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Pre-clinical characterization of AV5080, a new oral influenza neuraminidase inhibitor, active against oseltamivir-resistant virus

This study is focused on the discovery and development of new oral small molecule influenza neuraminidase inhibitors, L active against Oseltamivir-resistant virus strains. A number of compounds was designed, synthesized and evaluated for antiviral properties in vitro and in vivo. A 3D Molecular docking, assisted by a pharmacophore model, was applied to rank compounds within different series by the predicted antiviral potency. The most promising compound, AV5080[(3R,4R,5S)-5-[(diaminomethylene)amino]-3-(1-ethylpropoxy) 4[(fluoroacetyl)amino]cyclohex-1-ene-1-carboxylic acid], is currently in pre-clinical development for treatment of influenza. This compound was stable in rat, dog and human plasma (>93% remaining after 24 h). AV5080 demonstrated picomolar activity against influenza neuraminidase in vitro, similar or better than Oseltamivir (the IC50 values of 0.03 nM and 0.07 nM against NA of A/duck/Minnesota/1525/1981, H5N1, and A/ Perth/265/2009, H1N1, 275H, respectively). In the influenza-infected cultured MDCK cells, this compound demonstrated high potency against influenza strains A and B (EC90 = 0.71 ± 0.24 nM, 28 times lower than that for Oseltamivir against A/California/07/2009/H1N1 isolate). Most importantly, AV5080 was highly active against Oseltamivir-resistant influenza strains. The efficacy of AV5080 in mice, challenged with a lethal dose of A/Aichi/2/1969/H3N2 isolate, was similar to that of Oseltamivir (90% and 100% survival rate at 25 mg/kg dose). In the safety pharmacology studies with AV5080 in vitro and in vivo (AMES test, chromosomal aberration, hERG test), no signs of geno-or cardiotoxicity was observed. In summary, AV5080 is a promising novel oral drug candidate for treatment of influenza, including Oseltamivir-resistant virus strains. Further preclinical development of AV5080 is warranted.

Biography

Vadim Bichko is Vice President and Head, Infectious Diseases at ChemDiv, Inc. (San Diego, US). He also serves as a Chief Scientific Officer of Viriom, Ltd. (US), a ChemDiv-Roche Alliance company, developing HIV and HBV antivirals. He received his PhD in Molecular Biology in 1986 from the University of Latvia in Riga, Latvia, and subsequently held various academic positions at Fox Chase Cancer Center in Philadelphia, US, Max-Plank Institute for Biochemistry in Munich, Germany, and the Institute of Organic Synthesis in Riga, Latvia. He is the author of numerous publications and patents in molecular virology.

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