Review

Nucleotide and nucleoside-based drugs: past, present, and future

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ABSTRACT

Nucleotide and nucleoside-based analogue drugs are widely used for the treatment of both acute and chronic viral infections. These drugs inhibit viral replication due to one or more distinct mechanisms. It modifies the virus's genetic structure by reducing viral capacity in every replication cycle. Their clinical success has shown strong effectiveness against several viruses, including ebolavirus, hepatitis C virus, HIV, MERS, SARS-Cov, and the most recent emergent SARS-Cov2. In this review, seven different types of inhibitors have been selected that show broad-spectrum activity against RNA viruses. A detailed over-view and mechanism of actionof both analogues are given, and the clinical perspectives are discussed. These inhibitors incorporated the novel SARS-CoV-2 RdRp, further terminating the polymerase activity with variable efficacy. The recent study provides a molecular basis for the inhibitory activity of virus RdRp using nucleotide and nucleoside analogues inhibitors. Furthermore, to identify those drugs that need more research and development to combat novel infections. Consequently, there is a pressing need to focus on present drugs by establishing their cell cultures. If their potencies were evidenced, then they would be explored in the future as potential therapeutics for novel outbreaks.

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Contents

1. Introduction

Nucleotide and nucleoside analogues are both similar in structure that acts as antimetabolites. Nucleotide inhibitors consist of phosphate groups, sugar, and nucleic acid analogue with one to three phosphates. Nucleoside inhibitors consist of sugar and nucleic acid analogue. Both inhibitors are used in antiviral prod-

ucts and therapeutic drugs to inhibit virus replication in infected cells (Seley-Radtke et al., 2018). The efficacy of nucleotide analogs was confirmed both in *vitro* and in*vivo* against various retroviruses and DNA viruses (Eyer et al., 2018). Based on structure, nucleotide analogs are also known as acyclic nucleoside phosphonates (nucleoside monophosphates). It prevents the first step of phosphorylation, which is necessary to activate nucleoside analogs, including lamivudine, adenosine, stavudine, abacavir, and zidovudine (Groaz et al., 2021). Nucleoside analogues are an introductory class of antiviral agents commonly used in the therapy of herpes simplex virus (HSV), human immunodeficiency virus (HIV), and cytomegalovirus (CMV) infection, varicella-zoster (VZV), hepatitis B and C viruses (Liver Tox, 2021). The nucleoside analogues are similar to the natural nucleotides that terminate the nascent DNA chain. Primarily, these agents are safe and well-tolerated, used by the virus but not human polymerases in DNA replication (Ewald et al., 2008). Nucleoside analogues are the fundamental agents in which several drugs are available against cancer and bacterial antibacterial (Thomson et al., 2019). Nucleotide and nucleoside analogues are significant antiviral agents inhibiting polymerases and showing clinical efficacy. They are currently used to treat herpes simplex, hepatitis B- and HIV-1 infection and are crucial in HAART therapy. It suppresses the RNA-dependent RNA polymerase NS5Bof HCV in its activated form (Chien et al., 2020). The analysis of coronavirus, hepatitis C virus replication, viral inhibitors' activities, and molecular structures have shown that Sofosbuvir triphosphate acts as an effective inhibitor of the SARS-CoV-2 RdRp (Ju et al., 2020; Wang et al., 2022). A previous study indicates that Sofosbuvir, Remdesivir, Ribavirin, Tenofovir, and Galidesivir could show inhibitory activity against SARS-CoV-2 RdRp (Hasan et al., 2021). Remdesivir is a phosphoramidite prodrug in which 1′-cyano modification occurs on the sugar. The virus-infected cells convert it into adenosine triphosphate analogue by inhibiting RdRps of MERS-CoV, SARS-CoV, and SARS-CoV-2 (Gordon et al., 2020a, 2020b). Similarly, FDA has announced that Remdesivir can be used against COVID-19 in emergency cases (FDA, 2021). These analogues have not been documented in detail as an agent against anti-hepatitis virus agents and anti-human immunodeficiency virus (HIV). Moreover, these are at different testing phases, such as the preclinical phase, excluded from trials or approved as drugs. The knowledge gained by various metabolism pathways shows that the future nucleotide prodrugs designed will be more inclusive. It would be either the combination of existing drugs or the tissue-targeted drugs with one or more prodrugs against several viral infections. The discovery of nucleotide/nucleoside drugs has been a remarkable scientific approach over the last 15 years. It may act as a fundamental target for developing nucleotide/nucleoside prodrugs in the future.

