Synthesis of Novel Diarylpyrimidine Analogues and Their Antiviral Activity against Human Immunodeficiency Virus Type 1

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This paper reports the synthesis and the antiviral properties of new diarylpyrimidine (DAPY) compounds as nonnucleoside reverse transcriptase inhibitors (NNRTIs). The synthesis program around this new DAPY series was further optimized to produce compounds displaying improved activity against a panel of eight clinically relevant single and double mutant strains of human immunodeficiency virus type 1 (HIV-1).

Introduction

The reverse transcriptase (RT) of the human immunodeficiency virus type 1 (HIV-1) is a key enzyme, which plays an essential and multifunctional role in the replication cycle. This enzyme is responsible for the conversion of a single-stranded RNA genome of HIV-1 into a double-stranded DNA chain that subsequently is incorporated into the DNA of the infected host cell. Nonnucleoside inhibitors of HIV-1 reverse transcriptase[1] (NNRTIs) inhibit the enzyme by occupation of an induced allosteric binding site very close to the active site.[2] The emergence of resistant HIV viral strains is a limitation for all therapeutic classes.[3,4] The emerging cross-resistance among the approved drugs[5−7] (Figure 1) has particularly limited the use of the NNRTIs class. In addition, there is the need to develop new NNRTIs with enhanced side effect profiles and improved characteristics influencing drug compliance.

TMC125,[8,9] **4a** (Figure 2), an early diarylpyrimidine (DAPY) compound, was the first NNRTI demonstrating a beneficial effect on HIV-infected patients with NNRTI-resistant viruses. TMC125[9] is currently in phase IIB clinical trials.

However, criteria like drug compliance, adverse effects, and cross-resistance restrict the development of new drug candidates. As a result of these factors, there is a real medical need to develop new NNRTIs, which do not give rise to cross-resistance and are effective against clinically relevant mutant strains.

The DAPY compounds were developed from the DATA series.[10] The modifications were inferred from molecular modeling studies by use of available crystallographic structures of RT complexes with NNRTIs and was synthetically straightforward.[10] This modeling approach indicated that molecular interaction energy with certain conserved key amino acids of HIV-RT could be improved by replacement of the NH_2 moiety with a hydrogen atom on the central pyrimidine ring, which was subsequently confirmed by in vitro HIV activity.[10] Furthermore, comparison of the binding energies of compounds **4b** (dapivirine) and **5** indicated that improving the interaction between the para substituent on the trisubstituted phenyl ring and the conserved W229 region within the RT enzyme could give rise to novel variations of DAPY analogues with improved activity against wt LAI virus

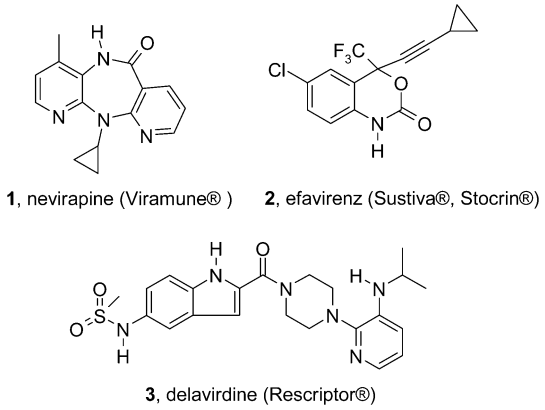

Figure 1. NNRTIs approved by the FDA.

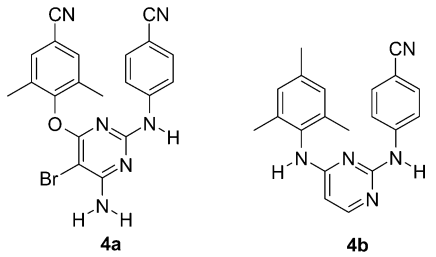

Figure 2. TMC125 (R165335) **4a** and TMC120 (R147681) **4b**.

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▽ This paper is dedicated to the memory of Dr. Paul Adriaan Jan Janssen (1926−2003).

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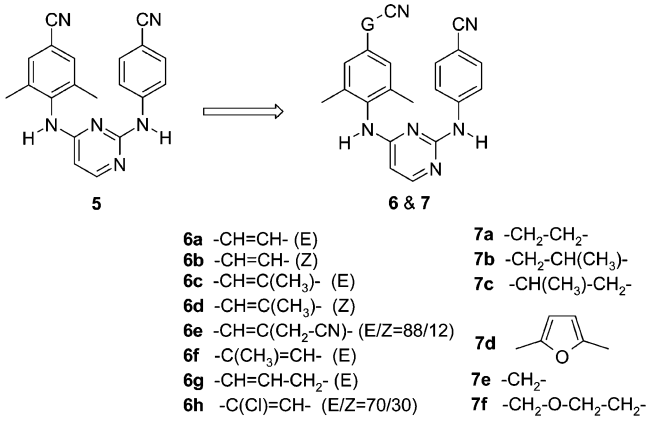


Figure 3. Introduction of G spacer group between the aryl ring and the cyano group.

and probably should have beneficial effects on activity against mutants. This observation also lead to the introduction of a spacer group **G** between the cyano group in 4-position and the trisubstituted phenyl ring (Figure 3). Subsequently, DAPY compounds **6** and **7** were based both on structure−activity relationships (SAR)[10] and on molecular modeling studies[11] of the 2-(4-cyanoanilino)-4-(4-cyano-2,6-dimethylanilino)pyrimidine **5** family by use of X-ray crystal structures studies of the RT−R147681 (**4b**, dapivirine) complex.[12] The resulting compounds were tested for in vitro activities against the wild type (WT) and against a panel of clinically relevant single and double NNRTI mutant strains of HIV activity.

These efforts resulted in the synthesis of a new class of DAPY compounds, **6** and **7**, which combine very high potency against the wild type and a panel of single and double mutant strains of HIV-1 with minimal in vitro toxicity.

