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Non-nucleoside structured compounds with antiviral activity—past 10 years (2010–2020)

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ABSTRACT

Nucleosides and their derivatives are a well-known and well-described class of compounds with antiviral activity. Currently, in the era of the COVID-19 pandemic, scientists are also looking for compounds not related to nucleosides with antiviral properties. This review aims to provide an overview of selected synthetic antiviral agents not associated to nucleosides developed against human viruses and introduced to preclinical and clinical trials as well as drugs approved for antiviral therapy over the last 10 years. The article describes for the first time the wide classification of such antiviral drugs and drug candidates and briefly summarizes the biological target and clinical applications of the compounds. The described compounds are arranged according to the antiviral mechanism of action. Knowledge of the drug's activity toward specific molecular targets may be the key to researching new antiviral compounds and repositioning drugs already approved for clinical use. The paper also briefly discusses the future directions of antiviral therapy. The described examples of antiviral compounds can be helpful for further drug development.

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Contents

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1. Introduction

Viruses cause a broad spectrum of diseases, ranging from chronic to severe ones that may lead to sudden death. Antiviral drug development began six decades ago, and the first antiviral drug, nucleoside analogue - idoxuridine, was described by William "Bill" Prusoff [1]. Idoxuridine was used in the treatment of infant keratitis, which is caused by herpes simplex virus (HSV, *Herpesviridae* family), after the drug was approved by the U.S. Food and Drug Administration (FDA) in 1963 [1]. Since then, many antiviral medications have been developed for clinical use. However, the AIDS (Acquired Immune Deficiency Syndrome) epidemic in the 1980s, caused by the human immunodeficiency virus (HIV, *Retroviridae* family), was a breakthrough in recognizing antiviral agents which led to an increase in research interest, and consequently, the emergence of novel antiviral drugs. Unfortunately, many of the antiviral drugs that have been approved so far have some limitations, such as poor bioavailability, severe adverse effects, or drug resistance. Long-acting and extended-release formulations are one of the most important considerations to improving the treatment and prevention of HIV infection. The latest trends, including those involving the application of nanotechnology, have been published recently [2–4].

Two approaches play an essential role in the development of new antiviral therapies—de novo drug discovery and repositioning of the currently approved drugs for the treatment of well-known viral diseases. Preclinical research is the first stage of development for drug candidates. It involves especially assessment of biological properties. After obtaining the beneficial results, the tested compound may enter clinical trials (CT). FDA drug approval process is presented on Fig. 1. Combined antiviral therapy might also be beneficial [5]. Especially at present, in the face of novel coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2, *Coronaviridae* family), there is an urgent need to develop effective antiviral therapies. Numerous commonly used drugs, as well as new compounds, are applied or being developed for the treatment of COVID-19 [6,7]. Up-to-date information on the COVID-19 pandemic, in particular, the epidemiology, pathogenesis, prevention and treatment strategies has been described in the following publications [8,9].

It is worth mentioning, that crystallographic methods are very important in research of new antiviral compounds, also against COVID-19. Crystal structures of biological targets alone and in complex with ligands and inhibitors provide crucial information about the mechanisms of actions of enzymes and their conformational changes upon ligand binding. Recently, this method has been extended and now often include the identification of hits by structure-based virtual screening methods. Several biologically active compounds discovered by structure-based design are now commercially available, confirming the important role played by structural biology in drug development process [10]. The well-known examples are anti-HIV drugs, such as amprenavir (trade name Agenerase) and nelfinavir (trade name Viracept), which were developed using the crystal structure of HIV protease [11]. Crystal structures are currently used in the design of an anti-COVID-19 drug based on SARS-CoV-2 main protease structure (SARS-CoV-2 M^{pro}) [12,13]. Such methods are also helpful in the study of the mechanisms of action of compounds, including the mechanism of drug resistance – for example crystal structures of influenza virus polymerase basic protein 2 (PB2) and pimodivir [14].

2. Nucleoside analogues

Nucleoside analogues are the most common group among the FDA-approved antiviral drugs. Several nucleoside-based antiviral drugs have been validated for therapy, and many are being tested in preclinical and clinical trials. Inside the cell, nucleosides are first phosphorylated by a nucleoside kinase, resulting in the production of monophosphate metabolite. The second and third phosphorylation processes are performed by cellular kinases (Fig. 2). Active forms of nucleosides—mono-, di-, and triphosphorylated ones—act as inhibitors of intracellular enzymes and are also incorporated into newly synthesized DNA and RNA molecules [16].

Examples of the latest nucleoside analogues with excellent and promising results in clinical trials are islatravir and galidesivir (Fig. 3). Islatravir (MK-8591, 4′-ethynyl-2-fluoro-2′-

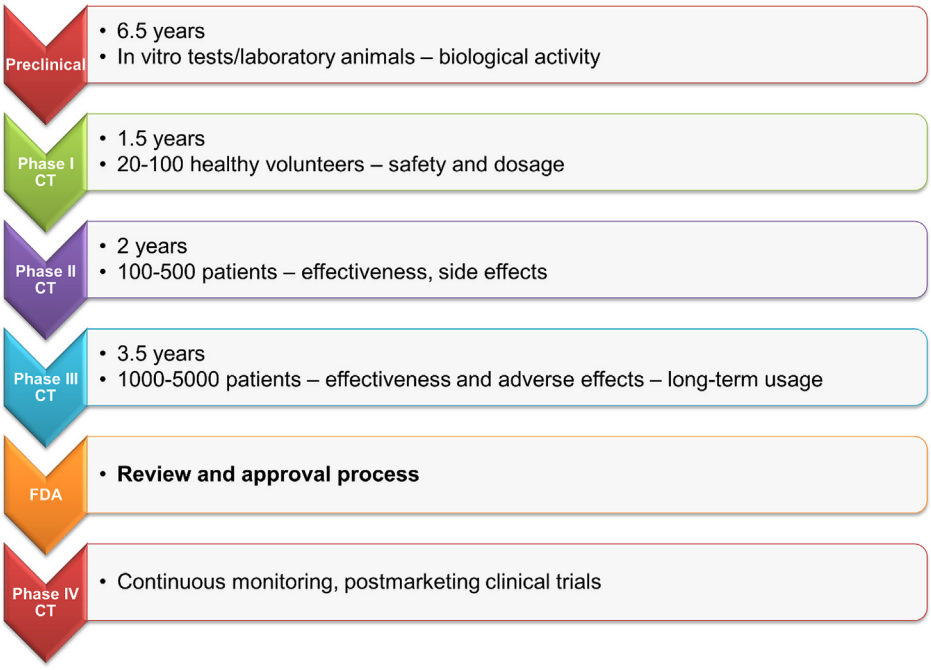


Fig. 1. FDA drug approval process. Preclinical studies and clinical trial phases (according to: The Drug Development and Approval Process [15]).

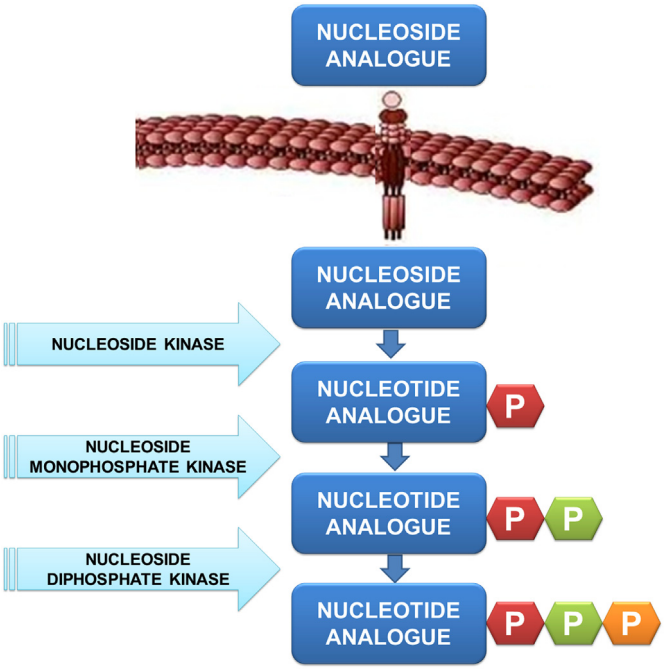


Fig. 2. Nucleoside analogue phosphorylation process.

deoxyadenosine) is a novel nucleoside reverse transcriptase translocation inhibitor (NRTTI), which appears to be promising and is currently evaluated in a clinical trial for the treatment of HIV-1 infection. The active form of islatravir, islatravir triphosphate, leads to an efficient incorporation of islatravir into the viral DNA [17]. Previous in vitro and preclinical studies suggested that islatravir is characterized by a high barrier to resistance [18,19]. In another preclinical study, islatravir used in combination with two other antiviral drugs—doravirine and lamivudine—demonstrated high viral suppression in HIV-infected individuals [20]. The results of the phase 1b single-dose trial conducted in HIV-1-infected adults confirmed the high antiviral potency, beneficial physical properties, and promising resistance profile of islatravir [17].

