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Review

Quest for a COVID-19 Cure by Repurposing Small-Molecule Drugs: Mechanism of Action, Clinical Development, Synthesis at Scale, and Outlook for Supply

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ABSTRACT: The outbreak of the COVID-19 pandemic has spurred an intense global effort to repurpose existing approved drugs for its treatment. In this review, we highlight the development of seven small-molecule drugs that are currently being assessed in clinical trials for the treatment of COVID-19. Three sections are presented for each drug: (1) history, mechanism of action, and status of clinical trials; (2) scalable synthetic routes and final forms; and (3) outlook for supply should clinical trials show treatment efficacy. A brief overview of diagnostic testing and vaccine development is also presented.

KEYWORDS: *COVID-19, repurposed drugs, mechanism of action, synthesis, supply*

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1. CORONAVIRUS DISEASE 2019 (COVID-19) OUTBREAK

Human coronaviruses were first discovered in the 1960s[1] and are a large group of related viruses that are known to cause respiratory illness ranging in severity from common colds to diseases such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS).[2]

The novel coronavirus is a previously unidentified strain of coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[3] by the World Health Organization (WHO), and the resulting coronavirus disease 2019 (COVID-19) has become an ongoing global pandemic since its initial detection in Wuhan, China, in December 2019. SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA β-coronavirus that targets cells through the viral structural spike (S) protein that binds to angiotensin-converting enzyme 2 (ACE2).[4] Upon receptor binding, the virus particle uses host cell receptors and endosomes to enter cells. The host cellular protease transmembrane protease serine 2 (TMPRSS2) helps cell entry via the S protein. Viral polyproteins are then synthesized that encode for the replicase−transcriptase complex. Viral RNA synthesis is then achieved using RNA-dependent RNA polymerase. Epidemiological studies have shown that each infection can result in 1.4−3.9 new cases when no one is immune or preventative measures such as social distancing have not been undertaken. It is primarily spread between humans through small droplets from the nose or mouth when an infected person coughs or sneezes.[5]

As of May 30, 2020, there have been over 6 million confirmed cases of COVID-19, which have resulted in 370 000 deaths worldwide.[6a] Although the majority of cases of COVID-19 infection were first reported in China, the virus has now spread to 185 countries,[6b] with the U.S. now leading the world in both total number of infections and deaths. Symptoms can show up anywhere from 2 to 14 days after exposure, and it also possible for an infected person to show no symptoms (so-called asymptomatic disease). The disease is known to particularly afflict elderly people with pre-existing respiratory conditions or cardiovascular disease.

Currently no drugs are available for a fully effective treatment of COVID-19. Therefore, the pandemic has spurred an intense, collaborative, and global effort to repurpose existing approved drugs for its treatment. In this review, we highlight the development of seven small-molecule drugs that are currently being assessed in clinical trials for the treatment of COVID-19. Three sections are presented for each drug: (1) history, mechanism of action, and status of clinical trials; (2) scalable synthetic routes and final forms; and (3) outlook for supply should clinical trials show treatment efficacy. The review starts with a brief overview of diagnostic testing and vaccine development.

2. SARS-CoV-2 DIAGNOSTIC TESTING

Testing for SARS-CoV-2 is becoming increasingly available, with two broad categories of testing for the virus: nucleic acid amplification tests (NAATs), which can detect the SARS-CoV-2 genetic material from a patient's respiratory system, and a serology (or antibody) test, which can measure the amount of antibodies present in the blood when the body is responding to the COVID-19 infection. Table 1 lists commercialized SARS-CoV-2 diagnostic tests with U.S. Food and Drug Administration (FDA) emergency use authorization (EUA).

Table 1. Commercialized SARS-CoV-2 Diagnostic Tests with Approval by U.S. FDA EUA

test name	company	test type	result time (h)
ID NOW COVID-19	Abbott	isothermal amp.	<1
Abbott RealTime SARS-CoV-2 Assay	Abbott	PCR	4−6
ANDi SARS-CoV-2 RT-qPCR Detection Kit	3D Medicines	PCR	4−6
Atila iAMP COVID-2019 Detection Kit	Atila Biosystems, Inc.	isothermal amp.	1
BioGX SARS-CoV-2 Reagents for BD MAX systems	Becton Dickinson		
BioFire COVID-19 Test	Biofire Defense, LLC	PCR	<1
Xpert Xpress SARS-CoV-2	Cepheid	PCR	<1
Simplexa COVID-19 Direct RT-PCR Kit	DiaSorin	PCR	1
ePlex SARS-CoV-2 Test	GenMark Diagnostics	PCR	2
Panther Fusion SARS-CoV-2 Assay	Hologic	PCR	3
ARIES SARS-CoV-2 Assay	Luminex Corp.	PCR	2
New Cornavirus RT-PCR Test	PerkinElmer	PCR	4−6
Quest SARS-CoV-2 RT-PCR	Quest	PCR	96−120
QIAstat-Dx Respiratory Panel 2019-nCoV	QIAGEN GmbH	PCR	1
Lyra SARS-CoV-2 Assay	Quidel	PCR	4−6
Cobas SARS-CoV-2	Roche	PCR	3−8
TaqPath COVID-19 Combo Kit	Thermo Fisher Scientific	PCR	4

At the time of writing, 22 companies have been issued authorization by the FDA to distribute NAATs, and >50 additional companies have notified the FDA that they will be submitting authorization requests. According to the Foundation for Innovative New Diagnostics (FIND), there are over 590 diagnostics, either developed or under development, for SARS-CoV-2 worldwide.[7] Estimates in the U.S. suggest that 52 people per thousand have been tested for COVID-19 as of May 30, 2020, a number that continues to grow daily as more people are tested.[6a] The majority of NAATs focus on detecting SARS-CoV-2 viral RNA through quantitative reverse-transcriptase polymerase chain reaction (RT-qPCR) tests.[8] One of the first tests to get approved by the FDA was the Abbott RealTime SARS-CoV-2 Assay,[9] which is a real-time RT-qPCR test intended for the qualitative detection of nucleic acid from SARS-CoV-2 collected from either nasal, nasopharyngeal (NP), or oropharungeal (OP) swabs. Results from these tests, which require in-house clinical amplification and detection machines, can take 4−6 h for a result. Most recently, the same company has developed an even faster test called ID NOW COVID-19, which cuts the processing time from hours to as little as 5 min for a positive result and 13 min for a negative result.[10] This particular test utilizes isothermal nucleic acid amplification for qualitative detection of SARS-

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Table 2. Serology Assays

test type	result time (h)	readout	limitations
rapid diagnostic test (RDT)	<1	qualitative presence or absence of antibodies against the virus in patient serum	not a quantitative readout; cannot detect antibodies that are able to protect against future infection
enzyme-linked immunosorbent assay (ELISA)	1−5	quantitative presence or absence of antibodies against the virus present in patient serum	cannot detect whether antibodies are able to protect against future infection
neutralization assay	72−120	presence of active antibodies in patient series that are able to inhibit virus growth ex vivo in a cell culture system	may miss antibodies to viral protein that are not involved in replication

Table 3. SARS-CoV-2 Vaccines in Development

	general attributes					
vaccine type	single-dose?	licensed platform?	speed	current scale	companies in preclinical development	clinical candidate, phase, company, and clinical trial
DNA	no	no	fast	medium	Applied DNA Sciences, Takis Biotech, and EvviVax; Zydus Cadila	INO-4800, Phase I, Inovio Pharmaceuticals, NCT04336410
RNA	no	no	fast	low to medium	CureVac; Stermina Therapeutics, Tongji University, and Chinese Center for Disease Control and Prevention; Imperial College London	mRNA-1273, Phase I, Moderna Pharmaceuticals, NCT04283461
inactivated	no	yes	slow	high	Sinovac; Wuhan Institute of Biological Products (Sinopharm)	
live attenuated	yes	yes	slow	high	Codegenix/Serum Institute of India	
nonreplicating viral vector	yes	no	fast	high	GeoVax/BravoVax; Janssen Pharmaceutical Companies; Altimmune; Greffex; Vaxart; ExpreS^{2}ion Biotechnologies	Ad5-nCov, Phase II, CanSinoBio, NCT04341389 ChAdOX1nCoV-19, Phase I, University of Oxford, NCT04324606
protein-based	no	yes	medium to fast	high	Novavax; Clover Pharmaceuticals with GSK; Baylor College of Medicine, University of Texas Medical Branch, New York Blood Center, and Fudan University (China); University of Saskatchewan (Canada); University of Queensland (Australia), and Dynavax Technologies; Vaxart; Generex Biotechnology; ExpreS^{2}ion Biotechnologies; Vaxil Bio; Sanofi Pasteur; iBio/CC-Pharming	
replicating viral vector	yes	yes	medium to fast	high	Zydus Cadila	

CoV-2 viral RNA collected by the same means as above. The FDA has now authorized the first molecular test that uses saliva (instead of nose or throat swabs), which is being developed by Rutgers RUCDR Infinite Biologics.[11]

An emerging group of tests can now detect antibodies to the disease (viz., serology tests), which can be used to better quantify the number of people infected with COVID-19, including those that could be asymptomatic or have recovered. These tests will also help authorities in diagnosis, population surveillance, and potential return-to-work actions. These blood-derived tests fall into three categories: (1) rapid diagnostic tests (RDTs), (2) enzyme-linked immunosorbent assays (ELISAs), and (3) neutralization assays.[12] In most cases, these test for patient antibodies (immunoglobulin M (IgM) and immunoglobulin G (IgG) titer) in a qualitative or quantitative readout (Table 2).[13]

Currently, the U.S. Centers for Disease Control and Prevention (CDC) is evaluating two serological tests, and multiple other manufacturers have tests under development. It is worth noting that there are still limitations associated with serology testing, as it may take many days postinfection to generate these initial IgM antibodies that are indicative of an active or recent infection. Over time, the body develops secondary antibodies (IgG) in response to the infection, which are known to take approximately 4 weeks to develop.

3. COVID-19 VACCINE TREATMENTS

Diverse approaches are being taken to develop vaccines for SARS-CoV-2, with multiple platforms under development. These include viral vector (replicating and nonreplicating) vaccines, DNA and RNA vaccines, live attenuated vaccines, and protein-based vaccines (Table 3).[14] DNA and RNA vaccines have been delivered rapidly, with Moderna testing its mRNA-1273 vaccine 2 months after sequence identification. A phase I study (45 healthy adults) is underway (NCT04283461) to evaluate both the safety and immunogenicity at three dose levels of mRNA-1273 (25, 100, and 250 μg) administered on a two-dose vaccination schedule 28 days apart. The patients will be followed for 12 months after the second vaccination.

INO-4800 is a DNA vaccine that is being tested in up to 40 healthy adults at the University of Pennsylvania's Perelman School of Medicines and at the Center for Pharmaceutical Research in Kansas City, MO (NCT04336410). Participants will be administered two doses of INO-4800 (1 and 2 mg) 4 weeks apart.

Ad5-nCoV is a genetically engineered vaccine candidate with the replication-defective adenovirus type 5 as a vector to express SARS-CoV-2 spike protein. A single-center, open-label, dose-escalating Phase I clinical trial will investigate the antibody response in healthy adults who will receive one of three doses.

More than 56 confirmed active COVID-19 vaccine candidates are being developed across North America, Europe, China, and

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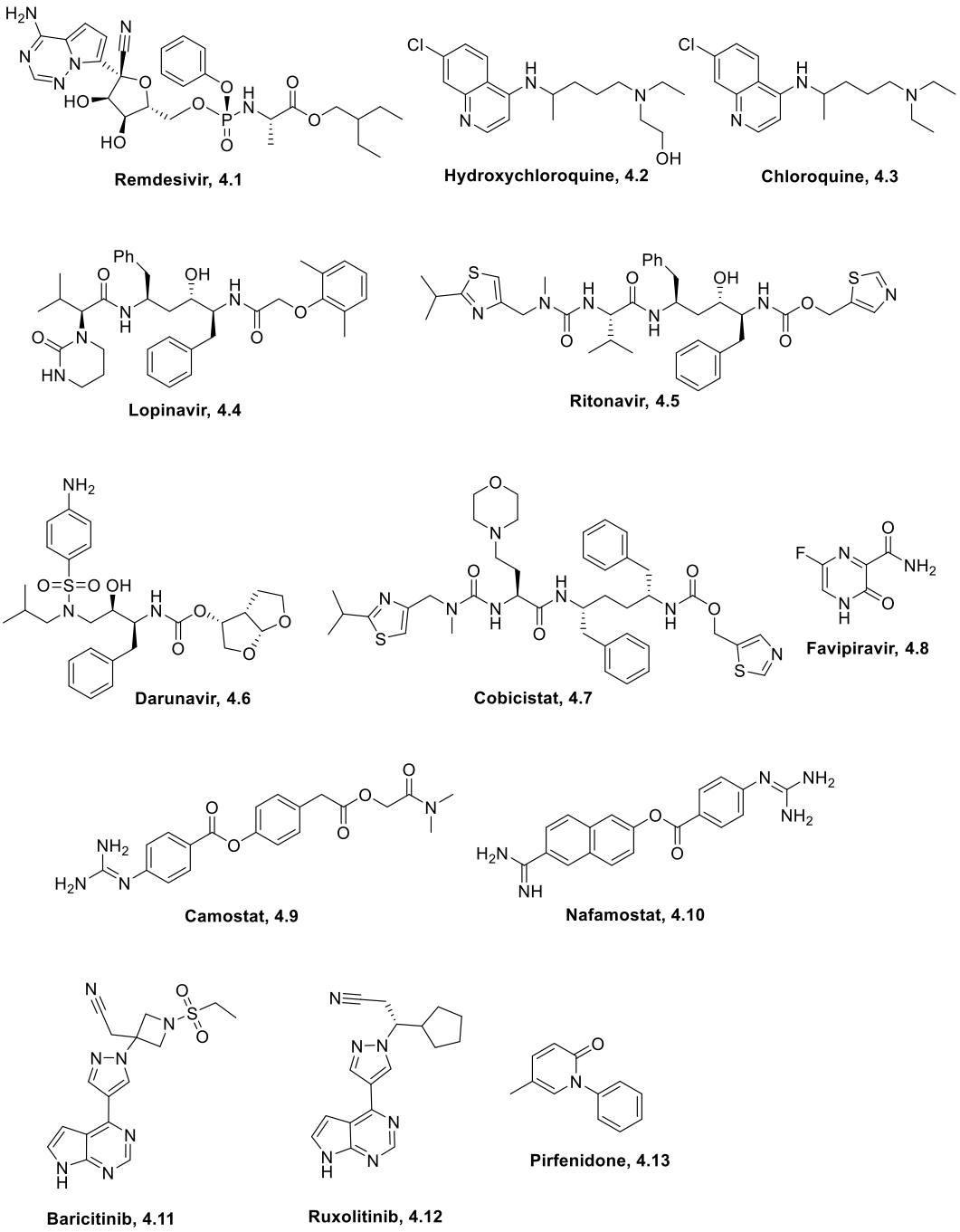

Figure 1. Repurposed small-molecule drugs for the potential treatment of COVID-19.

Australasia, and it is well-known that vaccine development is a lengthy and expensive process with high attrition.[15] Many of the vaccines in development are from small developers, so it will be important that both manufacturing and supply will be there to meet demand.

4. REPURPOSED SMALL-MOLECULE TREATMENTS FOR COVID-19

There are currently no drugs or vaccines available for a fully effective treatment or prevention of COVID-19, and this has accelerated drug repurposing efforts, that is, the investigation of approved existing drugs for the treatment of new diseases. Multiple existing antiviral medications that have been used for SARS, MERS, HIV/AIDS, and malaria are being tested in clinical trials today.[16] Because of the immense pressure COVID-19 is placing on world health systems, WHO has established an international "Solidarity" clinical trial to help find an effective treatment for this disease.[17a] This trial will compare four treatment options against standard of care to assess their relative effectiveness against COVID-19. WHO chose an experimental antiviral called remdesivir (**4.1**); the malaria medications hydroxychloroquine (**4.2**) and chloroquine (**4.3**); the combination of HIV drugs called Kaletra, consisting of lopinavir (**4.4**) and ritonavir (**4.5**); and other combinations, including interferon beta-1a. (Figure 1).

Interestingly, most of the drugs being repurposed in clinical trials inhibit key components of the coronavirus infection pathway (Figure 2), including (1) viral entry into the host cell,

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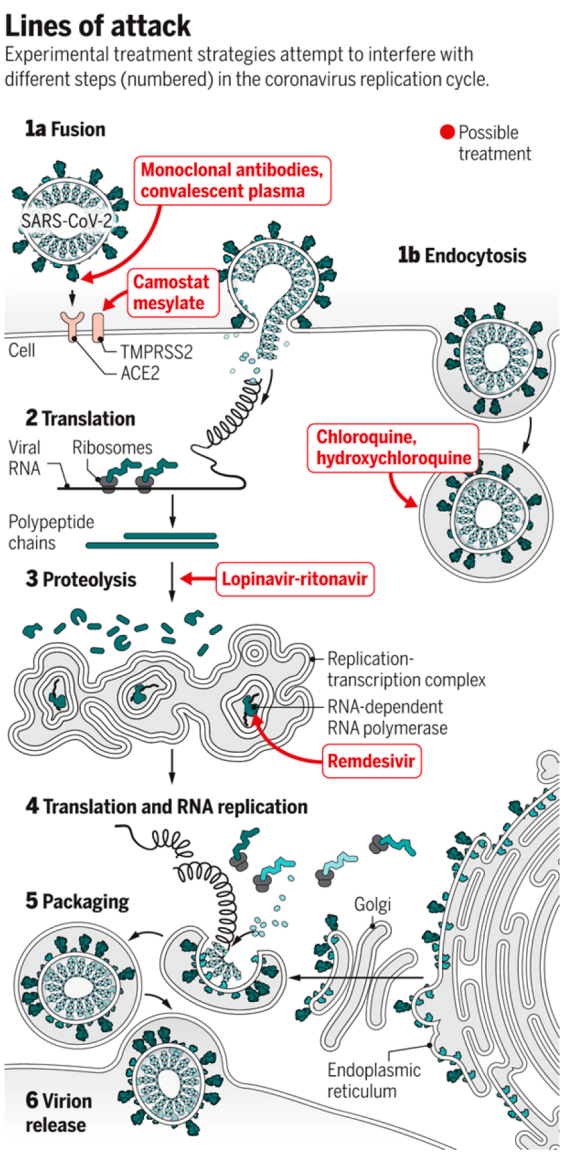

Figure 2. Experimental treatment strategies to interfere with different steps in the coronavirus replication cycle. Reproduced with permission from V. Altounian/*Science*.

inhibited by **4.2**/**4.3** and interferon beta-1a; (2) viral replication, inhibited by **4.4** and **4.5** as well as darunavir (**4.6**) and cobicistat (**4.7**), which inhibit the 3C-like protease (3CLpro); and (3) viral RNA synthesis, inhibited by RNA polymerase inhibitors such as **4.1** and favipiravir (**4.8**).

SARS-CoV-2 also uses ACE2 and TMPRSS2 to enter target cells. A number of marketed TMPRSS2 inhibitors such as camostat mesylate (**4.9**) and nafamostat (**4.10**) block cellular entry of the SARS-CoV-2 virus. The Janus-associated kinase (JAK) inhibitor Olumiant (baricitinib, **4.11**), approved for rheumatoid arthritis, was identified using machine learning algorithms on the basis of its inhibition of ACE2-mediated endocytosis. Another JAK inhibitor, Jakafi (ruxolitinib, **4.12**), is also in clinical trials (combined with mesenchymal stem cell infusion) for COVID-19 (Figure 1).

