Physicochemical Property-Driven Optimization of Diarylaniline Compounds as Potent HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitors

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Abstract

Using physicochemical property-driven optimization, twelve new diarylaniline compounds (DAANs) (**7a–h**, **11a–b** and **12a–b**) were designed and synthesized. Among them, compounds **12a–b** not only showed high potency (EC_{50} 0.96–4.92 nM) against both wild-type and drug-resistant viral strains with the lowest fold change (FC 0.91 and 5.13), but also displayed acceptable drug-like properties based on aqueous solubility and lipophilicity (LE > 0.3, LLE > 5, LELP < 10). The correlations between potency and physicochemical properties of these DAAN analogues are also described. Compounds **12a–b** merit further development as potent clinical trial candidates against AIDS.

Keywords

anti-HIV agents; diarylaniline; NNRTIs; physicochemical property

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) with diverse structures are a key component of antiretroviral therapy (ART) for HIV infection and AIDS, because they exhibit high efficacy and low toxicity, as well as synergistic activity in combination with

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other anti-HIV drugs.[1,2] Two new-generation NNRTIs, etravirine (TMC125, **1a**) and rilpivirine (TMC278, **1b**) (Fig. 1), which were recently approved by the FDA for anti-AIDS therapy, have much better potency and pharmacological profiles than early NNRTIs, such as nevriapine, delavirdine, and efavirenz, and can efficiently inhibit a broad spectrum of drug-resistant viral strains.[3] However, clinical trials revealed novel resistance mutations[4] conferred against drugs **1a** and **1b**, which are both diarylpyrimidine (DAPY) compounds, similar to the early NNRTIs. However, these newly produced resistance mutations differ from those affecting the early NNRTIs and from each other, suggesting that a subtle structural difference between the drugs was sufficient to cause the occurrence of distinct HIV mutations. This discovery underscores the necessity for developing new NNRTI drugs with diverse scaffolds in order to provide more choices for AIDS treatment and overcome new resistance mutants. Accordingly, a number of new-generation NNRTI agents with diverse structures have been discovered[5] and are currently undergoing preclinical and clinical trials.

In our prior studies, several diarylanilines (DAANs) were identified as novel class of HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI) agents with low nanomolar anti-HIV potency against wild-type and mutated viral strains[6,7], both comparable to and better than new-generation NNRTI drugs **1a** and **1b**. These DAANs are shown in Figure 1 as leads **2a** and **2b**. However, their poor aqueous solubility (< 1 µg/mL) resulted in very low absorption *in vivo*. To improve molecular aqueous solubility, several polar groups[8,9], including carboxyl, ester, amide, hydroxyl, and CF_3, were introduced at the R^1 group on the central phenyl ring, a point known to be modifiable for anti-HIV potency, while also associated with molecular physicochemical properties. These efforts led to the discovery of hydroxymethyl-DAAN **2c** (Fig. 1) with high potency against wild-type and multi drug-resistant viral strains (EC_{50} 0.53 nM and 0.4 nM, respectively) and improved aqueous solubility of 3.23 µg/mL at pH 7.4 and 20.9 µg/mL at pH 2.0. Unfortunately, **2c** displayed low oral bioavailability (F% 6.10) in pharmacokinetics assays *in vivo*. Herein, we have again modified the DAAN compounds to identify potential drug candidates with balanced potency and a desirable absorption, distribution, metabolism, and excretion (ADME) profile.

To explore the correlations between potency and physicochemical properties associated with ADME profile, we continued to focus on the R^1 substituent on the central phenyl ring. In our newly designed series of DAAN analogues (**7a–h, 11a–b, 12a–b**), R^1 was altered to alkylamines or alkoxyethers with different shapes, lengths or volumes. After anti-HIV evaluations, the new active DAAN compounds were further assessed for multiple physicochemical properties, including aqueous solubility and lipophilicity, as estimated by log P. Apart from aqueous solubility, lipophilicity is another major physicochemical property that contributes to potency, affects compound solubility, determines the passive permeability of small molecules through biological membranes, impacts drug metabolism and pharmacokinetics, and influences adverse effects and compound-related toxicity. Most recently, new lipophicilic parameters, *i.e.*, lipophilic efficiency (LE), lipophilic ligand efficiency (LLE),[10] and ligand-efficiency-dependent lipophilicity (LELP),[11] have been proposed and applied in many medicinal chemistry programs[12,13,14] to efficiently guide lead optimization. Herein, the synthesis, anti-HIV potency, and assessments of multiple

physicochemical properties of three series of new DAAN compounds (**7a–h, 11a–b, 12a–b**) are reported. The results will be helpful in guiding our further lead optimization aimed at the discovery of new clinical trial candidates as potent anti-AIDS drugs.

