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Review IJEM

Exploring Antiviral Organic Compounds

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Abstract

Antiviral drugs are a class of medication used for treating viral infections. Most antivirals target specific viruses, while a broad-spectrum antiviral is effective against a wide range of viruses. Antiviral drugs are a class of antimicrobials, a larger group which also includes antibiotic (also termed antibacterial), antifungal and antiparasitic drugs or antiviral drugs based on monoclonal antibodies. Most antivirals are considered relatively harmless to the host, and therefore can be used to treat infections. They should be distinguished from virucides, which are not medication but deactivate or destroy virus particles, either inside or outside the body. Natural virucides are produced by some plants such as eucalyptus and Australian tea trees.

Keywords: Antiviral drugs, antiparasitic drugs, antifungal, antibacterial

INTRODUCTION

Viruses cause numerous diseases in humans, animals, and plants. Despite medical advances, the development of effective and safe antiviral drugs remains a significant challenge. The exploration of organic compounds offers an opportunity to develop drugs that target different stages of the viral life cycle, such as viral attachment to the cell, gene replication and the action of key viral proteins like polymerases and proteases. Antiviral agents are essential for controlling viral infections because they interfere with viral replication and assembly using various mechanisms. These mechanisms include inhibiting the virus's entry into the host cell, blocking the synthesis of viral genetic material or proteins, preventing the assembly of new viral particles, and stopping the release of viruses from the host cell [1-6].

LITERATURE REVIEW

Approved Antiviral Drugs Over the past 50 Years

The first antiviral drug, idoxuridine, was approved in 1963.

About 90 antiviral drugs categorized into 13 functional groups have been formally approved for the treatment of the following 9 human infectious diseases [7–9].

- HIV infections (protease inhibitors, integrase inhibitors, entry inhibitors, nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and acyclic nucleoside phosphonate analogues).
- hepatitis B virus (HBV) infections (lamivudine, interferons, nucleoside analogues, and acyclic nucleoside phosphonate analogues).
- hepatitis C virus (HCV) infections (ribavirin, interferons, NS3/4A protease inhibitors, NS5A inhibitors, and NS5B polymerase inhibitors).
- herpesvirus infections (5-substituted 2′-deoxyuridine analogues, entry inhibitors, nucleoside analogues, pyrophosphate analogues, and acyclic guanosine analogues).

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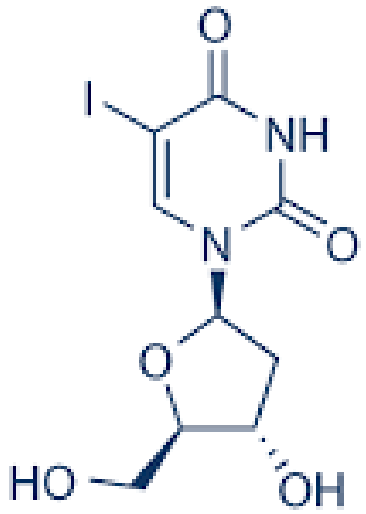
- influenza virus infections (ribavirin, matrix 2 protein inhibitors, RNA polymerase inhibitors, and neuraminidase inhibitors).

- human cytomegalovirus infections (acyclic guanosine analogues, acyclic nucleoside phosphonate analogues, pyrophosphate analogues, and oligonucleotides).
- varicella-zoster virus infections (acyclic guanosine analogues, nucleoside analogues, 5-substituted 2′-deoxyuridine analogues, and antibodies).
- respiratory syncytial virus infections (ribavirin and antibodies).
- external anogenital warts caused by human papillomavirus infections (imiquimod, sinecatechins, and podofilox).



Idoxuridine

Classification of Antiviral Compounds

Antiviral organic compounds can be classified into

- Viral entry inhibitors: such as heparin sulfate.
- Polymerase inhibitors: such as acyclovir.
- Protease inhibitors: such as ritonavir.
- Integrase inhibitors: such as raltegravir.
- The antiviral Nitazoxanide [3].

