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MODERN PHARMACEUTICAL DRUGS FEATURING ALIPHATIC FLUORINE-CONTAINING GROUPS.

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This review profiles ten marketed pharmaceuticals approved by the US Food and Drug Agency within the last five years that feature aliphatic fluorination – a key structural feature pivotal to their biological activity. These include ivosidenib, developed for the treatment of acute myeloid leukemia and cholangiocarcinoma (bile duct cancer); ubrogepant, approved for the acute treatment of migraines; asciminib, prescribed for the treatment of chronic myeloid leukemia in the chronic phase; omaveloxolone, used in the treatment of Friedreich's ataxia, a rare genetic disorder causing progressive damage to the spinal cord, peripheral nerves, and brain; flurpiridaz (^{18}F), a radioactive diagnostic agent for myocardial perfusion imaging by positron emission tomography; upadacitinib, designed to address several inflammatory and autoimmune conditions, including rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, ulcerative colitis, Crohn's disease, ankylosing spondylitis, and non-radiographic axial spondyloarthritis; tezacaftor, approved for the treatment of cystic fibrosis as an effective remedy; alpelisib, prescribed for the treatment of breast cancer, effectively inhibiting tumor growth and abnormal cell proliferation; pretomanid, used in combination therapies for the treatment of extensively drug-resistant and multi-drug-resistant tuberculosis; and atogepant, approved for the preventive treatment of migraines in adults, targeting both episodic and chronic

migraines. Molecules featuring aliphatic fluorination present challenges due to higher production costs and the complexity of predicting their biological profiles. However, the undeniable medicinal benefits of aliphatic fluorination invigorate this area of research, paving the way for the development of more innovative drugs to enter the pharmaceutical market. Beyond the incorporation of aliphatic fluorine atoms, six of the pharmaceuticals discussed in this review feature residues of amino acids or their derivatives as pivotal structural design elements. Another characteristic shared by all these drugs is their chirality, with each molecule possessing between one and six stereogenic carbons. Special attention should be directed toward the phenomenon of self-disproportionation of enantiomers (SDE), a behavior observed in enantiomerically enriched compounds. The SDE properties of chiral drugs, particularly those containing fluorine and/or amino acid residues, represent a vital public safety concern, necessitating rigorous evaluation of enantiomeric purity. Additionally, caution should be exercised in light of growing public concerns over the potential harmful effects of fluorine on human health. Since fluoride is recognized as the final metabolite of organic fluorinated compounds, patients prescribed fluorine-containing drugs should consult their physicians about non-fluorinated alternatives where available or take steps to limit fluoride exposure from other sources, such as fluoridated water and industrially produced foods treated with fluorinated agrochemicals. Despite these concerns, it remains an undeniable fact that fluorine-containing drugs are indispensable in modern medicine. They provide life-saving treatments, improve quality of life, and drive medical innovation addressing urgent health challenges and laying the foundation for future advancements in healthcare.

Key words: Fluorine, Aliphatic Fluorination, Pharmaceutical Drugs, Drug Design, Synthesis, Chirality, Bioactivity, Self-Disproportionation of Enantiomers (SDE), Public Health Concerns, Human and Environmental Overload with Fluorine.

INTRODUCTION. Pharmaceutical drugs are indispensable components of modern civilization, significantly shaping public health and quality of life. Their impact is multifaceted, beginning with their fundamental role in treating and managing a vast spectrum of diseases, both acute and chronic [1, 2]. Antibiotics, for instance, have revolutionized the management of bacterial infections, saving countless lives, while medications for chronic conditions like diabetes, hypertension, and cardiovascular diseases enable individuals to maintain productivity and longevity [3]. Similarly, advancements in cancer therapies, including chemotherapy and targeted treatments, have drastically improved survival rates [4]. The widespread availability of pharmaceuticals has also contributed to a substantial increase in life expectancy with vaccines eradicating or significantly reducing the incidence of formerly devastating infectious diseases. Beyond disease management, pharmaceuticals enhance quality of life by alleviating pain, controlling symptoms, and improving overall well-being. Medications for mental health disorders, such as depression and anxiety, allow individuals to function ef-

fectively within society, and pain management drugs enable participation in daily activities [5]. Furthermore, pharmaceuticals are essential for modern medical procedures, including surgery, organ transplantation, and intensive care where anesthesia, immunosuppressants, and other drugs are critical. They are also vital for public health initiatives, such as vaccination campaigns and disease control programs, playing a crucial role in preventing the spread of infectious diseases [6]. The pharmaceutical industry's continuous investment in research and development drives the discovery of new drugs and therapies ensuring ongoing progress in addressing emerging health challenges.

Fluorine plays a pivotal role in the design of modern pharmaceuticals, revolutionizing drug development and enhancing therapeutic efficacy. Its unique properties make it an invaluable element in medicinal chemistry [7–11]. Fluorine atoms can block metabolic oxidation sites, preventing drugs from being broken down too quickly in the body, which increases the drug's half-life and ensures sustained therapeutic effects [7, 10, 11]. Its high electronegativity can modulate the electronic properties of a molecule, improving its interaction with biological targets like enzymes or receptors, leading to greater potency and selectivity. Incorporating fluorine can improve a drug's solubility, membrane permeability, and bioavailability ensuring it reaches its intended site of action more effectively. By fine-tuning a molecule's properties, fluorine can help minimize off-target interactions and reduce the likelihood of adverse effects [7–11]. Fluorine isotopes, such as fluorine-18, are widely used in positron emission tomography (PET) imaging aiding in early disease detection and monitoring [12–17]. Fluorine's versatility has made it a cornerstone in the development of life-saving drugs, from cholesterol-lowering agents to cancer therapies, and its continued exploration in pharmaceutical research promises even greater advancements in medicine [18, 19].

The pharmaceutical industry favors aromatic fluorination over aliphatic fluorination due to several key factors that impact drug design and development. Aromatic fluorinated compounds often exhibit enhanced metabolic stability, increased lipophilicity, and improved binding affinity to target proteins, all critical properties for drug candidates. The aromatic ring provides a rigid scaffold that allows for predictable structure–activity relationships, facilitating the optimization of drug properties [20–22]. In contrast, aliphatic fluorination can introduce significant conformational flexibility, making it challenging to predict and control drug–target interactions. Furthermore, the direct introduction of fluorine into aliphatic chains can lead to unpredictable metabolic pathways and potential toxicity issues [23, 24]. The relative ease of synthesizing diverse aromatic fluorinated compounds, coupled with the well-established understanding of their impact on drug properties, makes them more attractive for pharmaceutical applications. Additionally, the ability to fine-tune the electronic and steric properties of aromatic rings through strategic fluorination allows for the optimization of drug–receptor interactions. Finally, the relative stability of aromatic fluorinated compounds compared to their aliphatic counterparts contributes to their suitability for pharmaceutical development where long shelf life and consistent performance are essential.

According to comprehensive surveys spanning the last 25 years [7, 25–32], over 450 fluorine-containing pharmaceuticals have received

US Food and Drug Agency (FDA) approval. This comprehensive data analysis demonstrates that the structural and functional characteristics of fluorinated drugs align closely with those of non-fluorinated pharmaceuticals. Heterocyclic compounds, integral to medicinal chemistry, are present in over 85% of approved drugs. Their diverse biological activities and structural versatility make them indispensable as backbones in drug design [33–40]. Similarly, amino acid-derived compounds play a crucial role in drug development. Data reveal that over 30% of small-molecule drugs incorporate amino acid residues or their derivatives such as amino-alcohols and diamines. Amino acid residues enhance structural diversity and, by introducing chirality, facilitate three-dimensional designs that optimize biological activity [41–54]. Chirality is a critical aspect of drug design with more than 70% of pharmaceutical drugs on the market being chiral [55–60]. One metric unique to fluorinated drugs is the relative proportion of aromatic versus aliphatic fluorination. Surveys indicate a ratio of approximately one aliphatic to five aromatic substitutions in such drugs. As previously mentioned, the incorporation of aliphatic fluorine poses significant synthetic challenges and introduces complexities related to reactivity, chirality, electrostatic effects, steric hindrance, and the chemical properties of the resultant structural modifications [61–65]. Nevertheless, the biological advantages conferred by aliphatic fluorination frequently outstrip these obstacles, solidifying its importance as a strategic and valuable method in drug development.

In this review, we profile ten recently approved pharmaceutical drugs featuring aliphatic fluorination. These include ivosidenib **1** (Fig. 1), marketed under the brand name Tibsovo, which is primarily used for the treatment of acute myeloid leukemia (AML) and cholangiocarcinoma (bile duct cancer). It is specifically effective for patients with a susceptible mutation in the IDH1 gene which is involved in cancer cell growth. Ubrogepant **2**, marketed under the brand name Ubrelvy™, is used for the acute treatment of migraines in adults, with or without aura. It belongs to the class of calcitonin gene-related peptide (CGRP) receptor antagonists which work by blocking CGRP, a protein involved in migraine pain. Asciminib **3**, marketed under the brand name Scemblix®, is used for the treatment of chronic myeloid leukemia (CML) in the chronic phase. It is particularly effective for patients who have resistance or intolerance to at least two prior tyrosine kinase inhibitors or those with the T315I mutation. Asciminib **3** is a first-in-class allosteric inhibitor that specifically targets the myristoyl pocket of the BCR-ABL1 protein offering a novel mechanism of action in CML therapy. Omaveloxolone **4**, marketed under the brand name Skyclarys™, is used for the treatment of Friedreich's ataxia. This rare genetic disorder causes progressive damage to the spinal cord, peripheral nerves, and brain, leading to uncoordinated muscle movement, difficulty walking, and other complications. Omaveloxolone **4** works by activating the Nrf2 pathway, which helps mitigate oxidative stress and improve mitochondrial function thereby addressing key aspects of the disease. Flurpiridaz (^{18}F) **5**, marketed under the brand name Flyrcado®, is a radioactive diagnostic agent used for PET myocardial perfusion imaging. It is indicated for adults with known or suspected coronary artery disease to evaluate myocardial ischemia and infarction. This imaging process helps assess blood flow through the heart mus-

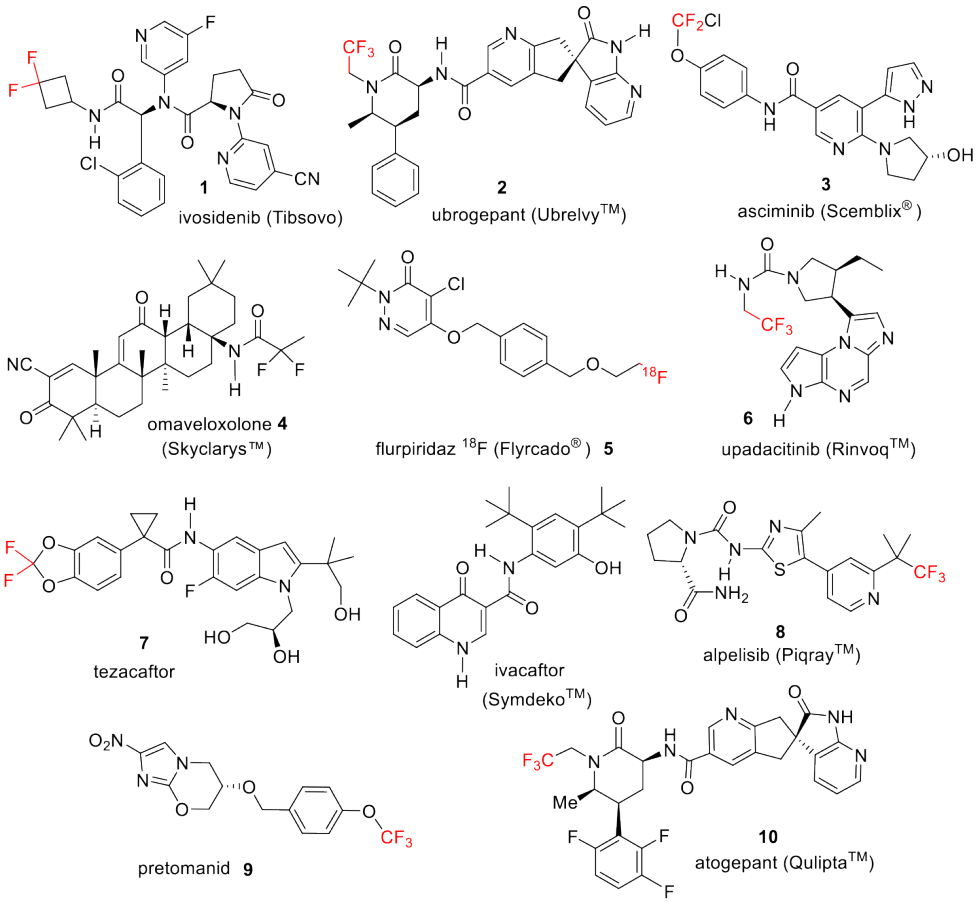


Fig. 1. The structures of marketed pharmaceutical drugs highlighted in this review with aliphatic fluorination as a key structural feature.