As shown in Scheme 1, target DAAN compounds **7a–h** were prepared through a short synthetic route, starting from commercially available 4-hydroxy-3,5-dimethylbenzonitrile (**3**). The previously synthesized intermediate 5-chloro-N^1-(4-cyanophenyl)-4-methoxycarbonyl-2-nitroaniline (**4**)[8] was coupled with **3** in the presence of potassium carbonate in DMF under 120 °C for 6 h to afford 2,4-diarylnitrobenzene **5**. By using lithium borohydride (LiBH$_4$), the ester group on the central phenyl ring in **5** was reduced to a hydroxymethyl group in the key intermediate **6a**. Subsequently, **6a** was treated with 2,4,6-trichloro-[1,3,5]triazine followed by nucleophilic substitution with methylamine, cyclopropanamine, 3-aminopropan-1-ol, or 1-methyl-piperazine to produce the corresponding compounds **6b–e**, respectively, with different alkylamines at the R^1 position. Alternatively, **6a** was reacted with isopropanol or methanol in the presence of bismuth chloride (BiCl$_3$) to afford the corresponding alkoxymethyl-DAAN compounds **6f** and **6g**. Furthermore, the hydroxyl group in **6a** was esterified with acetic anhydride to yield compound **6h**. Finally, the nitro group on the central ring of **6a–h** was reduced via catalytic hydrogenation in the presence of Pd-C (10%) in either EtOAc or anhydrous ethanol to furnish new DAAN compounds **7a–h**. The structures of these new DAAN compounds were identified from proton NMR and MS spectra.[15]

Newly synthesized DAAN compounds **7a–h** were initially evaluated against wild-type HIV-1 (IIIB) replication in MT-2 cells in parallel with drug **1b**. The data are presented in Table 1. As expected, most new DAANs, except **7e** with a bulky *N*-methylpiperazinyl group at the R^1 position (EC$_{50}$ 170 nM), exhibited low nanomolar potency with EC$_{50}$ values ranging from 1.06 to 14 nM and high selective index (SI) values of 1,142 to 114,019. The new **7**-series compounds were also evaluated against K103N/Y181C mutant-derived, NNRTI-resistant viral strain A17. However, their potencies against the wild-type viral strain were clearly reduced, as demonstrated by EC$_{50}$ values of greater than 33 to 2,000 nM.

Based on previous SAR results,[9] we then designed and synthesized two pairs of compounds **11a–b** and **12a–b** with a *para*-cyanovinyl and *para*-cyanoethyl (R^2) group, respectively, on the phenoxy ring (C-ring), as shown in Scheme 2. Similarly to the preparation of **7g** and **7h**, methoxymethyl-DAAN **9** and acetoxymethyl-DAAN **10** were synthesized from N^1-(4-cyanophenyl)-5-(4′-cyanovinyl-2′,6′-dimethylphenoxy)-4-hydroxymethyl-2-nitroaniline (**8**).[9] Subsequently, the nitro group in **9** and **10** was reduced with iron powder in the presence of NH$_4$Cl to afford corresponding *para*-cyanovinyl-DAAN compounds **11a** and **11b**,[15] respectively, while the nitro group (R^1) and the conjugated double bond in the cyanovinyl group (R^2) of **9** and **10** were reduced simultaneously using catalytic hydrogenation with Pd/C to produce *para*-cyanoethyl-DAAN compounds **12a** and **12b**.[15] The two pairs of compounds, **11a–b** and **12a–b**, exhibited high potency against wild-type HIV-1 replication with sub- to low nanomolar EC$_{50}$ values ranging from 0.83 to 5.74 nM, and were as or more potent than **7g** and **7h**, regardless of whether R^2 was *p*-cyanovinyl or *p*-cyanoethyl. More importantly, compounds **12a–b** showed high potency against resistant

viral strain A17. Specifically, cyanoethyl-DAAN **12a** (EC_{50} 2.95 nM) was more potent than cyanovinyl-DAAN **11a** (14.7 nM), while both were more potent than cyano-DAAN compound **7g** (298 nM). Similar differences in potency were observed when comparing acetoxymethyl-DAAN compounds **12b** (4.92 nM), **11b** (36.5 nM), and **7h** (374 nM). These results clearly demonstrate that the R^2 group on the phenoxy ring (C-ring) directly affects molecular potency against wild-type, as well as resistant, viral strains. A cyanoethyl group, which is more flexible due to its linearity, was more favorable than a cyanovinyl or cyano group. Notably, highly potent **12a** and **12b** had low fold change (FC) between A17 and wild-type IIIB virus with FC values of 0.91 and 5.13, respectively, much lower than that of **1b** (FC 18.4) in the same assay.

