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REVIEW

Reviews on Biological Activity, Clinical Trial and Synthesis Progress of Small Molecules for the Treatment of COVID-19

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Abstract

COVID-19 has broken out rapidly in nearly all countries worldwide, and has blossomed into a pandemic. Since the beginning of the spread of COVID-19, many scientists have been cooperating to study a vast array of old drugs and new clinical trial drugs to discover potent drugs with anti-COVID-19 activity, including antiviral drugs, antimalarial drugs, immunosuppressants, Chinese medicines, M^{pro} inhibitors, JAK inhibitors, etc. The most commonly used drugs are antiviral compounds, antimalarial drugs and JAK inhibitors. In this review, we summarize mainly the antimalarial drugs chloroquine and hydroxychloroquine, the antiviral drugs Favipiravir and Remdesivir, and JAK inhibitor Ruxolitinib, discussing their biological activities, clinical trials and synthesis progress.

Keywords COVID-19 · Remdesivir · Favipiravir · Chloroquine · Hydroxychloroquine · Ruxolitinib

Abbreviations

ACE2	Angiotensin-converting enzyme 2
ARDS	Acute respiratory distress syndrome
BCL-2	β-Cell lymphoma 2
CLQ-OH	Hydroxychloroquine
CNS	Central nervous system

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COVID-19	Corona virus disease 2019
CRP	Levels of C-reactive protein
CXCR4	Cxc chemokin receptor 4
CXCL-12	Cxc chemokin ligand 12
DAAs	Direct-acting antivirals
EC_{50}	Concentration for 50% of maximal effect
EC_{90}	Concentration for 90% of maximal effect
EFDA	European Food and Drug Administration
FDA	Food and Drug Administration
G-CSF	Granulocyte colony-stimulating factor
hrs ACE2	Human recombinant soluble angiotensin-converting enzyme 2
IC_{50}	The half maximal inhibitory concentration
ICU	Intensive care unit
IL	Interleukins
INF	Interferon
JAK	Janus kinase
MCP-1	Monocyte chemoattractant protein-1
MERS-CoV	Middle East respiratory syndrome coronavirus
MIP-1α	Recombinant human chemokine CCL3
PBPK	Physiologically-based pharmacokinetic models
RBD	Receptor binding domain
RdRp	RNA dependent RNA polymerase
SARS-CoV	Severe acute respiratory syndrome coronavirus
STAT	Signal transducer and activator of transcription
SHLH	Secondary hemophagocytic lymphohistiocytosis
T-ALL	T cell acute lymphoblastic leukemia
TNF	Tumor necrosis factor

1 Introduction

Coronavirus disease 2019 (COVID-19) has broken out rapidly in nearly all countries worldwide, and has blossomed into a pandemic. COVID-19 infections normally manifest with symptoms of high temperature, cough, myalgia, weakness, polypnea and other symptoms [1]. In grievous cases, it can also cause acute respiratory distress syndrome (ARDS), and result in fluids around in the lungs, eliciting infectious shock. Since the beginning of the COVID-19 spread, scientists have investigated cooperatively, examining abundant old drugs and new clinical treatments, such as Chinese medicines [2], vaccine development [3, 4], convalescent plasma [5–7], interferon-based therapies [8], monoclonal antibodies [9], cell-based therapies [10], immunopathology therapies [11] and small molecule drugs, aiming to discover drugs with potent anti-COVID-19 activity. However, the pathway to develop a new drug or vaccine usually takes more than 1 year or even 3–5 years. Monoclonal antibodies, cell-based therapies, interferon-based therapies, and immunopathology therapies are unacceptable for their high cost. Considering cost and time constraints, small molecule drugs, including existing drugs, e.g., those used to treat influenza,

HBV, HCV, HIV, antimalarial and anti-filovirus drugs, have evoked great interest among researchers as they might allow more rapid development [12].

As traditional small molecule drugs used for treating malaria and certain autoimmune diseases, chloroquine (CLQ) and hydroxychloroquine (CLQ-OH) (Fig. 1) were demonstrated recently to exhibit certain activity against COVID-19 both in vitro and in vivo. Preliminary clinical results showed that CLQ has potential for use in the treatment of COVID-19 patients [13]. Compared with CLQ, CLQ-OH is more effective and has better safety properties in vitro [14]. Recently, the Gautret group [15] conducted a clinical trial using CLQ-OH in combination with Azithromycin to treat patients with COVID-19; the results showed that this was effective. But, afterwards, it was reported that use of these two antimalarial drugs may be fatal in some cases [16].

Shah et al. [17] reviewed a total of 61 antiviral drugs to screen efficient drugs against COVID-19 as shown in Tables 1, 2, 3, 4, 5, 6 and Figs. 2, 3, 4, 5, 6, 7. Some biological activities against COVID-19 are also listed based on literature reports [18–37].

Yan and Muller [37] provided a detailed analysis and described the use of the parent nucleoside of remdesivir, GS-441524 (Fig. 8), over remdesivir for the treatment of COVID-19, and appealed to Gilead Science to ditch GS-441524.

Riva et al. [38] identified 100 known drugs that can inhibit COVID-19 replication in mammalian cells, and found 21 compounds exhibiting effective dose response relationships with antiviral activity and confirmed their dose/activity relationships. Then, they found 13 compounds harboring EC_{50} values < 500 nM in at least one cell line (Table 7); for structures of these compounds see Fig. 9.

In addition to antimalarial and antiviral drugs, M^{pro} has also attracted the interest of researchers as a drug target for COVID-19 as it can mediate virus duplication and transcription. Jin and co-workers [39] reported the mechanism of M^{pro} inhibitor N_3 via computer-aided drug design, and confirmed the crystal structure of COVID-19 M^{pro} and N_3. Their results showed that N_3 had the strongest antiviral COVID-19 effects at a concentration of 10 μM, the inhibition against COVID-19 EC_{50} value was 16.77 μM. They also discovered the crystal structure of the M^{pro}-Carmofur complex, confirming that Carmofur covalently links to the Cys145 residue via the carbonyl group, while the fatty acid group married with the hydrophobic S2 subsite of M^{pro} [40]. Su and co-workers [41] investigated the inhibition of COVID-19 M^{pro} by natural products derived from Chinese traditional medicines. They found that baicalin and baicalein showed non-covalent,

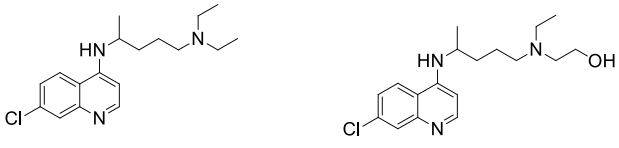


Fig. 1 Structure of chloroquine (CLQ) and hydroxychloroquine (CLQ-OH)

Table 1 Hepatitis C virus (HCV) antiviral agents against COVID-19

Entry	Name	Biological activity against COVID-19	Mechanism
1	ABT450	ND	Inhibits NS3/4A serine protease
2	Asunaprevir	IC_{50}: 53.9 ± 1 μM [18]	Protease inhibitor
3	Beclabuvir	ND	Inhibits NS5B protein
4	Boceprevir	IC_{50}: 2.7 ± 0.05 μM [19]	NS3/4A protease inhibitor
5	Dasabuvir	ND	Inhibits the action of NS5B polymerase
6	Danoprevir	CC_{50}: > 50 μM [20]	NS3/4A protease inhibitor
7	Daclatasvir	EC_{50}: 0.8 μM [20]	NS5A inhibitor
8	Faldaprevir	ND	Protease inhibitor
9	Elbasvir	ND	NS5A inhibitor
10	Grazoprevir	K_i: 172.33 nM [21]	Blocks NS3
11	Mericitabine	ND	Inhibitor of RdRp
12	Radalbuvir	ND	NS5B inhibitor
13	Simeprevir	EC_{50}: 4.08 μM, CC_{50}: 19.33 μM [22]	HCV protease inhibitor
14	Ombitasvir	ND	NS5A inhibitor
15	Sofosbuvir	EC_{50}: 381 ± 34 μM [20]	Inhibits viral RNA synthesis by inhibiting NS5B protein
16	Ravidasvir	ND	NS5A inhibitor
17	Telaprevir	IC_{50}: 10.7 ± 0.4 μM [18]	NS3/4a protease inhibitor
18	Velpatsvir	EC_{50}: 0.77–2.74 μM [23]	NS5A protein inhibitor
19	Vedroprevir	ND	Inhibits HCV NS3
20	Vaniprevir	ND	NS3/4A protease inhibitor
21	Uprifosbuvir	EC_{50}: > 50 μM [24]	NS5B polymerase inhibitor

ND, not determined, IC_{50} half maximal inhibitory concentration

Table 2 Hepatitis B virus (HBV) antiviral agents against COVID-19

Entry	Name	Biological activity against COVID-19	Mechanism
1	Famciclovir	ND	Inhibits viral DNA polymerase
2	Entecavir	EC_{50}: > 10 μM, CC_{50}: > 50 μM [23]	Inhibits reverse transcription
3	Telbivudine	ND	Reverse transcriptase inhibitor
4	Foscarnet	ND	Viral DNA polymerases inhibitor

non-peptidomimetic inhibition of COVID-19 M^{pro}, and had strong antiviral activities both in vitro and in a cell-based system. The in vitro study results and favorable safety data from clinical trials showed that baicalein has great potential to become a candidate for a much needed anti-coronaviral drug. Dai and coworkers [42] designed two M^{pro} inhibitors **11a** and **11b**, which showed perfect anti-COVID-19 activity. The structure–function relationship showed that the aldehyde group of the two compounds can covalently link to the M^{pro} Cys145

Table 3 Human immunodeficiency virus (HIV) antiviral agents against COVID-19

Entry	Name	Biological activity against COVID-19	Mechanism
1	Amprenavir	EC_{50}: 31.32 µM, CC_{50}: > 81 µM [25]	Protease inhibitor
2	Adefovir	ND	Reverse transcriptase inhibitor
3	Azidothimidine	ND	Inhibits reverse transcriptase
4	Darunavir	K_d: 57.30 nM (3CL protease), 6.09 nM (RdRp) and 46.16 nM (papain-like protease) [26] EC_{50} > 100 µM [27]	Inhibits HIV protease enzyme
5	Delavirdine	ND	Non-nucleoside reverse transcriptase inhibitor
6	Didanosine	ND	Nucleoside reverse transcriptase inhibitor
7	Elvitegravir	ND	Integrase inhibitor
8	Efavirenz	EC_{50}: > 9.6 µM, CC_{50}: 37.6 ± 10.7 µM [23]	Inhibits non-nucleoside reverse transcriptase enzyme
9	Ritonavir	C_{50}: 8.63 µM, CC_{50}: 74.11 µM [25]	HIV Protease inhibitor
10	Indinavir	EC_{50}: 59.14 µM CC_{50}: > 81 µM [25]	Protease inhibitor
11	Maraviroc	EC_{50}: 2.7 µM [28]	C–C chemokine receptor type 5 allosteric modulator
12	Lopinavir	EC_{50}: 5.73 µM, CC_{50}: 74.44 µM [25]	Protease inhibitor
13	Raltegravir	ND	HIV-1 integrase inhibitor
14	Nevirapine	ND	Non-nucleoside reverse transcriptase inhibitor
15	Sequinavir	EC_{50}: 8.83 µM, CC_{50}: 44.43 µM [25]	Protease inhibitor
16	Stavudine	ND	Inhibits HIV reverse transcriptase enzyme
17	Zalcitabine	ND	Inhibits nucleoside reverse transcriptase
18	Tenofovir	EC_{50}: 100 µM [29]	HIV-1 reverse transcriptase inhibitor

Table 4 Influenza antiviral agents against COVID-19

Entry	Name	Active against	Biological activity against COVID-19	Mechanism
1	Arbidol (Umifenovir)	Influenza	EC_{50}: 4.11 μM [29]	Inhibits membrane fusion
2	Favipiravir	Influenza	EC_{50}: 22.5 μM [30]	Inhibits viral RNA dependent RdRp
3	Amantadine	Influenza A	IC_{50} > 100 μM [31]	The influenza virus A-M2 proton channel agonist
4	Zanamivir	Influenza viruses	ND	Neuraminidase inhibitor
5	Oseltamivir	Influenza viruses A	EC_{50}: > 100 μM [32]	Inhibits the neuraminidase enzyme

Table 5 Ebola antiviral agents against COVID-19

Entry	Name	Active against	Biological activity against COVID-19	Mechanism
1	Galidesivir	Ebola	EC_{50}: > 100 μM [32]	RNA polymerase inhibitor
2	Remdesivir	Ebola virus, Respiratory syncytial virus	EC_{50}: 0.77 μM [33]	Viral RNA polymerase

residue. Zhang and co-workers [43] reported the complex structure of COVID-19 M^{pro} and **11r**, found that **11r** showed excellent inhibitory activity and potent anti-COVID-19 activity. **11r** could be used as a lead compound to develop potent inhibitors of COVID-19 M^{pro} (Fig. 10).

Vitner et al. [44] examined a Glucosyl Ceramide synthase (GCS) inhibitor GENZ-123346 (analogue of Cerdelga) and GENZ-66761 (structure unknown) for their antiviral effects on COVID-19. Both drugs can inhibit COVID-19 virus, and could be assessed further in preclinical and clinical trials (Fig. 11).

Cytokine storm is a driver of pathology and mortality in viral infections. In COVID-19-infected patients, cytokine storm increases the risk of death and other severe symptoms [45]. Plenty of COVID-19 patients with cytokine storm syndrome encounter a sharp respiratory function obstacle [46]. Secondary hemophagocytic lymphohistiocytosis (sHLH) is a hyper inflammatory syndrome characterized by noteworthy augmentation of cytokines, with multi-organ failure and high mortality rate [47]. COVID-19 patients with cytokine storm syndrome exhibit increased levels of several interleukins: IL-2, IL-6, IL-7, granulocyte colony-stimulating factor (G-CSF), interferon-gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α). The study showed that COVID-19 patients who died have higher plasma levels of ferritin and IL-6 [48]. Four United States Food and Drug Administration (FDA)-approved Janus kinase (JAK) inhibitors have proved useful for the treatment of COVID-19 [49]: Jakafi/Ruxolitinib; Xeljanz/Tofacitinib; Olumiant/Baricitinib; and Rinvoq/Upadacitinib (Fig. 12). Among these four JAK inhibitors, Ruxolitinib can significantly reduce the IL-6 and TNF-α level in spleen [50].

