Heterocyclic compounds as antiviral drugs: synthesis, structure-activity relationship and traditional applications

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Abstract: A virus outbreak challenges the economic, medical and public health infrastructure worldwide. More than one virus capable of triggering diseases have been identified per year since 1972, which requires the development of new ways of treatment and prevention, however, such processes are not rapid and easy. With the pandemic scenario experienced since early 2020, several drugs with well-known purposes have gained prominence, due to speculation of their use in the treatment against the new coronavirus. Among the main drugs studied, the vast majority contain a heterocyclic structure. In this review, we presented the traditional and efficient synthesis of 15 drugs that have been studied for the COVID-19 treatment, containing in their structure heterocycles like indole, quinoline, pyrimidone, tetrahydrofuran, pyrrolidine, triazole, pyridazine, pyrazole, pyrrolopyrimidine, azetidine, pyrrolotriazine, pyrazine, tetrahydropyran, benzofuran, spiroketal, and thiazole. Furthermore, we have shown the original applications, as well as their structure-activity relationship and what is their situation as a drug candidate against COVID-19. Thus, the objective was to consolidate the main synthetic and pharmacological aspects involving clinically developed heterocycles that at some point were presented as promising against SARS-CoV-2.

Keywords: Heterocycles, antiviral, Synthesis, SAR.

Introduction

Viruses have the simplest biological structure, basically composed of few strands of RNA or DNA and an outer shell of protein, that can be enveloped by a lipid layer. Being cell parasites, viruses can only replicate within the host cells. As infectious agents, the viruses can trigger an immune response in the host body, which in some cases can control the infection and in others not, leading to pathological effects and even death.[1–3]

Unfortunately, viral infections and their consequent pandemics have marked the history of humanity, such as the Spanish flu that killed about 40 million people worldwide in the early 1900s.[4] In the last 48 years, more than 50 new viruses capable of triggering diseases in humans have been identified, such as African Swine Fever (ASF), Acquired Immunodeficiency Syndrome (AIDS), Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) and Hepatitis, that have required the development of new drugs and vaccines. However, these processes of development are usually slow and with several hurdles. Still, with scientific and technological advances, new and more accurate diagnoses were possible in addition to the development of sophisticate drugs and vaccines very efficient against infections. According to World Health Organization (WHO) data released in 2020, diseases caused by viruses represent a good share of global deaths, such as lower respiratory infections, that claimed 2.6 million lives in 2019. This emphasizes the continuing need for the development of new drugs and vaccines to combat viruses responsible for such diseases.[5]

In the last year, the pandemic scenario caused by the new coronavirus SARS-CoV-2 (COVID-19) started a race in academic research and the pharmaceutical industries in the entire world to find an effective drug or develop a vaccine against this new desease. However, the process of developing new drugs or even adapting the existing ones and establishing treatments for a new disease usually take years. The main strategy in researching new diseases treatment is to test already developed and well-known drugs against the new disease, aiming to find an effective one,[6–8] since these drugs have already been clinically tested and more serious adverse effects have been ruled out in certain situations, shortening the path of the long phase of clinical trials and reducing research costs.[8]

In this context, several antivirals with well-known applications have raised attention as possible effective treatments against SARS-CoV-2. Unfortunately, almost none of these drugs so far have shown good scientific evidence of their effectiveness against the new coronavirus.[9] Among the main drugs studied, the vast majority of them contain a heterocyclic fragment.[10–12] Synthetic heterocyclic compounds correspond to about 87% of drugs, since, thanks to organic synthesis these analogues can imitate natural ones, interacting with biological targets, being able to present a wide range of biological activity.[13]

In this work, we are showing an overview regarding 15 antiviral compounds with well-known applications that gained prominence in the last year as possible candidates as drugs against SARS-CoV-2. For each of these compounds, it is discussed synthesis methodologies, as well as the SAR (Structure-Activity Relationship), emphasizing how the functional groups and chemical structure are linked to their mechanisms of action, facilitating the understanding of the logic involved in the repositioning of these drugs. It is also showed the traditional use of each molecule, and what is their situation regarding the new coronavirus.

Antiviral Heterocyclic Compounds

Ritonavir and Lopinavir

Ritonavir (**8**) was designed as an inhibitor for HIV-1 protease, based on its C_2-symmetric homodimer structure. This drug is characterized by a reduced rate of metabolism and high oral bioavailability.[14] This compound was approved for use as an antiretroviral agent in 1996, but its adverse effects resulted in its discontinuation in the late nineties.[15] Because of ritonavir potent activity as an inhibitor of cytochrome P450 (CYP) enzymes, primarily CYP3A, it has been administered as a pharmacoenhancer (or booster) with CYP3A-metabolized HIV protease inhibitors, such as atazanavir, darunavir, and lopinavir.[15,16]

Lopinavir (**27**) was designed as a substitute of ritonavir as an HIV protease inhibitor, since ritonavir activity was dependent on the interaction between the isopropyl substituent in its thiazolyl group and the isopropyl side chain of HIV-1 protease valine-82, which was compromised in mutations of the HIV.[17] Lopinavir is often administered in conjunction with ritonavir, since a small dose of ritonavir inhibits the metabolism of lopinavir by the CYP3A, increasing the plasma concentration of lopinavir.[18] In the effective treatment of the HIV infection in adults, ritonavir and lopinavir often needs to be applied in combination with other antiretroviral drugs, such as IFN, Arbidol and Novaferon.[19]

Ritonavir has a C2-pseudosymmetric inhibitor center (Figure 1), so it can interact with HIV-1 protease. This protease has a symmetric structure in its cleaving site. Therefore, the use of a symmetric or pseudosymmetric inhibitor gives better specificity for the retroviral protease over the human one, which has less symmetric binding sites, and also allow for the development of inhibitors

which are less peptide-like, enhancing their stability *in vivo*.[20] The valine amino acid in its structure interacts directly with valine-32 of the HIV-1 protease.[16] The N-methyl group is responsible for higher water solubility and oral bioavailability of the compound.[16,21,22] The isopropylthiazolyl group of ritonavir interacts with the side chain of valine-82 of HIV protease, which was confirmed by the X-ray crystal structure of ritonavir bound to HIV-1 protease.[16] The unsubstituted thiazolyl group is important in the CYP inhibition since its nitrogen atom binds to the heme group in the CYP active site.

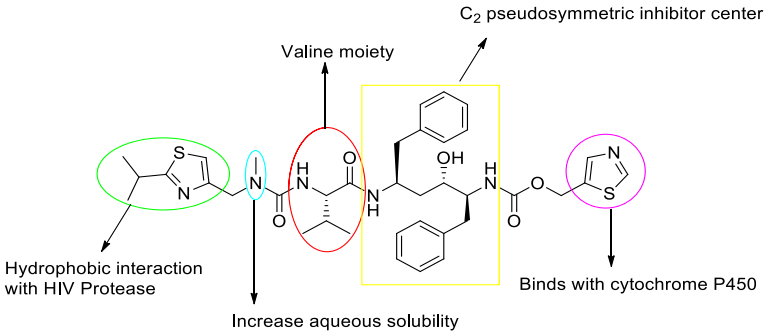


Figure 1. Ritonavir SAR.

Lopinavir structure is similar to ritonavir since it was designed from the former, with modifications to enhance its activity. It has the same *C2* pseudosymmetric inhibitor center (Figure 2), responsible for the interaction with HIV-1 protease.[21] Different from ritonavir, it has a cyclic urea, which interacts via hydrogen bond with HIV-1 protease. This cyclic urea does not interact with the valine-82 of HIV protease like ritonavir's isopropylthiazolyl, making it less susceptible to mutations in that position.[17] The 2,6-dimethylphenoxyacetyl group in lopinavir is lipophilic, which helps in cell membrane crossing.[21]

Further enhancement of lopinavir efficacy could be made by concentrating on the improvement of the lipophilic group, aiming to maintain the cell membrane lipophilicity and increasing the hydrophobic interaction of this group with hydrophobic residues on viral protease, favoring flexible hydrophobic groups.[23] Alternatively, the modification of the cyclic urea group could be made, aiming to obtain stronger hydrogen bonds with viral protease, avoiding interaction with the valine-82 residue, which is prone to mutations.[17,21]

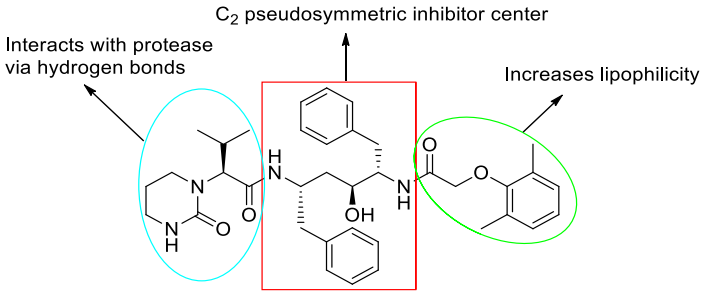


Figure 2. Lopinavir SAR.

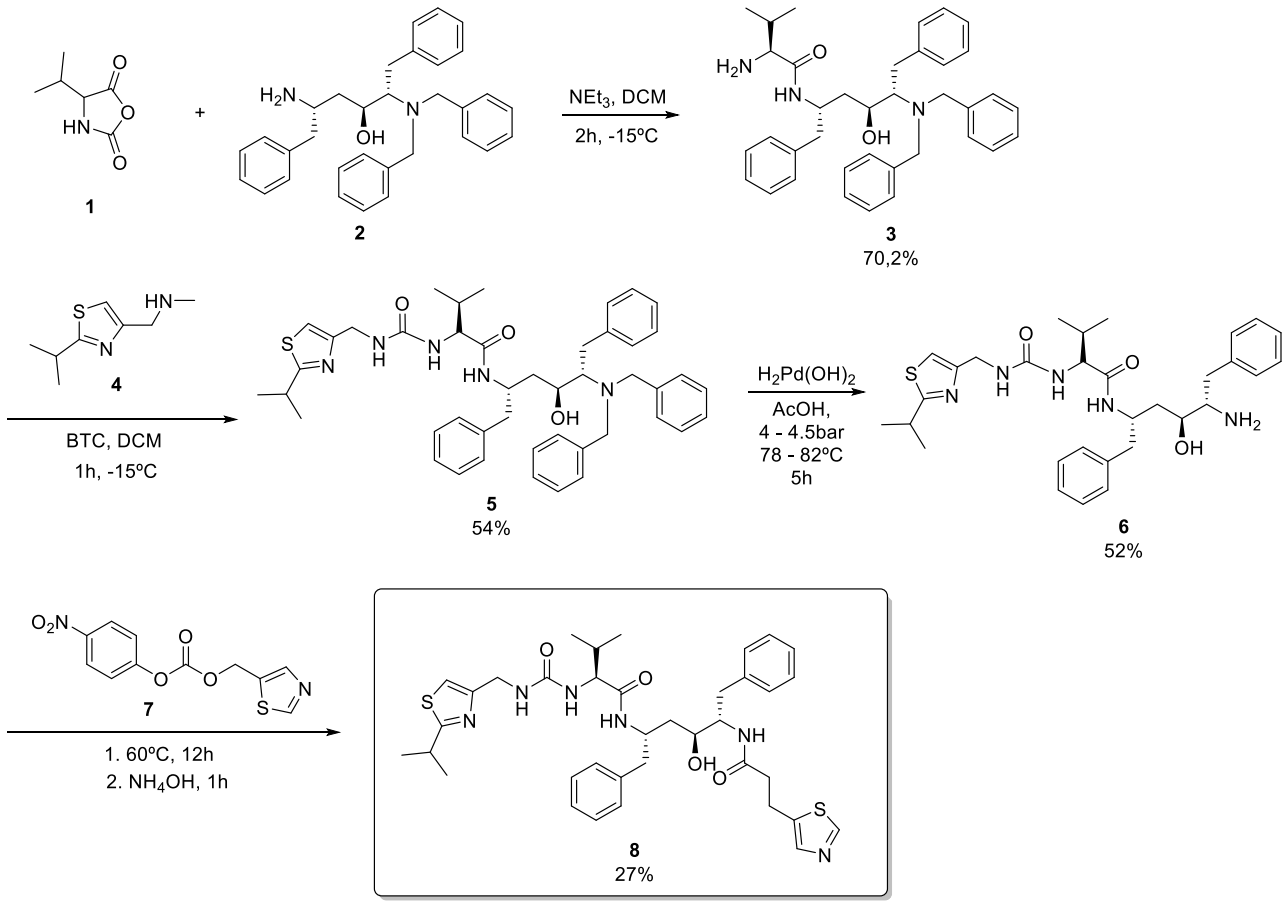
Besides HIV treatment, ritonavir and lopinavir have also been studied for application in other diseases. Ritonavir was studied as a booster in the treatment against the hepatitis C virus (HCV), MERS-CoV and SARS-CoV, but without conclusive positive results.[22,24–26] Lopinavir had its activity studied against SARS-CoV and MERS-CoV, both alone and in conjunction with ritonavir, *in vitro*, *in vivo* and in clinical trials, showing itself as a potential candidate for treatment.[27,28]

Cao *et al.* conducted a randomized, controlled, open-label trial involving hospitalized adult patients with confirmed SARS-CoV-2 infection. Patients were randomly assigned in a 1:1 ratio to receive either lopinavir-ritonavir (400 mg and 100 mg, respectively) twice a day for 14 days, in addition to standard care, or standard care alone. It was not observed any benefit with the lopinavir-ritonavir treatment beyond standard care.[29] The study conducted by *Li et al.* enrolled 86 patients with mild/moderate COVID-19

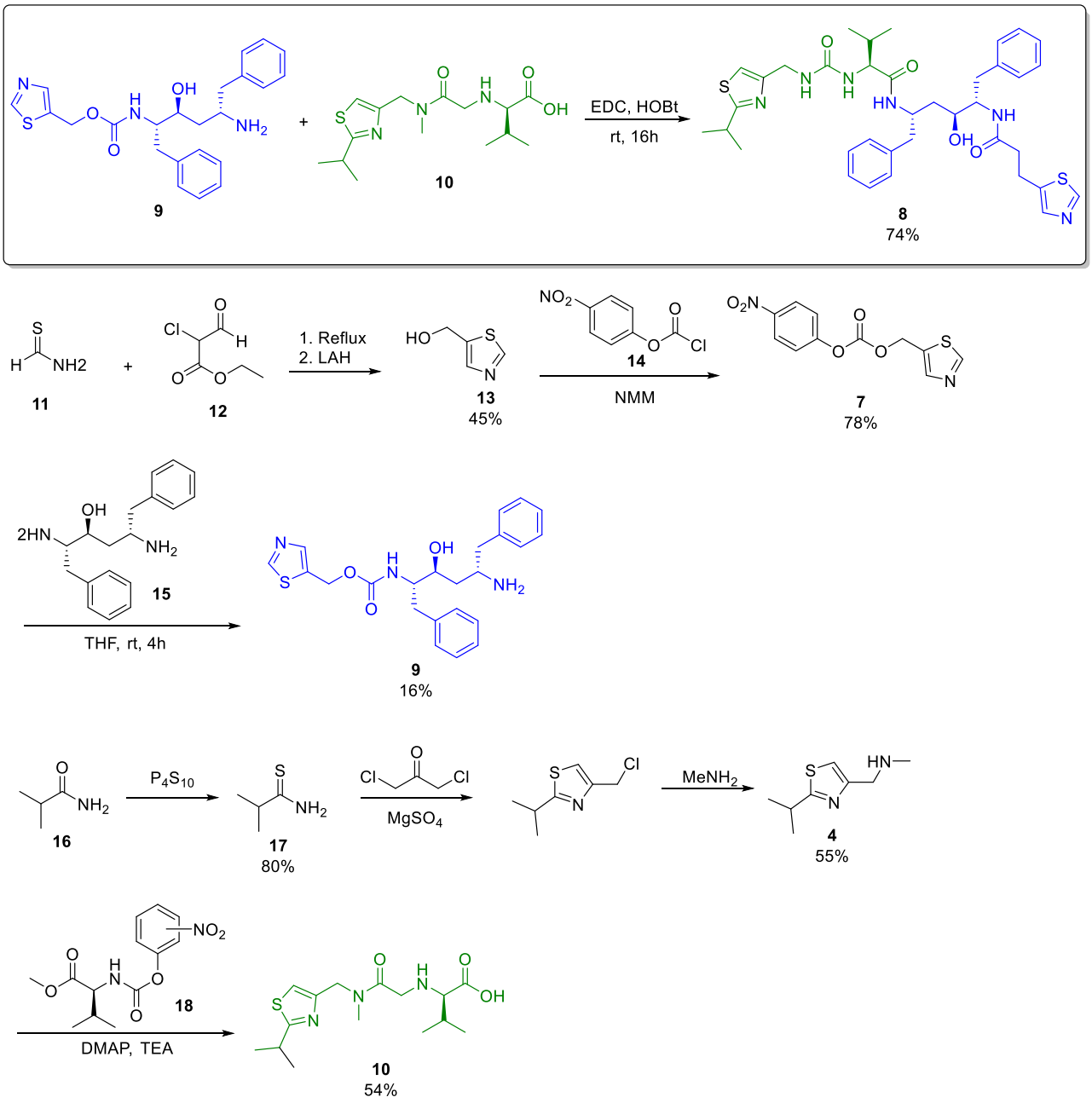
with 34 randomly assigned to receive lopinavir/ritonavir, 35 to Umifenovir (arbidol) and 17 with no antiviral medication as control. As a result, the baseline characteristics of the three groups were comparable and the lopinavir/ritonavir or arbidol monotherapy presented little benefit for improving the clinical outcome of patients hospitalized with mild/moderate COVID-19 over supportive care.[30] A large multicenter retrospective study by Lora-Tamayo *et al* with COVID-19 patients receiving early treatment with lopinavir/ritonavir found no benefits of this early treatment.[31] The RECOVERY group published results of its randomized, controlled, open-label, platform trial ongoing in the United Kingdom, and concluded that lopinavir/ritonavir was not associated with mortality reduction or symptom improvements.[32] However, larger clinical trials to study the potential effectiveness of ritonavir and lopinavir in reducing mortality are still ongoing. At this moment, there is no survival or clinical benefit of ritonavir and lopinavir treatment of COVID-19 infection.[33] Not even the combinations of lopinavir-ritonavir with other antiviral drugs that are effective for HIV treatment, when studied for COVID -19 treatment have not showed good efficacy.[34]

The ritonavir synthetic routes are complicated, requiring several reaction steps and non-simple reagents to obtain the drug with low overall yields.[35–37] In 2001, Bellani and coworkers described the Ritonavir (**8**) synthesis, starting from the compounds **1** and **2**,[37] whose synthesis was described previously in the literature.[35] In the first step, the intermediate **3** is obtained with moderate yield from the condensation of **1** with the structurally complex reagent **2**. In sequence, compound **4** is added to **3**, leading to the formation of compound **5** in 54% yield. After a debenzylation reaction with Pearlman's Catalyst ($H_2Pd(OH)_2$) and the reaction with a carbonate derivative **7**, the Ritonavir (**8**) is obtained (Scheme 1).[37]

The synthesis of Ritonavir performed by Bellani and coworkers has some minor disadvantages, such as pressure and temperature conditions. Compared to this synthesis, Ghosh and coworkers synthesis presents milder reactional conditions. In this synthesis, the Ritonavir is obtained from simpler reagents in a convergent synthesis, as shown in Scheme 2.[38] Firstly, the synthesis of intermediate **9** starts from the reaction between thioformamide (**11**) and ethyl-2-chloro-2-formylacetate (**12**), leading to the formation of **13** in a condensation reaction. After that, the carbonate derivative **7** is obtained through the coupling of **13** and **14**. In sequence, the carbonate is transformed in carbamate through the reaction with **15**, affording the intermediate **9,** with only 16% of yield. The other ritonavir fragment, the intermediate **10**, is synthesized in four steps starting from iso-butyramide (**16**). First, the amide group is converted to the thioamide group via treatment with P_4S_{10}, affording the compound **17**. This compound is converted into the compound **4**, in a two reaction steps with 1,3-dichloroacetone/$MgSO_4$ and $MeNH_2$. Finally, the intermediate **10** is obtained through the coupling reaction between **4** and valine derivative **18** via treatment with triethylamine (TEA) and 4-dimethyl aminopyridine (DMAP). With the two fragments in hand (**9** and **10**), the ritonavir (**8**) is synthesized through a coupling reaction in standard conditions.[36] In general, the two chiral centers of ritonavir makes the synthesis laborious with some stereoselective reaction steps.

