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New Ribonucleosides with Surrogate Bases: Synthesis, Enzymology, Molecular Docking Studies and Antiviral Activity

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In an ongoing drug discovery program on antiviral ribonucleosides in our laboratories, we have been utilizing the enzyme, inosine monophosphate dehydrogenase (IMPDH), as a probe for the initial identification of potential molecules that have antiviral activity. IMPDH catalyzes the conversion of IMP to XMP, utilizing the coenzyme, NAD^+, as the hydride acceptor. IMPDH is an important rate-determining enzyme of de novo guanine nucleotide biosynthesis. It has been considered a significant target enzyme for the discovery of therapeutic agents, including antiviral agents. Consistent with this is the observation that some inhibitors of IMPDH have been found to have antiviral activity against pox-, bunya-, arena-, adeno-, flavi-, and paramyxoviruses. The focus of our molecular design has been exploitation of the Michael-type interaction between the sulfhydryl group of cysteine-331 of IMPDH and the C-2 or C-6 position of purine nucleotides. The synthetic work required the development of new methodologies for specific double functionalization at appropriate positions of purine nucleobases. Details of the concise syntheses developed will be presented. Kinetic parameters of the reversible and irreversible inhibition of IMPDH, which were monitored by UV spectral methods involving the monitoring of the formationof NADH, will be discussed. Molecular differences in IMPDH docking results with various inhibitors will be illustrated. Correlation of antiviral activity (pox, fluA, fluB, dengue, HSV, VZV) with IMPDH inhibition will be presented and explained.

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Novel Synthetic Approaches to Cidofovir and Foscarnet Prodrugs

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Cidofovir (HPMPC, Vistide®) and foscarnet (phosphonoformic acid, PFA) are broad spectrum antiviral agents used to treat AIDS-related CMV retinitis. Cidofovir is currently the only drug approved for the treatment of smallpox. Both drugs exhibit very low bioavailability due to the presence of negatively charged phosphonate (HPMPC, PFA) and carboxylate (PFA) groups at physiological pH and thus are important targets for prodrug design. In contrast to cyclic cidofovir which has only a single free POH (cf. # 180), HPMPC in acid form has two POH functionalities, while foscarnet additionally has a polar COOH group. Here we describe an approach to HPMPC prodrug design in which a P(O)(OR)(OR′) form of the drug is created, with R = an alkyl ester and R′ = a peptide moiety. We also present a new HPMPC monoesterification methodology that may have application to other phosphonate drug modifications. Additionally, a series of novel foscarnet dipeptide prodrugs has been synthesized. The potential of the new prodrug approaches will be assessed based on preliminary biological evaluations.

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Chloroquine a Novel and Versatile Anti viral Agent with Nine Prong Modes of Anti viral Actions and Postive Approach in Radical Cure of Viral Hepatitis Varieties B and C Both Acute and Chronic Forms

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Billions of chronic Hepatitis B and C (HBV and HCV) infection sufferers with emerging drug resistance viruses have a propensity for cirrhosis liver and carcinoma liver; the medical fraternity's imperative approach to find a radical cure with positive approach using combination of antivirals after early detection. After self medication tiral (1978) and literature survey we found popular antimalarial chloroquine (CQ) has got nine modes of anti-viral actions against 12 human pathogenic viruses; HepatitisA, B and C, HIV, SARS, etc. Modes of action