Fluorine in Medicinal Chemistry: In Perspective to COVID-19

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ABSTRACT

Over two years into the outbreak of COVID-19, the quest for effective and economical drugs has become starkly clear to reduce the risk of progression of coronavirus disease. A number of drugs have been investigated and they can be taken orally at home and be used after exposure to SARS-CoV-2 or at the first sign of COVID-19. Fluorinated oral anti-COVID-19 drugs—including Paxlovid, the first oral tablet for the treatment of COVID-19—is an important subgroup. Fluorine has been widely used in pharmaceuticals market and can lead to improved selectivity indices, increased lipophilicity, greater metabolic stability, and in this case the improved anti-COVID-19 efficacy. In this mini-review, we will give an update on fluorinated anti-COVID-19 drugs by providing the key information and current knowledge of these drugs, including chemical structure, drug metabolism and pharmacokinetics, and mechanism of action.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, Figure 1).[1] The disease has spread worldwide, and the threat to global health is ongoing since the first known case was identified in December 2019. As of February 23 2022, SARS-CoV-2 has caused a combined total of more than 428,196,000 confirmed infections and more than 5,925,000 reported deaths in 213 different countries.[2]

Starting in late 2020, numerous types of COVID-19 vaccines have been developed to protect people before they are exposed to SARS-CoV-2, providing an opportunity to restrict the transmission of the virus, and reduce the number of hospitalizations and deaths. The US Food and Drugs Administration (FDA) has approved the Pfizer-BioNTech, Moderna, and Janssen COVID-19 vaccines for emergency use in the USA, while the European Medicines Agency (EMA) also authorized the vaccine developed by AstraZeneca.[3] By early 2022, 10.6 billion doses of COVID-19 vaccine have been administered around the world, mostly in high-income countries. Only 12% of people in low-income countries have received at least one dose.[4] Therefore, the quest for effective and economical antiviral drugs to treat COVID-19 has been a priority since the outbreak of the disease.[5]

Several direct-acting small-molecule SARS-CoV-2 antiviral drugs have been developed to treat COVID-19. These drugs have received approval or under emergency use authorization, and can be used after exposure to SARS-CoV-2 or at the first sign of COVID-19. They can be divided into two groups: 1) agents that target proteins or RNA of the virus (e.g. viral RNA-dependent RNA polymerase (RdRp), viral main protease (M^{pro} or $3CL^{pro}$), and etc.); 2) drugs that target host proteins (e.g. angiotensin converting enzyme-2 (ACE-2), transmembrane protease serine 2 (TMPRSS2), and etc.).[3] An important sub-group belonging to these antivirals is the fluorine-containing drugs, including Paxlovid—the first oral tablet for the treatment of COVID-19. Until March 2022, there are already over 15 different types of fluorinated anti-COVID-19 drugs have been reported, counting for > 20% of the total drugs in the market for the treatment of COVID-19. An important consideration

of inclusion of fluorine is to increase the drug's selectivity, enable it to dissolve in fats, and decrease the speed at which the drug is metabolized, thus allowing it more time to work.