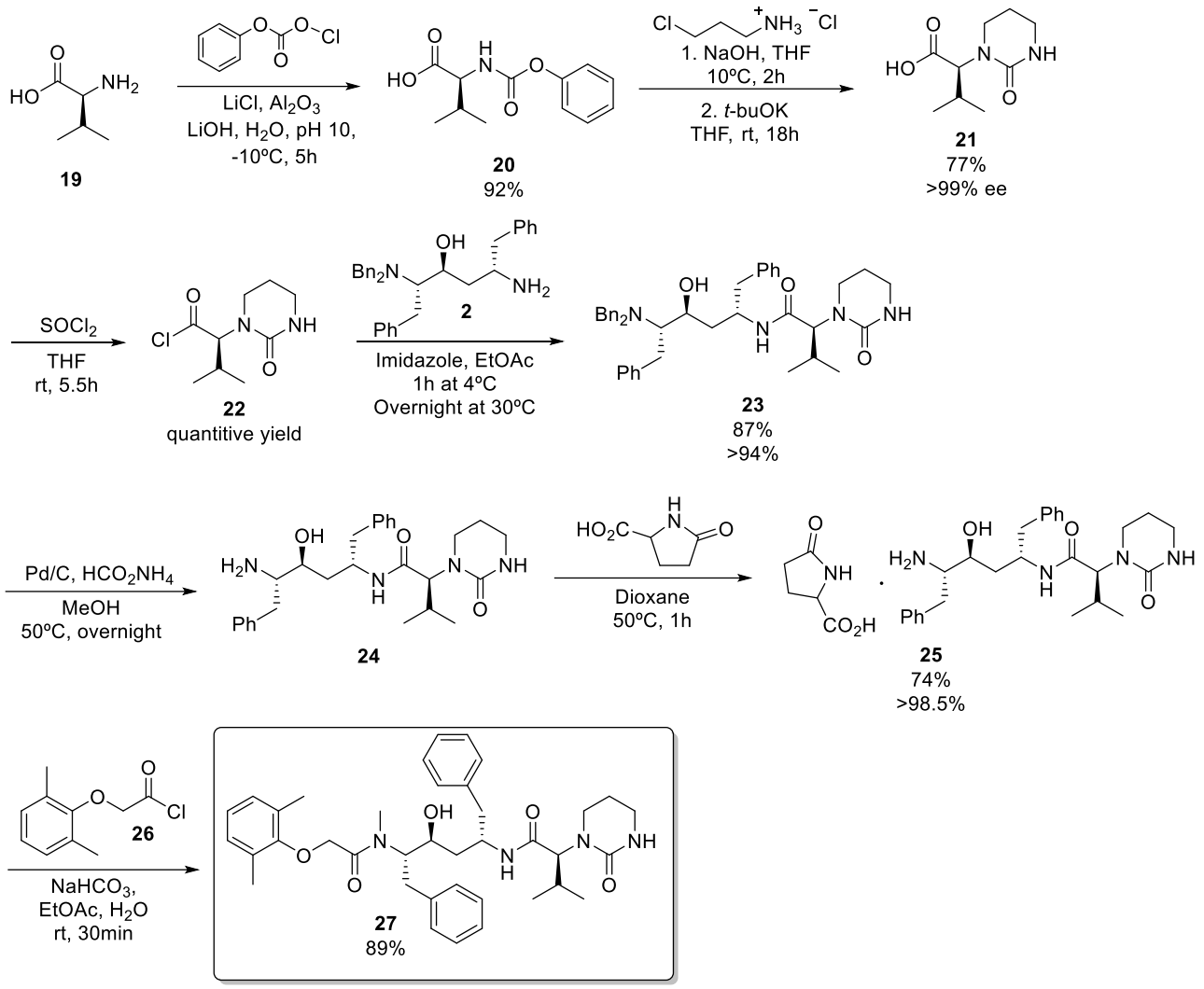


Scheme 1. Ritonavir synthesis described by Bellani and coworkers.



Scheme 2. Ritonavir synthesis described by Ghosh and coworkers.

The first synthesis of lopinavir (**27**) was described in the late 1990s.[39] Here, we have described the synthesis carried out in 2000 by Stoner and coworkers, with an improved methodology regarding the classic one used for ritonavir and lopinavir (Scheme 3).[40] Firstly, L-valine (**19**) is converted to N-phenoxycarbonyl-L-valine (**20**) with phenylchloroformate. After, the compound **21** is obtained in two steps, first the treatment of **20** with 3-chloropropylamine hydrochloride in THF/basic medium, followed by cyclization via treatment with *t*-BuOK. The hydroxyl group is then converted into a chlorine atom, by a classic reaction with thionyl chloride, affording the compound **22** in quantitative yield. Subsequently, compound **23** is prepared through the reaction between the previously prepared **22** with compound **2**. Then, the amino group is deprotected through the reaction with Pd/C affording **24**, that is used in sequence without purification to produce the pyroglutamate salt (**25**). Finally, this compound is subjected to reaction with **26**, to afford the lopinavir (**27**). The synthesis of Lopinavir according to Stoner and coworkers, is performed in mild reaction conditions, where some steps are carried out at room temperature, with relatively low-cost reagents and affording the desired products with enantiomeric excess, which make this synthesis more interesting industrially. Due to the structural similarity with Ritonavir, many of the intermediates used in the synthesis of Lopinavir were developed according to Ritonavir synthesis procedures.



Scheme 3. Synthesis of Lopinavir by Stoner and coworkers.

Heparin

Heparin (**30**) is commercialized since the 1920s, and it is still one of the most important medications in use today. This drug is composed of a complex mixture of polysaccharides of the glycosaminoglycan class. Its main application is as an anticoagulant, in thrombi formation prevention, in circumstances such as surgeries and blood dialysis.[41] It is also used in affinity chromatography, as a ligand for protein isolation and purification, especially binding with viral particles.[42]

The structure-activity relationship of heparin is not completely elucidated since heparin is not a compound with a single chemical structure. Besides that, heparin is not even a mixture of defined substances, since it can vary in polysaccharide chain length and distribution, in disaccharides sequences and it can also have changed due to processing, not only for different processes but also for different batches of the same process.[41] Nevertheless, observations were made that both the binding and the activity of heparin are related to its sequences and charge together.[43]

At long range heparin, as a highly sulfated and therefore, charged species (Figure 3), attracts the positive binding sites of proteins (especially lysine and arginine).[43] As the interacting species distance decreases, a combination of charge and shape becomes important, with strong attractive and repulsive forces leading to conformational changes in both the protein and heparin. It is also important to notice that heparin interacts with hundreds of proteins, with evidence supporting a selectivity with some redundancy instead of sequences specificity.[43]

The study of Mycroft-West *et al.* supports the repurposing of heparin and its derivatives as antiviral agents, to provide a rapid countermeasure against the current SARS-CoV-2 outbreak and future emerging viral diseases.[44] Further studies of the same

group showed that heparin interacts with the SARS-CoV-2 spike S1 receptor-binding domain, inhibiting cell invasion of SARS-CoV 2, suggesting a therapeutic use against COVID-19.[45] Negri *et al.* have conducted a retrospective study, without a control arm, with 27 patients in São Paulo – Brazil. Due to the conditions of the study, it is not possible to determine the efficiency of the heparin. However, their early findings in those patients suggest the importance of disseminated intravascular coagulation as one of the main mechanisms of organ failure in COVID-19 and showed a potential response to anticoagulation therapy.[46] Tang *et al*. have conducted a retrospective study with 449 patients with severe COVID-19 in Tongil hospital, in China. They have concluded that anticoagulant therapy may be beneficial for patients meeting the sepsis-induced coagulopathy criteria or with elevated D-dimer.[47]

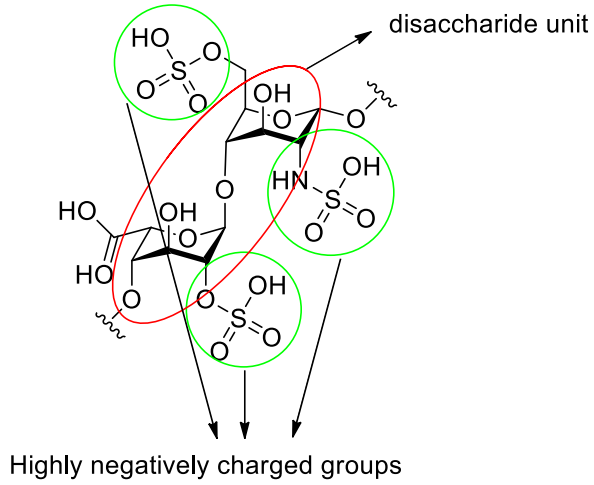


Figure 3. Heparin most common disaccharide unit SAR.

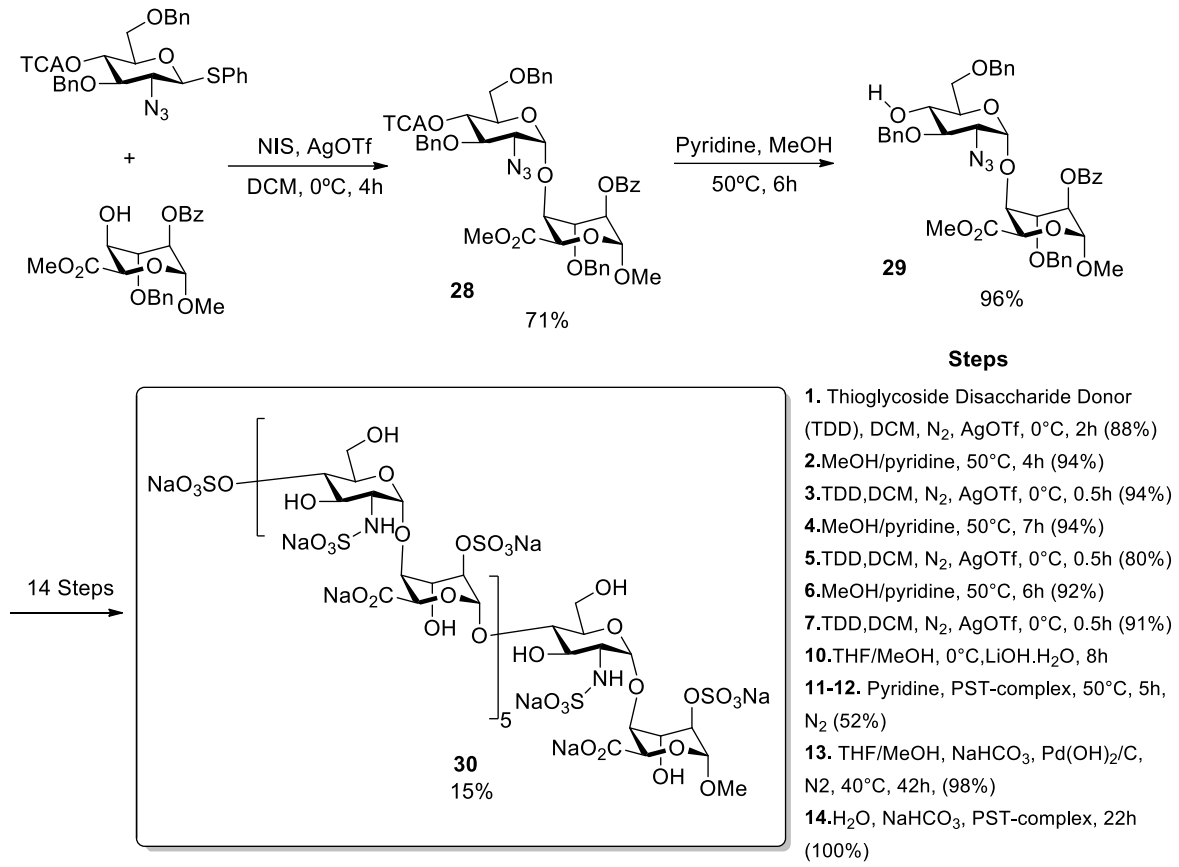
The efficacy of the use of heparin in therapeutic anticoagulation prior to the development of thrombosis in COVID-19 has not been systematically evaluated, but it may prove beneficial in treating the coagulopathy of this disease. Also, the non-anticoagulant effects of heparin may be beneficial in COVID-19 treatment. For the balance of the benefits and risks of the heparin use, randomized clinical trials of in COVID-19 are urgently needed.[48,49]

More recently, Gozzo *et al.*[50] have shown that the use of coagulants in patients with severe COVID-19 is recommended although a final guidance cannot be implemented yet. Besides, heparin administration may be beneficial for patients with COVID-19, beyond the anticoagulant effect due to their properties as anti-inflammatory, immunomodulatory, anti-viral, and anti-complement activity. There is also some evidence that heparin may help preventing delirium in COVID-19 patients.[51]

Also, heparin was one of the drugs for emergency use authorization approved by the U.S. Food and Drug Administration (FDA) in April 2020 for the COVID-19 treatment.[52]

The heparin was first extracted in 1916 from the liver of dogs by Jay McLean.[53] However, due to its structural complexity, it was only in the late 1960s that its structure could be established.[54] Currently, heparin is obtained from extraction methods, and its major source is the porcine intestinal mucosa, where the material is present in low concentrations of ~160–260 mg/kg.[55] The methodologies for the extraction of heparin consist in the use of substances that promote digestion, hydrolysis and pH regulation, which are essential to release heparin from cells and proteoglycans.[55]

Since the heparin structure establishment, several studies were developed aiming to obtain it synthetically and in suitable quantities for large-scale production. For example, Arixta (Fondaparinux), a medication chemically related to low molecular weight heparins, is commercially available and it is synthesized in 50 steps. Another example was reported by Hansen and coworkers in 2012, where a heparin-related dodecasaccharide was obtained in 16 steps and 10% of overall yield, as shown in Scheme 4.[56,57] The synthesis performed by Hansen and coworkers, has the disaccharides **28** and **29** as intermediates, was the first example of a gram-scale synthesis of this compound. Considering the number of steps, a good overall yield is obtained.



Scheme 4. The first gram-scale synthesis described by Hansen and coworkers.

Nitazoxanide

Nitazoxanide (**33**) was first described in 1975 as a veterinary antihelminthic anti intestinal nematodes, cestodes, and liver trematodes. It has been reported in various human pathogens since then. It showed activity against enteric protozoa (Cryptosporidium parvum, Giardia lamblia, Entamoeba, Blastocystis hominis, Cyclospora, Isospora, etc.), helminths (Taenia saginata and Hymenolepisnanal) and bacteria (Clostridium, Bacteroides, Helicobacter) *in vitro* and some cases in clinical trials.[58] It has also shown activity against viruses (such as Hepatitis B and C viruses, Ebola virus (EBOV), and respiratory viruses of orthomyxoviridae, paramyxoviridae and coronaviridae classes, among others).[59–61] When in blood, nitazoxanide is rapidly hydrolyzed into its desacetyl derivative (tizoxanide) by plasma esterases. Tizoxanide is, hence, the active metabolite and can suffer glucuronidation, forming tizoxanide glucuronide. Only tizoxanide and its glucuronide form are eliminated in urine and feces.[59,62]

Nitazoxanide works as a noncompetitive inhibitor of pyruvate: ferredoxin oxidoreductase (PFOR). PFOR catalyzes the oxidative decarboxylation of pyruvate to CO_2 and acetyl coenzyme A in anaerobic bacteria and protozoa, which is an electron transfer reaction essential for their energy metabolism. Mammals' pyruvate dehydrogenase complex does not require ferredoxin and is not affected by nitazoxanide.[63] Nitazoxanide anionic form (pKa = 6.18) has four resonance structures, with a negative charge on the 5-nitro, N2', N3 nitrogen atoms, or the amide oxygen atom of its thiazolide structure (Figure 4). This anion, which has a favorable formation in physiological conditions, is required for the PFOR inhibition, interacting with the thiamine pyrophosphate (TPP) vitamin co-factor and abstracting a proton from its N4' amino group, thus preventing pyruvate binding to TPP.[64]

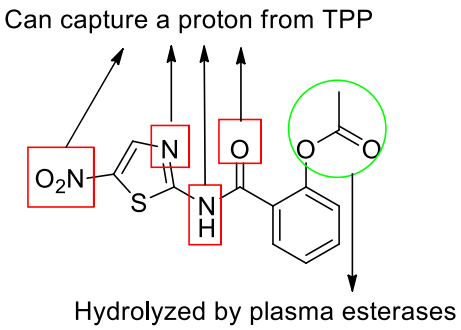
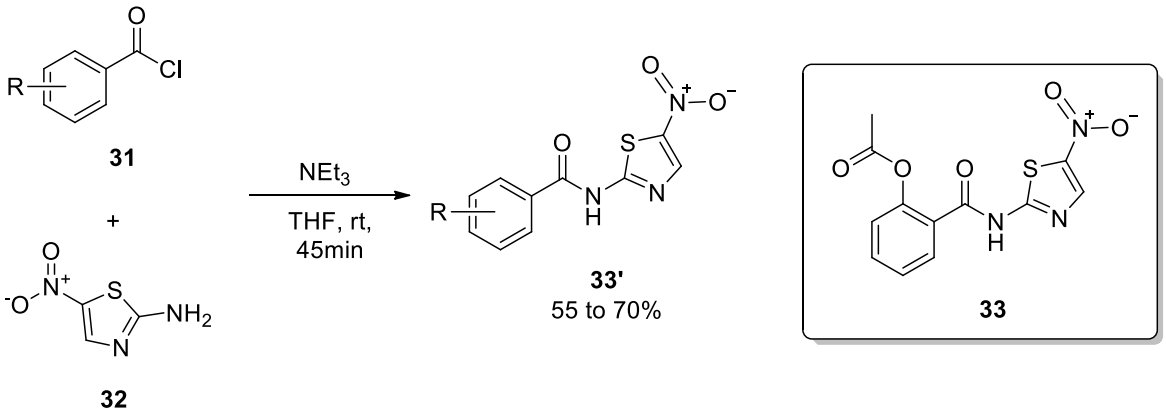


Figure 4. Nitazoxanide SAR.