cle under rest or stress conditions (pharmacologic or exercise). Upadacitinib **6**, marketed under the brand name Rinvoq™, is used to treat several inflammatory and autoimmune conditions, including rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, ulcerative colitis, Crohn's disease, ankylosing spondylitis, and non-radiographic axial spondyloarthritis. Tezacaftor **7** is used in the treatment of cystic fibrosis CF. It is often combined with other drugs, such as ivacaftor (brand name Symdeko™) or elexacaftor and ivacaftor (brand name Trikafta), to improve the function of the cystic fibrosis transmembrane conductance regulator (CFTR) protein in patients with specific gene mutations such as the F508del mutation. Tezacaftor **7** acts as a corrector helping the CFTR protein fold properly and reach the cell surface thereby enhancing its activity. Alpelisib **8**, marketed under the brand names Piqray™ and Vijoice, is used in the treatment of breast cancer and PIK3CA-Related Overgrowth Spectrum (PROS). Alpelisib **8** is a PI3K-alpha inhibitor targeting the PIK3CA mutation to inhibit tumor growth or abnormal cell proliferation. Pretomanid **9** is used in combination with other medications, such as bedaquiline and linezolid, for the treatment of extensively

drug-resistant tuberculosis (XDR-TB) or multi-drug-resistant tuberculosis (MDR-TB) of the lungs. It is specifically indicated for patients who cannot tolerate or do not respond to other TB treatments. Pretomanid **9** works by inhibiting the growth of the tuberculosis bacteria. Atogepant **10**, marketed under the brand name Qulipta™, is used for the preventive treatment of migraines in adults, including both episodic and chronic migraines. It belongs to the class of CGRP receptor antagonists, which work by blocking CGRP, a protein involved in migraine pain and inflammation. For each drug, we discuss its discovery, mode of biological activity, and detailed synthesis. Whenever possible, we examine the impact of fluorination on the biological profile of the drug.

***Ivosidenib (Tibsovo)* 1**.

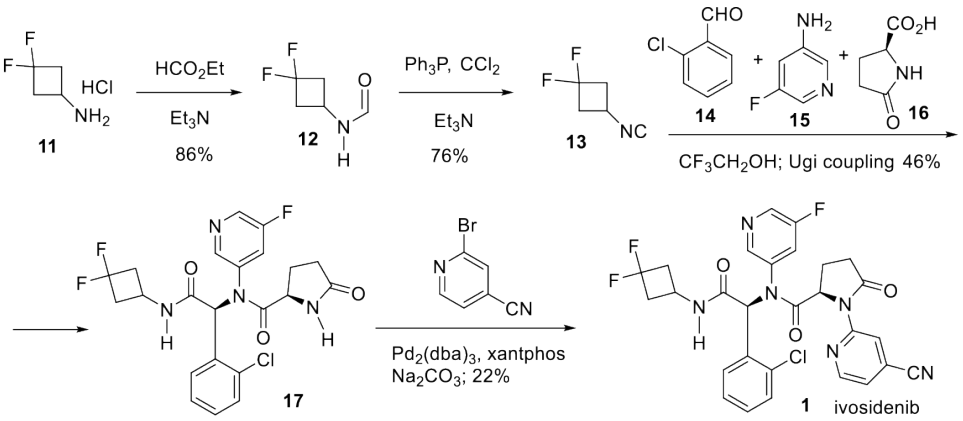
Ivosidenib was approved as an inhibitor of mutated cytosolic isocitrate dehydrogenase (IDH1) for the treatment of patients with relapsed or refractory AML. Following FDA approval, ivosidenib received orphan drug status for glioma in the United States. The drug was developed and licensed by Agios Pharmaceuticals in collaboration with Celgene Corporation and CStone Pharmaceuticals. Ivosidenib **1** has also shown promising potential for the treatment cholangiocarcinoma with an IDH1 mutation [66].

Fluorine plays a fundamental role in the bioactivity of ivosidenib as substitution of fluorine at the 5-position of the pyridine ring imparts nanomolar potency in enzyme and cell-based assays while also enhancing metabolic stability. The introduction of a difluorocyclobutyl moiety contributes to metabolic stability, albeit causing a slight reduction in potency [67].

A multihundred gram-scale synthesis [67, 68] of **1** starts with the preparation of isocyanide **13** from commercially available 3,3-difluorocyclobutan-1-amine hydrochloride (**11**) (Scheme 1). This two-step process starts with the reaction of **11**, trimethylamine, and an excess of ethyl formate at 85 °C. After extraction with ethyl acetate and trituration with hexane, *N*-(3,3-difluorocyclobutyl)formamide (**12**) is isolated in 86% yield. In the second step, formamide **12** is treated with triphenylphosphine and triethylamine under nitrogen at 45 °C. Subsequent purification by chromatography over silica gel provides isocyanide **13** in 76% yield. Alternatively, a synthesis developed by Agios Pharmaceuticals uses the same strategy but derives amine **11** from 3-oxocyclobutanecarboxylic acid. Here, the amino group replaces the carboxylic acid through a Curtius rearrangement of the corresponding acyl azide while fluorine is introduced via the reaction of the keto group with diethylaminosulfur trifluoride. Two protocols were employed differing in the sequence of functionalization [69].

A four-component Ugi coupling reaction [70] involving isocyanide **13**, benzaldehyde **14**, 5-fluoropyridin-amine **15**, and (*S*)-pyroglutamic acid **16** yielded a diastereomeric mixture of the phenyl glycine intermediate **17** in 46% yield after purification by chromatography over silica gel. The final step involved a Buchwald–Hartwig Pd-mediated coupling reaction [71, 72] of compound **17** with 2-bromoisonicotinonitrile resulting in a diastereomeric mixture of compound **1**. Chiral resolution through crystallization provided ivosidenib **1** in 22% isolated yield. While chromatographic purification facilitates isolated yield, it significantly increases the overall cost. In this regard it is worth highlighting the recently developed in-

tegrated simulated moving bed and self-disproportionation of enantiomers (SDE) techniques as a potentially highly efficient method for enantiomer purification [73, 74].



Scheme 1. Synthesis of ivosidenib **1**.

Ubrogepant (Ubrelvy™) 2.

Ubrogepant **2** (Fig. 2), developed by Allergan and licensed from Merck, has received FDA approval for the acute treatment of migraines. Employing a similar structural design of cyclic α,δ-diamino acid and a chiral spirotetracyclic moiety, Merck successfully synthesized several non-fluorinated compounds, e.g. **18**, **19**, as piperidinone carboxamide azaindane CGRP receptor antagonists [75]. The treatment of migraines and CGRP receptor antagonists target the CGRP pathway which plays a crucial role in migraine pathophysiology. CGRP is a neuropeptide involved in vasodilation and pain transmission and its overactivity is associated with migraine attacks. CGRP receptor antagonists, such as piperidinone carboxamide azaindane derivatives, work by blocking the CGRP receptor thereby preventing the peptide's effects and alleviating migraine symptoms. This mechanism aligns with the bioactivity of other migraine treatments that target the CGRP pathway, including monoclonal antibodies and small-molecule antagonists like ubrogepant **2** and atogepant **10** [76–78].

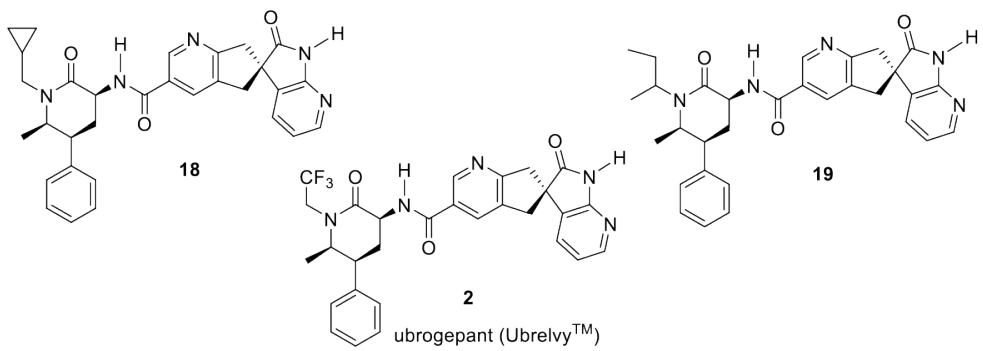
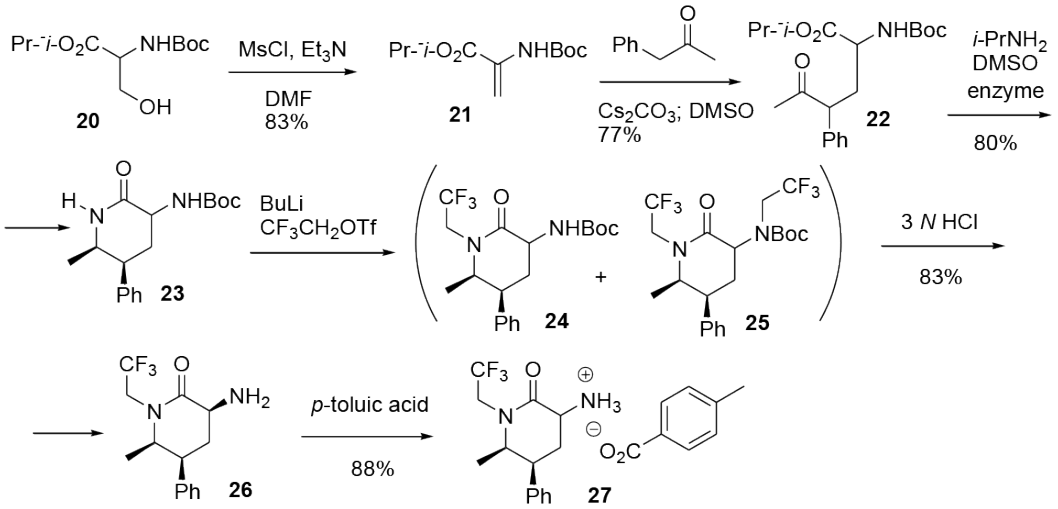


Fig. 2. The structures of ubrogepant **2** and its non-fluorinated analogs **18** and **19**.

The structure and preparation of ubrogepant **2** and its related molecules were initially detailed in a patent filed by Merck [79]. The synthesis involved separately preparing the two key components of ubrogepant–a spirocyclic carboxylic acid and an aminopiperidinone molecule–before utilizing a coupling agent to form the amide bond between them. Subsequent Merck patents [80, 81] introduced slight modifications to the original synthesis.