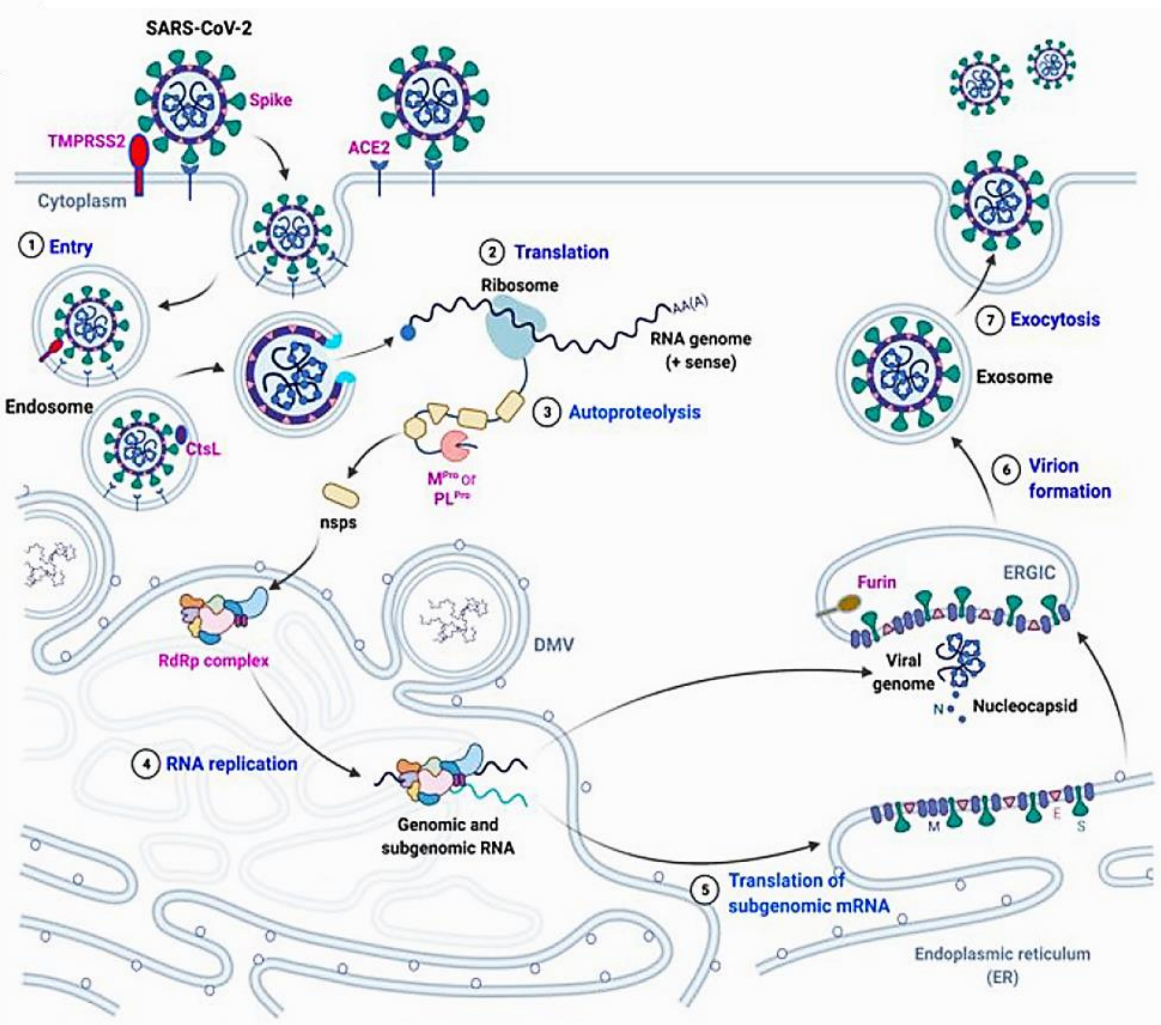

Figure 1. Cartoon diagram illustrating the life cycle of SARS-CoV-2. Seven sequential steps are labeled in blue. Proteins that are labeled in pink are targets for the development of antivirals. TMPRSS2, CtsL, and furin are three host proteases that prime Spike for viral entry and new virion packaging. Reproduced with permission from ref 5. Copyright 2022 American Chemical Society.

An increasing number of studies by our and other groups have shown that the inclusion of fluorinated segments in therapeutic agents has great potential to advance the performance of drugs.[6-18] This review will provide an update on the progress of fluorine-containing drugs that has been recently made in clinical trials to combat COVID-19. A detailed discussion regarding the role of fluorine in advancing the performance of antiviral drugs against SARS-CoV-2 will be included.

Finally, an outlook for the future discovery of new fluorinated drugs to treat COVID-19 will be provided.

2. Fluorinated anti-COVID-19 drugs

Fluorine is absent in most biological systems, however, it has been widely used to tailor the biological behavior of drugs for the enhancement of therapeutic efficacy.[12,17,19] Fluorine substitution productively influences the conformation, membrane permeability, metabolic pathways, and pharmacokinetic properties of certain drugs.[20-22] It is notable that a number of blockbuster drugs contain fluorine with ***single F***, ***aromatic F***, ***CF_3*** or ***aliphatic CF_2*** substitution.[23, 24] Fluorine-containing drugs account for over 20% of the total pharmaceuticals market as reviewed by other and our groups.[7, 19, 24-26] A wide range of therapeutic areas have been covered by these newly developed fluorinated pharmaceutical drugs, for example, the treatment of cancer (e.g. 5-fluorouracil; alpelisib (Piqray™); selinexor (Xpovio™)), schizophrenia (e.g. lumateperone (Caplyta™)), migraine (e.g. ubrogepant (Ulbrelvy™)), rheumatoid arthritis (e.g. upadacitinib (Rinvoq™)), tuberculosis (e.g. pretomanid (PA-824)), and more recently for curing COVID-19.

