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REVIEW

Fluorine-a small magic bullet atom in the drug development: perspective to FDA approved and COVID-19 recommended drugs

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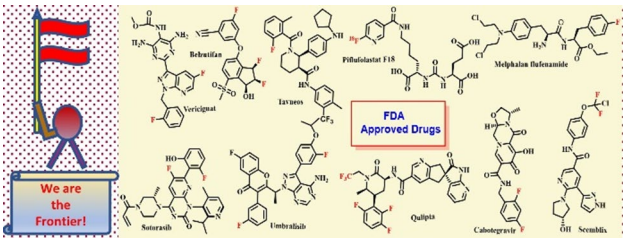
Abstract

During the last twenty years, organic fluorination chemistry established itself as an important tool to get a biologically active compound. This belief can be supported by the fact that every year, we are getting fluorinated drugs in the market in extremely significant numbers. Last year, also ten fluorinated drugs have been approved by FDA and during the COVID-19 pandemic, fluorinated drugs played a very crucial role to control the disease and saved many lives. In this review, we surveyed all ten fluorinated drugs approved by FDA in 2021 and all fluorinated drugs which were directly-indirectly used during the COVID-19 period, and emphasis has been given particularly to their synthesis, medicinal chemistry, and development process. Out of ten approved drugs, one drug pylarify, a radioactive diagnostic agent for cancer was approved for use in positron emission tomography imaging. Also, very briefly outlined the significance of fluorinated drugs through their physical, and chemical properties and their effect on drug development.

Graphical abstract



Keywords Fluorinated drugs · FDA · Synthesis · Drug design and development · PET · Covid-19

Brief Outlook of fluoro Compounds

Over the last twenty years, a strong belief has been grown up that by the introduction of the fluorine atom in the molecule, chances to get better therapeutically useful compounds increases. And, this belief was supported by the fact that every year we are witnessing a growing number of fluorinated drugs which are coming to the market to treat different diseases. At present, approximately 20% of pharmaceuticals and 50% of agrochemicals marketed are fluorinated compounds. Also in the year 2021, out of fifty drugs approved by FDA, ten were fluorinated compounds (Fig. 1a) (U.S. Food Drugs Administrations: Novel Drug Approvals for 2021). Not only the development of drugs but other areas of science and engineering like material science, (Padamata

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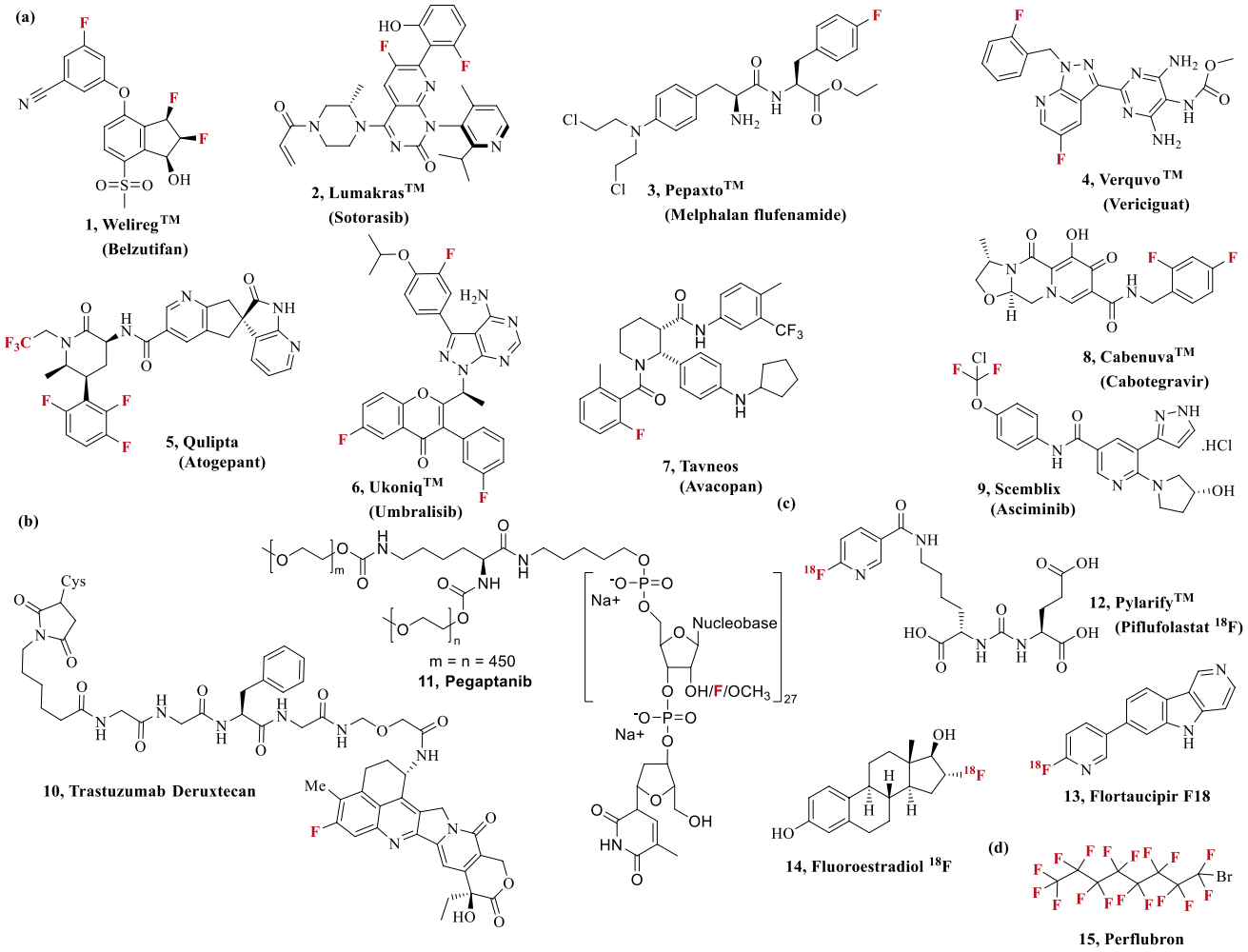


Fig. 1 **a** FDA-approved fluorinated drugs in 2021; **b** FDA-approved fluorinated biologics in 2019; **c** FDA-approved fluorinated drugs for PET imaging in 2021 and 2020; **d** ^{19}F tracer for MRI

et al. 2022; Berger et al. 2011) agrochemicals, (Ogawa et al. 2020; Fujiwara and O'Hagan 2014) polymers, (Peng 2019) catalysis, (Cahard and Bizet 2014), etc. are also getting incredible benefits from fluoro organic compounds. Refrigerants, (Sicard and Baker 2020) liquid crystal application, (Hird 2007; Lopes and Merlo 2022).photovoltaic solar cells (Ouedraogo et al. 2021; Fan et al. 2019), adhesive, coating of textiles dye, and surfactants (Hussain et al. 2022) are a few applications in material science (Inoue et al. 2020).

Fluorinated mineral is very enriched in the universe and the 13th most abundant element in the earth's crust (available as Fluorspar, CaF_2), but mother nature seems not to be very specialized in fluorination chemistry to transform this element to make fluorinated natural products, since up to now we have isolated only twelve natural products those containing fluorine atom and that they too are very simple and the most of them are plant secondary metabolites. In 2003, O'Hagan's isolated the first fluorinating enzyme 'fluorinase' (O'Hagan et al. 2002) which supports the formation of the fluorinated compound in nature (O'Hagan et al. 2002). Although scarcity in nature, numerous fluorinated compounds were synthesized in the research lab, since the incorporation of the fluorine atom in the compound furnishes an unusual and unique property to the compound which is in general not available by using regular other atoms (Yamazaki et al. 2009; Dehnen et al. 2021).

Due to the unique properties of fluorine atom-like small size (1.47 Å), inherent highest electronegativity (3.98 Pauling), robust C–F bond (472 $KJmol^{-1}$), and very high reactivity of F_2 posed a lot of challenges initially to the synthetic chemist to develop a suitable method for the introduction of the fluorine atom in the organic molecules. Also, there is a significant perturbation in the electronic property (physical and chemical) of fluorinated compounds compared to parent compounds due to changes in the energy levels of HOMO and LUMO, so dramatically changing the reactivity

pattern. This creates a problem to understand and manipulate further new analogs. Based on this observation, a proverb become very popular 'A small atom with a big ego' which justifies the unpredictable behavior, and reactivity of fluorinating reagents and compounds. During the last fifty years, many good methodologies and reagents have been developed which are suitable to react with electron-rich, neutral, and deficient substrates. Traditionally, we introduce fluorine atom/s by electrophilic or nucleophilic reagents and a good number of reagents have been developed (Caron 2020). In the last ten years, a growth of interest has been seen in the development of methods of fluorination through thermal (Nonn et al. 2022; Dong and Tsui 2021; Campbell and Ritter 2014) or photochemical radical reactions (Sibi and Landais 2013; Kindt and Heinrich 2014; Li et al. 2013; Cui et al. 2016; Meyer et al. 2018). We have now good methods of regio- and enantioselective introduction of a fluorine atom or fluorine-containing substituent in organic compounds. These developments in fluorination chemistry are now fulfilling the requirement of fluoro-compounds in different areas of science (Britton et al. 2021).

The presence of fluorine has a significant role in the development of drugs (Barnes-Seeman et al. 2014). Both the pharmacokinetics and dynamic properties of the drug are distinctly affected by the introduction of fluorine in the compound. The low metabolic stability of drugs is one of the important concerns during the development of drugs, but this could be easily circumvented by blocking the metabolically labile sites with fluorine substituent (Johnson et al. 2020). Since the C–F bond is very strong and the presence of an electronegative fluorine atom also affects other bond strengths, it becomes comparatively easy to survive for the different enzymes to undergo metabolization and thus prolonging the curative effect (Pal et al. 2022; Shet et al. 2022).

Lipophilicity is another important concern in drug development. For passive transportation, where the drug has to pass through the cell membrane, the drug must be such that it could easily pass the lipid membrane and should not be trapped inside it. For a better drug, moderate lipophilicity is required. Fluorination in most cases provides a better option due to its high lipophilicity and increases the absorption of drugs. So judicial use of fluorine atoms in the molecule increases the bioavailability and increases potency of drugs.

Also, the most important characteristic of fluoro compounds is their electronic effects that change the physicochemical properties. Thus, the pKa value of drugs could be easily adjusted by the introduction of a fluorine atom which thus increases the bioavailability of amine functional group-containing drugs (Morgenthaler et al. 2007). There are significant conformational biases that have a dramatic effect on biological activities. And, also fluorine atoms further add inter and intramolecular sites on fluoro compounds to interact properly, strongly, and selectively with different macromolecules like enzymes and receptors, etc. which further adds the flavor of fluoro-organic compounds (Purser et al. 2008; Zhang 2022).

Last year up to ten fluoro-containing drugs was approved by FDA for the treatment of different diseases. These are belzutifan, **1** (to treat von Hippel-Lindau disease under specific conditions), sotorasib, **2** (for non-small cell lung cancer), melphalan flufenamide, **3** (for refractory or relapsed multiple myeloma), vericiguat, **4** (to alleviate the risk of cardiovascular death and hospitalization for chronic heart failure), atogepant, **5** (qulipta, to prevent episodic migraines), umbralisib, **6** (for marginal zone lymphoma and follicular lymphoma), avacopan, **7** (tavneos, to treat severe active anti-neutrophil cytoplasmic autoantibody-associated vasculitis), cabotegravir and rilpivirine, **8** (co-packaged, for HIV), asciminib, **9** (scemblix, for philadelphia chromosome-positive chronic myeloid leukemia with a disease that meets certain criteria) (Fig. 1a) (U.S. Food Drugs Administrations: Novel Drug Approvals for 2021; Tiz et al. 2022; Hea et al. 2022). These trends were also reported in previous years (Mei et al. 2019a, b).

