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ORGANOFLUORINE CHEMISTRY IN ONCOLOGY: A REVIEW OF US FDA-APPROVED ANTICANCER DRUGS IN 2025 (review).

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In 2025, seven fluorine-containing anticancer agents received approval from the US Food and Drug Administration, underscoring the continued and growing impact of strategic fluorination in modern oncology drug design. These newly authorized therapies represent a diverse portfolio spanning a broad spectrum of malignancies, molecular targets, and innovative mechanisms of action, further validating fluorine's unique ability to enhance drug performance. Sunvozertinib (Zegfrovy®) was approved for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring specific EGFR mutations. The combination of defactinib and avutometinib (Avmapki®) provides a much-needed targeted option for patients with KRAS-mutated recurrent low-grade serous ovarian cancer, addressing a historically challenging disease setting. Imlunestrant (Inluriyo®) offers a next-generation selective estrogen receptor degrader (SERD) as an effective endocrine therapy for estrogen receptor-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer. Ziftomenib (Komzifti®) enables precision therapy for adults with relapsed or refractory (AML) carrying susceptible NPM1 mutations, representing a significant advancement in targeted hematologic oncology.Datopotamab deruxtecan (Datroway®), a novel TROP2-directed antibody–drug conjugate (ADC) with a topoisomerase I inhibitor payload, expands treatment options for previously treated hormone receptor-positive, HER2-negative metastatic breast cancer and for certain TKI-experienced NSCLC populations. Taletrectinib

(Ibtrozi®), a potent next-generation ROS1 tyrosine kinase inhibitor, received approval for ROS1-positive NSCLC in both TKI-naïve and TKI-experienced patients, offering improved central nervous system penetration and activity against resistant mutations.Collectively, these seven agents vividly illustrate the remarkable versatility of fluorine incorporation in enhancing molecular potency, metabolic stability, binding selectivity, and overall pharmacokinetic performance across vastly different therapeutic modalities — from small-molecule kinase inhibitors and degraders to complex antibody–drug conjugates. The strategic placement of fluorine atoms or fluorinated groups in these molecules often leads to improved lipophilicity, stronger target engagement, reduced clearance, and better safety profiles.For each compound, we provide a comprehensive integrated discussion covering its discovery history, detailed biological mechanism of action, primary therapeutic applications, recommended clinical administration and dosing regimens, the specific role of fluorination in optimizing its pharmacological and physicochemical properties, as well as the detailed chemical synthesis routes employed in its industrial-scale production.

Key words: Fluorine; Drug Design; Oncology; Synthesis; Chirality; Pharmacology; Therapeutics.

Dedication: *Dedicated to the memory of Professor Volodymyr Brovarets whose rare combination of intellect, kindness, and curiosity enriched everyone around him. Your legacy remains alive in our hearts and in the science you loved.*

INTRODUCTION. Pharmaceutical drugs are essential to modern civilization, profoundly shaping public health and quality of life. They treat and manage a wide range of acute and chronic diseases, from bacterial infections–transformed by antibiotics in the modern era–to long-term conditions such as diabetes, hypertension, and cardiovascular disorders. Advances in oncology, including chemotherapy and targeted therapies, have markedly improved survival rates while vaccines have near eradicated or greatly reduced the incidence of a number of once devastating infectious diseases [1–3].

Beyond disease control, pharmaceuticals enhance daily functioning by relieving pain, managing symptoms, and supporting mental health, enabling individuals with depression, anxiety, or chronic pain to participate fully in society. They are indispensable to modern medical practice—surgery, transplantation, and intensive care all rely on anesthesia, immunosuppressants, and other critical drugs. Pharmaceuticals also underpin public health initiatives, including vaccination and disease-control programs. Continuous research and development within the pharmaceutical industry drives the discovery of new therapies ensuring progress against emerging health challenges [4–6].

Fluorine is a key element in modern drug design owing to properties that significantly enhance therapeutic performance [7–10]. By blocking metabolic oxidation sites, fluorine slows drug degradation, extending half-life, and sustaining efficacy. Its strong electronegativity fine tunes molecular electronics, improving interactions with biological targets and

increasing potency and selectivity. Fluorine incorporation can also enhance solubility, membrane permeability, and overall bioavailability, helping drugs reach their intended sites more effectively while reducing off-target effects [11–15].

Comprehensive surveys over the past 25 years [7, 16–22] indicate that more than 450 fluorine-containing pharmaceuticals have been approved by the US Food and Drug Administration (FDA). Structurally, heterocyclic scaffolds dominate modern drug design, appearing in over 85% of approved agents due to their broad biological activities and exceptional versatility as molecular backbones [23–31]. Amino acid-derived motifs are similarly influential: over 30% of small-molecule drugs incorporate amino acid residues or related derivatives such as amino alcohols and diamines. These fragments expand structural diversity and, by introducing defined stereochemistry, enable three-dimensional architectures that optimize target engagement [32–41]. Chirality is also very much a central principle of drug design with more than 70% of marketed pharmaceuticals chiral [42–46].

From a therapeutic perspective, fluorinated drugs span nearly all major disease areas. The most frequent activities include anticancer, anti-infective, antiviral, anti-inflammatory, cardiovascular, metabolic, and central nervous system (CNS) indications [7, 14, 16]. Among these, anticancer agents represent one of the most prominent and rapidly expanding categories. Fluorination is especially valuable in oncology because it enhances metabolic stability, improves target selectivity, and enables the fine tuning of physicochemical properties required for potent inhibition of oncogenic pathways. Many landmark cancer therapeutics—including fluoropyrimidines, kinase inhibitors, and modern targeted agents—rely on strategic fluorine incorporation to achieve clinical efficacy [7, 14, 16].

In this review, we profile seven recently approved fluorine-containing, anti-cancer drugs approved by the US FDA in the year 2025. These include sunvozertinib (Zegfrovy®) **1** (Fig. 1), approved for treatment in adults with locally advanced or metastatic non-small cell lung cancer (NSCLC). Defactinib **2** and avutometinib (Avmapki®) **3**, a co-approved oral combination regimen, are indicated for adults with KRAS-mutated recurrent low-grade serous ovarian cancer (LGSOC) after prior systemic therapy. Imlunestrant (Inluriyo®) **4** is indicated for adults with estrogen receptor (ER)-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer that has progressed after at least one line of endocrine therapy. Ziftomenib (Komzifti®) **5** is approved for adults with relapsed or refractory acute myeloid leukemia (AML) harboring susceptible NPM1 mutations. Datopotamab deruxtecan (Datroway®) **6** is a TROP2-directed antibody–drug conjugate (ADC) approved for adults with unresectable or metastatic hormone receptor-positive, HER2-negative breast cancer after prior endocrine therapy and chemotherapy, and for certain adults with previously treated advanced NSCLC. Taletrectinib (Ibtrozi®) **7** is indicated for adults with locally advanced or metastatic ROS1-positive NSCLC, including both TKI-naïve and TKI-experienced patients. For each drug, we outline its discovery, mechanism of biological activity, and detailed synthetic route. We also assess, when possible, how fluorination influences the drug's biological profile.