2.1 Inhibitors of main viral targets (M^{pro} or RdRp)

2.1.1 Paxlovid (M^{pro})

On December 22 2021, the U.S. Food and Drug Administration (FDA) issued an emergency use authorization for Paxlovid (Pfizer) for treating people with mild-to-moderate COVID-19 who have a high risk of progressing to severe disease, reducing admissions to hospital, intensive care unit and potential death. It is the first treatment for COVID-19 that is in the form of a pill and can be taken orally—a major step forward in the fight against COVID-19. Paxlovid consists of nirmatrelvir (PF-07321332), a fluorinated oral drug containing a ***CF_3*** group which inhibits the viral M^{pro} protease of SARS-CoV-2 to stop the virus from replicating, as well as ritonavir (**Figure 2**), which helps to maintain the high concentration of nirmatrelvir for a long period.[2,3] Although COVID-19 cases are currently treated using a comprehensive approach of anticoagulants, oxygen, and antibiotics, the novel Paxlovid can significantly reduce hospitalization time and death rates. Trial results released by

the manufacturer show that Paxlovid reduced risk of hospitalization or death for high-risk patients by 89% and 88% compared with the placebo, if given within three and five days of symptom onset, respectively.[27] Impressively, the half-maximal effective concentration (EC_{50}) for PF-0732133 is surprising low at 0.077 μM (**Table 1**).[28]

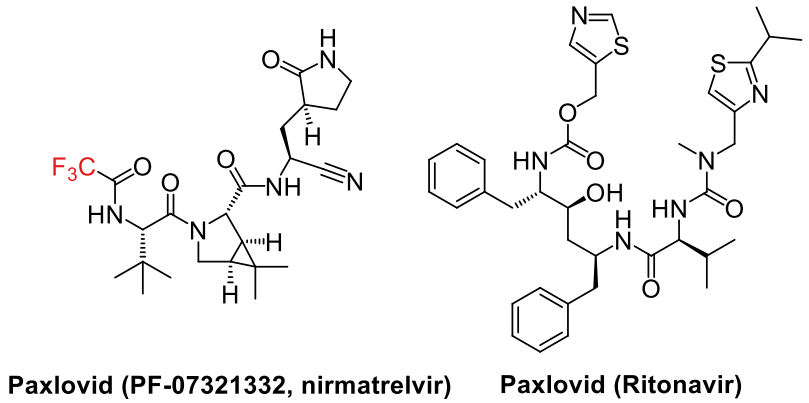

Figure 2. Chemical structures of Paxlovid containing PF-0732133 and ritonavir.

2.1.2 S-217622 (M^{pro})

S-217622 is an antiviral drug developed by Shionogi in partnership with Hokkaido University (**Figure 3**). It is the first non-peptidic, non-covalent SARS-CoV-2 M^{pro} inhibitor clinical candidate for treating COVID-19.[29] It was discovered via virtual screening followed by biological screening of an in-house compound library, and optimization of the hit compound using a structure-based drug-design strategy. S-217622 exhibited antiviral activity against a range of current outbreaking SARS-CoV-2 variants and coronavirus families. The drug has favorable pharmacokinetic profiles in vivo for once-daily oral dosing for the treatment of COVID-19 infection. To be more specific, S-217622 shows a biochemical activity of IC_{50} = 0.013 μM, an antiviral activity of EC_{50} = 0.37 μM (serine 2 gene-overexpressed VeroE6 cells), and preferable drug metabolism and pharmacokinetics profiles for oral dosing in rats (e.g. high metabolic stability: 96% and 88% in human and rat liver microsomes, respectively, and high oral absorption at 97%). Furthermore, S-217622 shows low clearance rate with long half-lives ($t_{1/2} \approx$ 10 and 30 h in monkeys and dogs, respectively), suggesting its potential use for once-daily treatment of COVID-19 without requiring a pharmacokinetics booster such as ritonavir. It has been recently tested to be effective against the recently emerged Omicron variant.[30]