Further, during the COVID-19 outbreak, a quest of searching for new drugs to treat has been started and here also fluorinated drugs appeared to show a significant contribution. Paxlovid combination of nirmatrelvir and ritonavir was the first oral drug that was recommended for the treatment of mild and moderate COVID-19 symptoms. During the tenure, many vaccines and small molecule drugs have been developed and there were more than ten fluorinated drugs have been recommended (Fig. 2) for the treatment in of COVID-19 on a case-to-case basis.[34] These drugs mostly target either proteins (or RNA) of the virus or host proteins and significantly contribute to the controlling of the COVID-19 pandemic.

It is well-known fact that the recognition abilities of biomacromolecules like receptors, enzymes, DNA, and polysaccharides are highly reliant on the specific conformation of ligands. The change in the conformation of the ligand changes the biological properties. So, in drug development, a biased conformation of the ligand is the essential requirement in the solution state. The presence of different kinds of bonds and substituents causes conformational flexibilities which relieve their different torsional strain and electronic strain. There are well-known examples available in the literature which confirms that the presence of fluoro substituent at a particular position in different therapeutically useful ligands fixes the conformation and alters or enhances the biological activities (Marquez et al. 2004, 1998; Maougal et al. 2013).

Let us consider two representative examples which demonstrate how the presence of fluorine influences the conformation of ligands. Thus, 2′-fluoro ribose nucleoside adopts north conformation (C-3′-endo) but on the other hand

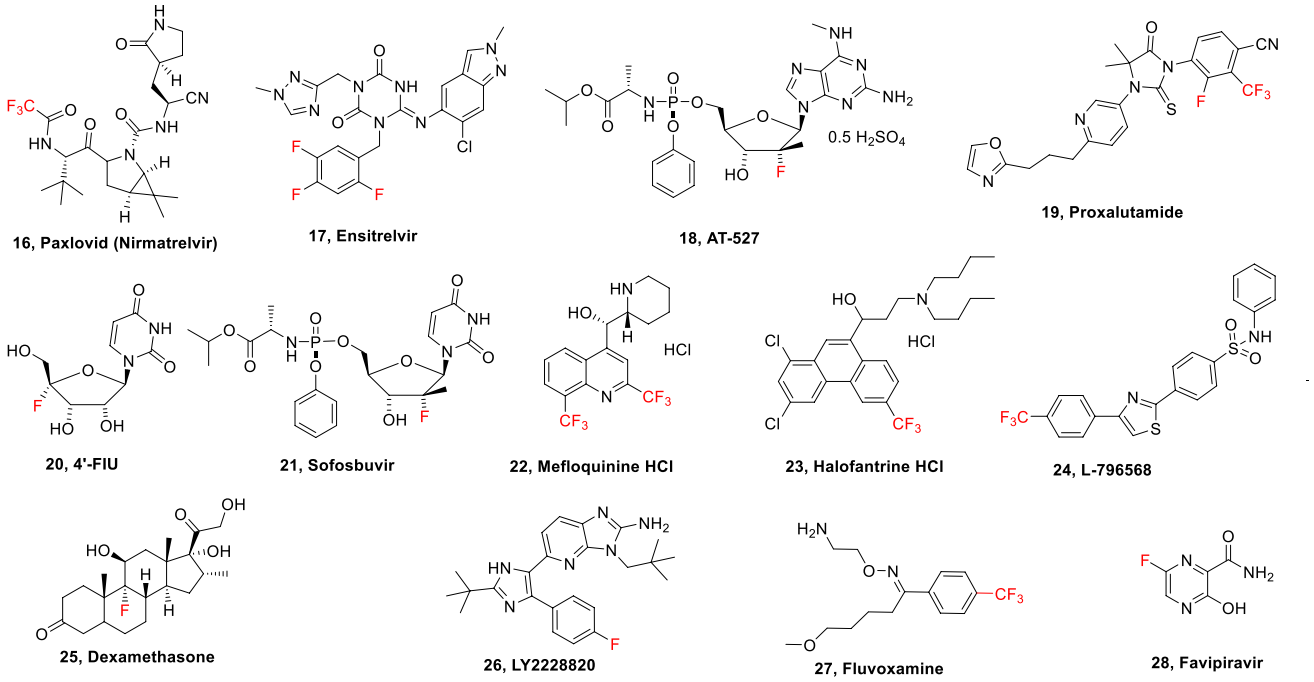


Fig. 2 Representative examples of drugs recommended for the treatment of SARS-CoV-2 during the COVID-19 pandemic

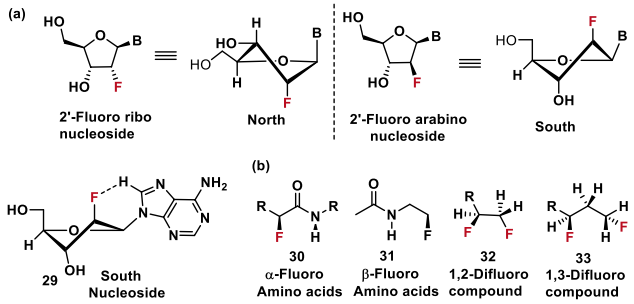


Fig. 3 **a** Different conformations of a nucleoside; **b** Most stable conformations of α-and β-amino acids and 1,2- and 1,3-difluoro compounds

arabinose analog, favors south conformation (C-2′-endo) (Fig. 3a). This was explained by having good proximity and interaction between 8-H and 2′-F of nucleobase and making a strong C–H…..F–C, H-bond (as in **29**) and thus suggested to stabilize the south conformation. But, with 2′-F-ribonucleoside, there was no such kind of interactions and fluorine hydrogen bond (Fig. 3b) (Caron 2020; Nonn et al. 2022).

Similarly, the amide bond is planar and has significant rotational freedom. But, the introduction of a fluorine atom at α-position, (as in **30**) restricts this freedom. Thus, it appeared that.

F–C–C=O prefers antiparallel arrangement or F–C bond always prefers cis to N–H bond. Also, the introduction of fluorine at β -position (as in **31**, Fig. 3b) then F–C and N–H bonds adopt gauche conformation. Further, if there are 1,2-difluoro substituents on open-chain (as in **32**, Fig. 3b) then it always prefers gauche conformation. But, on the other hand, 1,3-difluoro substituents (as in **33**, Fig. 3b) repel each other at gauche conformation, and in this case, staggered conformation dominates (Fig. 3b) (Dong and Tsui 2021).

Bio-pharmaceutical products or biologics (mimics compounds found within the body) like hormones, antibodies, antisense drugs, peptide therapeutics, clotting factors, vaccines, etc. are the fastest growing class of pharmaceuticals. The major challenge in this class of drugs is their in vitro stability and due to that, natural compounds cannot be used. Also, these macromolecules are generally membrane impermeable. So, these large molecules have a problem to reach intercellular targets. These problems could be easily circumvented by the introduction of fluoro substituent in the molecule due to its inherent high lipophilicity and increased metabolic stability. Thus, the positive influence of fluorine substitution has also been used to make different biologics like fluoro analogs of nucleic acid, proteins, and polysaccharides. The presence of fluorine increases nuclease resistance, limits the immune responses, and in some cases favors the in vivo and in vitro biological activity. Recently, fluorinated biologic trastuzumab deruxtecan, 10 (Fig. 1b) was also approved by FDA in 2019 to treat metastatic breast cancer (Campbell and Ritter 2014).

Further, there are extensive research going on to develop fluorinated RNA molecules, since it has a variety of application in nucleic acid-based therapeutics like aptamers, ribozymes, antisense, siRNA, miRNA,

splice-switching, etc (Egli et al. 2011; Patra et al. 2012; El-Khoury and Damha 2021). Fluorination on monomer nucleoside not only enhances the metabolic stability like oxidation of nucleoside base, glycosidic cleavage, and deamination reactions but also provides an extra intermolecular interaction site to stabilize the DNA or RNA duplexes (Guo et al. 2017). After continuous effort, pegaptanib, **11** a fluorinated nucleic acid drug for the treatment of neovascular was approved in 2004 (Ng et al. 2006).

A variety of fluorinated unnatural amino acids has also been synthesized which were further incorporated into protein structures. And it was realized in many cases that, the presence of fluorine atoms stabilizes protein structure against unfolding since fluorinated amino acids are more hydrophobic than their counterpart. Thus, this significant stability was utilized in protein-based therapeutics and vaccines, since this decreases the chances of degradation by protease and improves the potency and bioavailability. Further, to improve the drug delivery of the macromolecules, dendrimers like drugs fluoroamphiphiles and polyethyleneimines have been developed (Zhang et al. 2018).

Fluorine substituent has also been incorporated into carbohydrates for many purposes like to develop inhibitors, (Zephyr et al. 2022; Tysoe and Withers 2014) vaccines, (Dong et al. 2022) antibodies, (Linclau et al. 2020) ^{19}F tracer for MRI, (Chapelin et al. 2018) ^{18}F labeled sugar for PET imaging (Alauddin 2012; Cole et al. 2014), etc (Chandra et al. 2015). Also, the development of fluorinated glycomimetic drugs is a recent advancement (Hevey 2021; Meanwell et al. 2021). The native glycans were found to have limitations like low binding affinities due to their characteristic high polarity and low pharmacokinetics. Fluorination by replacement of the -OH group has been found to solve a few of the above problems (Choi et al. 2012).

In addition to fluorine use in therapeutic, it has a wide application in diagnostic tools. Thus, ^{18}F-containing compounds are used in positron emission tomography (PET). This is mainly used to study biochemical transformations, pharmacokinetics, and dynamics. This is a very good non-invasive diagnostic method to survey living tissue and study its functional process in humans. The ^{18}F isotope has a half-lifetime ($t_{1/2}$) of 110 min, so this tracer has a big advantage as compared to other radionuclides like ^{11}C which has only a half-life of 20 min. Recently, many ^{18}F labeled imaging agents have been developed and regularly used for the detection of various diseases (Zhang et al. 2020). Last year in 2021, pylarify (piflufolastat ^{18}F) **12**, a drug for PET has been approved by FDA to recognize prostate-specific membrane antigen (PSMA) (Fig. 1c) with prostate cancer, and in 2020, flortaucipir ^{18}F, **13** and fluoroestradiol 18F, **14** were approved as a diagnostic agent for patients with Alzheimer's disease and certain patients with breast cancer respectively (Approvals and for 2020, can be found under 2020; Yu et al. 2020).

On the same line, the ^{19}F isotope is regularly used as a non-invasive therapeutic agent in magnetic resonance imaging (Tirotta et al. 2015; Janasik and Krawczyk 2022; Du et al. 2022; Mali et al. 2021). There is a need to administer a low dose of tracer (contrast agent) that should be non-toxic and chemically inert and due to that sensitivity of the nucleus becomes a critical issue. Here, the use of ^{19}F solves all issues since the ^{19}F isotope is 100% natural abundant, its spin is ½, the gyromagnetic ratio is similar to hydrogen (40.08 vs. 42.58) and its sensitivity is 83% of the proton. Also, there is no endogenous movable fluorine, so it has short spin–spin relaxation (T_2) and consequently, it shows an extremely high contrast to noise ratio. Many fluorinated tracers have been developed. The representative example is perflubron (PFOB), **15** (Fig. 1d) which is also approved by FDA in the USA. The ^{19}F MRI has been extensively used to understand the mechanism of recognition behavior of ligands with different macromolecules like proteins, enzymes, receptors, lipids, etc.

Fluorinated drugs approved by FDA

Last year ten fluoro-containing drugs were approved by FDA for the treatment of different diseases. Here, we highlight the structural features of compound, their synthesis and biological activities. We tried to present the seminal work and synthesis of fluorinated compounds.

Scemblix™-ABL001 (asciminib)

Scemblix-ABL001, **9**, developed by Novartis, is the new drug approved by the FDA in October 2021. This drug is recommended for the treatment of philadelphia chromosome-positive chronic myeloid leukemia. This is a chiral compound having one (*R*)-configuration secondary carbon centre and difluorinated moiety. This is a protein kinase inhibitor and the active ingredient of this drug is asciminib.

