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Mini-Review

Repurposed Drugs during the Outbreak of Pandemic COVID-19: A Mini-Review on Their Molecular Structures and Hit-and-Trial Results

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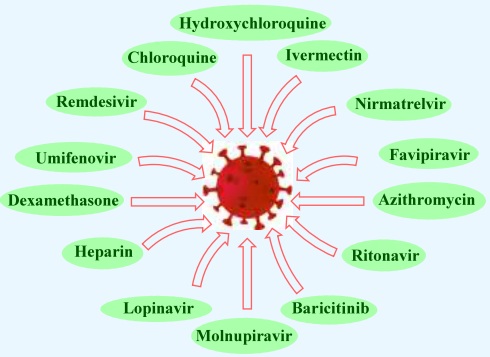
ABSTRACT: One of the most significant threats to global public health in the 21st century is the novel coronavirus disease (COVID-19) caused by SARS-CoV-2. It rapidly turned into a global pandemic after it was identified in late 2019, and the World Health Organization announced the end of the pandemic on May 5, 2023. Current strategies for managing this disease include vaccination and repurposing antimalarial and antibiotic medications to alleviate symptoms like fever and throat pain, which are associated with acute respiratory distress syndrome (ARDS). Antiviral drugs such as chloroquine, hydroxychloroquine, azithromycin, remdesivir, and favipiravir have been repurposed for the treatment of COVID-19. They were previously recommended for treating SARS-CoV and MERS-CoV. However, the inefficacy and adverse side effects of these repurposed drugs led to a decrease in their widespread use in treating COVID-19 patients. The lack of approved drugs for combating this coronavirus and its unpredictable variants remains a significant challenge.



1. INTRODUCTION

The whole world was intoxicated due to the COVID-19 pandemic during December 2019−May 2023, and everybody had the nervous apprehension of a nuclear-holocaust-like situation that might lead to the destruction of this planet. Those were the days when new words like pandemic, lockdown, quarantine, containment zone, doomsday warnings, political paranoia, etc., were the leading headlines of daily newspapers. According to the latest World Health Organization (WHO) report, as of July 26, 2024, COVID-19 touched 775 673 955 lives and caused 7 053 524 confirmed deaths.[1] The current social media are flooded with overwhelming reports of the new variants of this deadly virus. JN.1, KP.2, KP.3, etc. now collectively belong to the family of FLiRT, continuously flirting with all human beings.[2] In this mini-review we have selected a few drugs as mentioned in the cited references and discussed their pros and cons as repurposed drugs in the treatment of COVID-19 patients.

2. A BRIEF HISTORY OF SARS, MERS, AND COVID-19

Three viruses, specifically, severe acute respiratory syndrome (SARS, 2002, China), Middle East respiratory syndrome (MERS, 2012, Saudi Arabia), and coronavirus disease (COVID-19), may be considered as the worst viruses of mankind in the 21st century. The Chinese Centre for Disease Control and Prevention (CDC) detected a novel coronavirus from the throat swab sample of one patient at the end of December 2019, and it was subsequently named SARS-CoV-2, causative agent of novel coronavirus 2019 by World Health Organization (WHO). WHO declared the SARS-CoV-2 an outbreak, issued a Public Health Emergency of International Concern (PHEIC), and officially renamed SARS-CoV-2 as coronavirus disease 2019 (COVID-19).[3] In light of the rapidly increasing transmission speed and severity of the outbreak, surpassing 13-fold infected cases in countries outside China, on March 11, 2020, WHO declared the COVID-19 outbreak a global pandemic.[4]

Coronaviruses are single-stranded positive-sense RNA viruses and classified into four types: α-coronavirus (α-COV), β-coronavirus (β-COV), δ-coronavirus (δ-COV), and γ-coronavirus (γ-COV).[5] Coronaviruses, including SARS-CoV, MERS-CoV, and SARS-CoV-2, cause respiratory tract infections in humans, leading to a condition known as acute respiratory distress syndrome (ARDS). SARS-CoV-2 encodes four major structural proteins: the spike protein (S), the nucleocapsid protein (N), the membrane protein (M), and the envelope protein (E).[6] The receptor binding domain of the S protein of SARS-CoV-2 is similar to that of a coronavirus

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isolated from bat and pangolins, indicating the zoonotic origin.[7]

3. PREVENTION OF COVID-19 AND REPURPOSED DRUGS FOR TREATMENT ON HIT AND TRIAL

The transmission of coronaviruses from person to person occurs through various pathways, including droplets and direct or indirect contact with surfaces. COVID-19 infection syndrome begins with fever, cough, and fatigue. Signs of progression include sputum production, headache, hemoptysis, diarrhea, breathing disorders, and lymphopenia.

