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—constitute an important subgroup. Fluorine has been widely used in the pharmaceutical market and can lead to improved selectivity indices, increased lipophilicity, greater metabolic stability, and 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 their molecular design, 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, Scheme 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 10 April 2022, SARS-CoV-2 has caused a combined total of more than 494588000 confirmed infections and more than 6170000 reported deaths in 213 different countries.

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 Drug Administration (FDA) has approved 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. By early 2022, 11.3 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. Therefore, the quest for effective and economical antiviral drugs to treat COVID-19 has been a priority since the outbreak of the disease.

Several direct-acting small-molecule SARS-CoV-2 antiviral drugs have been developed to treat COVID-19. These drugs have received approval or are 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 main groups: (1) agents that target proteins or RNA of the virus (e.g., viral RNA-dependent RNA polymerase (RdRp), viral main protease (Mpro or 3CLpro), etc.) and (2) drugs that target host proteins (e.g., angiotensin converting enzyme 2 (ACE2), transmembrane protease serine 2 (TMPRSS2), etc.). Fluorine-containing drugs constitute an important subgroup of these antivirals, including Paxlovid—the first oral tablet for the treatment of COVID-19. As of March 2022, there are already over 10 different types of fluorinated anti-COVID-19 drugs that have been reported. An important consideration of the 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.

An increasing number of studies by our group and other groups have shown that fluorination has a great potential to advance the performance of drugs. This review will provide a summary of the molecular design, metabolism and pharmacokinetics, and mechanism of action of fluorinated anti-COVID-19 oral drugs. An outlook regarding the importance of fluorination in the design of antiviral SARS-CoV-2 drugs is 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 an enhancement of therapeutic efficacy. Fluorine substitution productively influences the conformation, membrane permeability, metabolic pathways, and pharmacokinetic properties of certain drugs. It is notable that a number of blockbuster drugs...
contain fluorine with single F, aromatic F, CF₃, or aliphatic CF₂ substitution. Fluorine-containing drugs account for over 20% of the total pharmaceuticals market, as reviewed by our group and others.⁷ 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)), and tuberculosis (e.g., pretomanid (PA-824)) and more recently for curing COVID-19. Figure 1 summarizes the chemical structures of fluorinated anti-COVID-19 oral drugs on the basis of the mechanism of action. Drugs serving as inhibitors against Mpro, RdRp, viral entry through TMPRSS2 or ACE2, and a few other targets, will be discussed in the following sections.

2.1. Inhibitors of Main Viral Targets (Mₚʳᵒ or RdRp).

2.1.1. Paxlovid (Mₚʳᵒ). 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 a hospital or 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 CF₃ group which inhibits the viral Mₚʳᵒ protease of SARS-CoV-2 to stop the virus from replicating, and ritonavir (Figure 2), which helps to maintain the high concentration of nirmatrelvir for a long period. 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 the risk of hospitalization or death for high-risk patients by 89% and 88% in comparison with a placebo, if given within 3 and 5 days of symptom onset, respectively.¹⁰ Impressively, the half-maximum effective concentration (EC₅₀) for PF-07321332 is surprisingly low at 0.077 μM (Table 1).¹¹

2.1.2. S-217622 (Mₚʳᵒ). S-217622 is an antiviral drug developed by Shionogi in partnership with Hokkaido University (Figure 3). It is the first nonpeptidic, noncovalent SARS-CoV-2 Mₚʳᵒ inhibitor clinical candidate for treating COVID-19.¹² 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 outbreaks of 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 IC₅₀ = 0.013 μM, an antiviral activity of EC₅₀ = 0.37 μM (serine 2 gene overexpressed VeroE6 cells), and preferable drug metabolism and pharmacokinetics profiles for oral dosing in rats (e.g., a high metabolic stability of 96% and 88% in human and rat liver microsomes, respectively, and high oral absorption at 97%). Furthermore, S-217622 shows a low clearance rate with long half-lives (t₁/₂ ≈ 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.\textsuperscript{13}

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.\textsuperscript{14} It is a synthetic prodrug, first discovered by the Japanese company Toyoma, as a backup choice for resistant influenza infection.\textsuperscript{14,15} It has shown broad-spectrum activity against a variety of RNA viruses including influenza, arenaviruses, bunyaviruses, and flaviviruses. 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. It is metabolized intracellularly into its active phosphoribosylated metabolite (favipiravir-RTP, Figure 4), selectively inhibiting viral RNA polymerase activity and preventing replication of the viral genome.\textsuperscript{14,15} 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 had failed to demonstrate a clear efficacy in treating coronavirus patients at an early stage of the disease. Additional clinical studies are needed before the effectiveness of using favipiravir for the treatment of COVID-19 can be confirmed. 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 1. Chemical structures of fluorinated anti-COVID-19 oral drugs categorized by the types of inhibition.