Another adenosine analogue, galidesivir (Immucillin-A, BCX4430, (2S,3S,4R,5R)-2-(4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-5-(hydroxymethyl) pyrrolidine-3,4-diol), was shown to inhibit the function of viral RNA polymerase by inducing RNA chain termination. Warren and colleagues [21] reported that galidesivir is active against a wide range of RNA viruses, including *Filoviridae*, *Togaviridae*, *Bunyaviridae*, *Arenaviridae*, *Paramyxoviridae*, *Flaviviridae*, *Orthomyxoviridae*, *Picornaviridae*, and *Coronaviridae* families. Currently, this drug is considered as a promising medication for COVID-19, as it was found to be effective in binding to the RNA-dependent RNA polymerase (RdRp) of SARS-CoV-2 [22,23]. Galidesivir was evaluated in a clinical trial for the assessment of safety, pharmacokinetics, and antiviral effects against yellow fever virus (YFV, *Flaviviridae*) or SARS-CoV-2 and completed phase 1 for the treatment of the Marburg Virus Disease (*Filoviridae* family).

Another nucleoside compounds worth mentioning are remdesivir (GS-5734, 2-ethylbutyl (2*S*)-2-[[[(2*R*,3*S*,4*R*,5*R*)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxyoxolan-2-yl]methoxy-phenoxyphosphoryl]amino]propanoate) and molnupiravir ([(2*R*,3*S*,4*R*,5*R*)-3,4-dihydroxy-5-[4-(hydroxyamino)-2-oxopyrimidin-1-yl]oxolan-2-yl]methyl 2-methylpropanoate) (Fig. 3). Remdesivir was approved by FDA as an antiviral drug for the treatment of COVID-19 in adult and pediatric patients requiring hospitalization (trade name Veklury). Veklury is the first drug to receive FDA approval for the treatment of COVID-19 [24]. Molnupiravir – a broad-spectrum antiviral drug candidate is a prodrug of the nucleoside analogue β-D-N4-hydroxycytidine (NHC). Molnupiravir targets the SARS-CoV-2 RdRp. The drug increases the frequency of SARS-CoV-2 RNA mutations and impairs SARS-CoV-2 replication. Molnupiravir is currently in phase 3 clinical trials for the treatment of COVID-19 [25–27].

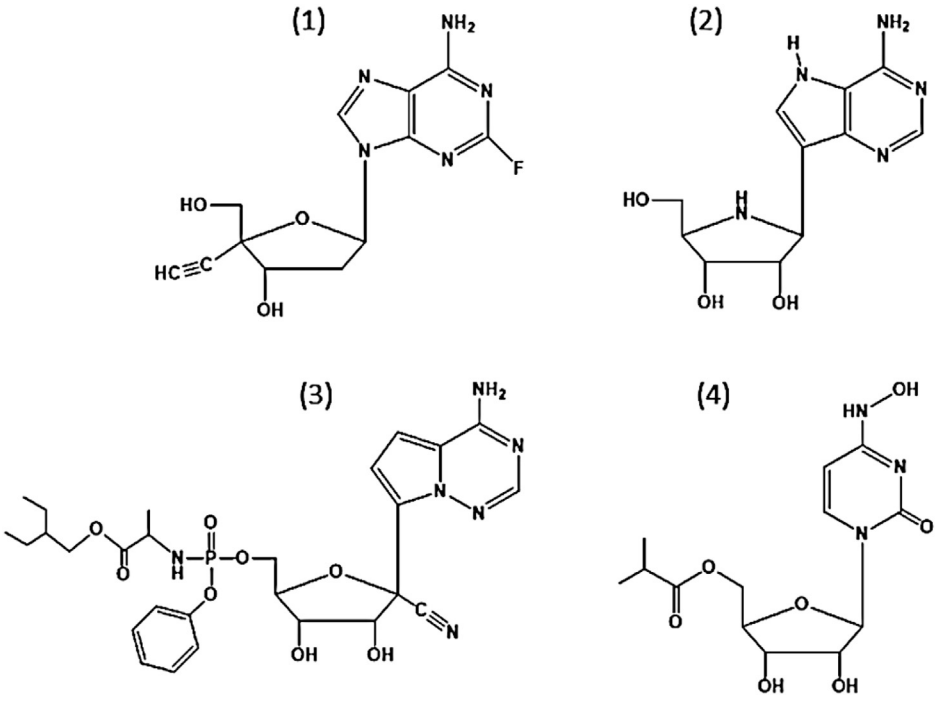


Fig. 3. Islatravir (1), galidesivir (2), remdesivir (3) and molnupiravir (4) – chemical structures of nucleoside drug and drug candidates.

There have been many publications describing the action of nucleoside analogues in antiviral therapy. In 2016, De Clercq and Li [28] presented a comprehensive overview of 90 antiviral drugs approved for the treatment of 9 human infectious diseases over the past 50 years. Additionally, review highlights several forthcoming antiviral regimens in phase 3 clinical trials.

Particularly noteworthy is the review published by Lin and colleagues [29] in 2021, describing individual modifications of the structure of nucleoside analogues and the mechanism of their antiviral activity. Importantly, the authors describe the influence of particular structural modifications on the biological activity of compounds.

Fig. 4 describes selected antiviral nucleoside analogues currently investigated in preclinical or clinical trials [30–39].

The present review aims to provide an overview of selected antiviral agents not related to nucleosides. The drugs described in this paper were developed over the past 10 years. The compounds have been ordered according to the mechanism of action. A brief description is also made of future directions of antiviral therapy.

3. Molecular mechanisms of action of non-nucleoside structured compounds

Another approach for the development of new antiviral drugs involves the use of compounds which structure is not derived from nucleosides. This strategy aims to overcome the resistance resulting from treatment with nucleoside-based antiviral drugs. Numerous agents have entered clinical trials (Table 1) and many of them were approved by FDA for use in antiviral therapy (Table 2). Molecular mechanisms of action of antiviral drugs/drug candidates mentioned in the article are presented on Fig. 5.

3.1. Cell entry/fusion inhibitors

Viral entry/fusion pathways represent promising targets for antiviral drugs. Most viral pathogens are membrane-enveloped viruses, characterized by a lipid bilayer (envelope), covering the virus particle. Viruses replicate within the host cell, disrupting various of cellular proteins and chemical pathways necessary to survive and replicate. At the first stage, enveloped viruses non-covalently bind to specific surface receptors of the target host cell membrane, which is followed by fusion between virus and host cell. Fusion is catalyzed by one type of viral glycoproteins or combinations of multiple viral glycoproteins (fusogens), activated by non-covalent interactions with surface receptors and/or by acidic endosomal pH, resulting in a conformational change, which drives the fusion process [81,82].

Chloroquine (4-*N*-(7-chloroquinolin-4-yl)-1-*N*,1-*N*-diethylpentane-1,4-diamine) (Table 1) is well-known FDA-approved antimalarial drug which synthesis was described more than seventy years ago [83]. One of the mechanisms of its action involves the inhibition of receptor binding and fusion of cell membrane. Chloroquine were found to inhibit novel coronavirus in vitro [40] and have shown clinical benefits in COVID-19 patients. Reports on the possible efficacy of chloroquine in the treatment of SARS-CoV-2 infections, in the absence of a drug for the COVID-19 disease, have resulted in a huge amount of research. Extended research sheds new light on the effects of chloroquine and its derivatives on COVID-19 patients. The pharmacokinetic and safety properties of chloroquine suggest that the drug usage should be limited to an acute virus infection, and patients ought to be routinely monitored for cardiovascular conditions to prevent lethal adverse events [84–86]. Before using chloroquine, an individual risk-benefit assessment should be taken into account, especially in COVID-19 patients with cardiovascular conditions and injury as well as kidney and liver diseases [86].

