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In Vitro and In Vivo Activity of T-705 Against Arenavirus and Bunyavirus Infections

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There is a need for the development of effective antivirals for the treatment of severe viral diseases caused by members of the *Bunyaviridae* and *Arenaviridae* virus families. The pyrazine derivative, T-705 (6-fluoro-3-hydroxy-2-pyrazinecarboximide), has demonstrated remarkable antiviral activity against influenza virus, and to a lesser degree, against some other RNA viruses (Furuta et al., 2002. Antimicrob. Agents Chemother. 46, 977–981). Here, we report that T-705 is highly active against a panel of bunyaviruses (La Cross, Punta Toro, Rift Valley fever, Sandfly fever) and arenaviruses (Junin, Pichinde, Tacaribe) by cytopathic effect and virus yield reduction cell-based assays. The 50% effective concentrations for T-705 ranged from 5 to 30 mg/ml and 0.7–1.2 mg/ml against the bunyaviruses and arenaviruses examined, respectively. We also demonstrate that orally administered T-705 is efficacious in treating Punta Toro virus in the mouse and hamster infection models, as well as Pichinde virus infection in hamsters. When administered twice daily for 5–6 days, beginning 4 h pre- or 24 h post-Punta Toro virus challenge, a 30 mg/kg/day dose provided complete protection from death and limited viral burden and liver disease. A dose of 50 mg/kg/day was found to be optimal for treating Pichinde infection and limiting viral replication and disease severity. In general, T-705 was found to be more active than ribavirin in cell-based assays and in vivo as reflected by substantially greater therapeutic indexes. Our results suggest that T-705 may be a viable alternative for the treatment of life-threatening bunyaviral and arenaviral infections.

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QSAR Studies On [(Biphenyloxy)propyl]isoxazole Derivatives With Anti-rhinovirus 2 Activity

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The objective of the present work is the quantitative structure-activity relationship (QSAR) analysis of antiviral activity of various 2-amino-3-nitropyrazole[1,5-α]pyrimidines and consequent drug design by means of QSAR.

The well established simplex representation of molecular structure (SiRMS) QSAR approach has been used to fulfil this objective. It allows the molecular design of new effective antiviral drugs. Thorough investigation of the relationship between: (a) cytotoxic (HeLa cells CC_{50}, μg/ml), (b) antiviral activity against the pleconaril-resistant clinical CVB3 isolate Nancy (IC_{50}, μg/ml) and (c) selectivity index (ratio of CC_{50} to IC_{50}) and the structure of 2-amino-3-nitropyrazole[1,5-α]pyrimidine derivatives have been carried out.

Statistic characteristics for PLS (Partial Least Squares) models are quite satisfactory ($R^2 = 0.96–0.99$, $Q^2 = 0.86–0.93$). The results are confirmed by experimental data. Structural fragments with positive or negative influence on antiviral activity as well as cytotoxicity and selectivity index have been determined on the base of these models. Additionally, obtained models provide the possibility to predict the antiviral activity and to design new well tolerated highly virus-specific drugs.

The analysis of competence regions for each QSAR model allows us to estimate additionally the quality of prognosis for all of designed compounds.

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Antiviral Activity of (−)-Carbocyclic Cytosine [(−)-Carbodine] Against Venezuelan Equine Encephalitis Virus (VEEV) in a Mouse Model

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C3H/HeN mice infected by intranasal (i.n.) installation with a vaccine strain (TC-83) of Venezuelan equine encephalitis virus (VEEV) have significant morbidity and mortality associated with disease. Intraperitoneal (i.p.) treatment of mice with enantiomerically pure (−)-carbocyclic cytosine [(−)-carbodine], previously shown to be active in vitro, administered bid −4 h