In this review, we discuss seven of the most promising small-molecule drugs, representing different mechanistic approaches, that are currently in clinical trials for the treatment of COVID-19, including remdesivir, hydroxychloroquine, favipiravir, pirfenidone, baricitinib, camostat, and lopinavir/ritonavir. Except for hydroxychloroquine, none of these drugs has been intended for commercial use in large patient populations such as COVID-19. Therefore, the economics of production and supply considerations may become critical, including the availability of raw materials, number of steps, process efficiency, and available capacity.[17b] An estimate of the cost of manufacture of several drugs being repurposed for COVID-19 was recently published by Hill et al.[17c]

5. REMDESIVIR

5.1. History, Mechanism of Action, and Status of Clinical Trials. Designed and developed by Gilead Sciences, remdesivir, formally known as GS-5734, is a broad-spectrum antiviral agent that has been studied clinically, so far unsuccessfully, for the treatment of Ebola. According to the Summary on Compassionate Use document provided by the European Medicines Agency (EMA), remdesivir is a prodrug of a monophosphate nucleoside analogue.[18]

Remdesivir is seen as a promising potential therapy for COVID-19 because of its broad-spectrum in vitro activity against several strains of coronavirus, including SARS-CoV-2, with EC_{50} and EC_{90} values of 0.77 and 1.76 μM, respectively.[19,20] Previously, in a mouse MERS-CoV lung infection model, remdesivir reduced viral lung titers more than lopinavir, ritonavir, and interferon beta-1a.[21] Remdesivir is administered via intravenous (iv) infusion, and the safety and pharmacokinetics have been evaluated in both single- and multiple-dose Phase I clinical trials for Ebola.[22]

In humans, remdesivir has a half-life of about 1 h in plasma, as it is rapidly converted to the intermediate monophosphate metabolite and the nucleoside metabolite GS-441524 (Scheme 1). Inside cells, the monophosphate is converted to a pharmacologically active analogue of adenosine triphosphate (ATP), GS-443902, that inhibits viral RNA polymerases. In vitro studies have shown that the nucleoside triphosphate acts as an analogue of ATP and competes with the natural ATP

Scheme 1. Metabolism of Remdesivir

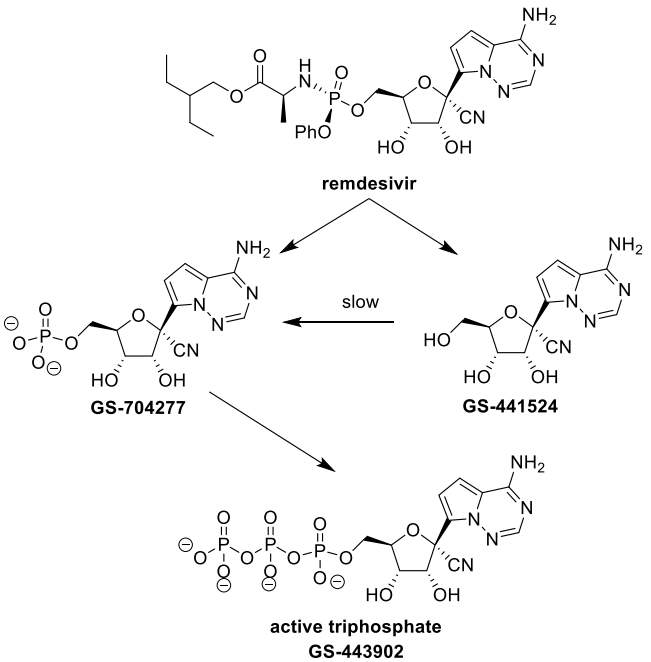

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Table 4. Sampling of Clinical Trials Underway with Remdesivir (RDV)[23]

clinical trial number	study title	estimated enrollment	study start/estimated completion dates	study arms	
				active	control
NCT04257656	A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir in Hospitalized Adult Patients with Severe 2019-nCoV Respiratory Disease	453	February 6, 2020/ May 1, 2020	RDV 200 mg loading dose on day 1, followed by 100 mg iv once-daily maintenance doses for 9 days	placebo
NCT04252664	A Phase 3 Randomized, Double-Blind, Placebo-Controlled Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir in Hospitalized Adult Patients with Mild and Moderate 2019-nCoV Respiratory Disease	306	February 12, 2020/ April 27, 2020	RDV 200 mg loading dose on day 1, followed by 100 mg iv once-daily maintenance doses for 9 days	placebo
NCT04280705	A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults	440	February 21, 2020/ April 2023	RDV 200 mg loading dose on day 1, followed by 100 mg iv once-daily maintenance doses for 9 days	placebo
NCT04292730	A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734) in Participants with Moderate COVID-19 Compared to Standard of Care Treatment	1600	March 15, 2020/ May 2020	Part A: (1) standard of care therapy together with RDV 200 mg on day 1 followed by RDV 100 mg daily on days 2−5 (2) standard of care therapy together with RDV 200 mg on day 1 followed by RDV 100 mg daily on days 2−10 Part B, extension: continued standard of care therapy together with RDV 200 mg on day 1 followed by RDV 100 mg daily on days 2−10	standard of care therapy
NCT04292899	A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734) in Participants with Severe COVID-19	2400	March 6, 2020/ May 2020	Part A: (1) participants who are not mechanically ventilated will receive continued standard of care therapy together with RDV 200 mg on day 1 followed by RDV 100 mg daily on days 2−5 (2) participants who are not mechanically ventilated will receive continued standard of care therapy together with RDV 200 mg on day 1 followed by RDV 100 mg daily on days 2−10 Part B: (1) extension will enroll participants after enrollment in Part A is complete; participants will receive continued standard of care therapy together with RDV 200 mg on day 1 followed by RDV 100 mg on days 2−10 (2) participants on mechanical ventilation will receive continued standard of care therapy together with RDV 200 mg on day 1 followed by RDV 100 mg daily on days 2−10	standard of care therapy
NCT04321616	The (Norwegian) NOR Solidarity Multicenter Trial on the Efficacy of Different Antiviral Drugs in SARS-CoV-2 Infected Patients	700	March 26, 2020/ November 2020	(1) hydroxychloroquine will be given orally (in the ICU in gastrointestinal tubes) with an 800 mg × 2 loading dose followed by 400 mg × 2 every day for a total of 10 days (2) RDV 200 mg loading dose on day 1, followed by 100 mg iv once-daily maintenance doses for 9 days	standard of care therapy
NCT04315948	Multicenter, Adaptive, Randomized Trial of the Safety and Efficacy of Treatments of COVID-19 in Hospitalized Adults	3100	March 22, 2020/ March 2023	1) standard of care + RDV (2) standard of care + lopinavir/ritonavir (3) standard of care + lopinavir/ritonavir plus interferon beta-1a (4) standard of care + hydroxychloroquine	standard of care therapy

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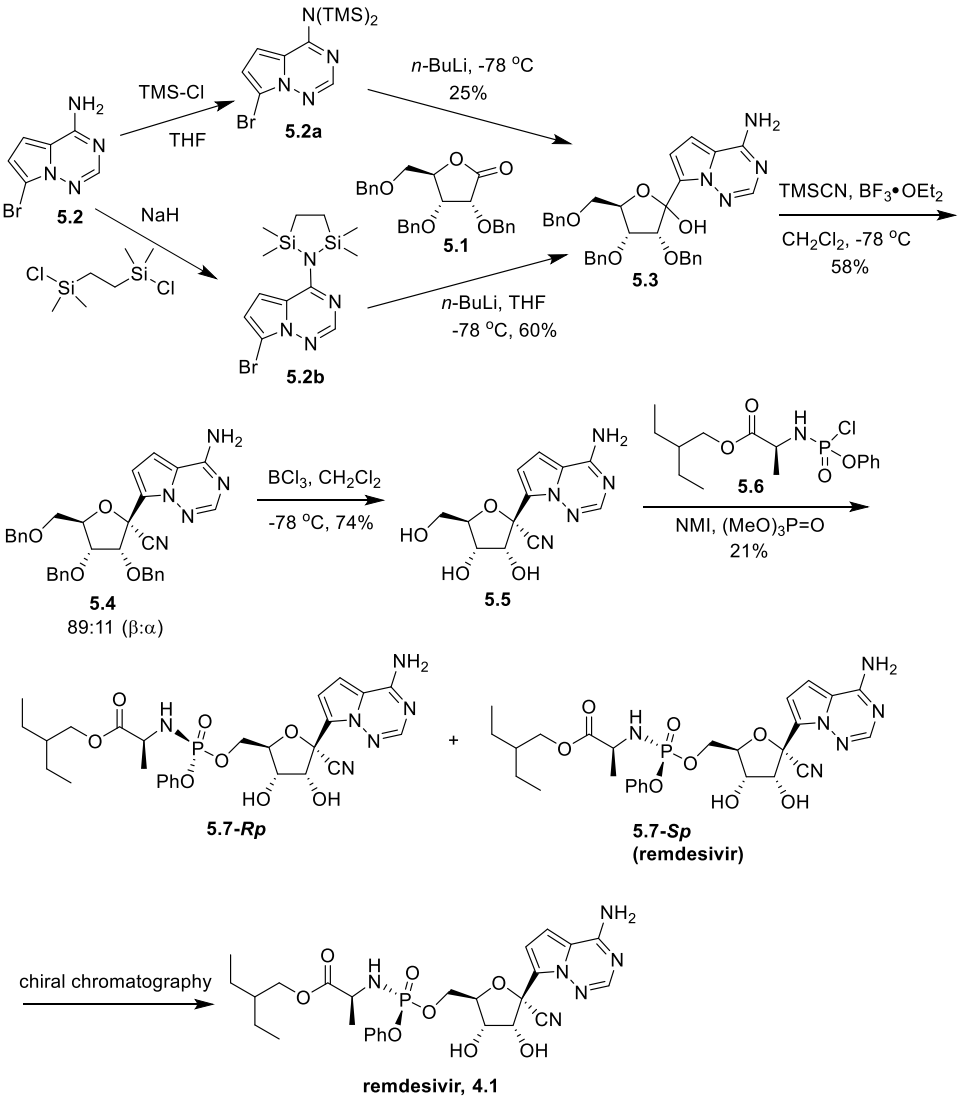
Scheme 2. First Gilead Route to Remdesivir



substrate to selectively inhibit RNA-dependent RNA polymerase.[18]

Clinical trials are underway to evaluate both the safety and antiviral activity in patients with mild to moderate or severe COVID-19. Table 4 summarizes seven clinical trials initiated in February and March 2020 that are planning to enroll about 9000 patients.[23] The first five studies listed compare 5 or 10 days of remdesivir (200 mg on day 1 followed by 100 mg daily), dosed intravenously either alone or on top of the standard of care, versus placebo or the standard of care. The last two trials listed compare remdesivir against other antiviral agents and against the standard of care. These trials are expected to enroll quickly, with some readouts in May and June 2020.

An early trial of open-label remdesivir was published in the *New England Journal of Medicine* on April 10, 2020.[24] This was a small compassionate use study that lacked a placebo arm and included 61 patients, of which 53 patients remained in the study. Over a median follow-up of 18 days after receiving the first dose of remdesivir, 36 out of 53 patients (68%) showed an improvement in the category of oxygen support, whereas eight out of 53 patents (15%) showed worsening.[24]

A recent unpublished Phase III clinical trial undertaken at the University of Chicago Medical Center that recruited 125 patients, most with severe COVID-19 disease, showed that remdesivir can quickly reduce both fever and respiratory symptoms associated with the infection. Again, this study did not have a control arm, with all patients receiving daily iv infusions of the drug.[25]

The Adaptive COVID-19 Treatment Trial, a 1063-patient clinical trial sponsored by the U.S. National Institute of Allergy and Infectious Diseases (NIAID), is a well-controlled clinical trial with remdesivir that reported out preliminary results on April 29, 2020.[26a,b] The independent Data and Safety Monitoring Board (DSMB) overseeing the trial concluded that hospitalized patients with advanced COVID-19 who received remdesivir recovered more quickly than patients who received placebo. The remdesivir cohort had a statistically significant 31% faster time to recovery than the placebo group (11 days vs 15 days). Recovery was defined as either hospital discharge or return to normal activity. Mortality improved from 11.6% to 8.0%, which was just outside of statistical significance ($p = 0.059$).[26a,b] On the basis of this study, the FDA approved the use of remdesivir as an emergency treatment for COVID-19 on May 1, 2020.[27]

A smaller multicenter study in China that enrolled 237 severe adult COVID-19 patients, published on April 29, 2020, found

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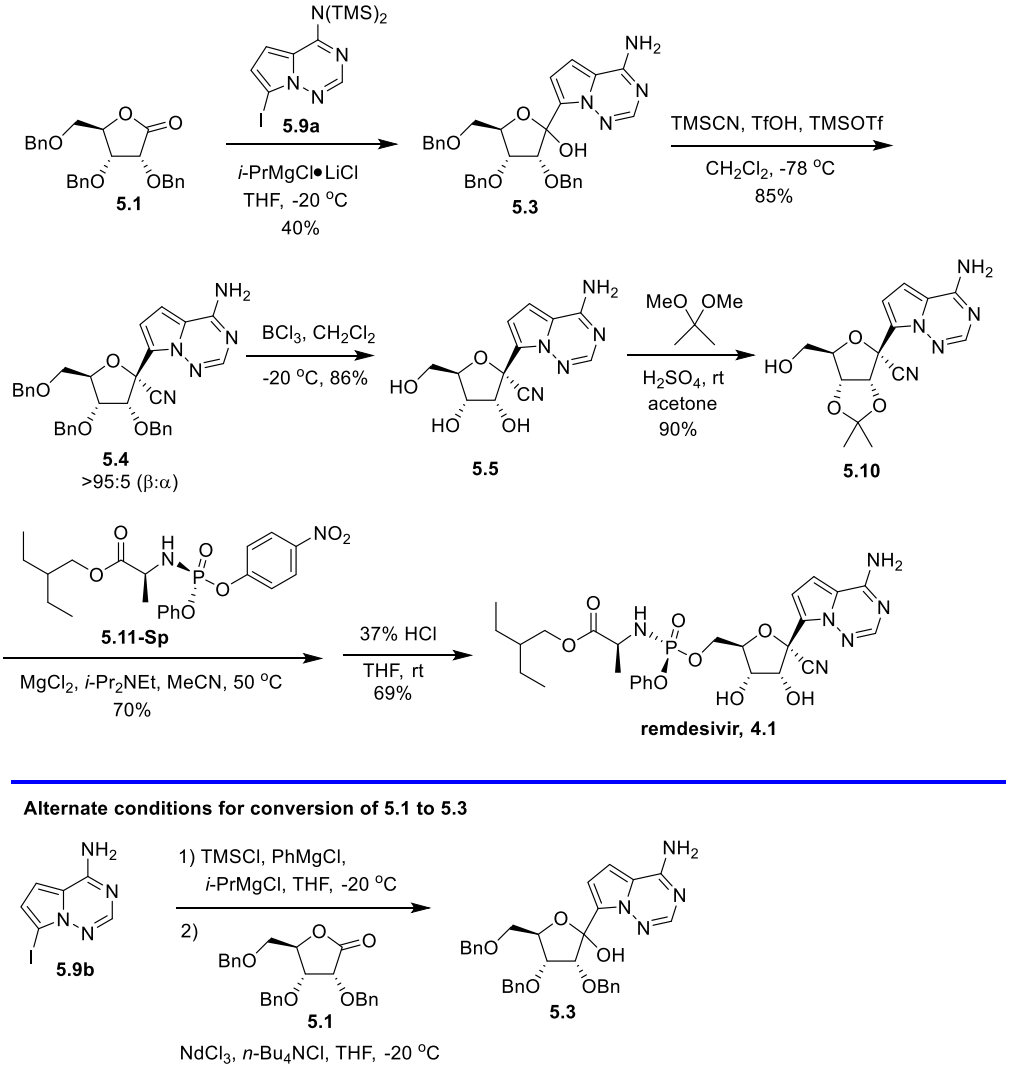
Scheme 3. Second Gilead Route to Remdesivir



that remdesivir (10 days of treatment) numerically improved clinical outcomes in hospitalized patients, but the results were not statistically significant. Remdesivir treatment was terminated early because of adverse events in 12% of patients versus 5% of patients on the placebo treatment.[26c]

5.2. Synthetic Routes to Remdesivir. An early medicinal chemistry route that has been further optimized has been published and patented by Gilead.[28−32] The first process to remdesivir generated both diastereomers (**5.7-*Rp*** and **5.7-*Sp***), requiring separation by chiral chromatography (Scheme 2).[28−32] The synthesis started with the glycosylation reaction of benzyl-protected ribolactone **5.1** with bromide **5.2**. Two methods for metal−halogen exchange were reported. In the first method, **2** was treated with trimethylsilyl chloride (TMSCl) in THF at room temperature to generate silylated **5.2a**, which was then cooled to −78 °C and treated with *n*-BuLi followed by addition of lactone **5.1**. The reaction was quenched with HOAc. After aqueous workup and chromatography, **5.3** was isolated in 25% yield as a 1:1 mixture of anomers. The second method involved treatment of **5.2** with NaH and 1,2-bis-(chlorodimethylsilyl)ethane to generate silyl compound **5.2b**, followed by lithiation with *n*-BuLi at −78 °C and addition of lactone **5.1**. This method provided **5.3** in 60% yield. The authors noted that both methods were capricious, with deprotonation likely occurring α to the lactone moiety. Cyanation of hydroxyl nucleoside **5.3** using TMSCN mediated by boron trifluoride etherate was carried out in dichloromethane at −78 °C to afford cyano nucleoside **5.4**, which was isolated as an 89:11 mixture of the α and β anomers in 58% yield after isolation by chromatography. Deprotection of the benzyl groups was conducted with boron trichloride in dichloromethane, and the desired β-anomer **5.5** was isolated in 74% yield after reversed-phase chromatography. Coupling with the diastereomeric mixture of phosphoramidoyl chloridate **5.6** was carried out in anhydrous trimethyl phosphate and THF with *N*-methylimidazole (NMI) (3 equiv) to furnish the diastereomeric mixture of **5.7-*Sp*** and **5.7-*Rp*** in 21% yield after preparative HPLC. The two diastereomers were separated by chiral chromatography using a Lux Cellulose-2 chiral column to afford remdesivir (**4.1**).

Because of the poor yields for several steps and the unreliability of the glycosylation step, an improved route was required as the compound advanced from the discovery laboratories to development.[28−32] In addition to improving the early steps, the second-generation route achieved a diastereoselective synthesis via selective crystallization of phosphorus coupling partner **5.11-*Sp***, thus avoiding preparative-scale chiral chromatography (Scheme 3). The glycosylation step employed iodide **5.9a** instead of bromide **5.2a**. Silyl

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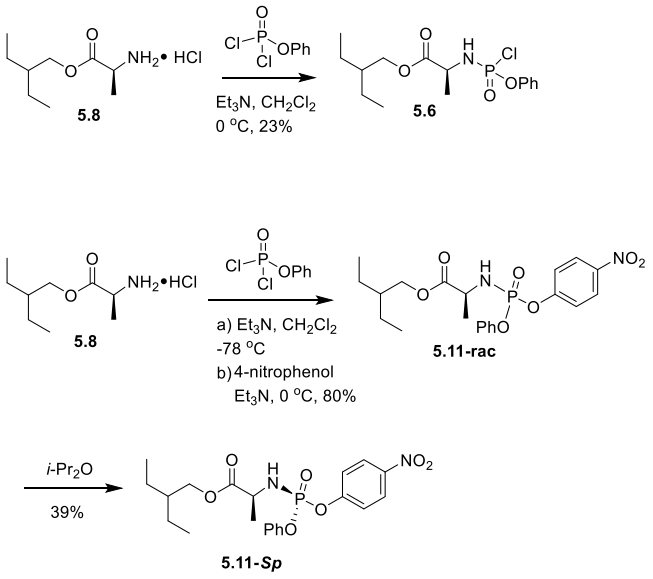
compound **5.9a** was generated from the corresponding amine with PhMgCl and TMSCl, after which metal−halogen exchange with *i*-PrMgCl·LiCl followed by addition of lactone **5.1** at −20 °C afforded **5.3** after flash chromatography in a modest but consistent yield of 40%. Installation of the cyano group was conducted using TMSCN, TMSOTf, and triflic acid (TfOH) at −78 °C to afford **5.4** in 85% yield with a >95:5 anomeric ratio favoring the desired *β*-anomer. When trifluoroacetic acid (TFA) was used instead of TfOH, the anomeric ratio was only 3.8:1. Treatment of **5.4** with boron trichloride in dichloromethane at −20 °C provided deprotected **5.5** in 86% yield after crystallization. To improve the yield in the coupling with the phosphorus reagent, triol **5.5** was protected as an acetonide to afford **5.10** in 90% yield. Coupling with diastereomerically pure **5.11-*Sp*** was then mediated by *i*-Pr_2NEt and $MgCl_2$ in acetonitrile at 50 °C. After aqueous workup, the product was concentrated and then dissolved in THF, and concentrated HCl was added to cleave the acetonide, providing remdesivir in 48% yield after purification by flash chromatography.

The routes to the two phosphoramidoyl chloridates used in the first- and second-generation processes are outlined in Scheme 4.[28−32] Chloridate **5.6** was prepared from alanate ester **5.8** with (PhO)P(O)Cl_2 in dichloromethane mediated by triethylamine at 0 °C in 23% yield as a mixture of diastereomers at the phosphorus center. Chloridate **5.11-*rac*** was prepared in 80% yield by initial generation of the ester at −78 °C followed by reaction with 4-nitrophenol at 0 °C. Because of the large difference in solubility of the two diastereomers in diisopropyl ether, the desired diastereomer **5.11-*Sp*** could be isolated with 39% recovery via crystallization in this solvent. The desired diastereomer could also be crystallized from *n*-heptane. On the basis of the X-ray crystal structures of both **5.11-*Sp*** and remdesivir, the coupling reaction of **5.10** with **5.11-*Sp*** occurs with inversion of stereochemistry at phosphorus.

Scheme 4. Routes to Phosphoramidoyl Chloridates 5.6 and 5.11-*Sp*



Compared with the first-generation route, the second-generation route provided higher and more consistent yields and afforded the single diastereomer of remdesivir without the need for chiral HPLC separation. The route was used to prepare 200 g of drug for toxicity studies and other preclinical studies.