In cases of viral diseases, the nitazoxanide action mechanism is not elucidated, but its broad-spectrum activity is attributed to host-regulated processes for viral replication, instead of a virus-targeted process, hence interacting with the host mechanisms that viruses target to bypass host cellular defenses.[65,66] Further modifications should be aimed at the nitro group of the thiazole ring, since work in the literature shows that a Cl group in that position results in good antiviral activity, although it diminishes the compound activity against anaerobic bacteria and protozoa. Another possible modification is in the ester group, aiming to change solubility and host absorption, lowering the dosage.[67]

It has a relatively favourable safety profile and has demonstrated *in vitro* antiviral activity against MERS and SARS-CoV-2.[68–70] However, Rossignol *et al.* have found that nitazoxanide is not efficient against other coronaviruses.[66,71] Rocco et *al*. have performed a randomized, double-blind, placebo-controlled trial, with 1,575 adult patients who presented up to 3 days after onset of COVID-19 symptoms (dry cough, fever, and/or fatigue). After confirmation of SARS-CoV-2 infection by RT-PCR on nasopharyngeal swab, patients were randomized 1:1 to receive either nitazoxanide (500 mg) or placebo, TID, for 5 days. Despite nitazoxanide not accelerating symptom resolution, the viral load was reduced significantly with no serious adverse events.[72] A recent study by Rossignol *et al.*, not yet peer-reviewed, showed evidence of disease progress reduction in mild and moderate cases of COVID-19 by early treatment with nitazoxanide in a double-blind randomized multicenter study with 379 patients.[73]

The first synthesis of nitazoxanide (**33**) was reported by Rossignol and coworkers.[74] In their study, N-(5-nitrothiazol-2-yl)benzamide derivatives (**33'**) were synthesized from the amidation reaction between benzoyl chloride derivatives (**31**) and 2-amino-5-nitrothiazole (**32**), in the presence of tetraethylamine (Scheme 5). The reaction yields ranged from 55 to 70%.[74] The reaction is advantageous, due the short reaction times in mild conditions. Other recent reactions are described in the literature; however, they are extremely similar to the one described by Rossignol in the 1970s, distinguishing in the solvent used or the reaction time.[59,74,75]



Scheme 5. The first synthesis of Nitazoxanide.

Ivermectin

Ivermectin (**35**) is commercialized since 1987 for use in humans as a treatment for onchocerciasis. Since then, it has been approved for other uses in humans against a broad spectrum of parasitic diseases, such as lymphatic filariasis, strongyloidiasis, and scabies. It is also used as an antiparasitic drug in veterinary medicine.[76–78] It works by irreversibly activating glutamate-gated chloride channels on the parasite's neurons, increasing their chloride conductance, and decreasing their response to excitatory inputs.[79]

As a derivative of the avermectins, ivermectin has a macrolide lactone structure, with a fused benzofuran structure, a disaccharide linked to carbon 13 and a spiroketal structure fused (Figure 5). Dehydrogenation of the double bond common to avermectins in carbons 22-23 of the ivermectin is responsible for a small increase in potency but accounts for a broader spectrum of action and better safety index.[80,81] The presence of the hydroxyl group in carbon 5 is also important for increasing nematicidal activity in the class.[79] The disaccharide is essential for biological activity, as species with a monosaccharide have highly reduced activity at glutamate-gated chloride channels.[82]

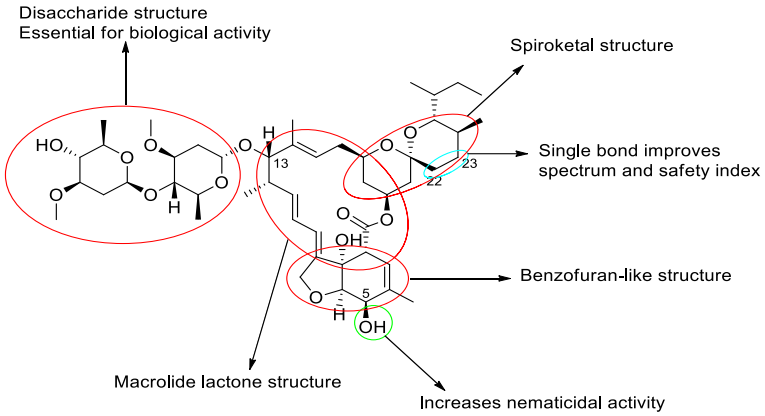


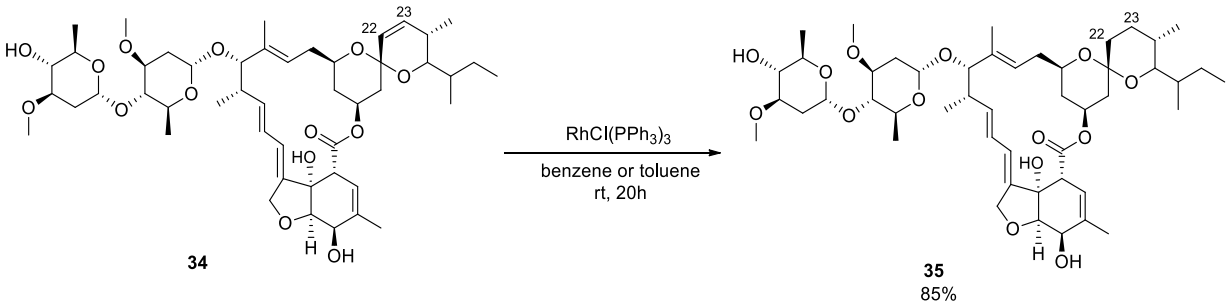
Figure 5: Ivermectin SAR.

More recently, it has been discovered that ivermectin has also antiviral activity, with a general proposed mechanism where it binds to host importin α nuclear transport protein, affecting its thermal stability and α-helicity, which prevents its binding to importin β1, therefore inhibiting virus protein nuclear transport.[83] The main problem with ivermectin as an antiviral is its poor oral bioavailability and high dosage needed for antiviral activity, so further modifications should focus on enhancing its solubility in water, while maintaining a good efficacy against viruses.[84]

Cali *et al.* have reported that Ivermectin has shown broad-spectrum antiviral activity *in vitro*, it is an inhibitor of the SARS-CoV-2, with a single addition to Veroh/SLAM cells 2 h post-infection.[78] However, despite being a well know medicine, the use in high doses, as such as in the previous study to combat COVID, could have adverse reactions.[85] Recently, the Merck group has published a statement on Ivermectin use in COVID-19 treatment, saying: "*No scientific basis for a potential therapeutic effect against COVID-19 from pre-clinical studies; No meaningful evidence for clinical activity or clinical efficacy in patients with COVID-19 disease, and; A concerning lack of safety data in the majority of studies*".[86] Despite that statement, more recent studies and reviews show evidence of symptom improvement and moratlity reduction, but cientifically-rigorous randomised controlled trials are still necessary to support its use.[87–94] Among those studies, it is important to highlight a systematic review with meta-analysis using the GRADE approach that concludes with moderate-certainty evidence that ivermectin is responsible for large death reductions of COVID-19 patients.[94] A double-blind, placebo-controlled, randomized trial with an estimated enrollment of 15000 participants is undergoing, sponsored by the National Center for Advancing Translational Science, of the USA, to evaluate the use of ivermectin treatment for COVID-19.[95]

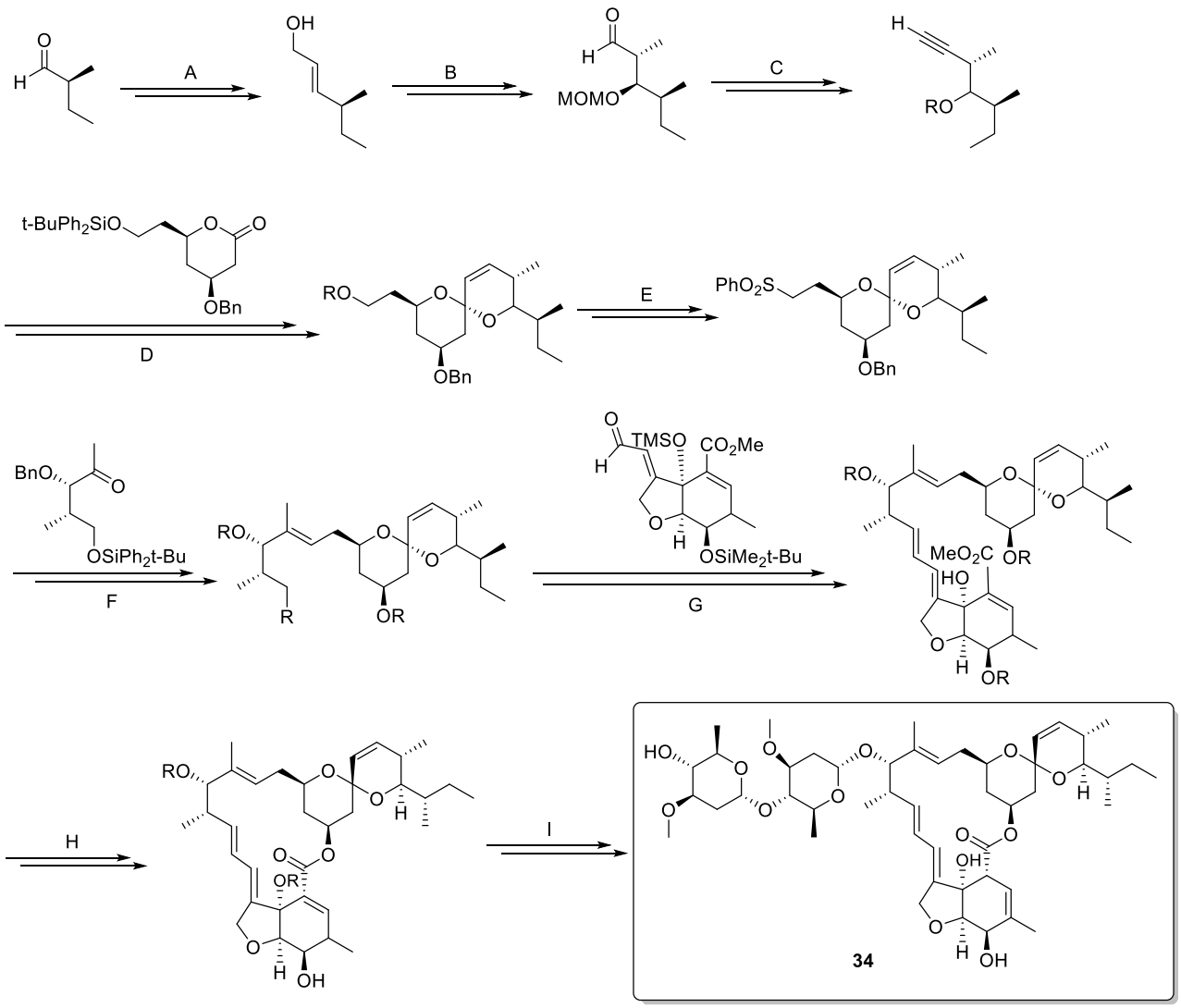
The avermectins are obtained from the fermentation of the fungus *Streptomyces avermitilis*.[96] The first reports on the ivermectin (**35**) synthesis date from the 1980s, where it was obtained from a structural modification of Avermectin B1a (**34**) (Scheme 6).[97] Avermectins and ivermectins differ from each other by the presence of a double bond. Such unsaturation present in Avermectin

B1a (**34**), can be selectively reduced with Wilkinson's catalyst ($RhCl(PPh_3)_3$), that is a very sensitive catalyst to the steric environment of an olefin, leading to the formation of ivermectin in 85% yield, over a reaction time of almost 1 day (Scheme 6).[97]



Scheme 6: Ivermectin synthesis from Avermectin B1a.

Several works about avermectins total synthesis have been published. The synthetic route described by Hanessian and coworkers is highlighted.[98] The avermectin B1a, the ivermectin precursor, is obtained in several multi-steps as shown in Scheme 7. Here, the details about some steps are not shown.[98] The synthesis of Avermectin B1a has many steps leading to extremely low overall yield (<0.003%). In addition, the molecule has 20 chiral centres, increasing the synthetic challenge.



*REACTION CONDITIONS AND STEPS: ***A (2 steps, 81.9%)***: (1) Ph_3=$CHCO_2CH_3$, benzene, reflux; (2) DIBAL-H, DCM. ***B (6 steps, 65.5%)***: (1) Ti(O-*i*-Pr)$_4$, D-diethyltartrate, *t*-BuO_2H, -45 ºC; (2) $Me_2Cu(CN)Li_2$, Et_2O, 0 ºC; (3) *t*-$BuPh_2SiCl$, imidazole, DCM, -10 ºC; (4) MOMCl, *i*-Pr_2NEt, DMAP; (5) n-Bu_4NF, THF; (6) PCC, 4Å sieves, DCM. ***C (4 steps, 65.5%)***: (1) *n*-BuLi, Et_2O, -78 ºC, add lactone (above the reaction arrow), PPTS; (2) Pd/$BaSO_4$-C, H_2, EtOAc, pyridine; (3) $BF_3.Et_2O$, THF; (4) *n*-Bu_4NF, THF. ***E (2 steps, 76.5%)***: (1) PhSSPh, Ph_3P, THF; (2) *m*-CPBA, DCM, -10 ºC. ***F (9 steps, 5%)***: (1) *n*-BuLi, THF, -78 ºC, add ketone (above the reaction arrow); (2) $SOCl_2$, pyridine, Na-Hg, MeOH; (3) *n*-Bu_4NF, THF; (4) Li/NH_3; (5) *t*-BuCOCl, Et_3N, DCM; (6) *t*-$BuMe_2SiCl$, imidazole, DMAP, DMF; (7) NaOMe, MeOH, DCM; (8) PhSSPh, *n*-Bu_3P, THF; (9) *m*-CPBA, DCM. ***G (3 steps, 14%)***: (1) *n*-BuLi, THF, - 78 ºC, add compound above the reaction arrow; (2) $SOCl_2$, pyridine, Na-Hg, MeOH; (3) *n*-Bu_4NF, THF. ***H (5 steps, 13.6%)***: (1) KOH(aq), THF, Dowex 50 (H^+); (2) DCC, DMAP, DCM; (3) *t*-$BuMe_2SiCl$, imidazole, DMF; (4) 2-pyridyl thioglycoside/DCM, AgOTf/toluene; (5) Me_3SiCl, Et_3N, DMAP, DCM. ***I (2 steps, 28%)***: (1) LDA, Me_3SiCl, THF, -78 ºC; (2) *n*-Bu_4NF, THF.

Scheme 7: Avermectin B1a (**34**) synthesis described by Hanessian.

Ribavirin

Ribavirin (**41**) was originally synthesized in 1972 as a guanosine analog and it is the first synthetic nucleoside to exhibit a broad-spectrum antiviral activity against both RNA and DNA viruses. It is used in HCV (Hepatitis C) treatment, although ribavirin monotherapy shows a modest effect on HCV RNA concentrations,[99,100] adding ribavirin to IFN-α-based therapy significantly improved the likelihood of achieving a cure,[101,102] therefore having a sustained virological response. Currently, the use of ribavirin in HCV therapy has decreased, but it continues to be recommended concomitantly with direct-acting antiviral treatments without Interferon,[103] especially for HCV genotype 3 infection. In addition, ribavarin is used in respiratory syncytial virus (RSV) infections, viral hemorrhagic fevers, chronic hepatitis E virus infections, among other viral infections,[104] and is also tested against infectious agents such as poliovirus[105] and influenza virus.[106,107] For example, among HCV decompensated cirrhotic patients enrolled in the ASTRAL-4 trial treated with sofosbuvir and velpatasvir, the highest sustained virological response rate was seen among those who

also received ribavirin.[108] Thus, ribavirin will likely continue to be part of the arsenal against HCV, especially in the context of decompensated cirrhosis (Child-Pugh B or C), as protease inhibitors are contraindicated in this scenario.[103,109]

Kinetic pharmacological studies carried out in healthy volunteers who received 150 mg of intravenous ribavirin followed after 1 h by an oral dose of 400 mg showed that ribavirin has an average bioavailability of 52% ± 22% and an average half-life of 37 ± 14 h.[110] Its elimination depends on renal function and therefore requires more than 4 weeks to reach steady state concentrations.[111–113] It is a prodrug when inside the host cells it suffers phosphorylation on the 5' hydroxyl group (Figure 6) to ribavirin mono-, di- and triphosphates,[114] which are the active species. Despite being a synthetic purine nucleoside, Ribavirin's carboxamide makes it behaves similarly to guanosine.[114] Further modifications could focus on modifying the phosphorylation site, aiming to increase cell permeation and further phosphorylation.[115]

The precise mechanism of action of Ribavirin is not clear, although five primary mechanisms have been proposed. The first mechanism is the competitive inhibition of inosine monophosphate dehydrogenase (IMPDH) by ribavirin monophosphate, which reduces guanosine monophosphate production, and results in a lack of guanosine triphosphate (GTP), essential for RNA and DNA replication.[104,114] A second mechanism is by the impact of host cell gene expression and immunomodulation since ribavirin alters the host level of GTP. The third mechanism is inhibition of viral and host mRNA capping, since ribavirin triphosphate acts as a competitive inhibitor in the process, leading to impaired translation.[104,114] A fourth mechanism is the inhibition of viral RNA polymerase by ribavirin triphosphate in competition with both adenosine triphosphate (ATP) and GTP. The fifth mechanism suggests that ribavirin enhances viral mutagenesis, by incorrect substitution of ribavirin triphosphate for GTP into viral RNA, leading to an error catastrophe, since ribavirin carboxamide makes it capable to pair both with uridine and cytidine triphosphates.[104,114]

A clinical concern in the development of antivirals is whether the target virus can develop resistance to the antiviral agent and what impact this resistance will have on disease progression and on the pathogenicity of the virus population. The discovery of populations of ribavirin-resistant viruses has begun to shed light on these issues and provides some information on the mechanism of action of ribavirin. Young and coworkers isolated the first clinical variant of ribavirin-resistant HCV from patients treated with ribavirin monotherapy.[116] An amino acid substitution in NS5B RdRp (F415Y in NS5B) was detected in all treated patients. After treatment interruption, reversion of this residue to phenylalanine was observed in some patients. The characterization of ribavirin-resistant viruses suggests that ribavirin may be especially potent in an antiviral "cocktail", where ribavirin is presumed to act by lethal mutagenesis. Ribavirin-induced mutagenesis should select for high-fidelity replication, reducing the number of variants in the virus population. This should reduce the population's ability to adapt to simultaneous antiviral therapy for an unrelated mechanism.

