New Antiviral Drugs from Bacterial Natural Products

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Overview

The increasing incidence of viral infections across the globe is driving the demand for antiviral drugs. Prof. Rotem Sorek and his team identified a new family of bacterial enzymes that produce various nucleotide analogs with antiviral properties (Bernheim, Nature 2021). With further chemical modifications, these molecules were shown to have potent antiviral activity against several human viruses for which no other drug is available. Notably, the active molecules were found to be stable in human plasma, and experiments in animal models showed no adverse effects upon IV/PO administration.

Background and Unmet Need

The increasing incidence of viral infections across the globe is driving the demand for new antiviral drugs. Although antiviral drugs are currently available for some viral infections, there is still no effective treatments for many viruses. Many of the approved antiviral drugs target the viruses by inhibiting virus-specific enzymes, such as the viral polymerase, integrase, and protease. Drugs that inhibit the viral DNA polymerase (i.e., acyclovir, tenofovir, valganciclovir, and valacyclovir) or RNA-dependent RNA polymerase (i.e., Remdesivir) are frequently nucleotide/nucleoside analogs that can induce chain termination or hyper mutation in the viral nucleic acids. Nucleotide/nucleoside analogs are crucial components of the antiviral medicinal chemistry arsenal, and new analogs that effectively inhibit viral infections with minimal side effects are constantly sought after.

The Solution

Prof. Rotem Sorek and his team identified a family of bacterial enzymes that produce novel modified nucleotides. These are naturally produced by bacteria to fend off viruses that infect them. The team demonstrated that chemically modified versions of these molecules have potent antiviral activity, high stability in serum, and no adverse effect in animal models.

Technology Essence

The bacterial enzymes identified by the Sorek team modify normal ribonucleotides into their 3â€²-deoxy-3â€²,4â€²-didehydro (ddh) NTP versions. While one of these modified nucleotides is known to be naturally produced by human cells to curb infections, several molecules identified by Sorek were not described before. Using new, IP-protected synthesis routes, the team produced the molecules as prodrugs, and tested their antiviral efficacy against multiple viruses. They demonstrated antiviral activity against several viruses for which no known drug is available. Furthermore, the molecules were shown to be stable in human and rat plasma. Experiments in vivo revealed no adverse effects upon IV/PO administration to rats.

Applications and Advantages

- New antiviral drugs, antiviral activity demonstrated in multiple assays.
- Stable in human and rat plasma
- No adverse events upon IV/PO administration to rats
- Organic synthesis of novel non-natural nucleotide analogs and their prodrug versions (IP-protected)
- Potentially improved potency, bioconversion, and pharmacokinetic properties, with low toxicity

References

Â Â Bernheim A, Millman A, Ofir G, et al. s. *Nature*. 2021;589(7840):120-124. doi:10.1038/s41586-020-2762-2 [1]

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