In a recently published paper, Gilead reported the optimization of the cyanation step (i.e., the conversion of **5.3** to **5.4**) as a batch process as well as the development of a continuous flow process.[33] The first goal was to determine whether the cryogenic conditions (reaction at −78 °C) could be avoided under batch conditions. A series of 14 experiments were reported with variation of the temperature and the equivalents of TFA, TMSOTF, and TMSCN as well as the examination of other acids, including HCO_2H, HOAc, MsOH, and TsOH. The original conditions remained optimal, with a 96:4 *β*:*α* ratio and 90% solution purity at −78 °C. The best alternative conditions were a reaction temperature of −30 °C and addition of TFA (3 equiv) to a dichloromethane solution of **5.3** followed by addition of a solution of TMSCN (6 equiv) and TMSOTf (6 equiv), which afforded **5.4** with a solution purity of 83% and an 85:15 *β*:*α* ratio. Although these conditions afforded a higher level of the undesired *α* isomer, the desired *β* isomer could be isolated with >99% purity in an overall yield of 70% by crystallization from EtOAc/heptane or toluene.[33] This batch process was described on a 23 kg scale and was used to prepare supplies of remdesivir for clinical trials for the treatment of Ebola.

However, key challenges remained for further scaling of this step, including the operational hazards of handling large quantities of acidic mixtures of cyanide and controlling the diastereoselectivity and potential degradation during the increased operational time at scale. To address these issues, a flow process was designed and developed.[33] The comprehensive account of the development of the flow process from the lab

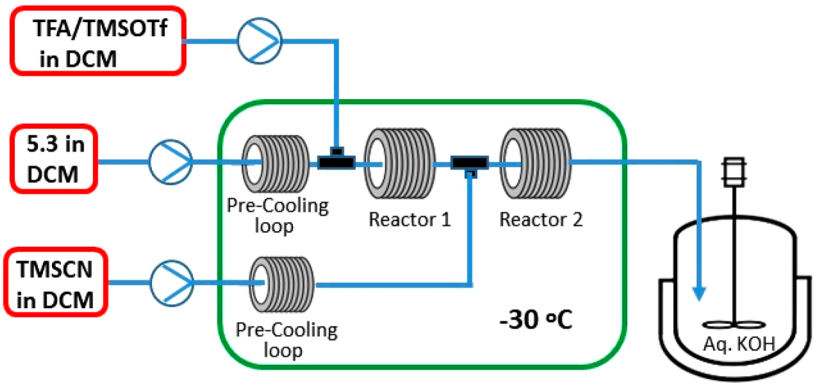


Figure 3. Flow cyanation step for remdesivir.

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scale to the manufacturing scale is very well written and provides an excellent case study for the development of a flow process for implementation at manufacturing scale in the pharmaceutical industry. We commend Gilead scientists and management for their willingness to publish the details of a key step in the remdesivir process. The reader is encouraged to read the Gilead account for the specifics of the development of the flow process. Herein we provide only the final manufacturing process, as presented in Figure 3.[33] The equipment consisted of two precooling loops, reactor 1 (0.5 L) and reactor 2 (2.0 L), all made of stainless steel. In the first step, a solution of compound **5.3** in dichloromethane (DCM) was pumped through a cooling loop (−30 °C) into reactor 1, where it was mixed with a solution of TFA (1.0 equiv) and TMSOTf (6 equiv) in DCM. The residence time in reactor 1 was 0.5 min. The outflow of reactor 1 was streamed into reactor 2 and mixed with a precooled solution of TMSCN in DCM, with a residence time of 2.0 min. The outflow of reactor 2 was streamed into a quench tank containing aqueous KOH, thereby neutralizing any HCN that may have been generated during the process. The β:α ratio was 94:6 with an overall solution purity of 90%. After workup and solvent turnover, nitrile **5.4** was crystallized in 72−78% yield with >99.6% purity on batch sizes of 86−280 kg. The reactor throughput was nearly 2 kg per h, meaning that 200 kg of **5.3** could be processed over a 4 day period. The flow process eliminates the need to cool large reaction vessels, provides precise control of the temperature and reaction time in order to improve diastereoselectivity and avoid decomposition, and maintains a small volume of the toxic mixture that is continuously quenched at the end of the reaction.

Although not discussed in the recent Gilead article, an improved process for conversion of lactone **5.1** to the cyanation precursor **5.3** on a 282 kg scale was described in the experimental section (Scheme 3).[33] This process involved in situ protection of **5.9b** and use of 1.0 equiv of neodymium chloride to facilitate the reaction with lactone **5.1**. In vessel 1, $NdCl_3$ (1.0 equiv), *n*-Bu_4NCl (1.0 equiv), and THF were combined and azeotropically dried, followed by addition of lactone **5.1** (1.0 equiv). After dissolution, the solution was cooled to −20 °C. In vessel 2, iodide **5.9b** (1.1 equiv) was dissolved in THF and cooled to 0 °C. TMSCl (1.1 equiv) was added, and the mixture was cooled to −10 °C. Next, PhMgCl (2.17 equiv) was added, and the mixture was cooled to −20 °C, after which *i*-PrMgCl (1.13 equiv) was added. After 2 h, this mixture was added to the solution in vessel 1, and the resulting mixture was stirred for 8 h at −20 °C. After aqueous workup, **5.3** was isolated in 69% yield after crystallization from 2-PrOAc, methyl *tert*-butyl ether (MTBE), and *n*-heptane with a reported 100% purity.

This recent publication from Gilead describing optimization of two manufacturing steps[33] indicates that significant process development has occurred relative to the initial publications and patents,[28−32] providing confidence that a robust manufacturing process has been developed that can be further scaled internally as well as transferred to contract manufacturing organizations to support the treatment of COVID-19.

5.3. Final Forms and Formulations of Remdesivir. Three crystalline forms of remdesivir free base have been disclosed by Gilead. Competition experiments wherein the different forms were slurried together in various solvents demonstrated conversion to form II, demonstrating that form II is the thermodynamically most stable free-base form. A crystalline maleate salt was also reported. None of the forms is hygroscopic.[34]

Several experiments at the 10−20 g scale were described for the final two steps (reaction of **5.10** and **5.11-*Sp*** followed by deprotection) and crystallization. The coupling reaction was carried out in THF at 20 °C for 4 h, followed by an aqueous quench and turnover to acetonitrile. Addition of concentrated aqueous HCl to this mixture at 0 °C effected deprotection of the acetonide. Workup was carried out with 2-methyltetrahydrofuran followed by turnover to 2-PrOAc. Crystallization provided a mixture of forms II and IV.[34]

According to the EMA Summary on Compassionate Use document,[18] the final form of the active pharmaceutical ingredient (API) may be either form II or a mixture of forms II and IV, which have similar solubilities. Remdesivir is provided in two dosage forms, a solution formulation (stored frozen) and a lyophilized formulation, both of which are then diluted for intravenous administration.[18] Betadex sulfobutyl ether sodium is used in the formulation as a solubilizing agent because of the limited aqueous solubility of remdesivir.[18] Oral delivery of remdesivir was not feasible because of rapid first-pass clearance in the liver.[18] Since remdesivir is administered as an intravenous solution, control of the final form is not required for bioavailability but may be important for purification, and the final form must have the appropriate solubility to support iv administration.

5.4. Outlook for Supply of Remdesivir. According to Gilead's CEO, Daniel O'Day, their existing supply as of April 4, 2020, was 1.5 million doses, or roughly 140 000 treatment courses based on 10 day treatment.[35] Much of the sterile formulation of drug product was manufactured from February to April 2020 at Gilead's La Verne, CA, facility.[36] Gilead plans to have 500 000 treatment courses available by October 2020 and 1 million by the end of 2020.[35] Over the past few months, the company has been able to halve the end-to-end manufacturing timeline from 1 year to about 6 months. In addition, the company has repurposed internal facilities and also increased its network of external manufacturing partners.[35] With a loading dose of 200 mg on day 1 and 100 mg maintenance doses on days 2−10, each treatment course requires 1.1 g of drug. A million treatments would thus require about 1100 kg of API, not accounting for any losses during formulation.

Anticipating FDA approval, on the 2020 first quarter earnings call on April 30, 2020, Chief Financial Officer Andrew Dickson stated that in addition to the ramped up internal manufacturing effort, Gilead was also working with other global companies to develop parallel supply chains and licensing agreements to make remdesivir available on a larger scale.[37a] On May 12, 2020, Gilead announced outlicensing of nonexclusive rights of remdesivir to five generic drug manufacturers in India and Pakistan, namely, Jubilant, Cipla, Ferozsons, Hetero, and Mylan, allowing manufacture as well as sales in 127 countries.[37b]

6. HYDROXYCHLOROQUINE

6.1. History, Mechanism of Action, and Status of Clinical Trials. Hydroxychloroquine (HCQ, **4.2**) and chloroquine (CQ, **4.3**) have been long-standing oral drugs for the treatment of malaria and chronic inflammatory conditions, including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).[38] HCQ, a racemic mixture, was first approved in the U.S. in 1955 and is considered the first-line treatment for SLE, raising potential concerns of drug shortages for these patients to treat COVID-19 during this crisis.

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In malaria, CQ is known to inhibit the action of heme polymerase in malarial trophozites, preventing the conversion of heme to hemozin.[39] This causes a buildup of toxic heme, killing the parasite. If HCQ proves to be effective for SARS-CoV-2, it will not act by the same mechanism by which the drug functions as an antimalarial. HCQ and CQ are lipophilic weak bases and passively diffuse through cell membranes and into endosomes, lysosomes, and Golgi vesicles, where they become protonated, trapping them in the organelles and raising the pH.[20] It is postulated that this increase in the pH in endosomes prevents virus particles from utilizing their activity for fusion and entry into the cell.[40] CQ is known to inhibit terminal glycosylation of ACE2, the receptor that SARS-CoV-2 targets for cell entry. When ACE2 is in its unglycosylated state, it may less efficiently interact with the SARS-CoV-2 S protein, further inhibiting viral entry.[40] CQ inhibits SARS-CoV-2 in vitro with a half-maximal effective concentration (EC_{50}) in the low micromolar range. HCQ has in vitro activity with a lower EC_{50} for SARS-CoV-2 compared with chloroquine after 24 h of growth (HCQ, EC_{50} = 6.14 μM; CQ, EC_{50} = 23.90 μM).[41] HCQ and CQ are relatively well tolerated drugs and have been extensively tested in patients with SLE and malaria. However, both compounds can cause serious adverse effects, including QTc prolongation, hypoglycemia, retinopathy, and neuropsychiatric effects.[42,43]

There is currently no high-quality clinical evidence that HCQ or CQ has efficacy versus SARS, MERS, or SARS-CoV-2. Currently there are over 142 trials that have been registered globally involving either CQ or HCQ alone or in combination with other drugs such as azithromycin. Clinicaltrials.gov currently has over 99 clinical trials registered for the use of HCQ to treat or prevent COVID-19 (Table 5).[44] Typical clinical doses vary between 200 and 400 mg orally either once or twice daily for 7−14 days (and up to 60 days). A 200 mg dose of HCQ has an exceptional human half-life of 537 h in blood and 2963 h in plasma.[45] In the body, HCQ is rapidly N-dealkylated by cytochrome P450 (CYP) 3A4 to its active metabolite desethylhydroxychloroquine in addition to the inactive metabolites desethylchloroquine (DCQ) and bidesethylchloroquine (BDCQ) (Scheme 5).[46]

A recent open-label nonrandomized study in France that was published on March 20, 2020, in the *International Journal of Antimicrobial Agents* described the treatment of 42 patients hospitalized with COVID-19, 26 of whom received hydroxychloroquine and 16 of whom received routine care.[47] Twenty patients receiving 200 mg of hydroxychloroquine orally every 8 h reported improved virological clearance versus the standard of care. By day 6, virological clearance was 70% (14/20) versus 12.5% (2/16) for the hydroxychloroquine and control groups, respectively. It was also reported that the addition of azithromycin, an antibiotic, to the hydroxychloroquine arm resulted in complete viral clearance (6/6, 100%) versus hydroxychloroquine alone (8/14, 57%).

A small placebo-controlled trial of 62 patients with mild COVID-19 in Remin Hospital, Wuhan, China (Chinese clinical trial ChiCTR2000029559)[48] showed that 31 patients given HCQ reported a normal body temperature and cessation of cough much quicker than the 31 patients given the placebo. A large proportion of the patients on HCQ also demonstrated improvement in chest CT scans.

In a non-peer-reviewed study published on May 2, 2020, addition of zinc sulfate to hydrochloroquine and azithromycin resulted in a statistically significant increase in the frequency of patients being discharged home (OR 1.53, 95% CI 1.12−2.09) and a reduction in mortality or transfer to hospice.[49a]

In contrast, there are a number of very recent reports where the use of HCQ has not met the study primary end points. One such multicenter, parallel, open-label randomized trial involved 150 patients hospitalized with COVID-19 in China.[49b] Half (75) of the patients were administered a 1200 mg loading dose of HCQ daily for 3 days followed by a maintained dose of 800 mg for 2−3 weeks of total treatment, depending on severity of disease. The primary end point, which was the number of negative SARS-CoV-2 tests at 28 days, did not show a statistically significant difference between the treated and standard of care groups. The secondary end points, which were negative SARS-CoV-2 conversion rates at earlier days (days 4, 7, 10, 14, and 21), were also similar between the two groups.

Despite these mixed reports, the FDA issued an EUA for the use of HCQ to treat COVID-19 in the U.S.; nonetheless, larger randomized clinical trials are underway and will be necessary to determine how effective the drug is, including its risk/benefit ratio.

6.2. Synthesis of Hydroxychloroquine. The synthesis of hydroxychloroquine was disclosed by Sterling-Winthrop in a 1950 publication and 1951 patent.[50] The route involves three steps, as outlined in Scheme 6. In the first step, 1-chloro-4-pentanone (**6.1**) was alkylated with *N*-ethyl-*N*-hydroxyethylamine (**6.2**) (2.0 equiv) for 3 h in refluxing xylene. The resulting tertiary amine **6.3** was isolated in 44% yield after vacuum distillation. The reductive amination of **6.3** was carried out in methanolic ammonia with 1000 psi hydrogen for 24 h at room temperature catalyzed by Raney nickel. Amine **6.4** was isolated in 89% yield after vacuum distillation. For the third step, amine **6.4** (1.7 equiv), 4,7-dichloroquinoline (**6.5**) (1.0 equiv), phenol, and catalytic KI were heated to 125−130 °C for 18 h. When the reaction was completed, the mixture was diluted with MeOH, and phosphoric acid was added, after which the side of the flask scratched with a glass rod to induce crystallization. The diphosphate salt of hydroxychloroquine was isolated in 42% yield.[50]

Protection of ketone **6.1** as its ketal (not shown) prior to displacement with amine **6.2** improved the yield to 83% (110 °C in toluene) but required two additional steps (ketalization and deprotection). The overall yield for the three-step sequence was 67%.[51]

The yield for the displacement reaction of **6.5** with **6.4** was subsequently improved as follows:

(1) Carrying out the reaction neat under a pressure of 10−20 bar allowed the use of a reduced reaction temperature of 100−110 °C for 4 h. Hydroxychloroquine free base was isolated in 78% yield after aqueous workup, pH swings, carbon and alumina treatment, and crystallization from dichloroethane.[52]

(2) A 78% yield was reported when a supported cobalt nitrate catalyst was used and the reaction was carried out at 90−110 °C in xylenes for 1.5−2.5 h.[53]

(3) The reaction was carried out using sodium ethoxide in 2-PrOAc, followed by slowly distilling off 2-PrOAc and increasing the temperature to 120−122 °C. After aqueous workup and crystallization from 2-PrOAc, hydroxychloroquine free base was isolated in 88% yield with 99.3% purity.[54]

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Table 5. Representative Phase III Clinical Trials Underway with Hydroxychloroquine (HCQ)[44]

clinical trial number	study title	estimated enrollment	study start/estimated completion dates	study arms	
				active	control
NCT04329611	A Randomized, Double-Blind, Placebo-Controlled Trial to Assess the Efficacy and Safety of Oral Hydroxychloroquine for the Treatment of SARS-CoV-2 Positive Patients for the Prevention of Severe COVID-19 Disease	1660	April 13, 2020/ July 31, 2020	HCQ 400 mg po bid loading dose for 1 day followed by 200 mg po twice daily for 4 days	placebo
NCT04342221	Randomized Controlled Trial of Hydroxychloroquine versus Placebo for the Treatment of Adult Patients with Acute Coronavirus Disease 2019 - COVID-19	220	March 29, 2020/ March 2021	800 mg loading dose on day 1; from the second day on, each patient will get 600 mg (three capsules) once a day until day 7 (six more doses of 600 mg)	placebo
NCT04329923	The PATCH Trial (Prevention and Treatment of COVID-19 with Hydroxychloroquine)	400	April 9, 2020/ April 1, 2021	Cohort 1 HCQ: COVID-19 PCR+ patients quarantined at home randomized to this arm will be treated with HCQ 400 mg twice a day for up to 14 days Cohort 2 HCQ high dose: hospitalized COVID-19 PCR+ patients randomized to this arm will be treated with HCQ 600 mg twice a day for up to 14 days Cohort 2 HCQ low dose: hospitalized COVID-19 PCR+ patients randomized to this arm will be treated with HCQ 600 mg once a day for up to 7 days Cohort 3 HCQ: health care workers at high risk of contracting COVID-19 randomized to this arm will be treated with HCQ 600 mg once a day for 2 months	placebo
NCT04345692	A Randomized, Controlled Clinical Trial of the Safety and Efficacy of Hydroxychloroquine for the Treatment of COVID-19 in Hospitalized Patients	350	March 26, 2020/ December 30, 2021	HCQ 400 mg twice daily by mouth on day 1, followed by 200 mg twice daily by mouth on days 2−5	standard of care
NCT04334382	Hydroxychloroquine versus Azithromycin for Outpatients in Utah with COVID-19 (HyAzOUT): A Prospective Pragmatic Trial	1550	April 2, 2020/ December 31, 2020	(1) HCQ 400 mg po bid on day 1, then 200 mg po bid on days 2−5 (dose reductions for weight <45 kg) (2) azithromycin 500 mg po on day 1 plus 250 mg po daily on days 2−5	none
NCT04344379	Randomized Multicenter Study Evaluating the Efficacy of Azithromycin and Hydroxychloroquine in the Prevention of SARS-CoV-2 Infection in the Hospital Population Exposed to Virus	900	April 15, 2020/ August 31, 2020	(1) HCQ 200 mg bid (2) azithromycin 200 mg per day	placebo
NCT04328285	Chemoprophylaxis of SARS-CoV-2 Infection (COVID-19) in Exposed Healthcare Workers: A Randomized Double-Blind Placebo-Controlled Clinical Trial	1200	April 14, 2020/ November 2020	(1) HCQ 200 mg: two tablets in the evening on day 1, two tablets in the morning on day 2, and 1 tablet once daily afterward (2) lopinavir/ritonavir 200 mg/50 mg: two tablets twice daily	placebo
NCT04331834	Pre-exposure Prophylaxis with Hydroxychloroquine for High-Risk Healthcare Workers during the COVID-19 Pandemic: A Unicentric, Double-Blinded Randomized Controlled Trial	440	April 3, 2020/ October 2020	HCQ 400 mg daily during the first 4 days, followed by 400 mg weekly during 6 months	placebo
NCT04315896	Hydroxychloroquine Treatment for Severe COVID-19 Respiratory Disease: Randomized Clinical Trial (HYDRA Trial)	500	March 20, 2020/ October 2020	HCQ tablet 200 mg every 12 h for 10 days	placebo
NCT04318015	Chemoprophylaxis with Hydroxychloroquine in Healthcare Personnel in Contact with COVID-19 Patients: A Randomized Controlled Trial (PHYDRA Trial)	400	April 14, 2020/ December 2020	HCQ 200 mg daily for 60 days	placebo
NCT04341441	Will Hydroxychloroquine Impede or Prevent COVID-19: WHIP COVID-19 Study	3000	April 7, 2020/ June 2020	(1) HCQ 200 mg po daily following the day 1 dose of 400 mg orally once (2) HCQ for prophylaxis of malaria is 6.5 mg/kg per dose (maximum of 400 mg per dose) administered orally weekly on the same day of each week	placebo
NCT04328012	Comparison of Therapeutics for Hospitalized Patients Infected with SARS-CoV-2 in a Pragmatic Adaptive Randomized Clinical Trial during the COVID-19 Pandemic (COVID MED Trial)	4000	April 6, 2020/ January 2021	(1) lopinavir/ritonavir 400 mg/200 mg po bid for 5−14 days depending on availability (2) HCQ sulfate 400 mg bid on day 0, 200 mg bid on days 1−4 (days 1−13 if available) (3) losartan 25 mg po qd for 5−14 days depending on availability	placebo
NCT04332991	Outcomes Related to COVID-19 Treated with Hydroxychloroquine among In-patients with Symptomatic Disease	510	April 2, 2020/ April 2021	HCQ 400 mg twice on day 1, then 200 mg twice daily for the next 4 days for a 5 day total course	placebo

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Table 5. continued

clinical trial number	study title	estimated enrollment	study start/estimated completion dates	study arms	
				active	control
NCT04325893	Hydroxychloroquine versus Placebo in Patients Presenting COVID-19 Infection and at Risk of Secondary Complication: a Prospective, Multicenter, Randomized, Double-Blind Study	1300	April 2020/ September 2020	the first dose of 400 mg will be taken immediately after inclusion on day 0, the second dose of 400 mg will be taken on the same evening, and the treatment will then be continued for the following 8 days at a rate of 200 mg in the morning and evening	placebo
NCT04341727	WU 352: Open-label, Randomized Controlled Trial of Hydroxychloroquine Alone or Hydroxychloroquine Plus Azithromycin or Chloroquine Alone or Chloroquine Plus Azithromycin in the Treatment of SARS CoV-2 Infection	500	April 4, 2020/ April 2021	(1) HCQ 400 mg orally twice a day for 1 day, followed by 200 mg twice a day for four consecutive days (5 days total) (2) HCQ 400 mg orally twice a day for 1 day, followed by 200 mg twice a day for four consecutive days (5 days total) AND azithromycin 500 mg orally for 1 day, followed by 250 mg daily for four consecutive days (5 days total) (3) chloroquine phosphate 1000 mg orally once, followed in 12 h by 500 mg, then 500 mg orally twice daily for 4 days (5 days total) (4) chloroquine phosphate 1000 mg orally once, followed in 12 h by 500 mg, then 500 mg orally twice daily for 4 days (5 days total) AND azithromycin 500 mg orally once, followed by 250 mg daily for 4 consecutive days (5 days total); the drug will be supplied in 250 mg tablets	

(4) The reaction was carried out neat at 120−130 °C for 13−24 h, followed by aqueous workup and crystallization of the crude free base from EtOAc or 1,2-dichloroethane in 88−89% yield with 95−96% purity. Crystallization of the sulfate salt from EtOH improved the purity to >99%.[55]

(5) A yield of 78% was achieved by carrying out the reaction in *i*-Pr_2NEt at 125−135 °C for 3−4 days. The product was isolated by silica chromatography.[56] We note also in this paper that resolution of **6.4** using mandelic acid was described, providing gram quantities of each enantiomer of **6.4**,[56] although hydroxychloroquine is approved as a racemate.

