124
Synthesis, Antiviral and Cytotoxic Activities of SomeNovel 2,3-Disubstituted Quinazolin-4(3H)-Ones

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2-Phenyl-benzoxazin-4-ones were condensed with primary amine to form the 2,3-disubstituted quinazolin-4(3H)-ones. Their chemical structure was elucidated by means of spectral (FT-IR, ^{1}H NMR, MS) and elemental analysis. The antiviral activity and cytotoxicity of the compounds were tested in HeLa cells (vesicular stomatitis virus, Coxsackie virus B4 and respiratory syncytial virus), HEL cells [herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), vaccinia virus], Vero cells (parainfluenza-3, reovirus-1, Sindbis virus, Coxsackie virus B4 and Punta Toro virus). Among the new derivatives evaluated, specific antiviral activity was noted with compounds QAA against vaccinia virus, parainfluenza-3 virus and Punta Toro virus, QOPD against HSV-1, HSV-2 and vaccinia virus, and QONA and PD-NFIN against Coxsackie virus B4.

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125
Combined Anti-Influenza Virus Effects of a Plant Polyphenol-rich Extract and E-aminocaproic Acid *In Vitro* and *In Vivo*

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126
Differential Pathogenesis of Cowpox Virus Intranasal Infections in Mice Induced by Low and High Inoculum Volumes, and Effects of Cidofovir Treatment

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The causes of death from intranasal cowpox virus infections in mice remain unclear. Hypotheses include severe pneumonitis, hepatitis, and/or hyperproduction of cytokines and chemokines. We explored these hypotheses by studying the influence of low and high volume virus inoculums on viral pathogenesis, and examines the effects of cidofovir treatment on the infections. BALB/c mice were infected intranasally with a syncytium-forming variant of cowpox virus (Brighton strain) in 5- or 50-μl volumes containing the same infectious virus challenge dose; this resulted in different disease manifestations. The 50-μl infection produced a more rapidly lethal disease associated with severe pneumonitis, high lung and nasal virus titers, and increases in cytokine and chemokine levels in lungs and nasal tissue, while liver infection was minimal. The 5-μl inoculum infection was also lethal, but the infection was primarily confined to the upper respiratory tract, and included elevated cytokine and chemokine levels especially in nasal tissue. The pro-inflammatory cytokine, interleukin-6, was particularly high in both infections. Treatment of the infections with cidofovir (100 mg/kg/day for 2 days starting 24 h after virus exposure) led to survival and suppression of tissue virus titers. Treatment reduced pneumonitis in the 50-μl infection, and lessened cytokine hyperproduction in both types of infection. We conclude that 5-μl volume inoculum of cowpox virus results in a highly lethal infection restricted to the upper respiratory tract, with minimal pneumonitis, while the 50-μl inoculum leads to greater dissemination and more rapid lethality, with excessive release of systemic pro-inflammatory factors likely contributing to the accelerated time to death. Cidofovir effectively treated both infections and slowed viral replication sufficiently to subdue the exaggerated release of pro-inflammatory mediators.

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127
Herpes Simplex Virus Type 2 Exposed to Rigid Amphipathic Fusion Inhibitors (RAFIs) are not Infectious in a Mouse Vaginal Model

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We presented in 2007 a novel family of fusion inhibitors, nucleoside derivatives with rigid polyaryl substituents in position 5, which target the lipid bilayers of several otherwise unrelated DNA and RNA viruses to inhibit their fusion with cellular membranes. Structure-Activity-Relationship (SAR) analyses indicate that amphipathicity and "inverted cone" shape, together with rigidity, planarity, size and hydrophobicity of the aryl group, are all important for antiviral activity. We named the compounds rigid amphipathic fusion inhibitors (RAFIs). We now tested whether the most potent RAFI, dUY11 (IC_{50}, 20 nM; IC_{99}, 700 nM; SI> 7,500), inhibits vaginal infection with a sexually transmitted virus. Synchronized 4–6 week old female mice were vaginally infected with $1–3 \times 10^3$ infectious particles of HSV-2 strain 186. As expected, all 10 mice infected with vehicle exposed virus shed $\sim 10^4$ infectious virions on days 2–4, and lower amounts until day 8, showed severe clinical signs,