

REVIEW

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Recent advances in the synthesis of fluorinated heterocycles and a review of recent FDA-approved fluorinated drugs

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Since the inception of artificial drugs and agrochemicals in human society, the presence of a heterocyclic framework in the drug dominates and this could be due to the inspiration of many heterocyclic compounds from nature with significant and diverse biological activity, which are useful for alleviating different diseases. Furthermore, in recent decades, fluorinated compounds have emerged as a prominent and rapidly growing class, securing a vital role in the research and development of new drugs. This could be attributed to the significant inherent properties of the fluorine atom, which, in many cases, solve the problems related to the metabolic stability of drugs, enhance their lipophilicity, and change the pK_a value in favor of drugs. Now, the belief in fluorinated compounds has become so strong that the judicious incorporation of fluorine into organic compounds has become one of the important tools for improving the chances of getting better therapeutically effective compounds. The fusion of the above two individually dominating fields—heterocyclic framework and fluorine atom—in the potential drug compounds offers an even greater likelihood of discovering therapeutically useful agents. This is one of the main reasons why a significant number of fluorinated heterocyclic drugs are being approved by the FDA each year. Although fluorinated compounds have many benefits, the introduction of fluorine substituents remains challenging; particularly, the introduction of fluorine atoms into heterocyclic frameworks can increase the complexity of synthesis. Over the last few decades, several methods have been developed to introduce fluorine into organic compounds; however, fluorination of heterocyclic compounds remains an elusive task, although it is gradually being addressed. In this review, we present the most recent developments in the fluorination of heterocyclic compounds and discuss the chemistry of fluorinated heterocyclic compounds approved in the last and current years.

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1 Introduction

It would be no exaggeration to say that over the past few decades, fluorinated compounds have dominated research and development in the pharmaceutical and agrochemical sectors.¹ This is because the addition of a fluorine atom to a molecule can significantly enhance the prospect of generating improved, therapeutically useful medicinal compounds. This belief is supported by the fact that each year, a growing number of fluorinated drugs are introduced in the market to treat various diseases. The first fluorinated drug, fludrocortisone, a corticosteroid, was introduced in 1954,² and since

then, there has been an exponential increase in the number of publications in the field. At present, approximately 50% of agrochemicals and 20% of pharmaceuticals marketed are fluorinated compounds.³ Interestingly, around 30% of marketed fluorinated drugs are blockbuster pharmaceuticals, such as Fluoxetine, Lipitor, Linezolid, and Fluticasone.⁴ Over the last few years, a substantial number and proportion of fluorinated drugs have been approved by the FDA. For instance, in 2021, ten out of fifty approved drugs were fluorinated;^{5,6} four out of thirty-seven in 2022;⁷ twelve out of fifty-five in 2023;⁸ and eleven out of fifty in 2024.⁹ Notably, this year (up to March 2025), two hetero-fluorinated drugs, suzetrigine and datopotamab deruxtecan-dlnk, have been approved by the FDA.

The heterocyclic framework is present in many natural products, such as alkaloids, vitamins, antibiotics, and peptides, which have shown diverse biological activities and hold tremendous significance for human society. Many of these natural products are used as prescribed drugs, such as serotonin, thiamine, atropine, morphine, codeine, papaverine,

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coniine, caffeine, and nicotine.^{10,11} Thus, inspired by the above facts, the introduction of heteroatoms and heterocyclic scaffolds for the development of drugs has become an important strategy. Indeed, heterocyclic moieties are present in more than 85% of bioactive compounds.¹² Thus, heterocyclic compounds play a vital role in modern drug design and discovery.¹³

Combining the features of fluorinated compounds and heterocycles creates new possibilities and opens new avenues to further improve the biological activities in drug development. This new scope leverages the unique properties of both fluorinated compounds and heterocycles, which have been extensively utilized by medicinal chemists to develop a variety of biologically significant compounds. Thus, fluorinated heterocyclic compounds^{14,15} have become an important motif and structural feature in many pharmaceuticals¹⁶ and agrochemicals. In most cases, the fluorinated substituent has a key impact on both the physicochemical and biological properties of these molecules.¹⁷ Representative examples include enoxacin, used for the treatment of urinary tract infections and gonorrhea, and favipiravir (or Avigan), approved in 2014 in Japan as an antiviral drug used to treat influenza and the recently emerged A(H7N9) avian virus.¹⁸ The fluorinated nucleoside Sofosbuvir (Sovaldi) was developed for the treatment of hepatitis C, and Claudine is used for the treatment of the hepatitis B virus.^{19,20} Furthermore, several top-selling drugs contain both heteroaryl and fluorinated substituents. Representative examples are raltegravir (Isentress), sitagliptin (Januvia), Atorvastatin (Lipitor), risperidone (Risperdal), Ezetimibe (inhibitor of cholesterol adsorption) and Efavirenz (non-nucleoside inhibitor of the reverse transcriptase of HIV), *etc.* (Fig. 1).

The presence of a fluorinated substituent dramatically influences the pharmacokinetics and dynamic properties of drugs. One major and long-standing concern in drug develop-

ment is metabolic stability, which can be partially solved by the introduction of fluorine atoms into the drug compound. The inherent strength of the C–F bond, along with fluorine's high electronegativity, can stabilize the drug during the enzymatic metabolization process.²¹ Further, the introduction of heteroatom/s, which act like an electron-withdrawing group, can assist by interfering with the oxidative metabolic processes, further enhancing metabolic stability. Fluorinated compounds have comparatively high lipophilicity, which increases the absorption of drugs. Therefore, the judicious incorporation of fluorine substituents at suitable positions in organic compounds can increase the bioavailability and potency of drugs. Moreover, the presence of heteroatoms can change the pK_a of the drugs, which ultimately influences their lipophilicity profile, solubility, permeability, and protein binding ability. This affects the overall potency, selectivity, toxicity, and pharmacokinetic properties and thus plays a critical role. Thus, the strategic introduction of fluorine substituents can fine-tune the pK_a and modulate various physicochemical and biological properties of drugs. Furthermore, the mutual interaction of fluorine and heteroatoms can affect the conformational preferences through intra- or intermolecular interactions, ultimately influencing the drug's activities. Thus, for the above reasons, the use of heteroaromatic rings with fluorinating substituents has become a common practice in drug discovery, and can provide valuable insights into structure–activity relationships (SAR), increasing the prospects of obtaining effective lead compounds.²²

Due to the inherent properties of the fluorine atom—namely its exceptionally high electronegativity (3.98 on the Pauling scale), small atomic radius (1.47 Å), strong C–F bond (472 kJ mol^{−1}), and the extreme reactivity of molecular fluorine (F₂)—the synthesis of fluorinated organic compounds initially faced significant challenges.



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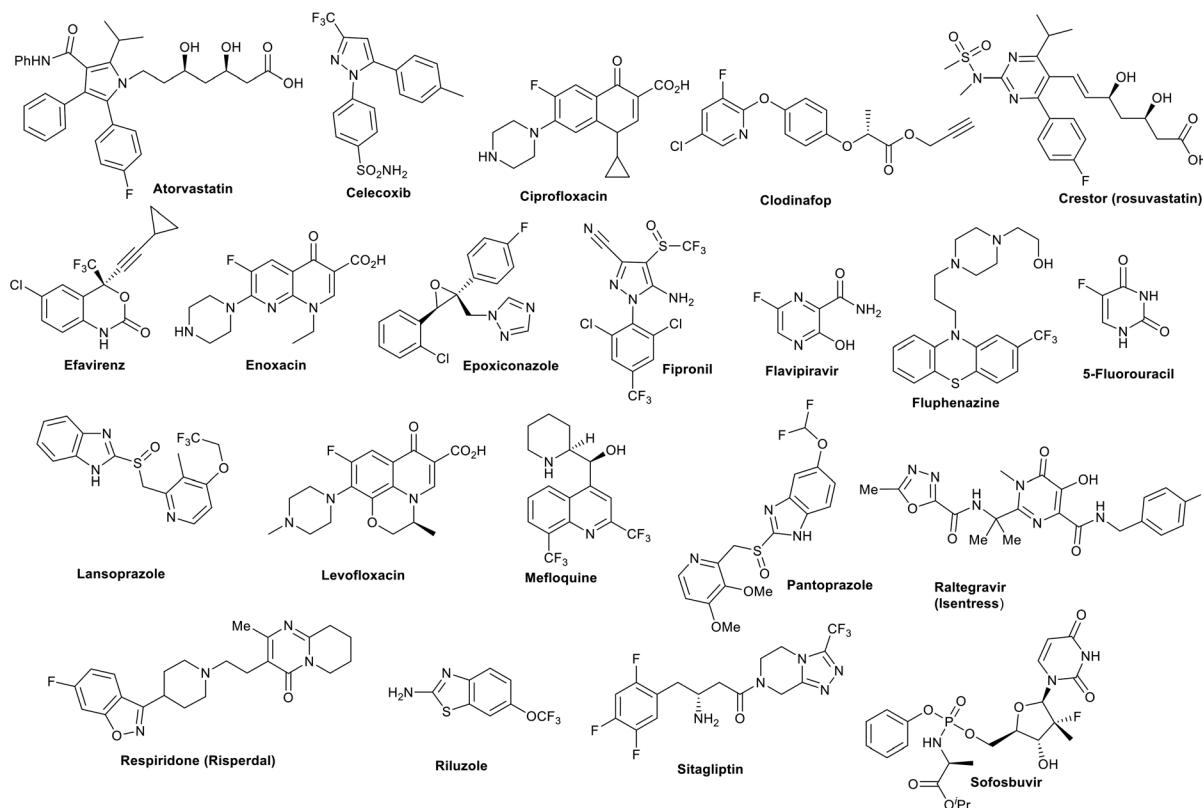


Fig. 1 Top-selling pharmaceuticals and agrochemicals containing a heterocyclic core and an aryl fluoride.

Furthermore, the presence of fluorine substituents in organic compounds significantly alters the energy levels of the HOMO and LUMO, thereby perturbing the electronic properties, both physical and chemical, of fluorinated com-

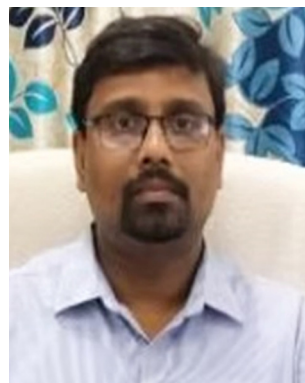
pounds, as well as their reactivity patterns.⁶ Thus, early-stage fluorination poses a challenge to subsequent functional group modifications for the synthesis of new products. Although fluoride minerals are abundant in Earth's crust,



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unfortunately, naturally fluorinated compounds are very rare due to the limited number of natural fluorination reactions that can convert elemental fluoride into fluorinated natural products.²³ Thus, there is a lack of natural sources of fluorinated compounds that can be used in long and complex synthetic pathways.

Fortunately, over the past fifty years, a wide range of reagents have been developed for fluorination reactions, and methods of fluorinating a diverse set of compounds with various functional groups are being consistently improved. Classically, these reagents are either electrophilic or nucleophilic in nature, but due to the presence of heteroatoms in the ring, heterocyclic systems are relatively unreactive compared to regular aromatic compounds, presenting additional challenges in fluorination chemistry. Recently, free radical fluorination reagents and reactions have been developed through thermal or photochemical pathways.²⁴ However, radical fluorination reactions through aromatic substitution on azaarenes, such as Minisci-type reactions, do not lead to C–F bond formation.²⁵ Although metal catalytic methods to achieve aromatic and heteroaromatic compounds through C–H functionalization are gaining momentum and are emerging as one of the hot fields in fluorination chemistry,^{26–28} the selective fluorination of aromatic C–H bonds in functionalized heterocyclic compounds remains elusive and is far from being established, since the formation of C–F bonds is linked to a high activation barrier.^{29,30} Hartwig *et al.*³¹ reported a C2-selective fluorination that was realized through a silver(II) fluoride (AgF₂)-mediated Chichibabin-type reaction. Most recently, Ritter *et al.* demonstrated C-4 fluorination using a nucleophilic fluorination strategy.³² A large number of electrophilic and nucleophilic fluorinating reagents have been developed to execute the fluorination.³³ However, the presence of a heteroatom poses challenges in early-stage transformations, often due to potential competing homolytic cleavage and *ipso* aromatic substitutions on phenyl and heteroaromatic rings. Consequently, late-stage fluorination is generally preferred.

Due to the high energy of the corresponding Wheland intermediates, the introduction of many electrophiles on electron-deficient N-heterocycles has remained elusive. Similarly, nucleophilic fluorination of electron-deficient heterocycles is difficult because the generated Meisenheimer intermediate after fluoride attack is generally reversible, with fluoride elimination to regenerate the substrate preferred over hydride elimination to form the product.

Herein, “fluorinated heterocycles” include those compounds in which fluorine atom(s) are directly connected to the annular carbon of the heterocyclic ring and also fluorine atom(s) attached to a substituent linked to the annular carbon or heteroatom. Here, we report the most recent developments in the fluorination of heterocyclic compounds and discuss the chemistry of fluorinated heterocyclic compounds approved in the last year and current year.

2 Synthesis of fluorinated heterocycles

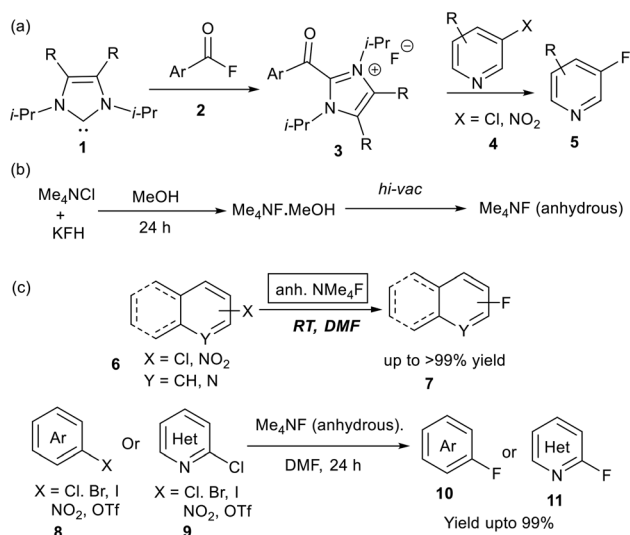
2.1 Synthesis of fluorinated pyridines and pyrimidines

Many well-known bioactive compounds contain fluorinated pyridines and pyrimidines. Representative examples are gemifloxacin and trovafloxacin mesylate, which both contain a 3-fluoropyridine moiety and show excellent biological activities.^{34,35} Additionally, several drugs contain fluorinated aminopyrimidine structures, for example, fostamatinib disodium hydrate,³⁶ abemaciclib mesylate,³⁷ rosuvastatin³⁸ and fluorinated imatinib base.³⁹ A focused review dedicated to the medicinal chemistry perspective of pyridine-containing drugs approved by the FDA over the past decade was published by Bhupinder *et al.*⁴⁰

The position of the fluorine substituent on a heterocyclic ring has an extreme impact on the chemical, physical, and biological properties of the compound. Thus, regioselective fluorination of heterocyclic rings is highly desirable; however, this remains a challenging task. Traditionally, C(sp²)–F bonds in heterocyclic rings are formed *via* nucleophilic aromatic (S_NAr) fluorination reactions of fluoride salts with aryl electrophiles. However, fluorination specifically at electron-rich 3- and 5-positions is very difficult to achieve. Powerful and anhydrous nucleophiles are required to carry out the fluorination reaction. Anhydrous KF or CsF are common reagents used as fluoride sources, but their low solubilities in organic solvents and low nucleophilicity mean that long reaction times and elevated temperatures (>130 °C) are required, which restrict the functional group compatibility and often lead to the formation of side products.⁴¹ To address these limitations, many fluorinating reagents have been developed in the last few decades that operate under mild, room-temperature conditions. For example, anhydrous tetrabutylammonium fluoride (NBu₄F), which is generated *in situ* from tetrabutylammonium cyanide and hexafluorobenzene, was developed by Sun and DiMaggio.⁴² Although this procedure provides a highly soluble and anhydrous source of fluoride, its high cost and the requirement for stoichiometric amounts of reagents (C₆F₆, NHCs) limit its use on an industrial-process scale. To address this issue, Sanford *et al.* developed anhydrous acyl azolium fluorides **3** from acid fluorides **2** and N-heterocyclic carbenes **1**, which were found to be effective in S_NAr fluorinations at room temperature with a variety of aryl chlorides and nitroarenes **4** to give fluorinated pyridine derivatives **5** (Scheme 1a).⁴³ Sanford *et al.* also contributed to the development of tetramethylammonium fluoride [Me₄NF(anh)] (Scheme 1b),⁴⁴ which works efficiently at room temperature. This reagent is suitable for converting aryl and heteroaromatics-X **8**, **9** (X = Cl, Br, I, NO₂, OTf) into aryl and heteroaryl-F **10** and **11** under mild conditions (Scheme 1c).⁴⁴

The issue of moisture sensitivities was addressed by the development of Bu₄NF·(*t*-BuOH)₄ by Kim and co-workers;⁴⁵ this reagent was found to be less hygroscopic than anhydrous Bu₄NF. For the general applicability of the above reagent for