Next, several physicochemical properties of newly generated DAANs ($EC_{50} < 11$ nM) (**7a–d**, **7g–h**, **11a–b**, **12a–b**) and drug **1b** were assessed, and the resulting data are summarized in Table 2. Aqueous solubility was measured by HPLC at pH 2.0 and 7.4 to reflect the physiological conditions encountered by these compounds in stomach and plasma, respectively. As expected, alkylamine-DAAN compounds **7b**, **7c,** and **7d** displayed greatly improved solubility at both pH 2.0 (263, 285, and 290 μg/mL, respectively) and pH 7.4 (159, 13, and 236 μg/mL, respectively) compared with drug **1b** (pH 2.0, 74 μg/mL; pH 7.4, 0.29 μg/mL). Thus, the introduction of suitable alkylamino groups at the R^1 position could greatly improve the molecular aqueous solubility. Active compounds hydroxymethyl-DAAN **7a** ($R^1 = CH_2OH$), methoxymethyl-DAANs **7g**, **11a**, and **12a** ($R^1 = CH_2OMe$), and acetoxymethyl-DAANs **7h**, **11b**, and **12b** ($R^1 = CH_2OAc$) also demonstrated improved aqueous solubility at pH 2.0 (1.7–9.10 μg/mL), but not at pH 7.4 (< 1 μg/mL). For oral drug candidates, better aqueous solubility at pH 2.0 is desirable to enhance absorbability in the stomach.[18] Meanwhile, we observed that all 10 new active compounds had lower melting points than **1b**. This difference might be explained by the assumption that the R^1 group on the central phenyl ring might disrupt molecular planarity and crystal packing,[19] which could also enhance molecular aqueous solubility. To estimate molecular lipophilicity, the log P parameters of these active compounds were measured by HPLC at pH 7.4.[9] The experimental log P values fell within an acceptable range of 1.80–4.40, which is consistent with the measured aqueous solubilities, and showed the same trend as the clog D values predicted by ACD software. Additionally, topological polar surface area (*t*PSA) parameters of all active compounds were calculated by ChemDraw Ultra 12.0 and met the criterion[20] of < 140 $Å^2$ for potential oral drug candidates.

To estimate the possible ADME profiles and potential of our drug candidates, we focused next on their lipophilic indices, including lipophilic efficiency (LE), lipophilic ligand efficiency (LLE), and ligand-efficiency-dependent lipophilicity (LELP). Defined as the difference between the negative logarithm of the measured potency (pEC_{50}) and log P, LLE quantifies the contribution of lipophilicity to potency, whereas LELP[17] correlates with ADME properties. Thus, compounds with a low LELP value would most likely have a high chance of passing all ADME and safety criteria,[21] while compounds with high LELP values (typically > 10) would have a higher propensity to fail because of ADME and safety risks. Accordingly, lipophilic parameters of the new active DAANs were calculated from their experimental EC_{50} and log P values by the formulas cited at the bottom of Table 2.

Consequently, compounds **7a**, **7b**, **7d**, **12a**, and **12b** met acceptable levels for all three ligand lipophilic-efficiency indices (LE > 0.3, LLE > 5, LELP < 10),[21] while the remaining compounds in Table 2 did not, having either LLE values lower than 5 or LELP values higher than 10. Among the five promising compounds, **7b** and **7d** showed higher aqueous solubility at different pH conditions as well as lower log P and LELP values than the other compounds, suggesting better ADME profiles. On the other hand, the **7** series of DAANs were not efficient against resistant viral strain A17. Compounds **12a** and **12b** did show more balanced potency between the HIV-1 wild-type and resistant viral strains, as well as met acceptable lipophilic criteria, as determined by the LE, LLE and LELP indices. However, the aqueous solubility of both compounds was obviously lower than that of either **7b** or **7d**. Thus, to avoid the risk of potential oral absorption, these results suggested that the **12a–b** pair requires additional optimization to improve aqueous solubility.

