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COVID-19 into Chemical Science Perspective: Chemical Preventive Measures and Drug Development

Bimalendu Adhikari* and Nihar Sahu[a]

COVID-19 facts and literature are discussed into chemical science intuition highlighting the direct role of chemistry to the ongoing global pandemic by covering structural identification of the virus, chemical preventive measures and development of drugs. We reviewed the four most promising repurposed drugs which are presently being investigated in mass clinical trials on COVID-19 infected persons and synthetic routes of these drugs with their recent advancement. Chemical preventive measures such as soap water, hand sanitizer and disinfectant are the only available options in the arsenal to fight against COVID-19, till an effective medicine or vaccine will be made available. As such the present review will focus on the mode of action of the major chemical preventives.

1. Introduction

COVID-19 (Corona Virus Disease 2019) is an infectious disease caused by the novel severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). It has developed into a global pandemic over a course of few months, disrupting modern society on a large scale that most of the people in the world have never witnessed in their lifetimes.[1–4] It has been believed that this virus had its origin in a species of bat and it was transmitted to human via a host. Since then, human to human rapid spreading has been observed.[5] This novel corona virus is very close to earlier reported coronaviruses SARS-CoV-1, MERS-CoV (Middle East respiratory syndrome) with regard to causing severe acute respiratory distress,[6] their surface protein and host cell receptor. The viruses can cause severe disease with pneumonia and acute respiratory distress disorder. This virus has already infected millions of people, resulting in over one million deaths as of this writing and the figures are continuously rising.[7] Overall, people's lives and the global economy are being greatly affected.

To address the current global challenge, public healthcare workers are working at the forefront to diminish the spreading of this disease. With immense effort, rapid developments have been done by biologists and biomedical scientists to understand the biological responses against this viral infection, including detection of the virus, gene sequencing and determining protein structures.[1,8,9] Personal preventive measures[10] including chemical protective measures such as soap water, bleach solution, alcohol-based hand sanitizers, and hydrogen peroxide have been conceptualized and prepared to destroy the viruses.[11] Advancement of various testing tools,[12–19] antiviral drugs,[20–29] vaccines,[30–32] and other medical involvements[10] are being developed in a fast-paced manner. These activities apparently seem far away from the areas of chemistry which usually deal with elements and chemical compounds. However, there is much scope for chemists, in fact, they have significantly contributed, and can do more to help in such a worldwide crisis[10] as chemistry occupies an intermediate place between physics and biology. According to bio-chemistry, we all are alive and healthy by a series of biochemical reactions which occur in a highly regulated manner with almost no mistake and any disturbance or malfunction of these reactions leads to diseases and even death. Looking at the SARS-CoV-2, it binds to the human cell receptor namely angiotensin-converting enzyme 2 (ACE2) and affects the lung cells that may lead to demise.[9] In this regard, biochemistry has a key role to understand the viral structure specifically, the structure of viral proteins, genome and their mode of action.

There have been several reviews published recently on COVID-19 addressing the recent advancement on the analysis, testing and treatment of this virus.[10–43] In this review, we have discussed COVID-19 facts and literature starting from host binding events of SARS-CoV-2, chemical preventive measures and synthesis of repurposed drugs into chemical science perspective. Herein, we have highlighted COVID-19 at the interface of chemistry and biology where biochemistry reveals the structure and mode of action of the virus. Similarly, biomaterial chemistry offers elegant ways to develop better products for preventive measures such as sanitizers, face masks with improved property. The preparation and mechanism of action of chemical preventive measures (like washing hands with soap water, use of hand sanitizer and sanitization of fomite surfaces by disinfectants) in destroying the virus are discussed by combining principles of both chemistry and biology. Computational chemistry has modelled proteins of COVID-19 to identify chemical compounds[22] that can fight against this virus whereas medicinal and organic chemistry are contributing by synthesizing these anti-viral compounds. Herein, we have also reviewed the four most potential repurposed

[a] Dr. B. Adhikari, N. Sahu
Department of Chemistry
National Institute of Technology Rourkela
Rourkela, Odisha 769008, India
E-mail: adhikarib@nitrkl.ac.in

drugs, emphasizing their synthetic routes with recent advancement, namely Hydroxychloroquine, Remdesivir, Lopinavir and Dexamethasone, which are being examined in mass clinical trials on the patients of COVID-19 showing some promising results.

SARS-CoV-2 structure

Chemistry especially biochemistry has responded quickly to this global pandemic. Biochemists help us to understand the structure of this virus better. The transmission electron microscopic (TEM) image of SARS-CoV-2 inside a cell displays spherical viral particles that are colorized in blue (Figure 1).[44] The virus comprises of three basic building blocks: a single-stranded RNA genome, viral membrane composed of lipid-bilayer and surface proteins. The RNA genome is composed of 30000 nucleotides and it encodes four structural proteins namely, Nucleocapsid (N) protein, Membrane (M) protein, Envelop (E) protein, Spike (S) protein, and many non-structural proteins (nsps) (Figure 1). The nucleocapsid (N) protein is a multi-purpose protein, which helps in the formation of nucleocapsid to protect the genome. The nucleocapsid is formed by packaging the viral RNA genome into a ribonucleoprotein complex.[45] The M-protein is the most copious in the viral surface and its key role is to support viral assembly as a central organizer due to its membrane-bending properties.[46] The E-protein is the smallest membrane protein comprising of approximately 76–109 aminoacid residues and it has a crucial role in virus assembly, envelope formation, membrane permeability of the host cell and virulence.[47,48] The S protein is an important structural transmembrane protein comprising of 1200–1400 amino acid residues on the outer envelope of the virus. The S protein is responsible for virus entry as it recognizes the specific host-receptors located on the human cell surface. Host-guest recognition is virus-specific, and the specificity decides both virus tropism and pathogenesis.[49,50] S protein exists as a self-assembled homotrimer in which each of the monomers is composed of two functional units, S1 and S2. S1 subunit is accountable for host recognition whereas the S2 subunit is in charge of host-guest membrane fusion.[50] The N-terminal domain of S1 subunit is considered as carbohydrate recognition domain and the C-terminal domain is called

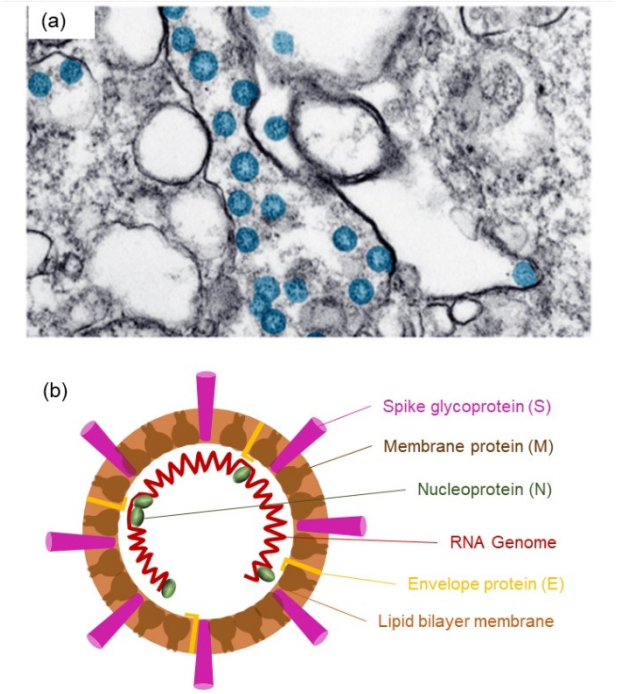


Figure 1. SARS-CoV-2 Structure. (a) Transmission electron microscopic image of SARS-CoV-2 spherical viral particles in a cell (taken from ref 44), (b) The virus is comprising of following basic building blocks: a single-stranded RNA genome (ssRNA), lipid bilayer membrane and different proteins like nucleoprotein (N), envelope protein (E), membrane protein (M), spike protein (S protein).

receptor-binding domain (RBD) as it supports host-guest interaction and particularly responsible for virus entry by recognizing protein receptors of the infected lung cells.

The mechanism of viral entry, replication and RNA packing in the human cell is described in Figure 2. The S protein mediates the virus entry into the cell by binding its receptor, followed by fusion and endocytosis. So, the virus has spike protein that recognizes human cell receptor namely ACE2. It is believed that the fusion occurs at a low pH between viral and host target membranes via S2 subunit. After the entry, the viral genome a single-stranded RNA is launched into the cytoplasm and translated into two large polypeptides (pp1a and pp1ab),

Bimalendu Adhikari was born in 1983 in West Bengal (India) and received his PhD at IACS (Kolkata) in 2012. He then worked at the University of Toronto as a postdoc and subsequently at Chiba University as a JSPS postdoc fellow. Then, he moved to IISER Mohali (India) as Inspire Faculty and currently he is Assistant Professor of chemistry at NIT Rourkela. His research interests include bioorganic chemistry, peptides, supramolecular chemistry, gels, and nanomaterials.

Nihar Sahu was born in 1997 in Kuchinda (Odisha, India). He completed his masters in 2020 from Central University of Jharkhand. Prior to this he completed his graduation from Government Autonomous College Rourkela, Sambalpur University in 2018. Now he has joined NIT Rourkela for his PhD in Chemistry. His research interests include bioorganic chemistry, nano materials and organic synthesis.

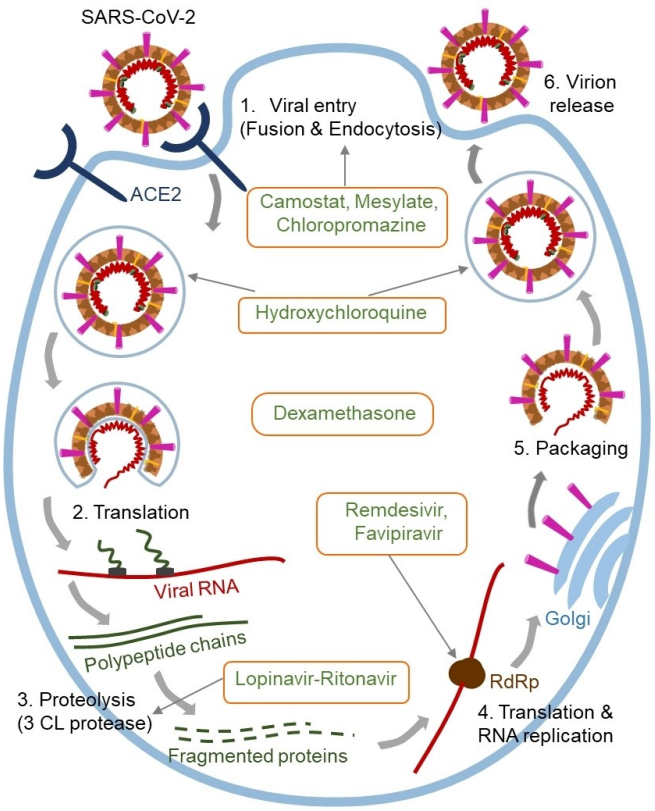


Figure 2. SARS-CoV-2 infection cycle displaying different steps. Potential targets for some selected antiviral drugs to interfere in different steps of infection cycle are shown. Use of camostat and mesylate to block virus/host cell interaction and inhibition of virus entry, use of Hydroxychloroquine lowers the pH that inhibits endosome maturation; use of Lopinavir-Ritonavir as protease inhibitors to inhibit viral polypeptide synthesis; Remdesivir as nucleoside/nucleotide analogues to inhibit RNA polymerase intervening viral genome replication; Dexamethasone as anti-inflammatory drug to control immune response. These are well discussed in the drug development section (vide infra).

which are fragmented and transformed into mature nsps (also called functional proteins) by the two viral proteases $3CL^{pro}$ (3 C-like protease or main protease) and PL^{pro} (papain-like protease).[51] Also, the RNA replication occurs producing multiple copies of genome and the process is mediated by the viral replication complex, including the RNA-dependent RNA polymerase (RdRp), helicase, and other accessory (non-structural) proteins. Structural viral proteins such as M, S and E-proteins are synthesized in the cytoplasm and then placed to endoplasmic reticulum-Golgi intermediate compartment.[48] Hence, plenty of these building blocks are formed in a virus-infected cell and spontaneously self-assemble to generate new viruses (Figure 2). Finally, these viruses are exported from the infected cell through a process called exocytosis and infect other cells. Basically, the virus has a spherical supramolecular structure in which all the building blocks are associated by weak noncovalent interaction. Hence very mild chemicals such as soap/detergent are enough to split the units and destroy the virus (vide infra). Although understanding the structure and property of the virus seems to be out of the territory of chemistry, supramolecular self-assembled structure, surfactant like lipid bilayers (vide infra), molecular recognition, structure of the protein and nucleic acid are familiar subjects in the broad range of chemistry.