Presatovir (GS-5806, *N*-[2-[(2*S*)-2-[5-[(3*S*)-3-aminopyrrolidin-1-yl]-6-methylpyrazolo [1,5-a]pyrimidin-2-yl]piperidine-1-carbonyl]-4-chlorophenyl]methanesulfonamide) (Table 1) is an orally bioavailable antiviral compound. Its mechanism of action is based on the inhibition of respiratory syncytial virus (RSV, *Paramyxoviridae* family) fusion with host cell membranes. The piperidine ring has been revealed to facilitate the formation of an appropriate dihedral angle between the pyrazolo [1,5-a]pyrimidine scaffold and the plane of the amide bond for exertion of anti-RSV activity [106]. Presatovir showed potent antiviral activity in vitro against 75 RSV clinical isolates [42] and dose-dependent antiviral efficacy in vivo in the Sprague-Dawley rat model of RSV infection. The drug was found to be safe and showed beneficial antiviral effects with a reduction in disease severity in phase 2 clinical trial (Table 1, NCT01756482) in healthy adults [43,44]. However, a phase 2b trial conducted in hematopoietic cell transplant recipients with RSV infection of the lower respiratory tract revealed that presatovir did not improve viral or clinical outcomes versus placebo (Table 1, NCT02254421) [45].

3.2. Polymerase inhibitors

Viral DNA and RNA polymerases responsible for the replication are the main components in the life cycle of viruses. The reverse transcriptase (RT) of the retroviruses and the hepadnaviruses is the crucial viral enzyme required for the synthesis of DNA from viral RNA. Another well-known target is NS5B (nonstructural protein 5B) – a RdRp that catalyzes the replication of HCV RNA. Viral polymerases are therefore an extremely favorable target for the development of antiviral therapy [107].

3.2.1. Reverse transcriptase inhibitors

Rilpivirine hydrochloride (4-[[4-[4-[(*E*)-2-cyanoethenyl]-2,6-dimethylanilino]pyrimidin-2-yl]amino]benzonitrile hydrochloride) is a second-generation NNRTI approved for use with NRTIs

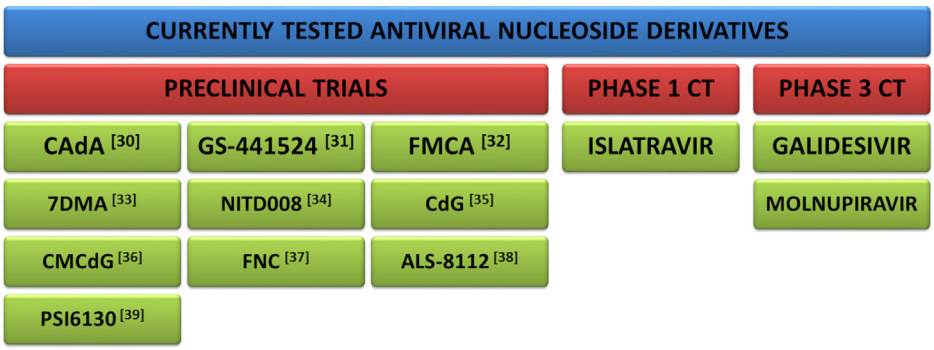
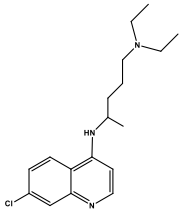
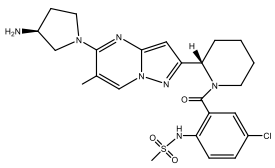
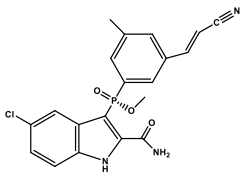
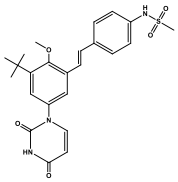
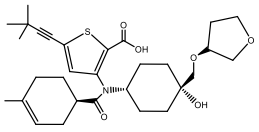
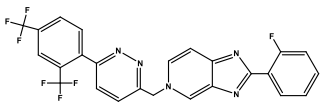
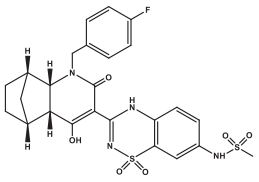
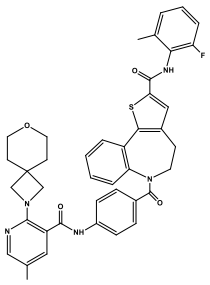
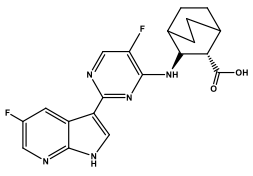


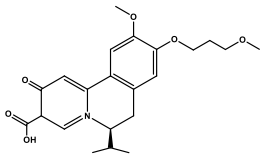
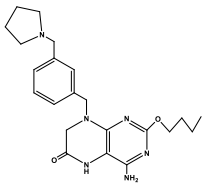
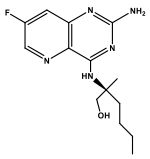
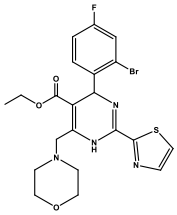
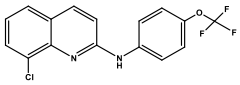
Fig. 4. Selected antiviral nucleoside derivatives currently tested in preclinical or clinical trials [30–39].

Table 1
Antiviral agents tested in preclinical or clinical trials.

Name	Structure	Mechanism of action	Phase of development
Chloroquine		Cell entry inhibitor [40,41]	Phase 4 clinical trials: NCT01980745, NCT02463331, NCT02058173, NCT04316377, NCT04286503, NCT02564471
Presatovir/GS-5806		Cell entry inhibitor [42–45]	Phase 2 clinical trials: NCT01756482, NCT02534350, NCT02254408, NCT02135614, NCT02254421
Fosdevirine/FDV/ GSK2248761/ IDX89[a]		Polymerase inhibitor (NNRTI) [46–48]	Discontinued after phase 2 clinical trial NCT01199731
ABT-072		Polymerase inhibitor (RdRp) [49,50]	Phase 2 clinical trials: NCT01221298, NCT00872196, NCT01074008
Radalbuvir/GS9669		Polymerase inhibitor (RdRp) [51–53]	Phase 2 clinical trials: NCT01984294, NCT01260350, NCT01805882, NCT01826981
Tegobuvir/GS-9190		Polymerase inhibitor (RdRp) [54–57]	Phase 2 clinical trials: NCT01435226, NCT01434498, NCT01353248, NCT01371578, NCT01271790, NCT01072695, NCT01225380, NCT00743795
Setrobuvir/ANA598		Polymerase inhibitor (RdRp) [58–60]	Phase 2 clinical trials: NCT01903954, NCT00978497
PC-786		Polymerase inhibitor (RdRp) [61,62]	Phase 2 clinical trial: NCT03382431
Pimodivir/JNJ-63623872[c]		Polymerase inhibitor (RdRp) [63–66]	Phase 2 clinical trial: NCT02342249

(*continued on next page*)

Table 1 (*continued*)

Name	Structure	Mechanism of action	Phase of development
RG7834		Polymerase inhibitor[b] [67,68]	Preclinical
Vesatolimod/GS-9620[c]		TLR-7[d] agonist [69–72]	Phase 2 clinical trials: NCT04364035, NCT02579382, NCT02166047
Selgantolimod/GS-9688		TLR-8[d] agonist [73]	Phase 2 clinical trials: NCT03491553, NCT03615066
Morphothiadin/GLS-4		Capsid assembly inhibitor [74–77]	Phase 2 clinical trials: NCT04147208, NCT03638076
ABX464		Viral RNA biogenesis inhibitor [78,79]	Phase 3 clinical trial: NCT04393038; Phase 2 clinical trials: NCT02990325, NCT02735863, NCT02452242

NNRTI - non-nucleoside reverse transcriptase inhibitor.
TLR - Toll-like receptor.
[a] Discontinued due to safety concerns [48].
[b] Host RNA polymerase inhibitor.
[c] Discontinued [71,72,80].
[d] Host-based target.

