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Highlights on U.S. FDA-Approved Fluorinated Drugs over the Past Five Years (2018–2022)

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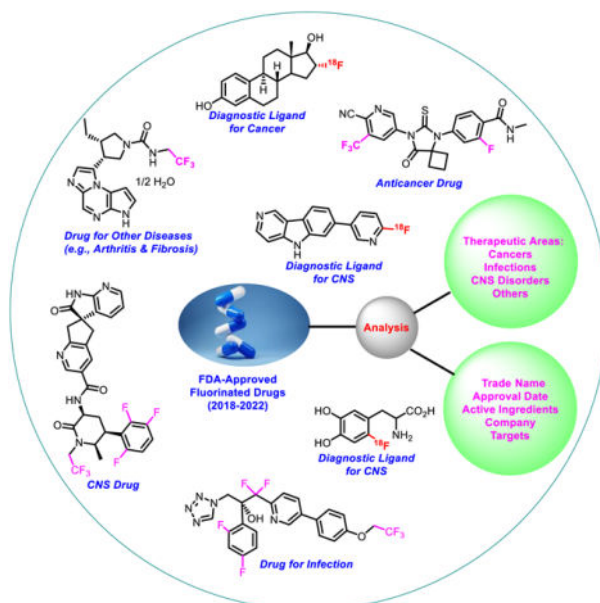
Abstract

The objective of this review is to provide an update on the fluorine-containing drugs approved by U.S. Food and Drug Administration in the span of past five years (2018–2022). The agency accepted a total of fifty-eight fluorinated entities to diagnose, mitigate and treat a plethora of diseases. Among them, thirty drugs are for therapy of various types of cancers, twelve for infectious diseases, eleven for CNS disorders, and six for some other diseases. These are categorized and briefly discussed based on their therapeutic areas. In addition, this review gives a glimpse about their trade name, date of approval, active ingredients, company developers, indications, and drug mechanisms. We anticipate that this review may inspire the drug discovery and medicinal chemistry community in both industrial and academic settings to explore the fluorinated molecules leading to the discovery of new drugs in the near future.

Graphical Abstract

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1. Introduction

Fludrocortisone [1, 2] as the first fluorine-containing drug was introduced to the market for commercial use in 1954 (Fig. 1). Shortly thereafter, 5-fluorouracil [3, 4] was another fluorinated drug brought to the clinic for the treatment of cancer in 1957 (Fig. 1). Introduction of these two drugs drew the attention of pharmaceutical industry toward the biological applications of fluorine in drug discovery and development. In 1972, Ili Lilly and Company discovered a blockbuster antidepressant drug Prozac (Fluoxetine) and marketed it for medical use in 1986 (Fig. 1). Extensive literature survey has revealed that more than 50% blockbuster drugs are the molecules having fluorine atom(s) or trifluoromethyl group [5]. Notably, among these medicines, Lipitor is considered the most profitable one ever launched to the market [6]. Over the past two decades, fluorine chemistry has demonstrated its potential applications in diverse domains, such as food, health, and energy industries. In addition, fluorine-containing compounds have been exploited for the advancement of technologies due to their unique electronic, physicochemical, and biological properties [7–12].

One of the exciting contributions of fluorine in the innovation of technology is the use of its isotope ^{18}F containing molecules in positron emission tomography (PET) in potential diagnosis, drug discovery and development [13–22]. It is well known that fluorine is extensively utilized in magnetic resonance imaging (MRI) as a diagnostic tool for early monitoring the different illnesses [23–26]. Furthermore, fluorine has shown its potential applications in peptide/protein engineering [27–30]. In fact, most important application of fluorine lies in the drug design to discover new entities. Judicious installation of fluorine or groups of fluorine atoms (e.g., CF_3 , CHF_2 , OCF_3) in a drug candidate may lead to improved pharmacological and pharmacokinetic profiles with increased potency, decrease in pK_a , higher permeability, decrease in clearance, and conformational constraint [31–34]. The prevalence of fluorine in pharmaceuticals attracts the attention of synthetic community

and encourages developing new synthetic methodologies to access structurally diverse fluorinated molecules. Consequently, numerous novel methods for the synthesis of unique fluorinated compounds have been reported in literature [35–45] in past few years. Recently, some review articles nicely covered FDA-approved fluorinated drugs year-wise until 2021 [46–50]. However, no update is available on FDA-approved fluorinated drugs in 2022. Moreover, there is no report available in the literature that presents a concise information about fluorinated drugs approved by FDA based on their therapeutic areas in a single document in the past five years (2018–2022). Therefore, there is a need of a concise and informative summary on fluorine-containing therapies to provide the latest update for the drug discovery and medicinal chemistry research community. The bar graph displays the total numbers of FDA-approved drugs along with fluorinated drugs spanning from 2018 to 2022 (Fig. 2A).

The Center for Drug Evaluation and Research (CDER) of the U.S. FDA approved a total of 247 drugs including small and macromolecules from 2018 to 2022. Fifty-eight out of them are fluorinated small molecules for various therapeutic purposes, such as cancers, infections, CNS disorders and some other diseases (Fig. 2B). This review presents an overview with highlights on the fluorinated drugs for diagnosis, mitigation, and the treatment of various types of cancers, infectious diseases, CNS disorders and some other diseases. It also provides the details about these approved fluorinated drugs, such as trade name, approval date, active ingredients, company developers, indications, and drug mechanisms.

2. U.S. FDA-Approved Fluorinated Anti-Cancer Drugs (2018–2022)

Cancer is a major threat to the human health across the globe and responsible for large number of deaths each year. According to the World Health Organization (WHO)'s classification of cancers, five most common cancer types are lung, breast, liver, stomach and colorectal among the hundreds of types of cancers [52]. Very recently, the American Cancer Society has estimated around 2 million new cancer cases and more than half million cancer deaths are likely to occur in 2023 [53]. Discovering an anti-cancer drug is a great challenge because each kind of cancer requires different diagnosis and target-based treatment strategy. Nevertheless, significant growth was witnessed in the development of drugs for the treatment of cancers [54] after the first anticancer remedy in the 1940s using nitrogen mustards and antifolate drugs [55]. The CDER of U.S. FDA agency approved a total of thirty fluorine-containing medicines **1–30** for the treatment of various cancers from 2018 to 2022 (Fig. 3; Table 1). The agency approved Erleada **1**, Orgovyx **23** and Pylarify **26** for the treatment or diagnosis of prostate cancer. Erleada **1** and Orgovyx **23** act as androgen receptor inhibitor and GnRH receptor antagonist, respectively. While Pylarify **26** is an advanced diagnostic imaging agent, containing ^{18}F isotope of fluorine has been extensively utilized in developing PET imaging ligands [56–58].