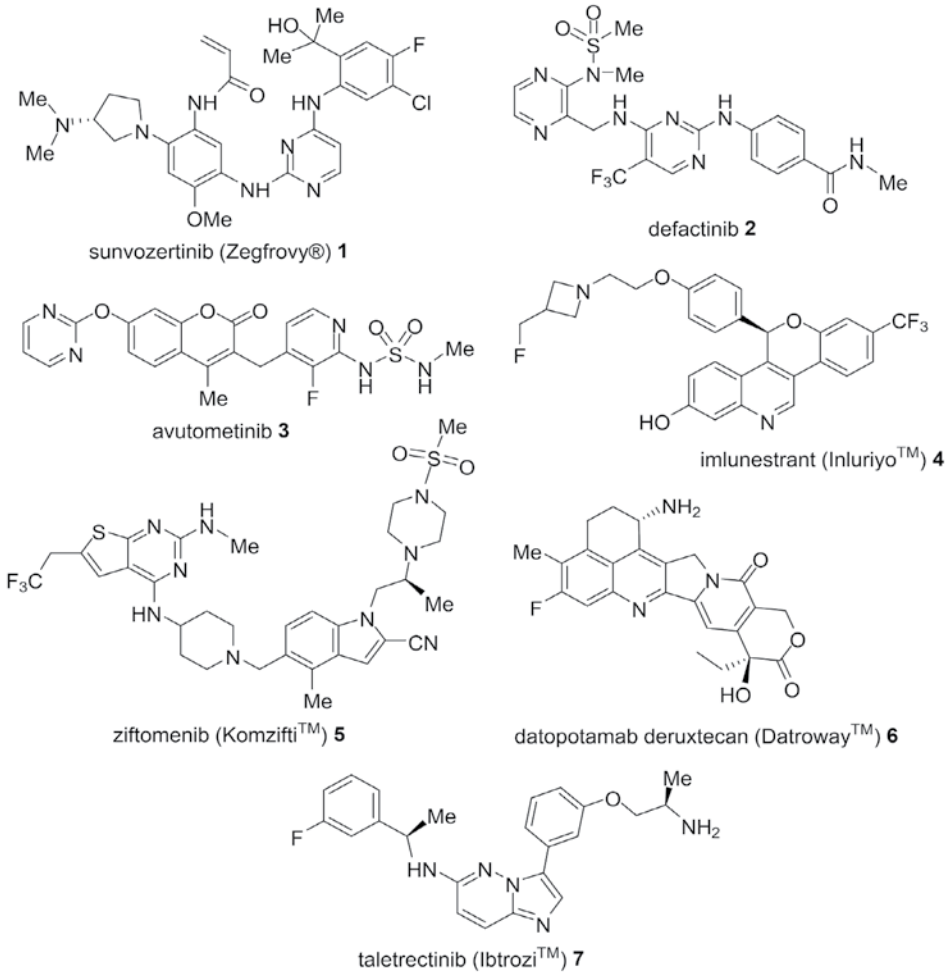
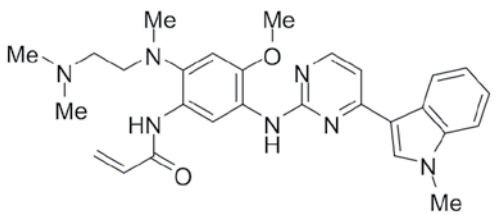


Fig. 1. Fluorine-containing oncologics that have been introduced into the pharmaceutical market in 2025.

EXPERIMENT AND DISCUSSION OF THE RESULTS. Sunvozertinib (Zegfrovy©, DZD9008) **1** is an oral, irreversible, pyrimidine-based epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) developed by Dizal (Jiangsu) Pharmaceutical Co., Ltd. It represents the first approved targeted oral therapy specifically designed to address the therapeutic challenges posed by EGFR exon 20 insertion mutations (exon20ins) in NSCLC [47].

Sunvozertinib **1** was discovered through rational, structure-guided medicinal chemistry optimization starting from the osimertinib **8** (Fig. 2) scaffold. The design focused on overcoming the unique steric hindrance and conformational constraints introduced by exon20ins in the EGFR kinase domain while preserving high potency against a wide spectrum of EGFR exon20ins variants and minimizing off-target activity against wild-type EGFR. Preclinical evaluation demonstrated

potent enzymatic and cellular inhibition of diverse EGFR exon20ins (as well as classical sensitizing mutations and T790M) coupled with robust antitumor efficacy in patient-derived xenograft models and favorable pharmacokinetic properties [48, 49].



osimertinib **8**

Fig. 2. Structure of osimertinib **8**.

Following promising preclinical data, sunvozertinib **1** entered clinical development with a phase 1 dose-escalation and expansion study that established initial safety, pharmacokinetics, and preliminary antitumor activity in heavily pre-treated EGFR exon20ins NSCLC patients, including those with prior monoclonal antibody amivantamab exposure or baseline brain metastases. Pivotal efficacy was subsequently demonstrated in two key phase 2 trials: the single-arm WU-KONG6 study conducted in China and the multinational, open-label, dose-randomized WU-KONG1B global study. These results supported regulatory milestones, including Breakthrough Therapy Designation by both the US FDA and China's National Medical Products Administration (NMPA). Sunvozertinib **1** received accelerated approval in China in August 2023 (the first oral agent targeted for this indication worldwide) and accelerated approval by the US FDA in July 2025 [47].

Sunvozertinib **1** is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC harboring EGFR exon20ins (as detected by a US FDA-approved test) whose disease has progressed during or after platinum-based chemotherapy. It fills a longstanding unmet need in this molecularly defined subgroup (approximately 1–4% of NSCLC) which has historically exhibited intrinsic resistance to earlier-generation EGFR TKIs and limited post-platinum options [48, 49].

The recommended dose is 200 mg orally administered once daily, taken with food and swallowed whole, until disease progression or unacceptable toxicity results. Dose reductions to 150 mg are recommended for selected grade ≥ 3 adverse reactions (e.g., severe gastrointestinal or dermatologic toxicities) with permanent discontinuation indicated for interstitial lung disease/pneumonitis or intolerance to the reduced dose. Administration with food was found to improve tolerability and exposure consistency [50, 51].

In the primary efficacy population of the pivotal WU-KONG1B trial (n = 85 patients treated with the approved 200 mg dose), sunvozertinib **1** achieved a confirmed objective response rate (ORR) of 46% (95% CI: 35–57%; 6% complete response, 40% partial response) by blinded, independent central review per RECIST v1.1 with a median duration of response (DOR) of 11.1 months (95% CI: 8.2–not estimable); 72% of responses lasted ≥ 6 months. Efficacy was consistent across subgroups, including patients with baseline brain metastases and prior amivantamab treatment. Supporting data from the Chinese WU-KONG6 trial (300 mg cohort, n = 97) showed a higher ORR of 61% (95% CI: 50–71%) with responses observed irrespective of exon20ins variant subtype, prior lines of therapy, or immunotherapy exposure. These outcomes establish sunvozertinib **1** as a clinically meaningful advance for a previously difficult-to-treat population [50, 51].

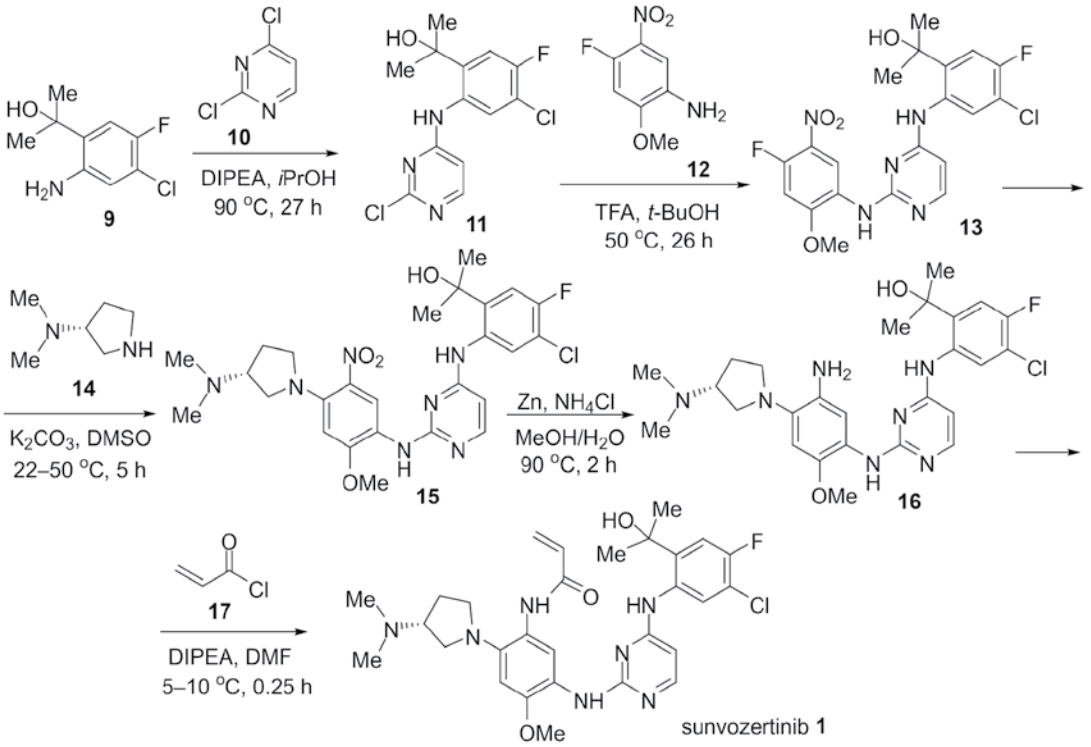
Fluorine and chlorine atoms were introduced to address oxidative metabolic liability identified on the unsubstituted phenyl ring of earlier leads. Thus, dual 4-fluoro- and 5-chloro substitution reduced human hepatocyte clearance from 34 to 7.1 μL/min per 10^6 cells—a > 4-fold improvement–while preserving EGFR mutant activity [48]. The fluorine atom plays a particularly critical role in metabolic stability. By blocking *para*-hydroxylation (a major CYP-mediated oxidative pathway on the aniline ring), the 4-fluoro substituent markedly improves systemic exposure and oral bioavailability without compromising target engagement. In co-crystal modeling (PDB 4LRM overlay), the fluorine atom projects toward the solvent-accessible region and does not form direct polar interactions with the protein; its primary contribution is pharmacokinetic rather than direct binding affinity. The paired 5-chloro substitution further augments steric and electronic modulation, collectively enabling the low clearance required for once-daily oral dosing at the approved 200 mg level. These halogens also subtly tune electron density on the aniline NH group, supporting optimal hinge and back-pocket interactions, but the dominant bioactivity benefit documented in the discovery SAR is the dramatic reduction in metabolic turnover [48, 49].