Chemistry

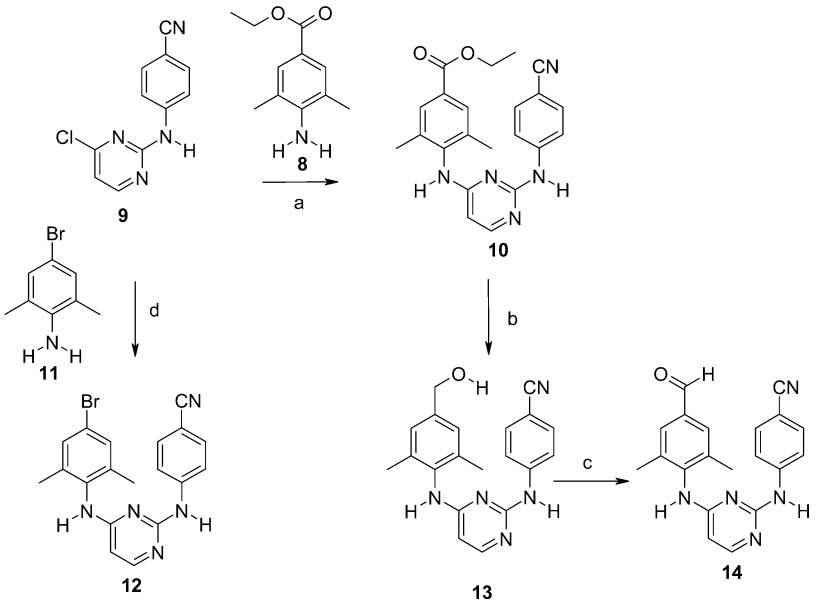
Newly designed compounds **6** and **7** were obtained from key intermediates **12** and **14** as depicted in Scheme 1. Aldehyde **14** was easily synthesized in three steps. Ester **10** was prepared by mixing ethyl 4-amino-3,5-dimethylbenzoate **8** and chloropyrimidine derivative **9**[10] at 150 °C for 2 h. Thereupon carboxylic ester **10** was reduced to alcohol **13** with lithium aluminum hydride ($LiAlH_4$) without affecting the cyano function present on the scaffold. Manganese dioxide (MnO_2) oxidation of alcohol **13** furnished the corresponding aldehyde **14**. Bromine derivative **12** was synthesized according to the same method as described for compound **10**.

Two methods have been used to gain access to these new DAPY compounds. Two basic methods were utilized, either Wadsworth−Emmons[13] or Wittig reaction conditions starting from aldehyde **14** (Scheme 2) or alternatively making use of the Heck reaction[14] starting from bromine derivative **12** as an intermediate (Scheme 3).

First of all, we investigated the Wittig and Wadsworth−Emmons reactions. Aldehyde **14** was condensed with either cyanomethyl triphenylphosphonium chloride **15a** (R_1=H) (Scheme 2) or diethyl (1-cyanoethyl) phosphonate **15b** (R_1 = Me) by use of *t*-BuOK in tetrahydrofuran (THF) as condensing agent to give the corresponding vinylcyanides **6,** which were isolated with the following stereoselectivity: **6a** (*E*)/**6b** (*Z*) = 80/20 and **6c** (*E*)/**6d** (*Z*) = 44/56. Hydrogenation of vinyl cyanides **6** with palladium on activated carbon (Pd/C 10%) as a catalyst in methanol afforded the expected reduced compounds **7**. Target compound **6e** (ratio *E*/*Z* = 12/88) could be prepared by treatment of aldehyde **14** in THF with fumaronitrile **16a** in the presence of tri-*n*-butylphosphine.[15]

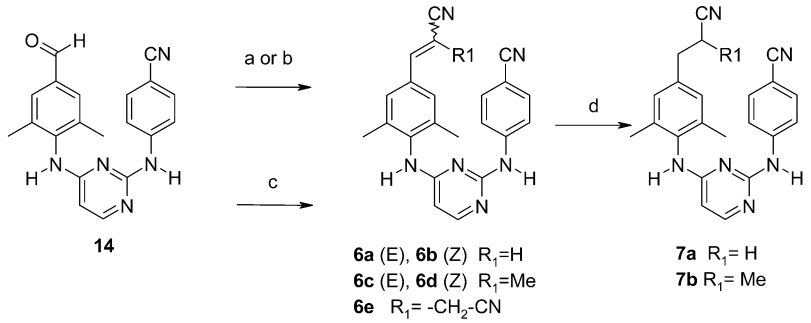
As a second method we used the Heck reaction (Scheme 3) in order to introduce the acrylonitrile group (either substituted or not) directly. Compounds **6a** and **6b** (ratio *E*/*Z* = 90/10) have been obtained via this method after treatment of aryl bromide **12** with acrylonitrile **16b** in the presence of triethylamine and palladium acetate as a catalyst in acetonitrile. Under the same conditions, compound **6f** (*E*) has been prepared from the crotononitrile reagent **16c**. Compound **7c** was

Scheme 1[a]



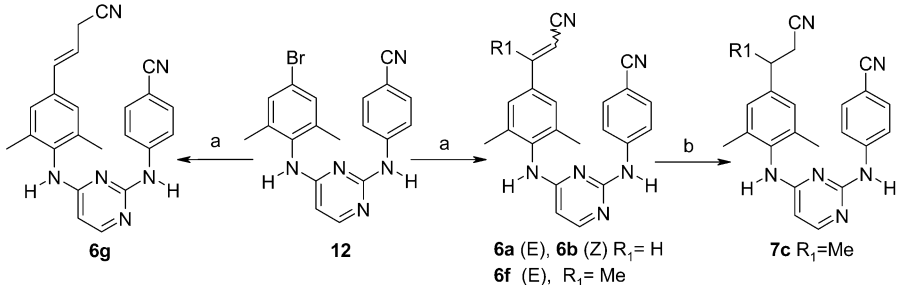
[a] Conditions: (a) 150 °C, 2 h; (b) $LiAlH_4$, THF, 0 °C to room temperature; (c) MnO_2, CH_2Cl_2, room temperature, 20 h; (d) 150 °C, 1 h.

Scheme 2[a]



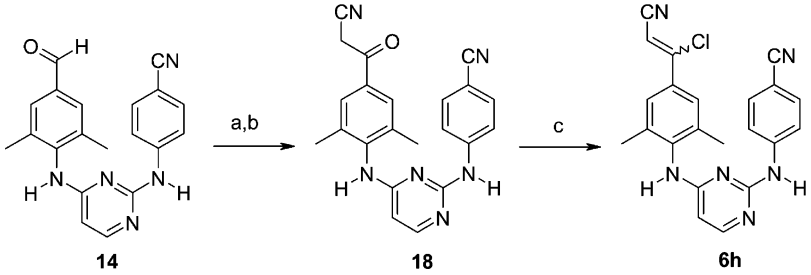
[a] Conditions: (a) tBuOK, THF, cyanomethyl triphenylphosphonium chloride **15a**, room temperature; (b) tBuOK, THF, diethyl (1-cyanoethyl)phosphonate **15b**, room temperature; (c) fumaronitrile **16a**, $P(Bu_3)$, THF, reflux; (d) Pd/C, MeOH, H_2 (3 bar).

Scheme 3[a]



[a] Conditions: (a) CH_2=CH−CN (**16b**) or Me-CH=CH−CN (**16c**) or CH_2=CH−CH_2−CN (**16d**), $Pd(OAc)_2$, P(*o*-tol)$_3$, Et_3N, CH_3CN, 150 °C; (b) Pd/C, MeOH, H_2 (3 bar).