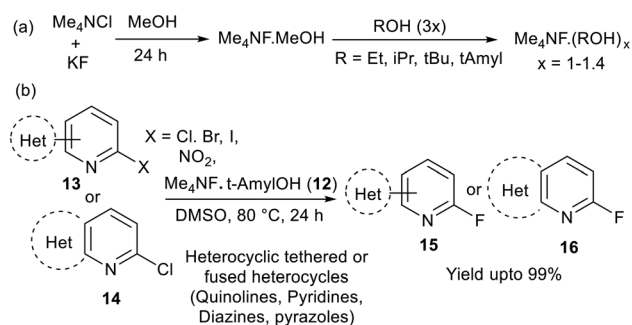




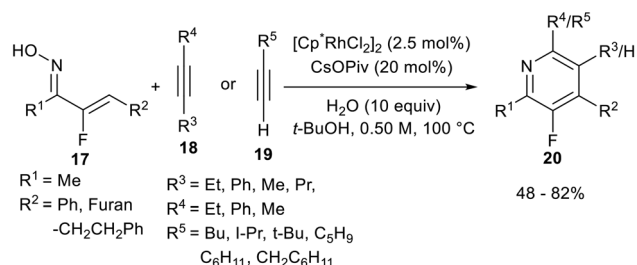
Scheme 1 (a) Use of N-heterocyclic carbenes for fluorination reactions. (b and c) Development of anhydrous Me_4NF reagents and their use in fluorination reactions at room temperature.

nucleophilic aromatic ($\text{S}_{\text{N}}\text{Ar}$) fluorination, Sanford *et al.* tuned and modified the alcohol component, which resulted in a reagent with enhanced reactivity and selectivity without exclusion of ambient air/moisture.⁴⁶ After screening various alcohols, *tert*-amyl alcohol and the corresponding reagent ($\text{Me}_4\text{NF} \cdot t\text{-AmylOH}$) **12** was found to be the most suitable for $\text{S}_{\text{N}}\text{Ar}$ fluorination under mild and convenient conditions at 80 °C in DMSO (Scheme 2a and b).⁴⁶ Thus, heterocycle-tethered (fused **14**) heterocyclic halides **13** or nitroheterocycles undergo smooth $\text{S}_{\text{N}}\text{Ar}$ fluorination to **15** and **16**. Overall, this reagent is an inexpensive, practical, and bench-stable reagent that works for diverse sets of heteroaromatic compounds without the need for pre-drying of the reagent or solvent.⁴⁶

Ellman *et al.* reported a new method for the preparation of 3-fluoropyridines **20** having multiple substituents *via* Rh(III)-catalyzed C–H functionalization of α -fluoro- α,β -unsaturated oximes **17** and alkynes **18** or **19** with a variety of alkyl, aryl, and heteroaryl substituents.⁴⁷ The reactions show high selectivity and provide single isomers of the 3-fluoropyridine products **20**



Scheme 2 (a and b) Development of $\text{Me}_4\text{NF} \cdot (\text{ROH})_x$ reagents and their use in fluorination reactions.



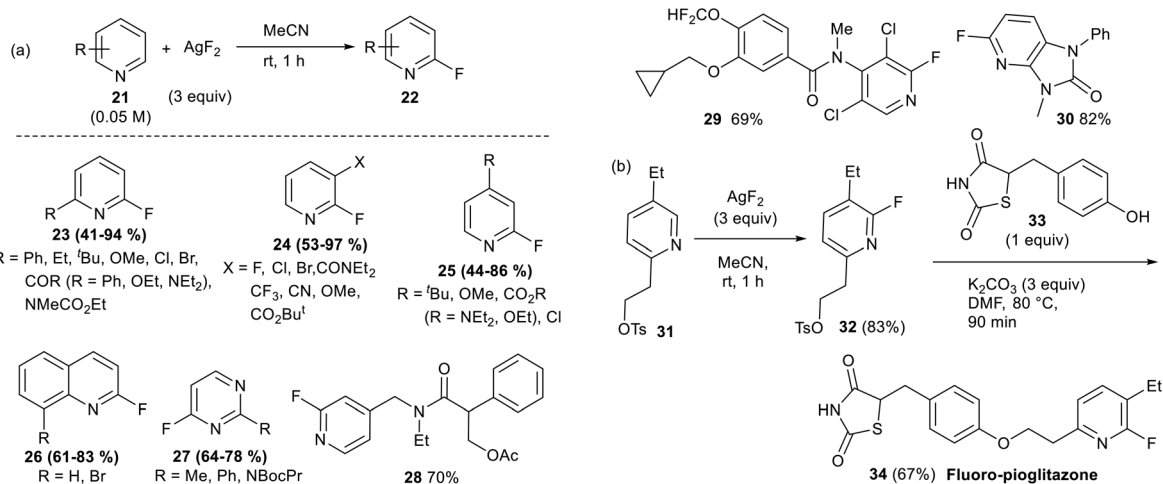
Scheme 3 Synthesis of 3-fluoropyridines **20** from α -fluoro- α,β -unsaturated oximes **17** and alkynes **18** or **19**.

with predictable regioselectivity (Scheme 3). Interestingly, terminal alkynes were also found to be suitable for Rh(III)-catalyzed fluorinated pyridine formation. More recently, fluorinated pyrimidine derivatives have been synthesized under different metal-free reaction conditions, such as through [4 + 2]-annulation of trifluoromethylated α,β -unsaturated imines with *N*-cyano-*N*-aryl-*p*-toluenesulfonamides (NCTS),⁴⁸ and *via* photocatalytic (blue LED 461 nm) α -perfluoroalkenylation of aldehydes.⁴⁹

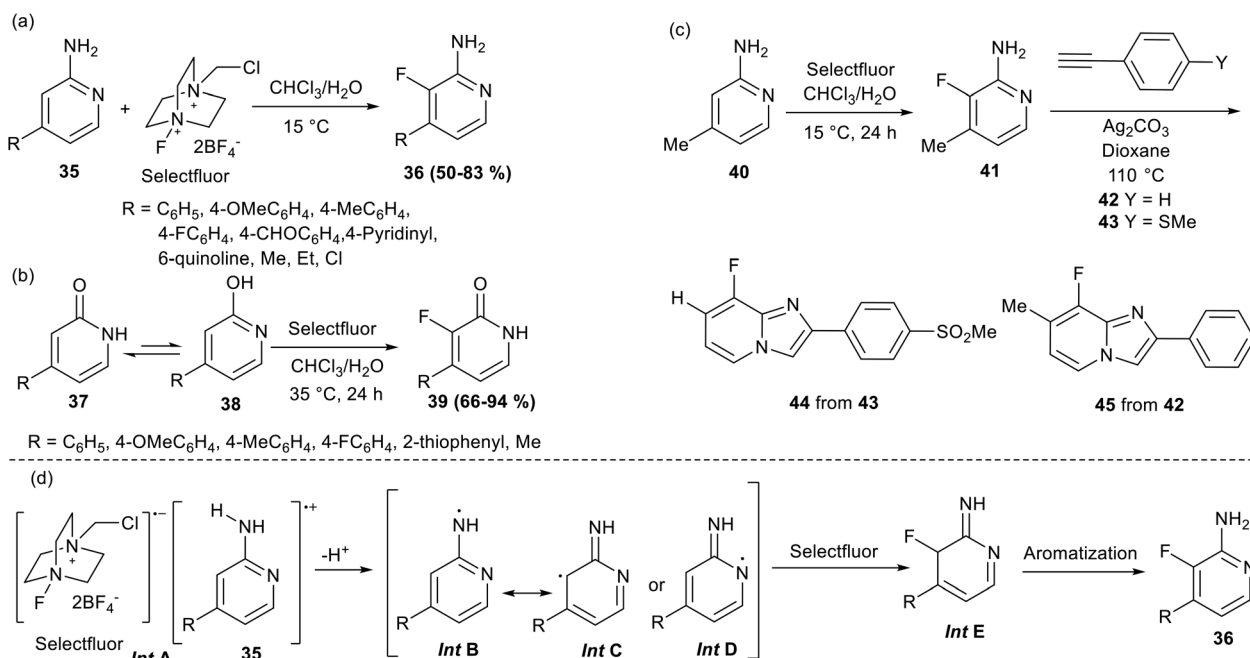
Classically, fluorinated pyridine derivatives are synthesized by the use of the Balz–Schiemann reaction or through nucleophilic aromatic substitution of chloro- or nitropyridines with anhydrous fluoride. However, these methods have inherent limitations. To form the diazonium salt intermediate, strongly acidic and oxidizing conditions are needed, and the subsequent fluorination step involves potentially explosive species that are heated in anhydrous HF or used as isolated tetrafluoroborate salts.

To overcome these challenges, new methods have been developed wherein the C2–H bond is activated using a metal-based catalyst. Thus, commercially available AgF_2 was used to prepare 2-fluoropyridine derivatives **22–25** from substituted pyridines **21**, employing the concept of the Chichibabin reaction, in which the C2–H bond is activated through $\text{N} \cdot [\text{Ag}] \cdot \text{F}$ complexation. The reaction was performed at room temperature under CH_3CN solvent.³¹ The reaction conditions were also found to be suitable for the synthesis of monofluorinated quinolines, pyrazines, pyrimidines, and pyridazines. The utility of this method was demonstrated by the synthesis of several medically important fluorinated compounds **26–30** (Scheme 4a), and fluoro-pioglitazone **34** (Scheme 4b).

Zhao *et al.* used 4-substituted 2-aminopyridine derivatives **35** to activate the C3–H bond to introduce the fluorine substituents into compound **36** by using Selectfluor, water, and chloroform, with high regioselectivities (C3 > C5). The mild conditions enabled the efficient synthesis of various fluorinated 2-aminopyridines **36**.⁵⁰ The concept was further extended to pyridin-2(1H)-one (substituted at the 4-position) compounds **37**, which exclusively provided the corresponding 3-substituted fluoro derivatives **39** (Scheme 5a and b).⁵⁰ To create bioactive imidazo[1,2-*a*]pyridine compounds, intermediate compound **41** was further manipulated using the [3 + 2] annulation reaction with ethynylbenzene **42** or **43** in the presence of Ag_2CO_3 ; thus, this reaction selectively provided



Scheme 4 (a and b) Synthesis of fluorinated pyridine derivatives and their application in the synthesis of medicinally important compounds.



Scheme 5 (a and b) Synthesis of 4-substituted 2-aminopyridine derivatives **36** and pyridin-2(1H)-ones **39**. (c) Synthesis of bioactive imidazo[1,2-a]pyridine compounds **44**, **45**. (d) Plausible radical mechanism.

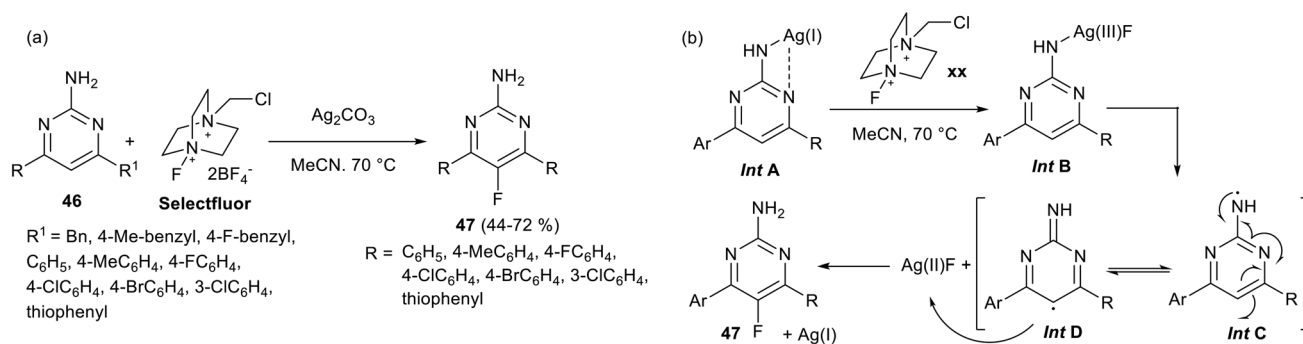
8-fluoro-7-methyl-3-phenylimidazo[1,2-a]pyridine **45** and fluorinated zolimidine **46**, respectively, in good yields (Scheme 5c).⁵⁰ A radical mechanism was proposed, as shown in (Scheme 5d), in which the release of a proton *via* single-electron transfer generates the radical intermediate **Int B** from compound **35**. Subsequent isomerization and fluorination to afford **Int E** are followed by aromatization to afford 3-fluoro-2-aminopyridines **36**.⁵⁰

Zhao *et al.* also developed a direct method for the synthesis of 4,6-disubstituted 5-fluoro-2-aminopyrimidines **47** with different aminopyridines **46** using Selectfluor in the presence of Ag(I), with good yield.⁵¹ A variety of substituents present at

the 4,6-position were well tolerated under the conditions. The presence of phenyl substituents was found to be essential, as no fluorinated products were observed in their absence (Scheme 6a). Electron-deficient substituents were found to be better than electron-rich groups. Based on control experiments, a radical reaction mechanism was proposed in which the Ag reagent coordinates with the amino group in compound **46** to generate intermediate **Int A**, which activates the aromatic ring and finally affords 5-fluoro-2-aminopyrimidine **47** while regenerating Ag(I) (Scheme 6b).

Although *ortho*- and *para*-difluoromethylation of pyridines is well known,^{52,53} recently, Studer *et al.* demonstrated a





Scheme 6 (a) Synthesis of 4,6-disubstituted 5-fluoro-2-aminopyrimidines **47** with Selectfluor, and (b) a plausible mechanism.

unique method to synthesize the more challenging *meta*- and *para*-substituted difluoromethylated pyrimidine derivatives.⁵⁴ Thus, temporary dearomatization to oxazino-pyridine intermediates through *meta*-C–H difluoromethylation of pyridines in a radical process, ultimately led to the *meta*-fluorinated products. Interestingly, the selectivity was found to switch to *para* by the *in situ* transformation of the oxazino pyridines into pyridinium salts upon acid treatment.

2.2 Synthesis of fluorinated pyrrole, imidazole, pyrazole, and triazole derivatives

Pyrroles, imidazoles, and pyrazoles are privileged aza-heterocycles owing to their abundance in the core structural scaffolds of many pharmaceuticals and natural products, and they are often associated with intriguing biological properties. Representative examples of these compounds are shown in Fig. 2.^{51–57} The introduction of fluorinated groups into these heterocycles⁵⁸ has become a topic of increasing interest, and remarkable progress has been made in this area.^{59–61}

As with other heterocycles, fluorination reactions on the above heterocycles are challenging, particularly in the case of pyrroles, which are highly sensitive to oxidation and polymerization, particularly in the presence of strong electrophiles.⁵⁴ Therefore, special care is needed, and fluorination methods should ideally proceed under mild and neutral conditions.

Trifluoromethylation of heterocycles is an important tool in medicinal chemistry because the trifluoromethyl group has a dramatic impact on the metabolic stability, lipophilicity, and bioavailability of potential drugs. Consequently, the synthesis and application of novel trifluoromethylated heterocycles have been extensively explored in library design and drug discovery.^{62,63}

Chen *et al.* developed a formal [4 + 1] annulation method for the synthesis of CF_3 -substituted dihydropyrroles **50** using fluorinated sulfonium salt **48** and cyclic unsaturated imines **49**. This method provides a structurally diverse set of dihydropyrroles in acceptable to excellent yields with excellent diastereoselectivities. Furthermore, the resulting CF_3 -contain-

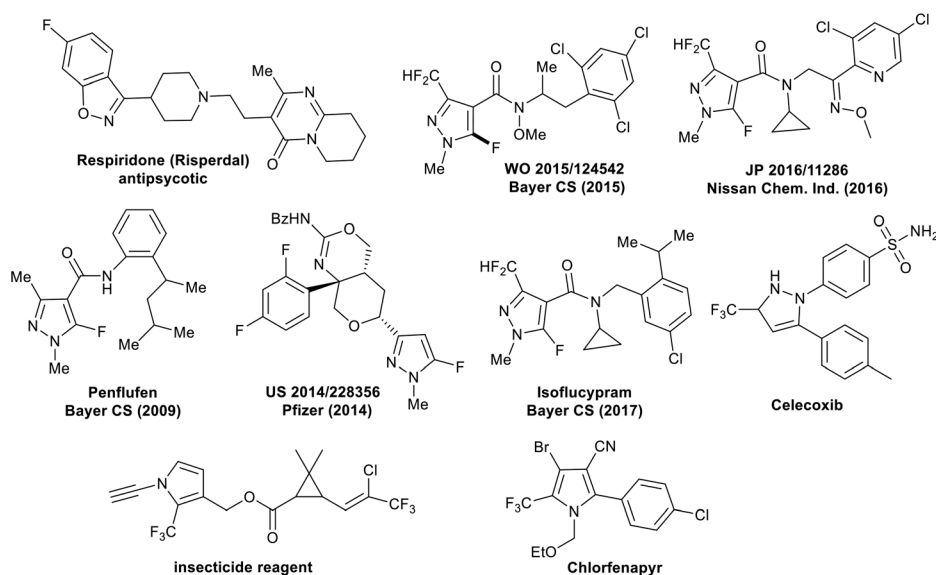
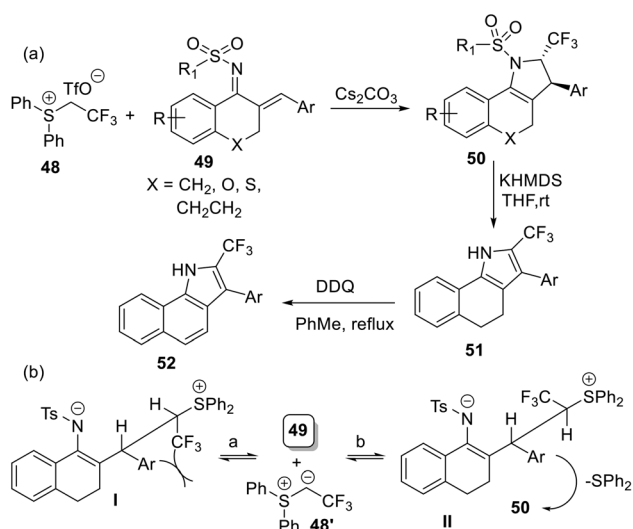


Fig. 2 Biologically significant fluorinated pyrrole compounds.



ing dihydropyrroles **50** were transformed into pyrroles **51** in good yields under basic conditions, without the use of transition metals (Scheme 7).⁶⁴ The mechanism involves the addition of the deprotonated ylide **48'** on **49**, to generate intermediate **II** through pathway **b**, followed by intramolecular nucleophilic substitution to give the *trans*-product **50** (Scheme 7b).

