Discovery of Thiophene[3,2-*d*]pyrimidine Derivatives as Potent HIV-1 NNRTIs Targeting the Tolerant Region I of NNIBP

Dongwei Kang,[†] Xiao Ding,[†] Gaochan Wu,[†] Zhipeng Huo,[†] Zhongxia Zhou,[†] Tong Zhao,[†] Da Feng,[†] Zhao Wang,[†] Ye Tian,[†] Dirk Daelemans,[§] Erik De Clercq,[§] Christophe Pannecouque,[§] Peng Zhan,^{*,†} and Xinyong Liu^{*,†}

[†]Department of Medicinal Chemistry, Key Laboratory of Chemical Biology (Ministry of Education), School of Pharmaceutical Sciences, Shandong University, 44 West Culture Road, 250012 Jinan, Shandong, P. R. China

[§]Rega Institute for Medical Research, Laboratory of Virology and Chemotherapy, K.U. Leuven, Herestraat 49 Postbus 1043 (09.A097), B-3000 Leuven, Belgium

Supporting Information

ABSTRACT: Our previous studies led us to conclude that thiophene[3,2-*d*]pyrimidine is a promising scaffold for diarylpyrimidine (DAPY)-type anti-HIV agents with potent activity against resistance-associated human immunodeficiency virus (HIV) variants (*J. Med. Chem.* **2016**, *59*, 7991–8007; *J. Med. Chem.* **2017**, *60*, 4424–4443). In the present study, we designed and synthesized a series of thiophenepyrimidine derivatives with various substituents in the right wing region of the structure with the aim of developing new interactions with the tolerant region I of the binding pocket of the HIV-1 non-nucleoside reverse transcriptase (NNRTI), and we evaluated their activity against a panel of mutant HIV-1 strains. All the derivatives exhibited moderate to excellent potency against wild-type (WT) HIV-1 in MT-4 cells. Among them, sulfonamide compounds **9b** and **9d** were single-figure-nanomolar inhibitors with EC₅₀ values of 9.2 and 7.1 nM, respectively. Indeed, **9a** and **9d** were effective against the whole viral panel except RES056. Notably, both compounds showed potent antiviral activity against K103N (EC₅₀ = 0.032 and 0.070 μM) and E138K (EC₅₀ = 0.035 and 0.045 μM, respectively). Furthermore, **9a** and **9d** exhibited high affinity for WT HIV-1 RT (IC₅₀ = 1.041 and 1.138 μM, respectively) and acted as classical NNRT inhibitors (NNRTIs). These results are expected to be helpful in the design of thiophenepyrimidine-based NNRTIs with more potent activity against HIV strains with RT mutations.

KEYWORDS: HIV-1, NNRTIs, thiophene[3,2-*d*]pyrimidine, tolerant region I, drug design

Mutations in the viral reverse transcriptase can reduce the effectiveness of the first-generation FDA-approved HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs), including nevirapine (NVP), delavirdine (DLV), and efavirenz (EFV).^{1–3} On the other hand, second-generation diarylpyrimidine (DAPY) agents, such as etravirine (ETV) and rilpivirine (RPV) (Figure 1), have enjoyed considerable clinical

success. However, drug-resistant mutants with reduced susceptibility to ETV and RPV have emerged rapidly. Among the various mutations, K103N and E138K are the most frequently selected by ETV and RPV, respectively.^{4,5} Therefore, the development of novel NNRTIs with improved efficacy against resistant mutants remains an important research objective in medicinal chemistry.^{6,7}

Previous research in our lab showed that the thiophene[3,2-*d*]pyrimidine can be a useful skeleton for DAPY inhibitors with improved potency against drug-resistant HIV-1 variants.^{8,9} In particular, compound **3** (K-5a2) exhibited low-nanomolar anti-HIV activity against HIV-1 WT and a panel of NNRTI-resistant mutant strains. Our previous work indicated that extensive main-chain hydrogen-bonding interactions (double hydrogen-bonding chelation with the amino acid backbone) could contribute to increased activity toward drug-resistant mutants.