The synthesis of sunvozertinib **1** from the commercially available and inexpensive starting materials 2-(2-amino-4-chloro-5-fluorophenyl)propan-2-ol (**9**) and 2,4-dichloropyrimidine (**10**) is outlined in Scheme 1 [52,53]. Nucleophilic aromatic substitution between **9** and **10**, conducted in isopropanol at 90 °C for 27 h in the presence of the non-nucleophilic base *N*,*N*-diisopropylethylamine (DIPEA) [54] afforded intermediate **11** in 50% yield. A second SNAr reaction of **11** with 4-fluoro-2-methoxy-5-nitrobenzenamine (**12**) was performed under acidic conditions (trifluoroacetic acid, TFA) in *n*-butanol at 50 °C for 26 h, delivering the core aromatic scaffold **13** in 86% yield. Functional elaboration of intermediate **13** was achieved in three final steps. First, reaction with (*R*)-*N*,*N*-dimethylpyrrolidin-3-amine (**14**) under basic conditions in DMSO at temperatures up to 50 °C for 5 h furnished intermediate **15** in 87% yield. Subsequent reduction of the nitro group in **15** using Zn/NH_4Cl in methanol–H_2O at 90 °C for 2 h provided aniline derivative **16** in 63% yield. The synthesis concluded with acylation of the amine in **16** using acryloyl chloride **17** in the presence of DIPEA in dimethyl formamide (DMF) at 5–10 °C for 30 min affording sunvozertinib **1** in high yield. Overall, this route features operationally simple transformations, mild and easily controlled reaction conditions, and is readily scalable for the preparation of sunvozertinib **1** in process-relevant quantities.

Defactinib **2** (VS-6063) is a selective inhibitor of focal adhesion kinase (FAK), a non-receptor tyrosine kinase involved in cell adhesion, migration, survival, and cancer stem cell maintenance. It was discovered and developed by Verastem Oncology, with additional clinical research support from the National Cancer Institute and several academic cancer centers. Over the past decade, defactinib **2** has advanced through numerous clinical studies, including more than thirty trials evaluating its activity across a range of solid tumors [55].

The therapeutic rationale for defactinib **2** centers on the role of FAK signaling in tumor progression, metastasis, and the survival of cancer stem cell populations. Its principal areas of clinical investigation include low-grade

serous ovarian cancer, pancreatic cancer, and endometrial cancer, often in combination with avutometinib **3**, a RAF/MEK inhibitor. The combination of defactinib **2** and avutometinib **3** has received US FDA Orphan Drug Designation for metastatic pancreatic cancer, reflecting its potential in RAS/MAPK-driven malignancies. Additional exploratory studies have examined its activity in glioblastoma, mesothelioma, and breast cancer [56].



Scheme 1. Synthesis of sunvozertinib **1**.

Defactinib **2** is administered orally. In its most clinically advanced regimen, it is given at a dose of 200 mg twice daily on days 1–21 of a 28-day cycle in combination with avutometinib **3**. In early glioblastoma studies, single preoperative doses of 200–400 mg were used to assess tumor penetration and pharmacodynamic effects.

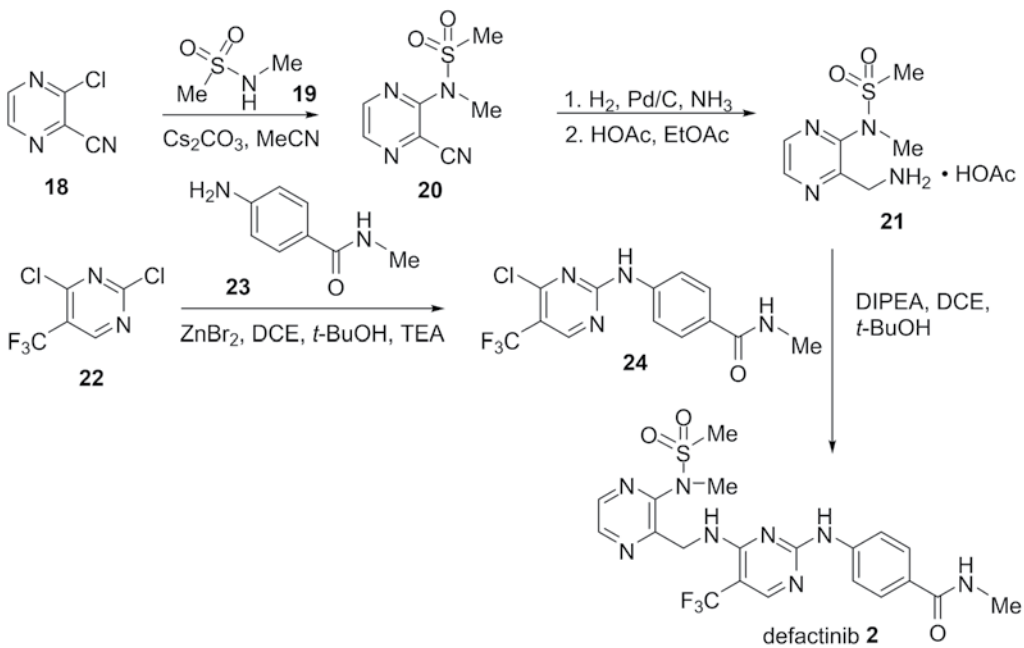
Preclinical studies demonstrate potent inhibition of FAK and Pyk2, suppression of cancer stem cell populations, and significant tumor growth inhibition in xenograft models. Clinical data further support its activity. In RAMP 205, a pancreatic cancer study, the combination of defactinib **2**, avutometinib **3**, and standard chemotherapy produced partial responses in most evaluable patients with substantial reductions in target lesion size and a manageable safety profile. In glioblastoma, defactinib **2** was detectable in tumor tissue within hours of administration and produced a marked reduction in Pyk2 phosphorylation confirming target engagement [57].

In defactinib **2**, the CF_3 group on the pyrimidine ring plays an important role in potency, stability, and overall pharmacological

behavior. The CF_3 substituent is a very strong electron-withdrawing group, and on a heteroaromatic core it modulates the electronics of the hinge-binding region in a way that improves hydrogen-bond geometry, π-stacking, and polarization of nearby heteroatoms. These effects typically strengthen kinase binding, which is consistent with the behavior of fluorinated pyridines and pyrimidines in medicinal chemistry. The CF_3 group also increases metabolic stability. Because it strongly resists oxidative metabolism, it blocks common metabolic soft spots such as aromatic hydroxylation and N-oxidation. This generally leads to improved half-life and better systemic exposure, which is desirable for an orally administered kinase inhibitor [58,59].

Overall, these findings position defactinib **2** as a promising component of combination regimens targeting tumors driven by aberrant FAK and RAS/MAPK signaling, with ongoing development focused on ovarian and pancreatic cancers [55–60].