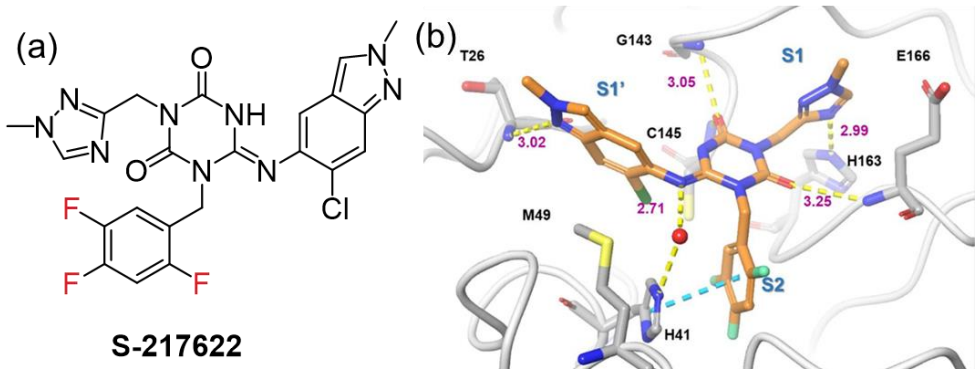

Figure 3. (a) Chemical structure of S-217622 and (b) its X-ray crystal co-structure with M^{pro} protease. S-217622 is colored in orange and the protein is colored in gray; water molecules are shown as red spheres; hydrogen bonds are indicated as yellow dashed lines; π-π stacking is indicated as a cyan dashed line. Reproduced with permission from ref 29. Copyright 2022.[29]

2.1.3 Favipiravir (RdRp)

Favipiravir (T-705, **Figure 4**), a fluorinated purine nucleic acid analogue, is one of the anti-COVID-19 candidates considered in several clinical trials.[31] It is a synthetic prodrug, first discovered by the Japanese company Toyoma, as a backup choice for resistant influenza infection.[31, 32] It has shown broad-spectrum activity against variety of RNA viruses including influenza, arenaviruses, bunyaviruses, and flaviviruses.[33] In 2020, favipiravir was first used against SARS-CoV-2 in Wuhan at the very epicenter of the pandemic for the treatment of patients with mild to moderate COVID-19 disease. Favipiravir is an inhibitor of RdRp of the SARS-CoV-2 virus.[34] It is metabolized intracellularly into its active phosphoribosylated metabolite (favipiravir-RTP, Figure 4), selective inhibiting viral RNA polymerase activity and prevents replication of the viral genome.[31, 32] However, the outcomes of clinical studies of favipiravir for the treatment of COVID-19 were conflicting. In July 2020, a clinical study by Fujita Health University showed that favipiravir has failed to demonstrate a clear efficacy in treating coronavirus patients at an early stage of the disease. Additional clinical studies are needed before it can confirm the effectiveness of using favipiravir for the treatment of COVID-19. There are currently 39 studies registered on clinicaltrials.gov to assess the utility of this drug in the management of COVID-19 (19 completed, 10 recruiting).

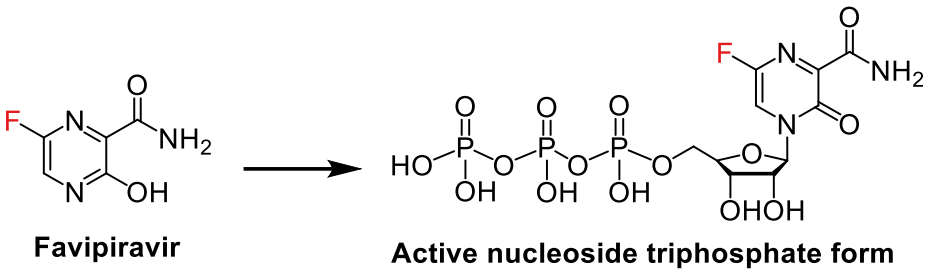

Figure 4. Chemical structures of favipiravir (T-705) and its active phosphoribosylated form.

2.1.4 4′-Fluorouridine (RdRp)

4'-Fluorouridine (4'-FlU, EIDD-2749, **Figure 5**) was invented by Plemper et al. in 2022 by 4'-fluorine substitution of molnupiravir.[35] Molnupiravir (Figure 5) has been recently granted emergency use authorization by the US FDA. The focus on 4'-fluorine ribose substitutions was motivated by the small atomic radius and strong stereoelectronic effect of fluorine that can influence backbone conformation flexibility, which may lead to improved selectivity indices, increased lipophilicity, and greater metabolic stability. These properties obtained using fluorination define 4'-FlU as a broad-spectrum candidate for the treatment of SARS-CoV-2, and related RNA virus infections. Unlike the Paxlovid inhibits the SARS-CoV-2 M^{pro}, 4'-FlU targets the RNA-dependent RNA polymerase—the same enzyme targeted by Merck's oral antiviral molnupiravir. However, the mechanism of 4'-FlU is distinct from molnupiravir. Molnupiravir introduces errors in the viral replication process, which produces mutants of the virus that are not viable, while 4'-FlU causes the polymerase to stall so the virus's genome doesn't get copied.[35] As shown in Figure 4, 4′-FlU-TP is the bioactive 5′-triphosphate form of 4'-FlU. The study by Plemper et al. also shows that 4'-FlU was effective with a single daily dose, while molnupiravir must be taken twice daily. 4'-FlU was effective at fighting SARS-CoV-2 12 and 24 h after initial infection with the virus in tests with ferrets and mice, respectively, corresponding to several days post-infection in human.