Figure 1. Chemical structures of second-generation NNRTI drugs and thiophene[3,2-*d*]pyrimidine lead **3** (K-5a2).

Received: September 1, 2017

Accepted: October 19, 2017

Published: October 19, 2017

Figure 2. Design of novel NNRTIs utilizing the thiophene[3,2-*d*]pyrimidine scaffold. The illustration of the cocrystal structure of K-Sa2/RT was generated using PyMOL (www.pymol.org).

Scheme 1. Synthesis of Target Compounds^a

^aReagents and conditions: (i) 3,5-dimethyl-4-hydroxybenzonitrile, DMF, K₂CO₃, r.t.; (ii) *tert*-butyl(4-aminocyclohexyl)carbamate, DMF, K₂CO₃, 120 °C; (iii) TFA, DCM, r.t.; (iv) substituted acyl chloride or sulfonyl chloride, DCM, Et₃N, 0 °C to r.t.

Therefore, we considered that sulfonamide and amide functional groups would be promising substituents, as they are highly polar and can readily accept or donate a proton, so that they should easily form hydrogen bonds with amino acid residues of the target receptor or receptor-bound water molecules. In addition, the sulfonamide motif could act as a scaffold to orient pharmacophore elements into the proper geometry for binding.^{9–11}

In the present work, we examined the properties of a series of analogs of **3** synthesized by introducing sulfonamide and amide substituents at the right wing (interacting with tolerant region I) (Figure 2). We retained the left wing (A-ring) and the thiophene[2,3-*d*]pyrimidine core (B-ring). Thus, we aimed to further explore the tolerant region I of the NNRTI binding pocket (NNIBP), based on the idea that the newly introduced hydrogen-bonding donors or receptors might form hydrogen bonds with amino acid residues of the NNIBP, resulting in stronger binding and greater potency against resistance-associated variants. The 4-aminopiperidine moiety of the lead **3** was replaced with cyclohexanediamine, and then acylation and sulfonylation with various acyl and sulfonyl chlorides afforded our target compounds bearing substituents varying in size and polar group substitution. We expected the newly introduced sulfonamide group would increase the binding affinity of the drug molecules with the target proteins.¹² Herein,

we report the synthesis, anti-HIV activity, and preliminary SAR evaluation of ten thiophene[3,2-*d*]pyrimidine derivatives.

The synthetic protocols for the newly designed derivatives are outlined in Scheme 1.⁸ Commercially available 2,4-dichlorothiophene[3,2-*d*]pyrimidine (**4**) was selected as the starting material. Successive nucleophilic substitution reactions with 4-hydroxy-3,5-dimethylbenzonitrile gave the known intermediate **5**. Subsequent reaction with *tert*-butyl (4-aminocyclohexyl)carbamate afforded **6**, which was directly deprotected without further purification to provide the key intermediate **7**. Treatment of **7** with substituted acyl chloride or sulfonyl chloride in the presence of triethylamine yielded the final products **8a–e** and **9a–e**. All the novel thiophene[3,2-*d*]pyrimidine derivatives were fully characterized by means of proton nuclear magnetic resonance (¹H NMR), carbon nuclear magnetic resonance (¹³C NMR), and high resolution mass spectrometry (HRMS) measurements.

The antiviral potency of the synthesized compounds was evaluated in MT-4 cell cultures infected with WT HIV-1 strain (IIB) or with a panel of NNRTI-resistant single and double mutant strains, including L100I, K103N, Y181C, Y188L, E138K, F227L + V106A, and K103N + Y181C (RES056). Etravirine (ETV) and azidothymidine (AZT) were selected as control drugs. The results, expressed as EC₅₀ (anti-HIV