Besides being approved for the treatment of HCV and RSV, Ribavirin has been evaluated in patients with SARS and MERS, that could have an uncertain potency against COVID-19, but it has side effects such as anaemia, that may be severe at high doses.[117] A multicenter, retrospective cohort study of 2037 COVID-19 patients admitted to 4 hospitals in Hubei Province in China, from 31 December 2019 to 31 March 2020, with 1281 receiving ribavirin, interferon-α or a combination of both treatments and 756 receiving none of these treatments concluded that there was no evidence of improvement of clinical outcome for those therapies with Ribavirin against COVID-19.[118]

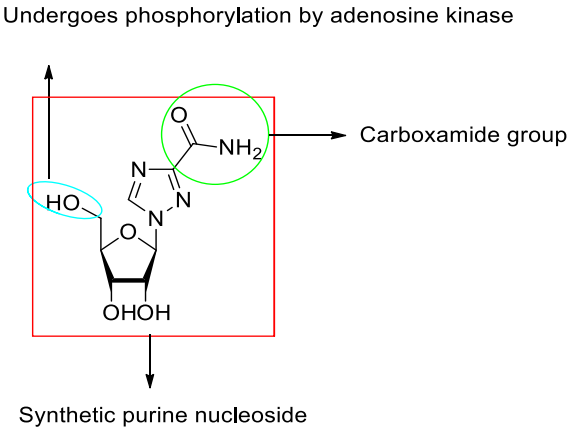
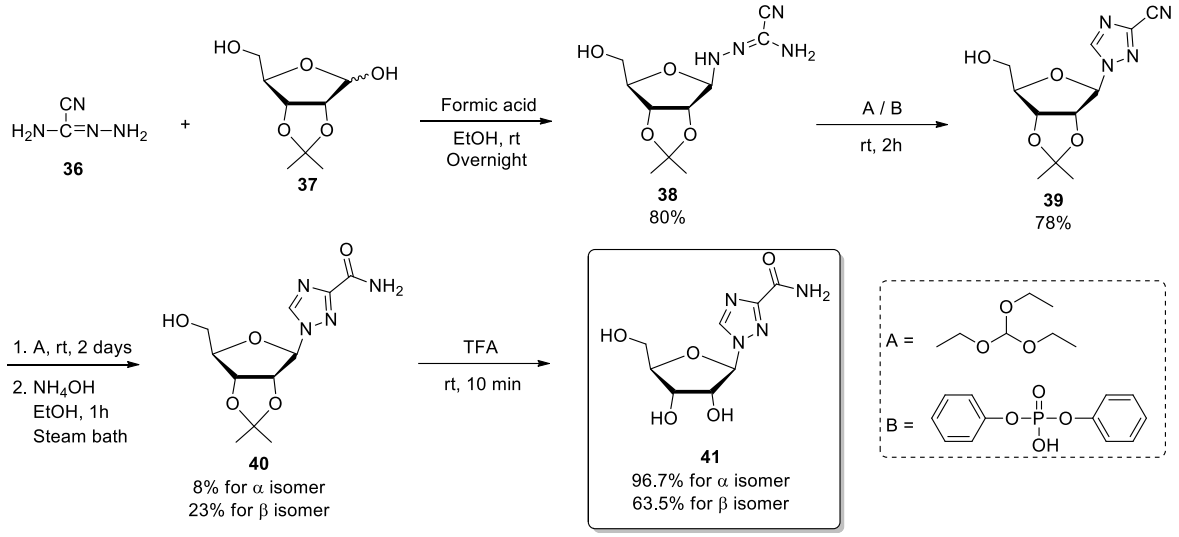


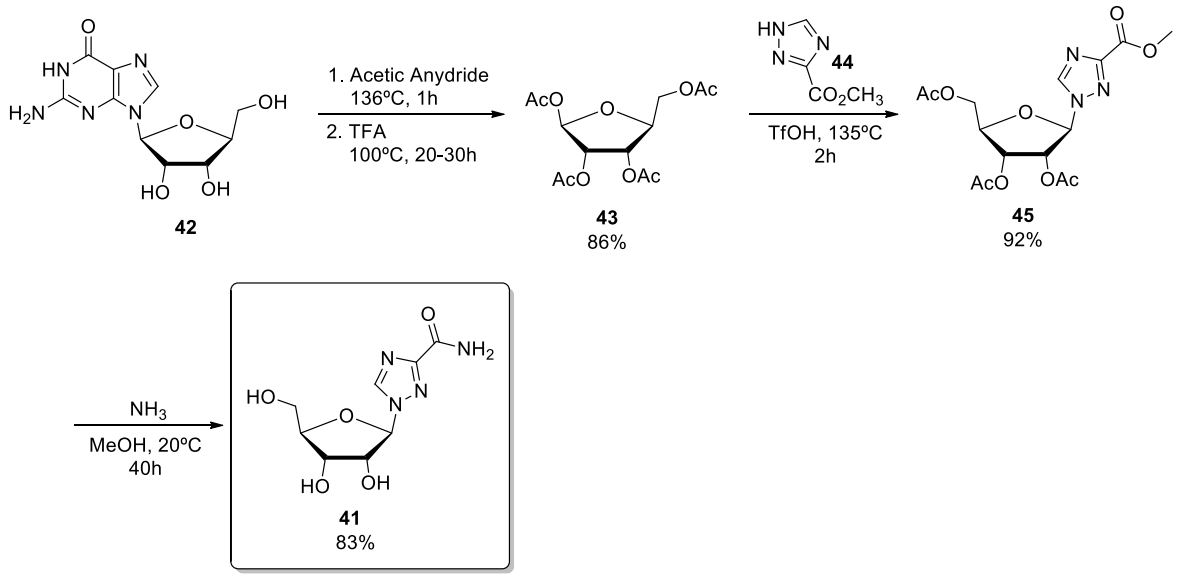
Figure 6. Ribavirin SAR.

One of the first synthesis of ribavirin is described in Scheme 8. In the first step of this route, the reaction between the carbamohydrazonoyl cyanide (**36**) and the protected D-ribose (**37**) lead to the formation of compound **38**, in a condensation reaction. In sequence, through a cyclization reaction the intermediate **39** is obtained. After that, the ribavirin (**41**) is obtained by nitrile hydration reaction of **39**, affording the compound **40**, followed by the removal of the isopropylidene protecting group.[119]



Scheme 8. One of the first synthesis of Ribavirin.

A more recent approach to the synthesis of ribavirin and its analogues, is the use of nucleosides as starting material.[120,121] This methodology has been described by Li and coworkers, where ribavirin (**41**) was synthesized in just three steps from guanosine (**42**) with better global yield, as can be seen in Scheme 9.[120] In this methodology the guanosine (**42**) is subjected to an acetylation reaction, followed by a cleavage of purine nucleosides to obtain **43**. The compound **43** reacts with a triazole-carboxylate derivative (**44**) to afford **45**, which undergoes an ammonolysis to produce ribavirin (**41**).[120,121]



Scheme 9. Ribavirin Synthesis from nucleosides.

Favipiravir

Favipiravir (**51**) was developed as an antiviral drug and was subsequently approved as an anti-influenza medicine in Japan in 2014.[122] In addition, it has been stored as a countermeasure for new strains of influenza. It has a broad-spectrum activity against RNA viruses *in vitro*, including arenaviridae, bunyaviridae, flaviviridae, orthomyxoviridae, and paramyxoviridae, among others; but it has no activity against DNA viruses.[122,123] It has also been used for the treatment of human infection with Ebola virus, Lassa virus, rabies and severe fever with thrombocytopenia syndrome (SFTS).

This compound is a prodrug, it is phosphoribosylated in cells to favipiravir triphosphate (Figure 7), which inhibits viral replication.[122] The fluoro group in the structure improves favipiravir binding energy with the RNA polymerase.[124] The literature shows that the nitrogen atom that suffers phosphoribosylation is a good target for structural modifications, although the attempts to obtain the favipiravir riboside or the monophosphate showed that its bond is prone to cleavage and the compound had poor solubility.[125]

The best feature of favipiravir as an antiviral agent is the apparent lack of generation of favipiravir-resistant viruses. In monotherapy treatments, this drug maintains its therapeutic efficacy from the first to the last patient in an influenza pandemic or epidemic lethal RNA virus infection.[21] Favipiravir is expected to be an important therapeutic agent for severe influenza, the next strain of influenza pandemic and other serious RNA virus infections for which there are no standard treatments available.[123] It has been experimentally found that favipiravir cured all mice in a model of lethal influenza infection, while oseltamivir (Tamiflu) could not cure the animals. Thus, favipiravir contributes to the cure of animals with a lethal infection. The ability to predict the onset of an avian influenza pandemic remains a challenge, but a strategy adopted is to stock vaccines and anti-influenza drugs for new strains of this virus to deal with pandemics. The specific characteristics, the mechanism of action and the fact that favipiravir does not produce resistant viruses among anti-influenza drugs suggests that it will play a central role among anti-influenza drugs in the treatment of an alleged lethal influenza pandemic.[122,123,126]

Although approved as an anti-influenza drug, favipiravir is only considered for administration in patients when the government judges that this drug will be used as a countermeasure for novel or re-emerging influenza viruses. In addition, favipiravir is contraindicated for use in pregnant women because it exerts teratogenic and embryotoxic effects on animals. Recent clinical trials have been performed to assess its efficacy in treating SFTS in Japan[127] and as a combination therapy with oseltamivir to treat patients with severe influenza in China.[128,129] In addition to influenza, favipiravir has been submitted for additional indications for SFTS in Japan, based on clinical trials, indicating its outstanding feature as a broad-spectrum anti-RNA virus drug.[122,123]

Regarding Ebola virus infection, the effectiveness of favipiravir in post-exposure prophylaxis (PEP) was demonstrated in a study with mice.[130,131] These trials concluded that early treatment with favipiravir was effective in mice, but when the disease is advanced the effectiveness in prolonging survival is limited, indicating that treatment should be started before liver damage progresses to irreversible levels. Therefore, favipiravir may be able to cure an infection with the Ebola virus in the early stage of the infection, but the curative activity of favipiravir may be limited in patients with advanced infection. The dose of favipiravir used to treat a human with Ebola virus infection is 6,000 mg on the first day and 2,400 mg / day on days 1-9 for a total of 27,600 mg when administered for both PEP and treatment.[130–135]

The active form of favipiravir is incorporated in viral RNA in place of one of the purine nucleotides, guanosine, and adenosine. Some studies suggest that the incorporation of only one unit of favipiravir triphosphate prevents the RNA chain elongation and others that the consecutive incorporation of two units causes the chain termination.[122,123]

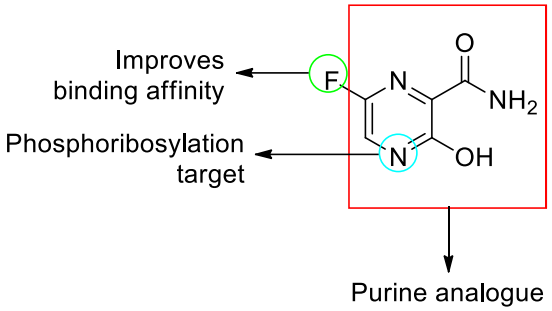
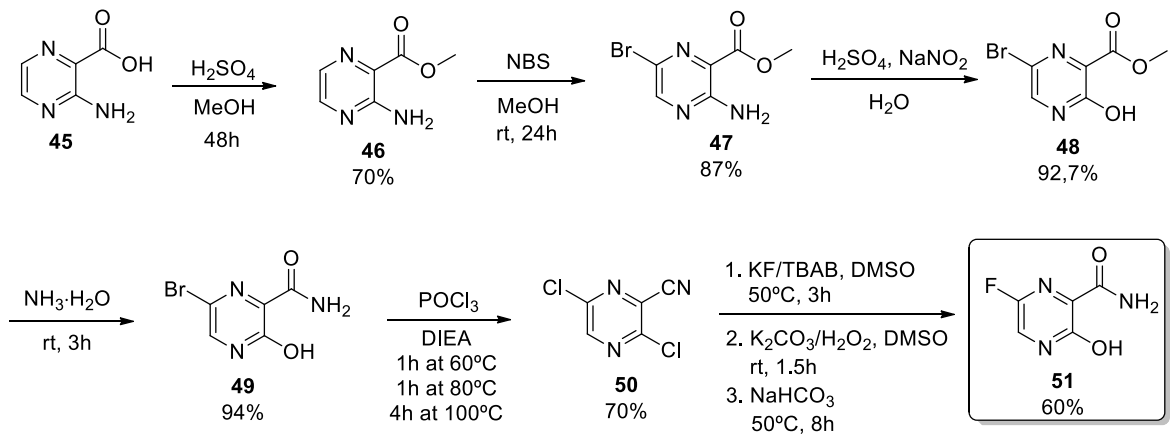


Figure 7. Favipiravir SAR.

Favipiravir has been studied in patients with 2019-nCoV in randomized trials in mice, the results suggest further *in vivo* studies are recommended to evaluate this antiviral nucleoside efficiency.[68] Clinical trials in China and Japan showed good potential for favipiravir use against COVID-19.[136]

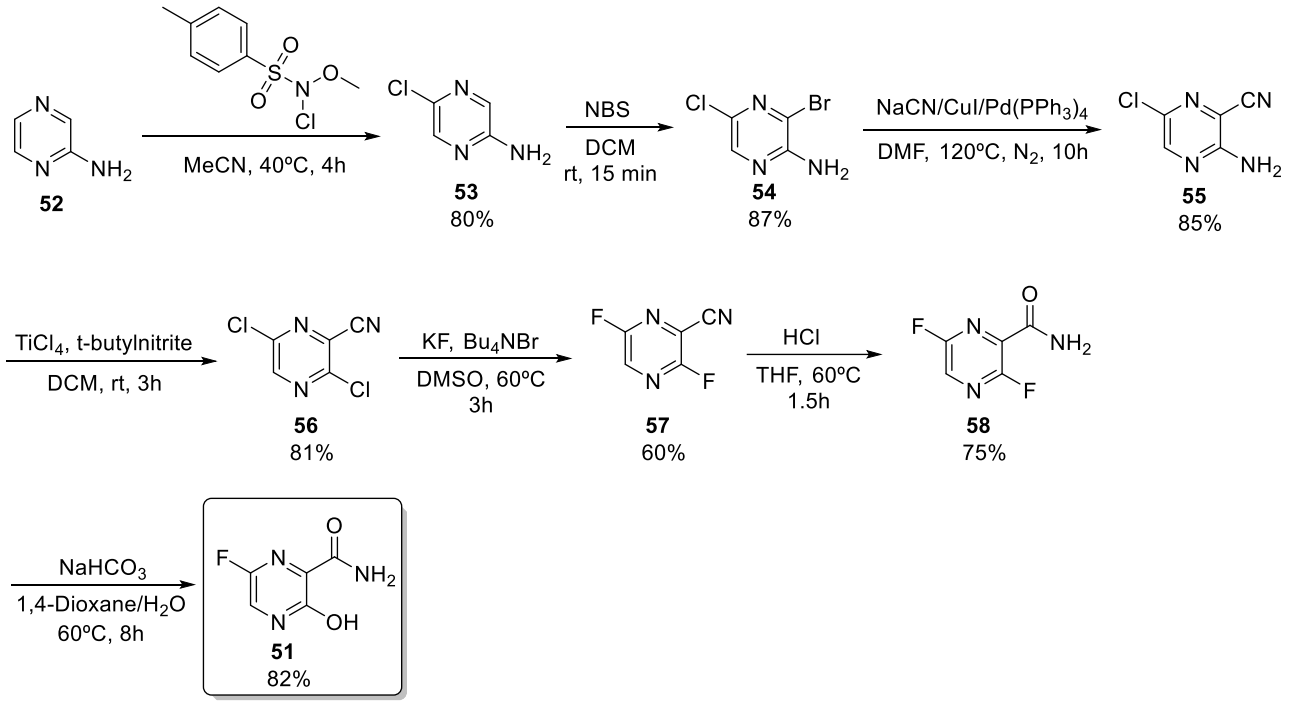
More recently, Dabbous and coworkers have conducted a clinical study using favipiravir in treatment of COVID-19. In this multicenter randomized controlled study patients with COVID-19 were randomly assigned to chloroquine (CQ) group and favipiravir group. In summary, they have found that in the favipiravir group none of the patients needed mechanical ventilation and one patient died, in comparison, two patients of the chloroquine group died. It is a promising result regarding the decreasing of the need of mechanical ventilation and hospital stay.[137] A systematic review and meta-analysis, conducted by Manabe *et al.* concluded that favipiravir can promote viral clearance and clinical improvement, especially in mild to moderate cases, but point to the need for additional evidence.[138]

The synthetic routes for Favipiravir (**51**) also known as T-705, use a pyrazine derivative as a starting material.[139–141] Some of these routes have disadvantages for industrial applications, such as low global yield and the use of expensive and toxic reagents. Based on that, Liu and coworkers recently reported a modified synthetic route of favipiravir (Scheme 10), obtaining the product with an overall yield of 22.3%.[139] In the first step of this synthesis, the compound **46** is easily obtained from the 3-aminopyrazine-2-carboxylic (**45**) in an esterification reaction. The bromation of the pyrazine ring of **46** is performed with NBS to afford the compound **47**. In the next step, the amino group is converted into a hydroxyl (**48**), followed by the transformation of the ester group into amide (**49**). Finally, a replacement of hydroxyl and bromine by two chlorines, as well as the conversion of the amide into a cyano group using a Hunig's base (N,N-Diisopropylethylamine or DIEA) and $POCl_3$ leading to the compound **50** in high yields. In the last step, the favipiravir (**51**) is obtained by a one-pot reaction from **50**, through an improvement of a previous methodology described by Zhang and coworkers, with 60% yield. The reaction described by Zhang and coworkers, provided the favipiravir in 3 steps with only 40% yield.[139,140]



Scheme 10. Favipiravir synthesis described by Liu and coworkers.

Another interesting synthetic approach for the synthesis of favipiravir was described by Quo and coworkers, through the use of simpler starting material, such as aminopyrazine (**52**), as shown in Scheme 11.[141] In the first two steps of this synthetic route, the aminopyrazine (**52**) is converted to compound **54** through two halogenation reactions, using N-chloro-N-methoxy-4-methylbenzenesulfonamide for chlorination (**53**) and NBS for bromination (**54**). The compound **55** is obtained when the bromine atom is replaced by a nitrile group using NaCN, which is a good nitrile donor in the coupling reaction catalyzed by $Pd(PPh_3)_4$.[141] In sequence, a Sandmeyer reaction occurs using $TiCl_4$/*t*-butylnitrile to obtain **56**, a nucleophilic fluorination using KF/Bu_4NBr gives **57** and an acid-mediated nitrile hydration leads to the formation of the compound **58**. Finally, the favipiravir (**51**) is obtained from compound **58** in a selective reaction using anhydrous $NaHCO_3$, replacing just one of the fluorine atoms.[141]



Scheme 11. Favipiravir synthesis from aminopyrazine.

Thus, as can be seen, despite the apparent structural simplicity of Favirapir (MW = 157.1 $g.mol^{-1}$), the synthesis of this drug has several steps, which use procedures well known to those working with organic synthesis. Even with these various steps, high global yields are achieved.