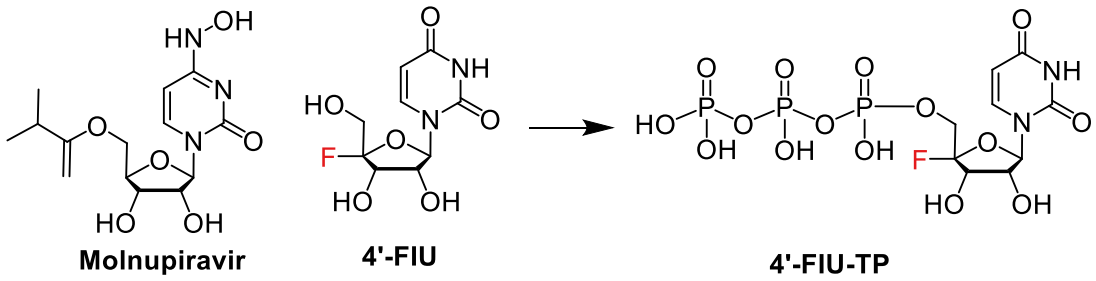

Figure 5. Chemical structures of molnupiravir, 4'-FlU and its bioactive 5′-triphosphate form 4′-FlU-TP.

2.1.5 AT-527 (RdRp)

AT-527 is an orally administered double prodrug of a guanosine nucleotide analog, and has previously demonstrated in vitro and in vivo antiviral activity against several enveloped single-stranded RNA viruses, including human flaviviruses and coronaviruses SARS-CoV-2.[36] This highly selective purine nucleotide prodrug was designed to uniquely inhibit RdRp, an enzyme that is essential for the replication of RNA viruses. The active triphosphate metabolite of AT-527, AT-9010, which cannot penetrate to cell membranes and is formed only after intracellular delivery of the prodrug (**Figure 6**). In normal human airway epithelial cells, the concentration of the drug required to inhibit replication of SARS-CoV-2 by 90% (EC_{90}) is 0.47 μM and has a maximum concentration of 0.64 μM after oral administration by nonhuman primates (**Table 1**).[33] AT-527 is not yet licensed or approved for any indication in the United States or any other country. In October 2021, Atea announced that AT-527 failed to meet the primary goal of the international Phase II MOONSONG clinical trial in subjects with mild or moderate COVID-19 in the outpatient setting.

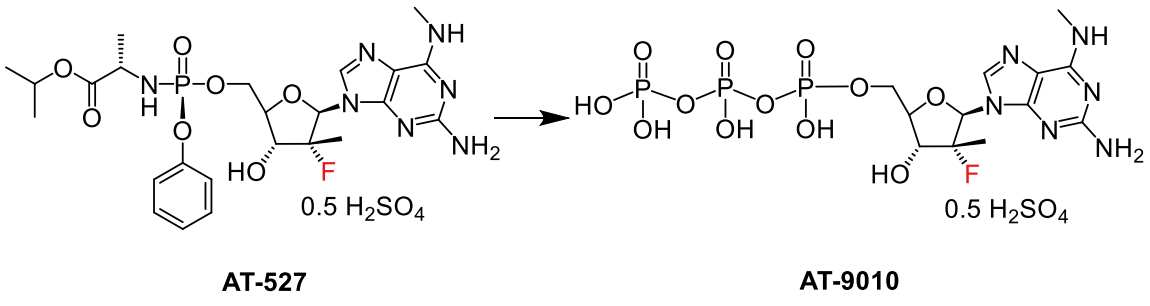

Figure 6. Chemical structures of AT-527 and its active triphosphate metabolite AT-9010.

