proceedings

Abstract

FDA Approved Drugs Efavirenz, Tipranavir, and Dasabuvir Inhibit Replication of Multiple Flaviviruses In Vitro †

Michal Stefanik [1,2,*], Fortunatus C Ezebuo [3], Jan Haviernik [1,4], Ikemefuna C. Uzochukwu [3], Martina Fojtikova [1], Jiri Salat [1], Ludek Eyer [1,5] and Daniel Ruzek [1,5]

[1] Department of Virology, Veterinary Research Institute, Hudcova 70, CZ-62100 Brno, Czech Republic; haviernik@vri.cz (J.H.); fojtikova@vri.cz (M.F.); salat@vri.cz (J.S.); eyer@vri.cz (L.E.); ruzekd@paru.cas.cz (D.R.)
[2] Department of Chemistry and Biochemistry, Mendel University in Brno, Zemedelska 1, CZ-613 00 Brno, Czech Republic
[3] Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, PMB 5025 Awka 420281, Nigeria; fc.ezebuo@unizik.edu.ng (F.C.E.); ic.uzochukwu@unizik.edu.ng (I.C.U.)
[4] Faculty of Science, Masaryk University, Kamenice 5, 625 00 Brno, Czech Republic
[5] Institute of Parasitology, Biology Centre of the Czech Academy of Sciences, Branisovska 31, CZ-37005 Ceske Budejovice, Czech Republic
* Correspondence: michal.stefanik2@gmail.com
† Presented at Viruses 2020—Novel Concepts in Virology, Barcelona, Spain, 5–7 February 2020.

Published: 2 June 2020

Abstract: Arthropod-borne flaviviruses such as tick-borne encephalitis virus (TBEV), West Nile virus (WNV), Zika virus (ZIKV), Dengue virus (DENV), and yellow fever virus (YFV) cause several serious life-threatening syndromes (encephalitis, miscarriages, paralysis, etc.). No effective antiviral therapy against these viruses has been approved yet. We selected, via in silico modeling, 12 U.S. Food and Drug Administration (FDA)-approved antiviral drugs (paritaprevir, dolutegravir, raltegravir, efavirenz, elvitegravir, tipranavir, saquinavir, dasabuvir, delavirdine, maraviroc, trifluridine, and tauroursodeoxycholic acid) for their interaction with ZIKV proteins (NS3 helicase and protease, non-structural protein 5 (NS5) RNA-dependent RNA polymerase, and methyltransferase). Only three of them were active against ZIKV, namely, dasabuvir (ABT-333), efavirenz, and tipranavir. These compounds inhibit virus replication of ZIKV (MR-766 and Paraiba_01) in Vero cells; therefore, we tested these compounds against other medically important flaviviruses WNV (13-104 and Eg101) and TBEV (Hypr). Dasabuvir was originally developed as an antiviral drug against hepatitis C virus (HCV); tipranavir and efavirenz are used for treating human immunodeficiency virus (HIV) infection. The antiviral effects of efavirenz, tipranavir, and dasabuvir were tested for ZIKV in HUH-7, astrocytes (HBCA), and UKF-NB-4 cells, where we also identified a significant inhibition effect of these compounds. For Vero cells, efavirenz inhibited all investigated viruses with EC_{50} ranging from 9.70 to 29.26 μM; the tipranavir inhibition effect was from 16.19 (WNV 13-104) to 27.47 μM (TBEV), while the strongest and most robust antiviral effect was demonstrated in the case of dasabuvir (EC_{50} values ranging from 9.09 (TBEV) to 10.85 μM (WNV 13-104)). These results warrant further research of these drugs, either individually or in combination, as possible pan-flavivirus inhibitors.

Keywords: flaviviruses; dasabuvir; tipranavir; efavirenz; antiviral drug