Structures of these compounds are shown in Figure 1.

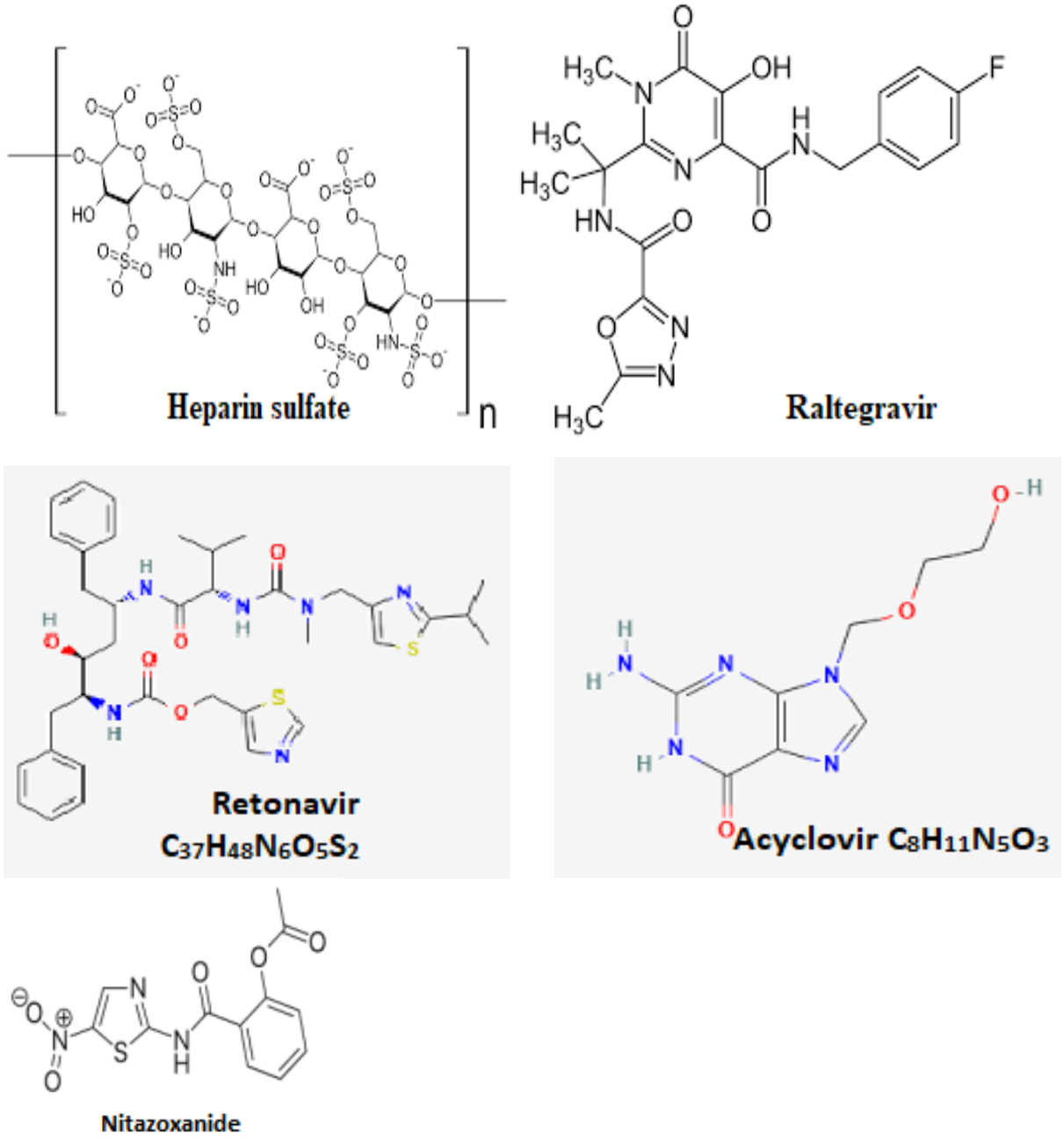


Figure 1. Antiviral organic compounds.