The synthetic route to defactinib **2** relies on the convergent assembly of two key intermediates, **21** and **24**, as outlined in Scheme 2 [61]. The sequence begins with nucleophilic aromatic substitution between 3-chloropyrazine-2-carbonitrile (**18**) and *N*-methyl methanesulfonamide (**19**) under basic conditions in acetonitrile to afford adduct **20**. Subsequent catalytic hydrogenation of the nitrile group in **20** over Pd/C in the presence of ammonia furnishes cleanly the corresponding primary amine **21**. In a parallel branch, 2,4-dichloro-5-(trifluoromethyl) pyrimidine (**22**) undergoes selective displacement of the chlorine located on C-4 by the amino group of 4-amino-*N*-methylbenzamide (**23**) to generate intermediate **24**. The final step involves coupling amine **21** with pyrimidine **24**



Scheme 2. Synthesis of defactinib **2**.

via another nucleophilic aromatic substitution in 1,2-dichloroethane (DCE)–*t*-BuOH using DIPEA as a non-nucleophilic base to provide defactinib **2**. Overall, this synthetic strategy is operationally simple, employs inexpensive and readily available starting materials, and proceeds under mild, easily controlled reaction conditions, thus rendering it an efficient preparation of defactinib **2** either on a laboratory or an industrial scale.

Avutometinib **3** (also known as VS-6766 or CH5126766) is an orally administered dual RAF/MEK inhibitor distinguished by its unique "RAF/MEK clamp" mechanism which prevents MEK phosphorylation by RAF while simultaneously inhibiting MEK kinase activity. This dual action results in sustained suppression of ERK signaling, a pathway frequently activated in RAS- and RAF-driven malignancies. The compound was originally discovered through collaborative efforts involving Japanese and US research groups and was subsequently advanced clinically by Verastem Oncology. Its development has focused on tumors characterized by MAPK pathway dependence, particularly those harboring KRAS mutations [56].

The therapeutic rationale for avutometinib **3** aligns closely with the strategy described above for defactinib **2**, as the two agents were co-developed and clinically evaluated as a combination regimen. Avutometinib **3** has shown promise in treating low-grade, serous ovarian cancer (LGSOC), a disease in which KRAS mutations and MAPK pathway activation are common and where standard therapies often only yield limited benefits. The combination of avutometinib **3** with defactinib **2** has also received US FDA Orphan Drug Designation for metastatic pancreatic cancer, reflecting its potential in RAS-driven tumors. Additional areas of investigation include endometrial cancer, NSCLC with KRAS mutations, and other solid tumors exhibiting MAPK pathway dysregulation [62–64].

Avutometinib **3** is administered orally. In the combination regimen with defactinib **2**, the clinically established dosing schedule consists of a 3.2 mg dose twice weekly, typically on days 1 and 4 of each 7-day period within a 28-day cycle. This intermittent schedule is designed to optimize pathway suppression while maintaining tolerability, a strategy supported by pharmacodynamic studies demonstrating prolonged ERK inhibition after each dose [65].

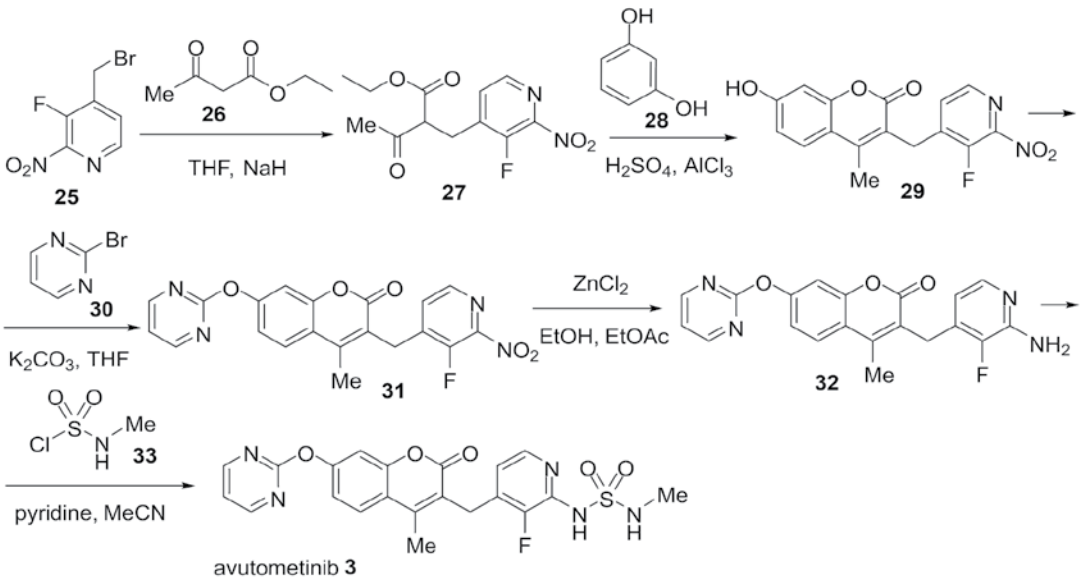
Preclinical studies show that avutometinib **3** produces sustained suppression of MEK and ERK phosphorylation, induces apoptosis in RAS-mutant cancer models, and enhances antitumor activity when combined with FAK inhibition. Clinically, avutometinib **3** has demonstrated meaningful activity in LGSOC, including objective responses and durable disease control in patients previously treated with multiple lines of therapy. In pancreatic cancer, early-phase data from combination studies with defactinib **2** and standard chemotherapy have shown encouraging response rates and reductions in tumor burden, supporting further development [66].

In avutometinib **3**, the CF_3 group plays a structural role that is closely tied to the drug's unusual mechanism as a dual RAF–MEK "clamp" inhibitor. Rather than simply boosting lipophilicity or metabolic stability, the CF_3 group helps enforce a preferred three-dimensional shape of the inhibitor, stabilizing the conformation that allows simultaneous engagement of RAF and MEK. This conformational steering is important because avutometinib **3** does not behave like classical MEK inhibitors–it relies on a cooperative binding mode in

which MEK is held in a catalytically inactive state while remaining associated with RAF. The CF_3 group contributes to this by shifting the electronic distribution of the heterocycle and subtly altering torsional angles that favor the clamp-competent geometry [63, 64].

Another consequence of the CF_3 group is its impact on the drug's kinetic behavior. Avutometinib **3** shows unusually durable suppression of ERK signaling despite intermittent dosing. The CF_3 group influences this by slowing conformational relaxation and dissociation from the RAF–MEK complex, which prolongs target engagement even when plasma levels begin to fall. This kinetic stabilization is a hallmark of many fluorinated kinase inhibitors, but in avutometinib **3** it directly supports the intermittent dosing schedule used clinically [63–66]. Finally, the CF_3 group helps balance the molecule's physicochemical properties so that it can reach intracellular RAF–MEK assemblies without excessive polarity or rapid clearance. In avutometinib **3**, this balance is less about maximizing permeability and more about ensuring that the inhibitor maintains the conformational rigidity and binding kinetics required for its distinctive mechanism. This fundamentally differs from how the CF_3 group in defactinib **2** impacts its attributes [62–66].

The synthesis of avutometinib **3** (Scheme 3), as disclosed in a US Patent [67], begins with the core building block 4-(bromomethyl)-3-fluoro-2-nitropyridine (**25**). Nucleophilic substitution of **25** with ethyl 3-oxobutanoate (**26**) in the presence of NaH in tetrahydrofuran (THF) furnishes the substituted keto-ester **27**. Subsequent condensation of **27** with resorcinol provides the chromenone scaffold **29**. Further elaboration involves coupling **29** with 2-bromopyrimidine **30** under basic conditions to introduce the pyrimidinol ester fragment, affording intermediate **31**. Reduction of the nitro group in **31** then yields the corresponding aniline **32**. Finally, acylation of the newly formed amino group with methylsulfamoyl chloride delivers the target compound, avutometinib **3**. Overall, the sequence is concise, employs inexpensive reagents, and is readily adaptable for scale up.



Scheme 3. Synthesis of avutometinib **3**.

Imlunestrant (Inluriyo®) **4** is an orally administered, next-generation selective estrogen receptor degrader (SERD) approved for the treatment of adults with estrogen receptor (ER)-positive, HER2-negative, ESR1-mutated advanced, or metastatic breast cancer that has progressed following at least one line of endocrine therapy. This patient population typically includes postmenopausal women, although the indication formally applies to adults regardless of sex [68].

Clinically, imlunestrant **4** addresses a major mechanism of endocrine resistance: ESR1 ligand-binding domain mutations which stabilize the receptor in an active conformation and diminish the effectiveness of aromatase inhibitors and earlier SERDs. Unlike fulvestrant–the long-standing standard in this class–imlunestrant **4** is fully oral, exhibits high ER-binding affinity, and induces efficient receptor degradation across a broad spectrum of ESR1 mutations. Its pharmacokinetic profile enables consistent systemic exposure without the limitations of intramuscular administration [69].

