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Review

FDA-Approved Trifluoromethyl Group-Containing Drugs: A Review of 20 Years

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Abstract: As people around the world regard 2020 as the year of COVID-19, the medical community considers this year to be the second-best year, shared with the year 1996, with respect to the number of drug molecules approved by the US Food and Drug Administration (FDA). Both years, 2020 and 1996, had a record of 53 new drug molecules approved by the FDA. In the year 2020, 53 new chemical entities and 13 biological medicines were approved, including 10 monoclonal antibodies, 2 antibody-drug conjugates, 3 peptides, and 2 oligonucleotides. Among them, most of the compounds were found to have fluorine or fluorine-containing functional groups exhibiting numerous pharmacological activities. Herein, we summarized the trifluoromethyl (TFM, -CF_3)-group-containing FDA-approved drugs for the last 20 years. This article specially features and details the previous 20-year literature data, covering CF_3-incorporated potential drug molecules, including their syntheses and uses for various diseases and disorders. The review covers the detailed chemistry of 19 FDA-approved drugs in the past 20 years, which contains the TFM group as one of the pharmacophores.

Keywords: trifluoromethyl group; FDA-approved drugs; syntheses; uses

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1. Introduction

Organo-fluorine chemistry is a unique branch of organic chemistry, as the fluorine incorporation in the organic molecules exhibits bizarre behaviors; hence, several applications are witnessed in medicines, electronics, agrochemicals, and catalysis [1]. Since fluorine-containing compounds significantly affect pharmaceutical growth, they make up more than 50 percent of the best-selling drug molecules approved by the US Food and Drug Administration (FDA) [2,3].

The fluorine's electronegativity, size, electrostatic interactions, and lipophilicity are widely recognized factors that significantly impact the chemical reactivity, physico-chemical behavior, and biological activity [4]. According to a recent study by Hagmann, about 15–20 percent of all licensed drugs introduced annually in the market contain fluorine/fluorine-containing functional groups [5]. Fluorine's role in medicinal chemistry and drug design has been extensively discussed recently. It is difficult to offer even a cursory description of the considerable progress that has been reported in organo-fluorine chemistry [6]. The influence of fluorine on a metabolic cascade of chemical events is greatly amplified; thus, even a single fluorine atom can fully transform the biological characteristics of a natural product. The first was published as a series of papers from a symposium titled "Fluorine in the Life Sciences" held in Switzerland in July 2003; the papers focused on the biological activities, compositions, and properties of organo-fluorine compounds [7]. Fluorine substitution has been studied widely in drug development to improve biological activity, chemical or metabolic activity, and chemical or metabolic stability [8]. For determining the exact location

of fluorine's introduction in the target molecule, extensive structure–activity relationship (SAR) investigations are generally required. The so-called fluorine scan is now a standard procedure in developing medication candidates. Despite this, the vast amount of scientific, biological, and pharmaceutical data that has been gathered so far allows for some broad predictions regarding fluorine's influence on biological activity [9]. A large number of studies are being conducted on fluorine-containing pharmaceuticals. Some such interesting studies emphasized the market's overall incidence of fluoropharmaceuticals and its division into several categories based on the chemotype of their fluoro-functional groups and their intended use [10,11].

Although fluorine is larger in size than hydrogen, it is capable of mimicking hydrogen atoms on several occasions and exerting only a small steric hindrance at the receptor sites [12]. Fluorine is now widely used in materials engineering, including thermal-transfer agents, melted metals, surfactants, dyes, acrylics, thermoplastic, membranes, and other products. Many fluorine-containing physiologically active compounds are also employed as pharmaceuticals and agricultural chemicals.

Trifluoromethylation has become of broader interest among chemists and medicinal chemists after Lehmann's first report on the relationship of the trifluoromethyl (TFM or -CF_3) group with biological activity in 1958 [13,14]. For instance, the SAR studies showed that the inclusion of a -CF_3 group in the *para*-position of the phenolic ring increased the potency for inhibiting 5-hydroxytryptamine (5-HT) uptake by 6-fold, when compared to the corresponding non-fluorinated analog. A molecule with a -CF_3 group, attached to a tertiary stereogenic center in a hetero aliphatic ring exhibited improved drug potency toward reverse transcriptase enzyme inhibition by lowering the pK_a of the cyclic carbamate by a key hydrogen bonding interaction with the protein. Recently, numerous reagents have been developed for introducing the -CF_3 group into the organic compound of interest, such as trifluoromethylsilane, sodium trifluoroacetate, sodium trifluoromethanesulfinate (CF_3SO_2Na), trifluoromethanesulfonyl chloride, trifluoromethyl sulfone, and trifluoromethyl-metal. Trifluoromethylation is usually performed by aromatic coupling reactions [15], radical trifluoromethylation [16], nucleophilic trifluoromethylation [17], electrophilic trifluoromethylation [18], and asymmetric trifluoromethylation [19]. A wide range of articles have explored various aspects of trifluoromethylation reagents, among which a novel fluorinated Johnson-type reagent for electrophilic trifluoromethylation of carbon-centered nucleophiles is a remarkable finding [20,21].

Halogen bonding is a non-covalent interaction that is commonly found in many ligand–enzyme bindings [22]. It is the alluring interaction between an electrophilic region and a nucleophilic region of another molecule. It can also be defined as the consortium between an electrophilic section of a polarized halogen and a Lewis base section [23]. There are enumerable reactions that involve halogen bonds, such as reactions involving the activation of the XB donor, reactions leading to the activation of the XB acceptor, and catalytic reactions such as the Diels–Alder reaction, Aza–Diels–Alder reaction, Michael addition, and Nazarov cyclization [24]. Halogens present as monodentate and bridging ligands for a wide group of metals in a large group of organic compounds. Halogen bonding has extended its application to structural chemistry, material chemistry, synthetic chemistry, and much more [25].

Several research groups have created new synthetic protocols in recent years, resulting in a vastly comprehensive toolkit for R and D chemists, including -CF_3-containing compounds that perform a wide range of biological and chemical functions [26]. In medicinal chemistry, TFM is commonly used to replace the methyl group. In comparison to other alkyl groups, the -CF_3 group has a substantially higher electronegativity [27]. Because of its strong electron-withdrawing nature, broad hydrophobic domain, poor polarizability, and very inert carbon–fluorine linkages, this group must be introduced to therapeutic candidates. Some of the reagents containing the -CF_3 group are trifluoromethyl trimethylsilane, trifluoromethane, and trifluoromethyl sulfone [28]. The TFM group has also been involved in several chemical reactions, such as coupling reactions, nucleophilic reactions, and elec-

trophilic reactions. In this review, we exclusively focus on the CF_3-group-containing drugs approved by the FDA over the past 20 years and document the synthesis of the drug molecules and their importance for treating diseases.

2. FDA-Approved Drugs Containing TFM

2.1. Ubrogepant

Ubrogepant is a medicament used for acute migraine with or without visual disturbances. The meningeal blood vessels and dura are pain sensitive and innervated by peripheral sensory trigeminal nerves, producing this neurotransmitter, a calcitonin gene-related peptide (CGRP) receptor antagonist. During a migraine attack, levels of CGRP rise in the cranial circulation, and CGRP has been shown to cause migraine-like headaches. The synthesis and structure of ubrogepant is shown in Figure 1. Compound (3S, 5S, 6R)-6-methyl-2-oxo-5-phenyl-1-(2,2,2-trifluoroethyl)piperidin-3-aminium **1** was taken and reacted with 4-methylbenzoate **1a** and MTBE in the presence of 0.6 N HCl (1.2 equiv) to give intermediate (3S, 5S, 6R)-6-methyl-2-oxo-5-phenyl-1-(2,2,2-trifluoroethyl)piperidin-3-aminium **1b**. Then, the intermediate was reacted with (S)-2′-oxo-1′,2′,5,7-tetrahydrospiro[cyclopenta[b]pyridine-6,3′-pyrrolo [2,3-b]pyridine]-3-carboxylic acid in the presence of EDC (1.2 equiv), HOPO (0.1 equiv), MeCN, EtOH, and H_2O to give product **2** [29].

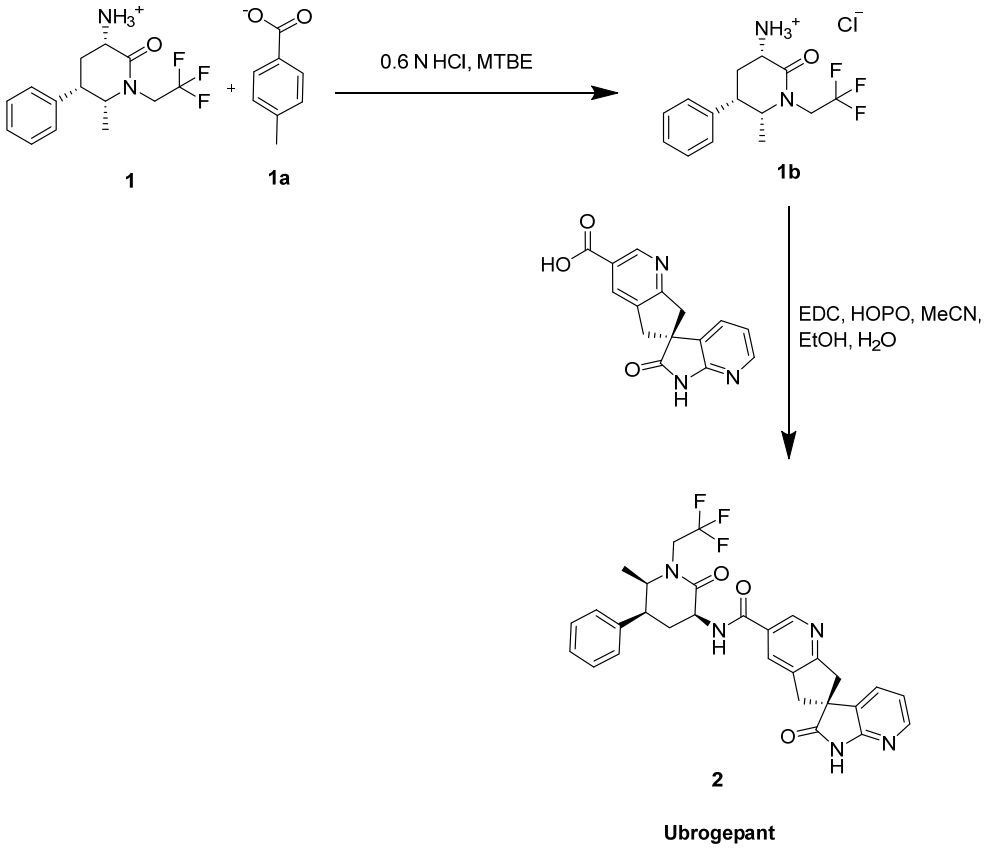

Figure 1. Synthesis and structure of ubrogepant.

2.2. Alpelisib

Alpelisib is a slightly hygroscopic crystalline powder, which is a phosphatidylinositol-3-kinase (PI3K) inhibitor, targeting a particular class of enzyme. PI3Ks are grouped in a type of lipid kinase involved in cell proliferation, apoptosis, motility, and cell invasion, as well as glucose metabolism. Alpelisib contains trifluoromethyl alkyl substituted pyridine, aminothiazole, and pyrrolidine carboxamide moieties attached through urea linkage (Figure 2). It was determined to be the best choice in this family of PI3K inhibitors. TFM

moiety inclusion was also observed to inhibit PI3K-dependent Akt activation at double-digit nanomolar range [30].