Coronaviruses And Drug Discovery

In humans, infections with the human coronavirus (HCoV) strains HCoV-229E, HCoV-OC43, HCoV-NL63 and HCoV-HKU1 usually result in mild, self-limiting upper respiratory tract infections, such as the common cold. By contrast, the CoVs responsible for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), which were discovered in Hong Kong, China, in 2003, and in Saudi Arabia in 2012, respectively, have received global attention over the past 12 years owing to their ability to cause community and health-care-associated outbreaks of severe infections in human populations. These two viruses pose major challenges to clinical management because there are no specific antiviral drugs available [8].

Sources of Antiviral Compounds

The preparation of antiviral drugs involves both natural extraction and chemical synthesis

- *Natural Extraction:* isolating bioactive compounds such as flavonoids, alkaloids, and terpenes from plants.
  - A good example of antiviral drug discovery derived from the natural sources came from the curcumin derivatives which were used against monkeypox and smallpox infection [7].
  - Another example was found when the antiviral effect of Australian tea tree oil (TTO) and eucalyptus oil (EUO) against herpes simplex virus was examined [6].
- *Synthetic Methods:* modifying chemical structures to improve antiviral activity and reduce toxicity (e.g., synthesis of remdesivir and favipiravir).
- *Biotechnological Approaches:* using recombinant DNA technology to design molecules that target specific viral enzymes.

Examples of Synthesis of Antiviral Drugs

Synthesis of Favipiravir

Favipiravir (T-705) is a pyrazinecarboxamide derivative developed as a broad-spectrum antiviral drug. It is prepared from pyrazine or pyrazinone precursors by introducing amide and carboxamide functional groups, followed by controlled oxidation and amination steps to form the ribofuranosyl analogue. The active compound is then phosphorylated inside host cells to its active form, Favipiravir-RTP (Figure 2).

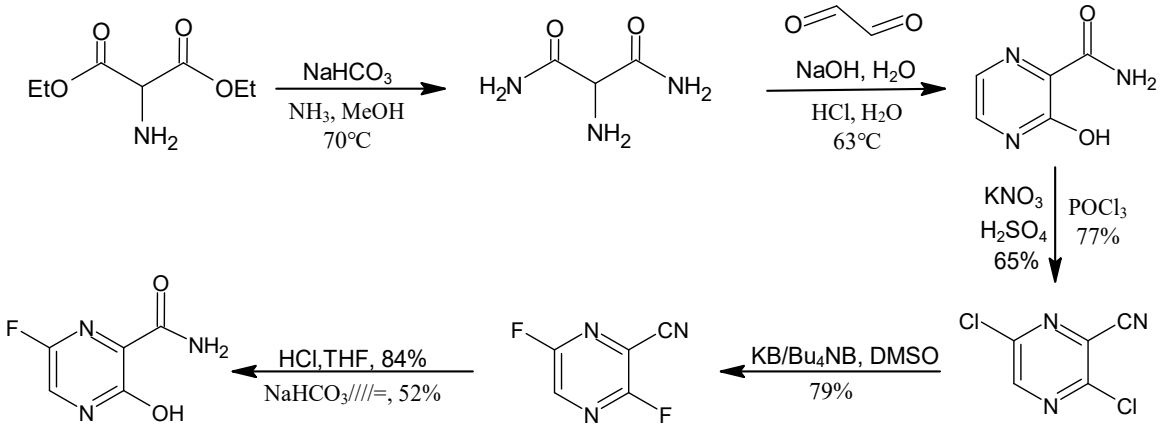


Figure 2. Synthesis of Favipiravir.