3.1. Self-Precaution. The most effective way to avoid getting infected is by minimizing exposure to the virus. The primary preventive measures are social and physical distancing, washing hands with soap and water or using hand sanitizers, and wearing masks, gloves, and personal protective equipment (PPE) for frontline workers such as healthcare and security professionals.

3.2. Vaccine Discovery. Effective vaccines within 1 year of the emergence of COVID-19 was unprecedented. However, in view of the urgency of the outbreak, the development of vaccines or oral pills and testing them in hit-and-trial (trial-and-error) experiments and dissemination of the results of their effectiveness in combating the pandemic were the only targets of cutting-edge research during 2020−2023. More than 30 vaccines have received approval for general or emergency use in countries globally. Vaccines based on viral vector and nucleic acid technologies for COVID-19 have been extensively used in clinical practice, resulting in high effectiveness in preventing severe disease and death. However, many of these vaccines have merits and demerits. To put an end to the pandemic, we must address new challenges in the global immunization process. These include dealing with new virus strains and addressing public vaccine hesitancy.

Some drawbacks of these vaccines include allergic reactions, soreness, pain at the injection site, fatigue, headaches, fever, and muscle or joint pains. Additionally, their effectiveness against specific variants of SARS-CoV-2, such as Delta and Omicron, is reduced. There have also been reports of reinfection occurring after receiving the full prescribed doses of the vaccine.[8,9]

3.3. Repurposing of Drugs. Patients with COVID-19 disease who have comorbidities, such as bronchitis, pneumonia, severe acute respiratory distress syndrome (ARDS), hypertension, and diabetes mellitus, are more likely to develop a more severe course and progression of the disease. In severe cases, antiviral, antiparasitic, and antibiotic drugs have emerged as important therapeutic tools against COVID-19. Drug repurposing is a cost-effective and rapid approach to discovering new applications for existing drugs with well-established safety profiles. In 2020, the United States Food and Drug Administration (U.S. FDA) and the National Institutes of Health (NIH) recommended the use of remdesivir, and emergency approval was given to all repurposed therapeutics.[10] Thus, many countries started advocating several drugs to affected patients fighting different stages of symptoms like viral fever, flu, and respiratory problems related to lungs on a clinical trial basis. Several potential therapeutic agents, including lopinavir, ritonavir, oseltamivir, umifenovir, remdesivir, favipiravir, chloroquine, hydroxychloroquine, interferon, ribavirin, tocilizumab, and sarilumab, have been repurposed for clinical trials and emergency cases.[11] Among the antiviral drugs, chloroquine, hydroxychloroquine, remdesivir, favipiravir, and the antibiotic azithromycin are considered the most effective. This mini-review provides an overview of the chemical structures of these synthetic drugs and their potential applications in COVID-19 treatment through hit-and-trial reactions.

3.3.1. Chloroquine (CQ) and Hydroxychloroquine (HCQ). Chloroquine (CQ; Figure 1) and hydroxychloroquine (HCQ; Figure 2) belong to the class of heterocyclic compounds called 4-aminoquinolines. They are synthetic drugs and are considered substituted drugs for the antimalarial natural product quinine. CQ was reported to possess strong antiviral, anti-inflammatory, and immunomodulatory properties and thus was considered to be a suitable drug candidate for the treatment of COVID-19-associated pneumonia in 2020.[12] As drug discovery research advances rapidly, a more effective drug for the treatment of malaria called hydroxychloroquine has been discovered and is sold under the brand name Plaquenil. It is used to prevent and treat malaria in areas where the disease is still sensitive to chloroquine. HCQ, considered less toxic than chloroquine with fewer side effects, is extensively used for the treatment of malaria, lupus erythematosus, and rheumatoid arthritis.

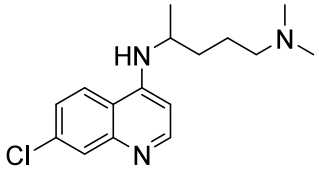

Figure 1. Structure of chloroquine.

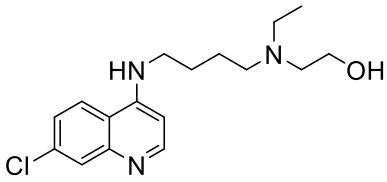

Figure 2. Structure of hydroxychloroquine.