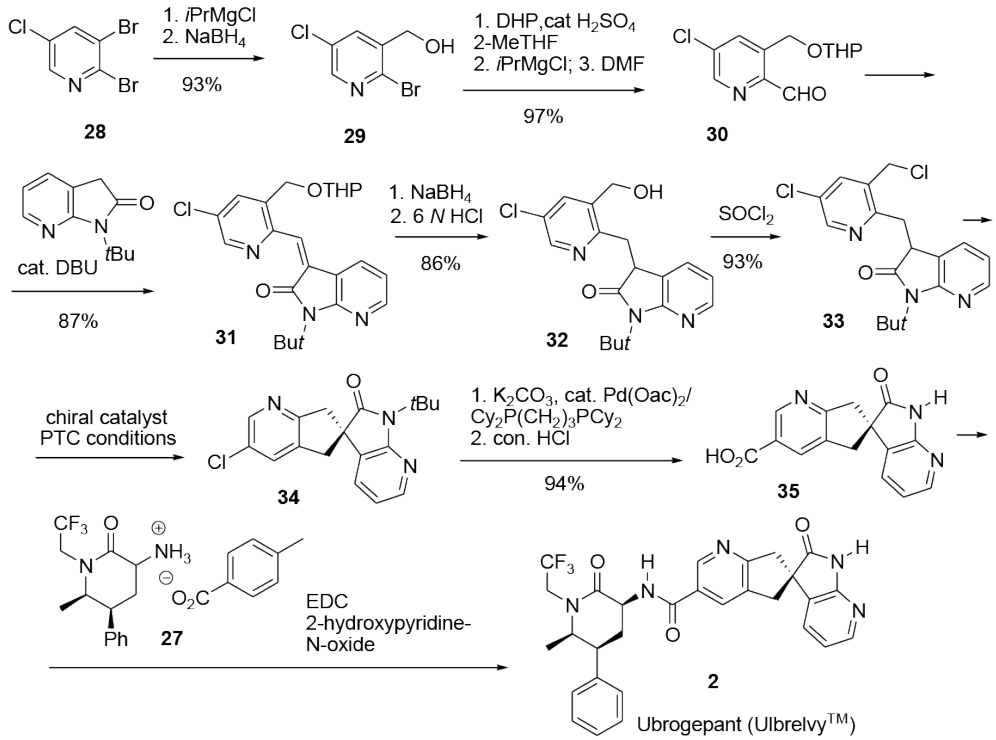
A comprehensive description of these synthetic advancements, including yields, was later published in an academic article [82]. In the improved synthesis, the N-protected racemic serine ester **20** (Scheme 2) underwent dehydration to yield compound **21** which was then subjected to a Michael addition to produce keto amino ester **22**. Compound **22** was cyclized into product **23**, comprising a mixture of C-3 epimers, through dynamic kinetic transamination with an enzyme tailored specifically for this reaction. Under basic conditions, the C-3 stereogenic center inverts favoring the desired configuration. N-alkylation of the diastereomeric mixture **23** was then performed requiring the highly reactive reagent CF_3CH_2OTf. Careful optimization was crucial to minimize alkylation on both nitrogen atoms. The crude products **24** and **25** were subjected to selective Boc deprotection whereby unreacted compound **23** was initially deprotected and removed followed by the deprotection and separation of **24** from the double alkylated byproduct **25**. The mixture of diastereomeric amines **26** was treated with *p*-toluic acid to form a crystalline salt and a 3,5-dichlorosalicylaldehyde catalyst for C-3 epimerization via reversible imine formation inducing a diastereoselective transformation.



Scheme 2. Preparation of fluorinated aminopiperidinone **27**.

The preparation of spirocyclic carboxylic acid **35** began with 2,3-dibromo-5-chloropyridine **28** (Scheme 3). Selective halogen–lithium exchange was followed by the introduction of a formyl group at the C-3 position and its immediate reduction using $NaBH_4$. The resulting

compound **29** was O-protected with 3,4-dihydro-2*H*-pyran (DHP). A second selective halogen–lithium exchange facilitated the addition of a formyl group at the C-2 position. Condensation of aldehyde **30** with *N*-(*tert*-butyl)-azaindolone yielded alkene **31** with a *Z* configuration for the double bond. Subsequent reduction of the newly formed C=C double bond and O-deprotection produced racemic alcohol **32**. The hydroxyl group was replaced with chlorine by reaction with $SOCl_2$ yielding **33**. Enantioselective spirocyclization of compound **33** was achieved using a cinchona-derived chiral phase-transfer catalyst forming product **34**. The final steps included carbonylation and removal of the *N*-*tert*-butyl group to yield spirocyclic carboxylic acid **35**. This compound was then coupled with aminopiperidinone salt **27** in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) ultimately leading to the formation of ubrogepant **2**.



Scheme 3. Synthesis of ubrogepant **2**.

***Asciminib (Scemblix®)* 3.**

Asciminib **3** is a potent, small-molecule, orally bioavailable, and selective allosteric inhibitor developed by Novartis for the treatment of hematologic malignancies, including Philadelphia chromosome-positive (Ph+) CML [83, 84]. It received FDA approval for two distinct indications in CML [83]. *In vitro* anticancer activity tests against leukemia cell lines MV411 (ATCC) and K562 (ATCC) demonstrated that asciminib **3** exhibits significant inhibitory activity with cellular IC_{50} values

of 8.65 μmol/L and 0.32 μmol/L for K562 and MV411, respectively. In contrast, its structurally similar analog **36** (Fig. 3) displayed only moderate activity against these cell lines (K562, $IC_{50} > 30$ μmol/L and MV411, $IC_{50} > 30$ μmol/L). These findings highlight the importance of the chlorodifluoro group in asciminib **3** which plays a crucial role in inducing inactive target conformations. Additionally, the pyrazole ring in asciminib **3**'s structure helps mitigate human ether-a-go-go-related gene (hERG) toxicity [84, 85]. As an allosteric inhibitor, asciminib **3** targets ABL1 by binding to its myristoyl pocket, thereby inhibiting BCR-ABL1 activity. This mechanism distinguishes it from competitive inhibitors like imatinib, dasatinib, and nilotinib which act at the ATP binding site [86–89]. Due to its unique allosteric regulatory mechanism, asciminib **3** not only inhibits wild-type ABL1 kinase but also demonstrates potent activity against the T315I-mutated ABL1 significantly minimizing the off-target effects associated with ATP-binding site inhibitors. The FDA granted accelerated approval to asciminib **3** for the treatment of newly diagnosed adult patients with Philadelphia chromosome-positive CML in the chronic phase (Ph+ CML-CP) [83].

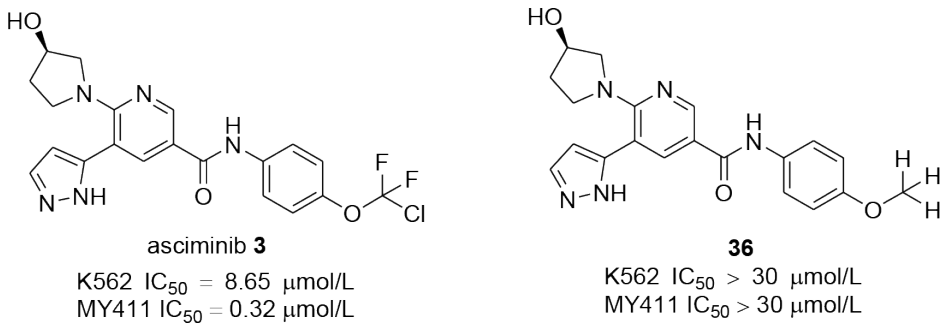
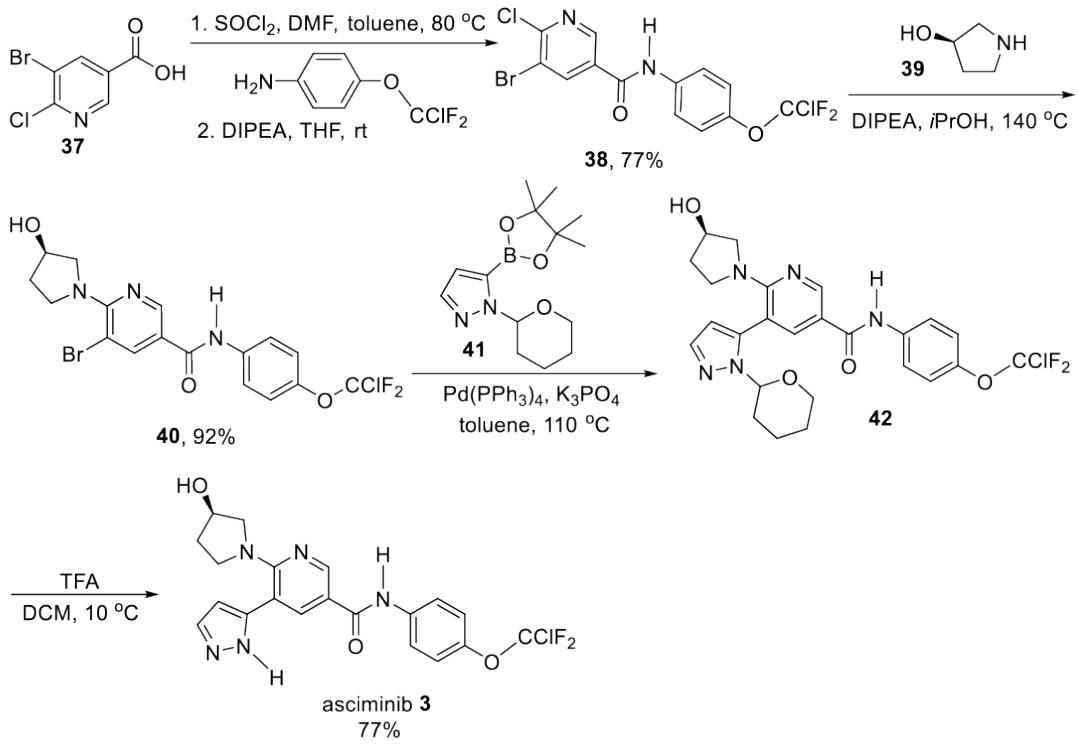


Fig. 3. The structures and bioactivity data for asciminib **3** and its fluorine-free analog **36**.

Several research groups [84, 90, 91] have detailed the synthesis of asciminib **3**. One streamlined approach (Scheme 4) utilizes 5-bromo-6-chloronicotinic acid (**37**) as the starting material [84] which is reacted with $SOCl_2$ in the presence of dimethyl formamide (DMF) to yield the acyl chloride intermediate. The acid chloride is then treated with 4-(chlorodifluoromethoxy)aniline and diisopropylethylamine (DIPEA) as the base in tetrahydrofuran (THF) at room temperature producing amide **38** in 77% yield. Next, amide **38** undergoes substitution by (*R*)-pyrrolidin-3-ol (**39**) under basic conditions [92] at elevated temperatures forming intermediate **40**. A Suzuki–Miyaura coupling reaction in which compound **40** reacts with (1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-5-yl)boronic acid pinacol ester (**41**) creates intermediate **42**. The final step involves treating intermediate **42** with trifluoroacetic acid (TFA) in dichloromethane (DCM) providing asciminib **3** in an impressive 77% yield. This method showcases efficient synthetic strategies with significant yields highlighting the precision required for the development of such a complex molecule.



Scheme 4. Synthesis of asciminib **3**.

***Omaveloxolone (Skyclarys™)* 4.**

Omaveloxolone **4**, an orally active small molecule developed by Reata Pharmaceuticals Inc., stands out as a powerful activator of the transcription factor Nrf2 (Fig. 4) [93]. Nrf2 serves as the primary regulator of phase II cellular antioxidant responses playing a critical role in neuroprotection and detoxification [94]. Under normal conditions, Nrf2 remains bound to the protein KEAP1 in the cytosol where it is ubiquitinated and degraded [95]. However, during oxidative stress, ubiquitination is inhibited allowing Nrf2 to translocate to the nucleus and activate genes that contain antioxidant response elements (ARE).