Synthesis of Remdesavir Which was originally developed to treat hepatitis C, and was subsequently investigated for Ebola virus disease and Marburg virus infections before being studied as a post-infection treatment for COVID-19 (Figure 3).

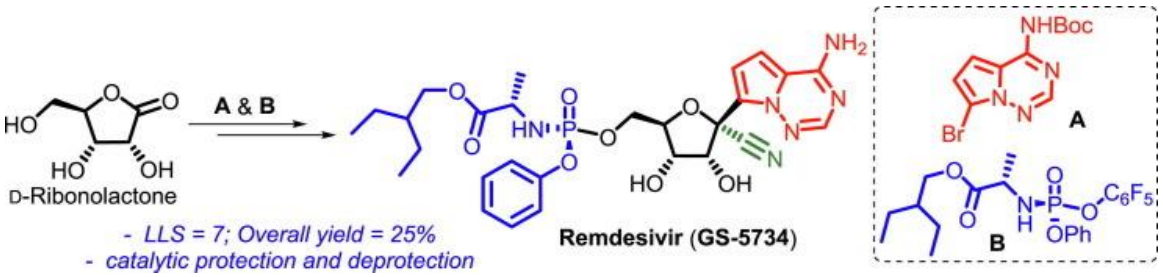


Figure 3. Synthesis of Remdesavir.

Synthesis of Acyclovir Which is used to treat the symptoms of chickenpox, shingles, herpes virus infections of the genitals (sex organs), the skin, the brain, and mucous membranes (lips and mouth),

and widespread herpes virus infections in newborns. Acyclovir is also used to prevent recurrent genital herpes infections (Figure 4).

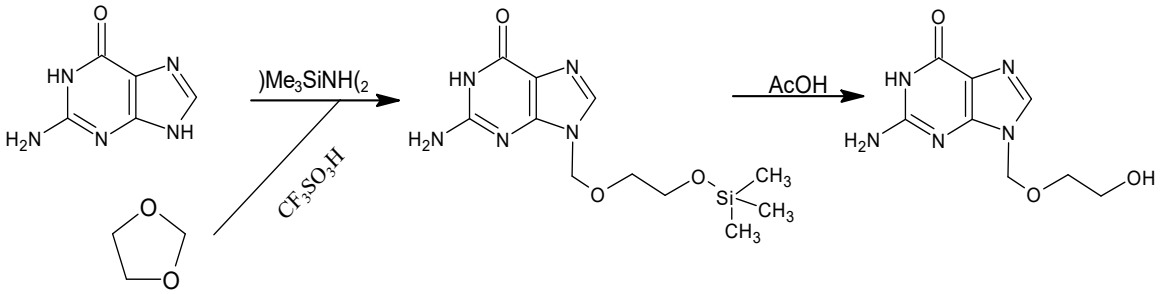


Figure 4. Synthesis of Acyclovir.

The Relationship Between Viruses and Body Organs

Viruses can infect specific organs depending on their tropism

- Hepatitis viruses → liver
- Influenza viruses → respiratory system
- Herpes simplex virus → skin and nervous system
- HIV → immune system ($CD4^+$ T cells)

Organ-specific infection often determines the symptoms, severity, and complications of the disease.

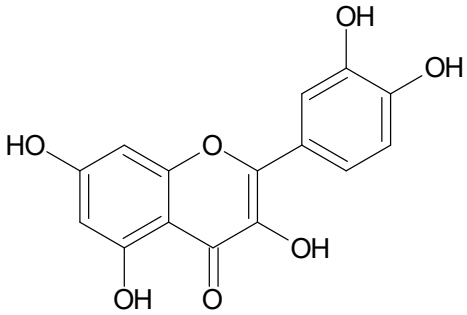
Natural Antiviral Compounds

Natural antiviral compounds include flavonoids, alkaloids, and terpenes.

- Flavonoids block viral entry into host cells.
- Alkaloids interfere with viral replication enzymes.
- Terpenes inhibit viral gene transcription.