Scheme 4[a]



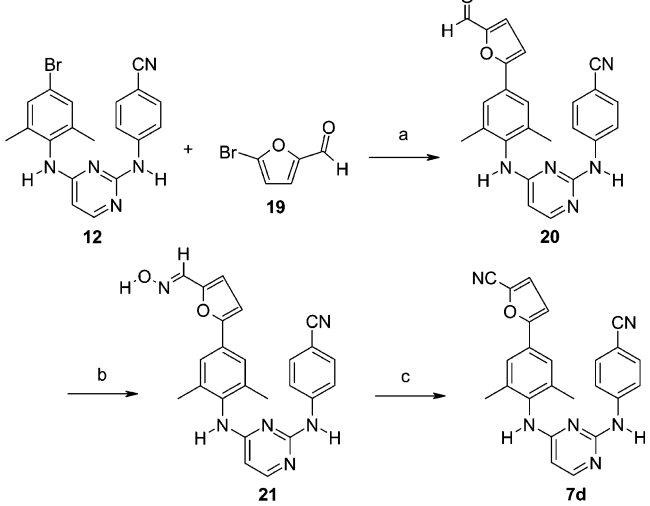
[a] Conditions: (a) LDA, THF, CH_3CN, −70 °C, 2 h; (b) Jones' reagent, acetone, 0 °C, 2 h; (c) $POCl_3$, 80 °C, 24 h.

prepared by catalytic hydrogenation with palladium on activated carbon (Pd/C 10%) in methanol from compounds **6f**. *E* isomer compound **6g** could specifically be prepared via Heck reaction conditions starting from allylcyanide **16d** and **12**. The synthesis of β-chloroacrylonitrile compound **6h** is depicted in Scheme 4. Aldehyde **14** was reacted with the lithium salt of acetonitrile to give the hydroxycyano intermediate **17** (indicated in Scheme 4). Oxidation of **17** with Jones reagent in acetone led to ketone **18**. Subsequently this ketone was then converted with phosphorus oxychloride to give the desired compound **6h** (ratio *E*/*Z* = 70/30).

The synthesis of 2-furyl heterocycle derivatives **20**, **21**, and **7d** is described in Scheme 5. The first step involved a modified in situ Suzuki cross-coupling reaction the coupling of 4-bromofurylcarboxaldehyde **19** with the bromo derivative **12** by use of the tetraalkoxydiboron derivative **22**,[16] which is thermally stable and can be easily handled in air. Moreover it has been shown to be a useful boron nucleophile for the cross-coupling reaction with heterocycles halides containing base-sensitive functionalities.[17]

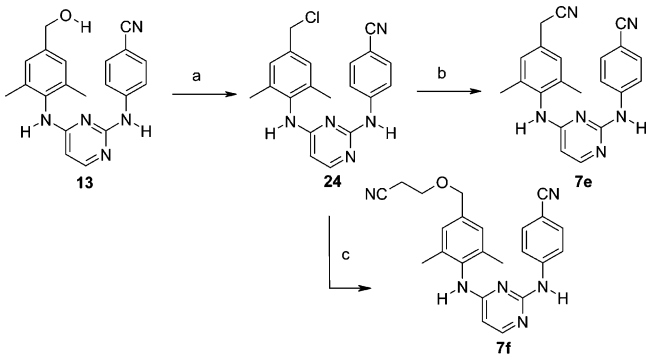
Furylaldehyde derivative **20** was transformed with hydroxylamine chloride **23** in ethanol into oxime **21** in the presence of sodium hydroxide in ethanol. Subsequently cyano derivative **7d** was then obtained from **23**

Scheme 5[a]



[a] Conditions: (a) Bis(pinacolato)diboron **22**, $Pd(PPh_3)_4$, K_2CO_3, toluene, EtOH, H_2O, reflux, 48 h; (b) NH_2OH, HCl, **23**, EtOH, NaOH (5 N), 50 °C, 2 h; (c) CDI, THF, reflux, 9 h.

Scheme 6[a]



[a] Conditions: (a) $SOCl_2$, CH_2Cl_2, room temperature, 9 h; (b) NaCN, DMF, 80 °C, 9 h; (c) 3-hydroxypropionitrile **25**, 80 °C, 9 h.

by reaction with the 1,1′-carbonyldiimidazole (CDI) in tetrahydrofuran (THF).

Alkyl or alkyloxy chains have been introduced as spacer groups according to the synthesis pathway described in Scheme 6. Compounds **7e** and **7f** were easily synthesized from the chlorine derivative **24** derived from methyl alcohol **13**.

Biological Results and Discussion

All compounds were tested for potency (EC_{50}, nanomolar), indicating concentrations required to achieve 50% protection of MT-4 cells from HIV-1 cytopathicity according to the MTT method.[18] The compounds were tested against a panel consisting of wild-type LAI virus (IIIB), single (103N, 181C, 188L, 100I, and 227C) and double mutant (103 + 181, 100I + 103N, 227L + 106A) strains derived from it. Cytotoxicity (CC_{50}) was also determined to assess selectivity of the antiviral effect. Table 1 lists EC_{50} and CC_{50} values for the compounds of formula **6** and **7**. The ratio between the CC_{50} and EC_{50} values, which is called the selectivity index (SI), indicates the specificity of the antiviral effect.

Table 1 shows the results of our SAR strategy. Introduction of the G spacer groups into derivative **5** led to very potent compounds demonstrating high activity against the LAI virus and the panel of mutant strains with a good selectivity index (SI).

The new series of DAPY compounds (**6**−**7**) was much more potent against wild-type virus than nevirapine and delavirdine and showed a comparable efficacy to the cyano derivative **5** and efavirenz against this virus type.

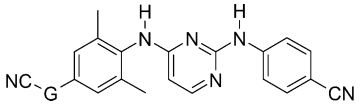
Replacement of the cyano substituent (**5**) by an acrylonitrile group **6a** (G = vinyl, pure *E*-isomer) led to a very potent compound highly active against single and double mutant strains, resulting in EC_{50} values equal or lower than 2 nM against LAI virus and single mutants. Moreover the 100I + 103N double mutant, which is completely resistant to efavirenz, was strongly inhibited (EC_{50} = 7.95 nM). Compared to compound **5**, the acrylonitrile derivative **6b** (*Z*-isomer) showed slightly increased potency against single and double mutants but was clearly less active than the corresponding *E*-isomer **6a**.

Differences of potency between **6a** (*E*) and **6b** (*Z*) were in agreement with the docking studies, which have suggested stronger interactions of the cyano group in *E*-orientation with the W229 region in the binding site of the RT enzyme but were less favorable for the compound with the *Z*-orientation.

With the introduction of a methyl group in the α or β position to the cyano substituent in compound **6a**, activity against mutant strains was not much affected except for the increased potency on the 100I +103N [EC_{50} = 7.95 nM (**6c**) and 2.51 nM (**6f**)] double mutant strain. Upon comparison of **6c** (*E*-isomer) with **6d** (*Z*-isomer), the data indicated a somewhat lower activity level of the *Z*-isomer compared to the *E*-isomer, which was somewhat more outspoken in the 188L, 103 + 181, and 100I + 103N mutant strains with this modification. Introduction of an acetonitrile group (compound **6e**) instead of a methyl group (compound **6d**) had a decreasing effect on activity against the panel of mutant strains but on the other hand was more potent against LAI virus (compound **6e**).