It binds to malignant prostate cancer cells to identify tumor in prostate. Melanoma is a type of skin cancer for which FDA approved a couple of medications, such as Mektovi **2** and Braftovi **3**. Mektovi **2** in combination with Braftovi **3** treats melanoma having specific gene BRAF V600E or V600K mutation as a MEK1/2 inhibitor. Interestingly, Braftovi **3** with Mektovi **2** can also be used to treat melanoma but as a BRAF inhibitor. In addition, FDA

approved Tibsovo **4** and Scemblix **29** to treat acute myeloid and philadelphia chromosome–positive chronic myeloid leukemia as an IDH1 inhibitor and kinase inhibitor, respectively. We noted that pharmaceutical companies made remarkable progress in the development of new therapies for lung cancers in the past five years. The CDER of U.S. FDA approved a total of seven fluorine-containing drugs for lung cancers. Vizimpro **5**, Tabrecta **17**, Gavreto **21** and Lumakras **27** received approval for the treatment of nonsmall-cell lung cancer as an irreversible EGFR inhibitor, MET inhibitor, RET fusion inhibitor, and KRAS G12C inhibitor, respectively. Lorbrina **6** is a drug used to treat ALK-positive metastatic non-small-cell lung cancer as an ALK inhibitor. Additionally, FDA approved Rozlytrek **12** as an ROS1 and NTRK inhibitor to treat non-small-cell lung cancer whose tumors are ROS1 positive. Further, Krazati **30** was approved as an effective medication of KRAS G12C–mutated non-small-cell lung cancer, which acts as an irreversible inhibitor of KRAS G12C. Fluorine-containing pharmaceuticals continued to be proven valuable in the drug discovery and development. The CDER of U.S. FDA approved three medications having fluorine for the breast cancer. FDA approved Talzenna (**7**) and Piqray **9** to treat breast cancer with germline BRCA mutations and breast cancer as a PARP inhibitor and PI3Ka inhibitor, respectively. Cerianna **19** also received approval as a diagnostic imaging agent for patients with breast cancer. FDA accepted Vitrakvi **8**, as a TRK inhibitor for the treatment of NTRK gene fusion–positive solid tumors. Xpovio **10** and Pepaxto **25** were approved for multiple myeloma and relapsed or refractory multiple myeloma, by inhibiting nuclear export and DNA alkylation, respectively. FDA approved Turalio **11** for symptomatic tenosynovial giant-cell tumors as a CSF1R, KIT, and FLT3-ITD inhibitor. FDA also approved Inqovi **20**, a combination of decitabine and cedazuridine for the treatment of myelodysplastic syndromes as a nucleoside metabolic inhibitor and a cytidine deaminase inhibitor. FDA approved Ayvakit **13** and Qinlock **18** to treat gastrointestinal-stromal tumors as KIT and PDGFRA kinase inhibitors, respectively.

As a cortisol synthesis inhibitor, Isturisa **14** received approval for the treatment of Cushing’s disease in adults. FDA approved Koselugo **15** to treat neurofibromatosis type 1, a genetic disorder that causes tumors to grow on nerves as a MEK1/2 inhibitor. As an FGFR inhibitor, Pemazyre **16** was approved as a remedy for cholangiocarcinoma, a rare form of cancer that forms in bile ducts. Orladeyo **22**, Ukoniq **24** and Welireg **28** received approval for prevention of hereditary angioedema, marginal zone lymphoma or follicular lymphoma and Von Hippel-Lindau disease as a plasma kallikrein inhibitor, kinase inhibitor, and hypoxia-inducible factor-2 α inhibitor, respectively.

From the structure-activity/property relationship perspective, meticulous deployment of fluorine or groups of fluorine atoms (e.g., CF₃, CHF₂, OCF₃) in a drug candidate may result in enhanced pharmacological and pharmacokinetic profiles with increased potency, decrease in pK_a, higher permeability, decrease in clearance, and conformational constraint [31–34]. Over the past two decades, it has become a common practice using fluorine, CF₃, and OCF₃ at the suitable positions of aromatic/heteroaromatic rings to avoid metabolic liabilities [31–34]. The effect of the presence of fluorine or groups of fluorine atoms in drug candidates can be explained based on literature precedents. As we can see (Fig. 3), fluorine atoms and/or CF₃ group are positioned directly on aromatic/heteroaromatic rings in drugs

1-8, 10-19, 22-24 and **27**. The presence of fluorine atoms or CF₃ group on aromatic ring may improve metabolic stability (decrease in clearance) [59–63], diminishing the basicity of neighboring basic group [64–70], increasing the membrane permeability [71–75] and enhancing the binding affinity to the target proteins through non-bonding ligand-protein interactions involving fluorine (improving potency) [76–80]. Similarly, the presence of geminal difluoro group either on cyclic or aliphatic system, such as those in drugs **4, 20, 29** (Fig. 3) can be rationalized. Literature reveals that geminal difluoro group may improve the potency and metabolic stability of these drugs [81–83]. The role of CF₃ group on aliphatic system like in drugs **9** and **12** may be resulting in increased potency and decreased liver microsomal clearance as per some resembling reports in literature [81, 83]. In case of **28**, two vicinal fluorine atoms increased the potency and metabolic stability as compared to other pharmacophores [84]. Vinylic fluorine in **30** may improve the metabolic stability while maintaining the potency [85].

3. U.S. FDA-Approved Fluorinated Drugs for Infectious Diseases (2018–2022)

The main cause of the infectious diseases is entering the pathogenic microorganisms, such as viruses, bacteria, parasites, or fungi into the body. Being contagious in nature, infectious diseases spread rapidly within the society and sometimes cause pandemic. A wide variety of infectious diseases includes malaria, coronavirus, flavivirus, HBV, HIV/AIDS, influenza, HPV, RSV, smallpox and many more. Particularly, novel effective broad spectrum antiviral drugs are urgently needed, attracting tremendous research efforts in the field [86–91]. During the recent global pandemic, a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was added to list of devastating infectious diseases [92, 93]. We came across that the CDER of U.S. FDA approved a total of twelve fluorine-containing drugs **31–42** for the treatment of various types of infections over the past five years (Fig. 4; Table 2). Each of these drugs has been briefly discussed based on their therapeutic targets in this section. Four drugs **31, 36, 39** and **42** were approved for the treatment of HIV infection. Biktarvy **31** has three active ingredients, such as Bictegravir Sodium, Emtricitabine, and Tenofovir alafenamide fumarate used for therapy of HIV infection as integrase strand transfer inhibitor, and two HIV nucleoside analog reverse transcriptase inhibitors. However, Pifeltro **36** acts as an antiviral, reverse transcriptase inhibitor. Cabenuva **39** is a combination of Cabotegravir and Rilpivirine (fluorinated). Sunlenca **42** received approval to treat HIV infections in adults that cannot be successfully managed with other previously available treatments. It is important to note that both Cabenuva **39** and Sunlenca **42** are HIV-1 antiretroviral agents. FDA approved Akynzeo **32** as a remedy of nausea. It is a combination of Netupitant and Palonosetron hydrochloride and found to be NK1 receptor antagonist and 5-HT3 receptor antagonist. As an orthopoxvirus VP37 envelope wrapping protein inhibitor, TPOXX **33** was approved for the treatment of smallpox. Krintafel **34** is an 8-aminoquinoline antiparasitic being used to prevent the relapse of malaria caused by parasites. FDA approved Xerava **35** to treat complicated intra-abdominal infections caused by bacteria. It is an antibiotic that binds 30S ribosomal subunit to block protein synthesis.