Examples Include

Quercetin is a plant pigment (flavonoid). It is found in many plants and foods, such as red wine, onions, green tea, apples, and berries. Quercetin has antioxidant and anti-inflammatory effects that might help reduce swelling, kill cancer cells, control blood sugar, and help prevent heart disease. People sometimes use quercetin for arthritis, bladder infections, and many other conditions, but there is no good scientific evidence to support these uses. There is also no good evidence to support using quercetin for COVID-19 [2].



Quercetin $C_{15}H_{10}O_7$

A step-wise synthesis for the synthesis of quercetin analogues is shown in Figure 5 & Figure 6.

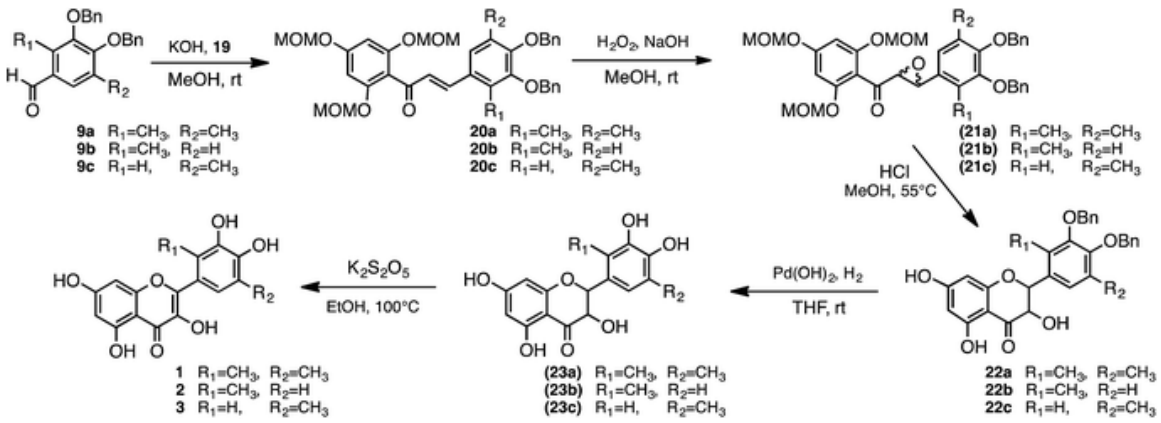
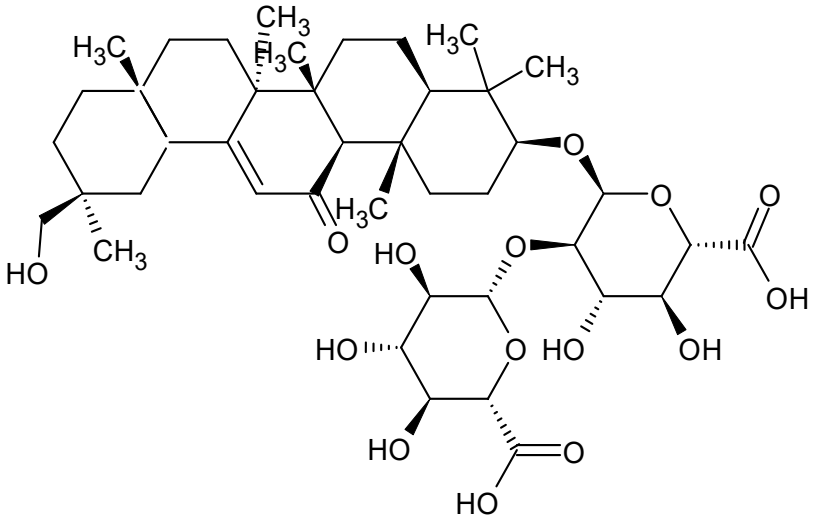


Figure 5. Synthesis of Quercetin analogues.

