L), which was comparable to that of ETR (EC_{50} = 3.13 nmol/L) and EFV (EC_{50} = 2.49 nmol/L). Compound **5e** with the quinazoline central core showed acceptable activity against HIV-1 IIIB and K103N (EC_{50} = 6.06 and 16.2 nmol/L, respectively), and introducing nitrogen atom at the C-8 position of the quinazoline core led to a similar potency (**5f**, EC_{50} = 6.53 and 12.2 nmol/L, respectively). However, these compounds still showed low activities against the double-mutant strain RES056. **5i** exhibited high potency against WT HIV-1 (EC_{50} = 4.87 nmol/L) and the single mutant K103N (EC_{50} = 5.98 nmol/L), being equipotent to that of ETR (EC_{50} = 3.13 and 3.33 nmol/L, respectively). Moreover, **5k** displayed moderate activity (EC_{50} = 15.1–71.8 nmol/L) against L100I, Y181C, Y188L and E138K. Introduction of sulfur or oxygen atoms at the C-6 position of **5i** yielded compounds **5h** and **5j,** among which, **5h** displayed moderate potency against HIV-1 IIIB and K103N (EC_{50} = 6.60 and 10.2 nmol/L, respectively). Compound **5j** was also effective against IIIB and K103N (EC_{50} = 7.01 and



Scheme 2. Synthesis of **10j**[a]. [a]Reagents and conditions: i) 4-hydroxy-3,5-dimethylbenzaldehyde, K_2CO_3, DMF, r.t.; ii) $(EtO)_2P(O)CH_2CN$, *t*-BuOK, THF, 0 °C to r.t.; iii) BINAP, $Pd_2(dba)_3$, Cs_2CO_3, 1,4-dioxane, 90 °C, N_2; iv) TFA, DCM, r.t.; v) (4-(chloromethyl)phenyl)boronic acid, K_2CO_3, DMF, r.t.

Table 1
Anti-HIV activity and cytotoxicity of **5a–k** and **10j**.



Compd.	R	Central core	EC_{50} (nmol/L)[a]							CC_{50} (μmol/L)[b]
			IIIB	L100I	K103N	Y181C	Y188L	E138K	F227L + V106A	RES056	
5a	CN		8.10 ± 1.98	49.7 ± 29.8	6.19 ± 2.03	34.5 ± 9.62	51.6 ± 19.9	39.4 ± 5.83	158 ± 58.9	1300 ± 407	> 244
5b	CN		7.85 ± 2.12	46.5 ± 18.2	8.18 ± 1.18	47.5 ± 10.6	52.4 ± 11.8	39.3 ± 13.1	225 ± 70.0	1111 ± 461	126 ± 5.35
5c	CN		13.5 ± 10.9	59.9 ± 12.4	11.3 ± 1.69	32.1 ± 5.22	98.5 ± 29.5	35.6 ± 5.93	381 ± 100	618 ± 98.7	30.8 ± 6.13
5d	CN		6.71 ± 2.12	133 ± 117	14.6 ± 3.16	26.0 ± 6.27	125 ± 44.6	36.0 ± 4.74	374 ± 59.1	760 ± 196	99.4 ± 9.11
5e	CN		6.06 ± 1.94	162 ± 90.6	16.2 ± 4.69	66.1 ± 20.2	136 ± 48.7	16.0 ± 5.11	319 ± 84.0	2219 ± 336	25.9 ± 0.661
5f	CN		6.53 ± 1.61	55.2 ± 26.6	12.2 ± 5.77	35.3 ± 6.44	61.8 ± 6.71	24.5 ± 6.60	134 ± 29.5	1439 ± 213	27.2 ± 1.56
5g	CN		2.73 ± 0.521	94.1 ± 37.3	7.44 ± 2.14	20.4 ± 2.95	326 ± 101	15.7 ± 1.86	288 ± 121	1003 ± 221	17.0 ± 2.48
5h	CN		6.60 ± 1.91	45.5 ± 21.8	10.2 ± 2.45	29.4 ± 3.10	40.8 ± 18.7	31.5 ± 3.02	311 ± 126	1776 ± 542	> 243
5i	CN		4.87 ± 1.54	71.8 ± 37.1	5.98 ± 1.82	27.1 ± 11.4	30.7 ± 9.81	15.1 ± 4.79	94.4 ± 15.7	861 ± 317	> 251
5j	CN		7.01 ± 2.09	37.7 ± 12.8	7.11 ± 1.21	20.4 ± 4.49	47.9 ± 9.18	13.6 ± 0.633	146 ± 38.6	1262 ± 580	82.2 ± 4.96
5k	CN		15.6 ± 6.02	105 ± 10.5	33.8 ± 2.78	76.3 ± 13.1	79.9 ± 31.9	50.5 ± 8.64	387 ± 57.9	3312 ± 901	> 244
10j			7.23 ± 1.82	9.85 ± 2.21	7.19 ± 0.547	19.7 ± 6.45	39.9 ± 6.02	17.3 ± 3.78	43.2 ± 9.66	77.9 ± 11.2	25.6 ± 0.929
EFV	–	–	2.49 ± 0.547	33.9 ± 8.39	75.4 ± 10.8	5.42 ± 0.994	196 ± 54.8	4.36 ± 1.05	254 ± 65.5	260 ± 47.6	> 6.34
ETR	–	–	3.13 ± 0.902	5.94 ± 1.60	3.33 ± 0.589	14.8 ± 2.47	14.1 ± 3.83	6.46 ± 1.71	15.7 ± 3.69	32.2 ± 12.2	> 4.59

[a] EC_{50}: concentration of compound required to achieve 50% protection of MT-4 cell cultures against HIV-1-induced cytopathic effect, as determined by the MTT method.
[b] CC_{50}: concentration required to reduce the viability of mock-infected cell cultures by 50%, as determined by the MTT method.