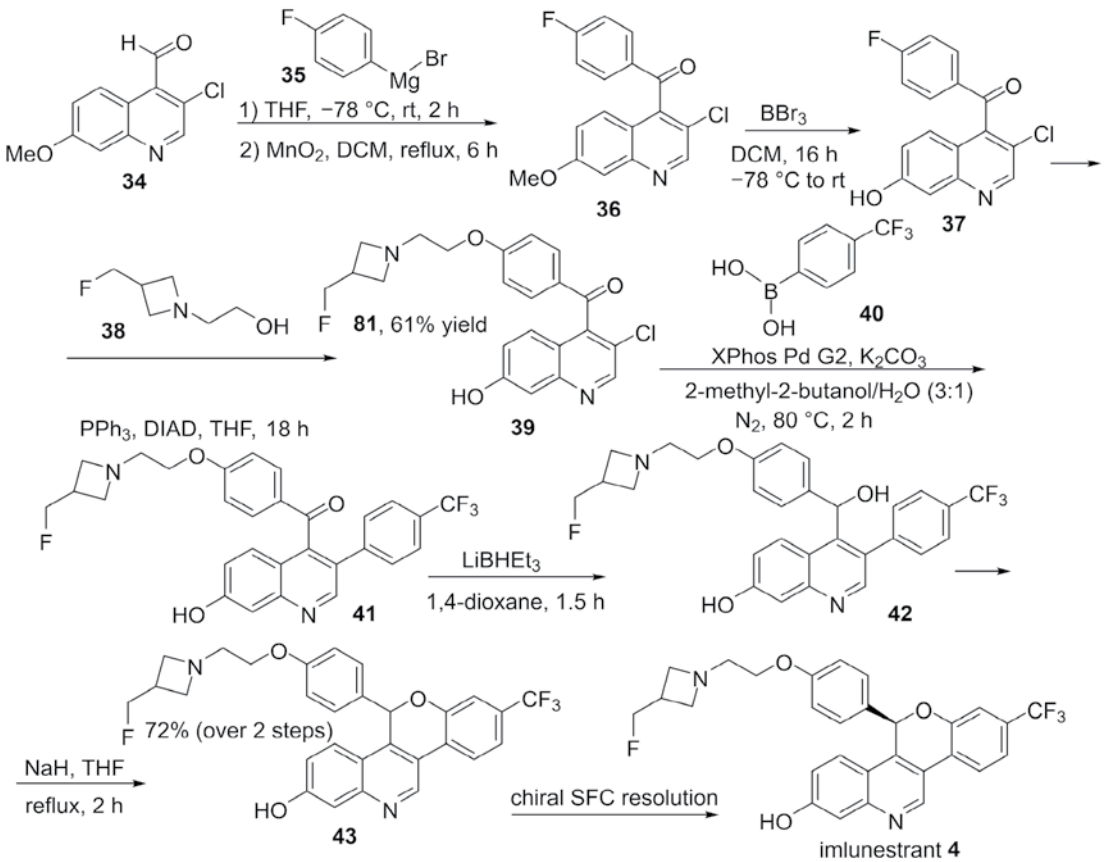
Imlunestrant **4** has been evaluated both as monotherapy and in combination with targeted agents such as CDK4/6 inhibitors, demonstrating its role in modern endocrine-based regimens for advanced breast cancer. The drug represents a significant step forward in the evolution of SERDs offering improved convenience, broader activity against resistance-associated ER variants, and a favorable safety profile suitable for long-term outpatient therapy [70].

Imlunestrant **4** is administered orally once daily, with or without food, using a fixed dosing schedule designed to maintain continuous estrogen receptor suppression suitable for long-term outpatient therapy. The regimen is compatible with combination strategies, including co-administration with CDK4/6 inhibitors reflecting its integration into modern endocrine-based treatment paradigms for advanced breast cancer [71].

Fluorine plays a strategically important role in the biological performance of imlunestrant **4**. The drug contains multiple fluorine substituents positioned to optimize both ER binding and pharmacokinetic behavior, features that distinguish it from earlier SERDs such as fulvestrant. From a structural perspective, fluorine's strong inductive effect and its ability to modulate local conformational preferences help stabilize the ligand in a bioactive geometry that favors high-affinity engagement with the ER ligand-binding domain, including clinically relevant ESR1 mutations. These mutations often shift the receptor toward a constitutively active conformation, but the fluorinated scaffold of imlunestrant **4** maintains potent antagonism and efficient receptor degradation across these variants. Fluorination also contributes significantly to the drug's metabolic stability. By blocking oxidative metabolism at key positions, the fluorine atoms prolong systemic exposure and support the once-a-day oral regimen, a major advantage over fulvestrant's intramuscular administration. Additionally, fluorine fine tunes lipophilicity and membrane permeability improving oral absorption and ensuring adequate intracellular concentrations for sustained ER degradation [68–71].

The practical synthesis of imlunestrant **4** (Scheme 4) was recently disclosed in a patent application [72]. The sequence begins with the addition of Grignard reagent **35** to the carbonyl group of 3-chloro-7-methoxyquinoline-4-carbaldehyde (**34**) followed by MnO_2 oxidation affording (3-chloro-7-methoxyquinolin-4-yl)(4-fluorophenyl)methanone (**36**) in

68% yield. Treatment of **36** with BBr_3 in DCM at low temperature effected demethylation of the aromatic methoxy group to give the corresponding phenol **37**. Nucleophilic substitution of **37** with 2-(3-(fluoromethyl)azetidine-1-yl)ethanol (**38**) furnished ether **39**, isolated in 61% yield. Suzuki–Miyaura coupling of **39** with 4-(trifluoromethyl)phenylboronic acid (**40**) introduced the second and final fluorinated aromatic fragment to yield biaryl intermediate **41**. Subsequent reduction of **41** with $LiBHEt_3$ produced alcohol **42** which cyclized with NaH treatment in refluxing THF to generate the target **43**. Racemic imlunestrant **43** was resolved into its enantiomers by supercritical fluid chromatography (SFC). In this context, it is worth noting the recently recognized convergence between achiral simulated moving bed chromatography and the self-disproportionation of enantiomers (SDE) phenomenon [73–75] which potentially offers significant advantages for large-scale chiral separations.



Scheme 4. Synthesis of imlunestrant **4**.

Ziftomenib (Komzifti©) **5**, is a first-in-class, orally bioavailable inhibitor of the menin–KMT2A (MLL) protein–protein interaction, a central epigenetic driver in leukemias characterized by KMT2A rearrangements (KMT2A-r) or NPM1 mutations. These AML subtypes

rely on menin-dependent transcriptional programs that maintain leukemic stemness and block differentiation. By selectively disrupting the menin–KMT2A complex, ziftomenib **5** suppresses HOX/MEIS oncogenic signaling, thereby promoting differentiation and apoptosis of leukemic blasts [76].