Gupton's group at Virginia Commonwealth University recently adapted the hydroxychloroquine synthesis to continuous flow.[57] A few modifications were made to the original synthesis to render it practical for flow synthesis: (1) iodide **6.7** was used instead of chloride **6.1** to accelerate the displacement reaction and minimize side reactions; (2) to facilitate telescoping reactions, THF was chosen as the primary solvent; and (3) instead of direct reductive amination of the ketone, a two-step process via oxime **6.8** was developed, allowing both steps to be carried out in THF (Scheme 7).

For the first step in flow, lactone **6.6** and 55% aqueous HI were flowed into a tubular reactor at 80 °C with a residence time of 5 min (Figure 4). The crude mixture of **6.7** was advanced into a mixer along with streams of sodium bicarbonate and hexanes/MTBE. The two phases were then passed through a hydrophobic membrane separator (Zaiput). The product in the organic layer was concentrated to dryness and used without purification in the next sequence.

The next three steps were telescoped (Figure 5). Streams of iodide **6.7** and amine **6.2** in THF were combined and preheated prior to flowing into a packed bed of potassium carbonate at 100 °C. The output stream of **6.3** was combined with hydroxylamine in THF and flowed through a packed bed of potassium carbonate at 100 °C to afford a solution of oxime **6.8**. This solution was then advanced into a continuous stirred tank reactor (CSTR), where it was combined with Raney nickel and hydrogen gas (10 bar) at a temperature of 80 °C. The product was collected and worked up in batch mode. After concentration and vacuum distillation, amine **6.4** was isolated in 68% yield for the three steps.

The final step, the reaction of **6.4** with **6.5**, was carried out in batch mode and described only on a 200 mg scale. The best conditions involved mixing of triethylamine and potassium carbonate in EtOH followed by removal of the EtOH and warming to 125 °C, which afforded hydroxychloroquine in 78% yield after purification by silica chromatography.[57]

6.3. Hydroxychloroquine Final Form and Formulation.

The final form of hydroxychloroquine is a monosulfate salt. Both the tertiary amine and quinoline nitrogens are protonated in the crystalline sulfate salt.[58] Two polymorphs have been reported, one melting at 240° and the other at ∼198°.[59]

The oral formulation is provided as a film-coated tablet containing 200 mg of the sulfate salt, equivalent to 155 mg of the free base.[45]

6.4. Outlook for Supply of Hydroxychloroquine.

Substantial quantities of hydroxychloroquine have been promised over the next few months from seven manufacturers.[60]

In a March 20, 2020, press release, the Sandoz division of Novartis reported that it had 50 million doses (200 mg tablets) in stock and planned to donate up to 130 million doses by the

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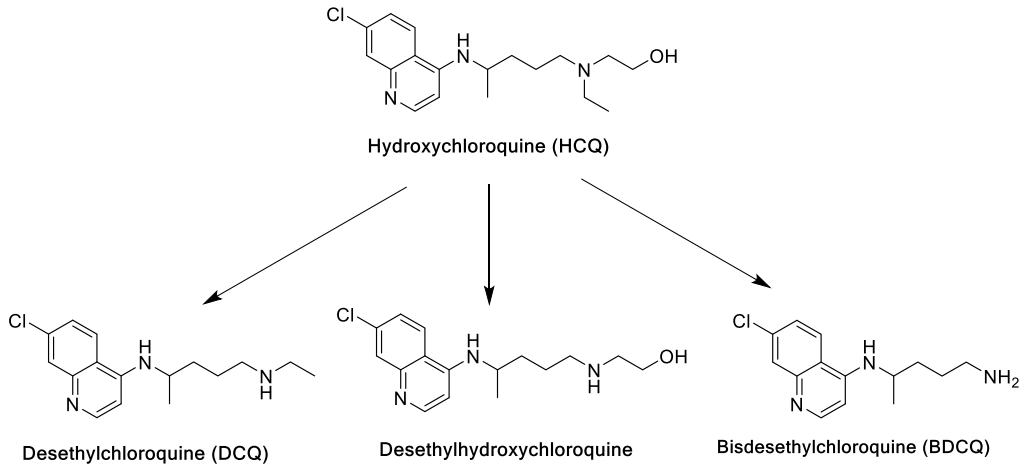
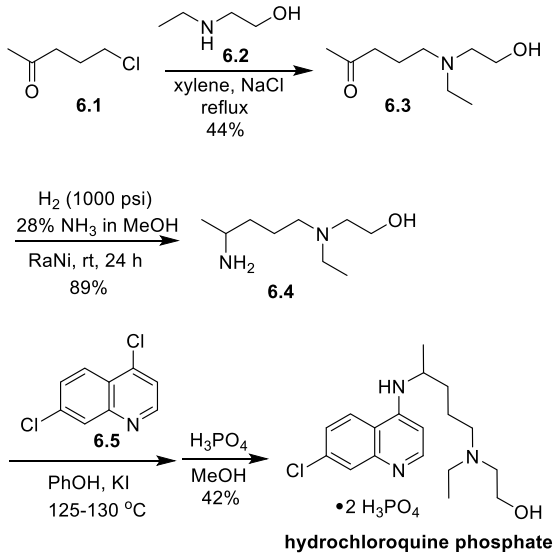
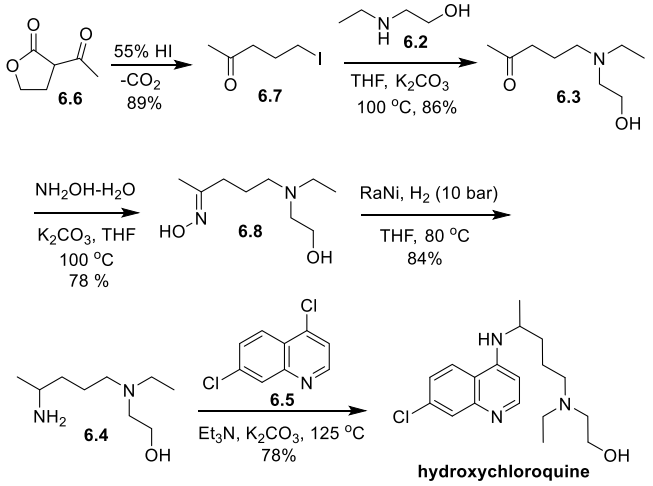
Scheme 5. Metabolism of Hydroxychloroquine



Scheme 6. Initial Route to Hydroxychloroquine



Scheme 7. Hydroxychloroquine Route Adapted to Flow Synthesis



end of May 2020. The company is also evaluating increasing production capacity internally and with external partners.[61]

In a March 19, 2020, press release, Mylan stated that the company had restarted production of hydroxychloroquine sulfate tablets at its West Virginia facility and was exploring options to initiate production outside the U.S. With the API currently available, the company expected to begin supplying drug by mid-April with the goal to ramp up manufacture to supply 50 million doses.[62]

On March 19, 2020, Teva announced that it would provide 6 million doses of hydroxychloroquine sulfate tablets by March 31, 2020, and more than 10 million by the end of April 2020.[63]

On March 20, 2020, Amneal announced an increase in production of hydroxychloroquine sulfate and expected to provide 20 million tablets by mid-April 2020.[64]

On April 10, 2020, Sanofi announced its intent to donate 100 million doses of hydroxychloroquine across 50 countries. Sanofi has doubled its incremental production capacity across its eight hydroxychloroquine manufacturing sites worldwide and is on track to quadruple production by the summer of 2020.[65]

According to a Bloomberg article, India manufactures 47% of the world's supply of hydroxychloroquine.[66] The country initially banned its export on March 25, 2020, but reversed this decision on April 8, 2020, after the U.S. requested supplies.[67] Zydus Cadila is increasing production from 3000 kg/month to 20000−30000 kg/month with the possibility of further increasing to 50 000 kg/month if needed. Ipca Laboratories has a 20 000 kg capacity, can manufacture 100 million tablets per month, and can increase its capacity to 26 000 kg. Ipca Laboratories has been barred from selling its products in the U.S. since 2015 for violations of GMP regulations, but on March 20, 2020, the FDA made an exception for the import of hydroxychloroquine.[67] Dr. Reddy's also manufactures hydroxychloroquine sulfate tablets.[68a]

Production in China was also curtailed by a lack of raw materials but is expected to recover by June 2020. Manufacturers in China include Chongqing Kangle Pharmaceutical Co., Ltd., Nantong Jinghua Pharmaceutical Co., Ltd., and Chongqing Southwest No. 2 Pharmaceutical Factory Co., Ltd.[68b]

7. FAVIPIRAVIR

Favipiravir (FPV, **4.8**; sold under the trade name Avigan), a broad-spectrum antiviral discovered by Toyoma Chemical Company, Ltd. (Fujifilm Group), is a modified pyrazine analogue that was originally approved for influenza resistance in Japan.[69] It inhibits replication of both influenza A and B and

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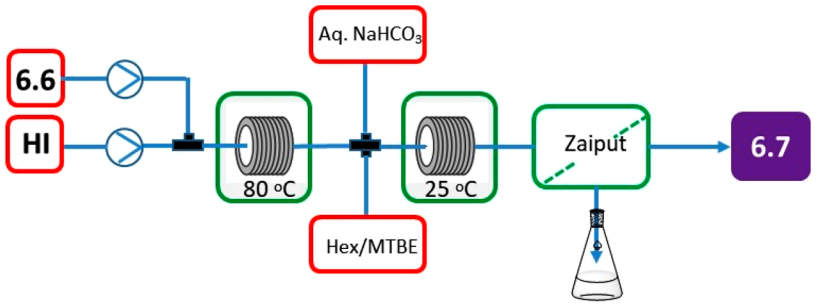


Figure 4. Flow schematic for conversion of lactone **6.6** to 1-iodo-4-pentanone (**6.7**).

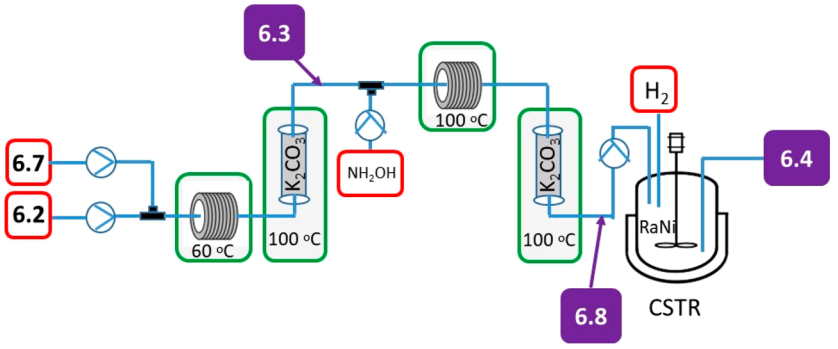
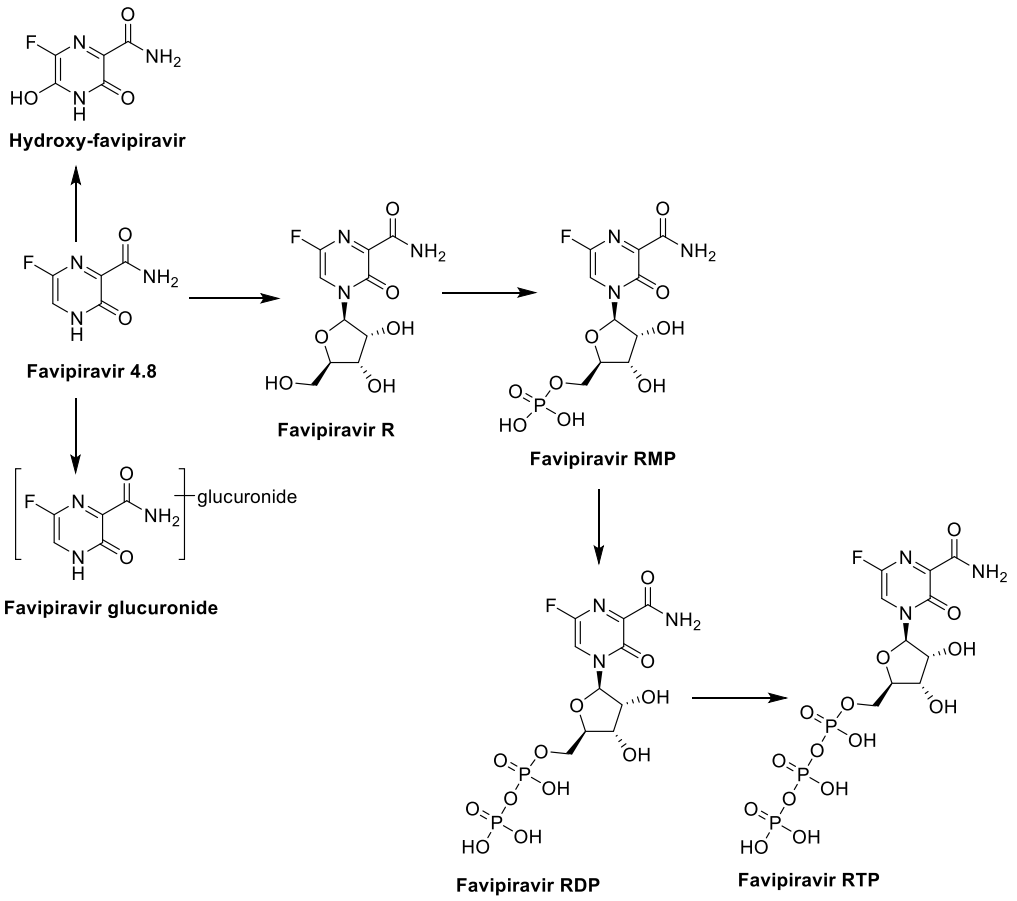


Figure 5. Flow schematic for the conversion of 1-iodo-4-pentanone (**6.7**) to amine **6.4**.

Scheme 8. Metabolism of Favipiravir



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has also shown activity versus avian influenza.[70] FPV is a prodrug that undergoes intracellular ribosylation and phosphorylation to become the active drug favipiravir RTP (Scheme 8).[69,71]

7.1. History, Mechanism of Action, and Status of Clinical Trials. Favipiravir RTP is an inhibitor of RNA-dependent RNA polymerase that prevents viral transcription and replication.[72] Several hypotheses as to how favipiravir RTP interacts with RNA-dependent RNA polymerase have been generated, which show that it is incorporated into a nascent RNA strand, preventing RNA strand elongation and viral proliferation.[69] The presence of purine nucleoside analogues can significantly reduce FPV's antiviral activity, suggesting that there is competition between FPV and the purine nucleosides for the same binding site. Most of favipiravir's preclinical data are associated with its influenza and Ebola activity, but the compound has demonstrated broad activity versus other RNA viruses.[69] The in vitro EC_{50} of favipiravir against SARS-CoV-2 is 61.88 μM/L in Vero E6 cells.[20]

The human bioavailability of FPV is very high at 98%; its metabolites are predominantly renally cleared, and its half-life is estimated to range from 2 to 5.5 h.[70]

The most frequent adverse events of FPV reported during the development for influenza treatment include mild to moderate diarrhea, asymptomatic increase of blood uric acid and transaminases, and decrease of neutrophil count.[73]

FPV has been approved for use in clinical trials for COVID-19 in China and also for experimental use in Italy, especially in the most affected regions.[74]

Limited and smaller-patient-number clinical trials are underway using an FPV starting dose of 1600 mg twice daily on day 1 followed by 600 mg twice daily for the next 9 days (Table 6).[75] A few of these trials are comparing FPV with chloroquine or in combination with other drugs such as tocilizumab.

To date, there is little clinical evidence that this drug has benefit for COVID-19, so further clinical trials are warranted. A nonplacebo open-label trial undertaken in Shenzhen, China, compared oral favipiravir (1600 mg twice daily for 1 day and then 600 mg twice daily thereafter) plus inhaled interferon with a historical cohort of patients receiving lopinavir/ritonavir for 14 days. Those treated with FPV and interferon had median shedding of virus of 4 days, compared with 11 days in the lopinavir/ritonavir group.[76] Radiographic improvement of chest CT scans was also seen in 91% of FPV/interferon-treated patients, compared with 62% of those on lopinavir/ritonavir. Again, this was not a randomized, placebo-controlled clinical trial, so much caution is required in interpreting these results. A prospective, randomized, controlled, open-label multicenter trial based in China (China clinical trial CHiCTR20000302540) compared FPV (1600 mg twice on day 1 followed by 600 mg twice daily on days 2−10) to umifenovir (Arbidol) (200 mg thrice daily for 10 days) in adult COVID-19 patients. Favipiravir did not significantly improve the clinical recovery rate at day 7 (61%) versus umifenovir (52%).[77]

7.2. Synthesis of Favipiravir. *7.2.1. Routes from the Innovator Company, Toyama Chemicals.* While favipiravir is a very small molecule, with a molecular weight of only 157, its synthesis is not trivial. The first route to favipiravir reported by Toyama Chemicals (Scheme 9) required six steps with an overall yield of about 2%.[78] As is often the case with medicinal chemistry routes, which are designed to quickly generate analogues, several steps were unoptimized with low yields. The synthesis started with methyl 3-amino-6-bromopyrazine-2-carboxylate (**7.1**), which was diazotized in concentrated sulfuric

Table 6. Clinical Trials Underway with Favipiravir (FPV)[75]

clinical trial number	study title	estimated enrollment	study start/ estimated completion dates	study arms	
				active	control
NCT04336904	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Clinical Study Evaluating the Efficacy and Safety of Favipiravir in the Treatment of Patients with COVID-19-Moderate Type	100	March 25, 2020/ July 2020	FPV 1800 mg bid on day 1; 600 mg tid on day 2 and thereafter for a maximum of 14 days	placebo
NCT04349241	Efficacy and Safety of Favipiravir in Management of COVID-19	100	April 20, 2020/ October 2020	FPV 3200 mg (1600 mg each 12 h) loading dose on day 1 followed by a 1200 mg maintenance dose (600 mg each 12 h) on days 2−10	standard of care
NCT04310228	Favipiravir Combined with Tocilizumab in the Treatment of Corona Virus Disease 2019—A Multicenter, Randomized, and Controlled Clinical Trial Study	150	March 8, 2020/ May 2020	(1) FPV 1600 mg bid on day 1, then 600 mg bid on days 2−7 AND tocilizumab 4−8 mg/kg iv (2) FPV 1600 mg bid on day 1, then 600 mg bid on days 2−7 (3) tocilizumab 4−8 mg/kg iv	none
NCT04333589	The Mechanism, Clinical Outcome, and Therapeutic Intervention of Corona Virus Disease 2019 Patients Whose Nucleic Acids Changed from Negative to Positive	210	April 1, 2020/ September 2020	FPV 1600 mg, twice daily on day 1; 600 mg, twice daily on days 2−7. Maximum number of treatment days should not exceed 14.	standard of care
NCT04346628	A Phase 2 Randomized, Open Label Study of Oral Favipiravir Compared to Standard Supportive Care in Subjects with Mild COVID-19	120	April 2020/ April 2021	FPV 1800 mg on day 1 followed by 800 mg bid for the next 9 days (days 2−10)	standard of care
NCT4319900	Clinical Trial of Favipiravir Tablets Combined with Chloroquine Phosphate in the Treatment of Novel Coronavirus Pneumonia	900	March 5, 2020/ April 2020	(1) FPV 1600 mg bid on day 1 then 600 mg bid on days 2−10 AND chloroquine 500 mg bid on day 1 then 500 mg qd on days 2 and 3 and 250 mg qd on days 4−10 (2) FPV 1600 mg bid on day 1 then 600 mg bid on days 2−10	placebo