Xofluza **37** is an antiviral inhibitor of influenza polymerase acidic protein, which is used to treat influenza (flu). Pretomanid **38** is a nitroimidazooxazine antimycobacterial drug to treat lung tuberculosis (TB). It is used to treat TB when other available drugs do not work. Voquezna **40** is composed of three components, such as Vonoprazan, Amoxicillin, and Carithromycin. It acts as a proton pump inhibitor and antimicrobials to treat helicobacter pylori infection. Vivjoa **41** was approved as a 14 α -demethylase inhibitor to treat the recurrent vulvovaginal candidiasis. Structurally, fluorine atoms and/or CF₃ group are directly attached to the aromatic rings in drugs **31-37** and **39-42** (Fig. 4). As we discussed early, fluorine or CF₃ group may be playing an essential role in improving metabolic stability (decrease in clearance) [59–63], decreasing pKa [64–70], increasing the membrane permeability [71–75] and enhancing the binding affinity to the target proteins (improving potency) [76–80]. Interestingly, the OCF₃ group attached to the aromatic ring in **38** (Fig. 4) may increase the metabolic stability because demethylation of OCF₃ is less readily when compared with that of OMe [94].

4. U.S. FDA-Approved Fluorinated CNS Drugs (2018–2022)

Central nervous system disorders include a wide range of diseases, such as schizophrenia, Alzheimer's disease (AD), Parkinson's disease (PD), depression, migraines, insomnia, and many more that are major health issues across the globe in the present time. As per a recent report, CNS disorders has contributed 11.6% of global disability adjusted life years (DALYs) and 16.5% (2nd leading cause) of deaths from all causes [95]. Highly sophisticated protection system of brain makes the CNS research one of most challenging in the drug discovery and development. Excitingly, in the past five years, the CDER of the U.S. FDA approved a total of ten fluorinecontaining drugs **43–52** as therapeutics for the CNS disorders (Fig. 5; Table 3). Mayzent **43** was approved as a selective sphingosine 1-phosphate receptor modulator for the treatment of adults with relapsing forms of multiple sclerosis (RMS), such as clinically isolated syndrome, active secondary progressive disease, and relapsing-remitting disease. Fluorodopa F-18 **44** was approved as a diagnostic agent used in positron emission tomography to detect Parkinsonian Syndromes (PS) in adults [96–99]. Tauvid **49** was another approved drug for use as a diagnostic agent in positron emission tomography to identify the aggregated neurofibrillary tangles (NFTs) in the brain of patients with suspected AD [100–102].

FDA also accepted Reyvow **45**, Ubrelvy **48**, Nurtec ODT **49**, and Qulipta **51** for migraines as 5-HT_{1F} receptor agonist, CGRP receptor antagonist, calcitonin gene-related peptide receptor antagonist, and calcitonin gene-related peptide receptor antagonist, respectively.

Caplyta **46** is a drug used to treat schizophrenia. Dayvigo **47** was approved for the treatment of insomnia as orexin receptor antagonist. Verquvo **52** is a soluble guanylate cyclase stimulator that alleviates the risk of cardiovascular death and hospitalization. The role of fluorine or CF₃ group in drugs **43–52** (Fig. 5) can be explained as per the discussion in sections 2 and 3 above.

5. U.S. FDA-Approved Fluorinated Drugs for Other Diseases (2018–2022)

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutation in the cystic fibrosis trans-membrane conductance regulator (CFTR) gene [103, 104]. It is most commonly found at least 1 out of 3500 births in Caucasia population [105], 1 out of 3000 births in north Europeans, and 1 out of 30000 in Asian Americans [106]. Immune thrombocytopenia (ITP) is a kind of platelet disorder that is caused due to the destruction of platelets by immune system. Low platelet counts lead to easy bleeding and bruising. Endometriosis is a chronic with most common symptoms, such as infertility and pelvic pain [107, 108]. It is a gynecological disorder occurring in around 10% of women of reproductive age [109]. The prime cause of this debilitating disease is the presence of endometrial tissues outside the uterus where the implanted cells secrete multiple cytokines and prostaglandin E2 that obtain an inflammatory response [107, 108]. Rheumatoid arthritis (RA) is a chronic disease affecting joints as well as extra-articular or organs, including kidney, eye, digestive system, heart, lung, skin, and nerve system [110, 111]. Antineutrophil cytoplasm antibody-associated vasculitides are small-vessel vasculitides that include eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis, and microscopic polyangiitis [112–114]. In addition to drugs to combat cancers, infectious diseases, and CNS disorders, the CDER of U.S. FDA approved six drugs **53–58** having fluorine for the treatment of some other diseases as described above (Fig. 6; Table 4). Symdeko **53** and Trikafta **57** were approved to treat cystic fibrosis (CF). Symdeko **53** is a combination of Tezacaftor and Ivacaftor, which functions as a CFTR corrector and a CFTR potentiator [115]. Trikafta **57** has three active ingredients, such as Tezacaftor, Ivacaftor and Elexacaftor that acts as CCFTR corrector, CFTR potentiator, and CFTR corrector [116]. As a SYK inhibitor, Tavalisse **54** was approved to treat chronic immune thrombocytopenia. Orilissa **55** is a drug for moderate to severe pain associated with endometriosis, which acts as a GnRH receptor antagonist [117]. To treat adults with moderately to severely active rheumatoid arthritis, Rinvoq **56** was approved as a JAK inhibitor. Tavneos **58** is a C5a receptor antagonist utilized to treat severe active antineutrophil cytoplasmic autoantibody-associated vasculitis [118]. The critical role of fluorine atoms and/or CF₃ group in drugs **53–58** (Fig. 6) can also be manifested as discussed earlier from the structure-activity/property relationship perspective.

6. Summary and Conclusion

This review has highlighted fluorinated drugs approved by the CDER of U.S. FDA over the past five years (2018–2022). It is noteworthy that 58 out of 247 representing nearly a quarter of the total are fluorine-containing drugs. Each of these drugs has been summarized and briefly discussed based on their therapeutic application areas, such as cancers, infectious diseases, CNS disorders and some other diseases. Despite the great challenge in finding the anticancer drugs given that each kind of cancer requires different specific diagnosis and target-based treatment strategies, FDA approved thirty fluorinated drugs **1–30** to diagnose, mitigate and treat various types of cancers including prostate, melanoma, acute myeloid, philadelphia chromosome-positive chronic myeloid leukemia, lung, breast cancer and so on in the last five years. Among them, Cerianna **19** and Pylarify **26** were approved as diagnostic imaging agents for their use in positron emission tomography to detect breast and prostate

cancer, respectively. Twelve fluorine-containing drugs **31–42** received approval to treat a big array of infectious diseases including HIV, nausea, smallpox, influenza and many more. CNS research is one of the most challenging in the drug discovery and development due to highly sophisticated protection system of brain. Nevertheless, in the past five years, FDA approved ten fluorinated drugs **43–52** as novel therapeutic agents for CNS disorders, such as schizophrenia, insomnia, migraines, and Parkinson's disease. In addition, Fluorodopa F-18 **44** and Tauvid **50** were approved for the diagnosis of Parkinson's disease and Alzheimer's disease. Last but not least, FDA approved six fluorinated drugs **53–58** for other diseases, such as cystic fibrosis, chronic immune thrombocytopenia, endometriosis, rheumatoid arthritis, and severe active antineutrophil cytoplasmic autoantibody-associated vasculitis. In summary, the unique and successful applications of the fluorine and/or fluorine-containing groups may inspire the drug discovery and medicinal chemistry community in both industrial and academic settings to explore the fluorinated molecules in the early rational drug design process.