2. Nucleotide and nucleoside analogue inhibitors (NIs)

Recently, NIs have been used to treat acute and chronic viral infections. They were administered as nucleoside or nucleotide prodrugs or precursors to metabolize intracellularly to their active triphosphate due to viral or host kinases. NIs inhibits viral replication due to one or more discrete exclusive mechanisms. The improper corporation of foreign nucleotides in the replication of virus genomes leads to chain termination and disruption of transcription or replication. The mechanism of chain termination is spontaneous (obligate) or occurs in a limited range after the continuous synthesis of DNA or RNA (non-obligate (Pruijssers et al., 2019). Additionally, NIs are integrated into elongating nucleotide chains that do not incorporate and replace natural nucleotides. Hence the introduction of mutations that may inhibit RNA synthesis, interaction, or structure of RNA proteins or functions of the protein. The development of mutations and failure of the virus's capability is known as error catastrophe or lethal mutagenesis. NIs modifies the virus's genetic structure with these mechanisms, which causes a reduction in viral capacity with all successive replication cycles (Pruijssers et al., 2019; Parang et al., 2020).

2.1. Remdesivir

Remdesivir (GS-5734) is a nucleotide analogue capable of inhibiting the RNA-dependent RNA polymerase (RdRp), a significant protein for virus replication (Fig. 1). Gilead Sciences discovered Remdesivir, and further development occurred as the collaboration became stronger between Gilead, the US Army Medical Research Institute of Infectious Diseases (USAMRIID), and the U.S. Centers for Disease Control and Prevention (CDC). Primarily, the drug was used to treat Marburg infections and Ebola (EBOV) but has not shown any clinical efficacy. In addition, antiviral activity has been demonstrated against single-stranded RNA viruses, including MERS and SARS-Cov (Scavone et al., 2020; Eastman et al., 2020). Recent results from preclinical studies suggest that Remdesivir-related drugs may be more potent in countering the COVID-19 disease (Sheahan et al., 2017a). The case report indicated that a coronavirus patient in the United States with deteriorating clinical health had been treated with Remdesivir. His condition improved significantly within two days of treatment. He no longer needed supplementary oxygen, with only a few symptoms such as a sore throat, dry cough, and mild rhinorrhea. An additional case of patient recovery with Remdesivir has been reported. Nevertheless, data are inadequate for the case report; Remdesivir may be a potential treatment option (Wang et al., 2020). Animal experiments have shown that Remdesivir may be potent in reducing the virus load in the lung tissue of infected mice with MERS-CoV-, improving the function of the lungs, and reducing pathological damage to lung tissue (Martinez et al., 2021). The significance of Remdesivir in *vivo* against COVID-19 disease, prevents infection at low micro molecular concentrations (EC_{50} = 0.77 μM); CC_{50} = 100 μM; SI = 129.87) (Sheahan et al., 2020a). RDV triphosphate (RDV-TP) acts as a substrate for multivitamin RNA polymerase complexes (RdRp) and delayed chain termination mechanisms. It is also used to inhibit RNA synthesis in the case of all three types of corona viruses (SARS-CoV, SARS-CoV-2, and MERS-CoV). RDV-TP virus is analogous to the specific adenosine triphosphate (ATP) molecule during the viral synthesis of RNA. Once Remdesivir binds, RdRp ceases to incorporate RNA subunit, which causes inhibition of covid genome replication (Wang et al., 2020). A physics-based molecular modeling study of the binding
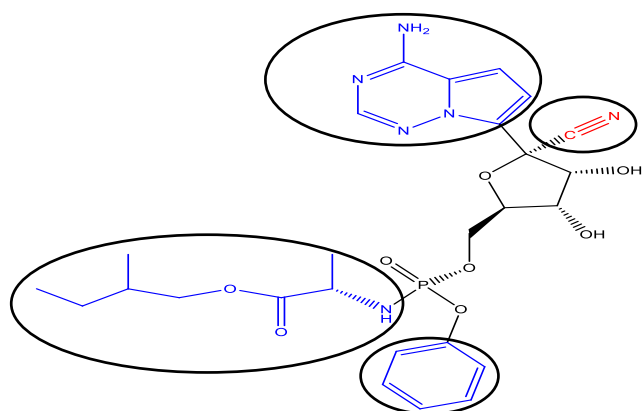