Even though hydroxychloroquine sulfate tablets are approved for the treatment of malaria, lupus erythematosus, and rheumatoid arthritis, a dearth in finding suitable lead molecules to control the outbreak pushed the U.S. Food and Drug Administration issued an emergency use authorization of HCQ for treatment of COVID-19.[13] In spite of the global debate regarding its efficacy and side effects, it is considered one of the most promising drugs since the number pf cases started to spike. It has been reported that hydroxychloroquine (HCQ) can increase the pH of the cell and, when combined with zinc, potentially block the entry of the virus into the cell.[14]

However, the use of hydroxychloroquine in combination with other antibiotics led to complications in COVID-19 patients with comorbidities, particularly cardiovascular diseases.[15] Axfors and co-workers found no improvement in the mortality rate when hydroxychloroquine and chloroquine were given to COVID-19 patients.[16]

3.3.2. Favipiravir and Umifenovir. The anti-influenza medicine favipiravir (Figure 3) has been repurposed and approved as an experimental treatment for COVID-19 infections. The drug has been found to be effective in treating

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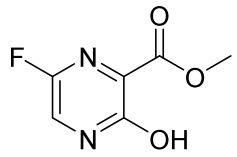

Figure 3. Structure of favipiravir.

mild to moderate cases of COVID-19 infection. It has prevented the replication of the virus and improved the condition of the lungs, as confirmed by X-rays.[17,18]

Umifenovir (shown in Figure 4), another drug candidate commonly known as Arbidol in medical parlance, is a highly

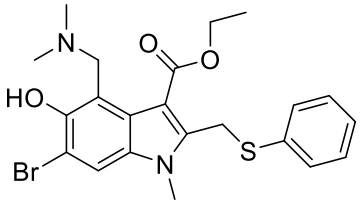

Figure 4. Structure of umifenovir.

substituted derivative of indole. This small molecule demonstrates potential inhibitory activity against various viruses such as influenza A and B, parainfluenza, and hepatitis.The hemaglutinin envelope glycoprotein (HA) of the influenza virus is the target of this antiviral drug, which can reduce the growth of the virus. A group of researchers from China reported that COVID-19 patients in China showed no detectable virus after 14 days of umifenovir monotherapy.[19] The most likely mechanism of action is the prevention of virus−cell membrane fusion and virus−endosome internalization through the incorporation of umifenovir molecules into the cell membrane. Umifenovir could enhance the humoral immune response and interferon production. Another possible mechanism was based on the combination of umifenovir with interferons, which may lead to a synergistic therapeutic effect against SARS-CoV-2.[20] However, randomized clinical trials showed no improvement in the mortality rates of COVID-19 patients, and thus, the widespread application of umifenovir was reduced again in subsequent years.[21]

3.3.3. Lopinavir, Ritonavir, and Nirmatrelvir. Lopinavir (Figure 5) and ritonavir (Figure 6) are commonly used for the treatment of AIDS.[22] Ritonavir, also known as Norvir, is used to treat HIV/AIDS and hepatitis C as it inhibits proteases.

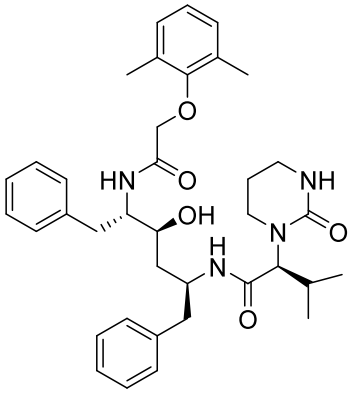

Figure 5. Structure of lopinavir.

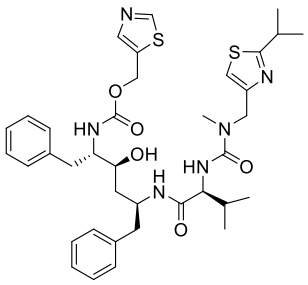

Figure 6. Structure of ritonavir.

Ritonavir is also used in the management of COVID-19 in combination with other antiviral and antiretroviral agents such as lopinavir, nirmatrelvir, simnotrelvir, ombitasvir, and paritaprevir. These medications are oral antiviral agents that target the 3-chymotrypsin-like protease, which is essential for SARS-CoV-2 viral replication.[23]

Figure 7 displays the structure of nirmatrelvir, an oral drug used to treat mild coronavirus symptoms effectively.[24]

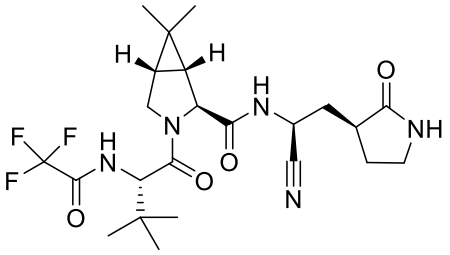

Figure 7. Structure of nirmatrelvir.

