Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitors

Part 13[1])

Synthesis of Fluorine-Containing Diaryltriazine Derivatives for *in vitro* Anti-HIV Evaluation against Wild-Type Strain

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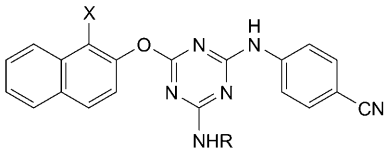
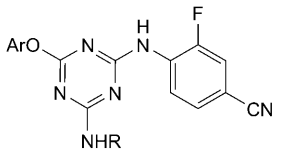
A series of diaryltriazine derivatives modified at C(2) of the triazine ring with a fluorinated phenyl group has been synthesized and tested for the ability to inhibit HIV-1 replication. Most of these F-containing compounds showed low-to-moderate anti-HIV activity in MT-4 cells.

Introduction. – The reverse transcriptase (RT) of human immunodeficiency virus type 1 (HIV-1) is a multifunctional key enzyme. The inhibition of RT is considered as one of the most valuable and practicable approaches to suppress AIDS spreading. Subsequent to the discovery of diaryltriazine analogues (DATAs) as a class of novel potent and selective compounds for non-nucleoside reverse transcriptase inhibitors (NNRTIs) of HIV-1 [2–5], attention has been focused on the alteration of the substitution at C(4) and C(6) of the triazine nucleus in DATAs, leading to the synthesis of novel DATA analogues, **1**–**3**, with potency against HIV-1 replication. However, there are unexplored aspects in changing the functionality in the phenyl ring moiety at C(2).



1 X = Br, R = H
2 X = Br, R = Me
3 X = Cl, R = H



4 Ar = 4-MeC_6H_4, naphthalen-2-yl, or 1-Br/Cl-naphthalen-2-yl
R = H, C_1 – C_3 alkyl, allyl

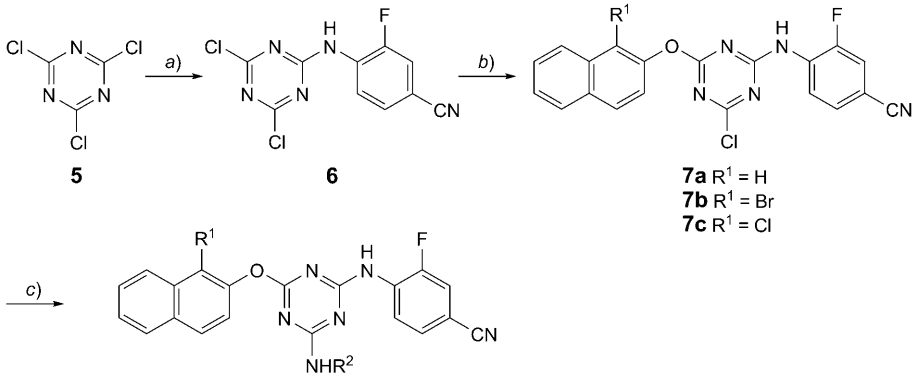
It is well-known that the introduction of F substituents to biologically active substances, especially incorporating a F-atom into an aromatic or heterocyclic ring, can

[1]) For Part 12, see [1].

affect their biological properties associated with lipophilicity, absorption, and transportation because of the highest electronegativity, high thermal stability, and lipophilicity [6]. As part of our continuing interest in DATA series as NNRTIs [2], we direct our attention to investigate whether or not introduction of a F-atom into a phenyl ring at C(2) of a triazine skeleton will impact the antiviral activity. Herein, the synthesis, biological evaluation, and preliminary SAR profile of fluorinated DATA congeners **4** are described.

Results and Discussion. – 1. *Chemistry.* The typical synthetic routes for the title compounds are outlined in *Schemes 1* and *2*. Condensation of 2,4,6-trichloro-1,3,5-triazine with 4-amino-3-fluorobenzonitrile gave the key intermediate **6** according to the protocol described in [2]. Nucleophilic substitution of **6** by different β-naphthols (= naphthalen-2-ols) and *p*-cresol (= 4-methylphenol) in the presence of 60% NaH at 50–60° provided **7a**–**7c** and **9**, respectively, in 50–55% yield. Treatment of **7a**–**7c** with appropriate primary amines in 1,4-dioxane at 60–70° afforded the desired DATA analogues **8a**–**8n** in 40–50% yield (*Scheme 1*). Further target compounds, **10a**–**10e**, were conveniently synthesized by reaction of **9** with the corresponding amines in 1,4-dioxane at 60–70° (*Scheme 2*). All synthesized compounds were characterized by spectroscopic data as IR, MS, and NMR.