Fig. 1. The structure of Remdesivir.

mechanism has been performed between SARS-CoV-2 RdRp and Remdesivir. The relative free binding energy of Remdesivir was calculated to be −8.28 ± 0.65 kcal/mol. It is higher than the natural ATP substrate required for polymerization (-4.14 ± 0.89 kcal/mol). These results suggest that Remdesivir acts as a chain terminator for SARS-CoV-2 RNA. Both efficiently inhibit RNA proliferation by replacing "local ligand" ATP upon introduction to the binding grip of SARS-CoV-2 (Saha et al., 2020). The results of the molecular docking demonstrate that possible targets of Remdesivir is E-channel (mfScore = −125.1), RdRp (mfScores = −112.8), and Nsp3b (score = −36.5), TMPRSS2 (score = −36.23, mfScores = 109.4) (Wu et al., 2020). In the case of RdRp, the generated docking model allows binding of Remdesivir to the SARS-CoV-2 RdRp with RNA binding channel. The dual role of Remdesivir (1′-cyano group) is the inhibition of nucleotide proofreading and addition. A single Remdesivir is not enough to inhibit RNA synthesis by adding Nucleotides In contrast, the polar 1 E-sine group of RAM presence in the upper region causes instability through its electrolyte interaction with the salt bridge developed by ASP865 and Lys 593, which results in unfavorable translocation. It ultimately leads to a delay of three nucleotides in the RNA extension. Remdesivir inhibits the cleavage through a steric clash between the Asn104 and 1′-cyano group for proofreading. Its binding pocket (1′-cyano group) is located on the lower side of the RNA template channel, a significant locus of the nucleotide acceptor template. The organization of the compound with a pocket shape forms three hydrogen bonds with Asp684, Arg569, and Asn497. Furthermore, hydrophobic interactions withTyr687, Ala685, and Leu576 directed the preferred confirmation of Remdesivir (Zhang et al., 2020; Wu et al., 2020). The half-life (plasma) is 0.39A upon 10 mg/kg intravenous dose in non-human primates. The half-life of the nucleoside triphosphate metabolite in non-human primates and humans is 14 h; 20 h, respectively (Zhang et al., 2020).

2.2. Sofosbuvir

Sofosbuvir (GS-7977 or SOF; specifically known as PSI-7977) was primarily introduced by Pharmasset ltd in 2010. The company aims to find novel antiviral drugs, later acquired in 2011 by Gilead Science, which sustained the drug's development in various preclinical and clinical trials (Sheahan et al., 2017b). Sofosbuvir, a nucleotide analogue, has been approved primarily to treat the infection of the hepatitis C virus (HCV) (Gentile et al., 2015). Its primary function is to inhibit the NS5B RNA-dependent RNA polymerase of HCV and play a role in chain termination and replication of the virus. The cellular enzyme converts the sofosbuvir phosphorylation inside the host cell (hepatocyte) into the active form of the nucleoside triphosphate. It demonstrates substantial efficacy in the assay of HCV sub genomic replicon < 1 μM. In the in vivo administration, high levels of triphosphate and primary hepatocytes were produced in the liver of rats, monkeys, and dogs which inhibit HCV RNA-dependent RNA polymerase NS5B. Activated drug (2-, Me-UTP) binds to the active RdRp site. It further combines RNA and inhibits RNA chain extension due to modification in methyl and fluoro at position 2, which halts RNA replication and viral growth (Götte and Feld, 2016; Sofia et al., 2010). The analysis of YFV RNA polymerase showed that binding of sofosbuvir triphosphate occurred between the palm and the region of the finger, resulting in hydrogen compounds with Lys 693, Trp539, Ser603, and Gly538 residues and salt bridge interactions with Lys359 and two Mg^{2+} ions (Fig. 2) (Kayali and Schmidt, 2014). Theoretically, it was confirmed with experimental observation showing that after oral administration of one or more doses, the systemic circulation absorbed at least 80 %, with a median Tmax of 1 h (range: 0.5–3 h). The SOF is metabolized in the liver and produces GS-461203; after the next stage of dephosphorylation releases the primary circulating metabolite GS-331007-SOF, which accounts for the exposure of systemic drug (90 %) both in healthy and HCV patients (Mc Quaid et al., 2015). Following oral administration, the maximum concentration of SOF dose was determined within 0.5 to 2 h post-dose. Nevertheless, the administered dose, GS-331007 Cmax, occurred after SOF delivery within 2 to 4 h post (Geddawy et al., 2017).