Paxlovid, a combination of ritonavir and nirmatrelvir, demonstrated an 89% efficacy in reducing hospitalization and death.[25]

However, the popularity of the drugs declined soon due to ineffectiveness. This was evidenced by the rebound of the viral load, risk factors, or negative results of the clinical trials, similar to the previous drugs. Controversy surrounding the effectiveness of these drugs in reducing patient numbers and mortality in hospitalized patients led to the discontinuation of testing by WHO-promoted Solidarity.[26,27]

3.3.4. Molnupiravir and Remdesivir. Molnupiravir (Figure 8) has a heterocyclic pyrimidine structure based on a class of nucleosides known as cytidine NHC (*β*-D-*N*(4)-hydroxycytidine). The drug was initially developed to treat diseases caused by RNA viruses like influenza and encephalitic alphaviruses. However, it was later discovered that it has broad-spectrum antiviral activity and can be used as a repurposed drug to treat several coronaviruses, including SARS-CoV-2. It exhibits

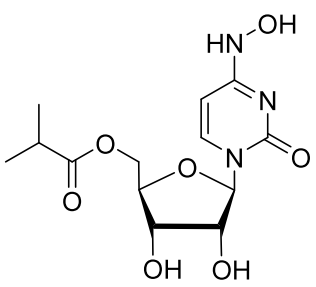

Figure 8. Structure of molnupiravir.

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antiviral activity against SARS-CoV, SARS-CoV-2, MERS-CoV, influenza virus, respiratory syncytial virus (RSV), bovine viral diarrhea virus (BVDV), hepatitis C virus (HCV), and Ebola virus (EBOV). In animal models, molnupiravir demonstrated beneficial effects as a potent therapeutic and prophylactic agent in clinical trials against various coronaviruses, including SARS-CoV-2, SARS-CoV, and MERS-CoV.[28] This drug is available for oral application and has potent antiviral activity. It has been reported as a suitable therapeutic candidate against COVID-19. Its best application for antiviral activity has been in reducing hospitalization or death in mild COVID-19 cases that test positive for SARS-CoV-2 in nasopharyngeal samples.[29]

Figure 9 shows remdesivir, a complex heterocyclic compound with a nucleotide analogue known as an RNA

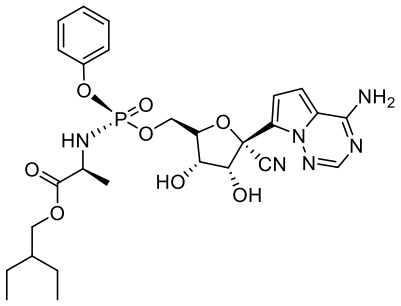

Figure 9. Structure of remdesivir.

polymerase inhibitor. Remdesivir was applied in treatment of diseases related to hepatitis C, Ebola, and Marburg viruses. It was repurposed for the treatment of COVID-19 early in the pandemic, and it was approved by the FDA as a prescription drug.[30]

The efficacy of remdesivir has been disputed and shrouded in controversy due to the lack of evidence demonstrating a decrease in mortality rates, as well as various adverse effects such as respiratory failure, kidney injury, anemia, hypotension, constipation, and hepatocellular toxicity.[31,32]

3.3.5. Ivermectin. Ivermectin (Figure 10) is an antiparasitic drug used orally for onchocerciasis, strongyloidiasis, and other

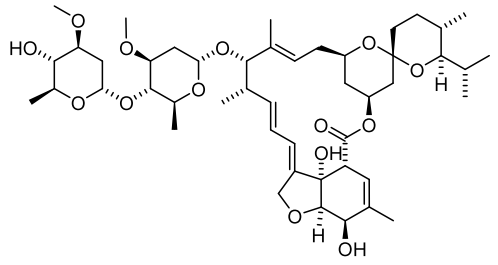

Figure 10. Structure of ivermectin.

diseases caused by helminthiasis. It is approved by FDA for the treatment COVID-19 based on its inhibitory effects on the *in vitro* replication of SARS-CoV-2.[33] Several research groups have reported a decrease in SARS-CoV-2 replication after applying ivermectin at higher concentrations than the limited authorized doses.[34] Initially, ivermectin was found to be well-tolerated at lower concentrations, but adverse side effects were also reported with much higher concentrations.[35]