Omaveloxolone **4**, along with related triterpenoids bardoxolone methyl **44** and 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO) **43**, features a cyanoenone moiety that enables covalent and reversible binding to KEAP1. This binding blocks ubiquitination and proteasomal degradation of Nrf2 thereby stimulating the intracellular antioxidative pathway [95, 96]. Among these triterpenoids, omaveloxolone **4**, modified with a 1,1-difluoroethylamide moiety, has been identified as one of the most potent activators of ARE activity exhibiting over a 16-fold increase at 62.5 nM in an Nrf2-GST-ARE luciferase reporter assay [97].

Omaveloxolone **4** has also earned FDA approval as the first therapeutic for Friedreich's ataxia, a rare inherited degenerative disorder that impacts the nervous system. This condition manifests through symptoms such as

impaired muscle coordination, difficulty walking, poor balance, and changes in speech and swallowing [98]. The unique mechanism and therapeutic efficacy of omaveloxolone highlight its significant contribution to modern medicine.

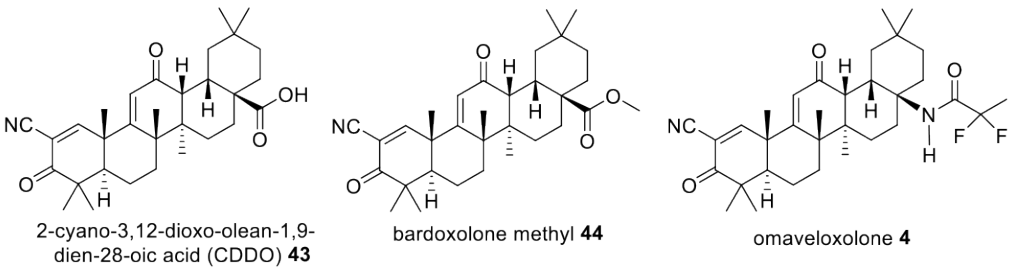
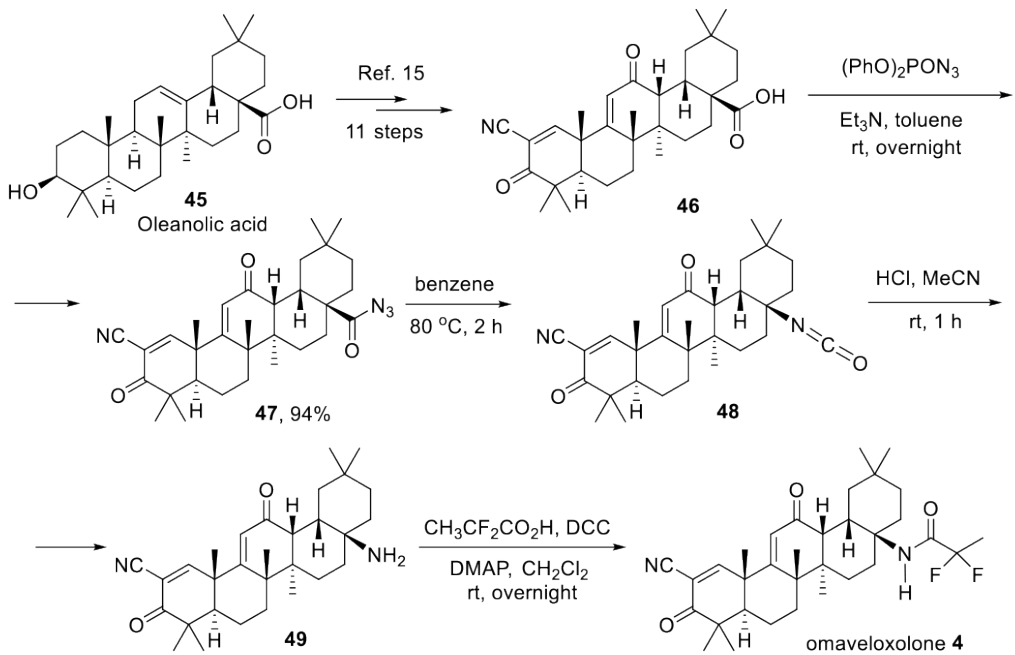


Fig. 4. The structures of compounds **43**, **44**, and omaveloxolone **4**.

The synthesis of omaveloxolone **4**, developed by Reata Pharmaceuticals Inc., begins with compound **46** as the starting material (Scheme 5) [99]. The precursor, diketo acid CDDO **46**, is derived in 11 steps from the naturally occurring oleanolic acid **45** in an overall yield of 29% [100]. To transform compound **46** into azide derivative **47**, diphenylphosphoryl azide is used in the presence of triethylamine with toluene as the solvent at room temperature. After purification by chromatography over silica gel, acyl azide **47** is obtained in an impressive 94% yield.



Scheme 5. Synthesis of omaveloxolone **4**.

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The acyl azide **47** then undergoes a Curtius rearrangement through heating in anhydrous benzene forming isocyanate **48**. Without requiring isolation, isocyanate **48** is hydrolyzed by treatment with HCl in acetonitrile at room temperature yielding amine **49** with preservation of its configuration. Omaveloxolone **4** is finally obtained through peptide-like coupling reactions between amine **49** and 2,2-difluoropropanoic acid. The carboxylic group of 2,2-difluoropropanoic acid is pre-activated using dicyclohexylcarbodiimide (DCC), enabling the formation of the desired product. After purification by chromatography over silica gel, omaveloxolone **4** is obtained in a commendable 73% yield from compound **46** over 4 steps. This synthesis reflects the precision and efficiency required to produce such a complex molecule demonstrating innovative approaches in modern medicinal chemistry.

***Flurpiridaz (^{18}F) (Flyrcado®)* 5.**

Flurpiridaz (^{18}F) **5** has received FDA approval as a radioactive drug for myocardial perfusion imaging, a critical tool in diagnosing coronary artery disease [101]. Labeled with the radioisotope fluorine-18 (β^+ decay), this diagnostic agent serves as a tracer for PET. PET-MPI using flurpiridaz (^{18}F) **5** has demonstrated superiority over the more widely used single photon emission computed tomography (SPECT) which typically employs technetium-99m [102, 103].

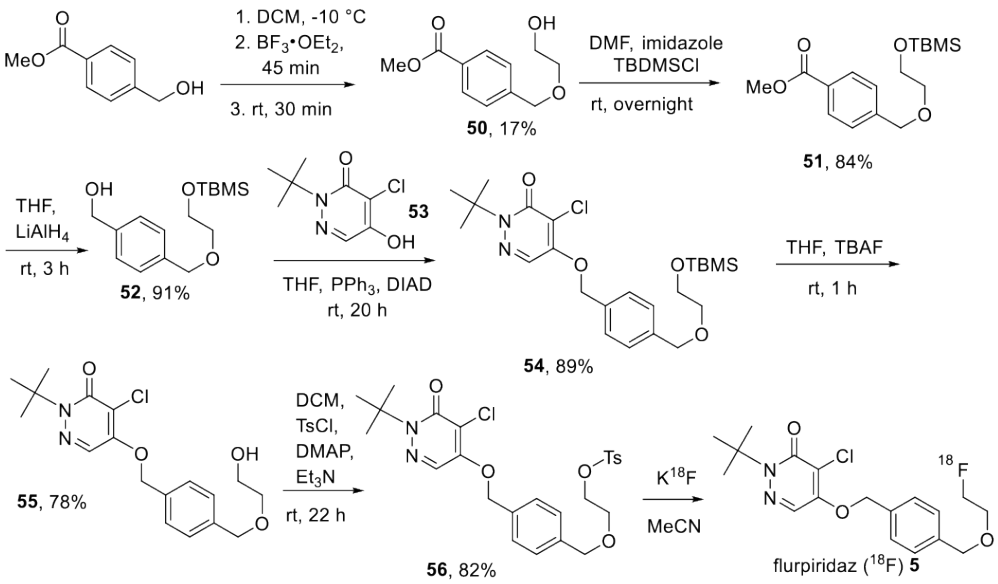
The efficacy of flurpiridaz (^{18}F) **5** in PET imaging is made possible by radiofluoroalkylation, leveraging the unique properties of fluorine-18. This isotope offers distinct advantages, including a clinically practical half-life of 109.8 minutes compared to other PET radiotracers such as nitrogen-13 (~10 minutes), oxygen-15 (~2 minutes), and rubidium-82 (~76 seconds), or the SPECT radiotracer technetium-99m (6 hours) [104]. The extended half-life of fluorine-18 eliminates the need for on-site cyclotron facilities as transportation from an off-site facility becomes feasible [105]. Moreover, radiofluorination provides additional benefits, such as reduced positron energy, which enhances image resolution [106]. This improvement translates into superior diagnostic and prognostic capabilities enabling the detection of even subtle circulatory abnormalities [107]. Flurpiridaz (^{18}F) **5** exemplifies how cutting-edge radiotracer technology can revolutionize medical imaging and disease detection.

Flurpiridaz (^{18}F) **5** exhibits rapid uptake and slow excretion by myocardial cells ensuring effective imaging while being well tolerated and demonstrating a high myocardial extraction fraction [104, 108]. Pharmacologically, its mechanism of action involves binding to and inhibiting mitochondrial complex 1 (MC1) in the heart [104]. Structure–activity studies have revealed that introducing fluorine into the alkyl side chain significantly enhances MC1 binding affinity compared to its incorporation into the pyridazinone core [109].

From a chemical perspective, flurpiridaz (^{18}F) **5** is a derivative of the pesticide pyridaben due to its *tert*-butyl-substituted pyridazinone moiety [108]. Its molecular architecture is composed of two main components: a lipophilic heterocyclic headpiece (the *tert*-butyl-substituted pyridazinone) and an alkylated phenyl sidechain. These two units are bridged by a linker containing an ether group which contributes to the molecule's unique properties [109].

The synthesis of flurpiridaz (^{18}F) **5** begins with 4-hydroxymethyl benzoate as the

starting material (Scheme 6) [109]. The first step is the ring-opening of ethylene oxide by 4-hydroxymethyl benzoate in DCM facilitated by $BF_3{\cdot}OEt_2$ to provide methyl-4-(2-hydroxyethoxymethyl)benzoate (**50**) in 17% yield. Subsequently, the alcohol functionality is protected at room temperature using *tert*-butyldimethylsilyl chloride (TBDMSCl) yielding 4-[2-(*tert*-butyldimethylsilanyloxy)ethoxymethyl]benzoic acid methyl ester (**51**). Reduction of **51** with $LiAlH_4$ provides alcohol **52** in an impressive 91% yield.



Scheme 6. Synthesis of flurpiridaz (^{18}F) **5**.

The next critical step employs a Mitsunobu-like reaction in which alcohol **52** reacts with 4-chloro-5-hydroxy-2-*tert*-butyl-(2*H*)-pyridazin-3-one (**53**) using PPh_3 and DIAD as reagents to produce intermediate **54** [110]. The synthesis of pyridazinone derivative **53** has been well-documented in the literature [111]. Removal of the TBDMS protecting group from ether **54** is achieved with tetra-*n*-butylammonium fluoride (TBAF) in THF yielding alcohol **55** [112]. This intermediate is then converted into the sulfonate ester **56**. Finally, the sulfonate ester **56** undergoes substitution by potassium fluoride ($K^{18}F$) in the presence of Kryptofix222 [113] (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosan) at 90 °C for 10 minutes, culminating in the formation of the desired flurpiridaz (^{18}F) **5**. This method elegantly showcases the precision and optimization required to create such a sophisticated molecule.

The aforementioned synthesis faced significant challenges, primarily due to its inefficiency and reliance on hazardous reagents. The overall yield falls below 10% with the first step—forming ether **50**—achieving a meager yield of just 17%. Compounding the issue, this step involved the use of ethylene oxide, a volatile and

carcinogenic gas known to cause respiratory irritation [114, 115]. Handling this reagent proved problematic, not only due to its toxicity, but also because of its high volatility posing risks in both safety and practicality. To address these limitations, Ahmed and co-workers devised an alternative synthesis pathway that entirely circumvented the risky alkylation process. Instead, they employed a silver oxide-promoted reaction between methyl 4-(bromomethyl)benzoate and 2-((*tert*-butyldimethylsilyl) oxy)ethanol to produce intermediate **50**. This innovative approach not only enhanced safety but also significantly improved efficiency, boosting the overall yield approximately fivefold [107]. Their work stands as a testament to the potential of optimized synthesis routes in overcoming challenges while achieving superior results.