The plasma protein binding of sofosbuvir is 61 to 65 %, but less in human plasma (GS-331007). The main pathway of SOF metabolism is the degradation by hydrolases leading to GS-331007, while in phase I trials, SOF has rapidly removed with an average half-life (t½) of 0.48 to 0.75 h (Smolders et al., 2016). Nevertheless, the GS-331007 metabolite possessed a wide-ranging Tmax (range: 1.5 to 8 h; median: 4 h) and a wide-ranging half-life (range: 7.27 to 11.80 h); both GS-331007 and SOF have shown appropriate assembly (Babusis et al., 2018).
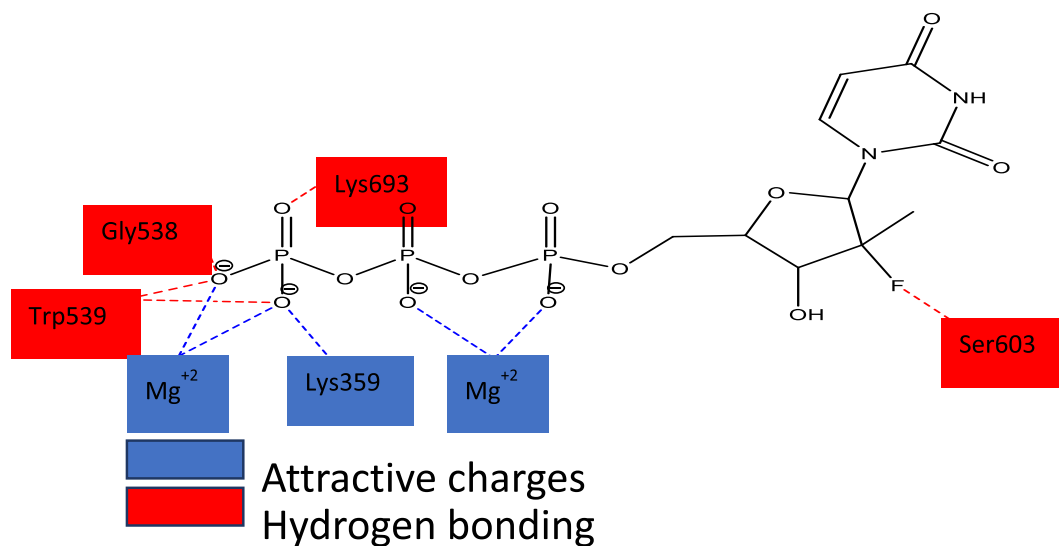

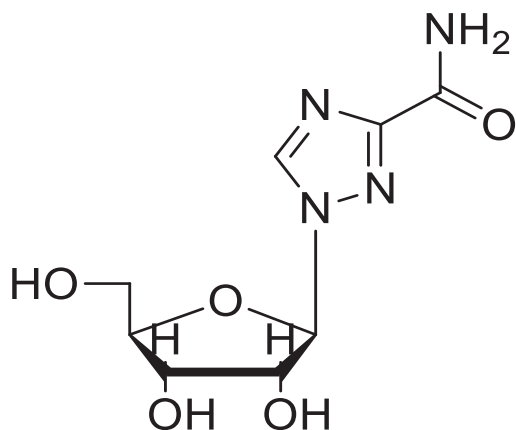**Fig. 2.** H-bonding and hydrophobic interactions of Sofosbuvir COVID −19 RdRp.

Fig. 3. The chemical structure of Ribavirin.