The replacement of the methyl group in compound **6f** by an electron-withdrawing group such as a chlorine

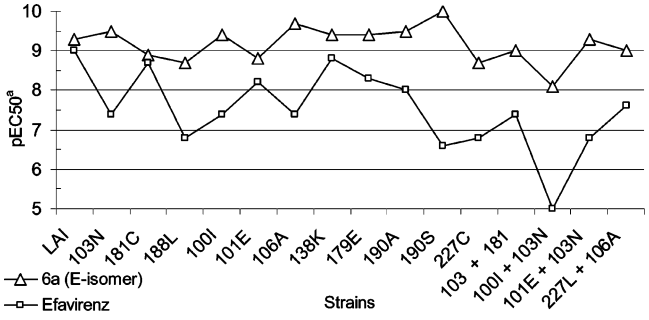
Table 1. Cytotoxicity and Inhibition of HIV-1



						EC_{50} (nM)							
cmpd	G-CN	*E/Z*	LAI	CC_{50}	SI[a]	103N	181C	188L	100I	227C	103N + 181C	100I + 103N	227L + 106A
5	−CN		0.4	5000	12 500	2	6.3	7.9	31	100	31	1000	12.6
6a	−CH=CH−CN	100/0	0.5	30 000	60 000	0.3	1.26	2	0.4	2	1	7.95	1
6b	−CH=CH−CN	0/100	0.6	30 000	50 000	1.6	5	31	6.3	4	39.8	794	4
6c	−CH=C(Me)−CN	100/0	0.8	20 000	25 000	0.6	1.6	3.16	0.6	2.51	2	31.6	4
6d	−CH=C(Me)−CN	0/100	0.8	3000	3750	1	4	31.6	3.16	5	20	>10 000	5
6e	−CH=C(CH_2−CN)−CN	12/88	0.4	2000	5012	6.31	6.31	31.6	31.6	12.5	nd[b]	nd	25.1
6f	−C(Me)=CH−CN	100/0	1	30 000	30 000	1	2.51	4	0.8	5	2.51	25.1	5
6h	−CH=CH−CH_2−CN	100/0	1	10 000	10 000	2.51	31.6	20	40	40	1	251	50
6i	−C(Cl)=CH−CN	70/30	4	30 000	7500	2	6.31	7.95	2.51	31.6	6.31	31.6	7.95
7a	−CH_2−CH_2−CN		0.63	3000	4782	0.4	12.5	20	7.95	4	2.51	31.6	4
7c	−CH_2−CH(Me)−CN		0.63	1000	1578	0.63	2	50	1	6.31	5	12.5	3.16
7d	−2−furyl−5−CN		4	10 000	3162	7.95	40	31.6	31.6	31.6	nd	500	31.6
7e	−CH_2−CN		0.8	10 000	12 589	7.95	25.1	251	40	10	nd	nd	25.1
7f	−CH_2−O−$(CH_2)_2$−CN		0.63	10 000	15 873	3.16	31.6	40	25.1	10	nd	nd	125
2	efavirenz		1	10 000	10 000	40	2	160	40	160	40	>10 000	25.1
1	nevirapin		39.8	20 000	>500	6310	10 000	>10 000	316	nd	>10 000	nd	nd
3	delavirdine		63.1	>20 000	>300	2510	2000	1260	2510	nd	20 000	nd	nd

[a] SI = CC_{50}/EC_{50}. [b] nd, not determined.

Chart 1. Comparison of Antiviral Activity between Compound **6a** and Efavirenz



[a] $pEC_{50} = -\log EC_{50}$.

atom (**6h**) resulted in a somewhat reduced potency. To evaluate the influence of the chain length, a homologous compound **6g** derived from **6a** was prepared and this modification resulted in a reduced activity against the panel of mutant strains.

When a 2-furyl heterocycle (**7d**) was inserted as G spacer group instead of the double bond into compound **5**, this also resulted in reduced activity.

The reduction of the double bond in **6a** and **6c** led to very attractive compounds in terms of activity (**7a** and **7c**). The potency against single and double mutant strains was not affected by the presence of a methyl group on the side chain. Nevertheless, these two compounds were slightly less active than the corresponding vinylcyanide derivatives **6a** and **6c**, especially on 188L and 100I + 103N. Omission of one carbon in the side chain (**7e**) or the incorporation of an alkyloxy group (**7f**) caused a decrease of the potency against the mutant strains when compared to **6a**.

Structural analogues of **5**, therefore, have demonstrated high activity as inhibitors of HIV-1 reverse transcriptase. The trend of the potency is

−CH=CH−CN (*E*) **6a** > −CH=C(Me)−CN (*E*) **6c** > −C(Me)=CH−CN (*E*) **6f** > $-CH_2-CH_2-CN$ **7a**.

Derivative **6a** was found to be extremely potent not only against the wild-type virus (EC_{50} = 0.5 nM) but moreover against a panel of 15 clinically relevant mutant strains (Chart 1).

Considering activity against single or double mutant strain in this panel, the DAPY derivative **6a** had a better overall profile compared to efavirenz. The gain in activity was substantial, especially on the double mutant 100I + 103N (>1000 times more active than efavirenz). In DAPY compounds, like TMC125 and compound **6a**, the number of mutations generally plays a more important role in resistance than a single particular mutation, and up to now no pattern could be found, notwithstanding that the 181C mutation is part of the picture. Compound **6a** has been assessed against a series of HIV-1 strains harboring one or two RT-associated mutations (obtained by site-directed mutagenesis), which are considered resistant to currently approved NNRTIs. From the available data, only the 179F + 181C mutant strain showed a >10-fold increase in EC_{50} for **6a**. This combination of mutations was observed upon in vitro selection experiments with TMC125,[19] and hence cross-resistance between the two compounds is not altogether unexpected. It should be noted that, in the case of NNRTIs, in vitro results rarely are predictive for the clinical situation.

Conclusion

This study clearly demonstrated that introduction of new spacer groups G on DAPY compounds **6** and **7** was crucial to generate very potent derivatives against the HIV-1 wild-type and a number of clinically relevant single and double mutants. The integrated structure−activity relationship strategy has led to the identification of **6a,c,f** and **7c**. These derivatives have displayed an excellent in vitro potency with better antiviral activity against HIV-1 resistant strains in comparison with other currently approved NNRTIs tested. Several members of this class of compounds are being considered as promising candidates for clinical evaluation.