SARS-CoV-2 has 16 highly conserved non-structural proteins (nsps) which present different functions. Some of these proteins have specific and very important roles and these are the main protease (M^{pro}, also called $3CL^{pro}$ refereed as 3 C-like protease), the papain-like protease (PL^{pro}), the RNA-dependent RNA polymerase (RdRp) and these nsps have been exploited as druggable targets due to availability of the crystal structures along with their essential roles in viral infection. Both the proteases $3CL^{pro}$ and PL^{pro} are accountable for cleavage of polyproteins and they have a key role in virus replication and regulating the host cell response. Hence, they are exploited as main targets for antiviral drug development. RdRp is a crucial enzyme, which intercedes the transcription and replication of the RNA in the SARS-CoV-2 life cycle. Moreover, this enzyme does not have any human counterpart and hence it has an opportunity to be a drug target for antiviral development.[53] There are interesting compounds that can inhibit the activities of these proteases. Potential targets and mechanism of action for some selected antiviral drugs are discussed in the drug development section. Earlier studies attempted on the first SARS-CoV-1 revealed that the mechanism of viral interaction with a cell was most likely assisted by the RBD with the S protein that ties up with the peptidase domain of the ACE2.[54] In the same way, SARS-CoV-2 is also believed to go into the cells by the interaction between RBD and ACE2.[9,49,50,55] In order to understand the higher infection rate for SARS-CoV-2 and to figure out a way to reduce this high infection rate, structure of the SARS-CoV-2 was recently discussed in comparison to the SARS-CoV-1. It has been recently found that the mutations in the spike (S) protein of SARS-CoV-2 is presumably accountable for its enhanced affinity toward the ACE2.[56] McLellan and coworkers solved the structure of the SARS-CoV-2 Spike trimer in its prefusion conformation at a resolution of 3.5 Å by cryo-electron microscopy.[9] The structural and biophysical studies suggested that the SARS-CoV-2 S protein binds ACE2 with enhanced affinity compared to SARS-CoV-1 S protein. This atomic-level structural data of the SARS-CoV-2 spike assists the evaluation of its mutations and provides further protein-engineering efforts that can enhance protein expression toward the vaccine development.

To get the structural insight of ACE2 recognition by SARS-CoV-2, Li and coworkers crystallized the complex formed by ACE2 and SARS-CoV-2 and solved the crystal structure of the RBD of the S protein in complex with ACE2.[57] The results showed that an ACE2-binding point in SARS-CoV-2 RBD adopts a more compact conformation than that of SARS-CoV-1 RBD and several residues mutate in the SARS-CoV-2 RBD for stabilization of virus-binding hotspots at the interface of RBD and ACE2. The structural characteristic of SARS-CoV-2 RBD is responsible for its increased binding affinity to human ACE2.

Recently, a group of computational chemists led by Amin studied binding affinity among the amino acid residues between the ACE2 and the S protein for SARS-CoV-1 as well as

SARS-CoV-2 individually by using molecular dynamics (MD) simulations as well as Monte Carlo (MC) sampling approach.[58] It was found that the protein surface of the ACE2 at the RBD has negative electrostatic potential, whereas a positive potential is noticed for the SARS-CoV-1 S proteins or SARS-CoV-2 S proteins. The total binding energy between ACE2 and SARS-CoV-2 is marginally greater than that of SARS-CoV-1 due to higher electrostatic interactions. The electrostatic binding energies mostly originated from the salt bridges between R426 and ACE-2-E329 for SARS-CoV-1, whereas it is between K417 and ACE2-D30 for SARS-CoV-2. The increased binding energy is not because of a single mutant, rather this is due to the overall structural changes caused by all the mutations collectively. These results likely support the thought that the SARS-CoV-2 virus is a consequence of biological evolution, not a lab-engineered virus.[59] Ching and coworkers earlier reported a method to measure inter-amino acid interactions relying on the concept of accurately evaluating the amino acid bond pairs (AABP). They have very recently utilized this approach to the RBD of the spike protein of SARS-CoV-2. The results exhibit that along with the large AABP arising from nearest-neighbor AAs in the primary sequence, there is significant AABP contributed by the other nonlocal AAs through both covalent and hydrogen bonding.[60] The high transmission rate in the spreading of SARS-CoV-2 can be understood from Figure 3. Overall, the mutation resulted in a strong chemical interaction between the S protein and receptor on the human cell surface and this strong interaction is responsible for the high transmission rate for COVID-19. In the absence of any intervention, an infected person can transmit on an average two to three people with a basic reproduction number (R_0) of 2–3.[61,62] R_0 is a representation of the transmissibility of a virus, suggesting the average number of fresh infections caused by an infectious person in a native population. Again each of the newly infected persons can go ahead to infect three others. It continues in this manner and rapidly expands the infection in the population (Figure 3a). On the other hand, upon application of intervention, like medical testing of the infected person, isolation of the infected person and use of personal preventive measures can restrict the transmission to other people (Figure 3b).

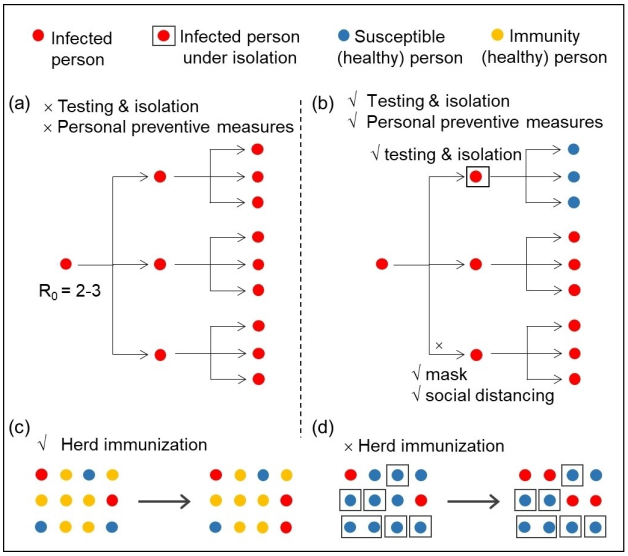


Figure 3. The spread of COVID-19. (a) In the absence of any intervention, infection can spread freely in the population with high value for basic reproduction number (R_0), (b) In the presence of intervention, isolated individuals and application of personal preventive measures such as using mask and social distancing can slow down the spread of infection. (c) Herd immunity developed in person who recovered from COVID-19 or acquired vaccine, so the infection cannot pass freely among the individuals/ population, and (d) In the absence of herd immunity (blue circle in the box represents the susceptible person under isolation) the infection can pass among the population.

Chemical preventive measures

Personal preventive measures are playing a vital role in stopping the spread of the SARS-CoV-2 virus in the absence of any medicine and vaccine. Generally, these preventive measures can be physical, chemical or immunological in nature. For instance, spreading can be regulated by following social distancing of one meter at least and using face mask which comes under physical preventive measures. Chemical preventive measures include disinfecting surfaces using chemicals, washing hands with soap water or hand sanitization. Herd immunity, developed in the person who already recovered from the COVID-19 or who acquired vaccine, can break the chain of infection in a population. The role of herd immunity can be understood from Figure 3c,d. Until we have vaccine or medicine in our hands, it is very important for us to follow personal protective measures strictly to avoid infection from SARS-CoV-2.

Face masks

It has been already well established that wearing face coverings in public is the most useful personal preventive measure.[63] A group of chemists led by Molina have determined the transmission pathways of COVID-19 by investigating the tendency and mitigation measures in Wuhan, Italy, and New York City, the three major epicenters in the period of January to May, 2020.[64] Their analysis showed that the airborne transmission route is extremely infectious and the main route for spreading COVID-19. The results concluded that the difference between wearing and not wearing a face mask signifies the main element to restrict the trends of the pandemic by reducing the number of infections. In order to prevent inter-human transmission, the wearing of face covering in public domain is the most useful measure, compared to concurrent social distancing, quarantine as well as contact tracing.

A common surgical or N95 mask was not recommended to use for multiple times until recently. Because, it was unable to self-sterilize for reuse and this caused a high economic cost for a single mask. Moreover, shortage of masks was experienced at the early stage of the pandemic. Hence, there is a need for proper methods to decontaminate the masks in order to extend the life of available supply. The decontamination process should not compromise the proper fit and function of

masks.[65,66] In 2009, a group of researchers reported decontamination methods where a single treatment with hydrogen peroxide vapor, UV light or dry heat below 100 °C did not affect the ability of N95 mask to filter small particles.[67] In the context of the current pandemic by COVID-19, there have been several more recent investigations. Recently Schwartz and coworkers developed a procedure for sterilizing N95 masks using hydrogen peroxide vapor. The technique does not alter the fit of the mask and it leaves no residue other than water as a byproduct in the process of decontamination. Although their study did not use SARS-CoV-2, but instead tested with other biological indicators. The study suggests that most of the masks could undergo this decontamination process at least 30 cycles without loss of any fit.[68] Very recently, Cui and coworkers at Stanford University examined several methods to disinfect N95 masks.[69] They found that heating ($\leq$85 °C) under several humidities was the most encouraging, nondestructive method for decontamination without altering filtration ability of N95-mask. They initially started by heating the mask at a temperature of 75 °C because of the wide availability of 75 °C blanket warming temperature oven in hospitals and later further investigations used 85 °C, and found that that 75 °C was not sufficient to inactivate SARS-CoV-2. The optimized condition for decontamination at 85 °C with 30% relative humidity was able to continue up to 50 cycles without compromising the function of the mask. Notably, alcohol and chlorine based disinfectants such as bleach interfere with the electrostatic charge on the masks, which is an important component of the filter and significantly reduce their filtering efficiency. Although, these are good candidates for sanitizing hard surfaces, they should not be used to clean N95 masks.