Remdesivir

Remdesivir or GS-5734 (**68**) is a monophosphoramidate prodrug of an adenine analog presenting a broad spectrum antiviral activity, including filoviruses, paramyxoviruses, pneumoviruses, and coronaviruses.[142] The Nucleoside analogs are a class of small-molecule antivirals which can directly inhibit viral transcription and replication by targeting the viral RNA-dependent RNA polymerase.[142,143] The remdesivir was selected from a library of candidates to target RNA viruses, like the Coronaviridae family (responsible for SARS, MERS, and COVID-19), Flaviviridae family (responsible for Dengue and Zika) and Filoviridae (responsible for Ebola Virus Disease) and have been also used as backbone components of combination therapies against both Human immunodeficiency virus (HIV) and Hepatitis C virus (HCV),[142,144,145] showing activity against dengue virus (DenV), parainfluenza type 3 virus (hPIV3), and severe acute respiratory syndrome coronavirus (SARS-CoV).[146] Due to the West Africa outbreak of Ebola Virus Disease (EVD) that occurred between 2013-2016 that library was tested against the EBOV, and remdesivir was one of the compounds that showed good activity against the virus.[147]

The compound activity was tested *in vitro* and *in vivo* for EVD,[147,148] and it is in the clinical trial phase, with a randomized clinical trial from the PALM Consortium Study Team.[149,150] It also showed good activity *in vitro* and *in vivo* for the *pneumoviridae*

(responsible for various upper respiratory infections) and *paramyxoviridae* (responsible for a great range of infections, from measles and mumps to bronchiolitis and pneumonia) families.[142,151]

Regarding SAR, remdesivir is a prodrug, so after administration, it is metabolized by intracellular nucleoside kinases to generate the respective nucleoside triphosphate (NTP) metabolite which is the pharmacologically active drug. Since the first phosphorylation is often rate-limiting, remdesivir has a phosphoramidate group so it can bypass this initial step to the triphosphate metabolite. The phosphoramidate group also improves cell membrane permeation.[152] Recent work in the literature suggests that remdesivir can be modified in the NH_2 group of the adenosine analogue, to enhance binding with viral proteins.[153] There is also some works suggesting modifications in the ester alkyl group to enhance protein binding.[154,155]

Remdesivir was the first approved antiviral drug by the FDA, in October 2020, for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms for the treatment of COVID-19 requiring hospitalization.[156] It is also approved by regulatory agencies of other countries, such as ANVISA in Brazil.[157]

As an adenosine analogue (Figure 8), remdesivir NTP metabolite competes with ATP binding with the virus RdRp. By bonding with the virus RdRp the metabolite can inhibit virus replication, probably by the delayed chain termination mechanism.[158] The presence of the cyano group in remdesivir structure is responsible for its selectivity toward viral polymerases without significant toxicity for the host.[147]

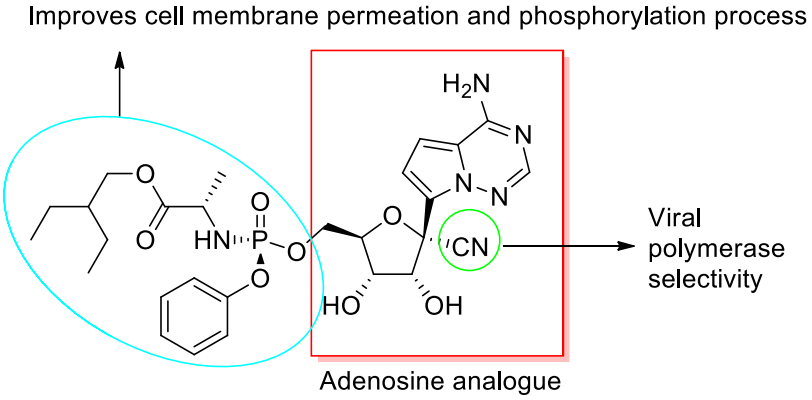
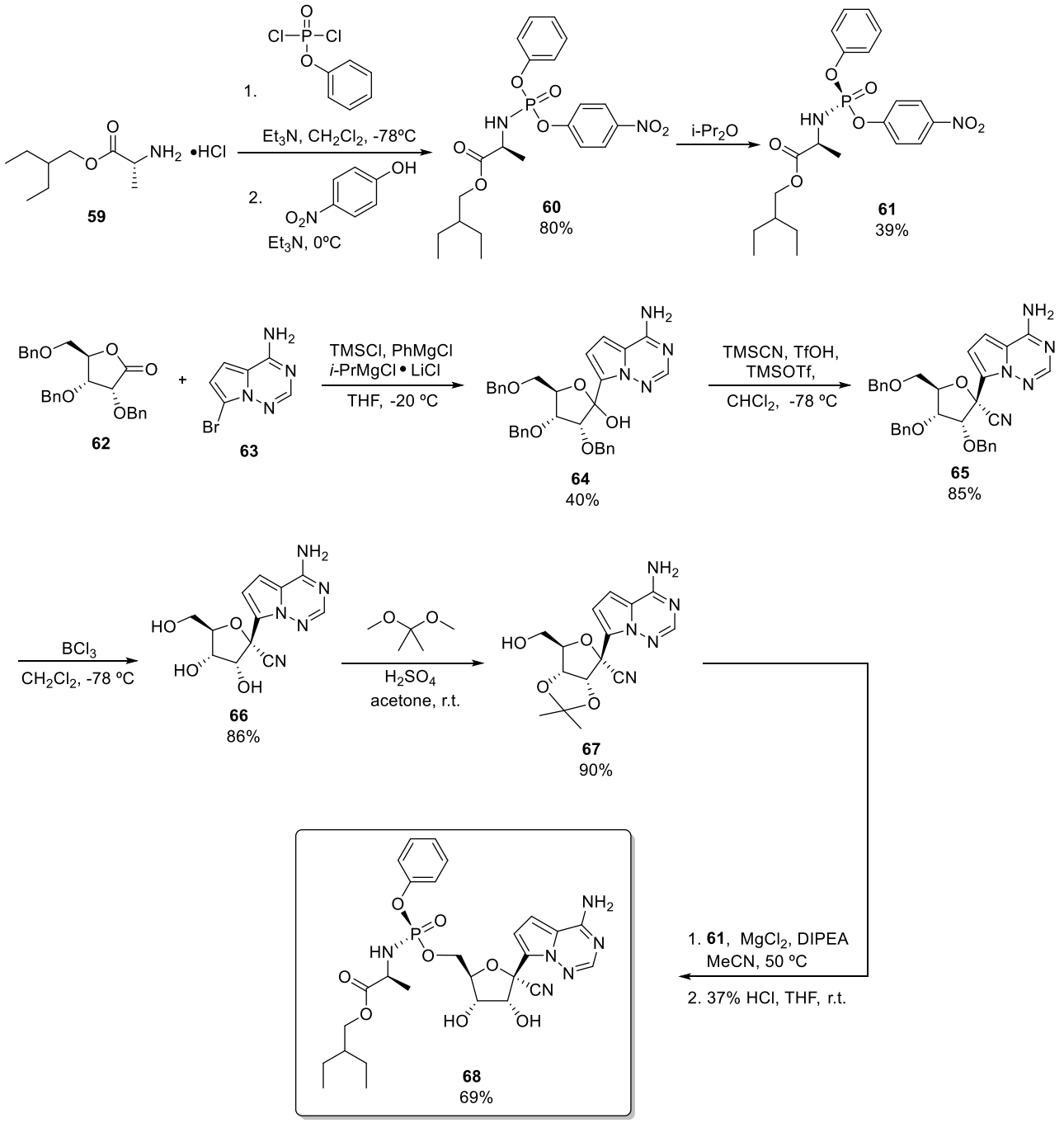


Figure 8. Remdesivir SAR.

Therapeutic remdesivir treatment has a clear clinical benefit in SARS-CoV-2-infected rhesus monkeys. When the treatment is initiated early during infection, the remdesivir administration seems to exert significant antiviral and clinical effects (reduced pulmonary infiltrates and virus titres in bronchoalveolar lavages *vs* vehicle only). These data supported early remdesivir treatment initiation in COVID-19 patients to prevent progression to severe pneumonia.[159,160] Recent studiesindicated that remdesivir has beeneffective in the treatment of children aged 7-16 years with comorbidities in severe cases of COVID-19, with a low rate of serious adverse events.[161] Furthermore, other studies indicate that remdesivir is able to promote clinical improvement in a retrospective study with patients aged 46-69 years, predominantly non-white hospitalized and that co-administration of corticosteroid does not reduce time to death compared with redemsivir administered alone.[162] A more detailed study funded by the WHO Solidarity Trial Consortium indicated that remdesivir, as well as other drugs mentioned in this Review (hydroxychloroquine and lopinavir) had little or no effect in patients hospitalized with COVID-19, indicated by the overall mortality, onset of ventilation and hospital ventilation.[163] As one of the most promising drugs so far, remdesivir was studied in both non-randomized tests and randomized ones.[164–166] A systematic review and meta-analysis of both randomized controlled trials and non-randomized studies concluded that use of remdesivir attenuates the COVID-19 progression, indicating a significant improvement in the 28-day recovery rate, lowering the odds of mechanical ventilation or extracorporeal membrane oxygenation of the patients and presenting lower adverse drug reactions than the control group.[167]

Remdesivir was developed by Gilead Sciences in 2009.[168] Later, another synthesis was described in the literature. Here, a recent one is highlighted, where the prodrug is obtained in a diastereoselective synthesis, as described in Scheme 12.[143] The precursor **61** is prepared from 2-ethylbutyl-L-alanine (**59**) in two steps, firstly the compound **60** is obtained in a diastereomeric mixture, followed by crystallization in diisopropyl ether to obtain only the isomer **61**. In sequence, the nucleoside (**64**) is obtained through glycosylation reaction between **62** and **63**. Then, the hydroxyl group is replaced by the cyano group to afford the compound **65**. After that, a benzyl deprotection followed by acetonide protection with 2',3'-hydroxyl moieties, leads to the formation of **67** with 90% yield. Finally, remdesivir (**68**) is obtained in two steps reaction between **67** and **61,** using a Hunig's base in $MgCl_2$, followed by deprotection of the acetonide with concentrated HCl.[143] Reactional conditions for Remdesivir can be a problem, due to steps that are dependent on cryogenic temperatures and chiral chromatography. Besides, the crystallization step does not offer a high yield.



Scheme 12. Synthesis of Remdesivir.

Galidesivir

Galidesivir (**73**), also known as Immucillin A and BCX4430, a potent viral RNA-dependent RNA polymerase inhibitor, and another nucleoside derivative, was reported in 2014, as a broad-spectrum antiviral agent. It has activity against a wide range of viruses, such as arenaviridae, bunyaviridae, coronaviridae, flaviviridae, filoviridae, orthomyxoviridae, paramyxoviridae, picornaviridae and togaviridae families.[169,170] It is undergoing clinical trials to evaluate its safety, tolerability, and pharmacokinetics.[171]

This compound is an adenosine analogue (Figure 9), which is phosphorylated inside cells to galidesivir triphosphate. When incorporated in the viral RNA polymerase, it alters the polymerase electrostatic interaction, which causes premature termination of the RNA chain.[38,171,172] Due to its similarity with remdesivir, similar modifications could be made to galidesivir structure, aiming to enhance its selectivity to viral polymerase with the insertion of a CN group, or another group that could have a similar effect. The hydroxyl group could also be modified, to facilitate the phosphorylation of the prodrug into the active compound.

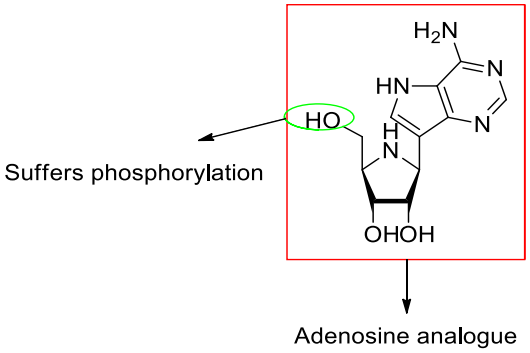


Figure 9. Galidesivir SAR.

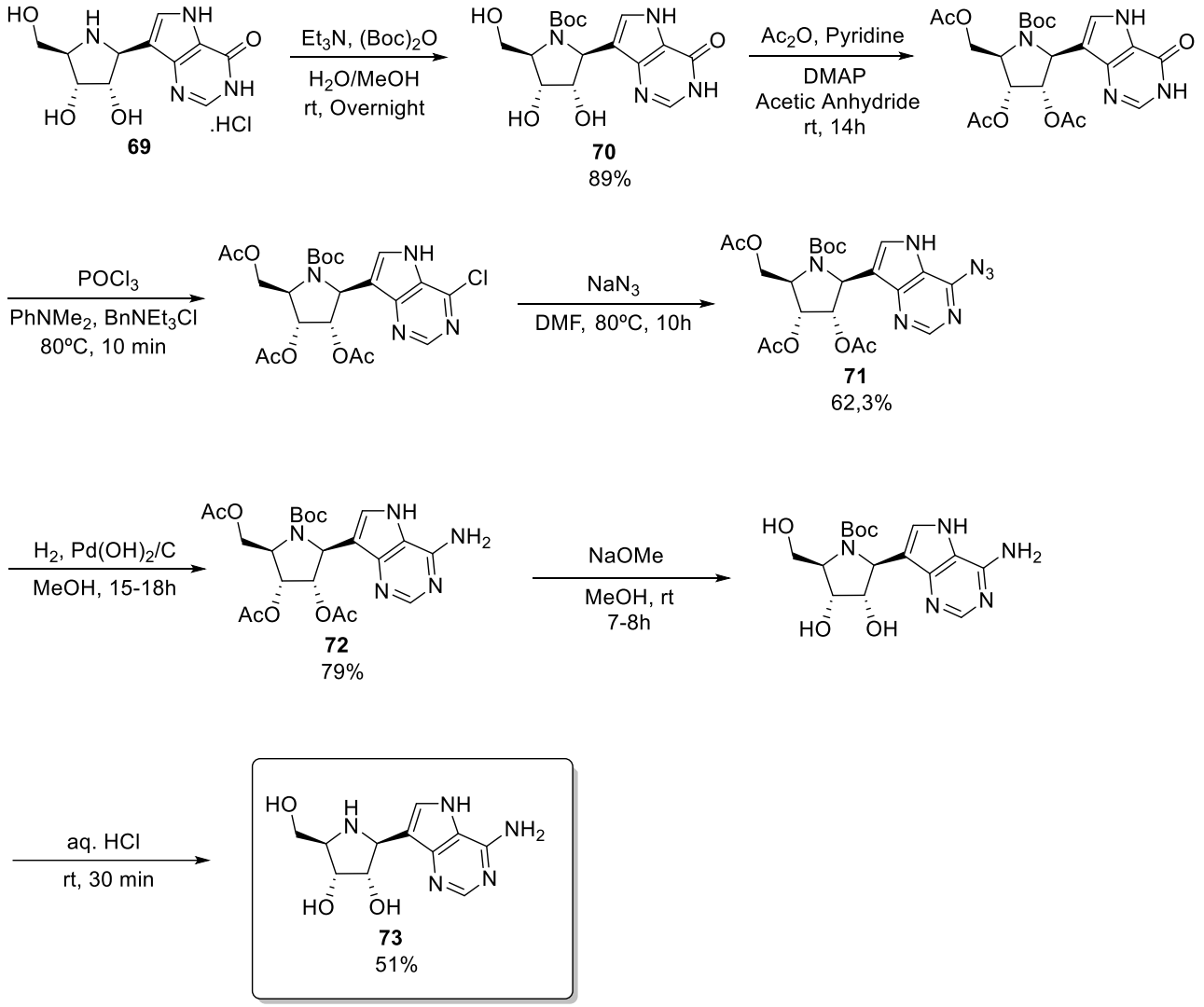
Galidesivir, although originally developed for HCV, has shown antiviral activities in preclinical studies against many RNA viruses, including SARS-CoV and MERS-CoV.[117] The use of this drug in the treatment of zikavirus (ZIKV) stands out for being interesting and efficient in pre-clinical studies in rhesus monkeys. The studies evaluated the efficacy of a range of loading and maintenance doses of galidesivir. The highest dose evaluated has been a loading dose of 100 mg/kg followed by a maintenance dose of 25 mg/kg for nine days. Animals infected on an intravaginal challenge were protected by galidesivir treatment, with no blood viremia and significant reductions in ZIKV RNA in the cerebrospinal fluid as compared with controls. Therefore, Galidesivir dosing in rhesus monkeys was well-tolerated and offered significant protection against ZIKV infection.[172,173]

Galidesivir has been shown to ameliorate hemorrhagic disease manifestations in Marburg virus infected cynomolgus macaques,[38,169] and could potentially be of value for other indications involving life-threatening viral diseases including Rift Valley Fever (RVF). The antiviral activity of this drug is known in preclinical *in vivo* analysis through evaluation in a lethal hamster model of RVF virus. Its high level of efficacy is comparable to that observed with another RdRP inhibitor, favipiravir, which was able to protect 70–80% of hamsters from lethal RVF virus challenge.[169,174] Galidesivir was considered in some initial assessments of candidate drugs for COVID-19 treatment due to its potential against SARS and MERS, but recent studies have not shown efficiency against SARS-CoV.[175–177]