7.11 nmol/L). Moreover, it turned out to be an effective inhibitor with EC_{50} values of 13.6 – 47.9 nmol/L against the other mutant strains, except for RES056.

Although compounds **5j** and **5i** exhibited potent activities against most mutant HIV-1 strains, their activities against the double-mutant strain RES056 (EC_{50} = 1262 and 861 nmol/L) need to be improved. Our previous research has demonstrated that dihydrofuro[3,4-*d*]pyrimidine was a privileged scaffold for improving the anti-HIV-1 activity and physiochemical properties [13]. So, the cyano group in the left wing of **5j** was replaced by cyanovinyl to obtain derivative **10j**, with the aim to establish more stronger interactions with highly conserved residues F227 and W229. As

Table 2
Inhibitory activity against WT HIV-1 RT.

Compd.	IC_{50} (μmol/L)[a]	Compd.	IC_{50} (μmol/L)[a]	Compd.	IC_{50} (μmol/L)[a]
5a	0.1977 ± 0.0234	**5f**	0.2804 ± 0.0153	**5k**	0.2425 ± 0.0083
5b	0.1091 ± 0.0028	**5g**	0.0678 ± 0.0155	**10j**	0.1837 ± 0.0094
5c	0.2644 ± 0.0082	**5h**	0.1504 ± 0.0124	**NVP**	0.4766 ± 0.2099
5d	0.2391 ± 0.0137	**5i**	0.1267 ± 0.0228	**EFV**	0.0067 ± 0.0014
5e	0.1232 ± 0.0042	**5j**	0.1663 ± 0.0057		

[a] IC_{50}: inhibitory concentration of test compound required to inhibit biotin deoxyuridine triphosphate (biotin-dUTP) incorporation into WT HIV-1 RT by 50%.

shown in Table 1, **10j** showed good inhibition against L100I with an EC_{50} value of 9.85 nmol/L, which was about 3.8-fold more potent than **5j** (EC_{50} = 37.7 nmol/L). Especially, it is noteworthy that **10j** inhibited the double-mutant F227L + V106A strain and RES056 with EC_{50} values of 43.2 and 77.9 nmol/L, which were 3.4- and 16.2-fold more potent than those of **5j** (EC_{50} = 146 and 1262 nmol/L). Besides, **10j** showed acceptable antiviral activity against other viral strains, it was equipotent (IIIB, EC_{50} = 7.23 nmol/L; K103N, EC_{50} = 7.19 nmol/L; Y181C, EC_{50} = 19.7 nmol/L; Y188L, EC_{50} = 39.9 nmol/L; E138K, EC_{50} = 17.3 nmol/L) with **5j** (EC_{50} = 7.01, 7.11, 20.4, 47.9 and 13.6 nmol/L). These results verified that introducing the cyanovinyl group in the left wing of **10j** remarkably increased the antiviral activities, especially against the double-mutant strains. Moreover, **10j** demonstrated higher SI values towards HIV-1 IIIB and all the tested mutant strains (Table S1).

In order to confirm their binding target, all derivatives were evaluated for their inhibitory activity against recombinant WT HIV-1 RT enzyme (Table 2). All compounds showed high binding-affinity with WT HIV-1 RT (IC_{50} = 0.0678–0.6585 μmol/L) as compared to that of NVP (IC_{50} = 0.4766 μmol/L). Among these, compound **5g**, with a pyrimidine scaffold, exhibited the highest RT inhibitory activity (IC_{50} = 0.0678 μmol/L), which was in accordance with the anti-HIV-1 potency. These results suggest that the newly synthesized derivatives behave as typical NNRTIs.

Furthermore, we carried out the molecular dynamics analysis of **10j**–RT complexes (Supporting information). The results were substantiated with molecular dynamics simulation for 100 ns that indicated the stability of all three protein structures with < 0.5% outlier residues in the Ramachandran plot (Fig. S2 and Table S4 in Supporting information). The boronic acid group of the compound **10j** displayed H-bond interaction to K223 residue for wildtype RT while the similar interaction was shown with K104 for mutant K103N/Y181C RT (Fig. S5 in Supporting information). Therefore, the boronic acid group helps formation of multiple hydrogen bonds to improve the antiviral activity of the compounds.

In this study, a series of boronic acid-containing diarylpyrimidine derivatives were designed, synthesized and evaluated for their anti-HIV-1 potency. The results demonstrated that compounds **5j** and **5i** displayed nanomolar activities against HIV-1 IIIB and single-mutant strains (EC_{50} = 4.87 – 71.8 nmol/L), while their activities against the double-mutant strains F227L + V106A and RES056 decreased sharply. Equipment with a cyanovinyl group at the left wing of **5j** yielded the most potent inhibitor **10j** with EC_{50} values of 7.23 nmol/L (IIIB), 9.85 nmol/L (L100I), 7.19 nmol/L (K103N), 19.7 nmol/L (Y181C), 39.9 nmol/L (Y188L), 17.3 nmol/L (E138K), 43.2 nmol/L (F227L + V106A) and 77.9 nmol/L (RES056), which was comparable with those of ETR. The HIV-1 RT enzyme activity inhibition assay suggest that **10j** (IC_{50} = 0.1837 μmol/L) acted as a typical NNRTIs. Finally, based on molecular dynamics simulation, we propose the molecule **10j** promising for fighting against HIV-1 infection through inhibiting RT activity. Consequently, the compound **10j**, the best inhibitor of this series, could serve as a lead for further modification to get more potent NNRTIs of important practical significance.

Declaration of competing interest

The authors report no declarations of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2021.02.033.

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