International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2022.1340.1352

Review Article
A Spotlight on the Development, Pharmaceutical Trends, Innovations and Patents of Nirmatrelvir (Paxlovid™)

[1]Namy George, [2]Mohd. Imran, [1]Shah Alam Khan, [1]Khalid Al Balushi, [3]Syed Mohammed Basheeruddin Asdaq and [4]Shahamah Jomah

[1]College of Pharmacy, National University of Science and Technology, P.O. Box 620, PC 130, Muscat, Sultanate of Oman
[2]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Northern Border University, Rafha 91911, Saudi Arabia
[3]Department of Pharmacy Practice, College of Pharmacy, AlMaarefa University, Dariyah, Riyadh 13713, Saudi Arabia
[4]Department of Pharmacy, Dr. Sulaiman Al-Habib Medical Group, Riyadh, Saudi Arabia

Abstract

Paxlovid™ is a combination of Nirmatrelvir and Ritonavir antiviral pills with good oral bioavailability. In clinical studies, treatment of the patients infected with SARS-CoV-2 with Paxlovid™ within three to five days of the appearance of symptoms significantly reduced the hospitalization rate as well as mortality. It is the first oral antiviral treatment for the COVID-19 which received USFDA approval for EUA on 22nd December, 2021. Nirmatrelvir inhibits the replication of SARS-CoV-2 while another antiviral drug, Ritonavir, is given in combination to enhance the bioavailability of Nirmatrelvir. Molecular interaction studies have shown that Nirmatrelvir binds covalently with the catalytic triad of the active site of the viral protease enzyme ($3CL^{PRO}$). It, therefore, acts by stopping the SARS-CoV-2 replication by its ability to block the translation of the viral genetic materials. Research studies conducted have proven the efficacy of this oral anti-viral drug in mild to moderate COVID-19 patients beside its ease of oral administration and good oral bioavailability. Alternative synthetic methods to scale up the synthesis of this potent molecule are needed to reduce the treatment cost of the COVID-19. Extensive clinical research on a larger group population is also underway for ensuring the safety and efficacy of this medication in the battle against the COVID-19 pandemic.

Key words: SARS-CoV-2, COVID-19, Nirmatrelvir, Ritonavir, Paxlovid™, pandemic, antiviral

Citation: George, N., M. Imran, S.A. Khan, K. Al Balushi, S.M.B. Asdaq and S. Jomah, 2022. A spotlight on the development, pharmaceutical trends, innovations and patents of Nirmatrelvir (Paxlovid™). Int. J. Pharmacol., 18: 1340-1352.

Corresponding Author: Shah Alam Khan, College of Pharmacy, National University of Science and Technology, P.O. Box 620, PC 130, Muscat, Sultanate of Oman

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Coronavirus disease-2019 (COVID-19) is a highly infectious disease that has infected more than 499 million people globally in just over two years. Till 11th April, 2022, it has caused more than 6.18 million mortalities across all age groups[1]. It is transmitted through the respiratory route and affects the pulmonary system therefore based on clinical symptoms it is named a severe acute respiratory syndrome-corona virus-2 (SARS-CoV-2). Available data indicates that the elderly population, smokers and persons with pre-existing chronic diseases such as diabetes, cardiovascular, cancer and respiratory disease are at a higher risk[2,3]. Concerted efforts have been put in by the scientific fraternity to treat COVID-19 which has threatened global health. Remdesivir, monoclonal antibodies, convalescent plasma therapy etc., were authorized by USFDA for emergency use in the past two years to treat the COVID-19 (Table 1)[4,5]. These are administered parenterally and are somewhat successful in preventing the progression of mild COVID-19 disease to severe disease in hospitalized patients. However, an effective and safe oral therapy was needed that could be used conveniently in all settings to reduce the burden of this infectious disease.

In the ongoing pandemic, several viral mutated variants of SARS-CoV-2 (alpha, beta, gamma, delta and omicron) are being identified which further complicates the existing complex discovery process to identify and develop prophylactic and therapeutic modalities for COVID-19. It has been reported that most of the mutations are occurring in the spike (S) protein of the viral structure and these mutations have been originated and identified in different countries such as England, Brazil, South Africa and India[6]. Vaccines have been proved to be the main weapon in reducing the transmission of COVID-19[7]. So far, USFDA has granted Emergency Use Authorization (EUA) to three successful vaccines developed by Pfizer-BioNTech, Moderna and Janssen. But the approved vaccines are neither 100% effective against all the variants nor do prevent transmission completely[8]. Therefore, the best way to put an end to the pandemic is through mass vaccination drive and the development of cost-effective and convenient pharmacological treatment. Recently on December 22, 2021, the USFDA granted EUA to Paxlovid™, the first oral antiviral therapy to fight against the COVID-19 pandemic[9,10]. Molnupiravir, another oral antiviral drug to combat COVID-19 also received approval on December 23, 2021. But, studies have shown that molnupiravir, an RNA-dependent RNA polymerase (RdRp) inhibitor which is three times more effective than placebo in reducing either mortality or hospitalization in non-hospitalized patients, could induce mutations in human DNA and may lead to the development of new viral variants[11,12].

Nirmatrelvir (PF-07321332), an active pharmaceutical ingredient of Paxlovid™, was developed by Pfizer, Inc., the USA for the treatment of SARS-CoV-2 infection. In clinical studies, it significantly reduced the hospitalization or mortality rate by 89%[13]. Its emergency use has been approved in nearly

Table 1: USFDA approved therapeutics for emergency use in the treatment of COVID-19[14]

Drug name(s) (Dosage form)	Manufacturer	Date of EUA granted	Indication
Bebtelovimab-(IV injections)	Lilly, USA	February 11, 2022	"Mild to moderate COVID-19 adults and children above 12 years of age"
Molnupiravir-oral	Merck and Co	December 23, 2021	Mild to moderate COVID-19
Paxlovid™ (Nirmatrelvir tablets and Ritonavir tablets, co-packaged)-(tablets)	Pfizer	December 22, 2021	"Mild to moderate COVID-19 adults and children above 12 years of age"
Evusheld™ (Tixagevimab co-packaged with Cilgavimab)-(IM injections)	AstraZeneca	First issuance: December 8, 2021 Reissuance: February 24, 2022	Pre-exposure prophylaxis for prevention of COVID-19 in adults and children above 12 years of age who are not currently infected, moderate to severe immune-compromised and who cannot be vaccinated due to a history of severe allergic reactions
Actemra® (Tocilizumab)-(IV infusion)	Genentech	June 24, 2021	Hospitalized COVID-19 adults and children above 12 years of age who are on systemic corticosteroids and require supplemental oxygen
Sotrovimab-(IV injections)	GlaxoSmith Kline (GSK)	First issuance: May 26, 2021 (reissued October 8, 2021, December 16, 2021 and February 23, 2022)	Mild to moderate COVID-19 adults and children above 12 years of age
Baricitinib (Olumiant)-(oral as tablets)	Eli Lilly and Incyte	November 19, 2020, revised on December 20, 2021	"Hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen"
COVID-19 convalescent plasma (IV)		August 23, 2020 Reissued: February 23, 2021, March 9, 2021 and December 28, 2021	COVID-19 patients with the immunosuppressive disease or on immunosuppressive therapy
Remdesivir-(IV injections)	Gilead	May 1, 2020 (Reissued August 28, 2020, October 1, 2020, October 22, 2020 and January 21, 2022)	Mild-to-moderate COVID-19 pediatric patients weighing 3.5 to 40 kg or less than 12 years of age and weighing at least 3.5 kg who are hospitalized or not hospitalized