3.3.6. Azithromycin. Azithromycin (Figure 11) is an antibiotic used to treat gastrointestinal and respiratory

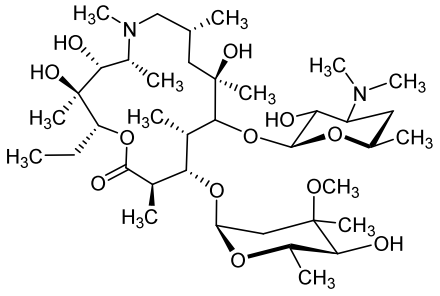

Figure 11. Structure of azithromycin.

problems, as well as inflammatory infections causing throat pain and enteric fever. Chemically, it is an azalide, a subclass of macrolide antibiotics. Structurally, it consists of a complex heterocyclic structure with oxygen and nitrogen as the heteroatoms. It is known to inhibit bacterial protein synthesis and is used in the treatment of various bacterial infections, including pneumonia, some sexually transmitted diseases, bronchitis, and certain infections of the ear, throat, lungs, and sinuses. Azithromycin decreased the SARS-CoV-2 virus binding to host cells by raising the pH of the trans-Golgi network. This action can halt the spike protein binding to target cells through glycosylation of the hACE2 receptor. A few recent studies have received significant media attention for suggesting that the combination of hydroxychloroquine and azithromycin may be effective in treating COVID-19.[36] Perhaps these reports influenced some public figures during the early days of the COVID-19 pandemic in 2020, leading to the endorsement of emergency applications of hydroxychloroquine, chloroquine, azithromycin, and remdesivir. However, multiple research studies have shown that either the combination of repurposed drugs or azithromycin alone is not effective.[37] According to international guidelines from the WHO and NIH, there is a strong recommendation against using azithromycin in conjunction with hydroxychloroquine or azithromycin alone.

3.3.7. Dexamethasone. Dexamethasone (Figure 12) is a tetracyclic ring structure that belongs to the glucocorticoid

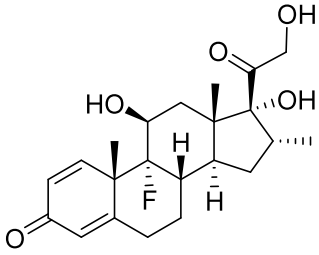

Figure 12. Structure of dexamethasone.

class of steroid drugs. It is a synthetic drug possessing the potential for pleiotropic effects on multiple signaling pathways and has been widely used in many disorders such as severe allergies, asthma, several forms of arthritis, intestinal disorder, blood or bone marrow problems, kidney problems, and skin conditions. Owing to its potent anti-inflammatory and immunosuppressant properties, it was recommended in 2020 for treating COVID-19 patients requiring mechanical

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ventilation or supplemental oxygen. Dexamethasone has been reported as the first drug that can reduce the mortality rate of COVID-19 patients admitted to the hospital by 20−35%.[38] However, like the previous drugs, the adverse side effects of dexamethasone also became apparent soon after, leading to a sudden decrease in its popularity for the treatment of COVID-19.[39]

3.3.8. Heparin. Heparin (Figure 13) belongs to glucosaminoglycans, which are polysaccharide carbohydrates that

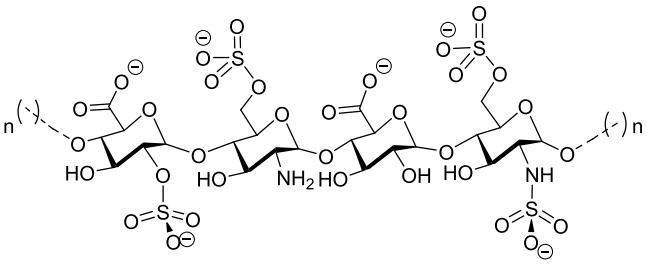

Figure 13. Structure of heparin.

naturally occur in the liver and other tissues. It inhibits blood coagulation. The potential of heparin, with its antiviral and anti-inflammatory properties, in reducing mortality rates among COVID-19 patients was tested in several clinical trials. One of these trials was a multicenter study involving 2075 hospitalized COVID-19 patients across 17 hospitals in Spain.[40] Out of the total, 1447 patients recovered, while 301 patients died. The use of low molecular weight heparins (LMWH) reduced the mortality rate in patients with high D-dimer levels, which is a byproduct of the blood clotting and breakdown process. Additionally, COVID-19 patients with elevated D-dimer levels, an abnormal coagulation parameter, exhibited a poor prognosis when treated with this medication.[41] Therefore, more randomized clinical trials are necessary to investigate the effectiveness of heparin in COVID-19 patients.