Chronic myeloid leukemia (CML) is a blood and bone marrow disease that develops due to the generation of too many white blood cells. CML arises from the activity of the BCR-ABL1 protein. The BCR-ABL1 fusion protein, which contains an active ABL1 kinase domain lead to the abnormal activation of numerous signalling pathways that result in the dysregulated differentiation, growth, and survival of leukemic cells. Tyrosine kinase inhibitors (drugs) that act on BCR-ABL1 by targeting its ATP-binding site will transform CML into a chronic manageable disease. Based on this concept, many drugs have been discovered. The first drug imatinib (Gleevec) **34**, was approved in 2001 as a BCR-ABL1 kinase inhibitor for the treatment of CML

and followed by dasatinib **35** (Sprycel, 2006), nilotinib **36** (Tasigna, 2007), etc. were also approved (Fig. 4).

Despite the success of these drugs, the major problem arises development of drug-resistant due to ATP-site mutation, resulting in obstruction to binding the drug properly.

The new drug asciminib (ABL001), was developed by Novartis, which binds to the myristate pocket of BCR-ABL1 and maintains activity (Wylie et al. 2017; Manley and Stiefl 2017; Manley et al. 2020; Schoepfer et al. 2018a). It was observed from the X-ray studies, fluorine atom makes a interaction with the carbonyl carbon of leucine L359 present in the deep pocket of the target Breakpoint Cluster Region-c-abl Oncogene 1 (BCR-ABL1) oncoprotein.

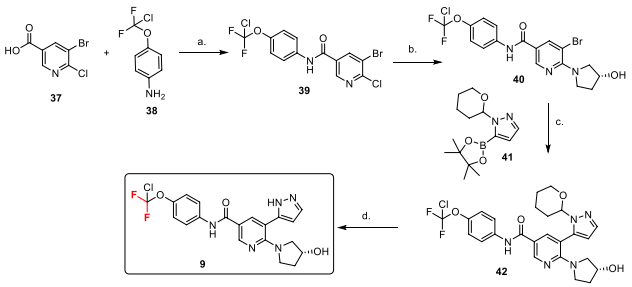
The synthesis route was effectively developed and the strategy started with the conversion of 5-bromo-6-chloronicotinic acid **37** to the corresponding chloride derivative on treatment with thionyl chloride and this was condensed in situ with 4-(chloro-difluoromethoxy)aniline, **38** to the corresponding nicotinamide **39.** Nicotinamide **39** was then treated with enantiomerically pure (*R*)-pyrrolidine-3-ol derivative, which afforded the corresponding substituted bromonicotinamide **40** in very good yield. The standard Suzuki – Miyaura coupling reaction was used to couple the compound **40** with 1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)boronic acid pinacol ester, **41** gave the compound **42**. In the last step, the pyranyl group was cleaved under acidic conditions to get the final compound, **9**. The overall yield of the above four steps reaction was 47% (Scheme 1) (Schoepfer et al. 2018b; Blank et al. 2020).

Qulipta™ (atogepant)

Qulipta, **5** developed by AbbVie, is the new drug approved by FDA in September 2021 for preventive episodic migraines. It is a chiral compound containing multiple chiral centres and tri-fluorinated phenyl moiety. This is a calcitonin gene-related peptide receptor (CGRPR) antagonist. The active ingredient of this drug is atogepant.

Migraine is the most common neurological disorder. During the stock of migraine, there is an increase in the level of the calcitonin gene-related peptide (CGRP) hormone in the cranial blood circulation. And thus, a class of drugs that are antagonist called gepants was developed for the acute treatment of migraine. In this category of the antagonist, olcegepant **43** (Fig. 5) and olcegepant were developed but discontinued due to compound-related adverse effects and difficulty in formulating orally administered olcegepan. In this category, ubrogepant **44**, and Rimegepant **45** (2019, and 2020, respectively) are the recently approved oral drug (Fig. 5). And in 2021, the atogepant **5** was approved by FDA (Leung et al. 2021; Dubowchik et al. 2020; Ailani et al. 2021). The trifluorobenzene moiety in atogepant led to higher affinity ($K_i = 0.015$ nM), compared to unsubstituted derivative ($K_i = 0.067$ nM).

The synthesis of the first part of the molecule started with the fluorinated carboxylic acid compound **46** to introduce the amide, **47**. Thus, carboxylic acid in **46** was manipulated to *N*-methoxy-*N*-methyl amide, **47** through chlorination by use of $POCl_3$ followed by amidation by using the reagent NHMe(OMe).HCl which gave compound which on methylation by use of MeMgCl–$CeCl_3$ afforded compound **48**. Compound **48** was then subjected to alkylation with **49** under *tert*-BuOK and $ZnBr_2$ which gave desired alkylated keto ester compound **50** in good yield. Base catalysed cyclization of compound **50** led to lactam **51** in > 60:1 diastereomeric ratio. This was further epimerized to a deprotonation strategy to desired compound **52**. Thus, compound **53** was treated with *tert*-BuOK, which gave an 85% yield of compound **52**. Trifluoromethyl substituent was introduced by the use of compound **53** in presence of base *tert*-BuOLi/DMPU, which provided the desired compound **54** as a mixture of diastereomers, *N*, *N*'-dialkylated compound. This was



Scheme 1 Synthesis of Asciminib. Reagents and conditions: **a** $SOCl_2$, DMF, toluene, 80 °C then DIPEA,THF, −16 °C to r.t., 77%; **b** DIPEA, (*R*)-pyrrolidin-3-ol, *i*-PrOH, 140 °C, 92%; **c** $Pd(PPh_3)_4$, K_3PO_4, toluene, 110 °C, 77%; **d** TFA, DCM, 10 °C to r.t., 78%

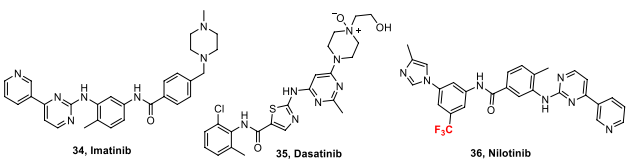


Fig. 4 Representative examples of previously approved drugs for the treatment of CML

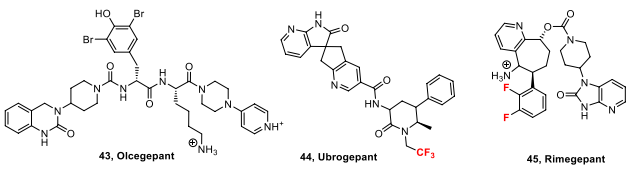


Fig. 5 Ubrogepant and Rimegepant were approved for the treatment of migraine, and Olcegepant showed promising competitive inhibitor CGRPR but was discontinued

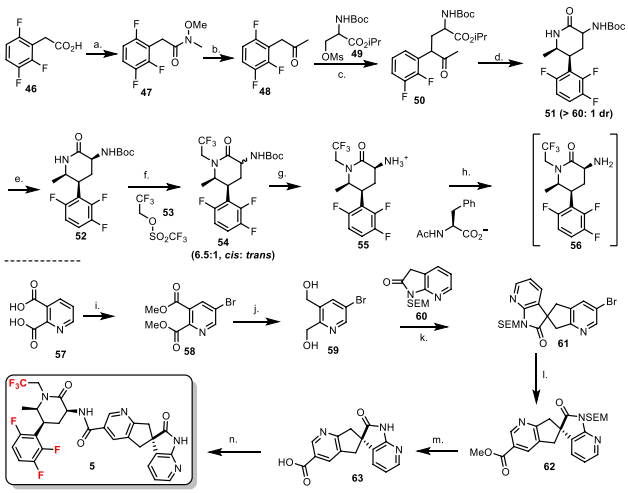
used for the next step for deprotection of the -Boc protecting group followed by treatment with *N*-acetyl *L*-phenylalanine to give salt **55** in very good yield.

The synthesis of the 2nd part of the compound started with the esterification of dicarboxylic acid of pyridine derivative **57**, followed by bromination which gave compound **58**. This was on treatment with reducing agent $NaBH_4$ in presence of $CaCl_2$, furnished diol **59**. Mesylation of diol followed by base-catalyzed alkylation by using SEM-protected azaoxindole **60**, afforded the spirocyclic compound **61**. Esterification by use of palladium-catalysed carbonylation in methanol gave compound **62** which on the chiral resolution provided chiral ester **62** as a single enantiomer. Finally, the removal of SEM protecting group under acidic conditions followed by saponification provided carboxylic acid derivative **63** (Scheme 2).

Finally, both above fragments were coupled through in situ generations of compound **56** from **55** by heating the corresponding salt with K_3PO_4 followed by treatment with coupling agent HOBt and EDC to final compound **5** (Scheme 2) (Belyk et al. 2013).

Tavneos™ (avacopan)

Tavneos, **7** developed by ChemoCentryx, is the new drug approved by FDA in July 2021. This is recommended for the



Scheme 2 Synthesis of Atogepant. Reagents and conditions: **a** i. $POCl_3$, DMF, *i*PAc, ii. NHMe(OMe)HCl, K_2CO_3, water, **b** i. $CeCl_3$, THF, MeMgCl, THF, ii. HCl (2N), MTBE, **c** i. MTBE, $ZnBr_2$, **37** ii. *tert*-BoOLi, 40 °C, **d** DMSO, 50 wt% SEQ, ID No. 1, sodium tetraborate decahydrate, H_2O, isopropyl amine, pH = 10.5, pyridoxal-5-phosphate, 55 °C, **e** *tert*-BuOK, 2-Me-THF, **f** i. THF, DMPU, *tert*-BuOLi, ii. **53**, **g** *p*-toluene sulfonic acid, 55 °C, K_2CO_3, *N*-acetyl *L*-phenylalanine, **h** K_3PO_4, *i*PrAc, **i** i. MeOH, H_2SO_4, ii. Br_2, MeOH, **j** $NaBH_4$, $CaCl_2$, MeOH, **k** i. MsCl, NEt_3, CH_2Cl_2, ii. Cs_2CO_3, EtOH, **60**, **l** i. CO, $Pd(dppf)Cl_2$, NaOAc, MeOH, 80 °C, ii. the chiral resolution, **m** i. HCl, ii. NaOH, MeOH, **n** **56**, HOBt, EDC, MeCN-H_2O, r.t.,

use of the severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis and microscopic polyangiitis) in combination with standard therapy, including glucocorticoids. It is a chiral compound containing multiple chiral centres and contains monofluoro and tri-fluorinated phenyl moiety. This is an inhibitor of the complement C5a receptor. The active ingredient of this drug is avacopan.

Vasculitides are diseases that lead to inflammation that causes changes in the blood vessel walls and thus blood vessel walls get thickened and become narrow. Thus, blood supply gets reduced to tissues and organs, which can result in ischemic end-organ destruction or death. Small vessel vasculitides, which are not immune complexes are characterized by the presence of anti-neutrophil cytoplasm antibody (ANCA) autoantibodies in patients with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). Many times, patients require glucocorticoid (GC), **64,** and other immunosuppressive agents (**65**–**67**) (Fig. 6) to induce remission. However, many of these patients grow numerous complications from GC therapy (Ailani et al. 2021). Avacopan a competitive inhibitor of the C5a receptor 1 (C5aR1) antagonist provides a complement activation pathway in the pathogenesis of ANCA-associated vasculitis.

2-Chloronicotinoyl chloride, **68** was condensed with trifluoromethylated aniline analogue **69** in presence of K_2CO_3 to provide pyridine amide derivative **70**. Compound **70** was further transferred to compound **72** through coupling with boronic acid derivative **71** in presence of palladium catalyst $Pd(PPh_3)_4$. Hydrogenation of compound **72** with PtO_2 under high pressure led to compound **73**. The chiral resolution of compound **73** with di-toluoyl-*L*-tartaric acid provided the desired compound, **74** with proper configuration (2*R*, 3*S*). Condensation of compound **74** with compound **75** led to compound **76** which was treated with 4N HCl and provided free amine **77**. Compound **77** on reductive amination with cyclopentanone finally gave compound **7** (Scheme 3) (Pingchen Fan et al. 2017; Fan et al. 2013).

