World Academy of Science, Engineering and Technology
International Journal of Pharmacological and Pharmaceutical Sciences
Vol:15, No:01, 2021

Tenofovir-Amino Acid Conjugates Act as Polymerase Substrates: Implications for Avoiding Cellular Phosphorylation in the Discovery of Nucleotide Analogs

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Abstract : Nucleotide analogs are used for treating viral infections such as HIV, hepatitis B, hepatitis C, influenza, and SARS-CoV-2. To become polymerase substrates, a nucleotide analog must be phosphorylated by cellular kinases, which are rate-limiting. The goal of this study is to develop dNTP/NTP analogs directly from nucleotides. Tenofovir (TFV) analogs were synthesized by conjugating with natural or unnatural amino acids. It demonstrates that some conjugates act as dNTP analogs, and HIV-1 reverse transcriptase (RT) catalytically incorporates the TFV part as the chain terminator. X-ray structures in complex with HIV-1 RT/dsDNA showed binding of the conjugates at the polymerase active site, however, in different modes in the presence of Mg^{2+} vs. Mn^{2+} ions. The adaptability of the compounds is seemingly essential for catalytic incorporation of TFV by RT. 4d with a carboxyl sidechain demonstrated the highest incorporation. 4e showed weak incorporation and rather behaved as a dNTP-competitive inhibitor. This result advocates the feasibility of designing NTP/dNTP analogs by chemical substitutions to nucleotide analogs.

Keywords : dNTP analogs, nucleotide analogs, polymerase, tenofovir, X-ray structure
Conference Title : ICTTMC 2021 : International Conference on Therapeutic Targets and Medicinal Chemistry
Conference Location : Amsterdam, Netherlands
Conference Dates : January 21-22, 2021

Open Science Index, Pharmacological and Pharmaceutical Sciences Vol:15, No:01, 2021 publications.waset.org/abstracts/130804.pdf