In summary, three series of new DAAN compounds (**7a–h**, **11a–b**, and **12a–b**) with interchangeable R^1 and R^2 modification/optimization were successfully synthesized as part of our ongoing anti-HIV NNRTI program. Our current physicochemical property-driven optimization resulted in the discovery of two promising compounds, **12a** and **12b**, with high potency against wild-type and drug-resistant viral strains, low nanomolar EC_{50} values (0.96–4.92 nM), low fold change resistance (FC 0.91 and 5.13), and acceptable lipophilicity, as demonstrated by meeting acceptable values for all lipophilic parameters (LE > 0.3, LLE > 5, LELP < 10; log P < 5, tPSA < 140 Å^2)[21], even though their aqueous solubility needs further improvement. Optimization of the series **7** compounds revealed that (1) the presence of an alkylamine substituent at the R^1 position can greatly improve molecular aqueous solubility (see **7b–d**) without loss of antiviral potency, (2) a bulky R^1 group can result in substantially impaired antiviral activity (see **7e**), and (3) introducing an H-bond acceptor or donor at the R^1 position (such as **7a–b**, **7d–g**) might regulate the molecular lipophilicity to meet desired drug criteria. Our optimization efforts at the R^2 position on the phenoxy ring (C-ring) indicated that a more flexible and longer linear cyanovinyl (**11** series) or, preferably, cyanoethyl (**12** series) substituent, rather than a cyano group (**7** series) is crucial for high potency against both wild-type and double-mutant drug-resistant viral strains (compare **7g–h**, **11a–b**, and **12a–b**). Consequently, a number of compounds from this series are being considered for *in vivo* pharmacokinetic evaluation, and the results will be reported later.

Acknowledgments

References and Notes

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15. Synthetic procedure for 4-substituted 1,5-diarylbenzene-1,2-diamines (**7a–h** and **12a–b**). A solution of diarylnitrobenzene in 20 mL of anhydrous EtOAc (for **7a–c**, **7e–f**) or anhydrous EtOH (for **7d**, **7g–h**, **12a–b**) in the presence of excess Pd/C (5%) was shaken with hydrogen gas under 50–55 p.s.i. until the hydrogen was no longer absorbed (ca. 4 h). The catalyst was filtered from the solution and washed with EtOAc several times. After the solvent was removed under reduced pressure, the residue was purified by flash column chromatography (gradual elution: MeOH/CH$_2$Cl$_2$, 0–5%) with the Combiflash® flash chromatography system (Teledyne ISCO Company, Inc., Lincoln, NE) to obtain pure target compounds **7a–h** and **12a–b**. Otherwise, *para*-cyanovinyl-compounds **11a** and **11b** were obtained from **9** and **10** by reaction with excess iron powder in the presence of NH$_4$Cl at reflux temperature in a mixed solvent of THF/water/MeOH (v/v/v 1:1:1) for 4 h. **7a**: yield 73%, white solid, mp 230.0–232 °C; ^{1}H NMR (CDCl$_3$) δ ppm 2.14 (6H, s, 2 × CH$_3$),4.88 (2H, s, CH$_2$), 5.51 (1H, s, NH) 5.99 (1H, s, ArH-6), 6.54 (2H, d, J = 8.4 Hz, ArH-2′,6′), 6.97 (1H, s, ArH-3), 7.40 (2H, s, ArH-3″,5″), 7.41 (2H, d, J = 8.4 Hz, ArH-3′,5′); MS *m/z* (%) 385.2 (M + 1, 100). **7b**: white solid, mp 201–203 °C; ^{1}H NMR (CDCl$_3$) δ ppm 2.13 (6H, s, 2 × CH$_3$), 2.56 (3H, s, NCH$_3$), 3.58 (2H, s, NH$_2$), 3.95 (2H, s, ArCH$_2$), 5.51 (1H, s, NH), 5.96 (1H, s, ArH-6), 6.53 (2H, d, J = 8.4 Hz, ArH-2′,6′), 6.93 (1H, s, ArH-3), 7.38 (2H, s, ArH-3″,5″), 7.39 (2H, d, J = 8.4 Hz, ArH-3′,5′); MS *m/z* (%) 398.1 (M + 1, 1), 358 (M − 30, 100). **7c**: yield 83%, white solid, mp 72.0–73.3 °C; ^{1}H NMR (CDCl$_3$) δ ppm 0.49 (4H, m, CH$_2$CH$_2$), 2.14 (6H, s, 2 × CH$_3$), 2.24 (3H, m, CH), 3.53 (2H, s, NH$_2$), 4.00 (2H, s, ArCH$_2$), 5.48 (1H, s, NH), 5.96 (1H, s, ArH-6), 6.53 (2H, d, J = 8.8 Hz, ArH-2′,6′), 6.93 (1H, s, ArH-3), 7.38 (2H, s, ArH-3″,5″), 7.39 (2H, d, J = 8.8 Hz, ArH-3′,5′); MS *m/z* (%) 434.2 (M + 1, 3), 367.2 (M − 56, 100). **7d**: yield 38%, white solid, mp 76.0–78.0 °C; ^{1}H NMR (CDCl$_3$) δ ppm 1.79 (2H, f, J = 5.6 Hz, CH$_2$), 2.13 (6H, s, 2 × CH$_3$), 3.01 (2H, t, J = 5.6 Hz, NCH$_2$), 3.87 (2H, t, J = 5.6 Hz, CH$_2$O), 3.95 (2H, s, ArCH$_2$), 5.51 (1H, s, NH), 5.96 (1H, s, ArH-6), 6.54 (2H, d, J = 8.8 Hz, ArH-2′,6′), 6.86 (1H, s, ArH-3), 7.39 (2H, s, ArH-3″,5″), 7.41 (2H, d, J = 8.8 Hz, ArH-3′,5′); MS *m/z* (%) 442.6 (M + 1, 20), 367.2 (M − 74, 100). **7e**: yield 40%, white solid, mp 210.2–212.0 °C; ^{1}H NMR (CDCl$_3$) δ ppm 2.09 (3H, s, CH$_3$), 2.08 (3H, s, CH$_3$), 2.12 (6H, s, 2 × CH$_3$), 2.78 (4H, t, J = 4.8 Hz, CH$_2$CH$_2$), 3.05 (4H, s, J = 4.8 Hz, CH$_2$CH$_2$), 3.72 (2H, s, ArCH$_2$), 5.87 (1H, s, NH), 6.01 (1H, s, ArH-3), 6.60 (2H, d, J = 8.4 Hz, ArH-2′,6′), 7.44 (2H, d, J = 8.4 Hz), 7.69 (2H, s, ArH-3″,5″), 8.62 (1H, s, ArH-6); MS *m/z* (%) 467.6 (M + 1, 31), 367.3 (M − 99, 100). **7f**: yield 33%, white solid, mp 140.9–142.9 °C; ^{1}H NMR (CDCl$_3$) δ ppm 1.28 (6H, d, J = 6.4 Hz, 2 × CH$_3$), 2.14 (6H, s, 2 × CH$_3$), 3.81 (1H, q, J = 6.4 Hz, CH), 4,69 (2H, s, ArCH$_2$), 5.53 (1H, s, NH), 5.96 (1H, s, ArH-6), 6.53 (2H, d, J =