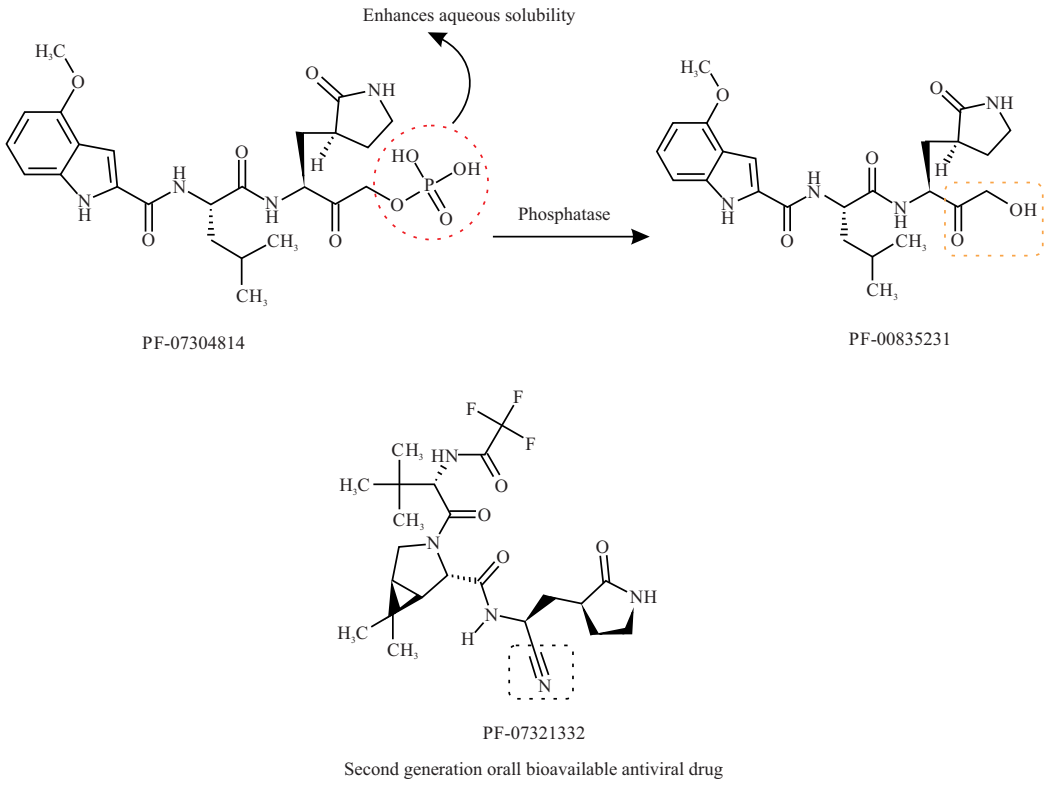

Fig. 1: Structures of PF-07304814 (Lufotrelvir), PF-00835231 and PF-07321332 (Nirmatrelvir)[17]

40 countries. European Medicines Agency (EMA) authorized its use across the EU in January, 2022 while China issued conditional approval in February, 2022 to fight against omicron strain. It stops the SARS-CoV-2 replication by inhibiting the $3CL^{PRO}$ protein. While the other drug in combination, Ritonavir, an HIV-1 protease inhibitor, enhances the bioavailability of Nirmatrelvir by preventing its breakdown and thus allowed a higher concentration of Nirmatrelvir to stay in the body for a longer period. Paxlovid™ has been authorized to treat adults and children above the age of 12 years with mild to moderate COVID-19 symptoms for a maximum of five consecutive days. This review article highlights the development, pharmacology (indication, pharmacokinetic profile, mechanism of action, drug interaction and contraindications), clinical studies and patents granted to Paxlovid™ along with future perspectives.

Development of Paxlovid™: Nirmatrelvir [CAS registry no, 2628280-40-8, PF-07321332, Molecular formula: $C_{23}H_{32}F_3N_5O_4$, Molecular weight: 499.54, IUPAC name: (1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-[(2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamide) butanoyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide] is an orally bioavailable antiviral drug that can inhibit $3CL^{PRO}$. It is packed with another antiretroviral drug known as Ritonavir and has shown promising results in patients with mild-to-moderate COVID-19 infection[15]. Initially in March 2021, Pfizer, Inc., researched and developed another plausible antiviral therapeutic for SARS-CoV-2 known as PF-07304814. This drug is administered intravenously to the patients and requires hospitalization for administration. The drug PF-07304814 is the phosphate form of PF-00835231 and in the body, it gets converted into the active form PF-00835231 in the presence of phosphatase enzyme. The PF-00835231 was converted into its phosphate form (PF-07304814) so that the solubility of the compound could be enhanced and can be continuously infused during administration to the infected patient (Fig. 1). It was developed during the outbreak of SARS in 2002-2003 and the drug was abandoned as the outbreak was self-restrained. This drug is known to show a synergistic effect with remdesivir in hospitalized COVID-19 infected patients[16]. PF-00835231 is a peptide-like structure with a sufficient number of Hydrogen Bond Donors (HBDs)[17]. The HBD provides the compound with a polar surface area and thus it gets trapped in the gut. The apt route of administration of the drug is through the intravenous route and requires hospitalization of the patient. Medicinal chemists removed the HBDs that are not required by the molecule to bind to the viral protein and

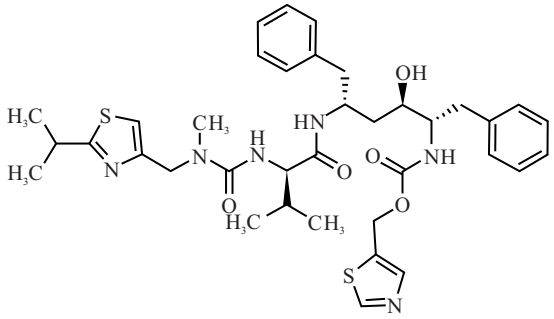

Fig. 2: Chemical structure of Ritonavir
Source: PubChem compound CID: 392622

thus tried to design a second generation of orally bioavailable anti-viral (PF-00835232). The α-hydroxymethyl ketone is one of the HBD's removed by the medicinal chemist to make the drug cross gut to develop an oral antiviral agent. The α-hydroxymethyl ketone group interacted with the cysteine group of the viral protease and thus it was replaced with another group that is not capable of acting as HBD. From the leucine structure, the HBD of PF-00835231 was also removed and replaced by a cyclic amino group that knocks the -NH bond but the structure looks like leucine. Another structural fragment that obtains a leucine-like motif is the fused cyclopropyl ring with two methyl groups. Knocking out the HBDs from the initial molecule also resulted in losing the interaction of the molecule with the glycine moiety present in the active site of the target protease. To replace this interaction, different moieties were tried the including methanesulfonamide acetamide and a trifluoroacetamide and among these moieties' trifluoroacetamide in *in vitro* assays was found to be successful in penetrating the gut barriers. Molecular docking studies revealed the ability of the designed molecules to bind at the binding site of the target protease. Pfizer Inc., developed two compounds with two different reactive groups, benzothiazolyl ketone and one with a nitrile reactive group. From this point onwards, the group chose to proceed with nitrile as the reactive group because of three reasons, (i) Nitrile was more soluble than the counterpart and hence easier to make the higher concentration of the drug solution for toxicology studies, (ii) It was easier to scale up the compound and (iii) Benzothiazole-2-yl ketone is more prone to epimerize by the chiral hydrogen. On July 22, 2020, Pfizer Inc., chemists synthesized Nirmatrelvir (PF-07321332). The oral formulation containing Nirmatrelvir has received USFDA Emergency Use Authorization (EUA) on December 22, 2021, which is the provided in combination with Ritonavir, a well-known HIV1-protease inhibitor.

