Small-Molecule Anti-Cancer Drugs From 2016 to 2020: Synthesis and Clinical Application

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Abstract
Malignant tumors have become a significant public health problem that severely threatens human health. Drug-targeting therapy is essential for tumor therapy, along with surgery and radiotherapy. Of the 378 novel drugs approved over the past five years, those for oncological therapy remains at the top (25%). These drugs are used to treat patients with various cancers by acting on corresponding targets, such as EGFR, JAK, BTK, IDH, and FLT3. This review examines anti-tumor agents approved between 2016 and 2020, classifying them according to indication (such as lung cancer, leukemia, breast cancer, and myeloma). These drugs are reviewed according to their route of administration, first-in-class designation, approval dates, and expedited review categories. Furthermore, this paper summarizes the targets and modes of action of the approved anti-tumor drugs while systematically discussing their synthetic routes for medicinal chemistry or industrial use, which will benefit next-generation drug discovery.

Keywords
Approved drugs, anti-cancer, synthetic routes, bioactivity, clinical application

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1. Introduction
From 2016 to 2020, 228 drugs, including 168 chemical entities, were developed by pharmaceutical companies and approved to treat various diseases.¹ These drugs include anti-infective drugs, central nervous system drugs, cardiomypathic drugs, metabolic drugs, dermatologic drugs, gastrointestinal drugs, and oncological drugs. A record number of drugs were approved in 2018 (59), while the fewest approvals occurred in 2016 (22). However, of the different therapeutic categories, anti-cancer drugs have consistently ranked first. The past five years have witnessed the approval of 61 drugs or drug combinations, including 42 small-molecule drugs for treating various types of cancers (Figure 1).

These drugs are classified according to the type of cancer, such as leukemia, breast cancer, lung cancer, prostate cancer, melanoma, gastrointestinal stromal tumors (GIST), lymphoma, myeloma, and others (Figure 2). As shown, the dominant therapeutic areas are represented by anti-leukemia, anti-breast cancer, and anti-lung cancer medications, where 18 related new drugs have been approved for the market. Anti-prostate cancer drugs received three approvals. Moreover, two anti-melanoma drugs, two anti-GIST drugs, three anti-lymphoma agents, two anti-myeloma drugs, and two anti-ovarian cancer drugs were also approved for the market. In addition, ten other anti-tumor agents were also released into the market for the targeted treatment of cancer. The information pertaining to the drugs approved between 2016 and 2020, including drug name, the research and development company, active ingredients, approval dates, and clinical applications, is summarized in Table 1.

Furthermore, to provide insight into next-generation drug discovery, the medicinal chemistry synthetic routes and large-scale synthetic methods of 42 approved anti-cancer small-molecule drugs are discussed in this review. Chemical structure analysis and synthetic route discussion are beneficial for the contemporary medicinal chemistry strategies of next-generation drug discovery.

2. Anti-leukemia Drugs

2.1. Gilteritinib (I)
Gilteritinib (I), a dual FMS-like tyrosine kinase 3 (FLT3)/AXL inhibitor, was co-developed by Astellas and Kotohuki

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Pharmaceuticals. It was approved in November 2018 to treat adult patients with acute myeloid leukemia (AML) displaying a mutation in the FLT3 gene, relapsed AML, or who have shown no improvement after previous treatment.2

The synthesis of giltertinib (I), as described in a Chinese patent, is depicted in Scheme 1. The starting material, 3-bromo-5-chloro-6-ethyl-pyrazine-2-carbonitrile (I), was reacted with aminopyran (2) to yield intermediate 3 in 87% yield. Then, intermediate 3 was treated with compound 4 in the presence of a Pd catalyst and K2CO3 to yield compound 5 at 80%. Finally, the cyanic group of compound 5 underwent hydrolysis to produce giltertinib (I) in 85% yield.3

2.2. Glasdegib (II)

Owning to its critical role in various cancers, the Hedgehog signaling pathway has attracted significant attention as a potential avenue for developing new oncological therapies.4,5 Therefore, Pfizer has developed glasdegib (II), the first Hedgehog pathway inhibitor, to treat adult patients with newly-diagnosed AML, who are at least 75 years old and precluded from the use of standard chemotherapy.6 It has been demonstrated that glasdegib (II) binds to the transmembrane protein, Smoothened (SMO), to inhibit the Hedgehog pathway. Recent evidence suggests that several other drugs targeting this pathway have been

![Figure 1. Bar graph illustration of the number of approved drugs from 2016 to 2020.](image1)

![Figure 2. Approved anti-cancer drugs (small-molecule) from 2016 to 2020.](image2)
| No. | Drug name | Active ingredients | Company | Target | Approval date | Clinical applications |
|-----|-----------|-------------------|---------|--------|---------------|-----------------------|
| I   | Xospata   | Gilteritinib      | Astellas Pharma | IDT, TKD, FLT3, AXL, and ALK Tyrosine kinase inhibitor | 11/28/2018 | To treat patients who have relapsed or with refractory AML |
| II  | Daurismo  | Glasdegib         | Pfizer   | Hedgehog pathway Inhibitor Smoothened (Smo) receptor inhibitor | 11/21/2018 | To treat newly-diagnosed acute AML in adult patients |
| III | Tibsovo   | Ivosidenib        | Agios Pharmaceuticals | IDH-1 | 7/20/2018 | To treat patients with relapsed or refractory AML |
| IV  | Idhifa    | Enasidenib        | Celgene  | IDH2 enzyme | 8/1/2017 | To treat relapsed or refractory AML |
| V   | Rydapt    | Midostaurin       | Novartis | FLT3 | 4/28/2017 | To treat AML and advanced systemic mastocytosis |
| VI  | Venexela  | Venetoclax        | AbbVie Inc. and Genentech USA, Inc. | BCL-2 | 4/11/2016 | To treat chronic lymphocytic leukemia in patients with specific chromosomal abnormalities |
| VII | Tukysa    | Tucatinib         | Seattle Genetics | HER2 | 4/17/2020 | To treat advanced unresectable or metastatic HER2-positive breast cancer |
| VIII| Piqray    | Alpelisib         | Novartis | PI3K | 5/24/2019 | To treat breast cancer |
| IX  | Talzenna  | Talazoparib       | Pfizer   | PARP-1 and two enzymes | 10/16/2018 | To treat locally advanced or metastatic breast cancer patients with a germline BRCA mutation |
| X   | Verzenio  | Abemaciclib       | Eli Lilly and Company | CDK4 and CDK6 | 9/28/2017 | To treat certain advanced or metastatic breast cancers |
| XI  | Nerlynx   | Neratinib maleate | Puma Biotechnology, Inc. | HER2 | 7/17/2017 | To reduce the recurrence risk of breast cancer |
| XII | Kisqali   | Ribociclib        | Novartis | CDK4 and CDK6 | 3/13/2017 | To treat postmenopausal women with a type of advanced breast cancer |
| XIII| Tabrecta  | Capmatinib        | Novartis | e-Met/HGFR Alkylating drug | 5/6/2020 | To treat patients with NSCLC |
| XIV | Zepzelca  | Larbinectedin     | PharmaMar | ALK and ROS1 inhibitor | 6/15/2020 | To treat metastatic small-cell lung cancer |
| XV  | Gavreto   | Pralsetinib       | Blueprint Medicines | RET | 9/4/2020 | To treat NSCLC |
| XVI | Lorbrena  | Lorlatinib        | Pfizer   | ALK, EGFR, ROS1, and IGF-1 | 11/2/2018 | To treat patients with ALK-positive metastatic NSCLC |
| XVII| Vizimpro  | Dacomitinib       | Pfizer   | EGFR | 9/27/2018 | To treat metastatic NSCLC |
| XVIII| Alunbrig | Brigatinib        | Ariad Pharmaceuticals, Inc. | ALK, EGFR, ROS1, and IGF-1 | 4/28/2017 | To treat patients with progressed ALK-positive metastatic NSCLC or who are intolerant to crizotinib |
| XV  | Orgovyx   | Relugolix         | Myovant Sciences Bayer | GnRHR Nonsteroidal androgen receptor | 12/18/2020 | To treat advanced prostate cancer |
| XX  | Nubeqa    | Darolutamide      | Bayer    | Nonsteroidal androgen receptor | 7/30/2019 | To treat adult patients with non-metastatic castration-resistant prostate cancer |
| XXI | Erleada   | Apalutamide       | Johnson & Johnson | Androgen receptor (AR) | 2/14/2018 | To treat certain types of prostate cancer, using novel clinical trial endpoints |
| XXII| Braftovi  | Encorafenib       | Array Biopharma | Kinase (BRAF gene) | 6/27/2018 | To treat unresectable or metastatic melanoma |
| XXIII| Mektovi  | Binimetinib       | Array Biopharma | MAPK 1/2 | 6/27/2018 | To treat unresectable or metastatic melanoma |
| XXIV| Ayvakit   | Avapritinib       | Blueprint Medicines Corporation | PDGFRA | 1/9/2020 | To treat adults with an unresectable or metastatic GIST |
| XXV | Qnilock   | Ripretinib        | Deciphera Pharmaceuticals | KIT, PDGFRA-α | 5/15/2020 | To treat advanced GIST |

(Continued)
approved for advanced basal-cell carcinoma and are now being investigated for other indications.\(^7\)

The synthetic route to glasdegib (II) is depicted in Scheme 2.\(^8\)

The starting material, 4-methoxypyridine (6), was converted to pyridinium salt 7. The N-Ts benzimidazole (9), obtained from benzimidazole (8), was fully deprotonated with LDA at \(-15^\circ C\) and added to pyridinium triflate (7) to produce the corresponding dihydroxypyrine (9a). Then, intermediate 9a, without further purification, was immediately treated with \(\text{H}_3\text{PO}_4\) to produce 10 in 75%. In \(\text{LiAl(O-}\text{t-Bu})_3\text{H}\) and \(\text{CuBr}\) conditions, the reduction of enone 10 produced a significant amount of piperidone 11 (95%). Removing the Ts group of 11 using hot HCl in THF