(nucleoside reverse transcriptase inhibitors) in treatment-naïve HIV-1 patients (Table 2) [87]. NNRTIs represent one of the most significant classes of drugs designed for the treatment of HIV infection and are a crucial component of current antiretroviral therapy. NNRTIs block HIV-1 replication by preventing RT from completing reverse transcription of the viral single-stranded RNA genome into DNA [108]. Rilpivirine hydrochloride (component of Complera®) was approved by FDA in 2011. Synthesis has been developed but is constantly being refined [109].

Another NNRTI – doravirine (3-chloro-5-[1-[(4-methyl-5-oxo-1*H*-1,2,4-triazol-3-yl)methyl]-2-oxo-4-(trifluoromethyl)pyridin-3-yl]oxybenzonitrile) (Table 2), is a safe and well-tolerated compound used so far in treatment switch without the development of resistance. Doravirine yields an advantageous safety profile and may be most beneficial to patients who wish to reduce pill burden or toxicity of other treatment regimens. In 2018, doravirine was approved by the FDA (trade name Pifeltro™) for treatment of adults living with HIV [88].

Fosdevirine (FDV, GSK2248761; IDX899, 5-chloro-3-[[3-[(*E*)-2-cyanoethenyl]-5-methylphenyl]-methoxyphosphoryl]-1*H*-indole-2-carboxamide), seems to be a very potent, selective reverse transcriptase inhibitor of HIV-1 (Table 1). The compound was active at low nanomolar concentrations in vitro and effective against a broad range of HIV-1 strains [46]. In phase 1 clinical trials, FDV was well tolerated with no significant adverse effects [47]. Unfortunately, in a phase 2b clinical trial (NCT01199731), five subjects experienced new-onset seizures after at least 4 weeks of treatment, and as a result, the clinical development of FDV was terminated [48].

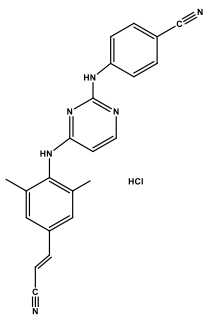
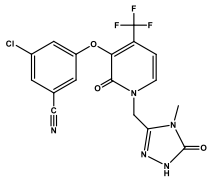
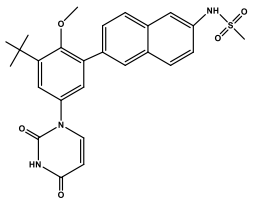
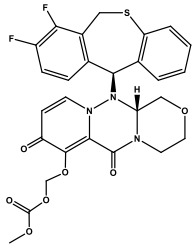
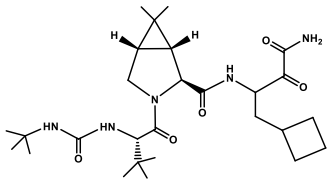
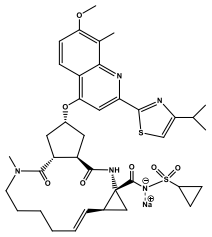
3.2.2. RdRp inhibitors

RNA viruses encode a unique class of RdRps to carry out their fully RNA-based genome replication and transcription. Well-known HCV NS5B is a viral-specific enzyme that is essential for HCV replication (the catalytic subunit of the replicase complex) which contains all the sequence motifs highly conserved among all the known RdRps. HCV RdRp is considered an important target for anti-HCV drug development [110,111].

Dasabuvir (N-[6-[3-*tert*-butyl-5-(2,4-dioxopyrimidin-1-yl)-2-methoxyphenyl]naphthalen-2-yl]methanesulfonamide) (Table 2) is a non-nucleoside NS5B inhibitor of HCV used in combination with ombitasvir for the treatment of chronic HCV infections. It is primarily metabolized by cytochrome P450. Biotransformation of dasabuvir forms the M1 metabolite, which retains antiviral activity. Dasabuvir (trade name Viekira Pak) was approved by FDA in 2014 for the treatment of patients with chronic genotype 1 HCV infections [89].

ABT-072 (*N*-[4-[(*E*)-2-[3-*tert*-butyl-5-(2,4-dioxopyrimidin-1-yl)-2-methoxyphenyl]ethenyl]phenyl]methanesulfonamide)

Table 2
Antiviral drugs approved by FDA in 2010–2020[a].

Generic name	Trade name	Structure	Mechanism of action	FDA approval year
Rilpivirine hydrochloride	Component of Complera®		Polymerase inhibitor (NNRTI) [87]	2011
Type of treatment: in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-naïve adult patients				
Doravirine	Pifeltro™, component of Delstrigo™		Polymerase inhibitor (NNRTI) [88]	2018
Type of treatment: treatment of HIV-1 infection in adult patients with no prior antiretroviral treatment history				
Dasabuvir	Component of Viekira Pak		Polymerase inhibitor (RdRp) [89]	2014
Type of treatment: as monotherapy or in combination with ribavirin for the treatment of patients with chronic genotype 1 Hepatitis C Virus (HCV, *Flaviviridae* family) infections				
Baloxavir marboxil	Xofluza™		Polymerase inhibitor (RdRp) [90]	2018
Type of treatment: treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 h				
Boceprevir	Victrelis™		Protease inhibitor [91]	2011
Type of treatment: treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients, 18 years of age and older				
Simeprevir sodium	Olysio™		Protease inhibitor [92]	2013

(*continued on next page*)

Table 2 (*continued*)

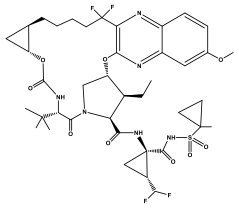
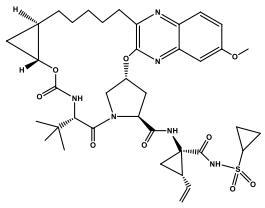
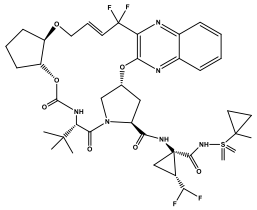
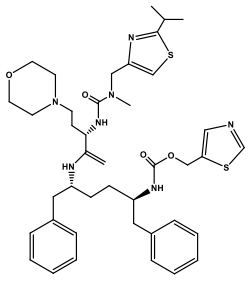
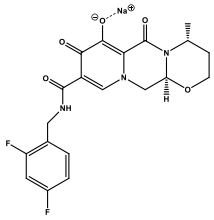
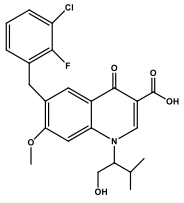
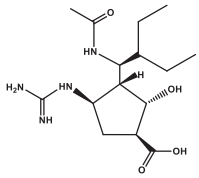
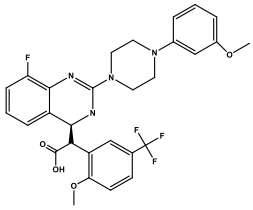
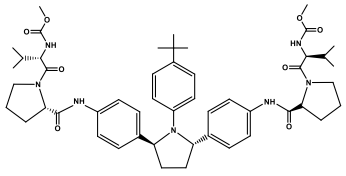
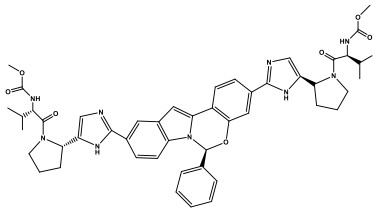
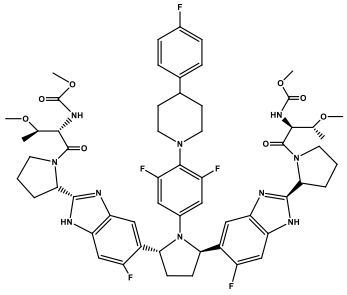
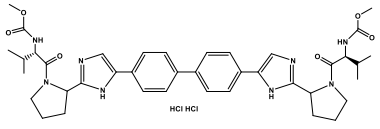
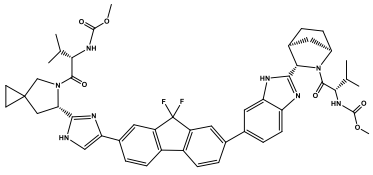
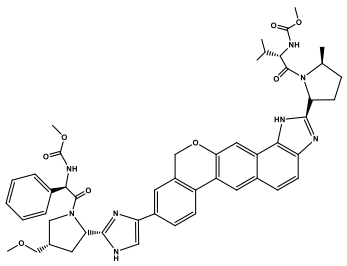
Generic name	Trade name	Structure	Mechanism of action	FDA approval year
Type of treatment: treatment of CHC infection, as a component of a combination antiviral treatment regimen				
Voxilaprevir	Component of Vosevi™		Protease inhibitor [93]	2016
Type of treatment: treatment of adult patients with chronic HCV infection without cirrhosis or with compensated cirrhosis				
Grazoprevir	Component of Zepatier™		Protease inhibitor [94]	2016
Type of treatment: indicated with or without ribavirin for the treatment of chronic HCV genotype 1 or 4 infections in adults				
Glecaprevir	Component of Mavyret™		Protease inhibitor [95]	2017
Type of treatment: treatment of chronic HCV genotype 1, 2, 3, 4, 5, or 6 infections without cirrhosis or with compensated cirrhosis; for patients with HCV genotype 1 infection who previously have been treated with a regimen containing a HCV nonstructural protein 5A (NS5A[b]) inhibitor or an nonstructural protein 3–4A (NS3/4A) protease inhibitor				
Cobicistat	Component of Stribild®		Cytochrome P450 inhibitor [96]	2012
Type of treatment: complete regimen for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older who have no antiretroviral treatment history or to replace the current antiretroviral regimen				
Dolutegravir sodium	Tivicay™		Integrase inhibitor (INSTI) [97]	2013
Type of treatment: in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients				
Elvitegravir	Component of Stribild®		Integrase inhibitor (INSTI) [98]	2012