Welireg™ (belzutifan)

Welireg, **1** developed by Merck, is the new drug approved by the FDA in August 2021. This drug is recommended for the treatment of von Hippel-Lindau disease, which requires therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic

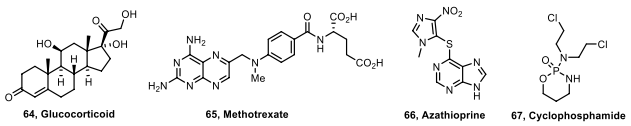
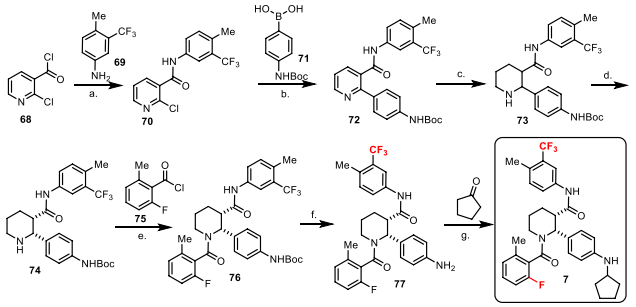
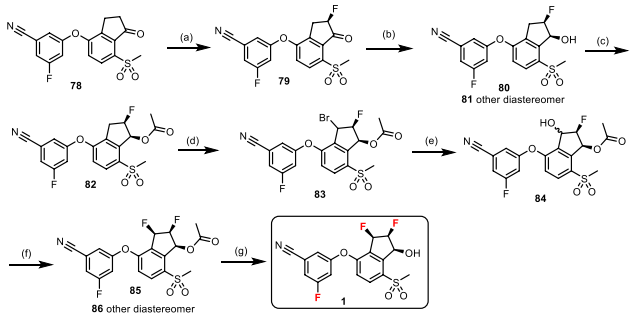


Fig. 6 Commonly used drugs for the treatment of vasculitis



Scheme 3 Synthesis of Avacopan. Reagents and conditions: **a 68**, K_2CO_3, aq. MTBE, 0 °C; **b 71**, 4 mol% $Pd(PPh_3)_4$, PhMe, H_2O, K_2CO_3, 118 °C; **c** 4 mol% PtO_2, 1.4 eq HCl, EtOH, 30–35 psi, H_2; **d** di-toluoyl-*L*-tartaric acid, H_2O, CH_3CN, EtOAc, $NaHCO_3$, H_2O; **e 75**, $^iPr_2NEt$, CH_2Cl_2; **f** 4N HCl/dioxane, CH_2Cl_2; **g** cyclopentanone, $NaB(OAc)_3H$, AcOH, CH_2Cl_2



Scheme 4 Synthesis of Belzutifan. Reagents and conditions: **a** F-TEDA-BF_4, MeOH, reflux; **b** [(*R*,*R*)-Ts- DPEN]RuCl(*p*-cymene), HCO_2H, Et_3N, CH_2Cl_2, 4 °C; **c** Ac_2O, Et_3N, DMAP, CH_2Cl_2, r.t.; **d** NBS, AIBN, 1,2-dichloroethane or carbon tetrachloride, 80 °C; **e** Ag_2CO_3 or $AgClO_4$, 1,2-dimethoxyethane, water; **f** DAST, CH_2Cl_2, − 78 °C to 0 °C; **g** LiOH, THF, H_2O, rt

neuroendocrine tumors (pNET), for those who not requiring immediate surgery. It is a chiral compound containing one F-atom attached to phenyl moiety and two fluorinated chiral centres. This is a hypoxia-inducible factor-2 alpha (HIF-2α) inhibitor. The active ingredient of this drug is belzutifan. von Hippel-Lindau disease (VHL) is a rare genetic disorder that causes tumors and crysts to grow in a certain part of the body. Tumors are non-cancerous but some may be malignant. Most people suffering from this disease develop renal carcinoma during their lifetime. Constant surveillance and endless surgery were the only options to treat VHL, particularly for patients who develop multiple tumors throughout their lives. VHL causes due to the mutation of the von Hippel-Lindau tumor suppressor gene which resides on chromosome 3p25. This gene controls the growth of the cell, but when the gene undergoes mutation then cell growth starts multiplying in uncontrollable ways. von Hippel–Lindau tumor suppressor (pVHL) negatively regulates protein levels of hypoxia-inducible factor-α (HIF-α), which provides fuel to the tumor cell. Thus, loss of pVHL leads to HIF-α accumulation, which contributes to the pathogenesis of von Hippel-Lindau (VHL) disease (Okumura et al. 2017; Deeks 2021; Hasanov 2021).

The strategy started with the keto compound **78** with the introduction of fluoro at α-position as in **79** with F-TEDA-BF_4 in MeOH which was converted into *cis*-fluorohydrin **80** which was readily achieved by the use of the Noyori reduction condition. The dynamic kinetic resolution provided the desired compound in excellent yield in addition to compound **81** as a minor product.

Acetylation of the alcohol **80** to compound **82** followed by benzylic bromination under NBS, AIBN system provided compound **83**. Hydrolysis of bromo to -OH containing compound **84** was achieved by Ag_2CO_3/H_2O. Another fluoro substituent as in **86** was introduced by the replacement of the -OH group by using DAST followed by deprotection gave a diastereomeric mixture (**85**:**86**) which was readily separated by column chromatography to get the desired compound **1** (Scheme 4) (Xu et al. 2019; Wehn et al. 2018).

Cabenuva™ (cabotegravir)

Cabenuva, **8** developed by Janssen Pharmaceutical Companies of Johnson & Johnson, is the new drug approved by the FDA in January 2021. This is recommended for the treatment of HIV. This is a combination of two medications, Healthcare's cabotegravir, and Janssen Pharmaceuticals' rilpivirine. It is a chiral compound containing two F-atoms attached to phenyl moiety. This is an integrase inhibitor. The active ingredient of this drug is cabotegravir.

Human immunodeficiency virus (HIV) attacks the human body's immune system and if not checked then it leads to acquired immunodeficiency syndrome (AIDS) which further threatens the opportunistic infection. Seven mechanism-based concepts and drugs have been developed to fight against HIV viz non-nucleoside reverse transcriptase inhibitors (NNRTIs), nucleoside reverse transcriptase inhibitors (NRTIs), fusion inhibitors, protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), CCR5 antagonists, and post-attachment inhibitors.

HIV first targets the cell in the immune system of the type cluster of differentiation 4 (CD4) cell and transfers its own genetic information to CD4 and consequently CD4 slowly stops working properly. Since the CD4 cell is important, this directs another cell to fight against infection. So, over time, after infection with HIV, the number of CD4 cells declines, and thus the body becomes vulnerable to infection. For this whole mechanism, HIV needs the help of integrase, without this enzyme HIV will not get inside the cell and starts replication. The development of integrase inhibitors is one of the active research fields to treat different kinds of viruses (Engelman 2021). FDA-approved integrase inhibitors for the treatment of HIV like Raltegravir **87** (2007),

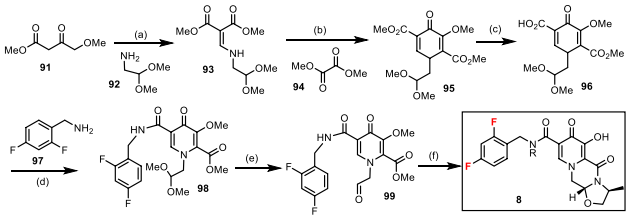
dolutegravir **88** (2013), elvitegravir **89** (combination with other drugs, 2012), and bictegravir **90** (combination with other drugs, 2018) (Fig. 7). Cabenuva is a metal chelator and blocks the binding of host DNA to metal cofactors in the active catalytic site of the integrase (Johns et al. 2013). Cabotegravir is a highly effective integrase inhibitor with a half-life of 54 days, allowing parenteral administration every other month. It has low water solubility, long half-life, high activity, and slow metabolic clearance.β-Keto ester **91** was converted into vinylogous amide **93,** through condensation with compound **92,** which was utilized for cyclization reaction to pyridinone **95** with dimethyl oxalate in the presence of LiOMe. Selective hydrolysis of the C-5 ester group was achieved with LiOH to get compound **96**. All the above four steps were achieved in one pot with a very impressive 61% yield. Now, from here many experiments were done to get the final product with a respectable yield. Finally, the best strategy found was to couple compound **96** with 2,4-difluorobenzylamine, **97** to compound **98** followed by deprotection of the acetal group to aldehydic compound **99**. Compound **99** was subjected to alaninol in the presence of $Mg(OTf)_2$ which underwent smooth ring closure and finally, removal of methyl by the simple addition of NaBr led to desired compound **8** with very good diastereoselectivity (dr, 297:1) (Scheme 5) (Wang et al. 2015).

Fluorine atoms in cabotegravir play an important role in improving the metabolic stability and optimizing the pharmacological parameters, like lipophilicity and permeability.

Pepaxto™ (melphalan flufenamide)

Pepaxto, **3** developed by Oncopeptides, is the new drug approved by the FDA in February 2021 for the treatment of relapsed or refractory multiple myeloma. It is a chiral peptide derivative compound containing mono F-atom attached to phenyl moiety. This is a peptidase-enhanced cytotoxic drug. The active ingredient of this drug is melphalan flufenamide.

Since the discovery of bis(2-chloromethyl) methylamine, or chlormethine (nitrogen mustards) as the first antitumor agent during the 2nd world war, continuous efforts started to develop a better alkylating agent. Nitrogen alkylating



Scheme 5 Synthesis of Cabotegravir. Reagents and conditions: **a** i. DMF-DMA, ii. **92**; **b** LiOMe, 94; **c** LiOH; **d 97**, CDI, then DFBA, **e** HCO_2H; **f** i. l-alaninol, $Mg(OTf)_2$, CH_3CN; ii. NaBr

agents are strong electrophilic and covalently bind with two guanine bases of DNA (N-7 nitrogen) on the same strand and make a cross-link between the DNA chain. This masks the function of that DNA portion to do its work and in this manner, the overall growth of the cell gets hampered. Since nitrogen can react with another nucleophilic base such as with proteins, this lack of selectivity is the cause of side effects. Also, nitrogen mustards can themselves may give rise to secondary malignancies because healthy cells are also affected. To reduce the reactivity of mustard gas, in many varieties, an aromatic ring is placed adjacent to the nitrogen atom, only more reactive N-7 of guanine can react. Thus, for improvement many varieties of nitrogen-based cytotoxic drugs have been developed, particularly peptide-based was the leading ones in drug development. Few of them were also approved by FDA like bis(2-chloromethyl) methylamine **100** (1949), chlorambucil **101** (1957), melphalan **102** (1964), cyclophosphamide **67** (1959), bendamustine **103** (2008), estramustine **104** (1981), uramustine **105** (1962) and ifosfamide **106** (1987) (Fig. 8) (Lehmann and Wennerberg 2021, 2020; Dhillon 2021). The introduction of fluorine substitution in melphalan increases the metabolic stability as compared to unsubstituted analogue.

The crystallized 4-nitro-*L*-phenylalanine **107** was first protected to the Boc-protected group using *di-tert*-butyl decarbonate, **108** in aqueous sodium carbonate to compound **109** which was then coupled with compound **110** with EDC and HOBt to give amide product **111** in good yield. A better yield was achieved by optimizing the reaction condition with the use of 1.03 eq. of HOBt in 10% excess of EDC.

