Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Infection and Public Health 14 (2021) 1075–1086

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: http://www.elsevier.com/locate/jiph

Review

Trends in the development of remdesivir based inventions against COVID-19 and other disorders: A patent review

Mohd. Imran[a,*], Ahmed Subeh Alshrari[b], Syed Mohammed Basheeruddin Asdaq[c], Abida[a]

[a] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Northern Border University, Rafha, Saudi Arabia
[b] Department of Biological Sciences, Faculty of Science, Northern Border University, Saudi Arabia
[c] Department of Pharmacy Practice, College of Pharmacy, AlMaarefa University, Dariyah, 13713, Riyadh, Saudi Arabia

ARTICLE INFO

Article history:
Received 20 May 2021
Received in revised form 17 June 2021
Accepted 21 June 2021

Keywords:
Remdesivir
COVID-19
Patent
Composition
Combination
Delivery system
New indication

ABSTRACT

The development of remdesivir has been a breakthrough for COVID-19 treatment. It has been approved in about 50 countries, including Saudi Arabia, since 2020. The generic structure of remdesivir was first disclosed in 2009. This patent review summarizes the remdesivir based inventions to treat/prevent COVID-19 and other disorders from 2009 to May 16, 2021, emphasizing the patents related to medical and pharmaceutical sciences. The primary patents/patent applications of remdesivir are related to its compositions, new combinations with other therapeutic agents, delivery systems, and new indications. The inventive combinations have displayed synergistic effects against COVID-19, whereas the delivery systems/compositions have improved patient compliance. The inventions related to new indications of remdesivir to treat Ebola, hepatitis, idiopathic pulmonary fibrosis, diabetic nephropathy, and cardiovascular complications enhance its therapeutic area. Many new innovative combinations and delivery systems of remdesivir are anticipated to provide better treatment for COVID-19.

Contents

* Corresponding author.
E-mail addresses: imran.pchem@gmail.com, imran_inderlok@yahoo.co.in (Mohd. Imran), alshrari@live.com (A.S. Alshrari), sasdag@mcst.edu.sa (S.M.B. Asdaq), aqua_abkhan@yahoo.com (Abida).

https://doi.org/10.1016/j.jiph.2021.06.013

Introduction

COVID-19, a communicable pandemic infection, was first noticed in Wuhan, China, in December 2019. It is triggered by a new single-stranded virus (SARS-CoV-2). The general signs of COVID-19 comprise fatigue, fever, cough, loss of smell/taste, and shortness of breath. Some people may develop ARDS (acute respiratory distress syndrome) due to cytokine release, septic shock, and blood clots. Accordingly, it may be fatal in some patients [1]. By May 16, 2021, about 162,177,376 confirmed cases of COVID-19 had been reported globally, approximately 3,364,178 people have died of COVID-19, and 1,264,164,553 people have been vaccinated [2]. The World Health Organization (WHO) has issued guidelines, advice, and situation reports regularly to the general public and health workers about COVID-19 [3]. Many reviews have discussed the epidemiology, diagnosis, treatment, vaccines, and challenges of dealing with COVID-19 [4–9].

Remdesivir (GS-5734)

Remdesivir (Fig. 1) is a tetrahydrofuran based pyrrolo-triazine derivative (MF: $C_{27}H_{35}N_6O_8P$; MW: 602.6; CAS Number: 1809249-37-3), which has been developed by Gilead Sciences [7]. In May 2020, the United States Food and Drug Administration (USFDA) approved an Emergency Use Authorization (EUA) to remdesivir [10], wherein the USFDA fully approved it on October 22, 2020. Remdesivir is indicated to treat COVID-19, which is subjected to certain conditions (Table 1). First, it must be administered in a healthcare center or hospital, providing acute care similar to inpatient hospital care because remdesivir intravenous (IV) infusion must be administered by a trained professional. Second, remdesivir is approved for COVID-19 patients >12 years of age and weighing >40 kg because of the established safety and efficacy clinical studied. The recommended dosage of remdesivir in COVID-19 patients comprises a single loading IV infusion of remdesivir (200 mg) on day 1 followed by a maintenance dose (100 mg) from day 2 via IV infusion (30−120 min). The recommended treatment duration is not less than 5 days and not more than 10 days. The USFDA has also allowed the EUA to remdesivir to pediatric COVID-19 patients of <12 years of age and weighing between 3.5 to 40 kg because of the severity of COVID-19, higher benefit to risk ratio, and lack of adequate or suitable alternative of remdesivir [11]. As of May 16, 2021, remdesivir has been approved in about 50 countries since 2020 to treat COVID-19. These countries include Australia, India, United Arab Emirates, Argentina, Japan, Canada, Lebanon, Russia, Great Britain, European Union (about 30 countries), United States of America, Brazil, Israel, Guatemala, Qatar, Iraq, Saudi Arabia, South Korea, Kuwait, Hong Kong, Turkey, Switzerland, Singapore, Bahrain, Mexico, Jordan, and Taiwan [12].

Pharmacology of remdesivir

The SARS-Cov-2 mainly affects the respiratory tract and the enterocytes of the gastrointestinal tract. It requires RNA-dependent RNA polymerase (RdRp) to replicate [13–16] (Scheme 1).

Remdesivir, a phosphoramidite prodrug, enters the cell and breaks into its monophosphate form. This monophosphate form

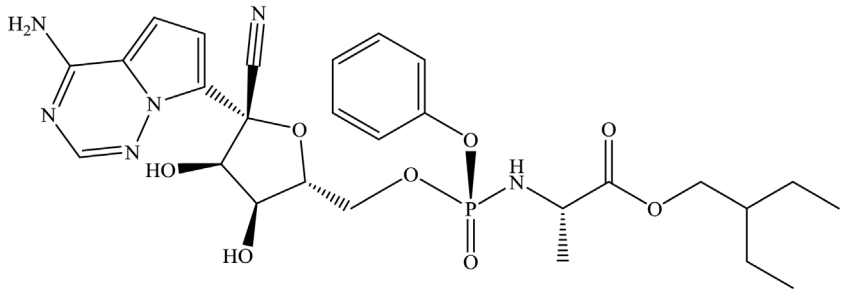
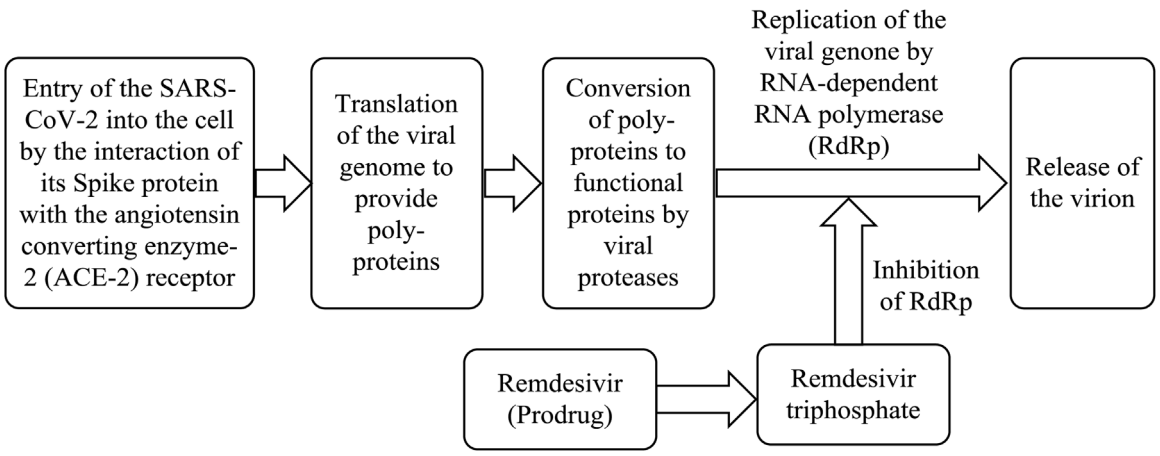


Fig. 1. Remdesivir (GS-5734).

Table 1
The Rx data of remdesivir.

Active ingredient (Proprietary name; Applicant name; NDA number)	Dosage form (Route; Strength)	Approval date (Marketing status)	Indication	Exclusivity (Expiry date)
Remdesivir (Veklury; Gilead Sciences; N214787)	Powder (Intravenous; 100 mg/vial)	October 22, 2020 (Prescription)	Treatment of COVID-19 in adults and pediatric patients (at least 12 years of age and 40 kg) requiring hospitalization	New chemical entity (October 22, 2025)
	Solution (Intravenous; 5 mg/ml)			



Scheme 1. Life cycle of SARS-CoV-2 in host cell and mechanism of action of remdesivir.

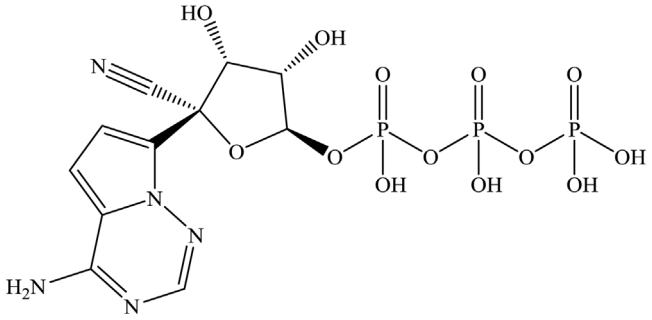


Fig. 2. Remdesivir triphosphate (GS-443902).