2.1.6 Sofosbuvir (RdRp)

Sofosbuvir is a direct-acting antiviral agent and serves as an RdRp inhibitor (**Figure 7**). It was firstly approved for the treatment of Hepatitis C virus (HCV) infection in 2013.[37] In 2020, Sadeghi et al.[38] reported encouraging results from a clinical trial using sofosbuvir and daclatasvir as a potential combination treatment for moderate or severe COVID-19 patients. In this study, 66 patients were recruited and allocated to either the treatment arm or the control arm ($n = 33$ each group). These results show that sofosbuvir and daclatasvir combination treatment increased 14-day clinical recovery rates (88% vs. 67%) and reduced the length of hospital stays (6 days vs. 8 days). Another report by Ju et al. demonstrates for the first time that the active triphosphate form (sofosbuvir-TP, **Figure 7**) not only serves as an efficient terminator of the RdRp, but it terminates RNA confers a substantial level of resistance to excision by exonuclease. Sofosbuvir is removed at a lower rate by the SARS-CoV-2 exonuclease complex compared with remdesivir (the first anti-COVID-19 drugs approved by FDA, administered via injection into a vein, Figure 7) upon incorporation of the triphosphate form of Sofosbuvir into RNA by the SARS-CoV-2 RdRp. Sofosbuvir inhibits SARS-CoV-2 replication in human hepatoma-derived (Huh-2) and Type II pneumocyte-derived (Calu-3) cells with EC_{50} values of 6.2 and 9.5 μM, respectively.[39]

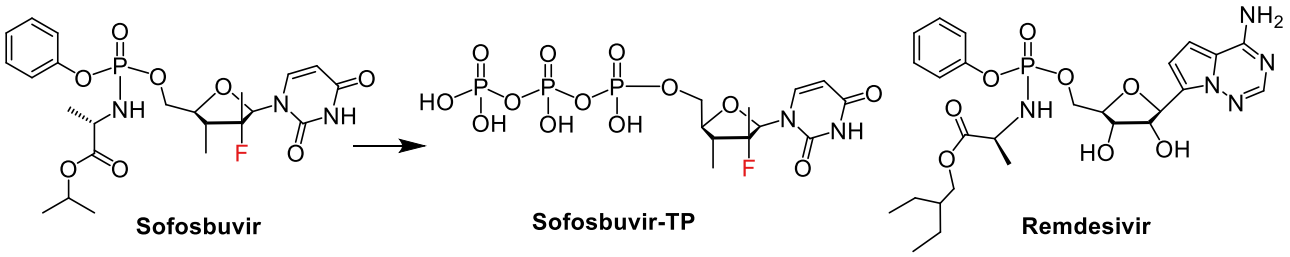

Figure 7. Chemical structures of sofosbuvir and its active triphosphate form sofosbuvir-TP. The chemical structure of related purine nucleotide remdesivir is also shown.

2.2 Inhibitors of virus entry into cells

SARS-CoV-2 uses the SARS-CoV receptor angiotensin-converting enzyme 2 (ACE2) for cell entry through its receptor-binding domain (RBD) and the serine protease transmembrane protease, serine 2 (TMPRSS2) for viral spike protein priming.[40, 41] Therefore, drugs act as TMPRSS2 inhibitors could

potentially block the entry and might constitute a treatment option. A number of drugs have been demonstrated to be effective to SARS-CoV-2 infection, including mefloquine, proxalutamide, and etc..

2.2.1 Mefloquine HCl

Mefloquine (MFQ) is a fluorinated derivative of hydroxychloroquine (HCQ) originally used for anti-malarial therapy and prophylaxis (**Figure 8**).[42] It was identified as a potential drug to effectively treat patients with COVID-19 by Watashi and coworkers from the Tokyo University of Science and collaborating institutions in Japan in 2021.[43] After fluorination, MFQ performs a higher anti-SARS-CoV-2 activity than HCQ in several SARS-CoV-2 infection models, such as the serine 2 gene-overexpressed VeroE6 cells (EC_{50} = 1.28 vs. 1.94 μM; EC_{90} = 2.31 vs. 7.96 μM) and human lung-derived Calu-3 cells. MFQ serves as an anti-SARS-CoV-2 entry inhibitor and can effectively inhibits the viral entry process.

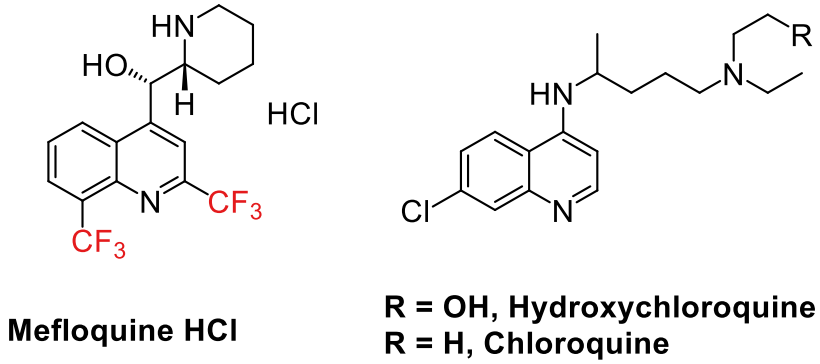

Figure 8. Chemical structures of mefloquine, hydroxychloroquine and chloroquine. Mefloquine is a fluorinated derivative of hydroxychloroquine and chloroquine, exhibiting enhanced anti-COVID-19 activities.