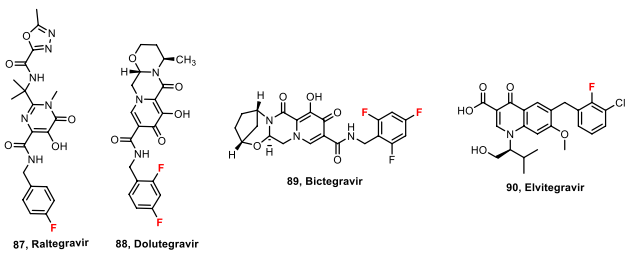


Fig. 7 FDA-approved integrase inhibitors for the treatment of HIV

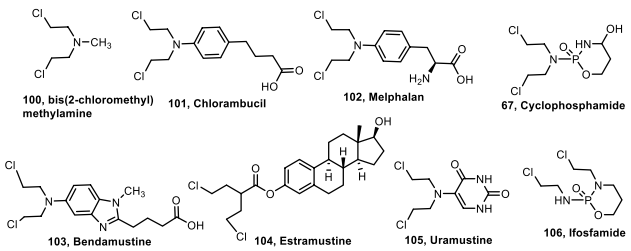
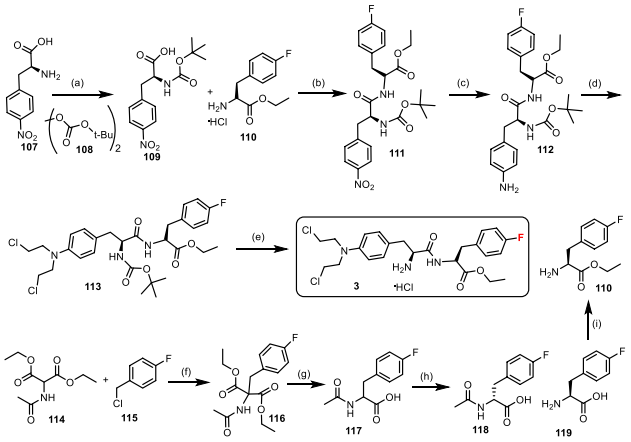


Fig. 8 Nitrogen-based alkylating agents approved by FDA



Scheme 6 Synthesis of Melphalan. Reagents and conditions: **a** $(Boc)_2$, Na_2CO_3; **b** EDC, 1.1 equiv., HOBt, 0.1 equiv., NMM 3.5 equiv., acetone; **c** H_2, Pd/C, EtOH-CH_3CO_2Et, 2 bar, 35–40 °C; **d** $ClCH_2CO_2H$, $ClCH_2CO_2Na$, $BH_3.Me_2S$, 13 equiv., THF, 20–25 °C: **e** HCl in EtOH; **f** NaOEt, EtOH, 60–70 °C; **g** i. KOH, ii. HCl; **h** Amano acylase 2%, pH 8.5, 45–50 °C; **i** $SOCl_2$, EtOH, toluene, 55–65 °C

Hydrogenation of the -NO_2 group in the presence pf Pd/C and a combination of solvents of EtOH-ethyl acetate gave an impressive yield of corresponding amine **112**. Compound **112** was transferred to compound **113** with the addition of reagents $ClCH_2CO_2H$, and $ClCH_2CO_2Na$, followed by the slow addition of $BH_3.Me_2S$. Finally, desired compound **3** was obtained by deprotection of the Boc group followed by salt formation was achieved by treatment with ethanolic HCl.

Starting material **110** was synthesized in a few steps. Thus, compound **114** was treated with compound **115** in presence of NaOEt provided **116** which was hydrolyzed and decarboxylated to yield compound **117** in good yield. Enzymatic resolution with amino acylase yielded the corresponding compound **119** (*S*-configuration). Esterification of compound **119** to desired compound **110** was achieved through the use of $SOCl_2$ in ethanol (Scheme 6) (Hadidi 2022; Gullbo et al. 2003; Wahlstroem 2016).

Lumakras™ (sotorasib)

Lumakras, 2 developed by Amgen, is the new drug approved by the FDA in May 2021. This is recommended for the treatment of non-small cell lung cancer. This drug specifically targets a mutation called G12C present in the protein KRAS which is responsible for various forms of cancer. It is a chiral compound containing two mono F-atoms attached to two phenyls and pyridyl.moieties. This is the first approved targeted therapy for tumors with any KRAS mutation. The active ingredient of this drug is sotorasib.

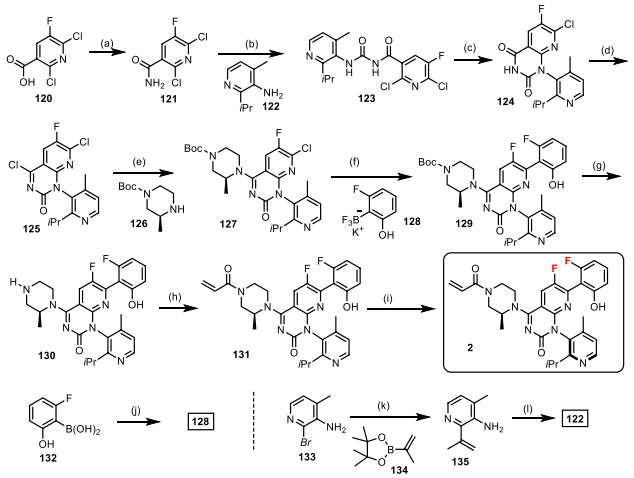
Rat sarcoma viral oncogene homologs (RAS), are small GTPase enzymes that function as cellular signal transducers flipping between an inactive GDP-bound and active GTP-bound state. The RAS gene family has three isoforms HRAS, KRAS, and NRAS. Mutations in the RAS oncogene are the most common activating mutation in human cancer. The majority of RAS-driven cancers are caused by mutations in the KRAS isoform and mutations occurring most frequently in solid tumors such as lung adenocarcinoma, pancreatic ductal carcinoma, and colorectal carcinoma (Blair 2021; Chen et al. 2020; Cox et al. 2014). Initially considered an undruggable protein, becomes druggable due to the identification of cryptic pocket (H95/Y96/Q99) in KRAS. This covalent inhibitor targets the mutant cysteine-12 residue and thus disrupts the signaling pathway (Awad et al. 2021; Canon et al. 2019; Uprety and Adjei 2020; Addeo et al. 2021).

Synthesis of sotorasib started with the compound 2,6-dichloro-5-fluoro-nicotinic acid **120**, which was transformed to corresponding amide **121** through chlorination or carboxyl acid group followed by treatment with ammonium hydroxide solution. Now, this nicotinamide **121** was further treated with oxalyl chloride followed by the addition of compound amine derivative **122**, to give carbamoyl nicotinamide derivative **123**. Treatment of compound **123** with KHMDS gave cyclized product **124** in quantitative yield. Compound **124** on chlorination with $POCl_3$ gave **125** which was condensed with (*S*)-4-Boc-2-methyl piperazine **126** in presence of DIPEA yielded the desired compound **127** in very good yield. Further, compound **127** was coupled with (2-fluoro-6-hydroxyphenyl)potassium trifluoroborate **128**, in presence of palladium(II) catalyst provided coupled compound **129** with a very good yield. Deprotection of the Boc protecting group to **130** followed by treatment with acryloyl chloride gave compound **131**, which on resolution through chiral chromatography gave the desired compound **2** (*R*-configuration) in 43% yield.

Compound **128** was prepared from compound **132** on treatment with KF followed by the addition of tartaric acid. Similarly, compound **122** was obtained from **133** in two steps. Thus, compound **133** on coupling with 2-isopropenylboronic acid, pinacol ester **134** in presence of palladium(II) catalyst introduces the isopropenyl group which on reduction gave compound **122** (Scheme 7) (Lanman et al. 2020).

Verquvo™ (vericiguat)

Verquvo, **4** co-developed by Bayer and Merck, is the new drug approved by the FDA in January 2021 to mitigate the risk of cardiovascular death and hospitalization for chronic heart failure. It is a chiral compound containing two mono F-atoms attached to two phenyl and pyridyl moieties. This is a soluble guanylate cyclase (sGC) stimulator. The active ingredient of this drug is vericiguat.

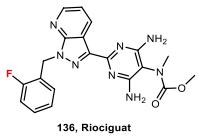


Scheme 7 Synthesis of Sotorasib. Reagents and conditions: **a** i. $(COCl)_2$, CH_2Cl_2, DMF, NH_4OH solution., 0 °C; **b** $(COCl)_2$, THF, DIPEA, THF, 0 °C; **c** KHMDS, THF, rt.; **d** $POCl_3$, DIPEA, 80 °C; **e** **126**, CH_3CN, DIPEA; **f** **128**, [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), CH_2Cl_2, 1,4-dioxane, H_2O, 90 °C; **g** CF_3CO_2H, CH_2Cl_2; **h** CH_2Cl_2, DIPEA, acryloyl chloride, 0 °C; **i** chiral supercritical fluid chromatography (chiralpak IC 30×250 nm, 5 mm, 55% MeOH/CO_2, 120 mL/min); **j** KF, H_2O, CH_3CN, *L*-(+) tartaric acid, THF; **k** [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II), CH_2Cl_2, 134, aq. $NaCO_3$, 1,4-dioxane, 110 °C; **l** H_2, Pd/C, EtOH

Verquvo's working function is novel and different as compared to the existing heart failure treatment method. The NO-sGC-cGMP pathway, which plays an important role in the progression of heart failure and aggravation of disease symptoms. The NO-sGC-cGMP axis belongs to the key signal transduction pathways involved in regulating the cardiovascular system. This drug specifically restores the defective NO-sGC-cGMP pathway. Central to this pathway is soluble guanylate cyclase (sGC), an intracellular enzyme presents in the smooth muscle cells of blood vessels and platelets but also various other cell types like cardiomyocytes. Vericiguat is the first-in-class stimulator of soluble guanylate cyclase (sGC). Riociguat **136** was the first sGC stimulator that was approved by the FDA in 2013 for the treatment of pulmonary arterial hypertension (Fig. 9) (Follmann et al. 2013; Buys et al. 2018; Mittendorf et al. 2009; Markham 2021). This compound contains two F-atoms and one of which present at the meta position of the pyridine ring demonstrate the superior pharmokinetic properties compared to its non-fluorinated analogue.

The strategy started with the activation of 2,2,3,3-tetrafluoropropan-1-ol **137** with trifluoromethanesulfonic acid and treatment with morpholine to get compound **138**. This was methylated to quaternized derivative **139** followed by conversion into fluoroalkene **140** through base promoted elimination reaction. Further reaction of **140** with morpholine and triethylamine yielded compound **141**, which on condensation with compound **142** yielded compound **143**. This compound was converted into amidine derivative **146** in three steps through conversion into amide **144** and nitrile **145**. Pinner-type reaction with sodium methoxide and ammonium chloride delivered the corresponding amidine derivative **146**. This on treatment with phenyldiazenyl substituted malononitrile **147** led to compound **148** which on hydrogenation gave triamine **149**. Finally, selective formylation provided the desired compound **4** (Scheme 8) (Follmann et al. 2017).

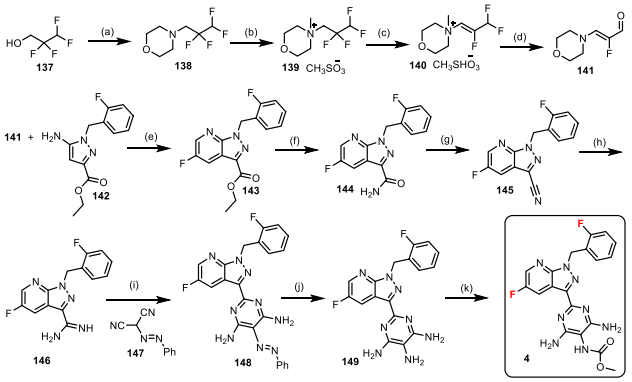
Fig. 9 The first sGC stimulator was approved by the FDA



Ukoniq™ (umbralisib)

Ukoniq, **6** developed by TG Therapeutics, is the new drug approved by FDA in January 2021 for marginal zone lymphoma and follicular lymphoma. It is a chiral compound containing three mono F-atoms attached to three phenyl moieties. This is a kinase inhibitor including PI3K-delta and casein kinase CK1-epsilon. The active ingredient of this drug is umbralisib.