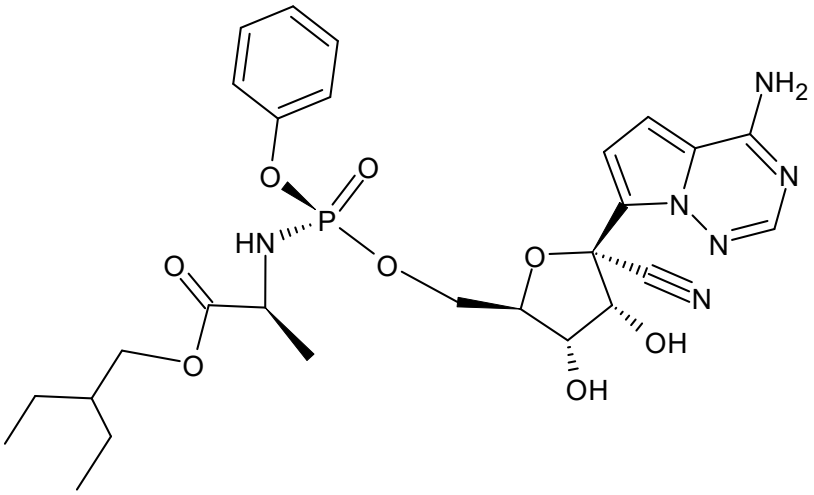
Glycyrrhizin (from licorice root) is a triterpene glycoside derived from Glycyrrhiza glabra and related species which is a renowned phytochemical used to cure a variety of ailments such as inflammation, sore throat, hepatitis [10].



Glycyrrhizin

Pharmacokinetics And Metabolism

- Absorption, distribution, hepatic metabolism, and excretion
- Example: Remdesivir → metabolized to active nucleoside triphosphate



Remdesivir

Virus Resistance Mechanisms

- Mutations in the polymerase or target proteins.
- Reduced drug efficacy.

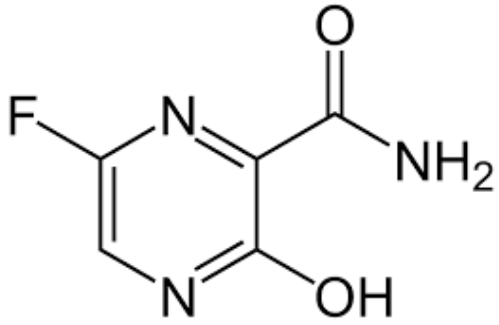
Drug Interaction

- Interactions with CYP450 or other drugs
- Example: Remdesivir + strong CYP344 inhibitors

Mechanism of Action of Antiviral Compounds

Favipiravir

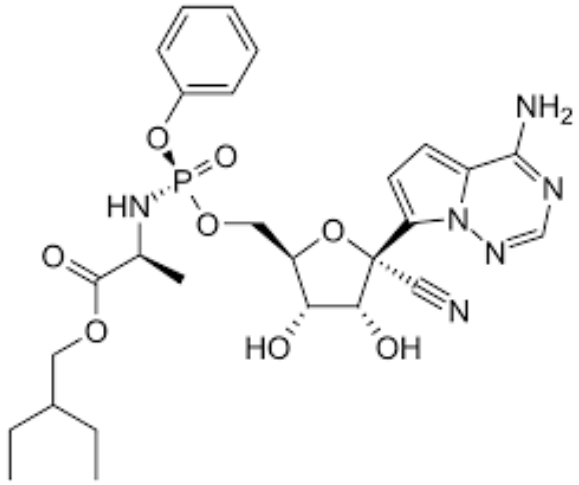
- Enters the cell as a prodrug → Converts to RTP (ribofuranosyl triphosphate) → Incorporates into the viral RNA chain → Leads to the termination of viral RNA synthesis
- Favipiravir → (phosphorylation in host cell) → Favipiravir-RTP
- Favipiravir-RTP + viral RNA polymerase → incorporation into viral RNA → chain termination