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**Table 1. Continued**

| No. | Drug name | Active ingredients | Company | Target | Approval date | Clinical applications |
|-----|-----------|--------------------|---------|-------|---------------|-----------------------|
| XXVI | Brukinsa | Zanubrutinib | BeiGene | BTK | 11/14/2019 | To treat certain patients with mantle cell lymphoma, a form of blood cancer |
| XXVII | Calquence | Acalabrutinib | AstraZeneca Pharmaceuticals LP | BTK | 10/31/2017 | To treat adults with mantle cell lymphoma |
| XXVIII | Aliqopa | Copanlisib | Bayer | PI3K-\(\alpha\) and PI3K-\(\delta\) | 9/14/2017 | To treat adults with relapsed follicular lymphoma |
| XXIX | Inrebic | Fedratinib | Celgene Corp. | JAK2 | 8/16/2019 | To treat adult patients with intermediate-2 or high-risk primary or secondary myelofibrosis |
| XXX | Xpovio | Selinexor | Karyopharm Therapeutics Inc. | XPO1 inhibitor | 7/3/2019 | To treat adult patients with RRMM |
| XXXI | Rubraca | Rucaparib | Clovis Oncology, Inc. | PARP-1,2 and 3 | 12/19/2016 | To treat women with a certain type of ovarian cancer |
| XXXII | Zejula | Niraparib | Tesaro, Inc. | PARP-1,2 and 3 enzymes | 3/27/2017 | For the maintenance treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancers |
| XXXIII | Pemazyre | Pemigatinib | Incyte | FGFRs, FGFR1, FGFR2 | 4/17/2020 | To treat certain patients with cholangiocarcinoma, a rare form of cancer that forms in bile ducts |
| XXXIV | Tazverik | Tazemetostat | Epizyme | EZH2 and EZH1 | 1/23/2020 | To treat epithelioid sarcoma |
| XXXV | Koselugo | Selumetinib | AstraZeneca | MEK2, MEK1 | 4/10/2020 | To treat neurofibromatosis type 1, a genetic disorder of the nervous system causing tumors to grow on nerves |
| XXXVI | Balversa | Erdafitinib | Janssen Products, LP | — | 4/12/2019 | To treat adult patients with locally advanced or metastatic bladder cancer |
| XXXVII | Xermelo | Telotristat etyl | Lexicon Pharmaceuticals, Inc. | — | 2/28/2017 | To treat carcinoid syndrome diarrhea |
| XXXVIII | Turalio | Pexidartinib | Daichi Sanko Inc. | CSF1 receptor; KIT; FLT3 | 8/2/2019 | To treat adult patients with symptomatic tenosynovial giant-cell tumors |
| XXXIX | Vitracki | Larotrectinib | Bayer, LOXO Oncology | TRKA, TRKB, and TRKC | 11/26/2018 | To treat patients whose cancer displays a specific genetic feature (biomarker) |
| XXXX | Rozlytrek | Entrectinib | Genentech, Inc. | NTRK | 8/15/2019 | To treat adult patients with metastatic NSCLC whose tumors are ROS1-positive. To treat adult and pediatric patients 12 years of age and older with solid tumors |
| XXXXI | Retevmo | Selpercatinib | Eli Lilly and Company | RET | 5/8/2020 | To treat lung and thyroid cancer |
| XXXXII | Copiktra | Duvelisib | Verastem, Inc | PI3 K inhibitor | 9/24/2018 | To treat relapsed or refractory chronic lymphocytic leukemia, small lymphocytic lymphoma, and follicular lymphoma |

Abbreviations: ALK, anaplastic lymphoma kinase; AML, acute myeloid leukemia; GIST, gastrointestinal stromal tumor; NSCLC, non-small cell lung cancer; RRMM, relapsed or refractory multiple myeloma.
Scheme 1. Synthesis of gilteritinib (I).

Scheme 2. Synthesis of glasdegib (II).
obtained dihydrochloride monohydrate salt 12 as a racemate in 95% yield.

Key intermediate 13 was synthesized, starting with the reaction between 12 and the ATA-036 transaminase enzyme in DMSO/borate buffer (pH = 10). The reaction was maintained at 50 °C for 50 to 60 h to generate amine 13 in 85% yield with an anti/syn ratio of >10 : 1 and a 99% ee value. Furthermore, 15 was prepared via the reaction of 4-aminobenzonitrile (14) with CDI in the presence of DBU in toluene at ambient temperature. Finally, the reaction between 15 (mixture with imidazole) and the tritosylate salt of 13 proceeded in the presence of Et₃N in THF to obtain glasdegib (II) in 95% yield.

2.3. Ivosidenib (III)

Due to its crucial role in the formation and progression of AML, gliomas, and other cancers, 2-hydroxyglutarate (2-HG), a metabolite produced from the mutated form of the IDH1 enzyme, has been identified as an important biomarker. Elevated 2-HG levels interfere with cellular metabolism and epigenetic regulation, contributing to oncogenesis.9 Therefore, mIDH1 is considered a promising drug target for cancer treatment. Ivosidenib (III), a first-in-class orally available inhibitor developed by Agios Pharmaceuticals, was approved in July 2018 for treating adult patients with relapsed or refractory AML with a susceptible IDH1 mutation.10 Ivosidenib (III) targets the IDH1 metabolic pathway to facilitate a profound oncometabolic 2-HG reduction in tumor models.7,11

The synthetic route to ivosidenib (III) is shown in Scheme 3.12 First, a Schiff base (18) was achieved via the reductive amination of 5-chloropyridin-3-amine (19) with 2-chlorobenzaldehyde (20). Moreover, amine 16 was converted to N-(3, 3-difluorocyclobutyl) formamide by reacting with ethyl formate in the presence of triethylamine. The formamide was then dehydrated using POCl₃ in the presence of Et₃N to obtain isonitrile 17, which was then subjected to a three-step reaction with 18 and 19 to acquire a diastereomer mixture. The desired diastereomer 20 was isolated from the mixture via acid/base extraction and crystallization in >99.9% optical purity. Finally, compound 20 was combined with 2-chloroisocotonitrile (21) to produce ivosidenib (III) in 91% yield.

2.4. Enasidenib (IV)

Similar to mIDH1, IDH2 is primarily located in mitochondria, mutating in many adult patients with AML. This increases 2-HG production to restrict cell differentiation, causing cells to lose their ability to advance from an immature to a fully differentiated state. However, IDH2 mutations are more common (8%-19% of patients) than mIDH1 (7%-14%) in adults with AML. Furthermore, the oncometabolite produced by mIDH2 is higher than mIDH1.13–15 Consequently, mIDH2 is considered a...
vital anti-cancer drug target. Enasidenib (IV) is a first-in-class, oral, selective mIDH2 inhibitor developed by Agios and later licensed to Celgene. It was approved in August 2017 for treating patients with relapsed or refractory AML with an IDH2 mutation.

The synthesis route of enasidenib (IV) was released by Agio in 2015 and involved seven steps described in Scheme 4. No yields were reported in the transformations. It began with the reaction between 2-(trifluoromethyl)pyridine (22) and carbon dioxide, followed by exposure to acetyl chloride to obtain methyl ester 23. Next, condensation occurred involving the methyl ester 23 and carbamyl urea 24 in the presence of sodium ethoxide in ethanol-induced triazine dione 25. The triazine dione 25 was chlorinated using phosphorous pentachloride and phosphorous oxychloride to generate 26. Then, successive SNAr reactions were performed with 2-(trifluoromethyl)pyridin-4-amine (27) and 1-amino-2-methylpropan-2-ol to access 29. Finally, 29 was subjected to methanesulfonic acid in acetone to yield enasidenib mesylate (IV).

2.5. Midostaurin (V)

Midostaurin (V) is a natural multikinase inhibitor developed by Novartis Pharmaceuticals and was approved in April 2017 and combined with chemotherapy medications (daunorubicin and cytarabine) to treat adult patients with FLT3 mutation-positive AML, or aggressive systemic mastocytosis (SM) with associated blood cancer and mast-cell leukemia. Approximately 30% of adult patients suffering from AML with FLT3 mutations. Midostaurin (V) is the first multikinase inhibitor approved for the FLT3-mutant subtype.17–19

Midostaurin (V) was synthesized from the natural product staurosporine (30), as depicted in Scheme 5. The acylation reaction between staurosporine (30) and benzoic anhydride (31) obtained Midostaurin (V) in 82% yield.

2.6. Venetoclax (VI)

B cell lymphoma subtype 2 (BCL-2) is often overexpressed in malignant cells, making this protein the rational target for anti-cancer therapy.21 Venetoclax (VI) is a selective oral inhibitor of BCL-2 and was approved in April 2016 for treating chronic lymphocytic leukemia (CLL) in patients with 17p deletion who have received at least one prior therapy. The drug was co-developed by AbbVie and Genentech.

The synthetic route to venetoclax (VI) is depicted in Scheme 6. The acquisition of the three key intermediates, 38, 42, and 46, was crucial. The synthesis of compound 38 began with cyclohexanone (32). The formylation of 32 in the presence of POCl3 delivered a quantitative yield of vinyl

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Scheme 4. Synthesis of enasidenib (IV).
chloride 33. Combining vinyl chloride 33 with aryl boronate 34 yielded 35 in 78% without isolation. Crude 35 and N-Boc piperazine (36) were reacted under reductive amination conditions, yielding 37 in 74%. Finally, intermediate 38 was obtained at 95% yield in conditions consisting of concentrated HCl in IPA at 65 °C.

Moreover, intermediate 42 was generated in two steps using 4-bromo-2-fluoro-1-iodobenzene (39). Then, protection with Boc₂O yielded tert-butyl ester 40 without purification. Aromatic substitution of 40 with azaindole 41 produced 42 in 86% yield. Intermediate 46 was obtained from 44 via another aromatic substitution.