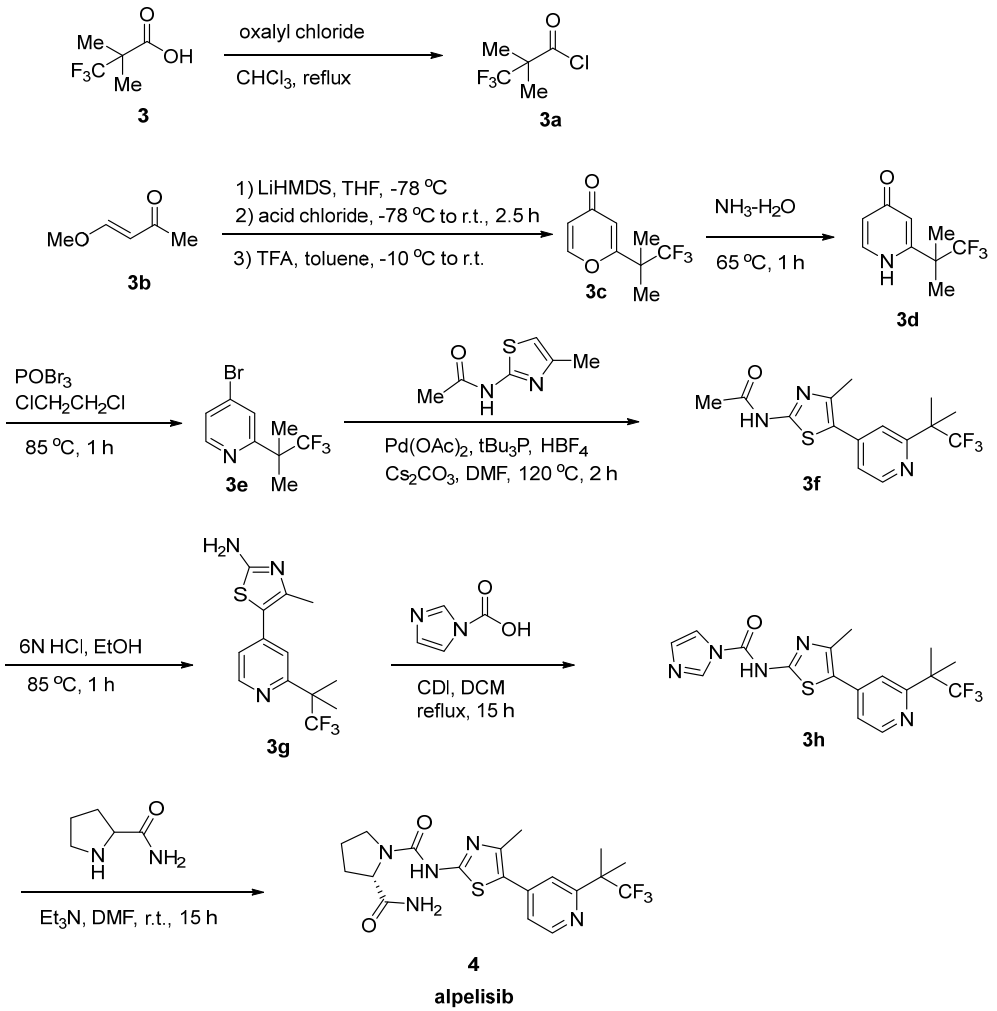

Figure 2. Synthesis and structure of alpelisib.

The main step of this synthetic route was the coupling process of 4-methyl-2-acetaminothiazole with a 4-bromopyridine intermediate catalyzed by Pd, which yielded alpelisib. Initially, oxalyl chloride was used to convert 3,3,3-trifluoro-2,2 dimethyl propanoic acid **3** to chloride **3a** with a quantitative yield [31]. The chloride was transformed into 4H-pyran-4-one **3c** intermediate by the synthesis of (E)-4-methoxybut-3-en-2-one **3b** with LiHMDS at −78 °C, followed by TFA-mediated cyclization. An amination replacement reaction involving 4H-pyran-4-one 3c intermediate with ammonia at 65 °C gave pyridin-4(1H)-one **3d**, which was subsequently treated with $POBr_3$ to generate the bromide intermediate **3e** in 51 min. The intermediate **3f** was then formed by a Pd-catalyzed coupling reaction between intermediate **3e** and 4-methyl-2-acetaminothiazole, which was then hydrolyzed in the presence of 6 M HCl and gave intermediate **3g**. Condensation of the acquired amine with 1H-imidazole-1-carboxylic acid yielded the imidazole intermediate **3h**, which was subsequently replaced by (S)-pyrrolidine-2-carboxamide at room temperature to generate alpelisib **4**. Condensation of the generated amine using 1H-imidazole-1-carboxylic acid yielded the imidazole intermediate, which was replaced using (S)-pyrrolidine-2-carboxamide at room temperature to create alpelisib [32].

2.3. Selinexor

Selinexor is a first-in-class exportin-1 receptor that has shown to be effective in patients who have relapsed or are refractory to other treatments. Selinexor has a half-life ($t_{1/2}$) of about 6–8 h when taken orally [33]. Selinexor is only approved for multiple refractory myelomas or relapsed patients that have refused to respond to at least four or five other treatments (referred to as "quad-refractory" or "penta-refractory" myeloma) and who have no alternative options for therapy [34].

Selinexor works by interacting with the CRM1 (also known as exportin 1 protein). CRM1 is a karyopherin that transports proteins from the nucleus to the cytoplasm, such as oncogenes, tumor suppressors, and proteins associated with cell growth regulation; it is frequently overexpressed, and its function is dysregulated in many cancers. SINEs cause an accumulation of tumor suppressors in malignant cell nuclei and lower amounts of oncogene products that stimulate cell proliferation by restoring the natural nuclear transport of these proteins. This causes cancer cells to enter a cell cycle arrest and die as a result of apoptosis [35].

Trifluoromethylated phenyl, 1,2,4-triazole, and 2-hydrazinylpyrazine are three main moieties in selinexor (Figure 3). Selinexor was shown to be highly cytotoxic in several myeloid leukemia cell lines, having IC_{50} values less than 0.5 mM. Furthermore, synergistic anticancer activity was observed when selinexor was used in conjunction with other drugs in preclinical trials. The mechanism for producing selinexor begins with 3,5-bis(trifluoromethyl)benzonitrile **5**. The 3,5-bis(trifluoromethyl)benzamide **5a**, which reacted with N,N-dimethyl formamide dimethyl acetal to yield the imine as the intermediate **5b**, was obtained by the hydrolysis of benzonitrile with K_2CO_3 in the presence of 30% H_2O_2. The 1,2,4-triazole intermediate **5c** was generated by a hydrazine's HOAc-catalyzed cyclization reaction of the intermediate imine at 50–55 °C. The ester was generated most of the time by substituting (Z)-methyl 3-iodoacrylate **5d** via the DMF intermediate (Z)-methyl 3-iodoacrylate) and treating it with LiOH. Selinexor 6 was then obtained in 83% yield by combining acid and 2-hydrazinylpyrazine **5e** in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC-HCl) [36].

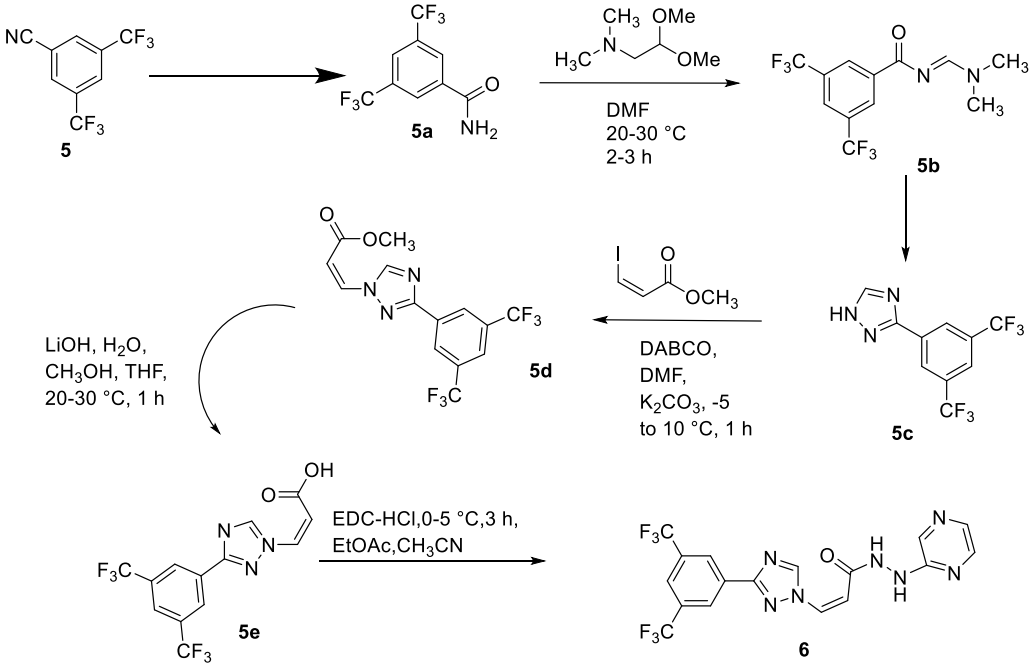

Figure 3. Synthesis and structure of selinexor.

2.4. Pexidartinib

Pexidartinib is a small chemical molecule, orally accessible tyrosine kinase inhibitor with selective activity against the KIT proto-oncogene, receptor tyrosine kinase (KIT), CSF1 receptor, and FMS-like tyrosine kinase 3 with an internal tandem replication mutation (FLT3-ITD) used to treat tenosynovial giant cell tumors [37]. Pexidartinib was discovered by Plexxikon Inc., Daiichi Sankyo's small molecule structure-guided research and development center. The Shanghai Institute of Pharmaceutical Industry developed a synthetic method for pexidartinib in 2019 that begins with 5-bromo-N-(4-methoxybenzyl)pyridine-2-amine **7** and involves a central tandem Tsuji–Trost reaction and Heck coupling. In the presence of BuLi, the reaction with DMF produces aldehyde **7a** in a 73% yield (Figure 4). Boc protection was then used to generate the intermediate **7b**, which was then followed by an aldol reaction between vinyl magnesium chloride and aldehyde. The central 1H-pyrrolo[2,3-b]pyridine intermediate **7c** was obtained in 69% yield using a tandem Tsuji–Trost reaction catalyzed by Pd and Heck coupling among pyridine intermediate and intermediate **7d**. After the Boc and PMB groups were deprotected, the free amine was transformed into pexidartinib **8** by reducing amination [38].

