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Study of Anti-Epstein–Barr Virus Activity of Novel Fluorinated Heterocyclic Nucleoside Analogues

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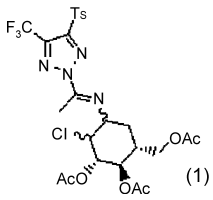
Although a number of the antiviral drugs can inhibit EBV replication, none of them has been licensed for the treatment of EBV infection in the clinic [1]. Search of new effective preparations capable to inhibit herpesviruses reproduction is conditioned by their certain resistance to different groups of chemical preparations. Synthesis of nucleoside analogues with triazole substituents which could be used as pharmaceuticals are of great interest [2]. We prepared new fluorinated 1,2,3-triazole derivatives (1–3) (Fig. 1) and studied their antiEBV activity. The activity of triazole substituents against EBV—lymphotropic and oncogenic virus was the object of present investigation. The line of lymphoblastoid B-cells Raji was used as a model of EBV-infection in vitro. The analysis of cytotoxicity of substances for cell line Raji was first stage of their investigation. They were studied in concentrations of 1000–1 μg/ml. In 48 h the MTT-analysis of investigated samples was conducted. The concentrations which inhibited the quantity of alive cells on 50% (CD_{50}) were for substance No. 1 – 600 μg/ml, No. 2 – 255 μg/ml and No. 3 – 800 μg/ml. An inhibition of reproduction of EBV in a cell culture was determined by reduction of a accumulation of the virus capsid antigen proteins on a cell. The anti-virus activity was determined by a cellular ELISA method, using Mab to VCA EBV (AbD Serotec, GB). Drugs were investigated in concentrations 100–0.1 μg/ml. The analysis of obtained data allowed to determine concentrations, which oppressed the accumulation of the virus proteins on 50 %. ED_{50} for No. 1 and No. 3 was 10 μg/ml, for No. 2 – 50 μg/ml. Thus, proceeding from the index of selectivity for the compound No. 1 – 60, No. 3 – 80, it is possible to make a conclusion about their availability for the further researches as of drugs that are active against an EBV.



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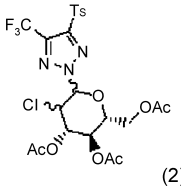

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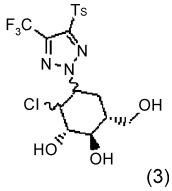

(3)

References

Gershburg, E., Pagano, J., 2005. Journal of Antimicrobial Chemotherapy 56, 277–281.

Joubert, N., Schinazi, R., Agrofoglio, L., 2005. Tetrahedron 61, 11744–11750.

doi:10.1016/j.antiviral.2009.02.113

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Induction of Lytic Cytotoxicity by NF-(B Inhibitors in Epstein-Barr Virus-associated Gastric Carcinoma Cells

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Epstein-Barr virus (EBV) has been associated with epithelial malignancies like nasopharyngeal carcinoma (NPC), lymphoepitheliomas of several organs, and recently, it has been linked to gastric carcinoma (GC). Worldwide, EBV-associated GC represents about 10% of GC. EBV is found in every tumor cell in EBV-positive cancers, but not in normal cells, suggesting that EBV targeted strategies could be used to treat these tumors. EBV infection in tumor cells is generally restricted to the latent forms of viral infection. The antiviral nucleoside analogue ganciclovir (GCV) has been successful in eradicating virus-infected cells with the lytic, but not the latent, form of EBV. The switch from the latent to the lytic form can be induced by expression of either one of two immediate-early gene products, BZLF1 and BRLF1. Both genes are able to induce the entire program of lytic EBV gene expression. High levels of nuclear factor (NF)-(B can inhibit EBV lytic replication, suggesting that NF-(B inhibitors might reactivate the viral lytic cycle. In this study, we tested the effects of NF-(B inhibitors on inducing EBV lytic infection. We found that NF-(B inhibitors, including acetylsalicylic acid, induced the expression of the lytic genes BZLF1, BRLF1 and BMRF1, in an EBV-positive GC cell line. Cells exhibited decreased viability in a dose- and time-dependent manner when incubated with NF-(B inhibitors. In contrast, there was no significant effect on EBV-negative GC cells. The combination of GCV and NF-(B inhibitors enhanced the cytotoxic effect of GCV after lytic induction by NF-(B inhibitors. In conclusion, the combination of NF-(B inhibitors with anti-viral nucleoside analogues might be a useful therapeutic strategy for EBV-associated human gastric cancer.

doi:10.1016/j.antiviral.2009.02.114

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Anti-cytomegalovirus Activity of Membranotropic Polyacidic Agents Effects In Vitro

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The human cytomegalovirus (CMV) is the infectious agent lethally danger at HIV/AIDS and other immunodeficiency states. The carboxy-mimickers of polymeric backbone of nucleic acids, potential agonists (antiviral responses stimulators) or antagonists for viral genomes, were developed as promising candidates to multifunctional antiviral protecting counter-agents (AVA). The AVA membrane-tropic derivatives as have been shown [Antiviral Res. 1999–2007] are able efficiently prevent infecting the cells by various HIV-1 strains. Here we present and discuss the new data in focus of AVA modification by the cage-hydrocarbon and/or sulfoacidic pharmacophores and followed evaluation on the CMV infection experimental models in vitro (fig/tab). Within the tested AVA the active modifications were detected as the efficient inhibitors of CMV with high selectivity indexes up to 250, 4286 and 7500 at the prophylactic, therapeutic, and viricidal experimental schemes