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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.

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 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 nevirapine, 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

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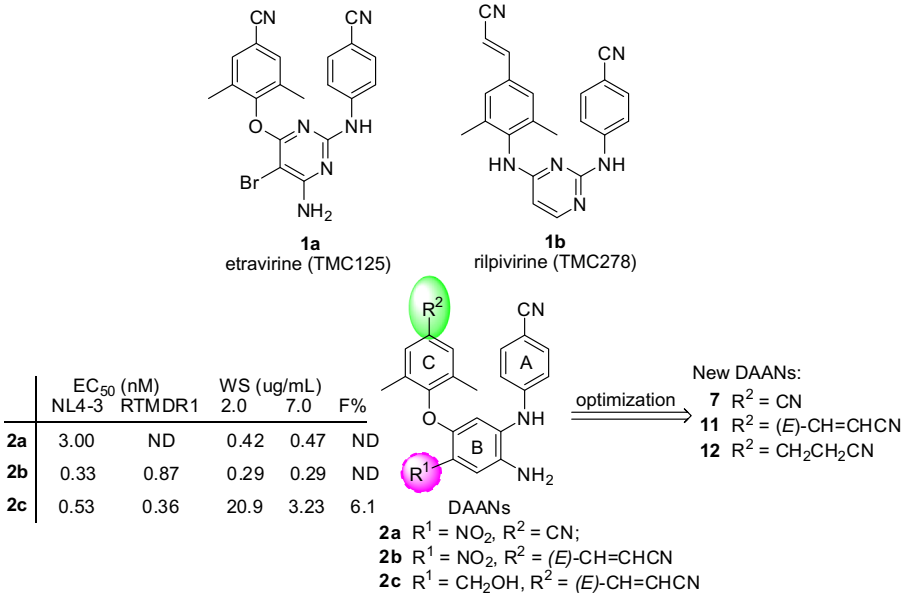

Figure 1. Next-generation NNRTI drugs, diarylaniline leads (DAANs), and new DAAN analogues.

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**, and **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 lipophilic parameters, that is, 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[12–14] 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**, and **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 1142–114,019. 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 33–2000 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_4Cl 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