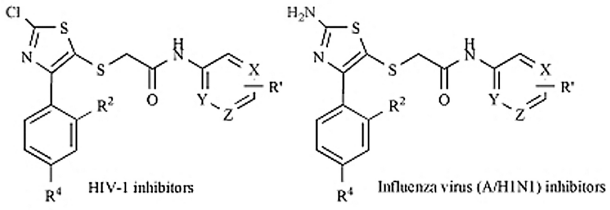
150

Thiazolylthioacetamides as a Novel Class of Potential Antiviral Agents

Peng Zhan[1,*], Xuwang Chen[1], Xinyong Liu[1], Christophe Pannecouque[2], Lieve Naesens[2], Erik De Clercq[2], Ailin Liu[3], Guanhua Du[3]

[1] *Department of Medicinal Chemistry, School of Pharmaceutical Sciences, ShanDong University, Ji'nan, China*
[2] *Rega Institute for Medical Research, Minderbroedersstraat, Belgium*
[3] *Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

In continuation of our endeavor to develop new, potent, and less toxic antiviral agents, a novel series of 2-amino/chloro substituted thiazolylthioacetamide derivatives have been synthesized and evaluated for in vitro anti-HIV activities in MT-4 cells for inhibition of the wild-type HIV-1 (strain IIIB), clinically relevant mutant HIV-1 strains, and HIV-2 (strain ROD). The bioactivity results showed that three compounds possessed potent activity against wild-type and several key mutant strains (E138K, K103N, L100I) of HIV-1 with EC50 values in submicromolar range. Based on the chemical structures, these molecules can be proposed to act as HIV-1 NNRTIs. Meanwhile, these 2-amino/chloro substituted thiazole derivatives were also evaluated for anti-influenza virus activities in Madin-Darby canine kidney (MDCK) cells infected with different strains of human influenza virus (A/H1N1, A/H3N2 and B viruses). Encouragingly, two derivatives A8g and A8h within 2-amino substituted thiazole series inhibit the influenza A/H1N1 replication with EC50 much lower than that of oseltamivir carboxylate, ribavirin, amantadine and rimantadine. However, no activity was observed for A/H3N2 and B viruses. Additionally, compounds A8g and A8h showed almost no activity in the neuraminidase (H1N1) inhibition assay, thus pharmacological studies are in progress to confirm their mechanism of action.



Newly synthesized thiazolylthioacetamide derivatives

doi:10.1016/j.antiviral.2011.03.136

151

Antiviral Effectivity of Ceria Colloid Solutions

Nadiya Zholobak[1,*], Alexander Shcherbakov[1], Vladimir Ivanov[2], Zoya Olevinskaya[1], Nikolay Spivak[1]

[1] *Zabolotny Institute of Microbiology and Virology NASU, Kiyv, Ukrenia*
[2] *Kurnakov Institute of General and Inorganic Chemistry, Moskow, Russia*

Nanotechnology is one of the fast developing areas of industry and science. Substances having novel and unexpected properties are created basing on its principles. One of the most interesting objects of nanotechnology is nanocrystal cerium dioxide (NCD). NCD of 1–3 nm has minimal toxicity, participates in redox processes and has regenerative ability like enzymes. The mentioned properties depend on the precursor, the method of synthesis of nanoparticles, the used stabilizers, etc. We have created the NCD nanoparticles of such dimensions, stabilized them by sodium/ammonium polyacrylate (PAA) or citrate and investigated their cytotoxicity and influence on viral reproduction and cytopathic action in the cell cultures L929, EPT, VERO. The minimal diagnostic cytotoxic effect has been determined for NCD stabilized by citrate 10 mM. For PAA-stabilized nanoparticles the toxicity decreases from the mice cells to the primates ones. The antiviral activity of synthesized nanoparticles in the systems of L929/VSV and RF/HSV-1 was determined. It was shown, that in prophylactic (24 h before infecting) scheme PAA-stabilized NCD forms antiviral resistance in working concentrations 0.1–0.01 mM. In vitro citrate-stabilized nanoceria forms virus-resistant condition both in prophylactic and therapeutic (1 h after infecting) schemes, and also demonstrates a significant virucidal effect, reducing the virus titer in the investigated model systems into 2.6–4.8 lg. It is well-known, that the violation of the redox balance against viral infection is accompanied by the development of pathologic intracellular processes. The abilities to adjust ROS level and to inhibit the development of oxidative degradation are the main properties of NCD, which, in turn, affect the way of a cascade of the intracellular regulatory processes. Thus, the nanoceria ensures the survival of the infected cells. The obtained results are very interesting, because they open the prospect for further in-depth study of the synthesized aqueous sols of NCD for their future practical applications both for prevention and treatment of viral infections.

doi:10.1016/j.antiviral.2011.03.137

152

Computer-aided Design and Evaluation of Novel Anti-CHIKV Compounds

Marcella Bassetto[1,*], Tine De Burghgraeve[2], Pieter Leyssen[2], Johan Neyts[2], Andrea Brancale[1]

[1] *The Welsh School of Pharmacy, Cardiff University, Cardiff, United Kingdom*
[2] *Rega Institute for Medical Research, Leuven, Belgium*

Chikungunya virus (CHIKV) is a mosquito-borne alphavirus with a single-stranded, positive-sense RNA genome. This pathogen is responsible for outbreaks of febrile arthralgia in humans. Recent cases of CHIKV infections have been recorded in Asia, Africa and Europe. To date, no antiviral drugs are available for the treatment of infections with this important emerging virus. The viral genome encodes four non-structural proteins (nsP), which could be considered potential antiviral targets. In particular the nspP2 is a protease involved in the processing of the non-structural polyprotein, an important step in viral replication. Based on the previously developed homology model of the CHIKV nsP2, we have performed a series of molecular modeling simulations to find a possible inhibitor of this enzyme. Initially we have carried out a virtual screening simulation using a database of 350,000 compounds, and we have identified one compound which prevented virus-induced cell death at low μM concentration. In order to optimize this hit, we carried out a series of molecular dynamics simulations on the nsP2/natural substrate and nsP2/hit complexes. Based on these studies we have selected a new series of compounds to be tested versus the CHKV. In this presentation we will discuss the results obtained and the initial SARs of these compounds.

doi:10.1016/j.antiviral.2011.03.138