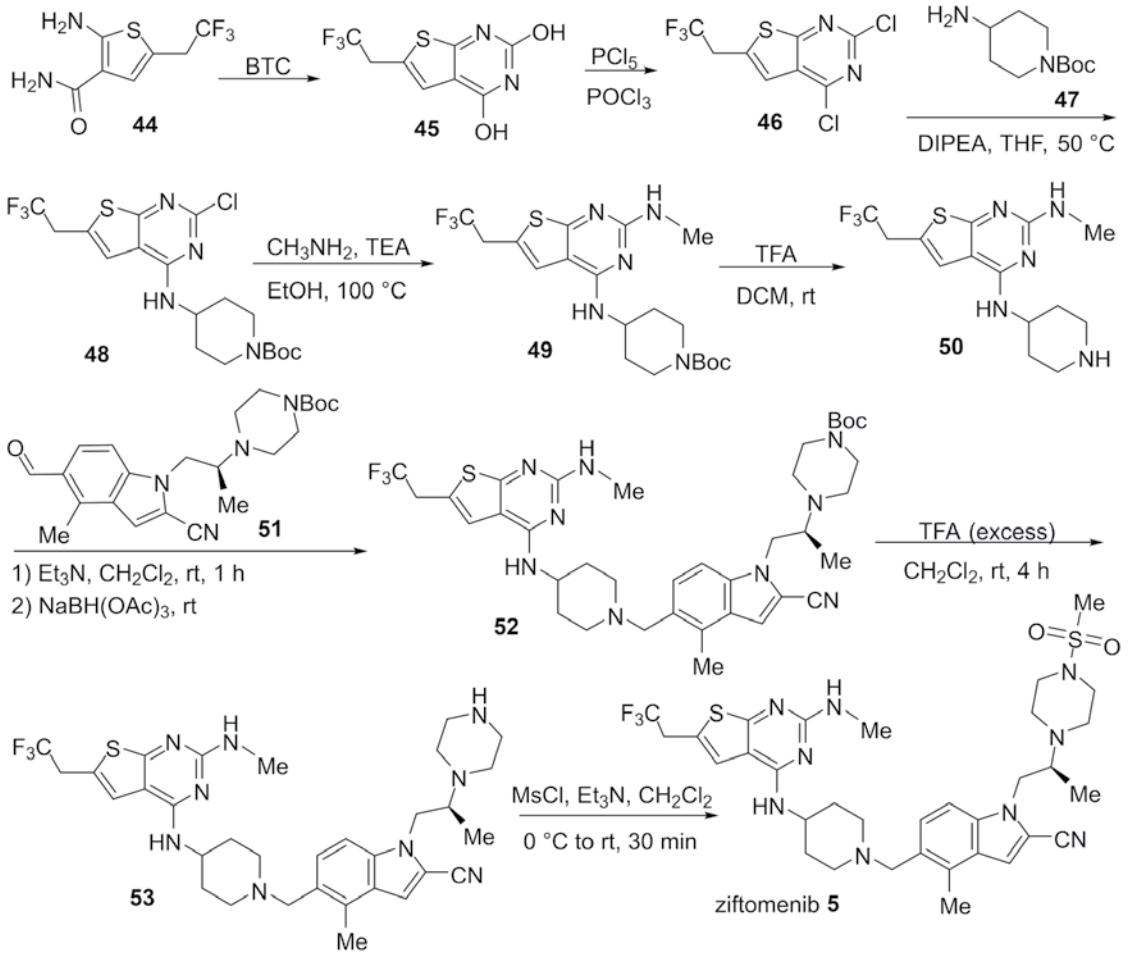
The compound was discovered and developed by Kura Oncology, a company specializing in precision oncology and epigenetic therapeutics. Following promising clinical activity in heavily pre-treated patients, ziftomenib (Komzifti©) received US FDA approval in November 2025 for the treatment of relapsed or refractory acute myeloid leukemia (AML) with susceptible NPM1 mutations, addressing a population with historically poor prognosis and limited therapeutic options. Clinical responses include durable complete remissions and measurable residual disease (MRD) negativity. Combination regimens with venetoclax or hypomethylating agents are currently under evaluation and may broaden its therapeutic utility [77].

From a medicinal chemistry standpoint, ziftomenib **5** incorporates a strategically positioned fluorinated aromatic unit which contributes to its high-binding affinity, optimized physicochemical properties, and favorable pharmacokinetic profile—hallmarks of modern fluorine-enabled drug design. The molecule demonstrates a refined selectivity profile avoiding off-target interactions that limited earlier generations of menin inhibitors [78].

Overall, ziftomenib **5** represents a significant advance in targeted epigenetic therapy offering a precision-guided treatment option for genetically defined AML subsets and exemplifying the sophisticated use of fluorine in contemporary anticancer drug development [76–79].

The synthesis of ziftomenib **5** (Scheme 5) has been disclosed in two US patents [80, 81] and begins with the activation of 2-amino-5-(2,2,2-trifluoroethyl)thiophene-3-carboxamide (**44**) using bis(trichloromethyl) carbonate (BTC) to afford bicyclic intermediate **45**. Subsequent treatment of 6-(2,2,2-trifluoroethyl)thieno[2,3-*d*]pyrimidine-2,4-diol (**45**) with PCl_5 exchanges the aromatic hydroxy group for a chloro substituent to yield compound **46**. Nucleophilic substitution of this chlorine atom with *t*-butyl 4-aminopiperidine-1-carboxylate (**47**) furnishes intermediate **48** and displacement of the second chlorine with methylamine in refluxing ethanol provides compound **49**. Boc-deprotection with TFA then yields the corresponding diamine **50**. The resulting fragment undergoes reductive amination with the (*S*)-indole derivative **51** in the presence of triethylamine and $NaBH(OAc)_3$ to give the protected indole–piperazine conjugate **52**. Subsequent Boc removal with excess TFA affords the free indole–piperazine amine **53**. Finally, mesylation with methanesulfonyl chloride and triethylamine furnishes ziftomenib **5**.

Datopotamab deruxtecan **6**, is a next-generation TROP2-targeted ADC designed to deliver a highly potent topoisomerase I inhibitor (DXd) selectively to tumor cells. The agent consists of a humanized IgG1 monoclonal antibody against TROP2 conjugated via a cleavable tetrapeptide linker to the exatecan-derived DXd payload. Upon binding to TROP2 on the tumor cell surface, the ADC is internalized and trafficked to lysosomes where enzymatic cleavage releases DXd inducing DNA double-strand breaks and apoptosis in TROP2-expressing cancer cells [82].



Scheme 5. Synthesis of ziftomenib **5**.

Clinically, datopotamab deruxtecan **6** has demonstrated significant antitumor activity in hormone receptor-positive, HER2-negative metastatic breast cancer, and in EGFR-mutated NSCLC previously treated with targeted therapy and platinum chemotherapy. The drug received US FDA approval in January 2025 for unresectable or metastatic HR+/HER2– breast cancer with expanded approval in June 2025 for EGFR-mutated NSCLC. It was also approved in the EU (April 2025) and Japan (December 2024) for similar indications [83].

Pharmacologically, datopotamab deruxtecan **6** employs an optimized drug-to-antibody ratio of 4 balancing payload potency with systemic tolerability. The DXd payload is more potent than SN-38, the payload used in sacituzumab govitecan, and the linker is engineered for high plasma stability with tumor-selective cleavage. The agent is administered intravenously at 6 mg/kg every 3 weeks until progression or unacceptable toxicity occurs [84].

The safety profile is consistent with the DXd-ADC class, with notable risks including

interstitial lung disease/pneumonitis, ocular toxicities (e.g., dry eye, keratitis), stomatitis, nausea, fatigue, and myelosuppression. Careful monitoring for respiratory and ocular symptoms is required and dose modifications are recommended based on severity [85].

Although datopotamab deruxtecan **6** is structurally defined by its ADC architecture, the critical fluorine element resides within the DXd payload, an exatecan-derived topoisomerase I inhibitor. Fluorination plays a central role in shaping the pharmacological performance of the payload and, consequently, the therapeutic index of the entire ADC [86].

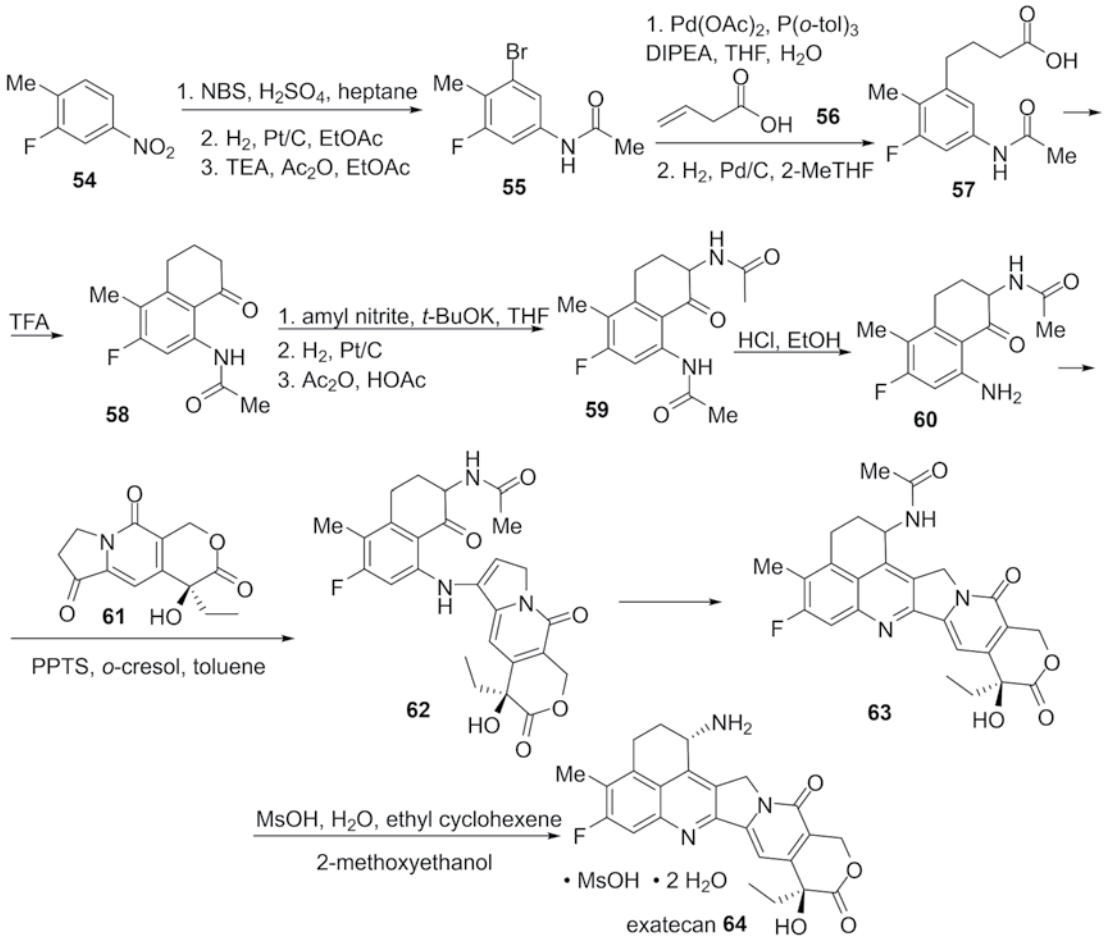
From a chemical perspective, fluorine enhances the metabolic stability of the DXd scaffold, reducing susceptibility to oxidative degradation, and prolonging the intracellular persistence of the active species following lysosomal release. This increased stability contributes directly to the high cytotoxic potency characteristic of DXd-based ADCs. Fluorination also modulates the lipophilicity and membrane permeability of the payload enabling efficient intracellular diffusion while maintaining a controlled bystander effect–an essential balance for ADCs targeting heterogeneously expressed antigens such as TROP2 [82, 85].