Table 1. Activity and Cytotoxicity against HIV-1 (IIIB) and HIV-2 (ROD) Strains in MT-4 Cells

compd	X	R	EC ₅₀ (μM) ^a		CC ₅₀ (μM) ^b	SI ^c IIIB
			IIIB	ROD		
8a	CO	H	0.013 ± 0.007	>3.930	3.930 ± 0.662	294
8b	CO	4-F	0.026 ± 0.002	>3.182	3.182 ± 1.346	121
8c	CO	4-Br	0.030 ± 0.005	>2.849	2.849 ± 1.225	93
8d	CO	4-CN	0.138 ± 0.018	>2.617	2.617 ± 1.655	19
8e	CO	3-CF ₃	0.196 ± 0.086	>3.241	3.241 ± 0.671	17
9a	SO ₂	4-NHCOCH ₃	0.010 ± 0.008	>3.734	3.734 ± 0.157	340
9b	SO ₂	4-F	0.0092 ± 0.001	>3.527	3.527 ± 0.372	383
9c	SO ₂	4-Br	0.025 ± 0.006	>5.861	5.861 ± 3.624	231
9d	SO ₂	4-CN	0.0071 ± 0.0005	>9.287	9.287 ± 6.187	1308
9e	SO ₂	3-CF ₃	0.086 ± 0.029	>6.683	6.683 ± 3.436	78
ETV			0.0028 ± 0.0002		2.18 ± 0.029	776
AZT			0.011 ± 0.005	0.008 ± 0.001	>7.484	>664

^aEC₅₀: concentration of compound required to achieve 50% protection of MT-4 cell cultures against HIV-1-induced cytotoxicity, as determined by the MTT method. ^bCC₅₀: concentration required to reduce the viability of mock-infected cell cultures by 50%, as determined by the MTT method.

^cSI: selectivity index, the ratio of CC₅₀/EC₅₀.

Table 2. Anti-HIV-1 Activity against Mutant Strains in MT-4 Cells

compd	EC ₅₀ (μM) ^a						
	L100I	K103N	Y181C	Y188L	E138K	F227L + V106A	RES056
8a	>3.922	0.273 ± 0.045	≥1.508	>3.922	0.183 ± 0.039	>3.922	>3.922
8b	>3.183	0.478 ± 0.023	>3.183	>3.183	0.230	>3.183	>3.183
8c	>2.851	0.519 ± 0.023	>2.851	>2.851	0.370 ± 0.086	>2.851	>2.851
8d	>2.623	≥1.436	>2.623	>2.623	0.736 ± 0.017	>2.623	>2.623
8e	>3.237	>3.237	>3.237	>3.237	≥1.327	>3.237	>3.237
9a	0.562 ± 0.487	0.032 ± 0.002	0.513 ± 0.415	0.903 ± 0.248	0.035 ± 0.001	1.208 ± 0.333	>3.727
9b	0.410 ± 0.350	0.103 ± 0.006	0.472 ± 0.323	>3.519	0.076 ± 0.018	>3.519	>3.519
9c	0.841 ± 0.884	0.131 ± 0.003	0.852 ± 0.655	2.250 ± 0.011	0.126 ± 0.014	≥6.136	5.874 ± 0.925
9d	0.424 ± 0.361	0.070 ± 0.025	0.428 ± 0.294	0.675 ± 0.091	0.045 ± 0.001	3.583 ± 0.241	>9.280
9e	≥4.092	0.569 ± 0.31	≥4.341	>6.687	0.642 ± 0.009	>6.687	>6.687
ETV	0.0097 ± 0.003	0.0034 ± 0.0003	0.019 ± 0.007	0.020 ± 0.0034	0.014 ± 0.0025	0.023 ± 0.011	0.026 ± 0.0041
AZT	0.0054 ± 0.0004	0.0078 ± 0.0005	0.0063 ± 0.0009	0.008 ± 0.001	0.017 ± 0.0056	0.0053 ± 0.0011	0.011 ± 0.0029

^aEC₅₀: concentration of compound required to achieve 50% protection of MT-4 cell cultures against HIV-1-induced cytotoxicity, as determined by the MTT method.

potency), CC₅₀ (cytotoxicity), and SI (selectivity index, CC₅₀/EC₅₀ ratio), are summarized in Tables 1 and 2.