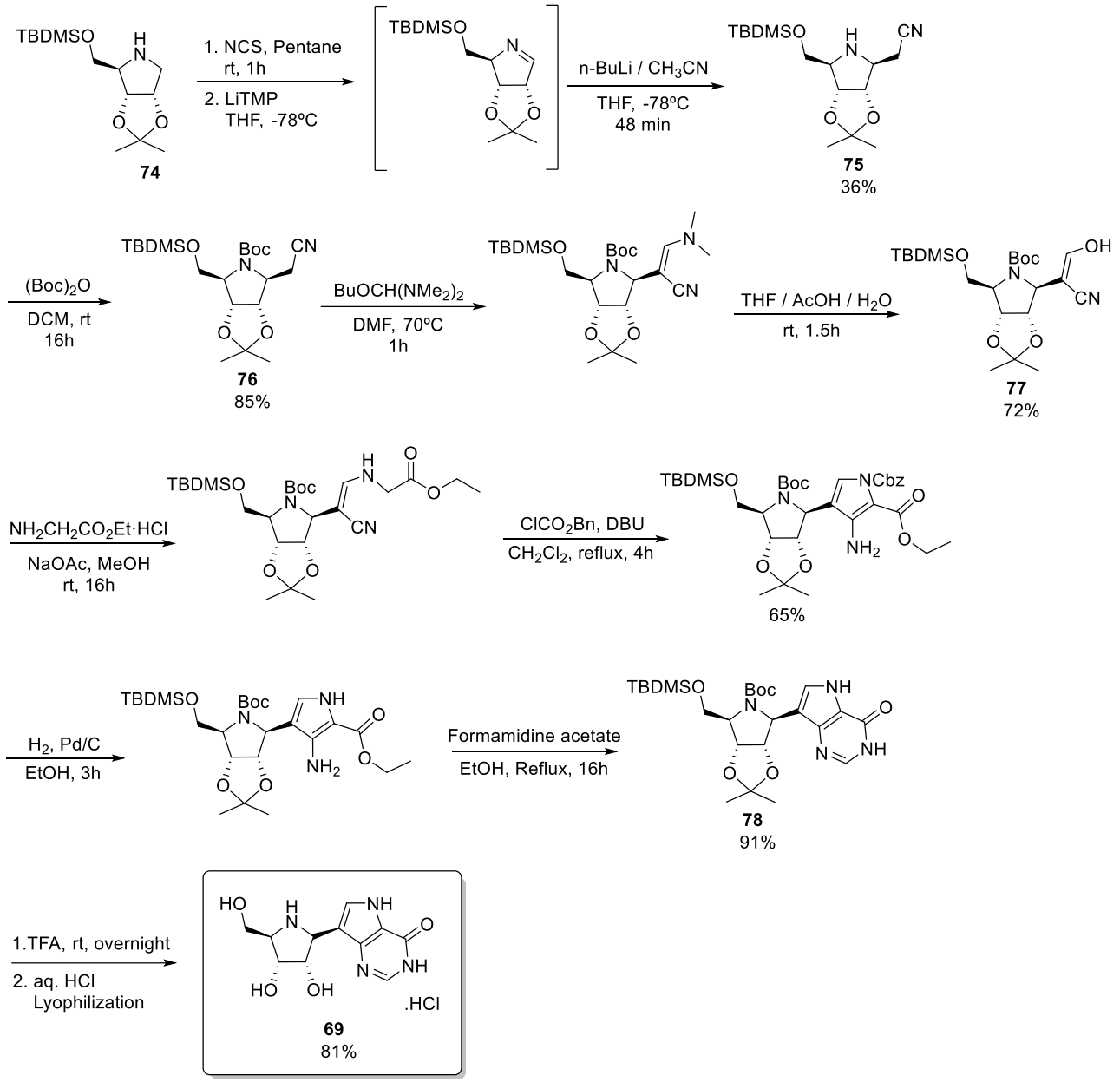
The first synthesis for Galidesivir is shown in Scheme 13. In this route, the Galidesivir (**73**) was synthesized from another nucleoside analogue, the Immucillin H or BCX1777 (**69**).[38] In the first step of this synthetic route, the nitrogen atom of pyrrolidine is protected with *tert*-Butyloxycarbonyl group (Boc), to afford the compound (**70**). After that, the compound **71** is obtained with 62.3% yield in three reaction steps, where the hydroxyl groups are acetylated, and the carbonyl oxygen is replaced by an N_3 group. Then, this group is reduced to amino via Pearlman's catalyst, to afford the compound **72**. Finally, in the last two steps, the hydroxyl groups and pyrrolidinic nitrogen are deprotected, leading to the formation of Galidesivir (**73**).[38]

The immucillin H, starting material in the galidesivir synthesis, can be synthesized in a few different ways as described in the literature.[38,172,178] Here, is described the synthetic route performed by Evans and coworkers in 2000, where the Immucillin H (**69**) is obtained in 10 reactional steps.[173] In the first two steps, a nitrile group is added to the pyrrolidine ring, to afford compound

75 with a yield of 36%. The pyrrolidinic nitrogen of this compound is protected with Boc, leading to the formation of **76** with 85% yield. In sequence, the compound **77** is obtained after the addition of $CHN(CH_3)_2$ and consequent replacement of the NMe_2 by OH, with 72% yield. After four more steps, the addition of $NHCH_2CO_2Et$ with ethyl glycinate hydrochloride/sodium acetate, cyclization of the pyrrole ring, reduction with Pd/C and cyclization of the pyrimidine ring, respectively, occurs the formation of **78**. Lastly, the Immucillin H (**69**) is obtained after deprotection, treatment with HCl and lyophilization (Scheme 14). Here, the steps of protection/deprotection, cryogenic temperatures and steps with long reaction times, make the synthesis of Galidesivir laborious.



Scheme 13. Galidesivir synthesis from Immucillin H (BCX1777).



Scheme 14. Immucillin H (BCX1777) synthesis.

Baricitinib

Baricitinib (**85**) was approved for use in 2017 in EU and in 2018 in USA by the FDA in patients with rheumatoid arthritis, as a targeted synthetic disease-modifying antirheumatic drug, a Janus-associate kinase (JAK) inhibitor affecting JAK 1 and JAK 2.[179,180] It is being tested against other diseases, such as atopic dermatitis (AD), a common chronic cutaneous inflammatory disease of childhood that reaches up to 25% of children, the treatment with baricitinib improved the signs and symptoms of moderate-to-severe AD. In addition, baricitinib is investigated as a treatment for systemic lupus erythematosus.[181,182]

The structure of baricitinib has a pyrrolo-pyrimidine core (Figure 10), which binds to JAK proteins adenine pocket, forming two hydrogen bonds with the hinge region of these proteins. The pyrazolyl, cyano, and sulfonyl groups interact with other JAK residues, via hydrogen or van der Waals bonds. This way baricitinib inhibits JAK 1 and JAK 2 signaling, which inhibit various proinflammatory cytokines involved in autoimmune diseases.[183–185] Modifications on baricitinib structure should preserve the pyrrolo-pyrimidine core, as this group is important for JAK binding. Possible targets for modification, according to the literature, could be both the sulfonyl group and the 3-cyanomethylazetidine moiety, aiming to enhance the efficacy as JAK inhibitor.[183]

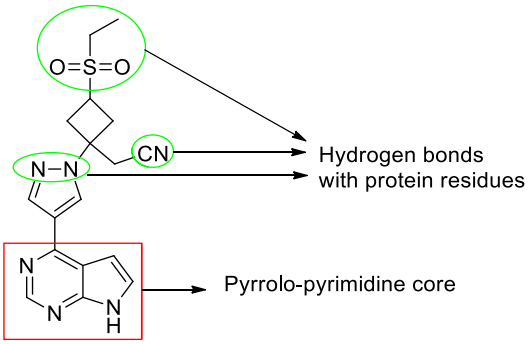
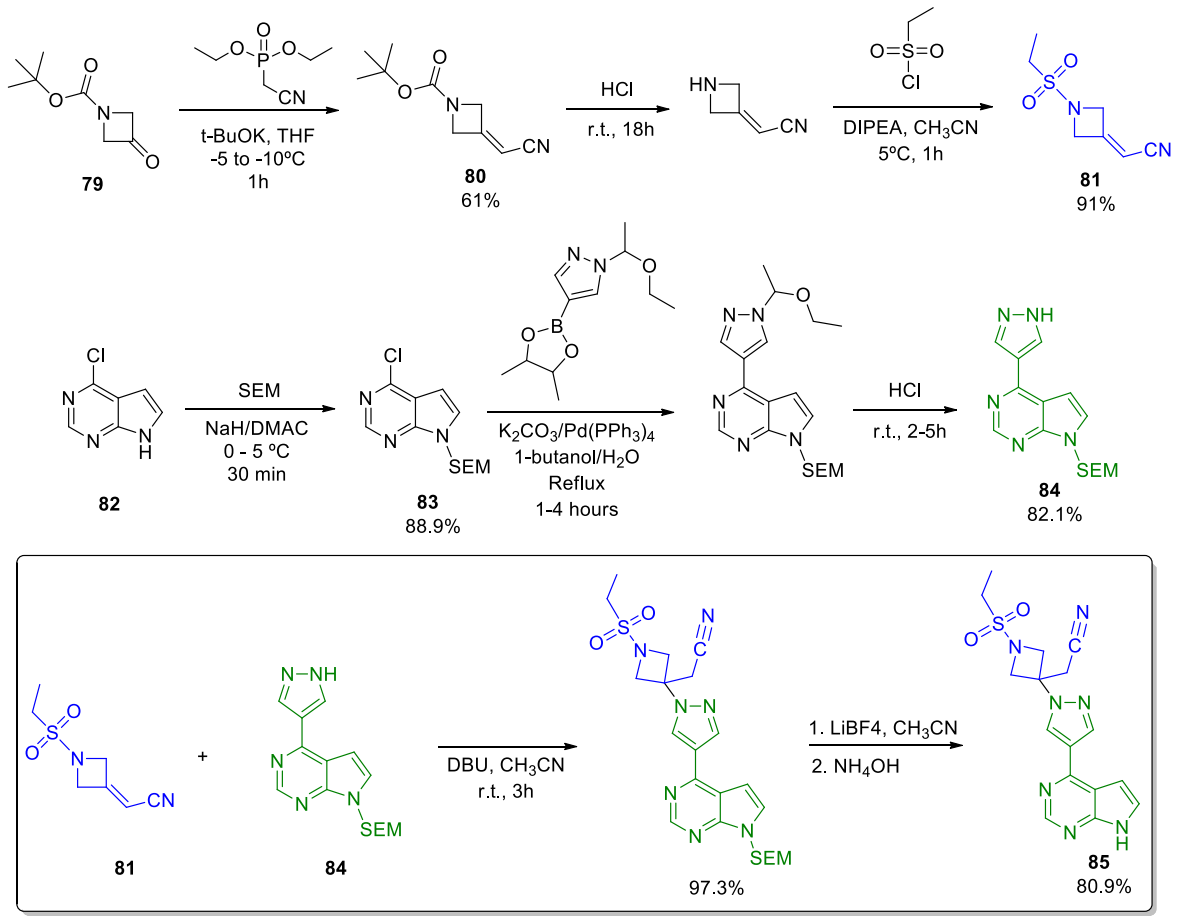


Figure 10. Baricitinib SAR.

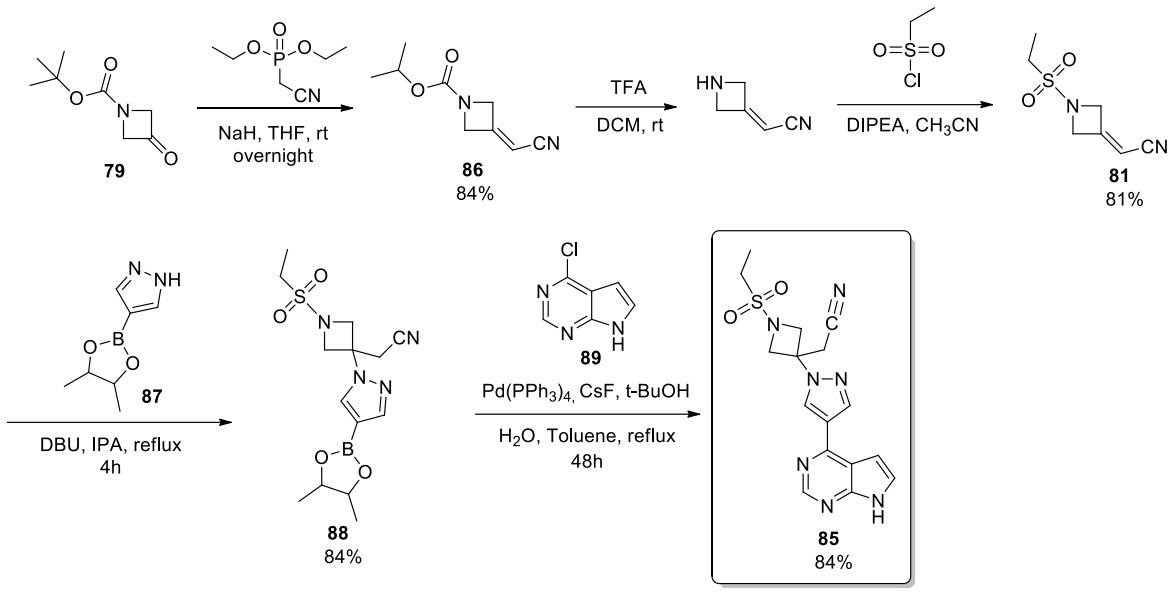
Cantini *et al.* have studied the efficiency of baricitinib in a therapy combined with lopinavir-ritonavir in moderate COVID-19 pneumonia patients and evaluated its clinical impact. The study was open-label design with no randomization and with a low number of treated patients. The patients were treated with baricitinib tablets 4 mg/day added to ritonavir-lopinavir therapy for 2 weeks. The control group, admitted before the date of the first baricitinib-treated, was treated with lopinavir/ritonavir tablets 250 mg/bid and hydroxychloroquine 400 mg/day/orally for 2 weeks. The preliminary results confirm the safety of baricitinib therapy and improved clinical and laboratory parameters.[186] Kalil and coworkers recently published a double-blind, randomized, placebo-controlled trial evaluating baricitinib in combination with remdesivir in 1033 hospitalized patients with Covid-19. All the enrolled patients received remdesivir and either baricitinib (515 patients) or placebo (518 patients, control). The primary outcome was the time to recovery. The key secondary outcome was clinical status at day 15. The combination of baricitinib and remdesivir was superior to remdesivir alone, slightly reducing the recovery time and giving 30% higher odds of improvement in clinical status at day 15.[187] Baricitinib has recently been studied as an anti-inflammatory agent for COVID-19 infection, it was found that a daily oral dose of 8 mg given for 14 days led to an early normalization of respiratory function, reduced need for ICU and intubation support, in addition to a decrease in the 30-day mortality rate. [188]

The first baricitinib convergent synthesis was described by Rodgers and coworkers in 2007. The baricitinib (**85**) is obtained through a nucleophilic addition reaction followed by the deprotection of trimethylsilylethoxymethyl group (SEM), between the intermediates **81** and **84**, as shown in Scheme 15.[189–191] The intermediate **81** is synthesized from tert-butyl 3-oxoazetidine-1-carboxylate (**79**). Firstly, the compound **79** is transformed into the compound **80** through the Horner–Emmons reaction, followed by the deprotection of N-Boc group in acidic conditions. Without further purification, this compound is subjected to a sulfonation reaction with ethanesulfonylchloride to obtain the compound **81**. The other intermediate, **84**, is synthesized from 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (**82**) through a synthetic methodology that involves the protection reaction with the SEM group to afford the compound **83**, followed by a Suzuki coupling reaction and hydrolysis reaction to afford the intermediate **84**. [189–191]



Scheme 15. Baricitinib synthesis described by Rodgers and coworkers.

In order to improve the baricitinib synthesis methodology, some new synthetic routes have been described in the literature in recent years.[189–192] In 2016, Xu and coworkers developed a new synthesis of baricitinib with an overall yield of 49%, in five steps, with simple operating requirements, low costs and plausible for industrial production.[189] In this methodology (Scheme 16) the starting material is the same as Rodgers's synthesis, tert-butyl 3-oxoazetidine-1-carboxylate (**79**). In the first step, the compound **79** is transformed into **86**, by Horner-Emmons reaction with NaH acting as a base. Followed by the deprotection of the N-Boc group and a sulfonation reaction with ethanesulfonyl chloride, without further purification, leading to the formation of compound **81**. The compound **88**, is obtained by the nucleophilic addition reaction between compound **81** and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-lH-pyrazole (**87**) in presence of DBU. Finally, the baricitinib (**85**) is obtained through Suzuki coupling reaction between the compounds **88** and **89**.[189]



Scheme 16. Baricitinib synthesis described by Xu and coworkers.

Bemcentinib

Bemcentinib (**92**) was licensed from Rigel Pharmaceuticals by BerGenBio and is an AXL receptor tyrosine kinase inhibitor. AXL overexpression is seen in a majority of human cancers, such as acute myeloid leukemia, breast, gastric and lung cancers, melanoma osteosarcoma, and renal cell carcinoma, among others.[193] Therefore, AXL inhibition could be a main or complementary strategy for cancer treatment.[194–196] This inhibitor is currently on phase I and II clinical trials.[197–201] Bemcentinib is a highly selective AXL inhibitor, working in nanomolar concentration (IC50 = 14 nM). It was the first AXL-specific tyrosine kinase inhibitor to enter clinical trials, in 2014.[196] There is also some evidence that AXL promotes zikavirus entry in human Sertoli cells, and it modulates the antiviral response of the host negatively. The use of Bemcentinib as an AXL inhibitor in Sertoli cells culture prior to viral infection decreases AXL expression, enhancing the antiviral response of the host and resulting in attenuation of the viral replication.[202]

Bemcentinib competes with ATP in the AXL kinase ATP-binding pocket, in the aspartate-phenylalanine-glycine active loop-in, which, in the end, inhibits cell growth and proliferation.[193,195]

There is some evidence that Bemcentinib also targes lysosomes. Due to its structure containing some amine (weak bases) groups (Figure 11), it can accumulate inside lysosomes in its protonated form, causing a pH changing, blocking protein degradation and recycling, and ultimately cell apoptosis.[203] A work in the literature suggests that changing the pyrrolidine ring for other groups could improve AXL binding and maintain selectivity.[193]

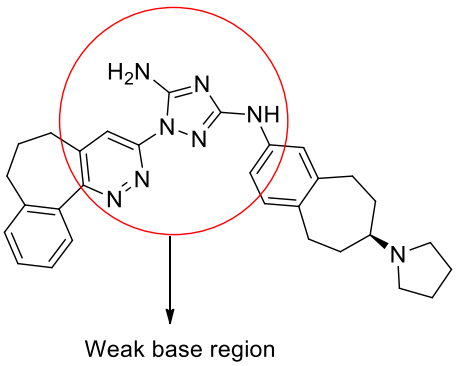
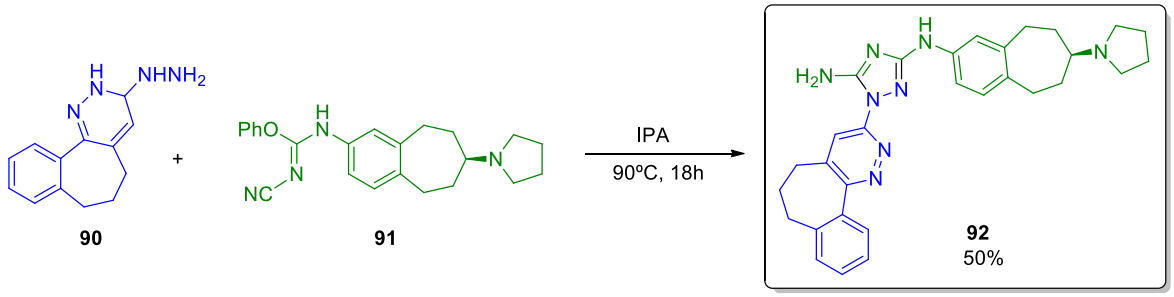


Figure 11. Bemcentinib SAR.