Experimental Section

General. All analytically pure compounds were dried under vacuum in a drying pistol by use of a Buchi Glass Oven B-580 apparatus. Melting points were determined on a Leica VMHB apparatus and are uncorrected. TLC analyses were run on silica gel 60 F_{254} plates (Merck) with a variety of solvent systems and a fluorescent indicator for visualization. Spots were visualized under 254 nm UV illumination. Column chromatography was performed with silica gel 60 (Merck) (0.015−0.040 mm) or Kromasyl (Akzo Nobel) (0.010 mm). Proton NMR spectra were recorded on Bruker Avance 300 (300 MHz) and Bruker Avance 400 (400 MHz) spectrometers with internal deuterium lock. Chemicals shifts are reported to internal dimethyl sulfoxide (DMSO) (δ 2.54) in parts per million (ppm) and coupling constants (J) are given in hertz (Hz). Mass spectral data (MS) were collected on a Applied Biosystems API100 electrospray/quadripole instrument. High-resolution mass spectral data (HRMS) were recorded on a Waters LCT electrospray/time-of-flight instrument. Elemental analyses were performed on Thermo Electron Corporation instruments EA 1110 or EA 1108 for C, H, N and the results were within ±0.4% of the theoretical values. Compound **6d** analysis showed the percent H found to be 0.5% lower than percent H calculated. However, ^{1}H NMR spectroscopic analysis and TLC revealed a pure compound. Chemicals or solvents were purchased from either Acros Co or Aldrich Chemical Co. Yields refer to purified products and are not optimized.

4-[2-(4-Cyanophenylamino)pyrimidin-4-ylamino]-3,5-dimethylbenzoic Acid Ethyl Ester 10. A mixture of 4-amino-3,5-dimethylbenzoic acid ethyl ester **8** (3.48 g, 18 mmol) and 4-(4-chloropyrimidin-2-ylamino)benzonitrile **9**[8] (4.15 g, 18 mmol) was stirred at 150 °C in an oil bath for 2 h. The residue was crystallized from diisopropyl ether and CH_2Cl_2. Compound **10** (6.5 g, 93%) was obtained as a pale yellow solid, mp 200 °C; ^{1}H NMR (DMSO-d_6) δ 1.4 (3 H, t, J = 7 Hz), 2.2 (6 H, s) 4.4 (2 H, q, J = 7.0 Hz), 6.5 (1 H, br s), 7.2−7.6 (4 H, m), 7.8 (2 H, s), 8.07 (1 H, d, J = 5.5 Hz), 10−10.6 (2 H, m). Anal. ($C_{22}H_{21}N_5O_2$) C, H, N.

4-[4-(4-Bromo-2,6-dimethylphenylamino)pyrimidin-2-ylamino]benzonitrile 12. A mixture of 4-(4-chloropyrimidin-2-ylamino)benzonitrile **9**[8] (3 g, 13 mol) and intermediate 4-bromo-2,6-dimethylphenylamine **11** (2.6 g, 13 mol) was stirred at 150 °C for 1 h. The residue was poured into 10% aqueous K_2CO_3 and extracted with 5% of CH_3OH in CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was crystallized from diisopropyl ether and CH_3CN to afford **12** (3.2 g, 62%) as a pale yellow solid, mp 221 °C; ^{1}H NMR (DMSO-d_6) δ 2.15 (6 H, s), 6.08 (1 H, br s), 7.38 (2 H, s), 7.45 (1 H, d, J = 8.6 Hz), 7.77 (2 H, d, J = 8.6 Hz), 8.02 (2 H, d, J = 5.5 Hz), 8.56 (1 H, s), 9.3 (1 H, s). Anal. ($C_{19}H_{16}BrN_5$) C, H, N.

4-[4-(4-Hydroxymethyl-2,6-dimethylphenylamino)-pyrimidin-2-ylamino]benzonitrile 13. Lithium aluminum hydride (1.55 g, 41 mmol) was added portionwise at 5 °C to a mixture of **10** (4.26 g, 11 mmol) in THF (100 mL) under nitrogen. The mixture was stirred at 0 °C for 1 h and at room temperature overnight. Ethyl acetate was added, and then water, and the mixture was filtered over Celite. The organic

layer was separated, dried ($MgSO_4$), and concentrated under vacuum. The residue was crystallized from diisopropyl ether to give **13** (3 g, 79%) as a white solid, mp 246 °C; ^{1}H NMR (DMSO-d_6) δ 2.16 (6 H, s), 4.5 (2 H, s), 4.88 (1 H, s), 6 (1 H, br s), 7.11 (2 H, s), 7.4−7.8 (4 H, m), 7.97 (1 H, d, J = 5.5 Hz), 8.45 (1 H, s), 9.23 (1 H, s). HRMS: calcd for $C_{20}H_{20}N_5O$ $(MH)^+$ *m/z* 346.1668, found 346.1663.

4-[4-(4-Formyl-2,6-dimethylphenylamino)pyrimidin-2-ylamino]benzonitrile 14. To a solution of **13** (5.4 g, 16 mmol) in CH_2Cl_2 (100 mL) was added MnO_2 (5.4 g, 62 mol). The mixture was stirred at room temperature for 20 h, filtered through Celite, and concentrated under vacuum. The residue was crystallized from 10% AcOEt in diisopropyl ether to give **14** (3.8 g, 69%) as a pale yellow solid, mp 228 °C; ^{1}H NMR (DMSO-d_6) δ 2.3 (6 H, s), 6.15 (1 H, d, J = 5.6 Hz), 7.4 (2 H, d, J = 8.6 Hz), 7.7−7.75 (4 H, m), 8.04 (1 H, d, J = 5.6 Hz), 8.82 (1 H, s), 9.3 (1 H, s), 10.02 (1 H, s). Anal. ($C_{20}H_{17}N_5O$) C, H, N.

(*E*)- and (*Z*)-4-{4-[4-(2-Cyanovinyl)-2,6-dimethylphenylamino]pyrimidin-2-ylamino}benzonitrile 6a and 6b: First Method (Scheme 2). Potassium terbutoxide (0.25 g, 2.2 mmol) was added at 5 °C under nitrogen to a solution of cyanomethyl triphenylphosphonium chloride **15a** (0.74 g, 2.2 mmol) in THF (7 mL). The mixture was stirred at 5 °C for 30 min and then at room temperature for 30 min. A solution of the aldehyde **14** (0.5 g, 1.5 mmol) in THF (7 mL) was added dropwise, and the reaction was stirred at room temperature for 8 h, followed by addition of H_2O and extraction with AcOEt. The organic layer was separated, dried ($MgSO_4$), and concentrated. Compounds **6a** and **6b** were separated by silica gel column chromatography (96:4:0.1 toluene/^{i}PrOH/NH_4OH) and crystallized from CH_3CN and Et_2O.

Compound **6a** (0.262 g, 48%) white solid, mp 245 °C; ^{1}H NMR (DMSO-d_6) δ 2.2 (6 H, s), 6.1 (1 H, d, J = 5.6 Hz), 6.35 (1 H, d, J = 16.7 Hz), 7.43 (2 H, d, J = 7.7 Hz), 7.46 (2 H, s), 7.58 (1 H, d, J = 16.7 Hz), 7.77 (2 H, d, J = 7.7 Hz), 8.02 (1 H, d, J = 5.6 Hz), 8.6 (1 H, br s), 9.2 (1 H, br s). Anal. ($C_{22}H_{18}N_6$) C, H, N.