Table 2 (*continued*)

Generic name	Trade name	Structure	Mechanism of action	FDA approval year
Type of treatment: complete regimen for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older who have no antiretroviral treatment history or to replace the current antiretroviral regimen				
Peramivir	Rapivab™		Neuraminidase inhibitor [99]	2014
Type of treatment: treatment of acute uncomplicated influenza in patients 18 years and older who have been symptomatic for no more than 2 days				
Letermovir	Prevymis™		Terminase inhibitor[c] [100]	2017
Type of treatment: for the prophylaxis of cytomegalovirus (CMV, *Herpesviridae* family) infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant				
Ombitasvir	Component of Viekira Pak		NS5A inhibitor [101]	2014
Type of treatment: as monotherapy or in combination with ribavirin for the treatment of patients with chronic genotype 1 HCV infections				
Elbasvir	Component of Zepatier™		NS5A inhibitor [94]	2016
Type of treatment: indicated with or without ribavirin for the treatment of chronic HCV genotype 1 or 4 infections in adults				
Pibrentasvir	Component of Mavyret™		NS5A inhibitor [95]	2017
Type of treatment: treatment of chronic HCV genotype 1, 2, 3, 4, 5, or 6 infections without cirrhosis or with compensated cirrhosis; for patients with HCV genotype 1 infection who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor				
Daclatasvir	Daklinza™[d]		NS5A inhibitor [102]	2015
Type of treatment: in combination with sofosbuvir for the treatment of HCV genotype 3 infections				
Ledipasvir	Component of Harvoni™		NS5A inhibitor [103]	2014

(*continued on next page*)

Table 2 (*continued*)

Generic name	Trade name	Structure	Mechanism of action	FDA approval year
Type of treatment: treatment of chronic HCV genotype 1 infections in adults				
Velpatasvir	Component of Epclusa®		NS5A inhibitor [104]	2015
Type of treatment: treatment of adult patients with chronic HCV genotypes 1, 2, 3, 4, 5, or 6				

INSTI - integrase strand transfer inhibitor.
[a] According to the FDA Drug Approvals and Databases [105].
[b] Essential component of HCV replication complex.
[c] CMV DNA terminase complex inhibitor.
[d] Discontinued.

(Table 1) is another promising compound for the treatment of HCV infections. This *trans*-stilbene analogue acts as an NS5B polymerase inhibitor. It was developed by Randolph's team [49] and selected among other compounds for clinical evaluation. ABT-072 was characterized by excellent oral bioavailability. Phase 2 clinical studies (NCT01221298) showed ABT-072 as effective in the treatment of HCV genotype 1-infected patients in combination with ABT-450, ritonavir (ABT-450/r), and ribavirin [50].

Radalbuvir (GS-9669, 5-(3,3-dimethylbut-1-ynyl)-3-[[4-hydroxy-4-[[(3*S*)-oxolan-3-yl]oxymethyl]cyclohexyl]-[(1*R*)-4-methylcyclohex-3-ene-1-carbonyl]amino]thiophene-2-carboxylic acid) (Table 1), an inhibitor of HCV NS5B thumb site II, was discovered in 2013 by Lazerwith and co-workers [51]. The drug was active against the clinically relevant NS5B M423T mutant, relative to the wild type. Lazerwith's group reported that this activity was related to both the N-alkyl substituent and N-acyl group [51]. Radalbuvir completed phase 2 clinical trials for the treatment of HCV and was found to be generally well tolerated [53].

Tegobuvir (GS-9190, 5-[[6-[2,4-bis(trifluoromethyl)phenyl]pyridazin-3-yl]methyl]-2-(2-fluorophenyl)imidazo [4,5-c]pyridine) (Table 1) exhibits anti-HCV activity by targeting NS5B polymerase and inhibiting viral replication [54]. The compound undergoes cytochrome P450-mediated activation, and the resulting metabolite specifically interacts with NS5B. A study indicated that tegobuvir showed high potency in vitro [55]. According to reports from phase 1 clinical trials [56,57], the drug induced QT prolongation at high doses. Therefore, its further development was limited to a dose of 40 mg [56].

Basing on the promising results observed in the in vitro studies of tegobuvir, Liu's team [57] designed and synthesized a series of novel inhibitors of HCV NS5B polymerase to improve the antiviral activity and reduce the adverse effects of tegobuvir. However, only one of the investigated compounds showed beneficial effects and safety and was selected for further studies [57].

Inhibitor of the palm pocket of HCV polymerase, setrobuvir (ANA598, *N*-[3-[(1*R*,2*S*,7*R*,8*S*)-3-[(4-fluorophenyl)methyl]-6-hydroxy-4-oxo-3-azatricyclo[6.2.1.$0^{2,7}$]undec-5-en-5-yl]-1,1-dioxo-4*H*-1λ^6,2,4-benzothiadiazin-7-yl]methanesulfonamide) (Table 1), showed moderate-to-high bioavailability and low clearance in clinical trials [59,112].

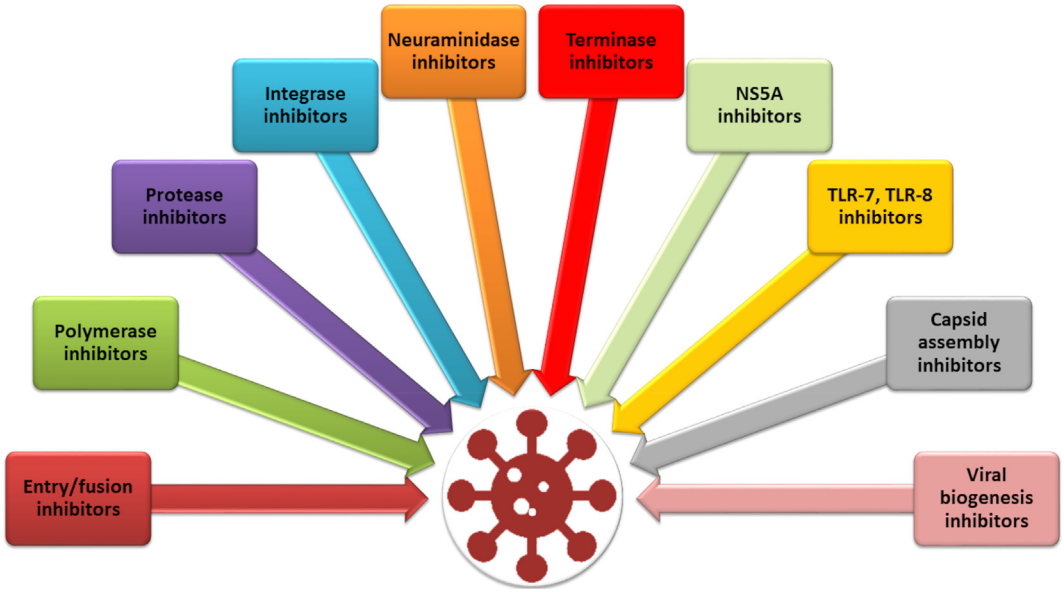


Fig. 5. Molecular mechanisms of antiviral agents action.