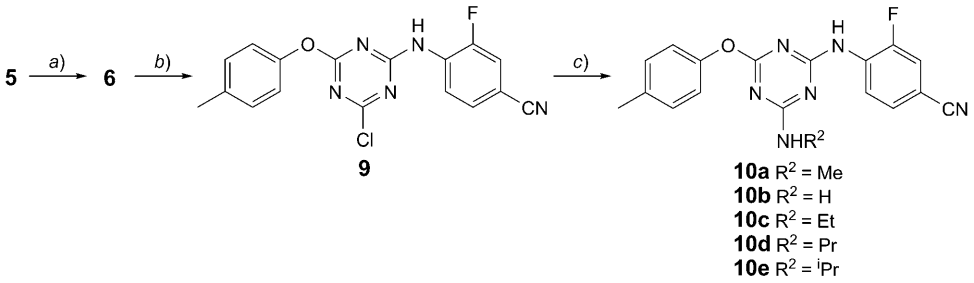
Scheme 1



a) 4-Amino-3-fluorobenzonitrile, Et_3N, anh. THF, 0–5°, 4.5 h. *b*) β-Naphthols (= naphthalen-2-ols), 60% NaH, anh. THF, N_2, 50–60°, 4.5 h. *c*) R^2NH_2, 1,4-dioxane, 60–70°, 1–4 h.

2. *Biological Activities.* The novel fluorinated DATA derivatives synthesized in this study are evaluated for their inhibitory activity against HIV-1 IIIB strains including

Scheme 2



a) 4-Amino-3-fluorobenzonitrile, Et_3N, anh. THF, 0–5°, 4.5 h. *b*) *p*-Cresol (=4-methylphenol), 60% NaH, anh. THF, N_2, 50–60°, 4.5 h. *c*) NH_3 or R^2NH_2, 1,4-dioxane, 60–70°, 1–4 h.

cytopathology in MT-4 cell using the MTT[2]) method [7]. The results are listed in the *Table*, together with the antiviral data of 2′,3′-dideoxyinosine (DDI) and 1-[(2-hydroxyethoxy)methyl]-6-(phenylsulfanyl)thymine (HEPT), which are included in the *Table* for comparison.

As seen from the *Table*, most of the newly synthesized F-containing DATA analogues were active against HIV-1 replication with a wide range of IC_{50} values from 18.3 ± 8.05–0.36 ± 0.067 μM; two compounds, **8e** and **8f**, endowed with IC_{50} values of 0.36 and 0.41 μM, respectively, were almost 14-fold higher in activity than DDI. However, these analogs showed less potency compared with the corresponding compounds reported in the literature [2]. In addition, the effect of the substituent at C(6) of the triazine ring was examined; it was found that all compounds with a substituent on the naphthyl or the phenyl ring were potent against wild-type HIV-1, whereas compounds **8a**–**8d** without any substitution on the naphthyl ring were devoid of any antiviral activity, indicating that increasing volume of the substituent at C(6) of the triazine ring might be beneficial for strengthening π–π stacking interaction between inhibitors and Tyr188 or Tyr181 of RT. The nature of the substituent at C(4) of the nuclei plays an important role in the inhibitory activity as previously observed [2]. It is worth nothing that the alkylation of the amino group at C(4) with different alkyl group such as Et, Pr, i-Pr provided *N*-alkylated derivatives which were less potent than their counterparts, for example, as in case of **8i**, the potency of which was 22-fold lower compared to that of **8f**. Interestingly, most of the compounds were endowed with a CC_{50} value higher than 240 μM except five compounds, *i.e.*, **8e**, **8f**, **8j**, **10b**, and **10d** (CC_{50} 98–180 μM).

Conclusions. – A series of novel DATA analogues with F-substituent was synthesized and evaluated for their anti-HIV activities. The bioassay results demonstrated that most of the compounds show inhibitory potency against HIV-1.

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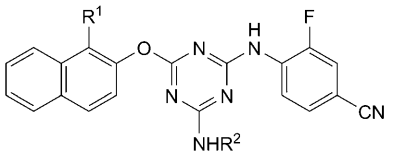
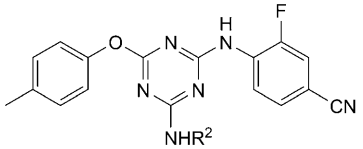
[2]) MTT = 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium hydrobromide.