Figure 2. Chemical structures of Paxlovid containing PF-07321332 and ritonavir.
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. 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 the 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 Paxlovid, which inhibits the SARS-CoV-2 Mpro, 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 that of 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 does not get copied. 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 postinfection in humans.

2.1.5. AT-527 (RdRp). AT-527 is an orally administered double prodrug of a guanosine nucleotide analogue and has

Table 1. Summary of Fluorinated Oral Drugs with Activity and Selectivity to SARS-CoV-2

| Drug          | Mol wt (g/mol) | Mechanism                        | C_{max} (μM) | t_{1/2} (h) | EC_{50} (μM) | Ref  |
|---------------|----------------|----------------------------------|--------------|------------|-------------|------|
| Paxlovid      | 499.54         | M^pro inhibitor                  | 1.6 (human oral, 200 mg) | 7.7        | 0.077       | 11, 22 |
| S-217622      | 511.88         | M^pro inhibitor                  | 254 (hamster oral, 100 mg/kg) | 10 (monkey) and 30 (dogs) | 0.29–0.50 | 12 |
| halofantrine  | 500.42         | M^pro inhibitor                  | 1.0 (human oral) | 58         | 0.33        | 23 |
| favipiravir   | 167.10         | RdRp inhibitor                    | ~400 (human oral, 200 mg) | 2–5.5      | 61.88       | 15 |
| 4′-fluorouridine | 246.19         | RdRp inhibitor                    | 63.3 (ferret oral, 50 mg/kg) | 9.7        | 0.61–1.2    | 16 |
| AT-527        | 581.54         | RdRp inhibitor                    | 0.64 (nonhuman primates) | 0.7        | 0.47 (EC_{50}) | 17 |
| sofosbuvir    | 529.46         | RdRp inhibitor                    | 1.1 (human oral) | >24        | 6.2–9.5     | 24 |
| mefloquine    | 378.31         | TMPRSS2 inhibitor                 | 4.58 (human oral) | >400       | 2.31        | 20 |
| proxalutamide | 517.50         | ACE2 and TMPRSS2 inhibitor        | ~27 (human oral, 100 mg) | 21.1       | 21         |
| ralmetinib (LY2228820) | 420.54         | p38 mitogen-activated protein kinase inhibitor | 5.0 (human, oral) | 190        | 1.75        | 25 |
| L-796568      | 697.62         | β-3 adrenergic receptor agonist   | 0.3 (dog, oral) | 13         | 1.15        | 26 |
| dexamethasone | 392.46         | anti-inflammatory                 | ~3           | 21         | 27         |
| fluvoxamine   | 318.34         | selective serotonin reuptake inhibitor | 0.6 (human oral, 60 mg daily) | ~80        | 0.69        | 28 |

Figure 3. (a) Chemical structure of S-217622 and (b) its X-ray crystal structure with M^pro protease. S-217622 is shown in orange, the protein is shown in gray, water molecules are shown as red spheres, hydrogen bonds are indicated as yellow dashed lines, and π−π stacking is indicated as a cyan dashed line. Reproduced with permission from ref 12. Copyright 2022 American Chemical Society.

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

Figure 5. Chemical structures of molnupiravir, 4′-FlU, and its bioactive 5′-triphosphate form 4′-FlU-TP.
EC50 values of 6.2 and 9.5 (Huh-2) and Type II pneumocyte-derived (Calu-3) cells with inhibits SARS-CoV-2 replication in human hepatoma-derived sofosbuvir into RNA by the SARS-CoV-2 RdRp. Sofosbuvir Figure 7) upon incorporation of the triphosphate form of approved by the FDA, administered via injection into a vein; comparison with remdesivir (the fi

lower rate by the SARS-CoV-2 exonuclease complex in resistance to excision by exonuclease. Sofosbuvir is removed at a

RdRp but also terminates RNA to confer a substantial level of TP, Figure 7) not only serves as an e

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stays (6 days vs 8 days). Another report by Ju et al. demonstrated

recovery rates (88% vs 67%) and reduced the length of hospital
daclatasvir combination treatment increased 14-day clinical

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 a 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. demonstrated for the first time that the active triphosphate form (sofosbuvir-TP, Figure 7) not only serves as an efficient terminator of the RdRp but also terminates RNA to confer a substantial level of resistance to excision by exonuclease. Sofosbuvir is removed at a lower rate by the SARS-CoV-2 exonuclease complex in comparison with remdesivir (the first anti-COVID-19 drugs approved by the 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 EC50 Values of 6.2 and 9.5 μM, respectively.