7. Future Perspectives

The prevalence of fluorine or groups of fluorine atoms or its isotope in the FDA-approved drugs manifests its significant role in the pharmaceutical research in terms of diagnosis and therapeutics. Judicious deployment of fluorine or groups of fluorine atoms in a molecule under investigation may lead to enhanced pharmacological and pharmacokinetic profiles with improved potency, decrease in pKa, higher permeability, decrease in clearance, and conformational constraint [31–34]. Inspired by the outstanding performance, sustainability, and a high pace of approval of fluorinated drugs in the past decade, pharmaceutical companies continued to explore fluorine-containing entities in an expectation to discover new medications to combat deadly diseases. It is noteworthy that FDA granted approval to four fluorine-containing drugs **59–62** within merely three months of 2023 (Fig. 7). FDA approved Rykindo **59** and Jaypirca **60** for the treatment of schizophrenia and mantle cell lymphoma, respectively. Subsequently, Skyclaris **61** received approval for the therapy of Friedrich's Ataxia. In addition, FDA granted approval to Joenja **62** for the treatment of activated phosphoinositide 3-kinase delta syndrome. The approval of these four drugs within such a short period of this year warrants that fluorine or group of fluorine atoms play a pivotal role in the pharmaceutical industry, indicating a great potential in the future trends of drug discovery and development.

During the literature survey, excitingly we came across a number of fluorinated investigational new drugs (INDs) under different phases of clinical trials for the treatment of various human diseases [125]. Some of these INDs with their name (application number), indication, drug mechanism, and phases have been described. There are several fluorinated INDs under clinical trials for the treatment of various types of cancers that are discussed along one by one. BAY 2965501 ([NCT05614102](#)) is the first-in-class diacylglycerol kinase zeta inhibitor (DGKzi), which is being evaluated in phase I for the treatment of advanced solid tumor. BI 907828 ([NCT05372367](#)) is another MDM2 inhibitor in phase I studies to treat solid tumor [119]. MRTX1133 ([NCT05737706](#)) is a potent, selective, and non-covalent KRAS inhibitor [120]. It is in phase I/II evaluation for solid tumor (advanced solid tumor, non-small cell lung cancer, colorectal cancer, and pancreatic adenocarcinoma).

CFT1946 (NCT05668585) is under phase I/II study to characterize the safety, tolerability, and preliminary efficacy as monotherapy and in combination with trametinib in patients with BRAF V600 mutant solid tumors. MRTX 1719 (NCT05245500) is in phase I/II evaluation in solid tumors with MTAP deletion. GB 1211 (NCT05240131) is a galectin-3 inhibitor being tested in phase I for the treatment of non-small cell lung cancer. AZD9833 (NCT04818632) is under investigation in phase I for the treatment of breast cancer. Additionally, BLU-945 (NCT04862780) is another IND in the phase I/II, in the patients with EGFR mutant non-small cell lung cancer. Ziftomenib (NCT04067336) is an inhibitor of menin-MLL(KMT2A), which is in phase I/II clinical studies to treat patients with relapsed or refractory acute myeloid leukemia. Mezigdomide (NCT03989414) is under investigation in the phase I/II clinical trial in participants with relapsed or refractory multiple myeloma and newly diagnosed multiple myeloma. AZD4573 (NCT05140382) is in phase II for multicenter study to assess AZD4573 efficacy and safety as monotherapy or in combination with anti-cancer agents in patients with relapsed/refractory peripheral t-cell lymphoma or classical hodgkin lymphoma. Nirogacestat (NCT05348356) is in phase II clinical trial to learn its effectiveness in ovarian granulosa cell tumors (OvGCTs). Nirogacestat is a γ -secretase inhibitor (GSI), which is hypothesized to decrease the growth and activity of ovarian granulosa tumors. Inavolisib (NCT05306041) is a PI3K Inhibitor, which is under evaluation in phase II for the treatment of HER2-positive breast cancer [121]. Paltusotine (NCT05361668) is in phase II to evaluate the safety, PK, and dose response in subjects with carcinoid syndrome. Emraclidine (CVL-231) (NCT05443724) is a selective M4 receptor PAM, which is currently in phase II clinical trial to evaluate safety and tolerability in adult patients with Schizophrenia [122]. In addition, as a novel GlyT1 inhibitor, BI 425809 (NCT05211947) is under phase III studies to evaluate the long-term safety in the patients with Schizophrenia [123]. MK-0616 (NCT05070390) is a macrocyclic peptide that binds to PCSK9 and inhibits the interaction of PCSK9 with LDL receptors. It is in phase I being tested in participants with moderate renal impairment. Zunsemetinib (NCT05511519) is an investigational oral mitogen-activated protein kinase-activated protein kinase 2 (MK2) inhibitor. Currently, it is in phase II study to investigate the efficacy, safety, tolerability, and PK/PD of ATI-450 versus placebo in patients with moderate to severe psoriatic arthritis. Asundexian (NCT05686070) is an FXIa Inhibitor [124]. It is under investigation in phase III to learn more about asundexian for prevention of ischemic stroke in male and female patients aged 18 years and older who already had such a stroke due to a blood clot that formed outside the heart and travelled to the brain. In the view of above, we anticipate that some of these fluorine containing INDs in different phases of clinical trials will reach to FDA-approval for clinic use.

Collectively, we believe that this concise review may further attract the attention of the drug discovery and medicinal chemistry community in both industrial and academic settings towards the intelligent application of fluorine and fluorine-containing groups in rational drug design to bring more and better medications to the clinic to improve the health and enhance the life expectancy of human beings.

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Declaration of competing interest

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Highlights

- Small molecule FDA-approved fluorinated drugs in the past five years have been reviewed.
- The therapeutic areas of these drugs such as cancers, infections and CNS disorders are classified.
- Drug action targets and mechanisms of fluorinated drugs are provided.
- The attempts to rationalize the presence of fluorination in approved drugs have been made.
- Perspectives for the future of fluorinated drug development are discussed.

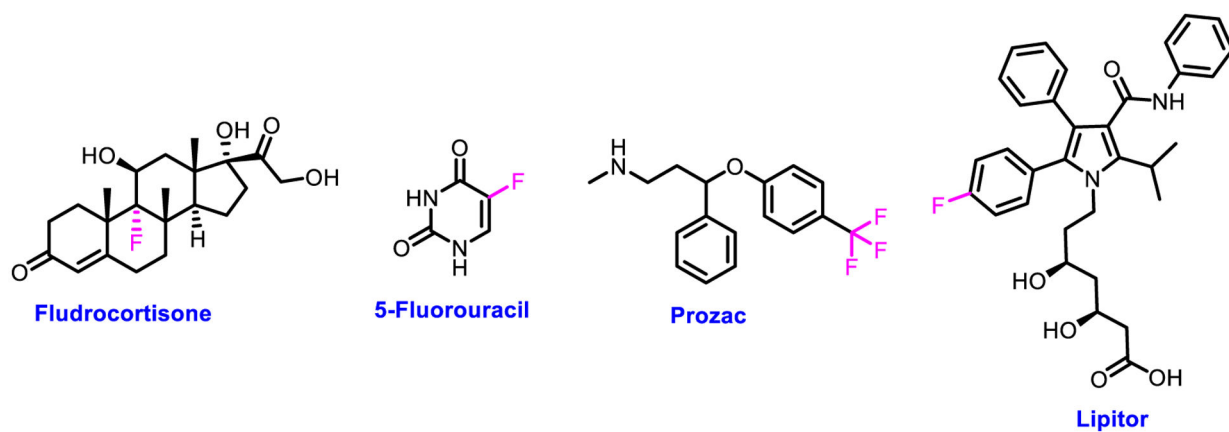


Fig. 1. Structures of selected representative drugs Fludrocortisone, 5-Fluorouracil, Prozac, and Lipitor.