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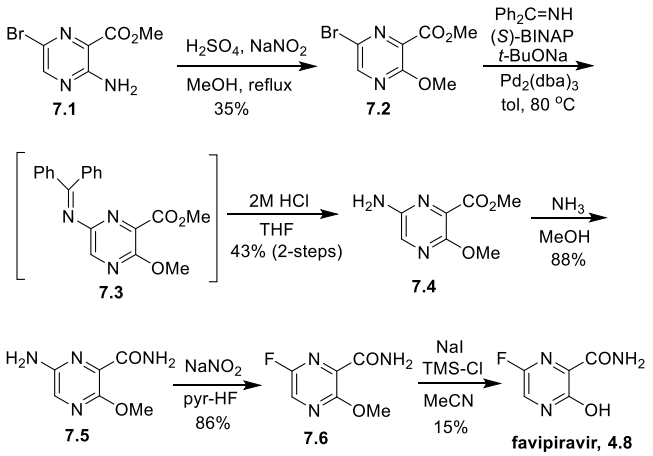
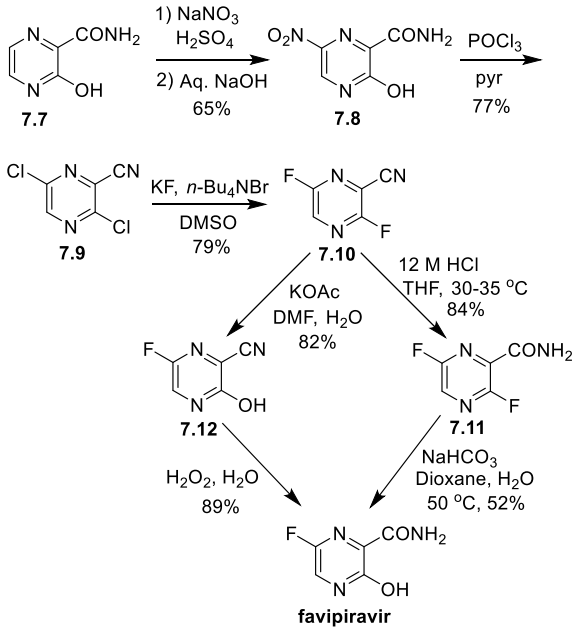
Scheme 9. First-Generation Route to Favipiravir



acid with sodium nitrite and then added to MeOH to generate methoxy compound **7.2** in 35% yield. Cross-coupling of **7.2** with benzophenone imine under Pd catalysis provided adduct **7.3**, which was then hydrolyzed with 2 M HCl to furnish amine **7.4** in 43% yield for the two steps. Methyl ester **7.4** was converted to primary amide **7.5** with methanolic ammonia in 88% yield. Diazotization/fluorination was conducted using sodium nitrite in 70% pyridinium hydrofluoride to afford fluoro compound **7.6** in 86% yield. In the final step, conversion of the methoxy group to the hydroxyl group was accomplished with in situ-generated TMSI in acetonitrile to furnish favipiravir in 15% yield.[78]

A second-generation route was disclosed on a multigram to a few hundred gram scale by Toyama in 2001 (Scheme 10).[79] The

Scheme 10. Second-Generation Route Disclosed by Toyama

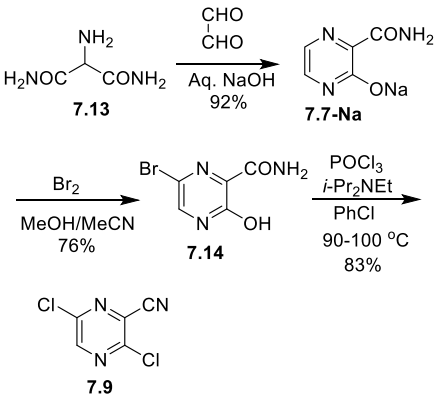


synthesis started with 3-hydroxypyrazine-2-carboxamide (**7.7**),[80] which was nitrated with sodium nitrate in concentrated sulfuric acid at 30−40 °C. Nitro compound **7.8** was crystallized by adding the reaction mixture to water and then slurried in dilute NaOH, resulting in an isolated yield of 65%. Nitropyrazine **7.8** was treated with phosphorus oxychloride and pyridine with a ramp in temperature from 60 to 100 °C, resulting in displacement of both the nitro and hydroxyl groups with chlorine and dehydration of the amide to the nitrile. After aqueous workup and silica chromatography, 3,6-dichloropyrazine-2-carbonitrile (**7.9**) was isolated in 77% yield. Displacement of both chlorines with fluorines was accomplished with KF and *n*-Bu_4NBr in DMSO at 90−100 °C for 6 h. After aqueous workup and silica chromatography, **7.10** was isolated in 79% yield. Hydrolysis of the nitrile to the carboxamide was carried out with 12 M HCl and THF at 30−35 °C to afford 3,6-difluoropyrazine-2-carboxamide (**7.11**) in 84% yield. Selective hydrolysis of the 3-F group with sodium bicarbonate at 50 °C in dioxane/water provided crystalline favipiravir in 52% yield. The overall yield for the five-step synthesis was 17%, with two purifications by column chromatography.

An alternate sequence for conversion of **7.10** to favipiravir was disclosed by Toyama in 2009 (Scheme 10).[81] The 3-F position was hydrolyzed first using KOAc in aqueous DMF, and the resulting hydroxyl compound **7.12** was purified by crystallization as its dicyclohexylamine salt in 82% yield. The crystallization of the salt was carried out directly on the reaction mixture, thereby avoiding a difficult workup since **7.12** is a water-soluble compound. In the final step, the nitrile of **7.12** was hydrolyzed to the carboxamide using aqueous hydrogen peroxide, affording favipiravir in 89% yield after crystallization from the acidified solution.

An improved route to **7.9** was developed by Nippon Soda (Scheme 11).[82] The sodium salt of **7.7** was first prepared from 2-

Scheme 11. Improved Route to 3,6-Dichloropyrazine-2-carbonitrile (7.9)



aminomalonic acid diamide (**7.13**) and glyoxal in an alkaline aqueous solution with the product crystallized from the reaction mixture in 92% yield. Bromination with molecular bromine was conducted in a MeOH/acetonitrile mixture. After reaction completion, water was added to crystallize product **7.14** in 76% yield. Chlorination of the 3- and 6-positions was accomplished using phosphorus oxychloride and diisopropylethylamine in chlorobenzene at 90−100 °C. After aqueous workup, **7.9** was generated as a solution in toluene that was used directly in the next fluorination step under conditions similar to those outlined in Scheme 10.

A third-generation route from Toyama was disclosed in a 2013 patent application.[83a−c] This route was longer (nine steps) but built the core pyrazine ring system from simple and inexpensive starting materials (Scheme 12). This route used an isoxazole as a masking group for the ortho amide and hydroxyl functional groups.[83a−c] The early steps were described on a kilogram scale, with gram-scale experimentals for the final steps.

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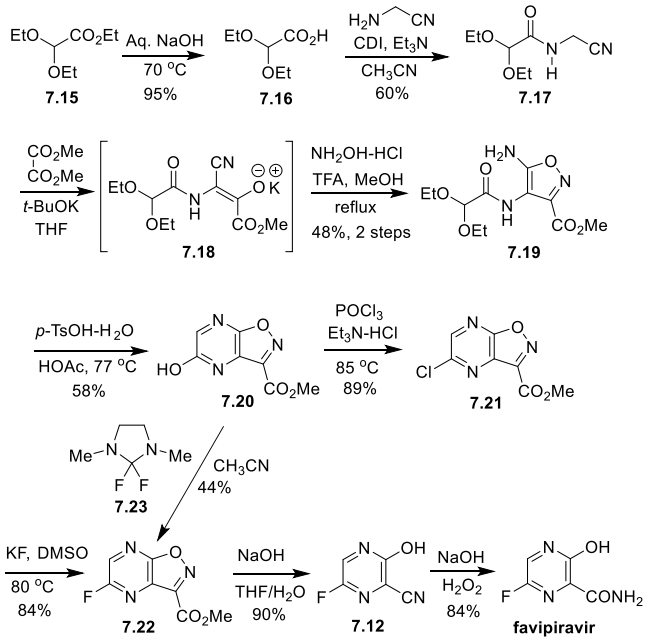
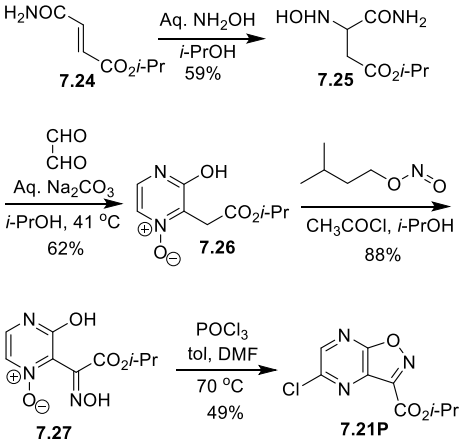
Scheme 12. Third-Generation Toyama Route to Favipiravir



Scheme 13. Alternate Route to Chloride 7.21P



The synthesis started with the saponification of ethyl diethoxyacetate (**7.15**) to obtain diethoxyacetic acid (**7.16**) in 95% yield, followed by amide bond formation with amino-acetonitrile mediated by CDI to afford **7.17** in 60% yield. Next, reaction with dimethyl oxalate in THF mediated by *t*-BuOK generated **7.18**, which was not isolated but reacted with hydroxylamine hydrochloride and TFA in MeOH at reflux to furnish isoxazole **7.19** in 48% yield for the two steps. Formation of the pyrazine ring was accomplished by hydrolysis of the acetal group with *p*-TsOH-H_2O in HOAc at 77 °C to provide **7.20** in 58% yield. Conversion of the hydroxyl group to chloride was conducted in $POCl_3$ with triethylamine hydrochloride at 85 °C to provide **7.21** in 89% yield. At this point in the synthesis, several different esters were prepared, some of which gave somewhat better yields and ease of operation in the next steps. Fluorination was carried out with KF in DMSO at 80 °C to afford **7.22** in 84% yield. In some cases it was found that addition of 1-chloro-2,4-dinitrobenzene reduced the amount of black tar generated in the reaction, perhaps as a sink for excess fluoride. Alternatively, hydroxyl compound **7.20** could be directly converted to fluoro compound **7.22** with 2,2-difluoro-1,3-dimethylimidazolidine (**7.23**);[83d] however, the yield with this expensive fluorinating agent was modest at 44% after isolation by silica chromatography. Opening of the isoxazole with aqueous NaOH in THF revealed the nitrile **7.12**, which was purified by treatment with an ion-exchange resin and then hydrolyzed to the amide (favipiravir) with basic hydrogen peroxide. Favipiravir could be purified to 99.0% by crystallization of its dicyclohexylamine salt.[83a−c]

An alternate four-step route to intermediate **7.21P** from maleic amide−ester **7.24** was also disclosed by Toyama (Scheme 13).[83a−c] Michael addition of hydroxylamine to **7.24** in aqueous 2-PrOH afforded ester−amide **7.25** in 59% yield after crystallization from the reaction mixture. Condensation of **7.25** with an aqueous solution of glyoxal in 2-PrOH at 41 °C, with control of the pH at 9.0 by dropwise addition of sodium carbonate, provided pyrazine *N*-oxide **7.26** in 62% yield after crystallization, which was converted to oxime **7.27** in 88% yield by treatment with isoamyl nitrite and acetyl chloride in 2-PrOH and crystallization from the reaction mixture. Ring closure and chlorination upon treatment with phosphorus oxychloride in toluene/DMF at 70 °C afforded isopropyl ester **7.21P** in 49% yield. While the yields for this preparation are modest, all of the compounds are crystalline, and several directly crystallize from the reaction mixture.

7.2.2. Summary of Innovator Routes to Favipiravir. The initial route from Toyama was intended solely as a way of generating small quantities of material for initial testing and was not appropriate for scale-up.

The second-generation route, with contributions from both Toyama and Nippon Soda, provides a scalable six-step route to favipiravir in 33% yield. This includes the three-step process from Nippon Soda from the commercially available diamide **7.13** to 3,6-dichloropyrazine-2-carbonitrile **7.9** (Scheme 11)[82] followed by the improved Toyama route (the sequence **7.9** → **7.10** → **7.12** → favipiravir; Scheme 10) that integrates purification of the penultimate intermediate **7.12** as a dicyclohexylamine salt.[81]

The overall yield for the third-generation route is 9% (nine steps, Scheme 12) or 10% (Schemes 12 and 13). The length of the synthesis and lower yield make this route less attractive than the second-generation route. In addition, the intermediates up to and including **7.19** were reported to be liquids that are isolated by concentration to oils, such that purification can be carried out only by vacuum distillation. However, this route has one important safety advantage. As noted in the patent specification, 3,6-difluoropyrazine-2-carbonitrile (**7.10**), a key late-stage intermediate in the second-generation route, has high skin irritancy and is volatile, thus requiring special equipment for handling. On the other hand, compounds **7.20**, **7.21**, and **7.22** are solids with low volatility and no skin irritancy that require no special handling.

7.2.3. Alternate Routes to Favipiravir from Academic Laboratories and Generic Companies. Several alternate routes to favipiravir have been disclosed either in journal publications or the patent literature. The following routes are presented in chronological order. Routes that involve only minor variations of previously disclosed routes are not included here.

A short route to favipiravir was disclosed in 2012 by Zheng and co-workers at Shandong Qidu Pharmaceutical Co. (Scheme 14).[84] Nitro compound **7.8** was prepared via nitration of **7.7** as outlined in Scheme 10 (75% yield). Reduction of the nitro group was carried out by hydrogenation with Pd/C in HOAc to afford

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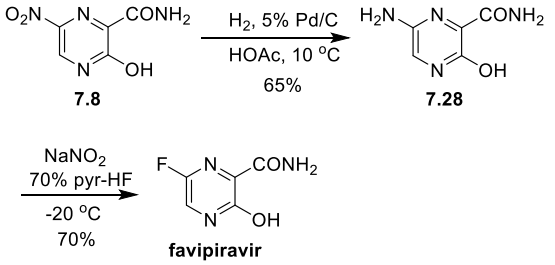
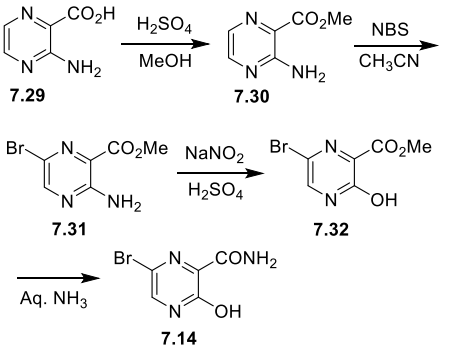
Scheme 14. Alternate Route to Favipiravir from 3-Hydroxy-6-nitropyrazinecarboxamide



amine **7.28** in 65% yield after crystallization from EtOAc. Amine **7.28** was dissolved in 70% pyridinium hydrofluoride and treated with sodium nitrite at −20 °C. After aqueous workup favipiravir was isolated in 70% yield with no purification. No details were provided on product purity. The three step route from **7.7** provides favipiravir in 34% yield.[84]

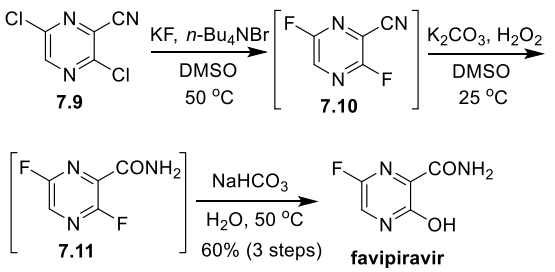
A route published by Zhang and co-workers at Shandong Qidu Pharmaceutical Co. in 2013 (Scheme 15)[85] intersects with

Scheme 15. Alternate Preparation of 6-Bromo-2-hydroxypyrazinecarboxamide (7.14)



intermediate **7.14** of the Nippon Soda synthesis (Scheme 11). The synthesis starts with 3-amino-2-pyrazinecarboxylic acid (**7.29**). After ester formation, bromination with NBS provided **7.31**. Diazotization and hydrolysis followed by amide formation afforded **7.14**. The route appears scalable but longer than the two step synthesis of Nippon Soda.[82] Further optimization of this route was reported by Liu and co-workers, with the most important contribution perhaps being the development of a one-pot process for the final three steps of the process, thus avoiding isolating of volatile 3,6-difluoro-2-pyrazinecarbonitrile (**7.10**) that has high skin irritancy (Scheme 16).[86] According to the experimental provided on a 400 mg scale, 3,6-dichloro-2-

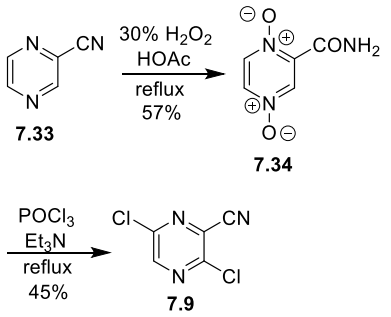
Scheme 16. One-Pot Process for Conversion of 7.9 to Favipiravir



pyrazinecarboxamide (**7.9**) was treated with KF (6 equiv) and *n*-Bu_4NBr (0.4 equiv) in DMSO at 50 °C for 3 h to generate **7.10**. Then potassium carbonate and aqueous 30% hydrogen peroxide were added at 0 °C, then stirred at 25 °C for 1.5 h to form amide **7.11**. Water and sodium bicarbonate were then added and the mixture warmed to 50 °C for 8 h to generate favipiravir. After aqueous workup, favipiravir was isolated in 60% yield after crystallization from EtOH.[86]

Li at Zhengzhou University disclosed a two-step process for conversion of pyrazine-2-carbonitrile (**7.33**) to 3,6-dichloropyrazine-2-carbonitrile (**7.9**) (Scheme 17).[87] In the first step, both

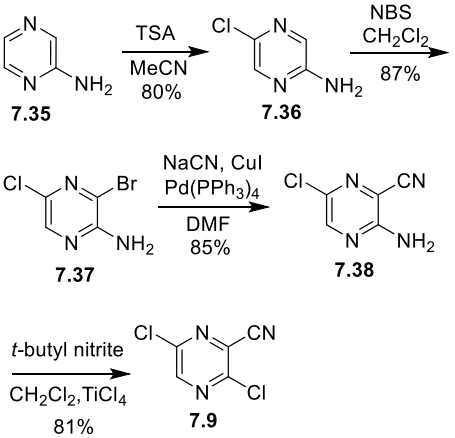
Scheme 17. Two-step Route to 7.9 from 2-Pyrazinecarbonitrile



pyrazine nitrogens were oxidized using aqueous hydrogen peroxide in HOAc at reflux to generate the bis-N-oxide **7.34**, which was isolated in 57% yield after crystallization from MeOH. While no mention of safety issues were noted, compound **7.34** appears to be a highly energetic compound that could be shock sensitive. This was followed with chlorination using $POCl_3$ and Et_3N at reflux to afford **7.9** in 45% yield after isolation by silica chromatography. The final three steps were also telescoped into a one-pot process using conditions similar to those in Scheme 14, with a yield of 65% over the final three steps after crystallization of favipiravir from EtOH.[87]

An alternate four step synthesis of **7.9** from 2-aminopyrazine (**7.35**) in 48% yield was reported by Xie and co-workers (Scheme 18).[88] 2-Aminopyrazine (**7.35**) was chlorinated in MeCN with *N*-chloro-*N*-methoxy-4-toluenesulfonamide (TSA) in 80% yield followed by bromination with NBS in dichloromethane to afford **7.37**. Installation of the nitrile group was

Scheme 18. Synthesis of 7.9 from 2-Aminopyrazine



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accomplished with Pd-catalyzed cyanation with NaCN mediated by CuI to furnish **7.38** in 85% yield. Conversion of the amine to chloride was carried out with *t*-butyl nitrite and titanium tetrachloride in dichloromethane to provide **7.9** in 81% yield, and 48% yield overall for the four steps.

7.2.4. Summary of Alternate Routes to Favipiravir. Several alternate routes to favipiravir have been disclosed starting from a variety of starting materials, including 3-hydroxypyridine-2-carboxamide,[84] 3-aminopyridine-2-carboxylic acid,[85,86] pyrazine-2-carbonitrile,[87] and 2-aminopyrazine.[88] Most of the routes are undeveloped, requiring isolation by silica chromatography; none has been described on scales of more than a few grams, and none provides any insight into product purity and the impurity profile. Nonetheless, two of the most notable advances in this collection of routes are (1) the three-step synthesis of favipiravir from 3-hydroxypyridine-2-carboxamide (**7.7**) (Schemes 10 and 14),[74] a starting material that can be synthesized in one step from 2-aminomalonic acid diamide (**7.13**), and (2) the one-pot conversion of 3,6-dichloropyrazine-2-carbonitrile (**7.9**) to favipiravir that avoids isolation of the skin irritant **7.10**.[86,87]

7.3. Final Forms and Formulation of Favipiravir. Two crystalline forms of neutral favipiravir are known, designated as forms A and B. Form A is the thermodynamically stable form and the form generated by the manufacturing process.[73] A crystal form of neutral favipiravir, crystallized from EtOH or 2-PrOH, was disclosed by Weihai Guanbiao Information Technology Co.[89] It is not known whether this is the same crystal form that is generated in the Fujifilm Toyama manufacturing process.