Table. *Anti-HIV-1 Activity of DATA Derivatives in MT-4 Cells.* For details, see *Exper. Part.*



8a – 8n



10a – 10e

Drug	R^1	R^2	HIV-1 IIIB IC_{50} [μM][a])	CC_{50} [μM][b])	SI[c])
8a	H	Me	236	236	<1
8b	H	H	336	336	<1
8c	H	Et	222	222	<1
8d	H	allyl	229	229	<1
8e	Br	Me	0.36±0.067	98.84	274
8f	Br	H	0.415±0.042	109.91	543
8g	Br	Et	2.05±1.06	>261.51	>128
8h	Br	allyl	1.173±0.096	>255.1	>218
8i	Br	^{i}Pr	9.49±2.09	>254.07	>27
8j	Cl	Me	0.802±0.41	148.95	186
8k	Cl	H	0.709±0.187	251.58	354
8l	Cl	Et	1.618±0.014	>269.58	>167
8m	Cl	allyl	1.98±0.37	280.27	140
8n	Cl	Pr	4.911±0.78	>279.02	>57
10a		Me	2.884±0.54	247.76	86
10b		H	1.078±1.36	162.68	151
10c		Et	8.89±0.74	243.19	27
10d		Pr	4.35±1.38	185.62	43
10e		^{i}Pr	18.3±8.56	278.38	15
DDI[d])			5.37	≥529	≥98
HEPT[e])			5.06	405	80

[a]) 'Inhibitory Concentration fifty': drug concentration required to protect the cell against viral cytopathogenicity by 50% in MT-4 cells. [b]) 'Cytotoxic concentration fifty': drug concentration reducing the normal uninfected in MT-4 cell viability by 50%. [c]) 'Selectivity index': $SI = CC_{50}/IC_{50}$. [d]) DDI = 2′,3′-dideoxyinosine (positive control). [e]) HEPT = 1-[(2-hydroxyethoxy)methyl]-6-(phenylsulfanyl)thymine.

Experimental Part

General. All chemicals and solvents were reagent-grade and purified by standard methods prior to use. M.p.: *WRS-1* digital melting-point apparatus; uncorrected. IR Spectra (KBr): *Jasco FT/IR-4200* instrument; in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker AV* 400 MHz spectrometer; chemical shifts expressed in ppm downfield from Me_4Si, which was used as an internal standard. MS: *Agilent MS/5975* mass spectrometer; in *m*/*z*.

Preparation of 4-[(4,6-Dichloro-1,3,5-triazin-2-yl)amino]-3-fluorobenzonitrile (**6**). To a stirred soln. of *2,4,6-trichloro-1,3,5-triazine* (**5**; 7.28 g, 0.04 mol) in anh. THF (100 ml) was added 4-amino-3-fluorobenzonitrile (5.38 g, 0.04 mol) dropwise at 0–5° under N_2. The resulting soln. was stirred at this temp. for 1 h, and Et_3N (3.03 g, 0.04 mol) was added into the mixture. Stirring was continued for another h. The precipitate was collected by filtration, washed with H_2O, and dried to afford **6** (5.38 g, 65%). Off-white solid. M.p. 285.3° (dec.). FT-IR (KBr): 2220 (CN). ^{1}H-NMR ($CDCl_3$): 7.41–7.80 (*m*, 3 arom. H); 10.80 (*s*, NH). EI-MS: 283 (M^+).

General Procedure for the Preparation of the Target Compounds **7a**–**7c**. To a stirred soln. of the appropriate naphthalen-2-ol (11.3 mmol) in anh. THF (100 ml) was added 60% NaH (0.452 g, 11.3 mmol) at r.t. under N_2. The resulting soln. was stirred at this temp. for 30 min, and **6** (3.03 g, 11.3 mmol) was added to the mixture. Stirring was continued for another 4 h at 50–60°. The precipitate was collected by filtration, washed with H_2O, and recrystallized from MeOH to afford the desired products **7a**–**7c**.

4-({4-Chloro-6-[(naphthalen-2-yl)oxy]-1,3,5-triazin-2-yl}amino)-3-fluorobenzonitrile (**7a**). Yield: 2.23 g (50%). Off-white solid. M.p. 152° (dec.). ^{1}H-NMR ($CDCl_3$): 7.42–8.08 (*m*, 10 arom. H); 10.87 (*s*, 1 H, NH). ^{13}C-NMR ($CDCl_3$): 108.1 (CN); 117.4; 118.3; 119.6; 120.1; 121.0; 121.2; 125.9; 126.1; 126.3; 127.0; 127.7; 128.1; 129.8; 129.9; 134.0; 147.0 (Ar); 165.7; 170.6; 170.8 (triazine). EI-MS: 391 (M^+).