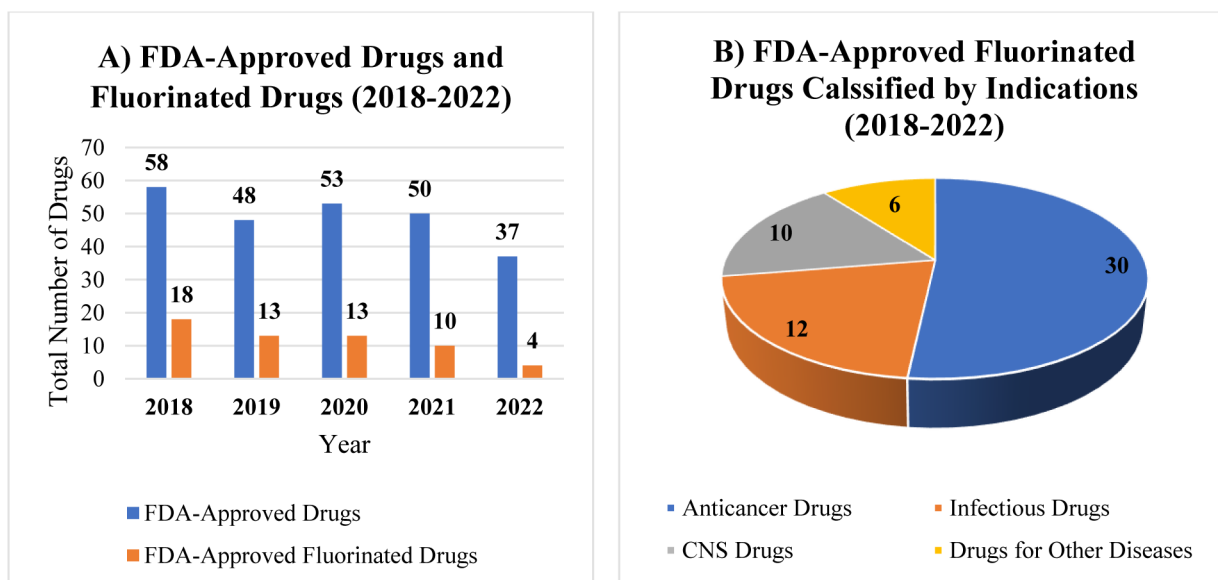


Fig. 2.

A) Bar graph illustration of U.S. FDA-approved total numbers of drugs and fluorinated drugs from 2018 to 2022; **B)** Pie chart presents the numbers of fluorinated drugs approved by FDA from 2018 to 2022 classified by indications such as cancers, CNS disorders, infections, and some other diseases. The source of the data is the U.S. FDA Web site [51].

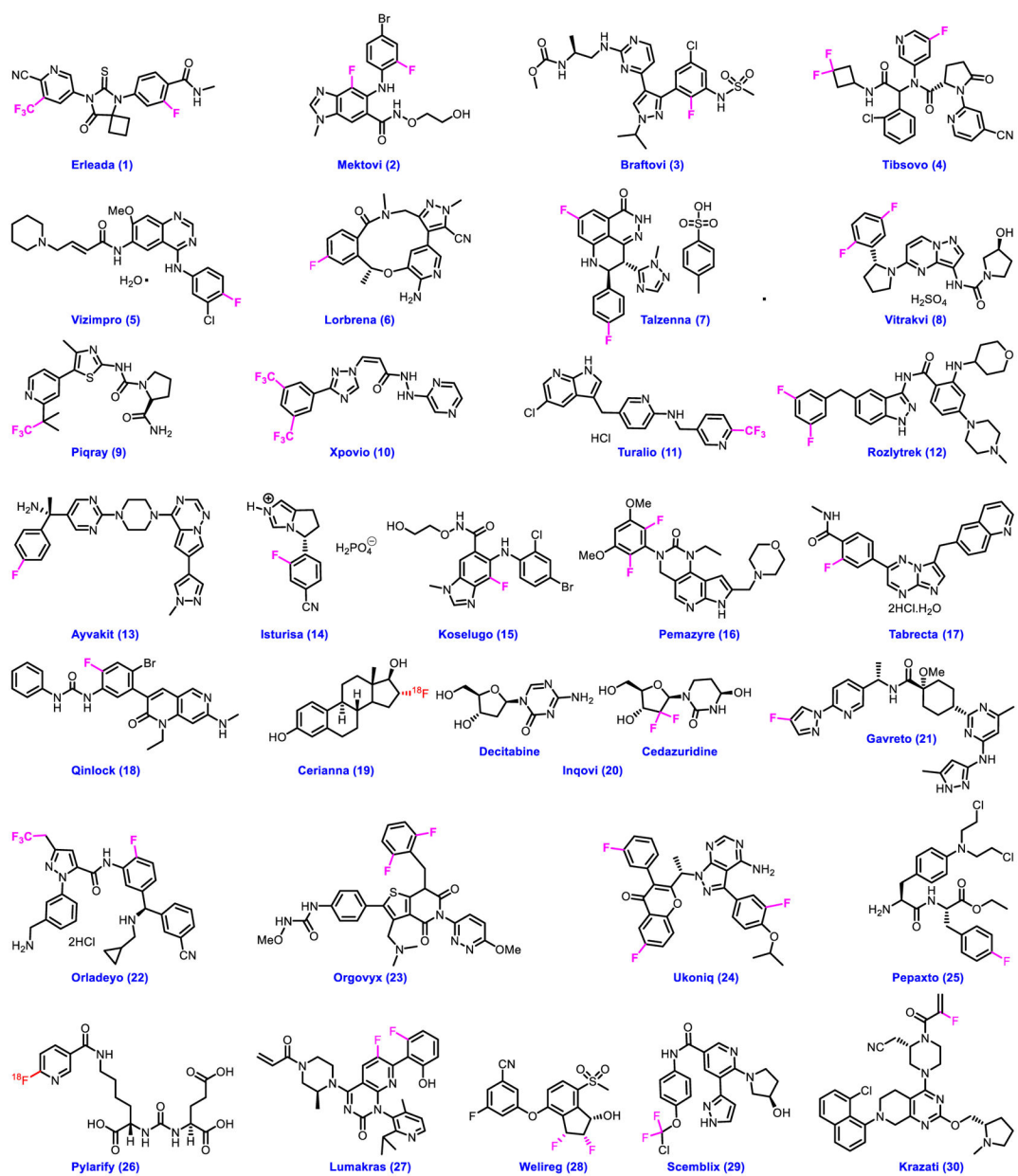


Fig. 3. Chemical structures of U.S. FDA-approved drugs for various types of cancers from 2018 to 2022.

