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Design, Synthesis, and Evaluation of Diarylpyridines and Diarylanilines as Potent Non-nucleoside HIV-1 Reverse Transcriptase Inhibitors

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On the basis of the structures and activities of our previously identified non-nucleoside reverse transcriptase inhibitors (NNRTIs), we designed and synthesized two sets of derivatives, diarylpyridines (**A**) and diarylanilines (**B**), and tested their anti-HIV-1 activity against infection by HIV-1 NL4-3 and IIIB in TZM-bl and MT-2 cells, respectively. The results showed that most compounds exhibited potent anti-HIV-1 activity with low nanomolar EC_{50} values, and some of them, such as **13m**, **14c**, and **14e**, displayed high potency with subnanomolar EC_{50} values, which were more potent than etravirine (TMC125, **1**) in the same assays. Notably, these compounds were also highly effective against infection by multi-RTI-resistant strains, suggesting a high potential to further develop these compounds as a novel class of NNRTIs with improved antiviral efficacy and resistance profile.

Introduction

Acquired immunodeficiency syndrome (AIDS[a]), caused by human immunodeficiency virus (HIV), threatens human health and life, spreading rapidly worldwide and resulting in more than 60 million people infected by HIV and about 25 million patients dying of AIDS (www.unaids.org). Because there is no effective vaccine to prevent HIV infection, development of anti-HIV therapeutics is critical to improve the quality and save the lives of HIV infected individuals. To date, 26 anti-HIV drugs have been approved for the clinical treatment of HIV infection and AIDS (www.fda.gov/oashi/aids/virals.html), including reverse transcriptase inhibitors (RTIs), protease inhibitors (PIs), integrase inhibitors, fusion inhibitor, and entry inhibitor (CCR5 coreceptor antagonist). Highly active antiretroviral therapies (HAART), which use a combination of three to four drugs, can significantly reduce the morbidity and mortality of AIDS. However, as a result of emerging drug-resistant HIV mutants, increasing numbers of HIV-infected patients cannot use or fail to respond to HAART. Therefore, the development of new anti-HIV drugs is urgently required.

HIV-1 reverse transcriptase (RT) is one of the most important viral enzymes and plays a unique role in the HIV-1 life cycle. It has two known drug-target sites, the substrate catalytic site and an allosteric site that is distinct from, but located closely to, the substrate site.[1,2] Non-nucleoside reverse transcriptase inhibitors (NNRTIs) interact with the allosteric site in a noncompetitive manner to distort the enzyme's active conformation and thus disrupt the function of the enzyme. The first-generation NNRTI drugs (nevirapine, delavirdine, and efavirenz) exhibit very potent anti-HIV-1 activity and low toxicity. However, rapid drug-resistance emergence, due to single point mutations (especially K103 mutant)[3] in the NNRTI binding site, compromises their clinical usefulness. Etravirine (TMC125, **1**),[4] a diarylpyrimidine (DAPY, Figure 1), was recently approved as a next-generation NNRTI for AIDS therapy. It exhibits high potency against wild-type and a number of mutated viral strains with nanomolar EC_{50} values and has a higher genetic barrier[5] to delay the emergence of drug-resistance. The success of **1** greatly encouraged further research to explore additional novel NNRTIs.[6−8] The most advanced NNRTI in development is another DAPY derivative rilpivirine (TMC278, **2**)[9] in phase III, which showed better potency and pharmacological profiles than **1**, such as once-daily administration.[10]

By using an isosteric replacement strategy on the central pyrimidine ring of DAPYs, our prior studies discovered two series of active compounds, diarylpyridine (**A**, DAPD),[11] with one pyrimidine nitrogen replaced by carbon, and diarylaniline (**B**, DAAN),[12] with both pyrimidine nitrogens replaced by carbon. Exemplary di-*para*-cyanophenylpyridine compound **3** and di-*para*-cyanophenylaniline compound **4** (Figure 1)

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[a] Abbreviations: AIDS, acquired immunodeficiency syndrome; CC_{50}, concentration for 50% cytotoxicity; DAPYs, diarylpyrimidines; DAPDs, diarylpyridines; DAANs, diarylanilines; EC_{50}, effective concentration for 50% inhibition; HAART, highly active antiretroviral therapies; HIV, human immunodeficiency virus, NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PDB, protein database; RF, resistant fold; RT, reverse transcriptase; RTI, reverse transcriptase inhibitor; SAR, structure−activity relationship; SI, selective index (ratio of CC_{50}/EC_{50}).

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