Scheme 5. Synthesis of midostaurin (V).
3. Anti-breast Cancer Drugs

3.1. Tucatinib (VII)

Tucatinib (VII), also known as irbinitinib, ARRY-380, or ONT-380, is a selective, oral human epidermal growth factor receptor 2 (HER2) (also called ErbB-2) inhibitor developed by Array BioPharma and Seattle Genetics. It was approved in April 2020 and combined with trastuzumab and capecitabine to treat adult patients with advanced, unresectable, or metastatic HER2-positive breast cancer and colorectal cancer.

Its synthetic route was developed by Array BioPharma Inc., as shown in Scheme 7. Starting with picolinic acid (47), a chlorination reaction with thionyl chloride followed by ammonium hydroxide substitution yielded compound 48 in 85%. Then, the Hofmann rearrangement of 48 produced 49. Hydrolysis of 49 and substitution with 51 yielded 52 in 67%. Cyclization of 52 using DMF-DMA yielded 53 in 88%, after which 53 was reduced to amine 54. Intermediate 55 was synthesized from 57 in three steps, producing in 34% overall yield, which was cyclized with 54, yielding 56 in 62%. Finally, 56 was treated with i-PrOAc to obtain tucatinib (VII) in 62% yield. A new, improved synthetic route was designed by L. Yin et al., involving three key intermediates, as shown in Scheme 8. The first intermediate 54, was prepared in 33% yield in five steps. Next, intermediate 66 was isolated in 71% yield using three steps, after which intermediate 67 was prepared in mild conditions in 67% yield by two steps. Finally, tucatinib (VII) was obtained in 17% yield in nine steps.

3.2. Alpelisib (VIII)

Approximately 40% of patients with hormone receptor (HR)-positive, HER2-negative breast cancer reportedly have activated mutations in the PIK3CA gene, which encodes the catalytic (p110α) subunit of phosphatidylinositol 3-kinase (PI3 K). Therefore, targeting α-specific PI3 K provides a promising approach for anti-cancer therapy. Novartis Oncology has developed alpelisib as an orally bioavailable, α-specific PI3 K inhibitor, which was approved in May 2019 to treat advanced or metastatic breast cancer patients who are HR-positive and HER2-negative with PIK3CA mutations. Alpelisib (VIII) selectively inhibits p110α approximately 50 times more than other isoforms.

The synthesis approach of alpelisib (VIII) is shown in Scheme 9. Compound 68 was reacted with (COCl)₂ to

Scheme 7. Synthetic route 1 to tucatinib (VII).
produce 69, followed by a cycloaddition reaction with 70 to obtain pyranone 71 in 55% yield. Then, a palladium-catalyzed cross-coupling reaction between 4-bromopyridine 73 and 74 was carried out to acquire 75 in 88% yield. Next, 75 was hydrolyzed with an aqueous HCl solution in refluxing EtOH to obtain 76 in 95% yield. Finally, 76 was treated with CDI to procure 77, which was substituted with L-prolineamide to produce alpelisib (VIII) in 87% yield.

3.3. Talazoparib (IX)

Polyadenosine 5′-diphosphoribose polymerase (PARP) plays a crucial role in repairing DNA single-strand breaks via the BER pathway. Therefore, as a promising drug target, inhibiting PARP results in an accumulation of DNA single-strand breaks, leading to cell death.29 Talazoparib (IX) is an oral PARP inhibitor developed by Pfizer and approved in October 2018 to treat locally advanced or metastatic breast cancer patients with a germline BRCA mutation.30

Scheme 10 shows the talazoparib (IX) synthetic route.31 An aldol reaction between 78 with 79 was performed to access 80 in 75% yield. The cycloreversion of 80 was conducted in HCl conditions to provide 81. Then, 81 was subjected to 4-fluorobenzaldehyde and chiral separation to produce 82 in 73% yield in two steps. Next, 82 was finally converted to talazoparib (IX) via a condensation reaction with hydrazine monohydrate.

3.4. Abemaciclib (X)

Abemaciclib (X) is an oral inhibitor that targets cyclin-dependent kinases (CDK) 4 and 6. It was developed by Eli Lilly and approved in September 2017 for treating HR-positive and HER2-negative advanced breast cancer.14 It is combined with fulvestrant when the breast cancer worsens after hormonal therapy or taken alone when the breast cancer worsens after hormonal therapy and chemotherapy.32,33

The synthesis of abemaciclib (X) is shown in Scheme 11.34 Key intermediate 93 was obtained via the reaction between 90 and 91 using two steps in 54% yield. Intermediate 89 was synthesized, starting with phenylamine 83. The condensation of phenylamine 83 with N-isopropylacetamide (84) produced compound 85, which was then subjected to cyclization to obtain 86 in 73% yield. The Suzuki coupling of 88 with borate ester 87 produced 89. Finally, palladium-catalyzed Buchwald-Hartwig amination with aminopyridine 83 and 89 produced abemaciclib (X) in 88% yield.

3.5. Neratinib (XI)

In July 2017, an oral, irreversible inhibitor of HER1 (EGFR), HER2, and HER4, known as neratinib (XI), was discovered by Wyeth and is currently being developed by Puma Biotechnology.35 The drug was approved for treating early-stage HER2-positive breast cancer in women who have received previous trastuzumab and chemotherapy treatment as an adjuvant,
Scheme 9. Synthesis of alpelisib (VIII).

Scheme 10. Synthesis of talazoparib (IX).
as well as treating patients with HER2-positive early breast cancer at high risk of recurrence.\textsuperscript{36}

The synthesis of neratinib (XI) is described in Scheme 12.\textsuperscript{37} 4-Acetamido-3-ethoxyaniline (94) was condensed with ethyl cyanoacetate 95 to yield acetamido intermediate 96. Cyclization of 96 was conducted in Dowtherm at 250 to 255 °C to yield 6-acetamido-4-hydroxyquinoline-3-carbonitrile (97). Then, chlorination of 97 generated 4-chloro intermediate 98, which was reacted with a substituted aniline 107 (obtained from 104 after two steps) to obtain 99. The acetamido group of 99 was deacetylated to produce amine 100, which was reacted with crotonyl chloride 102 to yield neratinib (103). Finally, dissolving neratinib (XI) and malic acid (1:1) in \( \nu \)-propanol/water (9:1) produced a neratinib (XI) maleate.

3.6. Ribociclib (XII)

The overexpression of CDK4/6 is often evident in HR-positive breast cancer, while CDK4/6 inhibition can lead to cell cycle arrest.\textsuperscript{38} Consequently, CDK4/6 represents promising drug targets for breast cancer treatment. Ribociclib (XII) is an oral CDK 4 and 6 inhibitor developed by Novartis and approved for treating advanced HR-positive and HER2-negative breast cancer in postmenopausal women.

Several synthetic routes to ribociclib (XII) have been described in various patents. One of the efficient approaches is shown in Scheme 13.\textsuperscript{39} The reaction of 2,4-dichloropyrimidine (108) with cyclopentanamine produced 109 in 92% yield. Bromooxylate 111 was obtained via the
reaction of commercially available compound 2-oxopropanoic acid (110) after two steps in 82% yield. Key pyrrolopyrimidine fragment 112 was synthesized via the reaction between 109 and 111. Finally, 112 was subjected to piperazine 113 to obtain ribociclib (XII) in 84% yield during a two-step sequence.

4. Anti-lung Cancer Drugs

4.1. Capmatinib (XIII)

Mesenchymal-epithelial transition (MET) is considered an attractive target for therapeutic blockade in lung cancer. Capmatinib (XIII), a highly selective, potent small-molecule MET inhibitor, was developed by Novartis and approved in May 2020 for treating metastatic non-small cell lung cancer (NSCLC) with MET exon 14 mutations.

The synthetic method for capmatinib (XIII) is shown in Scheme 14. The chlorination of 4-bromo-3-fluorobenzoic acid (114) produced 115, which was substituted with N,O-dimethylhydroxylamine (116) to obtain 117 in 96% yield using two steps. Then, 117 was methylated using Grignard reagent MeMgCl to acquire acetophenone 118 in 98% yield. The oxidation of 119, followed by acetalization of the formyl group, produced 120 in 92% yield. The cycloaddition reaction between 120 and 121 provided 122 under a basic environment, which was then reacted with key intermediate 130 to produce imidazole 123 in 50% yield. Treating 123 with Zn(CN)₂ and Pd(dppf)Cl₂ provided 124 in 73% yield. The hydrolysis of 124, followed by the acylation of 125, produced the final capmatinib (XIII) in an 85% yield. Key intermediate 130 can be synthesized using one of three methods outlined in Scheme 14. The most efficient way is method B, which started with compound 126, finally producing 130 in 54% yield after four steps.

Scheme 12. Synthesis of neratinib (XI).
4.2. Lurbinectedin (XIV)

Lurbinectedin (XIV) is an oncogenic transcription inhibitor developed by Pharma Mar and approved in June 2020 for treating adult patients with metastatic small-cell lung cancer (SCLC) displaying disease progression on or after platinum-based chemotherapy. The drug covalently binds to DNA, causing DNA damage and apoptotic cell death.43,44

The total synthesis of lurbinectedin (XIV) is described in Scheme 15.45 Protecting the amino group in the starting compound 131 with benzylcarbonyl chloride (CbzCl) produced 132, which was reacted with HCHO to obtain 133 in 85% yield. Methylation and dihydroxylation of 133 produced 134 in 92% yield after two steps. Intermediate 134 was reacted with 135 to produce 136 in 92% yield. Treating 136 with 3-chloroperbenzoic acid (m-CPBA) and a LiBH₄ reduction produced 137 in 80% yield after two steps. Then, 137 was deprotected to provide 138 in 98% yield. The cycloaddition of 138 using two steps produced 139, followed by oxidation with O₂ to obtain 140 in 85% yield. Irradiating 140 with blue light led to compound 141. Protecting the hydroxyl group with a benzyl group, and oxidizing the alcoholic hydroxy into aldehyde, produced compound 143. The intermolecular Pictet-Spengler reaction between 143 and 144 produced 145 as a major isomer in 67% yield. After reductive amination to introduce the methyl group and protection of compound 145 with an allyl group, 146 was obtained in 88% yield. Then 146 oxidized, deprotected, and subjected to a Strecker reaction, after which intermediate 146 was converted into 147 in 92% yield. The deprotection of 147 with boron trichloride produced 148 in 92% yield. Oxidizing 148 with benzeneselenic anhydride produced 149 in 86% yield. The condensation of 149 with (R)-N-Alloc-S-Fm-Cys provided 150 in 84% yield. Lactone 151 was obtained via the macrocyclization of 150 in 51% yield. Treating 151 with Pd(PPh₃)₄ to remove two protective groups provided 152, which was oxidized to produce 153 in 52% yield. Finally, 153 was reacted with 154 to obtain lurbinectedin (XIV) in 77% in two steps.

