Abstract ID : **97**

Prodrugs of the Phosphoribosylated Forms of Hydroxypyrazinecarboxamide Pseudobase T-705 and its De-Fluoro-Analogue T-1105 as Potent Influenza Virus Inhibitors

Content

The nucleobase analogue T-705 (6-fluoro-3-hydroxy-2-pyrazinecarboxamide; favipiravir) is a unique antiviral drug possessing broad anti-RNA virus activity and a high barrier for resistance. When we compared the influenza virus inhibition by T-705 and its non-fluorinated analogue T-1105, the latter proved to be four-fold more potent in Madin-Darby canine kidney (MDCK) cells. In an enzymatic RNA elongation assay with influenza virus-derived viral ribonucleoproteins, T-1105 ribosyl 5'-triphosphate (RTP) was even six-fold superior to T-705 RTP (IC50 values: 0.48 μM vs. 2.7 μM) in inhibiting GTP incorporation into viral RNA.

We previously reported (Naesens et al., Mol Pharmacol 84, 615-629, 2013) that human hypoxanthine guanine phosphoribosyltransferase (HGPRT) is crucial to convert T-705 and T-1105 into their ribosyl-5'-monophosphates which are then further phosphorylated to the active RTP metabolites. Since both pyrazine derivatives are poor HGPRT substrates, we applied our DiPPro and TriPPPro prodrug approaches to increase the intracellular RTP levels.

We demonstrated efficient T-1105-RDP- and -RTP-release from the DiPPro- and TriPPPro-compounds by esterase activation. Using crude enzyme extracts, we saw rapid phosphorylation of T-1105-RDP into T-1105-RTP. In sharp contrast, phosphorylation of T-1105-RMP was not seen, indicating a yet unrecognized bottleneck in T-1105's metabolic activation. Accordingly, DiPPro- and TriPPPro-compounds displayed improved cell culture activity against influenza A and B virus, which they retained in HGPRT-deficient MDCK cells, indicating that they release a phosphoribosylated metabolite inside the cells. DiPPro-T-1105-RDP showed four-fold higher potency in suppressing one-cycle viral RNA synthesis versus T-1105. Hence, our T-1105-RDP- and -RTP-prodrugs improve antiviral potency and achieve efficient metabolic bypass.

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Vaccines and antivirals

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Comments:

Two weeks ago, I submitted another abstract entitled "Aniline-based inhibitors of influenza H1N1 virus acting on hemagglutinin-mediated fusion" (assigned id #72) as poster presentation. In case you would like me to select one abstract, I prefer this one entitled "Prodrugs of the Phosphoribosylated Forms of Hydroxypyrazinecarboxamide Pseudobase T-705 and its De-Fluoro-Analogue T-1105 as Potent Influenza Virus Inhibitors"