Electronically, the presence of fluorine fine tunes the pharmacophore, improving binding affinity to topoisomerase I and stabilizing the ternary drug–enzyme–DNA cleavage complex. These effects underpin the superior potency of DXd relative to earlier camptothecin analogs such as SN-38. In addition, the fluorinated structure contributes to the chemical robustness of the payload–linker system supporting high plasma stability and minimizing premature drug release. Collectively, these fluorine-driven properties enable datopotamab deruxtecan **6** to achieve potent, selective, and clinically meaningful antitumor activity while preserving an acceptable safety profile [83–86]. Overall, datopotamab deruxtecan **6** represents an important advancement in TROP2-directed therapy offering a potent and clinically validated option for patients with heavily pre-treated breast cancer and EGFR-mutated NSCLC.

The fluorine-containing component of datopotamab deruxtecan **6** is exatecan **64** (Scheme 6) [87, 88]. Its synthesis begins from 2-fluoro-1-methyl-4-nitrobenzene **54** which undergoes bromination with *N*-bromosuccinimide in sulfuric acid–heptane followed by platinum-catalyzed hydrogenation of the nitro group in EtOAc to afford the corresponding aniline. Acetylation with acetic anhydride and triethylamine furnishes the brominated anilide **55**. This aryl bromide then participates in a palladium-catalyzed C–C coupling with but-3-enoic acid (**56**) in the presence of DIPEA yielding an alkene intermediate that is subsequently hydrogenated in 2-Me-THF to provide the saturated acid **57**.

Activation of the carboxylic acid with TFA promotes an intramolecular Friedel–Crafts acylation producing the tetrahydronaphthalenone **58**. Nitration at the α position of the ketone is achieved using amyl nitrite and potassium *t*-butoxide in THF; catalytic hydrogenation of the resulting nitro group then provides the corresponding primary amine followed by acetylation with Ac_2O in acetic acid to afford compound **59**. Selective deacetylation of the anilide—leaving the aliphatic amide intact–is accomplished by heating with hydrochloric acid in ethanol yielding amine **60**. Condensation of **60** with ketone **61** in *o*-cresol–toluene with catalytic amounts of pyridinium *p*-toluenesulfonate (PPTS) forms enamine **62** which

undergoes dehydrative cyclization to quinoline **63**. Treatment with aqueous methanesulfonic acid in ethyl cyclohexene–2-methoxyethanol affords the mesylate salt of exatecan dihydrate **64**, along with the *epi*-exatecan diastereomer. The latter is recycled through an amine protection–deprotection–crystallization sequence to complete the synthesis [87, 88].



Scheme 6. Synthesis of exatecan **64**, the fluorine-containing component of datopotamab deruxtecan **6**.

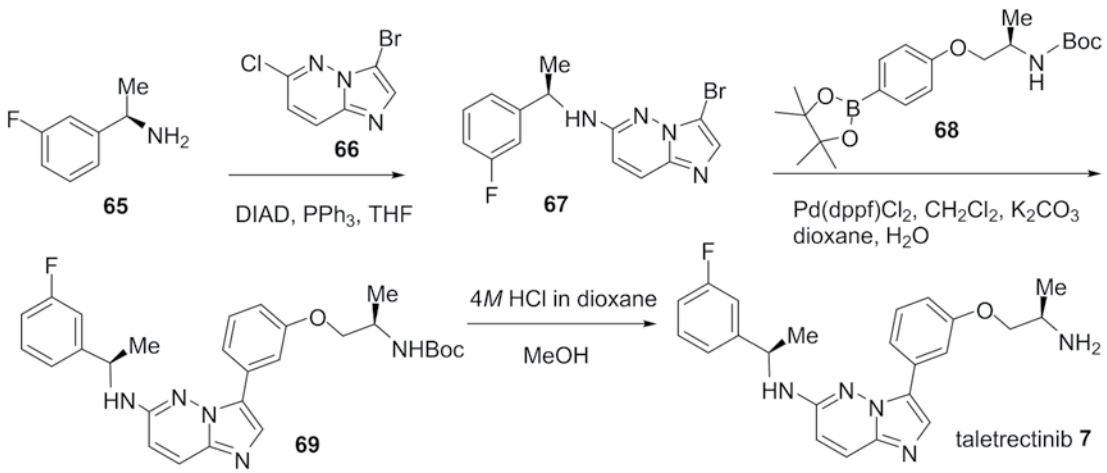
Taletrectinib (Ibtrozi©) **7** is an orally administered, next-generation selective inhibitor of ROS1 and NTRK fusion kinases approved for adults with ROS1-positive metastatic NSCLC, including patients previously treated with first-generation ROS1 inhibitors such as crizotinib. The drug was designed to overcome the two major limitations of earlier ROS1-targeted therapies: poor CNS penetration and vulnerability to resistance-conferring kinase-domain mutations, particularly the solvent-front mutation G2032R which is a common mechanism of acquired resistance to crizotinib and entrectinib. Taletrectinib **7** exhibits high potency

across a broad spectrum of ROS1 alterations, including clinically relevant resistance mutations, and demonstrates robust intracranial activity, an essential feature given the high incidence of brain metastases in ROS1-rearranged NSCLC [89–91].

Compared with existing ROS1 inhibitors, taletrectinib **7** offers a more mutation-agnostic profile, improved CNS exposure, and a favorable tolerability pattern with reduced off-target TRK-related adverse effects. Its activity in both TKI-naïve and TKI-experienced patients positions represents a meaningful advancement in the management of ROS1-driven lung cancer, particularly for individuals whose disease has progressed on from earlier generation agents. The approved indication applies to adults of all ages, though the typical patient population skews toward younger non-smokers, reflecting the epidemiology of ROS1-rearranged NSCLC [92, 93].

Taletrectinib **7** is administered orally once daily using a fixed dosing regimen suitable for long-term outpatient therapy. The drug's fluorine-containing structural elements contribute to its kinase-binding affinity, metabolic stability, and CNS penetration–properties central to its clinical performance. Overall, taletrectinib **7** represents a significant step forward in precision oncology for ROS1-positive lung cancer offering durable systemic and intracranial responses in a population with limited targeted options after resistance emerges [93].