Recently, a group of material chemists developed an exotic method to functionalize surgical masks with self-cleaning properties[70] and hence these commercially available masks could be reusable and recyclable where they deposited a few layers of graphene on the surface of the mask.[70] The superhydrophobic graphene surface does not allow incoming aqueous droplets of virus to stick and more importantly, the surface temperature of this mask can rapidly increase to approximately 80 °C under the exposure to sunlight, which endows the masks to be reusable just after sunlight sterilization and such mask can give better protection against SARS-CoV-2. Recently, a company IST also developed a similar mask by coating nanofilms that create a hydrophobic molecular barrier which prevents the absorption of droplets into protective face masks.[71]

Apart from blocking the virus droplets by wearing mask, it would be useful to deactivate the fluid droplets of viruses while passing through the mask. For this deactivation, antiviral or mild sanitizing molecules can be placed within the mask so that virions get deactivated when they pass through the mask. However, this strategy of on-mask chemical modulation has to be planned in such a way that the sanitizing molecules should only be released from the mask during exhalation.[10]

Overall, physical treatments like UV irradiation, heating and dehydration are useful for deactivation of the virus. This can also be done by chemical sanitization using mild acids, mild oxidants, alcohols, or surfactants.[72,73] Such chemical approaches can be very effective to restrict the spread and transmission of the virus.[74]

Chemistry of Soaps/detergents in killing SARS-CoV-2

Soaps and detergents are extremely effective in killing the viruses (Figure 4). Both soaps and detergents chemically contain surfactants (short form for surface-active agents). Surfactant molecules are basically sodium salt of long-chain fatty acid (for instance $C_{17}H_{35}COONa$, sodium stearate) known as amphiphile. Amphiphile has two parts, fat-like long-chain called hydrophobic tail that avoids water and $COO^{-}Na^{+}$ end, called hydrophilic (or lyophobic) head. The normal cleaning mechanism of detergents is as follows. When soap or detergent is dissolved in water, many detergent molecules are arranged together forming tiny bubbles called micelle where the hydrophilic head groups are oriented outward facing the water whereas hydrophobic or lipophilic tails are hidden inside forming a hydrophobic pocket that potentially traps normal dirt from our skin or garments (Figure 4). Now, these amphiphiles are structurally similar to the lipid molecules of the biological membranes.[75] So the surfactant molecules compete with the lipids in the virus membrane and replace them easily, because the virus is a self-assembled structure where the weakest connection is in the lipid bilayer. The attached surfactant molecule (at the membrane) bonds to water at one end and bonds to lipid at the other end resulting in push-pull interactions that break the virus membrane. In this way, soap breaks the fat membrane and hence the virus structurally falls apart and gets destroyed (Figure 4). Similar to dirt, the constituents of the virus gets washed away with water as the micelle, formed by the soap molecules in water, forms a hydrophobic pocket that traps the viral fragments. Apart from breaking the virus structure, the other role of detergent is that virus cannot stay stuck to the skin in the presence of soap, and washed out with water flow. For the occurring of all these reactions effectively, it is recommended to wash the hands with soap water for minimum 20 sec.

Hand sanitizers

Similar to soap/detergent, hand sanitizers are also very useful to get rid of the virus. It is always recommended to carry a hand sanitizer when someone goes outside the home where soap-water is not accessible or handy. How does hand sanitizer kill the SARS-CoV-2? Chemistry can explain well. First of all, the sanitizers that we are using to inactivate the SARS-CoV-2 are alcohol based hand sanitizers (Figure 5). According to formulation provided by WHO,[76,77] a hand sanitizer basically contains four components: (a) alcohol that can be either ethyl alcohol or isopropanol, (b) water, (c) glycerol and (d) hydrogen peroxide. The selection criteria for ethanol or isopropanol in the manufacture of hand-sanitizer is presumably due to their good water solubility and non-toxicity. The alcohol is mainly responsible for destroying the virus. Because, lipid bilayer of the virus membrane cannot survive in the presence alcohol

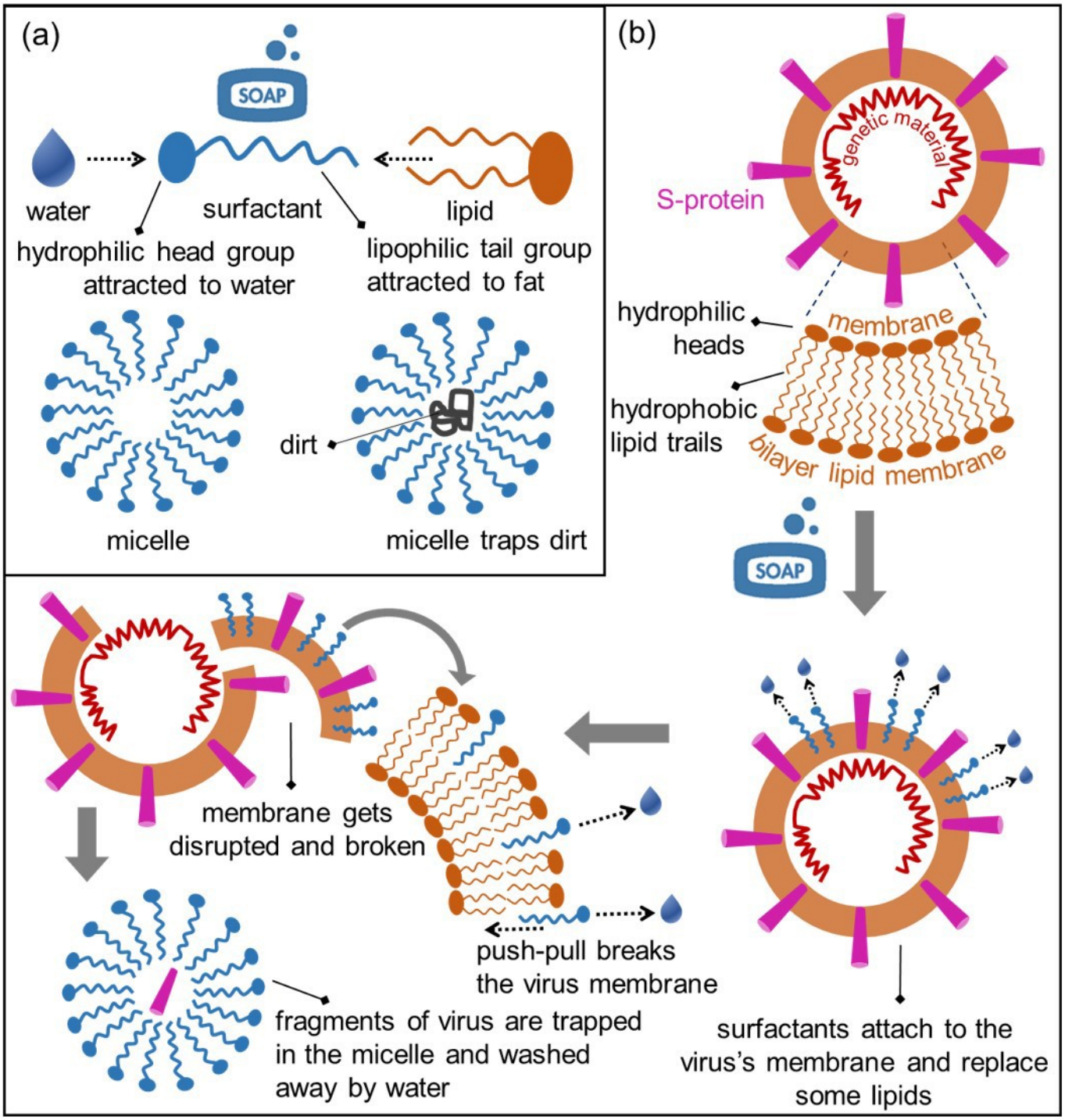


Figure 4. Mechanism of soap in destroying the virus. (a) Normal cleaning mechanism of soap (surfactant) by the formation of micelle, (b) Soap destroys SARS-CoV-2. Structure of the SARS-CoV-2 highlighting the membrane consisting of surfactant like lipid bilayer. Soap molecules attach to the virus's membrane and then disrupt the bonds in the later and break it into smaller fragments which are trapped by micelle and washed away by water.

that dissolves the lipid molecules in it and hence the virus membrane melts and virus gets inactivated (Figure 5). Moreover, alcohol causes denaturation of viral proteins where folded proteins are converted to unfolded proteins leading to loss of their biological activities (Figure 5).Thus alcohol plays an important role in destroying the virus by melting the lipid membrane and denaturing the protein of the virus. It can be noted that alcohol particularly in the range of 60–90% is rapidly virucidal. When the concentration of alcohol is below 50%, effectiveness for disinfection is reduced abruptly. More-

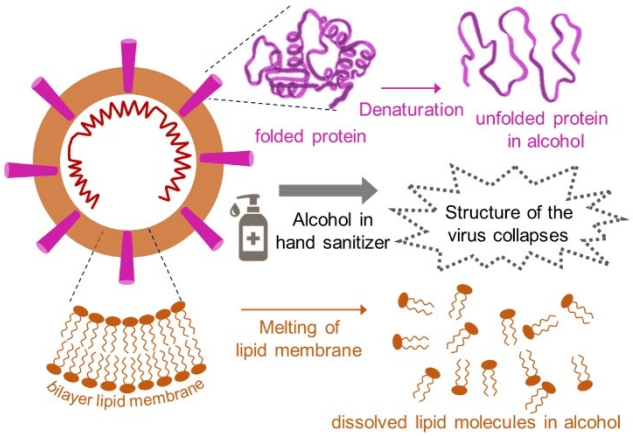


Figure 5. Mechanism of alcohol (hand sanitizer) in destroying the virus through melting the lipid membrane and denaturation of viral proteins.

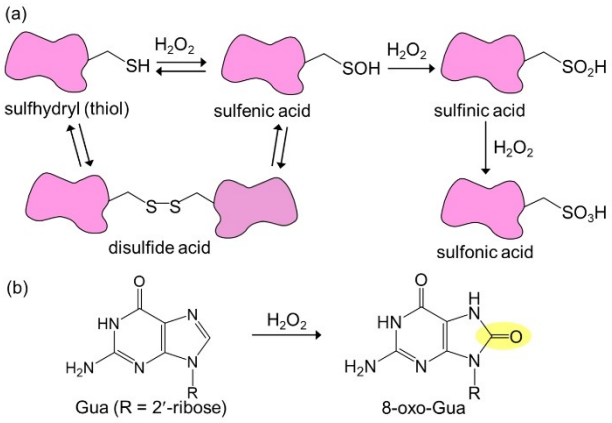


Figure 6. H_2O_2 in destroying the virus by oxidizing the viral protein. (a) Schematic representation displaying steps involved in H_2O_2 -induced oxidation of protein's cysteine residues containing thiol group to disulphide and other analogues, (b) Oxidation of Guanosine unit of RNA to 8-oxo-Guanosine.

over, a higher concentration of alcohol does not necessarily generate more effectiveness. Increasing alcohol percentage concomitantly reduces the percentage of water in sanitizer, while water content also has an important function in destroying viruses. In particular, water is essential as it acts as a catalyst for denaturing the proteins of the cell walls. For instance, 70% isopropyl alcoholic solutions penetrate the cell membrane efficiently which diffuses the entire cell, denature all proteins, and hence the virus gets destroyed. Significant water content in solution slows down the evaporation process, leading to increase in effectiveness by higher surface contact time. When isopropyl alcohol concentration goes over 91%, it coagulates proteins instantly and as a result, a protective coating is developed which guards other proteins from further coagulation.[78] The third component glycerol acts as a moisturizing agent preventing skin drying out and the fourth component hydrogen peroxide is generally included to prevent bacterial contamination into the hand sanitizer. Moreover, H_2O_2 can assist in destroying virus proteins and genetic materials by its oxidizing property (Figure 6), where this is reduced to water. It can be mentioned that chemical processes are the basis for the production of these materials including hand sanitizers. Apart from sanitizing our hands, hand sanitizers can also be applied on hard/fomite surfaces.