4-({4-[(1-Bromonaphthalen-2-yl)oxy]-6-chloro-1,3,5-triazin-2-yl}amino)-3-fluorobenzonitrile (**7b**). Yield: 2.60 g (49%) Off-white solid. M.p. 170° (dec.). ^{1}H-NMR ($CDCl_3$): 7.52–8.27 (*m*, 9 arom. H); 10.84 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 104.4 (CN); 114.1; 117.2; 119.3; 119.9; 121.8; 122.7; 123.9; 125.7; 126.0; 127.2; 128.1; 129.8; 131.5; 132.1; 147.0 (Ar); 165.9; 169.9; 170.8 (triazine). EI-MS: 471 (M^+).

4-({4-Chloro-6-[(1-chloronaphthalen-2-yl)oxy]-1,3,5-triazin-2-yl}amino)-3-fluorobenzonitrile (**7c**). Yield: 2.40 g (50%). Off-white solid. M.p. 213.8° (dec.). ^{1}H-NMR ($CDCl_3$): 7.52–8.27 (*m*, 9 arom. H); 10.98 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 104.7, 114.5, 117.1, 120.0, 121.2, 121.7, 122.3, 124.6, 126.9, 128.4, 128.7, 129.2, 129.8, 130.1, 131.8, 139.3, 145.1 (Ar); 165.6, 169.0, 170.5 (triazine). EI-MS: 425 (M^+).

General Procedure for the Preparation of Compounds **8a**–**8n**. Amine R^2NH_2 (5.48 mmol) was added to a soln. of **7a**–**7c** (1.37 mmol) in 1,4-dioxane (150 ml) at r.t. under stirring. The resulting soln. was stirred at 60–70° for 1–4 h, and then precipitation took place. The solid was collected by filtration, dissolved in AcOEt (20 ml), washed with 4% NaOH (1 × 10 ml), sat. aq. $NaHCO_3$ soln (3 × 20 ml), and brine (3 × 20 ml), and dried ($MgSO_4$), and the org. layer was concentrated *in vacuo* at 80° to give crude products, which were recrystallized from MeCN to afford **8a**–**8n**.

3-Fluoro-4-({4-(methylamino)-6-[(naphthalen-2-yl)oxy]-1,3,5-triazin-2-yl}amino)benzonitrile (**8a**). Yield: 0.26 g (50%). Off-white solid. M.p. 245.3°(dec.). ^{1}H-NMR ($CDCl_3$): 2.76 (*dd*, *J* = 4.0, Me); 7.31–8.14 (*m*, 10 arom. H); 9.45 (*s*, MeN*H*); 9.65 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 27.3 (Me); 105.4 (CN); 118.3, 119.0, 122.2, 124.6, 125.5, 126.2, 127.2, 128.4, 128.6, 129.3, 130.5, 132.0, 133.4, 149.7 (Ar); 165.3, 167.0, 170.8 (triazine). EI-MS: 386 (M^+).

4-({4-Amino-6-[(naphthalen-2-yl)oxy]-1,3,5-triazin-2-yl}amino)-3-fluorobenzonitrile (**8b**). Yield: 0.25 g (50%). Off-white solid. M.p. 270° (dec.). ^{1}H-NMR ($CDCl_3$): 7.17–8.14 (*m*, 10 arom.H); 9.55 (*s*, NH); ^{13}C-NMR ($CDCl_3$): 105.7 (CN); 118.3, 119.4, 122.2, 125.1, 125.5, 126.5, 127.4, 127.6, 128.5, 128.6, 129.2, 130.8, 133.5, 149.8, 151.8, 154.3 (Ar); 166.9, 168.3, 171.1 (triazine). EI-MS: 372 (M^+).

4-({4-(Ethylamino)-6-[(naphthalen-2-yl)oxy]-1,3,5-triazin-2-yl}amino)-3-fluorobenzonitrile (**8c**). Yield: 0.27 g (51%). Off-white solid. M.p. 195.9°(dec.). ^{1}H-NMR ($CDCl_3$): 1.02–1.08 (*m*, Me); 3.16–3.38 (*m*, CH_2); 7.33–8.10 (*m*, 10 arom. H); 9.44 (*s*, EtN*H*); 9.60 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 105.4 (CN); 117.7, 118.2, 119.2, 122.2, 124.7, 125.5, 126.2, 127.2, 127.7, 128.5, 129.2, 131.0, 132.0, 133.7, 149.8, 151.8 (Ar); 165.3, 166.6, 170.6 (triazine). EI-MS: 400 (M^+).