Toyama Chemical Co. has disclosed three crystal forms of the sodium salt of favipiravir, one anhydrate and two hydrates.[90] They have also disclosed a crystalline meglumine salt.[91] Both salts appear to have high water solubility, but the meglumine salt had better solubility properties when formulated as a lyophilized cake.[91]

Favipiravir is currently available as a tablet containing 200 mg of the active ingredient. The approved favipiravir dose for influenza in Japan is 1600 mg twice daily on day 1 followed by 600 mg twice daily for 4 days. The dose for Ebola virus infection is 6000 mg on day 1 and 2400 mg/day on days 2−9.[73]

7.4. Outlook for Supply of Favipiravir. Fujifilm Toyama announced on March 31, 2020, that it has increased production of Avigan (favipiravir) at its domestic sites and with its international partners in order to supply the Japanese government and other countries. Favipiravir is included in the national strategic stockpile of medicines of Japan, with up to two million doses available.[92] On April 15, 2020, Fujifilm stated that it is freeing up capacity at its Wako Pure Chemical facility in Japan and is exploring partnerships with external companies.[93] By July 2020 the company expects to be able to manufacture 100 000 treatments per month, increasing to 300 000 treatments per month by September 2020.[93]

The company noted that it is sourcing the starting material, diethyl malonate, from chemical producer Denka, who will reopen a facility that was shuttered in 2017 because of lack of demand.[94] We note that diethyl malonate could be used to generate the three-carbon starting material in Scheme 11, indicating the commercial route does not start with a pyrazine derivative. On April 27, 2020, Fujifilm announced that it has teamed up with two Japanese companies. Ube Industries will manufacture intermediates, while Kaneka will supply the drug substance with the goal to have initial supplies available by July 2020.[95]

In 2016 Fujifilm licensed the active ingredient of favipiravir to the Chinese company Hisun Pharmaceutical, allowing them to develop, manufacture, and market the drug in China. In February 2020, Hisun received approval to manufacture favipiravir in China.[96]

Lasa SuperGenerics announced on March 20, 2020, that it will work with the Institute of Chemical Technology in India to develop favipiravir with the goal to begin manufacturing of the drug within a few months.[97]

On April 30, 2020, Glenmark Pharmaceuticals announced that it had completed development of the API and formulation processes and had received approval from the Government of India to initiate clinical trials of favipiravir in COVID-19 patients in India.[98]

8. PIRFENIDONE

Pirfenidone (5-methyl-1-phenyl-2-[1*H*]-pyridone, **4.13**), marketed by Roche under the trade name Esbriet, is an immunosuppressant that has been approved in many regions for the treatment of idiopathic pulmonary fibrosis.[99]

8.1. History, Mechanism of Action, and Status of Clinical Trials. In vitro evidence shows that pirfenidone inhibits collagen synthesis, downregulates profibrotic cytokines, and decreases fibroblast proliferation,[100−102] and this has translated well into animal models of fibrosis.[103] Pirfenidone has also been shown to reduce the production of tumor necrosis factor α (TNF-α) and interleukin-1β (IL-1β) in both cells and isolated human peripheral blood mononuclear cells (PBMCs), which is consistent with both the antifibrotic and anti-inflammatory activities seen in fibrosis animal models.[104,105]

The absolute bioavailability of pirfenidone has not been determined in humans. Pirfenidone is primarily metabolized in the liver by CYP1A2 to yield 5-carboxypirfenidone, its inactive metabolite.[106] The mean terminal half-life is approximately 3 h in healthy volunteers, and the drug is excreted predominantly as 5-carboxypirfenidone in the urine (up to 80% of the dose). Pirfenidone increases hepatic enzyme levels, including aspartate and alanine transaminases and γ-glutamyl transpeptidase, and is contraindicated in patients with severe hepatic impairment.[106]

The FDA recently granted breakthrough therapy designation to Esbriet for unclassifiable interstitial lung disease (uILD). The Phase II trial was shown to slow disease progression and supported its efficacy on a number of lung function parameters, including forced vital capacity (FVC) in patients with uILD.[107] On the basis of the encouraging results seen in the treatment of both invasive pneumococcal disease (IPD) and uILD, pirfenidone is being repurposed to treat patients with severe COVID-19 infection (NCT04282902).[108] This multicenter, randomized, placebo-controlled Phase III clinical study will first assess the efficacy and safety of pirfenidone in 147 hospitalized adult patients diagnosed with COVID-19 and will be compared to the standard of care. Primary outcome measures include (1) absolute changes in baseline lesion area, finger pulse oxygen, and blood gas from baseline at 4 weeks of chest CT images and (2) total score of King's Interstitial Lung Disease Short Questionnaire (K-BILD) and week 4 absolute change from baseline. Secondary measures include time to death within 4 weeks due to respiratory causes and time to disease progression or death within 4 weeks in addition to multiple other pulmonary fibrosis survival measures. Pirfenidone was to be administered orally three times a day, two tablets each time, for a period of 4 weeks. The estimated primary completion date was April 30, 2020, and thus far the study data have not yet been reported.

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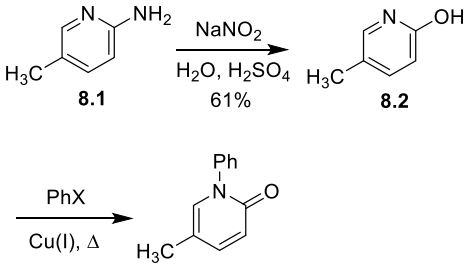
8.2. Synthetic Routes to Pirfenidone. Pirfenidone is synthesized in two steps from 2-amino-5-methylpyridine (**8.1**) (Scheme 19). Most of the focus in the patent literature has been on optimization of the cross-coupling step to improve the yield and impurity profile.

Scheme 19. Route to Pirfenidone



The route starts with readily available **8.1**, which is diazotized with $NaNO_2$ in aqueous sulfuric acid to generate 2-hydroxy-5-methylpyridine (**8.2**). The published procedures are based on the initial work by Adams and Schrecker in 1949 on the synthesis of 2-hydroxy-6-methylpyridine.[109] The primary issue with the synthesis is isolating the water-soluble product from the aqueous reaction mixture. In the Adams−Schrecker procedure, the isolation involves neutralizing the reaction mixture, concentrating to dryness, grinding the resulting solids, and then extensively extracting with boiling benzene. An improved isolation process was developed by a team at Smith Kline French by neutralization of the reaction mixture to pH 6.5−7.0 and extraction into EtOAc at 60 °C followed by crystallization from EtOAc.[110] This procedure was applied to the preparation of **8.2**, which was isolated in 61% yield.[111]

Conversion of **8.2** to pirfenidone was disclosed in 1974 by Affiliated Medical Research Inc.[112] The process involved reacting **8.2** with potassium carbonate and a catalytic amount of zinc-precipitated copper powder in refluxing iodobenzene (188 °C) for 18 h. At the end of the reaction, benzene was added, and the mixture was decolorized with charcoal and then filtered and concentrated to an oil. The oil was titurated in petroleum ether to afford pirfenidone in 85% yield.[112]

In the patent application from the innovator company, Intermune, pirfenidone was prepared from **8.2**, bromobenzene (1.8 equiv), potassium carbonate (1.2 equiv), and cuprous oxide (5 mol %) in DMF (2 volumes) at 125 °C for 18−20 h. After aqueous workup, pirfenidone was isolated in 85% yield after crystallization from toluene/heptane. The material was further purified by recrystallization from water (pH 11) to afford pirfenidone with the content of dimeric impurities less than 0.03% and the contents of all other impurities less than 0.05%. The inventors noted that the starting bromobenzene should be highly pure and contain very low levels of dibromo impurities since these form dimers that are difficult to remove.[113]

Many other patent applications have been filed on the conversion of **8.2** to pirfenidone that include different conditions, stoichiometries, and other copper catalysts. Of note, Procos has developed a process using chlorobenzene as the solvent at 175 °C, sodium carbonate, CuI, and the ligand *N*,*N*′-dimethylethylene-1,2-diamine. The product is isolated by crystallization from EtOAc/hexane followed by recrystallization from water in an overall yield of 72−84%.[114]

8.3. Pirfenidone Final Form and Formulation. Pirfenidone exists as a single crystalline form designated as form A.[99] The drug substance is milled to less than 150 μm.[113]

The drug product is formulated as an immediate-release hard capsule containing 266.7 mg of pirfenidone drug substance. The recommended daily dose is three capsules three times daily with food for a total of 2400 mg/day.[99] An 801 mg tablet is also available.[115]

8.4. Outlook for Supply of Pirfenidone. Pirfenidone has orphan drug status in the U.S. and EU, suggesting that large supplies may not be available. Roche has not provided an update on the supply situation for expanded use in COVID-19 treatment. The Indian manufacturer Cipla supplies generic pirfenidone but also has not provided any update on supply through May 14, 2020.

9. BARICITINIB

Baricitinib phosphate (sold under the trade name Olumiant by Lilly) was approved in the EU in February 2017 and in the U.S. in May 2018 for the treatment of moderate to severe rheumatoid arthritis in adult patients whose disease is not well-controlled by other TNF antagonists.[116]

9.1. History, Mechanism of Action, and Status of Clinical Trials. Baricitinib is a selective and reversible inhibitor of Janus-associated kinase 1 (JAK1) and 2 (JAK2). JAKs belong to the protein tyrosine kinase family and play important roles in the proinflammatory signaling pathways that are frequently overactivated in autoimmune disorders such as RA.[117] Upon binding of extracellular cytokines and growth factors, JAKs are phosphorylated and activate signal transducers and activators of transcription (STATs). Via these signaling cascades, inflammatory cytokine and chemokine transcription is induced to form inflammatory mediators, including IL-2, IL-6, IL-12, IL-15, and IL-23. The majority of viruses enter cells through receptor-mediated endocytosis. The receptor that SARS-CoV-2 uses to infect lung cells is ACE2, a cell-surface protein on multiple cells, including lung AT2 alveolar cells. AT2 cells are particularly prone to viral infection.[118] One of the regulators of endocytosis is the AP-2 associated protein kinase 1 (AAK1). Inhibiting AAK1 might interrupt the passage of the SARS-CoV-2 virus into cells and also the intracellular assembly of virus particles.[119] In addition to baricitinib's potent JAK1 and JAK2 activity, it also potently inhibits AAK1 and binds cyclin G-associated kinase, another regulator of endocytosis.[120]

It is postulated that the therapeutic dose of 2 or 4 mg daily is sufficient to inhibit AAK1 and could be trialed in patients to treat COVID-19. The JAK1/2 activity may also inhibit the cytokine release associated with SARS-CoV-2 virus and dampen the cytokine storm that frequently manifests during Acute Respiratory Distress Syndrome (ARDS).[121]

In humans, baricitinib is rapidly absorbed with an oral bioavailability of 79%. It takes approximately 1 h to reach peak plasma concentration. Baricitinib is metabolized by Cyp3A4, but <10% of the total dose is prone to this biotransformation. Baricitinib is excreted primarily as unchanged active drug in the urine (69%) and feces (15%), and only minor oxidative metabolites have been identified. The mean half-life in patients with RA is 12.5 h.[122]

On May 8, 2020, NIAID announced that it is initiating a clinical trial to study baricitinib as a treatment for COVID-19 in combination with remdesivir.[123] The study is expected to enroll about 1000 hospitalized patients and will compare remdesivir alone with remdesivir plus baricitinib (4 mg oral daily).[123]

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Table 7. Clinical Trials Underway with Baricitinib[124]

clinical trial number	study title	estimated enrollment	study start/ estimated completion dates	study arms: active	study arms: control
NCT04340232	Safety and Efficacy of Baricitinib for COVID-19	80	April 2020/ August 2020	2 mg oral dose of baricitinib	placebo
NCT04362943	Clinical−Epidemiological Characterization of COVID-19 Disease in Hospitalized Older Adults	576	April 20, 2020/ July 2020	Arm 1: baricitnib Arm 2: anakinra	none
NCT04346147	Prospective, Phase II, Randomized, Open-Label, Parallel Group Study to Evaluate the Efficacy of Hydroxychloroquine Together with Baricitinib, Imatinib, or Early Lopinavir/Ritonavir in Patients with SARS Cov2 Pneumonia	165	April 13, 2020/ September 2020	Arm 1: HCQ 200 mg bid oral Arm 2: lopinavir/ritonavir 200 mg/50 mg of bid oral Arm 3: imatinib 400 mg qd oral Arm 4: baricitinib 4 mg qd oral	standard of care
NCT04321993	Treatment of Moderate to Severe Coronavirus Disease (COVID-19) in Hospitalized Patients	1000	April 17, 2020/ February 2021	Arm 1: lopinavir/ritonavir 200 mg/50 mg tablets bid for 10 days Arm 2: HCQ 200 mg bid for 10 days Arm 3: baricitinib 2 mg po daily for 10 days	standard of care
NCT04320277	Baricitinib Combined with Antiviral Therapy in Symptomatic Patients Infected by COVID-19: an Open-Label, Pilot Study	200	May 16, 2020/ June 2020	baricitinib 4 mg/day orally and lopinavir/ritonavir tablets 200 mg/50 mg bid	standard of care
NCT04345289	Efficacy and Safety of Novel Treatment Options for Adults with COVID-19 Pneumonia. A Double-Blinded, Randomized, Multistage, 6-Armed Placebo-Controlled Trial in the Framework of an Adaptive Trial Platform	1500	April 20, 2020/ June 2021	Arm 1: convalescent anti-SARS-CoV-2 plasma, iv infusion (2 × 300 mL) Arm 2: sarilumab 200 mg sc injection Arm 3: baricitinib 4 mg/day for 7 days Arm 4: HCQ 600 mg/day for 7 days	placebo

The majority of clinical trials using baricitinib to date have been short duration (2 weeks) open-label trials to treat patients with mild to moderate COVID-19 infection (Table 7).[124] Furthermore, as baricitinib is primarily eliminated by renal excretion, clinicians are also combining it with antivirals such as lopinavir/ritonavir (NCT04320277).

9.2. Synthetic Routes to Baricitinib. Two main routes to baricitinib have been disclosed. The original route from Incyte involves coupling the lower and central fragments (disconnection B, Figure 6), followed by appending the upper portion (disconnection A).[125] Lilly has disclosed an alternate disconnection with initial coupling at point A followed by coupling at point B.[126,127] Both routes require the synthesis of fragment **9.1**. Several routes to **9.1** have been disclosed; three of these are discussed below.

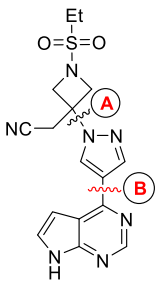
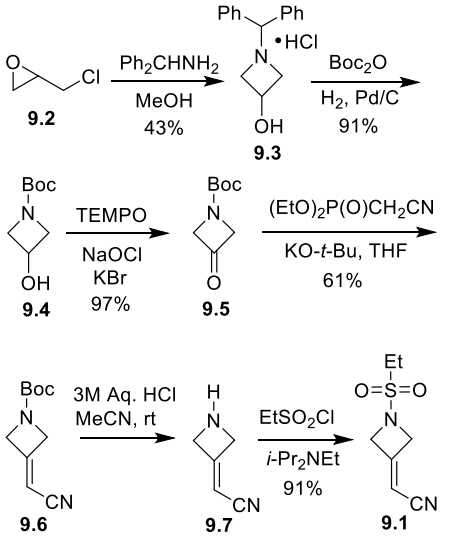


Figure 6. Retrosynthetic disconnections of baricitinib.

The original Incyte route is outlined in Scheme 20.[125] In the first step, described on a 15 mol scale, epichlorohydrin (**9.2**) was reacted with benzhydrylamine in MeOH for 3 days at room temperature and 3 days at reflux to afford **9.3**, which was crystallized as its HCl salt in 43% yield.[128] After salt break, **9.3** was subjected to hydrogenation using Pd/C in THF in the presence of Boc_2O to afford Boc-azetidinol **9.4** in 91% yield after

Scheme 20. Incyte Route to Sulfonamide 9.1



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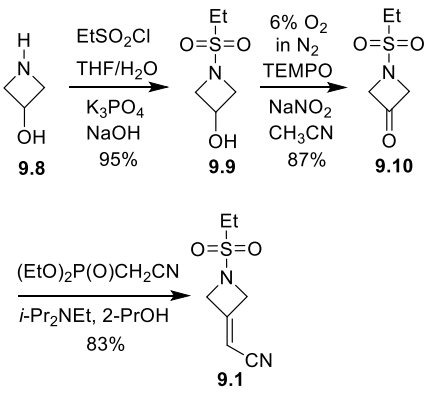
purification by silica chromatography. Oxidation of **9.4** was carried out with sodium hypochlorite, aqueous sodium bicarbonate, and catalytic amounts of KBr and 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO). After workup, the product layer was concentrated to dryness to provide crude ketone **9.5** in 97% yield. For the Horner−Emmons reaction, the anion of diethyl cyanomethylphosphonate was generated with KO*t*-Bu in THF for 3 h at −10 °C. Then ketone **9.5** was added, and the reaction mixture was stirred overnight at room temperature. After aqueous workup, **9.6** was isolated in 61% yield after purification by silica chromatography. A solution of **9.6** in MeCN was treated with 3 N aqueous HCl for 18 h at room temperature, and then concentrated to dryness. The resulting crude **9.7** was suspended in MeCN and then treated with diisopropylethylamine and ethanesulfonyl chloride at room temperature overnight. After aqueous workup, sulfonamide **9.1** was isolated after silica chromatography. Two reactions were described on a 1 kg scale for the final two steps under similar reaction conditions with yields of 59% and 91%.

The Lilly approach to **9.1** involved three steps from unprotected azetidin-3-ol (**9.8**) and requires no protecting groups (Scheme 21).[126,129] In the first step, **9.8** was reacted with

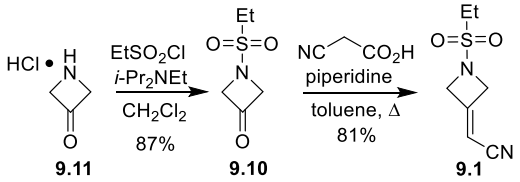
Scheme 21. Lilly Route to Sulfonamide 9.1



$EtSO_2Cl$ in aqueous THF to generate sulfonamide **9.9**, which was most efficiently isolated by continuous countercurrent extraction. In the first extraction using water/toluene, the product of reaction at both the amine and alcohol was extracted into the toluene layer, leaving product **9.9** in the water layer. This was then extracted with EtOAc to bring the product into the organic layer in a yield of 95% for the step. Oxidation to the ketone was described in both batch and flow modes. Batch processing using 6% oxygen in nitrogen (a concentration of oxygen that will not support combustion) with sodium nitrite, HOAc, and TEMPO in acetonitrile was carried out over 17 h at 500 psi, with the headspace being refreshed every minute. For the reaction in flow, the reactants and reagents were supplied in four feeds: (1) TEMPO in CH_3CN, (2) $NaNO_2$ in water, (3) alcohol **9.9** in 1:6 HOAc/CH_3CN, and (4) 6% O_2 in N_2. The back pressure was set at 500 psi, and the residence time was 12 h, resulting in an assay yield of 98%. At the end of the reaction in either batch or flow, a batchwise aqueous workup was followed by a solvent switch into 2-PrOH to afford ketone **9.10** in a step yield of 87−94%. The advantages of the flow route include (1) no need for a specialized large-scale vessel rated to >500 psi, (2) no need for continuous replacement of oxygen in the headspace, and (3) improved safety considering the smaller footprint for the high-pressure reaction. Several other oxidation procedures were also described. The 2-PrOH solution of **9.10** was combined with diethyl cyanomethylphosphonate and diisopropylethylamine. Product **9.1** crystallized as the reaction proceeded and was isolated in 83% yield after addition of heptane to increase the crystallization recovery.

A third route to **9.1** was disclosed by Hangzhou Cheminspire Technology Co. (Scheme 22).[130] The HCl salt of 3-azetidinone

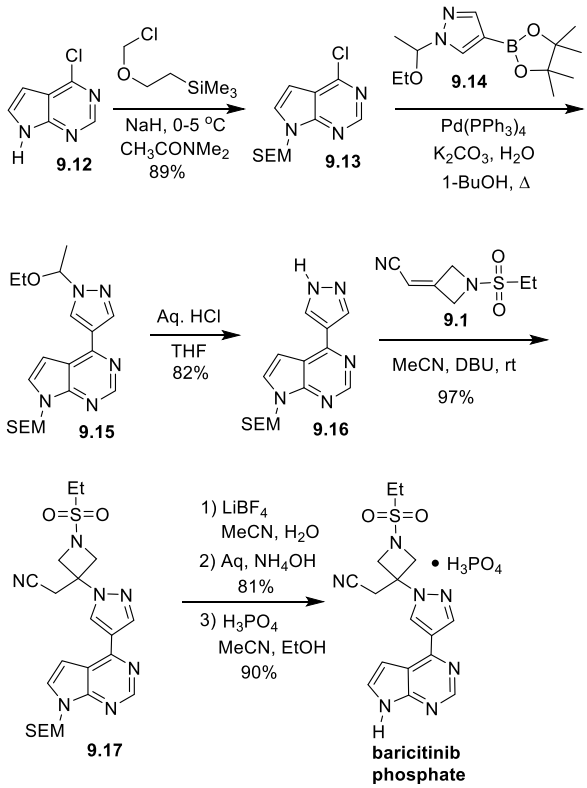
Scheme 22. Hangzhou Route to Fragment 9.1



(**9.11**) was reacted with ethanesulfonyl chloride mediated by diisopropylethylamine in dichloromethane to afford sulfonamide **9.10** in 87% yield after silica chromatography. Reaction of **9.10** with cyanoacetic acid in refluxing toluene mediated by piperidine afforded vinyl nitrile **9.1** in 81% yield after isolation by silica chromatography. The use of cyanoacetic acid instead of the high-molecular-weight phosphonate required for the Horner−Emmons reaction (Schemes 20 and 21) reduces the waste and product mass intensity for this step.