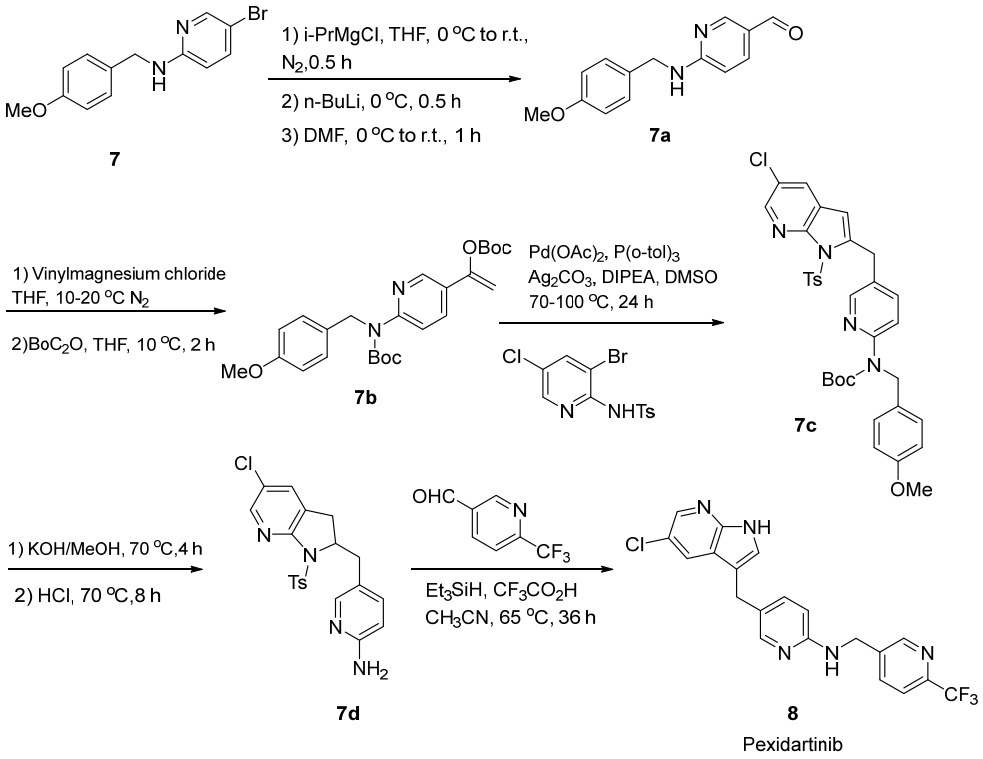

Figure 4. Synthesis and structure of pexidartinib.

2.5. Elexacaftor

Elexacaftor is chemically known as N-(1,3-dimethylpyrazol-4-yl)sulfonyl-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide [39]. The pathway begins with the conversion of 4-bromo-6-fluoronicotinic acid to nicotinamide. The fluoride was subsequently displaced by an S_NAr reaction mediated via potassium carbonate with pyrrolidine (Figure 5). The following two processes were sulfonamide production and C-N cross coupling. The sulfonamide was first formed by reacting sulfonyl chloride to lithium t-amoxide in 2-methyltetrahydrofuran to give elexacaftor [40].

Elexacaftor is a CFTR corrector that acts at a different binding site on the CFTR protein than tezacaftor to improve the CFTR protein's functioning at the cell surface. Elexacaftor,

tezacaftor, and ivacaftor improved the activity of the mutant CFTR protein at the outer cell surface, resulting in increased chloride ion transfer when used together [41].

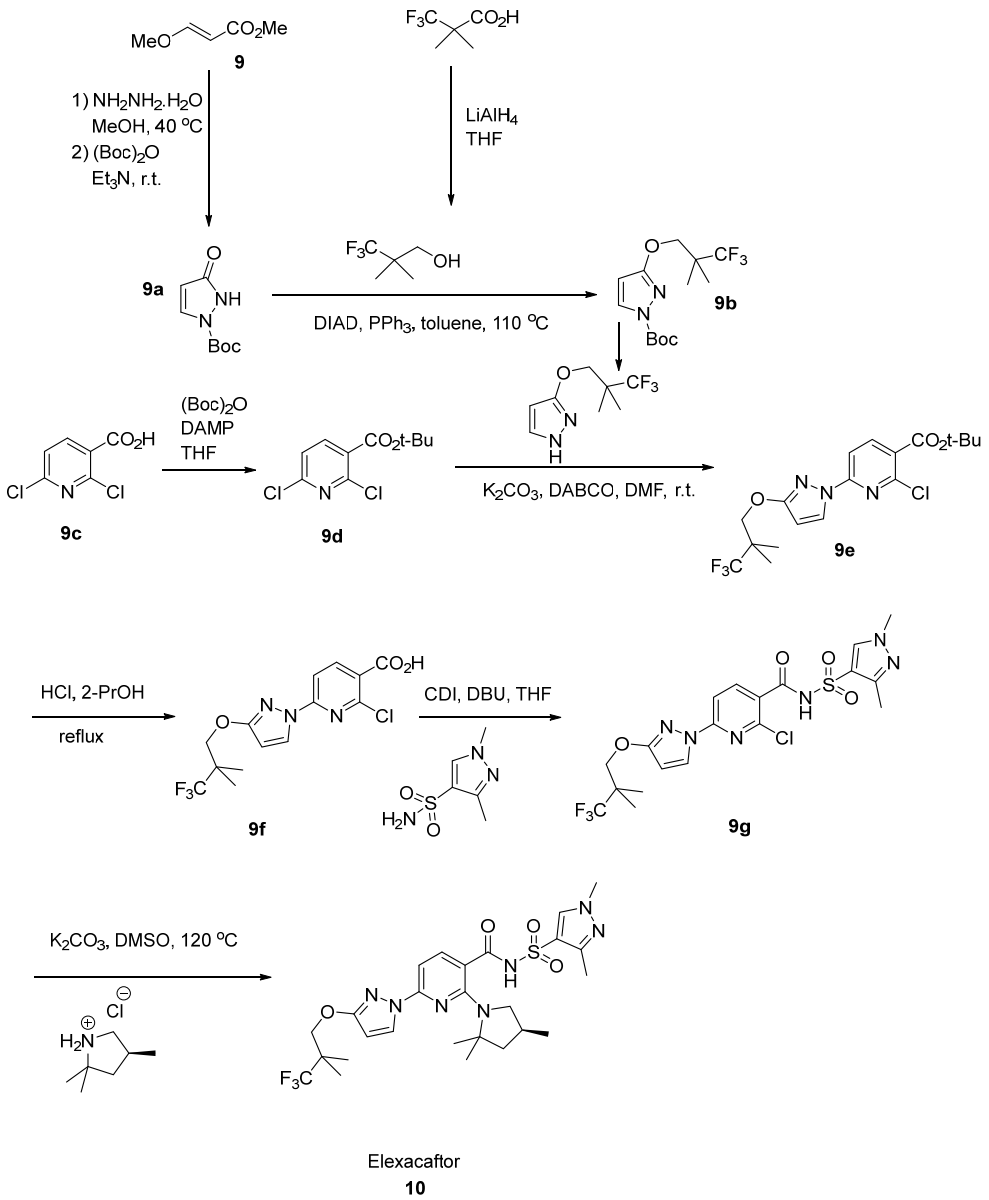

Figure 5. Synthesis and structure of elexacaftor.

2.6. Pretomanid

The Global Alliance for Tuberculosis Drug Development (TB Alliance) created pretomanid, an oral nitroimidazooxazine antimycobacterial agent used in the BPaL (linezolid, pretomanid and bedaquiline) and BPaMZ (pretomanid, moxifoxacin, pyrazinamide and bedaquiline) tuberculosis treatment regimens, under license from Novartis. Pretomanid sensitivity was similar to poly- and multidrug-resistant MTB strains, suggesting that there is no cross resistance with new MTB drugs. Pretomanid's structural resemblance to metronidazole indicated that it was also a prodrug, presumably enabled by nitro group bio-reduction [42].

TFM-substituted benzyl ether and bicyclic nitroimidazole with an (S) absolute structure carbon core are the two main moieties in pretomanid. It obtained FDA clearance for the first time in 2019 to treat adults with drug-resistant tuberculosis.

Reider et. al. developed a four-step procedure to synthesize pretomanid in 2010. The ester was obtained by esterifying (R)-3-chloro-1,2-propanediol **11a** with p-methoxybenzoyl chloride

11 in DCM with imidazole as the base (Figure 6). The formation of 4-(trifluoromethoxy)benzyl trichloroacetimidate **11d** was achieved by treating 4-(trifluoromethoxy)benzyl alcohol **11c** with sodium hydride in methyl t-butyl ether at 37 °C and then adding it to trichloroacetonitrile at 0 °C. After stirring at room temperature in the presence of stoichiometric toluene sulfonic acid, the trichloroacetimidate intermediate was transformed into glycidol-derived alkyl chloride **11e**. The intermediate was then replaced by 2-chloro-4-nitroimidazole in DMF at 120 °C in the presence of NaI and K_2CO_3, yielding the intermediate **11f**. Finally, by exposing the p-methoxybenzoyl group to simple conditions, the p-methoxybenzoyl group was deprotected, and intramolecular cyclization was achieved, yielding pretomanid **12** [43].

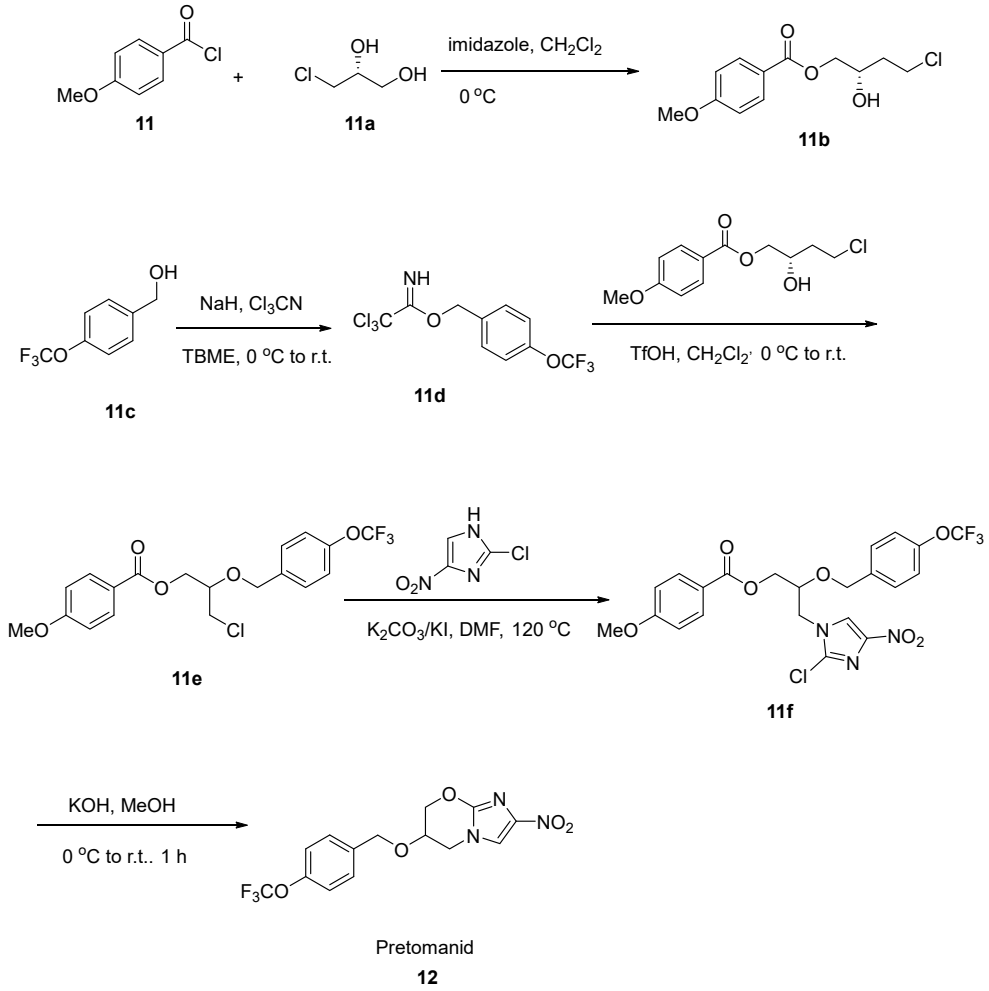

Figure 6. Synthesis and structure of pretomanid.