2.3. Ribavirin

In 1972, Whitkovsky and colleagues discovered Ribavirin (Fig. 3), aguanosine nucleoside analog with wide-ranging activity against several viruses, DNA, and RNA. It was initially synthesized as monotherapy to treat viral infections (interferon-alpha (IFN-alpha) or with the respiratory syncytial virus as a combined therapy (HCV) (Elfikyet al., 2020; Witkowski et al., 1972).The molecular basis of Ribavirin antiviral activity against HCV was vulnerable due to the lack of HCV replication animal models, availability, and efficient HCV culture systems. The results of an RNA virus and limited data on HCV itself show that the antiviral potential of Ribavirin acts as a single agent was determined in four ways: (1) To inhibit the HCV replication directly, (2) To suppress the inosine monophosphate dehydrogenase (IMPDH), a host enzyme (3) the speeding up the viral replicating due to induction of mutagenesis behind the threshold to error catastrophe, (4) Immunomodulation to persuade immune response (Th1). In particular, it was not obvious which mechanism is most prominent in the synergic action of Ribavirin with IFN alfa. Due to adenosine kinase, the intracellular conversion of Ribavirin occurs into Ribavirin monophosphate (RMP), which is converted further into different forms such as diphosphorylated and triphosphorylated by diphosphate kinases and nucleoside monophosphate. Mostly, in every type of cell, the formation of ribavirin triphosphate (RTP) becomes dominant, which is covered at concentrations 20 times higher than RMP. The RTP is bound to the nucleotide-binding site of RNA polymerase, which halts the proper binding of Nucleotide, causing a reduction of viral replication or forming defective virions (Sidwell et al., 1972; Hofmann et al., 2008). Ribavirin showed excellent antiviral activity against RSV with CC_{50} = 24.0 μM and IC_{50} = 20.9 μM (Te et al., 2007). It can block the RNA-dependent RNA polymerase activity (Feld, 2005). In the previous study, 75 patients with SARS were treated with intravenous Ribavirin
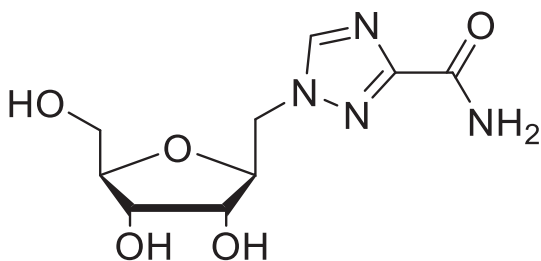
8 mg/kg every 8 h for 14 days, while others depended on the patient's condition. Improvements were observed in 46 patients in which 11 were stable, 18 patients health deteriorated, and five died Khalili et al, 2020). The docking report suggested that Ribavirin with 7.8 kcal/mol of energy binds to RdRp of SARS-CoV-2, which contradicts polymerase's function. The single interactions observed with docking are the 13H-bonds with N582, Y510, D514, W508, K512, W691, A653, D651, and C513 of the (RdRp) SARS-CoV-2 Therefore, it was considered a potent candidate for anti-COVID-19 possible drugs (Hofmann et al., 2008). Ribavirin has been studied for its metabolism in EBV-transformed lymphoblasts, cultured skin fibroblasts, and intact human erythrocytes. At 35 PM, the extracellular concentration of Ribavirin, all types of cells synthesized Ribavirin mono-, di-, and triphosphates. Their nucleotide concentrations are peaked at 210, 245, and 267 min for erythrocytes, lymphoblasts, and fibroblasts. The ratio of mono-, di-, and triphosphates was 1:5:17 in erythrocytes. 2,3:1:8 in lymphoblasts, and ca 4: 1:40 in fibroblasts. Its evacuation from the medium increases the Ribavirin nucleotides' half-life to 24 hr in erythrocytes (Page et al., 1990).

2.4. Galidesivir

Galidesivir (Fig. 4) was developed by Bio Cryst Pharmaceuticals (Arora et al., 2021). It is a nucleoside analogue of adenosine, primarily developed against filoviruses. It is active against different viruses; tick-borne encephalitis virus, yellow fever virus, Japanese encephalitis virus, West Nile virus, and dengue virus, both in small animal models and in vitro cell cultures (Warren et al., 2014; Bugert et al., 2020; Julanderet al., 2017; Taylor et al., 2016). It inhibits the viral synthesis of RNA by blocking RNA-dependent RNA polymerase (RdRP) activity using non-obligate RNA chain termination. The parental compound Galidesivir is primarily converted to Galidesivir-triphosphate binds with the newly RNA virus by the RdRP, resulting in early transcription termination through the 3′-hydroxyl group that causes additional accumulation of a nucleotide. Their Direct action on the virus RDRP enables Galidesivir to show a broad-ranging antiviral activity against various viruses (Julander et al., 2014). Docking studies explained that this drug binds tightly to RdRpof SARS-CoV-2 (binding energy = -7.0 kcal/mol), inhibiting the polymerase function. It is considered an effective anti-COVID-19 possible drug (Elfiky et al., 2020). Upon incubation with liver fractions of S9 from a variety of animal species, it is metabolically stable (elimination half-life (t1/2) > 54 min). The pharmacokinetics of BCX4430 in guinea, rats, Cynomolgus macaques, mice, and pigs are characterized by rapid plasma elimination (half-life = <5 min). Similarly, the half-life of the active form BCX4430-TP was significantly higher in the liver of rats at 6.2 h (Eyer et al., 2017). The interaction of Galidesivir occurs with a
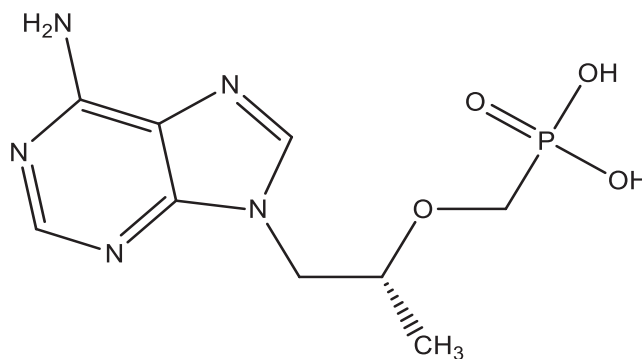