Table 6 Other antiviral agents against COVID-19

Entry	Name	Active against	Biological activity against COVID-19	Mechanism
1	Acyclovir	Cytomegalovirus infections	ND	Inhibits viral DNA polymerase
2	Baricitinib	Rheumatoid arthritis	IC_{50}: 400–800 nM [34]	Inhibits Janus kinase
3	Brivudin	Herpes zoster	ND	Locks the action of DNA polymerases
4	Camostate	Pancreatitis	EC_{50}: 107 nM [35]	Serine protease inhibitor
5	CGP42112A	Vasodilation and blood pressure reduction	ND	Angiotensin AT2 receptor agonist
6	Dihydroxy propyladenine	Herpes Virus	ND	Inhibits viral replication
7	Ganciclovir	Cytomegalovirus	ND	Inhibits viral DNA polymerases
8	Iodoxuridine	Herpes simplex virus	ND	Interferes viral DNA replication
9	Marboram/Methisazone	Small pox virus	ND	Inhibits mRNA and protein synthesis
10	Nitrazoxanide	Broad-spectrum antiviral	EC_{50}: 2.21 μM [36]	Pyruvate:ferred oxinoxidoreductase (PFOR) enzyme
11	NSC306711 (Ferristatin II)	Flavivirus	ND	Degradation of Transferrin receptor-1

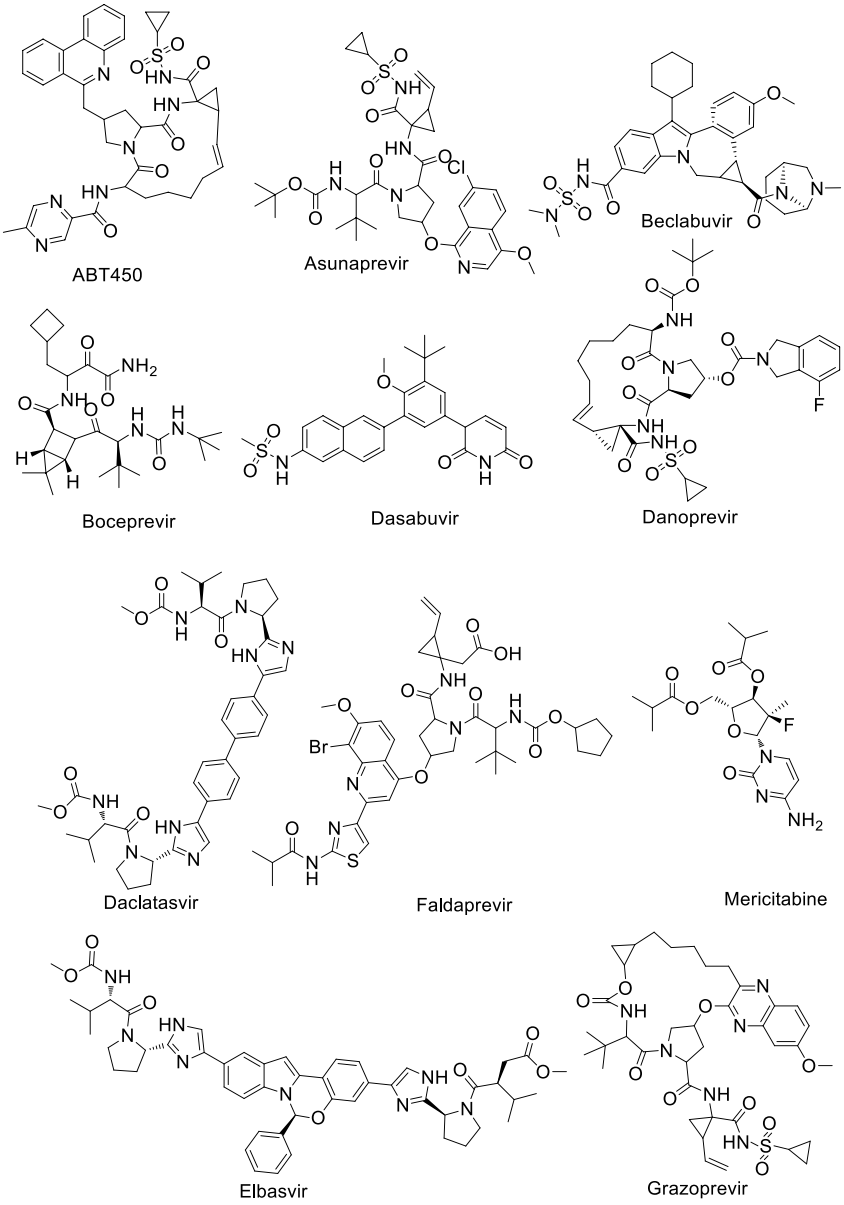
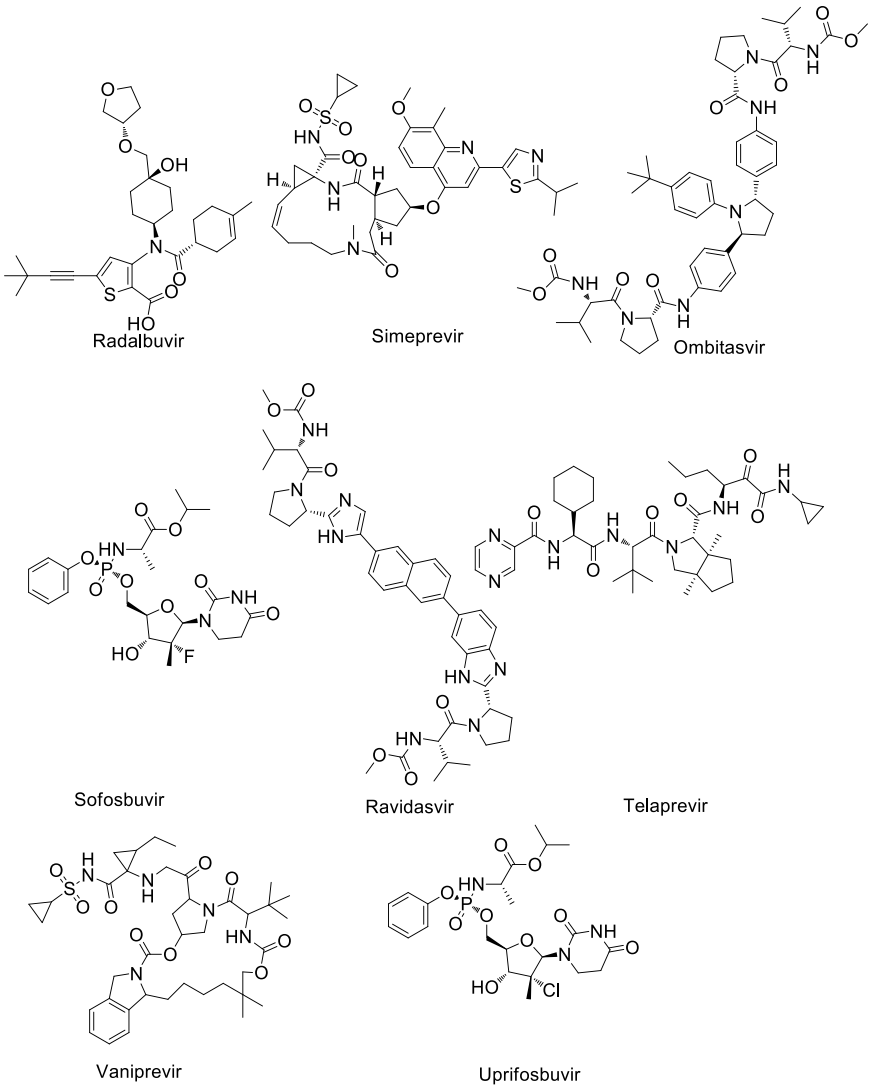


Fig. 2 Structure of hepatitis C virus (HCV) antiviral agents against COVID-19

Of all the above-mentioned drugs that have potential activity in inhibiting COVID-19, CLQ, CLQ-OH, Favipiravir, Remdesivir and Ruxolitinib attracted our interest due to extensive research on these drugs worldwide.



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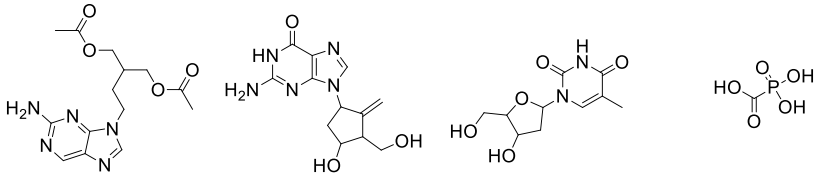


Fig. 3 Structure of hepatitis B virus (HBV) antiviral agents against COVID-19

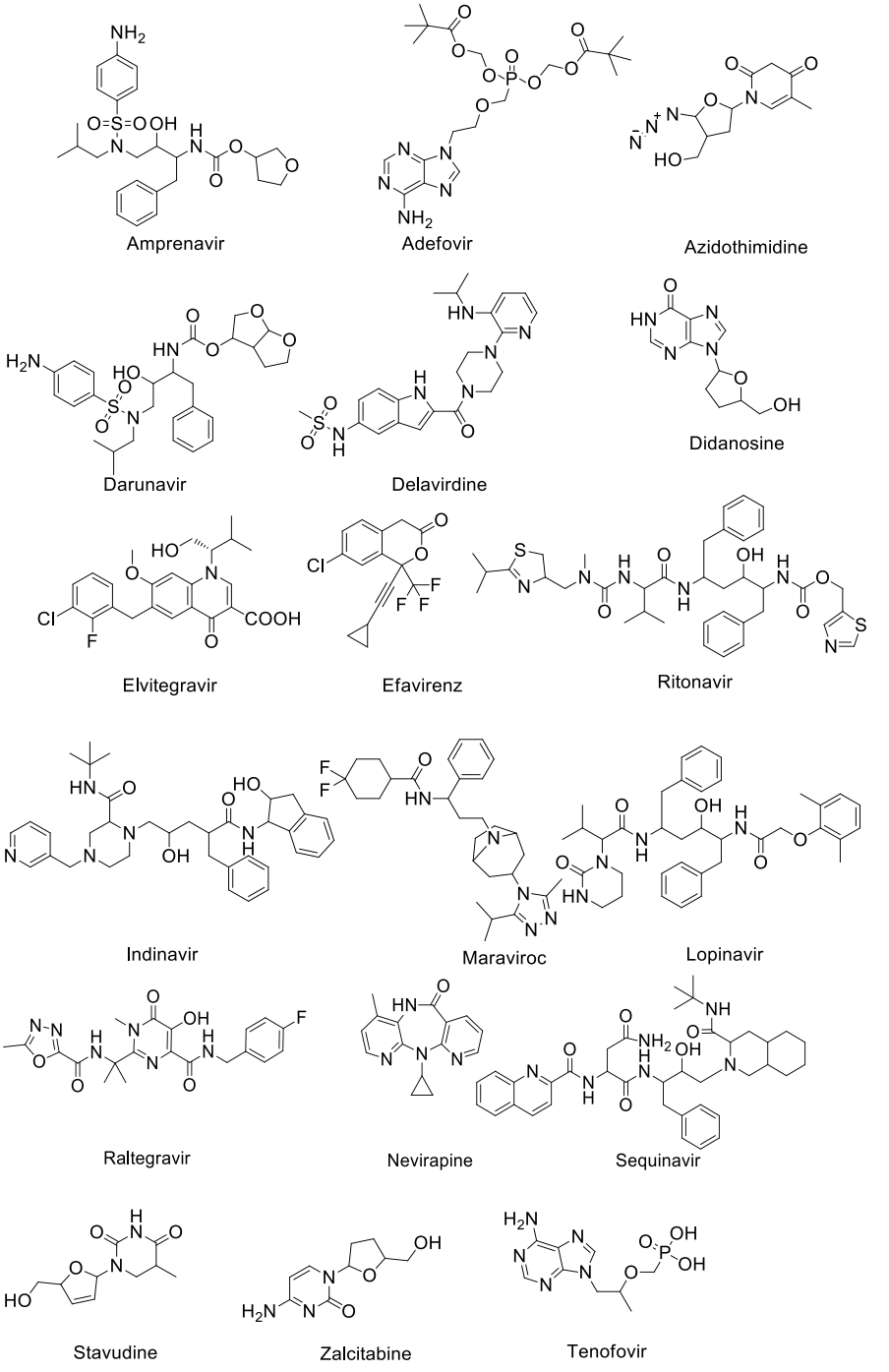
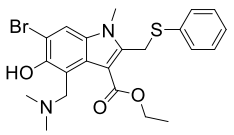
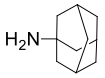


Fig. 4 Structure of human immunodeficiency virus (HIV) antiviral agents against COVID-19

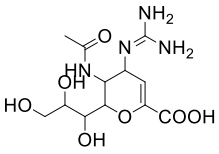


Arbidol(Umifenovir)

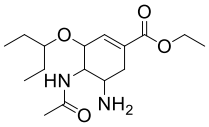
Favipiravir



Amantadine



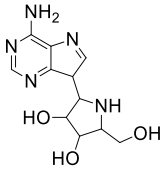
Zanamivir



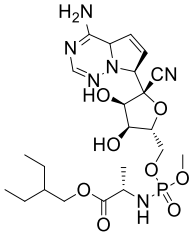
Oseltamivir

Fig. 5 Structure of Influenza antiviral agents against COVID-19

Fig. 6 Structure of Ebola antiviral agents against COVID-19



Galidesivir



Remdesivir

2 Characteristics of COVID-19

Coronavirus is a positive sense, single-chain RNA virus [51]. Coronaviruses are classified as α-, β-, γ-, and δ-coronavirus. Only α-coronavirus and β-coronavirus can infect humans [52]. γ-Coronavirus and δ-coronavirus can affect humans indirectly through animals [53]. The coronavirus (severe acute respiratory syndrome coronavirus (SARS-CoV)-2) causing COVID-19 is a β-coronavirus and shares about 80% RNA sequence consistency with SARS-CoV [54]. The SARS-CoV-2 genome encodes four main non-structural proteins: helicase, M^{pro}, RNA-dependent papain-like protease, and RNA polymerase [55], which are absolutely necessary for the survival of SARS-CoV-2. Initial analyses found that the four main SARS-CoV-2 enzymes mentioned above are highly conserved [56], and the spike glycoprotein is indispensable for SARS-CoV-2 invading the host cell [57]. Similar to SARS-CoV, SARS-CoV-2 encodes a large spike protein with two domains (S1 and S2); SARS-CoV-2 virus binds and enters a host cell via this spike protein [58, 59] (Fig. 13).

New research has shown that SARS-CoV-2 engages a receptor binding domain (RBD), binding to angiotensin-converting enzyme 2 (ACE2) to invade its human host cell [60] (Fig. 14).