2.7. Gemigliptin

Gemigliptin is a new pyrimidino piperidine derivative-based structure. It binds to the DPP-4 enzyme's S1, S2, and S2 extensive subsites. Gemigliptin's piperidinone group connects to the S1 subsite, where an equatorial fluorine atom of piperidine ring makes hydrogen bonding interaction with Tyr631 residue, while an axial fluorine atom of piperidine ring forms a hydrophobic interaction with Tyr666 and Tyr662 residues. Furthermore, the main association exists between the CF3 groups on the DPP-4 substrate's S2 comprehensive subsite and the pyrimidino piperidine, which improves the drug's potency and selectivity. The association of the active component of the DPP-4 enzyme's S2 comprehensive subsite with CF3 groups on the pyrimidine piperidine increases gemigliptin's selectivity and potency as opposed to its competitors [44].

The preparation of two primary intermediates, dihydropyrido[3,4-d] pyrimidine **13c** moiety and amino acid moiety **13d**, was needed for gemigliptin synthesis (Figure 7). The

compound was formed by producing enolate from the compound with LHMDS and adding trifluoroacetate. The compound after Boc deprotection yielded a main amine intermediate in a reflux state. The amino derivative was made using a cyclization reaction, which gave the desired amino intermediate ((S)-3-((tert-butoxycarbonyl)amino)-4-(5,5-difluoro-2-oxopiperidin-1-yl)butanoic acid) **13g** after benzyl deprotection with Pd/C. Gemigliptin **14** was generated by combining this intermediate with EDC/HOBt and then Boc deprotection [45].

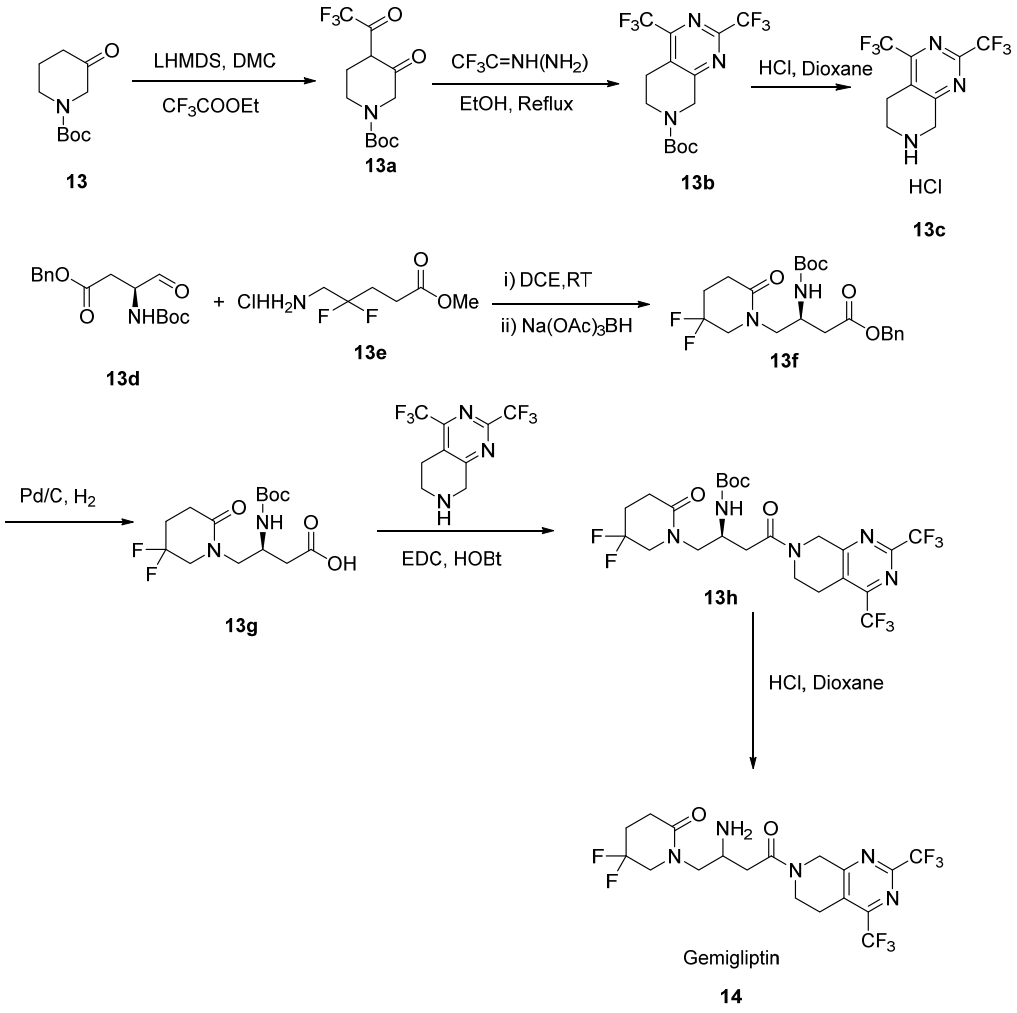

Figure 7. Synthesis and structure of gemigliptin.

2.8. Doravirine

Doravirine, the most recent non-nucleoside reverse transcriptase inhibitor (NNRTI), has been licensed as first-line medication as well as for those that are virologically suppressed on a safe antiretroviral (ARV) regimen. The widely available materials 2-bromoacetic acid and 2-chloro-3-fluoro-4-(trifluoromethyl)pyridine **15** were used to begin the synthetic work. The intermediate **15a** was obtained at 80 °C by treating it with 3-chloro-5-hydroxybenzonitrile, which was then irradiated in the microwave at 150 °C in the presence of NaOH to yield the main intermediate **15b** (Figure 8). Second, 2-bromoacetic acid was refluxed with $SOCl_2$, and at room temperature, a sequence of nucleophilic substitution reactions involving various substituted amines yielded the main intermediate [46].

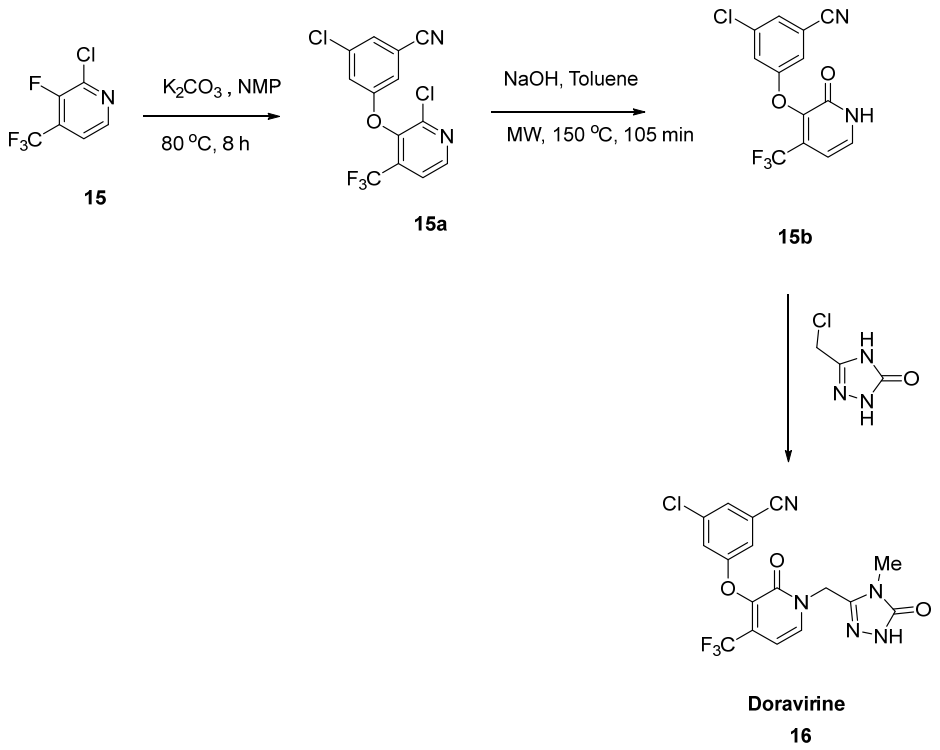

Figure 8. Synthesis and structure of doravirine.

2.9. Apalutamide

Aplutamide, an androgen receptor inhibitor, has been licensed to treat non-metastatic castration-resistant prostate cancer (nmCRPC). The only difference between this and enzalutamide is that it has a cyclobutane instead of a dimethyl appendage on the thiohydantoin and a pyridyl instead of a phenyl community [47].

In 2007, a UCLA patent application revealed a convergent path to apalutamide. The development of thiohydantoin is the final step on the road to apalutamide, which uses the same technique as enzalutamide. Isothiocyanate and cyanoamine were mixed in DMF for 20 h under microwave conditions at 80 °C, accompanied by the addition of 2N HCl/MeOH and 2 h of reflux (Figure 9). Apalutamide **18** was isolated by chromatography after an aqueous workup [48].

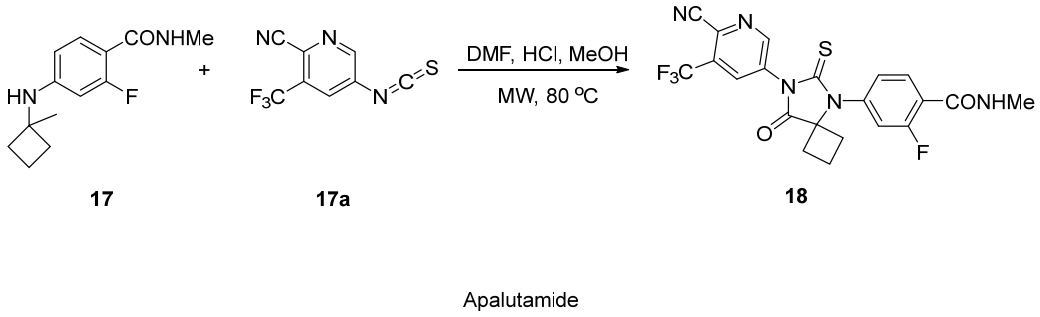

Figure 9. Synthesis and structure of apalutamide.

2.10. Enasidenib

Enasidenib is a novel small molecule inhibitor of mutated isocitrate dehydrogenase-2 taken orally. It is now approved for usage at a dosage of 100 mg daily. Enasidenib is metabolized by the enzymes cytochrome (CYP) and upper gastrointestinal tract (UGT). It can induce the enzymes CYP3A4 and CYP2B6 in particular. However, since it activates certain hepatic enzymes, the cumulative effects on other drugs are unknown at this point [49].

Tetrahydrofuran, 2,4-dichloro-6-(6-trifluoromethyl-pyridin-2-yl), 3,5-triazine **19**, 4-amino-2-(trifluoromethyl)pyridine, and $NaHCO_3$ were added to the reaction tank at a temperature of 20–35 °C (Figure 10). The resultant mixture was heated to reflux (75–80 °C) for 20–24 h. After the reaction has cooled to between 30 and 40 °C, THF was evaporated under decreased pressure at a temperature below 45 °C. The reaction mixture was washed with ethyl acetate and water after cooling to between 20 and 35 °C, and the ethyl acetate coating was removed and rinsed with brine solution and 0.5 N HCl. The organic layer was reduced under vacuum at temperatures beneath 45 °C, subsequently cleaned using dichloromethane and hexanes, filtered and washed using hexanes, after which it was vacuum dried about 5–6 h at 45–50 °C to give 4-chloro-6-(6-(trifluoromethyl)pyridin-2-yl)-N-(2-(trifluoromethyl)pyridin-4-yl)-N-(2-(trifluoro-l,3,5-triazin-2-amine **19a** having the formula l,3,5-triazin-2-amine [50], and 1,1-dimethylaminoethanol was added to the reaction vessel at 20–35 °C to obtain enasidenib **20**.