Eight compounds (8a–c, 9a–e) exhibited high potency against WT HIV-1 strain with nanomolar EC₅₀ values ranging from 0.0071 to 0.086 μM, which were comparable to that of the reference drug AZT (EC₅₀ = 0.011 μM). Among them, 9b and 9d turned out to be the most potent NNRTIs with EC₅₀ values of 0.0092 and 0.0071 μM, being slightly more potent than AZT, though their activity was about 3-fold lower than that of ETV (EC₅₀ = 0.0028 μM). Importantly, compound 9d exhibited the lowest cytotoxicity (CC₅₀ = 9.287 μM) and the highest selectivity index (SI = 1308), being superior to ETV (CC₅₀ = 2.18 μM, SI = 776). As expected, the target compounds did not exhibit activity against the HIV-2 strain.

Preliminary SAR analysis indicated that the type of functional group (X) in the cyclohexanediamine significantly influenced anti-HIV activity. The compounds of the 9 subseries (X = SO₂) showed better activity than those of the 8 subseries (X = CO), i.e., 9b (EC₅₀ = 0.0092 μM) > 8b (EC₅₀ = 0.026 μM); 9c (EC₅₀ = 0.025 μM) > 8c (EC₅₀ = 0.030 μM); 9d (EC₅₀ = 0.0071 μM) > 8d (EC₅₀ = 0.138 μM); 9e (EC₅₀ = 0.086 μM) > 8e (EC₅₀ = 0.196 μM). These results suggested that the tetrahedral structure of the sulfonamide is better than the planar structure of the amide for hydrogen bonding with amino acid residues of

the NNIBP. In the 9 subseries, the order of anti-HIV-1 activity was CN > F > Br > CF₃, whereas in the 8 subseries, the order was slightly different: F > Br > CN > CF₃.

Compounds 9a, 9b, and 9d showed moderate activity toward mutant HIV-1 strain L100I (EC₅₀ = 0.562, 0.410, and 0.424 μM, respectively), being far more potent than DLV (EC₅₀ = 3.613 μM) or NVP (EC₅₀ = 3.251 μM). However, all the compounds in the 8 subseries lacked activity toward this mutant strain. In the case of the K103N, compounds in the 9 subseries also exhibited more potent activity than those in the 8 subseries. In particular, 9a and 9d were notably potent (EC₅₀ = 0.032 and 0.070 μM). Furthermore, 9d showed the most potent activity against the single mutants Y181C and Y188L (EC₅₀ = 0.428 and 0.675 μM, respectively). Intriguingly, except for 8e, all the target compounds displayed good activity against E138K with EC₅₀ values in the range of 0.035–0.736 μM, although 9a and 9d were the most potent (EC₅₀ = 0.035 and 0.045 μM, respectively). Moreover, 9a and 9d were effective inhibitors of the double mutant strain F227L + V106A with EC₅₀ values of 1.208 and 3.583 μM, respectively. However, both of them were inactive toward RES056 (EC₅₀ > 3.727 and 9.280 μM, respectively).

In order to validate the binding target of these newly synthesized thienopyrimidine derivatives, we further tested the

representative compounds **9a** and **9d** for the ability to inhibit recombinant WT HIV-1 RT enzyme versus NVP and ETV as reference drugs (Table 3). The results demonstrated that **9a**

Table 3. Inhibitory Activity of the Representative Compound against WT HIV-1 RT

compd	9a	9d	NVP ^b	ETV ^b
IC ₅₀ (μM) ^a	1.041	1.138	1.39	1.00

^aIC₅₀: inhibitory concentration of test compound required to inhibit biotin deoxyuridine triphosphate (biotin-dUTP) incorporation into WT HIV-1 RT by 50%. ^bThe data were obtained from the same laboratory with the same method.¹³

and **9d** exhibit remarkable anti-RT potency (IC₅₀ = 1.041 and 1.138 μM, respectively), being superior to NVP but slightly inferior to ETV. Therefore, these novel thienopyrimidine derivatives have high affinity for WT HIV-1 RT and act as classical NNRTIs.