Role of Ritonavir combination in bioavailability of Nirmatrelvir: Ritonavir (Fig. 2) is known as a suicide inhibitor of the CYP3A4 cytochrome enzyme and it is used in combination with other HIV protease inhibitors as a bio enhancer. Nirmatrelvir is primarily metabolized by CYP3A4. Hence, co-administration of a CYP3A4 inhibitor such as Ritonavir can enhance its therapeutic serum concentration. It is, therefore, administered with Nirmatrelvir to achieve its higher serum concentration for a better therapeutic outcome. Ritonavir forms an isocyanate intermediate, which interacts with the nucleophilic site on the CYP3A4, leading to the carbamylation of the residue at the enzyme site and thus inactivating the metabolizing enzyme[18]. The mechanism of action of Ritonavir in inhibiting the CYP3A4 is illustrated in Fig. 3.

Structure of SARS-COV-2 and the target of Nirmatrelvir: Coronavirus (CoV) falls under the family of Coronaviridae, subgenus sarbecovirus and belongs to the genus Betacoronavirus[19]. The CoV can be found in birds and mammals[20]. Both, SARS-CoV and MERS-CoV have the same genome. It is a positive-strand RNA virus. The viral genome contains 30,000 nucleotides and four genes that code for the surface proteins on the virus's outer surface. The spike protein found on the virus is made up of Glycoprotein S and this exists as a homotrimer and has an S1 subunit, S2 subunit and ACE2 recognition site. With the help of the ACE2 recognition site on the spike protein, it can penetrate the human cells. The virus is provided with an outer shield, the envelope protein (E). This shield is connected to the inner matrix with the help of a membrane protein (M). The viral genome is incorporated in the nucleocapsid (N)[21].

There is an extended range of inhibitors designed by the medicinal chemists for the main target of $3CL^{PRO}$ protease, which is used by the CoV for replication and transcription. This enzyme consists of two domains and the active site

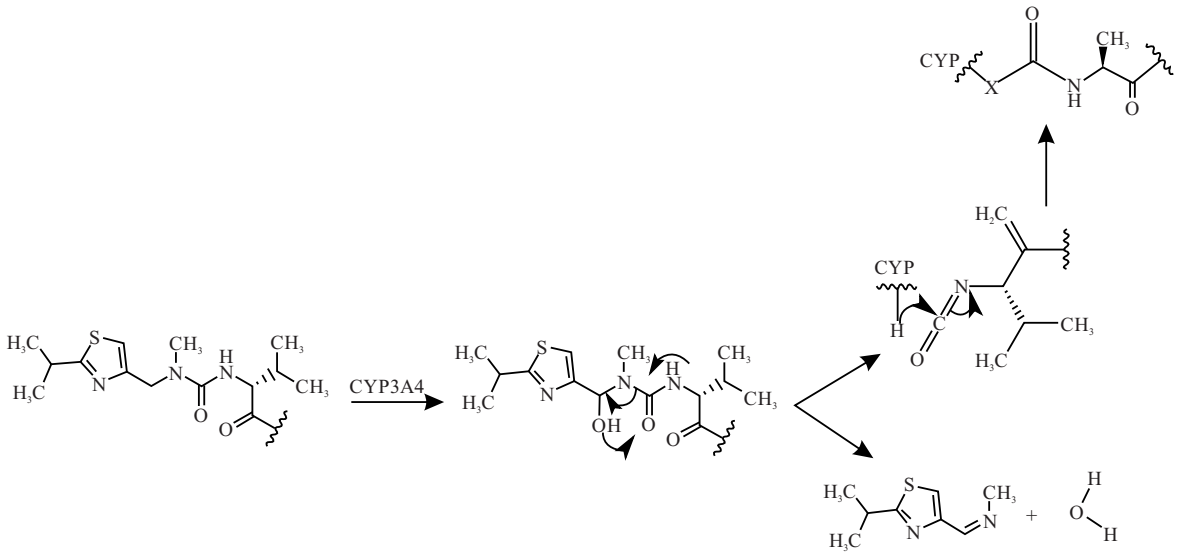

Fig. 3: Inactivation of CYP3A4 enzyme by Ritonavir
Source: It is slightly modified as given in reference 21

lies between these two domains. The $3CL^{PRO}$ consists of 306 amino acid residues. They can cleave 11 sites on the polyproteins. This protein forms a homodimer and each unit consists of three subunits. They have two polypeptide chains namely pp1a and pp1ab. These polypeptides can transform themselves into non-structural proteins with the help of two main viral cysteine proteases called 3-chymotrypsin-like protease ($3CL^{PRO}$) and papain-like protease. The polyprotein is then cleaved by the main protease into non-structural proteins (nsps). These nsps are responsible for the formation of the subgenomic RNAs, which are useful for the formation of the main structural proteins of the corona virus like the spike (S), envelope (E), membrane (M) and nucleocapsid (N) proteins. They also contribute to the conversion of accessory proteins[22,23]. The spike glycoproteins (S) of SARS-CoV-2 have been targeted most by the scientific community to develop COVID-19 vaccines[24].

Chemical synthesis of Nirmatrelvir: Owen *et al.*[13] reported the synthetic route for the preparation of Nirmatrelvir. Among the series of steps in the synthesis of Nirmatrelvir, the important step in the formation is the coupling reaction that takes place between homochiral amino acid and homochiral amino amide by using EDCI as a coupling reagent.

Covalent interaction of Nirmatrelvir with protease enzyme: The formation of three hydrogen bond interactions between $3CL^{PRO}$ and Nirmatrelvir were observed[25-27]. Covalent interactions of the drug molecules, O_2 and H_9 with Cys145 were observed although these atoms were intact during the simulation. The Cys145 is a part of the catalytic dyad of the active site in the viral protease. All the interaction distances remained within 4 A° units. The nitrile group of the drug molecule formed a covalent bond with Cys145-Sγ. The pyrrolidinyl group occupies itself in between the space of Glu166 and Gln189 and also shows an important inhibitory interaction with the drug molecules. It also forms a hydrogen bond with Gln189. The Trifluoroacetamide group is observed to exhibit Gln189-H_2O interaction and this interaction allows the cyclo-propyl-proline moiety to preoccupy the centre position of the binding site. Research conducted on the SARS-CoV-2 main protease has shown a new conformational space in the important regions of the enzyme. The oxyanion group is involved in substrate identification and enzymatic action. It can acquire a new conformation. As mentioned in the structure of SARS-CoV-2 main protease has two regions in the substrate-binding sites known as S_1 and S_2. The new confirmation of the S_1 unit will reshape itself because of which a small new subunit is formed. Leu141 and Gln142 interact with PF-07321332 and these amino acids are part of the oxyanion group and it is involved in the stabilization of the tetrahedral acyl transition state[26].

