Favipiravir ProTides: Enhancing Antiviral Efficiency Against Various Viruses

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Favipiravir, a broad-spectrum antiviral, has gained attention during the COVID-19 pandemic. It is a prodrug that converts into active favipiravir ribofuranosyl-5'-triphosphate (favipiravir-RTP) through intercellular ribosylation and phosphorylation. Favipiravir-RTP functions as an RNA-dependent RNA polymerase (RdRp) inhibitor, interrupting viral replication through chain termination or mutations. Although previous studies have demonstrated desired activities against the influenza virus (New ReF), another study has indicated low activity of favipiravir against SARS-CoV-2.[1] To enhance the efficacy of favipiravir, we explored the application of Prodrug nucleotides, also known as ProTides technology, which serves as an effective approach for intracellular delivery of nucleoside monophosphates.[2] In this study, we presented novel derivatives of Favipiravir-ProTides and evaluated their antiviral activity against SARS-CoV-2, influenza, and additionally, the dengue virus. We synthesized Favipiravir-ribonucleoside and a series of novel Favipiravir-ProTide derivatives with varying amino acid ester moieties. Among these derivatives, **BION-141**, a ProTide derivative containing a 2-ethylbutyl group, exhibited notable activity against SARS-CoV-2 and dengue virus, while favipiravir and favipiravir-ribonucleoside did not demonstrate significant activity. However, when assessing the inhibitory activities against influenza virus, **BION-141** unexpectedly displayed lower potency than the parent compound favipiravir. This result implies the existence of confounding factors or off-target mechanisms that differ among various viruses and host cells.[3] **BION-141** was not toxic to Calu-3 and HaCaT cells. Furthermore, we conducted further investigations and explorations of the activities of novel derivatives at the X group as part of the lead optimization process. These efforts could lead to the development of a more effective favipiravir-ProTides as a pan-antiviral agent.

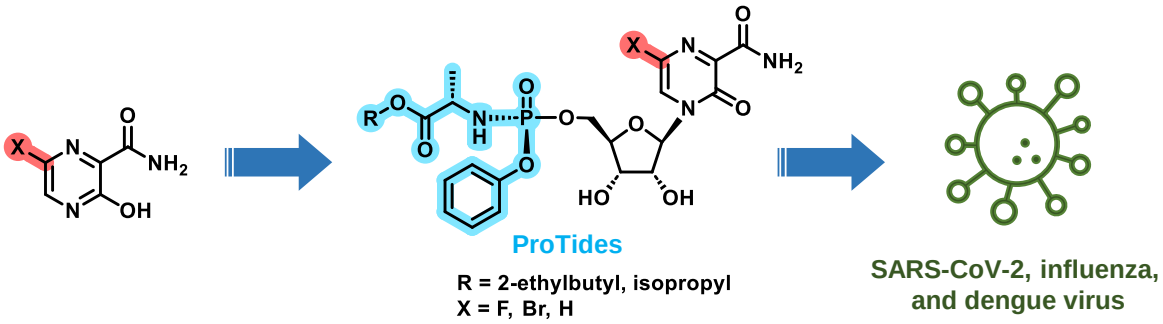

Figure 1. Structure of favipiravir-ProTide derivatives.

References
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