8.4 Hz, ArH-2′,6′), 7.04 (1H, s, ArH-3), 7.38 (2H, s, ArH-3″,5″), 7.40 (2H, d, J = 8.4 Hz, ArH-3′, 5′); MS m/z (%) 427.4 (M + 1, 100). **7g**: yield 33%, white solid, mp 140.9–142.9 °C; ^{1}H NMR (CDCl$_3$) δ ppm 1.28 (6H, d, J = 6.4 Hz, 2 × CH$_3$), 2.14 (6H, s, 2 × CH$_3$), 3.81 (1H, q, J = 6.4 Hz, CH), 4,69 (2H, s, ArCH$_2$), 5.53 (1H, s, NH), 5.96 (1H, s, ArH-6), 6.53 (2H, d, J = 8.4 Hz, ArH-2′, 6′), 7.04 (1H, s, ArH-3), 7.38 (2H, s, ArH-3″,5″), 7.40 (2H, d, J = 8.4 Hz, ArH-3′,5′); MS m/z (%) 427.4 (M + 1, 100). **7h**: yield 34%, white solid, mp 161.0–162.8 °C; ^{1}H NMR (CDCl$_3$) δ ppm 2.14 (9H, s, 2 × CH$_3$, COCH$_3$), 3.55 (2H, s, NH$_2$), 5.29 (2H, s, ArCH$_2$), 5.52 (1H, s, NH), 6.00 (1H, s, ArH-6), 6.56 (2H, d, J = 8.4 Hz, ArH-2′,6′), 6.94 (1H, s, ArH-3), 7.39 (2H, s, ArH-3″,5″), 7.42 (2H, d, J = 8.4 Hz, ArH-3′,5′); MS m/z (%) 427.5 (M + 1, 62), 367 (M − 99, 100). **11a**: 50% yield, white solid, mp 170.5–172.0 °C; ^{1}H NMR (CDCl$_3$) δ ppm 2.13 (6H, s, 2 × CH$_3$), 3.54 (5H, s, OCH$_3$, NH$_2$), 4.67 (2H, s, CH$_2$O), 5.51 (1H, s, NH), 5.79 (1H, d, J = 16.4 Hz, =CH), 6.03 (1H, s, ArH-6), 6.55 (2H, d, J = 8.8 Hz, ArH-2′,6′), 6.99 (1H, s, ArH-3), 7.17 (2H, s, ArH-3″,5″), 7.31 (2H, d, J = 16.4 Hz, CH=), 7.40 (2H, d, J = 8.8 Hz, ArH-3′,5′); MS m/z (%) 425.3 (M + 1, 100). **11b**: 35% yield, white solid, mp 194.1–195.9 °C; ^{1}H NMR (CDCl$_3$) δ ppm 2.14 (6H, s, 2 × CH$_3$), 2.15 (3H, s, CH$_3$CO), 3.53 (2H, s, NH$_2$), 5.30 (2H, s, ArCH$_2$O), 5.51 (1H, s, NH), 5.78 (1H, d, J = 16.8 Hz, =CH), 6.05 (1H, s, ArH-6), 6.55 (2H, d, J = 8.8 Hz, ArH-2′,6′), 6.93 (1H, s, ArH-3), 7.17 (2H, s, ArH-3″,5″), 7.30 (1H, d, J = 16.8 Hz, CH=), 7.40 (2H, d, J = 8.8 Hz, ArH-3); MS m/z (%) 393.2 (M − 59, 100), 453.3 (M + 1, 97.2). **12a**: 79% yield, white solid, mp 103.6–104.8 °C; ^{1}H NMR (CDCl$_3$) δ ppm 2.09 (6H, s, 2 × CH$_3$), 2.61(2H, t, J = 7.2 Hz, CH$_2$CN), 2.87 (2H, t, J = 7.2 Hz, ArCH$_2$), 3.52 (3H, s, OCH$_3$), 4.67 (2H, s, CH$_2$O), 5.56 (1H, s, NH), 6.03 (1H, s, ArH-6), 6.55 (2H, d, J = 8.8 Hz, ArH-2′,6′), 6.92 (2H, s, ArH-3″,5″), 6.99 (1H, s, ArH-3), 7.39 (2H, d, J = 8.8 Hz, ArH-3′,5′); MS m/z (%) 427.3 (M + 1, 100). **12b**: 40% yield, white solid, mp 164.1–165.7 °C; ^{1}H NMR (DMSO-d_6) δ ppm 2.04 (6H, s, 2 × CH$_3$), 2.09 (3H, s, COCH$_3$), 2.78 (4H, s, 2 × CH$_2$), 4.58 (2H, s, NH$_2$), 5.19 (2H, s, CH$_2$O), 5.90 (1H, s, NH), 6.54 (2H, d, J = 8.8 Hz, ArH-2′, 6′), 6.87 (1H, s, ArH-6), 7.04 (2H, s, ArH-3″5″), 7.45 (2H, d, J = 8.8 Hz, ArH-3′,5′), 8.08 (1H, s, ArH-3); MS m/z (%) 395.2 (M − 59, 100), 455.3 (M + 1, 17).