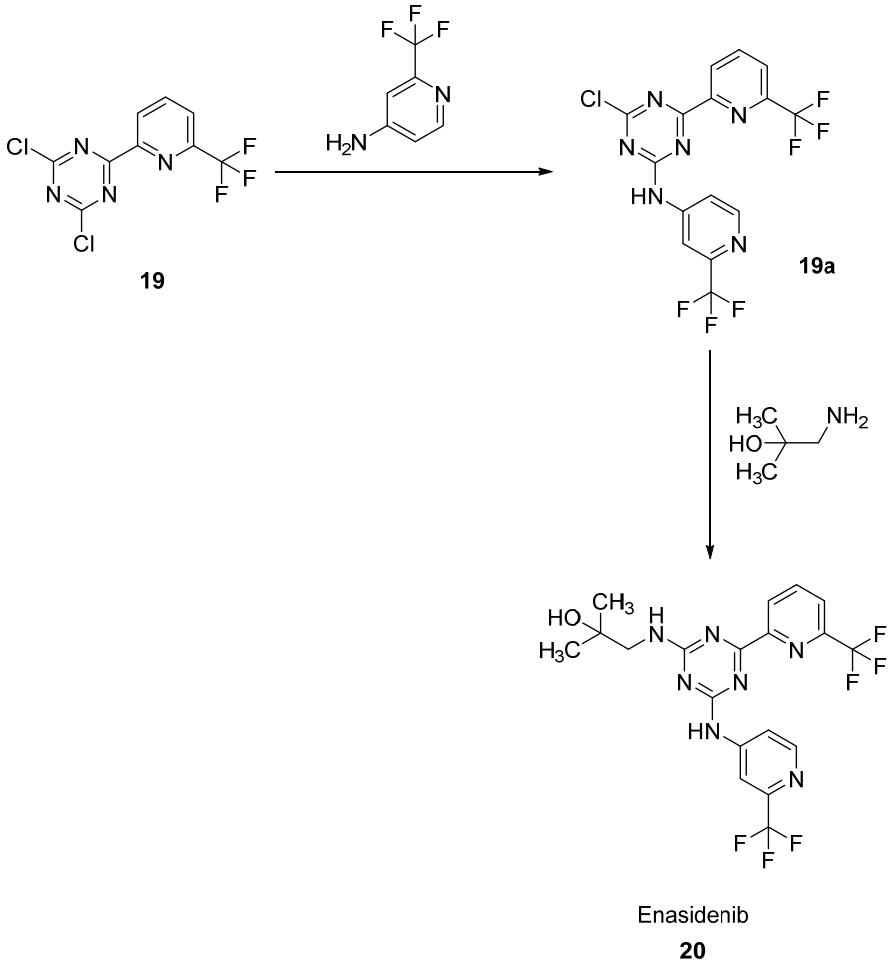

Figure 10. Synthesis and structure of enasidenib.

2.11. Tecovirimat

After a high-throughput screening of 350,000 chemically complicated libraries, a potent drug molecule, tecovirimat **21** (previously known as ST-246) was found (Figure 11). It was shown to be specific for orthopoxviruses that cause severe diseases in humans, including cowpox, vaccinia, rabbitpox, ectromelia, and the clinically important VARV and monkeypox. Tecovirimat is a nucleoside analog that suppresses viral DNA replication and thus is completely potent toward the cidofovir-resistant cowpox virus. The tecovirimat target is a virally encoded protein (usually known as p37) present in all orthopoxviruses but with no mammalian counterpart [51].

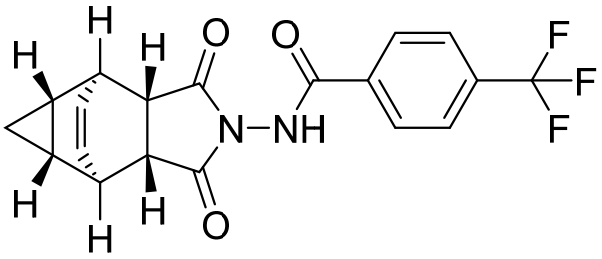

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Figure 11. Structure of tecovirimat.

2.12. Tafenoquine

In the 1980s, the Walter Reed Army Institute of Research developed tafenoquine (WR 238605). More than 4000 people have received it as a part of various survey. By delivering a radical solution in a single dosage, tafenoquine tackles the potentially severe question of inadequate adherence to regular primaquine. Tafenoquine is an 8-aminoquinoline that was recently approved for use against all stages of malaria. It may be used for Plasmodium vivax causal prophylaxis or radical cure [52].

In the feeding vacuoles, tafenoquine, an analogue of primaquine, accumulates and prevents the malarial parasite from detoxifying heme to hemozoin. It does this by attaching to the hematin dimer and blocking the synthesis of hemozoin, which is composed of cyclic heme dimers arranged in an ordered crystalline structure by intermolecular hydrogen bonding. Through its hydroxylated metabolites, tafenoquine causes the hexose monophosphate shunt to open, raise methemoglobin levels, and decrease glutathione levels in cells. Its exoerythrocytic schizontocidal activity and erythrocytic schizontocidal activity are both correlated with the pro-oxidant characteristics of its metabolites [53].

The synthesis of tafenoquine began with the nitration of veratrole **22** in positions 4 and 5 (Figure 12). The quinoline system **22c** was built using a Skraup reaction involving methyl vinyl ketone, and one nitro group was reduced by ammonia in methanol. Phosphorus oxychloride was used to selectively demethylate the 5-methoxy group and transform the hydroxy group into the 5-chloroquinoline **22e**. Following the action of 3-hydroxybenzotrifluoride and the reduction of the 8-nitro group, the main intermediate **22f** was obtained in a 7% yield [54], which reduced to give tafenoquine **23**.

2.13. Fluoxetine

Fluoxetine is a selective serotine reuptake inhibitor that is used as an anti-depressant drug. It is used to treat conditions such as panic disorder, bulimia nervosa, and obsessive–compulsive disorder. The chemical name for fluoxetine is N-methyl-3-phenyl-3-[4-(trifluoromethyl) phenoxy] propan-1-amine [55]. The mechanism of action shows that the fluoxetine blocks the reuse of serotonin by blocking the reuptake transporter protein, which is located in the presynaptic terminal. It also inhibits the expression of pro-inflammatory cytokines, preventing heIL-6-mediated inflammation. The synthesis of fluoxetine starts with p-trifluoromethylphenol reacted with the 3-(chloro)-N-methyl-3-phenylpropylamin in the presence of potassium carbonate (Figure 13). The drug is currently marketed in its racemic form, and the studies show that the two racemic forms have different activities. Most antidepressant drugs contain halogens, especially fluorine, for the high-affinity interaction between protein and ligand because fluorine serves as hydrogen bond acceptors. Fluoxetine shows six-fold selective serotine reuptake inhibitor activity, as it contains the TMF group on the phenolic ring at the para position [56].

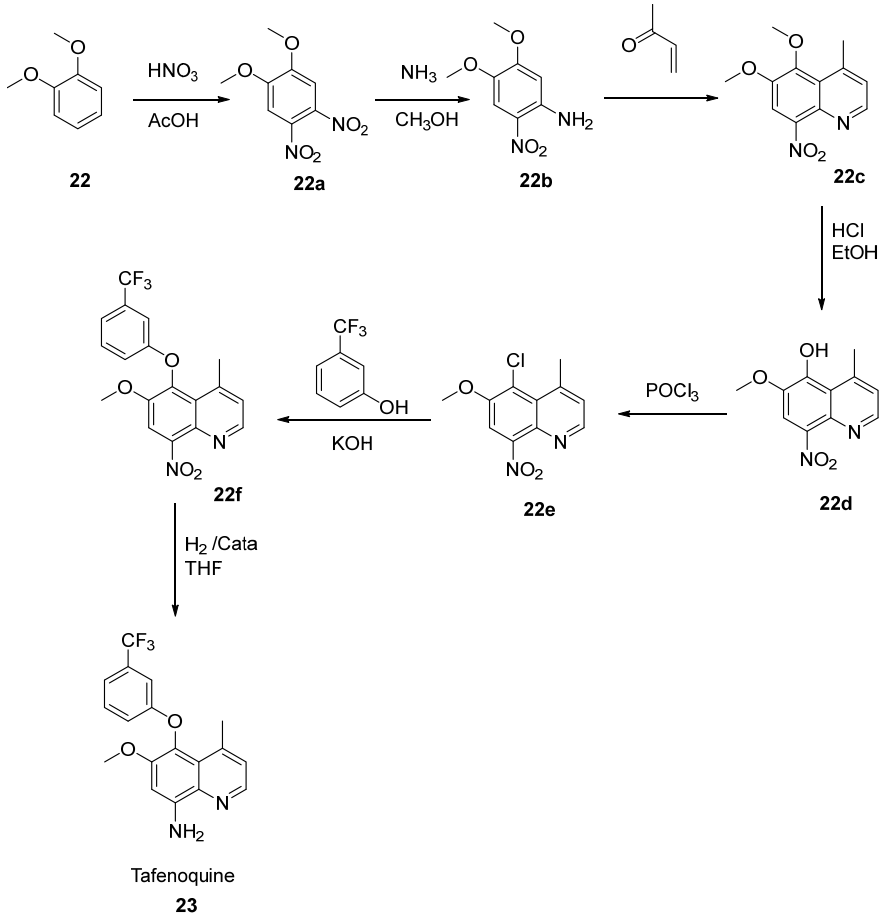


Figure 12. Synthesis and structure of tafenoquine.

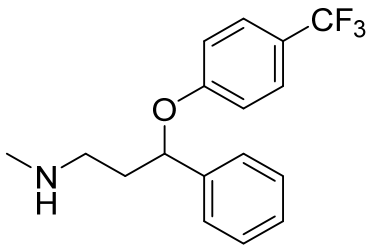
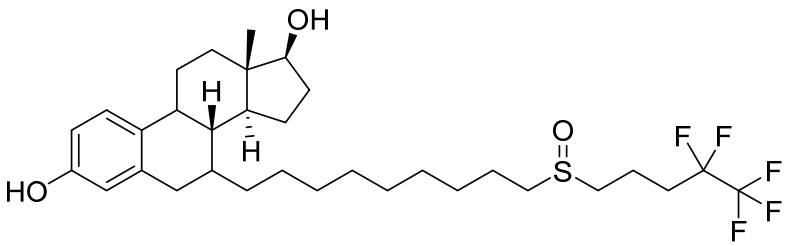


Figure 13. Structure of fluoxetine.

2.14. Fulvestrant

Fulvestrant is a selective down regulator of the estrogen receptor. It is used in the therapy of hormone-receptor-positive metastatic breast cancer. The IUPAC name of fulvestrant is (7*R*,8*R*,9*S*,13*S*,14*S*,17*S*)-13-methyl-7-[9-(4,4,5,5,5-pentafluoropentylsulfinyl)nonyl]-6,7,8,9,11,12,14,15,16,17-decahydrocyclopenta[a]phenanthrene-3,17-diol (Figure 14). Fulvestrant injection is used to treat a specific type of advanced hormone receptor-positive breast cancer, either alone or in conjunction with ribociclib [57]. The drug's mechanism of action is the down regulation of the estrogen receptors when the drug binds to the receptor. Fulvestrant degrades the receptors to which they bind. This helps achieve the anti-estrogen effect, which can inhibit the estrogen-sensitive human breast cancer cell lines. In the production of fulvestrant, a combination of sulfoxide isomers is produced. The major

step in the synthesis of stereoselective 1,6-addition is the conversion of an organocuprate to a steroidal dienone, followed by copper-mediated A-ring aromatization. In a report test in HepG2 cells transiently transfected with ER, side chain lengths of 15–19 atoms were ideal for pure antiestrogenicity. Shorter side chains (13 or 14 carbon side chains) result in either agonist or SERM action [58].