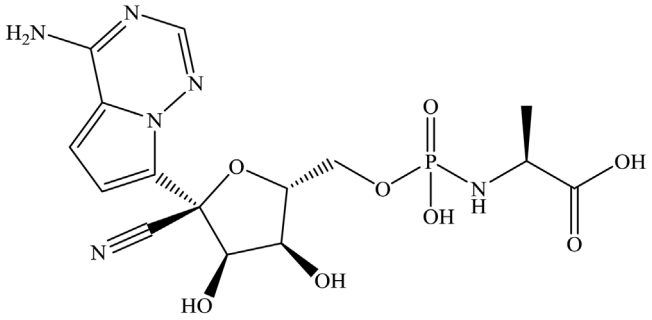


Fig. 3. GS-704277.

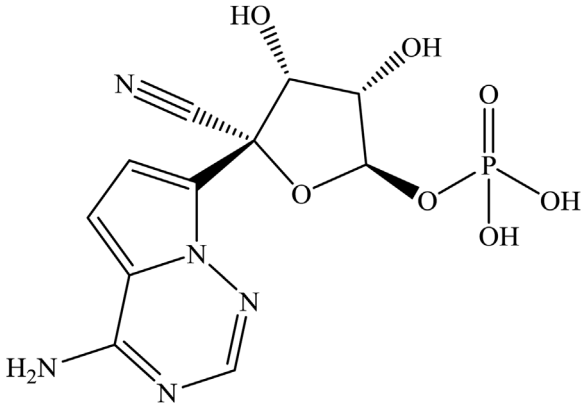


Fig. 4. GS-441524-MP.

converts to remdesivir triphosphate (RDV-TP, GS-443902, Fig. 2) after phosphorylation. The RDV-TP incorporates into the RdRp complex in place of ATP and inhibits its activity [11,14].

Remdesivir shows poor affinity towards RNA polymerase II and mitochondrial RNA polymerase. Accordingly, it is supposed to possess a good safety profile in humans [8]. The single-dose (3–225 mg) clinical studies of remdesivir have demonstrated its non-toxic and tolerable effects [8]. Remdesivir is absorbed fast, has a moderate duration of action with an elimination half-life of about one hour, shows protein binding of about 88–93%, and about 74% is excreted via urine [11,17]. The significant metabolites of remdesivir are GS-704277 (Fig. 3), GS-441524-MP (Fig. 4), and GS-441524 (Fig. 5) [10,17,18] (Scheme 2).

Nausea is the most common side effect of remdesivir. Remdesivir can cause allergic reactions during its infusion or after the infusion. Consequently, the remdesivir treatment must be discontinued in patients showing clinically significant hypersensitivity to remdesivir or any component of its product. The remdesivir dose (150 mg) for 7–14 days revealed a reversible increase in the liver enzymes, for example, alanine aminotransferase and aspartate transaminase [8]. Besides, remdesivir can also lead to an increase in the prothrombin time [11]. Therefore, liver function tests and determination of the prothrombin time are recommended before and during the remdesivir therapy. The injection of remdesivir is prepared in sulfobutylether-β-cyclodextrin (SBECD), which can cause renal dysfunction due to its accumulation in the kidney. Consequently, patients exhibiting an eGFR of <30 ml/min are not recommended to take remdesivir [8,11]. Accordingly, the testing of the eGFR has to be done before the start of remdesivir therapy [8–11]. As of date, there is no data on the overdose and antidote of remdesivir. The overdose cases must be monitored and handled based on the sign, symptoms, and clinical status of the patient [11]. No published report establishes reproductive, teratogenic, developmental toxicity of remdesivir [8].

Clinical trials on remdesivir

Many combinations of remdesivir with other drugs, for example, lopinavir, ritonavir, interferon beta-1a & 1b, merimepodib, NA-831, baricitinib, dexamethasone, tocilizumab, risankizumab, lenzilumab, plitidepsin, and hydroxychloroquine, are in a clinical trial to treat COVID-19 [19]. However, it is also in a clinical trial for other conditions [20], which is provided in Table 2.

Some critical patent reviews on coronavirus have been published [21–25]. These articles mention the name of remdesivir but are silent about its patent literature. The authors believe no review discusses remdesivir based patent inventions/innovations to treat

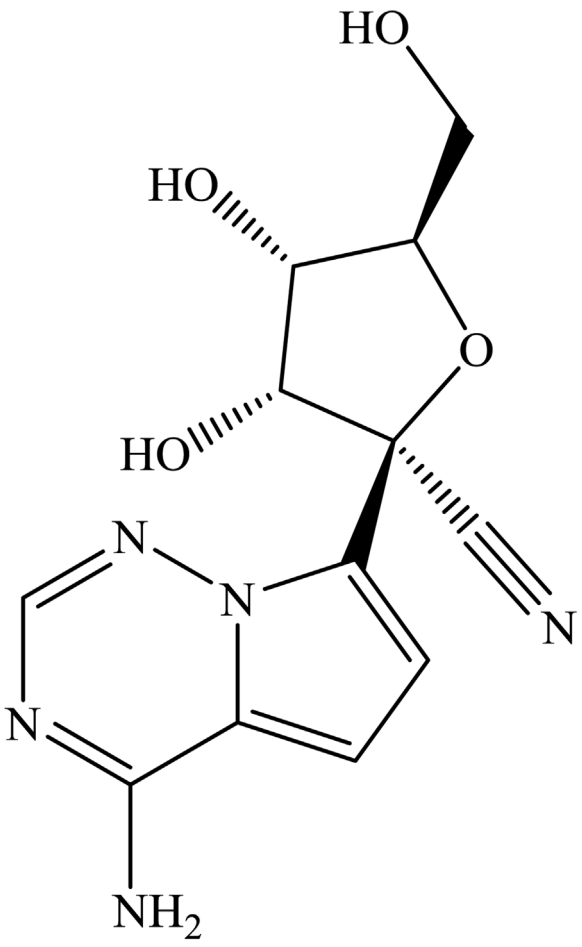


Fig. 5. GS-441524.

COVID-19. This review updates the scientific fraternity about the existing inventions/innovations of remdesivir. It will help them generate innovative ideas to provide better remdesivir based treatments for COVID-19.

Methodology

Patent literature searching

The updated patent searching (June 14, 2021) was performed through Espacenet, WIPO, USPTO, and Scifinder databases. The exact structure search of remdesivir and its CAS number search was done by the Scifinder database. The keywords remdesivir and GS-5734 were used for patent search in the Espacenet, WIPO, and USPTO databases (Scheme 3). The compound patents of remdesivir were identified using the exact structure search of remdesivir in the Scifinder database.

Exclusion criteria

The patents/patent applications that do not use the terms "remdesivir or GS-5734" or the chemical structure of remdesivir specifically or generically in the claim section of the patent/patent application were excluded from the final list. The patents/patent applications related to the novel synthetic compounds as antiinfective/antiviral agents have not been included in this review because these compounds have never been tested in humans. The data of cited patents/applications in this review are provide in Table 3.

Translation of non-English patents/patent applications

The translation of the non-English patents/patent applications was obtained from Espacenet and WIPO databases.

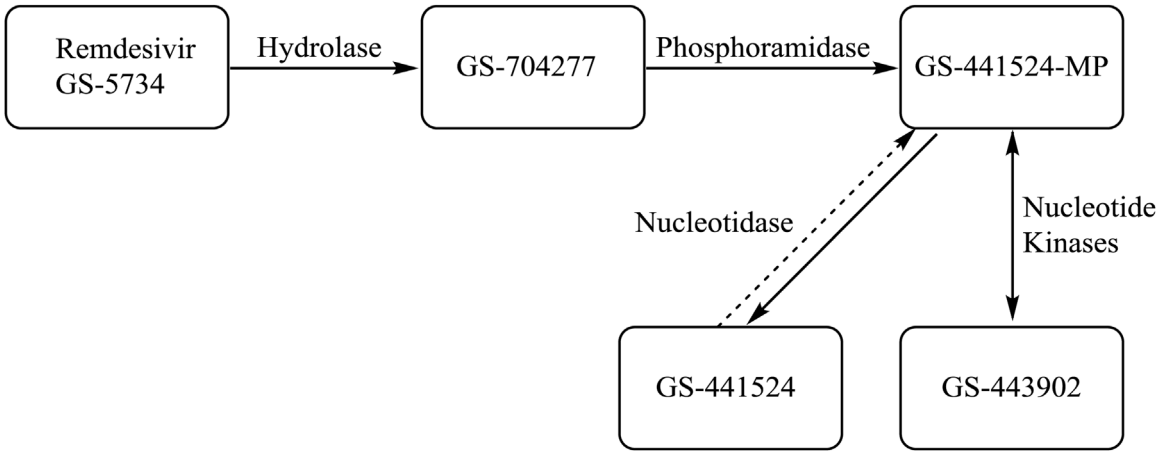
Results

Compound patents of remdesivir

US10065958B2 provides ribosides, riboside phosphates, and prodrugs for treating infections caused by the Paramyxoviridae virus family, particularly for respiratory infections of syncytial parainfluenza virus. This patent covers remdesivir and its salts. The patent exemplifies the respiratory syncytial virus antiviral activity of the disclosed compounds and their cytotoxicity assays [26].

US8008264B2 claims the general structure of remdesivir. It also claims a method of treating a viral infection (dengue, yellow fever, etc.) using the disclosed compounds alone or in a combination of other therapeutic agents [27]. **US8318682B2** [28] and **USRE46762E** [29] also claim the general structure of remdesivir to treat viral diseases. These three patents exemplify the antiviral activity of the disclosed compounds, including the IC_{50} and EC_{50} values of the Hepatitis C virus.