Favipiravir

Remdesivir

- Prodrug → metabolized to GS-441524 triphosphate → integrates into viral RNA → stops viral gene transcription.
- Remdesivir (prodrug) → liver metabolism → GS-441524 triphosphate
- GS-441524 triphosphate + viral RNA polymerase → incorporation → chain termination



Remdesivir

Molnupiravir

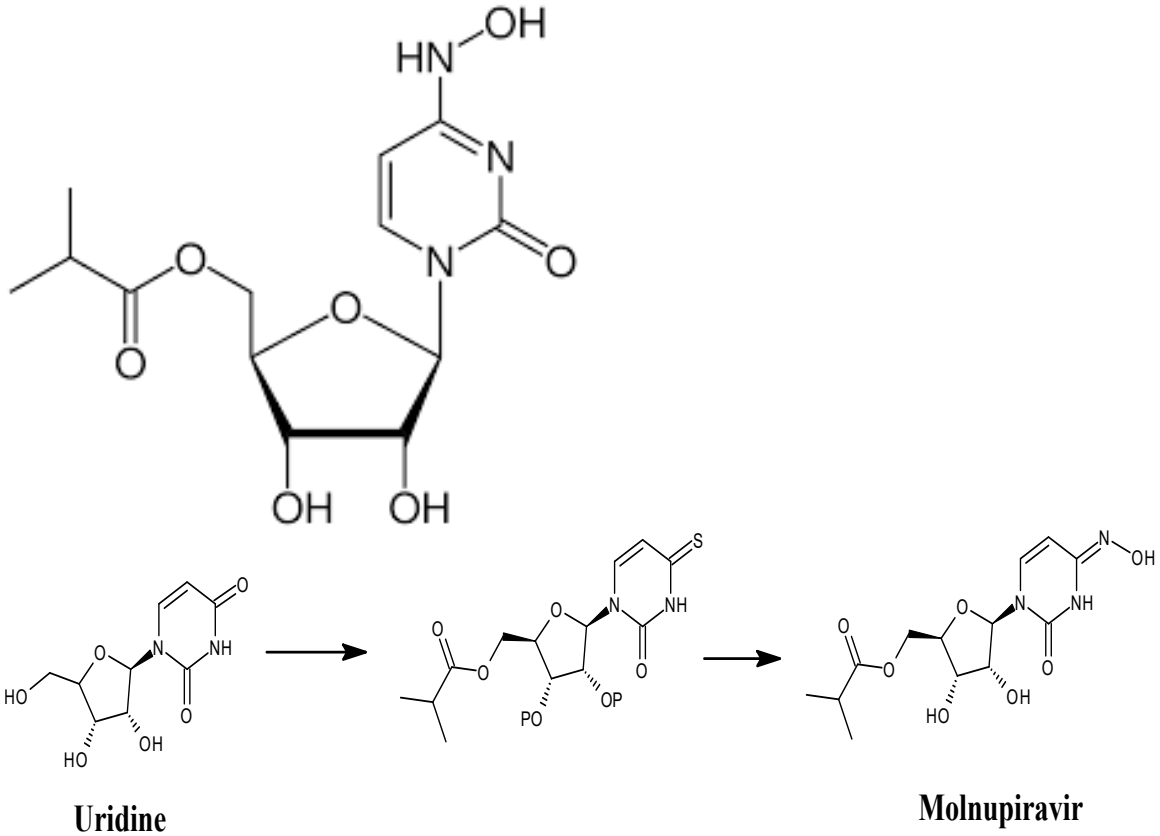


Figure 6. Short-Synthesis of Molnupiravir.

CONCLUSION

- Product → converted to NHC-triphosphate → misincorporation in viral RNA → induces lethal mutagenesis
- Molnupiravir → (host cell metabolism) → NHC-TP NHC-TP + viral RNA polymerase → incorporation into viral RNA → mutations → viral replication inhibition

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