Hand sanitizers are portable and hence these provide an advantage over soap water, which is not accessible or handy at all places. But in the context of destroying the virus, soap water is more effective than the sanitizer (Figure 4, 5).[79] We have already discussed the mechanism of action for both sanitizer and soap water to inactivate the virus but their effectiveness can be explained by the way we use them. Use of large amount of sanitizer is certainly not a pragmatic choice as we need to restrict the amount of single time use to a few ml in volume. Moreover, extreme volatility of alcohol is a major setback as the alcohol based sanitizer evaporates very quickly and leaves only a little contact time with virus. Within the limited time of evaporation, the sanitizer may not effectively react and inactivate the viruses especially those reside inside our palm lines. Consequently, the following rub of both hands after sanitizer application becomes less effective at least by some extents. On contrary, cleaning our hands with soap solution for a minimum of 20 seconds followed by large amount of water ensure the complete exposure of viruses for inactivation. Soap solutions are neither volatile nor expensive as alcohol based sanitizers. Thus the cost to performance ratio clearly gives an advantage to the use of soap solution over alcohol based sanitizers.

Bleach for surface sanitization

Fomite surfaces are generally sanitized by disinfectant spray, for instance, chlorine-based bleach, which is an aqueous solution of sodium hypochlorite (NaClO). The chlorine based bleach is commonly used for household disinfection and cleaning.[80] NaClO is unstable in solution and relatively stable as dilute conditions that have solvated Na^+ and ClO^- ions and this stoichiometric solution is alkaline in nature with $pH \geq 11$. Because hypochlorous acid is a weak acid whereas NaOH is a strong base as given in the following equation.

$$NaOCl + H_2O \rightleftharpoons HOCl + NaOH$$

The following species are formed in solutions.

$$HOCl\ (aq) \rightleftharpoons H^+ + ClO^-$$

$$HOCl\ (aq) + Cl^- + H^+ \rightleftharpoons Cl_2\ (aq) + H_2O$$

Hypochlorite shows a broad range of antimicrobial activity and is useful to kill a number of common pathogens at different concentrations. For instance, hypochlorite is used against rotavirus at the concentration of 0.05%, whereas a

higher concentration of 0.5% is needed for some highly resistant pathogens for example *C. difficile*.[81] In the context of COVID-19, hypochlorite concentration of 0.1% is recommended.[82] Bleach oxidizes and destroys virus proteins and genetic materials, as NaClO is unstable in solution and easily decomposes to chlorine. The surfaces should be exposed to hypochlorite solution for at least 10 mins for killing the viruses. Unlike soap water or hand sanitizers, it can only be applied on hard fomite surfaces, not on our hands. Hypochlorite can be used for washing hands only when the concentration of hypochlorite is very low about 0.05%, and this hypochlorite solution is usually prepared with calcium hypochlorite.[78] To achieve these final desired concentrations of hypochlorite, it is necessary to dilute the commercially available chlorine-based bleach products where the chlorine concentrations usually vary between 4% and 6%.[80,83] It can be noted that high concentrations of chlorine in commercial bleach can cause corrosion of metal, alloy, many thermoplastic and irritation of skin with potential side-effects.

Hydrogen peroxide for surface sanitization

H_2O_2 solution can only be applied on hard/fomite surfaces, not on our hands and the minimum concentration should be 0.5%.[80] It oxidizes and destroys virus proteins and genetic materials (Figure 6) and it should be left on the surfaces for at least 10 mins for effective killing of viruses. H_2O_2 oxidizes the proteins and RNA of the viruses. Protein's Cys residue contains thiol group and it is oxidized to disulphide and other analogues like sulfenic acid, sulfinic acid and finally sulfonic acid by H_2O_2.[84] Moreover, the Guanosine unit of genome is oxidized to 8-oxo Guanosine.[85] However, the use of these chemical disinfectants or sanitization is materials restricted, as it is unable to cover all sorts of exposed areas. In practical application, sanitizers may not act uniformly across the entire surfaces due to concerns regarding volatility and dewetting. Moreover, it requires repeated application of sanitization periodically to keep the surface virus free. Therefore, it is necessary to develop self-sanitizing surfaces that would gently release disinfecting molecules to clean the surface and thus diminish transmission through objects. It can be noted that that such coatings should be nontoxic, long-lasting, and resilient against rubbing and washing where material chemists can contribute to this new research area to combat against COVID-19.

Drug development

Through a series of studies, researchers have already identified the potential binding sites between SARS-CoV-2 and human proteins. The S protein of SARS-CoV-2 is accountable for the host binding and successive fusion of the viral membrane and host-cell membrane.[49,50,55] This binding event is activated by the binding of the S1 subunit of S protein to ACE2. This mapping helped the researchers to identify possible treatments for COVID-19. Computer simulation of virus with atomic resolution was used, that helped to understand the morphology of the virus and also to take important steps into having new treatment.[86] Computational studies have been exploited to find out potential therapeutics against SARS-CoV-2 protease.[22] Moreover, screening of effective drug candidates against the S protein of SARS-CoV-2 afforded low molecular weight compounds that have a high binding affinity. In a recent work, Král et al designed and simulated several peptide inhibitors against SARS-CoV-2, on the basis of the recently solved crystal structure.[87] These inhibitors are based on two α-helical peptides originated from the protease domain (PD) of ACE2 and these peptides sustain their secondary structure and bind to SARS-CoV-2 with high specificity. Being low molecular weight peptides, these inhibitors can offer a direction in antigen recognition and designing of antibodies (Figure 2).

Ultimately vaccine and medicine are essential for the fight against COVID-19. Though both vaccine and medicine are utilized to counter the disease, vaccine is given to healthy persons in advance to prevent the disease while medicines are used to cure infected persons. There are no committed drugs available to us for a totally efficient treatment of COVID-19 as of today. The complete development of a new drug from the scratch for the treatment of COVID-19 would be a time-consuming work, as a drug candidate usually takes several years for its testing in animals and multi-phase clinical trials on humans. As an alternative shorter route, repurposed drugs are being currently investigated in clinical trials and some of these candidates are used for the treatment to reduce the massive pressure created on world health systems in this trying time.[20,21,22,88,89] It can be mentioned that repurposed drugs are the approved existing drugs that have already been tested to be safe and effective against other well-known diseases. In the context of COVID-19, several well-known antiviral drugs that have long been applied to treat malaria, SARS, MERS and AIDS, are being explored in clinical trials with the hope that they may be effective against SARS-CoV-2.[21] Herein, we discussed the four most promising repurposed drugs which are presently being investigated in mass clinical trials on COVID-19 patients (Figure 7). These drugs are Hydroxychloroquine, Remdesivir, Lopinavir and Dexamethasone which are already identified by international bodies for post-infection therapies. We have mainly discussed development of synthetic routes to these drugs and their mechanism of action. Viral enzymes and proteins that are responsible for major functions such as replication and controlling host cell response are generally potential targets for drugs in the search for therapeutic agents for COVID-19. Molecular targets for COVID-19 drug development are already discussed in Figure 2.

Hydroxychloroquine

Hydroxychloroquine (HCQ) has been a well-known drug for the treatment of malaria and this is being used in some countries during this crisis in the context of drug shortages for the COVID-19 patients. However, the mechanism of action of HCQ for SARS-CoV-2 is different from its antimalarial function. In case of malaria, it interferes in the function of heme polymerase in malarial trophozites, destroying the parasite.[90] For SARS-

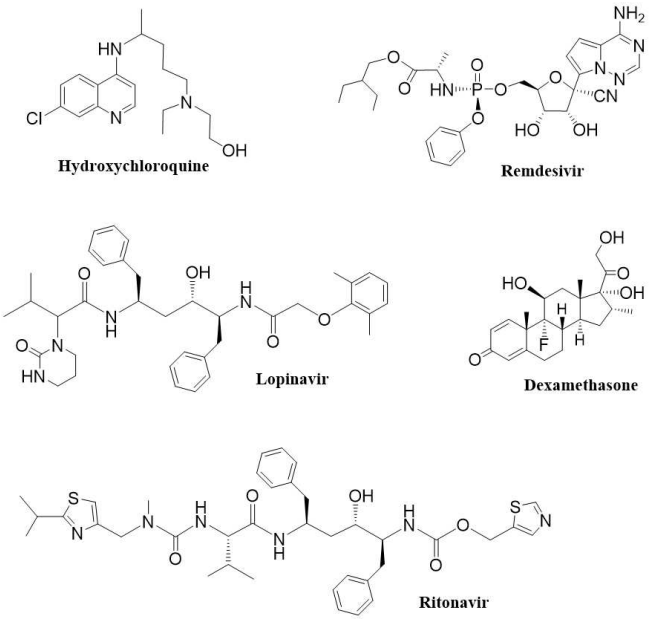


Figure 7. Chemical structures of repurposed drugs for the effective treatment of COVID-19.

CoV-2, HCQ, being a weak organic base, passively diffuses via cell membranes, gets protonated and results in an increase in the pH in endosomes inhibiting virus particles from fusion followed by entry into the cell (Figure 2). It was found that a combination of HCQ and azithromycin, an antibiotic, showed much better effectiveness in viral clearance compared to HCQ alone.[91] However, some recent studies revealed that HCQ was not enough active against the SARS-CoV-2 even though it decreased the death rates in HCQ-treated COVID-19 patients.[92,93] It can be mentioned that clinical trials of HCQ are going on worldwide and retrospective results on HCQ efficacy against COVID-19 is still inconsistent and inconclusive. By the use of molecular dynamics approaches with atomistic insights, Iannone and coworkers demonstrated that HCQ may slightly inhibit functional proteins which are required for SARS-CoV-2 replication. The degree of inhibition by HCQ increases in order PL^{pro}, $3CL^{pro}$ and RdRp.[94]

