dent RNA polymerase activity has critically important role in HCV RNA replication and so considered as attractive therapeutic target for designing newer classes of compounds. Present work is to investigate the molecular modelling studies of quinoline derivatives such as Chloroquine, Hydroxychloroquine and Primaquine with HCV RNA polymerase. Results of the modelling studies indicate that the quinoline derivatives strongly interacts with the residues in the primer grip site of the polymerase. Quinoline derivatives were also subjected to HCV RNA subgenomic replicon assay and the results are; HCV RNA synthesis inhibited by Chloroquine at 10.75 mM and Hydroxychloroquine at 6.6 mM. Details of modelling studies will be presented.

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Identification and Characterization of Pyrimidinediones as Potent Non-nucleoside Reverse Transcriptase Inhibitors of Hepatitis B virus

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Based on extensive data demonstrating that pyrimidinediones are potent non-nucleoside inhibitors of HIV-1 reverse transcriptase (NNRTI), we hypothesized that these compounds may inhibit hepatitis B virus (HBV) reverse transcription. We have thus assessed the ability of 68 pyrimidinedione congeners to inhibit HBV replication using a HepG2.2.15 cell culture system and a quantitative PCR assay for the detection of HBV viral DNA in treated cell culture supernatants. Initial screening using a 3-dose concentration scheme resulted in the identification of twelve pyrimidinedione molecules (SJ26, SJ44, SJ46, SJ49, SJ50, SJ53, SJ56, SJ59, SJ68, SJ59, SJ80, and SJ86) which displayed submicromolar EC_{50} values and TC_{50} values greater than 10 mM. Expanded analysis of the anti-HBV activity of these twelve compounds using 9-dose concentration points with half logarithmic dilutions of the compounds demonstrated that 3 of the 12 compounds (SJ59, SJ68, and SJ80) had EC_{50} values less than 1 mM in the expanded full dose response evaluations and two additional compounds (SJ26 and SJ49) had EC_{50} values less than 2.5 mM. Anti-viral activity against a broad range of RNA and DNA viruses indicated that these compounds specifically inhibited the replication of HIV and HBV, supporting the hypothesis that they inhibit reverse transcriptase and providing a rationale for development of a first-in-class NNRTI of HBV and/or HIV–HBV co-infection. Each of these SJ compounds inhibit HIV-1 RT at nanomolar concentration levels. Based on these data, compounds SJ26, SJ49, SJ59, SJ68, and SJ80 are being subjected to further characterization and development as therapeutic agents. Results will be presented detailing the in vitro characterization of these compounds for anti-viral efficacy and toxicity in combination with approved HBV therapeutics (interferon, lamuvidine, and tenofovir), analysis of anti-viral efficacy against lamuvidine-resistant virus, accumulation of intracellular cccDNA and rcDNA, inhibition of HBV reverse transcriptase activity, and toxicity against primary hepatocytes.

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Prophylactic Efficacy of Intranasally Administered HSP Nanoparticles for Treating a Lethal SARS-CoV Infection in BALB/c Mice

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HSP nanoparticle (sHsp-PCN) is a small heat shock protein cage nanoparticle that elicits the formation of inducible bronchoalveolar lymphatic tissue (iBALT) in the lungs. iBALT is a transient tertiary lymphatic tissue that acts like conventional secondary lymphatic tissues in that it generates local primary immune responses—B and T cell protective responses is induced by antigen presentation by APCs. Thus, it might be useful in priming the local immune environment of the lung to prophylactically treat infectious lung disease. A series of experiments were done to determine how to treat a lethal SARS-CoV infection in BALB/c mice with sHsp-PCN. In each experiment, 15 mice were treated intranasally (I.N.) with PSS and10 mice were treated I.N. with sHsp-PCN or with Poly IC:LC at 1 mg/kg, a known inhibitor of death in the lethal SARS-CoV mouse model. When mice were pretreated with sHsp-PCN one time at days −17, −13, −9, −5, −2, all mice survived the infection as did mice treated I.N. with Poly IC:LC (1 mg/kg, qd X +4, +24) with all untreated, infected mice dying. sHsp-PCN was well tolerated in sham infected and infected mice; all mice gained weight. When sHsp-PCN was administered less often prophylactically (qd X1, days −17, −13; qd X1, days −9, −5, −2; qd X1, days −5, −2; qd X1, day −2; or qd X1, day −2, +8 h), the percentage of survivors decreased to 45%, 50%, 50%, 30%, 10%, respectively. As expected, when sHsp-PCN was administered therapeutically (bid X1 at −4 h, +8 h; qd X1 on day 1; qd X2 on days 1, 2; or −4 h, +8 h, days 1, 2), it did not significantly prevent death. In a moderately lethal infection, sHsp-PCN pretreatment appeared to be dose responsive, with 80% survivors at a 5-mg/kg dose, 60% survival with a 2-mg/kg dose, and 40% survivors in mice 0.1 mg/kg; 40% of mice survived receiving PSS. Thus, sHsp-PCN appears to be an effective prophylactic treatment for lethal infections in BALB/c mice induced by mouse-adapted SARS-CoV. The data suggest that this technology might represent a novel way of ameliorating if not preventing pulmonary virus infections in general and should be further pursued.

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The Activity of New Cage Compounds Against Avian Influenza Virus (H5N1)

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High pathogenic strains of influenza type A (H5N1) virus have been the cause of large-scale death in poultry and death of over 200 humans. Functional derivatives of cage compounds are known as one of perspective classes of organic compounds for search of antiviral agents. During our investigation we have synthesized series of functional derivatives of adamantane: amides, hydrazones, amino, hydroxy, carboxy, carbamoylamino derivatives and wide range of adamantyl substituted oxygen, sulfur and nitrogen containing heterocycles. Antiviral activity of synthesized compounds