2.2.2 Proxalutamide

Proxalutamide (GT0918, **Figure 9**) is a second-generation non-steroidal androgen receptor (AR) antagonist. It has a dual mechanism of action in suppressing AR and was primarily developed for treatment of castration-resistant prostate cancer. In addition to direct AR antagonism, proxalutamide also acts as a suppressor of AR gene expression and regulates ACE2, a receptor of the new coronavirus SARS-CoV-2 entering the host cells, which would be beneficial for preventing the entry

of SARS-CoV-2 into lung cells.[44] Goren, Zimerman and coworkers have previously reported their preliminary analysis of the effects of proxalutamide in COVID-19 patients by taking 200 mg per day. The results are encouraging and show an overall 74% reduction in nasopharyngeal detection of SARS-CoV-2 on the day seven of treatment.[44] In a later study from the same group, a randomized, double-blinded, placebo-controlled clinical trial was conducted at two outpatient centers at Brasilia in Brazil.[45] It was demonstrated that proxalutamide can reduce the hospitalization rate in treated men by 91% compared to usual care.

2.3 Other fluorinated drugs

Several other fluorinated drugs having the same or different mechanisms as above in the treatment of SARS-CoV-2 infection have been invented and studied, including halofantrine (M^{pro} inhibitor), ralimetinib (LY2228820, p38 mitogen-activated protein kinase inhibitor), L-796568 (β-3 adrenergic receptor agonist), dexamethasone (anti-flammatory), fluvoxamine (selective serotonin reuptake inhibitor), and etc.. **Figure 9** and **Table 1** summarize the chemical structures and anti-COVID-19 activities of these drugs.