Pharmacology of Paxlovid™

Mechanism of action of PF-07321332: The SARS-CoV-2 enters the human cells, reproduces itself and spreads the virus in the host body. The oral antiviral drug inhibits the main protease enzyme that produces viral proteins. There are several steps involved in the host cell for the reproduction of SARS-CoV-2 (Fig. 4):

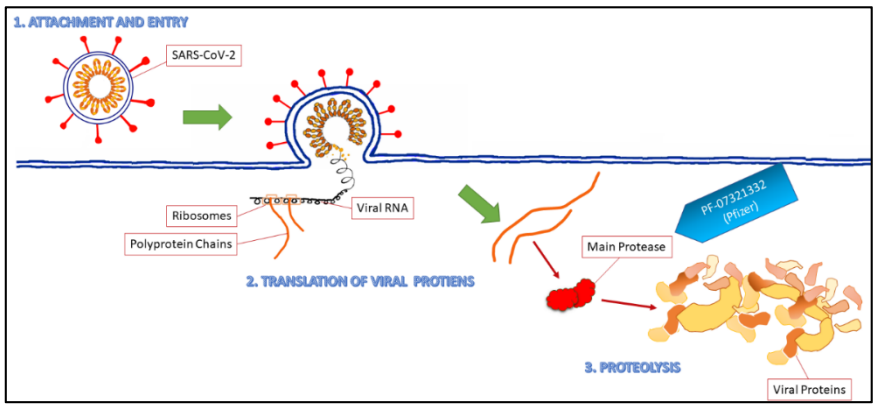

Fig. 4: Schematic representation of the mechanism of action of the oral anti-viral pill for SARS-CoV-2

Table 2: Pharmacokinetic properties of Nirmatrelvir in healthy humans

Pharmacokinetic parameter	Values
Median T_{max}	3 hrs
C_{max}	2.21 μg mL^{-1}
AUC_{inf}	23.01 μg/hr/mL
Mean volume of distribution (V_d)	104.7 L
Bound to plasma protein (%)	69%
Metabolizing enzyme	Substrate of CYP3A4 but minimal in the presence of Ritonavir
Half-life ($t_{1/2}$)	6.05 hrs
Major route of elimination	Renal
Excretion	35.3% in the urine and 49.6% of drug-related material in the faeces

- Attachment of the virus to the host cell
- After attachment of the virus to the plasma membrane, the virus will release the viral RNA from the nucleus which will then be translated into viral proteins
- Viral proteins are synthesized with the action of the main protease enzyme that causes proteolysis of polyproteins
- Replication of transcription complex which results in the formation of circulating RNA
- Structural and accessory proteins are then subjected to transcription and translation
- These synthesized proteins are then assembled into the virus structure and then released

The PF-07321332 is involved in the inhibition of step 2 that involves the translational of viral proteins by inhibiting main protease $3CL^{PRO}$.

Pharmacokinetic profile: Administration of a single oral dose of Nirmatrelvir (300 mg) and Ritonavir (100 mg) in healthy subjects shows the following pharmacokinetic parameters for Nirmatrelvir (Table 2) which is present in the Paxlovid™ (Nirmatrelvir, Ritonavir) product monograph (https://www.paxlovid-hcp.ca/files/PAXLOVID_PM_EN_17Jan2022.pdf).

Indication for Paxlovid™ therapy: Nirmatrelvir is to be co-administered with Ritonavir, to maintain the therapeutic level of the drug in the blood. This combination therapy is indicated for patients with mild to moderate infection and is to be provided orally. One of the advantages of this drug includes the safety of this drug being administered to the pediatric patients under the age category of 12 years and above and weighing at least 40 kg. This can be prescribed to patients with mild to moderate COVID-19 infection and to patients having the chance to develop into a severe infection in the future.

Dosage and administration of Paxlovid™: Commencement of the treatment with Paxlovid™ should be initiated within 5 days of onset of symptoms. As mentioned in the limitations the drug treatment is to be prescribed for only 5 consecutive days. The drug Nirmatrelvir is co-packed with Ritonavir. Each Nirmatrelvir tablet contain 150 mg of Nirmatrelvir and Ritonavir tablet contain 100 mg API. The daily dosing regimen includes 300 mg Nirmatrelvir (2 tablets) and 100 mg Ritonavir (1 tablet each), twice daily for 5 consecutive days. These three tablets should be taken together with or without food twice a day ($3 \times 2 \times 5 = 30$ tablets).

Dosage adjustment is required for patients suffering from renal impairment as the drug mostly gets eliminated through the renal pathway. The dose is reduced to half for patients with moderate renal impairment (eGFR $\geq$30-<60 mL min^{-1}) but should not be used in patients with eGFR <30 mL min^{-1}. It is also contraindicated in patients suffering from a severe hepatic impairment which falls under the category of Child-Pugh Class C classification.

The patient should not double the intake of a dose if missed any dose before and should continue with the next dose as the prescribed dosage regimen.

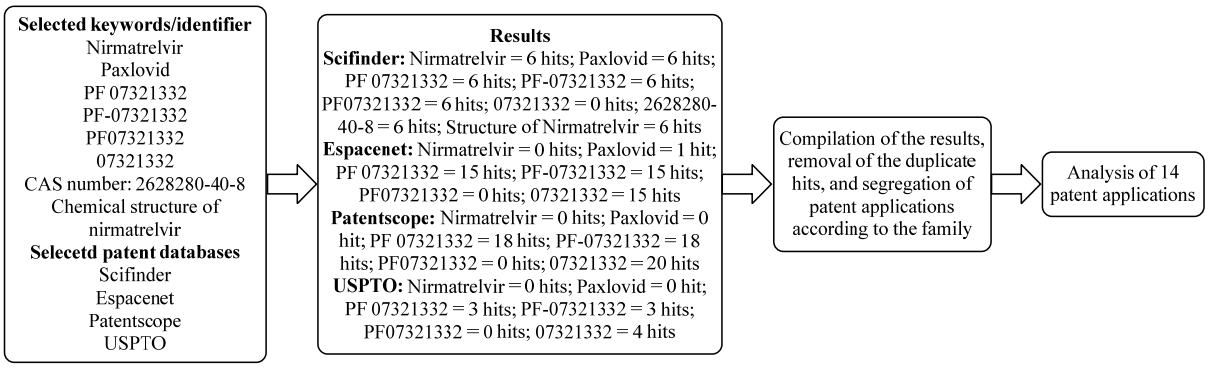

Fig. 5: Patent searching methodology for Nirmatrelvir

Limitations for prescribing Paxlovid™: The USFDA has stated some limitations regarding prescribing this medication to the public. It is not authorized to be prescribed as a pre-exposure and post-exposure regimen for COVID-19. The drug should not be prescribed for more than 5 consecutive days. It is not authorized for administration for initiating treatment for patients suffering from severe COVID-19 infection and hospitalized patients.

Contraindications: Co-administration of Paxlovid™ with any medication, whose elimination depends on the interaction with the CYP3A enzyme should be avoided. The CYP3A inducers can bring down the concentration of Nirmatrelvir and Ritonavir to sub-therapeutic levels and can procreate the virus to become resistant to the treatment. Therefore, CYP3A inducers are the contraindicated with this formulation. Alteration is not required for co-administering Ritonavir and Cobicistat with Paxlovid™. The medication is also known to be contraindicated in patients with a relevant history of clinical hypersensitivity reaction to any of the content in the formulation. Close monitoring or withdrawal of the treatment is required if the co-administered drug is having a narrow therapeutic index and the clearance of the drug is dependent on CYP3A. Immediate administration of this formulation after the sudden withdrawal of CYP3A inducer drugs like apalutamide (anti-cancer agent), carbamazepine (anti-convulsant agent), phenobarbital (anti-convulsant agent), phenytoin (anti-convulsant agent), rifampin (Antimycobacterial) and St. John's Wort (Herbal product) should be avoided.

Adverse drug reaction (ADR): Dysgeusia, diarrhoea, hypertension and myalgia are some of the ADRs reported in patients with an incidence rate of less than 1% for Paxlovid™.

