

International Conference on Flu

June 08-10, 2015 Chicago, USA

Design, synthesis and antiviral evaluation of phenyl piperazine containing benzyl trizole derivatives against pandemic swine flu (H1N1) influenza virus

Gaurav Joshi and Manmohan Parida

Defense Research & Development Establishment, India

The pandemic swine flu virus (H1N1pdm) continues to be a global health concern with the emergence of antigenically shifted highly virulent strains. The development of Oseltamivir and Nucleozin resistant strains has demanded for conserved antiviral target and novel drugs for control of H1N1pdm infection. The aim of this study was to screen phenyl piperazine containing benzyl trizole derivatives against H1N1pdm infection. Based on docking studies and structure activity relationship, a series of 14 nucleocapsid proteins (NP) antagonist (DC-3 to DC-16) were designed, synthesized using phenyl piperazine containing benzyl trizole as a lead molecule. These inhibitors were evaluated for their *in vitro* (in MDCK Cells) and *in vivo* (in BALB/c mice) antiviral efficacy against H1N1pdm virus through various assay. Among all the molecules, DC-12 was the most potent inhibitor with IC₅₀ value 4.6±0.23 μM with a selectivity index 15.5 better than Nucleozin, the known NP antagonist. The protective efficacy of DC-12 was further established through reduction in viral nucleocapsid mRNA and protein expression. Moreover, the treatment of BALB/c mice with DC-12 following infection resulted in reduced pathogenesis as indicated through increased survivability and more than 99.9% reduction in lung viral titre. Furthermore, the docking analysis and *in vitro* drug resistance test also confirmed that DC-12 not only assumes more favourable conformation at the binding pocket of NP but also overcome the problem of Nucleozin resistance. These findings clearly suggested that DC-12 is a promising small molecule inhibitor for control of H1N1pdm virus including the newly emerged drug resistance strains.

gjoshi13@gmail.com

Metered dose inhaler containing aprotinin, a protease inhibitor as a drug against influenza

Oleg P Zhirnov¹, Elena I Isaeva¹, Natasha O Bokova² and Nikolai A Malyshev²

¹The D I Ivanovsky Institute of Virology, Russia

²Moscow Infectious Clinics N1, Russia

Influenza virus is activated by host respiratory proteases to maintain infection in respiratory epithelium and pathogenesis of disease. Inhalations of aprotinin, a natural protease inhibitor, were found to provide therapeutic effect in influenza. Antiviral efficacy of inhalations of aprotinin aerosol generated by meter dose manual inhaler (MDI) was studied in influenza patients. Clinical trials were performed during outbreak in Moscow region caused with pandemic Influenza H1N1pdm09 virus. Propellant type MDI (AerusTM, Russia) containing aprotinin as an active substance was used. Patients inhaled nasally 2 aerosol doses of aprotinin (160 Kallikrein-inhibiting Units (KIU)) each 2 hours for 5 days. In comparison group, patients were treated with ingavirinTM (a synthetic peptidoamine with unknown antiviral target), 90 mg per day for 5 days. On day 2 after treatment virus loads in nasal-pharyngeal washes were determined by real time PCR. Because amounts of host cells in nasopharyngeal washes varied from patient to patient, amounts of viral RNA were normalized to host ribosomal 18S RNA determined by real time PCR with human ribosome specific primers. About 10 fold decrease of virus load in aprotinin patients were determined in comparison to ingavirin patients. Duration of clinical symptoms such as headache, sore throat, cough, sore thorax, rhinorrhea, weakness and fever was 1-2 days shorter in aprotinin than in ingavirin group. About 35 patients were observed and no side effects were documented in aprotinin-treated patients. Aprotinin MDI can be recommended as a drug of choice against influenza caused by different viruses because phenomenon of virus activation by host proteases is a major pathogenesis mechanism in all influenza viruses.

zhirnov@inbox.ru