Compound **6b** (0.127 g, 23%) as a white solid, mp 258 °C; ^{1}H NMR (DMSO-d_6) δ 2.2 (6 H, s), 5.9 (1 H, d, J = 12.1 Hz), 6.35 (1 H, br s), 7.35−7.67 (7 H, m), 8 (1 H, d, J = 5.6 Hz), 9.0 (1 H, br s), 9.6 (1 H, br s). HRMS: calcd for $C_{22}H_{19}N_6$ $(MH)^+$ *m/z* 367.1871, found 367.1682.

Second Method (Scheme 3). A mixture of **12** (0.08 g, 0.21 mmol), acrylonitrile **16b** (0.14 mL, 2.13 mmol), $Pd(OAc)_2$ (0.009 g, 0.043 mmol), Et_3N (0.03 mL, 0.21 mmol), and tri-*o*-tolylphosphine (0.064 g, 0.21 mmol) in CH_3CN (7 mL) was stirred in a sealed vessel at 150 °C overnight. H_2O was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was silica gel column chromatographed (80:20 CH_2Cl_2/AcOEt) to give a residue of **6a** and **6b** (*E*/*Z* = 80/20). Crystallization from CH_3CN and Et_2O afforded **6a** (0.035 g, 55%).

(E)- and (Z)-4-{4-[4-(2-Cyano-2-methylvinyl)-2,6-dimethylphenylamino]pyrimidin-2-ylamino}benzonitrile 6c and 6d. Potassium terbutoxide (2.21 g, 19.6 mmol) was added at 5 °C under nitrogen to a solution of diethyl cyanoethylphosphonate **15b** (3.44 mL, 19.6 mL) in THF (45 mL). The mixture was stirred at 5 °C for 30 min and then at room temperature for 30 min. A solution of the aldehyde **14** (4.5 g, 13 mmol) in THF (45 mL) was added dropwise, and the reaction was stirred at room temperature for 3 h, followed by addition of H_2O and extraction with AcOEt. The organic layer was separated, dried ($MgSO_4$), and concentrated. Compounds **6c** and **6d** were separated by silica gel column chromatography (85:15:1 cyclohexane/^{i}PrOH/NH_4OH) and crystallized from 5% ^{i}PrOH in diisopropyl ether.

Compound **6c** (1.23 g, 25%) white solid, mp 201 °C; ^{1}H NMR (DMSO-d_6) δ 2.15 (3 H, s), 2.2 (6 H, s), 6.2 (1 H, br s), 7.25 (2 H, s), 7.38−7.83 (5 H, m), 8.0 (1 H, d, J = 5.5 Hz), 8.85 (1 H, s), 9.55 (1 H, s). Anal. ($C_{23}H_{20}N_6$) C, H, N.

Compound **6d** (1.56 g, 31%) white solid, mp 246 °C; ^{1}H NMR (DMSO-d_6) δ 2.15 (3 H, s), 2.2 (6 H, s), 6.2 (1 H, br s), 7.25 (1 H, s), 7.4−7.75 (6 H, m), 8.05 (1 H, d, J = 5.5 Hz), 8.9 (1 H, s), 9.65 (1 H, s). Anal. ($C_{23}H_{20}N_6$) C, H, N.

2-{4-[2-(4-Cyanophenylamino)pyrimidin-4-ylamino]-3,5-dimethylbenzylidene}succinonitrile 6e (*E*/*Z* 12/88). Tributylphosphine (0.44 mL, 1.75 mmol) was added at room temperature to a solution of (2*E*)-but-2-enedinitrile **16a** (0.14 g, 1.75 mmol) in THF (7 mL), and the mixture was refluxed for 2 h. A solution of **14** (0.2 g, 0.58 mmol) in THF (5 mL) was added. The mixture was refluxed overnight, followed by addition of H_2O and extraction with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was silica gel column chromatographed (99:1 CH_2Cl_2/CH_3OH). Crystallization from diisopropyl ether and CH_3CN (50:50) gave **6e** (0.036 g, 15%) as a white solid, mp 204 °C; ^{1}H NMR (DMSO-d_6) δ 2.2 (6 H, s), 4 (2 H, s), 6.35 (1 H, br s), 7.28−7.8 (7 H, m), 8.02 (1 H, d, J = 5.6 Hz), 8.98 (1 H, br s), 9.63 (1 H, br s). HRMS: calcd for $C_{24}H_{20}N_7$ $(MH)^+$ *m/z* 406.1780, found 406.1791.

(*E*)-4-{4-[4-(2-Cyano-1-methylvinyl)-2,6-dimethylphenylamino]pyrimidin-2-ylamino}benzonitrile 6f. A mixture of **12** (0.6 g, 1.52 mmol), crotononitrile **16c** (*E*/*Z* = 33/66) (0.87 mL, 10.68 mmol), $Pd(OAc)_2$ (0.066 g, 0.29 mmol), Et_3N (0.216 mL, 1.52 mmol), and tri-*o*-tolylphosphine (0.462 g, 1.52 mmol) in CH_3CN (15 mL) was stirred in a sealed vessel at 150 °C for 72 h. H_2O was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was silica gel column chromatographed (98:2 CH_2Cl_2/CH_3OH) and only the *E* isomer was isolated. Crystallization from diisopropyl ether and CH_3CN (50:50) gave **6f** (0.032 g, 11%) as a white powder, mp 224 °C; ^{1}H NMR (DMSO-d_6) δ 2.2 (6 H, s), 2.45 (3 H, s), 5.5−6.4 (2 H, m), 7.3−7.8 (6 H, m), 8.02 (1 H, d, J = 5.6 Hz), 8.92 (1 H, s), 9.6 (s, 1 H). Anal. ($C_{23}H_{20}N_6$) C, H, N.

(*E*)-4-{4-[4-(3-Cyanopropenyl)-2,6-dimethylphenylamino]pyrimidin-2-ylamino}benzonitrile 6g. A mixture of **12** (0.2 g, 0.51 mmol), allylcyanide **16d** (0.41 mL, 5.1 mmol), $Pd(OAc)_2$ (0.023 g, 0.1 mmol), Et_3N (0.14 mL, 0.1 mmol) and tri-*o*-tolylphosphine (0.155 g, 0.51 mmol) in CH_3CN (10 mL) was stirred in a sealed vessel at 150 °C overnight. H_2O was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was silica gel column chromatographed (99:1 CH_2Cl_2/CH_3OH). Crystallization from 5% AcOEt in diisopropyl ether yielded **6g** (0.04 g, 21%) as a white solid, mp 213 °C; ^{1}H NMR (DMSO-d_6) δ 2.18 (6 H, s), 3.52 (2 H, dd, J = 6.1 and 1.5 Hz) 6.0 (1 H, br s), 6.23 (1 H, dt, J = 15.7 and 6.1 Hz), 6.7 (1 H, d, J = 15.7 Hz), 7.25 (2 H, s), 7.45 (2 H, d, J = 8.1 Hz), 7.8 (2 H, d, J = 8.1 Hz), 8.0 (1 H, d, J = 6.1 Hz), 8.5 (1 H, s), 9.3 (1 H, s). Anal. ($C_{23}H_{20}N_6$) C, H, N.