Upadacitinib (Rinvoq™) 6.

Upadacitinib **6**, a remarkable innovation first discovered by Abbott Laboratories and further refined by its spin-off AbbVie Inc., achieved a major breakthrough with FDA approval. This approval was granted for the treatment of adults with moderate to severe rheumatoid arthritis who had an inadequate response or were intolerant to methotrexate (Fig. 5). The journey to upadacitinib's creation involved a thorough and meticulous structural investigation centered on its critical tricyclic core. By systematically varying the heterocyclic cores, the side chain, and the amido moiety, researchers fine-tuned the molecule's design. This effort ultimately led to the development of upadacitinib **6**, distinguished by a 2,2,2-trifluoroethyl substitution on the nitrogen atom—an essential feature that enhances its therapeutic effectiveness [116, 117].

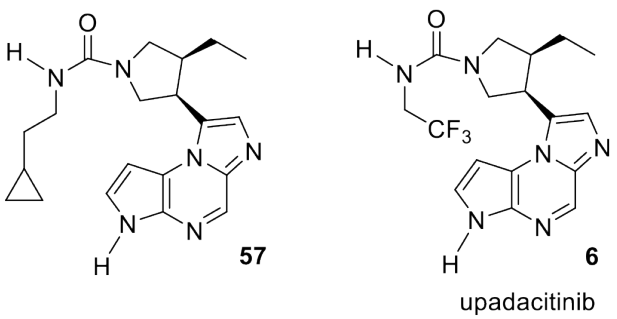


Fig. 5. Structure of upadacitinib **6** and its non-fluorinated analog **57**.

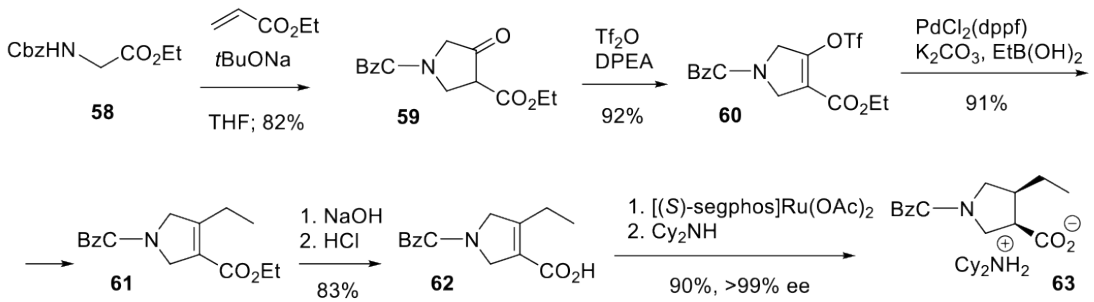
Rheumatoid arthritis is a complex systemic autoimmune disorder marked by chronic inflammatory synovitis and the relentless destruction of joints. At its core, these pathological processes are driven by inflammatory cytokines and autoreactive T cells. A critical player in this cascade is the family of Janus kinases (JAKs), which serve as pivotal mediators in cytokine-activated cell signaling pathways. Their phosphorylation triggers a chain of events that exacerbate rheumatoid arthritis and other autoimmune diseases. The JAK family comprises four members–JAK1, JAK2, JAK3, and TYK2–each with unique and highly specialized roles in regulating immune responses. Recognizing this, researchers have developed a spectrum of JAK inhibitors with varying selectivities, many of which have progressed to clinical trials

including upadacitinib **6** [116]. Upadacitinib **6**, a selective JAK1 inhibitor, boasts impressive specificity with an IC_{50} of 0.043 mmol/L for JAK1 compared to 0.2 mmol/L for JAK2, 2.3 mmol/L for JAK3, and 4.7 mmol/L for TYK2. This targeted selectivity has translated into demonstrated efficacy, safety, and tolerability during clinical trials in patients with various autoimmune conditions showcasing its potential as a transformative treatment option.

For rheumatoid arthritis, following the success of Phase II trials, multiple Phase III trials were conducted on patients who had either an inadequate response to conventional synthetic disease-modifying antirheumatic drugs or were refractory to biologic disease-modifying antirheumatic drugs [118–120]. Across all trials, upadacitinib **6** demonstrated both safety and efficacy, though higher doses were associated with a slight increase in infection risk. Notably, an additional Phase III trial revealed that upadacitinib **6** outperformed adalimumab in terms of efficacy [121]. In patients with moderate to severely active Crohn's disease who had not responded well to or could not tolerate immunomodulators or anti-TNF therapy, a Phase II trial demonstrated both symptomatic and endoscopic remission [122]. The safety profile observed was consistent with other studies of upadacitinib **6** and Phase III trials are currently underway [123]. Similarly, a Phase II study evaluating upadacitinib **6** in patients with ulcerative colitis revealed a clear dose-response relationship [124]. For individuals with active ankylosing spondylitis who failed to respond adequately to or could not tolerate non-steroidal anti-inflammatory drugs, the Phase II/III SELECT-AXIS 1 trial established that a 15 mg dose of upadacitinib **6** was both effective and welltolerated. Notably, no cases of serious infections, herpes zoster, malignancy, venous thromboembolic events, or deaths were reported. Recruitment for a Phase III study is currently ongoing. In the case of moderate to severe atopic dermatitis, upadacitinib **6** demonstrated strong efficacy and maintained a favorable benefit–risk profile. While infections were more common among upadacitinib-treated patients compared to those receiving a placebo, serious infections were rare [125]. Additionally, Phase III trials are advancing for psoriatic arthritis and giant cell arteritis further expanding the therapeutic potential of upadacitinib **6**.

Synthetic pathways leading to upadacitinib **6** are documented exclusively within patents. The initial patent from Abbott Laboratories, which first disclosed the structure of upadacitinib **6**, includes details of its synthesis. However, the fragmented presentation of substeps scattered throughout the document renders the reconstruction of the complete synthetic pathway particularly challenging [126]. A subsequent patent filed by AbbVie is comparatively more accessible, but its vague procedural descriptions introduce ambiguity complicating the reproducibility of the synthesis [127]. In contrast, a 2017 AbbVie patent provides a detailed and coherent synthetic pathway offering greater clarity and precision in the step-by-step process. The synthesis begins with the construction of the pyrrolidine-containing segment derived from a Cbz-protected glycine ester **58** (Scheme 7). This compound undergoes a reaction with ethyl acrylate through conjugate addition followed by an intramolecular Claisen condensation leading to the formation of ester intermediate **59**. Subsequently, intermediate **59** undergoes O-sulfonylation to prepare **60** for use in the next step where an

ethyl group is introduced via a Suzuki cross-coupling reaction producing compound **61**. The ester functionality in **61** is then hydrolyzed to afford acid **62** followed by enantioselective hydrogenation to give cyclic β-amino acid [128] isolated as a salt with dicyclohexylamine **63**. While it has been reported that [(*S*)-segphos]Ru(OAc)$_2$-catalyzed enantioselective hydrogenation proceeded with >99% enantioselectivity, this claim is not supported by ruling out enantiomeric enrichment via SDE [129, 130] during the isolation procedure.

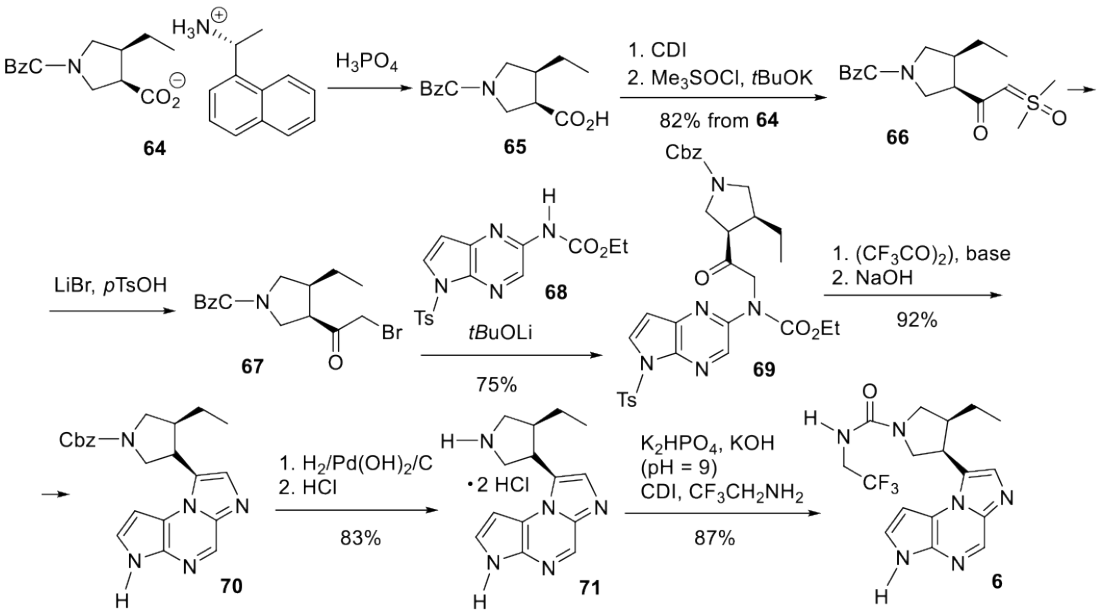


Scheme 7. Asymmetric synthesis of cyclic amino acid **63** from glycine **58**.

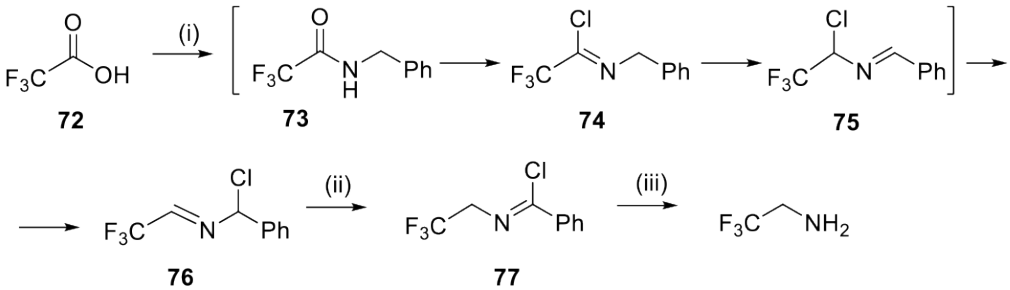
Following purification, salt **63** was converted into (*R*)-1-(naphthalen-1-yl)ethanamine salt **64** (Scheme 8) which was subsequently transformed into pyrrolidine carboxylic acid **65**. The carboxylic acid group of **65** was modified into a $COCH_2Br$ group, compound **67**, using sulfoxonium ylide **66**. This reactive intermediate, compound **67**, was then employed in the N-alkylation of the carbamate moiety within heterocyclic compound **68**.

The resulting intermediate, compound **69**, underwent cyclization with trifluoroacetic anhydride to form compound **70**. This was followed by hydrogenolytic deprotection of the Cbz group yielding compound **71**. In the final step, carbonyldiimidazole (CDI) and 2,2,2-trifluoroethylamine were utilized to establish the carbamide functionality to complete the synthesis of the target molecule upadacitinib **6** [131, 132].

2,2,2-Trifluoroethylamine, along with other trifluoromethyl amines and amino acids, can be synthesized through biomimetic transamination of corresponding carbonyl compounds using benzylamine or its derivatives [133–136]. Particularly noteworthy, as shown in Scheme 9, is the preparation of 2,2,2-trifluoroethylamine from TFA (**72**) through a 'double' biomimetic transamination involving a single molecule of benzylamine. This innovative approach begins with the *in situ* formation of amide **73** which is subsequently transformed into imidoyl chloride **74**. Following this, the first biomimetic 1,3-proton transfer generates imine **75**. A chlorotropic shift then converts imine **75** into imine **76** which undergoes a second biomimetic 1,3-proton transfer yielding imidoyl chloride **77**. This intermediate **77** can be isolated and, through two hydrolytic steps, transformed into the desired 2,2,2-trifluoroethylamine. Remarkably, despite involving a seven-step process, this method achieves an exceptional isolated yield of over 90% underscoring its efficiency and practicality [137].