In April 2020 the UK Government's ACCORD (Accelerating COVID-19 Research & Development) selected Bemcentinib as the first candidate for Phase II clinical trial in patients with COVID-19. The ongoing study has been done with 120 patients - 60 hospitalized

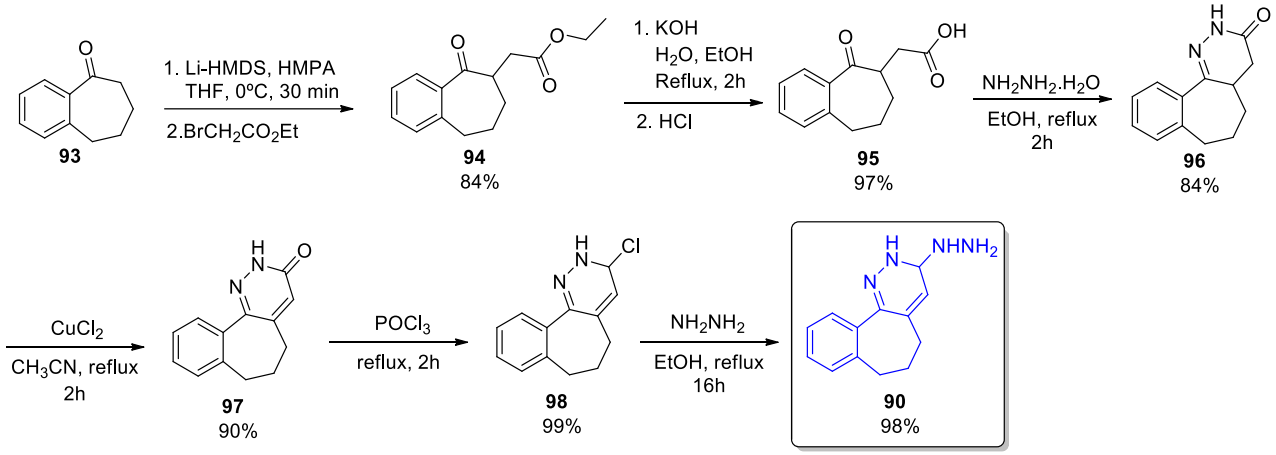
COVID-19 patients and 60 control group patients - receiving standard of care treatment. The preclinical data suggest that bemcentinib is potentially useful for the treatment of early SARS-CoV-2 infection.[204]

The first bemcentinib (**92**) synthesis was reported in 2008.[205] In this methodology, the fragments **90** and **91** are prepared separately, and react with each other through a cycloaddition reaction with the formation of a triazole ring, as shown in Scheme 17.



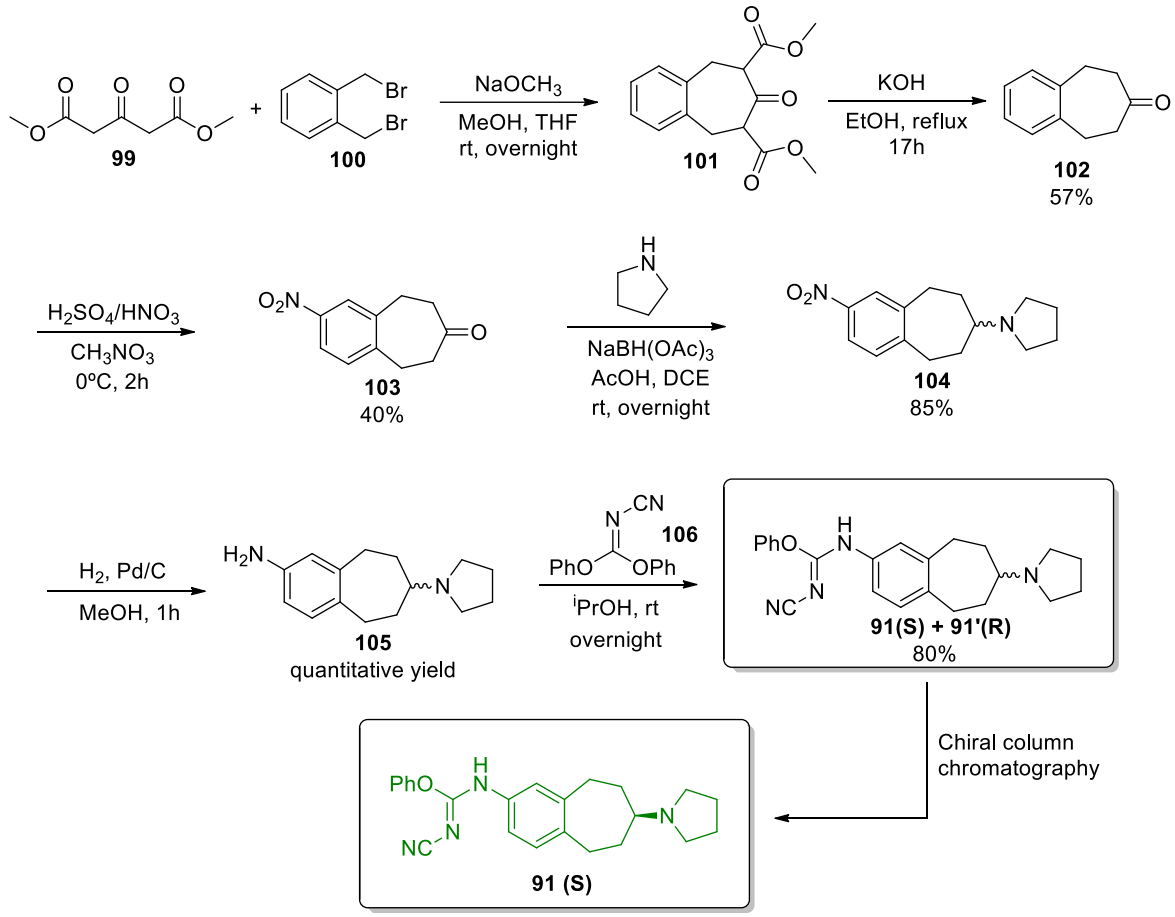
Scheme 17. Synthesis of Bemcentinib (R428).

Fragment **90** is synthesized as shown in Scheme 18 from 1-benzosuberone (**93**), which is commercially available. In the first step, an ethyl acetate group is added in compound **93** in the presence of a strong base to afford the compound **94**. As follow, **95** is obtained through hydrolysis of **94** followed by the treatment with hydrazine hydrate provide compound **96**. The unsaturated **97** is obtained after the treatment of **96** with $CuCl_2$. Aiming to aromatize and chlorinate the ring containing the N-N linkage (**98**), compound **97** is subjected to reaction with $POCl_3$. Finally, the last compound is treated with hydrazine to afford the fragment **90**.[205]



Scheme 18. Synthesis of intermediate **90**.

The other intermediate, fragment **91**, is synthesized in 6 steps as shown in scheme 19. Firstly, dimethyl-3-oxopentanedioate (**99**) reacts with 1,2-bis(bromomethyl)benzene (**100**) in protic/aprotic solvent with sodium methoxide. The resulting compound **101** is transformed into **102,** without purification, through basic hydrolysis conditions. In sequence, **103** is obtained from nitration of compound **102**. Next, reductive amination of the keto group followed by reduction of the nitro group leads to the formation of compound **104** and **105** respectively. Lastly, the compound **105** reacts with diphenyl cyanocarbonimidate **106** to afford a racemic mixture of **91** and **91'** in 80% yield. The compound **91** is obtained from chiral column chromatography.[205] The synthesis of intermediate **90** is easy to work with high yields, using easily accessible reagents. On the contrary, in the synthesis of intermediate **91** some steps do not show high yields, which combined with the final cycloaddition reflects in the overall reaction yield.



Scheme 19. Synthesis of intermediate **91**.

EIDD-2801 (Molnupiravir)

Molnupiravir, also known as EIDD-2801 (**114**), is an antiviral drug still in clinical trial that presents good oral bioavailability and broad-spectrum anti-influenza efficacy (*in vitro* and *in vivo* studies).[206] It is a prodrug, being hydrolyzed in plasma to its active form, N^4-Hydroxycytidine, which is a cytidine analogue (Figure 12). The hydroxylamine group in the molecule can suffer tautomerization, behaving both as cytidine and uridine. Accordingly, the drug can bind to virus RNA polymerase, and undergo tautomeric interconversion from cytidine to uridine, causing viral error catastrophe.[206] A work in the literature published recently suggests modifications in the ribose structure of EIDD-2801, aiming for reduction of possible side effects of the drug.[207] The active form N^4-Hydroxycytidine was studied not only for Influenza, but also against other viruses, such as RSV, Venezuelan equine encephalitis virus (VEEV) and some *Flaviviridae*, *Coronaviridae*, and *Togaviridae* family members.[206,208]

EIDD-2801 was developed due to the low plasma concentration of the N^4-Hydroxycytidine drug in cynomolgus macaques, which could indicate low human bioavailability. The addition of the isopropylester present in EIDD-2801 increased the bioavailability in nonhuman primates and ferrets. *In vitro* studies of the N^4-Hydroxycytidine in Madin-Darby canine kidney cells infected with influenza A viruses showed EC50 values from 0.1 to 3.4 µM, while for the influenza B viruses the drug showed EC50 values from 6 to 15 nM. Studies in HEp-2 cells infected with RSV strains presented EC50 values from 0.51 to 0.69 µM.[209]

In vivo studies using the EIDD-2801 prodrug in ferrets determined that a dose of 7 mg/kg administered twice a day was sufficient for antiviral efficacy against H1N1 influenza strains. These studies also showed a good window for treatment start, of 36 hours, with a 1.5 days duration.[209]

Sheahan *et al.* have studied mice infected with SARS-CoV or MERS-CoV, both prophylactic and therapeutic administration of EIDD-2801 have improved pulmonary function, reduced virus titer and body weight loss. *In vitro* studies in primary human airway epithelia (HAE) cell cultures infected with SARS-CoV and MERS-CoV showed EC50 values of 0.14 µM and 0.024 µM respectively. They also have shown a great potential of EIDD-2801 utility as an effective antiviral against SARS-CoV-2 and other future zoonotic

coronaviruses.[129] *In vivo* studies against the SARS-CoV-2 using the ferret model, similar to the influenza strains one, showed a reduction of SARS-CoV-2 load in upper respiratory tract and supressed spread to untreated animals.[210] The first study to evaluate the safety, tolerability, and pharmacokinetics of EIDD-2801 in healthy human volunteers was completed on August 11th, 2020.[211] The drug is still on phase I and II trials.[212–214]

More recently, Wahl and coworkers have shown phase II/III clinical trials. The results present that the EIDD-2801, orally administered therapeutically, efficiently inhibited SARS-CoV-2 replication in human lung tissue from human lung-only mice and prevented SARS-CoV-2 infection when administered as pre-exposure prophylaxis.[215] In addition, Painter and coworkers reported that EIDD-2801 was well absorbed after oral administration and that it was minimally affected by food intake, nor was accumulation observed in a multiple ascending dose study. A small amount of the drug was detected in the urine, attributed to the metabolism of EIDD-2801 to cytidine and uridine.[216] Ongoing studies by Holman and coworkers seek to describe the safety, tolerability and pharmacokinetic profile of EIDD-2801.[217]

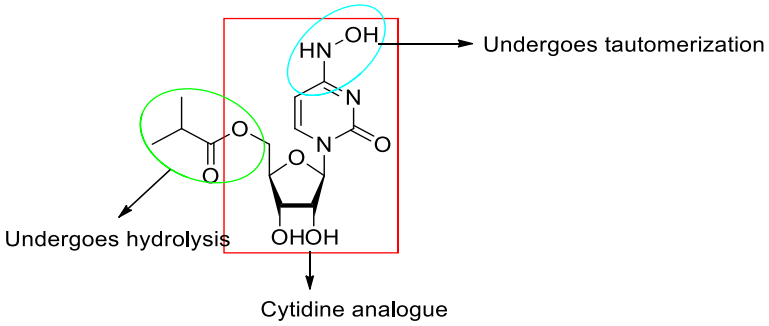
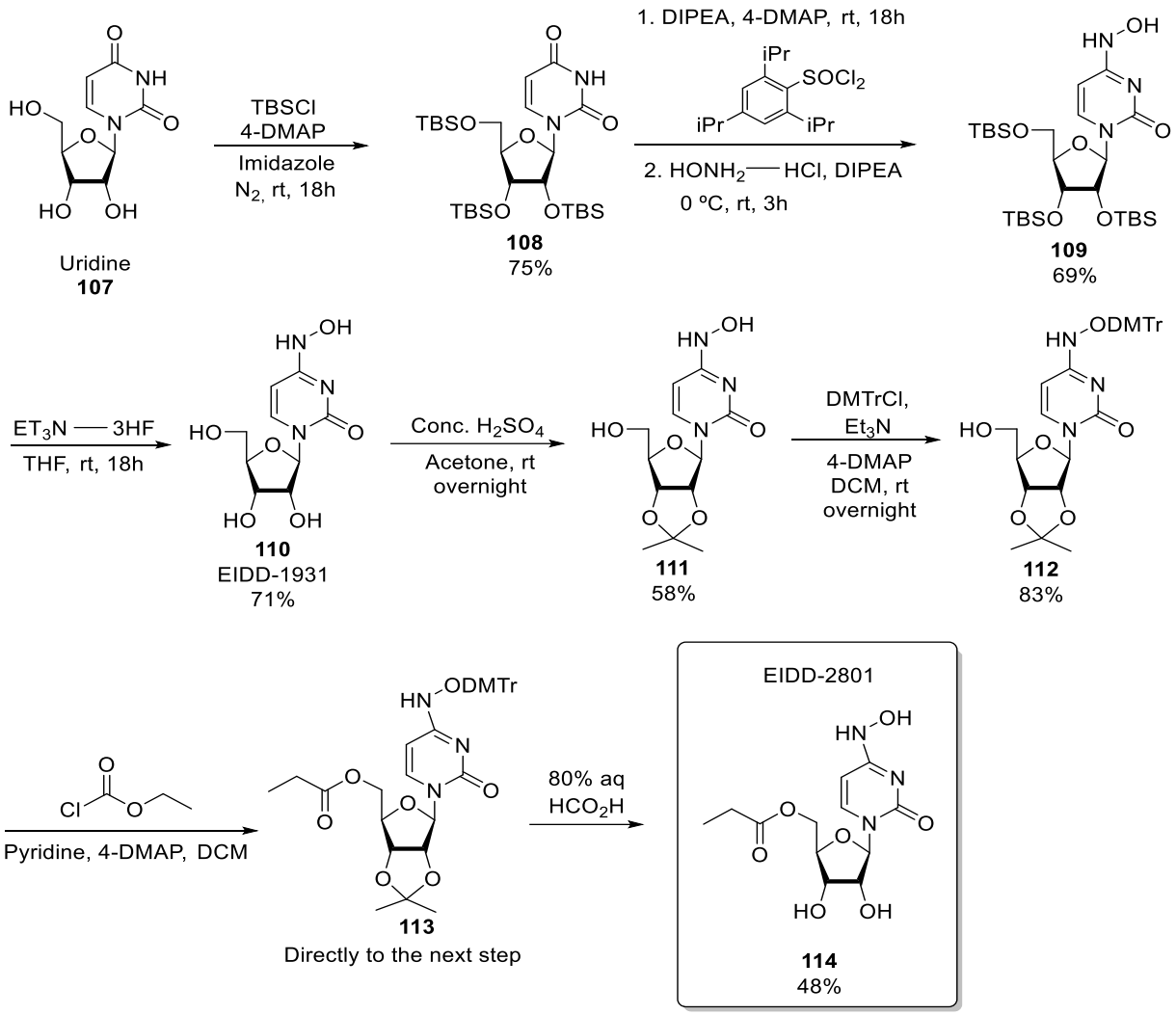


Figure 12. EIDD-2801 SAR.

The synthesis of this compound has been little explored compared to the others; therefore, few routes are described.[218] The initial reagent is the uridine (**107**), that in the first step of the synthesis is protected by tert-butyldimethylsilyl chloride (TBSCl). With hydroxyl groups protected by TBS (**108**), the next step is the reduction of α-ketone to a hydroxyamine to afford the compound **109** in 69% yield. In sequence, a deprotection of all hydroxyl groups (**110**), followed by a new protection of the two vicinal hydroxyls by acetonide leads to the formation of **111**. After that, compound **112** is obtained through the protection of hydroxyamine group with DMTr. Finally, the EIDD-2801 (**114**) is obtained after an esterification reaction and deprotection of all hydroxyl groups. Here, the protection/deprotection steps increase the number of total steps in the synthesis and consequently the production costs of this compound.



Scheme 20. Synthesis of EIDD-2801

Chloroquine and hydroxychloroquine

Chloroquine was first used in the 1940s for the treatment of malaria. It has several advantages, compared to other antimalarial drugs, such as low cost and toxicity, easy synthesis, and simple treatment with high efficacy. Unfortunately, the *plasmodium falciparum* has developed a high and widespread resistance to the drug.[219,220] Hydroxychloroquine was developed in the 1950s as a chloroquine derivative and was found to have less adverse effects than chloroquine.[221]

In the 1950s chloroquine and hydroxychloroquine were first tested in clinical studies against autoimmune diseases with positive results.[222] Since then, both compounds are used to treat diseases such as rheumatoid arthritis, systemic lupus erythematosus, antiphospholipid syndrome, and primary Sjögren syndrome.[221,223] The antiviral activity of chloroquine and its derivative hydroxychloroquine were also investigated, first against HIV, then to several others such as members from the coronaviridae, flaviviridade, orthomyxoviridae, picornaviridae and togaviridae families.[224,225]

In vitro studies of chloroquine in MT-4 and peripheral blood mononuclear cells against HIV-1 and HIV-2 strains showed EC50 values of 3.0 µM and 3.1 µM respectively.[226] For hydroxychloroquine in CEM and U-937 cells against HIV-1 strains, it showed EC50 values 10 µM and 1 µM respectively.[227] Against SARS-CoV, in Vero E6 cells, chloroquine showed an EC50 value of 4.4 uM.[228]

Several clinical trials were made using chloroquine for HIV infected patients. A systematic review and meta-analysis of the clinical evidence of use of chloroquine and hydroxychloroquine as antiviral agents concluded that the use of these drugs is at best, doubtful, and probably no longer relevant with the number of effective treatments available now. The same review assessed the use of these drugs against dengue and chikunguya infections, concluding that it is ineffective for the former and probably the same for the latter, due to not enough evidence of efficacy.[229]

Chloroquine and hydroxychloroquine suffer the action of CYP enzymes, being dealkylated in their active metabolites, desethylchloroquine, and desethylhydroxychloroquine, respectively. Against malaria protozoa, the 4-aminoquinoline nucleus (Figure 13) binds with the protozoan hematin, and its 7-chloro group is responsible to inhibit its transformation in hemozoin. Further modifications should be focused in changing the alkyl group that binds to the amine group, aiming to decrease toxicity and side effects while maintaining or enhancing activity.[230]

The aminoalkyl sidechain is also important for this activity, probably assisting in drug accumulation in the parasite food vacuole.[231,232] Against autoimmune diseases these drugs activity is related to its effects on lysosomal activity. They are known to accumulate in lysosomes, increasing its pH and interfering in its functions, which might inhibit lymphocytes and autophagosomes, impairing immune activation. Another effect of these compounds in pH changing is on endosomes, which interferes with Toll-like receptors processing, preventing their activation. They can also directly bind to nucleic acids, blocking the Toll-like receptors interaction with its ligands on an intracellular level.[223] Chloroquine and hydroxychloroquine accumulation on lymphocytes and macrophages results in a reduction of proinflammatory cytokines, reducing anti-inflammatory response.[233]

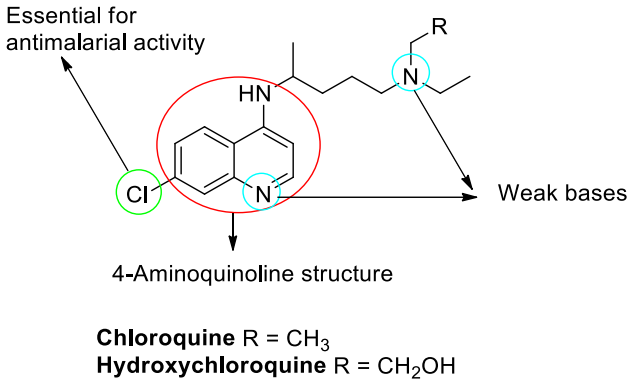


Figure 13. Chloroquine and Hydroxychloroquine SAR.