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. Therefore, drugs acting as TMPRSS2 inhibitors could potentially block the entry of the virus and might constitute a treatment option. A number of drugs have been demonstrated to be effective for SARS-CoV-2 infection, including mefloquine, proxalutamide, etc.

2.2.1. Mefloquine HCl. Mefloquine (MFQ) is a fluorinated derivative of hydroxychloroquine (HCQ) originally used for antimalarial therapy and prophylaxis (Figure 8). It was identified as a potential drug to effectively treat patients with COVID-19 by Watashi and co-workers from the Tokyo University of Science and collaborating institutions in Japan in 2021.20 After fluorination, MFQ has a higher anti-SARS-CoV-2 activity in comparison to HCQ in several SARS-CoV-2 infection models, such as the serine 2 gene overexpressed VeroE6 cells (EC50 = 1.28 vs 1.94 μM; EC90 = 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 inhibit the viral entry process. 2.2.2. Proxalutamide. Proxalutamide (GT0918, Figure 1) is a second-generation nonsteroidal 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.21 Goren, Zimerman, and co-workers have previously reported their

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

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

Figure 8. Chemical structures of mefloquine, hydroxychloroquine and chloroquine. Mefloquine is a fluorinated derivative of hydroxychloroquine and chloroquine, exhibiting enhanced anti-COVID-19 activities.
preliminary analysis of the effects of proxalutamide in COVID-19 patients taking 200 mg per day. The results are encouraging and show an overall 74% reduction in nasopharyngeal detection of SARS-CoV-2 on day 7 of treatment.11 In a later study from the same group, a randomized, double-blind, placebo-controlled clinical trial was conducted at two outpatient centers at Brasilia in Brazil. It was demonstrated that proxalutamide can reduce the hospitalization rate in treated men by 91% in comparison to the usual care.

2.3. Other Fluorinated Drugs. Several other fluorinated drugs having different mechanisms of action in the treatment of SARS-CoV-2 infection have been invented and studied, including ralimetinib (LY2228820, p38 mitogen-activated protein kinase inhibitor), L-796568 (β-3 adrenergic receptor agonist), dexamethasone (anti-inflammatory), fluvoxamine (selective serotonin reuptake inhibitor), etc. Figure 1 and Table 1 summarize the chemical structures and anti-COVID-19 activities of these drugs.

3. FUTURE OUTLOOK
Fluorinated compounds have been very successful in the long history of medicinal chemistry. Fluorine has both hydrophobic and lipophobic characters, and the judicious introduction of fluorine into a drug can productively improve its membrane permeability and cellular uptake, influence its pharmacokinetic properties, and subsequently increase the therapeutic efficacy of SARS-CoV-2. A key consideration in the design of future anti-COVID-19 oral drugs is chirality, which has become a crucial factor in drug discovery. As can be seen in Figure 1, most of the drugs discovered are chiral, leading to a three-dimensional chemical structure space with enhanced affinity and higher levels of specificity when the drugs interact with their targets and thus are more efficient and safer.

Fluorinated oral drugs appear to be an important new weapon for the treatment of COVID-19 due to their superior antiviral performance in comparison with nonfluorinated analogues. It may be predicted that the number of anti-COVID-19 fluorinated drugs on the market will continue to increase. It is exciting to see that a number of countries have approved the use of anti-COVID-19 oral drugs: for example, Australia and China have approved the use of Pfizer’s drug Paxlovid on January 18, 2022, and February 12, 2022, respectively. COVID antivirals are an important complement to vaccines. The rapid discovery and investigation of new oral drugs for COVID-19, together with prevention and vaccination, are believed to be crucial in ending the COVID-19 pandemic.

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Notes
The author declares no competing financial interest.

Biography
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