4.3. Pralsetinib (XV)

Pralsetinib (XV) is a selective rearranged during transfection (RET) inhibitor, developed by Blueprint Medicines Corporation and approved for treating NSCLC, and is a once-daily, oral, RET-targeted therapy. Approximately 1% to 2% of NSCLC patients display RET alterations.46 The synthesis of pralsetinib (XV) is described in Scheme 16.47 2,4-Dichloro-6-methylpyrimidine (155) was reacted with sodium methanethiolate to obtain 156 in 42% yield. Treating 156 with 157 and Zn produced 158 in 70% yield, which was then oxidized

![Scheme 13. Synthesis of ribociclib (XII).](image-url)
using m-CPBA, producing 159 in 89% yield. Then, 159 was hydroxylated to obtain 160 in 79% yield. After the chlorination of 160 using phosphorus oxychloride, 161 was obtained in 85% yield, which was then treated with 162 to acquire 163 in 53% yield. Finally, 163 underwent a condensation reaction with 164, producing pralsetinib (XV) in 43% yield after three steps.

4.4. Lorlatinib (XVI)

Lorlatinib (XVI) is a potent, selective, brain-penetrating, third-generation anaplastic lymphoma kinase (ALK)/ROS1 tyrosine kinase inhibitor (TKI), developed by Pfizer and approved in November 2018 for treating ALK-positive NSCLC.48

A convergent approach was designed to synthesize lorlatinib (XVI) as depicted in Scheme 17.49 First, pyrazole 165 was treated with NBS and benzoyl peroxide to obtain 166 in 58% yield. The condensation of 166 with tert-butyldimethylcarbamate produced 167 in 33% yield. Intermediate 168 was obtained from 167 during a three-step reaction. Reducing 169 with biocatalytic reagent produced 170 in 91% yield, displaying a high ee value exceeding 99%. Then, the S$_2$N$_2$ displacement of 170 was performed using 2-amino-3-hydroxypyridine (171) to synthesize 172 in 39% yield after two steps. The carbonylation of 172 with carbon monoxide in the presence of Pd(dppf)Cl$_2$ produced 173 in 79% yield. To generate the key 174 intermediate, 173 was brominated and protected via Boc$_2$O and borylation. A Suzuki coupling reaction was performed between 174 and 168 in the presence of Pd(dppf)Cl$_2$ to obtain 175, after which the three Boc groups were removed using HCl and hydrolyzed with KOTMS to obtain 176 in 79% yield from 174. In the presence of HATU and triethylamine in EtOAc, intermolecular macrocyclic amidation 176 produced lorlatinib (XVI) in 55% yield.
4.5. Dacomitinib (XVII)

Dacomitinib (XVII) is an orally administered, small-molecule irreversible inhibitor of HER1 (EGFR), HER2, and HER4, developed by Pfizer and approved in September 2018 for treating patients with metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations. Unlike first-generation EGFR TKIs (gefitinib and erlotinib), dacomitinib, as a second-generation EGFR TKIs, was designed to overcome some of the issues related to the acquired resistance caused by first-generation agents.\(^{50,51}\)

The dacomitinib (XVII) synthesis process was reported by Pfizer, as shown in Scheme 18.\(^{52}\) The nitro group of 177 was subjected to catalytic hydrogenation in the presence of Pd/C.
to obtain 178, which was used for the next transformation without purification. Intermediate 180 was obtained from 179 in two steps. Amide compound 181 was synthesized via the condensation reaction between 178 and 180 in 75% yield. Finally, dacomitinib (XVII) was synthesized via the Dimroth rearrangement reaction between 181 and 182 in 82% yield.

4.6. Brigatinib (XVIII)

On April 28, 2017, brigatinib (XVIII), developed by Ariad Pharmaceuticals, was approved for treating patients with metastatic ALK-positive NSCLC who have progressed on or are crizotinib intolerant. It is a second-generation ALK inhibitor and...
is active in vitro against L1196 M, E1210 K, and G1202R ALK domain mutations, which may mediate acquired resistance to other ALK inhibitors.53,54

A synthetic route to brigatinib (XVIII) has been reported by Ariad Pharmaceuticals and is outlined in Scheme 19.55 2-Iodoaniline (182) was treated with dimethylphosphine oxide to obtain 183, which was reacted with trichloropyrimidine (184) via an SNAr reaction in basic conditions to produce intermediate 185. Moreover, an S_NAr fluoro displacement of 4-fluoro-2-methoxy-1-nitrobenzene (186) was conducted using 1-methyl-4-(piperidin-4-yl)piperazine (187) in the presence of K2CO3, followed by nitro reduction to routinely acquire 188 in high yield. Finally, 185 underwent subsequent acid-promoted chlorine displacement with 188 to synthesize brigatinib (XVIII).

5. Anti-prostate Cancer Drugs

5.1. Relugolix (XVX)

Relugolix (XVX) is a marketed, orally selective antagonist of the human gonadotropin-releasing hormone (GnRH) receptor, which was developed by Myovant Sciences, and approved in December 2020 to treat advanced prostate cancer. Relugolix (XVX) rapidly inhibits the pituitary release of the luteinizing hormone and FSH and has been shown to lower testosterone levels in multiple phase 1 and phase 2 studies. During the phase 3 trial, relugolix (XVX) achieved rapid and sustained suppression of testosterone levels, which was superior to the results obtained with leuprolide, with a 54% lower risk of major adverse cardiovascular events.56,57

One of the synthetic routes to relugolix (XVX) is described in Scheme 20.58 Intermediate 189 was condensed with ethyl chloroformate in refluxing toluene to obtain 190 in 94% yield, which was subsequently substituted with 2-(chloromethyl)-1,3-difluorobenzene (191) to form 192 in 93% yield. Treating 192 with N-bromosuccinimide (NBS) in the presence of azobisisobutyronitrile (AIBN) generated brominated product 193 at a quantitative yield. Then, 193 was reacted with 2-methoxy-N-methylethan-1-amine (194) to obtain 195, followed by the catalytic hydrogenation of the nitro group under Pd/C-catalyzed conditions to produce 196 in 97% yield. Amine 196 was treated with CDI and MeONH2 to generate 197 in 89% yield. Hydrolyzing 197 in a NaOH aqueous solution produced 198 in 96% yield. The condensation of 198 with 6-methoxypyridazin-3-amine 199 in the presence of DEPC and T3P produced 200 in 69% yield. Finally, relugolix (XVX) was obtained from 200 after two steps in 44% yield.

5.2. Darolutamide (XX)

Darolutamide (XX) is an androgen-receptor antagonist developed by Bayer and approved in July 2019 for treating adult patients with non-metastatic castration-resistant prostate
cancer. Darolutamide (XX) inhibits AR variants, including W741L, T877A, H874Y, and F876L mutants. It competitively binds to lacking AR-ligand binding domains (LBD) with high binding affinity, significantly inhibiting the growth of enzalutamide-resistant prostate cancer cells in vivo. Compared with enzalutamide and apalutamide, darolutamide (XX) exhibited poor brain penetrance, decreasing seizure risk.59,60

An efficient large-scale approach has been reported by Orion Corporation, as shown in Scheme 21.61 A coupling reaction between starting compound 201 and 44,4',4,55,5',5'-octamethyl-2,2'-bi(13,2-dioxaborolane) produced 202 in 68% yield after two steps. Treating 202 with 4-bromo-2-chlorobenzonitrile (203) in the presence of catalysts, Pd(OAc)2 and PPh3 produced 204 in high yield of 92%. Hydrochloric acid was used to catalyze the hydrolysis of 204, producing 205 in 96% yield, which was then reacted with tert-butyl (S)-(1-hydroxypropan-2-yl)carbamate (206) to introduce chiral isopropylamine to the scaffold, generating 207. Then, intermediate 207 underwent an amide condensation reaction with 208 to synthesize compound 209, which was reduced with NaBH4 to obtain darolutamide (XX) in 76% yield.

Scheme 19. Synthesis of brigatinib (XVIII).

5.3. Apalutamide (XXI)

Apalutamide (XXI) is a non-steroidal next-generation oral androgen receptor (AR) inhibitor developed by Janssen Biotech and was approved in 2018 for treating non-metastatic and castration-resistant prostate cancer. By binding to the LBD of the AR, apalutamide (XXI) blocks the effect of androgens, inhibiting nuclear translocation, DNA binding, and AR-mediated transcription.62,63

The synthetic route to apalutamide (XXI) was reported by Aragon.64,65 As shown in Scheme 22, the hydroxyl group of the starting material, 5-nitro-3-(trifluoromethyl)pyridin-2-ol (210), was substituted with a cyano group, yielding 211 in two steps. Then, reducing the nitro group of 211 in the presence of Pt/C under H2 atmosphere produced amine 212. An amide condensation reaction was performed between 1-[(tert-butoxycarbonyl)amino]cyclobutane-1-carboxylic acid (213) and 212, followed by Boc deprotection to produce 215 in 80% yield. Subsequently, intermediate 215 was substituted with 216 to obtain 217 in 84% yield, which was finally reacted with 218 in the presence of DMAP and DMA to produce apalutamide (XXI) in 80% yield.
6. Anti-melanoma Drugs

6.1. Encorafenib (XXII)

BRAF\textsuperscript{V600E} mutations are observed in approximately 50% of melanomas. BRAF\textsuperscript{V600E} mutation occurs in 35% to 50% of patients with melanoma. Combining a BRAF inhibitor with a MEK inhibitor simultaneously enhances efficacy and reduces toxicity. Encorafenib (XXII) is a BRAF inhibitor developed by Array BioPharma and approved in June 2018 in combination with binimetinib (XXIII) to treat unresectable or metastatic melanoma with a BRAF\textsuperscript{V600E} or \textsuperscript{V600K} mutation.