Phosphorylation is an important biochemical reaction in the living system which regulates protein function, transmits signals throughout the cell, and changes the functional group to a more labile functional group which assists the compound to associate with other molecules. It regulates many of the cellular processes including cell cycle, growth, apoptosis, proliferation, differentiation, and signal transduction



Scheme 8 Synthesis of Vericiguat. Reagents and conditions: **a** Tf_2O, 70 °C, then morpholine, 5 °C, then 40 °C; **b** $MeSO_3Me$, 135 °C, then 100 °C; **c** 45% aq NaOH, 50 °C; **d** morpholine, Et_3N, reflux; **e** MsOH, LiCl, EtOH, reflux; **f** formamide, NaOMe, MeOH, EtOH, 95–125 °C; **g** $POCl_3$, sulfolane, 107 °C; **h** NaOMe, NH_4Cl, MeOH, EtOH, 65 °C; **i** **146**, DMF, Et_3N, 100 °C; **j** H_2 (60 bar), 5% Pd/C, DMF, 60 °C; **k** methyl chloroformate, *i*-PrOH, MeOH, then Et_3N, 50 °C

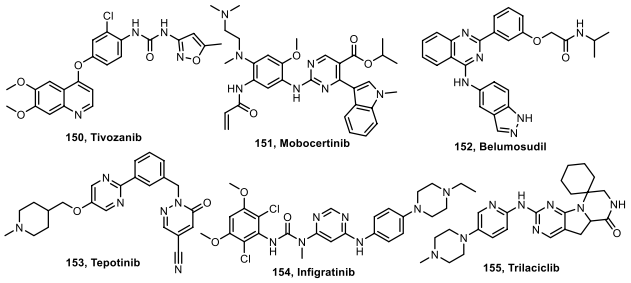


Fig. 10 Kinase inhibitor drugs were approved by the FDA in 2021

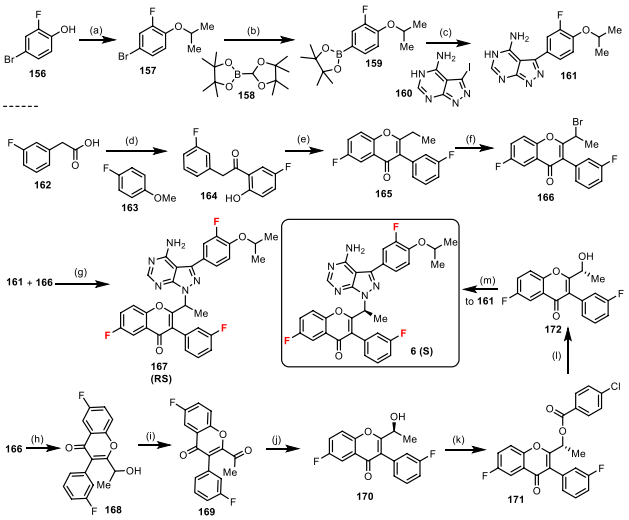
pathways. Kinases help the catalytic transfer of a phosphate group from ATP to specific proteins or small biomolecules, including lipids and carbohydrates. Thus, dysregulation of kinase activity is directly involved in numerous progressive disorders, including cancer. Lipid and protein kinase are the active drug targets for different diseases and till now more than ninety kinase inhibitors have been approved (Ayala-Aguilera et al. 2022). This year also other than umbralisib, seven kinase inhibitors have been approved by FDA in 2021. These are tivozanib **150,** mobocertinib **151,** belumosudil **152**, tepotinib **153**, infigratinib **154**, trilaciclib **155** (Fig. 10). Umbralisib **6** is an inhibitor of phosphoinositide 3-kinase (PI3Kδ) (Feng et al. 2019) and casein kinase 1(CK1ε) (Jiang et al. 2018) which reduces the levels of the transcription factor MYC in lymphoma cells (Dhillon and Keam 2021). Umbralisib shows a better pharmacokinetic profile as compared to the related compounds in this categories since it contains the higher number of fluorine atoms on the aromatic rings.

The first fragment of the final compound was synthesized starting from 4-bromo-3-fluorophenol **156** which was condensed with isopropyl alcohol to **157**. This was then converted into borolane intermediate **159** with the use of compound **158** in presence of a palladium (II) catalyst. Compound **159** was utilized to couple with the iodo derivative of compound **160** to get product **161**. The second fragment was synthesized from fluorophenyl acetic acid **162** to compound **164** through chlorination of carboxylic acid followed by alkylation on aromatic derivative **163**. Treatment with propionic anhydride led to compound **165** which was converted into bromide derivative **166** through benzylic bromination. Now, compounds **161** and **166** were coupled together which provided desired compound **167** as a racemic compound. Enantiomerically pure compound **6** was also synthesized starting from compound **166**. Thus, compound **154** was converted into keto derivative **169** in two steps, followed by enantioselective reduction of the keto group to alcohol **170** (*S*) by use of *R*-alpine borane. Configuration of carbon was inverted as in **171** (R) through reaction with PPh_3 and benzoic acid and then hydrolysis gave compound **172**. This condensation with compound **161** gave desired compound **6** (*S*) in enantiomerically pure form (Scheme 9) (Michael Weiss et al. 2014).

Unfortunately, FDA withdrew approval of this drug to treat as a cancer medicine in June 2022.

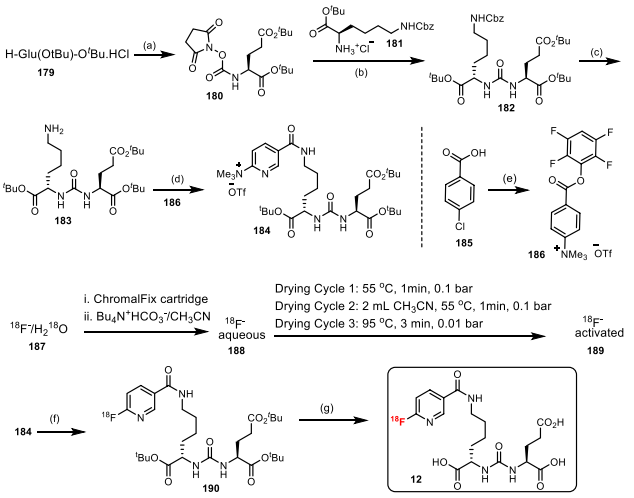
Pylarify™ (Piflufolastat ^{18}F)

Pylarify, **12** developed by Lantheus, is the new drug approved by FDA in January 2021 to identify prostate-specific membrane antigen-positive lesions in prostate cancer. It is a chiral dipeptide compound containing one mono ^{18}F-atom attached to pyridyl moiety. This is a radioactive diagnostic agent, used in positron emission tomography imaging. The active ingredient of this drug is Piflufolastat ^{18}F. Before this approval, many other ^{18}F radioactive diagnostic agents have been approved for different diseases. Important one is ^{18}F-florbetaben **173** (Alzheimer's Disease 2014), ^{18}F-flucicovine 174 (prostate cancer, 2016), ^{18}F-fludeoxyglucose **175** (glucose metabolism, 1999), ^{18}F-florbetapir **176** (Alzheimer's Disease, 2012), ^{18}F-flutemetamol **177** (Alzheimer disease, 2013), ^{18}F-sodium fluoride **178** (osteogenic activity, 2011) (Fig. 11), ^{18}F-flortaucipir **13** (Alzheimer's disease, 2020) and ^{18}F-fluoroestradiol **14** (breast cancer, 2020) (Fig. 1c) (Keam 2021).



Scheme 9 Synthesis of Umbralisib. Reagents and conditions: **a** isopropyl alcohol, THF, Ph_3P, diisopropylazidocarboxylate, 45 °C to reflux; **b** CH_3CO_2K, bis (pinacolato)diboron in dioxane, [1,1'-bis(diphenylphosphino) ferrocene] dichloropalladium(II), CH_2Cl_2, 80 °C; **c 160**, C_2H_5OH, DMF, H_2O, Na_2CO_3, tetrakis (triphenylphosphine)palladium(0), 80 °C; **d** i. CH_2Cl_2, oxychloride in DMF, 0 °C, ii. 151, °C; iii. $AlCl_3$, 0 °C-rt; **e** Et_3N, propionic anhydride, reflux; **f** NBS, CCl_4, 80 °C, AIBN; **g** K_2CO_3, DMF; **h** DMSO, *n*-butanol, 120 °C; **i** DMSO, oxychloride, CH_2Cl_2, Et_3N, −78 °C; **j** *R*-alpine borane, THF, 60 °C; **k** 4-chloro benzoic acid, THF, PPh_3, 45 °C; **l** K_2CO_3, MeOH; **m 161**, THF, PPh_3, diisopropyl azodicarboxylate, 45 °C

The synthesis started with the activation of tert-butyl ester-protected amino acid H-Glu(O^{t}Bu)-O^{t}Bu.HCl, **179** with *N*, *N*′-disuccinimidyl carbonate to give the corresponding ester of carbamic acid **180**. Coupling of this activated ester **180** with µ-benzyloxycarbonyl-*L*-lysine *tert*-butyl ester **181** afforded **182** in 92% yield. Removal of the protecting group in compound **182** using hydrogenation on Pd/C gave provided compound **183** with high chemical yields of 95% (Maresca et al. 2009). Now, salt **184**, which was the starting material for the introduction of radiofluorination was prepared by acylation reaction of compound **183** with activated ester *N*,*N*,*N*-trimethyl- 5-((2,3,5,6-tetrafluorophenoxy) carbonyl)-pyridine- 2-aminium triflate **186**. Compound **186** was prepared from 6-chlorobenzoic acid **185**, this was coupled with 2,3,5,6-tetrafluorophenol followed by treatment with triethylamine and then TMSOTf. ^{18}F labeled radiosynthesis of pylarify was achieved by using an automated reactor set-up in three steps involving drying and activation of cyclotron-generated no-carrier-added [^{18}F]fluoride, followed by incorporation of activated [^{18}F]fluoride into compound **184** via nucleophilic heteroaromatic substitution to **190**, and removal of the tert-butyl protecting groups through treatment with HCl and subsequent HPLC purification to give final product **12** (Scheme 10) (Bouvet et al. 2016). The incorporation of ^{18}F into compound **184** is well documented in the literature (Chen et al. 2011; Ravert et al. 2016; Dornan et al. 2018).



Scheme 10 **Synthesis of Pylarify**. Reagents and conditions: **a** *N*,*N*'-disuccinimidyl carbonate, Et_3N, 15 h, 25 °C; **b** **181**, Et_3N, 25 °C; **c** Pd/C, H_2, MeOH; **d** DIPEA, CH_2Cl_2, 25 °C, then HPLC separation; **e** 2,3,5,6-tetrafluorophenol, DCC, Me_3N, TMSOTf; **f** activated 18F$^-$, 0.5 mL, CH_3CN, 60 °C; **g** 1.0 mL of CH_3CN, ii. 1.5 mL HCl (10 N), 40 °C, 5 min, iii. 2 mL, NaOAc buffer (0.1 M), Ph = 5.8, iv. HPLC separation

Fluorinated drugs recommended during the COVID-19 pandemic

During the last three years, after the spread of corona virus disease (COVID-19), more than 500 million people got infected and approximately 6.5 million people reported death, and till today threat of the virus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) is still present. Focused research to develop medication had started throughout the world and many vaccines and drugs have been investigated and few of them have been approved for emergency use. Out of them, few of the approved drugs were newly developed for the treatment of SARS-CoV-2 and few were repurposed. Initially, 88 antiviral compounds were identified for further investigation and after scrutiny 25 compounds were selected as drug candidates. Overall, there were more than ten fluorinated drugs have been recommended (Fig. 2) for the treatment in of COVID-19. This again signifies the importance of the fluorine atom (Assmus et al. 2022; Ghosh et al. 2022; Li et al. 2022; Veeramani et al. 2023; Chen et al. 2023; Gahbauer et al. 2023; Kneller et al. 2022; Sasaki et al. 2023).