25

Figure 14. Structure of fulvestrant.

2.15. Sorafenib

Sorafenib is an approved drug for the therapy of primary kidney and liver cancer. Sorafenib binds to a variety of intracellular but also cell surface kinases. Sorafenib lowers blood flow to the tumor because many of these kinases are considered to be engaged in angiogenesis. Sorafenib targets the Raf/Mek/Erk pathway. The blocking of these kinases and thus genetic transcription affecting cell growth and angiogenesis are suppressed [59]. The IUPAC name of sorafenib is 4-[4-[[4-chloro-3-(trifluoromethyl)phenyl]carbamoylamino] phenoxy]-N-methylpyridine-2-carboxamide. The FDA has also granted it "Fast Track" designation for the therapy of advanced hepatocellular carcinoma (primary liver cancer). The tosylate salt of sorafenib is used to make it.

Picolinic acid **26** is converted to acid chloride salt **26a** by reacting it using thionyl chloride into DMF. Carboxamide **26c** is generated by reacting this salt using methylamine dissolved in tetrahydrofuran (THF). As this carboxamide is reacted in the presence of 4-aminophenol into anhydrous DMF and potassium tert-butoxide, the product is 4-(2-(N-methylcarbamoyl)-4-pyridyloxy)aniline **26d**. Sorafenib **27** is synthesized by reacting the aniline in methylene chloride with 4-chloro-3-(trifluoromethyl) phenyl isocyanate (Figure 15) [60].

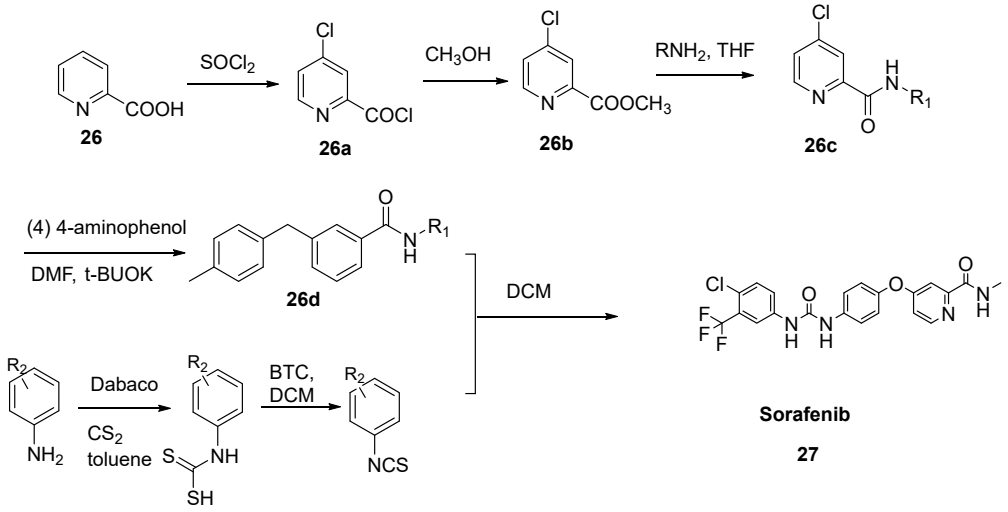


Figure 15. Synthesis and structure of sorafenib.

2.16. Tipranavir

Tipranavir is an anti-HIV drug that was approved in 2005. It was the first non-peptidic protease inhibitor which is used in the treatment of multidrug-resistant HIV. It was used along with ritonavir as a combination medicine [61]. Tipranavir is the first protease inhibitor (PI) explicitly developed against PI-resistant viruses. This is due to their ability to bind to the active site of the protease enzyme more efficiently with fewer H bonds. Moreover, they form a strong H-bonding with the amide backbone of the protease enzyme. The trifluoromethyl-2-pyridyl moiety in tipranavir contributes to multiple interactions at the enzyme site. It interacted with S3 subsite of the protease enzyme [62].

Trost and Anderson developed a concise synthesis of tipranavir by using the DYKAT strategy. Tipranavir was obtained in 92% yield. It was based on a retrosynthetic approach, where the drug was retro synthesized back into corresponding aldehyde, ester, and sulphonyl chloride. The chiral aldehyde **28** was synthesized from vinyl epoxide using asymmetric allylic alkylation using palladium as a catalyst, whereas another key ester intermediate **28a** was synthesized using asymmetric allylic alkylation from a carbonate using molybdenum as the catalyst (Figure 16). The synthesis was completed by the aldol coupling of intermediate aldehyde and ester. A β-ketoester **28b** was formed after the Dess–Martin oxidation of the above product. After removing the protecting group, the pyrone **28c** formation took place, which was then followed by hydrogenation to form an amine compound. The amine was then treated with (5-trifluoro methyl)-2-pyridine sulfonyl chloride to give the product **29** [63].

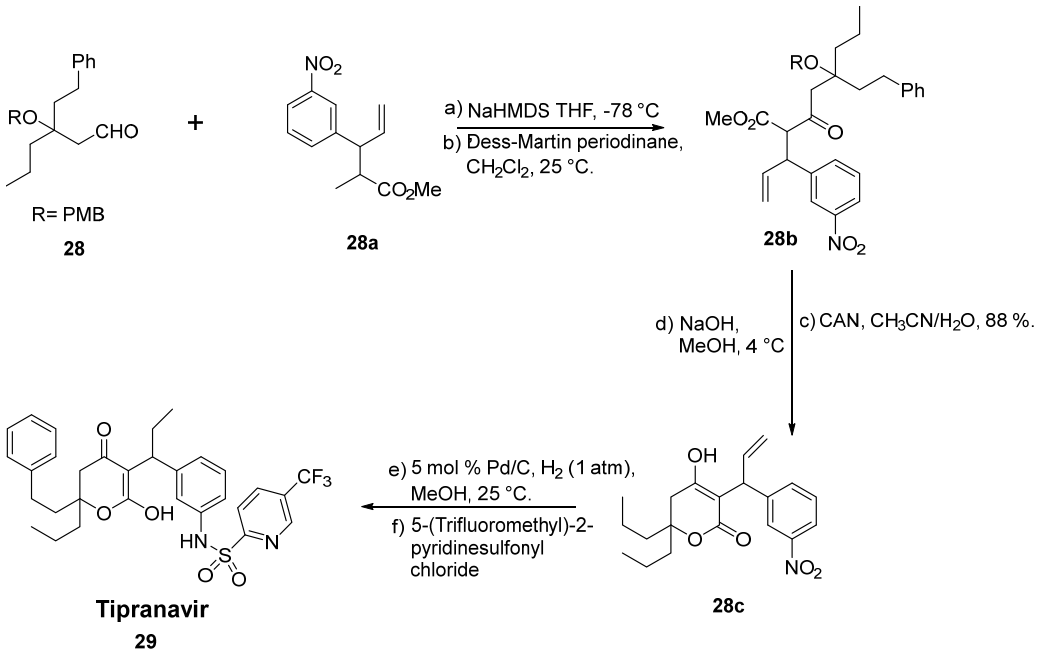


Figure 16. Synthesis and structure of tipranavir.

2.17. Travoprost

Its IUPAC name is propan-2-yl (Z)-7-[(1R, 2R, 3R, 5S)-3,5-dihydroxy-2-[(E, 3R)-3-hydroxy-4-[3-(trifluoromethyl)phenoxy]but-1-enyl]cyclopentyl]hept-5-enoate. Travoprost, a PGF2α analogue, is a potent prostaglandin F receptor agonist. In 2001, it was authorized for the treatment of glaucoma in adults. There have been many studies regarding the efficacy of travoprost for treating glaucoma. It is chemically an isopropyl ester of PGF2α. Travoprost reduces intraocular pressure through prostaglandin F receptors. Being an ester prodrug gives them lipophilic properties and increases penetration through the corneal epithelium, unlike natural prostaglandin PGF2α [64].

A more convergent synthesis of travoprost was developed, where a prostaglandin phenyl sulfone was treated with enantiomerically pure aldehyde via Julia–Lythogoe olefination. The initial step was the synthesis of aldehyde ω side-chain synthon from solketal,

which involved a six-step process. An enantiomerically pure acetonide was synthesized from solketal **30** (Figure 17). Solketal was converted to tosylate using *p*-toluenesulfonyl chloride in pyridine. Tosylate was then converted to acetonide using 3-trifluoromethylphenol via o-alkylation. The acetonide as well as its enantiomeric impurity was also synthesized by the same procedure. The acetonide was then converted to the corresponding diol **30b** using hydrochloric acid. The secondary hydroxyl group of the diol was then esterified to α-hydroxy ester. The ester **30c** was protected using TBDMS (tert-butyl dimethylsilyl). The deprotection of ester **30d** using DIBAL-H gave the corresponding alcohol **30e**. The alcohol was then converted to the target aldehyde **30f** via Dess–Martin periodinane. The aldehyde was then added to the phenyl sulfone prostaglandin **30g** using LDA as the base (lithium diisopropyl amide). The corresponding hydroxyl sulfone **30i** was subjected to reductive elimination in the presence of sodium amalgam to yield a prostaglandin precursor **30j**. Deprotection to 2,2-bis(hydroxymethyl)propyl ester **30k**, followed by the treatment with lithium hydroxide and citric acid yielded fluprostanol **30l,** which was then converted to travoprost **31** [65].

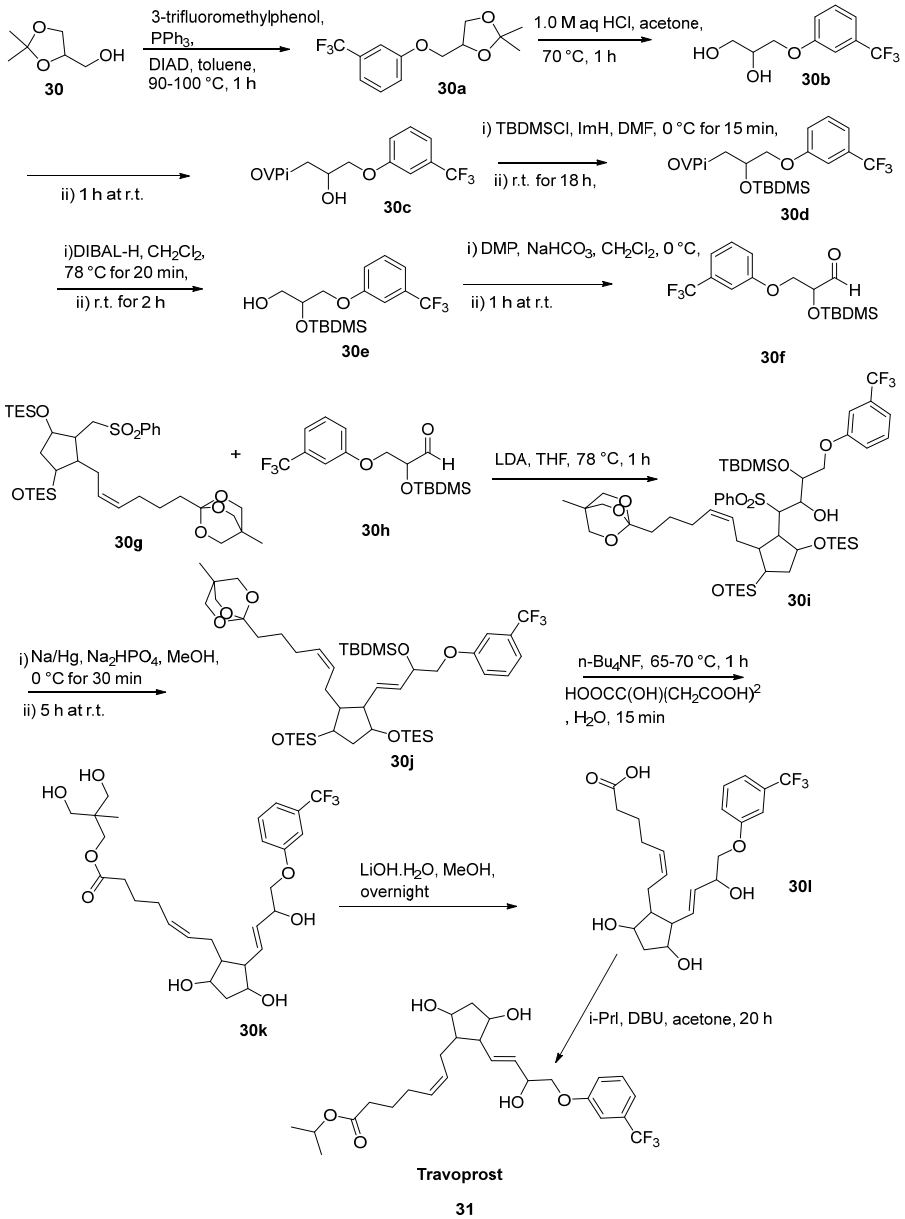


Figure 17. Synthesis and structure of travoprost.