Nevertheless, non-conserved mutations are highly accumulated in regions S1 and S2 which interact directly with ACE2. Mercurio et al. [61] performed a comparative in silico modeling analysis, and gained new insights into the spike protein of SARS-CoV-2. SARS-CoV-2 spike protein can interact with the ACE2

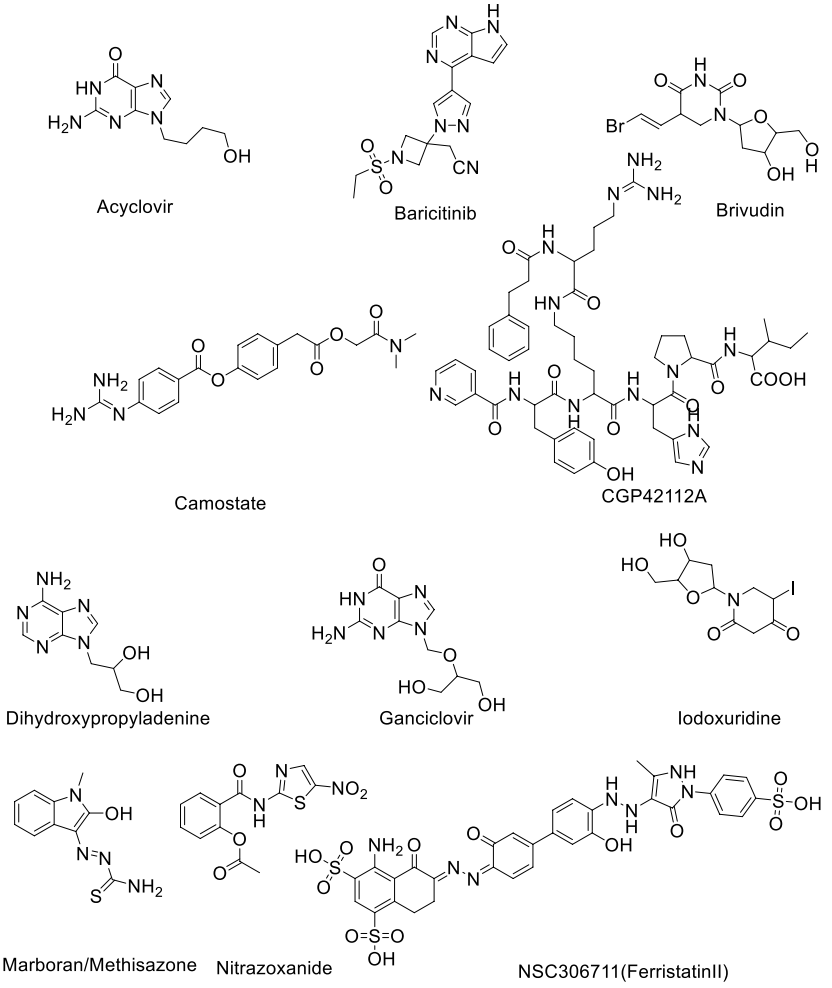


Fig. 7 Structure of other antiviral agents against COVID-19

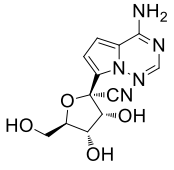


Fig. 8 Structure of GS-441524 (remdesivir)

receptor on human cells at the RBD. This analysis can supply an ideal pipeline to identify characterized antibodies that might target the SARS-CoV-2 spike protein RBD to prevent interacting with human ACE2. Laurini et al. [62] reported an atomistic-based, reliable in silico structure of the viral transmembrane spike

Table 7 Drugs with known activity against COVID-19 in cell lines

Entry	Drug name	EC_{50} value (μM)	Cell line
1	AMG2674[a]	0.023	Vero E6 cells
2	AMG2674	0.3	293T-ACE2 cells
3	AMG2674	0.41	Hub-7-ACE2 cells
4	Astemizole	~1.2	Vero E6 cells
5	Astemizole	0.87	293T-ACE2 cells
6	Astemizole	1.3	Hub-7-ACE2 cells
7	Clofazimine	0.31	Vero E6 cells
8	Clofazimine	ND	293T-ACE2 cells
9	Clofazimine	0.49	Hub-7-ACE2 cells
10	Elopiprazole	1.6	Vero E6 cells
11	Elopiprazole	0.13	293 T-ACE2 cells
12	Elopiprazole	~2.7	Hub-7-ACE2 cells
13	Hanfanychin A	~1.2	Vero E6 cells
14	Hanfanychin A	0.56	293T-ACE2 cells
15	Hanfanychin A	0.64	Hub-7-ACE2 cells
16	MLN-3897	0.65	Vero E6 cells
17	MLN-3897	0.41	293T-ACE2 cells
18	KW 8232	~1.2	Vero E6 cells
19	KW 8232[a]	~0.091	293T-ACE2 cells
20	KW 8232	1	Hub-7-ACE2 cells
21	*N*-tert-Butylisoquine	~1.2	Vero E6 cells
22	*N*-tert-Butylisoquine	0.29	293T-ACE2 cells
23	*N*-tert-Butylisoquine	0.37	Hub-7-ACE2 cells
24	SB 616234-A	~1.2	Vero E6 cells
25	SB 616,234-A	~0.29	293 T-ACE2 cells
26	SB 616234-A	0.64	Hub-7-ACE2 cells
27	SDZ-62-434	0.63	Vero E6 cells
28	SDZ-62-434	0.12	293T-ACE2 cells
29	SDZ-62-434	0.11	Hub-7-ACE2 cells
30	SL-11128	~0.25	Vero E6 cells
31	SL-11128	ND	293T-ACE2 cells
32	SL-11128	~2.5	Hub-7-ACE2 cells
33	YH-1238	~0.95	Vero E6 cells
34	YH-1238	1.1	293T-ACE2 cells
35	Apilimod[a]	0.0203	Vero E6 cells
36	Apilimod[a]	0.012	293T-ACE2 cells
37	Apilimod[a]	0.088	Hub-7-ACE2 cells
37	VBY-825	0.3	Vero E6 cells
38	VBY-825[a]	0.071	293T-ACE2 cells
39	VBY-825[a]	0.052	Hub-7-ACE2 cells
40	ONO 5334	0.41	293T-ACE2 cells
41	ONO 5334[a]	0.042	Vero E6 cells
42	ONO 5334[a]	0.078	293T-ACE2 cells

Table 7 (continued)

Entry	Drug name	EC_{50} value (μM)	Cell line
43	Z LVG CHN2	0.19	Vero E6 cells
44	Z LVG CHN2[a]	0.0011	293T-ACE2 cells
45	Z LVG CHN2[a]	0.0069	Hub-7-ACE2 cells
46	MDL 28170	0.22	Vero E6 cells
47	MDL 28170[a]	0.021	293T-ACE2 cells
48	MDL 28170[a]	0.086	Hub-7-ACE2 cells
49	DS-6930	0.36	Vero E6 cells
50	R 82913	0.21	Vero E6 cells

[a]Compounds harboring EC_{50} values < 500 nM in at least one cell line.

glycoprotein (S-protein)/ACE2 complex (Fig. 15), showing that residues D38, K31, E37, K353, Y41 on ACE2 and Q498, T500, R403 on the SARS-CoV-2 S-protein RBD are true hot spots to shaping and determining the stability of the relevant protein–protein interface. These results could be used in the structure-based design and development of neutralizing antibodies, vaccines, and protein–protein inhibitors against COVID-19.

Monteil et al. [63] afforded a molecular explanation for the severe lung failure and death due to COVID-19, and proved that APN01 (human recombinant soluble ACE2, also named hrsACE2) can inhibit SARS-CoV-2 infections, which can be used for treatment of COVID-19 patients.

3 Chloroquine

CLQ is an old antimalarial drug used to treat malaria, amebiasis, rheumatoid, arthritis and lupus erythematosus syndrome. It inhibits the heme polymerase in malarial trophozoites via preventing heme conversion to hemozoin [64]. CLQ has strong antiviral effects on SARS-Cov infection [65] and Ebola in vitro [66], and is also able to inhibit influenza A virus replication in vitro [67]. Moreover, CLQ also has been shown to have some level of anti-HIV [68] and anti-H5N1 [69] activity.

3.1 Biological Activity of CLQ

CLQ can increase the pH value of host cell vacuoles. In lysosomes of the host cell, CLQ can change the catalytic activity of acidic hydrolases, affecting protein degradation, endosomal macromolecule composition, and post-translational modifications in Golgi [70]. In macrophages and antigen-presenting cells, an antirheumatic response is present that interrupts the immunological process [71]. Recent literature reports [72–74] assist our understanding of the three probable mechanisms of CLQ activity (Fig. 16).

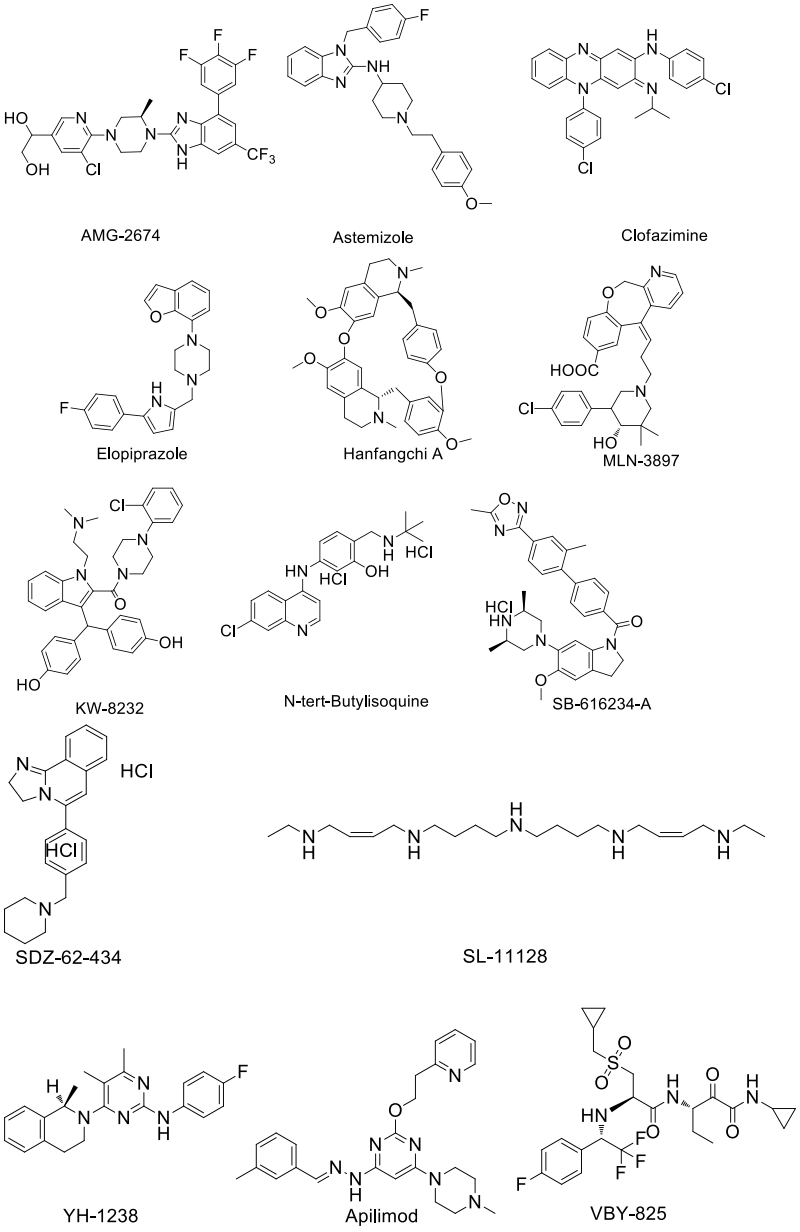


Fig. 9 Compounds exhibiting good effectiveness in COVID-19 cell lines

Gao et al. [13] found an EC_{50} value of 1.13 μM and a CC_{50} value greater than 100 mM for CLQ anti-COVID-19. Wang et al. [33] evaluated the efficiency of CLQ and six other drugs against SARS-CoV-2 in vitro, obtaining an EC_{50} value for CLQ of 1.13 μM and EC90 value of 6.90 μM in Vero E6 cells.

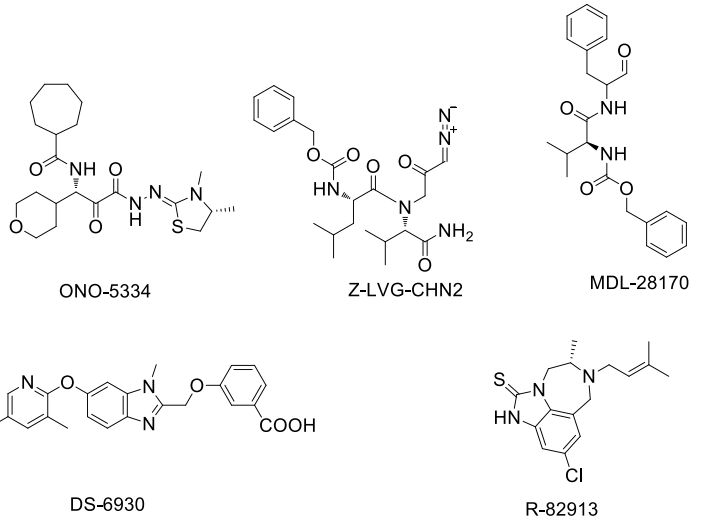
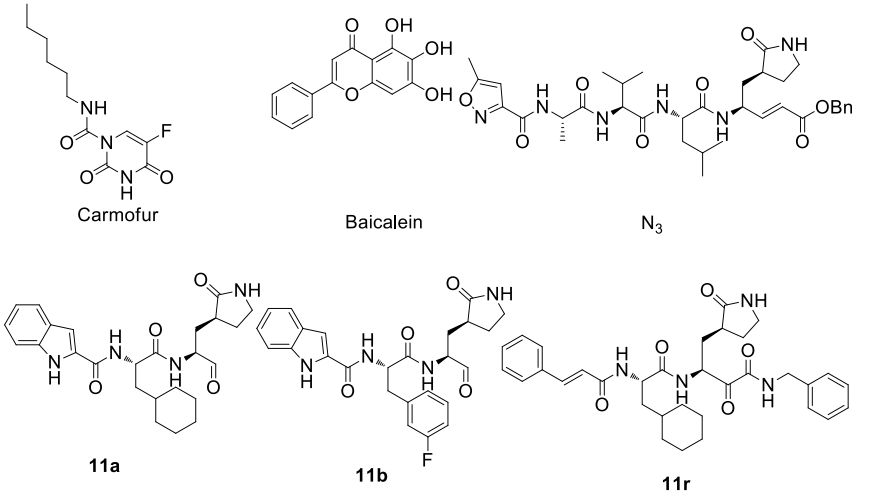


Fig. 9 (continued)



Carmofur $EC_{50} = 24.30\mu M$; **11a** $IC_{50} = 0.053 \pm 0.005\mu M$;

11b $IC_{50} = 0.040 \pm 0.002\mu M$; **11r** $IC_{50} = 2.39 \pm 0.63\mu M$;

N_3 $EC_{50} = 16.77\mu M$

Fig. 10 Structure and biological activity of Carmofur, Baicalein, 11a, 11b, 11r and N_3

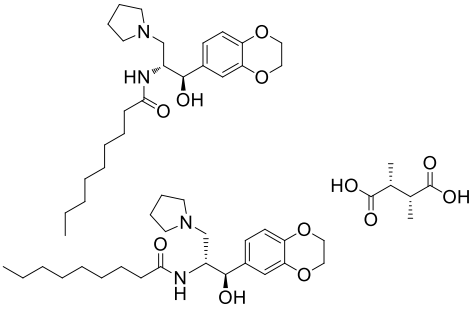


Fig. 11 Structure of GENZ123346

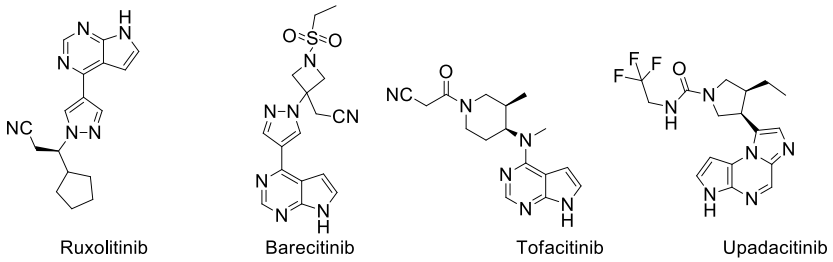


Fig. 12 Structure of four Janus kinase (JAK) inhibitors

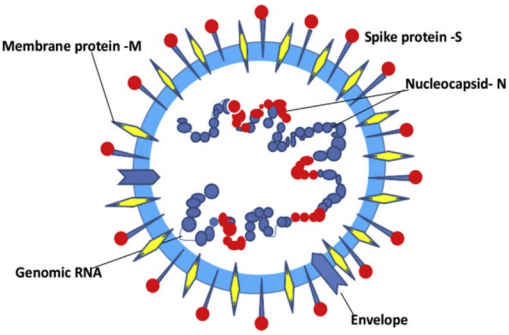


Fig. 13 Schematic representation of a coronavirus virion. Image reproduced from Ref. [59] with permission from Elsevier