A modified version of the $-\text{CF}_3$ group, *i.e.* the introduction of a $-\text{SCF}_3$ (trifluoromethylthio) group in place of a $-\text{CF}_3$ group in the target compounds, is increasingly being recognized as a promising strategy for designing new candidate drugs in research and development. This is because the electron-withdrawing effect of $-\text{SCF}_3$ is comparable to that of $-\text{CF}_3$, while its lipophilicity ($\pi_{\text{R}} = 1.44$) is the highest among all fluorinated functional groups. These unique properties are attributed to the distinctive character of the $-\text{SCF}_3$ group.⁶⁵ Consequently, the development of the trifluoromethyl thiolation reaction is an expanding subcategory of fluorination chemistry,^{65–72} and several reagents have been developed for the efficient introduction of the $-\text{SCF}_3$ group (Fig. 3).



Scheme 7 (a) CF_3 -substituted dihydropyrroles **50** and pyrroles **52**, and (b) the proposed reaction mechanism.

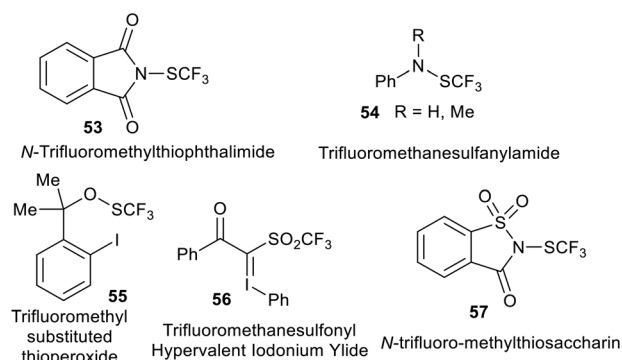
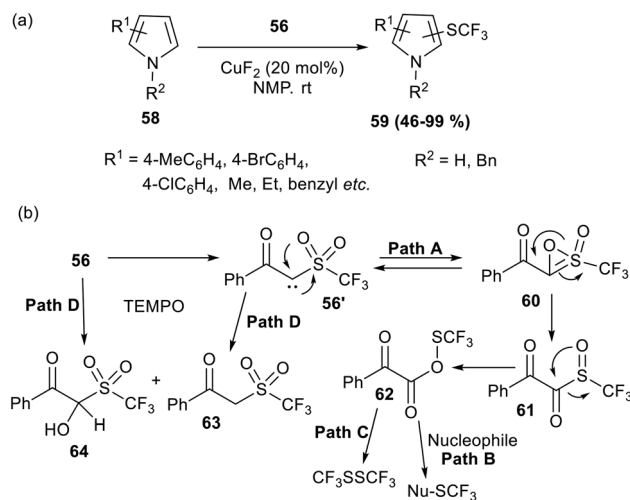


Fig. 3 Electrophilic trifluoromethylthiolation reagents **53**–**57**.

Recently, significant efforts have focused on developing methods for the trifluoromethylthiolation of pyrrole. Initially, the use of toxic ClSCF_3 and stable trifluoromethanesulfanylamide was adopted; however, results were not satisfactory due to low yields and undesired polymerization reactions.^{73,74} Shibata *et al.* later demonstrated a copper-catalysed method for synthesizing trifluoromethylthio derivatives of pyrroles **59** using trifluoromethanesulfonyl hypervalent iodonium ylide **56**.⁷⁵ After screening various Lewis acid catalysts, CuF_2 was found to be the most effective. Using *N*-methyl-2-pyrrolidone (NMP) **58**, a series of fluorinated pyrrole derivatives **59** were obtained in good to excellent yield (46–99%) (Scheme 8a). The progress of the reaction was monitored by ^{19}F NMR spectroscopy along with control experiments, which demonstrated that the formation of CF_3SSCF_3 (**62** + CuF_2) decreases the yield of the product; thus, the method is highly dependent on the reaction procedure. Based on the results of control experiments, a mechanism for the electrophilic fluorination reaction was proposed, as shown in Scheme 8b.

The copper-mediated carbene formation of **56'** leads to the generation of oxa-thiirene **60**, which rearranges to sulfoxide **61**. This then undergoes an intramolecular nucleophilic collapse to form thioperoxoate **62**, followed by trifluoromethylthiolation with the nucleophile *via* the electrophilic path **A** to yield the desired product Nu-SCF_3 . In the absence of a nucleophile, thioperoxoate **62** is proposed to convert into CF_3SSCF_3 through radical path **C** (Scheme 8b).

The fluoro-imidazole-containing framework also exhibits interesting biological activities.⁴⁰ Over the years, several methods have been developed for the fluorination of imidazole, such as lithiation with 2,2,6,6-tetramethylpiperidine (LTMP) followed by fluorination.^{76,77} Classically, the Balz-Schiemann reaction was first used by Kirk in 1971.⁷⁸ Subsequently, various nucleophilic $\text{S}_{\text{N}}\text{Ar}$ fluorination strategies involving suitable leaving groups, including halides or tri-



Scheme 8 (a) Trifluoromethylthiolation reaction on pyrrole. (b) Proposed reaction mechanism for trifluoromethylthiolation by reagent **56**.



methyltin groups, with dried potassium fluoride were explored to obtain fluorinated imidazole. Electrophilic fluorinating agents, such as perchloric fluoride and Selectfluor, have also been successfully used to gain fluoroimidazole derivatives.⁷⁹ Furthermore, a Pd(OAc)₂-catalyzed annulation approach has been developed to prepare 2,5-disubstituted imidazole with fluorinated propargyl amidines and iodoarene.⁸⁰

Albertshofer *et al.* reported a regioselective method for the synthesis of fluorinated imidazole derivatives at the C5- and C4-positions *via* base LTMP promoted electrophilic fluorination using *N*-fluorobenzenesulfonimide. The strategy involved the use of the protecting group, ethoxymethyl ether (PG), on imidazole **65**, which, upon *ortho*-fluorination, gave 5-fluorinated imidazole **66**. It was observed that the C5-fluorinated and C2-substituted imidazole that was obtained underwent protecting group migration in the presence of acetic acid at 80 °C, resulting in the exclusive formation of the C4-substituted imidazole **67** (Scheme 9a).

This method provides an efficient synthesis of a diverse set of polysubstituted fluorinated imidazole derivatives. A S_N2-type intermolecular mechanism was proposed as shown in Scheme 9b.

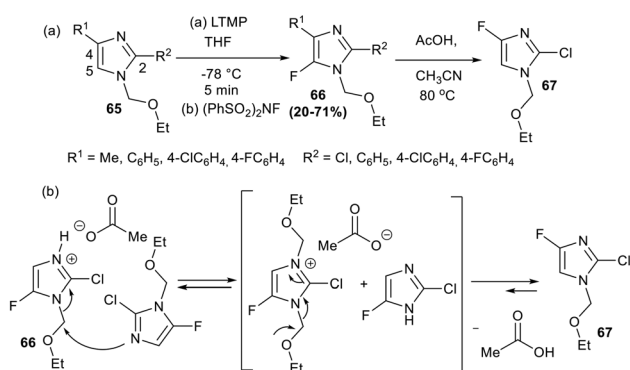
The Pd-catalyzed cross-coupling of aryl halides with metal fluoride salt is a key strategy for synthesizing fluorinated aromatic compounds.^{81–90} These methods have also been extended to the synthesis of nitrogen-containing six-membered heteroaryl fluoride compounds.^{82,83} However, the use of Pd-catalyzed cross-coupling to synthesize hetero-fluorinated compounds is not straightforward. In the catalytic cycle, C–F reductive elimination has a high kinetic barrier from Pd(II), which becomes even more significant in the five-membered rings.⁹¹

Furthermore, nitrogen-containing heterocycles tend to coordinate with the Pd centre and thereby inhibit Pd-catalyzed reactions.⁹² Buchwald *et al.* made a significant effort to synthesize five-membered heteroaryl fluorinated compounds with the catalyst [(L₃-Pd)₂(1,5-COD)] (L₃ = **70**), which was previously used to successfully construct six-membered rings. However, all attempts were futile. Guided by DFT analysis, 2-substituted

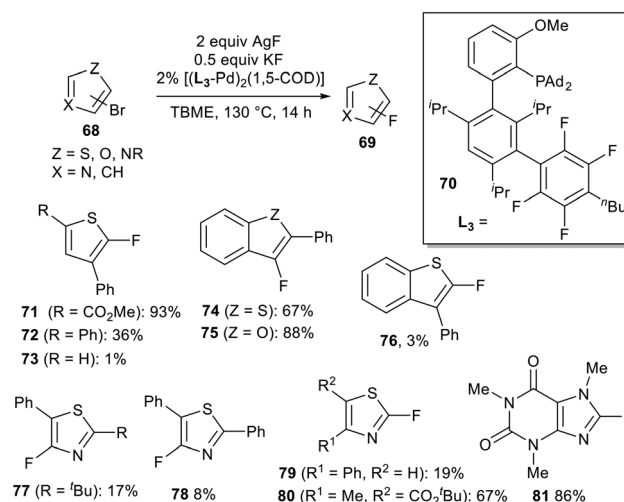
3-bromothiophene was chosen, and a bulky phenyl group at the 2-position successfully furnished the desired fluorinated product. Thus, the first successful method for the transition-metal-catalyzed fluorination of a five-membered heteroarene **69** was evolved in which AgF and the above catalyst with **68** were used in *tert*-butyl methyl ether (Scheme 10). The method is suitable for the synthesis of a diverse array of fluorinated heterocycles, such as electron-deficient and *ortho*-substituted benzo[*b*]furans, *ortho*-substituted benzo[*b*]thiophenes, and highly activated 2-bromo-1,3-azoles **71–81**.⁹³

The pyrazole framework is an important component in many marketed drugs and agrochemicals. In particular, fluorinated pyrazoles have shown very interesting results. The importance of the dual combination of fluorine and pyrazole can be highlighted by the fact that, after the approval of Celebrex (named celecoxib in 1998), an anti-inflammatory drug, the number of drugs that contain both features continues to grow. In recent years, many biologically relevant pyrazole derivatives have been reported.^{94–96} A dedicated review has highlighted recent developments in the synthesis and mechanisms of fluorinated pyrazoles.⁹⁷ Furthermore, a substantial number of robust and versatile synthetic methods have recently been developed for the preparation of fluorinated pyrazole derivatives.^{98–108}

Nie *et al.* recently reported a highly regioselective synthesis of 3-di/trifluoroalkyl-5-fluoropyrazoles **84** with a base-mediated [3 + 2] cycloaddition reaction between di/trifluoromethylated hydrazonoyl chlorides and fluorinated nitroalkenes.⁵⁸ This is a unique method that demonstrates the efficiency of introducing a second fluorine substituent in a fluorinated substrate. In this transformation, α-fluorinated nitroalkenes **83** were employed as synthetic equivalents of fluoroalkynes, serving as key partners in the annulation reaction. Thus, the nitro group plays a dual role—as an activating group and a directing group—in the cycloaddition reactions with di/trifluoromethylated hydra-



Scheme 9 (a) Regioselective fluorination of rationally designed imidazole derivatives. (b) Plausible mechanism for the protecting group migration.



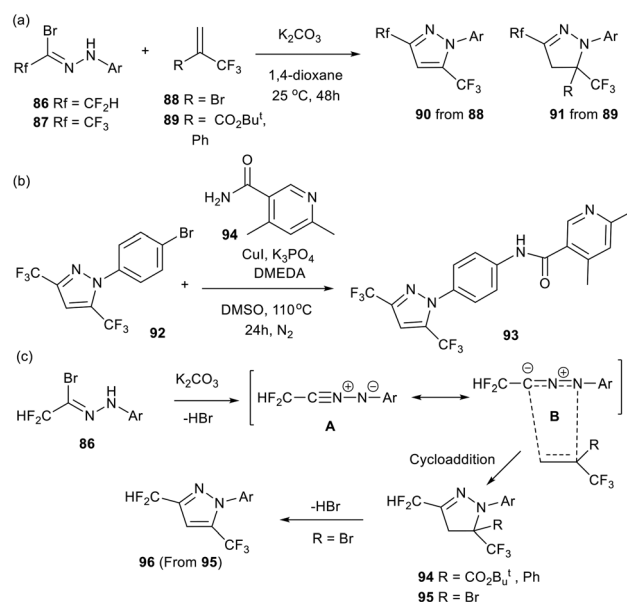
Scheme 10 Fluorinations to give five-membered heteroarenes **69** and **71–81** with AgF and catalyst [(L₃-Pd)₂(1,5-COD)] (L₃ = **70**).



zonoyl chlorides **82**. The di/trifluoromethylated hydrazonoyl chlorides **82** were conveniently prepared from inexpensive and abundant di- and tri-fluoroacetic anhydrides. The method is suitable for a wide variety of substrates and tolerates different functional groups. The synthetic utility of the method was extended to the synthesis of fluorinated analogues of celecoxib, deracoxib, mavacoxib, and 3-di/trifluoromethyl-5-fluoropyrazoles **84** (Scheme 11a). The ^{19}F NMR spectra confirmed the formation of intermediate **82'**, and mass spectrometry data support a plausible mechanism that was proposed for the cycloaddition reaction (Scheme 11b).

Previously, Yang *et al.* also used ethyl-4,4-difluoro-3-oxobutanoate with methylhydrazine for a sequence of cycloaddition to make fluorinated pyrazole derivative and further used for the second fluorination by halogen exchange with KF, and late-stage C–H functionalization.^{109,110} Building on this, Nie *et al.* further developed a method for the synthesis of fluorinated and trifluorinated pyrazoles by using a silver-catalyzed regioselective one-pot cyclization reaction of diazo reagents with fluoronitroalkenes.¹¹¹

Very recently, Hu *et al.* reported an efficient method for the synthesis of a variety of 3,5-bis(fluoroalkyl)pyrazoles **88**/pyrazolines **89** through [3 + 2] cycloaddition reaction between difluoromethyl or trifluoromethyl hydrazonoyl bromides **86** or **87**, and trifluoromethyl-substituted alkenes **88** or **89**.¹¹² The method is general and provides a diverse set of fluorinated pyrazoles and pyrazoline derivatives in moderate to good yield. The method was extended to synthesize compound **93**, a selec-

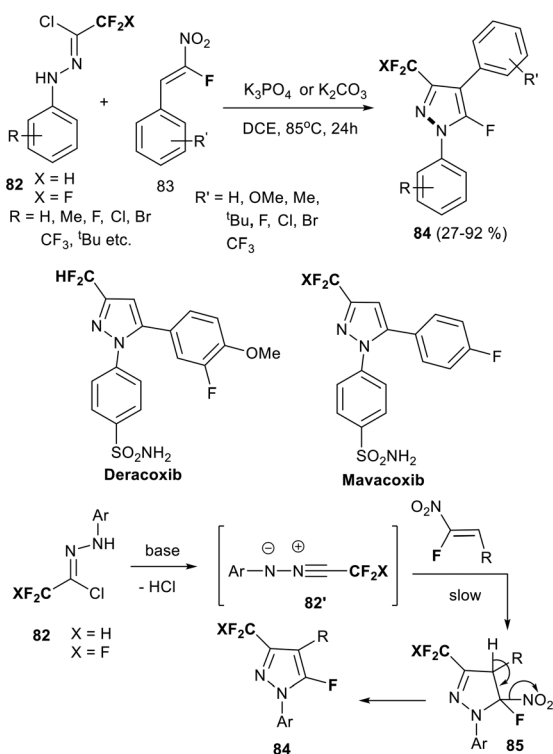


Scheme 12 (a) Synthesis of 3,5-bis(fluoroalkyl)pyrazoles **88**/pyrazolines **89**. (b) Synthesis of compound **93**. (c) A plausible reaction mechanism.

tive CRAC inhibitor with potential for treating inflammatory diseases (Scheme 12a and b). A mechanism is outlined as shown in Scheme 12c, wherein fluorinated nitrile imine intermediates **A** and **B** are formed, which undergo a [3 + 2] cycloaddition reaction with the alkene to afford the desired compounds.