Clinical studies on Nirmatrelvir: The clinical trials database of NIH, US National Library of Medicine was used to search the clinical studies based on Nirmatrelvir utilizing keywords (Paxlovid, Nirmatrelvir and PF-07321332). The literature also provided information about some clinical studies in Nirmatrelvir (NCT04960202, NCT05011513 and NCT05047601)[10,28]. The summary of the identified clinical studies is provided in Table 3.

The results of phase 2-3 clinical trial (NCT04960202, sponsored by Pfizer) of the combination of Nirmatrelvir (300 mg) and Ritonavir (100 mg) on unvaccinated, symptomatic and non-hospitalized COVID-19 patients have been published. This study is related to the USFDA-regulated product (Paxlovid™). The results revealed that the incidence of hospitalization in the combination-treated group was only 0.77% with 0% death in comparison to the placebo (7.01% hospitalization and 7 deaths) by 28 days. The combination therapy also demonstrated a decrease in the viral load after day 5 of the treatment. The progression of the diseases with the combination therapy was lower by 89% in comparison to the placebo group with a promising safety profile.

Patent searching and analysis: Ritonavir was approved by the USFDA in 1996 to treat HIV infection[29]. The structure of Ritonavir was disclosed in US5541206A as a retroviral protease inhibitor[30]. The US5541206A has expired in 2013 in the United States. The term of a patent is generally 20 years[31]. Accordingly, all the compound patents of Ritonavir around the world should have expired by now. This opens free use of Ritonavir by pharmaceutical industries.

The patent literature of Nirmatrelvir was searched on different patent databases (Scifinder, Espacenet, Patentscope and the United States Patent and Trademark Office (USPTO)[32-35] on March 12, 2022. The methodology is depicted in Fig. 5 and the summary of the selected patent application was provided in Table 4.

Table 3: Summary of the clinical studies on Nirmatrelvir against COVID-19

NCT number (intervention, other)	Phase (status, number enrolled, results)	Primary purpose (sponsor, location, start date, actual completion date)
NCT04960202 (safety and efficacy of oral nirmatrelvir+ritonavir combination two times a day for 5 days among non-hospitalized COVID-19 patients)	3 (active, not recruiting, 246, not posted)	Treatment (Pfizer, United States, July 16, 2021, December 9, 2021)
NCT05011513 (safety and efficacy of oral nirmatrelvir+ritonavir combination two times a day for 5 days among non-hospitalized COVID-19 high-risk patients)	2/3 (active, not recruiting, 1150, not posted)	Treatment (Pfizer, United States, August 25, 2021, December 13, 2021)
NCT05047601(prevention of COVID-19 in adults exposed to COVID-19 patients using oral nirmatrelvir+ritonavir combination two times a day for 5 days)	3 (recruiting, 2880, not posted)	Prevention (Pfizer, United States, September 9, 2021, April 18, 2022)
NCT05261139 (safety, efficacy and pharmacokinetics of oral nirmatrelvir+ritonavir combination among pediatric patients)	3 (not yet recruiting, 140, not posted)	Treatment (Pfizer, United States, March 2, 2022, March 4, 2023)
NCT05263908 (observational study to examine the safety and efficacy of Paxlovid in real medical practice)	Not mentioned (not yet recruiting, 3300, not posted)	Post-marketing study (Pfizer, Japan, March 1, 2022, July 10, 2023)
NCT05263921 (estimation of the relative bioavailability of commercial tablet (nirmatrelvir+ritonavir combination) and oral powder (nirmatrelvir+ritonavir combination) in healthy participants)	1 (not yet recruiting, 12, not posted)	Basic Science (Pfizer, Not mentioned, March 11, 2022, May 18, 2022)
NCT04909853 (effect of the renal impairment on the safety, tolerability and pharmacokinetics of nirmatrelvir+ ritonavir combination)	1 (completed, 35, not posted)	Basic Science (Pfizer, United States, June 15, 2021, October 7, 2021)
NCT05178654 (to understand the ADME of radiolabelled nirmatrelvir in healthy participants in combination with ritonavir)	1 (withdrawn, 0, not posted)	Basic Science (Pfizer, Not mentioned, February 22, 2022, April 1, 2022)
NCT05129475 (effect of a high-fat meal on the bioavailability of nirmatrelvir (150 mg tablet two times a day) in combination with ritonavir (100 mg once a day) in healthy participants)	1 (completed, 12, not posted)	Basic Science (Pfizer, United States, November 12, 2021, January 12, 2022)
NCT04962230 (pharmacokinetic interaction between carbamazepine (CYP3A4 inducer) and oral nirmatrelvir+ritonavir combination)	1 (completed, 12, not posted)	Basic Science (Pfizer, United States, July 15, 2021, October 9, 2021)
NCT05064800 (pharmacokinetic interaction between dabigatran (P-gp substrate) and oral nirmatrelvir+ritonavir combination)	1 (completed, 24, not posted)	Basic Science (Pfizer, United States, September 21, 2021, December 6, 2021)
NCT04962022 (interaction of itraconazole (CYP3A4 inhibitor) on the pharmacokinetics of nirmatrelvir+ritonavir combination)	1 (completed, 12, not posted)	Basic Science (Pfizer, Belgium, July 20, 2021, September 30, 2021)
NCT05005312 (effect of hepatic impairment on the pharmacokinetics of oral nirmatrelvir +ritonavir combination to develop dosing regimen)	1 (completed, 17, not posted)	Basic Science (Pfizer, United States, August 31, 2021, December 7, 2021)
NCT05032950 (pharmacokinetic interaction of midazolam (CYP3A4 substrate) and oral nirmatrelvir+ritonavir combination in healthy participants)	1 (completed, 12, not posted)	Basic Science (Pfizer, Belgium, September 17, 2021, December 9, 2021)
NCT05263895 (study the bioavailability of different formulations of nirmatrelvir)	1 (not yet recruiting, 12, not posted)	Basic Science (Pfizer, Not mentioned, March 3, 2022, May 14, 2022)
NCT04756531 (safety, efficacy and tolerability of nirmatrelvir in healthy participants)	1 (completed, 70, not posted)	Other (Pfizer, United States, February 11, 2021, September 1, 2021)