Concerning the viral activity of chloroquine and its derivative, a general mechanism is proposed where it impairs viral replication in two ways. First, it inhibits pH-dependent cell entry processes by endocytosis that some viruses use, which hinders its replication. The second mechanism is inhibition of low pH-dependent post-translational modification of envelope glycoproteins of some enveloped virus, that occurs within endoplasmic or trans-Golgi network vesicles, places where the chloroquine accumulates. This inhibition can result in non-infectious virus particle accumulation.[233]

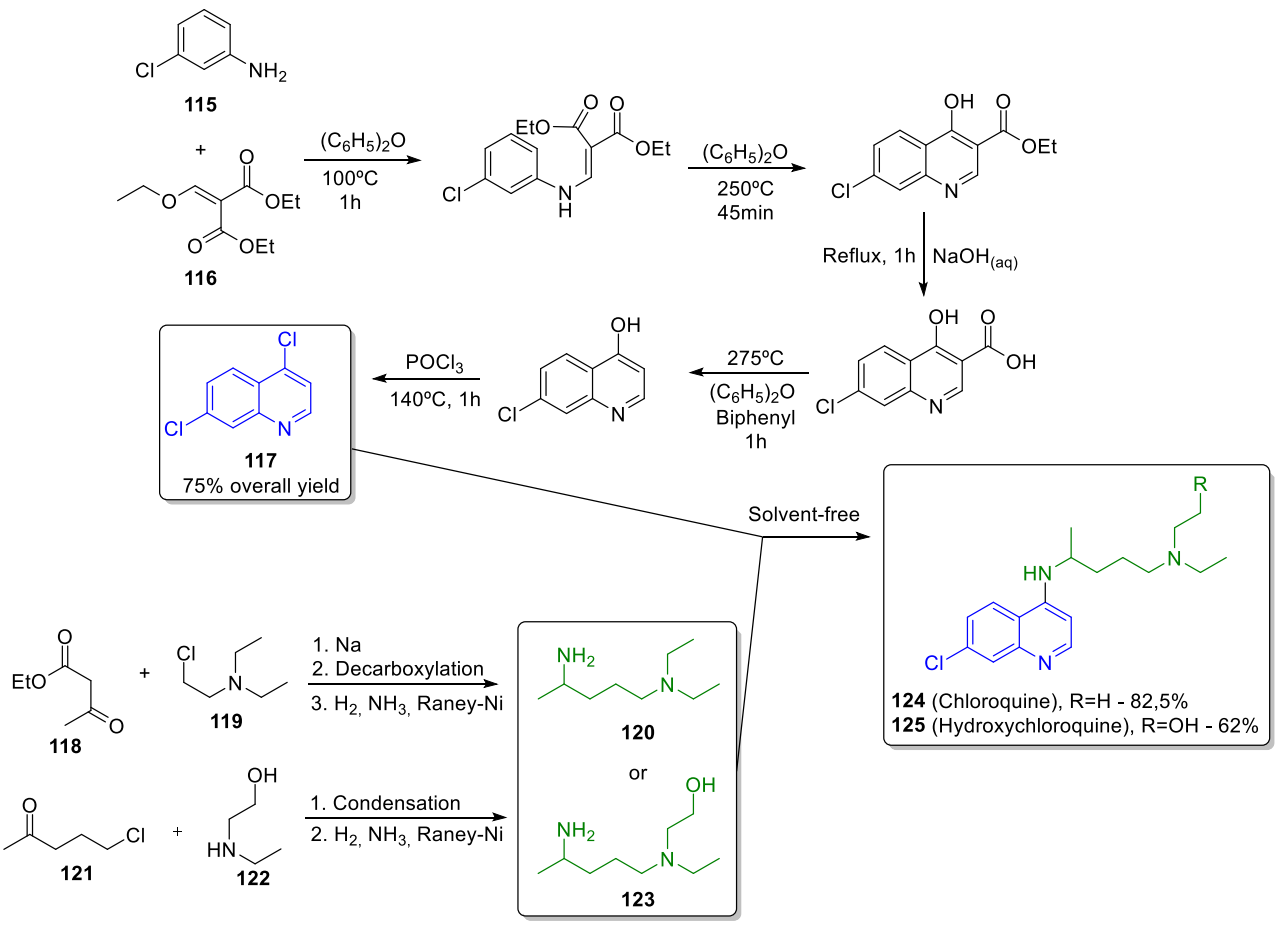
Chloroquine phosphate presents *in vitro* activity against various viruses, including coronaviruses, SARS-CoV-2, and MERS-CoV.[228,232] A small, randomized study with adults in China compared chloroquine with lopinavir/ritonavir. The results suggested that chloroquine was associated with shorter time to RT-PCR (reverse transcription-polymerase chain reaction) conversion and quicker recovery than lopinavir/ritonavir.[234] Borba *et al.* have done a double-blind randomized phase 2b study in Brazil, to evaluate two different chloroquine dosages as therapy in hospitalized adults with severe COVID-19. The patients also received azithromycin and ceftriaxone and some also received oseltamivir. The arm with higher doses was halted because of toxicity concerns, such as QTc prolongation and ventricular tachycardia. Also, a high number of deaths was observed in this arm. Data were insufficient to evaluate efficacy.[234] More recently, it was published a study by Hoffman *et al.*[235] which infers that chloroquine does not inhibit infection of human lung cells with SARS-CoV-2. Million *et al.* have evaluated the use of hydroxychloroquine with azithromycin in an uncontrolled, observational, retrospective study in France. A group of 1061 patients treated with hydroxychloroquine sulphate (200 mg 3 times daily for 10 days) and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5) was analysed for clinical outcomes and persistence of viral shedding. Within 10 days of treatment, good clinical outcomes were reported for 973 patients and poor clinical outcomes for 46 patients. The authors also concluded that the administration of the hydroxychloroquine and azithromycin combination before COVID-19 complications occur is safe and associated with a very low fatality rate in patients.[236] Mehra *et al.* have performed a large retrospective study with hospitalized COVID-19 patients to evaluate the effect of chloroquine and

hydroxychloroquine. The results obtained suggest that the use of those 4-aminoquinoline derivatives, with or without a macrolide (azithromycin or clarithromycin) was associated with a higher risk of mortality and ventricular arrhythmia during hospitalization.[237,238] The authors have requested that the paper be retracted due to no longer being able to vouch for the veracity of the primary data sources.[239]

Based on many studies,[240–243] the clinical data are insufficient to recommend either for or against the use of these drugs for the treatment of COVID-19.[244,245] A systematic review and meta-analysis concluded that hydroxychloroquine lack efficacy in reducing short-term mortality and risk of hospitalization in COVID-19 patients both in monotherapy and in conjunction with azithromycin.[246] Also, since July 4th, 2020, the World Health Organization (WHO) accepted the recommendation from the Solidarity Trial's International Steering Committee to discontinue the trial's hydroxychloroquine and lopinavir/ritonavir arms.[247]

The Chloroquine (**124**) and hydroxychloroquine (**125**) were firstly synthesized in the 1930s and 1950s respectively, in a similar way, as shown in Scheme 21.[248–250] The drugs are obtained from the reaction between 4,7-dichloroquinoline (**117**) with pentane-1,4-diamino derivatives (**120** or **123**), in a solvent-free reaction. [248–250]

The 4,7-dichloroquinoline (**117**), common intermediate for the synthesis of both drugs, can be synthesized in several ways and an advantageous example is described in the following Scheme 21.[251] In this synthesis the 4,7-dichloroaniline is obtained from *m*-chloroaniline (**115**) and ethoxymethylenemalonic ester (**116**) in 5 steps (condensation, cyclization, carboxylation, deesterification and chlorination) with 75% overall yield. The other fragments for the chloroquine and hydroxychloroquine synthesis (**120** and **123**), can be synthesized from the reaction between amine derivatives and carbonyl compounds. For the synthesis of **120**, a condensation reaction of Ethyl 3-oxobutanoate (**118**) with 2-chloro-N,N-diethylethanamine (**119**), followed by decarboxylation and reductive amination is necessary. The compound **120** produces chloroquine in a condensation reaction with compound **117**. For the synthesis of compound **123**, a condensation reaction is performed with 5-chloropentan-2-one (**121**) and 2-(ethylamino)ethanol (**122**), followed by a reductive amination. The compound **123** produces hydroxychloroquine in a condensation reaction with compound **117**, in the same way as the chloroquine reaction.[248,249]



Scheme 21. Chloroquine and Hydroxychloroquine synthesis

Umifenovir

Umifenovir was licensed as an oral antiviral drug in Russia in 1993 and China in 2006. It has shown *in vitro* and *in vivo* activity against various viruses, such as influenza types A and B, adenovirus, hepatitis B and C Viruses, RSV, SARS-CoV, rhinovirus, West Nile virus and Zika virus.[252]

In vitro studies in Madin-Darby canine kidney cells against Influenza A, B and C strains showed IC50 values ranging from 3 µg/ml to 12.5 µg/ml. Against HCV in Huh7 cells, umifenovir showed IC50 values of 1-6 µg/ml.[253] Against RSV in HEp-2 cells, the IC50 of umifenovir was 10.4 µg/ml.[254] Against zikavirus strains in Vero cells, the drug showed IC50 values from 10.57 to 12.09 µM. Umifenovir was also studied in vitro against the west nile virus in Vero cells, showing IC50 ranging from18.78 to 19.16 µM.[255]

In vivo studies in mice infected with Influenza A H1N1 and H3N2 strains showed a 70-80% mortality rate reduction with a dose of 60-120 mg/kg/day of umifenovir, within 24 hours of infection, in a 5 days treatment.[253] Umifenovir has also shown good efficacy both in treatment and prophylaxis against several Influenza strains in various clinical trials.[253]

The drug has some types of antiviral activity, both as a direct-acting antiviral and a host-targeting agent. It has an affinity both to proteins and lipids membranes, so it can bind with viral envelope or key residues in the structural proteins of virions, having a virucidal effect. This effect is more pronounced at acidic pH, with the protonation of umifenovir amine groups (Figure 14). These properties can also alter intracellular trafficking, by impairing the release of clathrin-coated pits from the plasma membrane and inhibiting fusion between endocytic vesicles and endosomes.[256] Umifenovir can also inhibit viral fusion. It is assumed that it impairs conformational changes in viral fusion proteins during fusion initiation and can also increase the cell membrane's rigidity, making them resistant to viral fusion. The drug can also inhibit viral replication, by impregnating the lipidic membranes the viruses create to form replication organelles or webs, and therefore impeding their formation and replication.[256] There are several works in the literature with modification of umifenovir structure aiming for enhancement of activity against specific viruses, but usually these modifications are not favorable for other viruses. This observation can be explained by the several types of antiviral activity the compound has, with different groups being necessary for its broad-spectrum activity. It is important to note that the indole core is maintained in all those studies, with variations in the ring's substituents.[256–260]

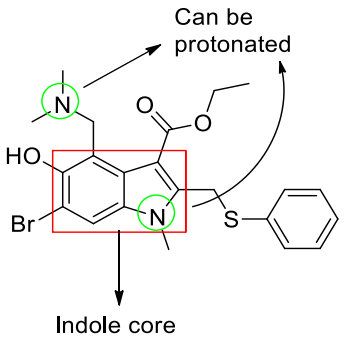
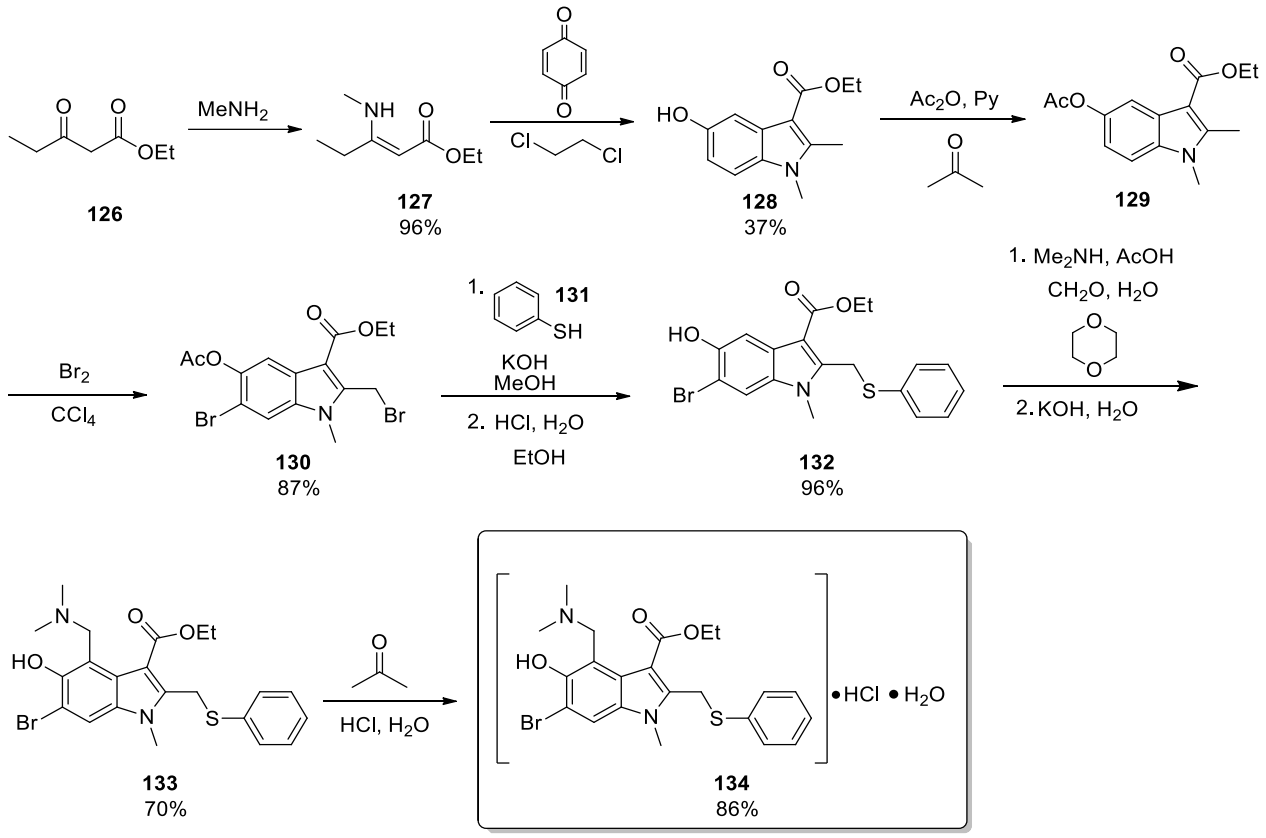


Figure 14. Umifenovir SAR.

A systematic review and meta-analysis of efficacy and safety of umifenovir for COVID-19 treatment found that although the drug was safe and associated with higher negative PCR rates on day 14 of adult patients, it could not alleviate hospital time, improve symptoms or decrease the disease progression, concluding that there is no evidence to support its use against COVID-19.[261] Some previous studies sought to administer umifenovir together with lopinavir/ritonavir, but recently Zhu and coworkers studied a group of 50 COVID-19 positive patients, where half were treated with lopinavir/ritonavir and half were treated with umifenovir alone. The data obtained showed that none of the patients developed severe pneumonia or ARDS, there was also no difference in the duration of fever between the groups. After 14 days of treatment no viral load was found in the umifenovir group, but in the lopinavir/ritonavir group a viral load was found in 15 (44.1%) patients. Furthermore, patients in the umifenovir group had

a shorter duration of positivity in the RNA test compared to the other group. No side effects were found in any of the groups. Overall, the study authors indicate that monotherapy with umifenovir may be superior to treatment with lopinavir/ritonavir.[262] Another recent study looked at the effect of umifenovir in 252 patients admitted with COVID-19 to the Cancer Center at the University of Science and Technology, Wuhan, China. The results indicated a significantly greater clinical improvement among patients treated with umifenovir compared to those who did not receive this drug (86.8% vs. 54.2%). Among moderately and severely ill patients, clinical improvement rates were between 95.6% and 81.7% respectively, a significantly higher value compared to those not treated with this medication (66.6% and 53.8%). Thus, the authors reported that the use of umifenovir may represent an affordable and accessible pharmacological approach for developing countries in urgent need of antiviral therapies.[263]

The first reported synthesis of this drug is dated in 1993. Several other syntheses are known and suitable for the scalable production, one of them is shown in the Scheme 22.[264,265] Firstly, a simple starting material, such as the acetoacetic ester (**126**) is converted into 3-(methylamino)crotonate (**127**).[266] Then it is subjected to Nenitzescu indole reaction to afford the compound **128** in 37% yield, which is the lowest yielding step. Followed by two steps, an acetylation to obtain **129** and a bromination leading to the formation of compound **130,** obtained in 87% yield. In sequence, a thiophenol ring (**131**) is added to afford the compound **132**. Lastly, the umifenovir (**134**) is obtained in two steps from **132**, a dimethylaminomethylation to obtain **133** followed by a hydrochloride salt formation.



Scheme 22. Synthesis of Umifenovir.

CONCLUSIONS

We know that vaccination is the most effective way to fight a virus, because it makes the individual resistant to infection. It is also essential to study new and powerful antivirals that can act directly against the microorganisms that cause various viral diseases, as well as the use of modern drug planning tools, including computational modeling, studies of Three Dimensional Quantitative Structure Activity Relationship (3D -QSAR) and artificial intelligence (AI). However, the development and research of new antivirals is a time-consuming and expensive process. The lack of success in some studies is often due to the fact that antiviral

molecules not only interfere with virus replication, but also negatively affect the host cells, since the viral cycle is closely linked to cellular functions. Therefore, we believe that the repositioning of medications already clinically approved seems to be the quickest response in pandemic situations. We have hereby presented drugs containing heterocyclic scaffolds that are used or investigated as antiviral agents. It is presented many of action mechanisms of drugs used against viruses and, many compounds can be used in these strategies. The Structure-Activity Relationship also shows that these compounds can be structurally modified to achieve greater efficiency with lesser side effects. Furthermore, after reaching target molecules, the organic synthesis comes as an essential tool to reduce molecule production costs through reduction of reaction steps and use of more accessible reagents. It can be observed that the synthesis of many of these compounds is not trivial, involving difficult conditions, expensive reagents, and many reaction steps that end up reducing the overall reaction yield. Hence, the synthesis of these compounds continues to evolve every year. Recently, with the advancement of the COVID-19 pandemic, much is said about these compounds showed here in the treatment of this disease. However, no definitive evidence exists for the efficacy in the treatment of this new coronavirus. Some of these drugs, such as ivermectin, favipiravir, remdesivir, baricitinib, bemcentinib and EIDD-2801 have potential use against the new coronavirus, with clinical studies showing improvement in patients infected the SARS-CoV-2 in various conditions, but they are still under investigation.

To the present moment, the best weapon to combat the virus is still prevention, including social isolation, washing hands, and keeping distance, associated to the extensive vaccination of the world population.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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