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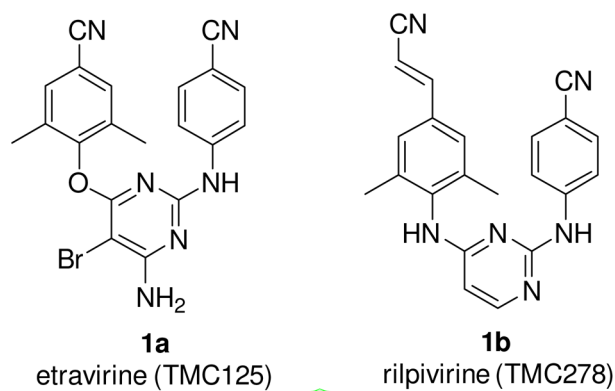
	EC$_{50}$ (nM)		WS (ug/mL)		
	NL4-3	RTMDR1	2.0	7.0	F%
2a	3.00	ND	0.42	0.47	ND
2b	0.33	0.87	0.29	0.29	ND
2c	0.53	0.36	20.9	3.23	6.1

DAANs

2a R^1 = NO$_2$, R^2 = CN;

2b R^1 = NO$_2$, R^2 = (E)-CH=CHCN

2c R^1 = CH$_2$OH, R^2 = (E)-CH=CHCN

New DAANs:

7 R^2 = CN

11 R^2 = (E)-CH=CHCN

12 R^2 = CH$_2$CH$_2$CN

Figure 1.
Next-generation NNRTI drugs, diarylaniline leads (DAANs), and new DAAN analogues
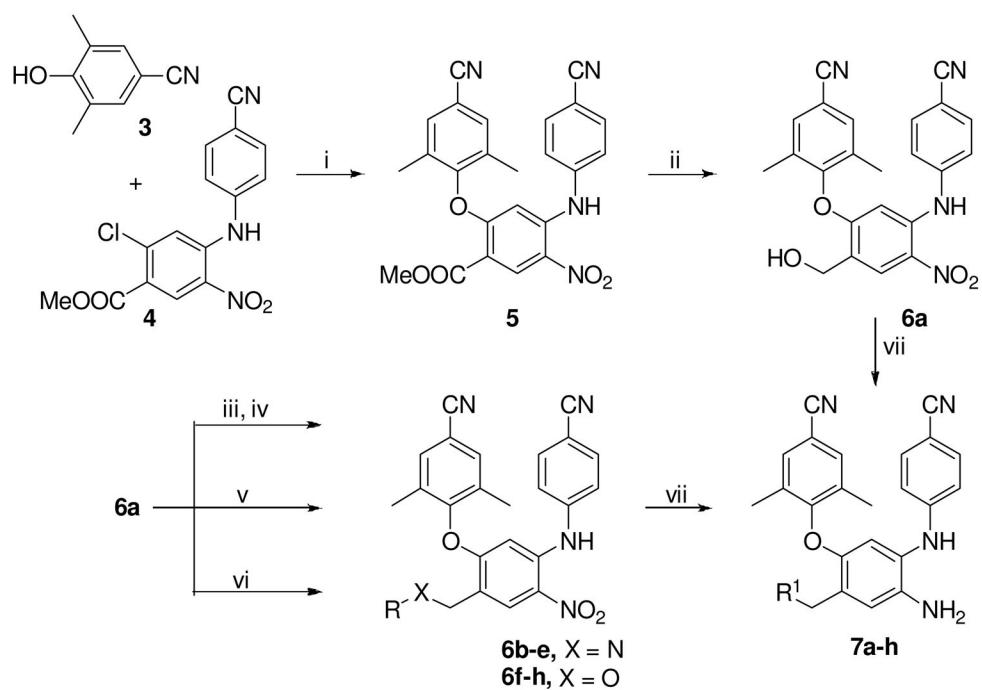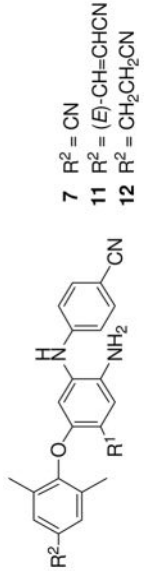
Scheme 1.
i) K_2CO_3/DMF, 120 °C, 6 h; ii) LiBH$_4$, THF/MeOH, 0 °C, 7 h; iii) 2,4,6-trichloro-[1,3,5]triazine, DMF/CH$_2$Cl$_2$, rt, 4 h; iv) amine, THF, 0 °C, 0.5 h; v) ROH/BiCl$_3$, CH$_2$Cl$_2$/CCl$_4$, rt, 4 h; (vi) Ac$_2$O, 100 °C, Microwave, 5 min; vii) H$_2$/Pd-C in EtOAc or EtOH.
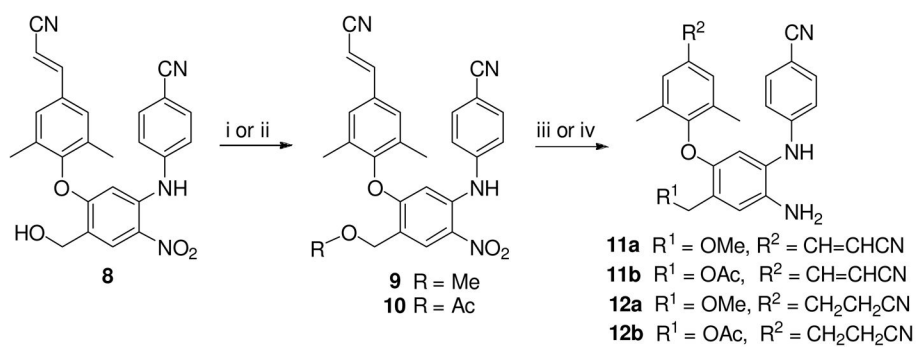
Scheme 2.
i) ROH/BiCl₃, CH₂Cl₂/CCl₄, r.t. 4 h; ii) Ac₂O, 100 °C, Microwave, 5 min; iii) Fe, NH₄Cl, THF/MeOH/H₂O, reflux, 3 h; iv) H₂/Pd-C in EtOH.

