

DISCOVERY, STRUCTURE-ACTIVITY-RESISTANCE RELATIONSHIPS AND PHARMACOLOGY OF THE 3'-AZIDO-2',3'-DIDEOXYPURINES, A POTENT LEAD CLASS OF NUCLEOSIDE ANALOGS ACTIVE AGAINST DRUG-RESISTANT HIV-1

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Nucleoside analog reverse transcriptase inhibitors (NRTI) are integral components of therapy for HIV-1 infection. The currently approved NRTI have significant limitations that include short- and long-term toxicity, pharmacokinetic interactions with other antiretroviral drugs, and the selection of drug-resistant HIV-1 variants that are cross-resistant with other NRTI. Accordingly, there is a critical need to develop new NRTI that have excellent activity and safety profiles and exhibit little or no cross-resistance with existing drugs. Using data derived from structure-activity-resistance relationship studies, we identified the 3'-azido-2',3'-dideoxypurines (ADPs) as a lead class of compounds that retain potent activity against drug-resistant variants of HIV-1 that (i) increase the ability of HIV-1 reverse transcriptase (RT) to discriminate between the natural dNTP substrate and the NRTI-triphosphate (e.g. K65R, L74V, M184), and/or (ii) enhance the excision of the chain-terminating NRTI-monophosphate from the prematurely terminated DNA chain (i.e. thymidine analog mutations). Pre-steady-state kinetic analyses demonstrate that the ADP-triphosphates are incorporated by HIV-1 RT as efficiently as the natural dGTP or dATP substrates. Importantly, the ADPs do not exhibit cytotoxicity in primary lymphocytes, epithelial or T-cell lines, and 3'-azido-ddG does not decrease the mitochondrial DNA content of HepG2 cells. Furthermore, 3'-azido-ddG is efficiently phosphorylated to 3'-azido-ddG-triphosphate in primary human mononuclear cells with an intracellular half-life of the nucleoside triphosphate of 9 hr. Taken together, these studies show that the ADPs exhibit favorable activity, toxicity and cellular pharmacology profiles, and we are currently investigating novel base modified ADPs to identify the most promising candidates for further development.