Coates and co-workers [61] described the in vitro and in vivo activity of the novel inhaled anti-RSV drug, PC-786 (*N*-(2-fluoro-6-methylphenyl)-6-(4-(5-methyl-2-(7-oxa-2-azaspiro[3.5]nonan-2-yl)nicotinamido)benzoyl)-5,6-dihydro-4H-benzo[b]thieno [2,3-d] azepine-2-carboxamide) (Table 1). Their in vitro studies on Hep-2 cells indicated that PC-786 potently inhibited the activity of RSV RdRp. In addition, sustained antiviral effects were observed in vivo in human bronchial epithelial cells and in lung homogenates from RSV-infected mice and cotton rats. Brookes [62] reported that PC-786 caused concentration-dependent inhibition of viral replication with better effects compared to the nucleoside analogue ALS-8112. PC-786 has completed phase 2 clinical trials (Table 1).

Pimodivir (JNJ-63623872, (2*S*,3*S*)-3-[[5-fluoro-2-(5-fluoro-1*H*-pyrrolo [2,3-b]pyridin-3-yl)pyrimidin-4-yl]amino]bicyclo[2.2.2] octane-2-carboxylic acid) (Table 1) is an inhibitor of PB2 [14]. It prevents the polymerase from binding the 7-methyl GTP cap structures on the host capped RNA, thus causing the inhibition of viral gene transcription. It is worth noting that pimodivir acts selectively against influenza A but not influenza B virus, due to the structural differences in the PB2 cap-binding pocket [63]. In mice influenza model, pimodivir was found to increase survival and reduce lung infections. Smee and co-workers [64] observed that lung viral titers were 100−10,000-fold lower in pimodivir-treated mice than those exposed to placebos. In phase 2 clinical trials, pimodivir was well tolerated, and patients did not experience any complications typically associated with influenza, such as bronchitis, sinusitis, or otitis [65]. These beneficial results led to recent research on its analogues. In the search for novel influenza inhibitors, McGowan and his team evaluated 7-fluoro-substituted indoles as bioisosteric replacements for the 7-azaindole scaffold of pimodivir [66].

Baloxavir marboxil is a single dose oral agent for the treatment of influenza A and B. It suppresses influenza replication by inhibition of cap-dependent endonuclease (CEN, an enzyme required for initiation of influenza mRNA synthesis). CEN is a part of a PA subunit, which constitutes the RdRp of influenza virus. Baloxavir marboxil inhibits mRNA synthesis by binding to RdRp and prevents the replication of the influenza virus [90,113]. Baloxavir marboxil was approved by FDA in 2018 (trade name Xofluza™, Table 2) for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 h.

In the face of the COVID-19 pandemic, a huge increase of interest in RdRp was observed, as it is an important therapeutic target in RNA virus-caused diseases, including SARS-CoV-2. For this reason, many known RdRp inhibitors (such as described in this paragraph dasabuvir [114], pimodivir [115], radalbuvir [116,117] and tegobuvir [118]) have been also included in the research of an effective drug for COVID-19. Elfiky and colleagues [119] made attempts to assess the possibility of using several antiviral drugs or drug candidates (including setrobuvir and mentioned earlier galidesivir) for the treatment of SARS-CoV-2 virus infections (in silico drug-repurposing). In this study, the RdRp of the SARS-CoV-2 was modeled, validated, and after that, molecular docking was performed. Both galidesivir and setrobuvir were able to bind the SARS-CoV-2 RdRp (galidesivir was able to bind with binding energies comparable to those of native nucleotides). However, it should be taken into account that such studies are the first, preliminary step in the search for compounds active against the SARS-CoV-2 virus, and their results may not be consistent with the results of further in vivo studies [60,119]. Researchers have also made attempts to synthetize new RdRp inhibitors. The current state of the knowledge, including both nucleoside analogues and non-nucleoside compounds, has been summarized in a comprehensive review published by Tian and colleagues [107].

3.2.3. Host noncanonical poly(A) RNA polymerase inhibitor

In 2018, Han and co-workers discovered RG7834 [67] ((6*S*)-10-methoxy-9-(3-methoxypropoxy)-2-oxo-6-propan-2-yl-6,7-dihydrobenzo[a]quinolizine-3-carboxylic acid) (Table 1) as a lead compound from the dihydroquinolizinone chemical series based on a phenotypic screening. RG7834 reduced viral messenger RNA and accelerated RNA degradation by targeting host noncanonical poly(A) RNA polymerase-associated domain containing protein 5 and 7 (PAPD5 and PAPD7). Both PAPD5 and PAPD7 are very important host components that are required for hepatitis B virus (HBV, *Hepadnaviridae* family) RNA stabilization, identified as the protein targets of dihydroquinolizinone series [120]. Interestingly, screening studies showed that RG7834 was highly specific for HBV and showed no inhibitory effects against the other 15 DNA or RNA viruses in the panel. RG7834 more strongly inhibited HBV DNA production in vitro in HepaG2.2.15 cell line compared to lamivudine. The drug was well tolerated in vivo studies in rats and monkeys and was found to be orally bioavailable and highly selective. In the same year, RG7834 was investigated by Mueller and colleagues [68]. The researchers confirmed that RG7834 is highly selective for HBV and inhibits the expression of viral proteins specifically by reducing HBV mRNAs.

3.3. Protease inhibitors

Viral proteases are essential in the life cycle of many viruses by affecting the cleavage of viral polyprotein precursors to yield functional products or by catalyzing the processing of the structural proteins necessary for assembly and morphogenesis of virus particles. Most recently, several of the HCV-encoded enzymes, specifically the NS3 protease, have been the focus of intensive research [121]. The NS3/4A serine protease is a non-covalent, heterodimer complex formed by the catalytic subunit of the N-terminal serine protease domain of NS3 and the activation subunit of the NS4A cofactor. The multi-functional property of NS3/4A protease has been an attractive target for drug development [91].

NS3/4A protease inhibitors (PIs) constitute the first class of direct antiviral agents (DAAs) that were approved for HCV treatment. Boceprevir ((1R,2S,5S)−N-(4-amino-1-cyclobutyl-3,4-dioxobutan-2-yl)-3-[(2S)-2-(tert-butylcarbamoylamino)-3,3-dimethylbutanoyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide), component of the drug Victrelis™, is an oral HCV NS3 protease inhibitor that had been approved by FDA in May 2011 for treating chronic genotype 1 HCV infection in combination with peginterferon alfa and ribavirin, in adult patients, 18 years of age and older (Table 2).

Simeprevir sodium (sodium; cyclopropylsulfonyl-[(1R,4R,6S,7Z,15R,17R)-17-[7-methoxy-8-methyl-2-(4-propan-2-yl-1,3-thiazol-2-yl)quinolin-4-yl]oxy-13-methyl-2,14-dioxo-3,13-diazatricyclo[13.3.0.04,6]octadec-7-ene-4-carbonyl]azanide) (Table 2) − a small molecular drug targeting the NS3/4A protease of HCV was approved by FDA in 2013 as a component of Olysio™, for the treatment of chronic hepatitis C (CHC) infection [92]. Chemical work on the industrial-scale synthesis of this drug using ring-closing metathesis [122], for example, is still in progress.