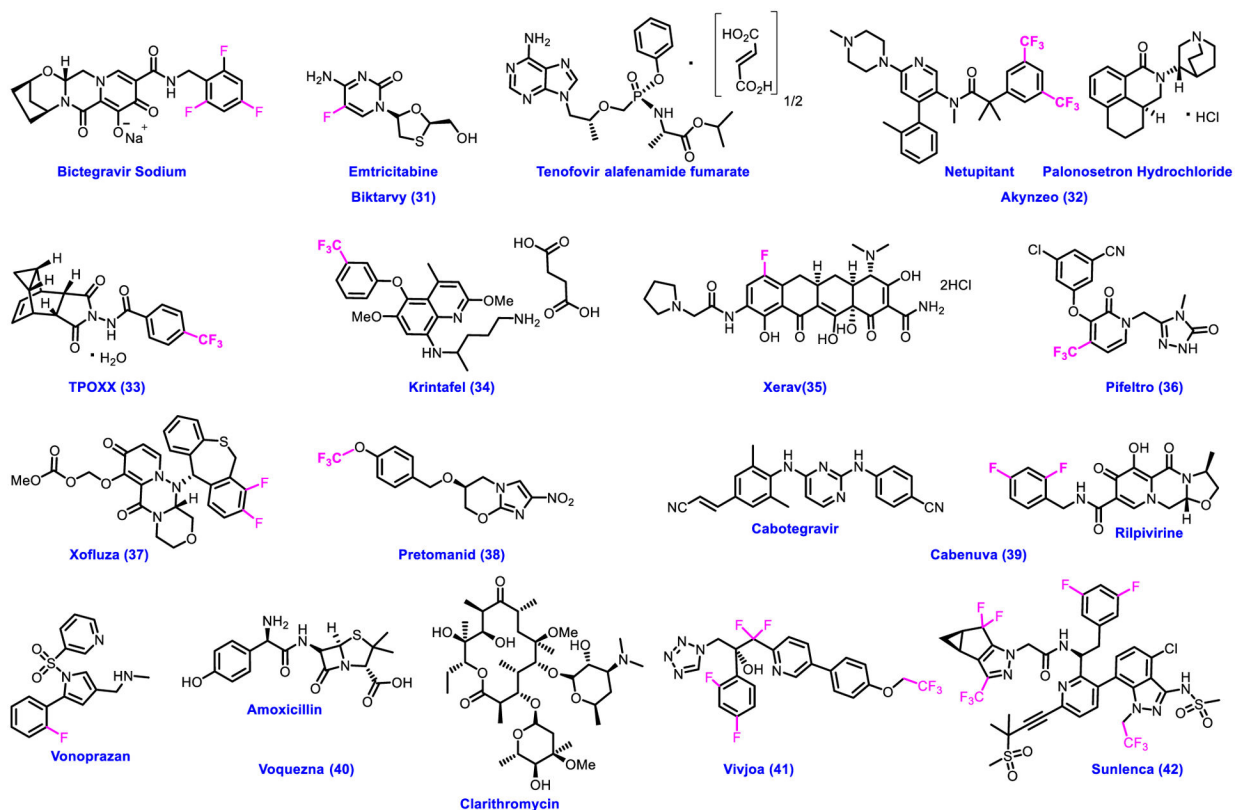


Figure 4.
Chemical structures of U.S. FDA-approved drugs for infectious diseases from 2018 to 2022.

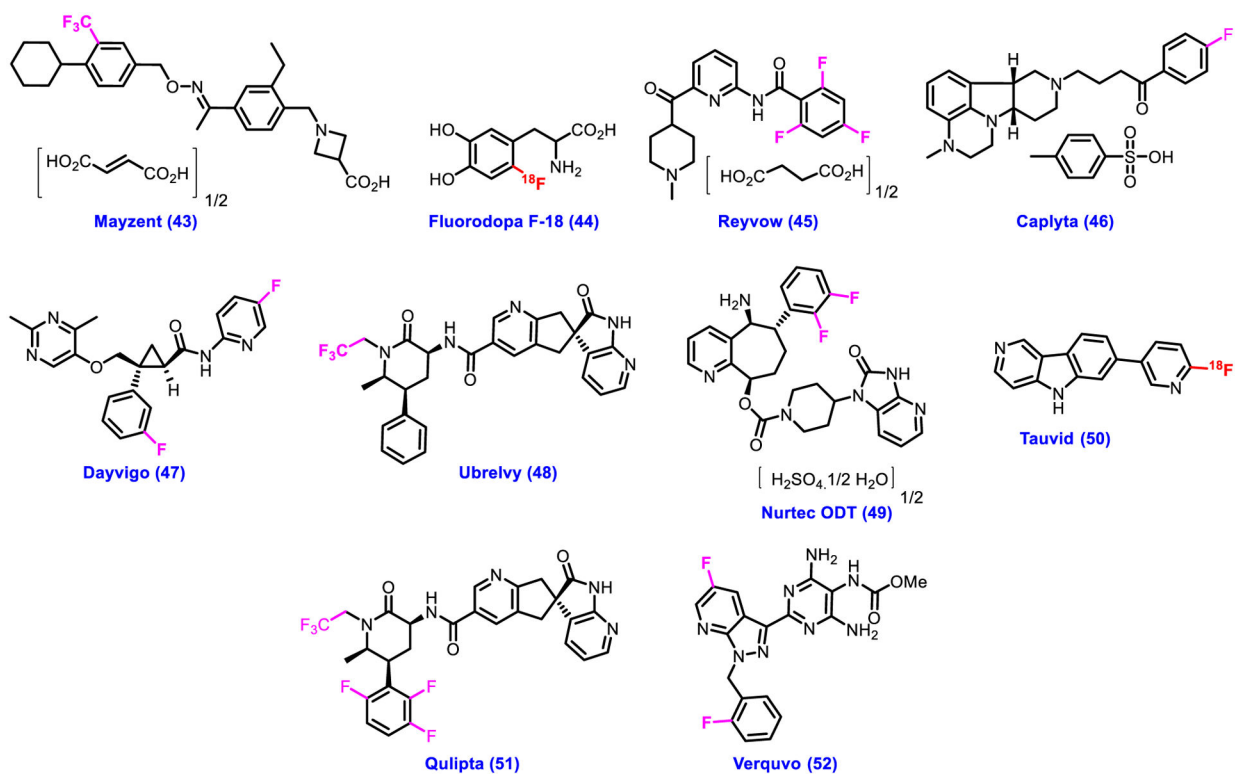


Fig. 5.
Chemical structures of U.S. FDA-approved CNS drugs from 2018 to 2022.