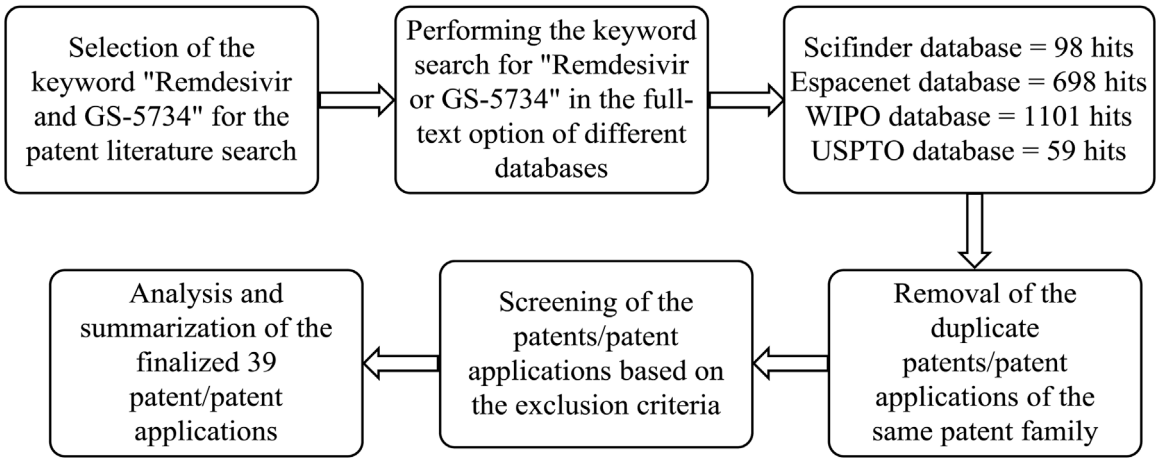
US9724360B2 [30] and **US9949994B2** [31] unveil ribosides, riboside phosphates, prodrugs thereof, and their pharmaceuticals compositions to treat Ebola, Cueva, and Marburg viral infections. These patents specifically cover the specific isomer of remdesivir (Fig. 1) to prepare its marketed dosage forms. They also exemplify



Scheme 2. The intracellular metabolic pathway of remdesivir.

Table 2
Clinical trial on remdesivir for new conditions.

Condition (Intervention) (NCT number)	Phase (Location)	Sponsor/collaborator (Funder type)	Status (Study start)	Study completion (Last update)
Ebola/HIV/AIDS (Remdesivir) (NCT04385719)	2 (Uganda)	Makerere University; University of Liverpool, and EDCTP (Other)	The study has not started recruiting participants (July 2020)	June 2021 (May 13, 2020)
Pneumonia/viral (Remdesivir) (NCT04728880)	Unknown (Egypt)	Mansoura University (Other)	Recruiting (January 26, 2021)	May 30, 2021 (January 28, 2021)
COVID-19 pneumonia (Remdesivir and Tocilizumab) (NCT04409262)	3 (United States)	Hoffmann-La Roche, and Gilead Sciences (Industry)	Completed (June 16, 2020)	March 8, 2021 (March 11, 2021)
Ebola (GS-5734) (NCT02818582)	2 (Guinea and Liberia)	National Institute of Allergy and Infectious Diseases, and National Institutes of Health Clinical Center (NIH)	Completed (July 1, 2016)	August 31, 2020 (September 30, 2020)
Acute respiratory distress syndrome (Remdesivir and hydroxychloroquine) (NCT04321616)	3 (Norway)	Oslo University Hospital (Other)	Recruiting (March 28, 2020)	November 2020 (April 14, 2020)
Ebola virus (Remdesivir, ZMapp, MAb114, and REGN-EB3) (NCT03719586)	2/3 (United States and The Democratic Republic of the Congo)	National Institute of Allergy and Infectious Diseases, and National Institute of Allergy and Infectious Diseases (NIH)	Completed (November 21, 2018)	August 18, 2020 (December 4, 2020)



Scheme 3. Methodology of the patent literature search.

the anti-Ebola virus activity and the cytotoxicity assays of the stated compounds.

Polymorph patents of remdesivir

US10836787B2 claims the crystalline form of remdesivir. The disclosed crystalline form is claimed to have a bioavailability advantage, physical stability and is suitable to manufacture the solid dosage forms for the intended therapeutic use. The patent also mentions the method of preparation of the claimed polymorph [32].

Pharmaceutical compositions of remdesivir to treat/prevent COVID-19

Pharmaceutical composition of remdesivir for monotherapy

US10695361B2 claims a method of treating Coronaviridae infection (SARS, MERS, 229E, NL63, OC43, and HKU1) by administering a pharmaceutical composition (solid dosage forms, injectable, and emulsion, etc.) of remdesivir. This is the primary patent that covers the use of remdesivir to treat SARS-CoV-2 infection. The patent exemplifies the activity of the compounds against SARS-CoV in Mice and MERS-CoV in rhesus monkeys [33].

US10675296B2 relates to a lyophilized composition containing remdesivir (1%–10%) and cyclodextrin, for example, sulfobutylether-β-cyclodextrin sodium (90%–99%), for treating infections caused by Arenaviridae, Coronaviridae, Filoviridae, Flaviviridae, or Paramyxoviridae family viruses. The claimed composition showed enhanced solubility and improved usability for parenteral administration. The claimed composition may optionally contain a pH adjusting agent like sodium hydroxide or hydrochloric acid. The composition of remdesivir with β-cyclodextrin can deliver varying required doses of remdesivir without precipitation of remdesivir and are compatible with other IV solvents. This patent covers the marketed dosage form of remdesivir to treat COVID-19. The patent exemplifies the preparation of lyophilized/injectable composition and its stability testing [34].

US20200360292A1 discloses an anhydrous composition (e.g. liquid, or capsule) comprising an oil-soluble hydrophobic drug (e.g. remdesivir), an oil-soluble hydrophobic surfactant (e.g. dodecyl maltoside), and a pharmaceutically acceptable carrier (e.g., Miglyol.RTM. 812, and Vitamin E), wherein the drug and the surfactant are dissolved in the pharmaceutically acceptable carrier. This oral formulation is claimed to possess enhanced bioavailability of the hydrophobic drug from the gastrointestinal tract. Since remdesivir is a hydrophobic drug, such formulation (e.g. soft gel capsules) is ideal for it. This patent exemplifies the preparation of oil-based formulations of cannabinoid, which is also a hydrophobic drug [35].

WO2020210376A1 claims a composition comprising highly porous activated carbon (microporous carbon) and an antiviral

Table 3
Data of the cited patents/patent applications.

Patent/patent application number[a]	Assignee	Expiry date[b]	Status[c]	Ref. no.
US10065958B2	Gilead Sciences	September 16, 2031 (Due to patent term adjustment (PTA) of 230 days)	Patent term extension (PTE) filed at USPTO	[26]
US8008264B2	Gilead Sciences	September 6, 2029 (PTA of 198 days)	PTE filed at USPTO	[27]
US8318682B2	Gilead Sciences	April 22, 2029	PTE filed at USPTO	[28]
USRE46762E	Gilead Sciences	April 22, 2029	PTE filed at USPTO	[29]
US9724360B2	Gilead Sciences	October 29, 2035	PTE filed at USPTO	[30]
US9949994B2	Gilead Sciences	October 29, 2035	PTE filed at USPTO	[31]
US10836787B2	Gilead Sciences	April 27, 2038	Patented case	[32]
US10695361B2	Gilead Sciences	September 16, 2036	Patented case	[33]
US10675296B2	Gilead Sciences	July 10, 2038	Patented case	[34]
US20200360292A1	Aegis Therapeutics	May 15, 2040	Under examination	[35]
WO2020210376A1	University of Illinois	April 8, 2040	No national phase entry	[36]
CN111494349A	The Fourth Military Medical University	April 30, 2040	Under examination	[37]
CN112675143A	Gu Shihai	February 8, 2041	Publication	[38]
CN112402371A	Nanjing Zhengji Medical Research Company Limited	November 19, 2040	Under examination	[39]
CN112656759A	Henan Taifeng Biotechnology Company Limited	January 23, 2041	Publication	[40]
US11020349B1	Jubilant Generics Limited	July 14, 2040	Patented case	[41]
US10925889B2	Gholam Peyman	May 12, 2035	Patented case	[42]
WO2020227530A1	Massachusetts Institute of Technology and The General Hospital Corporation	May 7, 2040	No national phase entry	[43]
WO2020202111A1	Tarsus Pharmaceuticals	April 3, 2040	No national phase entry	[44]
CN111467362A	Beijing Aohe Drug Institute Company Limited	May 9, 2040	Under examination	[45]
CN112168956A	Hefei Tiantai Technology Company Limited	September 30, 2040	Under examination	[46]
CN111297838A	Ningbo Hekang Biomedical Technology Company Limited	April 8, 2040	Under examination	[47]
CN111149804A	Jiangsu Refontech Industrial Company Limited	February 24, 2040	Under examination	[48]
CN111956630A	Dalian University of Technology	August 20, 2040	Under examination	[49]
CN112515258A	Jiangsu Xinshijie Advanced Functional Fiber Innovation Center Company Limited	October 30, 2040	Under examination	[50]
US11013688B1	Softhale NV	July 16, 2040	Patented case	[51]
CN112891327A	Chen Xijing	March 3, 2041	Publication	[52]
CN111603408A	Huang Zhulin	June 23, 2040	Under examination	[53]
US10251898B2	Gilead Sciences	October 29, 2035 (Due to terminal disclaimer with US9949994B2)	Patented case	[54]
US10695357B2	Gilead Sciences	October 29, 2035 (Due to terminal disclaimer with US10251898B2)	Patented case	[55]
CN112618557A	Beijing Jianmu Technology Company Limited	January 19, 2041	Publication	[56]
CN112494500A	Beijing Jianmu Technology Company Limited	November 26, 2040	Under examination	[57]
CN112274520A	Tianjin Jikun Pharmaceutical Technology Company Limited	November 23, 2040	Under examination	[58]
WO2021067480A1	University of Washington	September 30, 2040	No national phase entry	[59]
CN112843073A	Institute of Animal Science and Veterinary Medicine	March 30, 2041	Publication	[60]
US20200384034A1	Spiritus Therapeutics	June 4, 2040	Under examination	[61]
CN112522203A	The Fifth Affiliated Hospital of Sun Yat-Sen University	November 23, 2040	Under examination	[62]
CN111592594A	Peking University	March 13, 2040	Under examination	[62]
WO2021038296A2	Tonix Pharma Holdings Limited	August 27, 2040	No national phase entry	[64]
WO2021001458A1	Tonix Pharma Holdings Limited	July 1, 2040	No national phase entry	[65]
CN112135625A	Guangzhou Xinchuangyi Medicine Clinical Research Company Limited	May 9, 2040	No national phase entry	[66]