Source: Data is retrieved from a clinical database https://clinicaltrials.gov

Table 4: Patent data of the selected patent applications

Patent applications number (Applicant, Priority country, Status on March 12, 2022)	Family members (International patent classification)	Summary of the claims
US2022062232A1 (Pfizer, United States, Under examination)	WO2021250648A1, EP3953330A1, CL2021002965A1, AU2021266232B1 (A61K31/403, A61K31/427, A61P31/14, C07D403/12)	It claims nirmatrelvir and its solvates/hydrates. It also claims solid amorphous form, crystalline form and a pharmaceutical composition comprising nirmatrelvir for treating COVID-19[37]
US2021361688A1 (Riveros Carlos Alberto, United States, Under examination)	WO2021234668A1, UY39226A (A61K31/573, A61K31/7048, A61K9/00, A61P31/14)	An inhalation or nebulizer system for administering medication (nirmatrelvir, remdesivir, molnupiravir, ivermectin, etc.) alone or in combination with anti-inflammatory drugs (baricitinib, prednisone, dexamethasone and methylprednisolone) for reducing viral (SARS-CoV-2) replication in the upper and lower airways mucosae[38]. No experimental details are available for the claims related to nirmatrelvir
WO2021231872A1 (Healion Bio Inc., United States, No national phase entry)	None (A61K41/00)	A synergistic composition of an anti-COVID-19 drug (nirmatrelvir, favipiravir, remdesivir, molnupiravir, etc.) with a mammalian protease inhibitor (cathepsin inhibitor like balicatib). The composition is claimed to have improved efficacy and lower toxicity/dose of the anti-COVID-19. However, no experimental support is mentioned for the composition of nirmatrelvir[39]
WO2021221043A1 (Fujifilm Toyama Chemical Co. Ltd., Japan, No national phase entry)	None (A61K31/07, A61K31/11, A61K31/121, A61K31/122, A61K31/137, A61K31/138, A61K31/216, A61K31/343, A61K31/351, A61K31/352, A61K31/357, A61K31/366, A61K31/395, 61K31/403)	It claims novel pyrazine derivatives that can be used to treat COVID-19 in combination with anti-COVID-19 drugs (nirmatrelvir, remdesivir, molnupiravir, etc.). No experimental support is mentioned for the composition of nirmatrelvir with the claimed pyrazine derivatives[40]
WO2021207632A1 (The Regents of the University of California, United States, No national phase entry)	None (A61K31/436, A61K31/497, A61K31/506, A61K31/5377, A61K45/06, A61K9/00, A61P11/00, A61P31/12, A61P31/14)	A composition of anti-COVID-19 drugs (nirmatrelvir, remdesivir, molnupiravir, etc.) with many drugs, including anticancerous kinase inhibitors to treat COVID-19. However, no experimental support is mentioned for the composition of nirmatrelvir[41]
WO2022035911A2 (Tutela Pharmaceuticals, United States, No national phase entry)	None (A61K41/00)	A synergistic composition encompassing an FKBP ligand or derivative (tacrolimus, everolimus, sirolimus, etc.) and a sub-therapeutic dose of an antiviral drug (nirmatrelvir, remdesivir, molnupiravir, etc.) to prevent/treat SARS-CoV-2 infection. This composition is claimed to have no suppressive effect on the patient's immune system. However, no experimental support is mentioned for the composition of nirmatrelvir[42]
CN114057627A (Nanjing Huaguan Biotechnology & Jindawei Biotechnology, China, Publication of the application)	None (C07D209/52)	It claims the process for the preparation of intermediates used in the synthesis of nirmatrelvir[43]
WO2021211609A1 (Buck Institute for Research on Aging, United States, No national phase entry)	None (G01N33/50, G01N33/58, G01N33/60)	A prophylactic/therapeutic composition for COVID-19 comprising an antiviral exogenous ketone-like (R)-3-hydroxybutyrate and an antiviral agent (nirmatrelvir, remdesivir, molnupiravir, etc.). However, no experimental support is mentioned for the composition of nirmatrelvir[44]
US2021322351A1 (Immune AG, Europe, Notice of Allowance mailed)	WO2021214033A1, EP3900717A4, EP3900717A1 (A61K31/196, A61K31/706, A61K45/06, A61K9/00, A61K9/20, A61P31/14)	It claims a composition of DHODH inhibitor (vidofludimus) and an antiviral (nirmatrelvir, remdesivir and molnupiravir) to treat COVID-19. However, no experimental support is mentioned for the composition of nirmatrelvir[45]
WO2021212183A1 (Centre for Digestive Diseases Pty Ltd., United States, No national phase entry)	None (A61K31/165, A61K31/215, A61K31/351, A61K31/375, A61K31/426, A61K31/4409, A61K31/4706, A61K31/495, A61K31/4965)	It is related to devices (inhaler, nebulizer, nasal spray, respirator, etc.) for delivering anti-COVID-19 drugs like nirmatrelvir. However, no device has been exemplified with nirmatrelvir[46]
WO2021250038A1 (Apteeus, Europe, No national phase entry)	None (A61K31/05, A61K47/20, A61K9/08, A61P31/14)	A composition of clofoctol that optionally may contain nirmatrelvir, for use in the prevention or treatment of COVID-19[47]
WO2021262825A2 (Genetic Networks, United States, No national phase entry)	None (A61K31/122, A61K31/216, A61K31/343, A61K31/4422, A61K31/519, A61K31/7048)	A method of treating COVID-19 using a fatty acid synthesis inhibitor, optionally in the combination of nirmatrelvir[48]
CN113999160A (Jiangsu Institute of Materia Medica Co., Ltd., China, Under examination)	None (C07D209/52)	It claims the process for preparing an intermediate of nirmatrelvir[49]
US2022040227A1 (Reverspah, United States, No national phase entry)	WO2022035813A1 (A61K31/381, A61K31/495, A61K33/24, A61K45/06)	A composition comprising a copper chelator (tetrathiomolybdate salt), optionally in combination with nirmatrelvir for treating COVID-19

DISCUSSION

Paxlovid™ containing a combination of Nirmatrelvir-Ritonavir chemicals is the first oral nitrile peptidomimetic drug granted a EUA by USFDA for the treatment of SARS-CoV-2. Paxlovid™ and molnupiravir, another orally administered antiviral drug, are indicated in the treatment of mild to moderate COVID-19. Especially, the development of Paxlovid™ has been seen as a milestone in the fight against the SARS-CoV-2 pandemic as it has demonstrated better efficacy than molnupiravir in reducing hospitalization and death rate in clinical studies.

Pfizer, the innovator of Paxlovid™, has conducted many clinical trials on Paxlovid™ and Nirmatrelvir. These trials relate to prevention, treatment and pharmacokinetic interactions (Table 3). However, the results of many clinical studies have not yet been published. The USFDA has already authorized Paxlovid™ to treat COVID-19 based on the safety and efficacy data of Paxlovid™. However, very few interaction studies, including drug-drug interaction, drug-food interaction, drug-vaccine interaction, drug-disease interaction and physicochemical interaction studies have been reported for Paxlovid™ or Nirmatrelvir (Table 3). This keeps many unresolved concerns alive (Fig. 6). The drug interaction studies are directly related to the patient safety and efficacy of a drug. Therefore, the authors anticipate further drug interaction-based clinical studies on Paxlovid™ and Nirmatrelvir. Further, new variants of SARS-CoV-2 possessing different pathogenicity and transmission rates have appeared recently[28]. This makes it imperative to assess the safety, efficacy and tolerability of Paxlovid™ and Nirmatrelvir among patients infected with new strains of SARS-CoV-2.

The patent search revealed a total of 14 patent applications related to Nirmatrelvir. Among the 14 patent applications, 8 have been filed in the United States, three in China, two in Europe and one in Japan. The equivalents of the compound patent of Nirmatrelvir[36] have been filed in Europe, Chile and Australia. The equivalent filing of the compound patent is expectable in most countries around the globe. If the compound patent application of Nirmatrelvir is granted in the United States, its estimated expiry will be August 5, 2041. This expiry date may also be extended based on the patent term extension law of the United States[31]. The patent applications have claimed different aspects of Nirmatrelvir (Fig. 7). However, many patent application filings are foreseeable also (Fig. 6). It is interesting to note that most of the patent applications did not exemplify the outcomes of their claimed compositions/combinations. This opens a research portal to study these combinations. It is believed that Nirmatrelvir encompasses a lot of scope for further research in pharmaceutical/biomedical sciences.