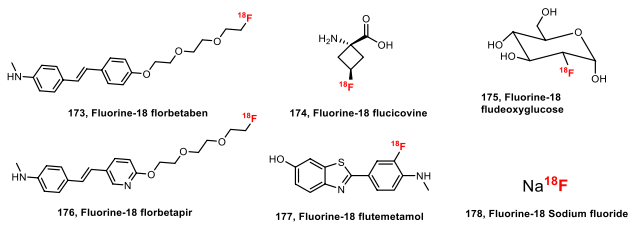


Fig. 11 ^{18}F radioactive diagnostic agents have been approved for different diseases

Nirmatrelvir or PF-07321332 (paxlovid, combination with ritonavir)

Paxlovid, an antiviral drug, developed by Pfizer which is a combination of Nirmatrelvir **16** and ritonavir **191** (Fig. 12) was the first oral drug issued by the FDA for emergency use to treat COVID-19 patients having mild and moderate symptoms. Nirmatrelvir, is a fluorinated drug that contains -CF_3 group and is a protease inhibitor of SARS-CoV-2, it stops the virus replication, and ritonavir which helps to maintain the high concentration of nirmatrelvir for a long period. The half-maximum effective concentration (EC_{50})

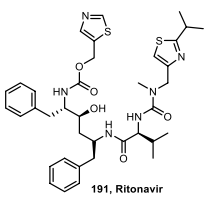


Fig. 12 ^{18}F radioactive diagnostic agents have been approved for different diseases

for nirmatrelvir is very impressive (0.077 µM) (Owen et al. 2021; Marzi et al. 2022; Burki 2022).

The synthesis started with the preparation of two coupling ingredients **196** and **201**. Thus, for the synthesis of **196**, azabicyclo carboxylate **192** was condensed with *N*-Boc protected *L*-valine**193** by use of coupling reagent HATU to compound, which on deprotection gave carboxylic acid compound **194** which further trifluoroacetylation reaction provided compound **196**. On the other hand, *N*-Boc-protected *L*-alaninate **200** was converted to compound **201** on treatment with NH_3 followed by deprotection. Both components were coupled through EDCI to get compound **198** which was converted to desired compound **16** by use of Burgess reagent **199** (Scheme 11) (Marzi et al. 2022).

Ensitrelvir

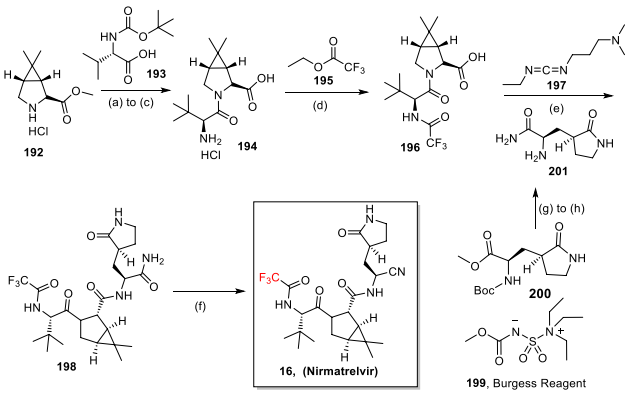
Ensitrelvir, **17** is an antiviral compound developed by Shionogi in partnership with Hokkaido University and is a protease. It works on a range of SARS-CoV-2 variants and coronavirus families. This is the first nonpeptidic, noncovalent, oral $3CL^{pro}$ (3C-like protease) inhibitor. This drug was systematically discovered through proper de novo screening followed by biological screening for nonpeptidic $3CL^{pro}$ inhibitors. This shows a very good preclinical profile with promising antiviral activities to known variants of concern (IC_{50} = 0.013 µM, an antiviral activity of EC_{50} = 0.37 µM), a long elimination half-life in vivo, especially in monkeys and dogs ($t_{1/2} \approx 10$ and 30 h respectively), excellent oral bioavailability, a high metabolic stability of 96% and 88% in human and rat liver microsomes, respectively, and steep efficacy in an in vivo mouse model infected with SARS-CoV-2 (Unoh et al. 2022).

The synthesis started with the alkylation of compound **202** with 1- (bromomethyl)-2,4,5-trifluorobenzene gave compound **203**. The 3-*t*-Bu group in compound **203** was removed to **204** and followed by the introduction of the triazole unit as **205** through an alkylation reaction. Finally, the substitution of the -SEt moiety with the indazole unit finally gave compound **17** (Scheme 12) (Unoh et al. 2022).

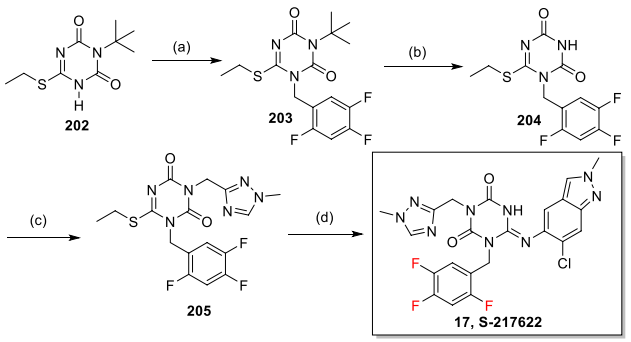
Favipiravir

Favipiravir, **28** a purine nucleic acid analog is an antiviral compound and it shows activity against many types of RNA viruses like influenza A, B, C, arenovirus, bunyavirus, flavivirus, alphavirus, norovirus, as well as the Zika, Usutu, and Ebola viruses (Joshi et al. 2021; Titova and Fedorova 2020; Furuta and Egawa 2000; Liu et al. 2017). Recently, this compound was highlighted during COVID-19 tenure as a potential candidate to treat SARS-CoV-2. Favipiravir is an inhibitor of RNA-dependent RNA polymerase (RdRp) of the SARS-CoV-2 virus first used in Wuhan at the very epicenter of the pandemic for the treatment of patients with mild to moderate COVID-19 disease (Zhang 2022). It is a kind of prodrug and converted into a more active form to its triphosphoribosylated (favipiravir-RTP), and thus selectively inhibiting viral RNA polymerase activity and preventing replication of the viral genome. It is still under clinical trial and more study is needed to be fully approved by FDA.

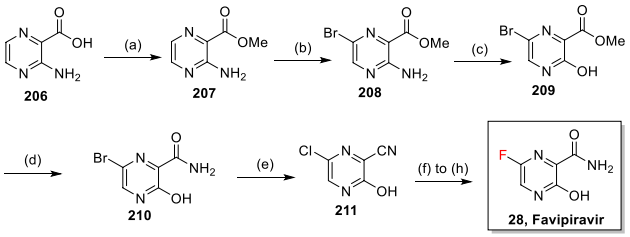
Several methods are available for the synthesis of favipiravir. The first synthesis was reported in 2000 by Furuta et.al (Joshi et al. 2021; Titova and Fedorova 2020; Furuta and Egawa 2000; Liu et al. 2017). synthesized compound with improved yield, starting from compound **206**. Thus, compound **206** was converted to **207** through esterification followed by bromination giving compound methyl 3-amino-6-bromopyrazine-2-carboxylate **208**. This compound was transformed into 3,6-dichloropyrazine-2-carbonitrile **211** in a few steps. *Ipso*-substitution by fluoride ion, followed by amidation and hydrolysis gave compound **28** in 22% over



Scheme 11 Synthesis of Nirmatrelvir. Reagents and conditions: **a** **193**, HATU, DIEA, DMF/MeCN; **b** LiOH, H_2O/THF; **c** 4 M HCl, dioxane, DCM; **d** **195**, DIEA, MeOH; **e** **201**, EDCI (**197**), HOPO, DIEA, MEK; **f** MTBE:EtOAc; **g** NH_3, MeOH; **h** HCl, IPA



Scheme 12 Synthesis of S-217622. Reagents and conditions: **a** 1-(Bromomethyl)-2,4,5-trifluorobenzene, K_2CO_3, MeCN, 80 °C; **b** TFA, rt; **c** 3-(chloromethyl)-1-methyl-1H-1,2,4-triazole hydrochloride, K_2CO_3, DMF, 60 °C; (d) 6-chloro-2-methyl-2H-indazol-5-amine, LHMDS, THF, 0 °C to rt



Scheme 13 Synthesis of Flavipiravir. Reagents and conditions: **a** H_2SO_4, MeOH, 0 °C; **b** NBS, MeCN, rt; **c** H_2SO_4, $NaNO_2$, H_2O rt; **d** $NH_3.H_2O$, rt; **e** $POCl_3$, DIEA, 60 °C to 100 °C; **f** KF, Bu^4NBr, DMSO, 50 °C; **g** K_2CO_3, H_2O_2, DMSO, rt; **h** $NaHCO_3$, H_2O, 50 °C

all yield (Scheme 13) (Joshi et al. 2021; Titova and Fedorova 2020; Furuta and Egawa 2000; Liu et al. 2017).

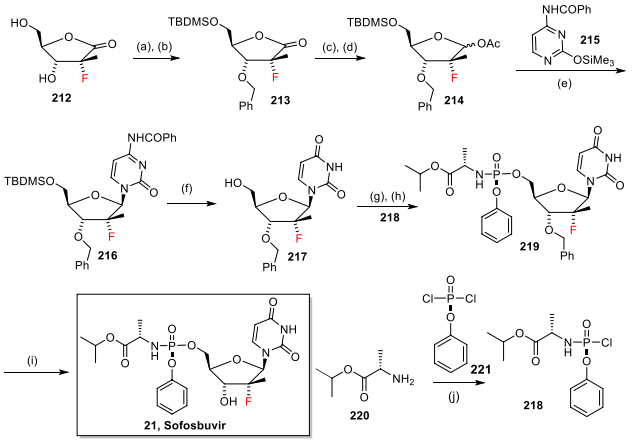
Sofosbuvir

Sofosbuvir, **21** a pro-antiviral drug, was first approved by FDA for the treatment of Hepatitis C Virus (HCV) infections in 2013. This is a fluorinated modified nucleotide and RNA-dependent RNA polymerase (RdRp) inhibitor drug. In 2020, studies of this drug on moderate or severe COVID-19 patients, in combination with daclatasvir showed very encouraging results. 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 (Zhang 2022).

Few methods of synthesis of advanced intermediates **217** of sofosbuvir were reported.[118] Recently, Taddei *et.al.* reported the synthesis by the use of lactone **212**.[118] Thus, compound **212** on the protection of two -OH group provided compound **213**, which on reduction followed by acetylation on generated -OH gave compound **214**. Condensation with silylated cytosine base **215** gave compound **216**. Deprotection of TBDMS followed by treatment with acetic acid provided a uracil analog of compound **217**. Compound **217** was then used for phosphorylation reaction with reagent **218** at 5'OH after activation with *i*-PrMgCl LiCl complex and finally, deprotection of benzyl group with Pd/C, H_2 gave final compound **21**. The phosphorylation reagent chloro(phenoxy) phosphoryl amino)propanoate was prepared in situ from phenyl dichlorophosphate **221** and the isopropyl ester of L-alanine **220** (Scheme 14) (Sadeghi et al. 2020; Jockusch et al. 2020; Simmons et al. 2017; Wang et al. 2009; Cini et al. 2018).