2.18. Dutasteride

The role of 5α-reductase in the development of prostate cancer and benign prostatic hyperplasia has been established. Dutasteride was marketed in 2001 as an inhibitor of 5α-reductase, unlike finasteride, which inhibits both of its isoforms. Dutasteride is a finasteride analogue with the tert-butyl amide moiety being replenished with a 2,5-bis(trifluoromethyl)phenyl group. This replacement at the C17 position of finasteride has brought a significant inhibitory constant value (K_i value) of 6 and 7 nM for both the isoforms of 5α-reductase, making it 40-fold more potent than finasteride [66].

Efficient synthesis of dutasteride with 3-oxo-4-aza-5α-androstane-17 carboxylic acid **32** as the starting material was developed (Figure 18). It was oxidized in the presence of DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), BSTFA (N,O-bis(trimethylsilyl)trifluoroacetamide), and trifilic acid to form a decarboxylic acid intermediate **32a**, which, upon treatment with thionyl chloride followed by treatment with ammonia, gives an amide intermediate **32b**. The amide when treated with a Cu powder and potassium carbonate in o-xylene gives dutasteride **33** [67].

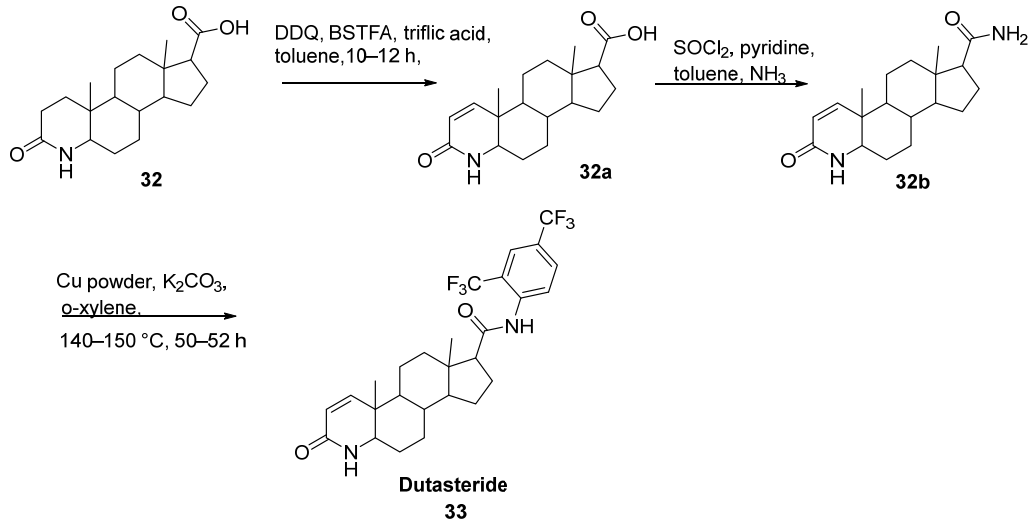


Figure 18. Synthesis and structure of dutasteride.

2.19. Berotralstat

Berotralstat is a medication used in the prophylaxis of attacks in HAE (hereditary angioedema) in the age group of about 12 years or above. The IUPAC name of berotralstat is 2-[3-(aminomethyl) phenyl]-N-[5-[(R)-(3-cyanophenyl)- (cyclopropylmethylamino) methyl]-2-fluorophenyl]-5-(trifluoromethyl)pyrazole-3-carboxamide, with molecular formula is $C_{30}H_{26}F_4N_6O$. HAE is an uncommon condition resulting from a mutation in the SERPING1 gene, which causes significant inflammation of the skin and upper respiratory tracts [68]. Berotralstat was developed by Bio Cryst Pharmaceuticals (Durham, CA, USA), and it is available as a capsule for oral administration for HAE attack. It acts by inhibiting the enzymatic reactions of plasma kallikrein in releasing bradykinin, the primary biological peptide responsible for the swelling and discomfort associated with HAE attacks. Berotralstat was approved by the FDA on 3 December 2020. Berotralstat was only used to avert HAE attacks, not to cure them. Prior treatments used for prophylaxis, such as androgens, are restricted due to many unappealing adverse effects.

The preparation of berotralstat was performed in a four-step process (Figure 19). At first, 3-((3-amino-4-fluorophenyl)(hydroxy)methyl)benzonitrile was prepared. The solution of 3-formylbenzonitrile **34** was taken in THF (tetrahydrofuran), freshly prepared Grignard reagent cooled to 0 °C was added (in solution), and the solution was stirred on 0 °C up to 1 h, or for 18 h into room temperature. The reaction mixture was stirred for 3 h by mixing with 1 N HCl, adding NaOH till pH = 8.0. Ethyl acetate was added to extract the mixture, and brine was added to the combined mixture for washing, dried up on $MgSO_4$, and then filtered

and passed into a vacuum for the product's concentration. Flash column chromatography was used for purification of the product, and elution was performed with hexanes/ethyl acetate as a solvent to obtain 3-((3-amino-4-fluorophenyl)(hydroxy)methyl)benzonitrile **34a** as a brown-color gummy material, which was used in the next step of the process. In the solution of a 3-((3-amino-4-fluorophenyl)(hydroxy)methyl)benzonitrile **34a** in DMF, l-(3-((tert- butoxycarbonylamino)methyl)phenyl)-3-(trifluoromethyl)-lH-pyrazole-5-carboxylic acid, N-ethyl-N-isopropylpropan-2-amine, and bromotripyrrolidin-l-ylphosphonium hexafluorophosphate were included, and the mixture was stirred for 19 h at 37 °C. Ethyl acetate was included in to obtain the diluted reaction mixture, and water and brine were added for washing; then, drying was performed with $MgSO_4$ and the mixture was filtered and passed in vacuum for a concentrated product. Flash column chromatography was used for purification of the product, and elution was performed with hexanes/ethyl acetate as a solvent to obtain tert-butyl 3-(5-(5-((3-cyanophenyl)(hydroxy)methyl)-2-fluorophenylcarbamoyl)-3-(trifluoromethyl)-lH-pyrazol-l-yl)benzylcarbamate **34b** as a yellow-color solid. To the solution **34b** in DMF, thionyl chloride was added and kept at room temperature. Then flash chromatography was used to purify the product by elution with hexanes/ethyl acetate as a solvent to obtain gummy compound **34c** as a colorless compound. Then, to a tert-butyl 3-(5-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenylcarbamoyl)-3- (trifluoromethyl)-lH-pyrazol-l-yl)benzylcarbamate **34c** in 1,4-dioxane as a solution, HCl was added and continuously stirred for 16 h at room temperature. Then the reaction mixture was washed with hexanes and decanted two times. Flash column chromatography was used to purify the insoluble crude product to obtain l-(3- (aminomethyl)phenyl)-N-(5-((3-cyanophenyl)(cyclopropyl-methylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazole-5-carboxamide. Methanol was used as a solvent to dissolve the pure product, and 4 N HCl was added. The mixture was concentrated in vacuum till dry to obtain the HCl salt of l-(3- (aminomethyl)phenyl)-N-(5-((3-cyanophenyl)(cyclopropyl-methylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-lH-pyrazole-5-carboxamide **35**.

Hereditary angioedema (HAE) attacks are the major indication for using berotralstat. Abdominal discomfort, back pain, heartburn, nausea, vomiting, bloating, excessive gas in the intestines, a sense of being full, diarrhoea, headaches, rapid or irregular heartbeats, and unusual weariness or weakness are among the adverse effects. Berotralstat's pharmacological characteristics were observed in high absorbing quality. For 6 to 12 days following the first dose, berotralstat's balanced state was attained. After a once-daily dose, berotralstat's concentration maxima and area under the curve were around five times higher than they were after a single dose. With the administration of berotralstat once daily by the oral route, the constant-state C_{max} at 150 mg was 158 ng/mL (range: 110 to 234 ng/mL) and 97.8 ng/mL (range: 63 to 235 ng/mL) at 110 mg. At 110 mg, the dosage interval AUC was 2770 ng.h/mL (range: 1880 to 3790 ng.h/mL) and 1600 ng.h/mL (range: 950 to 4170 ng.h/mL). In a fasting condition, the median T_{max} is 2 h, while a high-fat meal delays T_{max} to 5 h. T_{max} might range between 1 and 8 h. For the volume of distribution, the ratio of blood to plasma was almost 0.92, following an individual dose of 300 mg radiolabeled berotralstat administered. Berotralstat was metabolized primarily thorough CYP2D6 and CYP3A4, though the metabolic pathway has not yet been characterized. In the biological half-life, following a single oral dosage of 300 mg radiolabelled berotralstat, the average elimination half-life was 93 h, ranging from 39 to 152 h. In the elimination path, following a single oral dosage of 300 mg radiolabeled berotralstat, roughly 9% of the medication was eliminated in the urine, with the unmodified parent drug accounting for 1.8% to 4.7% of the total radiolabeled molecule. Approximately 79% of the medication was eliminated in the feces [69].

The structures, names, and therapeutic uses of all FDA-approved drugs containing the TFM group are depicted in Table 1.

The year 2020 is recognized as COVID-19 year, according to the general public and the pharmaceutical business environment. Between the time the illness was discovered and the first immunizations were given out, only approximately a year had passed. Although

the general public may believe this is a long time, those in the medical sector understand that it is a blip on the radar when compared to the time it takes to study and approve a vaccine. Indeed, in this short time, the illness was discovered, two first-in-class vaccinations were approved, with sophisticated production and shipping logistics, and the vaccines were mass rolled out across North America, Europe, and other areas of the world. These accomplishments are a reflection of the pharmaceutical ecosystem's strength and stability, which comprises biotech businesses, academic groups, major pharma corporations, contract research and production organizations and, last but not least, regulatory authorities. Fluorine-containing pharmaceuticals do not provide any additional challenges in terms of synthesis since most of the examples listed here may be made using standard procedures for non-fluorinated analogues. Except in rare situations of polyfluorinated moieties directly impacting the reaction centers, the presence of fluorine atoms and groups may need certain changes to the reaction conditions or isolation technique [70].