In the Incyte route, the conversion of **9.1** to baricitinib was completed as shown in Scheme 23, with completion of the "B" connection first, followed by the "A" connection (Figure 6).[125] First, 6-chloro-7-deazapurine (**9.12**) was protected with 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl) using NaH as the base in *N*,*N*-dimethylacetamide to furnish **9.13** in 89% yield after silica chromatography. Cross-coupling with pyrazole

Scheme 23. Incyte's Final Steps to Baricitinib



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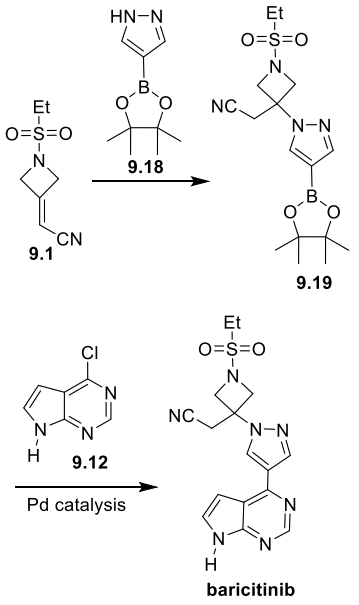
boronate ester **9.14** was accomplished with Pd catalysis in 1-BuOH/water at 90 °C to provide crude **9.15**, which was deprotected with aqueous HCl in THF. The resulting product **9.16** was crystallized from acetonitrile in 82% yield for the two steps. Michael addition of imidazole **9.16** to vinyl nitrile **9.1** was conducted in acetonitrile mediated by 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU). The addition adduct **9.17** was isolated in 97% yield by addition of water to the reaction mixture and crystallization. Deprotection of the SEM group was carried out in two steps. First, the silyl group was removed using lithium tetrafluoroborate in aqueous acetonitrile at 80 °C overnight, followed by cooling to 10 °C, addition of ammonium hydroxide, and reaction overnight at room temperature to remove the hydroxymethyl group. Isolation consisted of adding the reaction mixture to water to crystallize crude baricitinib free base followed by purification via silica chromatography in 81% yield. The crystalline phosphate salt was generated in 90% yield by treatment with phosphoric acid in acetonitrile/EtOH. The six-step sequence to the phosphate salt with an overall yield of 52% was described on the multikilogram to multihundred gram scale but required two chromatographic purifications.

The alternate assembly of the building blocks via connection "A" followed by connection "B" was disclosed by three independent groups in 2016 (Scheme 24). The conditions for

Scheme 24. Alternate Final Steps to Baricitinib



nucleophilic addition of pyrazine **9.18** to vinyl nitrile **9.1** are compiled in Table 8, all with comparable yields of 83–86%, although purification by crystallization was reported only by the Lilly team.[126] The Lilly[126] and Southeast University[132] groups used DBU as the base, while the Sun group[131] used potassium carbonate in aqueous dioxane. For the palladium-catalyzed cross-coupling of boronate ester **9.19** with **9.12**, the reported yields ranged from 71% to 99%, although again the Lilly group was the only one to isolate and purify the product by crystallization (Table 9).[126]

9.3. Potential Manufacturing Route to Baricitinib. The five-step route outlined in Schemes 21 and 24 is a short and efficient route to baricitinib but is apparently not the commercial manufacturing route. One of the attractive features of the five-step route is that it requires no protecting groups. However,

Table 8. Conditions for the Synthesis of 9.19 from 9.1 and 9.18

institution/ company (ref)	conditions	scale	yield
Lilly (126)	DMF, DBU, rt, 22 h; concentrate to dryness and then crystallize from 2-PrOH	15 g	83%
Sun (131)	dioxane/H_2O, K_2CO_3, rt, 18 h; after aqueous workup, crude **78** was isolated after concentration to dryness	2 g	86%
Southeast University (Nanjing, China)[a] (132)	MeCN, DBU, 60 °C, 4 h, concentrate to dryness, then silica chromatography	156 mg	84%

[a]Institution of senior author.

according to the European Public Assessment Report (EPAR) for Olumiant, the final step of the process involves a deprotection reaction.[133] Some considerations for selecting a longer route that includes a protecting group include the following:

(1) the purity of the final step from **9.19** may generate related substance impurities that are difficult to control at acceptable levels;
(2) Pd may be difficult to remove from the final product;
(3) the conversion of **9.19** to baricitinib is a relatively complex reaction that may be difficult to reproduce reliably as a final step, whereas a straightforward deprotection may be more readily reproducible;
(4) Lilly may not believe that they have clear freedom to operate the protection-free route;
(5) given the low dose of baricitinib (2 and 4 mg per day), the cost of the API per tablet is very low regardless of the efficiency of the synthesis, so freedom to operate, product quality, and reproducibility would outweigh cost considerations.

The likely manufacturing route is disclosed in the same set of patent applications as the protection-free route, with the final steps outlined in Scheme 25.[126] Compound **9.12** was Boc-protected using Boc_2O and *t*-BuOK in THF at 55–60 °C. To the resulting cooled solution of **9.20** were added aqueous potassium phosphate, boronate ester **9.19**, and $PdCl_2$–XantPhos (0.25 mol %) in THF, and the mixture was warmed to 55–60 °C for 4 h to afford a 97% assay yield of Boc-baricitinib (**9.21**).[134] The resulting solution was passed through a thiol-containing silica resin column to remove Pd and then heated to 140 °C under pressure (300 psi) to effect removal of the Boc group. The THF solution was then solvent-switched to 1-BuOH, and crystallization afforded baricitinib in 90% yield.

9.4. Final Form and Formulation of Baricitinib. According to the Olumiant EPAR, several crystalline forms of baricitinib free base were identified. Crystalline form I, the thermodynamically stable anhydrous form, was selected for Phase 3 clinical studies and commercial development.[133]

The finished product is an immediate-release film-coated tablet in a dose strength of 2 or 4 mg. The bioavailability after oral administration of baricitinib from the commercial tablet was 79%. Early clinical studies were conducted with the phosphate salt. A comparative bioavailability study on the 8 mg Phase 2 capsule of the phosphate salt versus the 8 mg Phase 2 tablet of the free base showed no statistical difference in AUC or C_{max} in fasted volunteers.[133]

9.5. Outlook for Supply of Baricitinib. In an April 10, 2020 press release, Lilly indicated that it does not anticipate

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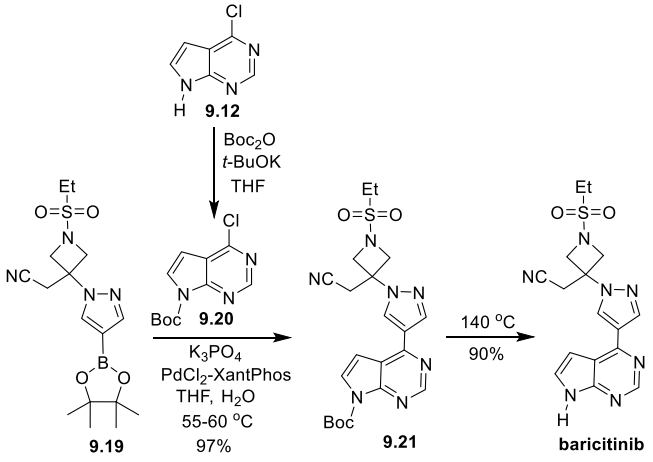
Table 9. Conditions for Conversion of 9.19 to Baricitinib

institution/company (ref)	conditions	scale	yield
Lilly (126)	THF, H_2O, K_3PO_4, dichloro[1,1′-bis(dicyclohexylphosphino)ferrocene]palladium(II), 90 °C, 19 h; crystallization from 1-BuOH	5 g	71%
Sun (131)	dioxane/H_2O, K_2CO_3, $Pd(PPh_3)_4$, 80−85 °C, 5 h, rt, 18 h; workup and then concentrate to dryness	2 g	99%
Southeast University (Nanjing, China)[a] (132)	*t*-BuOH, H_2O, toluene, CsF, $Pd(PPh_3)_4$, reflux, 48 h, purification by silica chromatography	870 mg	84%

[a]Institution of senior author.

Scheme 25. Potential Final Steps of the Manufacturing Route for Baricitinib



shortages of baricitinib, which is widely available in countries where it is approved.[135]

10. CAMOSTAT

Camostat (**4.9**) was first reported in a patent by Ono Pharmaceutical Co., Ltd. in 1977.[136] The mesylate salt of camostat was approved in Japan in 1985 as a tablet formulation (Foipan) for the treatment of reflux esophagitis and chronic pancreatitis.[137] The drug is well-tolerated and has a relatively short human half-life requiring a three-times-daily dose regimen of 100−300 mg.[138] Camostat mesylate has additionally been investigated for the treatment of a wider range of indications, including oral squamous cell carcinoma,[139] dystrophic epidermolysis,[140] exocrine pancreatic enzyme inhibition,[141] and chronic pancreatitis.[137,142]

10.1. History, Mechanism of Action, and Status of Clinical Trials. Camostat is an inhibitor of TMPRSS2. As described earlier in section 1, SARS-CoV-2 uses the SARS-CoV receptor ACE2 for entry and the serine protease TMPRSS2 for S protein priming. TMPRSS2 cleaves the S protein, allowing the virus to fuse with the cell and start to replicate inside it.

A study in 2012 demonstrated that inhibition of TMPRSS2 by camostat partially blocked infection by SARS-CoV and human coronavirus NL63 in HeLa cells.[143] Further recent in vitro studies have shown that camostat significantly reduces the infection of Calu-3 lung cells by SARS-CoV-2 and inhibits entry into primary human lung cells.[144] In mice, camostat dosed at concentrations similar to the clinically achievable concentration in humans reduced mortality following SARS-CoV infection from 100% to 30−35%.

There are only four clinical trials underway to explore the efficacy of camostat in COVID-19 patients (Table 10).[145] A randomized, placebo-controlled Phase IIa Danish trial (NCT4321096) is now underway in 180 patients. Patients receive 2 × 100 mg of camostat mesylate or placebo three times a day for 5 days, the maximum dose given to patients with pancreatitis in Japan. The estimated primary completion date is December 31, 2020, and the estimated study completion date is May 1, 2021.[145]

10.2. Synthesis of Camostat. The first synthesis of camostat mesylate, originally known as FOY-305, was reported on a gram scale in the initial 1977 disclosure by Ono Pharmaceutical.[136] The synthesis of camostat is relatively simple and constitutes two consecutive esterification reactions, as outlined in Scheme 26. 4-Hydroxyphenylacetic acid (**10.1**) was alkylated with *N*,*N*-dimethyl-2-bromoacetamide in refluxing acetonitrile to afford O-alkylated intermediate **10.2**, which precipitated in 58% isolated yield upon removal of acetonitrile under reduced pressure followed by water addition. In the subsequent esterification, the crude acyl chloride **10.3** prepared from *p*-guandinobenzoic acid was used to synthesize camostat, followed by precipitation of camostat mesylate from a methanol/diethyl ether mixture. A Chinese patent published in 2015 claimed higher yields on a low-gram scale by modification of the esterification reaction conditions,[146] but the application of that method to any production-scale syntheses of camostat mesylate remains unpublished.

10.3. Formulations and Salt Forms of Camostat. Camostat has been demonstrated to be readily hydrolyzed by human liver esterase and other esterases.[147] In an effort to alleviate extensive gut hydrolysis and thereby increase the resulting camostat in vivo half-life, Ono Pharmaceutical patented a variety of soft gel capsules containing mixtures of camostat mesylate and middle-chain triglycerides.[148] Such soft gel capsules displayed significantly improved camostat bioavailability compared with intravenous administration of a saline solution of camostat mesylate when tested in rat intestine. In a later development, Novartis described the formation of a number of additional crystalline camostat salt forms in good to excellent yields, including salts with hydrogen succinate (88%), succinate (88%), phosphate (75%), acetate (90%), hydrogen tartrate hemihydrate (99%), glycolate (96%), xinafoate (99%), hippurate (83%), adipate (98%), and glutarate (98%).[149] These salt forms as well as a novel polymorph of camostat free base (designated as form II) were evaluated for their potential use in inhaled formulations of camostat.

10.4. Outlook for Supply of Camostat. Camostat mesilate (or mesylate) is supplied for the Japanese market by Ono Pharmaceuticals under the trade name Foipan.[137] A number of generic suppliers in Japan and South Korea also manufacture the drug. Little information is available on the expected future worldwide supply of camostat mesylate other than the announcement by Ono Pharmaceuticals that shipment of the drug would be limited because of increased demand based on initial reports that it might be effective in the treatment of COVID-19.[150] In view of the short synthesis of camostat from

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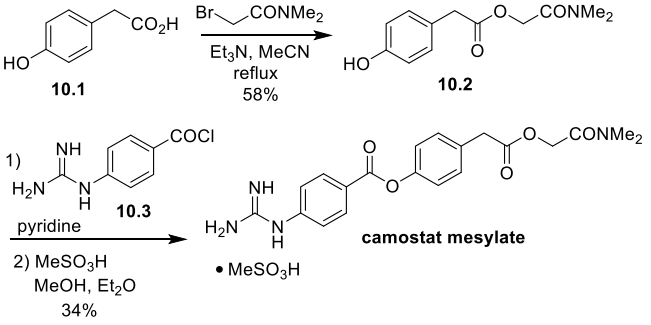
Table 10. Clinical Trials Underway with Camostat[145]

clinical trial number	study title	estimated enrollment	study start/ estimated completion dates	study arms: active	study arms: control
NCT04321096	The Impact of Camostat Mesilate on COVID-19 Infection: An Investigator-Initiated Randomized, Placebo-Controlled, Phase IIa Trial	180	March 31, 2020/ December 2020	camostat mesylate 2 × 100 mg pills three times daily for 5 days	placebo
NCT04353284	The Effect of Camostat Mesylate on COVID-19 Infection in Ambulatory Patients: An Investigator-Initiated Randomized, Placebo-Controlled, Phase IIa Trial	114	April 30, 2020/ May 2021	camostat mesylate 200 mg taken for 7 days	placebo
NCT-4338906	Evaluation of the Efficacy and Safety of Camostat Mesilate + Hydroxychloroquine Combination Therapy in Hospitalized Patients with Moderate COVID-19 Infection	334	June 1, 2020/ June 2021	Arm 1: camostat 400 mg tid + HCQ 400 mg bid on day 1, 200 mg bid on days 2−7 Arm 2: placebo tid + HCQ 400 mg bid on day 1, 200 mg bid on days 2−7	none
NCT04355053	An Open-Label Study to Compare the Efficacy, Safety, and Tolerability of Hydroxychloroquine Combined with Azithromycin Compared to Hydroxychloroquine Combined with Camostat Mesylate and to "No Treatment" in Hospitalized Patients Suffering from a Mild or Moderate SARS CoV 2 Virus	250	April 11, 2020/ October 2020	Arm 1: HCQ 400 mg bid on day 1 then 200 mg bid on days 2−5 + azithromycin 500 mg qd on day 1 and 250 mg qd on days 2−5 Arm 2: HCQ 400 mg bid on day 1 then 200 mg bid on days 2−5 + camostat mesylate 200 mg tid for 10 days	placebo

Scheme 26. Original Synthesis of Camostat Mesylate Disclosed in 1977



readily available raw materials, supply could likely be ramped up quickly if needed.

11. LOPINAVIR/RITONAVIR

11.1. History, Mechanism of Action, and Status of Clinical Trials. The treatment of HIV was revolutionized in the mid-1990s when a number of HIV protease inhibitors emerged, resulting in a dramatically reduced death rate for AIDS.[151] The chemical structures of these successful HIV protease inhibitors generally resemble small peptides and typically incorporate highly modified synthetic amino acids.[152,153] The first HIV protease inhibitor to reach the market was saquinavir, which was developed by Hoffmann-La Roche and approved in December 1995. Ritonavir (RTV, **4.5**) is a contemporary HIV protease inhibitor developed by Abbott Laboratories that received FDA approval in March 1996. Soon thereafter, Abbott Laboratories reported an improved second-generation HIV protease inhibitor, ABT-738, that later became known as lopinavir (LPV, **4.4**).[154] As described in more detail below, dramatically improved bioavailability of lopinavir is observed in the presence of ritonavir. These findings led to the development of Kaltera, an FDA-approved fixed-dose combination of lopinavir and ritanovir for the treatment of HIV/AIDS in several countries, in which lopinavir is the predominant active drug and ritanovir functions primarily as a P450 CYP3A4 inhibitor.[155]

LPV is an inhibitor of the enzyme HIV-1 protease, a dimeric aspartate protease that is responsible for cleaving the Gag polyprotein, which functions as the major structural protein of the virus and plays a vital role in the HIV viral life cycle.[156] LPV is a peptidomimetic drug containing a hydroxyethylene scaffold that mimics the normal peptide linkage (cleaved by HIV protease) but cannot be cleaved.[151] Inhibition of HIV-1 protease activity and subsequent proteolysis of the Gag polyprotein results in the production of immature, noninfectious HIV-1 virus particles.

When administered alone, LPV has a very low human bioavailability of ∼25%, primarily because of extensive oxidative metabolism by P450 CYP3A4 enzymes.[154] It is exclusively coadministered with RTV, which reduces drug metabolism and significantly improves the bioavailability of LPV. In healthy human volunteers, codosing of 400 mg of LPV and 50 mg of RTV significantly increases the area under the concentration curve (AUC) of LPV in plasma by 77-fold over that observed after dosing with LPV alone. This results in concentrations of LPV that exceed the antiviral EC_{50} for >24 h.[154]

To date, no in vitro SARS-CoV-2 data have been reported for lopinavir/ritonavir, but nonetheless, lopinavir was found to weakly inhibit both MERS-CoV and SARS-CoV replication in

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Table 11. Clinical Trials Underway with Lopinavir (LPV)/Ritonavir (RTV)[161]

clinical trial number	study title	estimated enrollment	study start/estimated completion dates	study arms	
				active	control
NCT04307693	Randomized Controlled Clinical Trials of Lopinavir/Ritonavir or Hydroxychloroquine in Patients with Mild Coronavirus Disease (COVID-19)	150	March 11, 2020/ May 2020	Arm 1: LPV/RTV 200 mg/100 mg, two tablets by mouth, every 12 h for 7−10 days Arm 2: HCQ 200 mg, two tablets by mouth, every 12 h for 7−10 days	placebo
NCT04359095	Effectiveness and Safety of Medical Treatment for SARS-CoV-2 (COVID-19) in Colombia: A Pragmatic Randomized Controlled Trial	1600	May 11, 2020/ October 2020	Arm 1: HCQ 400 mg po every 12 h for 24 h, then 200 mg every 12 h for 10 days. Arm 2: HCQ 400 mg po every 12 h for 24 h, then 200 mg every 12 h for 10 days + LPV/RTV 400 mg/100 mg po every 12 h for 10 days Arm 3: HCQ 400 mg po every 12 h for 24 h, then 200 mg every 12 h for 10 days + azithromycin 500 mg po once daily for 5 days	standard of care
NCT04328285	Chemoprophylaxis of SARS-CoV-2 Infection (COVID-19) in Exposed Healthcare Workers: A Randomized Double-Blind Placebo-Controlled Clinical Trial	1200	April 14, 2020/ November 2020	Arm 1: HCQ 200 mg, two tablets in the evening on day 1, two tablets in the morning on day 2, and one tablet once daily afterwards Arm 2: LPV/RTV 200 mg/50 mg, two tablets twice daily	placebo
NCT04328012	Comparison of Therapeutics for Hospitalized Patients Infected with SARS-CoV-2 in a Pragmatic Adaptive Randomized Clinical Trial during the COVID-19 Pandemic (COVID MED Trial)	4000	April 6, 2020/ January 2021	Arm 1: LPV/RTV 400 mg/200 mg po bid for 5−14 days, depending on availability Arm 2: HCQ sulfate 400 mg bid on day 0, 200 mg bid on days 1−4 (days 1−13 if available) Arm 3: losartan 25 mg po qd for 5−14 days depending on availability	placebo
NCT04330690	A Multicenter, Adaptive, Randomized, Open-Label, Controlled Clinical Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Patients (CATCO: Canadian Treatments for COVID-19), in Conjunction with the Public Health Emergency Solidarity Trial (World Health Organization)	440	March 18, 2020/ March 2022	Arm 1: LPV/RTV 400 mg/100 mg orally for a 14 day course or until discharge from hospital, whichever occurs first Arm 2: HCQ 800 mg bid for 1 day then 400 mg bid for 10 days, plus optimized supportive care Arm 3: remdesivir 200 mg iv on day 1 followed by 100 mg iv daily infusion for 9 days, plus optimized supportive care	standard of care
NCT04372628	Trial of Early Therapies during Nonhospitalized Outpatient Window (TREAT NOW) for COVID-19	900	May 1, 2020/ December 2020	Arm 1: HCQ 400 mg po bid for two doses (day 1), then 200 mg bid for the subsequent eight doses (days 2−5), then placebo twice daily for the subsequent 18 doses (days 6−14) Arm 2: LPV/RTV 400 mg/100 mg po bid for 28 doses (days 1−14)	placebo
NCT04364022	Efficacy of Pragmatic Same-Day Ring COVID-19 Prophylaxis for Adult Individuals Exposed to SARS-CoV-2 in Switzerland: An Open-label Cluster Randomized Trial	420	April 2020/ October 2020	single dose of HCQ 800 mg po and LPV/RTV 2 × 200 mg/ 50 mg po bid for 5 days	placebo

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cell cultures with EC_{50} values of 8 and 17 μM, respectively.[157] Most clinical studies have investigated the use of lopinavir/ritonavir to treat SARS-CoV, but these studies have been mostly retrospective and observational in nature.[158] One such retrospective matched cohort study of SARS patients showed that treating SARS-CoV patients with LPV (400 mg)/RTV (100 mg) orally every day for 14 days significantly reduced ARDS. Patients also appeared to run a milder disease course in recurrence of fever, reduction of viral load, and worsening of chest radiographs.[159] It was also noted that the timing of administration was critical during the early viral replication phase (initial 7−10 days) because delaying therapy further had no effect on clinical outcomes.