Scheme 8. Synthesis of upadacitinib **6**.



Key: (i) $BnNH_2$ (1 eq), Ph_3P (4 eq)/CCl_4 (4 eq), TEA (1.5 eq), $CHCl_3$ reflux, 40 min.; (ii) TEA (3 eq)/H_2O; (iii) MeOH/HCl (conc), reflux, 24 hr

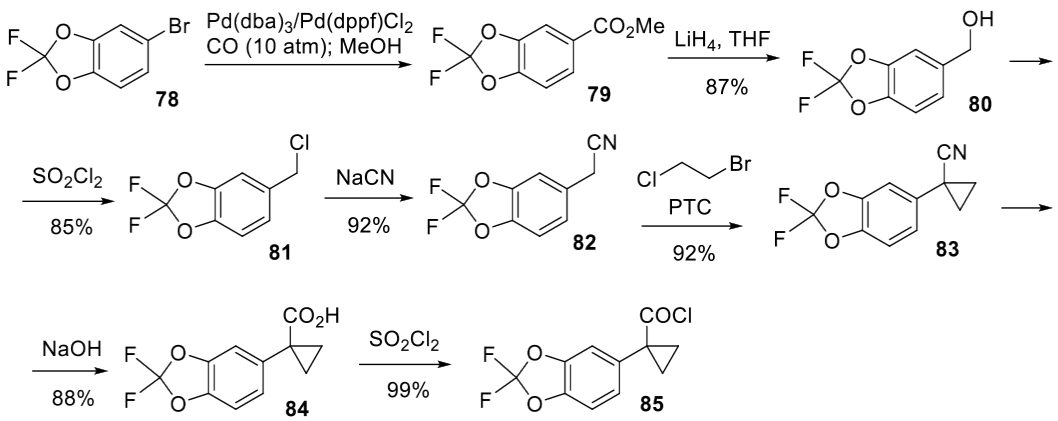
Scheme 9. Synthesis of 2,2,2-trifluoroethylamine via 'double' biomimetic transamination.

Tezacaftor (Symdeko™) 7.

Symdeko™, a coformulation of tezacaftor **7** and ivacaftor (Fig. 1) developed by Vertex Pharmaceuticals, represents a significant advancement in the treatment of cystic fibrosis. Approved by the FDA, it addresses this debilitating condition marked by the buildup of thick, sticky mucus in the lungs, pancreas, gastrointestinal tract, and reproductive system [138]. The root cause lies in mutations of the CFTR gene with the F508del mutation being one of the most prevalent [139]. Tezacaftor **7** and ivacaftor function in a complementary manner to combat the effects of this mutation. Tezacaftor **7** acts as a corrector, enhancing the transport of functional CFTR protein to the

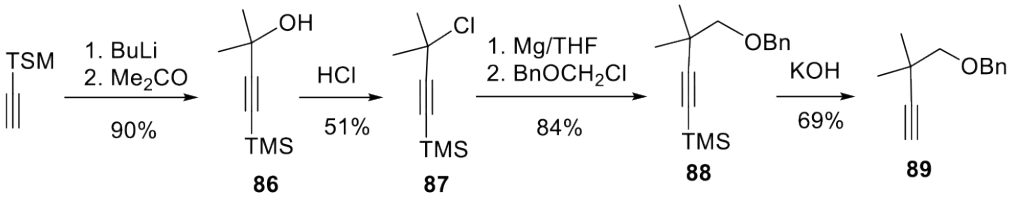
cell membrane. Meanwhile, ivacaftor serves as a potentiator helping to open the chloride channel within the CFTR protein. This dual mechanism promotes water movement out of the cells effectively reducing mucus viscosity and alleviating symptoms associated with cystic fibrosis.

The synthesis of tezacaftor **7**, developed by Auspex Pharmaceuticals, is a sophisticated process involving the preparation of two key intermediates [140]. The process begins with the carbonylation of aryl bromide **78** (Scheme 10) where palladium catalysts and an atmosphere of carbon monoxide in methanol are employed to produce methyl ester **79**. This intermediate is then reduced using $LiAlH_4$ to yield primary alcohol **80**. To further functionalize the molecule, the alcohol group in compound **80** is replaced with a chloride forming compound **81**. A nucleophilic substitution with sodium cyanide transforms **81** into nitrile derivative **82**. The cyclopropane ring is then introduced via phase-transfer catalysis utilizing 1-bromo-2-chloroethane, to produce cyclopropane derivative **83**. In the next step, compound **83** undergoes nitrile hydrolysis with aqueous hydroxide yielding free acid **84**. Finally, the carboxylic acid group of **84** is converted into the reactive chloroanhydride **85** through treatment with thionyl chloride. This meticulously designed, high yielding synthetic pathway highlights the precision and strategic optimization integral to the development of tezacaftor **7**.



Scheme 10. Synthesis of key compound **85**.

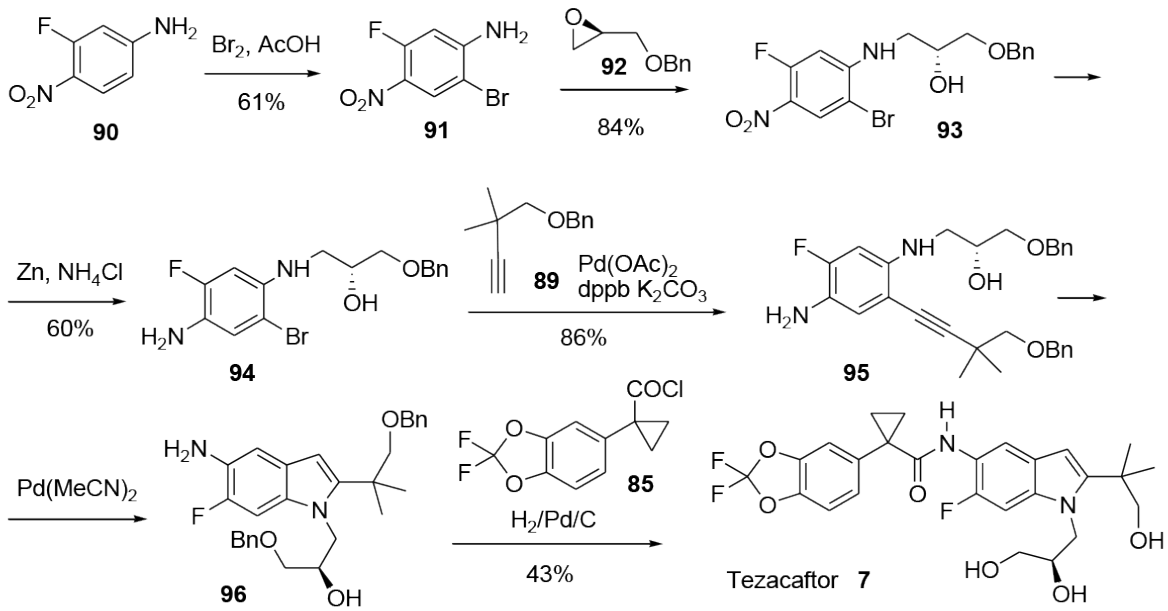
The synthesis of the second key intermediate began with the preparation of terminal alkyne **89** (Scheme 11). This process involved a precise four-step sequence. First, ethynyltrimethylsilane was added to acetone in the presence of butyllithium resulting in the formation of alcohol **86**. Next, alcohol **86** was transformed into alkyl chloride **87**. In the third step, the corresponding Grignard reagent was generated and reacted with compound **87** yielding benzyl ether **88**. Finally, the trimethylsilane protecting group was removed through a potassium hydroxide-mediated methanolysis producing the target alkyne ether **89**.



Scheme 11. Synthesis of intermediate **89**.

The synthesis of the second key intermediate and the assembly of tezacaftor **7** began with the bromination of 3-fluoro-4-nitroaniline (**90**) (Scheme 12) yielding aryl bromide **91**. This was followed by alkylation of the amino group using optically pure epoxide **92** producing amino alcohol **93**. The nitro group in **93** was then reduced using a combination of zinc and ammonium chloride in ethanol resulting in aniline derivative **94**. Aniline **94** was subsequently subjected to a palladium-catalyzed coupling reaction with acetylene derivative **89** (Scheme 11) forming product **95**. The next step involved a palladium-catalyzed intramolecular cyclization of **95** which generated the second key intermediate indole **96**.

The synthesis of tezacaftor **7** was accomplished by coupling indole derivative **96** with acyl chloride **85** (Scheme 10) by straightforward amide bond formation where the amino group of **96** reacts with the acyl chloride group of **85** in the presence of triethylamine. A hydrogenation step completes the process yielding tezacaftor **7** in moderate yield. This synthesis showcases a logical and efficient sequence of transformations to achieve the desired molecule.



Scheme 12. Synthesis of tezacaftor **7**.

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***Alpelisib (Piqray™)* 8.**

Alpelisib **8**, a highly potent phosphatidylinositol-3 kinase α (PI3Kα) inhibitor, was developed by Novartis for the treatment of breast cancer [141–143]. The 2-aminothiazole scaffold has proven to be an exceptional template for designing selective PI3K inhibitors, particularly when paired with a urea-linked, sterically constrained (*S*)-pyrrolidine carboxamide unit (an amide of pyroglutamic acid) attached to the 2-amino group of **97** (Fig. 6) [144].

Alpelisib **8** stands out as a chiral 2-aminothiazole derivative, optimized with an (*S*)-pyrrolidine carboxamide moiety linked via a urea bond, making it the most effective candidate within this PI3K inhibitor class. The inclusion of a trifluoromethyl group significantly enhanced its potency delivering robust double-digit nanomolar inhibition of PI3Kα-dependent Akt activation. In comparison, compound **98** (Fig. 6), which featured a *tert*-butyl group instead of a trifluoromethyl group, displayed noticeably reduced activity.

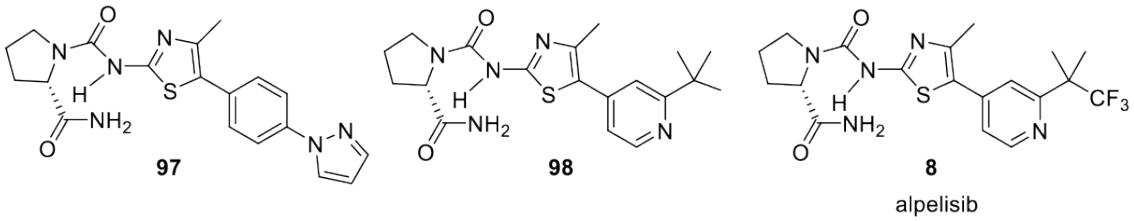
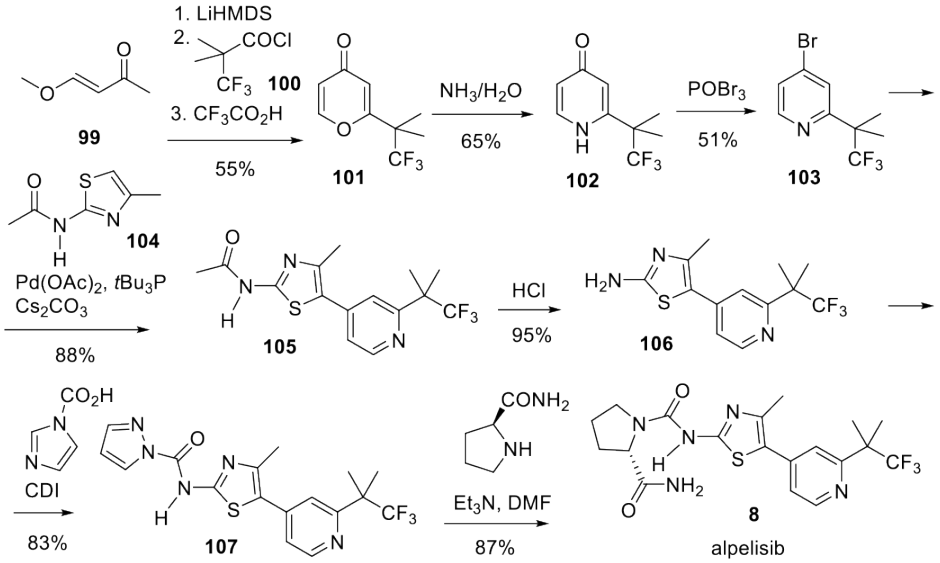


Fig. 6. The structures of alpelisib **8** and its fluorine-free analogs **97** and **98**.