4-{4-[4-(2-Cyano-1-hydroxyethyl)-2,6-dimethylphenylamino]pyrimidin-2-ylamino}benzonitrile 17. *n*-Butyllithium (1.6 M in hexane, 2.4 mL, 3.8 mmol) was added dropwise at −70 °C to a solution of diisopropylamine (0.5 mL, 3.8 mmol) in THF (5 mL) under nitrogen. The mixture was stirred at −20 °C for 30 min and recooled at −70 °C before dropwise addition of a solution of CH_3CN (0.2 mL, 3.8 mmol) in THF (2 mL). The mixture was stirred at −20 °C for 1 h and cooled again at −70 °C. A solution of **14** (0.3 g, 0.95 mmol) in THF (2 mL) was added. The mixture was stirred for 2 h, followed by addition of H_2O and extraction with AcOEt. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was silica gel column chromatographed (98:2 CH_2Cl_2/CH_3OH). Crystallization from diisopropyl ether and CH_3CN (50:50) afforded **17** (0.18 g, 49%) as a white solid, mp 252 °C; ^{1}H NMR (DMSO-d_6) δ 2.20 (6 H, s), 2.82−3.97 (2 H, m), 4.91 (1 H, br s), 5.68 (1 H, br s), 6.0 (1 H, br s), 7.21 (2 H, s), 7.48 (2 H, d, J = 8.0 Hz), 7.29 (2 H, d, J = 8.0 Hz), 7.98 (1 H, d, J = 5.5 Hz), 8.48 (1 H, s), 9.25 (1 H, s). HRMS: calcd for $C_{22}H_{21}N_6O$ $(MH)^+$ *m/z* 385.1777, found 385.1805.

4-{4-[4-(2-Cyanoacetyl)-2,6-dimethylphenylamino]-pyrimidin-2-ylamino}benzonitrile 18. Jones's reagent (3 M, 1.87 mL, 5.6 mmol) was added at 5 °C to a mixture of intermediate **17** (1.11 g, 2.9 mmol) in 2-propanone (20 mL) under nitrogen. The mixture was stirred at 0 °C for 2 h and then poured out into H_2O, basified with 10% aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was silica gel column chromatographed (98:2:0.1 $CH_2Cl_2/CH_3OH/NH_4OH$) and the concentrated product fractions were crystallized from 10% ^{i}PrOH in diisopropyl ether to give **18** (0.056 g, 5%) as a white powder, mp 150 °C; ^{1}H NMR (DMSO-d_6) δ 2.25 (6 H, s), 4.7 (2 H, br s), 6.12 (1 H, d, J = 5.5 Hz), 7.45 (2 H, d, J = 8.5 Hz), 7.73 (4 H, m), 8.05 (1 H, d, J = 5.5 Hz), 8.8 (1 H, s), 9.35 (1 H, s). HRMS: calcd for $C_{22}H_{19}N_6O$ $(MH)^+$ m/z 383.1620, found 383.1599.

4-{4-[4-(1-Chloro-2-cyanovinyl)-2,6-dimethylphenylamino]pyrimidin-2-ylamino}benzonitrile 6h (*E*/*Z* 70/30). A solution of **18** (0.2 g, 0.52 mmol) in phosphorus oxychloride (1.5 mL) was stirred at 80 °C for 24 h. The mixture was then poured into ice water, basified by use of solid K_2CO_3, and extracted with 10% CH_3OH in CH_2Cl_2. The residue was silica gel column chromatographed (99:1 CH_2Cl_2/CH_3OH). The pure fractions were concentrated to afford **6h** (0.026 g, 13%) as a white powder; ^{1}H NMR (DMSO-d_6) δ 2.2 (6 H, s), 6.0−6.95 (2 H, m), 7.4−8.05 (7 H, m), 9.0 (1 H, s), 9.65 (1 H, br s). MS (ESI): m/z 401 $(MH)^+$.

4-{4-[4-(2-Cyano-ethyl)-2,6-dimethylphenylamino]-pyrimidin-2-ylamino}benzonitrile 7a. A solution of **6a** and **6b** (*E*/*Z* = 50/50) (0.15 g, 0.41 mmol) in CH_3OH (10 mL) was hydrogenated under 3 atm of H_2 for 5 h at room temperature, with Pd/C 10% (0.07 g) as the catalyst. The catalyst was removed by filtration through Celite and washed with CH_2Cl_2, and the filtrate was concentrated. After crystallization from diisopropyl ether, the residue was silica gel column chromatographed (99:1 CH_2Cl_2/CH_3OH). Crystallization from CH_3CN and diisopropyl ether afforded **7a** (0.04 g, 27%) as a white powder, mp 208 °C; ^{1}H NMR (DMSO-d_6) δ 2.15 (6 H, s), 2.82 (2 H, t, J = 7.7 Hz), 2.9 (2 H, t, J = 7.7 Hz), 6.0 (1 H, br s), 7.1 (2 H, s), 7.45 (2 H, d, J = 8 Hz), 7.8 (2 H, d, J = 8 Hz), 7.95 (1 H, d, J = 6.1 Hz), 8.4 (1 H, s), 9.2 (1 H, s). Anal. ($C_{23}H_{20}N_6$) C, H, N.

4-{4-[4-(2-Cyano-2-methylethyl)-2,6-dimethylphenylamino]pyrimidin-2-ylamino}benzonitrile7b. This compound was prepared from **6c** and **6d** (*E*/*Z* = 50/50) (0.35 g, 0.92 mmol) as described for **7a**. Compound **7b** (0.147 g, 42%) was obtained as a white solid, mp 187 °C; ^{1}H NMR (DMSO-d_6) δ 1.3 (3 H, m), 2.13 (6 H, s), 2.8 (2 H, m), 3.2 (1 H, br s), 6.3 (1 H, s), 7.1 (2 H, s), 7.35−8.1 (5 H, m), 8.7 (1 H, m), 9.6 (1 H, m). Anal. ($C_{23}H_{22}N_6$) C, H, N.

4-{4-[4-(2-Cyano-1-methylethyl)-2,6-dimethylphenylamino]pyrimidin-2-ylamino}benzonitrile 7c. A solution of **6f** (0.065 g, 0.171 mmol) in CH_3OH (5 mL) and THF (5 mL) was hydrogenated under 3 atm of H_2 for 48 h at room temperature, with Pd/C 10% (0.065 g) as the catalyst. The catalyst was removed by filtration through Celite and washed with CH_2Cl_2, and the filtrate was concentrated. The residue was silica gel column chromatographed (99:1 CH_2Cl_2/CH_3OH) to give **7c** (0.035 g, 54%) as a white powder, mp 208 °C; ^{1}H NMR (DMSO-d_6) δ 1.38 (3 H, d, J = 7 Hz), 2.18 (6 H, s), 2.81 (2 H, d, J = 7 Hz), 3.15 (1 H, st, J = 7 Hz), 6.0 (1 H, br s), 7.12 (2 H, s), 7.45 (2 H, d, J = 8 Hz), 7.80 (2 H, d, J = 8 Hz), 7.98 (1 H, d, J = 5.5 Hz), 8.46 (1 H, s), 9.28 (1 H, s). Anal. ($C_{23}H_{22}N_6$) C, H, N.