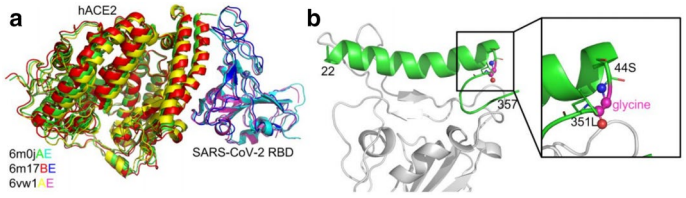


Fig. 14 Comparison of severe acute respiratory syndrome coronavirus (SARS-CoV)-2 receptor binding domain (RBD)/human angiotensin-converting enzyme 2 (hACE2) complex structures (**a**) and the constructed SARS-CoV-2 RBD/hACE2 peptide complex (**b**). Image reproduced from Ref. [60] with permission from bioRxiv

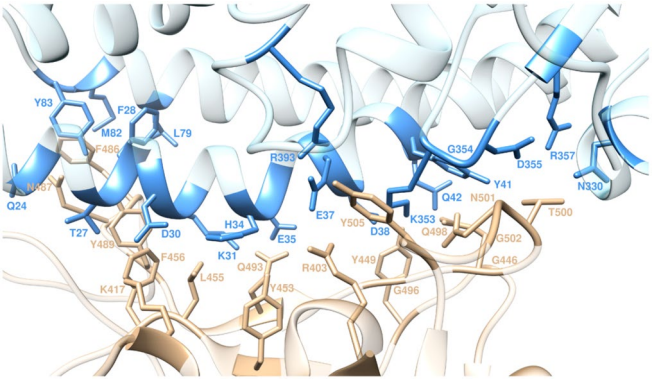


Fig. 15 Structure of S-Protein/ACE2 complex. Image reproduced from Ref. [62] with permission from ACS

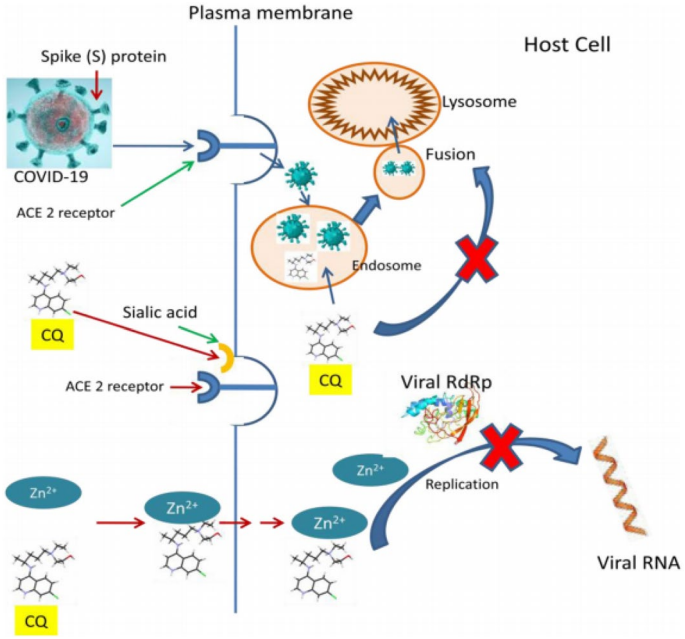


Fig. 16 Proposed mechanism of action for CLQ. *CQ* CLQ, *RdRp* RNA dependent RNA polymerase. Image reproduced from Ref. [74] with permission from Elsevier

3.2 Clinical Trials of CLQ

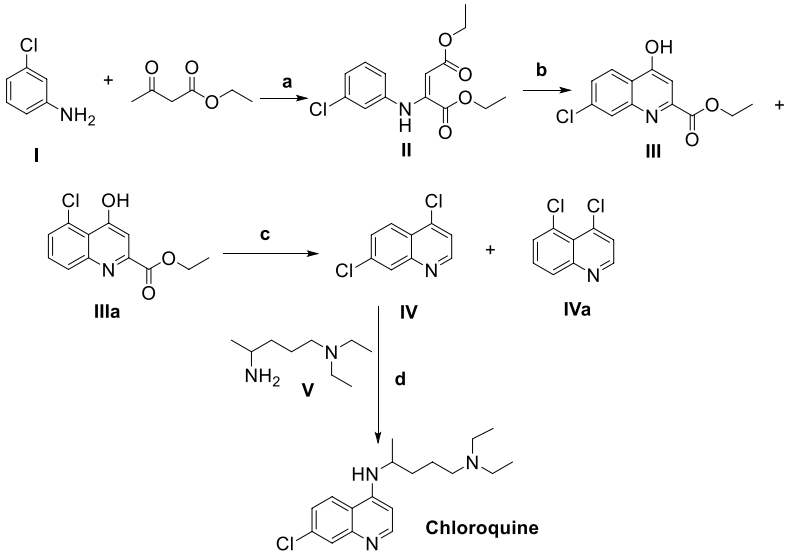
Since the outbreak of COVID-19, CLQ has been used extensively to treat COVID-19 patients. Sun et al. [75] reported using CLQ phosphate at a dose of 500 mg to treat COVID-19 with a duration not exceeding 10 days in elderly patients; these authors summarized the main adverse reactions of CLQ in elderly patients: cardiac

arrest, effects on skeletal musculoskeletal system, nerve irritability, medicated psychosis, granulocytopenia, aplastic anemia, thrombocytopenia, irreversible visual impairment, and others. Verscheijden et al. [76] established the best-evidence pediatric CLQ (free base) doses: 35 mg/kg, children 0–1 month, 47 mg/kg; children 1–6 months, 55 mg/kg; children 6 months to 12 years; and adolescents 44 mg/kg. Gao et al. [13] revealed that CLQ used in an intervention group had potent efficacy compared with a control group. Borba et al. [77] performed a parallel phase IIb clinical trial study to evaluate the safety and efficacy of high (0.6 g) and low (0.45 g) dose CLQ. Double-blinded and randomized participants were treated in intervention and control groups; the results suggested that the high dose of CLQ is hazardous to COVID-19 patients. Huang et al. [78] undertook a multicenter prospective observational study. Patients received a CLQ dose of 500 mg once or twice daily; patients treated with non-CLQ therapy were used as historical controls. In total, 197 patients used CLQ treatment, and 176 patients were treated as the historical control group. The duration of fever was clearly shortened. No serious adverse events were found in patients treated with CLQ. Patients treated with half dose CLQ experienced a lower rate of adverse events than with full dose. This study provides evidence for the safety and efficacy of CLQ in treatment of COVID-19 patients. Smit et al. [79] introduced pharmacokinetic and safety properties of CLQ for treatment of COVID-19, revealing that, for the use of CLQ to treatment of COVID-19 infection, early achievement of high 'target' concentrations is necessary, but, due to the high loading dose of CLQ and slow elimination, it can cause severe life-threatening toxicity and increased risk of mortality. Sinkeler [80] conducted a retrospective and observational study in a total of 397 patients aged over 18 years, found the CLQ gradually increased the QTc interval during treatment, which may result in ventricular tachycardia in patients. Sinkeler [80] suggested to measure the QTc interval before adjusting the dose of CLQ or withdrawing this potentially beneficial medication. While the pathogenesis of COVID-19 is still unknown, and because it does not show any anti SARS-Cov effect in an in vivo model, CLQ could be useless in treatment of COVID-19 patients and might even be harmful [81]; hence, before the pathogenesis of COVID-19 is known and the effect of CLQ is evaluated in clinical trials, it should be used cautiously.

3.3 Synthesis of CLQ

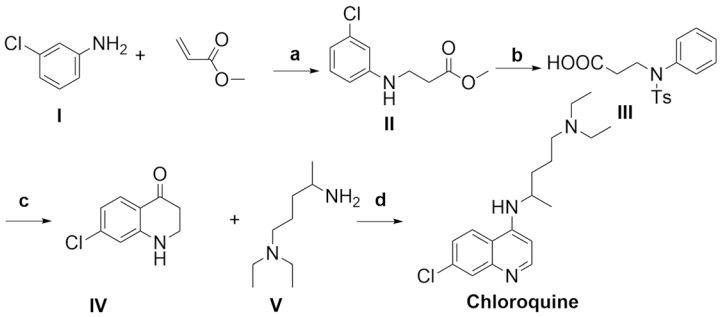
Surrey and Hammer [82] reported the first synthesis of CLQ (Scheme 1).

Ethyl ethoxalylacetate reacting with *m*-chloroaniline (**I**) in the presence of HOAc under mild condition obtained **II**, then ring-closure at high temperature in a short time yields **III** and its isomer **IIIa**; **III** and **IIIa** were refluxed in strong base solution to obtain a mixture of **IV** and **IVa**, with a final coupling of **IV** and **V** at high temperature obtaining CLQ. This synthetic route was unacceptable due to steps (ii) and (iii) producing nearly half of an isomer byproduct and steps (ii) and (iv) proceeding at high temperature.



Reaction conditions: a) ethyl ethoxalylacetate, *m*-chloroaniline, HOAc, 40-50 ºC, 4 h, then r.t. 15-18 h, yield 78.1%; b) 250 ºC, 15-18 min, yield (III) and (IIIa) 86.8%; c-1) 35% NaOH, 2 h, then con HCl; c-2) mineral oil 270 ºC 5 min, yield 96.2%

Scheme 1 First generation synthesis of Chloroquine (CLQ)



Reaction conditions: a) HOAc, reflux, 12 h; b) (1)tosyl chloride, Et_3N; (2) 35%NaOH, reflux, 3 h, then HCl, a and b total yield 80%; c) PCl_5, $AlCl_3$, reflux; d. phenol, 154 ºC , 6 h, yield 68%.

Scheme 2 Compound II should be added an C-Cl at meta position

Jonnson and Buell [83] reported a second generation synthesis of CLQ (Scheme 2).

Methyl acrylate and *m*-chloroaniline (**I**) were refluxed in HOAc to obtain **II**, then **II** was protected by TsCl and ring-closure obtained **IV**. Finally, **IV** and **V** were

refluxed in the presence of phenol to obtain CLQ. The total yield of this procedure is about 24.7%, which is higher than the first generation process, but, in step d, the reaction temperature is as high as more than 150 °C, at which temperature byproducts are easily produced, and the solvent phenol is harder to recover.

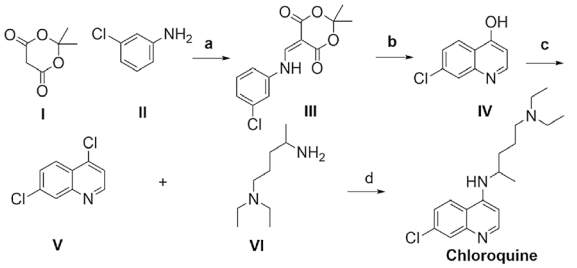
Margolis et al. [84] reported a third generation synthesis of CLQ (Scheme 3). **I** and **II** were refluxed without solvent and ring-closure obtained **IV**, then chlorination in the presence of $POCl_3$ obtained **V**. Finally, **V** and **VI** coupling via Suzuki coupling obtained CLQ. The totally yield of this procedure is approximately 58% in mild conditions, which is suitable for large-scale production.

4 Hydroxychloroquine

4.1 Biological Activity of CLQ-OH

CLQ-OH is similar to CLQ, and. as an old antimalarial drug, also has potential effects on COVID-19 and lower toxicity than CLQ [85]. Moreover, it showed better anti-SARS-CoV-2 efficiency compared to CLQ in vitro [86]. Yao et al. [14] used physiologically-based pharmacokinetic models (PBPK) models to ensure the most efficacious concentrations of CLQ-OH and its safety profile, and found its EC_{50} value to be 0.72 μM in vitro. Fantini et al. [74] used an assembly of structure-molecular modeling methods and found that CLQ-OH can prevent binding of the SARS-CoV-2 spike to gangliosides, which is helpful in understanding the mechanism of CLQ-OH as an anti-COVID-19 drug (Figs. 17, 18).

Zhang et al. [87] systematically evaluated the treatment of COVID-19 with CLQ and CLQ-OH for efficacy and safety, and asserted a potential mechanism involving COVID-19-induced injury of multiple organs as well as the pharmacological effects of CLQ-OH on COVID-19 (Fig. 19); the authors concluded that COVID-19 is actually a multisystem disease, with respiratory symptoms as the major clinical manifestation. Therefore, the treatment of COVID-19 with CLQ and CLQ-OH should be evaluated systematically, and patients should be monitored carefully for cardiovascular conditions to prevent lethal adverse events.



Reaction conditions: a) triethyl orthoformate, reflux 4 h, yield 82%; b) Ph_2O reflux; c) $POCl_3$, reflux, yield 95%; d) 4 mol% $Pd(OAc)_2$, 8 mol% DPEphos, 2.5 eq K_3PO_4, N_2, Dioxane, 85 °C, 18 h, yield 74%.

Scheme 3 Third generation synthesis of CLQ

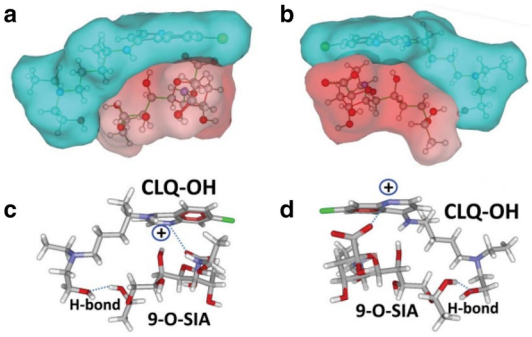


Fig. 17 Molecular model of CLQ-OH interaction with sialic acids. Image reproduced from Ref. [74] with permission from Elsevier

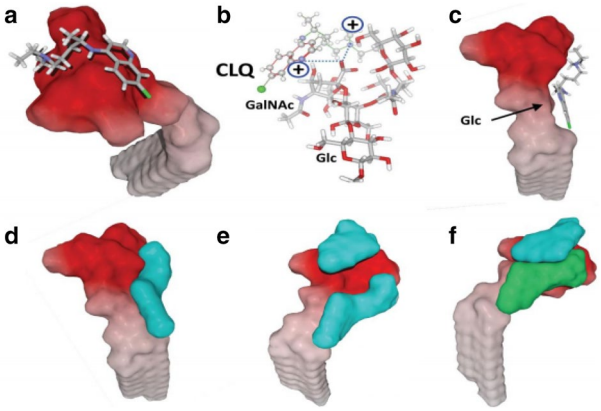


Fig. 18 Molecular modeling simulations of CLQ and CLQ-OH binding to ganglioside. Image reproduced from Ref. [74] with permission from Elsevier

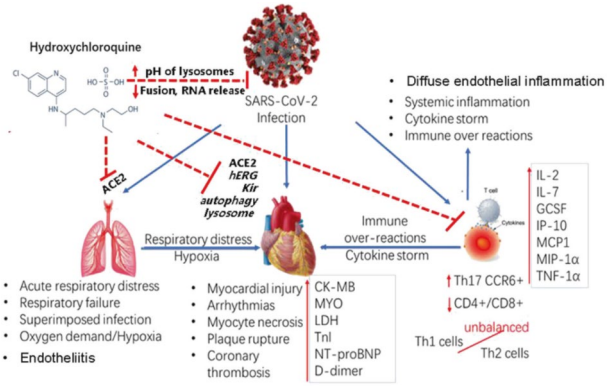


Fig. 19 Potential mechanisms of SARS-COV-2-induced injury of multiple organs and pharmacological effects of CLQ-OH on COVID-19. *Blue arrows* indicate the actions of SARS-COV-2. ACE2 is key for SARS-COV-2 entering cells in human organs. *Red dashed lines* indicate the potential mechanisms of the therapeutic and toxic effects of CLQ-OH on SARS-COV-2 and organs in COVID-19 patients. Image reproduced from Ref. [87] with permission from Elsevier