3.3.9. Baricitinib. Baricitinib (Figure 14) is a heterocyclic compound based on a pyrrolo[2,3-*d*]pyrimidine structural

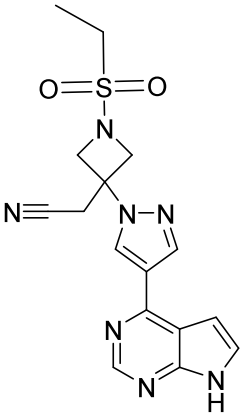

Figure 14. Structure of baricitinib.

framework with two other heterocycles, pyrazole and azetidine, as substituents. Baricitinib inhibits Janus-associated kinases 1 and 2 (JAK1 and JAK2). This inhibition interferes with the signal transduction from growth receptors or cytokines, leading to a decrease in immune cell function and hematopoiesis. Baricitinib can also bind to the associated protein kinase 1 of the virus, preventing the formation of viral particles and the intracellular passage of viral cells. It was identified as a potential repurposed drug for treating SARS-CoV-2 based on its mechanism of action, which involves modulating the cytokine storm caused by the infection and inhibiting the virus from entering host cells. The combination of baricitinib with remdesivir has been found to be more effective than either baricitinib or remdesivir alone. Several clinical trials have demonstrated that the use of baricitinib with remdesivir was more effective in reducing recovery time in COVID-19 patients receiving high-flow oxygen or noninvasive ventilation compared to remdesivir alone.[42,43] Baricitinib remains a highly recommended drug for COVID-19 treatment, especially when compared to previously mentioned medications. However, it is crucial to prioritize safety and adhere to standard care for treating critically ill hospitalized adults.[44]

4. CONCLUSION

The coronavirus disease (COVID-19) poses a serious global health issue and a threat to our normal lives. The rate of contagion and transmission patterns makes us feel like we have no control, but the safety measures in place also require us to keep our distance from others. This means we cannot engage in activities we naturally enjoy, such as spending time with friends and family and finding solace in the company of others. We have faced various forms of lockdown situations during the COVID-19 pandemic. The COVID-19 pandemic appears to be lingering for the foreseeable future. It is essential to conduct more clinical trials to confirm the effectiveness and safety of vaccines and repurposed drugs in treating COVID-19. Randomized clinical trials (RCTs) testing various COVID-19 therapies are currently being carried out in several countries, but the results are not yet published. There is a global effort to develop more effective vaccines and drugs in addition to those already recognized or branded.

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Notes

The authors declare no competing financial interest.

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Mayanglambam Maneeta Devi has been a Ph.D. student in chemistry at Manipur University, India, since 2021. She completed her master's degree with a specialization in organic chemistry in 2018 and her bachelor's degree with honors in chemistry in 2016, both from Manipur University. Her current research focuses on the synthesis, functionalization, and characterization of the imidazole moiety and its applications in various biological properties. She has published several articles based on nitrogen-containing heterocycles and their applications. Additionally, she has participated in workshops and national scientific conferences.

Monika Okram is currently in the final year of the M.Sc. in chemistry program at the Department of Chemistry, Chandigarh University, India. She obtained her bachelor's degree in chemistry from D.M. College of Science, Manipur, in 2023. Monika is a recipient of the DST INSPIRE Scholarship (India) for pursuing graduate and master's courses for a period of five years.

Dr. Okram Mukherjee Singh is a professor in the Department of Chemistry at Manipur University, India. He obtained his M.Sc. in chemistry in 1989 from North Eastern Hill University, Shillong, India. In 1997, he completed his Ph.D. in chemistry from the same university under the supervision of Prof. H. Junjappa and Prof. H. Ila. Dr. Singh pursued postdoctoral research at the University of Utah, U.S.A., in 2005−2006, funded by DST, India, and at the University of Manchester, U.K., in 2013 under a UGC India and British Council Commonwealth Academic Staff Fellowship award. He has authored and coauthored numerous original research articles, reviews, and book chapters. Dr. Singh's current research focuses on the synthesis and functionalization of organic compounds, particularly heterocycles, and their applications in medicinal chemistry and material sciences.

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■ DEDICATION

Dedicated to Professor H. Ila on the occasion of her 80th birthday.

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