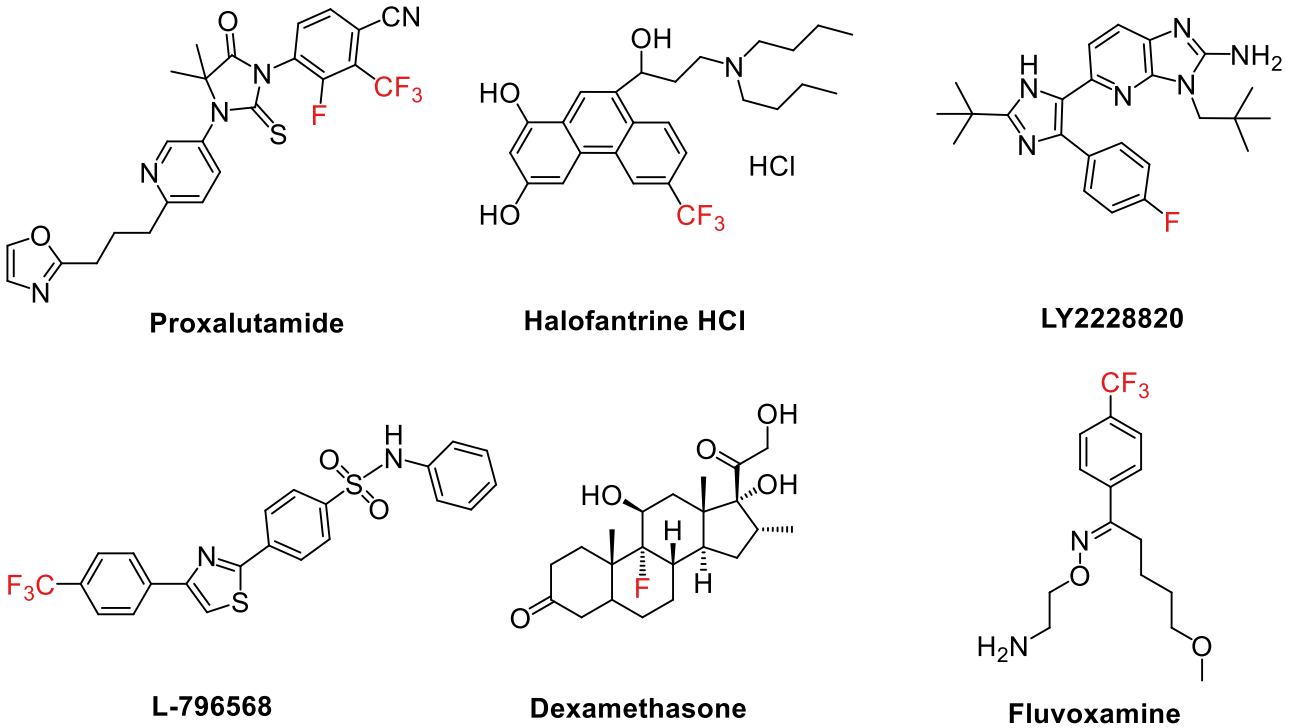

Figure 9. Chemical structures of other fluorinated anti-COVID-19 oral drugs.

Table 1. Summary of attractive fluorinated oral drugs with activity and selectivity to SARS-CoV-2.

Name	Molecular weight (g/mol)	Mechanism	PK Exposure		SARS-CoV-2 EC_{50} (μM)	Ref
			Approx. C_{max} (μM)	Approx. $t_{1/2}$ (h)		
Paxlovid	499.54	M^{pro} inhibitor	1.6 (human oral, 200 mg)	7.7	0.077	28, 46
S-217622	531.88	M^{pro} inhibitor	254 (hamsters oral, 100 mg/kg)	10 (monkey) and 30 (dogs)	0.29–0.50	29, 47
Favipiravir	157.10	RdRp inhibitor	~ 400 (human oral, 200 mg)	2-5.5	61.88	32, 48-50
4′-Fluorouridine	246.19	RdRp inhibitor	63.3 (ferrets oral, 50 mg/kg)	9.7	0.61–1.2	35
AT-527	581.54	RdRp inhibitor	0.64 (Nonhuman primates)	0.7	0.47 (EC_{90})	36
Sofosbuvir	529.46	RdRp inhibitor	1.1 (human oral)	> 24	6.2	51
Mefloquine	378.31	TMPRSS2 inhibitor	4.58 (human oral)	> 400	2.31	43, 52, 53
Proxalutamide	517.50	ACE2 and TMPRSS2 inhibitor	~27 (human oral, 100 mg)	21.1	Not applicable	44, 54
Halofantrine	500.42	M^{pro} inhibitor	1.0 (human oral)	58	0.33	55, 56
Ralimetinib (LY2228820)	420.54	p38 mitogen-activated protein kinase inhibitor	5.0 (human, oral)	190	1.75	57
L-796568	697.62	β-3 adrenergic receptor agonist	0.3 μM (dog, oral)	13	1.15	58
Dexamethasone	392.46	anti-inflammatory	Not applicable	~ 3	Not applicable	59, 60
Fluvoxamine	318.34	Selective serotonin reuptake inhibitor	0.6 (human oral, 60 mg daily)	~ 80	0.69	61

3. Conclusions

Fluorinated compounds are very successful in the long history of medicinal chemistry. Fluorine has both hydrophobic and lipophobic characters,[21, 25, 62, 63] and the judicious introduction of fluorine into

a drug can productively improve its membrane permeability and cellular uptake, influence pharmacokinetic properties, and subsequently increase the therapeutic efficacy of SARS-CoV-2. Fluorinated oral drugs appear to be an important new weapon for the treatment of COVID-19 due to the superior antiviral performance compared with the non-fluorinated analogues. It may be predicted that the number of anti-COVID-19 fluorinated drugs on the market will continue to increase.

While it is exciting to see the rapid discovery and investigation of many new oral drugs for COVID-19, prevention and vaccination are still the best strategy. COVID antivirals are an important complement to vaccines, and they serve an important function. The main reason not to rely only on the new pills is that antiviral medications, which stop the virus from replicating in the body, must be taken in a narrow window at the early phases of COVID-19. Antiviral drugs are not going to provide much benefit once a shortness of breath or other serious symptoms has been developed.

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fellow in the Whittaker group to develop advanced medical imaging agents. In 2019, he was awarded an NHMRC Fellowship and relocated to UCSB working with Professor Craig J. Hawker, Professor Christopher M. Bates and Professor Glenn H. Fredrickson on block copolymer chromatography separation and self-assembly projects. His research focuses on the development of advanced polymerization, purification and characterization techniques to prepare well-defined functional polymers with precisely-tailored properties for important applications from PFAS remediation, energy materials e.g. solid electrolytes to functional biomaterials e.g. imaging and therapeutic agents.

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