To further understand the binding interactions between the newly designed compounds and the target, we conducted molecular docking studies of the representative compounds **8d** and **9d** with the SurflexDock SYBYL-X 2.0 software. The X-ray crystal structure of HIV-1 wild-type RT (PDB code:

3M8Q)¹⁴ was used as the input structure for docking calculations. PyMOL was used to visualize the results. The docking protocol is described in the computational section.

As shown in Figure 3C, **9d** showed similar binding modes to the lead compound **3**.⁹ As with other DAPY NNRTIs, **9d** adopted a horseshoe-like conformation in the NNIBP, whereas the conformation of **8d** showed significant changes. This result suggests that the conformational preference of sulfonamides provides a unique way to control the molecular shape. In contrast to the flat and linear amides, sulfonamides are bent, and this feature has a critical influence on the activity of many NNRTIs, including pyrrolyl aryl sulfones¹⁵ and 1,3-dihydro-benzimidazol-2-one.¹⁶ As illustrated in Figure 3B, we can conclude that **9d** displays the following characteristic interactions: (i) the left substituted 4-cyanovinyl-2,6-dimethyl-phenyl moiety effectively occupies the hydrophobic cavity surrounded by Tyr 181, Tyr 188, Phe 227, and Trp229 and especially is stabilized by π -stacking interactions with Tyr188; (ii) the thiophene ring of **9d** is directed toward the NNIBP entrance channel, and there is an electrostatic interaction between the sulfur atom and Val179; (iii) the N atom of the central ring and NH linker are involved in crucial double hydrogen-bonding with the backbone of Lys101. However,

Figure 3. (A,B) Predicted binding modes of **8d** and **9d** with the HIV-1 WT RT crystal structure (PDB: 3M8Q). (C) Superimposition of **9d** and **3** with WT RT (yellow, **9d**; magenta, **3**). Hydrogen bonds are indicated with dashed lines (yellow). Nonpolar-hydrogen atoms are omitted for clarity.

compared to the lead **3**, **9d** lacks the double hydrogen-bonding (chelate type) interactions with the backbone of Lys104 and Val106, which are important for the activities of the lead toward resistant strains. Fortunately, the newly introduced 4-cyanobenzenesulfonyl group of **9d** extends to the protein–solvent interface, and the amino group of the sulfonamide can form double hydrogen-bonding interactions with oxygen of His235 and Tyr318, which may account for the modest potency toward mutant strains. Compared to **9d**, **8d** shows the double hydrogen bonding interaction with the backbone of Lys101, while the amide functional group of **8d** does not have any other interaction with the NNIBP, providing a rational explanation of the decreased activity of **8d**.

In summary, we have designed and synthesized a novel series of thiophene[3,2-*d*]pyrimidine HIV-1 NNRTIs targeting the tolerant region I of the NNIBP, and evaluated their activities against HIV-1WT and a panel of mutant strains, as well as HIV-2 (ROD). All the target compounds exhibited moderate to excellent potency against WT HIV-1 with EC₅₀ values ranging from 0.0071 to 0.196 μM, and the two most potent compounds **9b** and **9d** proved to be single-figure-nanomolar inhibitors (EC₅₀ = 9.2 and 7.1 nM, respectively), being more potent than AZT. These two compounds also showed moderate potency against most of the mutant strains examined. In particular, they exhibited promising activity against K103N (EC₅₀ = 0.032 and 0.070 μM) and E138K (EC₅₀ = 0.035 and 0.045 μM, respectively). Molecular simulation confirmed that the newly introduced sulfamide group, distinguished from its isostere amide, could develop additional interactions with amino acid residues in tolerant region I of the NNIBP. We believe these results will be helpful in extending the scope for the design of thiophenepyrimidine-based NNRTIs with more potent activity against RT mutant HIV strains.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acsmmedchemlett.7b00361](https://doi.org/10.1021/acsmmedchemlett.7b00361).

Experimental protocols for synthesis and characterization of compounds, *in vitro* anti-HIV assay, and modeling study (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: zhanpeng1982@sdu.edu.cn. Phone: 086-531-88382005.