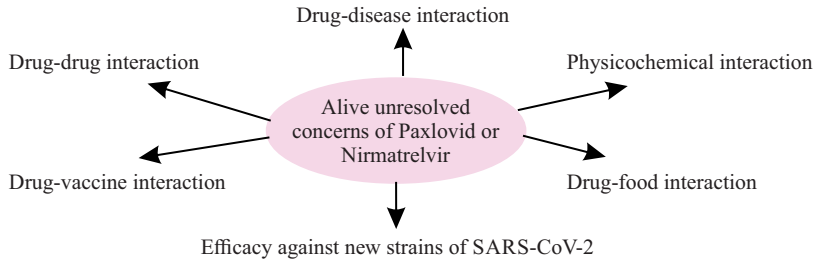

Fig. 6: Unresolved concern about Paxlovid™ and Nirmatrelvir

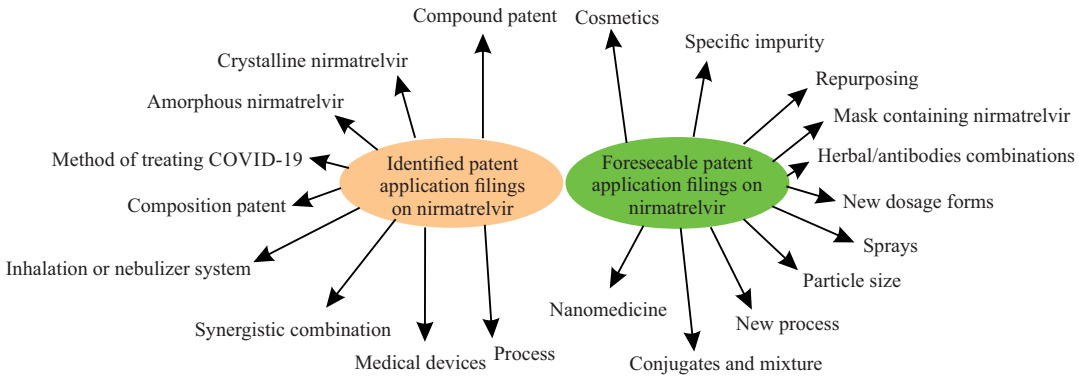

Fig. 7: Current and foreseeable patent application filing on Nirmatrelvir

CONCLUSION

Paxlovid™ is observed to be more effective than the rest of the anti-viral drugs approved for the treatment of SARS-CoV-2 infected individuals to date. It is also observed to be more effective than the antiviral drugs available on the market. This oral antiviral drug is responsible for slashing the hospitalization of COVID-19 patients and helps to clear the virus more quickly from the infected body. The treatment can be challenging since this oral antiviral drug should be administered to the patients within three days of onset of symptoms. Being a combination and one of the drugs Ritonavir inhibits CYP3A4, it may show drug interactions which are a major concern with Paxlovid™. Furthermore, the current synthetic route to prepare Nirmatrelvir involves many steps, hence, it is foreseeable that efficient and shorter synthetic methods will be developed that may cut down the treatment cost of the COVID-19 and increase the yield (%). Also, attempts will likely be made to improve its potency by structural modification and to formulate this in other oral dosage forms. Therefore, extensive research on a larger group of populations is essential for ensuring the safety and efficacy of this medication.

SIGNIFICANCE STATEMENT

This review article provides an insight into the pharmaceutical development of Nirmatrelvir (Paxlovid™), the first oral nitrile peptidomimetic drug, effective in the treatment of SARS-CoV-2. It succinctly covers the drug design strategies, pharmacology, clinical studies and patents granted to this antiviral drug. Therefore, researchers looking for specific information about either pharmacology or pharmaceutical aspects of Nirmatrelvir will find it a useful source. This is the first study in which all the patents granted to Nirmatrelvir are compiled in one place with an expert opinion. It also opens up a window to study various combinations of Nirmatrelvir to develop products of pharmaceutical interest.

ACKNOWLEDGMENTS

The authors are thankful to Dr. Sulaiman Al-Habib Medical Group's research centre for their tremendous support. All the authors of this manuscript are thankful to their respective Institutes/Universities for the successful completion of this study.

REFERENCES

1. Imran, M., S.A. Khan, Abida, M.K. Alshammari and S.M. Alkhaldi *et al*., 2022. *Nigella sativa* L. and COVID-19: A glance at the anti-COVID-19 chemical constituents, clinical trials, inventions, and patent literature. Molecules, Vol. 27. 10.3390/molecules27092750.
2. Kim, L., S. Garg, A. O'Halloran, M. Whitaker and H. Pham *et al*., 2021. Risk factors for intensive care unit admission and in-hospital mortality among hospitalized adults identified through the US coronavirus disease 2019 (COVID-19)-associated hospitalization surveillance network (COVID-NET). Clin. Infect. Dis., 72: e206-e214.
3. Thakur, B., P. Dubey, J. Benitez, J.P. Torres and S. Reddy *et al*., 2021. A systematic review and meta-analysis of geographic differences in comorbidities and associated severity and mortality among individuals with COVID-19. Sci. Rep., Vol. 11. 10.1038/s41598-021-88130-w.
4. Hsu, J.Y., Y.C. Mao, P.Y. Liu and K.L. Lai, 2021. Pharmacology and adverse events of emergency-use authorized medication in moderate to severe COVID-19. Pharmaceuticals, Vol. 14. 10.3390/ph14100955.
5. Moshkovits, I. and D. Shepshelovich, 2022. Emergency use authorizations of COVID-19-related medical products. JAMA Internal Med., 182: 228-229.
6. Mallapaty, S., 2021. India's massive COVID surge puzzles scientists. Nature, 592: 667-668.
7. Kashte, S., A. Gulbake, S.F. El-Amin III and A. Gupta, 2021. COVID-19 vaccines: Rapid development, implications, challenges and future prospects. Hum. Cell, 34: 711-733.
8. Pascolo, S., 2021. Vaccines against COVID-19: Priority to mRNA-based formulations. Cells, Vol. 10. 10.3390/cells10102716.
9. Saravolatz, L.D., S. Depcinski and M. Sharma, 2022. Molnupiravir and nirmatrelvir-ritonavir: Oral COVID antiviral drugs. Clin. Infect. Dis., 10.1093/cid/ciac180.
10. Hung, Y.P., J.C. Lee, C.W. Chiu, C.C. Lee, P.J. Tsai, I.L. Hsu and W.C. Ko, 2022. Oral nirmatrelvir/ritonavir therapy for COVID-19: The dawn in the dark? Antibiotics, Vol. 11. 10.3390/antibiotics11020220.
11. Gandhi, R.T., P.N. Malani and C. del Rio, 2022. COVID-19 therapeutics for nonhospitalized patients. JAMA, 327: 617-618.
12. Lee, C.C., C.C. Hsieh and W.C. Ko, 2021. Molnupiravir-a novel oral anti-SARS-CoV-2 agent. Antibiotics, Vol. 10. 10.3390/antibiotics10111294.
13. Owen, D.R., C.M.N. Allerton, A.S. Anderson, L. Aschenbrenner and M. Avery *et al*., 2021. An oral SARS-CoV-2 M^{pro} inhibitor clinical candidate for the treatment of COVID-19. Science, 374: 1586-1593.