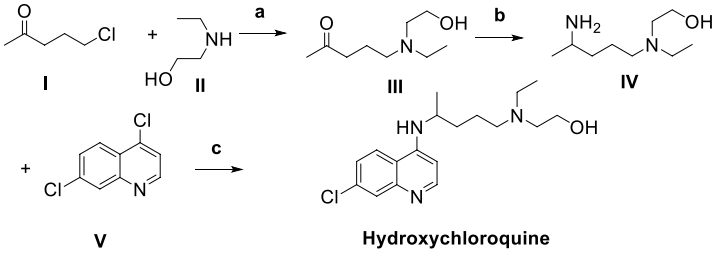
4.2 Clinical Trials of CLQ-OH

Based on clinical studies [88], CLQ-OH is considered to be safer than CLQ. Gautret et al. [89] conducted a phase III clinical trial treating 80 mildly infected inpatients with CLQ-OH in combination with Azithromycin, demonstrating its therapeutic effect. Furthermore, the cost of this treatment is negligible. The suggested dose of CLQ-OH is 400 mg daily on the 1st day, then 200 mg daily for the next 3 days [90]. A total of 62 COVID-19 patients were assigned stochastically to the CLQ-OH (0.4 g daily, 0.2 g bid) and the control groups. After 5 days of treatment, patients in the CLQ-OH groups were clearly recovering in a shorter time [91]. To evaluate toxicity in patients who received high doses of CLQ-OH, a total of 63 patients were included [92], 58 females and 5 males. The mean dosage of CLQ-OH was 3.9 mg/kg, but 14 patient had doses higher than 5 mg/kg. A total of 36 patients were treated with CLQ-OH for more than 5 days. Only one (1.58%) patient exhibited CLQ-OH toxic retinopathy over a mean of 8 years treatment period. Patients on doses of >5 mg/kg of CLQ-OH may be put at higher risk for retinal toxicity. Gautret et al. [15] used CLQ-OH, alone (0.6 g daily) or in combination with Azithromycin to treat COVID-19 patients in a small clinical trial. The results showed that Azithromycin combined with CLQ-OH was more efficient than CLQ-OH alone. A recent report [93] also confirmed significant efficacy of CLQ-OH in combination with Azithromycin. On the contrary, Sharma et al. [94] found opposite consequences in CLQ-OH combination with Azithromycin in a small, non-randomized clinical trial. Moreover, the risk of arrhythmia and prolonged QT interval was increased. Singh et al. [95] studied the efficacy of CLQ-OH in a treatment group compared with a control group in COVID-19, and concluded that there was no positive result in the CLQ-OH group, and that the death rate even increased in the CLQ-OH group compared to the control group. Gendelman et al. [96] performed a retrospective study based on a database including COVID-19 patients treated with CLQ-OH from February to March. A total sample of 14,520 were screened for COVID-19 infection, with 1317 being found positive. These findings raise doubts about the safety and efficacy of CLQ-OH against COVID-19 infection. Lauriola et al. [97] performed a retrospective study including 337 consecutive COVID-19 patients; 297 patients received CLQ-OH and azithromycin combination treatment, 17 patients CLQ-OH treatment alone and 63 patients did not recieve either of these two drugs due to contraindications. In this study, 146 patients died, including 102 in the combination treatment, 7 in the CLQ-OH treatment and 35 in the no treatment groups.

4.3 Synthesis of CLQ-OH

Alexander et al. [98] first reported the synthesis of CLQ-OH (Scheme 4).

I and **II** were refluxed in xylene to get **III**, then ammoniation and hydrogenation by Raney Nickel in high pressure obtained **IV**; finally, **IV** and **V** refluxed in phenol

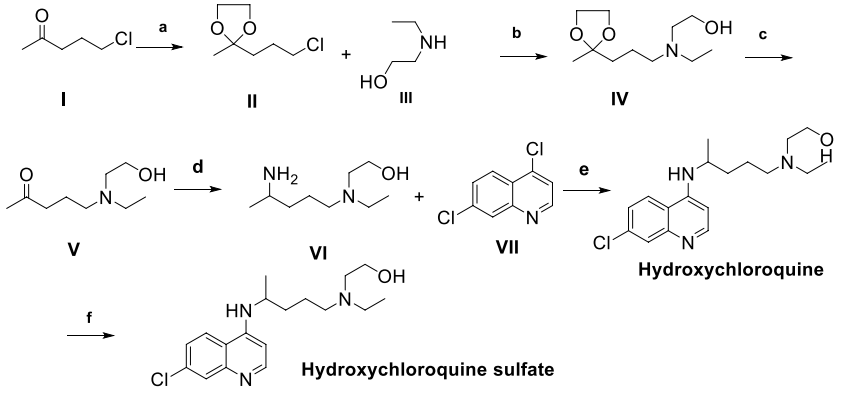


Reaction conditions: a) NaCl, xylene, reflux 2 h, yield 30%; b) ammoniacal methanol, Raney Nickel, 1000 pounds pressure, rt 24 h, yield 89%; c) phenol, KI, 125-130 °C, 18 h, yield 66%

Scheme 4 Method for preparation of Hydroxychloroquine (CLQ-OH) by Alexander et al. [98]

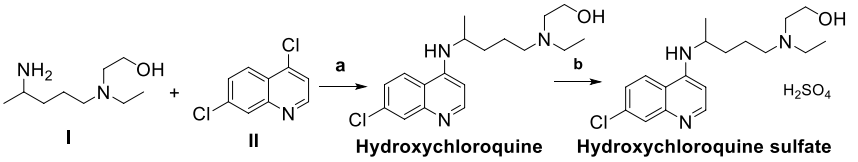
CLQ-OH. The overall yield of this procedure is as low as 17.6%, in step (b) intermediate (**III**) ammoniation and reduction by Raney Nickel requires high pressure, and in step (c) the solvent phenol is hard to recover. Hence, this method is unacceptable for large-scale production.

Ashok et al. [99] reported another synthetic route for the preparation of CLQ-OH (Scheme 5). Compound **I** was protected by ethylene glycol then reacted with **III** in refluxing toluene obtained **IV**, **IV** via deprotection, ammoniation and hydrogenation with Raney Nickel in high pressure to get **VI**, **VI** reacted with **VII** obtained CLQ-OH; finally, treatment of CLQ-OH with sulfuric acid yields CLQ-OH sulfate. The overall yield of this procedure is about approximately 40% via



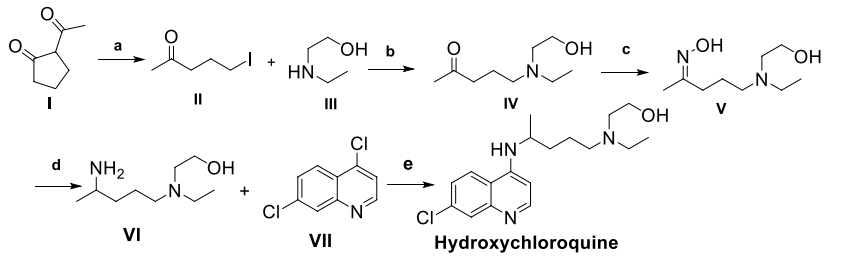
Reaction conditions: a) ethylene glycol, PTSA, 80-90 °C, 20-25 h, yield 100%; b) toluene, 125-130 °C, 15-18 h, yield 83%; c) con HCl, water, 30-40 °C, 4-5 h, yield 100%; d) ammonical methanol, Raney Nickel 40-80 °C, 20 kg hydrogen pressure, 4-5 h, yield 80%; e) NaOH, KI, 110-115 °C, 40-50 h, yield 76%; f. H_2SO_4, MeOH, 5-100 °C, 3-4 h, yield 77%.

Scheme 5 Method for preparation of CLQ-OH by Ashok et al. [99]



Reaction conditions: a) Nitrogen gas 20 bars pressure, 80 °C, 30 min, 100-110 °C, 4 h, yield 78%; b) ethanol, conc. sulfuric acid, 10 °C, yield 85%.

Scheme 6 Method for preparation of CLQ-OH by Min et al. [100]



Reaction conditions: a) 55% Hydroiodic acid, 80 °C, yield 89%; b) Dry THF, nitrogen gas, K_2CO_3, 100 °C, yield 86%; c) hydroxylamine, K_2CO_3, 100 °C, yield 100%; d) Raney Nickel, hydrogen gas 10 bar pressure, 80 °C, yield 84%; e) triethylamine, K_2CO_3, ethanol, 125 °C, 6 h, yield 88%.

Scheme 7 Preparation of CLQ-OH with a continuous-flow method

six steps, but in step (d), the Raney Nickel reduction of intermediate (**IV**) requires high pressure, which is a potential safety hazard.

In 2010, Min et al. [100] reported a method for preparation of CLQ-OH (Scheme 6). **I** and **II** reacted in nitrogen conditions at high pressure obtained CLQ-OH with a yield of 78%; treatment sulfuric acid obtained CLQ-OH sulfate. This procedure led to CLQ-OH sulfate via two steps with an approximate total yield of 77%, but in step (a) the reaction proceeded in high pressure, which has safety implications.

Yu et al. [101] and Frank et al. [102] used continuous-flow method for high-yield preparation of CLQ-OH (Scheme 7), which is not suitable for large-scale production. Iodization of **I** with hydroiodic acid and reaction with **III** in the presence of K_2CO_3 yielded **IV**, then oxime was obtained with hydroxylamine, and hydrogenation using Raney Nickel in high pressure obtained **VI**; finally, **VI** and **VII** reacted at high temperature in base conditions yielded CLQ-OH. This procedure yielded CLQ-OH in mild conditions, but the final step using ethanol as a solvent at high temperature is unacceptable, as ethanol volatilizes easily.

5 Favipiravir

Favipiravir (T-705) has been developed by Toyama Chemical Co., Ltd (Tokyo, Japan) as a broad spectrum antiviral drug against RNA viruses [103]. It shows good efficacy in the treatment of influenza infections [104] and pathogenic avian influenza A (H5N1). Favipiravir was also used as a potential drug for Ebola virus [105] and severe influenza [106], with EC_{50} values of 0.014–0.55 μg/mL to seasonal influenza and oseltamivir-resistant virus [107]. Favipiravir has an antiviral effect on SARS-CoV-2 by inducing a reduction in virus-induced cytopathic effect [108]. Observations show that Favipiravir induced the mutagenic effect responsible for the inhibition of replication; it was shown to act through lethal mutagenesis for several viruses, predominantly by competing with guanosine to cause transition mutations.

5.1 Biological Activity of Favipiravir

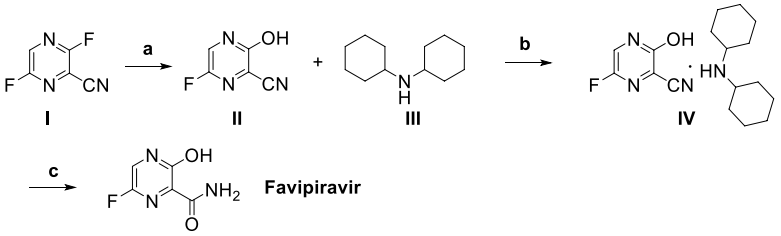
Favipiravir is a virus RdRp inhibitor. EC_{90} values for H5N1 resistance are in the 1.3–7.7 μM range [109]. Research in a P388D1 cell-based system [110] showed that Favipiravir can clearly inhibit the generation of TNF-α. Shirak et al. [111] established an influenza infection animal model to study the activity of Favipiravir, and proved that Favipiravir was significantly effective in alleviating influenza infection in mice. Janowski et al. [112] demonstrated that Favipiravir has EC_{50} values of 246 ± 76 μM (VA1), > 1000 μM (HAstV4) and 4.73 μM (IAV).

5.2 Clinical Trials of Favipiravir

Survival and virological characteristics were observed [113]. Randomized, multicenter phase II [114] and phase III [115] trials demonstrated clinical efficacy and safety of Favipiravir in Influenza. Lou [116] assessed the antiviral activity of Favipiravir and Baloxavir against COVID-19. Patients were randomized and assigned into three groups: Baloxavir group: dose 80 mg daily orally on Day 1 and Day 4, for patients still positive in virological test, given again on Day 7; Favipiravir group: The first dose 1.600 g or 2.2 g, followed by dose 0.6 g, 3 times daily; Control group: Continue existing antiviral treatment. The results showed that Favipiravir did not have any dramatic efficiency against COVID-19 even at high concentration. Cai et al. [117] conducted an Open-Label Controlled trial to test the efficacy of Favipiravir compared to Lopinavir (LPV)/Ritonavir (RTV) as anti-COVID-19 agents. Patients were randomly allocated to Favipiravir group (dose 1.6 g twice a day for the 1st day; dose 0.6 g twice a day for 2–14 days) and LPV/RTV group (dose 0.4 g/0.1 g twice a day); the results showed that the Favipiravir group patients exhibited higher efficacy than the LPV/RTV group.

5.3 Synthesis of Favipiravir

Takamatsu and Yonezawa [118] disclosed a method for producing Favipiravir and its intermediates in high yields (Scheme 8). Hydroxylation of **I** at room

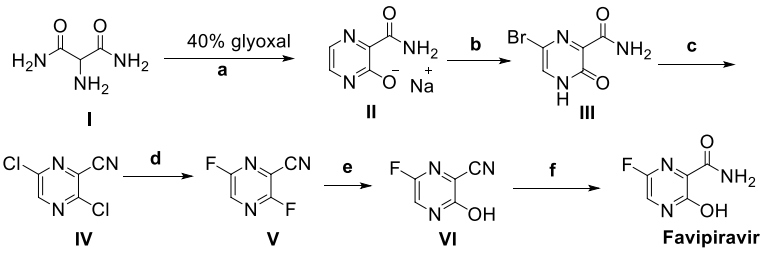


Reaction conditions: a) DMF, H_2O, KOAc, 25-35 °C, 2 h; b) NH_4OH, pH = 9.4, acetone/toluene, dicyclohexylamine, 20-30 °C, 45min, step a and b totally yield 83.2%; c) toluene, H_2O, NaOH, 30% H_2O_2, 20-30 °C, 1 h, yield 89%.

Scheme 8 Synthesis of Favipiravir by Takamatsu and Yonezawa [118]

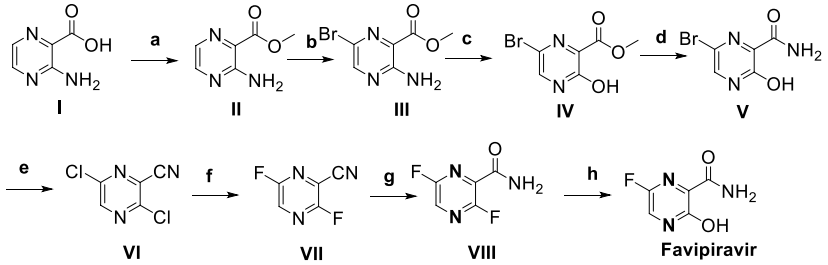
temperature in the presence of KOAc gives **II**. **II** reacted with **III** in the presence of ammonium hydroxide to give **IV** in 83.2% yield. Finally, cyan oxidation of **IV** by hydrogen peroxide in strong base solution gives Favipiravir in total yield of 74%. This procedure obtained Favipiravir via three steps under mild conditions. The process has the advantages of easy post-processing, low toxicity, and high yield for high purity of Favipiravir, and is suitable for large-scale production.

Hara et al. [119] reported a method for producing Favipiravir via six steps (Scheme 9), witha total yield of 53% under mild conditions. Compound **I** reacted with glyoxal in the presence of NaOH solution at lower temperature to obtain **II**, bromination, chlorination and dehydration obtained **IV**, fluoro-substitution in the presence of KF and tetra-n-butylammonium bromide (TBAB) gives **V**, hydrolyzation of 2-fluoro group of **V** in sulfuric acid and 3-cyan group of **VI** in NaOH solution obtained Favipiravir.