Scheme 20. Synthesis of relugolix (XVX).

Scheme 21. Synthesis of darolutamide (XX).
The synthesis of encorafenib (XXII) is shown in Scheme 23.68 Two intermediates (223 and 225) were separately synthesized from (S)-propane-1,2-diamine (227) and 2-bromo-4-chloro-1-fluorobenzene (229) in two and three steps, respectively. Isopropylhydrazine (218) was treated with benzaldehyde, followed by alkylation with (ethoxyethylidine) malononitrile, after which acid-promoted cyclization yielded 219. A Sandmeyer conversion of 219 was performed to obtain iodide 220, which was cyclized with 221 to acquire 222 in two steps. Then, intermediate 222 was reacted with 223 in three steps to obtain 224, which was coupled with 225 to yield 226 in Suzuki reaction conditions. Finally, 226 was acidified with HCl, treated with methanesulfonyl chloride, and exposed to sodium hydroxide to produce encorafenib (XXII).

6.2. Binimetinib (XXIII)

Binimetinib (XXIII), a MEK inhibitor, has been developed by Array BioPharma and was approved in June 2018 for treating unresectable or metastatic melanoma with a BRAFV600E or V600K mutation. Binimetinib (XXIII) reversibly inhibited MEK1 and MEK2. Combining binimetinib (XXIII) with encorafenib (XXII) displayed more significant anti-proliferative activity toward BRAF-mutant cell lines than either drug alone.66,69

One of the synthetic routes to binimetinib (XXIII) is shown in Scheme 24.70 23,4-Trifluoro-5-nitrobenzoic acid (232) was condensed with O-(2-[tert-butoxy]ethyl)hydroxylamine (233) in the presence of CDI and diisopropylethylamine to synthesize 234 in 88% yield. Then, 234 was treated with ammonia to produce 235 in 90% yield, which was cyclized with formic acid in the presence of palladium hydroxide on carbon to produce 236 in 79% yield. Intermediates 236 and 237 were subjected to Pd(dba)₃ to obtain 238 in 85% yield. Subsequently, it was treated with methyl iodide and K₂CO₃ in DMF, followed by aqueous phosphoric acid in acetonitrile, resulting in tert-butyl ether cleavage to produce binimetinib (XXIII).

7. Anti-GIST Tumor Drugs

7.1. Avapritinib (XXIV)

Avapritinib (XXIV) is a potent and highly selective inhibitor of KIT and PDGFRα and was approved in 2020. Avapritinib (XXIV) was granted two breakthrough therapy designations, one for treating unresectable or metastatic GIST harboring the PDGFRα D842 V mutation and another for treating...
advanced SM, including the subtypes of aggressive SM, SM with an associated hematologic neoplasm, and mast-cell leukemia. The synthesis of avapritinib (XXIV) was reported by Zhang in 2019 (Scheme 25). The key intermediates, 239 and 240, were treated with HCl and DIPEA at room temperature for 18 h to obtain compound 241 in 43% yield, which was reacted with (S)-2-methylpropane-2-sulfonamide (242) and ethyl orthotitanate at 70 °C for 18 h to acquire intermediate 243 in 100% yield. Then, 243 and methylmagnesium bromide, were reacted in THF at 0 °C for 65 min to obtain 244 in 61.5% yield. Treating 244 with HCl in 1,4-dioxane/Methanol at room temperature for 1 h produced 245 in 100% yield. Finally, 245 were purified via chiral SFC to obtain avapritinib (XXIV) in 68.3% yield. The key intermediates, 239 and
were synthesized from 246 and 252, respectively, in five steps, as shown in Scheme 25.

7.2. Ripretinib (XXV)

Since mutations of the gene encoding receptor tyrosine kinases, KIT and platelet-derived growth factor receptor α (PDGFRα), have been found in more than 85% of GIST cases, KIT and PDGFRα have been considered promising targets for cancer treatment. Ripretinib (XXV) is a novel type II tyrosine switch control inhibitor developed by Deciphera Pharmaceuticals and was approved in May 2020 to treat adult patients with advanced GIST who have received prior treatment with ≥ 3 kinase inhibitors, including imatinib. It inhibits not only the wild-type KIT and PDGFRα kinase but also the secondary mutations. Furthermore, it inhibits other kinases, such as PDGFRβ, TIE2, VEGFR2, and BRAF.73

The preparation of ripretinib (XXV) and its fragments are described in Scheme 26.74 Intermediate 262 was synthesized from the starting material, diethyl 3-oxopentanedioate (258) after seven steps. First, a cycloaddition reaction was performed between 258 and triethyl orthoformate in the presence of ammonium hydroxide, producing 259 in a satisfactory yield of 60%. Subsequently, it was subjected to POCl3 to obtain 260 in a good yield of 90%. Then, treating 260 with ethylamine in acetonitrile produced 261 in 91% yield. Ester 261 was reduced to alcohol 262 via LiAlH4 in 79% yield. The oxidation reaction between intermediate 262 and MnO2 produced 263 in 89% yield.

Then, a nitration reaction was conducted between 263a and nitric acid to acquire 264 in 92% yield. The esterification of 264 with ethanol in the presence of conc. H2SO4 produced 265 in a moderate yield of 49%. The nitro group of 265 was then reduced to an amino group via an iron powder and ammonium chloride system, producing 266 in a high yield of 93%. The cycloaddition of 266 with 263 formed 267 in 89% yield. Substituting 267 with methylamine produced 268 in 89% yield. The condensation of 268 with isocyanatobenzene (269) in the presence of triethylamine produced ripretinib (XXV) in 64.5% yield.

Scheme 24. Synthesis of binimetinib (XXIII).
8. Anti-lymphoma Drugs

8.1. Zanubrutinib (XXVI)

Zanubrutinib (XXVI) is a potent and highly selective Bruton tyrosine kinase (BTK) inhibitor, developed by BeiGene, and was approved for treating adult patients with mantle-cell lymphoma (MCL) who have received at least one prior treatment for cancer.\textsuperscript{75,76}

The synthetic route to zanubrutinib (XXVI) is described in Scheme 27.\textsuperscript{77} First, acid 270 was treated with thionyl chloride to prepare the acyl chloride that was reacted with malononitrile to produce 271 in 93\% yield in two steps. Then, a substitution reaction between 271 and TMOF produced 272 in 48\% yield. Intermediate 272 underwent a cycloaddition reaction with hydrazine hydrate, generating 273 in 69\% yield. Another cycloaddition reaction between 275 and 274 was performed in the presence of AcOH, producing 275 in high yield. The cyano group of 275 was hydrolyzed under basic conditions to generate amide 276. Then, the Boc group was removed under acidic conditions to obtain amine 277. Finally, amine 277 was reacted with acryloyl chloride (278) to acquire the racemate, which was separated via chiral resolution to obtain zanubrutinib (XXVI).

8.2. Acalabrutinib (XXVII)

Developed by AstraZeneca Pharmaceuticals, acalabrutinib (XXVII) is a BTK inhibitor that was approved in October 2017 for treating adult patients with MCL who have received at least one prior cancer treatment. It is a second-generation BTK inhibitor that displays better selectivity and potency of ibrutinib, and it has received accelerated approval for MCL treatment.\textsuperscript{78,79}

An efficient synthesis method for obtaining acalabrutinib (XXVII) is depicted in Scheme 28.\textsuperscript{80,81} First, POCl\textsubscript{3} was used to prepare 4-bromobenzoyl chloride, which was then condensed with 2-aminopyridine to produce the precursor of 280. Then, the borylation of the precursor, when exposed to
Pd(dppf)Cl$_2$ and hydrolysis, produced 280, which was subsequently treated with 3-chloropyrazine-2-carbaldehyde to obtain racemic amine 281 in 81% yield. This precursor was cyclized with 282 to yield 283 in three steps. Finally, 283 was treated with ammonia in isopropyl alcohol to obtain acalabrutinib (XXVII) in 86% yield.

Scheme 26. Synthesis of eipretinib (XXV).

Scheme 27. Synthesis of zanubrutinib (XXVI).
8.3. Copanlisib (XXVIII)

Follicular lymphoma is a slow-growing type of non-Hodgkin lymphoma.\textsuperscript{82} Copanlisib (XXVIII), developed by Bayer, is a pan-class I PI3 K inhibitor. Copanlisib (XXVIII) exhibits excellent inhibitory activity against class I PI3 K\textsubscript{α}, \textsubscript{β}, \textsubscript{γ}, and \textsubscript{δ} isoforms with IC\textsubscript{50} values of 0.5 nmol/L, 3.7 nmol/L, 6.4 nmol/L, and 0.7 nmol/L, respectively. It was approved to treat patients with relapsed follicular lymphoma who have received at least two prior systemic therapies.

The standard synthetic route to copanlisib (XXVIII) was released by Bayer.\textsuperscript{83} As shown in Scheme 29, nitration of 4-formyl-2-methoxyphenyl acetate (284) under HNO\textsubscript{3} and H\textsubscript{2}SO\textsubscript{4} conditions produced \textsuperscript{285}. The acetyl group of 285 was replaced with benzyl group to give 286. The formyl group of 286 was cyclized with ethylenediamine in the presence of NBS and DCM, producing 287 in 81% yield after two steps. Then, Catalytic hydrogenation of the nitro group with iron and Pt/C provided the amine 288. Subsequently, amine 288 was cyclized with BrCN, producing 289 in high yield. The deprotection of the benzyl group produced 290, which was reacted with 291 to obtain 292 in 86% yield. Finally, amine 292 was reacted with 2-aminopyrimidine-5-carboxylic acid (293) to ultimately acquire the target compound, copanlisib (XXIII), in 96% yield.