3-Fluoro-4-({4-[(naphthalen-2-yl)oxy]-6-[(prop-2-en-1-yl)amino]-1,3,5-triazin-2-yl}amino)benzonitrile (**8d**). Yield: 0.28 g (51%). Off-white solid. M.p. 174.8° (dec.). ^{1}H-NMR ($CDCl_3$): 3.79–3.87 (*m*, $CH_2CH{=}CH_2$); 5.01–5.15 (*m*, $CH_2CH{=}CH_2$); 5.77–5.82 (*m*, $CH_2CH{=}CH_2$); 7.31–8.12 (*m*, 10 arom. H); 9.58 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 15.1 ($CH_2CH{=}CH_2$); 42.5 ($CH_2CH{=}CH_2$); 64.8 ($CH_2CH{=}CH_2$); 105.5 (CN); 115.4, 118.3, 119.2, 122.1, 124.8, 125.2, 125.5, 126.4, 126.8, 127.3, 128.4, 129.0, 131.1, 131.9, 133.6, 135.1, 149.7, 151.5, 154.2 (Ar); 165.2, 167.0, 170.6 (triazine). EI-MS: 412 (M^+).

4-({4-[(1-Bromonaphthalen-2-yl)oxy]-6-(methylamino)-1,3,5-triazin-2-yl}amino)-3-fluorobenzonitrile (**8e**). Yield: 0.31 g (48%). Off-white solid. M.p. 220.4° (dec.). ^{1}H-NMR ($CDCl_3$): 2.50 (*s*, Me); 7.64–8.26 (*m*, 9 arom. H); 8.53 (*s*, MeN*H*); 9.70 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 27.2 (Me); 105.7 (CN); 114.4, 117.5, 123.1, 124.5, 125.0, 125.4, 128.2, 129.1, 131.9, 147.6 (Ar); 165.5, 167.1, 169.1 (triazine). EI-MS: 464 (M^+).

4-({4-Amino-6-[(1-bromonaphthalen-2-yl)oxy]-1,3,5-triazin-2-yl}amino)-3-fluorobenzonitrile (**8f**). Yield: 0.31 g (50%). Off-white solid. M.p. 222.0° (dec.). ^{1}H-NMR ($CDCl_3$): 6.52 (*s*, NH_2); 7.31–8.23 (*m*, 9 arom. H); 10.07 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 103.6 (CN); 114.9, 119.8, 120.1, 123.1, 123.7, 126.5,

127.1, 128.6, 128.9, 129.5, 130.1, 132.6, 133.5, 148.1, 148.4 (Ar); 165.5, 168.8, 171.0 (triazine). EI-MS: 450 (M^+).

4-({4-[(1-Bromonaphthalen-2-yl)oxy]-6-(ethylamino)-1,3,5-triazin-2-yl}amino)-3-fluorobenzonitrile (**8g**). Yield: 0.30 g (46%). Off-white solid. M.p. 264.7° (dec.). ^{1}H-NMR ($CDCl_3$): 1.00 (*dd*, *J* = 7.6, Me); 3.12–3.42 (*m*, CH_2); 7.23–8.24 (*m*, 9 arom. H); 9.65 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 14.4 (Me); 35.2 (CH_2); 105.6 (CN); 113.8, 114.1, 117.6, 119.3, 123.4, 125.0, 126.0, 126.5, 127.9, 128.3, 128.4, 129.1, 147.8, 151.6, 154.0 (Ar); 165.3, 166.5, 169.8 (triazine). EI-MS: 478 (M^+).

4-({4-[(1-Bromonaphthalen-2-yl)oxy]-6-[(prop-2-en-1-yl)amino]-1,3,5-triazin-2-yl}amino)-3-fluorobenzonitrile (**8h**). Yield: 0.30 g (45%). Off-white solid. M.p. 198.4° (dec.). ^{1}H-NMR ($CDCl_3$): 3.89 (*d*, *J* = 4.6, $CH_2CH{=}CH_2$); 5.02–5.21 (*m*, $CH_2CH{=}CH_2$); 5.84–5.91 (*m*, $CH_2CH{=}CH_2$); 7.34–8.25 (*m*, 9 arom. H); 10.00 (*s*, 1 H, $NHCH_2CH{=}CH_2$); 10.14 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 43.2 ($CH_2CH{=}CH_2$); 72.4 ($CH_2CH{=}CH_2$); 88.5 ($CH_2CH{=}CH_2$); 104.0 (CN); 114.9, 116.0, 116.6, 119.7, 119.9, 120.2, 123.6, 126.1, 127.0, 128.4, 128.6, 129.2, 129.8, 132.6, 133.1, 135.4, 144.4 (Ar); 165.7, 167.4, 170.5 (triazine). EI-MS: 490 (M^+).