4-{4-[4-(5-Formylfuran-2-yl)-2,6-dimethylphenylamino]-pyrimidin-2-ylamino}benzonitrile 20. A mixture of **12** (2 g, 5.1 mmol), bis(pinacolato)diboron **22** (1.4 g, 5.5 mmol), tetrakis(triphenylphosphine) palladium(0) (0.29 g, 0.3 mmol), and K_2CO_3 (2.8 g, 20 mmol) in toluene (100 mL), EtOH (5 mL), and H_2O (10 mL) was refluxed for a weekend. 5-Bromofuran-2-carbaldehyde **19** (0.98 g, 5.5 mmol) and K_2CO_3 (1.4 g, 10 mmol) were sequentially added to the previous solution and the mixture was refluxed overnight. The residue was silica gel column chromatographed (99:1 CH_2Cl_2/CH_3OH 99/1). Concentration of the pure fractions provided **20** (0.13 g, 6%) as a pale yellow oil.

4-(4-{4-[5-(Hydroxyiminomethyl)furan-2-yl]-2,6-dimethylphenylamino}pyrimidin-2-ylamino)benzonitrile 21. Aqueous NaOH (5 N, 2 mL) was added dropwise at 50 °C to a mixture of **20** (0.13 g, 0.3 mmol) and hydroxylamine chloride **23** (0.03 g, 0.41 mmol) in EtOH (10 mL). The mixture was stirred at 50 °C for 2 h and $^2/_3$ of this mixture was concentrated before addition of H_2O and then extraction with CH_2Cl_2. The organic layer was washed with 10% aqueous K_2CO_3, dried over $MgSO_4$, filtered, and concentrated. Intermediate **21** (0.21 g) was obtained as a pale yellow oil.

5-{4-[2-(4-Cyanophenylamino)pyrimidin-4-ylamino]-3,5-dimethylphenyl}-furan-2-carbonitrile7d. 1,1-Carbonyldiimidazole (0.16 g, 1.3 mmol) was added to a mixture of **21** (0.32 mmol) in THF (20 mL). The mixture was refluxed overnight, poured out into H_2O, and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was silica gel column chromatographed (98:2 CH_2Cl_2/CH_3OH). Crystallization from 5% AcOEt in Et_2O provided **7d** (0.05 g, 38%) as white solid, mp > 260 °C; ^{1}H NMR (DMSO-d_6) δ 2.2 (6 H, s), 6.3 (1 H, m), 7.25 (1 H, d, J = 3.5 Hz), 7.3−7.7 (6 H, m), 7.75 (1 H, d, J = 3.5 Hz), 8.02 (1 H, s), 8.92 (1 H, s), 9.6 (1 H, s). Anal. ($C_{24}H_{18}N_6O_2$) C, H, N. HRMS: calcd for $C_{24}H_{19}N_6O$ $(MH)^+$ m/z 407.1620, found 407.1630.

4-[4-(4-Chloromethyl-2,6-dimethylphenylamino)pyrimidin-2-ylamino]benzonitrile 24. Thionyl chloride (1 mL, 14 mmol) was added dropwise at 5 °C to a solution of **13** (0.85 g, 3 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at room temperature overnight and concentrated to afford **24** (1 g, 100%) as a pale yellow oil; ^{1}H NMR (DMSO-d_6) δ 2.15 (6 H, s), 4.82 (2 H, s), 6.53 (1 H, d, J = 5.5 Hz), 7.31 (2 H, s), 7.38, (2 H, d, J = 8.6 Hz), 7.50 (2 H, d, J = 8.6 Hz), 8.12 (1 H, d, J = 5.5 Hz), 10.82 (1 H, s), 11.3 (1 H, s).

4-[4-(4-Cyanomethyl-2,6-dimethylphenylamino)pyrimidin-2-ylamino]benzonitrile 7e. A mixture of **24** (0.36 g, 0.99 mmol) and sodium cyanide (0.097 g, 1.9 mmol) in DMF (7 mL) was stirred at 80 °C overnight and poured out into water. After extraction with CH_2Cl_2, the organic layer was dried ($MgSO_4$) and concentrated. The residue was silica gel column chromatographed (60:40 CH_3OH/NH_4, HCO_3). Crystallization from CH_3CN and diisopropyl ether yielded **7e** (0.035 g, 10%) as a white powder, mp 210 °C; ^{1}H NMR (DMSO-d_6) δ 2.18 (6 H, s), 3.97 (2 H, s), 6.05 (1 H, br s), 7.16 (2 H, s), 7.46 (2 H, d, J = 8.6 Hz), 7.76 (2 H, d, J = 8.6 Hz), 8.0 (1H, d, J = 5.5 Hz), 8.57 (1 H, s), 9.28 (1 H, s). Anal. ($C_{21}H_{18}N_6$) C, H, N.

4-{4-[4-(2-Cyanoethoxymethyl)-2,6-dimethylphenylamino]pyrimidin-2-ylamino}benzonitrile 7f. A solution of **24** (0.2 g, 5.5 mmol) in 3-hydroxypropionitrile **25** (2 mL) was stirred at 80 °C overnight, poured out into H_2O, and extracted with CH_2Cl_2. The combined organic layer were dried ($MgSO_4$) and concentrated. The residue was silica gel column chromatographed (99:1:0.1 $CH_2Cl_2/CH_3OH/NH_4OH$). The residue was washed with 3 N HCl, extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated. After crystallization from 5% AcOEt in diisopropyl ether, **7f** (0.039 g, 18%) was obtained as a white solid, mp > 260 °C; ^{1}H NMR (DMSO-d_6) δ 2.17 (6 H, s), 2.82 (2 H, t, J = 6.1 Hz), 3.71 (2 H, t, J = 6.1 Hz), 4.54 (2 H, s), 6.0 (1 H, br s), 7.15 (2 H, s), 7.43−7.82 (4 H, m), 7.98 (1H, d, J = 6 Hz), 8.61 (1 H, s), 9.38 (1 H, s). Anal. ($C_{23}H_{22}N_6O$) C, H, N.

Test Method. The antiviral activity of compounds was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay method.[17] Different concentrations of the test compounds were added to wells of a flat-bottom microtiter plate. Then, virus and MT-4 cells were introduced to a final concentration of 200−250 50% cell culture infectious doses ($CCID_{50}$)/well and 30,000 cells/well, respectively. Cytotoxicity of the test compound was determined in parallel by use of mock-infected cell cultures containing an identical compound concentration range but no virus. After 5

days of incubation at 37 °C with 5% CO_2, the viability of the HIV and mock-infected cells was assessed by the MTT method.[17] This method allows the calculation of both the 50% effective concentration for inhibition of viral cytopathicity (EC_{50}) and the 50% cytotoxic concentration (CC_{50}).

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