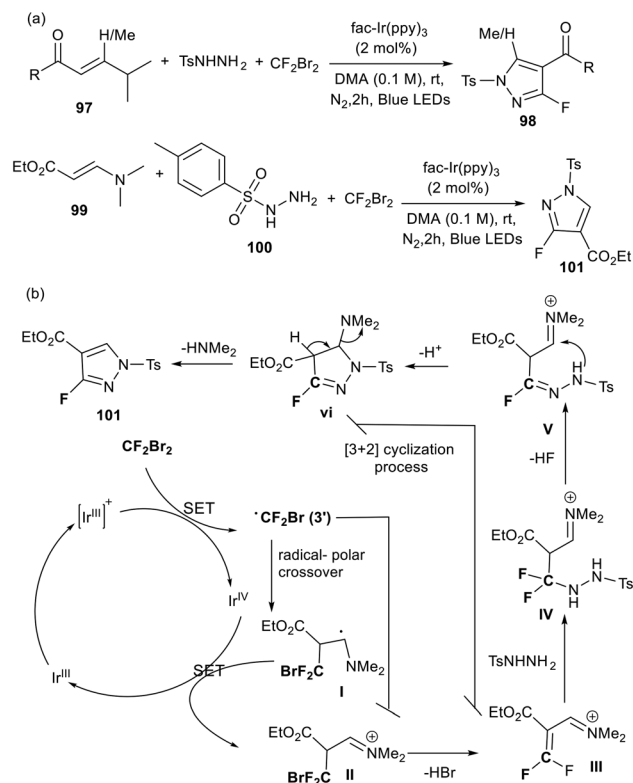
Wang *et al.* developed a single-electron transfer reaction for the synthesis of polysubstituted fluoropyrazoles **98** by using a three-component cyclization strategy using CF₂Br₂ as a novel C1F1 synthon.¹¹³ Thus, treatment of ethyl 3-(*N,N*-dimethylamino)acrylate **99**, *p*-TsNHNH₂ **100**, and CF₂Br₂ in the presence of the photocatalyst *fac*-Ir(ppy)₃ (2 mol%), under irradiation with blue LEDs (450–455 nm) at room temperature in DMA as the solvent, gave fluoropyrazole product **101** in good yield (71%) (Scheme 13). This method was found to be compatible with a variety of ester and acyl substituted enamines, enaminones, and various aryl sulfonyl hydrazines. Based on the radical and intermediate trapping experiments, a plausible mechanism was proposed as shown in Scheme 13b. The photoexcited-state [Ir^{III}]^{*} reduces CF₂Br₂ to generate radical species [•]CF₂Br. This undergoes radical addition with enamine **99** to give carbon radical intermediate **I**, with a subsequent single-electron transfer oxidation by [Ir^{IV}] to give **II**, which is then converted into **III** via the elimination of HBr. The intermolecular nucleophilic addition between **III** and TsNHNH₂, followed by elimination of HF, furnishes intermediate **V**. Finally, intramolecular cyclization and elimination of dimethylamine generate the target fluoropyrazole product **101**.

Triazoles are vital motifs in biochemistry and medicinal chemistry due to their H-bonding donor and acceptor properties.⁴⁸ Furthermore, their high thermal, chemical, and bio-



Scheme 11 Synthesis of 3-di/tri-fluoroalkyl-5-fluoropyrazoles, and a plausible mechanism.



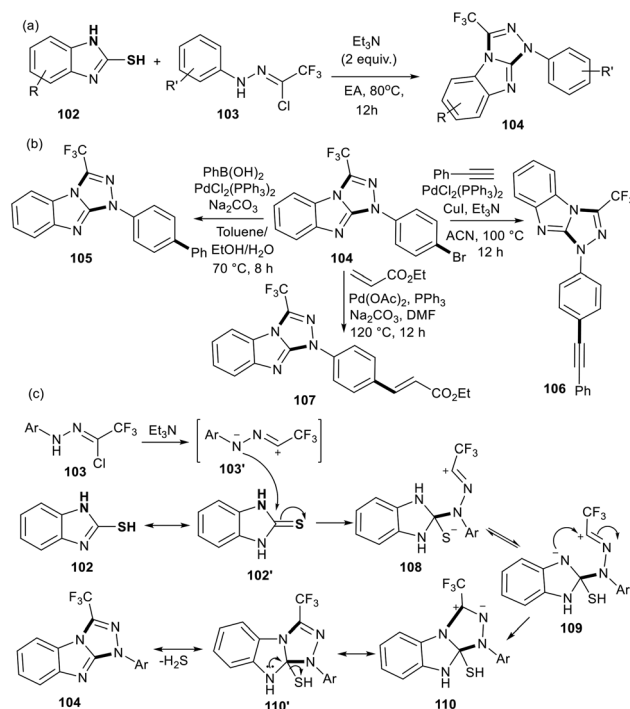


Scheme 13 (a) Synthesis of polysubstituted fluoropyrazoles and (b) a plausible SET reaction mechanism.

logical stabilities make them valuable scaffolds for a wide range of applications. As a result, numerous fluorinated triazole derivatives have found use in diverse fields. A good review dedicated to fluorinated triazole synthesis has been published.^{114,115} Several strategies have been developed to access C-4, C-5, and N-fluoro-substituted triazoles.

Triazoles exist in two main structural forms, 1,2,3-triazoles and 1,2,4-triazoles, and both show a broad spectrum of pharmacological activities. Among the various synthetic approaches, the [3 + 2] cycloaddition reaction of 1,3-dipoles is one of the most efficient and straightforward methods for the synthesis of triazoles.¹¹⁶ The trifluoromethyl-substituted nitrile amines **103** have been used as 1,3-dipoles in cycloaddition reactions with different sets of polarophiles, such as dicyanoalkenes and chalcones, for the synthesis of pyrazoles.^{117–119} Additionally, nitrile imine **103** has been used for the synthesis of 1,2,4-triazoles with amidines or imidates.^{58,115,118,119}

Recently, Cai *et al.* demonstrated a facile strategy for the synthesis of fused 3-trifluoromethyl-1,2,4-triazoles **104**, in good yields through a triethylamine-promoted intermolecular [3 + 2] cycloaddition pathway involving 2-mercapto or 2-methylthio 1H-benzimidazole derivatives **102** and fluorinated nitrile imines **103** under basic conditions (Scheme 14a).¹²⁰ The method was found to be suitable for many substrates, and was particularly effective when symmetrically disubstituted 1H-benzo[d]imidazole-2-thiols were used. The utility of this method was demonstrated by the gram-scale synthesis of com-

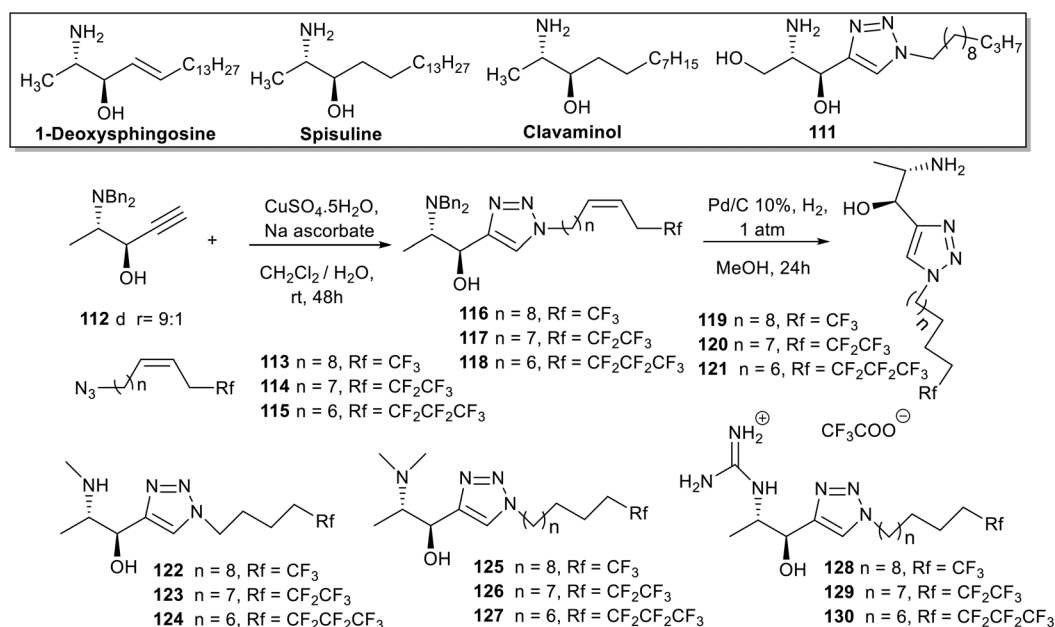


Scheme 14 (a) Synthesis of 3-trifluoromethyl-1,2,4-triazoles, (b) synthesis of **105**, **106** and **107**, and (c) the proposed mechanism.

pounds **105** and **107** (Scheme 14b). A plausible mechanism for this transformation was discussed, as shown in Scheme 14c. The base-promoted formation of the intermediate **103'** from the nitrile imines initiates addition to substrate **102'**. This is followed by a [1,3]-hydrogen migration to give **108**, which, on intramolecular nucleophilic attack of the intermediate **109**, followed by isomerization, gives **110'**. The latter then releases H_2S to generate the triazole product **104**. In related developments, fluorinated pyrrole and triazole derivatives were synthesized by using Pd-catalysed fluoroallylation of pyrroles with *gem*-difluorinated cyclopropanes¹²¹ and defluorinative [3 + 2] annulations of substituted hydrazines with N- CF_3 imidoyl chloride derivatives to obtain monofluorinated 1,2,4-triazoles, respectively.¹²²

The enzyme sphingosine kinase (SphK) regulates the sphingolipid rheostat, which governs the dynamic balance between ceramide (Cer) and sphingosine 1-phosphate (S1P).¹²³ Interest has focused on 1-deoxysphingolipids and their analogs owing to their remarkable biological properties.^{124,125} Matheu *et al.* developed sphingosine analog **111** by incorporating a rigid 1,2,3-triazole moiety into the aliphatic chain, thereby mimicking the conformational restriction imposed by the 4,5-double bond in sphingosine.^{126,127} They found that compounds bearing a heptafluoro tail displayed the highest inhibitory activity against SphK2, in the low micromolar range, while presenting the highest SphK2/SphK1 selectivity. The synthesis of these fluorinated analogues started with CuAAC-mediated [3 + 2] cycloaddition between propargyl alcohol **112** and fluorinated azides **113–115**, followed by deprotection and hydrogen-





Scheme 15 Synthesis of 1,2,3-triazole derivatives of a sphingosine analog.

ation, which provided compounds **119–121** in good yields. These intermediates were further manipulated to generate derivatives **122–130** (Scheme 15).

The substitution reaction was also explored to obtain the fluorinated triazoles. The first example was reported by Fokin *et al.*, who used 5-iodo-1,2,3-triazoles for substitution with the basic fluoride nucleophile KF and KHF₂.¹²⁸ Chu *et al.* used AgF and N¹,N¹,N²,N²-tetramethylethane-1,2-diamine (TMEDA) as a ligand to achieve improved yields.¹²⁹ Previously, Fokin *et al.* also developed a microwave-assisted protocol for the synthesis of fluorinated triazole having the antibacterial potency against *S. aureus* (ATCC 49775).¹³⁰

2.3 Synthesis of fluorinated indole derivatives

The presence of the indole framework in the amino acid tryptophan, biogenic amine tryptamine, neurotransmitter serotonin, and numerous alkaloids gives it a special position in medicinal chemistry, and it has become an important pharmacophore displaying a wide range of biological activities. A selection of important biologically active fluorinated indole derivatives is shown in Fig. 4. The importance of the framework has been further increased by the addition of fluoro substituents to generate fluoroindole derivatives, which is an important strategy for the development of drugs.

A good number of elegant methods have been developed for the direct introduction of an F substituent at the 2- or 3-position to trimethylstannyl indoles *via* electrophilic substitution using various fluorinating agents.¹³¹ Similarly, methods have been developed for other positions *viz.* 4-, 7-, 3-positions or the benzenic ring using reagents such as NFSI, DAST, and Selectfluor.^{132–136} Additionally, methods for the trifluorination of indoles were also achieved.¹³⁷

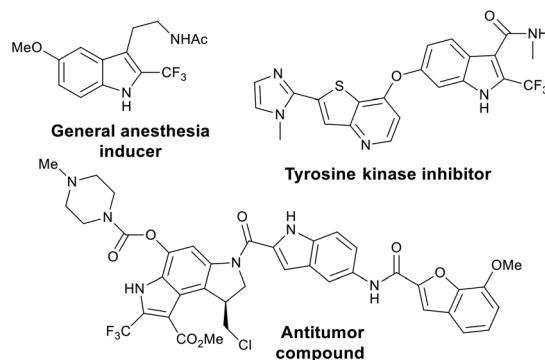


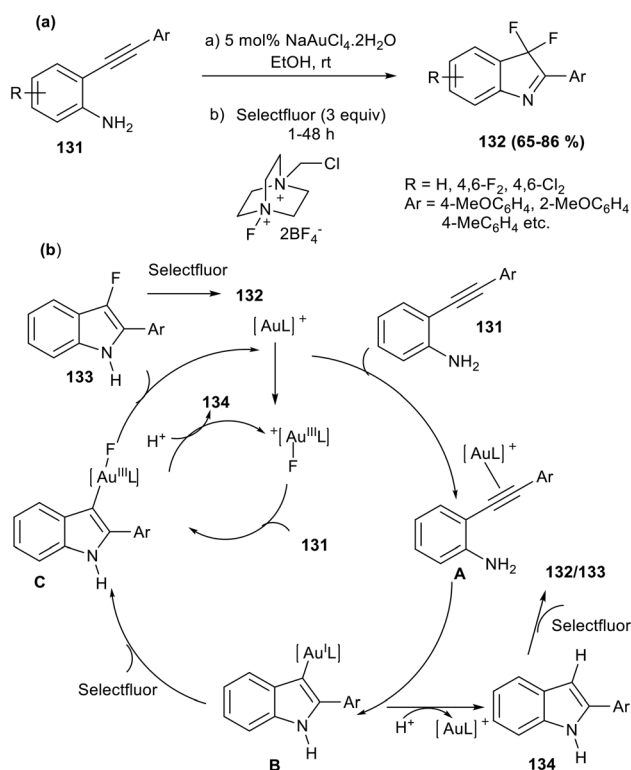
Fig. 4 Examples of medicinally relevant fluorinated indole derivatives.

Michelet *et al.* developed a general method for the synthesis of 3,3-difluoro-2-substituted-3H-indoles **132** by using a tandem Au(I)-catalyzed aminocyclization/fluorination sequence in a two-step, one-pot protocol. This methodology was further extended to access 2-aryl-3-fluoro-1H-indoles in good yields.¹³⁸ Thus, after screening various catalysts and solvents, NaAuCl₄·2H₂O in ethanol was found to be the optimal system. Under these conditions, 2-alkynyl anilines **131** and Selectfluor (3 equiv.) underwent cyclization/fluorination smoothly to provide indoles **132** in good yields. Characteristically, the process is environmentally benign, as the procedure uses green ethanol and does not require any additional base, acid, or N-protective group. When the amount of Selectfluor was reduced to 1.1 equivalents, monofluorinated indoles were obtained selectively. The developed protocol exhibited broad substrate scope and high functional group tolerance. A mechanism was proposed wherein two pathways were suggested



involving Au(I) intermediates **A** and **B**. Intermediate **B** is oxidized to **C**, which leads to the formation of indole **134** and both mono **133** and di-fluoro indoles **132** products. The Au(III) intermediate **C**, formed upon interaction with Selectfluor, undergoes reductive elimination to yield the mono-fluorinated product **133** (Scheme 16).

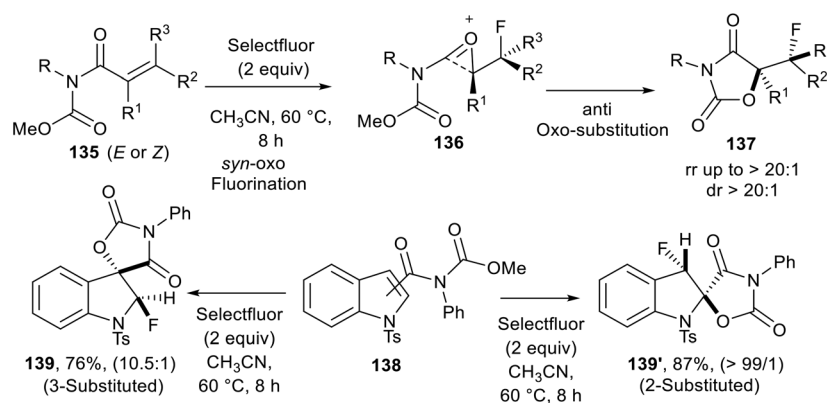
The group of Hongjian Lu reported an interesting result for the synthesis of fluorinated oxazolidine-2,4-diones by using an efficient stereospecific electrophilic fluorocyclization of α,β -unsaturated amides through a formal halocyclization process. This result represents the first example of this kind



Scheme 16 (a) Synthesis of fluorinated indole derivatives, and (b) the proposed mechanism.

