was evaluated against influenza A (H5N1) virus. Results of biological tests show that most of synthesized compounds reveal antiviral activity to a greater or lesser extent. Also adamantane containing hydrazide has marked antiviral potency against influenza A virus (H5N1), it inhibits their reproduction at 0.5 mM concentration. Amino derivative, containing adamantylidene unit, suppresses replication of H5N1 virus at 0.7 mM concentration. The presence of great number of high active compounds indicates some common principles of antiviral action of compounds, containing saturated cage moiety. It determines route to new virus inhibitors which block M2 ion channels.

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Oseltamivir-resistant Subpopulations of H5N1 Influenza Variants are Genetically Stable and Virulent in Ferrets

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H5N1 influenza viruses are emerging as human pathogens, and their high lethality warrants an urgent search for optimal antiviral therapy. While the neuraminidase (NA) inhibitor oseltamivir is currently our first line of defense against a pandemic threat, there is little information about mechanism(s) of emergence of drug-resistance, e.g. co-existence and selective advantage/disadvantage of H5N1 oseltamivir-resistant and sensitive viruses. Here we assessed the biological significance of minor subpopulations of oseltamivir-resistant H5N1 variants carrying H274Y NA mutation in a ferret model. Animals were inoculated with either recombinant wild-type A/Vietnam/1203/04 (clade 1) or A/Turkey/15/06 (clade 2.2) influenza viruses or mixtures containing different ratios of drug-resistant and sensitive variants, and their fitness was evaluated. Sequence analysis of individual clones obtained from nasal washes of ferrets (days 2, 4 and 6 p.i.) revealed genetic stability of the minor subpopulations of resistant and sensitive viruses for both H5N1 viruses. Ferrets inoculated with A/Vietnam/1203/04 oseltamivir-resistant variants were as virulent as sensitive viruses, e.g. animals experienced high fever, weight loss, anorexia, extreme lethargy, severe neurological impairment, and death. Titers of A/Vietnam/1203/04 oseltamivir-resistant and sensitive variants in the upper respiratory tract of ferrets did not differ significantly ($P < 0.05$). A/Turkey/15/06 (H5N1) virus is less pathogenic to ferrets and causes mild, non-lethal disease at infectious dose up to 10^6 EID_{50}/ferret. The animals inoculated with drug-resistant variants of A/Turkey/15/06 (H5N1) virus initially showed milder signs of disease on days 1–3 p.i., but at later time points the pathogenicity pattern was identical for resistant and sensitive variants. Our results suggest that minor subpopulations of oseltamivir-resistant H5N1 variants can be stably maintained in mammalian species and co-exist with drug-sensitive variants.

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Inhibition of Influenza Virus Replication: Discovery and Development of Therapeutic Compounds which Suppress Viral RNA Synthesis

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Although influenza outbreaks are usually self-limiting, over 500 million people are infected annually and significant morbidity and mortality result from these infections. Additionally, the potential appearance and spread of a highly virulent pandemic strain of influenza similar to outbreaks of H5N1 viruses in 1918 and 1997 emphasizes the need for new and novel inhibitors of influenza virus. At present, annual vaccinations based on predictions of expected circulating influenza viruses and the use of four approved compounds targeting ion channels and the viral neuraminidase represent the entire arsenal of available therapeutics and preventatives for influenza. Thus, continued development of new and novel antiviral agents for the control of influenza is urgently needed and these agents should be amenable for use in combination with the approved anti-influenza agents. ImQuest BioSciences has worked extensively to develop new anti-infective agents targeting the intracellular replication of RNA viruses, including HIV, hepatitis C virus and influenza/respiratory viruses. We have defined a specific series of compounds with activity against these pathogens that target novel and un-exploited viral replication pathways. These agents act as viral transcriptional inhibitors and appear to specifically interact with cellular microtubule macromolecule transport pathways specific to RNA viral pathogens. We have generated 110 compounds in a series of molecules identified as transcriptional inhibitors of HIV and HCV and these small molecules have been screened for activity against influenza A virus, resulting in the identification of three compounds with EC_{50} values in the ng/mL to low μg/mL range but with somewhat narrow therapeutic indices of approximately 25–50. Additional screening has been performed with a representative panel of influenza A and influenza B viruses, other respiratory viruses, including respiratory syncytial virus, rhinovirus, avian influenza virus and highly pathogenic human H5N1 influenza strains, as well as against other non-HIV RNA viruses in order to evaluate the breadth of activity and specificity of the active agents.

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Combinations of 5-Iodo-4′-thio-2′-deoxyuridine and ST-246 or CMX001 Synergistically Inhibit Orthopoxvirus Replication In Vitro

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The nucleoside analog, 5-iodo-4′-thio-2′-deoxyuridine (4′-thioIDU) has been reported to inhibit the replication of orthopoxviruses both in vitro and in vivo. This highly active compound appeared to be phosphorylated by the vaccinia virus thymidine kinase and acts by a mechanism distinct from that observed with either ST-246 or CMX001. Thus, combinations of 4′-thioIDU with these agents might be expected to result in the synergistic inhibition of viral replication. The evaluation of these