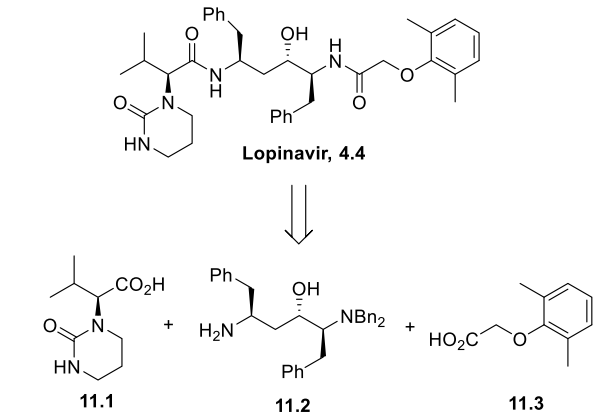
Initial reports of lopinavir/ritonavir for the treatment of COVID-19 involve small retrospective, nonrandomized cohort studies. A recent randomized, controlled open-label trial involving 199 hospitalized adults patients with SARS-CoV-2 in Wuhan, China, compared the efficacies of lopinavir/ritonavir and the standard of care.[160] Treatment with lopinavir/ritonavir was not associated with a difference from the standard of care in the time to clinical improvement. In addition, mortality at 28 days was similar in the lopinavir/ritonavir group and the standard of care group (19.2% vs 25%), and the percentages of patients with detectable viral RNA were similar at various time points.[161] Further clinical trials are underway to assess both the efficacy and safety of lopinavir/ritonavir (Table 11).[161] It has been reported that many clinicians are abandoning the use of lopinavir/ritonavir for the treatment of COVID-19 after the negative findings from the above study. A recent report sent to the editors of the *New England Journal of Medicine* suggests that this action is premature. The authors argued that the lowering of the mortality rate is significant, in addition to the lowering of ARDS. They advocated that therapeutic guidelines retain this combination as a treatment option against COVID-19, awaiting completion of the WHO Solidarity trial.[162a]

A recent report in *The Lancet* suggested that the combination of lopinavir, ritonavir, ribavirin, and interferon could be effective in treating COVID-19 in the early stages of the disease.[162b] Patients were randomly assigned (2:1) to a 14 day combination of lopinavir (400 mg) and ritonavir (100 mg) every 12 h, ribavirin (400 mg) every 12 h, and three doses of 8 million IU of interferon beta-1b on alternate days (combination group) or to 14 days of lopinavir (400 mg) and ritonavir (100 mg) every 12 h (control group). Between February 10 and March 20, 2020, 127 patients were recruited; 86 were randomly assigned to the combination group and 41 to the control group. The combination group had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab (7 days [IQR 5−11]) than the control group (12 days [8−15]) (hazard ratio 4.37 [95% CI 1.86−10.24], p = 0.0010).

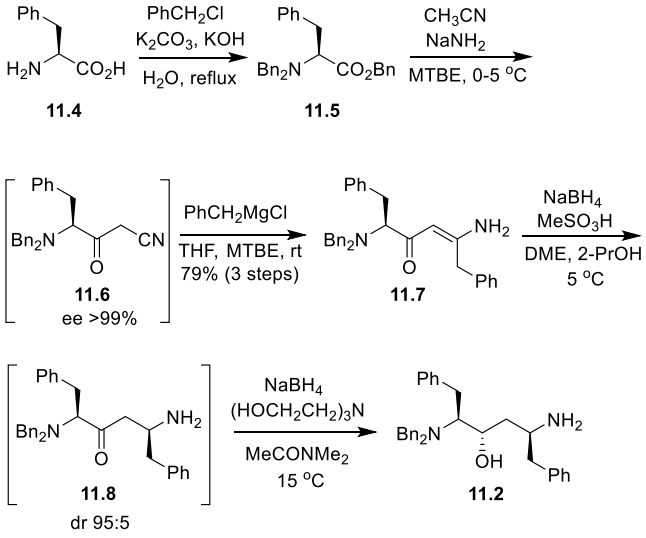
11.2. Synthesis of Lopinavir. A scalable synthesis of lopinavir was described in two publications[163,164] and a patent[165] by a team at the innovator company, Abbott Laboratories (now AbbVie), in 1999 and 2000.[166] The retrosynthesis of lopinavir is outlined in Scheme 27.

The central-core diamine containing three chiral centers, **11.2**, is the same for both ritonavir and lopinavir and is described in earlier publications from Abbott.[167] The first chiral center is derived from the chiral pool (L-phenylalanine), and this center is then used to direct the installation of the other two chiral centers, as outlined in Scheme 28. The process chemistry route to **11.2**, described on the 14−122 kg of substrate scale, began with the tribenzylation of phenylalanine (**11.4**) with benzyl

Scheme 27. Retrosynthetic Approach to Lopinavir



Scheme 28. Abbott Synthesis of the Lopinavir Chiral Central Core 11.2



chloride to afford ester **11.5**, which was isolated as a crude oil after aqueous workup. The next two steps, addition of the acetonitrile anion to the benzyl ester and reaction of the resulting nitrile with benzylmagnesium chloride, were carried out as a one-pot reaction in MTBE. Sodium amide was the base used to generate the acetonitrile anion. This is not a common base used at scale because of concerns with handling and flammability, but a survey of other bases, including KOH, KOtBu, NaH, KHMDS, and LiHMDS, led to incomplete reactions, slow conversions, or racemization.[167] MTBE was found to be a preferred solvent for the reaction, with no racemization occurring when the reaction was carried out at 0−5 °C. In an earlier procedure using THF as the solvent, the reaction was conducted at −45 °C to prevent racemization.[167] Upon formation of keto nitrile **11.6**, vacuum was applied to remove ammonia. Then benzylmagensium chloride was added at 25 °C, and the reaction mixture was stirred for 2 h. After aqueous workup, enaminone **11.7** was crystallized from EtOH with >99% ee in an overall yield of 79% for the three steps.

The diastereoselective reduction of enaminone **11.7** to amino alcohol **11.2** required extensive development. The use of a single reagent to effect reduction at both centers afforded mixtures of diastereomers. Sodium borohydride−TFA complex provided the best result, with a 72% yield of the desired diastereomer **11.2**

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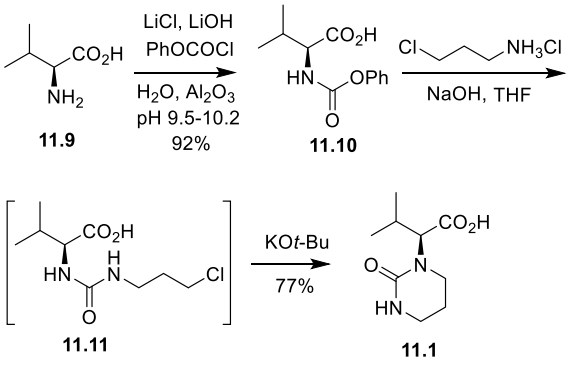
and a 28% yield of a mixture of the other three diastereomers. Reductions using $NaBH_4$ with mineral acids led to reduction of only the enamine double bond, generating **11.8** with a dr of approximately 95:5. This suggested that a stepwise process could be feasible: initial reduction of the enamine double bond followed by ketone reduction. The initial reduction using $NaBH_4$ with sulfuric acid followed by the ketone reduction by addition of $NaBH_2(TFA)_2$ in THF afforded **11.2** with a dr of 95:5. While this reaction worked well in the laboratory, scale-up resulted in thick mixtures due to ring-opening polymerization of THF. Addition of water helped minimize THF decomposition and, unexpectedly, also improved the diastereoselectvity. However, a better solution was to exchange sulfuric acid with $MeSO_3H$ and carry out the reaction in the alternative solvent dimethoxyethane (DME). While water improved the selectivity, it also slowed the reaction, so the final conditions used 2-PrOH as an additive instead. The role of the alcohol in improving the diastereoselectivity remains unknown.

The resistance of the keto nitrile to reduction was presumed to be due to complexation of the ketone, perhaps as a boron enolate. To enable the second reduction, a boron complexing agent was added. A survey of amino alcohols found triethanolamine to be optimal. The final conditions for the reduction of **11.8** to **11.2** were treatment of the solution of **11.7** in DME with triethanolamine, followed by addition of $NaBH_4$ in dimethylacetamide and stirring for 2 h at 15 °C. Aqueous workup provided **11.2** as a solution in EtOAc containing the desired diastereomer in 89−93% yield, with the remainder being a mixture of the other diastereomers.[163−165] This solution was used without further purification for downstream conversion to lopinavir (see Scheme 30). The reduction process (**11.7** to **11.2**) was described on a 400 kg scale.[165]

The Abbott synthesis of fragment **11.1** is outlined in Scheme 29.[163] In the first step, L-valine (**11.9**) was converted to

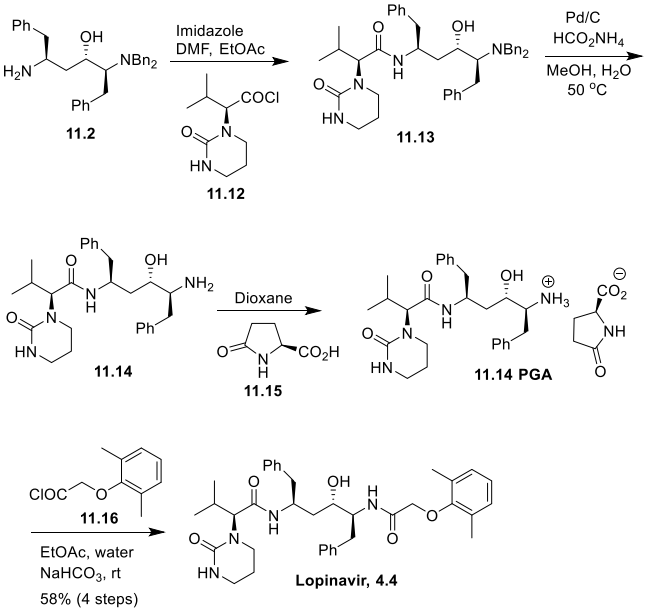
Scheme 29. Abbott Synthesis of Fragment 11.1



carbonate **11.10** using phenyl chloroformate. The reaction required significant development to ensure operability at scale. Lithium chloride was added to reduce the freezing point, allowing the reaction to be carried out at −10 °C. Control of the pH between 9.5 and 10.2 was critical to minimize the formation of valine dipeptide and acylated derivatives. Neutral alumina prevented gumming and emulsion formation, which was essential for mixing and maintaining pH control. After aqueous workup, carbonate **11.10** was isolated in 92% yield after crystallization from toluene/heptane. Treatment of **11.10** with 3-chloropropylamine hydrochloride and solid NaOH in THF at 10 °C for 2 h furnished alkylated product **11.11**, which was cyclized to obtain **11.1** by addition of KO-*t*-Bu in THF at 20 °C. After aqueous workup, **11.1** was isolated in 77% yield with >99% ee after crystallization from EtOAc.

The final steps to lopinavir are shown in Scheme 30.[163] Amine **11.2** was coupled to acid chloride **11.12**, generated from acid

Scheme 30. Final Steps to Lopinavir



11.1 with thionyl chloride, using imidazole (3.0 equiv) in EtOAc/DMF at 30 °C. After aqueous workup and concentration to an oil, the crude amide **11.13** was debenzylated in MeOH with Pd/C and ammonium formate in MeOH at 50 °C to furnish amine **11.14**. Upgrade of the diastereomeric purity was accomplished by crystallization of the salt with L-pyroglutamic acid (PGA) in 1,4-dioxane to generate **11.14 PGA** in 74% yield with >98.5% purity. The final amide coupling of **11.14 PGA** with acid chloride **11.16** (generated from **11.3** with thionyl chloride) was conducted under Schotten−Baumann conditions (EtOAc/aqueous $NaHCO_3$) at room temperature. Crystallization of lopinavir was originally carried out from EtOAc/heptanes, but removal of residual solvents proved to be problematic, so an alternate crystallization from EtOH/water was developed. The overall yield from **11.2** was 58%.

Abbott chose to upgrade the diastereomeric purity by formation of the PGA salt of amine **11.14**. In the experimental procedure provided, the yield for the crystallization of purified **11.14 PGA** was 74%. This is a significant yield loss for the penultimate intermediate in a lengthy synthesis. Laurus Laboratories recently disclosed a process wherein the diastereomeric purity upgrade was carried out at an earlier stage, amine **11.2**, by formation of the L-tartrate salt.[168] The two-step reduction from **11.7** to **11.2** was carried out similarly to the Abbott process (Scheme 28), and then the L-tartrate salt of **11.2** was crystallized from MTBE in 79% isolated yield with a purity of 99.0%. The levels of the three undesired diastereomers were 0.16%, 0.24%, and 0.38%.[168]

In the same patent application from Laurus, the inventors noted that the Abbott process produced up to 5% overacylated byproduct **11.17** (Figure 7) in the final step, an impurity that Laurus claimed to be difficult to remove by crystallization.[168] The Laurus team found that this impurity can be hydrolyzed to

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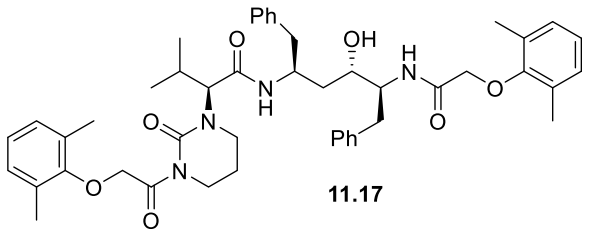

Figure 7. Structure of lopinavir impurity **11.17**.

lopinavir by treatment with base. In one example, lopinavir was prepared starting with 0.95 equiv of acid **11.3** and 1.00 equiv of salt **11.14 PGA**. The crude material contained 0.8% impurity **11.17**. This material was treated with methanolic ammonia and then crystallized from acetone to afford lopinavir in 90% yield with 99.9% purity and an undetectable level of impurity **11.17**. In the comparative example in the Laurus patent application, lopinavir was prepared starting with 1.00 equiv each of acid **11.3** and salt **11.14 PGA**. The crude product of this reaction was crystallized from EtOAc/heptane to provide lopinavir with 94% purity containing 3% impurity **11.17**. We note that in the Abbott publication, a 20% excess of acid **11.3** was used for this reaction, and a purity of 99% was obtained after crystallization from EtOAc/heptane.[163]

11.3. Salt Forms and Formulation of Lopinavir and Ritonavir. Since the formulation of Kaletra is a fixed-dose combination of lopinavir and ritonavir, the forms and physical characteristics of both drug substances must be considered for formulation development.

Abbott has disclosed four crystal forms of lopinavir: type I, a hydrated form containing 0.5−2.0 mol of water; type II, a solvated form containing either 2-PrOH, EtOAc, or chloroform; type III, a solvated form containing either EtOAc or MeCN and a desolvated form; and type IV, a nonsolvated form. Other solvates within type III were mentioned but not exemplified.[169] According to the EPAR for Kaletra, the commercial form is crystallized from EtOH and water and is a mixture of the amorphous form and crystalline type I.[170]

A cyclohexane solvate of lopinavir and its desolvated form were subsequently disclosed by Hetero.[171]

Two crystal forms of ritonavir, forms I and II, have been identified.[172] At the time of the initial approval of ritonavir (trade name Norvir) in 1996, only form I had been encountered in development and launch. Because of the low bioavailability of crystalline ritonavir, the two formulations that were marketed, an oral solution and a capsule, contained ritonavir as a solution in EtOH/water. In 1998, several lots of formulated drug undergoing release testing failed the dissolution specification. An investigation revealed that a new polymorph (designated as form II) was crystallizing in the capsules. Soon, the new polymorph showed up in other lots of formulated drug and the API. Form II was found to be the thermodynamically most stable form and is approximately 5-fold less soluble than form I in EtOH/water mixtures. This form was no longer fully soluble in the solution used for the capsule formulation nor under the refrigerated storage conditions for the oral solution. Therefore, both formulations of the product were withdrawn, and new formulations were investigated. A soft gelatin capsule formulation was developed with a solvent composition of EtOH, oleic acid, and water to ensure complete solubility of form II. Polyoxyl 35 castor oil was added to improve the bioavailability.[173] Subsequently, a film-coated tablet (100 mg) was developed and marketed.[174] The oral solution was reformulated in a mixed solvent system of water, EtOH, propylene glycol, and polyoxyl 35 castor oil.[173]

Both ritonavir and lopinavir drug substances have very low water solubility, and the crystalline forms have minimal bioavailability. This led to an initial marketed formulation (U.S. approval September 2000) of a soft gelatin capsule containing 133.3 mg of lopinavir and 33.3 mg of ritonavir as a solution in a mixture of oleic acid, propylene glycol, and water, with a storage condition of 2−8 °C.[170] To reduce the pill burden and avoid cold storage, a tablet formulation was subsequently developed using hot-melt extrusion technology to render each drug substance amorphous in the formulation. Film-coated tablets containing 200 mg of lopinavir and 50 mg of ritonavir were approved in the U.S. in October 2005 with room-temperature storage conditions.[175]

11.4. Outlook for Supply of Lopinavir/Ritonavir. On January 28, 2020, the Indian generic company Cipla announced that it has raw materials available to manufacture 10−12 million doses of lopinavir/ritonavir. The company noted, however, that current demand, and therefore supply, for HIV are low given the introduction of better drugs over the past 20 years.[176]

On March 9, 2020, AbbVie stated that it does not anticipate any disruption to its supply chain but continues to monitor its resources.[177]

On March 19, 2020, Israel approved the licensing of a generic version of ritonavir/lopinavir to treat patients infected with the coronavirus.[178]

On March 23, 2020, AbbVie announced that it would no longer enforce patents on the drug combination.[179] The composition of matter patent expired in 2016, but the tablet formulation patent would have been in effect in the U.S. until 2028.[180]

On March 25, 2020, Mylan announced that it would waive its exclusive rights to market generic lopinavir/ritonavir in the U.S. to allow other generic companies to manufacture the drugs.[181]

On April 7, 2020, the Philadelphia-based company Lannett announced that it was poised to increase production of lopinavir/ritonavir if demand increased.[182] Lannett currently markets the generic version of lopinavir/ritonavir oral solution.[183]

Other manufacturers of the drug combination include the India-based companies Aurobindo, Cipla, Hetero, and Macleods. The Government of India has asked these companies to increase production in anticipation of a greater need to treat COVID-19.[184]

12. SUMMARY AND CONCLUSIONS

Designing, developing, and testing a new drug for the treatment of COVID-19 is likely a multiyear endeavor even with accelerated development, as a drug candidate must first be shown to be safe in animals even before clinical trials can begin. Then, a series of three phases of clinical trials must be completed: Phase I to demonstrate safety and tolerability in healthy volunteers, Phase II to show efficacy in COVID-19 patients, and Phase III to confirm efficacy and safety in a larger cohort of patients. A shorter pathway to treatment would be to repurpose older drugs—those that have been shown to be safe and efficacious against other diseases and may have efficacy against SARS-CoV-2. A global collaboration of scientific groups, spearheaded by the University of California at San Francisco, has identified 29 approved drugs that may have activity against SARS-CoV-2.[185] In this review, we have discussed seven

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promising repurposed drugs that are currently being studied in large clinical trials in COVID-19 patients. One such drug, remdesivir, an antiviral drug originally developed for the treatment of Ebola virus, has shown efficacy in a well-controlled clinical trial and has now been granted approval for emergency use in the U.S. and Japan. An extraordinary effort has been underway since February 2020 at Gilead to ramp up production, with the goal of having 1 million doses available by the end of 2020. In the next few months we expect trial data for many other drugs, with the hope that a cocktail of repurposed drugs can provide a meaningful treatment for the majority of COVID-19 patients.

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