9. Anti-myeloma Drugs

9.1. Fedratinib (XXIX)

Approximately 20% of patients with myelofibrosis have died from leukemic transformation, which is most commonly due to the V617F mutation in the JAK2 protein.\textsuperscript{84,85} Fedratinib (XXIX), developed by Celgene, is an oral JAK2-selective inhibitor that can inhibit STAT3/5 phosphorylation, reduce cell proliferation, and induce apoptosis in cells with JAK2 V617F or FLT3/ITD mutations. It was approved in August 2019 for treating intermediate-2 or high-risk primary or secondary myelofibrosis.

Scheme 30 shows the efficient synthetic route to fedratinib (XXIX).\textsuperscript{86} First, a coupling reaction was carried out between compound 2-chloro-5-methylpyrimidin-4-amine (295) and \textsuperscript{296}. Then, alkoxy-aniline (297) was introduced to 296 via microwave irradiation to obtain fedratinib (XXIX) in 27% yield.

9.2. Selinexor (XXX)

As the major nuclear exporter of tumor suppressor proteins, the growth regulator and oncoprotein mRNAs, XPO1, are overexpressed in various cancer types and are identified as a promising drug target. Selinexor (XXX) is a first-in-class, oral, nuclear export protein exportin 1 (XPO1) inhibitor, which was developed by Karyopharm Therapeutics and was approved in July 2019 to treat adult patients with relapsed or refractory multiple myeloma (RRMM) in combination with dexamethasone. By forming a slowly reversible covalent bond with cysteine 528 in the binding pocket of XPO1, selinexor (XXX) selectively inhibits XPO1, leading to the accumulation of tumor suppressor proteins in the nucleus, decreasing oncoprotein levels, cell cycle arrest, and cancer cell apoptosis.\textsuperscript{87}

The synthesis of selinexor (XXX) was initiated with 3,5-bis(trifluoromethyl)benzonitrile (298) in five steps, which is described in Scheme 31.\textsuperscript{88} Treating 298 with NaSH produced 299 in 90% yield. Triazole compound 300 was obtained from the cycloaddition reaction between 299 and hydrazine hydrate.
and formic acid in 75% yield. Next, 300 was substituted with 301 to obtain 302 in 61% yield, which was then hydrolyzed in the presence of LiOH to acquire 303 in 94% yield. Finally, the condensation reaction between 303 and 304 produced selinexor (XXX) in 16% yield.

10. Anti-ovarian Cancer Drugs

10.1. Rucaparib (XXXI)

Rucaparib (XXXI), an oral, small-molecule poly (ADP-ribose) polymerase inhibitor, was developed by Clovis Oncology Inc. and approved for treating patients with deleterious BRCA mutations (germline and somatic) associated advanced ovarian cancer who have received two or more chemotherapy treatments. The drug inhibits PARP enzymes, including PARP-1, -2, and -3, which are integral in the DNA damage response system by activating the response pathways and facilitating repair.29,89

The most likely synthetic approach to rucaparib (XXXI) camsylate is described in Scheme 32.90 Starting material 305 was treated with aqueous HCl to obtain 306 in 62% yield. This was followed by methyl 6-fluoro-1H-indole-4-carboxylate (307) treatment to obtain 308. After an intramolecular cyclization reaction of 308 in the presence of methylamine and pyridinium tribromide, lactam compound 309 was formed in 74% yield from 306. A Suzuki coupling between 309 and boronic acid 310 produced 311 in 92% yield, followed by a Borch reduction amination reaction with MeNH2 to generate 312 in 76% yield. Finally, 312 was subjected to NaOH in MeOH and then treated with (S)-camphorsulfonic acid/IPA/H2O at 70 °C, producing the rucaparib camsylate (XXXI) in 75% yield in two steps.
10.2. Niraparib (XXXII)

Niraparib (XXXII) is an oral, once-daily, highly-selective poly (ADP-ribose) polymerase (PARP)-1 and PARP-2 inhibitor, developed by Tesaro, approved for treating adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy. It displays a highly selective inhibition toward PARP-1 and PARP-2 (IC₅₀ = 3.8 and 2.1 nmol/L, respectively), which represents a 100-fold higher selectivity than with other PARP-family members (PARP-3, v-PARP, and TANK-1).91

The synthesis approach of niraparib (XXXII) is described in Scheme 33.92 At first, Friedel-Crafts acylation was performed using succinic anhydride to prepare the acid intermediate, which was subsequently esterified with i-ProOH to obtain 315 in 86% yield. Then, 315 was epoxidized with Me₃SOI, followed by ZnBr₂-catalyzed isomerization to obtain 316, which was then reacted with NaHSO₃ to produce 317 without isolation and purification. Using PLP, 318, and the ATA-302 enzyme as co-catalyst, 317 was converted into 319 in 84% yield. Reduction of the amide carbonyl group followed by and Boc group protection produced 320.

The key intermediate, 320, was coupled with 322, synthesized from 321 with t-BuNH₂, to prepare the core structure of 323 in 94% yield. Finally, the Boc group was deprotected, and niraparib tosylate (XXXII) was obtained in the presence of MeSO₃H and p-TsOH in two steps.

11. Other Anti-Cancer Drugs

11.1. Pemigatinib (XXXIII)

Pemigatinib (XXXIII) is an oral fibroblast growth factor receptor (FGFR)1, FGFR2, and FGFR3 inhibitor, developed by Incyte Corporation and approved in April 2020 for treating adult patients with previously treated, unresectable, locally advanced, or metastatic cholangiocarcinoma, and an FGFR2 fusion or other rearrangements.93 Approximately 10% to 16% FGFR2 alterations are present in patients with intrahepatic cholangiocarcinoma. Pemigatinib (XXXIII) is a novel, potent drug that selectively inhibits the functionality of altered FGFR2.94,95

Wu has reported the synthesis of pemigatinib (XXXIII),96 as depicted in Scheme 34. After introducing the ethanamine side chain, the obtained 325 was subsequently reacted with 326, producing 327 in 83% yield. Then, 327 was treated with triphoshene to prepare cyclized compound 328, which was converted to indolin-2-one intermediate 329 in two steps. Next, the N-H was protected using the benzenesulfonyl group. A formyl group was introduced with LDA in DMF.

Scheme 30. Synthesis of fedratinib (XXIX).

Scheme 31. Synthesis of selinexor (XXX).
and THF at −78 °C, which then underwent a reductive amination reaction with morpholine to obtain 332 in 95% yield. Finally, the sulfamide bond cleavage of 332 via TABA generated pemigatinib (XXXIII).

11.2. Tazemetosat (XXXIV)

Tazemetostat (XXXIV), the first epigenetic drug for treating epithelioid sarcoma, was approved in 2020. It represents a new treatment strategy, especially for adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection. It was reported that, of the 62 participants with epithelioid sarcoma, about 10% experienced a reduction in their sarcoma after taking tazemetostat. Cancer proliferation ceased in more than 60% of the participants, even if their tumors did not shrink. What particularly stood out about the results was the duration of the benefit, lasting a year or more in many patients.

The most common adverse reactions (incidence ≥20%) were pain, fatigue, nausea, decreased appetite, vomiting, and constipation.\(^97\) The synthetic approach of tazemetostat (XXXIV) is shown in Scheme 35.\(^98\) First, dibromatin was used to derive 335 from 333. Then, the carboxyl group was methylated to obtain methyl benzoate derivative 336 by Na\(_2\)CO\(_3\) and CH\(_3\)I treatment in DMF at 60 °C for 8 h. The nitro group was reduced via iron powder and ammonium chloride treatment at 80 °C for 12 h to acquire amine compound 337 in 85% yield. A reductive amination reaction was employed to construct the core structure 338 using NaBH(OCOCH\(_3\))\(_3\). Base-promoted ester hydrolysis generated 340, which was reacted in 74% yield. Finally, a palladium-catalyzed coupling reaction of 343 with 342 using Pd(PPh\(_3\))\(_4\) and morpholine produced tazemetosat (XXXIV) in 71% yield.

11.3. Selumetinib (XXXV)

Selumetinib (XXXV) is a potent, orally bioavailable, mitogen-activated protein kinase 1 and 2 (MEK1/2) inhibitor developed by AstraZeneca. It was approved in April 2020 for treating pediatric patients aged ≥2 years with neurofibromatosis type 1, who had symptomatic, inoperable plexiform neurofibromas. Selumetinib (XXXV) impedes RAS/RAF/MEK/ERK signaling, resulting in the antiproliferation and pro-apoptosis of tumor cells.\(^99,100\) According to the previously disclosed patent, the synthetic approach of selumetinib (XXXV) is shown in Scheme 36.\(^101\) Nitration of 23,4-trifluorobenzoic (344) was conducted under HNO\(_3/\)H\(_2\)SO\(_4\) conditions to prepare 345 in 92% yield. Then,
346 was synthesized by introducing an amino group using ammonium hydroxide. In the presence of TMSCHN2, methyl ester 347 was obtained from 346 in 92% yield, which was subsequently reacted with aniline to obtain 348 in 90% yield. After reducing 348 using Pd(OH)2/C, the intermediate was treated with formic acid in ethanol to obtain 349 in 86% yield. The 4'-position and 2'-position of the newly introduced phenyl group was brominated and chlorinated using NBS and NCS successively, producing 351 in 87% yield. Then, the NH of the imidazole ring was methylated using CH3I in the presence of K2CO3 in DMF, producing 352 in a moderate yield of 35%. The ester bond of intermediate 352 was hydrolyzed in a NaOH solution consisting of a THF and water mixture to obtain 353. Finally, 353 was reacted with O-(2-[vinyloxy]ethyl) hydroxylamine in the presence of HOBT and EDCI to prepare 354, which was then hydrolyzed using hydrochloric acid in ethanol to obtain selumetinib (XXXV) in 100% yield.