Fig. 4. The chemical structure of Galidesivir.

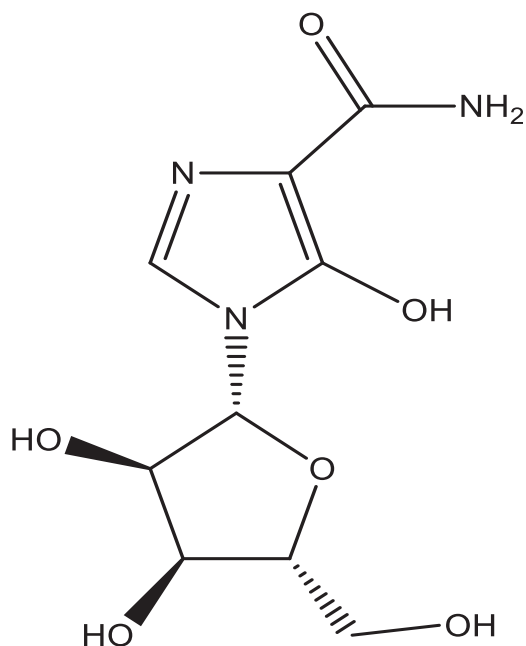Fig. 5. The chemical structure of Tenofovir.

Fig. 6. The chemical structure of Mizoribine.

receptor (RdRp). The green dot bar shows the residues of LYS-798, SER-814, AS-761, and ALA-762 of RdRp H-with inhibitor Galidesivir (Westover et al., 2018).

2.5. Tenofovir

Tenofovir [(R)-9-(2-phosphonylmethoxypropyl) adenine (Fig. 5) was firstly introduced in 1993 (). It is a nucleotide analog used to treat hepatitis B and HIV infection (Warren et al., 2014; Aftab et al., 2020; De Clercq et al., 2013). Tenofovir showed excellent antiviral activity against human immunodeficiency virus (Hall et al., 2021). It blocks reverse transcriptase, competing for inclusion into elongated DNA strands with natural nucleotide subunits, and with the lack of 3′-OH shows similarity to chain-terminators. According to the results of the docking study, it is an effective inhibitor of SARS-CoV-2 RdRp. Its higher binding ability with SARS-CoV-2 RdRp, (6.9 kcal/mol) interferes with the polymerase function (Parienti et al., 2021). A result from docking technique show that it forms 5H-bonds in with W508, D652, A653, W691, and E702, can be effective candidates as a possible drug anti-COVID-19 (Elfiky et al., 2020).

Plasma TFV has shown triphasic failure with the terminal exclusion of half-life median [interquartile range (IQR)] 69 h. Peripheral blood mononuclear cell (PBMC) TFV-DP has shown a terminal half-
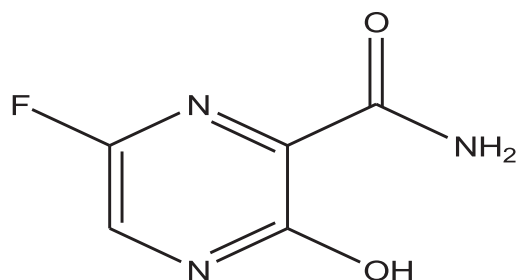

Fig. 7. The chemical structure of Favipiravir.

life of 48 h followed by biphasic peaks (median 12 h and 96 h) (James et al., 2004).