[a] Excluding process-related patents/applications.
[b] Based on the twenty years from the date of filing of the patent application. If the patent application is not granted to patent, or patent is lapsed/revoked, then it is available for public use.
[c] Status as of May 16, 2021, from USPTO and Espacenet.

agent (remdesivir). It states that charcoal has antiviral effects. The antiviral agents may be adsorbed and encapsulated within microporous carbon, causing a persistent release of the drug that generates a more considerable therapeutic effect. Due to the kidney function-related benefits, this charcoal-based drug delivery system avoids the renal toxicity issues associated with some antiviral agents, e,g. acyclovir. This patent application does not exemplify any formulation of remdesivir [36].

CN111494349A covers a fast-dissolving oral film of remdesivir comprising film-forming materials (e.g. methylcellulose and ethyl-

cellulose etc.,), surfactants (e.g. Tween 80 and lecithin), plasticizers (e.g. polyethylene glycol and polypropylene glycol), correctives (e.g. xylitol and fructose) and auxiliary materials (e.g. antioxidants and preservatives). The claimed film is fast-acting, easy-to-carry and use, simple to prepare, and patient compliant. The patent application exemplifies the preparation of the fast-dissolving oral film of remdesivir [37].

CN112675143A claims a film-coated tablet of remdesivir comprising a pH regulator (Eudragit L100-55, fumaric acid, sodium citrate, tartaric acid, succinic acid, and sodium hydroxide). The pH regulator of the tablet adjusts the pH to 3.4 ± 0.5 and 7.5 ± 0.5 of the gastric-coated tablet and the enteric-coated tablet, respectively. The claimed tablet showed long-term stability, good bioavailability, and is convenient to use. The patent exemplifies preparation of claimed tablet comprising remdesivir, carboxymethyl cellulose sodium (disintegrant), hydroxypropylmethyl cellulose or polyvinylpyrrolidone (binder), magnesium stearate (lubricant), microcrystalline cellulose (filler), and different pH regulators; disintegration time of tablets in artificial gastric juice and artificial intestinal juice; and stability testing of the tablets [38].

CN112402371A claims remdesivir injection comprising remdesivir (50–200 mg), polysorbate (e.g. polysorbate-20), and absolute ethanol. The injection has a short and straightforward production process. Remdesivir has excellent solubility in the non-viscous and non-aqueous mixture of absolute ethanol and polysorbate. The non-viscous mix is suitable for sterilization and injection preparation. The non-aqueous environment increases the stability of the injection. The injection's pH, close to neutral, ensures patient safety and compliance. The patent application exemplifies the preparation of remdesivir injection and the quality testing methods [39].

CN112656759A claims remdesivir eye drops (1 mg–200 mg/ml) comprising an osmotic pressure regulator (glycerin, sodium chloride, and potassium chloride), an antioxidant (sodium sulfite and sodium bisulfite), a pH regulator (e.g. boric acid), a bacteriostatic agent (benzalkonium chloride, and benzyl alcohol), and a solvent (water for injection). The claimed eyedrop can be used for treatment, including eyelid virus infection, conjunctival virus infection, corneal virus infection, and retinal virus infection. The patent application exemplifies the preparation of remdesivir eye drops and its stability testing [40].

US11020349B1 claims a sublingual tablet for COVID-19 treatment comprising remdesivir (0.1 mg to about 50 mg), a pH regulator (citric acid), and other excipients, wherein the tablet can release at least 80% of the remdesivir in 15 min or less. The pH regulator helps to prevent the degradation of remdesivir. The claimed tablet offers numerous advantages over other drug delivery systems, including better chemical stability of remdesivir due to the pH regulator, adequate shelf-life, respectable pharmaceutical properties, steady drug release, faster onset of action, lower dosage, enhanced efficacy, and promising safety profile of remdesivir. The patent mentions the formula of preparing the claimed sublingual tablet in its examples. One of the formula comprises remdesivir, mannitol (diluent), HPMC (binder), sodium starch glycolate (disintegrant), sodium alginate (carrier), sodium lauryl sulfate (surfactant), citric acid (pH adjusting/salivating agent), talc (glidant), magnesium stearate (lubricant), butylated hydroxyanisole (preservative), sucralose (sweetener), milk protein concentrate (mucoadhesive), and a solvent (aqueous, alcoholic or acidic) [41].

Pharmaceutical composition of remdesivir with other drugs

US10925889B2 claims treatment of a medical condition (COVID-19) by administering one or more antiviral medications (e.g. remdesivir) together with one or more cell pathway inhibitors (i.e. anti-inflammatory agents) dissolved in a non-toxic aerosolized semifluorinated alkane (e.g. F4H5, F4H6, F4H8, F6H6 F6H8, etc.). The semifluorinated alkane evaporates quickly after inhalation and leaves the biocompatible antiviral and anti-inflammatory drugs at the desired location to produce their respective effects. The patent exemplifies a clinical study wherein a CIVID-19 patient was treated with an inhaled combination comprising remdesivir, a Wnt inhibitor, and a protease inhibitor dissolved in a semifluorinated alkane for three weeks through which the patient recovered [42].

WO2020227530A1 relates to compositions comprising pyrimidine compound (uracil, uridine, thymine, thymidine, cytosine, and cytidine) and an antimicrobial agent (e.g., remdesivir) to treat an infection (COVID-19). The pyridine compound increases the susceptibility of microbe towards antimicrobial agents and potentiates antimicrobial agent efficacy. In one exemplary embodiment, the pyrimidine is administered together with remdesivir by intravenous infusion. However, the details of these examples are not provided in this patent application [43].

WO2020202111A1 reveals treatment of a viral infection (COVID-19) by administering a pharmaceutical composition comprising an isoxazoline parasiticide (fluralaner, sarolaner, lotilaner, afoxolaner, fluxametamide, and isocycloseram) and an antiviral agent (e.g. remdesivir). The claimed combination is said to have a synergistic effect. However, no experimental details of the combination of isoxazoline parasiticide and remdesivir have been provided in this patent application [44].

CN111467362A claims a pharmaceutical composition comprising azithromycin and remdesivir to treat an infectious disease (COVID-19), wherein the particle size of the azithromycin is 40−400 μm, and the D90 particle size is 200−400 μm. The particle size of azithromycin is responsible for its improved absorption. This patent application exemplifies the preparation of azithromycin compositions with different particle sizes and the effect of azithromycin particle size on blood concentration. There is no example wherein azithromycin has been combined with remdesivir [45].

CN112168956A claims an antiviral spray that contains a viral protease inhibitory polypeptide, ethanol extract of *Scutellaria serrate*, and remdesivir. The spray can inhibit SARS-CoV-2 replication, inhibit inflammation, promote mucosal repair, and achieve the preventive and therapeutic effects of the new coronavirus. The patent application mentions preparing the claimed spray without demonstrating its efficacy against COVID-19 [46].

CN111297838A discloses an antiviral drug inhalation spray comprising active antiviral agent (remdesivir), adjuvant (azithromycin, roxithromycin, clindamycin, and erythromycin), taste-masking agent (xylitol, sorbitol, and mannitol), and a solvent (water, propylene glycol, or glycerol). The claimed spray can deliver the drugs into the respiratory tract to prevent virus infection and its transmission. The combined medication spray produces a synergistic therapeutic effect that reduces the drug dose and the side effects. The patent application provides antiviral drug inhalation spray preparation but does not provide experimental efficacy against COVID-19 [47].

New delivery systems of remdesivir

CN111149804A provides a spray comprising antiviral agent (e.g. remdesivir), surfactant (disodium lauryl sulfosuccinate monoester), stabilizer (amino trimethylene phosphonate), protective agent (sodium sulfite), and deionized water. The spray is safe, durable, convenient to use, durable, and can inhibit the growth and reproduction of viruses. The patent application provides a process to prepare claimed spray but does not disclose its efficacy data against COVID-19 [48].

CN111956630A offers a liquid preparation (pH = 3.5–5.5) for nebulizers comprising 1−100 mg/ml of remdesivir and a solvent (e.g. sulfobutyl-β-cyclodextrin, ethanol, water, or their mixture). The atomized remdesivir released from the nebulizer acts on the primary site of infection (nasal cavity, oral cavity, and lungs), mak-

ing the medication more effective. This also reduces the systemic exposure of the drug in the body and helps to minimize the side effects of remdesivir. The patent application discloses the preparation method of remdesivir solution liquid preparation for nebulizer, but it is silent about the experimental efficacy of the claimed nebulizer [49].