4-({4-[(1-Bromonaphthalen-2-yl)oxy]-6-[(1-methylethyl)amino]-1,3,5-triazin-2-yl}amino)-3-fluorobenzonitrile (**8i**). Yield: 0.31 g (46%). Off-white solid. M.p. 232.8° (dec.). ^{1}H-NMR ($CDCl_3$): 1.12 (*dd*, *J* = 6.8, Me_2CH); 3.95–4.04 (*m*, Me_2CH); 7.44–8.11 (*m*, 9 arom. H); 9.95 (*s*, $CHMe_2NH$); 10.17 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 22.0 (Me); 42.5 (CH); 103.8 (CN); 114.8, 119.9, 120.5, 123.5, 126.9, 128.7, 128.9, 129.5, 132.4, 133.1, 133.5, 144.5, 148.6 (Ar); 165.8, 166.4, 170.2 (triazine). EI-MS: 492 (M^+).

4-({4-[(1-Chloronaphthalen-2-yl)oxy]-6-(methylamino)-1,3,5-triazin-2-yl}amino)-3-fluorobenzonitrile (**8j**). Yield: 0.29 g (49%). Off-white solid. M.p. 265.8° (dec.). ^{1}H-NMR ($CDCl_3$): 2.82 (*dd*, *J* = 4.4, Me); 7.49–8.26 (*m*, 9 arom. H); 9.97 (*s*, $MeNH$); 10.20 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 27.5 (Me); 103.8 (CN); 120.0, 122.3, 123.4, 123.8, 127.1, 128.7, 128.9, 131.1, 132.3, 132.9, 133.1, 144.5, 146.6 (Ar); 166.7, 167.8, 170.1 (triazine). EI-MS: 420 (M^+).

4-({4-Amino-6-[(1-chloronaphthalen-2-yl)oxy]-1,3,5-triazin-2-yl}amino)-3-fluorobenzonitrile (**8k**). Yield: 0.27 g (49%). Off-white solid. M.p. 186° (dec.). ^{1}H-NMR ($CDCl_3$): 1.64 (*s*, NH_2), 7.23–8.25 (*m*, 9 arom. H); 9.60 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 105.8 (CN); 117.9, 119.1, 119.4, 121.8, 122.5, 123.3, 125.2, 126.5, 128.0, 128.4, 130.5, 131.5, 145.1, 151.9, 154.4 (Ar); 166.7, 168.2, 170.3 (triazine). EI-MS: 406 (M^+).

4-({4-[(1-Chloronaphthalen-2-yl)oxy]-6-(ethylamino)-1,3,5-triazin-2-yl}amino)-3-fluorobenzonitrile (**8l**). Yield: 0.30 g (51%). Off-white solid. M.p. 231.8° (dec.). ^{1}H-NMR ($CDCl_3$): 1.01 (*t*, *J* = 6.4, Me); 3.12–3.40 (*m*, CH_2); 3.44 (*s*, $NHCH_2$); 7.29–8.28 (*m*, 9 arom. H); 9.63 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 14.3 (Me); 38.8 (CH_2); 105.5 (CN); 117.7, 119.5, 121.4, 121.8, 123.0, 123.3, 124.5, 125.4, 126.6, 127.9, 128.4, 130.5, 131.8, 146.1, 151.8, 154.3 (Ar); 165.5, 166.4, 169.9 (triazine). EI-MS: 434 (M^+).

4-({4-[(1-Chloronaphthalen-2-yl)oxy]-6-[(prop-2-en-1-yl)amino]-1,3,5-triazin-2-yl}amino)-3-fluorobenzonitrile (**8m**). Yield: 0.29 g (48%). Off-white solid. M.p. 240.9° (dec.). ^{1}H-NMR ($CDCl_3$): 3.75 (*d*, *J* = 4.4, $CH_2CH{=}CH_2$); 4.94–5.13 (*m*, $CH_2CH{=}CH_2$); 5.74–5.85 (*m*, $CH_2CH{=}CH_2$); 7.26–8.25 (*m*, 9 arom. H); 9.58 (*s*, NH); 9.74 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 42.8 (CH_2); 61.4 (CH_2); 88.3 (CH); 105.7 (CN); 115.6, 117.9, 119.4, 121.8, 122.6, 123.3, 125.5, 126.5, 128.0, 128.4, 130.6, 131.8, 134.8, 146.1, 151.7, 154.2 (Ar); 166.5, 166.9, 170.2 (triazine). EI-MS: 446 (M^+).