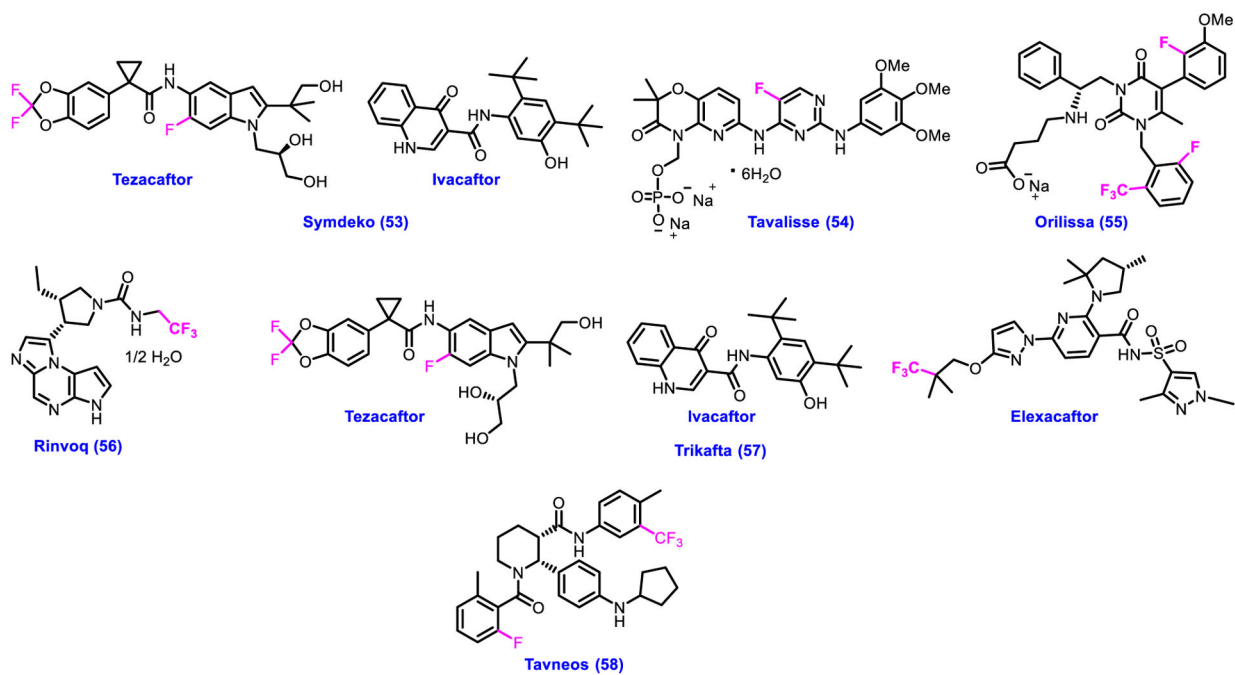
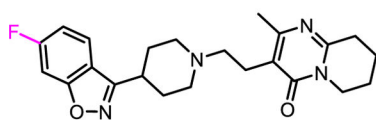
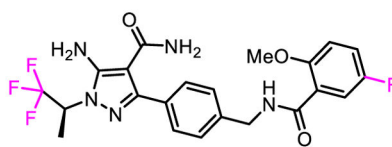


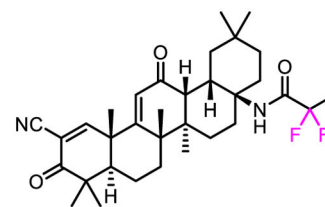
Fig. 6.
Chemical structures of U.S. FDA-approved drugs for other diseases from 2018 to 2022.

**Rykindo (59)**

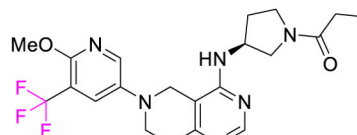
Company: Luye Pharma Group
Active ingredient: Risperidone
Approval Date: January 13, 2023
Indication: Schizophrenia, Bipolar Disorder

**Jaypirca (60)**

Company: Eli Lilly and Company
Active ingredient: Pirtobrutinib
Approval Date: January 27, 2023
Indication: Mantle Cell Lymphoma

**Skyclarys (61)**

Company: Reata Pharmaceuticals, Inc.
Active ingredient: Omaveloxolone
Approval Date: February 28, 2023
Indication: Friedreich's Ataxia

**Joenja (62)**

Company: Pharming
Active ingredient: Leniolisib
Approval Date: March 24, 2023
Indication: Activated phosphoinositide 3-kinase delta syndrome

Fig. 7.
Chemical structures of U.S. FDA-approved fluorinated drugs in the first quarter of 2023.

Table 1.

U.S. FDA-Approved Fluorinated Anti-Cancer Drugs (2018–2022).

Drug	Approval Date	Composition	Company	Indication	Drug Mechanism
Erleada	2/14/2018	Apalutamide	Johnson & Johnson	Prostate cancer	Androgen receptor inhibitor
Mektovi	6/27/2018	Binimetinib	Array BioPharma	BRAF V600E- or V600K- positive metastatic melanoma (in combination with Braftovi)	MEK1/2 inhibitor
Braftovi	6/27/2018	Encorafenib	Array BioPharma	BRAF V600E- or V600K- positive metastatic melanoma (in combination with Mektovi)	BRAF inhibitor
Tibsovo	7/20/2018	Ivosidenib	Agios Pharmaceuticals	Acute myeloid leukemia	IDH1 inhibitor
Vizimpro	9/27/2018	Dacomitinib	Pfizer	Non-small-cell lung cancer	Irreversible EGFR inhibitor
Lorbrena	11/2/2018	Lorlatinib	Pfizer	ALK-positive metastatic nonsmall-cell lung cancer	ALK inhibitor
Talzenna	10/16/2018	Talazoparib	Pfizer	Breast cancer with germline BRCA mutations	PARP inhibitor
Vitrakvi	11/26/2018	Larotrectinib	Loxo Oncology	NTRK gene fusion-positive solid tumors	TRK inhibitor
Piqray	5/24/2019	Alpelisib	Novartis	Breast cancer	PI3Ka inhibitor
Xpovio	7/3/2019	Selinexor	Karyopharm Therapeutics	Multiple myeloma	Nuclear export inhibitor
Turalio	8/2/2019	Pexidartinib	Daiichi Sankyo	Symptomatic tenosynovial giant-cell tumors	CSF1R, KIT, and FLT3-ITD inhibitor
Rozlytrek	8/15/2019	Entrectinib	Roche	Non-small-cell lung cancer whose tumors are ROS1 positive	ROS1 and NTRK inhibitor
Ayvakit	1/9/2020	Avapritinib	Blueprint Medicines	Gastrointestinal-stromal tumor	PDGFRA and KIT inhibitor
Isturisa	3/6/2020	Osilodrostat	Novartis	Cushing's disease in adults	Cortisol synthesis inhibitor
Koselugo	4/10/2020	Selumetinib	AstraZeneca	Neurofibromatosis type 1, a genetic disorder that causes tumors to grow on nerves	MEK1/2 inhibitor
Pemazyre	4/17/2020	Pemigatinib	Incyte	Cholangiocarcinoma, a rare form of cancer that forms in bile ducts	FGFR inhibitor
Tabrecta	5/6/2020	Capmatinib	Novartis	Non-small-cell lung cancer	MET inhibitor
Qinlock	5/15/2020	Ripretinib	Deciphera Pharmaceuticals	Gastrointestinal-stromal tumors	KIT and PDGFRA kinase inhibitor
Cerianna	5/20/2020	Fluoroestradiol F18	Zionexa and Siemens Medical Solutions	Diagnostic imaging agent for certain patients with breast cancer	Radiodiagnostic
Inqovi	7/7/2020	Decitabine and cedazuridine	Taiho Oncology	Myelodysplastic syndromes	Nucleoside metabolic inhibitor and cytidine deaminase inhibitor
Gavreto	9/4/2020	Pralsetinib	Roche/Blueprint Medicines	Non-small-cell lung cancer	RET fusion inhibitor
Orladeyo	12/4/2020	Berotrastat	BioCryst Pharmaceuticals	Prevention of hereditary angioedema	Plasma kallikrein inhibitor
Orgovyx	12/18/2020	Relugolix	Myovant Sciences	Prostate cancer	GnRH receptor antagonist
Ukoniq	2/5/2021	Umbralesib	TG Therapeutics	Marginal zone lymphoma or follicular lymphoma	Kinase inhibitor