*E-mail: xinyongl@sdu.edu.cn. Phone: 086-531-88380270.

ORCID

Dongwei Kang: 0000-0001-9232-953X

Peng Zhan: 0000-0002-9675-6026

Funding

The financial support from the National Natural Science Foundation of China (NSFC Nos. 81273354), Key Project of NSFC for International Cooperation (No. 81420108027), Young Scholars Program of Shandong University (YSPSDU, No. 2016WLJH32), Key Research and Development Project of Shandong Province (No. 2017CXGC1401), Major Project of Science and Technology of Shandong Province (No. 2015ZDJS04001), and KU Leuven (GOA 10/014) is gratefully acknowledged.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank K. Erven, K. Uyttersprot, and C. Heens for technical assistance with the HIV assays.

■ ABBREVIATIONS

AIDS, acquired immunodeficiency syndrome; CC₅₀, 50% cytotoxicity concentration; DAPY, diarylpyrimidine; EC₅₀, the concentration causing 50% inhibition of antiviral activity; HIV, human immunodeficiency virus; NRTIs, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; RT, reverse transcriptase; SAR, structure–activity relationship; SI, selection index; WT, wild-type; NVP, nevirapine; DLV, delavirdine; EFV, efavirenz; ETV, etravirine; RPV, rilpivirine; AZT, azidothymidine.

■ REFERENCES

- (1) Este, J. A.; Cihlar, T. Current status and challenges of antiretroviral research and therapy. *Antiviral Res.* **2010**, *85*, 25–33.
- (2) Johnson, V. A.; Brun-Vezinet, F.; Clotet, B.; Conway, B.; D'Aquila, R. T.; Demeter, L. M.; Kuritzkes, D. R.; Pillay, D.; Schapiro, J. M.; Telenti, A.; Richman, D. D. Drug resistance mutations in HIV-1. *Topics in HIV medicine* **2003**, *11*, 215–219.
- (3) Li, D.; Zhan, P.; De Clercq, E.; Liu, X. Strategies for the design of HIV-1 non-nucleoside reverse transcriptase inhibitors: lessons from the development of seven representative paradigms. *J. Med. Chem.* **2012**, *55*, 3595–3613.
- (4) Wainberg, M. A.; Zaharatos, G. J.; Brenner, B. G. Development of antiretroviral drug resistance. *N. Engl. J. Med.* **2011**, *365*, 637–646.
- (5) Xu, H. T.; Colby-Germinario, S. P.; Asahchop, E. L.; Oliveira, M.; McCallum, M.; Schader, S. M.; Han, Y.; Quan, Y.; Sarafianos, S. G.; Wainberg, M. A. Effect of mutations at position E138 in HIV-1 reverse transcriptase and their interactions with the M184I mutation on defining patterns of resistance to nonnucleoside reverse transcriptase inhibitors rilpivirine and etravirine. *Antimicrob. Agents Chemother.* **2013**, *57*, 3100–3109.
- (6) Chen, W.; Zhan, P.; Daelemans, D.; Yang, J.; Huang, B.; De Clercq, E.; Pannecouque, C.; Liu, X. Structural optimization of pyridine-type DAPY derivatives to exploit the tolerant regions of the NNRTI binding pocket. *Eur. J. Med. Chem.* **2016**, *121*, 352–363.
- (7) Zhan, P.; Pannecouque, C.; De Clercq, E.; Liu, X. Anti-HIV drug discovery and development: Current innovations and future trends. *J. Med. Chem.* **2016**, *59*, 2849–2878.
- (8) Kang, D.; Fang, Z.; Huang, B.; Lu, X.; Zhang, H.; Xu, H.; Huo, Z.; Zhou, Z.; Yu, Z.; Meng, Q.; Wu, G.; Ding, X.; Tian, Y.; Daelemans, D.; De Clercq, E.; Pannecouque, C.; Zhan, P. Structure-based optimization of thiophene[3,2-*d*]pyrimidine derivatives as potent HIV-1 non-nucleoside reverse transcriptase inhibitors with improved potency against resistance-associated variants. *J. Med. Chem.* **2017**, *60*, 4424–4443.
- (9) Kang, D.; Fang, Z.; Li, Z.; Huang, B.; Zhang, H.; Lu, X.; Xu, H.; Zhou, Z.; Ding, X.; Daelemans, D.; De Clercq, E.; Pannecouque, C.; Zhan, P.; Liu, X. Design, synthesis, and evaluation of thiophene[3,2-*d*]pyrimidine derivatives as HIV-1 non-nucleoside reverse transcriptase inhibitors with significantly improved drug resistance profiles. *J. Med. Chem.* **2016**, *59*, 7991–8007.
- (10) Liu, T.; Huang, B.; Tian, Y.; Liang, X.; Liu, H.; Liu, H.; Zhan, P.; De Clercq, E.; Pannecouque, C.; Liu, X. Design, synthesis, and biological evaluation of novel 4-aminopiperidinyl-linked 3,5-disubstituted-1,2,6-thiadiazine-1,1-dione derivatives as HIV-1 NNRTIs. *Chem. Biol. Drug Des.* **2015**, *86*, 107–113.
- (11) Di Santo, R.; Costi, R.; Artico, M.; Ragno, R.; Lavecchia, A.; Novellino, E.; Gavuzzo, E.; La Torre, F.; Cirilli, R.; Cancio, R.; Maga, G. Design, synthesis, biological evaluation, and molecular modeling