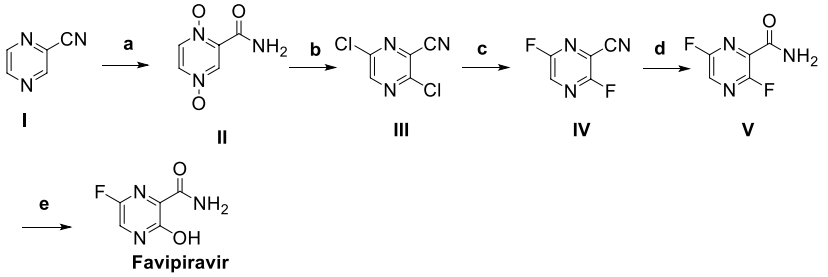
Reaction conditions: a) NaOH, H_2O, -10 to -5 °C, 1 h, then 22 °C, 3 h, yield 92%; b) MeOH/CH_3CN, Br_2, 15-20 °C, 1 h, yield 76%; c) monochlorobenzene, $POCl_3$, DIPEA, 60 °C, 0.5 h, 90-100 °C, 2.5 h, yield 83%; d) KF, TBAB, toluene/DMSO, 60 °C, 2.5 h, yield 92%; e) conc. H_2SO_4, 50 °C, 4 h; f) 28% NaOH, 10 °C, 0.5 h; e and f totally yield 92%.

Scheme 9 Preparation of Favipiravir by Hara et al. [119]



Reaction conditions: a) H_2SO_4, MeOH, 20-35 °C, 36 h, yield 76%; b) CH_3CN, NBS, 20-35 °C, yield 89%; c) H_2SO_4, $NaNO_2$, 0 °C 2 h, yield 90%; d) NH_4OH, rt, 3 h, yield 94%; e) $POCl_3$, DIPEA, 100 °C, 4 h, yield 70%; f) KF, TBAB, Toluene/DMSO, 55 °C 3 h; g) 30% H_2O_2, 27 °C 2 h; h) H_2O, $NaHCO_3$, 50 °C 8.5 h, f, g and h total yield 65%.

Scheme 10 Preparation of Favipiravir by Liu et al. [120]



Reaction conditions: a) HOAc, 30% H_2O_2, 95 °C 22 h, yield 58%; b) $POCl_3$, Et_3N, 50-96 °C, yield 45%; c) KF, TBAB, DMSO, 55 °C 3 h, yield 52.8%; d) 30% H_2O_2, 27 °C, 2 h; e) H_2O, $NaHCO_3$, 50 °C, 8.5 h, d, e total yield 65%.

Scheme 11 Preparation of Favipiravir by Li et al. [121]

Liu et al. [120] reported a method for preparation of Favipiravir (Scheme 10) via 8 steps with a total yield of 24%. Esterification of **I** gave **II**, bromination by NBS obtained **III**, diazotization of **III** and hydrolyzation in the presence of ammonium hydroxide gave **IV**, ester group amidation obtained **V**, chlorination and dehydration obtained **VI**, fluoro-substitution chloro group of **V** in the presence of KF and TBAB got **VII**, hydrolyzation 3-cyan group of **VII** in the presence of hydrogen peroxide and 2-fluro group of **VIII** in weak base solution obtained Favipiravir. This procedure needs long steps and the diazotization reaction in step (c) has potential safety issues.

Li et al. [121] reported a method for preparation of Favipiravir (Scheme 11) via 4 steps with a total yield of less than 10%. Oxidation of **I** using hydrogen peroxide in the presence of HOAc gives **II**. Chlorination and dehydration of **II** obtained **III**, and then fluoro-substitution in presence of KF and TBAB gives

Fig. 20 Structure of Remdesivir

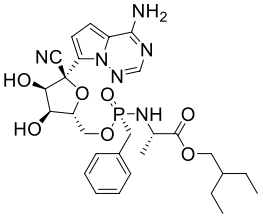
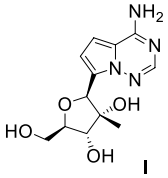


Fig. 21 Structure and activity of (1) EC_{50} = 1.98 μM; CC50 = 85 μM (Huh-7); C50 = 0.31 μM



IV. Hydrolyzation of 3-cyan group of **IV** in the presence of hydrogen peroxide gave **V**, followed by hydrolyzation of 2-fluoro group of **V** in weak base sulotion, obtained Favipiravir.

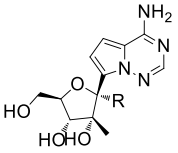
6 Remdesivir

Remdesivir (Fig. 20) also named GS-5734, is a broad-spectrum antiviral RdRp inhibitor against MERS, Ebola, SARS and the like. Research showed an EC_{50} value of 0.77 μM in Vero E6 cells inhibiting COVID-19 [122]. Holshue [123] reported the first case of a US COVID-19 patient. After the COVID-19 spread worldwide in March, phase III clinical trials were launched in the US and other countries extensively. On 2 May, the FDA issued Remdesivir emergency use for COVID-19 treatment.

6.1 History of Remdesivir

The HCV genome encodes two proteins, NS2 and NS5, that are important targets for drug design [124, 125]. The discovery of small molecules inhibiting virus replication has attracted more attention [25]. Abundant direct-acting antiviral (DAA) small molecules have been designed and tested in clinical trials over the last few decades. A number of DAAs have been proven to have anti-HCV activity. Nucleoside inhibitors (NIs) are the most outstanding due to their prominent therapeutic effect [126]. Most NIs used clinically are *N*-nucleosides, which have a 2′-C-Me in the sugar branch. The first 2′-C-Me branched *N*-nucleosides prepared in 1960s were used to treat HCV infection; their in vitro activity against HCV was test in the 2000s [127]. *N*-Nucleosides firstly metabolize into nucleoside triphosphates in cells, then link with the NS5B polymerase and insert into the viral RNA, inhibiting viral RNA extension and virus replication [128].

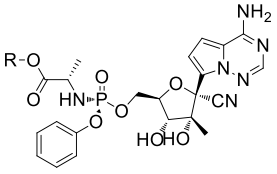
Table 8 *1′*-substituted analogs of (**1**) in the NS5B enzyme assay



Compound	R	EC_{50} (1b, μM)	IC_{50} (1b, μM)	mtRNA SNI (%)
1	H	1.98	0.31	21
2	Cyano	> 98	0.29	0.03
3	Methyl	> 98	55	0.08
4	Ethynyl	> 98	> 200	ND

SNI Single nucleotide incorporation, *ND* not determined

Table 9 HCV replicon activity of phosphoramidate prodrugs



Compound	R	EC_{50} (1b, μM)	CC50 (Huh-7, μM)
5	iso-Pr	1.45	> 89
6	Me	1.37	> 89
7	Et	1.05	> 89
8	(S)-sec-Bu	0.23	> 89
9	(R)-sec-Bu	0.98	> 89
10	t-Bu	> 89	> 89
11	cyc-pentyl	0.45	> 89
12	neo-pentyl	0.18	85
13	2-EtBu	0.44	35
14	Bn	0.33	63

In 2012, Cho et al. [129] synthesized a few 2′-C-Me C-nucleosides targeting NS5B, and screened compound (**1**) as a HCV inhibitor (Fig. 21).

On the basis of compound (**1**), abundant analogues of compound (**1**) were synthesized to improve selectivity (Table 8) [130].

Among these analogues of compound (**1**), it was found that compound (**2**) has perfect activity in the NS5B enzyme assay. Then compound (**2**) should be used as a lead nucleoside for further optimization (Table 9).

In 2013, Cho et al. [131] prepared the first HCV inhibitor C-nucleoside **GS-6620** (Fig. 22) with high efficiency in phase I clinical trials.

In 2017, based on GS-6620, Siegel et al. [132] discovered and synthesized Remdesivir, and found it had good activity against Ebola virus.

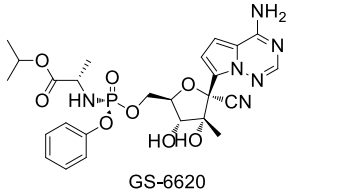


Fig. 22 Structure and activity of GS-6620

6.2 Biological Activity of Remdesivir

Remdesivir is RdRp inhibitor, suppressing virus genome replication [51]. RdRp controls the replication of virus RNA. Once Remdesivir metabolizes into the corresponding NTP, the latter competes with ATP for incorporation into the nascent RNA strand [133], leading to termination of virus RNA synthesis and prevention of the growth of RNA. Even though the virus can probe and delete C-nucleosides, resulting in tolerance, Remdesivir appears to be able to overcome this problem and maintain efficiency [134]. Yin et al. [135] reported the complex structure of Remdesivir and SARS-CoV-2 RdRp, where Remdesivir was covalently inserted into RdRp. This complex structure supplies a mechanism whereby Remdesivir inhibits SARS-CoV-2 replication, providing a platform for development of new drugs against COVID-19 (Fig. 23).

Remdesivir has EC_{50} values about 0.07 μM for either SARS-CoV or MERS-CoV [136, 137]. Emmiede et al. [138] tested the efficiency of Remdesivir against MERS-CoV virus. The result showed that Remdesivir can clearly inhibit virus replication. Wang et al. [33] first examined the effect of Remdesivir against COVID-19 in Vero E6 cells and found an EC_{50} value 0.77 μM for Remdesivir inhibiting COVID-19. Elfiky et al. [139] targeted a few anti-polymerase drugs targeting RdRp, and found Remdesivir, Sofosbuvir, Galidesivir and Tenofovir as potent drugs against COVID-19. Choy et al. [140] reported the efficiency of Remdesivir and three other drugs against COVID-19 in Vero E6 cells, with EC_{50} values of 23.15 μM (Remdesivir), 26.63 μM (Lopinavir), 2.55 μM (Homorringtonine) and 0.46 μM (Emetine), respectively. Zhang et al. [141] found that the 1′-cyano group of Remdesivir has dual roles in inhibition of nucleotide addition and proofreading. Pruijssers et al. [142] reported that Remdesivir potently inhibits SARS-CoV-2 replication in human lung cells and primary human airway epithelial cultures ($EC_{50}=0.01$ μM), in Vero E6 cells ($EC_{50}=1.65$ μM), respectively. Wu et al. [143] found that Remdesivir and GS-441524 can inhibit cell proliferation and the expression of fibrotic markers (fibronectin, pSmad3, and aSMA) in NRK-49F and HK2 cells. Brandi et al. [144] used rhesus macaque model of COVID-19, and showed that Remdesivir can be used in transient lower respiratory tract disease.

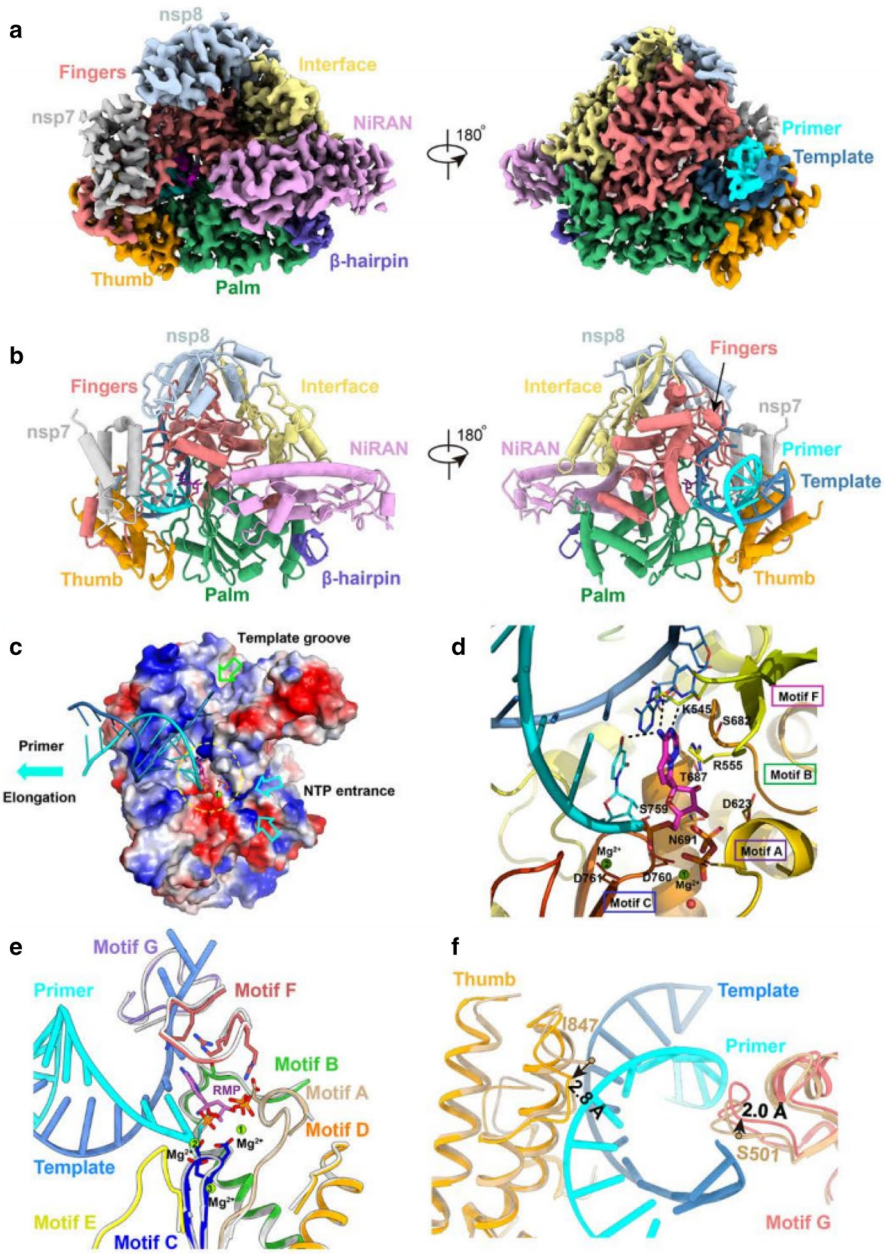


Fig. 23 The complex structure of Remdesivir and SARS-CoV-2 RNA bound to RdRp complex. Image reproduced from Ref. [135] with permission from Wiley-VCH

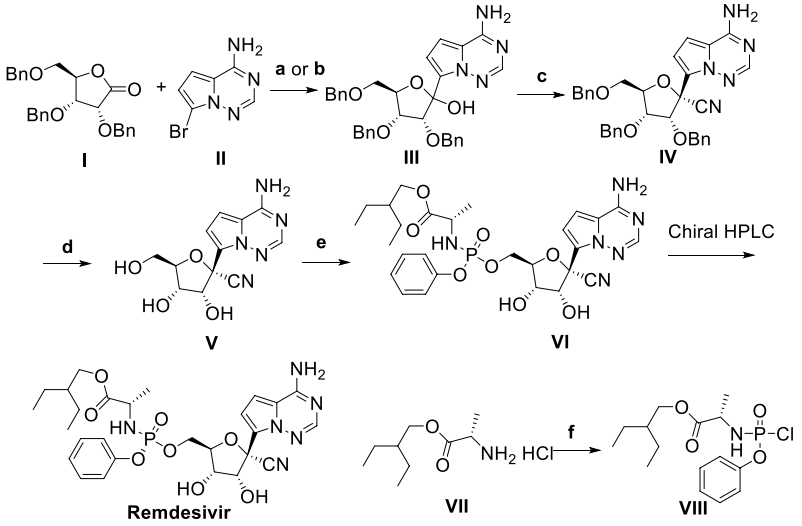
6.3 Clinical Trials of Remdesivir

The first case of a COVID-19 patient inthe US appeared in January 2020 [90]; his condition improved after 8 days' Remdesivir treatment, and no obvious adverse effect was observed during the treatment. Stephanie et al. [145] then described 12 US COVID-19 mild-to-moderate patients treated with Remdesivir, and all patients recovered at the end of this clinical trial. A randomized, controlled clinical trial was conducted [146] to investigate the safety and efficiency of Remdesivir against COVID-19 at the University of Nebraska Medical Center (UNMC). The clinical trial results showed no evidence that Remdesivir can improve clinical outcomes. A few phaseIII clinical trials have been conducted to evaluate the efficiency and safety of Remdesivir against mild and moderate COVID-19 patients [147–150]; the results do not support the efficacy and safety of Remdesivir. Grein et al. [151] reported 61 COVID-19 patients receiving compassionate use Remdesivir: 8 patients were not analyzed for various reasons, 22 patients were from the US, 22 patients from the EU or Canadian, 9 patients were Japanese. The results showed that 68% patients got well, 57% patients received mechanical ventilation, 47% patients were in recovery, and 13% patients died. Even though there were two absolutely contrary results in US and Chinese phase III clinical trials, on 2 May, the FDA authorized Remdesivir for compassionate use against COVID-19 for various reasons. Beige et al. [152] undertook a phase III trial using Remdesivir (dose 0.2 g daily in the first day, dose 0.1 g 2–10 days) in adult patients with COVID-19. A total of 1063 patients underwent randomization. The results, based on findings from analysis, showed that Remdesivir can shorten time to recovery. Goldman et al. [153] proceeded with a phase III clinical trial with Remdesivir (dose 0.2 g daily first day, 0.1 g the remaining days) against COVID-19 in 397 patients. Patients were allocated to two groups (10 days treatment and 5 days treatment). At baseline, prolonging treatment time did not improve clinical status.