The synthesis of taletrectinib (7) (Scheme 7) is described in patent literature [94, 95] and follows a convergent route centered on late-stage Suzuki–Miyaura cross-coupling. The sequence begins with a Mitsunobu reaction between the chiral amine **65** and derivative **66**. This reaction is typically performed using triphenylphosphine (PPh_3) and diisopropyl azodicarboxylate (DIAD) in anhydrous tetrahydrofuran (THF) at 0 °C to room temperature for 12–24 hours. The Mitsunobu coupling proceeds with clean stereochemical inversion, furnishing the corresponding adduct **67** in good yield (typically 70–85% after purification by column chromatography or recrystallization). This intermediate **67** then undergoes Suzuki–Miyaura cross-coupling with boronic acid **68**. The reaction is commonly carried out using a palladium catalyst such as $Pd(OAc)_2$ or $PdCl_2(dppf)\cdot CH_2Cl_2$ (2–5 mol%), in the presence of a base like K_3PO_4 or potassium carbonate, in a mixed solvent system such as DMAc/water or dioxane/water at 80–100 °C for 4–12 hours under inert atmosphere. These conditions afford the Boc-protected biaryl amine **69** in high yield (80–94% after aqueous workup and crystallization). Finally, Boc deprotection of intermediate **69** is achieved under acidic conditions, most commonly using 4 M HCl in 1,4-dioxane or HCl in dichloromethane/methanol at room temperature to 75 °C for 2–6 hours. This step delivers taletrectinib (**7**) as the free base in excellent yield (typically 85–95%). The free base can be further converted to the pharmaceutically preferred adipate salt by treatment with adipic acid in a suitable solvent (e.g., ethanol or isopropanol) followed by crystallization, often providing the final API in >90% yield and high purity. This synthetic route is relatively concise (3–4 linear steps from key building blocks), scalable, and features robust palladium-catalyzed coupling as the key bond-forming step. Purification at each stage is typically achieved through crystallization rather than extensive chromatography in optimized process versions, supporting its use in clinical and commercial manufacture.



Scheme 7. Synthesis of taletrectinib **7**.

CONCLUSIONS. This review highlights seven fluorine-containing oncology therapeutics that received US FDA approval in 2025. Sunvozertinib (Zegfrovy©) **1** was approved for adults with locally advanced or metastatic NSCLC. The co-approved oral regimen of defactinib **2** and avutometinib (Avmapki©) **3** is indicated for adults with KRAS-mutated recurrent low-grade serous ovarian cancer following prior systemic therapy. Imlunestrant (Inluriyo©) **4** received approval for the treatment of estrogen receptor-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer that has progressed after at least one line of endocrine therapy. Ziftomenib (Komzifti©) **5** was approved for adults with relapsed or refractory acute myeloid leukemia harboring susceptible NPM1 mutations. Datopotamab deruxtecan (Datroway©) **6**, a TROP2-directed ADC, was authorized for unresectable or metastatic hormone receptor-positive, HER2-negative breast cancer after endocrine therapy and chemotherapy, as well as for certain adults with previously treated advanced NSCLC. Finally, taletrectinib (Ibtrozi©) **7** was approved for adults with locally advanced or metastatic ROS1-positive NSCLC, including both TKI-naïve and TKI-experienced patients.

As discussed, fluorine plays a central role in shaping the pharmacological performance of all seven agents profiled in this review. Strategic fluorination is used throughout these molecules to fine tune electronic properties, enhance target binding, and improve physicochemical behavior essential for clinical success. Incorporation of fluorine often increases metabolic stability by blocking oxidative hotspots, thereby prolonging systemic exposure and enabling once-daily oral dosing for several of these therapies. Fluorine substitution also modulates lipophilicity and membrane permeability, contributing to improved tissue distribution and, in some cases, enhanced CNS penetration, as exemplified by taletrectinib **7**. In kinase inhibitors such as sunvozertinib **1**, avutometinib **3**, and imlunestrant **4**, fluorinated motifs help optimize potency, selectivity, and conformational control within ATP-binding pockets. For complex modalities like the ADC datopotamab deruxtecan **6**, fluorine contributes to

the stability and performance of both the payload and linker system. Across these diverse therapeutic classes, fluorine consistently serves as a powerful design element that enables medicinal chemists to balance potency, safety, and pharmacokinetics—ultimately supporting the successful translation of these compounds into effective anticancer medicines.

A further unifying feature of these agents is their chirality: five of the seven drugs are chiral and are administered exclusively enantiopure. In accordance with US FDA expectations for chiral pharmaceuticals [96–98], the continued development of robust asymmetric synthetic methods and advanced analytical tools for fluorine-containing chiral molecules remains essential. Particular attention should be given to the SDE phenomenon which can occur under various physicochemical conditions for enantioenriched samples [99–102]. SDE is especially relevant for chiral drugs incorporating fluorinated motifs [103–105] and/or amino acid-derived fragments [106–108] as these structural elements can amplify the propensity for enantiomeric redistribution. Because such behavior poses a tangible public safety concern, rigorous assessment of enantiomeric purity is required throughout the entire drug lifecycle [109–112]. Continuous monitoring of stereochemical integrity during synthesis [113,114], manufacturing, and even long-term storage is critical, particularly since sublimation-driven SDE has been documented as a specific challenge for fluorine-containing pharmaceuticals [115–118].

Growing public concern about the potential health risks associated with certain fluorine-containing substances, particularly persistent per- and polyfluoroalkyl substances (PFAS), warrants careful consideration [119–122]. While most organofluorine pharmaceuticals exhibit minimal defluorination and do not significantly contribute to inorganic fluoride burden [123], patients on long-term fluorinated medications may wish to discuss total fluoride exposure with their physicians when appropriate, including from sources such as fluoridated water and foods produced with fluorinated agrochemicals [124]. The broader environmental and health impacts of persistent perfluorinated "forever chemicals" (PFAS) [125], alongside other modern pollutants such as bioavailable plastics [126], underscore the need for continued vigilance and responsible management of fluorinated substances across industrial, agricultural, and pharmaceutical applications.

Despite these issues, the essential role of pharmaceuticals in modern medicine remains unquestionable. These agents provide life-saving interventions, enhance quality of life across countless conditions, and continue to drive therapeutic innovation. Their development not only addresses urgent medical needs but also lays the groundwork for future advances in healthcare.

AUTHORS' CONTRIBUTION. All authors have read the research results and approved the final version of the manuscript.

CONFLICT OF INTEREST. The authors declare no conflict of interest.

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ХІМІЯ ФТОРОРГАНІЧНИХ СПОЛУК В ОНКОЛОГІЇ: ОГЛЯД ПРОТИПУХЛИННИХ ПРЕПАРАТІВ, СХВАЛЕНИХ FDA США У 2025 РОЦІ (ОГЛЯД)

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У 2025 році Управління з продовольства та медикаментів США (FDA) схвалило сім протиракових препаратів, які містять фтор, що відображає продовження впливу стратегій фторування в сучасному дизайні онкологічних лікарських засобів. Ці новосхвалені терапії охоплюють широкий спектр злоякісних новоутворень і механізмів дії. Сунвозертиніб (Zegfrovy©) було схвалено для лікування місцево-поширеного або метастатичного недрібноклітинного раку легень (НДКРЛ). Комбінація дефактінібу та авуметинібу (Avmapki©) пропонує таргетну опцію для KRAS-мутованого рецидивного низькосортного серозного раку яєчників. Імлунестрант (Inluriyo©) є препаратом наступного покоління ендокринної терапії для естроген-рецептор-позитивного, HER2-негативного, ESR1-мутованого поширеного раку молочної залози. Зіфтоменіб (Komzifti©) представляє прецизійну терапію для рецидивного або рефрактерного гострого мієлоїдного лейкозу з чутливими мутаціями NPM1. Датопотамаб деруктекан (Datroway©) – це спрямований на TROP2 антитіло-лікарський кон'югат, який розширює можливості лікування гормон-рецептор-позитивного, HER2-негативного метастатичного раку молочної залози та окремих груп пацієнтів із раніше лікованим НДКРЛ. Талетректиніб (Ibtrozi©) – інгібітор ROS1 наступного покоління – було схвалено для лікування ROS1-позитивного НДКРЛ як у TKI-наївних, так і в TKI-досвідчених пацієнтів. У сукупності ці агенти демонструють універсальність фтору в підвищенні потужності, селективності та фармакокінетичних властивостей у різних терапевтичних модальностях.

Для кожної розглянутої сполуки ми надаємо комплексне обговорення її відкриття, біологічного механізму дії, терапевтичного застосування, клінічного введення, ролі фторування в оптимізації її властивостей, а також детальний опис хімічного синтезу.

Ключові слова: фтор, дизайн лікарських засобів, онкологія, синтез, хіральність, фармакологія, терапевтика.

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