CN112515258A claims a three-layered mask. The middle layer of the mask is removable and is an anti-viral medical nanofiber mask film material (polyvinyl alcohol, cellulose acetate, and polyvinylidene fluoride) with an antiviral drug (remdesivir). The claimed mask inhibits the proliferation of viruses, including SARS-CoV-2, during use, avoids the virus spreads, and protects the individual. The patent application exemplifies the preparation of a three-layered mask [50].

US11013688B1 claims a method for the treatment of a viral infection (COVID-19) by administering 1 μl–50 μl of a medically active liquid comprising remdesivir utilizing a soft-mist-inhaler. The soft-mist-inhaler described in this patent delivers remdesivir with high precision and reproducibility. This patent exemplifies the preparation of remdesivir solutions employing water, ethanol, and ethylene glycol, which were dispensed utilizing a soft-mist-inhaler [51].

CN112891327A provides a liquid preparation for remdesivir atomized inhalation and its preparation. The content of remdesivir in the liquid preparation ranges from 0.1% to 0.5% (w/v), and the pH ranges from 5 to 7. This delivery system increases the exposure of remdesivir in the lungs much higher than that of intravenous injection, which reduces the dosage, cost, and systemic side effects [52].

Cosmetic preparation of remdesivir

CN111603408A claims a lipstick containing remdesivir. The development of such lipstick has positive significance in the ongoing pandemic. The claimed lipstick inhibits SARS-CoV-2 propagation on the exposed parts of the human body, shortens the virus's survival time, and reduces the risk of infection. It has been demonstrated that the virus loses activity within 30 min after exposure to this lipstick. The examples of preparing remdesivir based lipstick are provided in the patent application [53].

New indications of remdesivir

US10251898B2 claims a method of treating infections caused by the Filoviridae virus, ebola virus, and other related viral conditions by administering a pharmaceutical composition (Solid dosage forms, injectable, and emulsion, etc.) of remdesivir. The composition may optionally contain another therapeutic agent (corticosteroid, bronchodilator, anticholinergic, and mucolytic agent). The patent exemplifies the activity of claimed compounds against the Ebola Virus and Nipah-GFP HMVEC-TERT Cells [54].

US10695357B2 claims treatment of Nipah virus infection using a pharmaceutical composition (solid dosage forms, injectable, emulsion, etc.) of remdesivir, alone or in combination with other drugs like ribavirin, favipiravir, and palivizumab. The patent exemplifies the activity of claimed compounds against the Ebola Virus and Nipah-GFP HMVEC-TERT Cells [55].

CN112618557A discloses pharmaceutical composition (powder, tablet, granule, capsule, oral liquid, emulsion, or mixture. Suspension) to treat or prevent cardiovascular complications of diabetes (coronary heart disease, atherosclerosis, hyperlipidemia, high cholesterol). The effective dose of remdesivir is 100 mg–200 mg per day for a 60 kg individual. The composition may optionally comprise an anti-diabetic and cardiovascular agent. Remdesivir displayed a protective effect on kidney function, reduced blood lipids, and the risk of cardiovascular disease in exemplified animal models [56].

CN112494500A discloses the application of remdesivir in the prevention/treatment of cardiotoxicity caused by the anti-tumor drug (anthracyclines, taxanes, fluorouracils, trastuzumab, and bevacizumab). Thus, remdesivir can effectively protect myocardial cells and maintain normal cardiac function. The patent application exemplifies the effects of remdesivir in animal models (doxorubicin-induced mouse injury model) [57].

CN112274520A claims the application of remdesivir and its salts to prepare a medicine for treating idiopathic pulmonary fibrosis. It has been demonstrated that remdesivir can improve forced vital capacity, inhalation, and exhalation airway resistance; reduce lung collagen content and the area of pulmonary fibrosis. The patent application exemplifies the claimed effect of remdesivir on bleomycin's idiopathic pulmonary fibrosis model [58].

WO2021067480A1 relates to a composition for treating a hepatitis B virus (HBV) infection using a RIG-I agonist (e.g. *N*-(6-benzamido-l,3-benzothiazol-2-yl)naphthalene-2-carboxamide), a vehicle for intracellular delivery (e.g. Liposome, nanocapsule, nanoparticle, exosome, microparticle, microsphere, and lipid particle), and a pharmaceutically acceptable carrier. This composition may further include an antiviral agent (e.g. remdesivir). The patent application does not provide any experimental evidence of the claimed treatment with remdesivir [59].

CN112843073A claims the application of remdesivir to treat Bovine parainfluenza virus type 3 (BPIV3). The invention states and exemplifies that remdesivir inhibits/inactivates the BPIV3 virus by blocking its replication without any toxic effect [60].

Miscellaneous

US20200384034A1 covers extracellular vesicles (EVs) recovered from a virus-infected (COVID-19) patient. These EVs can be used in combination with antiviral agents (remdesivir) to attenuate/treat the severity of the infection. No example of remdesivir and EVs combination has been provided in this patent application [61].

CN112522203A provides cell vesicles expressing a chimeric antigen receptor loaded with remdesivir to kill SARS-Co-2. The cell vesicles can also neutralize SARS-CoV-2 and avoid the production of antibody enhancement effects. The antiviral agent (e.g. remdesivir) can be better delivered to the site, where SARS-CoV-2 gathers, and the side effects of drugs can also be reduced. The patent application exemplifies the preparation of cell vesicles loaded with remdesivir [62].

CN111592594A provides new monoclonal antibodies with high binding activity and neutralizing activity against SARS-CoV-2 to provide effective means for preventing or treating COVID-19. The sequence IDs of the monoclonal bodies are depicted in the description of the patent application. It also claims a pharmaceutical composition comprising remdesivir with the claimed monoclonal antibody. However, no experimental evidence of the combination of remdesivir and the claimed monoclonal antibody has been exemplified in the patent application [63].

WO2021038296A2 claims a method for treating COVID-19 using a composition comprising a TFF2 polypeptide modified by PEGylation or polysialylation. The composition may also include an agent that inhibits or reduces SARS-CoV-2 replication (remdesivir). The TFF2 protects the gastrointestinal mucosa from injury by stabilizing and bolstering making gels, reducing inflammation, and stimulating epithelial reestablishment. The patent application is silent about the experimental details of the combination of remdesivir with TFF2 polypeptide [64].

WO2021001458A1 provides isolated anti-CD154 antibodies that bind to mammalian CD-154. The CD-154 is involved in cell-mediated immunity, and its activation boosts immunity. This patent application claims an isolated antibody that binds to CD

154. It also claims a pharmaceutical composition comprising an anti-CD154 antibody and an antiviral agent (e.g. remdesivir) to treat immune-related disease (e.g. COVID-19). However, no data of the composition of remdesivir and the claimed antibody has been disclosed in this patent application [65].

CN112135625A claims the use of lysozyme or a combination comprising lysozyme to prepare medicine or food for preventing or treating COVID-19. The lysozyme may be combined with an antiviral agent (remdesivir) and glycyrrhizic acid. The composition can be administered in an oral dosage form, injection dosage form, and inhalation dosage form. The patent application exemplifies the application of lysozyme in patients with new coronary pneumonia and high-risk infections, but without remdesivir [66].

Our search also revealed many Chinese patent applications and one US patent application related to the preparation of remdesivir, its intermediates, and pharmaceutical impurities. The list of these patent application include CN111393478A [67], CN112358504A [68], CN112321589A [69], CN112321642A [70], CN112279855A [71], CN111961079A [72], CN111848679A [73], CN111875638A [74], CN111793101A [75], CN111732618A [76], CN111484537A [77], CN111471070A [78], CN111470946A [79], CN111440215A [80], CN111393243A [81], CN111393392A [82], CN111269263A [83], CN111233931A [84], CN111233930A [85], CN111233870A [86], CN111233869A [87], CN111205327A [88], CN111187269A [89], CN111171078A [90], CN111116656A [91], CN112679542A [92], CN112645982A [93], CN212904707U [94], CN112592348A [95], CN212818228U [96], CN112500429A [97], CN112500417A [98], CN112457318A [99], CN112358513A [100], CN112920203A [101], and US2021161927A1 [102]. The economic route of synthesis is vital to drop and control the market price of a therapeutic agent. Accordingly, the authors trust that these patent applications may be helpful to the pharmaceutical scientists/chemists involved in the design of an economical synthetic route to prepare remdesivir.

Discussion

COVID-19, a novel pandemic disease, has been a global problem since December 2019. Countries worldwide have fallen into panic due to its infectious/transmissible nature and lack of proper treatments. Most COVID-19 patients are treated based on the severity of cases, symptoms, and supportive care. This is because of the availability of a few medicines. Scientists are dedicated to identifying appropriate treatment for this pandemic to treat and control its spread. For example, the drug repurposing approach has been utilized to develop an effective treatment for COVID-19, wherein azithromycin, baricitinib, and favipiravir (already approved in some countries) are in clinical trials in the USA [103]. The pharmaceutical industries, including Pfizer, Astra Zeneca, Johnson & Johnson, and Moderna, have developed vaccines for COVID-19 [104].