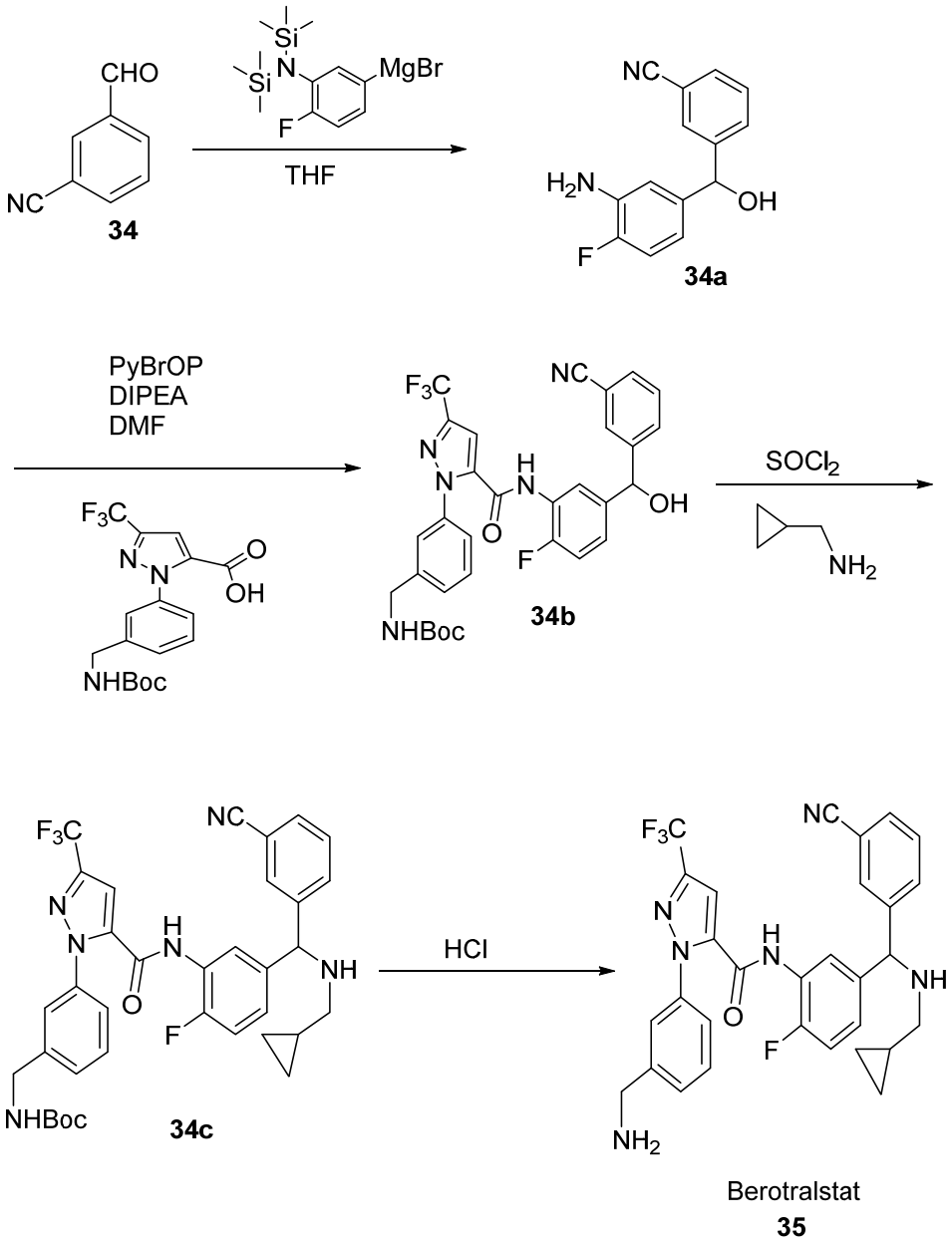


Figure 19. Synthesis and structure of berotralstat.

Table 1. Structures and names of trifluromethyl group containing FDA-approved drugs.

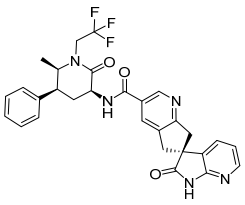
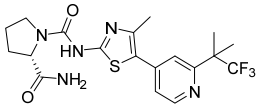
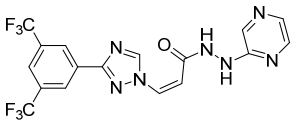
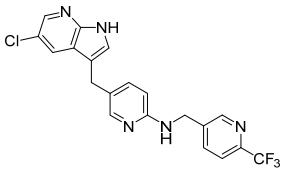
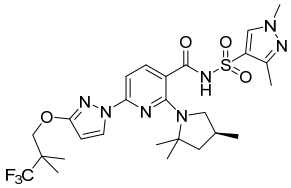
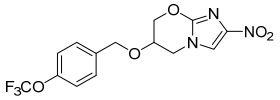
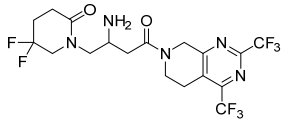
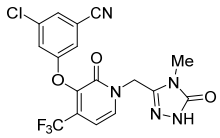
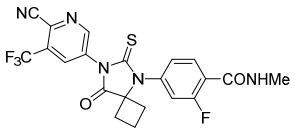
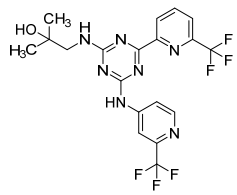
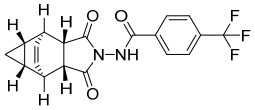
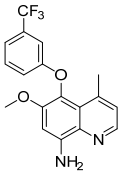
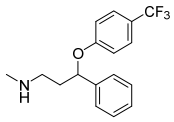
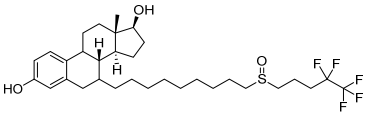
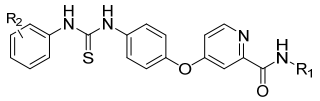
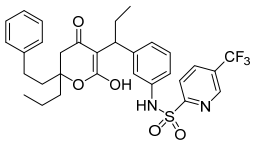
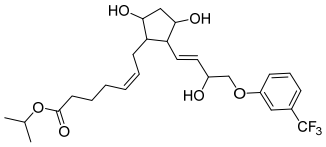
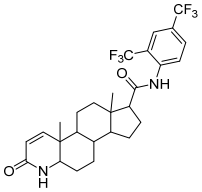
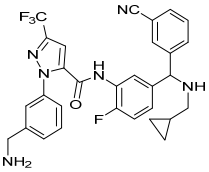
Structure	Name	Therapeutic Use	Ref.
	Ubrogepant	Migraine	[29]
	Alpelisib	Breast Cancer	[32]
	Selinexor	Anticancer	[36]
	Pexidartinib	Anticancer	[38]
	Elexacaftor	Cystic fibrosis	[41]
	Pretomanid	Tuberculosis	[43]
	Gemigliptin	Antihyper Glycemia	[45]
	Doravirine	Anti-HIV	[46]
	Apalutamide	Prostate Cancer	[48]
	Enasidenib	Leukemia	[50]

Table 1. *Cont.*

Structure	Name	Therapeutic Use	Ref.
	Tecovirimat	Antiviral	[51]
	Tafenoquine	Malaria	[54]
	Fluoxetine	Antidepressant	[56]
	Fulvestrant	Breast Cancer	[58]
	Sorafenib	Antineoplastic	[60]
	Tipranavir	Anti-HIV	[63]
	Travoprost	Glaucoma	[65]
	Dutasteride	Benign Prostatetic Hyperplasia	[67]
	Berotralstat	Hereditary Angioedema	[70]

3. Discussion

According to the general public and the pharmaceutical industry environment, the year 2020 will be acknowledged as the COVID-19 research year [71]. Although the medical profession will consider 2020, along with 1996, to be the year of COVID-19, it was the second best in terms of the number of medications licensed by the US FDA. A total of 53 new medicines were authorized in each of these two years. In 2020, 53 new chemical entities (NCEs) and 13 biologic medications (biologics) were authorized. These approved medicines included 10 monoclonal antibodies, 2 antibody-drug conjugates, 3 peptides,

and 2 oligonucleotides. The majority of these FDA-approved compounds were reported to be fluorine-substituted compounds, which display multiple pharmacological effects due to their superior electronegativity, size, electrostatic interactions, and omniphobicity/lipophilicity compared to hydrogen. Fluorine has been found to be a major halogen in around 15–20% of all NCEs. Fluorine's effect may be enhanced in a metabolic cascade of chemical reactions; thus, a single fluorine atom can completely change the biological properties of drug candidates. Fluorine substitution has been extensively researched in medication development as a means of improving biological activity, chemical or metabolic activity, and chemical or metabolic stability. Fluorine is currently widely employed in materials engineering applications such as heat transfer agents, melted metals, surfactants, dyes, acrylics, thermoplastics, membranes, and other products [10]. Many physiologically active fluorine compounds are also used as medications and agricultural chemicals. Trifluoromethylation refers to any chemical process that adds a TFM group to an organic product. The product was then purified from the insoluble crude product using flash chromatography and elution with hexanes/ethyl acetate as a solvent. Fluorine-containing medicines do not provide any extra synthesis problems. The presence of a trifluoromethyl group in the para-position of the phenolic ring improved drug potency by lowering the pK_a of the cyclic carbamate, which makes a key hydrogen bonding interaction with the protein, according to the SAR studies. Halogen bonding has expanded therapeutic applications into structural chemistry, material chemistry, synthetic chemistry, and many other fields [72]. TFM is commonly used to replace the methyl group because it has a significantly higher electronegativity than other alkyl groups. Because of its strong electron-withdrawing nature, poor polarizability, broad hydrophobic domain, and very inert carbon–fluorine linkages, this group must be introduced to therapeutic candidates [73]. Alpelisib, which inhibits lipid kinase implicated in cell proliferation, apoptosis, motility, and cell invasion, as well as glucose metabolism, is one of several medicinal possibilities that include fluorine in their structure. In a variety of myeloid leukemia cell lines, selinexor containing trifluoromethylated phenyl was demonstrated to be extremely cytotoxic, with IC_{50} values less than 0.5 mM. Enasidenib is an orally administered new small molecule inhibitor of mutant isocitrate dehydrogenase-2. Tecovirimat targets a virally encoded protein (p37) found in all orthopoxviruses that cause severe human illness, including rabbitpox, vaccinia, cowpox, ectromelia, and the clinically relevant VARV and monkeypox. Tafenoquine is an 8-aminoquinoline that was recently licensed for use in the treatment of all stages of malaria. Fluoxetine is an antidepressant medication that works by inhibiting selective serotonin reuptake. Because fluorine serves as a hydrogen bond acceptor, most antidepressant medications contain halogens, particularly fluorine, for the high- affinity contact between the protein and ligand. Fluoxetine has a six-fold selective serotonin reuptake inhibitor action because it has a TFM group at the para position of the phenolic ring. Fulvestrant works against hormone-receptor positive metastatic breast cancer by downregulating estrogen receptors when it binds to them. Tipranavir was the first non-peptidic protease inhibitor used to treat multidrug-resistant HIV. Travoprost has been approved for the treatment of adult glaucoma. Dutasteride, a 5α-reductase inhibitor that blocks both isoforms of the receptor, was first marketed in 2001. Berotralstat is a drug used in the prevention of HAE attacks in people aged 12 and up. Overall the presence of the TFM group in the drug candidates can impart better pharmacodynamic and kinetic profiles.

4. Conclusions

The present review focused on the number of synthetic strategies that have been reported for the synthesis of TFM groups-containing FDA-approved drugs. The presence of TFM groups showed a variety of pharmacological profiles, such as anti-cancer, antidepressant, antiviral, and antitubercular activities. The TFM group was introduced on various scaffolds by a variety of chemical reactions. This could help the design and development of a new class of TFM-derived compounds in the future.

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