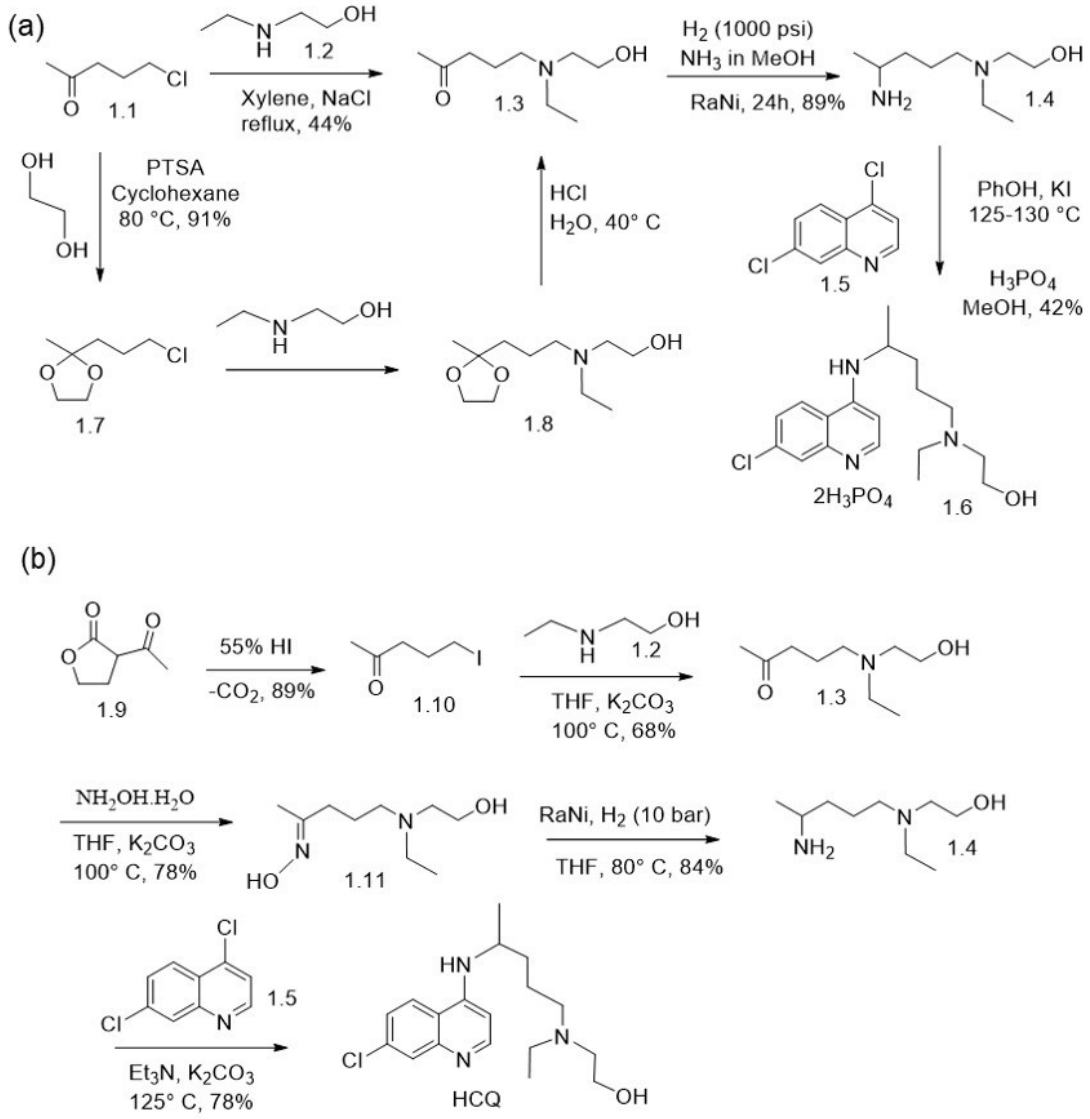
The synthesis of Hydroxychloroquine (HCQ) was first reported by organic chemists, Surrey and Hammer in their 1950 and 1951 reports.[95,96] The synthetic route of HCQ involves three major steps, as described in Scheme 1a. The first step is the alkylation of N-ethyl-N-hydroxyethylamine (1.2) with 5-chloropentan-2-one (1.1) which results in tertiary amine 1.3 in 44% yield. Alternatively, protection of ketone in 1.1 as its ketal (1.7) before displacement with amine 1.2 improved the overall yield to 67% which needed two further steps namely ketalization and subsequent deprotection.[96] In the second step, amine 1.4 was obtained in 89% yield by the reductive amination of 1.3. In the final step, Hydroxychloroquine was synthesized by nucleophilic aromatic substitution reaction between 4,7-dichloroquinolin (1.5) and amine 1.4. The mixture of products was diluted with MeOH and then addition of phosphoric acid produced Hydroxychloroquine (1.6) as diphosphate salt in 42% yield[96] and later the product was recrystallized in water-ethanol mixture. In a 2018 publication, Gupton and coworkers reported a high yield continuous flow synthesis of hydroxychloroquine[97] where two important modifications were done with respect to the original synthesis to make it practical for flow synthesis. Firstly, replacing the halide group from chloride (1.1) to iodide (1.10) facilitated the SN^2 displacement resulting in higher yield and also reduced side products. Secondly, the amine formation from ketone in a single step was avoided by a two-step procedure where an oxime (1.11) was formed followed by reduction to yield the amine 1.4 (Scheme 1b). It can be noted that both of the reactions were carried out in THF to facilitate telescoping reaction.

Remdesivir

Remdesivir was previously tested for the treatment of Ebola. Among all the tested drug candidates, Remdesivir is found as the most promising drug for COVID-19 because of its wide-range of in vitro activity against coronavirus that includes SARS-CoV-2.[98–100] Although U.S. Government was not fully satisfied with Remdesivir but they first authorized it for emergency use in fighting COVID-19. Remdesivir is a monophosphate nucleotide analogue prodrug, a compound that, after administration, is metabolized and converted to an active drug (Scheme 2). In case of Remdesivir, it is transformed to a pharmacologically active derivative of ATP in the cell and interferes in viral RNA replication process and thus reduces the time of recovery from COVID-19 by several days. It is not enough to be said a 'cure', but likely enough to relieve some pressure in this trying time.

From a structural point of view, Remdesivir is composed of three fragments: nucleobase (adenine) derivative, a pentose sugar and a phosphoramidate unit. The retrosynthesis of Remdesivir is described in Scheme 3(a) which shows key disconnections. Remdesivir is synthesized by late-stage coupling of nucleoside 2.6 with phosphoramidate 2.7. Again, nucleoside 2.6 is developed from C-glycosylation of ribolactone 2.1. In a forward approach, these disconnections are associated with several nontrivial transformations: efficient C-glycosylation, diastereoselective cyanation and stereoselective phosphoramidation of 2.6.

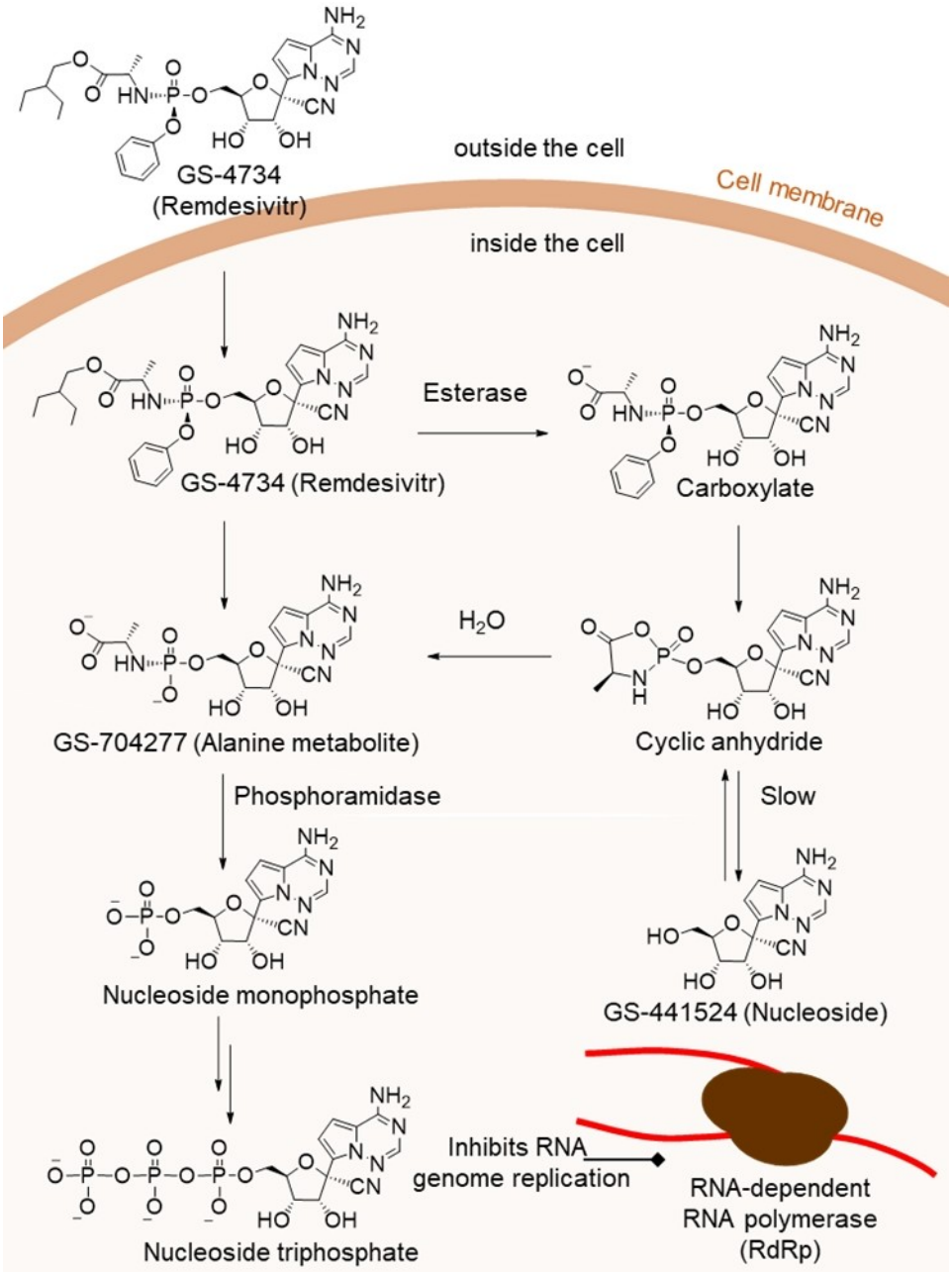
Synthesis of Remdesivir has been previously reported by Gilead in a number of reports through optimization of early medicinal chemistry route towards advanced route with improved yield.[101–105] The advanced (second-generation) synthesis of Remdesivir is described in Scheme 3. The first step is C-glycosylation reaction of 2.1 (benzyl-protected ribolactone) with nucleobase 2.2 and this is a key challenging step in the synthesis of this C-nucleoside analogue. The intermediate silyl compound (not shown) was formed from the corresponding amine reacting with PhMgCl and TMSCl, after that metal-halogen exchange reaction with i-PrMgCl·LiCl complex succeeded by adding lactone 2.1 at −20 °C produced glycosylation product 2.3 in 40% yield. In the next step, cyano group was diastereoselectively introduced by using TMSCN, TMSOTf, and



Scheme 1. (a) Synthesis of Hydroxychloroquine, (b) Modification in order to make the synthesis practical for flow synthesis.

TfOH to produce 2.4 in 85% yield with a $>95:5$ anomeric ratio preferring the desired β-anomer where it is believed that the presence of TfOH played a key role to promote the high anomeric selectivity. Benzyl deprotection was carried out using BCl_3 to afford 2.5 in 86% yield upon crystallization. To enhance the yield in the coupling between triol Nuc (2.5) and the phosphorus reagent, 2′,3′-hydroxyl moieties of 2.5 was protected as an acetonide by the treatment of 2,2-dimethoxypropane producing 2.6 in 90% yield. Subsequently, coupling between 2.6 and 2.7 (diastereomerically pure) was performed by i-Pr_2NEt and magnesium chloride at 50 °C. Then the product 2.8 was treated with concentrated HCl to cleave the acetonide, affording p-nitrophenolate 2-ethylbutyl-L-alaninate prodrug 2.9 (Remdesivir).