The development of remdesivir, a broad-spectrum antiviral agent, has been a breakthrough for COVID-19 treatment. It is the first approved treatment for COVID-19 that is clinically used in about 50 countries [12]. The generic structure of remdesivir was first disclosed in WO2009132123A1 [105] to treat hepatitis C, dengue, and Flaviviridae virus infections. WO2009132123A1 [105] is a family member of US8318682B2 [28] and USRE46762E [29] that have already been discussed. Later, it was reported to possess activity against corona infections [33]. Gilead Sciences has developed remdesivir as a freeze-dried preparation for injection. The drug has to be prepared fresh and injected under the supervision of professionals [11], which leads to poor patient compliance. Further, the freshly prepared injection is not stable for an extended period [40]. Therefore, novel compositions of remdesivir with improved patient compliance, safety, stability, and bioavailability have been invented. These include soft gel capsules [35], charcoal-based drug delivery systems [36], fast-dissolving oral film of remdesivir [37], and film-coated tablets [38]. The marketed freeze-dried powder for injection contains SBECD to enhance the aqueous solubility of remdesivir. However, the solubilization process is optimal at a pH < 4. On the other hand, remdesivir is unstable in an acidic aqueous solution. Accordingly, the marketed freeze-dried powder for injection also contains pH regulators (hydrochloric acid and sodium hydroxide) [39]. Therefore, the preparation of the freeze-dried powder for injection is a complex process. Further, at the time of injection, remdesivir injection is acidic, which causes poor patient compliance. Accordingly, a new stable, safe, and patient compliant injection of remdesivir in non-aqueous solvent (absolute ethanol and polysorbate) having a short production process has been invented [39]. The non-aqueous injection is also safe for the kidney, unlike SBECD based injection, which causes renal dysfunction [8].

The development of new delivery systems is directed to improve the biological effect and bioavailability of a drug; improve patient compliance; reduce the side effects of the drug, and solve solubility and biodistribution [106]. Accordingly, new spray [48] and nebulizer preparations [49] of remdesivir have been invented to address its side effects and improve its biological action. A stable and effective sublingual tablet of remdesivir having quality pharmaceutical properties has also been invented [41]. Such tablets increase patient compliance in comparison to the marketed injectable formulation of remdesivir. Remdesivir based masks [50] and cosmetics [53] have also been developed that help to prevent the spread of COVID-19. Some patents related to the combinations of remdesivir and other drugs, for example, cell pathway inhibitors (i.e. anti-inflammatory agents) [42], pyrimidine compound [43], isoxazoline parasiticides [44], azithromycin [45,47], and viral protease inhibitory polypeptide [46] have been identified. Such combinations have revealed the synergistic effects against COVID-19 compared to the monotherapy of remdesivir. Many combinations of remdesivir are in a clinical trial also [19]. The development of further inventive composition (monotherapy, combinations, and delivery systems) is anticipated to tackle this disaster of the century.

Remdesivir was first developed to treat Ebola infection. A patent has been granted for the use of remdesivir to treat Ebola infection [54]. Some patents/applications have been located that claim the use of remdesivir to treat different diseases that include cardiovascular complications of diabetes [56], cardiotoxicity caused by the anti-tumor drugs [57], idiopathic pulmonary fibrosis [58], and hepatitis B virus (HBV) [59]. The clinical trial information of remdesivir for its new conditions has been provided in Table 2.

The compound patents of remdesivir are supposed to expire in October 2035. Gilead Sciences has also applied for the legal PTE (that may be up to five years) for its compound patents [31,32]. The extension grant will extend the patent protection of remdesivir till October 2040 in many countries. The generic version of remdesivir may not be available to the patient by 2035–2040 in many countries. Accordingly, it is compulsory to look for alternative therapies also e.g. drug repurposing of the existing therapeutic agents.

Conclusion

The patent literature has revealed inventive compositions, combinations, delivery systems, and new indications of remdesivir. The primary inventions of remdesivir (compositions, combinations, and delivery systems) have been developed to provide synergistic treatment for COVID-19 and patient compliance. Some exciting innovations have also been disclosed to prevent COVID-19, for example, remdesivir based lipstick, masks, sprays, and nebulizers.

The inventions related to new indications of remdesivir increase its therapeutic scope. It is expected that the scientific fraternity will create new ideas based on this review to combat COVID-19.

Ethical approval

Not required.

Funding

No funding sources.

Competing interests

None declared.

References

[1] Kumar A, Singh R, Kaur J, Pandey S, Sharma V, Thakur L, et al. Wuhan to world: the COVID-19 pandemic. Front Cell Infect Microbiol 2021;11:596201, http://dx.doi.org/10.3389/fcimb.2021.596201.
[2] World Health Organization. WHO coronavirus (COVID-19) dashboard; 2021 [Accessed 16 May 2021] https://covid19.who.int/.
[3] World Health Organization. Coronavirus disease (COVID-19) pandemic; 2021 [Accessed 16 May 2021] https://www.who.int/emergencies/diseases/novel-coronavirus-2019.
[4] Fricke-Galindo I, Falfán-Valencia R. Pharmacogenetics approach for the improvement of COVID-19 treatment. Viruses 2021;13(3):413, http://dx.doi.org/10.3390/v13030413.
[5] Lamberghini F, Testai FD. COVID-2019 fundamentals. J Am Dent Assoc 2021;152(5):354–63, http://dx.doi.org/10.1016/j.adaj.2021.01.014.
[6] Rachel JB, Gururaj N, Smitha T, Daniel TD, Harishini BS, Rosaian AS. Innovative diagnostic approach and investigation trends in COVID19—a systematic review. J Oral Maxillofac Pathol 2020;24(3):421–36, http://dx.doi.org/10.4103/jomfp.jomfp_395_20.
[7] Guo Q, Xu W, Wang PF, Ji HY, Zhang XL, Wang K, et al. Facing coronavirus disease 2019: what do we know so far? (Review). Exp Ther Med 2021;21(6):658, http://dx.doi.org/10.3892/etm.2021.10090.
[8] Pardo J, Shukla AM, Chamarthi G, Gupte A. The journey of remdesivir: from Ebola to COVID-19. Drugs Context 2020;9, http://dx.doi.org/10.7573/dic.2020-4-14, 2020-4-14.
[9] Badker R, Miller K, Pardee C, Oppenheim B, Stephenson N, Ash B, et al. Challenges in reported COVID-19 data: best practices and recommendations for future epidemics. BMJ Glob Health 2021;6(5):e005542, http://dx.doi.org/10.1136/bmjgh-2021-005542.
[10] Humeniuk R, Mathias A, Kirby BJ, Lutz JD, Cao H, Osinusi A, et al. Pharmacokinetic, pharmacodynamic, and drug-interaction profile of remdesivir, a SARS-CoV-2 replication inhibitor. Clin Pharmacokinet 2021;60(5):569–83, http://dx.doi.org/10.1007/s40262-021-00984-5.
[11] United States Food and Drug Administration. Highlights of prescribing information; 2020 [Accessed 16 May 2021] https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf.
[12] Gilead Sciences. Veklury® global marketing authorization status; 2021 [Accessed 16 May 2021] https://www.gilead.com/purpose/advancing-global-health/covid-19/veklury-global-marketing-authorization.
[13] Malin JJ, Suarez I, Priesner V, Fatkenheuer G, Rybniker J. Remdesivir against COVID-19 and other viral diseases. Clin Microbiol Rev 2020;34(1), http://dx.doi.org/10.1128/CMR.00162-20, pii: 34/1/e00162-20.
[14] Gordon CJ, Tchesnokov EP, Woolner E, Perry JK, Feng JY, Porter DP, et al. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. J Biol Chem 2020;295(20):6785–97, http://dx.doi.org/10.1074/jbc.RA120.013679.
[15] Saqrane S, El Mhammedi MA, Lahrich S, Laghrib F, El Bouabi Y, Farahi A, et al. Recent knowledge in favor of remdesivir (GS-5734) as a therapeutic option for the COVID-19 infections. J Infect Public Health 2021;14(5):655–60, http://dx.doi.org/10.1016/j.jiph.2021.02.006.
[16] Eastman RT, Roth JS, Brimacombe KR, Simeonov A, Shen M, Patnaik S, et al. A review of its discovery and development leading to emergency use authorization for treatment of COVID-19. ACS Cent Sci 2020;6(5):672–83, http://dx.doi.org/10.1021/acscentsci.0c00489.
[17] Roshanshad A, Kamalipour A, Ashraf MA, Roshanshad R, Jafari S, Nazemi P, et al. The efficacy of remdesivir in coronavirus disease 2019 (COVID-19): a systematic review. Iran J Microbiol 2020;12(5):376–87, http://dx.doi.org/10.18502/ijm.v12i5.4597.
[18] Santoro MG, Carafoli E. Remdesivir: from Ebola to COVID-19. Biochem Biophys Res Commun 2021;538:145–50, http://dx.doi.org/10.1016/j.bbrc.2020.11.043.
[19] Chilamakuri R, Agarwal S. COVID-19: characteristics and therapeutics. Cells 2021;10(2):206, http://dx.doi.org/10.3390/cells10020206.
[20] National Library of Medicine. Remdesivir; 2021 [Accessed 16 May 2021] https://www.clinicaltrials.gov/ct2/results?cond=&term=remdesivir&cntry=&state=&city=&dist=.
[21] Spratt AN, Gallazzi F, Quinn TP, Lorson CL, Sönnerborg A, Singh K. Coronavirus helicases: attractive and unique targets of antiviral drug-development and therapeutic patents. Expert Opin Ther Pat 2021;31(4):339–50, http://dx.doi.org/10.1080/13543776.2021.1884224.
[22] Murza A, Dion Sp, Boudreault Pl, Désilets A, Leduc R, Marsault É. Inhibitors of type II transmembrane serine proteases in the treatment of diseases of the respiratory tract—a review of patent literature. Expert Opin Ther Pat 2020;30(11):807–24, http://dx.doi.org/10.1080/13543776.2020.1817390.
[23] Capasso C, Nocentini A, Supuran CT. Protease inhibitors targeting the main protease and papain-like protease of coronaviruses. Expert Opin Ther Pat 2021;31(4):309–24, http://dx.doi.org/10.1080/13543776.2021.1857726.
[24] Vicenti I, Zazzi M, Saladini F. SARS-CoV-2 RNA-dependent RNA polymerase as a therapeutic target for COVID-19. Expert Opin Ther Pat 2021;31(4):325–37, http://dx.doi.org/10.1080/13543776.2021.1880568.
[25] Nascimento Junior JAC, Santos AM, Quintans-Júnior LJ, Walker CIB, Borges LP, Serafini MR. SARS, MERS and SARS-CoV-2 (COVID-19) treatment: a patent review. Expert Opin Ther Pat 2020;30(8):567–79, http://dx.doi.org/10.1080/13543776.2020.1772231.
[26] Mackman RL, Parrish JP, Ray AS, Theodore DA. Methods and compounds for treating Paramyxoviridae virus infections. United States patent number US10065958B2, September 4, 2018. Application number US201514613719A.
[27] Butler T, Cho A, Kim CU, Parrish J, Saunders OL, Zhang L. 1'-substituted carbanucleoside analogs for antiviral treatment. United States patent number US8008264B2, August 30, 2011. Application number US42817609A.
[28] Butler T, Cho A, Kim CU, Parrish JP, Saunders OL, Zhang L. 1'-substituted carbanucleoside analogs for antiviral treatment. United States patent number US8318682B2, November 27, 2012. Application number US201113196117A.
[29] Butler T, Cho A, Kim CU, Parrish JP, Saunders OL, Zhang L. 1'-substituted carba-nucleoside analogs for antiviral treatment. United States patent number USRE46762E, March 27, 2018. Application number US201615288271A.
[30] Chun BK, Clarke MH, Doerffler E, Hui HC, Jordan R, Mackman RL, et al. Methods for treating Filoviridae virus infections. United States patent number US9724360B2, August 8, 2017. Application number US201514926062A.
[31] Chun BK, Clarke MH, Doerffler E, Hui HC, Jordan R, Mackman RL, et al. Methods for treating Filoviridae virus infections. United States patent number US9949994B2, April 24, 2018. Application number US201615246240A.
[32] Brak K, Carra EA, Heumann LV, Larson N. Crystalline forms of (S)-2-ethylbutyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(p-henoxy)phosphoryl)amino)propanoate. United States patent number US10836787B2, November 17, 2020. Application number US201815964597A.
[33] Clarke MH, Feng JY, Jordan R, Mackman RL, Ray AS, Siegel D. Methods for treating arenaviridae and coronaviridae virus infections. United States patent number US10695361B2, June 30, 2020. Application number US201916265016A.
[34] Larson N. Compositions comprising an RNA polymerase inhibitor and cyclodextrin for treating viral infections. United States patent number US10675296B2, June 9, 2020. Application number US201816031620A.
[35] Maggio ET. Oil-soluble drug containing compositions and methods of use thereof. United States patent application publication number US20200360292A1, November 19, 2020. Application number US202016875683A.
[36] Shukla D, Yadavalli T. Drug adsorbed highly porous activated carbon for enhanced drug delivery. PCT patent application publication number WO2020210376A1, October 15, 2020. Application number US2020027299W.
[37] Ding Y, Guo C, Li J, Wang J, Wen A, Zhao C. Remdesivir oral fast dissolving film and preparation method thereof. Chinese patent application publication number CN111494349A, August 7, 2020. Application number CN202010364496A.
[38] Ding Y, Yu Y, Zhang H, Hu X, Gu S. Remdesivir tablet and preparation method thereof. Chinese patent application publication number CN112675143A, April 20, 2021. Application number CN202110170345A.
[39] Teng Y, Luo L. Remdesivir injection and preparation method thereof. Chinese patent application publication number CN112402371A, February 26, 2021. Application number CN202011304345A.
[40] Ba Z, Sha W, Weng J, Gao J, Huang P. Remdesivir eye drops and preparation method and application thereof. Chinese patent application publication number CN112656759A, April 16, 2021. Application number CN202110092173A.
[41] Nandi I, Jain A, Gat GV. Transmucosal dosage forms of remdesivir. United States patent number US11020349B1, June 1, 2021. Application number US202016929005A.
[42] Peyman GA. Method of treating, reducing, or alleviating a medical condition in a patient. United States patent number US10925889B2, February 23, 2021. Application number US202016861128A.
[43] Alcantar MA, Bhattacharyya R, Collins JJ, Yang JH. Potentiators of antimicrobial and/or antiviral agents. PCT patent application publication number WO2020227530A1, November 12, 2020. Application number US2020031873W.
[44] Ackermann D, Azamian B, Hickok S, Stivers C. Systemic isoxazoline parasiticides for vector-borne and viral disease treatment or prophylaxis. PCT patent application publication number WO2020202111A1, October 8, 2020. Application number IB2020053229W.