4-({4-[(1-Chloronaphthalen-2-yl)oxy]-6-(propylamino)-1,3,5-triazin-2-yl}amino)-3-fluorobenzonitrile (**8n**). Yield: 0.30 g (49%). Off-white solid. M.p. 202.4° (dec.). ^{1}H-NMR ($CDCl_3$): 0.88 (*t*, *J* = 7.6, $MeCH_2CH_2$); 1.44–1.58 (*m*, $MeCH_2CH_2$); 3.10–3.33 (*m*, $MeCH_2CH_2$); 7.44–8.26 (*m*, 9 arom. H); 9.95 (*s*, $NHCH_3CH_2CH_2$); 10.14 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 11.3 ($MeCH_2CH_2$); 21.7 ($MeCH_2CH_2$); 42.3 ($MeCH_2CH_2$); 103.6 (CN); 119.2, 119.5, 121.9, 123.0, 123.0, 123.4, 126.5, 128.0, 128.2, 128.4, 130.7, 132.1, 132.7, 144.4, 146.6 (Ar); 165.5, 167.2, 169.9 (triazine). EI-MS: 448 (M^+).

Preparation of 4-{[4-Chloro-6-(4-methylphenoxy)-1,3,5-triazin-2-yl]amino}-3-fluorobenzonitrile (**9**). To a stirred soln. of *p*-cresol (4-methylphenol; 1.22 g, 11.3 mmol) in anh. THF (100 ml) was added **6** (3.03 g, 11.3 mmol) at r.t. under N_2, and stirring was continued for another 4 h at 50–60°. The precipitate was collected by filtration, washed with H_2O (3 × 20 ml), and recrystallized from MeOH to afford **9**. Yield: 2.0 g (50%). Off-white solid. M.p. 179.6° (dec.). ^{1}H-NMR ($CDCl_3$): 2.27 (*s*, Me); 7.48–7.99 (*m*, 7 arom. H); 9.96 (*s*, NH_2); 10.01 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 24.6 (Me); 105.6 (CN); 109.3, 116.3, 117.5, 118.1, 119.3, 119.6, 120.2, 123.9, 127.7, 128.8, 151.9 (Ar); 155.6, 164.8, 169.6 (triazine). EI-MS: 354 (M^+).

General Procedure for the Preparation of **10a**–**10e**. Amine (5.48 mmol) was added to a soln. of **9** (1.37 mmol) in 1,4-dioxane (150 ml) at r.t. under stirring. The resulting soln. was stirred at 60–70° for 1–4 h, then precipitation took place. The solid was collected by filtration, dissolved in AcOEt (20 ml), washed with 4% NaOH soln. (1 × 10 ml), sat. aq. $NaHCO_3$ soln (3 × 20 ml), and brine (3 × 20 ml), dried ($MgSO_4$), and the org. layer was concentrated *in vacuo* at 80° to give crude products, which were recrystallized from MeCN to afford **10a**–**10e**.

3-Fluoro-4-{[4-(methylamino)-6-(4-methylphenoxy)-1,3,5-triazin-2-yl]amino}benzonitrile (**10a**). Yield: 0.24 g (51%). Off-white solid. M.p. 209.2° (dec.). ^{1}H-NMR ($CDCl_3$): 2.24 (*s*, Me); 2.81 (*s*, *Me*NH); 6.94–7.22 (*m*, 3 arom. H); 7.51–7.89 (*m*, 4 arom. H); 8.42 (*s*, MeN*H*); 9.06 (*s*, NH); 9.23 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 20.8 (Me); 27.8 (MeNH); 105.2 (CN); 118.9, 119.4, 119.6, 120.5, 120.7, 124.5, 129.2, 129.3, 131.1, 133.5, 137.9 (Ar); 164.2, 164.5, 166.5 (triazine). EI-MS: 350 (M^+).