The diastereomerically pure 2.7 was prepared as follows. Chloridate (racemic) was first synthesized from alanate ester 2.10 by treatment with $(PhO)P(O)Cl_2$ mediated by Et_3N at −78 °C succeeded by reaction with 4-nitrophenol at 0 °C. It can be noted that 2.11 was formed as a diastereomeric mixture at the phosphorus center. Exploiting the big difference in solubility of these two diastereomers in the solvent of diisopropyl ether, the preferred diastereomer 2.7 was isolated

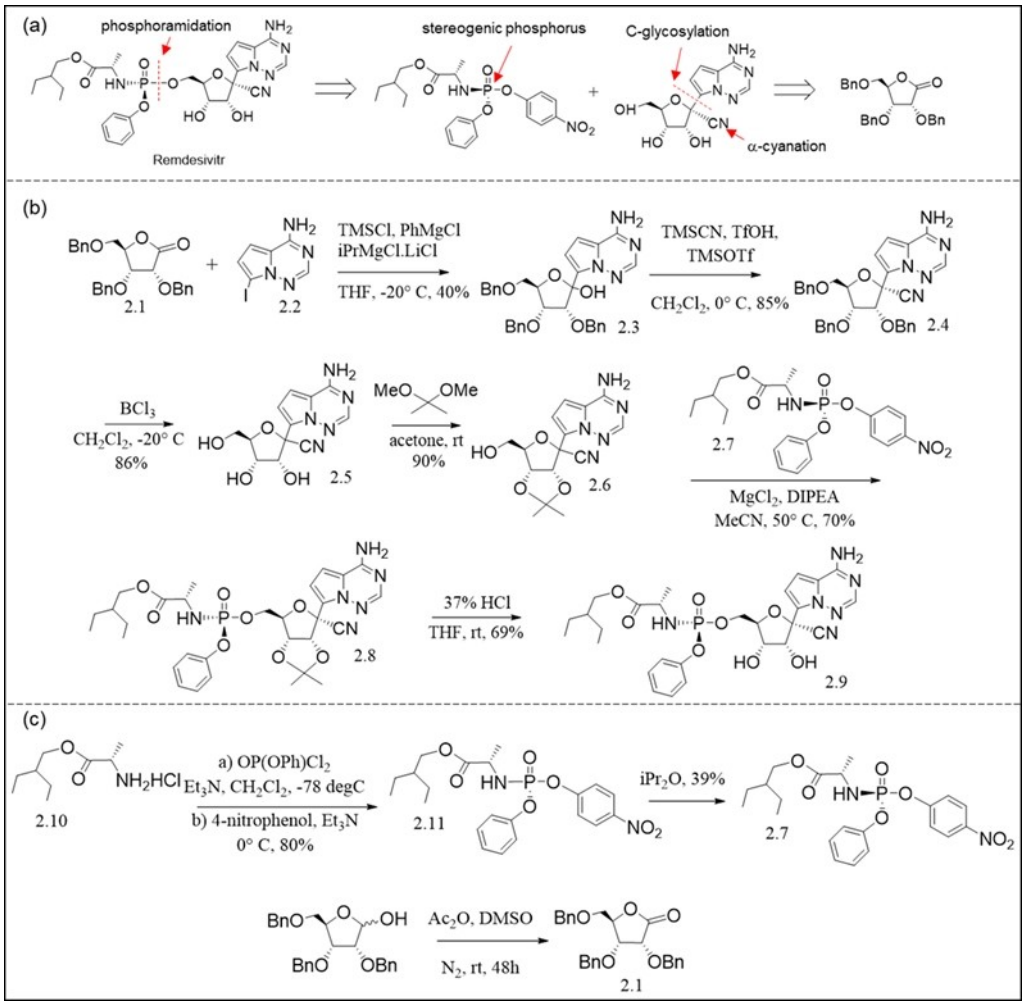


Scheme 2. Metabolism of Remdesivir.

by crystallization in this solvent. Another starting material, benzyl-protected ribolactone 2.1 was obtained from the corresponding sugar by the reaction with acetic anhydride in DMSO under an inert atmosphere.

C-glycosylation step: This C-glycosylation step is associated with some difficulties in β-anomer selectivity, in situ aniline protection and substituent effects, which leads to the reported low yield of 40%. Due to this low yield for the reaction between the base and pentose unit the bulk supply of this antiviral drug Remdesivir is hampered to a great extent. There is room for developing better coupling methods to improve the existing approach.[106] In the first generation synthesis, nucleoside bromide 2.2a and ribolactone 2.1 couple in the presence of TMSCl and n-BuLi at −78 °C to form the desired product in a low yield of 25% (method A; Scheme 4).[107] As we discussed, the second generation method produced 2.3 in a better yield of 40% (method B; Scheme 4). After COVID-19 outbreak, the Gilead scientists very recently optimized this step where $NdCl_3$ and n-Bu_4NCl were used to assist the coupling between 2.1 and 2.2 (Method C; Scheme 4).[108]

The large scale synthesis of 2.3 with a 69% yield proved the reliability of this method. As the latest improvement of this step, Qin and coworkers reported a significant improvement for the C-glycosylation step which has an optimal yield of 75%.

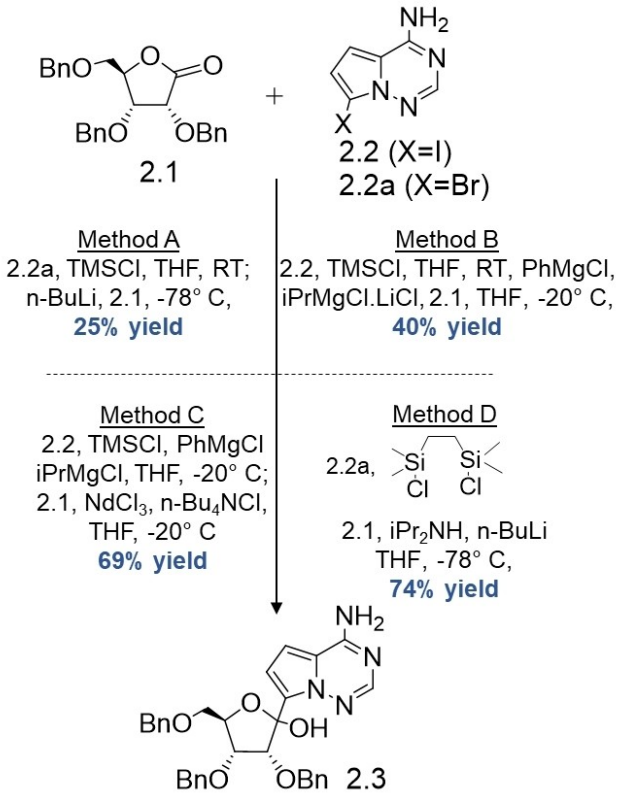


Scheme 3. Synthesis of Remdesivir. (a) The retrosynthesis of Remdesivir displaying main disconnections, (b) Synthetic steps of Remdesivir, and (c) Synthesis of the fragments phosphoramidate (2.7) and ribolactone (2.1).

The reaction between bromide 2.2a and lactone 2.1 was conducted employing disilane in the presence of n-BuLi with diisopropylamine and the reaction delivered the highest yield of 75% for the ribofuranoside adduct. Development of this C-glycosylation should make the synthesis of Remdesivir efficient towards the fulfilment of its current global demand.

However, this lengthy C-glycosylation of a pyrrolotriazinamine is associated with consumption of long time and energy due to the requirement of multiple prolonged addition of reagents for the exothermic reactions to happen in batch. In a very recent study, Keppe and coworkers improved this lengthy C-glycosylation by carrying out the organometallic reactions at a higher temperature in continuous flow processing instead of batch.[109] Thorough optimization of stoichiometry offered an improvement upon batch conditions with a total residence time of less than 1 min and the specific conditions were standardized to avoid solid formation and allow stable processing. Despite of these advantages, continuous flow procedure did not bring about a considerable advancement in yield compared to the second generation synthesis (47% vs 40%), still it showed a great improvement in terms of processability. The batch method has a reaction time of several hours due to the requirement of three different temperature zones (20, 0, and −20 °C) and extended addition times. On the contrary, the developed flow procedure requires only a single temperature regime and finishes the reaction in a residence time of less than 1 min, which is suitable for large scale synthesis. It is expected that these results of continuous processing will improve manufacturing of Remdesivir.

Stereogenic phosphoramidate synthesis: Synthesis of Remdesivir requires the formation of a stereogenic center on phosphorus (P) as a key step and the conversion of this prodrug into the active triphosphate drug directly depends on the high diastereomeric purity at phosphorus. However, unlike stereogenic carbons, construction of phosphorus stereocenters still remains a fundamental challenge and there is lack of general synthetic methods for the diastereoselective phosphoramidate synthesis for Remdesivir.[110] In case of first generation synthesis to Remdesivir (Scheme 5a), the required enantiopure S_P-phosphoramidate is synthesized by the coupling of the



Scheme 4. Different synthetic procedures for C-glycosylation step to enhance product formation by changing the reagents.

corresponding P-racemic phosphoryl chloride with the nucleoside GS441524 and subsequently separation of the two diastereoisomers by using chiral HPLC.[102] The second generation synthesis employed an alternative approach that involves selective nucleophilic displacement of the enantiopure phosphorylating agent isolated from the separately prepared mixture of two diastereoisomer intermediates as we have already discussed in the above section (Scheme 5b).[101] To prepare the enantiomerically pure P-stereogenic intermediate, chiral resolution and additional synthetic steps are involved and these certainly lead to low synthetic yield. To address this issue, very recently Zhang and coworkers have developed catalytic asymmetric synthesis of Remdesivir by the coupling between the P-racemic phosphoryl chloride and protected nucleoside 2.6 (Scheme 5c) in the presence of chiral bicyclic imidazole as catalyst.[111] Through a process of optimization, the authors found that the desired product 2.9 (Remdesivir) could be obtained in 96% yield with 21.6:1 d.r. at 10 mol% (−40 °C) catalyst loading and this synthetic methodology is promising in terms of an atom-economy and synthetic efficiency.