Structurally similar voxilaprevir ((1R,18R,20R,24S,27S,28S)-24-*tert*-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-[(1-methylcyclopropyl)sulfonylcarbamoyl]cyclopropyl]-28-ethyl-13,13-difluoro-7-methoxy-22,25-dioxo-2,21-dioxa-4,11,23,26-tetrazapentacyclo[24.2.1.03,12.05,10.018,20]nonacosa-3,5(10),6,8,11-pentaene-27-carboxamide), grazoprevir ((1R,18R,20R,24S,27S)-24-*tert*-butyl-N-[(1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-ethenylcyclopropyl]-7-methoxy-22,25-dioxo-2,21-dioxa-4,11,23,26-tetrazapentacyclo [24.2.1.03,12.05,10.018,20]nonacosa-3,5(10),6,8,11-pentaene-27-

carboxamide), and glecaprevir ((1R,14E,18R,22R,26S,29S)-26-*tert*-butyl-N-[(1R,2R)-2-(difluoromethyl)-1-[(1-methylcyclopropyl)sulfonylcarbamoyl]cyclopropyl]-13,13-difluoro-24,27-dioxo-2,17,23-trioxa-4,11,25,28-tetrazapentacyclo[26.2.1.03,12.05,10.018,22]hentriaconta-3,5,7,9,11,14-hexaene-29-carboxamide) (Table 2) bind reversibly to the NS3/4A protease active site. Voxilaprevir (Table 2), a component of Vosevi™, was approved in 2016 for the treatment of adult patients with chronic HCV infection without cirrhosis or with compensated cirrhosis [93]. Grazoprevir, a component of Zepatier™, was approved the same year by FDA to treat chronic HCV genotype 1 or 4 infections in adults [94].

Glecaprevir is a component of Mavyret™ (Table 2), which FDA approved in 2017 as the cure for chronic HCV genotype 1, 2, 3, 4, 5 or 6 infections without cirrhosis or with compensated cirrhosis as well as for patients with HCV genotype 1 infection, previously treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor [95].

The use of HIV protease as a potential target was documented in experiments that showed that mutations in the protease resulted in the production of defective, noninfectious viral particles. Clinical trials with protease inhibitors in monotherapy demonstrated the potency of this class of drugs, as evidenced by significant reductions in HIV-1 RNA levels in plasma [121]. Mentioned above cobicistat (1,3-thiazol-5-ylmethyl N-[(2R,5R)-5-[[(2S)-2-[[methyl-[(2-propan-2-yl-1,3-thiazol-4-yl)methyl]carbamoyl]amino]-4-morpholin-4-ylbutanoyl]amino]-1,6-diphenylhexan-2-yl]carbamate) (Table 2) is a pharmacoenhancer used with HIV protease inhibitors [96].

3.4. Integrase inhibitors

HIV-1 integrase (IN) catalyzes the insertion of the viral DNA into the genome of host cells. IN inhibition is an attractive therapeutic target for HIV-1 treatment because of its essential role in HIV-1 replication and the lack of homologue in human cells. Identification of IN led to the approval of specific drugs [123].

One of the examples of HIV integrase inhibitors is dolutegravir sodium (sodium; (3S,7R)-13-[(2,4-difluorophenyl)methylcarbamoyl]-7-methyl-9,12-dioxo-4-oxa-1,8-diazatricyclo[8.4.0.03,8]tetradeca-10,13-dien-11-olate) (trade name Tivicay™, Table 2), a second-generation integrase inhibitor approved by FDA in 2013 in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients. Dolutegravir is also an attractive option for HIV-positive liver transplant recipients because of its minimal dependence on cytochrome P450 (CYP)-3A-mediated metabolism, high potency, and high genetic barrier [97].

Another example is elvitegravir (6-[(3-chloro-2-fluorophenyl)methyl]-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxoquinoline-3-carboxylic acid (Table 2). It was approved by FDA in 2012 as a component of Stribild®, the four-drug combination (elvitegravir/cobicistat/emtricitabine/tenofovir). Elvitegravir requires coadministration with a CYP enzyme inhibitor. The aim of the CYP enzyme inhibitor was to increase the exposure to the study drug. FDA's ClinPharm Review for elvitegravir described the problem of excessive catabolism and also revealed the solution of using a “pharmacokinetic booster” – an inhibitor of cytochrome P450 3A (CYP3A) – mentioned above Stribild® component – cobicistat [124].

3.5. Neuraminidase inhibitors

Neuraminidase (NA) is an attractive target for antiviral therapy because of its crucial role in the pathogenicity of many respiratory viruses. NA removes sialic acid from the surface of virus particles and infected host cells, preventing viral self-aggregation and promoting efficient viral spread. NA also plays a role in the initial penetration of the mucosal lining of the respiratory tract [125].

Neuraminidase inhibitor peramivir ((1*S*,2*S*,3*S*,4*R*)-3-[(1*S*)-1-acetamido-2-ethylbutyl]-4-(diaminomethylideneamino)-2-hydroxycyclopentane-1-carboxylic acid) (trade name Rapivab™, Table 2) was approved by FDA in 2014 for the treatment of uncomplicated acute influenza in patients 18 years and older who have been symptomatic for no more than 2 days.

3.6. Terminase inhibitors

CMV genomic replication involves a mechanism that produces multiple genomic units (concatamers). The viral terminase complex cleaves concatameric viral DNA into full-length genomes and packages a single genome into the viral nucleocapsid as part of new virion formation. Thus, terminase complex represents an attractive therapeutic target. Letermovir (2-[(4*S*)-8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-4*H*-quinazolin-4-yl]acetic acid) (Table 2) was discovered by high-throughput screening to have activity against CMV. Letermovir (trade name Prevymis™) was approved by FDA in 2017 for the prophylaxis of CMV infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant [100].

3.7. NS5A inhibitors

NS5A is an essential component of the HCV replicase and exerts a wide range of effects on cellular pathways and processes, including innate immunity and host cell growth and proliferation. Therefore, NS5A has been widely investigated because of its ability to subvert the host interferon-induced antiviral response. There are several NS5A inhibitors approved for the treatment of different types HCV genotypes, usually in combination with other antiviral components [126].

Well-known NS5A inhibitors are ombitasvir (methyl *N*-[(2*S*)-1-[(2*S*)-2-[[4-[(2*S*,5*S*)-1-(4-*tert*-butylphenyl)-5-[4-[[(2*S*)-1-[(2*S*)-2-(methoxycarbonylamino)-3-methylbutanoyl]pyrrolidine-2-carbonyl]amino]phenyl]pyrrolidin-2-yl]phenyl]carbamoyl]pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl]carbamate) (Table 2) – a component of mentioned above drug Viekira Pak and elbasvir (methyl *N*-[(2*S*)-1-[(2*S*)-2-[5-[(6*S*)-3-[2-[(2*S*)-1-[(2*S*)-2-(methoxycarbonylamino)-3-methylbutanoyl]pyrrolidin-2-yl]-1*H*-imidazole-5-yl]-6-phenyl-6*H*-indolo [1,2-c] [1,3]benzoxazin-10-yl]-1*H*-imidazole-2-yl]pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl]carbamate) (Table 2, component of Zepatier™). Other examples are pibrentasvir (methyl *N*-[(2*S*,3*R*)-1-[(2*S*)-2-[6-[(2*R*,5*R*)-1-[3,5-difluoro-4-[4-(4-fluorophenyl)piperidin-1-yl]phenyl]-5-[6-fluoro-2-[(2*S*)-1-[(2*S*,3*R*)-3-methoxy-2-(methoxycarbonylamino)butanoyl]pyrrolidin-2-yl]-3*H*-benzimidazol-5-yl]pyrrolidin-2-yl]-5-fluoro-1*H*-benzimidazol-2-yl]pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl]carbamate) (Table 2, component of Mavyret™) and daclatasvir dihydrochloride (methyl *N*-[(2*S*)-1-[(2*S*)-2-[5-[4-[4-[2-[(2*S*)-1-[(2*S*)-2-(methoxycarbonylamino)-3-methylbutanoyl]pyrrolidin-2-yl]-1*H*-imidazole-5-yl]phenyl]phenyl]-1*H*-imidazole-2-yl]pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl]carbamate; dihydrochloride) – which is used in combination with mentioned above sofosbuvir for HCV treatment genotype 3 infections (Daklinza™, Table 2). In addition, ledipasvir (methyl *N*-[(2*S*)-1-[(6*S*)-6-[5-[9,9-difluoro-7-[2-[(1*R*,3*S*,4*S*)-2-[(2*S*)-2-(methoxycarbonylamino)-3-methylbutanoyl]-2-azabicyclo[2.2.1]heptan-3-yl]-3*H*-benzimidazol-5-yl]fluoren-2-yl]-1*H*-imidazole-2-yl]-5-azaspiro[2.4]heptan-5-yl]-3-methyl-1-oxobutan-2-yl]carbamate) and veplatasvir (methyl N-[(1R)-2-[(2*S*,4*S*)-2-[5-[6-[(2*S*,5*S*)-1-[(2*S*)-2-