4-{[4-Amino-6-(4-methylphenoxy)-1,3,5-triazin-2-yl]amino}-3-fluorobenzonitrile (**10b**). Yield: 0.23 g (50%). Off-white solid. M.p. 247.7° (dec.). ^{1}H-NMR ($CDCl_3$): 2.27 (*s*, Me); 3.38 (*s*, NH_2); 6.78 (*s*, 1 arom. H); 7.04–7.11 (*m*, 2 arom. H); 7.64–7.72 (*m*, 3 arom. H); 7.84 (*s*, 1 H, Ph). ^{13}C-NMR ($CDCl_3$): 20.8 (Me); 105.0 (CN); 118.7, 119.3, 119.5, 120.5, 129.2, 129.8, 129.8, 131.2, 131.5, 133.2 (Ar); 164.8, 167.3 (triazine). EI-MS: 336 (M^+).

4-{[4-(Ethylamino)-6-(4-methylphenoxy)-1,3,5-triazin-2-yl]amino}-3-fluorobenzonitrile (**10c**). Yield: 0.24 g (51%). Off-white solid. M.p. >300°. ^{1}H-NMR ($CDCl_3$): 1.24 (*t*, J = 4.8, Me); 1.57 (*s*, Me); 2.31–2.37 (*m*, CH_2); 7.08–7.23 (*m*, 3 arom. H); 7.31–7.57 (*m*, 4 arom. H); 6.90 (*s*, EtN*H*); 8.74 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 20.7 (Me); 35.4 (Me); 48.3 (CH_2); 105.9 (CN); 119.4, 119.7, 121.0, 125.1, 125.7, 129.5, 129.8, 131.6, 132.6, 136.3, 137.6 (Ar); 164.6, 170.2, 176.8 (triazine). EI-MS: 364 (M^+).

3-Fluoro-4-{[4-(4-methylphenoxy)-6-(propylamino)-1,3,5-triazin-2-yl]amino}benzonitrile (**10d**). Yield: 0.26 g (51%). Off-white solid. M.p. >300°. ^{1}H- NMR ($CDCl_3$): 0.99 (*t*, J = 7.6, Me); 1.63 (*s*, *Me*CH_2CH_2); 2.35–2.36 (*m*, Me*CH_2*CH_2); 5.09–5.23 (*m*, $MeCH_2$*CH_2*); 7.07–7.56 (*m*, 7 arom. H); 8.76 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 11.5 (*Me*CH_2CH_3); 20.5 (Me*CH_2*CH_2); 36.4 ($MeCH_2$*CH_2*); 104.5 (CN); 118.3, 119.4, 121.1, 124.4, 129.0, 129.3, 130.9, 133.7, 134.2, 134.5, 130.9, 137.8 (Ar); 163.3, 164.9, 166.3 (triazine). EI-MS: 378 (M^+).

3-Fluoro-4-{[4-(4-methylphenoxy)-6-[(1-methylethyl)amino]-1,3,5-triazin-2-yl]amino}benzonitrile (**10e**). Yield: 0.26 g (50%). Off-white solid. M.p. >300°. ^{1}H-NMR ($CDCl_3$): 1.25 (*s*, Me); 1.58 (*d*, J = 4.0, 6 H, CH*Me_2*CH); 2.34–2.37 (*m*, Me_2*C*H); 7.16–7.43 (*m*, 7 arom. H); 6.90 (*s*, NH); 8.74 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 20.3 (Me); 31.9 (*Me_2*CH); 42.4 (Me_2*C*H); 105.6 (CN); 118.4, 119.4, 121.0, 121.9, 125.1, 126.3, 129.1, 129.8, 132.0, 133.5, 135.4, 137.3 (Ar); 164.3, 165.5, 167.4 (triazine). EI-MS: 378 (M^+).

Bioassay. The anti-HIV activity and cytotoxicity were evaluated against wild-type HIV-1 strain IIIB in MT-4 cells by the MTT method. Briefly, virus stocks were titrated in MT-4 cells and expressed as the 50% cell culture infective dose ($CCID_{50}$). MT-4 Cells were suspended in culture medium (RPMI 1640 medium supplemented with 10% newborn calf serum, 2 mM L-glutamine, and 0.075% $NaHCO_3$) at 1 × 10^5 cells/ml and infected with HIV at a multiplicity of infection of 0.02. Immediately after virus infection, 100 µl of the cell suspension was brought into each well of a flat-bottomed microtiter tray containing various concentrations of the test compounds. The test compounds were dissolved in DMSO at 50 mM or higher. After incubation for 4 d at 37°, the number of viable cells was determined by the MTT method. Compounds were tested in parallel for cytotoxic effects in uninfected MT-4 cells.

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