14. Basu, D., V.P. Chavda and A.A. Mehta, 2022. Therapeutics for COVID-19 and post COVID-19 complications: An update. Curr. Res. Pharmacol. Drug Discovery, Vol. 3. 10.1016/j.crphar.2022.100086.
15. Lamb, Y.N., 2022. Nirmatrelvir plus ritonavir: First approval. Drugs, 82: 585-591.
16. Yavuz, S. and F.I.K. Çelikyurt, 2021. An update of anti-viral treatment of COVID-19. Turk. J. Med. Sci., 51: 3372-3390.
17. Halford, B., 2022. The path to paxlovid: How Pfizer scientists transformed an old drug lead into an oral COVID-19 antiviral. ACS Cent. Sci., 8: 405-407.
18. Patel, T.K., P.B. Patel, M. Barvaliya, M.K. Saurabh, H.L. Bhalla and P.P. Khosla, 2021. Efficacy and safety of lopinavir-ritonavir in COVID-19: A systematic review of randomized controlled trials. J. Infect. Public Health, 14: 740-748.
19. Lu, R., X. Zhao, J. Li, P. Niu and B. Yang *et al*., 2020. Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. Lancet, 395: 565-574.
20. Durai, P., M. Batool, M. Shah and S. Choi, 2015. Middle East Respiratory Syndrome Coronavirus: Transmission, virology and therapeutic targeting to aid in outbreak control. Exp. Mol. Med., Vol. 47. 10.1038/emm.2015.76.
21. Menéndez, J.C., 2022. Approaches to the potential therapy of COVID-19: A general overview from the medicinal chemistry perspective. Molecules, Vol. 27. 10.3390/molecules27030658.
22. Ramajayam, R., K.P. Tan and P.H. Liang, 2011. Recent development of 3C and 3CL protease inhibitors for anti-coronavirus and anti-picornavirus drug discovery. Biochem. Soc. Trans., 39: 1371-1375.
23. Ren, Z., L. Yan, N. Zhang, Y. Guo, C. Yang, Z. Lou and Z. Rao, 2013. The newly emerged SARS-Like coronavirus HCoV-EMC also has an "Achilles' heel": Current effective inhibitor targeting a 3C-like protease. Protein Cell, 4: 248-250.
24. Suryana, K.D., M. Simadibrata and K. Renaldi, 2021. Impact of COVID-19 on the gut: A review of the manifestations, pathology, management, and challenges. Acta Med. Indonesian-Indonesian J. Internal Med., 53: 96-104.
25. Hoffman, R.L., R.S. Kania, M.A. Brothers, J.F. Davies and R.A. Ferre *et al*., 2020. Discovery of ketone-based covalent inhibitors of coronavirus 3CL proteases for the potential therapeutic treatment of COVID-19. J. Med. Chem. 63: 12725-12747.
26. Ngo, S.T., T.H. Nguyen, N.T. Tung and B.K. Mai, 2022. Insights into the binding and covalent inhibition mechanism of PF-07321332 to SARS-CoV-2 M^{pro}. RSC Adv., 12: 3729-3737.
27. Ahmad, B., M. Batool, Qurat ul Ain, M.S. Kim and S. Choi, 2021. Exploring the binding mechanism of PF-07321332 SARS-CoV-2 protease inhibitor through molecular dynamics and binding free energy simulations. Int. J. Mol. Sci., Vol. 22. 10.3390/ ijms22179124.
28. Hammond, J., H. Leister-Tebbe, A. Gardner, P. Abreu and W. Bao *et al*., 2022. Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. N. Engl. J. Med., 386: 1397-1408.
29. Chandwani, A. and J. Shuter, 2008. Lopinavir/ritonavir in the treatment of HIV-1 infection: A review. Ther. Clin. Risk Manage., 4: 1023-1033.
30. Kempf, D.J., D.W. Norbeck, H.L. Sham and C. Zhao, 1996. Retroviral protease inhibiting compounds. https://patents.google.com/patent/US5541206A/en?oq=US5541206A
31. Imran, M., S.M.B. Asdaq, S.A. Khan, D.U. Meenakshi and A.S. Alamri *et al*., 2021. Innovations and patent trends in the development of USFDA approved protein kinase inhibitors in the last two decades. Pharmaceuticals, Vol. 14. 10.3390/ph14080710.
32. Imran, M., S.A. Khan, Abida, A.S. Alshrari and M.M.E. Mudawi *et al*., 2022. Small molecules as kinetoplastid specific proteasome inhibitors for leishmaniasis: A patent review from 1998 to 2021. Expert Opin. Ther. Pat., 32: 591-604.
33. Imran, M., S.A. Khan, M.K. Alshammari, M.A. Alreshidi and A.A. Alreshidi *et al*., 2021. Discovery, development, inventions, and patent trends on mobocertinib succinate: The first-in-class oral treatment for NSCLC with EGFR Exon 20 insertions. Biomedicines, Vol. 9. 10.3390/biomedicines9121938.
34. Imran, M., A.S. Alshrari, M. Tauseef, S.A. Khan, S.A. Hudu and Abida, 2021. Mucormycosis medications: A patent review. Expert Opin. Ther. Pat., 31: 1059-1074.
35. Imran, M., A.S. Alshrari, H.K. Thabet, Abida and M.A. Bakht, 2021. Synthetic molecules as DprE1 inhibitors: A patent review. Expert Opin. Ther. Pat., 31: 759-772.
36. Owen, D.R., M.Y. Pettersson, M.R. Reese, M.F. Sammons and J.B. Tuttle *et al*., 2022. Nitrile-containing antiviral compounds. https://patents.google.com/patent/US20220062232A1/en?oq=US2022062232A1
37. Riveros, C.A., 2021. System, method and use of a certain medication for reducing viral replication in the airways mucosae. https://patents.google.com/patent/US20210361688A1/en?oq=US2021361688A1
38. Bavari, S. and S. Newman, 2021. Compositions and methods for increasing efficacy of a drug. https://patents.google.com/patent/WO2021231872A1/en?oq=WO2021231872A1
39. Takashi, K. and Y. Nozomi, 2021. Coronavirus infection therapeutic agent formed through combination of pyrazine derivative and another coronavirus infection therapeutic drug. https://patents.google.com/patent/WO2021221043A1/en?oq=WO2021221043A1
40. Arumugaswami, V., H.R. Christofk, R. Damoiseaux, G. Garcia and P. Mullen, 2021. Small molecule therapeutics for the treatment of viral infections. https://patents.google.com/patent/WO2021207632A1/en?oq=WO2021207632A1

41. Fitzsimmons, W., 2022. Methods of treating coronavirus infections by co-administering an FKBP ligand and an antiviral agent. https://patents.google.com/patent/WO2022035911A2/en?oq=WO2022035911A2
42. Jian, C., Y. Changquan, G. Rong, X. Wei and Q. Yatao *et al*., 2022. Preparation method of hepatitis C and neocorolla drug intermediate and salt thereof. https://patents.google.com/patent/CN114057627A/en?oq=CN114057627A
43. Stubbs, B. and J.C. Newman, 2021. Treatment of viral pathologies with exogenous ketones. https://patents.google.com/patent/WO2021211609A1/en?oq=WO2021211609A1
44. Gröppel, M., D. Vitt, H. Kohlhof and A. Mühler, 2021. Vidofludimus for use in the treatment or prevention of viral diseases. https://patents.google.com/patent/US20210322351A1/en?oq=US2021322351A1
45. Borody, T.J., 2021. Products of manufacture and methods for treating, ameliorating or preventing microbial infections. https://patents.google.com/patent/WO2021212183A1/en?oq=WO2021212183A1
46. Apteeus, 2021. Compound and method for the treatment of coronaviruses. https://patents.google.com/patent/WO2021250038A1/en?oq=WO2021250038A1
47. D'urso, G. and K. Mcgary, 2021. Disrupting lipid synthesis: A novel target for broad-spectrum host-directed anti-virulence therapeutics. https://patents.google.com/patent/WO2021262825A2/en?oq=WO2021262825A2
48. Jun, X., L. Sheng, X. Bin, X. Chao, L. Yuan, Y. Haijun and C. Guoguang, 2022. Preparation method of 6, 6-dimethyl-3-azabicyclo [3.1.0] hexane. https://patents.google.com/patent/CN113999160A/en?oq=CN113999160A
49. Voelkel, N.F. and C. Magolske, 2022. Method and composition for treating corona virus, influenza, and acute respiratory distress syndrome. https://patents.google.com/patent/US20220040227A1/en?oq=US2022040227A1