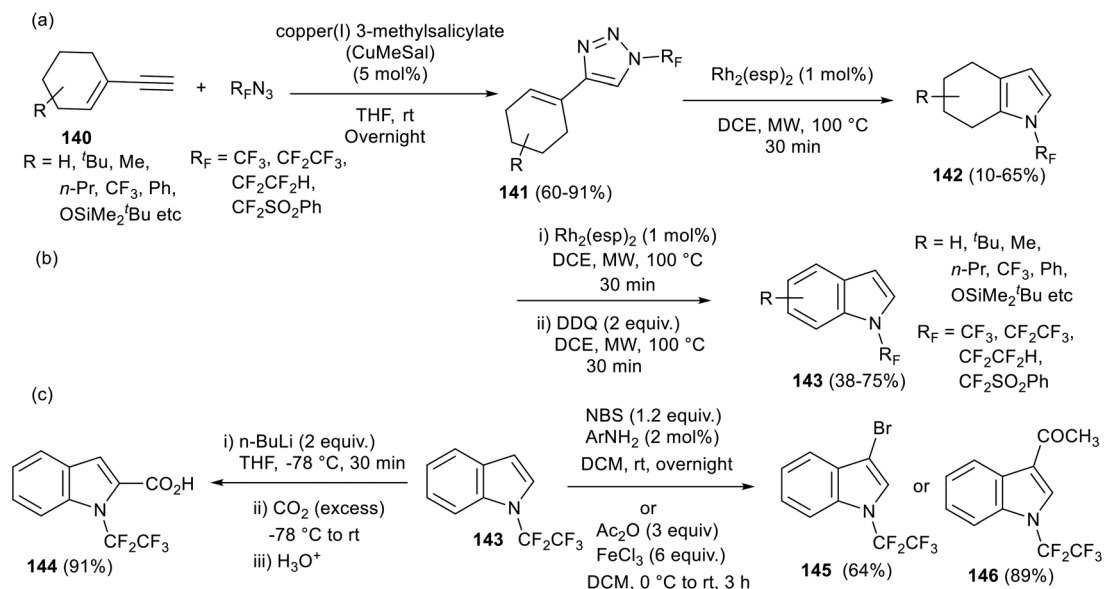
where stereospecific electrophilic fluorocyclization of α,β -unsaturated amides occurred through 5-*exo*-regioselective cyclization. Thus, disubstituted *E*-acrylamides **135** reacted with Selectfluor to give the 5-*exo* products, *N*-aryl (alkyl)-oxazolidine-2,4-diones **137**, in up to 97% yield with excellent diastereoselectivity (*dr* > 20/1) (Scheme 17). This reaction was found to be suitable for both electron-donating and electron-withdrawing aryl and alkyl substituents. Furthermore, the method was extended to the synthesis of fluorinated bi-heterocyclic spiro compounds such as **139** and **139'**, using indole derivative **138**, with the substituent at either the 2- or 3-position. Mechanistic investigations, supported by control experiments and DFT studies, suggested that the transformation proceeds through a cascade synergistic *syn*-oxo-fluorination, followed by an *anti*-oxo-substitution process.¹³⁹

Various methods have also been developed for the synthesis of trifluoromethylated indole derivatives. In particular, radical trifluoromethylation proceeds efficiently at the 2- or 3-position of indoles and their derivatives.¹⁴⁰ However, *N*-trifluorination of indoles through electrophilic fluorination remains difficult owing to the relatively low nucleophilicity of the nitrogen atom. Nonetheless, successful transformations have been achieved for indolides with the Togni reagents^{141,142} or Umemoto's oxonium reagents.¹⁴³ Recently, Beier *et al.* developed a copper(I)-catalyzed synthesis of 4-cyclohexenyl-substituted *N*-(per)fluoroalkylated 1,2,3-triazoles **141** through cycloaddition with substituted cyclohexenyl acetylenes **140** with azido(per)fluoroalkanes. Furthermore, these triazoles were subsequently subjected to a rhodium(II)-catalyzed transannulation to give **142**. Subsequent oxidation of the pyrroles then furnished the corresponding *N*-(per)fluoroalkyl indoles **143** (Scheme 18).¹⁴⁴ Notably, the above two-step process was successfully adapted to a one-pot process. Furthermore, the derivatization of *N*-perfluoroalkyl indole **143** by electrophilic aromatic acylation, bromination, and lithiation/carboxylation significantly expanded the structural diversity of accessible *N*-fluoroalkylated indole structures (**144–146**) (Fig. 5).



Scheme 17 Synthesis of fluorinated oxazolidine-2,4-diones derivatives.





Scheme 18 (a) Synthesis of (per)fluoroalkylated 1,2,3-triazoles, and fused *N*-(per)fluoroalkyl pyrroles. (b) One-pot synthesis of fluorinated indoles. (c) Derivatization of fluorinated indole.

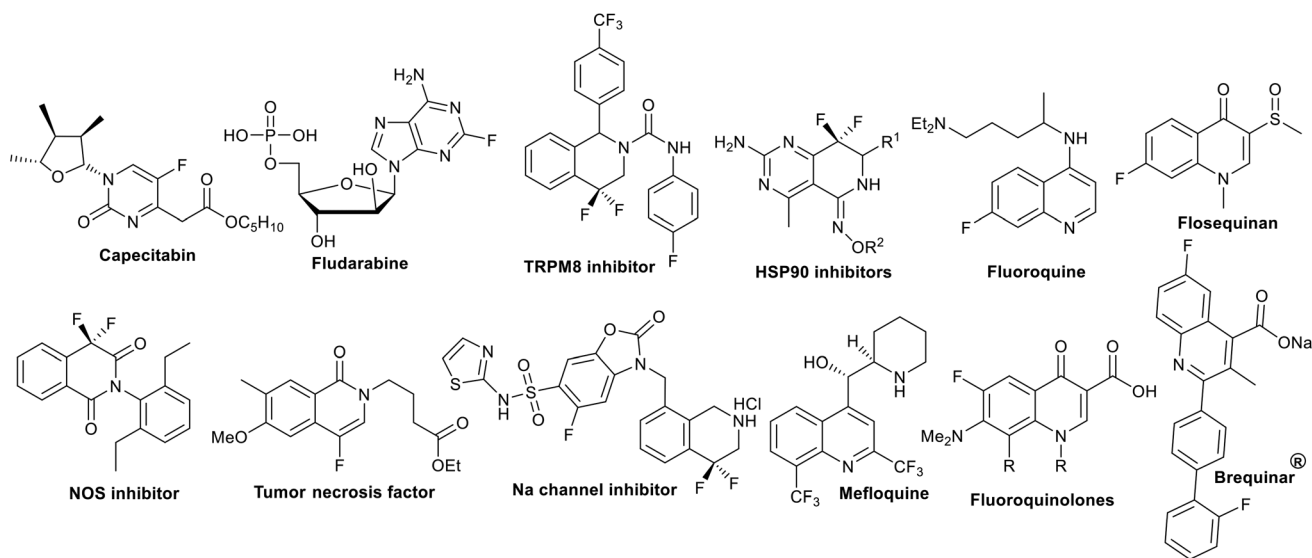


Fig. 5 Examples of medicinally relevant fluorinated quinoline and isoquinoline derivatives.

2.4 Synthesis of fluorinated quinoline and isoquinoline derivatives

Quinolines and quinolones have a special position in heterocyclic chemistry¹⁴⁵ and have retained long-standing interest among synthetic chemists. A number of methods have been developed that have enabled the synthesis of fluorinated quinolines and quinolones, and many of the derivatives exhibit remarkable biological properties. A few of them have been introduced to the pharmaceutical market, such as antimalarial drugs fluoroquine and mefloquine, the transplantation drug brequinar (used for the treatment of psoriasis and rheumatic

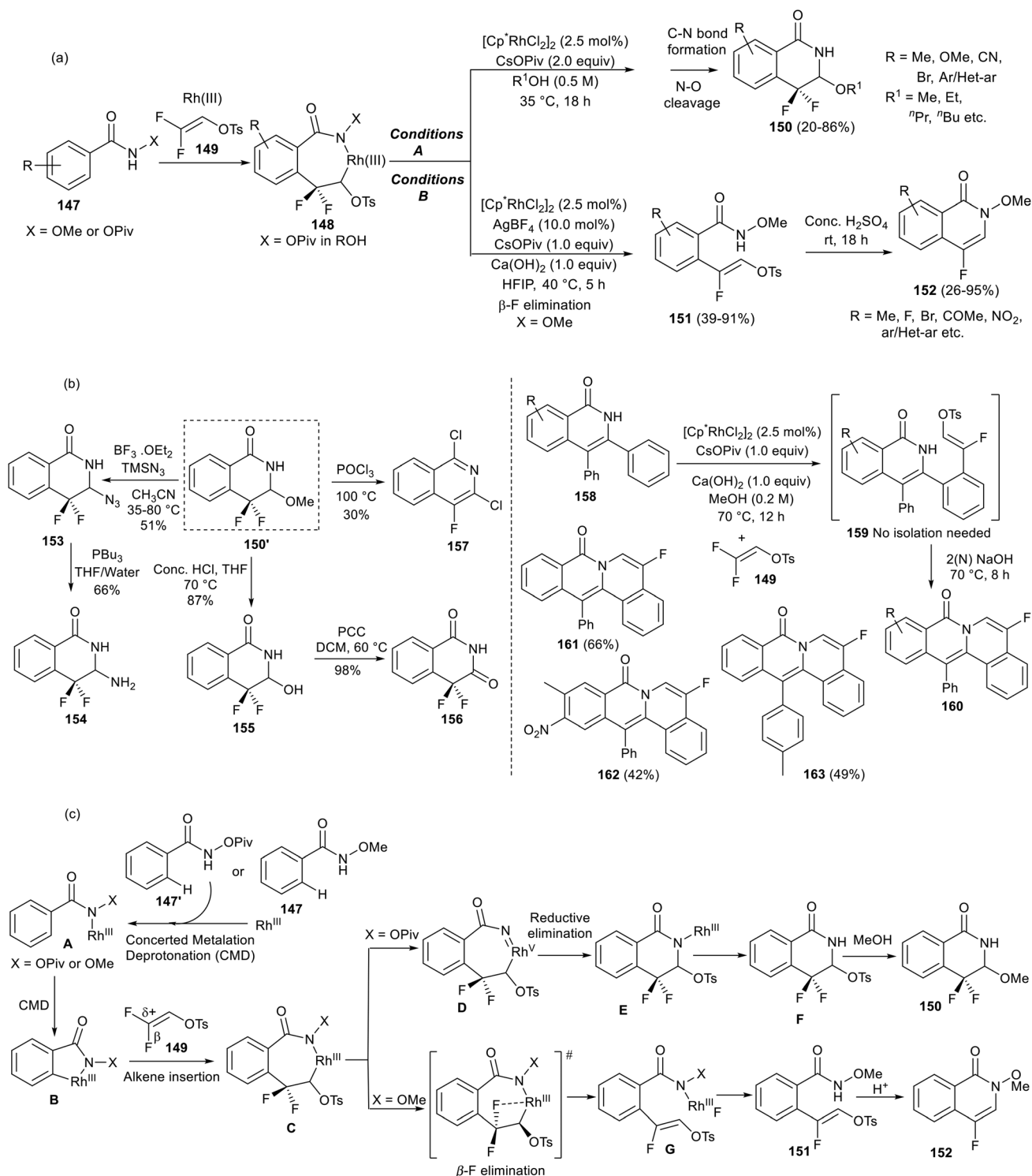
arthritis), and flosequin (used for the treatment of heart disease). Many of the fluoroquinolone derivatives exhibit a wide range of antibacterial activity.

Wang *et al.* developed an efficient method for the synthesis of fluorinated heterocycles, specifically *gem*-difluorinated dihydroisoquinolin-1(2*H*)-ones **150** and 4-fluoroisoquinolin-1(2*H*)-ones **152** via a rhodium(III)-catalyzed C–H activation strategy. The transformation involves the reaction of *N*-OMe/OPiv-substituted benzamides **148** with 2,2-difluorovinyl tosylate **149** through C–H functionalization of arenes or alkenes. The reaction proceeds smoothly under mild conditions, affording the desired fluorinated products in good yields. The synthesized



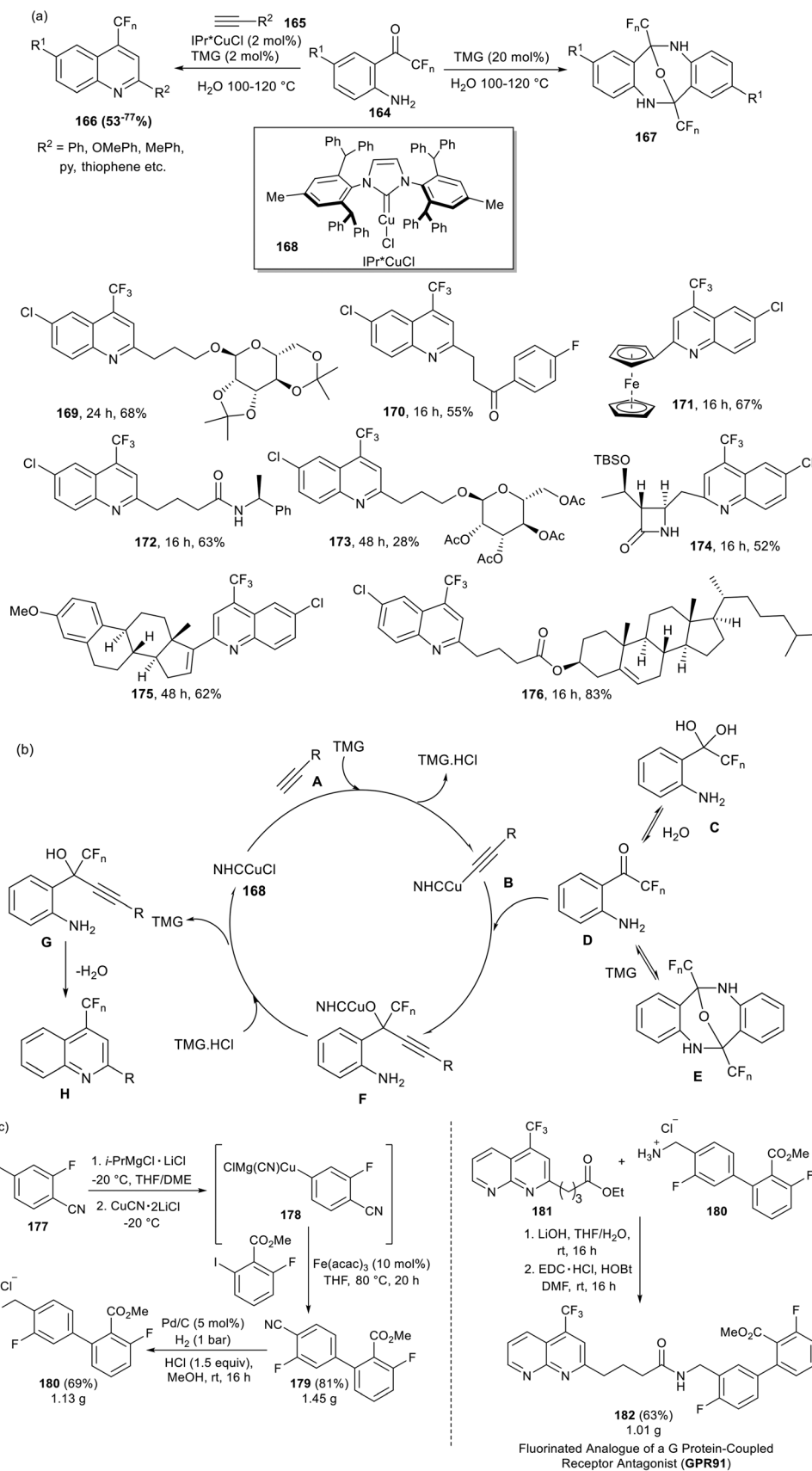
compound was further manipulated to generate diverse fluorinated products **153–163** (Scheme 19).¹⁴⁶ The mechanism of the reaction for the synthesis of both sets of compounds was systematically studied and supported by the DFT studies. This revealed that the transformation follows a sequence involving

N–H deprotonation, C–H activation, and olefin insertion, leading to the formation of a seven-membered rhodacycle intermediate **148**. This intermediate then undergoes β -fluoride elimination and C–N bond formation, resulting in the formation of the final fluorinated isoquinolinone products.



Scheme 19 (a and b) Synthesis of 4-fluoroisoquinolin-1(2*H*)-ones, 5-fluoropyridin-2(1*H*)-ones, and *gem*-difluorinated dihydroisoquinolin-1(2*H*)-ones and (c) the proposed mechanism.



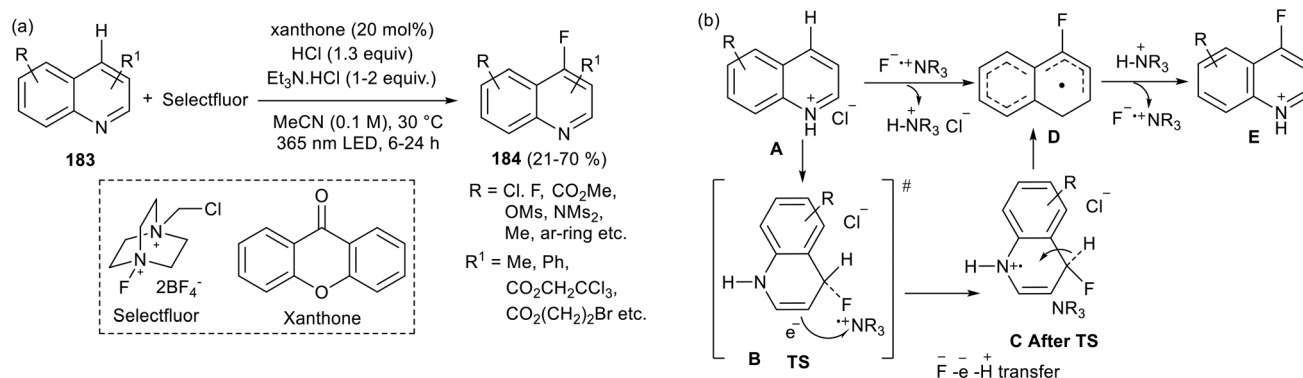


Scheme 20 (a) Synthesis of fluorinated trifuoromethylquinolines, naphthydrines and dibenzo[*b,f*][1,5]diazocines, and (b) the proposed mechanism. (c) Synthesis of a G-protein-coupled receptor antagonist (GPR91).