(methoxycarbonylamino)-3-methylbutanoyl]-5-methylpyrrolidin-2-yl]-21-oxa-5,7-diazapentacyclo[11.8.0.03,11.04,8.014,19]henicosa-1(13),2,4(8),5,9,11,14(19),15,17-nonaen-17-yl]-1H-imidazole-2-yl]-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl] carbamate) are compounds that also belong to the group of NS5A inhibitors and were approved as components of drugs approved for the treatment of HCV (Table 2, trade names Harvoni™ and Epclusa®, respectively).

3.8. TLR-7 and TLR-8 inhibitors

TLR-7, a member of the TLR family, is a pathogen recognition receptor. It is expressed in the cell membrane or the endosomal compartments of plasmacytoid dendritic cells and B cells. After a ligand binds TLR-7, recruitment of adaptor proteins occurs and a signal transduction cascade starts, resulting in both innate and adaptive immune response. Furthermore, due to its ability to drive an antiviral response, TLR-7 is considered a therapeutic host-based target for viral infections [69,70].

Vesatolimod (GS-9620, 4-amino-2-butoxy-8-{[3-(pyrrolidin-1-ylmethyl)phenyl]methyl}-5,7-dihydropteridin-6-one) (Table 1) is an oral TLR-7 agonist developed for the treatment of chronic viral hepatitis by Lanford [69]. In vivo studies on chimpanzees showed that vesatolimod activated TLR-7 signaling and caused a rapid reduction of viremia, a decrease in the levels of serum hepatitis B surface antigen (HBsAg) and hepatitis B e-antigen, and an apparent reduction in the number of infected hepatocytes. Pharmacokinetic studies indicated that vesatolimod is safe and generally well tolerated at low oral doses [70]. However, in phase 2 clinical studies (NCT02579382, NCT02166047) conducted with patients suffering from chronic HBV infection, vesatolimod did not result in a clinically significant decline in serum HBsAg level and hence was not tested further [71,72].

Another TLR agonist, selgantolimod (GS-9688, (2*R*)-2-[(2-amino-7-fluoropyrido [3,2-d]pyrimidin-4-yl)amino]-2-methylhexan-1-ol) (Table 1), was discovered by Mackman's group as a selective oral compound for the treatment of CHB [73]. It is an agonist of TLR-8. Contrary to TLR-7, human TLR-8 is located on the endosomal membrane of myeloid dendritic cells, macrophages, monocytes, and neutrophils and can recognize single-stranded RNA fragments. In vivo, the woodchuck CHB model displays many features of human CHB and is therefore commonly used to evaluate the antiviral efficacy of immunomodulatory compounds. In vivo studies conducted by Mackman's group on this model showed that selgantolimod is a selective TLR-8 agonist and exhibits good oral absorption and high clearance limiting the systemic exposure levels [73]. Selgantolimod completed phase 2 clinical trials.

3.9. Capsid assembly inhibitors

Capsid assembly is a critical step in the propagation of HBV [74]. Based on the previous reports that heteroaryldihydropyrimidines (HAPs) influence the accumulation of HBV capsid [127], Wang and colleagues synthesized another HAP compound, morphothiadin (GLS-4, ethyl 4-(2-bromo-4-fluorophenyl)-6-(morpholin-4-ylmethyl)-2-(1,3-thiazol-2-yl)-1,4-dihydropyrimidine-5-carboxylate) (Table 1) [74], first-in-class HBV capsid assembly modulator, that can inhibit HBV replication by interfering with the assembly and disassembly of HBV nucleocapsid. Authors observed that the compound exhibited promising in vitro dose-dependent activity against HBV. Moreover, its antiviral activity was found to be higher than lamivudine which is an antiviral drug used for HBV treatment. Adefovir-resistant mutants were also sensitive to the investigated compound. In vivo studies confirmed beneficial results with little evidence of hepatotoxicity as well as overall toxicity in the mice model [75]. In addition, the pharmacokinetic and toxicity profiles of the drug were favorable [76]. Morphothiadin in combination with ritonavir reached a phase 2 clinical trial for the treatment of chronic HBV infections (NCT04147208). Recently, based on the strategy of inhibiting HBV capsid assembly, Ren and co-workers [77] carried out further research on a series of morphothiadin derivatives with promising anti-HBV activity and improved pharmacokinetic properties.

3.10. Viral biogenesis inhibitor

ABX464 (8-chloro-*N*-[4-(trifluoromethoxy)phenyl]quinolin-2-amine) (Table 1) was selected as the most promising anti-HIV drug after the functional screening. Its mechanism of action was described for the first time in 2015 [78]. The activity of ABX464 is connected with Rev protein and is based on blocking viral inhibition by preventing the export of unspliced RNA to the cytoplasm, and by interacting with the Cap-Binding Complex (CBC). ABX464 is non-toxic and does not give rise to resistant HIV-1 variants. After favorable results obtained in humanized SCID mice models, ABX464 entered clinical trials. A recent study [79] confirmed that this new compound is characterized by good safety and tolerability. When included in an HIV-1 protease inhibitor-based regimen, it caused a reduction in the levels of HIV-1 DNA in peripheral blood mononuclear cells. ABX464 is currently tested for the treatment of patients with COVID-19 (phase 3) and HIV (phase 2).

4. Conclusions and future directions

The last decade has witnessed remarkable achievements in the field of antiviral drug discovery. Several new antiviral drugs have been introduced for the treatment of HIV, HCV, CMV, and influenza infections. The efforts included introduction of new molecules and repositioning of drugs already in clinical use. The search for new antiviral compounds was performed not only among nucleoside analogues but also not related to nucleosides chemical compounds. The adenosine analogue islatravir is an example of a new nucleoside analogue that has been successfully introduced into phase 3 clinical trials as an anti-HIV agent. ABX464 is an example of a non-nucleoside derivative that has entered phase 3 clinical trials. The antimalarial drug chloroquine, an example of drug repositioning, has currently completed phase 4 clinical trials for treating COVID-19 infection. Most of the tested antiviral agents are inhibitors of specific enzymes involved in various stages of the virus life cycle, such as viral polymerases and proteases.

Scientists are also interested in using biologically active metabolites in antiviral therapy. Such compounds have been considered for antiviral therapy and prophylaxis, due to their antioxidant, antibacterial, antifungal, and antiviral activities [128]. Articles published by Singh and colleagues, and Bibi and co-workers, describe the antiviral efficacy of plant-based therapeutics against SARS-CoV-2 [129,130]. Besides, nanoparticles have been widely investigated as carriers for known antiviral agents [131]. Search for new compounds with antiviral activity is currently supported by bioinformatics methods that enable a better understanding of pathophysiology of diseases and to introduce effective treatment [132], including design of antiviral agents for COVID-19 [133]. Furthermore, monoclonal antibodies [134–136] and the CRISPR-Cas system are considered as biotherapeutic alternatives to synthetic compounds in antiviral therapy [137–139].

At least 20 antiviral drugs have been approved for treatment by the FDA between 2010 and 2020, and 14 compounds described in this review show promising results in clinical or preclinical trials. As an update, it should also be added that on the December 22, 2021, the FDA authorized a new drug against COVID-19 – trade

name Paxlovid, which proves the rapid development of antiviral therapies.

Finding an effective antiviral therapy is a challenge for modern medicine. However, the variety of currently available treatment methods may contribute to further advances in this field, and although these methods are not a panacea, they could serve as means to control the broad range of viral infections.

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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