studies of TIBO-like cyclic sulfones as non-nucleoside HIV-1 reverse transcriptase inhibitors. *ChemMedChem* **2006**, *1*, 82–95.

(12) Zhao, Z.; Wolkenberg, S. E.; Sanderson, P. E.; Lu, M.; Munshi, V.; Moyer, G.; Feng, M.; Carella, A. V.; Ecto, L. T.; Gabryelski, L. J.; Lai, M. T.; Prasad, S. G.; Yan, Y.; McGaughey, G. B.; Miller, M. D.; Lindsley, C. W.; Hartman, G. D.; Vacca, J. P.; Williams, T. M. Novel indole-3-sulfonamides as potent HIV non-nucleoside reverse transcriptase inhibitors (NNRTIs). *Bioorg. Med. Chem. Lett.* **2008**, *18*, 554–559.

(13) Zhang, H.; Tian, Y.; Kang, D.; Huo, Z.; Zhou, Z.; Liu, H.; De Clercq, E.; Pannecouque, C.; Zhan, P.; Liu, X. Discovery of uracil-bearing DAPYs derivatives as novel HIV-1 NNRTIs via crystallographic overlay-based molecular hybridization. *Eur. J. Med. Chem.* **2017**, *130*, 209–222.

(14) Kertesz, D. J.; Brotherton-Pleiss, C.; Yang, M.; Wang, Z.; Lin, X.; Qiu, Z.; Hirschfeld, D. R.; Gleason, S.; Mirzadegan, T.; Dunten, P. W.; Harris, S. F.; Villasenor, A. G.; Hang, J. Q.; Heilek, G. M.; Klumpp, K. Discovery of piperidin-4-yl-aminopyrimidines as HIV-1 reverse transcriptase inhibitors. N-benzyl derivatives with broad potency against resistant mutant viruses. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4215–4218.

(15) Silvestri, R.; Artico, M.; La Regina, G.; De Martino, G.; La Colla, M.; Loddo, R.; La Colla, P. Anti-HIV-1 activity of pyrrol aryl sulfone (PAS) derivatives: synthesis and SAR studies of novel esters and amides at the position 2 of the pyrrole nucleus. *Farmaco* **2004**, *59*, 201–210.

(16) Monforte, A. M.; Logoteta, P.; Ferro, S.; De Luca, L.; Iraci, N.; Maga, G.; Clercq, E. D.; Pannecouque, C.; Chimirri, A. Design, synthesis, and structure-activity relationships of 1,3-dihydrobenzimidazol-2-one analogues as anti-HIV agents. *Bioorg. Med. Chem.* **2009**, *17*, 5962–5967.