Drug	Approval Date	Composition	Company	Indication	Drug Mechanism
Pepaxto	2/26/2021	Melphalan flufenamide	Oncopeptides	Relapsed or refractory multiple myeloma	DNA alkylation
Pylarify	5/26/2021	Piflufolastat F-18	Progenics Pharmaceuticals	Identification of lesions positive for prostate-specific membrane antigen in people with prostate cancer	Binds to malignant prostate cancer cells
Lumakras	5/28/2021	Sotorasib	Amgen	Non-small-cell lung cancer	KRAS G12C inhibitor
Welireg	8/13/2021	Belzutifan	Merck & Co.	Von Hippel-Lindau disease	Hypoxiainducible factor-2 α inhibitor
Scemblix	10/29/2021	Asciminib	Novartis	Philadelphia chromosome- positive chronic myeloid leukemia	Kinase inhibitor
Krazati	12/12/2022	Adagrasib	Mirati Therapeutics	KRAS G12C-mutated nonsmall-cell lung cancer	Irreversible inhibitor of KRAS G12C

The source of the data is the U.S. FDA Web site [51].

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Table 2.

U.S. FDA-Approved Fluorinated Drugs for Infectious Diseases (2018–2022).

Drug	Approval Date	Composition	Company	Indication	Drug Mechanism
Biktarvy	2/7/2018	Bictegravir Sodium, Emtricitabine and Tenofovir alafenamide fumarate	Gilead Sciences	HIV infection	Integrase strand transfer inhibitor, two HIV nucleoside analog reverse transcriptase inhibitors
Akynzeo	4/19/2018	Netupitant and palonosetron	Eisai	Nausea	NK1 receptor antagonist and 5-HT3 receptor antagonist
TPOXX	7/13/2018	Tecovirimat	SigaTechnologies	Smallpox	Orthopoxvirus VP37 envelope wrapping protein inhibitor
Krintafel	7/20/2018	Tafenoquine	GlaxoSmithKline	Malaria relapse prevention	8-aminoquinoline antiparasitic
Xerava	8/27/2018	Eravacycline	Tetraphase Pharmaceuticals	Complicated intraabdominal infections	Antibiotic, binds 30S ribosomal subunit to block protein synthesis
Pifeltro	8/30/2018	Doravirine	Merck & Co.	HIV-1 infection	Antiviral, reverse transcriptase inhibitor
Xofluza	10/24/2018	Baloxavir marboxil	Shionogi, Genentech	Influenza	Antiviral inhibitor of influenza polymerase acidic protein
Pretomanid	8/14/2019	Pretomanid	Global Alliance for TB Drug Development	Treatmentresistant tuberculosis	Nitroimidazooxazine antimycobacterial
Cabenuva	1/21/2021	Cabotegravir and Rilpivirine	ViiV Healthcare	HIV	HIV-1 antiretrovirals
Voquezna	5/3/2022	Vonoprazan, Amoxicillin, and Carithromycin	Phathom Pharmaceuticals	Helicobacter Pylori Infection	Proton pump inhibitor and antimicrobials
Vivjoa	4/26/2022	Oteseconazole	Mycovia Pharmaceuticals	Recurrent vulvovaginal candidiasis	14 α -Demethylase inhibitor
Sunlenca	12/22/2022	Lenacapavir	Gilead Sciences	HIV infections in adults that cannot be successfully treated with other available treatments	HIV-1 antiretroviral agent

The source of the data is the U.S. FDA Web site [51].

Table 3.

U.S. FDA-Approved Fluorinated Drugs for CNS Disorders (2018–2022).

Drug	Approval Date	Composition	Company	Indication	Drug Mechanism
Mayzent	3/26/2019	Siponimod	Novartis	Relapsing forms of multiple sclerosis	Selective sphingosine 1-phosphate receptor modulator
Fluorodopa F-18	10/10/2019	Fluorodopa F- 18	none	Diagnostic for Parkinson's disease	Positron-emission tomography
Reyvow	10/11/20219	Lasmiditan	Eli Lilly and Company	Acute migraines	5-HT1F receptor agonist
Caplyta	12/20/2019	Lumateperone tosylate	Intra-Cellular Therapies	Schizophrenia	Unknown
Dayvigo	12/20/2019	Lemborexant	Eisai	Insomnia	Orexin receptor antagonist
Ubrovelvy	12/23/2019	Ubrogepant	Allergan	Acute migraines	CGRP receptor antagonist
Nurtec ODT	2/27/2020	Rimegepant	Biohaven Pharmaceutical	Migraine	Calcitonin gene-related peptide receptor antagonist
Tauvid	5/28/2020	Flortaucipir F18	Eli Lilly and Company	Alzheimer's disease diagnostic	Radiodiagnostic
Qulipta	9/28/2021	Atogepant	AbbVie	Episodic migraines	Calcitonin gene-related peptide receptor antagonist
Verquvo	1/19/2021	Vericiguat	Merck & Co	Chronic heart failure	Soluble guanylate cyclase stimulator

The source of the data is the U.S. FDA Web site [51].

Table 4.

U.S. FDA-Approved Fluorinated Drugs for Other Diseases (2018–2022).

Drug	Approval Date	Composition	Company	Indication	Drug Mechanism
Symdeko	2/13/2018	Tezacaftor and Ivacaftor	Vertex Pharmaceuticals	Cystic Fibrosis	CFTR corrector and CFTR potentiator
Tavalisse	4/17/2018	Fostamatinib	Rigel Pharmaceuticals	Chronic immune thrombocytopenia	SYK inhibitor
Orilissa	7/23/2018	Elagolix sodium	AbbVie	Endometriosis	GnRH receptor antagonist
Rinvoq	8/16/2019	Upadacitinib	AbbVie	Rheumatoid arthritis	JAK inhibitor
Trikafta	10/21/2019	Tezacaftor, Ivacaftor and Elexacaftor	Vertex Pharmaceuticals	Cystic Fibrosis	CCFTR corrector, CFTR potentiator and CFTR corrector
Tavneos	10/7/2021	Avacopan	ChemoCentryx	Severe active antineutrophil cytoplasmic autoantibody-associated vasculitis	C5a receptor antagonist

The source of the data is the U.S. FDA Web site [51].