2.6. Mizoribine

Mizoribine (Fig. 6) is a novel immunosuppressive drug approved by the Government of Japan in 1984 (Tanaka et al., 2008). Mizoribine inhibits DNA synthesis but not protein synthesis with mouse lymphoma cell line L5178Y (Pyrc et al., 2006). The yield and plaque reduction assays determine mizoribine activity, an inosine-5-monophosphate dehydrogenase (IMPDH) inhibitor against SARS and its association with coronavirus. Mizoribine has played a significant role in the SARS-CoV replication. The Mizoribine has an IC_{50} of 50 % against SARS-CoV HKU39849, and SARS-CoV Frankfurt-1 was described in plaque reduction (3.5 μg/ml and 16 μg/ml). It's 50 % cytotoxic concentration for Vero E6 cells was higher than 200 μg/ml. The dosage of 10 μg/ml inhibited the SARS-CoV replication by reducing the infectious titers to one-tenth or less in the yield reduction assay. The significance of Mizoribine is the inhibition of SARS-CoV replication effectively but fails to completely inhibit SARS-CoV replication even at higher (100 μg/ml) concentrations (Sheahan et al., 2020b). Oral MZB spread within 2–3 h to the peak serum concentrations and is usually excreted through the kidney (65–100 % of dose), and the half-life of its serum was 3 h (Kawasaki et al., 2009).

2.7. Favipiravir

Favipiravir (6-fluoro-3-hydroxy-2-pyrazine-carboxamide) (Fig. 7) isalso called T-705. Favipiravir is a purine nucleoside analogue primarily developed and approved to treat influenza viruses in Japan. The significance of Favipiravir is to block the influenza virus (RdRps) selectively. Its active form is favipiravir-ribofuranosyl-5′-triphosphate (RTP) which can be obtained with phosphorribosylation by cellular enzymes. The addition of purine nucleic acids causes a reduction of the antiviral effect, which shows that the RNA polymerase of the virus identifies the favipiravir-RTP mistakenly as a purine nucleotide. It performs activity against wide-ranging influenza viruses such as A(H5N1), A(H1N1) pdm09, and the most recent A(H7N9) avian virus. Its activity was proven against the strains of influenza that showed resistance to the most recent antiviral drugs. It also has a synergistic effect with oseltamivir in the combined form, which greatly expands treatment options for influenza. Favipiravir and anti-influenza activity inhibit RNA viruses replication; hantaviruses (Prospect Hill, Dobrava, and Maporal); Western equine encephalitis virus; phleboviruses (Rift Valley, sandfly fever, and Punta Toro); respiratory syncytial virus; a paramyxovirus; alphavirus enteroviruses (polio, and rhinoviruses); noroviruses; flaviviruses (West Nile and yellow fever); arena viruses (Machupo, Pichinde, and Junin). Favipiravir's wide-ranging antiviral activity and unique mechanism are considered a successful drug candidate for RNA and influenza infection (Furuta et al., 2013; Du et al., 2018; Gowen et al., 2018). The recent study of Favipiravir shows excellent in vitro antiviral activity of (SI = > 6.46), CC_{50} = 400 μM, and EC_{50} = 61.88 μM) against SARS-CoV-2 (Kawasaki et al., 2009).

3. Conclusion

This review has compiled the most crucial literature regarding nucleotide and nucleoside developments and analogues to treat several viral infections. We examined that both analogues induced the essential effect on the viral life cycle. It has a central role in competitively inhibiting RdRp-mediated viral RNA synthesis. It was administered safely to the COVID-19 hospitalized patients

and was influential in critically affected people who had not received mechanical ventilation. There is an emergency need for further research in developing nucleoside/nucleoside precursors, initiating with novel synthetic structures, and comparing their evaluation against existing and unknown types of viruses. The significance of nucleotide and nucleoside analogue is too high against most virus types. Despite their sufficient efficacy against multiple kinds of viruses; still, further research would be needed to investigate whether these inhibitors can show optimum potency against SARS-CoV-2. Thus, it is pressing to focus on this field, and the scientific research should not be stopped and should continue with full enthusiasm. In addition, if novel viral infection outbreaks occur in the future, these inhibitors would be the primary choice to eliminate the infection burden.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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