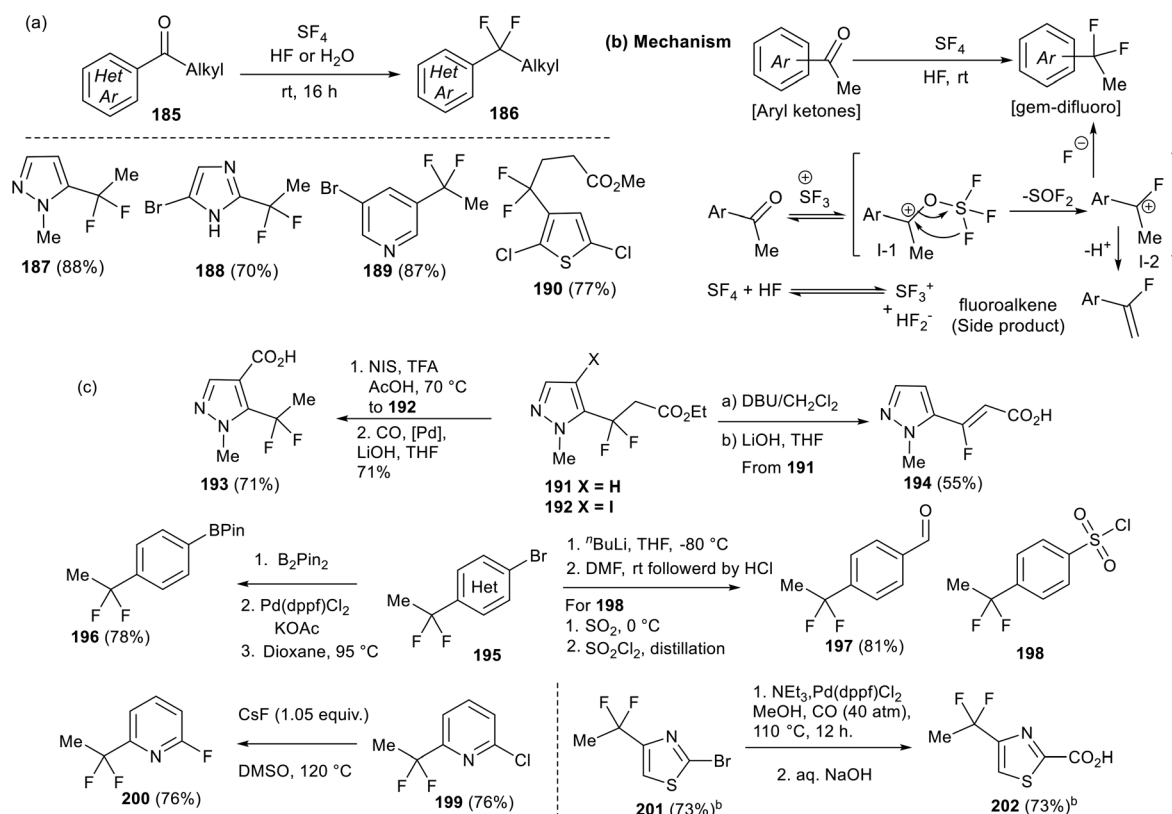


Michalak reported the use of *o*-aminotrifluoromethyl ketones (*o*-TFMKs) **164** and terminal alkynes **165** for the synthesis of 4-trifluoromethylquinolines **166** and naphthydrines (as well as their difluoro- and perfluoro-analogues) *via* a direct catalytic alkynylation/dehydrative cyclization sequence on water (Friedländer-type reaction) (Scheme 20). Significantly, this was the first application of N-heterocyclic carbene copper (i) complexes (NHCCuX) **168** as a catalyst in the synthesis of fluorine-containing quinolines **166**. The method is suitable for a large variety of terminal alkynes, such as β -lactam-, steroid-, and sugar-derived alkynes, and leads to the desired quinolines

and naphthydrines **169–176** with good yields. In addition to quinoline synthesis, *o*-FMKs were efficiently transformed into a rare class of heterocyclic compounds, namely, dibenzo [*b,f*] [1,5] diazocines **167**, through a base-catalyzed condensation in water. The applicability of this method was demonstrated by the gram-scale synthesis of a fluorinated analogue of G protein-coupled receptor antagonist (GPR91), **182** (Scheme 20c). A mechanistic pathway was proposed and is illustrated in Scheme 20b. The catalytic cycle begins with the interaction of the complex NHCCuCl with a terminal alkyne **A**, which leads to the formation of the mononuclear copper acety-



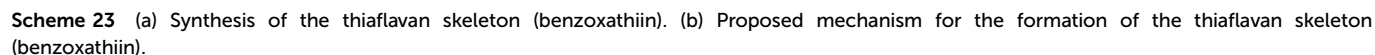
Scheme 21 (a) Synthesis of fluorinated quinolines through concerted nucleophilic aromatic substitution (CS_NAr) reactions, (b) Proposed reaction mechanism.



Scheme 22 (a) Fluorination of heteroaromatic compounds, (b) Proposed reaction mechanism, (c) More examples.

intermediates. In such cases, the attack of F^- ion, where fluoride elimination is more facile compared to hydride elimination, makes product formation difficult. To overcome this, Ritter *et al.* recently used a chain process involving an asynchronous concerted $F^-e^-H^+$ mechanism that enables C-H nucleophilic fluorination without the creation of an azaarene Meisenheimer intermediate. This method enabled selective fluorination at the C-4 position of azaarenes, which is considered the most electrophilic in nature.

The nucleophilic fluoride attack on azaarene is challenging owing to the formation of reversible Meisenheimer



To accomplish azaarene C–H fluorination, it was envisioned to go from a stepwise method to a concerted nucleophilic aromatic substitution ($\text{C}_\text{N}\text{Ar}$) pathway. This design circumvents the hurdle of removing a hydride from an already high-energy Meisenheimer complex. Conceptually, the concerted reaction was achieved by the fluoride attack on a protonated azaarene **A**, followed by an electron transfer and heterolytic C–H cleavage to a radical cation to release H^+ (Scheme 21b). Using this method, a wide variety of substituted quinolines **183** were used for the C-4 fluorination reaction to give the corresponding fluorinated products **184**, employing Selectfluor, 365 nm LED light, and a protic acid (Scheme 21).³²

2.5 Miscellaneous methods

The 2,2-difluoroalkyl substituent ($-\text{CF}_2\text{Me}$) is considered a valuable bioisoster of anisole and has been regularly utilized in drug discovery.^{147,148} Several novel synthetic methods have been developed for the synthesis of hetero(aromatic) derivatives bearing the $-\text{CF}_2\text{Me}$ group. Notable examples include radical fluorination using sodium (methyl-difluoromethyl) sulfinate ($\text{MeCF}_2\text{SO}_2\text{Na}$),¹⁴⁹ and deoxofluorination of (hetero) aromatic ketones using diethylaminosulfur trifluoride (DAST, SF_3NET_2).^{150,151} Mykhailiuk *et al.* reported a general method for the difluorination of heteroaromatics through the deoxofluorination of substituted acetophenones and trifluoromethane ketones using sulfur tetrafluoride (SF_4) in liquid hydrogen fluoride (HF). This approach is notable for being fast, high-yielding, and scalable (up to 70 g). The approach proved effective across a broad range of difluorinated products, encompassing aromatic and heteroaromatic compounds. For instance, pyrazole, imidazole, and thiazole derivatives provided the desired difluorinated products **187–190** in 53–88% yield. Although certain thiophene and furan derivatives underwent polymerization, others were compatible with the reaction conditions. Most difluorinated compounds were further manipulated to give a diverse range of fluorinated heterocyclic compounds **193**, **194**, **196**, **198**, **200**, **202** (Scheme 22).¹⁵²

Shibata *et al.* developed an efficient method for the synthesis of thiaflavan (benzoxathiin) derivatives **205** by employing a perfluorophenyl analogue of DAST, namely $\text{C}_6\text{F}_5\text{-DAST}$, in reactions with β -keto esters **203**, delivering the desired benzoxathiin products **204** in excellent yields.¹⁵³ Thus, activated acyclic α -methylene ketones such as β -keto esters, 1,3-diketone, and β -keto sulfones **203**, were used in the continuous penta-fluorophenylolation–cyclization reaction to provide tetra-fluorinated benzoxathiin derivatives **204** (Scheme 23a). The key fluorinating reagent, $\text{C}_6\text{F}_5\text{-DAST}$, was generated *in situ* via the reaction of $\text{C}_6\text{F}_5\text{-SiMe}_3$ with DAST in the presence of iPr_2NET . The reagent was then immediately employed for the subsequent transformation without reagent isolation. The synthesized benzoxathiin intermediate **204** was further manipulated to diverse fluorinated products **205–209**. The proposed mechanism for this synthesis is shown in Scheme 23b.

In addition to this work, recent advancements have also been made in the synthesis, and a wide range of fluorinated heterocycles, such as acylated 3- CF_3 -2-oxindoles, fluorinated imidazo[1,2-*a*]pyridines and fluorinated pyrrolo[2,1-*a*]isoquinolines, have been reported by using metal-mediated or metal-free reaction pathways.^{152,154,155}

3 Recent FDA-approved fluorinated drugs

In 2023, the U.S. Food and Drug Administration (FDA) approved 12 fluoro-containing drugs and several new fluorinated pharmaceuticals have also received approval in the current year for the treatment of different diseases. Notably, many of these compounds feature fluorinated heterocycles as key structural motifs (Fig. 6). In this section, we highlight the structural features of compounds, their synthetic strategies, and the biological activities of these newly approved, fluorinated drugs. We have focused on seminal works and the synthesis of fluorinated compounds.

3.1 Acoramidis (Attruby)

Acoramidis is a small fluorinated heterocycle developed and sold under the trade name Attruby by Pfizer¹⁵⁶ for the treatment of cardiomyopathy caused by amyloid deposition in the heart.¹⁵⁷ Acoramidis binds and stabilizes the thyroxine transporter (TTR) protein, thereby inhibiting aggregation and deposition of this protein as amyloid in the heart. As a result, it can slow the cardiomyopathy.¹⁵⁸

Acoramidis contains a pyrazole ring appended with substituted *p*-fluorobenzoic acid derivatives. The synthesis of Acoramidis is depicted in Scheme 24(i).¹⁵⁹ Initially, methyl 4-fluoro-3-hydroxybenzoate **210** underwent nucleophilic displacement reaction with 1,3-dibromopropane to obtain the ester derivative, which was followed by a nucleophilic substitution reaction with acetylacetone to generate the 1,3-diketo compound **211**. The latter then participated in a Mannich-type reaction with hydrazine hydrate to form a pyrazole ring appended with *p*-fluoromethylbenzoate. Finally, lithium hydroxide-mediated ester hydrolysis generated the target drug molecule Acoramidis (Fig. 6).

3.2 Crinicerfont (Crenessity)

Crinicerfont was developed and marketed under the brand name Crenessity by Corcept Therapeutics¹⁶⁰ and was approved for the treatment of congenital adrenal hyperplasia (CAH).¹⁶¹ CAH is an autosomal disorder that causes enzyme deficiencies in the adrenal biosynthesis pathway, resulting in the formation of impaired cortisol.¹⁶² Also, corticotropin-releasing hormone receptor 1 (CRH_1) controls the release of cortisol hormone *N*-propargylation from adrenal glands and crinicerfont selectively blocks the CRH_1 receptor, thereby increasing cortisol formation to inhibit CAH.

The synthesis of Crinicerfont is depicted in Scheme 24(ii).¹⁶³ In the first step, the alcoholic OH group of



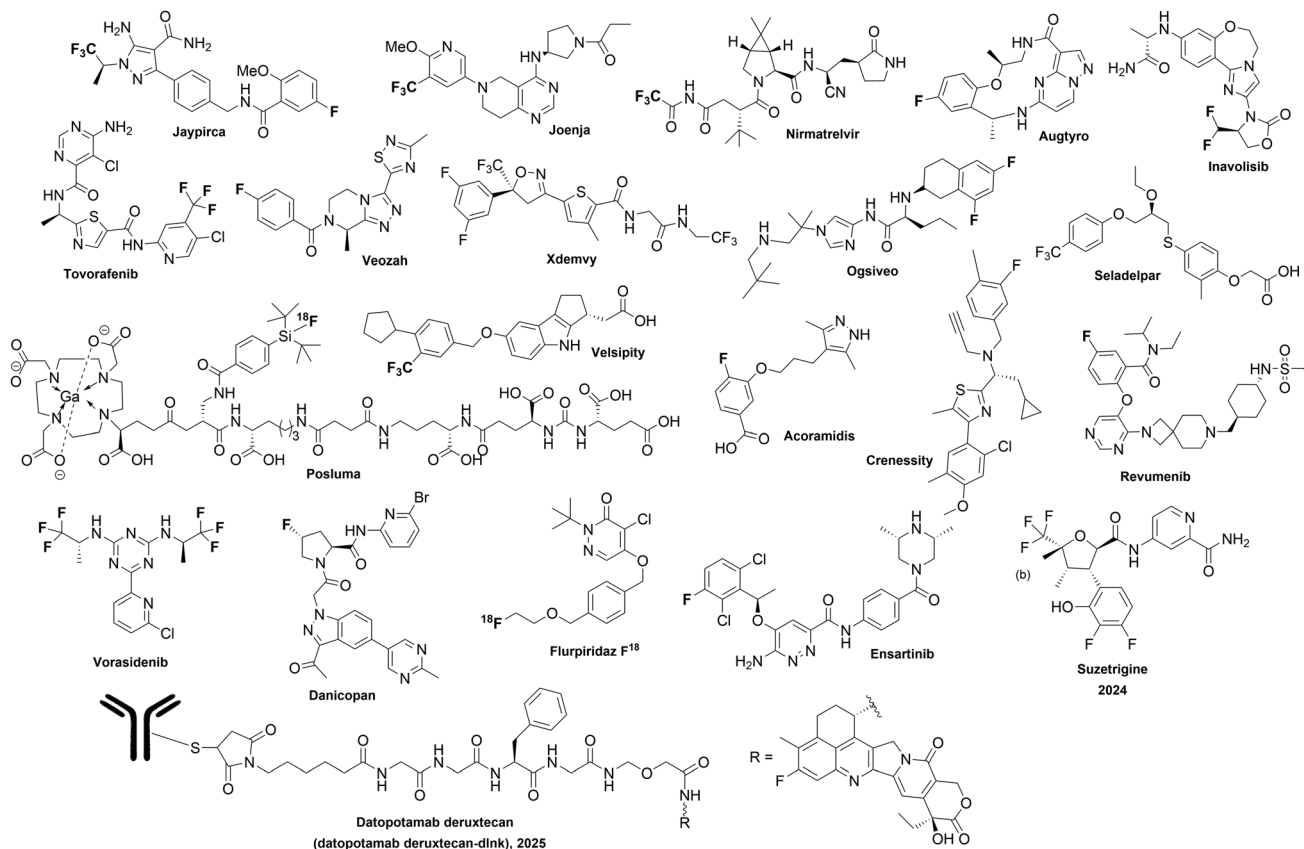
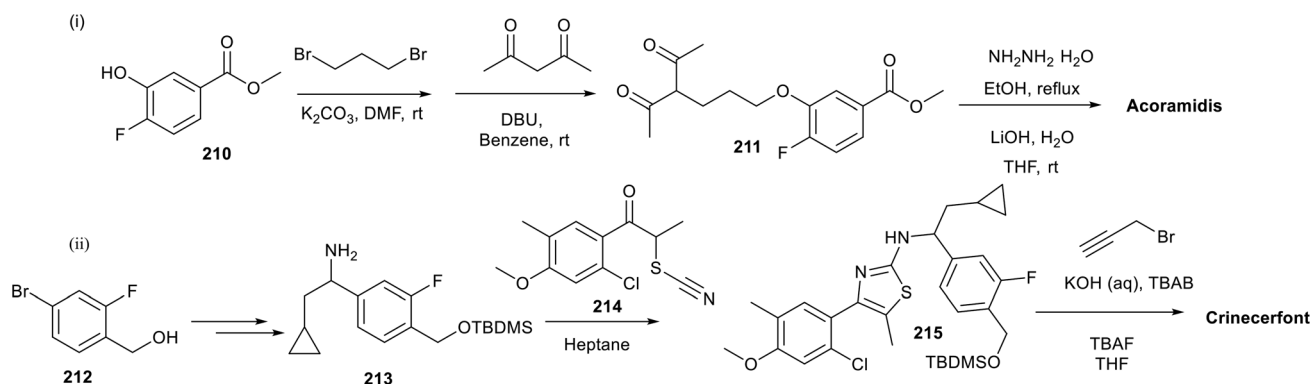


Fig. 6 List of FDA-approved drugs (2024 and 2025) in the category of fluorinated heterocycles.



