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Abstract

Discovery of Biphenyl-Substituted Diarylpyrimidines as New Non-Nucleoside HIV-1 Reverse Transcripttase Inhibitors †

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Although Rilpivirine (**1**, RPV, TMC278) was approved by the FDA in 2011 as a non-nucleoside HIV-1 reverse transcriptase inhibitor to treat Human Immunodeficiency Virus (HIV) [1] for its potent activity against many clinically relevant wild-type (WT) and mutant HIV-1 strains, the corresponding dosing complexity, drug-drug interactions and long-term toxicity of this drug have severely compromised its efficacy [2].

To solve the above problem, herein a novel series of biphenyl-substituted diarylpyrimidine analogues (DAPYs) was designed, synthesized to evaluate the in vitro activity against HIV-1 in MT-4 cells. Some of these compounds exhibited excellent activity with the low nanomolar EC_{50} to wild-type (WT), single-mutant, and double-mutant HIV-1 strains. The most potent compound **2a** displayed an EC_{50} value of 1 nM against HIV-1 ⅢB, 1.3 nM against L100I, 0.84 nM against K103N, 1.5 nM against Y181C, 11 nM against Y188L, 2 nM against E138K, 10 nM against K103N + Y181C, nearly 110 nM against F227L + V106 with a selectivity index (SI) value above 2059.

To investigate the possible interaction model between the new chemical entity and the biological target, compound **2a** was docked into the allosteric non-nucleoside bind pocket (NNIBP) of HIV-1 RT (PDB code: 2ZD1) [3] by using Sybyl-X 1.2. Compound **2a** exhibited a series of well-known kinds of interactions: the biphenyl moiety fitted well into the aromatic-rich sub-pocket consisting of amino acid residues including Tyr181, Tyr188, Phe227 and Trp229, showing the positive face-to-face π–π stacking interactions with the amino acid residues of Tyr181, Tyr188 and Trp229, excluding Phe227. The *p*-cyano group is protruding toward a tunnel formed by Phe227 and Trp229, indicating a possible polar interaction. The right aromatic ring extended to a solvent exposure region, which was surrounded by amino acid residues His235, Pro236 and Try 318. Additionally, two hydrogen bonds between compound **2a** and NNIBP of HIV-1 RT were formed altogether; one is between the *NH*-linker and the oxygen atom of the carbonyl group on the back-bone of Lys101, another is between the 1-nitrogen atom on pyrimidine between the terminal amino group of Lys101.

Deep SAR analysis of the anti-HIV-1 profile of all the compounds showed that beside keeping the 2,6-dimethyl groups on the left ring of DAPY analogues, introducing a *para*-substituted cyano group on the second phenyl ring (B) on the biphenyl group might be crucial for enhancing the biological activity against both wild-type and mutant-type HIV-1. This important discovery on the biphenyl-substituted DAPY analogs might guide the further structural modification of our ongoing project of HIV-1 RT inhibitors.

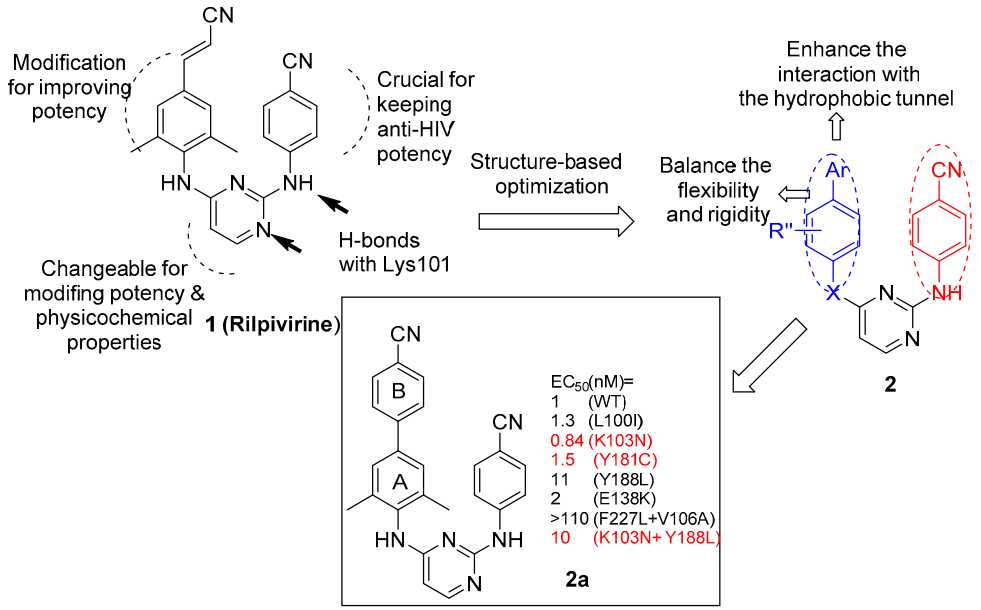

Figure 1. Design of new DAPY-NNRTIs based on the biphenyl-substituted pyrimidine scaffold.

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References

1. Chen, X.; Zhan, P.; Li, D.; De Clercq, E.; Liu, X. Recent Advances in DAPYs and Related Analogues as HIV-1 NNRTIs. *Curr. Med. Chem*. **2011**, *18*, 359.
2. Rimsky, L.; Vingerhoets, J.; Van Eygen, V.; Eron, J.; Clotet, B.; Hoogstoel, A.; Boven, K.; Picchio,.G Genotypic and phenotypic characterization of HIV-1 isolates obtained from patients on rilpivirine therapy experiencing virologic failure in the phase 3 ECHO and THRIVE studies: 48-week analysis. *J. Acquir. Immune Defic. Syndr*. **2012**, *59*, 39.
3. Lansdon, E. B.; Brendza, K. M.; Hung, M.; Wang, R.; Mukund, S.; Jin, D.; Birkus, G.; Kutty, N,; Liu, X. Crystal structures of HIV-1 reverse transcriptase with etravirine (TMC125) and rilpivirine (TMC278): implications for drug design. *Med. Chem*. **2010**, *53*, 4295.