[45] Jia W, Li Q, Zhao X. Azithromycin pharmaceutical composition, and preparation method and application of azithromycin pharmaceutical composition. Chinese patent application publication number CN111467362A, July 31, 2020. Application number CN202010385678A.
[46] Liu W, Xie F. Preparation method of active peptide sterilization antiviral spray. Chinese patent application publication number CN112168956A, January 5, 2021. Application number CN202011058799A.
[47] Shi X, Wang W. Inhalation spray of antivirus medicines. Chinese patent application publication number CN111297838A, June 19, 2020. Application number CN202010270299A.
[48] Du F. Sterilization and disinfection spray. Chinese patent application publication number CN111149804A, May 15, 2020. Application number CN202010130498A.
[49] Li J, Ma C, Ma C, Meng Q, Yu Z, Yun L, et al. Remdesivir liquid preparation for atomizer, and preparation method and application of remdesivir liquid preparation. Chinese patent application publication number CN111956630A, November 20, 2020. Application number CN202010841983A.
[50] Shen K, Wang X, Mo X, Zhao R, Wei T. Kind of pocket-plug-in mask. Chinese patent application publication number CN112515258A, March 19, 2021. Application number CN202011186440A.
[51] Rawert J, Tews JT. Methods of treatment of viral diseases. United States patent number US11013688B1, May 25, 2021. Application number US202016930340A.
[52] Xijing C, Dexuan K, Chang R. Liquid preparation for atomization inhalation of remdesivir and preparation method thereof. Chinese patent application publication number CN112891327A, Jun 4, 2021. Application number CN202110253130A.
[53] Huang Z. Lipstick with antiviral effect. Chinese patent application publication number CN111603408A, September 1, 2020. Application number CN202010575320A.
[54] Chun BK, Clarke MH, Doerffler E, Hui HC, Jordan R, Mackman RL, et al. Methods for treating Filoviridae virus infections. United States patent number US10251898B2, April 9, 2019. Application number US201815902690A.
[55] Chun BK, Clarke MH, Doerffler E, Hui HC, Jordan R, Mackman RL, et al. Methods for treating filoviridae virus infections. United States patent number US10695357B2, June 30, 2020. Application number US201916274049A.
[56] Zhou W, Cui Q. Application of remdesivir in the preparation of medicines for treating diabetic complications. Chinese patent application publication number CN112618557A, April 9, 2021. Application number CN202110069025A.
[57] Zhou W, Cui Q. Application of remdesivir in the preparation of anti-tumor drugs and cardiotoxic drugs. Chinese patent application publication number CN112494500A, March 16, 2021. Application number CN202011346800A.
[58] Li X, Yang C, Zhou H. Application of retegravir in preparation of medicine for treating idiopathic pulmonary fibrosis. Chinese patent application publication number CN112274520A, January 29, 2021. Application number CN202011322200A.
[59] Gale M, Lee S. Compositions and methods for treatment of hepatitis B virus infection. PCT patent application publication number WO2021067480A1, April 8, 2021. Application number US2020053606W.
[60] Kaihui C, Zhijun Y, Hongjun Y, Huimeng C, Tong Z, Yachu R. Application of remdesivir to preparation of medicine for resisting bovine parainfluenza virus 3. Chinese patent application publication number CN112843073A, May 28, 2021. Application number CN202110343034A.
[61] Glassberg CM, Gurney J. Methods for attenuating viral infection and for treating lung injury. United States patent application publication number US20200384034A1, December 10, 2020. Application number US202016893306A.
[62] Zhu T, Xiao Y, Huang X. Cell vesicle expressing chimeric antigen receptor and preparation method and application thereof. Chinese patent application publication number CN112522203A, March 19, 2021. Application number CN202011324758A.
[63] Cao Y, Sun W, Xie X. Anti-novel coronavirus monoclonal antibody and application thereof Chinese patent application publication number CN111592594A, August 28, 2020. Application number CN202010177710A.
[64] Daugherty B, Lederman S. Modified TFF2 polypeptides. PCT patent application publication number WO2021038296A2, March 4, 2021. Application number IB2020000699W.
[65] Lederman S. Anti-CD154 antibodies and uses thereof. PCT patent application publication number WO2021001458A1, January 7, 2021. Application number EP2020068589W.
[66] Li C, Sun M, Sun T. Medicine and food for preventing or treating COVID-19 and application thereof. Chinese patent application publication number CN112135625A, December 25, 2020. Application number CN202080000788A.
[67] Xujian L, Zhiwen M, Zengjun X, Donglu X, Tao X, Xuan Y, et al. Synthesis method of drug for novel coronavirus COVID-19 infected pneumonia drug. Chinese patent application publication number CN111393478A, July 10, 2020. Application number CN202010172995A.
[68] Mingwei F, Wen G, Yan M, Xiao Y. Remdesivir related substance as well as preparation method and application thereof. Chinese patent application publication number CN112358504A, February 12, 2021. Application number CN202011037978A.
[69] Chenchen F, Huaizhi J, Yihua W, Yiping Z, Xuchun Z. Synthesis method of antiviral drug ridexivir and intermediate thereof. Chinese patent application publication number CN112321589A, February 5, 2021. Application number CN202010101187A.
[70] Mingwei F, Wen G, Yan M, Xiao Ya. Retegravir related substance and preparation method and application thereof. Chinese patent application publication number CN112321642A, February 5, 2021. Application number CN202011037977A.
[71] Chen L, Duan X, Guo K, Liu J, Qin L, Qiu J, et al. Method for continuously preparing retegravir intermediate by using micro-channel reactor. Chinese patent application publication number CN112279855A, January 29, 2021. Application number CN202011170025A.
[72] Mingwei F, Min G, Wen G, Lingchao L, Yan M, Xiao Ya. Remdesivir related substance and preparation method and application thereof. Chinese patent application publication number CN111961079A, November 20, 2020. Application number CN202010690131A.
[73] Chenchen F, Huaizhi J, Yihua W, Yiping Z, Xuchun Z. Method for synthesizing retegravir by using micro-channel reaction technology. Chinese patent application publication number CN111848679A, October 30, 2020. Application number CN202010308090A.
[74] Donghui P, Lizhen W, Xinyu W, Yuping X, Junjie Y, Min Y. Preparation method of remdesivir derivative, remdesivir derivative and application of the remdesivir derivative. Chinese patent application publication number CN111875638A, November 3, 2020. Application number CN202010684736A.
[75] Song L, Bo L, Xiaoyu L, Yong Q, Hao S, Wang K, et al. Synthetic method of C-nucleoside compound. Chinese patent application publication number CN111793101A, October 20, 2020. Application number CN202010692306A.
[76] Ailong F, Chunyin Z. Synthesis method of a remdesivir key fragment. Chinese patent application publication number CN111732618A, October 2, 2020. Application number CN202010636935A.
[77] Lin C, Yusheng C, Xiu D, Kai G, Longzhou Q, Jiangkai Q, et al. Chinese patent application publication number CN111484537A, August 4, 2020. Application number CN202010426204A.
[78] Benshun C, Yi C, Tao J, Dawei L, Xiang M, Liping S, et al. Synthesis method of remdesivir. Chinese patent application publication number CN111471070A, July 31, 2020. Application number CN202010338730A.
[79] Zhijian B, Xinyu G, Jian S, Zhe W, Xuenong X, Jia X, et al. Preparation method of remdesivir intermediate 2-ethyl-1-butanol. Chinese patent application publication number CN111470946A, July 31, 2020. Application number CN202010363842A.
[80] Lin C, Yusheng C, Xiu D, Kai G, Longzhou Q, Jiangkai Q, et al. Method for preparing retegravir by using micro-channel reaction device. Chinese patent application publication number CN111440215A, July 24, 2020. Application number CN202010417307A.
[81] Xujian L, Zengjun X, Donglu X, Tao X, Xuan Y, Song Y. Synthesis method of phosphorus chiral nucleoside drug and drug obtained by method. Chinese patent application publication number CN111393243A, July 10, 2020. Application number CN202010320022A.
[82] Lihong D, Xiaohe G, Yujiang L, Hui L, Le T, Qiang W, et al. Synthesis of remdesivir key intermediate 2,3,5-tribenzyloxy-D-ribotide-1,4-lactone. Chinese patent application publication number CN111393392A, July 10, 2020. Application number CN202010377647A.
[83] Yi X, Mingxiang Z, Yanliang Z. Retegravir side chain intermediate and preparation method thereof. Chinese patent application publication number CN111269263A, June 12, 2020. Application number CN202010155623A.
[84] Benshun C, Yi C, Tao J, Dawei L, Xiang M, Liping S, et al. Synthesis method of retegravir. Chinese patent application publication number CN111233931A, June 5, 2020. Application number CN202010222507A.
[85] Benshun C, Gang C, Tao J, Ping Z. Preparation method of retegravir. Chinese patent application publication number CN111233930A, June 5, 2020. Application number CN202010143482A.
[86] Pingwu D, Zhishen G, Zhiyong H, Shiyong L, Feng W. Method for rapidly preparing remdesivir intermediate. Chinese patent application publication number CN111233870A, June 5, 2020. Application number CN202010169489A.
[87] Debao C, Jiansheng D, Yanhua L, Guoqiang S, Zhenhua W. Novel compound for preparing key intermediate of remdesivir and preparation method thereof. Chinese patent application publication number CN111233869A, June 5, 2020. Application number CN202010168364A.
[88] Kunpeng W. Preparation method of Remdesivir. Chinese patent application publication number CN111205327A, May 29, 2020. Application number CN202010096584A.
[89] Benshun C, Zhongqi G, Yang L, Liang Z, Yun Z. Synthesis method of remdesivir intermediate. Chinese patent application publication number CN111187269A, May 22, 2020. Application number CN202010122097A.
[90] Benshun C, Chao C, Bo L, Liang Z, Yun Z. Synthesis method of retegravir. Chinese patent application publication number CN111171078A, May 19, 2020. Application number CN202010122094A.
[91] Benshun C, Tao J, Tao Y, Ping Z. Preparation method of remdesivir. Chinese patent application publication number CN111116656A, May 8, 2020. Application number CN202010143490A.
[92] Kai G, Longzhou Q, Jiangkai Q, Xin Y. Method for preparing remdesivir using microchannel reactor. Chinese patent application publication number CN112679542A, April 20, 2021. Application number CN202011171430A.
[93] Shouhai Y, Jiawei C, Mingwei F, Feng L, Lin L. Method for preparing and purifying remdesivir key intermediate 2-ethylbutyl ((S)-(((3aR,4R,6R,6aR)-6-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-6-cyano-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methoxy)(phenoxy)phosphoryl)-L-alaninate (INT). Chinese patent