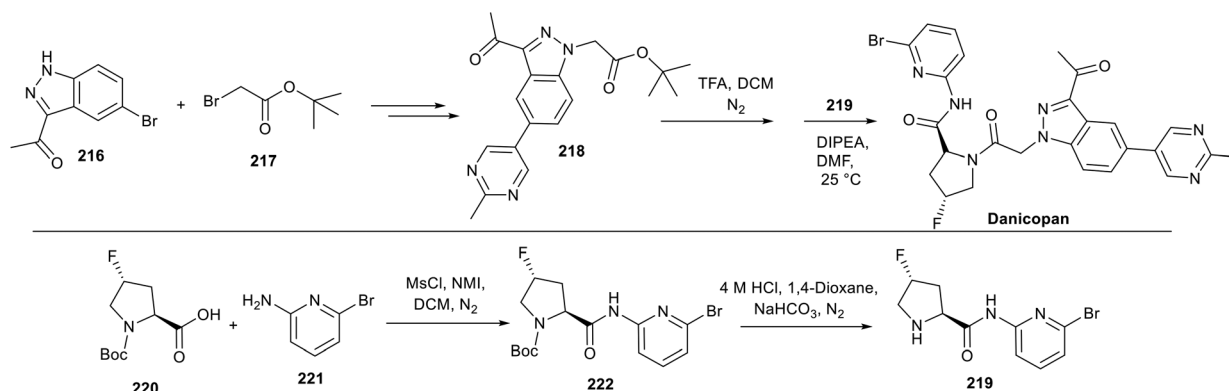
Scheme 24 (i) Synthesis of acoramidis and (ii) crinecerfont (Crenessity).

(4-bromo-2-fluorophenyl)methanol **212** was protected using TBDMSCl, followed by a nucleophilic substitution reaction with 2-cyclopropyl-*N*-methoxy-*N*-methylacetamide and amination to give the amine derivative **213**. Compound **213** then underwent a Knoevenagel condensation reaction with 1-(2-chloro-4-methoxy-5-methylphenyl)-2-thiocyanatopropan-1-one **214** to form the fluorinated thiazole derivative **215**. Subsequent *N*-propargylation followed by TBDMS deprotection were carried out to obtain Crinecerfont.

3.3 Danicopan (Voydeya®)

Danicopan developed by Alexion AstraZeneca Rare Disease and sold under the trade name Voydeya®¹⁶⁴ and is approved for the treatment of extravascular haemolysis. Danicopan is an orally administered factor D inhibitor that blocks the complement C5a receptor (C5aR) responsible for red blood cell destruction and therefore reduces haemolysis in Paroxysmal Nocturnal Haemoglobinuria (PNH) patients.





Scheme 25 Synthesis of danicopan (Voydeya®).

The synthetic route to Danicopan is shown in Scheme 25.¹⁶⁴ In the first step, *N*-acylation of 5-(bromo-1*H*-indazolyl)ethan-1-one **216** followed by Suzuki coupling with pyrimidine boronic ester was conducted to obtain compound **218**. Subsequent TFA-catalyzed ester hydrolysis of compound **218** generated the acid derivative, which underwent an amidation reaction with fluoropyrrolidine-2-carboxamide derivative **219** to obtain the target drug Danicopan.

3.4 Ensartinib (Ensacove™)

Ensartinib, marketed under the trade name Ensacove™ by Astellas Pharma,¹⁶⁵ has been approved for the treatment of adult patients with ALK-positive non-small cell lung cancer (NSCLC).¹⁶⁶ Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase (RTK) enzyme that acts as an oncogenic activator in malignancies for both adults and children. Ensartinib inhibits the ATP-binding site of the ALK enzyme by binding to ALK, thereby reducing tumor-cell growth.¹⁶⁷

Ensartinib acts by selectively binding to the ATP-binding pocket of the ALK enzyme, thereby inhibiting its kinase activity and ultimately suppressing tumor cell proliferation. This targeted mechanism of action makes ensartinib a valuable therapeutic option for ALK-driven cancers, particularly in cases where resistance to first-generation ALK inhibitors has developed.

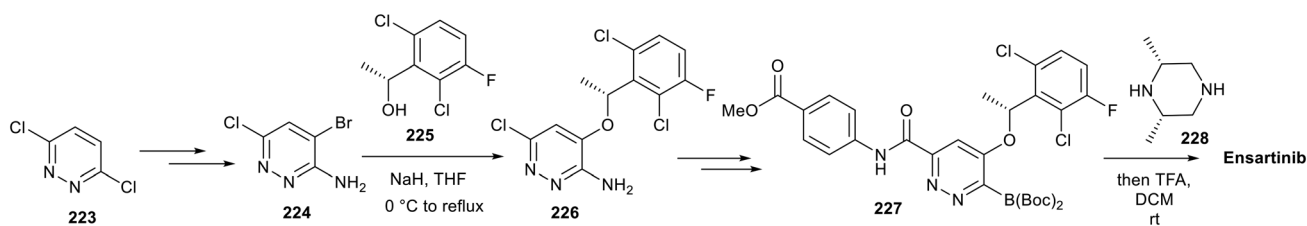
The synthetic route to Ensartinib is shown in Scheme 26.¹⁶⁸ Initially, 3,6-dichloropyridazine **223** underwent amination reaction followed by bromination to obtain compound **224**. Subsequently, nucleophilic substitution reaction with (*R*)-1-(2,6-dichloro-3-fluorophenyl)ethan-1-ol **225** formed the fluori-

nated pyridazine derivative **226**. Subsequently, pyridazine derivative **226** was converted into **227** in a few steps. Finally, ester hydrolysis followed by amidation with a secondary amine and deprotection of the amine gave the target compound Ensartinib (Fig. 6).

3.5 Etrasimod (Velsipity)

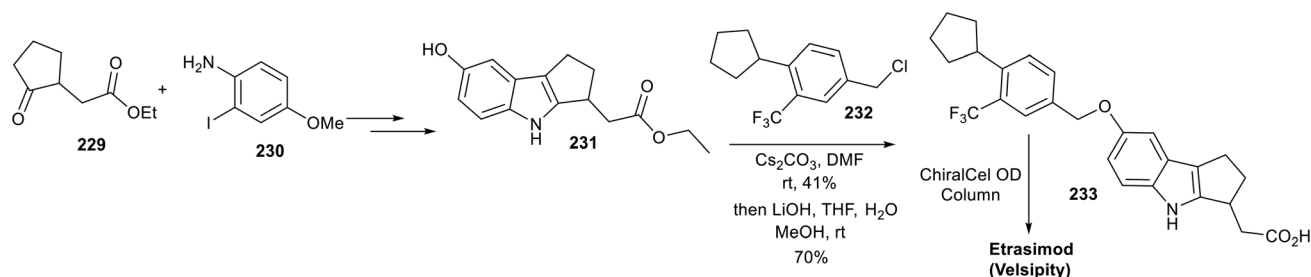
Etrasimod developed and sold under the marketed name VELSIPITY™ by Pfizer Inc.¹⁶⁹ and is approved for the treatment of ulcerative colitis (UC) in adults.¹⁷⁰ Etrasimod is a potent antagonist of the sphingosine-1-phosphate-1 (S1P₁) receptor (IC₅₀ = 1.88 nM). Ulcerative colitis is a chronic inflammatory disorder that mainly affects the colon. In this disease, ulcers are formed in the inner part of the large intestine and, as a result, symptoms such as frequent bowel movements, bloody diarrhoea, and discomfort in the abdomen are commonly observed.¹⁷⁰ Etrasimod controls the immune cell level in the blood by inhibiting the ability of lymphocytes to exit lymphoid organs, which indicates the presence of fewer immune cells in the lining of the colon, thereby reducing inflammation.

The synthetic route for drug development is described in Scheme 27.¹⁷¹ In the initial step, tetrahydrocyclopenta[*b*]indolyl-ol **231** was obtained by condensation and coupling of ethyl 2-(2-oxo-cyclopentyl)acetate **229** and 2-iodo-4-methoxyaniline **230** followed by boron tribromide mediated demethylation. The nucleophilic substitution with substituted trifluoromethyl benzyl chloride **232** was done to obtain the ether **231**, and lithium hydroxide-mediated hydrolysis of the ester was carried



Scheme 26 Synthesis of ensartinib (Ensacove™).





Scheme 27 Synthesis of etrasimod (Velsipity).

out to generate the carboxylic acid derivative 233. Finally, carboxylic acid derivative 233 was resolved using a chiral oligosaccharide derivatized (OD) column to obtain the targeted drug Etrasimod (Fig. 6).

3.6 Fezolinetant (Veoza)

Fezolinetant, sold under the brand name VEOZAHTM and developed by Astellas Pharma Inc.¹⁷² is approved for the treatment of vasomotor symptoms (VMS) or hot flushes or night sweats caused by the menopause.¹⁷³ The thermoregulatory centre of the hypothalamus is controlled by kisspeptin/neurokinin B/dynorphin (KNDy) neurons that are inhibited by estrogen and stimulated by neurokinin B (NKB). Most women have lower estrogen levels in menopause, which causes irregular stimulation of KNDy neurons and is responsible for vasomotor symptoms (VMS). Fezolinetant (VEOZAHTM) reversibly and selectively blocks NK B signaling, which causes a decrease in kisspeptin/neurokinin B/dynorphin (KNDy) neuron activity, thereby reducing VMS Symptoms.

Fezolinetant contains a fused heterocyclic triazolo[3,4-*c*]pyrazine core moiety with 4-fluoro-benzoyl substitution. The synthesis of Fezolinetant is shown in Scheme 28.¹⁶⁹ Initially, piperazinone 234 was alkylated using Meerwein's salt Et₃OBF₄, followed by an annulation reaction with carbohydrazide 235. Subsequent trifluoroacetic acid mediated elimination of 2,4-dimethoxybenzyl (DMB) generates the tetrahydro-triazolo[4,3-*a*]pyrazin-thiadiazole core structure 236. Finally, compound 236 was condensed with 4-fluorobenzoyl chloride to obtain the targeted drug Fezolinetant.

3.7 Inavolisib (Itovebi)

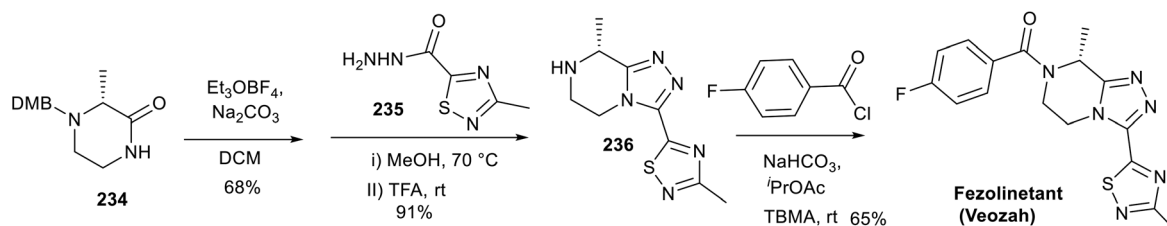
Inavolisib, developed by Arcus Biosciences and marketed under the trade name Itovebi, is an orally administered phosphoinosi-

tide 3-kinase (PI3K) δ and γ inhibitor.¹⁷⁴ It is primarily used for the treatment of metastatic breast cancer (IC₅₀ of 38 nM against mutant p110 α protein, a subunit of PI3K α).¹⁷⁴ The class I isoform(α , β , δ , and γ), PI3K α is most commonly responsible for the formation of solid tumors *via* activating mutations or gene amplification. Inavolisib is considered to be a highly selective inhibitor of PI3K α , and showed more than 300-fold greater selectivity than other class I PI3K isoforms β , δ , and γ .¹⁷⁵

Inavolisib consists of a benzoxazepin-oxazolidinone core structural moiety with difluoromethyl and aminopropanamide substituents. The synthetic route to Inavolisib is given in Scheme 29(i).¹⁷⁶ The starting material 237 was used to synthesize dihydrobenzo[*f*]imidazo[1,2-*d*][1,4]oxazepane 238 in a few steps, and the latter was converted into 239. Compound 239 then underwent a copper(II) catalyzed C–N coupling reaction with difluoromethyl substituted oxazolidinone 240 to obtain 242, which was then used to generate the target drug Inavolisib (Fig. 6).¹³

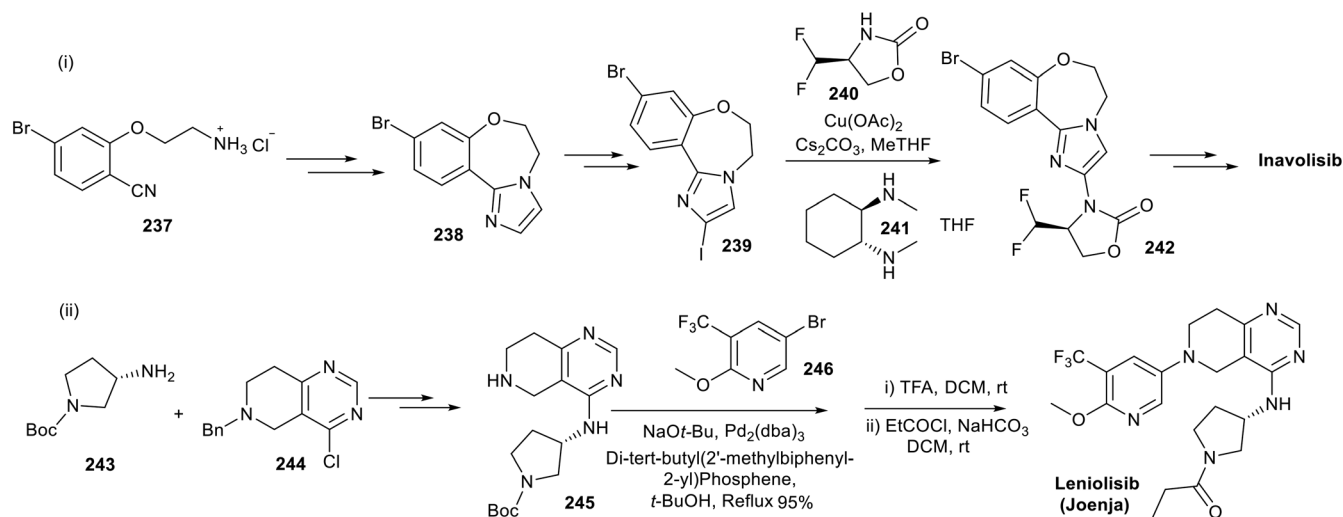
3.8 Leniolisib (Joenja)

Leniolisib, marketed under the trade name Joenja, is a small-molecule drug developed by Novartis Pharma AG for the treatment of activated phosphoinositide 3-kinase delta syndrome (APDS)—a rare primary immunodeficiency disorder caused by mutations in the gene encoding phosphatidylinositol-3-kinase δ (PI3K δ).¹⁷⁷ *In vitro* studies have demonstrated that leniolisib inhibits immune cell functions, as shown in B and T cells, monocytes, neutrophils, basophils, and mast cells. Leniolisib showed *in vivo* inhibitory activities on B cell activation in rats and monkeys. In cellular assays, leniolisib exhibits higher selectivity toward PI3K δ (IC₅₀ = 0.056 μ M) than PI3K α (30-fold) and PI3K β (40-fold).¹⁷⁸



Scheme 28 Synthetic route to fezolinetant (Veoza).





Scheme 29 (i) Synthetic route to inavolisib. (ii) Synthesis of leniolisib (Joenja).

This drug molecule contains a tetrahydropyrido[4,3-*d*]pyrimidine core structure with fluorinated pyridine substituents, which is essential for its biological activity. The synthetic approach to Leniolisib is shown in Scheme 29(ii). Aminopyrrolidine **243** and 4-chloro-tetrahydropyrido[4,3-*d*]pyrimidine **244** were used to construct compound **245** over a few steps. The 2-methoxy-3-(trifluoromethyl)pyridine **246** unit is then introduced into the core structure *via* C–N coupling. The final steps involve deprotection of the –Boc group, followed by acylation, to generate the targeted drug Leniolisib.

3.9 Lotilaner (Xdemvy)

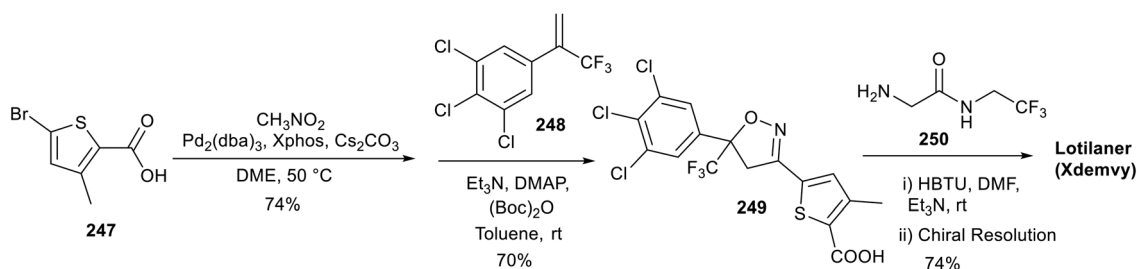
Lotilaner ophthalmic solution, sold under the brand name XDEMVMY™, developed by Tarsus Pharmaceuticals, is a γ -aminobutyric acid-gated chloride channel (GABA-Cl) selective inhibitor for mites.¹⁶⁹ It is approved for the treatment of *Demodex* blepharitis and meibomian gland dysfunction in patients with *Demodex* lid infestation. The most common symptoms of *Demodex* blepharitis are ocular itching, eye redness, tearing, pain, foreign body sensation, and blurred vision.¹⁷⁹ Lotilaner is an effective inhibitor of the chloride ion channel gated by GABA, and selectively targets mites. This drug shows a high affinity for the GABA receptor in *Drosophila*

sp. (IC₅₀ = 23.84 nM). Suppression of GABA chloride channels results in paralysis and eventual death of the target organism.