Table 1

Anti-HIV data of new DAANs against wild-type and resistant viral strains[a]

7   R^2 = CN
11 R^2 = (E)-CH=CHCN
12 R^2 = CH_2CH_2CN

	R^1	EC_{50} (nM) IIIB[b]	CC_{50} (µM)	SI	EC_{50} (nM) A17[c]	FC[d]
7a	OH	1.07 ± 0.25	122	114,019	33.1 ± 4.05	30.9
7b	NHMe	9.94 ± 1.57	12.7	1,278	115 ± 3.10	11.6
7c	$NHCH(CH_2)_2$	10.6 ± 0.64	12.1	1,142	130 ± 2.87	12.3
7d	$NH(CH_2)_3OH$	6.10 ± 1.10	15.1	2,475	>2000	>328
7e	$N(CH_2CH_2)_2NMe$	170 ± 5.60	96.9	570	>2000	>11.8
7f	$OCHMe_2$	14.0 ± 1.10	89.4	6,386	315 ± 25.7	22.5
7g	OMe	3.54 ± 0.62	146	41,243	298 ± 133	84.2
7h	OAc	1.06 ± 0.01	113	106,604	374 ± 111	353
11a	OMe	5.74 ± 2.20	50.3	8,763	14.7 ± 0.74	2.6
12a	OMe	3.25 ± 0.23	>200	>61,538	2.95 ± 0.50	0.91
11b	OAc	0.82 ± 0.07	96.3	117,439	36.50 ± 1.78	44.5
12b	OAc	0.96 ± 0.12	44.8	46,667	4.92 ± 0.12	5.1
1b	TMC278	0.49 ± 0.17	90.7	185,102	9.03 ± 0.74	18.4

[a] Experiments performed at least in triplicate in MT-2 cells and data presented as the mean ± SD.

[b] HIV-1 wild-type virus.

[c] Drug-resistant virus from NIH with mutated K103N and Y181C in the NNRTI binding pocket.

[d] Fold change resistance.

Table 2

Physicochemical parameters of new active DAAN compounds

	Aqueous solubility (μg/mL)[a]		mp °C	Log P[b] pH 7.4	clogD[c]	tPSA[d] (Å²)	Lipophilic efficiency indices[16,17]			
	pH 2.0	pH 7.4					pEC$_{50}$[e]	LE[f]	LLE[g]	LELP[h]
7a	9.12	0.86	230–2	3.57	3.23	115.1	8.97	0.42	5.40	8.50
7b	263	159	202–3	1.86	3.72	106.9	8.00	0.37	6.14	5.03
7c	286	13.0	72–3	3.84	4.08	106.9	7.97	0.34	4.13	11.30
7d	290	236	76–8	1.81	3.31	127.1	8.21	0.34	6.40	5.32
7g	3.75	0.07	176–8	3.84	4.16	104.1	8.45	0.39	4.61	9.85
7h	16.7	0.20	161–3	4.40	4.12	121.2	8.97	0.38	4.57	11.60
11a	1.70	0.11	171–2	4.13	4.48	104.1	8.24	0.35	4.11	11.80
12a	1.82	0.66	104–5	3.25	3.87	104.1	8.49	0.36	5.24	9.03
11b	1.87	0.49	194–6	4.48	4.45	121.2	9.08	0.37	4.60	12.20
12b	2.63	1.86	164–6	2.84	3.84	121.2	9.02	0.36	6.18	7.92
1b	86.8	0.24	246–8	> 5	3.62	97.4	9.31	0.46	5.69[i]	7.87[i]

[a,b] Measured by HPLC in triplicate.

[c] Predicted by ACD software.

[d] Topological polar surface area predicted by ChemDraw Ultra 12.0.

[e] Negative logarithm values of potency converted from experimental data against wild-type virus IIIB shown in Table 1.

[f] Calculated by the formula − G/HA(non-hydrogen atom), in which normalizing binding energy G = −RT lnK$_d$, presuming EC$_{50}$ ≈ K$_d$.

[g] Calculated by the formula pEC50 − log P.

[h] Defined as a ratio of measured log P and LE.

[i] Data calculated with clog D.