In an assay for the inhibition of p110α, p110β, p110δ, and p110γ activity, alpelisib **8** achieved impressive IC_{50} values of 0.005, 1.2, 0.29, and 0.25 mmol/L, respectively, while fluorine-free **98** exhibited weaker IC_{50} values of 0.014, 4.4, 0.33, and 0.43 mmol/L, respectively. Additionally, metabolic stability assessments using rat liver microsomes showed that alpelisib **8**, with a $-CF_3$ group, demonstrated dramatically reduced *in vitro* clearance compared to **98**. Despite its excellent activity against wild-type PI3Kα, alpelisib **8** displayed relatively lower efficacy against PI3Kβ, PI3Kδ, and PI3Kγ [141, 142]. Approved by the FDA under the trade name Piqray™ for the treatment of HR+, HER2-negative, and PIK3CA-mutated advanced or metastatic breast cancer, alpelisib **8** is administered in combination with fulvestrant, offering new hope for patients battling this challenging disease [145].

The synthesis of alpelisib **8** (Scheme 13) [141] hinges on a pivotal Pd-catalyzed coupling between 4-methyl-2-acetaminothiazole (**104**) and 4-bromopyridine intermediate **103**. The process begins with chloride **100** prepared from 3,3,3-trifluoro-2,2-dimethylpropanoic acid and oxalyl chloride. Chloride **100** is then reacted with 4-methoxybut-3-en-2-one **99** in the presence of lithium bis(trimethylsilyl) amide (LiHMDS) at −78 °C. The reaction progresses through enolization of **99**, substitution of the chlorine in **100**, a secondary enolization of the resulting 1,3-diketone, and a TFA-mediated cyclization which substitutes the methoxy group to yield 4*H*-pyran-4-one intermediate **101**. The next step involves amination of

4*H*-pyran-4-one intermediate **101** with ammonia at 65 °C, producing pyridin-4(1*H*)-one **102**. Treatment of **102** with $POBr_3$ affords bromide intermediate **103**, albeit in only 51% yield. The Pd-catalyzed coupling between intermediate **103** and 4-methyl-2-acetaminothiazole (**104**) produces compound **105** which is then hydrolyzed in the presence of 6 M HCl. The resulting amine **106** undergoes condensation with 1*H*-imidazole-1-carboxylic acid to form imidazole intermediate **107**. Finally, intermediate **107** is reacted with (*S*)-pyroglutamic acid at room temperature culminating in the formation of the target compound alpelisib **8**.



Scheme 13. Synthesis of alpelisib **8**.

Pretomanid 9.

Pretomanid **9**, developed by the Global Alliance for TB Drug Development (TB Alliance), has emerged as one of the most promising antituberculosis drug candidates [146–149]. This compound possesses two key structural features: a bicyclic nitroimidazole scaffold and a trifluoromethoxy-substituted benzyl ether with *S* absolute configuration at the stereogenic carbon. Related compounds, such as metronidazole **109** (Fig. 7) and OPC-67683, have also been identified as potential nitroimidazole-based drugs for tuberculosis. Pretomanid **9** demonstrated significant anti-TB activity, with IC_{50} values ranging from 0.015–0.25 mmol/L [148]. The *in vitro* evaluation of pretomanid **9** against H37Rv *Mycobacterium tuberculosis* in GAST and 7H12 media yielded IC_{50} values of 0.12 mmol/L and 0.09 mmol/L, respectively [149]. Notably, pretomanid **9** exhibited strong antibacterial efficacy against *M. tuberculosis in vitro* and underwent clinical trials for tuberculosis treatment. In sharp contrast, its *R* enantiomer, compound **108**, showed no activity against *M. tuberculosis* [147]. Pretomanid **9** received FDA approval under the trade name Pretomanid for the treatment of adults with drug-resistant tuberculosis. Its approval marks a significant step forward in combating this challenging disease [150].

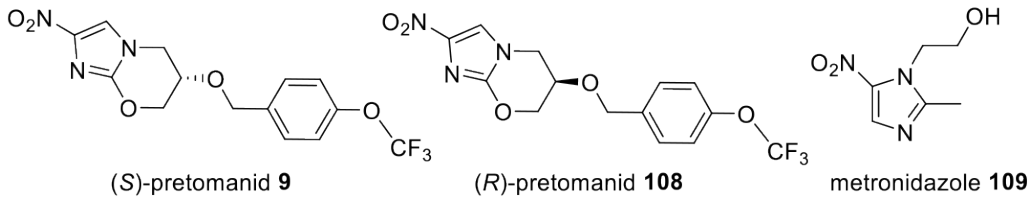
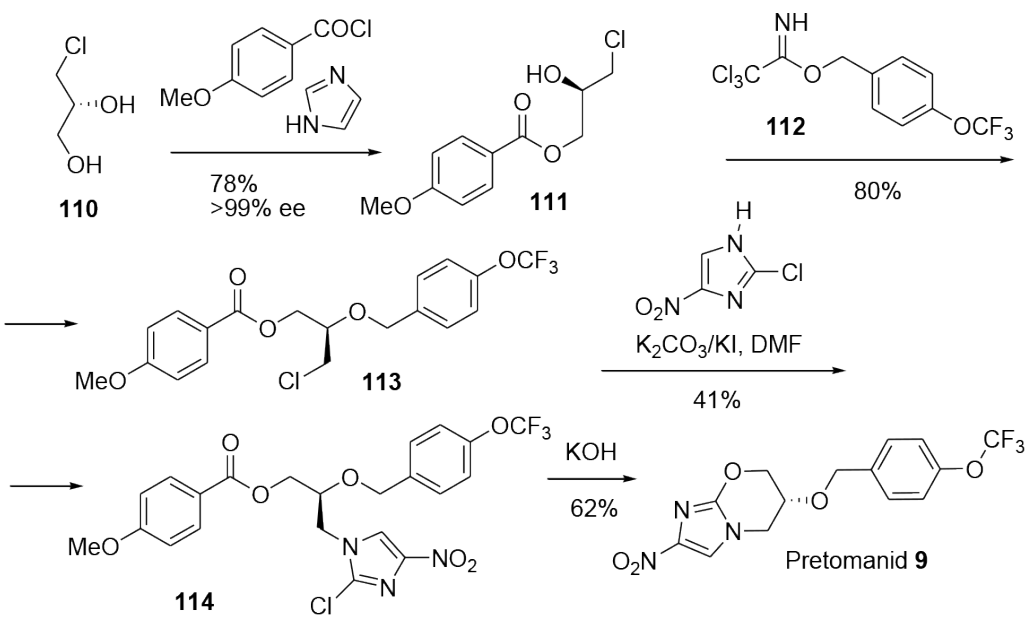


Fig. 7. The structures of pretomanid **9**, its *R* enantiomer **108**, and the related compound metronidazole **109**.

A four-step synthesis of pretomanid **9** [148] (Scheme 14) begins with the esterification of (*R*)-3-chloro-1,2-propanediol (**110**) with *p*-methoxybenzoyl chloride in DCM using imidazole as the base to provide ester **111** in 78% yield and >99% enantiomeric excess (ee). Next, 4-(trifluoromethoxy)benzyl trichloroacetimidate (**112**), derived from 4-(trifluoromethoxy)benzyl alcohol, reacts with ester **111** in the presence of a stoichiometric amount of *p*-toluenesulfonic acid (TsOH) providing glycidol-derived alkyl chloride **113** in 80% yield. Intermediate **113** next undergoes substitution with 2-chloro-4-nitroimidazole in the presence of sodium iodide and potassium carbonate in DMF at 120 °C to form intermediate **114**. The final step involves deprotection of the *p*-methoxybenzoyl group and an intramolecular cyclization under basic conditions to afford pretomanid **9** in 62% yield. Recrystallization from isopropanol–hexane provides pretomanid **9** with 99.9% ee.



Scheme 14. Synthesis of pretomanid **9**.

This method represents a significant improvement over the original synthesis which utilized 2,4-dinitroimidazole as the starting material [151] and it is also suitable for large-scale production. Notably, the synthesis of (*S*)-configured pretomanid **9** begins with (*R*)-3-chloro-1,2-propanediol (**110**). The apparent change in absolute configuration from *R* to *S* following the substitution step from **113** to **114** is not due to inversion of the stereogenic carbon but is a consequence of CIP priority rules [152, 153].

***Atogepant (Qulipta™)* 10.**

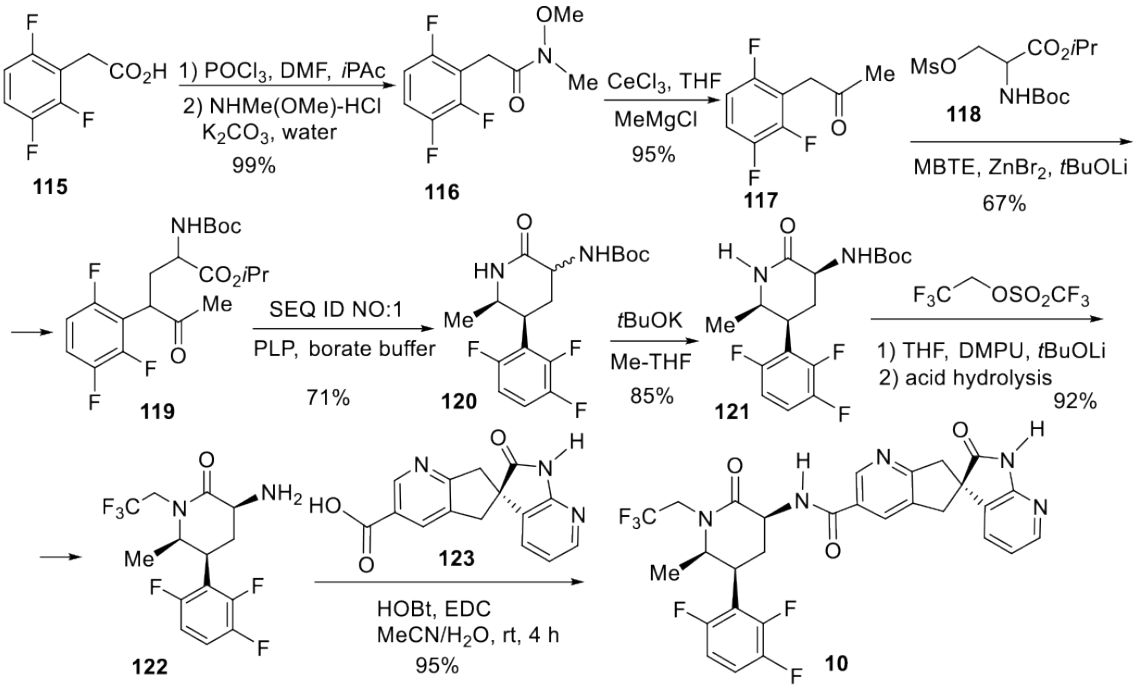
CGRP is a powerful, naturally occurring 37-amino acid neuromodulatory peptide found in the central and peripheral nervous systems. It plays a crucial role in various biological processes, including vasodilation. Research shows that CGRP receptors are prominently expressed in brain regions linked to migraine pathophysiology and CGRP levels are elevated during migraine episodes. This peptide exerts its biological effects by binding to specific cell surface receptors which activate the adenylyl cyclase enzyme [154–156].