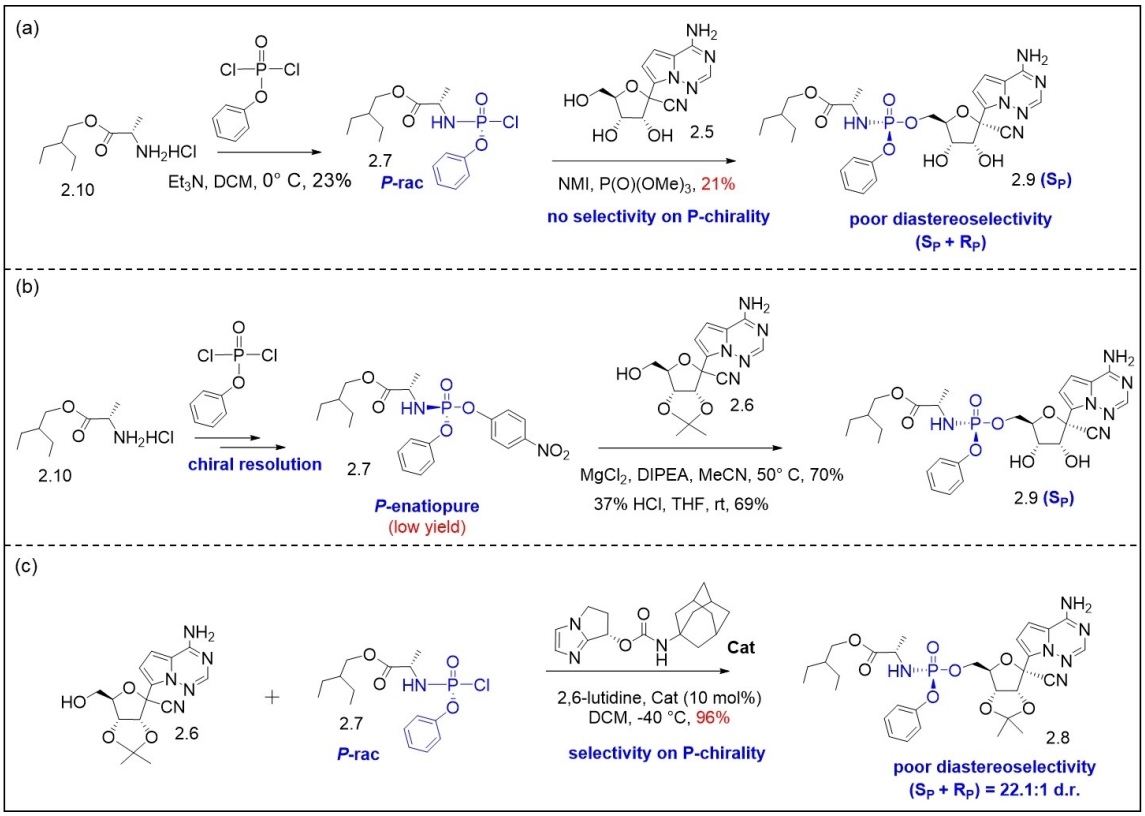
Supply Chain Improvements: Drug manufacturers throughout the world are experiencing problems of sourcing and supply-chain weaknesses in regard to unprecedented global demand, giving the biggest drug-making challenges. To address the high-throughput drug manufacturing, there is a genuine need for cost effective and short optimal routes for synthesizing the final active pharmaceutical ingredient (API). In other words, highly abundant, commoditized raw material inputs are essential. The subject of supply chain security issue has been discussed within the synthesis of pyrrolotriazine (pyrrolo[2,1-f][1,2,4]-triazin-4-amine) which is an early raw material for the synthesis of Remdesivir. Hence, massive amounts of pyrrolotriazine are required for Remdesivir synthesis meeting its current demand. Until very recently, the only total synthetic route to the pyrrolotriazine was reported by Bayer Healthcare[112,113] and the synthesis procedure has a few low yielding steps (Scheme 6a). However few steps in these synthetic procedures can be improved and ultimately these can help to overcome the prevailing challenges associated with supply and price. Firstly, the overall yield was reported to be 31% over four steps. Hence there is a scope for lowering the intake of raw materials by enhancing the overall yield. Secondly, Boc protection is required for hydrazine and the resulting carbamate (2.14) must be deprotected to obtain the free amine (2.15) in the reported Bayer Healthcare procedure. This causes increment of step-count lowering of overall yield. Thirdly, two early raw materials namely, 2,5-dimethoxytetrahydrofuran and tert-butyl carbamate are not commodity materials.

In order to strengthen the supply chain of Remdesivir, the ideal route to pyrrolotriazine should initiate from commodity materials and have improved overall yield with reduced step count. Very recently Snead and coworkers investigated the bond-forming steps to do so from pyrrole which is highly abundant and commoditized raw material (Scheme 6b).[114] Aldehyde group is generally easily introduced at the 2-position of pyrrole, and the resulting aldehydes can be oxidized to the corresponding nitriles through aldoxime intermediates. Herein, authors have developed one-pot nitrile (2.18) formation by using oxidative Vilsmeier cascade strategy. Next, N-amination of 2-cyanopyrrole (2.18) was performed by the use of chloramine, resulted in an intermediate (N-amino-2-cyanopyrrole) which participate in condensation with formamidine acetate to form pyrrolotriazine 2.16. In reality, these two steps namely amination and triazine formation are combined in one pot. The overall yield of triazine was almost doubled from 31% to 59% mainly because of the decreased step count from 4 to 2.

With the notion of lowering the cost for Remedesivir manufacturing, Garg and coworkers found an alternative approach (Scheme 6c) to the nucleobase from cyanoamidine intermediate by electrophilic aromatic substitution.[115] In their route, 2,5-dimethoxyfuran (2.12) is first converted to formamide (2.19) in two steps. Then 2.19 undergoes condensation with cyanamide to form cyanoamidine intermediate (2.20). Then Lewis acid mediated cyclization of the Z-isomer of 2.20 produced pyrrolotriazine (2.16). This synthetic route is strategically different from earlier routes and also atom economical.

Lopinavir/Ritonavir

Although, there is no antiviral drug currently available against SARS-CoV-2, a mixture of two HIV-1 protease inhibitors namely Lopinavir and Ritonavir, was recently known to be useful

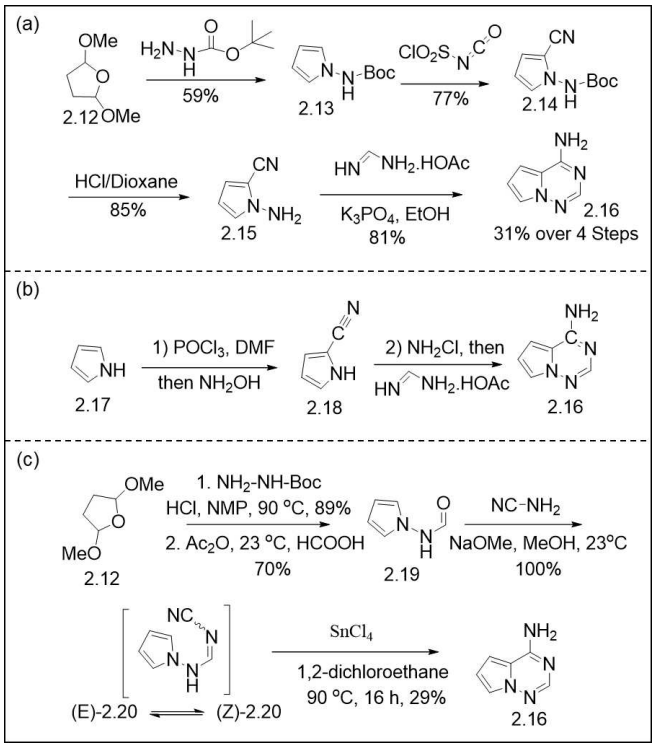


Scheme 5. (a)The first generation synthesis of Remdesivir, (b) The second generation synthesis of Remdesivir, and (c) Catalytic asymmetric synthesis of Remdesivir.

against SARS-CoV-1. When Lopinavir is administered alone, it has a very low human bioavailability of around 25%, mainly due to its extensive oxidative metabolism by P450 CYP3 A4 enzymes.[116] It is mostly coadministered with Ritonavir, which reduces drug metabolism and significantly improves the bioavailability of Lopinavir. It is reported that much better bioavailability of Lopinavir is noticed in the presence of Ritonavir and this mixture has been used for the treatment of HIV/AIDS in some countries.[117] The chemical structures of these drugs are similar to small peptides which include highly modified synthetic amino acids.[118,119] Previously, Lopinavir has been seen to inhibit the replication of MERS-CoV and SARS-CoV-1 to some extent and in this line, it is believed that Lopinavir might be useful for SARS-CoV-2, although there is no conclusive in vitro SARS-CoV-2 data so far. A recent study in The Lancet reported that the mixture of Lopinavir, Ribavirin, Ritonavir, and Interferon may be useful for the treatment of COVID-19 at its initial stage.[120]

After entering into the host cells, the SARS-CoV-2 virus replicate forming strands that contain multiple copies of RNA and the enzyme $3CL^{pro}$ (3-chymotrypsin-like protease) plays a key role in processing the viral RNA.[121,123] Being a protease inhibitor, Lopinavir may act as an inhibitor for $3CL^{pro}$ and hence it can interrupt the viral replication process. The antiviral activity of Lopinavir against SARS-COV-2 has been established by a recent study.[123] In a separate work, a group of computational chemists explained the reason behind the effectiveness of Lopinavir and Ritonavir against the SARS-CoV-2.[124] They have studied the molecular complexation between each drug and SARS-CoV-2 $3CL^{pro}$ by using all-atom molecular dynamics simulation, pair interaction energy analysis as well as free energy calculation. Both drugs showed significant interaction with the residues at the active site of SARS-CoV-2 $3CL^{pro}$. In contrast to Lopinavir, Ritonavir exhibited a greater number of main binding residues and slightly higher binding efficiency, and this is related to the somewhat lesser water accessibility at the active site of $3CL^{pro}$. In this study, the important factors in the event of drug binding were electrostatics, dispersion, and charge transfer interactions. This study suggests how repurposed anti-HIV drugs can be exploited to fight against COVID-19 and how computational chemistry knowledge at the atomic level is effective for the discovery of more specific drug in fighting against coronaviruses.

Synthesis of Lopinavir was earlier reported[120–124] majorly contributed by Abbott Laboratories. The retrosynthesis of Lopinavir (Scheme 7a) suggests the requirement of three fragments: central-core amino alcohol 3.2 and two side chain acids 3.1, and 3.3 for the synthesis of Lopinavir.[120] The synthesis of first fragment 3.1 is shown in Scheme 7(b) where L-valine (3.9) was first transformed to corresponding N-terminus carbonate 3.10 solid NaOH afforded 3.11 that was subsequently cyclized in presence of potassium tert-butoxide to give 3.1 through an



Scheme 6. Earlier (a) and current approaches (b, c) for the synthesis of pyrrolotriazine (2.16), the unnatural nucleobase acting as a key precursor to Remdesivir. (b) Increase in yield of pyrrolotriazine by reducing step count, and (c) Atom economical reaction for pyrrolotriazine.

intramolecular SN^2 mechanism. After crystallization from EtOAc, 3.1 was obtained in 77% yield with >99% ee.

The second fragment (3.2) is the same for both Ritonavir and Lopinavir and it has three chiral centers. The first chiral center is generated from the naturally occurring amino acid L-phenylalanine, and the point chirality of this amino acid is then exploited to guide the incorporation of two more stereogenic centers, as described in Scheme 7(c). The synthesis of the second fragment starts with the tribenzylation of phenylalanine (3.4) after exposed to benzyl chloride to produce benzylester 3.5.