**Scheme 33.** Synthesis of niraparib (XXXII).

**11.4. Erdafitinib (XXXVI)**

Erdafitinib (XXXVI) is a pan-FGFR inhibitor developed by Janssen Pharmaceutical Companies. It was approved in April 2019 for treating locally advanced or metastatic, or unresectable urothelial carcinoma (mUC). By binding to FGFR, erdafitinib (XXXVI) inhibits FGFR phosphorylation and suppresses FGFR-related signal transduction pathways, resulting in tumor cell proliferation and death.102,103

The synthetic route to erdafitinib (XXXVI) was released by Astex Pharmaceuticals, as shown in Scheme 37. The carbonyl group of starting material 355 was replaced with the chlorine...
atom to obtain 356 in 96% yield. Then, a cross-coupling reaction of 356 with 357 was performed in the presence of Pd(PPh₃)₄ and DME under N₂ atmosphere to obtain 358 in 82% yield. In the presence of Pd(OAc)₂ and BINAP, 358 was reacted with 359 to prepare 360 in a high yield of 97%, which was then substituted with 361 to produce 362. MsCl was employed to introduce a mesyl group into 362 to generate 363, which finally underwent another substitution reaction with isopropylamine to produce erdafitinib (XXXVI) in 87% yield.

11.5. Telotristat Ethyl (XXXVII)

Telotristat ethyl (XXXVII) is a first-in-class, small-molecule inhibitor of peripheral tryptophan hydroxylase (TPH) developed by Lexicon Pharmaceuticals and was approved in February 2017 for treating carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy alone. Patients treated for carcinoid syndrome with telotristat extirpate (XXXVII) displayed reduced bowel movement (BM) frequency and decreased u5-HIAA without overt adverse CNS effects.¹⁰⁵,¹⁰⁶ Although several synthetic routes to telotristat ethyl (XXXVII) have been released, the most efficient has been reported by Lexicon, as shown in Scheme 38.¹⁰⁷ First, the key intermediate pinacol boronate 365 was obtained from 364 in 88% yield in three steps. Then, a cross-coupling reaction was performed of 365 with 366 to obtain 367 in 84% yield. Treating 367 with 368 in the presence of Cs₂CO₃ and then

![Scheme 34. Synthesis of pemigatinib (XXXIII).](image_url)

![Scheme 35. Synthesis of tazemetosat (XXXIV).](image_url)
Scheme 36. Synthesis of selumetinib (XXXV).

Scheme 37. Synthesis of erdafitinib (XXXVI).
Scheme 38. Synthesis of telotristat ethyl (XXXVII).
Boc₂O, followed by 6N HCl, produced 369 in 75% yield. Deprotecting the Boc group of 369 provided 370 in 95% yield after two steps. Finally, 370 was treated with SOCl₂ and hippuric acid to prepare telotristat ethyl (XXXVII) in 66% yield.

In the route to telotristat ethyl (XXXVII), the key intermediate 368 was synthesized from 3-methyl-1H-pyrazole (371), as described in Scheme 42. A substitution reaction between 371 and 372 in the presence of potassium tert-butoxide in DMSO produced 373 in a satisfactory yield of 83%. Then,
treating \(373\) with \(i\)-PrMgCl and ethyl trifluoroacetate produced \(374\) in 62\% yield. Asymmetric transfer hydrogenation in the presence of \(375\) with iridium catalyst converted \(374\) to \(368\) in \(e\)e value of 94\% and a high yield of 99\%.

11.6. Pexidartinib (XXXVIII)

Pexidartinib (XXXVIII), developed by Daiichi Sankyo Inc., is an orally selective TKI against the colony-stimulating factor 1 (CSF1) receptor (IC\(_{50}\) = 0.02 \(\mu\)mol/L), KIT proto-oncogene receptor tyrosine kinase (KIT, IC\(_{50}\) = 0.01 \(\mu\)mol/L), and FLT3 harboring an internal tandem duplication mutation (FLT3-ITD, IC\(_{50}\) = 0.018 \(\mu\)mol/L).\(^{108}\) The drug was approved in August 2019 for treating symptomatic tenosynovial giant-cell tumors (TGCT) associated with severe morbidity or functional limitations and not amenable to surgery. As a rare and locally aggressive neoplasm that overexpresses CSF1, TGCT is commonly found in the synovium of joints or tendon sheaths of young adults.\(^{109}\)

The synthesis approach of pexidartinib (XXXVIII) is described in Scheme 39.\(^{110,111}\) Treating \(376\) with \(377\) in the

\[\text{OAc}_2, \text{DMAP, DCM, } t\text{-BuOH, rt, 54}\% \rightarrow \text{OAc}_2, \text{DMF, rt, 75}\% \rightarrow \text{OAc}_2, \text{MeCN, rt, 80}\% \rightarrow \text{OAc}_2, \text{Pd/C, MeOH, } H_2, \text{rt, 96}\% \rightarrow \text{OAc}_2, \text{TFA, NH}_2\text{BH(OAc)}_3, N_2, \text{DCM, rt, 78}\% \rightarrow \text{OAc}_2, \text{TFAA, TEA, DCM, rt, 57}\% \rightarrow \text{OAc}_2, \text{K}_2\text{CO}_3, \text{MeOH, } H_2O, N_2, \text{rt, 71}\% \rightarrow \text{OAc}_2, \text{N}_{2}, \text{rt, 84}\% \rightarrow \text{OAc}_2, \text{Pd/C, MeOH, } H_2, \text{rt, 96}\% \rightarrow \text{OAc}_2, \text{TFAA, TEA, DCM, rt, 57}\% \rightarrow \text{OAc}_2, \text{K}_2\text{CO}_3, \text{MeOH, } H_2O, N_2, \text{rt, 71}\% \rightarrow \text{OAc}_2, \text{N}_{2}, \text{rt, 84}\% \rightarrow \text{OAc}_2, \text{Pd/C, MeOH, } H_2, \text{rt, 96}\% \rightarrow \text{OAc}_2, \text{TFAA, TEA, DCM, rt, 57}\% \rightarrow \text{OAc}_2, \text{K}_2\text{CO}_3, \text{MeOH, } H_2O, N_2, \text{rt, 71}\% \rightarrow \text{OAc}_2, \text{N}_{2}, \text{rt, 84}\% \rightarrow \text{OAc}_2, \text{Pd/C, MeOH, } H_2, \text{rt, 96}\% \rightarrow \text{OAc}_2, \text{TFAA, TEA, DCM, rt, 57}\% \rightarrow \text{OAc}_2, \text{K}_2\text{CO}_3, \text{MeOH, } H_2O, N_2, \text{rt, 71}\% \rightarrow \text{OAc}_2, \text{N}_{2}, \text{rt, 84}\% \rightarrow \text{OAc}_2, \text{Pd/C, MeOH, } H_2, \text{rt, 96}\% \rightarrow \text{OAc}_2, \text{TFAA, TEA, DCM, rt, 57}\% \rightarrow \text{OAc}_2, \text{K}_2\text{CO}_3, \text{MeOH, } H_2O, N_2, \text{rt, 71}\% \rightarrow \text{OAc}_2, \text{N}_{2}, \text{rt, 84}\% \rightarrow \text{OAc}_2, \text{Pd/C, MeOH, } H_2, \text{rt, 96}\% \rightarrow \text{OAc}_2, \text{TFAA, TEA, DCM, rt, 57}\% \rightarrow \text{OAc}_2, \text{K}_2\text{CO}_3, \text{MeOH, } H_2O, N_2, \text{rt, 71}\% \rightarrow \text{OAc}_2, \text{N}_{2}, \text{rt, 84}\% \rightarrow \text{OAc}_2, \text{Pd/C, MeOH, } H_2, \text{rt, 96}\% \rightarrow \text{OAc}_2, \text{TFAA, TEA, DCM, rt, 57}\% \rightarrow \text{OAc}_2, \text{K}_2\text{CO}_3, \text{MeOH, } H_2O, N_2, \text{rt, 71}\% \rightarrow \text{OAc}_2, \text{N}_{2}, \text{rt, 84}\% \rightarrow \text{OAc}_2, \text{Pd/C, MeOH, } H_2, \text{rt, 96}\% \rightarrow \text{OAc}_2, \text{TFAA, TEA, DCM, rt, 57}\% \rightarrow \text{OAc}_2, \text{K}_2\text{CO}_3, \text{MeOH, } H_2O, N_2, \text{rt, 71}\% \rightarrow \text{OAc}_2, \text{N}_{2}, \text{rt, 84}\% \rightarrow \text{OAc}_2, \text{Pd/C, MeOH, } H_2, \text{rt, 96}\% \rightarrow \text{OAc}_2, \text{TFAA, TEA, DCM, rt, 57}\% \rightarrow \text{OAc}_2, \text{K}_2\text{CO}_3, \text{MeOH, } H_2O, N_2, \text{rt, 71}\% \rightarrow \text{OAc}_2, \text{N}_{2}, \text{rt, 84}\% \rightarrow \text{OAc}_2, \text{Pd/C, MeOH, } H_2, \text{rt, 96}\% \rightarrow \text{OAc}_2, \text{TFAA, TEA, DCM, rt, 57}\% \rightarrow \text{OAc}_2, \text{K}_2\text{CO}_3, \text{MeOH, } H_2O, N_2, \text{rt, 71}\% \rightarrow \text{OAc}_2, \text{N}_{2}, \text{rt, 84}\% \rightarrow \text{OAc}_2, \text{Pd/C, MeOH, } H_2, \text{rt, 96}\% \rightarrow \text{OAc}_2, \text{TFAA, TEA, DCM, rt, 57}\% \rightarrow \text{OAc}_2, \text{K}_2\text{CO}_3, \text{MeOH, } H_2O, N_2, \text{rt, 71}\% \rightarrow \text{OAc}_2, \text{N}_{2}, \text{rt, 84}\% \rightarrow \text{OAc}_2, \text{Pd/C, MeOH, } H_2, \text{rt, 96}\%

Scheme 41. Synthesis of entrectinib (XXXX).
presence of TBAHS and potassium tert-pentylate produced 378 in 91% yield. The dehydroxylation of 378 and the subsequent deprotection of the Boc group produced 379 in 78% yield after three steps. Finally, the reductive amination reaction between 379 and 380 produced pexidartinib (XXXVIII) in 89% yield.