Mefloquinine HCl

Mefloquinine **22** is an antimalarial drug that has been used for both malaria treatment and prophylaxis. It is a fluorinated derivative of hydroxychloroquine. In 2021, Watashi and coworkers identified this as a potential drug for the treatment



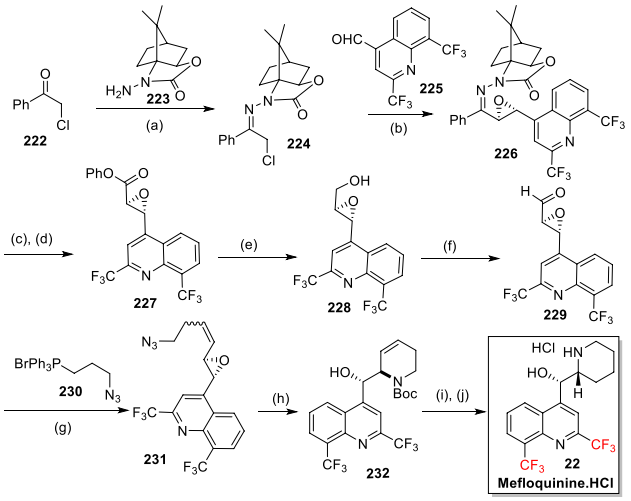
Scheme 14 Synthesis of Sofosbuvir. Reagents and conditions: **a** TBDMSCl, Im, DMF; **b** NaH, BnBr, THF, −10 °C; **c** DIBAL, THF, −78 °C; **d** Ac_2O; **e** **215**, $SnCl_4$; **f** TBAF, THF then CH_3CO_2H, H_2O, 45 °C; **g** *i*PrMgBr, LiCl, THF; **h** **218**; **i** Pd/C, H_2 (1 atm), MeOH; **j** **221**

of COVID-19 disease. It was further observed that fluorination, increases 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 (EC_{50} = 1.28 vs. 1.94 µM; EC_{90} = 2.31 vs. 7.96 µM) (Zhang 2022; Shionoya et al. 2021; Knight et al. 2011).

An asymmetric α-alkylation of ketones using chiral N-amino cyclic carbamate (ACC) auxiliaries was used by Coltart et al. for the synthesis of (+)-enantiomer of mefloquine hydrochloride. Thus, 2-chloroacetophenone **22** was converted to asymmetric hydrazone **224** with ACC auxiliary **223**. A diastereomeric mixture of Darzen's products **226** (92:8) was formed when compound **224** was treated with aldehyde **225**. The major diastereomer of **226** was then subjected to the removal of the chiral auxiliary, followed by oxidation gave compound **227**. This was then reduced and oxidized to the corresponding aldehyde **229**. Aldehyde on reaction with **230** provided azide compound **231** which on reductive cyclization followed by Boc protection gave compound **232**. Olefinic reduction, deprotection of the Boc group, and finally salt formation gave the final compound (+)-mefloquine hydrochloride **22** (Scheme 15) (Shionoya et al. 2021; Knight et al. 2011).

Fluvoxamine

Originally, fluvoxamine **27** is used to treat obsessive–compulsive disorder (OCD). This is a selective serotonin reuptake inhibitor. This drug was repurposed for the treatment of corona patients and recommended for early treatment which showed a notable reduction in the need for hospitalization (Reis et al. 2022).



Scheme 15 Synthesis of Mefloquinine. Reagents and conditions: **a 223**, *p*-TsOH.H_2O, $MgSO_4$, $CHCl_3$, reflux; **b** LDA, THF, **225**; **c** *p*-TsOH.H_2O, 3-pentanone; **d** *m*-CPBA, CH_2Cl_2; **e** $LiAlH_4$, Et_2O, −78 °C; **f** DMP, CH_2Cl_2; **g** KHMDS, THF, −78 °C, **230**; **h** Ph_3P, THF, reflux, then Boc_2O; **i** H_2, Pd/Alumina, EtOAc; **j** TFA, CH_2Cl_2; **i** Et_2O, HCl

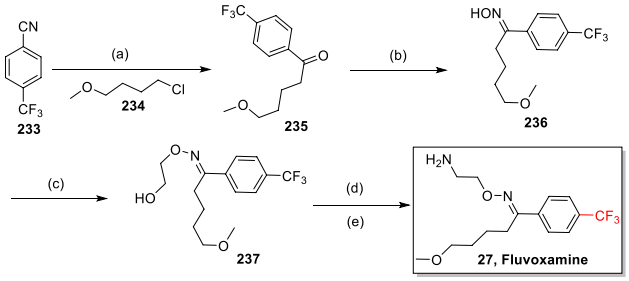
Welle and Claassen proposed three methods for the manufacture of fluvoxamine maleate. In one of the methods, trifluoromethyl benzonitrile **233** was used as a starting material to get the compound 5-methoxy pentane-one **235** derivative of **233**. Hydroxyl amine formation followed by treatment with ethylene oxide led to the corresponding –OH compound **237**. This on conversion to an amine through mesylation gave the desired compound **27** (Scheme 16) (Reis et al. 2022).

4′-Fluorouridine (4'-FIU)

4'-Fluorouridine (4'-FIU) **20** is an antiviral prodrug that acts as a RNA-dependent RNA polymerase and the active component is corresponding triphosphate (4'-FIU-TP). 4'-FIU was recommended for the treatment of SARS-CoV-2 and was found to be effective with a single daily dose. The half-maximum effective concentration (EC_{50}) for nirmatrelvir is very good (0.61 − 1.2 μM) (Sourimant et al. 2022; Owen et al. 1966).

The phosphate derivative of 4'-Fluorouridine **20** was reported by Moffatt *et.al*., starting from compounds, 4',5'-unsaturated uridine **238**. Thus, the activation of compound **238** with.

I_2, lead to anhydro compound **239** which was opened by treatment of AgF and then corresponding -OH was converted to azide **240**. This sluggish reaction was performed under DMF and heating conditions. Further conversation of **240** by treatment with nitrosyl tetrafluoroborate gave fluoro anhydro compound **241**. Acid hydrolysis gave compound

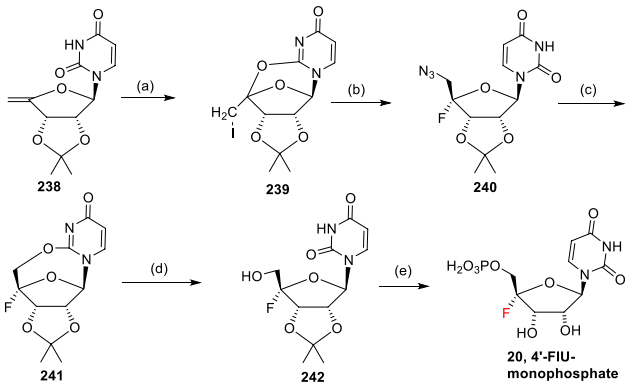


Scheme 16 Synthesis of Fluvoxamine. Reagents and conditions: **a 234**; **b** Na_2CO_3, $NH_2OH.HCl$, MeOH, rt − 50 °C; **c** ethylene oxide; **d** MsCl; **e** NH_3

242. Since it was observed that final deprotection leads to unstable compound 4'-FIU, so compound **242**, was first converted into ethyl phosphate derivative, which after hydrolysis and deprotection gave monophosphate compound **20** (Scheme 17) (Sourimant et al. 2022; Owen et al. 1966).

New entities

This year in 2022 few more fluorinated drugs have been approved by FDA like lenacapavir (sunlenca) **243** for the treatments of HIV, oteseconazole (vivjoa) **244** to reduce the incidence of recurrent vulvovaginal candidiasis (RVVC) in females with a history of RVVC who are not of reproductive potential, vonoprazan (voquezna) **245** to treat Helicobacter pylori infection and adagrasib (krazati) to treat KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer in adults who have received at least one prior systemic therapy **246** (Fig. 13) (U.S. Food & Drug Administration: Novel Drug Approval for 2022). Further, many efforts were made to design and develop fluorinated



Scheme 17 Synthesis of 4'-Fluorouridine. Reagents and conditions: **a** I_2, CH_2Cl_2, AgF; **b** LiN_3, DMF, 105 °C; **c** nitrosyl tetrafluoroborate, CH_3CN, 0 °C-rt; **d** CF_3CO_2H, THF:H_2O; **e** bis(2,2,2-trichloroethyl) phosphate, 2,4,6-triisopropyl benzene sulfonyl chloride, py; **f** 90% HCO_2H: **g** CH_3CO_2H, DMF, H_2O, Zn, AgOAc

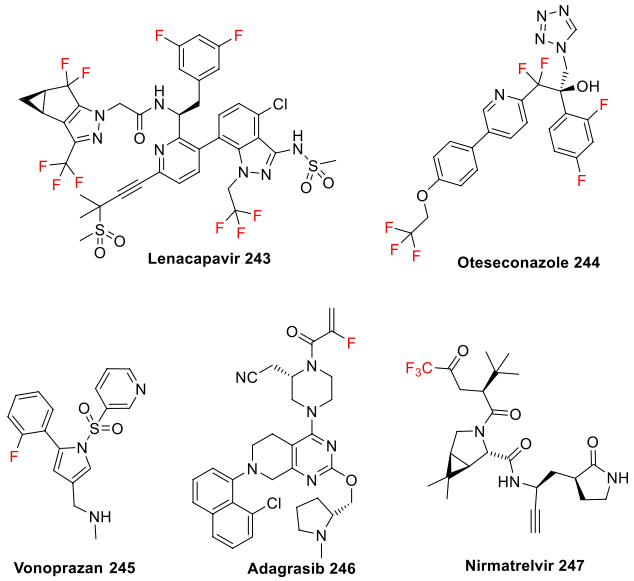


Fig. 13 Fluorinated drugs approved by FDA in 2022 (**243**–**246**)

compounds for the use of coronavirus-2 (SARS-CoV-2). Recently, fluorinated compounds like nirmatrelvir (PF-07321332) **247** etc. (Brewitz et al. 2023; Higashi-Kuwata et al. 2023; Abdallah et al. 2022; Fang et al. 2022).

From the above account, it is clear that a diverse method has been used for the synthesis of fluorinated compounds. In most of cases, fluorinated building blocks, which are either readily prepared or commercially available were used to synthesize the target compounds. Classically, electrophilic and nucleophilic fluorination strategies have been used, but most recently radical fluorination, thermal as well as photochemical approaches have been also developed. Since fluorination on organic compounds generally change the electronic properties, so late-stage fluorination is an important strategy. Further, the incorporation of fluorine into organic compounds is highly sensitive and dependent on the type of substituents, functional group, ring, etc. and thus methods are not always general, so the developments of new methods are always desirable (Campbell and Ritter 2015; Champagne et al. 2015).

Conclusion

Fludrocortisone, Florinef (Florinef acetate) was the first approved fluorinated drug, which was brought to the market in 1954, and after this introduction fluorinated drugs in the market become a regular phenomenon. Over the last thirty years, fluorination on organic compounds stood itself as a tool of choice to increase metabolic stability, potency, and bioavailability. It was found in many cases that chances to become marketable drugs increase by just substitution of a few atoms or functionality to fluorine. So, the introduction of F-atom becomes strategically fruitful in designing new drugs because it minimizes the unsuccess rate. Last year we also witnessed approval of new fluorinated drugs which are actively used in different therapeutic areas like multiple myeloma, HIV, chronic heart failure, lymphoma, chronic myeloid leukemia, migraines, (ANCA)-associated vasculitis, von Hippel-Lindau disease, non-small cell lung cancer etc. All compounds are of the diverse nature which contains multiple chiral centers and multiple fluorine atoms. Also not only drug development but also diagnosis and material science have also been getting tremendous benefits from fluoro compounds. Here, we presented the synthesis, biological properties of all individual approved compounds. Although there is a significant benefit of fluoro-organic compounds, the introduction of F-atom in the organic molecule is still very challenging. Methods are available but unfortunately, methods are not of general type, slight change in the functionalities in the compound, drastically changes the reactivity pattern. In the last ten years, many new methods have been reported particularly, by the use of organometallic reagents, free radical chemistry, and asymmetric transformation, which are fulfilling the gap in the fluorination chemistry. Many mild and stereoselective methods have been developed. Still there are a lot of scopes particularly need to have more fluorinated reagents library, understanding F-effect on bioactivities. And finally, we strongly believe that due to the high benefits, the development of fluorination strategy will continue in the near future and we will see more magical achievements in this field.

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Author Contributions GC carried out the literature search and wrote and finalized the manuscript. DVS revised the manuscript. GM and SP carried out the literature search, and proofread the manuscript.

Declarations

Conflicts of interest The authors declare that there is no conflict of interest.

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