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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

(1) viral endocytosis blocker (2) lysosomal decoating blocker, (3) HBV-DNA polymerase (HBV-DNA-P) intercalator, (4) duck HBV supercoiled DNA blocker, (5) inhibits HIV intergrase, etc.

Acute HBV-1232 treated with CQ menotherapy 2 mg/kg or combination with standard doses of Ribavirion (RN)/Lamivudine (LV) and Methyleneblue (MB/HBVDNA-P Blocker). Hepatitis marker HBS Ag cleared in 7–38 days and follow up for 10 years 3 months no recurrence at all. Chronic HBV patients (26) same regimen + Interferon Alpha (INFα); cleared HBSAg in 24–356 days, follow up for 3–7 years no recurrence at all. Eight acute HCV patients-treated with CQ, RN and INFα, anti-HCV cleared in 10–58 days followed up for 3–7 years found no recurrence. Same regimen for eight chronic HCV patients were given; clearance of anti-HCV and polymerase chain reaction (PCR) assay also in 24–356 days; followed up for 5 years, no recurrence. Chloroquine a cheap and long acting drug is an ideal combination drug to achieve radical cure in viral hepatitis varieties.

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Brivudin (Zostex^{R}) in the Treatment of Herpes Zoster in Immunosuppressed Patients

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Herpes zoster is caused by endogenous reactivation of varicella-zoster virus (VZV) latent within sensory ganglia after primary infection. Under immunocompromised conditions, the course of VZV infections can become extremely serious due to the development of visceral dissemination. In addition, immunocompromised patients are at high risk of progression of cutaneous rash and delayed healing of lesions. Bromovinyldeoxyuridine (BVDU, brivudin), one of the most potent inhibitors of VZV replication, is widely used in the therapy of herpes zoster in immunocompetent patients especially in Europe.

Here, the results of a prospective study are reported regarding brivudin for the treatment of herpes zoster in 25 immunosuppressed patients, mostly children.

The study included 14 male and 11 female patients with an age range of 3–25 years. Immunosuppression was due to hematopoietic stem cell transplantation in 11 patients, renal transplantation in 1 patient, chemotherapy due to a malignant disease in 12 patients and systemic lupus erythematodes in 1 patient. Concerning the localization of zoster, the trunk was involved in 16, the extremities in 5 and the head in 4 cases. Primary diagnosis was made clinically. VZV DNA could be detected by PCR in the fluid of lesions in 18 patients as well as in the blood in 1 patient. The drug was administered orally at a dose of 2–5 mg/kg/day in a single dose. The median duration of therapy was 10 days (range: 7–21 days). All patients responded promptly to antiviral treatment and recovered completely from their zoster infections without complications. Incrustation of lesions was reached after 3–10 days (median: 4 days). The full healing of efflorescences was ascertained after 7–20 days (median: 7 days). The brivudin therapy was well tolerated. No clinical side-effects due to the drug were observed. The compliance was very good because of the one-dose regimen of application per day. All patients were treated in an out-patient manner.

In conclusion, oral brivudin was a very effective and well tolerated therapy in herpes zoster in immunosuppressed patients. The oral administration offers the potential for out-patient treatment of herpes zoster in these patients.

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Proteflasid as Inhibitor of EBV-infection

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The groups of biologically active plant substances attract special attention in the chemotherapy of viral infections. Plant substances are characterized by relatively low toxicity and possess selective specific and pharmacological effect on human organism. Proteflasid is one of such preparations and it was obtained from wild grasses *Deschampsia caespitosa* L. and *Calamagrostis epigeios* L. (produced by "Ecopharm" in two solvents: propylene glycol and syrup).

Activity of these substances against Epshtein-Barr virus (EBV) was assessed in EBV-infected lymphoblastoid cells Raji. The substances were assayed within broad concentration ranges. CC_{50} was 40 μg/ml for preparation in propylene glycol, and 150 μg/ml—in syrup. It was shown, that antiviral action Proteflasid dissolved in two solvents was identical as at its entering into system simultaneously with infecting so in 24 h after infecting of cells (EC_{50} were 0.1 μg/ml and SI—400 in propylene glycol and 1500 in syrup accordingly). It was determined that antiviral action of Proteflasid was lower when it was entered 24 h before an infecting of cells. EC_{50} was 0.5 μg/ml as in propylene glycol so and in syrup, SI was 80 and 300 accordingly.

Thus, Proteflasid possesses anti-EBV activity and may be advantageous for the therapy of EBV-associated diseases.

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