11.7. Larotrectinib (XXXIX)

Larotrectinib (XXXIX) is an oral, highly selective inhibitor of tropomyosin receptor kinase (TRK). It was developed by Bayer Health Care Pharmaceuticals Inc. and approved in November 2018 for treating adult and pediatric patients with solid tumors that display neurotrophic receptor tyrosine kinase (NTRK) gene fusions. Larotrectinib (XXXIX) is a first-generation TRK inhibitor that selectively targets pan-TRK (TRKA, TRKB, and TRKC) with half-maximal inhibitory concentration (IC₅₀) values in the low nanomolar range, inhibiting the MAPK, PI3K–AKT, PKC, and STAT3 pathways. The synthesis of larotrectinib (XXXIX) is depicted in Scheme 40. A Schiff base 383 was obtained via a reaction between aldehyde 381 and 382, which, without further purification, was reacted with 384 to obtain 385 in 81% yield in two steps. A tetrahydropyrrrole ring was constructed via two deprotection reactions and an intramolecular cyclization of 385, which was isolated using D- (+)-malic acid, producing D- (+)-malic acid salt 386 in 96% yield. Then, a coupling reaction between 386 and 387 produced 388, followed by a nitro group reduction to obtain 389 in 83% yield. Treating 389 with phenyl chloroformate produced 390, which was reacted with 391 in the presence of sulfuric acid to prepare larotrectinib (XXXIX) in 92% yield.

11.8. Entrectinib (XXXX)

Entrectinib (XXXX) is an orally selective ALK, ROS1, and TRKs inhibitor displaying nanomolar activity (ALK IC₅₀ = 12 nM, ROS-1 IC₅₀ = 7 nM, TRKA IC₅₀ = 1 nM, TRKB IC₅₀ = 12 nM). The synthesis of selpercatinib (XXXXI) is depicted in Scheme 42. A Schiff base 383 was obtained via a reaction between aldehyde 381 and 382, which, without further purification, was reacted with 384 to obtain 385 in 81% yield in two steps. A tetrahydropyrrrole ring was constructed via two deprotection reactions and an intramolecular cyclization of 385, which was isolated using D- (+)-malic acid, producing D- (+)-malic acid salt 386 in 96% yield. Then, a coupling reaction between 386 and 387 produced 388, followed by a nitro group reduction to obtain 389 in 83% yield. Treating 389 with phenyl chloroformate produced 390, which was reacted with 391 in the presence of sulfuric acid to prepare larotrectinib (XXXIX) in 92% yield.
IC₅₀ = 3 nM, TRKC IC₅₀ = 5 nM) on the corresponding target-driven cell lines. It was developed by Roche and was approved in June 2019 for treating adult and pediatric patients with NTRK fusion-positive, advanced or recurrent solid tumors.¹¹⁵,¹¹⁶

The synthetic route to entrectinib (XXXX) is described in Scheme 41.¹¹⁷ At first, 392 was protected as Boc ester to provide 393 in 54% yield. Combining 393 with piperazine produced 394, which was substituted with a methyl group to generate 395 in 80% yield. Then, the nitro group reduction of 395 by Pd/C and hydrogen gas produced amine 396 in 96% yield. A reductive amination reaction was performed between 396 and 397 in the presence of TFA and NH₄BH(OAc)₃ to obtain 398 in 78% yield. Intermediate 398 was treated with TFA to obtain 399 in 57% yield. Then, the tert-butyl group was removed from 399, producing acid 400 in 84% yield. The amide condensation between 400 and amine intermediate 401, which was synthesized from (3-cyano-4-fluorophenyl)boronic acid (403) in two steps, generated 402 in 57% yield. Finally, 402 was treated with K₂CO₃ in MeOH to obtain entrectinib (XXXX) in 71% yield.

### 11.9. Selpercatinib (XXXXI)

Selpercatinib (XXXXI) is an ATP-competitive, highly selective receptor tyrosine kinase RET inhibitor. It was developed by
Loxo Oncology and approved in May 2020 for treating adult patients with metastatic RET fusion-positive NSCLC, adult and pediatric patients ≥ 12 years of age with advanced or metastatic medullary thyroid cancer (MTC), and adult and pediatric patients ≥ 12 years of age with advanced or metastatic thyroid cancer who have received radioactive iodine that did not work or is no longer working.118,119

The synthetic route to selpercatinib (XXXI) is depicted in Scheme 42.210 At first, the hydroxylamine group was introduced into the 24,6-trimethylbenzenesulfonyl chloride (406) to obtain 408 in 89% yield. Successively treating 408 with 409 and 411 generated 412 in 62% yield in two steps. Then 412 was decarboxylated with HBr to acquire 413 in 63% yield. After a Vilsmeier-Haack reaction, 413 was converted to 414 in 90% yield. The condensation of 414 with hydroxylamine at 50 °C in ethanol generated 415 in 84% yield, which was then dehydrated to give 416 in 95% yield. Further demethylation of 416 produced 417. Then, the hydroxyl group was protected as triflate, yielding 418. Next, core structure 420 was constructed by coupling 418 with 419. The side chain was introduced via a reaction between 420 and 421, which underwent a Suzuki-Miyaura reaction with 423 to obtain 424 in 87% yield. The Boc group was then removed from 424, generating 425 in 74% yield. Finally, the reductive amination of 425 with 426 in the presence of STAB and TEA produced selpercatinib (XXXI) in 74% yield.

11.10. Duvelisib (XXXXII)

Since the PI3 K signaling pathway plays an essential role in the activation, proliferation, and survival of B and T cells, PI3 K is considered a vital drug target. Duvelisib (XXXXII) is a first-in-class, small-molecule, selective dual inhibitor of PI3 K (PI3 K δ and PI3 K γ), which was initially created by Intellikine and further developed by Oncology (under the license of Infinity Pharmaceuticals). It was approved in September 2018 for treating adult patients with relapsed or refractory CLL/small lymphocytic lymphoma (SLL) after at least two prior therapies. Duvelisib (XXXXII) showed a 10-fold selectivity for PI3 K δ over PI3 K γ, while it was not active against other protein or lipid kinases.21,122

The synthesis of duvelisib (XXXXII) was released by Intellikine, as shown in Scheme 43.213 Intermediate 428 was prepared via the reaction between 427 and 3,4-dihydro-2H-pyran. Next, 429 was subjected to SOCl2 in the presence of 1 drop of DMF to obtain the acyl chloride intermediate, which, without further purification, was reacted with aniline to acquire amide 430 in 81% yield. Moreover, the carboxyl group of 431 was reacted with NHCH3(OCH3) HCl to obtain 432 in 95% yield. Then, the Grignard reagent was used to react with newly obtained intermediate 432 and 430 to synthesize 433, which was successively deprotected and cyclized to obtain 434 in 60% yield and an ee value exceeding 99%. Then, an SnAr reaction occurred between 434 and 428, yielding 435. Finally, the morphine group was removed from 435 to produce duvelisib (XXXXII).

12. Conclusions

In the past five years, apart from these small molecules that have been approved for cancer treatment, several oligonucleotides, protein-based candidates, fusion protein, ADCs, and mAbs have also been marketed to fight for the tough battle. These non-small molecule drugs have disadvantages, such as the only medication route is intravenous medication, and these drugs are very expensive for the patients. However, small-molecule drugs have good oral bioavailability and are readily affordable.

The pharmaceutical community and academic researchers have made significant efforts to develop small-molecule drugs for fighting malignant tumors that severely threaten human health. Over the past five years, 42 small-molecule anti-cancer drugs have been approved for treating various types of cancer. Anti-lung cancer drugs, anti-breast cancer drugs, and anti-leukemia drugs account for almost half of these. These drugs act by targeting various proteins, enzymes, factors, and receptors, such as JAK3, EGFR, CDK-4 and 6, and PARP. The drugs summarized in this paper feature promising pharmacophores, which will benefit next-generation drug discovery.

In addition, the medicinal chemistry synthetic routes and large-scale synthetic methods of 42 approved anti-cancer small-molecule drugs are reviewed. In particular, metal-catalyzed coupling reactions (Suzuki coupling and the Buchwald-Hartwig reaction) are used to prepare drugs, such as abemaciclib (X), lorlatinib (XVI), and encorafenib (XXII). Cyclization and intramolecular or intermolecular cycloaddition represent the most important reactions employed to construct the pharmacophores, such as tucatinib (VII), neratinib (XI), ribociclib (XII), and lurbinectedin (XIV). To obtain the single enantiomer of the chiral drugs, asymmetric synthesis or chiral resolution are employed to synthesize several agents, such as ivosidenib (III), talazoparib (IX), darolutamide (XX), and avapritinib (XXIV). In addition, other reactions, such as Borch reduction and the Friedel-Crafts reaction, represent vital strategies for introducing side chains into the scaffold. Consequently, it is believed that the chemical structure analysis and synthetic route discussion are beneficial for contemporary medicinal chemistry strategies, including pharmacophore-based drug design, drug repositioning, lead diversification, multiparameter optimization, and drug discovery from natural resources.

Even having several advantages, small-molecule drugs for cancer treatment have several challenges, such as poor selectivity which leads to side effects. Also, tumor cells that long term exposed to a single small-molecule drug will develop drug resistance. In addition, some important antitumor targets, such as p53, KRAS, and STAT3, have been being called undruggable targets and have no small-molecule drugs approved till date. It was demonstrated that these proteins have no druggable pocket that small molecules can bind,
which limited the development of small-molecule drugs. However, with the rapid development of chemical biology, new strategies such as PROTACs and molecular glues are the ideal solution to novel small-molecule antitumor drug discovery.

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These authors declare no conflict of interest.

Declaration of Conflicting Interests
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Informed Consent
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