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Small molecule inhibitors of viral polymerases: A new era in antiviral design.

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Introduction

The emergence and re-emergence of viral pathogens—from HIV and hepatitis viruses to influenza and coronaviruses—have underscored the urgent need for effective antiviral therapies. Central to the replication of most viruses is the activity of viral polymerases, enzymes responsible for synthesizing viral RNA or DNA. These polymerases are attractive drug targets due to their essential role in viral propagation and their structural divergence from host polymerases. In recent years, the development of small molecule inhibitors targeting viral polymerases has ushered in a new era of antiviral design, offering potent, selective, and often broad-spectrum therapeutic options [1].

Viral polymerases include RNA-dependent RNA polymerases (RdRp), DNA-dependent DNA polymerases, and reverse transcriptases. These enzymes catalyze the replication of viral genomes and are often error-prone, contributing to viral evolution and drug resistance. Their unique structural motifs and catalytic mechanisms make them ideal targets for small molecule inhibitors that can block replication without affecting host enzymes [2].

HIV reverse transcriptase is targeted by nucleoside and non-nucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs). HCV RdRp is inhibited by drugs like sofosbuvir. SARS-CoV-2 RdRp is targeted by remdesivir and molnupiravir. These mimic natural nucleotides and are incorporated into viral RNA or DNA, causing chain termination or mutations. A uridine analogue that inhibits RdRp by chain termination. An adenosine analogue that causes delayed chain termination. A nucleotide analogue that inhibits reverse transcriptase. These drugs often require intracellular phosphorylation to become active and may exhibit broad-spectrum activity. These bind to allosteric sites on polymerases, altering enzyme conformation and function. Binds to a hydrophobic pocket in reverse transcriptase. Targets the palm domain of NS5B polymerase [3].

Non-nucleoside inhibitors offer high specificity but may be more susceptible to resistance mutations. These mimic the pyrophosphate released during nucleotide incorporation and inhibit polymerase activity. A broad-spectrum inhibitor of DNA polymerases. Though effective, these agents can be nephrotoxic and are typically reserved for resistant infections. Advances in structural biology have revolutionized antiviral design. High-resolution crystal structures and cryo-electron microscopy have revealed the active sites and conformational dynamics of viral polymerases, enabling rational drug design. The structure of SARS-CoV-2 RdRp bound to remdesivir has guided the development of next-generation inhibitors. HIV reverse transcriptase structures have informed the design of NNRTIs with improved resistance profiles. Structure-based drug design allows for the optimization of binding affinity, selectivity, and pharmacokinetics. Some small molecule inhibitors exhibit activity against multiple viruses due to conserved polymerase motifs. This broad-spectrum potential is especially valuable during outbreaks of novel or re-emerging viruses. Active against influenza, Ebola, and SARS-CoV-2 by inducing lethal mutagenesis. A ribonucleoside analogue with activity against a range of RNA viruses. Broad-spectrum antivirals can serve as first-line defenses during pandemics, buying time for vaccine development and targeted therapies. Viral polymerases are prone to mutations, leading to drug resistance. Resistance can arise from changes in the

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active site or allosteric regions that reduce drug binding [4].

New inhibitors are being designed to retain efficacy against resistant strains by targeting conserved regions or using novel mechanisms. AI-driven drug discovery platforms are accelerating the identification of polymerase inhibitors by predicting binding affinities and optimizing lead compounds. Prodrugs enhance bioavailability and tissue penetration. For example, tenofovir alafenamide delivers active tenofovir more efficiently than its predecessor. Nanoparticles and liposomes are being explored to deliver polymerase inhibitors directly to infected tissues, reducing systemic toxicity [5].

Conclusion

Small molecule inhibitors of viral polymerases represent a cornerstone of modern antiviral therapy. Their ability to disrupt essential viral functions with precision has led to dramatic improvements in patient outcomes and public health. As structural insights deepen and drug design technologies evolve, the next generation of polymerase inhibitors promises to be more potent, selective, and resilient against resistance. In the ongoing battle against viral diseases, these molecules are leading the charge into a new era of antiviral innovation.

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