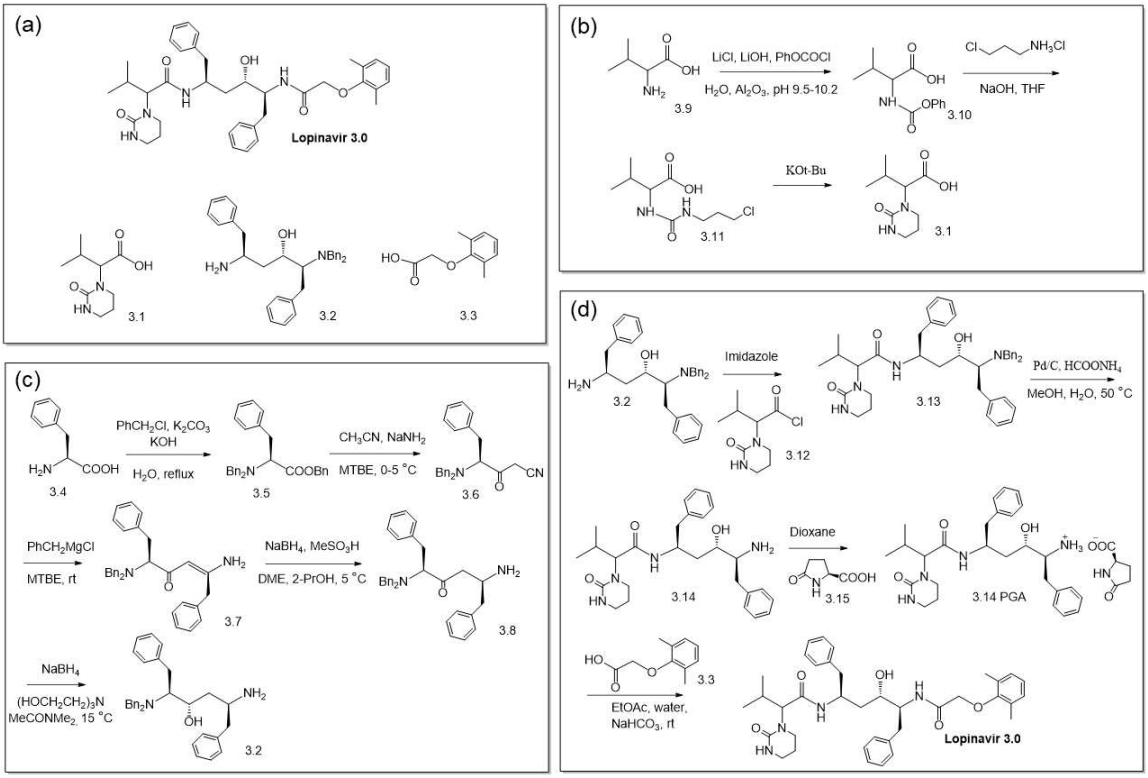
Next, incorporation of the acetonitrile anion generated by the base sodium amide to the benzyl ester and reaction of the resultant cyanomethylketone 3.6 with benzylmagnesium chloride, were performed as a one-pot reaction in the solvent methyl-t-butyl ether (MTBE). The acquired enaminone 3.7 was recrystallized from EtOH with >99% ee in an overall yield of 79%. The diastereoselective reduction of enaminone 3.7 to amino alcohol 3.2 needed extensive efforts to enhance the diastereomeric ratio (dr) of the desired product and according to advanced procedure, it was done by a stepwise process: enamine double bond reduction using $NaBH_4$ with $MeSO_3H$ to afford 3.8 with a dr of approximately 95:5. Then 3.8 to 3.2 was reduced by $NaBH_4$ in the presence of a triethanolamine as a boron complexing agent in the solvent dimethylacetamide. Aqueous workup afforded 3.2 having the preferred diastereomer in 89–93% yield,[125–127] which was directly used for preparation of Lopinavir (Scheme 7d).

The ultimate reaction steps for Lopinavir have been outlined in Scheme 7 (d)[125] in which amine 3.2 was first conjugated to 3.12 (obtained from acid 3.1 upon treatment with $SOCl_2$) to afford 3.13. Next, amide 3.13 was converted to amine 3.14. The diastereomeric purity of 3.14 was improved by crystallizing as a salt 3.14PGA having the purity of >98.5%. In the final step, conjugation between 3.14 PGA and 3.3 was carried out. After crystallization, 3.0 was obtained in 58% yield.

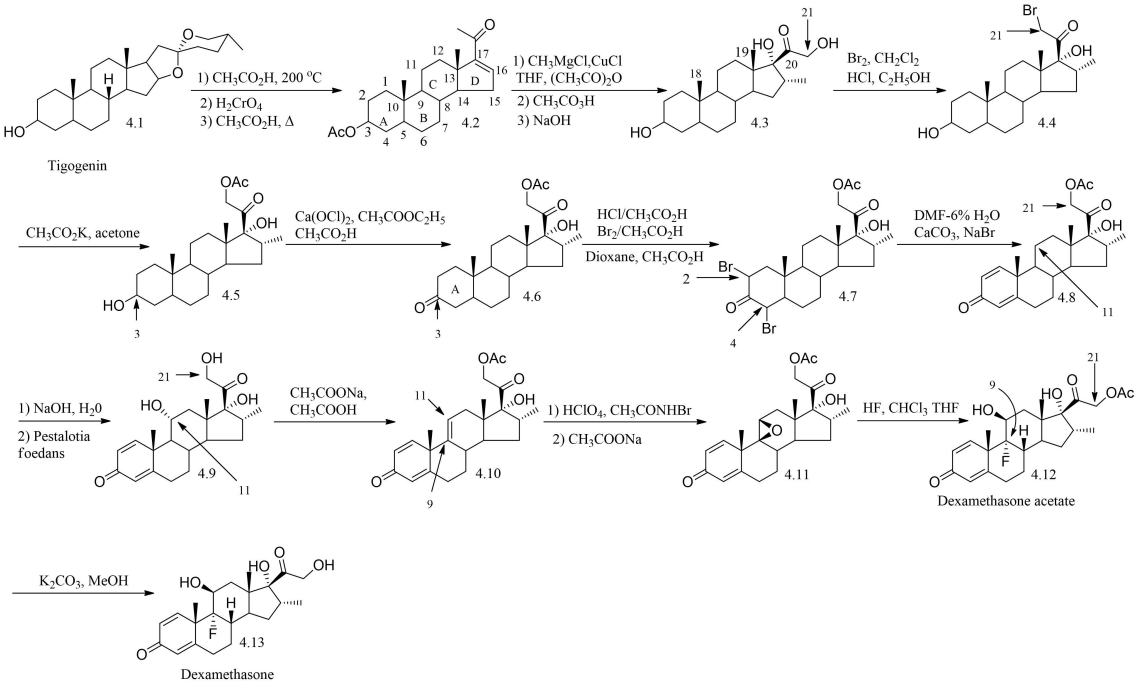
Dexamethasone

Dexamethasone (Figure 7) has been very recently found to have benefits for seriously ill COVID-19 patients on ventilators and the treatment was revealed to reduce mortality by approximately one third.[130] Dexamethasone is a well-known corticosteroid medication and has long been used in many conditions for its anti-inflammatory effect.

The sickest COVID-19 patients suffer a hyperinflammatory state, a cytokine storm, where immune suppression could help them. The $3CL^{pro}$ on SARS-CoV-2 inhibits HDAC2 transport into the nucleus, and hence weakens the way in which it mediates inflammation and cytokine responses. Therefore, it is assumed that Dexamethasone can activate histone deacetylase and directly inactivate SARS-CoV-2 infection. Dexamethasone is a derivative of cortisol (hydrocortisone) and chemically described as 1-dehydro-9α-fluoro-16α-methylhydrocortisone or as 9α-fluoro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione. Dexamethasone can be synthesized from 16α-methylpregnenolone[131] or tigogenin.[132] Due to relatively higher abundance of tigogenin in nature, it has been mostly utilized for the synthesis of Dexamethasone acetate (4.12). Oliveto et al. exploited 16α-methylpregnenolone,[131] whereas Ma et al. used tigogenin as the starting point for the synthesis of Dexamethasone acetate.[132] In the year 1997 Furukawa et al. improved few steps of the existing synthetic routes to obtain Dexamethasone acetate with higher yield.[133] The synthesis starts from tigogenin, (4.1) (Scheme 8) which undergoes ring opening in the presence of acetic acid at 200 °C, followed by oxidation with chromic acid and elimination by application of heat to form 4.2.[132] Then 4.2 was treated with $CH_3MgCl/CuCl$ for the introduction of methyl moiety at C-16 and further epoxidation was done using peracid followed by alkaline hydrolysis to produce 4.3. Then bromination at C-21 using Br_2 in dichloromethane formed 4.4, which was subjected to acetylation with potassium acetate in the next step yielding 4.5. Introduction of ketone at C-3 position was done by the oxidation of C-3 OH by the treatment of calcium hypochlorite to produce 4.6. In the next step, dibromination was carried out at C-2 and C-4 positions by using Br_2/AcOH in the mixture of dioxane-AcOH as solvent to produce 4.7, which was then treated with DMF containing 6% water for dehydrobromination reaction to introduce two double bonds in ring A (4.8).[133] Next, hydrolysis of C-21 acetyl group by NaOH and subsequent hydroxylation at C-11 in presence of a fungi *Peslalotia foedans* produced 4.9. Further, a double bond was incorporated in the C-ring



Scheme 7. Synthesis of Lopinavir. (a) Retrosynthesis of Lopinavir into three main fragments, (b) Synthesis of acid fragment 3.1, (c) Synthesis of amino alcohol fragment 3.2, and (d) Final synthetic steps to Lopinavir.



Scheme 8. Synthesis of Dexamethasone from Tigogenin.

(between C-9 and C-11) by the treatment with sodium acetate to produce 4.10. Then treatment of hypobromous acid (obtained from perchloric acid and N-bromo acetamide) followed by sodium acetate treatment resulted in epoxidation

to form 4.11. Introduction of fluorine at C-9 was carried out by treating HF in chloroform-THF to yield Dexamethasone acetate (4.12).[131] Finally hydrolysis of acetyl unit in 4.12 produced Dexamethasone (4.13).[134]

Summary and Outlook

In conclusion, we have discussed the importance of synergy between chemistry and biology to fight against COVID-19 outbreak. The following major areas of chemistry will have key role to find pragmatic solutions against COVID-19. Emphasis has been given to supramolecular self-assembled structure, surfactant bilayers, analyzing structure of the protein, molecular recognition in the context of structure and host binding of SARS-CoV-2 virus. Micelle formation by soap water, destruction of viral membrane by surfactant, oxidation of protein by disinfectants, denaturation of protein by alcohol are depicted as part of chemical preventive measures. Development of synthetic routes to the drugs and their mechanism of action are described in the course of drug development. Aforementioned topics are familiar in the broad range of chemistry and discussed in connection with COVID-19. Chemistry-based research organizations have refocused their efforts to fight against COVID-19. Biochemists reveal the structure of the viral components, computational chemists contribute by modelling COVID-19 proteins to identify anti-viral drug candidates, and medicinal and pharmaceutical chemists engage themselves for the identification of potential anti-viral drugs and finally, organic chemists are involved in the improvement of synthetic procedures of repurposed drugs. Importantly, chemists are also involved for the development of personal preventive measures. So, in these uncertain times, chemists' response to combat COVID-19 is of great importance. Chemists may have potential for making more contributions, however, one of the major obstacles for them is the deficiency of accessing virions, which is currently confined to a relatively small number of specialized laboratories. Apart from the chemists' response, nature conservation may have a role in the fight against the COVID-19 because lower COVID-19 mortality was found in some forested areas in Italy as described in a recent study.[135] In conclusion, the whole chemical science community has been contributing to fight against COVID-19. To address this big challenge, not only a prompt and collaborative approach between chemists and biomedical researchers but also a cohort formed from different chemical science communities is required. Until an effective medicine or vaccine will be made available, we have to consider "prevention is better than cure" where chemical sciences contribute in conceptualizing and developing the products for chemical preventive measures whose mechanism is well explained by chemists.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: biological and medicinal chemistry · chemical preventive measures · COVID-19 · receptors · repurposed drugs

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