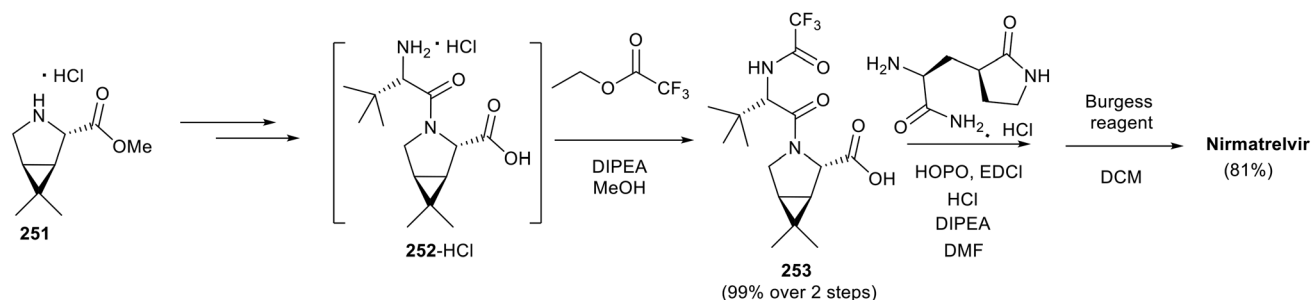
The lotilaner molecule contains an isoxazole core heterocyclic scaffold with trifluoromethyl (CF₃) substitution. The preparation of Lotilaner is depicted in Scheme 30.^{28,169} Initially, substituted 2-bromothiophene derivative **247** underwent Pd-catalysed coupling with nitromethane to generate 2-nitrothiophene, which participated in an alkali-mediated ring-closing reaction with benzene trifluoropropene **248** to obtain trifluoromethyl-substituted isoxazole **249**. In the last step, lotilaner (Fig. 6) was prepared by condensation reaction of **249** with 2-amino-*N*-(2,2,2-trifluoroethyl)acetamide **250**.

3.10 Nirmatrelvir

Nirmatrelvir, developed by Pfizer,¹⁸⁰ is a second-generation orally administered peptidomimetic M^{pro} inhibitor. The SARS-CoV-2 genome encodes two polyproteins, pp1a and pp1ab, and four structural proteins. M^{pro} cleaves the polyproteins at 11 sites to generate non-structural proteins that have a vital role in viral replication. Nirmatrelvir forms a complex with M^{pro}, thereby preventing the M^{pro}-mediated cleavage. As a result, viral replication and proliferation are inhibited.¹⁸¹ In December 2021, the FDA approved emergency use of Paxlovid, a combined drug product containing both M^{pro} inhibitor



Scheme 30 Synthesis of lotilaner (Xdemvy).



Scheme 31 Synthesis of nirmatrelvir.

Nirmatrelvir and CYP3A4 inhibitor Ritonavir, for the treatment of patients with mild-to-moderate COVID-19 infections.¹⁸¹

The Nirmatrelvir molecule contains pyrrolidone, nitrile, and trifluoromethyl amide functionalities. The synthetic strategy is depicted in Scheme 31.¹⁸² This drug molecule is synthesized starting from methyl (1*R*,2*S*,5*S*)-6,6-dimethyl-3-azabicyclo [3.1.0]hexane-2-carboxylate, HCl salt **251** over six consecutive steps. Compound **251** was converted into the primary amine **252** in a few steps, which was then readily reacted with ethyl trifluoroacetate to synthesize compound **253**. In the last two steps, amide coupling to **253**, followed by dehydration of the primary amide using Burgess reagent, generated the drug Nirmatrelvir (Fig. 6) with an overall yield of 81%.

3.11 Nirogacestat (Ogsiveo)

Nirogacestat was developed and marketed under the trade name of OGSIVEO™ by Pfizer Inc. The drug is approved for the treatment of Desmoid tumor (DT), which is also known as desmoid-type fibromatosis, that arises in the soft tissues, such as in the mesenteric root or abdominal and chest walls.¹⁷⁹ Nirogacestat is an orally administered γ -secretase inhibitor (IC_{50} = 6.2 nM). γ -Secretase is a transmembrane protease responsible for the cleavage of transmembrane proteins such as Notch, which are directly involved in fibromatosis growth. The γ -secretase inhibitor Nirogacestat plays a crucial role in tumor growth inhibition by blocking transmembrane protein cleavage, thereby acting as an anti-cancer agent.¹⁸³

The 6,8-difluorotetralin containing aminoimidazole moiety is present as a core structure in Nirogacestat. Synthesis of this drug is described in Scheme 32.¹⁸⁴ Initially, the reduction of imidazolyl propanoate **254** with DIBAL-H, followed by condensation with 2,2-dimethylpropan-1-amine and subsequent reduction of the nitro group with H_2 in Pd/C generated com-

pound **255**. In the final step, compound **255** was treated with 6,8-difluoro-tetraline-amino-pentanoic acid **256** to obtain the target drug Nirogacestat (Fig. 6).

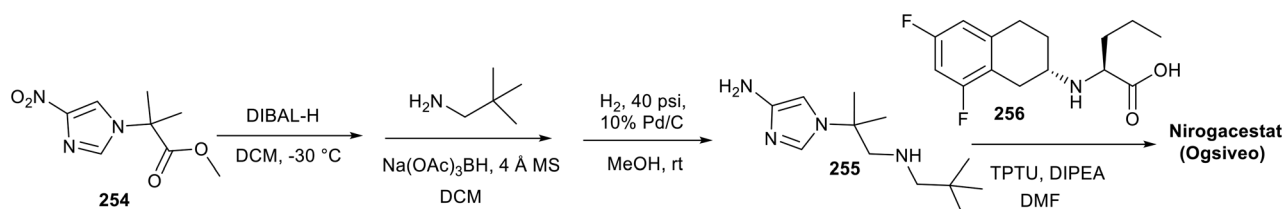
3.12 Pirtobrutinib (Jaypirca)

Pirtobrutinib is a fluorinated heterocycle small molecule, marketed under the trade name Jaypirca, and approved for the treatment of mantle cell lymphoma (MCL). It is a highly selective Bruton's tyrosine kinase (BTK) inhibitor that effectively suppresses different covalent BTK (Bruton's tyrosine kinase inhibitors) C481 substitution mutations, which are commonly associated with resistance to covalent BTK inhibitors.¹⁸⁵ Pirtobrutinib is highly effective for the treatment of both mantle cell lymphoma (MCL) and chronic lymphocytic leukaemia (CLL).¹⁸⁶

Pirtobrutinib contains a key *N*-trifluoromethyl substituted pyrazole core, which plays a crucial role in its biological activity. The synthetic route to the synthesis of pirtobrutinib is shown in Scheme 33.¹⁸⁷ Commercially available benzohydrazide **257** was condensed with 1,1,1-trifluoropropan-2-one **258** to furnish the imine intermediate, which was converted into [1,1,1]-trifluoropropan-2-yl hydrazine hydrochloride **259** in a few more steps. This intermediate undergoes cyclocondensation with the malonitrile derivative **260** to furnish the substituted pyrazole derivative **261**. Coupling of **261** with borate **262** gave benzamide, which was finally submitted to acidic hydrolysis of the nitrile group to generate the desired drug Pirtobrutinib (Jaypirca, Fig. 6).¹⁸⁸

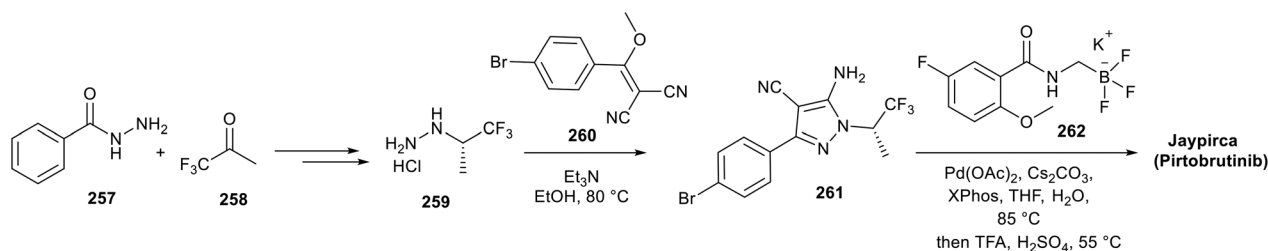
3.13 Revumenib (Revuforj)

Revumenib is a small fluorinated heterocyclic drug molecule available in the market under the brand name Revuforj, developed by Kura Oncology. It is approved for the treatment of refractory acute leukemia associated with a lysine methyltransferase 2A gene (KMT2A) translocation.¹⁶⁴ Revumenib is

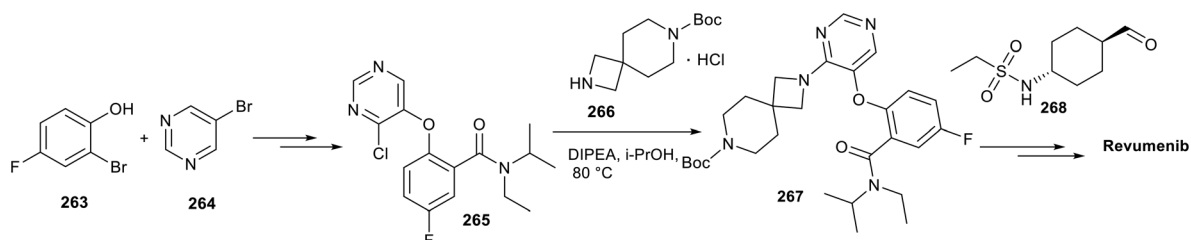


Scheme 32 Synthesis of nirogacestat (Ogsiveo).





Scheme 33 Synthetic route to pirtobrutinib.



Scheme 34 Synthesis of revumenib (Revuforj).

an orally administered menin inhibitor. The interaction between menin and KMT2A is responsible for acute leukemia. By inhibiting menin, Revumenib disrupts this interaction and, as a result, inhibits the refractory acute leukemia.¹⁶⁴

Revumenib contains a pyrimidine ring substituted with 5-fluoro-*N*-isopropylbenzamide and 2,7-diazaspiro[3.5]nonane moieties. The synthetic plan for the synthesis of Revumenib is shown in Scheme 34.¹⁸⁹ Nucleophilic substitution reaction of 2-bromo-4-fluorophenol **263** with 5-bromopyrimidine **264**, followed by many other steps, gave compound **265**. The latter compound underwent nucleophilic substitution with 2,7-diazaspiro[3.5]nonane-7-carboxylate hydrochloride **266** to generate compound **267**. Finally, deprotection of the amine followed by Mannich reaction with 4-formylcyclohexyl-ethanesulfonamide **268** led to the synthesis of Revumenib.

3.14 Tovorafenib (OJEMDA™)

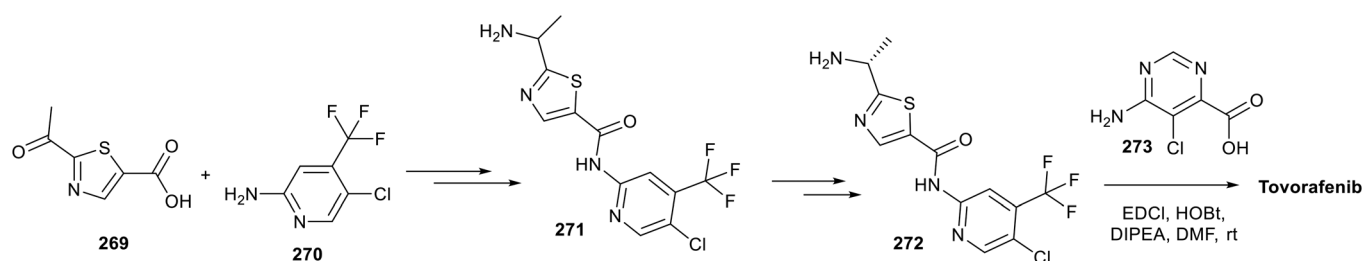
Tovorafenib is developed and sold under the brand name OJEMDA™ by Day One Biopharmaceuticals, Inc., and is approved for the treatment of paediatric low-grade glioma and solid tumors.¹⁷¹ Tovorafenib showed potent inhibitory activi-

ties against wild-type BRAF, BRAF V600, wild-type CRAF mutations, and BRAF fusions. By interacting with BRAF, tovorafenib inhibits downstream RAF signalling and tumor cell proliferation.

The preparation of tovorafenib is shown in Scheme 35.¹⁹⁰ Tovorafenib contains pyrimidine-4-carboxamide, trifluoromethyl-pyridinyl, and thiazole-5-carboxamide structural moieties. In the first step, an amide bond is formed between 2-acetylthiazole-5-carboxylic acid **269** and 5-chloro-4-(trifluoromethyl)pyridine-2-amine **270**, followed by oxime formation and reduction to obtain the amine derivative **271**. *D*-Ditoluoyl tartaric acid modifies the molecular architecture of **271**, enabling the formation of **272**. Finally, **272** underwent dehydration condensation reaction with 6-amino-5-chloropyrimidine-4-carboxylic acid **273** to obtain the target drug tovorafenib (Fig. 6).

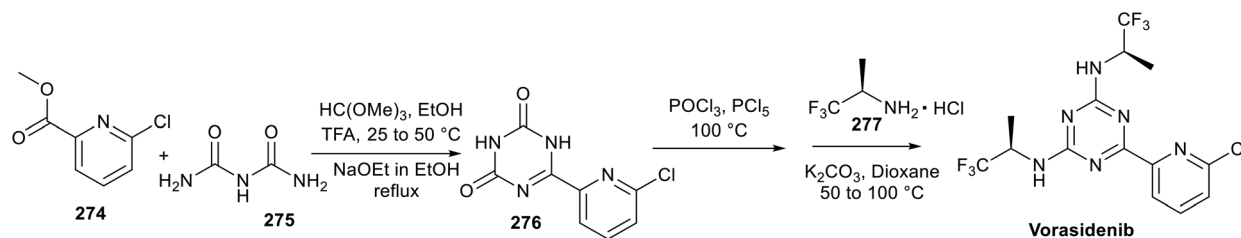
3.15 Vorasidenib (VORANIGO®)

Vorasidenib was developed and marketed under the trade name VORANIGO® by Agios Pharmaceuticals and approved for the treatment of oligodendroglioma.¹⁷⁶ Vorasidenib is a potent inhibitor of mutant isocitrate dehydrogenase 1 and 2



Scheme 35 Synthesis of tovorafenib.





Scheme 36 Synthetic route to vorasidenib.

(IDH1/IDH2) enzymes (IC_{50} values for mIDH1-R132H and mIDH2-R140Q enzymes of 0.006 μ M and 0.012 μ M, respectively).¹⁹¹ Vorasidenib inhibits the production of D-2-hydroxyglutarate (2-HG), a metabolite produced from the mIDH enzyme responsible for tumor growth. This drug reduces the 2-HG concentration and, as a result, reduces tumor growth in patients.¹⁹²

The synthetic route to Vorasidenib is shown in Scheme 36.¹⁹³ Initially, methyl 6-chloropicolinate **274** undergoes an addition reaction with biuret **275**, followed by intramolecular imination to obtain pyridine-tethered triazine derivative **276**, which, on chlorination followed by a substitution reaction with (*R*)-1,1,1-trifluoropropan-2-amine **277**, produced the target drug molecule Vorasidenib.

4. Conclusions

Fluorinated organic compounds are crucial for drug development and material chemistry. The incorporation of heteroatoms can enhance the biological properties of drug molecules in many cases. However, unlike regular organic compounds, heterocyclic moieties pose unique challenges for the site-selective introduction of fluorine atoms. Despite these challenges, a good number of methods and specific reagents have now been developed to achieve these reactions. The present review highlights recent advances in fluorination reactions for the synthesis of fluorinated heterocycles and categorizes them into different sections based on the type of heterocycles. Notably, in the last few years, many new methods have been introduced. In particular, the elusive C–H activation of heterocycles through metal-based catalysts was reported, albeit with relatively few examples.

The latest developments, *i.e.* free radical fluorination, either thermal or photochemical, have shown promise, but are rarely reported for the synthesis of fluoro-heterocycles. In the current and last year, many fluorinated heterocycles have been approved for medical use, reflecting their diverse medicinal value. Most of these compounds feature fluorinated aromatic groups, and a few of them also contain fluorinated chiral centres. Their biological importance and the steps involved in their synthesis have been discussed to showcase the importance of and challenges involved in the fluorination and further manipulation of functional groups. We believe that the comprehensive collection of the latest fluorination methods,

together with descriptions of the relevant mechanisms of fluorination, presented in this review, will serve as a valuable resource for researchers involved in the design of synthetic strategies for specific heterocyclic targets.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code has been included and no new data were generated or analysed as part of this review.

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