Clinical trials have demonstrated the effectiveness of CGRP antagonists in treating acute migraine attacks as well as neurogenic inflammation and inflammatory pain [157, 158]. Furthermore, multiple studies have reported that the vascular effects of CGRP can be diminished or reversed with CGRP antagonists [159–164]. Among these breakthroughs, Merck conducted a structure–activity relationship study, leading to the development of atogepant **10,** a potent and selective CGRP antagonist. This compound is noteworthy as the first orally administered CGRP antagonist to receive FDA approval for the prevention of episodic migraines and cluster headaches.

As illustrated in Fig. 1, atogepant **10** bears a close structural resemblance to ubrogepant **2**. Both feature a chiral spirotetracyclic moiety, a cyclic α,δ-diamino acid core [165–167], and a trifluoroethylamine residue. However, the key distinction lies in atogepant's incorporation of three additional aromatic fluorine atoms as part of the cyclic amino acid fragment. While seemingly minor, this structural variation results in differences in bioactivity and chemical synthesis. Ubrogepant **2** and atogepant **10**, though both CGRP receptor antagonists, differ in their clinical applications. Ubrogepant **2** is designed for the acute treatment of migraines; it is taken as needed during a migraine episode to provide rapid relief by blocking CGRP activity which contributes to migraine symptoms. In contrast, atogepant **10** was developed for the preventive treatment of episodic migraines. Administered regularly, it reduces the frequency of migraine attacks over time. While both drugs share the mechanism of blocking CGRP activity, their bioactivity is tailored to align with their specific purposes–ubrogepant **2** for immediate relief and atogepant **10** for long-term management. In summary, both medications have proven effective in their respective roles offering valuable options for individuals affected by migraines.

Scheme 15 outlines the synthesis of atogepant **10**. Starting with fluorinated 2-phenylacetic acid **115** [168, 169], the substrate was converted to its acid chloride by reacting with $POCl_3$ in DMF and isopropyl acetate (*i*PAc) at 0 °C for 30 minutes. The resulting mixture was added to a solution of K_2CO_3 and NHMe(OMe)·HCl in water below 8 °C providing compound **116** in an excellent 99% yield.

The synthesis continued with a $CeCl_3$-promoted reaction between intermediate **116** and MeMgCl in THF. This was followed by treatment with 2 *N* hydrochloric acid and methyl *tert*-butyl ether (MTBE) at 5–10 °C to produce l-(2,3,6-trifluorophenyl)propan-2-one (**117**) in 95% yield. Intermediate **117** then undergoes substitution with isopropyl *N*-(*tert*-butoxycarbonyl)-*O*-(methylsulfonyl)serinate (**118**) in the presence of $ZnBr_2$ and *t*BuOLi, affording intermediate **119** in 67% yield after 24 hours. The asymmetric cyclization of intermediate **119** was achieved by treating it with sodium tetraborate decahydrate, isopropylamine, pyridoxal-5-phosphate (PLP), and SEQ ID NO: 1 in borate buffer at 55 °C for 24 hours. This step resulted in the carbamate intermediate **120** as a mixture of *cis*- and *trans*-isomers in 71% yield. The crude mixture of **120** in Me-THF was treated with *t*BuOK at room temperature for 2 hours and subsequently crystallized from *i*PAc/heptane at 60 °C providing crystalline *cis*-**121** in 85% yield. This transformation involved α epimerization of the cyclic α,δ-diamino acid, a mechanism akin to dynamic kinetic resolutions commonly employed for preparing enantiomerically pure α-amino acids [170–172]. To introduce a trifluoroethyl group, trifluoroethyl trifluoromethanesulfonate was utilized followed by removal of the Boc group generating the free amine **122** in 92% yield. Finally, compound **122** was coupled with carboxylic acid **123** in the presence of hydroxybenzotriazole (HOBt) monohydrate and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) hydrochloride at room temperature for 4 hours resulting in atogepant **10** as a monohydrate in 95% yield. This optimized synthesis demonstrates efficient and high yielding steps suitable for the large-scale preparation of atogepant **10**.



Scheme 15. Synthesis of atogepant **10**.

CONCLUSIONS. In this review we have profiled ten marketed pharmaceuticals approved by the FDA within the last five years that feature aliphatic fluorination—a key structural feature pivotal to their biological activity. These include ivosidenib **1**, developed for the treatment of AML and cholangiocarcinoma (bile duct cancer); ubrogepant **2**, approved for the acute treatment of migraines; asciminib **3**, prescribed for the treatment of CML in the chronic phase; omaveloxolone **4**, used in the treatment of Friedreich's ataxia, a rare genetic disorder causing progressive damage to the spinal cord, peripheral nerves, and brain, leading to uncoordinated movement, difficulty walking, and other complications; flurpiridaz (^{18}F) **5**, a radioactive diagnostic agent for PET myocardial perfusion imaging; upadacitinib **6**, designed to address several inflammatory and autoimmune conditions, including rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, ulcerative colitis, Crohn's disease, ankylosing spondylitis, and non-radiographic axial spondyloarthritis; tezacaftor **7**, approved for the treatment of cystic fibrosis as an effective remedy; alpelisib **8**, prescribed for the treatment of breast cancer, effectively inhibiting tumor growth and abnormal cell proliferation; pretomanid **9**, used in combination therapies for the treatment of extensively drug-resistant and multi-drug-resistant tuberculosis; and atogepant **10**, approved for the preventive treatment of migraines in adults, targeting both episodic and chronic migraines. As highlighted in the discussion, molecules featuring aliphatic fluorination present challenges due to higher production costs and the complexity of predicting their biological profiles. However, the undeniable medicinal benefits of aliphatic fluorination are likely to invigorate this area of research paving the way for the development of more innovative drugs to enter the pharmaceutical market.

Beyond the incorporation of aliphatic fluorine atoms, six of the pharmaceuticals discussed in this review feature residues of amino acids or their derivatives as pivotal structural design elements. As noted in the discussion, the significance of asymmetric synthesis in producing tailor-made amino acids [173–175] and its profound impact on the modern pharmaceutical industry cannot be overstated. Another noteworthy characteristic shared by all these drugs is their chirality with each molecule possessing between one and six stereogenic carbons. In light of the FDA requirements for chiral drugs [176–178], continuous advancements in the asymmetric synthesis and characterization of chiral fluorine-containing compounds are critically important. Special attention should be directed towards the SDE phenomenon, a behavior observed in enantiomerically enriched compounds [179–181]. The SDE properties of chiral drugs, particularly those containing fluorine [182–184] and/or amino acid residues [185–187], represent a vital public safety concern necessitating rigorous evaluation of enantiomeric purity [188–191]. Monitoring the enantiomeric integrity of pharmaceutical drugs throughout synthesis [192, 193], production, and even storage is essential as SDE via sublimation poses a specific challenge for fluorine-containing drugs [194–196].

Additionally, caution should be exercised in light of growing public concerns over the potential harmful effects of fluorine on human health [197–199]. Since fluoride is recognized as the final metabolite of organic fluorinated compounds [197–201], patients prescribed

fluorine-containing drugs should consult their physicians about non-fluorinated alternatives where available or take steps to limit fluoride exposure from other sources such as fluoridated water and industrially produced foods treated with fluorinated agrochemicals [202]. Sadly, fluoride and the recent rise of perfluorinated "forever chemicals" (PFAS) [203] are notorious contributors to the persistent commercial-driven degradation of both the environment and human health [197] in addition to other contributions such as microplastics [204].

Despite these concerns, it remains an undeniable truth that pharmaceutical drugs are indispensable in modern medicine. They provide life-saving treatments, improve quality of life, and drive medical innovation addressing urgent health challenges and laying the foundation for future advancements in healthcare.

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СУЧАСНІ ФАРМАЦЕВТИЧНІ ПРЕПАРАТИ, ЩО МІСТЯТЬ АЛІФАТИЧНІ ФТОРВМІСНІ ГРУПИ

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У статті представлено десять лікарських засобів, що надійшли в продаж та були схвалені Управлінням з контролю за якістю харчових продуктів і медикаментів США (US FDA) протягом останніх п'яти років, які містять аліфатичне фторування – ключову структурну характеристику,

що має вирішальне значення для їхньої біологічної активності. Серед них: івосиденіб, розроблений для лікування гострого мієлоїдного лейкозу та холангіокарциноми (раку жовчних проток); уброгепант, схвалений для гострого лікування мігрені; аскімініб, що призначається для лікування хронічного мієлоїдного лейкозу в хронічній фазі; омавелоксолон, який використовують для лікування атаксії Фрідрайха, рідкісного генетичного розладу, що спричиняє прогресуюче ураження спинного мозку, периферичних нервів та головного мозку; флурпіридаз – радіоактивний діагностичний засіб для позитронно-емісійної томографії перфузії міокарда; упадацитиніб, розроблений для лікування кількох запальних та аутоімунних станів, включаючи ревматоїдний артрит, псоріатичний артрит, атопічний дерматит, виразковий коліт, хворобу Крона, анкілозуючий спондиліт та нерентгенографічний аксіальний спондилоартрит; тезакафтор, схвалений для лікування муковісцидозу як ефективний засіб; алпелісіб, що призначається для лікування раку молочної залози, ефективно інгібуючи ріст пухлини та аномальну проліферацію клітин; претоманід, який використовують у комбінованих терапіях для лікування туберкульозу з широкою та множинною лікарською стійкістю; атогоепант, схвалений для профілактичного лікування мігрені у дорослих, спрямований як на епізодичну, так і на хронічну мігрень. Молекули, що містять аліфатичне фторування, становлять труднощі через вищі виробничі витрати та складність прогнозування їхніх біологічних профілів. Однак незаперечні медичні переваги аліфатичного фторування, ймовірно, активізують цю галузь досліджень, відкриваючи шлях для розроблення більш інноваційних лікарських засобів, що вийдуть на фармацевтичний ринок. Окрім включення аліфатичних атомів фтору, шість із лікарських засобів, розглянутих у цій статті, містять залишки амінокислот або їхні похідні як ключові елементи структурного дизайну. Ще однією характеристикою, спільною для всіх цих препаратів, є їхня хіральність, причому кожна молекула має від одного до шести стереогенних атомів вуглецю. Особливу увагу слід приділити явищу самодиспропорціонування енантіомерів (SDE), нелінійній поведінці, що спостерігається в енантіомерно збагачених сполуках. SDE-властивості хіральних лікарських засобів, особливо тих, що містять фтор та/або залишки амінокислот, є важливою проблемою громадської безпеки, що вимагає ретельної оцінки енантіомерної чистоти. Крім цього, слід проявляти обережність у світлі зростаючої громадської стурбованості щодо потенційно шкідливого впливу фтору на здоров'я людини. Оскільки фторид визнано кінцевим метаболітом органічних фторованих сполук, то пацієнтам, яким призначено фторвмісні препарати, слід проконсультуватися зі своїми лікарями щодо нефторованих альтернатив, якщо такі є, або вжити заходів для обмеження впливу фториду з інших джерел, таких як фторована вода та промислово вироблені продукти харчування, оброблені фторованими агрохімікатами. Незважаючи на ці занепокоєння, залишається незаперечною істиною те, що фармацевтичні препарати є незамінними в сучасній медицині. Вони забезпечують життєво важливе лікування, покращують якість життя та стимулюють медичні інновації, вирішуючи нагальні

проблеми зі здоров'ям та закладаючи основу для майбутніх досягнень у сфері охорони здоров'я.

Ключові слова: фтор, аліфатичне фторування, фармацевтичні препарати, дизайн лікарських засобів, синтез, хіральність, біологічна активність, самодиспропорціонування енантіомерів (SDE), проблеми громадського здоров'я, перевантаження фтором організму людини та навколишнього середовища.

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