6.4 Synthesis of Remdesivir

The first generation [154] for the synthesis of Remdesivir was as follows (Scheme 12). Coupling **I** and **II** in the presence of *n*-BuLi, and chlorotrimethylsilane (TMSCl) or 1,2-bis(chlorodimethylsilyl)ethane, NaH, and *n*-BuLi at ultralow temperature gave **III**, cyanation of **III** by TMSCN in the presence of Lewis acid BF_3-Et_2O at ultralow temperature obtained **IV**, benzyl deprotection using BCl_3 gave **V**, **V** was reacted with **VIII** in the presence of NMI and $OP(OMe)_3$ to give **VI**, with Remdesivir finally achieved by chiral HPLC. In the first generation for synthesizing of Remdesivir, Remdesivir was obtained in total yield of less than 2%. The first four steps were conducted at −78 ℃ and the β-anomer **VII** was separated by chromatography [155], which hindered this synthetic route from large-scale development.

Second generation [138] Remdesivir was synthesized diastereoselectively via 7 steps in total 4% yield which is still unacceptable but suitable for large-scale production (Scheme 13). Compound **I** reacted with **II** in the presence of TMSCl



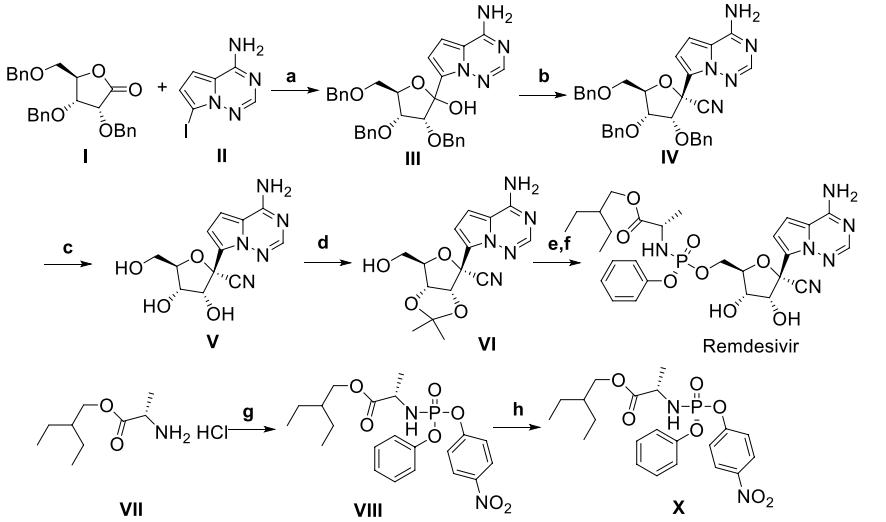
Reagents and conditions: a) *n*-BuLi, TMSCl, THF, -78 °C, yield 25%; b) *1,2*-bis(chlorodimethylsilyl) ethane, NaH, *n*-BuLi, THF, -78 °C, yield 60%; c)TMSCN, BF_3-Et_2O, CH_2Cl_2, -78 ºC, 58%; d) BCl_3, CH_2Cl_2, -78 ºC, yield 74%; e) VIII, NMI, $OP(OMe)_3$, yield 21%; f) $OP(OPh)Cl_2$, Et_3N, CH_2Cl_2, 0 ºC, yield 23%.

Scheme 12 First generation synthesis of Rendesivir

and Grignard reagent at low temperature yielded **III**, then cyanation of **III** using TMSCN and TMSOTf in the presence of TfOH at ultralow temperature obtained **IV**, benzyl deprotection using BCl_3 gave **V**, using 2,2-dimethoxypropane selectively protected two hydroxy of **V** to obtain **VI**, and then **VI** and **X** were reacted in the presence of DIPEA followed by deprotection to give Remdesivir.

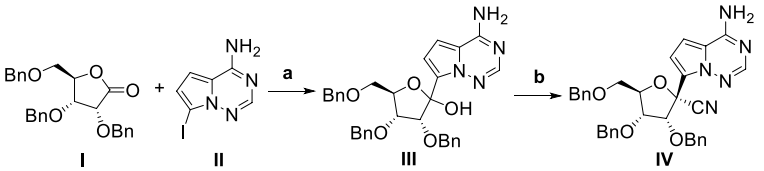
Vieira et al. [156] described a route to synthesize a key Remdesivir intermediate (**IV**) by using a continuous flow chemistry method, providing improved control over the reaction conditions and increasing the diastereoselectivity (Scheme 14). Coupling of **I** and **II** in the presence of TMSCl and Grignard reagent catalyzed by $NdCl_3$ at low temperature obtained **III** in yields of 69%, and cyanation of **III** using TMSCN in the presence of TMSOTf and TfOH at lower temperatures obtained intermediate **IV** in yields of 78%. This synthetic route obtained the key intermediate **IV** in total yield 54% in two steps. But this process requires continuous flow conditions which is unacceptable in industrial production.

Xue et al. [157] disclosed an improved methodology for the key C-glycosylation step for synthssis of Remdesivir using *i*-Pr_2NH as a cost-effective additive in yield 75% (Scheme 15). The reaction was conducted in the presence of *i*-Pr_2NH, and *n*-BuLi at ultralow temperature within 2 h using **III** as a protecting amino group of **I**. This procedure is unacceptable in large-scale production due to the ultralow temperature conditions.



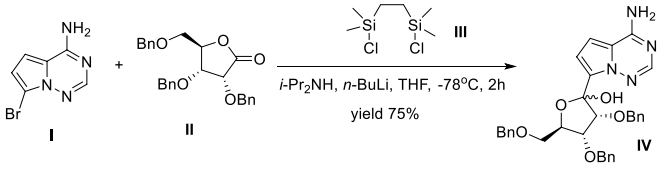
Reagents and conditions: a) TMSCl, PhMgCl, *i*-PrMgCl-LiCl, THF, -20 °C, yield 40%; b) TMSCN, TfOH, TMSOTf, CH_2Cl_2, -78 °C, yield 85%; c) BCl_3, CH_2Cl_2, -20 °C, yield 86%; d) *2,2*-dimethoxypropane, H_2SO_4, acetone, rt, yeld 90%; e) X, $MgCl_2$, $(i\text{-Pr})_2NEt$, MeCN, 50 °C, yield 70%; f) conc HCl, THF, rt, yield 69%. g) $OP(OPh)Cl_2$, Et_3N, CH_2Cl_2, -78 °C, then *4*-nitrophenol, Et_3N, 0 °C, yield 80%; h) *i*-Pr_2O, yield 39%.

Scheme 13 Second generation synthesis of Remdesivir

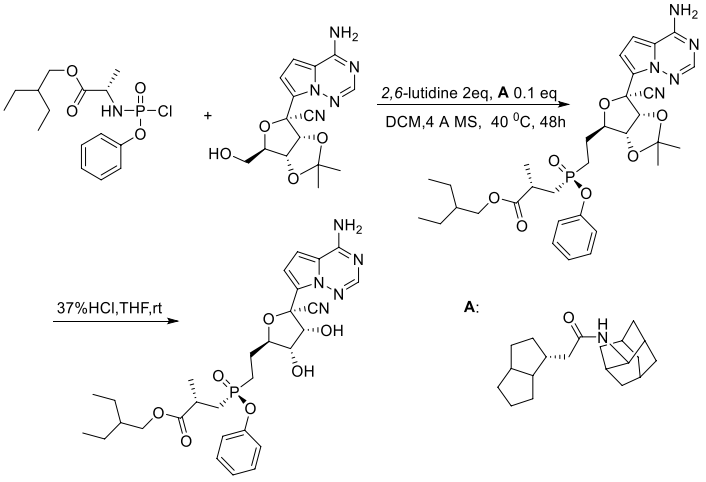


Reaction conditions: a-i) TMSCl, PhMgCl, *i*-PrMgCl, THF, -20 °C, a-ii) $NdCl_3$, *n*-Bu_4NCl, THF, -20 °C, i and ii total yield 69%; b) TfOH, TMSOTf, TMSCN, DCM, -40 °C, yield 78%.

Scheme 14 Large-scale cyanation process using continuous flow chemistry synthesis of Remdesivir key intermediate



Scheme 15 Improved methodology for the synthesis of Remdesivir key intermediate by Xue et al. [157]



Scheme 16 Catalytic asymmetric synthesis of a key step of Remdisivir by Wang et al. [158]

Wang et al. [158] reported a gram-scale catalytic asymmetric synthesis of a key step of Remdisivir in high chiral purity and yield (Scheme 16). Compound **I** was reacted with **II** in the presence of 2,6-lutidine, and 4 Å MS catalyzed by chiral catalyst **A** at lower temperature gave **III** in 89% yield with chiral purity higher than 99%. **III** was then deprotected by 37% HCl to obtain Remdesivir at a yield of 73%. In this procedure, Remdesivir was synthesized asymmetrically in short steps in high yield under mild conditions at gram-scale, and is thus suitable for large-scale production.

7 Ruxolitinib

7.1 Biological Activities of Ruxolitinib

Ruxolitinib is an FDA-approved targeting JAK1 and JAK2 inhibitor. It prevents the tyrosine phosphorylation of STAT1/3/5, which are downstream of cytokine receptors and drive T-ALL proliferation. Walker et al. [159] proved that Ruxolitinib and venetoclax worked synergistically to treat T-ALL in vitro, but were not effective in vivo. CXCR4-CXCL12 was implicated as the potential pathway that drives T-ALL infiltration into the central nervous system (CNS). By deleting the CXCR4 gene from T-ALL, they found prolonged survival in vivo with decreased neurologic clinical scores. Thus, T-ALL CNS infiltration should be blocked via CXCR4 inhibition. Ruxolitinib may be able to inhibit CXCR4 [160] (Fig. 24).

The 7H-pyrrolo[2,3]pyrimidine core of Ruxolitinib links to the hinge area of Cxc Chemokin Receptor 4 (CXCR4) by hydrogen bond, the nitrile function of Ruxolitinib binds to Ser936 by hydrogen bond, the pyrazole ring linking the side chain with the hinge binding adenine mimic acts as a structural template. Since it is not involved in direct interactions with the enzyme, bioisosteric replacement with a triazole ring is a promising strategy to increase synthetic accessibility.

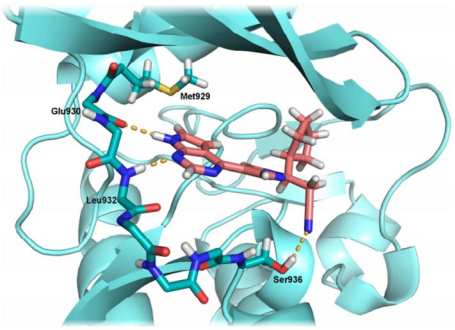


Fig. 24 Ruxolitinib (1) docked into JAK2. Image reproduced from Ref. [160] with permission from Elsevier

In in vitro experiments, Ruxolitinib was diluted into 50 μM in DMSO. In in vivo studies, Ruxolitinib dissolved in DMSO was added to 5% DMA in H_2O. To survey the relevance of the JAK/STAT and BCL2 pathways on T-ALL proliferation and cell survival, Jurkat (mature T-ALL) and Loucy (early precursor T-ALL with high BCL2 expression) were assessed following treatment with Ruxolitinib. These cell lines were treated with different doses of Ruxolitinib over 72 h and assessed using a trypan blue exclusion assay and MTT (3-(4, 5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide) proliferation assay. Ruxolitinib decreased the survival and proliferation of both Jurkat and Loucy cell lines after 24, 48, and 72 h of treatment in 2.5 μM. Ruxolitinib failed to treat T-ALL in vivo because of leukemia CNS infiltration. In 2011, the FDA and European Food and Drug Administration (EFDA) approved Ruxolitinib first in class in treatment of myelofibrosis [161]. Tuttle et al. [162] used two mouse models to prove that interferon receptor genes are overexpressed in mice, and that JAK1 inhibitors can clearly restrain cytokine storm. Increased evidence proves that mortality with COVID-19 infections is caused mainly by the overexpression of a immune response to SARS-CoV-2, resulting in a cytokine storm and ARDS [163]. Many cytokines and chemokines involved in the cytokine storm employ JAKs for signal transduction. Cytokine analysis of COVID-19 patients shows that C-reactive protein (CRP) and interleukin (IL)-6 levels are significantly higher in patients who eventually died compared to those who survived [50]. Similar to some other mortal lung infections, the overexpression of immune response to the COVID-19 virus causes a cytokine storm, along with infiltration and activation of diverse immune cells, then generation secondary cell factors and chemotactic factors [164]. In this study, patients admitted to intensive care units (ICUs) showed significantly higher levels of IL-2, IL-10, IL-7, IP-10, MCP-1, MIP-1α, G-CSF, and TNF-α relative to non-ICU patients. All in all, these discoveries support the combination of antiviral treatment and targeted immunosuppression as a therapeutic program in COVID-19 [165].