application publication number CN112645982A, April 13, 2021. Application number CN202011525338A.
[94] Xiao C. A double-pump gradient liquid chromatograph for producing Radixivir. Chinese patent application publication number CN212904707U, April 6, 2021. Application number CN202022218253U.
[95] Kunpeng W. Preparation of 4- amino- pyrrolo[2, 1- f] [1, 2, 4] triazine. Chinese patent application publication number CN112592348A, April 2, 2021. Application number CN202011514150A.
[96] Yue Z, Chen C, Li C, Xinfeng W, Jieming W, Shen Z, et al. A kind of reid intermediate raw material processing device. Chinese patent application publication number CN212818228U, March 30, 2021. Application number CN202021400137U.
[97] Mingliang W, Zhouyu J, Ke X, Meng W, Yuchao B, Yang C, et al. Preparation method of remdesivir intermediate 4- nitrophenyl phenyl ((2S, 3S) - 3- (2- ethylbutoxy) butan- 2- yl) phosphoramidate or perfluorophenyl phenyl ((2S, 3S) - 3- (2- ethylbutoxy) butan- 2- yl) phosphoramidate based on dynamic kinetic resolution. Chinese patent application publication number CN112500429A, March 16, 2021. Application number CN202011399535A.
[98] Yuedong L, Haichao S, Guozhi L, Shengwei N, Tianhui S, Chen M. Method for preparing 4- aminopyrrolo[2, 1- f] [1, 2, 4] triazine. Chinese patent application publication number CN112500417A, March 16, 2021. Application number CN202011615377A.
[99] Xiaolin Z, Jiayi C, Bing Z, Yangbao A, Songrui C. Synthetic process of remdesivir intermediate using phosphorus oxychloride. Chinese patent application publication number CN112457318A, March 9, 2021. Application number CN202011545041A.
[100] Tao L, Yantao Q, Changgang T, Bo W. Method for preparing retegravir intermediate by using continuous flow reactor. Chinese patent application publication number CN112358513A, February 12, 2021. Application number CN202011400831A.
[101] Kuang H, Renbao H, Jiahui K, Bofeng S, Hao C, Haijian X. Remdesivir related substance and preparation method thereof. Chinese patent application publication number CN112920203A, June 8, 2021. Application number CN202110102527A.
[102] Tripathi VS, Patel AN. Isomorphs of remdesivir and methods for synthesis of same. United States patent application publication number US2021161927A1, June 3, 2021. Application number US202117145274A.
[103] Neupane K, Ahmed Z, Pervez H, Ashraf R, Majeed A. Potential treatment options for COVID-19: a comprehensive review of global pharmacological development efforts. Cureus 2020;12(6):e8845, http://dx.doi.org/10.7759/cureus.8845.
[104] Forman R, Shah S, Jeurissen P, Jit M, Mossialos E. COVID-19 vaccine challenges: What have we learned so far and what remains to be done? Health Policy 2021;125(5):553–67, http://dx.doi.org/10.1016/j.healthpol.2021.03.013.
[105] Cho A, Kim Cu, Parrish J, Xu J. Carba-nucleoside analogs for antiviral treatment. PCT patent application publication number WO2009132123A1, October 29, 2009. Application number US2009041432W.
[106] Li C, Wang J, Wang Y, Gao H, Wei G, Huang Y, et al. Recent progress in drug delivery. Acta Pharm Sin B 2019;9(6):1145–62, http://dx.doi.org/10.1016/j.apsb.2019.08.003.