7.2 Clinical Trials of Ruxolitinib

Several clinical trials have evaluated the safety and efficacy of Ruxolitinib of IL-6 and JAK/STAT signaling. Jung et al. [50] conducted a phase II clinical trial to

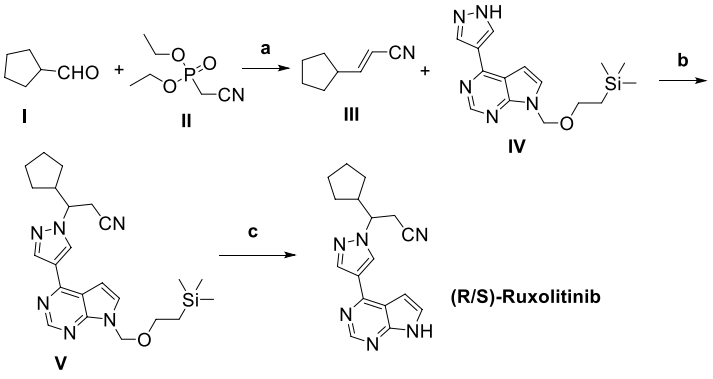
evaluate Ruxolitinib treatment of myelofibrosis. Their results proved the efficiency of Ruxolitinib to treat myelofibrosis. Studies on Ruxolitinib treatment of sHLH patients showed encouraging results on overall survival [166]. Cao et al. [167] carried out a phaseII clinical trial to treat severe COVID-19 patients using Ruxolitinib. A total of 20 patients were distributed to the Ruxolitinib and standard of care (SoC) group, 21 patients were distributed to placebo group (SoC treatment) randomly. The results showed that the patients in Ruxolitinib and SoC group recovered faster than the placebo group. Most importantly, there were no deaths in the Ruxolitinib and SoC group.

7.3 Synthesis of Ruxolitinib

Rodgers et al. [168] synthesized racemic Ruxolitinib via three steps with a total yield of 48% (Scheme 17). Condensation of **I** with malonic acid in strong organic base condition obtained **III**, then **III** reacted with **IV** in the presence of 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) gave **V**; finally, **V** was deprotected by TFA to racemate Ruxolitinib with a total yield of 48%.

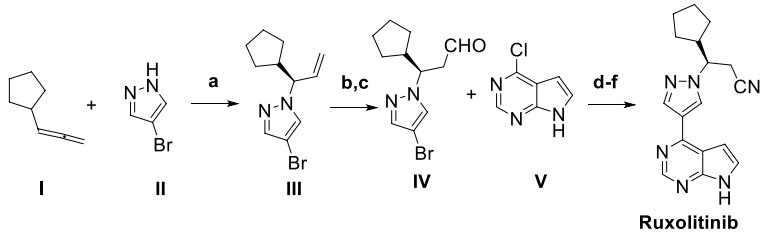
Haydl et al. [169] reported Rhodium-catalyzed asymmetric coupling of (**I**) with pyrazole derivatives (**II**) giving enantioenriched allylic pyrazoles, which can be used to synthesize the targeted drug Ruxolitinib (Scheme 18). They developed a Rhodium-catalyzed, enantioselective synthesis of (*R*)-Ruxolitinib in the presence of chiral ligand using cheap material **I**, **II** and **V** in high chiral purity and yield. Above all, there were only three reaction steps.

Deepshikha et al. [170] provided a method for preparation of Ruxolitinib and its phosphate giving a chiral purity of 99.96% but with a total yield as low as 5%, which is unacceptable (Scheme 19). In this synthetic route, **I** was protected by 2-(trimethylsilyl)ethoxymethyl chloride, then direct Suzuki coupling with **III** gave compound **IV** with a yield of 80.8% in two steps. **IV** reacted with **V** in base condition,



Reagents and conditions: a) THF, *t*-BuOK, 0 °C, 64 h, yield 89%; b) CH_3CN, DBU, rt, overnight, yield 93%; c) DCM, TFA, rt, 6 h, yield 58%.

Scheme 17 Preparation of racemic Ruxolitinib by Rodgers et al. [168]



Reagents and conditions: a) Cyclohexylallene, *4*-bromopyrazole, PPTS (20 mol%), [{Rh(cod)Cl}$_2$] (2.0 mol %), L_2 (5.0 mol%), toluene, 80 ºC, 24 h, yield 95%, 90% ee; b) *9*-BBN, THF, rt; then H_2O_2, NaOH, rt, yield 99%; c) $(COCl)_2$, DMSO, NEt_3, -78 ºC then rt, yield 97%; d) NH_4OH, THF, rt, yield 90%; e) B_2pin_2, [Pd(dppf)Cl_2](5.0mol%), KOAc, DMSO, 90 ºC; f. [$PdCl_2(PPh_3)_2$] (5.0 mol%), K_2CO_3, *1,4*-dioxane/H_2O (2:1), 120 ºC, step e and f total yield: 81%.

Scheme 18 Gram-scale synthesis of (R)-Ruxolitinib by Haydl et al. [169]

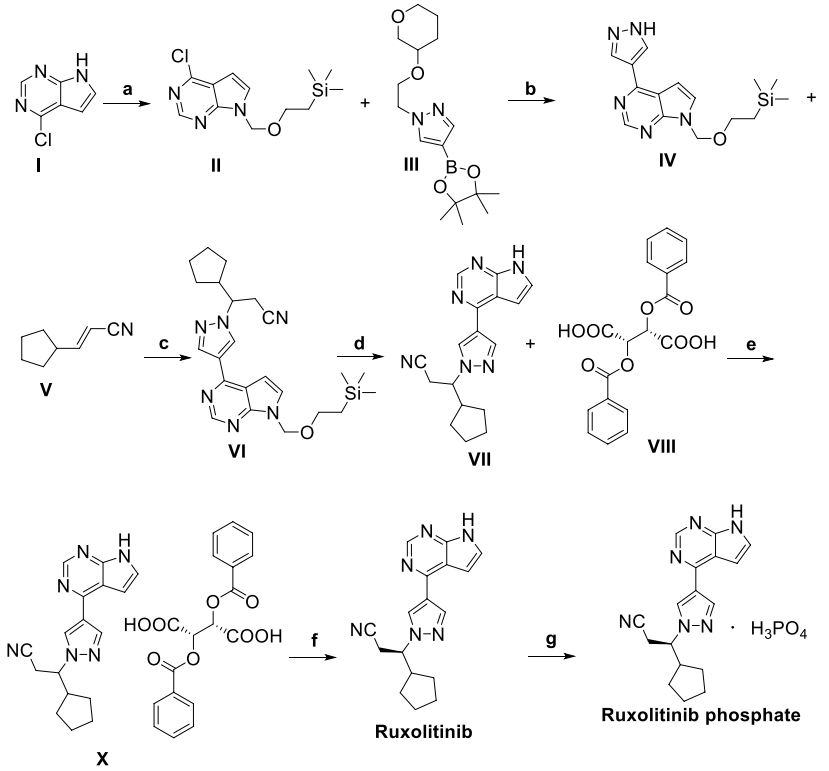
deprotection with Lewis acid BF_3-Et_2O and treated with (+)-2,3-dibenzoyl-D-tartaric acid to obtain **X** with a yield as low as 7% in three steps. Finally, compound **IV** was chirally resolved and treated with phosphoric acid to give Ruxolitinib phosphate with yield 88% in two steps.

Zhang et al. [171] reported two methods for preparation of Ruxolitinib, which have characteristics such as high stereoselectivity, mild reaction conditions and convenient post treatment, avoiding use expensive asymmetric catalysts and suitable for industrial production (Schemes 20, 21). As shown in Scheme 20, condensation of **I** with malonic acid in weak organic base condition gave **II**, which directed ring-closure with hydrazine hydrate in quantitative yield to **III**. Chiral resolution of **III** by using D-tartaric acid then gave **V**. Methylation of **VI** using methylmagnesium bromide gave **VII**, then **VIII** was obtained via Vilsmeier–Haack reaction. **VIII** and **IV** or **V** refluxed in base or acid conditions obtained **X**, then acyl chlorination using oxalyl chloride and amidation obtained **XII**. Finally, dehydration of **XII** obtained Ruxolitinib.

As shown in Scheme 21, compound **I** was protected by 2-(trimethylsilyl)ethoxymethyl chloride to **II**. Methylation of **II** using methylmagnesium bromide gave **III**, then **IV** was obtained via Vilsmeier–Haack reaction. **V** and **IV** or **V** were refluxed in ethanol to obtain **VI**, and then amidation and dehydration gave **VII**. Finally, deprotection of **VII** obtained Ruxolitinib.

8 Conclusions

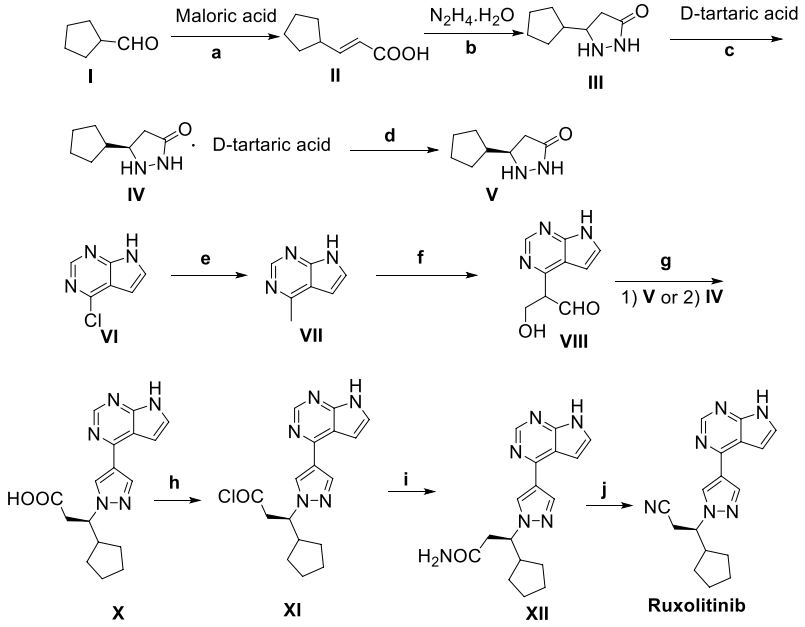
After the spread of COVID-19 worldwide, tens of thousands medical scientists and pharmacologists have made great efforts to search for potent drugs that can inhibit COVID-19, and they successfully found a few drugs like CLQ, CLQ-OH, Favipiravir and Remdesivir that are useful in the treatment of COVID-19 patients. But, in clinical trials to date, CLQ and CLQ-OH may increase mortality due to their



Reaction conditions: a) DMF, NaH, *2*-(trimethylsilyl)ethoxymethyl chloride, -10-0 °C, 2 h; b) DNS, K_2CO_3, H_2O, $Pd(PPh_3)_4$, N_2, 80 °C, 15 h, a and b totally yield 80.8%; c) DMSO, K_2CO_3, 45 °C, 24 h; d) $BF_3.Et_2O$, CH_3CN, 20-25 °C, 5 h; e) CH_3CN, 25 °C 2 h, 70 °C 0.5 h, yield 7%; f) NaOH, H_2O, rt, 15 mins; g) *i*-PrOH, phosphoric acid, 65 °C, 1 h, f and g total yield: 88%

Scheme 19 Preparation of Ruxolitinib and its phosphate by Deepshikha et al. [170]

high doses (CLQ 500 mg dose, twice daily; CLQ-OH 400–600 mg dose). Favipiravir has high efficiency in treating Chinese patients, but it also needed a high dose (600 mg dose, 2–3 times daily); especially, there is a lack of clinical data to prove its efficacy and safety outside of China. Gilead Sciences conducted clinical trials with Remdesivir after the spread of COVID-19 worldwide, and the FDA authorized Remdesivir for compassionate use in treating COVID-19 patients in May 2020. To date, COVID-19 patients who die with cytokine storm syndrome have higher levels of IL-6 in plasma; four JAK inhibitors, Ruxolitinib, Tofacitinib, Baricitinib and Upadacitinib, have proved useful in the treatment of COVID-19 patients. Most importantly, there were no deaths using Ruxolitinib to treat COVID-19 patients in a phase II clinical trial.

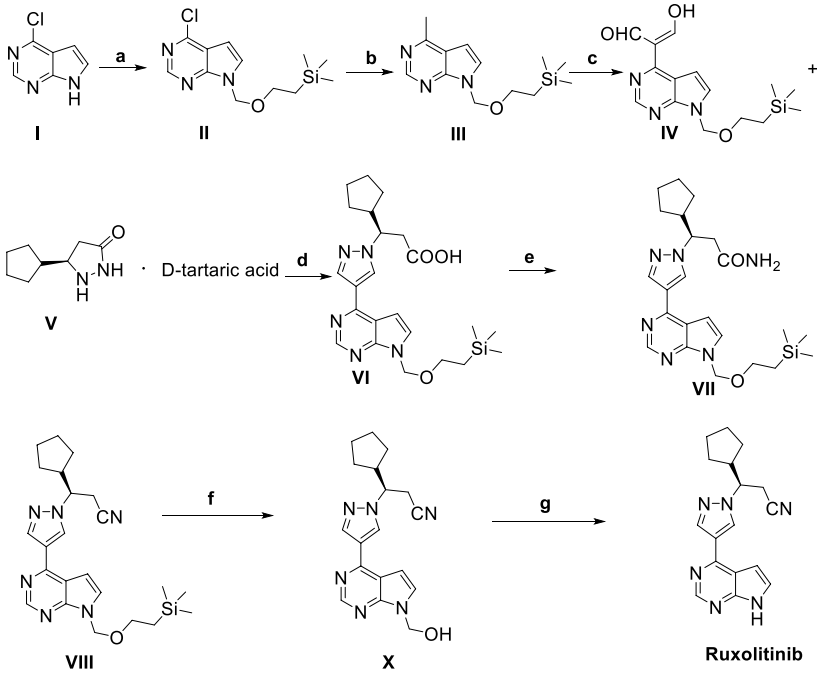


Reaction conditions: a) pyridine, piperidine, 80 °C, 5 h, yield 96.6%; b) 70-75 °C, 0.5 h, yield 77%; c) acetone, rt, 0.5 h, yield 99.4%; d) 3M NaOH, 0-5 °C, yield 76.2%; e) $Pd(bppf)_2Cl_2$, THF, 3 M methylmagnesium bromide, 60-65 °C, 2 h, yield 84.2%; f) DMF/Dioxane, $POCl_3$, 80 °C, 3 h, yield 60.2%; g-1)H_2O, NaOH, reflux 8 h, yield 73%; g-2) HOAc, H_2O, reflux 8 h, yield 60%; h) DCM, NMP, oxalyl chloride, 20-30 °C, 3 h; i) aqueous ammonia, rt, h and i total yield 62%; j) DCM, NMP, phosphorus oxychloride, lower than 30 °C, 3 h, yield 77.3%.

Scheme 20 Preparation of Ruxolitinib by Zhang et al. [171] synthetic route one

As far as we know, there is no specific medicine for treatment of COVID-19 patients, but COVID-19 is still spreading rapidly worldwide. Combinations of antivirial drugs such as Remdesivir or GS-441524 and JAK inhibitor drugs may be a useful therapentic schedule to reduce mortality before a specific medicine appears.

In this review, we introduced lots of small molecules that exhibit potent activity in inhibiting COVID-19, especially CLQ, CLQ-OH, Favipiravir, Remdesivir and Ruxolitinib, presenting their biological activities, clinical trials and synthesis processes, which may help researchers to systematically understand the processes of these potential drugs.



Reaction conditions: a) DMF, NaH, *2*-(trimethylsilyl)ethoxymethyl chloride -10 to -20 °C, 2 h, yield 97.2%; b) $Pd(bppf)_2Cl_2$, THF, 3M methylmagnesium bromide, 60-65 °C, 2 h; c) DMF, $POCl_3$, 80 °C, 3 h, b and c total yield 41.9%; d) EtOH, reflux 9 h, yield 79.6%; e) DMF, DCM, oxalyl chloride, 20-30 °C, 3 h, then aqueous ammonia, rt, yield 97.5%; f) DCM, NMP, phosphorus oxychloride, lower than 30 °C, 3 h, yield 77.3%; g) $POCl_3$, rt, 24 h, yield 93.8%.

Scheme 21 Preparation of Ruxolitinib by Zhang et al. [171] synthetic route 2

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